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2015

UNIVERSITY OF CALIFORNIA,
IRVINE

# Development of Stereospecific Nickel-Catalyzed Transformations of Benzylic Alcohol Derivatives

DISSERTATION

Submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

by

Michael R. Harris

Dissertation Committee:
Professor Elizabeth R. Jarvo, Chair
Professor Kenneth J. Shea
Professor Larry E. Overman

2015

# DEDICATION

For my family

for their love and support

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# ACKNOWLEDGEMENTS

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I thank the American Chemical Society for permission to include Chapter 2 and 3, which were originally published in the *Journal of the American Chemical Society*. I also thank John Wiley and Sons for permission to include portions of Chapter 1, which were originally published in *Angewandte Chemie*.

I thank Professor Liz Jarvo for all of her thoughtful mentorship over the last five years. I have learned so much while working in her lab. I am grateful for her support and guidance on research projects and for allowing me to pursue interesting chemistry.

I am grateful to my mentors at Willamette University for inspiring and fostering my love of science. I am grateful to Professor Chuck Williamson for sage advice and for serving as a role model for excellent scientific communication. I am especially indebted to Professor Andrew Duncan whose enthusiasm and support have both inspired and enabled me to pursue a career in organic chemistry.

I thank Professors Larry Overman and Ken Shea for many thoughtful conversations about research during my time at UCI. I am also grateful for the opportunities I have had to teach alongside Susan King. These experiences have helped me grow immensely as both a teacher and a scientist.

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I am incredibly grateful for the love from my family, particularly my mom and dad. They have always supported me and encouraged me to follow my dreams. I am grateful for their understanding and patience over the past five years.

Finally, I would like to thank my fiancée, Charlotte, who has been incredibly supportive over the last five years. She is a wonderful coworker and scientist, and someone whose opinions and input have been invaluable. Without her constant love and support, the sacrifices she has made on my behalf, her kindness and her encouragement, I would not have had the strength to finish my degree.

# Curriculum Vitae

## Michael R. Harris

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### EDUCATION

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| 2010–2015 | Ph.D. Candidate in Organic Chemistry, University of California, Irvine, Irvine, CA |
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### RESEARCH EXPERIENCE

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| 2010–present | NSF Graduate Research Fellow (University of California, Irvine)<br>*Development of Stereospecific Nickel-Catalyzed Transformations of Benzylic Alcohol Derivatives*<br>Advisor: Prof. Elizabeth R. Jarvo |
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*Analytical Characterization* – SFC (maintenance and repair), NMR, IR, GC-MS, HPLC.
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### PUBLICATIONS

"Nickel-Catalyzed Formation of Secondary Benzylic Zinc Reagents from 2-Pyridyl Carbinols."
**Harris, M. R.**; Hanna, L. E.; Jarvo, E. R. *Manuscript in Preparation.*

"Selective Synthesis of Either Enantiomer of an Anti-Breast-Cancer Agent via a Common Chiral Intermediate."
Johnson, A. G.; Tranquilli, M. M.; **Harris, M. R.**; Jarvo, E. R. *Tetrahedron Lett.* **2015**, *56*, 3486.

"Enantiospecific Intramolecular Heck Reactions of Secondary Benzylic Ethers."
**Harris, M. R.**; Konev, M. O.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 7825.
*Article highlighted in *Synfacts*, **2014**, *10*, 932.

"Retention or Inversion in Stereospecific Nickel-Catalyzed Cross-Coupling of Benzylic Carbamates with Arylboronic Esters: Control of Absolute Stereochemistry with an Achiral Catalyst."

**Harris, M. R.**; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303–3306.

“Synthesis of Enantioenriched Triarylmethanes by Stereospecific Cross-Coupling Reactions." Taylor, B. L. H.; **Harris, M. R.**; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790–7793.

## PRESENTATIONS

**Harris, M. R.**; Jarvo, E. R.
*New Modes of Reactivity for Stereospecific Nickel-Catalyzed Reactions of Benzylic Ethers and Esters*
American Chemical Society, 248th National Meeting, San Francisco, CA (Oral Presentation), Aug. 2014

**Harris, M. R.**; Jarvo, E. R.
*Enantioselective Synthesis of Methylenecyclopentanes by Intramolecular Nickel-Catalyzed Alkyl Heck Reactions*
ACS DOC 2014 Graduate Research Symposium, Irvine, CA (Oral Presentation), July 2014

**Harris, M. R.**; Jarvo, E. R.
*Development of Stereospecific Nickel-Catalyzed Cross-Coupling Reactions of Benzylic Alcohol Derivatives*
American Chemical Society, 247th National Meeting, Dallas, TX (Oral Presentation), March 2014

**Harris, M. R.**; Jarvo, E. R.
*Synthesis of Triarylmethanes by Stereospecific Cross-Coupling*
UCI Graduate Student & Postdoctoral Colloquium (Oral Presentation), April 2012

**Harris, M. R.**; Duncan, A. P.
*Stereocontrolled Organocatalytic Synthesis of Oxacycles*
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## ABSTRACT OF DISSERTATION

# Development of Stereospecific Nickel-Catalyzed Transformations of Benzylic Alcohol Derivatives

by

Michael R. Harris

Doctor of Philosophy in Chemistry

University of California, Irvine, 2015

Professor Elizabeth R. Jarvo, Chair

Transition metal catalyzed reactions are indispensable tools for the asymmetric construction of carbon–carbon bonds. Traditionally, cross-coupling reactions have relied on the use of aryl, vinyl or $1^o$ alkyl electrophiles. Advances in asymmetric catalysis have permitted the use of $2^o$ alkyl electrophiles in cross-coupling reactions allowing for the development of several stereoconvergent transformations. Herein, we report a complementary approach to asymmetric cross-coupling reactions by means of the development of stereospecific, nickel-catalyzed transformations of benzylic alcohol derivatives.

Our initial efforts were directed toward expanding upon a Kumada cross-coupling reaction of secondary benzylic ethers with methylmagnesium iodide previously reported by the Jarvo laboratory. We extended the scope of this reaction by developing conditions to enable the use of aryl Grignard reagents for the construction of enantioenriched triarylmethanes by stereospecific nickel-catalyzed cross-coupling of diaryl methanol derivatives. The reaction proceeds in high enantiospecificity and overall inversion. This methodology is used to prepare a single enantiomer of an anti-breast-cancer agent.

Further advances in our cross-coupling methodology are demonstrated in the development of a stereospecific Suzuki–Miyaura coupling of benzylic carbamates and pivolates with aryl- and heteroarylboronic esters. The reaction proceeds with selective inversion or retention at the electrophilic carbon depending on the nature of the ligand. Tricyclohexylphosphine ligand provides product with retention, while an NHC ligand provides product with inversion. The reaction proceeds in high enantiospecificity to afford *either* enantiomer of a variety of triarylmethanes.

Taking advantage of our growing expertise in nickel catalyzed reactions of secondary alkyl electrophiles, we designed the first alkyl Heck reaction with control of stereochemistry at the electrophilic carbon. Enantioenriched methylenecyclopentanes are synthesized by stereospecific, nickel-catalyzed Heck cyclizations of secondary benzylic ethers. The reaction proceeds in high yield and enantiospecificity for benzylic ethers of both π-extended and simple arenes. Ethers with pendant 1,2-disubstituted olefins form trisubstituted olefins with control of both absolute configuration and alkene geometry. The diastereoselective synthesis of a polycyclic furan is demonstrated.

In the final chapter of this work, we demonstrate a nickel-catalyzed generation of secondary benzylzinc reagents from 2-pyridyl carbinols that are phosphorylated in situ. A variety of benzylzinc reagents are formed in high yield, allowing for facile hydrogenolysis of 2-pyridyl carbinols. The utility of this transformation is highlighted in a high-yielding intramolecular addition of a secondary benzylzinc reagent to an α,β-unsaturated ester.

*Chapter One*

# Synthesis of Enantioenriched Triarylmethanes by Stereospecific Kumada Cross-Coupling Reactions

## 1.1 Introduction

Metal-catalyzed cross-coupling reactions provide efficient and general methods for the formation of aryl-aryl and aryl-vinyl carbon–carbon bonds.[1,2] Application of these methods to alkyl electrophiles, however, is challenging. Slow oxidative addition and competitive β-hydride elimination of alkylmetal intermediates in the course of $sp^3$–$sp^3$ cross-coupling reactions have contributed to the slow progress relative to cross coupling reactions of aryl and vinyl electrophiles.[3] In recent years, Knochel, Kambe and Fu have shown that these obstacles are not prohibitive to the development of alkyl-alkyl cross-coupling reactions by demonstrating methods for Suzuki, Negishi, Hiyama and Sonogashira cross-coupling reactions of alkyl halides.[4] While alkyl halides are effective electrophiles in nickel-catalyzed alkyl-alkyl cross-couplings, stereochemical information is often lost due to the formation of radical intermediates during oxidative addition.[5] Under the control of a chiral catalyst, achiral intermediates can be converted to single stereoisomers of product in stereoconvergent cross-coupling reactions.[6]

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[1] A portion of this chapter was originally published in journal format: Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790.

[2] Hartwig, J. F. *Organotransition Metal Chemistry*; University Science Books: Sausalito, 2010; pp 877–90.

[3] Luh, T. Y.; Leung, M. K.; Wong, K. T. *Chem. Rev.* **2000**, *100*, 3187.

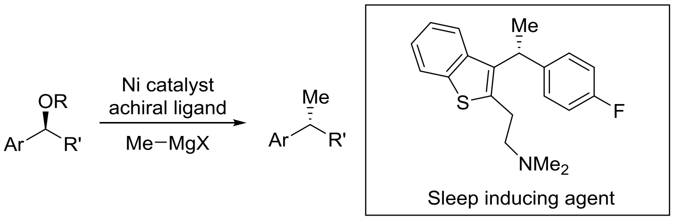
[4] (a) Fu, G. C.; Netherton, M. R. *Adv. Synth. Catal.* **2004**, *346*, 1525. (b) Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79. (c) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222.

[5] Stille, J. K.; Cowell, A. B. *J. Organomet. Chem.* **1977**, *124*, 253.

[6] (a) Swift, E. C.; Jarvo, E. R. *Tetrahedron* **2013**, *69*, 5799. (b) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299-309.

Jarvo and co-workers recognized that a stereospecific alkyl-alkyl cross-coupling reaction could be possible if a suitable electrophile was chosen. Based on examples of nickel-catalyzed substitution reactions of allylic ethers, it was proposed that alkyl ethers would undergo heterolytic bond cleavage during oxidative addition, thereby maintaining stereochemical fidelity throughout the cross-coupling reaction.[7,8] Benzylic ethers were shown to be competent electrophiles in stereospecific, nickel-catalyzed cross-coupling reactions with methylmagnesium iodide (Scheme 1.1).[9] Bioactive diarylethanes, a class of compounds that is difficult to synthesize in an enantioenriched fashion, were prepared using this methodology.[10,11] Extending our methodology to aryl Grignard reagents in the cross-coupling reactions of diarylmethyl ethers would provide a new strategy for the synthesis of enantioenriched triarylmethanes.

***Scheme 1.1.*** Stereospecific cross-coupling reaction of benzylic ethers



Triarylmethanes are attractive targets because of their application in materials and medicinal chemistry.[12] Traditionally used as dye precursors, triarylmethanes have more recently been identified as potential pharmacological agents against cancer, diabetes, and bacterial

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[7] Takahashi, T.; Kanno, K. Nickel-catalyzed Cross-coupling Reactions. In *Modern Organonickel Chemistry*; Tamaru, Y., Ed.; Wiley-VCH: Weinheim, 2005; p 47.

[8] Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *Tetrahedron* **1996**, *54*, 1117.

[9] Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389.

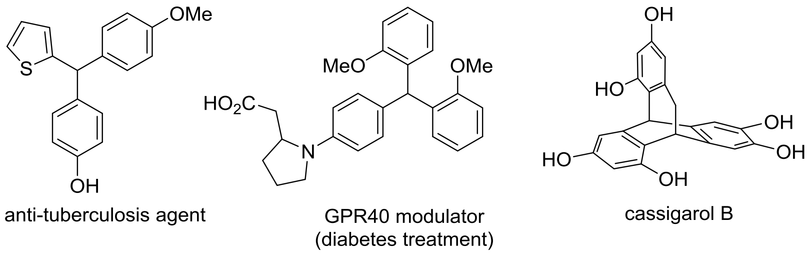
[10] Alami, M.; Messaoudi, S.; Hamze, A.; Provot, O.; Brion, J.-D.; Liu, J.-M.; Bignon, J.; Bakala, J. Patent WO/2009/147217 A1, Dec 10, 2009.

[11] Moree, W. J.; Jovic F.; Coon T.; Yu, J.; Li, B. F.; Tucci, F. C.; Marinkovic, D.; Gross, R. S.; Malany, S.; Bradbury, M. J.; Hernandez, L. M.; O'Brien, Z.; Wen, J.; Wang, H.; Hoare, S. R.; Petroski, R. E.; Sacaan, A.; Madan, A.; Crowe, P. D.; Beaton, G. *J. Med. Chem.* **2009**, *52*, 5307.

[12] (a) Duxbury, D. F. *Chem. Rev.* **1993**, *93*, 381; (b) Shchepinov, M. S.; Korshun, V. A. *Chem. Soc. Rev.* **2003**, *32*, 170; (c) Xu, Y.-Q.; Lu, J.-M.; Li, N.-J.; Yan, F.; Xia, X.; Xu, Q. *Eur. Polym. J.* **2008**, *44*, 2404.

infections (Figure 1.1).[13] The classical approach for synthesis of these compounds relies on Friedel-Crafts alkylation reactions.[14] These reactions are limited in scope and often suffer from poor regioselectivity.[15] Catalytic variants have been developed that address the lack of regioselectivity, allowing for reactions to be run under mildly acidic conditions, but the asymmetric synthesis of triarylmethanes remains difficult.[16,17] In a recent example, a chiral phosphoric acid is used in a Friedel−Crafts alkylation to form enantioenriched indole-containing triarylmethanes (Scheme 1.2a).[18] In another approach, prochiral triarylmethanes are desymmetrized through enantioselective palladium-catalyzed C–H bond activation (Scheme 1.2b).[19] These methods, however, are restricted to indole- and pyridine-containing substrates, respectively. Improved methods for the asymmetric synthesis of biologically relevant triarylmethanes are needed.[20]

***Figure 1.1.*** Bioactive triarylmethanes



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[13] (a) For a review on biologically relevant triarylmethanes, see (a) Mondal, F. S.; Panda, G. RSC Adv. 2014, 4, 28317. (b) Ajay, S.; Srivastava, K.; Sharma, R.; Mishra, R.; Balapure, A. K.; Murthy, P.; Panda, G. *Bioorg. Med. Chem.* **2006**, *14*, 1497–1505. (c) Yamato, M.; Hashigaki, K.; Yasumoto, Y.; Sakai, J.; Luduena, R.; Banerjee, A.; Tsukagoshi, S.; Tashiro, T.; Tsuruo, T. *J. Med. Chem.* **1987**, *30*, 1897.

[14] Nachtsheim, B. J.; Rueping, M. *J. Org. Chem.* **2010**, *6*, 6.

[15] Katritzky, A. R.; Lan, X. *Dyes and Pigments* **1994**, *25*, 303–324.

[16] Lu, X.; Lin, S. *J. Org. Chem.* **2007**, *72*, 9757–9760.

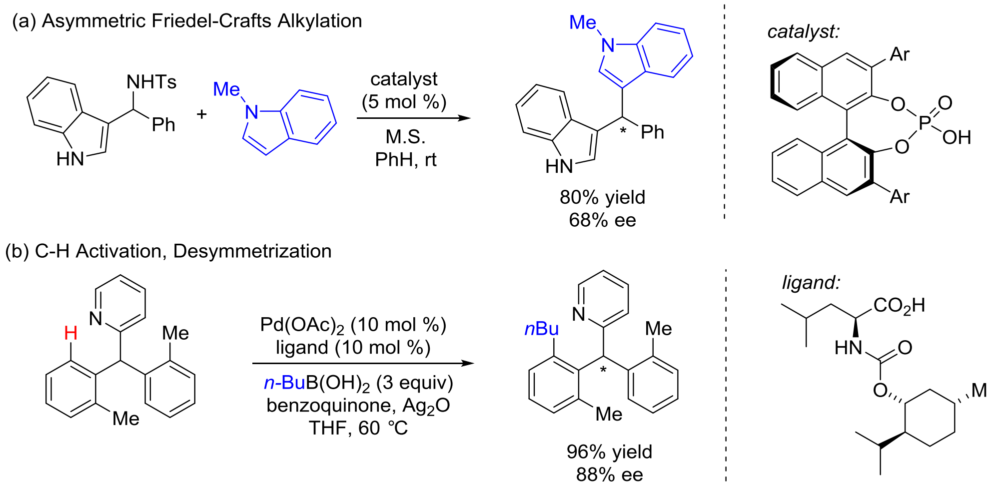
[17] Oshima, K.; Yorimitsu, H.; Niwa, T. *Org. Lett.* **2007**, *9*, 2373–2375.

[18] You, S.; Sun, F.; Zheng, X.; Gu, Q.; He, Q. *Eur. J. Org. Chem.* **2011**, 47–50.

[19] Yu, J.; Chen, X.; Engle, K.M.; Wang, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 4882–4886.

[20] For up to date examples of asymmetric preparation of triarylmethanes, see: (a) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790. (b) Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303. (c) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307. (d) Matthew, S. C.; Glasspoole, B. W.; Eisenberger, P.; Crudden, C. M. *J. Am. Chem. Soc.* **2014**, *136*, 5828 (e) Zhuo, M.-H.; Jiang, Y.-J.; Fan, Y.-S.; Gao, Y.; Liu, S.; Zhang, S. *Org. Lett.* **2014**, *16*, 1096. (f) Huang, Y.; Hayashi, T. *J. Am. Chem. Soc.* ASAP.

***Scheme 1.2.*** Asymmetric synthesis of triarylmethanes



## 1.2 Development of a Stereospecific Cross-Coupling Reaction of Aryl Grignard Reagents

Initial experiments investigating the application of the nickel-catalyzed cross-coupling reaction of benzylic ethers to the synthesis of triarylmethanes were performed by Buck Taylor. Triarylmethanes could be furnished at 40 °C in 51% yield and 33% enantiospecificity (Scheme 1.3).[21] A dramatic boost in yield and enantiospecificity for triarylmethane (*S*)-**1.3** was observed when bis(2-diphenylphosphinophenyl)ether (DPEphos) was replaced with 1,4-bis(diphenylphosphino)butane (DPPB), and when methyl ether (*S*)-**1.1** was substituted for methoxyethyl ether (*S*)-**1.2**. The reactivity of (*S*)-**1.2** is proposed to be increased by its ability to bind with Lewis acidic magnesium ions, which may activate the benzylic C–O bond toward oxidative addition (Figure 1.2).[22] With the objective of further increasing the concentration of activated substrate in solution through chelation of magnesium, we designed an alternative leaving group with a more Lewis-basic nitrogen donor atom (**1.4**, Figure 1.2).

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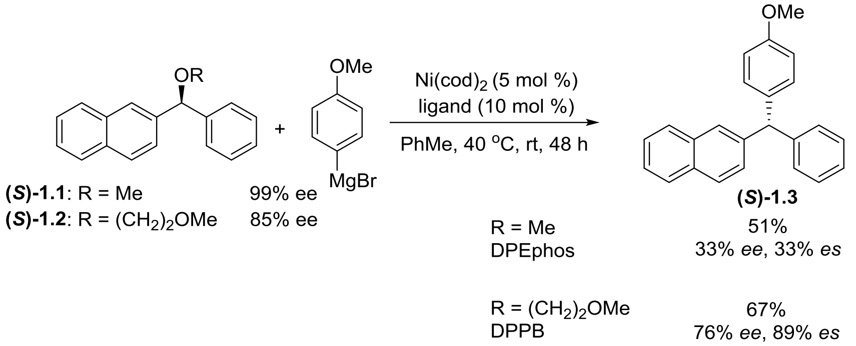
[21] Denmark, S. E.; Smith, R. C. *J. Am. Chem. Soc.* **2010**, *132*, 3612–3620.

[22] Greene, M. A., Yonova, I. M., Williams, F. J., Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293.

***Scheme 1.3.*** Initial reaction conditions for the cross-coupling reaction



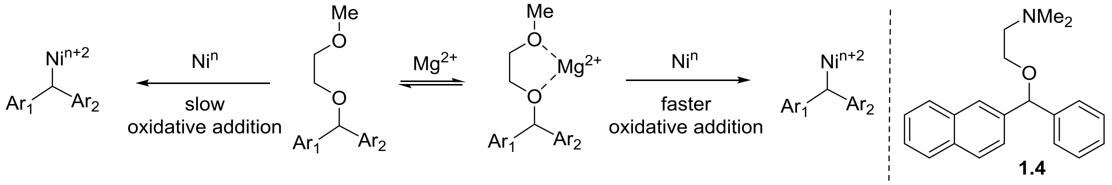


***Figure 1.2.*** Proposed effect of chelation to magnesium on the rate of oxidative addition

The synthesis of enantioenriched methoxyethyl ether (*S*)-**1.2** and dimethylaminoethyl substrate (*S*)-**1.4** began with the asymmetric arylation of naphthaldehyde (Scheme 1.4).[23] Subsequent alkylation of alcohol (*S*)-**1.5** with bromoethyl methyl ether afforded (*S*)-**1.2**, whereas alkylation with 2-chloro-*N*,*N*-dimethylethylamine hydrochloride produced (*S*)-**1.4**. Both alkylation reactions are expected to be stereospecific.

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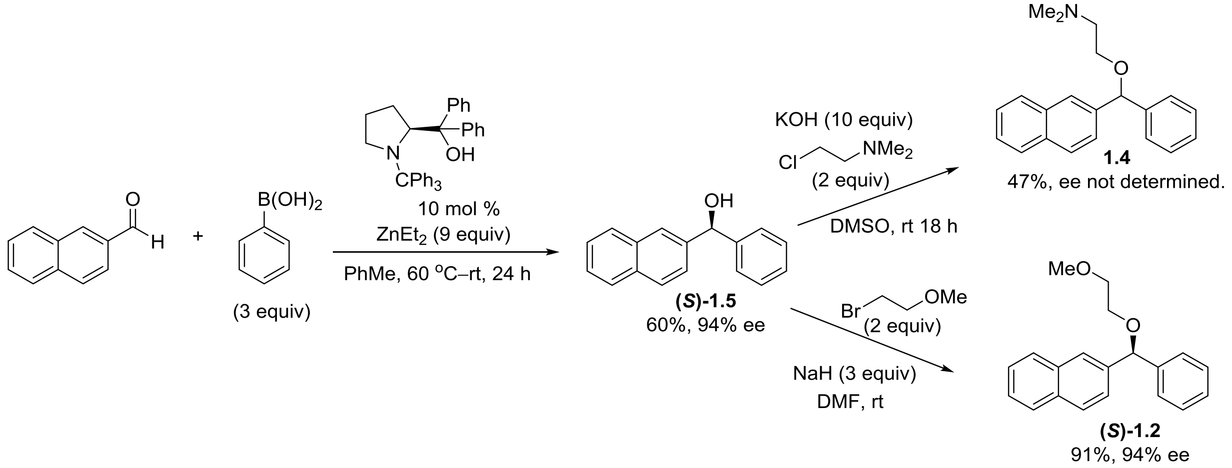
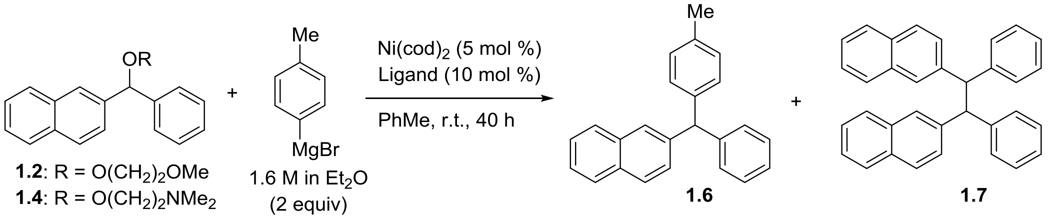
[23] Braga, A. L.; Paixão, M. W.; Westermann, B.; Schneider P. H.; Wessjohan, L. A. *J. Org. Chem.* **2008**, *73,* 2879.

***Scheme 1.4.*** Synthesis of starting materials



Before evaluating the enantiospecificity of the cross coupling reaction with (*S*)-**1.2** and **1.4**, optimal reaction conditions were identified. Early on, it was evident that careful tuning of reaction conditions would be necessary when the Grignard reagent is varied. While use of DPPB as ligand in the cross-coupling reaction of *p*-methoxyphenylmagnesium bromide and ether **1.2** provided the desired triarylmethane **1.3** in high yield, use of this ligand in cross-coupling reactions with *p*-methylphenylmagnesium bromide resulted in the formation of less than 10% of the desired triarylmethane **1.6** (Table 1.1, entries 2 and 5). After examination of an extensive number of ligands, 1,5-bis(diphenylphosphino)pentane (DPPPe) and DPEphos were identified as lead ligand candidates for cross-coupling reactions with *p*-methylphenylmagnesium bromide. The use of either ligand resulted in comparable yields of triarylmethanes, but the use of DPPPe resulted in less homocoupled product (**1.7**, Table 1.1). To avoid formation of complex product mixtures, DPPPe was used in experiments designed to probe the stereospecificity of the cross-coupling reaction with *p*-methylphenylmagnesium bromide.

***Table 1.1.*** Evaluation of ligands and leaving groups

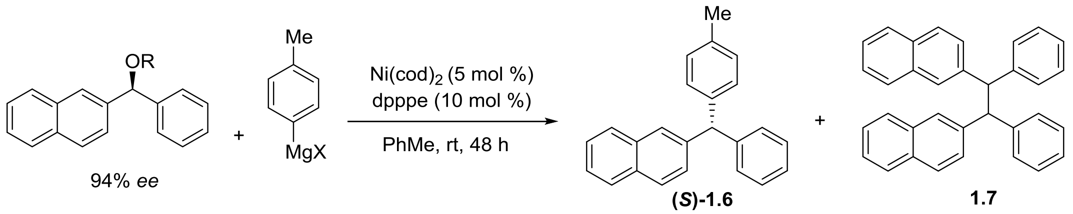


| Entry | Substrate | Ligand | Substrate (%)$^a$ | **1.6** (%)$^a$ | **1.7** (%)$^a$ |
|---|---|---|---|---|---|
| 1 | **1.2** | DPEphos | < 5 | 45 | 17 |
| 2 | **1.2** | DPPB | 50 | 7 | < 5 |
| 3 | **1.2** | DPPPe | < 5 | 50 | 5 |
| 4 | **1.4** | DPEphos | < 5 | 68 | 22 |
| 5 | **1.4** | DPPB | 48 | 10 | 4 |
| 6 | **1.4** | DPPPe | < 5 | 72 | 11 |

$^a$Yield determined by $^1$H NMR spectroscopy using PhSiMe$_3$ as internal standard.

Nickel-catalyzed cross-coupling reactions were run with enantioenriched substrates (*S*)-**1.2** and (*S*)-**1.4**, and triarylmethane (*S*)-**1.6** was analyzed by supercritical fluid chromatography to determine the enantiospecificity of the reaction. Benzylic ether (*S*)-**1.2** was converted to its corresponding triarylmethane (*S*)-**1.6** in high enantiospecificity (Scheme 1.5). However, employing amine (*S*)-**1.4** resulted in only 31% es over two steps. This erosion in enantiomeric excess may have occurred during the alkylation of the alcohol (*S*)-**1.5** or during the cross-coupling reaction. In light of the promising performance of methoxyethyl ether (*S*)-**1.2**, we opted to use dimethylamine (*S*)-**1.4** in further experiments.

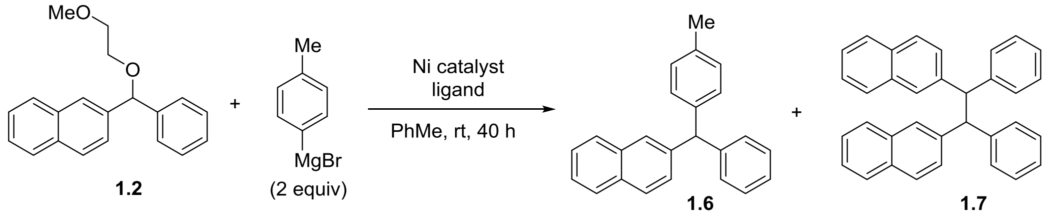
***Scheme 1.5.*** Determination of enantiospecificity of the cross-coupling reaction



|  | **(*S*)-1.6** | **1.7** |
|---|---|---|
| **(*S*)-1.2**: R = (CH$_2$)$_2$OMe | 60%<br>91% ee, 97% es | 6% |
| **(*S*)-1.4**: R = (CH$_2$)$_2$NMe$_2$ | 43%<br>29% ee, 31% es | 8% |

Our cross-coupling methodology was further improved by three important changes to the reaction conditions. First, we discovered that by doubling the ligand and catalyst loading, we could increase the yield of the reaction (Table 1.2, entry 2). Second, we found that we could replace Ni(cod)$_2$ with the less expensive, bench stable Ni(acac)$_2$ without affecting the reaction efficiency (Table 1.2, entry 4). Finally, we observed that the ligands 1,6-bis(diphenylphosphino)hexane (DPPH) and 1,8-bis(diphenylphosphino)octane (DPPO) offered enhanced selectivity for triarylmethane **1.6** over dimer **1.7** (Table 1.2, entries 5–6).

***Table 1.2.*** Optimization of reaction conditions

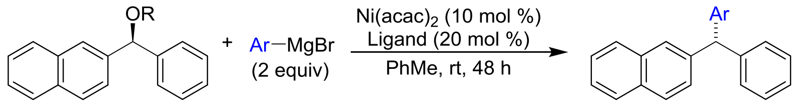


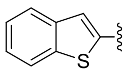
| Entry | Ni catalyst (mol %) | Ligand (mol %) | **2 (%)**$^a$ | **6 (%)**$^a$ | **7 (%)**$^a$ |
|---|---|---|---|---|---|
| 1 | Ni(cod)$_2$ (5) | DPPPe (10) | < 5 | 60 | 6 |
| 2 | Ni(cod)$_2$ (10) | DPPPe (20) | < 5 | 84 | 8 |
| 3 | Ni(cod)$_2$ (10) | DPPPe (20) | < 5 | 84 | 7 |
| 4 | Ni(acac)$_2$ (10) | DPPPe (20) | < 5 | 87 | 9 |
| 5 | Ni(acac)$_2$ (10) | DPPPe (20) | < 5 | 84 | 8 |
| 6 | Ni(acac)$_2$ (10) | DPPO (20) | < 5 | > 95 | < 5 |

$^a$Yield determined by $^1$H NMR spectroscopy using PhSiMe$_3$ as internal standard.

Having established optimal reaction conditions with previously unexplored ligands, we decided to re-examine the performance of the methyl ether leaving group in the reaction. In a direct comparison of the reactivity of the two substrates, (*S*)-**1.2**, containing the methoxyethyl ether leaving group, performed better than the methyl ether substrate (*S*)-**1.1** (Table 1.3). For certain Grignard reagents, use of methyl ether (*S*)-**1.1** resulted in only a small decrease in yield, and enantiospecificity was unaffected. However, for other Grignard reagents such as 2-benzothienylmagnesium bromide, yields decreased significantly when methyl ether (*S*)-**1.1** was employed (Table 1.3, entries 7–9). Additionally, we observed that monodentate triphenylphosphine could be used when the cross-coupling reaction was performed with *p*-methoxyphenylmagnesium bromide, without loss of yield and only a small loss of enantiospecificity. However, this ligand did not perform well in cross-coupling reactions of other Grignard reagents (Table 1.3, entries 6 and 9). The data presented in Table 1.3 suggest that the identity of the ligand has more influence over the outcome of the cross-coupling reaction than the choice of leaving group. Regardless, the methoxyethyl ether leaving group proved to be generally more reactive, and (*S*)-**1.2** was consequently used in examining the scope of the reaction with respect to the Grignard reagent.

***Table 1.3.*** Comparison of methyl ether (*S*)-**1.1** with methoxyethyl ether (*S*)-**1.2**



| entry | R | Ligand | Ar | yield (%) | ee (%)$^a$ | es (%)$^b$ |
|---|---|---|---|---|---|---|
| 1$^{c,d}$ | $CH_2CH_2OMe$ | DPPH | *p*-$MeOC_6H_4$ | 88 | 92 | 99 |
| 2$^e$ | Me | DPPO | | 76 | 99 | 99 |
| 3$^e$ | Me | $PPh_3$ | | 83 | 95 | 95 |
| 4$^{c,d}$ | $CH_2CH_2OMe$ | DPPO | *m*-$MeOC_6H_4$ | 77 | 90 | 97 |
| 5$^e$ | Me | DPPO | | 63 | 99 | 99 |
| 6$^e$ | Me | $PPh_3$ | | 60 | 66 | 67 |
| 7$^{c,d,f,g}$ | $CH_2CH_2OMe$ | DPPO |  | 83 | 87 | 94 |
| 8$^e$ | Me | DPPO | | 37 | 96 | 97 |
| 9$^e$ | Me | $PPh_3$ | | 8 | n.d. | n.d. |

[a] Determined by chiral SFC chromatography. [b] Enantiospecificity (es) = ($ee_{product}/ee_{starting\ material}$) x 100%. [c] Data is the average of two experiments. [d] Isolated yield after chromatography. [e] Isolated as a mixture of desired product and starting methyl ether **1a**. [f] $Ni(cod)_2$ was used in place of $Ni(acac)_2$. [g] Reaction run for 72 h.

## 1.3 Aryl Grignard Reagent Scope

After optimizing the reaction conditions for a variety of aryl Grignard reagents, we examined the enantiospecificity of the cross-coupling reaction with each Grignard reagent. A range of *para*-substituted electron-rich and electron-poor Grignard reagents are well tolerated in the reaction, furnishing triarylmethanes in greater than 98% enantiospecificity (Table 1.4, entries 2–5). Importantly, *m*-methoxyphenylmagnesium bromide provides a high yield of the corresponding triarylmethane, providing access to a substitution pattern that is difficult to achieve using Friedel–Crafts-based methodologies (entry 6).[14] Heterocyclic thiophene and benzothiophene derived Grignard reagents are also tolerated, providing triarylmethanes in greater than 98% enantiospecificity (entries 7 and 8). X-ray crystallography of the thiophene–containing triarylmethane (*R*)-**1.8** (entry 8) indicated that the reaction proceeds with inversion of stereochemistry (Scheme 1.6).[24]

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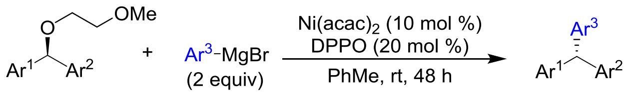
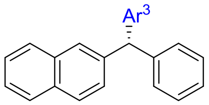
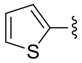
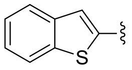
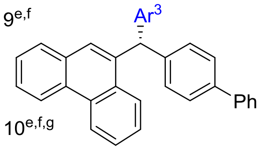
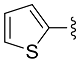
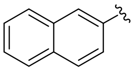
[24] See experimental section for more details.

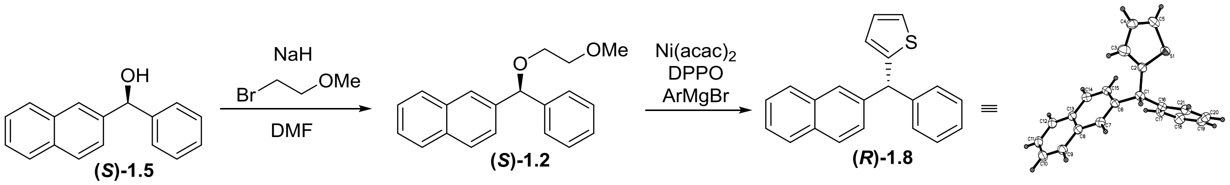
***Table 1.4.*** Investigation of the scope of aryl Grignard reagents and substrates



| **Entry** | **Product** | **Ar$^3$** | **Yield (%)$^a$** | **SM ee (%)$^b$** | **Product ee (%)$^b$** | **es (%)$^c$** |
|---|---|---|---|---|---|---|
| 1 |  | Ph | 82 | n.a. | n.a. | n.a. |
| 2 | | *p*-MeC$_6$H$_4$ | 86 | 93 | 91 | 98 |
| 3$^d$ | | *p*-MeOC$_6$H$_4$ | 88 | 93 | 92 | 99 |
| 4 | | *p*-(Me$_2$N)C$_6$H$_4$ | 68 | 93 | 91 | 98 |
| 5$^{e,f}$ | | *p*-FC$_6$H$_4$ | 92 | 93 | 91 | 98 |
| 6$^{[e]}$ | | *m*-MeOC$_6$H$_4$ | 77 | 93 | 90 | 97 |
| 7 | |  | 97 | 93 | 92 | 99 |
| 8$^{e,g}$ | |  | 83 | 93 | 87 | 94 |
| 9$^{e,f}$ |  |  | 85 | 81 | 74 | 92 |
| 10$^{e,f,g}$ | |  | 56 | 81 | 69 | 85 |

All data are averages of two experiments. $^a$Isolated yield after chromatography. $^b$Determined by chiral SFC chromatography. $^c$Enantiospecificity (es) = ee$_{product}$/ee$_{starting\ material}$ x 100%. $^d$DPPH was used in place of DPPO. $^e$Ni(cod)$_2$ was used in place of Ni(acac)$_2$. $^f$Reaction run for 72 h. $^g$Reaction run at 40 °C.

***Scheme 1.6.*** Stereochemical proof



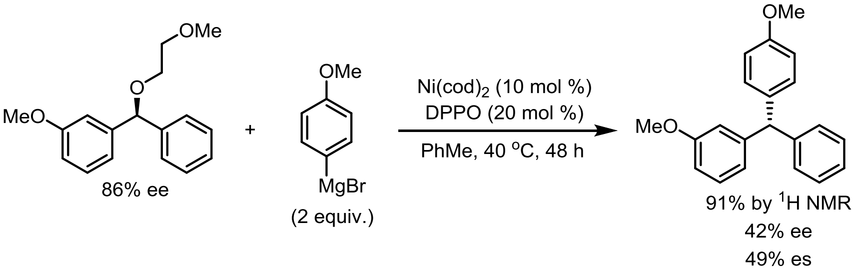
**(*S*)-1.5**
$[\alpha]^{23}_D$ = +11.1
lit$[\alpha]^{20}_D$ = +11.2 (Ref. [26])

**(*S*)-1.2**

**(*R*)-1.8**

Further exploration of the substrate scope of the cross-coupling reaction revealed that phenanthrene-based substrates are effective electrophiles in the cross-coupling reaction (Table 1.4, entries 9–10). Entry 10 exists as a mixture of rotamers following the cross-coupling reaction. Coalescence of diagnostic resonances in the $^1$H NMR spectrum of Entry 10 was observed when compound is heated to temperatures in excess of 250 °C.

***Scheme 1.7.*** Performance of substrates lacking a fused aromatic ring

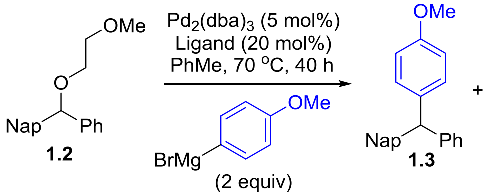


Substrates lacking a fused aromatic ring were also examined in the cross-coupling reaction. Although non-π-extended aromatic electrophiles can be used in the reaction to afford high yields of the corresponding triarylmethane, the enantiospecificity of the reaction suffers markedly (Scheme 1.7).

## 1.4 Investigation of Palladium and Copper Reagents

We were interested in contrasting reactivity of benzylic ether **1.2** and our nickel catalyst with the reactivity of **1.2** with palladium and copper reagents. After investigating the reactivity of a variety of palladium(0) catalysts, we found that at elevated temperatures Pd(DPPE) furnished **1.3** in modest yield but with low levels of stereospecificity (Table 1.5, entry 1). Subjection of **1.2** at 70 °C to Grignard reagent without addition of a catalyst resulted in almost identical yield of **1.3** when compared to the catalyzed reaction, indicating that a significant background reaction occurs at higher temperature (entry 2). The poor performance of other palladium catalysts in the cross-coupling reaction is disclosed in Table 1.5 (entries 3–5). We were also interested in determining whether or not benzylic ethers could undergo nucleophilic substitution with cuprates to form enantioenriched triarylmethanes. Reaction of **1.2** with cuprates resulted in quantitative recovery of starting material (Scheme 1.8), highlighting the importance of our nickel-catalyzed Kumada cross-coupling reaction for the preparation of enantioenriched triarylmethanes.

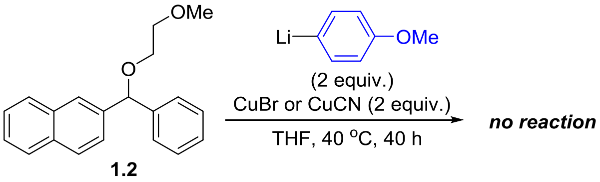
***Table 1.5.*** Performance of palladium catalysts in the cross-coupling reaction



| **Entry** | **Ether** | **Ligand** | **Yield 1.3 (%)**[a] | **Yield 1.7 (%)**[a] | **ee (%)**[b] | **es (%)**[c] |
|---|---|---|---|---|---|---|
| 1 | (*S*)-**1.2** | DPPE | 52 | 8 | 7 | 8 |
| 2[d] | (*S*)-**1.2** | none | 58 | < 5 | n.d. | n.d. |
| 3 | (±)-**1.2** | $PPh_3$ | 34 | 44 | n.a. | n.a. |
| 4 | (±)-**1.2** | DPPH | 15 | 53 | n.a. | n.a. |
| 5 | (±)-**1.2** | DPPO | 16 | 45 | n.a. | n.a. |

[a] Determined by $^1$H NMR using an internal standard ($PhSiMe_3$). [b] Determined by chiral SFC chromatography. [c] Enantiospecificity (es) = ($ee_{product}/ee_{starting\ material}$) x 100%. [d] Reaction run without $Pd_2(dba)_3$.

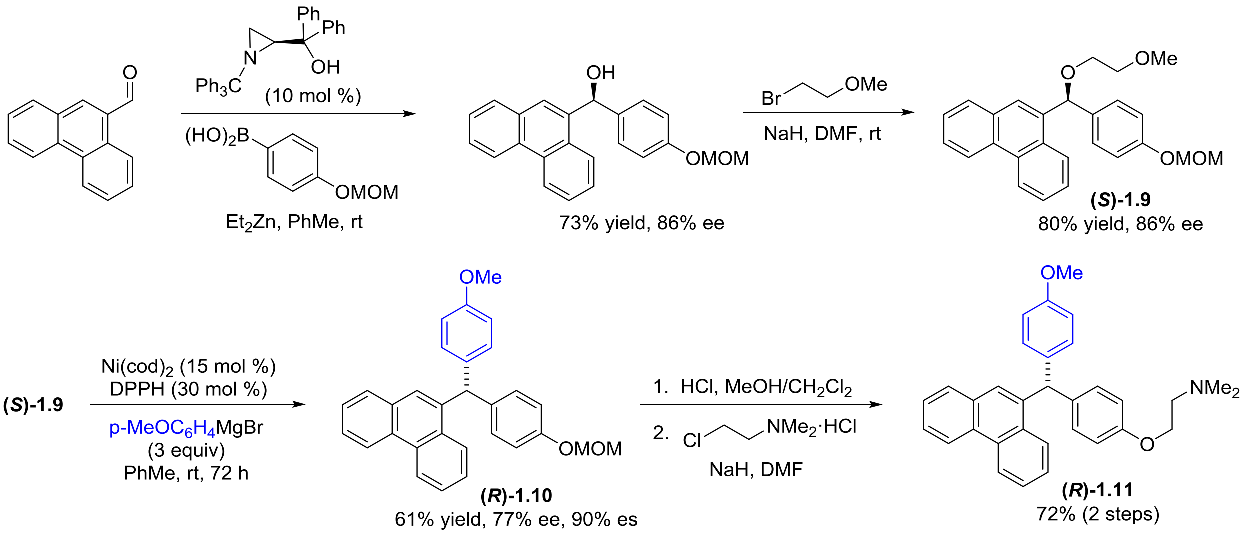
***Scheme 1.8.*** Reaction of benzylic ether **1.2** with a cuprate



## 1.5 Application to the Synthesis of a Biologically Active Triarylmethane

To demonstrate the utility of this methodology, we synthesized a single enantiomer of the anti-breast-cancer agent (*R*)-**1.11** (Scheme 1.9). The enantioenriched benzylic ether (*S*)-**1.9** was prepared by asymmetric arylation of 9-phenanthrenecarboxaldehyde followed by alkylation to install our chelating leaving group. Cross-coupling of (*S*)-**1.9** provided triarylmethane (*R*)-**1.10** in good yield and enantiospecificity. Deprotection of (*R*)-**1.10** followed by alkylation of the resulting phenol afforded the bioactive triarylmethane (*R*)-**1.11**.

***Scheme 1.9.*** Synthesis of an anti-breast-cancer agent



## 1.6 Conclusions

A stereospecific nickel-catalyzed cross-coupling reaction for the synthesis of triarylmethanes has been developed. A range of aryl Grignard reagents has been shown to undergo cross-coupling reactions with benzylic ethers in 56–95% yield and 85–99% enantiospecificity. The synthetic utility of our methodology was demonstrated in the synthesis of a single enantiomer of an anti-breast-cancer agent. Studies to further improve the scope of the reaction are underway.

## 1.7 Experimental Details

*General Procedures*

All reactions were carried out under an atmosphere of $N_2$, unless otherwise noted. All glassware was oven- or flame-dried prior to use. Tetrahydrofuran (THF), diethyl ether ($Et_2O$), dichloromethane ($CH_2Cl_2$), and toluene (PhMe) were degassed with Ar and then passed through two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; LaRoche Chemicals; activated under a flow of argon at 350 ºC for 12 h) to remove $H_2O$. All other solvents utilized were purchased "anhydrous" commercially, or purified as described. Molarities of organolithium reagents were determined by titration with menthol/bipyridine.[25] Molarities of Grignard reagents were determined by titration with iodine.[26] $^1H$ NMR spectra were recorded on Bruker DRX-400 (400 MHz $^1H$, 100 MHz $^{13}C$, 376.5 MHz $^{19}F$), GN-500 (500 MHz $^1H$, 125.7 MHz $^{13}C$), or CRYO-500 (500 MHz $^1H$, 125.7 MHz $^{13}C$) spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.00). Data are reported as follows: chemical shift (multiplicity [singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), doublet of triplets (dt), quartet (q), multiplet (m), apparent triplet (at)], coupling constants [Hz], integration). Carbon chemical shifts are reported in ppm (δ) with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.16 ppm). Unless otherwise indicated, NMR data were collected at 25 ºC. Infrared spectra were obtained on a Mattson Instruments *Galaxy 5000* spectrometer. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 F254 precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$. Flash chromatography was performed using Silica Gel 60Å (170-400 mesh) from Fisher Scientific. Melting points (m.p.) were obtained

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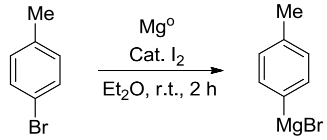
[25] Black, H.T. Titrating Alkyllithium Reagents. http://www.ux1.eiu.edu/~cfthb/research/handbook/titrating.htm (accessed August 2011).

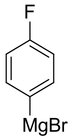
[26] Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890–891.

using a Mel-Temp melting point apparatus and are uncorrected. Optical rotations were measured with a Jasco P-1010 digital polarimeter. SFC determinations of enantiopurity were performed on a Berger Analytical instrument using a Daicel™ Chiralpak® column (OD-H, OJ-H, or AD-H; 100 bar, 50 °C). High resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center. Grignard reagents were freshly prepared from the respective halide precursors. Bis(1,5-cyclooctadiene)nickel was purchased from Strem, stored in a glovebox freezer (–20 °C) under an atmosphere of $N_2$, and used as received. Nickel(II) acetylacetonate and 1,8-bis(diphenylphosphino)octane were purchased from Strem and used as received. 1,6-bis(diphenylphosphino)hexane was purchased from TCI and used as received. 1,5-bis(diphenylphosphino)pentane was purchased from Aldrich and used as received. Magnesium turnings (puratronic grade) were purchased from Alfa Aesar, stored in a glovebox, and used as received. Magnesium bromide diethyl etherate was purchased from Aldrich, stored in a glovebox, and used as received.

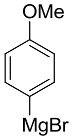
### *A. Representative procedure for preparation of Grignard reagents.*



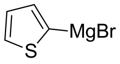
**4-Methylphenylmagnesium bromide.** Dry $Et_2O$ (2.0 mL) was added to magnesium turnings (0.18 g, 7.5 mmol, 1.5 equiv) and catalytic $I_2$ in a Schlenk flask. A solution of 4-bromotoluene (0.85 g, 5.0 mmol, 1.0 equiv) in $Et_2O$ (0.5 mL) was then added slowly over 30 min, so as to maintain a gentle reflux. The mixture was stirred for 1.5 hours at room temperature. The resulting Grignard reagent was then titrated (typically between 1.6 M and 2.1 M) and used within 6 hours.



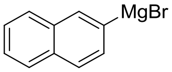
**4-Fluorophenylmagnesium bromide.** Using the representative procedure A outlined above, the following amounts of reagents were used: 1-bromo-4-fluorobenzene (0.55 mL, 5.0 mmol, 1.0 equiv), magnesium turnings (0.18 g, 7.5 mmol, 1.5 equiv), and $Et_2O$ (2.5 mL). The resulting Grignard reagent was typically between 1.5 M and 1.7 M.



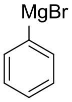
**4-Methoxyphenylmagnesium bromide.** Using the representative procedure A outlined above, the following amounts of reagents were used: 4-bromoanisole (0.63 mL, 5.0 mmol, 1.0 equiv), magnesium turnings (0.18 g, 7.5 mmol, 1.5 equiv), and $Et_2O$ (2.5 mL). The resulting Grignard reagent was typically between 1.6 M and 2.0 M.



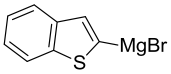
**2-Thienylmagnesium bromide.** Using the representative procedure A outlined above, the following amounts of reagents were used: 2-bromothiophene (0.48 mL, 5.0 mmol, 1.0 equiv), magnesium turnings (0.18 g, 7.5 mmol, 1.5 equiv), and $Et_2O$ (2.5 mL). The resulting Grignard reagent was typically between 1.9 M and 2.1 M.



**2-Naphthylmagnesium bromide.** Using the representative procedure A outlined above, the following amounts of reagents were used: 2-bromonaphthalene (1.04 g, 5.00 mmol, 1.00 equiv), magnesium turnings (0.18 g, 7.5 mmol, 1.5 equiv), and $Et_2O$ (2.5 mL). The resulting Grignard reagent was typically between 1.1 M and 1.4 M.



**Phenylmagnesium bromide.** Using the representative procedure A outlined above, the following amounts of reagents were used: bromobenzene (0.53 mL, 5.0 mmol, 1.0 equiv), magnesium turnings (0.18 g, 7.5 mmol, 1.5 equiv), and $Et_2O$ (2.5 mL). The resulting Grignard reagent was typically between 1.8 M and 2.0 M.



**2-Benzothienylmagnesium bromide.** The Grignard reagent was prepared according to a modified procedure by Guinchard.[27] A solution of benzothiophene (0.61 g, 5.0 mmol, 1.0 equiv) in $Et_2O$ (2.5 mL) was prepared in a 25 mL round bottom flask. A solution of *n*-butyllithium (2.4 mL, 5.3 mmol, 2.4 M in hexanes, 1.1 equiv) was added to the mixture, resulting in a clear, red solution. After stirring for 1 hour at room temperature, a solution of magnesium bromide diethyl etherate in diethyl ether (1.9 mL, 7.5 mmol, 4.0 M in $Et_2O$, 1.5 equiv) was added to afford a suspension of 2-benzothienylmagnesium bromide. The suspension was stirred at room temperature for an additional hour, and $Et_2O$ was added as needed to afford a homogeneous, clear solution. The Grignard reagent was typically between 0.8 M and 1.1 M.

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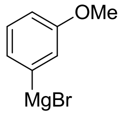
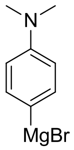
[27] Denis, J.; Guinchard, X. *J. Org. Chem.* **2008**, *73*, 2028–2031.



***m*-Methoxyphenylmagnesium bromide.** Dry $Et_2O$ (1.8 mL) was added to magnesium turnings (0.18 g, 7.5 mmol, 1.5 equiv) in a Schlenk flask. A solution of magnesium bromide diethyl etherate (5 mL, 7.5 mmol, 1.5 M, 1.5 equiv) and catalytic iodine were added to the reaction flask and allowed to stir for 10 min. Neat *m*-bromoanisole (0.63 mL, 5.0 mmol, 1.0 equiv) was then added over 30 min. The mixture was stirred for 1 hour at room temperature. The resulting Grignard reagent formed two layers, and the bottom layer was typically between 1.0 M and 1.2 M. *To maintain solubility of the Grignard reagent for satisfactory yields in the cross-coupling reaction, the Grignard reagent must be prepared with magnesium bromide diethyl etherate as described.*



***p*-(*N,N*-Dimethylamino)phenylmagnesium bromide.** The Grignard reagent was prepared according to a modified procedure by Katritzky.[28] Magnesium turnings (0.18 g, 7.5 mmol, 1.5 equiv) were finely ground with a mortar and pestle and added to a 25-mL round bottom flask fitted with a reflux condenser. THF (2.0 mL), catalytic iodine, and a solution of 4-bromo-*N*,*N*-dimethylaniline (1.0 g, 5.0 mmol, 1.0 equiv) in THF (0.5 mL) were added to the reaction flask. The mixture was heated to reflux and allowed to stir for 1 hour. The resultant brown solution was cooled to room temperature, transferred to a Schlenk flask, and concentrated in vacuo. Excess THF was removed by adding $Et_2O$ (1 mL), then concentrating the suspension in vacuo;

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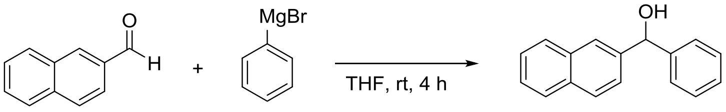
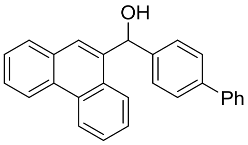
[28] Katritzky, A. R.; Lan, X. *Dyes and Pigments* **1994**, *25*, 303–324.

this procedure was repeated a total of five times. Solid *p*-(*N*,*N*-dimethylamino)-phenylmagnesium bromide was stored in a glovebox.

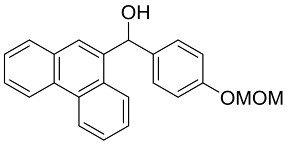
*B. Representative procedure for racemic carbinol synthesis.*



**Naphthalene-6-yl(phenyl)methanol (*rac*-1.5).** To a solution of 2-naphthaldehyde (6.24 g, 40.0 mmol, 1.00 equiv) in THF (25 mL) was added phenylmagnesium bromide (58 mL, 48 mmol, 0.83 M in THF, 1.2 equiv) at 0 °C. The mixture was warmed to room temperature and stirred for 4 hours. Saturated $NH_4Cl$ (25 mL) was added and the mixture was extracted with EtOAc (5 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude reaction mixture was purified by flash choromatography (5–20% EtOAc/hexanes) to afford the title compound as a white solid (6.74 g, 72%). Analytical data is consistent with the values listed below for (*S*)-**1.5**.

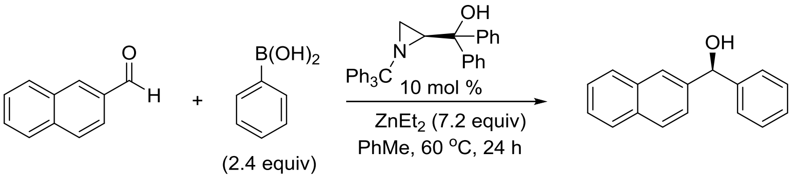


**Phenanthren-9-yl(*p*-biphenyl)methanol (*rac*-1.12).** Using the representative procedure B outlined above, the following amounts of reagents were used: phenanthrene-9-carboxaldehyde (1.24 g, 6.00 mmol, 1.00 equiv), 4-biphenylmagnesium bromide (8.0 mL, 8.0 mmol, 1.0 M in THF, 1.3 equiv), and THF (6 mL). The product was purified by flash column chromatography (dry loaded, 5–50% EtOAc/hexanes) to afford the title compound as a white solid (1.88 g, 87%). Analytical data is consistent with the values listed below for (*S*)-**1.12**.



**(4-(Methoxymethoxy)phenyl)(phenanthren-9-yl)methanol (*rac*-1.13).** Using the representative procedure B outlined above, the following amounts of reagents were used: 4-(methoxymethoxy)benzaldehyde[29] (1.66 g, 10.0 mmol, 1.00 equiv), 9-phenanthrylmagnesium bromide (12 mL, 12 mmol, 1.0 M in THF, 1.2 equiv), and THF (10 mL). The product was purified by flash column chromatography (10–20% EtOAc/hexanes) to afford the title compound as a colorless oil (1.80 g, 52%). Analytical data is consistent with the values listed below for (*S*)-**1.13**.

### *C. Representative procedure for asymmetric carbinol synthesis.*



(*S*)-**Naphthalene-6-yl(phenyl)methanol ((*S*)-1.5).** Enantioenriched alcohols were prepared according to a modified procedure by Braga.[30] A solution of diethyl zinc (18 mL, 18 mmol, 1.0 M in PhMe, 7.2 equiv) was added to a solution of phenylboronic acid (0.732 g, 6.00 mmol, 2.40 equiv) in PhMe (10 mL). The mixture was heated to 60 °C and stirred for 12 hours. Upon cooling to room temperature, a solution of (*S*)-α,α-diphenyl-1-(triphenylmethyl)-2-aziridinemethanol[14] (0.117 g, 0.250 mmol, 0.100 equiv) in PhMe (5 mL) was added to the reaction mixture. After stirring for 15 minutes, a solution of 2-naphthaldehyde (0.390 g, 2.50

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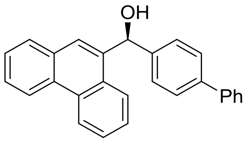
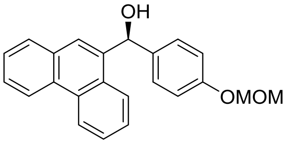
[29] Fruit, C.; Turck, A.; Plé, N.; Mojovic, L.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 9429–9435.
[30] Braga, A. L.; Paixão, M. W.; Westermann, B.; Schneider, P. H.; Wessjohan, L. A. *J. Org. Chem.* **2008**, *73*, 2879–2891.

mmol, 1.00 equiv) in PhMe (5 mL) was added. The reaction mixture was stirred for an additional 12 hours and subsequently quenched with 1 M HCl (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (1% EtOAc/benzene) to afford a white solid, which was recrystallized from hexanes to afford the title compound as a white solid (0.294 g, 50%). Analytical data is consistent with literature values.[3] **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.82 (dt, *J* = 9.2, 2.6 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.49–7.40 (m, 5H), 7.35 (at, *J* = 7.0 Hz, 2H), 7.29 (dt, *J* = 7.4, 1.5 Hz, 1H), 6.02 (d, *J* = 3.5 Hz, 1H), 2.29 (d, *J* = 3.5 Hz, 1H); **$[\alpha]^{23}_D$** +11.1 (*c* 1.25, $CHCl_3$), literature $[\alpha]^{20}_D$ +11.2 (*c* 0.83, $CHCl_3$);[3] **SFC** analysis (OD-H, 20% 2-propanol, 3 mL/min, 256 nm) indicated 94% ee: $t_R$ (major) = 6.3 min, $t_R$ (minor) = 7.3 min.



(*S*)-**Phenanthren-9-yl(*p*-biphenyl)methanol ((*S*)-1.12).** Using the representative procedure C outlined above, the following amounts of reagents were used: phenanthrene-9-carboxaldehyde (0.516 g, 2.50 mmol, 1.00 equiv), biphenyl-4-boronic acid (1.49 g, 7.50 mmol, 3.00 equiv), diethyl zinc (2.3 mL, 23 mmol, 1.0 M in PhMe, 9.2 equiv), (*S*)-α,α-diphenyl-1-(triphenylmethyl)-2-aziridinemethanol (0.117 g, 0.250 mmol, 0.100 equiv), and PhMe (50 mL). The product was purified by flash column chromatography (10–20% EtOAc/hexanes) to afford the title compound as a white foam (0.720 g, 80%). **TLC $R_f$** = 0.2 (9:1 hexanes:EtOAc); **m.p. =** 55–56 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.71 (d, *J* = 8.3 Hz, 1H), 8.66 (d, *J* = 8.3 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 1H), 7.98 (s, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.62–7.56 (m, 2H), 7.56–7.45 (m, 7H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 6.52 (s, 1H), 2.49 (s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 141.9, 140.82, 140.78, 136.8, 131.4, 131.0, 130.4, 129.8, 129.2, 128.9, 127.8, 127.49, 127.46, 127.2, 127.01, 126.96, 126.8, 126.5, 125.6, 125.0, 123.4, 122.6, 74.0; **IR** (thin film) 3330, 3054, 2883, 1600, 1487 $cm^{-1}$; **HRMS** (TOF MS EI+) *m* / *z* calcd for $C_{27}H_{20}O$ $(M)^+$ 360.1514, found 360.1510; **$[\alpha]^{23}_D$** +56.8 (*c* 1.25, $CHCl_3$). The enantiomers could not be separated by analytical SFC.



(*S*)-**(4-(Methoxymethoxy)phenyl)(phenanthren-9-yl)methanol ((***S***)-1.13)**. Using the representative procedure C outlined above, the following amounts of reagents were used: phenanthrene-9-carboxaldehyde (0.518 g, 2.50 mmol, 1.00 equiv), *p*-[(methoxymethyl)oxy]phenylboronic acid[31] (1.37 g, 7.50 mmol, 3.00 equiv), diethyl zinc (2.3 mL, 23 mmol, 1.0 M in PhMe, 9.2 equiv), (*S*)-α,α-diphenyl-1-(triphenylmethyl)-2-aziridinemethanol (0.117 g, 0.250 mmol, 0.100 equiv), and PhMe (50 mL). The product was purified by flash column chromatography (10–30% EtOAc:hexanes) to afford the title compound as a colorless oil (0.630 g, 73%). **TLC $R_f$** = 0.2 (8:2 hexanes:EtOAc); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 8.3 Hz, 1H), 8.67 (d, *J* = 8.2 Hz, 1H), 8.01 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.70–7.58 (m, 3H), 7.51 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.39–7.34 (m, 2H), 7.01–6.97 (m, 2H), 6.51 (d, *J* = 3.8 Hz, 1H), 5.15 (s, 2H), 3.45 (s, 3H), 2.32–2.29 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 157.0, 137.0, 136.4, 131.5, 131.0, 130.4, 129.8, 129.1, 128.8, 126.9 (2C), 126.7, 126.4, 125.3, 125.0, 123.3, 122.6, 116.5, 94.5, 73.7, 56.2; **IR**

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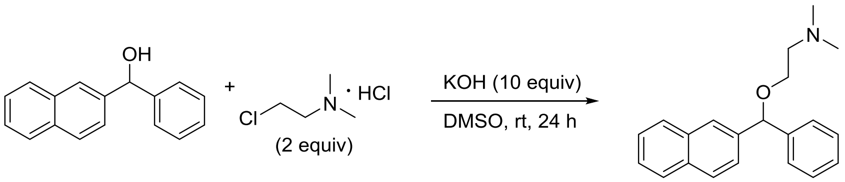
[31] Choshi, T.; Yamada, S.; Sugino, E.; Kuwada, T.; Hibino, S. *J. Org. Chem.* **1995**, *60*, 5899–5904.

(thin film) 3406, 3055, 2956, 1608, 1508, 1234 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{23}H_{20}O_3$ (M + Na)$^+$ 367.1310, found 367.1318; **[α]$^{23}$$_D$** +79.1 (*c* 1.35, $CHCl_3$); **SFC** analysis (AD-H, 35% MeOH, 3.5 mL/min, 256 nm) indicated 86% ee: $t_R$ (major) = 5.4 min, $t_R$ (minor) = 7.7 min.

*Preparation of Diaryl Alcohol Derivatives*

**2-((*S*)-Methoxy(phenyl)methyl)naphthalene ((*S*)-1.1)** was prepared according to a previously reported procedure.[32]



**2-(Naphthalene-6-yl)(phenyl)methoxy)-*N*,*N*-dimethylamine (1.4).** Dimethyl amine **1.4** was prepared according to a modified procedure by Brückner.[33] A suspension of alcohol **1.5** (2.34 g, 10.0 mmol), 2-(*N*,*N*-dimethylamino)ethyl chloride hydrochloride (2.88 g, 20.0 mmol, 2.00 equiv) and freshly ground KOH (5.60 g, 100 mmol, 10.0 equiv) were stirred in DMSO (20 mL) at room temperature for 24 hours. Aqueous 1 M NaOH (20 mL) and $Et_2O$ (10 mL) were added, and the layers were separated. The aqueous layer was extracted with $Et_2O$ (3 x 15 mL). The combined organic layers were washed with 1 M NaOH (2 x 10 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (30–70% EtOAc/hexanes) to afford the title product as a pale yellow solid (1.43 g, 47%). **TLC R$_f$** = 0.1 (9:1 hexanes:EtOAc); **m.p. =** 115–118 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.86–7.75 (m, 4H),

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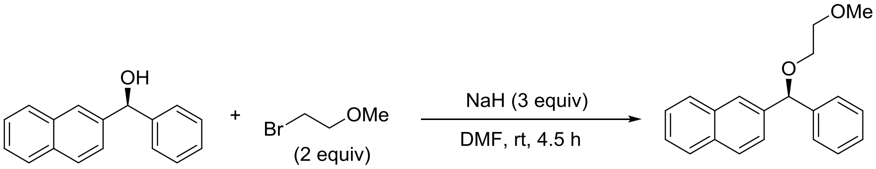
[32] Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389–391.

[33] Brückner, R.; Sälinger, D. *Chem. Eur. J.* **2009**, *15*, 6688–6703.

7.48–7.42 (m, 3H), 7.40 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 1H), 5.53 (s, 1H), 3.62 (t, *J* = 5.9 Hz, 2H), 2.63 (t, *J* = 5.9 Hz, 2H), 2.27 (s, 6H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 142.3, 139.8, 133.3, 133.0, 128.5, 128.4, 128.2, 127.8, 127.6, 127.2, 126.2, 125.98, 125.96, 125.3, 84.2, 67.8, 59.2, 46.3; **IR** (thin film) 3059, 3028, 2940, 1600, 1452 cm$^{-1}$; **HRMS** (TOF MS EI+) *m* / *z* calcd for $C_{21}H_{23}NO$ $(M)^+$ 305.1780, found at 305.1787.

*D. Representative procedure for ether synthesis.*



**2-((*S*)-(2-Methoxyethoxy)(phenyl)methyl)naphthalene (1d).** Alkylation of alcohols was performed according to a modified procedure by Lin.[34] Alcohol (*S*)-**4** (0.851 g, 3.64 mmol, 1.00 equiv) was dissolved in DMF (5.5 mL) and added to a slurry of NaH (0.271 g, 11.3 mmol, 3.10 equiv) in DMF (1.3 mL). The reaction mixture was stirred for 30 min, and a solution of bromoethyl methyl ether (0.38 mL, 4.0 mmol, 1.1 equiv) in DMF (4.2 mL) was slowly added over 30 min. The reaction was stirred for an additional hour, after which a second portion of bromoethyl methyl ether (0.38 mL, 4.0 mmol, 1.1 equiv) in DMF (4.2 mL) was slowly added over 30 min. After stirring for two hours, saturated aqueous $NH_4Cl$ (15 mL) and EtOAc (20 mL) were added. The layers were separated and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (5–10% EtOAc/hexanes) to afford the title compound as a white solid (0.989 g, 93%). **TLC $R_f$** = 0.4 (9:1 hexanes:EtOAc); **m.p.** = 47 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.86–7.75 (m, 4H),

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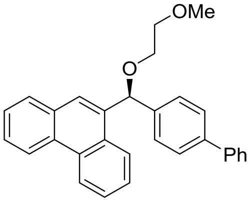
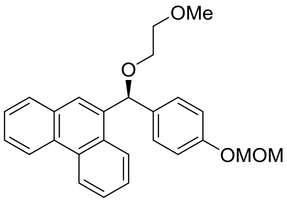
[34] Lin, Q. H.; Ball, G. E.; Bishop, R. *Tetrahedron* **1997**, *53*, 10899–10910.

7.48–7.43 (m, 3H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 5.57 (s, 1H), 3.65 (m, 4H), 3.40 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 142.2, 139.7, 133.4, 133.1, 128.6, 128.4, 128.2, 127.8, 127.6, 127.2, 126.1, 126.0 (2C), 125.2, 84.2, 72.2, 68.6, 59.2; **IR** (thin film) 3054, 2883, 1600, 1487 cm$^{-1}$; **HRMS** (TOF MS EI+) *m* / *z* calcd for $C_{20}H_{20}O_2$ $(M)^+$ 315.1361, found 315.1361; **$[\alpha]^{23}_D$** –22.9 (*c* 0.99, $CHCl_3$); **SFC** analysis (OD-H, 10% 2-propanol, 2.5 mL/min, 256 nm) indicated 93% ee: $t_R$ (major) = 8.2 min, $t_R$ (minor) = 6.5 min.



**9-((*S*)-(2-Methoxyethoxy)(*p*-biphenyl)methyl)phenanthrene ((*S*)-1.14).** Using the representative procedure D outlined above, the following amounts of reagents were used: Alcohol (*S*)-**1.12** (1.41 g, 3.90 mmol, 1.00 equiv), NaH (0.281 g, 11.7 mmol, 3.00 equiv), bromoethylmethyl ether (0.80 mL, 8.6 mmol, 2.2 equiv), and DMF (25 mL). The product was purified by flash column chromatography (10–20% EtOAc/hexanes) to afford the title compound as a white foam (0.720 g, 80%) **TLC $R_f$** = 0.2 (9:1 hexanes:EtOAc); **m.p. =** 55–56 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 8.4 Hz, 1H), 8.63 (d, *J* = 8.3 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.92 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.56 (t, *J* = 7.3 Hz, 2H), 7.54–7.46 (m, 7H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.11 (s, 1H), 3.75 (t, *J* = 4.8 Hz, 2H), 3.63 (t, *J* = 4.8 Hz, 2H), 3.37 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 140.9, 140.5, 140.3, 134.9, 131.4, 131.1, 130.5, 130.2, 129.1, 128.8 (2C), 128.1, 127.3, 127.2, 127.1, 126.9, 126.8, 126.6, 126.4, 125.4, 123.2, 122.6, 82.4, 72.2, 68.9, 59.1; **IR** (thin film) 3055, 2987, 1600, 1421 cm$^{-1}$; **HRMS** (TOF MS EI+) *m* / *z* calcd for $C_{30}H_{26}O_2$ $(M)^+$ 418.1933, found 418.1916; **$[\alpha]^{23}_D$**

+15.7 (*c* 0.96, $CHCl_3$); **SFC** analysis (AD-H, 30% MeOH, 3.5 mL/min, 256 nm) indicated 81% ee: $t_R$ (major) = 12.5 min, $t_R$ (minor) = 21.8 min.



**9-((*S*)-(2-Methoxyethoxy)(4-(methoxymethoxy)phenyl)methyl)phenanthrene ((*S*)-1.15).** Using the representative procedure D outlined above, the following amounts of reagents were used: Alcohol (*S*)-**1.13** (0.600 g, 1.74 mmol, 1.00 equiv), NaH (0.129 g, 5.39 mmol, 3.10 equiv), bromoethylmethyl ether (0.36 mL, 3.8 mmol, 2.2 equiv), and DMF (20 mL). The product was purified by flash column chromatography (20–30% $Et_2O$:hexanes) to afford the title compound as a white foam (0.557 g, 80%) **TLC** $\mathbf{R_f}$ = 0.2 (7:3 hexanes:$Et_2O$); $^{1}$**H NMR** (500 MHz, $CDCl_3$) δ 8.72 (d, *J* = 8.2 Hz, 1H), 8.67 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1 H), 7.93–7.89 (m, 2H), 7.68–7.57 (m, 3H), 7.54–7.48 (m, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.06 (s, 1H), 5.13 (s, 2H), 3.78–3.74 (m, 2H), 3.65 (t, *J* = 4.8 Hz, 2H), 3.45 (s, 3H), 3.40 (s, 3H); $^{13}$**C NMR** (125 MHz, $CDCl_3$) δ 156.8, 135.1, 134.6, 131.5, 131.1, 130.5, 130.3, 129.1 (2C), 126.9, 126.8, 126.59, 126.55, 126.3, 125.3, 123.2, 122.6, 116.2, 94.5, 82.1, 72.3, 68.8, 59.2, 56.1; **IR** (thin film) 3061, 2895, 1608, 1508, 1084 $cm^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{26}H_{26}O_4$ $(M + Na)^+$ 425.1729, found 425.1711; $[\boldsymbol{\alpha}]^{23}_{\mathbf{D}}$ +18.6 (*c* 2.63, $CHCl_3$); **SFC** analysis (AD-H, 10% MeOH, 3.5 mL/min, 256 nm) indicated 86% ee: $t_R$ (major) = 6.4 min, $t_R$ (minor) = 8.1 min.

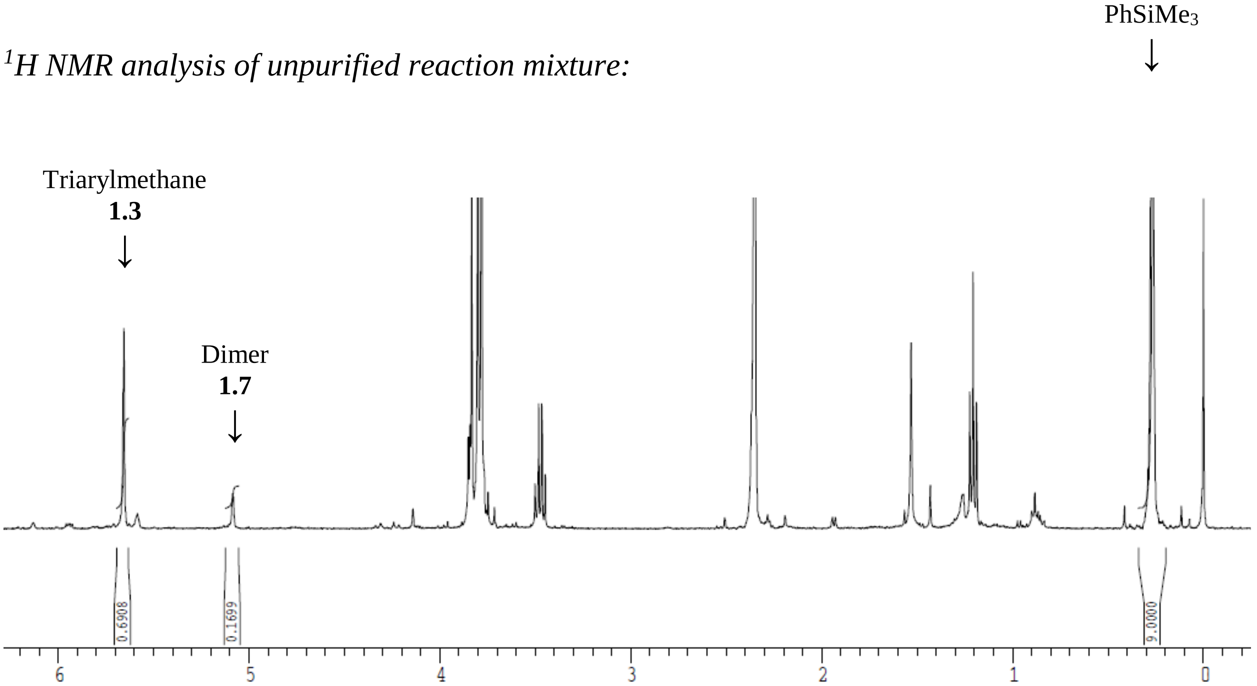
### *Cross-Coupling Reactions*

*Representative procedure for cross-coupling reaction optimization.*

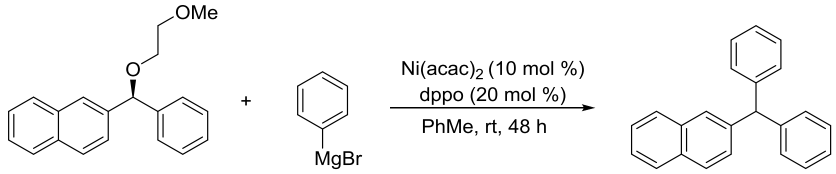
To a 7 mL vial in a glovebox was added bis(1,5-cyclooctadiene)nickel (2.8 mg, 0.010 mmol, 0.10 equiv), DPEphos (11 mg, 0.020 mmol, 0.20 equiv), and PhMe (1.6 mL). The mixture was stirred for 10 min and enantioenriched ether (*S*)-**1.2** (29.2 mg, 0.100 mmol, 1.00 equiv) was added. The vial was removed from the glovebox and *p*-methoxyphenylmagnesium bromide (0.10 mL, 0.20 mmol, 2.0 M in $Et_2O$, 2.0 equiv) was added dropwise. The reaction was stirred for 48 hours before quenching with 2-propanol (1.5 mL). The solution was eluted through a plug of silica and concentrated in vacuo. Phenyltrimethylsilane (0.017 mL, 0.10 mmol, 1.0 equiv) was added as an internal standard, and the mixture was dissolved in $CDCl_3$ for $^1H$ NMR analysis.

The phenyltrimethylsilane signal at 0.26 ppm was used to calibrate the integration (9H). NMR yields were determined based on the methine signals for triarylmethane **1.3** (5.65 ppm, 1H) and dimer **1.7** (5.08 ppm, 2H). Note that the yield of dimer **1.7** is based on a theoretical yield of 0.050 mmol (0.50 equiv). Therefore, the integral of the signal at 5.08 ppm would be a maximum of 1.0 (0.50 equiv x 2H) if a reaction were to give complete conversion to dimer **1.7**. The diastereomers of dimer **1.7** are indistinguishable by $^1H$ NMR.

*$^1$H NMR analysis of unpurified reaction mixture:*

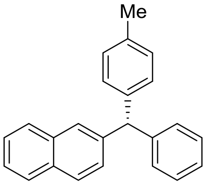


*E. Representative procedure for cross-coupling reactions (Table 2)*



**2-Benzhydrylnaphthalene (1.17).** To a 7 mL vial in a glovebox was added nickel(II) acetylacetonate (5.1 mg, 0.020 mmol, 0.10 equiv), 1,8-bis(diphenylphosphino)octane (19 mg, 0.040 mmol, 0.20 equiv), and PhMe (1.6 mL). The mixture was stirred for 10 min and enantioenriched ether (*S*)-**1.2** (58.4 mg, 0.200 mmol, 1.00 equiv) was added. The vial was removed from the glovebox and phenylmagnesium bromide (0.20 mL, 0.40 mmol, 2.0 M in $Et_2O$, 2.0 equiv) was added dropwise. The reaction was stirred for 48 hours before quenching with 2-propanol (1.5 mL). The solution was eluted through a plug of silica and concentrated in vacuo. The residue was purified by flash column chromatography (0–3% $Et_2O$/pentane) to afford the title compound as a white solid. First run: 50.3 mg (86%). Second run: 46.1 mg

(79%). **TLC R$_f$** = 0.2 (97:3 pentane:Et$_2$O); **m.p. =** 75–77 °C, literature m.p. = 77–78 °C;[35] **$^1$H NMR** (400 MHz, CDCl$_3$) δ 7.81–7.76 (m, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.71–7.65 (m, 1H), 7.47 (s, 1H), 7.40 (dt, *J* = 9.4, 3.8 Hz, 2H), 7.28 (at, *J* = 7.5 Hz, 5H), 7.24–7.18 (m, 2H), 7.15 (d, *J* = 7.0 Hz, 4H), 5.70 (s, 1H); **$^{13}$C NMR** (100 MHz, CDCl$_3$) δ 143.8, 141.7, 133.5, 132.3, 129.7, 128.5, 128.2, 128.0, 127.9, 127.7, 126.5, 126.1, 125.8, 57.1; **IR** (thin film) 3055, 2987, 1601, 1265 cm$^{-1}$; **HRMS** (TOF MS EI+) *m* / *z* calcd for $C_{23}H_{18}$ (M)$^+$ 294.1408, found at 294.1404.



**2-((*S*)-Phenyl(*p*-tolyl)methyl)naphthalene ((*S*)-1.6).** Using the representative procedure E outlined above, the following amounts of reagents were used: nickel(II) acetylacetonate (5.1 mg, 0.020 mmol, 0.10 equiv), 1,8-bis(diphenylphosphino)octane (19 mg, 0.040 mmol, 0.20 equiv), *p*-methylphenylmagnesium bromide (0.25 mL, 0.40 mmol, 1.6 M in Et$_2$O, 2.0 equiv), ether (*S*)-**1.2** (58.4 mg, 0.200 mmol, 1.00 equiv), and PhMe (1.6 mL). The product was purified by flash column chromatography (100% pentane) to afford the title compound as a colorless oil. First run: 56.0 mg (91%, 91% ee). Second run: 52.3 mg (85%, 91% ee). **TLC R$_f$** = 0.2 (100% pentane); **$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.81–7.65 (m, 3H), 7.47 (s, 1H), 7.41 (dt, *J* = 9.6, 3.3 Hz, 2H), 7.28 (at, *J* = 7.5 Hz, 3H), 7.24–7.20 (m, 1H), 7.15 (d, *J* = 7.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 5.66 (s, 1H), 2.32 (s, 3H); **$^{13}$C NMR** (100 MHz, CDCl$_3$) δ 144.1, 141.9, 140.9, 136.1, 133.6, 132.3, 129.7, 129.6, 129.2, 128.5, 128.3, 128.01, 127.98, 127.9, 127.7, 126.5, 126.1, 125.7, 56.7, 21.2; **IR** (thin film) 3054, 3023, 2921, 2867, 1599, 1510 cm$^{-1}$; **HRMS** (TOF MS EI+) *m* / *z* calcd for $C_{24}H_{20}$ (M)$^+$ 308.1565, found 308.1568; **$[\alpha]^{23}_{D}$** +4.76 (*c* 1.66,

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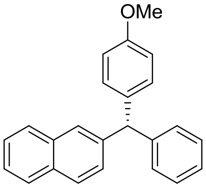
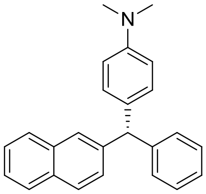
[35] McMullen, T. C. *J. Am. Chem. Soc.* **1922**, *44*, 2055–2060.

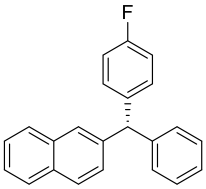
$CHCl_3$); **SFC** analysis (OJ-H, 15% 2-propanol, 2.5 mL/min, 256 nm) indicated 87% ee: $t_R$ (major) = 11.4 min, $t_R$ (minor) = 12.5 min.



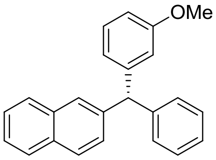
**2-((*S*)-(4-Methoxyphenyl)(phenyl)methyl)naphthalene ((*S*)-1.3).** Using the representative procedure E outlined above, the following amounts of reagents were used: nickel(II) acetylacetonate (5.1 mg, 0.020 mmol, 0.10 equiv), 1,6-bis(diphenylphosphino)hexane (18 mg, 0.040 mmol, 0.20 equiv), *p*-methoxyphenylmagnesium bromide (0.22 mL, 0.40 mmol, 1.8 M in $Et_2O$, 2.0 equiv), ether (*S*)-**1.2** (58.4 mg, 0.200 mmol, 1.00 equiv), and PhMe (1.6 mL). The product was purified by flash column chromatography (0–3% $Et_2O$:pentane) to give the title compound as a yellow oil. First run: 59.4 mg (92%, 91% ee). Second run: 54.5 mg (84%, 92% ee). **TLC $R_f$** = 0.4 (95:5 pentane:$Et_2O$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.81–7.76 (m, 1H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.72–7.67 (m, 1H), 7.46 (s, 1H), 7.42 (dt, *J* = 9.5, 3.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 3H), 7.24–7.19 (m, 1H), 7.15 (d, *J* = 7.2 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 5.65 (s, 1H), 3.78 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 158.2, 144.1, 142.0, 136.0, 133.5, 132.2, 130.6, 129.6, 128.4, 128.2, 128.0, 127.9, 127.8, 127.6, 126.4, 126.1, 125.7, 113.8, 56.2, 55.3; **IR** (thin film) 3057, 3025, 2931, 2835, 1608, 1250 cm$^{-1}$; **HRMS** (TOF MS EI+) *m* / *z* calcd for $C_{24}H_{20}O$ $(M)^+$ 324.1514, found 324.1498; **$[\alpha]^{23}_D$** +1.15 (*c* 1.08, $CHCl_3$); **SFC** analysis (AD-H, 15% 2-propanol, 2.5 mL/min, 256 nm) indicated 87% ee: $t_R$ (major) = 13.9 min, $t_R$ (minor) = 14.9 min.



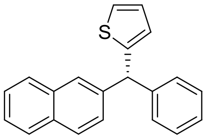
***N,N*-Dimethyl-4-((*S*)-(naphthalene-6-yl)(phenyl)methyl)benzenamine ((*S*)-1.18).** The title compound was prepared according to representative procedure E outlined above, with the following exception: the Grignard reagent was added inside the glovebox after addition of all other reagents. The following amounts of reagents were used: nickel(II) acetylacetonate (5.1 mg, 0.020 mmol, 0.10 equiv), 1,8-bis(diphenylphosphino)octane (19 mg, 0.040 mmol, 0.20 equiv), *p*-(*N*,*N*-dimethylamino)phenylmagnesium bromide (97 mg, 0.40 mmol, 2.0 equiv), ether (*S*)-**1.2** (58.4 mg, 0.200 mmol, 1.00 equiv), and PhMe (1.6 mL). The product was purified by flash column chromatography (0–10% pentane/$Et_2O$) to afford the title compound as a colorless oil. First run: 47.2 mg (71%, 91% ee). Second run: 43.7 mg (65%, 91% ee). **TLC $R_f$** = 0.3 (97:3 pentane:$Et_2O$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.80–7.75 (m, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.71–7.67 (m, 1H), 7.48 (s, 1H), 7.40 (dt, *J* = 9.4, 3.3 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 5.61 (s, 1H), 2.90 (s, 6H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 149.2, 144.6, 142.5, 133.6, 132.2, 131.8, 130.3, 129.6, 128.4, 128.0, 127.8, 127.7, 127.6, 126.3, 126.0, 125.6, 112.6, 56.2, 40.8 (2C); **IR** (thin film) 3054, 3023, 2879, 1612, 1350 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{25}H_{24}N$ (M + H)$^+$ 338.1909, found 338.1907; **[α]$^{23}_{D}$** +9.55 (*c* 1.09, $CHCl_3$); **SFC** analysis (AD-H, 25% MeOH, 3 mL/min, 256 nm) indicated 85% ee: $t_R$ (major) = 4.1 min, $t_R$ (minor) = 4.6 min.



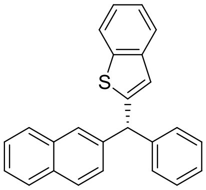
**2-((*S*)-(4-Fluorophenyl)(phenyl)methyl)naphthalene ((*S*)-1.19).** Using the representative procedure E outlined above, with the exception of stirring for 92 hours, the following amounts of reagents were used: bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,8-bis(diphenylphosphino)octane (19 mg, 0.040 mmol, 0.20 equiv), *p*-fluorophenylmagnesium bromide (0.24 mL, 0.40 mmol, 1.7 M in $Et_2O$, 2.0 equiv), ether (*S*)-**1.2** (58.4 mg, 0.200 mmol, 1.00 equiv), and PhMe (1.6 mL). The product was purified by flash column chromatography (100% pentane) to afford the title compound as a colorless oil. First run: 60.8 mg (97%, 91% ee). Second run: 54.5 mg (87%, 91% ee). **TLC $R_f$** = 0.2 (100% pentane); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.81–7.77 (m, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.71–7.67 (m, 1H), 7.45–7.39 (m, 3H), 7.31–7.21 (m, 4H), 7.15–7.07 (m, 4H), 6.97 (t, *J* = 8.8 Hz, 2H), 5.70 (s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 161.6 (d, *J* = 245 Hz), 143.6, 141.4, 139.5 (d, *J* = 3 Hz), 133.5, 132.3, 131.1 (d, *J* = 8 Hz), 129.6, 128.6, 128.1, 128.05, 127.99, 127.8, 127.7, 126.7, 126.2, 125.9, 115.3 (d, *J* = 21 Hz), 56.3; **IR** (thin film) 3055, 2987, 1600, 1454, 1265 $cm^{-1}$; **HRMS** (TOF MS EI+) *m* / *z* calcd for $C_{23}H_{17}F$ $(M)^+$ 312.1314, found 312.1308; **$[\alpha]^{23}_D$** –2.18 (*c* 1.05, $CHCl_3$); **SFC** analysis (OJ-H, 12% 2-propanol, 2.5 mL/min, 256 nm) indicated 87% ee: $t_R$ (major) = 8.9 min, $t_R$ (minor) = 9.8 min.



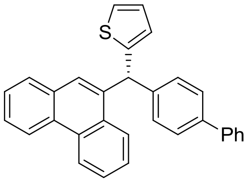
**2-((*R*)-(3-Methoxyphenyl)(phenyl)methyl)naphthalene ((*R*)-1.20).** Using the representative procedure E outlined above, the following amounts of reagents were used: bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,5-bis(diphenylphosphino)pentane (18 mg, 0.040 mmol, 0.20 equiv), *m*-methoxyphenylmagnesium bromide (0.40 mL, 0.40 mmol, 1.0 M in $Et_2O$, 2.0 equiv), ether (*S*)-**1.2** (58.4 mg, 0.200 mmol, 1.00 equiv), and PhMe (1.6 mL). The product was purified by flash column chromatography (4:1 benzene:pentane) to afford the title compound as a colorless oil. First run: 47.6 mg (74%, 92% ee). Second run: 51.7 mg (88%, 88% ee). **TLC $R_f$** = 0.3 (4:1 benzene:pentane); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.82–7.77 (m, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.72–7.66 (m, 1H), 7.48 (s, 1H), 7.41 (dt, *J* = 9.4, 3.1 Hz, 2H), 7.28 (at, *J* = 7.4 Hz, 3H), 7.25–7.13 (m, 4H), 6.76 (at, *J* = 7.4 Hz, 2H), 6.72 (d, *J* = 1.8 Hz, 1H), 5.67 (s, 1H), 3.71 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 159.8, 145.5, 143.7, 141.5, 133.6, 132.3, 129.7, 129.4, 128.5, 128.2, 128.02, 128.01, 127.9, 127.7, 126.6, 126.1, 125.8, 122.3, 115.9, 111.6, 57.1, 55.3; **IR** (thin film) 3055, 2987, 1585, 1421, 1265 $cm^{-1}$; **HRMS** (TOF MS EI+) *m* / *z* calcd for $C_{24}H_{20}O$ $(M)^+$ 324.1514, found 324.1520; $[\alpha]^{23}_D$ +2.52 (*c* 1.19, $CHCl_3$); **SFC** analysis (AD-H, 15% 2-propanol, 2.5 mL/min, 256 nm) indicated 75% ee: $t_R$ (major) = 8.5 min, $t_R$ (minor) = 9.2 min.



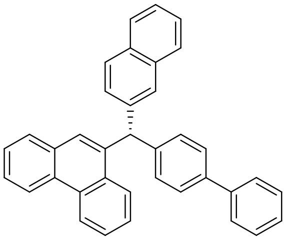
**2-((*R*)-(Naphthalene-6-yl)(phenyl)methyl)thiophene ((*R*)-1.8).** Using the representative procedure E outlined above, the following amounts of reagents were used: nickel(II) acetylacetonate (5.1 mg, 0.020 mmol, 0.10 equiv), 1,8-bis(diphenylphosphino)octane (19 mg, 0.040 mmol, 0.20 equiv), 2-thienylmagnesium bromide (0.20 mL, 0.40 mmol, 2.0 M in $Et_2O$, 2.0 equiv), ether (*S*)-**1.2** (58.4 mg, 0.200 mmol, 1.00 equiv), and PhMe (1.6 mL). The product was purified by flash column chromatography (0–3% $Et_2O$/pentane) to afford the title compound as a yellow solid. First run: 58.0 mg (97%, 92% ee). Second run: 58.2 mg (97%, 91% ee). **TLC $R_f$** = 0.5 (97:3 pentane:$Et_2O$); **m.p. =** 78–79 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.83–7.78 (m, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 7.75–7.71 (m, 1H), 7.60 (s, 1H), 7.44 (dt, *J* = 9.4, 3.2 Hz, 2H), 7.37 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.31 (at, *J* = 7.2 Hz, 2H), 7.28–7.20 (m, 4H), 6.95 (at, *J* = 4.3 Hz, 1H), 6.73 (d, *J* = 3.3 Hz, 1H), 5.84 (s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 147.8, 143.7, 141.5, 133.5, 132.5, 129.1, 128.6, 128.2, 128.1, 127.7, 127.5, 127.3, 127.0, 126.8, 126.7, 126.2, 125.9, 124.8, 52.3; **IR** (thin film) 3057, 3025, 2872, 1601, 1506, 698 $cm^{-1}$; **HRMS** (TOF MS EI+) *m* / *z* calcd for $C_{21}H_{16}S$ $(M)^+$ 300.0973, found at 300.0973; **$[\alpha]^{23}_D$** –4.46 (*c* 0.97, $CHCl_3$); **SFC** analysis (AD-H, 20% 2-propanol, 2.5 mL/min, 256 nm) indicated 86% ee: $t_R$ (major) = 6.5 min, $t_R$ (minor) = 7.3 min.



**2-(**(*R*)**-(Naphthalene-6-yl)(phenyl)methyl)benzo[*b*]thiophene (**(*R*)**-1.20).** Using the representative procedure E outlined above, with the exception of stirring for 72 hours, the following amounts of reagents were used: nickel(II) acetylacetonate (5.1 mg, 0.020 mmol, 0.10 equiv), 1,8-bis(diphenylphosphino)octane (19 mg, 0.040 mmol, 0.20 equiv), 2-benzothienylmagnesium bromide (0.40 mL, 0.40 mmol, 1 M in $Et_2O$, 2.0 equiv), ether (*S*)-**1.2** (58.4 mg, 0.200 mmol, 1.00 equiv), and PhMe (1.6 mL). The product was purified by flash column chromatography (0–3% $Et_2O$:pentane) to afford the title compound as a white solid. First run: 58.0 mg (83%, 88% ee). Second run: 58.2 mg (83%, 86% ee). **TLC $R_f$** = 0.3 (97:3 pentane:$Et_2O$); **m.p. =** 46–47 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.84–7.76 (m, 2H), 7.76–7.67 (m, 2H), 7.66 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.44 (dt, *J* = 9.4, 4.0 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.36–7.20 (m, 7H), 6.90 (s, 1H), 5.88 (s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 148.7, 142.9, 140.6, 140.2, 139.8, 133.5, 132.6, 129.2, 128.7, 128.3, 128.1, 127.8, 127.58, 127.54, 127.2, 126.3, 126.0, 124.3, 124.0, 123.6, 123.4, 122.3, 53.0; **IR** (thin film) 3057, 3025, 2926, 1599, 1434 cm$^{-1}$; **HRMS** (TOF MS EI+) *m* / *z* calcd for $C_{25}H_{18}S$ $(M)^+$ 350.1129, found at 350.1129; **$[\alpha]^{23}_D$** –5.31 (*c* 1.00, $CHCl_3$); **SFC** analysis (AD-H, 20% 2-propanol, 3.5 mL/min, 256 nm) indicated 85% ee: $t_R$ (major) = 22.3 min, $t_R$ (minor) = 23.8 min.



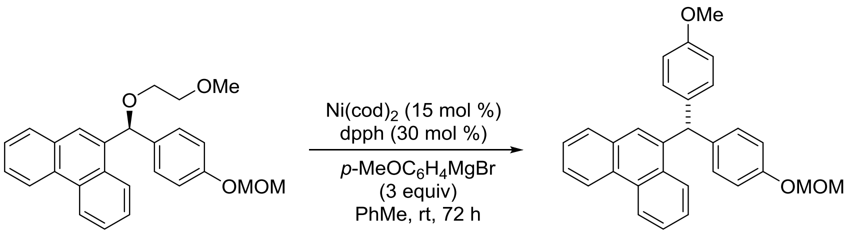
**2-((*R*)-(Phenanthrene-9-yl)(*p*-biphenyl)methyl)thiophene ((*R*)-1.21).** Using the representative procedure E outlined above, with the exception of stirring for 72 hours, the following amounts of reagents were used: bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,8-bis(diphenylphosphino)octane (19 mg, 0.040 mmol, 0.20 equiv), 2-thienylmagnesium bromide (0.17 mL, 0.40 mmol, 2.3 M in $Et_2O$, 2.0 equiv), ether (*S*)-**1.14** (83.6 mg, 0.200 mmol, 1.00 equiv), and PhMe (1.6 mL). The product was purified by flash column chromatography (0–3% $Et_2O$/pentane) to afford the title compound as a yellow solid. First run: 76.2 mg (89%, 74% ee). Second run: 72 mg (85%, 74% ee). **TLC $R_f$** = 0.4 (97:3 pentane:$Et_2O$); **m.p. =** 95–97 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 8.3 Hz, 1H), 8.65 (d, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.55–7.50 (m, 4H), 7.43–7.37 (m, 3H), 7.35–7.28 (m, 3H), 7.24 (d, *J* = 5.3 Hz, 1H), 6.95 (at, *J* = 5.4 Hz, 1H), 6.74 (d, *J* = 3.1 Hz, 1H), 6.47 (s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 147.4, 142.5, 140.8, 139.8, 138.1, 131.5, 130.96, 130.94, 130.1, 129.6, 129.0, 128.9, 128.1, 127.4 (2C), 127.2, 127.1, 126.95, 126.91, 126.8 (2C), 126.4, 124.94, 124.88, 123.3, 122.5, 48.2; **IR** (thin film) 3062, 3028, 2908, 1601, 1486, 741 $cm^{-1}$; **HRMS** (TOF MS EI+) *m* / *z* calcd for $C_{31}H_{22}S$ $(M)^+$ 426.1442, found at 426.1447; **$[\alpha]^{23}_D$** –28.3 (*c* 2.37, $CHCl_3$); **SFC** analysis (AD-H, 30% MeOH, 3.5 mL/min, 256 nm) indicated 71% ee: $t_R$ (major) = 8.8 min, $t_R$ (minor) = 7.9 min.



**9-((*S*)-(Naphthalene-2-yl)(*p*-biphenyl)methyl)phenanthrene ((*S*)-1.22).** Using the representative procedure E outlined above, with the exception of stirring for 72 hours at 40 °C, the following amounts of reagents were used: bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,8-bis(diphenylphosphino)octane (19 mg, 0.040 mmol, 0.20 equiv), 2-naphthylmagnesium bromide (0.31 mL, 0.40 mmol, 1.3 M in $Et_2O$, 2.0 equiv), ether (*S*)-**1.14** (83.6 mg, 0.200 mmol, 1.00 equiv), and PhMe (1.6 mL). The product was purified by flash column chromatography (0–3% $Et_2O$/pentane) to afford the title compound as a white solid. First run: 41.3 mg (44%, 70% ee). Second run: 61 mg (64%, 67% ee).

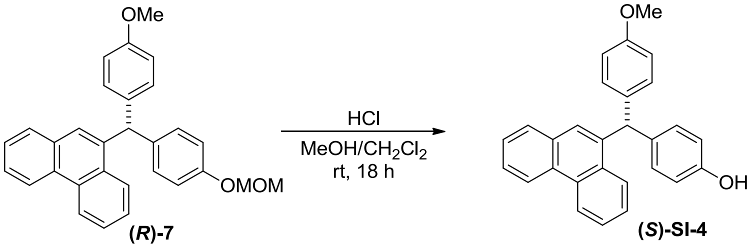
Analytic data ($^1$H NMR, $^{13}$C NMR, GC/MS) are consistent with this compound existing as a 4:1 mixture of rotamers which are separable by SFC. However, the methine signals did not converge in the following variable temperature $^1$H NMR experiment: A sample of the title compound (25 mg) was dissolved in nitrobenzene-$d_5$ (0.7 mL) and a $^1$H NMR spectrum was obtained at room temperature. The sample was heated to 175 °C in 50 °C increments, and a $^1$H NMR spectrum was obtained at each temperature (p S81). At elevated temperatures, the methine signals at 6.65 and 5.74 ppm did not converge.

The mixture of rotamers was interconverted by heating under microwave irradiation: The 4:1 mixture obtained above was dissolved in nitrobenzene-$d_5$ and heated to 250 °C under microwave irradiation. Upon cooling to room temperature, the $^1$H NMR spectrum indicated a 14:1 mixture of rotamers. In a control experiment ***rac*-1.14** was treated with 2-naphthylmagnesium bromide at 80 °C in the absence of nickel catalyst. The $^1$H NMR spectrum of the product indicated a >20:1 mixture of rotamers. **TLC R$_f$** = 0.4 (97:3 pentane:Et$_2$O); **m.p. =** 217–220 °C; **$^1$H NMR** (500 MHz, CDCl$_3$) δ 8.73 (d, *J* = 8.1 Hz, 1H), 8.67 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.80 (at, *J* = 9.1 Hz, 2H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.64–7.56 (m, 4H), 7.56–7.46 (m, 5H), 7.44–7.37 (m, 4H), 7.36–7.30 (m, 2H), 7.29–7.24 (m, 3H), 6.44 (s, 1H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) major rotamer resonances: δ 142.5, 141.2, 140.9, 139.5, 138.2, 133.6, 132.5, 131.6, 131.4, 131.0, 130.4, 129.6, 129.0, 128.94, 128.89, 128.5, 128.31, 128.29, 128.1, 127.7, 127.5, 127.3, 127.1, 126.9, 126.8, 126.7, 126.3, 126.1, 125.8, 125.3, 123.2, 122.5, 53.4; minor rotamer resonances: δ 140.7, 140.2, 140.1, 138.0, 136.8, 136.2, 133.5, 133.3, 133.1, 132.2, 130.0, 129.8, 128.9, 128.7, 128.5, 128.2, 128.0, 127.80, 127.78, 127.2, 127.1, 126.6, 125.94, 125.92, 125.6, 124.5, 123.4, 46.8; **IR** (thin film) 3055, 2875, 1601, 1265 cm$^{-1}$; **HRMS** (TOF MS EI+) *m* / *z* calcd for $C_{37}H_{26}$ (M)$^+$ 470.2035, found 470.2030; **[α]$^{23}$$_D$** –39.1 (*c* 0.42, CHCl$_3$); **SFC** analysis (AD-H, 30% MeOH, 3.5 mL/min, 256 nm) indicated 70% ee: t$_R$ (major) = 19.2 min, t$_R$ (minor) = 16.4 min.

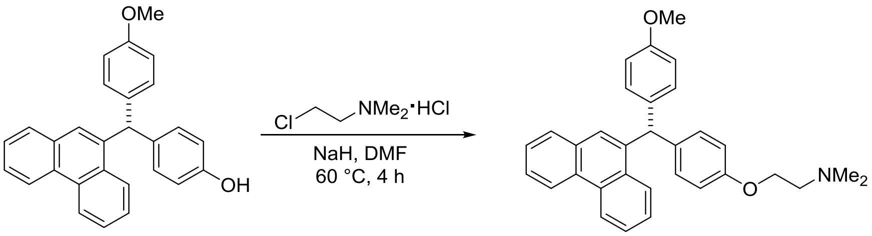


**9-((*R*)-(4-(Methoxymethoxy)phenyl)(4-methoxyphenyl)methyl)phenanthrene ((*R*)-1.10).** Using the representative procedure E outlined above, the following amounts of reagents were used: bis(1,5-cyclooctadiene)nickel (12.8 mg, 0.0465 mmol, 0.150 equiv), 1,6-bis(diphenylphosphino)hexane (42.3 mg, 0.0931 mmol, 0.300 equiv), *p*-methoxyphenylmagnesium bromide (0.47 mL, 0.93 mmol, 2.0 M in Et$_2$O, 3.0 equiv), ether (*S*)-

**1.9** (125 mg, 0.310 mmol, 1.00 equiv), and PhMe (4.8 mL). The product was purified by flash column chromatography (5–15% $Et_2O$/hexanes) to give the title compound as a colorless foam. First run: 82.7 mg (61%, 79% ee). Second run: 90.0 mg (60%, 75% ee). **TLC $R_f$** = 0.3 (9:1 hexanes:$Et_2O$); **m.p. =** 67–69 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 8.3 Hz, 1H), 8.62 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.59–7.54 (m, 2H), 7.51–7.44 (m, 2H), 7.16 (s, 1H), 7.07–7.03 (m, 4H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.14 (s, 1H), 5.13 (s, 2H), 3.74 (s, 3H), 3.45 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 158.2, 155.9, 138.9, 137.3, 135.9, 131.6, 131.3, 131.0, 130.8, 130.7, 129.9, 128.9, 128.5, 126.8, 126.7, 126.6, 126.2, 125.4, 123.2, 122.5, 116.3, 113.9, 94.7, 56.2, 55.4, 52.0; **IR** (thin film) 3055, 2954, 1608, 1508, 1244 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{30}H_{26}O_3$ $(M + Na)^+$ 457.1780, found 457.1768; **$[\alpha]^{23}_D$** –39.0 (*c* 2.91, $CHCl_3$); **SFC** analysis (AD-H, 10% MeOH, 3.5 mL/min, 256 nm) indicated 75% ee: $t_R$ (minor) = 11.5 min, $t_R$ (major) = 12.2 min.



**4-((*S*)-(4-Methoxyphenyl)(phenanthren-9-yl)methyl)phenol ((*S*)-1.16).** Triarylmethane (*R*)-**1.10** (90.0 mg, 0.207 mmol) was dissolved in $CH_2Cl_2$ (6 mL) and added to a solution of HCl (6 mL, 2.0 M in MeOH). The solution was stirred for 18 h, then quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, and concentrated in vacuo. The product was purified by flash column chromatography (30% EtOAc/hexane) to give the title compound as a colorless oil (72.9 mg, 90%). $^1$H NMR data were consistent with reported values.[36] **TLC $R_f$** = 0.4 (7:3 hexanes:EtOAc); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.72 (d, *J* = 8.4 Hz, 1H), 8.65 (d, *J* = 8.3 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.63–7.57 (m, 2H), 7.54–7.46 (m, 2H), 7.15 (s, 1H), 7.06 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 6.14 (s, 1H), 4.65 (br s, 1H), 3.77 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 158.2, 154.1, 138.9, 136.3, 136.0, 131.6, 131.3, 130.9 (2C), 130.7, 129.9, 128.9, 128.5, 126.8, 126.7, 126.6, 126.3, 125.4, 123.2, 122.5, 115.4, 113.9, 55.4, 51.9; **IR** (thin film) 3381, 3061, 2929, 1608, 1510, 1246 cm$^{-1}$; **HRMS** (TOF MS AP+) *m* / *z* calcd for $C_{28}H_{22}O_2$ $(M)^+$ 390.1620, found 390.1607; **[α]$^{23}_{D}$** –48.1 (*c* 2.86, $CHCl_3$); **SFC** analysis (AD-H, 25% MeOH, 2.5 mL/min, 256 nm) indicated 75% ee: $t_R$ (minor) = 5.5 min, $t_R$ (major) = 6.7 min.



**2-(4-((**R**)-(4-Methoxyphenyl)(phenanthren-9-yl)methyl)phenoxy)-*N*,*N*-dimethylethanamine ((*R*)-1.11).** A procedure by McCague was adapted.[37] Phenol (*S*)-**1.16** (57.2 mg, 0.147 mmol, 1.00 equiv) was dissolved in DMF (3 mL). Sodium hydride (54 mg, 2.3 mmol, 15 equiv) was added with stirring, and the mixture was heated to 60 °C for 10 min. The resulting yellow mixture was cooled to room temperature and 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (86 mg, 0.60 mmol, 4.1 equiv) was added. The mixture was then heated to 60 °C for 4 h. Upon completion, the reaction was cooled to room temperature and excess sodium hydride was quenched by addition of 2-propanol (1 mL). The mixture was poured into water (10 mL) and

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[36] Shagufta; Srivastava, A. K.; Sharma, R.; Mishra, R.; Balapure, A. K.; Murthyc, P. S. R.; Panda, G. *Bioorg. Med.Chem.* **2006**, 1497–1505.

[37] McCague, R.; Leclercq, G.; Jordan, V. C. *J. Med. Chem.* **1988**, *31*, 1285–1290.

extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The product was purified by flash column chromatography (3% $Et_3N$/EtOAc) to give the title compound as a yellow oil (54.4 mg, 80%). $^1$H NMR data were consistent with reported values.[21] **TLC R$_f$** = 0.4 (95:5 EtOAc:$Et_3N$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.72 (d, *J* = 8.3 Hz, 1H), 8.66 (d, *J* = 8.3 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.63–7.58 (m, 2H), 7.55–7.47 (m, 2H), 7.14 (s, 1H), 7.06 (at, *J* = 7.7 Hz, 4H), 6.84 (at, *J* = 9.1 Hz, 4H), 6.15 (s, 1H), 4.04 (t, *J* = 5.8 Hz, 2H), 3.79 (s, 3H), 2.72 (t, *J* = 5.8 Hz, 2H), 2.33 (s, 6H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 158.1, 157.4, 138.9, 136.04, 135.96, 131.5, 131.3, 130.9, 130.64, 130.59, 129.8, 128.8, 128.4, 126.7, 126.6, 126.4, 126.1, 125.3, 123.1, 122.4, 114.5, 113.8, 65.9, 58.4, 55.3, 51.9, 46.0; **IR** (thin film) 3049, 2941, 2823, 1608, 1508, 1256 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{32}H_{32}NO_2$ $(M + H)^+$ 462.2433, found 462.2426; **$[\alpha]^{23}_D$** –0.49 (*c* 1.79, $CHCl_3$).

*X-ray Data Collection, Structure Solution and Refinement for* (*R*)-**1.8**

Single crystals suitable for X-ray crystallographic analysis were grown by slow diffusion of pentane into a solution of (*R*)-**1.8** in benzene at ambient temperature.

A colorless crystal of approximate dimensions 0.13 x 0.17 x 0.28 mm was mounted on a glass fiber and transferred to a Bruker SMART APEX II diffractometer. The APEX2[38] program package was used to determine the unit-cell parameters and for data collection (45 sec/frame scan time for a hemisphere of diffraction data). The raw frame data was processed using SAINT[39] and SADABS[40] to yield the reflection data file. Subsequent calculations were carried out using the SHELXTL[41] program. The diffraction symmetry was *mmm* and the systematic absences were consistent with the orthorhombic space group $P2_12_12_1$ that was later determined to be correct.

The structure was solved by direct methods and refined on $F^2$ by full-matrix least-squares techniques. The analytical scattering factors[42] for neutral atoms were used throughout the analysis. Hydrogen atoms were included using a riding model. Atoms S(1) and C(3) were disordered resulting in mixed site-occupancies for the atoms of 0.875 S(1) and 1.33 C(3).

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[38] APEX2 Version 2011.4-1, Bruker AXS, Inc.; Madison, WI 2011.

[39] SAINT Version 7.68a, Bruker AXS, Inc.; Madison, WI 2009.

[40] Sheldrick, G. M. SADABS, Version 2008/1, Bruker AXS, Inc.; Madison, WI 2008.

[41] Sheldrick, G. M. SHELXTL, Version 2008/4, Bruker AXS, Inc.; Madison, WI 2008.

[42] International Tables for X-Ray Crystallography 1992, Vol. C., Dordrecht: Kluwer Academic Publishers.

At convergence, wR2 = 0.0840 and Goof = 1.067 for 199 variables refined against 2927 data (0.82Å), R1 = 0.0328 for those 2767 data with $I > 2.0\sigma(I)$. The absolute structure was assigned by refinement of the Flack parameter.[43]

*Definitions:*

$$wR2 = [\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$$

$$R1 = \Sigma||F_o| - |F_c|| / \Sigma|F_o|$$

$Goof = S = [\Sigma[w(F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$ where n is the number of reflections and p is the total number of parameters refined.

The thermal ellipsoid plot is shown at the 50% probability level.

***Table 1.6.*** Crystal data and structure refinement for (*R*)-**1.8**.

| | | |
|---|---|---|
| Identification code | (*R*)-**1.8** (Michael Harris) | |
| Empirical formula | $C_{21}H_{16}S$ | |
| Formula weight | 300.40 | |
| Temperature | 143(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12_1$ | |
| Unit cell dimensions | a = 6.4836(5) Å | □= 90°. |
| | b = 7.6581(5) Å | □= 90°. |
| | c = 31.028(2) Å | □ = 90°. |

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[43] Flack, H. D. Acta. Cryst., A39, 876-881, 1983.

| | |
|---|---|
| Volume | 1540.60(19) Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.295 Mg/m$^3$ |
| Absorption coefficient | 0.203 mm$^{-1}$ |
| F(000) | 632 |
| Crystal color | colorless |
| Crystal size | 0.28 x 0.17 x 0.13 mm$^3$ |
| Theta range for data collection | 2.74 to 25.68° |
| Index ranges | $-7 \le h \le 7$, $-9 \le k \le 9$, $-34 \le l \le 37$ |
| Reflections collected | 11891 |
| Independent reflections | 2927 [R(int) = 0.0253] |
| Completeness to theta = 25.50° | 99.8 % |
| Absorption correction | Numerical |
| Max. and min. transmission | 0.9738 and 0.9460 |
| Refinement method | Full-matrix least-squares on F$^2$ |
| Data / restraints / parameters | 2927 / 0 / 199 |
| Goodness-of-fit on F$^2$ | 1.067 |
| Final R indices [I>2sigma(I) = 2767 data] | R1 = 0.0328, wR2 = 0.0825 |
| R indices (all data, 0.82Å) | R1 = 0.0355, wR2 = 0.0840 |
| Absolute structure parameter | 0.04(8) |
| Largest diff. peak and hole | 0.299 and -0.263 e.Å$^{-3}$ |

***Table 1.7.*** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$)
for (*R*)-**1.8**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| S(1) | 5417(1) | 1583(1) | 2034(1) | 27(1) |
| C(1) | 7113(3) | 2686(2) | 1238(1) | 24(1) |
| C(2) | 5793(3) | 1422(2) | 1490(1) | 24(1) |
| C(3) | 4653(3) | -12(2) | 1313(1) | 40(1) |
| C(4) | 3524(3) | -868(3) | 1650(1) | 32(1) |
| C(5) | 3786(3) | -162(3) | 2045(1) | 34(1) |
| C(6) | 5874(3) | 3540(2) | 877(1) | 24(1) |
| C(7) | 6656(3) | 3641(2) | 470(1) | 26(1) |
| C(8) | 5558(3) | 4482(2) | 129(1) | 26(1) |
| C(9) | 6366(3) | 4624(3) | -291(1) | 31(1) |
| C(10) | 5293(3) | 5495(3) | -600(1) | 35(1) |
| C(11) | 3364(3) | 6251(3) | -509(1) | 34(1) |
| C(12) | 2513(3) | 6094(2) | -112(1) | 30(1) |
| C(13) | 3595(3) | 5203(2) | 222(1) | 26(1) |
| C(14) | 2778(3) | 5040(2) | 643(1) | 29(1) |
| C(15) | 3874(3) | 4227(3) | 959(1) | 28(1) |
| C(16) | 8171(3) | 3999(2) | 1536(1) | 25(1) |
| C(17) | 7429(3) | 5723(2) | 1602(1) | 27(1) |
| C(18) | 8369(3) | 6787(3) | 1896(1) | 38(1) |
| C(19) | 10047(3) | 6230(3) | 2129(1) | 34(1) |
| C(20) | 10819(3) | 4583(3) | 2063(1) | 33(1) |
| C(21) | 9906(3) | 3481(3) | 1771(1) | 29(1) |

***Table 1.8.*** Bond lengths [Å] and angles [°] for (*R*)-**1.8**.

| | |
|---|---|
| S(1)-C(5) | 1.705(2) |
| S(1)-C(2) | 1.7092(18) |
| C(1)-C(2) | 1.511(2) |
| C(1)-C(6) | 1.525(2) |
| C(1)-C(16) | 1.530(3) |
| C(2)-C(3) | 1.433(2) |
| C(3)-C(4) | 1.436(2) |
| C(4)-C(5) | 1.351(3) |
| C(6)-C(7) | 1.362(2) |
| C(6)-C(15) | 1.422(3) |
| C(7)-C(8) | 1.429(3) |
| C(8)-C(9) | 1.410(3) |
| C(8)-C(13) | 1.417(3) |
| C(9)-C(10) | 1.360(3) |
| C(10)-C(11) | 1.407(3) |
| C(11)-C(12) | 1.355(3) |
| C(12)-C(13) | 1.426(3) |
| C(13)-C(14) | 1.415(3) |
| C(14)-C(15) | 1.361(3) |
| C(16)-C(21) | 1.398(3) |
| C(16)-C(17) | 1.419(3) |
| C(17)-C(18) | 1.368(3) |
| C(18)-C(19) | 1.373(3) |
| C(19)-C(20) | 1.372(3) |
| C(20)-C(21) | 1.373(3) |
| | |
| C(5)-S(1)-C(2) | 93.00(10) |
| C(2)-C(1)-C(6) | 110.89(14) |
| C(2)-C(1)-C(16) | 111.21(14) |
| C(6)-C(1)-C(16) | 113.51(15) |
| C(3)-C(2)-C(1) | 125.76(15) |
| C(3)-C(2)-S(1) | 111.14(13) |
| C(1)-C(2)-S(1) | 123.07(13) |
| C(2)-C(3)-C(4) | 109.47(15) |

| | |
|---|---|
| C(5)-C(4)-C(3) | 114.49(18) |
| C(4)-C(5)-S(1) | 111.89(15) |
| C(7)-C(6)-C(15) | 119.01(17) |
| C(7)-C(6)-C(1) | 120.52(16) |
| C(15)-C(6)-C(1) | 120.46(16) |
| C(6)-C(7)-C(8) | 121.73(17) |
| C(9)-C(8)-C(13) | 119.49(18) |
| C(9)-C(8)-C(7) | 122.36(18) |
| C(13)-C(8)-C(7) | 118.15(17) |
| C(10)-C(9)-C(8) | 120.04(19) |
| C(9)-C(10)-C(11) | 120.96(19) |
| C(12)-C(11)-C(10) | 120.58(19) |
| C(11)-C(12)-C(13) | 120.20(19) |
| C(14)-C(13)-C(8) | 119.35(17) |
| C(14)-C(13)-C(12) | 121.96(18) |
| C(8)-C(13)-C(12) | 118.68(18) |
| C(15)-C(14)-C(13) | 120.63(18) |
| C(14)-C(15)-C(6) | 121.05(17) |
| C(21)-C(16)-C(17) | 117.53(17) |
| C(21)-C(16)-C(1) | 119.32(16) |
| C(17)-C(16)-C(1) | 123.10(16) |
| C(18)-C(17)-C(16) | 119.92(18) |
| C(17)-C(18)-C(19) | 121.2(2) |
| C(20)-C(19)-C(18) | 119.84(19) |
| C(19)-C(20)-C(21) | 120.35(19) |
| C(20)-C(21)-C(16) | 121.09(18) |

***Table 1.9.*** Anisotropic displacement parameters ($Å^{2}$x $10^{3}$) for (*R*)-**1.8**. The anisotropic displacement factor exponent takes the form: $-2\square^{2}[\, h^{2} a^{*2}U^{11} + \dots + 2\, h\, k\, a^{*}\, b^{*}\, U^{12}\, ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| S(1) | 34(1) | 26(1) | 22(1) | 1(1) | 2(1) | -1(1) |
| C(1) | 27(1) | 23(1) | 23(1) | 0(1) | 4(1) | 5(1) |
| C(2) | 27(1) | 22(1) | 24(1) | 3(1) | 0(1) | 3(1) |
| C(3) | 38(1) | 38(1) | 44(1) | 7(1) | 4(1) | 2(1) |
| C(4) | 31(1) | 24(1) | 39(1) | 4(1) | 1(1) | -1(1) |
| C(5) | 35(1) | 37(1) | 30(1) | 10(1) | 6(1) | 8(1) |
| C(6) | 33(1) | 18(1) | 22(1) | 0(1) | 0(1) | -2(1) |
| C(7) | 29(1) | 21(1) | 28(1) | -2(1) | 1(1) | 0(1) |
| C(8) | 32(1) | 20(1) | 26(1) | -3(1) | -2(1) | -3(1) |
| C(9) | 37(1) | 29(1) | 26(1) | -2(1) | 3(1) | -4(1) |
| C(10) | 46(1) | 35(1) | 24(1) | 0(1) | -2(1) | -8(1) |
| C(11) | 44(1) | 30(1) | 28(1) | 2(1) | -11(1) | -4(1) |
| C(12) | 37(1) | 23(1) | 31(1) | 1(1) | -6(1) | -1(1) |
| C(13) | 33(1) | 19(1) | 25(1) | -2(1) | -2(1) | -4(1) |
| C(14) | 28(1) | 24(1) | 34(1) | -1(1) | 3(1) | 2(1) |
| C(15) | 32(1) | 26(1) | 24(1) | 2(1) | 3(1) | 0(1) |
| C(16) | 27(1) | 25(1) | 22(1) | 3(1) | 3(1) | 0(1) |
| C(17) | 28(1) | 28(1) | 25(1) | 2(1) | -3(1) | 3(1) |
| C(18) | 47(1) | 27(1) | 40(1) | -4(1) | 0(1) | 1(1) |
| C(19) | 34(1) | 38(1) | 32(1) | -2(1) | 3(1) | -11(1) |
| C(20) | 26(1) | 42(1) | 31(1) | 4(1) | 0(1) | -3(1) |
| C(21) | 28(1) | 29(1) | 30(1) | 4(1) | 4(1) | 4(1) |

***Table 1.10.*** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters (Å$^2$x 10 $^3$) for (*R*)-**1.8**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | 8228 | 1986 | 1097 | 29 |
| H(3A) | 4646 | -344 | 1018 | 48 |
| H(4A) | 2663 | -1851 | 1599 | 38 |
| H(5A) | 3139 | -587 | 2299 | 41 |
| H(7A) | 7966 | 3138 | 412 | 32 |
| H(9A) | 7660 | 4112 | -359 | 37 |
| H(10A) | 5854 | 5596 | -882 | 42 |
| H(11A) | 2651 | 6876 | -728 | 40 |
| H(12A) | 1191 | 6579 | -56 | 36 |
| H(14A) | 1452 | 5501 | 706 | 34 |
| H(15A) | 3294 | 4117 | 1239 | 33 |
| H(17A) | 6282 | 6137 | 1441 | 32 |
| H(18A) | 7850 | 7933 | 1941 | 46 |
| H(19A) | 10672 | 6983 | 2334 | 41 |
| H(20A) | 11990 | 4202 | 2222 | 40 |
| H(21A) | 10464 | 2347 | 1727 | 35 |

***Table 1.11.*** Torsion angles [°] for (*R*)-**1.8**.

| | |
|---|---|
| C(6)-C(1)-C(2)-C(3) | 55.1(2) |
| C(16)-C(1)-C(2)-C(3) | -177.55(16) |
| C(6)-C(1)-C(2)-S(1) | -122.80(15) |
| C(16)-C(1)-C(2)-S(1) | 4.5(2) |
| C(5)-S(1)-C(2)-C(3) | -0.44(14) |
| C(5)-S(1)-C(2)-C(1) | 177.77(15) |
| C(1)-C(2)-C(3)-C(4) | -177.67(16) |
| S(1)-C(2)-C(3)-C(4) | 0.48(18) |
| C(2)-C(3)-C(4)-C(5) | -0.3(2) |
| C(3)-C(4)-C(5)-S(1) | 0.0(2) |
| C(2)-S(1)-C(5)-C(4) | 0.28(16) |
| C(2)-C(1)-C(6)-C(7) | -132.71(18) |
| C(16)-C(1)-C(6)-C(7) | 101.3(2) |
| C(2)-C(1)-C(6)-C(15) | 46.6(2) |
| C(16)-C(1)-C(6)-C(15) | -79.4(2) |
| C(15)-C(6)-C(7)-C(8) | 2.7(3) |
| C(1)-C(6)-C(7)-C(8) | -177.99(16) |
| C(6)-C(7)-C(8)-C(9) | 178.77(18) |
| C(6)-C(7)-C(8)-C(13) | -0.7(3) |
| C(13)-C(8)-C(9)-C(10) | 2.0(3) |
| C(7)-C(8)-C(9)-C(10) | -177.51(18) |
| C(8)-C(9)-C(10)-C(11) | -0.6(3) |
| C(9)-C(10)-C(11)-C(12) | -1.4(3) |
| C(10)-C(11)-C(12)-C(13) | 1.9(3) |
| C(9)-C(8)-C(13)-C(14) | 179.25(17) |
| C(7)-C(8)-C(13)-C(14) | -1.2(2) |
| C(9)-C(8)-C(13)-C(12) | -1.5(3) |
| C(7)-C(8)-C(13)-C(12) | 178.07(16) |
| C(11)-C(12)-C(13)-C(14) | 178.80(18) |
| C(11)-C(12)-C(13)-C(8) | -0.5(3) |
| C(8)-C(13)-C(14)-C(15) | 1.2(3) |
| C(12)-C(13)-C(14)-C(15) | -178.06(18) |
| C(13)-C(14)-C(15)-C(6) | 0.7(3) |
| C(7)-C(6)-C(15)-C(14) | -2.7(3) |

| | |
|---|---|
| C(1)-C(6)-C(15)-C(14) | 177.97(18) |
| C(2)-C(1)-C(16)-C(21) | 77.7(2) |
| C(6)-C(1)-C(16)-C(21) | -156.43(16) |
| C(2)-C(1)-C(16)-C(17) | -99.76(19) |
| C(6)-C(1)-C(16)-C(17) | 26.1(2) |
| C(21)-C(16)-C(17)-C(18) | -2.1(3) |
| C(1)-C(16)-C(17)-C(18) | 175.38(18) |
| C(16)-C(17)-C(18)-C(19) | 0.9(3) |
| C(17)-C(18)-C(19)-C(20) | 0.6(3) |
| C(18)-C(19)-C(20)-C(21) | -0.8(3) |
| C(19)-C(20)-C(21)-C(16) | -0.5(3) |
| C(17)-C(16)-C(21)-C(20) | 1.9(3) |
| C(1)-C(16)-C(21)-C(20) | -175.66(17) |

*Chapter Two*

# Retention or Inversion in Stereospecific Nickel-Catalyzed Cross-Coupling of Benzylic Carbamates with Arylboronic Esters: Control of Absolute Stereochemistry with an Achiral Catalyst

## 2.1 Introduction

The mechanisms of alkyl cross-coupling reactions are hardwired with implications for the stereochemical outcome at the reactive centers.[1] Simple changes to the reaction conditions do not typically perturb the inherent bias for racemization, retention, or inversion at the reactive centers. For example, palladium-catalyzed reactions of alkyl electrophiles are typically stereospecific and proceed with inversion at the stereogenic center,[2,3] while nickel-catalyzed reactions of alkyl halides proceed with racemization at the electrophilic carbon[4] and judicious use of chiral catalyst permits stereoconvergent reactions.[5] Overcoming the intrinsic preference, such that a reaction that typically proceeds with inversion at the stereogenic center can proceed with retention is quite unusual, and requires a significant change to the mechanism of the transformation. For stereospecific reactions, special cases using α-chiral *transmetallating agents* have been reported

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[1] Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417.

[2] (a) Lau, K. S. Y.; Fries, R. W.; Stille, J. K. *J. Am. Chem. Soc.* **1974**, *96*, 4983. (b) Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3910. (c) Legros, J.-Y.; Toffano, M.; Fiaud, J.-C. *Tetrahedron* **1995**, *51*, 3235. (d) Rodriquez, N.; de Arellano, C. R.; Asensio, G.; Medio-Simon, M. *Chem. Eur. J.* **2007**, *13*, 4223. (e) Lopez-Perez, A.; Adrio, J.; Carretero, J. C. *Org. Lett.* **2009**, *11*, 5514. (f) He, A.; Falck, J. R. *J. Am. Chem. Soc.* **2010**, *132*, 2524. (g) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1485.

[3] Pd-catalyzed *allylic* substitutions can occur with inversion or retention, depending on the nucleophile. See: Trost, B. M.; VanVranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

[4] Stille, J. K.; Cowell, A. B. *J. Organomet. Chem.* **1977**, *124*, 253.

where modification of reaction conditions or substrate structure can affect a switch in the sense of absolute stereochemistry.[6] Transmetallation typically occurs with retention at the stereogenic center;[7,8] select examples that proceed with inversion have been reported.[9] In seminal contributions, Hiyama demonstrated that palladium-catalyzed couplings of alkylsilanes could proceed with retention or inversion, depending on the reaction conditions.[10] Recently, the Suginome group has developed stereodivergent reactions of α-(acetylamino)benzylboronic esters that are controlled by choice of additive to afford, selectively, either retention or inversion (Scheme 2.1a).[11,12]

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[5] (a) Saito, B.; Fu, G.C. *J. Am. Chem. Soc.* **2008**, *130*, 6694. (b) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012** *134*, 5794, and cited therein. (c) Glorius, F. *Angew. Chem. Int. Ed.* **2008**, *47*, 8347.

[6] For a discussion, see: Molander, G. A.; Wisniewski, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 16856.

[7] For labeling studies, see: (a) Bock, P. L.; Boschetto, D. J.; Rasmussen, J. R.; Demers, J. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 2814. (b) Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458. (c) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461. (d) Taylor, B. L. H.; Jarvo, E. R. *J. Org. Chem.* **2011**, *76*, 7573.

[8] (a) Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1. (b) Hölzer, B.; Hoffmann, R. W. *Chem. Commun.* **2003**, 732. (c) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 3538. (d) Lange, H.; Fröhlich, R.; Hoppe, D. *Tetrahedron* **2008**, *64*, 9123. (e) Imao, D.; Glasspoole, B. W.; Laberge, S. V.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024. (f) Li, H.; He, A.; Falck, J. R.; Liebeskind, L. S. *Org. Lett.* **2011**, *13*, 3682. (g) See reference 5.

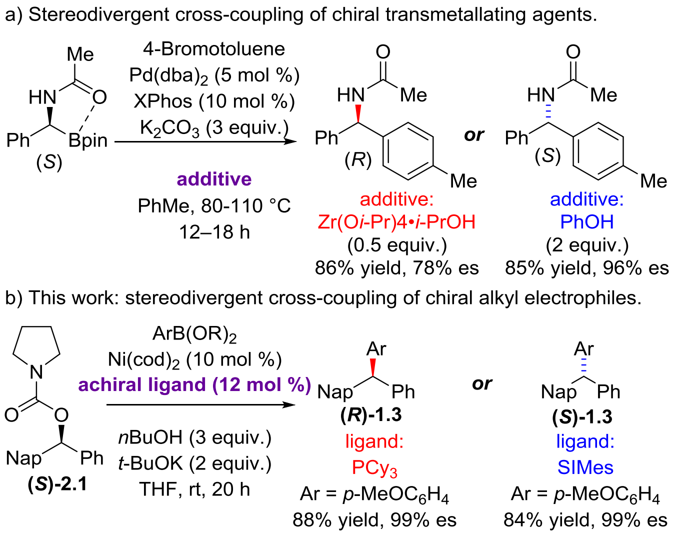
[9] (a) LaBadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 669. (b) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666. (c) Sandrock, D. L.; Jean-Gérard, L.; Chen, C.-Y.; Dreher, S. D.; Molander, G. A. *J. Am. Chem. Soc.* **2010**, *132*, 17108. (d) Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191. (e) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894.

[10] (a) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793. (b) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58.

[11] (a) Awano, T.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2011**, *133*, 20738. (b) reference 9d.

[12] For enantiodivergent reactions of alkyllithium reagents: Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. M. *Nature*, **2008**, *456*, 778.

***Scheme 2.1.*** Control of product stereochemistry in stereospecific reactions



In this chapter, we demonstrate catalyst control of the stereochemical course with respect to the *electrophilic* partner in a cross-coupling reaction. Stereospecific nickel-catalyzed cross-coupling reactions of benzylic alcohol derivatives typically proceed with inversion at the electrophilic carbon.[13,14] Herein, we report nickel-catalyzed cross-coupling of benzylic esters where the achiral ligand structure dictates whether the reaction proceeds with retention or inversion (Scheme 2.1b). Use of SIMes, an N-heterocyclic carbene (NHC) ligand, affords inversion, while $PCy_3$ gives retention. To the best of our knowledge, these results constitute the first cross-coupling reactions of alkyl electrophiles that undergo two distinct stereospecific mechanistic pathways to provide either retention or inversion at the electrophilic carbon.

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[13] (a) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389. (b) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem. Int. Ed.* **2012**, *51*, 7790. (c) Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293. (d) For a review, see: Taylor, B. L. H.; Jarvo, E. R. *Synlett*, **2011**, *19*, 2761.

[14] For recent studies of the stereochemical course of nickel-catalyzed reactions of epoxides and aziridines, see: (a) Beaver, M. G.; Jamison, T. F. *Org. Lett.* **2011**, *13*, 4140. (b) Sylvester, K. T.; Wu, K.; Doyle, A. G. *J. Am. Chem. Soc.* **2012**, *134*, 9541. (c) Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890.

In previous work, we established synthesis of enantioenriched triarylmethanes by stereospecific nickel-catalyzed cross-coupling of ethers with aryl Grignard reagents.[13b] The triarylmethane moiety is present in medicinal chemistry targets, natural products, and synthetic materials.[15,16] Despite recent advances in the preparation of racemic triarylmethanes,[17] there are few methods for their enantioselective synthesis.[18] As part of our ongoing interest in developing nickel-catalyzed stereospecific reactions of alkyl electrophiles, we chose to examine cross-coupling reactions of arylboronic esters for triarylmethane synthesis. The functional group tolerance and ready availability of a wide range of boronic esters makes them attractive coupling partners.

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[15] Biological activity: (a) Palchaudhuri, R.; Nesterenko, V.; Hergenrother, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 10274. (b) Shagufta; Srivastava, A. K.; Sharma, R.; Mishra, R.; Balapure, A. K.; Murthy, P. S. R.; Panda, G. *Bioorg. Med. Chem.* **2006**, *14*, 1497. (c) Parai, M. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 289. (d) Ellsworth, B. A.; Ewing, W. R.; Jurica, E. U.S. Patent Application 2011/0082165A1, Apr 7, 2011. (e) Baba, K.; Maeda, K.; Tabata, Y.; Doi, M.; Kozawa, M. *Chem. Pharm. Bull.* **1988**, *36*, 2977. Materials: (f) Herron, N.; Johansson, G. A.; Radu, N. S. US Patent Application 2005/0187364, Aug 25, 2005. (g) Xu, Y.-Q.; Lu, J.-M.; Li, N.-J.; Yan, F.; Xia, X.; Xu, Q. *Eur. Polym. J.* **2008**, *44*, 2404.

[16] Physical properties of triarylmethanes: (a) Breslow, R.; Chu, W. *J. Am. Chem. Soc.* **1973**, *95*, 411. (b) Finocchiaro, P.; Gust, D.; Mislow, K. *J. Am. Chem. Soc.* **1974**, *96*, 3198. (c) Duxbury, D. F. *Chem. Rev.* **1993**, *93*, 381.

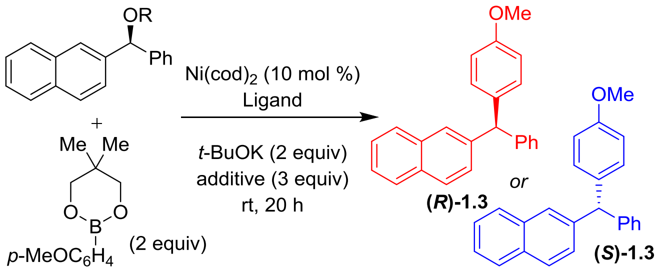
[17] (a) Zhang, J.; Bellomo, A.; Creamer, A. D.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 13765. (b) Yu, J.-Y.; Kuwano, R. *Org. Lett.* **2008**, *10*, 973. (c) Molander, G.A.; Elia, M. D. *J. Org. Chem.* **2006**, *71*, 9198. (d) Li, Y.-Z.; Li, B.-J.; Lu, X.-Y.; Lin, S.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2009**, *48*, 3817. (e) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3913. (f) For a representative Freidel–Crafts strategy, see: Esquivias, J.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 629.

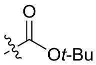
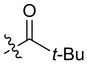
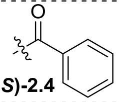
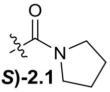
[18] (a) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 4882. (b) Sun, F.-L.; Zheng, X.-J.; Gu, Q.; He, Q.-L.; You, S.-L. *Eur. J. Org. Chem.* **2010**, 47.

## 2.2 Development of a Stereospecific Cross-Coupling Reaction of Arylboronic Esters

We began by examining a range of benzylic alcohol derivatives (Table 2.1). Our initial reaction conditions resulted in a modest conversion of carbonate **(*S*)-2.2** and low enantiospecificity (es) (entry 1).[19] To our surprise, in contrast to the Kumada coupling, the product, **(*R*)-1.3**, results from *retention* at the electrophilic carbon. An improvement to 43% es was observed when the solvent was changed from toluene to THF (entry 2). Alcohol additives further improved the yield and stereochemical fidelity of the reaction, with *n*-BuOH providing the highest es, 87% (entry 4). More sterically encumbered alcohols provided more modest improvements, while water and the electron-deficient alcohol trifluoroethanol proved detrimental to the reaction (entries 3, 5, and 7). The enantiospecificity of the reaction showed a marked dependence on the identity of the leaving group. While the use of pivalate **(*S*)-2.3** in the cross-coupling reaction resulted in lower enantiomeric excess of the product (entry 8), the benzoate and carbamate derivatives **(*S*)-2.4** and **(*S*)-2.1** showed a significant increase in product ee, providing 91 and 95% es, respectively (Table 1, entries 8, 10, and 12). An additional small improvement in yield and es resulted from using a 1:1 mixture of THF/toluene as the solvent (c.f. entries 12 and 15).

**Table 2.1.** Optimization of reaction conditions



| Entry | R | ligand[a] | solvent | additive | % yield[b] | es[c] | retention/ inversion |
|---|---|---|---|---|---|---|---|
| 1 |  <br>**(*S*)-2.2** | PCy$_3$ | PhMe | none | 46 | 7 | retention |
| 2 | | PCy$_3$ | THF | none | 53 | 43 | retention |
| 3 | | PCy$_3$ | THF | $H_2O$ | 74 | 10 | retention |
| 4 | | PCy$_3$ | THF | *n*-BuOH | 76 | 87 | retention |
| 5 | | PCy$_3$ | THF | *i*-PrOH | 46 | 78 | retention |
| 6 | | PCy$_3$ | THF | *t*-BuOH | 55 | 43 | retention |
| 7 | | PCy$_3$ | THF | $F_3CCH_2OH$ | < 5 | na | retention |
| 8 |  <br>**(*S*)-2.3** | PCy$_3$ | THF | *n*-BuOH | 53 | 76 | retention |
| 9 | | SIMes | THF | *n*-BuOH | 60 | 77 | inversion |
| 10 |  <br>**(*S*)-2.4** | PCy$_3$ | THF | *n*-BuOH | 57 | 91 | retention |
| 11 | | SIMes | THF | *n*-BuOH | 83 | >99 | inversion |
| 12 |  <br>**(*S*)-2.1** | PCy$_3$ | THF | *n*-BuOH | 62 | 95 | retention |
| 13 | | PCy$_3$ | THF/PhMe | none | 67 | 35 | retention |
| 14 | | SIMes | THF/PhMe | none | 82 | 92 | inversion |
| **15** | | **PCy$_3$** | **THF/PhMe** | ***n*-BuOH** | **88** | **99** | **retention** |
| **16** | | **SIMes** | **THF/PhMe** | ***n*-BuOH** | **84** | **99** | **inversion** |

[a]PCy3 (20 mol %), SIMes (11 mol %). [b]Isolated yield after column chromatography. [c]Enantiospecificity (es) = $ee_{product}/ee_{starting\ material}$ x 100%.

We examined other ligands[20] under the reaction conditions and found that the NHC ligand SIMes[21] afforded comparable yields and enantiospecificity of **1.3**, however, the major prod-

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[19] es: Denmark, S. E.; Vogler, T. *Chem.–Eur. J.* **2009**, *15*, 11737.
[20] For results with other ligands, see the Experimental Details.
[21] SIMes = (1,3-Bis(2,6-diisopropylphenyl)-4,5-di-hydroimidazoliumtetrafluoroborate

uct was the (*S*)-enantiomer, resulting from *inversion* at the electrophilic carbon.[22] Catalyst-control of the stereochemical outcome of the reaction was consistent across the range of esters and carbamates that we examined: $PCy_3$ and SIMes reliably afforded opposite enantiomers of product (entries 8–11, 15 and 16).[23] Under the optimal reaction conditions, addition of *n*-BuOH was found to improve stereochemical fidelity when using either ligand (c.f. entries 13–16).

Due to the dramatic effect that additives and the identity of the leaving group had on the enantiospecificity of the cross-coupling reaction, we became interested in investigating plausible background reactions that could lead to racemization of the benzylic carbamate starting material. We reasoned that upon exposure of our benzylic carbamate to one of the reagents in the cross-coupling reaction, epimerization could occur, leading to low enantiospecificity in the desired transformation. Indeed, we found that when carbmate **(*S*)-2.1** is dissolved in THF/PhMe and subjected to 2 equivalents of potassium *tert*-butoxide for 20 h, the enantiomeric excess of **(*S*)-2.1** decreases from 92% to 35%. Interestingly, no decline in ee is observed when **(*S*)-2.1** is subjected to *sodium tert*-butoxide (Scheme 2.2). These results are consistent with a mechanism for racemization of **(*S*)-2.1** that is promoted by the potassium counter-ion of the base. Sequestration of the potassium ion of *tert*-butoxide by polar solvents (THF) and alcohol additives may explain the observed increase in enantiospecificity of the cross-coupling reaction described in Table 1 (entries 2, 8–13, 15 and 16). Based on the poor performance of sodium *tert*-butoxide in the cross-coupling reaction we decided to continue using the optimized reaction conditions developed in Table 2.1 (Scheme 2.3).

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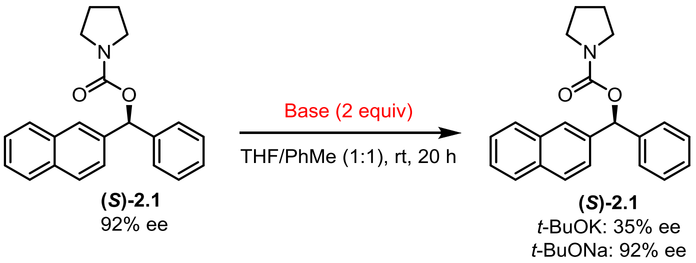
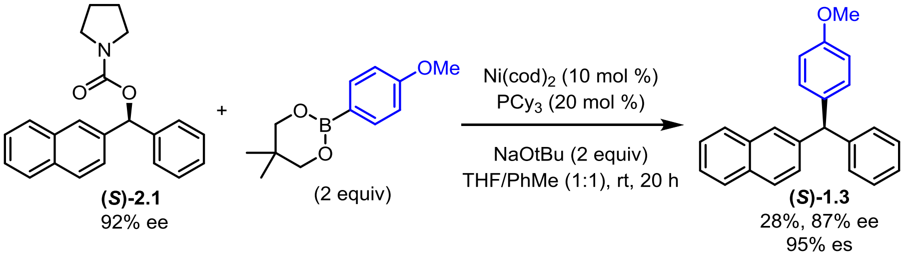
[22] Comparison of NHC to $PR_3$: Clavier, H.; Nolan, S. P. *Chem. Commun.* **2010**, *46*, 841.

[23] Changing $PCy_3$ loading from 20 mol % to 11 mol % does not affect the stereochemical outcome; see the Experimental Details.

***Scheme 2.2.*** Potassium *tert*-butoxide-promoted epimerization of starting material



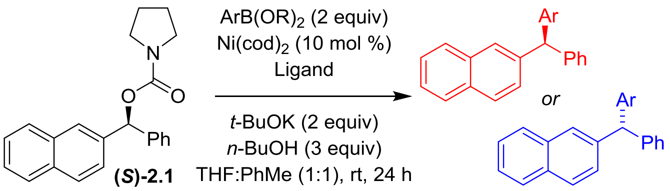
***Scheme 2.3.*** Effect of sodium *tert*-butoxide on cross-coupling reaction



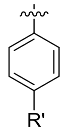
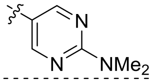
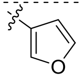
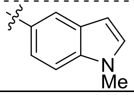
## 2.3 Arylboronic Ester Scope

Having optimized reaction conditions for stereospecfic synthesis of either enantiomer of product, we turned our attention to the scope of the reaction with respect to the boronic ester (Table 2.2). Electron-donating and withdrawing substituents on the arylboronic ester are well tolerated under the reaction conditions (entries 1–6). Reaction conditions are mild and allow for broad functional group tolerance. Boronic esters containing ketone, free alcohol and carbamate functional groups all undergo cross-coupling in good yield and es (entries 7–9). Heterocyclic boronic esters including pyrimidine, furan, and indole undergo smooth cross-coupling (entries 10–13). The reaction conditions developed for the formation of either enantiomer of **1.3** are general across the range of boronic esters that we examined: of 20 examples, 18 provide high es. Therefore, by choosing the appropriate ligand, PCy$_3$ or SIMes, either enantiomer of a given product can be obtained from the same enantiomer of starting material.

***Table 2.2.*** Scope with respect to arylboronic ester[a]



**(*S*)-2.1**

| Entry | Ar | ligand[b] | yield (%)[c] | SM ee (%)[d] | product ee (%)[d] | es (%) | retention/ inversion |
|---|---|---|---|---|---|---|---|
| 1 | R' = OMe | PCy$_3$ | 88 | 93 | 92 | 98 | retention |
| 2 |  OMe | SIMes | 84 | 93 | 93 | >99 | inversion |
| 3 | NMe$_2$ | PCy$_3$ | 86 | 93 | 92 | 99 | retention |
| 4 | NMe$_2$ | SIMes | 71 | 93 | 92 | 98 | inversion |
| 5 | F | PCy$_3$ | 82 | 93 | 90 | 97 | retention |
| 6 | F | SIMes | 80 | 97 | 88 | 91 | inversion |
| 7 | CF$_3$ | PCy$_3$ | 88 | 97 | 57 | 59 | retention |
| 8 | CF$_3$ | SIMes | 70 | 93 | 91 | 98 | inversion |
| 9 | COMe | PCy$_3$ | 76 | 93 | 89 | 96 | retention |
| 10 | COMe | SIMes | 99 | 98 | 97 | 99 | inversion |
| 11 | CH$_2$OH | PCy$_3$ | 67 | 93 | 82 | 88 | retention |
| 12 | CH$_2$NHBoc | PCy$_3$ | 84 | 93 | 91 | 98 | retention |
| 13 | CH$_2$NHBoc | SIMes | 84 | 98 | 95 | 97 | inversion |
| 14 |  | PCy$_3$ | 86 | 93 | 89 | 96 | retention |
| 15[d] |  | SIMes | 75 | 98 | 92 | 94 | inversion |
| 16 |  | PCy$_3$ | 79 | 93 | 94 | >99 | retention |
| 17 |  | SIMes | 65 | 98 | 82 | 84 | inversion |
| 18 |  | PCy$_3$ | 90 | 93 | 93 | 99 | retention |
| 19 |  | SIMes | 71 | 93 | 92 | 98 | inversion |

[a]All data are average of two experiments unless otherwise indicated. [b]PCy3 (20 mol %), SIMes (11 mol %). [c]Isolated yield after column chromatography. [d]Determined by chiral SFC chromatog-raphy. [e]Data obtained from a single experiment.

## 2.4 Stereochemical Course of the Cross-Coupling Reaction

In order to demonstrate the stereochemical course of the reaction with either catalyst, we utilized X-ray crystallographic analysis. We first showed that the reaction proceeds with inversion when SIMes is used as ligand by comparison of the optical rotation of the triarylmethane

**(*R*)-1.8** with the literature value (Scheme 2.4a).[24,25] This product corresponds to net inversion at the benzylic carbon during the Suzuki–Miyaura cross-coupling reaction. In Chapter 1, we demonstrated that cross-coupling of Grignard reagents also results in inversion at the benzylic carbon and assigned the absolute configuration of **(*R*)-1.8** based on X-ray crystallographic analysis. The stereochemical course of the Suzuki–Miyaura cross-coupling reaction when $PCy_3$ is used as ligand provides the opposite enantiomer. Based on the absolute configuration of **(*S*)-2.5**, the reaction proceeds with retention at the benzylic carbon (Scheme 2.4b).

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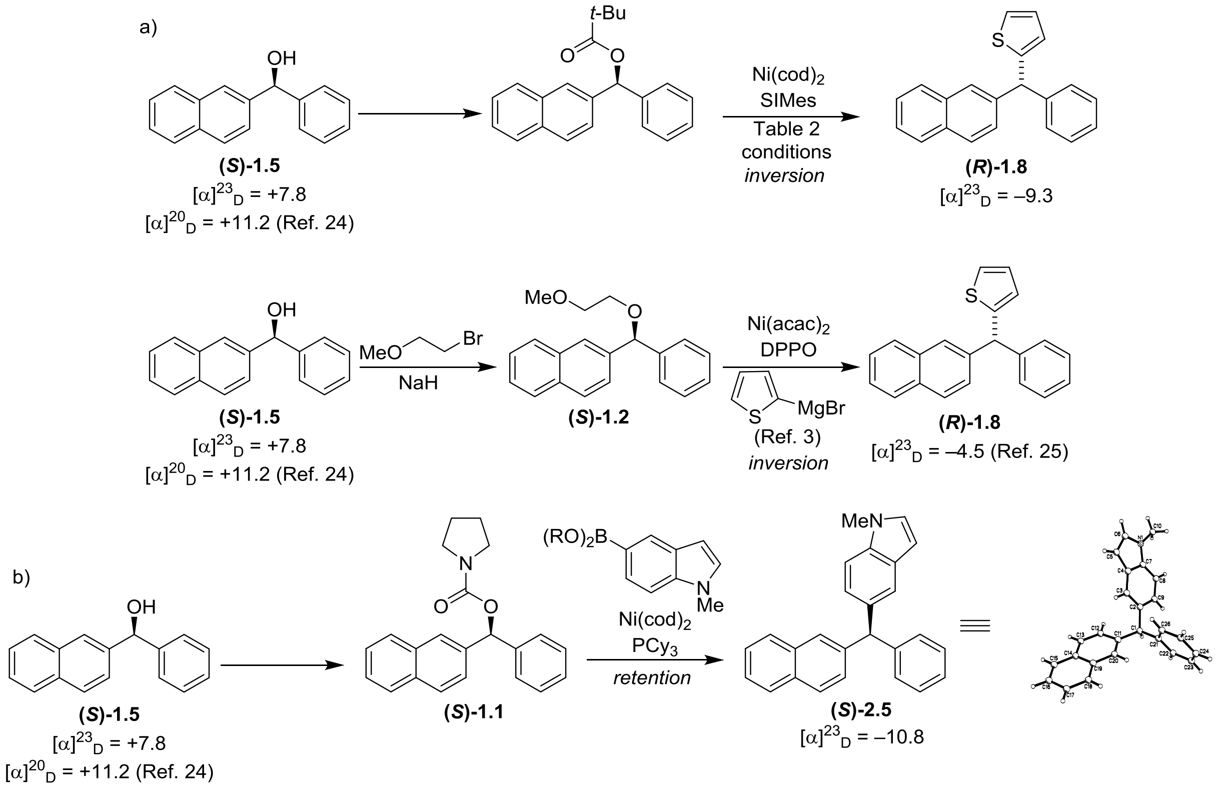
[24] For optical rotation data for **1.5**, see: (a) Yamamoto, Y.; Kurihara, K.; Miyaura, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 4414. (b) Shannon, J.; Bernier, D.; Rawson, D.; Woodward, S. *Chem. Commun.* **2007**, 3945. (c) Tjosaas, F.; Anthonsen, T.; Jacobsen, E. E. *ARKIVOC* **2008**, (6), 8190.

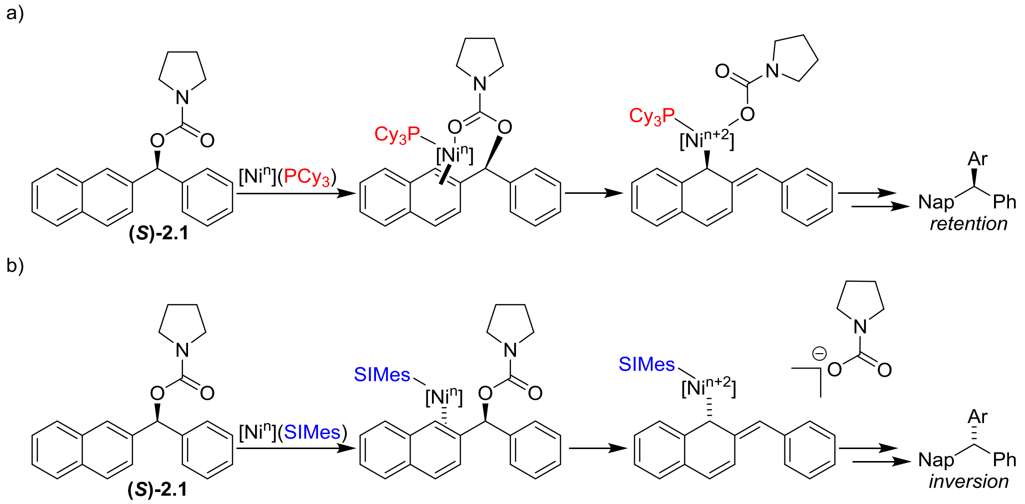
[25] For characterization data for **1.8** including optical rotation and X-ray crystallographic data, see: Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790.

***Scheme 2.4.*** Demonstration of stereochemical course of cross-coupling reaction



A mechanistic model for obtaining either product of retention or inversion is shown in scheme 2.5. We propose that when PCy3 ligand is employed, the carbamate leaving group coordinates to the nickel catalyst. This coordination event directs the oxidative addition of the catalyst to the substrate, resulting in oxidative addition with retention. Transmetalation followed by reductive elimination with retention leads to formation of product with overall retention. In contrast, when SIMes is used as ligand in the reaction, coordination of the carbamate to the catalyst prior to oxidative addition does not occur. Without precoordination of the nickel catalyst to the leaving group, oxidative addition proceeds with inversion, ultimately affording triarylmethane products with overall inversion.

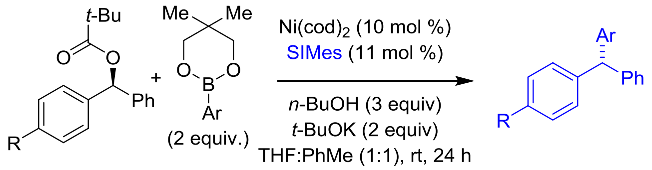
***Scheme 2.5.*** Proposed mechanistic model for stereodivergent pathways when employing $PCy_3$ or SIMes ligands

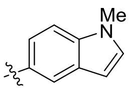
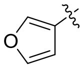
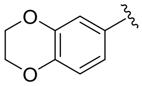


## 2.5 Scope of the Oxidative Addition Partner

We set as our goal the cross-coupling of oxidative additon partners that do not include a naphthylene moiety. These electrophiles are typically less reactive in cross-coupling reactions,[13c] and were not competent for triarylmethane synthesis via Kumada coupling.[13b] Indeed, neither the corresponding carbamates nor the use of $PCy_3$ as ligand provide acceptable yields of product. However, benzhydril pivalates undergo smooth cross-coupling under our optimized reaction conditions when SIMes is used as the ligand (Table 2.3). Efficient cross-coupling is achieved for pivalates with a range of arylboronic esters, including an indoleboronic ester (entries 1–3). Functionality is also tolerated on the electrophile: furan and benzodioxane substituted pivalates couple in good yield and excellent es (entries 4 and 5).

***Table 2.3.*** Scope of oxidative addition partner$^a$



| Entry | R' | Ar | yield (%)$^b$ | SM ee (%)$^c$ | product ee (%)$^c$ | es (%) |
|---|---|---|---|---|---|---|
| 1 | Ph | $p$-MeOC$_6$H$_4$ | 85 | 96 | 84 | 88 |
| 2 | Ph | $p$-(Me$_2$N)C$_6$H$_4$ | 75 | 82 | 79 | 96 |
| 3 | Ph |  | 66 | 96 | 96 | >99 |
| 4 |  |  | 80 | 93 | 87 | 94 |
| 5 |  |  | 60 | 93 | 93 | 99 |

$^a$All data are average of two experiments. $^b$Isolated yield after column chromatography. $^c$Determined by chiral SFC chromatography.

## 2.6 Conclusions

In summary, we have developed a nickel-catalyzed Suzuki-Miyaura cross-coupling reaction for the synthesis of enantioenriched triarylmethanes. Reactions proceed with high stereochemical fidelity. Achiral ligand identity controls whether the reaction proceeds with inversion or retention at the electrophilic carbon, therefore either enantiomer of product can be formed from a single enantiomer of starting material. This method expands the range of triarylmethanes that may be prepared in enantioenriched form, as simple benhydril pivalates and a variety of functionalized arylboronic esters, including heterocyclic compounds can be used in the reaction.

## 2.7 Experimental Details

*General Procedures*

All reactions were carried out under an atmosphere of $N_2$, or Ar when noted. All glassware was oven- or flame-dried prior to use. Tetrahydrofuran (THF), diethyl ether ($Et_2O$), dichloromethane ($CH_2Cl_2$), and toluene (PhMe) were degassed with Ar and then passed through two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; LaRoche Chemicals; activated under a flow of argon at 350 ºC for 12 h) to remove $H_2O$. All other solvents utilized were purchased “anhydrous” commercially, or purified as described. $^1H$ NMR spectra were recorded on Bruker DRX-400 (400 MHz $^1H$, 100 MHz $^{13}C$, 376.5 MHz $^{19}F$), GN-500 (500 MHz $^1H$, 125.7 MHz $^{13}C$), or CRYO-500 (500 MHz $^1H$, 125.7 MHz $^{13}C$) spectrometers. Proton chemical shifts are reported in ppm ($\delta$) relative to internal tetramethylsilane (TMS, $\delta$ 0.00). Data are reported as follows: chemical shift (multiplicity [singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), doublet of triplets (dt), doublet of doublet of triplets (ddt), triplet of triplets (tt), quartet (q), multiplet (m)], coupling constants [Hz], integration). Carbon chemical shifts are reported in ppm ($\delta$) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, $\delta$ 77.16 ppm). Unless otherwise indicated, NMR data were collected at 25 ºC. Infrared (IR) spectra were obtained on a Perkin-Elmer Spectrum 1000 FT-IR Systems and are reported in terms of frequency of absorption ($cm^{-1}$). Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 $F_{254}$ precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$, ceric ammonium molybdate (CAM), or *p*-anisaldehyde (PAA) solutions. Flash chromatography was performed using Silica Gel 60 (170-400 mesh) from Fisher Scientific. Melting points (m.p.) were obtained using a Mel-Temp melting point apparatus and are uncorrected. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Automatic Polarimeter. SFC determinations of enantiopurity were performed on a Berger Analytical instrument using a Daicel™ Chiralpak® column (OD-H, OJ-H, or AD-H; 100 bar, 50 °C, 215 nm). High resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center.

Boronic esters were prepared from the corresponding boronic acids and 2,2-dimethylpropane-1,3-diol.[26] Boronic acids were generously donated from Frontier, stored at 4 ºC, and used as received. 1,8-bis(1,5-cyclooctadiene)nickel was purchased from Strem, stored in a glovebox freezer (–20 °C) under an atmosphere of $N_2$, and used as received. Tricyclohexylphosphine ($PCy_3$), (1,3-Bis(2,6-diisopropylphenyl)-4,5-dihydroimidazoliumtetrafluoroborate (SIMes), and tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$) were purchased from Strem, stored in a glovebox, and used as received. All other reagents were purchased commercially and used as received.

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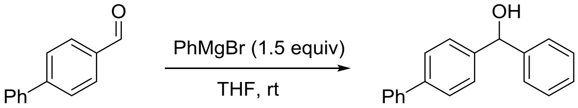
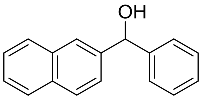
[26] Tivola, B. P.; Deagostino, A.; Prandi, C.; Venturello, P. *Org. Lett.* **2002**, *4*, 1275.

## Synthesis and Characterization of Substrates

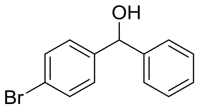
### A. *Representative procedure for racemic synthesis of diarylmethyl alcohols.*



***Rac*-2.7.** In a flame-dried round-bottom flask, to a solution of biphenyl-4-carboxaldehyde (1.04 g, 5.68 mmol, 1.00 equiv) in THF (10 mL) was added phenylmagnesium bromide (0.71 M in THF, 12 mL, 8.5 mmol, 1.5 equiv). After stirring at room temperature for 4 h, saturated ammonium chloride (10 mL) was added and the reaction was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 x 5 mL), dried over $MgSO_4$, and concentrated in vacuo to afford ***rac*-2.8** as a white solid (1.2 g, 4.7 mmol, 55%). Analytical data is consistent with the values listed for **(*S*)-2.8** (vide infra).

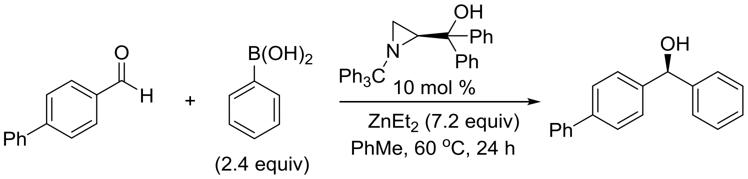


***Rac*-1.5.** Using the representative procedure A outlined above, the following amounts of reagents were used: 2-naphthaldehyde (6.24 g, 40.0 mmol, 1.00 equiv), phenylmagnesium bromide (58 mL, 0.83 M in THF, 48 mmol, 1.2 equiv), and THF (25 mL). The reaction mixture was purified by silica gel flash column chromatography (5–20% EtOAc/hexanes) to afford the product as a white solid (6.74 g, 28.7 mmol, 72%). Analytical data is consistent with the values listed for **(*S*)-1.5** (vide infra).



***Rac*-2.8**. Using the representative procedure A outlined above, the following amounts of reagents were used: 4-bromobenzaldehyde (1.85 g, 10.0 mmol, 1.00 equiv), phenylmagnesium bromide (7.0 mL, 1.7 M in THF, 12 mmol, 1.2 equiv), and THF (10 mL). The crude reaction mixture was purified by flash chromatography (5–20% EtOAc/hexanes) to afford the product as a white solid (1.92 g, 7.29 mmol, 73%). Analytical data is consistent with the values listed below for **(*S*)-2.9**.

B. *Representative procedure for enantioselective synthesis of diarylmethyl alcohols by asymmetric arylation.*



Enantioenriched alcohols were prepared according to a modified procedure of Braga and co-workers.[27]

**(*S*)-2.7**. To a solution of phenylboronic acid (0.732 g, 6.00 mmol, 2.40 equiv) in toluene (10 mL) was added diethylzinc (18 mL, 18 mmol, 1.0 M in toluene, 7.2 equiv), and the solution was allowed to stir at 60 °C for 12 h. Upon cooling to room temperature, (*S*)-(1-tritylaziridin-2-yl)diphenylmethanol (0.084 g, 0.06 mmol, 0.01 equiv) was added as a solution in toluene (5 mL) and the reaction mixture was allowed to stir for 10 minutes before the addition of a solution of

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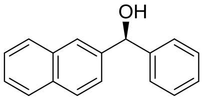
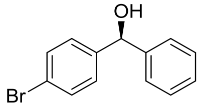
[27] Braga, A. R.; Paixao, M. W.; Westeman, B.; Schneider, P. H.; Wessjohan, L.A. *J. Org. Chem.* **2008**, *73*, 2879.

biphenyl-4-carboxaldehyde (0.456 g, 2.50 mmol, 1.00 equiv) in toluene (5 mL). After stirring 12 h at room temperature, 1 N hydrochloric acid (10 mL) was added and the product was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash column chromatography (0–1% EtOAc/benzene) and then recrystallized from hexanes and EtOAc to upgrade the ee (0.488 g, 1.85 mmol, 75% yield, 96% ee). **TLC $R_f$** = 0.2 (benzene); **m.p.** = 90–92 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.55 (m, 4H), 7.40 (m, 6H), 7.32 (m, 4H), 5.81 (s, 1H), 2.32 (d, *J* = 2.8, 1H); **$^{13}$C NMR** δ (100 MHz, $CDCl_3$) δ 143.8, 142.9, 140.9, 140.6, 128.9, 128.7, 127.8, 127.4, 127.38, 127.2, 127.1, 126.7, 76.1; **IR** (neat) 3361, 3029, 1408, 1006, 763 cm$^{-1}$; **HRMS (**TOF MS ES+) *m / z* calcd for $C_{19}H_{16}O$ $(M + Na)^+$ 283.1099, found 283.1110; **$[\alpha]^{23}{}_D$** +4.72 (*c* 1.10, $CHCl_3$); **SFC** analysis (AD-H, 15% IPA, 3 mL/min) indicated 96% ee: $t_R$ (major) = 18.9 minutes, $t_R$ (minor) = 20.5 minutes.

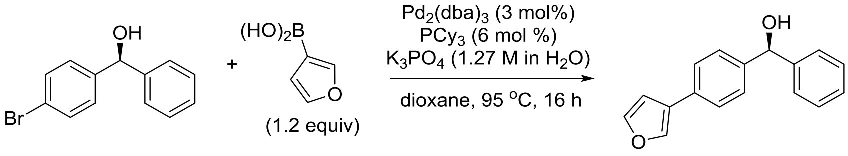


**(*S*)-1.5**. Using the representative procedure B outlined above, the following amounts of reagents were used: phenylboronic acid (0.732 g, 6.00 mmol, 2.4 equiv), diethylzinc (18 mL, 18 mmol, 1.0 M in toluene), (*S*)-diphenyl(1-tritylaziridin-2-yl)methanol (116 mg, 0.250 mmol, 0.100 equiv), and 2-naphthaldhyde (0.390 g, 2.50 mmol, 1.00 equiv). The product was purified by flash chromatography (10–20% EtOAc/hexanes) to afford the product as a white solid (0.608 g, 2.59 mmol, 93%, 89% ee). The product was then recrystallized from hexanes to upgrade the ee (99% ee). Analytical data is consistent with literature values.**Error! Bookmark not defined.** **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.82 (dt, *J* = 9.2, 2.6 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.49–7.40 (m, 5H), 7.35 (t, *J* = 7.0 Hz, 2H), 7.29 (dt, *J* = 7.4, 1.5 Hz, 1H), 6.02 (d, *J* = 3.5 Hz, 1H), 2.29 (d, *J* = 3.5 Hz, 1H); **$[\alpha]^{23}_{D}$** +7.8 (*c* 0.92, $CHCl_3$), literature $[\alpha]^{20}_{D}$ +11.2 (*c* 0.83, $CHCl_3$); **SFC** analysis (OD-H, 20% 2-propanol, 3 mL/min) indicated >99% ee: $t_R$ (major) = 6.4 min, $t_R$ (minor) = 7.3 min.



**(*S*)-2.8**. Using the representative procedure B outlined above, the following amounts of reagents were used: phenylboronic acid (0.732 g, 6.00 mmol, 2.4 equiv), diethylzinc (18 mL, 18 mmol, 1.0 M in toluene), (*S*)-(1-tritylaziridin-2-yl)diphenylmethanol (116 mg, 0.250 mmol, 0.100 equiv), and 4-bromobenzaldehyde (0.463 g, 2.50 mmol, 1.00 equiv). The product was purified by flash chromatography (10–20% EtOAc/hexane) to afford the product as a white solid (0.608 g, 2.31 mmol, 93%, 92% ee). The product was then recrystallized from hexanes to yield higher enantiopurity (96% ee). Analytical data is consistent with literature values.[28] **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.36–7.30 (m, 4H), 7.29–7.25 (m, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 5.76 (d, *J* = 3.3 Hz, 1H), 2.34 (d, *J* = 3.3 Hz, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 143.5, 142.8, 131.7, 128.8, 128.3, 128.0, 126.6, 121.5, 75.8; **$[\alpha]^{23}_{D}$** +17.5 (*c* 1.65, $CHCl_3$); **SFC** analysis (AD-H, 10% IPA, 2.5 mL/min) indicated 96% ee: $t_R$ (major) = 10.4 minutes, $t_R$ (minor) = 9.8 minutes.

*C. Representative procedure for the Suzuki cross-coupling of aryl bromide* ***(S)-2.9*** *with aryl boronic acids.*



**(*S*)-2.9.** The product was prepared according to a modified procedure by Fu and co-workers.[29] Tris(dibenzylideneacetone)dipalladium (55 mg, 0.060 mmol, 0.030 equiv) and tricyclohexylphosphine (39 mg, 0.14 mmol, 0.070 equiv) were weighed out into a flame dried two neck, round bottom flask inside a glovebox. The flask was fitted with septa, removed from the glovebox, and 3-furanboronic acid (0.262 g, 2.20 mmol, 1.10 equiv), **(*S*)-2.8** (0.526 g, 2.00 mmol, 1.00 equiv), aqueous potassium phosphate (2.7 mL, 3.4 mmol, 1.3 M in $H_2O$, 1.7 equiv) and dioxane (6 mL) were added. The reaction flask was fitted with a reflux condenser and heated to 95 °C for 16 h. After cooling, the solvent was removed under reduced pressure. The resultant residue was purified by flash column chromatography (10–20% EtOAc/hexane) to afford **(*S*)-2.9** as a yellow solid (0.437 g, 1.75 mmol, 87%, 97% ee). **TLC $R_f$** = 0.2 (4:1 hexane/EtOAc); **m.p.** = 97–99 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.45 (s, 2H), 7.43 (s, 1H), 7.37 (t, *J* = 8.2 Hz, 3H), 7.33 (t, *J* = 7.3 Hz, 3H), 7.27 (d, *J* = 7.4 Hz, 1H), 6.67 (s, 1H), 5.82 (s, 1H), 2.32 (s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 143.9, 143.8, 142.7, 138.6, 131.8, 128.7, 127.8, 127.1, 126.7, 126.2, 126.1, 108.9, 76.1; **IR** (neat) 3279, 1160, 1012, 780, 699 cm$^{-1}$; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{17}H_{14}O_2$ $(M + Na)^+$ 273.0891, found 273.0883; **$[\alpha]^{29}_D$** –37.3 (*c* 1.00,

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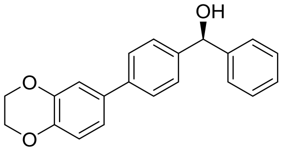
[28] Wu, X.; Liu, X.; Zhao, G. *Tetrahedron: Asymmetry* **2005**, *16*, 2299.

$CHCl_3$); **SFC** analysis (OD-H, 13% IPA, 2.5 mL/min) indicated 97% ee: $t_R$ (major) = 12.9 minutes, $t_R$ (minor) = 14.7 minutes.



**(*S*)-2.10.** Using representative procedure C outlined above, the following amounts of reagents were used: tris(dibenzylideneacetone)dipalladium (28 mg, 0.030 mmol, 0.030 equiv), tricyclohexylphosphine (20 mg, 0.07 mmol, 0.070 equiv), 1,4-benzodioxane-6-boronic acid (0.198 g, 1.10 mmol, 1.10 equiv), **(*S*)-2.8** (0.263 g, 1.00 mmol, 1.00 equiv), aqueous potassium phosphate (1.4 mL, 1.7 mmol, 1.3 M in $H_2O$, 1.7 equiv) and dioxane (3 mL). The product was purified by flash column chromatography (10–30% EtOAc/hexane) to afford **(*S*)-2.10** as a brown solid (0.296 g, 0.929 mmol, 93%, 96% ee). **TLC $R_f$** = 0.2 (4:1 hexane/EtOAc); **TLC $R_f$** = 0.3 (30% EtOAc/hexanes); **m.p.** = 108–110 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.7 Hz, 2H), 7.40 (q, *J* = 7.8 Hz, 4H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.27 (d, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 1.9 Hz, 1H), 7.04 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 5.85 (s, 1H), 4.36 (s, 4H), 2.35 (s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 143.9, 143.8, 143.3, 142.5, 140.0, 134.5, 128.7, 127.7, 127.1, 127.0, 126.6, 120.2, 117.7, 115.9, 76.2, 64.6, 64.5; **IR** (neat) 3550, 1494, 1304, 1284, 1070 $cm^{-1}$; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{21}H_{18}O_3$ $(M + Na)^+$ 341.1154, found 341.1147; **$[\alpha]^{29}_D$** +3.1 (*c* 1.04, $CHCl_3$); **SFC** analysis (AD-H, 14% IPA, 2.5 mL/min) indicated 96%: $t_R$ (major) = 6.9 minutes, $t_R$ (minor) = 8.8 minutes.

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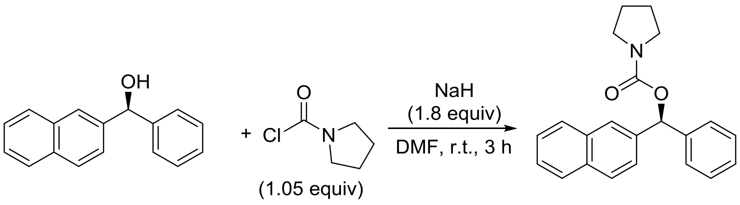
[29] Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1282.

*Preparation of protected carbinols.*



**(*S*)-2.1.** The product was prepared according to a modified procedure by Zhang and co-workers.[30] To a suspension of NaH (0.153 g, 6.37 mmol, 1.80 equiv) in DMF (3 mL) was added a solution of **(*S*)-1.5** (0.823 g, 3.54 mmol, 1.00 equiv) in DMF (2 mL) at 0 °C. The mixture was stirred for 1 h before addition of neat 1-pyrollidinecarbonyl chloride (0.41 mL, 3.7 mmol, 1.1 equiv) at room temperature. After stirring for 3 h, the reaction was quenched with saturated aqueous ammonium chloride (6 mL), and the product was extracted with methylene chloride (3 x 10 mL). The combined organics were washed with brine (5 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The product was purified by flash column chromatography (20% EtOAc/hexane) to afford **(*S*)-2.1** as a white solid (0.963 g, 2.91 mmol, 83%, 94% ee): **TLC $R_f$** = 0.2 (20% EtOAc/hexanes); **m.p.** = 151–153 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.82–7.77 (m, 3H), 7.47–7.44 (m, 3H), 7.41 (d, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.00 (s, 1H), 3.55 (t, *J* = 6.7 Hz, 2H), 3.40 (t, *J* = 6.7 Hz, 2H), 1.90 (dt, *J* = 13.3, 6.7 Hz, 2H), 1.84 (dt, *J* = 13.3, 6.7 Hz, 2H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 154.2, 141.4 138.7, 133.2, 133.0, 128.5, 128.4 128.3, 127.8, 127.7, 127.2, 126.3, 126.2, 126.1, 125.2, 77.4, 46.4, 46.0, 25.9, 25.0; **IR** (neat) 1690, 1412, 1102, 828, 765 cm$^{-1}$; **HRMS** (TOF MS ES+) *m / z* calcd

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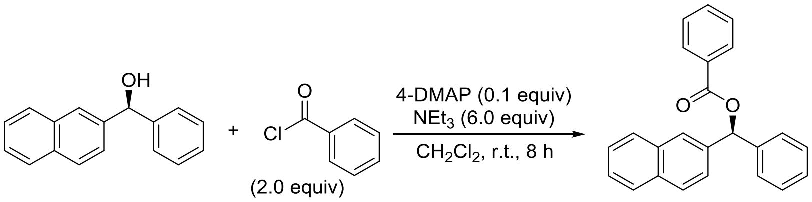
[30] DeKorver, K. A.; Johnson, W. L.; Zhang, Y.; Hsung, R. P.; Dai, H.; Deng, J.; Lohse, A. G.; Zhang, Y. S. *J. Org. Chem.* **2011**, *76*, 5092.

for $C_{22}H_{21}NO_2$ (M + Na)$^+$ 354.1470, found 354.1463; **[α]$^{29}$$_D$** +45.9 (*c* 1.15, $CHCl_3$); **SFC** analysis (OD-H, 18% IPA, 2.5 mL/min) indicated 93% ee: $t_R$ (major) = 7.1 minutes, $t_R$ (minor) = 6.6 minutes.



**(*S*)-2.4.** The product was prepared according to a modified procedure by Hassner and coworkers.[31] To a 25 mL round bottom flask was added alcohol **(*S*)-1.5** (0.175 g, 0.750 mmol, 1.00 equiv), and 4-(dimethylamino)pyridine (9.0 mg, 0.075 mmol, 0.10 equiv). The flask was evacuated and backfilled with nitrogen before addition of methylene chloride (6 mL), triethylamine (0.48 mL, 4.5 mmol, 6.0 equiv), and benzoyl chloride (0.18 mL, 1.5 mmol, 2.0 equiv). After stirring for 8 h, the reaction was quenched with 1 M HCl (6 mL), and the product was extracted with methylene chloride (3 x 10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash column chromatography (5–10% EtOAc/hexane) to afford **(*S*)-2.4** as a white solid (0.177 g, 0.523 mmol, 70%, 89% ee): **TLC R$_f$** = 0.4 (10% EtOAc/hexanes); **m.p.** = 91–93 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.9 Hz, 2H), 8.00 (s, 1H), 7.91–7.90 (m, 3H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.61–7.53 (m, 6H), 7.45 (t, *J* = 7.1 Hz, 2H), 7.39 (d, *J* = 7.2 Hz, 2H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 165.7, 140.3,

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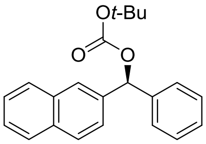
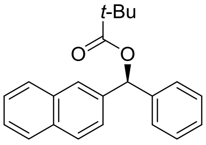
[31] Basel, Y.; Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368.

137.7, 133.3, 133.2, 133.1, 130.3, 130.0, 128.7, 128.6, 128.3, 128.2, 127.8, 127.4, 126.44, 126.40, 126.3, 125.1, 77.7; **IR** (neat) 1712, 1259, 1108, 732, 700 cm$^{-1}$; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{24}H_{18}O_2$ (M + Na)$^+$ 361.1205, found 361.1201; **[α]$^{29}$$_D$** +10.0 (*c* 0.99, $CHCl_3$); **SFC analysis** (OD-H, 10.0% IPA, 2.5 mL/min) indicated 89% ee: $t_R$ (major) = 6.5 minutes, $t_R$ (minor) = 6.3 minutes.

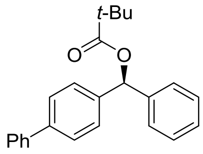


**(*S*)-2.2.** The product was prepared according to a modified procedure by Hassner and co-workers.[31] To a 25 mL round bottom flask was added alcohol **(*S*)-1.5** (0.234 g, 1.00 mmol, 1.00 equiv), and 4-(dimethylamino)pyridine (12 mg, 0.010 mmol, 0.10 equiv). The flask was evacuated and backfilled with nitrogen before addition of methylene chloride (8 mL), triethylamine (0.10 mL, 1.2 mmol, 1.2 equiv), and di-*tert*-butyl dicarbonate (0.228 g, 1.05 mmol, 1.05 equiv). After stirring for 8 h, the reaction was quenched with 1 M HCl (6 mL), and the product was extracted with methylene chloride (3 x 10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash column chromatography (5–10% EtOAc/hexane) to afford **(*S*)-2.2** as a white solid (0.284 g, 0.849 mmol, 85%, 88% ee): **TLC R$_f$** = 0.4 (9:1 hexane/EtOAc); **m.p.** = 90–92 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.83 (d, *J* = 7.0 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.48–7.45 (m, 2H), 7.43 (s, 1H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.27 (d, *J* = 7.7 Hz, 1H), 1.47 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 153.1, 140.1, 137.6, 133.2, 133.1, 128.7, 128.5, 128.3, 128.1, 127.8, 127.2, 126.4, 126.3, 126.0, 125.0, 82.7, 80.0, 27.9; **IR** (neat) 1742, 1270, 1251, 1150, 1081 cm$^{-1}$; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{22}H_{22}O_3$ (M + Na)$^+$ 357.1467, found

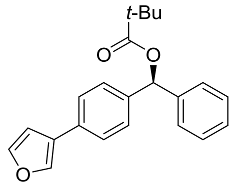
357.1467; **[α]$^{29}$D** –19.3 (*c* 0.90, $CHCl_3$); **SFC analysis** (AD-H, 5% IPA, 3.0 mL/min) indicated 88% ee: $t_R$ (major) = 5.6 minutes, $t_R$ (minor) = 6.1 minutes.



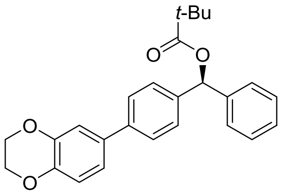
**(*S*)-2.3.** The product was prepared according to a modified procedure by Hassner and co-workers.[31] To a 25 mL round bottom flask was added alcohol **(*S*)-1.5** (0.281 g, 1.20 mmol, 1.20 equiv), and 4-(dimethylamino)pyridine (15 mg, 0.012 mmol, 0.10 equiv). The flask was evacuated and backfilled with nitrogen before addition of methylene chloride (8 mL), triethylamine (0.19 mL, 2.6 mmol, 2.2 equiv), and trimethylacetyl chloride (0.160 mL, 1.26 mmol, 1.05 equiv). After stirring for 8 h, the reaction was quenched with 1M HCl (6 mL), and the product was extracted with methylene chloride (3 x 10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash column chromatography (5–10% EtOAc/hexane) to afford **(*S*)-2.3** as a white solid (0.334 g, 1.05 mmol, 88%, 82% ee): **TLC R$_f$** = 0.5 (10% EtOAc/hexanes); **m.p.** = 80–83 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.82 (s, 2H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.48–7.45 (m, 2H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.1 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 1H), 1.27 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 177.4, 140.6, 138.0, 133.2, 133.0, 128.6, 128.5, 128.3, 127.9, 127.8, 127.1, 126.4, 126.3, 126.1, 125.0, 76.8, 39.1, 27.3; **IR** (neat) 1721, 1276, 1148, 1123, 823 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{22}H_{22}O_2$ $(M + Na)^+$ 341.1518, found 341.1526; **[α]$^{29}$D** –37.4 (*c* 1.18, $CHCl_3$); **SFC analysis** (AD-H, 5.0% IPA, 3.0 mL/min) indicated 82% ee: $t_R$ (major) = 6.8 minutes, $t_R$ (minor) = 7.1 minutes.



**(*S*)-2.11.** The product was prepared according to a modified procedure by Zhang and co-workers.[30] NaH (500 mg, 20.8 mmol, 4.00 equiv) was suspended in 40 mL of dry DMF and cooled to 0 °C. To this solution, alcohol **(*S*)-2.7** (1.28 g, 4.92 mmol, 1.00 equiv) in dry DMF (10 mL) was added dropwise. The mixture was allowed to stir at 0 °C for 30 minutes after which pivaloyl chloride (4.3 mL, 35 mmol, 7.0 equiv) was added dropwise. The reaction was stirred at 0 °C for 1.5 hours then warmed to room temperature and stirred for 22 hours. The reaction was quenched by consecutive addition of water (5 x 2 mL) and stirring for 3 minutes. The reaction was diluted with more water (10 mL) and the organics were extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by flash chromatography (0–1% $Et_2O$/petroleum ether) yielding **(*S*)-2.11** as a white solid (1.56 g, 4.53 mmol, 92%). **TLC $R_f$** = 0.4 (10% $Et_2O$:petroleum ether); **m.p.** = 109–110 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 6.1, 1.9 Hz, 4H), 7.35 (m, 10H), 6.87 (s, 1H), 1.27 (s, 9H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 177.4, 140.8, 140.6, 139.8, 128.9, 128.7, 127.9, 127.8, 127.5, 127.40, 127.38, 127.2, 127.0, 76.5, 39.1, 27.3; **IR** (neat) 3029, 2974, 1722, 1275, 1138 $cm^{-1}$; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{24}H_{24}O_2$ $(M + Na)^+$ 367.1674, found 367.1681; **$[\alpha]^{23}_D$** –23.6 (*c* 1.09, $CHCl_3$); **SFC** analysis (AD-H, 10% IPA, 3 mL/min) indicated 96% ee: $t_R$ (minor) = 4.0 minutes, $t_R$ (major) = 6.4 minutes.



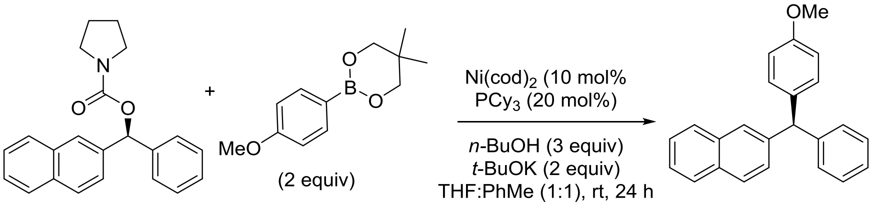
**(*S*)-2.12.** The product was prepared according to a modified procedure by Zhang and co-workers.[30] To a suspension of NaH (72 mg, 3.0 mmol, 2.0 equiv) in DMF (3 mL) was added a solution of **(*S*)-2.9** (0.374 g, 1.50 mmol, 1.00 equiv) in DMF (2 mL) at 0 ºC. The mixture was stirred for 1 h before addition of neat trimethylacetyl chloride (0.200 mL, 1.60 mmol, 1.05 equiv) at room temperature. After stirring for 3 h, the reaction was quenched with saturated aqueous ammonium chloride (6 mL), and the product was extracted with methylene chloride (3 x 10 mL). The combined organics were washed with brine (5 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The product was purified by flash column chromatography (30% $Et_2O$/hexane) to afford **(*S*)-2.12** as a pale yellow solid (0.427 g, 1.28 mmol, 85%, 93% ee): **TLC $R_f$** = 0.2 (4:1 hexane/$Et_2O$); **m.p.** = 105–108 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.45 (s, 2H), 7.43 (s, 1H), 7.35 (s, 4H), 7.33 (s, 2H), 7.29–7.26 (m, 1H), 1.26 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 177.4, 143.8, 140.6, 139.5, 138.7, 132.1, 128.6, 127.9, 127.6, 127.0, 126.2, 126.1, 108.9, 76.5, 39.0, 27.3; **IR** (neat) 1724, 1159, 1138, 757, 699 cm$^{-1}$; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{22}H_{22}O_3$ $(M + Na)^+$ 357.1467, found 357.1475; **$[\alpha]^{29}_D$** –26.0 (c 1.25, $CHCl_3$); **SFC** analysis (OJ-H, 8% IPA, 2.0 mL/min) indicated 93% ee: $t_R$ (major) = 3.6 minutes, $t_R$ (minor) = 4.2 minutes.



**(*S*)-2.13.** The product was prepared according to a modified procedure by Zhang and co-workers.[30] To a suspension of NaH (35 mg, 1.4 mmol, 1.8 equiv) in DMF (3 mL) was added a solution of **(*S*)-2.10** (0.254 g, 0.800 mmol, 1.00 equiv) in DMF (2 mL) at 0 °C. The mixture was stirred for 1 h before addition of neat trimethylacetyl chloride (0.103 mL, 0.840 mmol, 1.05 equiv) at room temperature. After stirring for 3 h, the reaction was quenched with saturated aqueous ammonium chloride (6 mL), and the product was extracted with methylene chloride (3 x 10 mL). The combined organics were washed with brine (5 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The product was purified by flash column chromatography (30% $Et_2O$/hexanes) to afford **(*S*)-2.13** as a tan solid (0.232 g, 0.576 mmol, 73%, 94% ee): **TLC $R_f$** = 0.1 (20% $Et_2O$/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.2 Hz, 2H), 7.37–7.32 (m, 6H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.08 (s, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.84 (s, 1H), 4.27 (s, 4H), 1.27 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 177.4, 143.8, 143.4, 140.7, 140.2, 139.3, 134.4, 128.7, 127.9, 127.4, 127.0, 126.9, 120.2, 117.7, 115.9, 76.5, 64.6, 64.5, 39.0, 27.3; **IR** (neat) 1723, 1494, 1309, 1147, 1068 $cm^{-1}$; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{26}H_{26}O_4$ $(M + Na)^+$ 425.1729, found 425.1715; **$[\alpha]^{29}_D$** –20.3 (c 0.96, $CHCl_3$); **SFC** analysis (OD-H, 30% MeOH, 2.5 mL/min) indicated 94% ee: $t_R$ (major) = 6.9 minutes, $t_R$ (minor) = 8.8 minutes.

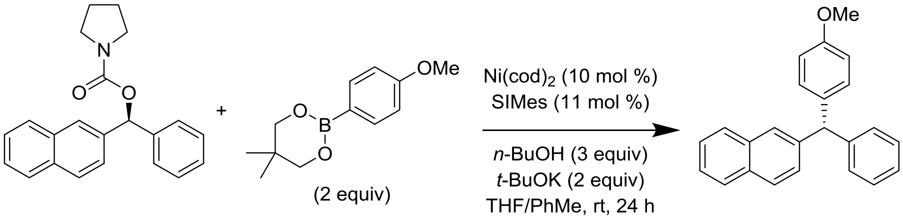
## Procedures for Cross-Coupling Reactions

### *A. Procedure for the synthesis of products with retention (Table 2).*



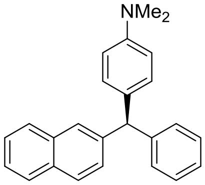
**(*R*)-1.3.** To a flame dried vial in a glovebox was added 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), tricyclohexylphosphine (11 mg, 0.040 mmol, 0.20 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 μL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-(4-methoxyphenyl)-1,3,2-dioxaborinane (88 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The reaction was stirred for 24 hours before removing the vial from the glovebox, opening to atmosphere, and running through a silica gel plug (1:1 $Et_2O$:hexane). The combined organics were concentrated in vacuo, internal standard (PhTMS, 0.20 mmol) was added and $^1H$ NMR yield was collected. The product was purified by flash chromatography (1–3% $Et_2O$/pentane) to afford **(*R*)-1.3** as a colorless oil. First run: (56.0 mg, 0.173 mmol, 86%, 93% ee). Second run: (56.4 mg, 0.174 mmol, 87%, 93% ee). Analytical data is consistent with literature values:[13b] **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.81–7.76 (m, 1H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.72–7.67 (m, 1H), 7.46 (s, 1H), 7.42 (dt, *J* = 9.5, 3.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 3H), 7.24–7.19 (m, 1H), 7.15 (d, *J* = 7.2 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 5.65 (s, 1H), 3.78 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 158.2, 144.1, 142.0, 136.0, 133.5, 132.2, 130.6, 129.6, 128.4, 128.2, 128.0, 127.9, 127.8, 127.6, 126.4, 126.1, 125.7, 113.8, 56.2, 55.3; **$[\alpha]^{23}_D$** –0.77 (*c* 2.70, $CHCl_3$); **SFC** analysis (AD-H, 15% IPA, 2.5 mL/min) indicated 93% ee: $t_R$ (major) = 13.9 minutes, $t_R$ (minor) = 13.2 minutes.

*B. Procedure for the synthesis of products with inversion of configuration.*

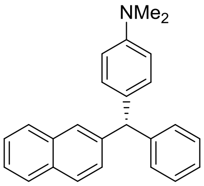


**(*S*)-1.3.** To a flame dried vial in a glovebox was added 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (8.27 mg, 0.0210 mmol, 0.105 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 μL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-(4-methoxyphenyl)-1,3,2-dioxaborinane (88 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The reaction was stirred for 24 hours before removing the vial from the glovebox, opening to atmosphere, and running through a silica gel plug (1:1 $Et_2O$:hexane). The combined organics were concentrated in vacuo, internal standard (PhTMS, 0.20 mmol) was added and $^1$H NMR yield was collected. The product was purified by flash chromatography (1–3% $Et_2O$/pentane) to afford **(*S*)-1.3** as a colorless oil. First run: (53.2 mg, 0.164 mmol, 82%, 93% ee). Second run: (56.0 mg, 0.173 mmol, 86%, 93% ee). Analytical data is consistent with the values listed above for **(*R*)-1.3**. **$[\alpha]^{23}_D$** +2.1 (*c* 2.70, $CHCl_3$); **SFC** analysis (AD-H, 15% IPA, 2.5 mL/min) indicated 90% ee: $t_R$ (major) = 13.2 minutes, $t_R$ (minor) = 13.9 minutes.

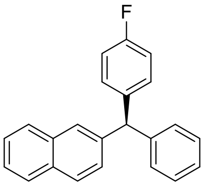
*Characterization Data for Products*



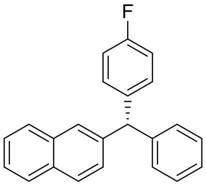
**(*R*)-1.18.** Using representative procedure A outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), tricyclohexylphosphine (11 mg, 0.040 mmol, 0.20 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 μL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-(4-dimethylaminophenyl)-1,3,2-dioxaborinane (83 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash chromatography (1–3% $Et_2O$/pentane) to afford the product as a colorless oil. First run: (49.8 mg, 0.148 mmol, 80%, 90% ee). Second run: (52.6 mg, 0.167 mmol, 84%, 90% ee). Analytical data is consistent with literature values:[13b] **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.80–7.75 (m, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.71–7.67 (m, 1H), 7.48 (s, 1H), 7.40 (dt, *J* = 9.4, 3.3 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 5.61 (s, 1H), 2.90 (s, 6H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 149.2, 144.6, 142.5, 133.6, 132.2, 131.8, 130.3, 129.6, 128.4 (2C), 128.0, 127.8, 127.7, 127.6, 126.3, 126.0, 125.6, 112.6, 56.2, 40.8; **IR** (neat) 3054, 3023, 2879, 1612, 1350 $cm^{-1}$; **$[\alpha]^{23}_D$** –9.43 (*c* 2.28, $CHCl_3$); **SFC** analysis (AD-H, 20% MeOH, 3 mL/min) indicated 92% ee: $t_R$ (major) = 4.2 min, $t_R$ (minor) = 4.8 min.



**(*S*)-1.18.** Using representative procedure B outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (8.27 mg, 0.0210 mmol, 0.105 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 μL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-(4-dimethylaminophenyl)-1,3,2-dioxaborinane (83 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash chromatography (1–3% $Et_2O$/pentane) to afford the product as a colorless oil. First run: (42.1 mg, 0.125 mmol 62%, 92% ee). Second run: (53.6 mg, 79%, 0.159 mmol, 92% ee). Analytical data is consistent with the values listed above for **(*R*)-1.18**. **$[\alpha]^{23}_{D}$** - +8.0 (*c* 1.00, $CHCl_3$); **SFC** analysis (AD-H, 20% MeOH, 3 mL/min) indicated 92% ee: $t_R$ (major) = 3.9 min, $t_R$ (minor) = 4.6 min.

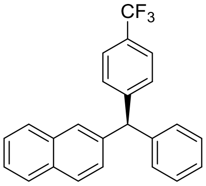


**(*R*)-1.19.** Using representative procedure A outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), tricyclohexylphosphine (11 mg, 0.040 mmol, 0.2 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 μL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-(4-fluorophenyl)-1,3,2-dioxaborinane (83 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash chromatography (1–3% $Et_2O$/pentane) to afford the product as a colorless oil. First run: (49.8 mg, 0.159 mmol, 80%, 90% ee). Second run: (52.6 mg, 0.168 mmol, 84%, 90% ee). Analytical data is consistent with literature values:[13b] **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.81–7.77 (m, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.71–7.67 (m, 1H), 7.45–7.39 (m, 3H), 7.31–7.21 (m, 4H), 7.15–7.07 (m, 4H), 6.97 (t, *J* = 8.8 Hz, 2H), 5.70 (s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 161.6 (d, *J* = 245 Hz), 143.6, 141.4, 139.5 (d, *J* = 3 Hz), 133.5, 132.3, 131.1 (d, *J* = 8 Hz), 129.6, 128.6, 128.1, 128.05, 127.99, 127.8, 127.7, 126.7, 126.2, 125.9, 115.3 (d, *J* = 21 Hz), 56.3; **$[\alpha]^{23}_D$** +4.5 (*c* 4.47, $CHCl_3$); **SFC** analysis (OJ-H, 12% IPA, 2.5 mL/min) indicated 90% ee: $t_R$ (major) = 9.4 minutes, $t_R$ (minor) = 8.7 minutes.

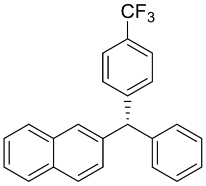


**(*S*)-1.19.** Using representative procedure B outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (8.27 mg, 0.0210 mmol, 0.105 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 µL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-(4-fluorophenyl)-1,3,2-dioxaborinane (83 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash chromatography (1–3% $Et_2O$/pentane) to afford the product as a colorless oil. First run: (49.8 mg, 0.159 mmol, 80%, 88% ee). Second run: (50.0 mg, 0.168 mmol, 84%, 88% ee). Analytical data is consistent with literature values:[13b] **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.81–

7.77 (m, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.71–7.67 (m, 1H), 7.45–7.39 (m, 3H), 7.31–7.21 (m, 4H), 7.15–7.07 (m, 4H), 6.97 (t, *J* = 8.8 Hz, 2H), 5.70 (s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 161.6 (d, *J* = 245 Hz), 143.6, 141.4, 139.5 (d, *J* = 3 Hz), 133.5, 132.3, 131.1 (d, *J* = 8 Hz), 129.6, 128.6, 128.1, 128.05, 127.99, 127.8, 127.7, 126.7, 126.2, 125.9, 115.3 (d, *J* = 21 Hz), 56.3; **$[\alpha]^{23}_{D}$** –3.6 (*c* 4.10, $CHCl_3$); **SFC** analysis (OJ-H, 12% IPA, 2.5 mL/min) indicated 88% ee: $t_R$ (major) = 9.7 minutes, $t_R$ (minor) = 10.6 minutes.

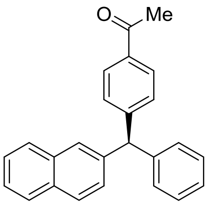


**(*S*)-2.14.** Using representative procedure A outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), tricyclohexylphosphine (11 mg, 0.040 mmol, 0.2 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 μL, 0.60 mmol, 3.00 equiv), 5,5-dimethyl-2-(4-trifluoromethylphenyl)-1,3,2-dioxaborinane (103 mg, 0.400 mmol, 2.00 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash column chromatography (1% $Et_2O$/pentane) to afford the product as a colorless oil. First run: (64.4 mg, 0.178 mmol, 89%, 57% ee). Second run: (62.1 mg, 0.172 mmol, 86%, 57% ee). **TLC $R_f$** = 0.4 (pentane); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.85–7.79 (m, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.74–7.68 (m, 1H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.49–7.41 (m, 3H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.29–7.22 (m, 4H), 7.14 (d, *J* = 7.6 Hz, 2H), 5.75 (s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 148.0, 142.9, 140.6, 133.5, 132.4, 130.0, 129.6, 128.9 (q, *J* = 32.4 Hz), 128.7, 128.3, 128.02, 128.00, 127.9, 127.7, 126.9, 126.4, 126.1, 125.5 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 271.9 Hz), 56.9; **IR** (neat) 3057, 1600, 1323, 1119 cm$^{-1}$; **HRMS** (TOF MS CI+) *m / z* calcd for $C_{15}H_{16}O$ $(M)^+$ 362.1282, found 362.1273; **[α]$^{23}$$_D$** +4.84 (*c* 0.915, $CHCl_3$); **SFC** analysis (AD-H, 5% IPA, 2.5 mL/min) indicated 57% ee: $t_R$ (major) = 7.7 minutes, $t_R$ (minor) = 7.0 minutes.

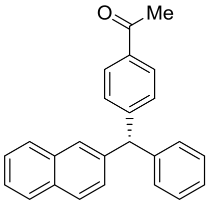


**(*S*)-2.14.** Using representative procedure B outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (8.27 mg, 0.0210 mmol, 0.105 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 µL, 0.60 mmol, 3.00 equiv), 5,5-dimethyl-2-(4-trifluoromethylphenyl)-1,3,2-dioxaborinane (103 mg, 0.400 mmol, 2.00 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash column chromatography (1% $Et_2O$/pentane) to afford the product as a colorless oil. First run: (52.8 mg, 0.146 mmol, 73%, 91% ee). Second run: (48.6 mg, 0.134 mmol, 67%, 90% ee). **TLC R$_f$** = 0.4 (pentane); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.85–7.79 (m, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.74–7.68 (m, 1H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.49–7.41 (m, 3H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.29–7.22 (m, 4H), 7.14 (d, *J* = 7.6 Hz, 2H), 5.75 (s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 148.0, 142.9, 140.6, 133.5, 132.4, 130.0, 129.6, 128.9 (q, *J* = 32.4 Hz), 128.7, 128.3, 128.02, 128.00, 127.9, 127.7, 126.9, 126.4, 126.1, 125.5 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 271.9 Hz), 56.9; **IR** (neat) 3057, 1600, 1323, 1119 cm$^{-1}$; **HRMS** (TOF MS CI+) *m / z* calcd for $C_{15}H_{16}O$ $(M)^+$ 362.1282, found 362.1273; **[α]$^{23}$$_D$** –16.5 (*c* 1.00, $CHCl_3$); **SFC** analysis

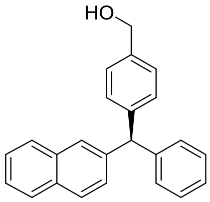
(AD-H, 5% IPA, 2.5 mL/min) indicated 89% ee: $t_R$ (major) = 6.6 minutes, $t_R$ (minor) = 7.3 minutes.



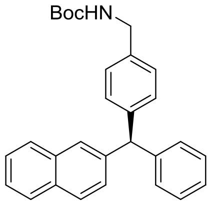
**(*R*)-2.15.** Using representative procedure A outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), tricyclohexylphosphine (11 mg, 0.040 mmol, 0.20 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 µL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-(4-acetylphenyl)-1,3,2-dioxaborinane (93 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the product as an amorphous white solid. First run: (50.8 mg, 0.151 mmol, 76%, 89% ee). Second run: (51.0 mg, 0.152 mmol, 76%, 89% ee). **TLC $R_f$** = 0.4 (20% EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.73–7.69 (m, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.63–7.57 (m, 1H), 7.40–7.30 (m, 3H), 7.21 (q, *J* = 7.7 Hz, 2H), 7.19–7.10 (m, 4H), 7.05 (d, *J* = 7.5 Hz, 2H), 5.65 (s, 1H), 2.47 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 197.9, 149.4, 142.9, 140.7, 135.6, 133.5, 132.3, 129.9, 129.6, 128.7, 128.6, 128.3, 127.97, 127.95, 127.9, 127.7, 126.9, 126.3, 126.0, 57.0, 26.7; **IR** (neat) 3055, 2923, 1679, 1600, 1506 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{25}H_{20}O$ $(M)^+$ 336.1514, found 3316.1514; **$[\alpha]^{23}_D$** –17.2 (*c* 2.3, $CHCl_3$); **SFC** analysis (OD-H, 20% IPA, 3.0 mL/min) indicated 89% ee: $t_R$ (major) = 6.3 minutes, $t_R$ (minor) = 5.9 minutes.



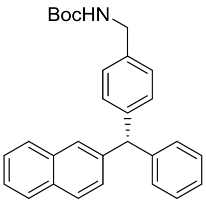
**(*S*)-2.15.** Using representative procedure B outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (8.67 mg, 0.0220 mmol, 0.11 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 μL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-(4-acetylphenyl)-1,3,2-dioxaborinane (93 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the product as an amorphous white solid. First run: (66.5 mg, 0.198 mmol, 99%, 97% ee). Second run: (66.0 mg, 0.196 mmol, 98%, 97% ee). **TLC $R_f$** = 0.4 (20% EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.73–7.69 (m, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.63–7.57 (m, 1H), 7.40–7.30 (m, 3H), 7.21 (q, *J* = 7.7 Hz, 2H), 7.19–7.10 (m, 4H), 7.05 (d, *J* = 7.5 Hz, 2H), 5.65 (s, 1H), 2.47 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 197.9, 149.4, 142.9, 140.7, 135.6, 133.5, 132.3, 129.9, 129.6, 128.7, 128.6, 128.3, 127.97, 127.95, 127.9, 127.7, 126.9, 126.3, 126.0, 57.0, 26.7; **IR** (neat) 3055, 2923, 1679, 1600, 1506 $cm^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{25}H_{20}O$ $(M)^+$ 336.1514, found 3316.1514; **$[\alpha]^{29}_D$** +5.05 (*c* 1.01, $CHCl_3$); **SFC** analysis (OD-H, 20% IPA, 3.0 mL/min) indicated 97% ee: $t_R$ (major) = 5.9 minutes, $t_R$ (minor) = 6.5 minutes.



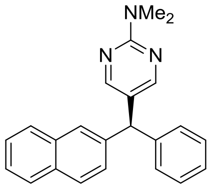
**(*R*)-2.16.** Using representative procedure A outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), tricyclohexylphosphine (11 mg, 0.040 mmol, 0.20 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 μL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-(4-hydroxymethylphenyl)-1,3,2-dioxaborinane (88 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash column chromatography (10% EtOAc/hexane) to afford the product as an oil. First run: (51.0 mg, 0.157 mmol, 79%, 82% ee). Second run: (50.0 mg, 0.154 mmol, 77%, 81% ee). **TLC R$_f$** = 0.2 (20% EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.82–7.76 (m, 1H), 7.74 (d, J = 8.7 Hz, 1H), 7.71–7.66 (m, 1H), 7.46 (s, 1H), 7.41 (dt, *J* = 9.5, 4.4 Hz, 2H), 7.34–7.24 (m, 5H), 7.24–7.19 (m, 1H), 7.15 (d, *J* = 8.4 Hz, 4H), 5.69 (s, 1H), 4.64 (d, *J* = 4 Hz, 2H), 1.77 (t, *J* = 4.5 Hz, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 143.7, 143.3, 141.5, 139.1, 133.5, 132.3, 129.9, 129.6, 128.5, 128.1, 128.02, 127.96, 127.9, 127.7, 127.3, 126.6, 126.1, 125.8, 65.2, 56.8; **IR** (neat) 3330 (br), 2953, 1600, 1506 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{24}H_{18}O$ (M – 2H)$^+$ 322.1358, found 322.1364; **[α]$^{23}$$_D$** –18.3 (*c* 1.66, $CHCl_3$); **SFC** analysis (AD-H, 30% MeOH, 2.5 mL/min) indicated 89% ee: t$_R$ (major) = 4.3 minutes, t$_R$ (minor) = 6.1 minutes.



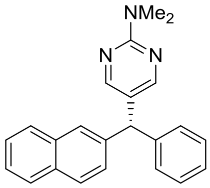
**(*R*)-2.17.** Using representative procedure A outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), tricyclohexylphosphine (11 mg, 0.040 mmol, 0.2 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 µL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-(4-{[(tert-butoxycarbonyl)amino]methyl}phenyl)-1,3,2-dioxaborinane (128 mg, 0.400 mmol, 2.00 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash column chromatography (15–25% $Et_2O$/hexanes) to afford the product as a white solid. First run: (71.0 mg, 0.168 mmol, 84%, 92% ee). Second run: (70.5 mg, 0.166 mmol, 83%, 89% ee). **TLC R$_f$** = 0.3 (20% EtOAc/hexanes); **m.p.** = 57 $^{o}$C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.81–7.76 (m, 1H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.71–7.66 (m, 1H), 7.45 (s, 1H), 7.41 (dt, *J* = 9.5, 1.0 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 3H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 5.67 (s, 1H), 4.83 (br s, 1H), 4.29 (d, *J* = 5.1 Hz, 2H), 1.45 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 156.0, 143.7, 142.9, 141.5, 137.1, 133.5, 132.2, 129.9, 129.6, 128.5, 128.1, 128.01, 127.95, 127.8, 127.64, 127.59, 126.5, 126.1, 125.8, 79.5, 56.7, 44.4, 28.5; **IR** (neat) 3346, 2876, 1698, 1600, 1365 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{29}H_{29}O_2N$ $(M + Na)^+$ 446.2096, found 446.2078; **$[\alpha]^{23}_D$** –14.3 (*c* 4.4, $CHCl_3$); **SFC** analysis (AS-H, 20% MeOH, 2.5 mL/min) indicated 92% ee: t$_R$ (major) = 4.3 minutes, t$_R$ (minor) = 4.7 minutes.



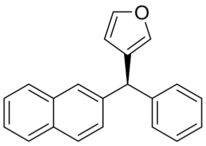
**(*S*)-2.17.** Using representative procedure B outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (8.27 mg, 0.0210 mmol, 0.105 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 µL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-(4-{[(tert-butoxycarbonyl)amino]methyl}phenyl)-1,3,2-dioxaborinane (128 mg, 0.400 mmol, 2.00 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash column chromatography (15–25% $Et_2O$/hexanes) to afford the product as a white solid. First run: (84.0 mg, 0.198 mmol, 99%, 96% ee). Second run: (75.4 mg, 0.178 mmol, 89%, 94% ee). **TLC R$_f$** = 0.3 (20% EtOAc/hexanes); **m.p.** = 57 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.81–7.76 (m, 1H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.71–7.66 (m, 1H), 7.45 (s, 1H), 7.41 (dt, *J* = 9.5, 1.0 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 3H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 5.67 (s, 1H), 4.83 (br s, 1H), 4.29 (d, *J* = 5.1 Hz, 2H), 1.45 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 156.0, 143.7, 142.9, 141.5, 137.1, 133.5, 132.2, 129.9, 129.6, 128.5, 128.1, 128.01, 127.95, 127.8, 127.64, 127.59, 126.5, 126.1, 125.8, 79.5, 56.7, 44.4, 28.5; **IR** (neat) 3346, 2876, 1698, 1600, 1365 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{29}H_{29}O_2N$ (M + Na)$^+$ 446.2096, found 446.2078; **[α]$^{29}_{D}$** +22.1 (*c* 1.01, $CHCl_3$); **SFC** analysis (AS-H, 20% MeOH, 2.5 mL/min) indicated 96% ee: $t_R$ (major) = 4.5 minutes, $t_R$ (minor) = 4.3 minutes.



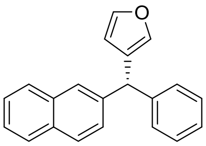
**(*S*)-2.18.** Using representative procedure A outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), tricyclohexylphosphine (11 mg, 0.040 mmol, 0.20 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 μL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-((dimethylamino)-5-pyrimidinylphenyl)-1,3,2-dioxaborinane (94 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash column chromatography (5% EtOAc/benzene) to afford the product as a white solid. First run: (58.2 mg, 0.171 mmol, 86%, 89% ee). Second run: (58.6 mg, 0.173 mmol, 86%, 89% ee). **TLC $\mathbf{R_f}$** = 0.5 (5% EtOAc/benzene); **m.p.** = 45–47 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.04 (s, 2H), 7.73–7.67 (m, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.64–7.59 (m, 1H), 7.40 (s, 1H), 7.33 (dt, *J* = 9.5, 3.5 Hz, 2H), 7.23–7.16 (m, 3H), 7.15–7.10 (m, 1H), 7.06 (d, *J* = 7.6 Hz, 2H), 2.39 (s, 1H), 3.08 (s, 6H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 161.3, 158.5, 142.9, 140.7, 133.5, 132.3, 129.8, 128.7, 128.3, 127.9, 127.67, 127.65, 127.6, 126.8, 126.3, 125.9, 123.6, 51.7, 37.2; **IR** (neat) 3054, 3023, 2861, 1599, 1531 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{23}H_{21}N_3$ $(M + H)^+$ 340.1814, found 340.1819; **$[\alpha]^{23}_D$** +15.7 (*c* 2.51, $CHCl_3$); **SFC** analysis (AD-H, 30% MeOH, 2.5 mL/min) indicated 89% ee: $t_R$ (major) = 4.6 minutes, $t_R$ (minor) = 6.4 minutes.



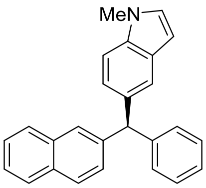
**(*S*)-2.18.** Using representative procedure B outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (8.27 mg, 0.0210 mmol, 0.105 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 μL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-((dimethylamino)-5-pyrimidinylphenyl)-1,3,2-dioxaborinane (94 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash column chromatography (5% EtOAc/benzene) to afford the product as a white solid (50.8 mg, 0.150 mmol, 75%, 92% ee). **TLC $R_f$** = 0.5 (5% EtOAc/benzene); **m.p.** = 45–47 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.04 (s, 2H), 7.73–7.67 (m, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.64–7.59 (m, 1H), 7.40 (s, 1H), 7.33 (dt, *J* = 9.5, 3.5 Hz, 2H), 7.23–7.16 (m, 3H), 7.15–7.10 (m, 1H), 7.06 (d, *J* = 7.6 Hz, 2H), 2.39 (s, 1H), 3.08 (s, 6H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 161.3, 158.5, 142.9, 140.7, 133.5, 132.3, 129.8, 128.7, 128.3, 127.9, 127.67, 127.65, 127.6, 126.8, 126.3, 125.9, 123.6, 51.7, 37.2; **IR** (neat) 3054, 3023, 2861, 1599, 1531 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{23}H_{21}N_3$ $(M + H)^+$ 340.1814, found 340.1819; **$[\alpha]^{29}_D$** –13.2 (*c* 0.675, $CHCl_3$); **SFC** analysis (AD-H, 30% MeOH, 2.5 mL/min) indicated 92% ee: $t_R$ (major) = 6.1 minutes, $t_R$ (minor) = 4.5 minutes.



**(*S*)-2.19.** Using representative procedure A outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), tricyclohexylphosphine (11 mg, 0.040 mmol, 0.20 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 μL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-(3-furanyl)-1,3,2-dioxaborinane (72 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash column chromatography (0.5–1% $Et_2O$/pentane) to afford the product as a white solid. First run: (45.8 mg, 0.161 mmol, 80%, 94% ee). Second run: (44.0 mg, 0.155 mmol, 78%, 94% ee). **TLC $R_f$** = 0.5 (1% $Et_2O$/pentane); **m.p.** = 65–67 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.83–7.69 (m, 3H), 7.60 (s, 1H), 7.47–7.37 (m, 3H), 7.34 (dd, *J* = 8.6, 1 Hz, 1H), 7.31–7.16 (m, 5H), 6.97 (s, 1H), 6.26 (s, 1H), 5.42 (s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 143.4, 143.3, 141.3, 141.1, 133.5, 132.4, 129.0, 128.6, 128.3, 128.1, 128.0, 127.7, 127.6, 127.1, 126.7, 126.2, 125.8, 111.6, 48.3; **IR** (neat) 3145, 3024, 1599, 1492 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{21}H_{16}O$ $(M)^+$ 284.1201, found 284.1203; **$[\alpha]^{23}_D$** +22.3 (*c* 1.67, $CHCl_3$); **SFC** analysis (AD-H, 5% IPA, 2.5 mL/min) indicated 94% ee: $t_R$ (major) = 12.2 minutes, $t_R$ (minor) = 11.3 minutes.

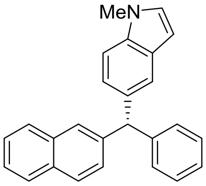


**(*R*)-2.19.** Using representative procedure B outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (8.27 mg, 0.0210 mmol, 0.105 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 µL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-(3-furanyl)-1,3,2-dioxaborinane (72 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash column chromatography (0.5–1% $Et_2O$/pentane) to afford the product as a white solid. First run: (35.5 mg, 0.125 mmol, 62.5 %, 82% ee). Second run: (38.7 mg, 0.136 mmol, 68%, 84% ee). **TLC R$_f$** = 0.5 (1% $Et_2O$/pentane); **m.p.** = 65–67 $^oC$; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.83–7.69 (m, 3H), 7.60 (s, 1H), 7.47–7.37 (m, 3H), 7.34 (dd, *J* = 8.6, 1 Hz, 1H), 7.31–7.16 (m, 5H), 6.97 (s, 1H), 6.26 (s, 1H), 5.42 (s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 143.4, 143.3, 141.3, 141.1, 133.5, 132.4, 129.0, 128.6, 128.3, 128.1, 128.0, 127.7, 127.6, 127.1, 126.7, 126.2, 125.8, 111.6, 48.3; **IR** (neat) 3145, 3024, 1599, 1492 $cm^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{21}H_{16}O$ $(M)^+$ 284.1201, found 284.1203; **$[\alpha]^{29}_D$** –22.0 (*c* 1.00, $CHCl_3$); **SFC** analysis (AD-H, 5% IPA, 2.5 mL/min) indicated 84% ee: $t_R$ (major) = 12.2 minutes, $t_R$ (minor) = 13.4 minutes.

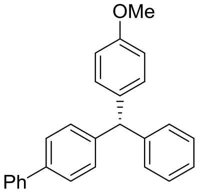


**(*S*)-2.5.** Using representative procedure A outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), tricyclohexylphosphine (11 mg, 0.040 mmol, 0.20 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 μL, 0.60 mmol, 3.0 equiv), 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-indole (97 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash column chromatography (5–20% $Et_2O$/hexane, 0.5% TEA) to afford the product as a white solid. First run: (63.4 mg, 0.182 mmol, 91%, 92% ee). Second run: (61.4 mg, 0.178 mmol, 89%, 93% ee). **TLC $R_f$** = 0.3 (20% $Et_2O$/hexane); **m.p.** = 49–52 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.80–7.75 (m, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.70–7.64 (m, 1H), 7.50 (s, 1H), 7.40 (dt, *J* = 9.3, 4.9 Hz, 2H), 7.37–7.31 (m, 2H), 7.27 (t, *J* = 7.3 Hz, 2H), 7.25–7.16 (m, 4H), 7.07 (dd, *J* = 8.7, 1.0 Hz, 1H), 6.98 (d, *J* = 2.9 Hz, 1H), 6.36 (d, *J* = 2.9 Hz, 1H), 5.83 (s, 1H), 3.72 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 144.7, 142.6, 135.6, 134.9, 133.5, 132.2, 129.8, 129.2, 128.55, 128.52, 128.4, 128.0, 127.9, 127.8, 127.6, 126.3, 126.0, 125.6, 123.9, 121.7, 109.2, 101.1, 57.1, 33.0; **IR** (neat) 3022, 2884, 1599, 1489 $cm^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{26}H_{21}N$ $(M + Na)^+$ 370.1572, found 370.1576; **$[\alpha]^{23}_D$** –10.8 (*c* 1.00, $CHCl_3$); **SFC** analysis (AD-H, 20% MeOH, 2.5 mL/min) indicated 93% ee: $t_R$ (major) = 8.1 minutes, $t_R$ (minor) = 9.0 minutes.

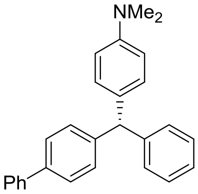
Single crystals suitable for X-ray crystallographic analysis were grown by slow diffusion of hexane into a solution of **(*S*)-2.5** in benzene at 4 °C.



**(*R*)-2.5.** Using representative procedure B outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (8.3 mg, 0.021 mmol, 0.11 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 μL, 0.60 mmol, 3.0 equiv), 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-indole (97 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.1** (66 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash column chromatography (5–20% $Et_2O$/hexanes, 0.5% TEA) to afford the product as a white solid. First run: (41.5 mg, 0.119 mmol, 57%, 92% ee). Second run: (57.0 mg, 0.164 mmol, 82%, 92% ee). Analytical data is consistent with the values listed above for **(*S*)-2.5**. **$[\alpha]^{23}_{D}$** +6.0 (*c* 0.9, $CHCl_3$); **SFC** analysis (AD-H, 20% MeOH, 2.5 mL/min) indicated 93% ee: $t_R$ (major) = 8.9 minutes, $t_R$ (minor) = 8.1 minutes.

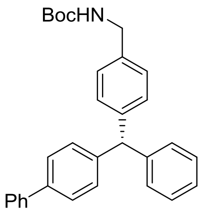


**(*R*)-2.20.** Using representative procedure B above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (8.3 mg, 0.0210 mmol, 0.11 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 μL, 0.60 mmol, 3.0 equiv), 5,5-dimethyl-2-(4-methoxyphenyl)-1,3,2-dioxaborinane (88 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.11** (69 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash column chromatography (1–3% $Et_2O$/hexanes) to afford the product as a colorless oil. First run: (54.8 mg, 0.156 mmol, 78%, 81% ee). Second run: (55.8 mg, 0.159 mmol, 80%, 81% ee). **TLC $R_f$** = 0.4 (10% $Et_2O$/Hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.2, 2H), 7.51 (d, *J* = 7.1, 2H), 7.42 (t, *J* = 7.1, 2H), 7.29 (m, 3H), 7.19 (m, 5H), 7.06 (d, *J* = 7.8, 2H), 6.83 (d, *J* = 8.2, 2H) 5.53 (s, 1H), 3.78 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 158.2, 144.3, 143.5, 141.0, 139.2, 136.2, 130.5, 129.9, 129.5, 128.9, 128.5, 128.3, 127.15, 127.14, 126.4, 113.9, 55.9, 55.4; **IR** (neat) 3020, 2996, 1508, 1244, 1030 $cm^{-1}$; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{26}H_{22}O$ $(M + Na)^+$ 350.1671, found 367.1679; **$[\alpha]^{23}_D$** +1.2 (*c* 1.01, $CHCl_3$), **SFC** analysis (AD-H, 10% MeOH, 2.5 mL/min) indicated 84% ee: $t_R$ (minor) = 21.5 minutes, $t_R$ (major) = 19.8 minutes.

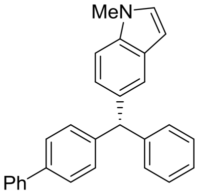


**(*R*)-2.21.** Using representative procedure B above, the following amounts and reagents: 1,8-bis(1,5-cyclooctadiene)nickel (8.3 mg, 0.030 mmol, 0.10 equiv), 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (12 mg, 0.030 mmol, 0.10 equiv), potassium *tert*-butoxide (64 mg, 0.60 mmol, 2.0 equiv), 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-*N*,*N*-dimethylaniline (134 mg, 0.600 mmol, 2.00 equiv), **(*S*)-2.11** (103 mg, 0.300 mmol, 1.00 equiv) and 1-butanol (54 µL, 0.90 mmol, 3.00 equiv). Purified by flash column chromatography (0–10% $Et_2O$/hexanes) to afford **(*R*)-2.21,** as a light yellow oil (55 mg, 0.15 mmol, 75%). **TLC $R_f$** =

0.3 (10% $Et_2O$/Hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.2, 2H), 7.49 (d, *J* = 8.2, 2H), 7.41 (t, *J* = 7.7, 2H), 7.29 (m, 3H), 7.27 (s, 1H) 7.21 (m, 5H), 7.02 (dd, *J* = 8.6, 2H) 6.67 (d, *J* = 8.9, 2H), 6.4 (d, *J* = 2.8, 1H), 5.5 (s, 1H), 2.9 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 149.2, 144.7, 143.9, 141.1, 139.0, 131.9, 130.2, 129.9, 129.5, 128.8, 128.4, 127.20, 127.15, 127.1, 126.3, 112.7, 55.7, 40.8; **IR** (neat) 3024, 2841, 2360, 1613, 1485, 1347, 763 cm$^{-1}$; **HRMS** (TOF MS EI+) *m / z* calcd for $C_{27}H_{25}O$ $(M + Na)^+$ 364.2065, found 364.2061; **$[\alpha]^{23}_D$** –2.9 (*c* 1.07, $CHCl_3$); **SFC** analysis (AD-H, 16% MeOH, 3.0 mL/min) indicated 79% ee: $t_R$ (minor) = 26.3 minutes, $t_R$ (major) = 11.6 minutes.

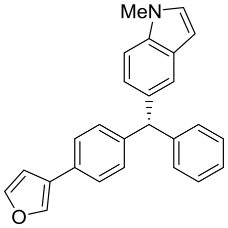


**(*S*)-2.22.** Using representative procedure B outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (8.67 mg, 0.022 mmol, 0.11 equiv), potassium *tert*-butoxide (45 mg, 0.4 mmol, 2.0 equiv), *tert*-butyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzylcarbamate (127.3 mg, 0.200 mmol, 2.00 equiv), **(*S*)-2.11** (68.9 mg, 0.200 mmol, 1.00 equiv) and 1-butanol (54 µL, 0.60 mmol, 3.0 equiv). Purified by flash column chromatography (0–15 % EtOAc/Hexane) to afford to afford the desired triarylmethane as a clear colorless oil (48.5 mg, 54%); **TLC R$_f$** = 0.1 (9:1 Hexanes:EtOAc); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 1.5, *J* = 8.4, 2H), 7.51 (d, *J* = 8.3, 2H), 7.39 (t, *J* = 7.5, 2H), 7.29 (m, 3H), 7.25 (m, 3H), 7.15 (m, 6H), 5.56 (s, 1H), 4.82 (s, 1H), 4.30 (d, *J* = 5.3, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 156.0, 143.9, 143.13, 143.05, 140.9, 139.3, 137.1, 129.9, 129.8, 129.5, 128.9, 128.5, 127.6, 127.3, 127.16, 127.14, 126.5, 56.3, 44.3, 28.5; **IR** (neat) 3294, 3028, 1695, 1486, 1316, 1016, 757 cm$^{-1}$; **HRMS** (TOF MS EI+) *m / z* calcd for $C_{31}H_{31}NO_2$ [M+Na]$^+$ 472.2253, found 472.2261. **[α]$^{29}$$_D$** –8.2 **SFC** analysis (AS-H, 20% MeOH, 2.5 mL/min) indicated 92% ee: $t_R$ (major) = 6.86 minutes, $t_R$ (minor) = 7.47 minutes.

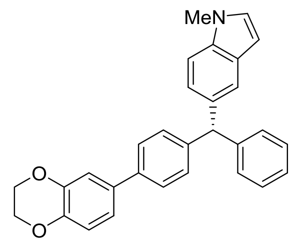


**(*R*)-2.23.** Using representative procedure B outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (8.27 mg, 0.0210 mmol, 0.105 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 µL, 0.60 mmol, 3.0 equiv), 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-indole (97 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.11** (69 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified by flash column chromatography (5–20% $Et_2O$/hexane, 0.5% TEA) to afford the product as a white solid. First run: (61.0 mg, 0.163mmol, 82%, 96% ee). Second run: (37.8 mg, 0.101 mmol, 51%, 96% ee). **TLC R$_f$** = 0.3 (10% EtOAc/hexanes); **m.p.** = 54–55 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.4, 2H), 7.49 (d, *J* = 8.2, 2H), 7.37 (t, *J* = 7.4, 2H), 7.27 (m, 3H), 7.26 (s, 1H) 7.22 (m, 9H), 7.07 (dd, *J* = 1.3, 8.6, 1H) 6.87 (d, *J* = 3.0, 1H), 6.37 (d, *J* = 2.8, 1H), 5.70 (s, 1H), 3.73 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 144.9, 144.2, 141.1, 138.9, 135.6, 135.1, 130.1, 129.7, 129.2, 128.8, 128.6, 128.4, 127.17, 127.15, 127.0, 126.2, 123.8, 121.6, 109.2, 101.1, 56.7, 32.9; **IR** (neat) 3025, 2360, 1486, 1449, 1246, 1006, 760 cm$^{-1}$;

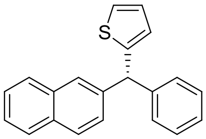
**HRMS** submitted; **$[\alpha]^{23}{}_D$** –5.2; **SFC** analysis (AD-H, 25% MeOH, 2.5 mL/min) indicated 96% ee: $t_R$ (major) = 11.3 minutes, $t_R$ (minor) = 16.1 minutes.



**(*R*)-2.24.** Using representative procedure B outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (8.27 mg, 0.0210 mmol, 0.105 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 µL, 0.60 mmol, 3.0 equiv), 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-indole (97 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.12** (67 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified twice by flash column chromatography (6% $Et_2O$/hexane and then 60% benzene/pentane) to afford the desired triarylmethane as a white solid. First run: (58.5 mg, 0.161 mmol, 80%, 87% ee). Second run: (58.5 mg, 0.161 mmol, 80%, 87% ee). **TLC $R_f$** = 0.6 (40% pentane/benzene); **m.p.** = 149–151 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.34 (s, 1H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.23 (s,1H), 7.18 (t, *J* = 7.4 Hz, 2H), 7.15–7.09 (m, 2H), 7.07 (t, *J* = 7.4 Hz, 4H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.90 (d, *J* = 2.8 Hz, 1H), 6.57 (s, 1H), 6.29 (d, *J* = 2.8 Hz, 1H), 5.58 (s, 1H), 3.63 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 144.9, 143.9, 141.7, 138.5, 135.6, 135.0, 130.3, 130.1, 129.7, 129.2, 128.5, 128.3, 126.4, 126.2, 125.8, 123.7, 121.5, 109.2, 109.0, 101.1, 56.7, 33.0; **IR** (neat) 3145, 3024, 1599, 1492 cm$^{-1}$; **$[\alpha]^{23}{}_D$** –3.1 (*c* 2.24, $CHCl_3$); **HRMS** submitted; **SFC** analysis (OJ-H, 30% MeOH, 3.0 mL/min) indicated 87% ee: $t_R$ (major) = 23.6 minutes, $t_R$ (minor) = 26.2 minutes.



**(*R*)-2.25.** Using representative procedure B outlined above, the following amounts of reagents were used: 1,8-bis(1,5-cyclooctadiene)nickel (5.5 mg, 0.020 mmol, 0.10 equiv), 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (8.27 mg, 0.0210 mmol, 0.105 equiv), potassium *tert*-butoxide (45 mg, 0.40 mmol, 2.0 equiv), 1-butanol (54 μL, 0.60 mmol, 3.0 equiv), 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-indole (97 mg, 0.40 mmol, 2.0 equiv), **(*S*)-2.13** (67 mg, 0.20 mmol, 1.0 equiv), tetrahydrofuran (1 mL) and toluene (1 mL). The product was purified twice by flash column chromatography (6% EtOAc/hexanes and then 70% benzene/pentane) to afford the desired triarylmethane as a white solid. First run: (51.4 mg, 0.119 mmol, 60%, 93% ee). Second run: (52.0 mg, 0.121 mmol, 60%, 93% ee). **TLC R$_f$** = 0.3 (40% pentane/benzene); **m.p.** = 81–84 °C; **$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.43 (s, *J* = 8.0 2H), 7.33 (s, 1H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.24 (s,1H), 7.22–7.14 (m, 5H), 7.10 (s, 1H), 7.06 (dt, *J* = 8.2, 2.0 Hz, 2H), 7.01 (d, *J* = 2.7 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.39 (d, *J* = 2.5 Hz, 1H), 5.69 (s, 1H), 4.27 (s, 4H), 3.76 (s, 3H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 144.9, 143.8, 143.7, 143.1, 138.4, 135.6, 135.1, 134.8, 130.0, 129.7, 129.2, 128.6, 128.4, 126.6, 126.2, 123.8, 121.6, 120.2, 117.6, 115.8, 109.2, 101.1, 64.58, 64.56, 56.7, 33.0; **IR** (neat) 2916, 1586, 1513, 1449 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{30}H_{25}O_2N$ (M + Na)$^+$ 454.1783, found 454.1772; **[α]$^{23}_{D}$** –8.2 (*c* 2.36, CHCl$_3$); **SFC** analysis (OD-H, 25% IPA, 2.5 mL/min) indicated 93% ee: t$_R$ (major) = 23.6 minutes, t$_R$ (minor) = 26.2 minutes.

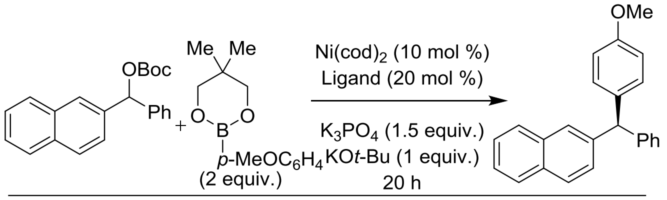


**(*R*)-1.8.** Prepared according to general procedure B using the following amounts and reagents: Ni(cod)$_2$ (2.8 mg, 0.010 mmol, 0.10 equiv), 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (3.9 mg, 0.010 mmol, 0.10 equiv), potassium *tert*-butoxide (22 mg, 0.20 mmol, 2.0 equiv), 5,5-dimethyl-2-(thiophen-2-yl)-1,3,2-dioxaborinane (39.2 mg, 0.200 mmol, 2.00 equiv), **(*S*)-2.1** (33.1 mg, 0.100 mmol, 1.00 equiv) and 1-butanol (27 µL, 0.30 mmol, 3.0 equiv). Purified by flash column chromatography (0–5% Et$_2$O/hexanes) to afford the desired triarylmethane as a yellow solid (11.4 mg, 0.0379 mmol, 38%). Analytical data is consistent with literature values.[13b] **$^1$H NMR** (400 MHz, CDCl$_3$) δ 7.84–7.72 (m, 3H), 7.61 (s, 1H), 7.37–7.41 (m, 2H), 7.37 (dd, *J* = 1.6, 8.5), 7.34–7.20 (m, 6H), 6.95 (t, *J* = 4.3), 6.73 (d, *J* = 3.3), 5.84 (s, 1H); **$^{13}$C NMR** δ (125 MHz, CDCl$_3$) δ 147.8, 143.7, 141.4, 133.5, 132.4, 129.1, 128.6, 128.2, 128.1, 127.7, 127.5, 127.4, 126.9, 126.8, 126.7, 126.2, 125.9, 124.8, 52.3 **$[\alpha]^{25}_{D}$** –9.3 (*c* 0.57, CHCl$_3$).

## Tables of results using alternative ligands and bases.

Other ligands and bases were tested under reaction conditions similar to Table 2.1. Representative examples are shown below.

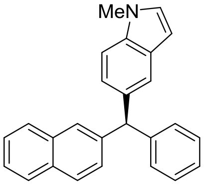
***Table 2.4.*** Examination of additional ligands in the cross-coupling reaction



| Entry | ligand | yield[a] |
|---|---|---|
| 1 | DPEphos (Bis[(2-diphenylphosphino)phenyl] ether) | < 5% |
| 2 | Cy-DPEphos (Bis[(2-dicyclohexylphosphino)phenyl] ether) | < 5% |
| 3 | DPPO (1,8-bis(diphenylphosphino)octane) | 13% |
| 4 | $PPh_3$ (triphenylphosphine) | 22% |
| 5 | $P(t\text{-}Bu)_3$ tri-*tert*-butylphosphine | < 5% |
| 6 | XPhos (2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) | < 5% |
| 7 | SPhos (2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl) | < 5% |
| 8 | SIPr-$HBF_4$ (1,3-Bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate | 31% |
| 9 | tricyclohexylphosphine | 86% |
| 10 | $PCy_3$ tricylohexylphosphine (11 mol %) | 83% |
| 11 | SIMes-$HBF_4$ 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate | 84% |
| 12 | None | < 5% |

[a] Determined by $^1$H NMR analysis using an internal standard ($PhSiMe_3$).

## Crystallographic Data



X-ray Data Collection, Structure Solution and Refinement for (*S*)-**2.5.**

A colorless crystal of approximate dimensions 0.22 x 0.28 x 0.33 mm was mounted on a glass fiber and transferred to a Nonius FR-591 rotating-anode system with Bruker APEX detector (Montels Optics). The APEX2[32] program package was used to determine the unit-cell parameters and for data collection (2.0 sec/frame scan time). The raw frame data was processed using SAINT[33] and SADABS[34] to yield the reflection data file. Subsequent calculations were carried out using the SHELXTL[35] program. The diffraction symmetry was 2/*m* and the systematic absences were consistent with the monoclinic space groups $P2_1$ and $P2_1/m$. It was later determined that space group $P2_1$ was correct.

The structure was solved by direct methods and refined on $F^2$ by full-matrix least-squares techniques. The analytical scattering factors[36] for neutral atoms were used throughout the analysis. Hydrogen atoms were located from a difference-Fourier map and refined (x,y,z and $U_{iso}$).

---

[32] APEX2 Version 2012.4-0,. Bruker AXS, Inc.; Madison, WI 2012.

[33] SAINT Version 7.68a, Bruker AXS, Inc.; Madison, WI 2009.

[34] Sheldrick, G. M. SADABS, Version 2008/1, Bruker AXS, Inc.; Madison, WI 2008.

[35] Sheldrick, G. M. SHELXTL, Version 2012/9, 2012.

[36] International Tables for X-Ray Crystallography 1992, Vol. C., Dordrecht: Kluwer Academic Publishers.

At convergence, wR2 = 0.0770 and Goof = 1.043 for 328 variables refined against 3454 data (0.82Å), R1 = 0.0297 for those 3412 data with $I > 2.0\sigma(I)$. The absolute structure was assigned according to the methods of Parsons and Flack[37,38].

Definitions:

$wR2 = [\Sigma[w(F_o^2-F_c^2)^2] / \Sigma[w(F_o^2)^2] ]^{1/2}$

$R1 = \Sigma||F_o|-|F_c|| / \Sigma|F_o|$

$Goof = S = [\Sigma[w(F_o^2-F_c^2)^2] / (n-p)]^{1/2}$ where n is the number of reflections and p is the total number of parameters refined.

The thermal ellipsoid plot is shown at the 50% probability level.

---

[37] Flack, H. D. Acta. Cryst., A39, 876-881, 1983.

[38] Parsons, S., Flack, H. D. Acta. Cryst., A60, s61, 2004.

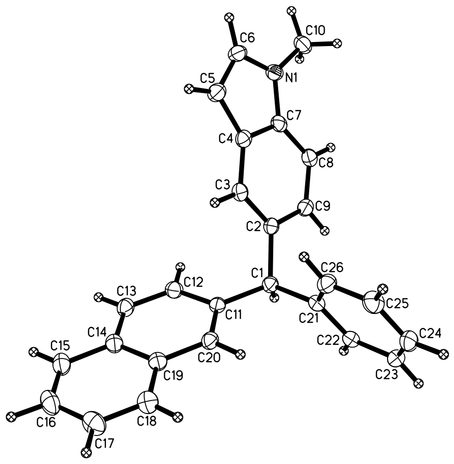


***Table 2.5.*** Crystal data and structure refinement for (*S*)-**2.5**.

| | | |
|---|---|---|
| Identification code | (*S*)-**2.5** (Michael Harris) | |
| Empirical formula | $C_{26} H_{21} N$ | |
| Formula weight | 347.44 | |
| Temperature | 173(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | $P2_1$ | |
| Unit cell dimensions | a = 8.6116(2) Å | $\alpha$= 90°. |
| | b = 11.5924(2) Å | $\beta$= 100.1452(7)°. |
| | c = 9.6267(2) Å | $\gamma$ = 90°. |
| Volume | 946.00(3) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.220 $Mg/m^3$ | |
| Absorption coefficient | 0.534 $mm^{-1}$ | |

|  |  |
|---|---|
| F(000) | 368 |
| Crystal color | colorless |
| Crystal size | 0.331 x 0.280 x 0.218 mm$^3$ |
| Theta range for data collection | 4.666 to 69.774° |
| Index ranges | $-9 \leq h \leq 10$, $-14 \leq k \leq 14$, $-11 \leq l \leq 11$ |
| Reflections collected | 24745 |
| Independent reflections | 3454 [R(int) = 0.0343] |
| Completeness to theta = 67.679° | 99.4 % |
| Absorption correction | Semi-empirical from equivalents |
| Refinement method | Full-matrix least-squares on F$^2$ |
| Data / restraints / parameters | 3454 / 1 / 328 |
| Goodness-of-fit on F$^2$ | 1.043 |
| Final R indices [I>2sigma(I) = 3412 data] | R1 = 0.0297, wR2 = 0.0765 |
| R indices (all data, 0.82Å) | R1 = 0.0302, wR2 = 0.0770 |
| Absolute structure parameter | -0.10(16) |
| Largest diff. peak and hole | 0.157 and -0.146 e.Å$^{-3}$ |

***Table 2.6.*** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for (*S*)-**2.5**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| N(1) | 13910(2) | 6748(1) | 9901(2) | 23(1) |
| C(1) | 9548(2) | 10396(1) | 8488(2) | 19(1) |
| C(2) | 10723(2) | 9410(1) | 8861(2) | 19(1) |
| C(3) | 10709(2) | 8428(2) | 8045(2) | 20(1) |
| C(4) | 11837(2) | 7559(2) | 8465(2) | 20(1) |
| C(5) | 12142(2) | 6453(2) | 7916(2) | 25(1) |
| C(6) | 13398(2) | 6000(2) | 8817(2) | 26(1) |
| C(7) | 12970(2) | 7715(2) | 9709(2) | 21(1) |
| C(8) | 13009(2) | 8707(2) | 10529(2) | 22(1) |
| C(9) | 11880(2) | 9540(2) | 10092(2) | 21(1) |
| C(10) | 15216(2) | 6573(2) | 11064(2) | 28(1) |
| C(11) | 7966(2) | 10000(1) | 7634(2) | 19(1) |
| C(12) | 7165(2) | 9073(2) | 8182(2) | 22(1) |
| C(13) | 5735(2) | 8692(2) | 7493(2) | 24(1) |
| C(14) | 4987(2) | 9213(2) | 6213(2) | 22(1) |
| C(15) | 3499(2) | 8845(2) | 5466(2) | 27(1) |
| C(16) | 2814(2) | 9384(2) | 4243(2) | 31(1) |
| C(17) | 3574(2) | 10329(2) | 3729(2) | 31(1) |
| C(18) | 5014(2) | 10701(2) | 4422(2) | 26(1) |
| C(19) | 5763(2) | 10152(2) | 5674(2) | 21(1) |
| C(20) | 7255(2) | 10522(2) | 6409(2) | 21(1) |
| C(21) | 10306(2) | 11392(1) | 7807(2) | 20(1) |
| C(22) | 10357(2) | 12484(2) | 8399(2) | 21(1) |
| C(23) | 11043(2) | 13406(2) | 7801(2) | 25(1) |
| C(24) | 11687(2) | 13242(2) | 6596(2) | 28(1) |
| C(25) | 11653(2) | 12143(2) | 5993(2) | 29(1) |
| C(26) | 10969(2) | 11228(2) | 6599(2) | 24(1) |

***Table 2.7.*** Bond lengths [Å] and angles [°] for (*S*)-**2.5**.

| | |
|---|---|
| N(1)-C(6) | 1.369(3) |
| N(1)-C(7) | 1.376(2) |
| N(1)-C(10) | 1.455(2) |
| C(1)-C(2) | 1.527(2) |
| C(1)-C(21) | 1.529(2) |
| C(1)-C(11) | 1.532(2) |
| C(1)-H(1A) | 0.96(2) |
| C(2)-C(3) | 1.382(2) |
| C(2)-C(9) | 1.416(2) |
| C(3)-C(4) | 1.409(2) |
| C(3)-H(3A) | 0.96(2) |
| C(4)-C(7) | 1.417(2) |
| C(4)-C(5) | 1.428(2) |
| C(5)-C(6) | 1.367(3) |
| C(5)-H(5A) | 0.96(3) |
| C(6)-H(6A) | 0.95(3) |
| C(7)-C(8) | 1.392(3) |
| C(8)-C(9) | 1.382(2) |
| C(8)-H(8A) | 0.95(2) |
| C(9)-H(9A) | 0.95(3) |
| C(10)-H(10A) | 0.96(3) |
| C(10)-H(10B) | 0.95(3) |
| C(10)-H(10C) | 0.94(3) |
| C(11)-C(20) | 1.370(2) |
| C(11)-C(12) | 1.427(2) |
| C(12)-C(13) | 1.365(3) |
| C(12)-H(12A) | 1.00(3) |
| C(13)-C(14) | 1.421(3) |
| C(13)-H(13A) | 0.96(3) |
| C(14)-C(15) | 1.420(3) |
| C(14)-C(19) | 1.421(2) |
| C(15)-C(16) | 1.370(3) |
| C(15)-H(15A) | 0.97(3) |
| C(16)-C(17) | 1.410(3) |
| C(16)-H(16A) | 0.99(3) |
| C(17)-C(18) | 1.371(3) |
| C(17)-H(17A) | 0.97(3) |
| C(18)-C(19) | 1.414(3) |
| C(18)-H(18A) | 0.94(3) |
| C(19)-C(20) | 1.420(2) |
| C(20)-H(20A) | 0.97(3) |
| C(21)-C(22) | 1.386(2) |
| C(21)-C(26) | 1.396(3) |

| | |
|---|---|
| C(22)-C(23) | 1.394(3) |
| C(22)-H(22A) | 0.95(3) |
| C(23)-C(24) | 1.384(3) |
| C(23)-H(23A) | 0.95(3) |
| C(24)-C(25) | 1.398(3) |
| C(24)-H(24A) | 0.95(3) |
| C(25)-C(26) | 1.390(3) |
| C(25)-H(25A) | 0.94(3) |
| C(26)-H(26A) | 0.94(3) |
| | |
| C(6)-N(1)-C(7) | 108.16(15) |
| C(6)-N(1)-C(10) | 126.79(15) |
| C(7)-N(1)-C(10) | 125.05(16) |
| C(2)-C(1)-C(21) | 110.53(14) |
| C(2)-C(1)-C(11) | 113.04(14) |
| C(21)-C(1)-C(11) | 113.75(14) |
| C(2)-C(1)-H(1A) | 105.5(14) |
| C(21)-C(1)-H(1A) | 108.4(14) |
| C(11)-C(1)-H(1A) | 105.1(13) |
| C(3)-C(2)-C(9) | 119.84(15) |
| C(3)-C(2)-C(1) | 122.97(15) |
| C(9)-C(2)-C(1) | 117.18(15) |
| C(2)-C(3)-C(4) | 119.34(15) |
| C(2)-C(3)-H(3A) | 123.2(15) |
| C(4)-C(3)-H(3A) | 117.5(15) |
| C(3)-C(4)-C(7) | 119.20(15) |
| C(3)-C(4)-C(5) | 134.29(16) |
| C(7)-C(4)-C(5) | 106.50(15) |
| C(6)-C(5)-C(4) | 106.67(16) |
| C(6)-C(5)-H(5A) | 126.2(17) |
| C(4)-C(5)-H(5A) | 127.1(17) |
| C(5)-C(6)-N(1) | 110.61(16) |
| C(5)-C(6)-H(6A) | 130.1(16) |
| N(1)-C(6)-H(6A) | 119.3(16) |
| N(1)-C(7)-C(8) | 129.92(16) |
| N(1)-C(7)-C(4) | 108.06(15) |
| C(8)-C(7)-C(4) | 122.02(16) |
| C(9)-C(8)-C(7) | 117.27(15) |
| C(9)-C(8)-H(8A) | 121.0(14) |
| C(7)-C(8)-H(8A) | 121.6(14) |
| C(8)-C(9)-C(2) | 122.32(16) |
| C(8)-C(9)-H(9A) | 119.6(14) |
| C(2)-C(9)-H(9A) | 118.1(14) |
| N(1)-C(10)-H(10A) | 109.4(18) |
| N(1)-C(10)-H(10B) | 110.4(18) |
| H(10A)-C(10)-H(10B) | 107(3) |
| N(1)-C(10)-H(10C) | 111.3(17) |

| | |
|---|---|
| H(10A)-C(10)-H(10C) | 110(2) |
| H(10B)-C(10)-H(10C) | 109(2) |
| C(20)-C(11)-C(12) | 118.63(16) |
| C(20)-C(11)-C(1) | 123.31(16) |
| C(12)-C(11)-C(1) | 118.00(15) |
| C(13)-C(12)-C(11) | 121.12(16) |
| C(13)-C(12)-H(12A) | 120.4(15) |
| C(11)-C(12)-H(12A) | 118.5(15) |
| C(12)-C(13)-C(14) | 121.11(16) |
| C(12)-C(13)-H(13A) | 119.9(14) |
| C(14)-C(13)-H(13A) | 118.9(14) |
| C(15)-C(14)-C(13) | 122.84(17) |
| C(15)-C(14)-C(19) | 119.03(17) |
| C(13)-C(14)-C(19) | 118.12(16) |
| C(16)-C(15)-C(14) | 120.77(19) |
| C(16)-C(15)-H(15A) | 120.4(14) |
| C(14)-C(15)-H(15A) | 118.8(14) |
| C(15)-C(16)-C(17) | 119.96(18) |
| C(15)-C(16)-H(16A) | 120.1(17) |
| C(17)-C(16)-H(16A) | 120.0(17) |
| C(18)-C(17)-C(16) | 120.64(19) |
| C(18)-C(17)-H(17A) | 119.3(16) |
| C(16)-C(17)-H(17A) | 120.0(16) |
| C(17)-C(18)-C(19) | 120.72(19) |
| C(17)-C(18)-H(18A) | 118.5(16) |
| C(19)-C(18)-H(18A) | 120.8(16) |
| C(18)-C(19)-C(20) | 121.68(17) |
| C(18)-C(19)-C(14) | 118.84(17) |
| C(20)-C(19)-C(14) | 119.47(16) |
| C(11)-C(20)-C(19) | 121.53(16) |
| C(11)-C(20)-H(20A) | 121.3(14) |
| C(19)-C(20)-H(20A) | 117.1(14) |
| C(22)-C(21)-C(26) | 118.62(16) |
| C(22)-C(21)-C(1) | 119.87(15) |
| C(26)-C(21)-C(1) | 121.51(15) |
| C(21)-C(22)-C(23) | 121.02(16) |
| C(21)-C(22)-H(22A) | 118.7(16) |
| C(23)-C(22)-H(22A) | 120.3(16) |
| C(24)-C(23)-C(22) | 120.19(17) |
| C(24)-C(23)-H(23A) | 120.3(15) |
| C(22)-C(23)-H(23A) | 119.5(15) |
| C(23)-C(24)-C(25) | 119.38(17) |
| C(23)-C(24)-H(24A) | 117.7(17) |
| C(25)-C(24)-H(24A) | 122.8(17) |
| C(26)-C(25)-C(24) | 120.04(17) |
| C(26)-C(25)-H(25A) | 121.9(19) |
| C(24)-C(25)-H(25A) | 118.0(19) |

|  |  |
|---|---|
| C(25)-C(26)-C(21) | 120.75(17) |
| C(25)-C(26)-H(26A) | 117.8(16) |
| C(21)-C(26)-H(26A) | 121.4(16) |

***Table 2.8.*** Anisotropic displacement parameters (Å$^2$x 10$^3$) for (*S*)-**2.5**. The anisotropic displacement factor exponent takes the form: -2$\pi^2$[ h$^2$ a*$^2$U$^{11}$ + ... + 2 h k a* b* U$^{12}$ ]

| | U$^{11}$ | U$^{22}$ | U$^{33}$ | U$^{23}$ | U$^{13}$ | U$^{12}$ |
|---|---|---|---|---|---|---|
| N(1) | 19(1) | 21(1) | 30(1) | 4(1) | 7(1) | 2(1) |
| C(1) | 19(1) | 18(1) | 20(1) | -1(1) | 4(1) | 0(1) |
| C(2) | 18(1) | 18(1) | 22(1) | 2(1) | 5(1) | -2(1) |
| C(3) | 19(1) | 22(1) | 21(1) | 1(1) | 4(1) | -2(1) |
| C(4) | 20(1) | 19(1) | 21(1) | 1(1) | 7(1) | -2(1) |
| C(5) | 26(1) | 21(1) | 28(1) | -2(1) | 7(1) | -1(1) |
| C(6) | 26(1) | 17(1) | 35(1) | 0(1) | 10(1) | 2(1) |
| C(7) | 17(1) | 21(1) | 25(1) | 5(1) | 7(1) | -1(1) |
| C(8) | 19(1) | 24(1) | 23(1) | 2(1) | 3(1) | -3(1) |
| C(9) | 22(1) | 19(1) | 22(1) | -1(1) | 5(1) | -2(1) |
| C(10) | 19(1) | 29(1) | 36(1) | 6(1) | 4(1) | 1(1) |
| C(11) | 17(1) | 17(1) | 23(1) | -2(1) | 6(1) | 0(1) |
| C(12) | 21(1) | 21(1) | 25(1) | 2(1) | 5(1) | 1(1) |
| C(13) | 22(1) | 21(1) | 30(1) | -1(1) | 10(1) | -3(1) |
| C(14) | 19(1) | 24(1) | 26(1) | -7(1) | 7(1) | -1(1) |
| C(15) | 22(1) | 30(1) | 31(1) | -9(1) | 8(1) | -4(1) |
| C(16) | 23(1) | 41(1) | 30(1) | -13(1) | 2(1) | -3(1) |
| C(17) | 30(1) | 41(1) | 21(1) | -5(1) | -1(1) | 2(1) |
| C(18) | 28(1) | 30(1) | 22(1) | -2(1) | 5(1) | -2(1) |
| C(19) | 21(1) | 22(1) | 22(1) | -5(1) | 6(1) | 1(1) |
| C(20) | 21(1) | 18(1) | 24(1) | -2(1) | 7(1) | -1(1) |
| C(21) | 16(1) | 20(1) | 23(1) | 1(1) | 1(1) | 1(1) |
| C(22) | 16(1) | 22(1) | 24(1) | 0(1) | 3(1) | 2(1) |
| C(23) | 22(1) | 18(1) | 34(1) | 1(1) | 1(1) | 0(1) |
| C(24) | 23(1) | 25(1) | 35(1) | 8(1) | 5(1) | -3(1) |
| C(25) | 26(1) | 32(1) | 29(1) | 3(1) | 11(1) | -1(1) |
| C(26) | 26(1) | 21(1) | 28(1) | -2(1) | 7(1) | 0(1) |

***Table 2.9.*** Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for (*S*)-**2.5**.

|  | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | 9310(30) | 10660(20) | 9370(20) | 18(5) |
| H(3A) | 9970(30) | 8310(20) | 7190(30) | 23(5) |
| H(5A) | 11600(30) | 6100(20) | 7070(30) | 35(7) |
| H(6A) | 13920(30) | 5280(20) | 8790(30) | 31(6) |
| H(8A) | 13750(30) | 8800(20) | 11380(20) | 20(5) |
| H(9A) | 11860(30) | 10220(20) | 10630(20) | 22(5) |
| H(10A) | 15640(40) | 5810(30) | 11000(30) | 45(8) |
| H(10B) | 16050(40) | 7100(30) | 11000(30) | 43(7) |
| H(10C) | 14890(30) | 6670(20) | 11940(30) | 33(6) |
| H(12A) | 7670(30) | 8710(20) | 9100(30) | 27(6) |
| H(13A) | 5210(30) | 8080(20) | 7880(30) | 25(6) |
| H(15A) | 2970(30) | 8210(20) | 5840(20) | 24(5) |
| H(16A) | 1800(40) | 9100(20) | 3710(30) | 40(7) |
| H(17A) | 3100(30) | 10700(20) | 2850(30) | 32(6) |
| H(18A) | 5490(30) | 11330(20) | 4050(30) | 31(6) |
| H(20A) | 7740(30) | 11170(20) | 6020(20) | 24(5) |
| H(22A) | 9900(30) | 12600(20) | 9230(30) | 30(6) |
| H(23A) | 11050(30) | 14150(20) | 8220(30) | 27(6) |
| H(24A) | 12190(30) | 13880(30) | 6240(30) | 37(7) |
| H(25A) | 12100(30) | 12050(30) | 5180(30) | 42(7) |
| H(26A) | 10990(30) | 10500(20) | 6180(30) | 31(6) |

***Table 2.10.*** Torsion angles [°] for (*S*)-**2.5**.

| | |
|---|---|
| C(21)-C(1)-C(2)-C(3) | -100.94(18) |
| C(11)-C(1)-C(2)-C(3) | 27.9(2) |
| C(21)-C(1)-C(2)-C(9) | 78.04(18) |
| C(11)-C(1)-C(2)-C(9) | -153.15(15) |
| C(9)-C(2)-C(3)-C(4) | 1.0(2) |
| C(1)-C(2)-C(3)-C(4) | 179.91(15) |
| C(2)-C(3)-C(4)-C(7) | -0.5(2) |
| C(2)-C(3)-C(4)-C(5) | 178.32(17) |
| C(3)-C(4)-C(5)-C(6) | -178.75(18) |
| C(7)-C(4)-C(5)-C(6) | 0.14(19) |
| C(4)-C(5)-C(6)-N(1) | -0.1(2) |
| C(7)-N(1)-C(6)-C(5) | 0.1(2) |
| C(10)-N(1)-C(6)-C(5) | -179.95(16) |
| C(6)-N(1)-C(7)-C(8) | 179.34(18) |
| C(10)-N(1)-C(7)-C(8) | -0.6(3) |
| C(6)-N(1)-C(7)-C(4) | 0.03(18) |
| C(10)-N(1)-C(7)-C(4) | -179.96(15) |
| C(3)-C(4)-C(7)-N(1) | 178.98(14) |
| C(5)-C(4)-C(7)-N(1) | -0.11(18) |
| C(3)-C(4)-C(7)-C(8) | -0.4(2) |
| C(5)-C(4)-C(7)-C(8) | -179.48(15) |
| N(1)-C(7)-C(8)-C(9) | -178.51(16) |
| C(4)-C(7)-C(8)-C(9) | 0.7(2) |
| C(7)-C(8)-C(9)-C(2) | -0.2(3) |
| C(3)-C(2)-C(9)-C(8) | -0.6(2) |
| C(1)-C(2)-C(9)-C(8) | -179.65(16) |
| C(2)-C(1)-C(11)-C(20) | -130.10(16) |
| C(21)-C(1)-C(11)-C(20) | -3.0(2) |
| C(2)-C(1)-C(11)-C(12) | 52.8(2) |
| C(21)-C(1)-C(11)-C(12) | 179.91(14) |
| C(20)-C(11)-C(12)-C(13) | 1.3(2) |
| C(1)-C(11)-C(12)-C(13) | 178.56(16) |
| C(11)-C(12)-C(13)-C(14) | -0.6(3) |
| C(12)-C(13)-C(14)-C(15) | -179.86(17) |
| C(12)-C(13)-C(14)-C(19) | -0.6(2) |
| C(13)-C(14)-C(15)-C(16) | 179.19(17) |
| C(19)-C(14)-C(15)-C(16) | -0.1(3) |
| C(14)-C(15)-C(16)-C(17) | -1.2(3) |
| C(15)-C(16)-C(17)-C(18) | 1.6(3) |
| C(16)-C(17)-C(18)-C(19) | -0.6(3) |
| C(17)-C(18)-C(19)-C(20) | -179.99(17) |
| C(17)-C(18)-C(19)-C(14) | -0.7(3) |
| C(15)-C(14)-C(19)-C(18) | 1.0(2) |

| | |
|---|---|
| C(13)-C(14)-C(19)-C(18) | -178.26(16) |
| C(15)-C(14)-C(19)-C(20) | -179.66(15) |
| C(13)-C(14)-C(19)-C(20) | 1.0(2) |
| C(12)-C(11)-C(20)-C(19) | -0.8(2) |
| C(1)-C(11)-C(20)-C(19) | -177.94(15) |
| C(18)-C(19)-C(20)-C(11) | 178.96(16) |
| C(14)-C(19)-C(20)-C(11) | -0.3(2) |
| C(2)-C(1)-C(21)-C(22) | -122.88(16) |
| C(11)-C(1)-C(21)-C(22) | 108.69(17) |
| C(2)-C(1)-C(21)-C(26) | 56.5(2) |
| C(11)-C(1)-C(21)-C(26) | -71.9(2) |
| C(26)-C(21)-C(22)-C(23) | 0.5(2) |
| C(1)-C(21)-C(22)-C(23) | 179.93(15) |
| C(21)-C(22)-C(23)-C(24) | 0.0(3) |
| C(22)-C(23)-C(24)-C(25) | -0.4(3) |
| C(23)-C(24)-C(25)-C(26) | 0.3(3) |
| C(24)-C(25)-C(26)-C(21) | 0.3(3) |
| C(22)-C(21)-C(26)-C(25) | -0.7(3) |
| C(1)-C(21)-C(26)-C(25) | 179.94(17) |

## *Chapter Three*

# Enantiospecific Intramolecular Heck Reactions of Secondary Benzylic Ethers

## 3.1 Introduction

The Mizoroki–Heck reaction is part of the foundation of modern organometallic chemistry and is a key disconnection in the synthetic chemist's repertoire.[1,2] Creative advances continue to expand our synthetic capabilities and refine our understanding of transition-metal-catalyzed reactions.[3] Traditional Heck reactions employ an aryl or vinyl halide or pseudohalide. Development of "alkyl-Heck reactions," where the electrophilic partner is an *alkyl* halide or pseudohalide, is undergoing revitalization,[4,5,6,7,8] in part due to synergy with recent advances in alkyl cross-coupling reactions.[9] Exciting results employing primary alkyl halides have been reported, where catalyst control suppresses undesired side reactions and provides regioselectivity and asymmetric

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[1] A portion of this chapter was originally published in journal format: Harris, M. R.; Konev, M. O.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 7825.

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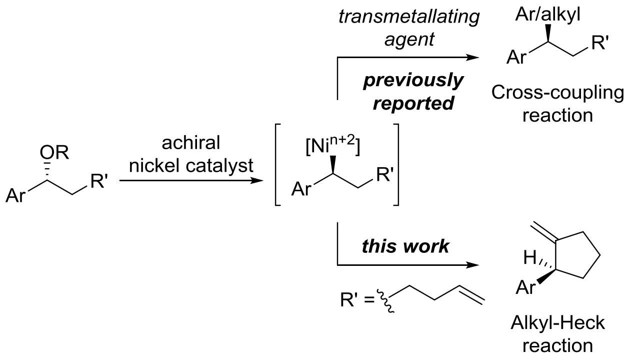
[9] For reviews, see: (a) Swift, E. C.; Jarvo, E. R. *Tetrahedron* **2013**, *69*, 5799–5817. (b) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417–1492.

induction in the migratory insertion step.[6,3d,3e] Heck-like reactions of secondary alkyl iodides that proceed through radical intermediates have also been reported, and provide substituted tetrahydrofurans and cyclopentanones with high diastereoselectivity.[8] Important challenges remain. For example, in reactions of secondary alkyl electrophiles, control of absolute configuration at the site of oxidative addition has not been reported.

We hypothesized that secondary ethers functionalized with a pendant alkene should undergo nickel-catalyzed Heck cyclization and that the reactions would be highly stereospecific (Scheme 3.1). This work builds on our development of related stereospecific nickel-catalyzed cross-coupling reactions of benzylic ethers.[10,11,12] We propose that oxidative addition occurs with inversion, providing a single enantiomer of the key secondary alkylnickel intermediate that can continue through the cross-coupling or Heck catalytic cycle.

***Scheme 3.1.*** Stereospecific nickel-catalyzed reactions of benzylic ethers and esters



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[10] (a) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389–391. (b) Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293–4296. (c) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790–7793. (d) Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303–3306. (e) Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 9083–9090. (f) Yonova. I. M.; Johnson, A. G.; Osborne, C. A.; Moore, C. E.; Morrissette, N. S.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 2422–2427.

[11] For related transformations, see: Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307–3310.

[12] For a lead reference of the complementary stereoconvergent strategy, see: Do, H.-Q.; Chandrashekar, E. R. R.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 16288–16291.

## 3.2 Development of Enantiospecific Nickel-Catalyzed Heck Cyclizations

We designed substrates to test for stereospecific Heck cyclization, informed by our prior development of stereospecific cross-coupling reactions of esters and ethers. Employing benzylic pivalate **3.1** with $Cs_2CO_3$ as the base, however, failed to furnish any of the desired methylenecyclopentane **3.2** (Table 3.1, entry 1).[13] Next, dimethylzinc was examined as a terminal reductant for the reaction, and a small amount of the desired methylenecyclopentane **3.2** was observed (entry 2). Encouraged by this result, we replaced dimethylzinc with methylmagnesium iodide, a stronger terminal reducing agent. To avoid undesired side reactions of the leaving group with a Grignard reagent, we replaced pivalate **3.1** with methyl ether **3.5**. Under these conditions, consumption of starting material increased significantly (entries 3–6).[14] When bidentate phosphine ligands were added to the reaction, the undesired product **3.4**, resulting from simple Kumada coupling, was the major product (entries 3 and 4). Remarkably, Kumada product **3.4** was not observed when catalysts ligated by monodentate phosphines were used in the reaction (entries 5 and 6). The desired Heck cyclization to afford methylenecyclopentane **3.2** proceeded in good yield with $PCy_3$ as the ligand (entry 5). Our optimized reaction conditions took advantage of the air stable $NiCl_2(PCy_3)_2$ catalyst and afforded the desired product in high yield (entry 7).

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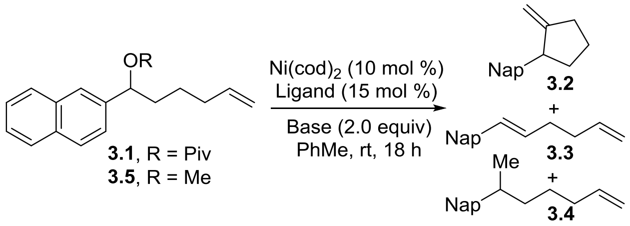
[13] Additional bases, ligands, and TESOTf as an additive were examined, but the only product observed was **3.3**. For acceleration of nickel-catalyzed Heck reactions using TESOTf, see: Matsubara, R.; Jamison, T. F. *J. Am. Chem. Soc.* **2010**, *132*, 6880–6881.

[14] Substitution of Grignard reagent with other bases in Heck cyclization of ether **3.5** resulted in quantitative recovery of **3.5**.

**Table 3.1.** Optimization of reaction conditions



| Entry | R | Ligand | Base | yield **3.2** (%)[a] | yield **3.3** (%)[a] | yield **3.4** (%)[a] |
|---|---|---|---|---|---|---|
| 1 | Piv | $PCy_3$ | $Cs_2CO_3$ | < 2 | 37 | < 2 |
| 2 | Piv | $PCy_3$ | $ZnMe_2$ | 7 | 39 | < 2 |
| 3 | Me | DPEphos | MeMgI | 4 | 23 | 47 |
| 4 | Me | dppf | MeMgI | < 2 | 27 | **66** |
| 5 | Me | $PCy_3$ | MeMgI | **64** | 17 | < 2 |
| 6 | Me | $PPh_3$ | MeMgI | 18 | 76 | < 2 |
| 7 | Me | $NiCl_2(PCy_3)_2$[b] | MeMgI | **82** | 11 | < 2 |

[a]Yield determined by $^1$H NMR based on comparison with $PhSiMe_3$ as internal standard. [b]$NiCl_2(PCy_3)_2$ was used in place of Ni(cod)$_2$ and added ligand.

Having established conditions for the cyclization of secondary ether **3.5**, we synthesized enantioenriched (*R*)-**3.5** with the goal of determining the stereospecificity of the reaction. Ether (*R*)-**3.5** was prepared in high enantiomeric excess by CBS reduction of the corresponding ketone.[15] Cyclization of (*R*)-**3.5** resulted in good yield and excellent enantiospecificity to afford the methylenecyclopentane (*R*)-**3.2** with inversion at the benzylic stereocenter (Table 3.2, entry 1).[16] The reaction is scalable with no observable deterioration in yield or enantiospecificity when performed on a 1.0 mmol scale of ether (*R*)-**3.5** (entry 2).

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[15] Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.

[16] Absolute configuration for starting material and product was determined for Table 3.2, entries 1 and 8, based on comparison of optical rotations to literature values or X-ray crystallography. For full details, see the experimental details.

## 3.3 Scope of the Heck Cyclization

We next examined the cyclization of a range of enantioenriched benzylic ethers. Benzylic methyl ethers of π-extended arenes proceed in excellent yield to afford highly enantioenriched methylenecyclopentanes (Table 3.2, entries 1 and 3). Simple heteroarenes such as thiophene **3.8** and furan **3.10** also perform well under the reaction conditions (entries 4 and 5). Taking advantage of the Thorpe–Ingold effect by substitution of the alkyl chain with geminal dimethyl substituents improves the yield of the cyclization in general (entries 6 and 7).[17] Simple benzylic substrates such as **3.16** presented a challenge, where high enantiospecificity but low conversion was typically observed (entry 8). In this case, geminal disubstitution failed to improve yield (entry 9), but modification of the ether provided a solution (entries 10–12). Our laboratory has previously developed the methoxyethyl ether as a traceless directing group that accelerates sluggish cross-coupling reactions.[10b] This strategy proved fruitful in the context of Heck reactions as well; methoxyethyl ethers **3.20**, **3.21,** and **3.23** afforded the desired methylenecyclopentanes at 60 $^{o}$C (entries 6–8). Yields of **3.17**, **3.19**, **3.22** and **3.24** could typically be further improved by approximately 10% with the addition of one equivalent of $MgI_2$ (1 equiv).[18]

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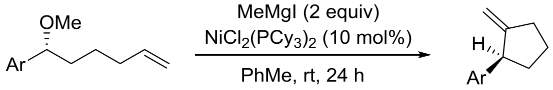
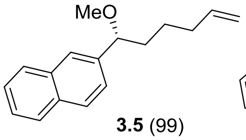
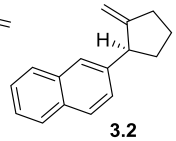
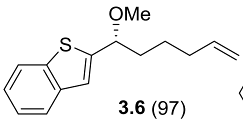
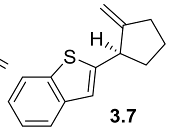
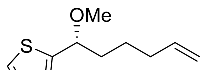
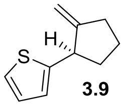
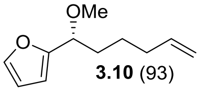
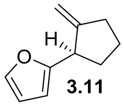
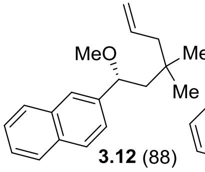
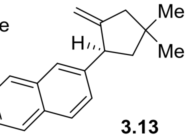
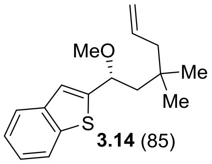
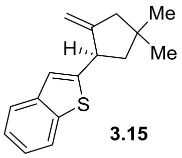
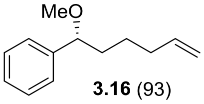
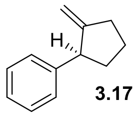
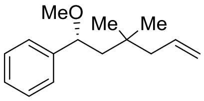
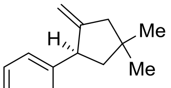
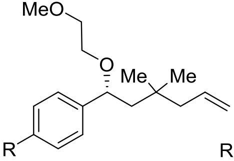
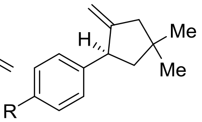
[17] Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc. Trans.* **1915**, *107*, 1080–1106.
[18] Greene, M. A. Diastereoselective Synthesis of Seven Membered Ring *trans*-Alkenes and Development of Stereospecific Nickel-Catalyzed Cross-Coupling Reactions. Ph.D. Thesis, The University of California, Irvine, May 2013.

***Table 3.2.*** Scope of Intramolecular Heck Cyclization

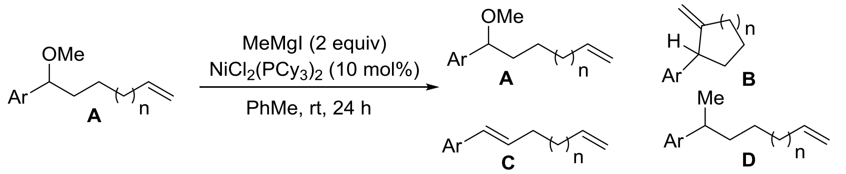


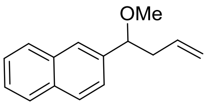
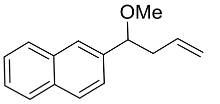
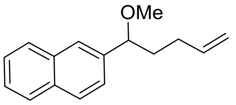
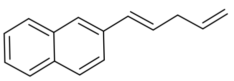
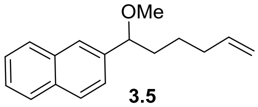
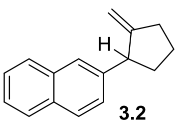
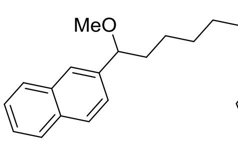
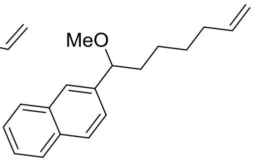
| Entry | Substrate (ee (%))[a] | Product | yield (%)[b] | product ee (%)[a] | es (%)[c] |
|---|---|---|---|---|---|
| 1 |  **3.5** (99) |  **3.2** | 74 | 99 | >99 |
| 2[d] | **3.5** (89) | **3.2** | 73 | 89 | >99 |
| 3 |  **3.6** (97) |  **3.7** | 81 | 97 | >99 |
| 4 |  **3.8** (97) |  **3.9** | 73 | 97 | >99 |
| 5[e] |  **3.10** (93) |  **3.11** | 76 | 93 | >99 |
| 6 |  **3.12** (88) |  **3.13** | 95 | 88 | >99 |
| 7 |  **3.14** (85) |  **3.15** | 74 | 84 | 99[f] |
| 8[g,h] |  **3.16** (93) |  **3.17** | 31 (64)[i] | 93 | >99 |
| 9[g] |  **3.18** (94) |  **3.19** | 35 (60)[i] | 94 | >99 |
| 10[g,h] |  **3.20** R = H (92) |  **3.19** R = H | 67 (81)[i] | 92 | >99 |
| 11[g,h] | **3.21** R = *p*-F (90) | **3.22** R = *p*-F | 57 (77)[i] | 90 | >99[f] |
| 12[g,h] | **3.23** R = *p*-TMS (92) | **3.24** R = *p*-TMS | 85 | 92 | >99[f] |

[a] Determined by chiral SFC. [b] Isolated yield after column chromatography. [c] Enantiospecificity (es) = (eeproduct/eesubstrate) x 100. [d] Reaction run on 1.0 mmol scale. [e] Determined by chiral GC. [f] Enantiospecificity was determined based on the ee of the corresponding alcohol, rather than the ether. [g] Reaction performed at 60 °C. [h] Reaction performed with added $MgI_2$ (1 equiv). [i] Yield determined by $^1H$ NMR based on comparison with $PhSiMe_3$ as internal standard.

Representative examples of other substrates are presented to illustrate the scope and limitations with respect to formation of different ring sizes and functional group compatibility. The length of the alkane tether was varied to determine whether or not alternate rings sizes could be formed in the Heck cyclization. When the tether length is too short, we observe only recovered starting material upon subjection of the substrate to cyclization conditions (Table 3.3, entry 1). Interestingly, no β-hydrogen elimination to form a conjugated styrenyl diene is detected by $^1H$ NMR spectroscopy. When the length of the alkane tether is such that 4-exo or 5-endo cyclization could occur, we observe high conversion to the elimination product (entry 2). When the tether is the appropriate length to form a 6-membered ring in the Heck cyclization, only recovered starting material is observed (entry 4).

***Table 3.3.*** Effect of tether length



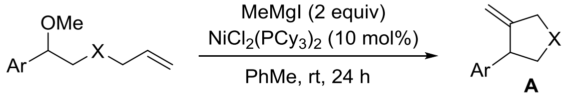
| Entry | Substrate | Major Product | yield **A** (%)$^a$ | yield **B** (%)$^a$ | yield **C** (%)$^a$ | yield **D** (%)$^a$ |
|---|---|---|---|---|---|---|
| 1 |  |  | 99 | < 5 | < 5 | < 5 |
| 2 |  |  | < 5 | < 5 | 61 | 36 |
| 3 |  **3.5** |  **3.2** | < 5 | 81 | 15 | < 5 |
| 4 |  |  | 99 | < 5 | < 5 | < 5 |

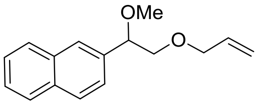
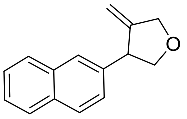
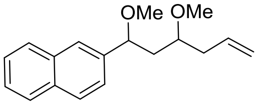
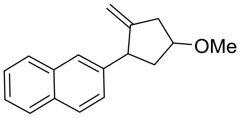
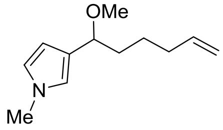
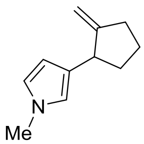
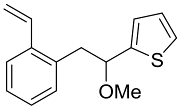
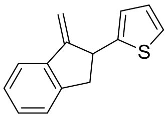
$^a$Determined by $^1$H NMR using an internal standard (PhSiMe$_3$).

Table 3.4 illustrates representative examples of substituent patterns that provide low yields or no desired Heck product. Heck cyclization of substrates containing oxygenation in the tether failed to produce the desired tetrahydrofuran (Table 3.4, entry 1). 1,3-Diol derivatives (entry 2) provided low yields of the desired product. Significant decomposition stems from formation of an allylic ether byproduct that further reacts to a variety of products under the reaction conditions. Whereas substrates containing furan and thiophene moieties performed well under the reaction conditions, pyrrole decomposed under the conditions for the Heck cyclization (entry 3).

We attempted to form indane products with the Heck cyclization, however, elimination to form a stillbene was competitive with formation of desired product (entry 4).

***Table 3.4.*** Functional group and substituent pattern compatibility



| Entry | Substrate | Heck Product | yield **A** (%)[a] |
|---|---|---|---|
| 1 |  |  | < 5 |
| 2 |  |  | 23 |
| 3 |  |  | < 5 |
| 4 |  |  | 18 |

[a]Determined by $^1$H NMR using an internal standard ($PhSiMe_3$).

To further test the limits of the transformation, an alkyne insertion/Kumada domino reaction was examined.[19] Benzylic ether **3.25** bearing a tethered TMS protected alkyne was subjected to the reaction conditions to afford tetrasubstituted olefin **3.26** in good yield and excellent enantiospecificity (Scheme 3.2). A 1.9:1 mixture of stereoisomers was obtained which could be separated by flash column chromatography with silver nitrate impregnated silica gel.[20] We hypothe-

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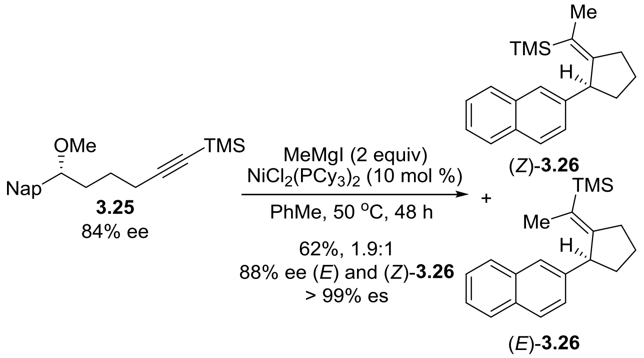
[19] For a recent example of an intramolecular palladium-catalyzed alkyne insertion/Suzuki reaction of alkyl iodides and aryl boronic esters, see: Monks, B. A.; Cook, S. P. *J. Am. Chem. Soc.* **2012**, *134*, 15297–15300.

[20] Williams, C. M.; Mander, L. N. *Tetrahedron* **2001**, *57*, 425–447.

size that the migratory insertion step proceeds with syn selectivity.[21] Therefore, the stereoisomeric mixture of products present in the cyclization of alkyne **3.25** is predicted to be the result of isomerization of the vinylnickel intermediate prior to reductive elimination.[22]

***Scheme 3.2.*** Alkyne insertion-Kumada reaction



### 3.4 Cyclization of Substituted Olefins

Trisubstituted olefins are valuable synthetic targets found in natural products, intermediates in biosynthetic pathways of steroids, and important building blocks for further functionalization by asymmetric catalysis.[23,24] Heck cyclization of 1,2-disubstituted olefins affords a strategy for synthesis of trisubstituted olefins as single stereoisomers, based on the stereochemical requirements of migratory insertion and β-hydride elimination.[21,25] Indeed, when (*E*)-**3.27** is subjected to the reaction conditions, the trisubstituted olefin (*E*)-**3.28** is formed in high yield and with high enantiospecificity at the benzylic stereocenter. The product is formed as a single olefin

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[21] Heck, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 6707–6714.

[22] For discussion of isomerization pathways of vinyl metal complexes, see: (a) Frohnapfel, D. S.; Templeton, J. L. *Coord. Chem. Rev.* **2000**, *206–207*, 199–235. For selected examples, see: (b) Tanke, R. S.; Crabtree, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 7984–7989. (c) Chung, L. W.; Wu, Y.-D.; Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2003**, *125*, 11578–11582.

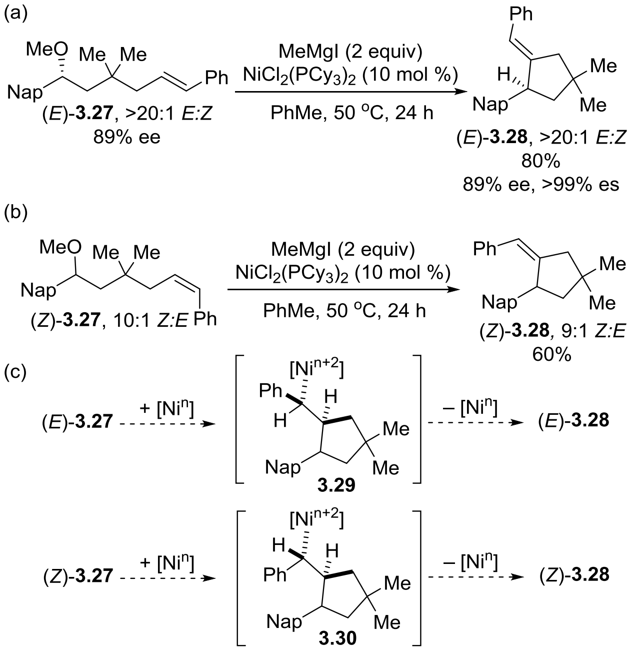
[23] Faulkner, J. D. *Synthesis*, **1971**, *4*, 175–189.

[24] Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley and Sons, Inc.: New York, 2005.

[25] Iimura, S.; Overman, L. E.; Paulini, R.; Zakarian, A. *J. Am. Chem. Soc.* **2006**, *128*, 13095–13101.

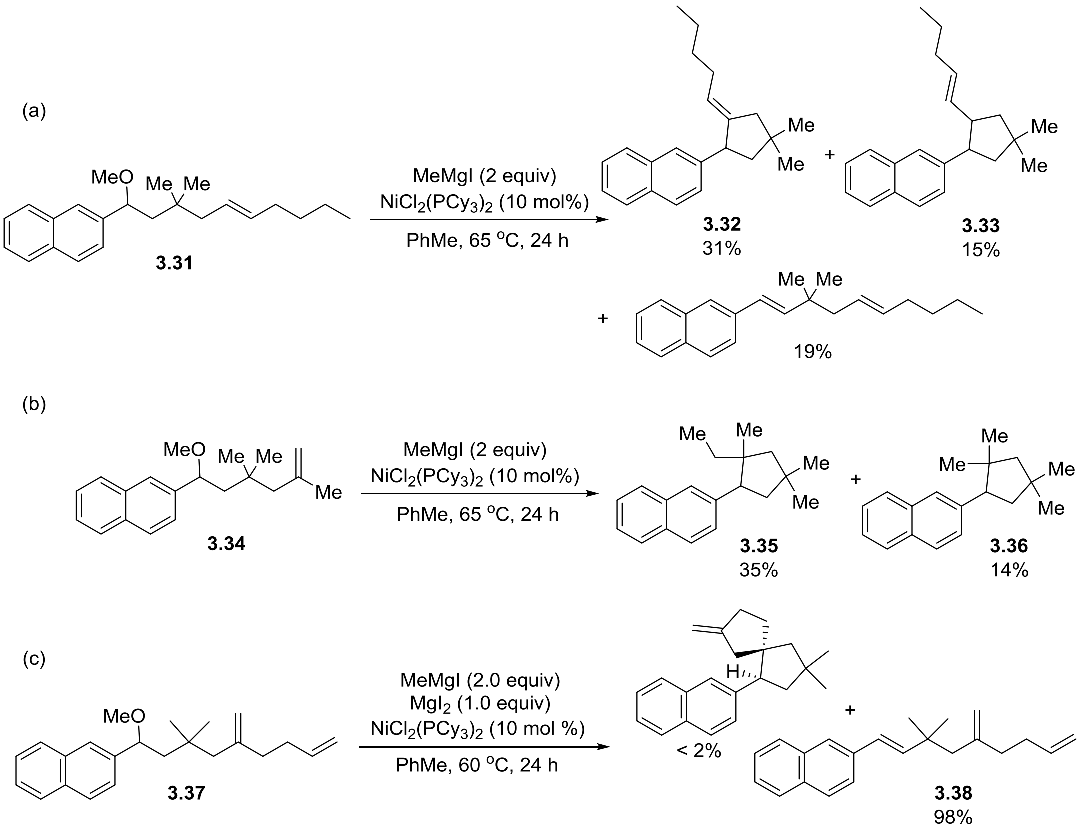
isomer in >20:1 dr (Scheme 3.3a). Next, (*Z*)-**3.27** was cyclized in good yield to form (*Z*)-**3.28** (Scheme 3.3b). Therefore, either isomer of the product can be accessed simply by selecting the appropriate isomer of starting material.

***Scheme 3.3.*** Stereoselective synthesis of trisubstituted olefins



The successful application of this chemistry to the synthesis of stereodefined trisubstituted olefins prompted us to examine olefins containing different substitution patterns. The Heck cyclization of 1,2-disubstituted olefin **3.31** was expected to provide facile access to an expanded range of stereodefined trisubstituted olefins (Scheme 3.4a). Heck cyclization occurred smoothly, however, an unselective β-hydride elimination step resulted in an inseparable 2:1 mixture of olefin isomers (**3.32** and **3.33**, 46% combined yield). Meanwhile, the 1,1-disubstituted olefin (**3.34**) was prepared for the formation of a quaternary center during the cyclization reaction (Scheme 3.4b). Cyclization of 1,1-disubstituted olefin **3.34** provided products containing a quaternary stereocenter. However, two major products were formed: **3.35**, from a Heck-Kumada sequence similar to that shown in Scheme 2, and **3.36**, from a reductive Heck reaction. Unfortunately these products were inseparable; a combined yield of 49% was obtained.  Finally, we attempted a Heck cascade reaction with **3.37** bearing both a 1,1-disubstituted olefin and a terminal olefin. When subjected to cyclization conditions, **3.37** was converted to styrene **3.38** in quantitative yield (Scheme 3.4c).

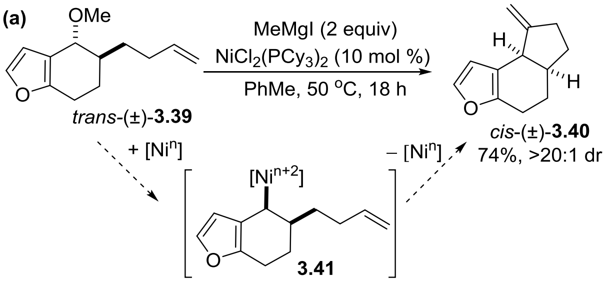
***Scheme 3.4.*** Cyclization of disubstituted olefins



## 3.5 Synthesis of a Polycyclic Furan and a Mechanistic Hypothesis

The classic Heck reaction has had a transformative impact on natural product synthesis because it can provide rapid assembly of complex polycyclic architectures.[1d] To challenge our alkyl-Heck reaction, we synthesized *trans*-**3.39** from the corresponding dihydrobenzofuranone by α-alkylation and reduction.[26] Cyclization of *trans*-**3.39** provided *cis*-**3.40** as the major product in >20:1 diastereoselectivity (Scheme 3.5a). The ring fusion was assigned as cis based on nOe correlations and a comparison of the *J*-coupling constants to calculated values for **3.40** and to literature values for related tricyclic terpenoids.[26] Tricyclic *cis*-**3.39** maps onto the core of furan terpenoid natural products such as pseudoferic acid C, and lactones such as nepalensolides A–C and brothenolide.[27,28,29]

***Scheme 3.5.*** Diastereoselective tricyclic ring formation with inversion at the benzylic position



This substrate class also provides mechanistic insight into the stereochemical and mechanistic aspects of the Heck cyclization. Cyclization of *trans*-**3.39** to afford *cis*-**3.40** is consistent

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[26] For details, see Section 3.8.

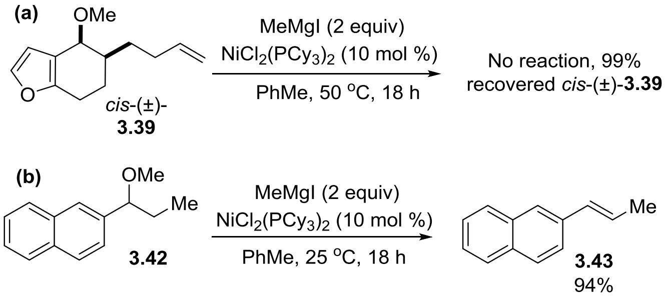
[27] Wu, X-D.; He, J.; Dong, L-B.; Pan, Z-H.; Xu, G.; Gong, X.; Song, L-D.; Leng, Y.; Li, Y.; Peng, L-Y.; Zhao, Q-S. *Tetrahedron Lett.* **2012**, *53*, 800–803.

[28] Asakawa, Y.; Lin, X.; Kondo, K.; Fukuyama Y. *Phytochemistry* **1991**, *30*, 4019–4024.

[29] Takeda, R.; Ohta, Y.; Hirose, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1120–1124.

with inversion at the benzylic stereogenic center. We attribute this outcome to inversion during the oxidative addition event to generate a cis substituted benzylnickel intermediate (**3.41**). Subsequent steps in the catalytic cycle, migratory insertion and β-hydride elimination, should not affect the benzylic stereogenic center. When the diastereomer, *cis*-**3.39**, was subjected to cyclization conditions, starting material was recovered in quantitative yield (Scheme 3.6a). It is worth noting that *cis*-**3.39** does not appear to undergo side reactions such as elimination or Kumada coupling.[30] In contrast, when benzylic ether **3.42** lacking a terminal olefin is subjected to cyclization conditions, it is converted to the styrene **3.43** in excellent yield (Scheme 3.6b). This observation is consistent with coordination of the olefin to the catalyst prior to oxidative addition.

***Scheme 3.6.*** Evidence for olefin coordination to catalyst prior to oxidative addition



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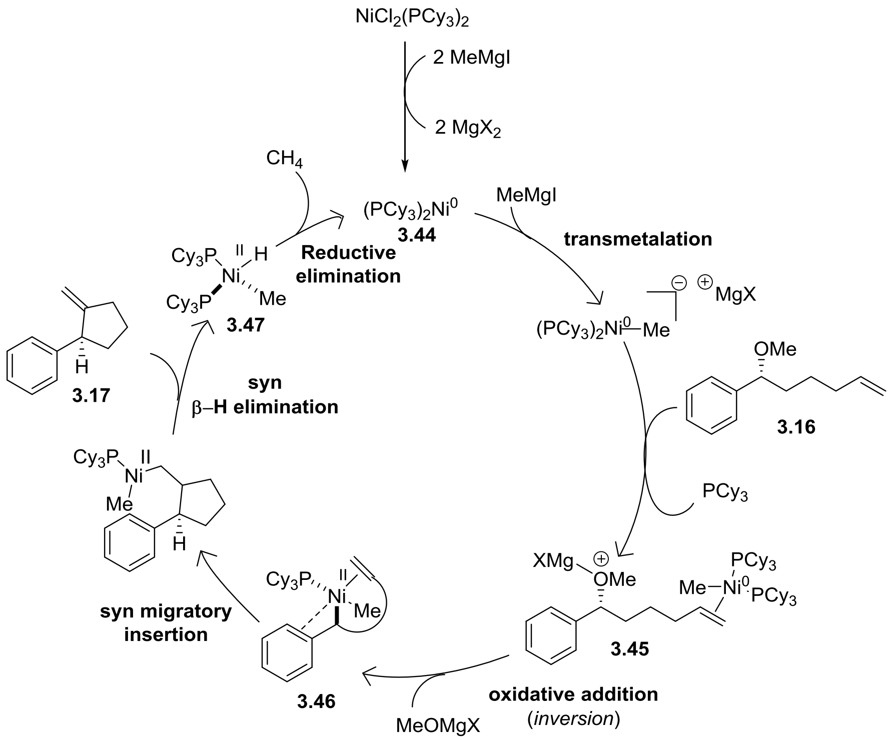
Having elucidated portions of the reaction mechanism, we propose a catalytic cycle for the Heck cyclization (Figure 3.1). The active catalyst **3.44** is formed by reduction of the precatalyst $NiCl_2(PCy_3)_2$ with two equivalents of methylmagnesium iodide. Upon transmetalation with another equivalent of Gringard reagent to form a nickelate, the catalyst coordinates to the olefin of the benzylic ether starting material to form activated complex **3.45**. Coordination of the ether to Lewis acidic salts facilities oxidative addition with inversion to form benzylnickel intermediate **3.46**. Syn migratory insertion of the catalyst with the terminal olefin, followed by syn β-hydrogen elimination generates the methylenecyclopentane product **3.17** and nickel hydride intermediate **3.47**. Reductive elimination produces methane gas and regenerates the active catalyst **3.44**.

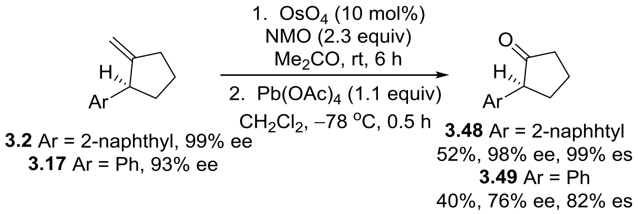
***Figure 3.1.*** Proposed catalytic cycle



### 3.6 Application to the Synthesis of Enantioenriched α-Aryl Ketones

Methylenecyclopentanes are valuable synthetic intermediates; the exocyclic olefin provides a synthetic handle for further elaboration to more complex products. For example, methylenecyclopentanes **3.2** and **3.17** are readily converted to the corresponding enantioenriched α-aryl cyclopentanones by a two-step procedure. Dihydroxylation of the olefin with $OsO_4$ followed by mild oxidative cleavage of the resultant diol with $Pb(OAc)_4$ affords α-aryl cyclopentanones **3.48** and **3.49** in good to excellent levels of enantiopurity (Scheme 3.7).

***Scheme 3.7.*** Synthesis of enantioenriched α-aryl cyclopentanones



**3.2** Ar = 2-naphthyl, 99% ee
**3.17** Ar = Ph, 93% ee

**3.48** Ar = 2-naphhtyl
52%, 98% ee, 99% es
**3.49** Ar = Ph
40%, 76% ee, 82% es

### 3.7 Conclusions

Selective formation of methylenecyclopentanes containing tertiary stereocenters has been achieved by stereospecific, nickel-catalyzed intramolecular Heck cyclization of secondary ethers. The reaction proceeds in high yield and enantiospecificity, and has been applied to the formation of synthetically challenging trisubstituted olefins. An alkyne insertion-Kumada domino reaction to prepare tetrasubstituted olefins is also demonstrated.

## 3.8 Experimental Details

*General Procedures*

All reactions were carried out under an atmosphere of $N_2$, or Ar when noted. All glassware was oven- or flame-dried prior to use. Tetrahydrofuran (THF), diethyl ether ($Et_2O$), dichloromethane ($CH_2Cl_2$), and toluene (PhMe) were degassed with Ar and then passed through two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; LaRoche Chemicals; activated under a flow of argon at 350 ºC for 12 h) to remove $H_2O$. All other solvents utilized were purchased "anhydrous" commercially, or purified as described. $^1H$ NMR spectra were recorded on Bruker DRX-400 (400 MHz $^1H$, 100 MHz $^{13}C$, 376.5 MHz $^{19}F$), GN-500 (500 MHz $^1H$, 125.7 MHz $^{13}C$), or CRYO-500 (500 MHz $^1H$, 125.7 MHz $^{13}C$) spectrometers. Proton chemical shifts are reported in ppm ($\delta$) relative to internal tetramethylsilane (TMS, $\delta$ 0.00). Data are reported as follows: chemical shift (multiplicity αsinglet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), doublet of triplets (dt), doublet of doublet of triplets (ddt), triplet of triplets (tt), quartet (q), quintet (quin), apparent doublet (ad), apparent triplet (at), multiplet (m)], coupling constants [Hz], integration). Carbon chemical shifts are reported in ppm ($\delta$) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, $\delta$ 77.16 ppm). Unless otherwise indicated, NMR data were collected at 25 ºC. Infrared (IR) spectra were obtained on a Thermo Scientific Nicolet iS5 spectrometer with an iD5 ATR tip (neat) and are reported in terms of frequency of absorption (cm $^{-1}$). Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 $F_{254}$ precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$, ceric ammonium molybdate (CAM), or *p*-anisaldehyde (PAA) solutions. Flash chromatography was performed using Silica Gel 60 (170-400 mesh) from Fisher Scientific. Melting points (m.p.) were obtained using a Mel-

Temp melting point apparatus and are uncorrected. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Automatic Polarimeter. SFC determinations of enantiopurity were performed on a Berger Analytical instrument using a Daicel™ Chiralpak® column (OD-H, OJ-H, or AD-H; 100 bar, 50 °C, 215 nm). High resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center.

Bis(tricyclohexylphosphine)nickel(II) chloride was purchased from Strem, stored in a glovebox under an atmosphere of $N_2$, and used as received. All other reagents were purchased commercially and used as received.

Where noted, silver nitrate impregnated silica gel was used to separate cyclization products from alkene byproducts, which was prepared as follows.[31] To a 1 L round bottom flask was added $AgNO_3$ (15 g) followed by $H_2O$ (5 mL) and $CH_3CN$ (100 mL), with the exclusion of light. The resulting solution was agitated for 15–20 min. Silica gel (100 mL) was added and agitated for 15–20 min. The solvent was removed in vacuo, the silica gel was dried overnight at reduced pressure (~ 1 torr), and then stored in the dark.

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[31] Williams, C. M.; Mander, L. N. *Tetrahedron* **2001**, *57*, 425–447.

## PREPARATION OF METHYLMAGNESIUM IODIDE

Under an argon atmosphere, dry $Et_2O$ (10 mL) was added to magnesium turnings (1.1 g, 45 mmol) in a 3-neck flask equipped with a reflux condenser and Schlenk filtration apparatus. Iodomethane (1.9 mL, 31 mmol) was then added slowly (over 30 min), so as to maintain a gentle reflux. The mixture was stirred for 2 h at room temperature then filtered through the fritted Schlenk filter into a Schlenk flask under an argon-atmosphere. The Schlenk flask was sealed and removed from the rest of the apparatus.

The resulting Grignard reagent titrated with LiCl and iodine and was typically between 2.5 and 3.0 M.[32] The Grignard reagent could be stored (sealed, under argon) for at least 4 weeks without detrimental effects. For satisfactory yields, the Grignard reagent must be prepared from the alkyl iodide in $Et_2O$ at a concentration of at least 2.0 M.

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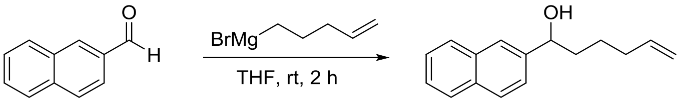
[32] Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890–891.

## SYNTHESIS AND CHARACTERIZATION OF SUBSTRATES FOR TABLE 3.2

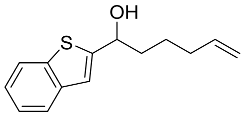
## Racemic substrates for entries 1–4

Racemic benzylic alcohols were prepared by Grignard addition to the corresponding aldehydes. Alkylation was performed according to the same procedure utilized for enantioenriched substrates (General Procedures G and H).

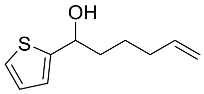
***General Procedure A.*** *Grignard addition to aldehydes.*



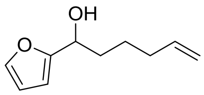
***rac*-3.50.** In a flame-dried round-bottom flask, to a solution of 2-naphthaldehyde (3.12 g, 20.0 mmol, 1.00 equiv) in THF (30 mL) was added at 0 ºC pent-4-en-1-ylmagnesium bromide (1.8 M in THF, 17 mL, 30 mmol, 1.5 equiv). After stirring at room temperature for 2 h, saturated ammonium chloride (25 mL) was added at 0 ºC and the reaction was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (1 x 40 mL), dried over $MgSO_4$, and concentrated in vacuo. The product was purified by column flash chromatography (10% EtOAc/hexanes) to afford the title compound as a white solid (4.30 g, 19.0 mmol, 95%). Analytical data is consistent with the values listed for (*R*)-**3.50** (vide infra).



***rac*-3.51.** Using representative procedure A outlined above, the following amounts of reagents were used: thianaphthene-2-carboxaldehyde (1.05 g, 6.48 mmol, 1.00 equiv), pent-4-en-1-ylmagnesium bromide (1.8 M in THF, 5.4 mL, 9.7 mmol, 1.5 equiv). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a white solid (1.47 g, 6.34 mmol, 98%). Analytical data is consistent with the values listed for (*R*)-**3.51** (vide infra).

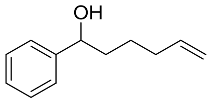


***rac*-3.52.** Using representative procedure A outlined above, the following amounts of reagents were used: 2-thiophenecarboxaldehyde (0.56 mL, 6.0 mmol, 1.0 equiv), pent-4-en-1-ylmagnesium bromide (1.8 M in THF, 5.0 mL, 9.0 mmol, 1.5 equiv). The product was purified by flash column chromatography (20% $Et_2O$/hexanes) to afford the title compound as a clear, colorless oil (1.09 g, 6.00 mmol, quantitative). Analytical data is consistent with the values listed for (*R*)-**3.52** (vide infra).



***rac*-3.53.** Using representative procedure A outlined above, the following amounts of reagents were used: furfural (0.83 mL, 10 mmol, 1.0 equiv), pent-4-en-1-ylmagnesium bromide (1.8 M in THF, 8.3 mL, 15 mmol, 1.5 equiv). The product was purified by flash column chromatography

(20% $Et_2O$/hexanes) to afford the title compound as a clear, colorless oil (1.47 g, 8.85 mmol, 86%). Analytical data is consistent with the values listed for (*R*)-**3.53** (vide infra).

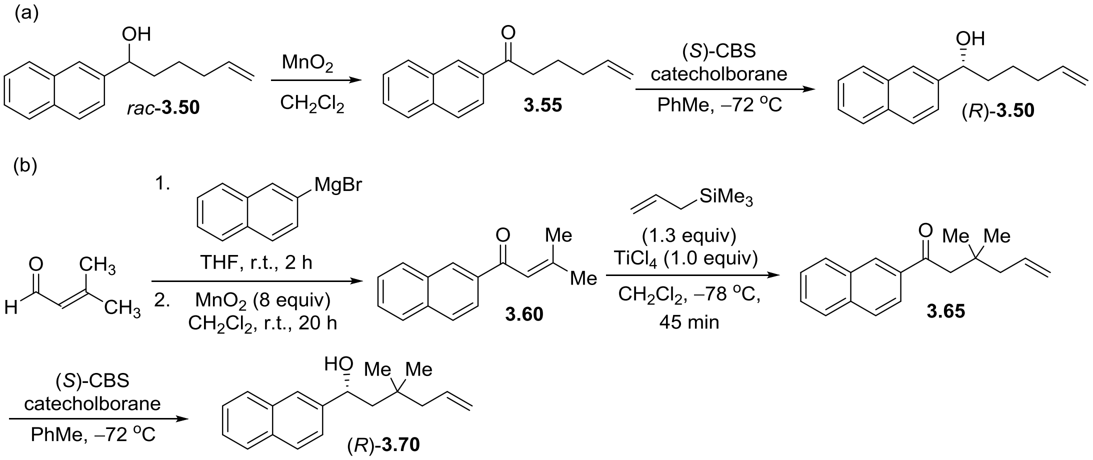


***rac*-3.54.** Using representative procedure A outlined above, the following amounts of reagents were used: benzaldehyde (0.71 mL, 7.0 mmol, 1.0 equiv), pent-4-en-1-ylmagnesium bromide (1.8 M in THF, 5.8 mL, 11 mmol, 1.5 equiv). The product was purified by flash column chromatography (15% $Et_2O$/hexanes) to afford the title compound as a clear, colorless oil (1.14 g, 6.44 mmol, 92%). Analytical data is consistent with the values listed for (*R*)-**3.54** (vide infra).

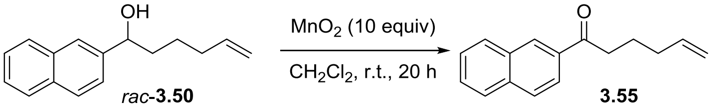
## Enantioenriched alcohols for Table 3.2, entries 1–9

Enantioenriched benzylic alcohols were prepared from the racemic benzylic alcohols by oxidation, enantioselective CBS reduction (Table 3.2, entries 1–4; Scheme 3.8a). Others were prepared by Grignard addition into 3-methyl-2-butenal, oxidation, Hosomi–Sakurai allylation and enantioselective CBS reduction (Table 3.2, entries 5–9; Scheme 3.8b).

***Scheme 3.8.*** Representative synthetic routes to enantioenriched alcohols



### ***General Procedure B:*** *Oxidation of benzylic alcohols*



**3.55.** The product was prepared according to a modified procedure reported by Wipf.[33] To a solution of ***rac*-3.50** (1.18 g, 5.20 mmol, 1.00 equiv) in wet $CH_2Cl_2$ (120 mL) was added in a single portion $MnO_2$ (4.52 g, 52.0 mmol, 10.0 equiv). The reaction was allowed to stir overnight at room temperature. The resulting slurry was filtered through celite, and the celite was washed with $Et_2O$. Solvent was removed in vacuo to afford the title compound as a yellow solid (1.08 g, 4.82 mmol, 93%). **TLC R$_f$** = 0.5 (10% EtOAc/hexanes, UV active); **m.p.** = 36–37 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.02 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.85 (t, *J* = 8.1 Hz 2H), 7.60–7.50 (m, 2H), 5.85 (ddt, *J* = 17.0, 10.2, 3.2 Hz, 1H), 5.07 (ad, *J* = 17.0

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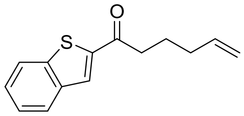
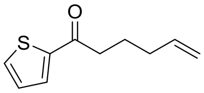
[33] Wipf, P.; Xu, W. *J. Org. Chem.* **1996**, *61*, 6556–6562.

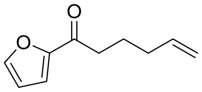
Hz, 1H), 5.02 (ad, *J* = 10.2 Hz, 1H), 3.08 (t, *J* = 7.7 Hz, 2H), 2.19 (q, *J* = 7.1 Hz, 2H), 1.90 (quin, *J* = 7.7 Hz 2H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 200.2, 138.2, 135.6, 134.4, 132.6, 129.7, 129.6, 128.5, 128.4, 127.8, 126.8, 124.0, 115.4, 37.8, 33.3, 23.5; **IR** (neat) 3058, 2829, 1678 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{16}H_{16}OH$ (M + H)$^+$ 225.1279, found 225.1278.



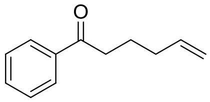
**3.56.** Using representative procedure B outlined above, the following amounts of reagents were used: Alcohol ***rac*-3.51** (0.72 g, 3.1 mmol, 1.0 equiv), MnO$_2$ (2.68 g, 31.0 mmol, 10.0 equiv), CH$_2$Cl$_2$ (40 mL). Further purification after celite plug was unnecessary. The title compound was isolated as a white solid (0.664 g, 2.88 mmol, 93%). **TLC R$_f$** = 0.6 (10% EtOAc/hexanes, UV active); **m.p.** = 75–76 °C; **$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.95 (s, 1H), 7.87 (t, *J* = 8.7 Hz, 2H), 7.46 (t, *J* = 7.1 Hz, 1H), 7.40 (t, *J* = 7.3 Hz, 1H), 5.83 (ddt, *J* = 16.9, 10.1, 3.4 Hz, 1H), 5.06 (d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.1 Hz, 1H), 3.01 (t, *J* = 7.3 Hz, 2H), 2.18 (q, *J* = 7.1 Hz, 2H), 1.90 (quin, *J* = 7.2 Hz, 2H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 194.9, 144.0, 142.6, 139.3, 138.0, 128.9, 127.5, 126.0, 125.1, 123.1, 115.7, 38.5, 33.3, 23.8; **IR** (neat) 3078, 2892, 1657 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{14}H_{14}OSH$ (M + H)$^+$ 231.0844, found 231.0847.



**3.57.** Using representative procedure B outlined above, the following amounts of reagents were used: Alcohol ***rac*-3.52** (0.73 g, 4.0 mmol, 1.0 equiv), MnO$_2$ (3.50 g, 40.0 mmol, 10.0 equiv), CH$_2$Cl$_2$ (50 mL). Further purification after celite plug was unnecessary. The title compound was isolated as a clear oil (0.69 g, 3.8 mmol, 95%). **TLC R$_f$** = 0.7 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 3.7, 1.0 Hz, 1H), 7.62 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.13 (dd, *J* = 4.9, 3.9 Hz, 1H), 5.82 (ddt, *J* = 17.1, 10.2, 3.3 Hz, 1H), 5.05 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.00 (d, *J* = 10.2 Hz, 1H), 2.91 (t, *J* = 7.6 Hz, 2H), 2.16 (q, *J* = 7.2 Hz, 2H), 1.86 (quin, *J* = 7.3 Hz, 2H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 193.3, 144.6, 138.0, 133.5, 131.8, 128.2, 115.5, 38.6, 33.3, 23.8; **IR** (neat) 3076, 2931, 1658 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{10}H_{12}OSH$ $(M + H)^+$ 181.0687, found 181.0693.

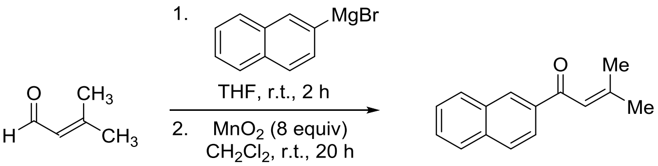


**3.58.** Using representative procedure B outlined above, the following amounts of reagents were used: Alcohol ***rac*-3.53** (0.70 g, 4.2 mmol, 1.0 equiv), $MnO_2$ (3.7 g, 42 mmol, 10 equiv), $CH_2Cl_2$ (50 mL). Further purification after celite plug was unnecessary. The title compound was isolated as a clear oil (0.63 g, 3.9 mmol, 92%). **TLC R$_f$** = 0.6 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.18 (d, *J* = 3.4, Hz, 1H), 6.53 (dd, *J* = 3.4, 1.6 Hz, 1H), 5.81 (ddt, *J* = 17.1, 10.1, 3.4 Hz, 1H), 5.04 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.00 (d, *J* = 10.1 Hz, 1H), 2.83 (t, *J* = 7.6 Hz, 2H), 2.14 (q, *J* = 7.3 Hz, 2H), 1.83 (quin, *J* = 7.3 Hz, 2H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 189.7, 152.9, 146.4, 138.0, 117.0, 115.5, 112.3, 37.7, 33.3, 23.4; **IR** (neat) 3076, 2933, 1646, 1569 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{10}H_{12}O_2H$ $(M + H)^+$ 165.0916, found 165.0920.



**3.59.** Using representative procedure B outlined above, the following amounts of reagents were used: Alcohol **3.54** (1.67 g, 9.50 mmol, 1.00 equiv), $MnO_2$ (8.26 g, 95.0 mmol, 10.0 equiv), $CH_2Cl_2$ (80 mL). Further purification after celite plug was unnecessary. The title compound was isolated as a clear oil (1.57 g, 9.00 mmol, 95%). Analytical data is consistent with literature values.[34] **TLC R$_f$** = 0.7 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.1 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 5.83 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.05 (d, *J* = 17.0 Hz, 1H), 5.00 (d, *J* = 10.3 Hz, 1H), 2.98 (t, *J* = 7.5 Hz, 2H), 2.16 (dd, *J* = 14.4, 7.2, Hz, 2H), 1.86 (tt, *J* = 14.4, 7.2 Hz, 2H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 200.4, 138.2, 137.2, 133.1, 128.7, 128.2, 115.4, 37.8, 33.3, 23.4.

***General Procedure C.*** *Preparation of α,β-unsaturated ketones.*



**3.60.** In a flame-dried round-bottom flask, to a solution of 3-methyl-2-butenal (1.93 mL, 20.0 mmol, 1.00 equiv) in THF (10 mL) was cooled to 0 °C. 2-Naphthylmagnesium bromide (1.0 M in THF, 30 mL, 30 mmol, 1.5 equiv) was added. After stirring at room temperature for 2 h, saturated ammonium chloride (25 mL) was added at 0 °C and the reaction was extracted with EtOAc

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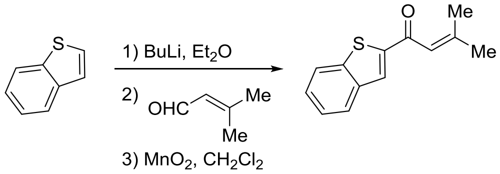
[34] Eddaif, A.; Laurent, A.; Mison, P.; Pellissier, N.; Carrupt, P. A.;Vogel, P. *J. Org. Chem.* **1987**, *52*, 5548–5560.

(3 x 25 mL). The combined organic layers were washed with brine (1 x 40 mL), dried over $MgSO_4$, and concentrated in vacuo. The unpurified product was redissolved in 125 mL of $CH_2Cl_2$ in a 250 mL round bottom flask. Solid $MnO_2$ (13.91 g, 160.0 mmol, 8.000 equiv) was added in a single portion at room temperature. The reaction was allowed to stir open to air for 20 h before it was filtered through celite. The celite was washed with $Et_2O$ and the solvents were removed in vacuo. The product was purified by flash column chromatography (5% EtOAc/hexanes) to afford a thick oil which was further purified by trituration with pentane to afford the title compound as a yellow solid (2.52 g, 12.0 mmol, 60%). **TLC $R_f$** = 0.4 (10% EtOAc/hexanes, UV active); **m.p.** = 52 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.87 (at, *J* = 9.9 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 6.90 (s, 1H), 2.25 (s, 3H), 2.06 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 191.5, 156.7, 136.7, 135.4, 132.7, 129.60, 129.58, 128.4, 128.2, 127.9, 126.7, 124.5, 121.4, 28.2, 21.4; **IR** (neat) 2057, 2909, 1655, 1610cm$^{-1}$; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{15}H_{14}ONa$ $(M + Na)^+$ 233.0942, found 233.0951.



**3.61.** Using representative procedure C outlined above, the following amounts of reagents were used: 3-methyl-2-butenal (3.80 mL, 39.4 mmol, 1.06 equiv) in THF (30 mL), 2-lithiobenzothiophene[35] (1.5 M, 25 mL, 37 mmol, 1.0 equiv) $CH_2Cl_2$ (100 mL), and manganese

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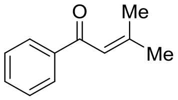
[35] Yamamoto, T.; Ogawa, S.; Sato, R. *Chem. Lett.* **2006**, *35*, 422–423.

dioxide (12.4 g, 142 mmol, 3.84 equiv). The product was purified by flash column chromatography (10% EtOAc/ hexanes) to afford the title compound as a yellow solid (5.11 g, 23.6 mmol, 63%). **TLC R$_f$** = 0.6 (15% EtOAc/hexanes, UV active); **m.p.** = 56–58 °C; **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.23 (m, 2H), 6.82 (quintet, *J* = 1.3 Hz, 1H), 2.30 (d, *J* = 1.1 Hz, 3H), 2.07 (d, *J* = 1.2 Hz, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 184.8, 158.5, 146.8, 142.6, 139.7, 127.9, 127.2, 126.0, 125.1, 123.1, 120.2, 28.4, 21.5; **IR** (neat) 3055, 2975, 1644, 1604, 1513, 1257, 1157 cm$^{-1}$; **HRMS** (TOF MS ES+) *m/z* calcd for $C_{13}H_{12}OSNa$ (M + Na)$^+$ 239.0507, found 239.0513.



**3.62.** Using representative procedure C outlined above, the following amounts of reagents were used: 3-methyl-2-butenal (1.93 mL, 20.0 mmol, 1.00 equiv) in THF (15 mL), phenylmagnesium bromide (2.0 M, 15 mL, 30 mmol, 1.5 equiv), $CH_2Cl_2$ (125 mL), and manganese dioxide (13.91 g, 160.0 mmol, 8.000 equiv). The product was purified by flash column chromatography (5% EtOAc/ hexanes) to afford the title compound as a pale yellow solid (2.02 g, 12.5 mmol, 83%). Analytical data is consistent with literature values.[36] **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 6.75 (s, 1H), 2.22 (s, 3H), 2.02 (s, 3H).

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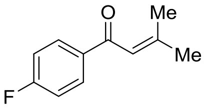
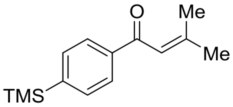
[36] Okamoto, K.; Hayashi, T. *Org. Lett.* **2007**, *9*, 5067–5069.

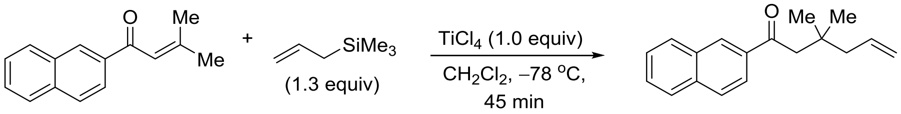


**3.63.** Using representative procedure C outlined above, the following amounts of reagents were used: 3-methyl-2-butenal (1.05 mL, 10.5 mmol, 1.00 equiv) in THF (15 mL), 4-fluorophenylmagnesium bromide (1.5 M, 7.0 mL, 10.5 mmol, 1.00 equiv), $CH_2Cl_2$ (50 mL), and manganese dioxide (4.47 g, 51.4 mmol, 4.90 equiv). The product was purified by flash column chromatography (10% EtOAc/ hexanes) to afford the title compound as a pale yellow oil (1.46 g, 8.19 mmol, 78%). **TLC $R_f$** = 0.6 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.98–7.92 (m, 2H), 7.11 (t, *J* = 8.7 Hz, 2H), 6.71 (br s, 1H), 2.21 (s, 3H), 2.02 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz) δ 190.0, 165.3 (d, *J* = 253 Hz), 157.1, 135.6 (d, *J* = 3 Hz), 130.8 (d, *J* = 9 Hz), 120.9 (d, *J* = 1 Hz), 115.5 (d, *J* = 22 Hz), 28.1, 21.2; **IR** (neat) 2977, 1661, 1613, 1597, 1233, 1010, 822 cm-1; $^1$; **HRMS** (TOF MS CI+) *m/z* calcd for $C_{11}H_{11}FOH$ $(M + H)^+$ 179.0872, found 179.0876.



**3.64.** Using representative procedure C outlined above, the following amounts of reagents were used: 3-methyl-2-butenal (1.10 mL, 11.4 mmol, 1.19 equiv) in THF (15 mL), 1-bromo-4-trimethylsilylphenylmagnesium bromide (1.4 M, 7.0 mL, 9.6 mmol, 1.0 equiv), $CH_2Cl_2$ (50 mL), and manganese dioxide (3.40 g, 39.1 mmol, 4.07 equiv). The product was purified by flash column chromatography (10% EtOAc/ hexanes) to afford the title compound as a pale yellow oil (1.33 g, 5.72 mmol, 60%). **TLC $R_f$** = 0.7 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.9 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 2H), 6.76 (br s, 1H), 2.23 (s, 3H), 2.03 (s, 3H), 0.3 (s, 9H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 191.8, 156.8, 146.3, 139.6, 133.6, 127.4, 121.5, 28.2, 21.4, -1.1; **IR** (neat) 2955, 1661, 1613, 1246, 821 cm$^{-1}$; **HRMS** (TOF MS CI+) *m/z* calcd for $C_{14}H_{20}OSiH$ (M + H)$^+$ 233.1362, found 233.1360.

***General Procedure D.*** *Hosomi–Sakurai reaction of benzylic enones*



**3.65.** The product was prepared according to a modified procedure reported by Coates and co-workers.[37] To a flame-dried 50 mL round bottom flask was added **3.60** (2.04 g, 9.71 mmol, 1.00 equiv) dissolved in 20 mL $CH_2Cl_2$. Under an inert atmosphere was added neat titanium tetrachloride (1.20 mL, 10.7 mmol, 1.10 equiv) dropwise over 5 min at –78 °C. The reaction was allowed to stir at this temperature for 10 min before dropwise addition of allyltrimethylsilane (2.05 mL, 12.6 mmol, 1.30 equiv). The reaction was allowed to stir for an additional 5 min at –78 °C before it was placed in a room temperature water bath and stirred for 30 min. The reaction was cooled to 0 °C in an ice water bath and quenched with 2.25 M HCl. The reaction was diluted with $Et_2O$ (80 mL) and washed with saturated $NaHCO_3$ (2 x 25 mL) and brine (1 x 30 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo to afford the title compound as a thick colorless oil (2.43 g, 9.63 mmol, 99%). **TLC $R_f$** = 0.4 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.87 (at, *J* = 7.7 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.2 Hz, 1H), 5.88 (ddt, *J* = 17.2, 10.1, 4.9 Hz, 1H), 5.09–5.02 (m, 2H), 2.99 (s, 2H), 2.22 (d, *J* = 7.3 Hz, 2H), 1.08 (s, 6H);

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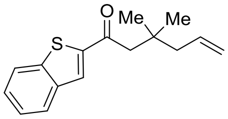
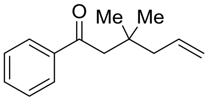
[37] Miles, B. R.; Davis, C. E.; Coates, R. M. *J. Org. Chem.* **2006**, *71*, 1493–1501.

**$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 200.4, 136.1, 135.5, 135.2, 132.6, 129.8, 129.7, 128.48, 128.45, 127.9, 126.8, 124.2, 117.9, 47.9, 46.9, 34.4, 27.7; **IR** (neat) 3060, 2957, 1682, 1596 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{18}H_{20}OH$ (M + H)$^+$ 253.1592, found 253.1582.

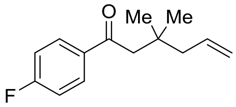


**3.66** Using representative procedure D outlined above, the following amounts of reagents were used: **3.61** (4.52 g, 20.9 mmol, 1.00 equiv), titanium tetrachloride (2.60 mL, 23.7 mmol, 1.13 equiv), allyltrimethylsilane (4.60 mL, 28.9 mmol, 1.38 equiv). The product was purified by flash column chromatography (25% EtOAc/hexanes) to afford the title compound as a yellow oil (1.73 g, 6.69 mmol, 32%). **TLC R$_f$** = 0.7 (15% EtOAc/hexanes, UV active); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.93–7.84 (m, 3H), 7.44 (m, 2H), 5.89 (quintet, *J* = 17.7, 10.4, 7.5 Hz, 1H), 5.13–5.04 (m, 2H), 2.88 (s, 2H), 2.21 (d, *J* = 7.5 Hz, 2H), 1.10 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 197.8, 146.0, 142.9, 139.5, 135.1, 129.2, 127.6, 126.2, 125.2, 123.2, 118.2, 49.0, 47.1, 34.7, 27.7 (2C); **IR** (neat) 3072, 2957, 1651, 1514, 1153 cm$^{-1}$; **HRMS** (TOF MS ES+) *m/z* calcd for $C_{16}H_{18}OSNa$ (M + Na)$^+$ 281.0976, found 281.0974.

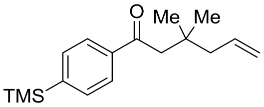


**3.67.** Using representative procedure D outlined above, the following amounts of reagents were used: **3.62** (1.98 g, 12.3 mmol, 1.00 equiv), titanium tetrachloride (1.4 mL, 12 mmol, 1.0 equiv), allyltrimethylsilane (2.54 mL, 16.0 mmol, 1.30 equiv). The product was purified by flash column chromatography (1–3% EtOAc/hexanes) to afford the title compound as a colorless oil

(1.50 g, 7.40 mmol, 60%). **TLC R$_f$** = 0.5 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.93 (d, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 5.85 (ddt, *J* = 17.2, 10.2, 4.2 Hz, 1H), 5.08–5.00 (m, 2H), 2.86 (s, 2H), 2.18 (d, *J* = 7.3 Hz, 2H), 1.05 (s, 6H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 200.4, 138.7, 135.2, 132.8, 128.6, 128.2, 117.8, 47.8, 46.9, 34.2, 27.7; **IR** (neat) 3077, 2957, 1689, 1673 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{14}H_{18}OH$ $(M + H)^+$ 203.1436, found 203.1432.

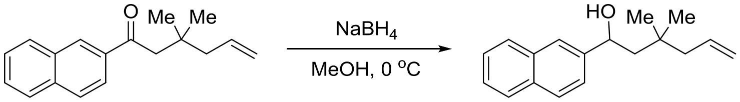


**3.68.** Using representative procedure D outlined above, the following amounts of reagents were used: **3.63** (1.35 g, 7.55 mmol, 1.00 equiv), titanium tetrachloride (0.91 mL, 8.8 mmol, 1.2 equiv), allyltrimethylsilane (1.60 mL, 10.1 mmol, 1.34 equiv). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a colorless oil (1.21 g, 5.49 mmol, 73%). **TLC R$_f$** = 0.7 (10% EtOAc/hexanes, UV active, stain with KMnO$_4$); **$^1$H NMR** (400 MHz, CDCl$_3$) δ 7.99–7.92 (m, 2H), 7.15–7.07 (m, 2H), 5.85 (ddt, *J* = 17.7, 10.2, 7.5 Hz, 1H), 5.09–5.00 (m, 2H), 2.83 (s, 2H), 2.18 (d, *J* = 7.6 Hz, 2H), 1.05 (s, 6H); **$^{13}$C NMR** (100 MHz, CDCl$_3$) δ 198.8, 165.7 (d, *J* = 254 Hz), 135.22 (d, *J* = 3 Hz), 135.18, 130.9 (d, *J* = 9 Hz), 118.0, 115.7 (d, *J* = 22 Hz), 47.8, 47.0, 34.3, 27.7; **IR** (neat) 2958, 1673, 1596, 1225, 1155 cm$^{-1}$; **HRMS** (TOF MS CI+) *m/z* calcd for $C_{14}H_{17}FOH$ $(M + H)^+$ 221.1342, found 221.1341.



**3.69.** Using representative procedure D outlined above, the following amounts of reagents were used: **3.64** (1.23 g, 5.28 mmol, 1.00 equiv), titanium tetrachloride (0.65 mL, 5.9 mmol, 1.1 equiv), allyltrimethylsilane (1.10 mL, 6.92 mmol, 1.31 equiv). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a colorless oil (1.13 g, 4.12 mmol, 78%). **TLC R$_f$** = 0.7 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.90 (ad, *J* = 8.4 Hz, 2H), 7.61 (ad, *J* = 8.4 Hz, 2H), 5.86 (ddt, *J* = 18.2, 10.3, 7.4 Hz, 1H), 5.10–5.01 (m, 2H), 2.86 (s, 2H), 2.19 (d, *J* = 7.6 Hz, 2H), 1.06 (s, 6H), 0.30 (s, 9H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 200.7, 146.9, 138.9, 135.3, 133.7, 127.3, 117.9, 47.9, 47.0, 34.3, 27.8, -1.1; **IR** (neat) 2955, 1687, 1387, 1224, 835 cm$^{-1}$; **HRMS** (TOF MS CI+) *m/z* calcd for $C_{17}H_{26}OSiH$ $(M + H)^+$ 275.1831, found 275.1837.

***General Procedure E.*** *Reduction of benzylic ketones with $NaBH_4$*



***rac*-3.70.** The product was prepared according to a modified procedure reported by Wang and Franzén.[38] A round bottom flask containing **3.65** (1.51 g, 6.00 mmol, 1.00 equiv) dissolved in MeOH (10 mL) was cooled to 0 °C in an ice water bath. Sodium borohydride (0.36 g, 9.6 mmol, 1.6 equiv) was added in a single portion and the reaction was stirred for 30 min at 0 °C. The re-

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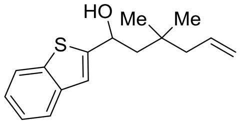
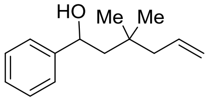
[38] Wang, Y.; Franzén, R. *Synlett*. **2012**, *23*, 925–929.

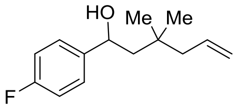
action was warmed to room temperature and stirred for an additional 1 h, after which time it was quenched with water. The reaction was extracted with $Et_2O$ (3 x 25 mL) and washed with brine (1 x 40 mL). The combined organic layers were dried with $MgSO_4$, filtered and dried in vacuo. The residue was purified by flash column chromatography (5–10% EtOAc/hexanes) to afford the title compound as a thick, colorless oil (1.25 g, 4.93 mmol, 82%). The analytical data is consistent with the values listed for (*R*)-**3.70** (vide infra).



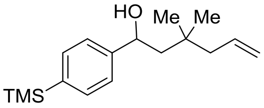
***rac*-3.71.** Using representative procedure E outlined above, the following amounts of reagents were used: **3.66** (0.67 g, 2.6 mmol, 1.0 equiv), MeOH (10 mL), sodium borohydride (0.15 g, 4.0 mmol, 1.5 equiv). The product was purified by flash column chromatography (15% EtOAc/hexanes) to afford the title compound as a pale yellow oil (0.58 g, 2.2 mmol, 85%). The analytical data is consistent with the values listed for (*R*)-**3.71** (vide infra).



***rac*-3.72.** Using representative procedure E outlined above, the following amounts of reagents were used: **3.67** (0.73 g, 3.6 mmol, 1.0 equiv), MeOH (8 mL), sodium borohydride (0.33 g, 8.7 mmol, 2.4 equiv). The product was purified by flash column chromatography (8–15% EtOAc/hexanes) to afford the title compound as a clear, colorless oil (0.64 g, 3.1 mmol, 86%). The analytical data is consistent with the values listed for (*R*)-**72** (vide infra).

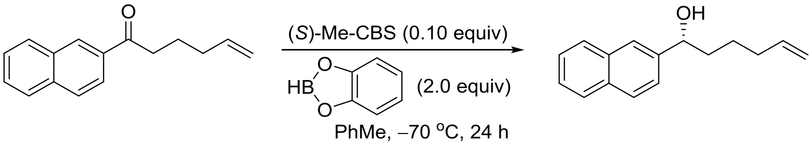


***rac*-3.73.** Using representative procedure E outlined above, the following amounts of reagents were used: **3.78** (0.50 g, 2.3 mmol, 1.0 equiv), MeOH (10 mL), sodium borohydride (0.30 g, 7.9 mmol, 3.4 equiv). The product was purified by flash column chromatography (3–10% EtOAc/hexanes) to afford the title compound as a clear, colorless oil (0.37 g, 1.7 mmol, 73%). The analytical data is consistent with the values listed for (*R*)-**3.73** (vide infra).



***rac*-3.74.** Using representative procedure E outlined above, the following amounts of reagents were used: **3.69** (0.49 g, 1.8 mmol, 1.0 equiv), MeOH (10 mL), sodium borohydride (0.33 g, 8.7 mmol, 4.8 equiv). The product was purified by flash column chromatography (3–10% EtOAc/hexanes) to afford the title compound as a clear, colorless oil (0.35 g, 1.3 mmol, 86%). The analytical data is consistent with the values listed for (*R*)-**3.74** (vide infra).

***General Procedure F.*** *Enantioselective reduction of benzylic ketones*



**(*R*)-3.50.** The product was prepared according to a modified procedure reported by Okamura.[39] In a glovebox, (*S*)-Me-CBS (103 mg, 0.454 mmol, 0.100 equiv) was added to a flame-dried round bottom flask equipped with a stir bar. The flask was capped with a septum and removed from the box. Ketone **3.55** (1.02 g, 4.54 mmol, 1.00 equiv) was added to the flask as a solution in PhMe (20 mL). The reaction was then cooled to –70 °C and catecholborane (0.97 mL, 9.1 mmol, 2.0 equiv) was added dropwise via syringe. After stirring for 24 h at –70 °C, the reaction was warmed to ambient temperature and quenched with water. Sat. $NH_4Cl$ was added to the reaction flask and the mixture was extracted with EtOAc (3 x 30 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The product was purified by flash column chromatography (8–12% EtOAc/hexanes) to afford the title compound as a white solid (0.95 g, 4.3 mmol, 94%, 93% ee). The solid was recrystallized from hexanes to improve enantiomeric excess (99% ee). **TLC $R_f$** = 0.2 (10% EtOAc/hexanes, UV active); **m.p.** = 58–60 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.88–7.80 (m, 3H), 7.78 (s, 1H), 7.52–7.43 (m, 3H), 5.78 (ddt, *J* = 17.3, 10.1, 3.3 Hz, 1H), 4.99 (dd, *J* = 17.1, 1.3 Hz, 1H), 4.94 (d, *J* = 10.3 Hz, 1H), 4.89–4.82 (m, 1H), 2.09 (q, *J* = 7.1 Hz, 2H), 1.96–1.77 (m, 3H), 1.62–1.50 (m, 1H), 1.46–1.36 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 142.3, 138.7, 133.4, 133.1, 128.5, 128.1, 127.8, 126.3,

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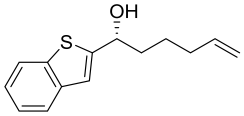
[39] Lee, A. S.; Norman, A. W.; Okamura, W. H. *J. Org. Chem.* **1992**, *57*, 3846–3854.

126.0, 124.7, 124.2, 114.9, 74.8, 38.5, 33.7, 25.2; **IR** (neat) 3279, 3056, 2932 cm$^{-1}$; **HRMS** (TOF MS CI+) *m / z* calcd for $C_{16}H_{18}ONH_4$ (M + $NH_4$)$^+$ 244.1701, found 244.1701; **[α]$^{26}$$_D$** +36 (*c* 3.6, $CHCl_3$); **SFC** analysis (OD-H, 8% IPA, 2.5 mL/min) indicated 99% ee: $t_R$ (major) = 7.2 minutes, $t_R$ (minor) = 6.5 minutes.

E.J. Corey's model for stereoselectivity of CBS reductions was used to assign the absolute configuration of benzylic alcohols prepared from this method. [40]



**(*R*)-3.51.** Using representative procedure F outlined above, the following amounts of reagents were used: ketone **3.56** (0.64 g, 2.8 mmol, 1.0 equiv), (*S*)-Me-CBS (63 mg, 0.23 mmol, 0.10 equiv), catecholborane (0.59 mL, 5.5 mmol, 2.0 equiv), and PhMe (20 mL). After extraction with $Et_2O$, the combined organics were removed in vacuo, with much care taken to avoid heating. Heating the mixture under vacuum prior to column chromatography causes irreversible complexation of the desired product with boron reagents present from the reaction. The remaining solvent (mostly PhMe) was removed by running the mixture through a plug of silica. Flash column chromatography (8–15% EtOAc/hexanes) afforded the title compound as a white solid (0.39 g, 1.7 mmol, 60%, 93% ee). The solid was recrystallized from hexanes to improve enantiomeric excess (98% ee). **TLC R$_f$** = 0.2 (10% EtOAc/hexanes, UV active); **m.p.** = 34–35 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.39–7.28 (m,

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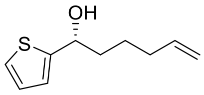
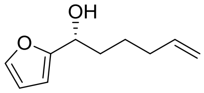
[40] Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.

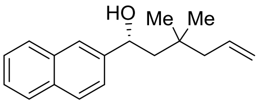
2H), 7.19 (s, 1H), 5.80 (ddt, *J* = 17.3, 10.1, 3.2 Hz, 1H), 5.05–4.94 (m, 3H), 2.12 (q, *J* = 7.0 Hz, 2H), 2.08–2.05 (m, 1H), 1.99–1.85 (m, 2H), 1.64–1.56 (m, 1H) 1.53–1.42 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 149.5, 139.6, 139.4, 138.5, 124.4, 124.3, 123.6, 122.7, 120.3, 115.1, 71.0, 38.5, 33.6, 25.0; **IR** (neat) 3289, 3074, 2932 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{14}H_{16}OSNH_4$ (M + $NH_4$)$^+$ 250.1266, found 250.1260; **$[\alpha]^{27}_D$** +19 (*c* 0.3, $CHCl_3$); **SFC** analysis (OD-H, 15% IPA, 2.5 mL/min) indicated 98% ee: $t_R$ (major) = 7.2 minutes, $t_R$ (minor) = 6.6 minutes.



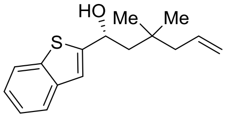
**(*R*)-3.52.** Using representative procedure F outlined above, the following amounts of reagents were used: ketone **3.57** (0.45 g, 2.5 mmol, 1.0 equiv), (*S*)-Me-CBS (57 mg, 0.25 mmol, 0.10 equiv), catecholborane (0.53 mL, 5.0 mmol, 2.0 equiv), and PhMe (15 mL). After extraction with $Et_2O$, the combined organics were removed in vacuo, with much care taken to avoid heating. Heating the mixture under vacuum prior to column chromatography causes irreversible complexation of the desired product with boron reagents present from the reaction. The remaining solvent (mostly PhMe) was removed by running the mixture through a plug of silica. Flash column chromatography (10% EtOAc/hexanes) afforded the title compound as a clear oil (0.40 g, 2.2 mmol, 88%, 96% ee). **TLC $R_f$** = 0.3 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 4.3, 1.6 Hz, 1H), 6.99–6.94 (m, 2H), 5.79 (ddt, *J* = 17.3, 10.1, 3.3 Hz, 1H), 5.01 (add, *J* = 17.1, 1.5 Hz, 1H), 4.96 (d, *J* = 10.3, Hz, 1H), 4.92 (dd, *J* = 6.9, 3.9 Hz, 1H), 2.10 (q, *J* = 7.1 Hz, 2H), 2.05–2.00 (m, 1H), 1.94–1.78 (m, 2H), 1.60–1.51 (m, 1H), 1.48–1.38 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 148.9, 138.6, 126.7, 124.7, 123.9, 115.0, 70.3, 38.8, 33.6, 25.2; **IR** (neat) 3342, 3074, 2934, 2859 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{10}H_{14}SOH$ (M + H)$^+$ 183.0844, found 183.0844; **[α]$^{26}$$_D$** +21 (*c* 1.0, $CHCl_3$); **SFC** analysis (OJ-H, 3% IPA, 2.5 mL/min) indicated 96% ee: $t_R$ (major) = 6.0 minutes, $t_R$ (minor) = 5.1 minutes.



**(*R*)-3.53.** Using representative procedure F outlined above, the following amounts of reagents were used: ketone **3.58** (0.52 g, 2.8 mmol, 1.0 equiv), (*S*)-Me-CBS (64 mg, 0.28 mmol, 0.10 equiv), catecholborane (0.60 mL, 5.6 mmol, 2.0 equiv), and PhMe (20 mL). After extraction with $Et_2O$, the combined organics were removed in vacuo, with much care taken to avoid heating. Heating the mixture under vacuum prior to column chromatography causes irreversible complexation of the desired product with boron reagents present from the reaction. The remaining solvent (mostly PhMe) was removed by running the mixture through a plug of silica. Flash column chromatography (10% $Et_2O$/hexanes) afforded the title compound as a clear oil (0.37 g, 2.2 mmol, 80%). Enantiomeric excess could not be determined for the title compound using SFC and chiral GC instrumentation. **TLC R$_f$** = 0.3 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.37 (s, 1H), 6.33 (dd, *J* = 1.7, 1.1 Hz, 1H), 6.23 (d, *J* = 2.9 Hz, 1H), 5.80 (ddt, *J* = 17.1, 10.2, 3.3 Hz, 1H), 5.01 (add, *J* = 17.1, 1.5 Hz, 1H), 4.96 (d, *J* = 10.2, Hz, 1H), 4.68 (t, *J* = 7.0 Hz, 1H), 2.10 (q, *J* = 7.0 Hz, 2H), 1.94 (br s, 1H), 1.90–1.83 (m, 2H), 1.55 (sep, *J* = 7.2 Hz, 1H), 1.42 (sep, *J* = 7.3 Hz, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 156.9, 142.0, 138.6, 114.9, 110.3, 106.0, 67.8, 35.1, 33.6, 24.9; **IR** (neat) 3348, 3077, 2932, 2861 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{10}H_{14}O_2NH_4$ (M + $NH_4$)$^+$ 184.1338, found 184.1329; **[α]$^{24}$$_D$** +14 (*c* 1.0, $CHCl_3$).

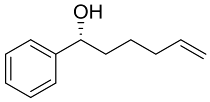


**(*R*)-3.70.** Using representative procedure F outlined above, the following amounts of reagents were used: ketone **3.65** (0.698 g, 2.77 mmol, 1.00 equiv), (*S*)-Me-CBS (63 mg, 0.28 mmol, 0.10 equiv), catecholborane (0.59 mL, 5.5 mmol, 2.0 equiv), and PhMe (20 mL). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a clear oil (0.295 g, 1.16 mmol, 42%, 88% ee). **TLC $R_f$** = 0.6 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 3H), 7.75 (s, 1H), 7.49–7.41 (m, 3H), 5.85 (ddt, *J* = 17.1, 10.1, 4.8 Hz, 1H), 5.07–4.97 (m, 3H), 2.15–2.04 (m, 2H), 1.90–1.85 (br s, 1H), 1.82 (dd, *J* = 14.7, 8.7 Hz, 1H), 1.66 (dd, *J* = 14.6, 3.3 Hz, 1H), 1.02 (s, 3H), 0.98 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 144.0, 135.7, 133.5, 133.0, 128.5, 128.0, 127.8, 126.3, 125.9, 124.27, 124.25, 117.3, 72.3, 50.7, 47.5, 33.5, 27.9, 27.8; **IR** (neat) 3392, 3057, 2956, 1601 $cm^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{18}H_{22}ONH_4$ $(M + NH_4)^+$ 272.2014, found 272.2009; **$[\alpha]^{23}_D$** +112 (*c* 0.5, $CHCl_3$); **SFC** analysis (OD-H, 10% IPA, 2.5 mL/min) indicated 88% ee: $t_R$ (major) = 11.5 minutes, $t_R$ (minor) = 10.1 minutes.



**(*R*)-3.71.** Using representative procedure F outlined above, the following amounts of reagents were used: ketone **3.66** (0.500 g, 1.94 mmol, 1.00 equiv), (*S*)-Me-CBS (57 mg, 0.25 mmol, 0.13 equiv), catecholborane (0.40 mL, 3.8 mmol, 2.0 equiv), and PhMe (20 mL). The product was purified by flash column chromatography (15% EtOAc/hexanes) to afford the title compound as a clear oil (0.280 g, 1.02 mmol, 56%, 85% ee). **TLC $R_f$** = 0.5 (15% EtOAc/hexanes, UV active);

**m.p**. = 54–56 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.84–7.80 (m, 1H), 7.74–7.70 (m, 1H), 7.33 (tdd, *J* = 14.6, 7.1, 1.4 Hz, 2H), 7.18 (s, 1H), 5.88 (, *J* = 16.8, 10.4, 7.4 Hz, 2H), 5.19 (dd, *J* = 7.7, 3.0 Hz, 1H), 5.11–5.03 (m, 2H), 2.13 (ddt, *J* = 7.4, 3.4, 1.3 Hz, 2H), 2.04 (s, 1H), 1.89 (d, *J* = 8.2, 1H), 1.85 (d, *J* = 3.8 Hz, 1H), 1.05 (s, 3H), 1.02 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 151.5, 139.7, 139.5, 135.6, 124.5, 124.4, 123.7, 122.7, 119.7, 117.6, 68.7, 50.8, 47.5, 33.6, 27.8, 27.7; **IR** (neat) 3403, 3071, 2956, 1458, 1436, 1366, 913 $cm^{-1}$; **HRMS** (TOF MS ES+) *m/z* calcd for $C_{16}H_{20}OSNa$ $(M + Na)^+$ 283.1133, found 283.1122. **$[\alpha]^{30}_D$** +25 (*c* 1.1, $CHCl_3$); **SFC** analysis (OD-H, 15% IPA, 2.5 mL/min) indicated 85% ee: tR (major) = 6.3 minutes, $t_R$ (minor) = 5.8 minutes.



**(*R*)-3.54.** Using representative procedure F outlined above, the following amounts of reagents were used: ketone **3.59** (0.435 g, 2.50 mmol, 1.00 equiv), (*S*)-Me-CBS (57 mg, 0.25 mmol, 0.10 equiv), catecholborane (0.53 mL, 5.0 mmol, 2.0 equiv), and PhMe (15 mL). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a clear oil (0.396 g, 2.26 mmol, 90%). Analytical data is consistent with literature values.[41] **TLC R$_f$** = 0.3 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.38–7.31 (m, 4H), 7.30–7.25 (m, 1H), 5.78 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 4.99 (d, *J* = 17.0 Hz, 1H), 4.94 (d, *J* = 10.3 Hz, 1H), 4.70–4.64 (m, 1H), 2.08 (dd, *J* = 14.2, 7.1 Hz, 2H), 1.86–1.76 (m, 2H), 1.76–1.68 (m, 1H), 1.57–1.48 (m, 1H), 1.43–1.33 (m, 1H); **$^{13}$C NMR** (125

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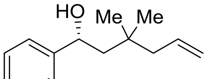
[41] Bussche-Hunnefeld, J. L.; Seebach, D. *Tetrahedron* **1992**, *18*, 5719–5730.

MHz, $CDCl_3$) δ 144.9, 138.7, 128.6, 127.7, 126.0, 114.8, 74.7, 38.6, 33.7, 25.2; **[α]$^{23}$$_D$** +38 (*c* 1.1, $CHCl_3$).



(*R*)-**SI-23**

**(*R*)-3.72.** Using representative procedure F outlined above, the following amounts of reagents were used: ketone **3.67** (0.42 g, 2.1 mmol, 1.0 equiv), (*S*)-Me-CBS (47 mg, 0.21 mmol, 0.10 equiv), catecholborane (0.44 mL, 4.1 mmol, 2.0 equiv), and PhMe (20 mL). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a clear oil (0.207 g, 1.01 mmol, 50%, 92% ee). Analytical data is consistent with literature values.[42] **TLC R$_f$** = 0.4 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 4.3 Hz, 4H), 7.29–7.23 (m, 1H), 5.85 (ddt, *J* = 17.2, 10.1, 4.9 Hz, 1H), 5.08–4.99 (m, 2H), 4.85 (dt, *J* = 8.6, 3.2 Hz, 1H), 2.13–2.03 (m, 2H), 1.80–1.72 (m, 2H), 1.59 (dd, *J* = 14.7, 3.3 Hz, 1H), 1.00 (s, 3H), 0.97 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 146.6, 135.7, 128.7, 127.5, 125.8, 117.3, 72.3, 50.9, 47.4, 33.5, 27.82, 27.79; **IR** (neat) 3392, 2956, 1366 cm$^{-1}$; **[α]$^{27}$$_D$** +55 (*c* 1.2, $CHCl_3$); **SFC** analysis (OD-H, 10% IPA, 2.5 mL/min) indicated 92% ee: t$_R$ (major) = 1.8 minutes, t$_R$ (minor) = 2.1 minutes.

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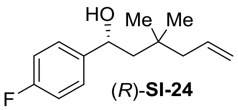
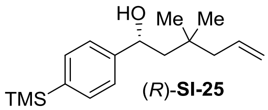
[42] Kim, H.; Park, Y.; Hong, J. *Angew. Chem,. Int. Ed.* **2009**, *48*, 7577–7581.



(*R*)-**SI-24**

**(*R*)-3.73.** Using representative procedure F outlined above, the following amounts of reagents were used: ketone **3.68** (0.632 g, 2.87 mmol, 1.00 equiv), (*S*)-Me-CBS (90 mg, 0.39 mmol, 0.17 equiv), catecholborane (0.62 mL, 5.8 mmol, 2.5 equiv), and PhMe (20 mL). The product was purified by flash column chromatography (15% EtOAc/hexanes) to afford the title compound as a clear oil (0.466 g, 2.10 mmol, 73%, 90% ee). **TLC $R_f$** = 0.3 (5% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.45–7.37 (m, 2H), 7.13 (at, *J* = 8.8 Hz, 2H), 5.97 (ddt, *J* = 17.6, 10.3, 7.4 Hz, 1H), 5.22–5.10 (m, 2H), 4.93 (dd, *J* = 8.5, 3.5 Hz, 1H), 2.19 (add, *J* = 7.4, 3.9 Hz, 1H), 2.15 (s, 1H), 1.85 (dd, *J* = 14.7, 8.6 Hz, 1H), 1.71 (dd, *J* = 14.7, 3.5 Hz, 1H), 1.11 (s, 3H), 1.08 (s, 3H); **$^{13}$C NMR** (100 MHz, $CDCl_3$) δ 162.2 (d, *J* = 245 Hz), 142.5 (d, *J* = 3 Hz), 135.7, 127.6 (d, *J* = 8 Hz), 117.4, 115.5 (d, *J* = 21 Hz), 71.6, 51.0, 47.5, 33.5, 27.91, 27.88; **IR** (neat) 3394, 2957, 1638, 1604, 1508, 1155 cm$^{-1}$; **HRMS** (TOF MS CI+) *m/z* calcd for $C_{14}H_{19}FOH$ $(M + H)^+$ 223.1498, found 223.1499; **$[\alpha]^{27}_D$** +45 (*c* 2.0, $CHCl_3$); **SFC** analysis (OJ-H, 10% IPA, 2.5 mL/min) indicated 90% ee: $t_R$ (major) = 9.5 minutes, $t_R$ (minor) = 10.3 minutes.

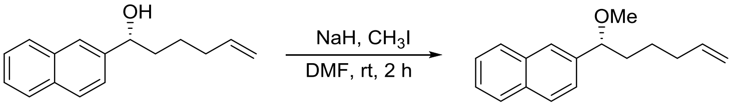


(*R*)-**SI-25**

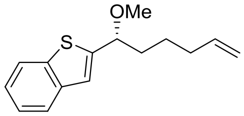
**(*R*)-3.74.** Using representative procedure F outlined above, the following amounts of reagents were used: ketone **3.69** (0.612 g, 2.25 mmol, 1.00 equiv), (*S*)-Me-CBS (63 mg, 0.28 mmol, 0.12 equiv), catecholborane (0.50 mL, 4.5 mmol, 2.0 equiv), and PhMe (20 mL). The product was purified by flash column chromatography (15% EtOAc/hexanes) to afford the title compound as a clear oil (0.283 g, 1.02 mmol, 46%, 92% ee). **TLC R$_f$** = 0.3 (5% EtOAc/hexanes, UV active, stain with KMnO$_4$); **$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 7.7 Hz, 2H), 5.84 (ddt, *J* = 17.6, 10.2, 7.5 Hz, 1H), 5.06–4.98 (m, 2H), 4.85–4.77 (m, 1H), 2.13–2.03 (m, 2H), 1.79–1.70 (m, 1H), 1.73 (ad, *J* = 8.8 Hz, 1H), 1.57 (dd, *J* = 14.8, 2.8 Hz, 1H), 1.00 (s, 3H), 0.97 (s, 3H), 0.25 (s, 9H); **$^{13}$C NMR** (125 MHz, CDCl$_3$ δ 147.2, 139.5, 135.7, 133.7, 125.1, 117.2, 72.2, 50.8, 47.4, 33.4, 27.8, 27.7, -1.0; **IR** (neat) 3388, 2955, 1638, 1600, 1386, 1248, 912 cm$^{-1}$; **HRMS** (TOF MS CI+) *m/z* calcd for $C_{17}H_{28}OSiH$ (M + H)$^+$ 277.1988, found 277.1990; **[α]$^{27}_D$** +38 (*c* 1.4, CHCl$_3$); **SFC** analysis (OJ-H, 10% IPA, 2.5 mL/min) indicated 92% ee: t$_R$ (major) = 1.9 minutes, t$_R$ (minor) = 2.3 minutes.

## Alkylations of enantioenriched alcohols for Table 3.2 entries 1–9

***General Procedure G.*** *Methylation of benzylic alcohols.*

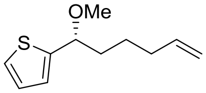


**(*R*)-3.5.** In a glovebox, NaH (42 mg, 1.8 mmol, 1.6 equiv) was added to a flame-dried round bottom flask equipped with a stir bar. The flask was removed from the glovebox, and anhydrous DMF (2 mL) was added. To this slurry was added a solution of alcohol (*R*)-**3.50** (0.244 g, 1.10 mmol, 1.00 equiv) in DMF (4 mL) at 0 °C. The solution was warmed to room temperature over 30 min, then cooled to 0 °C and neat methyl iodide (0.14 mL, 2.2 mmol, 2.0 equiv) was added. The reaction was warmed to ambient temperature and stirred an additional 1.5 h. The reaction was quenched at 0 °C with 1M HCl and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with water (1 x 50 mL) and brine (1 x 50 mL), dried over MgSO$_4$, and concentrated in vacuo. The product was purified by flash column chromatography (2–7% $Et_2O$/hexanes) to afford the title compound as a colorless oil (0.210 g, 0.890 mmol, 81%, 99% ee). **TLC $R_f$** = 0.7 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.88–7.80 (m, 3H), 7.70 (s, 1H), 7.51–7.41 (m, 3H), 5.76 (ddt, *J* = 17.1, 10.2, 3.2 Hz, 1H), 4.97 (ad, *J* = 17.1, Hz, 1H), 4.92 (d, *J* = 10.2 Hz, 1H), 4.25 (t, *J* = 6.9 Hz, 1H), 3.24 (s, 3H) 2.06 (q, *J* = 7.1 Hz, 2H), 1.95–1.86 (m, 1H), 1.77–1.68 (m, 1H), 1.58–1.48 (m, 1H) 1.41–1.31 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 139.9, 138.8, 133.3, 133.2, 128.5, 128.0, 127.9, 126.2, 126.0, 125.9, 124.6, 114.8, 84.2, 56.9, 37.6, 33.8, 25.3; **IR** (neat) 3057, 2859, 1601, 1098 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{17}H_{20}O$ $(M)^+$ 240.1514, found 240.1523; **$[\alpha]^{25}_D$** +82 (*c* 1.5, $CHCl_3$); **SFC** analysis (OD-H, 4% IPA, 2.5 mL/min) indicated 99% ee: $t_R$ (major) = 5.3 minutes, $t_R$ (minor) = 5.0 minutes.

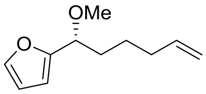


**(*R*)-3.6.** Using representative procedure G outlined above, the following amounts of reagents were used: alcohol (*R*)-**3.51** (76 mg, 0.33 mmol, 1.0 equiv), NaH (13 mg, 0.52 mmol, 1.6 equiv), methyl iodide (0.030 mL, 0.42 mmol, 1.3 equiv) and DMF (4 mL). The product was purified by flash column chromatography (2–10% EtOAc/hexanes) to afford the title compound as a colorless oil (52 mg, 0.21 mmol, 64%, 97% ee). **TLC $R_f$** = 0.7 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 7.3 Hz, 1H), 7.33 (at, *J* = 7.5 Hz, 1H), 7.29 (at, *J* = 7.3 Hz, 1H), 7.18 (s, 1H), 5.77 (ddt, *J* = 17.1, 10.3, 3.3 Hz, 1H), 4.99 (ad, *J* = 17.1 Hz, 1H), 4.94 (ad, *J* = 10.2 Hz, 1H), 4.43 (t, *J* = 6.7 Hz, 1H), 3.31 (s, 3H), 2.07 (q, *J* = 7.0 Hz, 2H), 2.01–1.91 (m, 1H), 1.84–1.75 (m, 1H), 1.59–1.49 (m, 1H) 1.46–1.35 (m, 1H); **$^{13}$C**

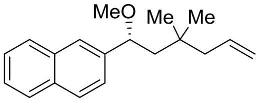
**NMR** (125 MHz, $CDCl_3$) δ 147.4, 139.8, 139.5, 138.6, 124.30, 124.26, 123.4, 122.7, 122.0, 114.9, 80.1, 56.9, 37.5, 33.6, 25.1; **IR** (neat) 3060, 2928, 2820, 1458 $cm^{-1}$; **HRMS** (TOF MS CI+) *m / z* calcd for $C_{15}H_{18}OS$ $(M)^+$ 246.1078, found 246.1075; **$[\alpha]^{24}_D$** +60 (*c* 3.0, $CHCl_3$); **SFC** analysis (OJ-H, 10% IPA, 2.5 mL/min) indicated 97% ee: $t_R$ (major) = 3.6 minutes, $t_R$ (minor) = 3.2 minutes.



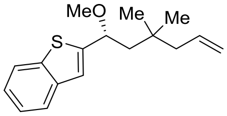
**(*R*)-3.8.** Using representative procedure G outlined above, the following amounts of reagents were used: alcohol (*R*)-**3.52** (0.219 g, 1.20 mmol, 1.00 equiv), NaH (46 mg, 1.9 mmol, 1.6 equiv), methyl iodide (0.15 mL, 2.4 mmol, 2.0 equiv) and DMF (6 mL). The product was purified by flash column chromatography (2–10% EtOAc/hexanes) to afford the title compound as a colorless oil (0.178 g, 0.910 mmol, 76%, 97% ee). **TLC $R_f$** = 0.8 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 5.1 Hz, 1H), 6.98–6.94 (m, 2H), 5.79 (ddt, *J* = 17.1, 10.4, 3.3 Hz, 1H), 4.99 (adq, *J* = 17.1, 1.5 Hz, 1H), 4.94 (d, *J* = 10.2, Hz, 1H), 4.36 (t, *J* = 7.0 Hz, 1H), 3.25 (s, 3H), 2.06 (q, *J* = 7.2 Hz, 2H), 1.97–1.88 (m, 1H), 1.79–1.70 (m, 1H), 1.56–1.46 (m, 1H), 1.43–1.32 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 146.3, 138.7, 126.4, 125.4, 125.0, 114.8, 79.4, 56.6, 37.9, 33.6, 25.2; **IR** (neat) 3075, 2935, 1440 $cm^{-1}$; **HRMS** (TOF MS CI+) *m / z* calcd for $C_{11}H_{16}OS$ $(M)^+$ 196.0922, found 196.0932; **$[\alpha]^{27}_D$** +70 (*c* 1.0, $CHCl_3$); **SFC** analysis (OD-H, 1% IPA, 2.5 mL/min) indicated 97% ee: $t_R$ (major) = 3.4 minutes, $t_R$ (minor) = 3.6 minutes.



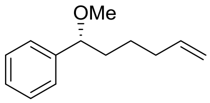
**(*R*)-3.10.** Using representative procedure G outlined above, the following amounts of reagents were used: alcohol (*R*)-**3.53** (0.20 g, 1.2 mmol, 1.0 equiv), NaH (46 mg, 1.9 mmol, 1.6 equiv), methyl iodide (0.15 mL, 2.4 mmol, 2.0 equiv) and DMF (6 mL). The product was purified by flash column chromatography (2–10% EtOAc/hexanes) to afford the title compound as a colorless oil (0.168 g, 0.936 mmol, 78%, 93% ee). **TLC R$_f$** = 0.8 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 6.34 (dd, *J* = 2.8, 1.7 Hz, 1H), 6.26 (d, *J* = 3.1 Hz, 1H), 5.78 (ddt, *J* = 17.1, 10.3, 3.1 Hz, 1H), 4.99 (adq, *J* = 17.1, 1.5 Hz, 1H), 4.94 (d, *J* = 10.2, Hz, 1H), 4.16 (t, *J* = 7.0 Hz, 1H), 3.25, (s, 3H), 2.06 (q, *J* = 7.0 Hz, 2H), 1.95–1.86 (m, 1H), 1.85–1.76 (m, 1H), 1.54–1.43 (m, 1H), 1.40–1.28 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 154.5, 142.3, 138.7, 114.8, 110.0, 108.0, 76.6, 56.5, 33.6 (2C), 25.0; **IR** (neat) 2979, 2820, 1641, 1504 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{11}H_{16}O_2$ $(M)^+$ 180.1150, found 180.1145; **[α]$^{26}_D$** +54 (*c* 1.3, $CHCl_3$); **GC** analysis: 93% ee (CYCLODEX B, inlet temp 220 °C, flow rate 5.3781 mL/min, initial temp 55 °C, hold 2 min, ramp 10 °C/min up to 180 °C, hold 3 min, ramp 40 °C/min up to 230 °C, hold 1 min, $t_{R1}$ = 33.72 min, $t_{R2}$ = 33.75.



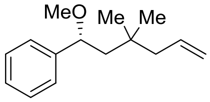
**(*R*)-3.12.** Using representative procedure G outlined above, the following amounts of reagents were used: alcohol (*R*)-**3.70** (0.255 g, 1.00 mmol, 1.00 equiv), NaH (48 mg, 2.0 mmol, 2.0 equiv), methyl iodide (0.081 mL, 1.3 mmol, 1.3 equiv) and DMF (4 mL). The product was purified by flash column chromatography (2–5% EtOAc/hexanes) to afford the title compound as a colorless oil (0.239 g, 0.890 mmol, 89%, 88% ee). **TLC R$_f$** = 0.8 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.86–7.80 (m, 3H), 7.71 (s, 1H), 7.50–7.41 (m, 3H), 5.85 (ddt, *J* = 16.9, 9.9, 4.9 Hz, 1H), 5.05–4.98 (m, 2H), 4.38 (dd, *J* = 8.9, 3.1 Hz, 1H), 3.19 (s, 3H), 2.12–2.02 (m, 2H), 1.87 (dd, *J* = 14.8, 8.6 Hz, 1H), 1.53 (dd, *J* = 14.8, 3.1 Hz, 1H), 0.99 (s, 3H), 0.96 (s, 3H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 141.4, 135.8, 133.4, 133.1, 128.5, 127.94, 127.85, 126.2, 125.8, 125.4, 124.7, 117.2, 81.8, 56.4, 50.0, 47.5, 33.5, 27.78, 27.75; **IR** (neat) 3056, 2925, 1601, 1154 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{19}H_{24}O$ (M)$^+$ 268.1827, found 268.1837; **[α]$^{23}_{D}$** +69 (*c* 1.3, CHCl$_3$); **SFC** analysis (OJ-H, 4% IPA, 2.5 mL/min) indicated 88% ee: t$_R$ (major) = 4.1 minutes, t$_R$ (minor) = 3.8 minutes.



**(*R*)-3.14.** Using representative procedure G outlined above, the following amounts of reagents were used: alcohol (*R*)-**3.71** (0.190 g, 0.730 mmol, 1.00 equiv), NaH (36 mg, 1.5 mmol, 2.1 equiv), methyl iodide (0.10 mL, 1.1 mmol, 1.5 equiv) and THF (3 mL). The product was purified by flash column chromatography (5% EtOAc/hexanes) to afford the title compound as a pale yellow oil (0.191 g, 0.696 mmol, 95%). **TLC R$_f$** = 0.9 (15% EtOAc/hexanes, UV active); **$^1$H NMR** (CDCl$_3$, 400 MHz) δ 7.86–7.82 (m, 1H), 7.76–7.72 (m, 1H), 7.34 (tdd, *J* = 14.8, 7.1, 1.4 Hz, 2H), 7.19 (s, 1H), 5.87 (m, 2H), 5.10–5.02 (m, 2H), 4.60 (dd, *J* = 8.5, 3.5 Hz, 1H), 3.30 (s, 3H), 2.09 (ddt, *J* = 7.5, 3.2, 1.1 Hz, 2H), 1.98, (dd, *J* = 14.7, 8.4 Hz, 1H), 1.70 (dd, *J* = 14.7, 3.4 Hz, 1H), 1.02 (s, 3H), 0.99 (s, 3H); **$^{13}$C NMR** (CDCl$_3$, 100 MHz) δ 149.2, 139.9, 139.6, 135.7, 124.4, 124.3, 123.5, 122.8, 121.2, 117.4, 77.8, 56.6, 50.1, 47.6, 33.6, 27.8, 27.7; **IR** (neat) 3071, 2955, 1458, 1438, 1098, 912 cm$^{-1}$; **HRMS** (TOF MS ES+) *m/z* calcd for $C_{17}H_{22}OSNa$ (M + Na)$^+$ 297.1289, found 297.1288; **[α]$^{29}_{D}$** +60 (*c* 1.5, CHCl$_3$).

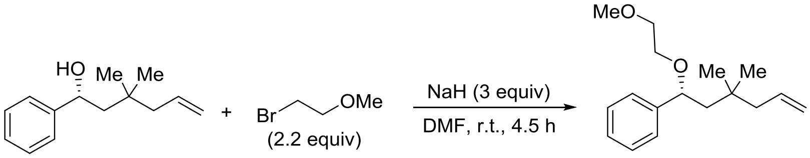


**(*R*)-3.16.** Using representative procedure G outlined above, the following amounts of reagents were used: alcohol (*R*)-**3.54** (0.264 g, 1.50 mmol, 1.00 equiv), NaH (43 mg, 1.8 mmol, 1.2 equiv), methyl iodide (0.13 mL, 2.1 mmol, 1.4 equiv) and DMF (3 mL). The product was purified by flash column chromatography (2–5% $Et_2O$/hexanes) to afford the title compound as a colorless oil (0.257 g, 1.35 mmol, 90%, 93% ee). **TLC $R_f$** = 0.7 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.1 Hz, 3H), 5.77 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 4.98 (d, *J* = 17.0 Hz, 1H), 4.92 (d, *J* = 10.3 Hz, 1H), 4.09 (t, *J* = 6.9 Hz, 1H), 3.20 (s, 3H), 2.04 (dd, *J* = 14.2, 6.7 Hz, 2H), 1.86–1.77 (m, 1H), 1.68–1.58 (m, 1H), 1.55–1.45 (m, 1H), 1.39–1.29 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 142.5, 138.8, 128.5, 127.6, 126.8, 114.7, 84.1, 56.8, 37.8, 33.8, 25.3; **IR** (neat) 3056, 2925, 1601, 1154 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{13}H_{18}ONH_4$ $(M + NH_4)^+$ 208.1701, found 208.1706; **$[\alpha]^{23}_D$** +77 (*c* 0.7, $CHCl_3$); **SFC** analysis (OD-H, 5% IPA, 2.5 mL/min) indicated 93% ee: $t_R$ (major) = 1.9 minutes, $t_R$ (minor) = 2.1 minutes.



**(*R*)-3.18.** Using representative procedure G outlined above, the following amounts of reagents were used: alcohol (*R*)-**3.67** (0.125 g, 0.610 mmol, 1.00 equiv), NaH (21 mg, 0.85 mmol, 1.4 equiv), methyl iodide (0.046 mL, 0.73 mmol, 1.2 equiv) and DMF (3 mL). The product was purified by flash column chromatography (2–5% EtOAc/hexanes) to afford the title compound as a colorless oil (0.116 g, 0.530 mmol, 87%, 94% ee). **TLC $R_f$** = 0.8 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.6 Hz, 2H), 7.30–7.231 (m, 3H), 5.84 (m, 1H), 5.05–4.97 (m, 2H), 4.22 (dd, *J* = 8.7, 2.3 Hz, 1H), 3.15 (s, 3H), 2.09–1.99 (m, 2H), 1.78 (dd, *J* = 14.8, 8.7 Hz, 1H), 1.45 (dd, *J* = 14.8, 2.3 Hz, 1H), 0.96 (s, 3H), 0.94 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ144.0, 135.8, 128.5, 127.4, 126.6, 117.1, 81.7, 56.3, 50.2, 47.5, 33.5, 27.7; **IR** (neat) 3056, 2925, 1601, 1154 $cm^{-1}$; **HRMS** (TOF MS EI+) *m* / *z* calcd for $C_{15}H_{22}O$ $(M)^+$ 218.1671, found 218.1667; **$[\alpha]^{23}_D$** +88 (*c* 1.0, $CHCl_3$); **SFC** analysis (OD-H, 1% IPA, 2.5 mL/min) indicated 94% ee: $t_R$ (major) = 3.0 minutes, $t_R$ (minor) = 3.2 minutes.

***General Procedure H.*** *Alkylation of benzylic alcohol with 2-bromoethyl methyl ether*



**(*R*)-3.20.** Alkylation of alcohols was performed according to a modified procedure reported by Lin.[43] Alcohol (*R*)-**3.67** (0.183 g, 0.900 mmol, 1.00 equiv) was dissolved in DMF (3.5 mL) and added to a slurry of NaH (65 mg, 2.7 mmol, 3.0 equiv) in DMF (1.3 mL) at 0 °C. The reaction mixture was stirred for 30 min at ambient temperature, and a solution of bromoethyl methyl ether (0.10 mL, 1.0 mmol, 1.1 equiv) in DMF (4.2 mL) was slowly added over 30 min at 0 °C. The reaction was stirred for an additional 1 h at ambient temperature, after which a second portion of bromoethyl methyl ether (0.10 mL, 1.1 mmol, 1.1 equiv) in DMF (4.2 mL) was slowly added over 30 min at 0 °C. After stirring for 2 h, saturated aqueous $NH_4Cl$ (15 mL) and EtOAc (20 mL)

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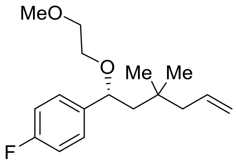
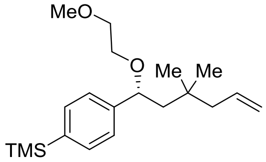
[43] Lin, Q. H.; Ball, G. E.; Bishop, R. *Tetrahedron* **1997**, *53*, 10899–10910.

were added at 0 °C. The layers were separated and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (5–10% EtOAc/hexanes) to afford the title compound as a colorless oil (0.185 g, 0.704 mmol, 78%, 92% ee). **TLC $R_f$** = 0.6 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.36–7.22 (m, 5H), 5.84 (ddt, *J* = 17.4, 9.8, 5.1 Hz, 1H), 5.04–4.97 (m, 2H), 4.39 (dd, *J* = 8.8, 2.6 Hz, 1H), 3.54–3.45 (m, 2H), 3.45–3.39 (m, 1H), 3.39–3.35 (m, 1H), 3.34 (s, 3H), 2.11–2.00 (m, 2H), 1.84 (dd, *J* = 14.6, 8.9 Hz, 1H), 1.44 (dd, *J* = 14.6, 2.2 Hz, 1H), 0.97 (s, 3H), 0.94 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 144.2, 136.0, 128.5, 127.4, 126.6, 117.0, 80.4, 72.2, 67.8, 59.0, 50.1, 47.4, 33.5, 27.8, 27.7; **IR** (neat) 2955, 2871, 1097 $cm^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{17}H_{26}O_2NH_4$ $(M + NH_4)^+$ 280.2277, found 280.2282; **$[\alpha]^{27}_D$** +66 (*c* 0.9, $CHCl_3$); **SFC** analysis (OD-H, 10% IPA, 2.5 mL/min) indicated 92% ee: $t_R$ (major) = 1.8 minutes, $t_R$ (minor) = 2.1 minutes.



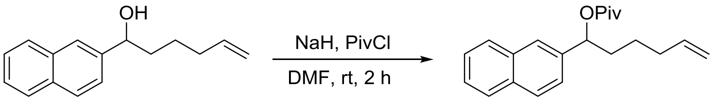
**(*R*)-3.21.** Using representative procedure H outlined above, the following amounts of reagents were used: alcohol (*R*)-**3.68** (0.377 g, 1.70 mmol, 1.00 equiv), NaH (100 mg, 4.08 mmol, 2.40 equiv), bromoethyl methyl ether (0.50 mL, 5.3 mmol, 3.1 equiv) and DMF (8 mL). The product was purified by flash column chromatography (5% EtOAc/hexanes) to afford the title compound as a colorless oil (0.252 g, 0.899 mmol, 53%). Enantiomeric excess could not be determined for the title compound using SFC and chiral GC instrumentation. **TLC $R_f$** = 0.6 (5% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.28–7.22 (m, 2H), 7.01 (at, *J* = 8.8 Hz, 2H), 5.86 (ddt, *J* = 17.6, 10.4, 7.5 Hz, 1H), 5.04–4.97 (m, 2H), 4.37 (dd, *J* = 8.7, 2.8 Hz, 1H), 3.53–3.31 (m, 4H), 3.34 (s, 3H), 2.10–1.99 (m, 2H), 1.82 (dd, *J* = 14.7, 8.8 Hz, 1H) 1.42 (dd, *J* = 14.7, 3.0 Hz, 1H), 0.96 (s, 3H), 0.93 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 162.0 (d, *J* = 245 Hz), 139.8 (d, *J* = 3 Hz), 135.8, 128.0 (d, *J* = 8 Hz), 117.0, 115.3 (d, *J* = 21 Hz), 79.7, 72.1, 67.7, 58.9, 50.0, 47.3, 33.4, 27.7, 27.6; **IR** (neat) 2955, 2871, 1638, 1603, 1507, 1220, 1092, 912 cm$^{-}$1; **HRMS** (TOF MS CI+) *m/z* calcd for $C_{17}H_{25}FO_2NH_4$ $(M + NH_4)^+$ 298.2182, found 298.2185; **$[\alpha]^{27}_D$** +54 (*c* 1.5, $CHCl_3$).



**(*R*)-3.23.** Using representative procedure H outlined above, the following amounts of reagents were used: alcohol (*R*)-**3.69** (0.197 g, 0.712 mmol, 1.00 equiv), NaH (52 mg, 2.2 mmol, 3.1 equiv), bromoethyl methyl ether (0.30 mL, 3.2 mmol, 4.5 equiv) and DMF (8 mL). The product was purified by flash column chromatography (5% EtOAc/hexanes) to afford the title compound as a colorless oil (0.128 g, 0.382 mmol, 54%). Enantiomeric excess could not be determined for the title compound using SFC and chiral GC instrumentation. **TLC $R_f$** = 0.6 (5% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 7.7 Hz, 2H), 5.86 (ddt, *J* = 17.9, 10.3, 7.5 Hz, 1H), 5.00 (m, 2H), 4.39 (dd, *J* = 9.2, 2.4 Hz, 1H), 3.53–3.35 (m, 4H), 3.35 (s, 3H), 3.36 (s, 3H), 2.11–2.01 (m, 2H), 1.83 (dd, *J* = 14.8, 9.2 Hz, 1H), 1.42 (dd, *J* = 14.8, 2.6 Hz, 1H), 0.98 (s, 3H), 0.95 (s, 3H), 0.25 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 144.7, 139.2, 135.9, 133.5, 125.8, 116.9, 80.3, 72.2, 67.8, 58.9, 50.1, 47.3, 33.5, 27.7, 27.6, -1.0; **IR** (neat) 2954, 1637, 1600, 1248, 1132, 911 cm$^{-1}$; **HRMS**

(TOF MS CI+) *m/z* calcd for $C_{20}H_{34}O_2SiNH_4$ $(M + NH_4)^+$ 352.2672, found 352.2670; **$[\alpha]^{29}_D$** +48 (*c* 1.4, $CHCl_3$).

**Esterification to provide benzylic pivalate 3.1**



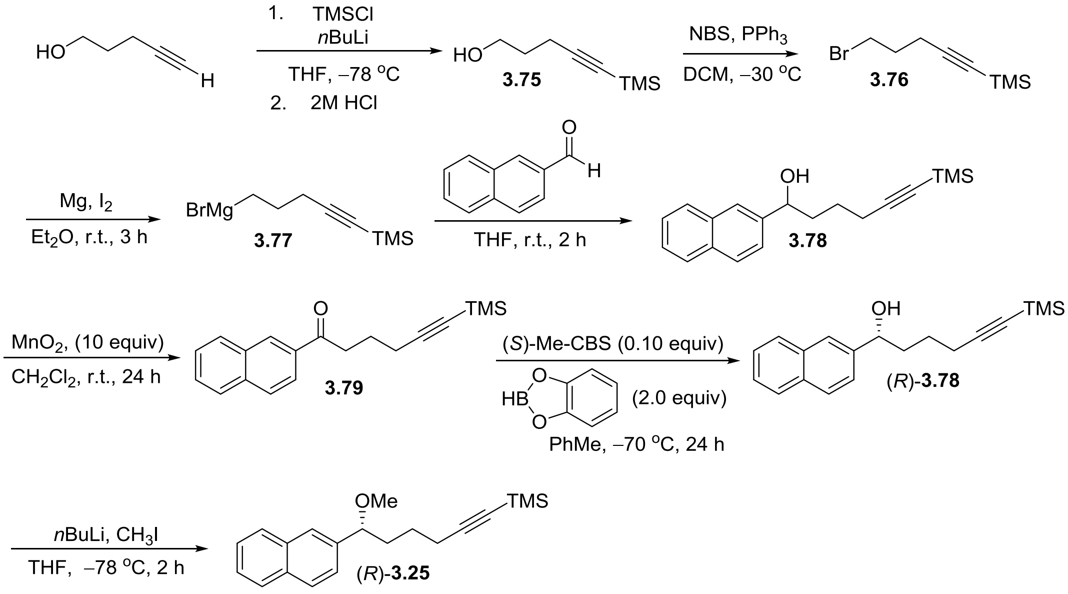
**3.1.** In a glovebox, a round bottom flask was equipped with a stir bar, and charged with NaH (84 mg, 3.5 mmol, 1.4 equiv). The flask was removed from the glovebox, and DMF (5 ml) was added, followed by a solution of *rac*-**3.50** (0.566 g, 2.50 mmol, 1.00 equiv) in DMF (8 mL). The reaction flask was cooled to 0 °C in an ice bath and pivaloyl chloride (0.30 mL, 2.5 mmol, 1.00 equiv) was slowly added over 15 min. The reaction was allowed to warm to room temperature and was stirred for 2 h before quenching with sat. $NH_4Cl$ (15 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine (1 x 25 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a clear, colorless oil (0.656 g, 2.20 mmol, 88%). **TLC $R_f$** = 0.5 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.85–7.78 (m, 3H), 7.75 (s, 1H), 7.50–7.41 (m, 3H), 5.86 (t, *J* = 6.8 Hz, 1H), 5.75 (ddt, *J* = 16.9, 9.9, 3.4 Hz, 1H), 4.99 (d, *J* = 17.2, Hz, 1H), 4.94 (d, *J* = 10.0 Hz, 1H), 2.12–1.94 (m, 3H), 1.91–1.81 (m, 1H), 1.55–1.33 (m, 2H), 1.22 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 117.8, 138.7, 138.4, 133.3, 133.1, 128.4, 128.2, 127.8, 126.3, 126.1, 125.5, 124.2, 115.0, 75.8, 39.0, 36.0, 33.5, 27.3, 24.9; **IR** (neat) 2976, 1721, 1153 $cm^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{21}H_{26}O_2Na$ $(M + Na)^+$ 333.1830, found 333.1821.

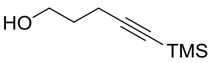
## SYNTHESIS AND CHARACTERIZATION OF SUBSTRATES FOR SCHEMES 3.2, 3.3, AND 3.5

### Alkyne 3.25 (Scheme 3.2)

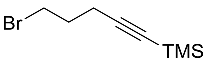
Alkyne (*R*)-3.**25** was prepared by Grignard addition of **3.77** into 2-naphthaldehyde. The resultant alcohol *rac*-**3.78** was oxidized and the ketone underwent enantioselective reduction and was alkylated.

***Scheme 3.9.*** Synthesis of alkyne (*R*)-**3.25** for Scheme 3.2





**3.75.** The TMS protected alkyne was prepared according to a modified procedure reported by Ramesh.[44] A flame-dried round bottom flask equipped with a stir bar was charged with 4-pentyn-1-ol (1.86 mL, 20.0 mmol, 1.00 equiv) and THF (50 mL) and cooled to –78 °C. *n*-Butyllithium (29 mL, 1.5 M in hexanes, 44 mmol, 2.2 equiv) was slowly added to the flask and stirred for 1 h at –78 °C. TMSCl (7.6 mL, 60 mmol, 3.0 equiv) was added and the reaction was allowed to warm slowly to ambient temperature overnight. The reaction was cooled to 0 °C and quenched with 2M HCl and stirred at ambient temperature until the *bis*-silylated product was no longer present by TLC. The reaction mixture was then extracted with $Et_2O$ (3 x 40 mL), and the combined organic layers were washed with brine, $NaHCO_3$ and with brine once more before drying over $MgSO_4$, filtration and concentration in vacuo. The product was purified by flash column chromatography (10–30% EtOAc/hexanes) to afford the title compound as a clear oil (2.64 g, 16.9 mmol, 84%). The analytical data is consistent with literature values.[13] **TLC $R_f$ =** 0.3 (10% EtOAc/Hexanes stain with $KMnO_4$); **$^1$H NMR** (400 MHz, $CDCl_3$) δ 3.76 (q, *J* = 5.9 Hz, 2H), 2.36 (t, *J* = 6.9 Hz, 2H), 1.78 (quin, *J* = 6.9 Hz, 2H), 1.59 (at, *J* = 5.9 Hz, 1H), 0.15 (s, 9H).



**3.76.** The bromide was prepared according to a modified procedure reported by Steliou.[45] A flame-dried round bottom flask equipped with a stir bar and septum was charged with anhydrous $CH_2Cl_2$ (40 mL) and alcohol **3.75** (2.64 g, 16.8 mmol, 1.00 equiv). Triphenylphosphine (5.3 g,

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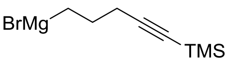
[44] Dener, J. M.; Hart, D. J.; Ramesh, S. *J. Org. Chem.* **1998**, *53*, 6022–6030.

[45] Yao, G.; Steliou, K. *Org. Lett.* **2002**, *4*, 485–488.

20 mmol, 1.2 equiv) was added in a single portion and the flask was cooled to –30 °C before addition of NBS (3.30 g, 18.5 mmol, 1.10 equiv) in a single portion. The reaction was then allowed to warm to ambient temperature over 5 h. $Et_2O$ (150 mL) was added to the reaction flask and the mixture was extracted with sat. $NaHCO_3$ (2 x 40 mL), washed with brine (1 x 50 mL), dried over $MgSO_4$ and concentrated in vacuo. A stir bar and 300 mL of hexanes were added to the remaining liquid and stirred for 15 min. The solution was filtered through celite and concentrated in vacuo. The product was purified by flash column chromatography (100% petroleum ether) to afford a colorless oil (2.33 g, 10.6 mmol, 63%). **TLC $R_f$** = 0.5 (100% petroleum ether, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.51 (t, *J* = 6.5 Hz, 2H), 2.42 (t, *J* = 6.5 Hz, 2H), 2.05 (quin, *J* = 6.6 Hz, 2H), 0.15 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 105.2, 85.9, 32.5, 31.6, 18.7, 0.2 (3C); **IR** (neat) 2959, 2177, 1248 cm$^{-1}$.



**3.77.** The Grignard reagent was prepared according to a modified procedure reported by Waldman.[46] A flame-dried 50 mL round bottom flask was equipped with a stir bar and charged with magnesium turnings (0.331 g, 13.8 mmol, 1.30 equiv), $Et_2O$ (8 mL) and a catalytic amount (1 mg) of iodine. Approximately 20% of the volume of neat **3.76** (2.32 g, 10.6 mmol, 1.00 equiv) was added in one portion. The reaction was heated briefly with a heat gun to reflux to initiate the reaction, and cooled to 0 °C after color change from red/pink to a colorless solution indicated initiation of the Grignard reagent. The remainder of the bromide **3.76** was added dropwise over

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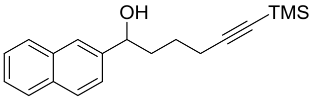
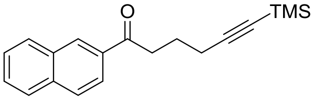
[46] Sommer, S.; Kühn, M.; Waldmann, H. *Adv. Synth. Catal.* **2008**, *350*, 1736.

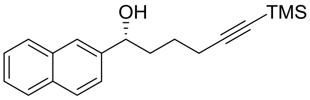
30 minutes. The reaction was warmed to ambient temperature and stirred for 2.5 h. The resultant Grignard reagent was titrated with iodine and LiCl (0.50 M).[2]



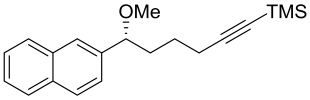
***rac*-3.78.** Using representative procedure A outlined above, the following amounts of reagents were used: 2-naphthaldehyde (0.610 g, 3.91 mmol, 1.00 equiv), **3.77** (0.50 M in $Et_2O$, 8.0 mL, 4.0 mmol, 1.0 equiv). The product was purified by flash column chromatography (5–10% EtOAc/hexanes) to afford the title compound as a white solid (1.03 g, 3.48 mmol, 89%). Analytical data is consistent with the values listed for (*R*)-**3.78** (vide infra).



**3.79.** Using representative procedure B outlined above, the following amounts of reagents were used: Alcohol *rac*-**3.78** (1.270 g, 4.480 mmol, 1.000 equiv), $MnO_2$ (3.89 g, 44.8 mmol, 10.0 equiv), $CH_2Cl_2$ (90 mL). Further purification after celite plug was unnecessary. The title compound was isolated as a white solid (1.28 g, 4.40 mmol, 98%). **TLC R$_f$** = 0.6 (10% EtOAc/hexanes, UV active,); **m.p.** = 65 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 9.3 Hz, 1H), 7.88 (d, *J* = 9.3 Hz, 1H), 7.61 (t, *J* = 7.0 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 3.25 (t, *J* = 7.5 Hz, 2H), 2.41 (t, *J* = 7.0 Hz, 2H), 2.03 (quin, *J* = 7.1 Hz, 2H), 0.16 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 199.9, 135.7, 134.4, 132.7, 129.8, 129.7, 128.59, 128.57, 127.9, 126.9, 124.0, 106.7, 85.7, 37.6, 23.3, 19.6, 0.3; **IR** (neat) 3059, 2957, 2230, 1680 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{19}H_{22}OSiH$ (M + H)$^+$ 295.1518, found 295.1519.



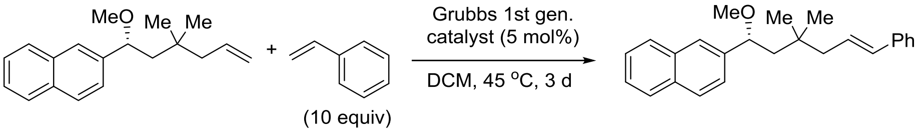
**(*R*)-3.78.** Using representative procedure F outlined above, the following amounts of reagents were used: ketone **3.79** (0.84 g, 3.0 mmol, 1.0 equiv), (*S*)-Me-CBS (68 mg, 0.30 mmol, 0.10 equiv), catecholborane (0.64 mL, 6.0 mmol, 2.0 equiv), and PhMe (25 mL). The product was purified by flash column chromatography (8–15% EtOAc/hexanes) to afford the title compound as a white solid (0.73 g, 2.6 mmol, 87%, 93% ee). **TLC $R_f$** = 0.2 (10% EtOAc/hexanes, UV active); **m.p.** = 48–49 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.87–7.81 (m, 3H), 7.79 (s, 1H), 7.51–7.45 (m, 3H), 4.92–4.87 (m, 1H), 2.33–2.22 (m, 2H), 2.03–1.90 (m, 3H), 1.73–1.63 (m, 1H), 1.61–1.51 (m, 1H), 0.14 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 142.0, 133.4, 133.1, 128.5, 128.1, 127.8, 126.3, 126.0, 124.8, 124.2, 107.2, 85.1, 74.3, 38.0, 24.9, 19.8, 0.3; **IR** (neat) 3266, 2941, 2173 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{19}H_{24}OSiNa$ $(M + Na)^+$ 319.1494, found 319.1498; **$[\alpha]^{24}_D$** +69 (*c* 2.8, $CHCl_3$); **SFC** analysis (OD-H, 12% IPA, 2.5 mL/min) indicated 93% ee: $t_R$ (major) = 11.6 minutes, $t_R$ (minor) = 9.5 minutes.



**(*R*)-3.25.** A flame-dried round bottom flask equipped with a stir bar and septum was charged with (*R*)-**3.78** (0.565 g, 2.00 mmol, 1.00 equiv) and anhydrous THF (15 mL). The flask was then cooled to –78 °C and *n*-butyllithium was slowly added (1.7 mL, 1.5 M in hexanes, 2.5 mmol, 1.3 equiv). The reaction was stirred for 45 min before the addition of methyl iodide (0.80 mL, 13 mmol, 5.0 equiv). The reaction was then allowed to warm to ambient temperature overnight before quenching with 1 M HCl at 0 °C. The mixture was extracted with $Et_2O$ (3 x 20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (8% EtOAc/hexanes) to afford the title compound as a colorless oil (0.565 g, 1.80 mmol, 91%, 84% ee). **TLC R$_f$** = 0.7 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.88–7.79 (m, 3H), 7.72 (s, 1H), 7.51–7.41 (m, 3H), 4.29 (t, *J* = 6.7 Hz, 1H), 3.24 (s, 3H), 2.29–2.18 (m, 2H), 2.02–1.93 (m, 1H), 1.89–1.80 (m, 1H), 1.69–1.58 (m, 1H), 1.55–1.45 (s, 1H), 0.13 (s, 9H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 139.7, 133.3, 133.2, 128.5, 128.0, 127.9, 126.3, 126.0, 125.9, 124.5, 107.2, 84.7, 83.7, 56.8, 37.1, 24.9, 19.9, 0.3; **IR** (neat) 2955, 2172, 1602 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{20}H_{26}OSiNH_4$ (M + NH$_4$)$^+$ 328.2097, found 328.2091; **[α]$^{24}_D$** +55 (*c* 1.1, CHCl$_3$); **SFC** analysis (OD-H, 10% IPA, 2.5 mL/min) indicated 84% ee: t$_R$ (major) = 3.6 minutes, t$_R$ (minor) = 3.9 minutes.

**Alkenes (*E*)-3.27 and (*Z*)-3.27 (Scheme 3.3)**

*Preparation of E 1,2-disubstituted olefin by cross-metathesis.*



**(*E*)-3.27.** The title compound was prepared according to a modified procedure reported by Grubbs.[47] In a glovebox, a flame-dried bomb flask was charged with a stir bar, (*R*)-**3.12** (0.178 g, 0.660 mmol, 1.00 equiv), and bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (27 mg, 0.053 mmol, 0.050 equiv). The flask was removed from the glovebox, and anhy-

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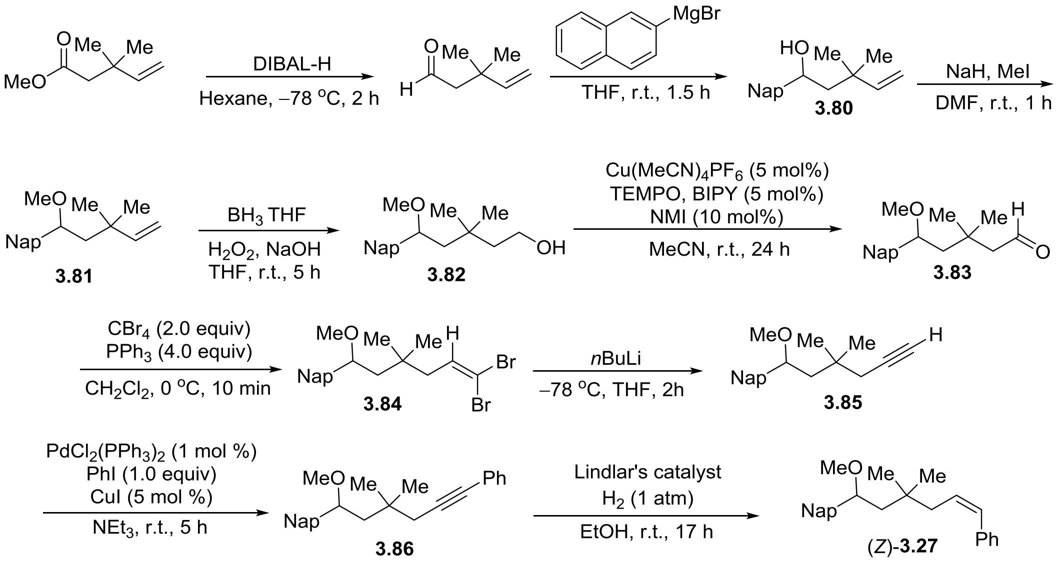
[47] Chatterjee, A. K; Choi, T–L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

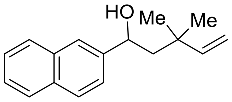
drous $CH_2Cl_2$ (25 mL) and styrene (0.76 mL, 6.6 mmol, 10 equiv) were added. The flask was sealed and heated to reflux over three days. The flask was then cooled to ambient temperature, and the solvent was removed in vacuo. The residue was purified by flash column chromatography to afford the title compound as a colorless oil (102 mg, 0297 mmol, 45%, 89% ee). **TLC $R_f$** = 0.9 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.86–7.77 (m, 3H), 7.71 (s, 1H), 7.51–7.41 (m, 3H), 7.33 (d, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 6.37 (d, *J* = 15.8 Hz, 1H), 6.27 (dt, *J* = 15.8, 7.4 Hz, 1H), 4.42 (dd, *J* = 8.6, 2.7 Hz, 1H), 3.20 (s, 3H), 2.27–2.16 (m, 2H), 1.93 (dd, *J* = 14.7, 8.8 Hz, 1H), 1.58 (dd, *J* = 14.8, 2.7 Hz, 1H), 1.06 (s, 3H), 1.02 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 141.3, 138.0, 113.4, 133.1, 132.4, 128.6, 128.5, 127.94, 127.86, 127.85, 127.0, 126.22, 126.15, 125.8, 125.5, 124.7, 81.9, 56.5, 50.2, 46.7, 34.3, 27.9 (2C); **IR** (neat) 3024, 3055, 2954, 1599 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{25}H_{28}O$ $(M)^+$ 344.2140, found 344.2131. **$[\alpha]^{24}_D$** +74 (*c* 2.6, $CHCl_3$); **SFC** analysis (OD-H, 10% IPA, 2.5 mL/min) indicated 89% ee: $t_R$ (major) = 7.3 minutes, $t_R$ (minor) = 8.3 minutes.

*Preparation of Z 1,2-disubstituted olefin.*

(*Z*)-**3.27** was prepared from 3,3-dimethyl-4-pentenoate by the sequence outlined in Scheme 3.10.

***Scheme 3.10.*** Synthesis of (*Z*)-3.27 for Scheme 3.3





**3.80.** The title compound was prepared according to a modified procedure reported by Roush.[48] To a solution of methyl 3,3-dimethyl-4-pentenoate (12 mL, 76 mmol, 1.0 equiv) in hexane (200 mL) was added at –78 °C, neat DIBAL-H (16.2 mL, 91.1 mmol, 1.2 equiv) dropwise over 45 min. The reaction was stirred for 1 h at this temperature and quenched with MeOH. A saturated solution of Rochelle's salt (100 mL) was added and the biphasic layer was stirred overnight. The

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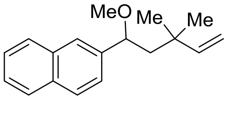
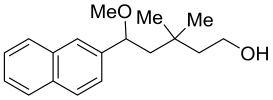
[48] Dineen, T. A.; Roush, W. R. *Org. Lett.* **2004**, *6*, 2043–2046.

layers were separated and the aqueous phase was extracted with $Et_2O$ (3 x 50 mL. The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. Vacuum distillation afforded the desired product (26%, as measured by $^1$H NMR) as a 2:1 mixture with the over-reduced, primary alcohol. This mixture was then dissolved in THF (40 mL) and was added to a solution of 2-naphthylmagnesium bromide. After stirring for 1 h at room temperature, the reaction was quenched with sat. $NH_4Cl$. The layers were separated, and the aqueous phase was extracted with (4 x 40 mL EtOAc). The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (3% EtOAc/hexanes) to afford the title compound as a white solid (3.92 g, 16.3 mmol, 22%). **TLC R$_f$** = 0.3 (10% EtOAc/hexanes, UV active); **m.p.** = 66 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.84–7.78 (m, 3H), 7.77 (s, 1H), 7.49–7.41 (m, 3H), 6.02 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.13–5.03 (m, 2H), 4.96 (d, *J* = 9.2 Hz, 1H), 2.23 (d, *J* = 1.8 Hz, 1H), 1.93 (dd, *J* = 14.7, 9.2 Hz, 1H), 1.75 (dd, *J* = 14.7, 1.8 Hz, 1H), 1.16 (s, 3H), 1.11 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 148.8, 143.0, 133.4, 132.9, 128.3, 128.0, 127.7, 126.1, 125.8, 124.2, 111.6, 72.4, 52.3, 36.8, 28.8, 26.0; **IR** (neat) 3397, 3056, 2926 cm$^{-1}$; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{17}H_{20}ONa$ $(M + Na)^+$ 263.1412, found 263.1413.



**3.81.** Using representative procedure G outlined above, the following amounts of reagents were used: alcohol **3.80** (3.70 g, 15.2 mmol, 1.00 equiv), NaH (0.511 g, 21.3 mmol, 1.4 equiv), methyl iodide (1.52 mL, 24.3 mmol, 1.60 equiv) and DMF (30 mL). The product was purified by flash column chromatography (2–5% EtOAc/hexanes) to afford the title compound as a colorless oil

(3.73 g, 14.7 mmol, 97%). **TLC R$_f$** = 0.7 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.85–7.79 (m, 3H), 7.69 (s, 1H), 7.50–7.41 (m, 3H), 5.89 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.01–4.94 (m, 2H), 4.27 (dd, *J* = 8.2, 2.8 Hz, 1H), 3.16 (s, 3H), 1.95 (dd, *J* = 14.6, 8.2 Hz, 1H), 1.64 (dd, *J* = 14.6, 3.0 Hz, 1H), 1.13 (s, 3H), 1.03 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 148.5, 141.1, 133.3, 133.0, 128.4, 127.9, 127.8, 126.1, 125.7, 125.4, 124.7, 110.4, 81.8, 56.3, 50.9, 36.8, 28.1, 26.9; **IR** (neat) 3056, 2926, 1601 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{18}H_{22}ONa$ $(M + Na)^+$ 277.1568, found 277.1575.



**3.82.** The title compound was prepared according to a modified procedure reported by Kumar.[49] In a 500 mL round bottom flask, a solution of **3.81** (3.70 g, 14.7 mmol, 1.00 equiv) in THF (60 mL) was cooled ot 0 °C and borane THF complex (29.4 mL, 1M in THF, 29.4 mmol, 2.0 equiv) was slowly added. The solution was stirred at ambient temperature for 3 h. The solution was cooled to 0 °C and 1M NaOH (17.2 mL, 103 mmol, 7.03 equiv) was added over 20 minutes. To this mixture was added 30% $H_2O_2$ (30.0 mL, 294 mmol, 20.0 equiv). The reaction was stirred another 2 h before diluting with EtOAc and extraction of the aqueous layer with EtOAc (3 x 30 mL). The combined organics were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (15% EtOAc/hexanes) to afford the title compound as a thick colorless oil (2.50 g, 9.18 mmol, 62%). **TLC R$_f$** = 0.2 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.87–7.79 (m,

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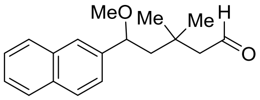
[49] Fernandes, R. A.; Bodas, M. R.; Kumar, P. *Tetrahedron*, **2002**, *58*, 1223–1227.

3H), 7.71 (s, 1H), 7.51–7.40 (m, 3H), 4.43 (d, *J* = 9.4 Hz, 1H), 3.83–3.71 (m, 2H), 3.22 (s, 3H), 2.54 (br s, 1H), 2.11 (dd, *J* = 15.1, 9.5 Hz, 1H), 1.86 (quintet, *J* = 7.3 Hz, 1H), 1.53 (dt, *J* = 14.2, 5.6 Hz, 1H), 1.46 (dd, *J* = 15.1, 1.6 Hz, 1H), 1.07 (s, 3H), 0.99 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 140.7, 133.3, 133.1, 128.5, 127.85, 127.78, 126.2, 125.9, 125.2, 124.4, 81.8, 59.9, 56.3, 49.9, 43.8, 32.6, 28.9, 28.8; **IR** (neat) 3353, 2928, 975 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{18}H_{24}O_2Na$ $(M + Na)^+$ 295.1674, found 295.1663.



**3.83.** The title compound was prepared according to a modified procedure reported by Stahl.[50] A solution of **3.82** (2.48 g, 9.10 mmol, 1.00 equiv) in dry MeCN (50 mL) was prepared in a 100 mL round bottom flask. To this solution was added tetrakis(acetonitrile)copper(I)hexafluorophosphate (170 mg, 0.455 mmol, 0.0500 equiv), 2,2’-dipyridyl (71 mg, 0.46 mmol, 0.050 equiv), 2,2,6,6-tetramethylpiperidinooxy (71 mg, 0.46 mmol, 0.050 equiv), and 1-methylimidazole (0.07 mL, 0.9 mmol, 0.1 equiv). The reaction was stirred open to air for 24 h. The solvent was removed in vacuo and the residue purified by flash column chromatography (5% EtOAc/hexanes) to afford the title compound as a slightly orange oil (2.09 g, 7.72 mmol, 85%). **TLC R$_f$** = 0.4 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 9.88 (at, *J* = 2.7 Hz, 1H), 7.87–7.79 (m, 3H), 7.71 (s, 1H), 7.51–7.39 (m, 3H), 4.41 (dd, *J* = 9.4, 1.8 Hz, 1H), 3.18 (s, 3H), 2.50 (dd, *J* = 15.0, 1.8 Hz, 1H), 2.36 (dd, *J* = 15.0, 2.6 Hz, 1H), 2.06 (dd, *J* = 15.0, 9.7 Hz, 1H), 1.63–1.55 (m, 1H), 1.20 (s, 3H), 1.14 (s, 3H); **$^{13}$C**

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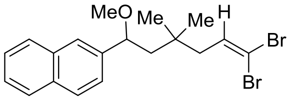
[50] Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901–16910.

**NMR** (125 MHz, $CDCl_3$) δ 203.7, 140.4, 133.3, 133.1, 128.6, 127.9, 127.8, 126.3, 125.9, 125.3, 124.4, 81.5, 56.3, 54.8, 50.4, 33.3, 29.2, 28.3; **IR** (neat) 2956, 1716, 1101 $cm^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{18}H_{22}O_2Na$ $(M + Na)^+$ 293.1518, found 293.1509.



**3.84.** The title compound was prepared according to a modified procedure reported by Hoppe.[51] A solution of triphenylphosphine (5.88 g, 22.4 mmol, 4.00 equiv) in $CH_2Cl_2$ (20 mL) was cooled to 0 °C in an ice bath. A solution of carbon tetrabromide (3.77 g, 11.1 mmol, 2.00 equiv) in $CH_2Cl_2$ (5 mL) was added (solution turns clear orange). After 2 minutes of stirring, a solution of **3.83** (1.52 g, 5.60 mmol, 1.00 equiv) in $CH_2Cl_2$ (5 mL) was added. The reaction was monitored by TLC for disappearance of **3.83**, and the reaction was complete after 10 min. The reaction mixture was run through a large plug of silica and eluted with $CH_2Cl_2$. The solvent was then removed in vacuo to afford the title compound as a thick pale yellow oil (2.28 g, 5.36 mmol, 96%). **TLC $R_f$** = 0.7 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.87–7.81 (m, 3H), 7.71 (s, 1H), 7.51–7.41 (m, 3H), 6.50 (t, *J* = 7.5 Hz, 1H), 4.41 (dd, *J* = 9.1, 2.0 Hz, 1H), 3.19 (s, 3H), 2.20–2.10 (m, 2H), 1.91 (dd, *J* = 15.0, 9.1 Hz, 1H), 1.52 (dd, *J* = 15.0, 2.0 Hz, 1H), 1.05 (s, 3H), 1.00 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 140.8, 136.5, 133.3, 133.1, 128.6, 127.9, 127.8, 126.2, 125.9, 125.4, 124.5, 89.4, 81.6, 56.4, 50.0, 45.7, 34.3, 28.0, 27.7; **IR** (neat) 2955, 2925, 818, 779 $cm^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{19}H_{22}Br_2ONa$ $(M + Na)^+$ 446.9935, found 446.9930.

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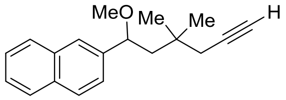
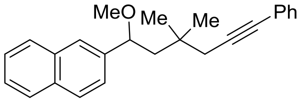
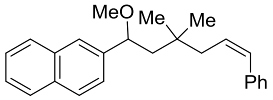
[51] Oestreich, M; Fröhlich, R.; Hoppe, D. *J. Org. Chem.* **1999**, *64*, 8616–8626.



**3.85.** The title compound was prepared according to a modified procedure reported by Hoppe.[17] In a 100 mL round bottom flask, a solution of **3.84** (2.25 g, 5.28 mmol, 1.00 equiv) in THF (30 mL) was cooled to –78 °C. To this solution was added *n*-butyllithium (4.30 mL, 2.50 M in hexanes, 10.6 mmol, 2.00 equiv) dropwise over 20 min. The reaction was stirred at this temperature for 1 h before warming to ambient temperature and stirring for another 1 h. The reaction was quenched with MeOH, followed by $H_2O$. The aqueous phase was extracted with $Et_2O$ (3 x 30 mL) and washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The product was purified by flash column chromatography (3% $Et_2O$/hexanes) to afford the title compound as a clear, colorless oil (1.01 g, 3.79 mmol, 72%). **TLC $R_f$** = 0.7 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.87–7.79 (m, 3H), 7.72 (s, 1H), 7.51–7.42 (m, 3H), 4.40 (dd, *J* = 9.2, 2.2 Hz, 1H), 3.19 (s, 3H), 2.25 (dd, *J* = 16.8, 2.1 Hz, 1H), 2.20 (dd, *J* = 16.5, 2.1 Hz, 1H), 2.00 (br s, 1H), 1.95 (dd, *J* = 14.6, 9.2 Hz, 1H), 1.65 (dd, *J* = 14.2, 2.2 Hz, 1H), 1.10 (s, 3H), 1.08 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 140.9, 133.3, 133.1, 128.4, 127.9, 127.8, 126.2, 125.8, 125.3, 124.6, 82.8, 81.8, 70.1, 56.4, 49.2, 33.5, 32.3, 27.7, 27.4;**IR** (neat) 3303, 2957, 2927 $cm^{-1}$; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{19}H_{22}ONa$ $(M + Na)^+$ 289.1568, found 289.1568.



**3.86.** The title compound was prepared according to a modified procedure reported by Hoppe.[17] In a glovebox, a flame-dried 50 mL round bottom flaks was equipped with a stir bar and charged with **3.85** (1.00 g, 3.75 mmol, 1.00 equiv), bis(triphenylphosphine)palladium(II) dichloride (26 mg, 0.038 mmol, 0.010 equiv), copper(I) iodide (36 mg, 0.18 mmol, 0.050 equiv), iodobenzene (0.42 mL, 3.8 mmol, 1.0 equiv), and $Et_3N$ (30 mL). The reaction was stirred in the glovebox at ambient temperature for 5 h. The round bottom flask was removed from the glovebox and quenched with 1M HCl (50 mL). The organic layer was separated and the aqueous phase was extracted with $Et_2O$ (3 x 30 mL). The combined organics were washed with brine, dried ($Na_2SO_4$), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (4% $Et_2O$/hexanes) to afford the title compound as a clear, colorless oil (1.19 g, 3.67 mmol, 98%). **TLC R$_f$** = 0.7 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.86–7.77 (m, 3H), 7.74 (s, 1H), 7.53–7.42 (m, 3H), 7.42–7.35 (m, 2H), 7.32–7.22 (m, 3H), 4.40 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.21 (s, 3H), 2.48 (d, *J* = 16.5 Hz, 1H), 2.39 (d, *J* = 16.5 Hz, 1H), 1.98 (dd, *J* = 14.6, 8.9 Hz, 1H), 1.75 (dd, *J* = 14.6, 2.5 Hz, 1H), 1.14 (s, 6H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 141.0, 133.3, 133.1, 131.6, 128.4, 128.2, 127.9, 127.8, 127.5, 126.1, 125.8, 125.4, 124.6, 124.2, 88.7, 82.5, 81.9, 56.4, 49.5, 34.1, 33.2, 27.9, 27.8; **IR** (neat) 3054, 2956, 2926 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{25}H_{26}ONa$ $(M + Na)^+$ 365.1881, found 365.1870.

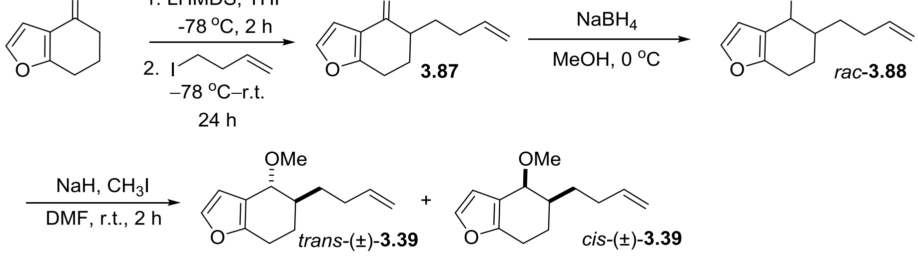


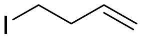
**(Z)-3.27**. A 25 mL round bottom flask was charged with a stir bar and a solution of alkyne **3.86** (200 mg, 0.620 mmol, 1.00 equiv) in EtOH (12 mL). The reaction flask was thoroughly purged with argon from a balloon and Lindlar's catalyst (69 mg, 0.020 mmol, 0.032 equiv with regard to palladium) was added neat. The argon atmosphere was exchanged with $H_2$ and the reaction was allowed to stir for 17 h, refilling the balloon with additional $H_2$ as necessary. At the end of the reaction, the $H_2$ atmosphere was exchanged with argon, and the reaction solution was filtered through a plug of celite, rinsing with 25% $Et_2O$/hexanes. The organics were concentrated in vacuo and the residue was purified by flash column chromatography on silver nitrate impregnated silica (1–5% $Et_2O$/hexanes with a final flush of 25% $Et_2O$/hexanes). The product was isolated as a clear oil (120 mg, 0.370 mmol, 60%, 10:1 Z:E). **TLC R$_f$** = 0.4 (5% $Et_2O$/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.86–7.76 (m, 3H), 7.61 (s, 1H), 7.51–7.41 (m, 2H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.35–7.25 (m, 4H), 7.25–7.18 (m, 1H), 6.52 (d, *J* = 12.0 Hz, 1H), 5.79 (dt, *J* = 14.4, 7.4 Hz, 1H), 4.27 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.09 (s, 3H), 2.42 (dd, *J* = 14.4, 7.4 Hz, 1H), 2.34 (dd, *J* = 14.4, 7.4 Hz, 1H), 1.89 (dd, *J* = 14.7, 8.6 Hz, 1H), 1.56 (dd, *J* = 14.7, 2.6 Hz, 1H), 1.01 (s, 3H), 0.99 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 141.2, 138.0, 133.4, 133.1, 130.3, 129.6, 129.0, 128.5, 128.2, 127.9, 127.8, 126.6, 126.2, 125.8, 125.5, 124.7, 81.7, 56.3, 49.9, 40.7, 33.9, 28.1, 27.9.

## Dihydrobenzofurans *cis*-3.40 and *trans*-3.40 (Scheme 3.5)

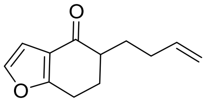
*cis* and *trans*-**3.39** were prepared by a-alkylation of 6,7-dihydro-4(5H)-benzofuranone, followed by reduction and methylation of the diastereomeric mixture of alcohol *rac*-**3.88**. Separation of the diastereomers by silica gel chromatography afforded *cis* and *trans*-**3.39.**

***Scheme 3.11.*** Synthesis of substrates for Scheme 3.5





**4-iodo-1-butene.** The iodide was prepared according to a modified procedure reported by Evans.[52] To a stirred solution of NaI (4.50 g, 30.0 mmol, 2.00 equiv) in acetone (50 mL) was added 4-bromobutene (1.52 mL, 15.0 mmol, 1.00 equiv) and the reaction mixture heated at reflux for 45 min. After removing most of the solvent in vacuo at ambient temperature (the compound is extremely volatile, bp 128–130 °C), the remaining liquid was run through a plug of silica (100% pentane) and concentrated in vacuo (care was taken not to raise the temperature of the bath or leave under vacuum for longer than necessary) to afford the title compound as a colorless liquid (1.05 g, 5.70 mmol, 38%). The product must be stored in the dark to avoid rapid decomposition, as evident by a color change to pink/ orange. The analytical data is consistent with literature values.[53] **$^1$H NMR** (400 MHz, $CDCl_3$) δ 5.46–5.41 (m, 1H), 5.18–5.07 (m, 2H), 3.19 (t, 2H, $J$ = 7.2), 2.62 (q, 2H, $J$ = 7.0).



**3.87.** The ketone was prepared according to a modified procedure reported by Li.[54] In a glovebox, LHMDS (1.36 g, 8.11 mmol, 1.00 equiv) was added to a flame-dried round bottom flask equipped with a stir bar and septum. The flask was removed from the glovebox, 10 mL of anhydrous THF (10 mL) was added, and the reaction cooled to –78 °C in a dry ice/acetone bath. 6,7-Dihydro-4(5H)-benzofuranone (1.10 g, 8.11 mmol, 1.00 equiv) was added as a solution in THF

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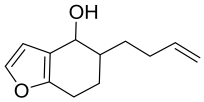
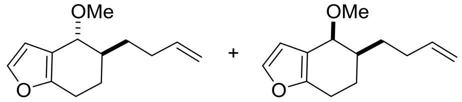
[52] Hodgson, D. M.; Kloesges, J.; Evans, B. *Org. Lett.* **2008**, *10*, 2781–2783.
[53] Díez, E; Dixon, D. J.; Ley, S. V.; Polara, A.; Rodríguez, F. *Helv. Chim. Acta* **2003**, *86*, 3717–3729.
[54] Zhang, Z.; Li, W-D. Z.; Li, Y. *Org. Lett.* **2001**, *3*, 2555–2557.

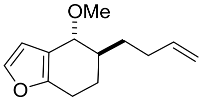
(10 mL). The mixture was allowed to stir for 1 h at this temperature before slow addition of 4-iodo-1-butene (1.49 g, 8.19 mmol, 1.01 equiv). The reaction was allowed to warm to room temperature over night and was quenched with sat. $NH_4Cl$. The mixture was extracted with $Et_2O$ (3 x 25 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (5% EtOAc/hexanes) to afford the title compound as a slightly yellow oil (0.771 g, 4.01 mmol, 50%). **TLC $R_f$** = 0.4 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 1.1 Hz, 1H), 6.66 (d, *J* = 1.4 Hz, 1H), 5.83 (ddt, *J* = 17.1, 10.5, 3.1 Hz, 1H), 5.06 (ad, *J* = 17.1, 1.1 Hz, 1H), 4.99 (d, *J* = 10.3 Hz, 1H), 2.84 (dt, *J* = 17.4, 5.4 Hz, 1H), 2.86 (ddd, *J* = 17.2, 8.7, 5.5 Hz, 1H), 2.45–3.78 (m, 1H), 2.32–1.90 (m, 5H), 1.56–1.47 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 196.6, 166.3, 142.8, 138.3, 120.8, 115.2, 106.9, 45.9, 31.5, 28.4, 27.8, 22.5; **IR** (neat) 2939, 1681, 1600 $cm^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{12}H_{14}O_2H$ $(M + H)^+$ 191.1072, found 191.1074.



***rac*-3.88.** Using representative procedure E outlined above, the following amounts of reagents were used: ketone **3.87** (0.227 g, 1.19 mmol, 1.00 equiv), MeOH (8 mL), sodium borohydride (0.108 g, 2.86 mmol, 2.40 equiv). The product was purified by flash column chromatography (8–15% EtOAc/hexanes) to afford a 1:1 mixture of diastereomers as a clear, colorless oil (0.224 g, 1.17 mmol, 98%). The diastereomeric ratio was determined based on integration of the benzylic methines in the $^1$H NMR spectrum. The diastereomers were not assigned cis and trans configurations, but were carried forward as a mixture. **TLC $R_f$** = 0.2 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 1.8 Hz, 1H), 6.39 (dd, *J* = 9.5, 1.5 Hz, 1H), 5.84 (ddt, *J* = 17.0, 10.5, 3.8 Hz, 1H), 5.05 (adq, *J* = 17.0, 1.5 Hz, 1H), 4.97 (d, *J* = 10.0 Hz, 1H), 4.57 and 4.36 (s, 1H), 2.72–2.50 (m, 2H), 2.27–2.15 (m, 1H), 2.15–2.03 (m, 1H), 1.79–1.43 (m, 5H), 1.38–1.24 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 153.2, 152.0, 141.5, 141.4, 138.9, 138.8, 120.3, 120.0, 114.84, 114.83, 109.8, 109.4, 69.5, 64.7, 42.5, 39.7, 31.7, 31.5, 30.7, 30.2, 24.7, 23.7, 23.4, 21.5; **IR** (neat) 3327, 3075, 2928 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{12}H_{16}O_2H$ $(M + H)^+$ 193.1228, found 193.1224.

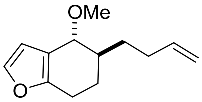


***trans*- and *cis*-(±)-3.39.** Using representative procedure G outlined above, the following amounts of reagents were used: alcohol *rac*-**3.88** (0.202 g, 1.09 mmol, 1.00 equiv), NaH (39 mg, 1.6 mmol, 1.5 equiv), methyl iodide (0.090 mL, 1.4 mmol, 1.3 equiv) and DMF (8 mL). The products were purified and separated by flash column chromatography (1–5% $Et_2O$/hexanes) to afford the title compounds as colorless oils: *trans*-(±)-**27** (92 mg, 0.44 mmol, 41%) and *cis*-(±)-**27** (86 mg, 0.42 mmol, 39%).



***trans*-(±)-3.39.** **TLC R$_f$** = 0.2 (5% $Et_2O$/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.27 (s, 1H), 6.36 (s, 1H), 5.81 (ddt, *J* = 17.1, 10.4, 3.6 Hz, 1H), 5.03 (ad, *J* = 17.1 Hz, 1H), 4.96 (d, *J* = 10.3 Hz, 1H), 4.01 (d, *J* = 4.0 Hz, 1H), 3.30 (s, 3H), 2.62–2.50 (m, 2H), 2.23–2.05 (m, 3H), 2.02–1.94 (m, 1H), 1.70–1.62 (m, 1H), 1.53–1.44 (m, 1H); **$^{13}$C NMR**

(125 MHz, $CDCl_3$) δ 152.5, 141.0, 138.7, 116.7, 114.8, 110.5, 77.2, 56.1, 37.2, 31.8, 29.4, 23.4, 20.4; **IR** (neat) 2975, 2929, 2818 $cm^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{12}H_{16}O_2H$ $(M)^+$ 206.1307, found 206.1298.



***cis*-(±)-3.39.** **TLC $R_f$** = 0.3 (5% $Et_2O$/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.35 (s, 1H), 5.84 (ddt, *J* = 17.1, 10.4, 3.4 Hz, 1H), 5.04 (ad, *J* = 17.1 Hz, 1H), 4.96 (d, *J* = 10.3 Hz, 1H), 4.06 (ad, *J* = 1.8 Hz, 1H), 3.38 (s, 3H), 2.69 (dd, *J* = 17.1, 5.8 Hz, 1H), 2.54 (ddd, *J* = 17.1, 10.6, 6.4 Hz, 1H), 2.21–2.08 (m, 2H), 1.93–1.81 (m, 1H), 1.77–1.64 (m, 3H), 1.51–1.40 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 153.3, 140.7, 139.1, 117.8, 114.6, 110.8, 77.3, 56.7, 39.2, 31.6, 30.4, 24.2, 23.2.

Relative stereochemical configurations for *trans*-(±)-**3.39** and *cis*-(±)-**3.39** were assigned based on the coupling constants of the protons of the benzylic methines.[55] For *trans*-(±)-**3.39,** *J* = 4.0 Hz, and for *cis*-(±)-**3.39**, *J* = 1.8 Hz.

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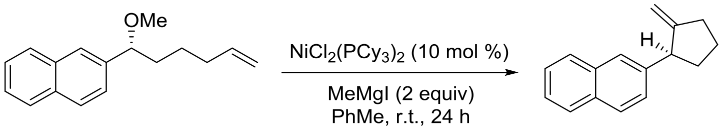
[55] Bifulco, G.; Dambruoso, P.; Gomez-Paloma, L.; Riccio, R. *Chem. Rev.* **2007**, *107*, 3744–3779.

## NICKEL-CATALYZED HECK CYCLIZATIONS OF BENZYLIC ETHERS AND CHARACTERIZATION DATA FOR PRODUCTS

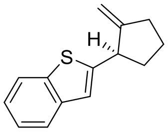
***General procedure I**. Heck cyclization of benzylic ethers*



**(*R*)-3.2.** In a glovebox, a flame fried 7 mL vial equipped with a stir bar was charged with (*R*)-**3.5** (47 mg, 0.20 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (14 mg, 0.020 mmol, 0.10 equiv), PhMe (1.6 mL) and methylmagnesium iodide (0.16 mL, 2.5 M in $Et_2O$, 0.40 mmol, 2.0 equiv). The reaction was stirred 24 h before removing the vial from the glovebox, opening to atmosphere, quenching with isopropanol, and eluted through a silica gel plug (30% $Et_2O$/hexanes). The combined organics were concentrated in vacuo, internal standard was added (PhTMS, 17.2 μL, 0.100 mmol, 0.500 equiv), and $^1$H NMR yield was collected. The product was purified by flash column chromatography with silver-impregnated silica gel (100% pentane) to afford the title compound as a clear, colorless oil (31 mg, 0.15 mmol, 74%, 99% ee). **TLC R$_f$** = 0.7 (100% pentane, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.79 (t, *J* = 9.3 Hz, 3H), 7.66 (s, 1H), 7.44 (t, *J* = 6.8 Hz, 1H), 7.41 (t, *J* = 7.0 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 5.01 (s, 1H), 4.56 (s, 1H), 3.72 (at, *J* = 8.2 Hz, 1H), 2.63–2.49 (m, 2H), 2.26–2.18 (m, 1H), 1.96–1.81 (m, 2H), 1.78–1.66 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 156.2, 142.5, 133.6, 132.3, 128.1, 127.72, 127.67, 126.88, 126.87, 126.0, 125.3, 107.7, 51.6, 36.6, 33.7, 25.0; **IR** (neat) 3070, 2954, 2865, 1600 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{16}H_{16}H$ $(M + H)^+$

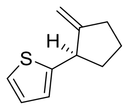
209.1330, found 209.1326; **$[\alpha]^{24}{}_D$** –126 (*c* 1.4, $CHCl_3$); **SFC** analysis (OJ-H, 10% IPA, 2.5 mL/min) indicated 99% ee: $t_R$ (major) = 6.2 minutes, $t_R$ (minor) = 5.8 minutes.

**Table 3.2, entry 2.** Using representative procedure I outlined above, the following amounts of reagents were used: (*R*)-**3.5** (0.24 g, 1.0 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (69 mg, 0.10 mmol, 0.10 equiv), PhMe (3.0 mL) and methylmagnesium iodide (1.0 mL, 2.0 M in $Et_2O$, 2.0 mmol, 2.0 equiv). The product was purified by flash column chromatography with silver-impregnated silica gel (100% pentane) to afford the title compound as a clear, colorless oil (149 mg, 0.73 mmol, 73%, 89% ee).

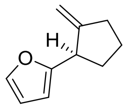


**(*R*)-3.7.** Using representative procedure I outlined above, the following amounts of reagents were used: (*R*)-**3.6** (49 mg, 0.20 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (14 mg, 0.020 mmol, 0.10 equiv), PhMe (1.6 mL) and methylmagnesium iodide (0.16 mL, 2.5 M in $Et_2O$, 0.40 mmol, 2.0 equiv). The product was purified by flash column chromatography with silver-impregnated silica gel (100% pentane) to afford the title compound as a clear, colorless oil (35 mg, 0.16 mmol, 81%, 97% ee). **TLC $R_f$** = 0.6 (100% pentane, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.09 (s, 1H), 5.07 (s, 1H), 4.88 (s, 1H), 3.93 (at, *J* = 7.3 Hz, 1H), 2.55–2.47 (m, 2H), 2.30–2.21 (m, 1H), 1.95–1.85 (m, 2H), 1.77–1.67 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 154.8, 149.7, 140.1, 139.6, 124.1, 123.6, 122.9, 122.4, 120.9, 108.4, 46.8, 37.0, 32.9, 24.9; **IR** (neat) 3069, 2955, 2866, 1436 $cm^{-1}$; **HRMS** (TOF MS CI+) *m* /

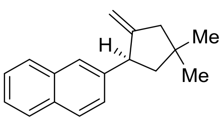
*z* calcd for $C_{14}H_{14}SH$ $(M + H)^+$ 215.0892, found 215.0893; **$[\alpha]^{26}_{D}$** –162 (*c* 1.3, $CHCl_3$); **SFC** analysis (OJ-H, 10% IPA, 2.5 mL/min) indicated 97% ee: $t_R$ (major) = 8.1 minutes, $t_R$ (minor) = 7.1 minutes.



**(*R*)-3.9.** Using representative procedure I outlined above, the following amounts of reagents were used: (*R*)-**3.8** (37 mg, 0.20 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (14 mg, 0.020 mmol, 0.10 equiv), PhMe (1.6 mL) and methylmagnesium iodide (0.16 mL, 2.5 M in $Et_2O$, 0.40 mmol, 2.0 equiv). Care must be taken during workup as the product is relatively volatile. The product was purified by flash column chromatography with silver-impregnated silica gel (100% pentane) to afford the title compound as a clear, colorless oil (24 mg, 0.15 mmol, 73%, 97% ee). **TLC $R_f$** = 0.7 (100% pentane, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 5.0 Hz, 1H), 6.94 (t, *J* = 4.9 Hz, 1H), 6.86 (d, *J* = 2.9 Hz, 1H), 5.01 (s, 1H), 4.80 (s, 1H), 3.86 (at, *J* = 7.3 Hz, 1H), 2.55–2.45 (m, 2H), 2.28–2.19 (m, 1H), 1.91–1.78 (m, 2H), 1.74–1.62 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 155.5, 148.6, 126.6, 124.3, 123.4, 107.7, 46.1, 37.3, 32.7, 24.6; **IR** (neat) 3072, 2957, 1440 $cm^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{10}H_{12}SH$ $(M + H)^+$ 165.0738, found 165.0739; **$[\alpha]^{27}_{D}$** –164 (*c* 1.0, $CHCl_3$); **SFC** analysis (OJ-H, 2% IPA, 2.5 mL/min) indicated 97% ee: $t_R$ (major) = 3.4 minutes, $t_R$ (minor) = 3.6 minutes.

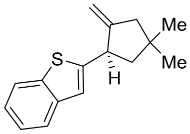


**(*R*)-3.11.** Using representative procedure I outlined above, the following amounts of reagents were used: (*R*)-**3.10** (36 mg, 0.20 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (14 mg, 0.020 mmol, 0.10 equiv), PhMe (1.6 mL) and methylmagnesium iodide (0.16 mL, 2.5 M in $Et_2O$, 0.40 mmol, 2.0 equiv). Care must be taken while working up the product as it relatively volatile. The product was purified by flash column chromatography with silver-impregnated silica gel (100% pentane) to afford the title compound as a clear, colorless and aromatic oil (22 mg, 0.15 mmol, 75%, 93% ee). **TLC R$_f$** = 0.7 (100% pentane, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.33 (s, 1H), 6.29 (s, 1H), 6.05 (d, *J* = 2.6 Hz, 1H), 5.00 (s, 1H), 4.83 (s, 1H), 3.67 (t, *J* = 8.3 Hz, 1H), 2.44 (at, *J* = 6.6 Hz, 2H), 2.13–2.04 (m, 1H), 1.96–1.79 (m, 2H), 1.72–1.61 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 157.7, 153.3, 141.3, 110.1, 107.4, 105.0, 43.9, 32.92, 32.91, 24.9; **IR** (neat) 3075, 2959, 2870 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{10}H_{12}OH$ $(M + H)^+$ 149.0966, found 149.0971; **[α]$^{24}_{D}$** –133 (*c* 0.7, $CHCl_3$); **GC** analysis: 93% ee (CYCLODEX B, inlet temp 220 ºC, flow rate 5.3781 mL/min, initial temp 55 °C, hold 2 min, ramp 10 °C/min up to 180 °C, hold 3 min, ramp 40 °C/min up to 230 °C, hold 1 min, $t_{R1}$ = 15.29 min, $t_{R2}$ = 15.48.



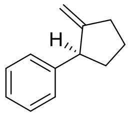
**(*R*)-3.13.** Using representative procedure I outlined above, the following amounts of reagents were used: (*R*)-**3.12** (54 mg, 0.20 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (14 mg, 0.020 mmol, 0.10 equiv), PhMe (1.6 mL) and methylmagnesium iodide (0.16

mL, 2.5 M in $Et_2O$, 0.40 mmol, 2.0 equiv). The product was purified by flash column chromatography with silver-impregnated silica gel (100% pentane) to afford the title compound as a white solid (45 mg, 0.19 mmol, 95%, 88% ee). **TLC $R_f$** = 0.8 (100% pentane, UV active, stain with $KMnO_4$); **m.p.** 84–86 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.83–7.73 (m, 3H), 7.66 (s, 1H), 7.47–7.38 (m, 2H), 7.33 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.00 (s, 1H), 4.58 (s, 1H), 3.94 (tt, *J* = 10.5, 2.5 Hz, 1H), 2.44 (ad, *J* = 16.3 Hz, 1H), 2.34 (d, *J* = 16.3 Hz, 1H), 1.99 (dd, *J* = 12.3, 8.3 Hz, 1H), 1.76 (at, *J* = 12.3 Hz, 1H), 1.17 (s, 3H), 1.09 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 156.6, 142.9, 133.6, 132.3, 128.1, 127.73, 127.66, 126.8, 126.7, 126.0, 125.3, 108.7, 51.0, 50.1, 49.2, 37.8, 29.3, 27.6; **IR** (neat) 3073, 2948, 2861, 1599 $cm^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{18}H_{20}H$ $(M + H)^+$ 237.1643, found 237.1650; **$[\alpha]^{26}_D$** –106 (*c* 1.7, $CHCl_3$); **SFC** analysis (OJ-H, 10% IPA, 2.5 mL/min) indicated 88% ee: $t_R$ (major) = 4.2 minutes, $t_R$ (minor) = 3.7 minutes.

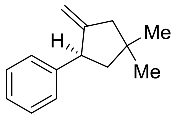


**(*R*)-3.15**. Using representative procedure I outlined above with the exception of adding magnesium iodide in the glovebox and heating the sealed reaction vial outside of the glovebox at 65 °C, the following amounts of reagents were used: (*R*)-**3.14** (55 mg, 0.20 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (14 mg, 0.020 mmol, 0.10 equiv), PhMe (1.6 mL), and methylmagnesium iodide (0.16 mL, 2.5 M in Et2O, 0.40 mmol, 2.0 equiv). The product was purified by flash column chromatography with silver-impregnated silica gel (100% pentane) to afford the title compound as a clear, colorless oil (36 mg, 0.15 mmol, 74%, 84% ee). **TLC $R_f$** = 0.9 (100% pentane, UV active); **$^1$H NMR** ($CDCl_3$, 400 MHz) δ 7.75 (d, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.27 (m, 2H), 7.10 (s, 1H), 5.06 (m, 1H), 4.87 (m, 1H), 4.17–4.09

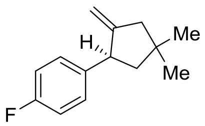
(m, 1H), 2.40 (dq, *J* = 15.8, 2.5 Hz, 1H), 2.28 (dd, *J* = 15.8, 1.8 Hz, 1H), 2.08 (ddd, *J* = 12.5, 8.0, 1.9 Hz, 1H), 1.81 (dd, *J* = 12.4, 10.8 Hz, 1H), 1.15 (s, 3H), 1.06 (s, 3H); **$^{13}$C NMR** (CDCl$_3$, 100 MHz) δ 154.9, 150.2, 140.2, 139.6, 124.2, 123.7, 123.0, 122.5, 120.7, 109.3, 51.1, 48.4, 45.5, 37.9, 29.2, 27.5; **IR** (neat) 3058, 2952, 2865, 1655, 1457, 885 cm$^{-1}$; **HRMS** (TOF MS CI+) *m/z* calcd for $C_{16}H_{18}SH$ (M + H)$^+$ 243.1207, found 243.1206; **$[\alpha]^{27}_{D}$** –94 (*c* 1.7, CHCl$_3$); **SFC** analysis (OJ-H, 20% hexanes, 3.0 mL/min) indicated 84% ee: tR (major) = 6.3 minutes, $t_R$ (minor) = 5.5 minutes.



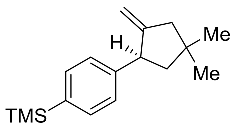
**(*R*)-3.17.** Using representative procedure I outlined above with the exception of adding magnesium iodide in the glovebox and heating the sealed reaction vial outside of the glovebox at 65 °C, the following amounts of reagents were used: (*R*)-**3.16** (38 mg, 0.20 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (14 mg, 0.020 mmol, 0.10 equiv), PhMe (1.6 mL), methylmagnesium iodide (0.15 mL, 2.7 M in Et$_2$O, 0.40 mmol, 2.0 equiv) and magnesium iodide (56 mg, 0.20 mmol, 1.00 equiv). Care must be taken during workup as the product is relatively volatile. Yield as determined by $^1$H NMR with PhTMS as internal standard was 64%. The product was purified by flash column chromatography with silver-impregnated silica gel (100% pentane) to afford the title compound as a clear, colorless oil (12 mg, 0.073 mmol, 36%, 93% ee). **TLC R$_f$** = 0.8 (100% pentane, UV active, stain with KMnO$_4$); **$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.30 (t, *J* = 7.3 Hz, 2H), 7.24–7.16 (m, 3H), 4.97 (s, 1H), 4.53 (s, 1H), 3.55 (t, *J* = 7.9 Hz, 1H), 2.58–2.44 (m, 2H), 2.21 (m, 1H), 1.91–1.83 (m, 1H), 1.82–1.71 (m, 1H), 1.71–1.64 (m, 1H), 1.06 (s, 3H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 156.7, 145.1, 128.41, 128.39, 126.1, 107.4, 51.4, 36.6, 33.6, 29.9, 24.9; **IR** (neat) 3028, 2952, 1601 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{12}H_{14}H$ (M + H)$^+$ 159.1174, found 159.1168; **[α]$^{25}$$_D$** –93 (*c* 0.5, $CHCl_3$); **SFC** analysis (AD-H, 10% IPA, 2.5 mL/min) indicated 93% ee: $t_R$ (major) = 1.7 minutes, $t_R$ (minor) = 1.9 minutes.



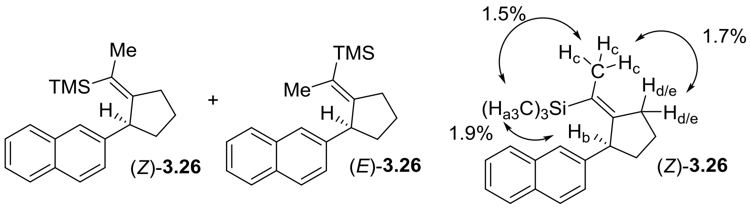
**(*R*)-3.19.** Using representative procedure I outlined above with the exception of adding magnesium iodide in the glovebox and heating the sealed reaction vial outside of the glovebox at 65 °C, the following amounts of reagents were used: (*R*)-**3.20** (52 mg, 0.20 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (14 mg, 0.020 mmol, 0.10 equiv), PhMe (1.6 mL), methylmagnesium iodide (0.16 mL, 2.5 M in $Et_2O$, 0.40 mmol, 2.0 equiv) and magnesium iodide (56 mg, 0.20 mmol, 1.00 equiv). Care must be taken during workup as the product is relatively volatile. Yield as determined by $^1$H NMR with PhTMS as internal standard was 81%. The product was purified by flash column chromatography with silver-impregnated silica gel (100% pentane) to afford the title compound as a clear, colorless oil (25 mg, 0.13 mmol, 67%, 92% ee). **TLC R$_f$** = 0.8 (100% pentane, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.6 Hz, 2H), 7.24–7.15 (m, 3H), 4.96 (s, 1H), 4.55 (s, 1H), 3.76 (tt, *J* = 10.6, 2.2 Hz, 1H), 2.38 (ad, *J* = 15.9 Hz, 1H), 2.29 (d, *J* = 15.9 Hz, 1H), 1.94 (dd, *J* = 12.5, 8.3 Hz, 1H), 1.76 (at, *J* = 12.0 Hz, 1H), 1.14 (s, 3H), 1.06 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 156.8, 145.6, 128.4, 128.3, 126.1, 108.3, 51.1, 49.9, 49.2, 37.7, 29.3, 27.6; **IR** (neat) 3027, 3063, 2952, 1602 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{14}H_{18}H$ (M + H)$^+$ 187.1487, found 184.1479; **[α]$^{25}$$_D$** –126 (*c* 1.0, $CHCl_3$); **SFC** analysis (OJ-H, 4% IPA, 2.5 mL/min) indicated 92% ee: $t_R$ (major) = 1.7 minutes, $t_R$ (minor) = 1.6 minutes.



**(*R*)-3.22.** Using representative procedure I outlined above with the exception of adding magnesium iodide in the glovebox and heating the sealed reaction vial outside of the glovebox at 65 °C, the following amounts of reagents were used: (*R*)-**3.21** (56 mg, 0.20 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (14 mg, 0.020 mmol, 0.10 equiv), PhMe (1.6 mL), methylmagnesium iodide (0.16 mL, 2.5 M in $Et_2O$, 0.40 mmol, 2.0 equiv) and magnesium iodide (56 mg, 0.20 mmol, 1.00 equiv). Care must be taken during workup as the product is relatively volatile. Yield as determined by $^1$H NMR with PhTMS as internal standard was 77%. The product was purified by flash column chromatography with silver-impregnated silica gel (100% pentane) to afford the title compound as a colorless solid (23 mg, 0.11 mmol, 57%, 90% ee). **TLC R$_f$** = 0.6 (100% pentane, UV active, stain with $KMnO_4$); **m.p.** 32–35 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.25–7.19 (m, 2H), 7.03 (at, *J* = 8.7 Hz, 2H), 5.02 (s, 1H), 4.59 (s, 1H), 3.81 (tt, *J* = 8.6, 2.2 Hz, 1H), 2.46–2.31 (m, 2H), 1.99 (ddd, *J* = 12.2, 8.1, 1.2 Hz, 1H), 1.67 (at, *J* = 11.9 Hz, 1H), 1.20 (s, 3H), 1.11 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 161.3 (d, *J* = 243 Hz), 156.6, 141.0 (d, *J* = 3 Hz), 129.5 (d, *J* = 8 Hz), 115.0 (d, *J* = 21 Hz), 108.3, 51.1, 49.1, 48.9, 37.5, 29.2, 27.5, ; **IR** (neat) 2952, 1653, 1603, 1508, 1463, 1223, 815 cm$^{-1}$; **HRMS** (TOF MS CI+) *m/z* calcd for $C_{14}H_{17}F$ $(M)^+$ 204.1314, found 204.1316; **$[\alpha]^{27}_D$** –90 (*c* 1.4, $CHCl_3$); **SFC** analysis (OJ-H, 4% IPA, 2.0 mL/min) indicated 90% ee: $t_R$ (major) = 2.1 minutes, $t_R$ (minor) = 2.3 minutes.

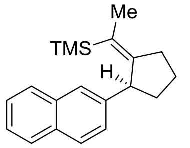


**(*R*)-3.24.** Using representative procedure I outlined above with the exception of adding magnesium iodide in the glovebox and heating the sealed reaction vial outside of the glovebox at 65 °C, the following amounts of reagents were used: (*R*)-**3.23** (67 mg, 0.20 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (14 mg, 0.020 mmol, 0.10 equiv), PhMe (1.6 mL), methylmagnesium iodide (0.16 mL, 2.5 M in $Et_2O$, 0.40 mmol, 2.0 equiv) and magnesium iodide (56 mg, 0.20 mmol, 1.00 equiv). The product was purified by flash column chromatography with silver-impregnated silica gel (100% pentane) to afford the title compound as a clear, colorless oil (44 mg, 0.17 mmol, 85%, 92% ee). **TLC R$_f$** = 0.3 (100% pentane, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 4.97 (s, 1H), 4.57 (s, 1H), 3.78–3.72 (m, 1H), 2.38 (ad, *J* = 15.7 Hz, 1H), 2.28 (ad, *J* = 15.7 Hz, 1H), 1.93 (dd, *J* = 12.2, 8.3 Hz, 1H), 1.66 (t, *J* = 11.9 Hz, 1H), 1.13 (s, 3H), 1.05 (s, 3H), 0.25 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 156.5, 146.2, 137.5, 133.4, 127.6, 108.3, 50.9, 49.7, 49.2, 37.6, 29.2, 27.4, –1.0; **IR** (neat) 3067, 2952, 1653, 1600, 1247, 1109, 835 cm$^{-1}$; **HRMS** (TOF MS CI+) *m/z* calcd for $C_{17}H_{26}SiH$ (M + H)$^+$ 259.1882, found 259.1877; **$[\alpha]^{27}_D$** –109 (*c* 1.6, $CHCl_3$); **SFC** analysis (OJ-H, 3% hexanes, 2.0 mL/min) indicated 92% ee: $t_R$ (major) = 2.6 minutes, $t_R$ (minor) = 2.2 minutes

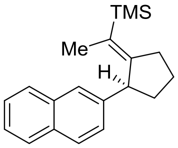


(*Z*)-**3.26** (*E*)-**3.26** (*Z*)-**3.26**

**3.26.** Using representative procedure I outlined above with the exception of heating the sealed reaction vial outside of the glovebox at 60 $^{o}$C for 48 h, the following amounts of reagents were used: ***(R)*-3.25** (62 mg, 0.20 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (14 mg, 0.020 mmol, 0.10 equiv), PhMe (1.6 mL), methylmagnesium iodide (0.16 mL, 2.5 M in $Et_2O$, 0.40 mmol, 2.0 equiv). The product was purified by flash column chromatography (100% pentane) to afford the title compound as a 2:1 Z:E mixture of stereoisomers (62% by $^1$H NMR with PhTMS as internal standard). The benzylic methane was integrated to determine the ratio of stereoisomers. Flash column chromatography with silver-impregnated silica gel (100% pentane) was used to separate the stereoisomers to afford (*Z*)-**3.26** (20 mg, 0.068 mmol, 34%) and (*E*)-**3.26** (10 mg, 0.034 mmol, 17%). The olefin geometry was assigned based on the nOe correlations shown for (*Z*)-**3.26** (see Appendix for relevant spectra).

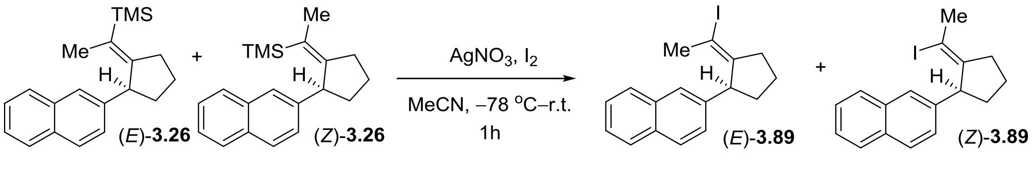


**(*Z*)-3.26. TLC $R_f$** = 0.8 (100% pentane, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.47–7.37 (m, 3H), 7.29 (d, *J* = 7.3 Hz, 1H), 4.11 (d, *J* = 7.1 Hz, 1H), 2.58 (d, *J* = 17.2, 9.2 Hz, 1H), 2.48–2.38 (m, 1H), 2.12–2.01 (m, 1H), 1.94–1.86 (m, 1H), 1.83 (s, 3H), 1.71–1.63 (m, 1H), 1.57–1.45 (m, 1H), –0.13 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 155.0, 144.6, 133.4, 132.0, 128.3, 127.80, 127.75, 127.6, 127.2, 126.0, 125.9, 125.2, 49.6, 37.1, 32.5, 22.1, 19.2, –0.3; **IR** (neat) 3052, 2952, 1600 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{20}H_{26}Si$ $(M)^+$ 294.1804, found 294.1798. **[α]$^{24}$D** –258 (*c* 0.8, $CHCl_3$).



**(*E*)-26. TLC R$_f$** = 0.8 (100% pentane, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 2H), 7.53 (s, 1H), 7.46–7.37 (m, 2H), 7.30 (d, *J* = 8.3 Hz, 1H), 4.07 (br s, 1H), 2.62–2.50 (m, 2H), 2.23–2.15 (m, 1H), 1.80–1.61 (m, 3H), 1.42 (s, 3H), 0.17 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 155.5, 143.9, 133.7, 132.0, 128.0, 127.9, 127.71, 127.68, 126.8, 125.9, 125.5, 125.1, 49.6, 37.1, 34.9, 25.2, 19.4, –0.2; **IR** (neat) 3053, 2951, 1599 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{20}H_{26}SiH$ $(M + H)^+$ 295.1882, found 295.1887. **[α]$^{24}$D** –88 (*c* 0.3, $CHCl_3$).

Enantiomers of **3.26** could not be separated by SFC. Derivatives of **3.26** were prepared to determine the enantiospecificity of the alkyne insertion/Kumada coupling of **3.25**.



**3.89.** The title compound was prepared according to a modified procedure reported by Xi.[56] Under an atmosphere of nitrogen, $AgNO_3$ (73 mg, 0.43 mmol, 1.2 equiv) was added to a solution of

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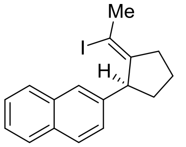
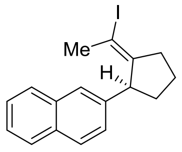
[56] Geng, W.; Zhang, W–X.; Hao, W.; Xi, Z. *J. Am. Chem. Soc.* **2012**, *134*, 20230–20233.

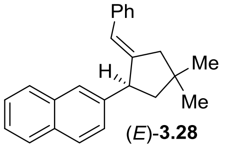
**(*Z*)-3.26** and **(*E*)-3.26** as a 2:1 mixture (110 mg, 0.360 mmol, 1.00 equiv) in MeCN (10 mL) at –78 °C. The solution was stirred for 15 min before addition of $I_2$ (119 mg, 0.470 mmol, 1.30 equiv). The reaction was allowed to warm to 0 °C in an ice water bath over 45 min and quenched with water. The mixture was extracted with $Et_2O$ and the combined organics were washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography afforded (*Z*)-**3.89** as a clear, colorless oil (46 mg, 0.12 mmol, 50%, 89% ee) and (*E*)-**3.89** (24 mg, .069 mmol, 58%).



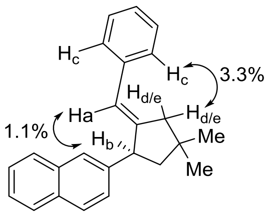
**(*Z*)-3.89. TLC $R_f$** = 0.7 (100% pentane, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.83–7.74 (m, 3H), 7.52 (s, 1H), 7.49–7.39 (m, 2H), 7.28 (d, *J* = 8.6 Hz, 1H), 4.06 (at, *J* = 5.1 Hz, 1H), 2.70–2.59 (m, 1H), 2.58–2.49 (m, 1H), 2.37 (ddd, *J* = 15.1, 12.5, 7.4 Hz, 1H), 2.20 (s, 3H), 2.01–1.93 (m, 1H), 1.82–1.64 (m, 2H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 150.6, 142.2, 133.6, 132.2, 128.4, 127.8, 127.7, 126.23, 126.17, 125.53, 125.50, 92.3, 49.2, 42.7, 39.6, 31.1, 23.9; **IR** (neat) 3051, 2953, 1600, 849 $cm^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{17}H_{17}I$ $(M)^+$ 348.0375, found 348.0375. **$[\alpha]^{23}_D$** –217 (*c* 2.3, $CHCl_3$); **SFC** analysis (OJ-H, 10% IPA, 2.5 mL/min) indicated 89% ee: $t_R$ (major) = 7.1 minutes, $t_R$ (minor) = 8.6 minutes.



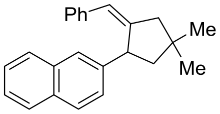
**(*E*)-3.89.** **TLC R$_f$** = 0.8 (100% pentane, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.79 (t, *J* = 8.0 Hz, 3H), 7.53 (s, 1H), 7.46–7.38 (m, 2H), 7.30 (d, *J* = 8.3 Hz, 1H), 3.98 (d, *J* = 7.7 Hz, 1H), 2.68–2.51 (m, 5H), 2.27–2.16 (m, 1H), 1.92–1.77; **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 150.0, 142.0, 133.6, 132.1, 128.1, 127.8, 127.7, 126.9, 126.1, 125.9, 125.3, 91.1, 56.9, 36.6, 32.5, 31.1, 25.4; **IR** (neat) 2956, 1600, 904 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{17}H_{17}INH_4$ $(M + NH_4)^+$ 366.0719, found 366.0709. **$[\alpha]^{23}_D$** –9.0 (*c* 0.8, $CHCl_3$); **SFC** analysis (AD-H, 7% IPA, 2.5 mL/min) indicated 89% ee: $t_R$ (major) = 6.1 minutes, $t_R$ (minor) = 6.8 minutes.



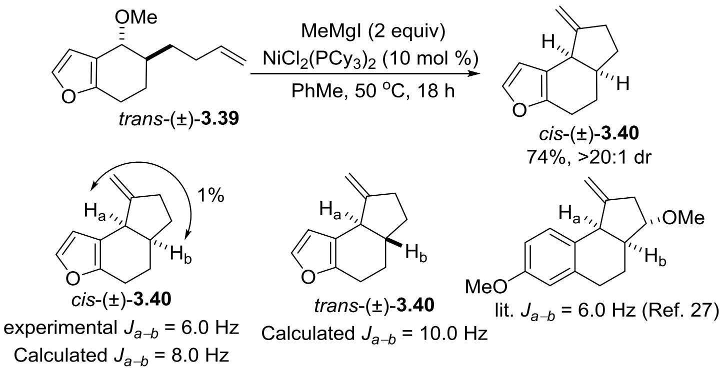
(*E*)-**3.28**



**(*E*)-3.28.** Using representative procedure I outlined above, the following amounts of reagents were used: (*E*)-**3.27** (69 mg, 0.20 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (14 mg, 0.020 mmol, 0.10 equiv), PhMe (1.6 mL) and methylmagnesium iodide (0.16 mL, 2.5 M in $Et_2O$, 0.40 mmol, 2.0 equiv). The product was purified by flash column chromatography with silver-impregnated silica gel (100% pentane) to afford the title compound as a white solid (50 mg, 0.16 mmol, 80%, 89% ee). The olefin geometry was assigned based on the nOe correlations indicated above (see section X for relevant spectra). **TLC R$_f$** = 0.7 (100% pentane, UV active, stain with $KMnO_4$); **m.p.** = 104–105 $^o$C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.79 (t, *J* = 8.8 Hz, 3H), 7.72 (s, 1H), 7.49–7.40 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.14 (t, *J* = 7.0 Hz, 1H), 5.98 (s, 1H), 4.16 (t, *J* = 9.5 Hz, 1H), 2.72 (d, *J* = 16.8 Hz, 1H), 2.66 (d, *J* = 16.8 Hz, 1H), 2.00 (dd, *J* = 12.1, 8.4 Hz, 1H), 1.79 (at, *J* = 12.1 Hz, 1H), 1.25 (s, 3H), 1.09 (s, 3H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 150.2, 143.1, 138.8, 133.6, 132.4, 128.3, 128.2, 127.8, 127.7, 127.2, 127.0, 126.1 (2C), 125.4, 125.1, 52.2, 50.4, 47.8, 38.8, 29.6, 27.8; **IR** (neat) 3053, 2951, 2865, 1600 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for C$_{24}$H$_{24}$NH$_4$ (M + NH$_4$)$^+$ 330.2222, found 330.2213; **[α]$^{23}$$_D$** +133 (*c* 1.0, CHCl$_3$); **SFC** analysis (AS-H, 4% IPA, 2.5 mL/min) indicated 89% ee: t$_R$ (major) = 5.4 minutes, t$_R$ (minor) = 6.0 minutes.



**(*Z*)-3.28.** Using representative procedure I outlined above, the following amounts of reagents were used: (Z)-**3.27** (10:1 Z:E) (69 mg, 0.20 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (14 mg, 0.020 mmol, 0.10 equiv), PhMe (1.6 mL) and methylmagnesium iodide (0.16 mL, 2.5 M in Et$_2$O, 0.40 mmol, 2.0 equiv). The product was purified by flash column chromatography with silver-impregnated silica gel (0–2%% Et$_2$O/pentane) to afford the title compound as a white solid (38 mg, 0.12 mmol, 60%, 9:1 Z:E). **TLC R$_f$** = 0.7 (100% pentane, UV active, stain with KMnO$_4$); **m.p.** = 86–92 °C; **$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.77–7.67 (m, 3H), 7.59 (s, 1H), 7.43–7.34 (m, 2H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.12–7.07 (m2H), 7.04 (t, *J* = 7.7 Hz, 2H), 6.96 (t, *J* = 6.8 Hz, 1H), 5.62 (s, 1H), 4.31 (t, *J* = 8.4 Hz, 1H), 2.75 (d, *J* = 14.7 Hz, 1H), 2.38 (d, *J* = 14.7 Hz, 1H), 2.25 (m1H), 1.71 (dd, *J* = 12.7, 8.4 Hz, 1H), 1.09 (s, 3H), 1.04 (s, 3H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 147.6, 143.5, 137.4, 133.9, 132.0, 128.51, 128.48, 128.0, 127.8, 127.7, 126.3, 126.0, 125.9, 125.2, 125.1, 124.8, 53.2, 52.9, 46.9, 37.6, 28.9, 27.3.



***trans*-(±)-3.40.** Using representative procedure I outlined above with the exception of heating the sealed reaction vial outside of the glovebox at 50 °C, the following amounts of reagents were used: *trans*-(±)-**3.39** (41 mg, 0.20 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (14 mg, 0.020 mmol, 0.10 equiv), PhMe (1.6 mL), methylmagnesium iodide (0.16 mL, 2.5 M in $Et_2O$, 0.40 mmol, 2.0 equiv). Care must be taken during workup as the product is relatively volatile. The product was purified by flash column chromatography with silver-impregnated silica gel (100% pentane) to afford the title compound as a clear, colorless oil (26 mg, 0.15 mmol, 74%, >20:1 dr). **TLC $R_f$** = 0.7 (100% pentane, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.34 (d, *J* = 1.1 Hz, 1H), 4.96 (s, 1H), 4.93 (s, 1H), 3.36 (d, *J* = 6.0 Hz, 1H), 2.58 (t, *J* = 6.3 Hz, 2H), 2.43 (t, *J* = 7.7 Hz, 2H), 2.39–2.31 (m, 1H), 1.88–1.66 (m, 3H), 1.61–1.51 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 154.9, 149.9, 140.6, 117.8, 110.6, 106.8, 42.8, 38.8, 30.9, 28.2, 25.4, 21.3; **IR** (neat) 2931, 2850, 1505 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{12}H_{14}OH$ $(M + H)^+$ 175.1123, found 175.1132.

NOESY and 1D nOe experiments show a strong nOe correlation between $H_a$ and $H_b$, consistent with a cis orientation (see section X for relevant spectra). The J-coupling between the protons indicated is consistent with literature values for structurally similar compounds with a cis relationship.[57] The experimentally measured J-coupling constants are consistent with computational calculations. All calculations were performed with Guassian 09.[58] The geometries of **3.40** were optimized with the B3LYP functional using the 6–31G(d,p) basis set.[59] J-coupling constants were obtained with the B3LYP functional using the 6–31+G(d,p) basis set with the SMD solvation model for chloroform.[60]

## Heck cyclization of 1,1-disubstituted olefin 3.34

A 1,1-disubstituted olefin (**3.34**) was prepared as a test for formation of a quaternary center during the cyclization reaction. The 1,1-disubstituted olefin **3.34** was prepared by Grignard addition into 3-methylcrotonaldehyde. Oxy-Cope rearrangement followed by Girgnard addition into the resultant aldehyde afforded alcohol **3.91**, which upon methylation formed the 1,1-disubstituted olefin **3.34**. Cyclization of 1,1-disubstituted olefin **3.34** was successful in providing products

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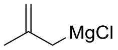
[57] Collins, M. P.; Drew, M. G. B.; Mann, J.; Finch, H. *J. Chem. Soc. Perkin Trans.* ***1992**, 1*, 3211–3217.

[58] Gaussian 09, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2010**.

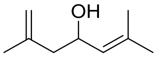
[59] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

[60] Marenich, A. V.; Cramer, C. J.; Truhlar, D. G., *J. Phys. Chem. B* **2009**, *113*, 6378.

containing a quaternary stereocenter. However, two major products were formed: **3.35**, from a Heck-Kumada sequence similar to that shown in Scheme 3.2, and **3.36**, from a reductive Heck reaction. Unfortunately these products were inseparable; a combined yield of 49% was obtained.



**Methallylmagnesium chloride.** The Grignard reagent was prepared according to a modified procedure by Moore.[61] A flame-dried 100 mL round-bottom flask was equipped with a stir bar and charged with magnesium turnings (0.91 g, 38 mmol, 1.3 equiv), THF (25 mL) and a catalytic amount of iodine. Neat methallyl chloride (2.5 mL, 30 mmol, 1.0 equiv) was added in one portion. The reaction flask was equipped with a reflux condenser and heated to reflux for 2 h, cooled to ambient temperature and titrated to 0.7 M.



**3.90.** Using representative procedure A outlined above, the following amounts of reagents were used: 3-methyl-2-butenal (1.45 mL, 15.0 mmol, 1.00 equiv), methallylmagnesium chloride (0.7 M in THF, 29 mL, 20 mmol, 1.3 equiv). The product was purified by flash column chromatography (10% EtOAc/hexanes) to afford the title compound as a clear, colorless oil (1.76 g, 12.6 mmol, 84%). **TLC R$_f$** = 0.2 (10% EtOAc/hexanes, stained with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.19 (d, *J* = 8.7 Hz, 1H), 4.87 (s, 1H), 4.81 (s, 1H), 4.52–4.46 (m, 1H), 2.24 (dd, *J* = 13.8, 5.0 Hz, 1H), 2.16 (dd, *J* = 13.8, 4.4 Hz, 1H), 1.78 (s, 3H), 1.73, (s, 3H), 1.71 (s, 3H), 1.67 (br s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 142.6, 135.4, 127.5, 113.6, 66.1, 46.4, 25.9, 22.6,

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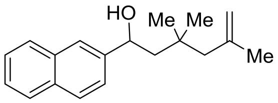
[61] Xu, X. A.; Xia, H.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 6094–6103.

18.3; **IR** (neat) 3346, 2876, 1698, 1600, 1365 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_9H_{16}ONH_4$ $(M + NH_4)^+$ 158.1545, found 158.1551.



**3.91.** The alcohol was prepared according to a modified procedure by Maynard.[62] In a glove-box, a flame dried 50 mL round bottom flask equipped with a stir bar and septum was charged with potassium hydride (0.607 g, 15.1 mmol, 1.3 equiv). A separate 25 mL round bottom flask was charged with 18-crown-6 ether (3.60 g, 13.6 mmol, 1.17 equiv). Both flasks was removed from the glovebox and a solution of alcohol **3.90** (1.633 g, 11.64 mmol, 1.000 equiv) and 18-crown-6 ether in THF (20 mL) was prepared. This mixture was added to the KH suspended in THF (5 mL) at 0 °C. The reaction was warmed to reflux and stirred for 3 h. Upon cooling, the reaction was quenched by pouring the contents of the reaction flask into a 250 mL round bottom flask containing 40 mL of sat. $NH_4Cl$. The mixture was extracted with ether (3 x 20 mL) and the combined organic layers were washed with brine (2 x 40 mL), dried over $MgSO_4$ filtered and concentrated in vacuo. This crude mixture of aldehyde was then used immediately in the next step. The aldehyde was redissolved in anhydrous THF, and added to a solution of 2-naphthylmagnesium bromide (15 mL, 1.0 M in THF, 15 mmol, 1.3 equiv) at 0 °C. The reaction was allowed to stir for 1.5 h before it was quenched with sat. $NH_4Cl$. The mixture was once again extracted with ether (3 x 25 mL) and the combined organic layers were washed with brine (1 x 40 mL), dried over $MgSO_4$ filtered and concentrated in vacuo. The product was purified by

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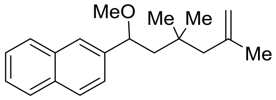
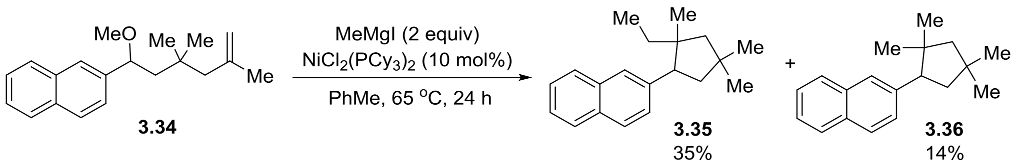
[62] Paquette, L. A.; Maynard, G. D. *J. Am. Chem. Soc.* **1992**, *114*, 5018–5027.

flash column chromatography (2–8% EtOAc/hexanes) to afford the title compound as a thick oil (0.877 g, 3.27 mmol, 28% over two steps). **TLC R$_f$** = 0.3 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.85–7.80 (m, 3H), 7.78 (s, 1H), 7.50–7.43 (m, 3H), 5.03 (d, *J* = 8.3 Hz, 1H), 4.87 (s, 1H), 4.68 (s, 1H), 2.09 (dd, *J* = 15.5, 12.8 Hz, 2H), 1.88 (dd, *J* = 14.5, 8.3 Hz, 1H), 1.83 (s, 1H), 1.79 (s, 3H), 1.73 (dd, *J* = 14.5, 3.2 Hz, 1H), 1.07 (s, 3H), 1.03 (s, 3H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 144.0, 143.6, 133.5, 133.0, 128.5, 128.1, 127.8, 126.3, 125.9, 124.34, 124.33, 114.7, 72.4, 51.6, 50.9, 34.2, 28.3, 28.2, 25.7; **IR** (neat) 3346, 2876, 1698, 1600, 1365 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{19}H_{24}ONa$ (M + Na)$^+$ 291.1725, found 291.1714.



**3.34.** Using representative procedure G outlined above, the following amounts of reagents were used: alcohol **3.91** (0.241 g, 0.900 mmol, 1.00 equiv), NaH (48 mg, 2.0 mmol, 2.2 equiv), methyl iodide (0.073 mL, 1.2 mmol, 1.3 equiv) and DMF (4 mL). The product was purified by flash column chromatography (2–5% EtOAc/hexanes) to afford the title compound as a colorless oil (0.19 g, 0.67 mmol, 75%). **TLC R$_f$** = 0.7 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, CDCl$_3$) δ 7.87–7.80 (m, 3H), 7.71 (s, 1H), 7.50–7.42 (m, 3H), 4.85 (s, 1H), 4.67 (s, 1H), 4.39 (dd, *J* = 8.5, 2.9 Hz, 1H), 3.18 (s, 3H), 2.06 (dd, *J* = 19.6, 13.2 Hz, 2H), 1.92 (dd, *J* = 14.8, 8.5 Hz, 1H), 1.78 (s, 3H), 1.58 (dd, *J* = 14.8, 3.1 Hz, 1H), 1.04 (s, 3H), 0.99 (s, 3H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 143.7, 141.4, 133.4, 133.1, 128.5, 127.94, 127.85, 126.2, 125.8, 125.5, 124.8, 114.6, 81.9, 56.4, 50.91, 50.89, 34.2, 28.2, 28.1, 25.1; **IR** (neat) 3055, 1602 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{20}H_{26}O$ (M)$^+$ 282.1984, found 282.1988.

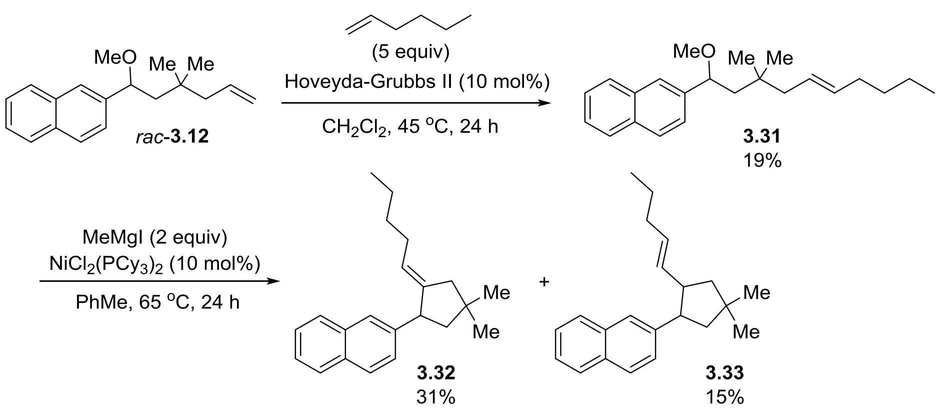


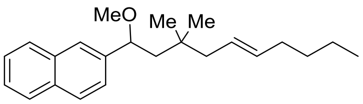
**3.35 and 3.36.** Using representative procedure I outlined above, with the exception of heating to 65 $^{o}$C, the following amounts of reagents were used: **3.34** (27 mg, 0.10 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (7 mg, 0.010 mmol, 0.10 equiv), PhMe (0.8 mL) and methylmagnesium iodide (0.07 mL, 2.7 M in Et$_2$O, 0.20 mmol, 2.0 equiv). The products were purified by flash column chromatography on silver impregnated silica gel (100% pentane) to afford a 3.5:1 mixture of desired product **3.35** and reduced product **3.36** (13 mg, 0.049 mmol, 49%). Annoted $^1$H NMR spectrum is provided in the Appendix.

## <u>Heck cyclization of a 1,2-dialkyl substituted olefin</u>

The Heck cyclization of 1,2-disubstituted olefin **3.31** was expected to provide a facile route to stereodefined trisubstituted olefins. Heck cyclization occurred smoothly, however, an unselective β-hydride elimination step resulted in an inseperable 2:1 mixture of olefin isomers (**3.32** and **3.33**, 46% combined yield).

***Scheme 3.12.*** Preparation and Heck cyclization of 1,2-disubstituted olefin **3.31**





**3.31.** The title compound was prepared according to a modified procedure reported by Grubbs.[63] In a glovebox, a flame-dried bomb flask was charged with a stir bar, *rac*-**3.12** (0.336 g, 1.25 mmol, 1.00 equiv), and (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(o-isopropoxyphenylmethylene)ruthenium (78 mg, 0.13 mmol, 0.10 equiv). The flask was removed from the glovebox, and anhydrous $CH_2Cl_2$ (25 mL) and 1-hexene (0.78 mL, 6.3 mmol, 5.0 equiv) was added. The flask was sealed and heated to reflux 15 h. The flask was then cooled to ambient temperature, and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silver impregnated silica gel to afford the title compound as a colorless oil (77 mg, 0.24 mmol, 19%). **TLC R$_f$** = 0.6 (100% hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.86–7.78 (m, 3H), 7.70 (s, 1H), 7.50–7.40 (m, 3H), 5.47–5.35 (m, 2H), 4.37

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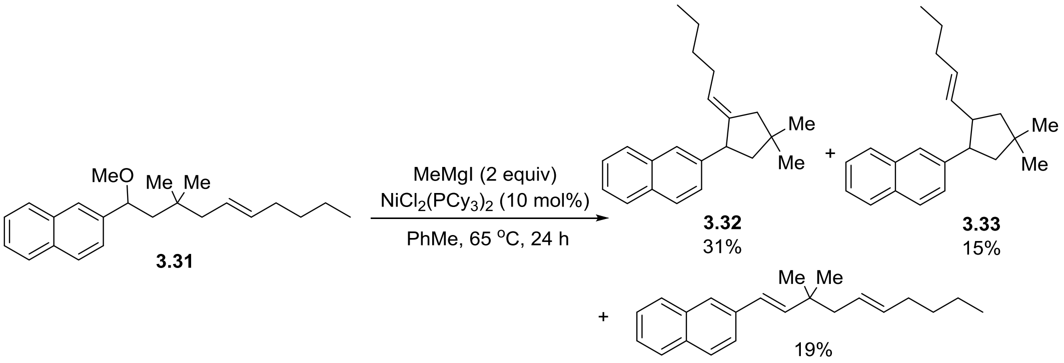
[63] Chatterjee, A. K; Choi, T–L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

(dd, *J* = 8.6, 2.8 Hz, 1H), 3.18 (s, 3H), 2.03–1.93 (m, 4H), 1.85 (dd, *J* = 14.7, 8.6 Hz, 1H), 1.52 (dd, *J* = 14.7, 2.8 Hz, 1H), 1.36–1.22 (m, 4H), 0.96 (s, 3H), 0.94 (s, 3H), 0.86 (t, *J* = 7.0 Hz, 3H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 141.5, 133.4, 133.1, 128.5, 127.9, 127.8, 126.8, 126.2, 125.8, 125.4, 124.8, 81.9, 56.4, 50.0, 46.2, 33.7, 32.6, 32.0, 27.83, 27.77, 22.4, 14.1; **IR** (neat) 3055, 1602 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{23}H_{32}ONa$ (M + Na)$^+$ 347.2351, found 347.2337.



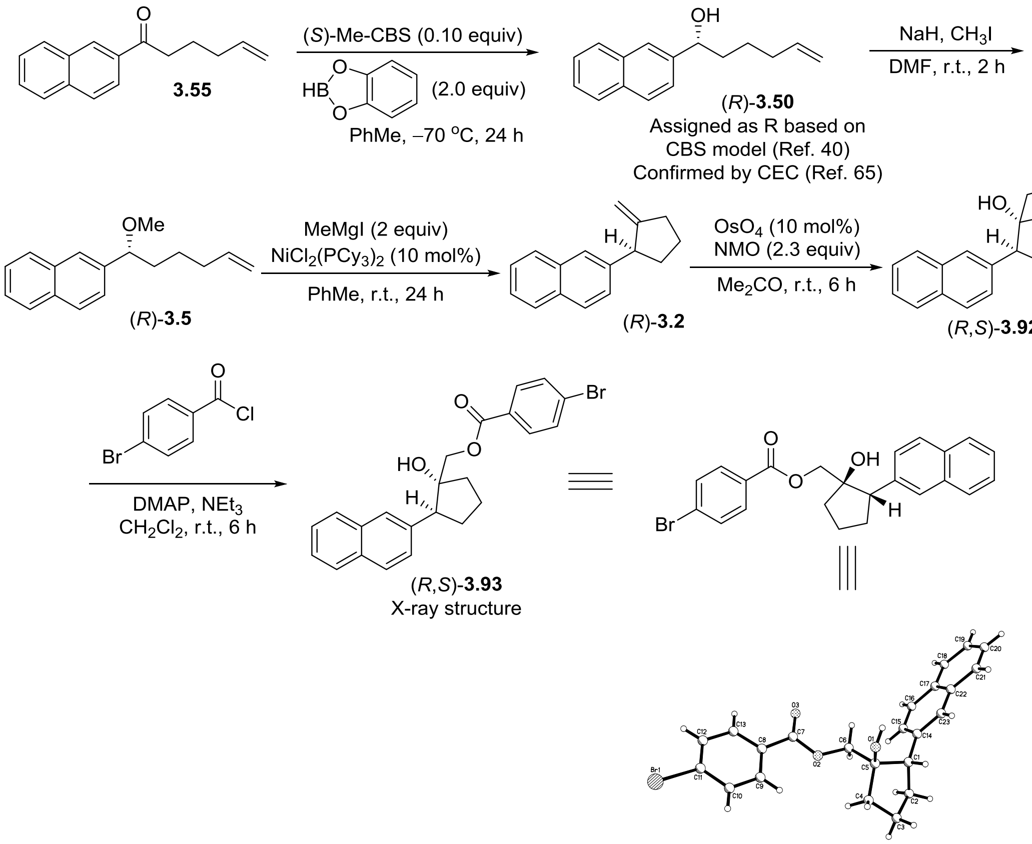
**3.32, and 3.33.** Using representative procedure I outlined above, with the exception of heating to 65 °C, the following amounts of reagents were used: **3.31** (33 mg, 0.10 mmol, 1.0 equiv), bis(tricyclohexylphosphine)nickel(II) dichloride (7 mg, 0.010 mmol, 0.10 equiv), PhMe (0.8 mL) and methylmagnesium iodide (0.07 mL, 2.7 M in Et$_2$O, 0.20 mmol, 2.0 equiv). After workup, phenyltrimethylsilane was added (8.6 µL, 0.050 mmol, 0.50 equiv) and a $^1$H NMR spectrum was collected to determine yields of products. Recovered **3.31** (15%), **3.32** (31%), **3.33** (15%), β-H elimination (19%). See the Appendix for annotated $^1$H NMR spectrum.

# STEREOCHEMICAL PROOFS

## Overview of stereochemical assignments

The stereochemical course of the Heck cyclization is demonstrated for three examples. Those experiments are summarized below. In all examples, we confirm that the Heck cyclization proceeds with inversion. Full experimental details and characterization data for the derivatives synthesized to assign absolute configuration of products are provided below.

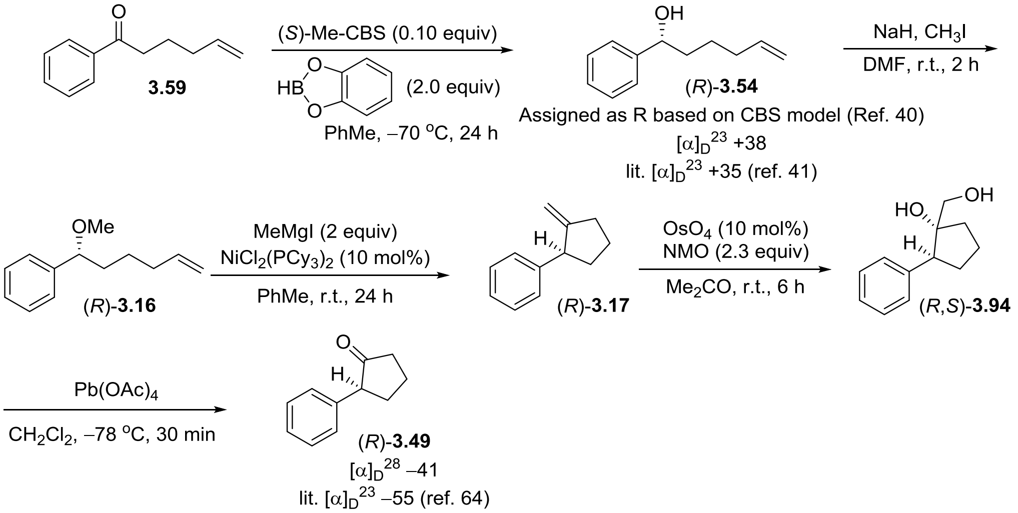
***Scheme 3.13.*** Stereochemical course of the Heck cyclization for (*R*)-**3.5**



Enantioenriched alcohol (*R*)-**3.50** was prepared by enantioselective CBS reduction (vida supra).

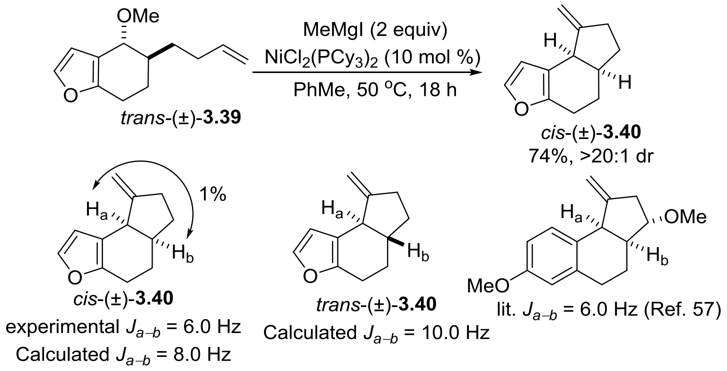
Absolute configuration was assigned based on the accepted model for selectivity in CBS reductions[9] and confirmed by Competing Enantioselective Conversion (CEC) (vifa infra). Conversion to methyl ether (*R*)-**5**, followed by stereospecific Heck cyclization produced (*R*)-**2**. Dihydroxylation of the olefin and conversion of the primary alcohol to the 4-bromobenzoate afforded (*R*,*S*)-**3.93**, the absolute configuration of which was determined by X-ray crystallography. This product corresponds to net inversion in the Heck cyclization.

***Scheme 3.14.*** Stereochemical course of the Heck cyclization for (*R*)-**3.16**



Enantioenriched alcohol (*R*)-**3.54** was prepared by enantioselective CBS reduction (vida infra). Absolute configuration was assigned based on the accepted model for selectivity in CBS reductions[40] and confirmed by comparison of the optical rotation to literature value.[41] Conversion to methyl ether (*R*)-**3.16**, followed by stereospecific Heck-cyclization produced (*R*)-**3.17**. Dihydroxylation of the olefin followed by oxidative cleavage of the diol (*R*,*S*)-**3.94** with Pb(OAc)$_4$ afforded α-aryl cyclopentanone (*S*)-**3.49**, the stereochemistry of which was determined by comparison of the optical rotation to the literature value.[64] This product corresponds to net inversion in the Heck cyclization.

***Scheme 3.15.*** Stereochemical course of the Heck cyclization for *trans*-(±)-**3.39**



NOESY and 1D nOe experiments show a strong nOe correlation between $H_a$ and $H_b$, consistent with a cis orientation (see Appendix for spectra). The J-coupling between the protons indicated is consistent with literature values for structurally similar compounds with a cis relationship.[57] The experimentally measured J-coupling constants are consistent with computational calculations. This product corresponds to net inversion in the Heck cyclization.

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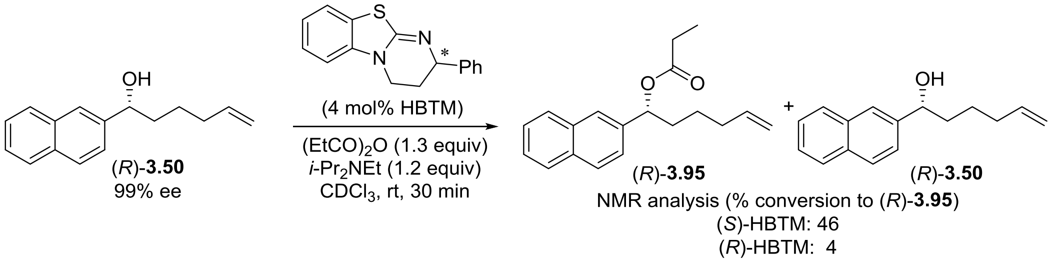
[64] Shen, Y-M.; Wang, B.; Shi, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 1429–1432.

***Scheme 3.16.*** Confirmation of absolute configuration of alcohol (*R*)-**3.50**



The competing enantioselective conversion experiment was performed according to the procedure outlined by Rychnovsky.[65] To a 7 mL vial under $N_2$ atmosphere was added alcohol (*R*)-**3.50** (11 mg, 0.050 mmol, 1.0 equiv), *i*-Pr$_2$NEt (11 μL, 0.060 mmol, 1.2 equiv), HBTM catalyst (0.20 mL, 0.010 M solution in CDCl$_3$, 0.0020 mmol, 0.040 equiv) and CDCl$_3$ (0.7 mL). The mixture was allowed to stir for 5 min before addition of propionic anhydride (8 μL, 0.07 mmol, 1.3 equiv). The reaction was stirred for 30 min and transferred to a NMR tube for $^1$H NMR analysis. Percent conversion was measured for two reactions, one run with (*S*)-HBTM catalyst (46% conversion) and one with (*R*)-HBTM catalyst (4% conversion). Based on the pneumonic described by Rychnovsky, we assigned alcohol (*R*)-**3.50** as the *S* enantiomer. This assignment is consistent with E.J. Corey's stereochemical model for CBS reductions.

## Synthesis of hydroxyester (*R*,*S*)-3.93

Hydroxyester (*R*,*S*)-**3.93** was prepared from methylenecyclopentane (*R*)-**3.2** by dihydroxylation and esterification.

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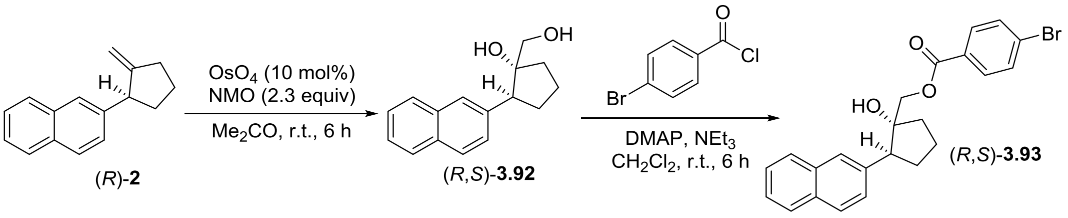
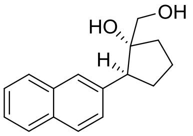
[65] Wagner, A. J.; David, J. G.; Rychnovsky, S. D.*Org. Lett.* **2011**, *13*, 4470–4473.





**(*R*,*S*)-3.92.** The title compound was prepared according to a modified procedure reported by Gaikwad.[66] A 20 mL scintillation vial charged with a stir bar and (*R*)-**3.2** (90 mg, 0.44 mmol, 1.0 equiv) and acetone (4 mL). To this solution was added *N*-methylmorpholine-*N*-oxide (119 mg, 1.01 mmol, 2.30 equiv) and $OsO_4$ (0.28 mL, 4% in $H_2O$, 0.044 mmol, 0.10 equiv). The reaction vessel was sealed and allowed to stir at ambient temperature until TLC indicated the reaction had proceeded to conversion (5 h). The reaction was diluted with EtOAc (5 mL) and quenched with sat. $NH_4Cl$ (4 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (3 x 2 mL) and the combined organic layers were washed with brine (1 x 4 mL), dried over $MgSO_4$ filtered and concentrated in vacuo. The diol was purified by flash column chromatography on silica gel (25% EtOAc/hexanes) to afford the title compound as a white, amorphous solid (88 mg, 0.36 mmol, 83%, >20:1 dr). **TLC $R_f$** = 0.3 (40% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.83–7.71 (m, 3H), 7.64 (s, 1H), 7.48–7.40 (m, 2H), 7.38 (d, *J* = 8.6 Hz, 1H), 3.32 (t, *J* = 8.2 Hz, 1H), 3.29–3.23 (m, 1H), 3.23–3.15 (m, 1H), 2.86 (s, 1H), 2.33–2.23 (m, 1H), 2.11–1.77 (m, 5H), 1.74 (br s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 138.8, 133.5, 132.4, 128.1, 127.8, 127.7, 126.8, 126.29, 126.26, 125.7,

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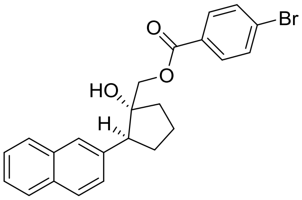
[66] Pandey, G.; Kapur, M; Khan, M. I.; Gaikwad, S. M. *Org. Biomol. Chem.* **2003**, *1*, 3321–3326.

84.0, 66.9, 55.2, 36.2, 30.6, 22.1; **IR** (neat) 3371, 2954, 2874 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{16}H_{18}O_2Na$ (M + Na)$^+$ 265.1205, found 265.1204; **[α]$^{27}$D** –29 (*c* 0.6, $CHCl_3$).



**(*R*,*S*)-3.93.** The title compound was prepared according to a modified procedure reported by Hassner.[67] Under an atmosphere of $N_2$, a 20 mL scintillation vial charged with a stir bar and (*R*,*S*)-**3.92** (40 mg, 0.17 mmol, 1.0 equiv) and dry $CH_2Cl_2$ (4 mL). To this solution was added 4-(dimethylamino)pyridine (2 mg, 0.02 mmol, 0.1 equiv), 4-bromobenzoylchloride (47 mg, 0.21 mmol, 1.3 equiv), and triethylamine (0.03 mL, 0.4 mmol, 2 equiv). The reaction was allowed to stir at ambient temperature until TLC indicated the reaction had proceeded to conversion (4 h). The reaction was diluted with EtOAc (5 mL) and quenched with sat. $NH_4Cl$ (4 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (3 x 2 mL) and the combined organic layers were washed with brine (1 x 4 mL), dried over $MgSO_4$ filtered and concentrated in vacuo. The product was purified by flash column chromatography on silica gel (15% EtOAc/hexanes) to afford the title compound as a white solid (62 mg, 0.15 mmol, 88%, 99% ee). A single crystal for X-ray crystallography was grown **TLC R$_f$** = 0.2 (20% EtOAc/hexanes, UV active, stain with $KMnO_4$); **m.p.** = 138 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.78–7.69 (m, 3H), 7.68 (s, 1H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.47–7.39 (m, 3H), 7.37 (d, *J* = 8.6 Hz, 2H), 4.11 (d, *J* = 11.7 Hz, 1H), 4.02 (d, *J* = 11.7 Hz, 1H), 3.45 (t, *J* = 8.5 Hz, 1H), 2.58 (br s, 1H), 2.39–2.30 (m,

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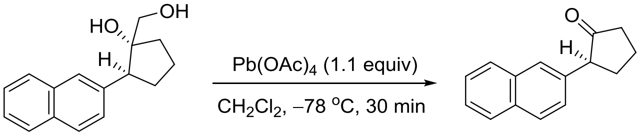
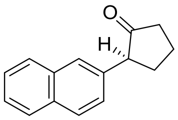
[67] Basel, Y.; Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368–6380.

1H), 2.22–2.12 (m, 1H), 2.09–1.92 (m, 4H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 165.9, 138.0, 133.5, 132.6, 131.6, 131.0, 128.5, 128.3, 128.1, 127.7, 127.6, 126.6, 126.5, 126.2, 125.7, 82.9, 69.3, 55.5, 36.7, 30.2, 21.8; **IR** (neat) 3487, 2956, 1717 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{23}H_{21}O_3BrNa$ (M + Na)$^+$ 447.0572, found 447.0581; **$[\alpha]^{29}_D$** –68 (*c* 2.8, $CHCl_3$); **SFC** analysis (Whelk-O (R,R), 10% IPA, 2.5 mL/min) indicated 99% ee: $t_R$ (major) = 24.6 minutes, $t_R$ (minor) = 23.5 minutes.

Single crystals suitable for X-ray crystallographic analysis were grown by slow diffusion of pentane into a solution of (*R*,*S*)-**3.93** in EtOAc at ambient temperature. See Experimental Details for crystallographic data.

## Synthesis of ketone (*S*)-34 via oxidative cleavage





**(*S*)-3.48.** The title compound was prepared according to a modified procedure reported by Wicha.[68] A 20 mL scintillation vial charged with a stir bar and (*R*,*S*)-**3.92** (36 mg, 0.15 mmol, 1.0 equiv) and $CH_2Cl_2$ (4 mL). The reaction was cooled to –78 °C to avoid epimerization of the benzylic stereocenter. To this solution was added $Pb(OAc)_4$ (73 mg, 0.17 mmol, 1.1 equiv) in a

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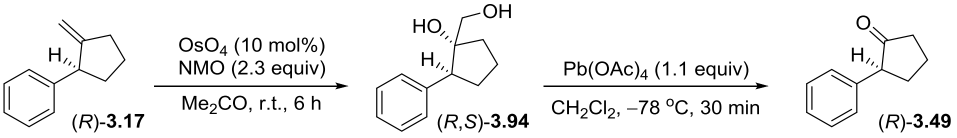
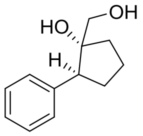
[68] Blakemore, P. R.; Kocienski, P. J.; Marzcak, S.; Wicha, J. *Synthesis* **1999**, *7*, 1209–1216.

single portion. The reaction was allowed to stir at –78 °C until TLC indicated the reaction had proceeded to conversion (30 min). The reaction was diluted with EtOAc (5 mL) and quenched with sat. $NH_4Cl$ (4 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (3 x 2 mL) and the combined organic layers were washed with brine (1 x 4 mL), dried over $MgSO_4$ filtered and concentrated in vacuo. The ketone was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound as a white solid (20 mg, 0.095 mmol, 63%, 98% ee). Analytical data is consistent with literature values.[34] **TLC $R_f$** = 0.2 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.85–7.76 (m, 3H), 7.64 (s, 1H), 7.49–7.41 (m, 2H), 7.31 (d, *J* = 8.6 Hz, 1H), 3.50 (at, *J* = 9.7 Hz, 1H), 2.61–2.54 (m, 1H), 2.52 (dd, *J* = 19.1, 8.6 Hz, 1H), 2.41–3.30 (m, 1H), 2.28–2.17 (m, 2H), 2.05–1.93 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 218.3, 136.0, 133.6, 132.6, 128.4, 127.82, 127.75, 126.9, 126.5, 126.2, 125.8, 55.6, 38.7, 31.9, 21.1; **$[\alpha]^{24}_D$** –37 (*c* 0.9, $CHCl_3$); **SFC** analysis (AS-H, 15% IPA, 2.5 mL/min) indicated 98% ee: $t_R$ (major) = 3.9 minutes, $t_R$ (minor) = 3.0 minutes.

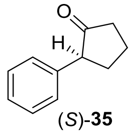
## Synthesis of ketone (*S*)-3.49 via oxidative cleavage

The ketone (*S*)-**3.49** was prepared from the methylenecyclopentane (*R*)-**3.17**. Dihydroxylation of (*R*)-**3.17** followed by oxidative cleavage with $Pb(OAc)_4$ afforded the ketone (*S*)-**3.49**.





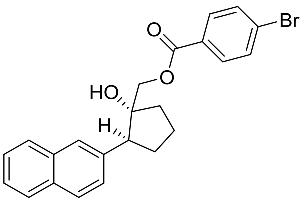
**(*R*,*S*)-3.94.** The title compound was prepared according to a modified procedure reported by Gaikwad.[36] A 20 mL scintillation vial charged with a stir bar and (*R*)-**3.17** (55 mg, 0.45 mmol, 1.0 equiv) and acetone (4 mL). To this solution was added *N*-methylmorpholine-*N*-oxide (122 mg, 1.03 mmol, 2.30 equiv) and $OsO_4$ (0.28 mL, 4% in $H_2O$, 0.045 mmol, 0.10 equiv). The reaction vessel was sealed and allowed to stir at ambient temperature until TLC indicated the reaction had proceeded to conversion (5 h). The reaction was diluted with EtOAc (5 mL) and quenched with sat. $NH_4Cl$ (4 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (3 x 2 mL) and the combined organic layers were washed with brine (1 x 4 mL), dried over $MgSO_4$ filtered and concentrated in vacuo. The diol was purified by flash column chromatography on silica gel (25% EtOAc/hexanes) to afford the title compound as clear oil (48 mg, 0.25 mmol, 56%, 7:1 dr). **TLC $R_f$** = 0.4 (40% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.33–7.28 (m, 2H), 7.27–7.20 (m, 3H), 3.30 (d, *J* = 11.5 Hz, 1H), 3.24–3.13 (m, 2H), 2.75 (br s, 1H), 2.28–2.18 (m, 1H), 2.00–1.90 (m, 2H), 1.90–1.78 (m, 3H), 1.55 (br s, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 141.3, 128.7, 128.0, 126.9, 83.8, 66.9, 55.2, 36.0, 30.5, 22.0; **IR** (neat) 3376, 2954, 2874 $cm^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{12}H_{16}O_2Na$ $(M + Na)^+$ 215.1048, found 215.1044.



(*S*)-**35**

**(*S*)-3.49.** The title compound was prepared according to a modified procedure reported by Wicha.[38] A 20 mL scintillation vial charged with a stir bar and (*R*,*S*)-**3.94** (35 mg, 0.18 mmol, 1.0 equiv) and $CH_2Cl_2$ (4 mL). The reaction was cooled to –78 °C to avoid epimerization of the benzylic stereocenter. To this solution was added $Pb(OAc)_4$ (89 mg, 0.20 mmol, 1.1 equiv) in a single portion. The reaction was allowed to stir at –78 °C until TLC indicated the reaction had proceeded to conversion (30 min). The reaction was diluted with EtOAc (5 mL) and quenched with sat. $NH_4Cl$ (4 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (3 x 2 mL) and the combined organic layers were washed with brine (1 x 4 mL), dried over $MgSO_4$ filtered and concentrated in vacuo. The ketone was purified by flash column chromatography on silica gel (10% EtOAc/hexanes) to afford the title compound as a white, amorphous solid (20 mg, 0.13 mmol, 72%, 76% ee). Analytical data is consistent with literature values.[34] **TLC $R_f$** = 0.2 (10% EtOAc/hexanes, UV active, stain with $KMnO_4$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.1 Hz, 2H), 7.28–7.22 (m, 1H), 7.19 (d, *J* = 7.1 Hz, 2H), 3.37–3.29 (m, 1H), 2.57–2.43 (m, 2H), 2.35–2.24 (m, 1H), 2.21–2.07 (m, 2H), 1.99–1.89 (m, 1H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 218.3, 138.6, 128.7, 128.3, 127.0, 55.5, 38.6, 31.9, 21.0; **$[\alpha]^{28}_D$** –41 (*c* 0.3, $CHCl_3$); **SFC** analysis (OD-H, 10% IPA, 2.5 mL/min) indicated 76% ee: $t_R$ (major) = 3.4 minutes, $t_R$ (minor) = 3.2 minutes.

## CRYSTALLOGRAPHIC DATA



(*R*,*S*)-**3.93**
Scheme 3.12

### X-ray Data Collection, Structure Solution and Refinement for (*R*,*S*)-3.93.

Single crystals suitable for X-ray crystallographic analysis were grown by slow diffusion of pentane into a solution of (*R*,*S*)-**3.93** in EtOAc at ambient temperature.

A colorless crystal of approximate dimensions 0.293 x 0.205 x 0.111 mm was mounted on a glass fiber and transferred to a Bruker SMART APEX II diffractometer. The APEX2[69] program package was used to determine the unit-cell parameters and for data collection (15 sec/frame scan time for a sphere of diffraction data). The raw frame data was processed using SAINT[70] and SADABS[71] to yield the reflection data file. Subsequent calculations were carried out using the SHELXTL[72] program. The diffraction symmetry was *mmm* and the systematic absences were consistent with the orthorhombic space group $P2_12_12_1$ that was later determined to be correct.

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[69] APEX2 Version 2014.1-1, Bruker AXS, Inc.; Madison, WI 2014.

[70] SAINT Version 8.34a, Bruker AXS, Inc.; Madison, WI 2013.

[71] Sheldrick, G. M. SADABS, Version 2012/1, Bruker AXS, Inc.; Madison, WI 2012.

[72] Sheldrick, G. M. SHELXTL, Version 2014/2, Bruker AXS, Inc.; Madison, WI 2014.

The structure was solved by direct methods and refined on $F^2$ by full-matrix least-squares techniques. The analytical scattering factors[73] for neutral atoms were used throughout the analysis. Hydrogen atoms were included using a riding model.

At convergence, wR2 = 0.0536 and Goof = 1.054 for 247 variables refined against 4644 data (0.73 Å), R1 = 0.0223 for those 4412 data with $I > 2.0\sigma(I)$. The absolute structure was assigned by refinement of the Flack parameter[74].

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Definitions:

$wR2 = [\Sigma[w(F_o^2-F_c^2)^2] / \Sigma[w(F_o^2)^2] ]^{1/2}$

$R1 = \Sigma||F_o|-|F_c|| / \Sigma|F_o|$

$Goof = S = [\Sigma[w(F_o^2-F_c^2)^2] / (n-p)]^{1/2}$ where n is the number of reflections and p is the total number of parameters refined.

The thermal ellipsoid plot is shown at the 50% probability level.

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[73] International Tables for X-Ray Crystallography 1992, Vol. C., Dordrecht: Kluwer Academic Publishers.

[74] Flack, H. D., Parsons, S., Wagner, T. Acta. Cryst., B69, 249-259, 2013.

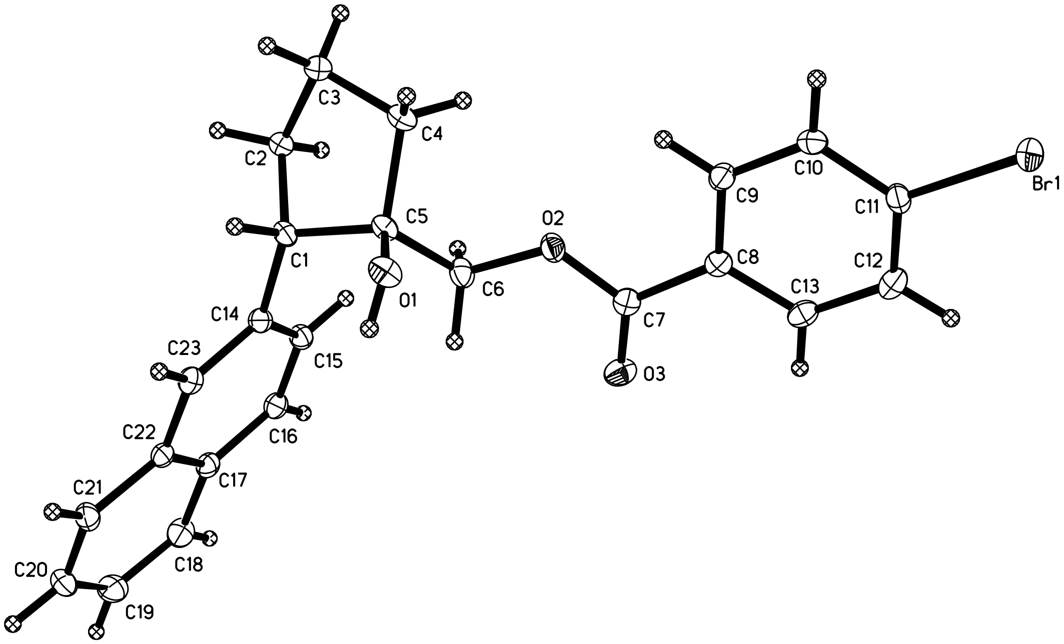

*Table 3.5.* Crystal data and structure refinement for (*R*,*S*)-**3.93**.

| | | |
|---|---|---|
| Identification code | (*R*,*S*)-**3.93** (Michael Harris) | |
| Empirical formula | $C_{23} H_{21} Br O_3$ | |
| Formula weight | 425.31 | |
| Temperature | 88(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12_1$ | |
| Unit cell dimensions | a = 7.9672(4) Å | α= 90°. |
| | b = 9.3042(4) Å | β= 90°. |
| | c = 24.7018(11) Å | γ = 90°. |

| | |
|---|---|
| Volume | 1831.11(15) Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.543 Mg/m$^3$ |
| Absorption coefficient | 2.266 mm$^{-1}$ |
| F(000) | 872 |
| Crystal color | colorless |
| Crystal size | 0.293 x 0.205 x 0.111 mm$^3$ |
| Theta range for data collection | 1.649 to 29.026° |
| Index ranges | $-10 \le h \le 10$, $-12 \le k \le 12$, $-32 \le l \le 32$ |
| Reflections collected | 22622 |
| Independent reflections | 4644 [R(int) = 0.0251] |
| Completeness to theta = 25.242° | 100.0 % |
| Absorption correction | Numerical |
| Max. and min. transmission | 0.8205 and 0.6133 |
| Refinement method | Full-matrix least-squares on F$^2$ |
| Data / restraints / parameters | 4644 / 0 / 247 |
| Goodness-of-fit on F$^2$ | 1.054 |
| Final R indices [I>2sigma(I) = 4412 data] | R1 = 0.0223, wR2 = 0.0528 |
| R indices (all data, 0.73 Å) | R1 = 0.0245, wR2 = 0.0536 |
| Absolute structure parameter | -0.007(2) |
| Largest diff. peak and hole | 0.597 and -0.299 e.Å$^{-3}$ |

***Table 3.6.*** Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for (*R*,*S*)-**3.93**. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Br(1) | 12231(1) | 12759(1) | 9891(1) | 21(1) |
| O(1) | 9393(2) | 5010(2) | 8236(1) | 17(1) |
| O(2) | 8218(2) | 7849(2) | 8350(1) | 17(1) |
| O(3) | 8638(2) | 9449(2) | 7682(1) | 19(1) |
| C(1) | 6594(3) | 4163(2) | 7945(1) | 13(1) |
| C(2) | 4933(3) | 4160(2) | 8260(1) | 15(1) |
| C(3) | 5549(3) | 4243(2) | 8848(1) | 19(1) |
| C(4) | 7006(3) | 5317(2) | 8826(1) | 19(1) |
| C(5) | 7648(3) | 5352(2) | 8234(1) | 13(1) |
| C(6) | 7414(3) | 6842(2) | 7985(1) | 16(1) |
| C(7) | 8726(3) | 9114(2) | 8156(1) | 14(1) |
| C(8) | 9453(3) | 10031(2) | 8591(1) | 14(1) |
| C(9) | 9538(3) | 9552(2) | 9125(1) | 15(1) |
| C(10) | 10340(3) | 10367(2) | 9517(1) | 15(1) |
| C(11) | 11033(3) | 11682(2) | 9366(1) | 15(1) |
| C(12) | 10900(2) | 12208(3) | 8842(1) | 18(1) |
| C(13) | 10105(3) | 11377(2) | 8455(1) | 16(1) |
| C(14) | 6411(3) | 4202(2) | 7334(1) | 13(1) |
| C(15) | 5344(3) | 5226(2) | 7076(1) | 14(1) |
| C(16) | 5088(3) | 5208(2) | 6529(1) | 15(1) |
| C(17) | 5859(3) | 4150(2) | 6198(1) | 14(1) |
| C(18) | 5577(3) | 4084(3) | 5629(1) | 19(1) |
| C(19) | 6305(3) | 3026(3) | 5325(1) | 22(1) |
| C(20) | 7352(3) | 1985(2) | 5571(1) | 20(1) |
| C(21) | 7666(3) | 2027(2) | 6119(1) | 17(1) |
| C(22) | 6920(2) | 3113(2) | 6443(1) | 13(1) |

| | | | | |
|---|---|---|---|---|
| C(23) | 7176(3) | 3179(2) | 7016(1) | 14(1) |

***Table 3.7.*** Bond lengths [Å] and angles [°] for (*R*,*S*)-**3.93**.

| | |
|---|---|
| Br(1)-C(11) | 1.895(2) |
| O(1)-C(5) | 1.426(3) |
| O(2)-C(7) | 1.334(3) |
| O(2)-C(6) | 1.450(2) |
| O(3)-C(7) | 1.212(3) |
| C(1)-C(14) | 1.515(3) |
| C(1)-C(2) | 1.535(3) |
| C(1)-C(5) | 1.562(3) |
| C(2)-C(3) | 1.535(3) |
| C(3)-C(4) | 1.533(3) |
| C(4)-C(5) | 1.551(3) |
| C(5)-C(6) | 1.527(3) |
| C(7)-C(8) | 1.490(3) |
| C(8)-C(9) | 1.394(3) |
| C(8)-C(13) | 1.397(3) |
| C(9)-C(10) | 1.387(3) |
| C(10)-C(11) | 1.393(3) |
| C(11)-C(12) | 1.388(3) |
| C(12)-C(13) | 1.384(3) |
| C(14)-C(23) | 1.377(3) |
| C(14)-C(15) | 1.427(3) |
| C(15)-C(16) | 1.367(3) |
| C(16)-C(17) | 1.420(3) |
| C(17)-C(22) | 1.419(3) |
| C(17)-C(18) | 1.425(3) |
| C(18)-C(19) | 1.366(3) |
| C(19)-C(20) | 1.415(3) |
| C(20)-C(21) | 1.375(3) |
| C(21)-C(22) | 1.420(3) |
| C(22)-C(23) | 1.430(3) |
| | |
| C(7)-O(2)-C(6) | 118.63(16) |

| | |
|---|---|
| C(14)-C(1)-C(2) | 114.94(18) |
| C(14)-C(1)-C(5) | 119.27(17) |
| C(2)-C(1)-C(5) | 103.50(16) |
| C(1)-C(2)-C(3) | 101.76(18) |
| C(4)-C(3)-C(2) | 104.03(17) |
| C(3)-C(4)-C(5) | 107.22(17) |
| O(1)-C(5)-C(6) | 108.87(17) |
| O(1)-C(5)-C(4) | 108.19(17) |
| C(6)-C(5)-C(4) | 110.96(17) |
| O(1)-C(5)-C(1) | 111.64(16) |
| C(6)-C(5)-C(1) | 113.18(16) |
| C(4)-C(5)-C(1) | 103.83(16) |
| O(2)-C(6)-C(5) | 106.40(16) |
| O(3)-C(7)-O(2) | 123.9(2) |
| O(3)-C(7)-C(8) | 124.8(2) |
| O(2)-C(7)-C(8) | 111.27(18) |
| C(9)-C(8)-C(13) | 119.7(2) |
| C(9)-C(8)-C(7) | 121.2(2) |
| C(13)-C(8)-C(7) | 119.0(2) |
| C(10)-C(9)-C(8) | 120.6(2) |
| C(9)-C(10)-C(11) | 118.4(2) |
| C(12)-C(11)-C(10) | 121.9(2) |
| C(12)-C(11)-Br(1) | 119.28(17) |
| C(10)-C(11)-Br(1) | 118.77(17) |
| C(13)-C(12)-C(11) | 118.9(2) |
| C(12)-C(13)-C(8) | 120.3(2) |
| C(23)-C(14)-C(15) | 117.97(19) |
| C(23)-C(14)-C(1) | 120.63(19) |
| C(15)-C(14)-C(1) | 121.22(19) |
| C(16)-C(15)-C(14) | 121.6(2) |
| C(15)-C(16)-C(17) | 120.9(2) |
| C(22)-C(17)-C(16) | 118.89(19) |
| C(22)-C(17)-C(18) | 119.1(2) |
| C(16)-C(17)-C(18) | 122.0(2) |
| C(19)-C(18)-C(17) | 120.3(2) |
| C(18)-C(19)-C(20) | 120.5(2) |

| | |
|---|---|
| C(21)-C(20)-C(19) | 120.7(2) |
| C(20)-C(21)-C(22) | 119.9(2) |
| C(17)-C(22)-C(21) | 119.47(19) |
| C(17)-C(22)-C(23) | 118.60(19) |
| C(21)-C(22)-C(23) | 121.92(19) |
| C(14)-C(23)-C(22) | 122.1(2) |

***Table 3.8.*** Anisotropic displacement parameters ($Å^2$x $10^3$) for (*R*,*S*)-**3.93**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[ h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12} ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Br(1) | 21(1) | 21(1) | 20(1) | -4(1) | 1(1) | -8(1) |
| O(1) | 14(1) | 22(1) | 15(1) | -3(1) | -2(1) | 3(1) |
| O(2) | 24(1) | 13(1) | 13(1) | -1(1) | -2(1) | -2(1) |
| O(3) | 16(1) | 25(1) | 16(1) | 4(1) | -2(1) | -4(1) |
| C(1) | 15(1) | 12(1) | 12(1) | -2(1) | 0(1) | 2(1) |
| C(2) | 18(1) | 15(1) | 12(1) | -1(1) | 2(1) | -2(1) |
| C(3) | 28(1) | 16(1) | 13(1) | 0(1) | 3(1) | -3(1) |
| C(4) | 25(1) | 21(1) | 12(1) | -3(1) | 1(1) | -3(1) |
| C(5) | 13(1) | 15(1) | 11(1) | -2(1) | -1(1) | 1(1) |
| C(6) | 20(1) | 15(1) | 15(1) | -2(1) | -4(1) | -1(1) |
| C(7) | 10(1) | 15(1) | 18(1) | 0(1) | 0(1) | 2(1) |
| C(8) | 11(1) | 13(1) | 16(1) | 1(1) | 2(1) | 2(1) |
| C(9) | 16(1) | 13(1) | 17(1) | 0(1) | 3(1) | -1(1) |
| C(10) | 15(1) | 16(1) | 13(1) | 1(1) | 3(1) | 1(1) |
| C(11) | 12(1) | 15(1) | 18(1) | -5(1) | 1(1) | -1(1) |
| C(12) | 15(1) | 14(1) | 24(1) | 2(1) | 2(1) | -1(1) |
| C(13) | 14(1) | 16(1) | 17(1) | 4(1) | 1(1) | 1(1) |
| C(14) | 13(1) | 15(1) | 12(1) | -1(1) | -1(1) | -2(1) |
| C(15) | 14(1) | 14(1) | 16(1) | -2(1) | 1(1) | 0(1) |
| C(16) | 14(1) | 14(1) | 17(1) | 1(1) | -1(1) | -1(1) |
| C(17) | 14(1) | 14(1) | 16(1) | 0(1) | -1(1) | -3(1) |
| C(18) | 21(1) | 19(1) | 17(1) | 2(1) | -4(1) | -3(1) |
| C(19) | 27(1) | 26(1) | 13(1) | -2(1) | -1(1) | -6(1) |
| C(20) | 22(1) | 19(1) | 18(1) | -6(1) | 4(1) | -2(1) |
| C(21) | 15(1) | 15(1) | 20(1) | -4(1) | 1(1) | -1(1) |
| C(22) | 11(1) | 13(1) | 16(1) | -1(1) | 1(1) | -3(1) |
| C(23) | 12(1) | 14(1) | 16(1) | 0(1) | -1(1) | -1(1) |

***Table 3.9***. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters (Å$^2$x $10^3$) for (*R*,*S*)-**3.93**.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | 7156 | 3230 | 8031 | 16 |
| H(2A) | 4288 | 3268 | 8193 | 18 |
| H(2B) | 4231 | 5001 | 8165 | 18 |
| H(3A) | 4647 | 4591 | 9091 | 23 |
| H(3B) | 5937 | 3292 | 8976 | 23 |
| H(4A) | 7917 | 5012 | 9074 | 23 |
| H(4B) | 6619 | 6284 | 8938 | 23 |
| H(6A) | 7940 | 6885 | 7622 | 20 |
| H(6B) | 6205 | 7068 | 7948 | 20 |
| H(9A) | 9043 | 8659 | 9221 | 18 |
| H(10A) | 10414 | 10037 | 9881 | 18 |
| H(12A) | 11346 | 13124 | 8752 | 21 |
| H(13A) | 10003 | 11724 | 8095 | 19 |
| H(15A) | 4799 | 5935 | 7289 | 17 |
| H(16A) | 4385 | 5914 | 6368 | 18 |
| H(18A) | 4879 | 4779 | 5459 | 23 |
| H(19A) | 6107 | 2988 | 4946 | 26 |
| H(20A) | 7842 | 1250 | 5357 | 24 |
| H(21A) | 8382 | 1331 | 6279 | 20 |
| H(23A) | 7897 | 2495 | 7182 | 17 |
| H(1) | 9750(40) | 4920(30) | 7940(12) | 21 |

*Chapter Four*

# Nickel-Catalyzed Formation of Secondary Organozinc Reagents From 2-Pyridyl Carbinols

## 4.1 Introduction

Organometallic reagents occupy a central role in modern organic synthesis.[1] In particular, functionalized organozinc reagents have been critical for the construction of natural products and other complex organic molecules.[2] The high proclivity of organozinc compounds to undergo selective reactions with transition metals enables the construction of new carbon–carbon bonds under mild reaction conditions. Methods to prepare functionalized organozinc reagents are diverse and an important topic of continuing research.[3] Typically, such reagents are made by one of three approaches: 1) Direct insertion of zinc dust into aryl or alkyl halides (Scheme 4.1a), 2) exchange of aryl or alkyl magnesium and boron reagents with a zinc (II) species (Scheme 4.1b), or 3) Direct metalation of arenes or heteroarenes with TMP bases of zinc (Scheme 4.1c).

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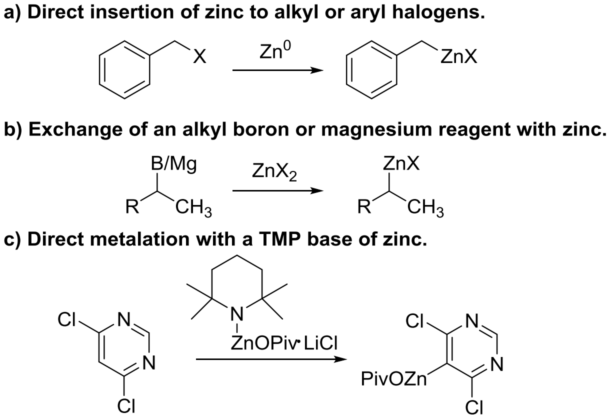
[1] (a) G. S. Silverman, in: P. E. Rakita (Ed.), Handbook of Grignard reagents, Marcel Dekker, New York, 1996. (b) Knochel, P.; Leuser, H.; Gong, L.-Z.; Perrone, S.; Kneisel, F. F. Handbook of Functionalized Organometallics: Applications in Synthesis; Knochel, P., Ed.; Wiley: Weinheim, 2005; p 251.

[2] (a) Knochel, P.; Leuser, H.; Gong, L.-Z.; Perrone, S.; Kneisel, F. F. Polyfunctional Zinc Organometallics for Organic Synthesis. In *Handbook of Functionalized Organometallics: Applications in Synthesis*; Knochel, P., Ed.; Wiley: Weinheim, 2005; p 251. For specific examples in total synthesis, see: (b) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817. (c) Masaki, H.; Maeyama, J.; Kamada, K.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *J. Am. Chem. Soc.* **2000**, *122*, 5216. (d) Aoyagi, S.; Hirashima, S.; Saito, K.; Kibayashi, C. *J. Org. Chem.* **2002**, *67*, 5517.

[3] (a) Klatt, T.; Markiewicz, J. T.; Sämann, C.; Knochel, P. *J. Org. Chem.* **2014**, *79*, 4253. (b) Stathakis, C. I.; Manolikakes, S. M.; Knochel, P. *Org. Lett.* **2013**, *15*, 1302. (c) Colombe, J. R.; Bernhardt, S.; Stathakis, C.; Buchwald, S. L.; Knochel, P. **2013**, *15*, 5754. (d) Quinio, P.; François, C.; Cuesta, A. E.; Steib, A. K.; Achrainer, F.; Zipse, H.; Karaghiosoff, K.; Knochel, P. *Org. Lett.* **2015**, *17*, 1010.

***Scheme 4.1.*** Methods for the formation of organozinc reagents



Transition metal catalysis offers alternative strategies for formation of organometallic reagents.[4,5,6] Nickel catalysts are known to undergo oxidative addition into benzylic electrophiles to generate benzylnickel intermediates.[7] We reasoned that, in the presence of a stoichiometric quantity of an organozinc reagent, transmetallation could occur to generate the benzylzinc intermediate (Scheme 4.1d). The Shi group has reported a related synthesis of primary benzylic Grignard reagents directly from benzylic alcohols (Scheme 4.2a).[8] In this Chapter we report nickel-catalyzed formation of secondary benzylzinc reagents from readily accessible 2-pyridyl carbinols, a concise and complementary approach to traditional methods of preparation (Scheme 4.2b).

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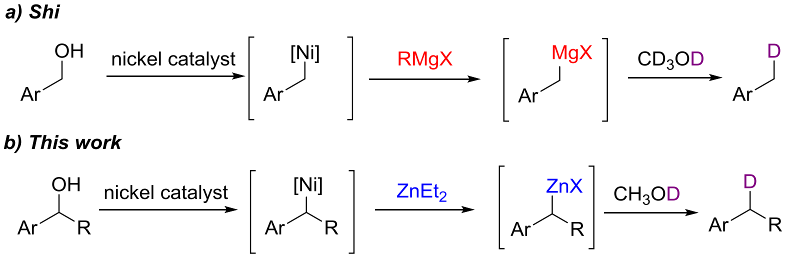
[4] (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Rosen, B. M.; Huang, C.; Percec, V. *Org. Lett.* **2008**, *10*, 2597. (c) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am Chem. Soc.* **2002**, *124*, 390.

[5] Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961.

[6] Dao, H. T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2014**, *53*, 14382.

[7] (a) Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 9083. (b) Do, H-Q.; Chandrashekar, E. R. R.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 16288

***Scheme 4.2.*** Nickel-catalyzed metalation of benzylic alcohols



We propose that the nitrogen of 2-pyridyl carbinols could promote the desired transformation by directing the transmetallation event to favor formation of the benzylzinc reagent from the benzylnickel intermediate.[9] The 2-pyridyl moiety is an ideal directing group because it is ubiquitous in bioactive molecules and is a privileged motif for ligands used in transition metal-mediated transformations.[10]

## 4.2 Development of a Nickel-Catalyzed Synthesis of Secondary Benzylic Zinc Reagents

Herein, we report a nickel-catalyzed method for the formation of secondary benzylic zinc reagents from diethyl phosphate esters generated in situ.[11] We chose 2-pyridyl carbinol **4.1** as our model substrate. We reasoned that quenching the benzylzinc reagent formed under the appropri-

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[8] Yu, D-G.; Wang, X.; Zhu, R-Y.; Luo, S.; Zhang, X-B.; Wang, B-Q.; Wang, L.; Shi, Z-J. *J. Am. Chem. Soc.* **2012**, *134*, 14638.

[9] Pyridine is a privileged directing group in C–H bond activation, see: (a) Suggs, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 489. (b) Lim, Y–G.; Kang, J–B.; Kim, Y. H. *J. Chem. Soc., Perkin Trans.* **1996**, *1*, 2201. (c) Jun, C–H.; Hwang, D–C.; Na, S–J. *Chem. Commun.* **1998**, 1405. (d) Chatani, N.; Ishii, Y.; Ie, Y.; Kakiuchi F.; Murai, S. *J. Org. Chem.* **1998**, *63*, 5129. (e) Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakuichi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882.

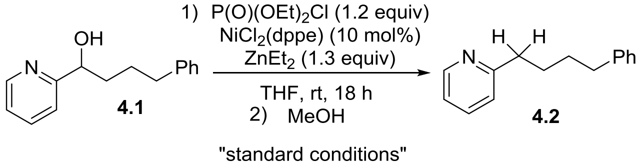
[10] (a) Shi, N.; Lu, C.; Ho, C. C.; Shen, Y. *Rec. Nat. Prod.* **2013**, *7*, 1. (b) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (c) Kubota, T.; Ishiguro Y.; Yamamoto, S.; Fromont, J.; Kobayashi, J. *Heterocycles* **2010**, *80*, 1407. (d) Fischer, D. F.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 5926 (e) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129.

[11] Phosphate esters generated in situ are effective electrophiles in nickel-catalyzed transformations, see: (a) Ackerman, L. K. G.; Anka-Lufford, L. L.; Naodovic, M.; Weix, D. J. *Chem. Sci.* **2015**, *6*, 1115.

ate reaction conditions with methanol would result in the deoxygenated product **4.2**. After examining an array of reaction conditions, we found that subjecting **4.1** to $NiCl_2$(dppe), diethyl chlorophosphate ($P(O)(OEt)_2Cl$) and $ZnEt_2$ for 18 h at room temperature furnishes the desired deoxygenated product **4.2** in high yield (Table 4.1, entry 1).

The data in Table 4.1 illustrate how changes in the reaction parameters affect the transformation. When nickel or $P(O)(OEt)_2Cl$ are omitted, the reaction does not afford desired product (entries 2–4). These results are consistent with a mechanism of benzylic alcohol activation prior to reaction with a nickel catalyst. The use of a non-polar solvent or $ZnMe_2$ instead of $ZnEt_2$ does not significantly affect the efficiency of the reaction (entries 5 and 6). A decreased yield of **4.2** was observed when catalysts ligated by bidendate ligands other than dppe were used in the reaction (entries 7 and 8). Similarly, deoxygenation of **4.1** was achieved in poor to moderate yields when monodentate phosphine ligands were employed (entries 9 and 10). Under optimized conditions, the reaction is quite scalable, providing desired product in high yield when performed on gram scale (entry 11).

***Table 4.1.*** Effect of reaction parameters on the efficiency of deoxygenation of **4.1**

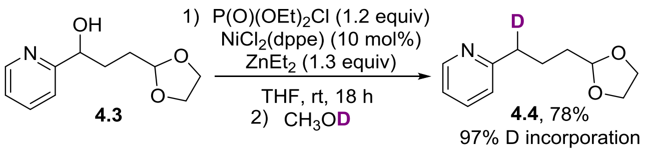


| entry | change from standard conditions | yield (%)[a] |
|---|---|---|
| 1 | none | 77 |
| 2 | dppe instead of $NiCl_2$(dppe) | < 5 |
| 3 | no $NiCl_2$(dppe) | < 5 |
| 4 | no $P(O)(OEt)_2Cl$ | < 5 |
| 5 | PhMe instead of THF | 72 |
| 6 | $ZnMe_2$ instead of $ZnEt_2$ | 74 |
| 7 | $NiCl_2$•DME / DPEphos instead of $NiCl_2$(dppe) | 42 |
| 8 | $NiCl_2$•DME / dppf instead of $NiCl_2$(dppe) | 55 |
| 9 | $NiCl_2$•DME / $PCy_3$ instead of $NiCl_2$(dppe) | 21 |
| 10 | $NiCl_2$•DME / $PPh_3$ instead of $NiCl_2$(dppe) | 50 |
| 11 | Run on 1.0 g scale of **4.1** | 72[b] |

[a]Yield determined by $^1$H NMR based on comparison with $PhSiMe_3$ as internal standard. [b]Isolated yield after column chromatography.

## 4.3 Scope of the Reaction

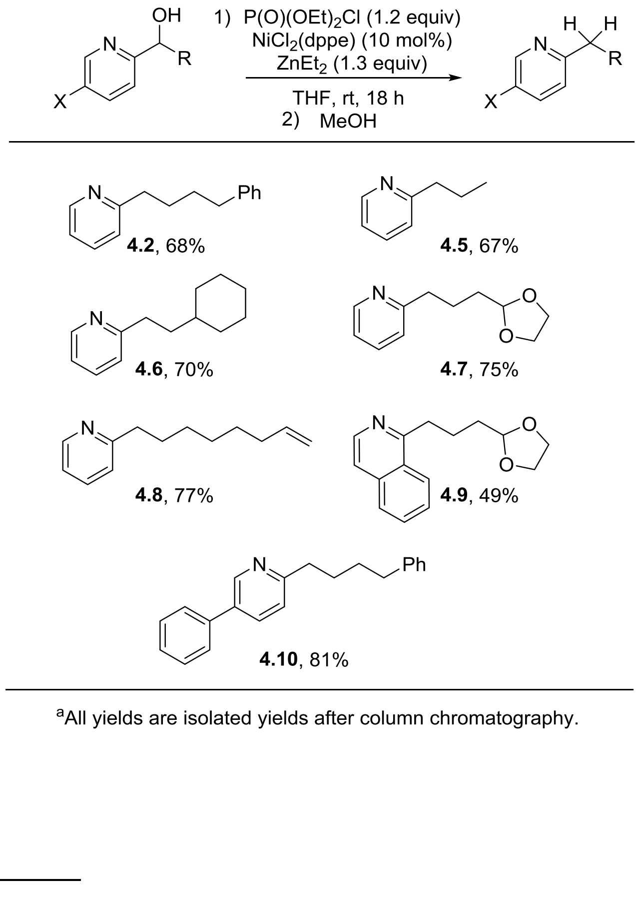
Having developed robust conditions for the deoxygenation of **4.1**, we turned our attention to investigating the source of "H" found in the product. We proposed that **4.2** is formed from the methanol quench of the benzylzinc reagent generated in situ. To test our hypothesis, we performed an isotopic labeling study with methanol-d. Upon quenching the deoxygenation reaction of **4.3** with $CH_3OD$, we observed high yield and high deuterium incorporation of the corresponding product **4.4** (eq 4.1). The result of the isotopic labeling experiment provides strong support for our proposed hypothesis that the reaction proceeds by formation of a benzylzinc reagent.



(4.1)

Next, we examined the formation of alkyl zinc reagents from a range of benzylic alcohols (Scheme 4.3). Secondary benzylic alcohols bearing alkyl chains are well tolerated under the reaction conditions (**4.2**, **4.5**, and **4.6**). Substrates containing acetal and olefin functionalities provide deoxygenated products in good yield (**4.7** and **4.8**). The high yield of **4.8** is particularly interesting because it demonstrates excellent orthogonality to hydroboration transmetallation procedures often used to prepare secondary benzylzinc reagents.[12] When the arene is changed from 2-pyridyl to a 1-isoquinoline derivative, a modest yield of the deoxygenated product is obtained (**4.9**). Substitution of the pyridine ring is well tolerated, affording deoxygenated pyridines in high yield (**4.10**).

***Scheme 4.3.*** Reaction scope[a]



[a]All yields are isolated yields after column chromatography.

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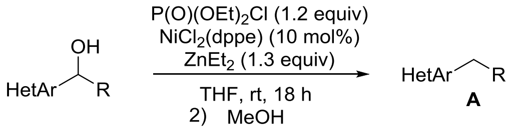
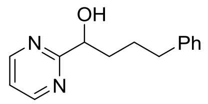
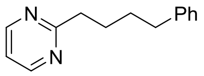
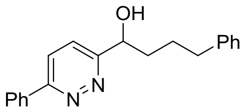
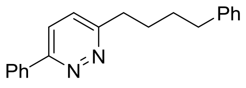
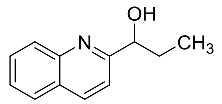
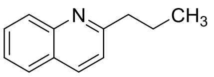
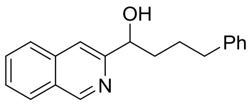
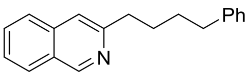
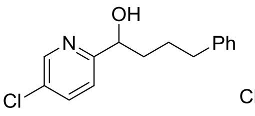
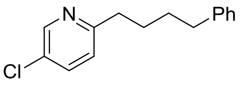
[12] Hupe, E.; Calaza, M. I.; Knochel, P. *J. Organomet. Chem.* **2003**, *680*, 136.

The identity of the heteroarene of the benzylic alcohols were varied to further expand the scope of benzylic zinc reagents formed under the reaction conditions (Table 4.2). Heterocycles containing more than a single nitrogen, such as pyrimidine and pyridazine, formed the desired product in low yield (entries 1 and 2). Other heterocycles, including 2-quinoline and 3-isoquinolines were not well tolerated under the reaction conditions (entries 3 and 4). Finally, halogen substitution of the pyridine ring proved detrimental to the desired transformation, affording the desired product in just 15% yield (entry 5).

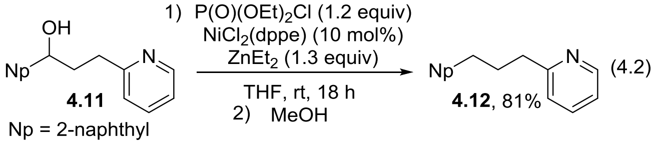
***Table 4.2***. Examination of additional substrate classes



| Entry | Substrate | Deoxygenation Product | yield **A** (%)[a] |
|---|---|---|---|
| 1 |  |  | 8 |
| 2 |  |  | 16 |
| 3 |  |  | 11 |
| 4 |  |  | 20 |
| 5 |  |  | 15 |

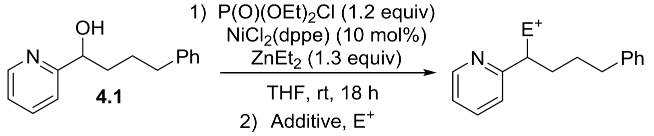
[a]Determined by $^1$H NMR using an internal standard (PhSiMe$_3$).

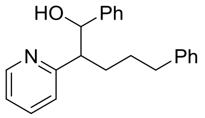
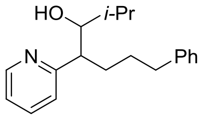
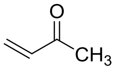
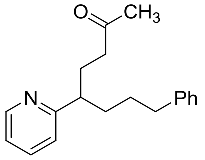
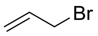
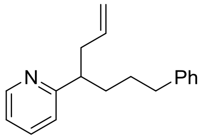
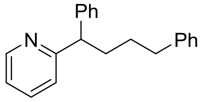
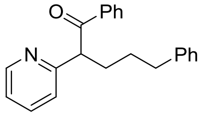
We reasoned that a pendant pyridine moiety could direct the formation of the desired organozinc reagent, which would improve the scope of the reaction beyond the use of 2-pyridyl carbinols. We synthesized benzylic alcohol **4.11**, which could generate a six-membered metallacycle chelate to direct the desired deoxygenation reaction. Indeed, when **4.11** was subjected to the reaction conditions, the expected deoxygenated product **4.12** is formed in high yield (eq 4.2).



To demonstrate the synthetic utility of our transformation, we attempted to capitalize on the reactivity of our benzylzinc reagents by nucleophilic addition to a number of electrophiles (Table 4.3). Titanium- and copper-assisted additions of the benzylzinc reagent derived from **4.1** proceed in modest yield (entries 1 and 2). Similarly, an intermolecular 1,4-addition to methyl vinyl ketone affords the desired product in just 30% yield (entry 3). Addition of the benzylzinc reagent to allyl bromide results in low yield of the alkylated product (entry 4). Cross-coupling of the benzylic zinc reagent with iodobenzene fails to produce desired product (entry 5). Finally, nickel-catalyzed coupling of the benzylic zinc reagent with benzoyl chloride results in low yields of the desired ketone (entry 6).

***Table 4.3.*** Addition of benzylzinc reagent to electrophiles

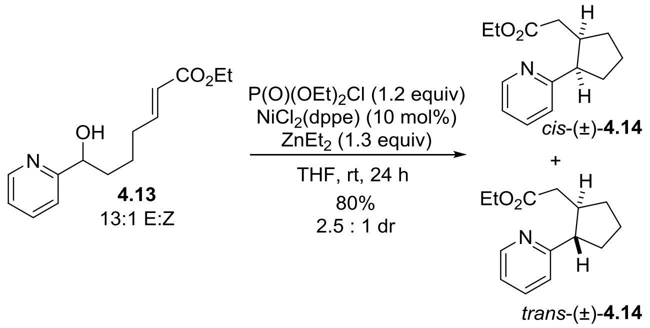


| Entry | Additive | $E^+$ | Product | yield **A** (%)[a] |
|---|---|---|---|---|
| 1 | Ti(O*i*-Pr)$_4$ | PhCHO |  | 21 |
| 2 | CuCN•2LiCl | *i*-PrCHO |  | 32 |
| 3 | none |  |  | 30 |
| 4 | CuCN•2LiCl |  |  | 12 |
| 5 | none | PhI |  | < 5 |
| 6 | none | benzoyl chloride |  | 11 |

[a] Determined by $^1$H NMR using an internal standard (PhSiMe$_3$).

Having obtained only modest reactivity of our benzylzinc reagents with exogenous electrophiles, we decided to try an intramolecular strategy. We reasoned that we could couple the formation of a benzylzinc reagent to an intramolecular 1,4-addition (Scheme 4.4). We anticipated that upon forming the corresponding benzylzinc reagent from **4.13**, cyclization should occur to afford carbocyclized product **4.14**. 2-Pyridyl carbinol **4.13** bearing a pendant α,β-unsaturated ester underwent smooth cyclization to produce the desired product in excellent yield and 2.5:1 diastereomeric ratio.

***Scheme 4.4***. Intramolecular 1,4-addition



## 4.4 Conclusions

In summary, we have developed a concise route to secondary organozinc reagents directly from benzylic alcohols. We have successfully applied this methodology to the deoxygenation of a range of 2-pyridyl carbinols. The reaction proceeds in high yield and has been applied to an intramolecular 1,4-addition. Further examination of the reactivity of the benzylzinc reagents and elucidation of mechanistic details are underway.

## 4.5 Experimental Details

*General Procedures*

All reactions were carried out under an atmosphere of $N_2$, or Ar when noted. All glassware was oven- or flame-dried prior to use. Tetrahydrofuran (THF), diethyl ether ($Et_2O$), dichloromethane ($CH_2Cl_2$), and toluene (PhMe) were degassed with Ar and then passed through two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; LaRoche Chemicals; activated under a flow of argon at 350 ºC for 12 h) to remove $H_2O$. All other solvents utilized were purchased "anhydrous" commercially, or purified as described. $^1H$ NMR spectra were recorded on Bruker DRX-400 (400 MHz $^1H$, 100 MHz $^{13}C$, 376.5 MHz $^{19}F$), GN-500 (500 MHz $^1H$, 125.7 MHz $^{13}C$), or CRYO-500 (500 MHz $^1H$, 125.7 MHz $^{13}C$) spectrometers. Proton chemical shifts are reported in ppm ($\delta$) relative to internal tetramethylsilane (TMS, $\delta$ 0.00). Data are reported as follows: chemical shift (multiplicity [singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), doublet of triplets (dt), doublet of doublet of triplets (ddt), triplet of triplets (tt), quartet (q), multiplet (m)], coupling constants [Hz], integration). Carbon chemical shifts are reported in ppm ($\delta$) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, $\delta$ 77.16 ppm). Unless otherwise indicated, NMR data were collected at 25 ºC. Infrared (IR) spectra were obtained on a Perkin-Elmer Spectrum 1000 FT-IR Systems and are reported in terms of frequency of absorption ($cm^{-1}$). Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 $F_{254}$ precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$, ceric ammonium molybdate (CAM), or *p*-anisaldehyde (PAA) solutions. Flash chromatography was performed using Silica Gel 60 (170-400 mesh) from Fisher Scientific. Melting points (m.p.) were obtained using a Mel-Temp melting point apparatus and are uncorrected. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Automatic Polarimeter. SFC determinations of enantiopurity were performed on a Berger Analytical instrument using a Daicel™ Chiralpak® column (OD-H, OJ-H, or AD-H; 100 bar, 50 °C, 215 nm). High resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center.

[1,2-Bis(diphenylphosphino)ethane]dichloronickel(II) was purchased from Strem, stored in a glovebox under an atmosphere of $N_2$, and used as received. Diethylzinc ($ZnEt_2$) and diethyl chlorophosphate were purchased from Sigma and used as received. 1-Isoquinolinecarboxaldehyde was prepared from selenium (IV) oxide oxidation of 1-methylisoquinoline by a procedure reported by Long.[13] All other reagents were purchased commercially and used as received.

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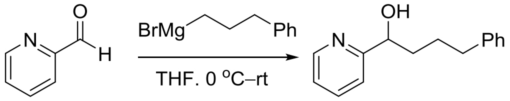
[13] Cao, B.; Wang, Y.; Ding, K.; Neamati, N.; Long, Y-Q. *Org. Biomol. Chem.* **2012**, *10*, 1239.

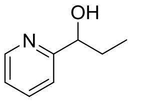
## SYNTHESIS AND CHARACTERIZATION OF ALL STARTING MATERIALS

## Synthesis of Benzylic Alcohols

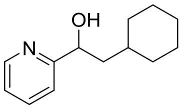
### ***General Procedure A.*** *Grignard addition to aldehydes.*



**4.1**. In a flame-dried round-bottom flask a solution of 2-pyridinecarboxaldehyde (1.43 mL, 15.0 mmol, 1.00 equiv) in THF (30 mL) was cooled to 0 °C and (3-Phenylpropyl)magnesium bromide (1.6 M in THF, 10 mL, 16 mmol, 1.1 equiv) was added over 15 minutes. After stirring at room temperature for 1 h the reaction as cooled to 0 °C, and saturated ammonium chloride (25 mL) was added. The reaction was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (1 x 40 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The product was purified by column flash chromatography (25–40% EtOAc/hexanes) to afford the title compound as a yellow solid (1.70 g, 7.50 mmol, 50%). **TLC R$_f$** = 0.16 (20% EtOAc/hexanes, UV active); **m.p.** = 58–60 °C; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.8 Hz, 1H), 7.66 (td, *J* = 7.8, 1.8 Hz, 1H), 7.29–7.23 (m, 2H), 7.22–7.13 (m, 5H), 4.75 (s, 1H), 4.19 (s, 1H), 2.71–2.59 (m, 2H), 1.91–1.82 (m, 1H), 1.80–1.67 (m, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 161.9, 148.2, 142.4, 136.7, 128.5, 128.3, 125.8, 122.3, 120.4, 72.5, 38.2, 35.8, 26.9; **IR** (neat) 3192, 2925, 2861, 1594, 1492, 1452 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{15}H_{17}NONa$ $(M + Na)^+$ 227.1310, found 227.1315.



**4.15**. Prepared according to a procedure reported by Braga[14], the following amounts of reagents were used: 2-pyridinecarboxaldehyde (0.38 mL, 4.00 mmol, 1.00 equiv), ethylmagnesium bromide (2.4 M in $Et_2O$, 2.0 mL, 4.8 mmol, 1.2 equiv), and THF (15 mL). Analytical data is consistent with literature values.[15] **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.55 (dt, *J* = 4.9, 1.3 Hz, 1H), 7.68 (td, *J* = 7.6, 1.8 Hz, 1H), 7.25 (dd, *J* = 7.8 Hz, 0.5 Hz, 1H), 7.20 (ddd, *J* = 7.6, 4.9, 0.5 Hz, 1H), 4.73–4.66 (m, 1H), 4.17 (d, *J* = 5.5 Hz, 1H), 1.95–1.84 (m, 1H), 1.78–1.66 (m, 1H), 0.95 (t, *J* = 7.3 Hz, 3H).



**4.16**. Using representative procedure A outlined above, the following amounts of reagents were used: 2-pyridinecarboxaldehyde (0.48 mL, 5.0 mmol, 1.0 equiv), (cyclohexylmethyl)magnesium bromide (0.56 M in THF, 9.8 mL, 11 mmol, 1.1 equiv), and THF (10 mL). The product was purified by column flash chromatography (20% EtOAc/hexanes) to afford the title compound as a yellow solid (0.453 g, 2.20 mmol, 44%). **TLC $R_f$** = 0.3 (20% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.7 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 6.0 Hz, 1H), 4.82 (t, *J* = 6.3, 1H), 4.28 (br s, 1H), 1.94 (d, *J* = 12.7 Hz, 1H), 1.75–1.54 (m, 7H) 1.32–1.11 (m, 3H), 1.02–0.90 (m, 2H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 163.4, 148.3, 136.7, 122.2, 120.4, 70.7, 46.9, 34.4, 34.2, 32.7, 26.7, 26.5, 26.2; **IR** (neat) 3217, 2919,

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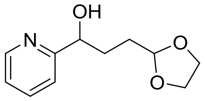
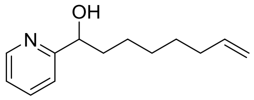
[14] Braga, A. L.; Paixao, M. W.; Ludtke, D. S.; Silveira, C. C.; Rodrigues, O. E. D. *Org. Lett.* **2003**, *5*, 2365.

1594 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{13}H_{19}NONa$ (M + Na)$^+$ 228.1364, found 228.1364.



**4.3**. Using representative procedure A outlined above, the following amounts of reagents were used: 2-pyridinecarboxaldehyde (0.95 mL, 10 mmol, 1.0 equiv), hept-6-en-1-ylmagnesium bromide (1.2 M in THF, 9.2 mL, 11 mmol, 1.1 equiv), and THF (10 mL). The product was purified by column flash chromatography (25–40% EtOAc/hexanes) to afford the title compound as a yellow oil (1.31 g, 6.38 mmol, 64%). Analytical data is consistent with literature values.[16] **TLC R$_f$** = 0.1 (50% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.55–8.50 (m, 1H), 7.67 (td, *J* = 7.8, 1.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.21–7.15 (m, 1H), 4.93–4.88 (m, 1H), 4.83–4.75 (m, 1H), 4.33 (d, *J* = 5.4 Hz, 1H), 3.99–3.80 (m, 4H), 2.07–1.95 (m, 1H), 1.87–1.74 (m, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 161.9, 148.3, 136.7, 122.3, 120.4, 104.4, 72.38, 64.9, 32.5, 29.5.



**4.17**. Using representative procedure A outlined above, the following amounts of reagents were used: 2-pyridinecarboxaldehyde (0.95 mL, 10 mmol, 1.0 equiv), hept-6-en-1-ylmagnesium bromide (1.2 M in THF, 9.2 mL, 11 mmol, 1.1 equiv), and THF (10 mL). The product was purified

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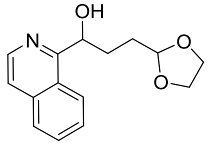
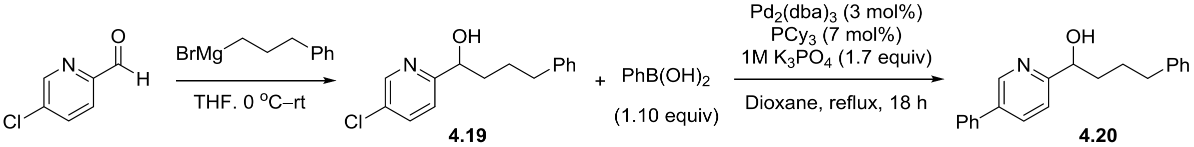
[15] Moody, C. J.; Morfitt, C. N. *Synthesis* **1998**, *7*, 1039.
[16] Gebert, A.; Barth, M.; Linden, A.; Widmer, U.; Heimgartner, H. *Helv. Chim. Acta* **2012**, *95*, 737.

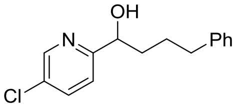
by column flash chromatography (25–40% EtOAc/hexanes) to afford the title compound as a red oil (1.31 g, 6.38 mmol, 64%). **TLC R$_f$** = 0.4 (40% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, CDCl$_3$) δ 8.53 (d, *J* = 4.7 Hz 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 5.5 Hz, 1H), 5.79 (ddt, *J* = 17.2, 10.2, 6.9 Hz, 1H), 4.98 (d, *J* = 17.2 Hz, 1H), 4.92 (d, *J* = 10.2 Hz, 1H), 4.73 (dd, *J* = 7.7, 4.4 Hz, 1H), 4.25 (br s, 1H), 2.03 (dd, *J* = 10.2, 6.9 Hz, 2H), 1.87–1.77 (m, 1H) 1.74–1.65 (m, 1H), 1.50–1.24 (m, 6H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 162.4, 148.3, 139.2, 136.7, 122.3, 120.4, 114.3, 72.9, 38.7, 33.8, 29.2, 28.9, 25.2; **IR** (neat) 3260, 2926, 1594 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{13}H_{19}ONNa$ $(M + Na)^+$ 228.1364, found 228.1364.



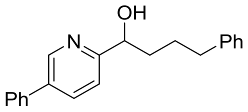
**4.18**. Using representative procedure A outlined above, the following amounts of reagents were used: 1-Isoquinolinecarboxaldehyde (0.47 g, 3.0 mmol, 1.0 equiv), (2-(1,3-dioxolan-2-yl)ethyl)magnesium bromide (0.95 M in THF, 3.5 mL, 3.3 mmol, 1.1 equiv), and THF (10 mL). The product was purified by column flash chromatography (40% EtOAc/hexanes) to afford the title compound as a tan solid (249 mg, 0.960 mmol, 32%). **TLC R$_f$** = 0.2 (40% EtOAc/hexanes, UV active); **m.p.** = 53–55 ºC; **$^1$H NMR** (500 MHz, CDCl$_3$) δ 8.43 (d, *J* = 5.8 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 5.8 Hz, 1H), 5.52 (d, *J* = 7.1 Hz, 1H), 5.18 (br s, 1H), 4.93 (t, *J* = 4.8 Hz, 1H), 4.00–3.89 (m, 2H), 3.87–3.78 (m, 2H) 2.12–2.02 (m, 1H), 2.06–1.97 (m, 1H), 1.90–1.81 (m, 1H), 1.80–1.72 (m, 1H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 161.1, 140.4, 136.5, 130.3, 126.6, 126.5, 124.9, 124.4, 120.6, 104.5, 69.2, 65.0, 64.9, 33.3, 29.6; **IR** (neat) 3390, 2957, 2882 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{15}H_{17}O_3NNa$ (M + Na)$^+$ 282.1106, found 282.1104.

## Synthesis of Alcohol 4.23 (Scheme 4.3)





**4.19**. Using representative procedure A outlined above, the following amounts of reagents were used: 5-chloro-2-formylpyridine (0.85 g, 6.0 mmol, 1.0 equiv), (3-phenylpropyl)magnesium bromide (1.6 M in THF, 4.1 mL, 6.6 mmol, 1.1 equiv), and THF (20 mL). The product was purified by column flash chromatography (20% EtOAc/hexanes) to afford the title compound as a red oil (0.88 g, 3.4 mmol, 56%). **TLC R$_f$** = 0.3 (20% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.47 (d, *J* = 1.7 Hz, 1H), 7.62 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.21–7.12 (m, 4H), 4.76–4.71 (m, 1H), 3.80 (br s, 1H), 2.72–2.58 (m, 2H), 1.87–1.78 (m, 1H), 1.77–1.68 (m, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 160.6, 147.3, 142.2, 136.6, 130.6, 128.5, 128.4, 125.9, 121.2, 72.7, 38.0, 35.8, 27.0; **IR** (neat) 3359, 2936, 2859 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{15}H_{16}ClNONa$ (M + Na)$^+$ 284.0818, found 284.0810.



**4.20**. The product was prepared according to a modified procedure by Fu.[17] Tris(dibenzylideneacetone)dipalladium (69 mg, 0.076 mmol, 0.030 equiv) and tricyclohexylphosphine (50 mg, 0.18 mmol, 0.070 equiv) were weighed out into a flame round bottom flask inside a glovebox. The flask was fitted with septa, removed from the glovebox, and phenylboronic acid (0.337 g, 2.77 mmol, 1.10 equiv), **4.19** (0.66 g, 2.5 mmol, 1.0 equiv), aqueous potassium phosphate (1.3 M in $H_2O$, 3.3 mL, 4.3 mmol, 1.7 equiv) and dioxane (13 mL) were added. The reaction flask was fitted with a reflux condenser and heated to 95 $^oC$ for 18 h. After cooling, the solvent was removed under reduced pressure. The resultant residue was purified by flash column chromatography (30% EtOAc/hexane) to afford the title compound as a pale yellow solid (0.488 g, 1.60 mmol, 64%). **TLC R$_f$** = 0.4 (40% EtOAc/hexanes, UV active); **m.p.** = 99–101 $^oC$; **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.75 (d, *J* = 2.0 Hz, 1H), 7.85 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.48 (t, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.31–7.23 (m, 3H), 7.21–7.14 (m, 3H), 7.85 (m, 1H), 4.15 (d, *J* = 5.1 Hz, 1H), 2.73–2.61 (m, 2H), 1.96–1.86 (m, 1H), 1.84–1.73 (m, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 161.0, 146.7, 142.4, 137.7, 135.5, 135.3, 129.2, 128.6, 128.4, 128.2, 127.2, 125.8, 120.3, 72.6, 38.2, 35.9, 27.1; **IR** (neat) 3286, 2946, 2914 $cm^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{21}H_{21}NONa$ $(M + Na)^+$ 326.1521, found 326.1516.

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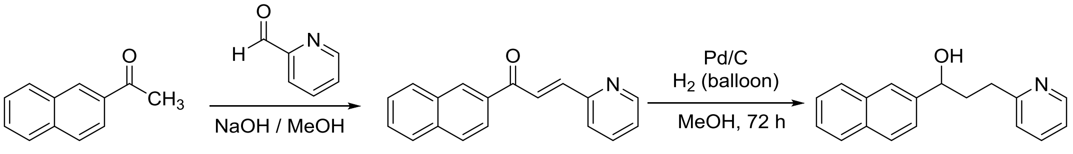
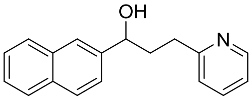
[17] Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1282.

## Synthesis of Substrate 4.11 (eq 4.2)



**4.11**



**4.11**. The product was prepared according to a modified procedures by Attar[18] and Hirota.[19] To a 100 mL round bottomed flask equipped with a stir bar was added 2-acetonaphthone (6.81 g, 40.0 mmol, 1.00 equiv), MeOH (10 mL) and 10% NaOH (20 mL). The mixture was stirred for 15 min at room temperature before addition of 2-pyridinecarboxaldehyde (6.85 mL, 72.0 mmol, 1.80 equiv). The reaction was stirred until complete by TLC analysis (2 h). Ice water was added to the reaction and the solid was filtered, washed with $Et_2O$ and dried in vacuo. The crude solid was then redissolved in MeOH (40 mL) and transferred to a round bottom flask containing stir bar and 10% Pd/C (0.68 g, 10% by weight relative to 2-acetonaphthone). The flask was flushed with nitrogen and then equipped with a balloon of hydrogen gas. The reaction was stirred under an atmosphere of hydrogen for 72 h. The reaction mixture was then filtered through a celite cake and the filtrate was poured into sat. aqueous $NaHCO_3$ (60 mL) and extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried with $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (10–30%

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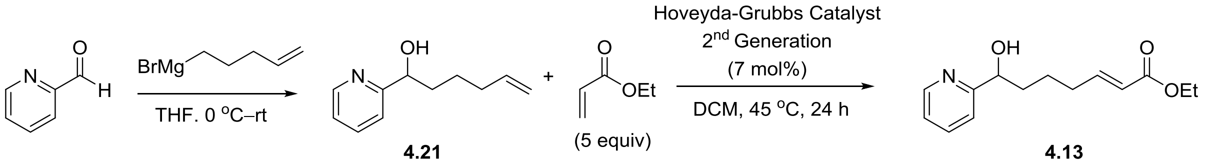
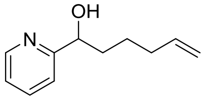
[18] Attar, S.; O'Brien, Z.; Alhaddad, H.; Golden, M. L.; Calderon-Urrea, A. *Bioorg. Med. Chem.* **2011**, *19*, 2055.
[19] Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2001**, *57*, 4817.

EtOAc/hexanes) to afford the title compound as a white solid (1.63 g, 6.20 mmol, 16%). **TLC R$_f$** = 0.2 (20% EtOAc/hexanes, UV active); **m.p.** = 76–77 °C; **$^1$H NMR** (500 MHz, CDCl$_3$) δ 8.46 (d, *J* = 4.8 Hz, 1H), 7.84 (s, 1H), 7.55 (td, *J* = 7.5, 1.3 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.46–7.39 (m, 2H), 7.13–7.05 (m, 2H), 5.98 (br s, 1H), 4.96 (dd, *J* = 7.8, 4.5 Hz, 1H), 2.97 (t, *J* = 6.6 Hz, 2H), 2.31–2.17 (m, 2H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 161.4, 148.6, 142.9, 136.9, 133.4, 132.8, 128.0, 127.7, 126.0, 125.5, 124.2, 123.3, 121.3, 73.7, 38.0, 34.5; **IR** (neat) 3250, 3054, 2919 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{18}H_{17}ONNa$ $(M + Na)^+$ 286.1208, found 286.1199.

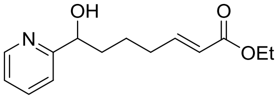
## Synthesis of Substrate 4.13 (Scheme 4.3)





**4.21**. Using representative procedure A outlined above, the following amounts of reagents were used: 2-pyridinecarboxaldehyde (0.95 mL, 10 mmol, 1.0 equiv), pent-4-en-1-ylmagnesium bromide (1.1 M in THF, 10 mL, 11 mmol, 1.1 equiv), and THF (15 mL). The product was purified by column flash chromatography (20–40% EtOAc/hexanes) to afford the title compound as a yellow oil (0.784 g, 4.40 mmol, 44%). **TLC R$_f$** = 0.4 (40% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, CDCl$_3$) δ 8.53 (d, *J* = 4.5 Hz, 1H), 7.68 (td, *J* = 7.6, 1.5 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.19 (dd, *J* = 6.9, 5.1 Hz, 1H), 5.79 (ddt, *J* = 17.1, 10.3, 6.7 Hz, 1H), 4.99 (dd, *J* = 17.1, 1.6

Hz, 1H), 4.94 (d, *J* = 10.3 Hz, 1H), 4.80–4.78 (m, 1H), 4.25 (s, 1H), 2.16–2.02 (m, 2H), 1.89–1.78 (m, 1H), 1.74–1.62 (m, 1H), 1.58–1.47 (m, 2H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 162.3, 148.3, 138.8, 136.8, 122.4, 120.4, 114.7, 72.7, 38.1, 33.8, 24.6; **IR** (neat) 3260, 2936, 1594 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{11}H_{15}ONNa$ $(M + Na)^+$ 200.1051, found 200.1056.



**4.13**. The title compound was prepared according to a modified procedure reported by Grubbs.[20] In a glovebox, a flame-dried bomb flask was charged with a stir bar, **4.27** (0.71 g, 4.0 mmol, 1.0 equiv), and Hoveyda-Grubbs Catalyst 2nd Generation (178 mg, 0.280 mmol, 0.0700 equiv). The flask was removed from the glovebox, and anhydrous $CH_2Cl_2$ (50 mL) and ethyl acrylate (2.2 mL, 20 mmol, 5.0 equiv) were added. The flask was sealed and heated to reflux over 24 h. The flask was then cooled to ambient temperature, and the solvent was removed in vacuo. The residue was purified by flash column chromatography to afford the title compound as a pale yellow oil (125 mg, 0.501 mmol, 13%, 13:1 E:Z). **TLC R$_f$** = 0.1 (40% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.4 Hz, 1H), 7.68 (td, *J* = 7.6, 1.5 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.20 (dd, *J* = 6.9, 5. Hz, 1H), 6.93 (dt, *J* = 15.5, 7.1 Hz, 1H), 5.80 (dt, *J* = 15.5, 1.5 Hz, 1H), 4.75 (dd, *J* = 7.2, 4.3 Hz, 1H), 4.33 (br s, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.28–2.18 (m, 2H), 1.90–1.81 (m, 1H), 1.75–1.66 (m, 1H), 1.64–1.55 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 166.8, 162.0, 148.9, 148.3, 136.8, 122.4, 121.7, 120.4, 72.5, 60.2,

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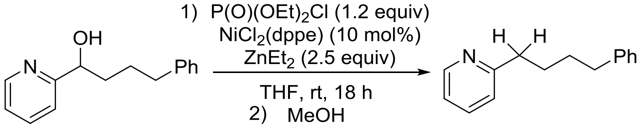
[20] Chatterjee, A. K; Choi, T–L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

38.0, 32.1, 23.7, 14.3; **IR** (neat) 2938, 1730 $cm^{-1}$; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{14}H_{19}NO_3Na$ $(M + Na)^+$ 272.1263, found 272.1271.

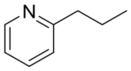
## NICKEL CATALYZED FORMATION OF ALKYL ZINC REAGENTS AND DEOXYGENATION OF BENZYLIC CARBINOLS

### Synthesis of Products for Scheme 4.3 (4.5–4.13)

***General Procedure B.*** *Deoxygenation of benzylic carbinols*



**4.2**. In a glovebox, a flame-dried 7 mL vial equipped with a stir bar was charged with $NiCl_2$(dppe) (11 mg, 0.020 mmol, 0.10 equiv), alcohol **4.1** (45 mg, 0.20 mmol, 1.0 equiv) and diethyl chlorophosphate (35 μl, 0.24 mmol, 1.2 equiv) and suspended in THF (1.6 mL). The reaction vial was capped with a screw-cap, fitted with a septum and removed from the glove box. The reaction was placed under $N_2$, and stirred at which point diethyl zinc (1 M in PhMe, 0.5 mL, 0.5 mmol, 2.5 equiv) was added at room temperature resulting in an immediate color change from slightly orange to transparent yellow. The reaction was then sealed with parafilm and allowed to stir for 18 hours at 24 °C after which the reaction typically is dark brown or black. The reaction was quenched with MeOH and filtered through a plug of silica gel (100% EtOAc). The solvent was removed under reduced vacuum and the crude purified by flash column chromatography (12% EtOAc, 1% triethyl amine in hexanes) to afford the title compound as a pale yellow oil (29 mg, 0.13 mmol, 69%). **TLC $R_f$** = 0.3 (20% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.52 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.56 (td, *J* = 2.0, 7.7 Hz, 1H), 7.29–7.23 (m, 2H), 7.19–7.14 (m, 3H), 7.13–7.06 (m, 2H), 2.81 (t, *J* = 7.3 Hz, 2H), 2.65 (t, *J* = 7.7 Hz, 2H), 1.83–1.74 (m, 2H) 1.74–1.64 (m, 2H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 162.2, 149.3, 142.6, 136.3, 128.5, 128.3, 125.7, 122.7, 120.9, 38.3, 35.8, 31.3, 29.6; **IR** (neat) 3025, 2926, 2855, 2359, 2341, 1598 $cm^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{16}H_{18}ONH_4$ $(M + NH_4)^+$ 211.1361, found 211.1351.



**4.5**. Using representative procedure B outlined above, the following amounts of reagents were used: $NiCl_2$(dppe) (11 mg, 0.020 mmol, 0.10 equiv), alcohol **4.18** (28 mg, 0.20 mmol, 1.0 equiv), diethyl chlorophosphate (35 µl, 0.24 mmol, 1.2 equiv), THF (1.6 ML) and diethyl zinc (1.0 M in PhMe, 0.50 mL, 0.50 mmol, 2.5 equiv). The product was purified by flash column chromatography (15% EtOAc/hexanes) to afford the title compound as a pale yellow oil (16 mg, 0.13 mmol, 67%). Analytical data is consistent with literature values.[21] **TLC $R_f$** = 0.3 (20% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.4 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.09 (t, *J* = 6.5 Hz, 1H), 2.77 (t, *J* = 7.8 Hz, 2H), 1.76 (sex, *J* = 7.7 Hz, 2H), 0.97 (t, *J* = 7.7 Hz, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 162.4, 149.3, 136.3, 122.9, 121.0, 40.5, 23.2, 14.0.

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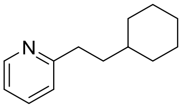
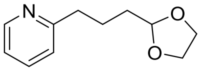
[21] Groenhagen, U.; Maczka, M.; Dickschat, J. S.; Schulz, S. *Beilstein J. Org. Chem.* **2014**, *10*, 1421.

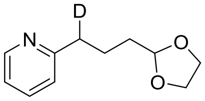


**4.6**. Using representative procedure B outlined above, the following amounts of reagents were used: $NiCl_2$(dppe) (11 mg, 0.020 mmol, 0.10 equiv), alcohol **4.19** (41 mg, 0.20 mmol, 1.0 equiv), diethyl chlorophosphate (35 μl, 0.24 mmol, 1.2 equiv), THF (1.6 ML) and diethyl zinc (1.0 M in PhMe, 0.50 mL, 0.50 mmol, 2.5 equiv). The product was purified by flash column chromatography (15% EtOAc/hexanes) to afford the title compound as a pale yellow oil (27 mg, 0.14 mmol, 70%). **TLC $R_f$** = 0.2 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.5 Hz, 1H), 7.57 (td, *J* = 7.7, 1.7 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.08 (dd, *J* = 7.7, 5.2 Hz, 1H), 2.83–2.76 (m, 2H), 1.78 (ad, *J* = 13.3 Hz, 2H), 1.74–1.67 (m, 2H), 1.67–1.58 (m, 3H), 1.34–1.10 (m, 4H), 1.00–0.90 (m, 2H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 163.0, 149.3, 136.4, 122.8, 120.9, 37.8, 37.7, 36.0, 33.4, 26.8, 26.5; **IR** (neat) 2920, 1589 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{13}H_{19}NH$ $(M + H)^+$ 190.1596, found 190.1594.



**4.7**. Using representative procedure B outlined above, the following amounts of reagents were used: $NiCl_2$(dppe) (11 mg, 0.020 mmol, 0.10 equiv), alcohol **4.3** (42 mg, 0.20 mmol, 1.0 equiv), diethyl chlorophosphate (35 μl, 0.24 mmol, 1.2 equiv), THF (1.6 ML) and diethyl zinc (1.0 M in PhMe, 0.50 mL, 0.50 mmol, 2.5 equiv). The product was purified by flash column chromatography (12% EtOAc/hexanes) to afford the title compound as a pale yellow oil (31 mg, 0.15

mmol, 74 %). Analytical data are consistent with literature values.[22] **TLC R$_f$** = 0.1 (20% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, CDCl$_3$) δ 8.52 (d, *J* = 4.9 Hz, 1H), 7.57 (td, *J* = 7.6, 1.6 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.10 (dd, *J* = 7.6, 5.3 Hz, 1H), 4.89 (t, *J* = 6 Hz, 1H), 4.00–3.79 (m, 4H), 2.84 (t, *J* = 7.7 Hz, 2H), 1.92–1.82 (m, 2H), 1.76–1.68 (m, 2H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 161.8, 149.3, 136.3, 122.8, 121.1, 104.5, 64.9, 38.1, 33.4, 24.2.



**4.4.** Using representative procedure B outlined above, the following amounts of reagents were used: NiCl$_2$(dppe) (11 mg, 0.020 mmol, 0.10 equiv), alcohol **4.3** (42 mg, 0.20 mmol, 1.0 equiv), diethyl chlorophosphate (35 μl, 0.24 mmol, 1.2 equiv), THF (1.6 ML) and diethyl zinc (1.0 M in PhMe, 0.50 mL, 0.50 mmol, 2.5 equiv). The reaction was quenched with CD$_3$OD from a sealed ampoule (1 mL) and the product was purified by flash column chromatography (12 % EtOAc, 1% triethyl amine, in hexane) to afford the title compound as a pale yellow oil (30 mg, 0.15 mmol, 78%). **TLC R$_f$** = 0.1 (20% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, CDCl$_3$) δ 8.52 (d, *J* = 4.6 Hz, 1H), 7.58 (td, *J* = 7.7, 1.9 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 7.11–7.08 (m, 1H), 4.89 (t, *J* = 4.7 Hz, 1H), 4.01–3.79 (m, 4H), 2.87–2.79 (m, 1H), 1.91–183 (m, 2H), 1.76–1.68 (m, 2H); **$^2$H NMR** (500 MHz, CHCl$_3$) 3.10 (s, 1D) **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 161.8, 149.3, 136.3, 122.8, 121.1, 104.5, 64.9, 38.1, 33.4, 24.2; **IR** (neat) 2922, 2874, 1591, 1567,

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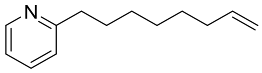
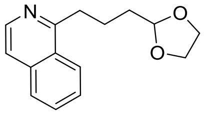
[22] Kitbunnadaj, R.; Zuiderveld, O.P.; Christophe, B.; Hulscher, S.; Menge, W.M.P.B.; Gelens, E.; Snip, E.; Bakker, R.A.; Celanire, S.; Gillard, M.; Talaga, P.; Timmerman, H.; Leurs, R. *J. Med. Chem*. **2004**, *47*, 2414.

1473, 1410 cm$^{-1}$; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_{16}H_{18}ONH_4$ (M + NH$_4$)$^+$ 195.1244, found 195.1251.

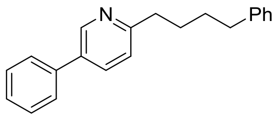


**4.8**. Using representative procedure B outlined above, the following amounts of reagents were used: NiCl$_2$(dppe) (11 mg, 0.020 mmol, 0.10 equiv), alcohol **4.20** (41 mg, 0.20 mmol, 1.0 equiv), diethyl chlorophosphate (35 µl, 0.24 mmol, 1.2 equiv), THF (1.6 ML) and diethyl zinc (1.0 M in PhMe, 0.50 mL, 0.50 mmol, 2.5 equiv). The product was purified by flash column chromatography (15% EtOAc/hexanes) to afford the title compound as a pale yellow oil (29 mg, 0.15 mmol, 77%). **TLC R$_f$** = 0.2 (20% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, CDCl$_3$) δ 8.52 (d, *J* = 4.5 Hz, 1H), 7.58 (td, *J* = 7.6, 1.5 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.09 (dd, *J* = 7.3, 5.5 Hz, 1H), 5.80 (ddt, *J* = 17.1, 10.4, 3.3 Hz, 1H), 4.98 (dd, *J* = 17.1, 1.1 Hz, 1H), 4.92 (d, *J* = 10.4 Hz, 1H), 2.78 (t, *J* = 7.8 Hz, 2H), 2.03 (dd, *J* = 13.5, 6.5 Hz, 2H), 1.72 (quint, *J* = 7.6 Hz, 2H), 1.44–1.30 (m, 6H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 162.2, 149.3, 139.3, 136.3, 122.8, 121.0, 114.3, 38.6, 33.9, 30.0, 29.6, 29.1, 28.9; **IR** (neat) 3075, 2925, 1589 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{13}H_{19}NNa$ (M + Na)$^+$ 212.1415, found 212.1406.



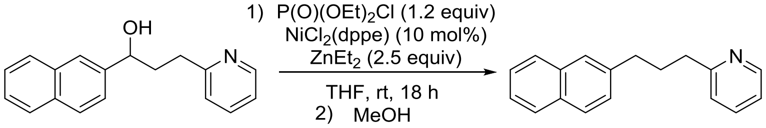
**4.9**. Using representative procedure B outlined above, the following amounts of reagents were used: NiCl$_2$(dppe) (11 mg, 0.020 mmol, 0.10 equiv), alcohol **4.21** (52 mg, 0.20 mmol, 1.0 equiv), diethyl chlorophosphate (35 µl, 0.24 mmol, 1.2 equiv), THF (1.6 ML) and diethyl zinc (1.0 M in PhMe, 0.50 mL, 0.50 mmol, 2.5 equiv). The product was purified by flash column chromatography (30–50% EtOAc/hexanes) to afford the title compound as a pale yellow oil (24 mg, 0.099

mmol, 49%). **TLC R$_f$** = 0.2 (40% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, CDCl$_3$) δ 8.43 (d, *J* = 5.6 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 5.6 Hz, 1H), 4.93 (t, *J* = 4.7 Hz, 1H), 4.00–3.92 (m, 2H), 3.89–3.81 (m, 2H), 3.36 (t, *J* = 8.0 Hz, 2H), 2.07–1.98 (m, 2H) 1.88–1.81 (m, 2H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 161.9, 142.1, 136.4, 129.9, 127.5, 127.14, 127.05, 125.4, 119.4, 104.5, 65.0, 35.2, 33.8, 24.1; **IR** (neat) 3050, 2877, 1562 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{15}H_{17}O_2NNa$ (M + Na)$^+$ 266.1157, found 266.1160.



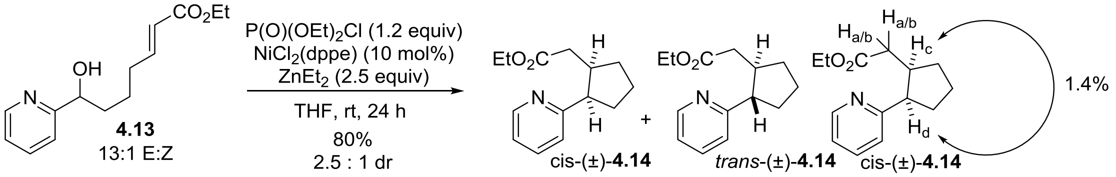
**4.10**. Using representative procedure B outlined above, the following amounts of reagents were used: NiCl$_2$(dppe) (11 mg, 0.020 mmol, 0.10 equiv), alcohol **4.23** (61 mg, 0.20 mmol, 1.0 equiv), diethyl chlorophosphate (35 μl, 0.24 mmol, 1.2 equiv), THF (1.6 ML) and diethyl zinc (1.0 M in PhMe, 0.50 mL, 0.50 mmol, 2.5 equiv). The product was purified by flash column chromatography (30–50% EtOAc/hexanes) to afford the title compound as a white solid (48 mg, 0.17 mmol, 83%). **TLC R$_f$** = 0.2 (10% EtOAc/hexanes, UV active); **m.p.** = 60 °C; **$^1$H NMR** (500 MHz, CDCl$_3$) δ 8.75 (s, 1H), 7.76 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 4H), 2.86 (t, *J* = 8.2 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.82 (quint, *J* = 7.6 Hz, 2H), 1.72 (quint, *J* = 7.5 Hz, 2H); **$^{13}$C NMR** (125 MHz, CDCl$_3$) δ 161.1, 147.7, 142.6, 138.0, 134.8, 134.0, 129.1, 128.5, 128.4, 127.9, 127.1, 125.8, 122.7, 38.0, 35.9, 31.3, 29.6; **IR** (neat) 3056, 2854 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{21}H_{21}NH$ (M + H)$^+$ 288.1752, found 288.1758.

## Deoxygenation of 4.14 (eq 4.2)

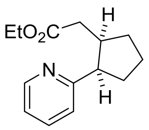


**4.12**. Using representative procedure B outlined above, the following amounts of reagents were used: $NiCl_2$(dppe) (11 mg, 0.020 mmol, 0.10 equiv), alcohol **4.11** (55 mg, 0.20 mmol, 1.0 equiv), diethyl chlorophosphate (35 µl, 0.24 mmol, 1.2 equiv), THF (1.6 ML) and diethyl zinc (1.0 M in PhMe, 0.50 mL, 0.50 mmol, 2.5 equiv). The product was purified by flash column chromatography (20% EtOAc/hexanes) to afford the title compound as a pale yellow oil (40 mg, 0.16 mmol, 81%). **TLC $R_f$** = 0.2 (20% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.4 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 2H), 7.62 (s, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.47–7.38 (m, 2H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.09 (at, *J* = 6.4 Hz, 1H), 2.90–2.81 (m, 4H), 2.16 (quint, *J* = 7.0 Hz, 2H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 162.0, 149.4, 139.8, 136.3, 133.7, 132.1, 128.0, 127.7, 127.53, 127.48, 126.6, 126.0, 125.2, 122.9, 121.1, 38.0, 35.8, 31.4; **IR** (neat) 3051, 2856, 1590 $cm^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{18}H_{17}NNa$ $(M + Na)^+$ 270.1259, found 270.1260.

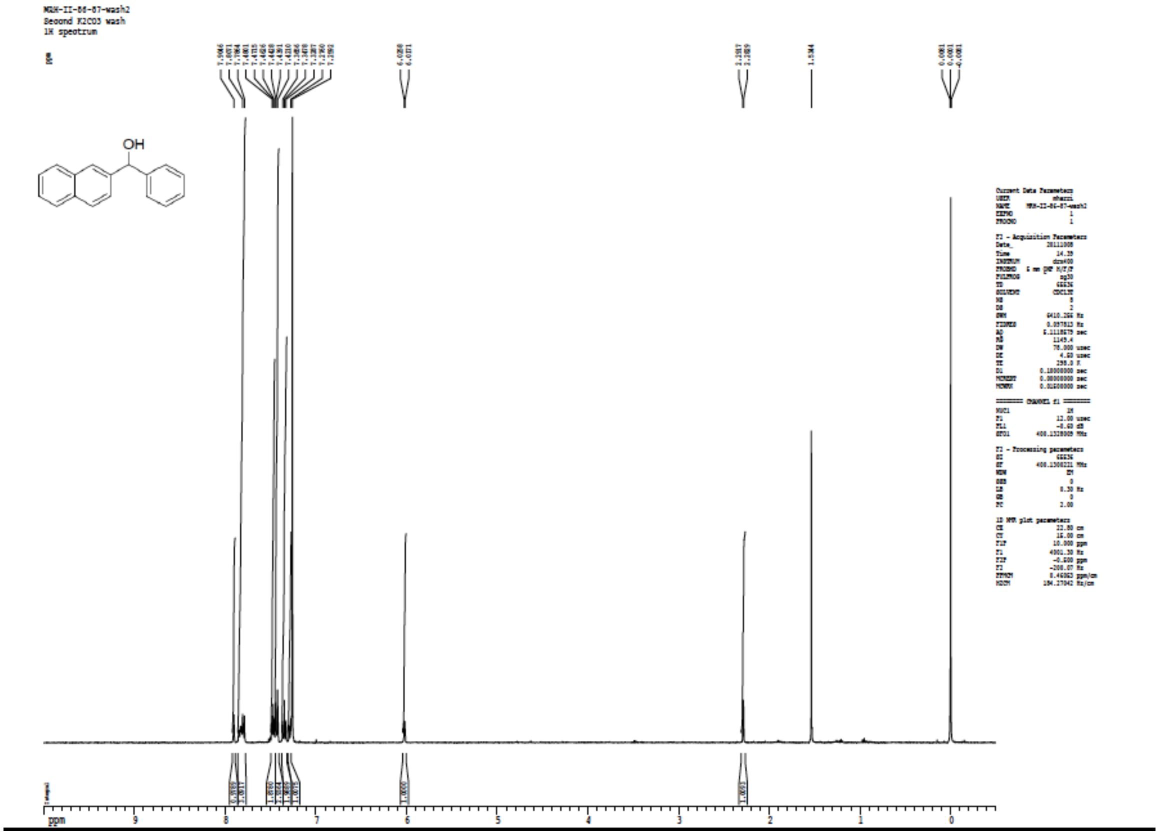
### Intramolecular 1,4-Addition (Scheme 4.3)

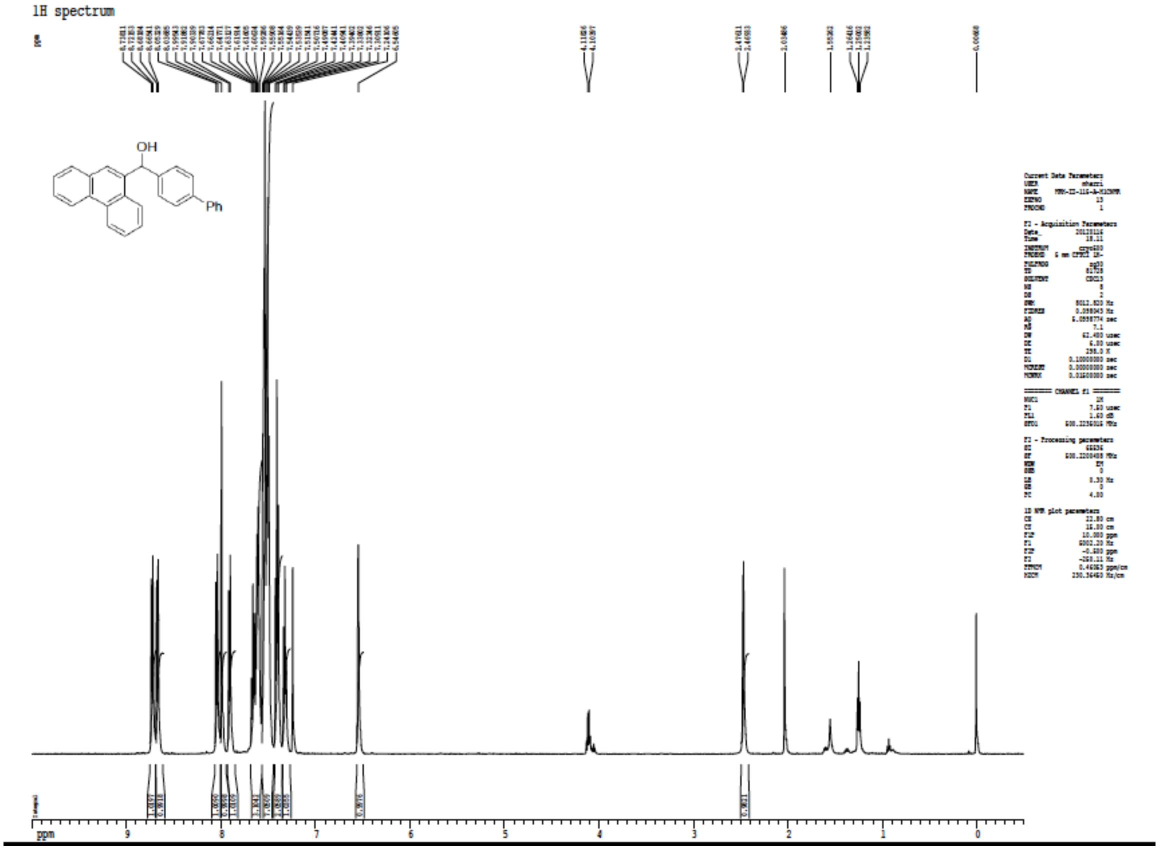


**4.14**. Using representative procedure B outlined above, the following amounts of reagents were used: $NiCl_2$(dppe) (11 mg, 0.020 mmol, 0.10 equiv), alcohol **4.13** (50 mg, 0.20 mmol, 1.0 equiv), diethyl chlorophosphate (35 µl, 0.24 mmol, 1.2 equiv), THF (1.6 ML) and diethyl zinc (1.0 M in PhMe, 0.50 mL, 0.50 mmol, 2.5 equiv). The product was purified by flash column chromatography (20% EtOAc/hexanes) to afford the title compound as a mixture 2.5:1 mixture of diastereomers (37 mg, 0.16 mmol, 80%). $H_c$ was integrated to determine the ratio of diastereomers. Flash column chromatography (5–10% EtOAc/hexanes) was performed a second time to isolate analytically pure cis diastereomer (19 mg, 0.081 mmol, 40%) and a 1:1 mixture of diastereomers (16 mg, 0.07 mmol, 34%). The cis diastereomer was assigned based on the nOe correlation shown.

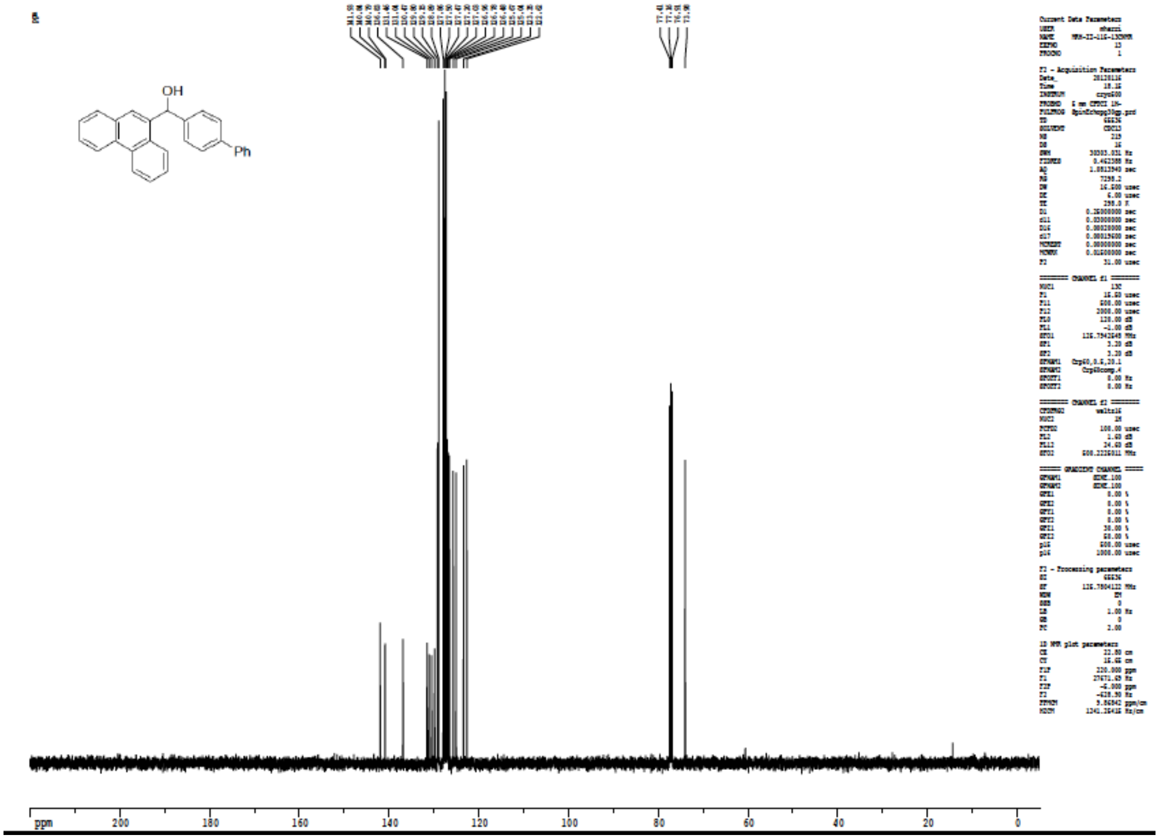


**TLC $R_f$** = 0.1 (10% EtOAc/hexanes, UV active); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.7 Hz, 1H), 7.56 (td, *J* = 7.7, 2.0 Hz, 1H), 7.12–7.07 (m, 2H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.43 (q, *J* = 8.0 Hz, 1H), 2.79–2.71 (m, 1H), 2.14–2.04 (m, 2H), 2.02–1.90 (m, 4H), 1.75–1.67 (m, 1H), 1.63–1.54 (m, 1H), 1.17 (t, *J* = 7.2 Hz, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 173.6, 163.2, 149.2, 136.0, 123.5, 121.2, 60.2, 49.8, 40.8, 36.2, 31.9, 30.2, 24.2, 14.3; **IR** (neat) 2935, 1716 cm$^{-1}$; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{14}H_{19}NO_2Na$ (M + Na)$^+$ 256.1313, found 256.1316.

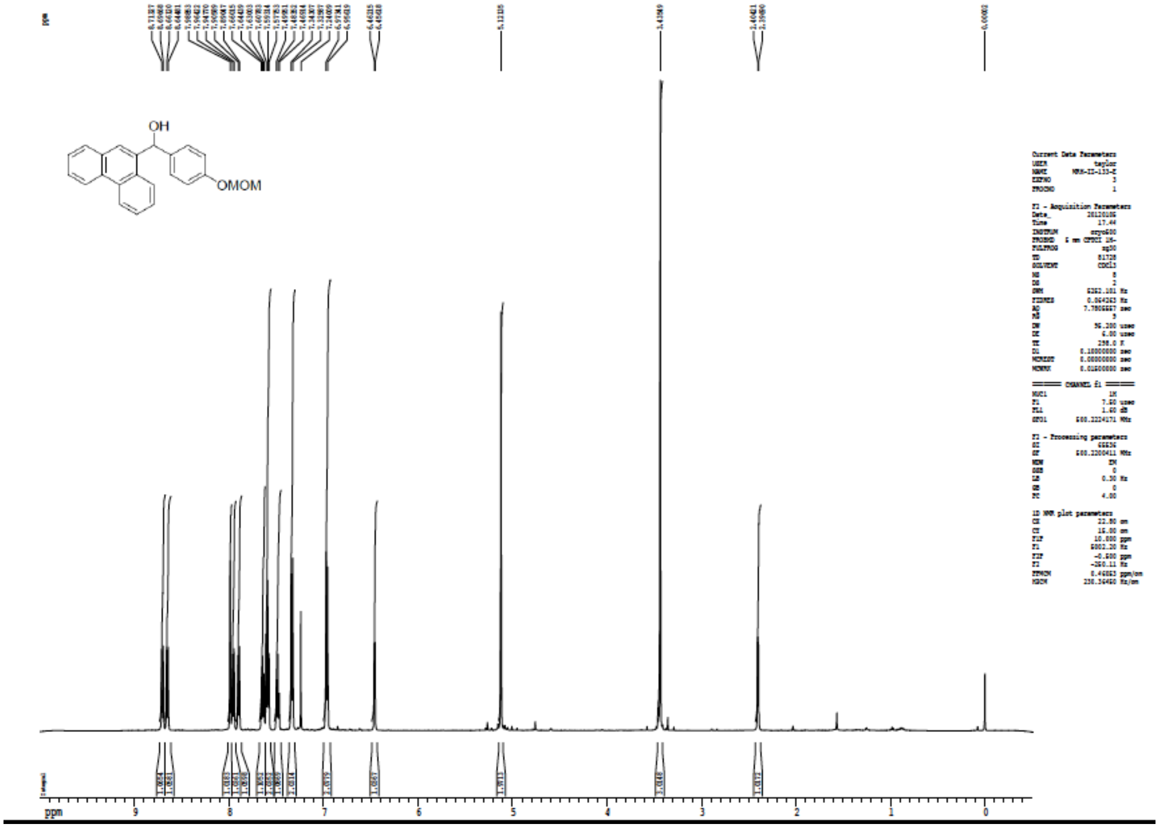

MRH-II-86-87-wash2
Second K2CO3 wash
1H spectrum
OH
ppm
9
8
7
6
5
4
3
2
1
0


1H spectrum
OH
Ph
ppm
9
8
7
6
5
4
3
2
1
0

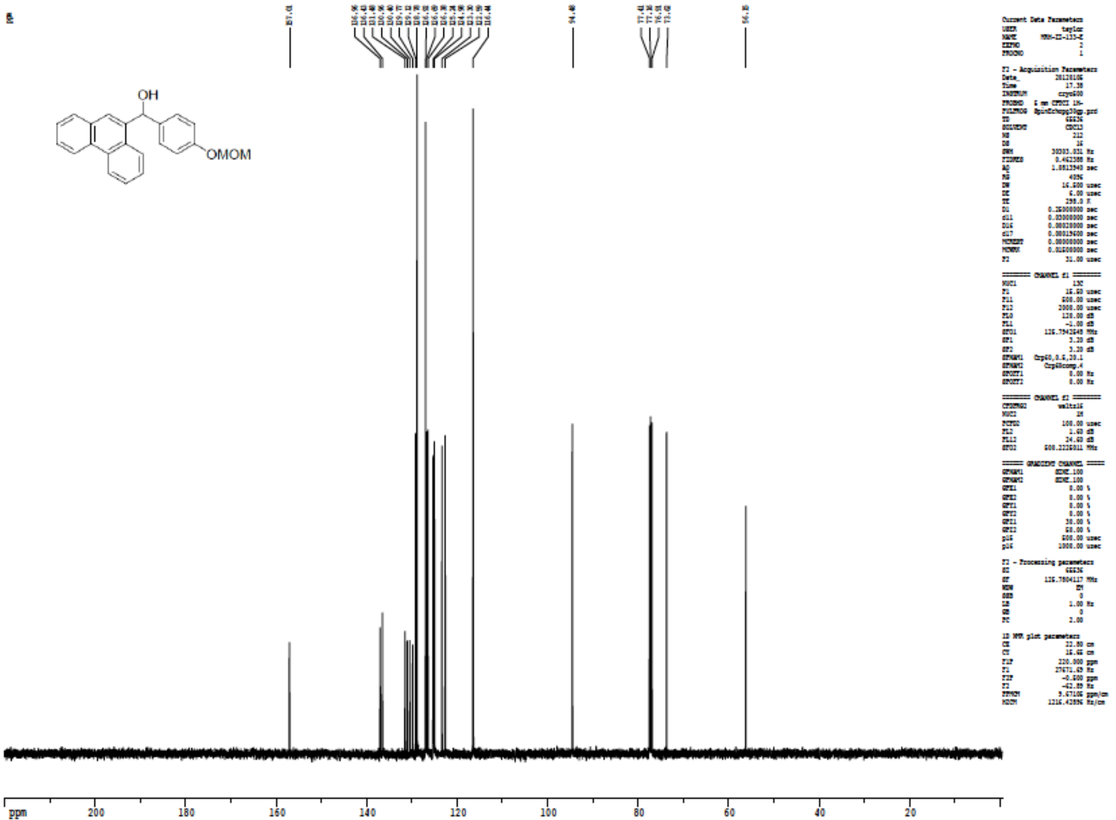
Z-restored spin-echo 13C spectrum with 1H decoupling



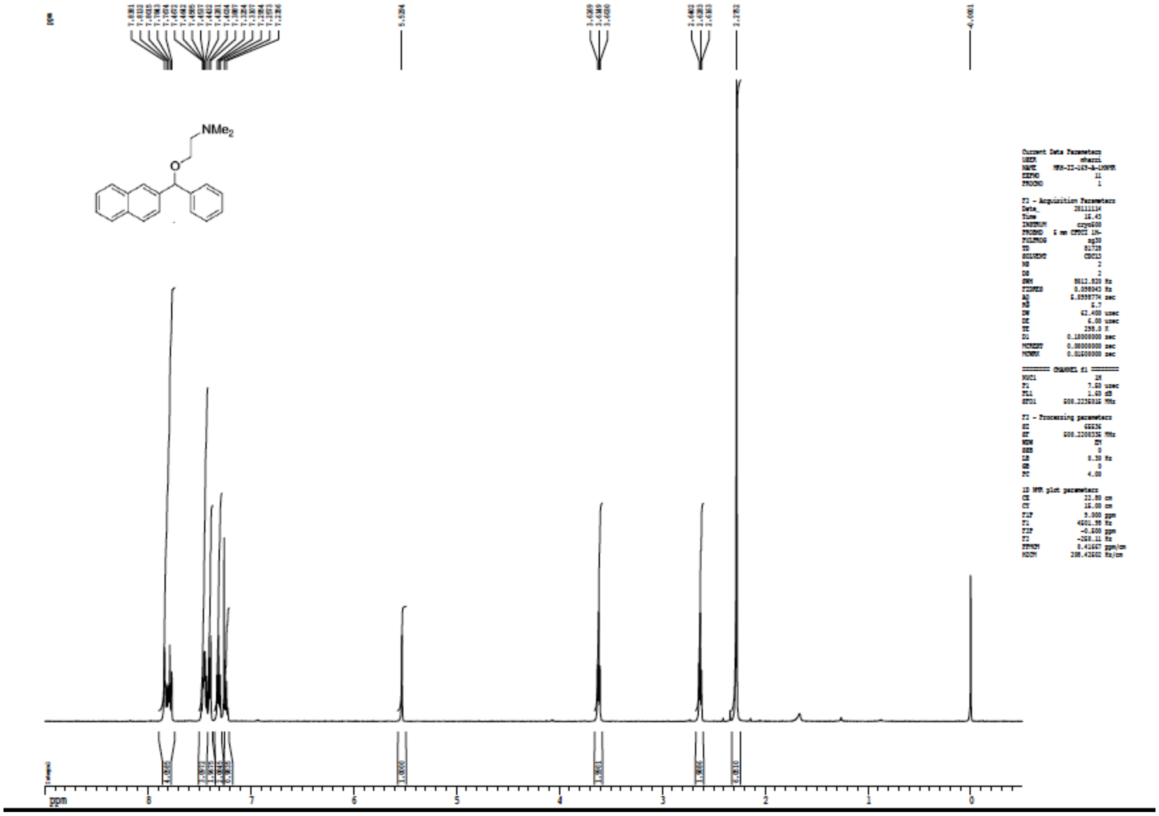
1H spectrum



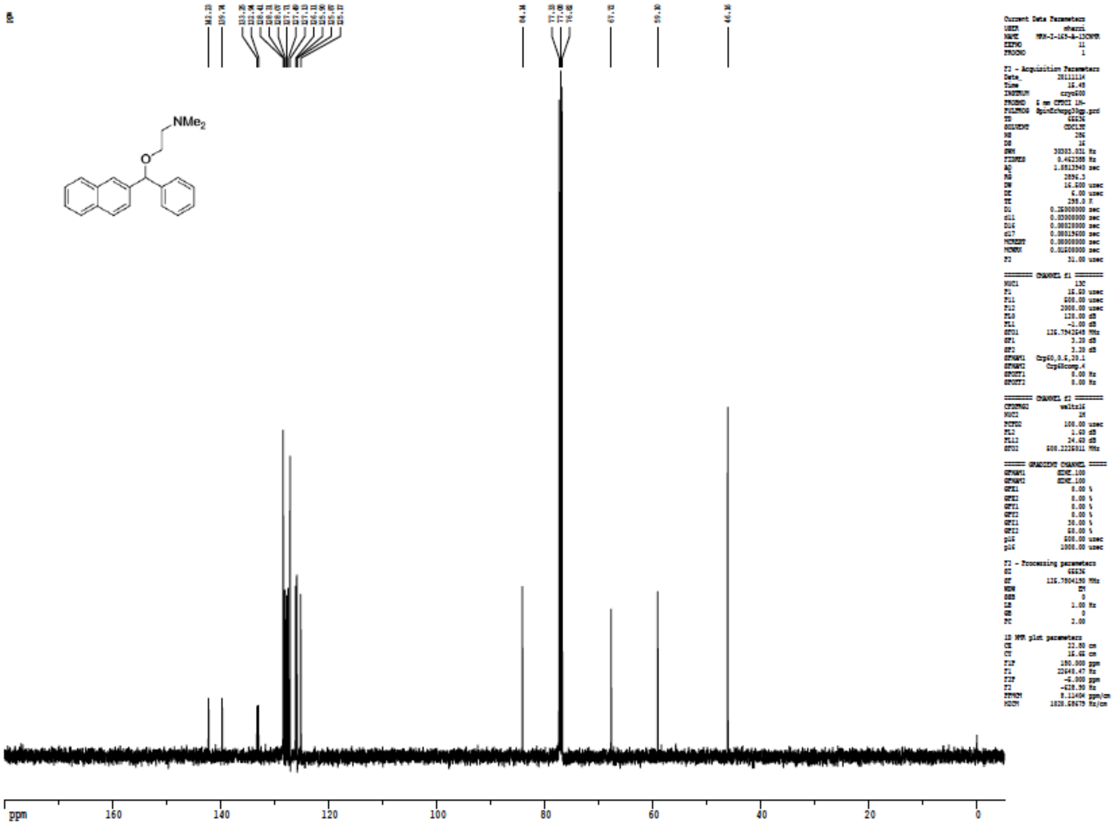
Z-restored spin-echo 13C spectrum with 1H decoupling



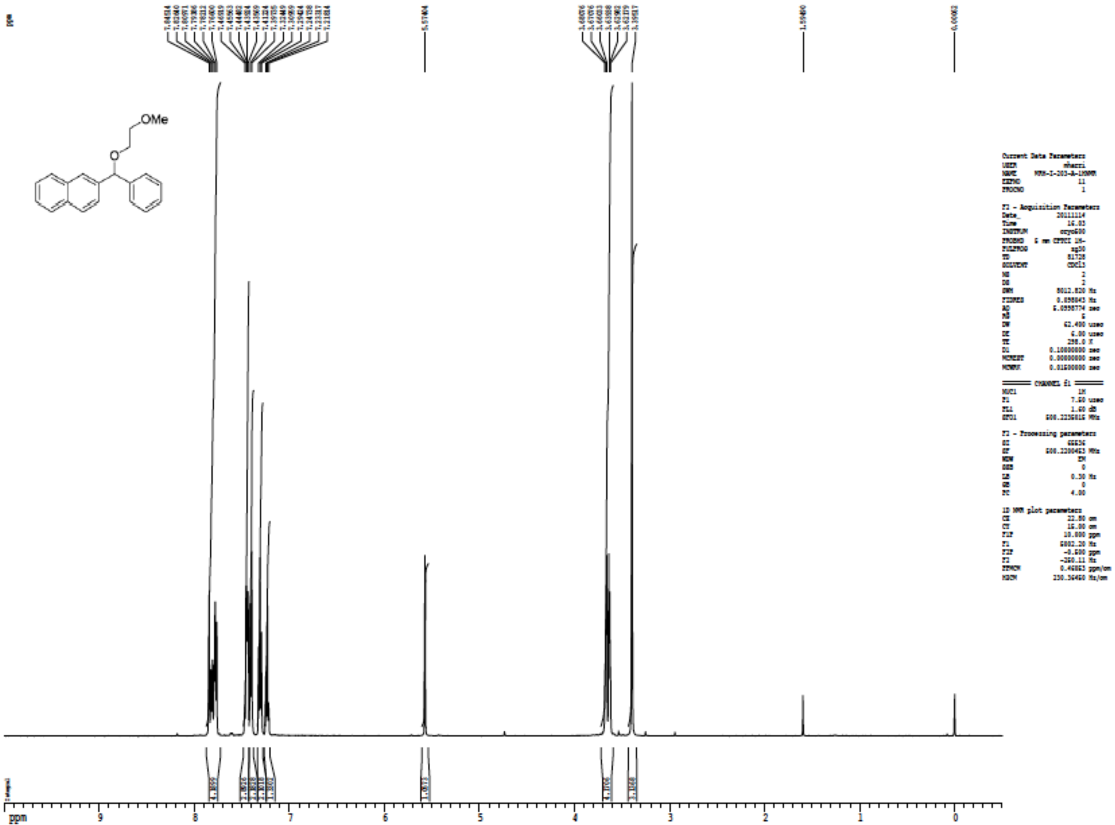
1H spectrum



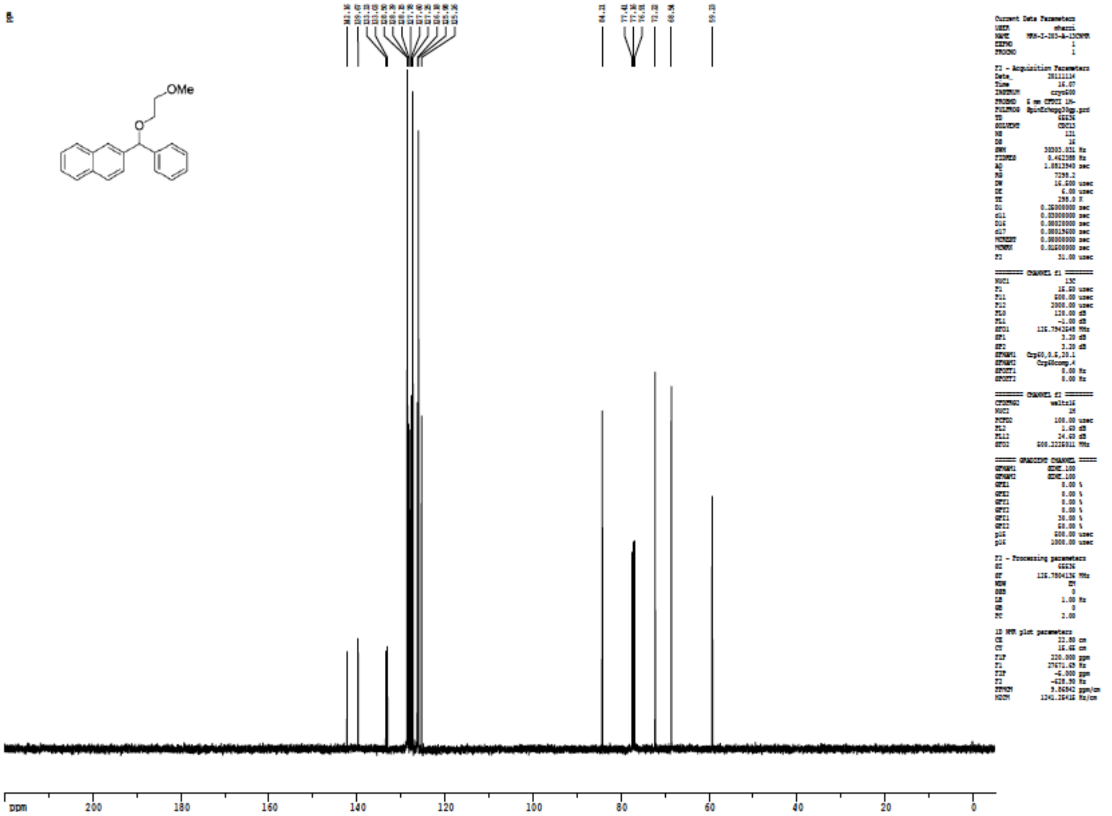
Z-restored spin-echo 13C spectrum with 1H decoupling



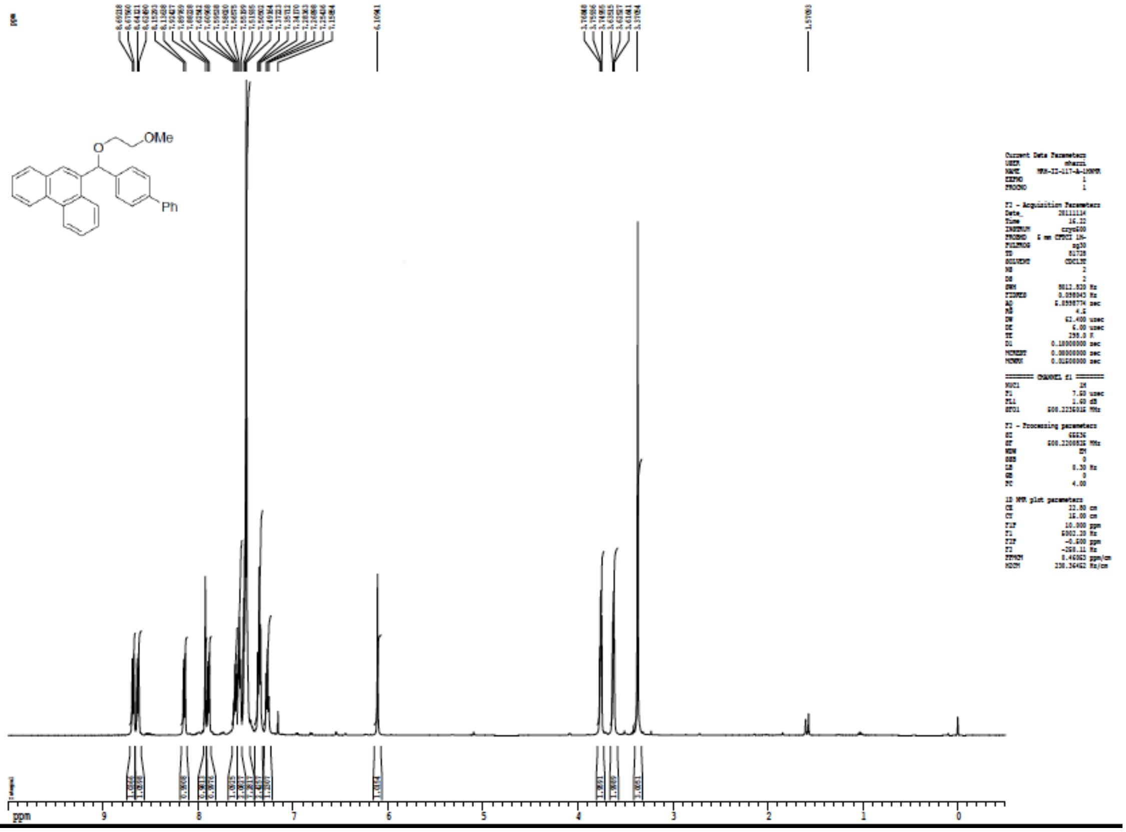
1H spectrum

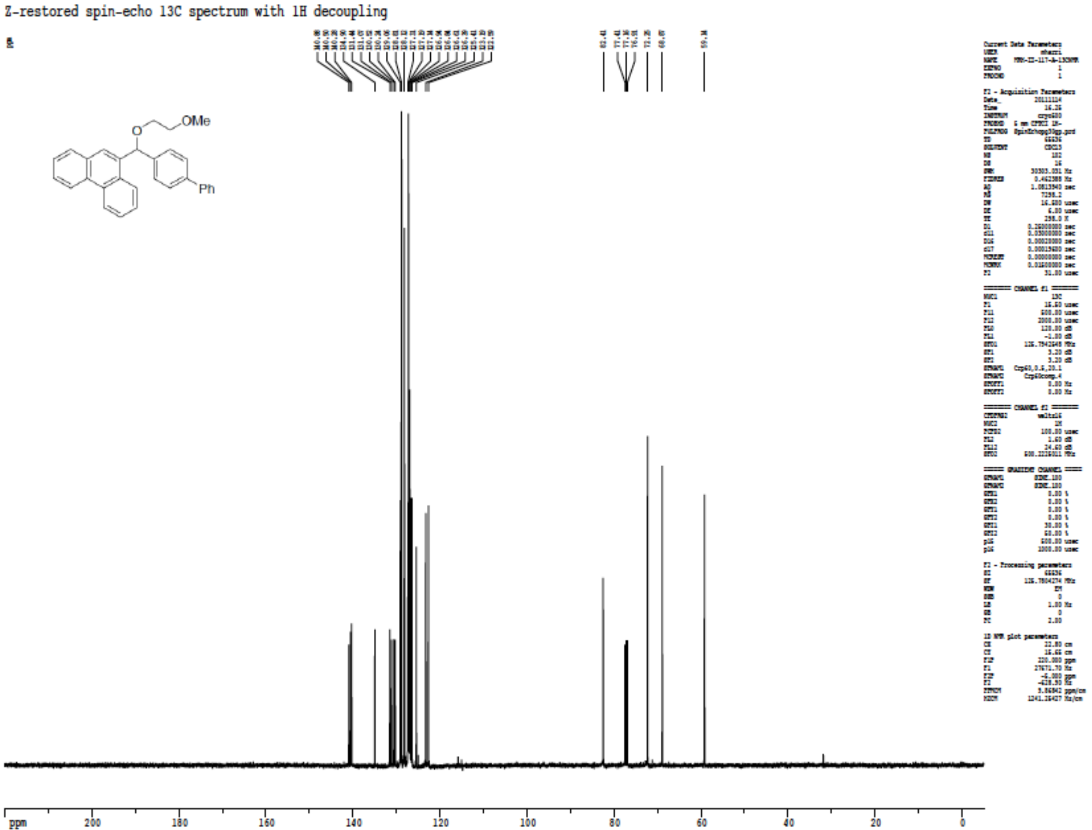


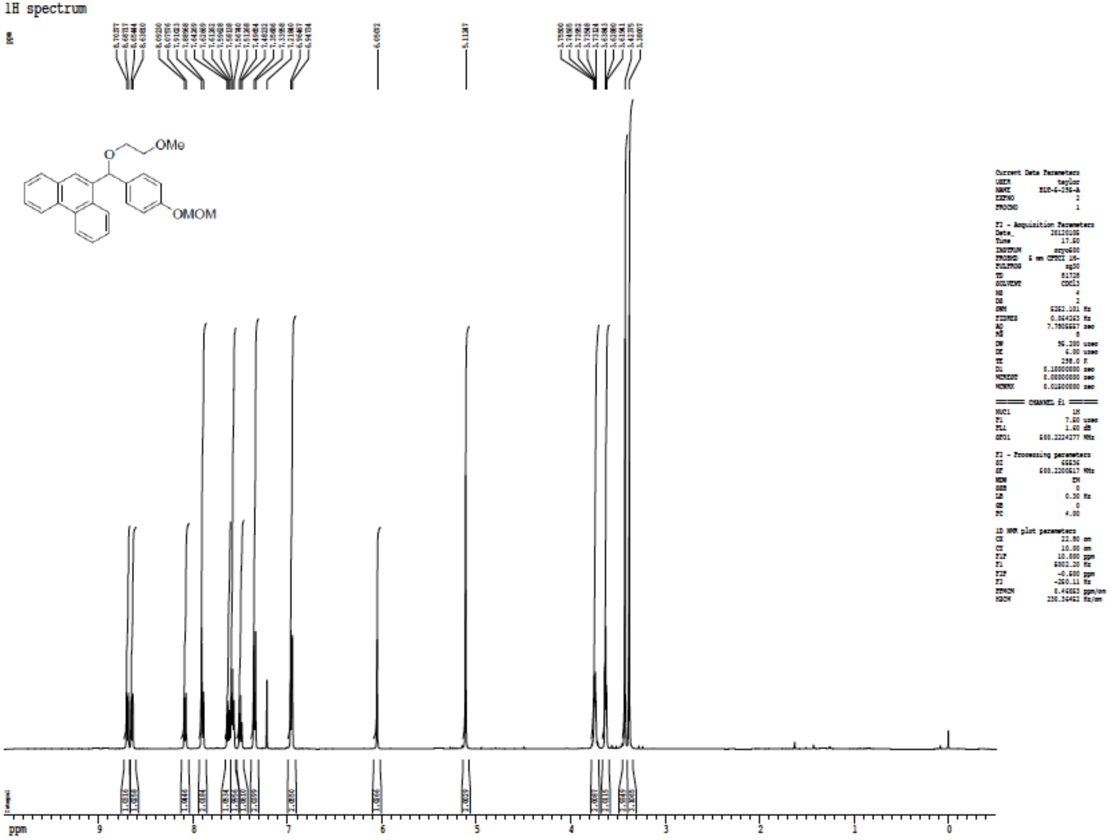
Z-restored spin-echo 13C spectrum with 1H decoupling



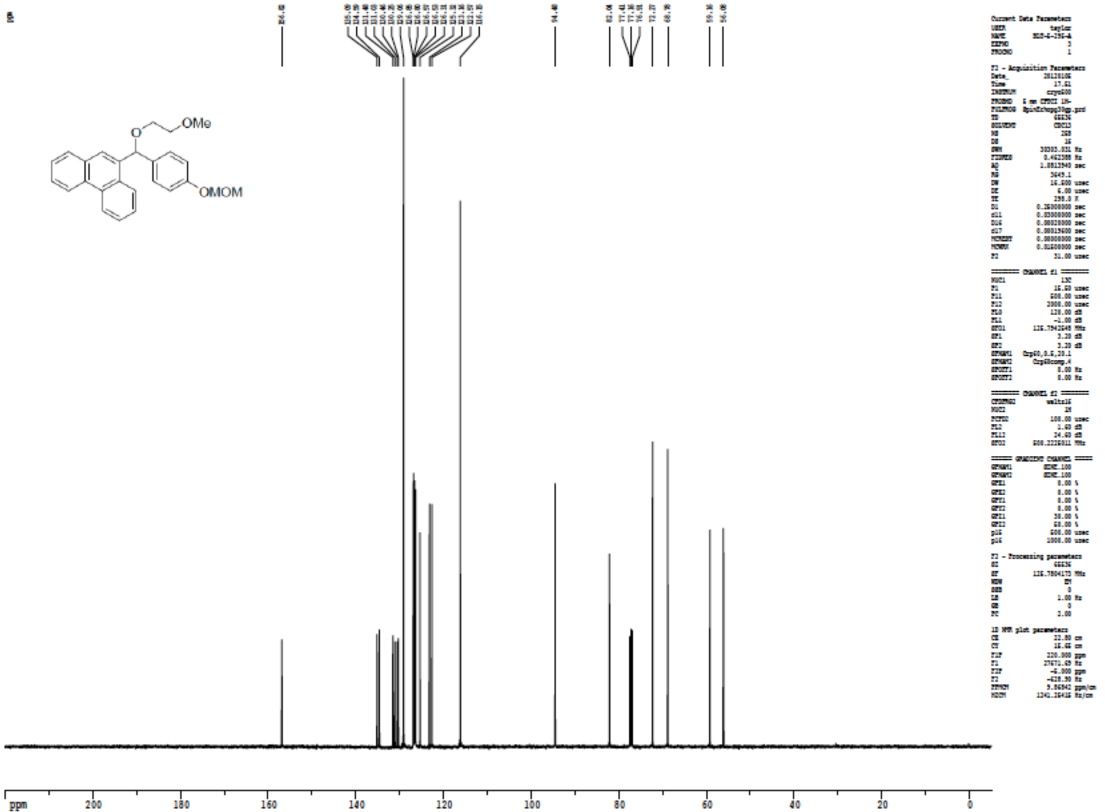
1H spectrum



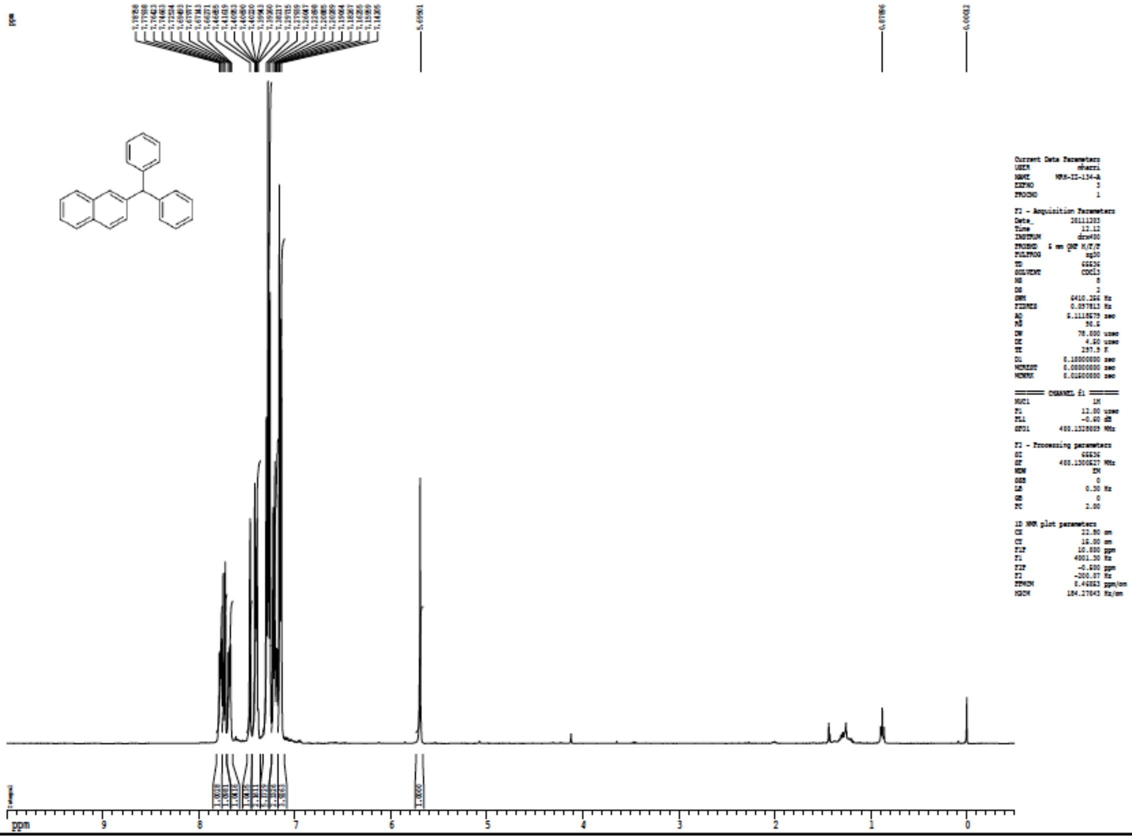

Z-restored spin-echo 13C spectrum with 1H decoupling
OMe
O
Ph
ppm
200
180
160
140
120
100
80
60
40
20
0


1H spectrum
OMe
O
OMOM
ppm
9
8
7
6
5
4
3
2
1
0

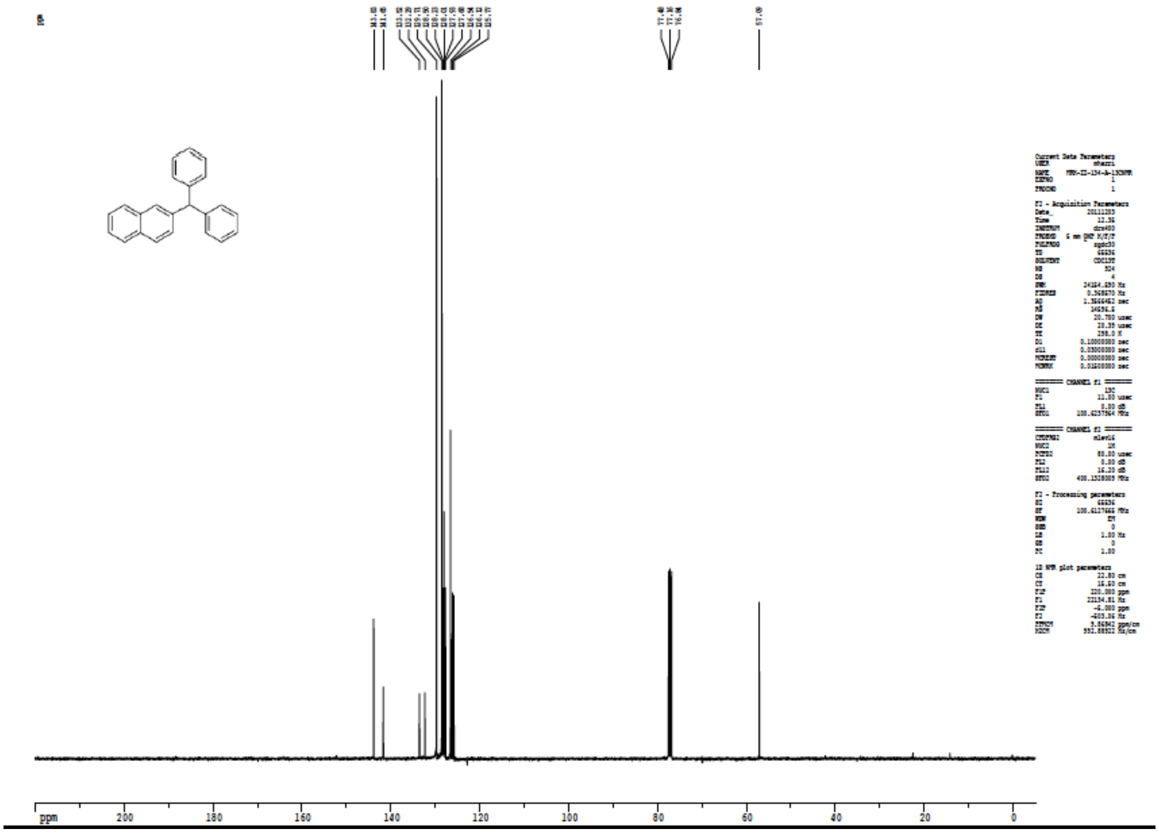
Z-restored spin-echo 13C spectrum with 1H decoupling



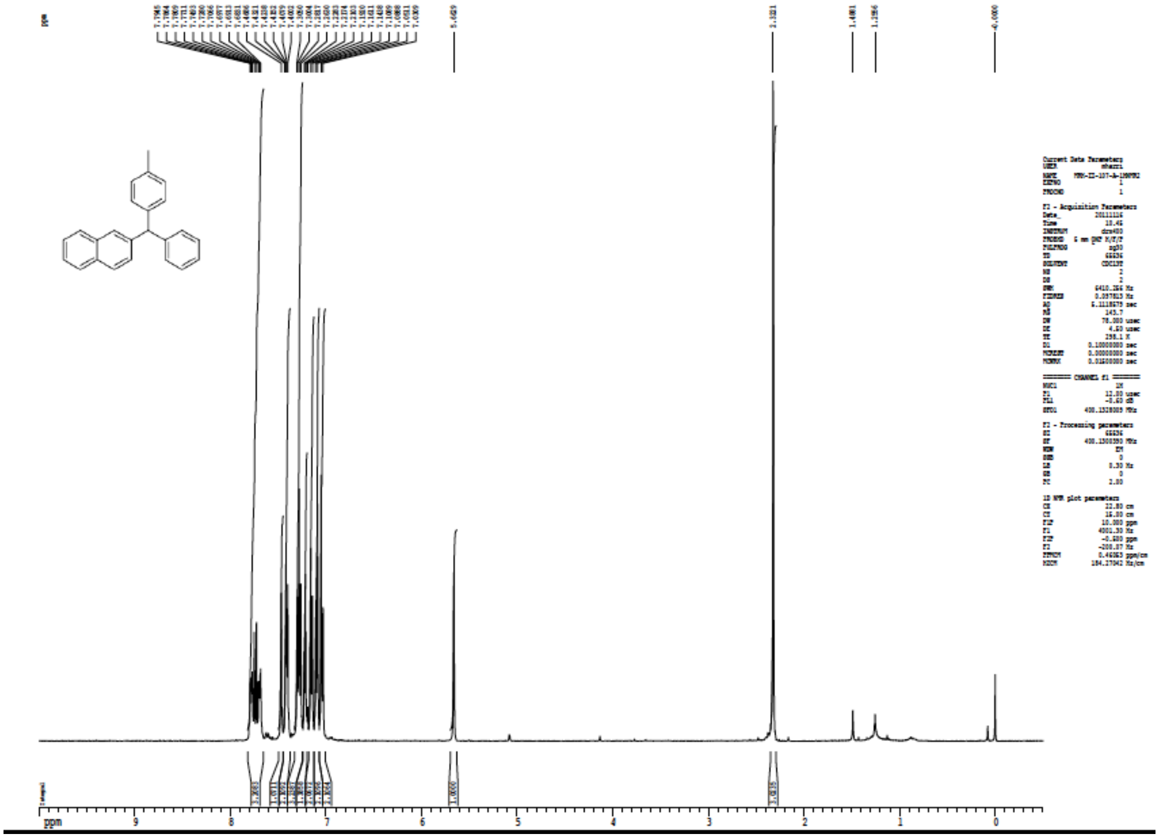
1H spectrum



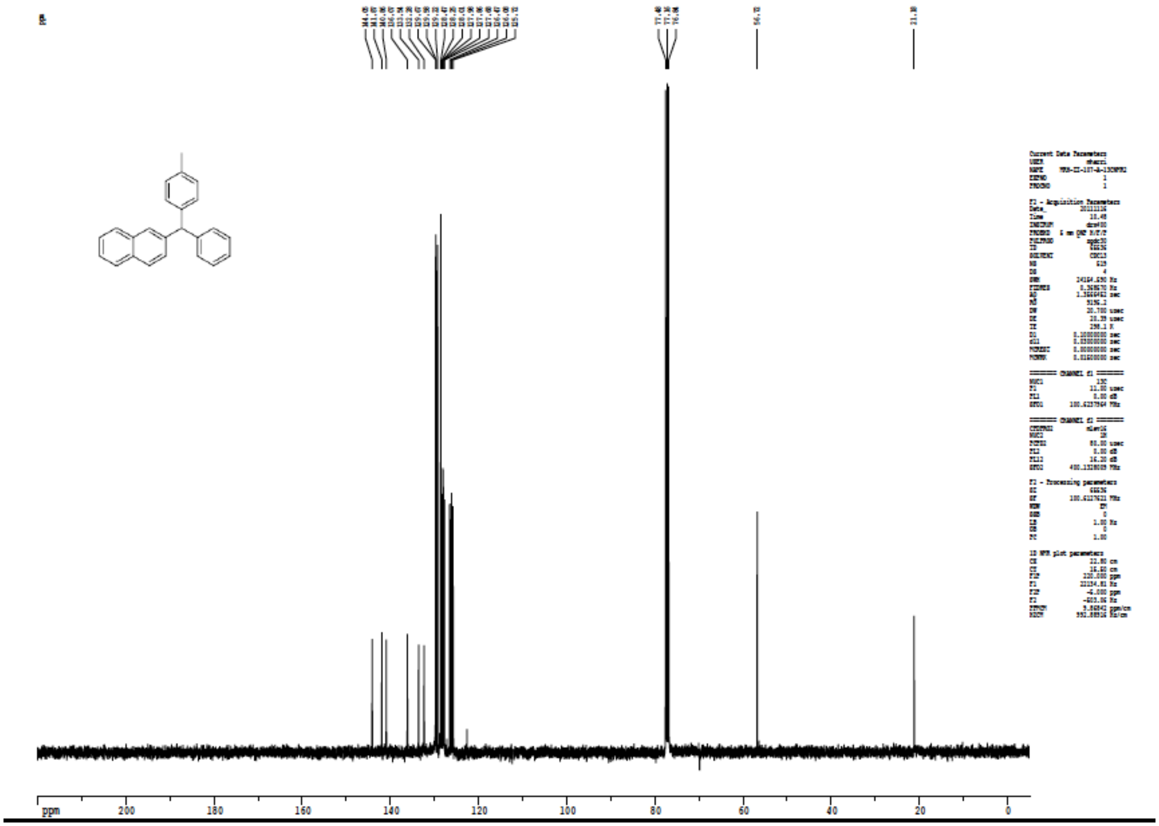
13C spectrum with 1H decoupling



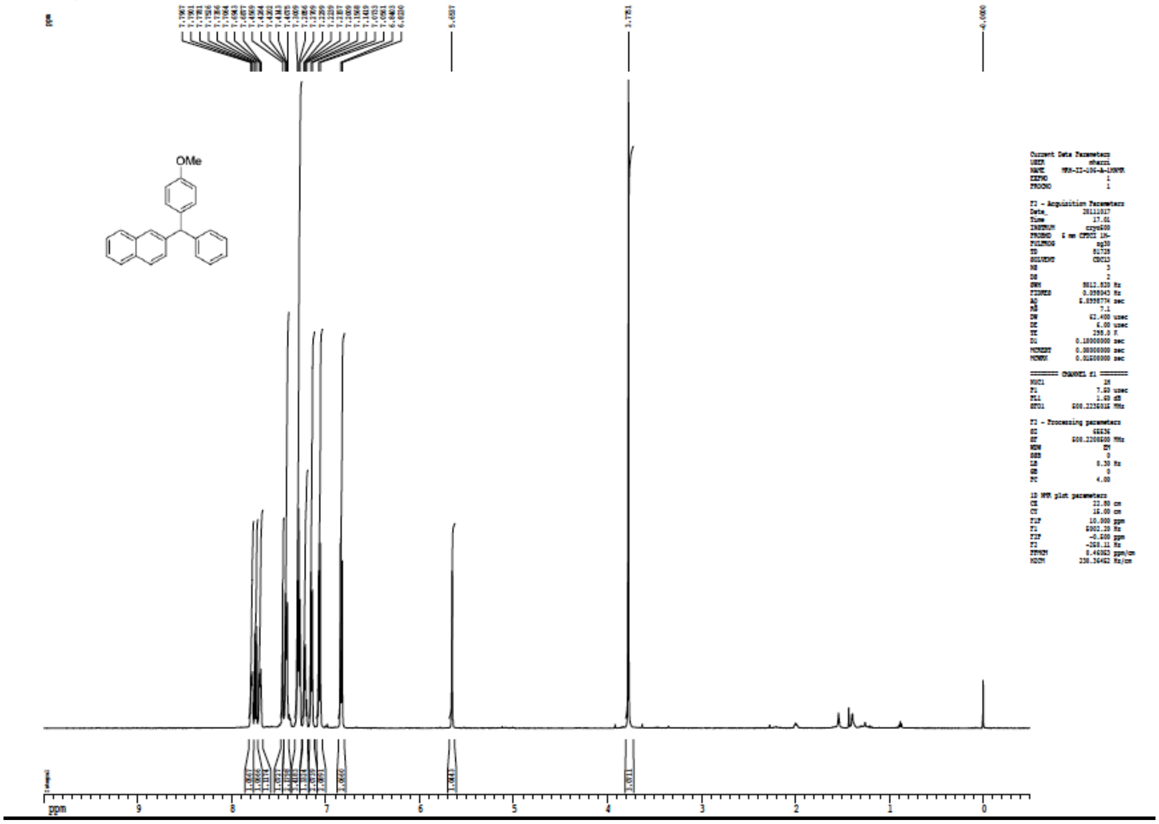
1H spectrum

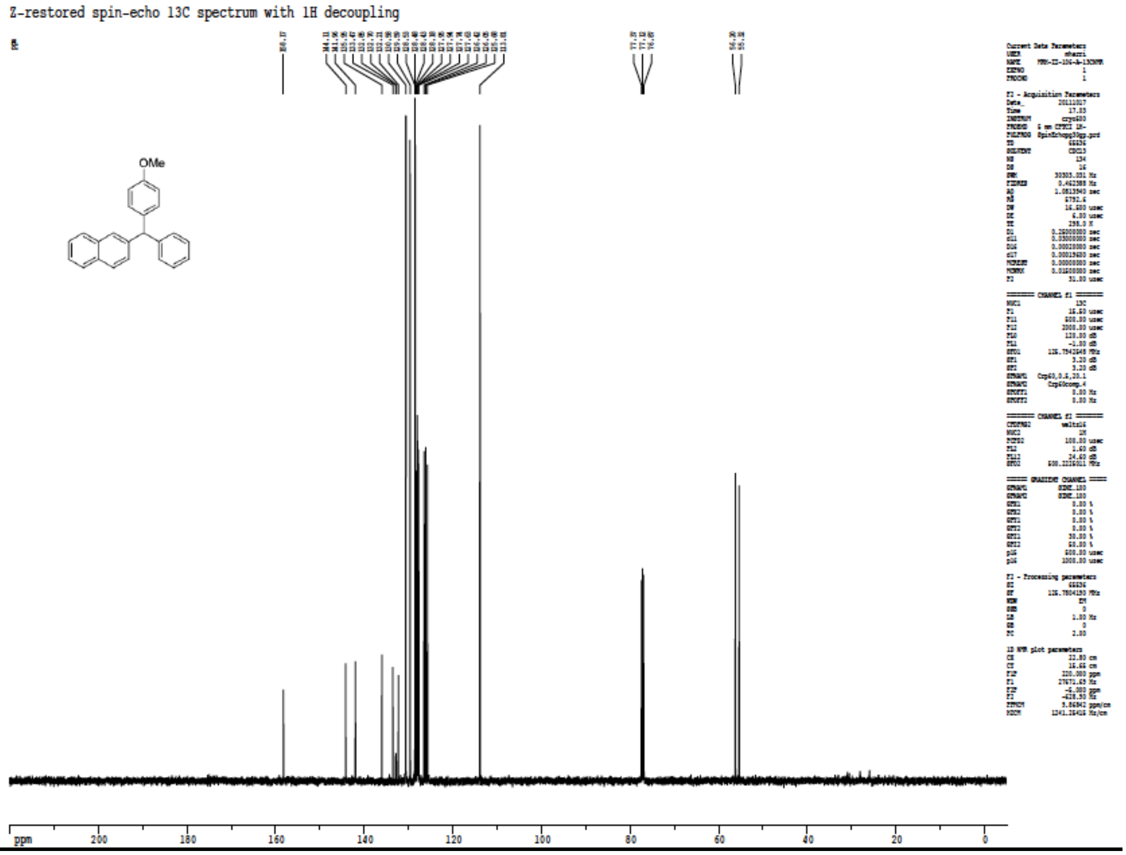


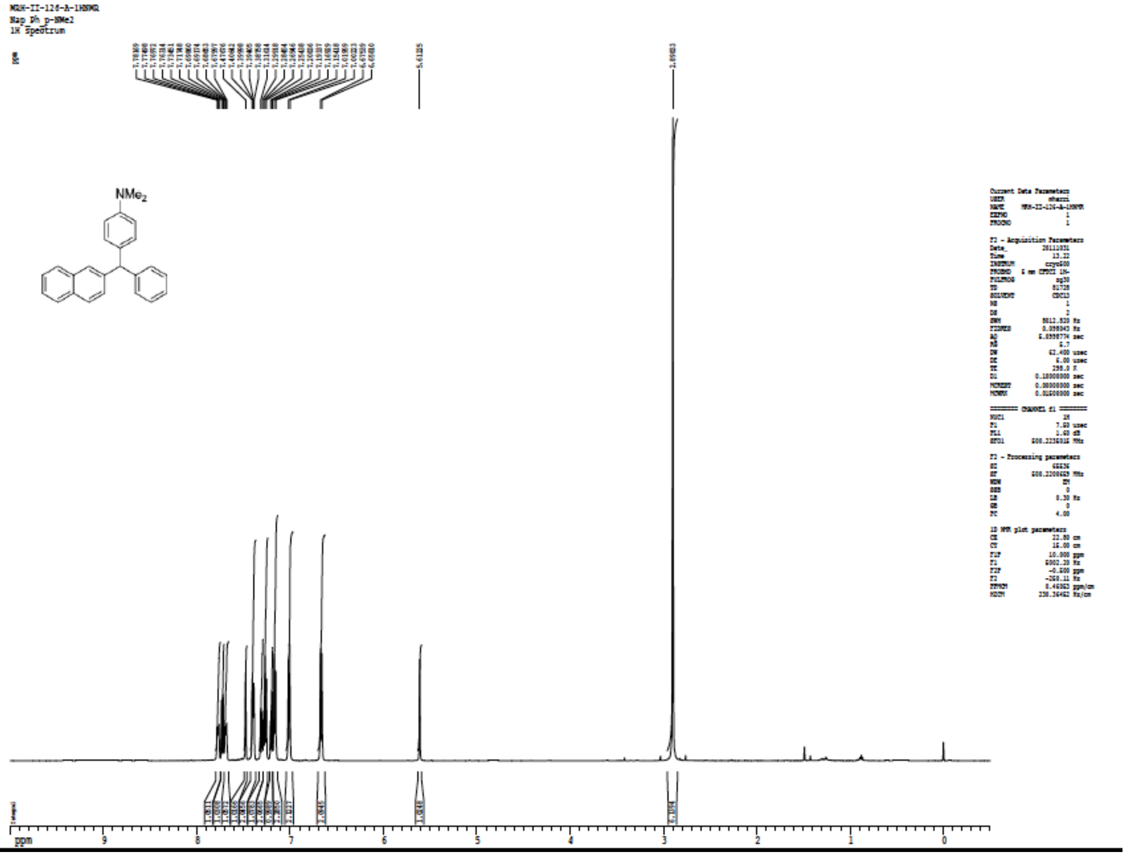
13C spectrum with 1H decoupling



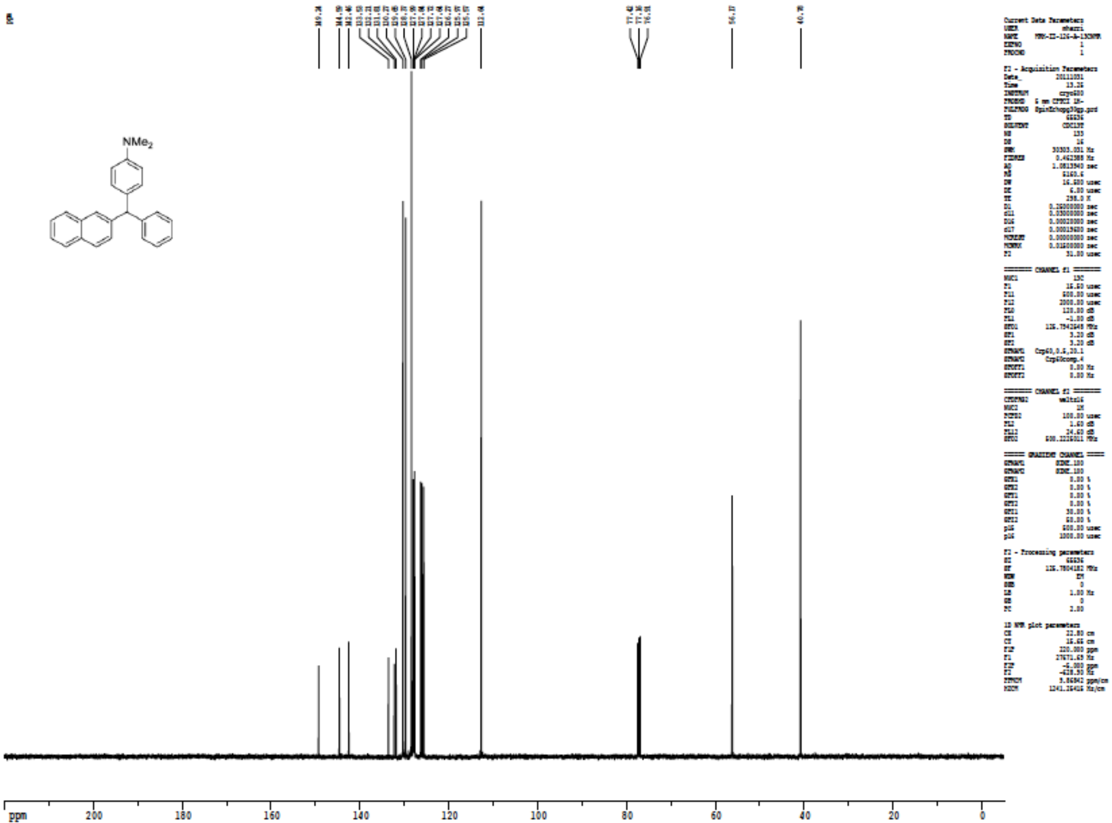
1H spectrum



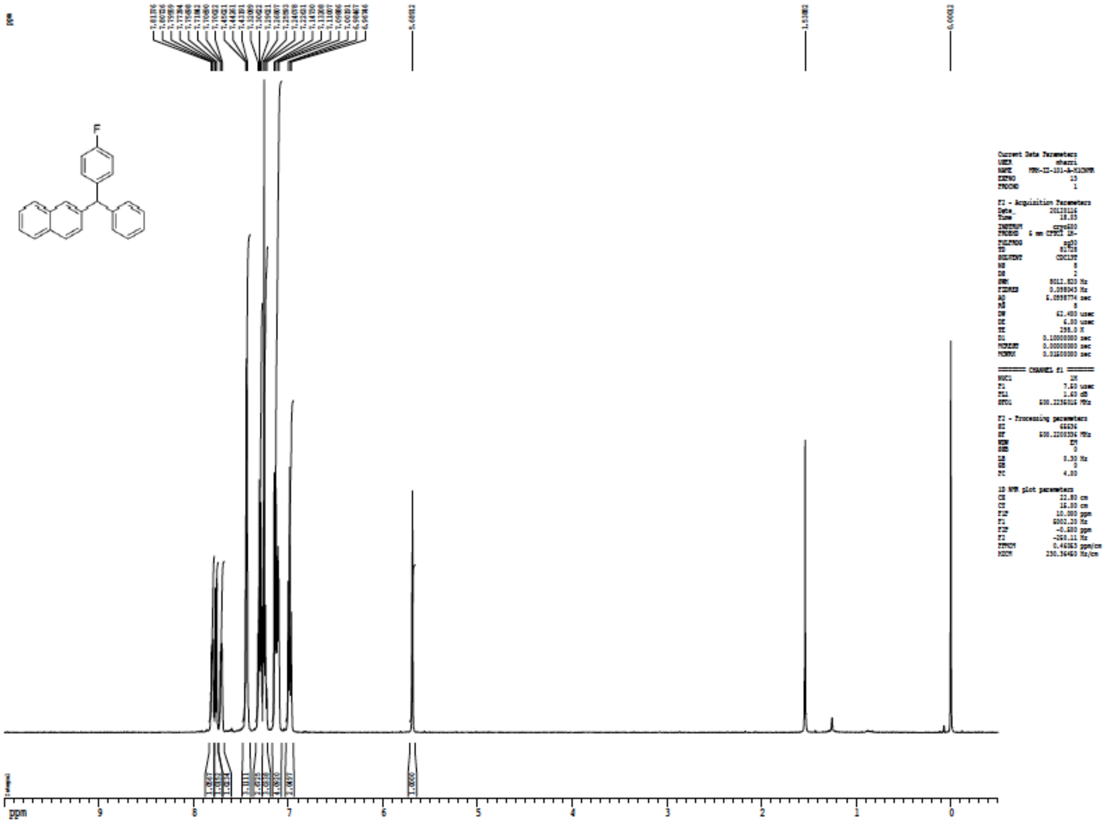

Z-restored spin-echo 13C spectrum with 1H decoupling
OMe
77.37
77.12
76.86
ppm
200
180
160
140
120
100
80
60
40
20
0


MRH-II-126-A-1HNMR
Nap_Ph_p-NMe2
1H Spectrum
NMe2
5.6125
2.8983
ppm
9
8
7
6
5
4
3
2
1
0

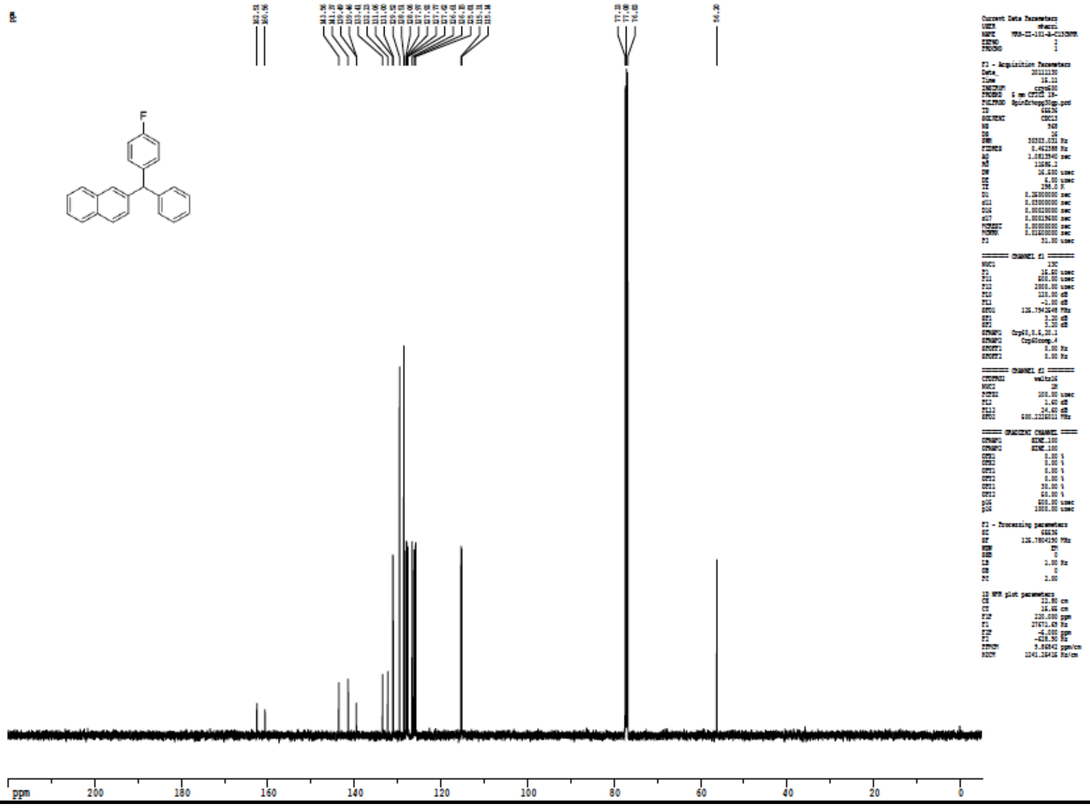
Z-restored spin-echo 13C spectrum with 1H decoupling



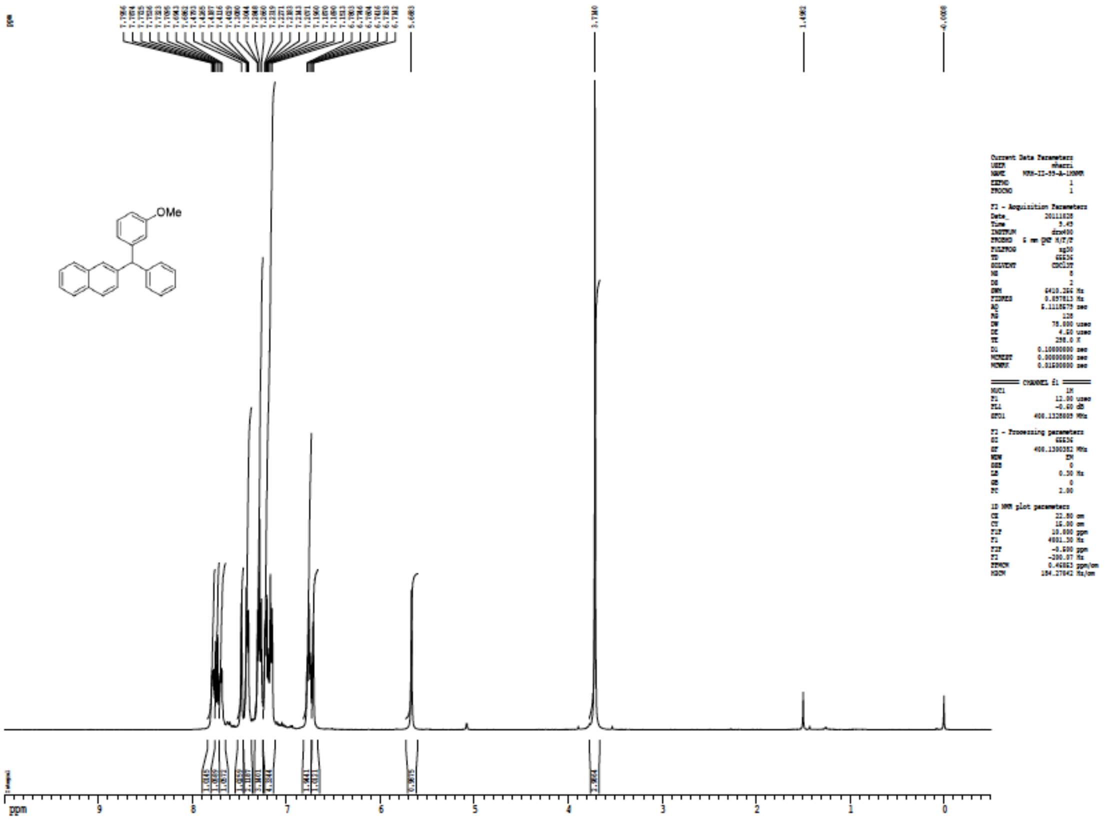
1H spectrum



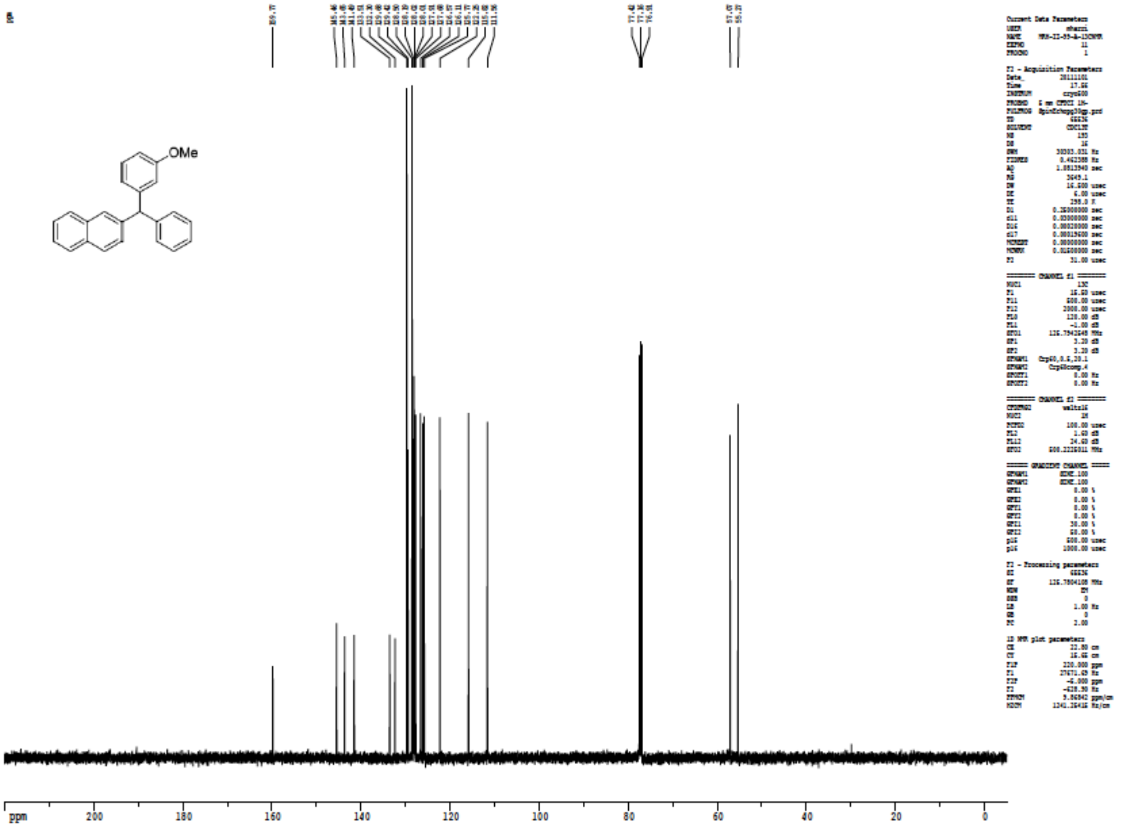
Z-restored spin-echo 13C spectrum with 1H decoupling



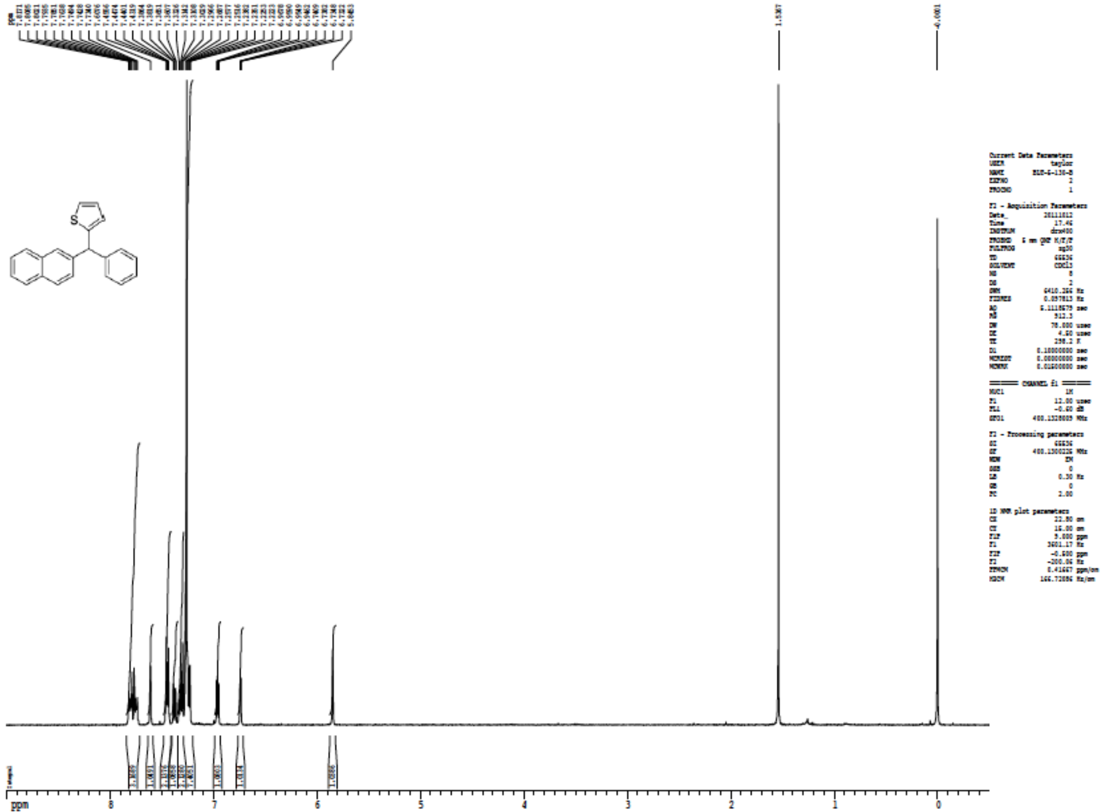
MRH-II-99-A
Nap Ph m-OMePh
1H Spectrum



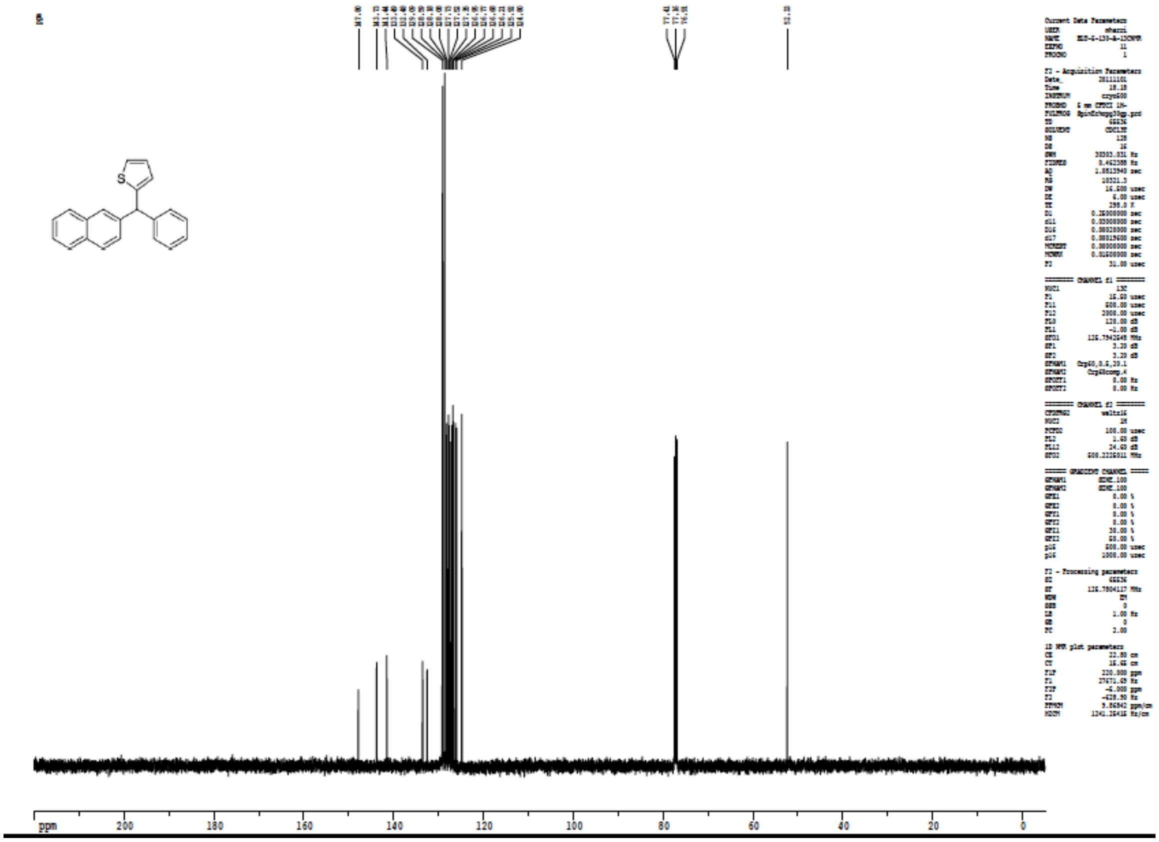
Z-restored spin-echo 13C spectrum with 1H decoupling



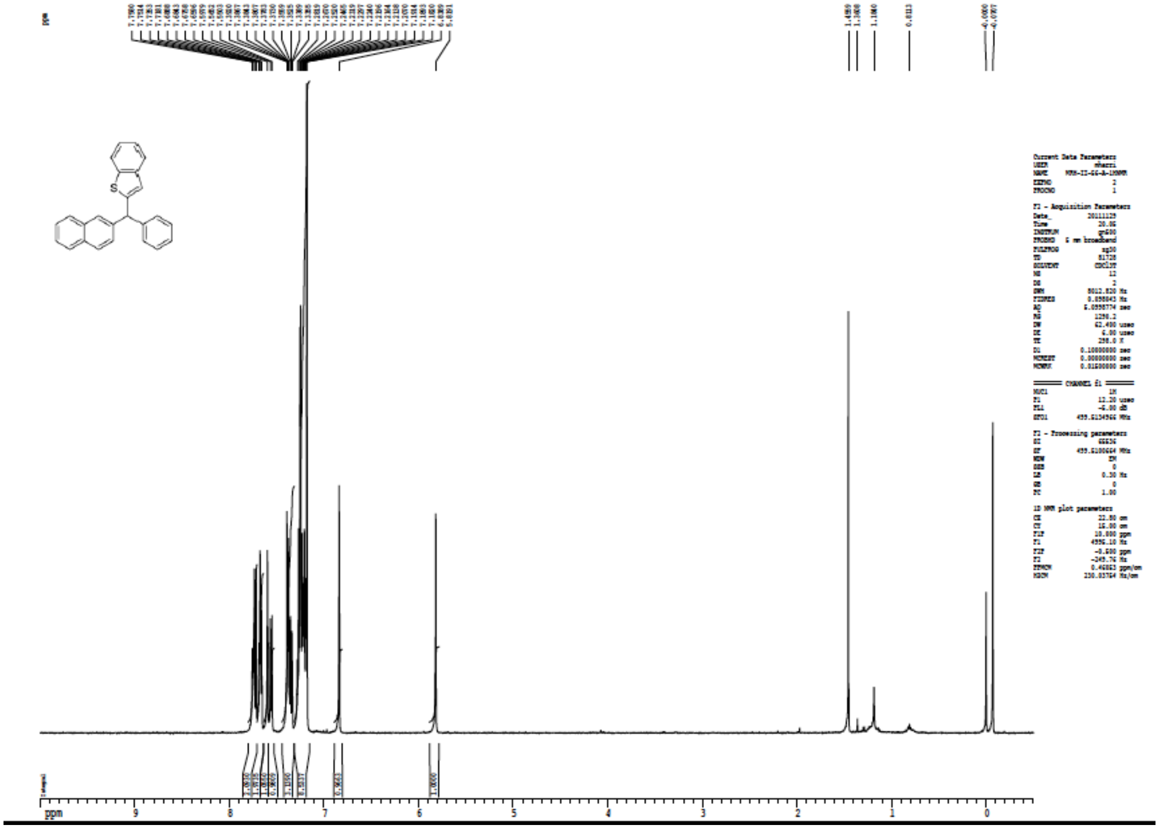
1H spectrum



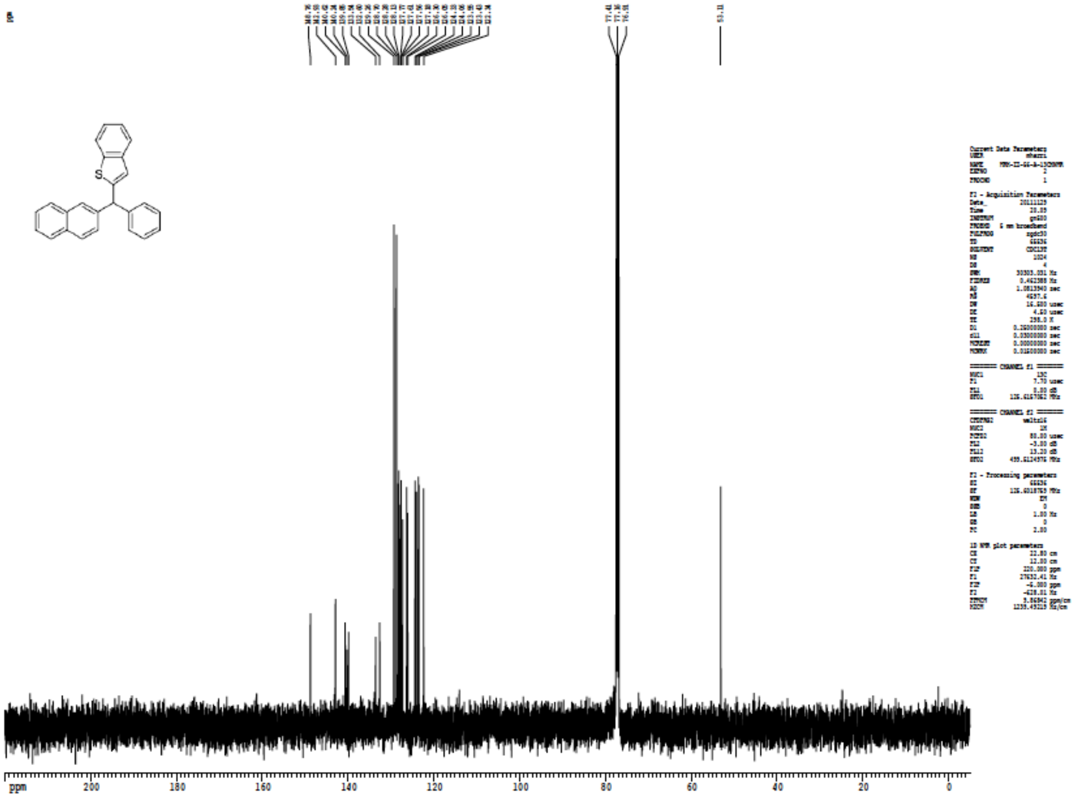
Z-restored spin-echo 13C spectrum with 1H decoupling



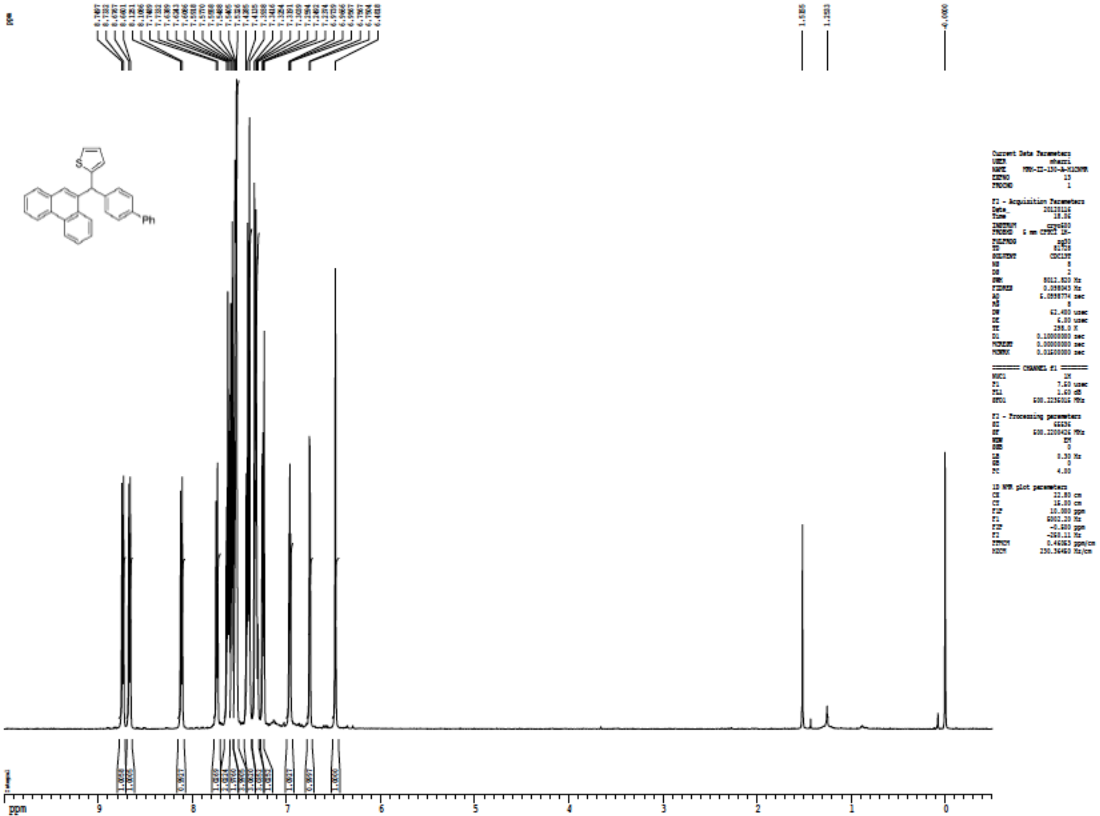
1H spectrum



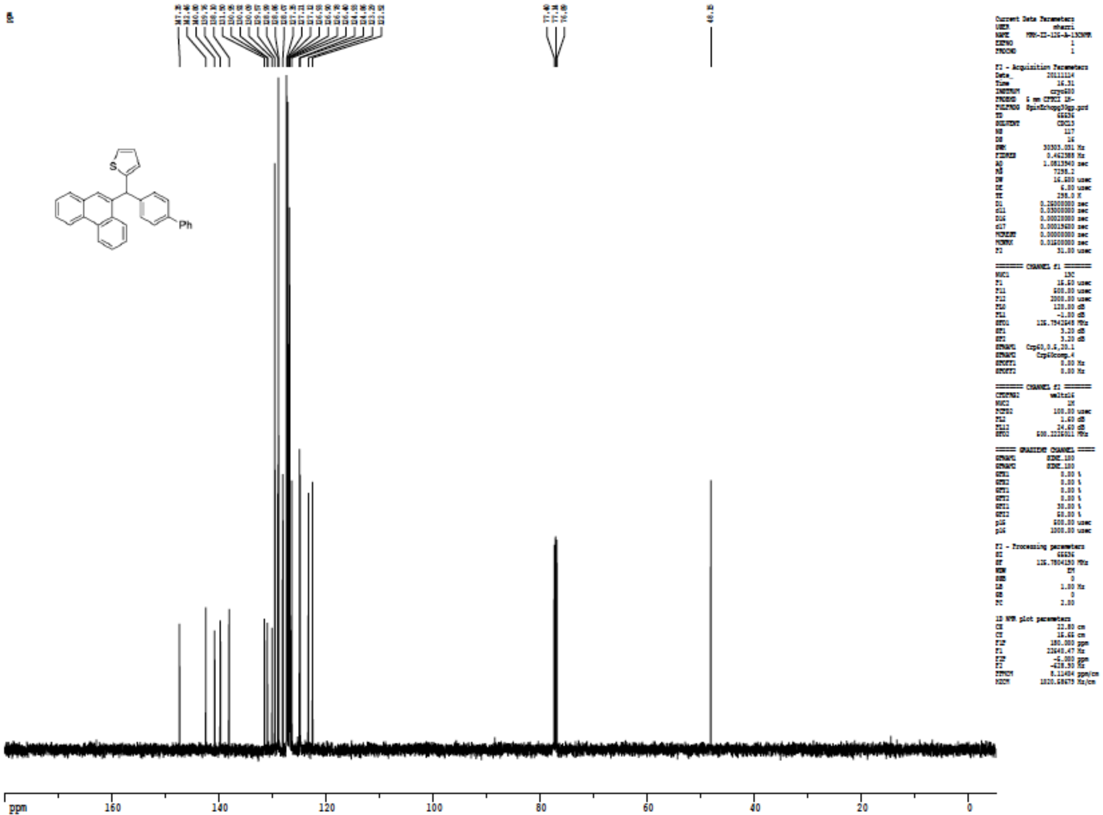
13C spectrum with 1H decoupling



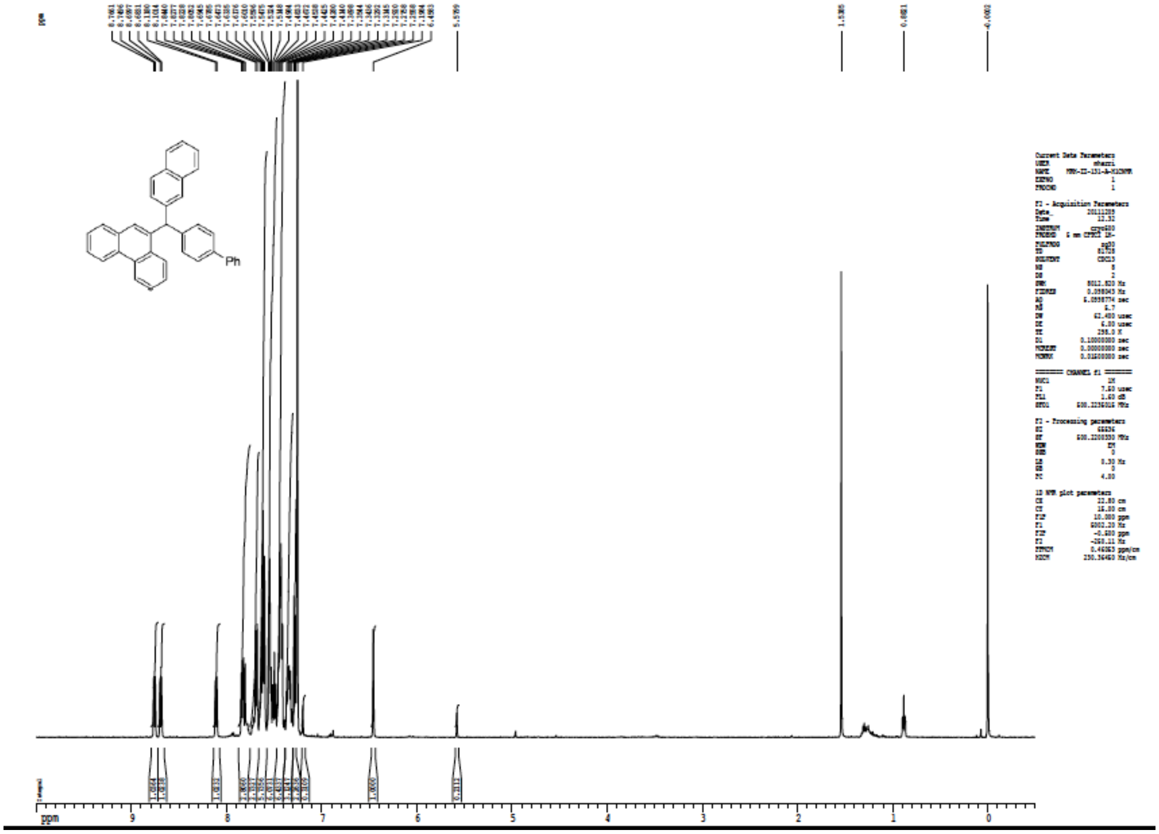
1H spectrum

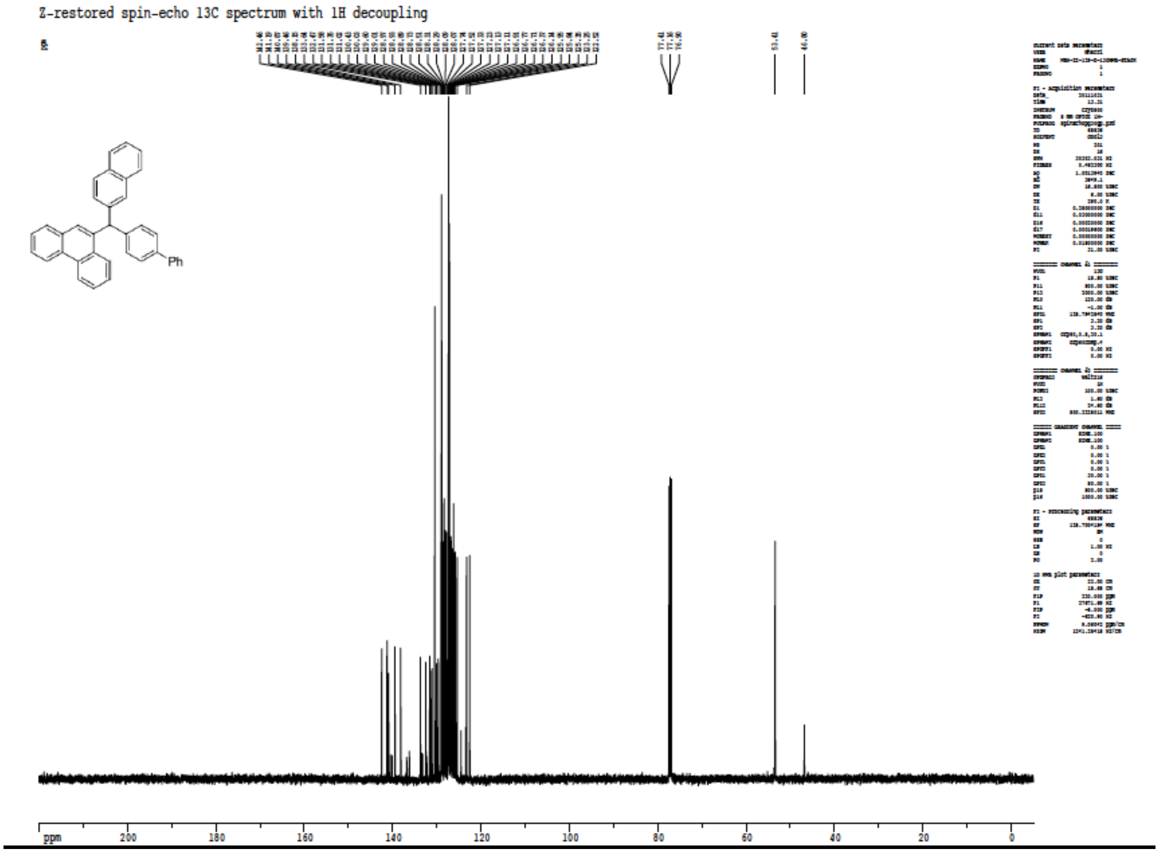


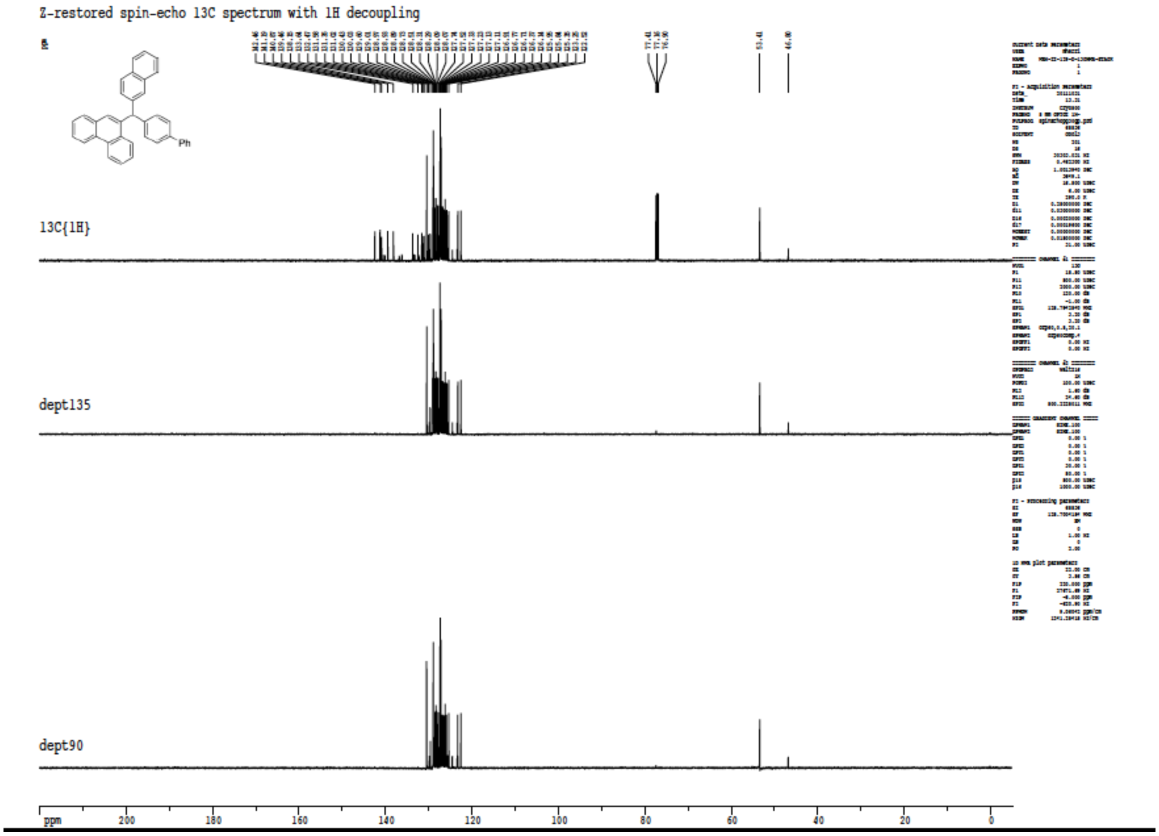
Z-restored spin-echo 13C spectrum with 1H decoupling



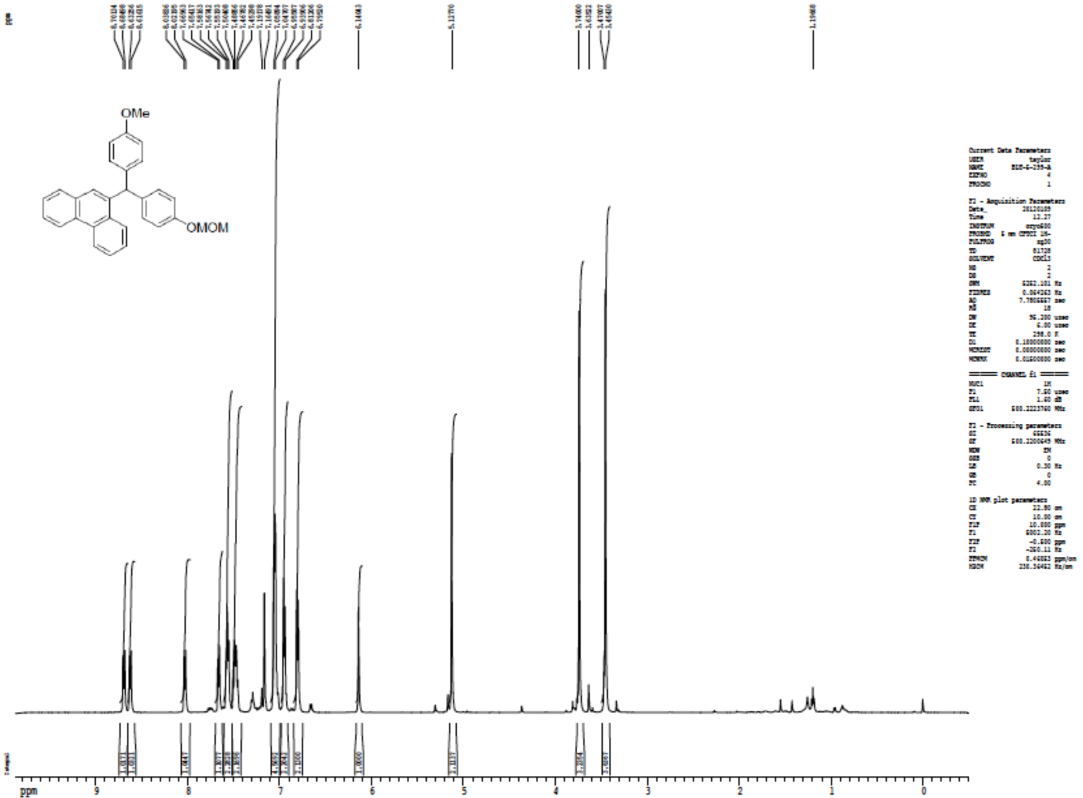
1H spectrum



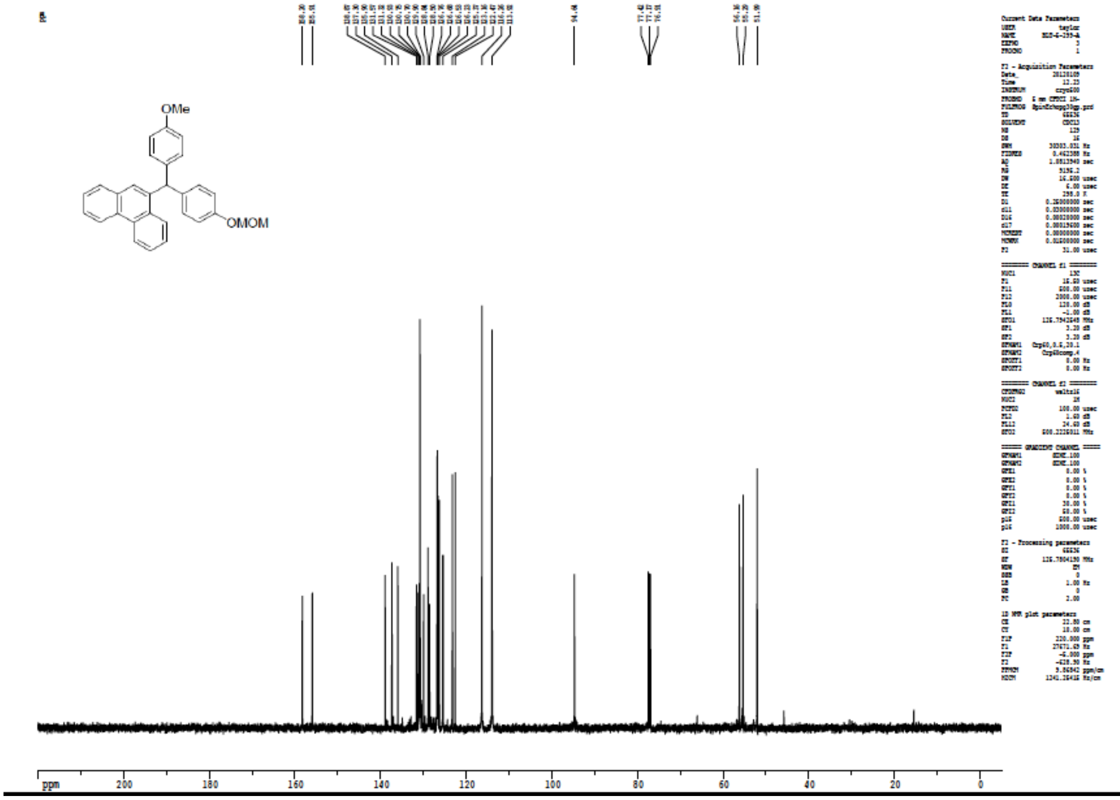

Z-restored spin-echo 13C spectrum with 1H decoupling
77.41
77.16
76.90
53.41
46.80
Ph
ppm
200
180
160
140
120
100
80
60
40
20
0


Z-restored spin-echo 13C spectrum with 1H decoupling
77.41
77.16
76.90
53.41
46.80
Ph
13C{1H}
dept135
dept90
ppm
200
180
160
140
120
100
80
60
40
20
0

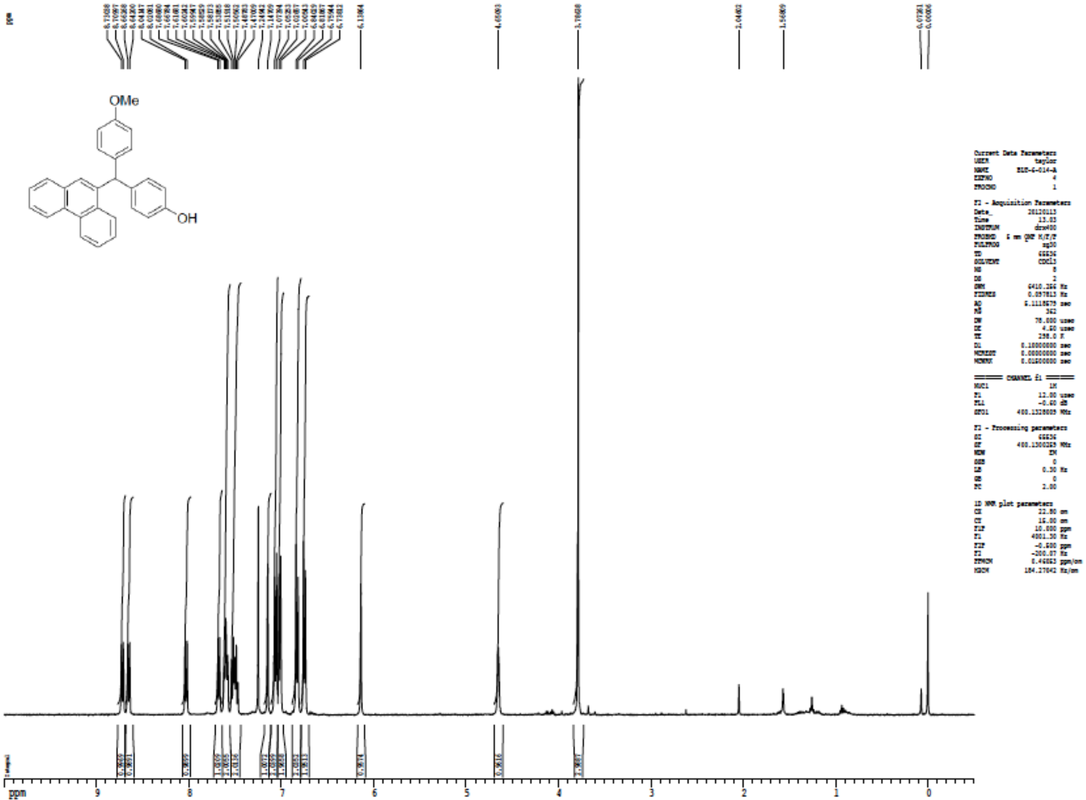
1H spectrum



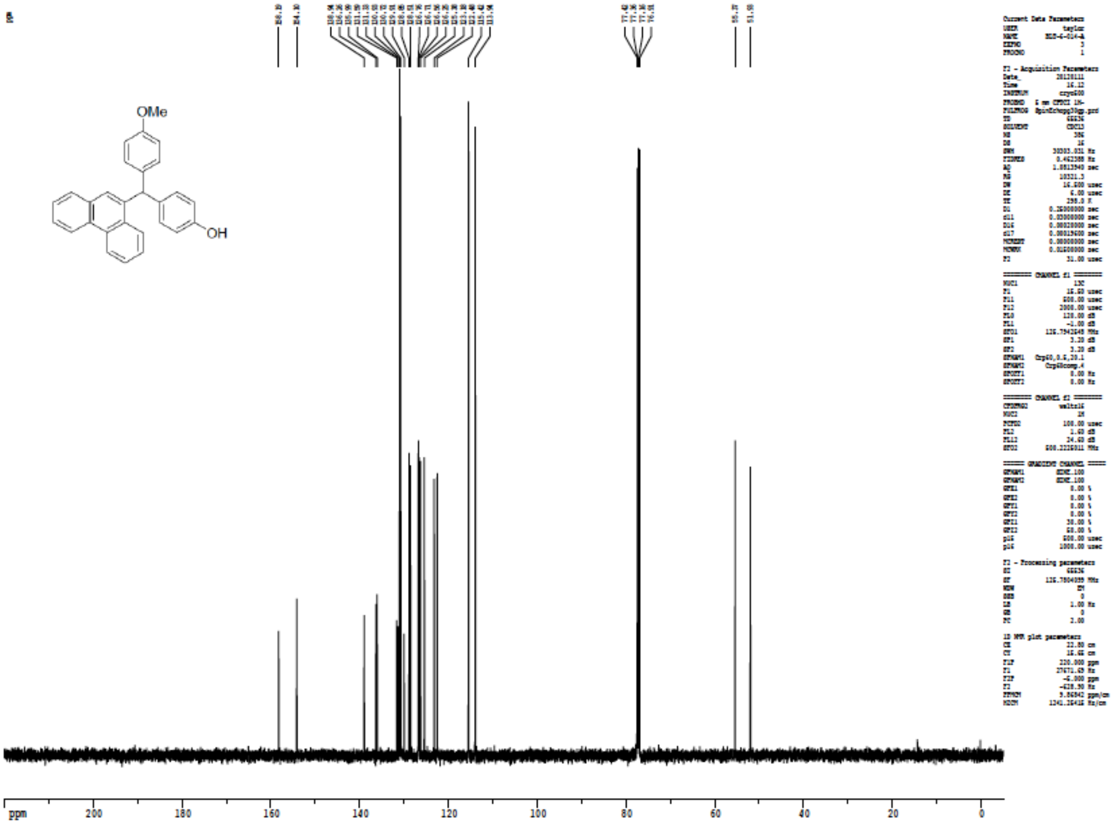
Z-restored spin-echo 13C spectrum with 1H decoupling



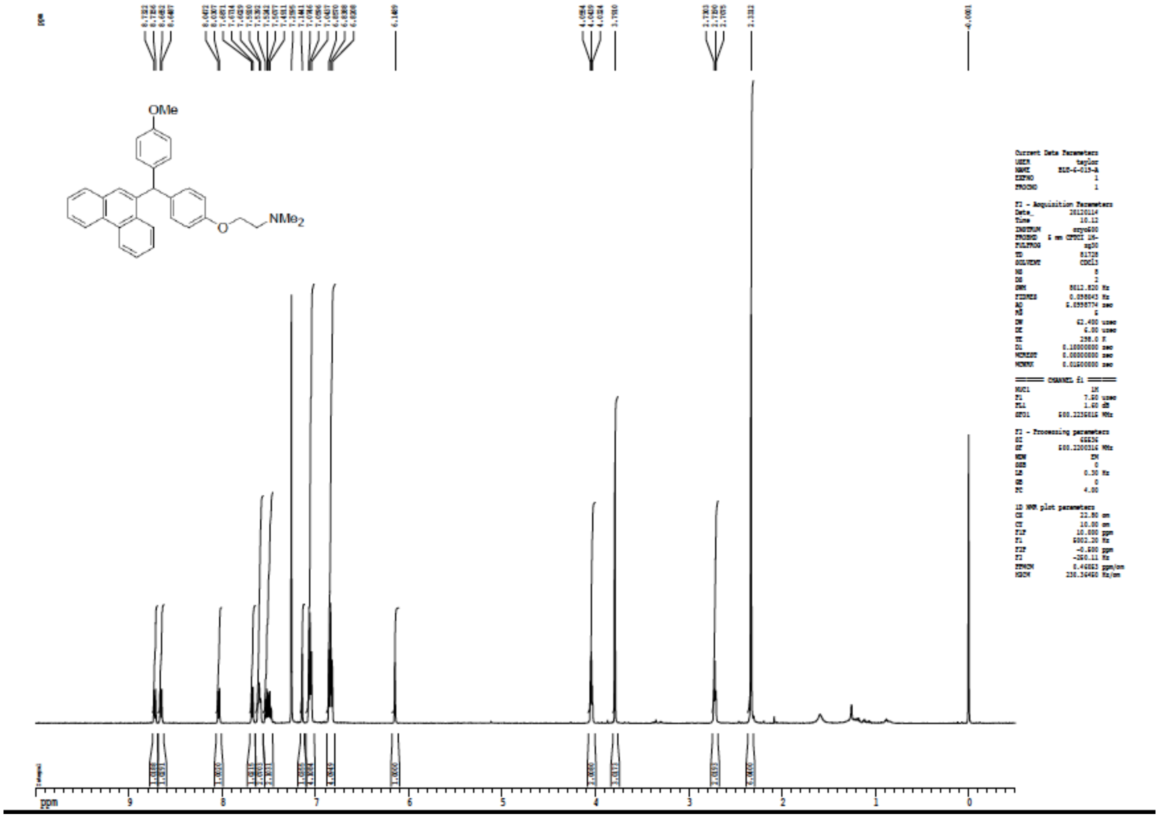
1H spectrum



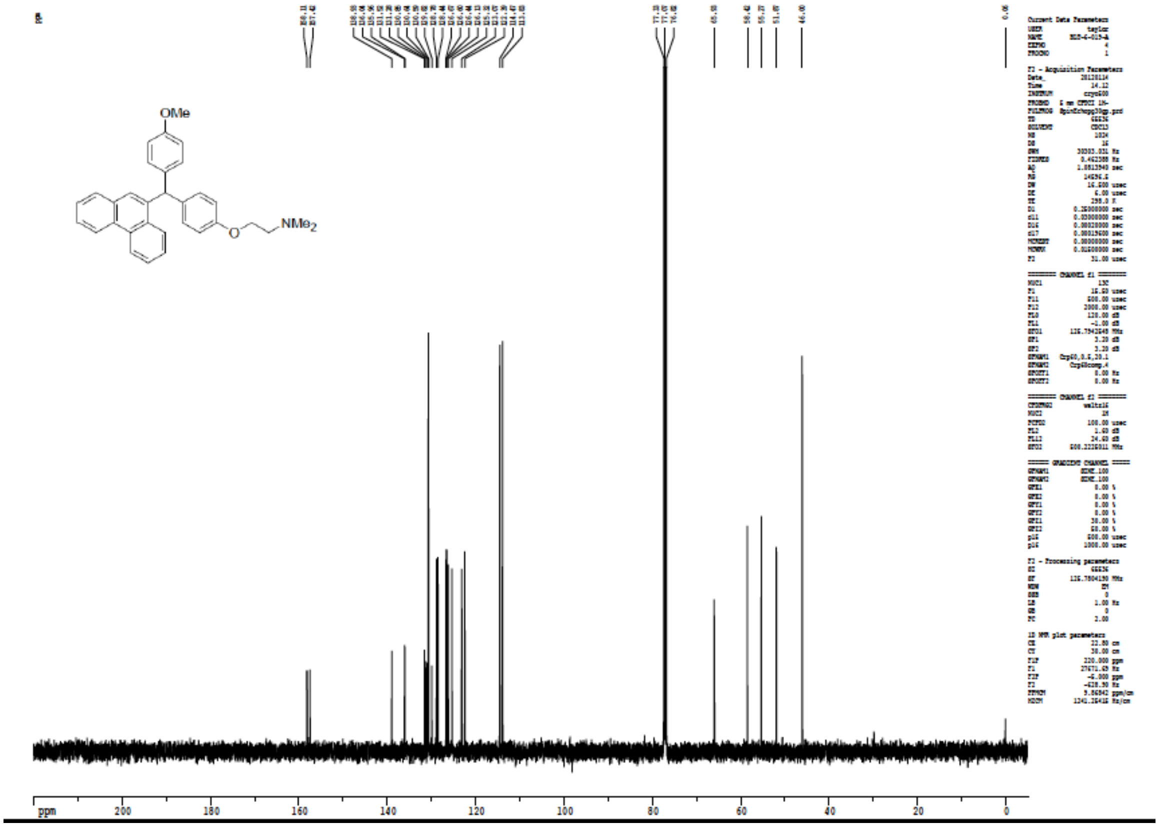
Z-restored spin-echo 13C spectrum with 1H decoupling

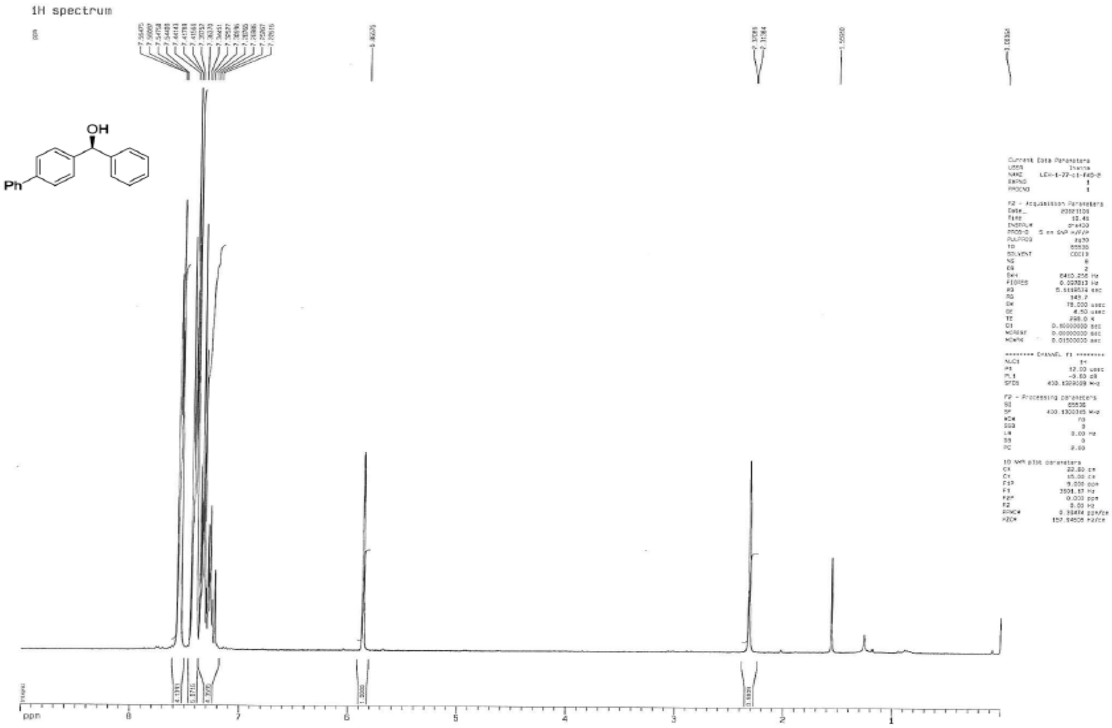


1H spectrum

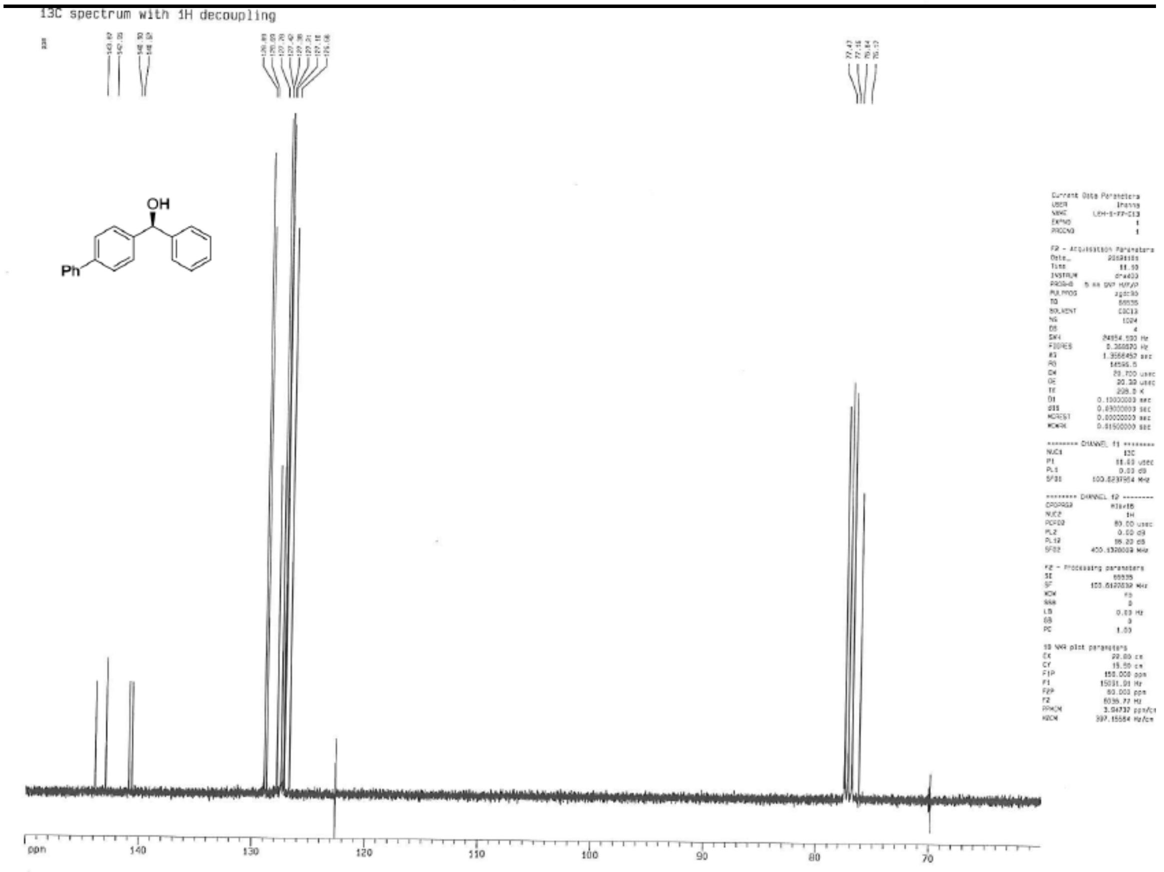


Z-restored spin-echo 13C spectrum with 1H decoupling



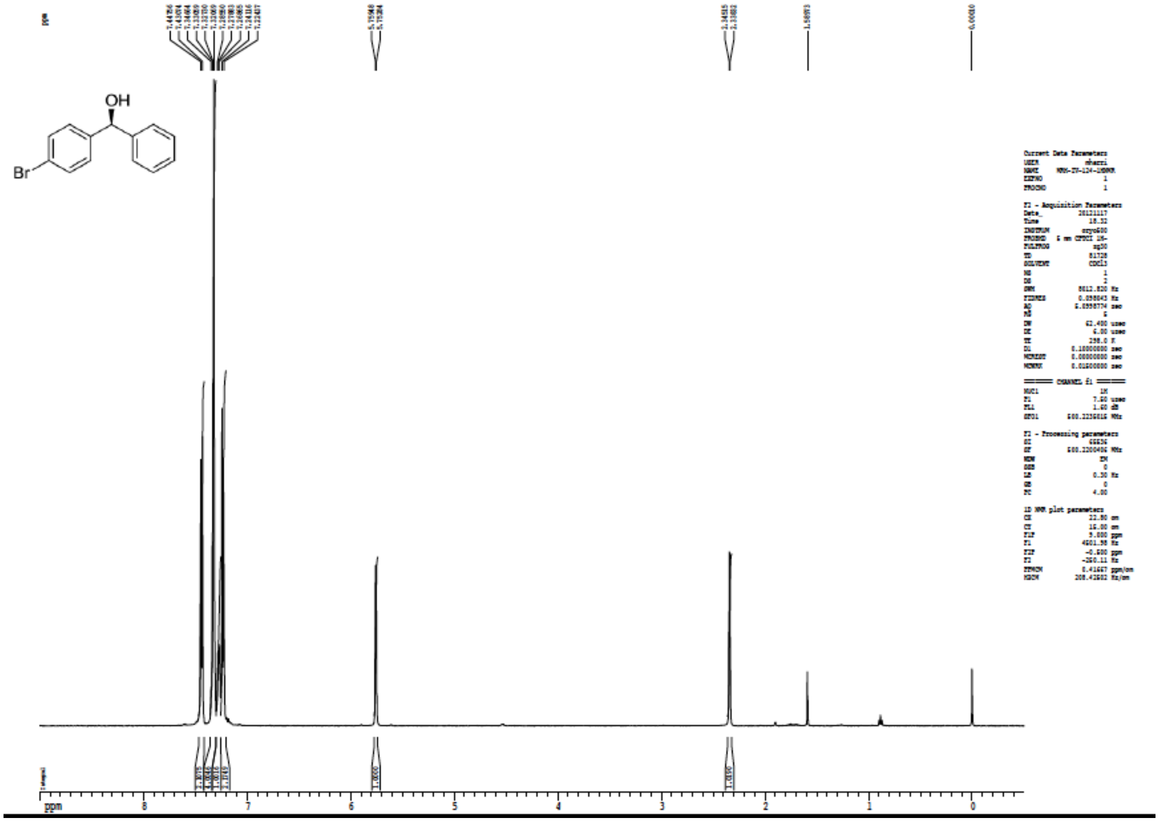


1H spectrum

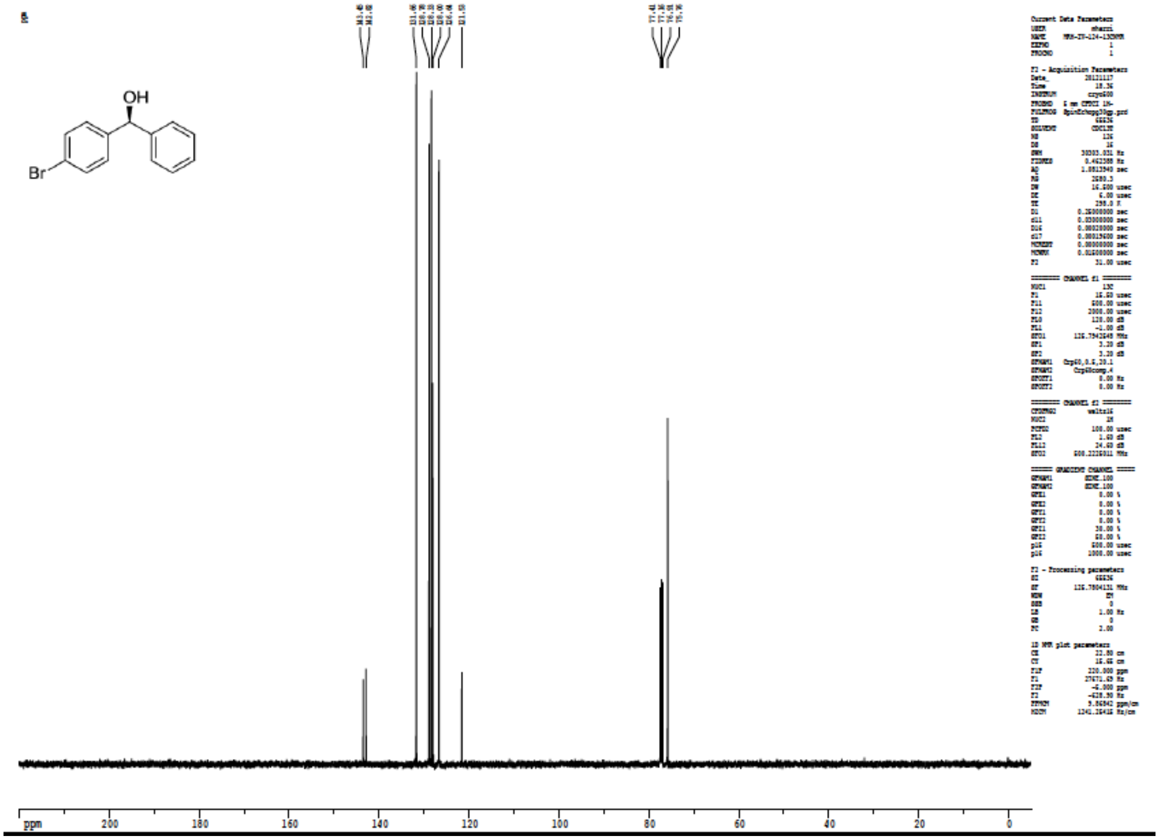


13C spectrum with 1H decoupling

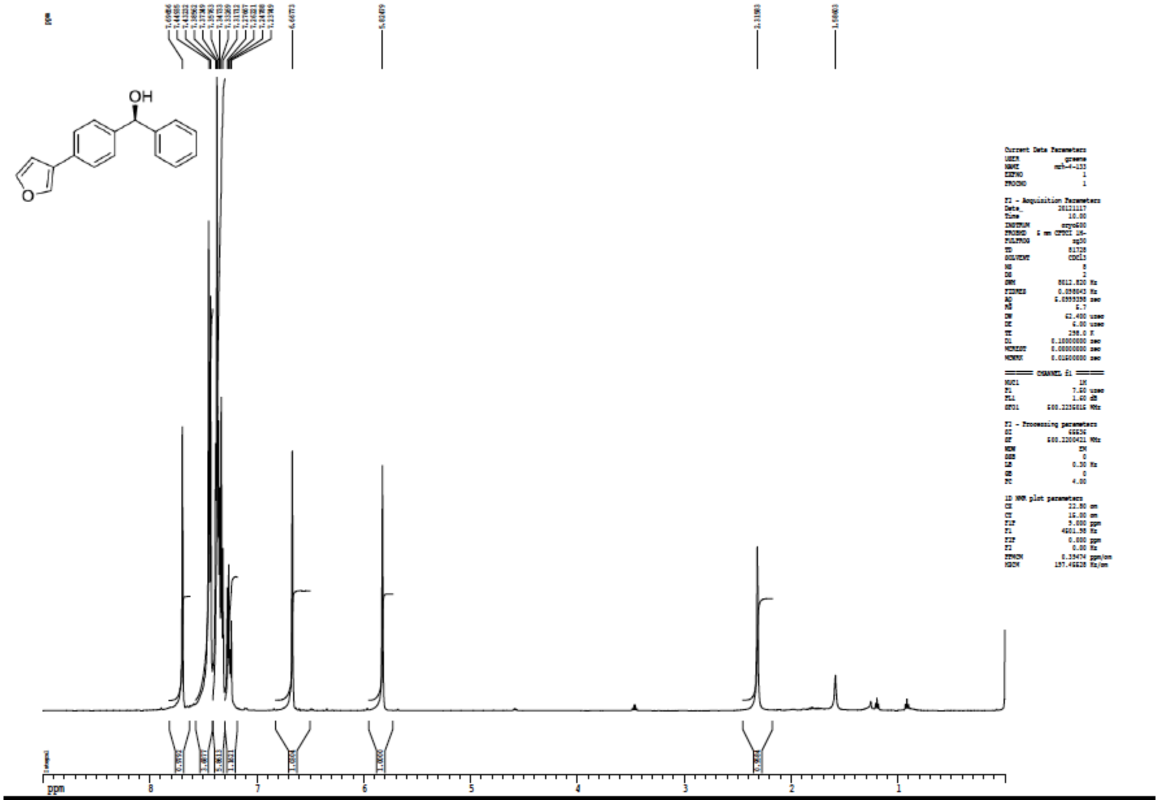
1H spectrum



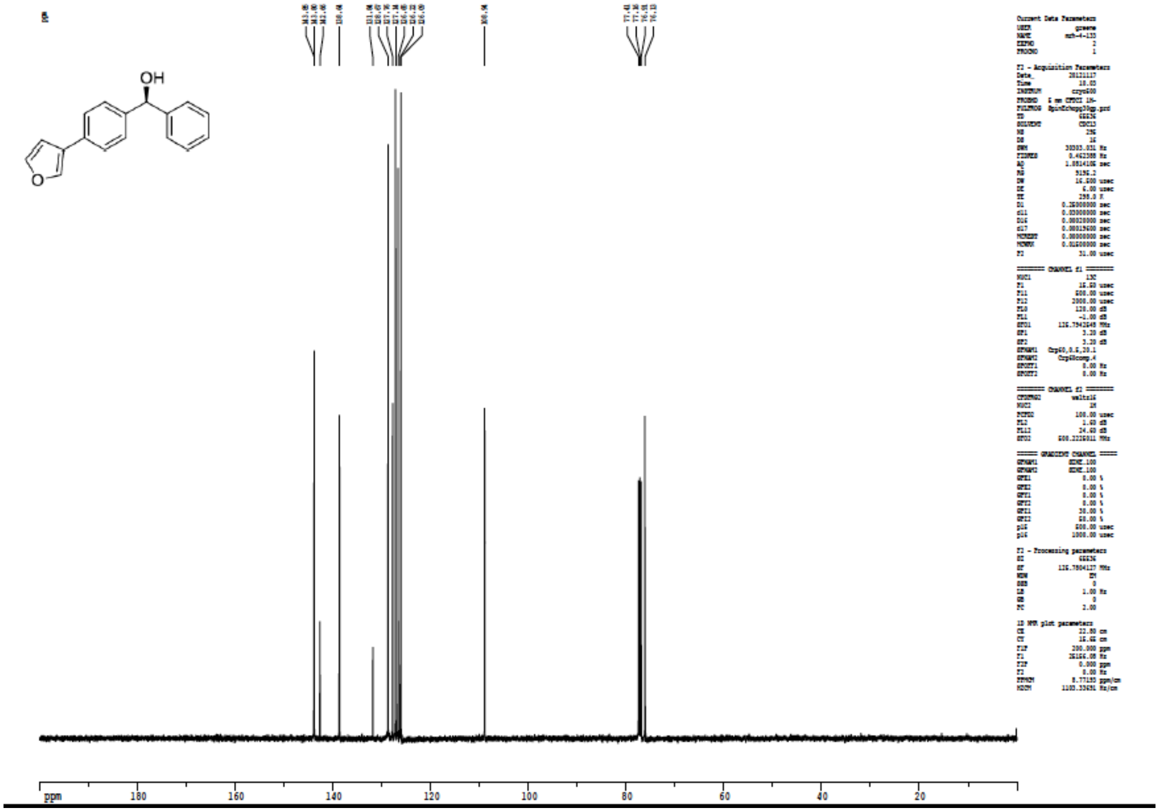
Z-restored spin-echo 13C spectrum with 1H decoupling



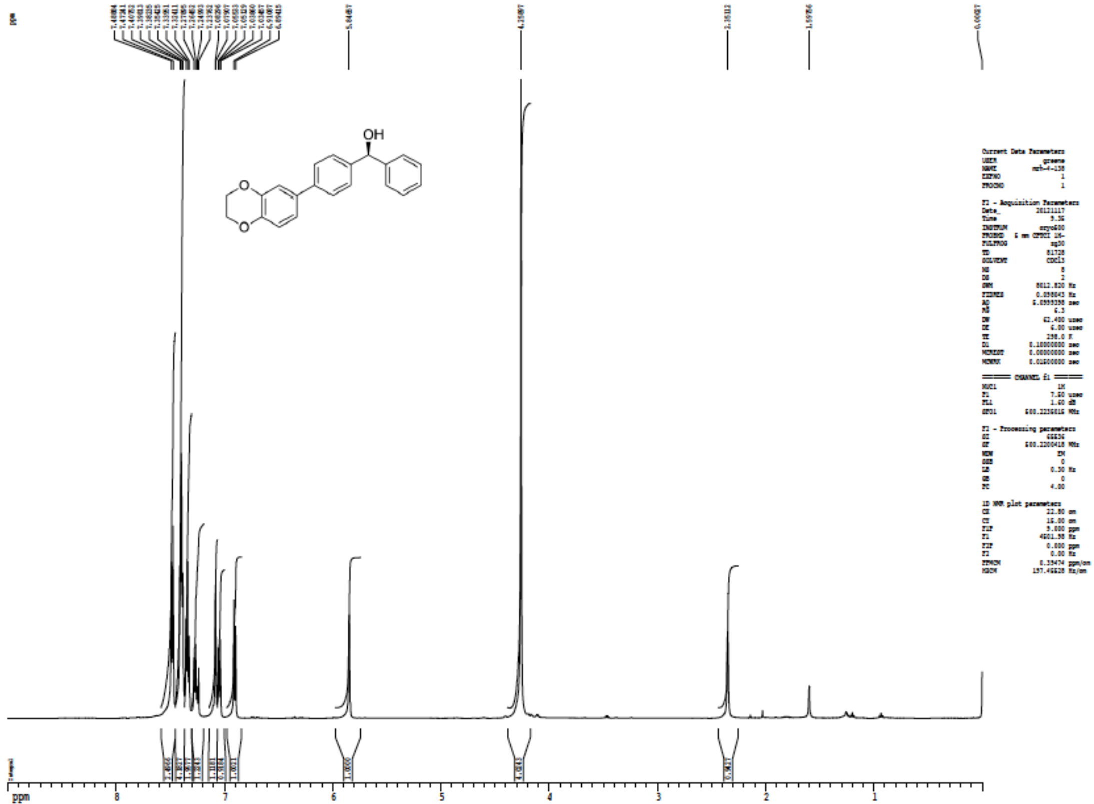
1H spectrum



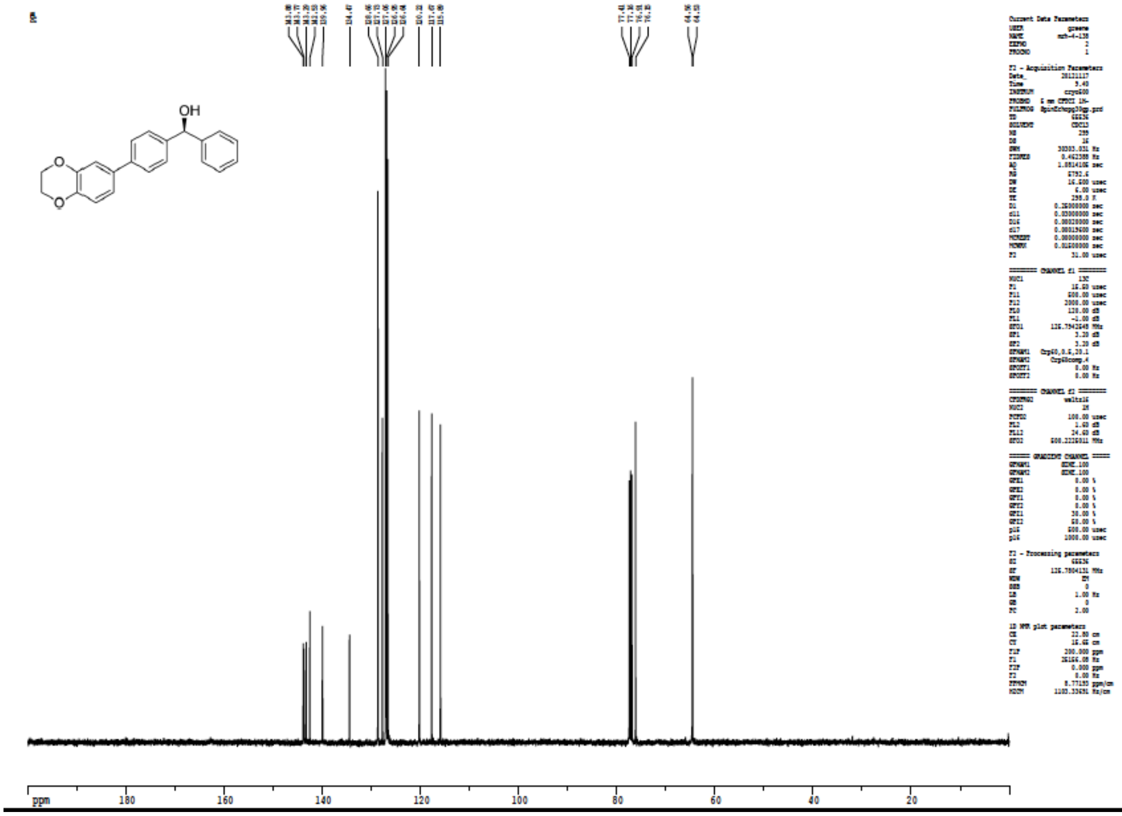
Z-restored spin-echo 13C spectrum with 1H decoupling



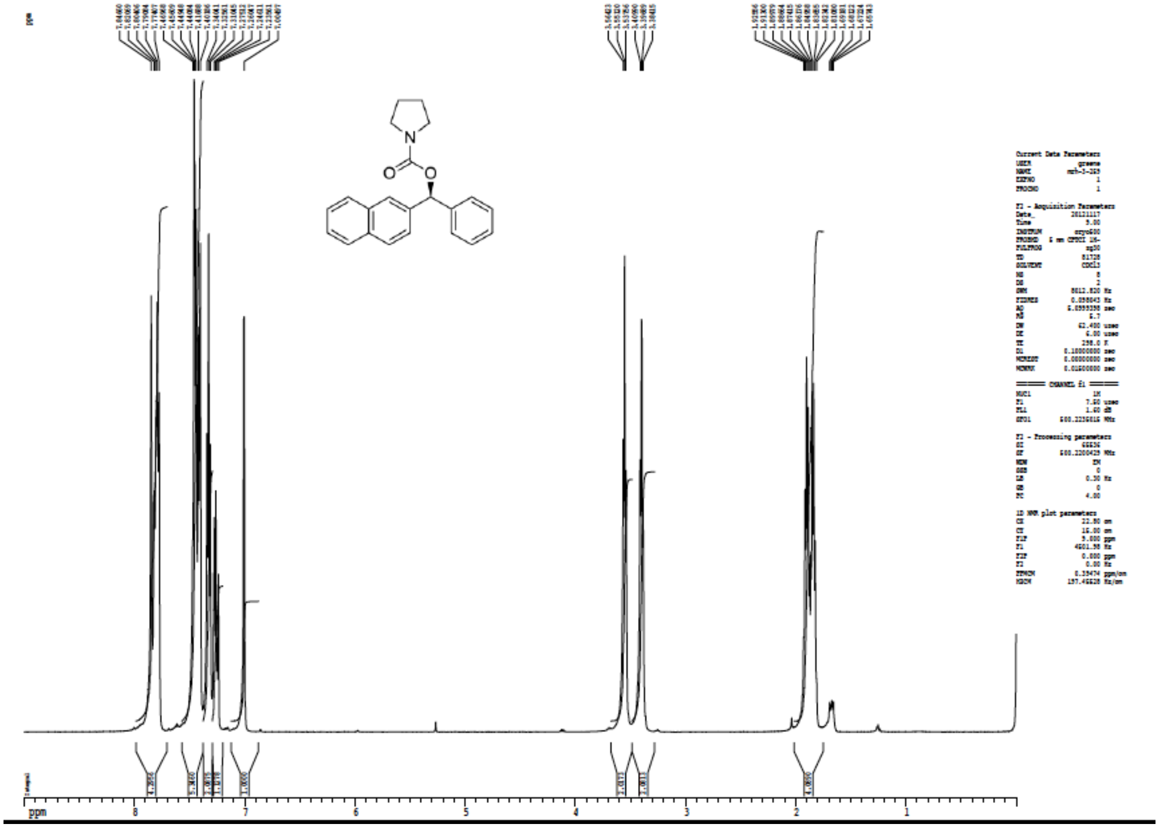
1H spectrum



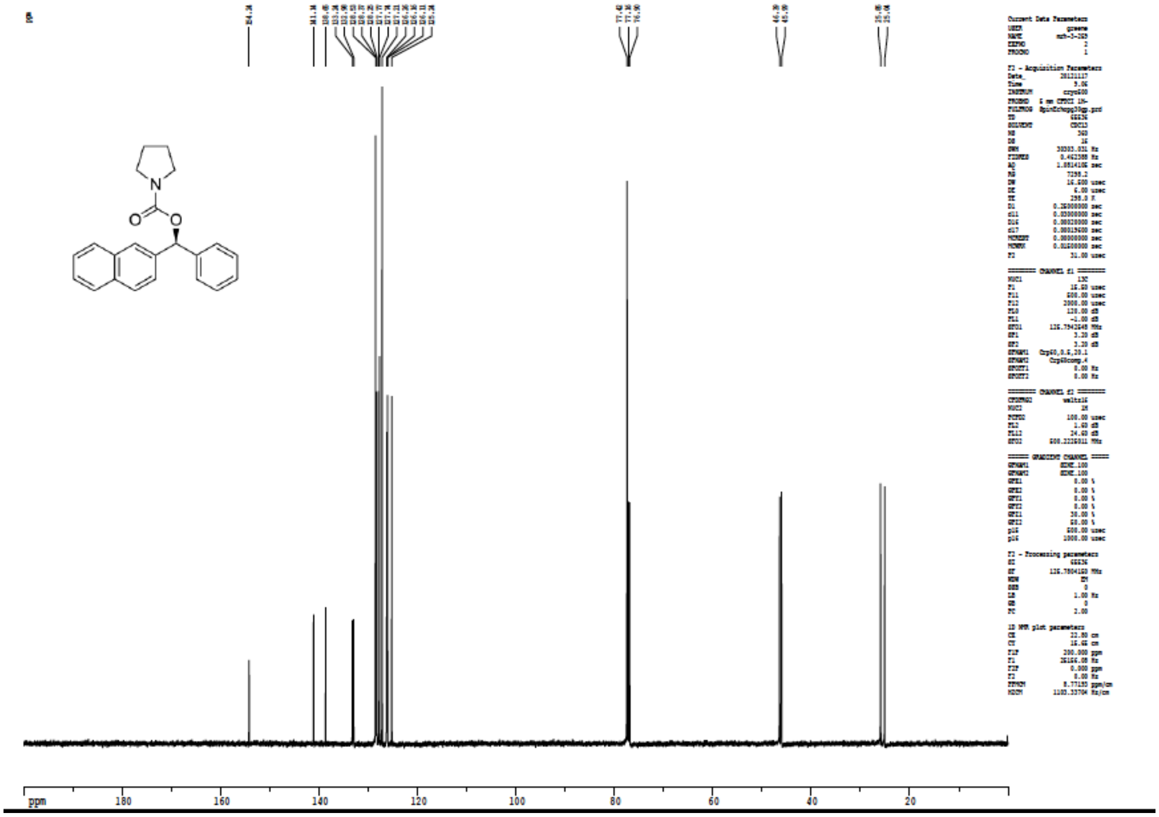
Z-restored spin-echo 13C spectrum with 1H decoupling



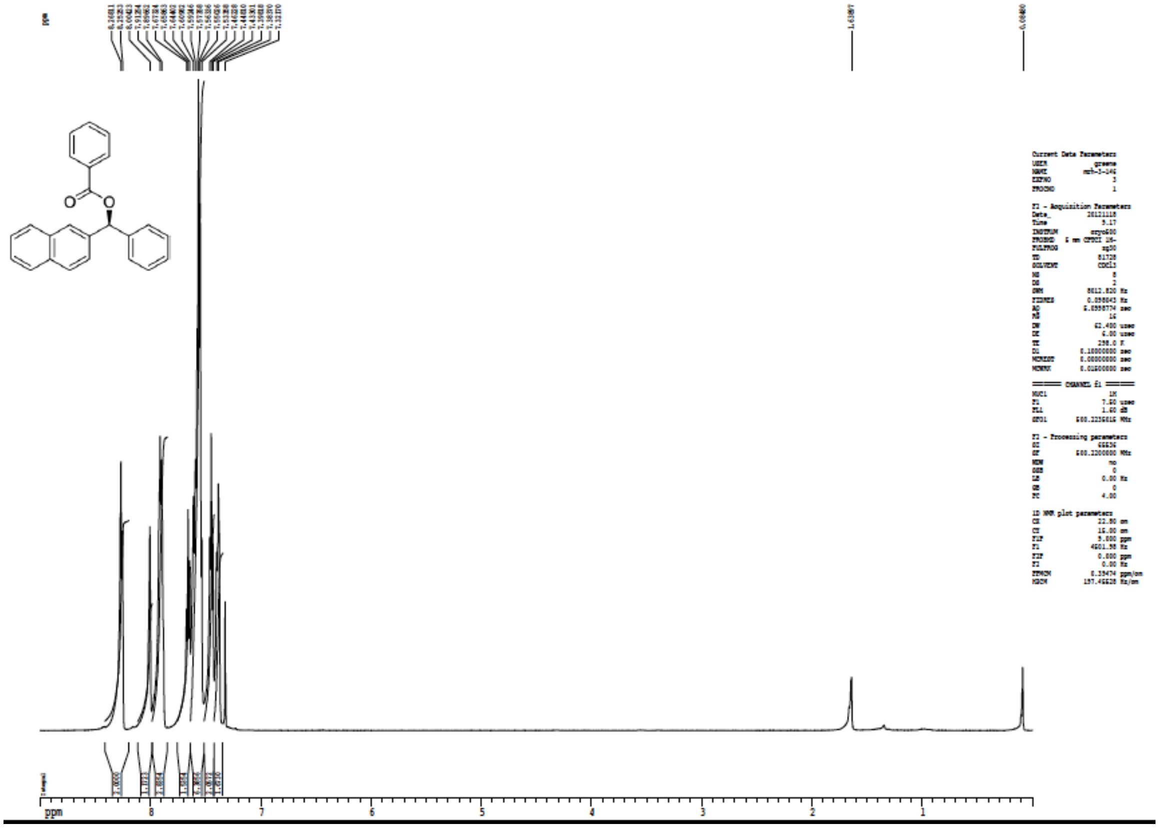
1H spectrum



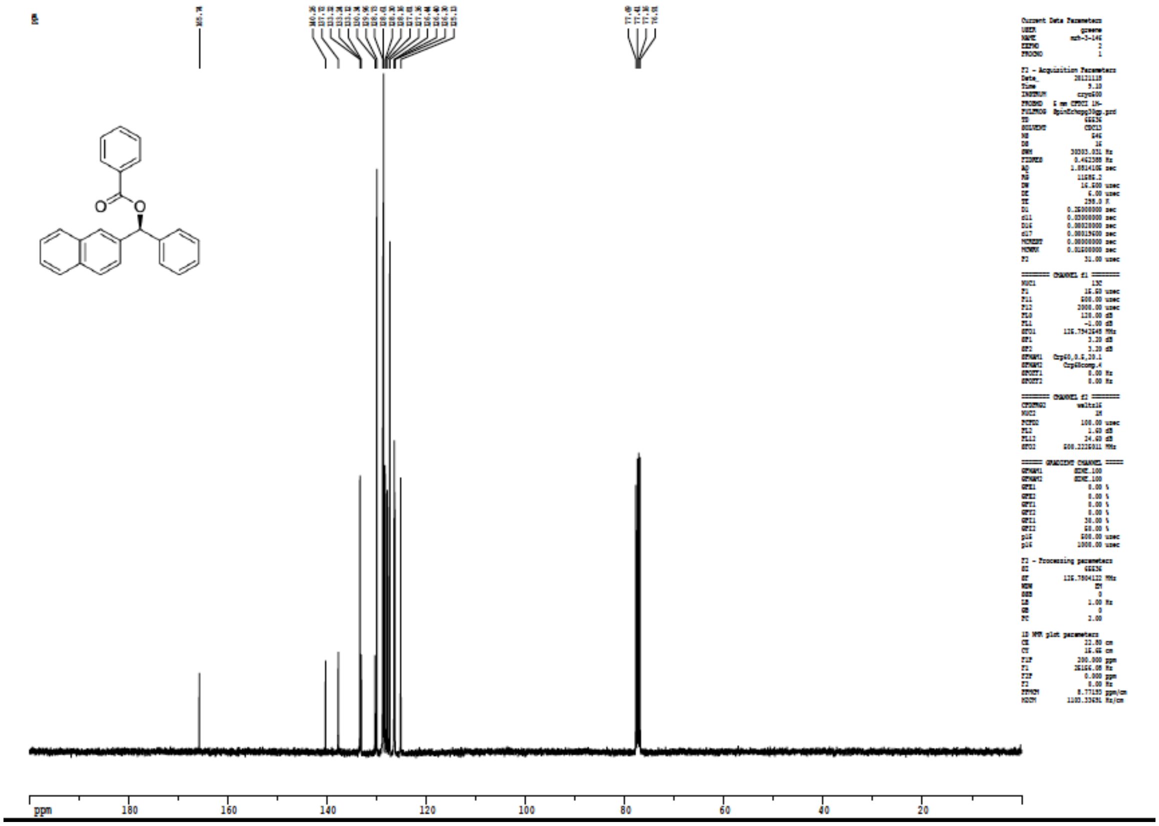
Z-restored spin-echo 13C spectrum with 1H decoupling



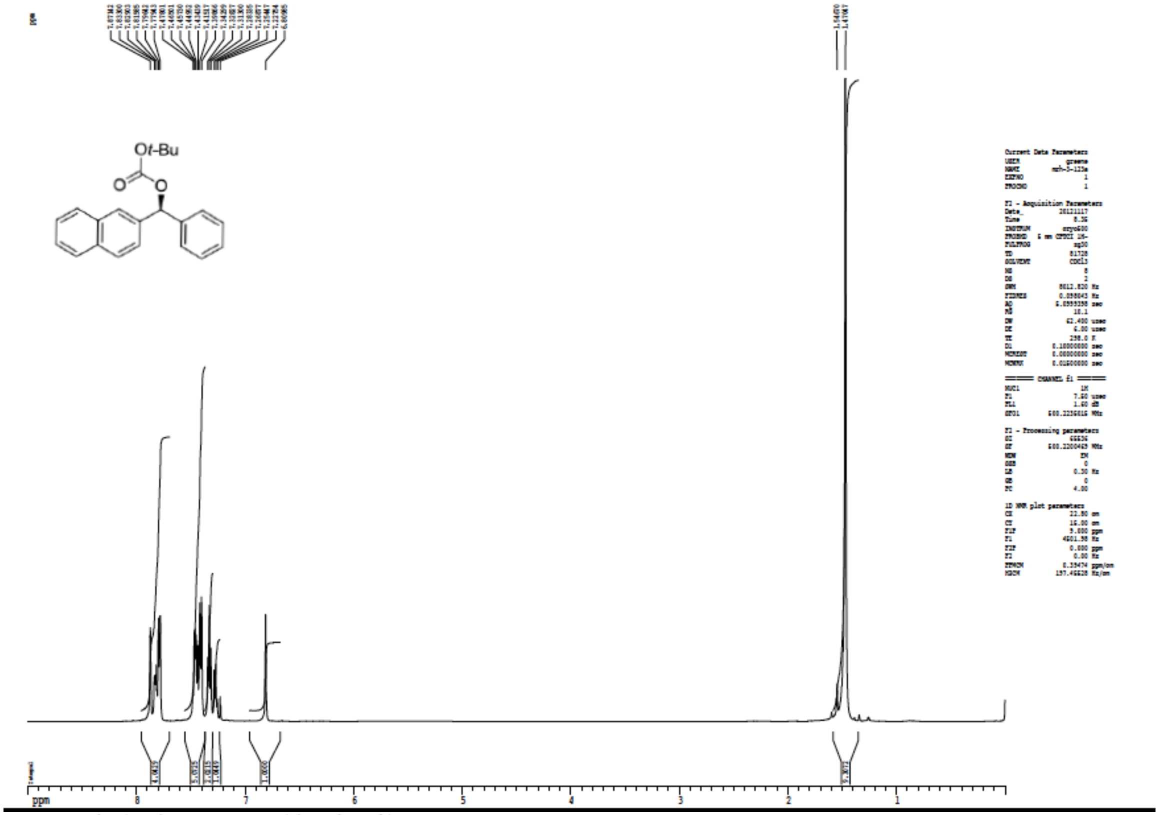
1H spectrum



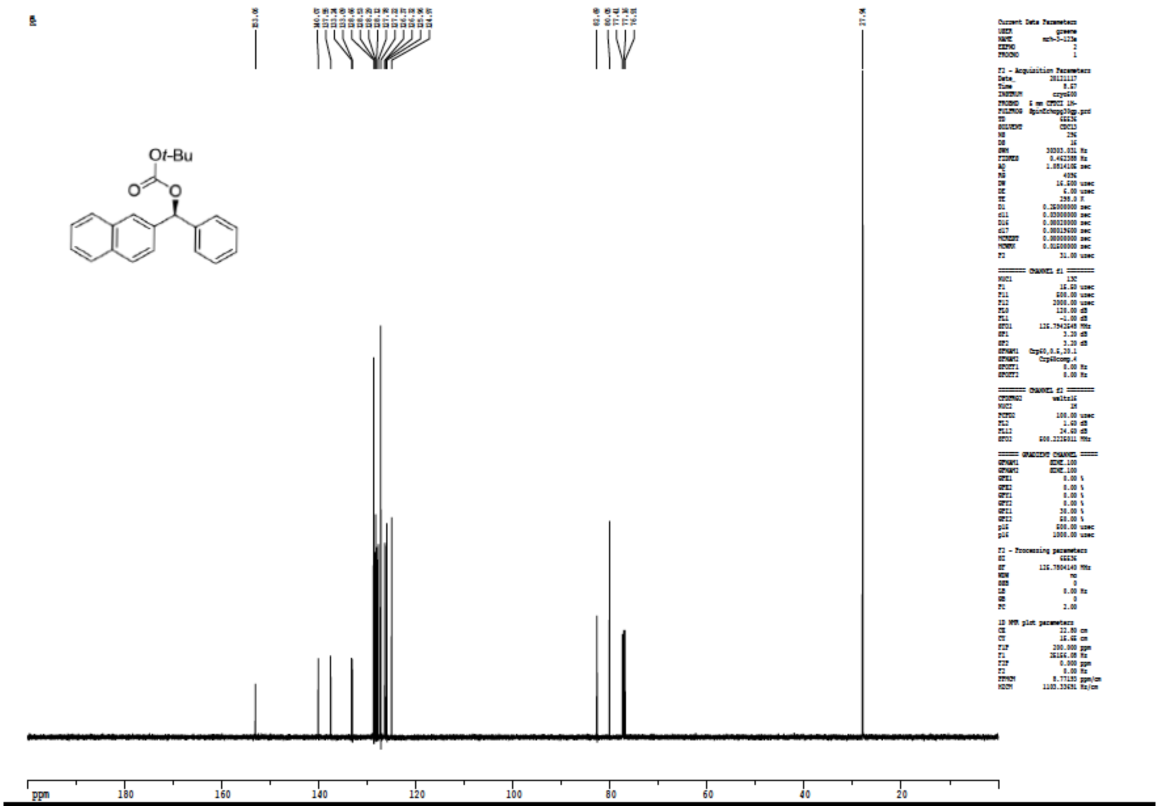
Z-restored spin-echo 13C spectrum with 1H decoupling



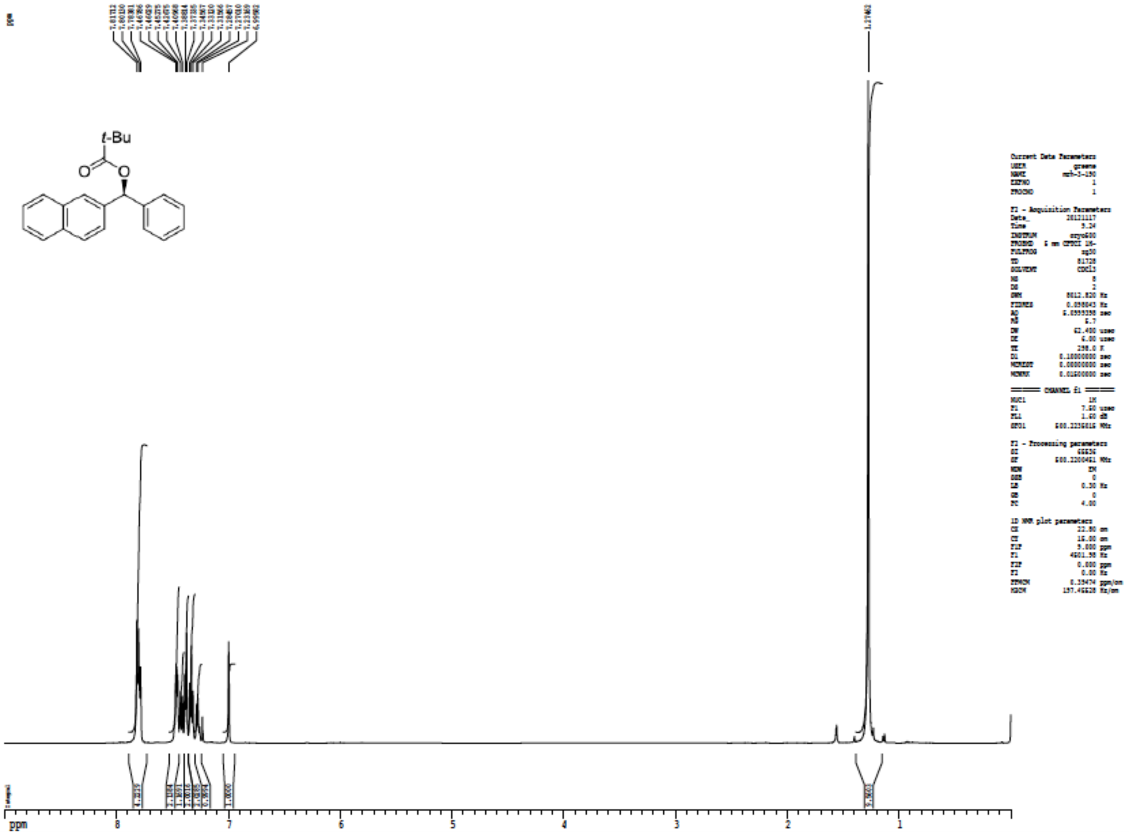
1H spectrum



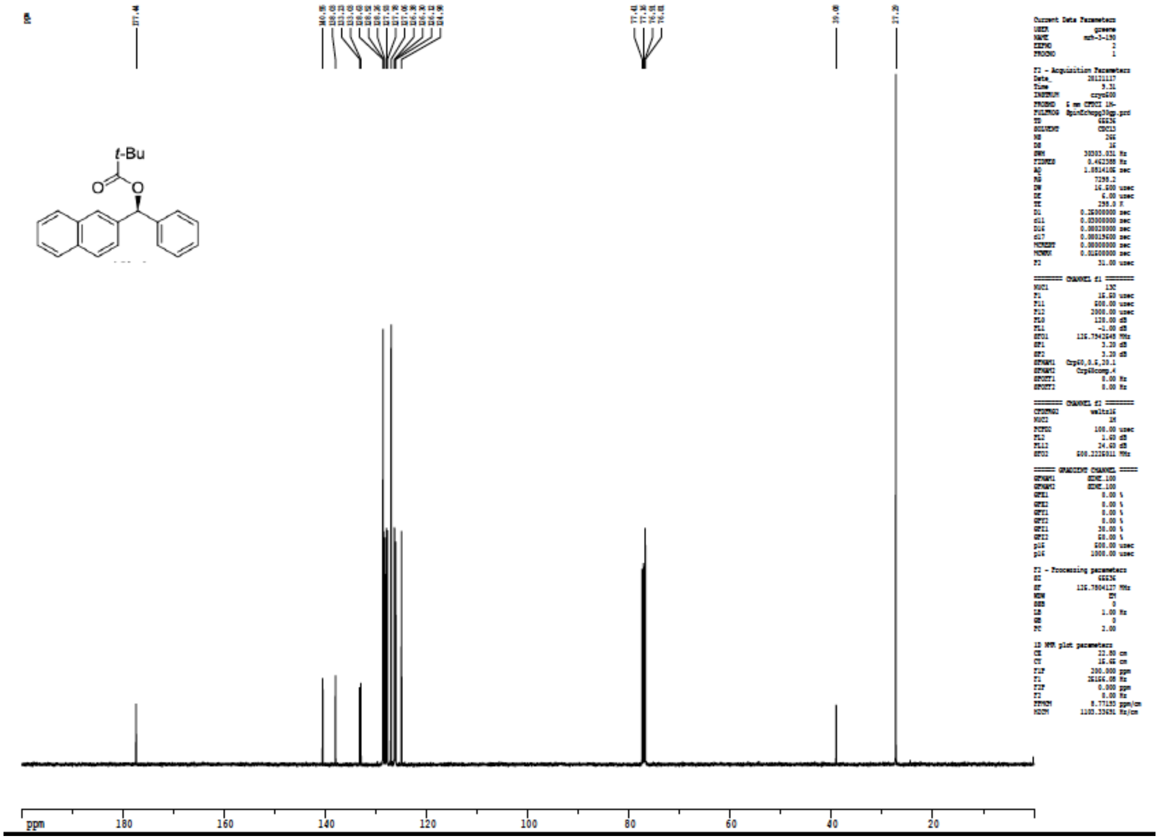
Z-restored spin-echo 13C spectrum with 1H decoupling

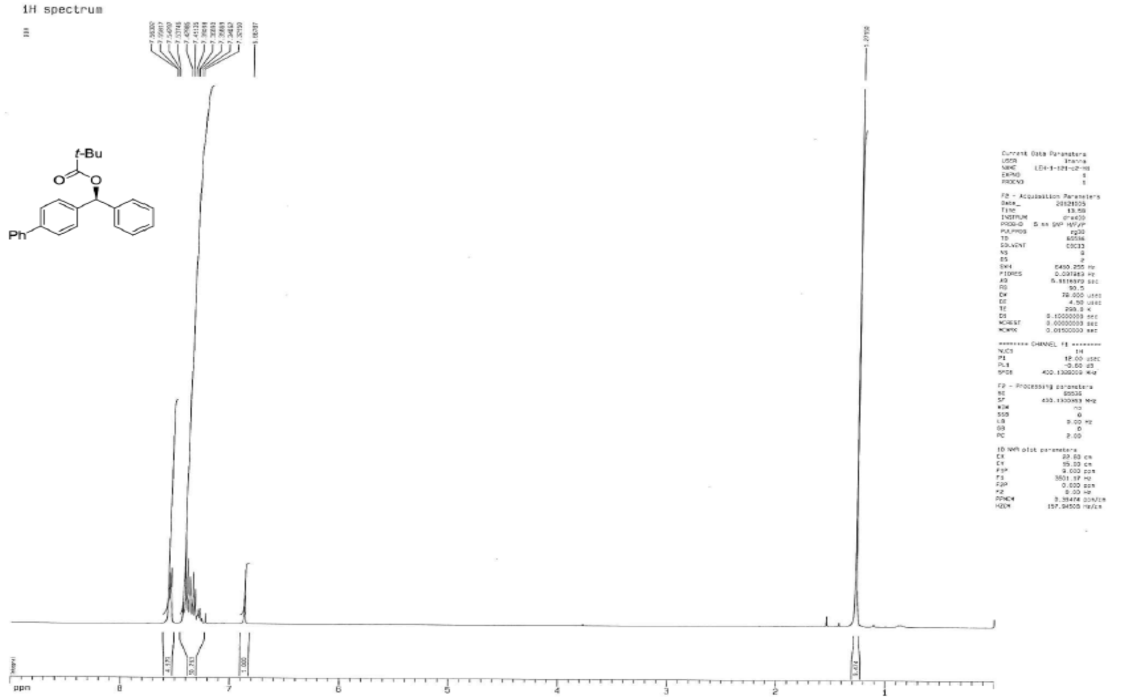


1H spectrum

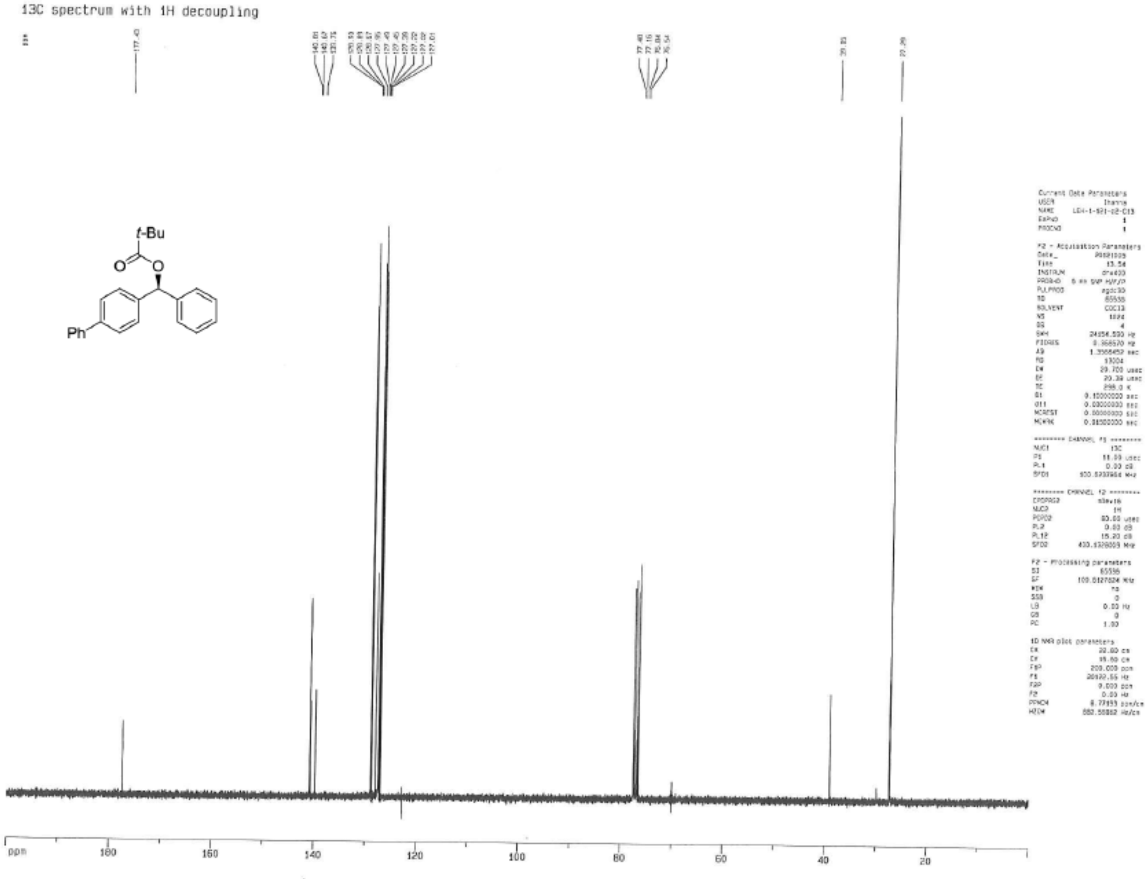


Z-restored spin-echo 13C spectrum with 1H decoupling



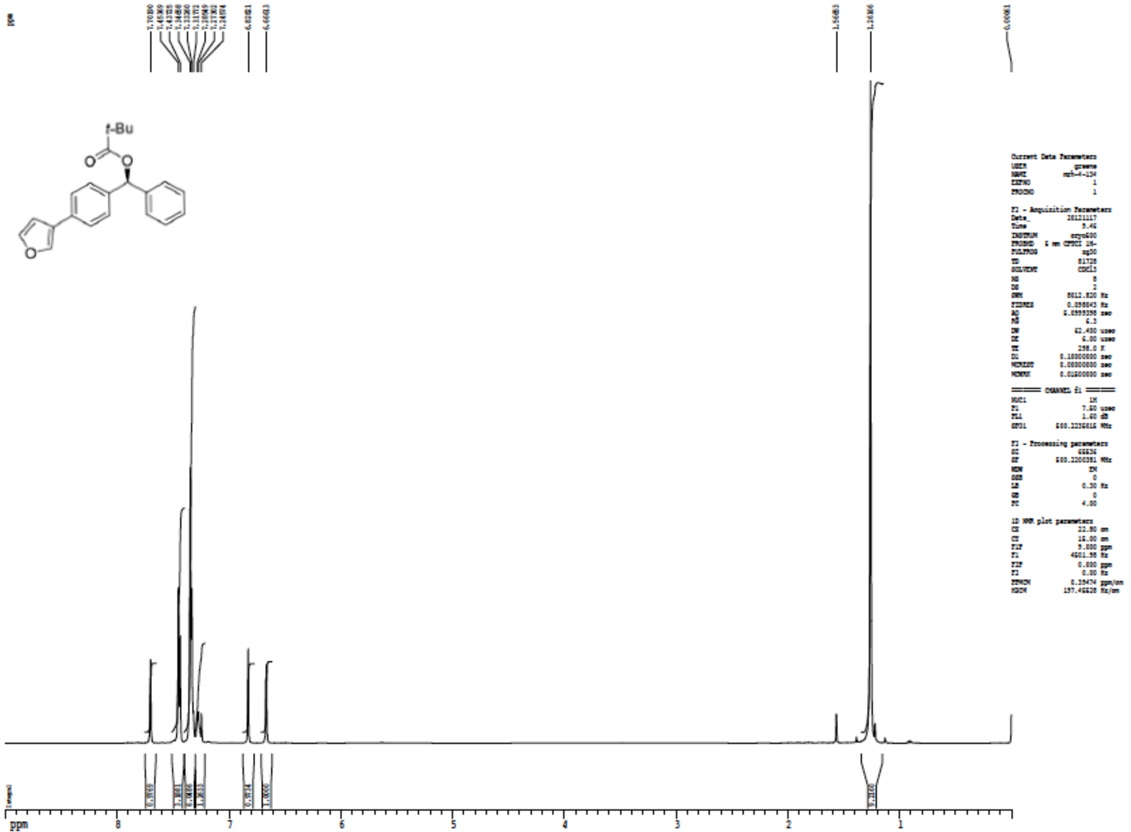


1H spectrum
t-Bu
O
O
Ph
ppm
8
7
6
5
4
3
2
1

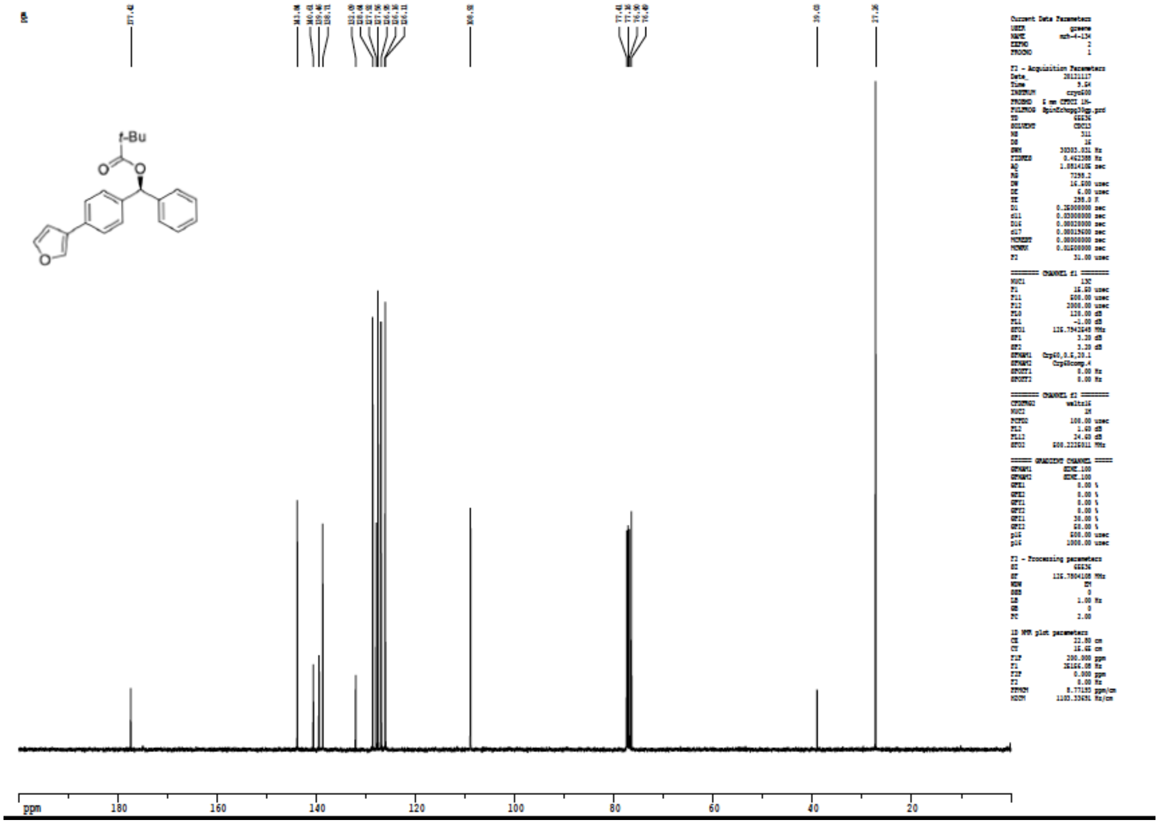


13C spectrum with 1H decoupling
177.43
t-Bu
O
O
Ph
ppm
180
160
140
120
100
80
60
40
20

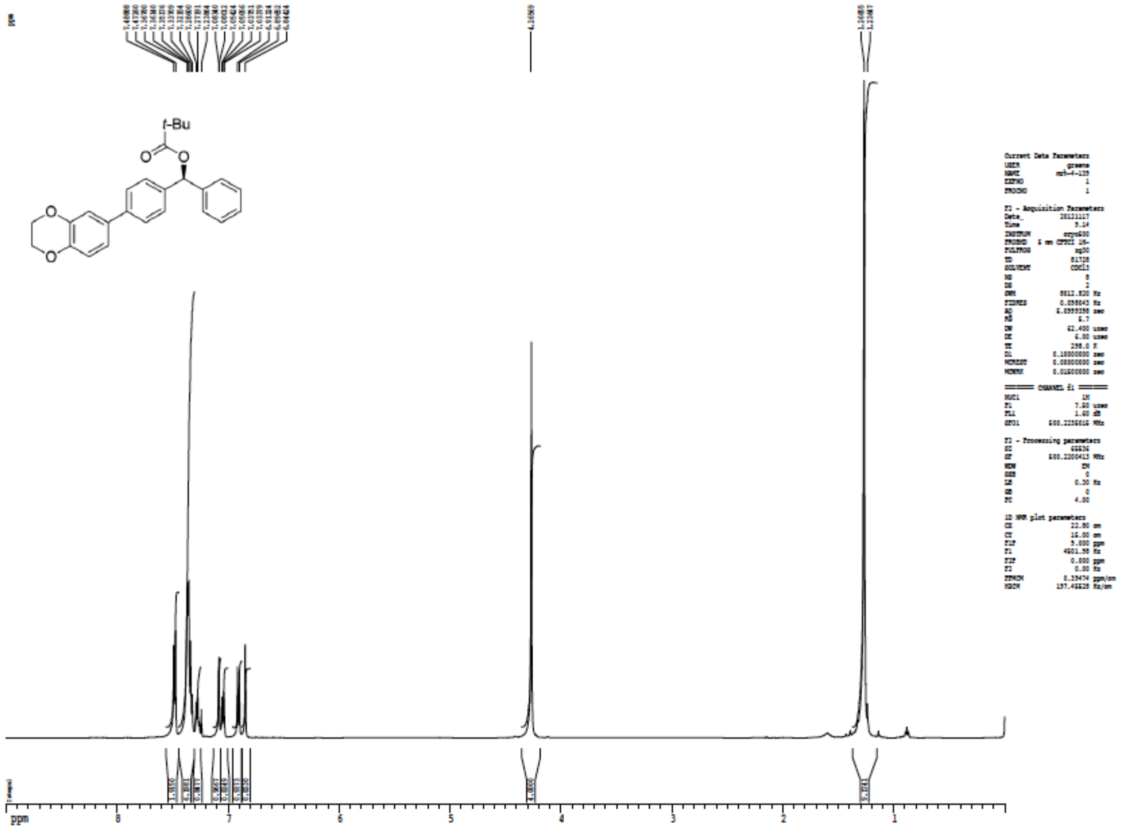
1H spectrum



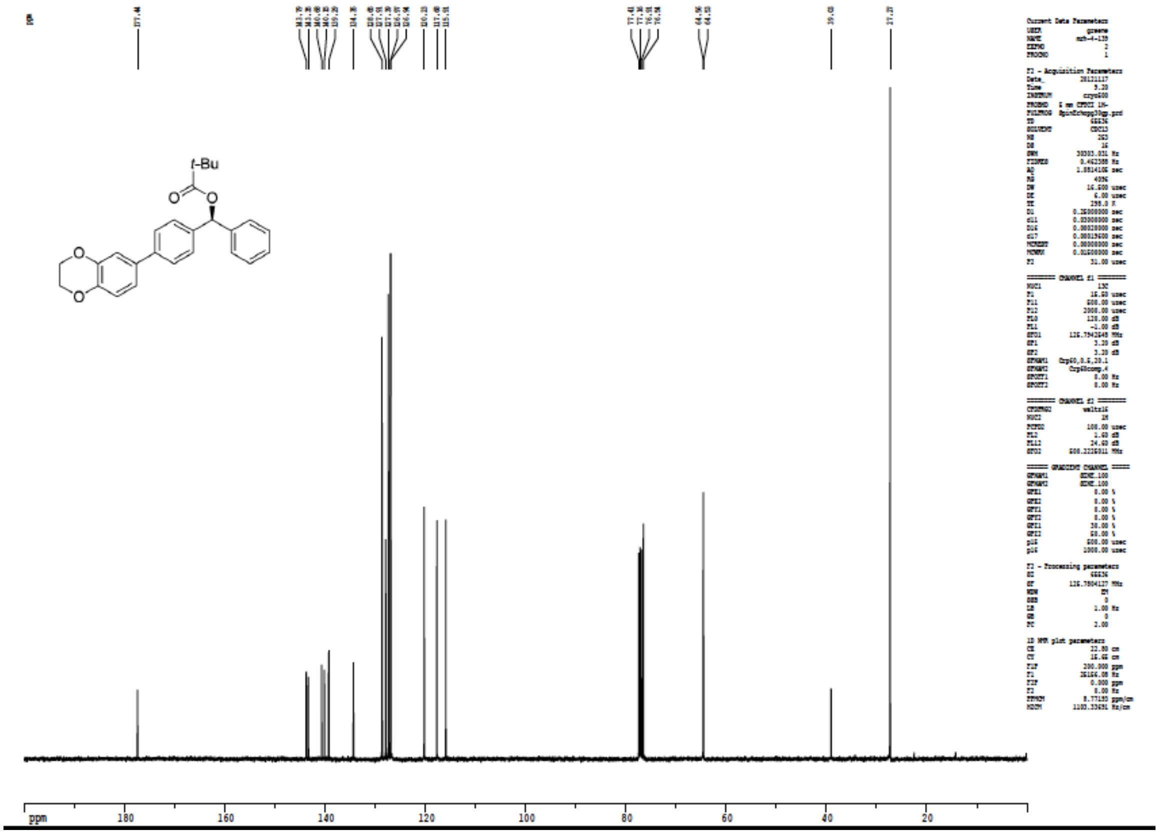
Z-restored spin-echo 13C spectrum with 1H decoupling



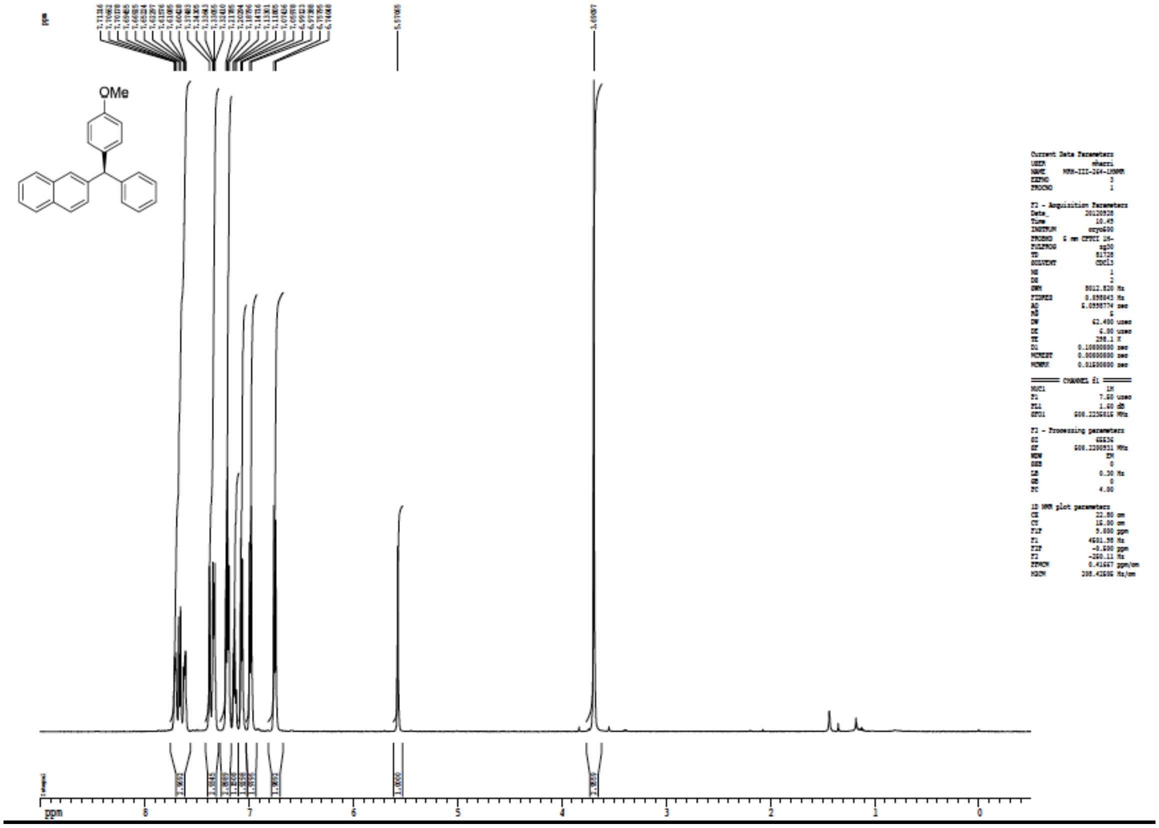
1H spectrum



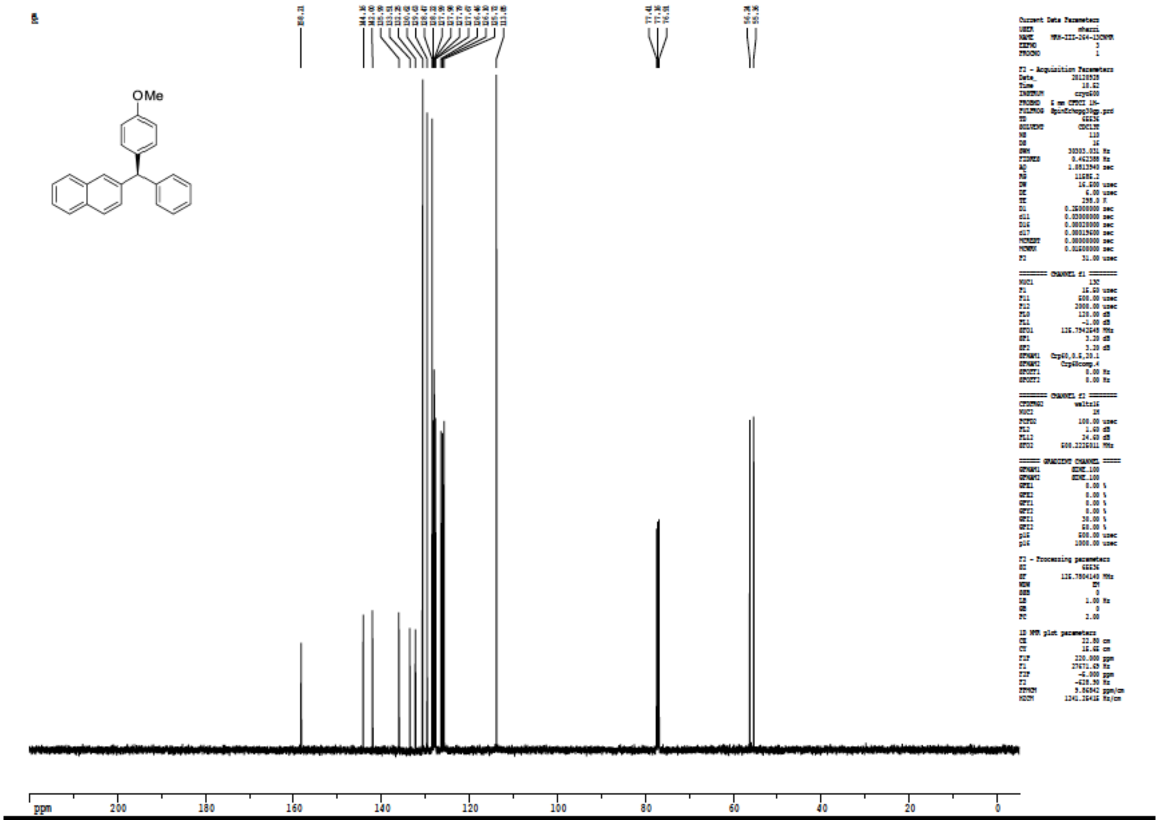
Z-restored spin-echo 13C spectrum with 1H decoupling

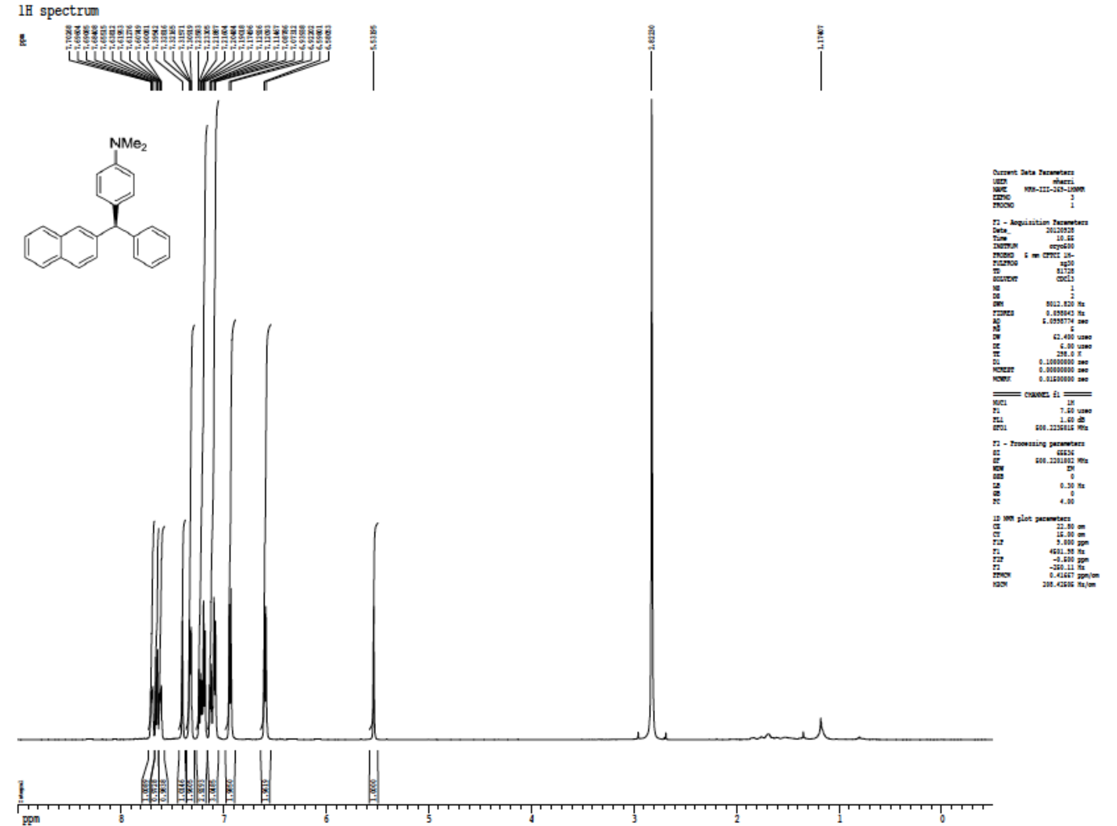


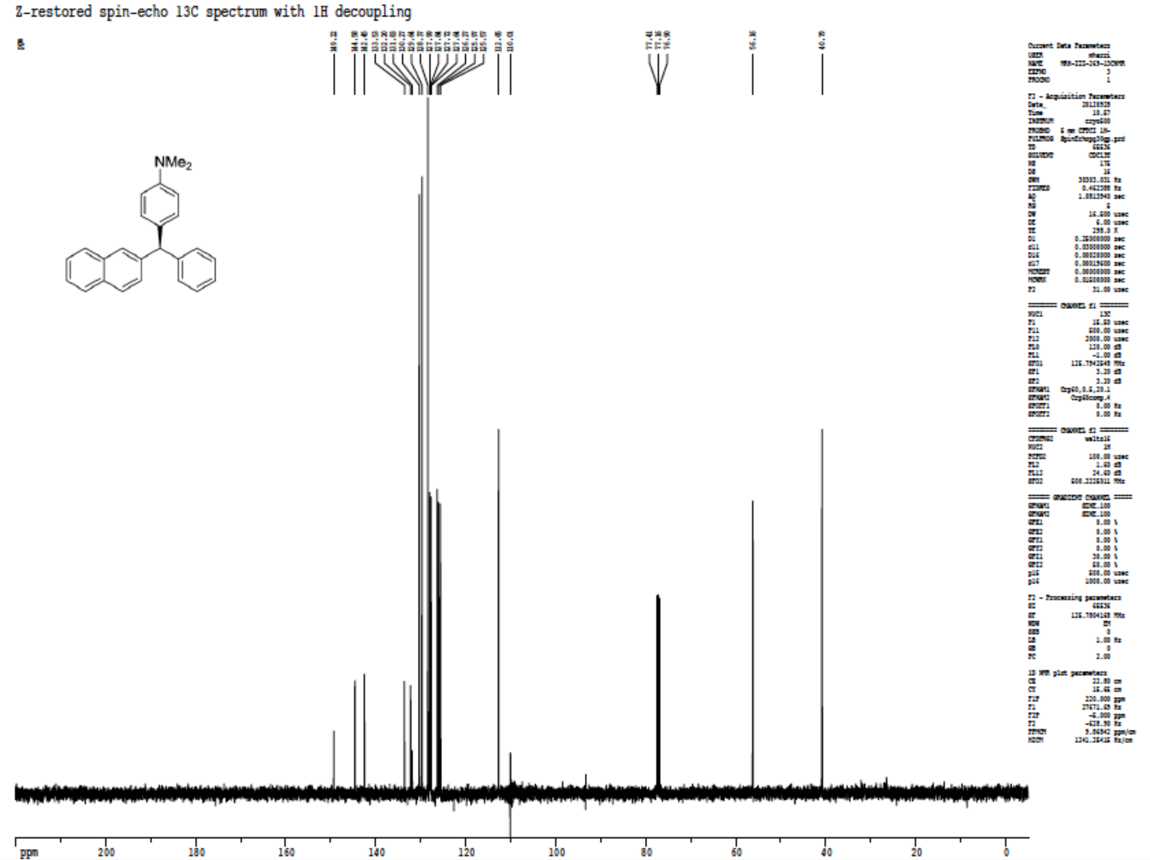
1H spectrum



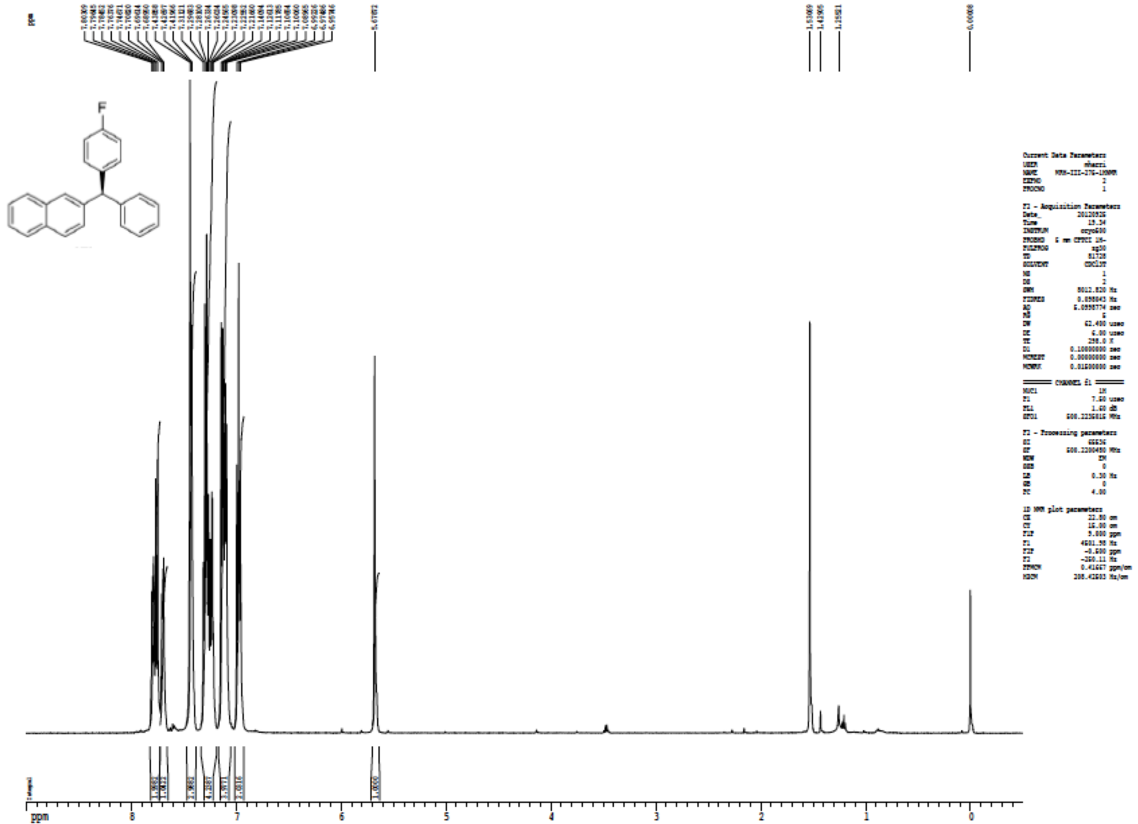
Z-restored spin-echo 13C spectrum with 1H decoupling



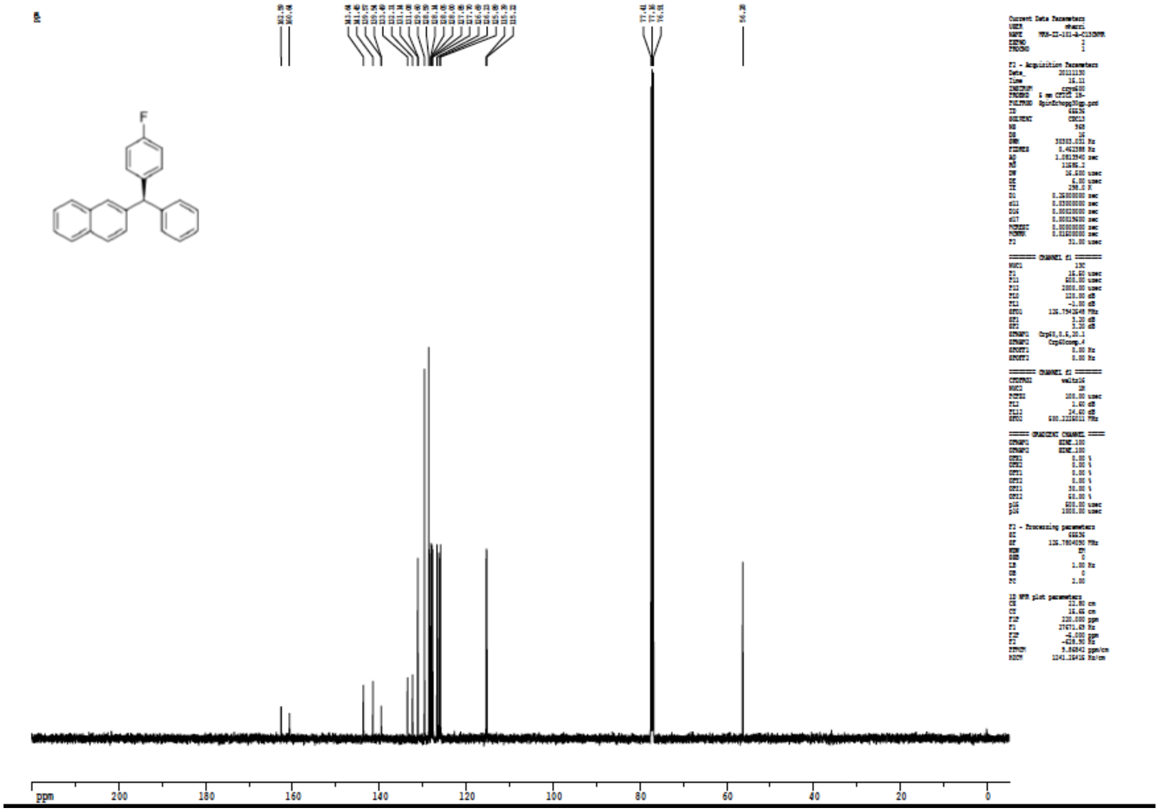

1H spectrum


Z-restored spin-echo 13C spectrum with 1H decoupling

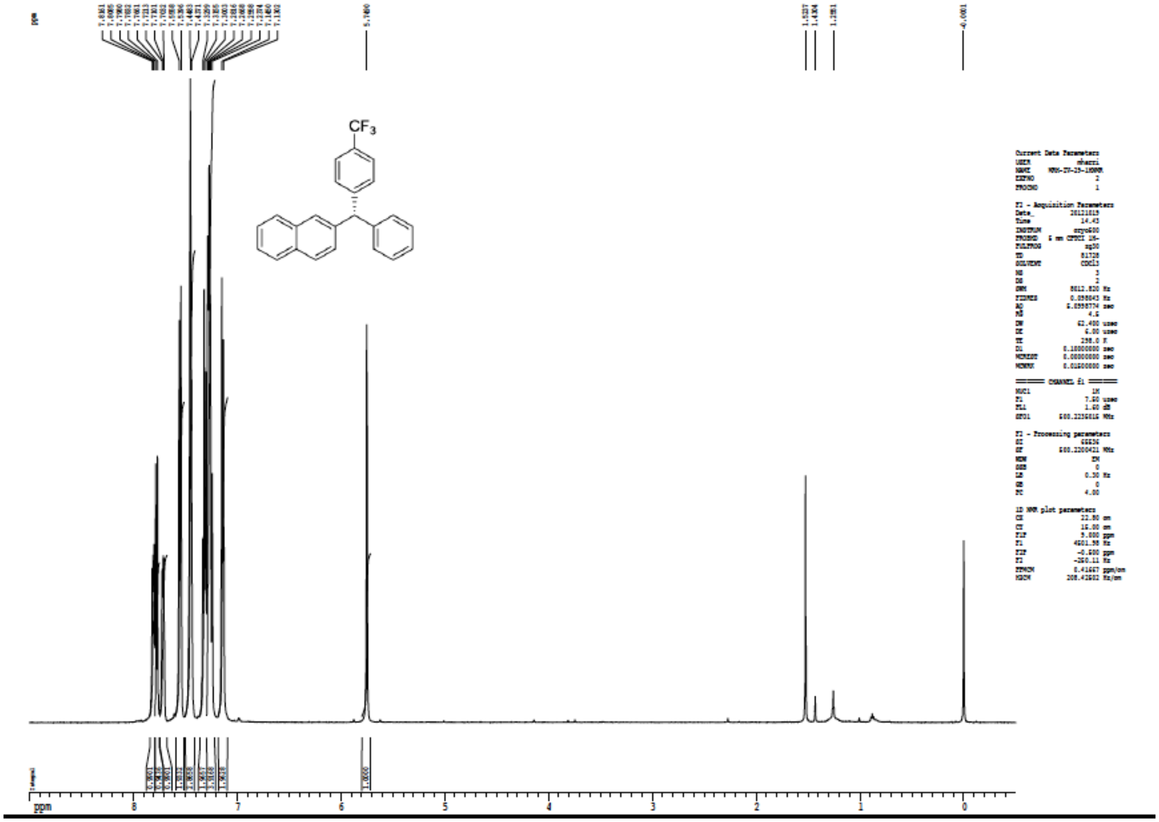
1H spectrum



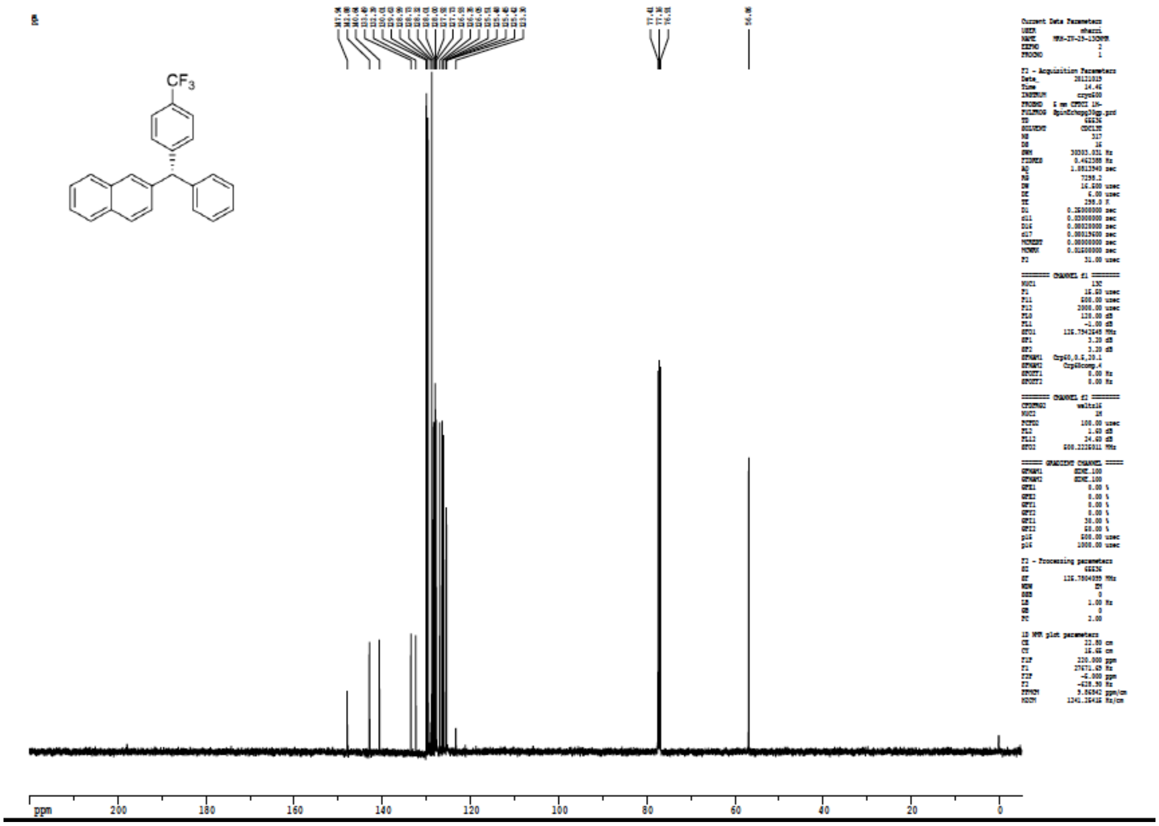
Z-restored spin-echo 13C spectrum with 1H decoupling



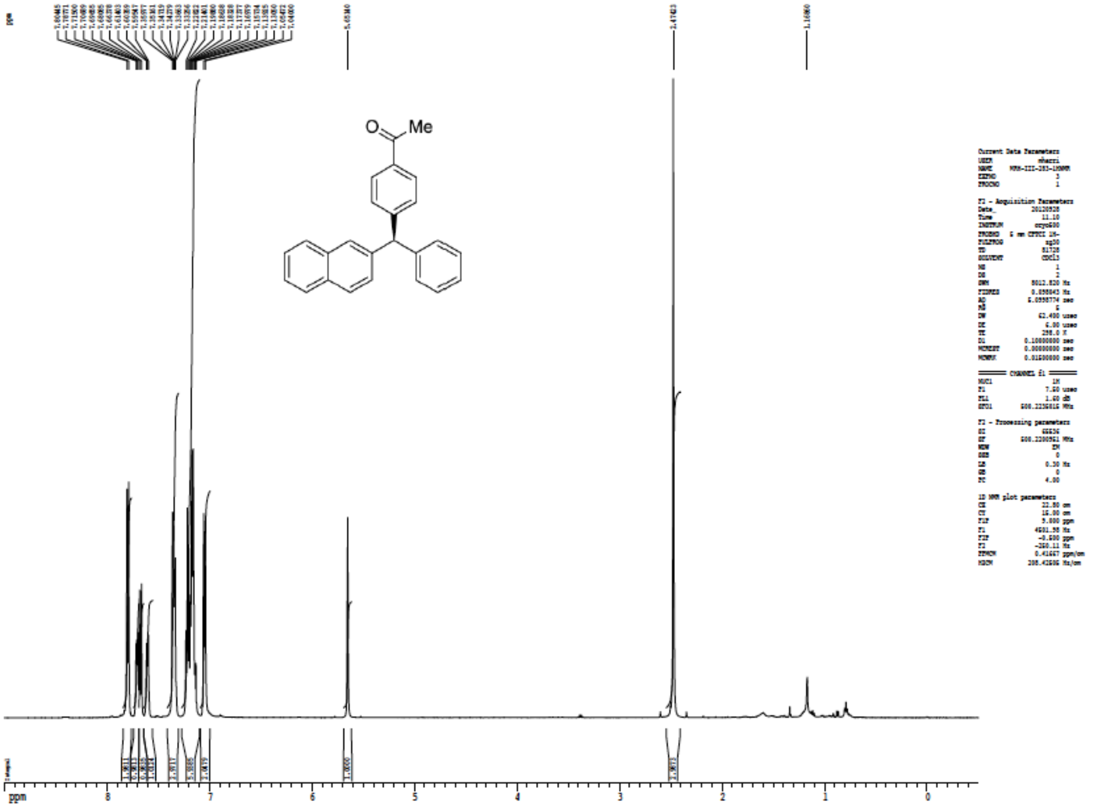
1H spectrum



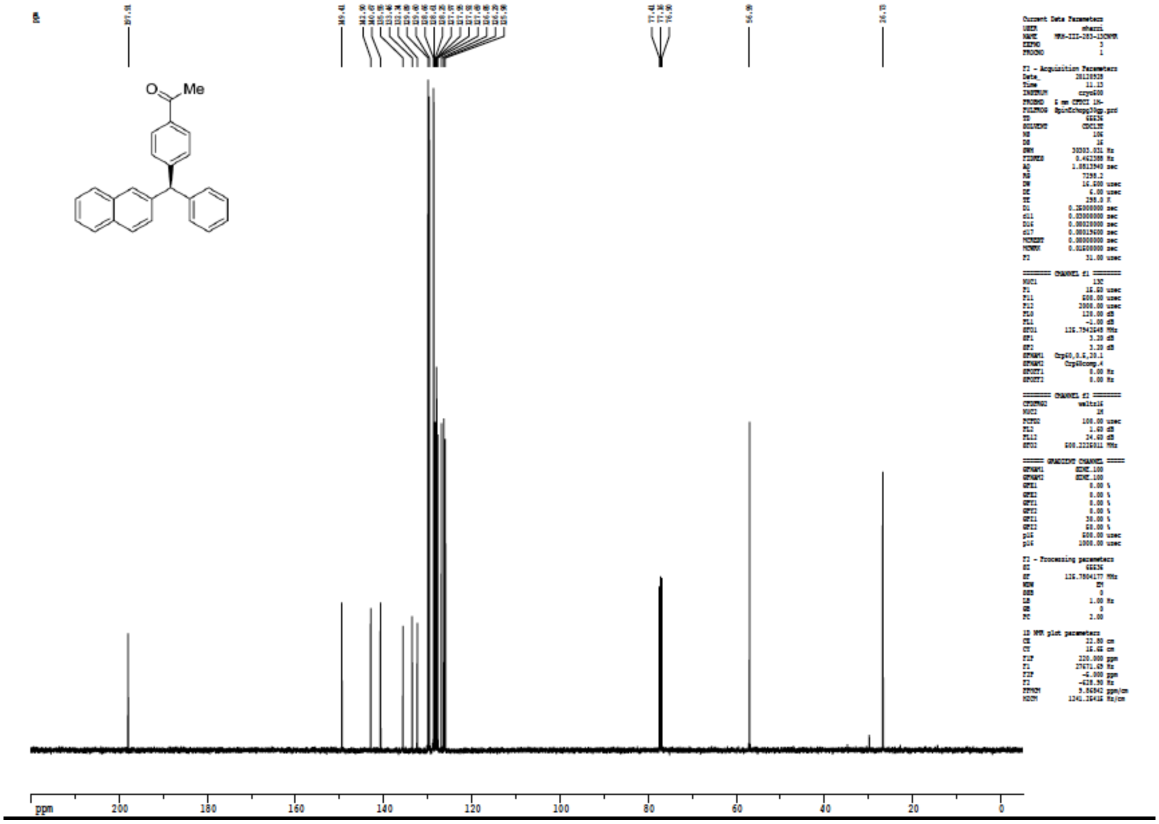
Z-restored spin-echo 13C spectrum with 1H decoupling



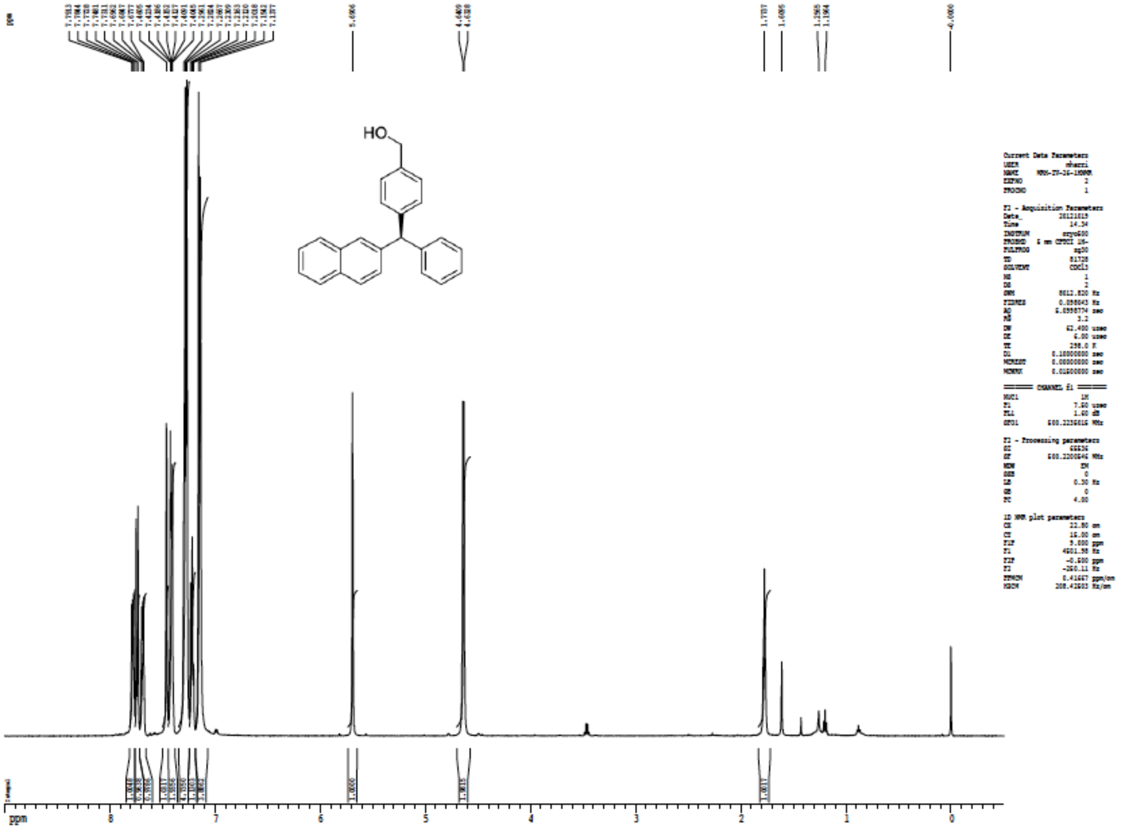
1H spectrum



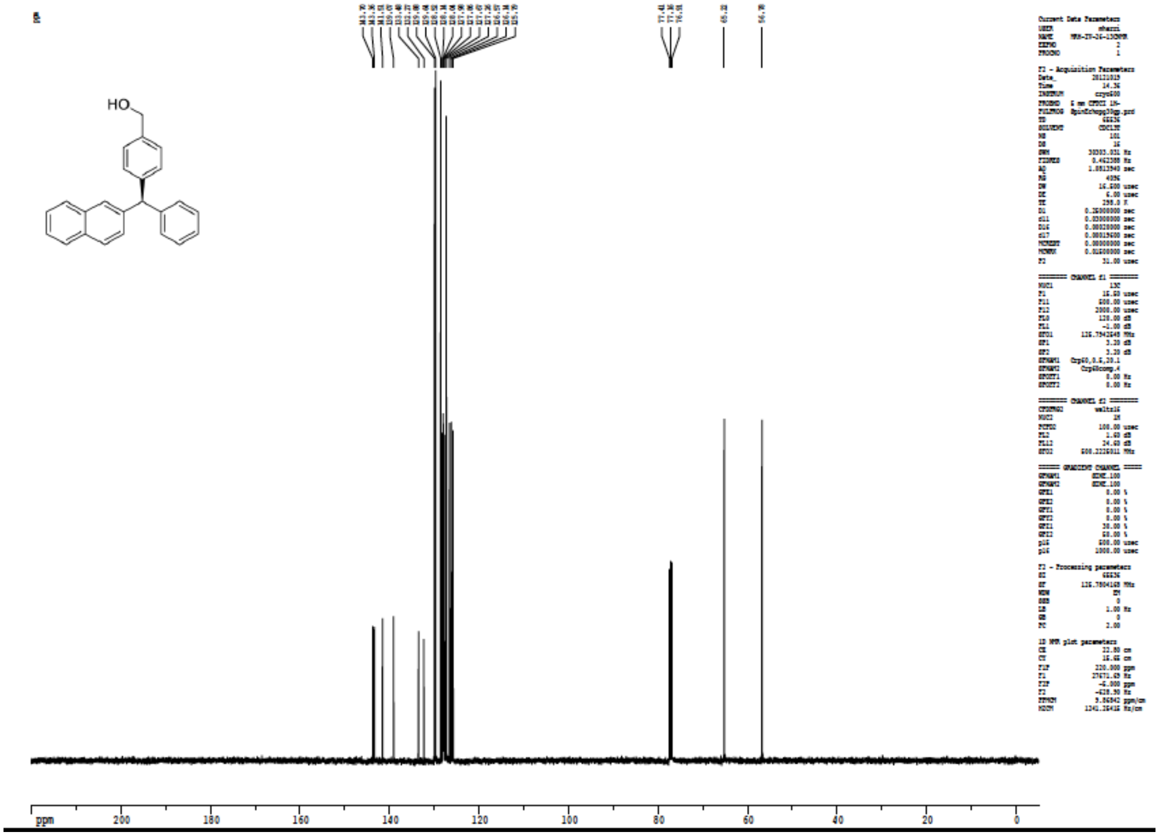
Z-restored spin-echo 13C spectrum with 1H decoupling



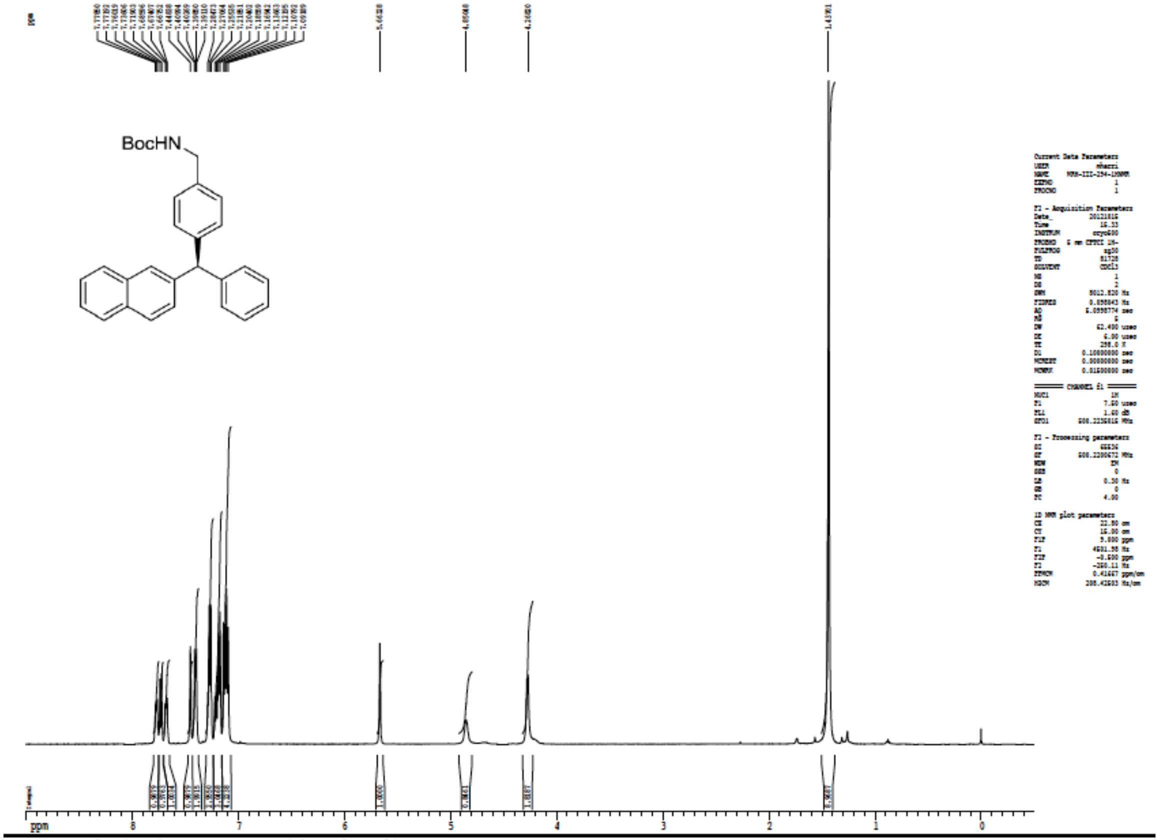
1H spectrum



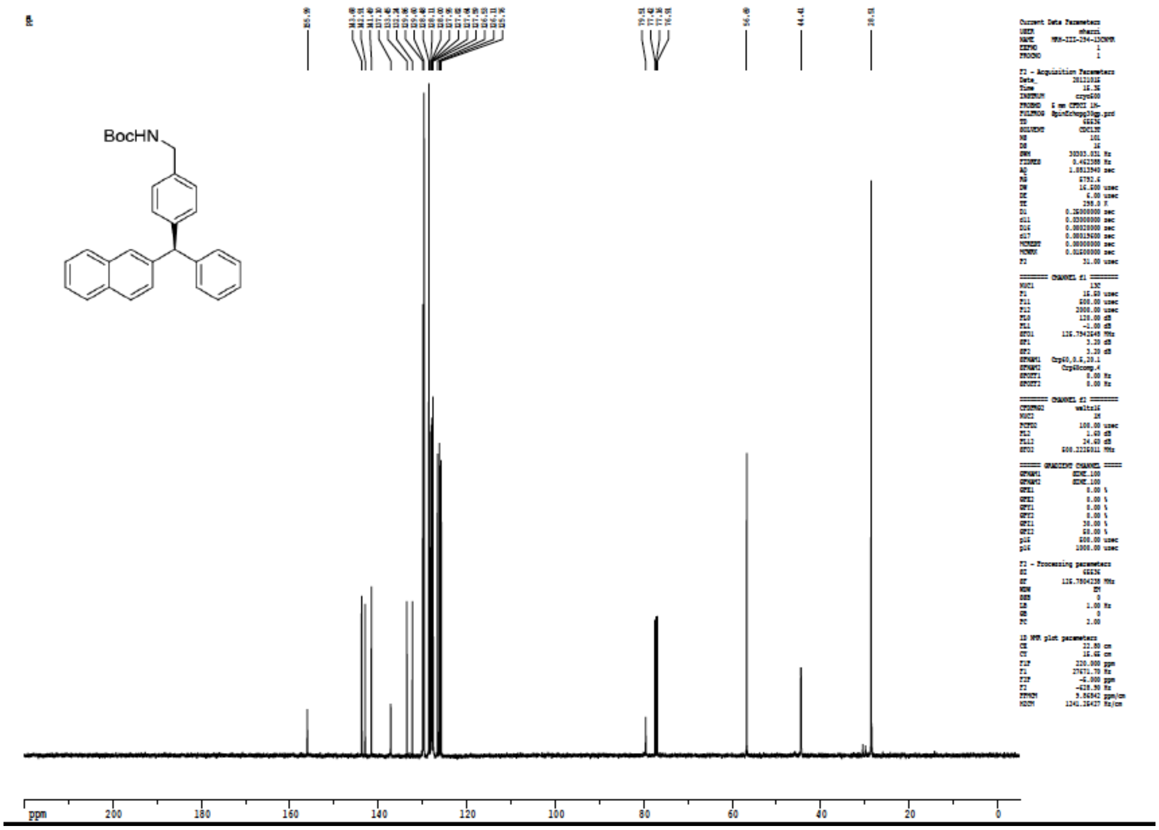
Z-restored spin-echo 13C spectrum with 1H decoupling



1H spectrum



Z-restored spin-echo 13C spectrum with 1H decoupling



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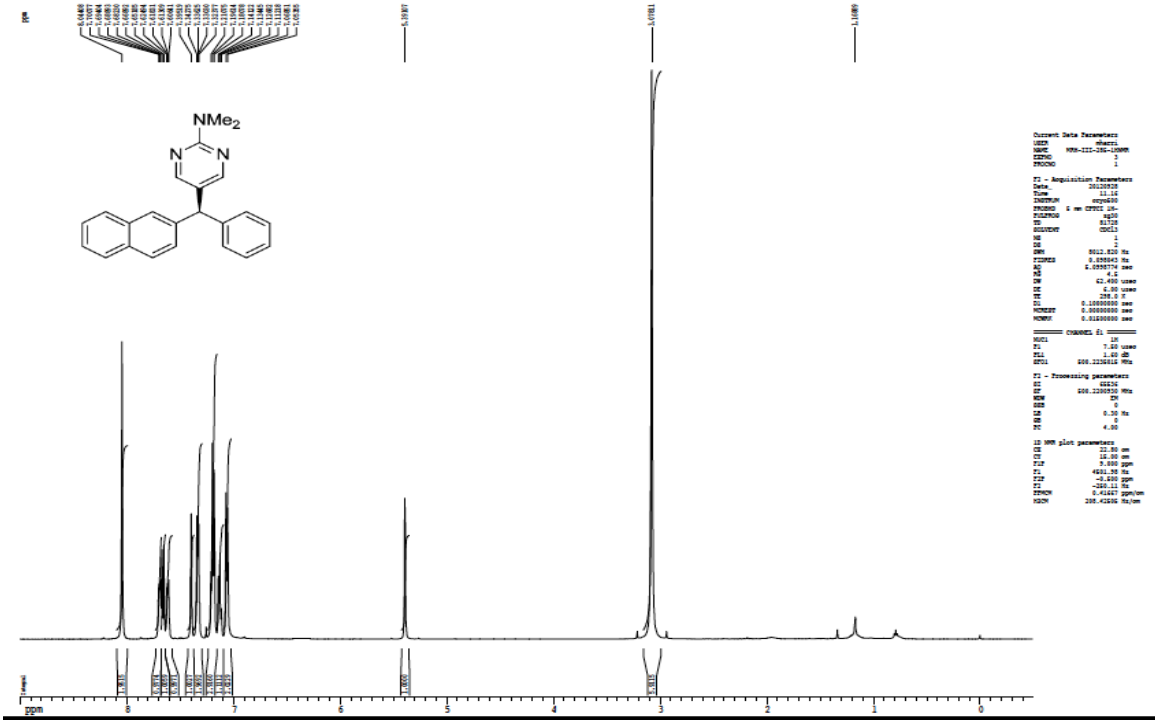
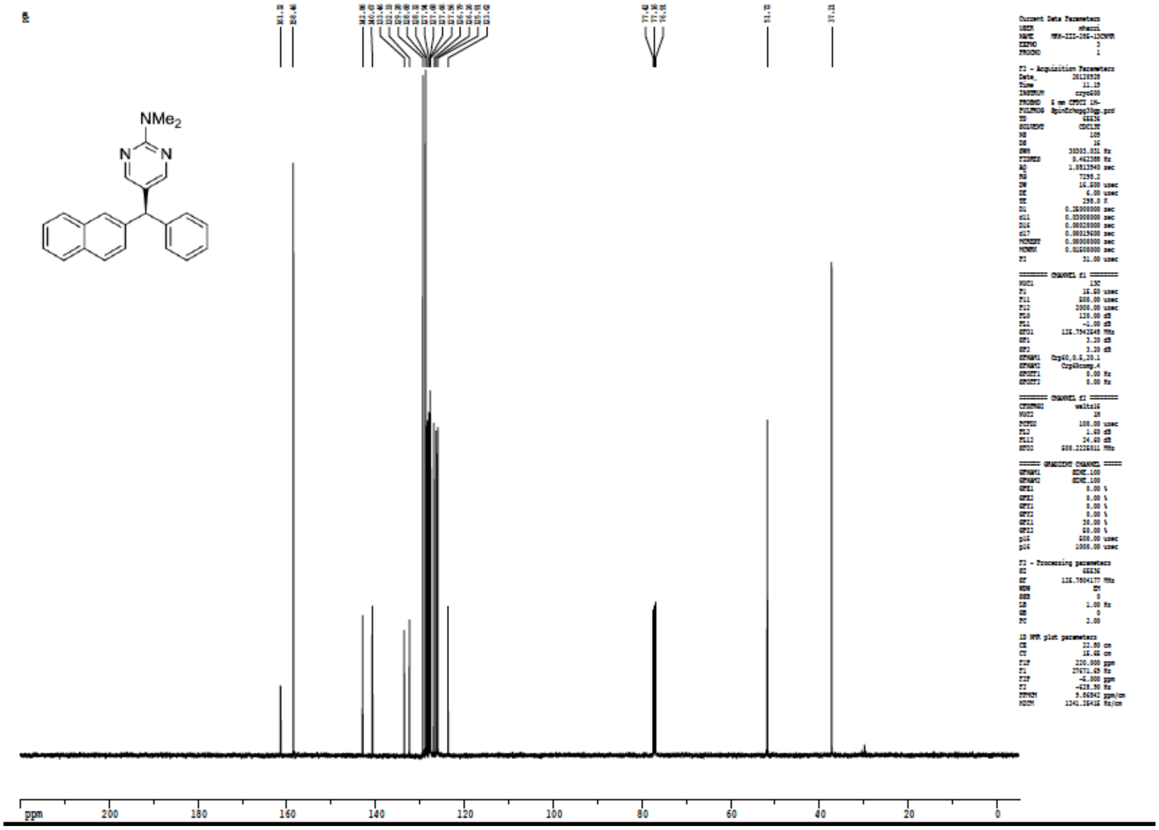


Z-restored spin-echo 13C spectrum with 1H decoupling



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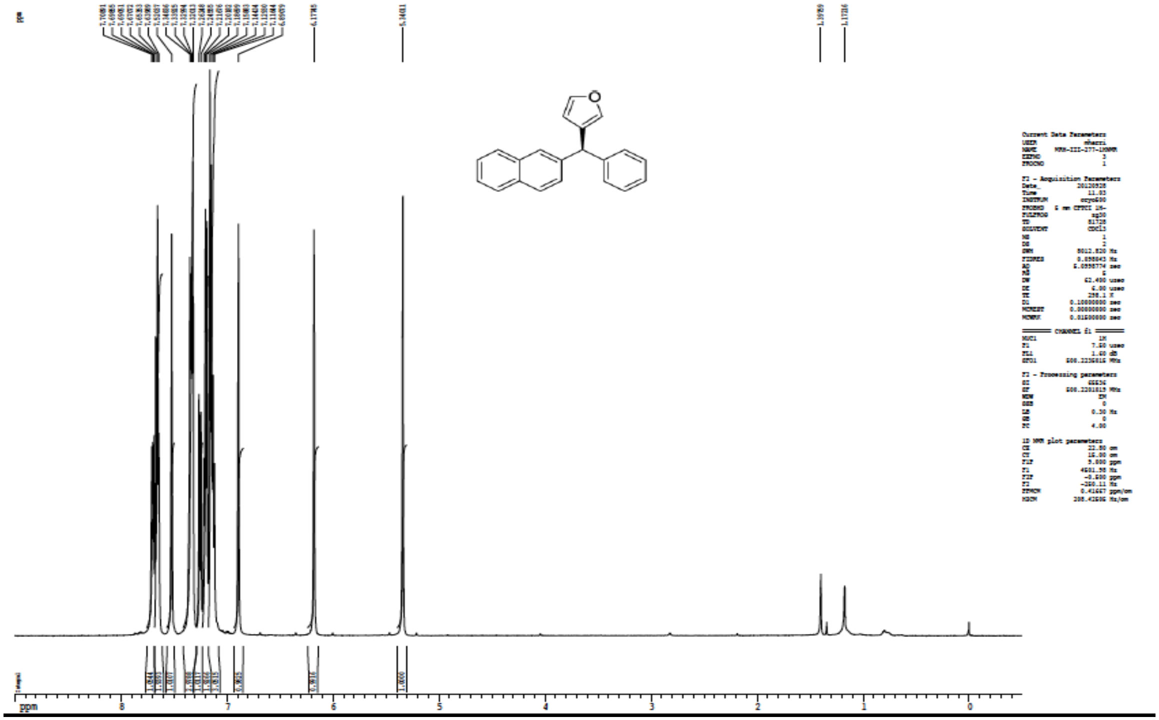
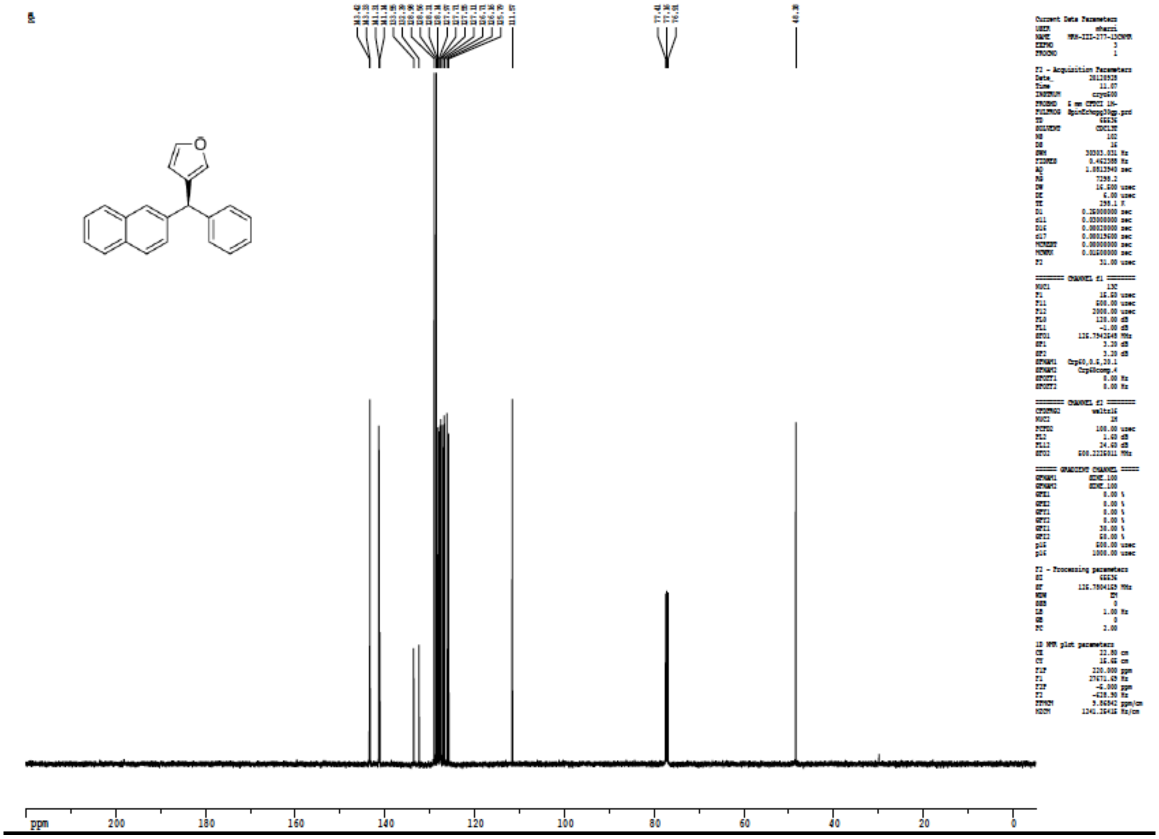
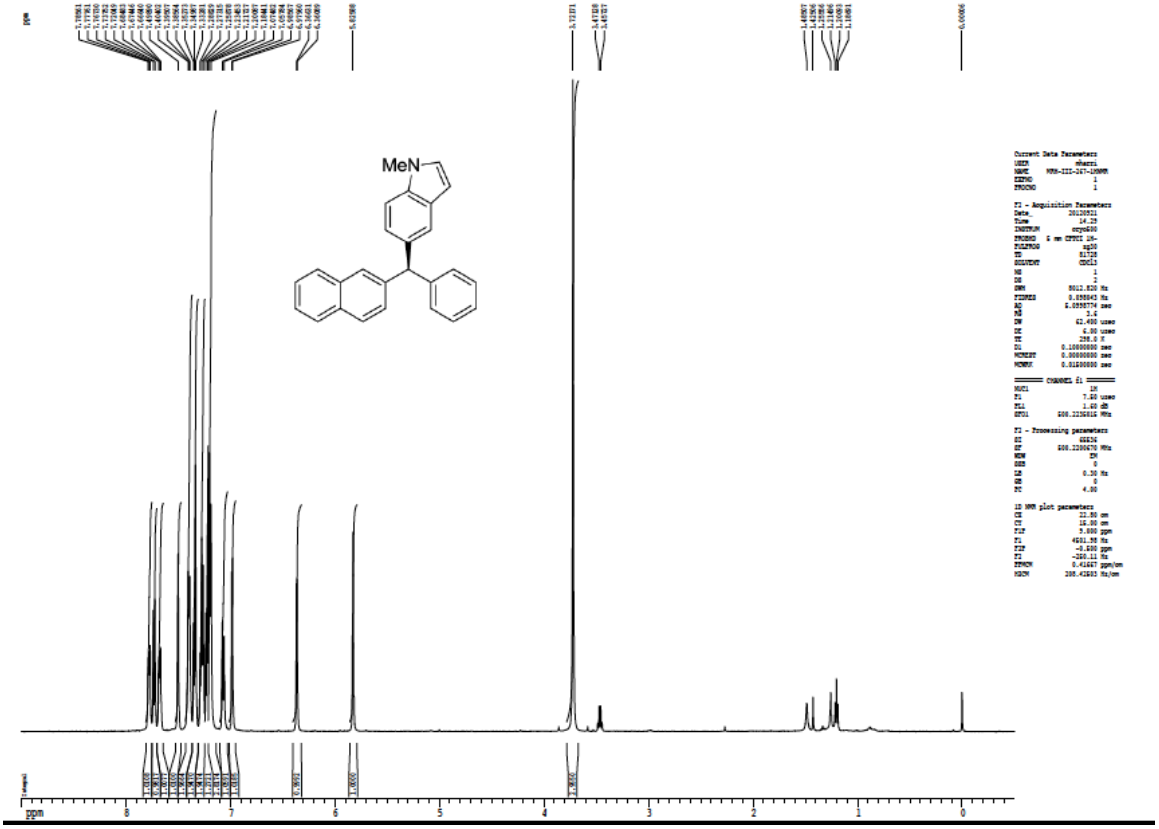


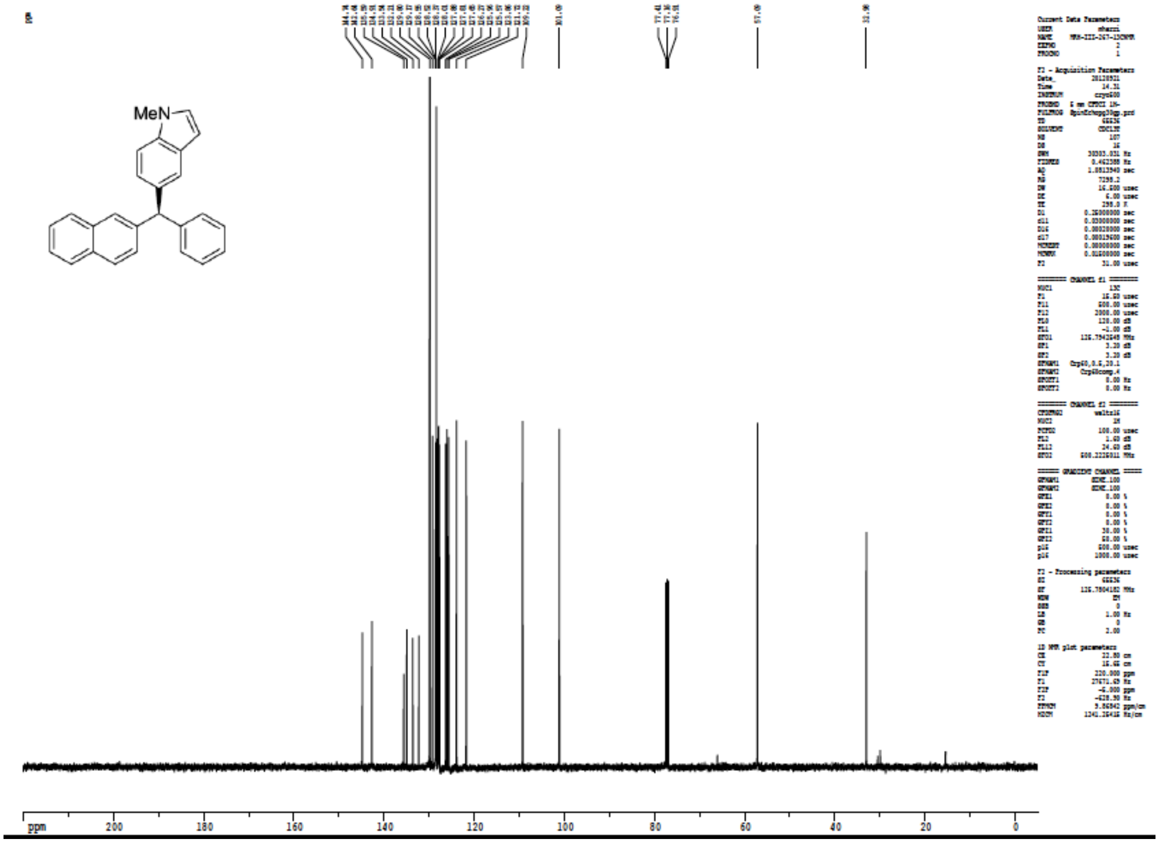
Z-restored spin-echo 13C spectrum with 1H decoupling



1H spectrum



Z-restored spin-echo 13C spectrum with 1H decoupling



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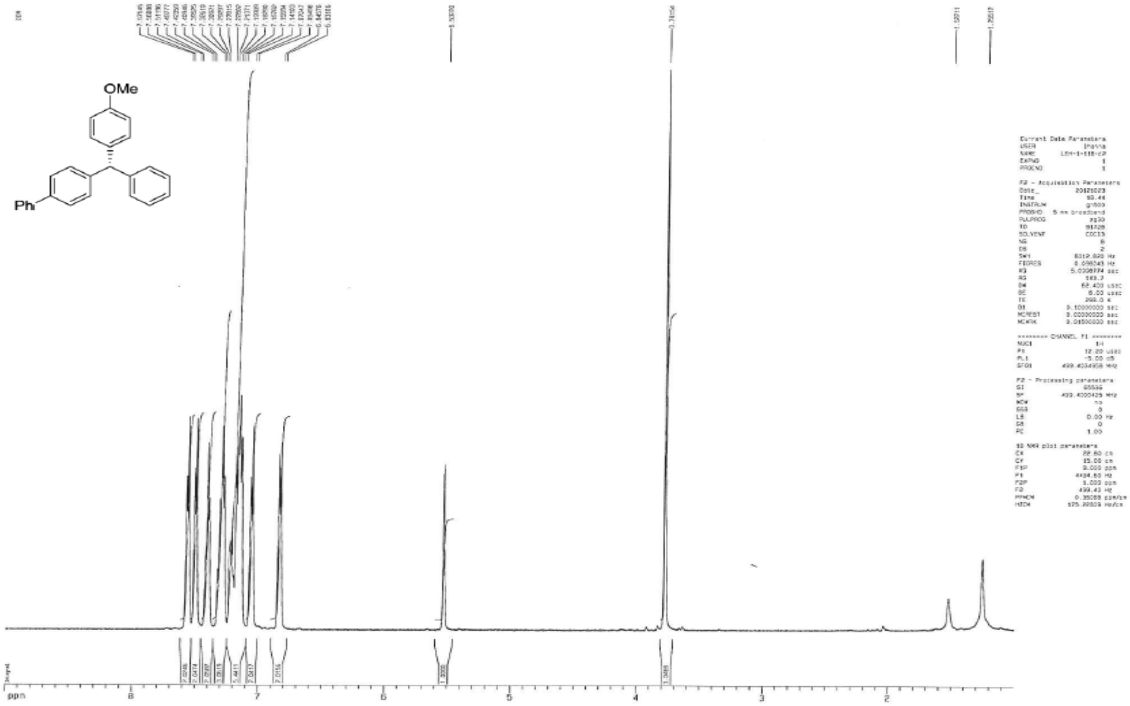
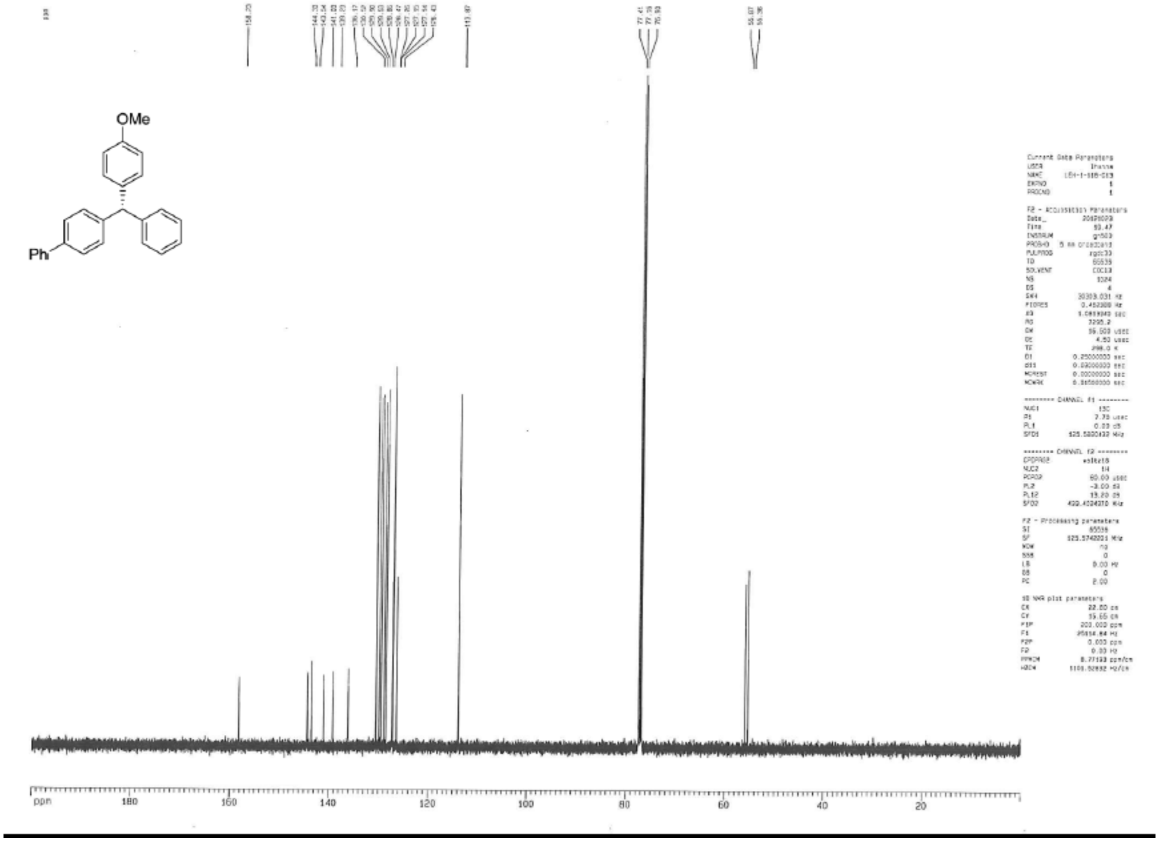
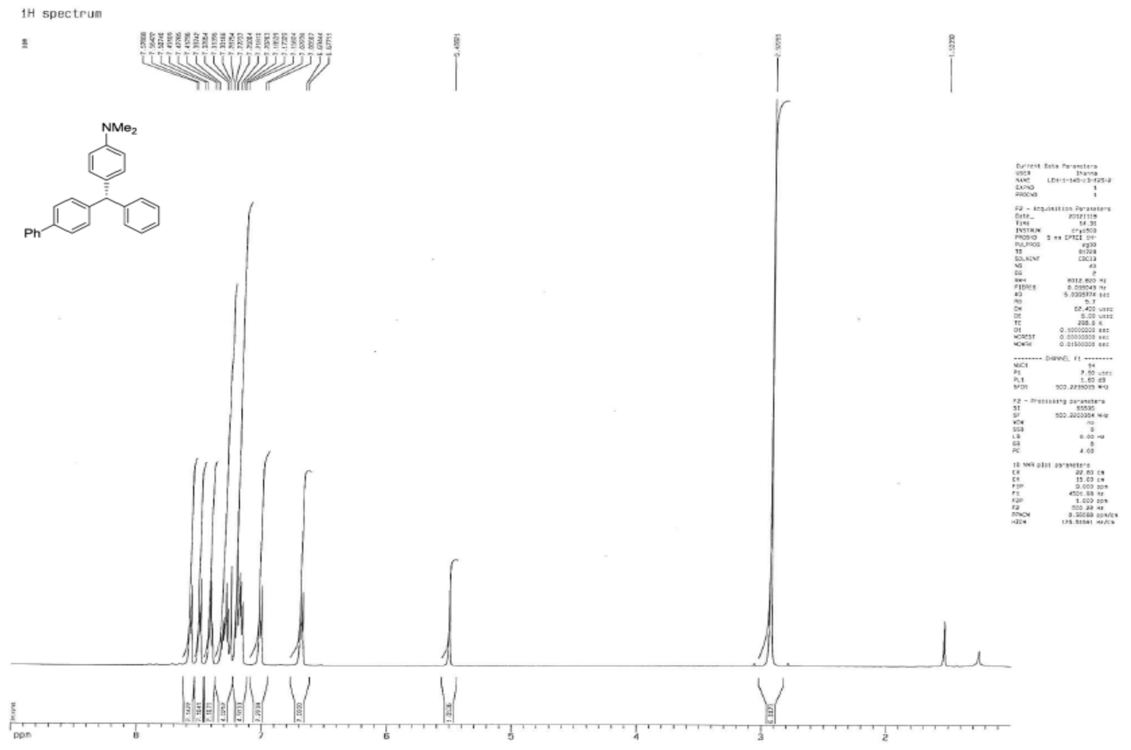
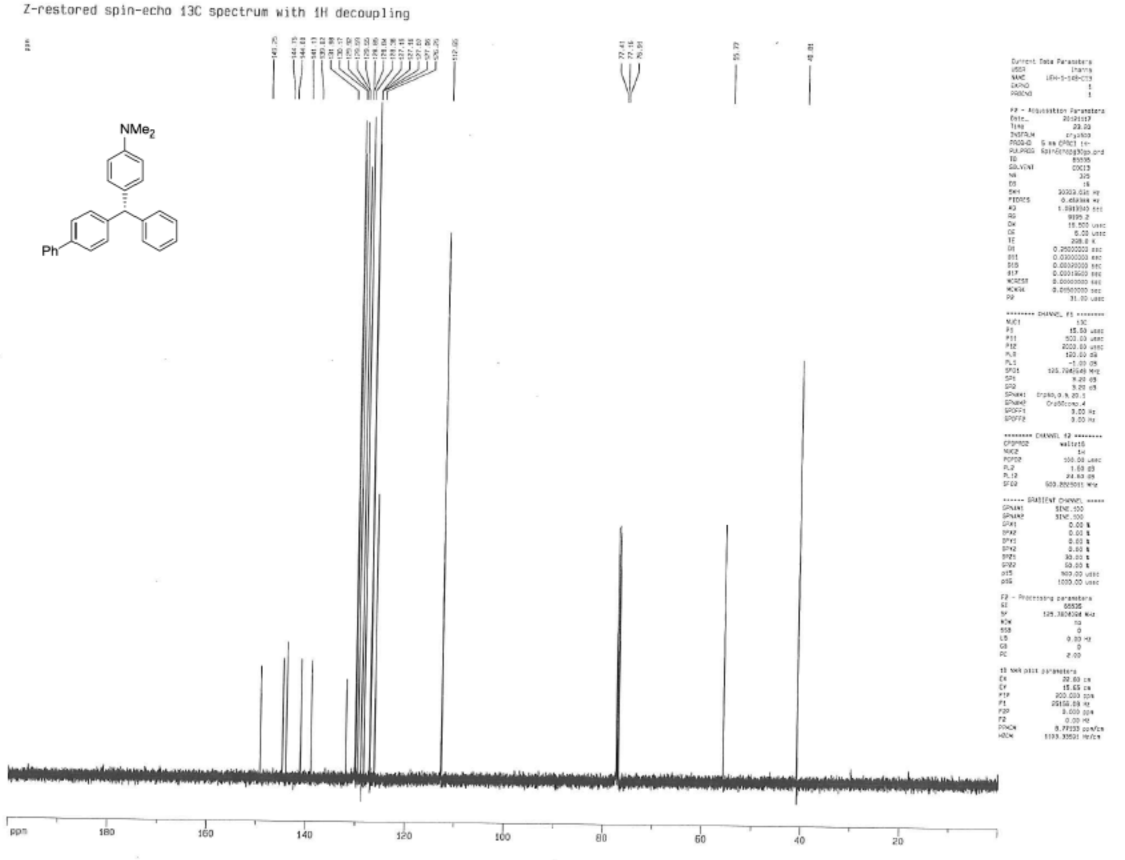


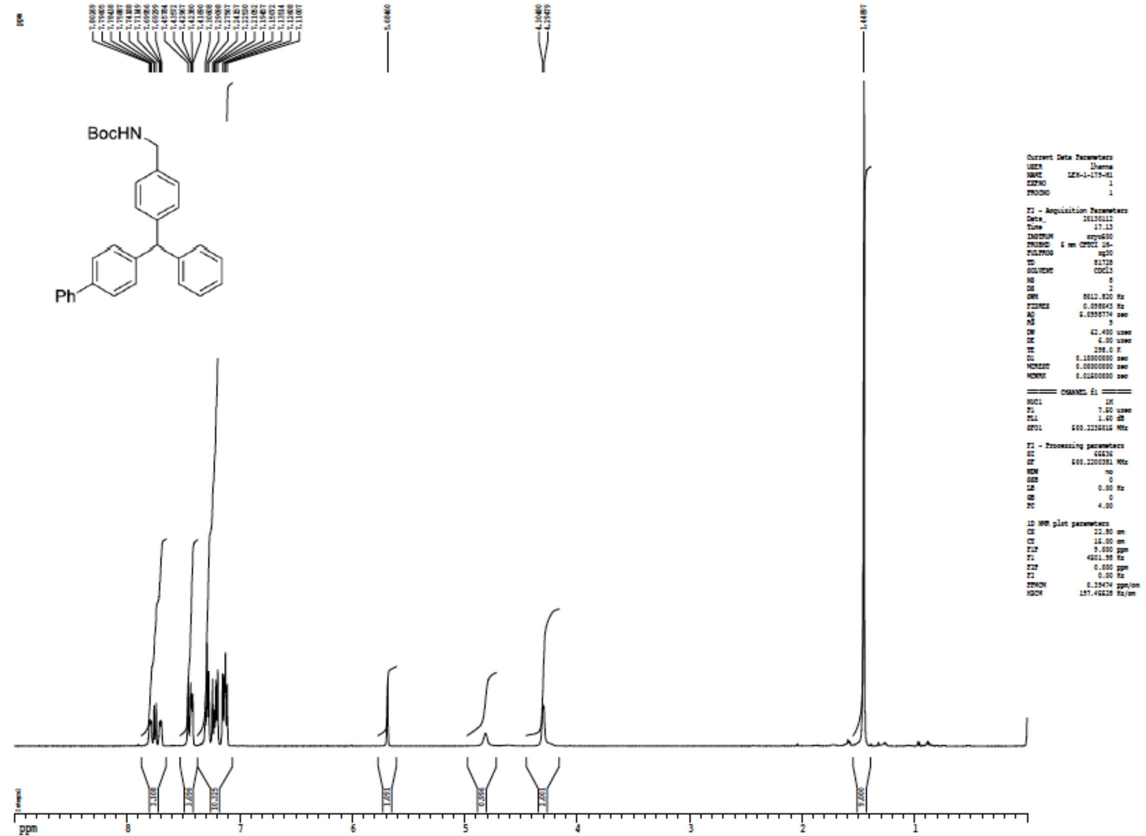
13C spectrum with 1H decoupling



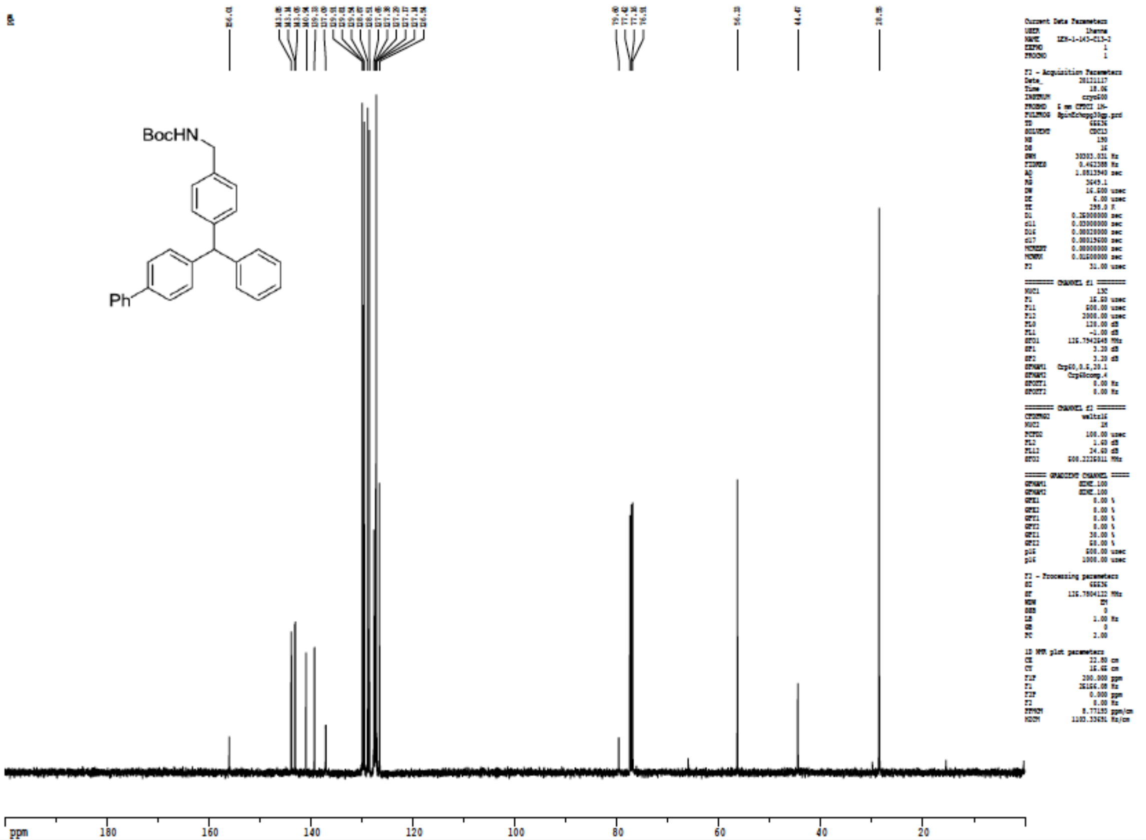

1H spectrum
NMe2
Ph
ppm
8
7
6
5
4
3
2

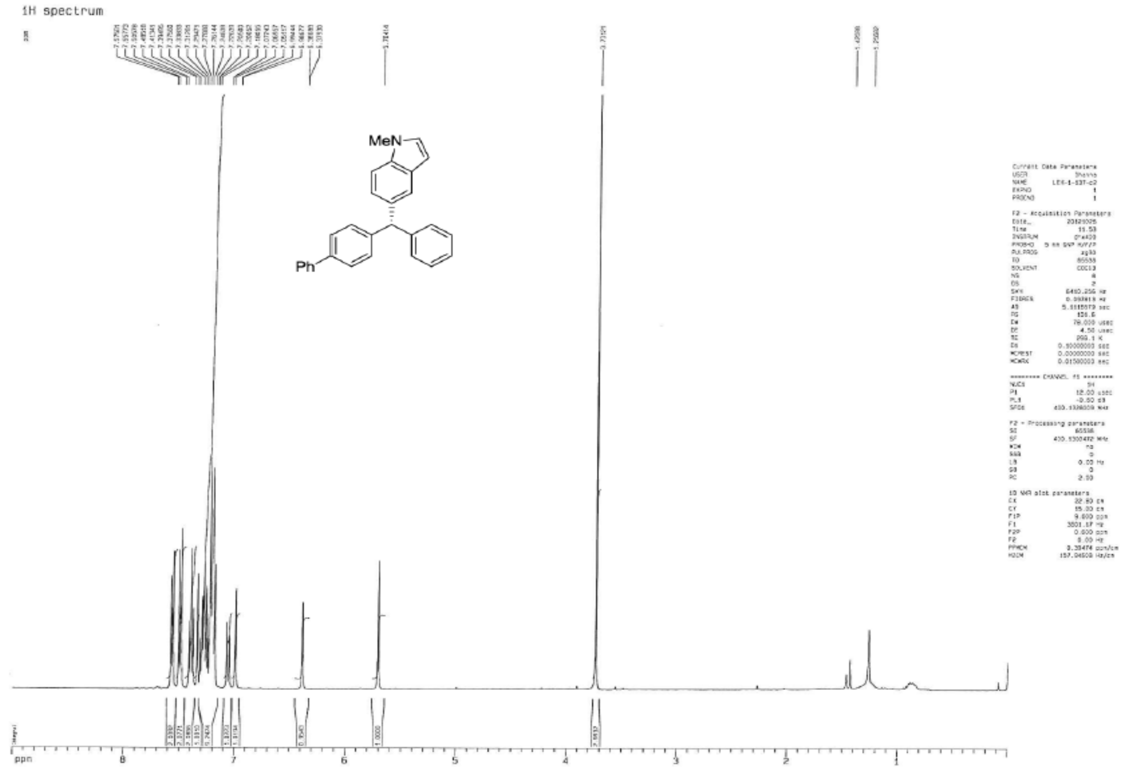

Z-restored spin-echo 13C spectrum with 1H decoupling
112.65
77.41
77.16
76.91
55.77
40.81
NMe2
Ph
ppm
180
160
140
120
100
80
60
40
20

1H spectrum



Z-restored spin-echo 13C spectrum with 1H decoupling

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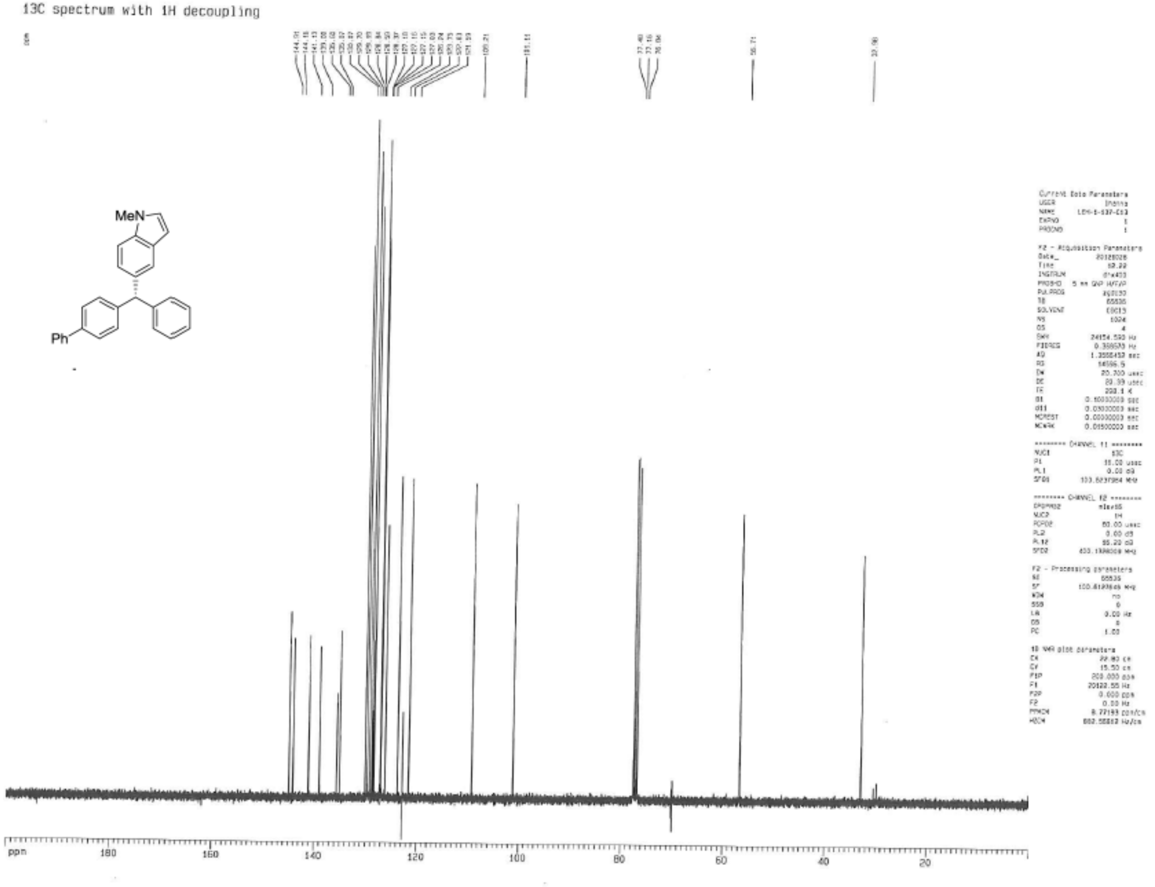
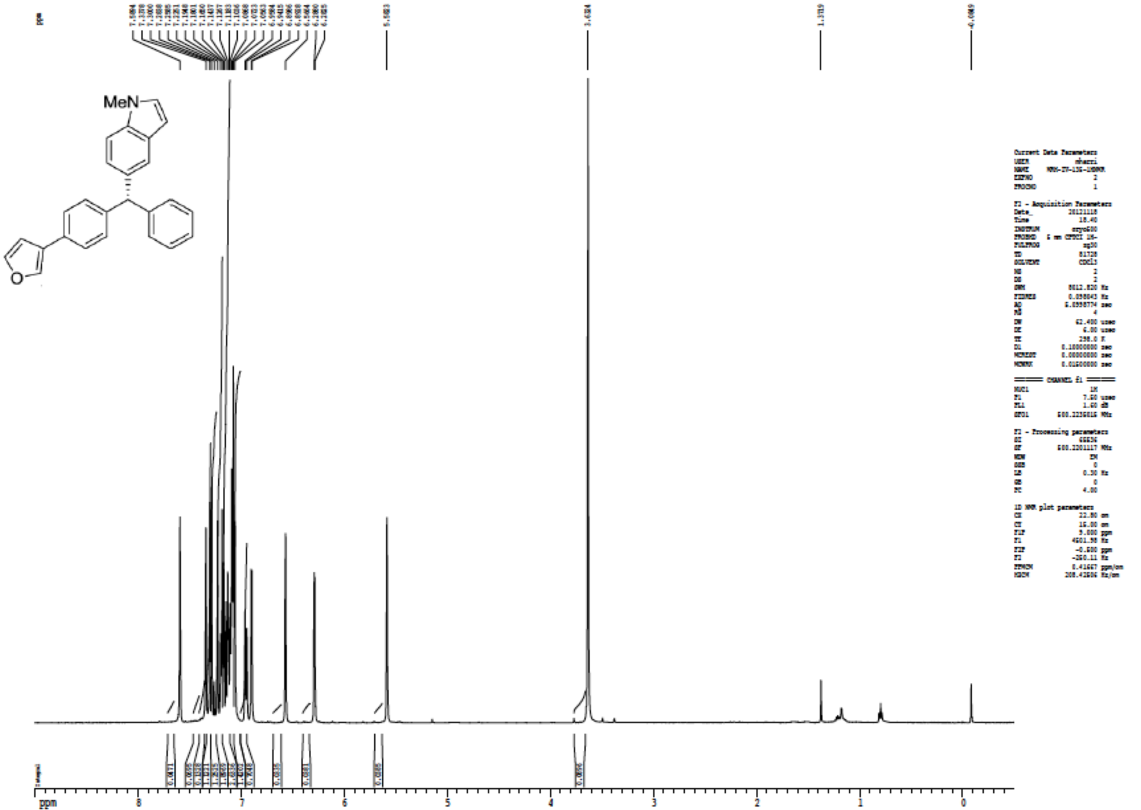
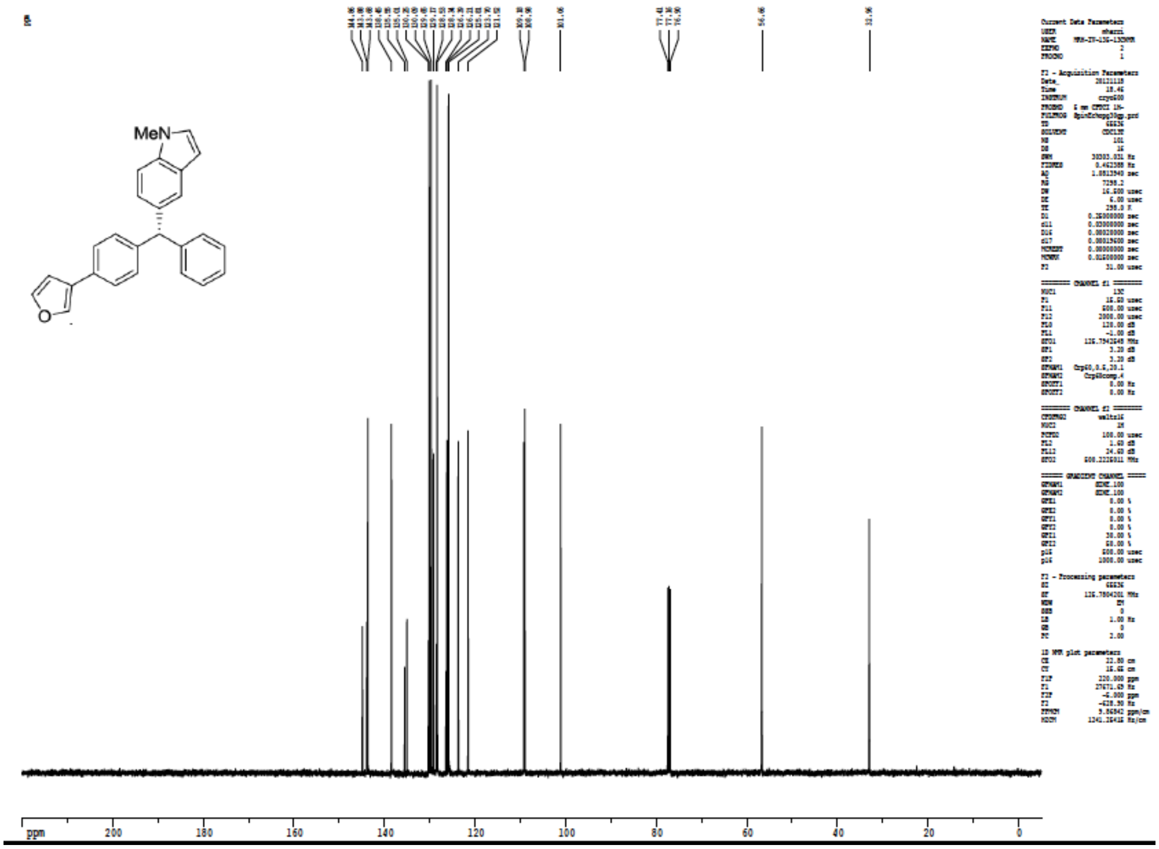
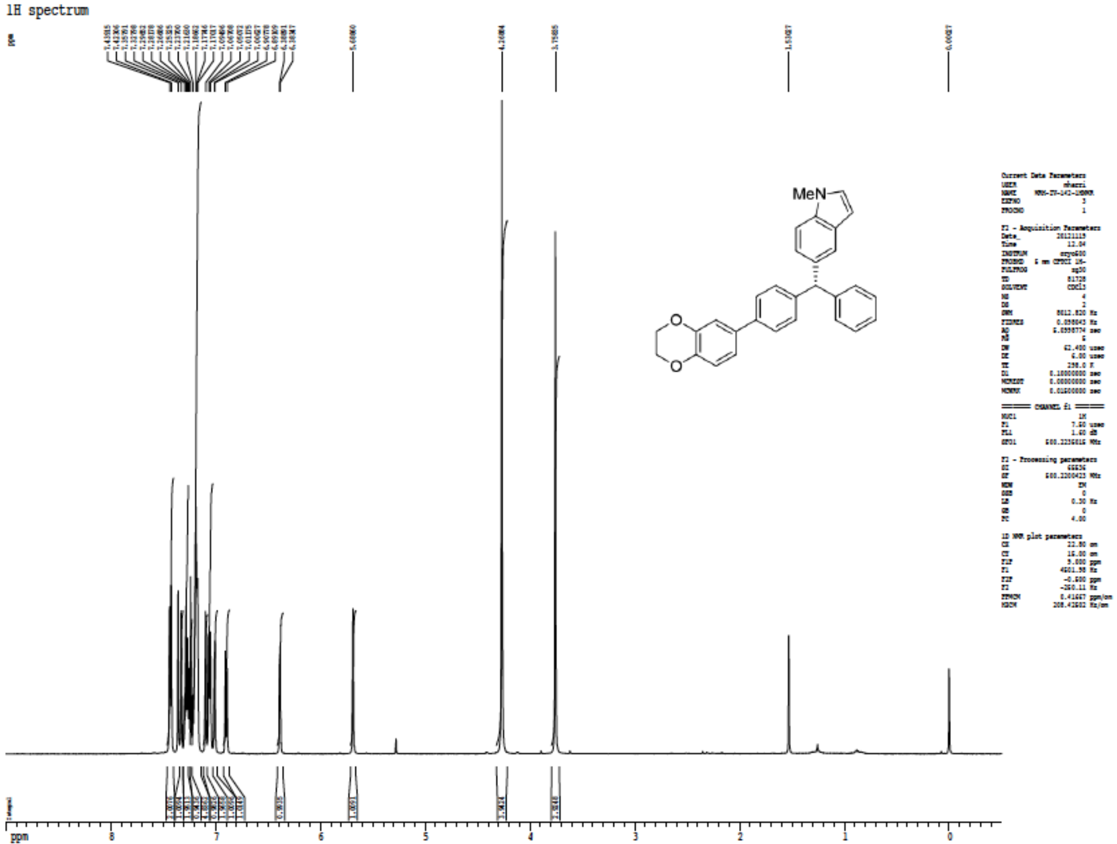

13C spectrum with 1H decoupling

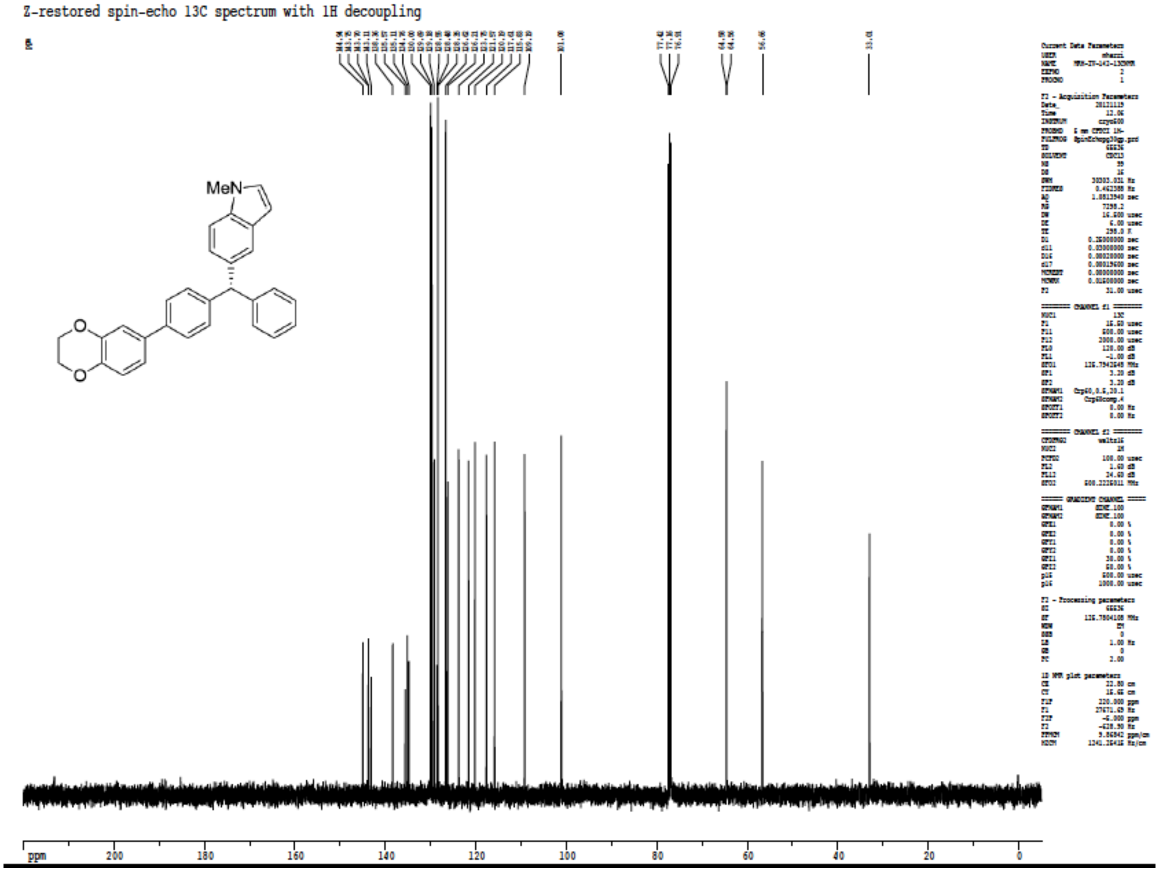
1H spectrum

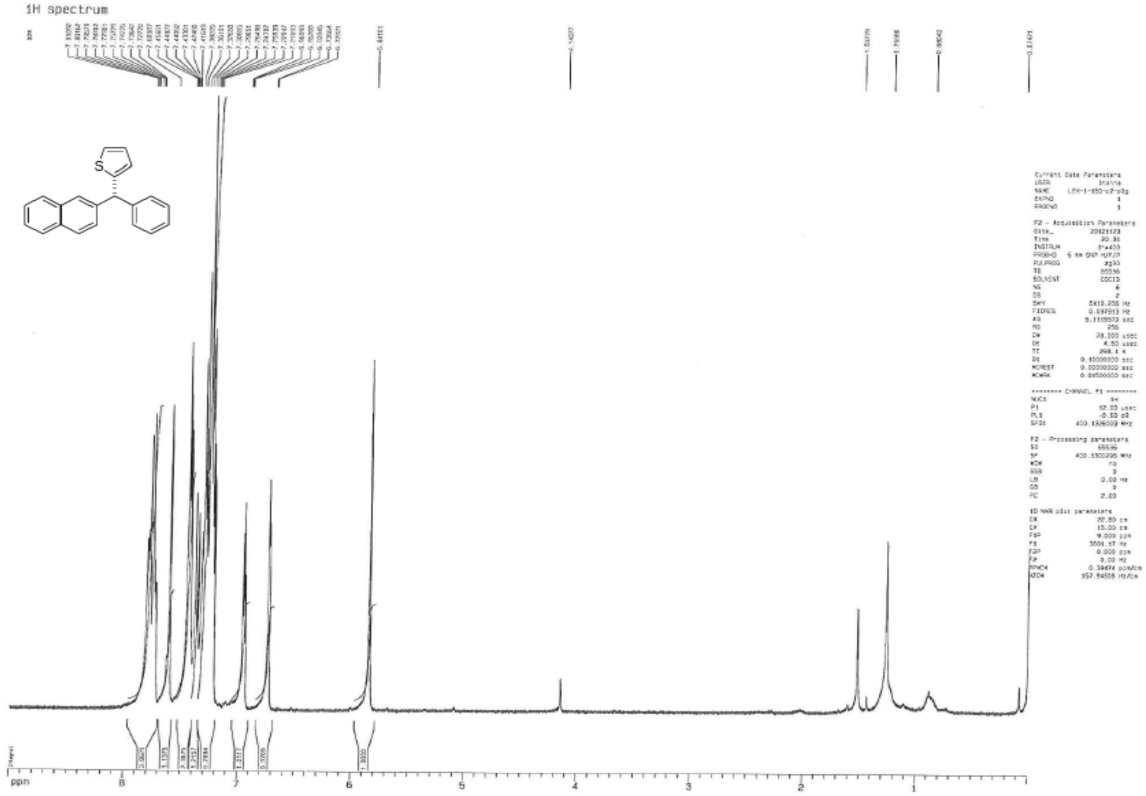


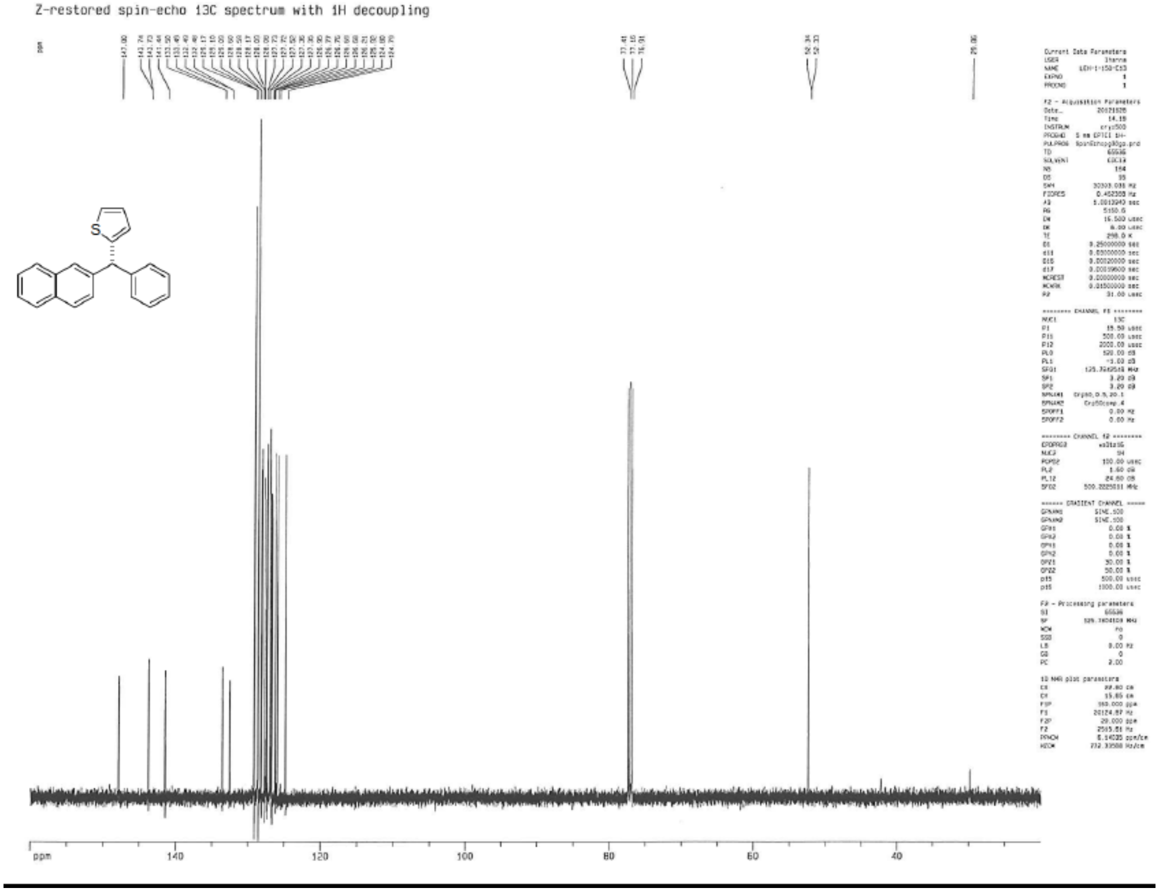
Z-restored spin-echo 13C spectrum with 1H decoupling

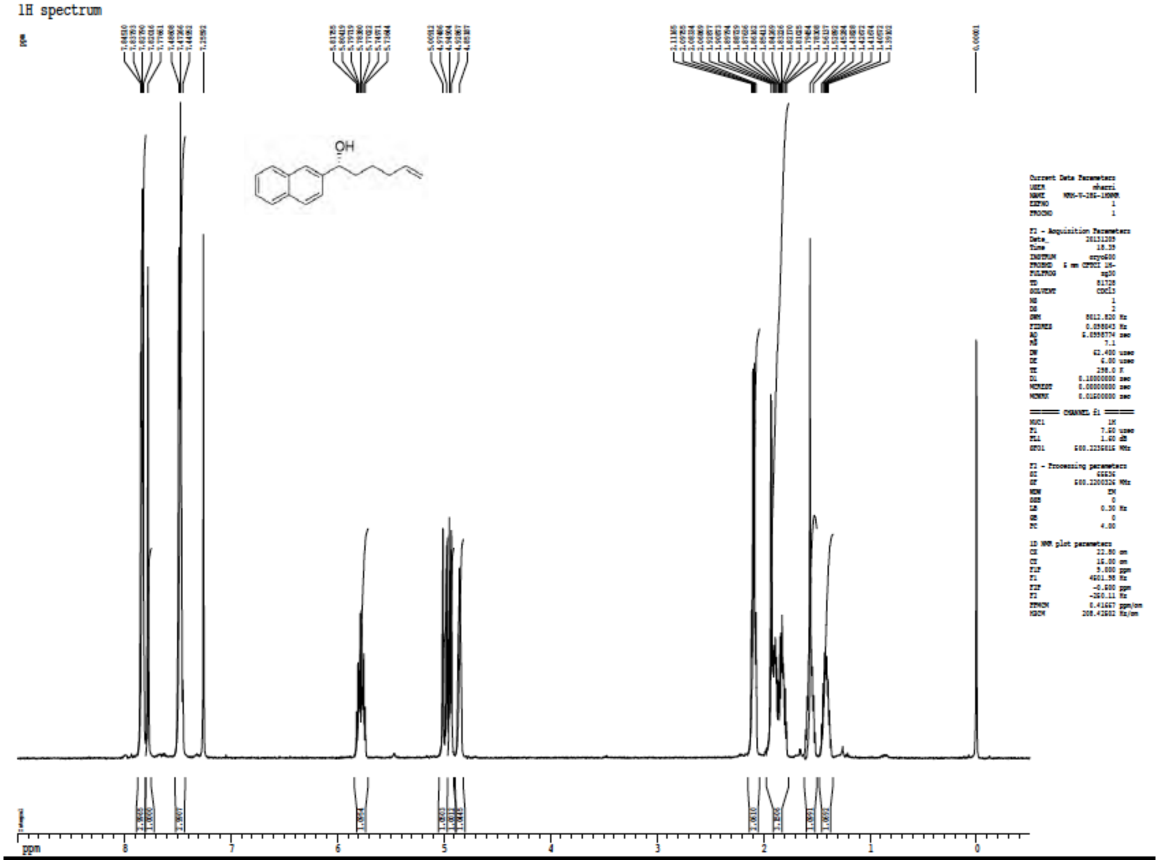


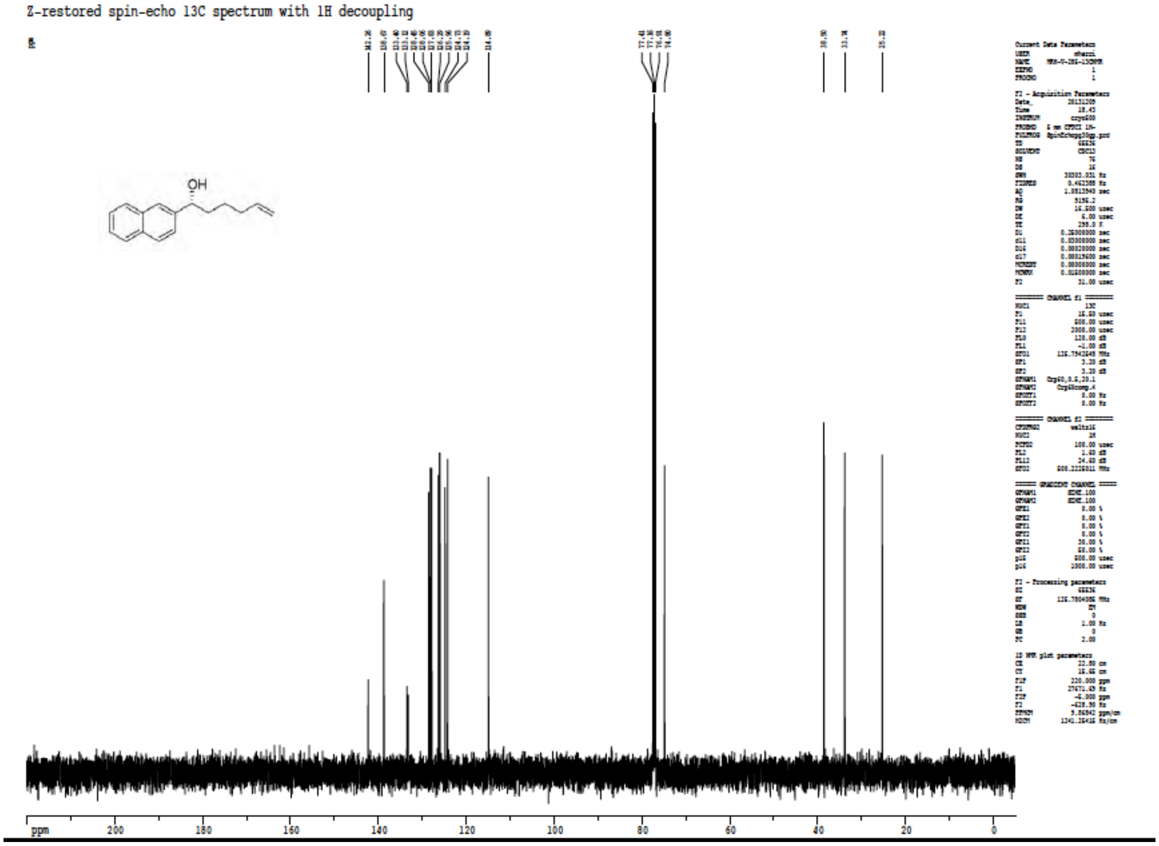

1H spectrum


Z-restored spin-echo 13C spectrum with 1H decoupling

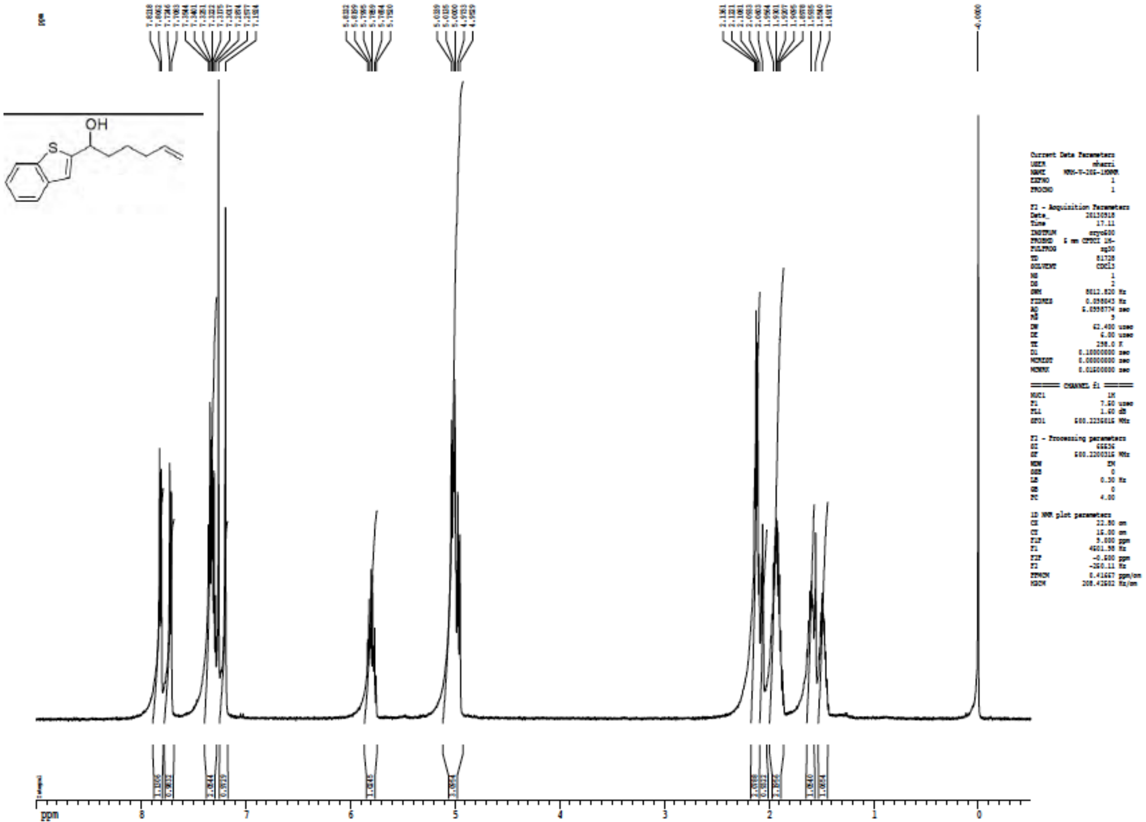

1H spectrum


Z-restored spin-echo 13C spectrum with 1H decoupling

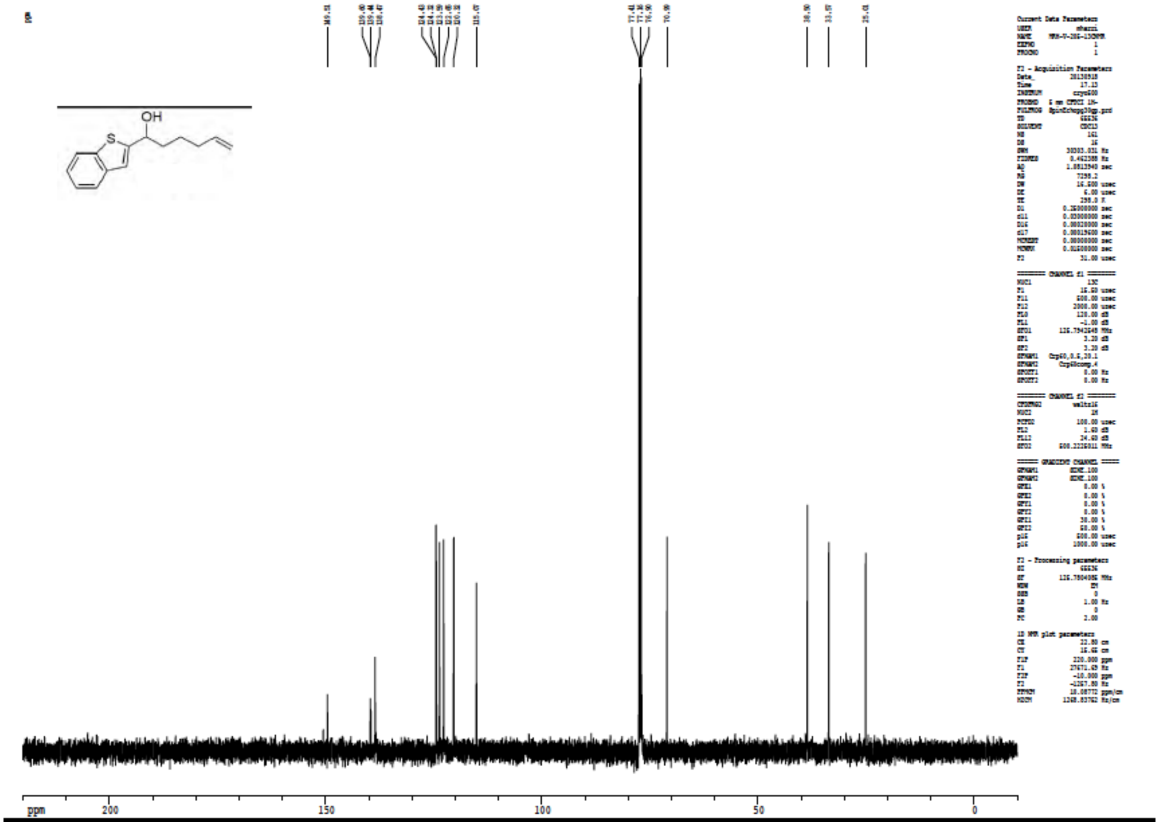

1H spectrum
OH
ppm
8
7
6
5
4
3
2
1
0


Z-restored spin-echo 13C spectrum with 1H decoupling
OH
ppm
200
180
160
140
120
100
80
60
40
20
0

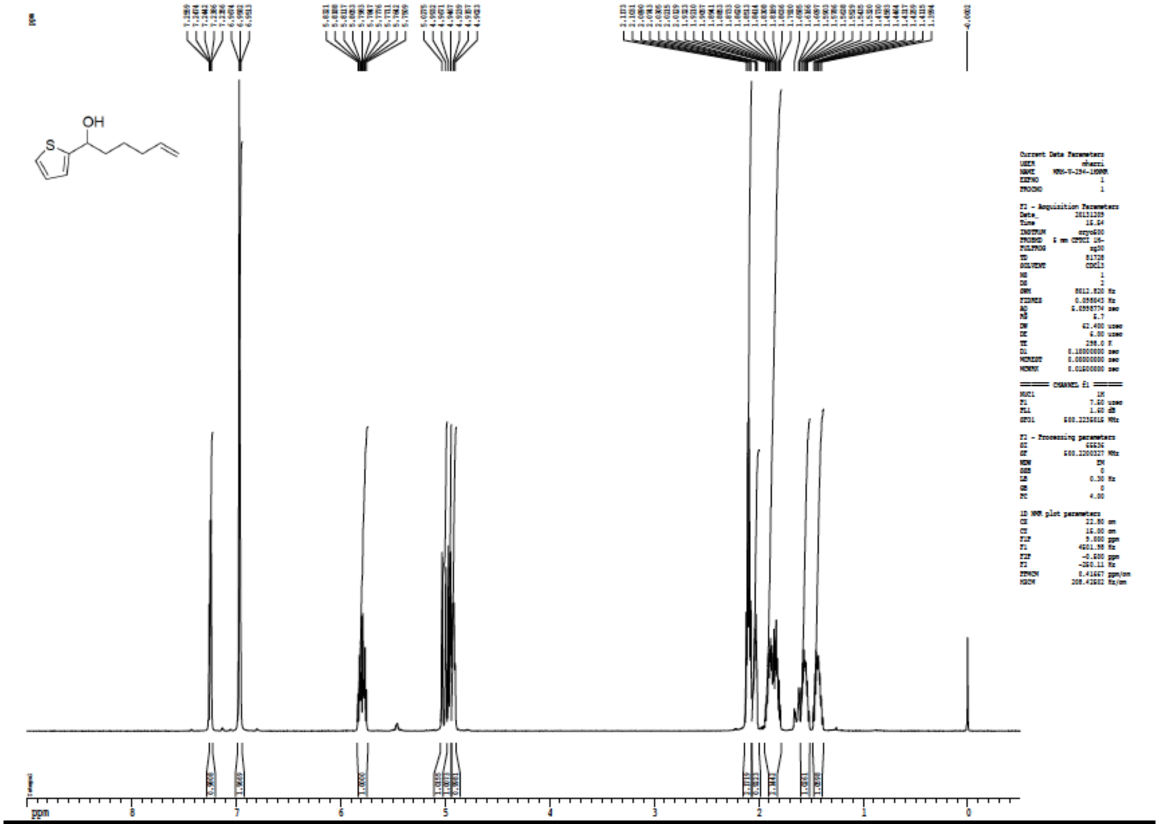
1H spectrum



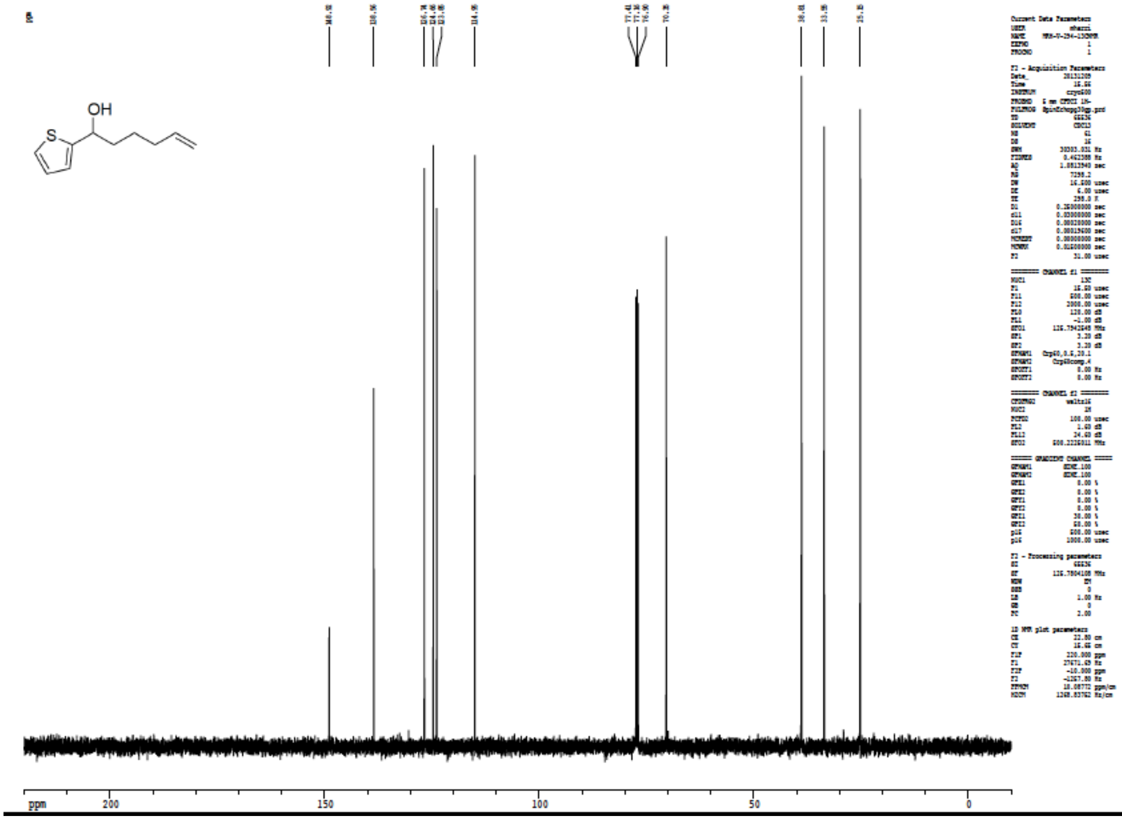
Z-restored spin-echo 13C spectrum with 1H decoupling



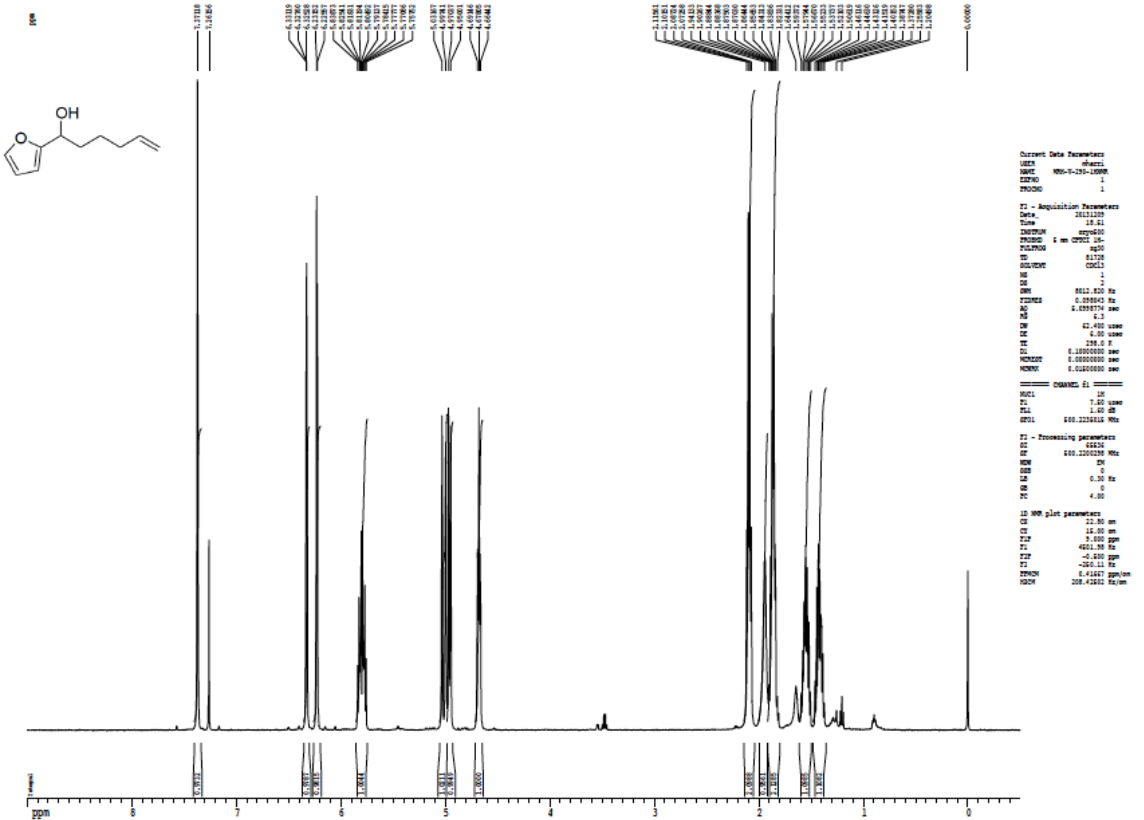
1H spectrum



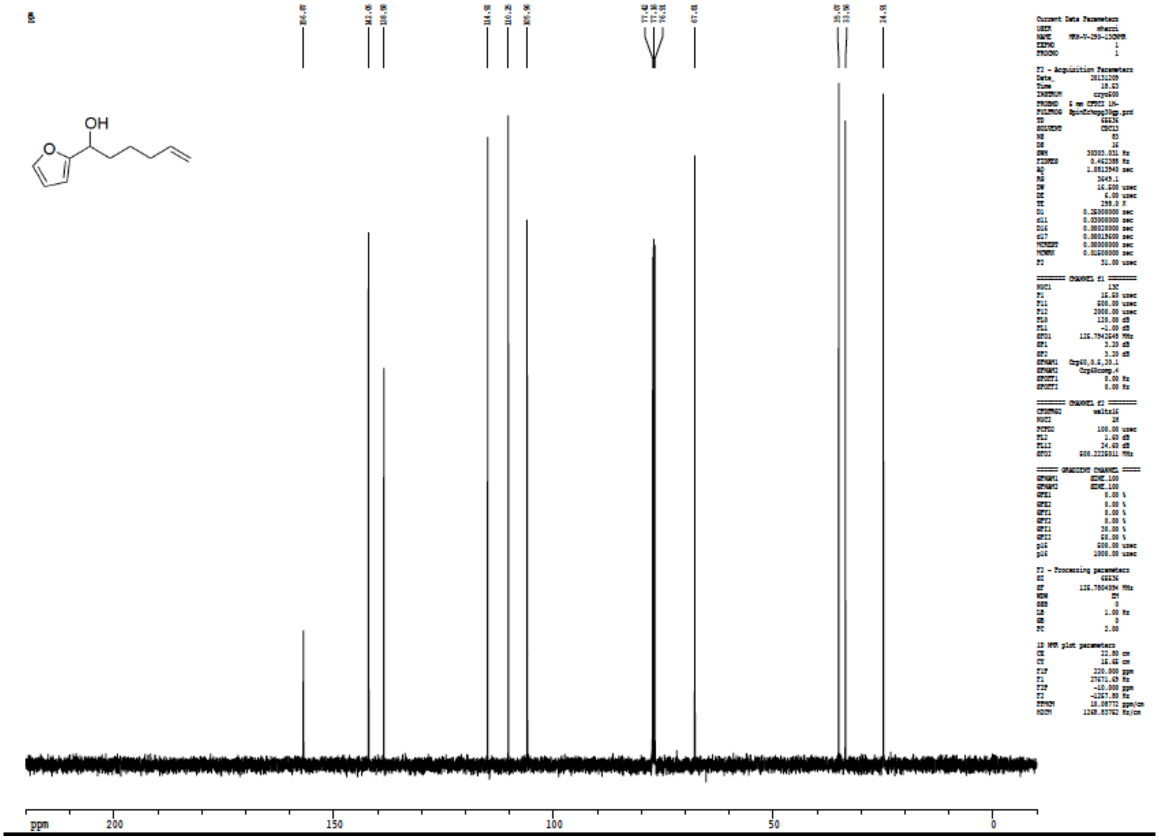
Z-restored spin-echo 13C spectrum with 1H decoupling



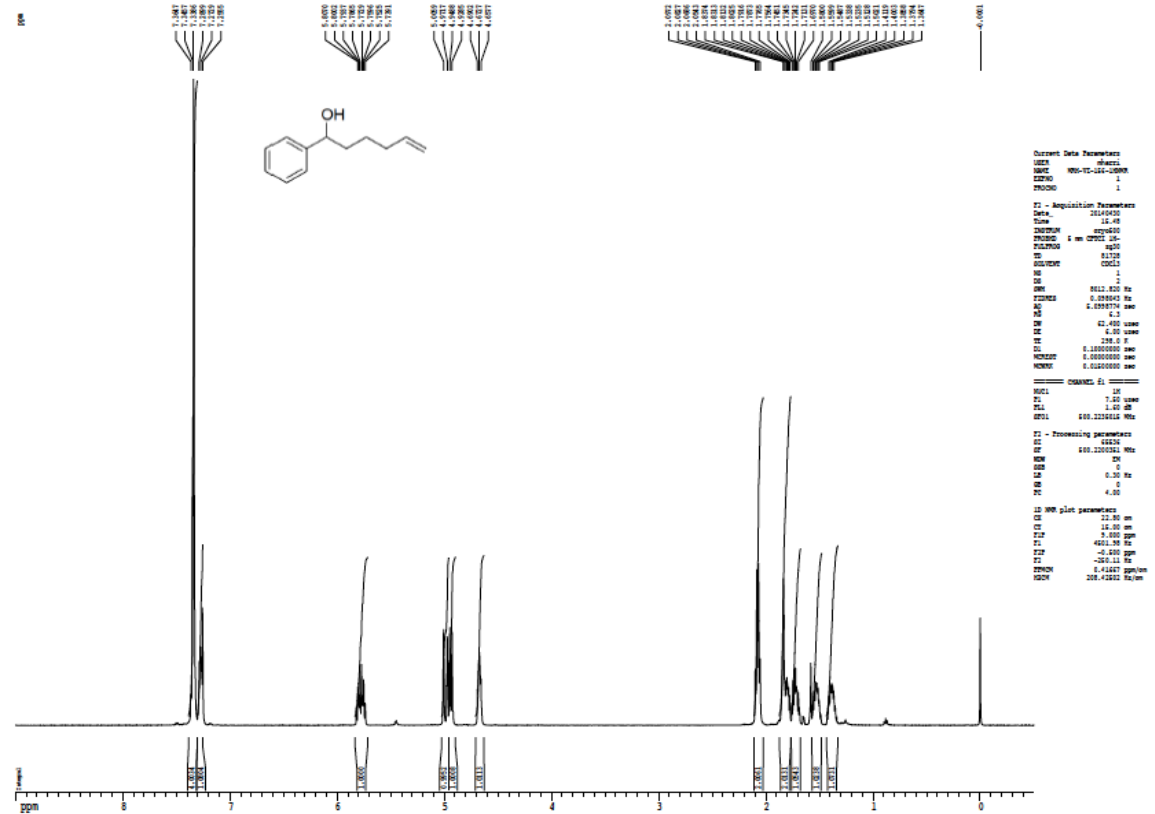
1H spectrum



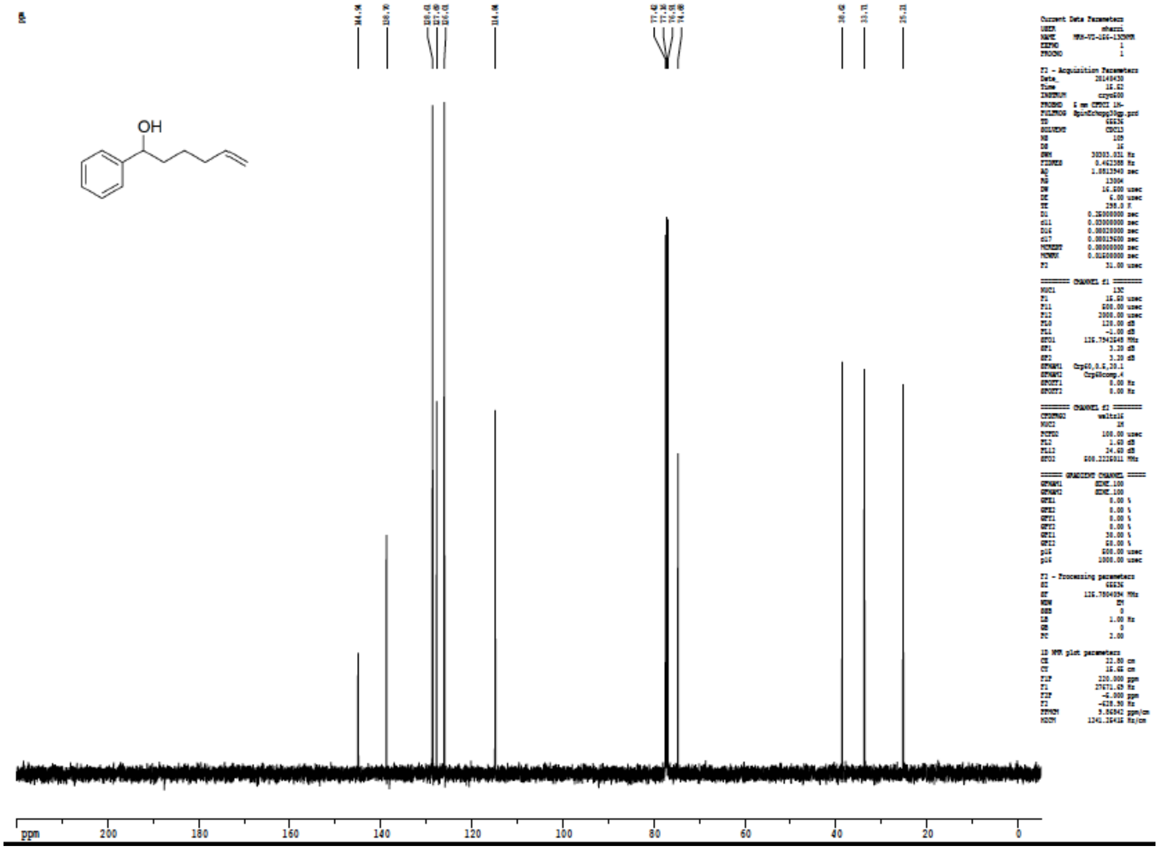
Z-restored spin-echo 13C spectrum with 1H decoupling



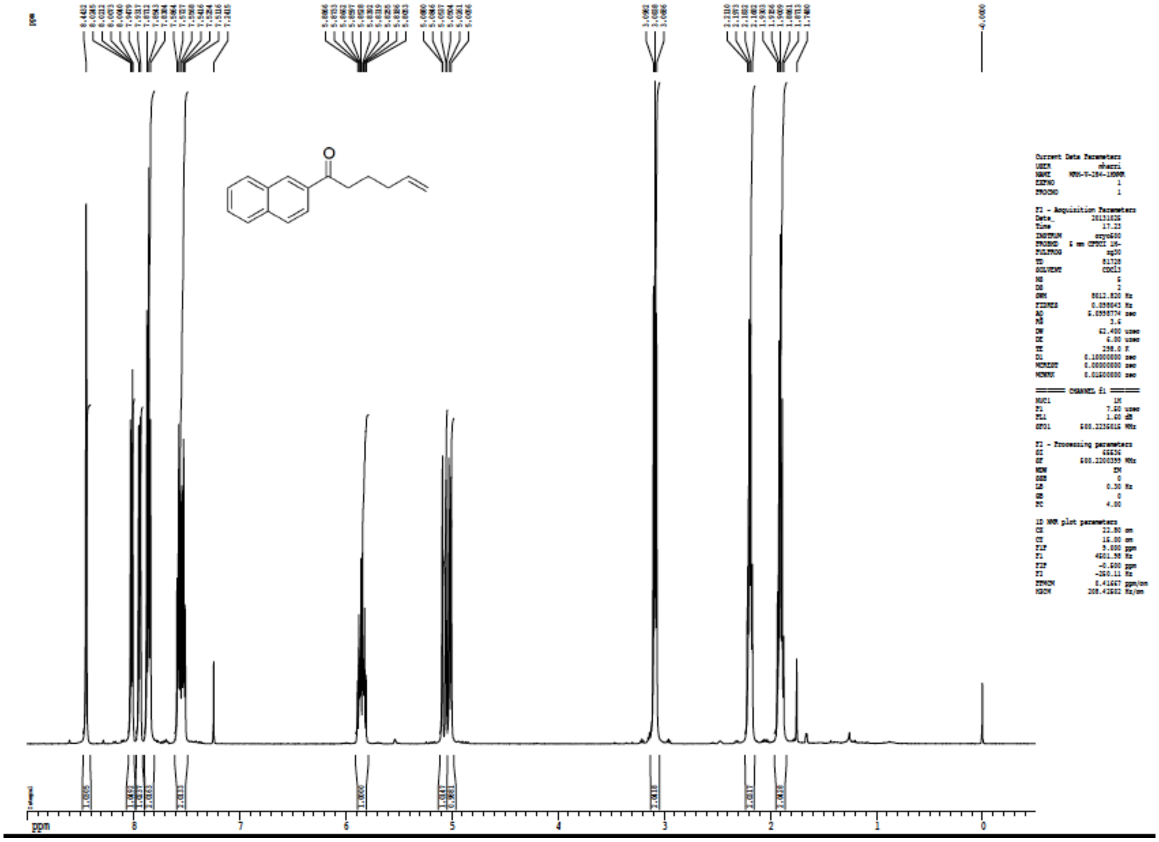
1H spectrum



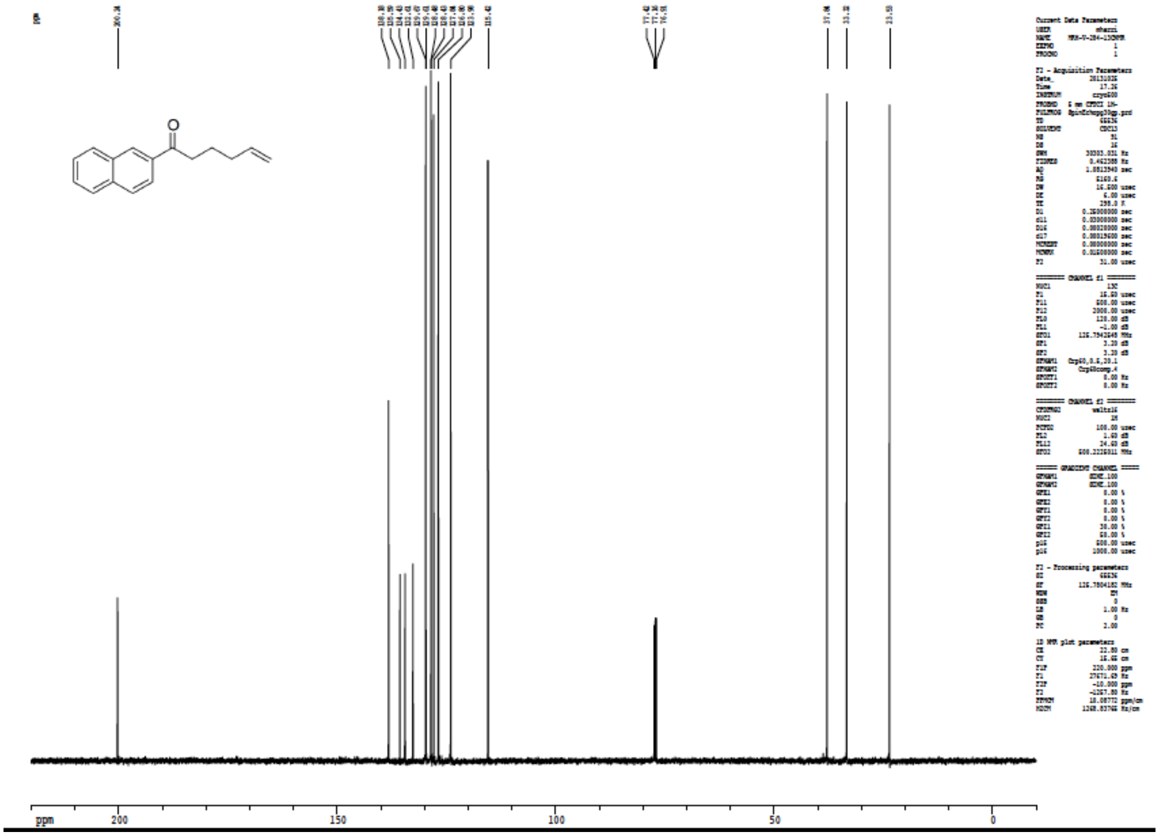
Z-restored spin-echo 13C spectrum with 1H decoupling



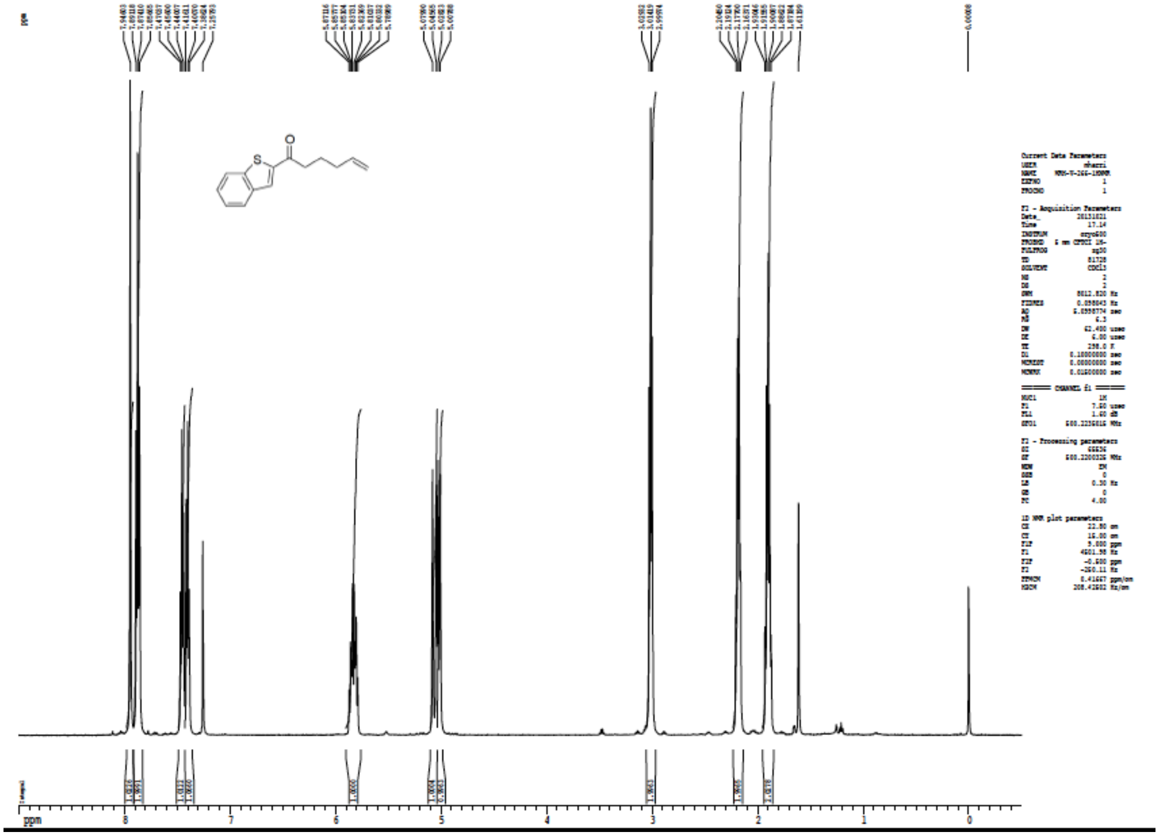
1H spectrum



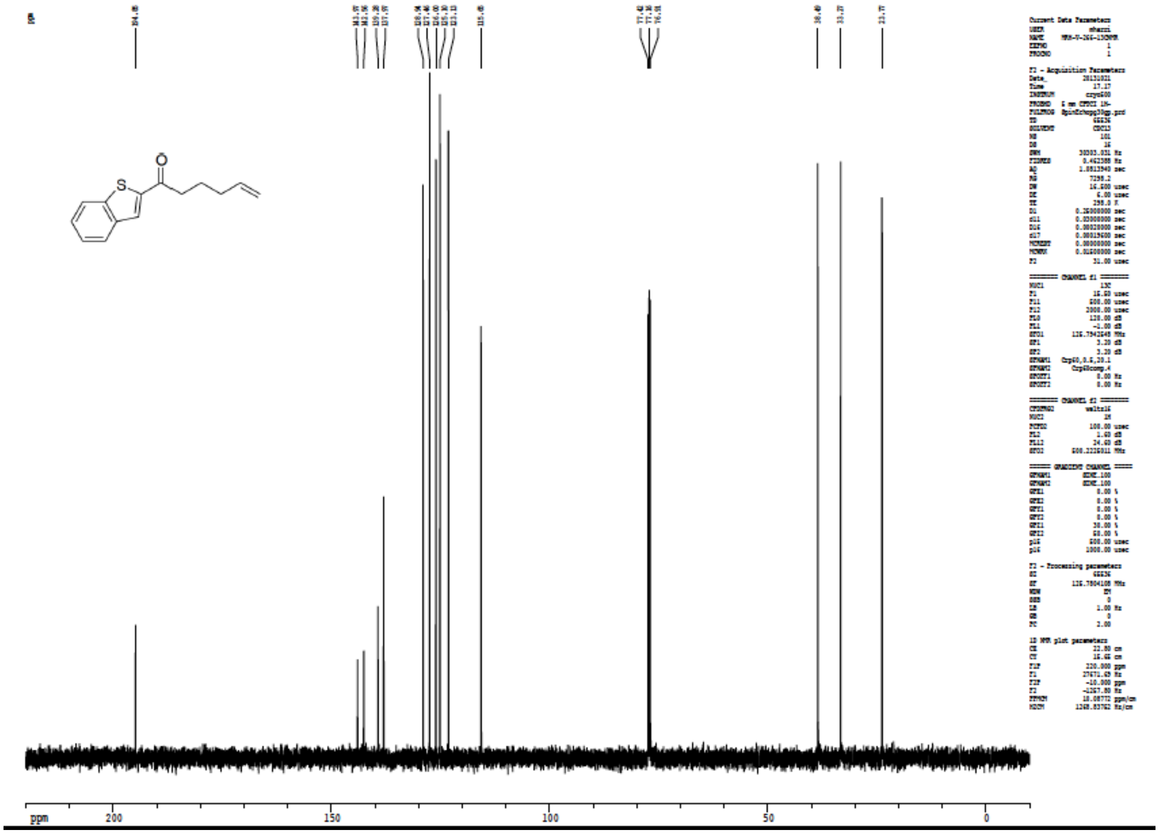
Z-restored spin-echo 13C spectrum with 1H decoupling



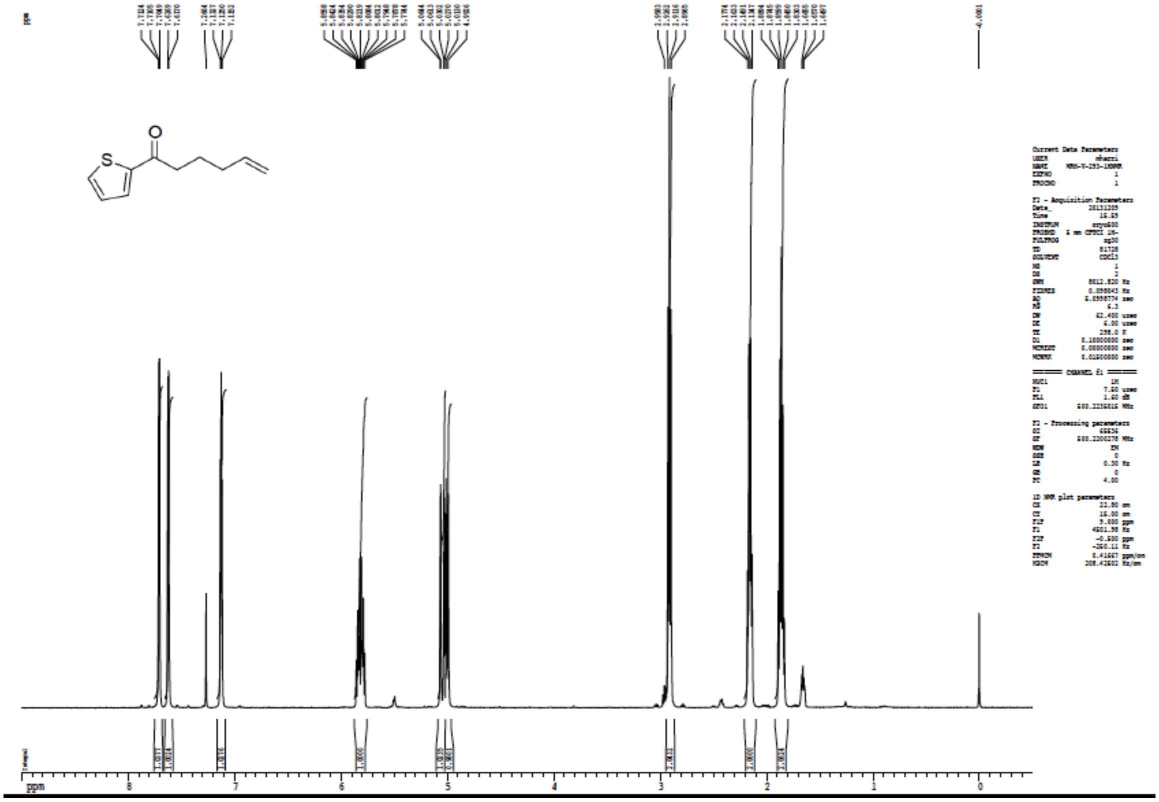
1H spectrum



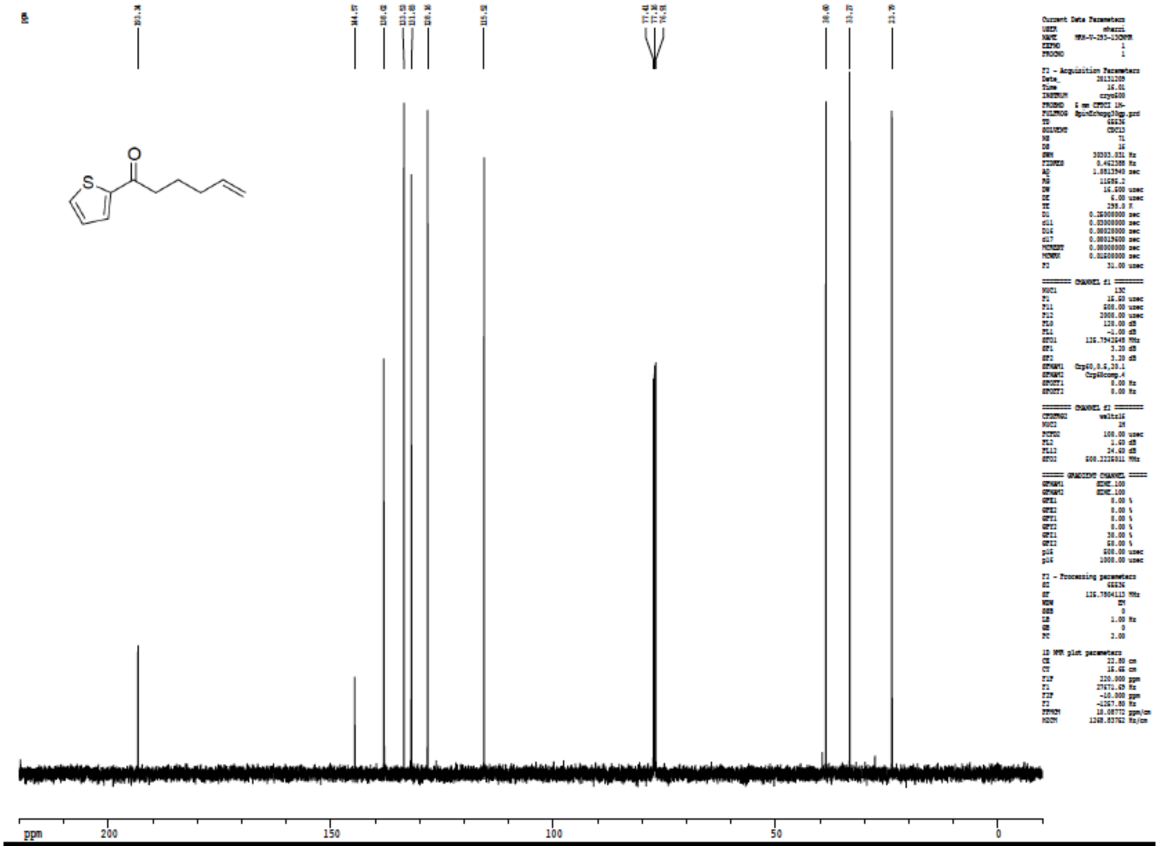
Z-restored spin-echo 13C spectrum with 1H decoupling



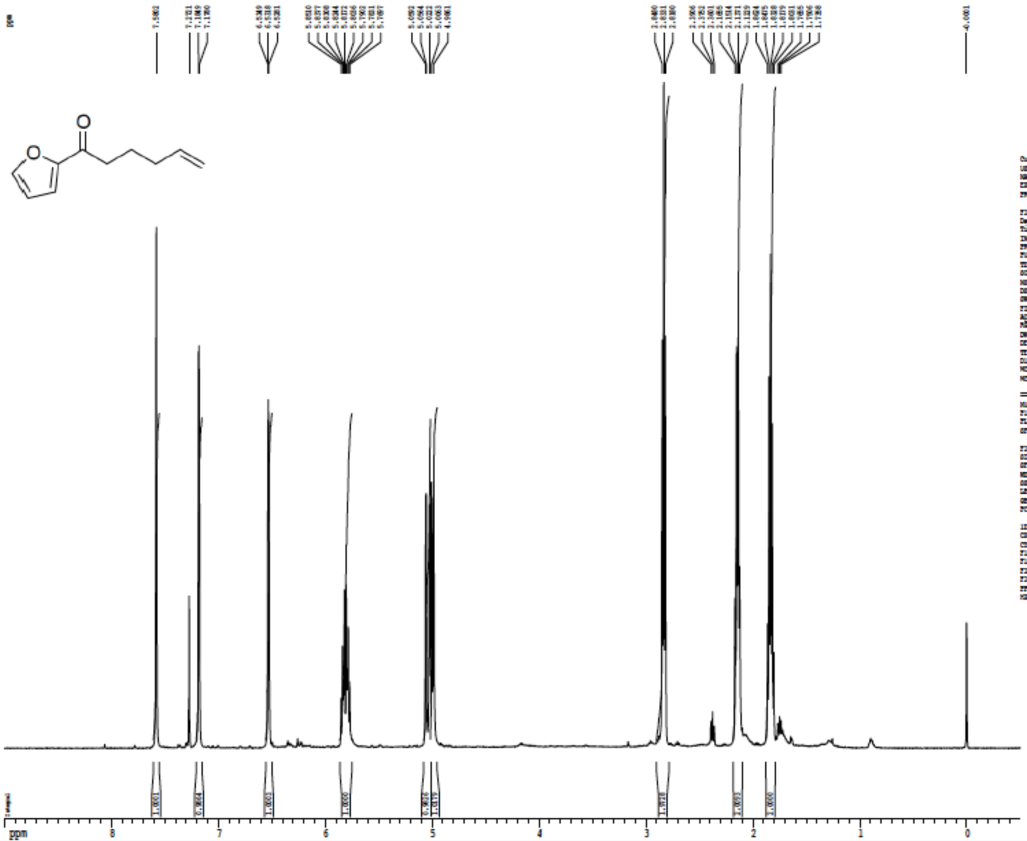
1H spectrum



Z-restored spin-echo 13C spectrum with 1H decoupling



1H spectrum



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EXPNO                   1
PROCNO                  1

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Time                18.33
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PULPROG              zg30
TD                  81728
SOLVENT             CDCl3
NS                      1
DS                      2
SWH              8012.820 Hz
FIDRES           0.098043 Hz
AQ              5.0998774 sec
RG                      4
DW                 62.400 usec
DE                   6.00 usec
TE                  298.0 K
D1             0.10000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   7.50 usec
PL1                  1.60 dB
SFO1          600.2236016 MHz

F2 - Processing parameters
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SF            600.2200247 MHz
WDW                    EM
SSB                     0
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GB                      0
PC                   4.00

1D NMR plot parameters
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CY                  15.00 cm
F1P                 9.000 ppm
F1                4501.98 Hz
F2P                -0.500 ppm
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HZCM            208.42602 Hz/cm
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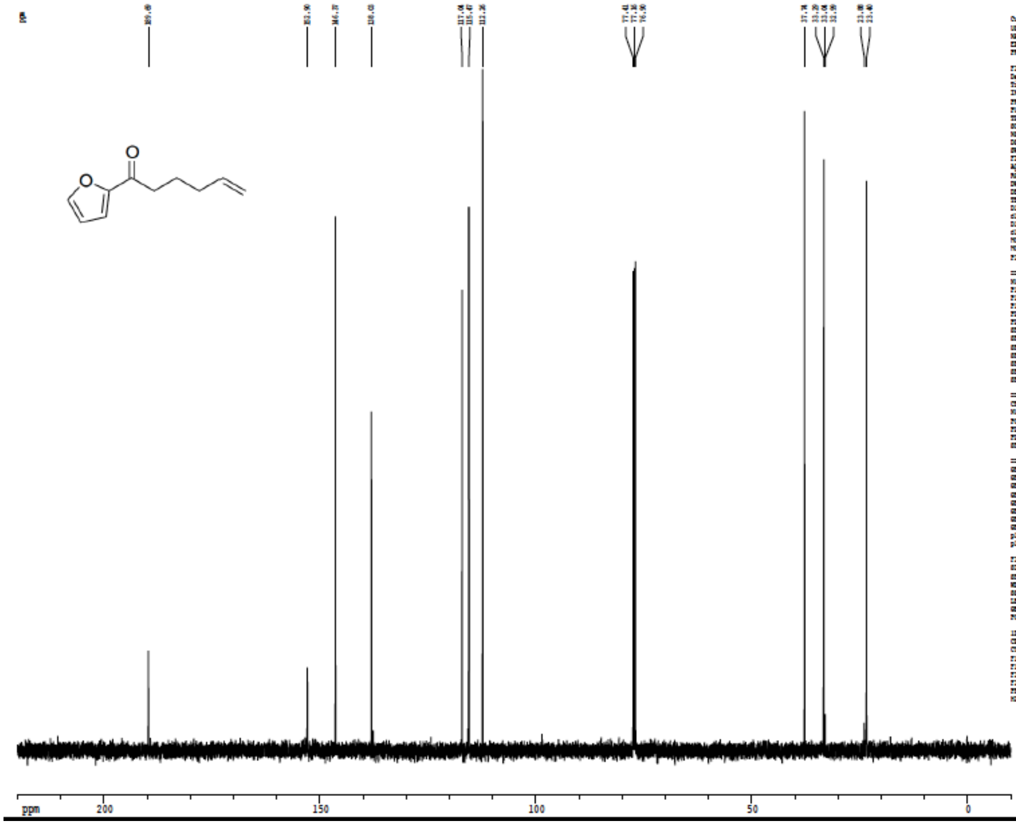
Z-restored spin-echo 13C spectrum with 1H decoupling



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NS                     56
DS                     16
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FIDRES           0.462388 Hz
AQ              1.0813940 sec
RG                 4597.6
DW                 16.500 usec
DE                   6.00 usec
TE                  298.0 K
D1             0.25000000 sec
d11            0.03000000 sec
D16            0.00020000 sec
d17            0.00019600 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec
P2                  31.00 usec

======== CHANNEL f1 ========
NUC1                  13C
P1                  15.50 usec
P11                500.00 usec
P12               2000.00 usec
PL0                120.00 dB
PL1                 -1.00 dB
SFO1          125.7942648 MHz
SP1                  3.20 dB
SP2                  3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFFS1              0.00 Hz
SPOFFS2              0.00 Hz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                  1.60 dB
PL12                24.60 dB
SFO2          600.2226011 MHz

===== GRADIENT CHANNEL =====
GPNAM1           SINE.100
GPNAM2           SINE.100
GPX1                 0.00 %
GPX2                 0.00 %
GPY1                 0.00 %
GPY2                 0.00 %
GPZ1                30.00 %
GPZ2                50.00 %
p15                500.00 usec
p16               1000.00 usec

F2 - Processing parameters
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SF            125.7804103 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   2.00

1D NMR plot parameters
CX                  22.80 cm
CY                  16.66 cm
F1P               220.000 ppm
F1               27671.69 Hz
F2P               -10.000 ppm
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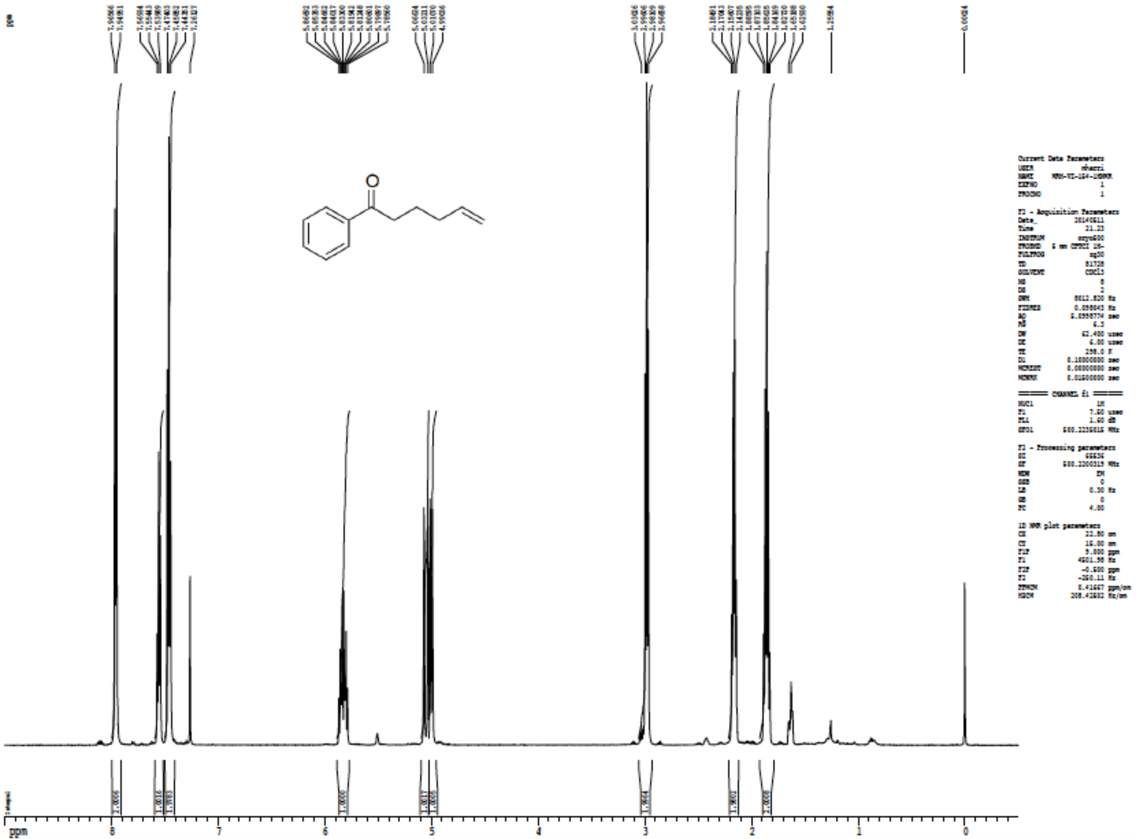
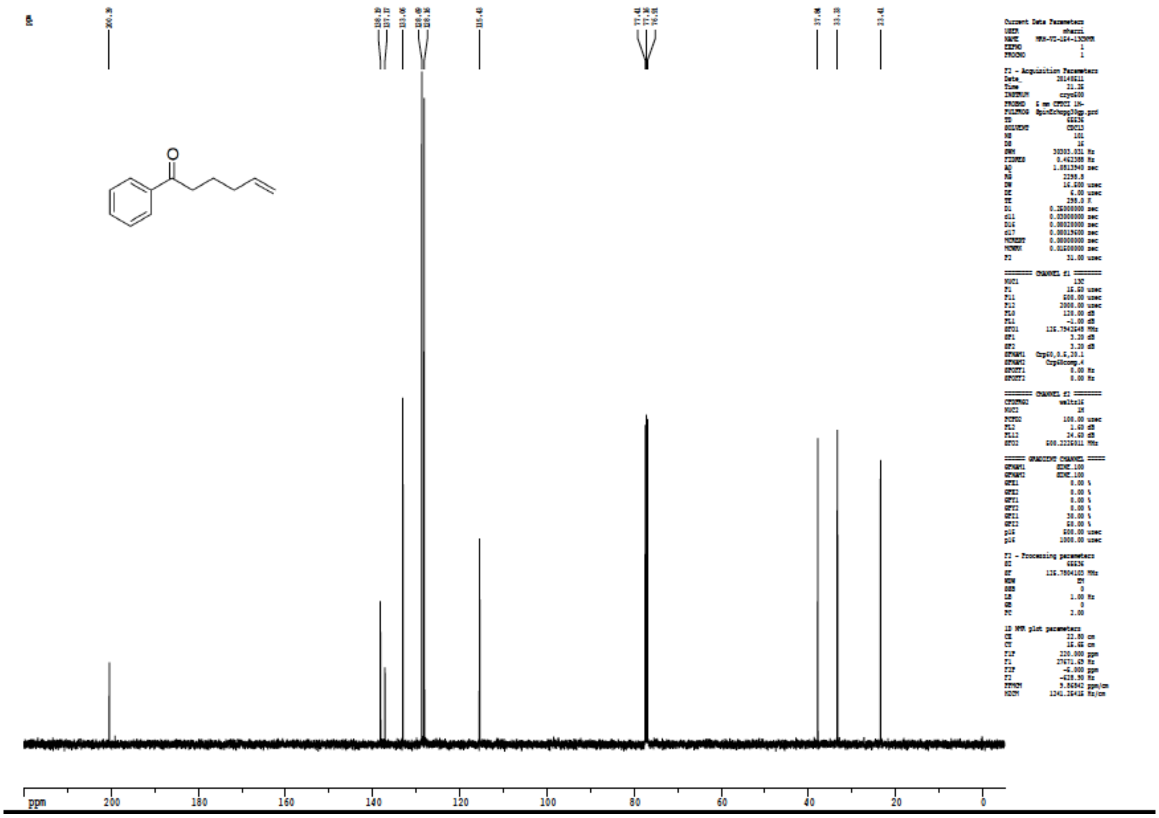
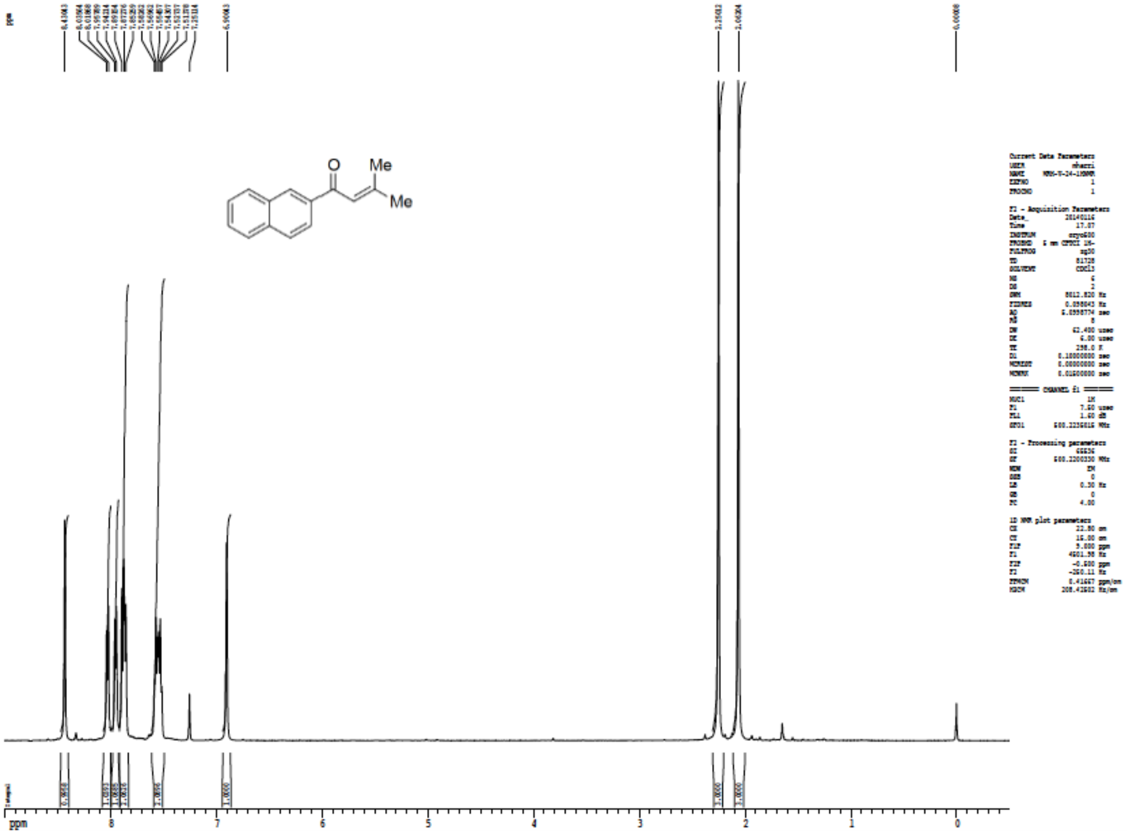


1H spectrum

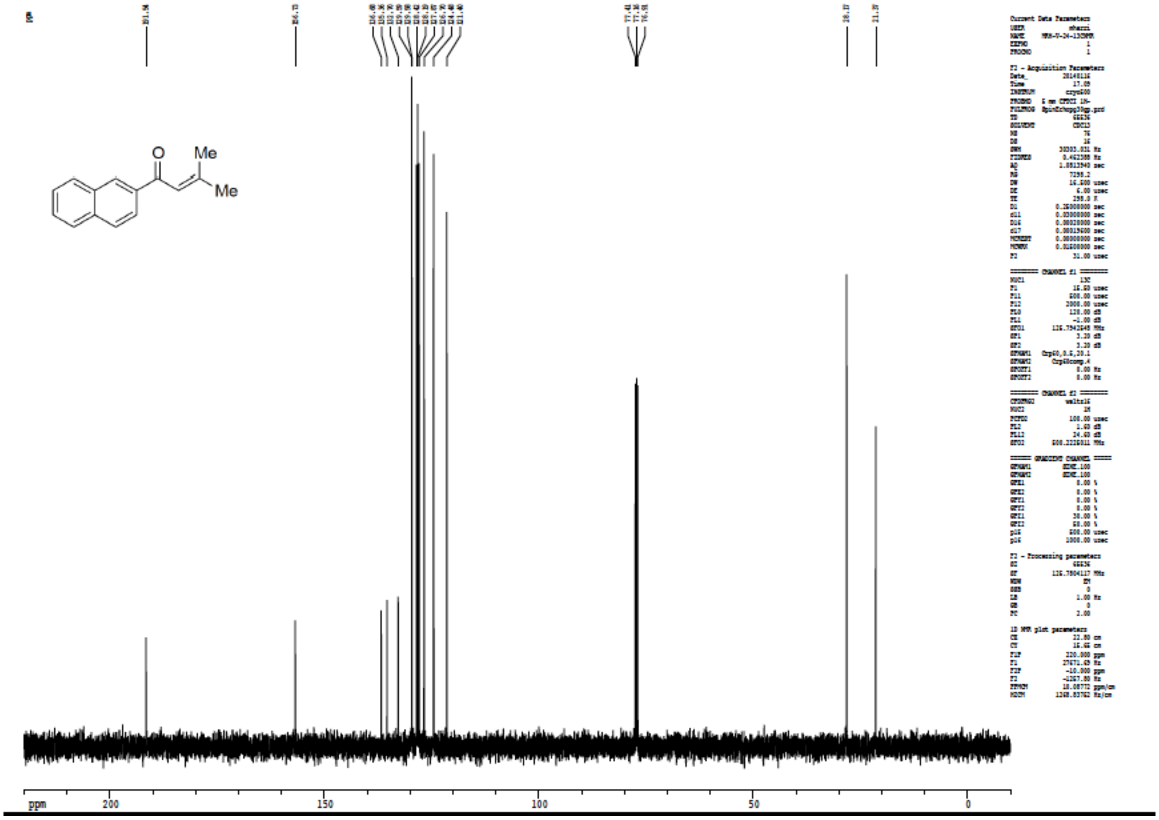


Z-restored spin-echo 13C spectrum with 1H decoupling

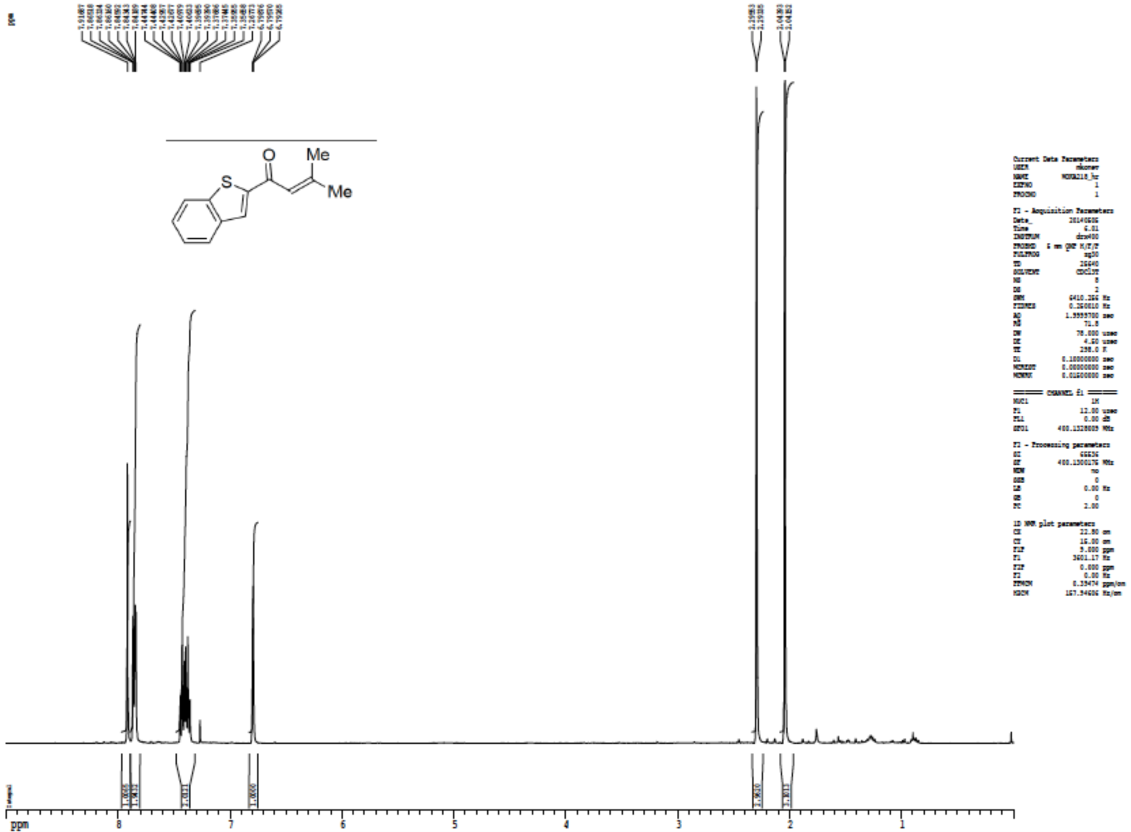
1H spectrum



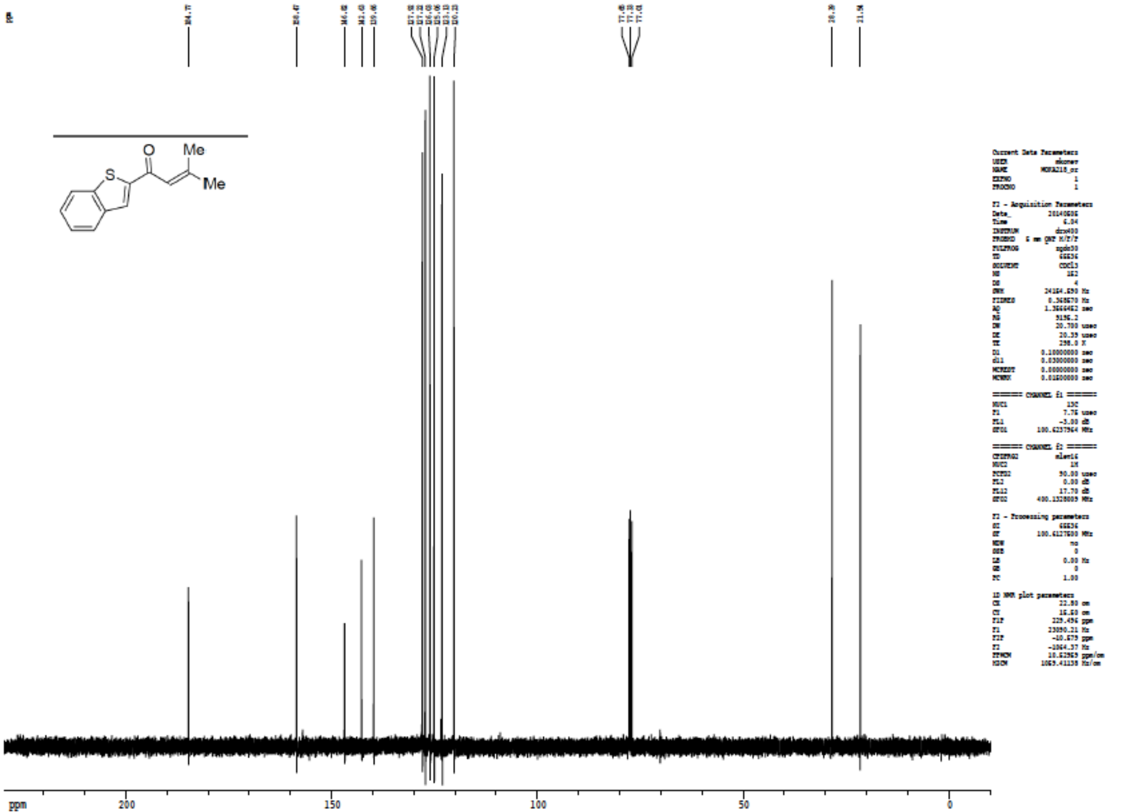
Z-restored spin-echo 13C spectrum with 1H decoupling



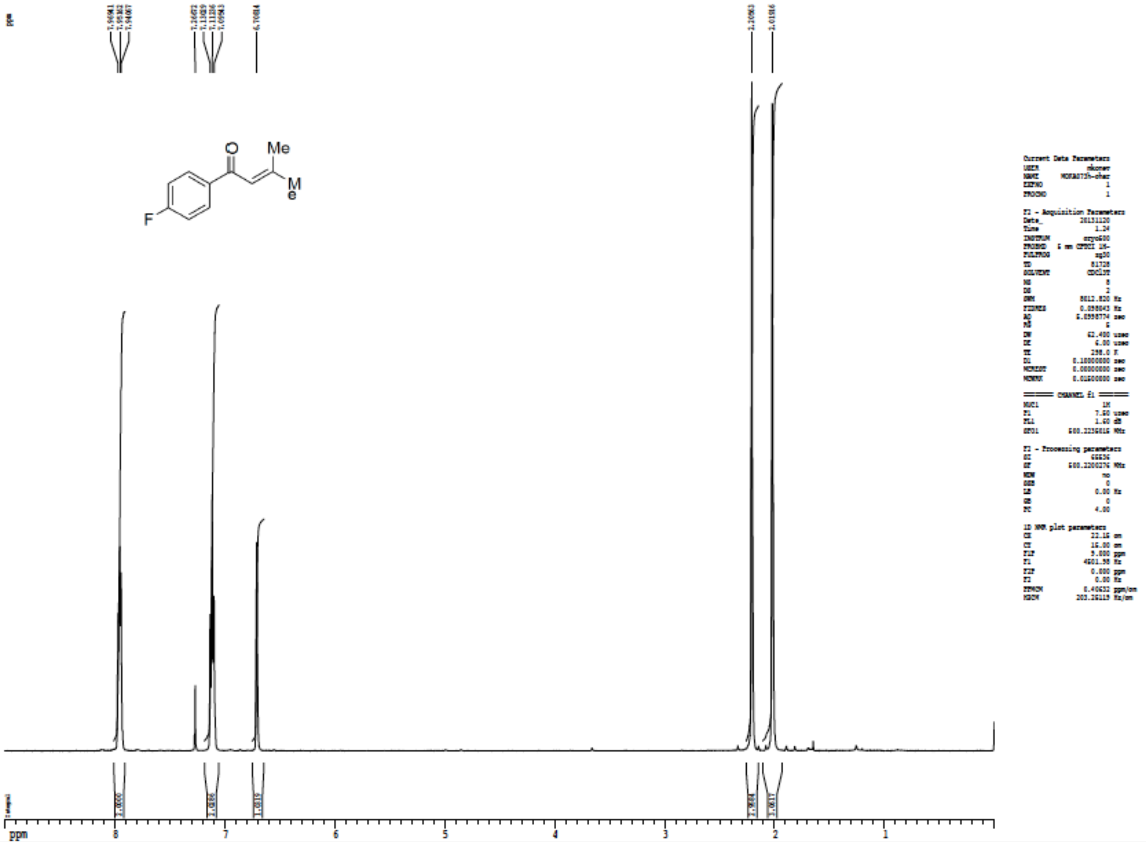
1H spectrum



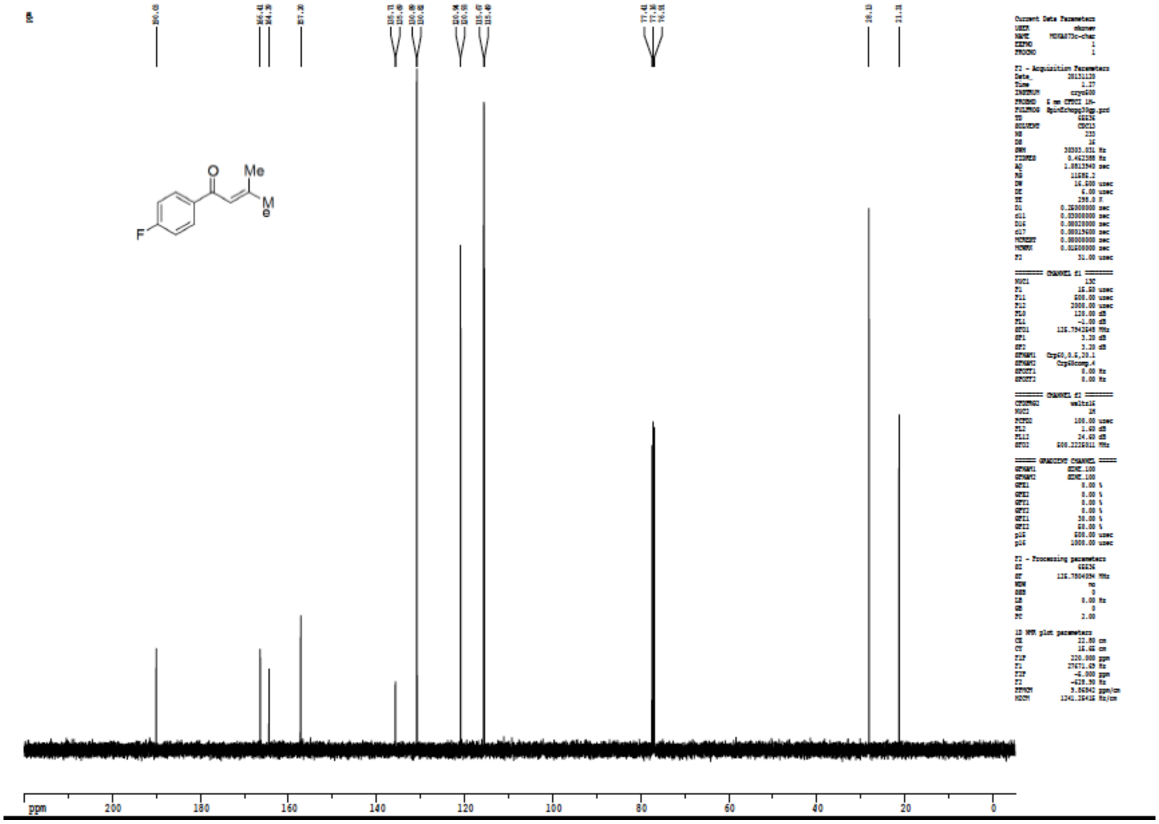
13C spectrum with 1H decoupling

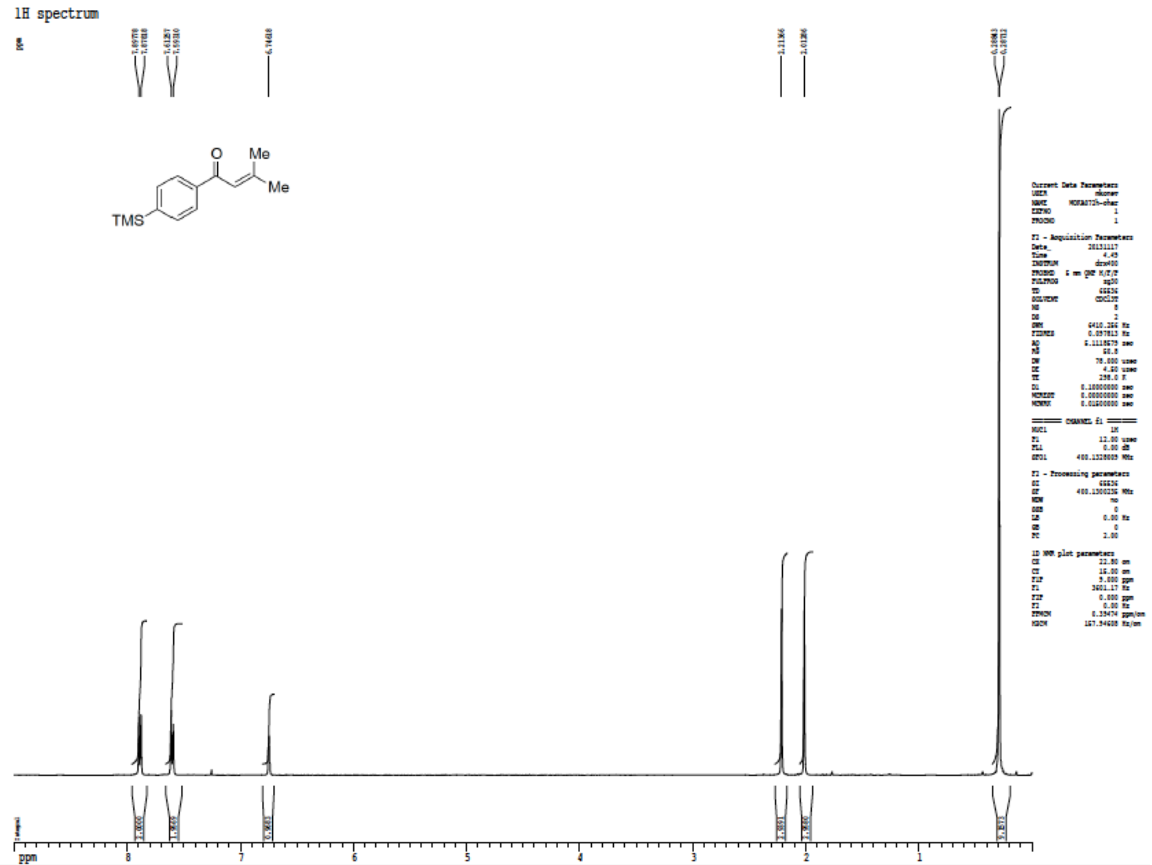


1H spectrum



Z-restored spin-echo 13C spectrum with 1H decoupling




1H spectrum
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Me
Me
TMS
ppm
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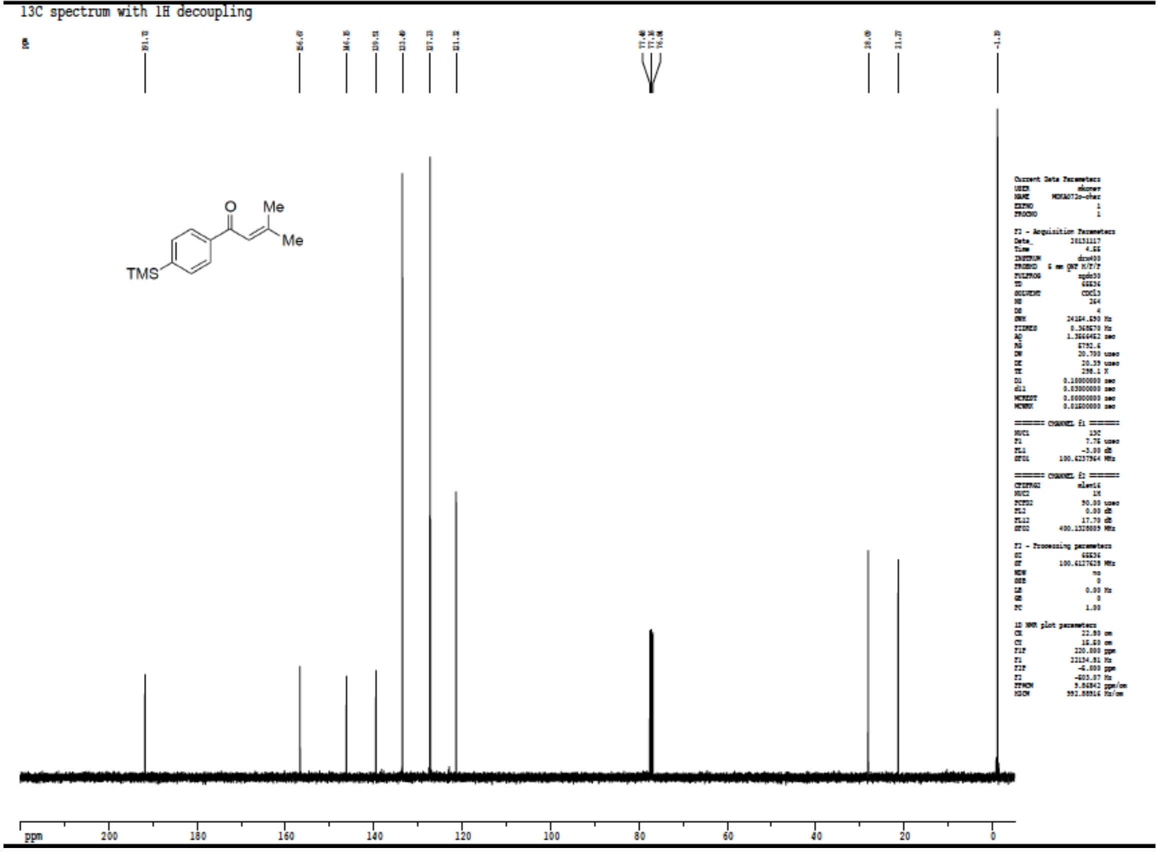
1


13C spectrum with 1H decoupling
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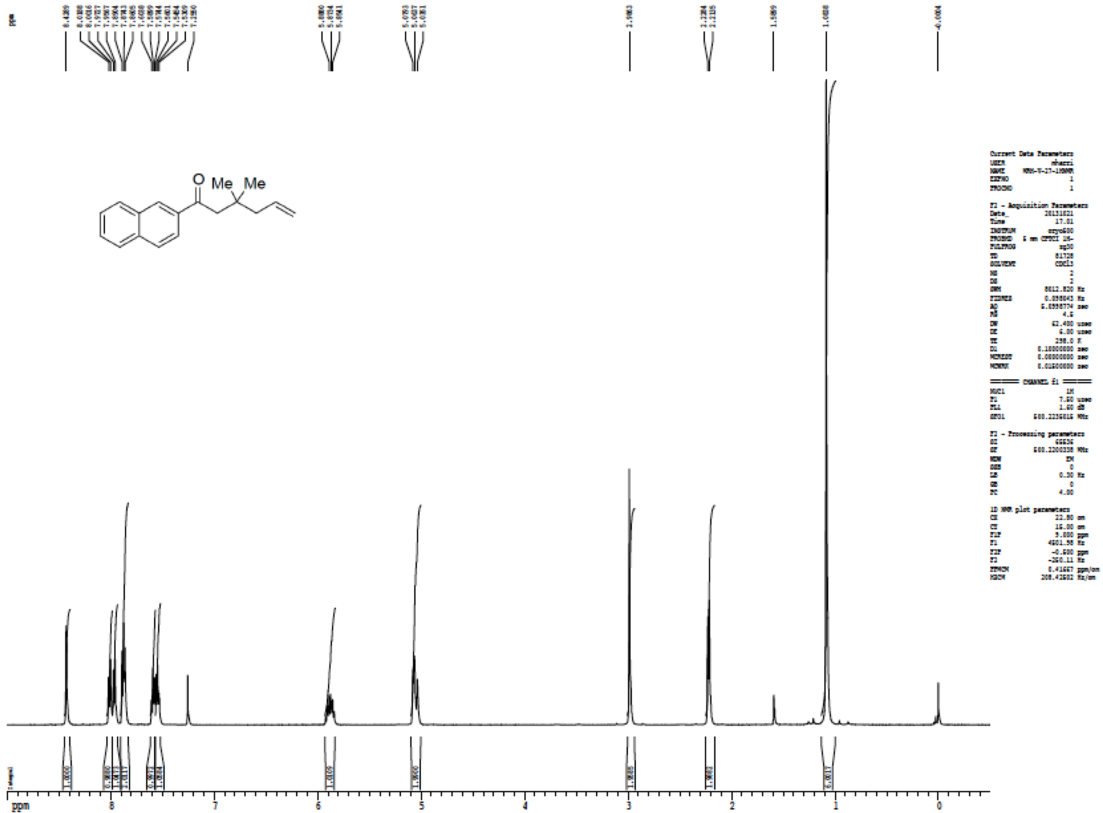
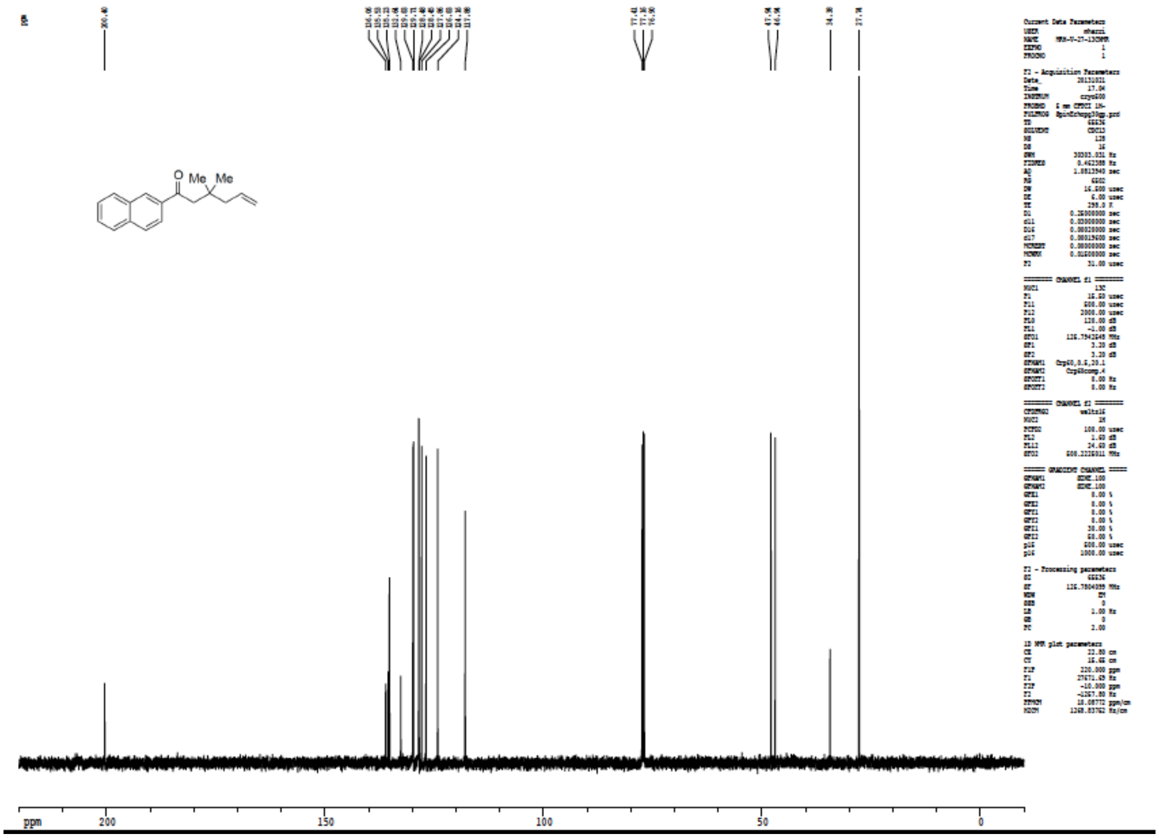
20
0

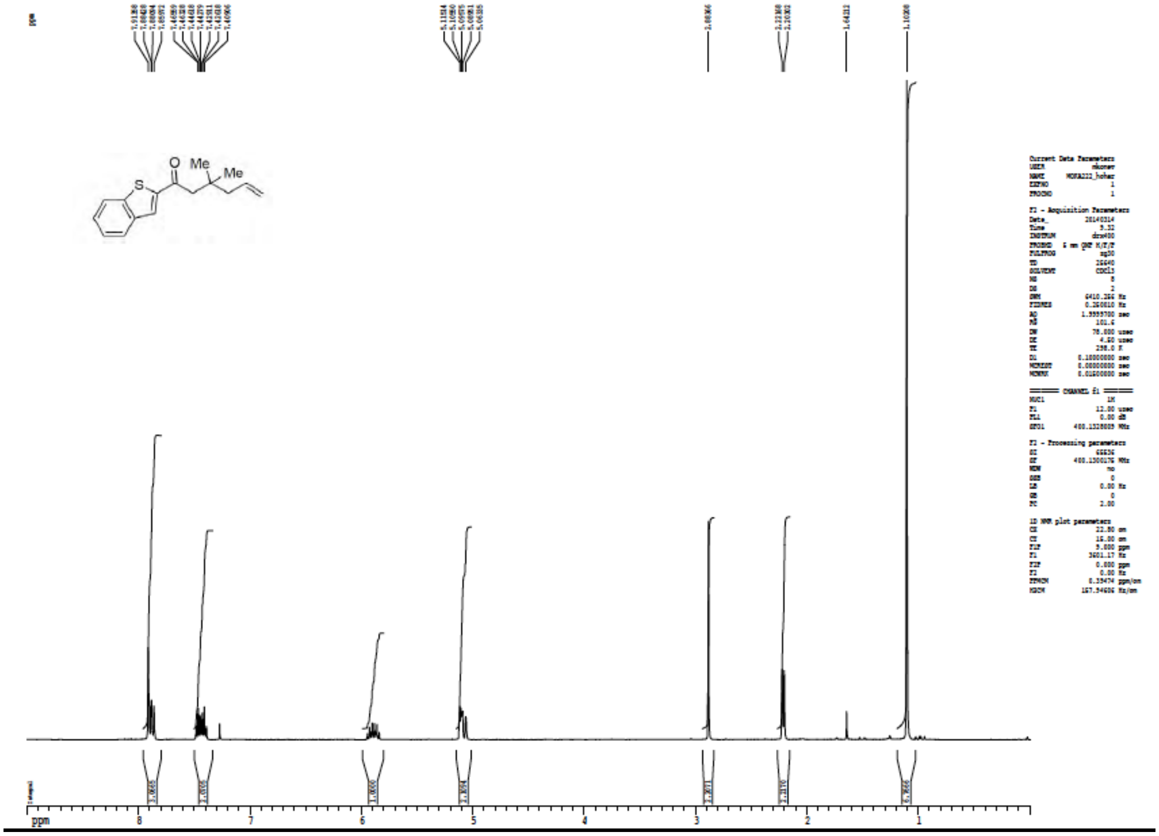
1H spectrum



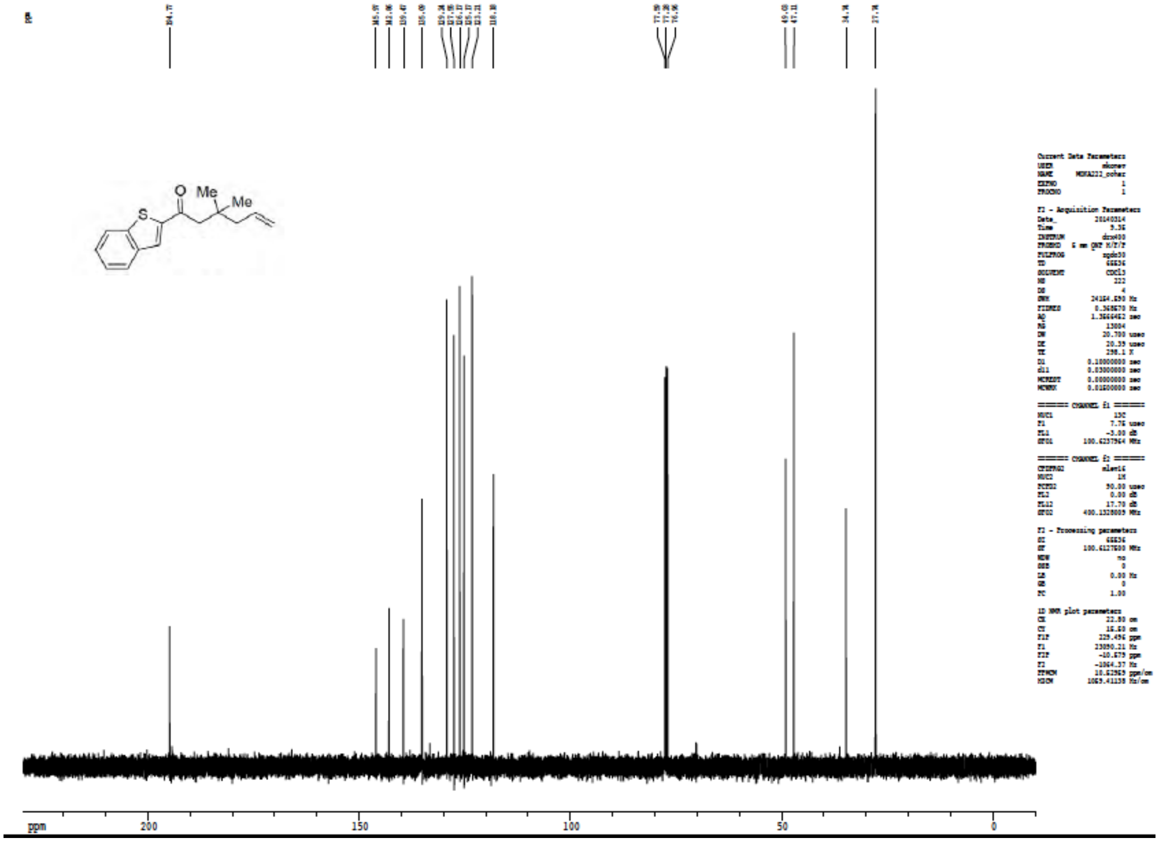
Z-restored spin-echo 13C spectrum with 1H decoupling



1H spectrum



13C spectrum with 1H decoupling



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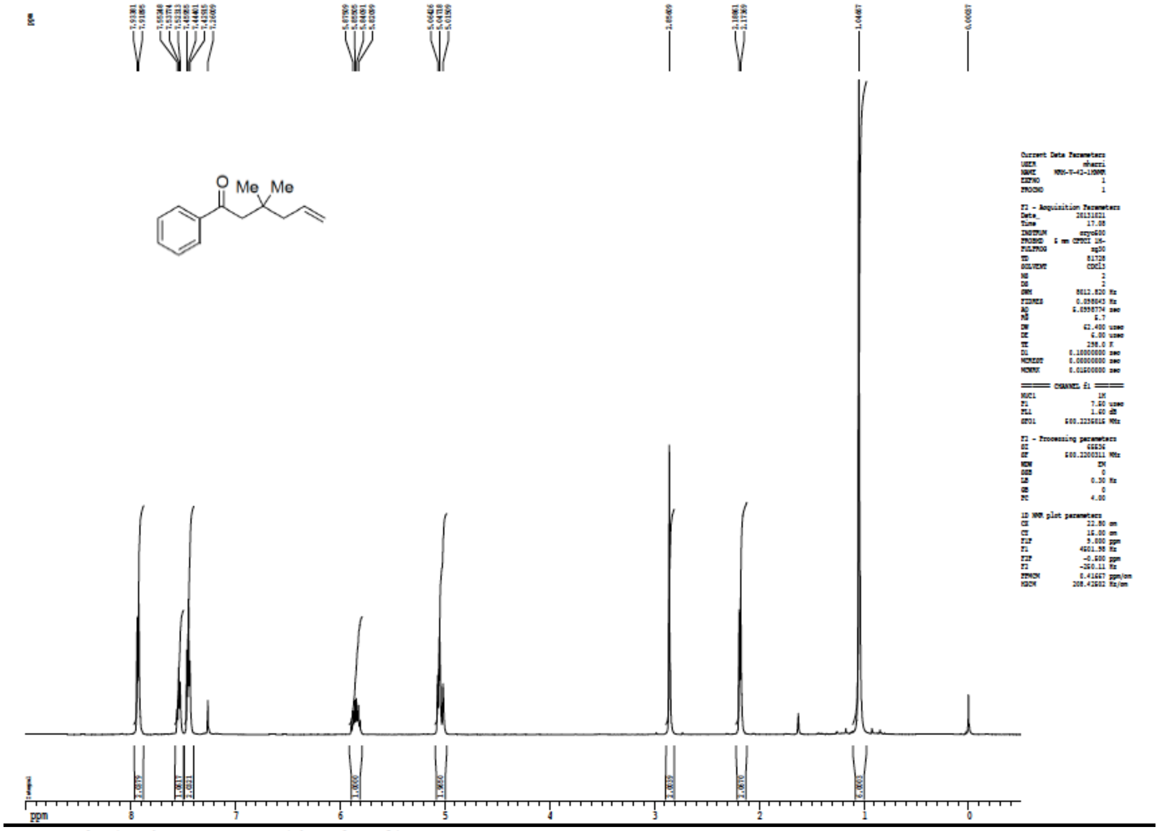
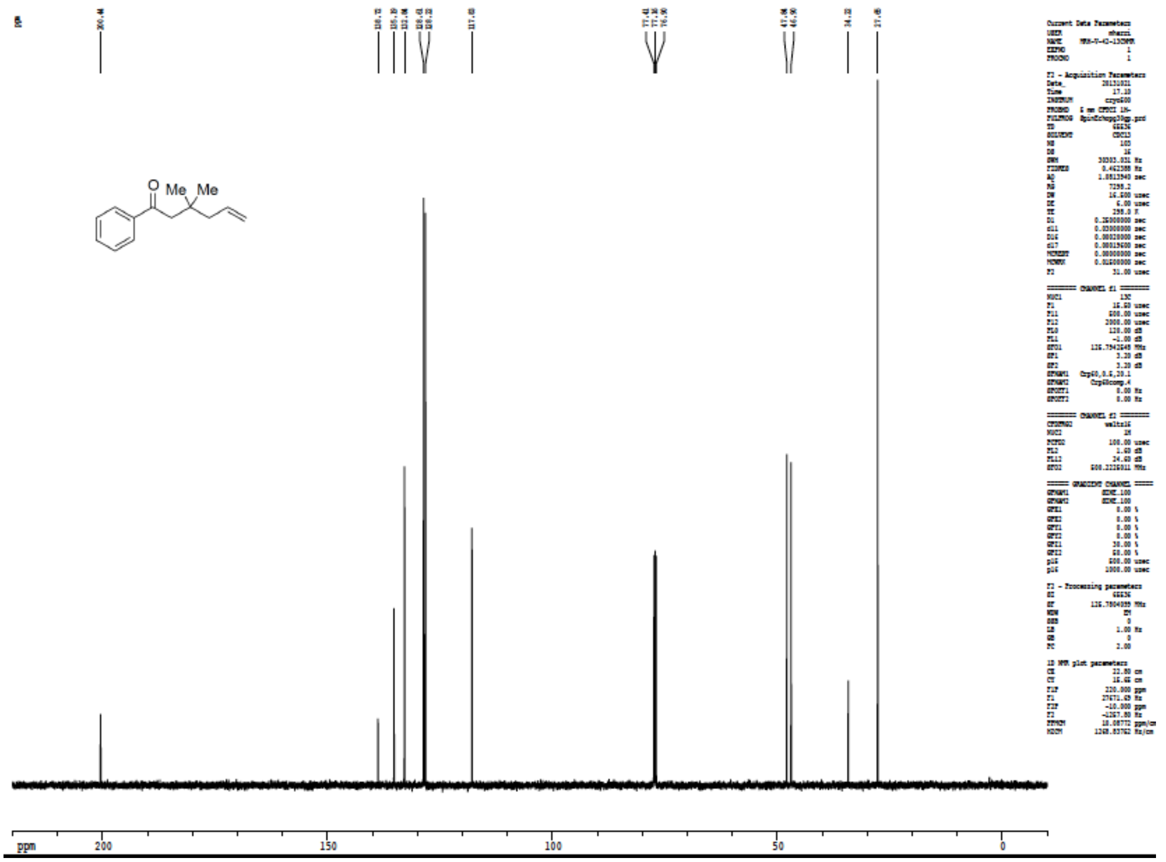
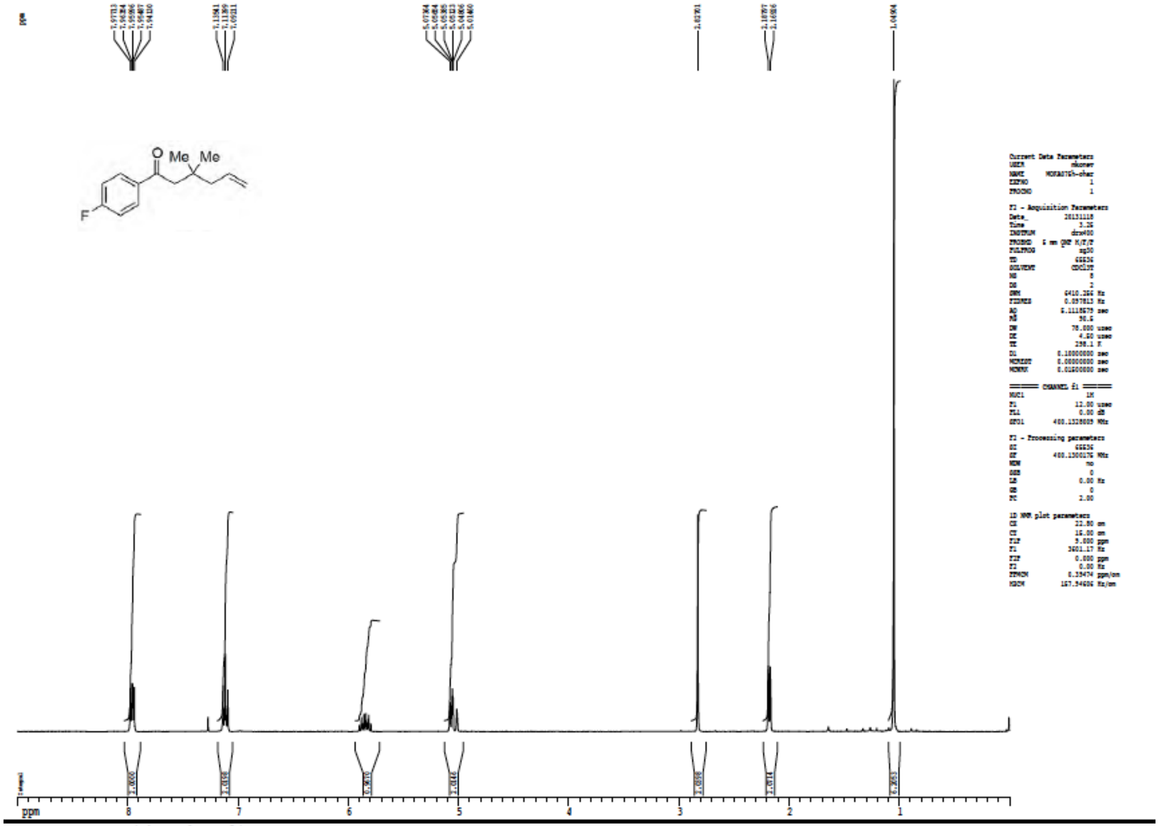


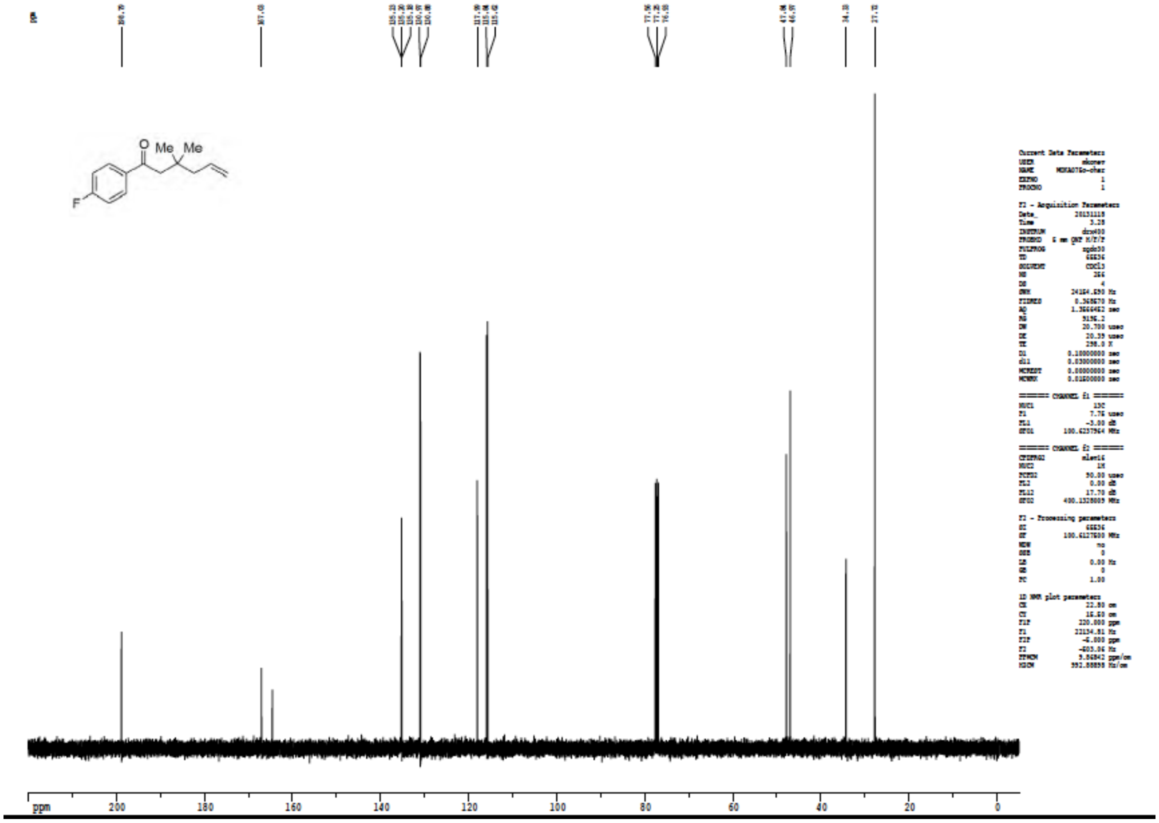
Z-restored spin-echo 13C spectrum with 1H decoupling



1H spectrum



13C spectrum with 1H decoupling



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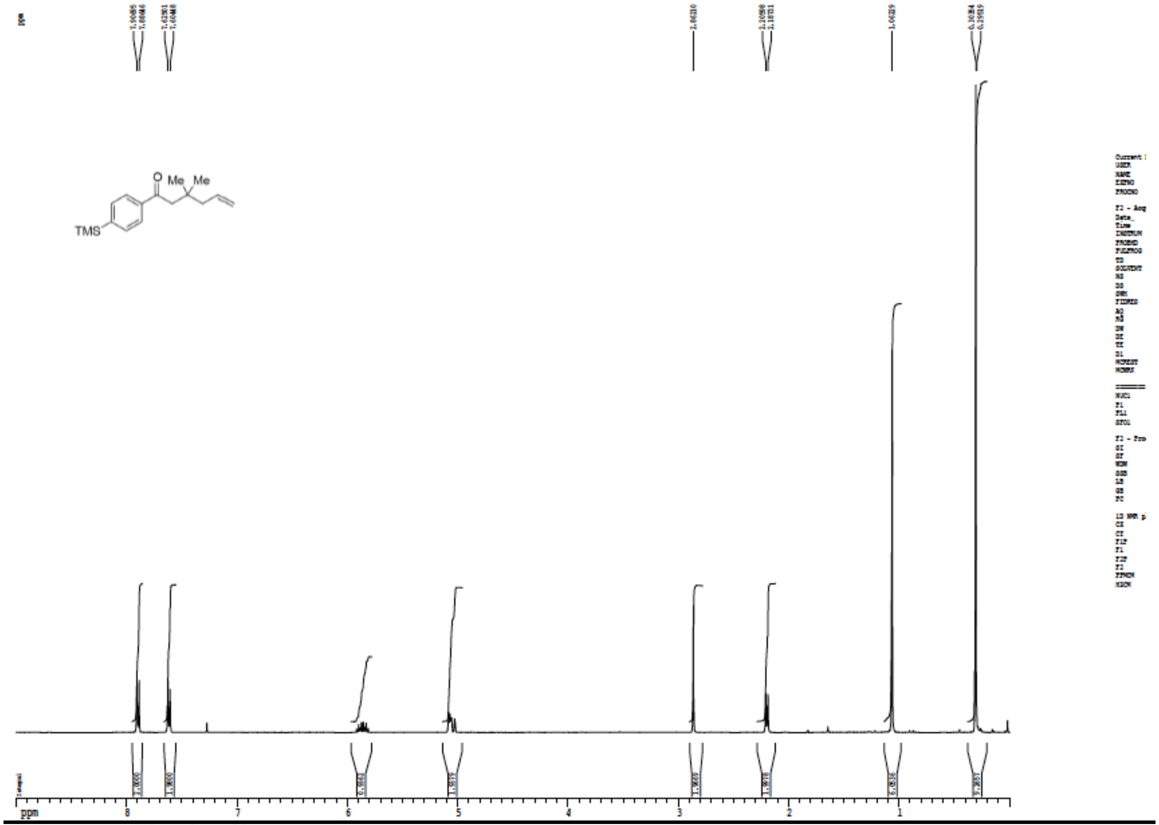
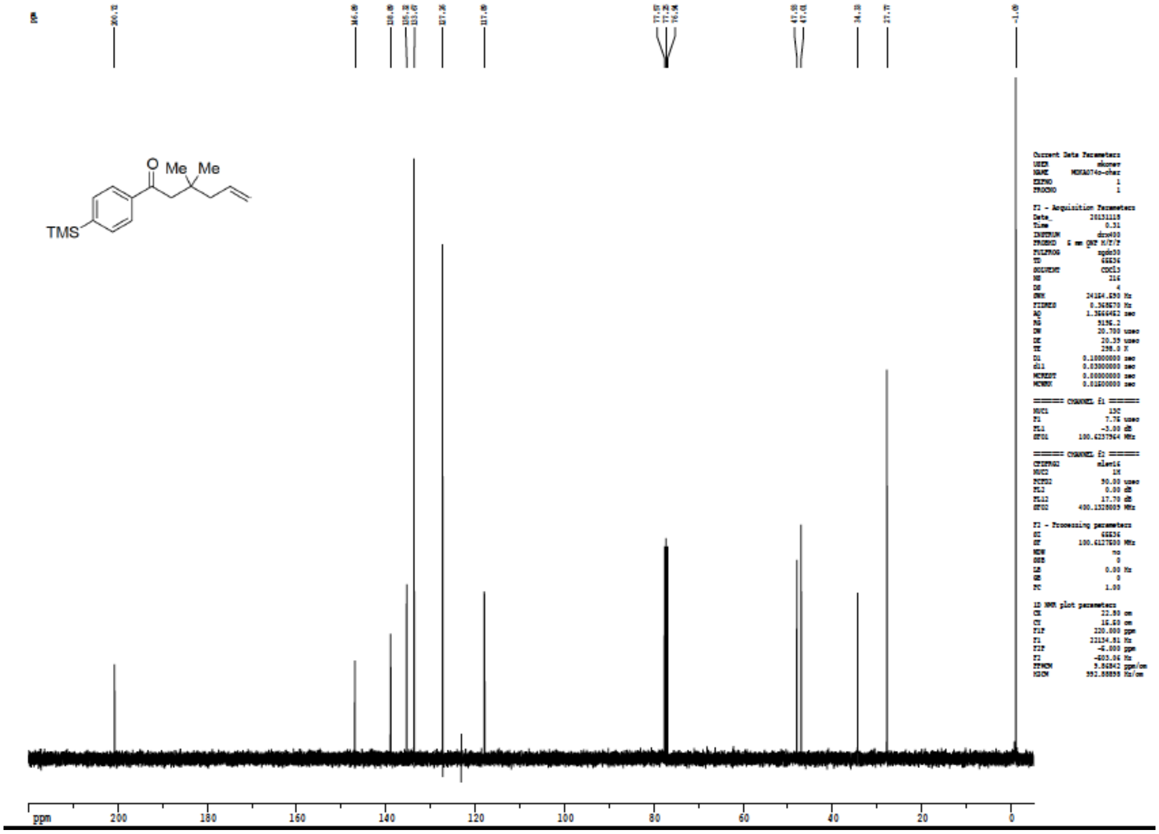


13C spectrum with 1H decoupling



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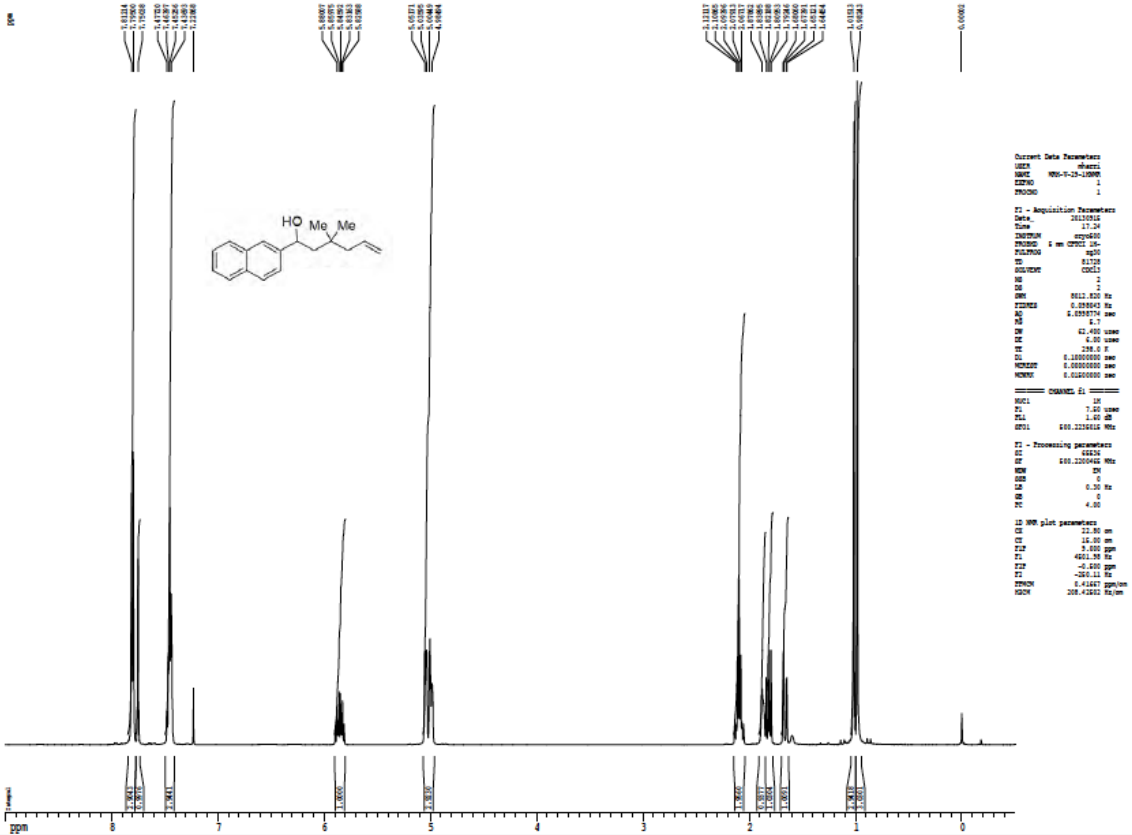
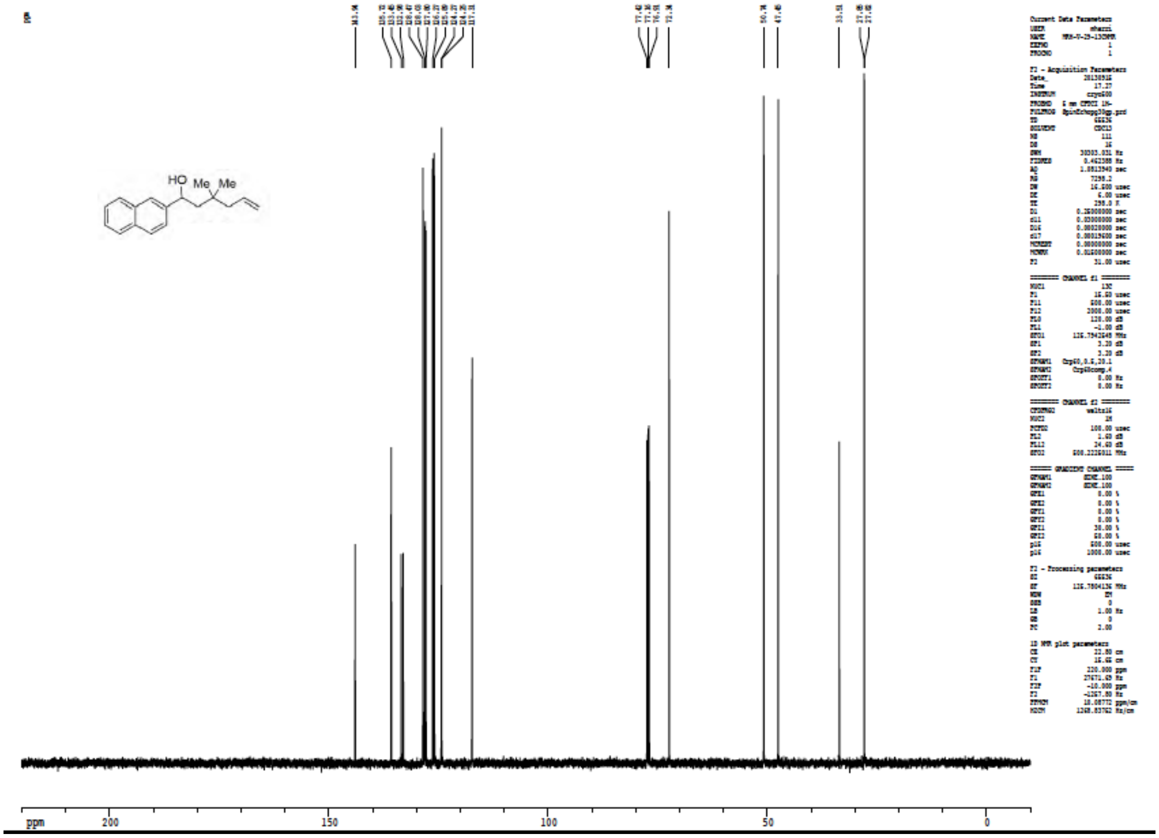
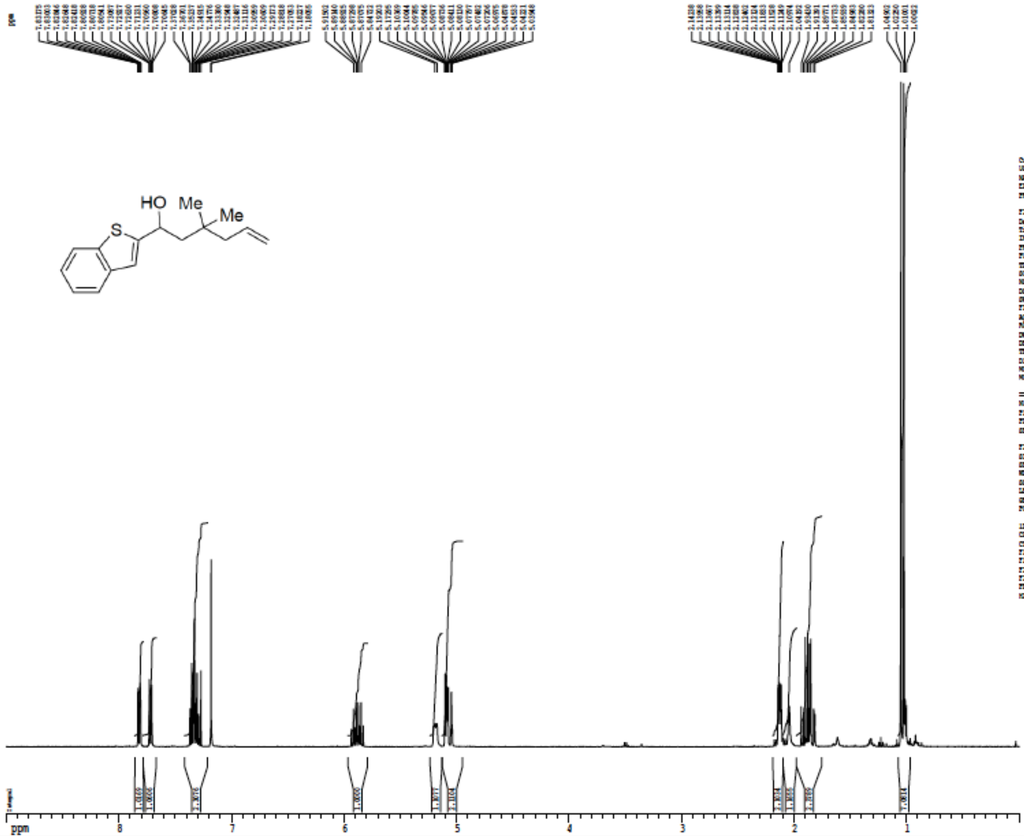


Z-restored spin-echo 13C spectrum with 1H decoupling



1H spectrum



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PROCNO                  1

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PULPROG              zg30
TD                  25640
SOLVENT            CDCl3T
NS                      8
DS                      2
SWH              6410.256 Hz
FIDRES           0.250010 Hz
AQ              1.9999700 sec
RG                    114
DW                 78.000 usec
DE                   4.50 usec
TE                  298.0 K
D1             0.10000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  12.00 usec
PL1                  0.00 dB
SFO1         400.1328009 MHz

F2 - Processing parameters
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SF           400.1300176 MHz
WDW                    no
SSB                     0
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GB                      0
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1D NMR plot parameters
CX                  22.50 cm
CY                  15.00 cm
F1P                 9.000 ppm
F1                3601.17 Hz
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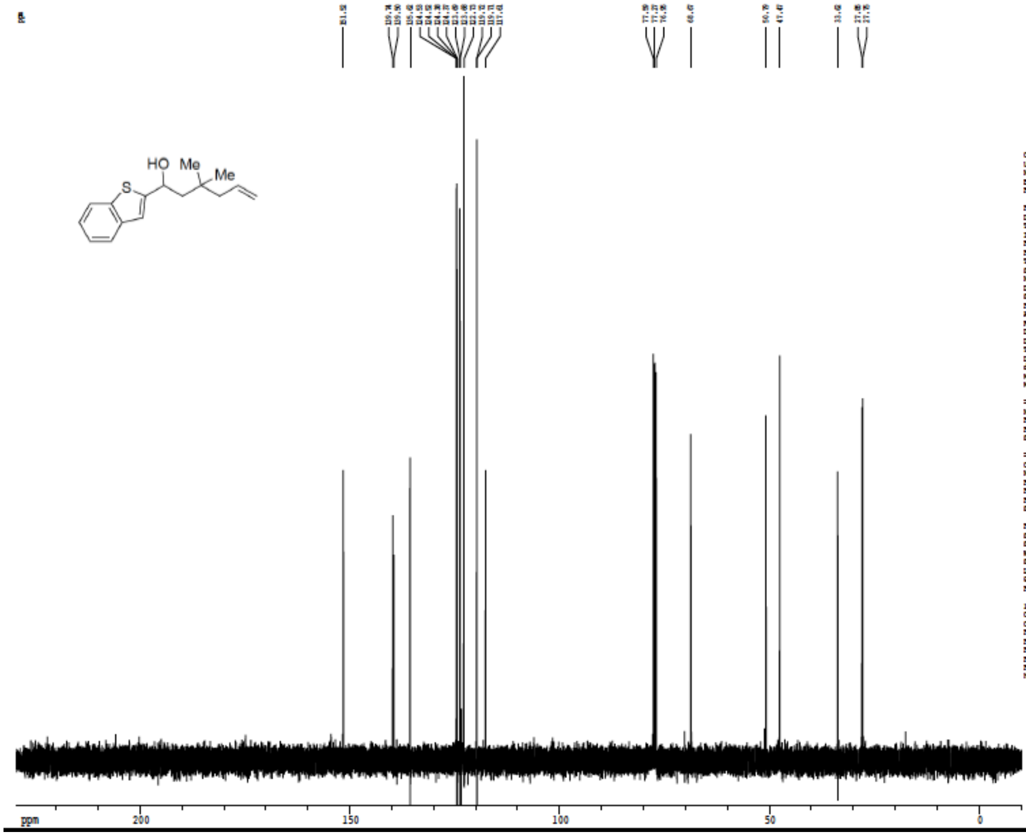
13C spectrum with 1H decoupling



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FIDRES           0.368570 Hz
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RG                14596.5
DW                 20.700 usec
DE                  20.35 usec
TE                  298.0 K
D1             0.10000000 sec
d11            0.03000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                  13C
P1                   7.75 usec
PL1                 -3.00 dB
SFO1         100.6237964 MHz

======== CHANNEL f2 ========
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NUC2                   1H
PCPD2               90.00 usec
PL2                  0.00 dB
PL12                17.70 dB
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F2 - Processing parameters
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GB                      0
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1D NMR plot parameters
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CY                  15.00 cm
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F1               23090.21 Hz
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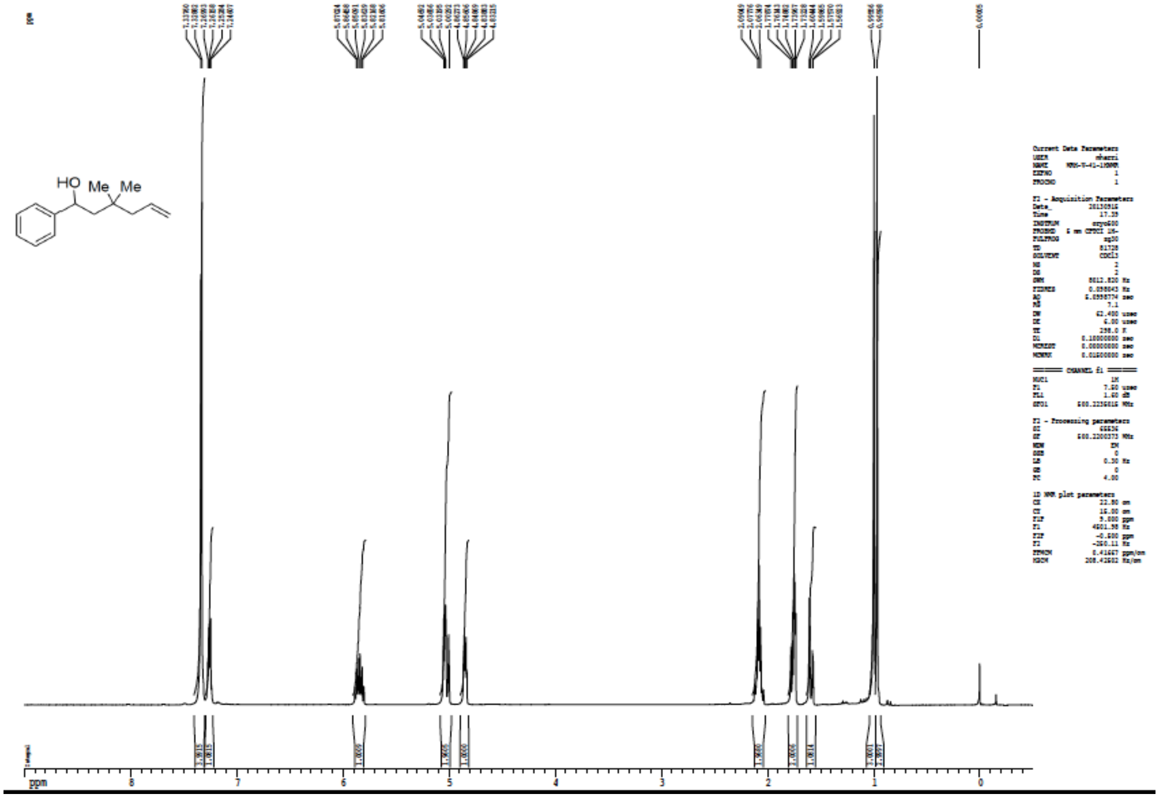
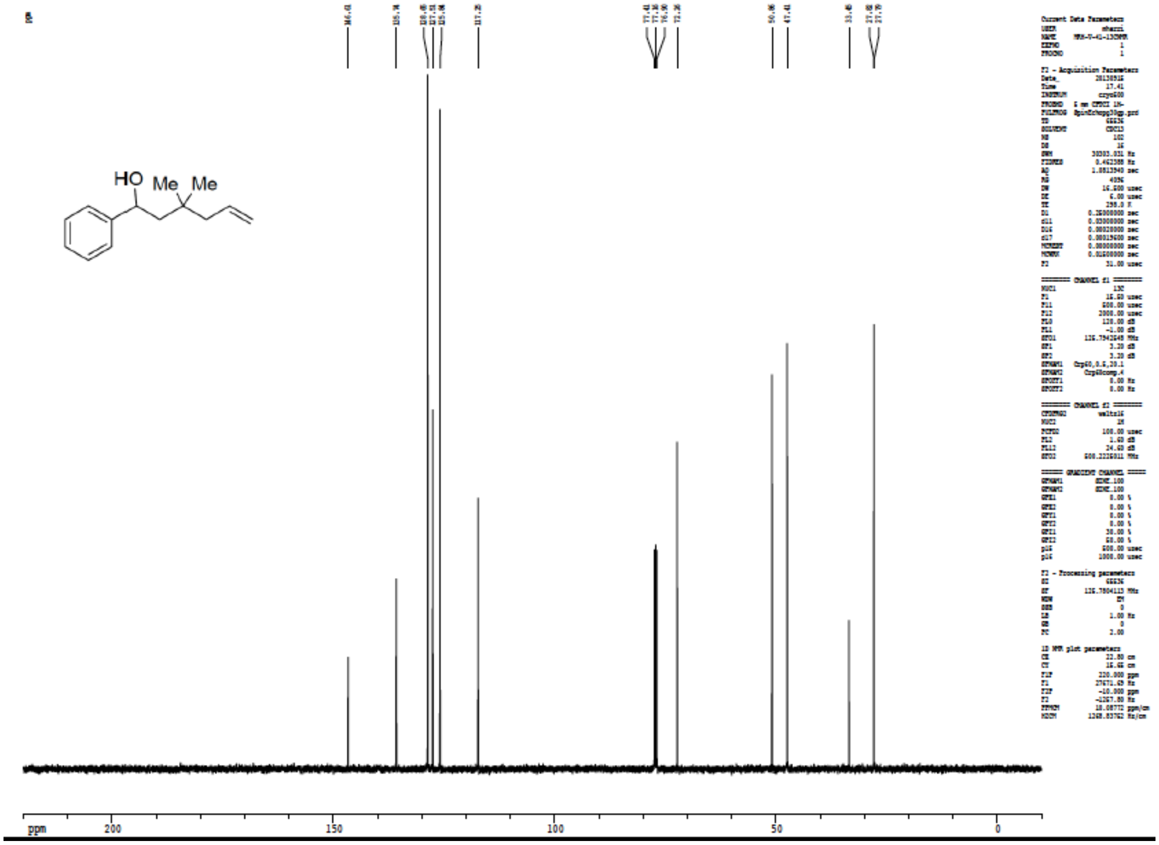
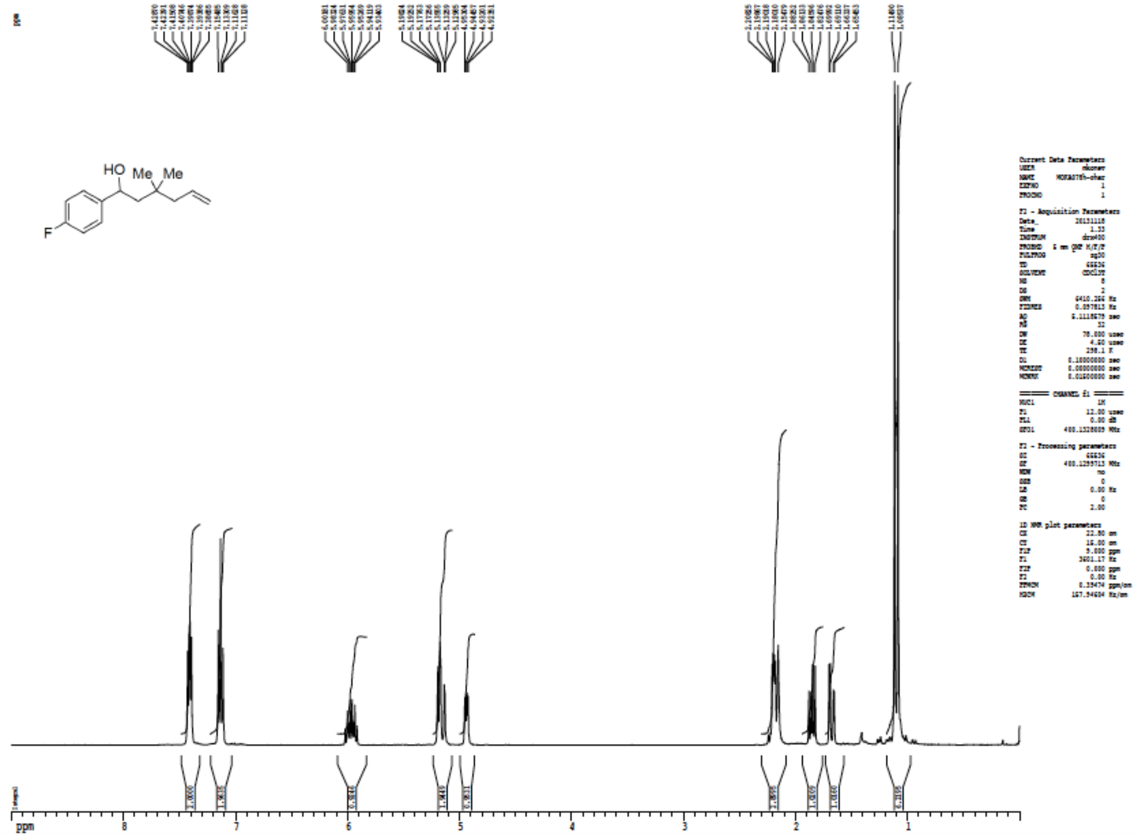
1H spectrum



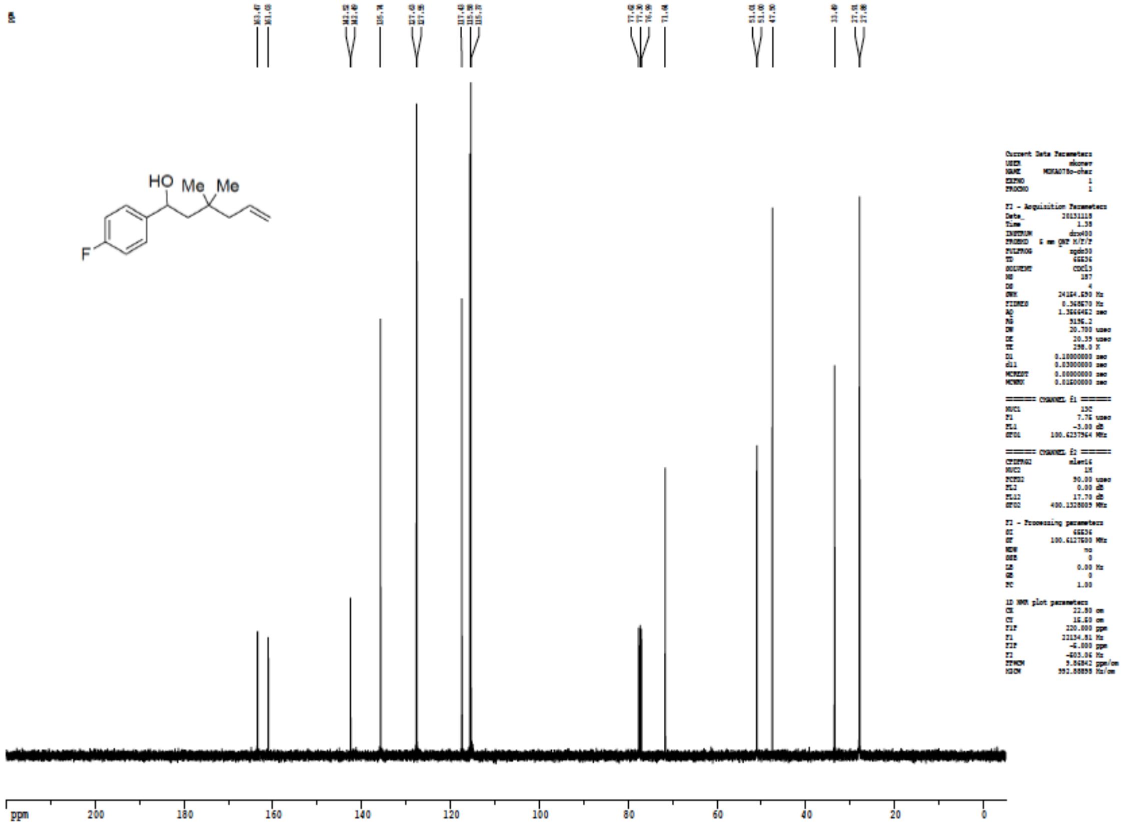
Z-restored spin-echo 13C spectrum with 1H decoupling



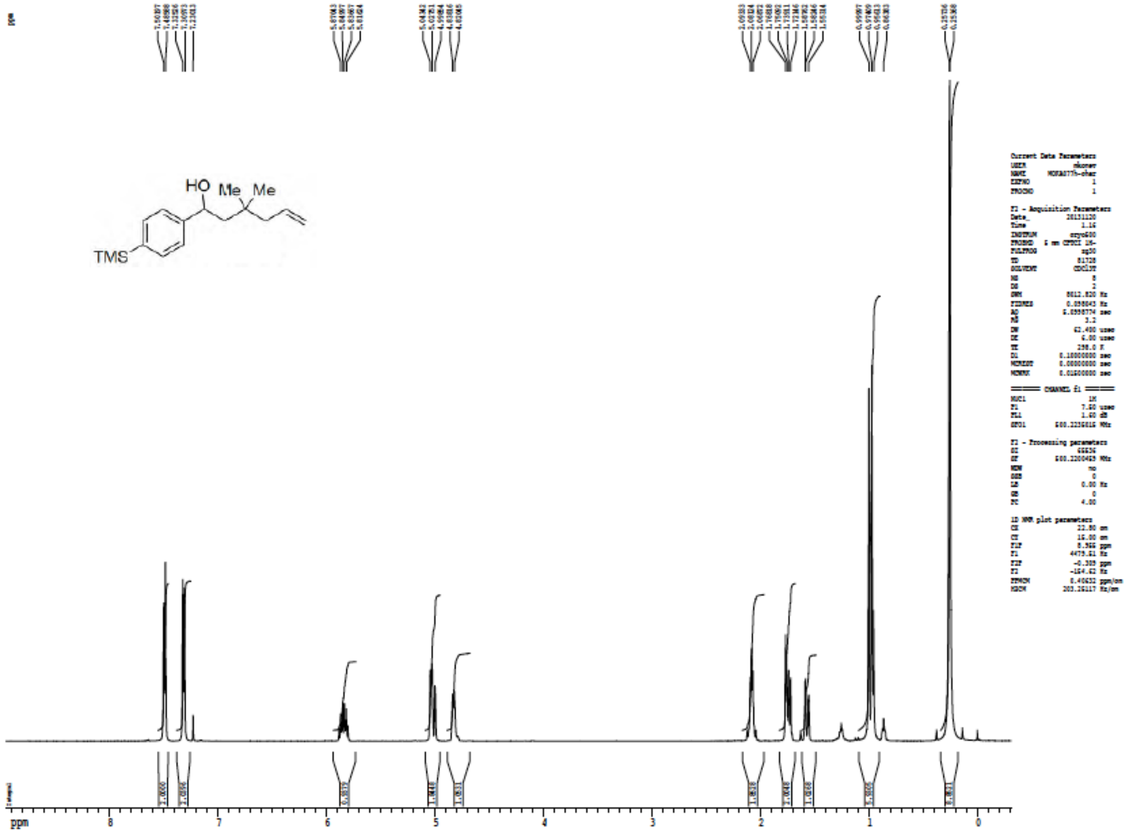
1H spectrum



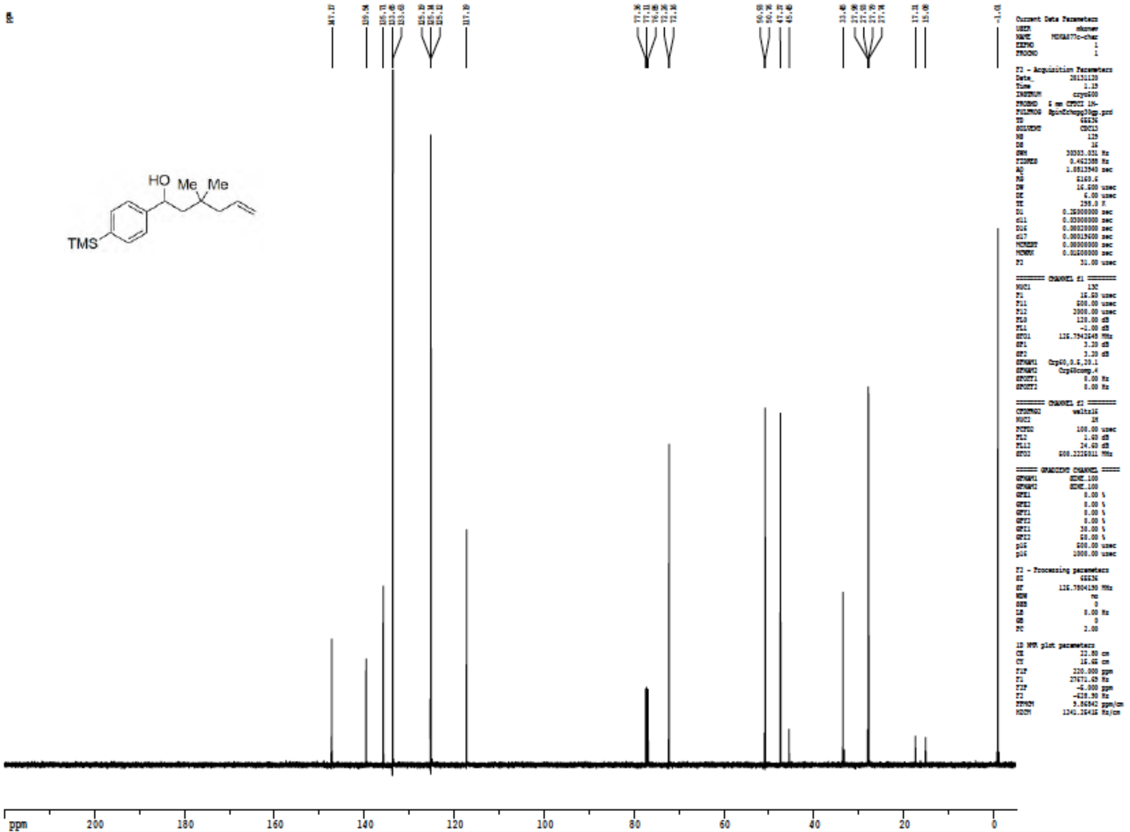
13C spectrum with 1H decoupling



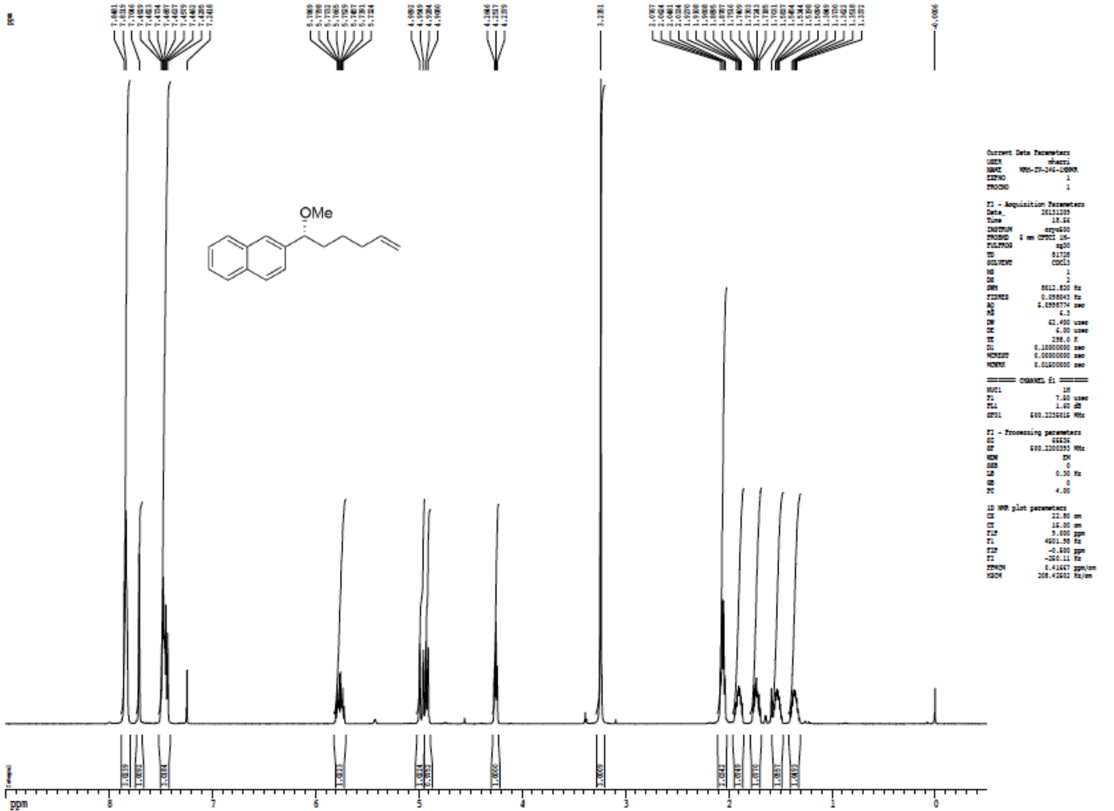
1H spectrum



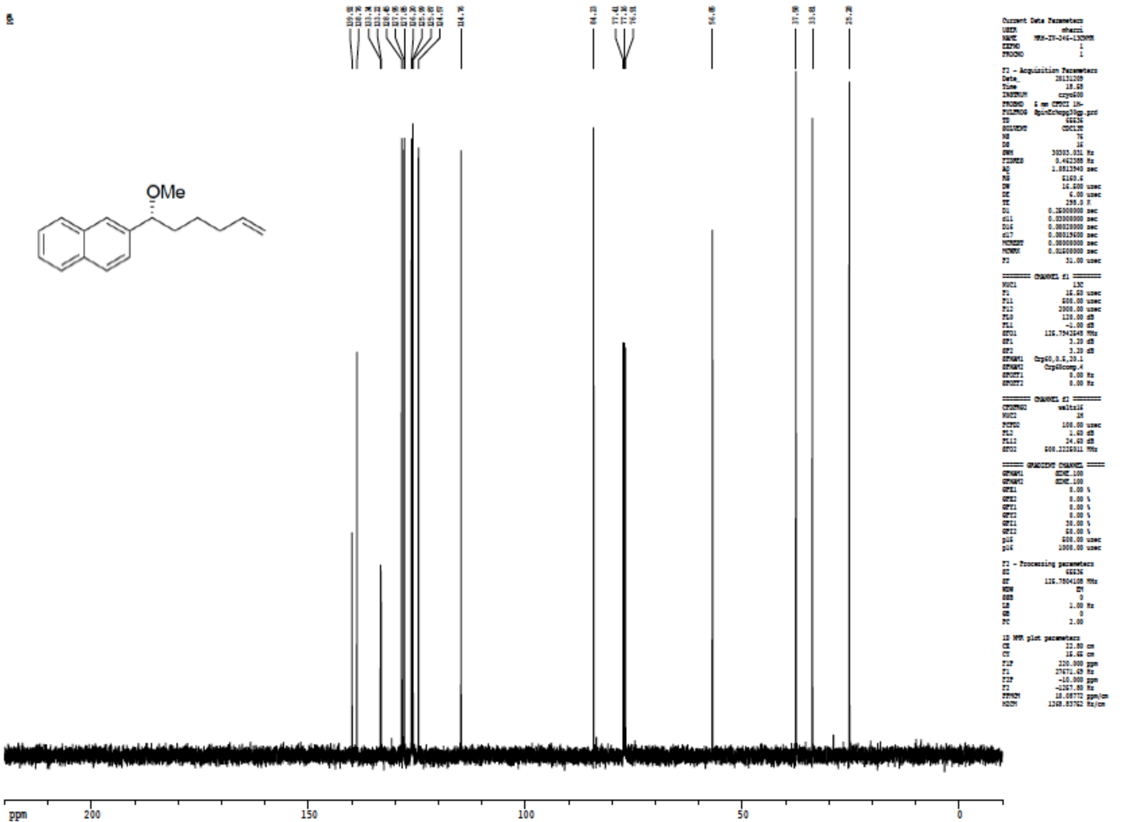
Z-restored spin-echo 13C spectrum with 1H decoupling



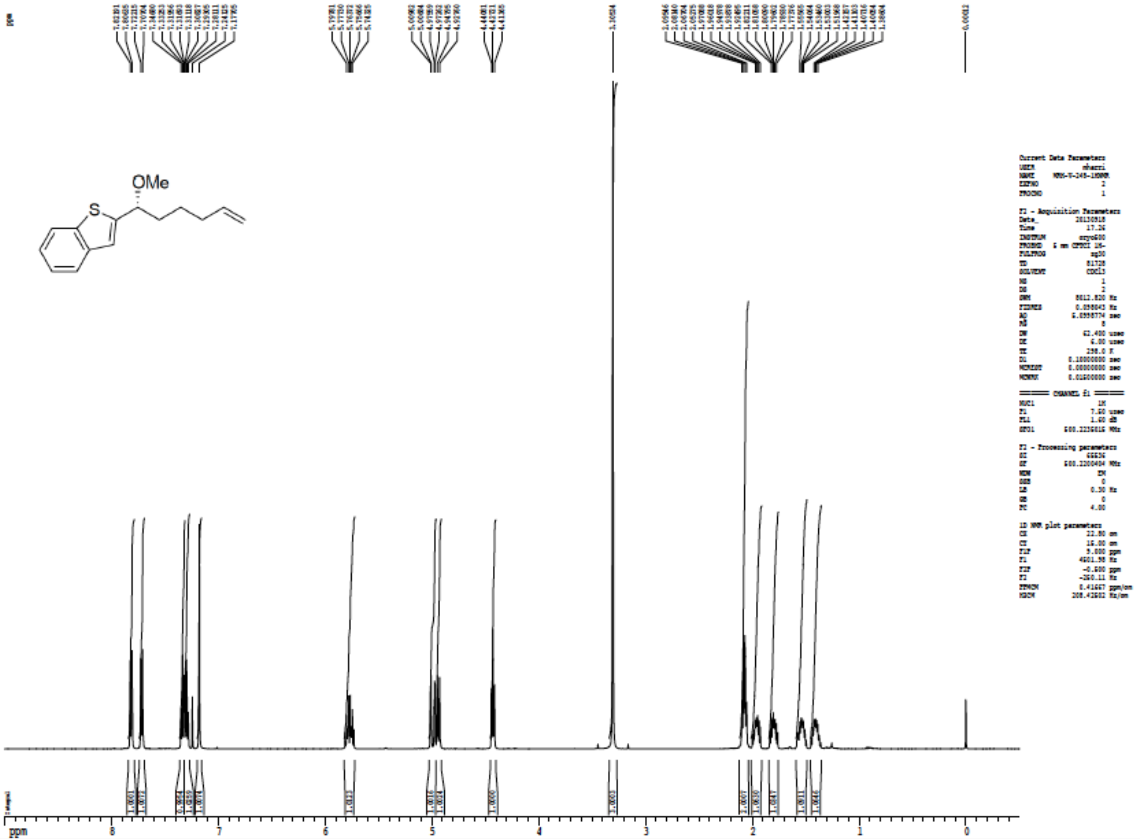
1H spectrum



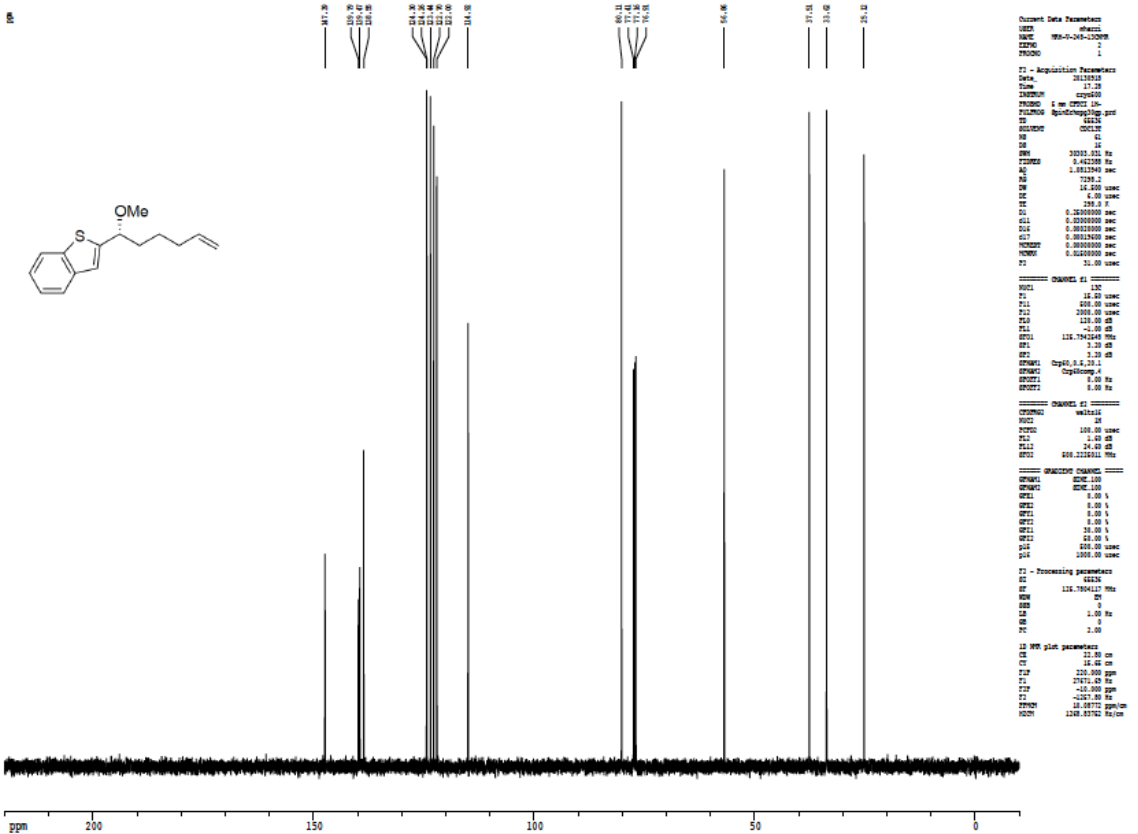
Z-restored spin-echo 13C spectrum with 1H decoupling

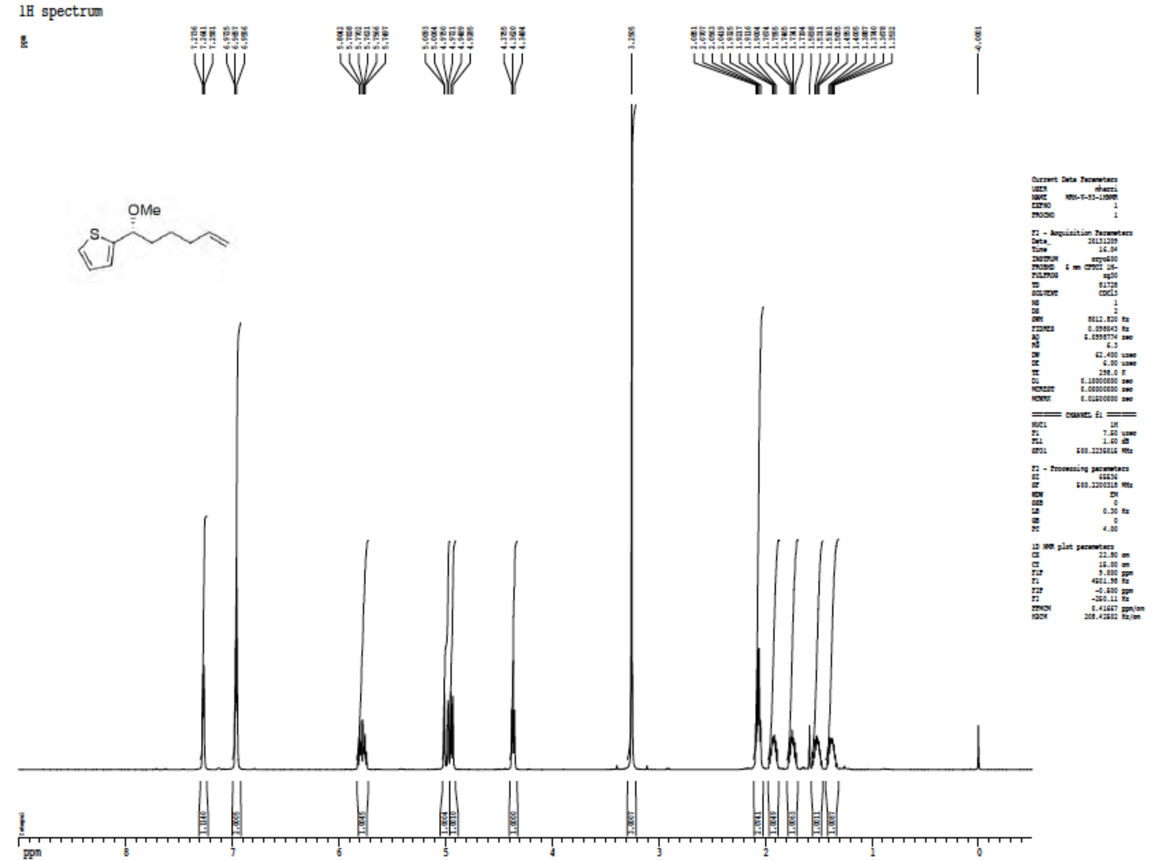


1H spectrum



Z-restored spin-echo 13C spectrum with 1H decoupling




1H spectrum
OMe
S
ppm
8
7
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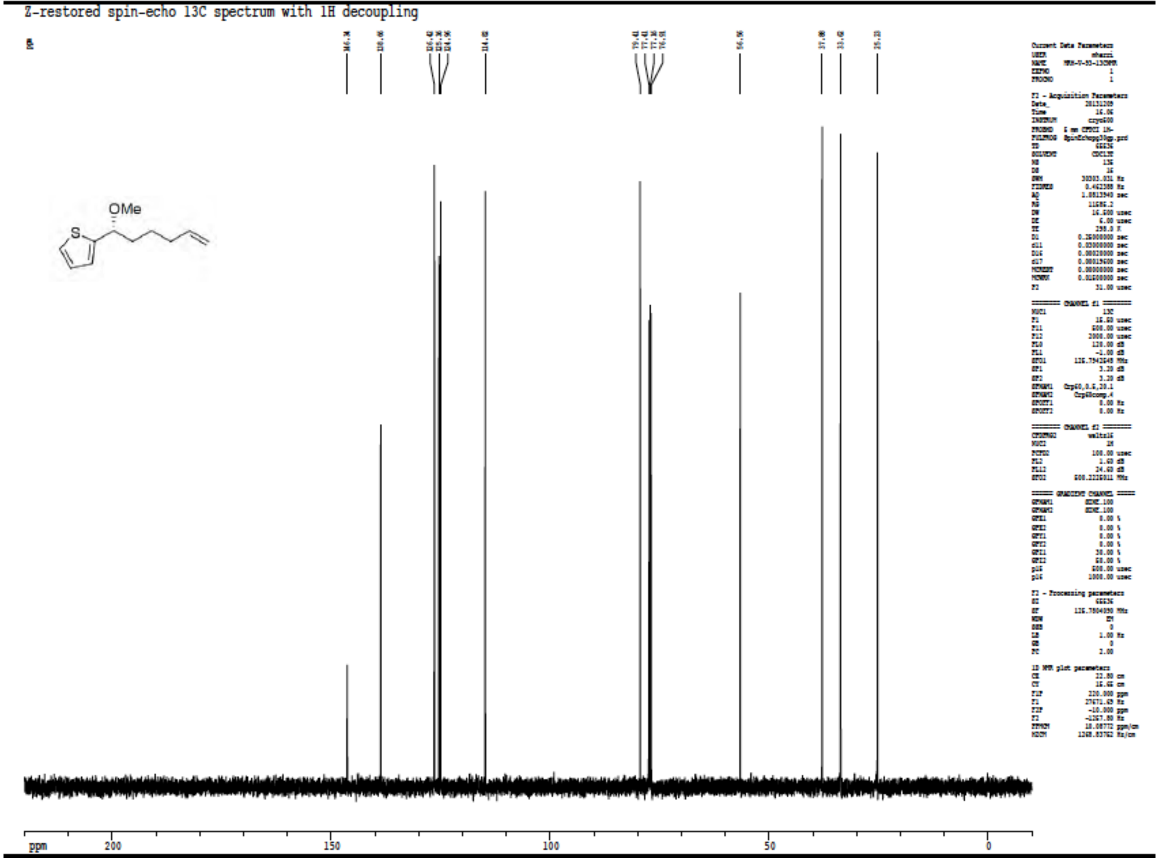
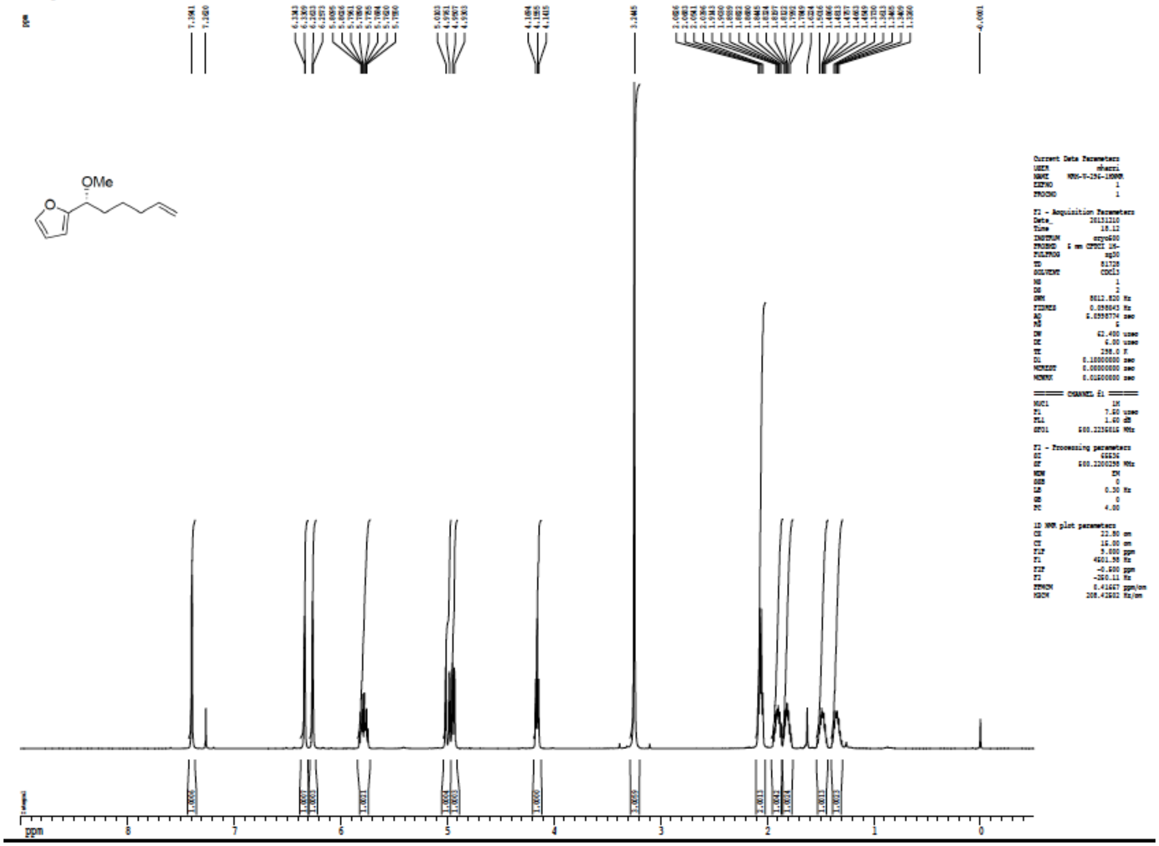
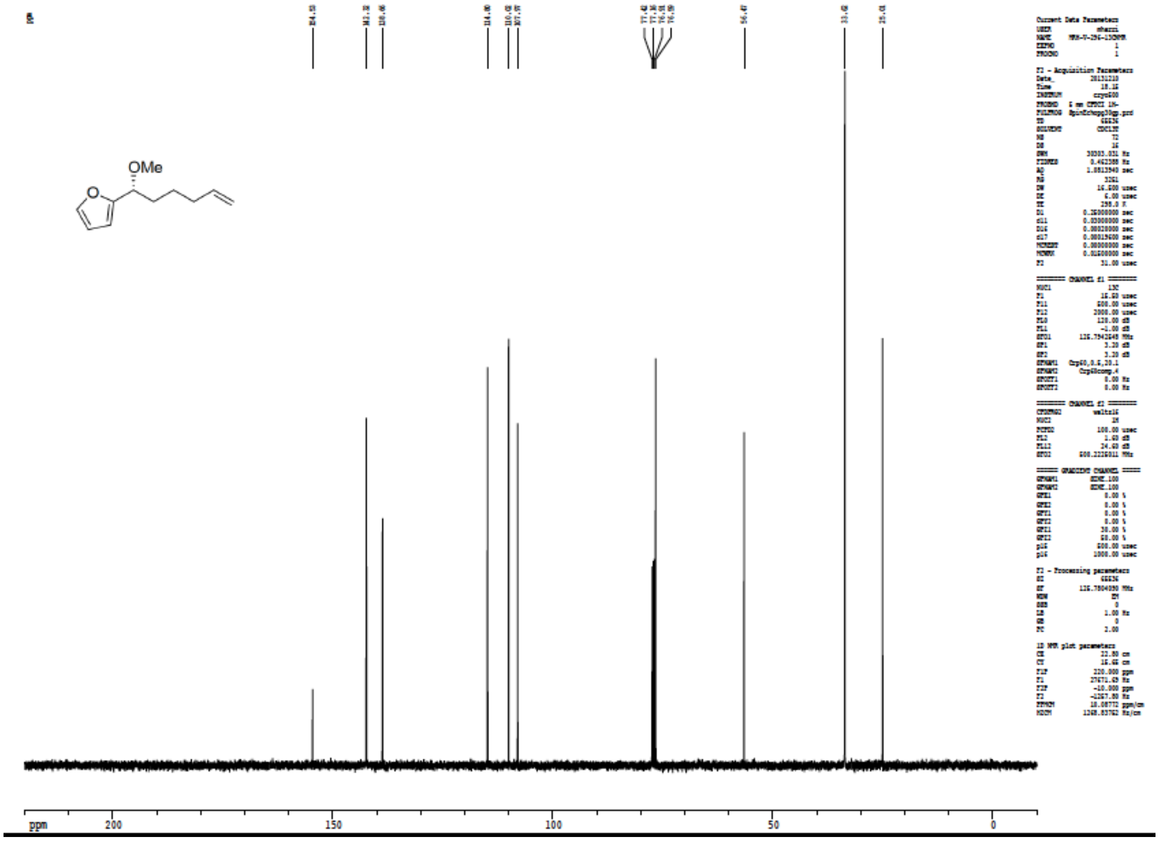
1
0


Z-restored spin-echo 13C spectrum with 1H decoupling
OMe
S
ppm
200
150
100
50
0

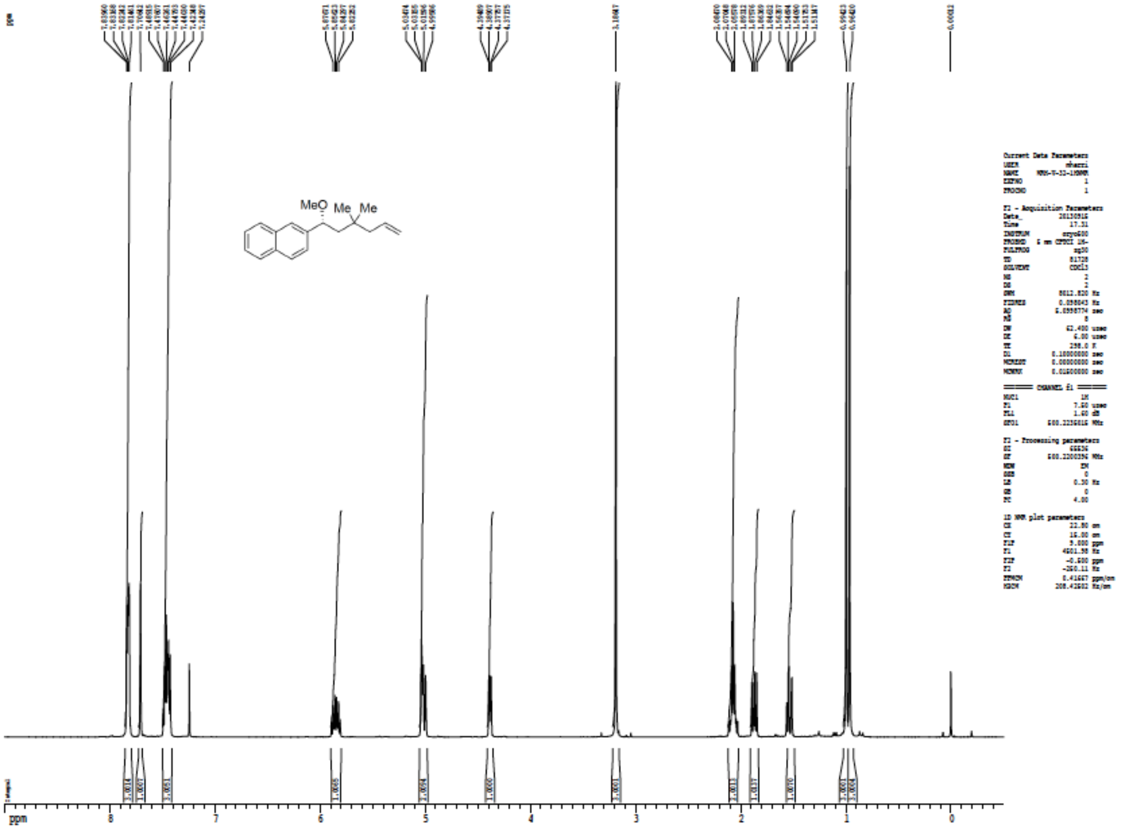
1H spectrum



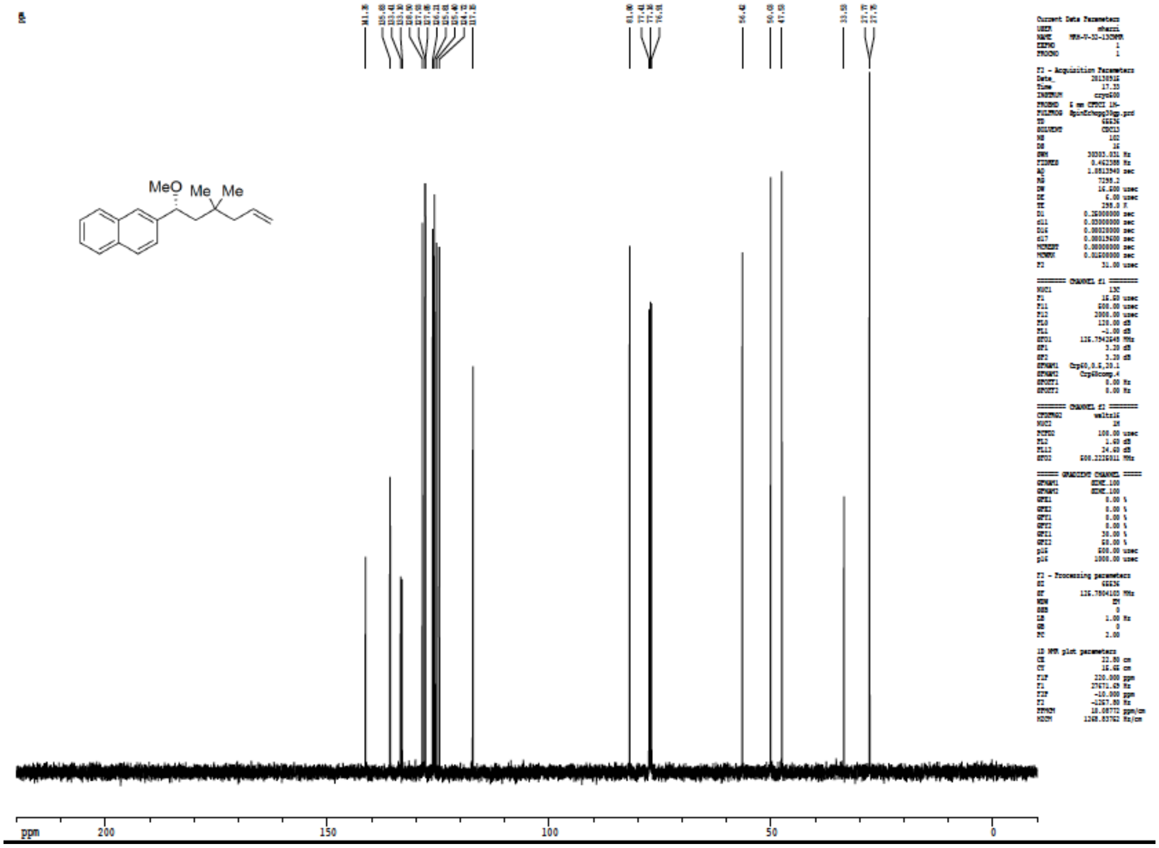
Z-restored spin-echo 13C spectrum with 1H decoupling



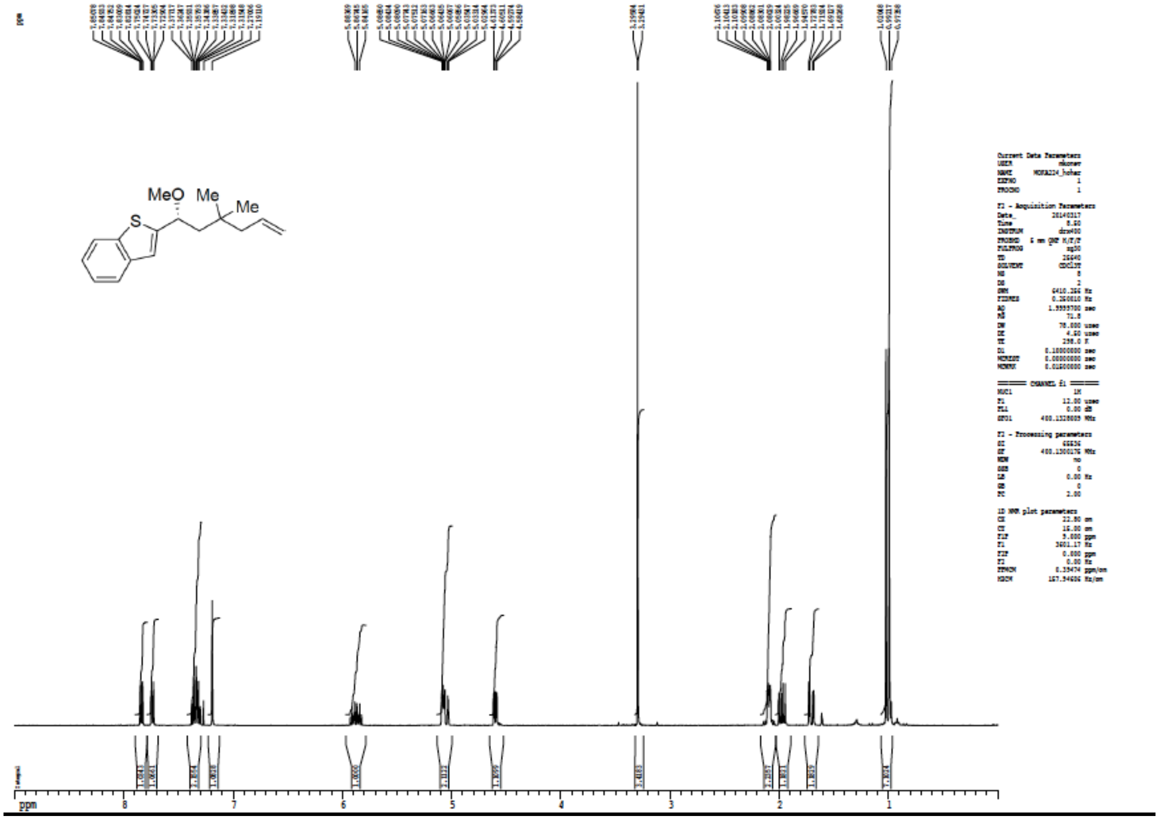
1H spectrum



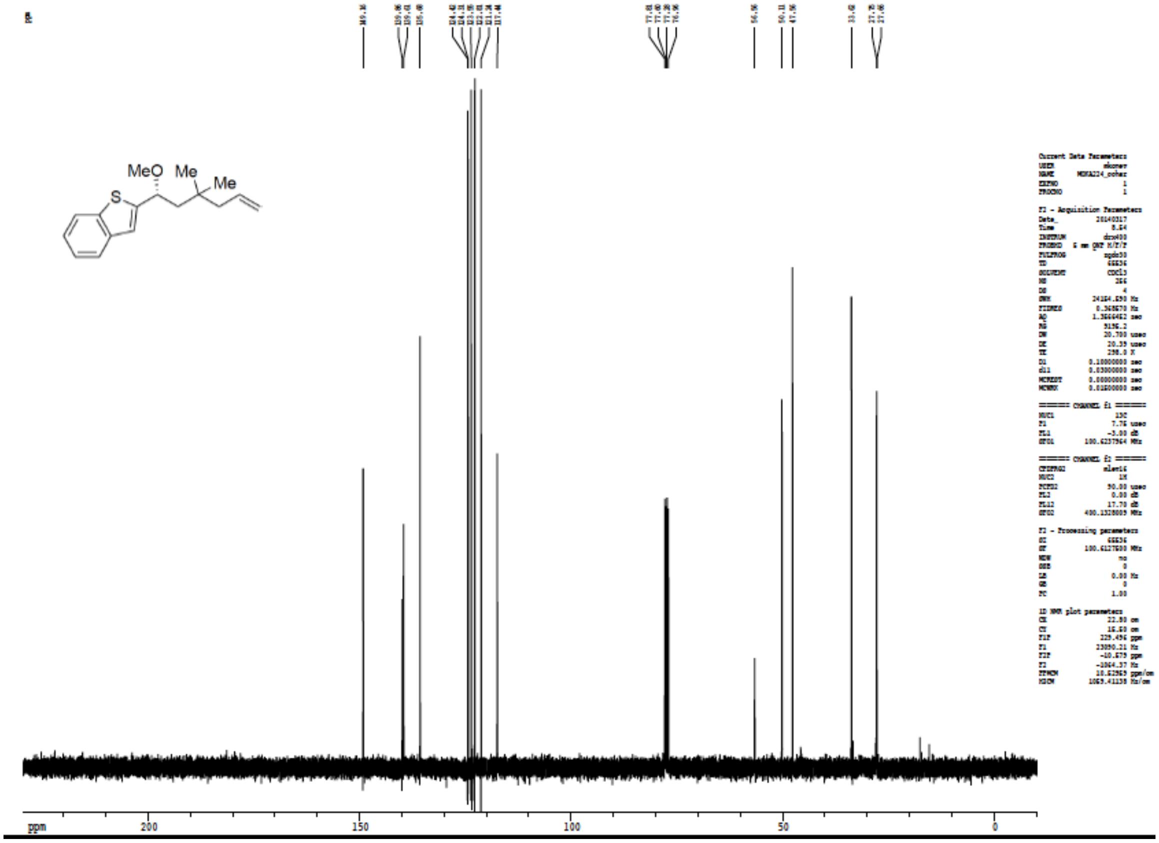
Z-restored spin-echo 13C spectrum with 1H decoupling



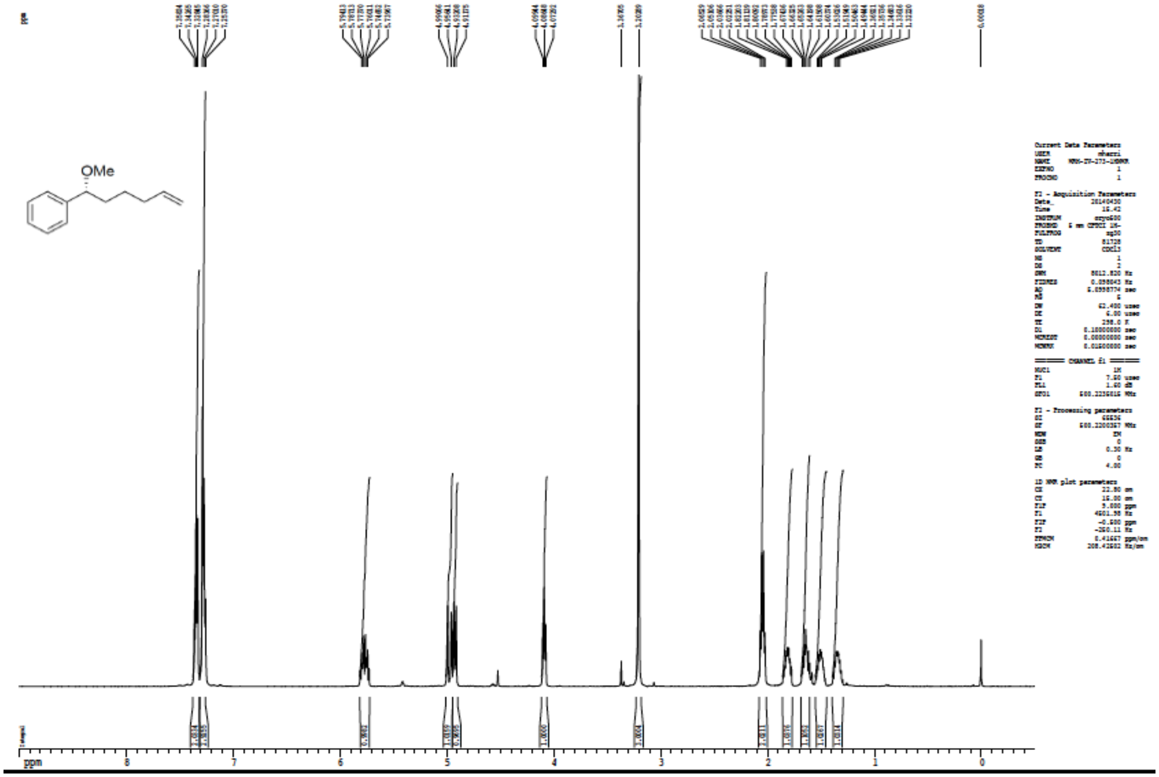
1H spectrum



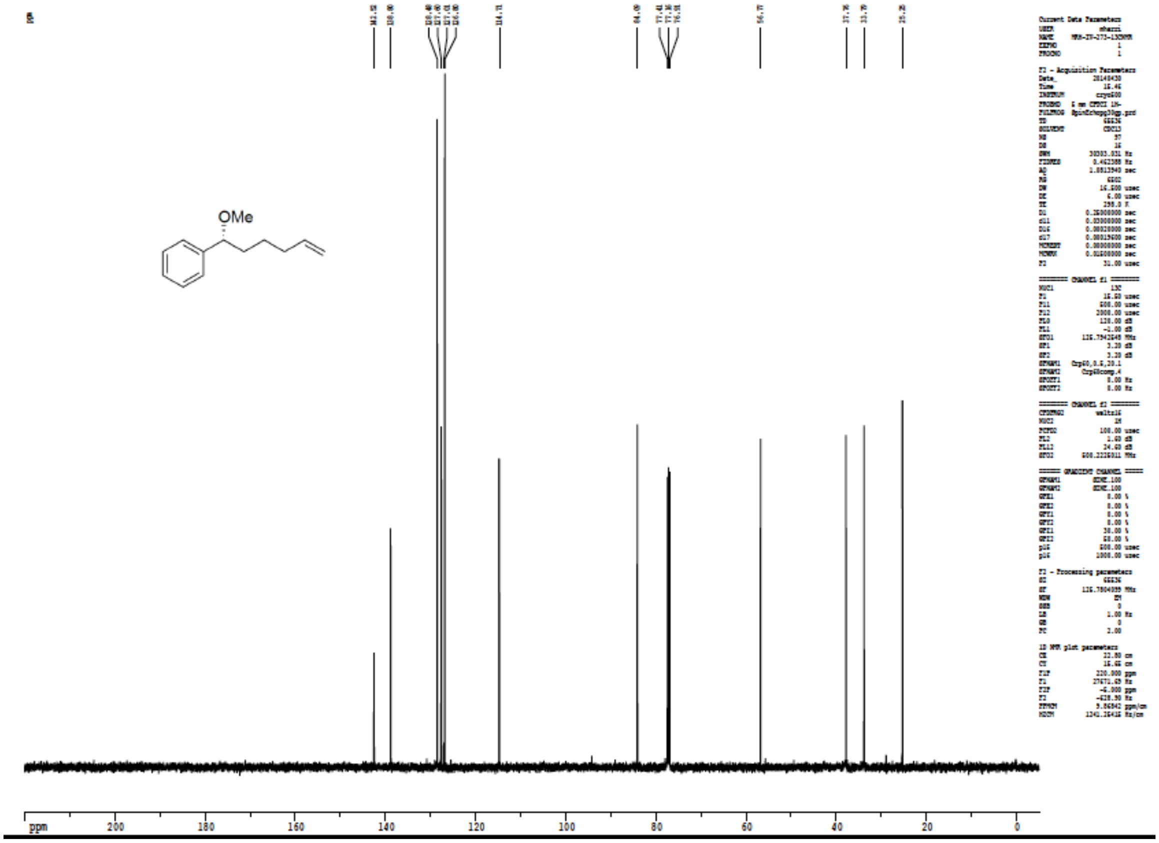
13C spectrum with 1H decoupling



1H spectrum



Z-restored spin-echo 13C spectrum with 1H decoupling



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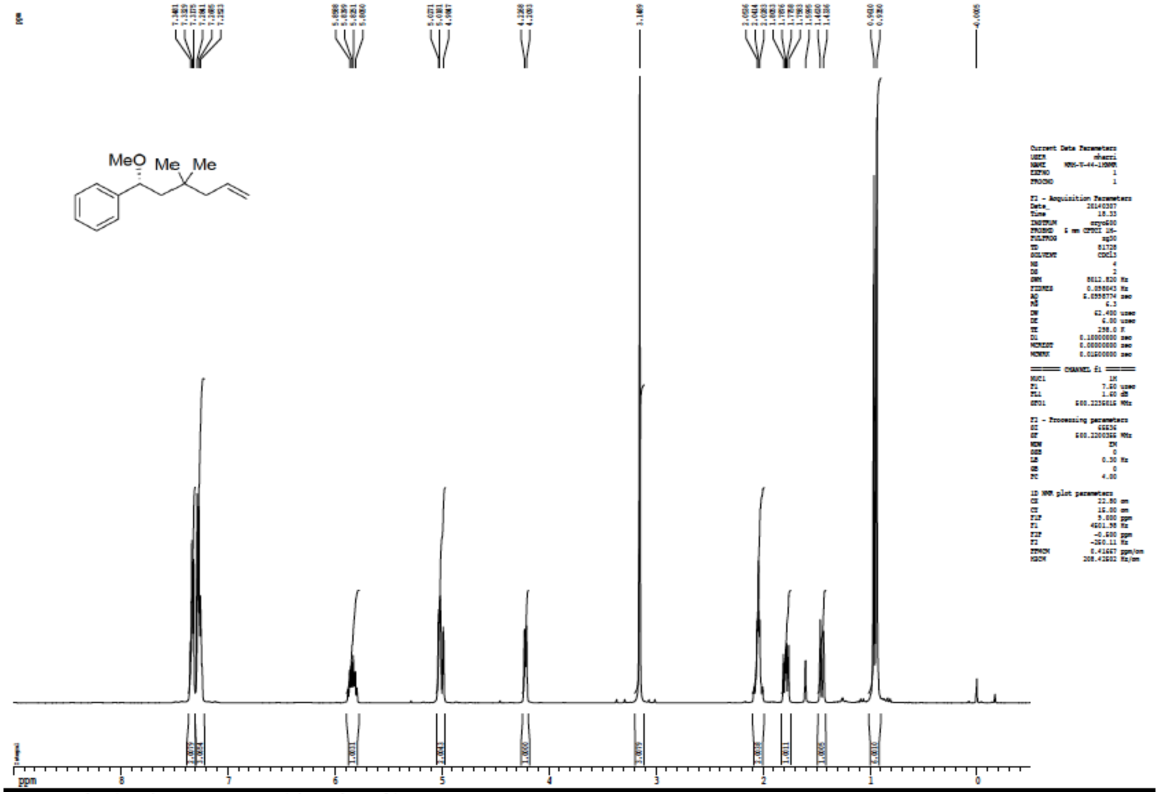
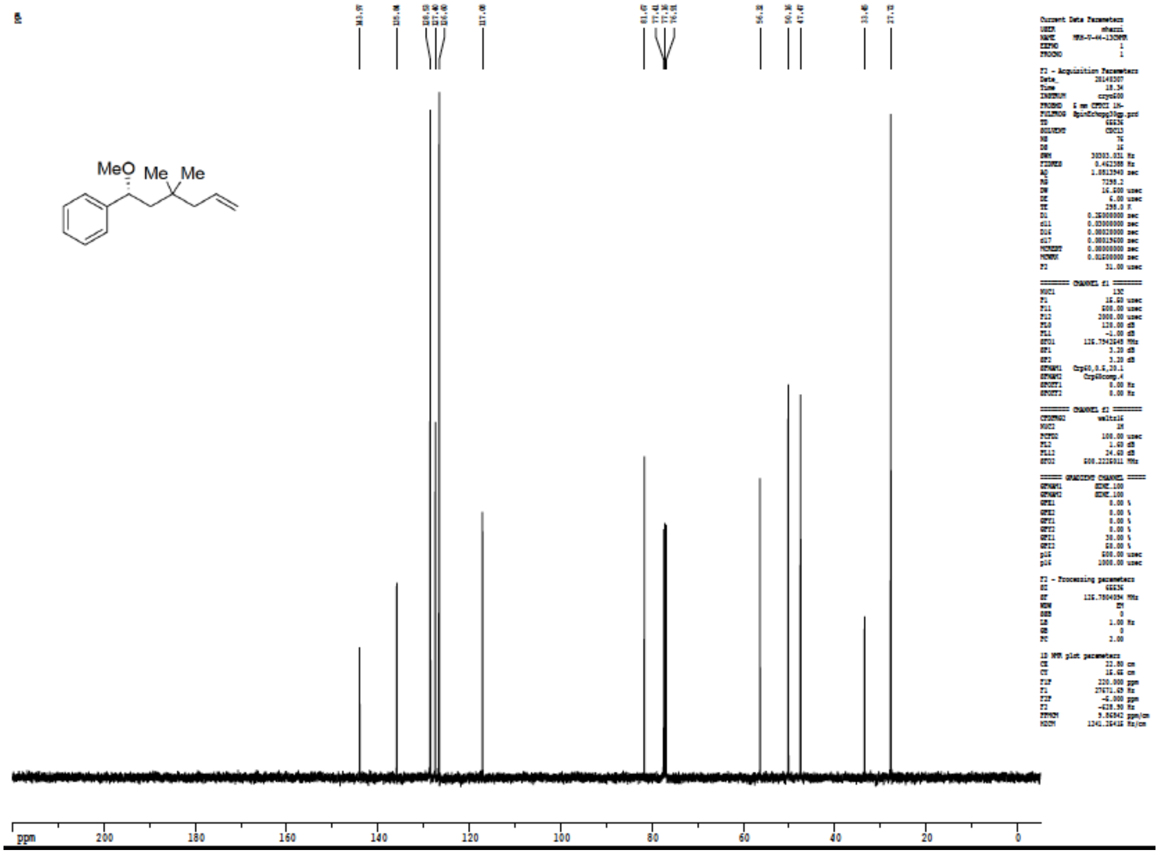


Z-restored spin-echo 13C spectrum with 1H decoupling



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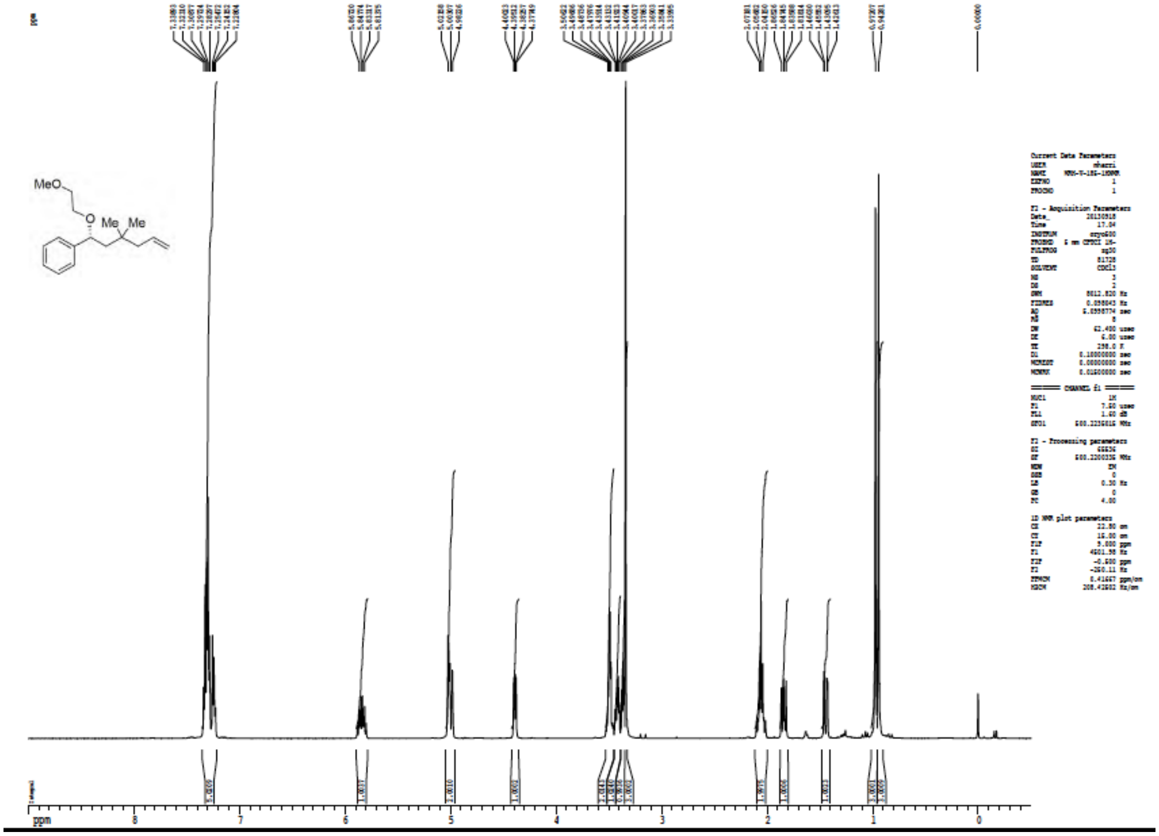
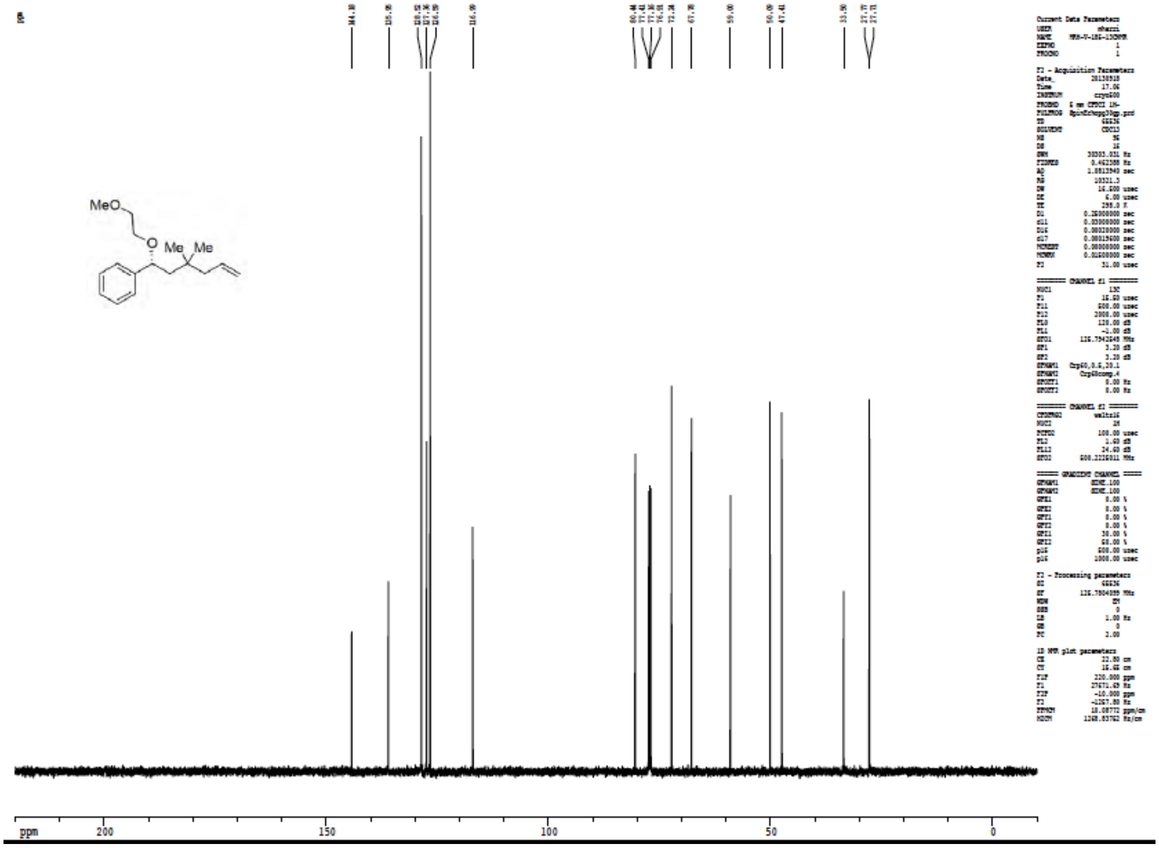


Z-restored spin-echo 13C spectrum with 1H decoupling



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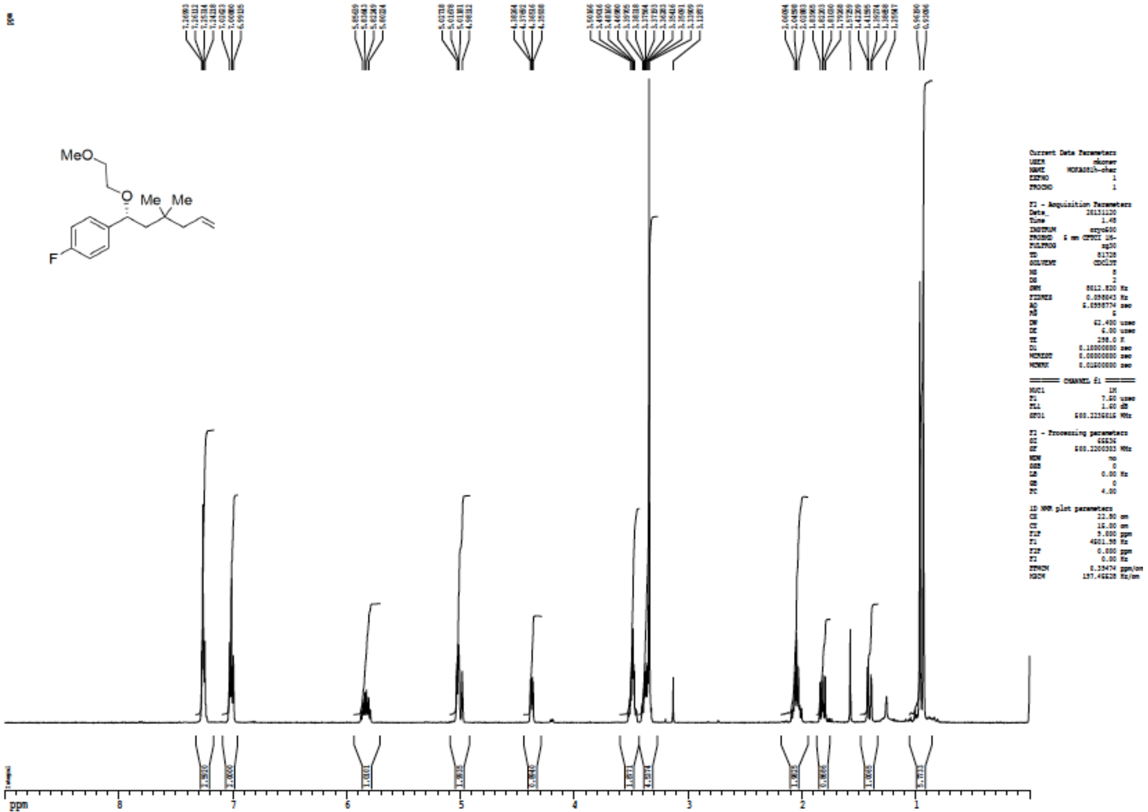
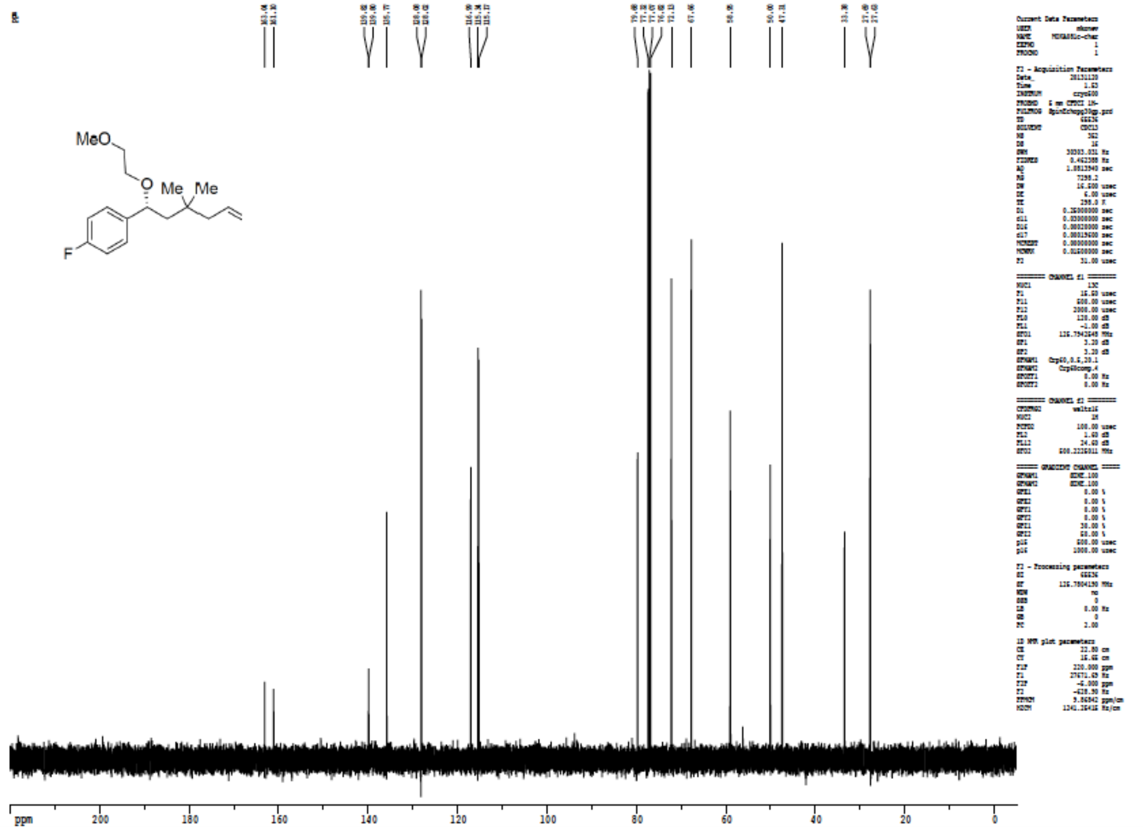


Z-restored spin-echo 13C spectrum with 1H decoupling



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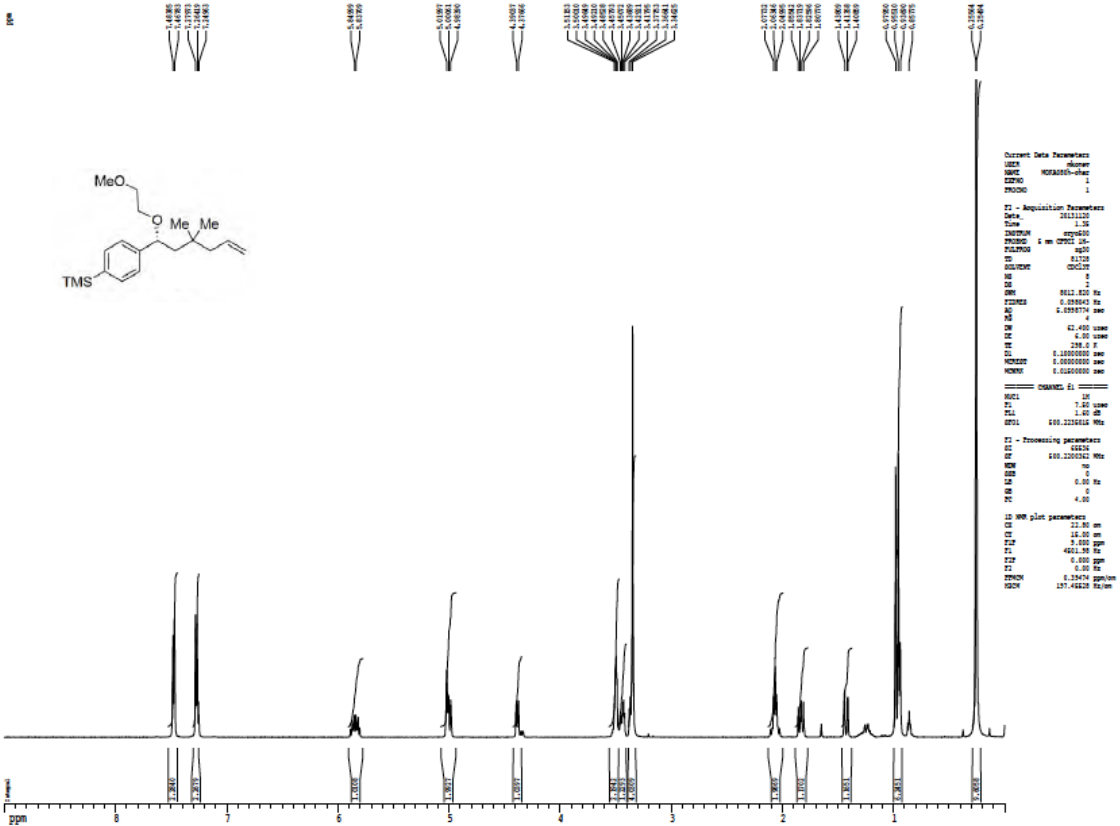
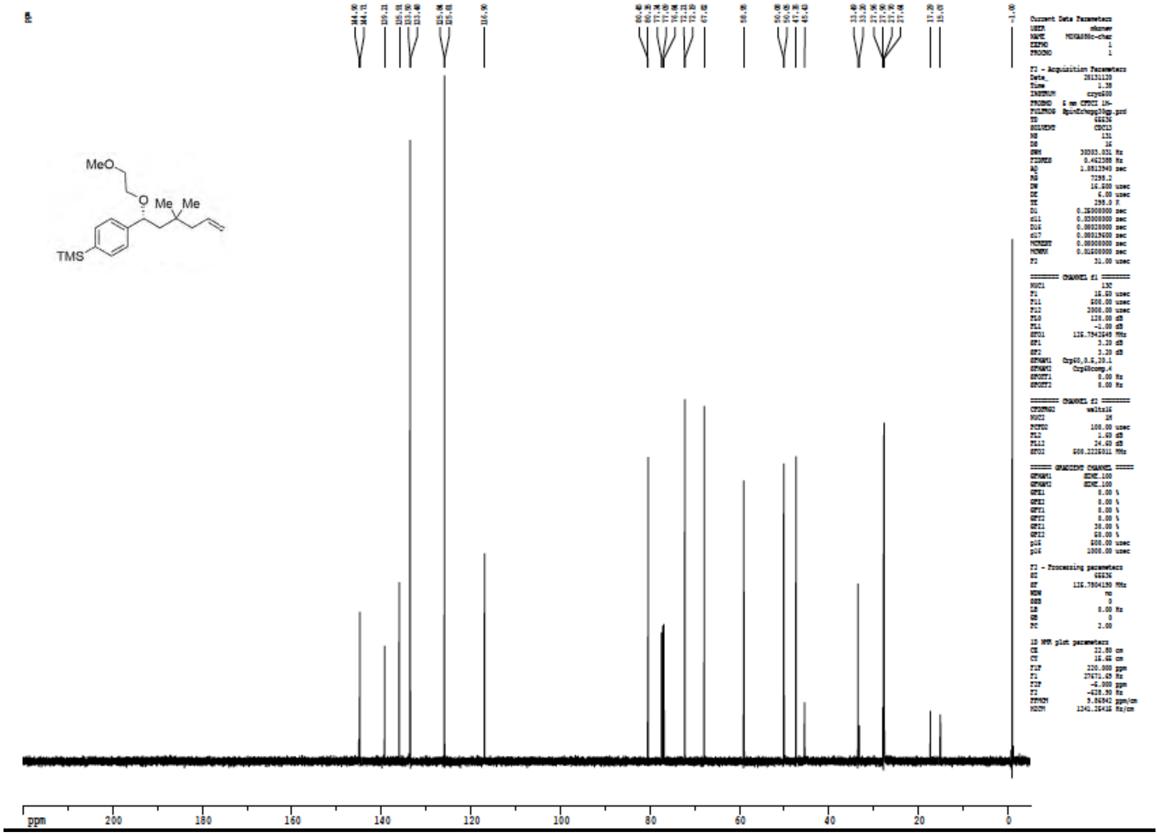
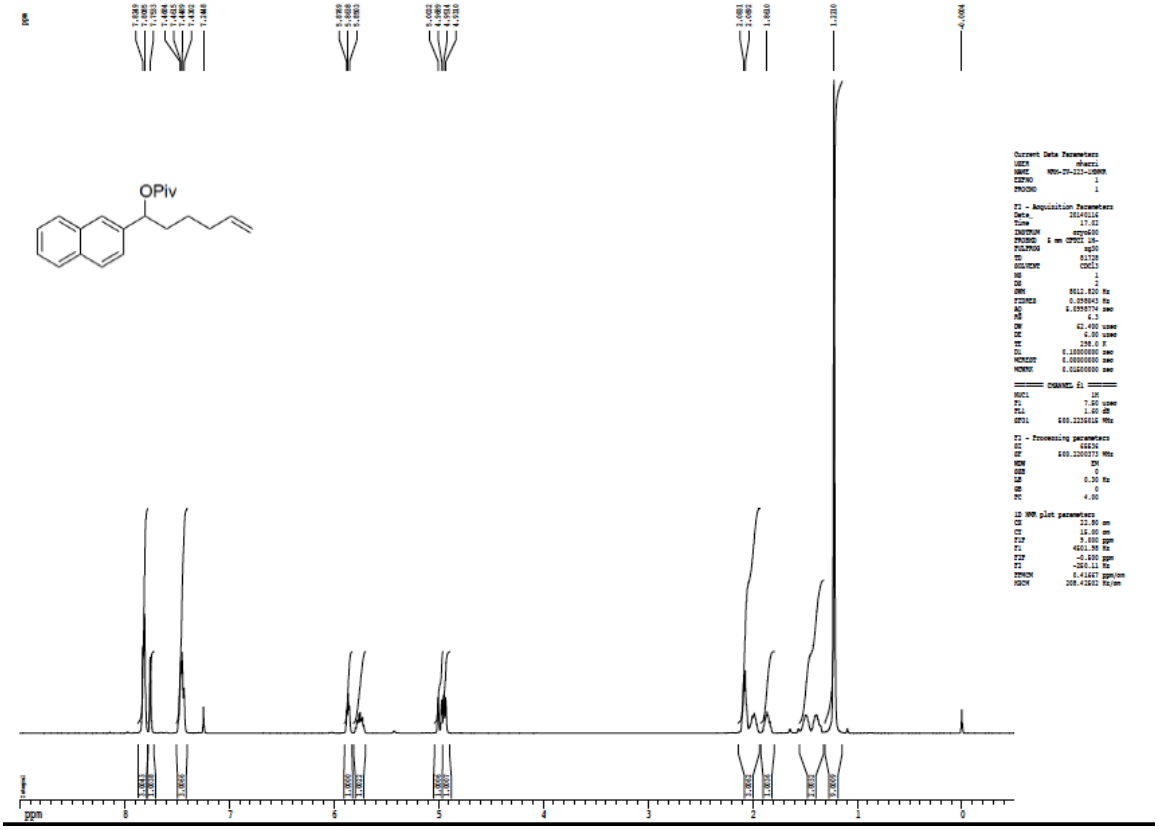


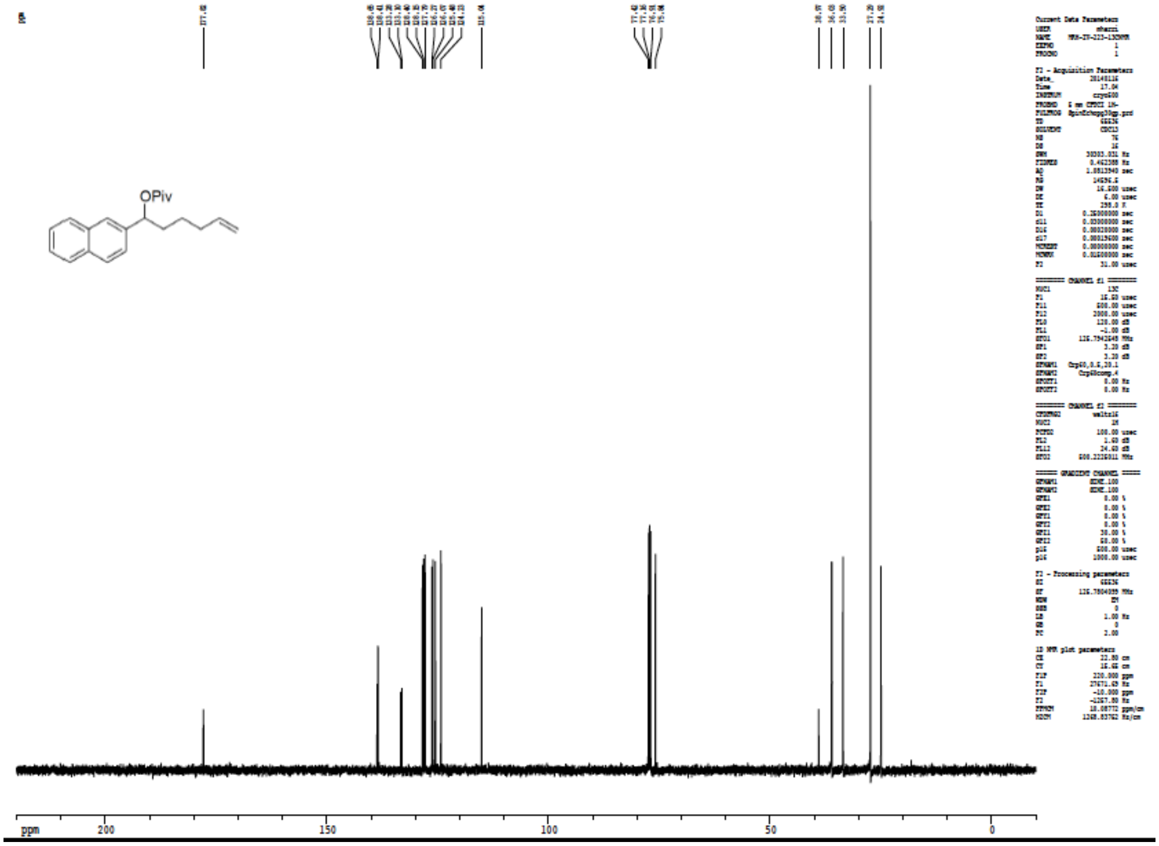
Z-restored spin-echo 13C spectrum with 1H decoupling



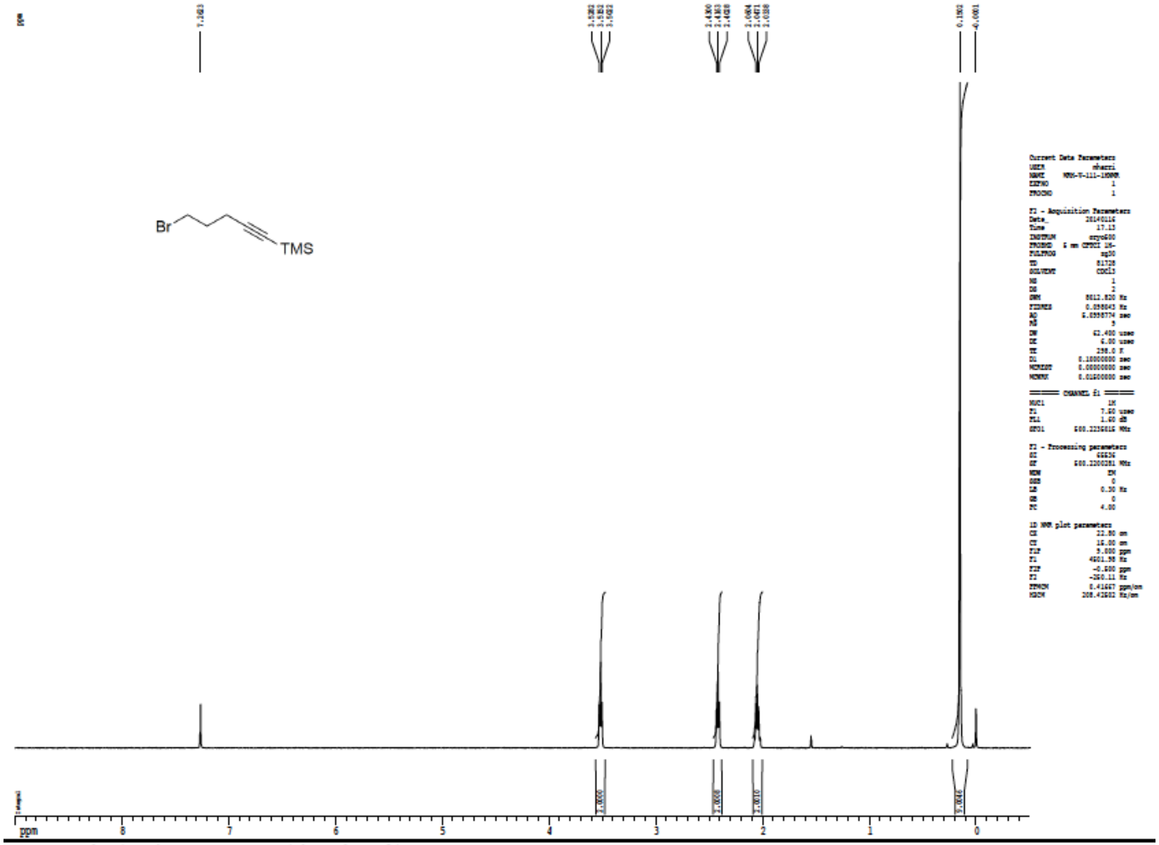
1H spectrum



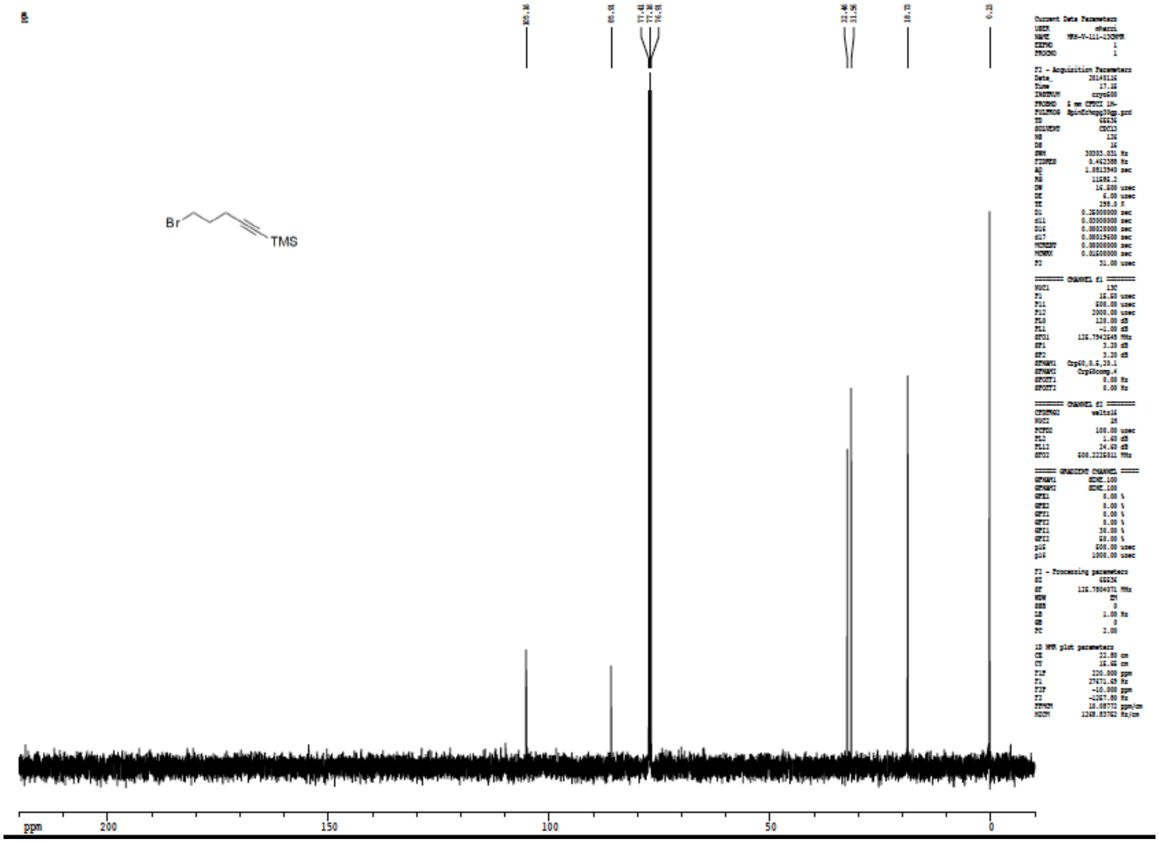
Z-restored spin-echo 13C spectrum with 1H decoupling



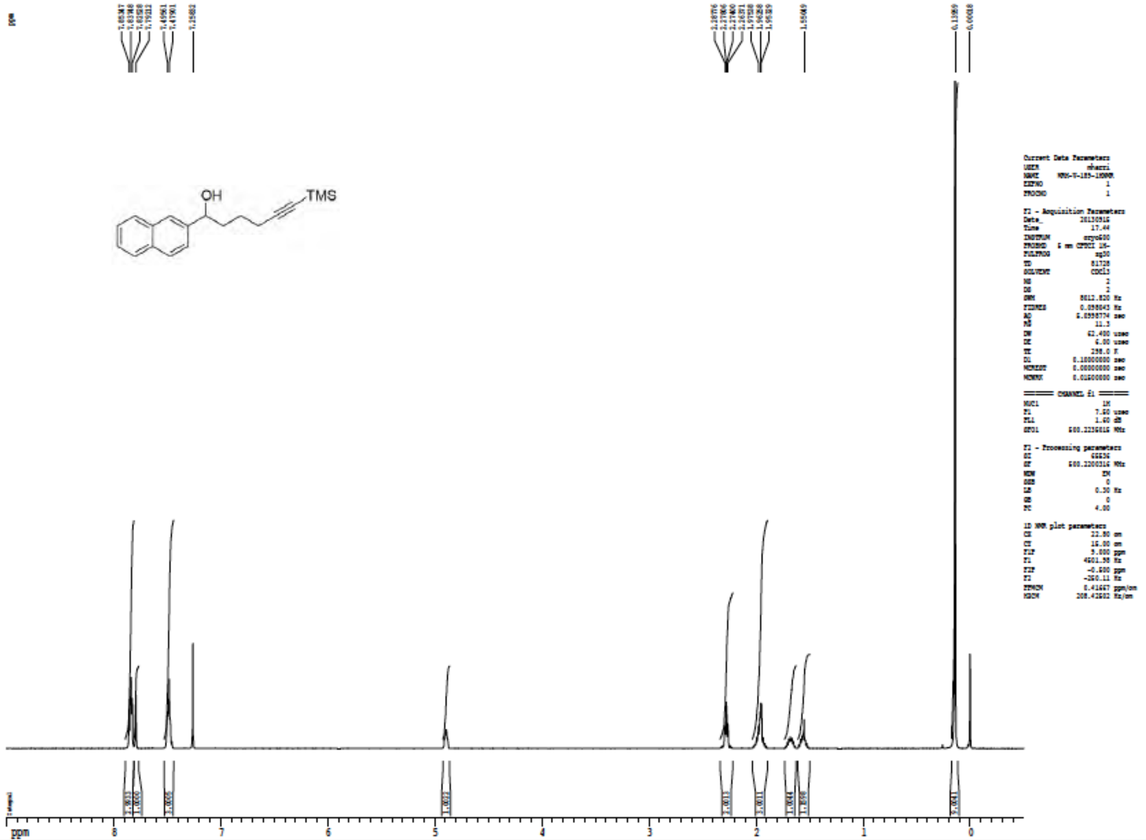
1H spectrum



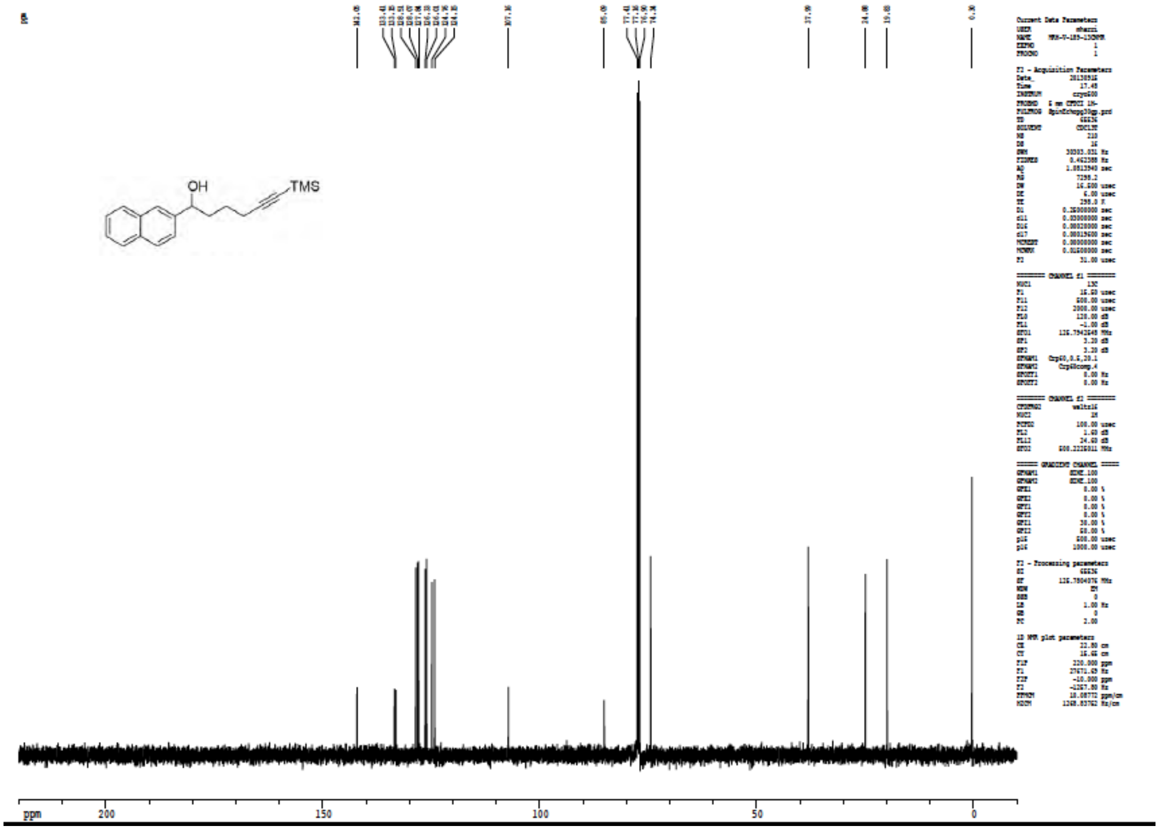
Z-restored spin-echo 13C spectrum with 1H decoupling

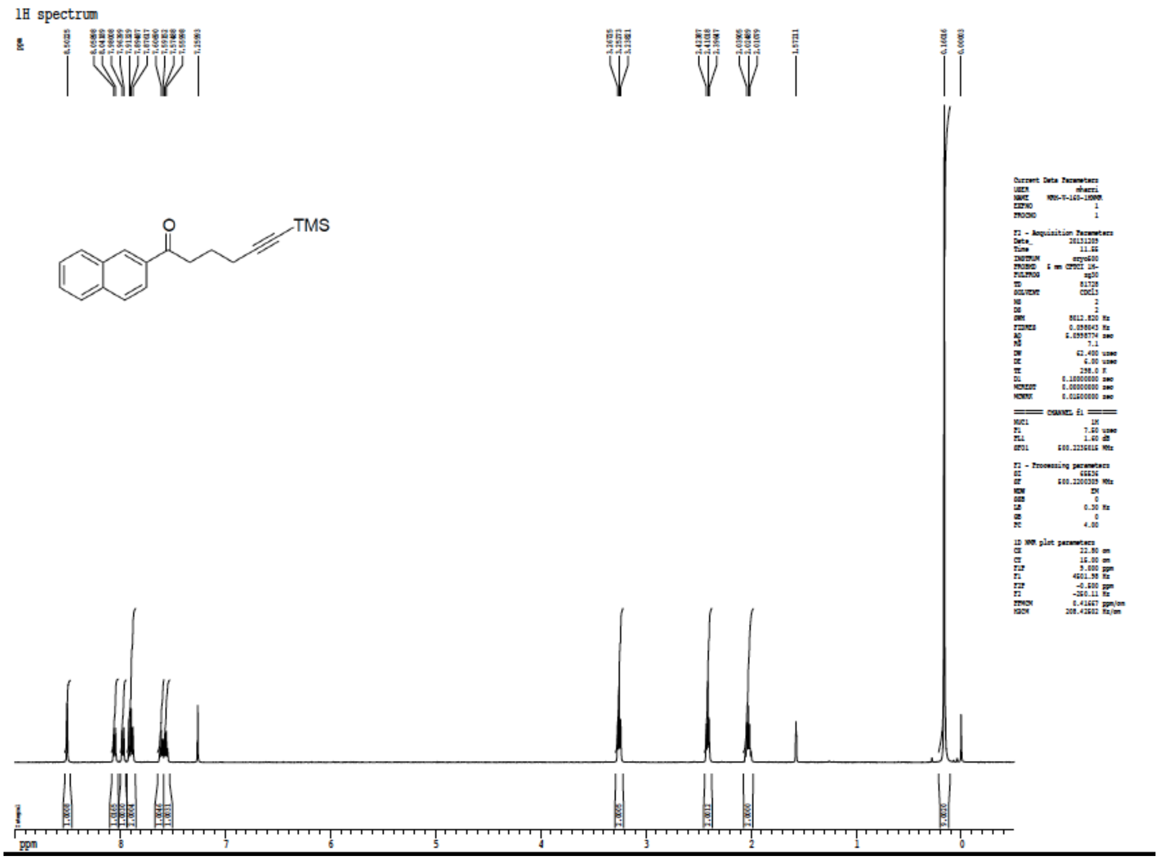


1H spectrum



Z-restored spin-echo 13C spectrum with 1H decoupling




1H spectrum
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TMS
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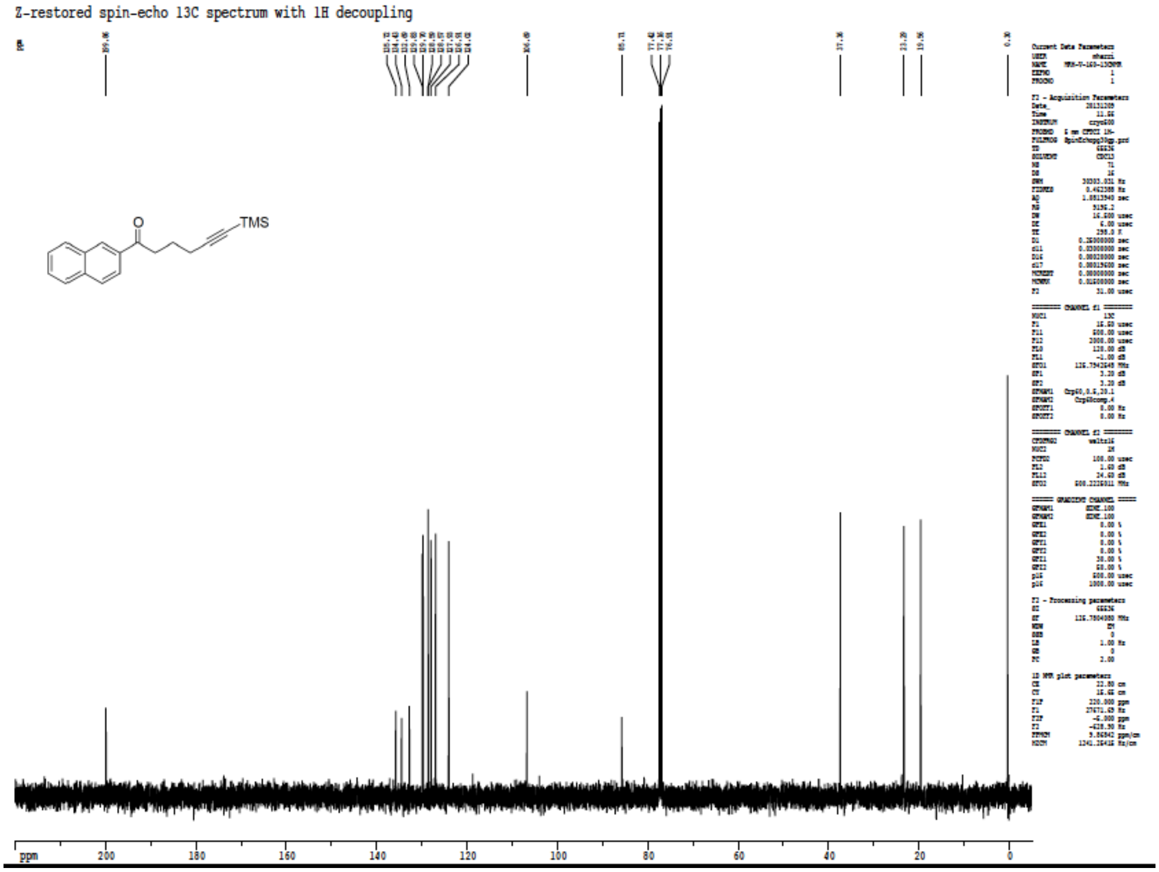
1
0


Z-restored spin-echo 13C spectrum with 1H decoupling
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76.91
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19.56
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TMS
O
ppm
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140
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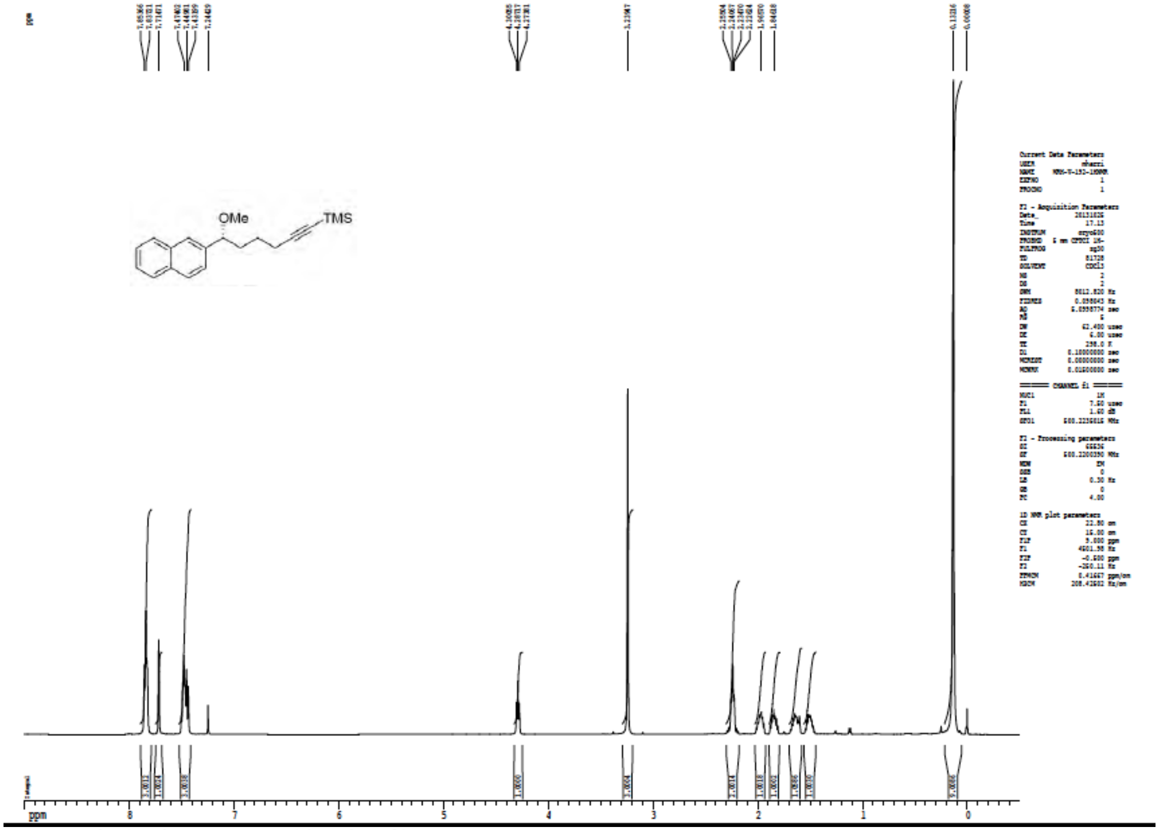
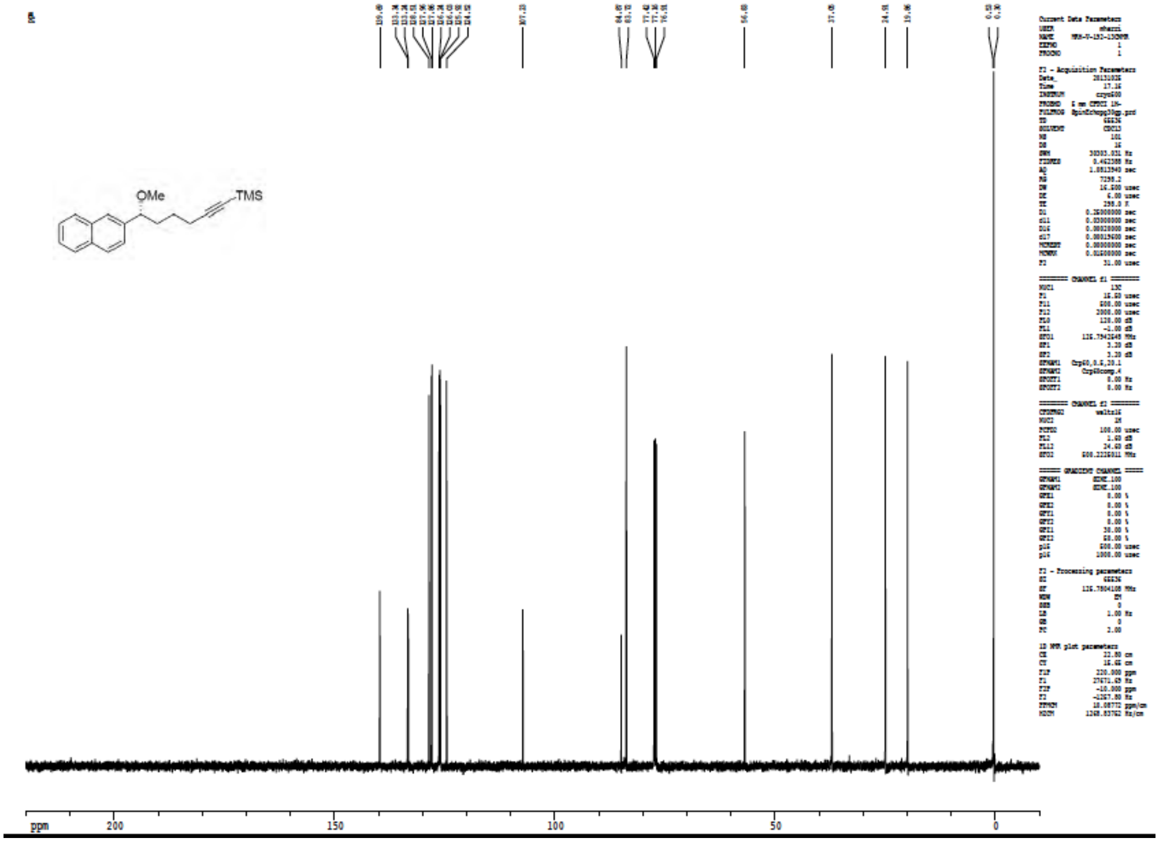
60
40
20
0

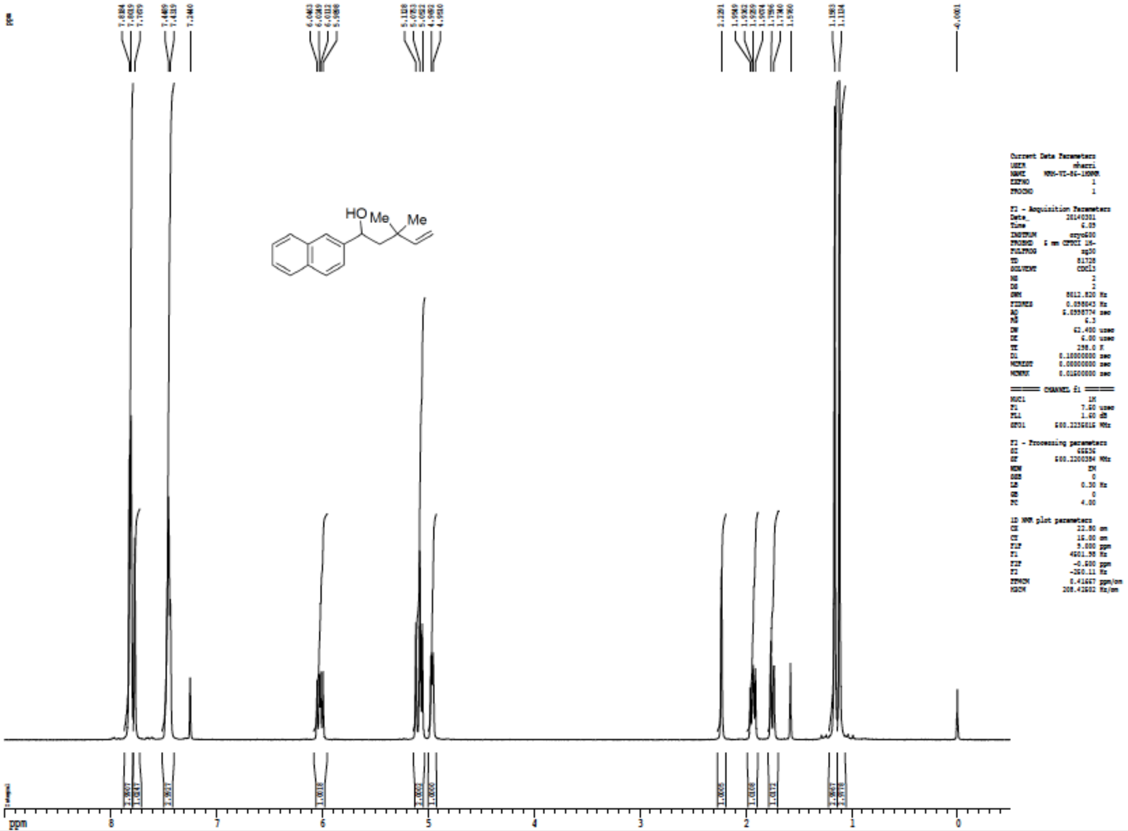
1H spectrum



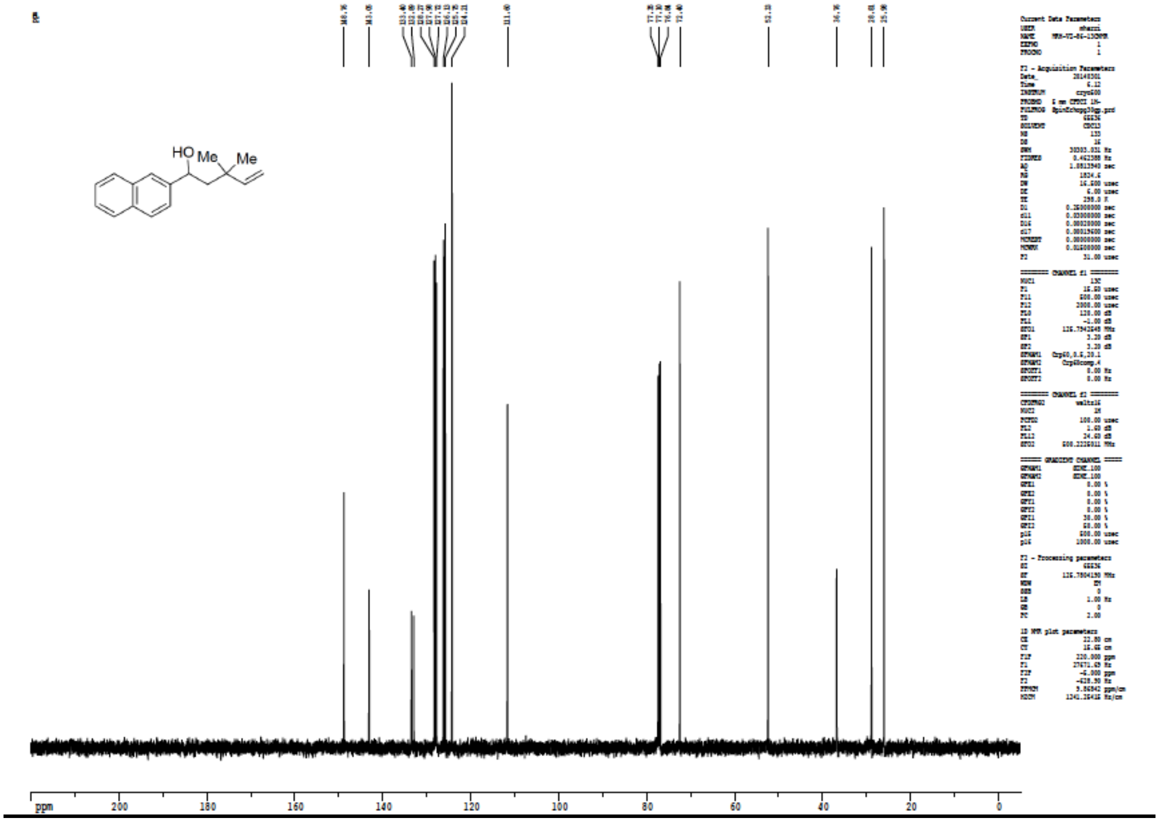
Z-restored spin-echo 13C spectrum with 1H decoupling



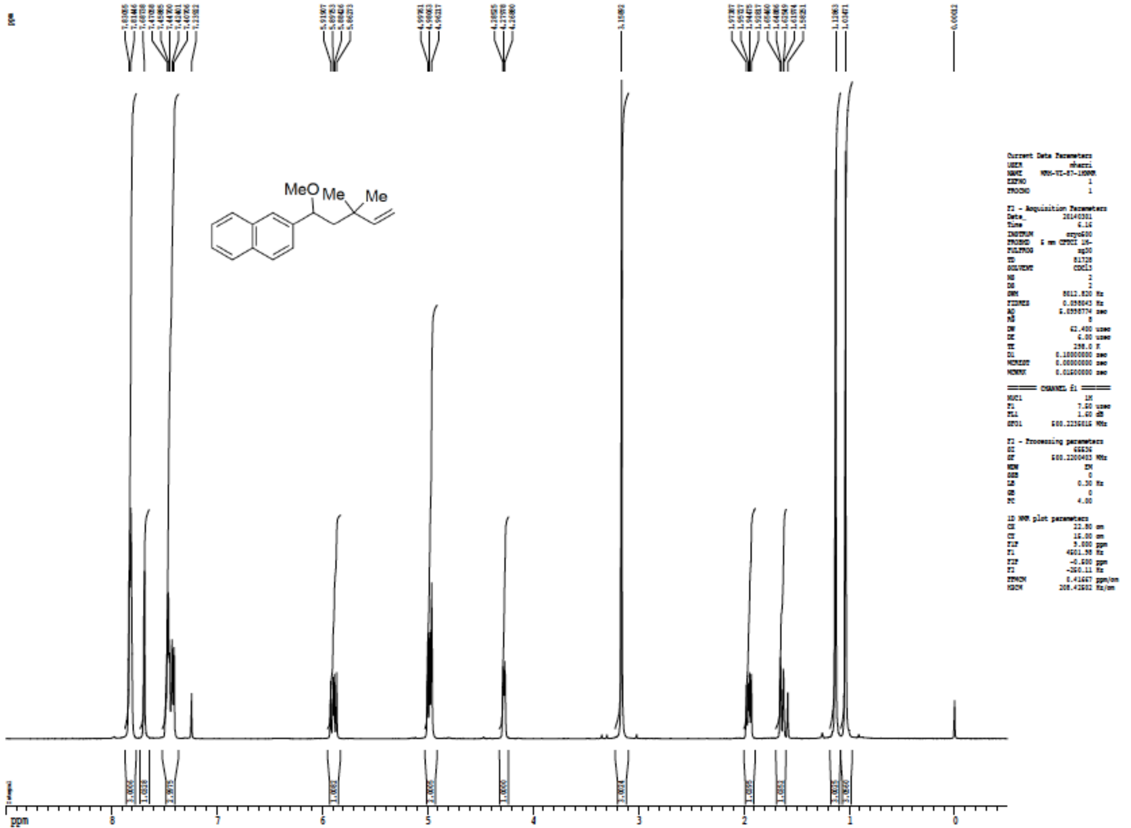
1H spectrum



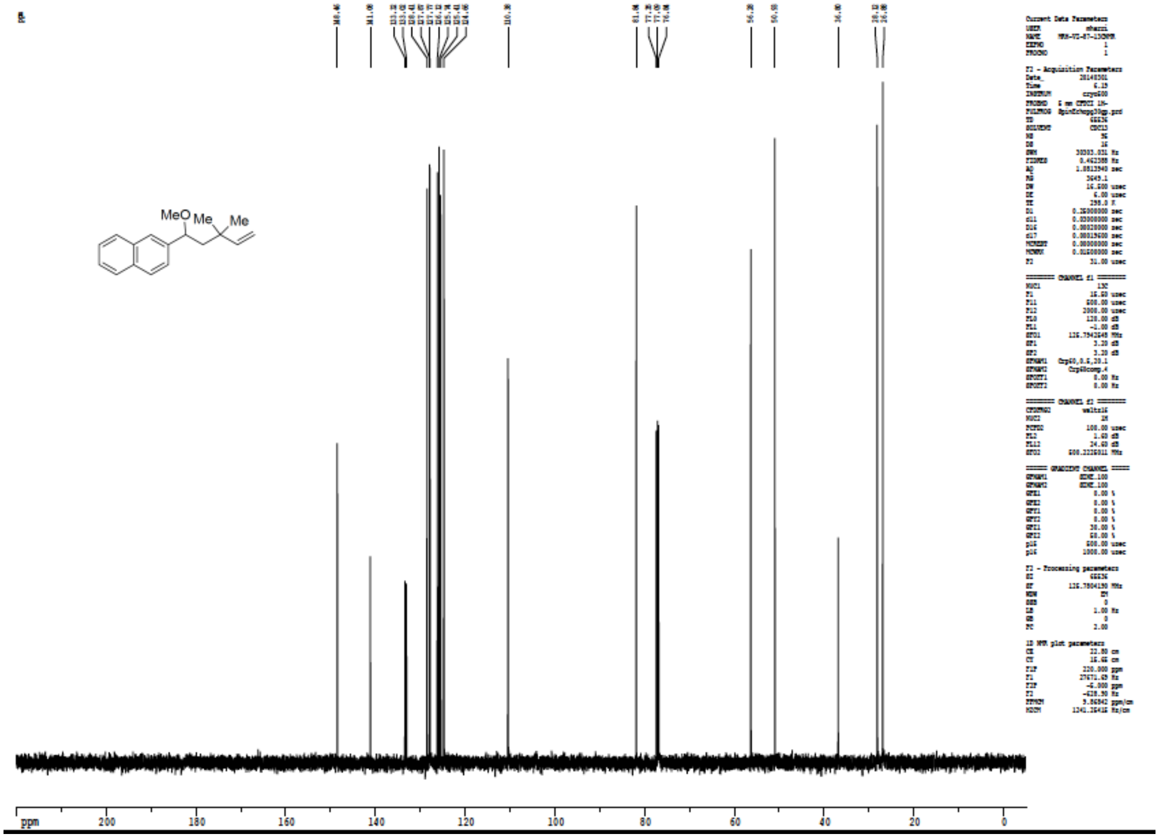
Z-restored spin-echo 13C spectrum with 1H decoupling



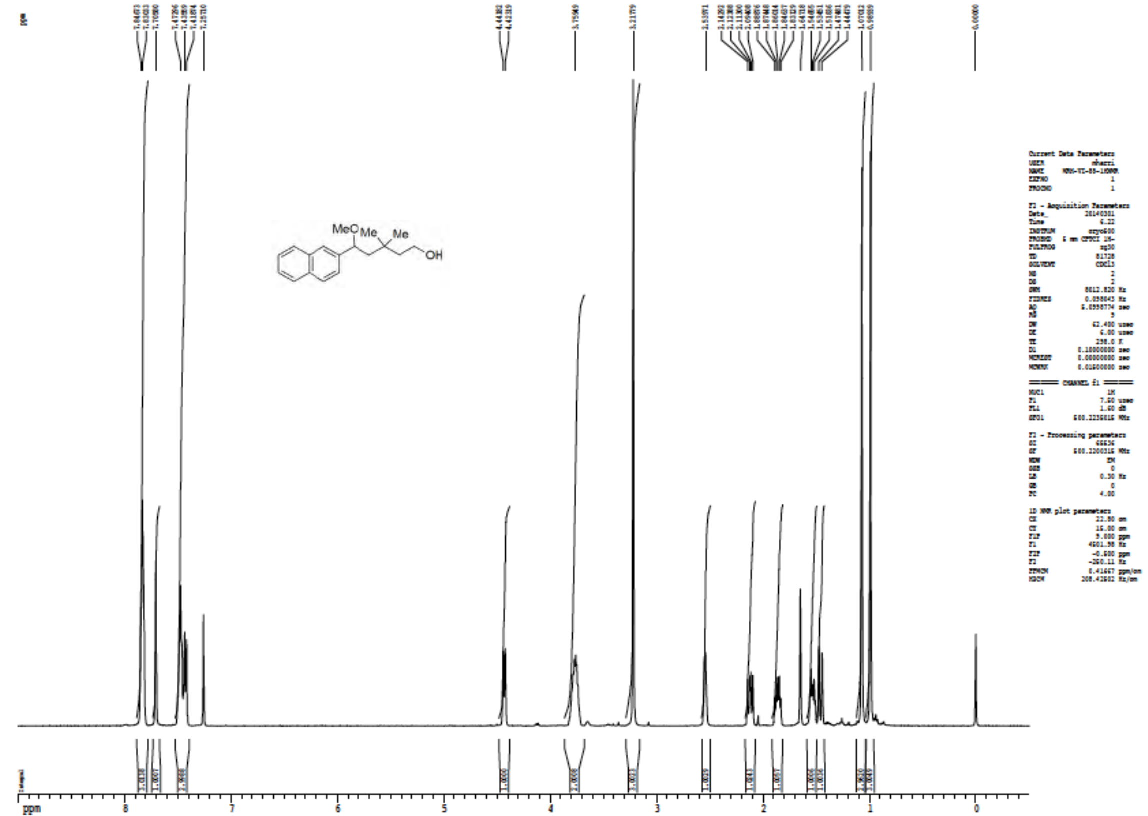
1H spectrum



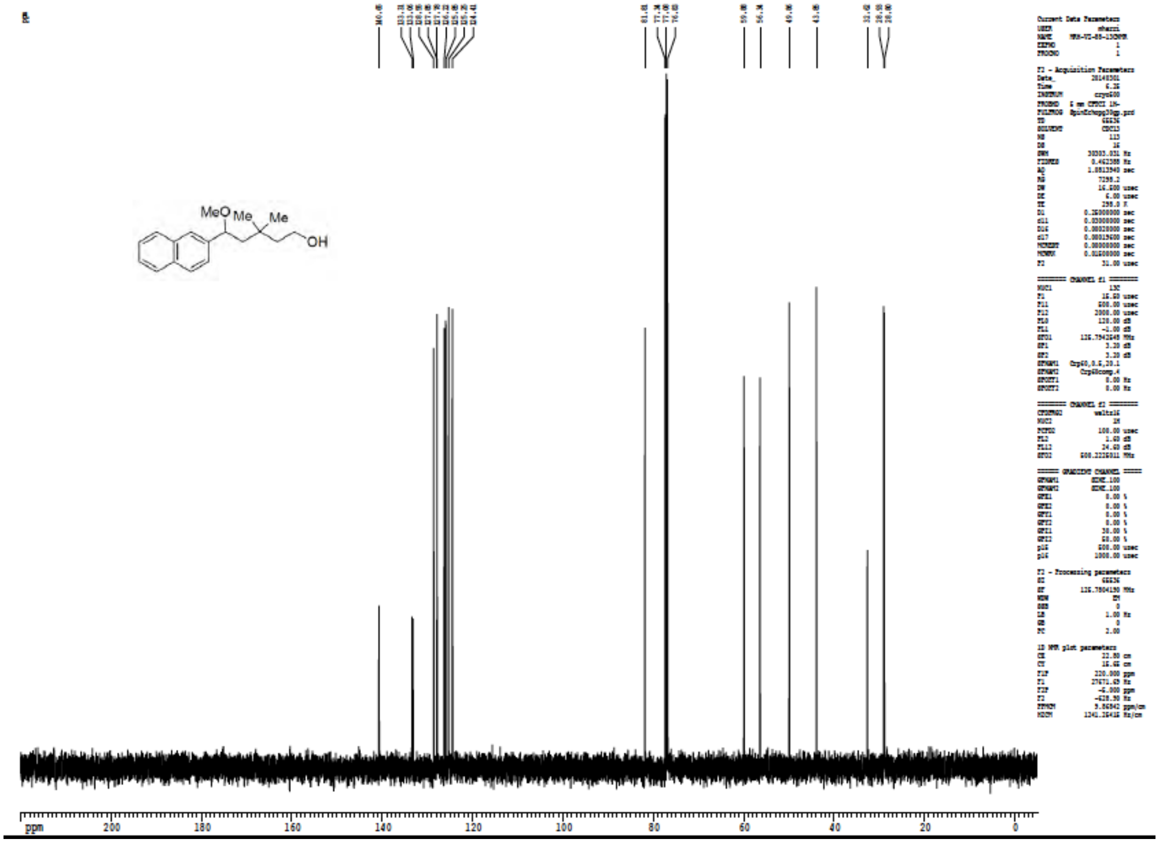
Z-restored spin-echo 13C spectrum with 1H decoupling



1H spectrum



Z-restored spin-echo 13C spectrum with 1H decoupling



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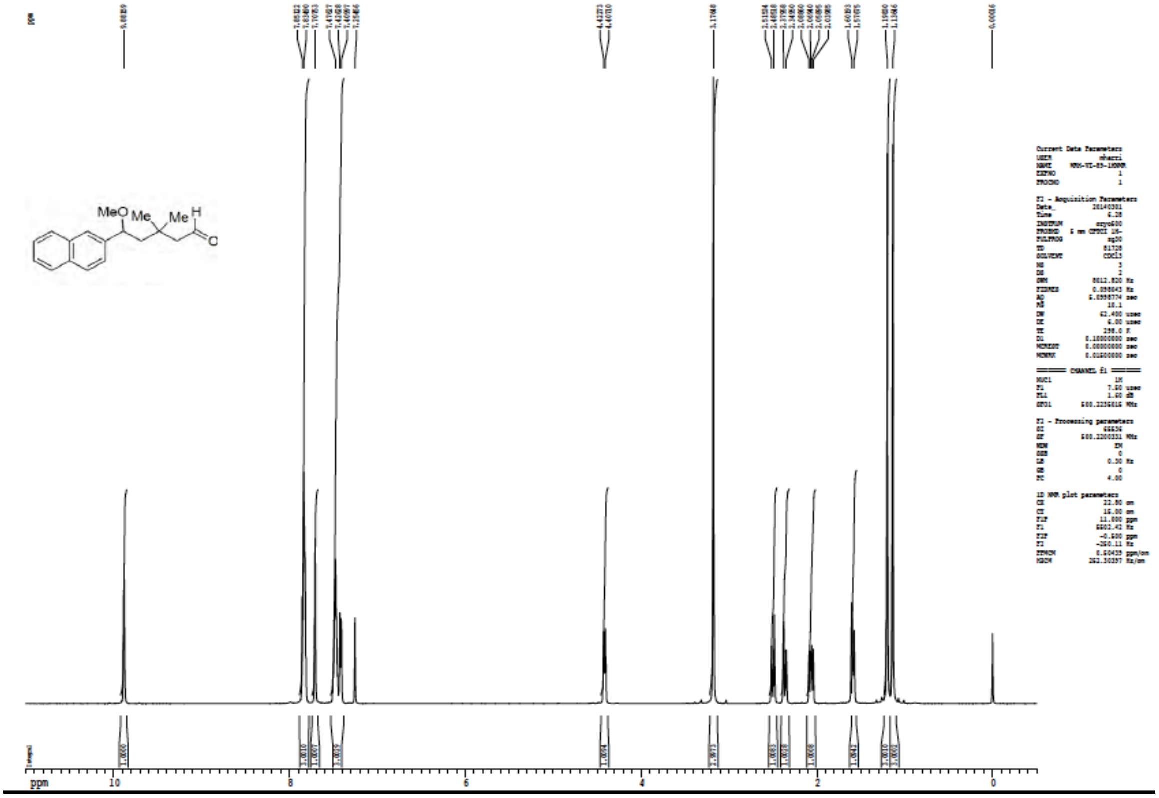
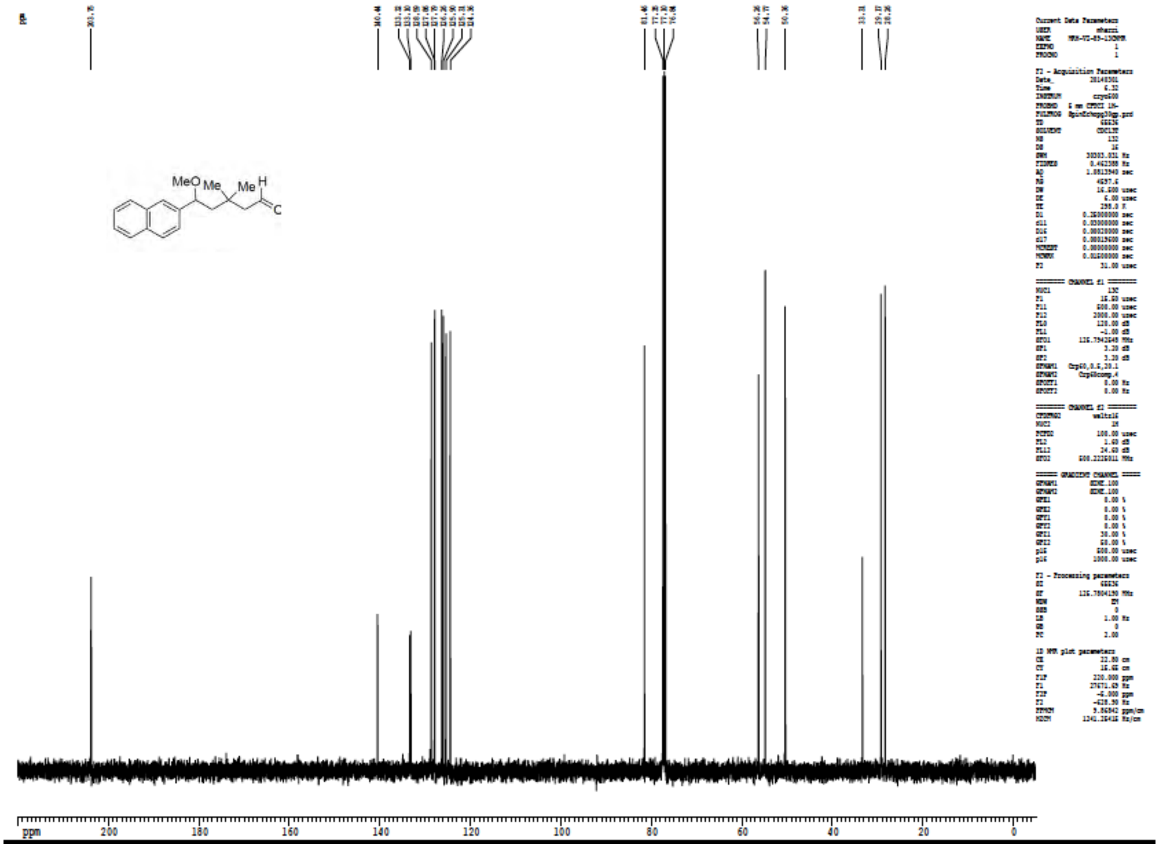


Z-restored spin-echo 13C spectrum with 1H decoupling



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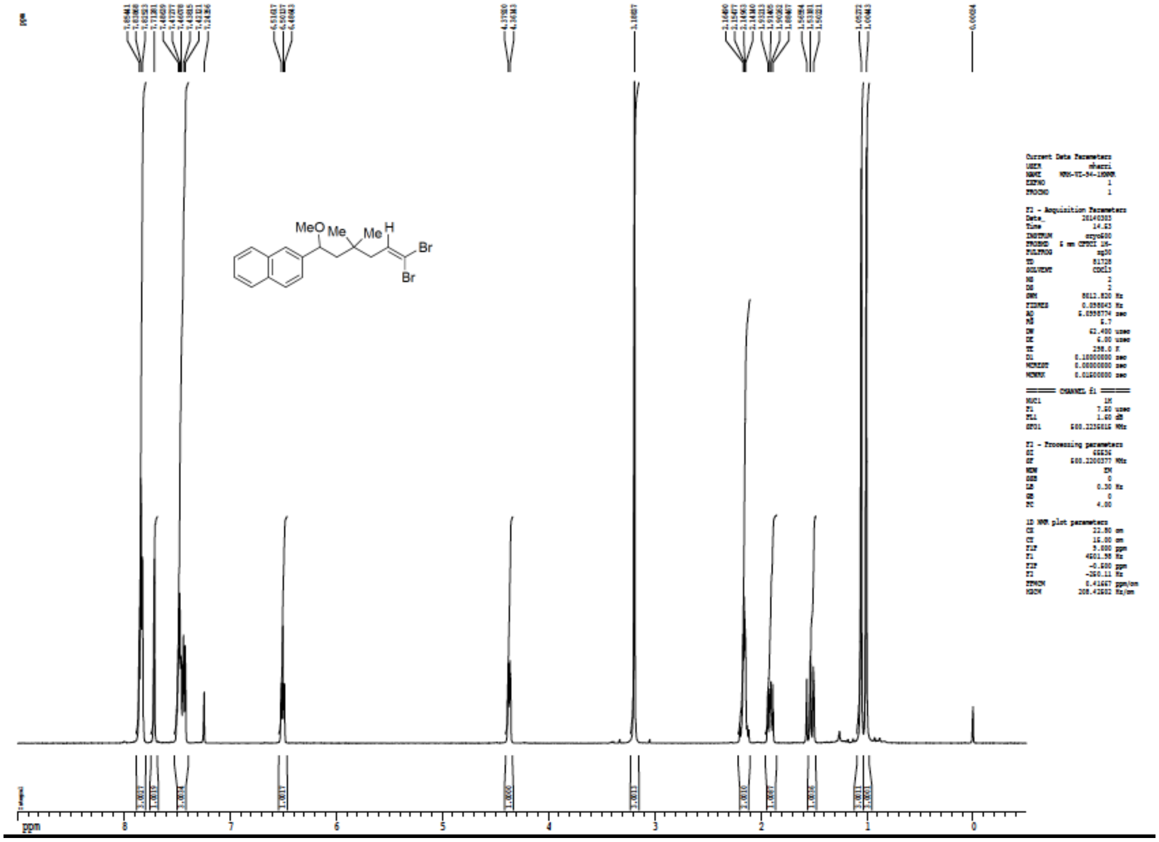
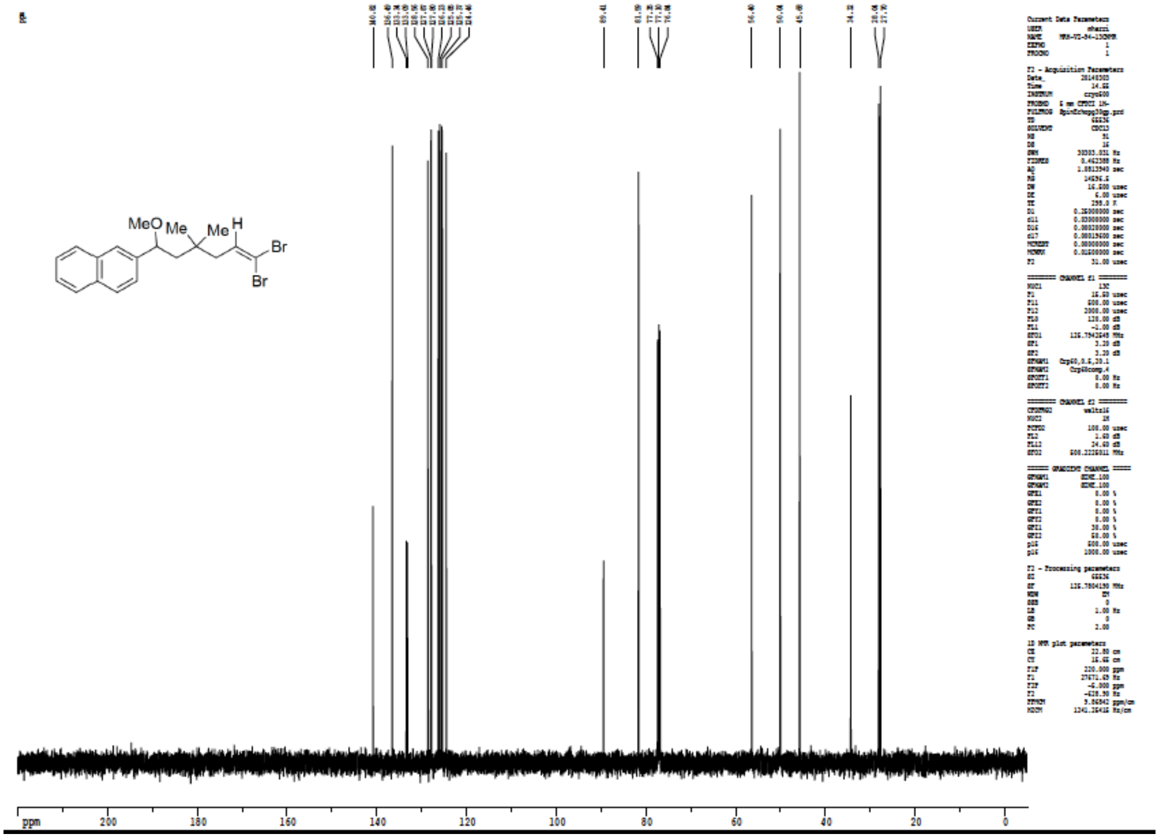
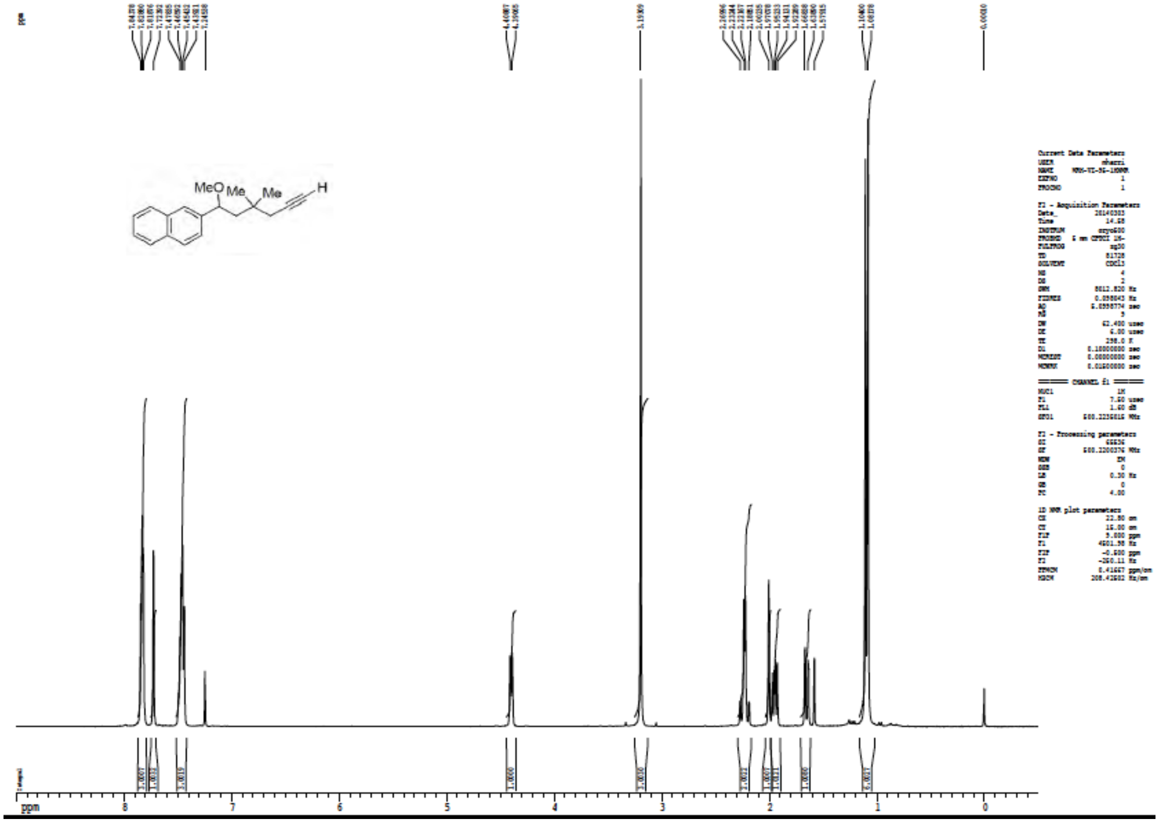


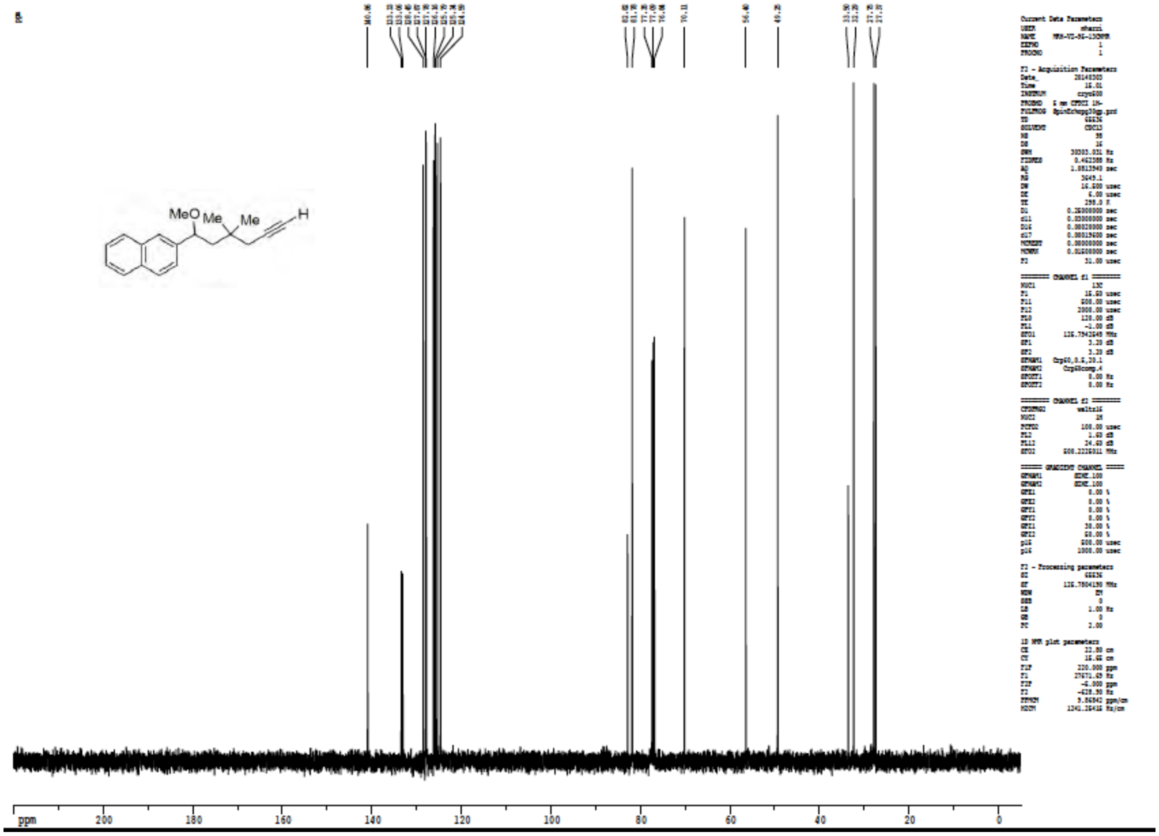
Z-restored spin-echo 13C spectrum with 1H decoupling



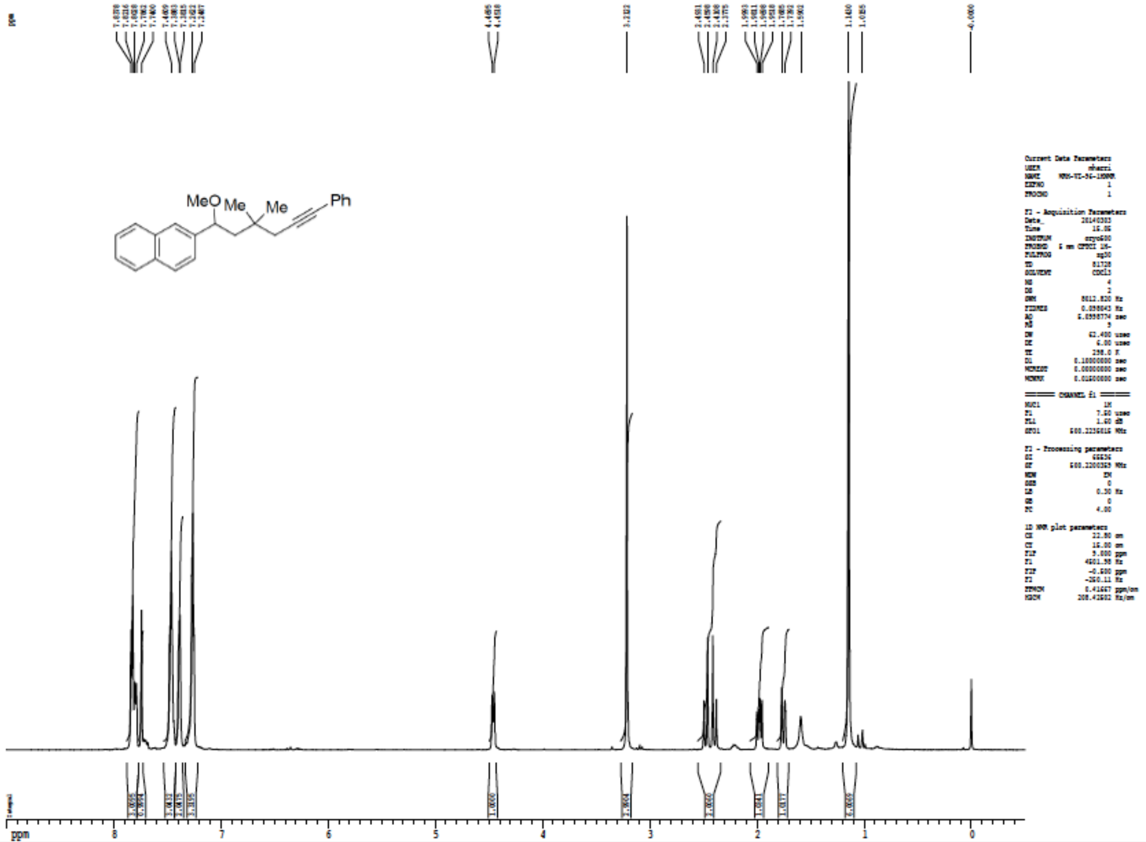
1H spectrum



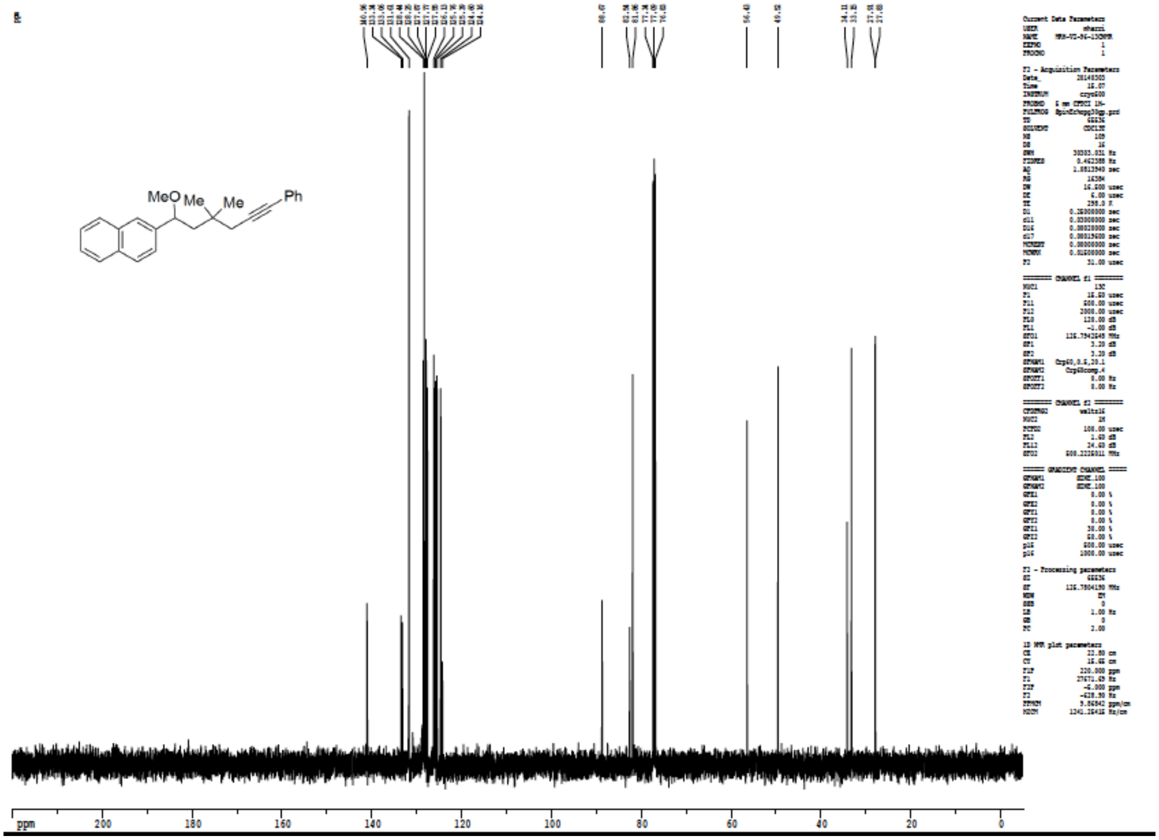
Z-restored spin-echo 13C spectrum with 1H decoupling



1H spectrum



Z-restored spin-echo 13C spectrum with 1H decoupling



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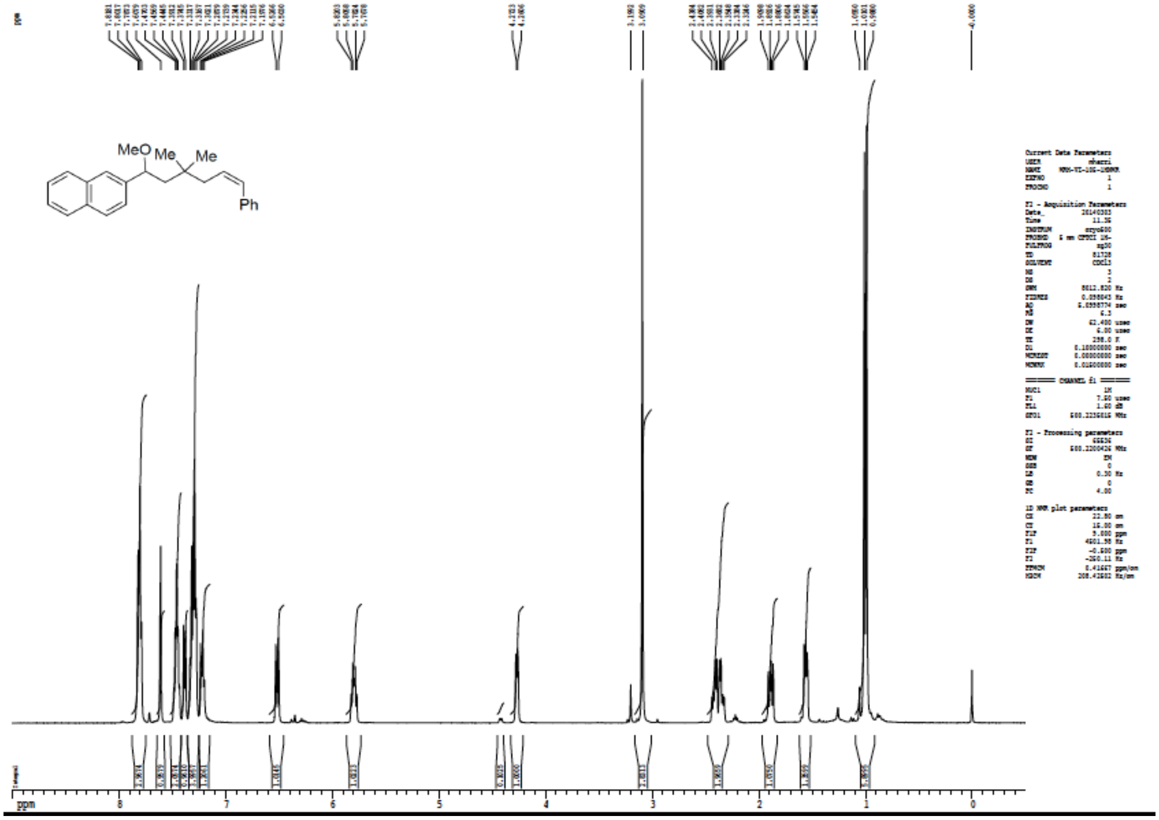
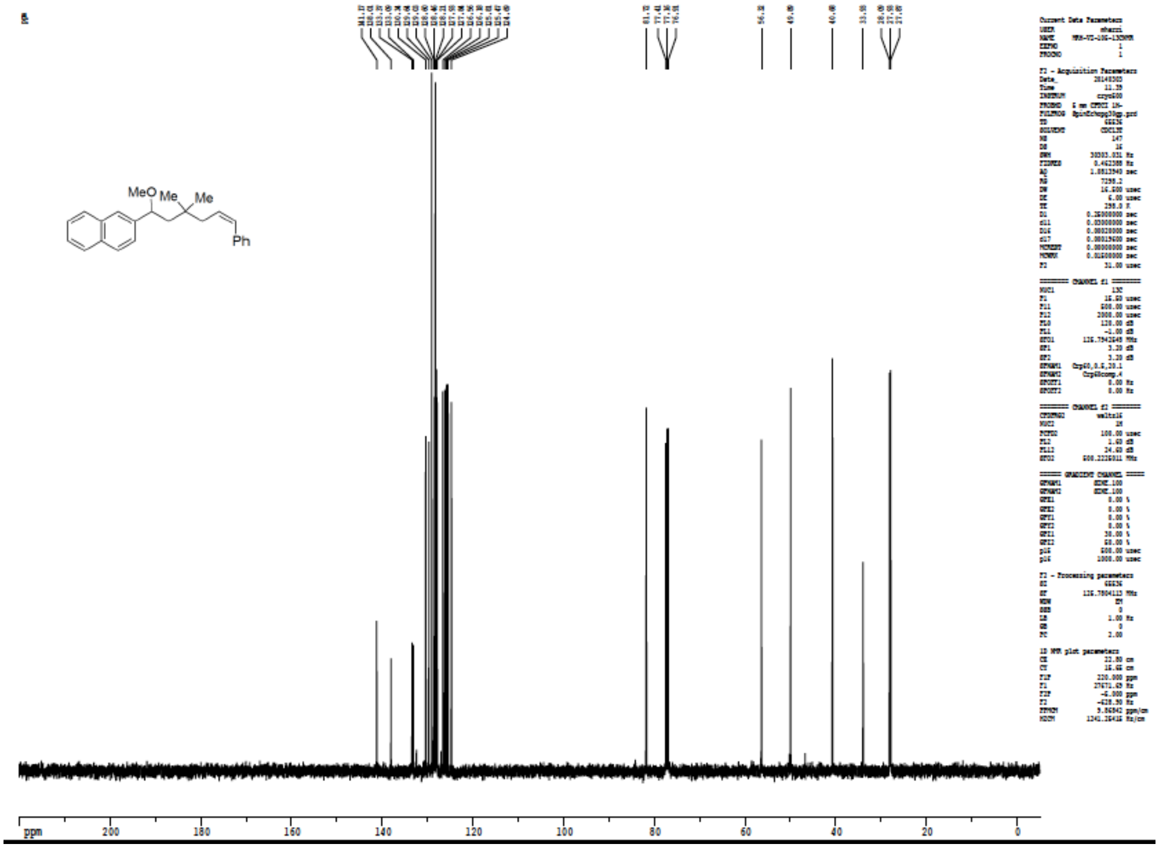
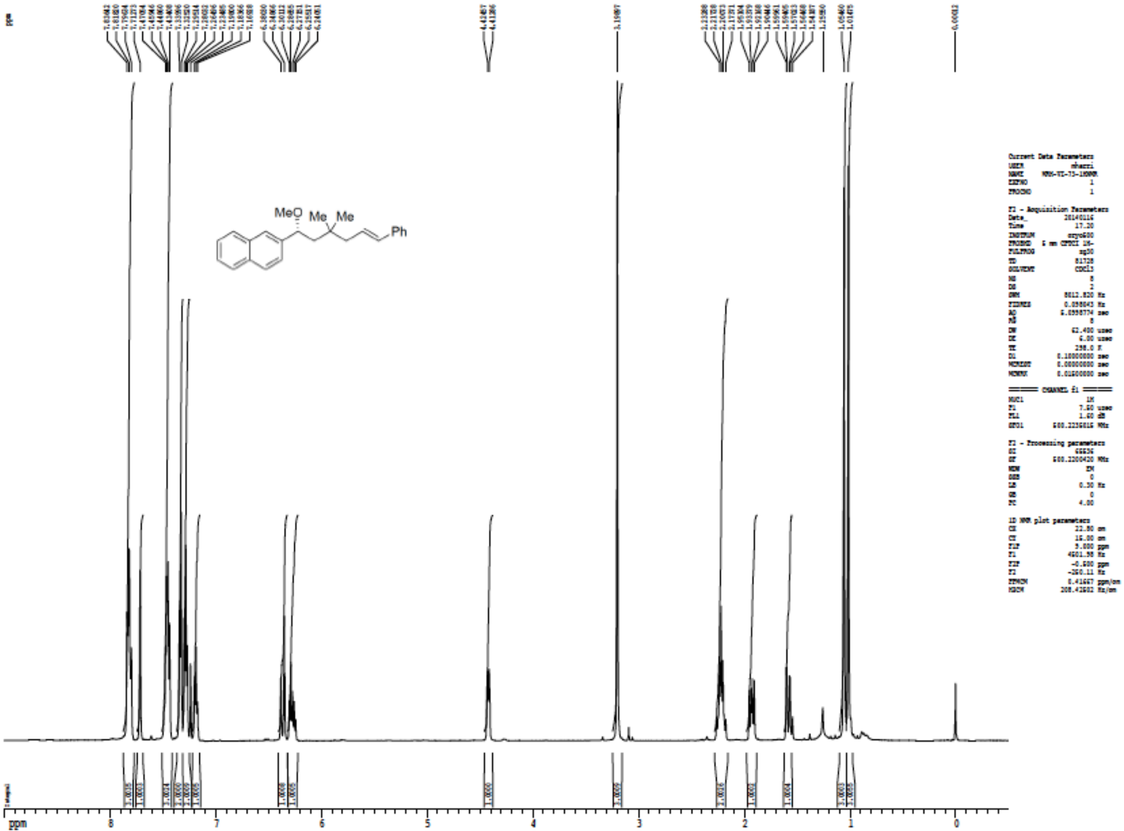


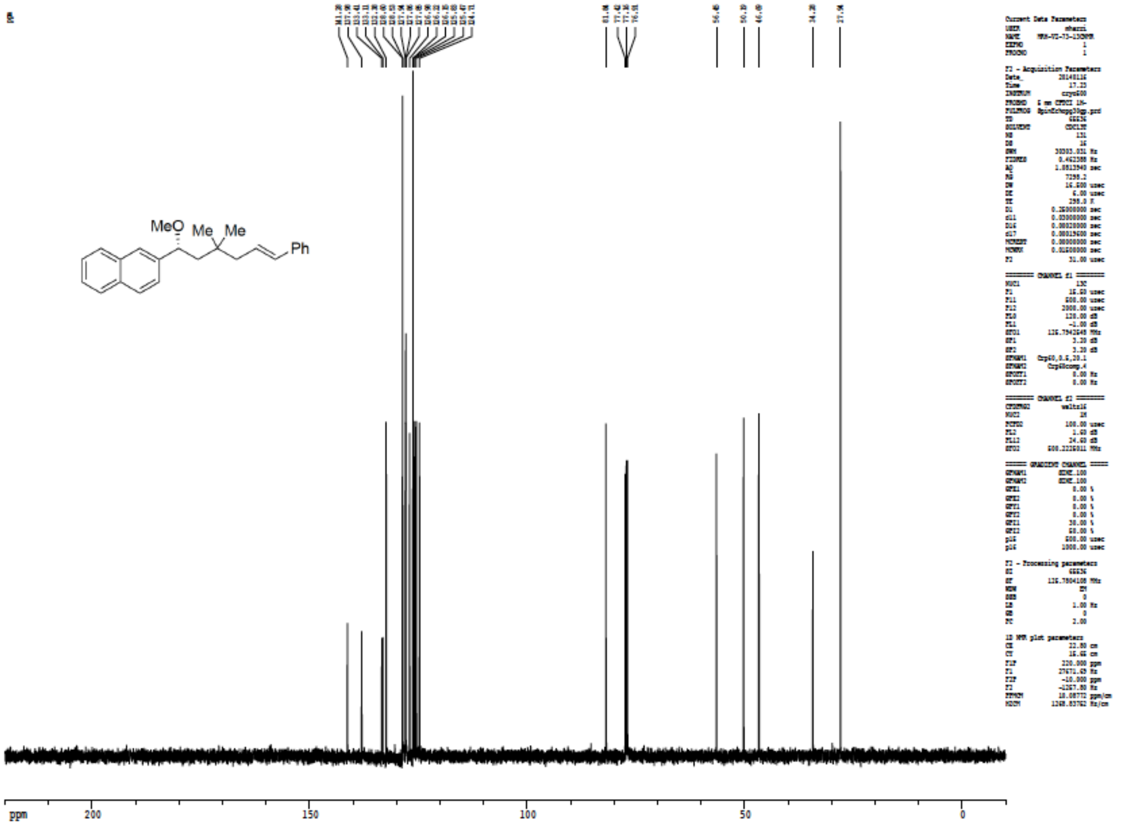
Z-restored spin-echo 13C spectrum with 1H decoupling



1H spectrum



Z-restored spin-echo 13C spectrum with 1H decoupling



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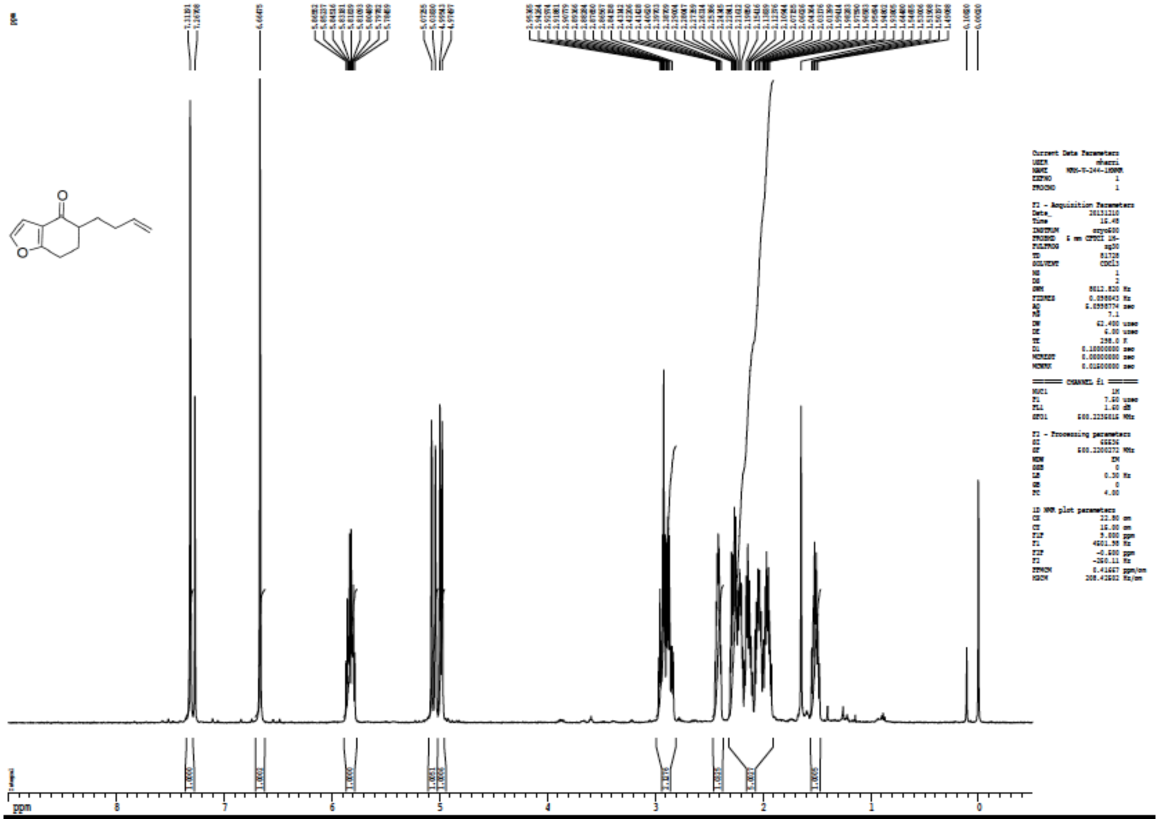
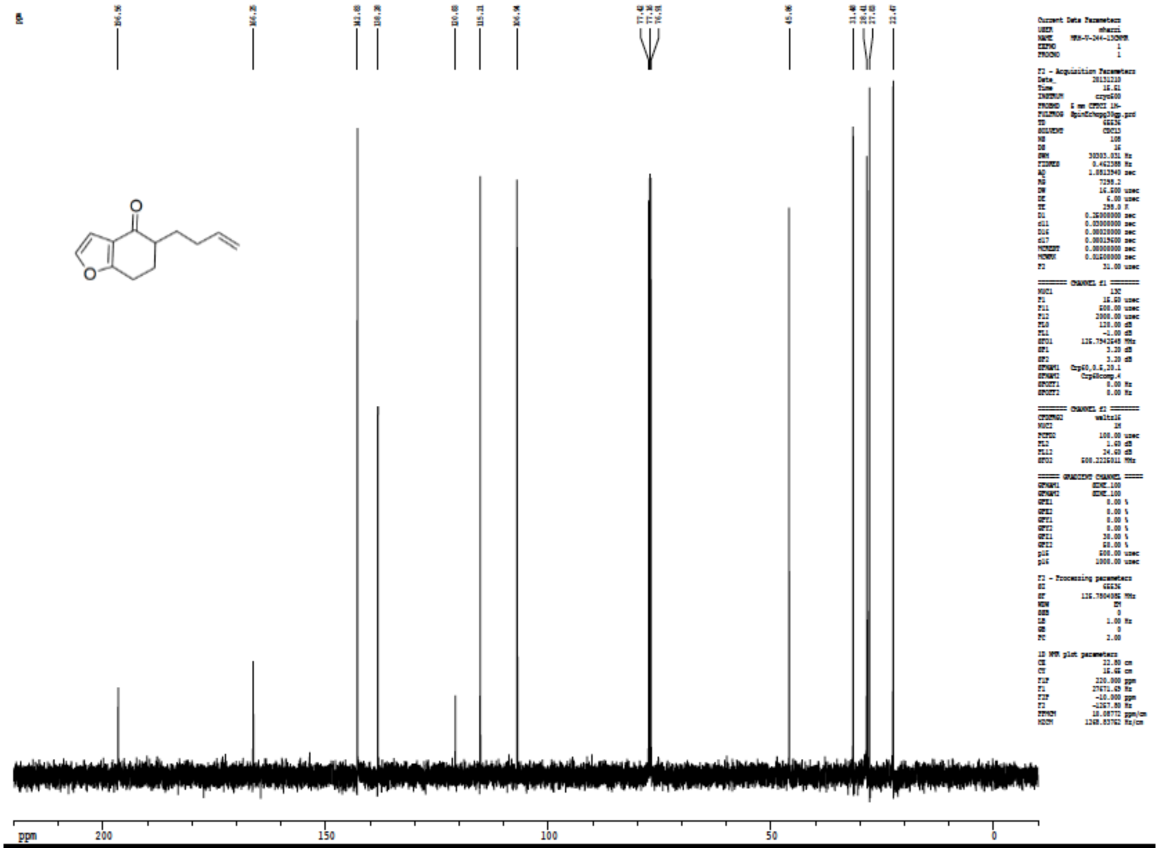
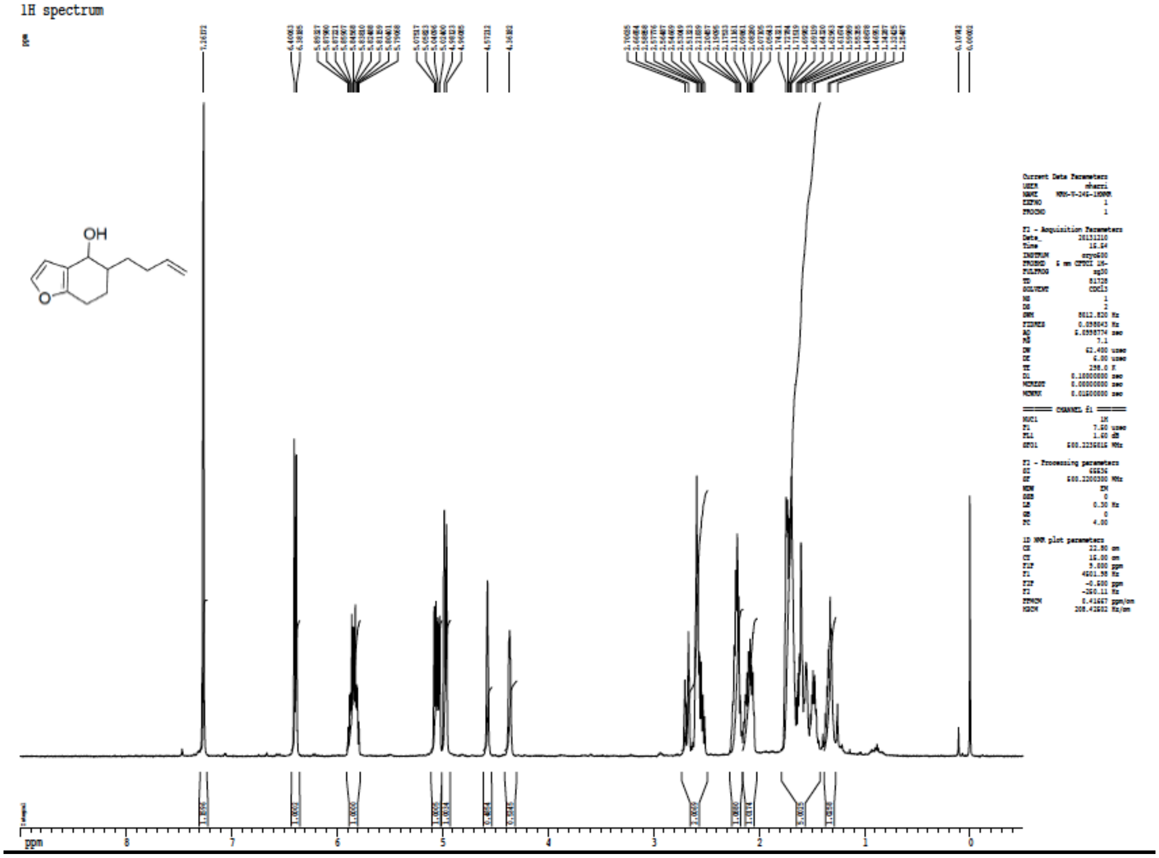


Z-restored spin-echo 13C spectrum with 1H decoupling




1H spectrum
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O
ppm
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6
5
4
3
2
1
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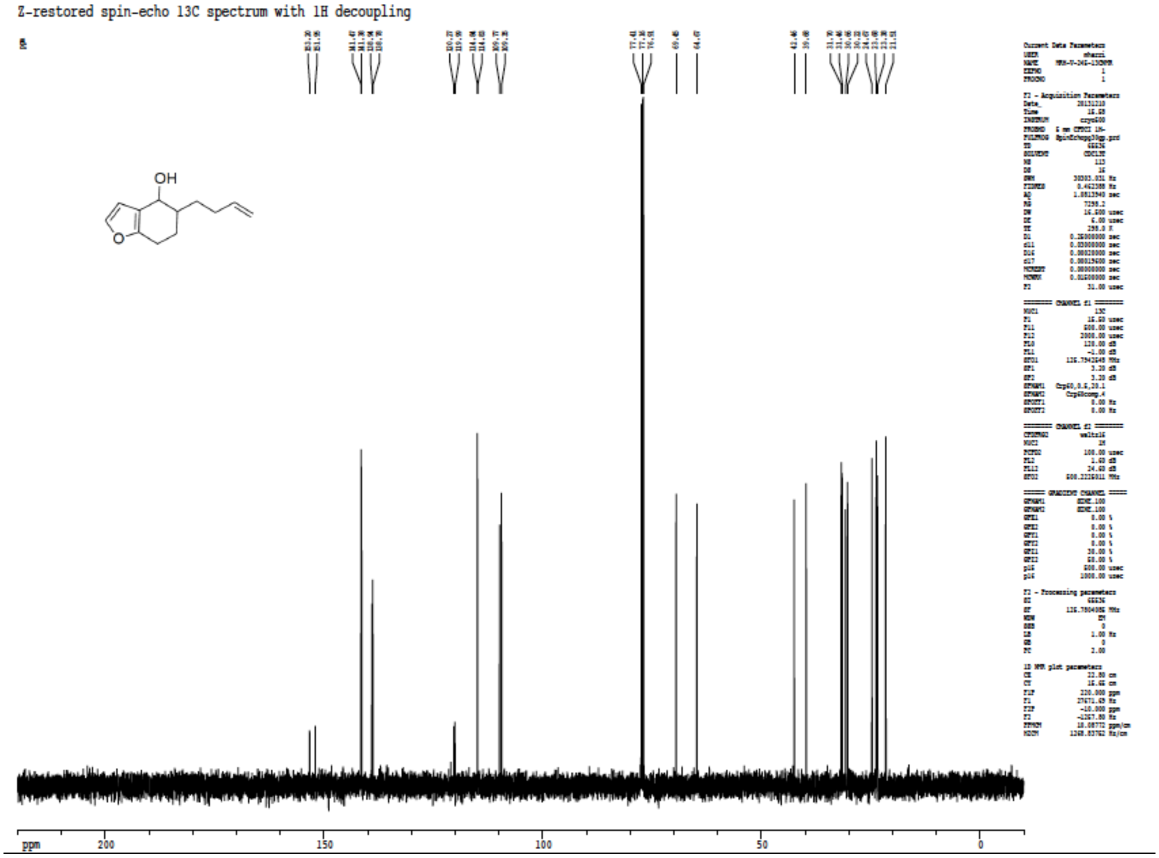
Z-restored spin-echo 13C spectrum with 1H decoupling
OH
O
ppm
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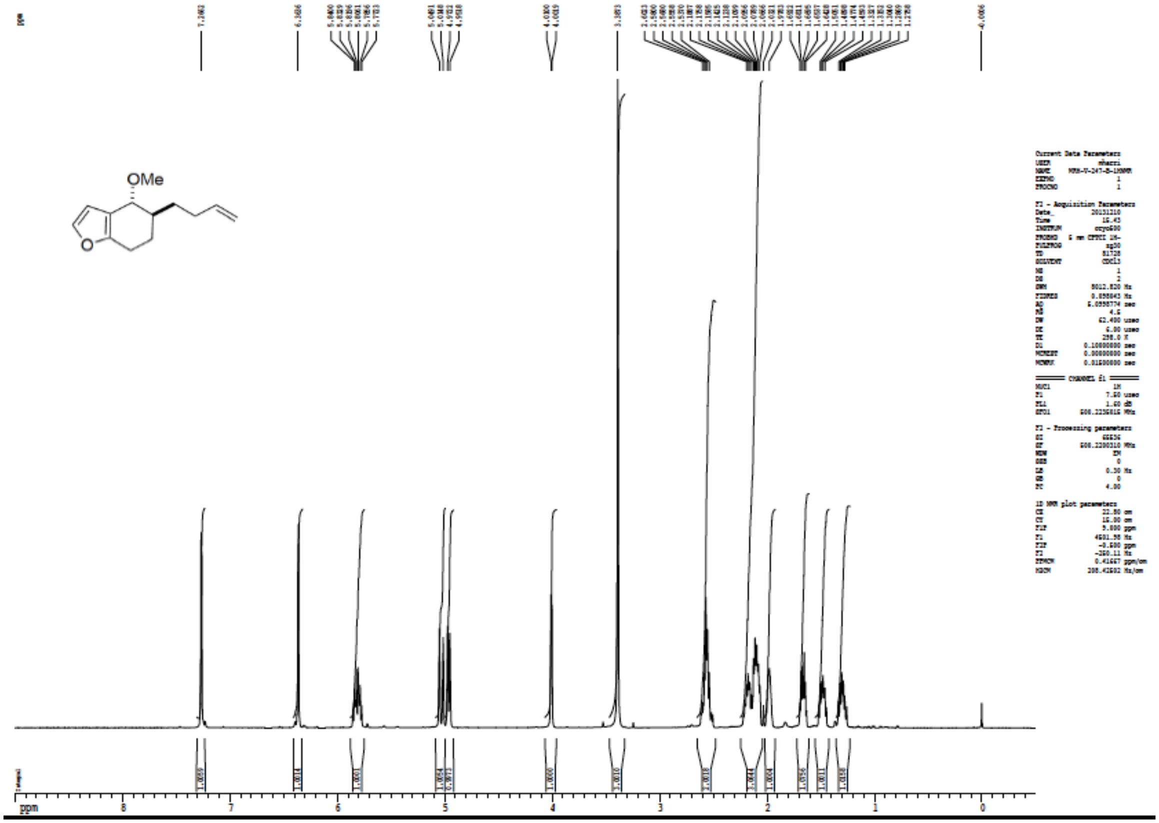
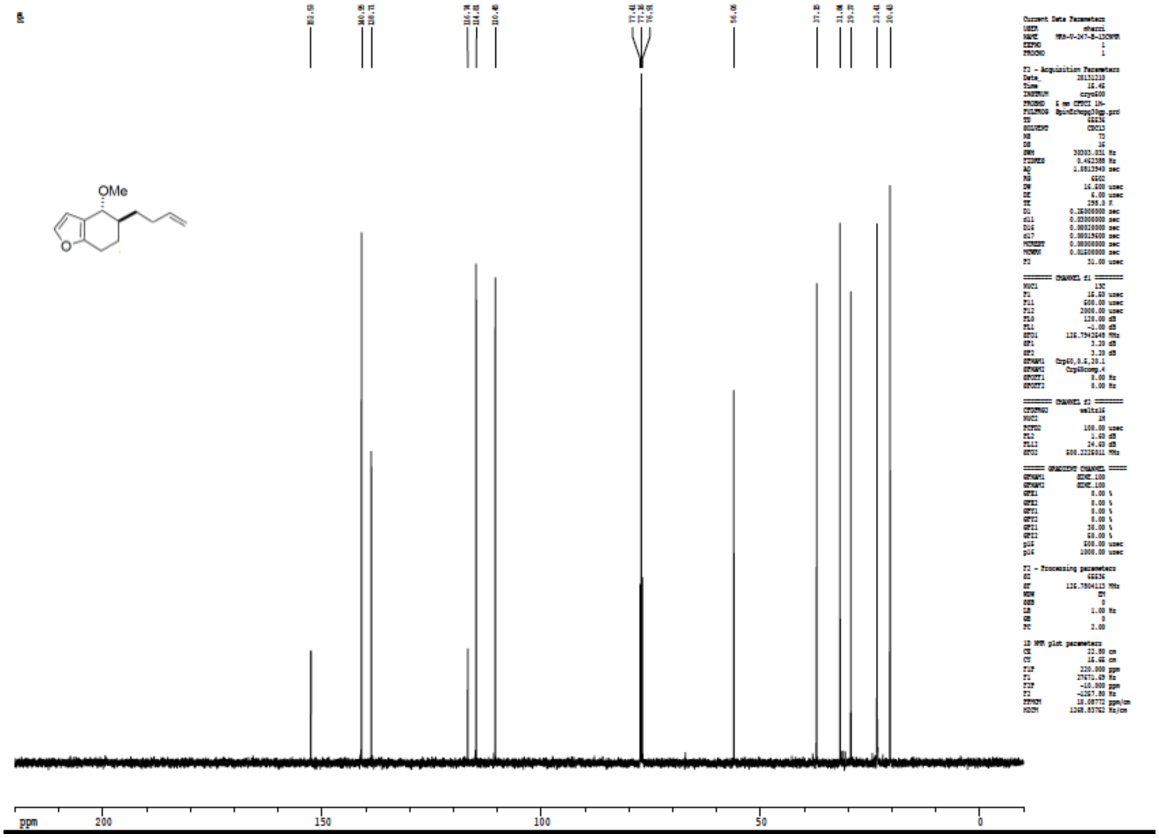
150
100
50
0
Current Data Parameters

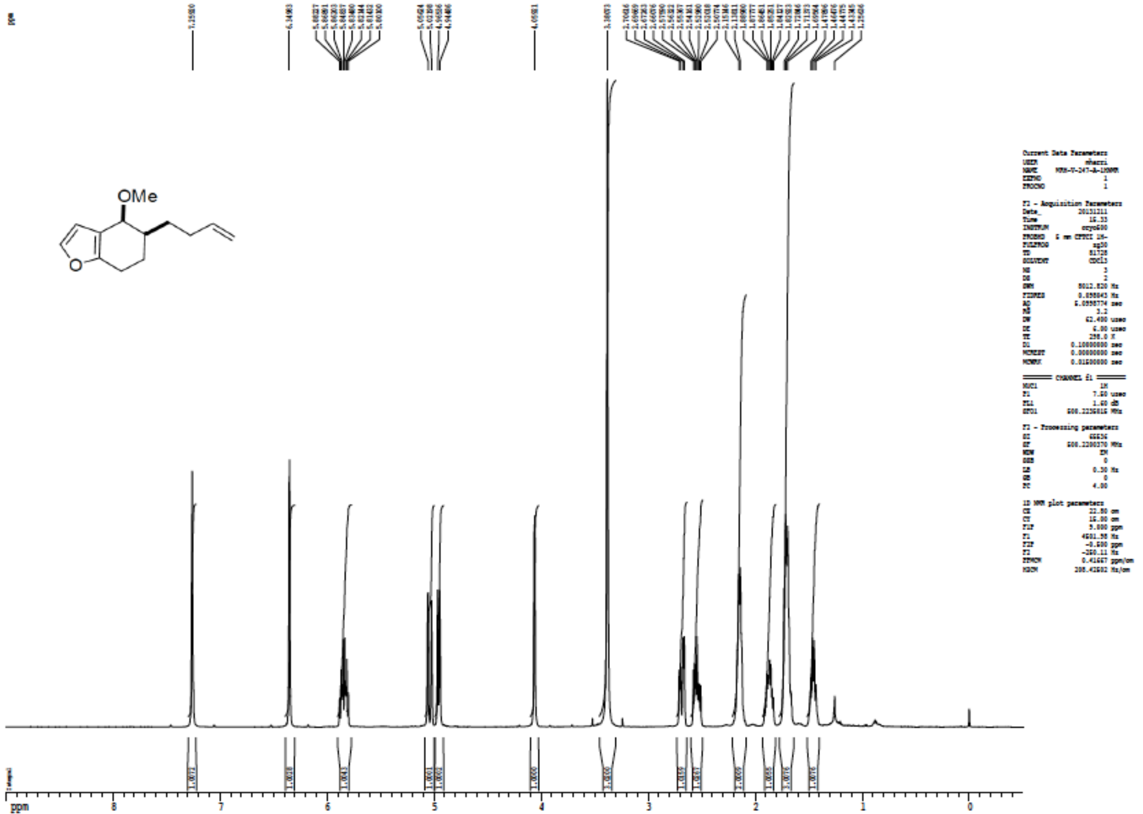
1H spectrum



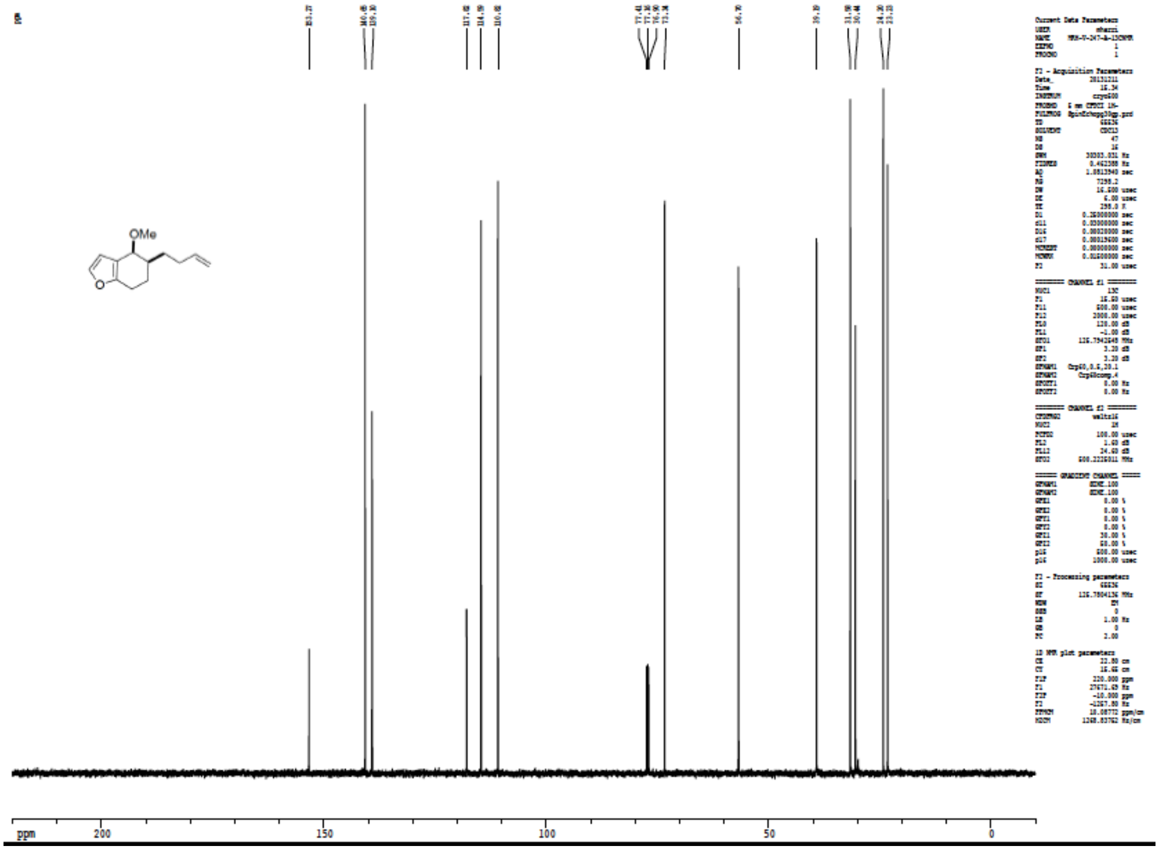
Z-restored spin-echo 13C spectrum with 1H decoupling



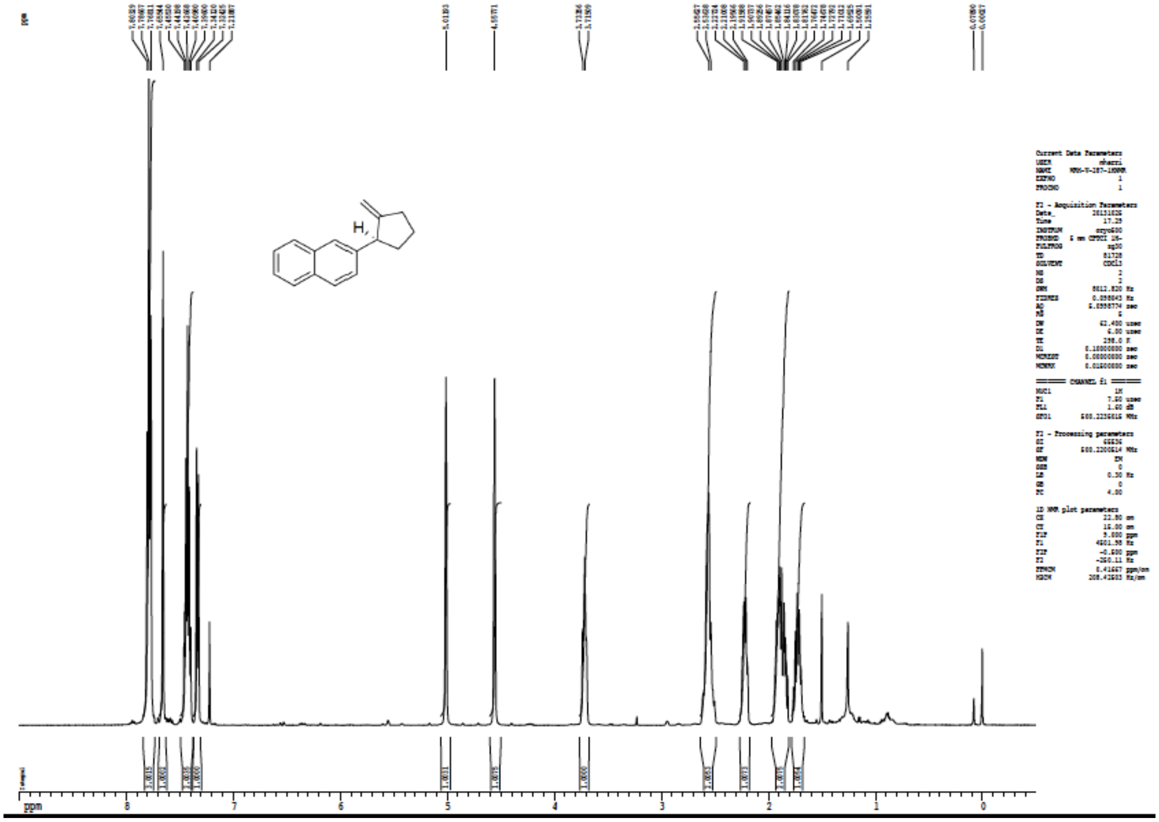
1H spectrum



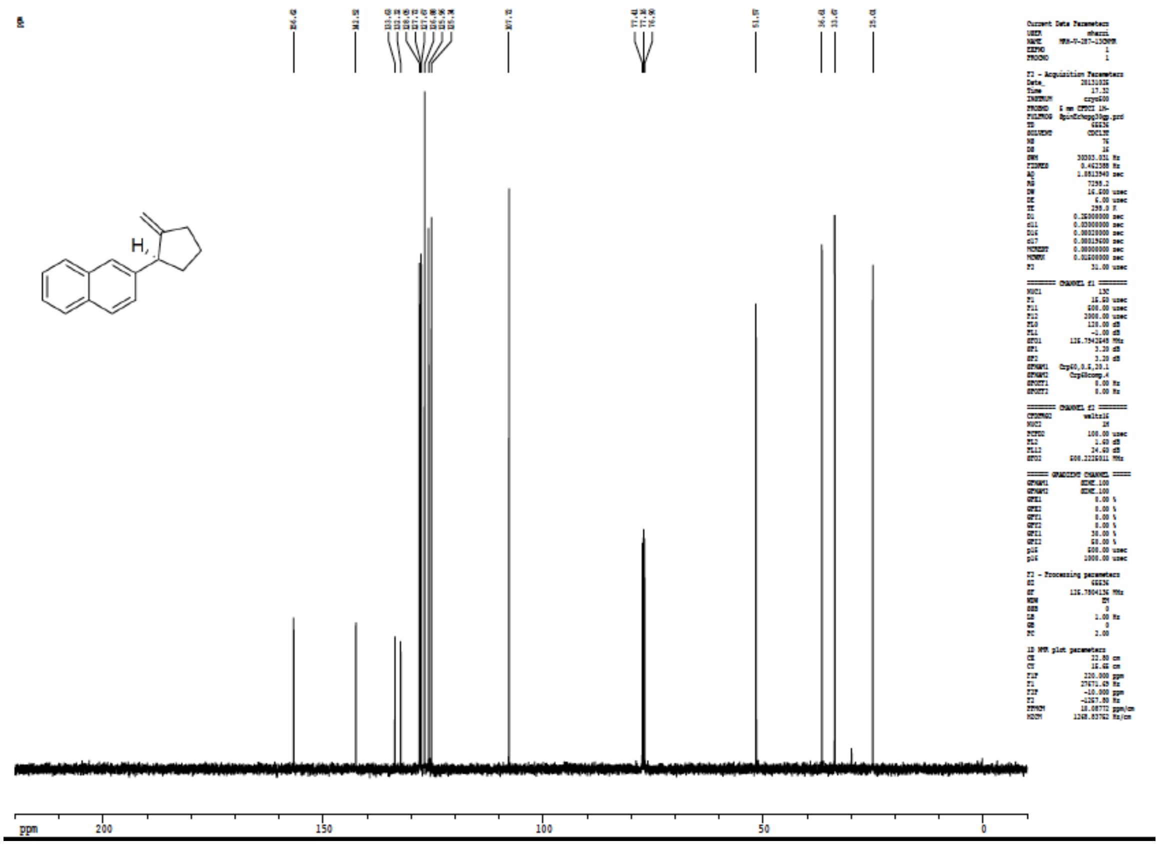
Z-restored spin-echo 13C spectrum with 1H decoupling



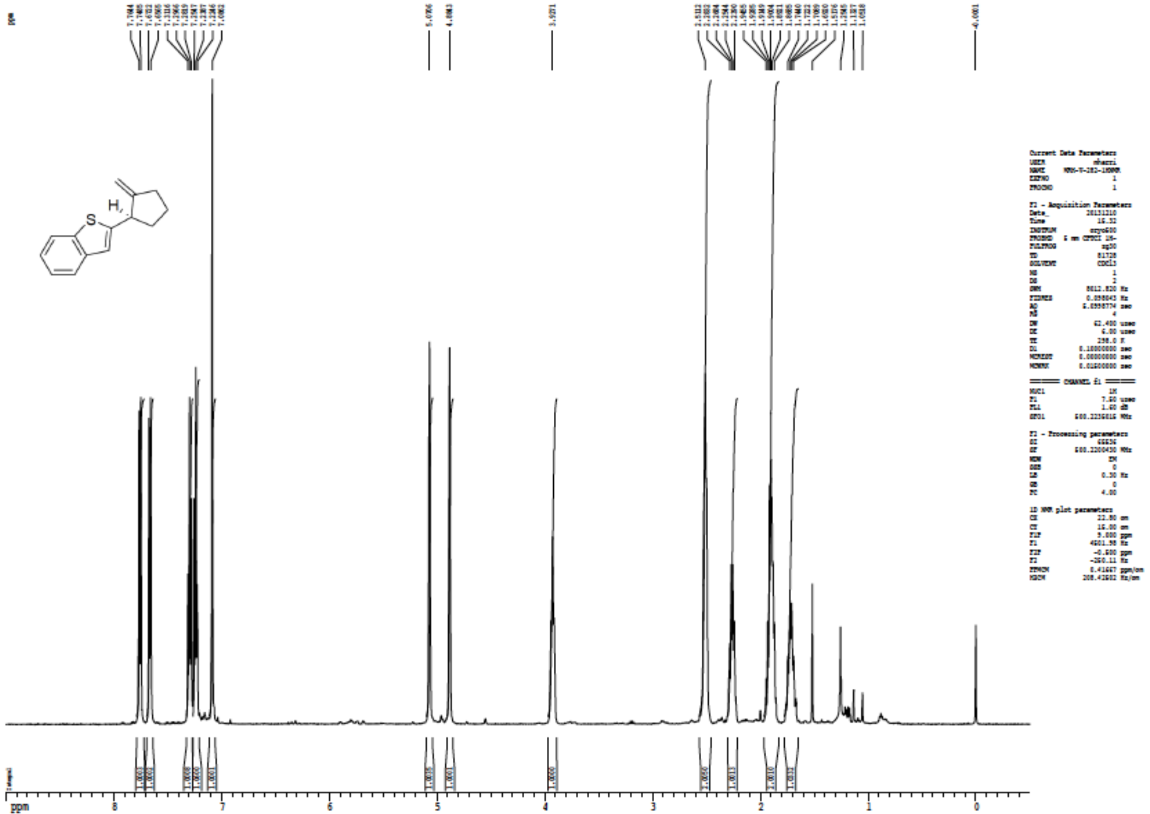
1H spectrum



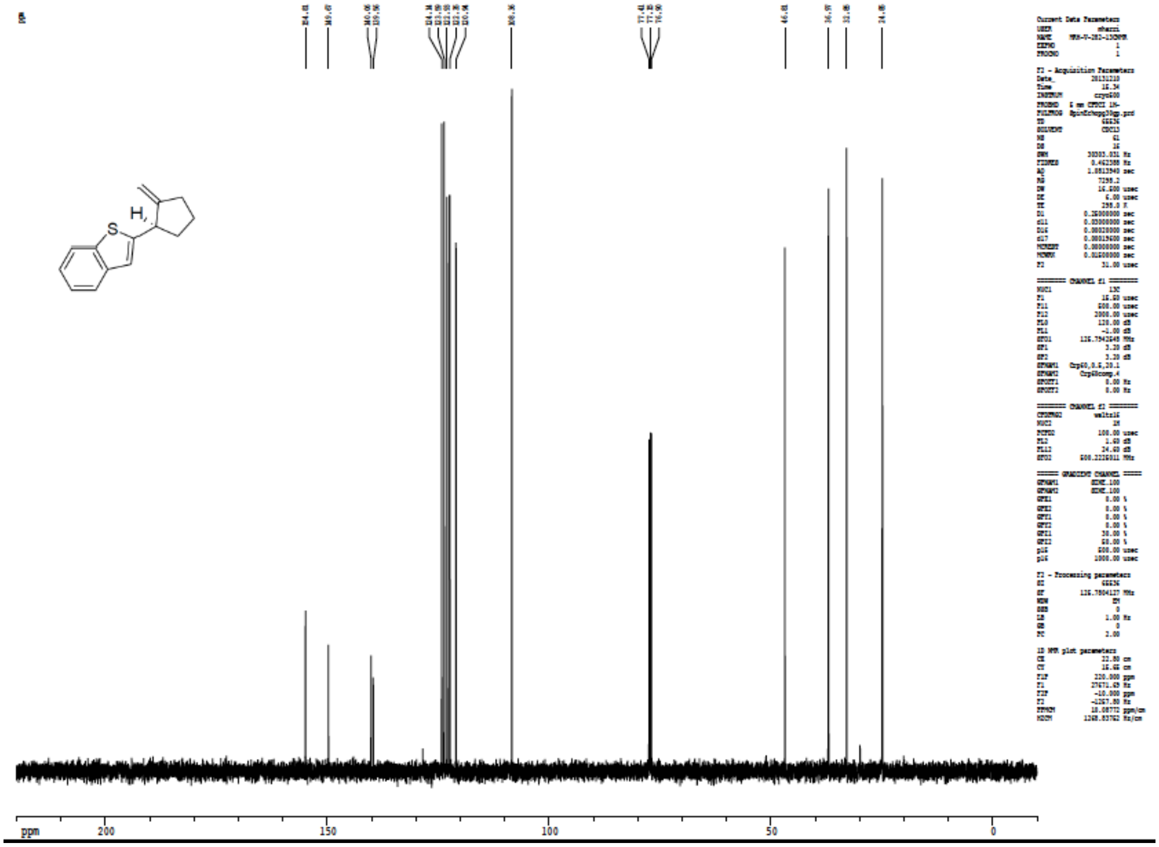
Z-restored spin-echo 13C spectrum with 1H decoupling



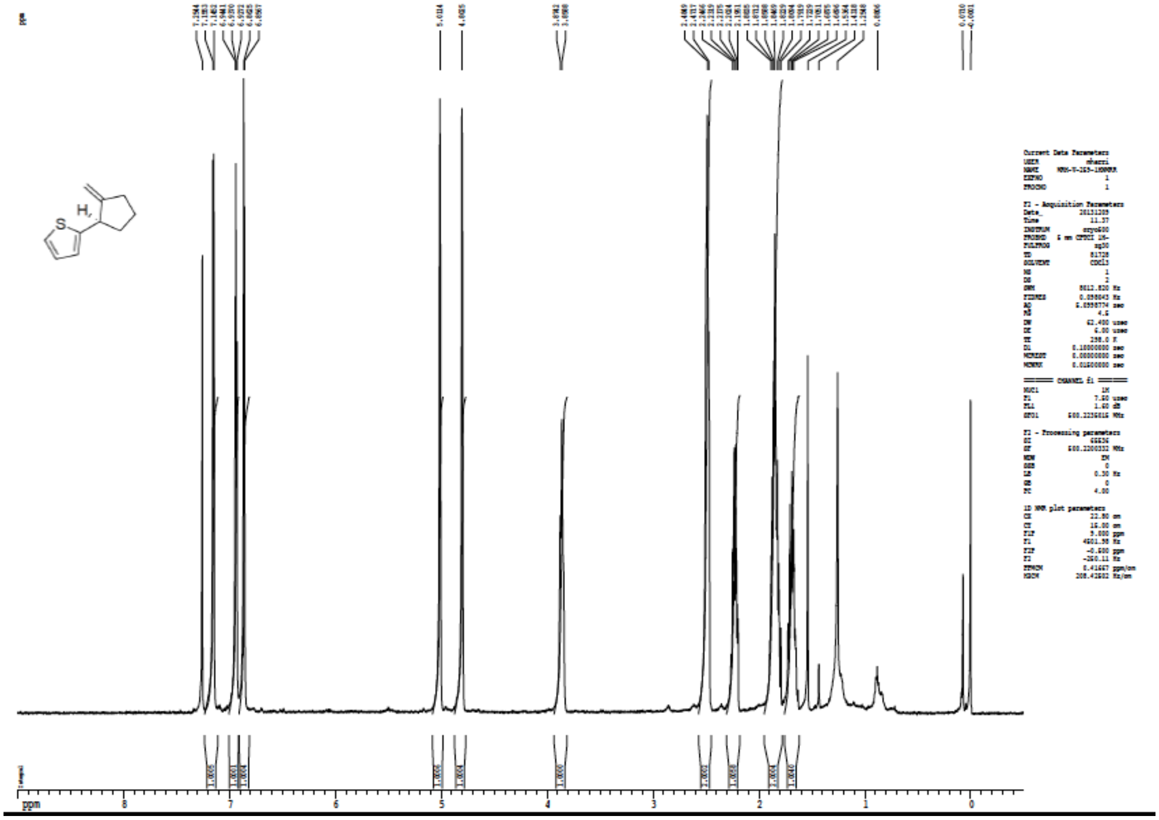
1H spectrum



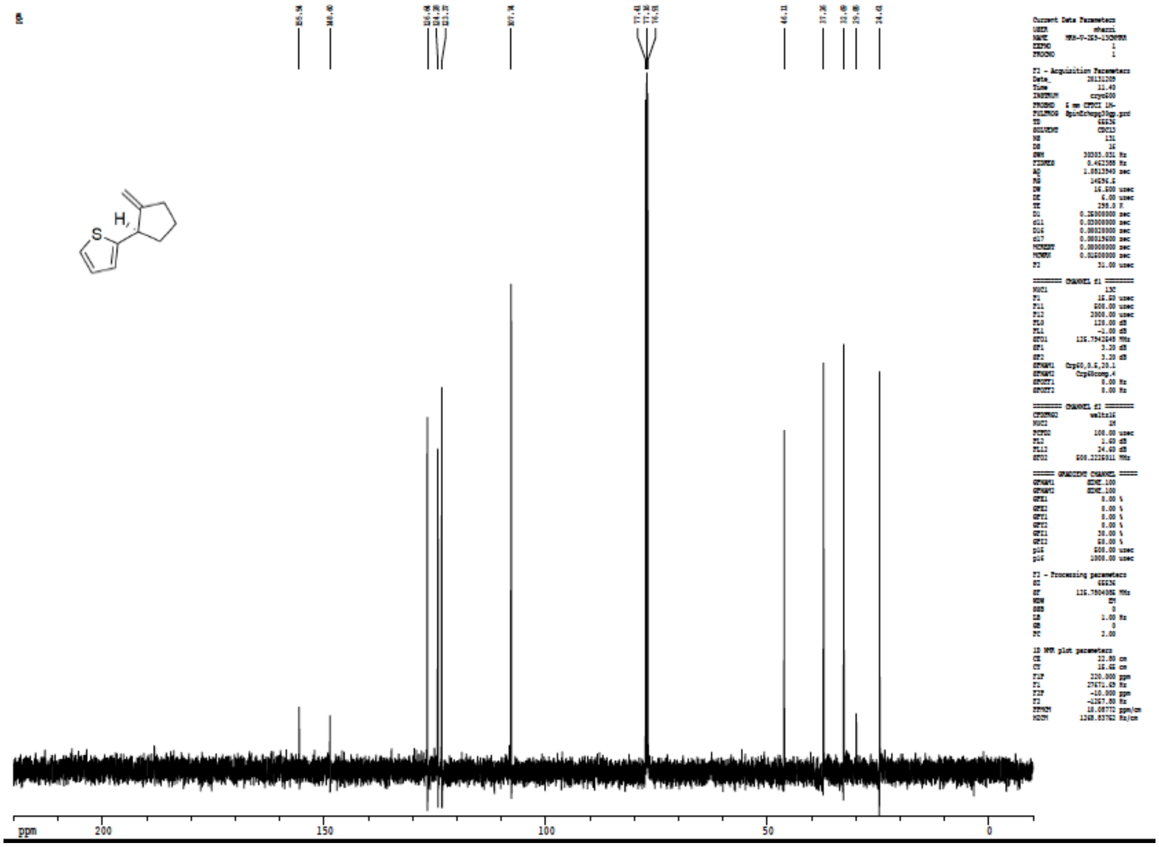
Z-restored spin-echo 13C spectrum with 1H decoupling



1H spectrum



Z-restored spin-echo 13C spectrum with 1H decoupling



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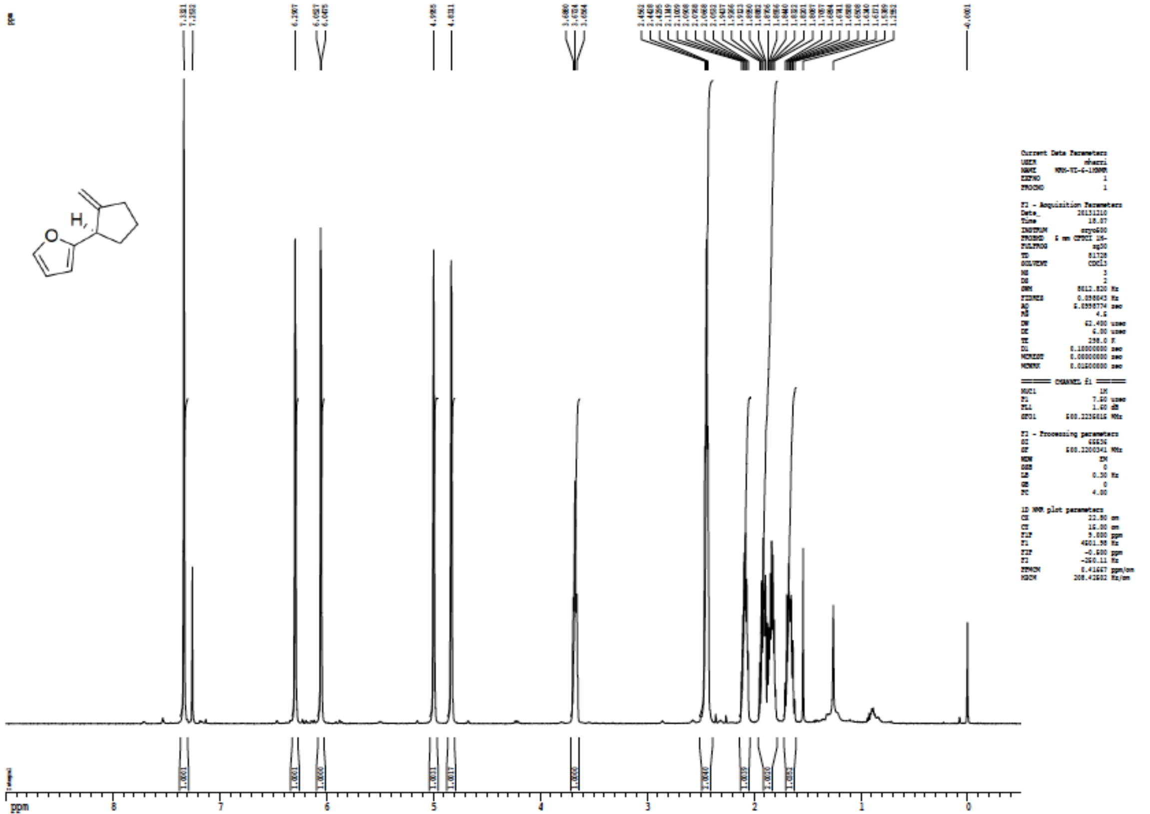
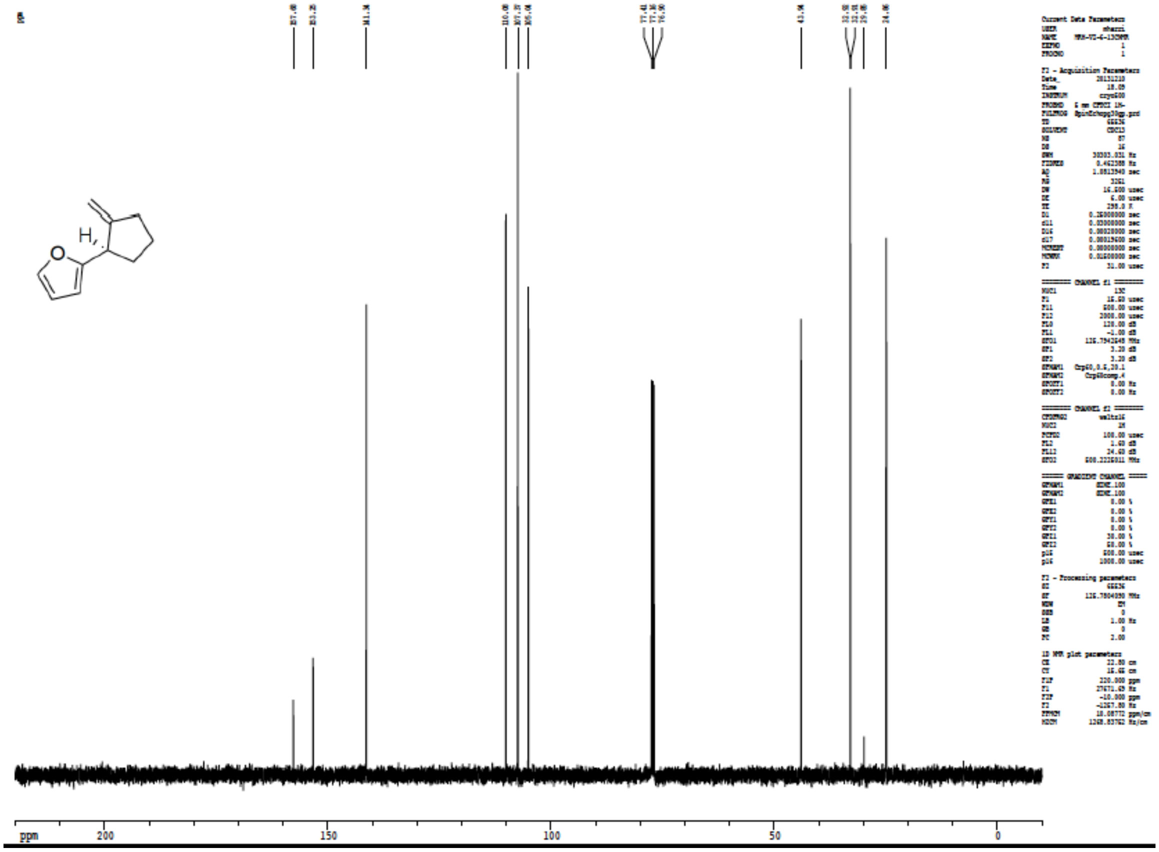


Z-restored spin-echo 13C spectrum with 1H decoupling



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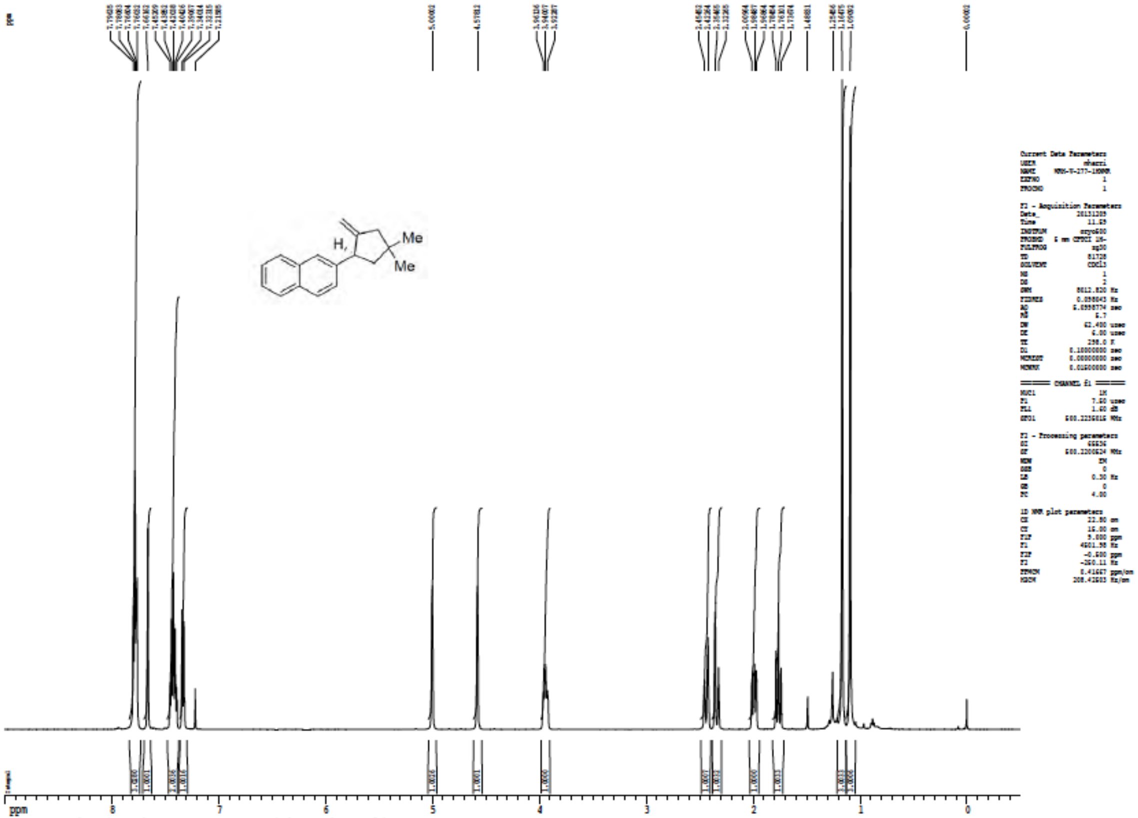
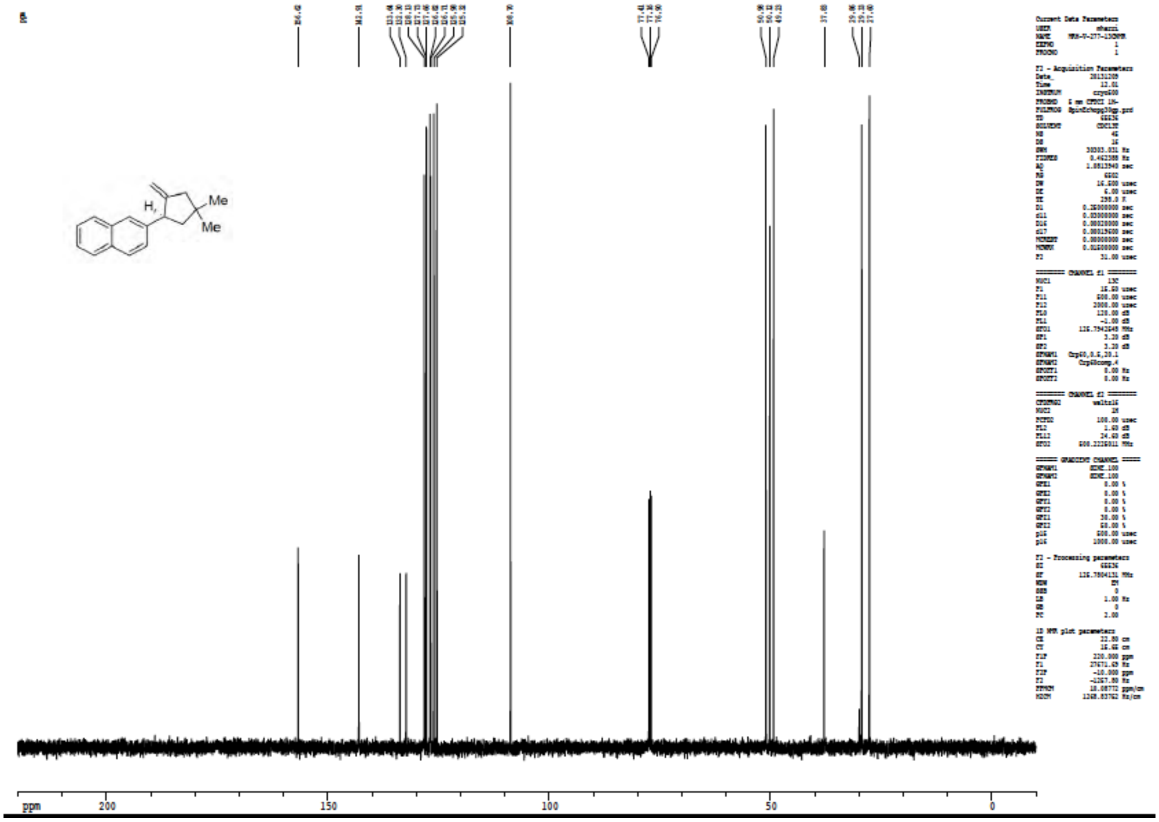


Z-restored spin-echo 13C spectrum with 1H decoupling



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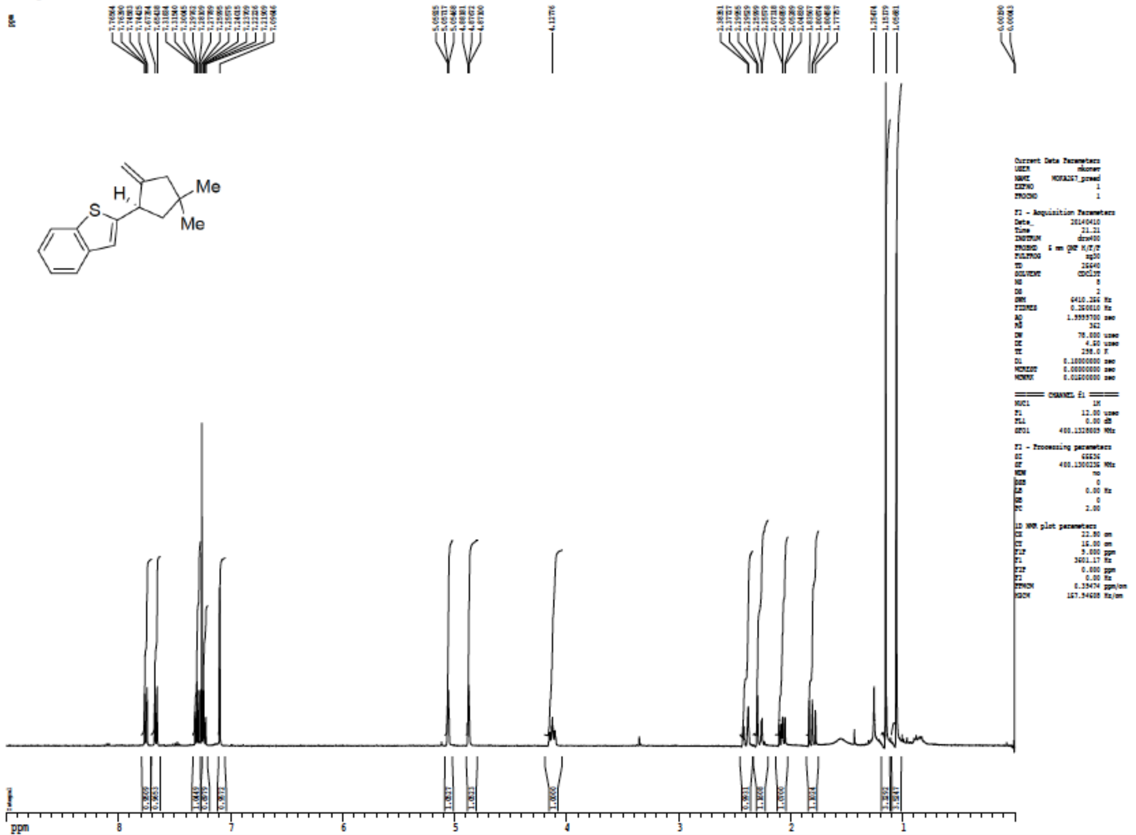
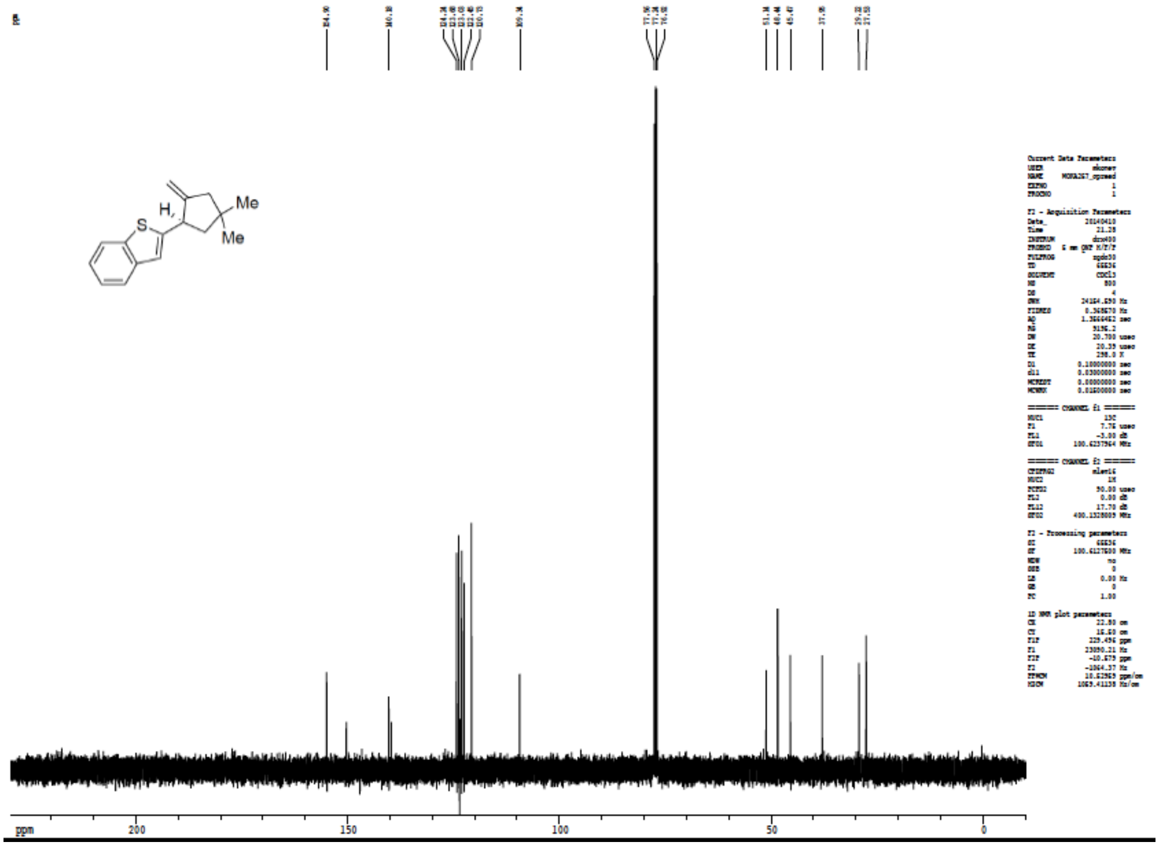


13C spectrum with 1H decoupling



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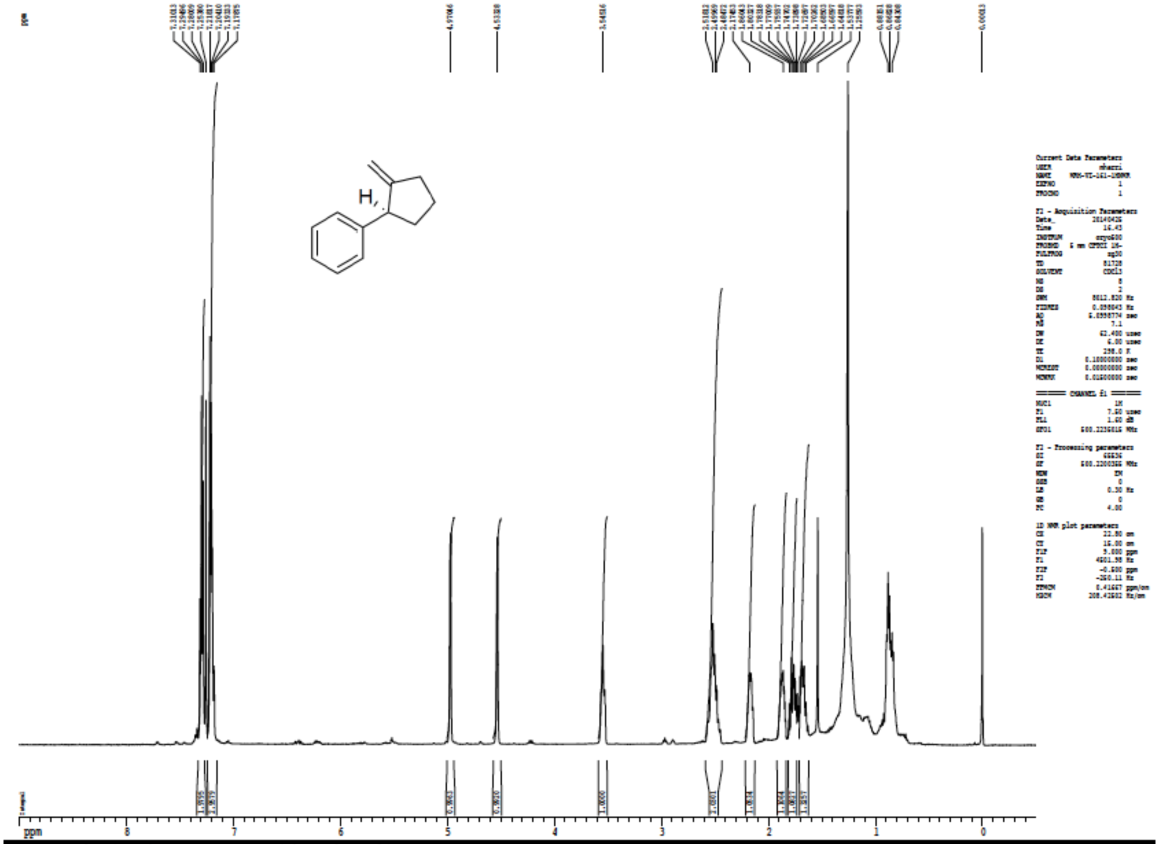
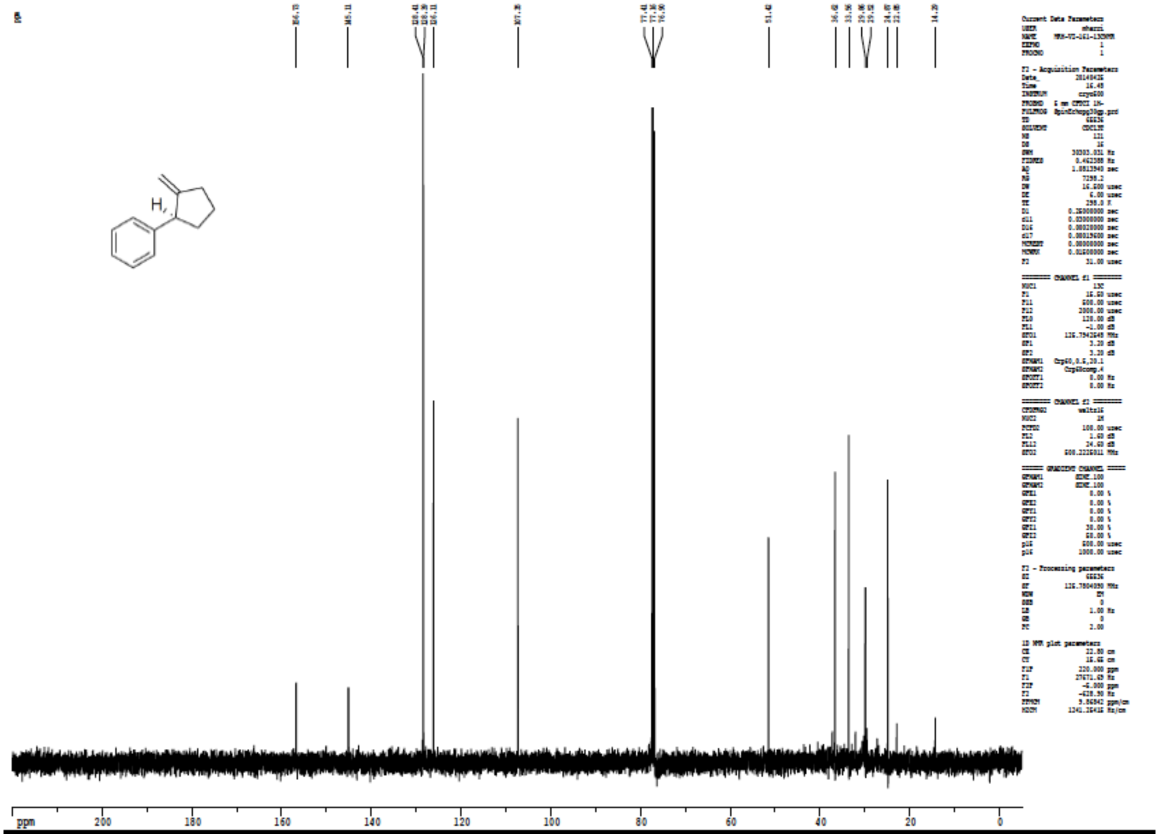


Z-restored spin-echo 13C spectrum with 1H decoupling



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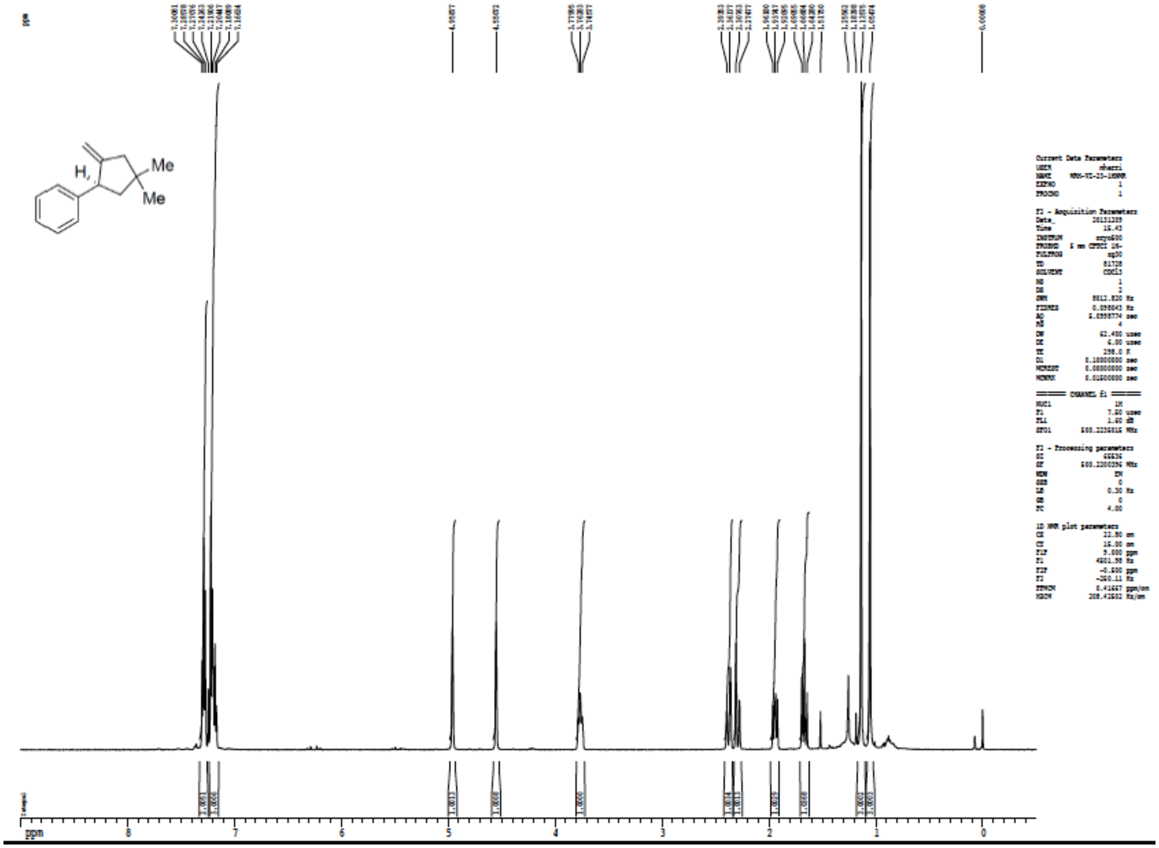
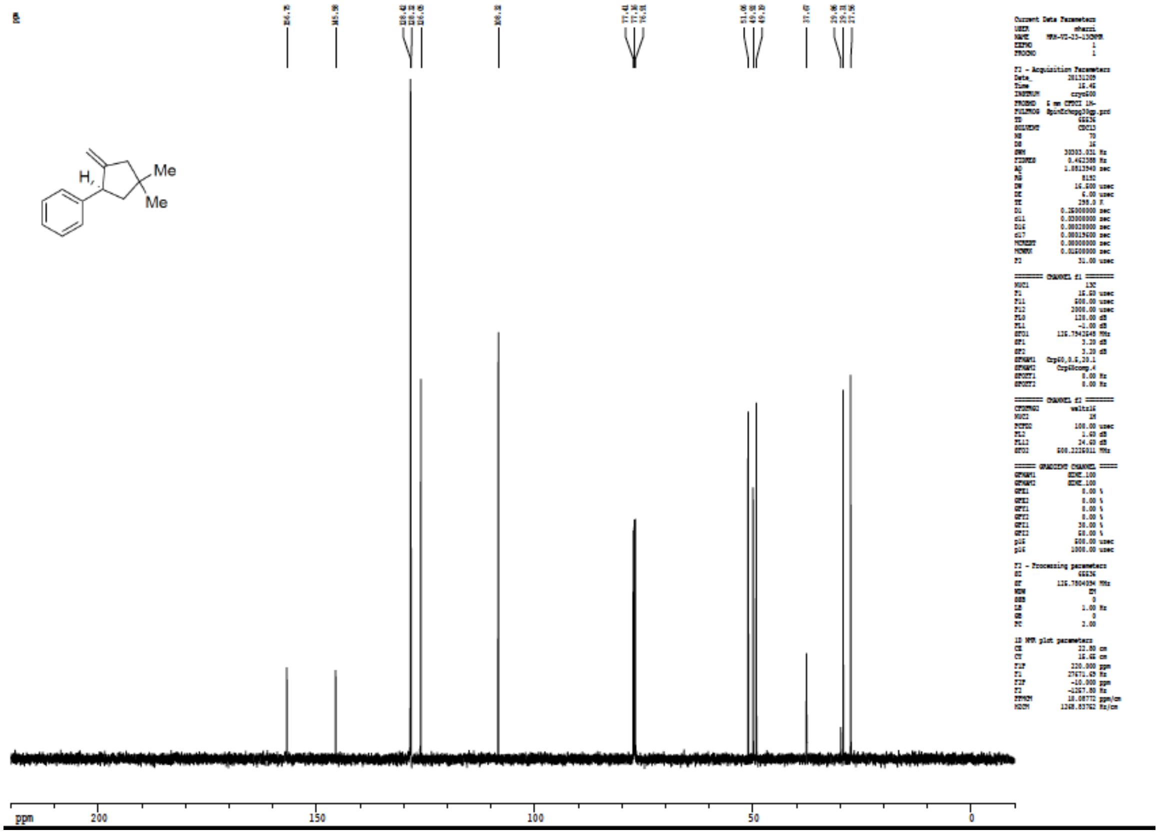


Z-restored spin-echo 13C spectrum with 1H decoupling



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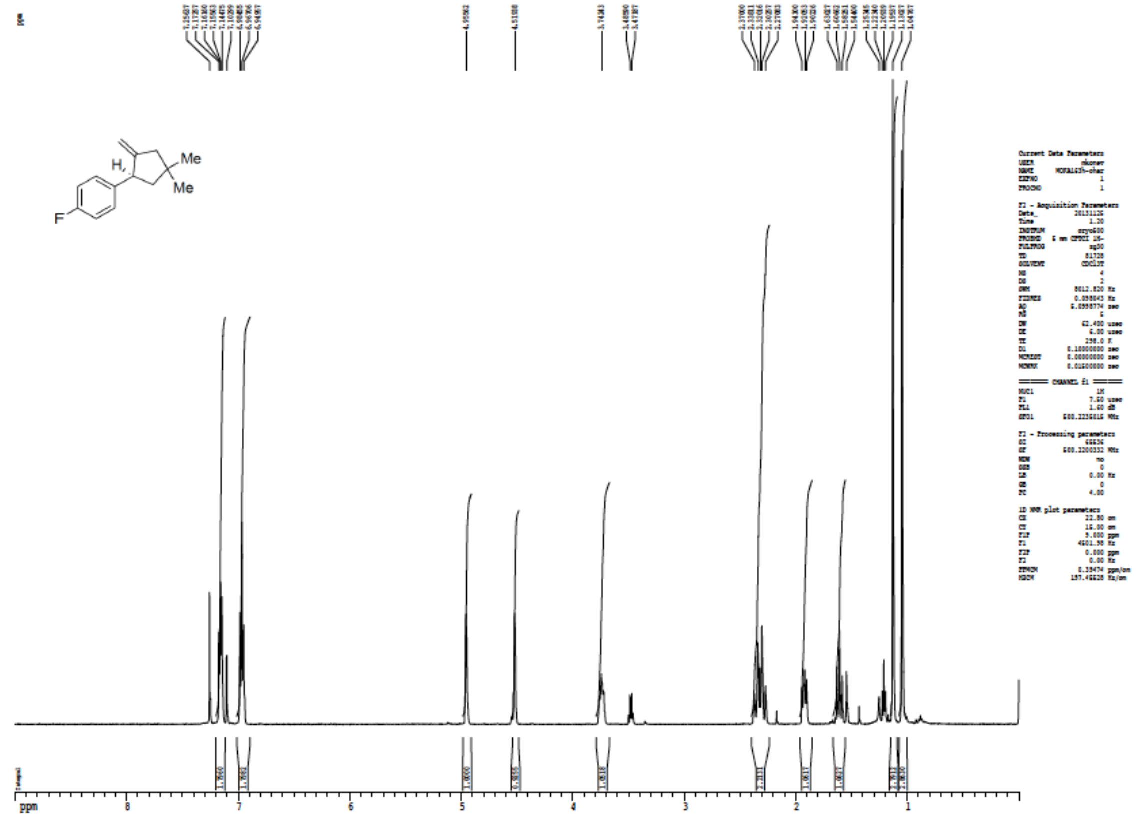
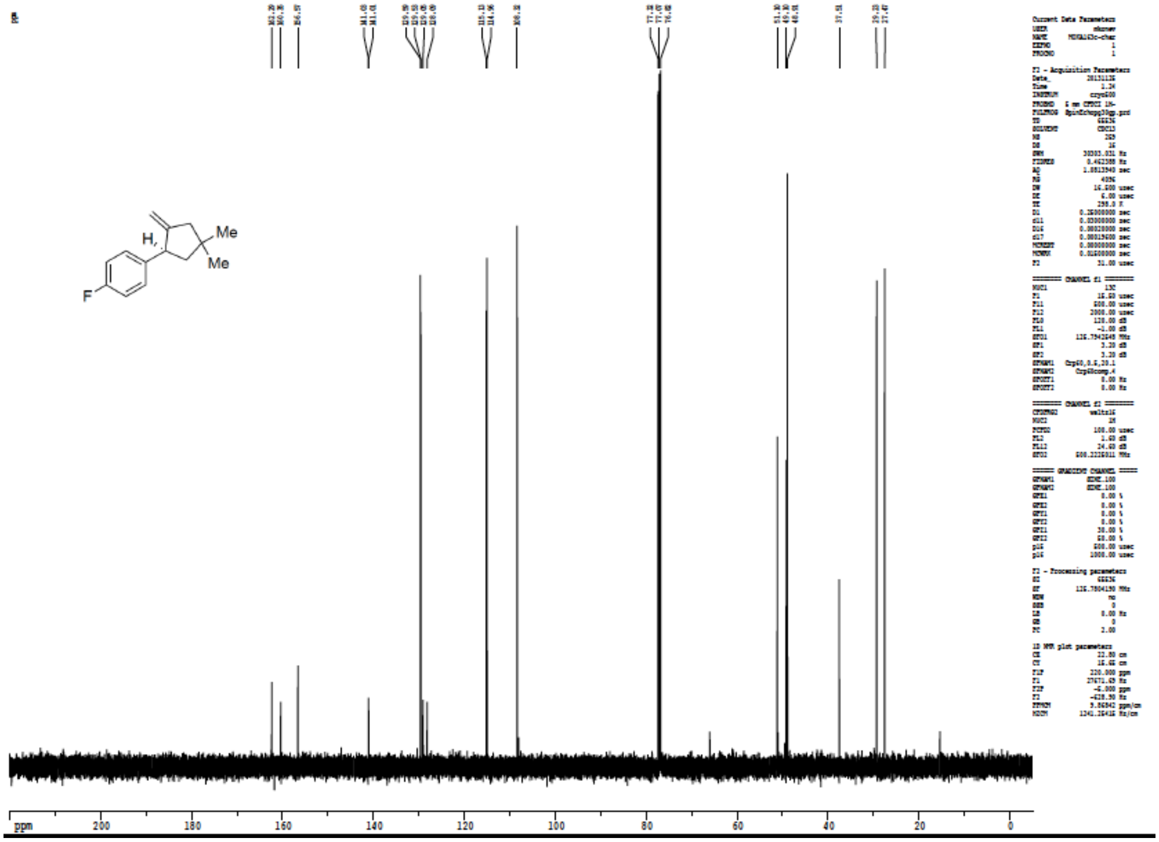
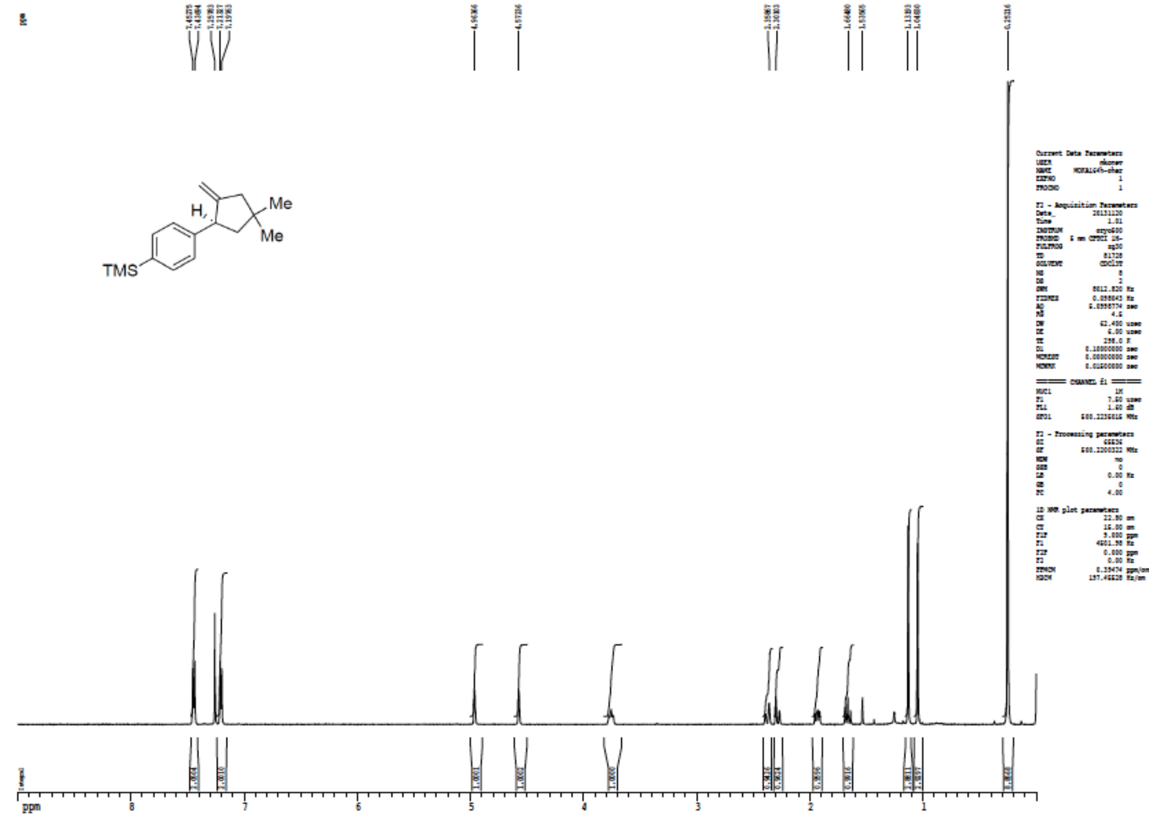


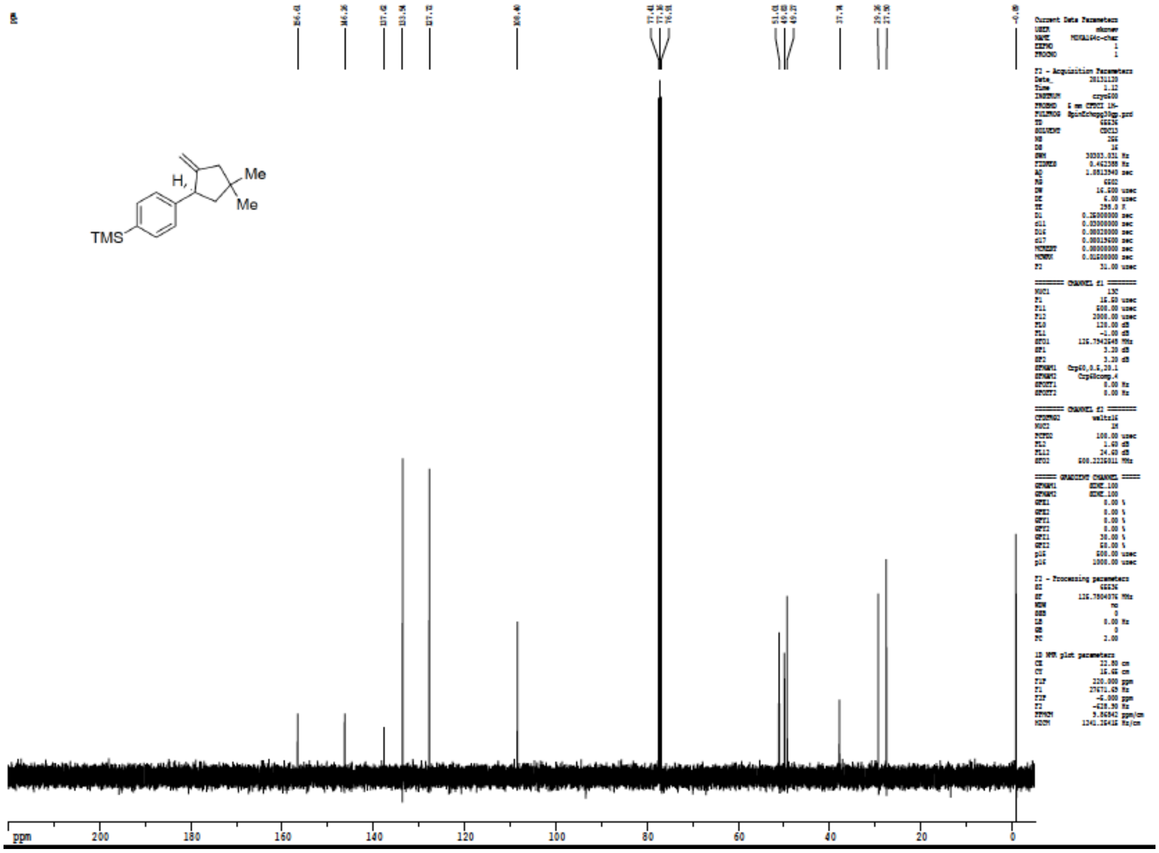
Z-restored spin-echo 13C spectrum with 1H decoupling



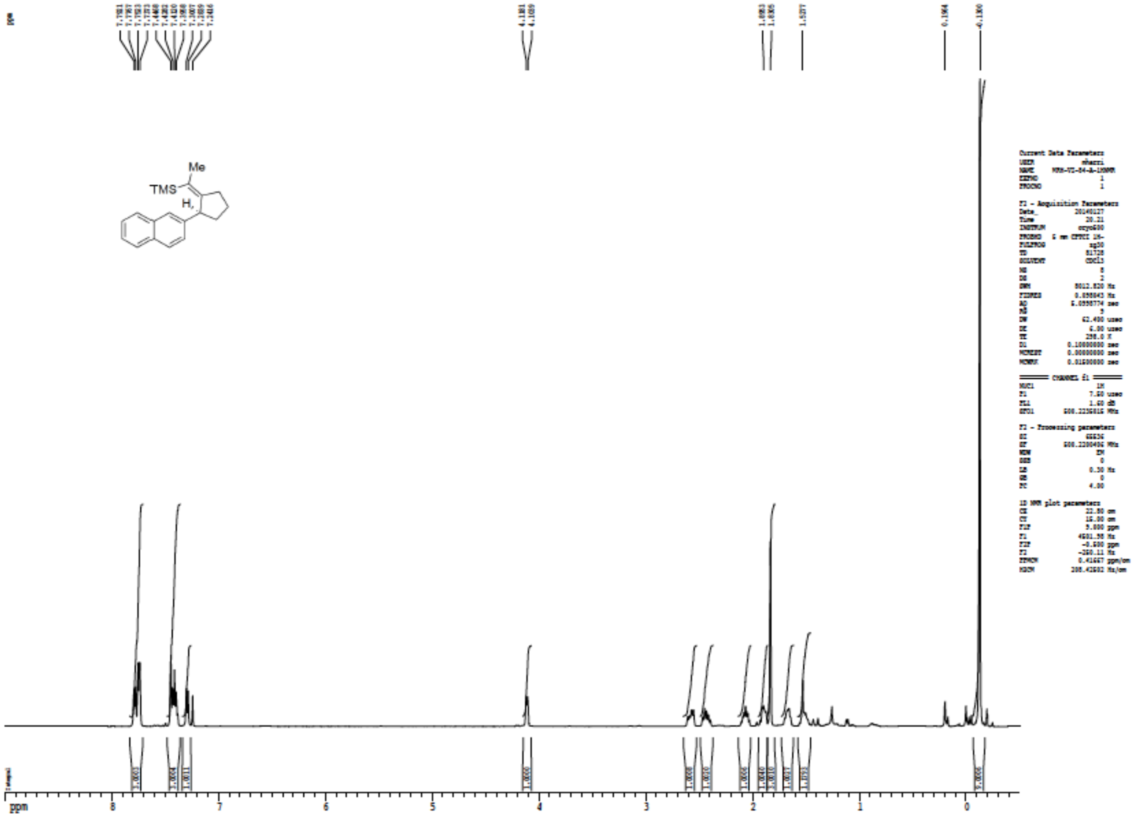
1H spectrum



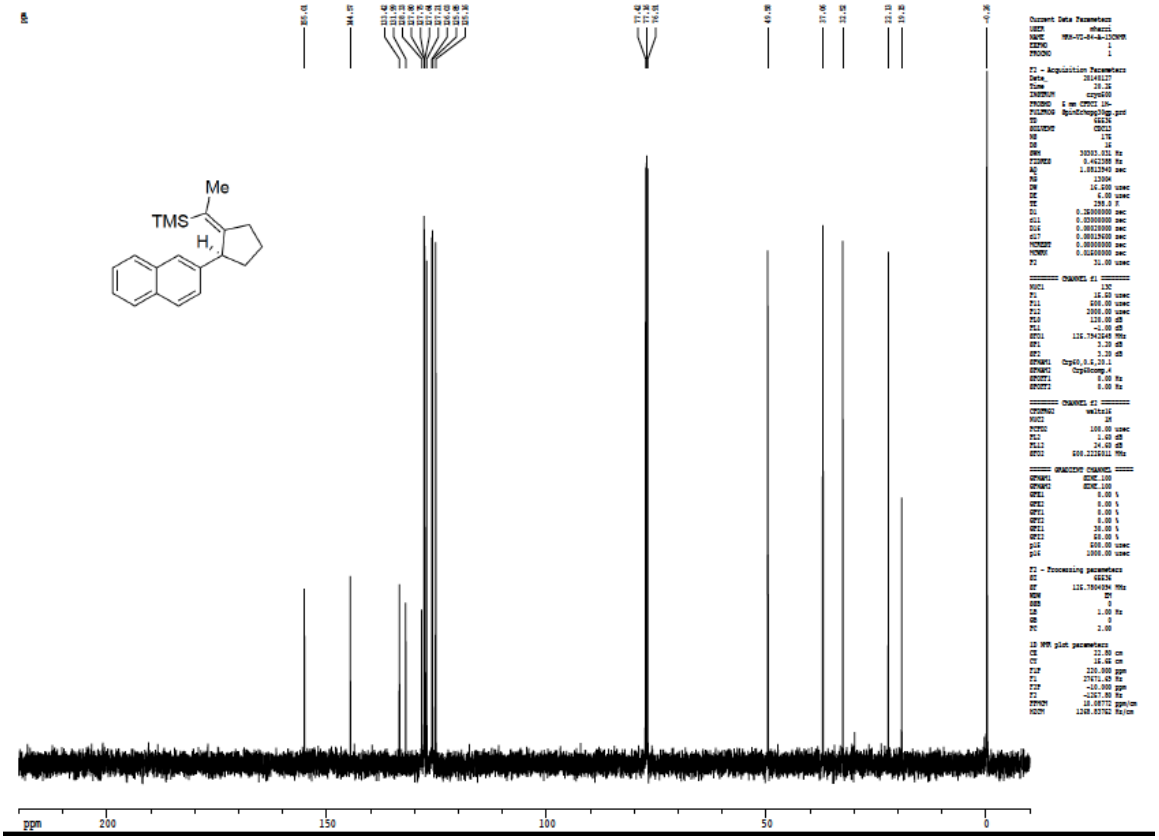
Z-restored spin-echo 13C spectrum with 1H decoupling

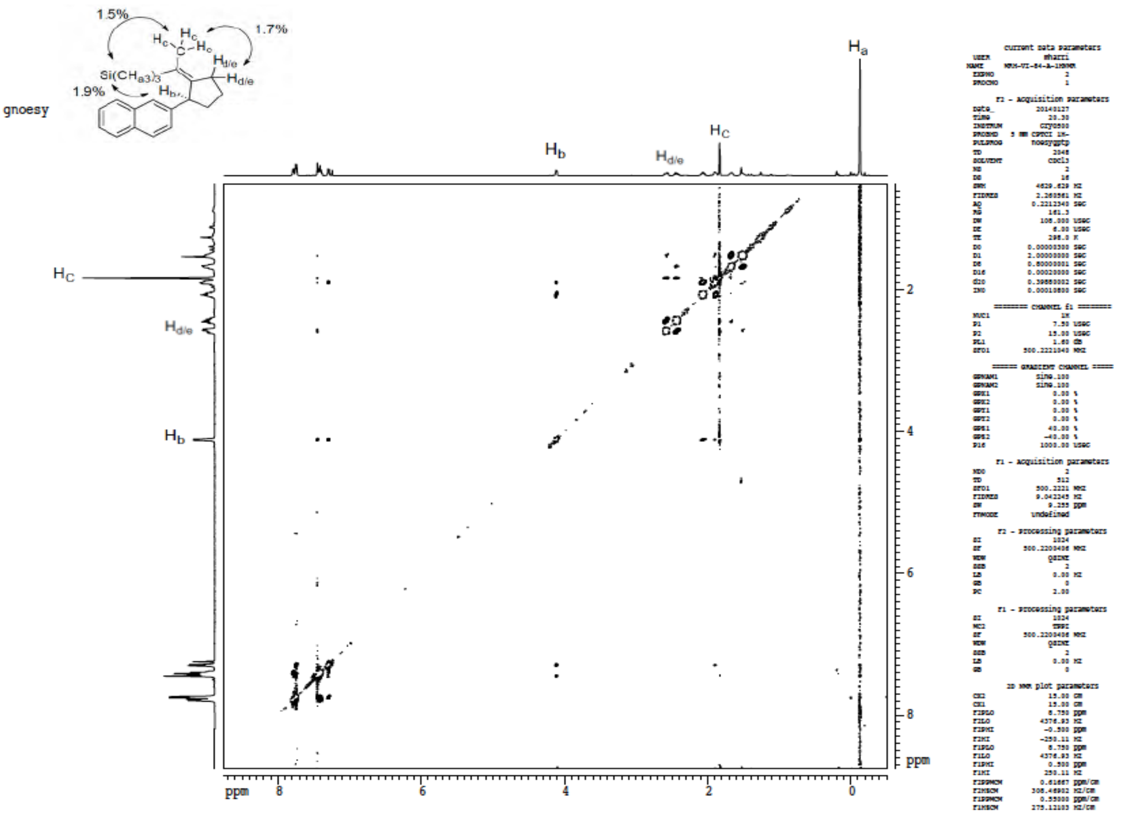


1H spectrum



Z-restored spin-echo 13C spectrum with 1H decoupling

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1.9%
Hc
Hc
Hc
Hd/e
Hd/e
Si(CHa3)3
Hb
Ha
Hb
Hd/e
Hc
Hc
Hd/e
Hb
ppm
8
6
4
2
0
2
4
6
8
ppm


gnoe
1.5%
1.7%
1.9%
Hc
Hc
Hc
Hd/e
Hd/e
Si(CHa3)3
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ppm
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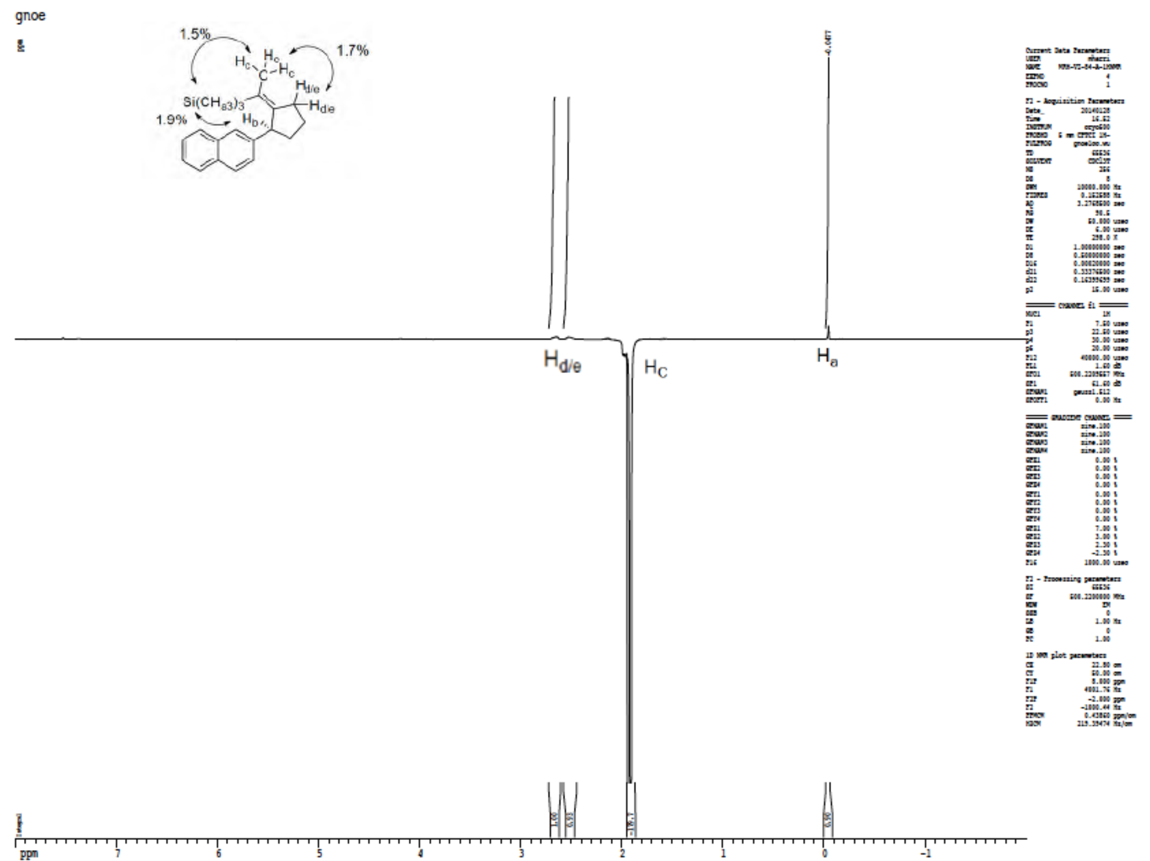
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1.5%
1.7%
1.9%
$H_c$
$H_c$
$H_c$
$H_{d/e}$
$H_{de}$
$Si(CH_{a3})_3$
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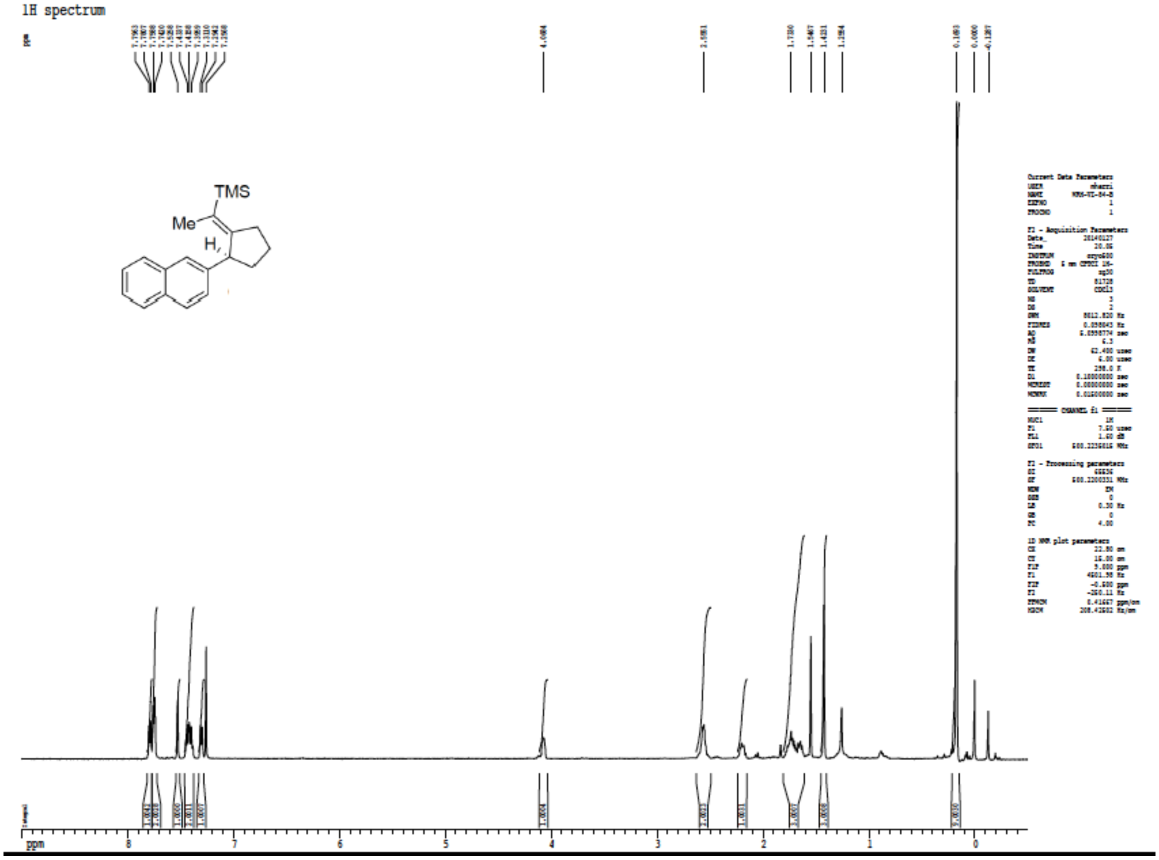
1H spectrum
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H
ppm
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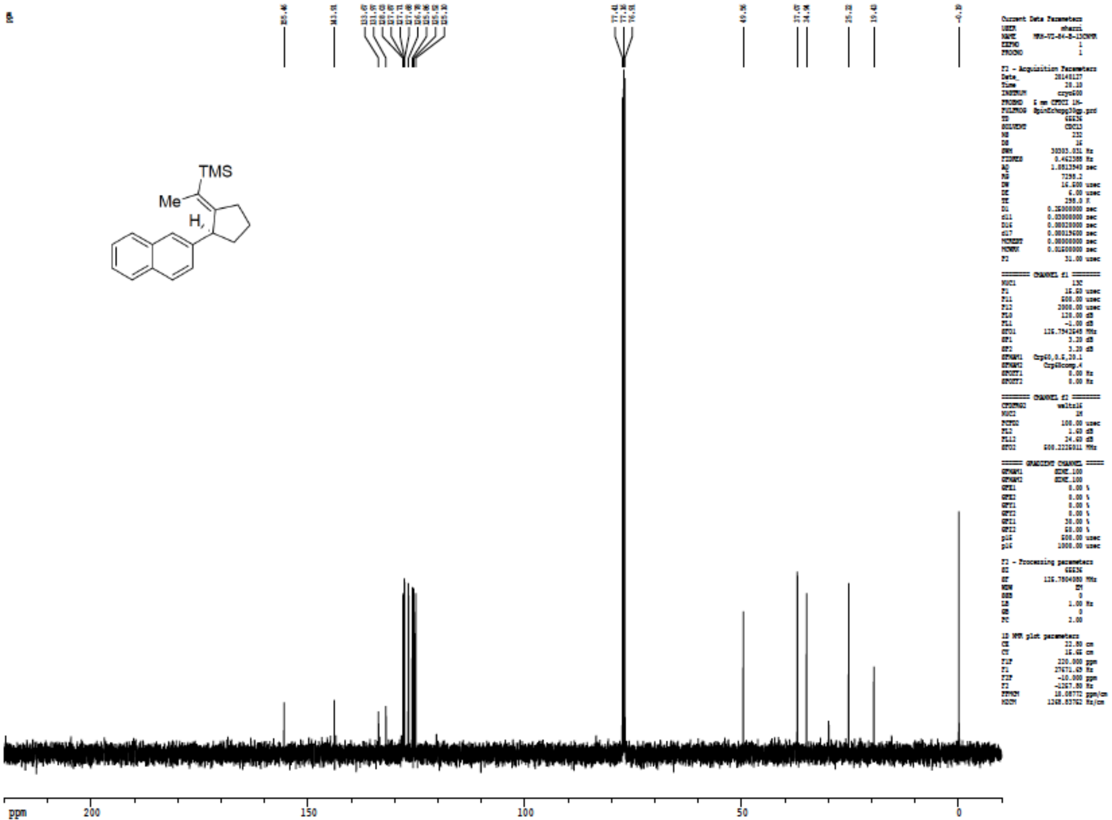
Z-restored spin-echo 13C spectrum with 1H decoupling



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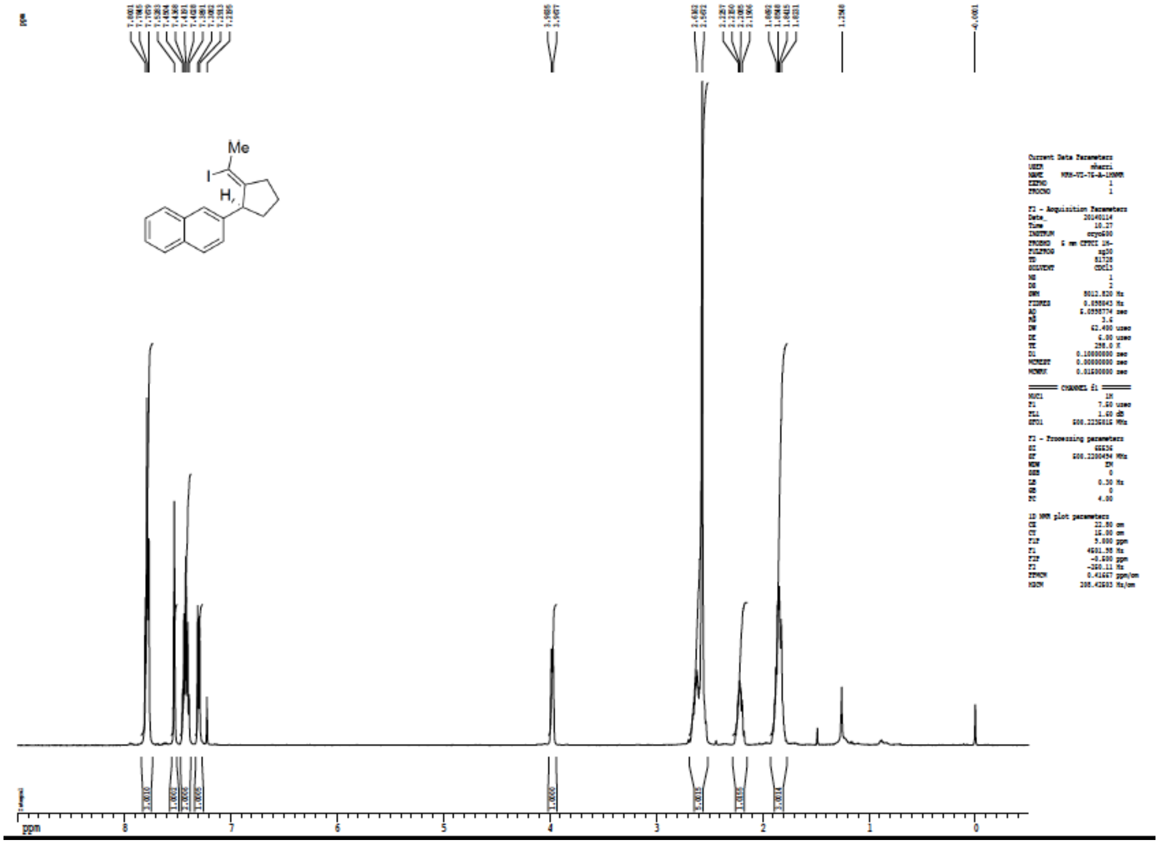
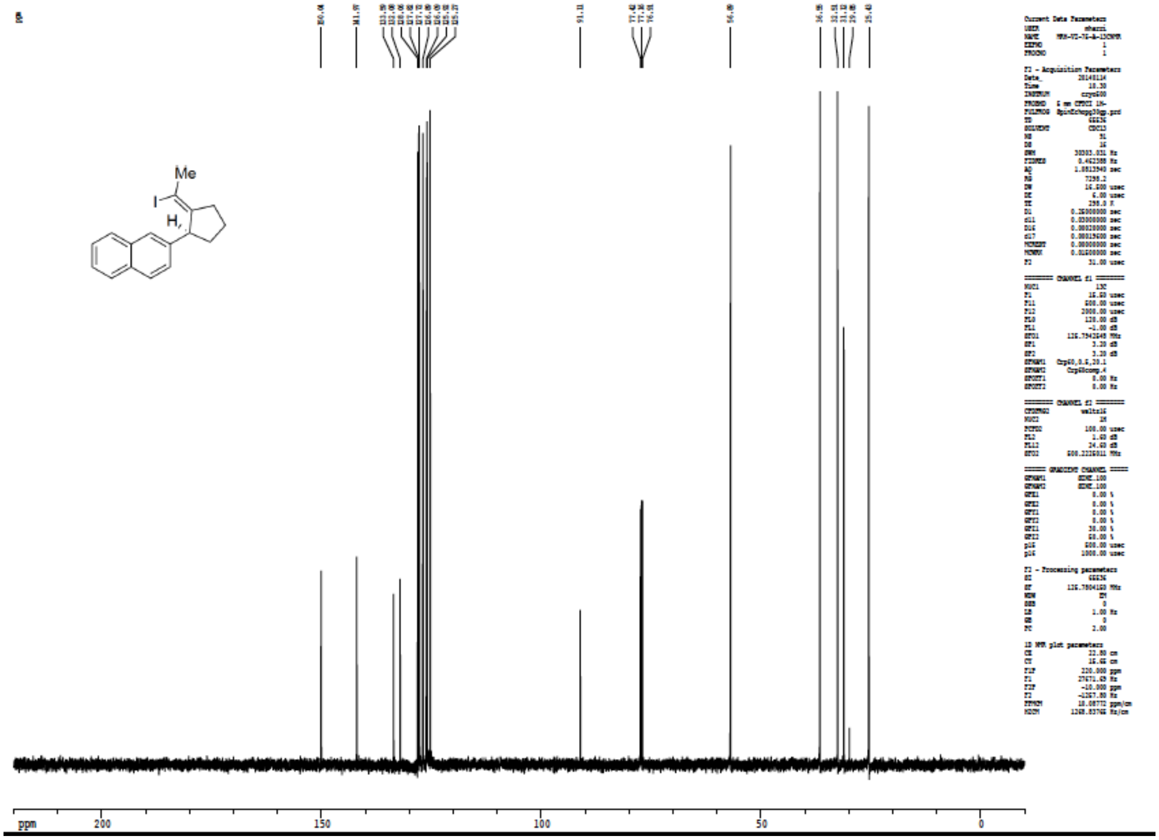
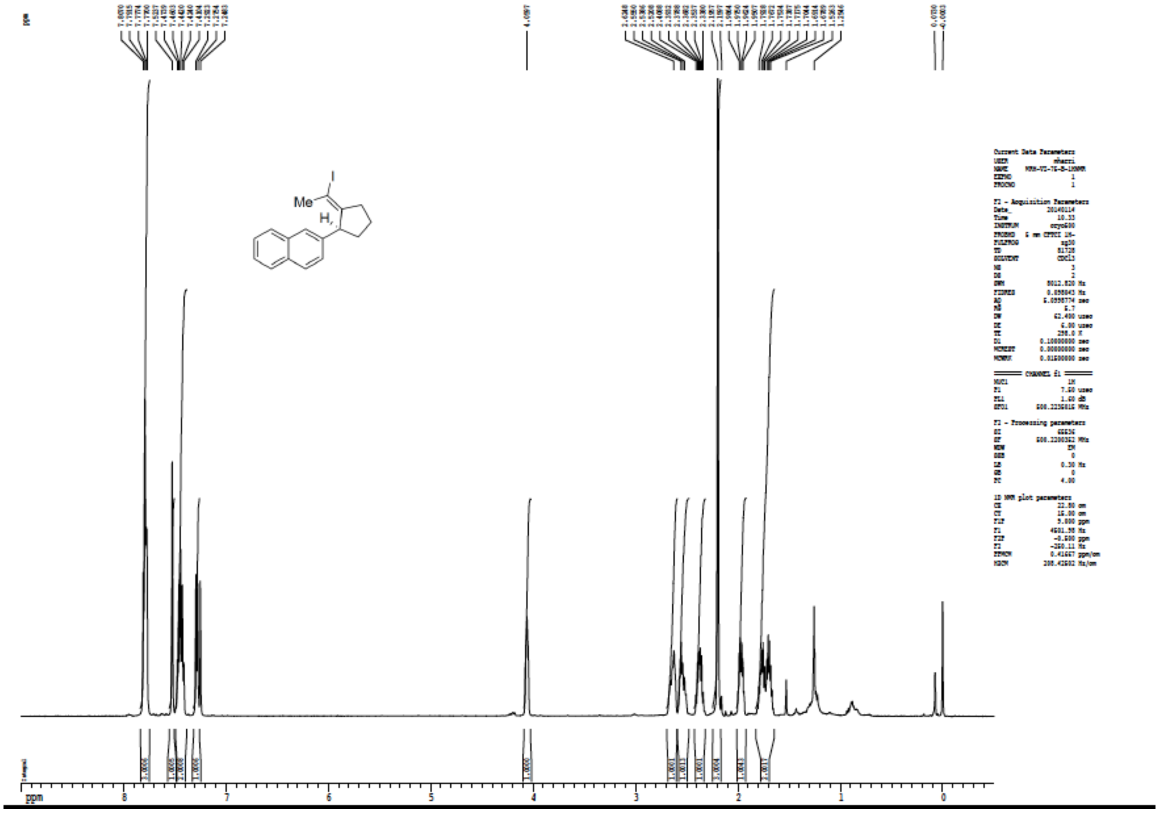


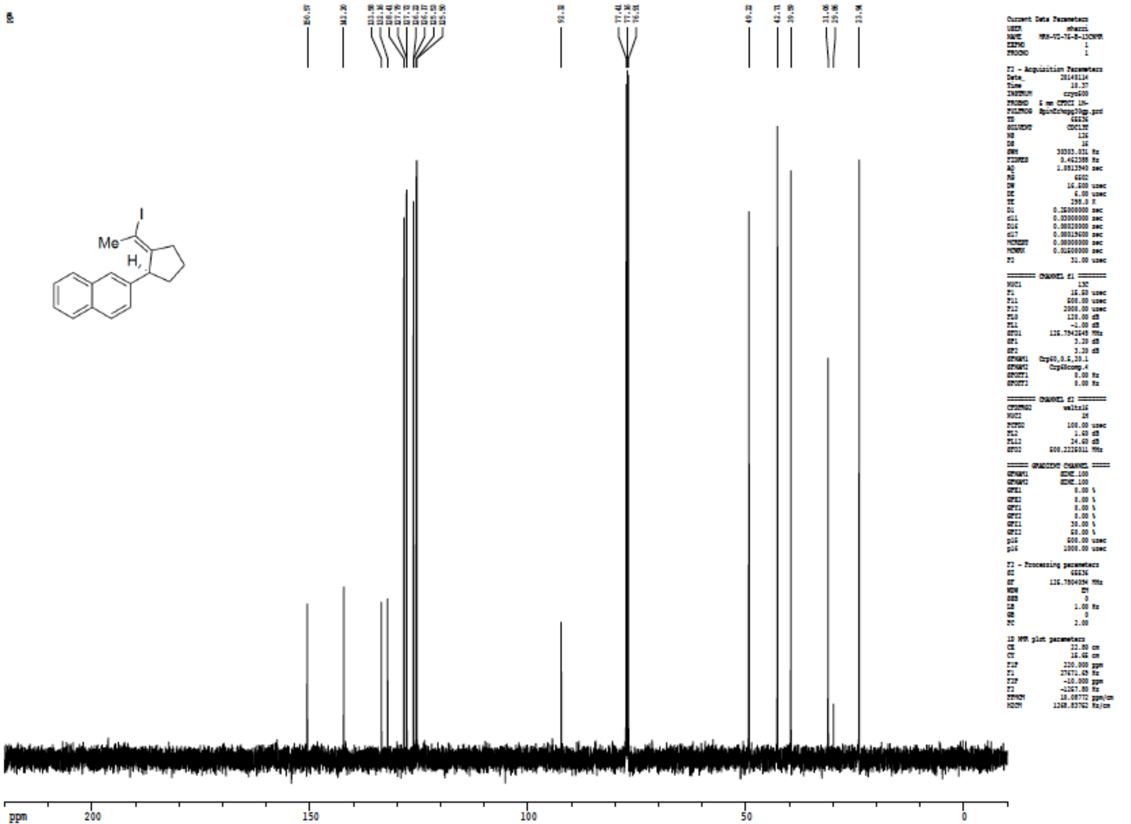
Z-restored spin-echo 13C spectrum with 1H decoupling



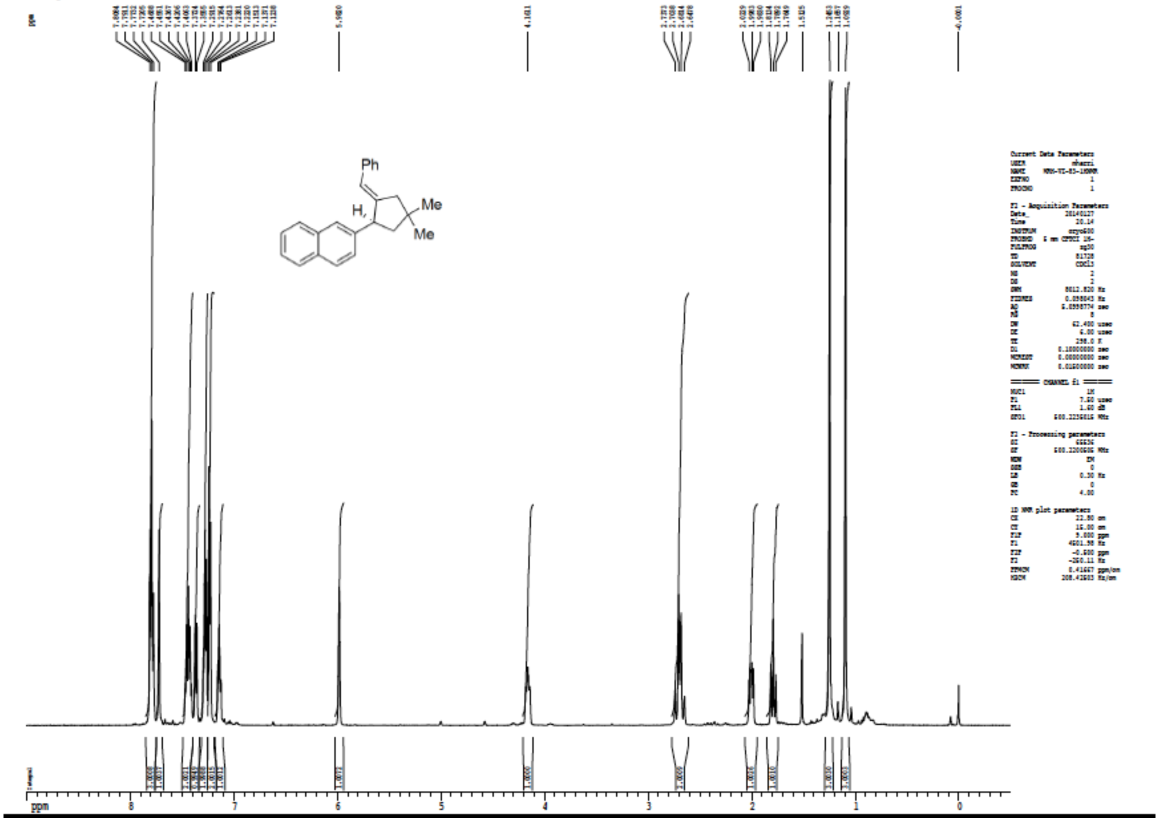
1H spectrum



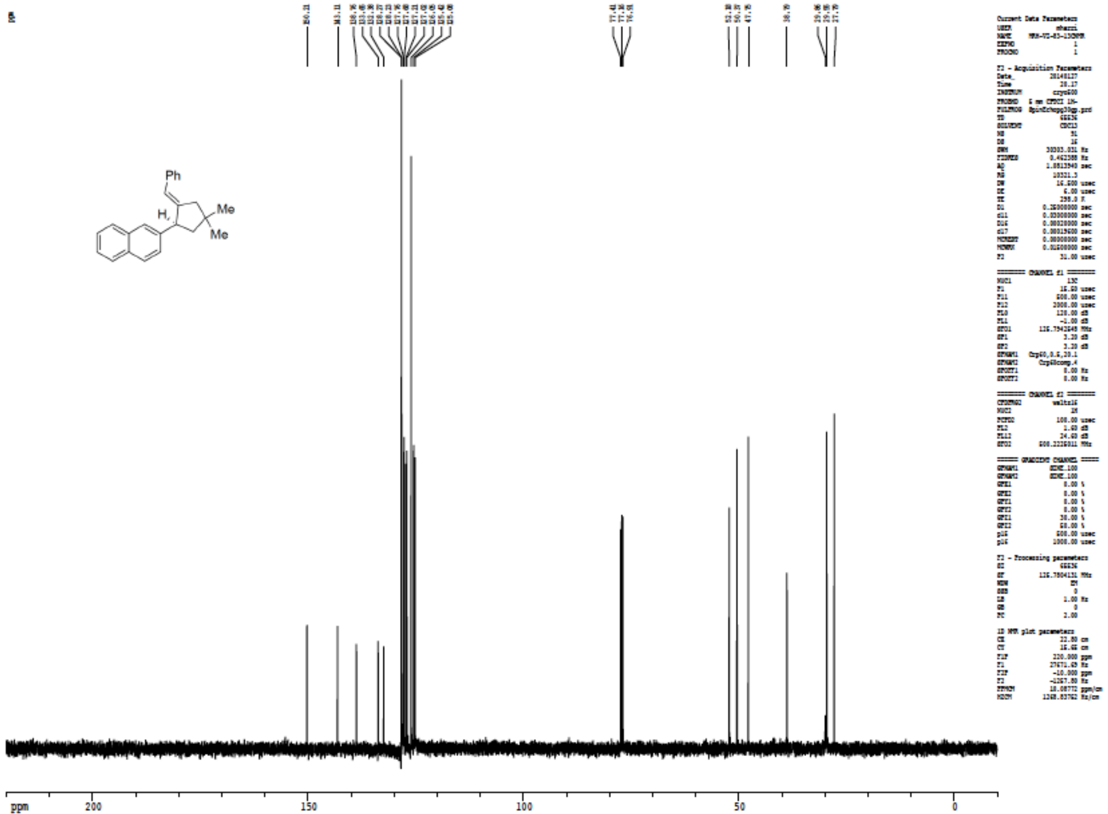
Z-restored spin-echo 13C spectrum with 1H decoupling

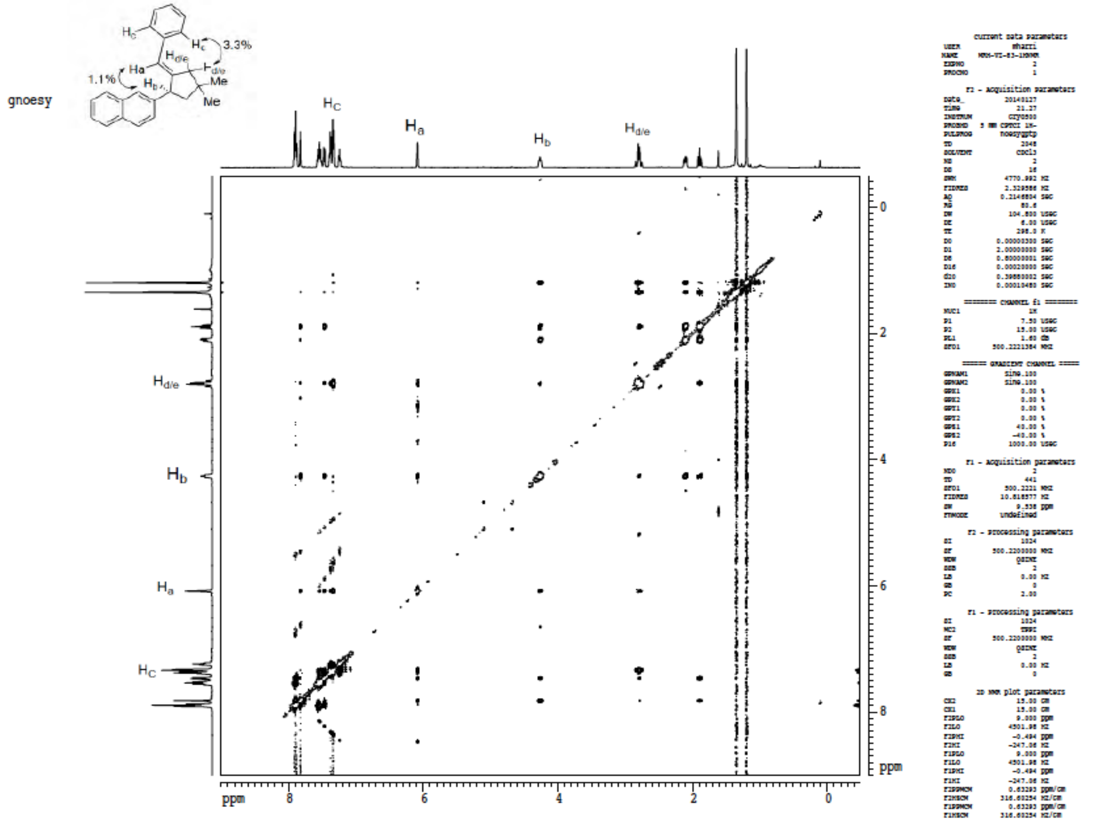


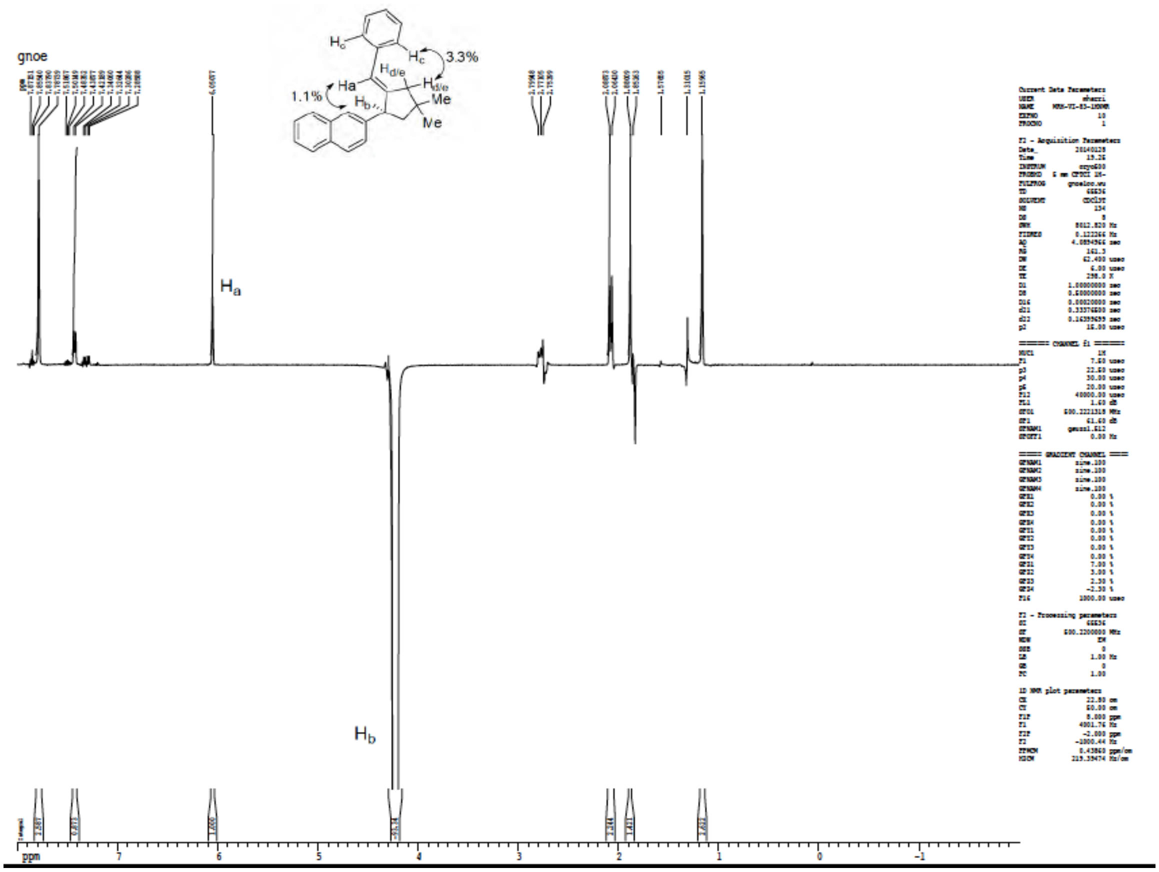
1H spectrum



Z-restored spin-echo 13C spectrum with 1H decoupling



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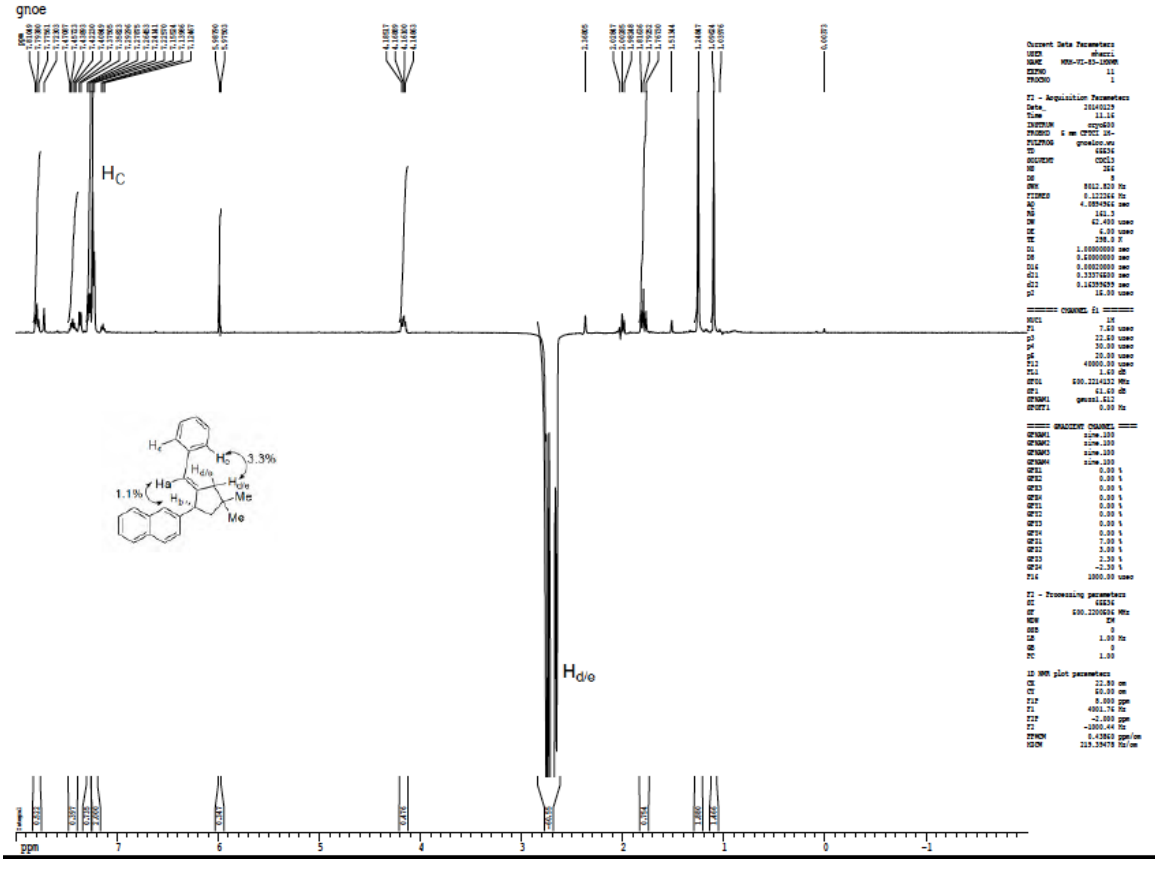
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Hd/e
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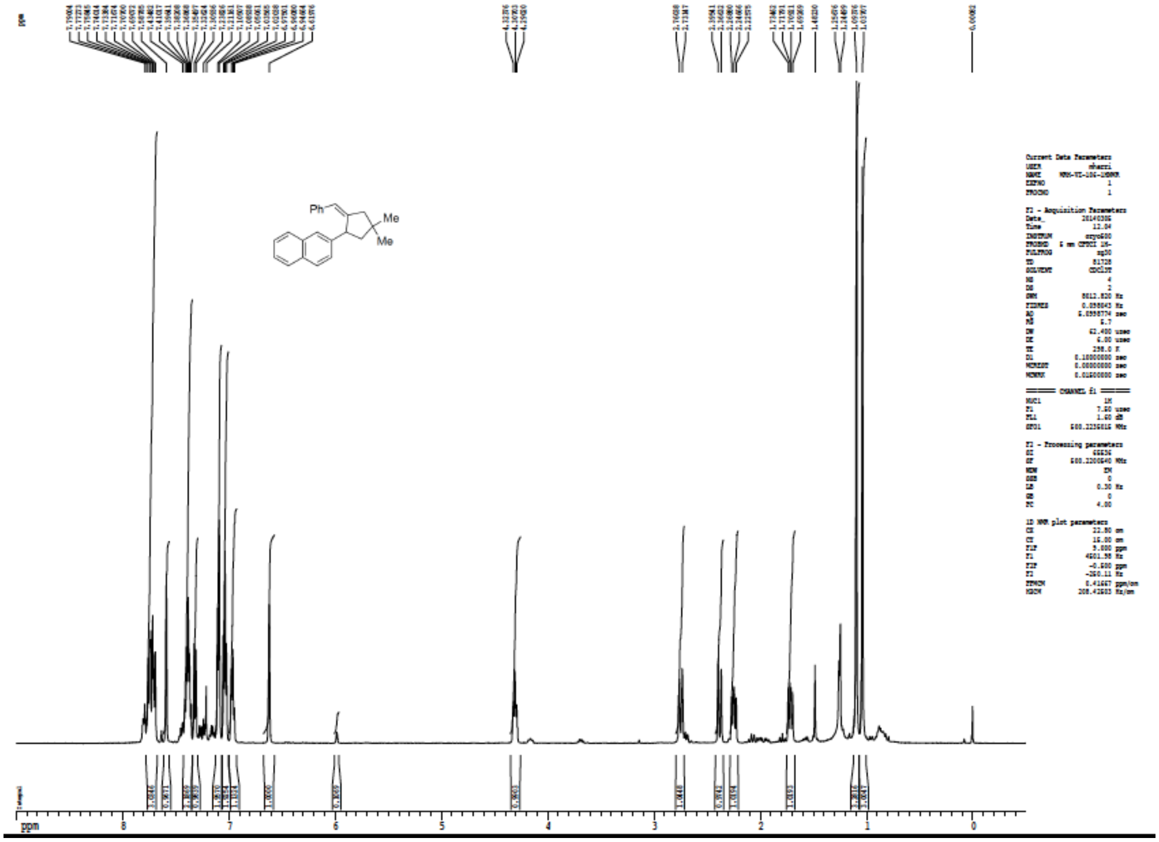
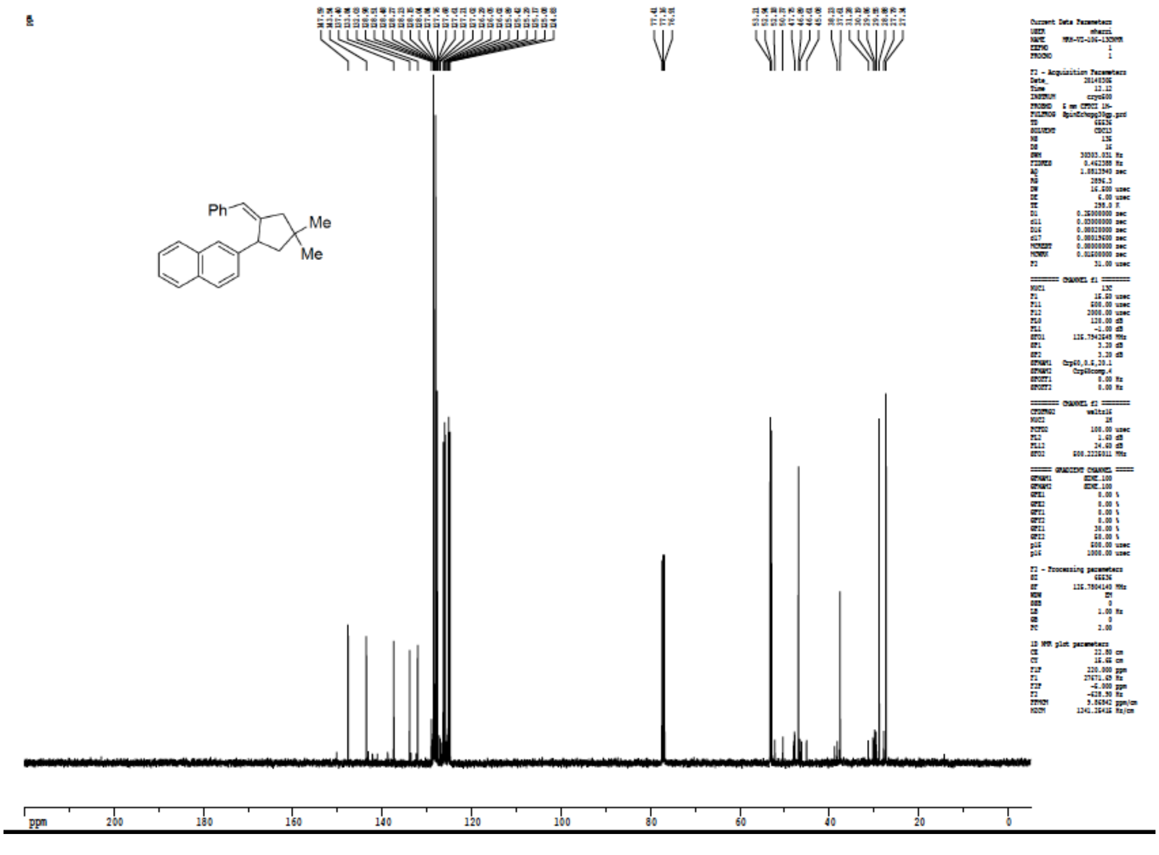
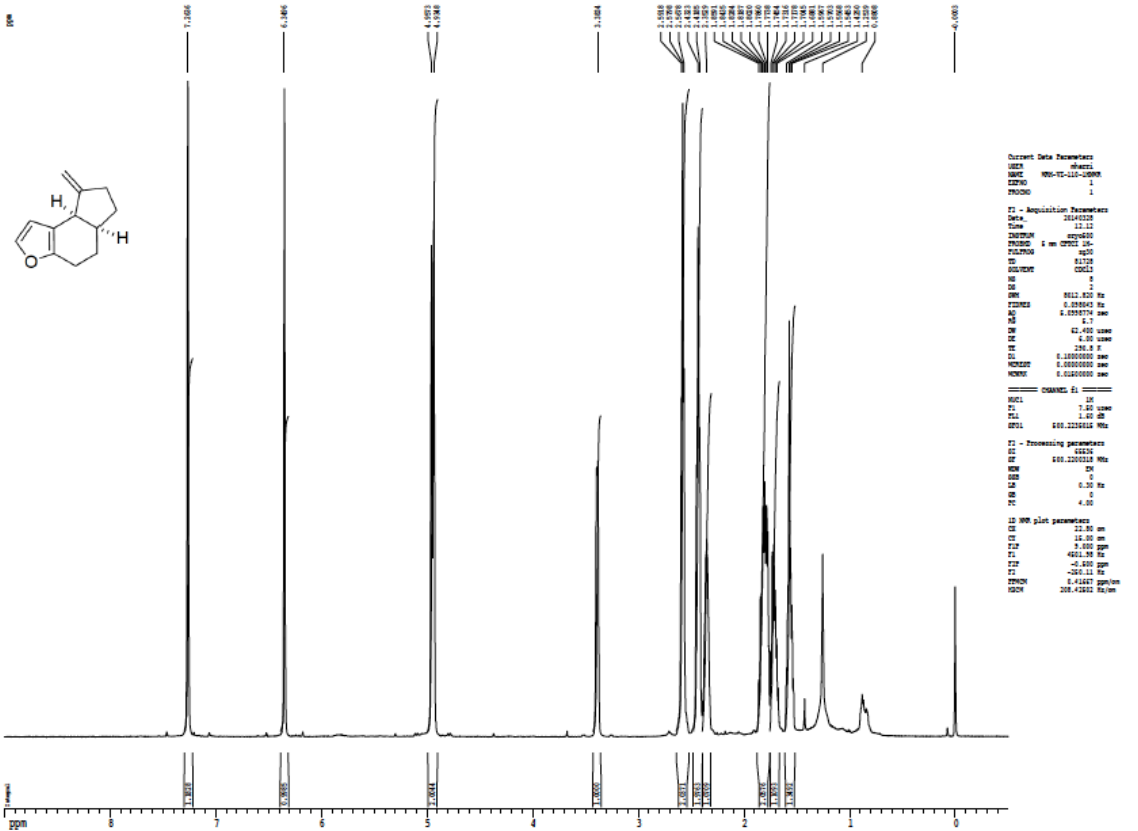
1H spectrum



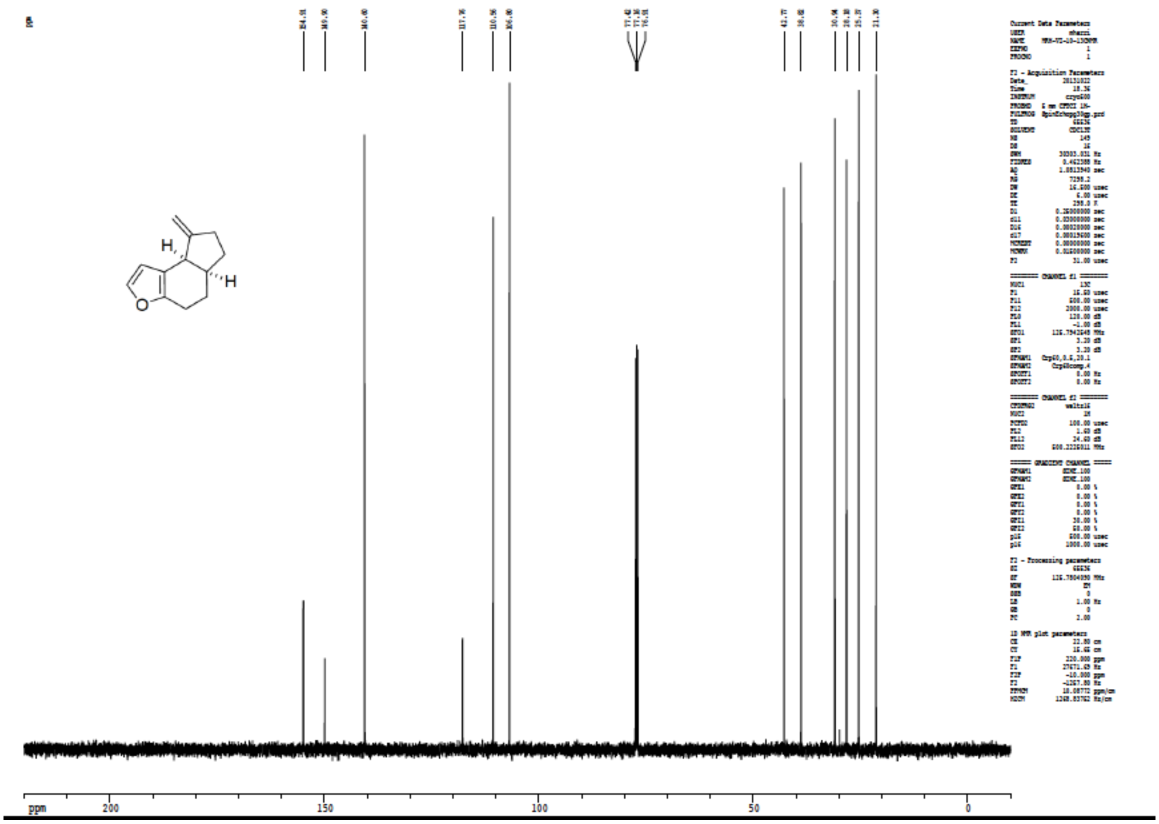
Z-restored spin-echo 13C spectrum with 1H decoupling

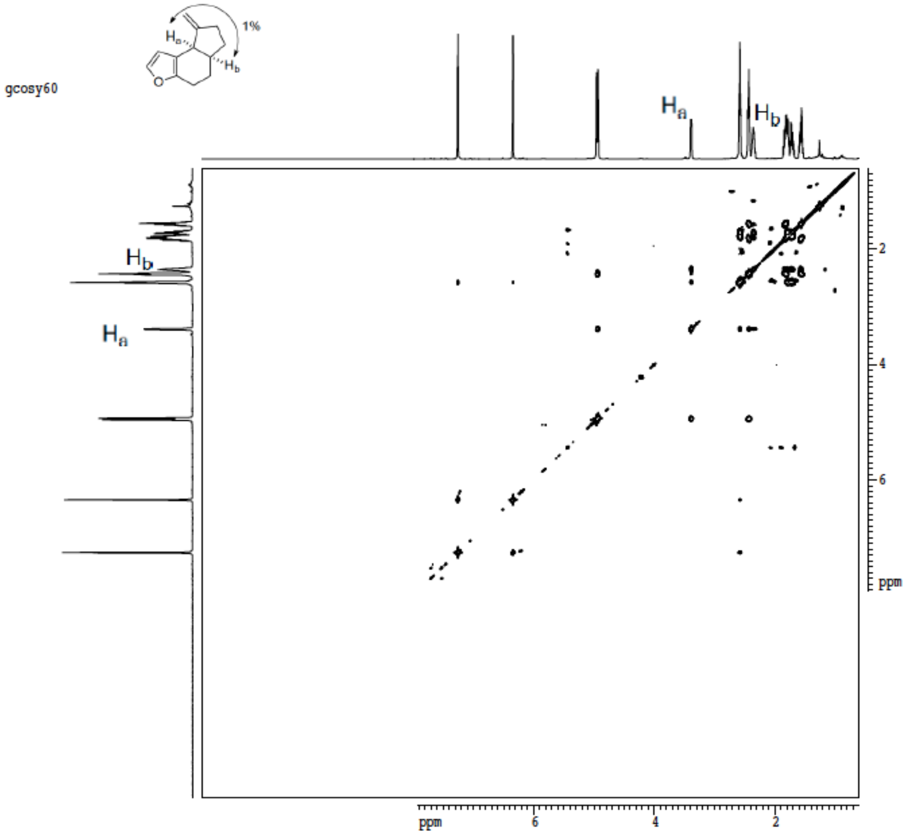


1H spectrum



Z-restored spin-echo 13C spectrum with 1H decoupling





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PROCNO                       1

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Time                     18.13
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TD                        2048
SOLVENT                 CDCl3T
NS                           2
DS                          16
SWH                   4496.403 Hz
FIDRES                2.195509 Hz
AQ                   0.2277876 sec
RG                         256
DW                     111.200 usec
DE                        6.00 usec
TE                       298.0 K
d0                  0.00000300 sec
D1                  1.00000000 sec
d13                 0.00000300 sec
D16                 0.00020000 sec
IN0                 0.00022240 sec

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NUC1                        1H
P1                        7.50 usec
PL1                       1.60 dB
SFO1               500.2217508 MHz

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GPNAM2                sine.100
GPX1                      0.00 %
GPX2                      0.00 %
GPY1                      0.00 %
GPY2                      0.00 %
GPZ1                     17.00 %
GPZ2                     17.00 %
P16                    1000.00 usec

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TD                         354
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GB                           0
PC                        4.00

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SI                        1024
MC2                         QF
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SSB                          0
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CX2                      15.00 cm
CX1                      15.00 cm
F2PLO                   11.500 ppm
F2LO                   5752.53 Hz
F2PHI                    0.600 ppm
F2HI                    300.13 Hz
F1PLO                   11.500 ppm
F1LO                   5752.53 Hz
F1PHI                    0.600 ppm
F1HI                    300.13 Hz
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F1PPMCM                0.72667 ppm/cm
F1HZCM               363.49323 Hz/cm
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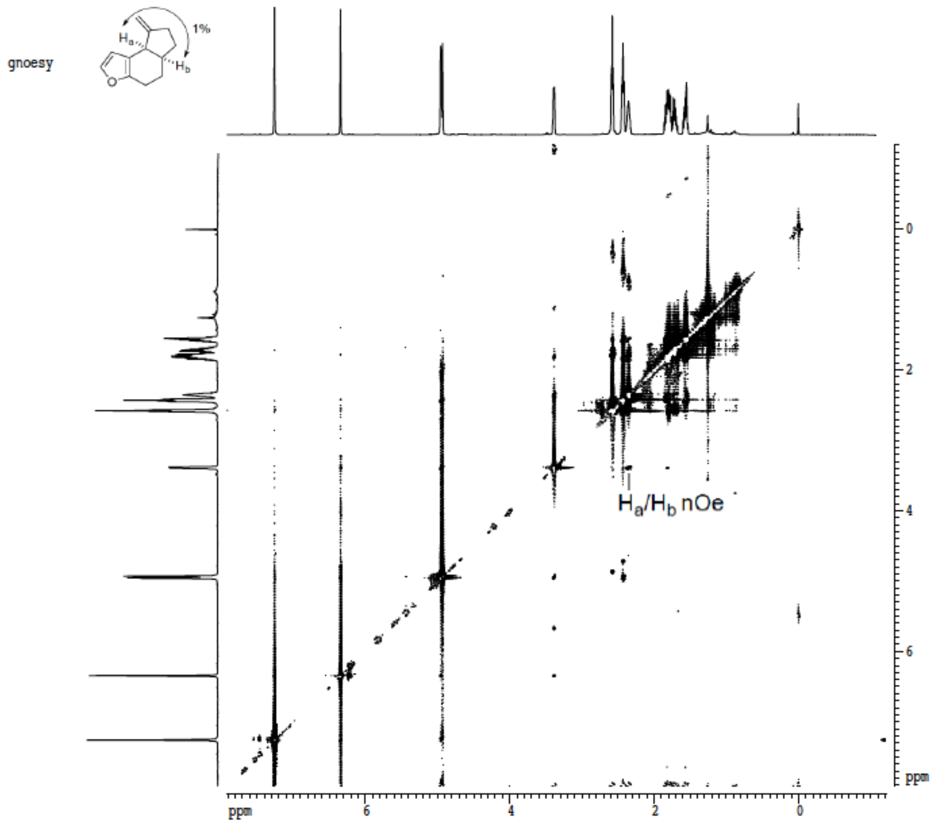

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TD                        2048
SOLVENT                 CDCl3T
NS                           2
DS                          16
SWH                   4562.044 HZ
FIDRES                2.227561 HZ
AQ                   0.2245108 SEC
RG                         114
DW                     109.600 USEC
DE                        6.00 USEC
TE                       298.0 K
D0                  0.00000300 SEC
D1                  2.00000000 SEC
D8                  0.80000001 SEC
D16                 0.00020000 SEC
d20                 0.39880002 SEC
IN0                 0.00010960 SEC

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NUC1                        1H
P1                        7.50 USEC
P2                       15.00 USEC
PL1                       1.60 dB
SFO1               500.2217081 MHZ

      ===== GRADIENT CHANNEL =====
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GPNAM2                sine.100
GPX1                      0.00 %
GPX2                      0.00 %
GPY1                      0.00 %
GPY2                      0.00 %
GPZ1                     40.00 %
GPZ2                    -40.00 %
P16                    1000.00 USEC

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TD                         432
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FnMODE               undefined

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SI                        1024
SF                 500.2200341 MHZ
WDW                      QSINE
SSB                          2
LB                        0.00 HZ
GB                           0
PC                        4.00

         F1 - Processing parameters
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MC2                       TPPI
SF                 500.2200341 MHZ
WDW                      QSINE
SSB                          2
LB                        0.00 HZ
GB                           0

           2D NMR plot parameters
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CX1                      15.00 CM
F2PLO                    7.909 ppm
F2LO                   3956.09 HZ
F2PHI                   -1.211 ppm
F2HI                   -605.85 HZ
F1PLO                    7.909 ppm
F1LO                   3956.09 HZ
F1PHI                   -1.211 ppm
F1HI                   -605.85 HZ
F2PPMCM                0.60800 ppm/CM
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F1PPMCM                0.60800 ppm/CM
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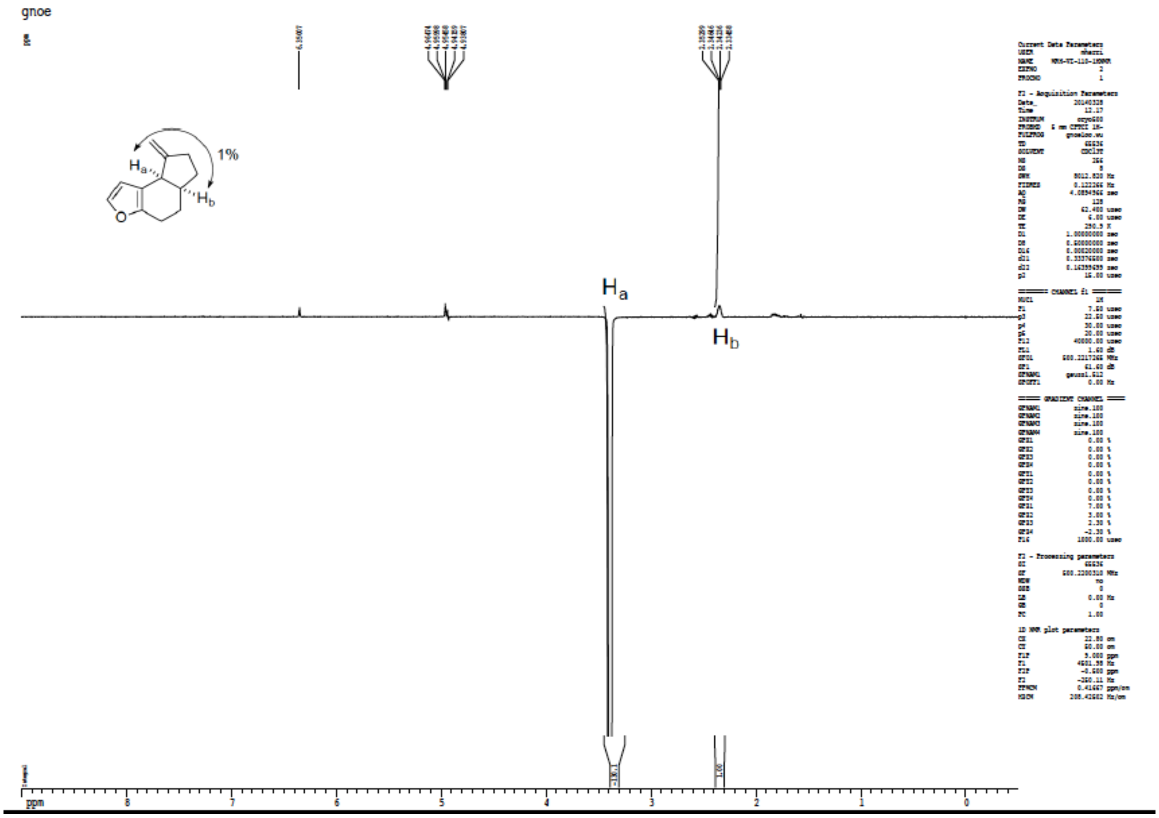
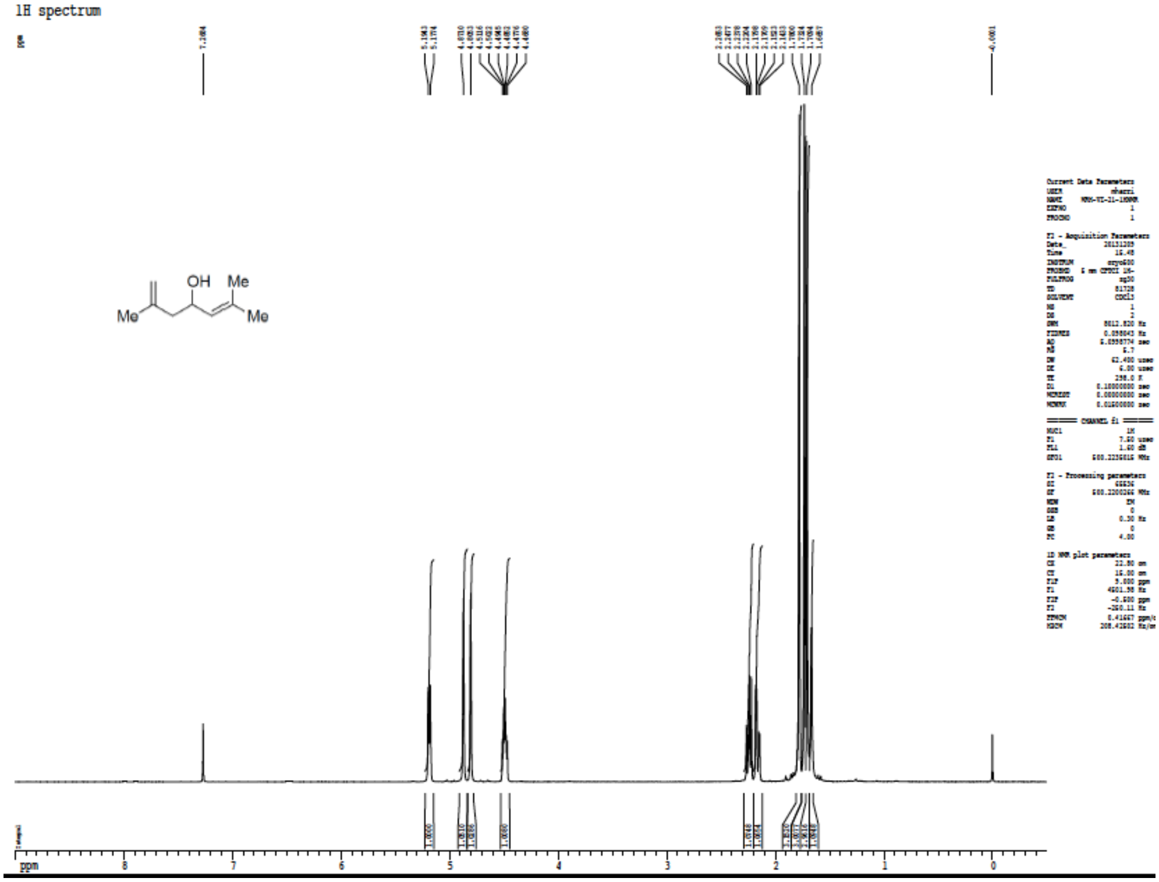
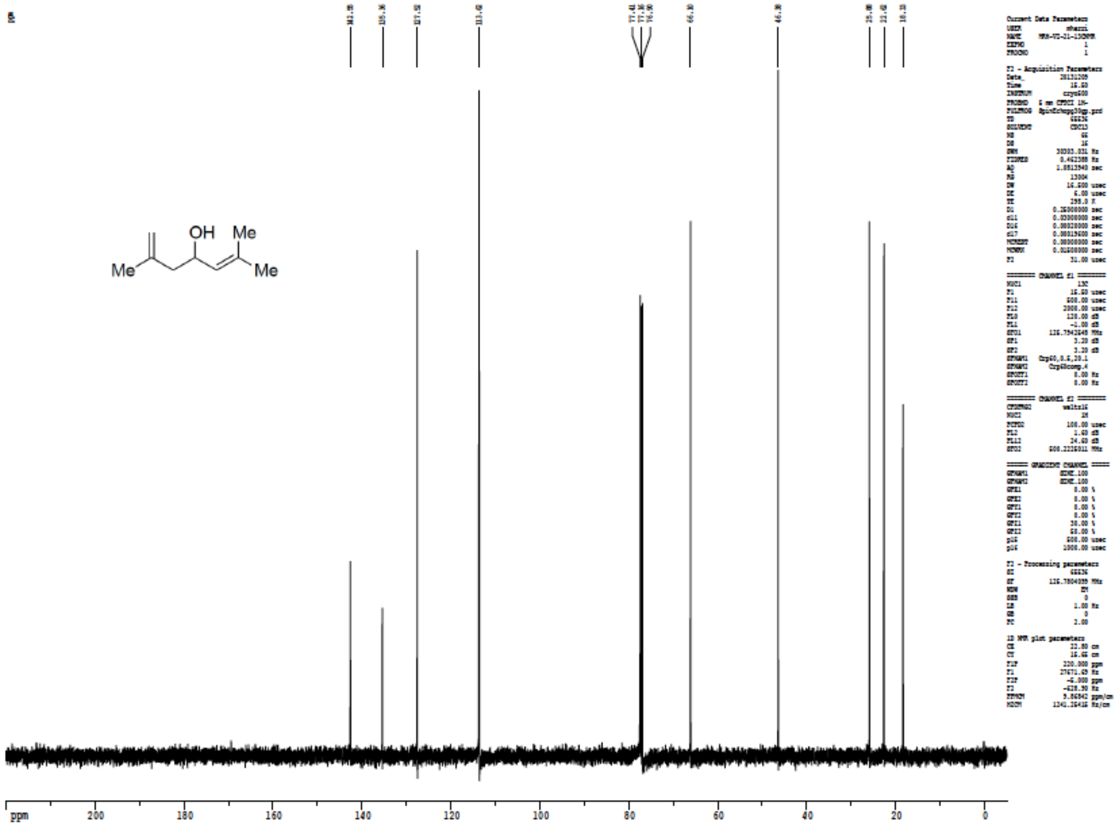
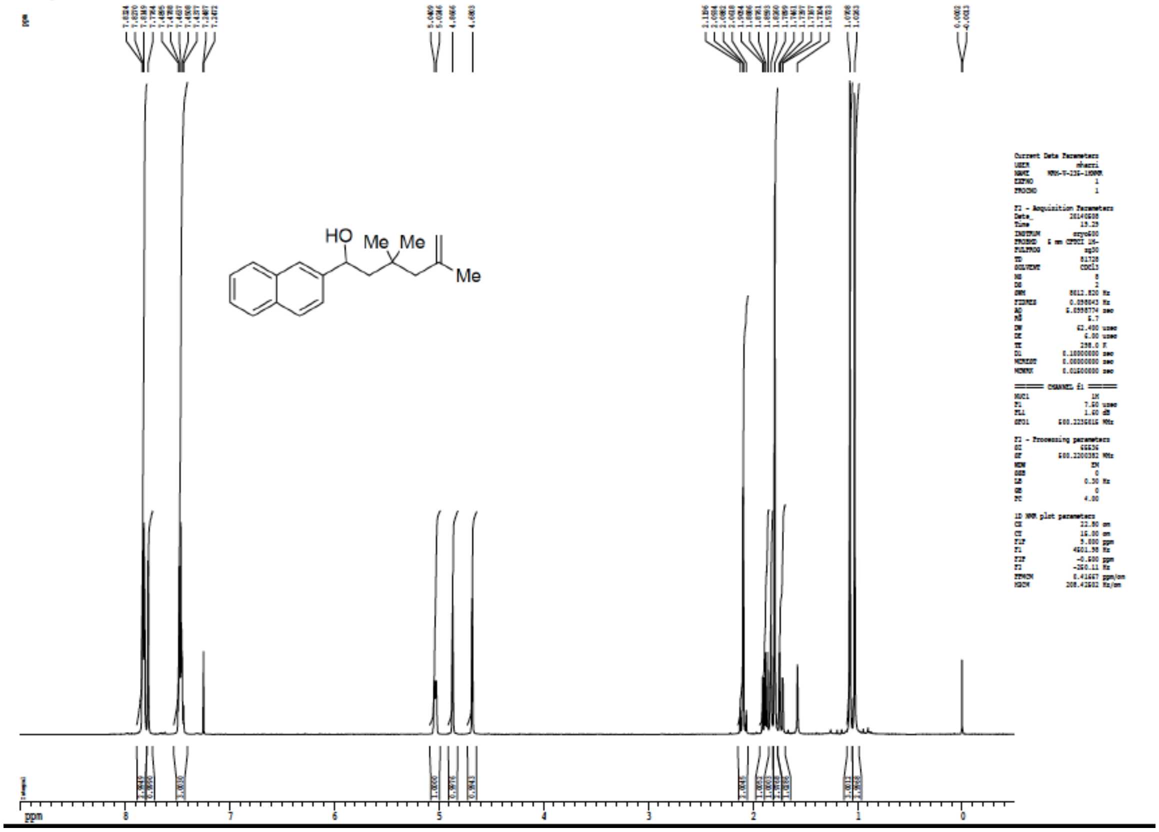
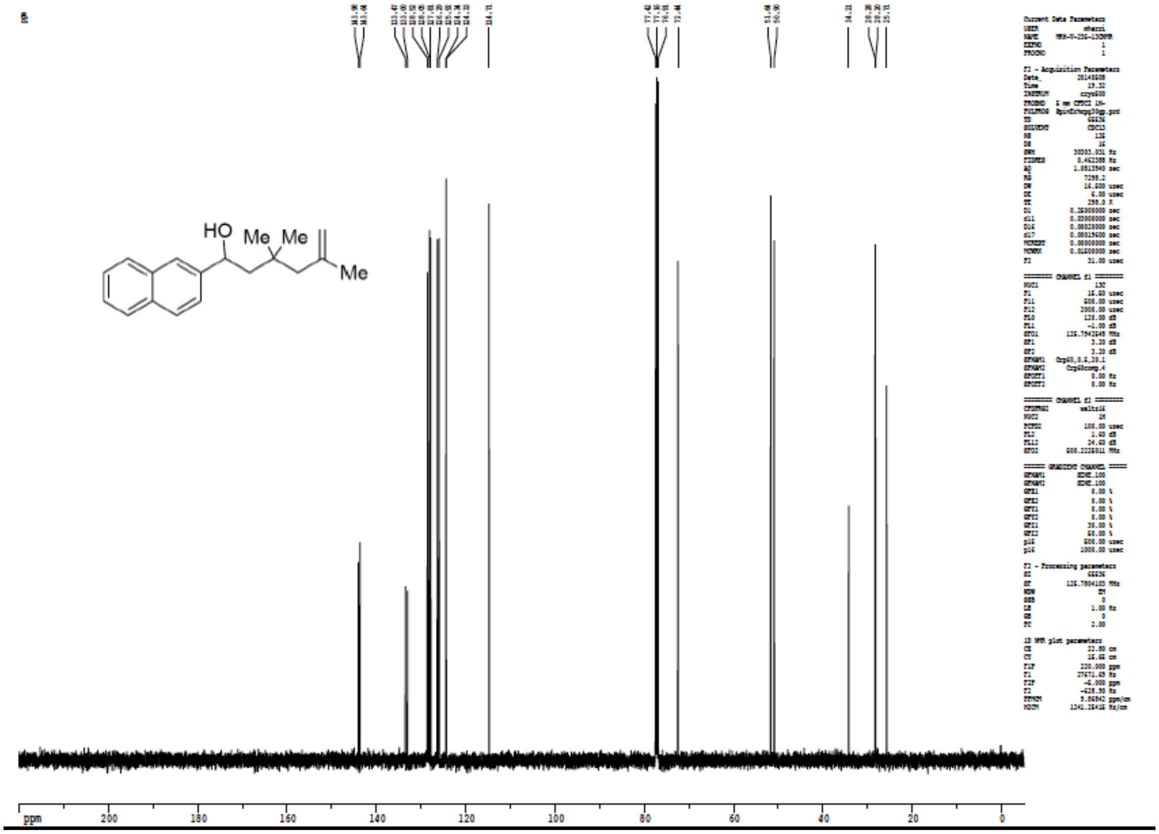

gnoe
1%
Ha
Hb
Ha
Hb
ppm
8
7
6
5
4
3
2
1
0


1H spectrum
OH
Me
Me
Me
ppm
8
7
6
5
4
3
2
1
0

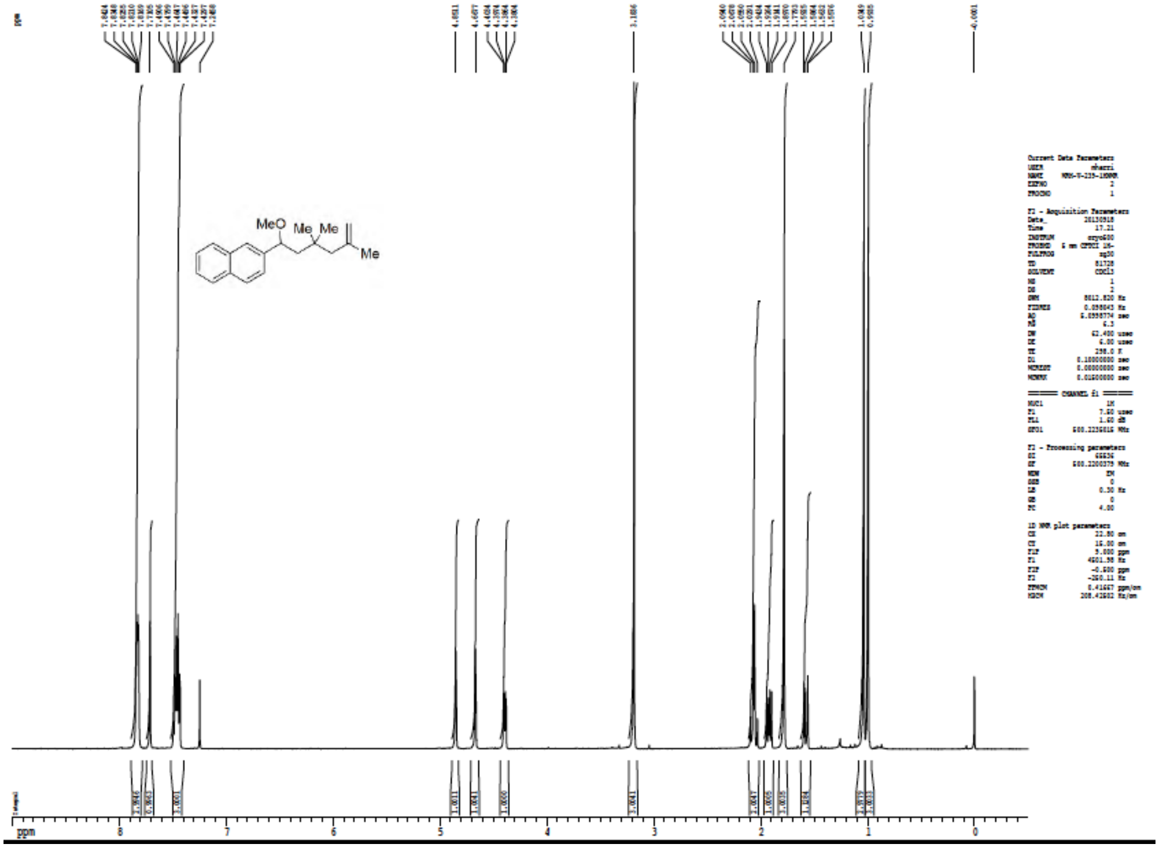

Z-restored spin-echo 13C spectrum with 1H decoupling


1H spectrum

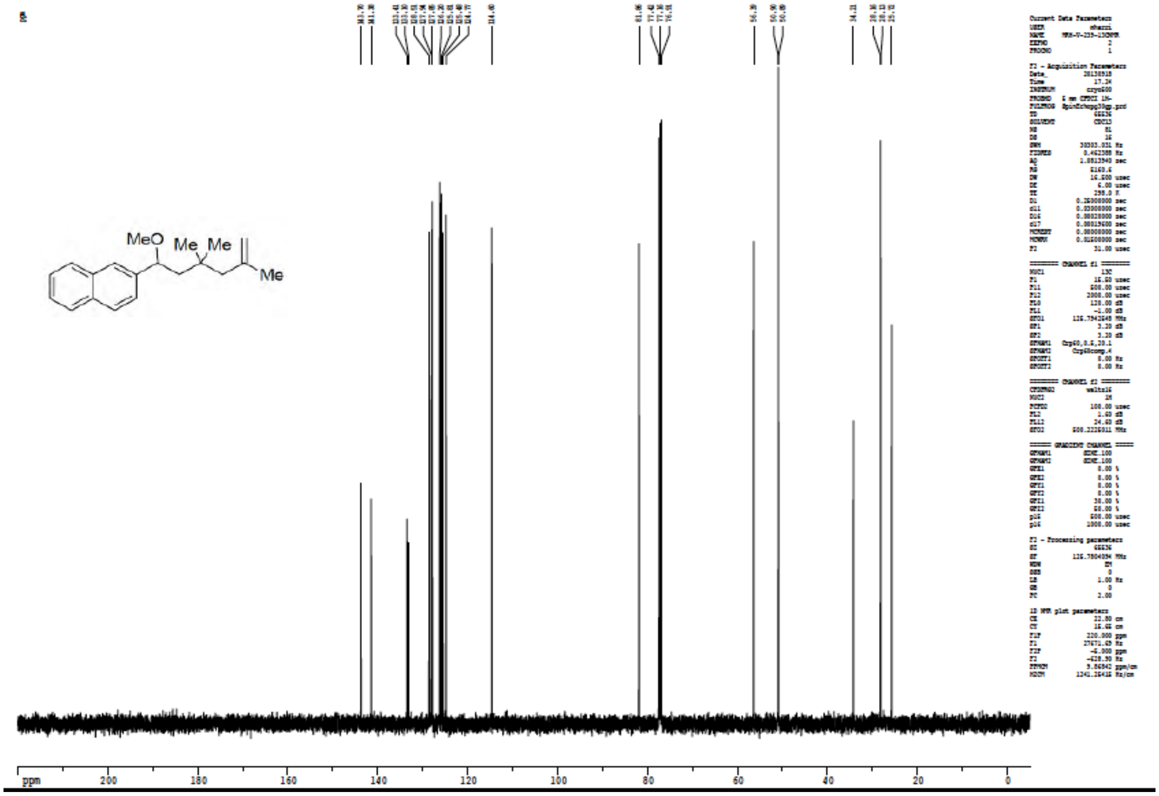
Z-restored spin-echo 13C spectrum with 1H decoupling



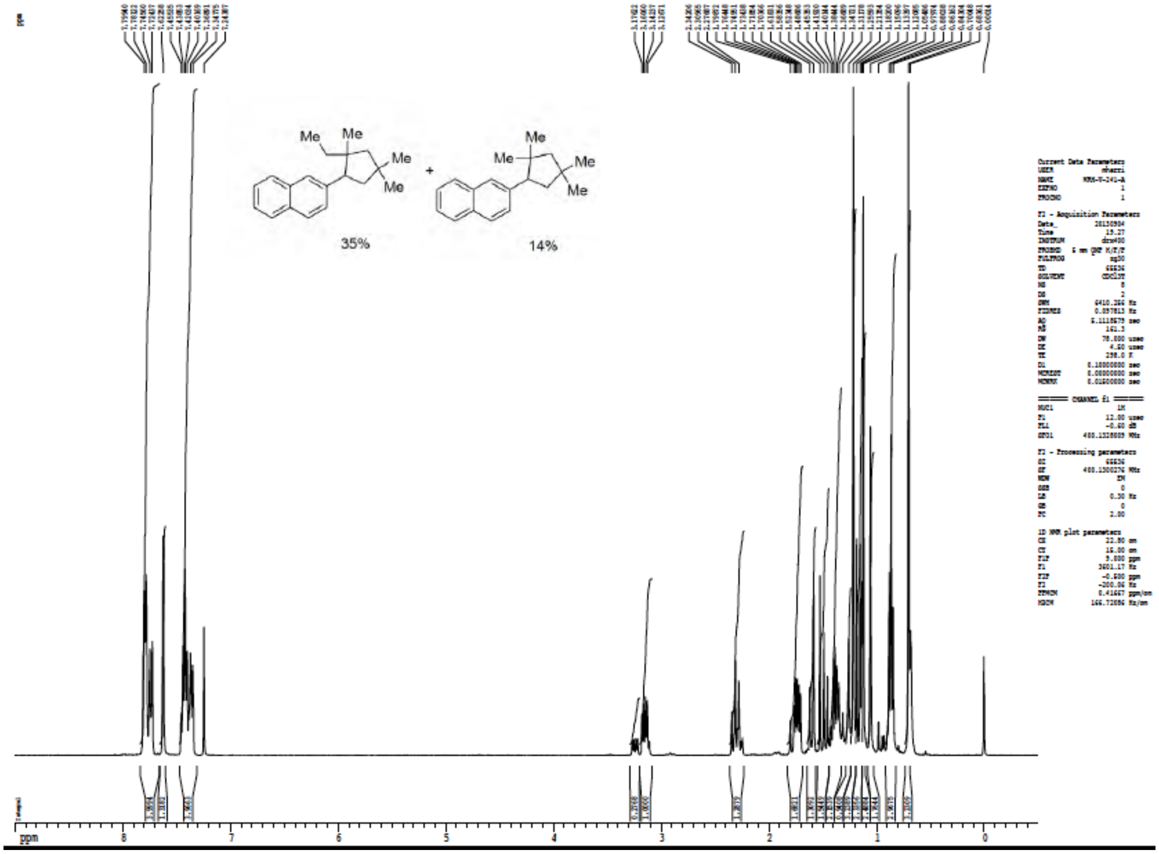
1H spectrum



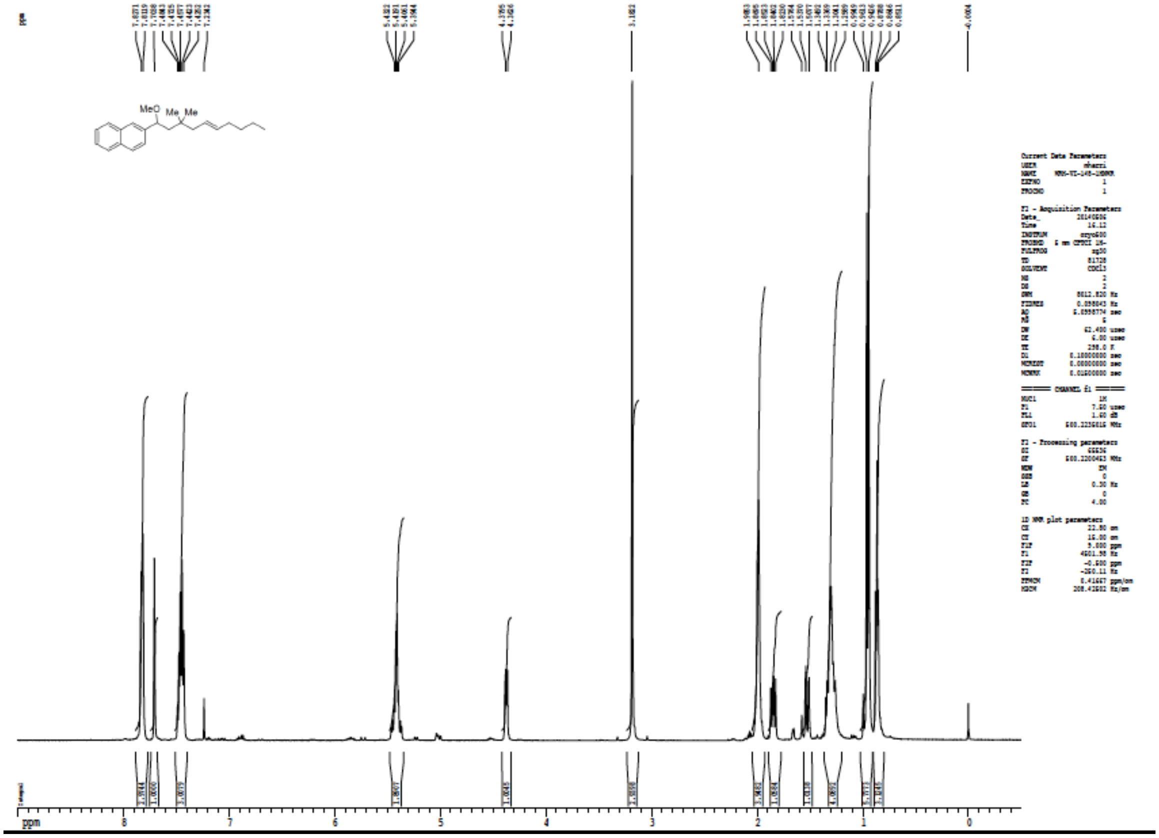
Z-restored spin-echo 13C spectrum with 1H decoupling



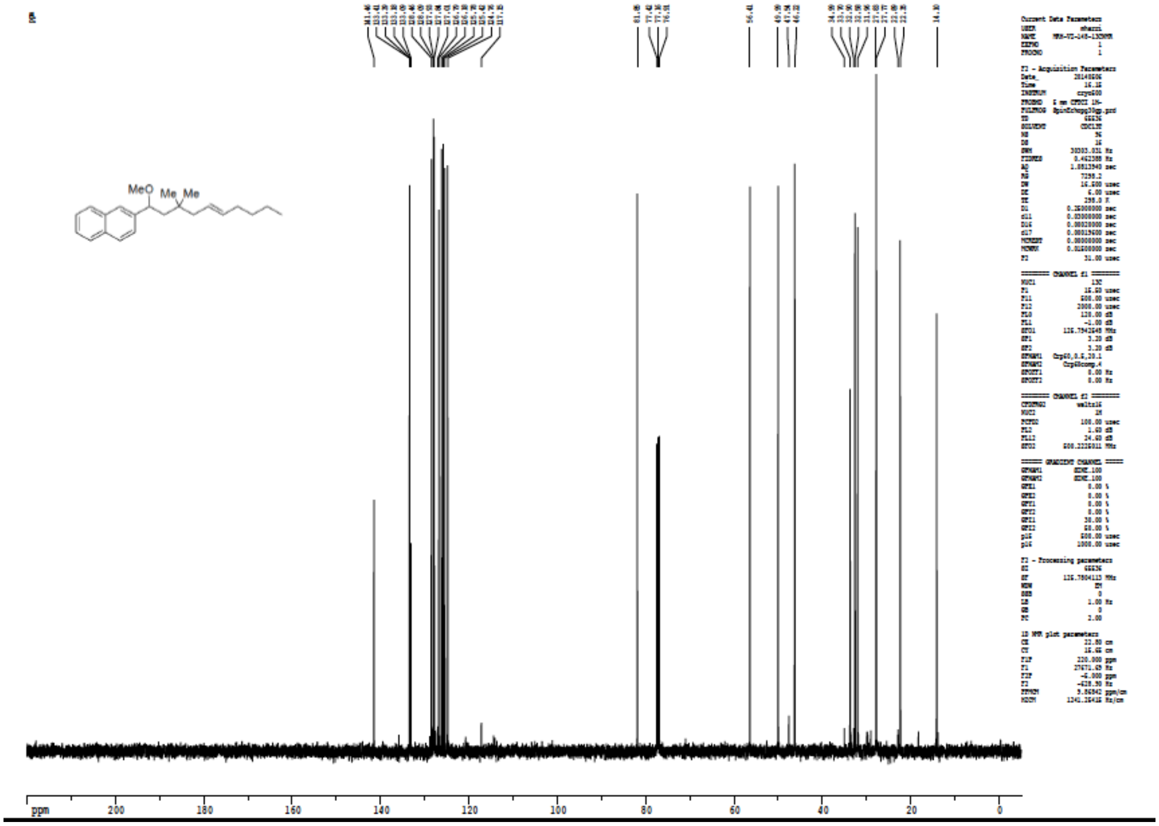
1H spectrum

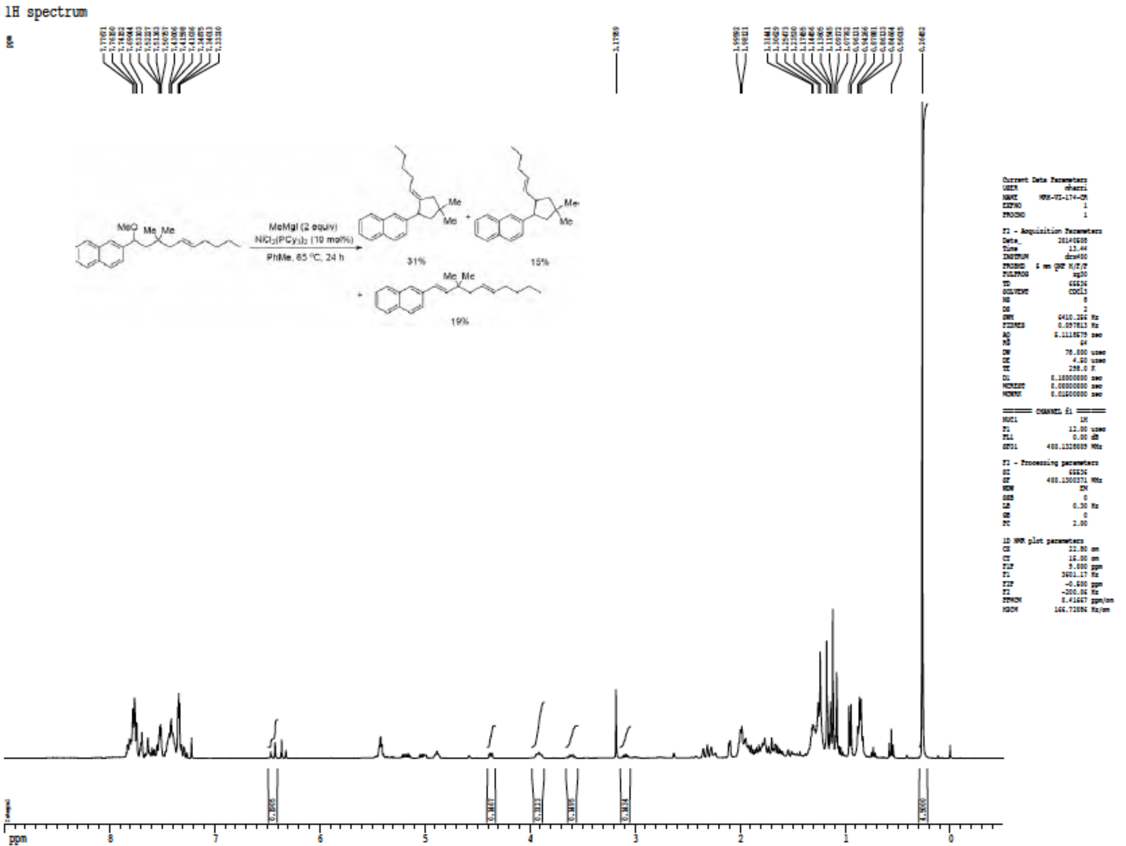


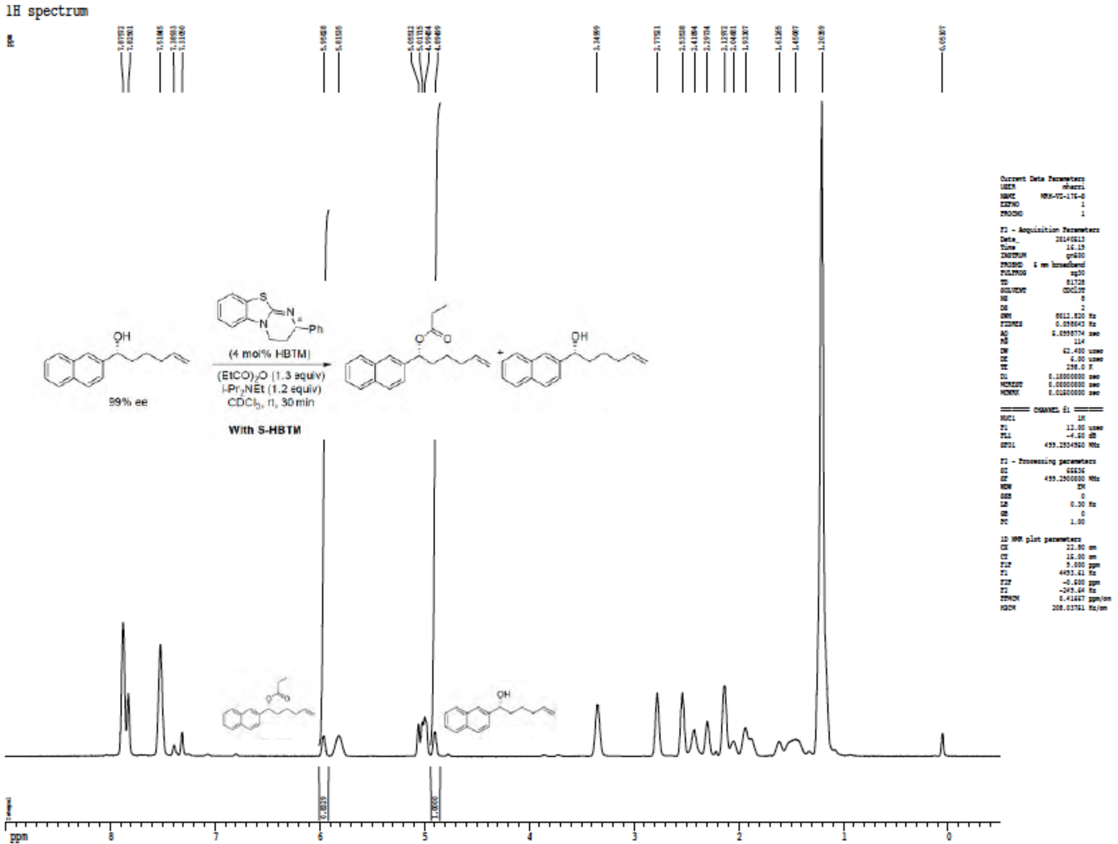
1H spectrum

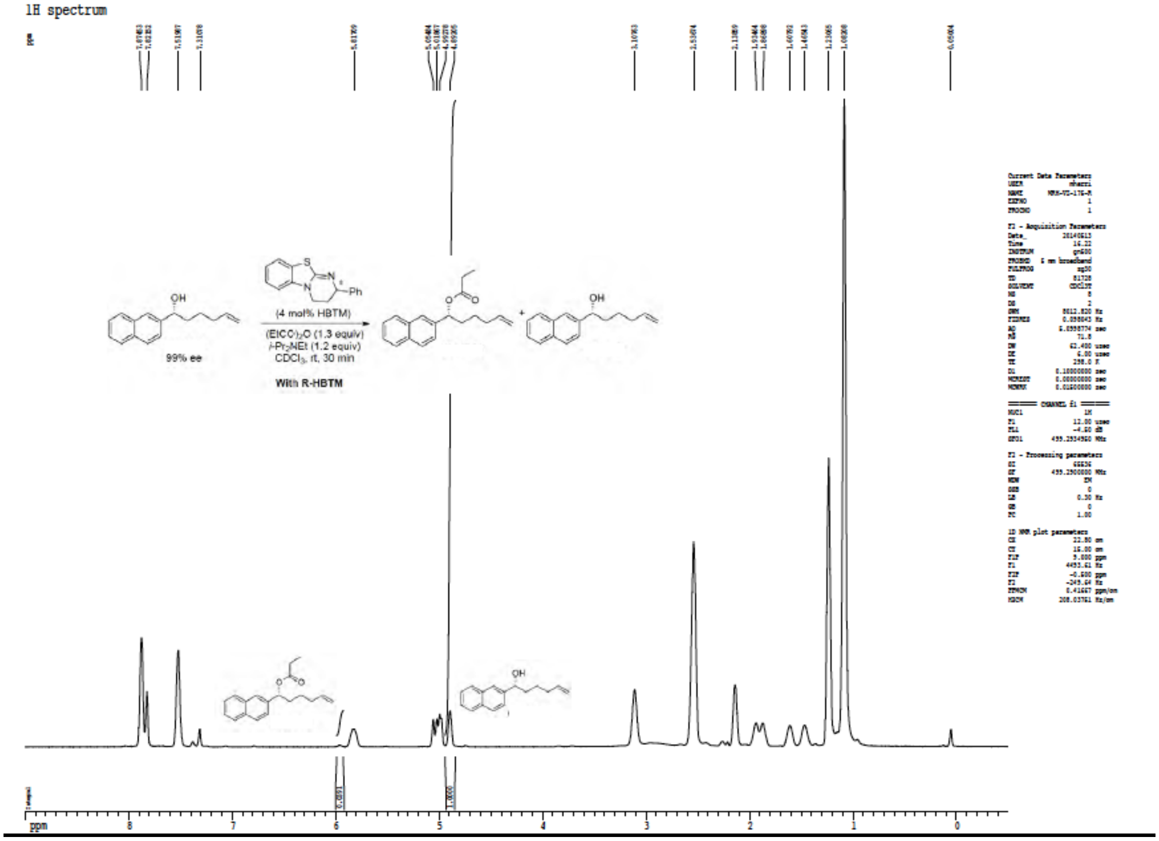


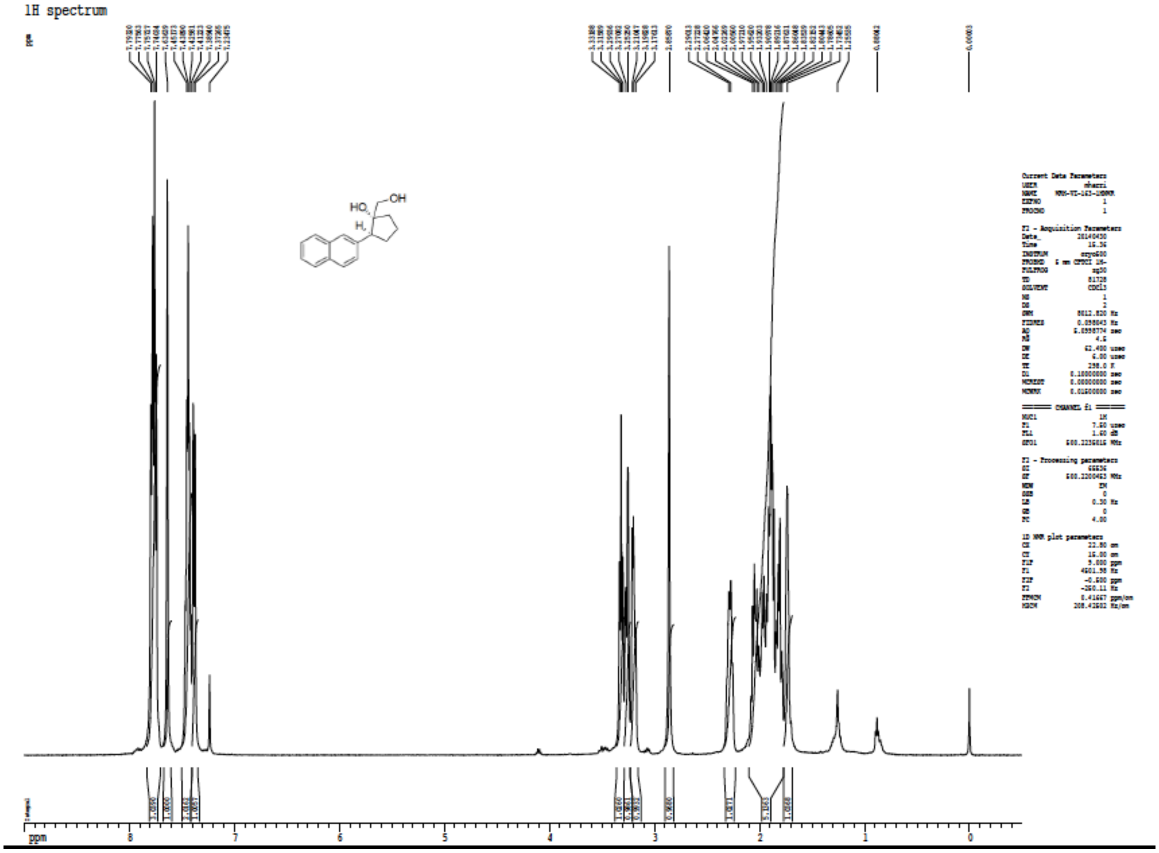
Z-restored spin-echo 13C spectrum with 1H decoupling



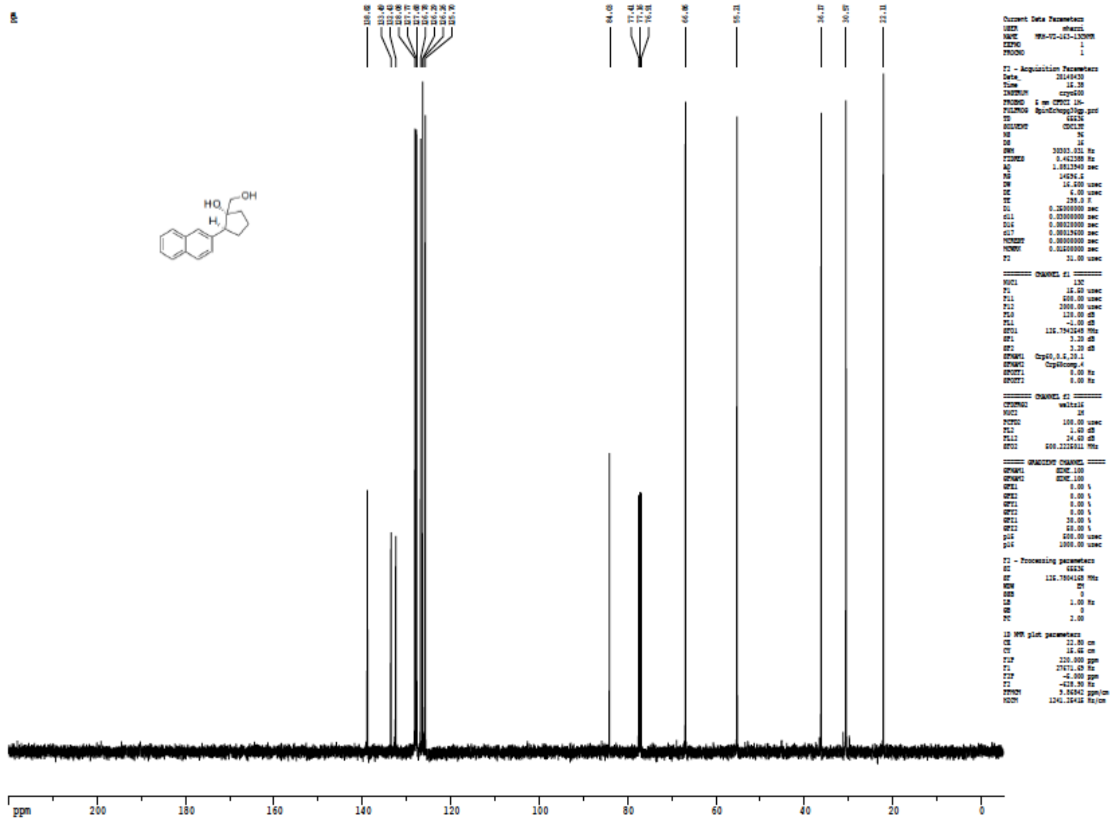

1H spectrum
MeO Me Me
MeMgI (2 equiv)
NiCl2(PCy3)2 (10 mol%)
PhMe, 85 °C, 24 h
Me
Me
31%
15%
Me Me
19%
ppm


1H spectrum
OH
99% ee
S
N
N
Ph
(4 mol% HBTM)
(EtCO)2O (1.3 equiv)
i-Pr2NEt (1.2 equiv)
CDCl3, rt, 30 min
With S-HBTM
OH
ppm

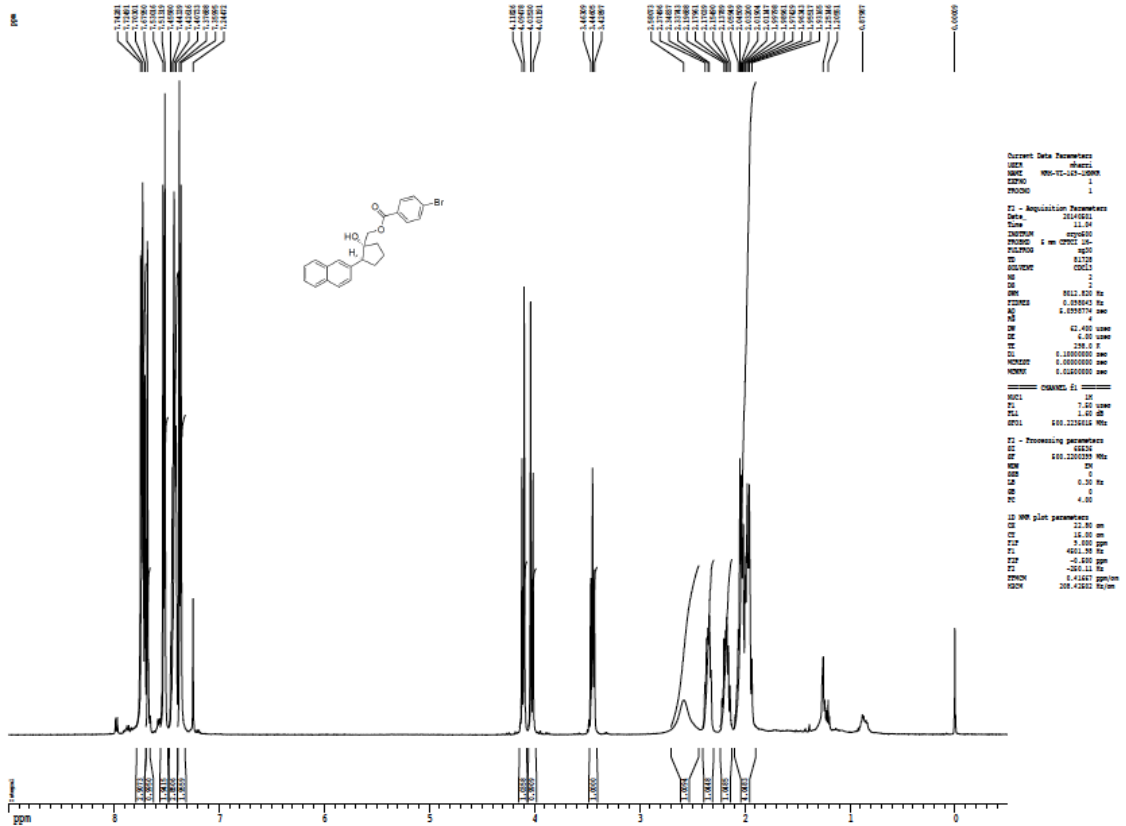

1H spectrum
ppm
(4 mol% HBTM)
(EtCO)₂O (1.3 equiv)
i-Pr₂NEt (1.2 equiv)
CDCl₃, rt, 30 min
99% ee
With R-HBTM
OH
Ph
8
7
6
5
4
3
2
1
0


1H spectrum
ppm
HO
OH
H
8
7
6
5
4
3
2
1
0

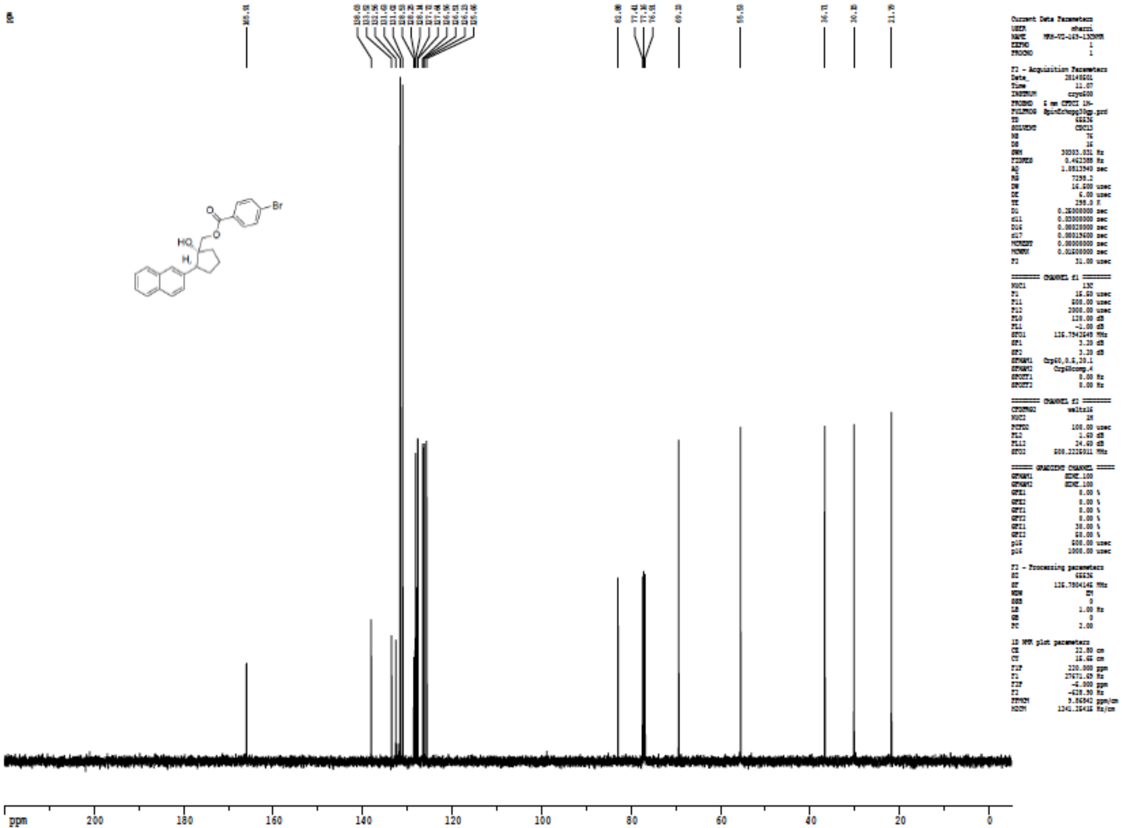
Z-restored spin-echo 13C spectrum with 1H decoupling



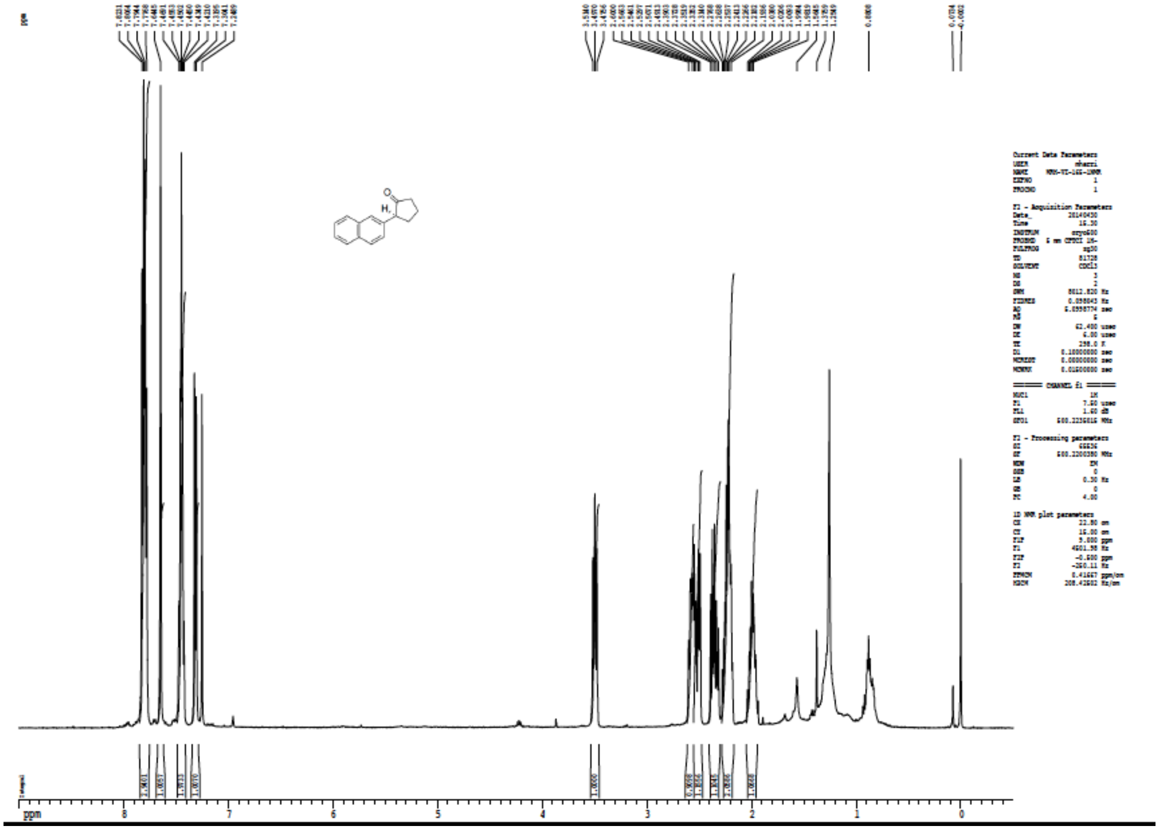
1H spectrum



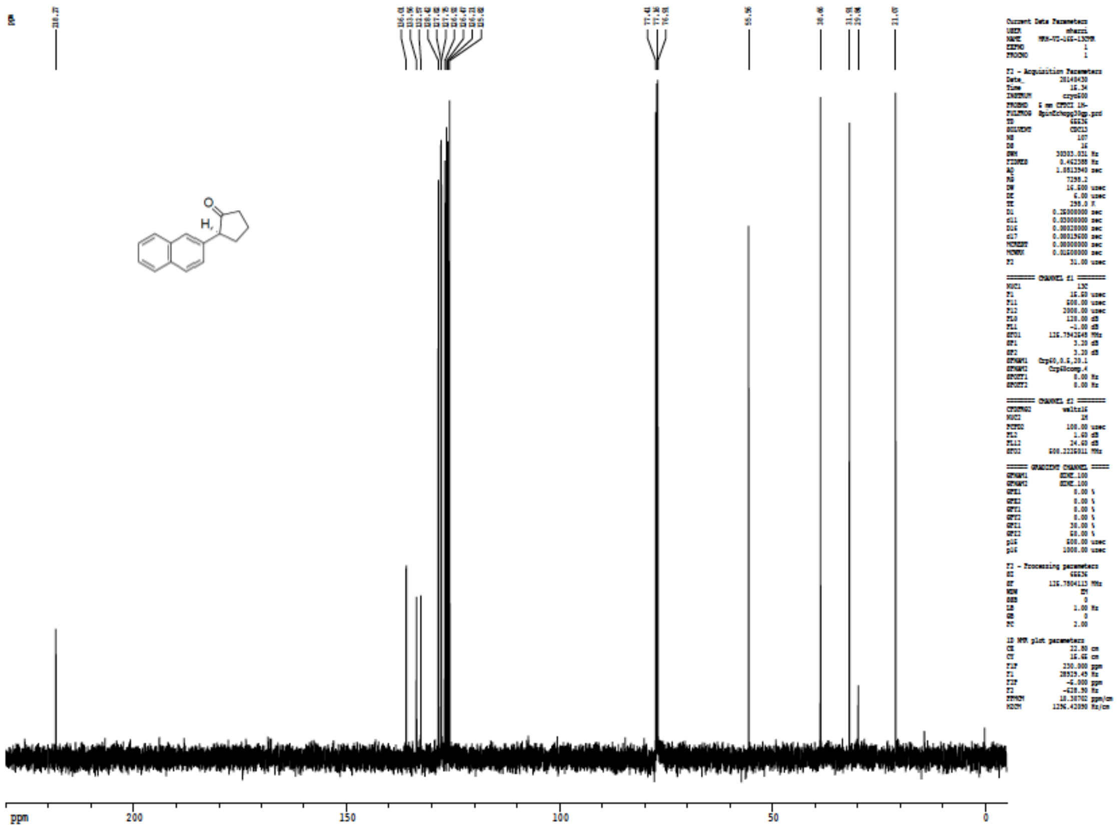
Z-restored spin-echo 13C spectrum with 1H decoupling



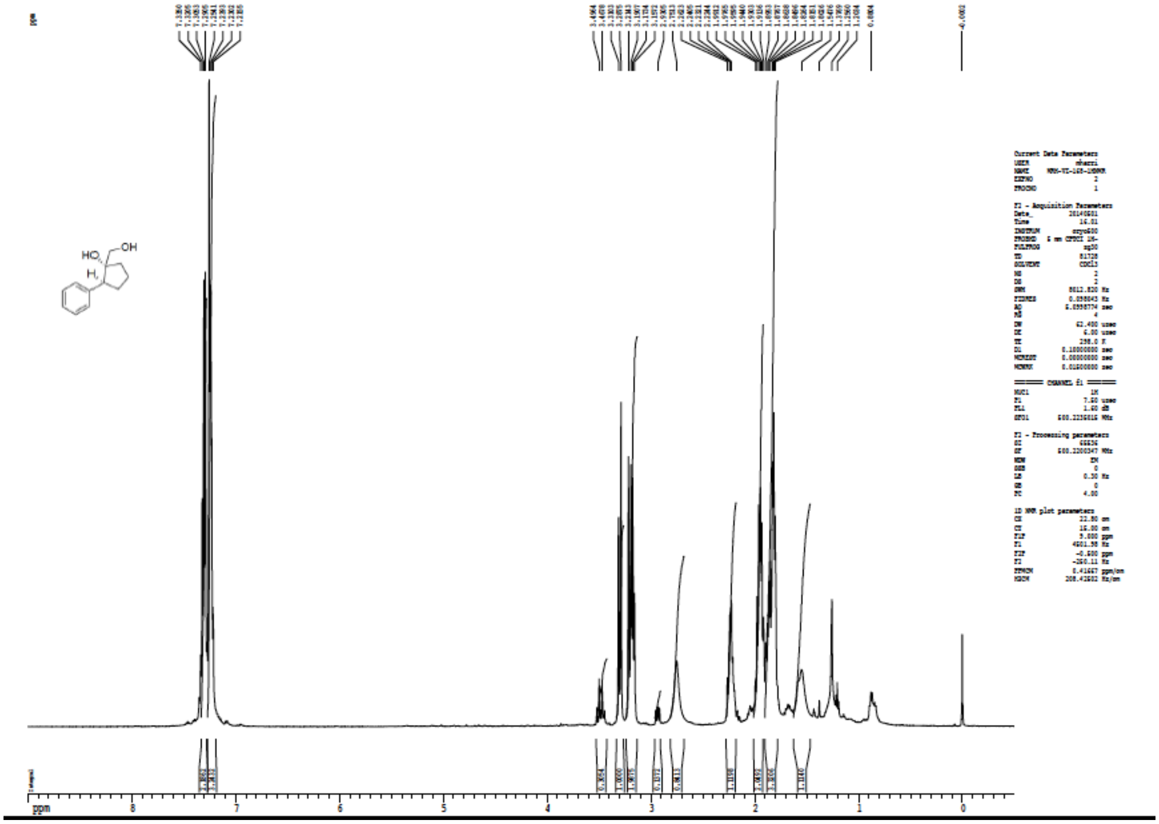
1H spectrum



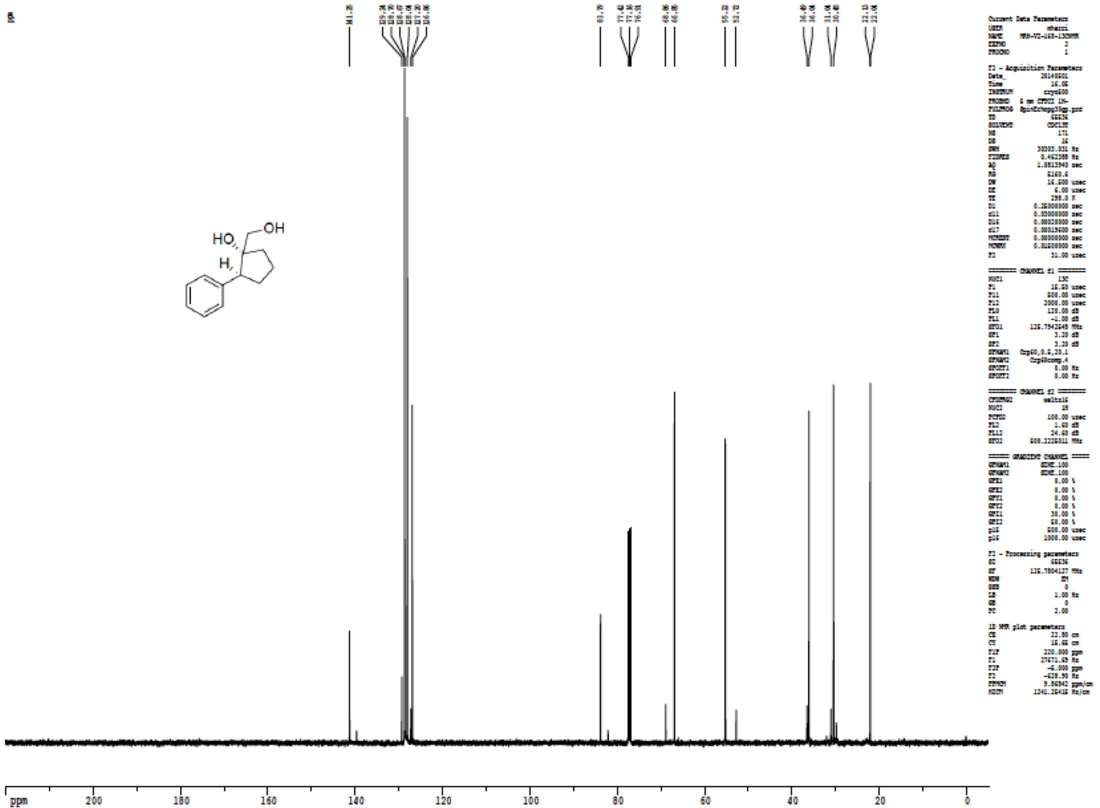
Z-restored spin-echo 13C spectrum with 1H decoupling



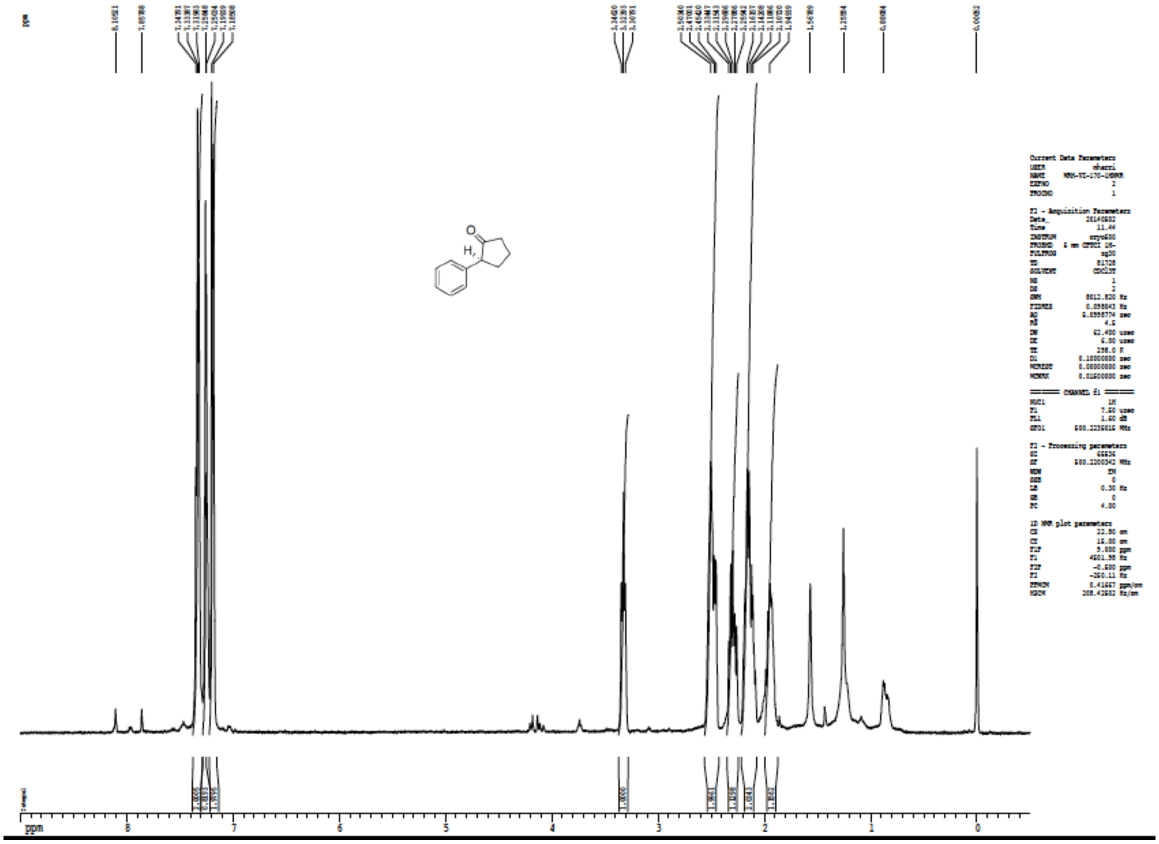
1H spectrum



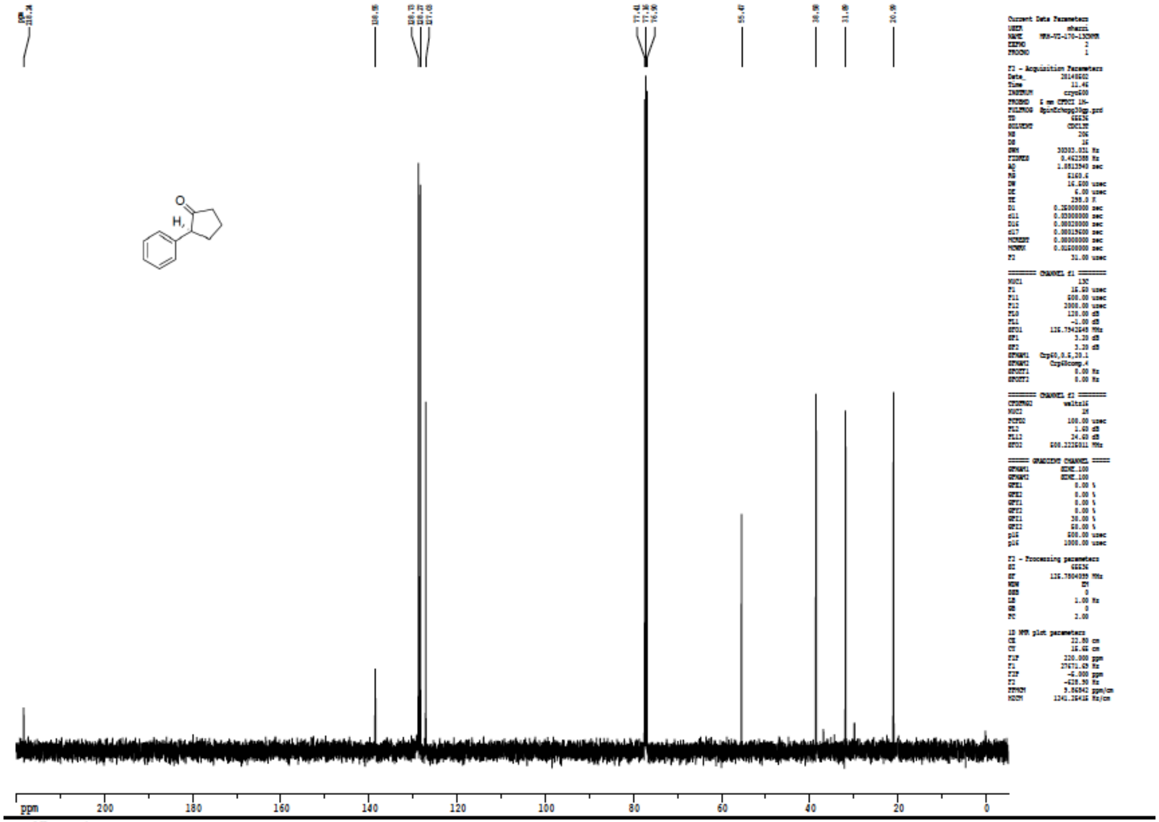
Z-restored spin-echo 13C spectrum with 1H decoupling



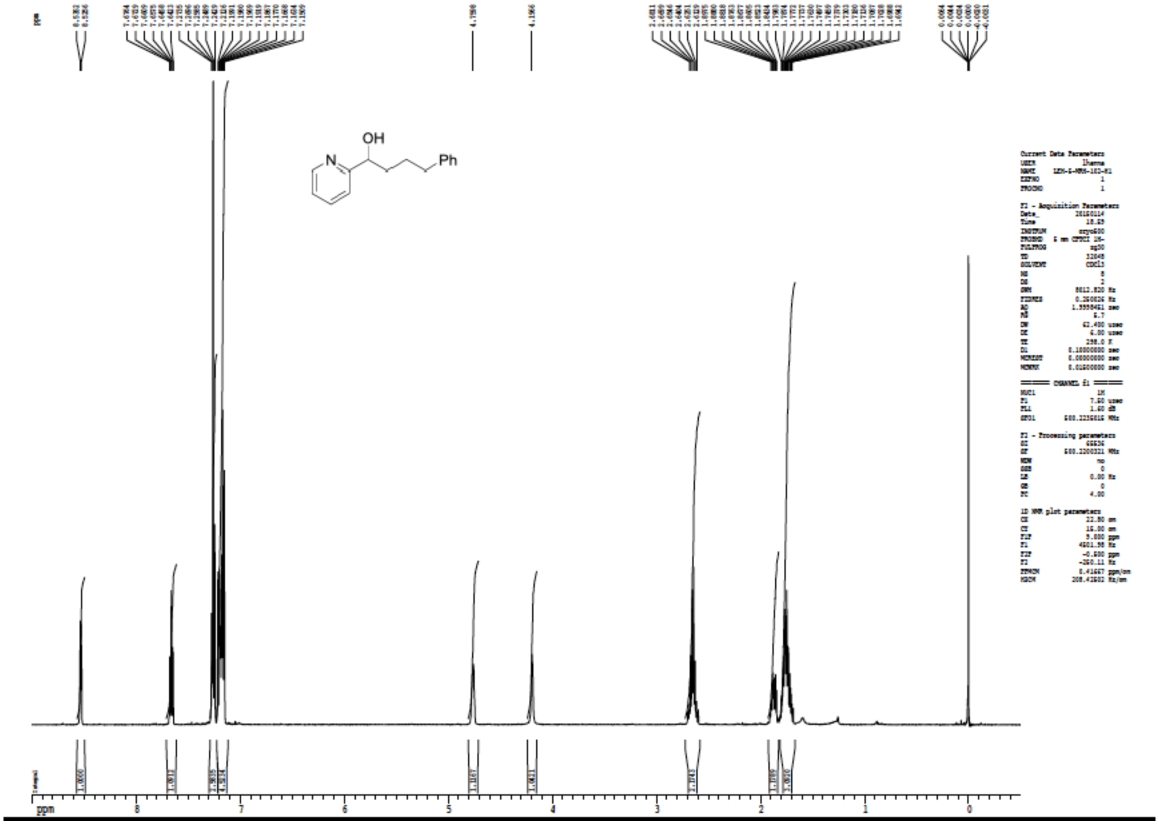
1H spectrum



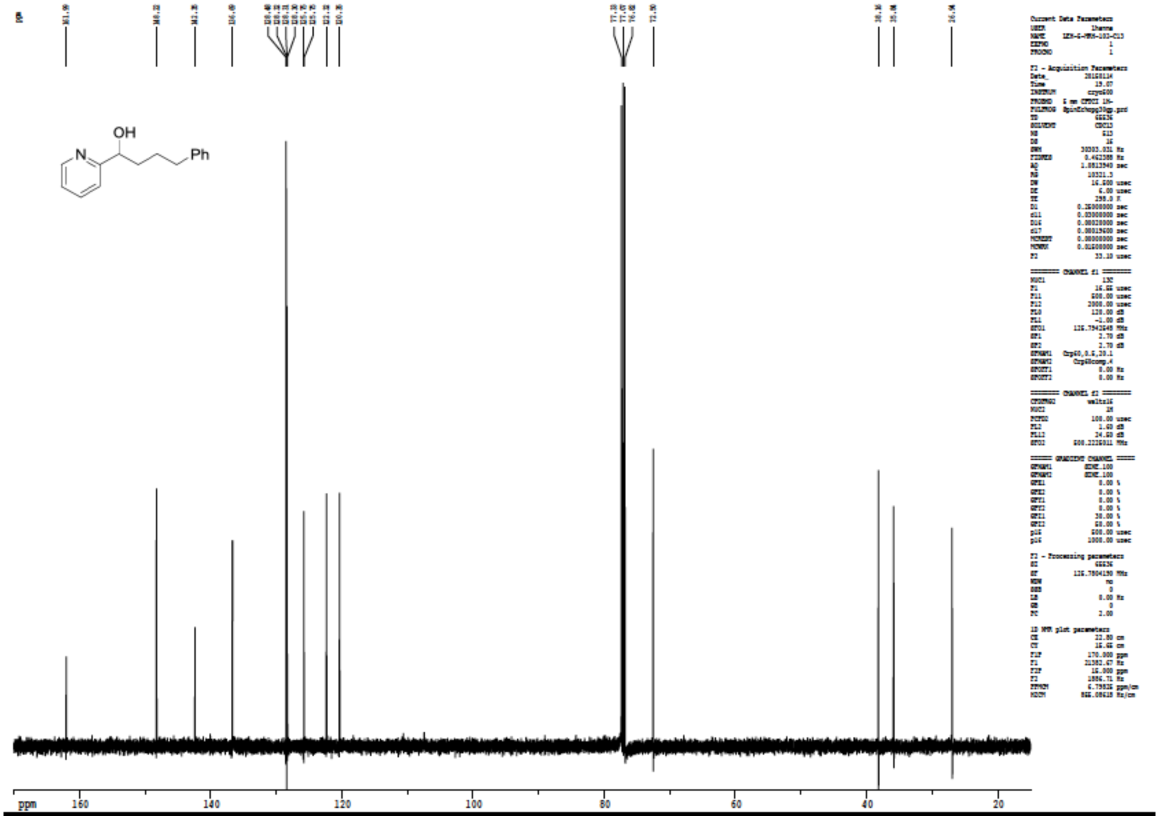
Z-restored spin-echo 13C spectrum with 1H decoupling



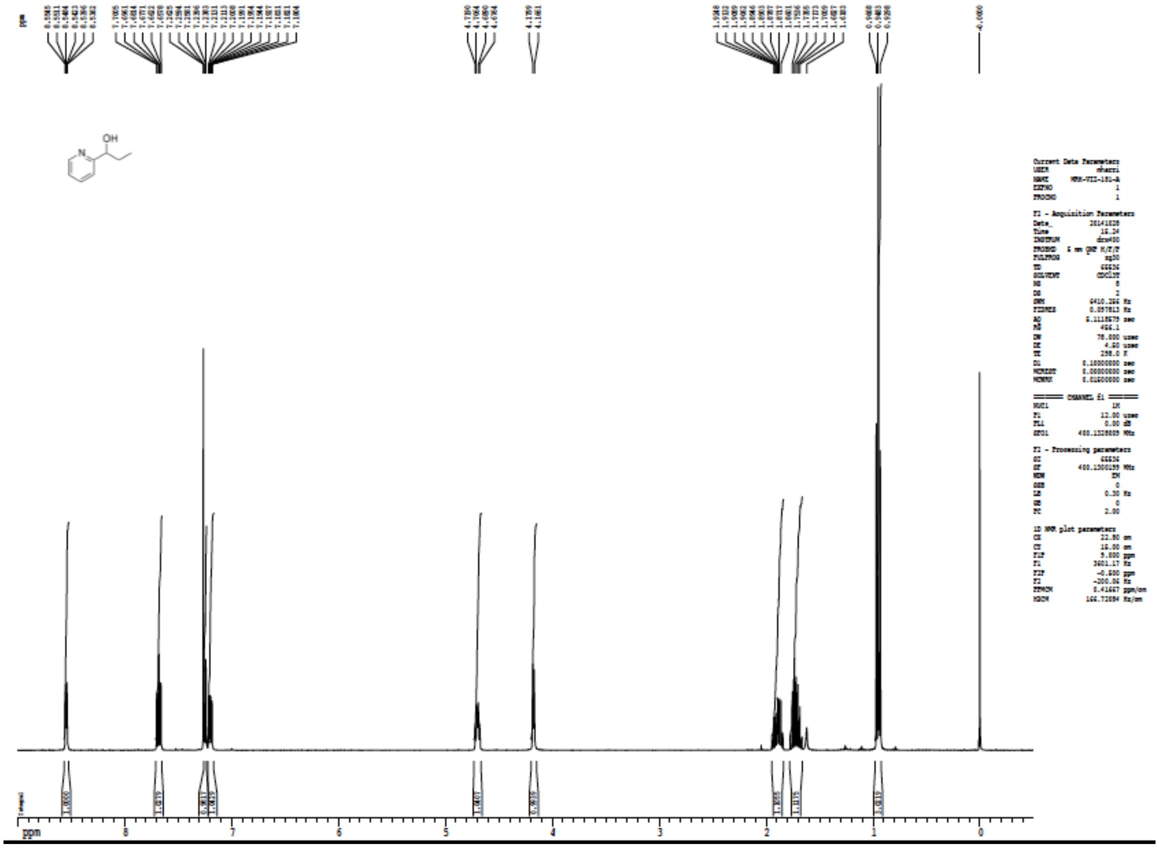
1H spectrum



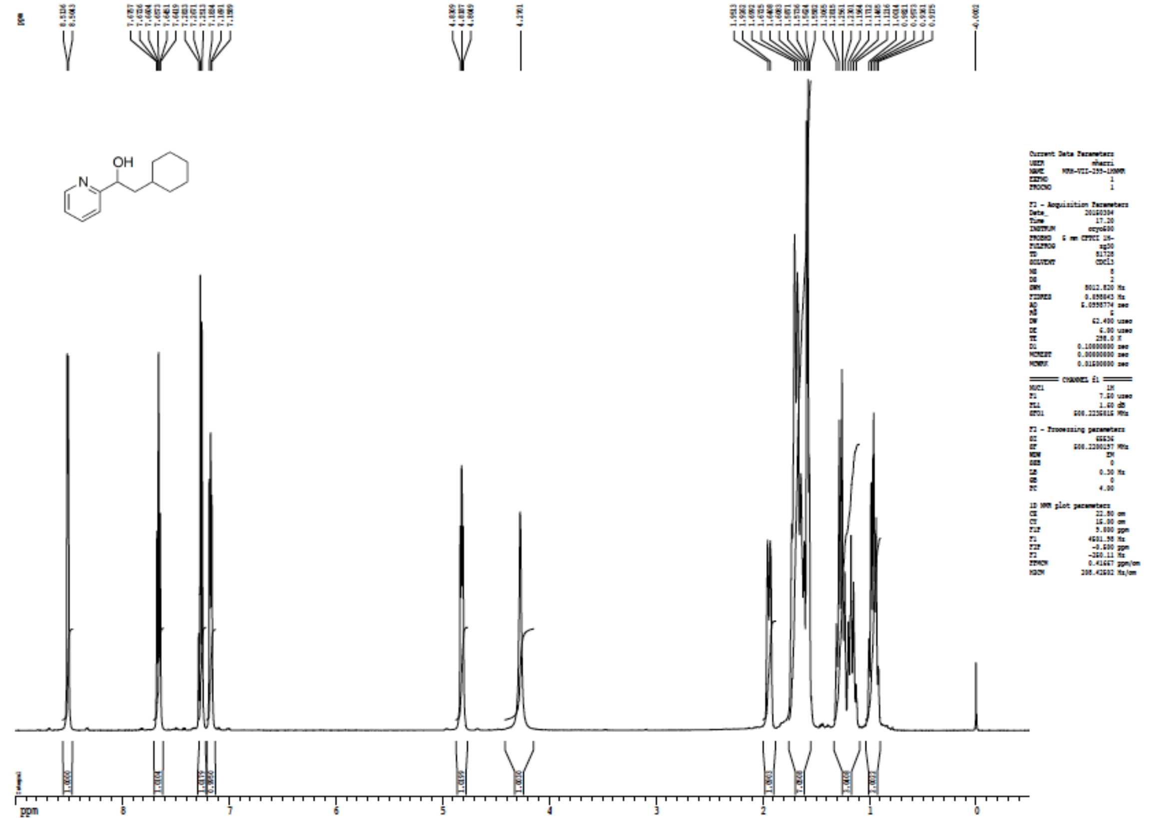
Z-restored spin-echo 13C spectrum with 1H decoupling



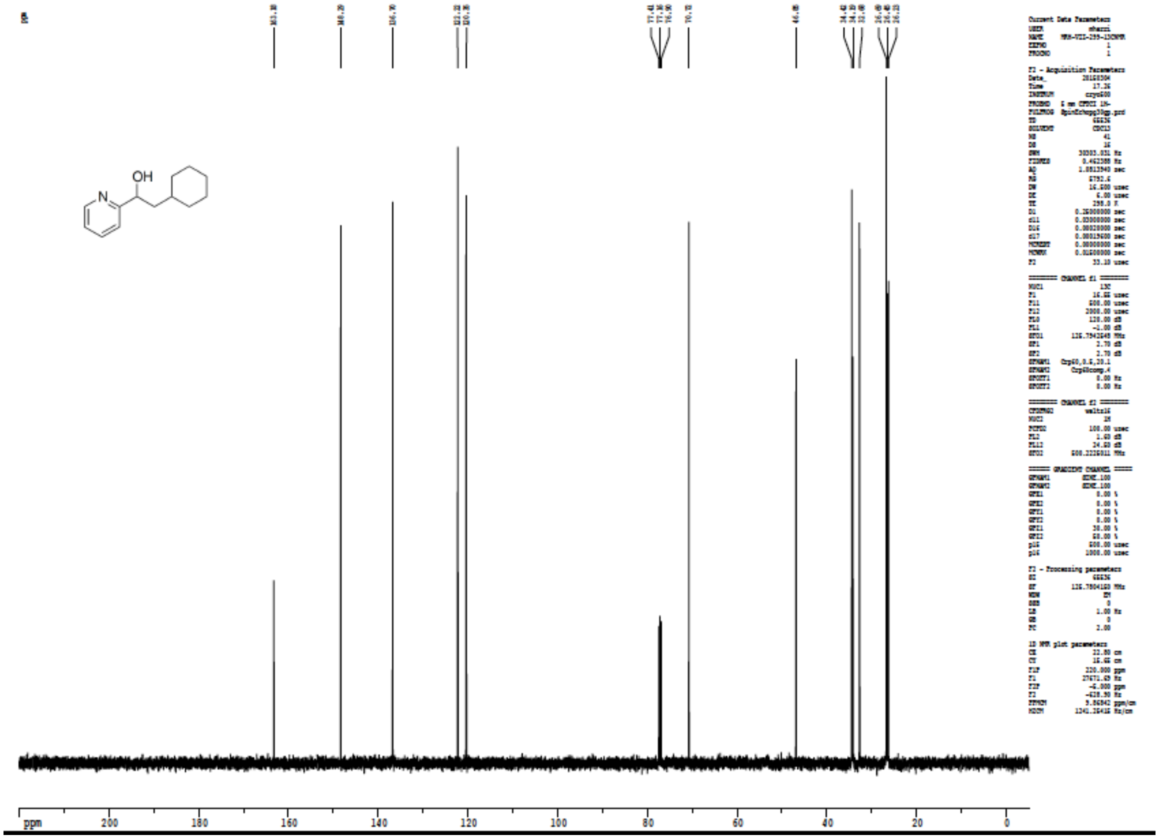
1H spectrum



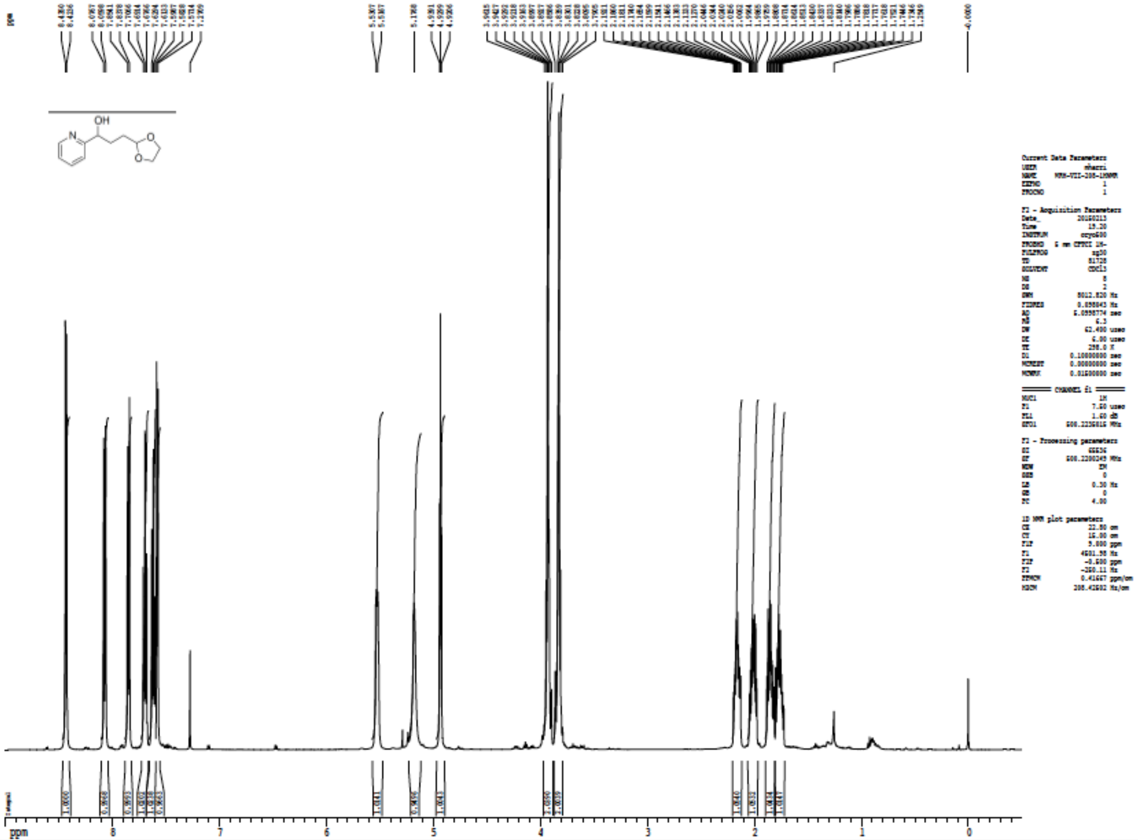
1H spectrum



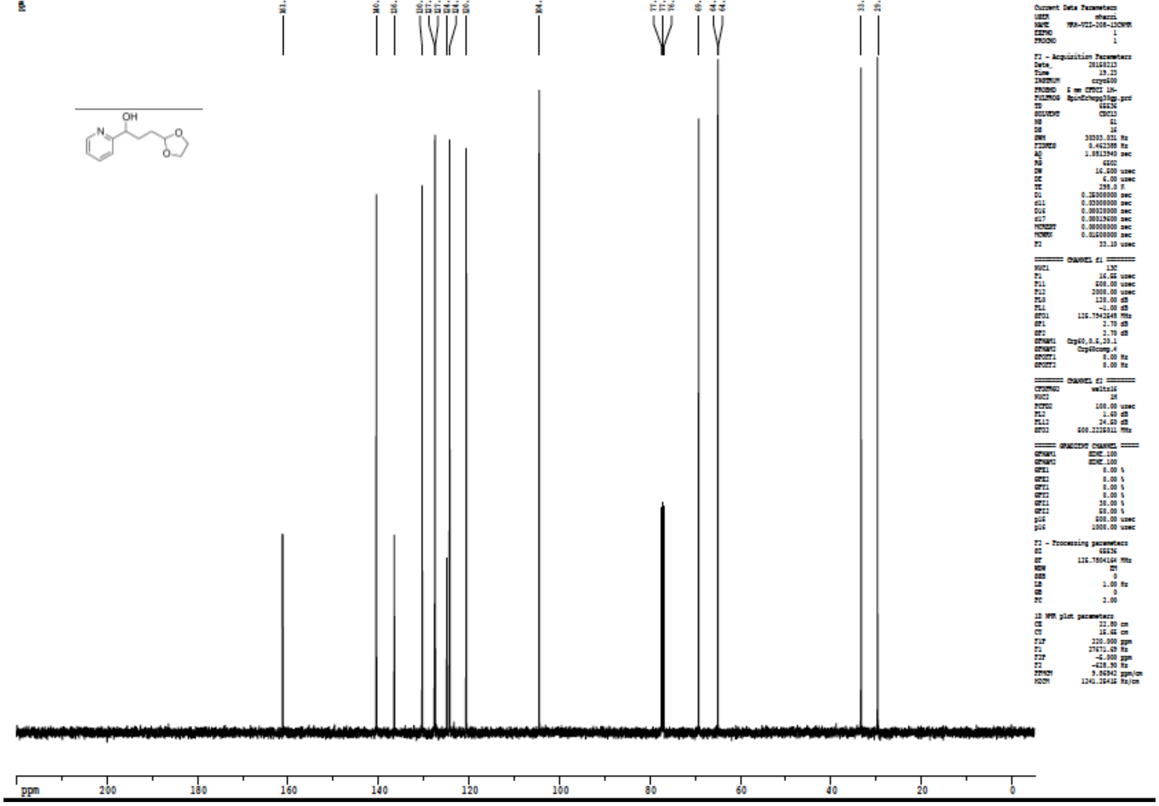
Z-restored spin-echo 13C spectrum with 1H decoupling

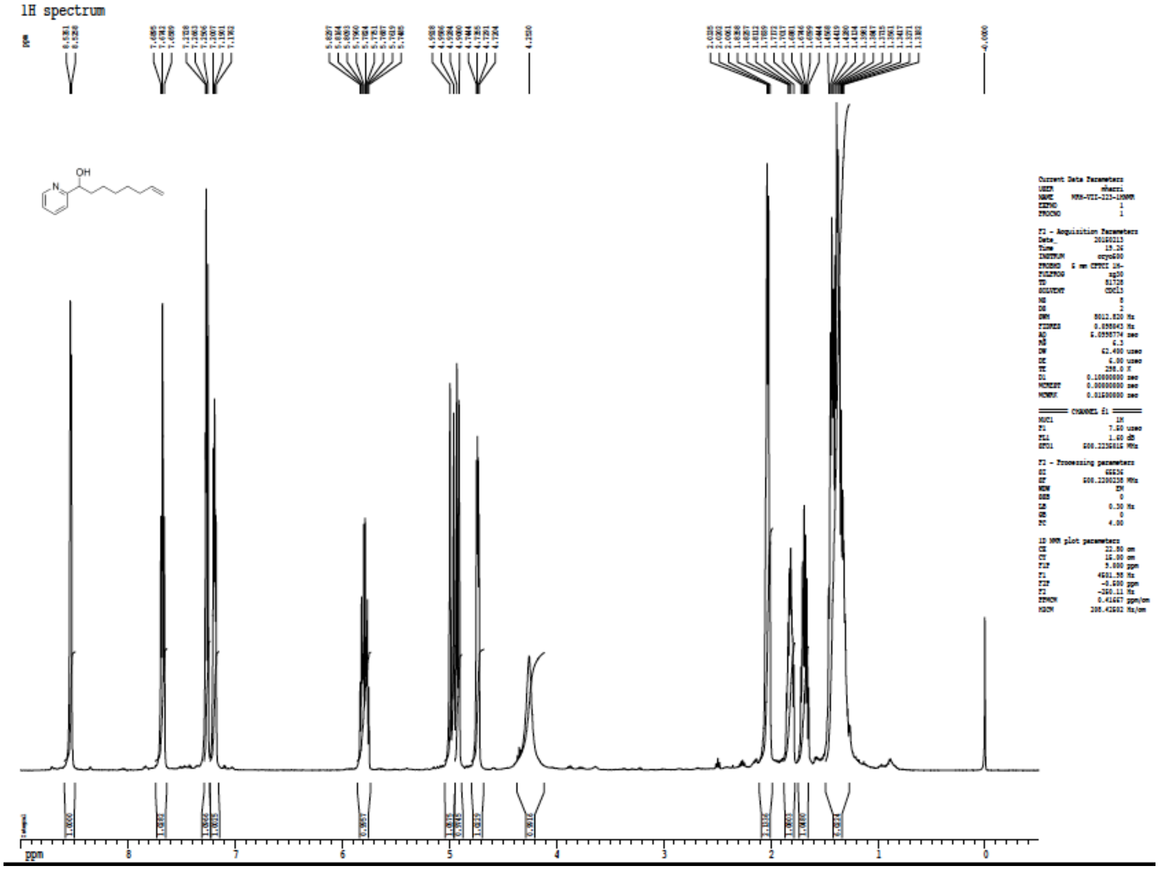


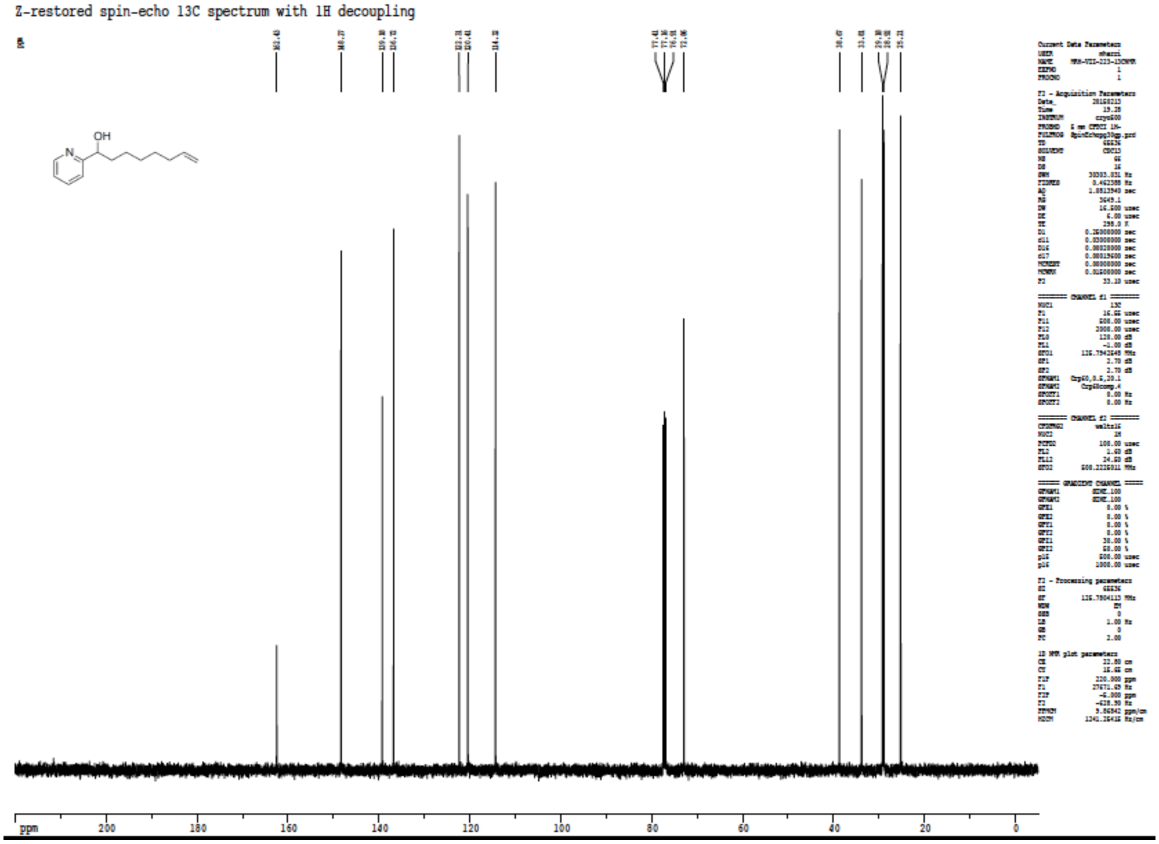
1H spectrum



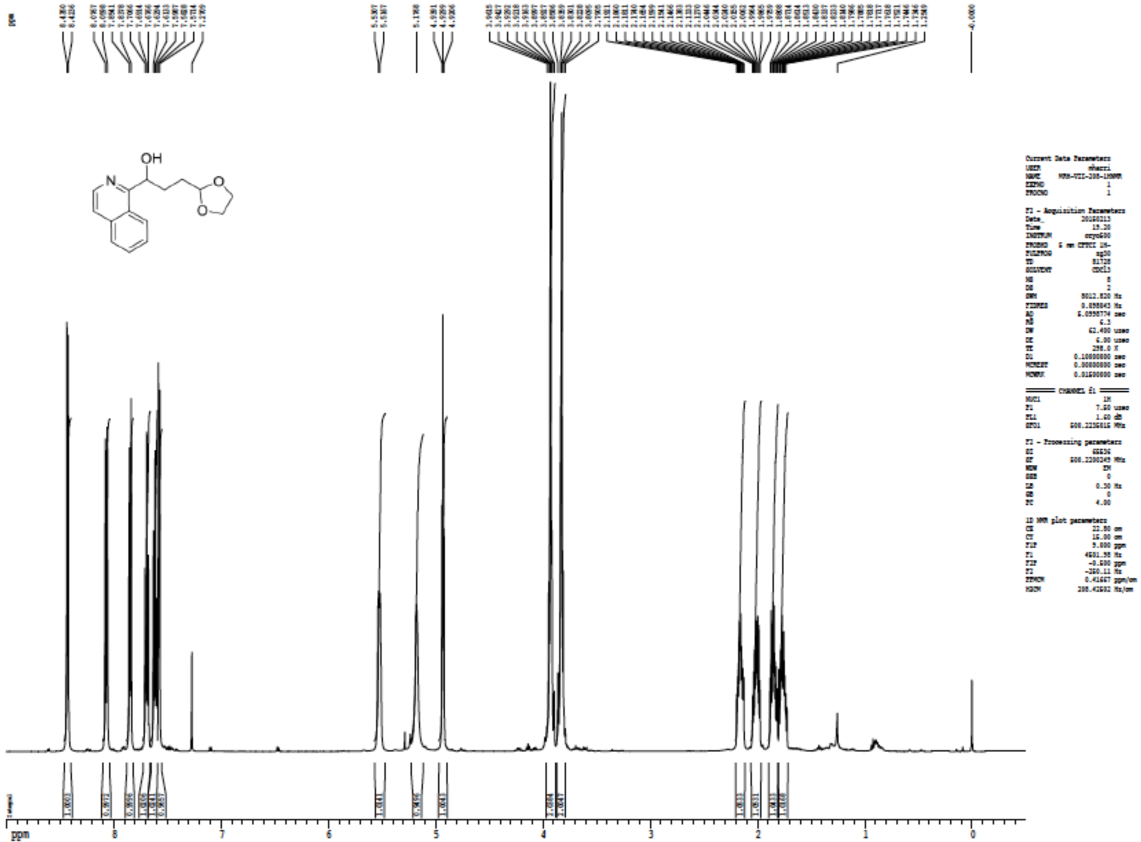
Z-restored spin-echo 13C spectrum with 1H decoupling



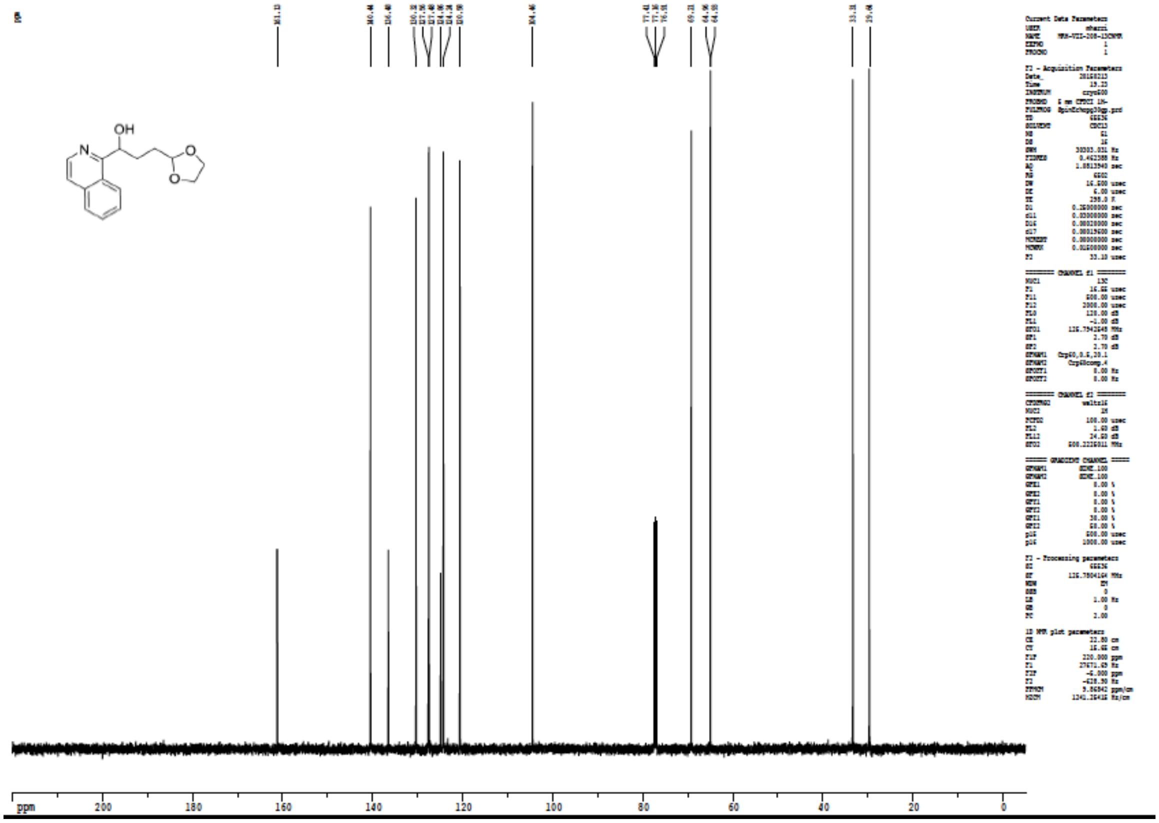

1H spectrum


Z-restored spin-echo 13C spectrum with 1H decoupling

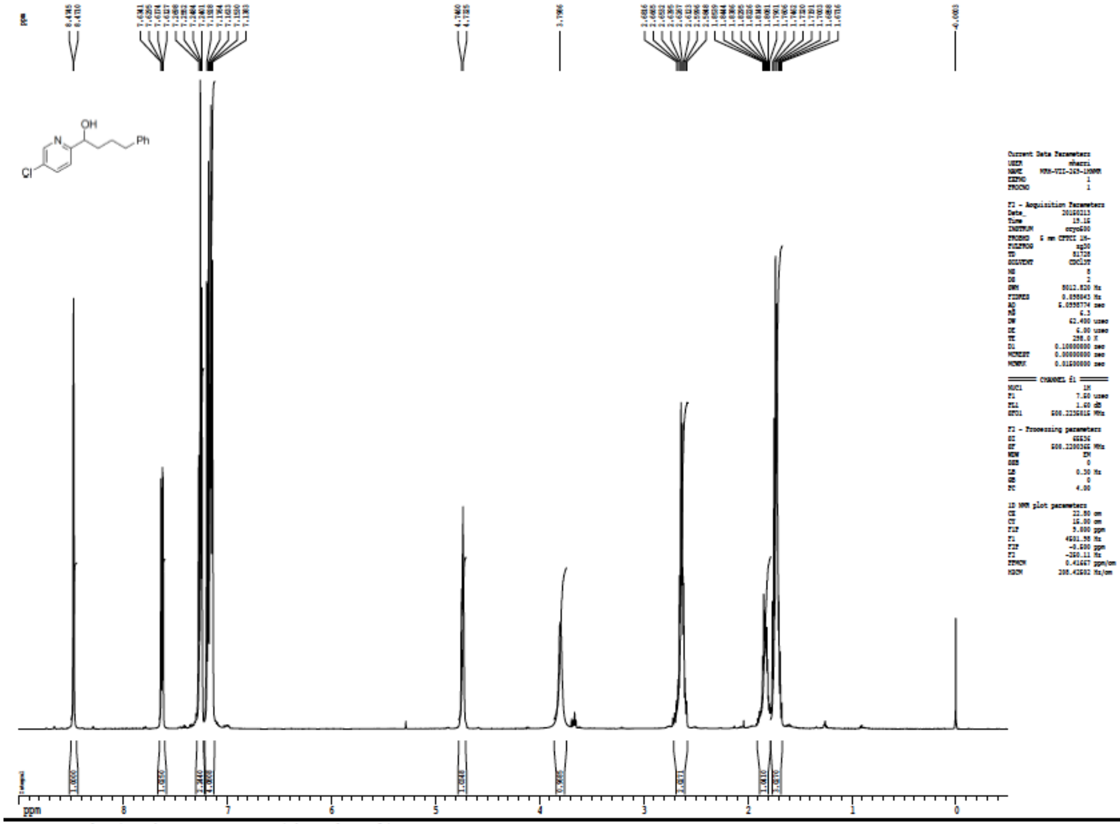
1H spectrum



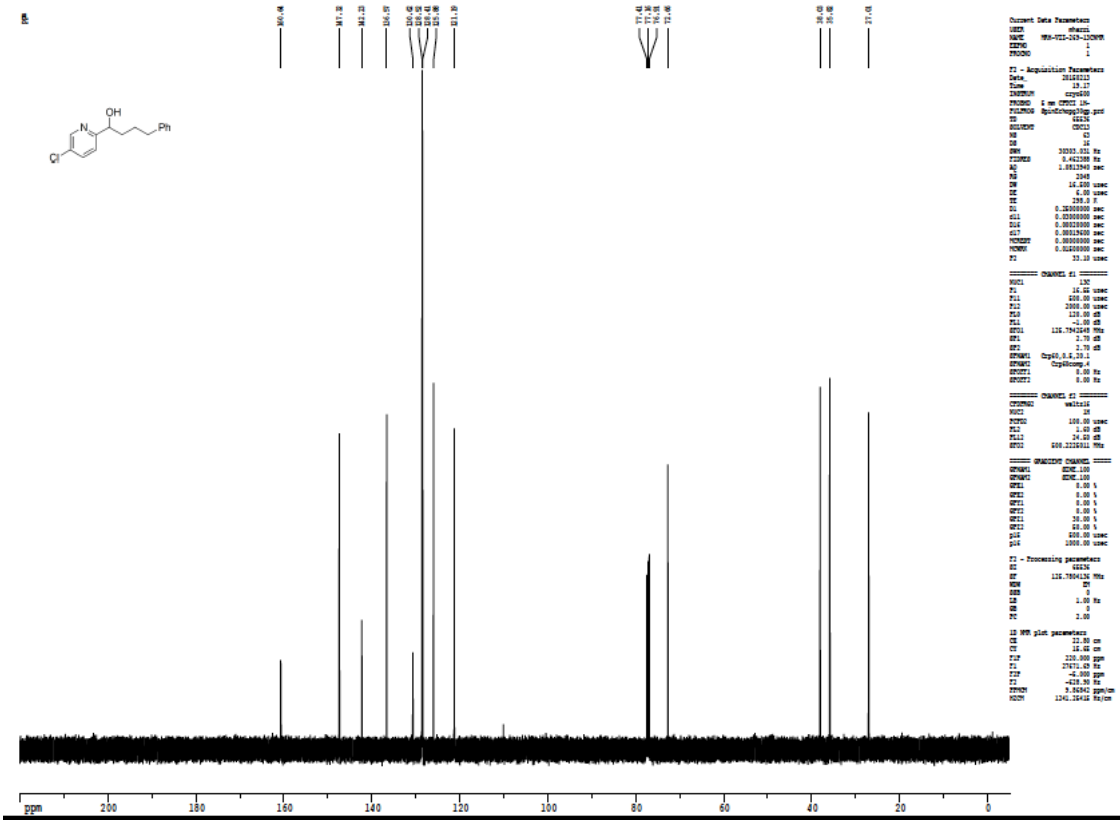
Z-restored spin-echo 13C spectrum with 1H decoupling



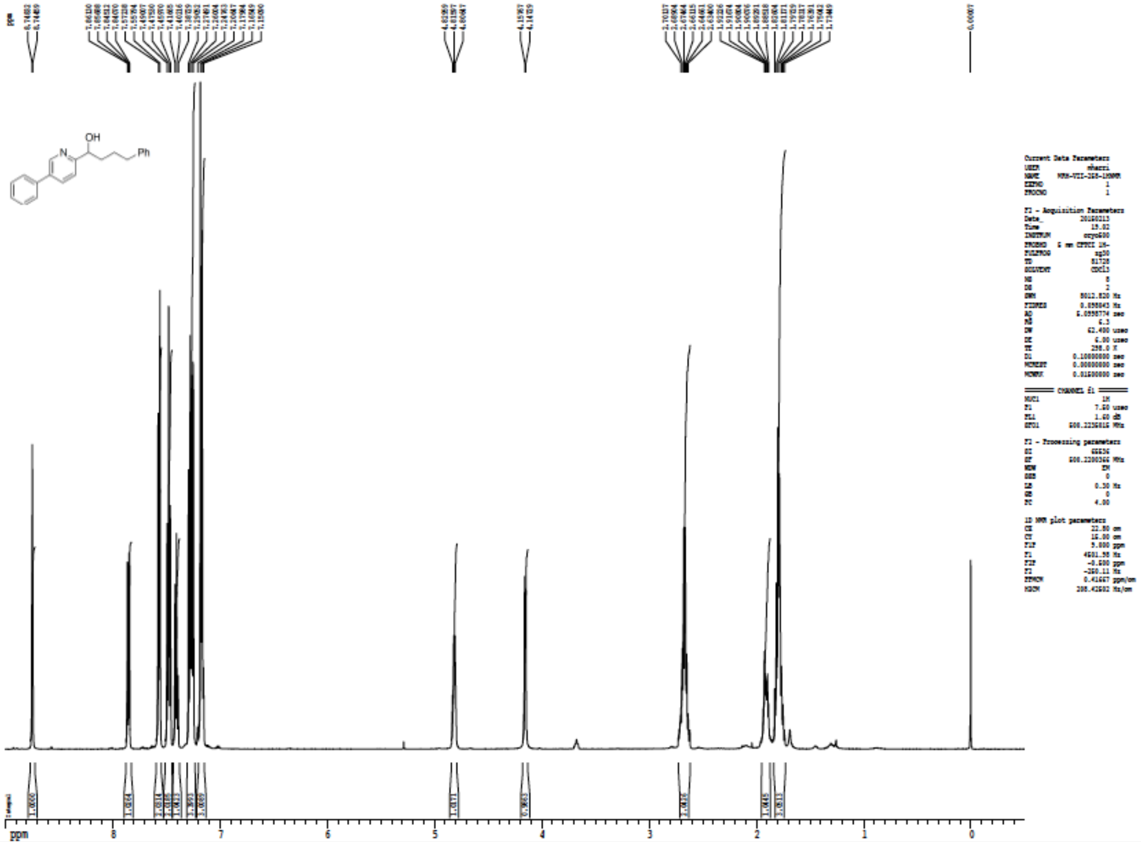
1H spectrum



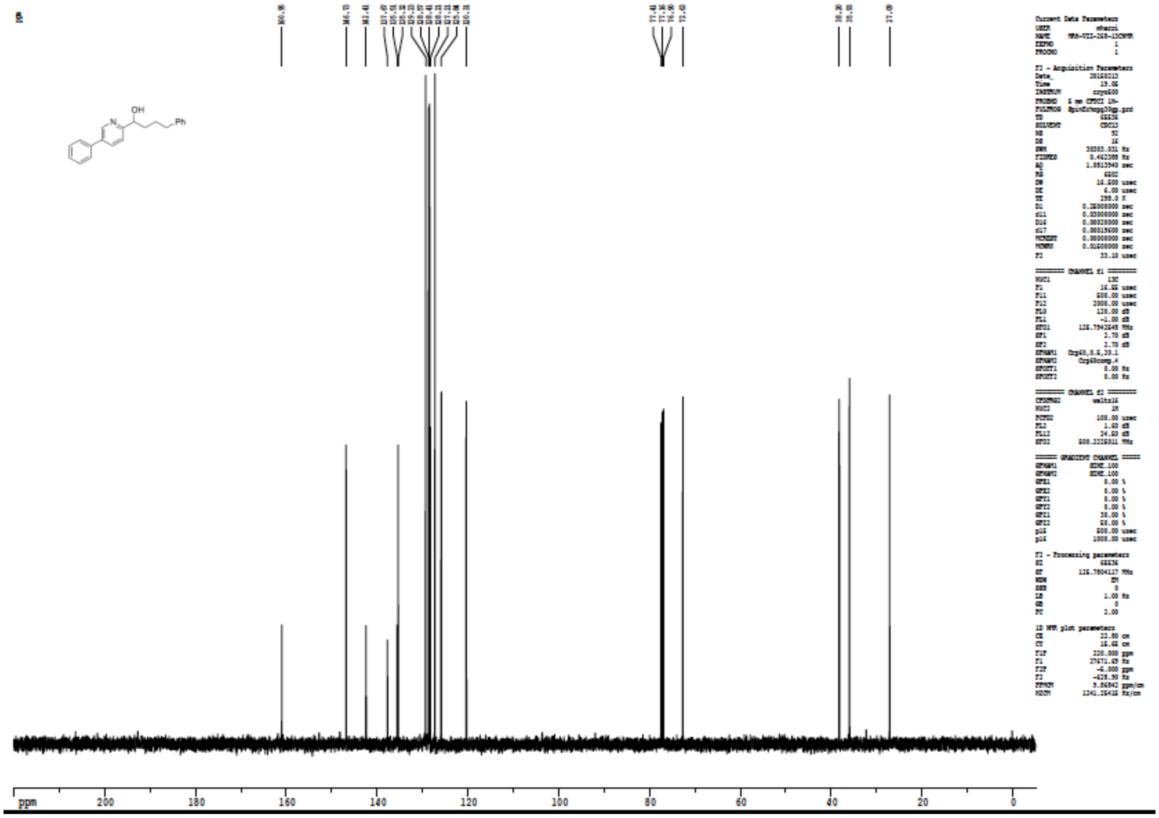
Z-restored spin-echo 13C spectrum with 1H decoupling



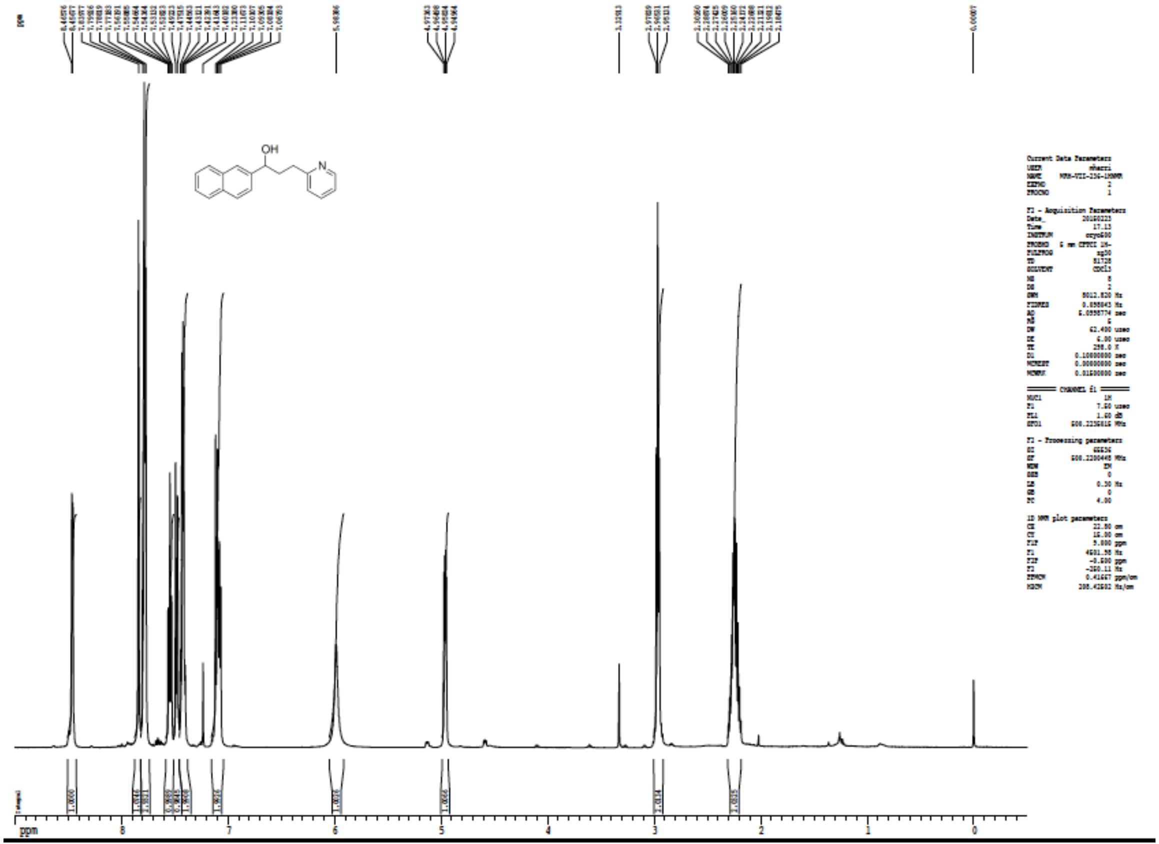
1H spectrum



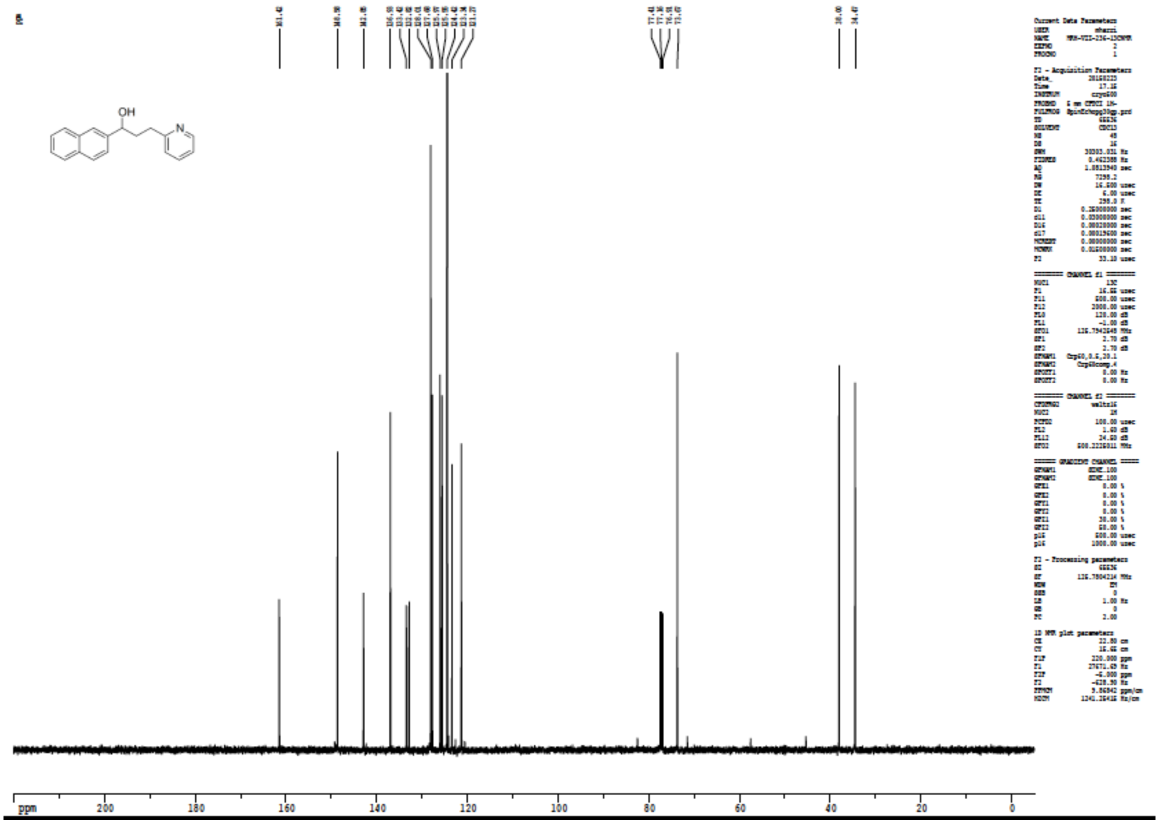
Z-restored spin-echo 13C spectrum with 1H decoupling



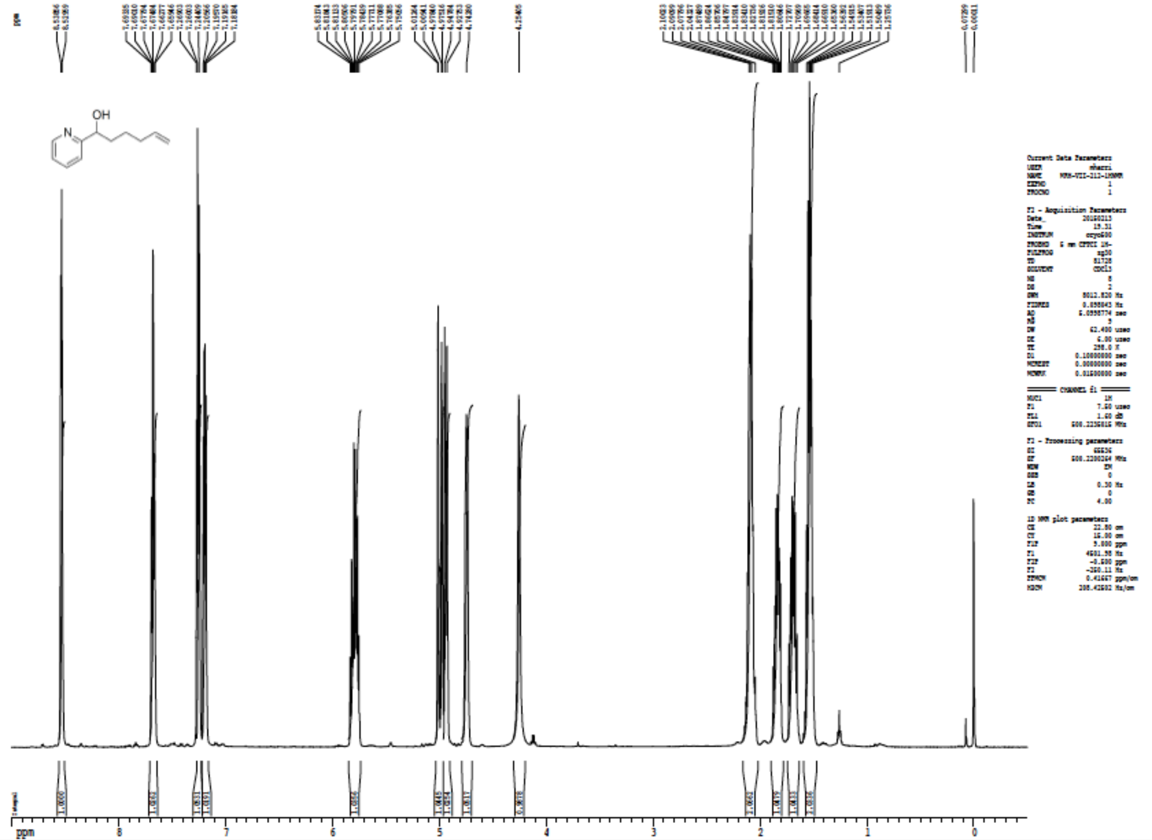
1H spectrum



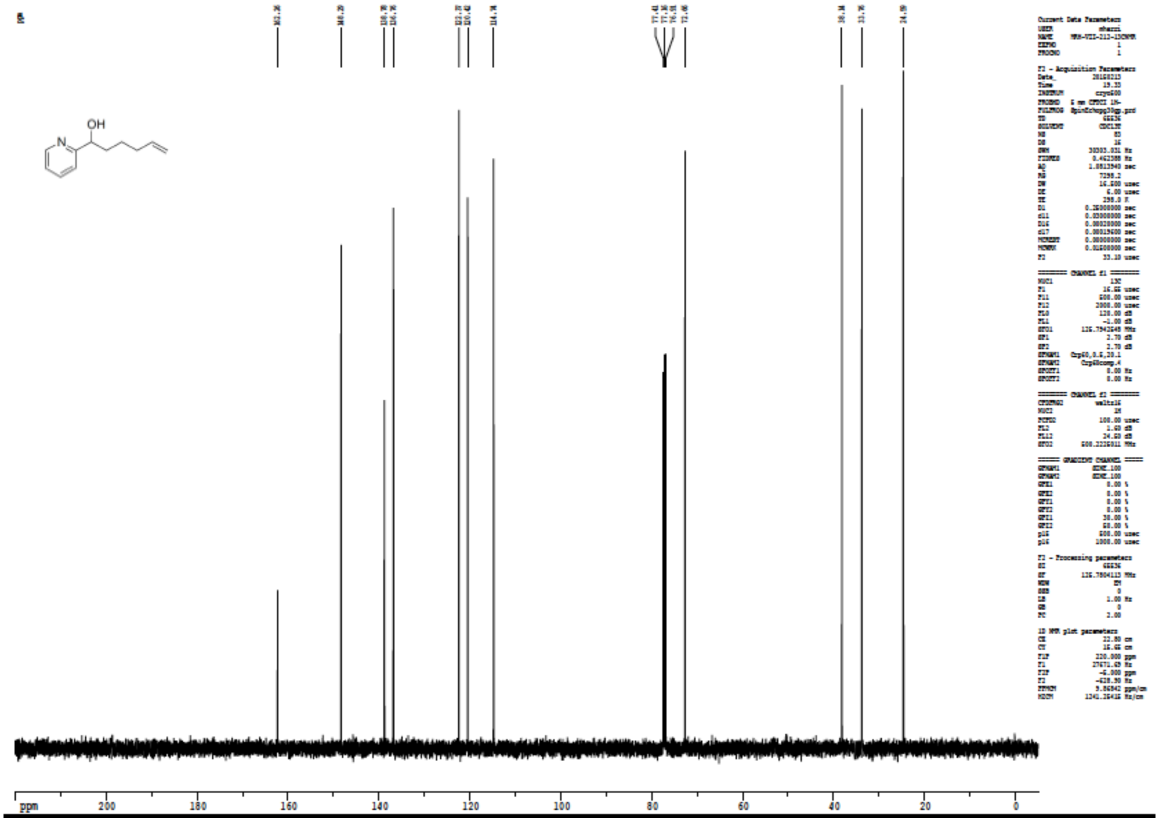
Z-restored spin-echo 13C spectrum with 1H decoupling



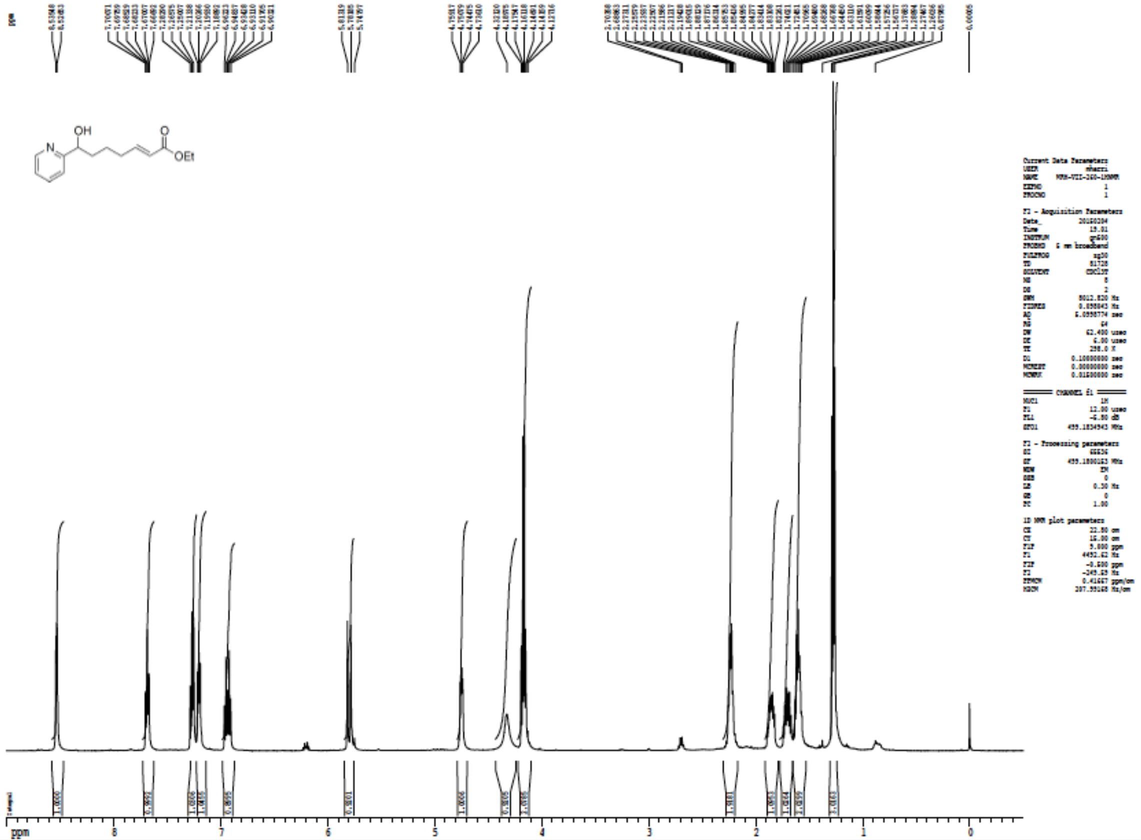
1H spectrum



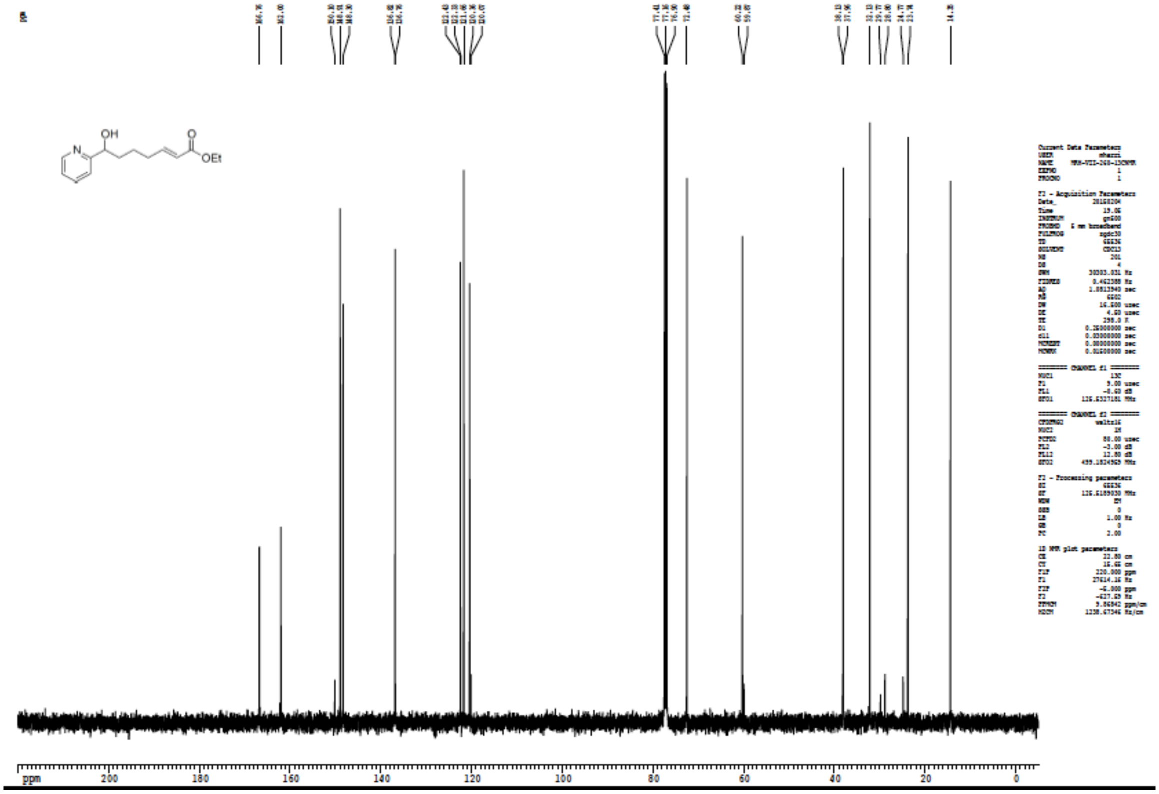
Z-restored spin-echo 13C spectrum with 1H decoupling



1H spectrum



13C spectrum with 1H decoupling



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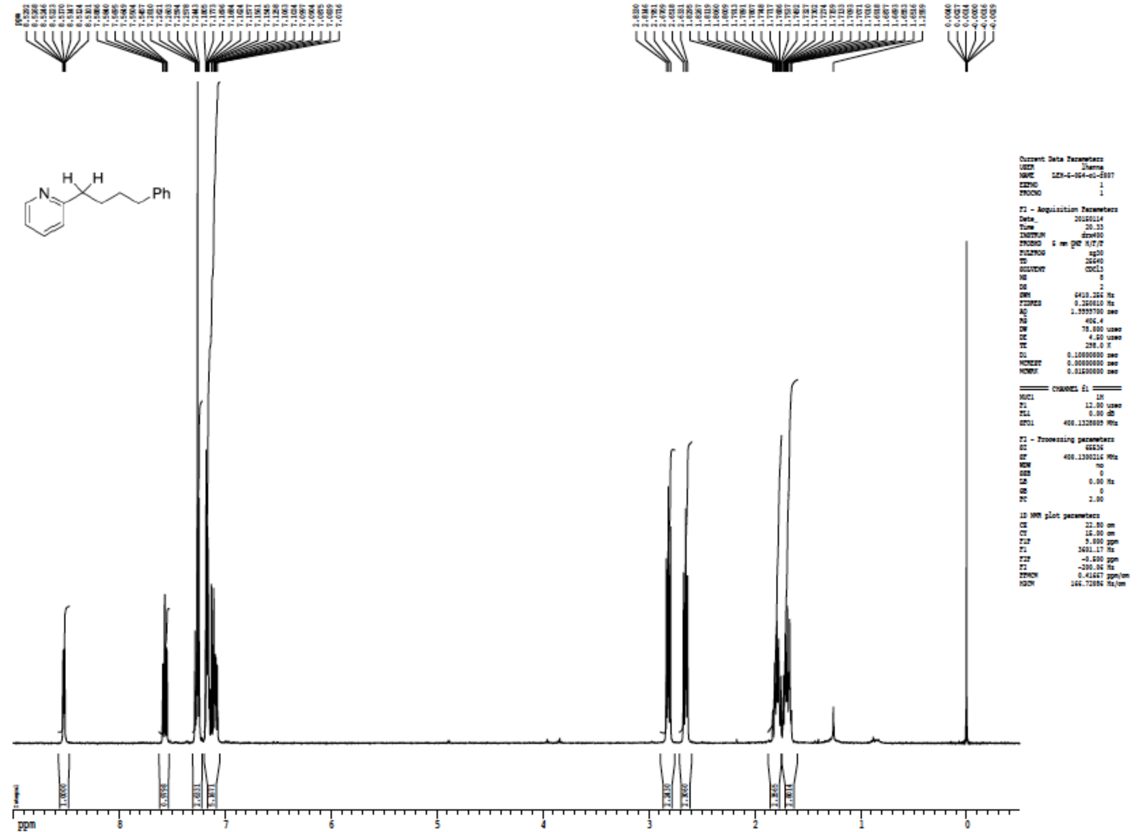
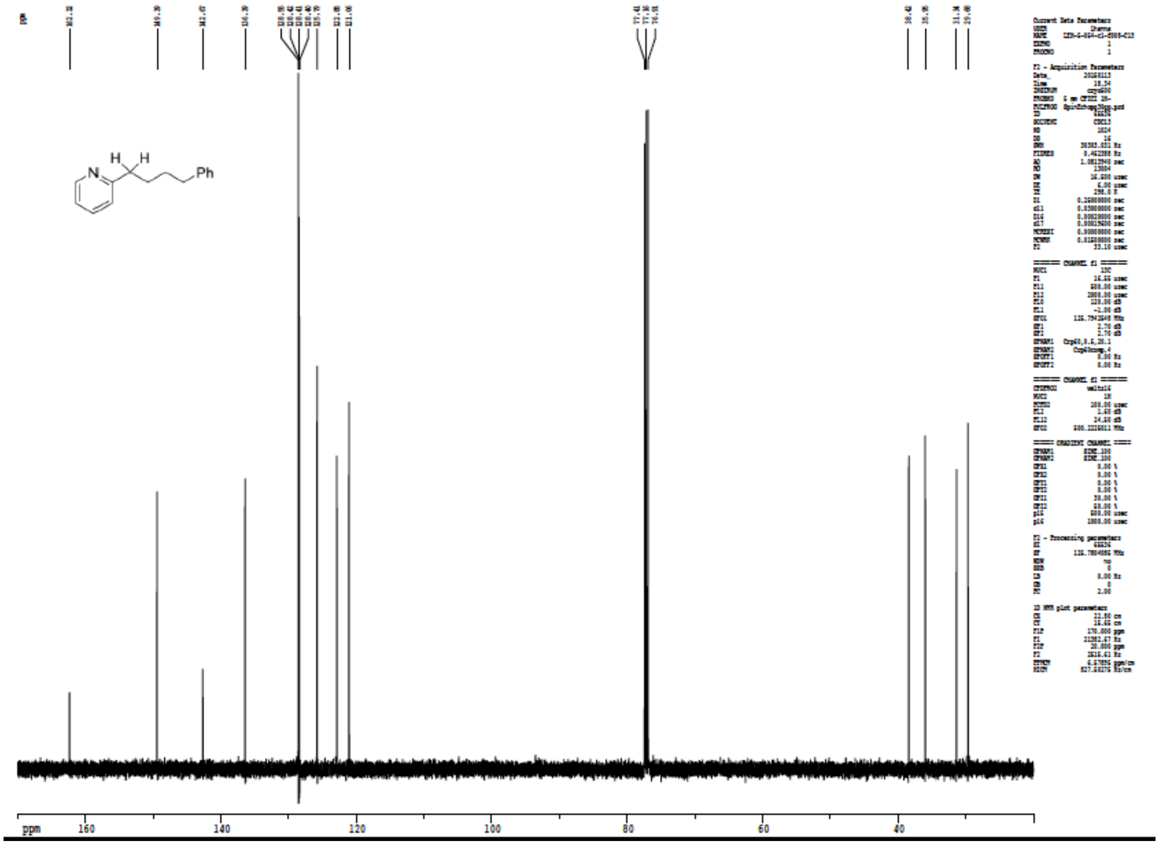
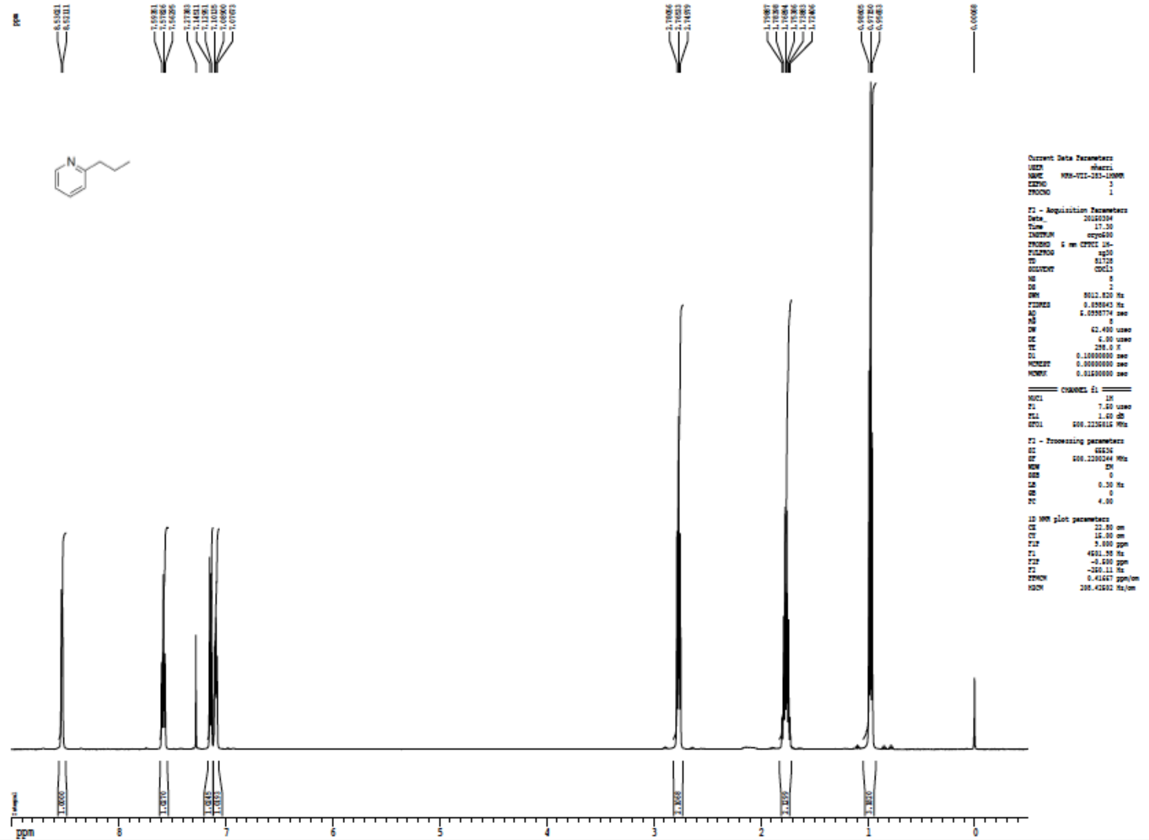


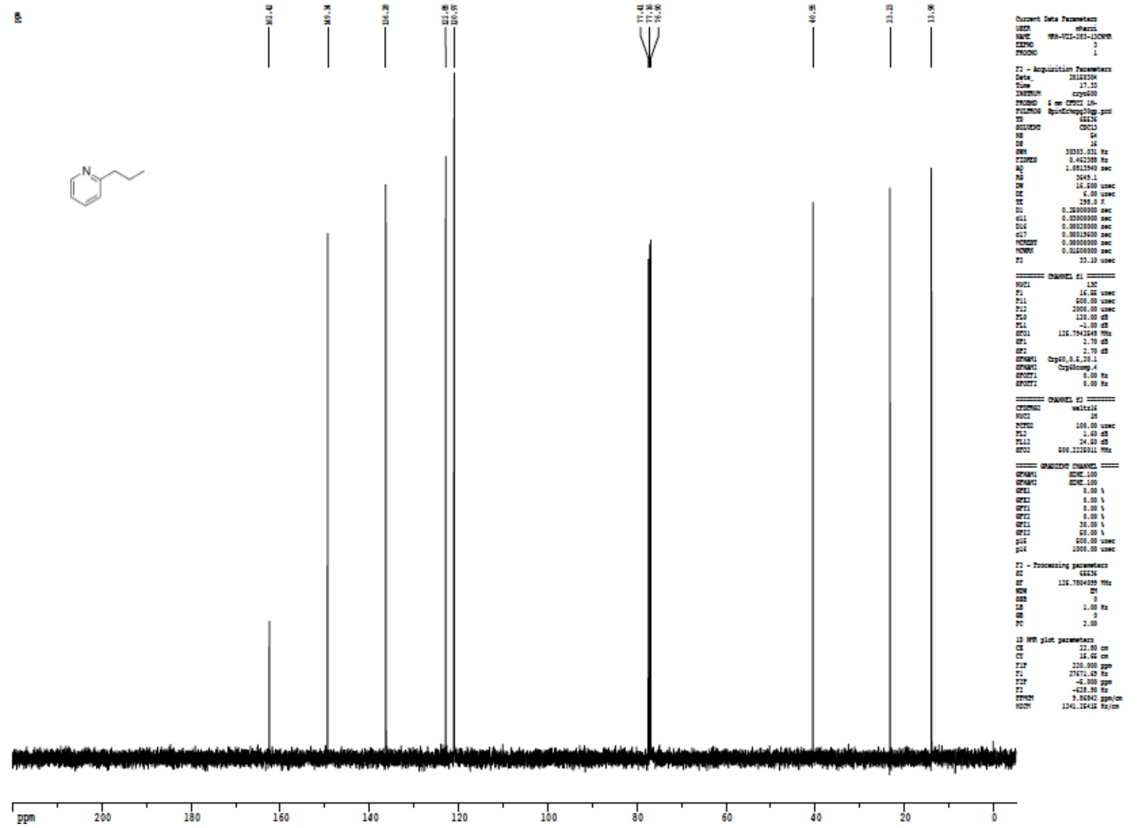
Z-restored spin-echo 13C spectrum with 1H decoupling



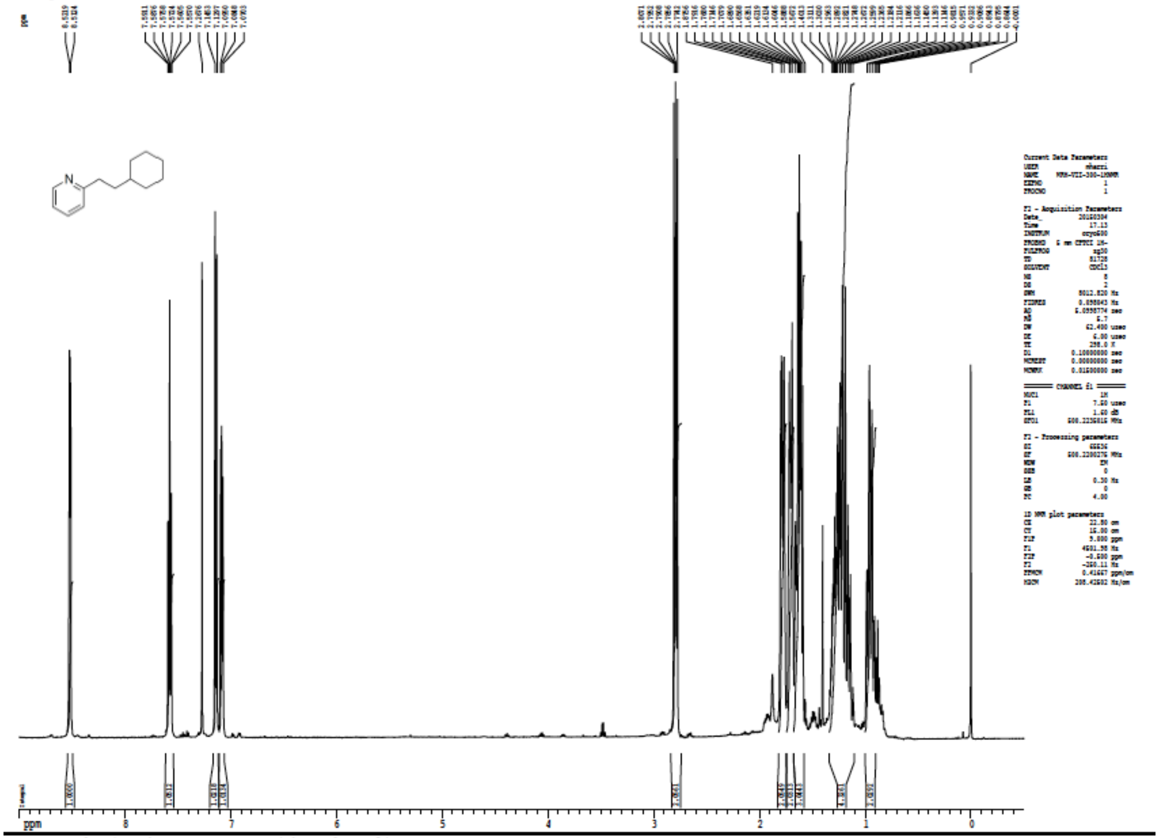
1H spectrum



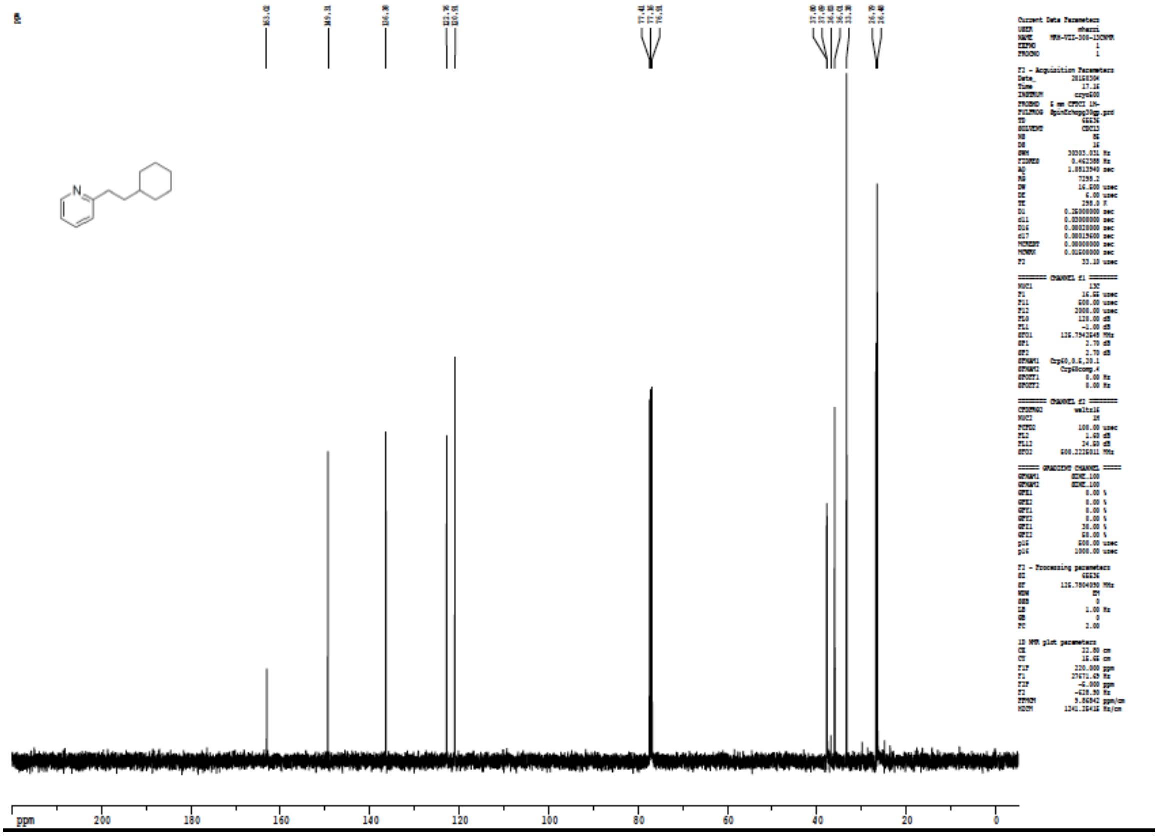
Z-restored spin-echo 13C spectrum with 1H decoupling



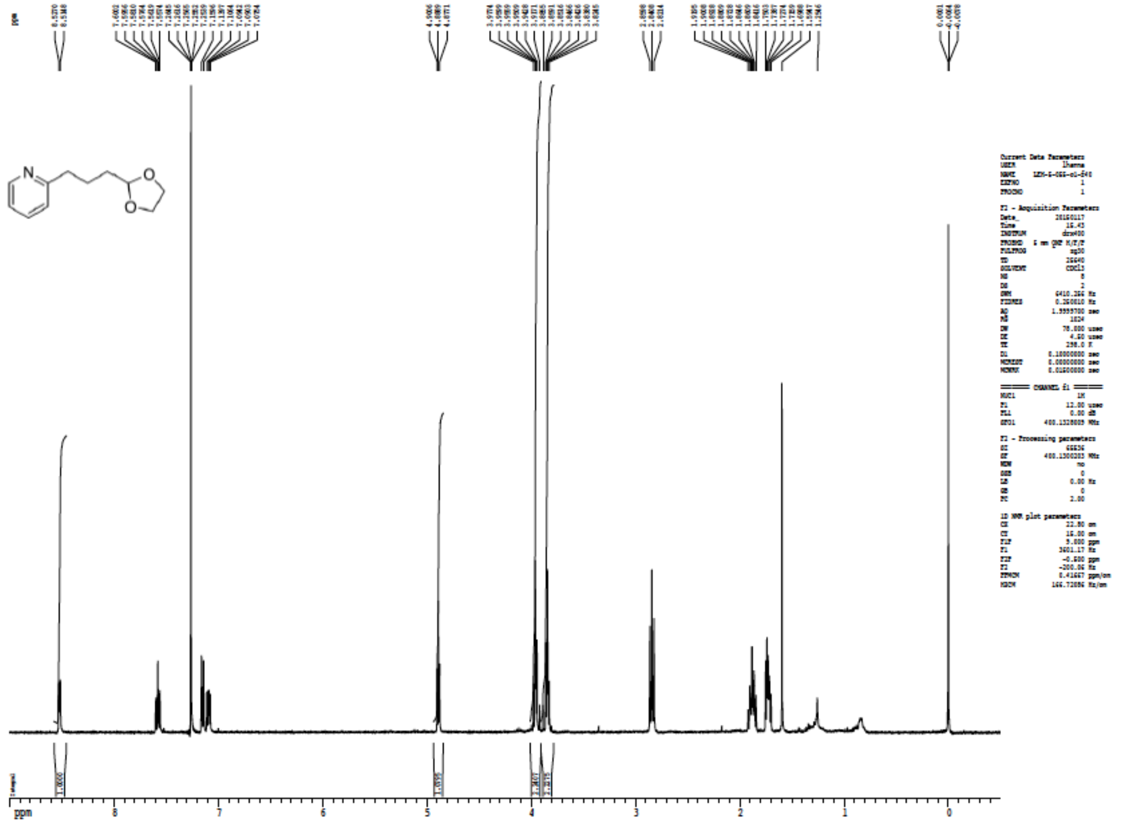
1H spectrum



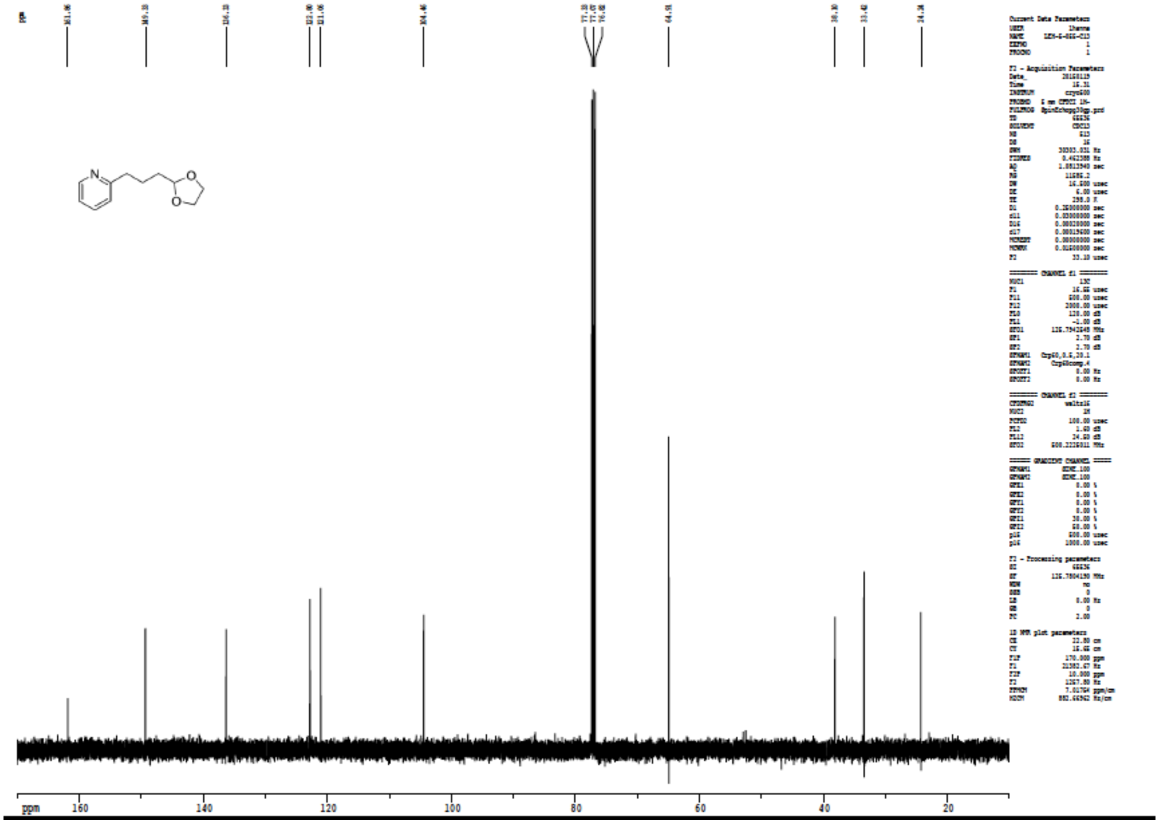
Z-restored spin-echo 13C spectrum with 1H decoupling



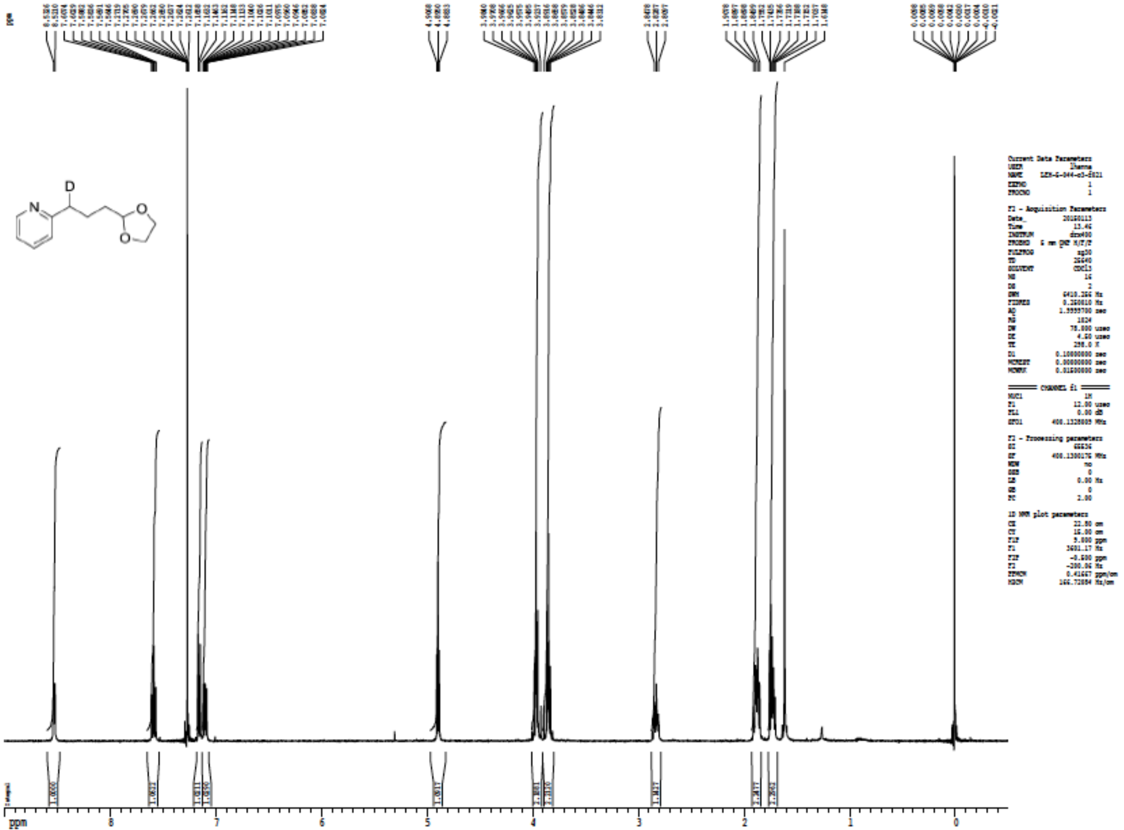
1H spectrum



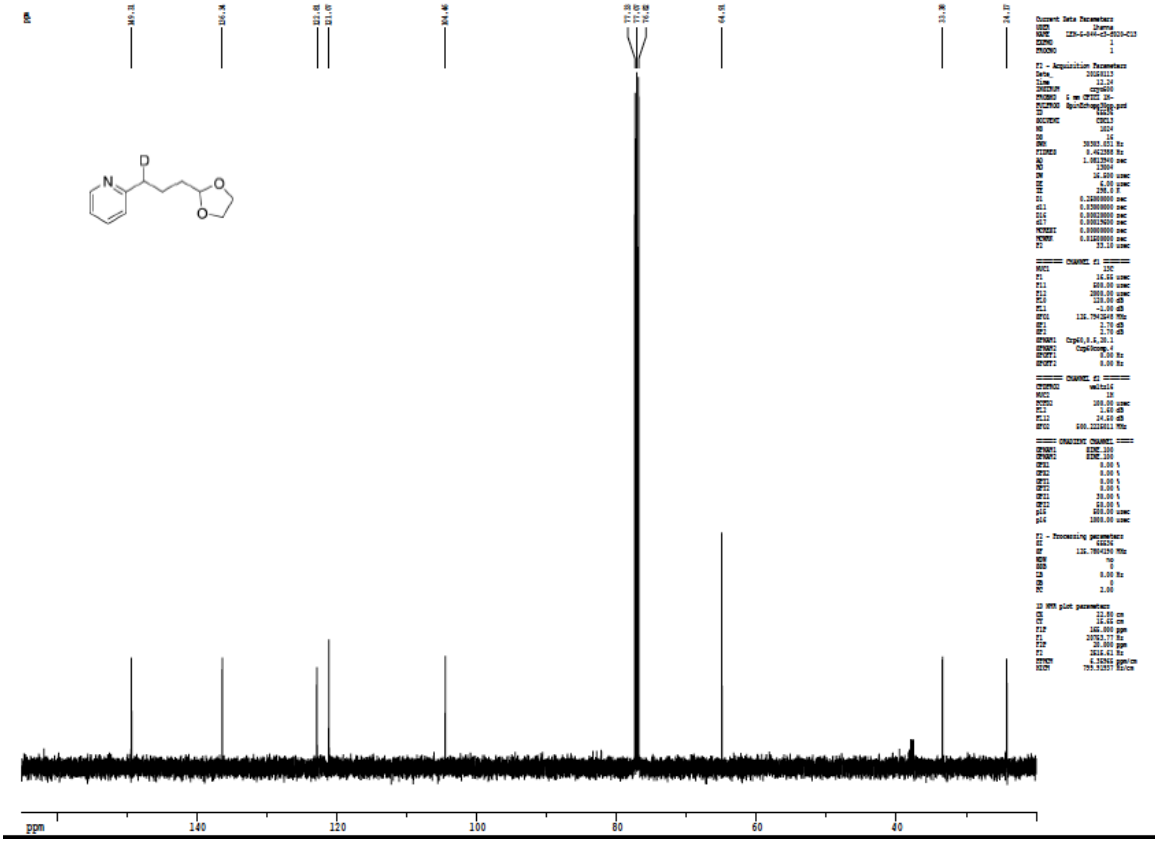
Z-restored spin-echo 13C spectrum with 1H decoupling



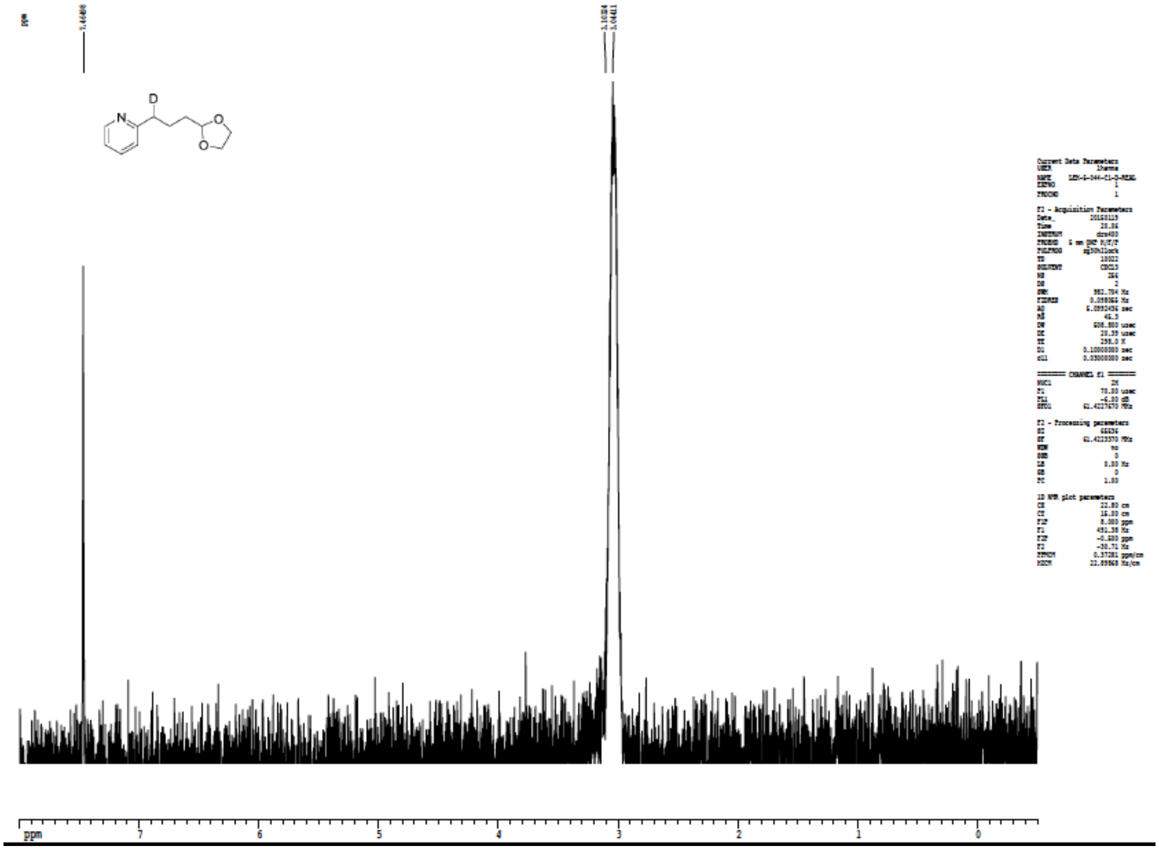
1H spectrum



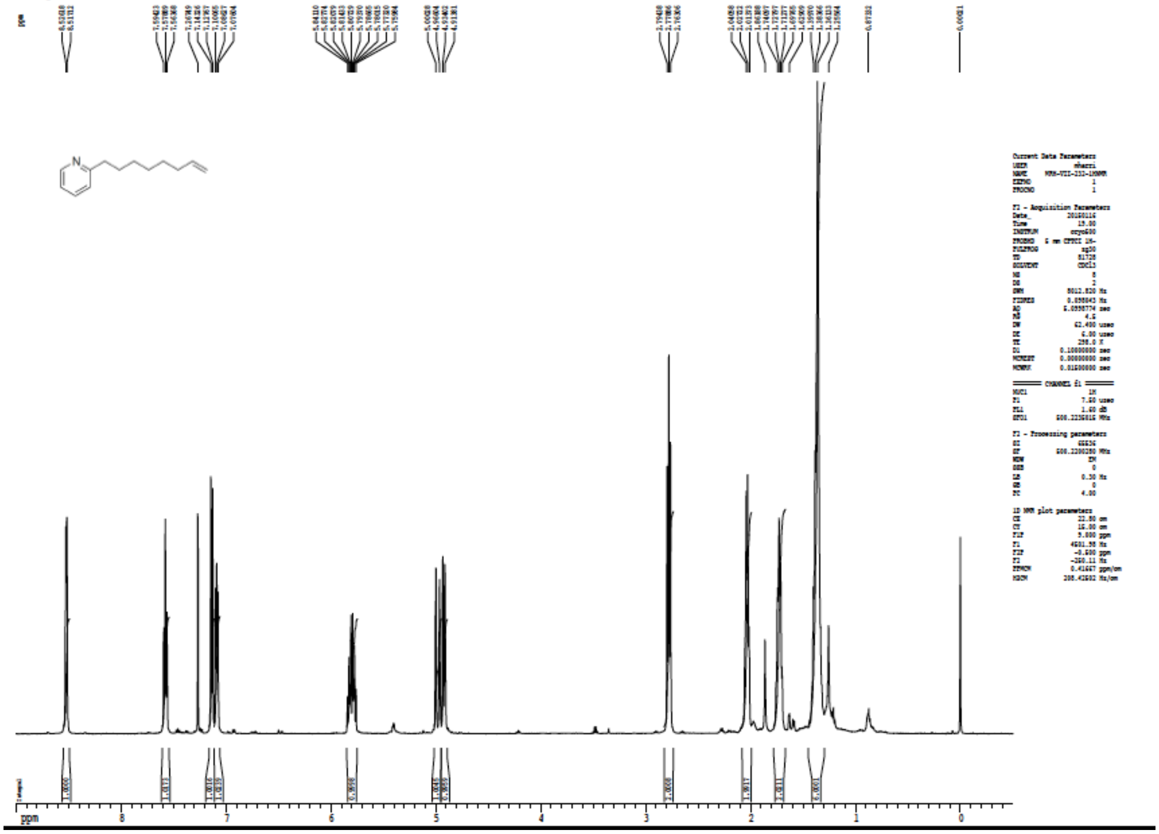
Z-restored spin-echo 13C spectrum with 1H decoupling

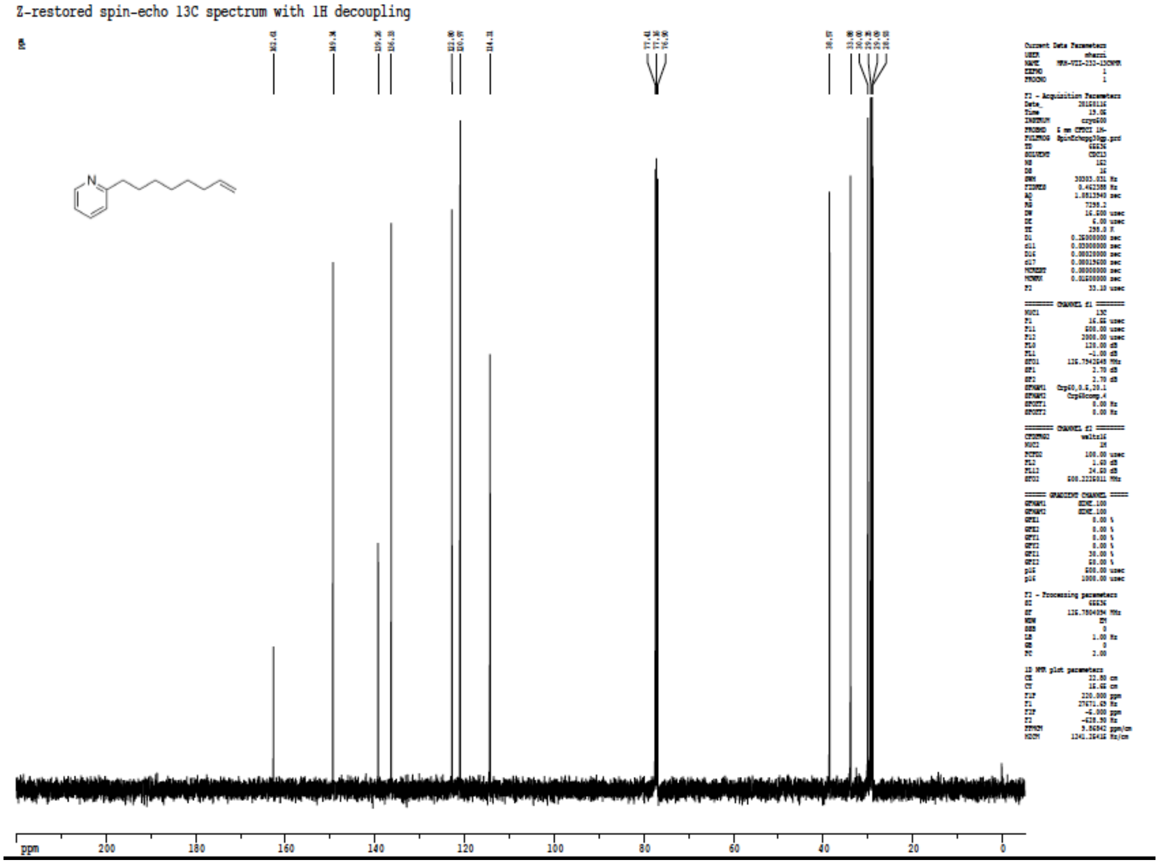


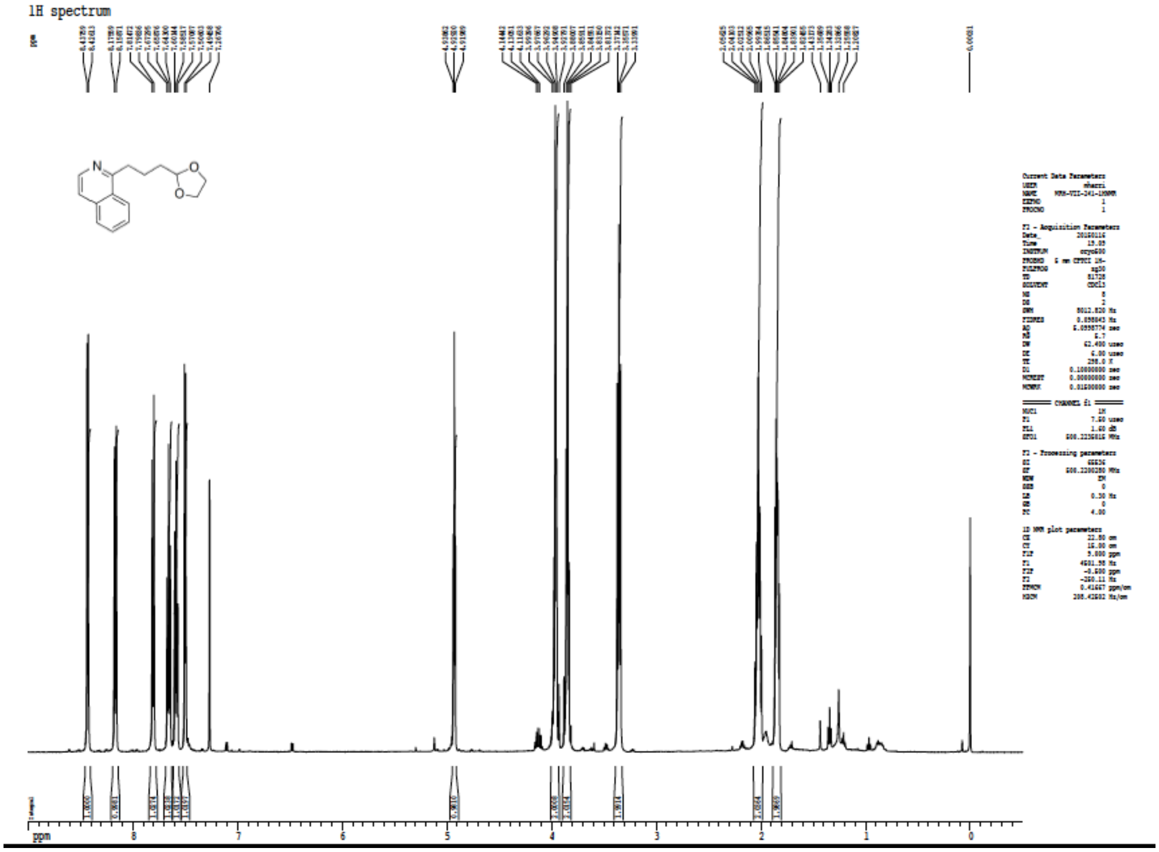
2H spectrum (measure via lock channel without changing any cables)



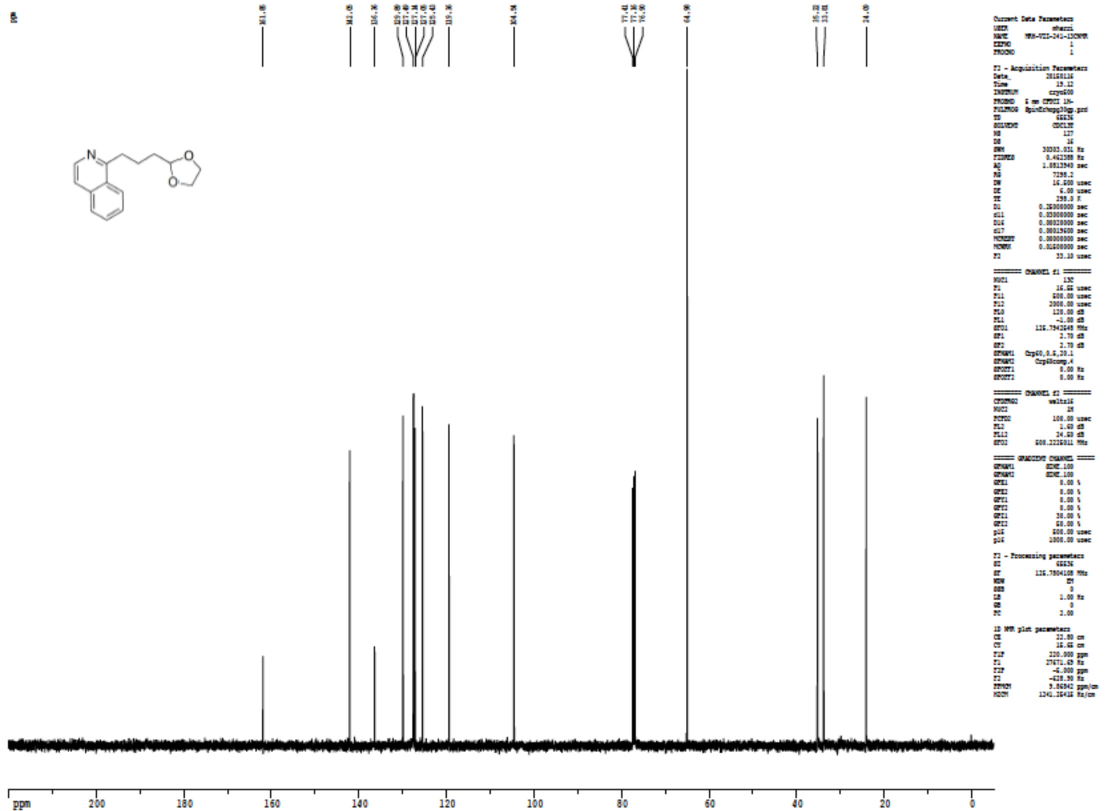
1H spectrum



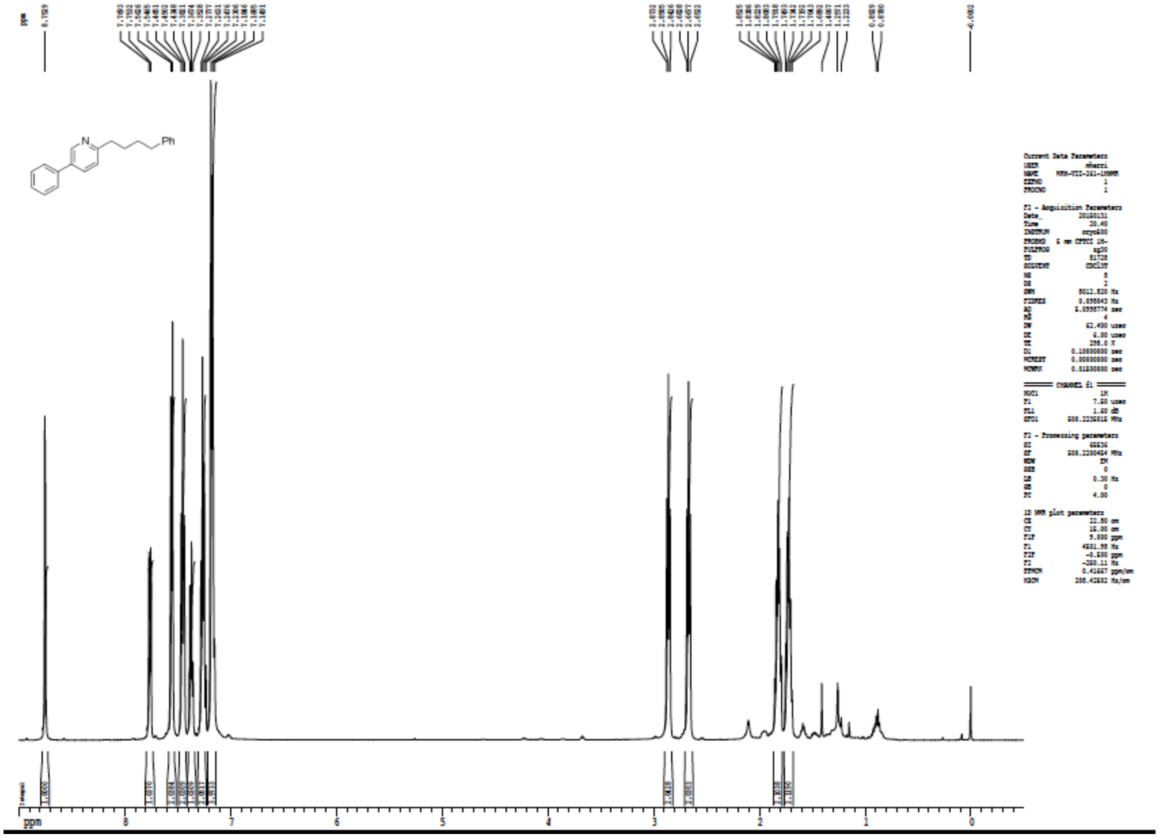

Z-restored spin-echo 13C spectrum with 1H decoupling


1H spectrum

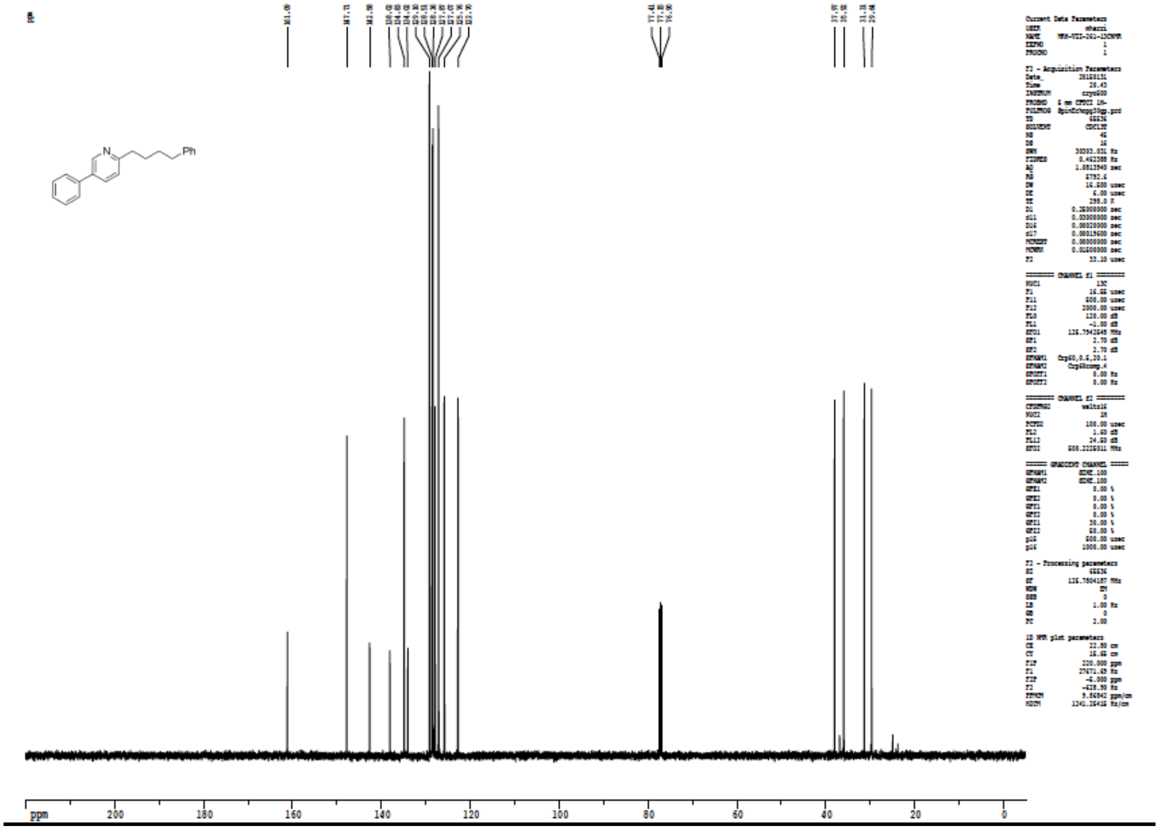
Z-restored spin-echo 13C spectrum with 1H decoupling



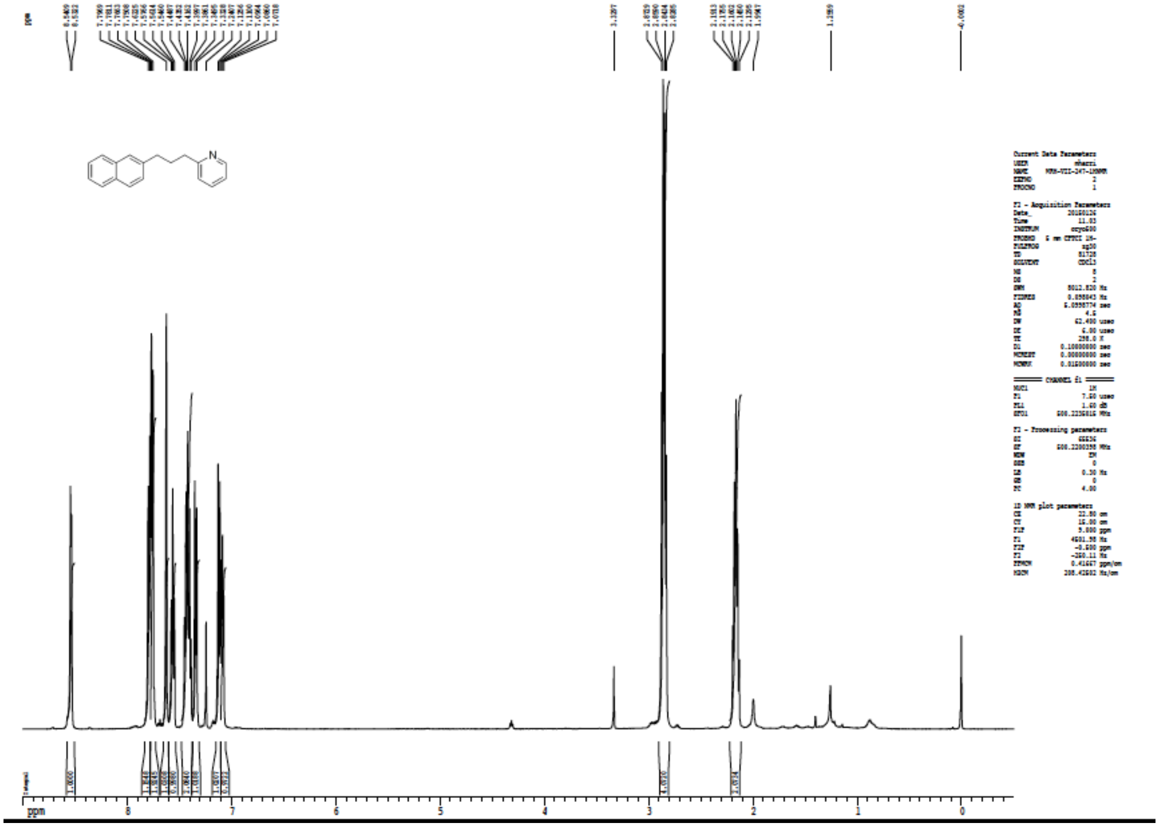
1H spectrum



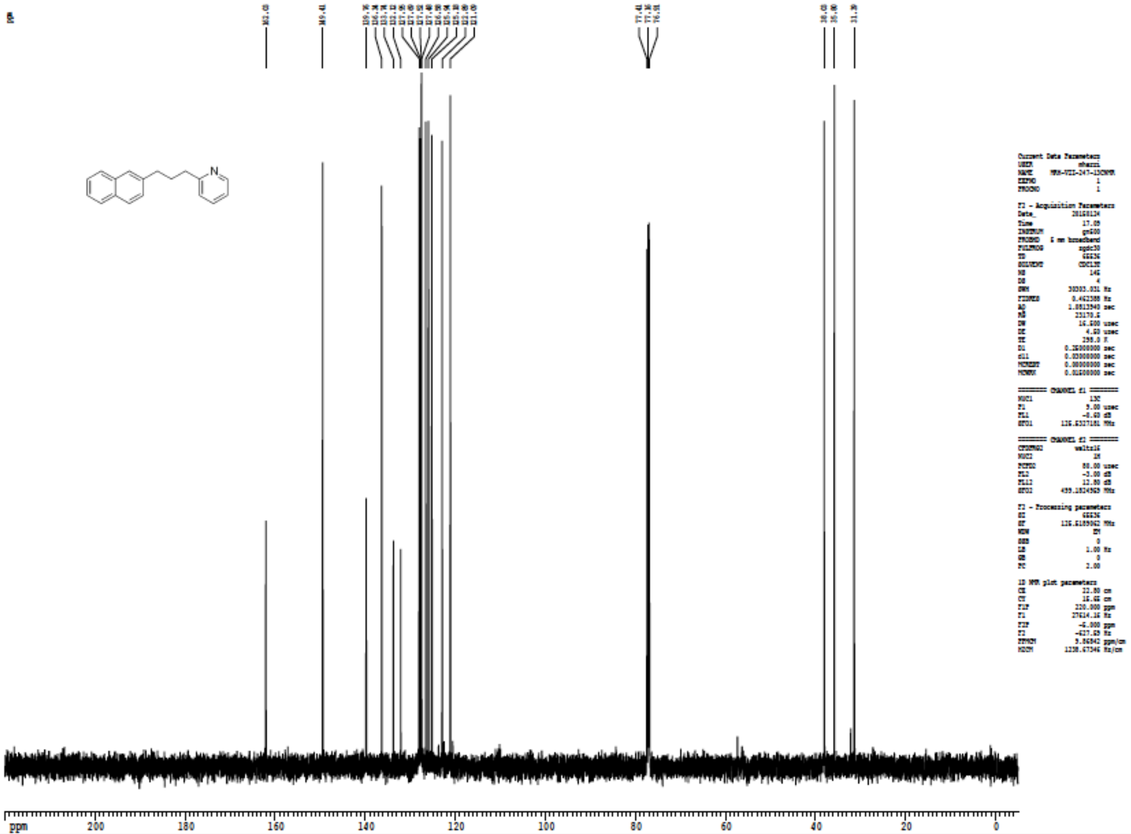
Z-restored spin-echo 13C spectrum with 1H decoupling



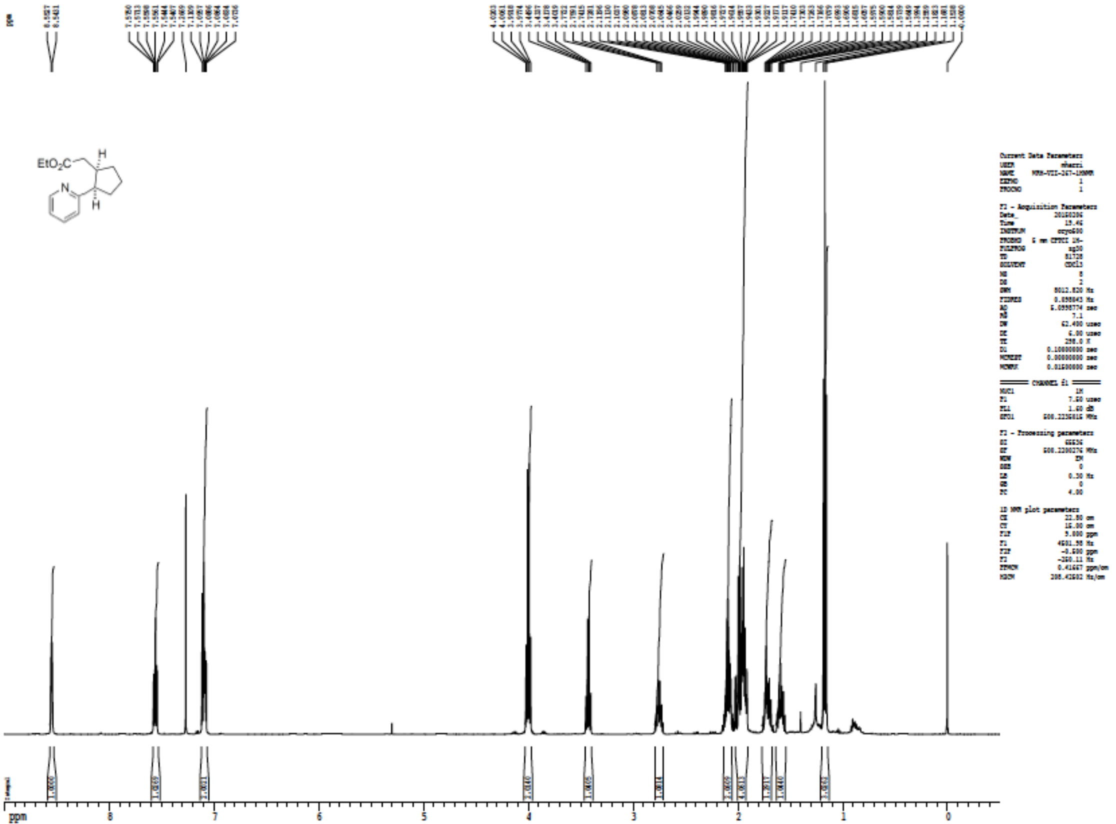
1H spectrum



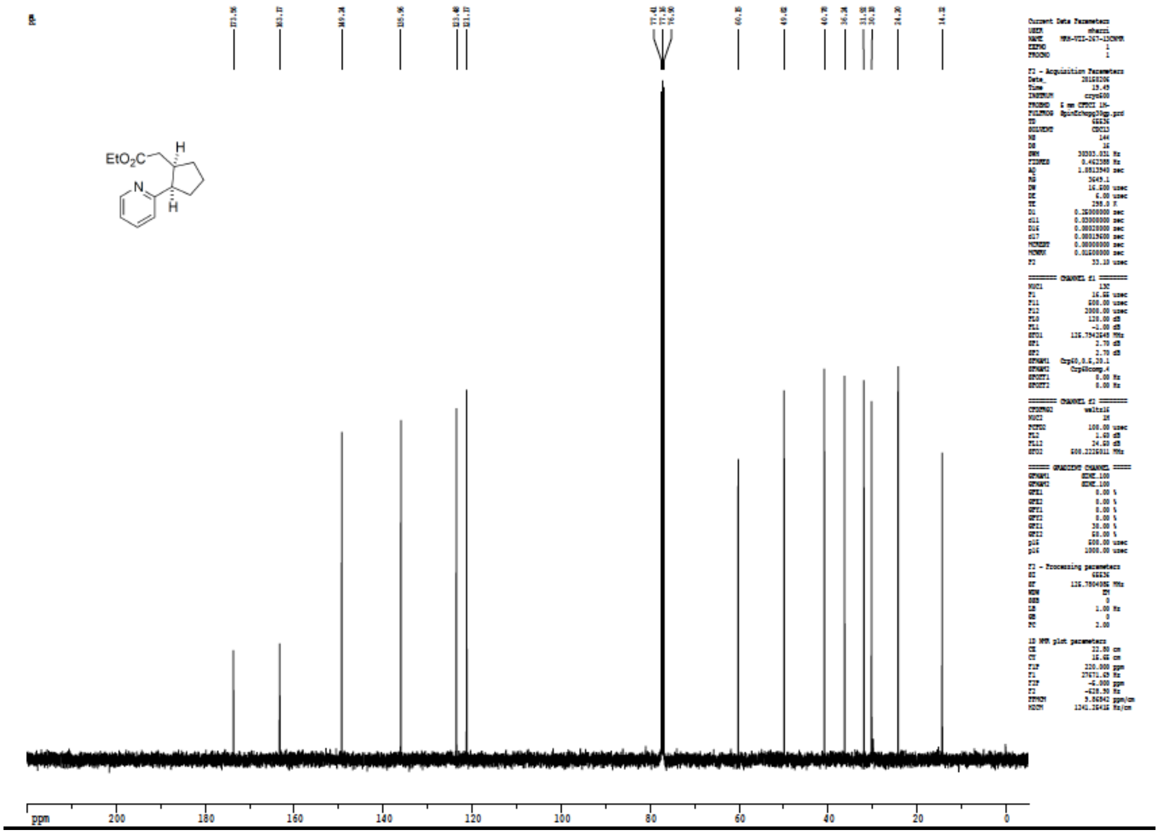
13C spectrum with 1H decoupling



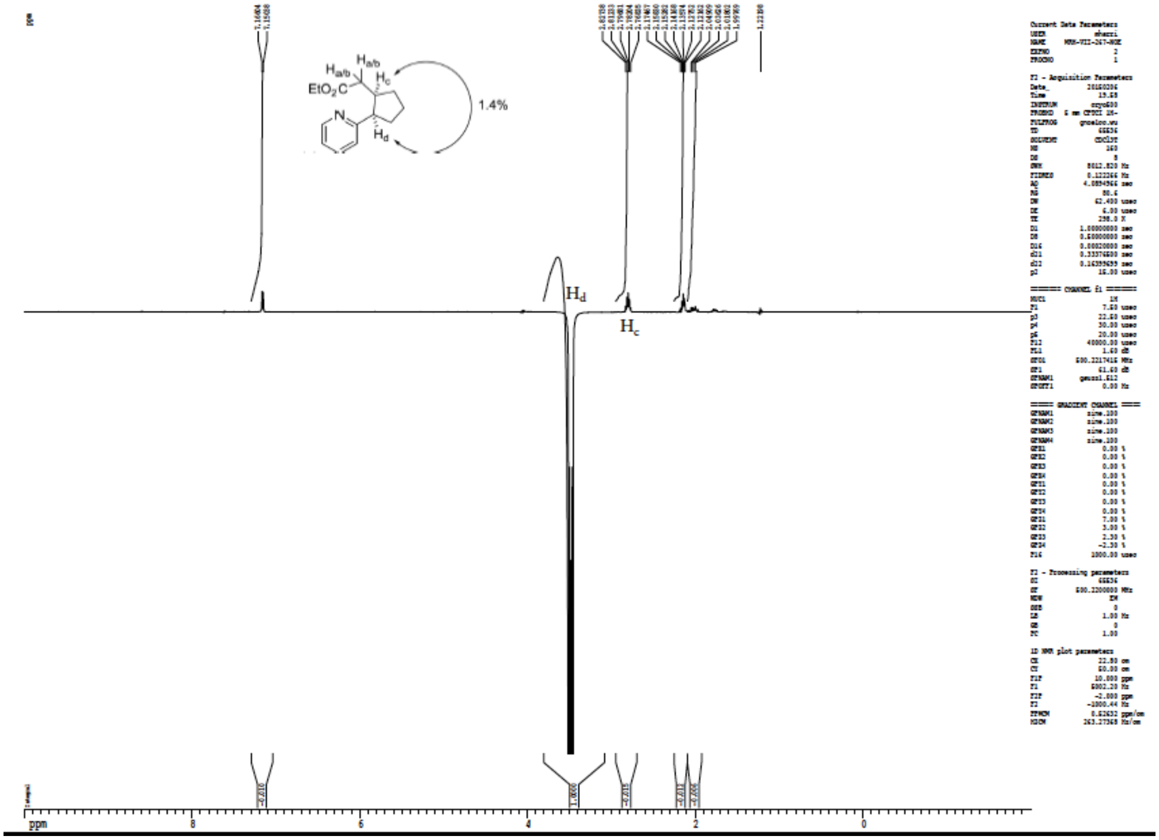
1H spectrum

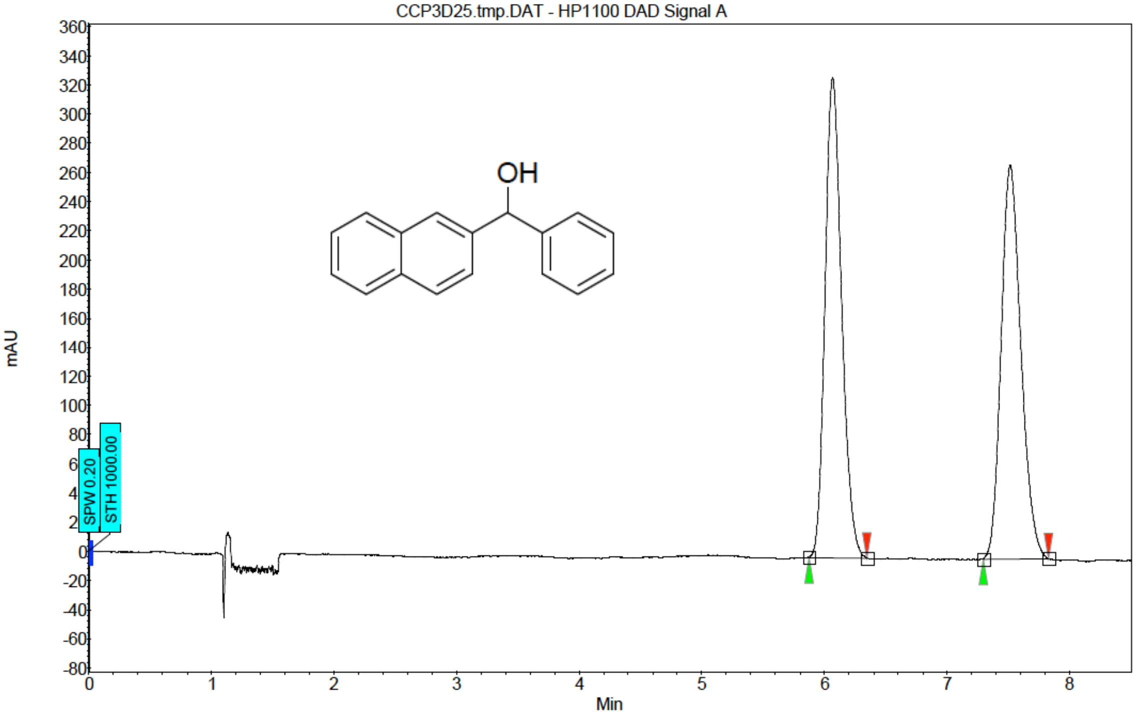


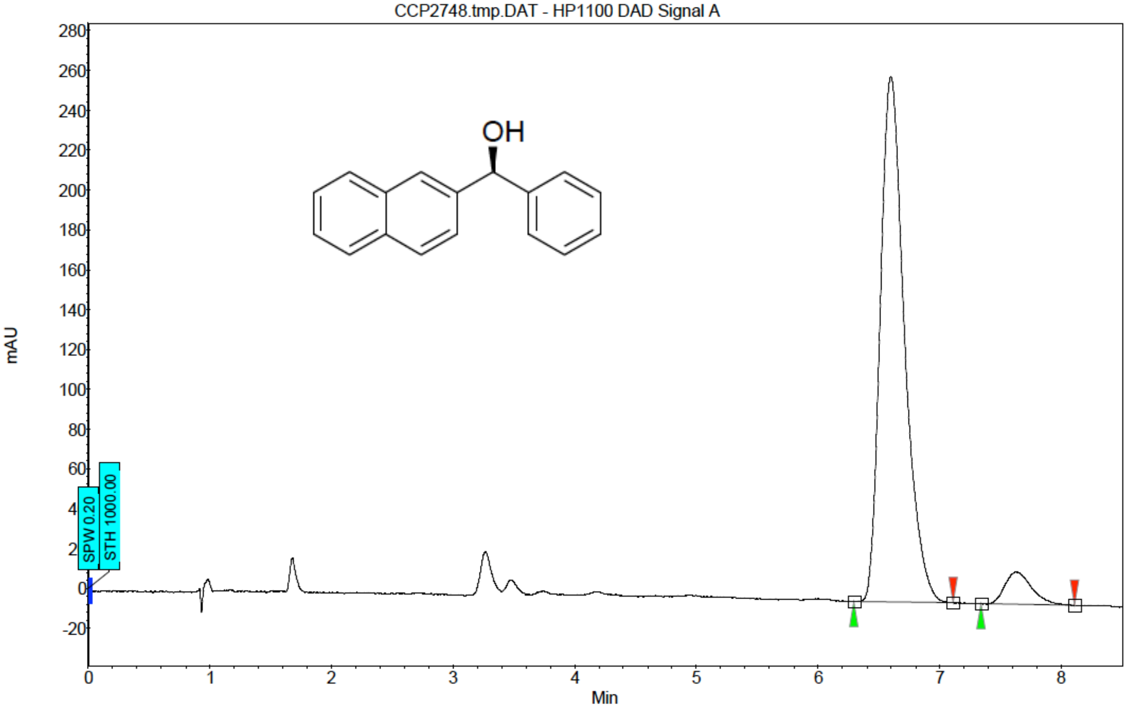
Z-restored spin-echo 13C spectrum with 1H decoupling



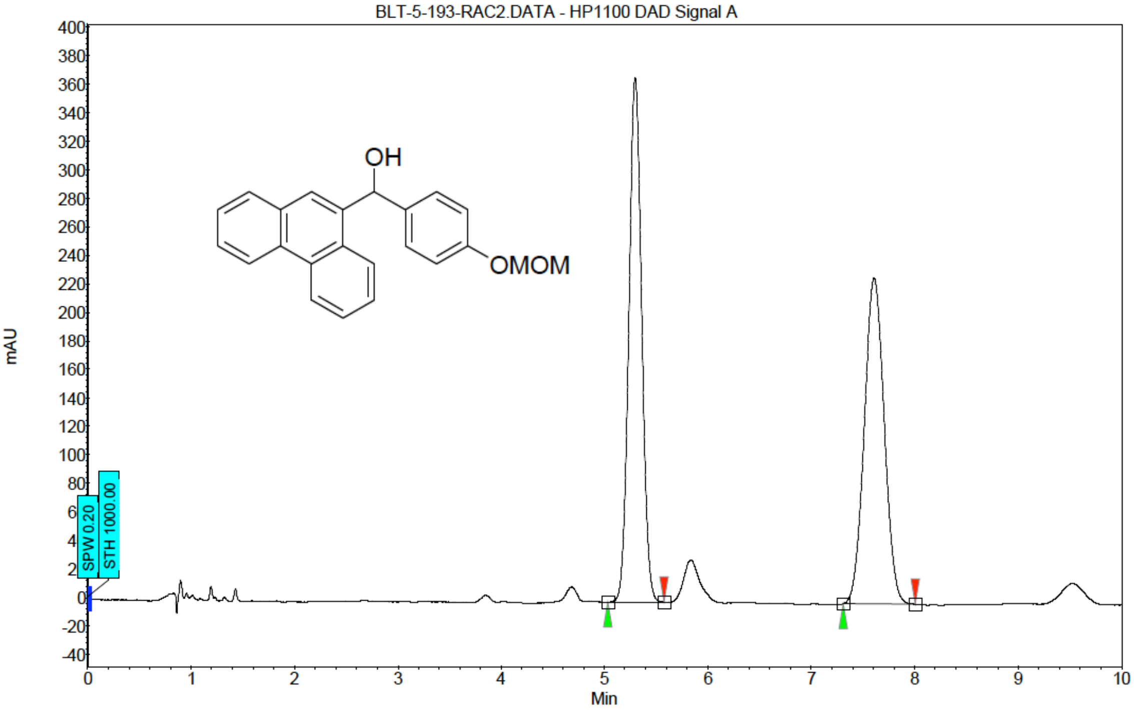
gnoe

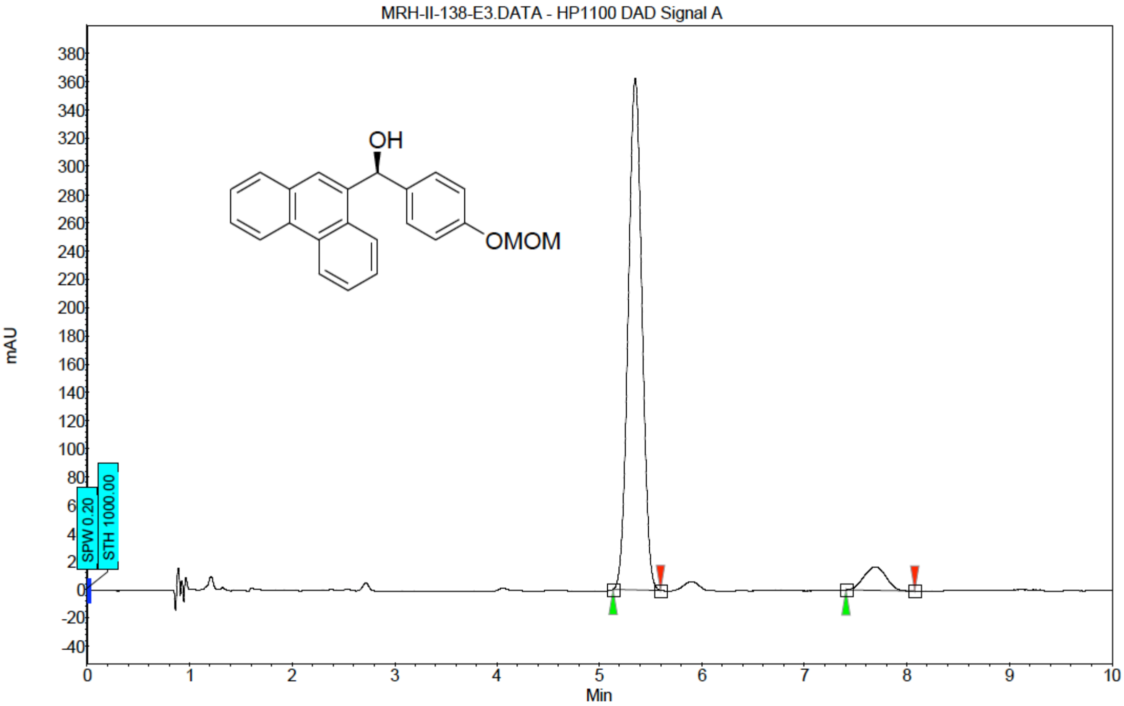




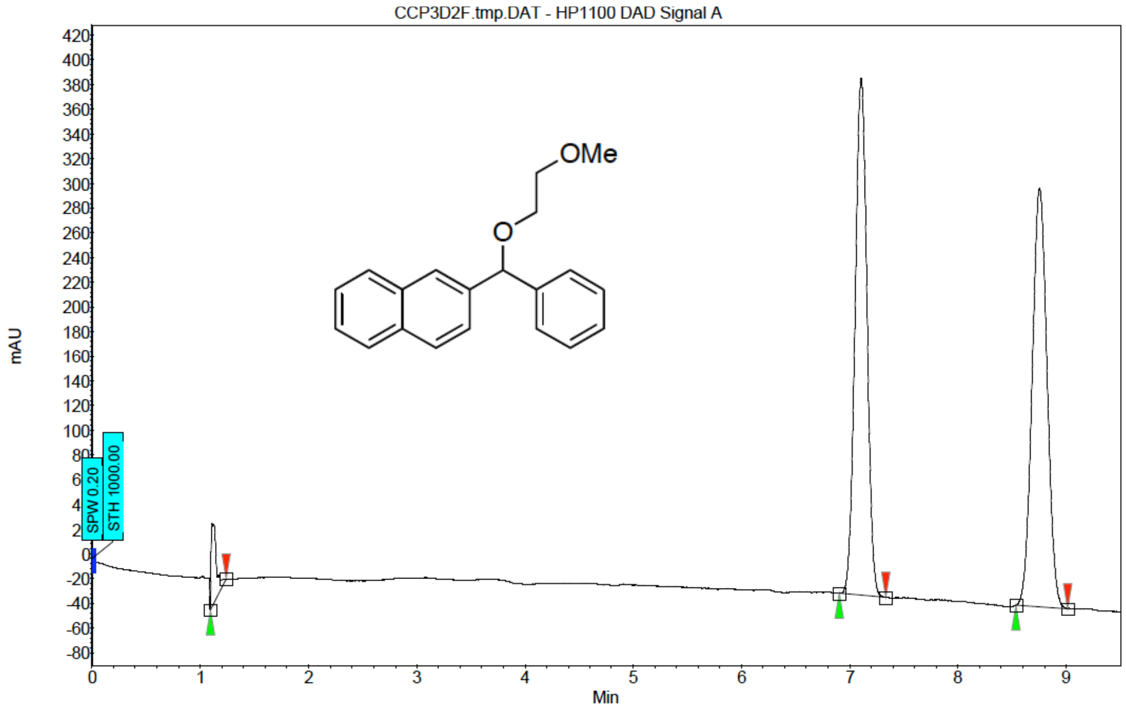


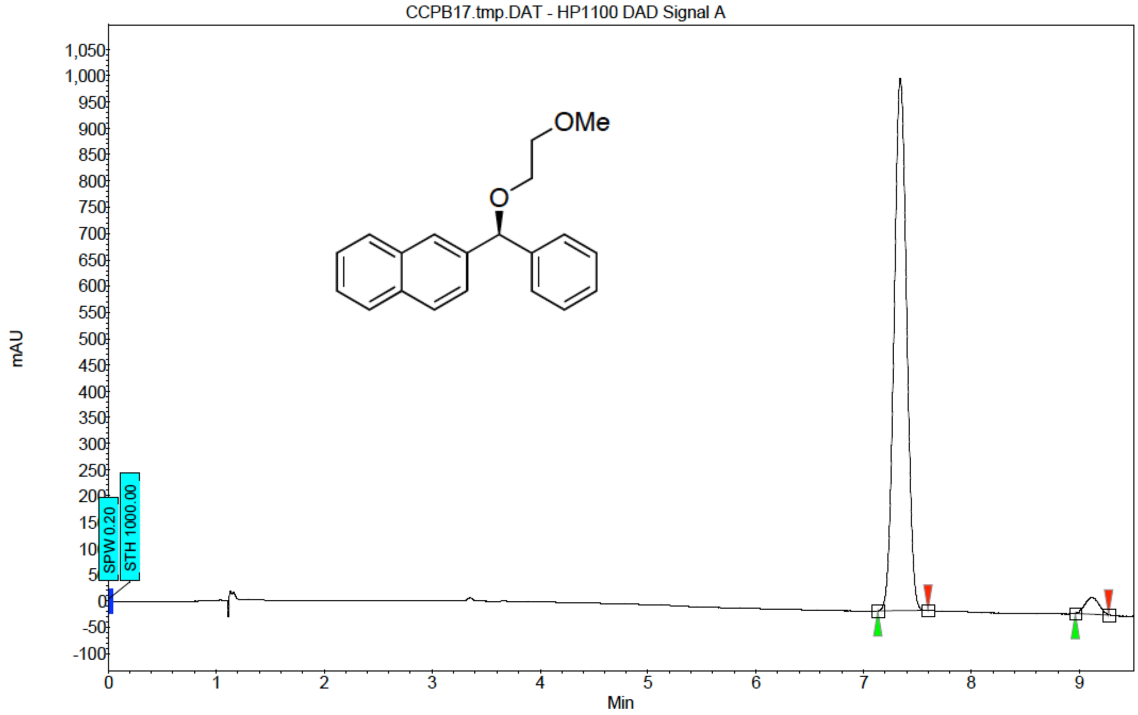
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 6.29 | 6.60 | 7.11 | 0.00 | 93.48 | 263.5 | 60.1 | 93.478 |
| 2 | UNKNOWN | 7.34 | 7.63 | 8.11 | 0.00 | 6.52 | 16.2 | 4.2 | 6.522 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 279.7 | 64.3 | 100.000 |



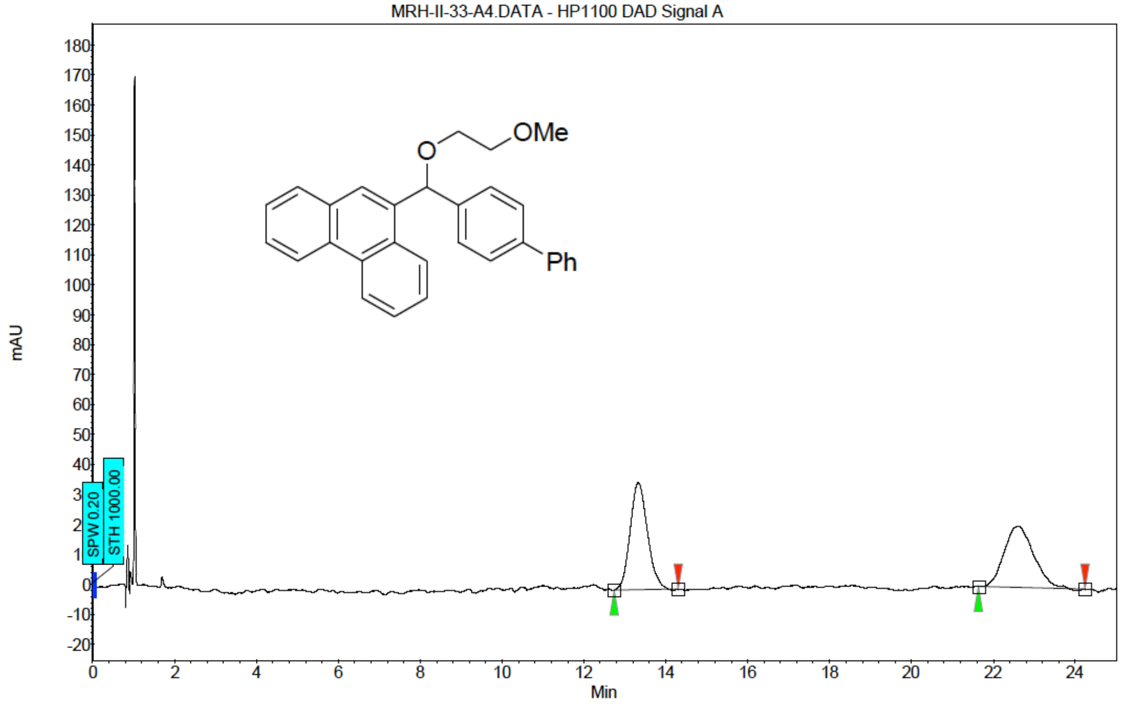


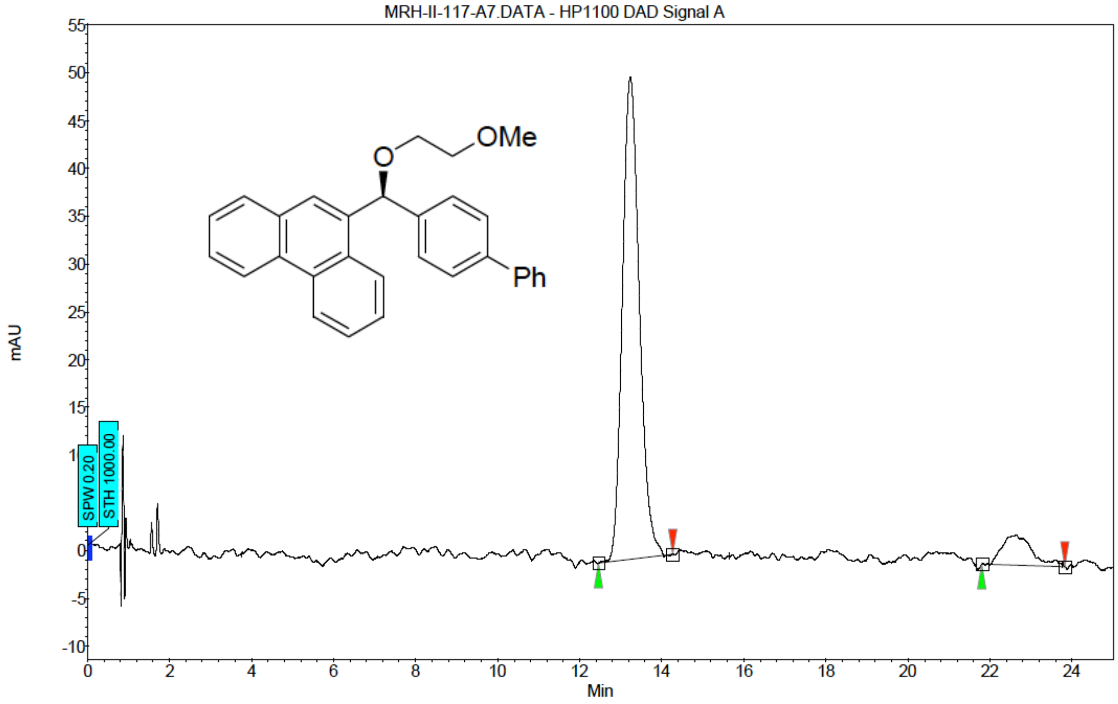
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 5.13 | 5.35 | 5.60 | 0.00 | 93.18 | 362.4 | 56.0 | 93.178 |
| 2 | UNKNOWN | 7.41 | 7.70 | 8.08 | 0.00 | 6.82 | 16.5 | 4.1 | 6.822 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 378.9 | 60.1 | 100.000 |



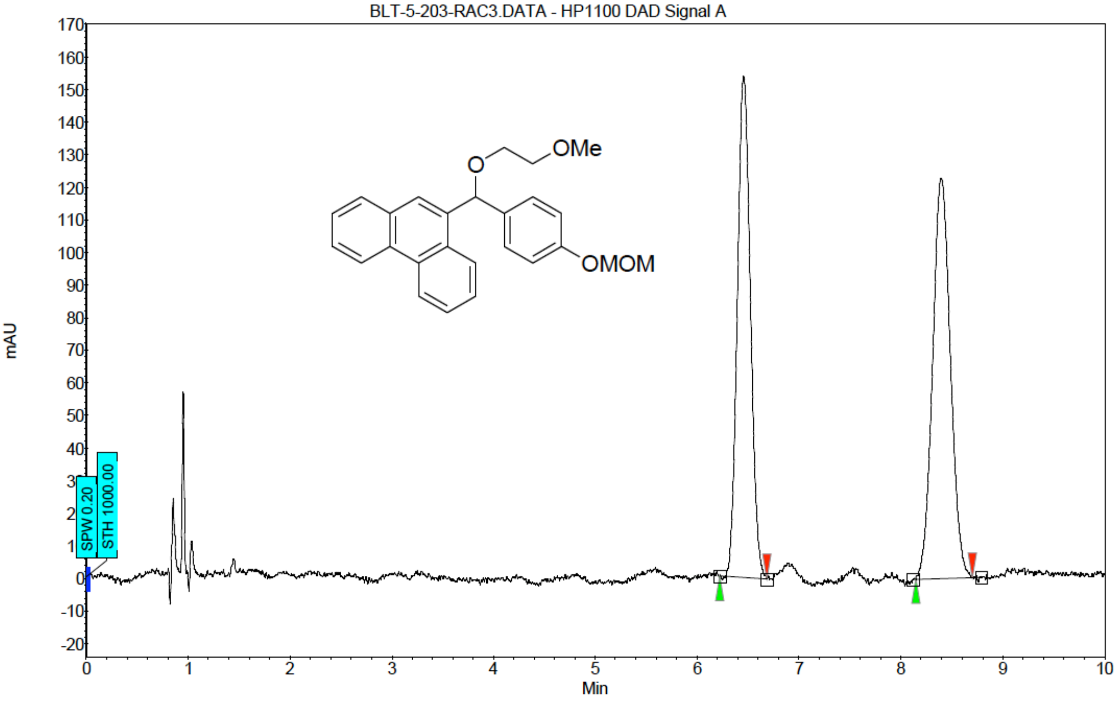


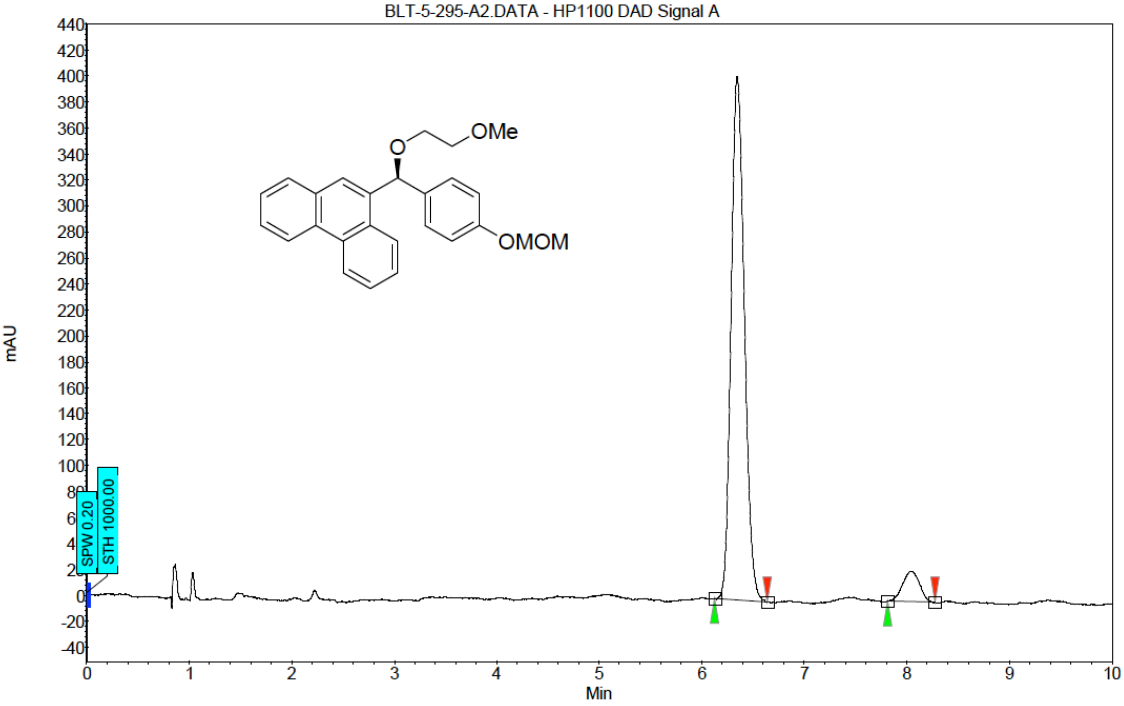
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 7.13 | 7.34 | 7.60 | 0.00 | 96.55 | 1012.7 | 136.1 | 96.550 |
| 2 | UNKNOWN | 8.96 | 9.12 | 9.27 | 0.00 | 3.45 | 32.3 | 4.9 | 3.450 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 1045.0 | 140.9 | 100.000 |



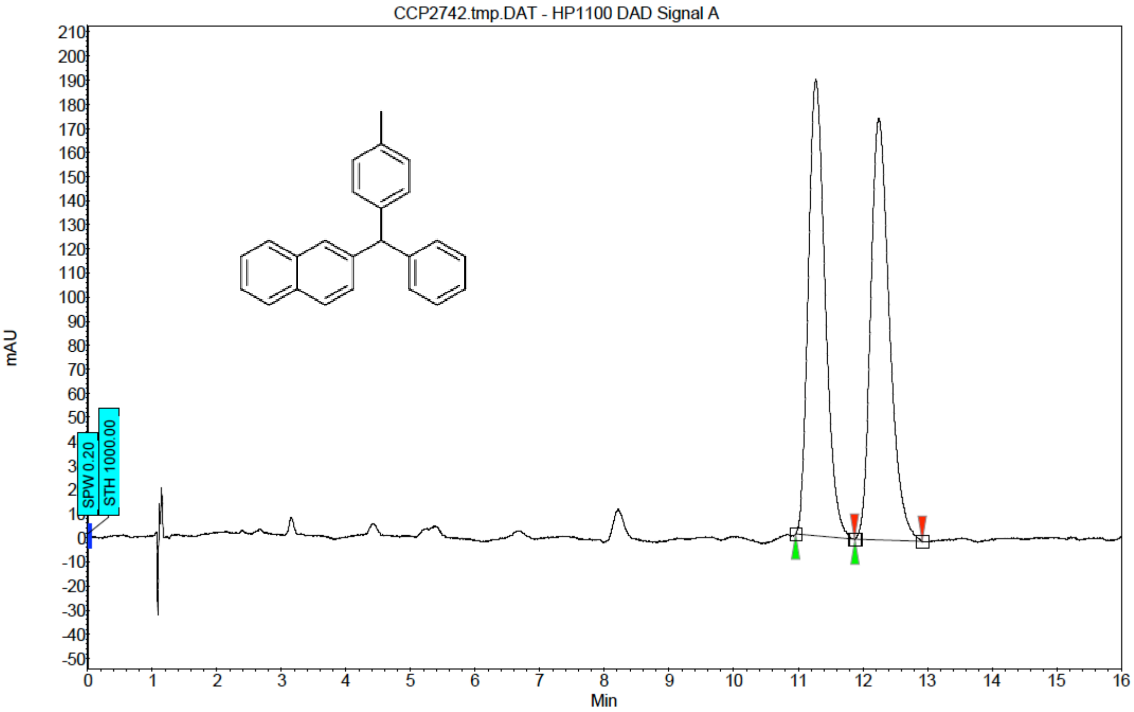


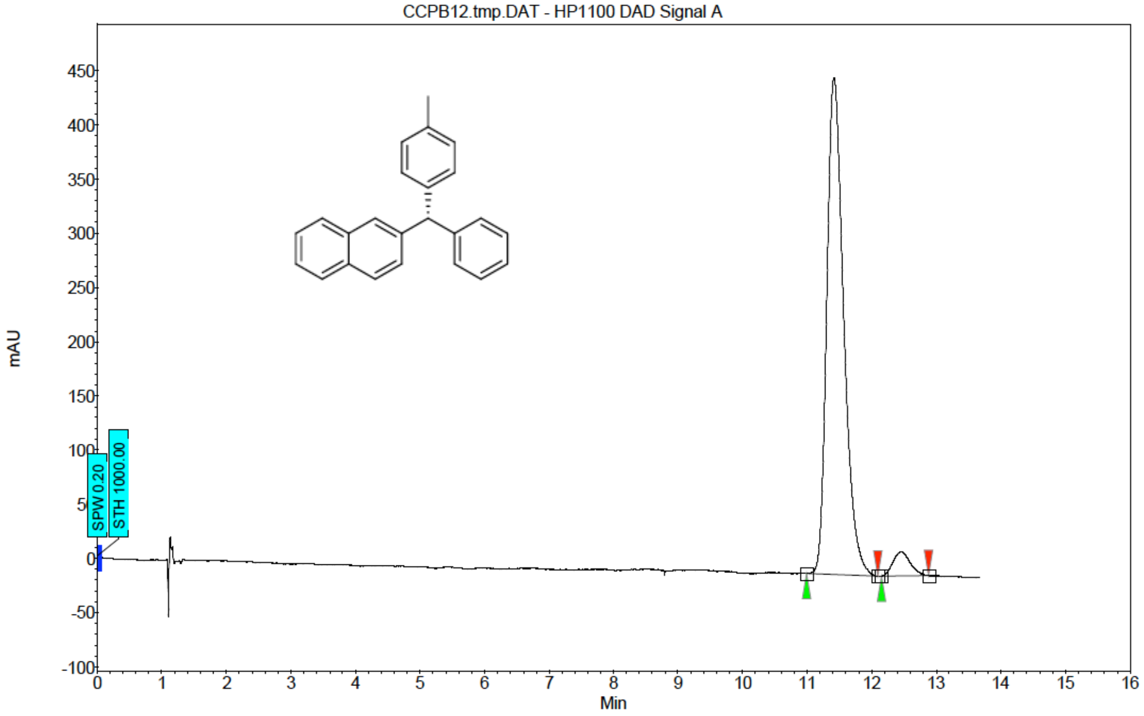
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 12.47 | 13.24 | 14.28 | 0.00 | 90.10 | 50.4 | 23.9 | 90.098 |
| 2 | UNKNOWN | 21.81 | 22.64 | 23.82 | 0.00 | 9.90 | 3.2 | 2.6 | 9.902 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 53.6 | 26.6 | 100.000 |



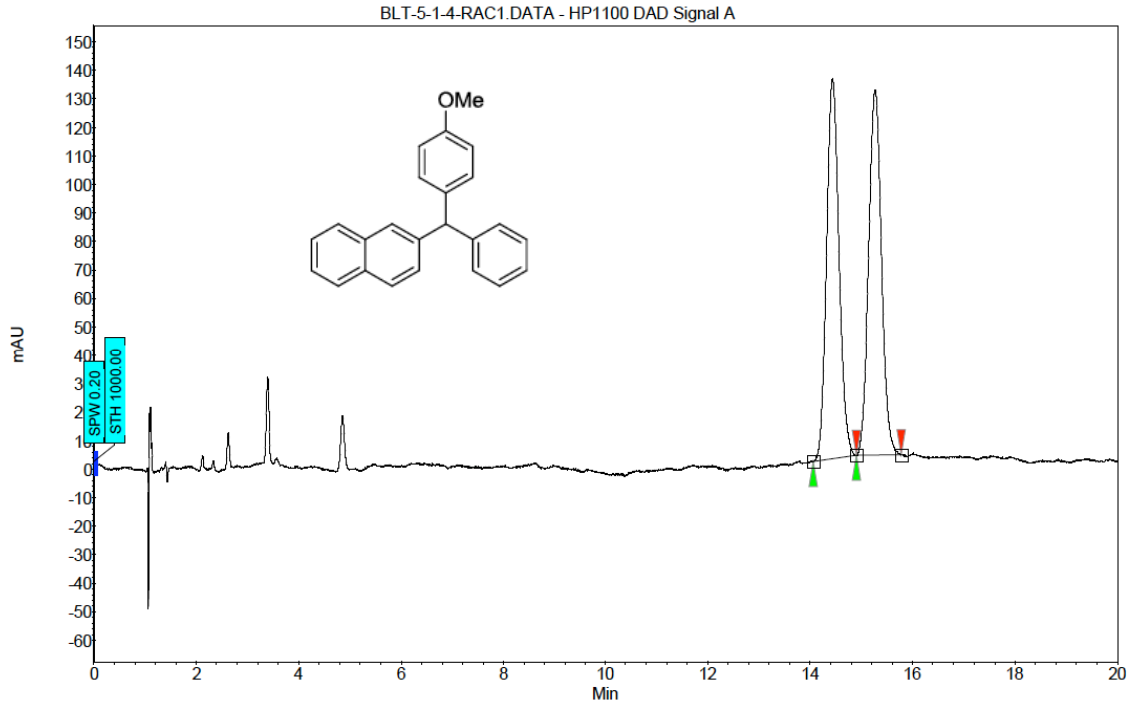


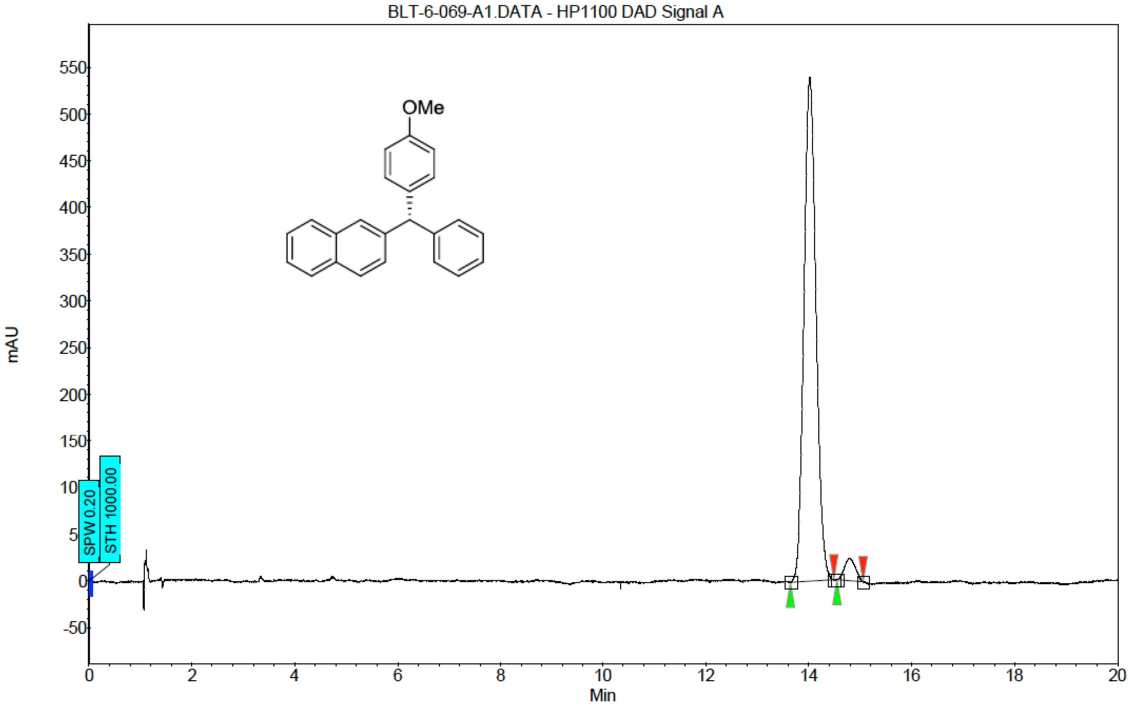
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 6.13 | 6.35 | 6.64 | 0.00 | 93.12 | 402.9 | 60.3 | 93.125 |
| 2 | UNKNOWN | 7.81 | 8.05 | 8.27 | 0.00 | 6.88 | 23.4 | 4.5 | 6.875 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 426.3 | 64.8 | 100.000 |



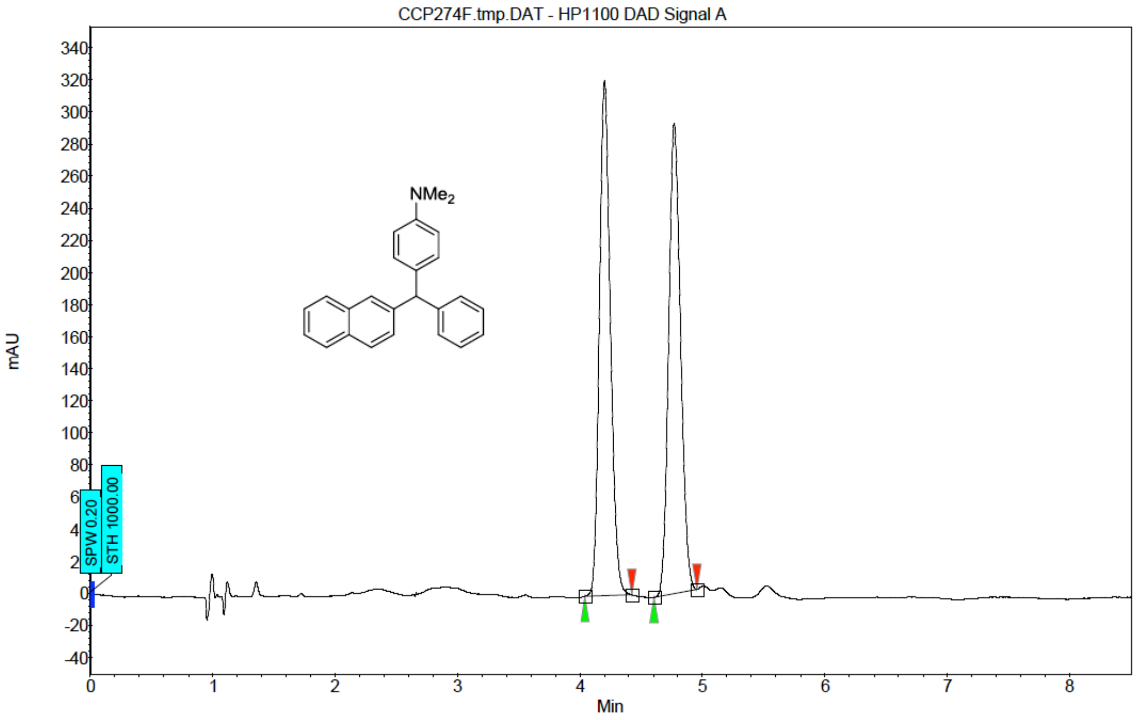


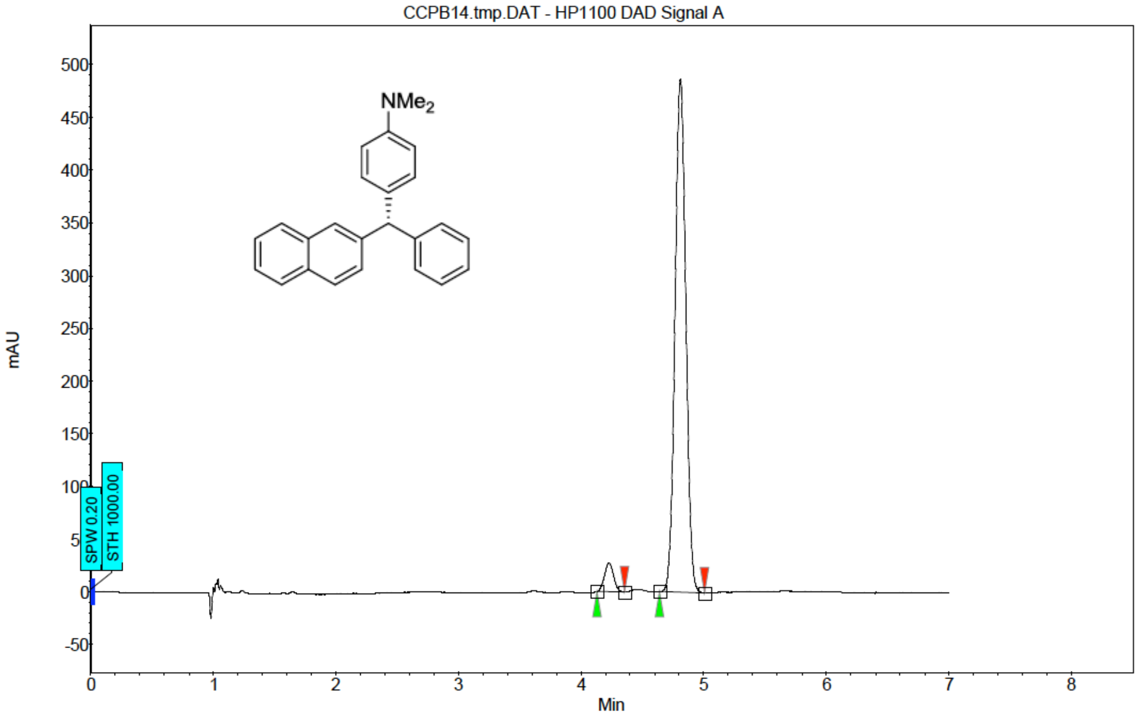
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 10.99 | 11.42 | 12.10 | 0.00 | 95.38 | 458.0 | 137.6 | 95.379 |
| 2 | UNKNOWN | 12.15 | 12.46 | 12.88 | 0.00 | 4.62 | 22.2 | 6.7 | 4.621 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 480.1 | 144.3 | 100.000 |



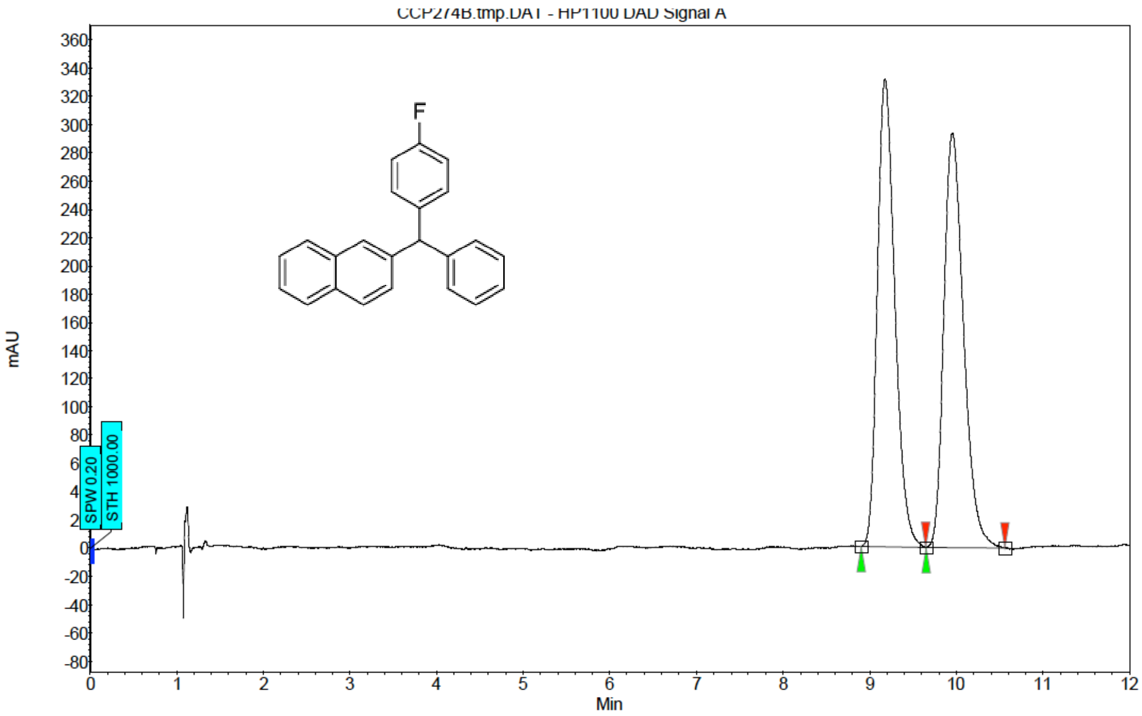


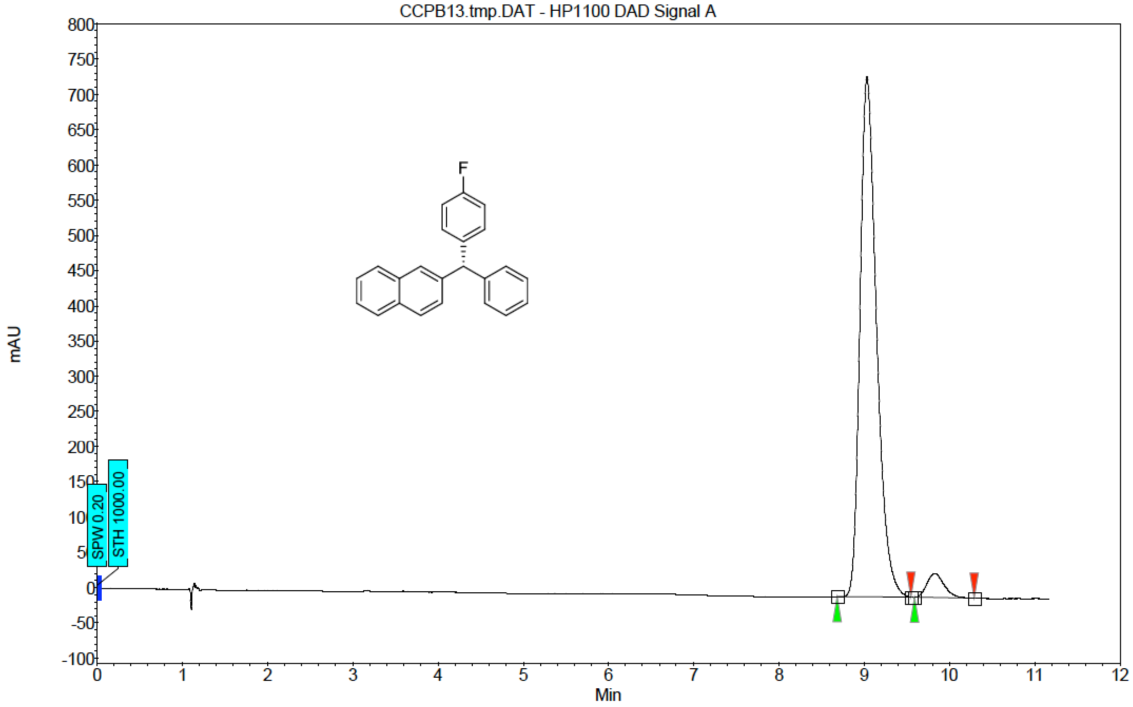
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 13.64 | 14.02 | 14.49 | 0.00 | 96.14 | 539.6 | 146.4 | 96.135 |
| 2 | UNKNOWN | 14.55 | 14.79 | 15.05 | 0.00 | 3.86 | 24.2 | 5.9 | 3.865 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 563.8 | 152.3 | 100.000 |



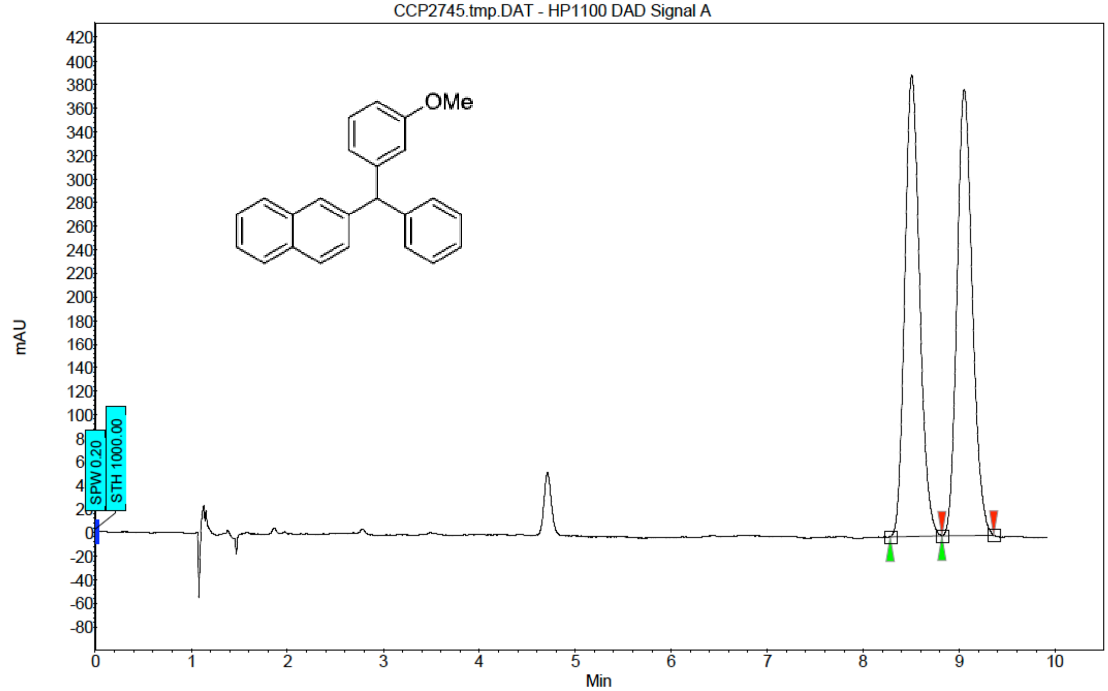


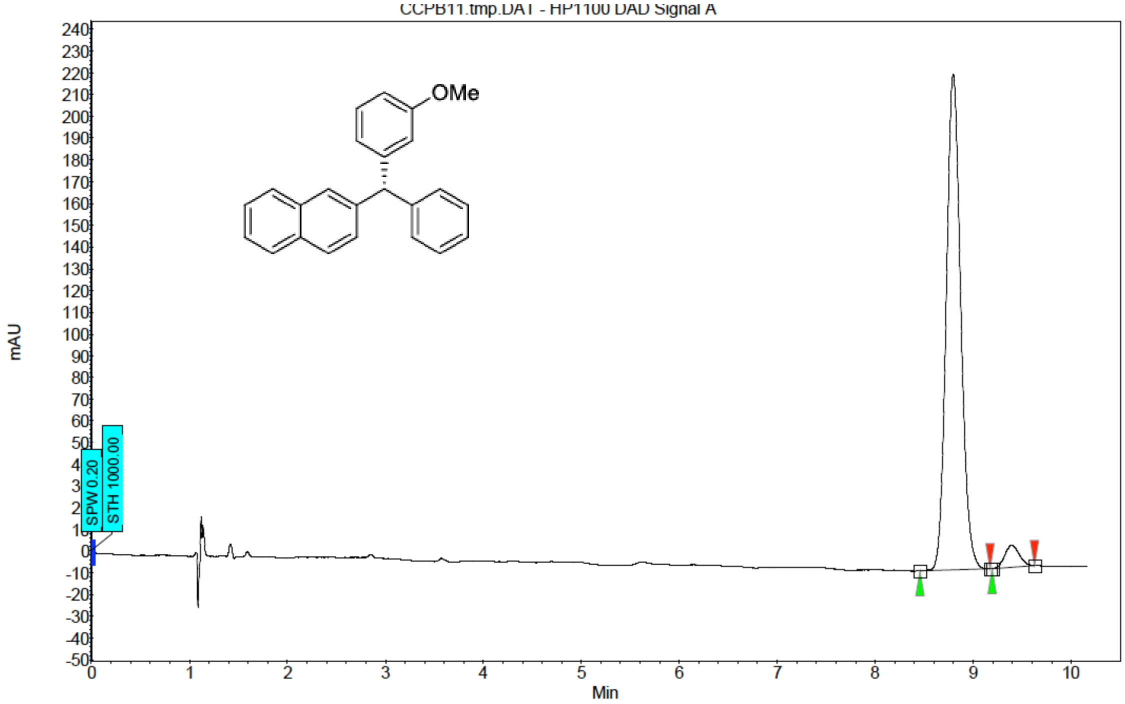
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 4.13 | 4.23 | 4.36 | 0.00 | 4.55 | 27.2 | 2.4 | 4.546 |
| 2 | UNKNOWN | 4.64 | 4.81 | 5.01 | 0.00 | 95.45 | 486.5 | 50.0 | 95.454 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 513.7 | 52.4 | 100.000 |


CCP274B.tmp.DAT - HP1100 DAD Signal A

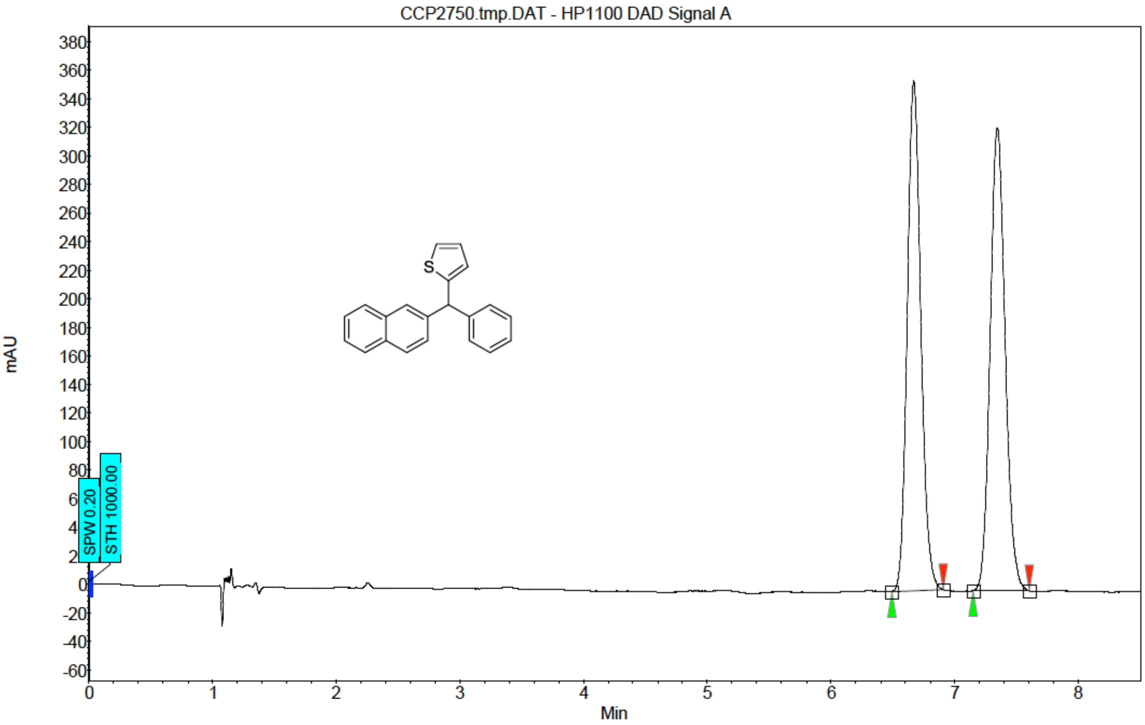

CCPB13.tmp.DAT - HP1100 DAD Signal A

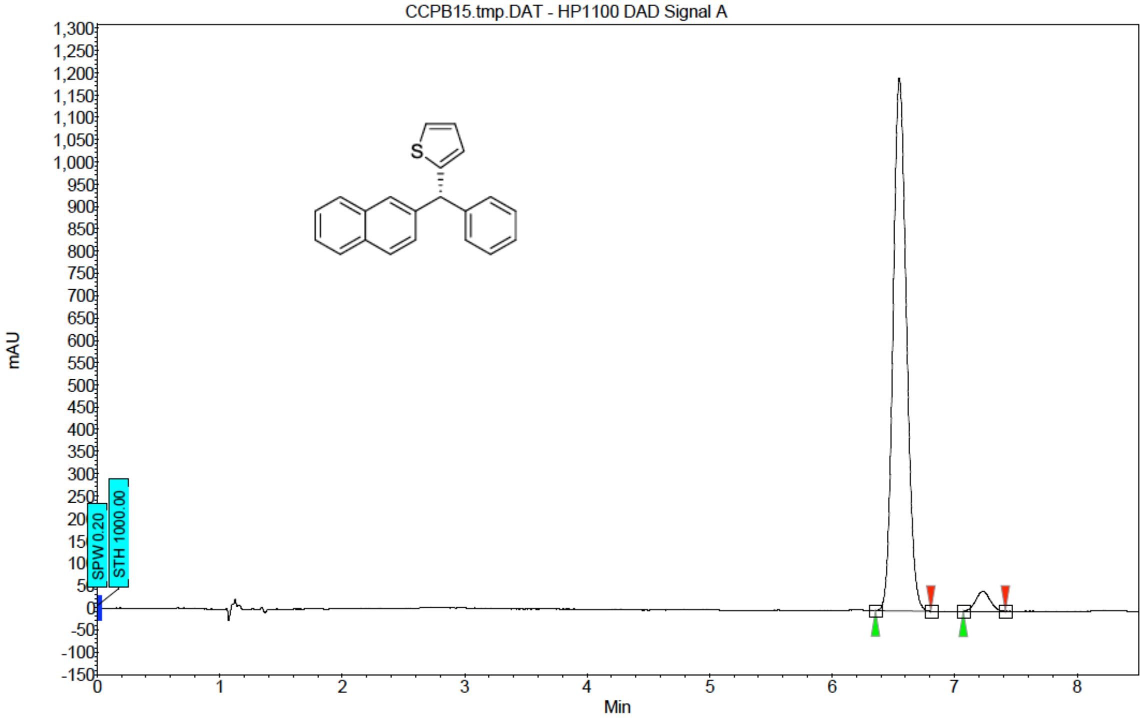
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 8.69 | 9.03 | 9.55 | 0.00 | 95.36 | 738.2 | 168.2 | 95.357 |
| 2 | UNKNOWN | 9.59 | 9.83 | 10.29 | 0.00 | 4.64 | 34.2 | 8.2 | 4.643 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 772.4 | 176.4 | 100.000 |



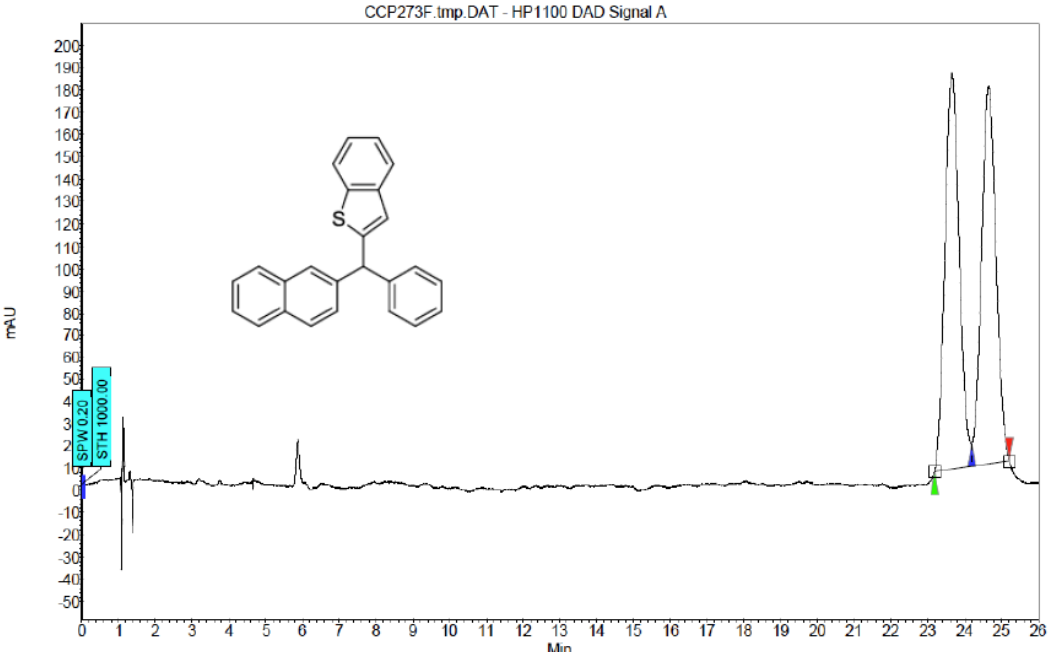


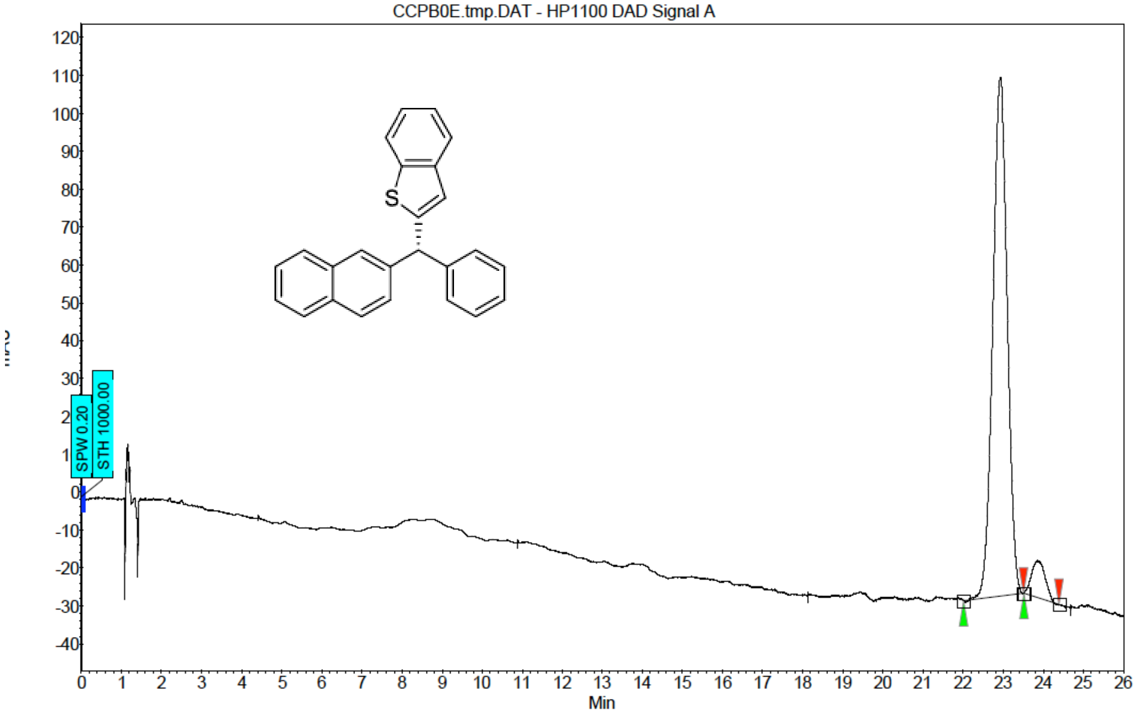
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 8.46 | 8.80 | 9.17 | 0.00 | 95.78 | 228.0 | 38.8 | 95.783 |
| 2 | UNKNOWN | 9.19 | 9.40 | 9.63 | 0.00 | 4.22 | 10.0 | 1.7 | 4.217 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 238.0 | 40.5 | 100.000 |



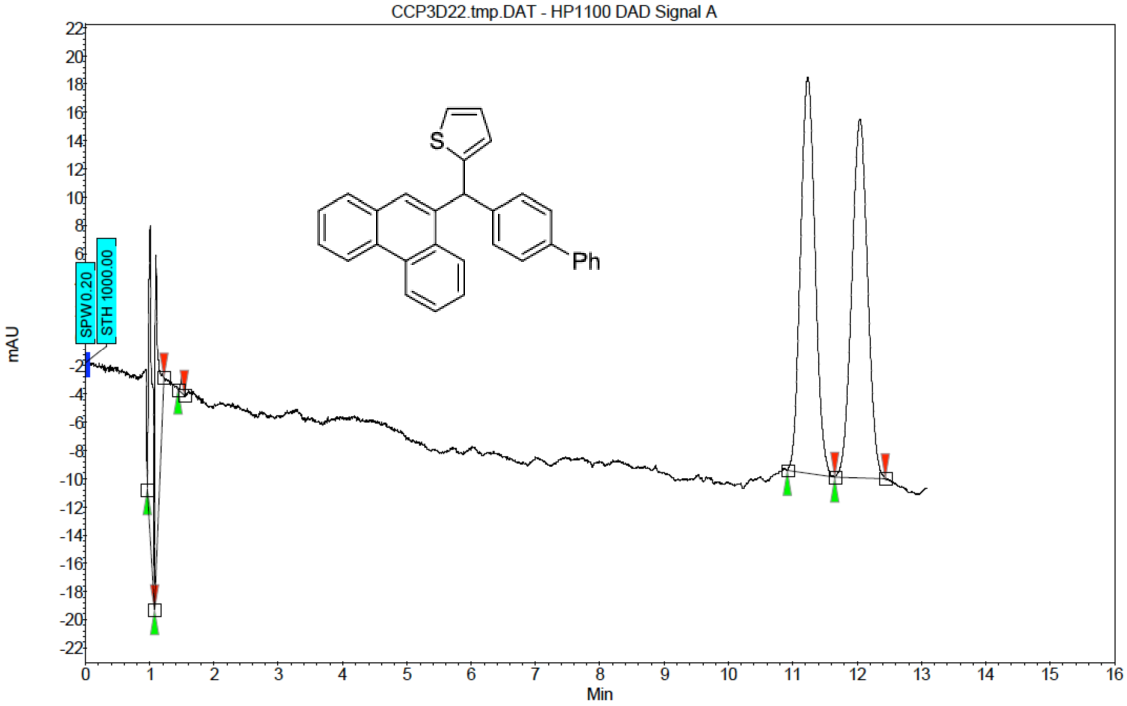


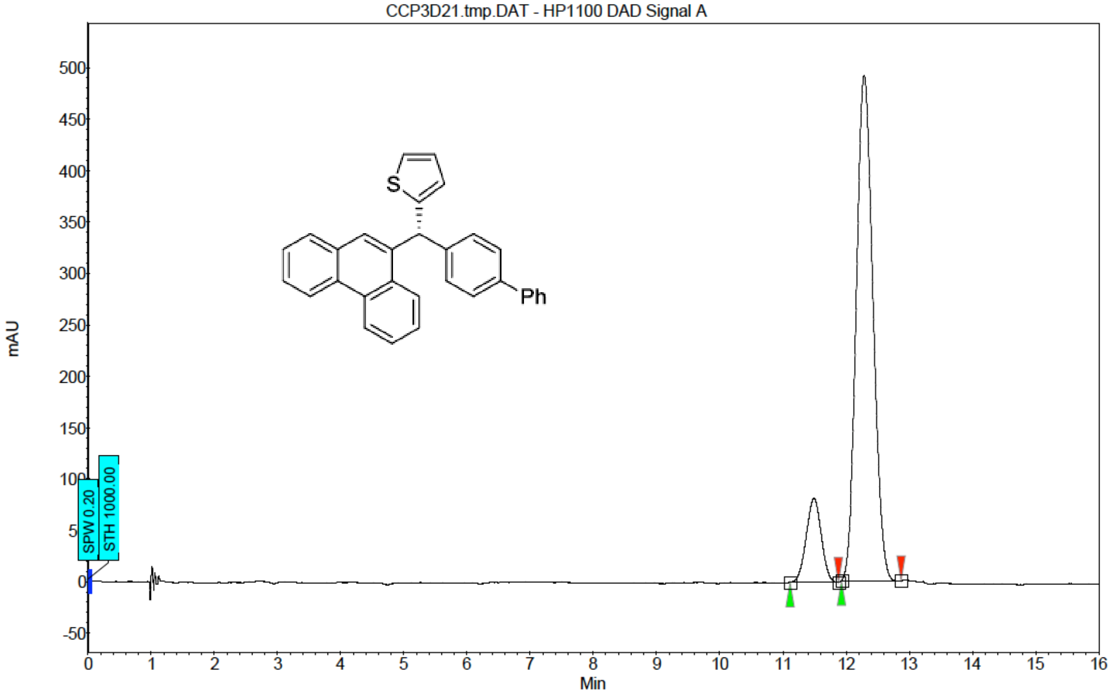
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 2 | UNKNOWN | 6.36 | 6.55 | 6.81 | 0.00 | 96.20 | 1195.2 | 150.9 | 96.205 |
| 1 | UNKNOWN | 7.07 | 7.23 | 7.42 | 0.00 | 3.80 | 44.1 | 6.0 | 3.795 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 1239.3 | 156.9 | 100.000 |



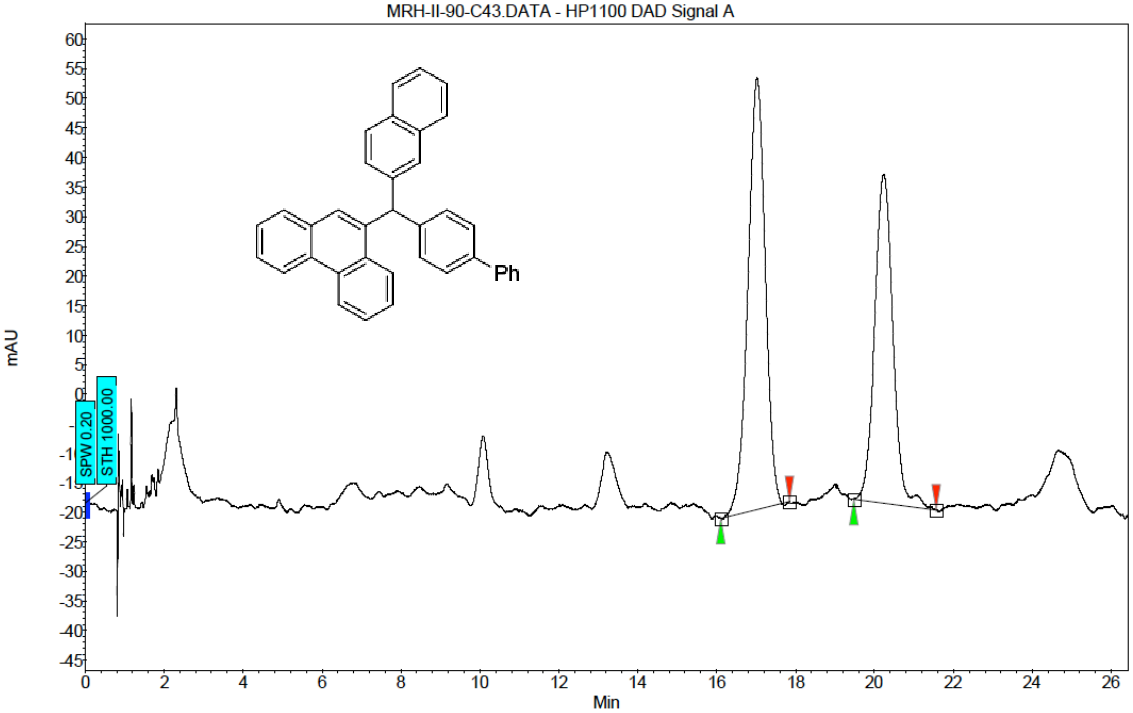


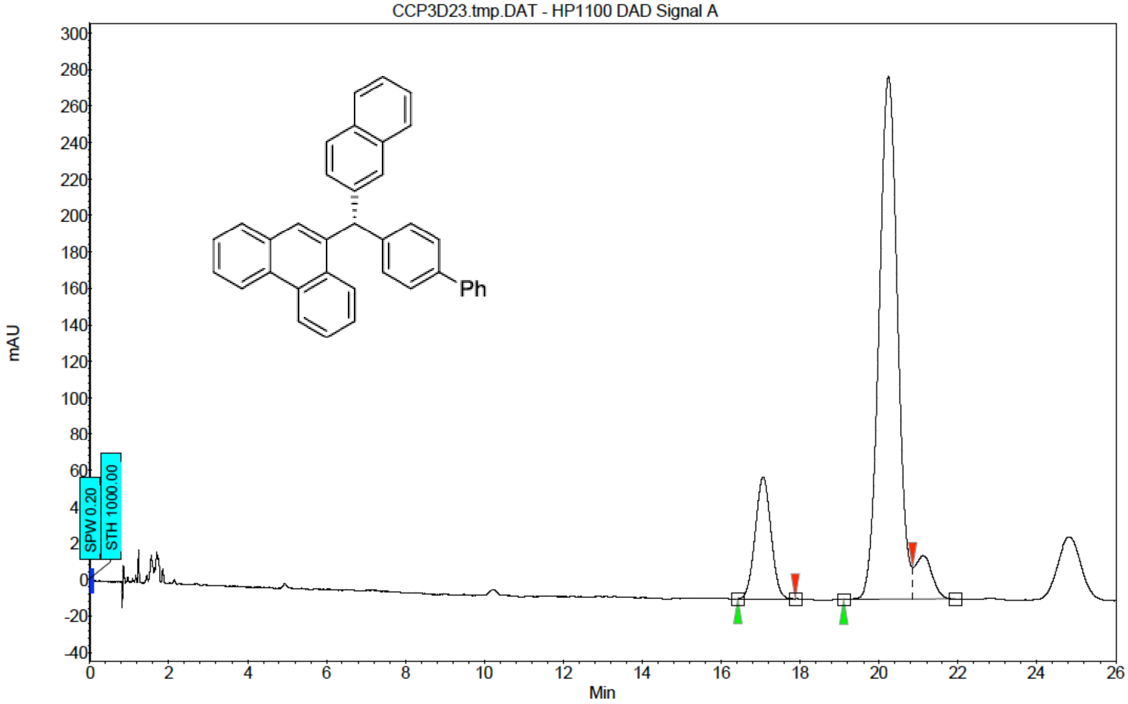
| ndex | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 22.01 | 22.93 | 23.50 | 0.00 | 93.94 | 136.8 | 58.1 | 93.945 |
| 2 | UNKNOWN | 23.52 | 23.86 | 24.39 | 0.00 | 6.06 | 9.7 | 3.7 | 6.055 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 146.5 | 61.8 | 100.000 |



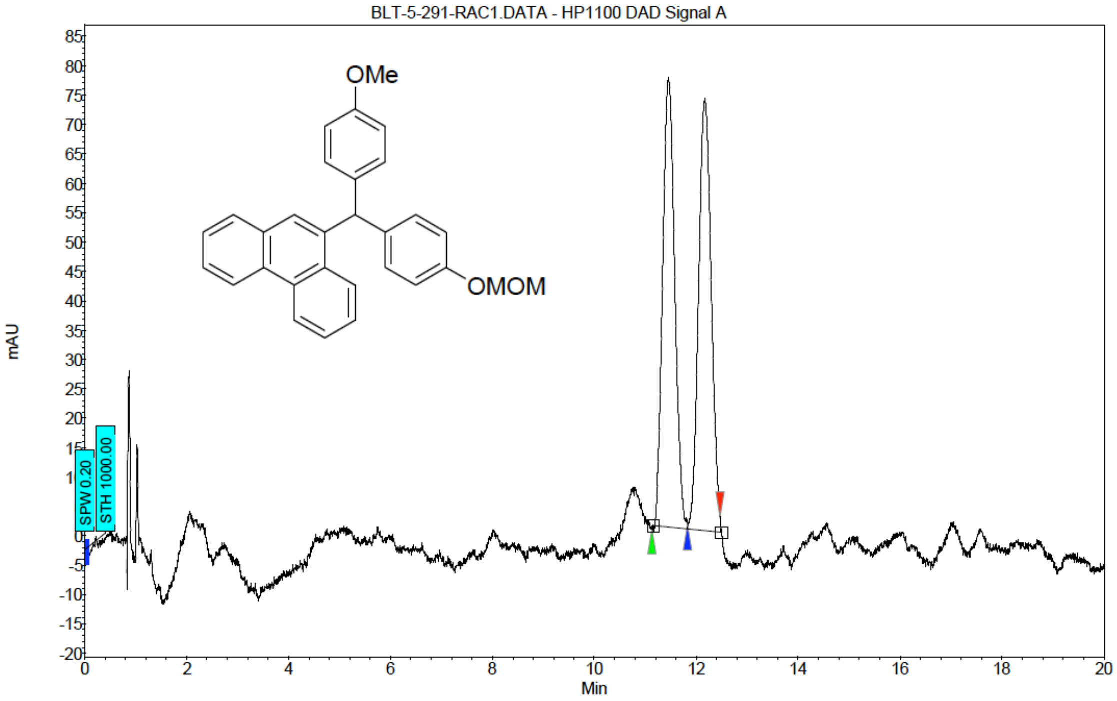


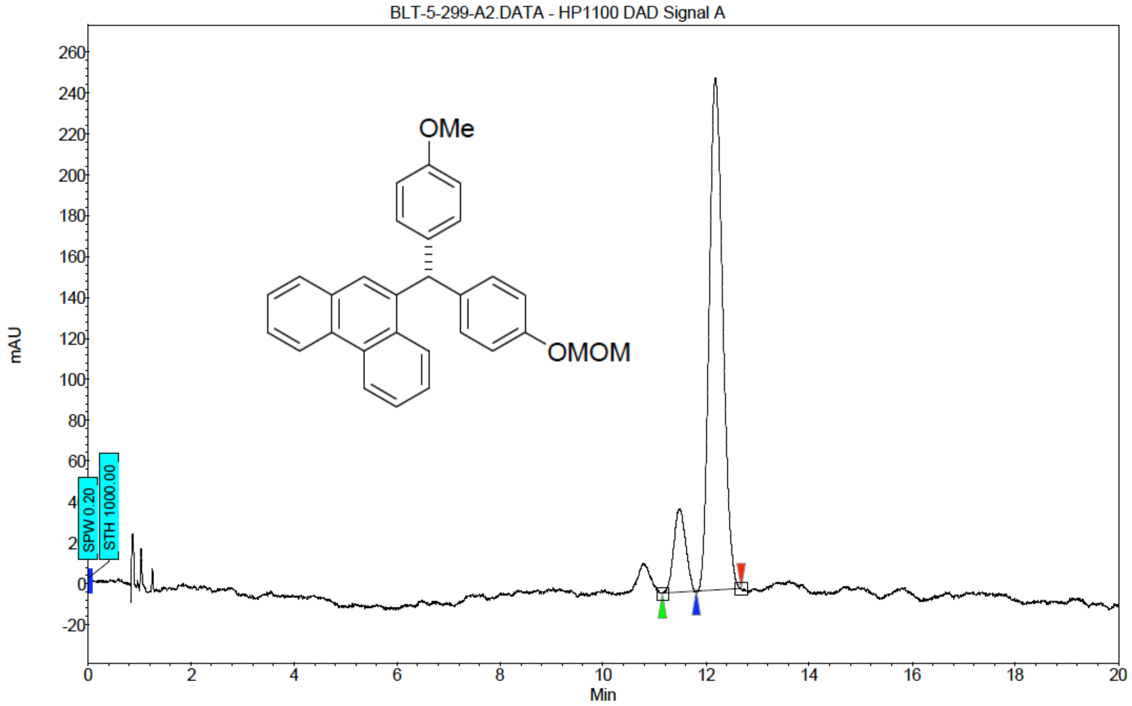
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 11.11 | 11.49 | 11.88 | 0.00 | 12.96 | 81.5 | 22.4 | 12.963 |
| 2 | UNKNOWN | 11.93 | 12.29 | 12.87 | 0.00 | 87.04 | 491.3 | 150.1 | 87.037 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 572.8 | 172.5 | 100.000 |



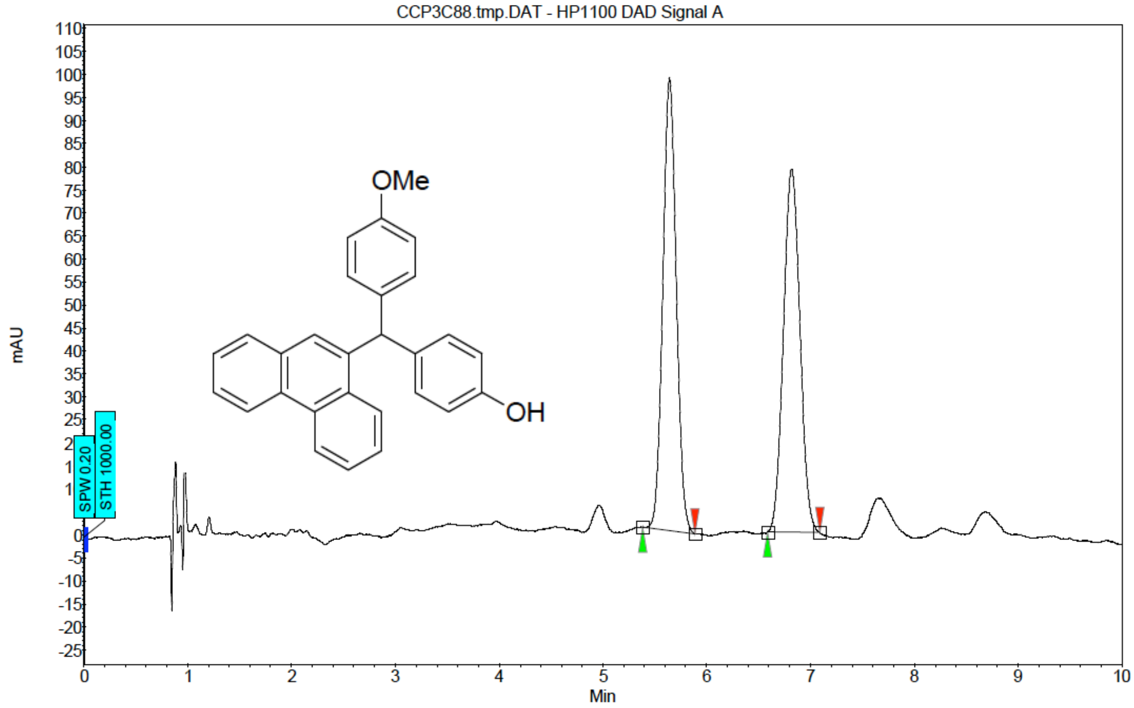


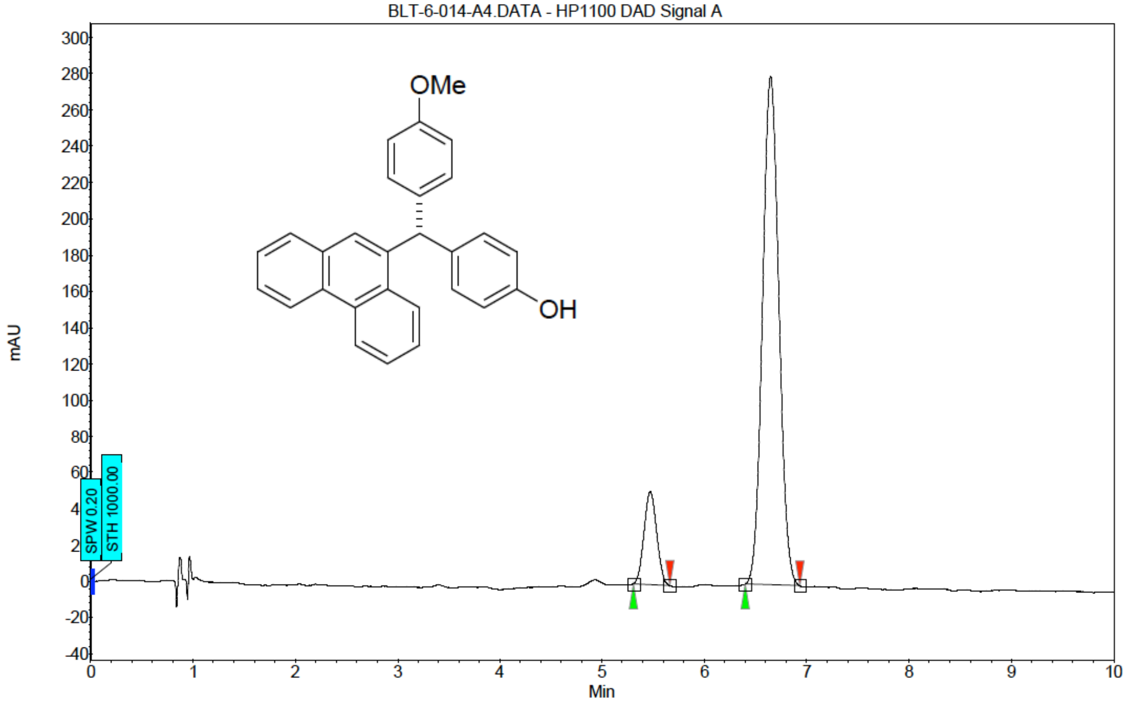
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 2 | UNKNOWN | 16.43 | 17.07 | 17.88 | 0.00 | 16.47 | 66.6 | 30.5 | 16.469 |
| 1 | UNKNOWN | 19.11 | 20.24 | 20.85 | 0.00 | 83.53 | 287.1 | 154.9 | 83.531 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 353.7 | 185.4 | 100.000 |



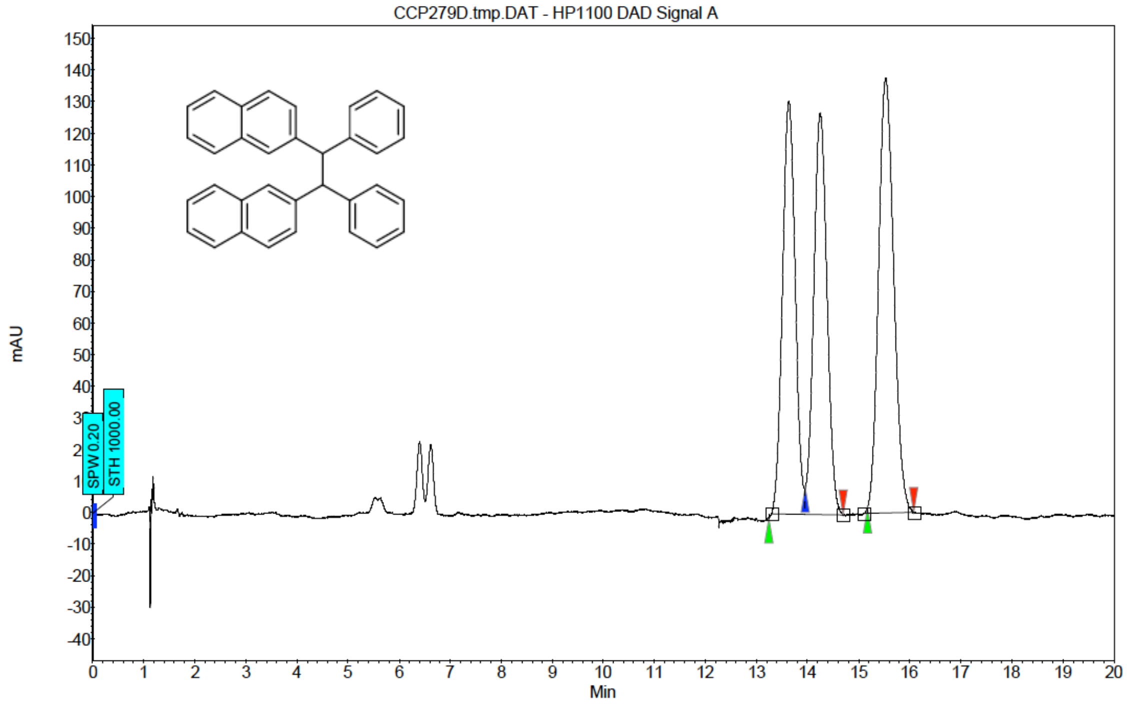


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 11.16 | 11.49 | 11.82 | 0.00 | 12.59 | 40.8 | 10.9 | 12.595 |
| 2 | UNKNOWN | 11.82 | 12.18 | 12.69 | 0.00 | 87.41 | 250.0 | 75.8 | 87.405 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 290.9 | 86.7 | 100.000 |

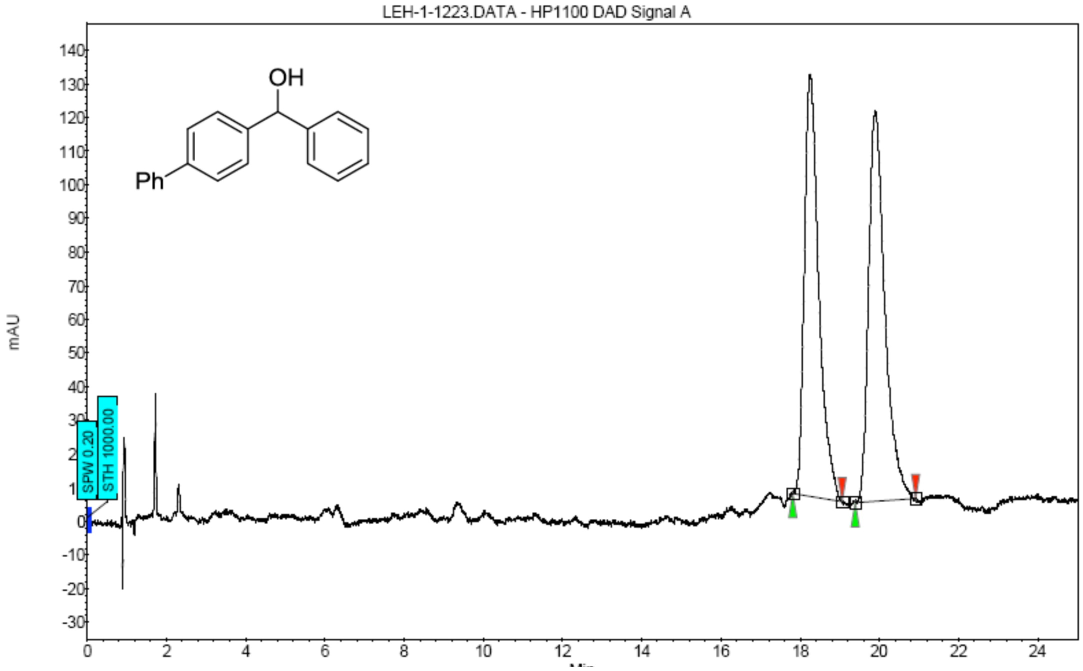


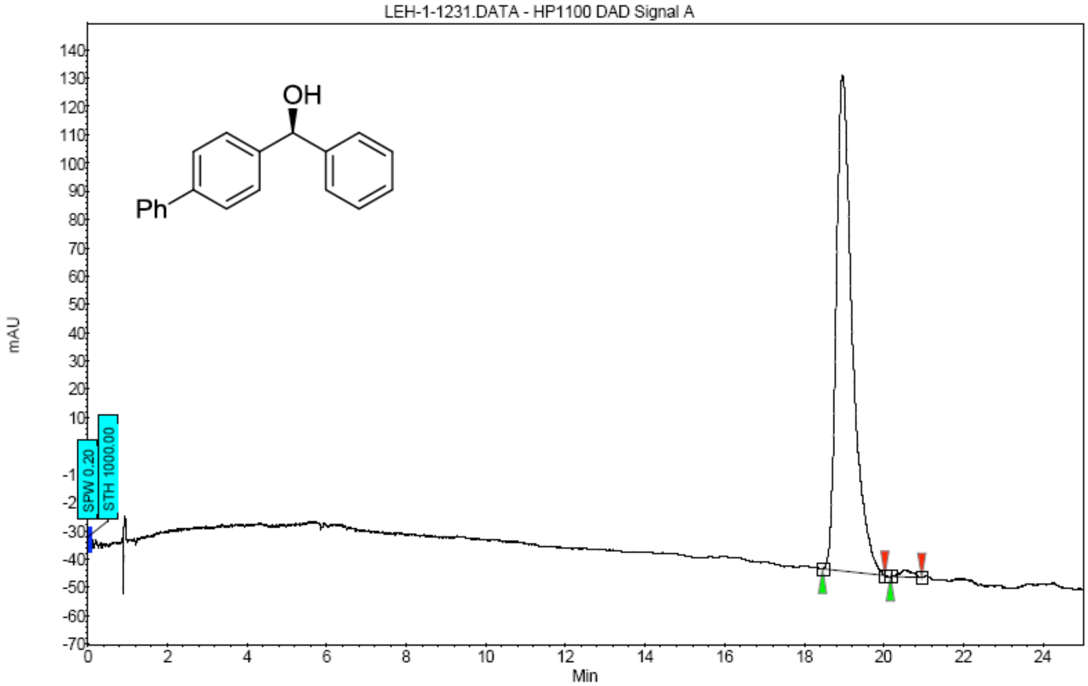


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 5.31 | 5.47 | 5.66 | 0.00 | 12.42 | 51.1 | 7.3 | 12.415 |
| 2 | UNKNOWN | 6.40 | 6.65 | 6.93 | 0.00 | 87.58 | 280.5 | 51.6 | 87.585 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 331.7 | 59.0 | 100.000 |

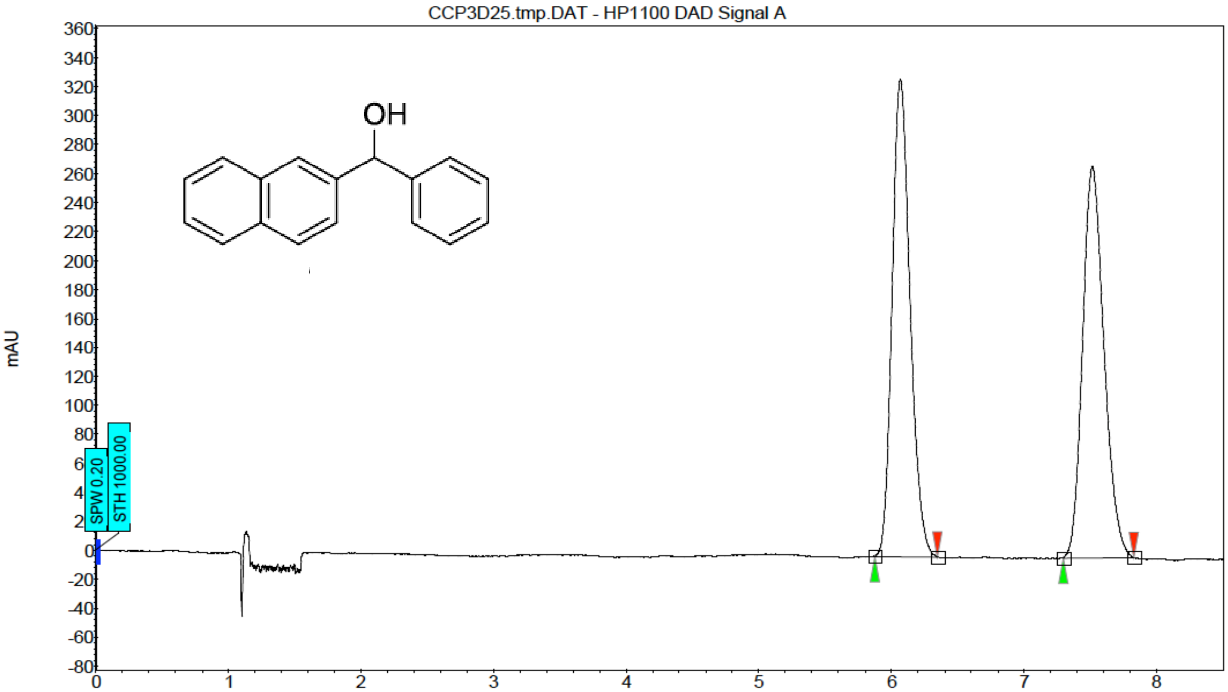


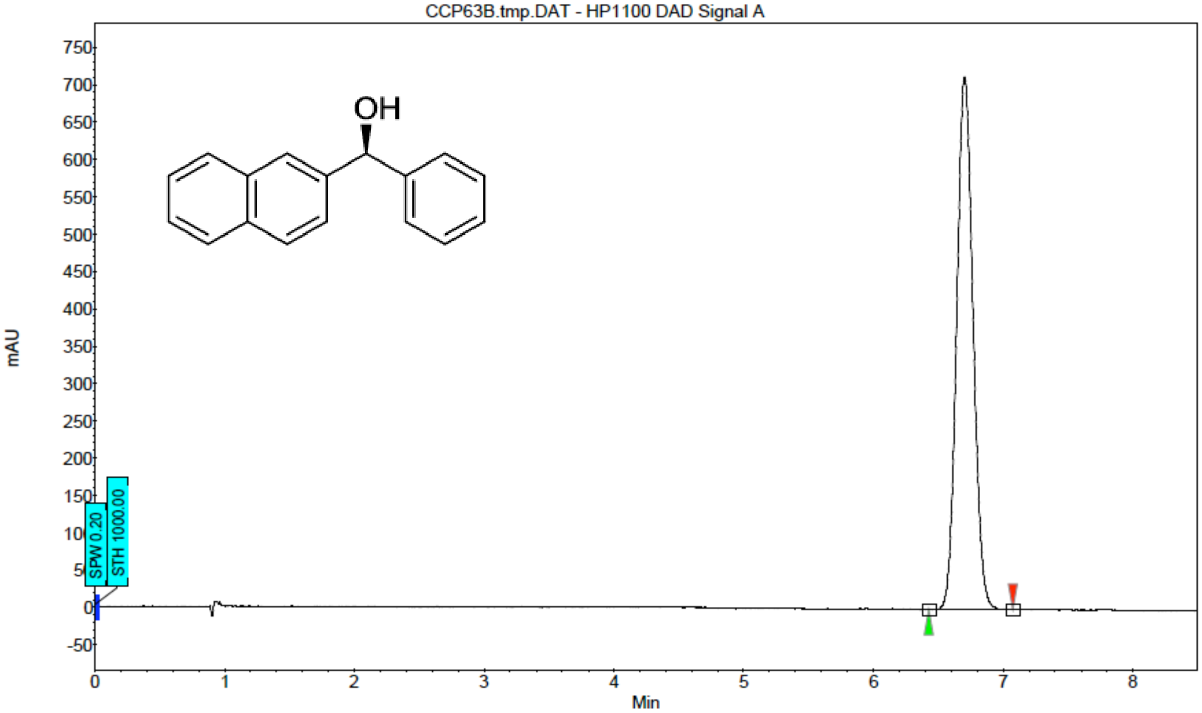
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 13.25 | 13.63 | 13.95 | 0.00 | 30.79 | 130.9 | 37.9 | 30.788 |
| 2 | UNKNOWN | 13.95 | 14.25 | 14.69 | 0.00 | 30.96 | 127.2 | 38.1 | 30.961 |
| 3 | UNKNOWN | 15.17 | 15.53 | 16.08 | 0.00 | 38.25 | 137.5 | 47.1 | 38.251 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 395.6 | 123.2 | 100.000 |



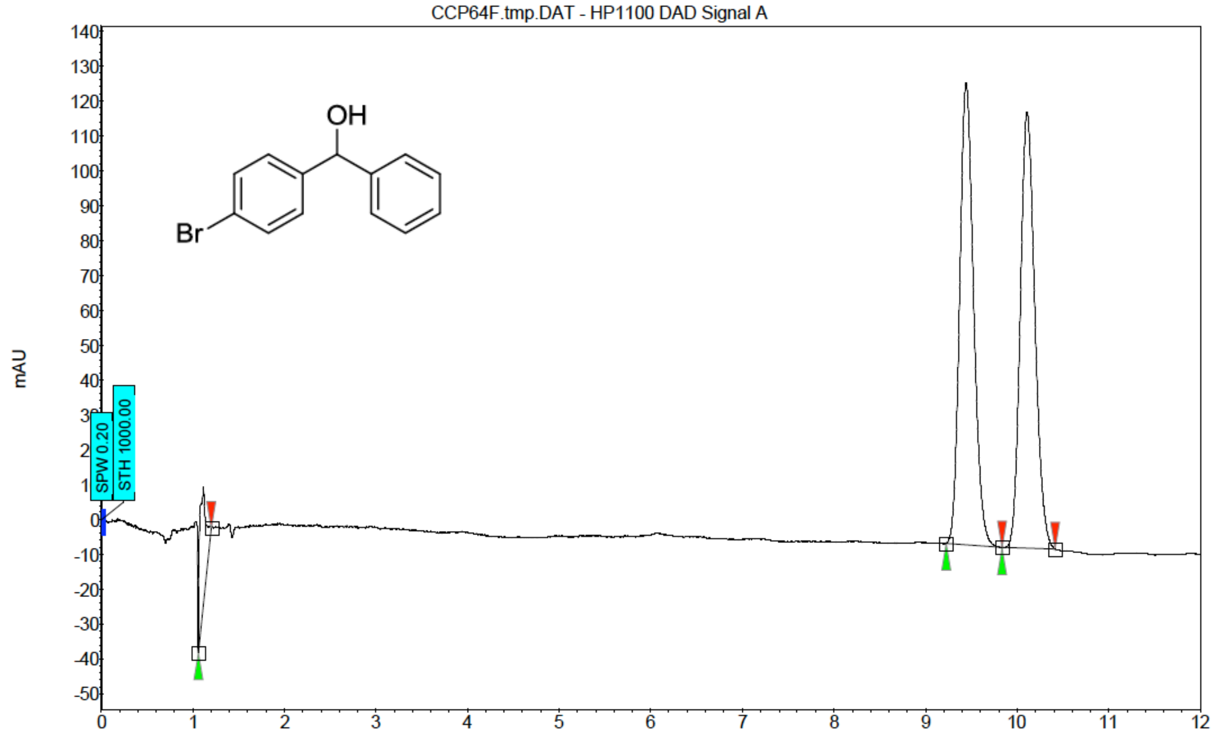


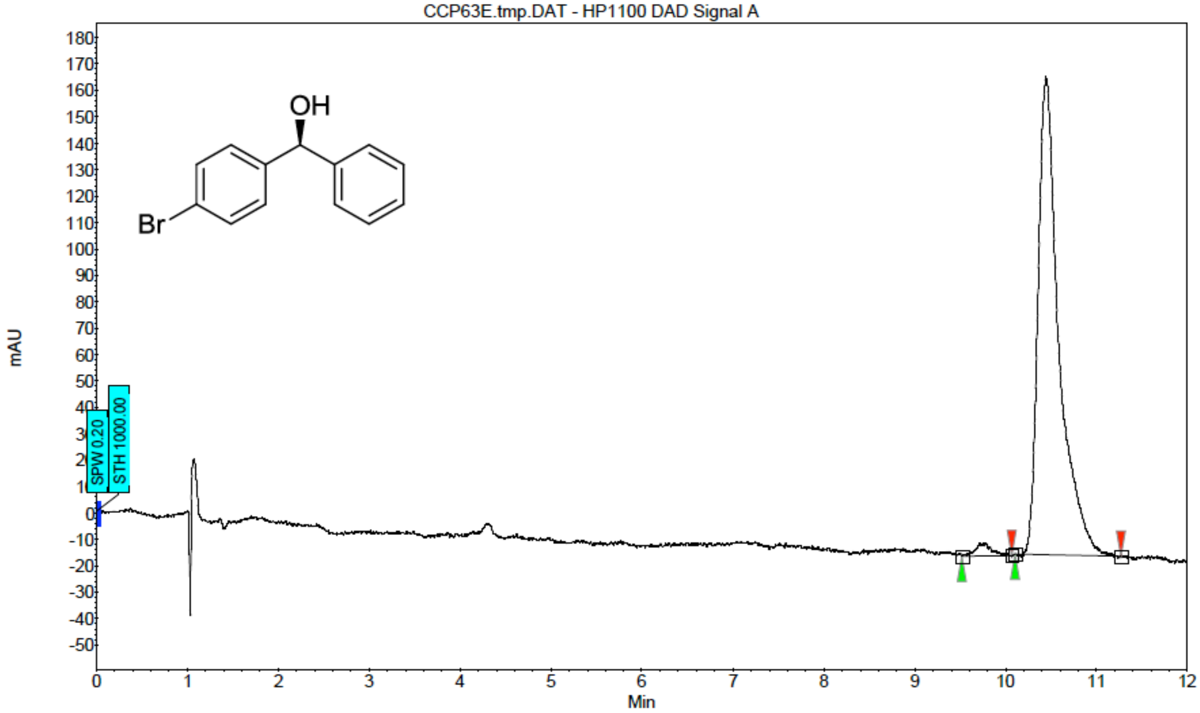
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 18.46 | 18.97 | 20.02 | 0.00 | 98.91 | 175.3 | 82.1 | 98.914 |
| 2 | UNKNOWN | 20.17 | 20.55 | 20.95 | 0.00 | 1.09 | 2.4 | 0.9 | 1.086 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 177.7 | 83.0 | 100.000 |



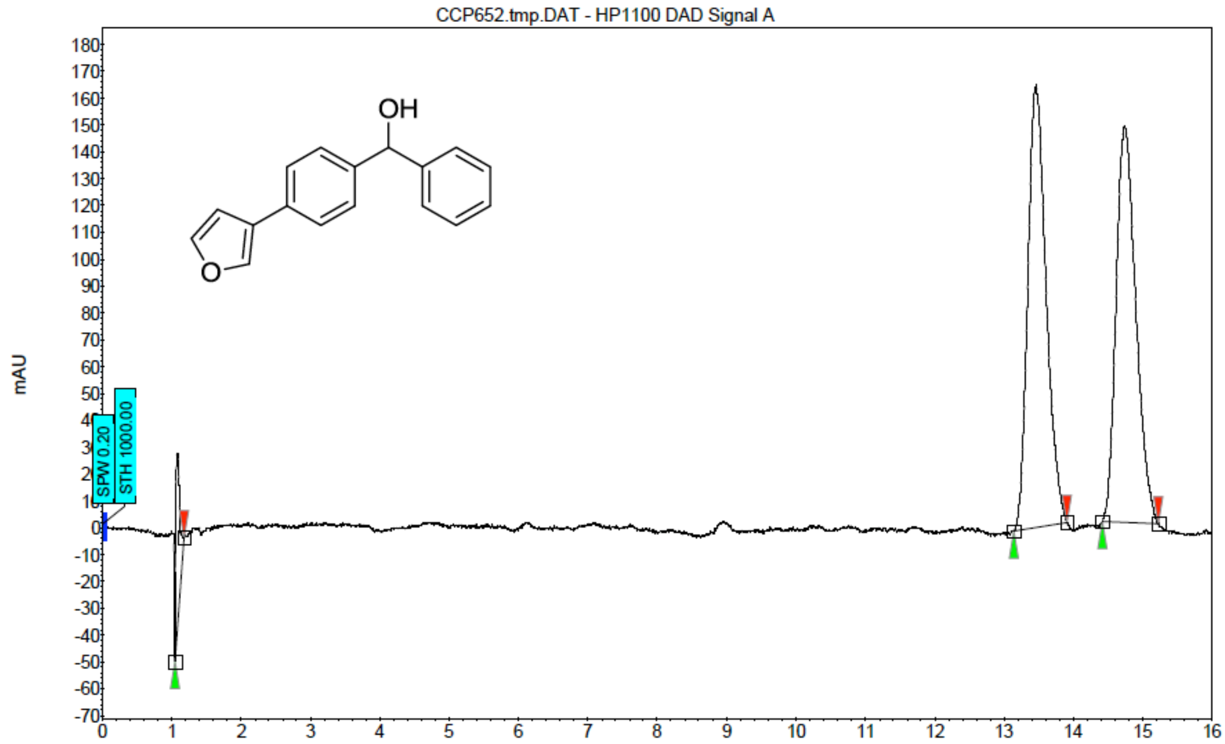


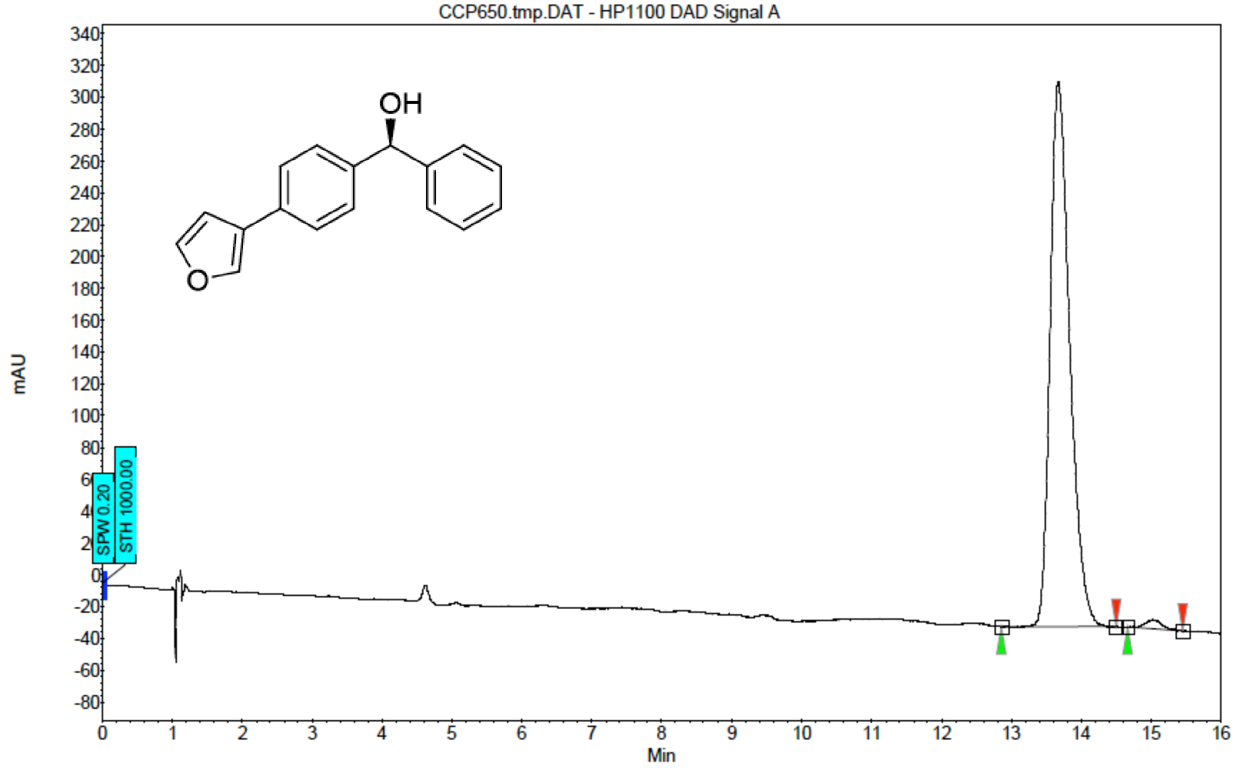
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 6.43 | 6.70 | 7.08 | 0.00 | 100.00 | 712.9 | 104.3 | 100.000 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 712.9 | 104.3 | 100.000 |



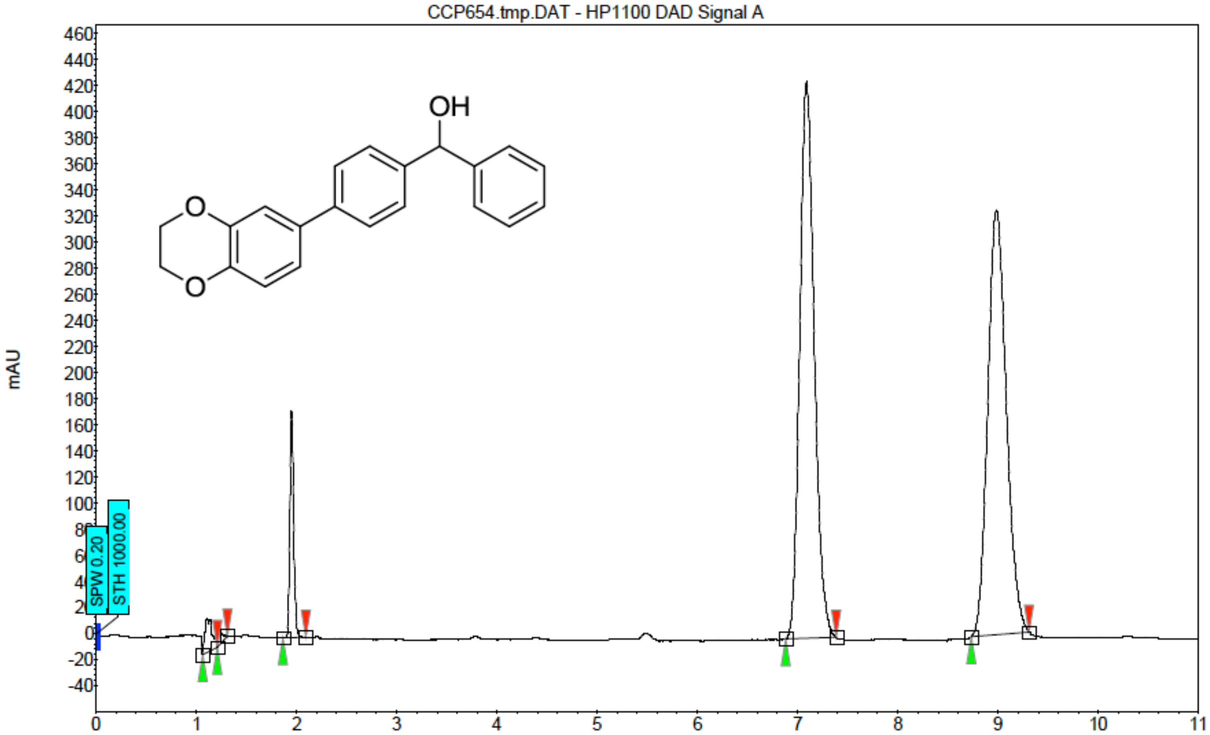


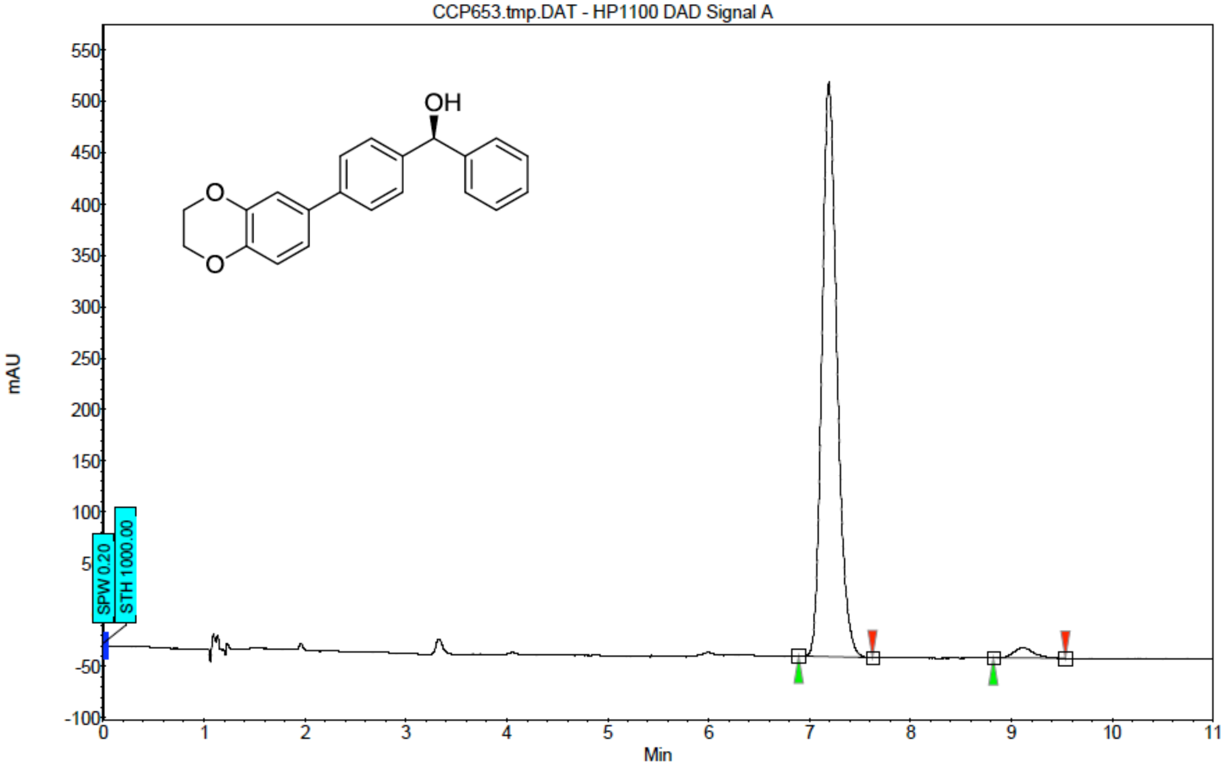
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 2 | UNKNOWN | 9.52 | 9.76 | 10.07 | 0.00 | 2.16 | 4.9 | 1.1 | 2.164 |
| 1 | UNKNOWN | 10.10 | 10.44 | 11.27 | 0.00 | 97.84 | 181.0 | 47.8 | 97.836 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 185.8 | 48.9 | 100.000 |



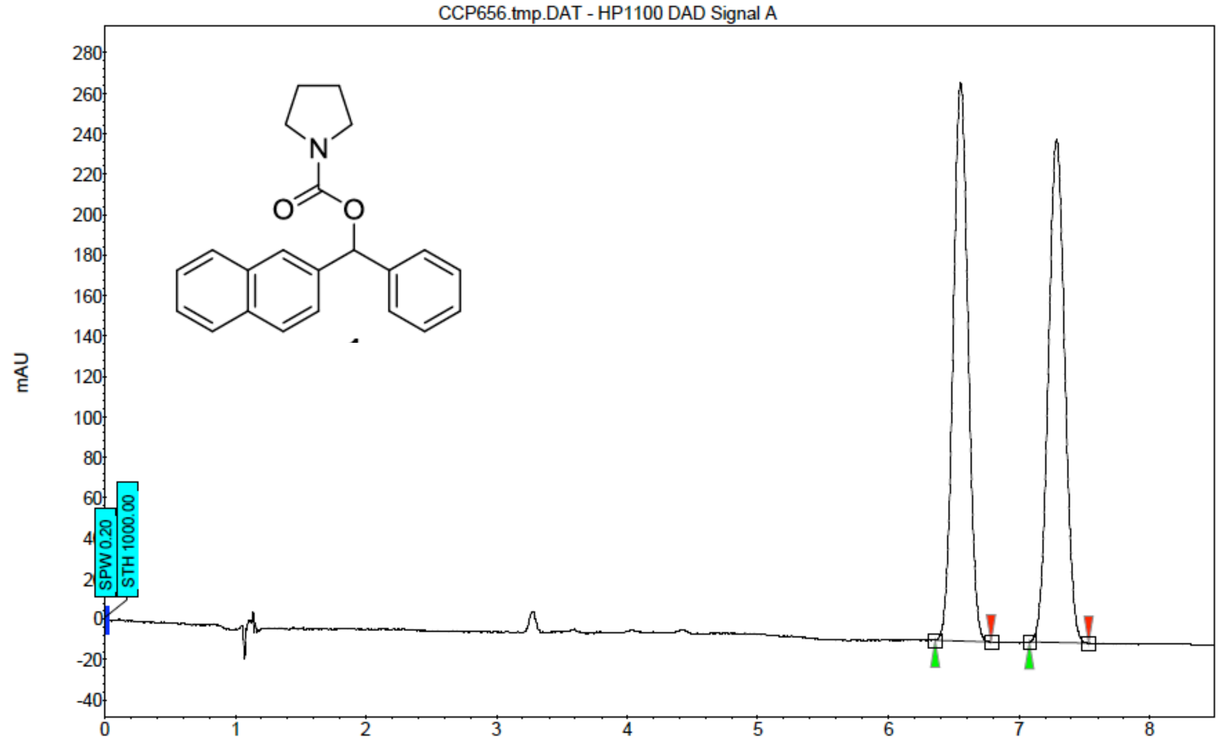


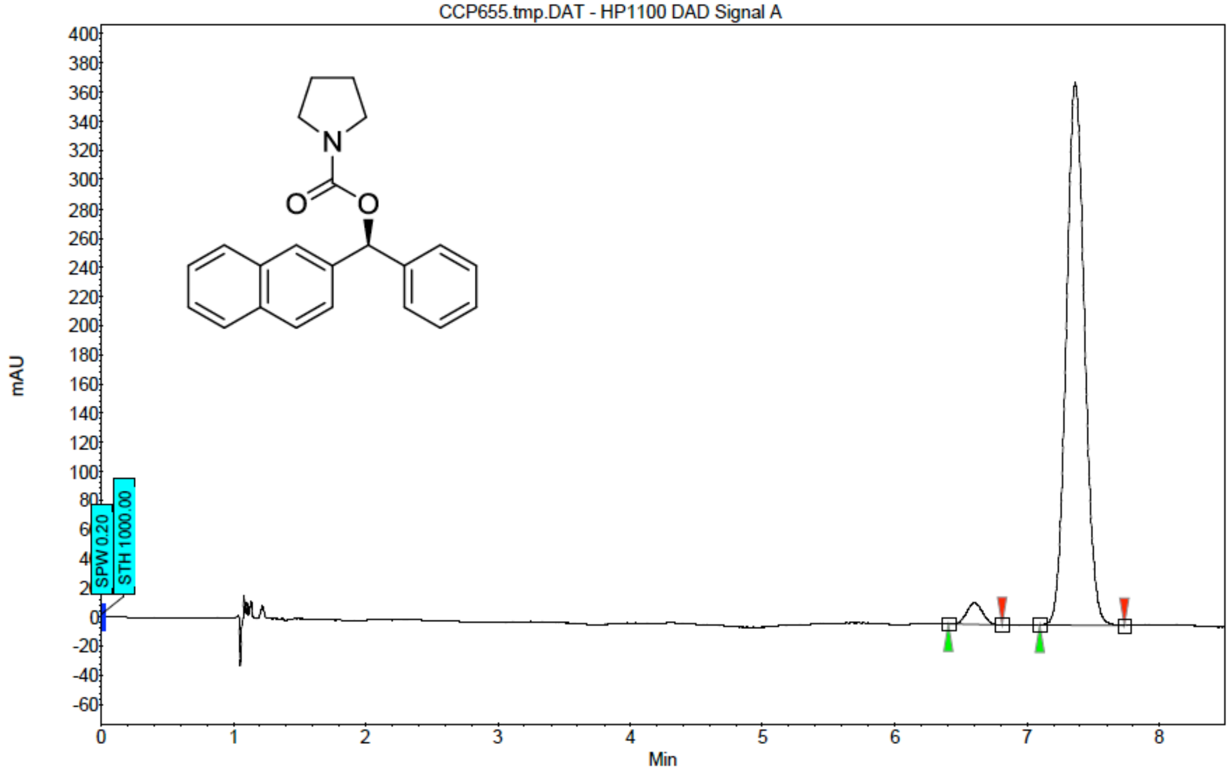
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 12.86 | 13.67 | 14.50 | 0.00 | 98.57 | 341.7 | 111.0 | 98.571 |
| 2 | UNKNOWN | 14.66 | 15.02 | 15.45 | 0.00 | 1.43 | 5.9 | 1.6 | 1.429 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 347.6 | 112.6 | 100.000 |



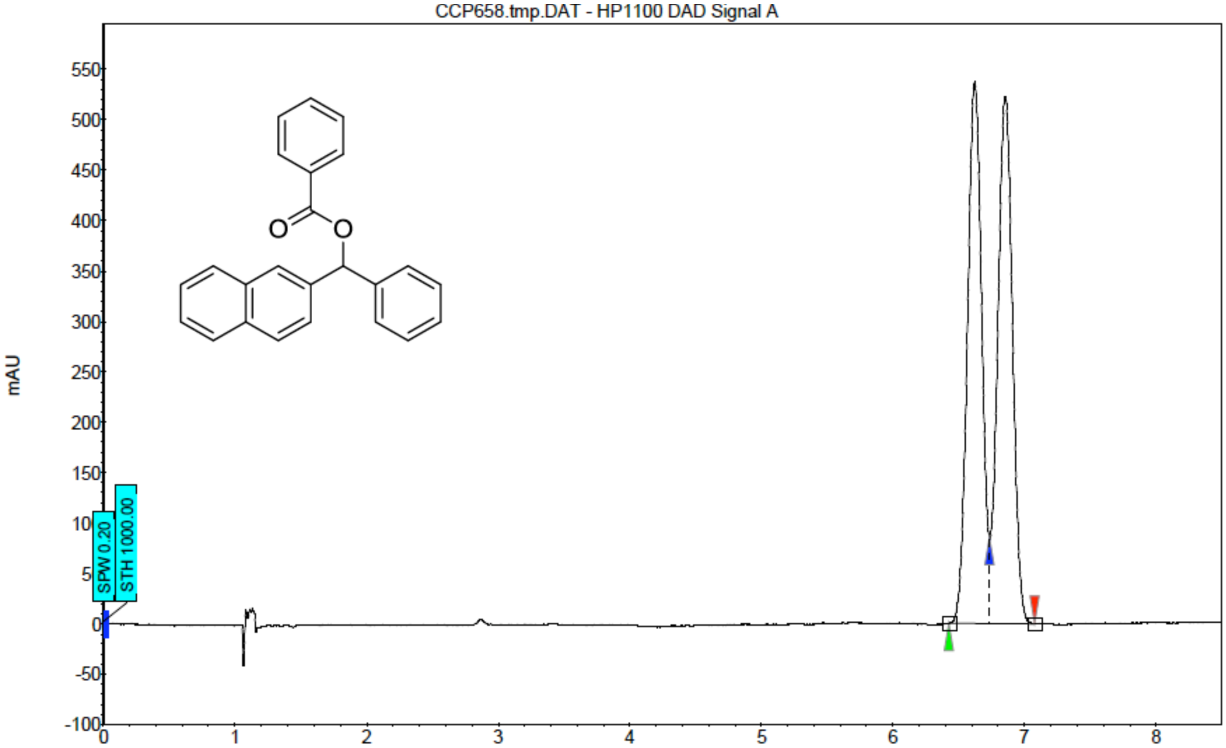


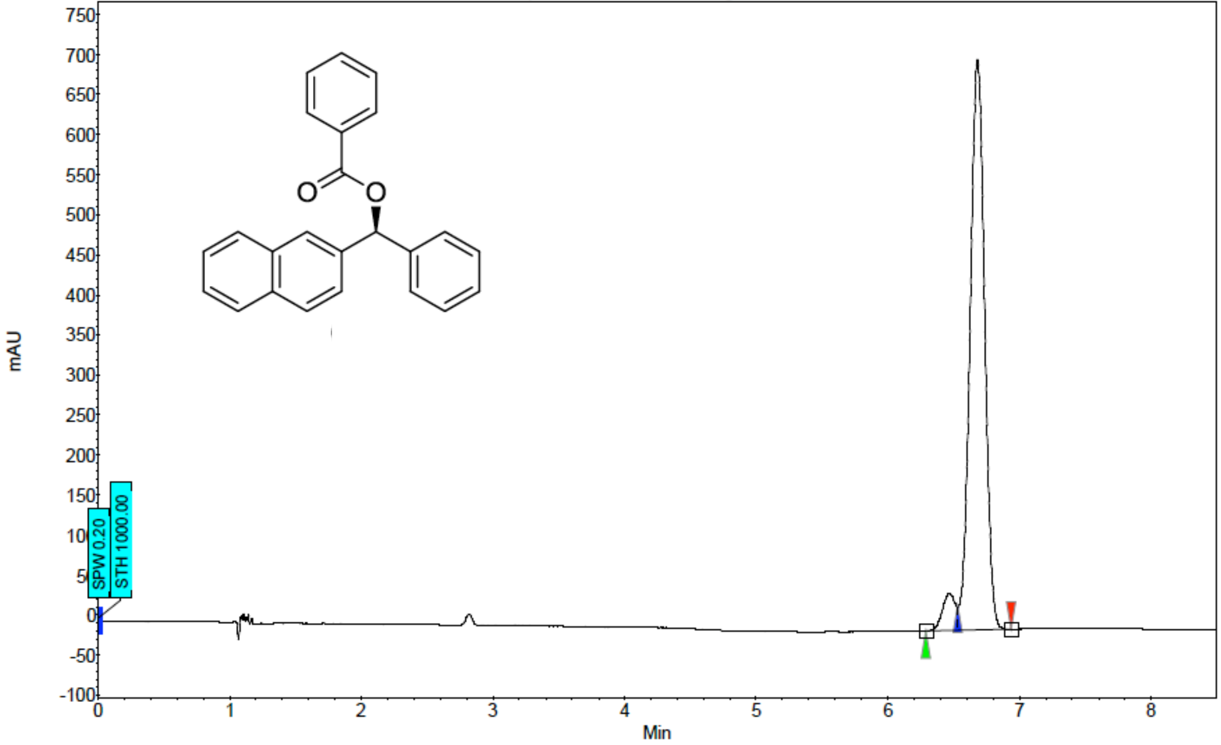
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 6.89 | 7.19 | 7.62 | 0.00 | 97.79 | 558.2 | 96.4 | 97.790 |
| 2 | UNKNOWN | 8.82 | 9.11 | 9.53 | 0.00 | 2.21 | 9.8 | 2.2 | 2.210 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 568.0 | 98.6 | 100.000 |



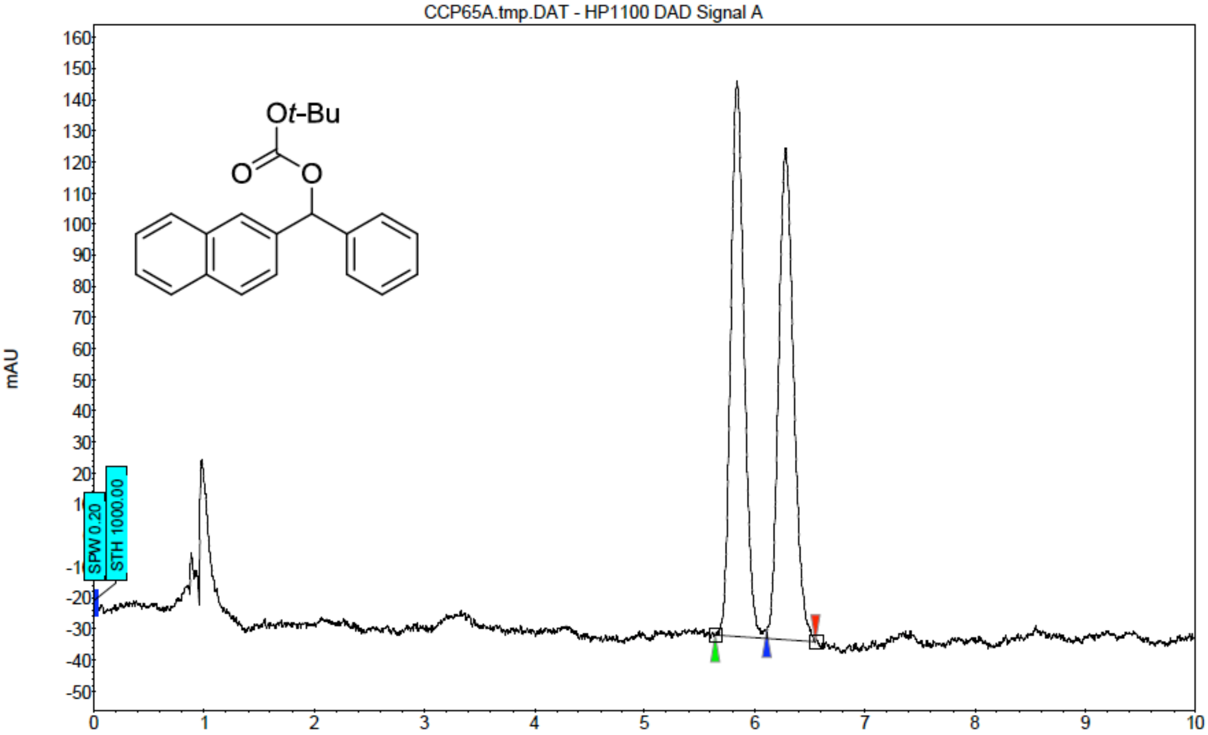


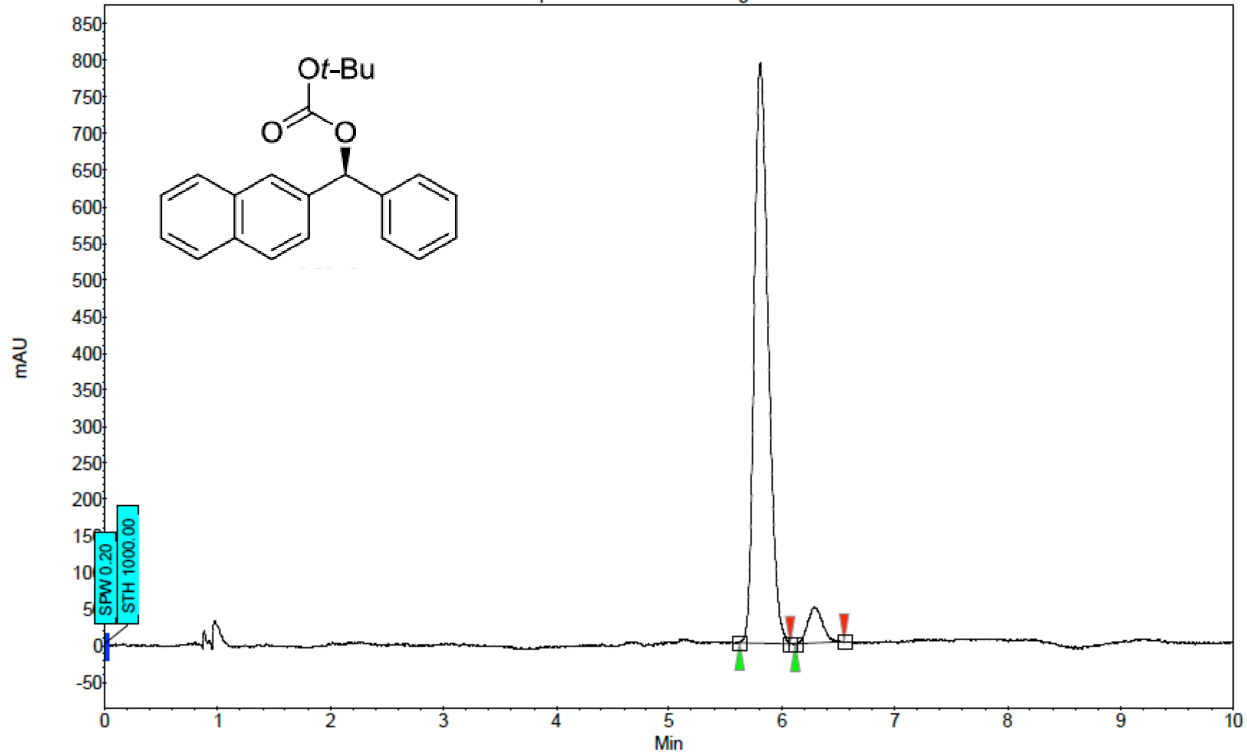
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 6.41 | 6.60 | 6.81 | 0.00 | 3.40 | 14.9 | 2.1 | 3.400 |
| 2 | UNKNOWN | 7.10 | 7.37 | 7.74 | 0.00 | 96.60 | 372.0 | 59.5 | 96.600 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 386.9 | 61.6 | 100.000 |



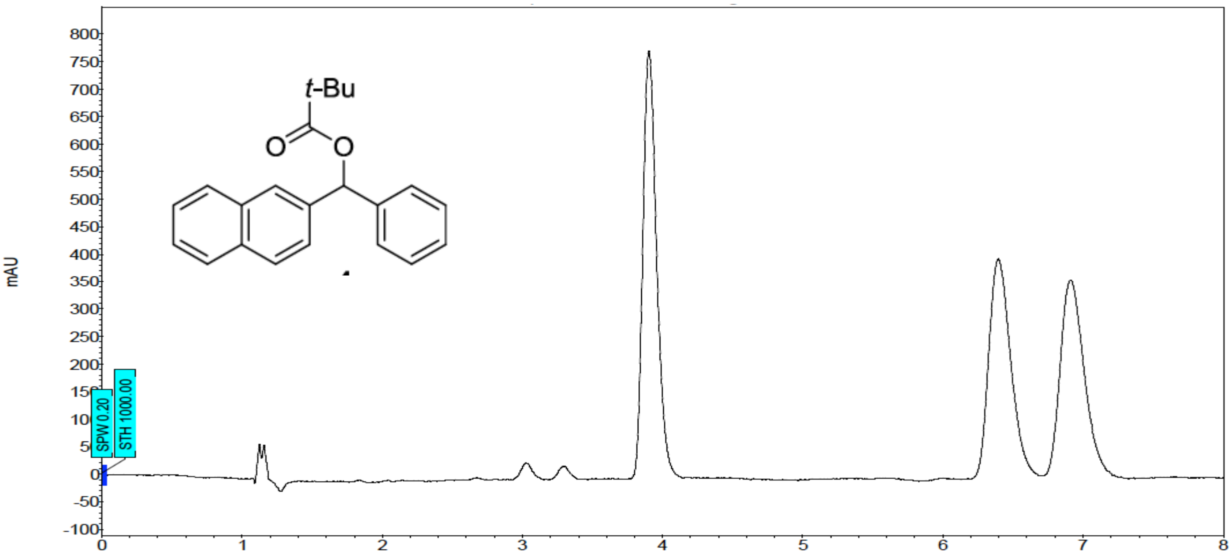


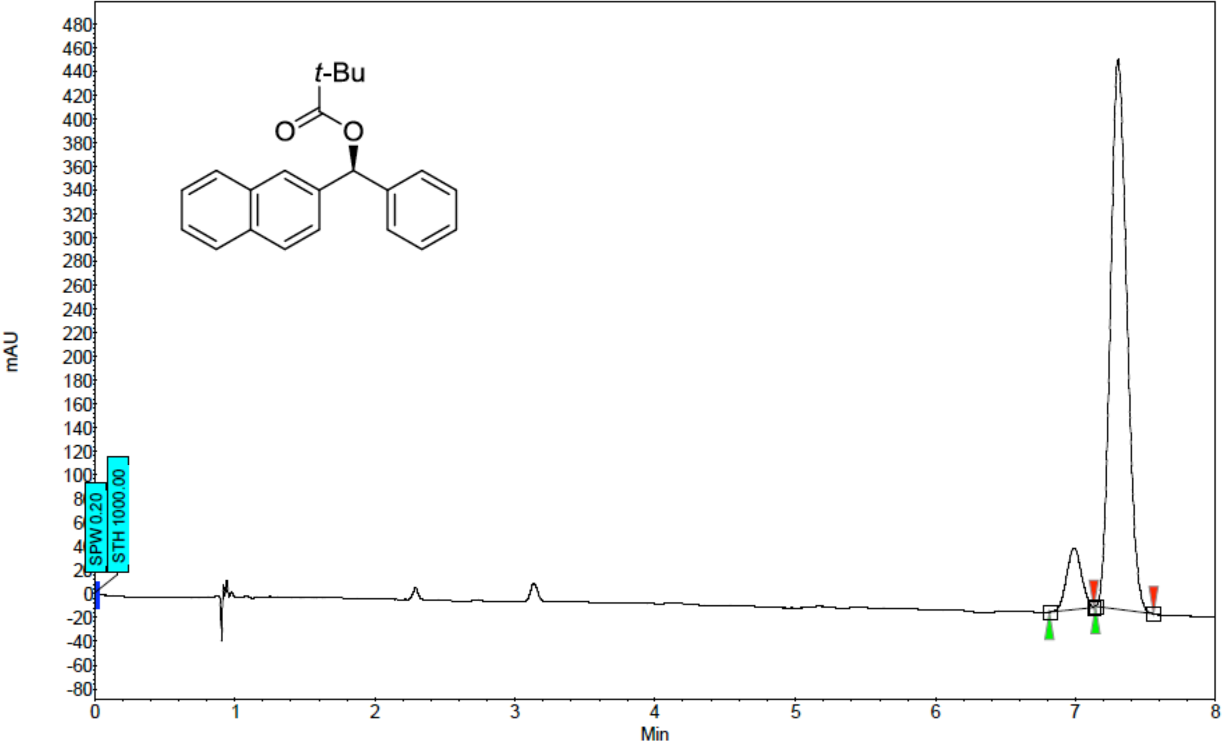
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 6.29 | 6.47 | 6.53 | 0.00 | 5.45 | 46.2 | 5.2 | 5.451 |
| 2 | UNKNOWN | 6.53 | 6.68 | 6.94 | 0.00 | 94.55 | 711.7 | 90.9 | 94.549 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 757.9 | 96.2 | 100.000 |



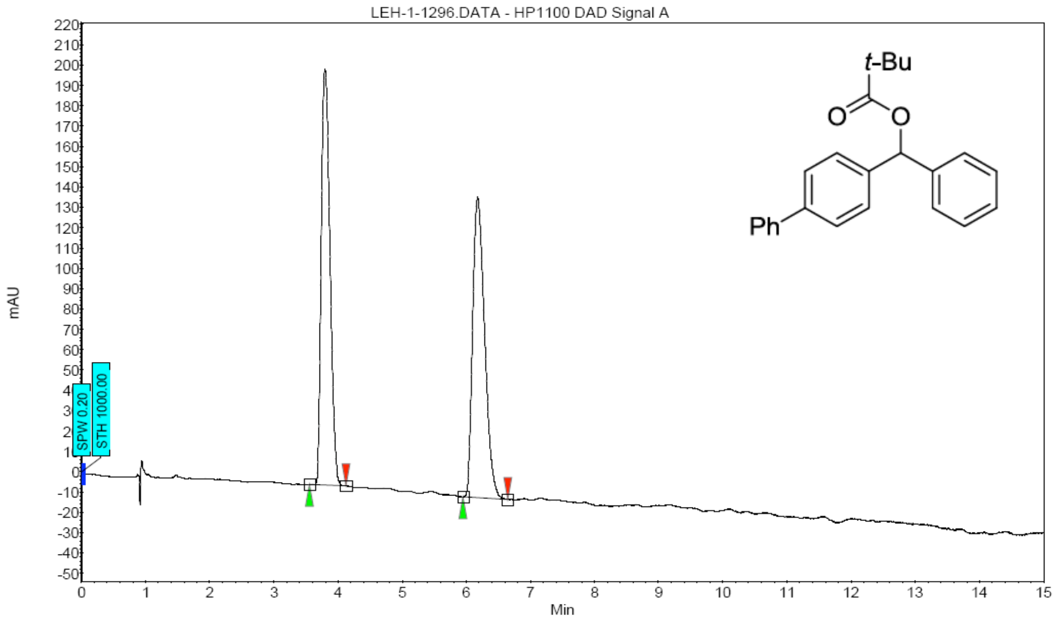


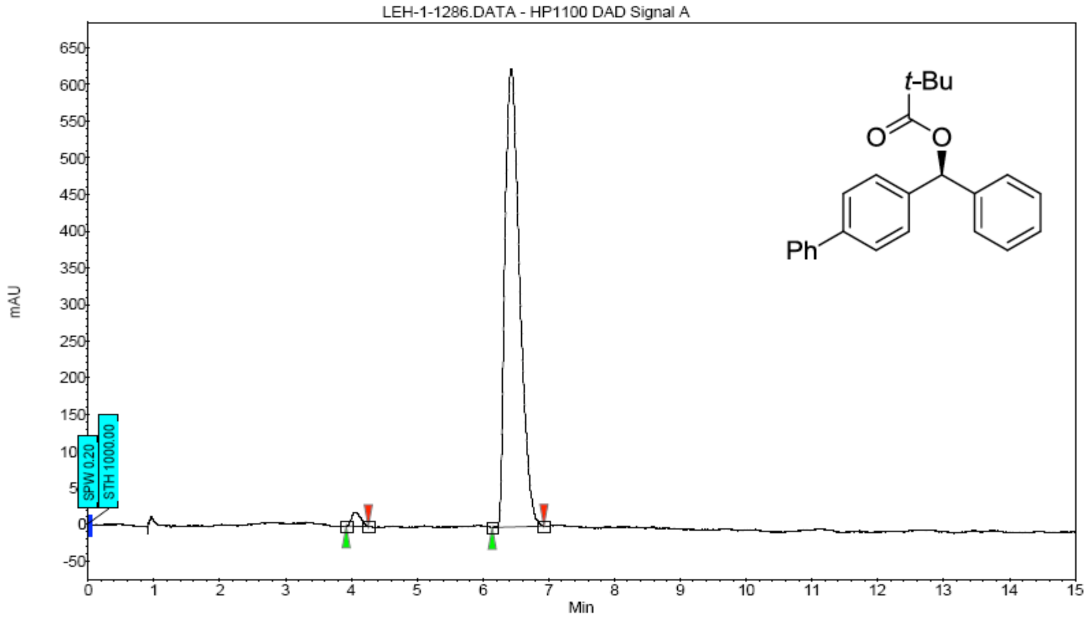
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 5.63 | 5.81 | 6.08 | 0.00 | 93.79 | 791.8 | 113.4 | 93.788 |
| 2 | UNKNOWN | 6.12 | 6.29 | 6.55 | 0.00 | 6.21 | 50.0 | 7.5 | 6.212 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 841.8 | 120.9 | 100.000 |



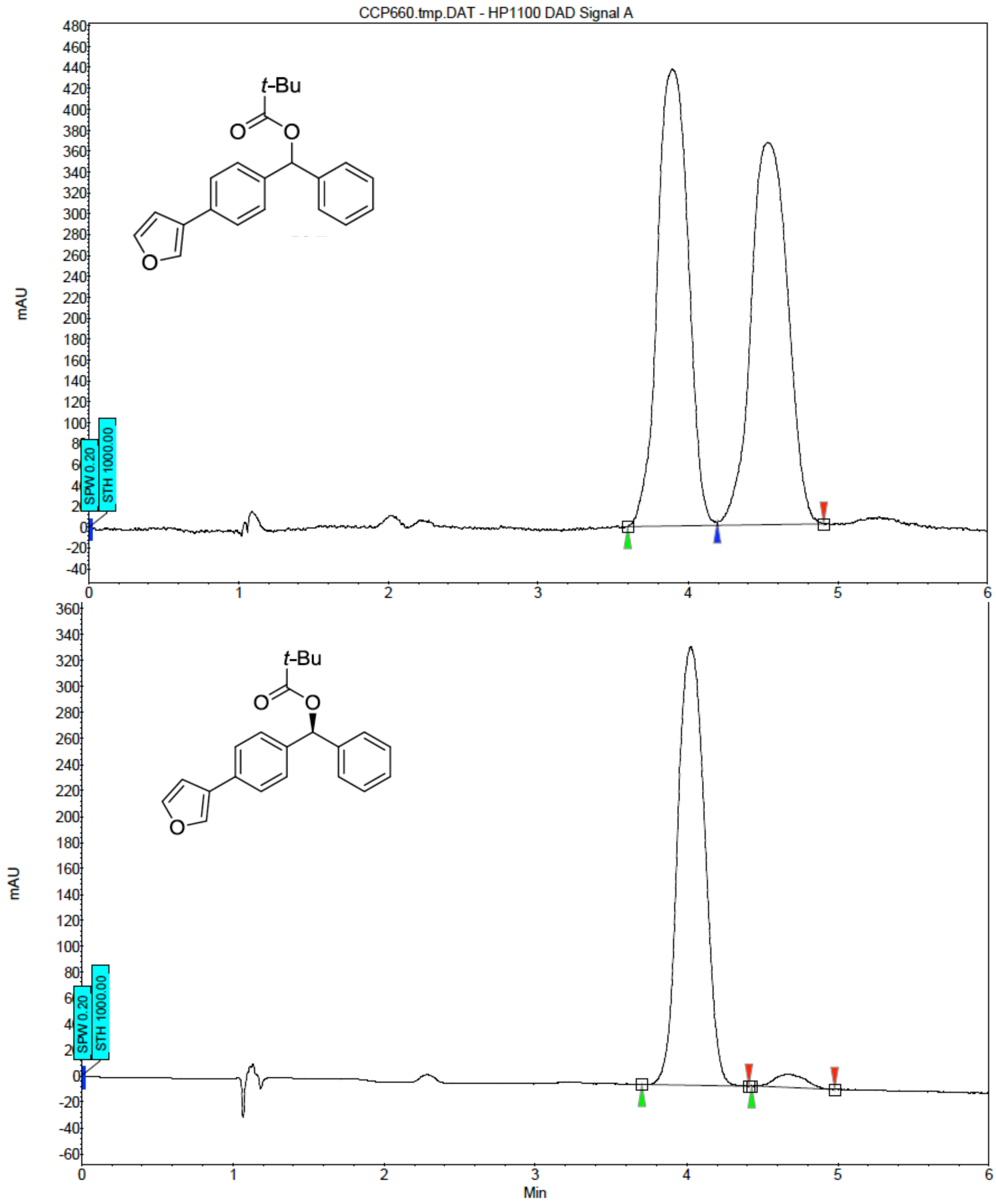


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 6.82 | 6.99 | 7.13 | 0.00 | 9.06 | 51.7 | 6.3 | 9.058 |
| 2 | UNKNOWN | 7.14 | 7.30 | 7.56 | 0.00 | 90.94 | 463.0 | 63.5 | 90.942 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 514.7 | 69.9 | 100.000 |

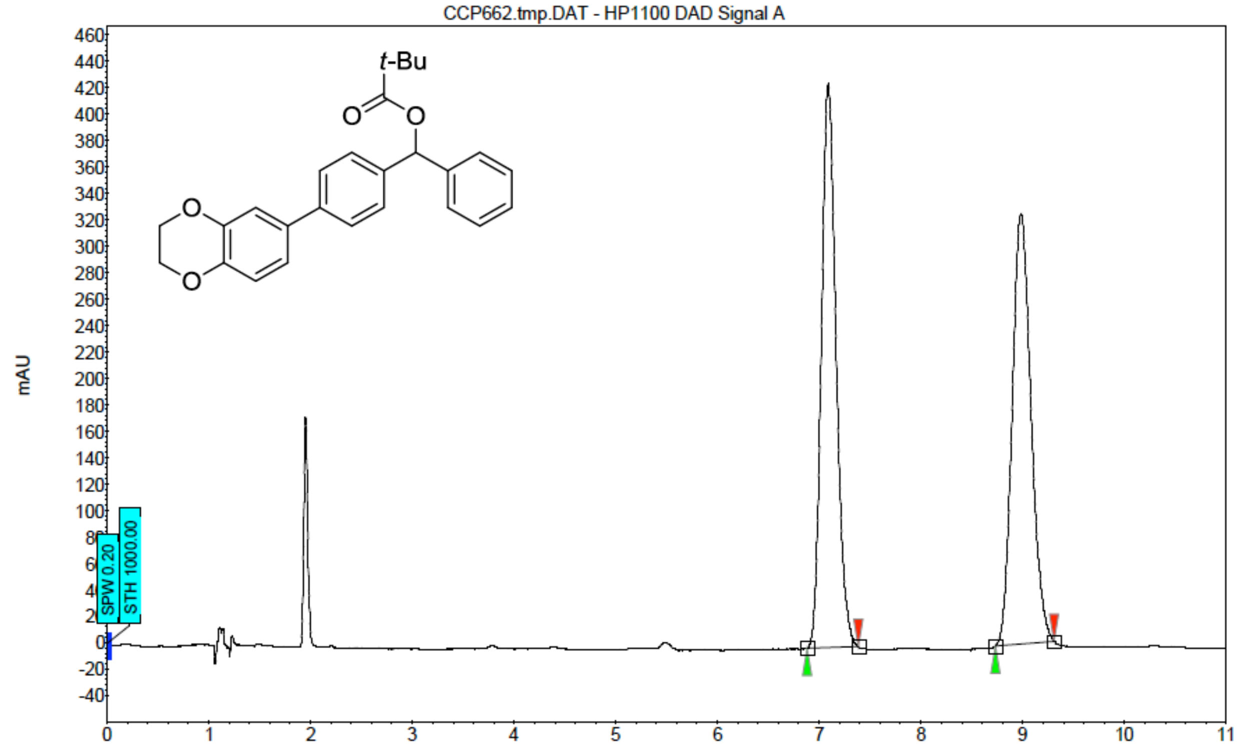


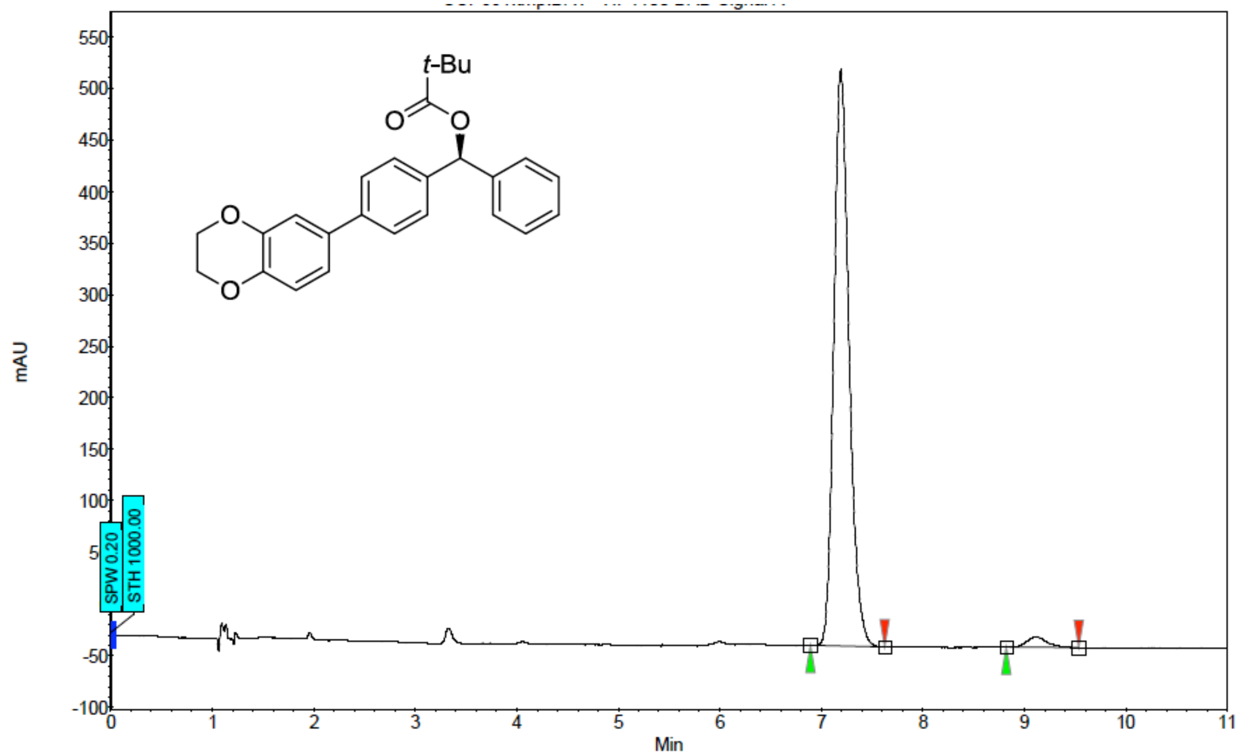


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 2 | UNKNOWN | 3.93 | 4.06 | 4.26 | 0.00 | 1.88 | 19.0 | 3.1 | 1.877 |
| 1 | UNKNOWN | 6.14 | 6.43 | 6.93 | 0.00 | 98.12 | 625.4 | 161.3 | 98.123 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 644.3 | 164.4 | 100.000 |

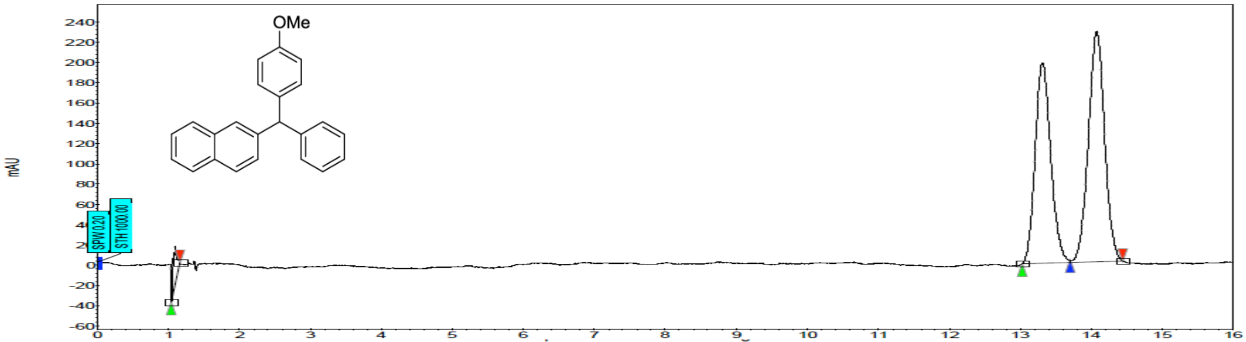


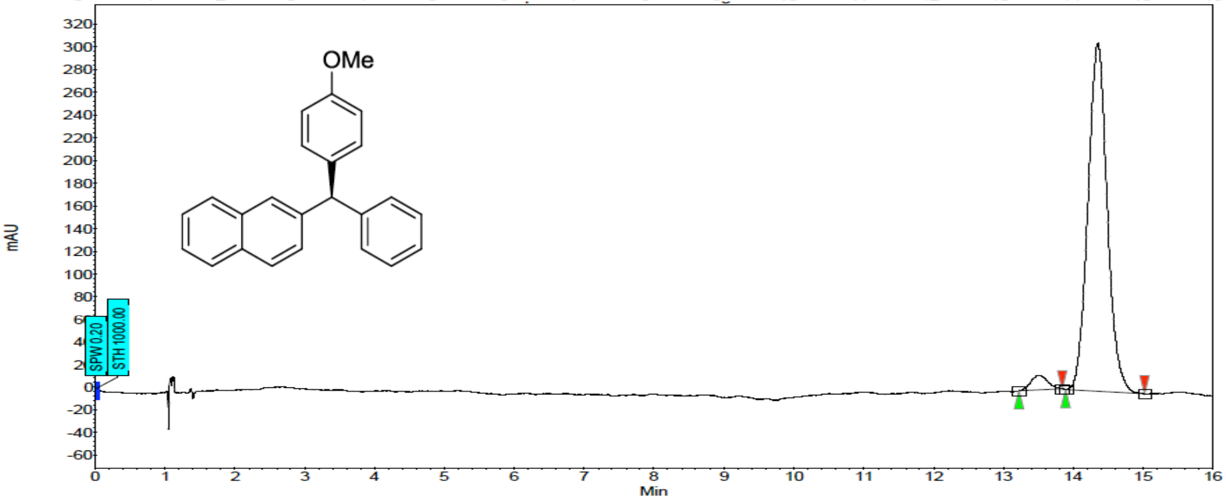
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 3.70 | 4.03 | 4.41 | 0.00 | 96.61 | 337.3 | 69.5 | 96.611 |
| 2 | UNKNOWN | 4.43 | 4.66 | 4.98 | 0.00 | 3.39 | 10.1 | 2.4 | 3.389 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 347.4 | 71.9 | 100.000 |



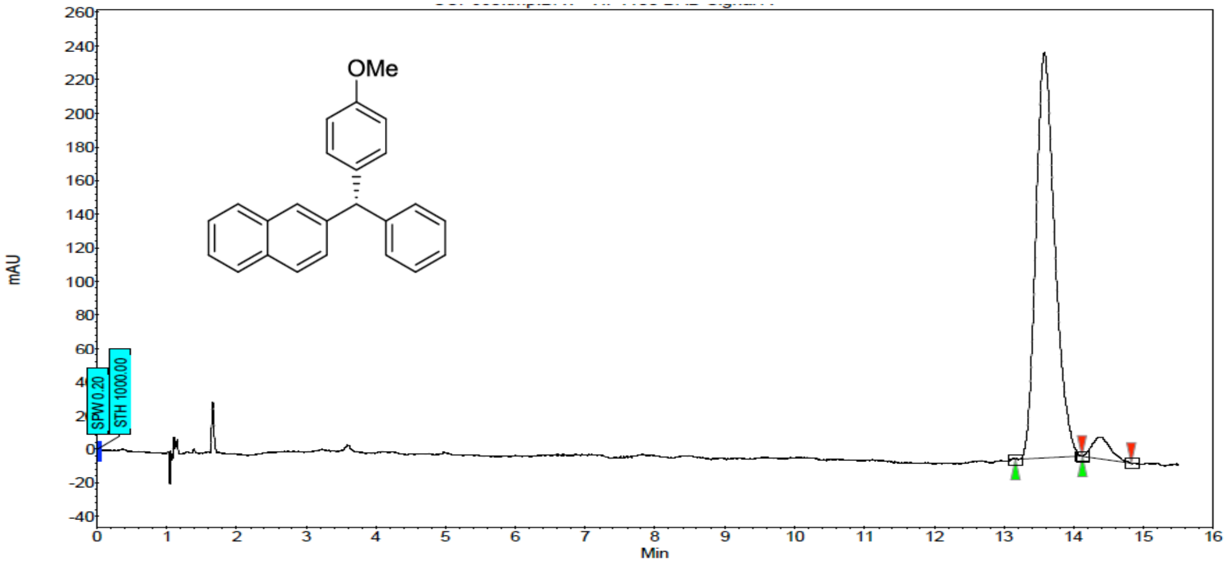


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [μV] | [μV.Min] | [%] |
| 1 | UNKNOWN | 6.89 | 7.19 | 7.62 | 0.00 | 97.79 | 558.2 | 96.4 | 97.790 |
| 2 | UNKNOWN | 8.82 | 9.11 | 9.53 | 0.00 | 2.21 | 9.8 | 2.2 | 2.210 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 568.0 | 98.6 | 100.000 |

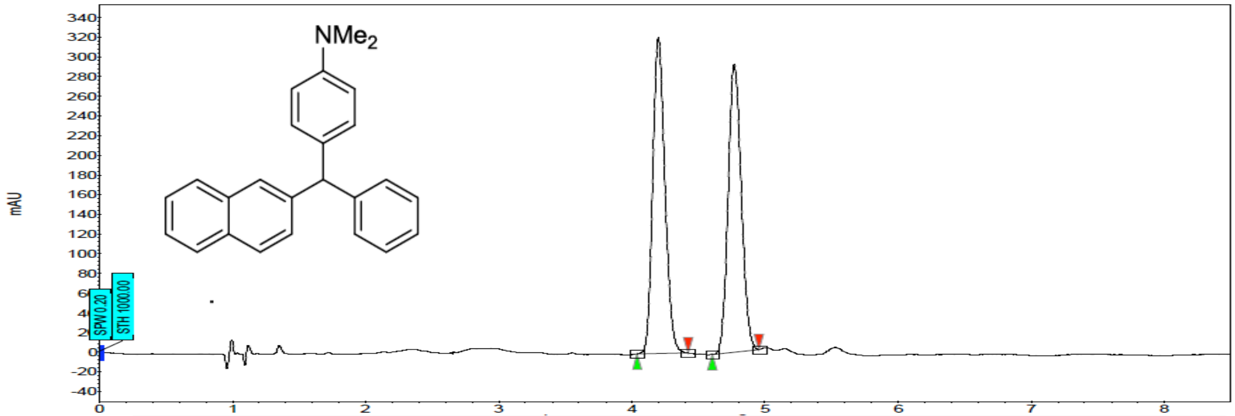


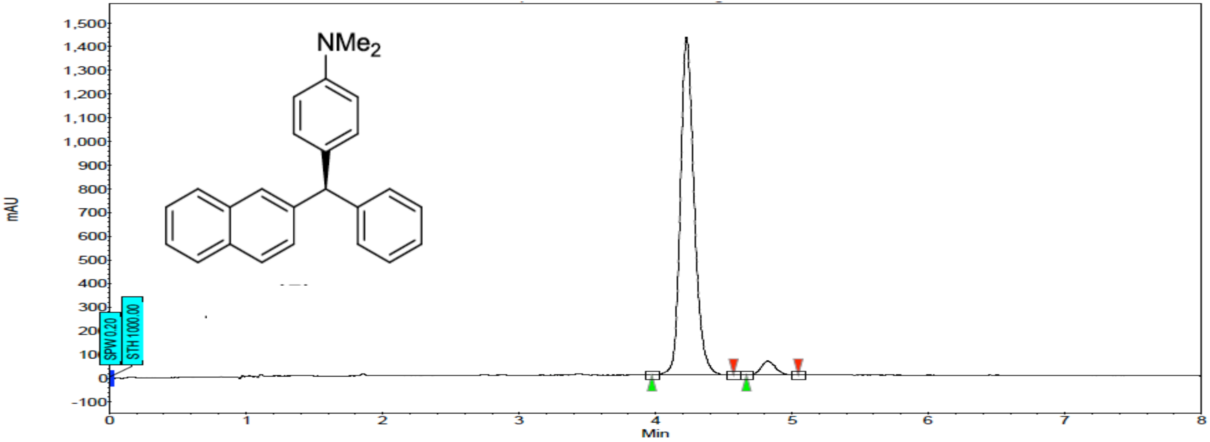


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 13.22 | 13.52 | 13.84 | 0.00 | 3.51 | 13.0 | 3.6 | 3.505 |
| 2 | UNKNOWN | 13.89 | 14.35 | 15.02 | 0.00 | 96.49 | 306.8 | 98.0 | 96.495 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 319.8 | 101.6 | 100.000 |

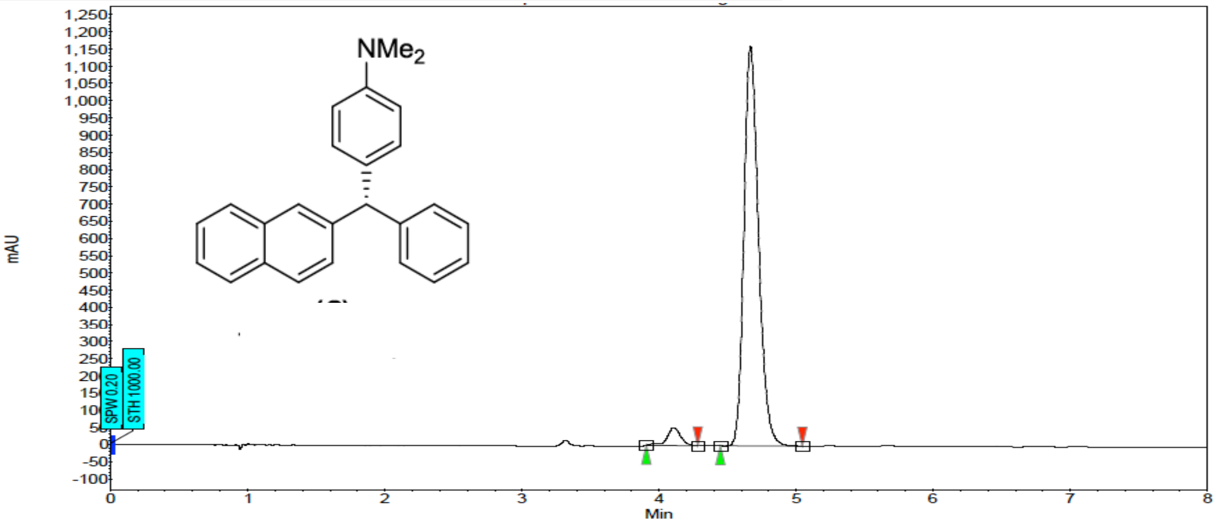


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 13.16 | 13.58 | 14.11 | 0.00 | 95.00 | 241.1 | 76.1 | 94.998 |
| 2 | UNKNOWN | 14.12 | 14.40 | 14.83 | 0.00 | 5.00 | 12.9 | 4.0 | 5.002 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 254.0 | 80.1 | 100.000 |

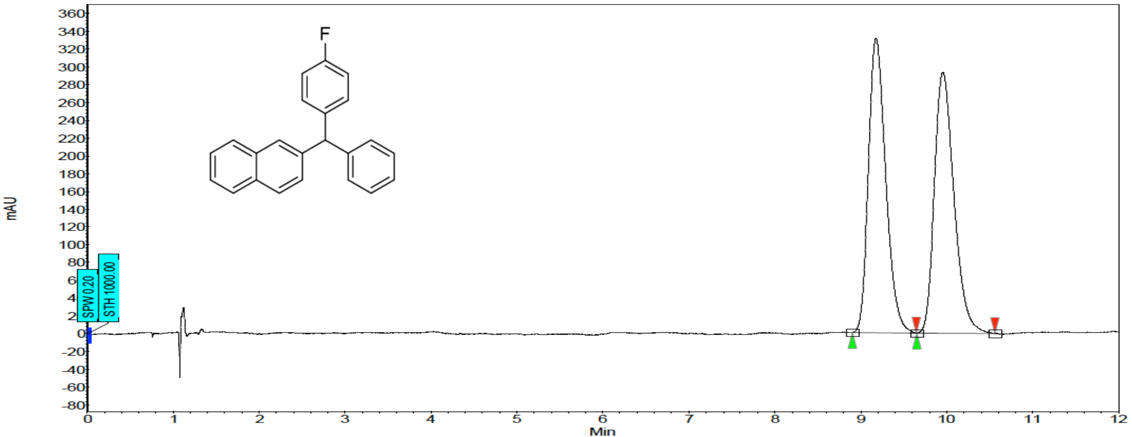


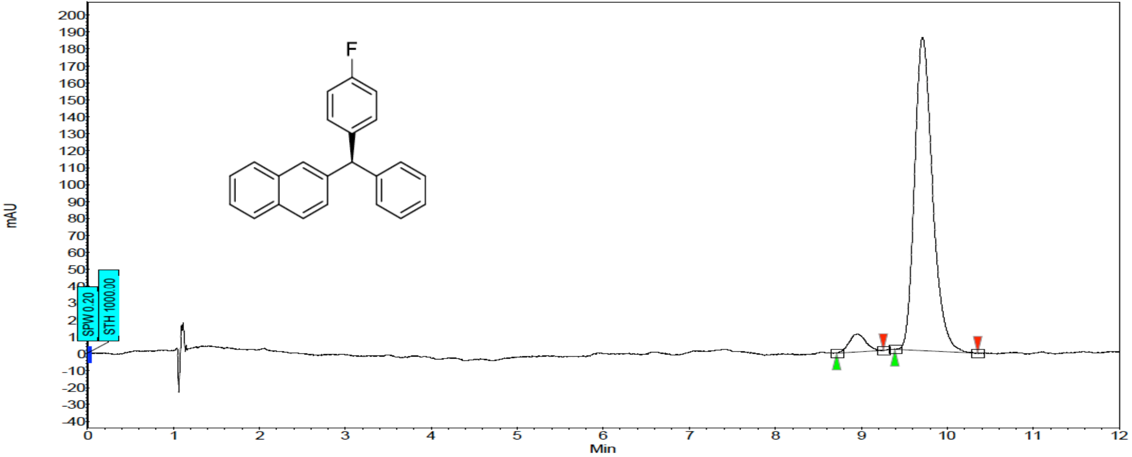


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 3.98 | 4.23 | 4.57 | 0.00 | 95.82 | 1425.1 | 166.4 | 95.819 |
| 2 | UNKNOWN | 4.67 | 4.83 | 5.05 | 0.00 | 4.18 | 59.1 | 7.3 | 4.181 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 1484.1 | 173.7 | 100.000 |

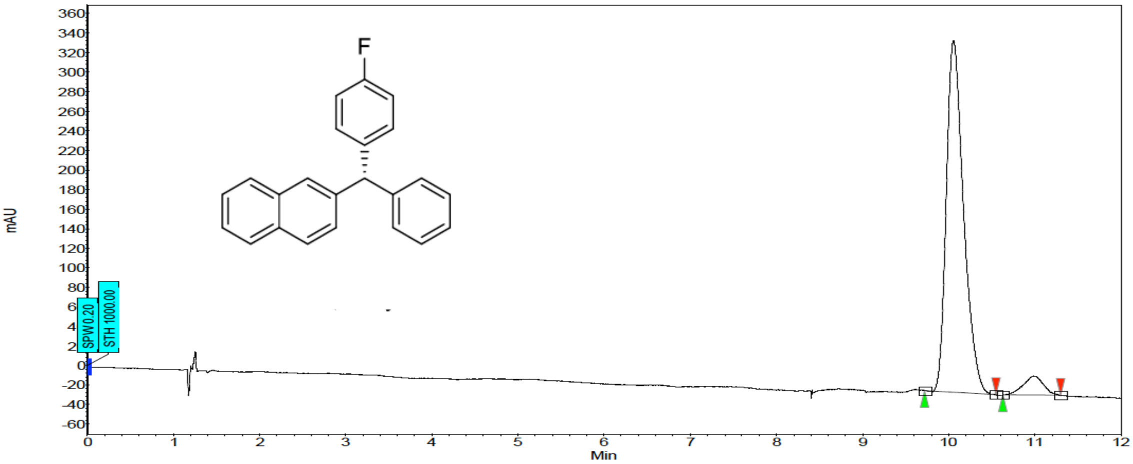


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 2 | UNKNOWN | 3.91 | 4.11 | 4.29 | 0.00 | 4.01 | 52.1 | 6.0 | 4.006 |
| 1 | UNKNOWN | 4.45 | 4.67 | 5.05 | 0.00 | 95.99 | 1160.9 | 143.0 | 95.994 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 1213.0 | 148.9 | 100.000 |

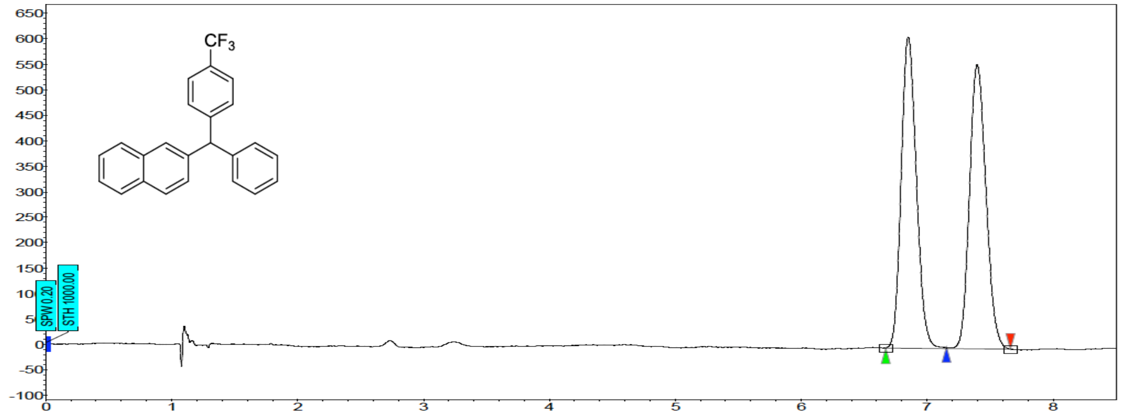


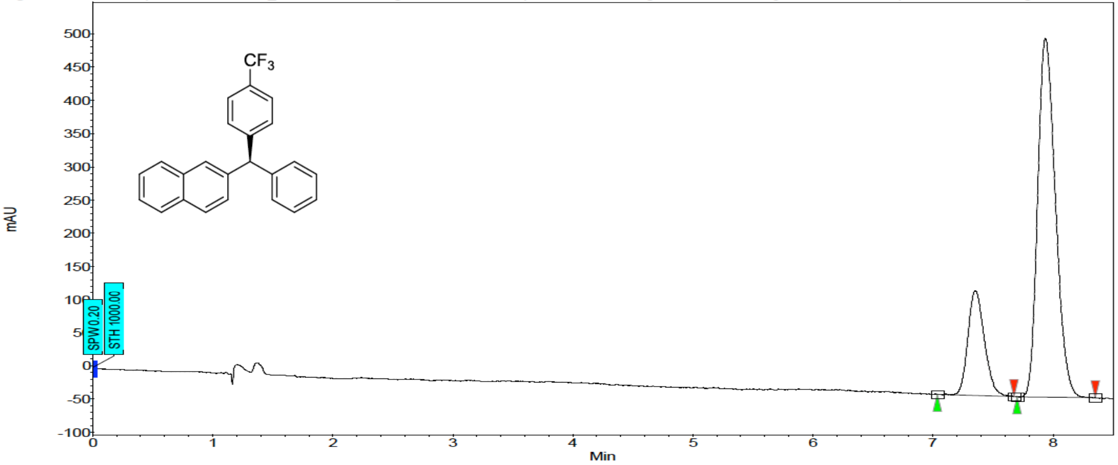


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 8.71 | 8.96 | 9.26 | 0.00 | 4.97 | 10.6 | 2.4 | 4.971 |
| 2 | UNKNOWN | 9.39 | 9.71 | 10.35 | 0.00 | 95.03 | 185.0 | 45.1 | 95.029 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 195.6 | 47.5 | 100.000 |

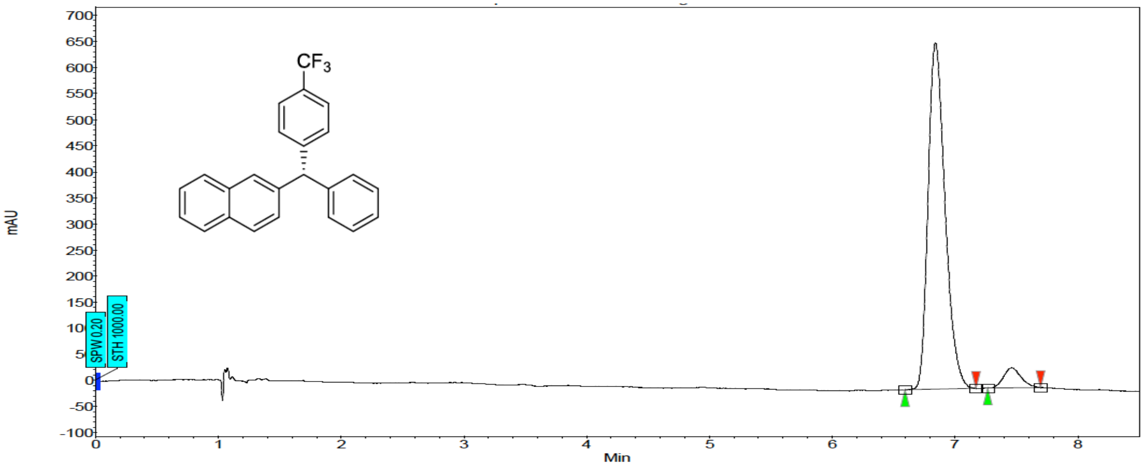


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 9.72 | 10.06 | 10.55 | 0.00 | 94.00 | 359.5 | 82.9 | 94.005 |
| 2 | UNKNOWN | 10.63 | 10.98 | 11.30 | 0.00 | 6.00 | 19.5 | 5.3 | 5.995 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 379.0 | 88.2 | 100.000 |

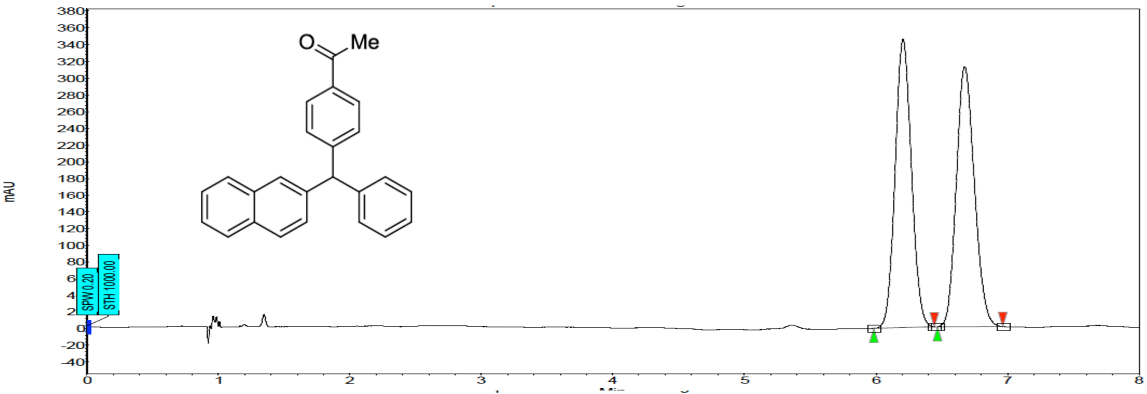


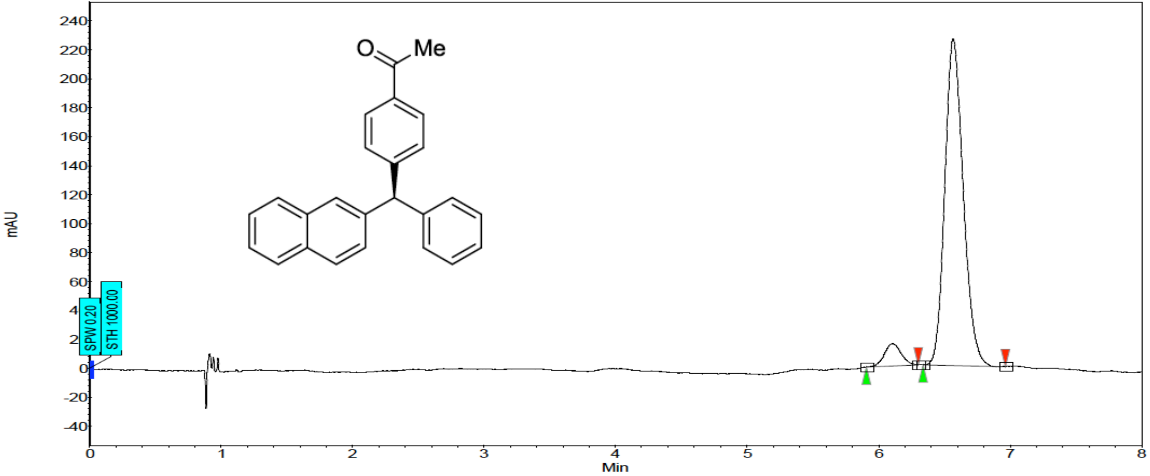


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 7.04 | 7.35 | 7.67 | 0.00 | 21.30 | 157.7 | 25.0 | 21.299 |
| 2 | UNKNOWN | 7.70 | 7.94 | 8.35 | 0.00 | 78.70 | 540.3 | 92.5 | 78.701 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 698.0 | 117.6 | 100.000 |

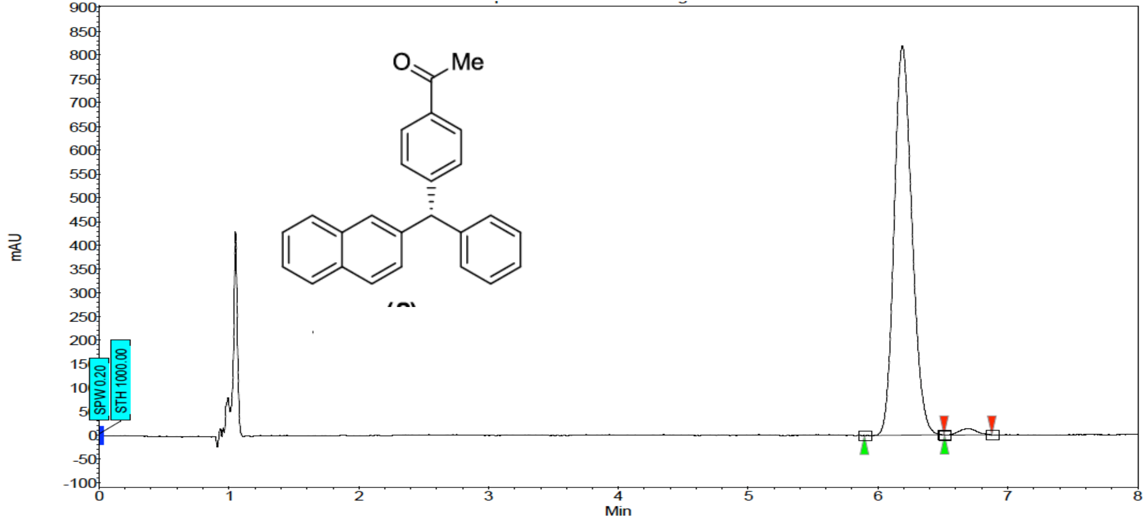


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 6.59 | 6.84 | 7.17 | 0.00 | 94.37 | 663.8 | 106.4 | 94.372 |
| 2 | UNKNOWN | 7.27 | 7.46 | 7.70 | 0.00 | 5.63 | 38.2 | 6.3 | 5.628 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 702.1 | 112.7 | 100.000 |

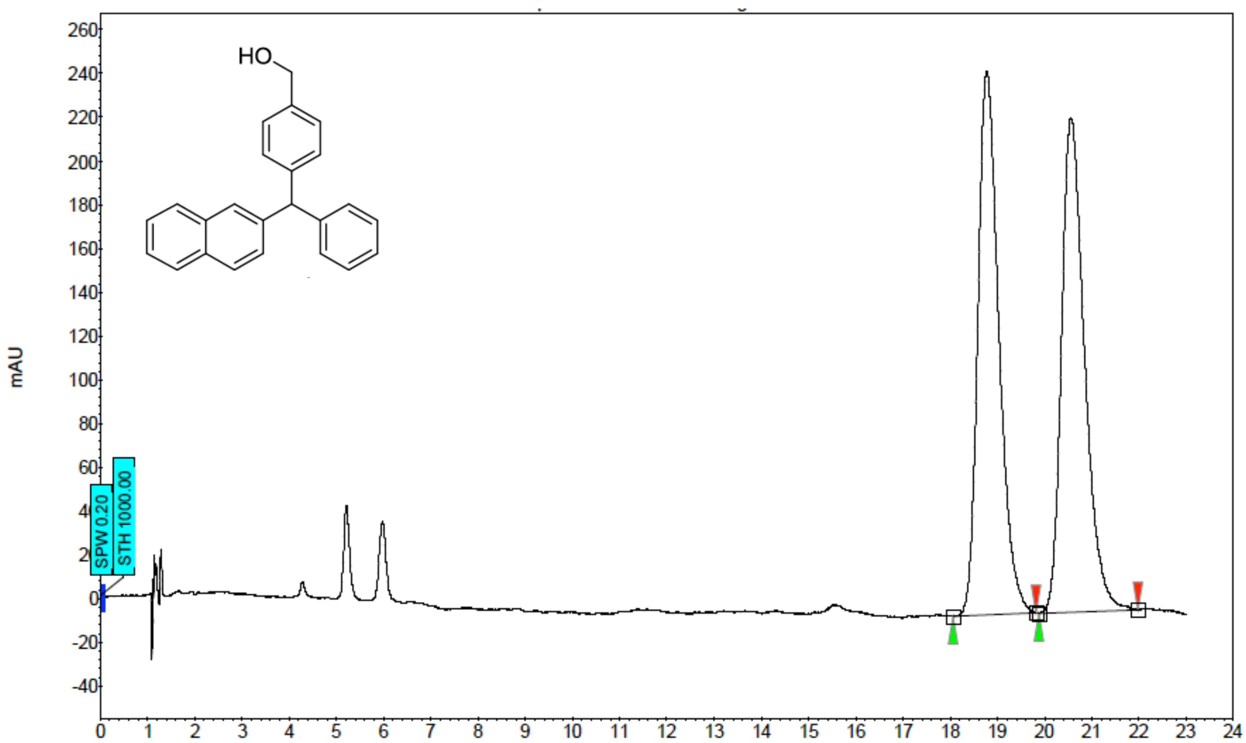


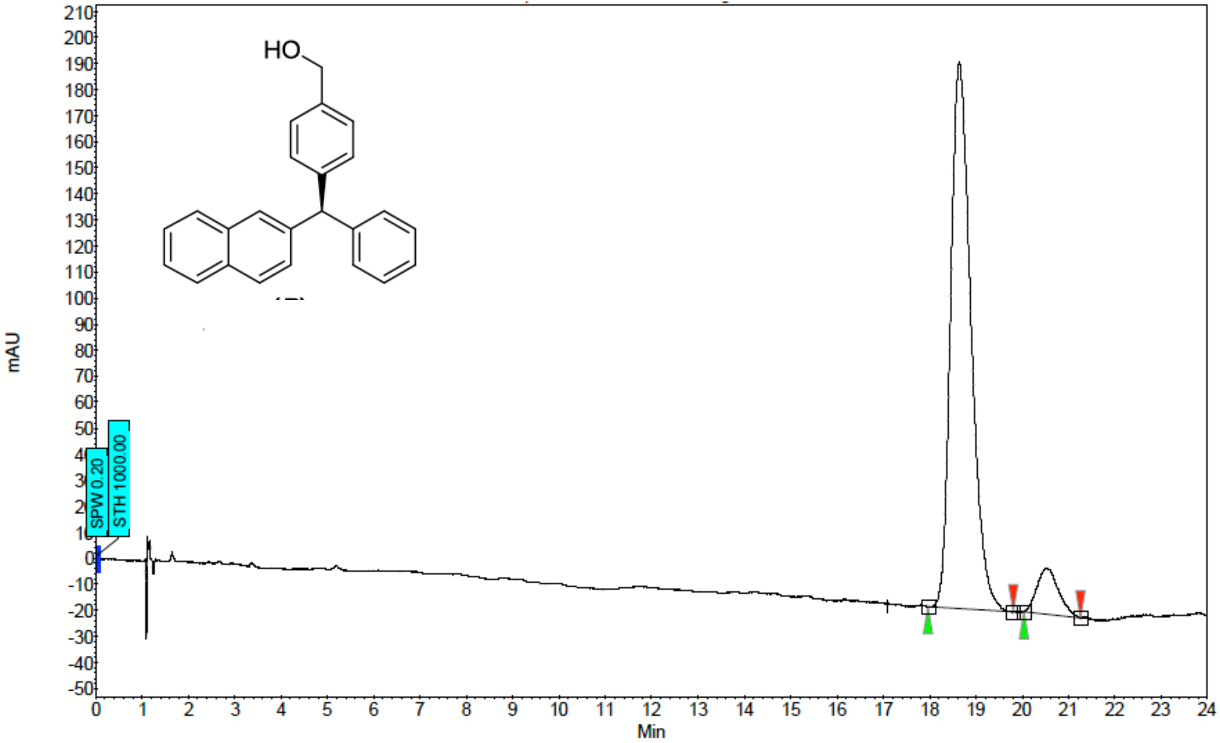


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 2 | UNKNOWN | 5.91 | 6.11 | 6.30 | 0.00 | 5.73 | 15.4 | 2.3 | 5.725 |
| 1 | UNKNOWN | 6.34 | 6.57 | 6.96 | 0.00 | 94.27 | 225.7 | 37.1 | 94.275 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 241.1 | 39.4 | 100.000 |

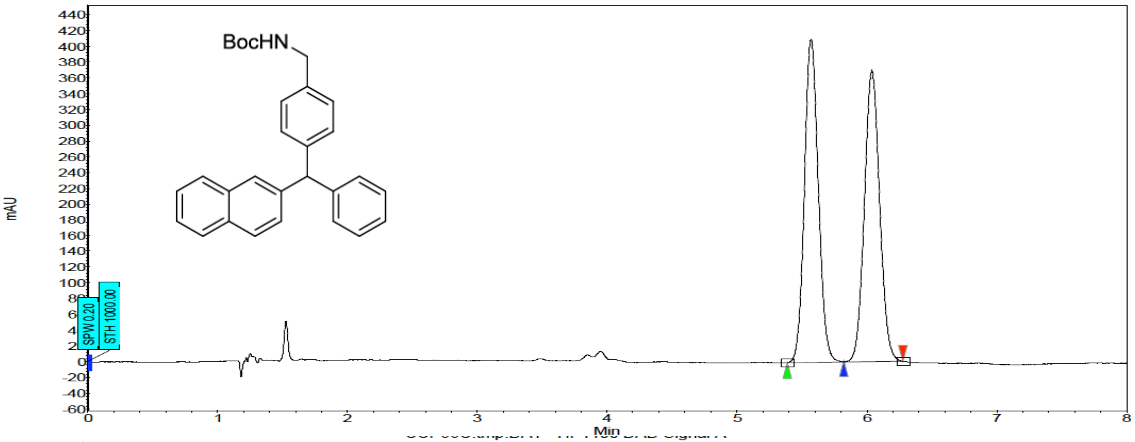


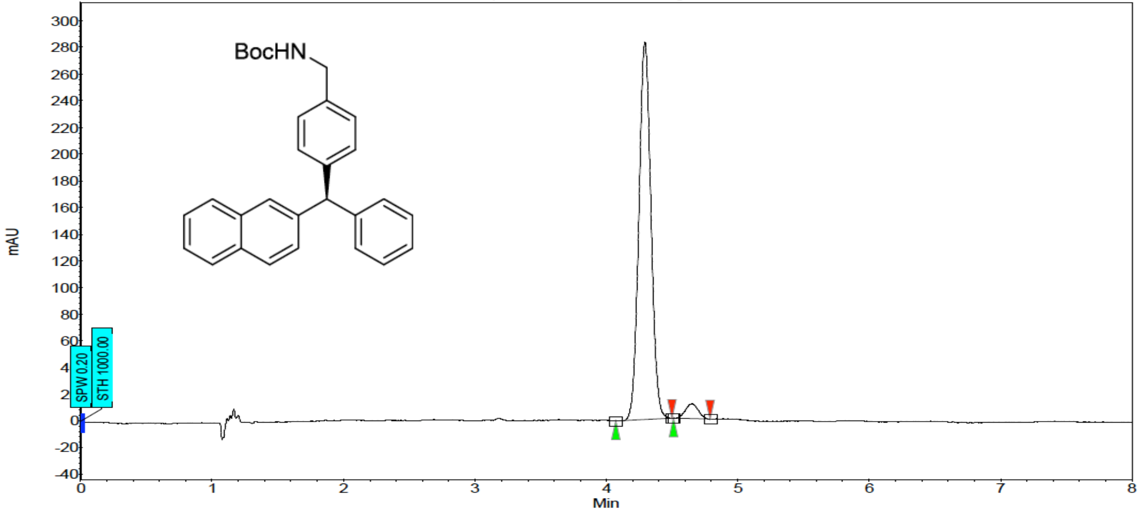
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 5.90 | 6.19 | 6.51 | 0.00 | 98.37 | 818.9 | 129.1 | 98.371 |
| 2 | UNKNOWN | 6.51 | 6.69 | 6.88 | 0.00 | 1.63 | 13.7 | 2.1 | 1.629 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 832.6 | 131.2 | 100.000 |



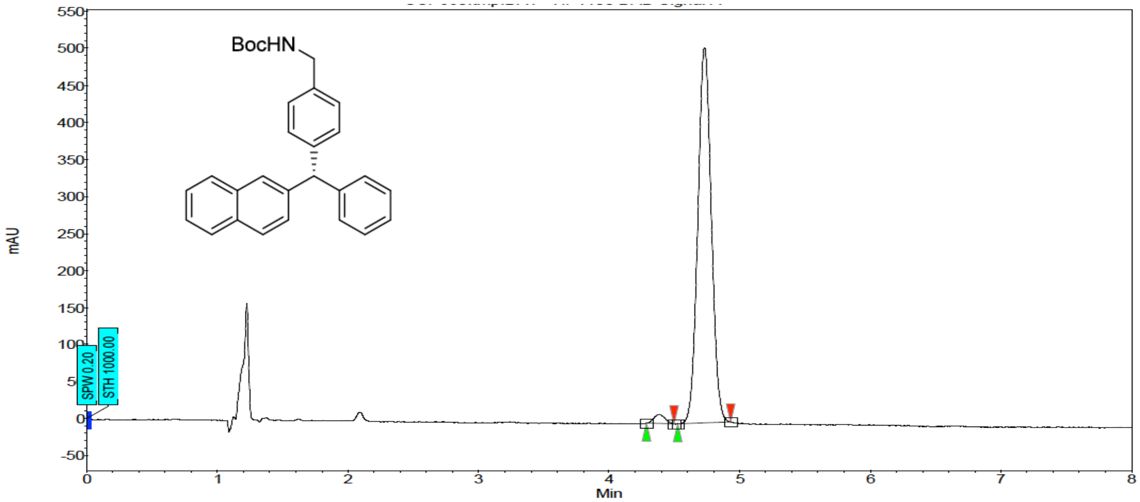


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 17.97 | 18.64 | 19.81 | 0.00 | 91.88 | 209.7 | 106.3 | 91.876 |
| 2 | UNKNOWN | 20.04 | 20.53 | 21.26 | 0.00 | 8.12 | 17.7 | 9.4 | 8.124 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 227.3 | 115.7 | 100.000 |

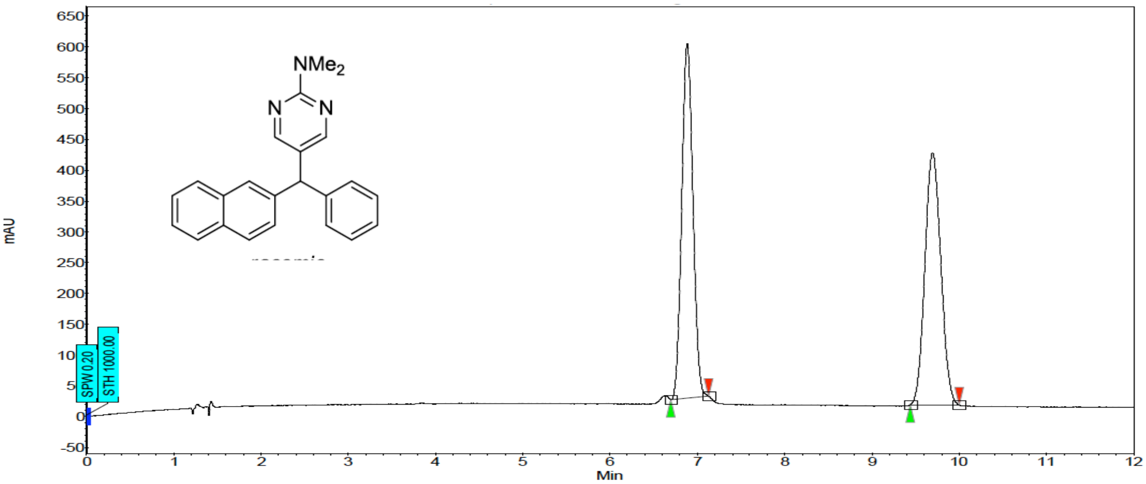


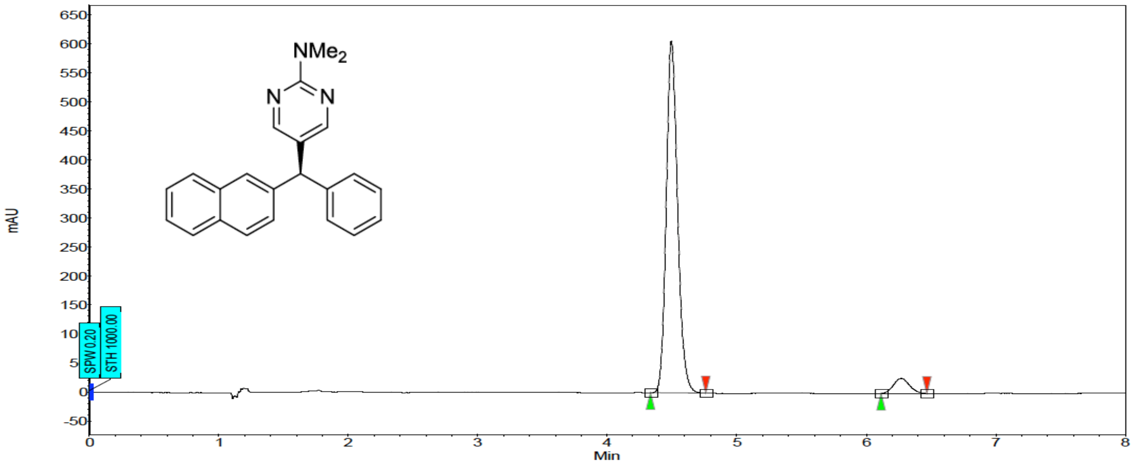


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 4.07 | 4.29 | 4.50 | 0.00 | 96.08 | 283.0 | 30.0 | 96.085 |
| 2 | UNKNOWN | 4.51 | 4.66 | 4.79 | 0.00 | 3.92 | 11.0 | 1.2 | 3.915 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 294.0 | 31.2 | 100.000 |

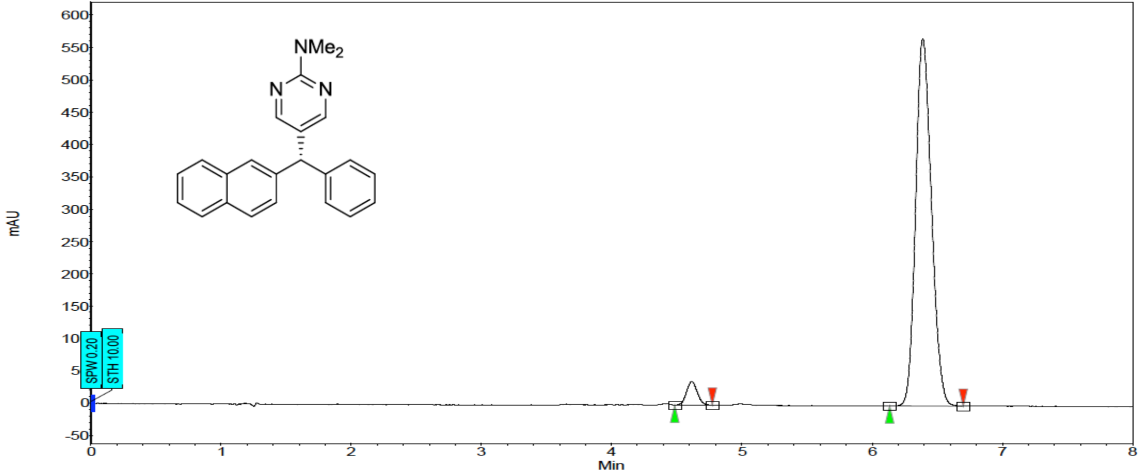


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 4.29 | 4.39 | 4.50 | 0.00 | 1.92 | 11.9 | 1.2 | 1.924 |
| 2 | UNKNOWN | 4.53 | 4.73 | 4.93 | 0.00 | 98.08 | 506.5 | 60.4 | 98.076 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 518.5 | 61.6 | 100.000 |

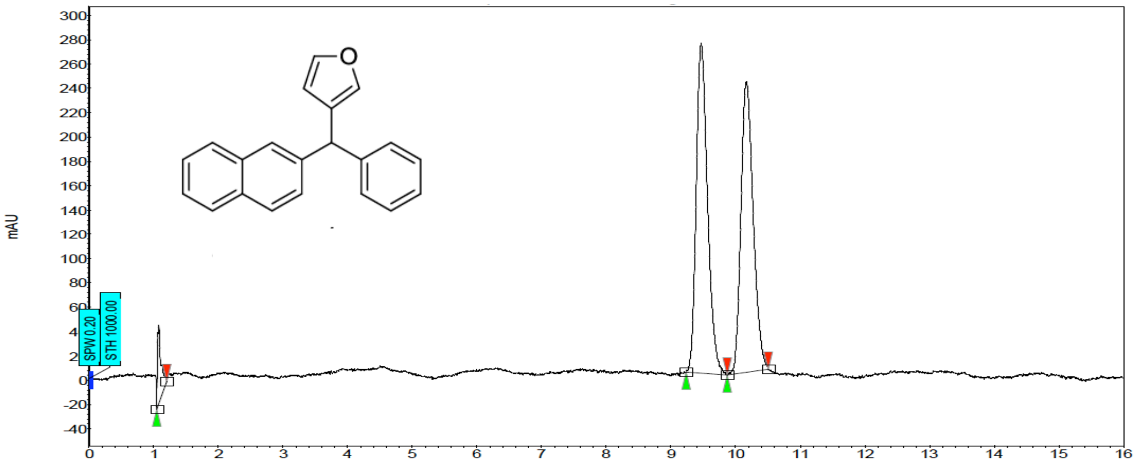


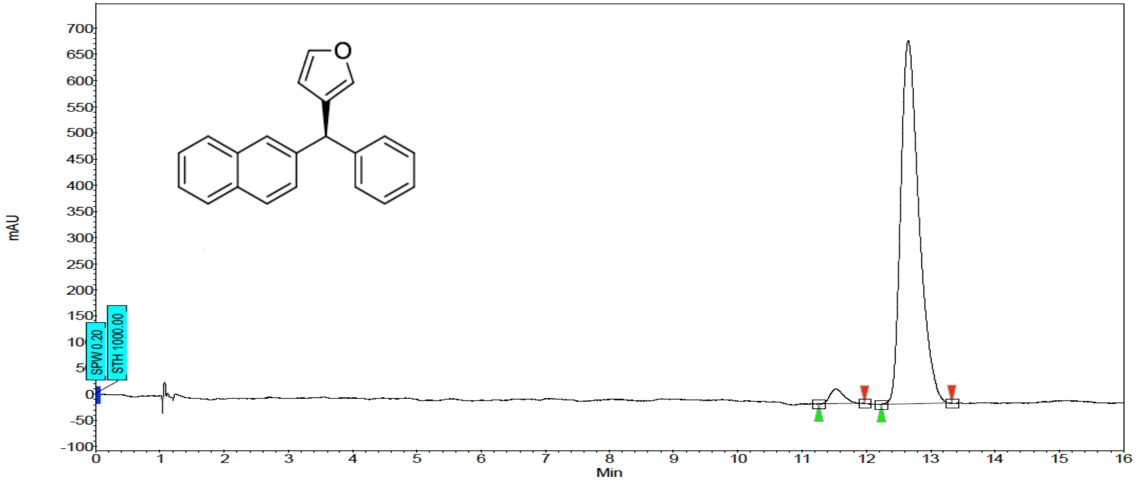


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 4.33 | 4.50 | 4.76 | 0.00 | 94.50 | 606.4 | 62.5 | 94.501 |
| 2 | UNKNOWN | 6.12 | 6.27 | 6.47 | 0.00 | 5.50 | 25.7 | 3.6 | 5.499 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 632.1 | 66.2 | 100.000 |

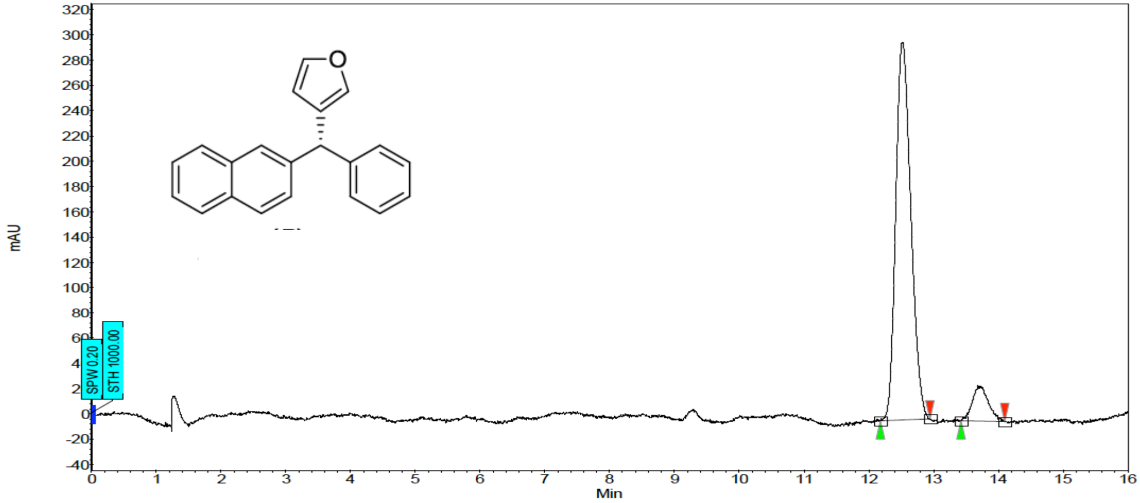


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 4.48 | 4.62 | 4.77 | 0.00 | 4.20 | 36.6 | 3.5 | 4.201 |
| 2 | UNKNOWN | 6.13 | 6.39 | 6.70 | 0.00 | 95.80 | 567.9 | 79.6 | 95.799 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 604.4 | 83.1 | 100.000 |

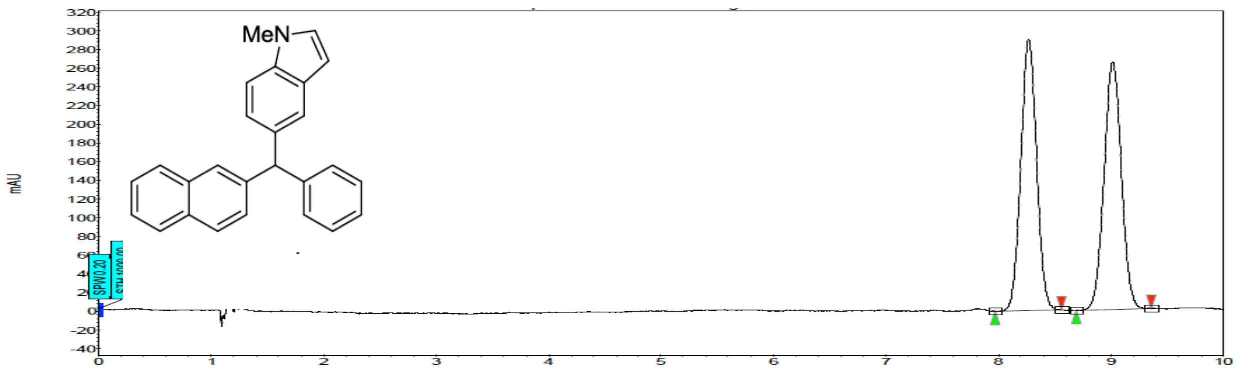


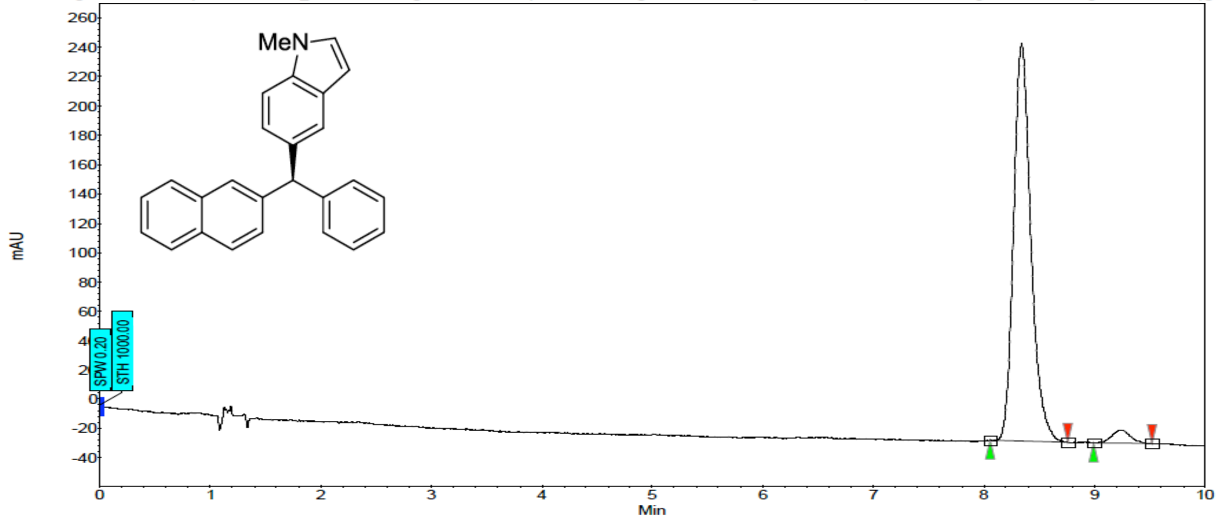


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 2 | UNKNOWN | 11.26 | 11.53 | 11.97 | 0.00 | 2.94 | 28.1 | 6.9 | 2.937 |
| 1 | UNKNOWN | 12.23 | 12.65 | 13.32 | 0.00 | 97.06 | 694.1 | 227.6 | 97.063 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 722.3 | 234.5 | 100.000 |

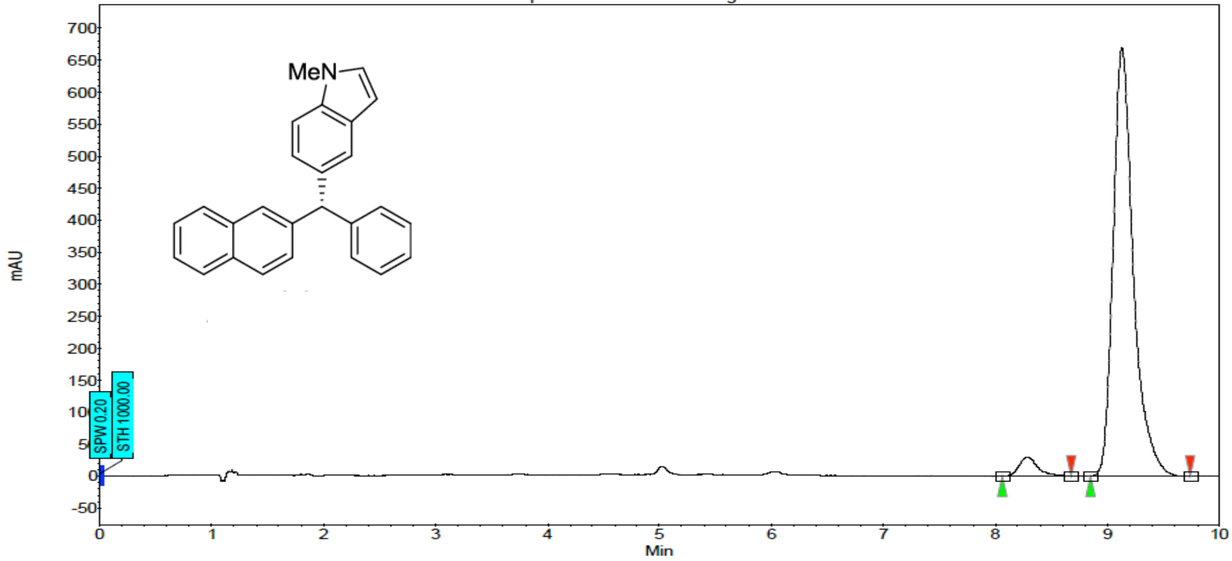


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 12.18 | 12.52 | 12.95 | 0.00 | 90.99 | 298.5 | 80.3 | 90.991 |
| 2 | UNKNOWN | 13.42 | 13.69 | 14.10 | 0.00 | 9.01 | 27.8 | 7.9 | 9.009 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 326.3 | 88.2 | 100.000 |

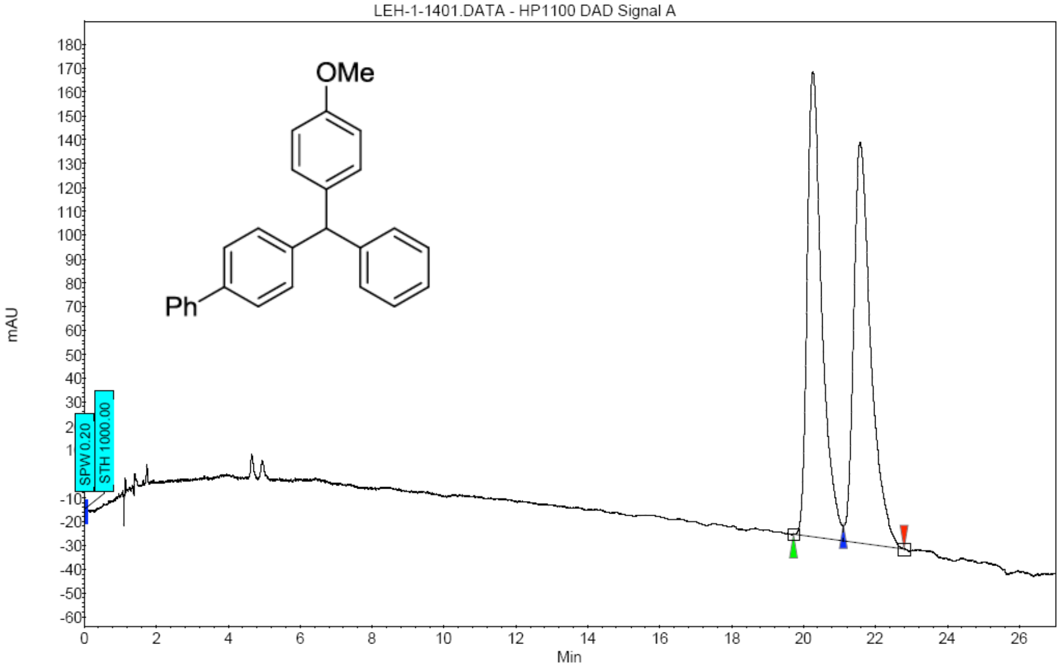


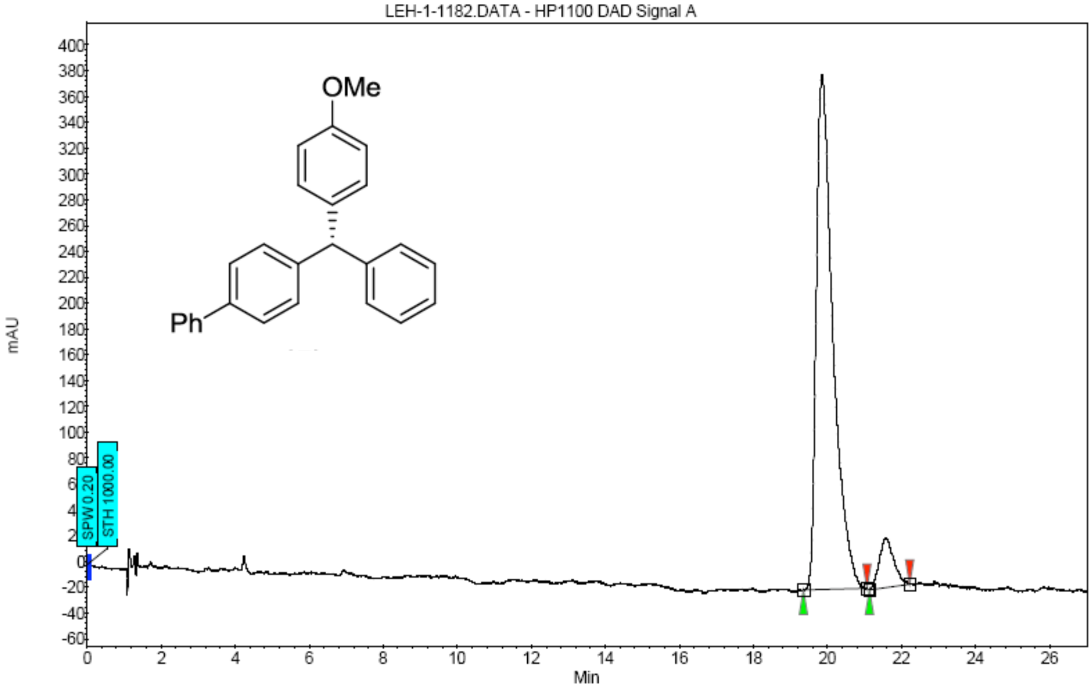


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 8.05 | 8.34 | 8.76 | 0.00 | 96.61 | 270.9 | 49.0 | 96.606 |
| 2 | UNKNOWN | 8.99 | 9.24 | 9.52 | 0.00 | 3.39 | 8.9 | 1.7 | 3.394 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 279.8 | 50.7 | 100.000 |

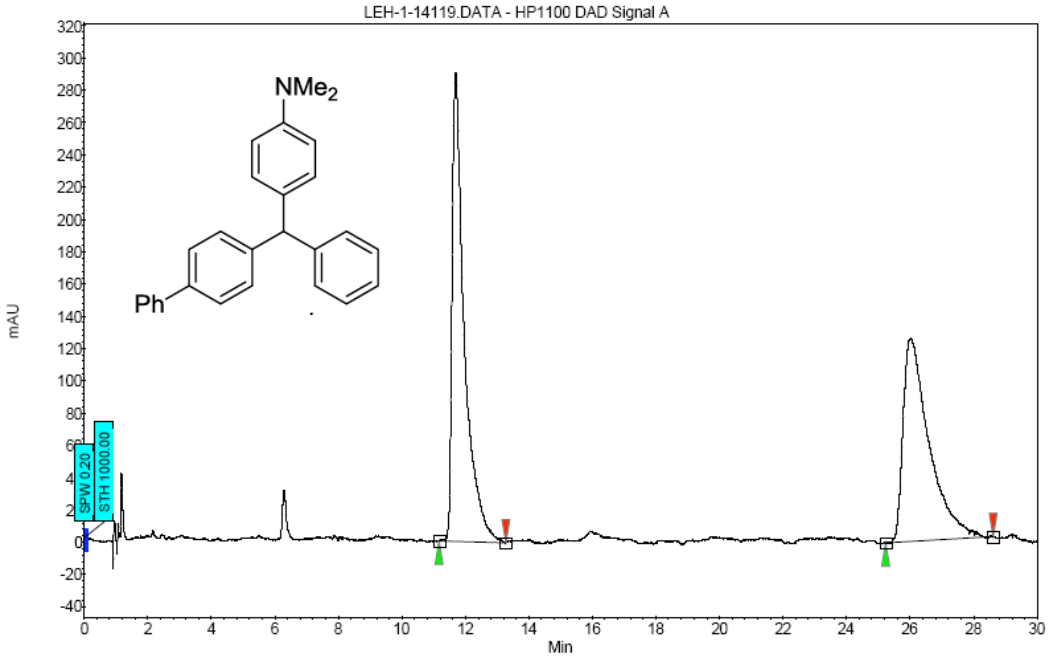


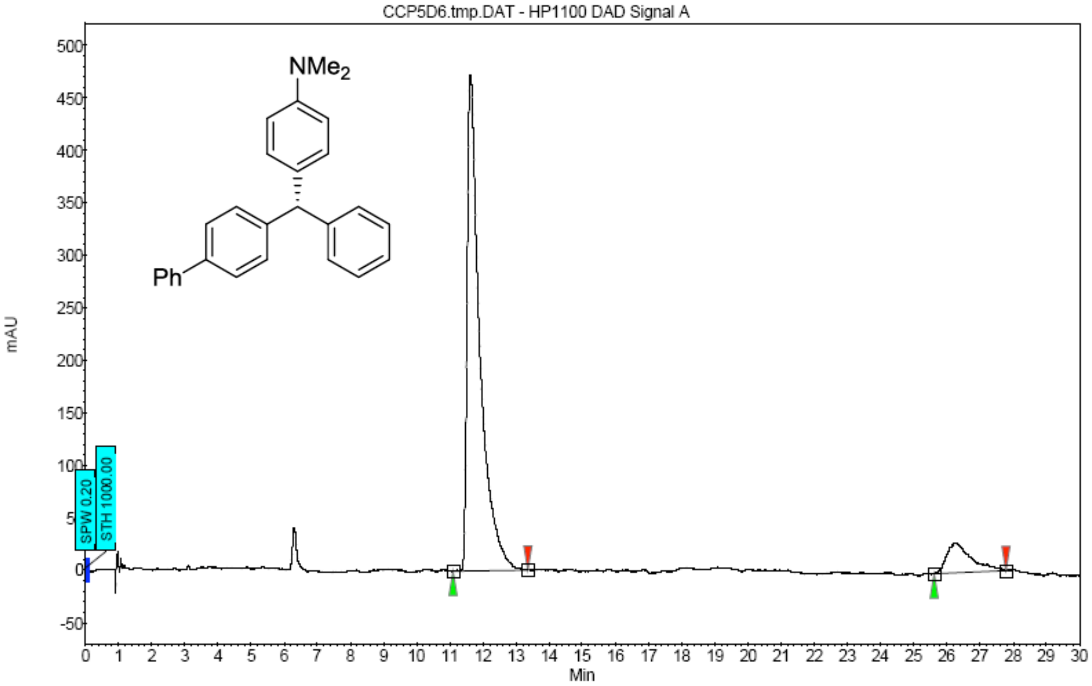
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 8.06 | 8.28 | 8.67 | 0.00 | 3.91 | 29.8 | 5.7 | 3.910 |
| 2 | UNKNOWN | 8.85 | 9.13 | 9.73 | 0.00 | 96.09 | 668.3 | 139.6 | 96.090 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 698.2 | 145.3 | 100.000 |



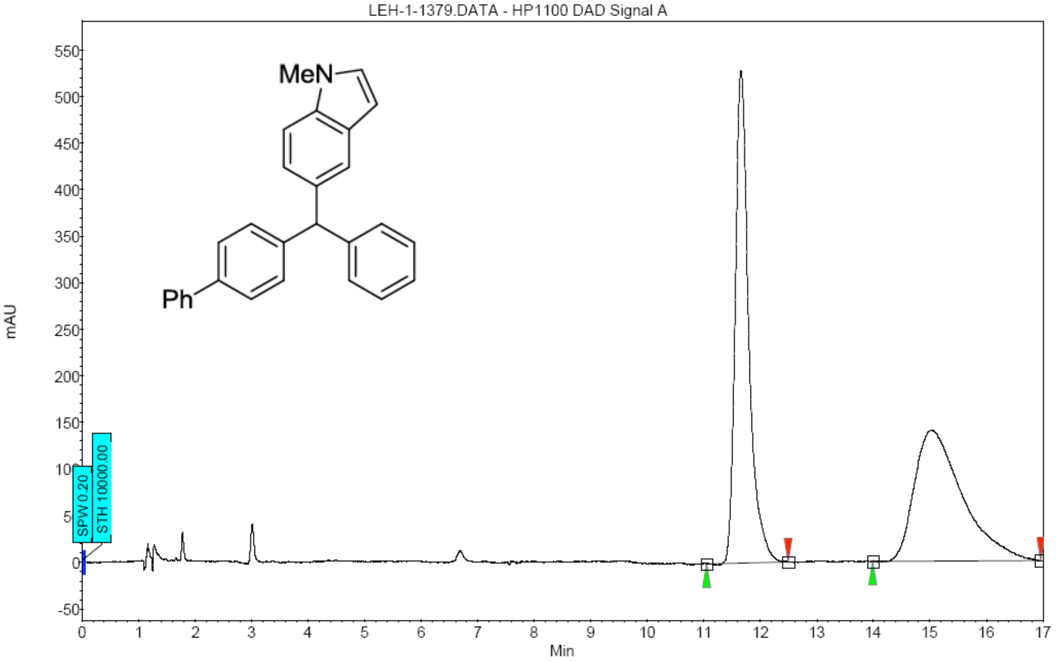


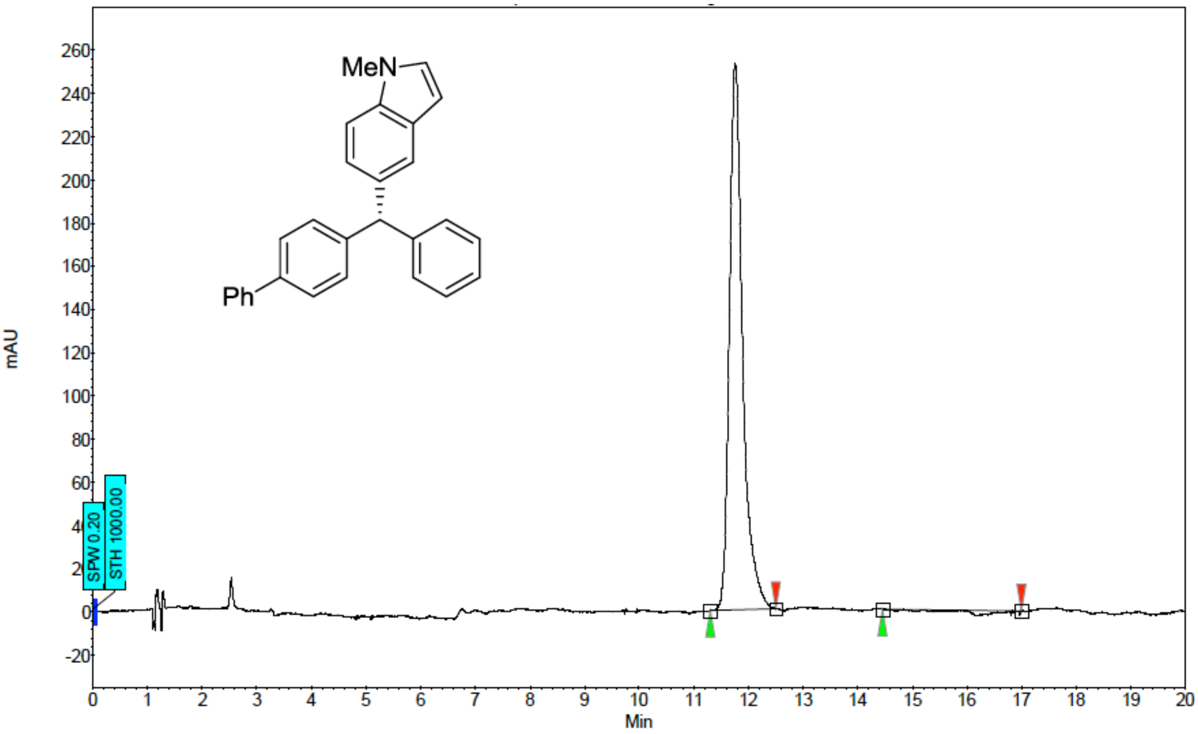
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 19.35 | 19.85 | 21.07 | 0.00 | 92.25 | 398.9 | 207.1 | 92.249 |
| 2 | UNKNOWN | 21.13 | 21.57 | 22.22 | 0.00 | 7.75 | 38.6 | 17.4 | 7.751 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 437.5 | 224.5 | 100.000 |



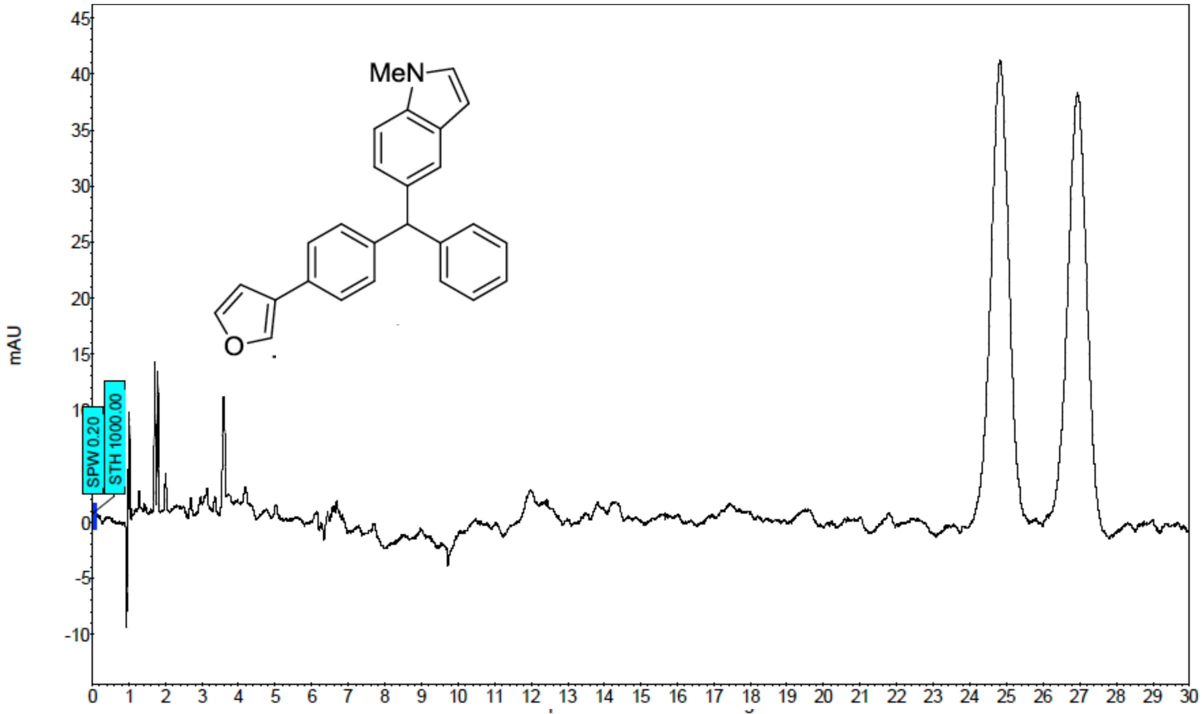


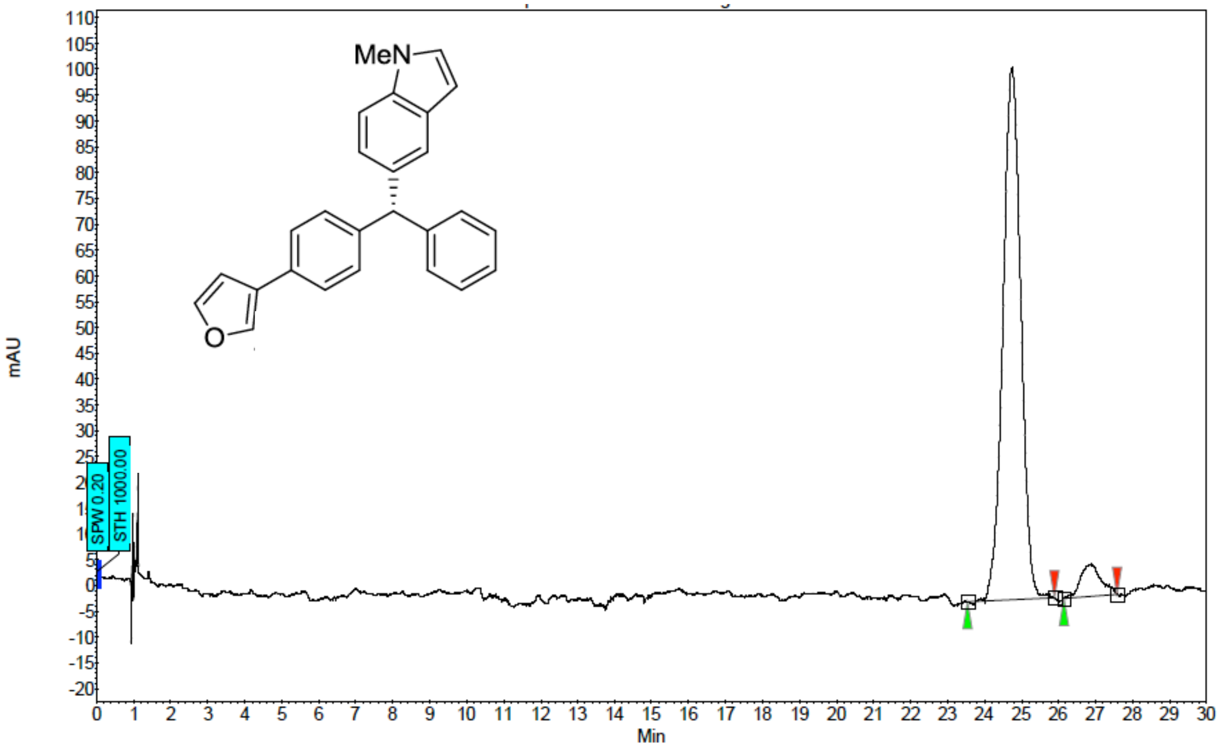
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 11.09 | 11.62 | 13.35 | 0.00 | 89.58 | 472.3 | 210.6 | 89.580 |
| 2 | UNKNOWN | 25.61 | 26.26 | 27.77 | 0.00 | 10.42 | 28.2 | 24.5 | 10.420 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 500.5 | 235.1 | 100.000 |



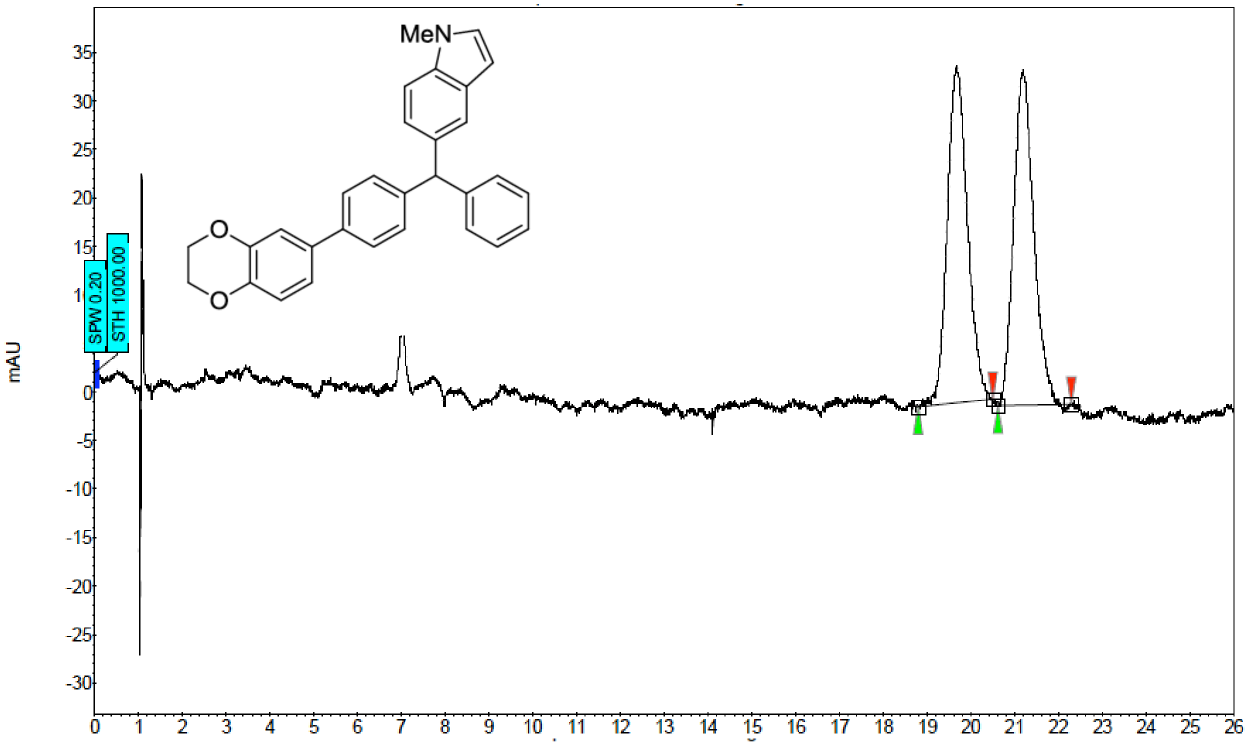


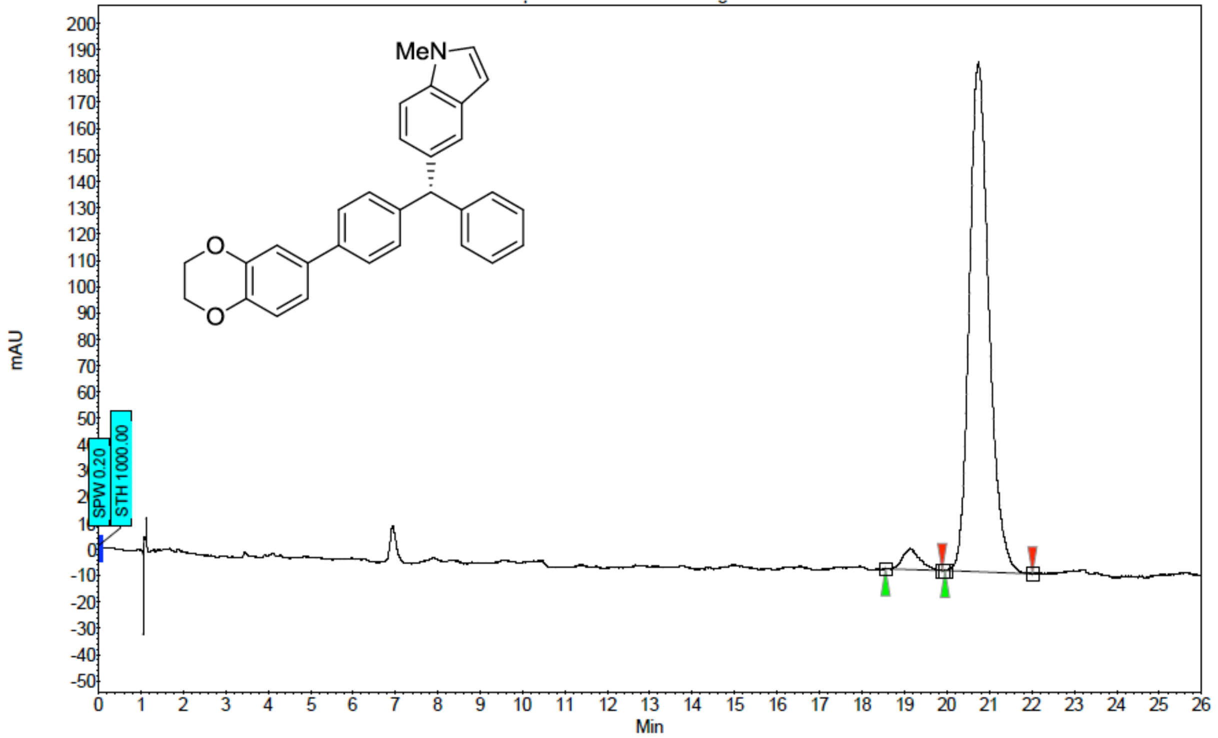
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 11.31 | 11.76 | 12.51 | 0.00 | 97.87 | 252.3 | 70.7 | 97.873 |
| 2 | UNKNOWN | 14.45 | 16.15 | 17.00 | 0.00 | 2.13 | 2.3 | 1.5 | 2.127 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 254.6 | 72.2 | 100.000 |



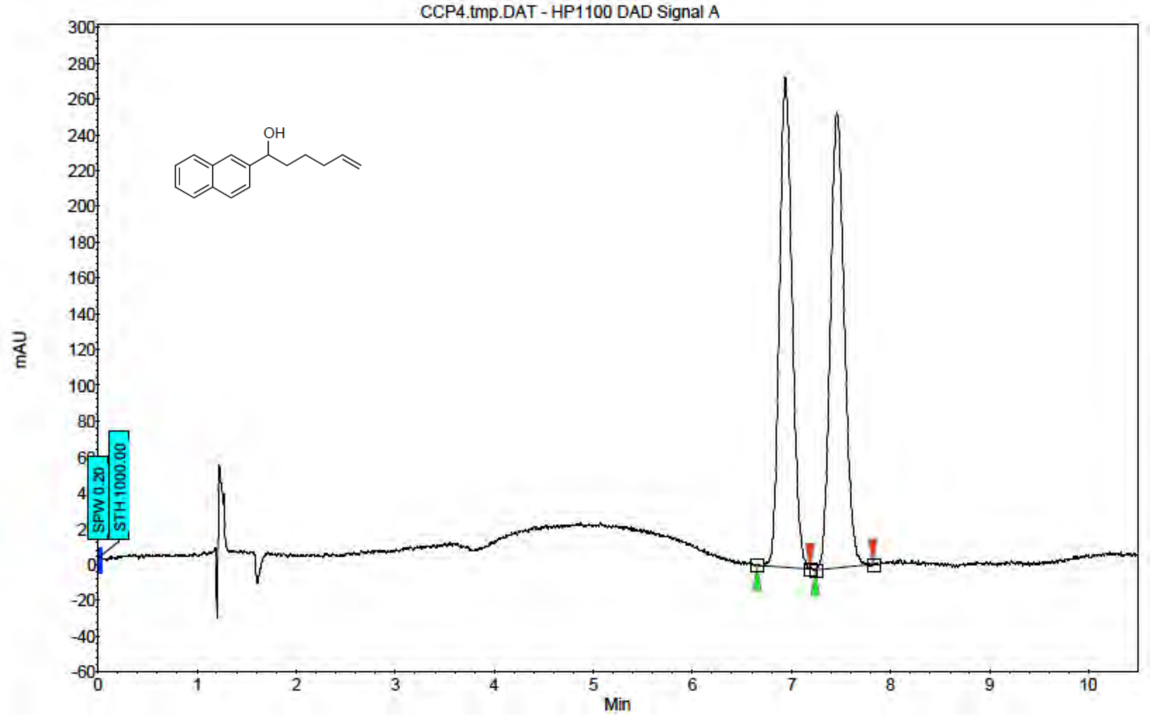


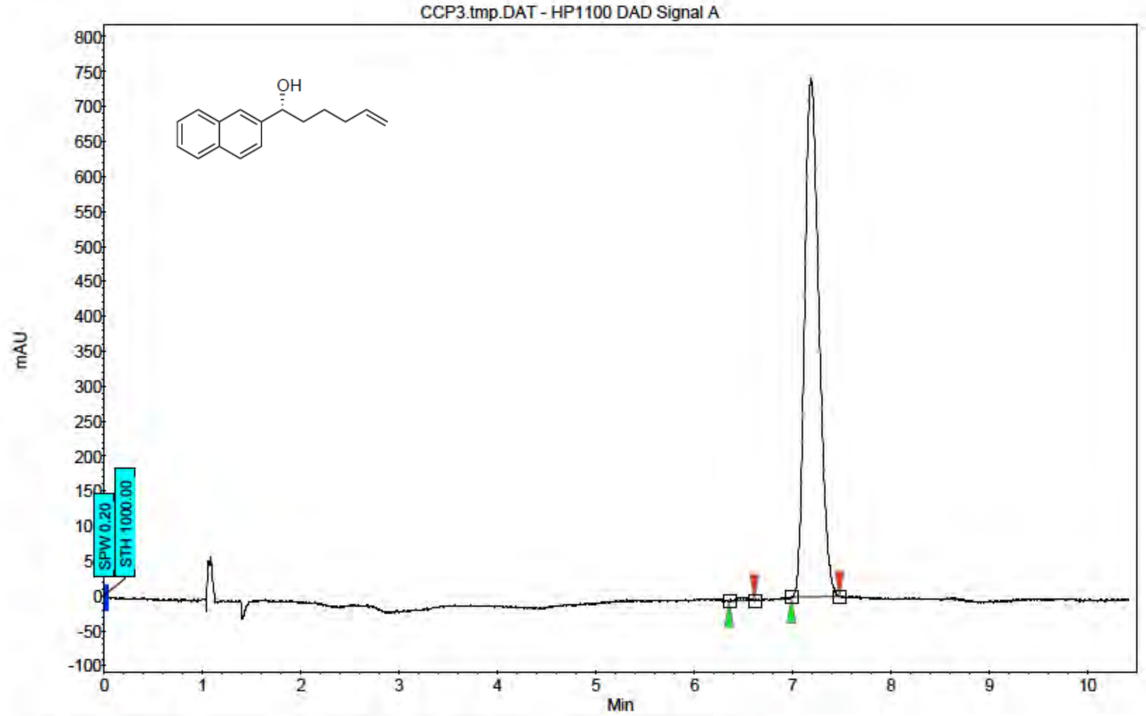
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 23.55 | 24.74 | 25.88 | 0.00 | 93.55 | 103.0 | 57.7 | 93.545 |
| 2 | UNKNOWN | 26.15 | 26.89 | 27.58 | 0.00 | 6.45 | 6.2 | 4.0 | 6.455 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 109.2 | 61.7 | 100.000 |



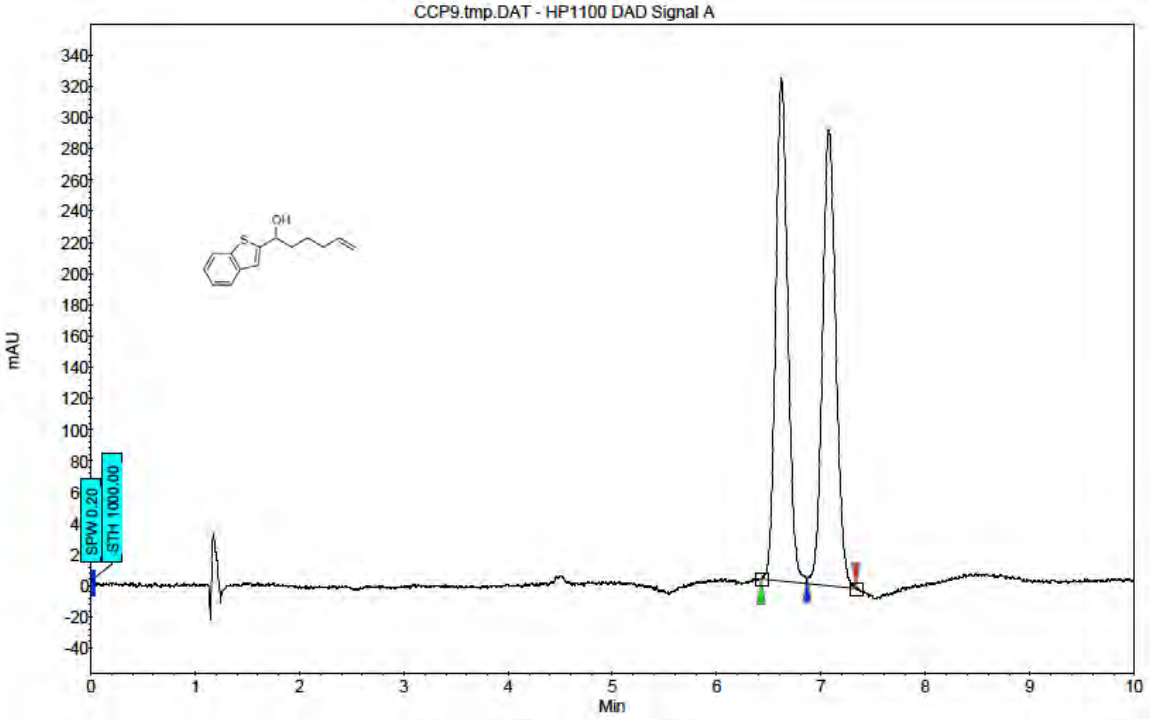


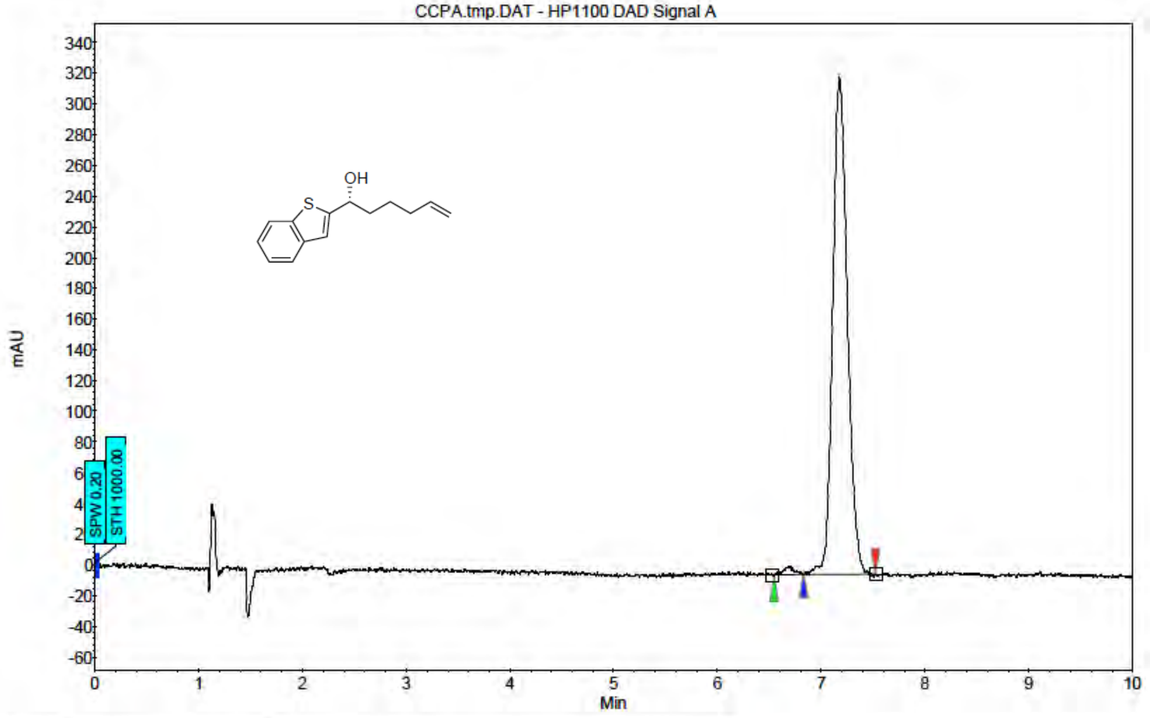
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 18.56 | 19.13 | 19.88 | 0.00 | 3.46 | 7.8 | 3.7 | 3.464 |
| 2 | UNKNOWN | 19.96 | 20.74 | 22.01 | 0.00 | 96.54 | 193.6 | 103.4 | 96.536 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 201.4 | 107.1 | 100.000 |



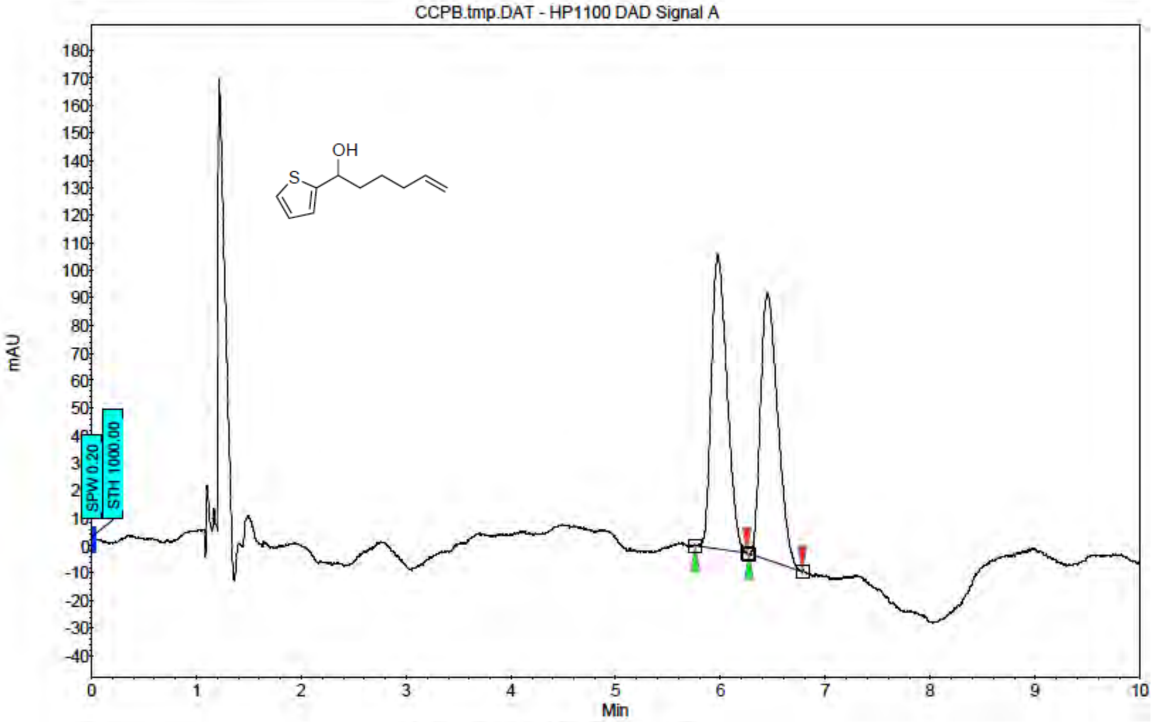


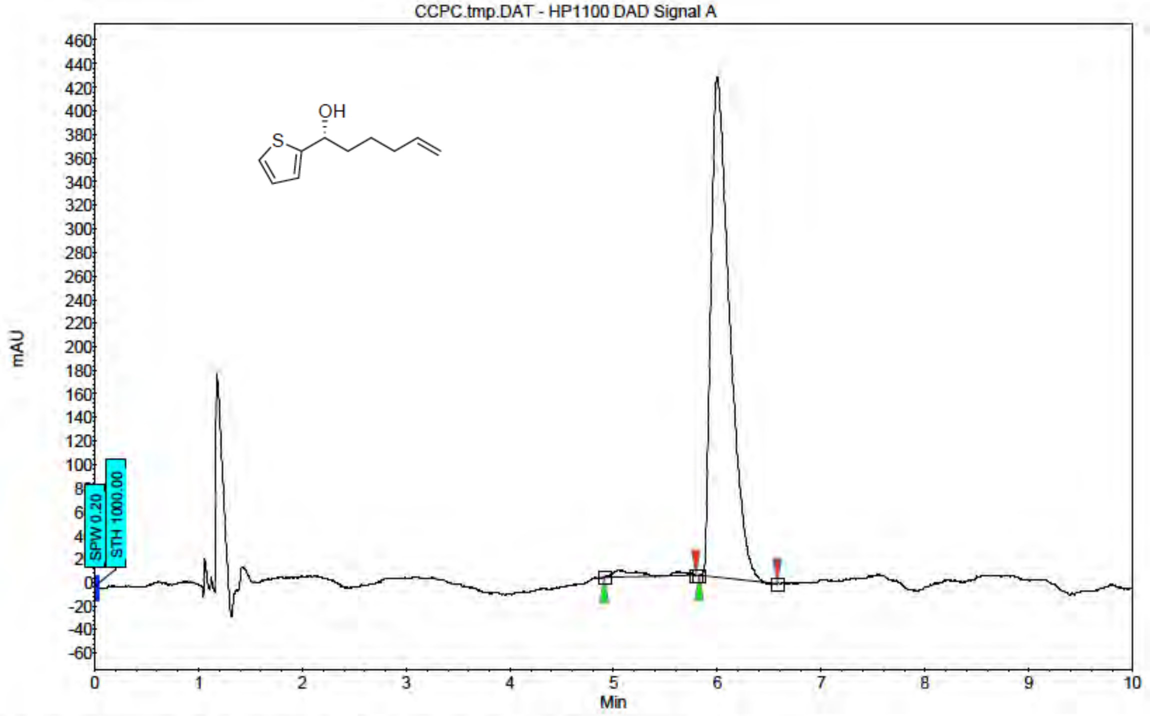
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 2 | UNKNOWN | 6.36 | 6.50 | 6.61 | 0.00 | 0.44 | 5.2 | 0.6 | 0.442 |
| 1 | UNKNOWN | 6.99 | 7.19 | 7.48 | 0.00 | 99.56 | 740.8 | 125.2 | 99.558 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 746.0 | 125.8 | 100.000 |



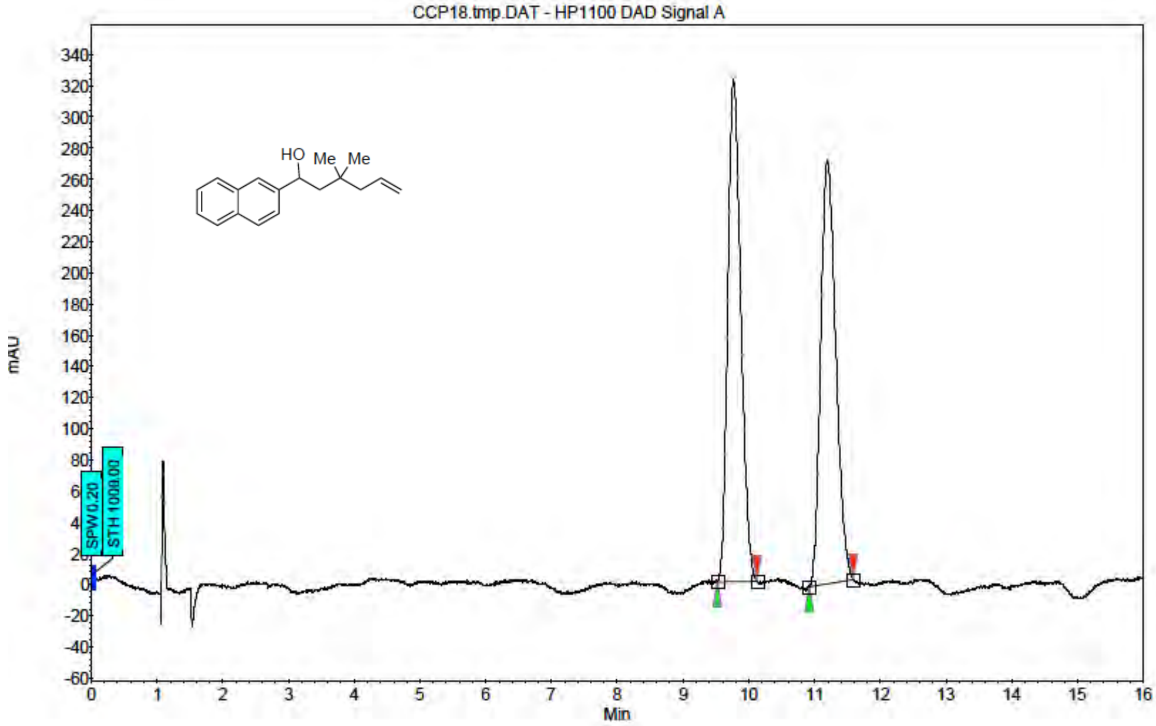


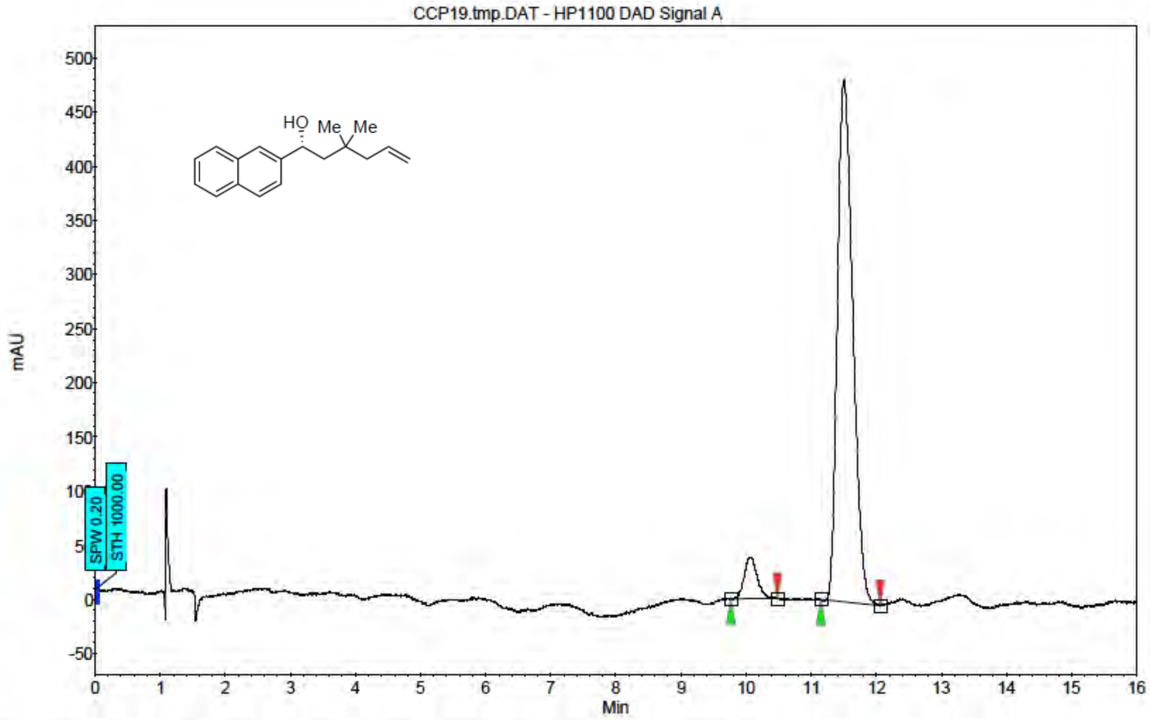
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 2 | UNKNOWN | 6.55 | 6.71 | 6.83 | 0.00 | 1.13 | 5.4 | 0.6 | 1.130 |
| 1 | UNKNOWN | 6.83 | 7.18 | 7.52 | 0.00 | 98.87 | 323.0 | 52.3 | 98.870 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 328.4 | 52.9 | 100.000 |



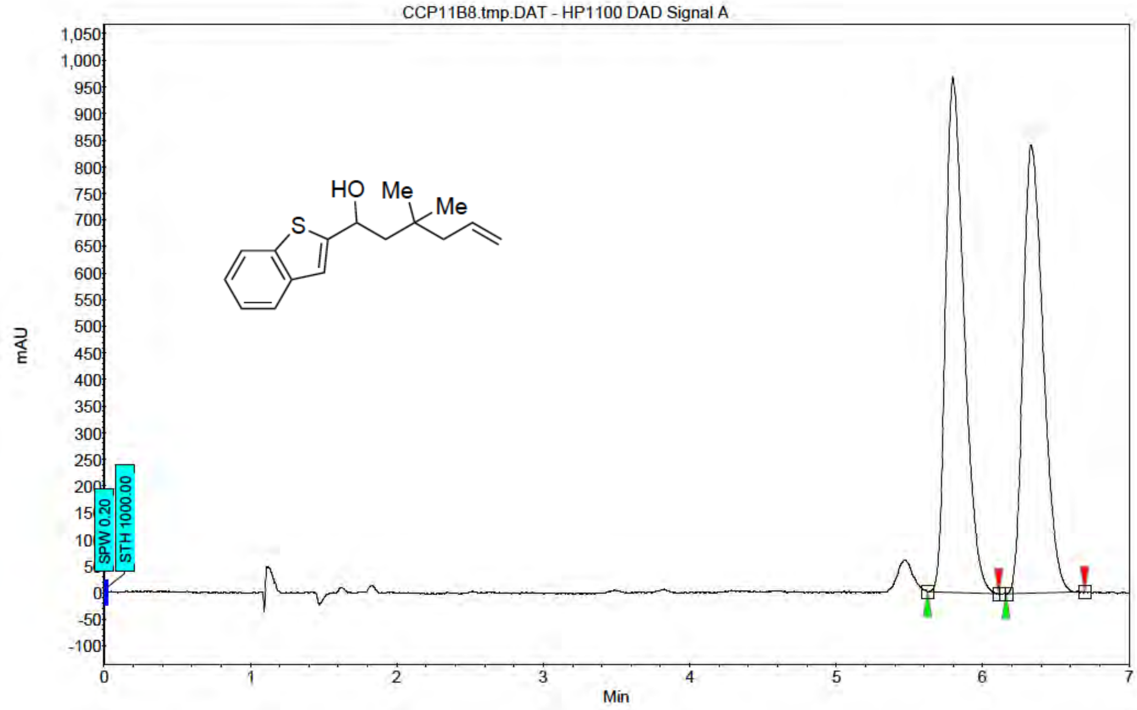


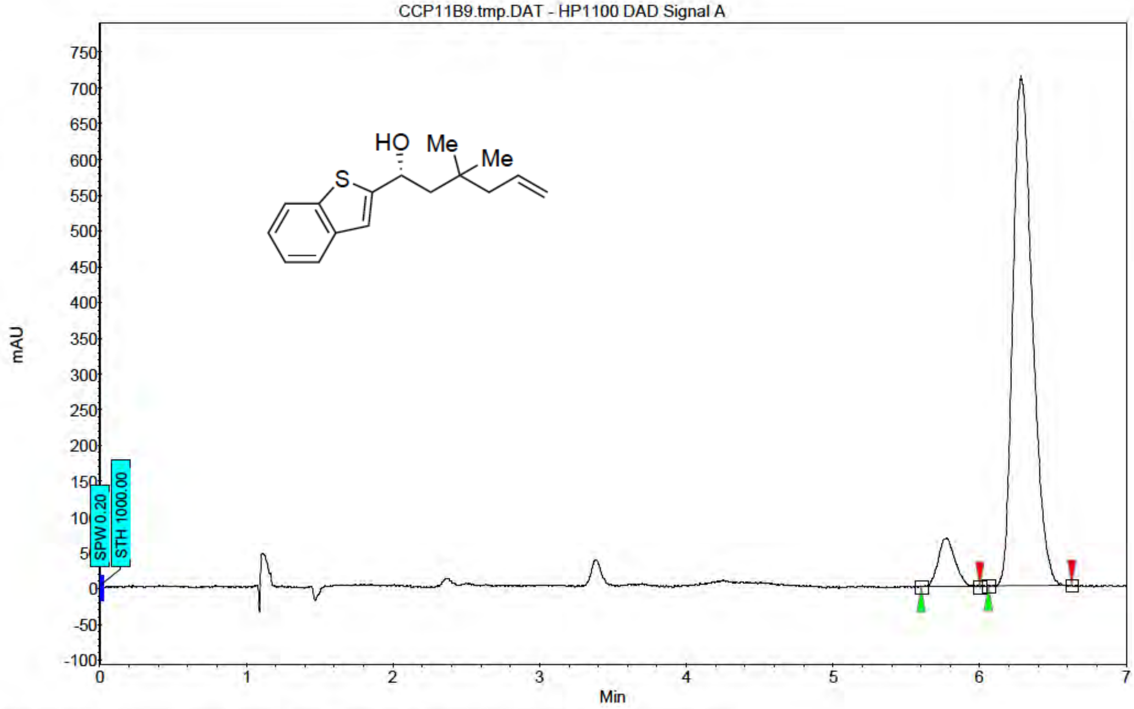
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 2 | UNKNOWN | 4.91 | 5.05 | 5.80 | 0.00 | 2.20 | 6.1 | 2.0 | 2.200 |
| 1 | UNKNOWN | 5.82 | 6.00 | 6.58 | 0.00 | 97.80 | 423.3 | 88.0 | 97.800 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 429.3 | 90.0 | 100.000 |



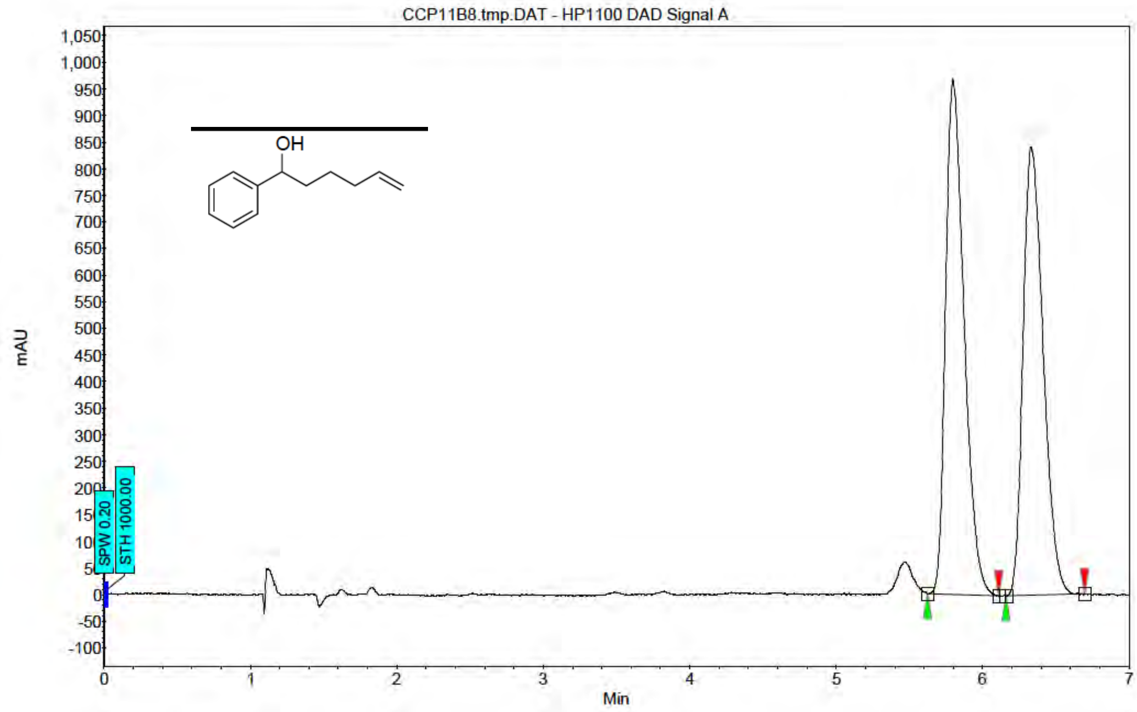


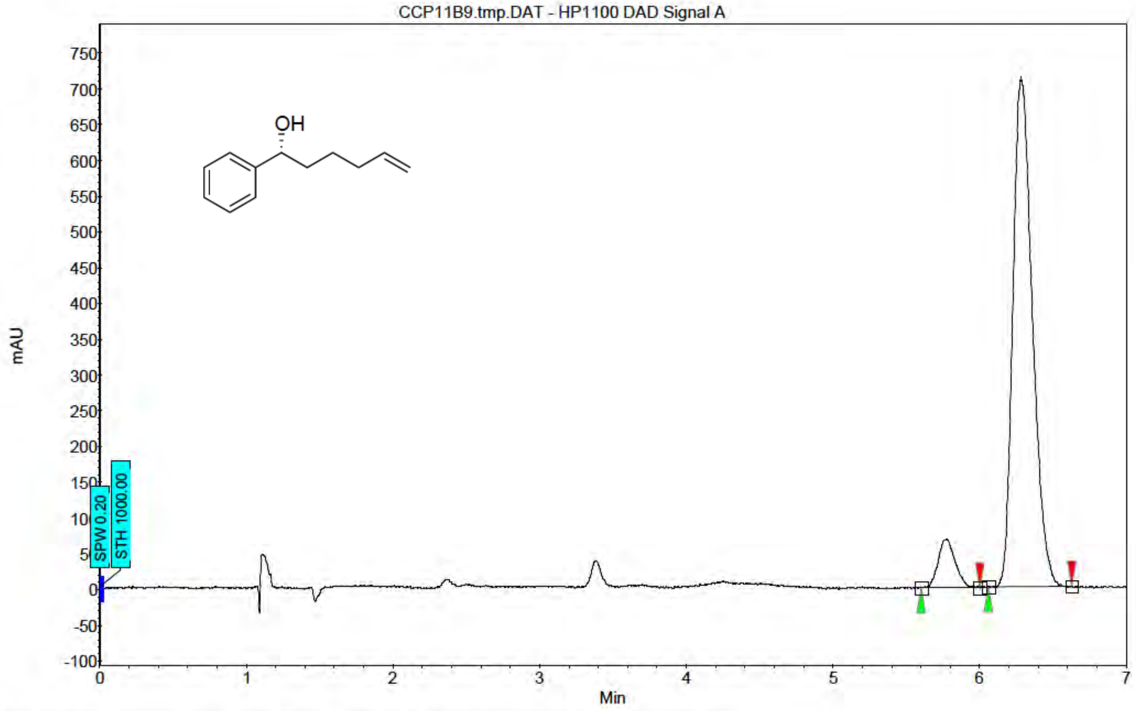
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 9.76 | 10.05 | 10.48 | 0.00 | 6.27 | 38.5 | 8.8 | 6.269 |
| 2 | UNKNOWN | 11.15 | 11.51 | 12.06 | 0.00 | 93.73 | 481.5 | 130.9 | 93.731 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 520.0 | 139.7 | 100.000 |



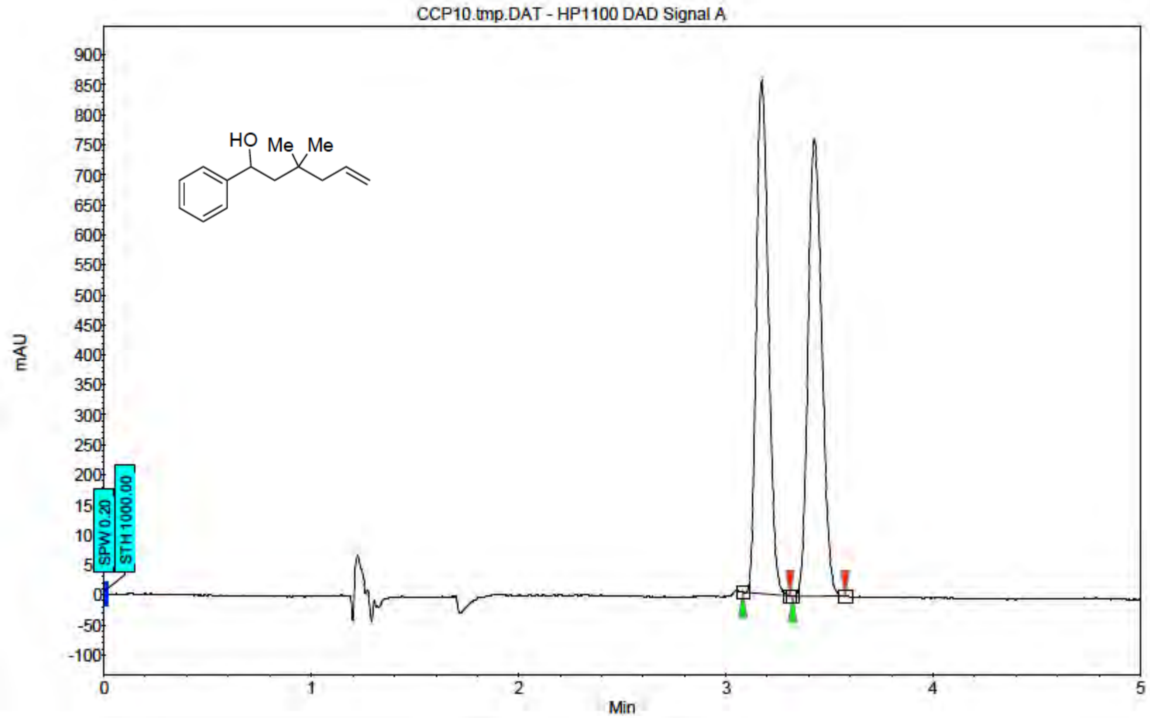


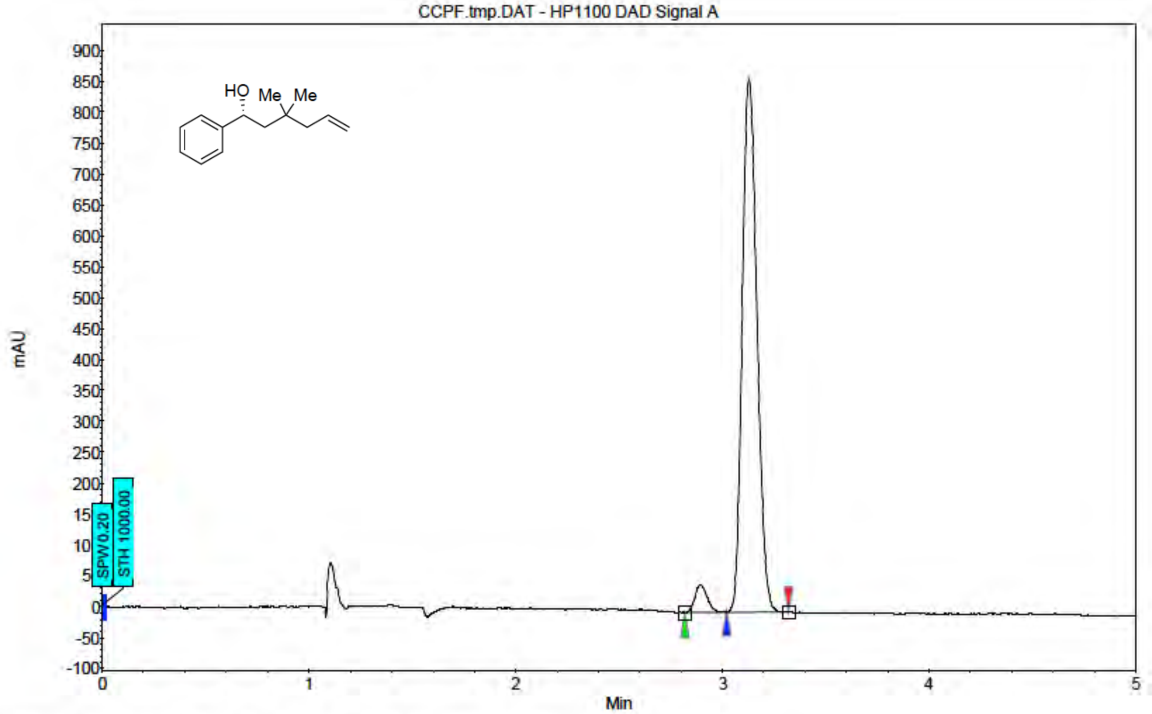
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 5.60 | 5.78 | 6.00 | 0.00 | 7.72 | 67.9 | 9.1 | 7.716 |
| 2 | UNKNOWN | 6.06 | 6.28 | 6.63 | 0.00 | 92.28 | 712.1 | 109.2 | 92.284 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 780.0 | 118.3 | 100.000 |



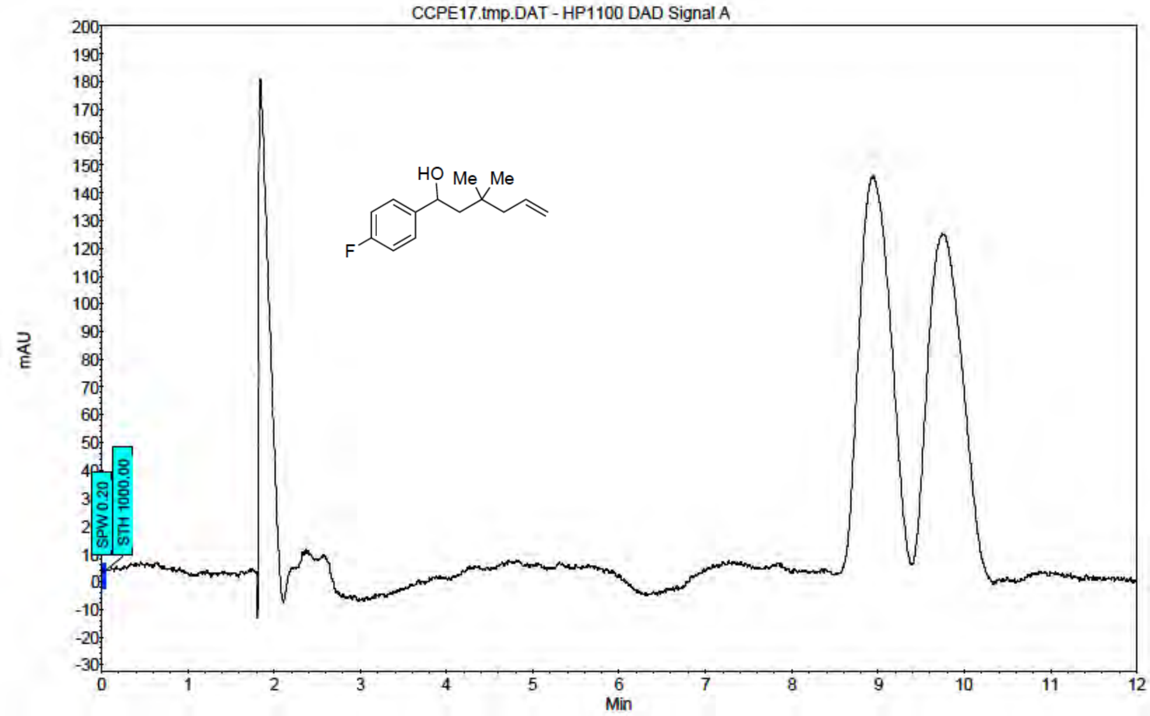


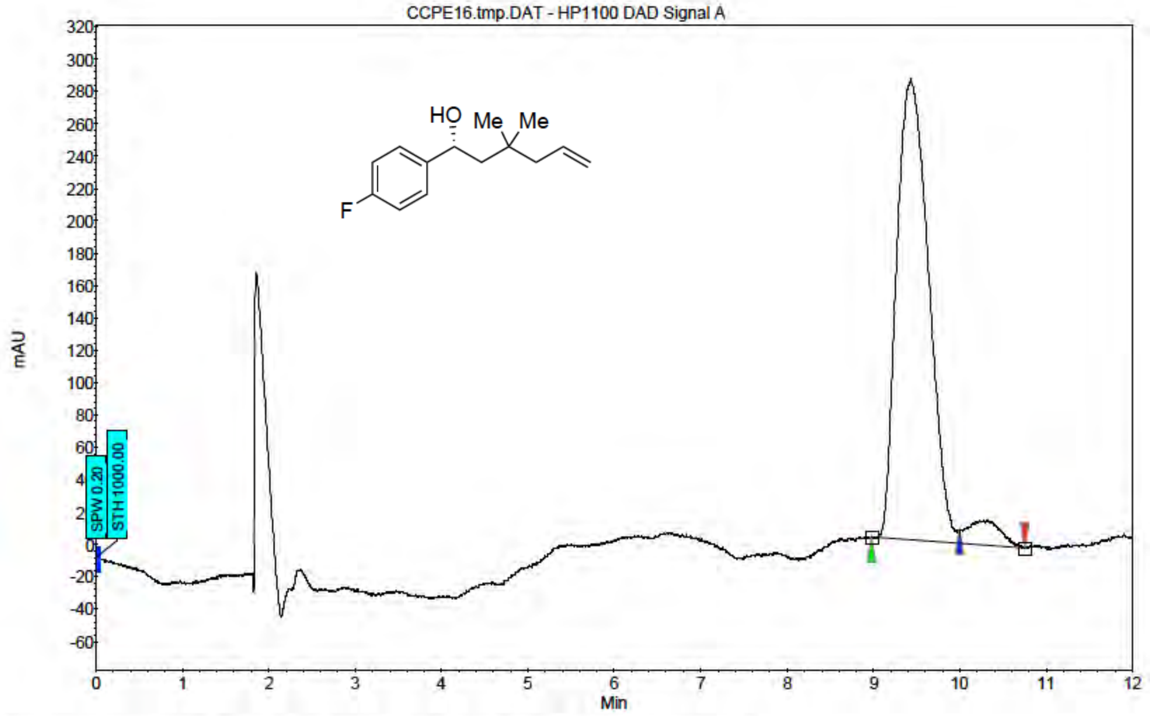
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 5.60 | 5.78 | 6.00 | 0.00 | 7.72 | 67.9 | 9.1 | 7.716 |
| 2 | UNKNOWN | 6.06 | 6.28 | 6.63 | 0.00 | 92.28 | 712.1 | 109.2 | 92.284 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 780.0 | 118.3 | 100.000 |



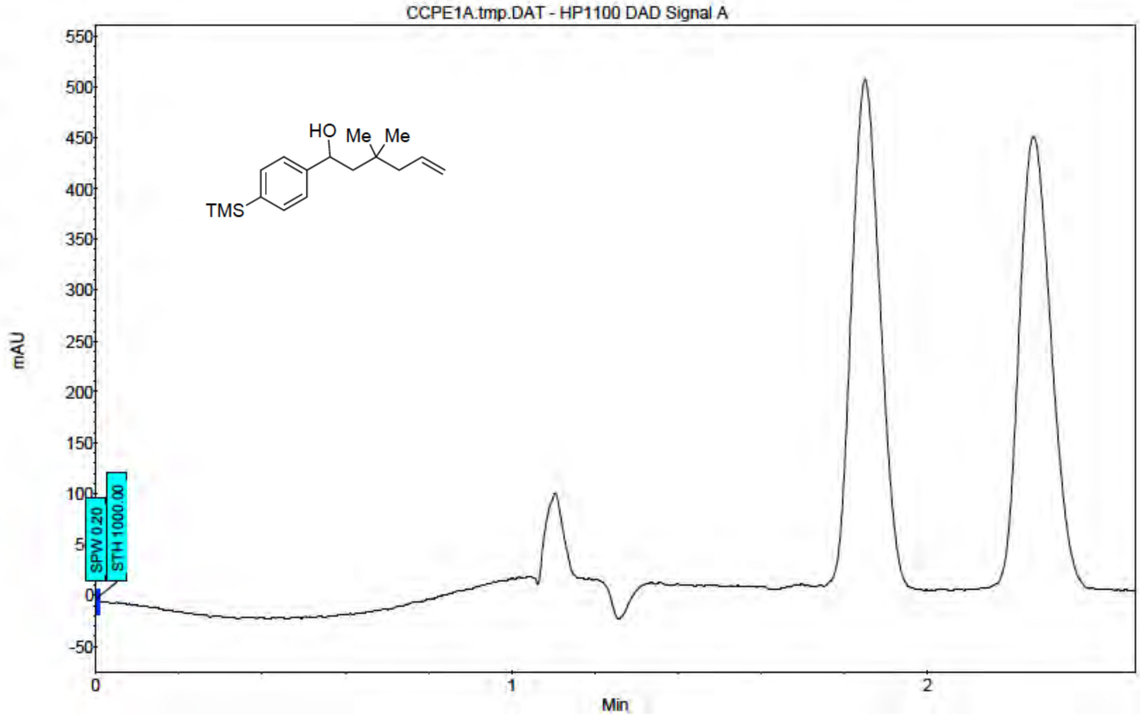


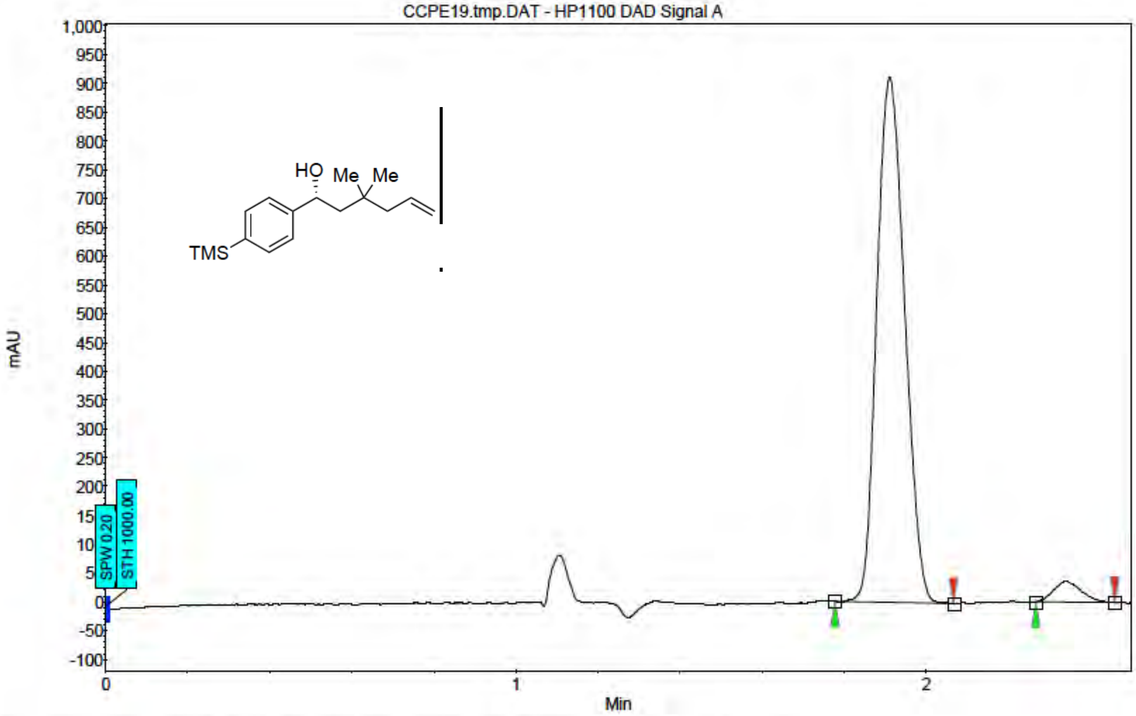
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 2.82 | 2.90 | 3.02 | 0.00 | 4.18 | 44.7 | 3.1 | 4.177 |
| 2 | UNKNOWN | 3.02 | 3.13 | 3.32 | 0.00 | 95.82 | 863.7 | 71.0 | 95.823 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 908.4 | 74.1 | 100.000 |



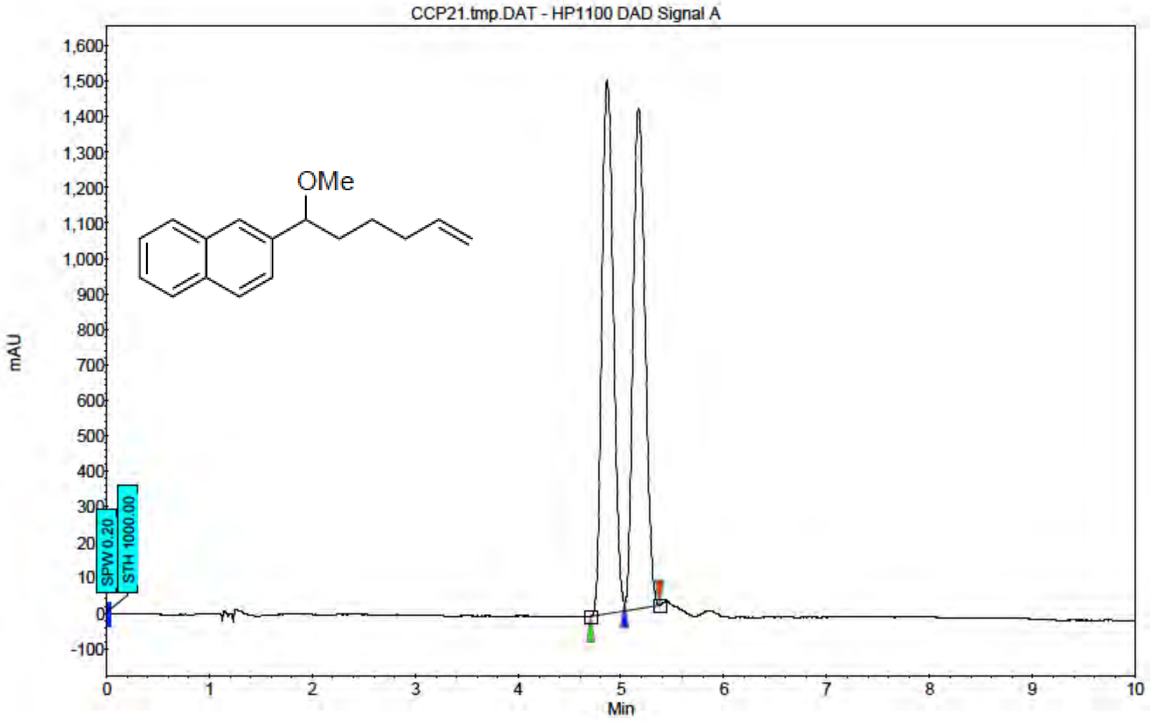


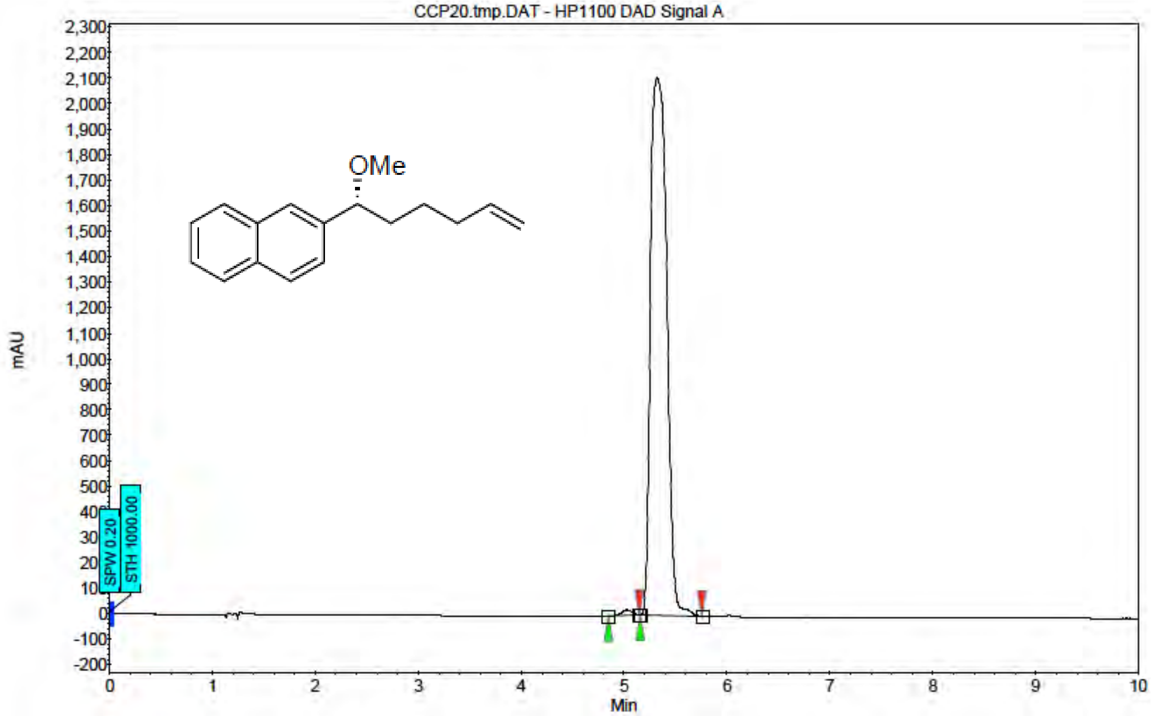
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 8.98 | 9.43 | 9.99 | 0.00 | 94.74 | 284.7 | 121.7 | 94.739 |
| 2 | UNKNOWN | 9.99 | 10.31 | 10.75 | 0.00 | 5.26 | 15.5 | 6.8 | 5.261 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 300.3 | 128.4 | 100.000 |



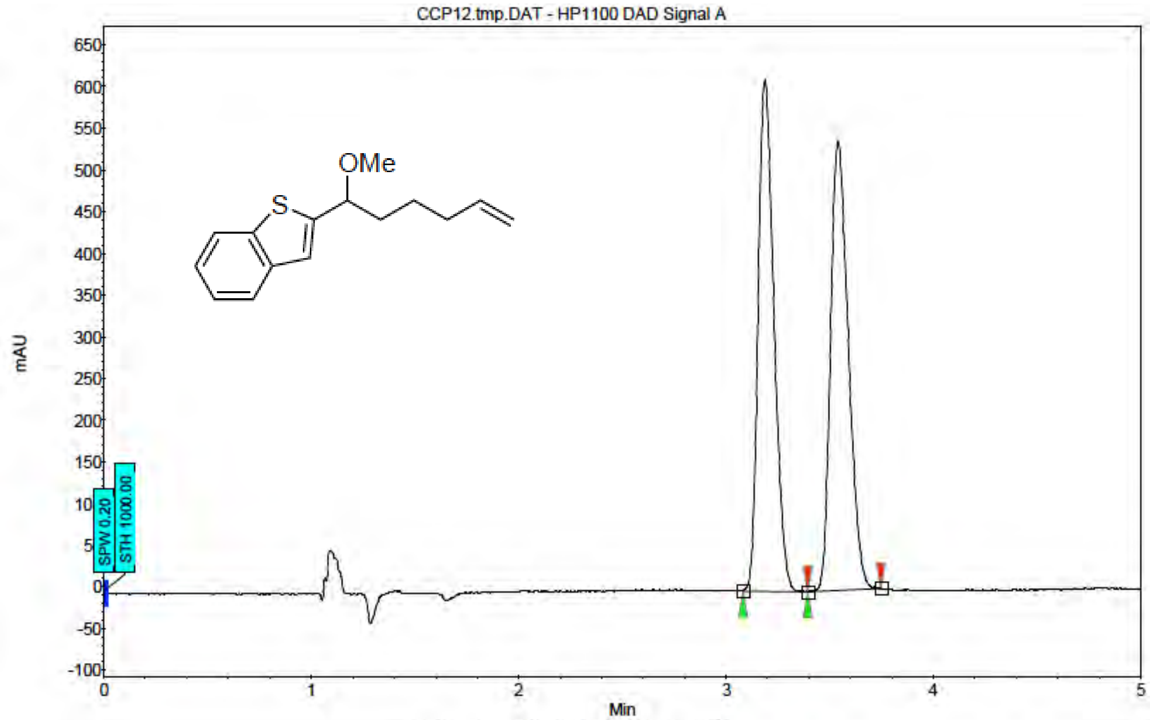


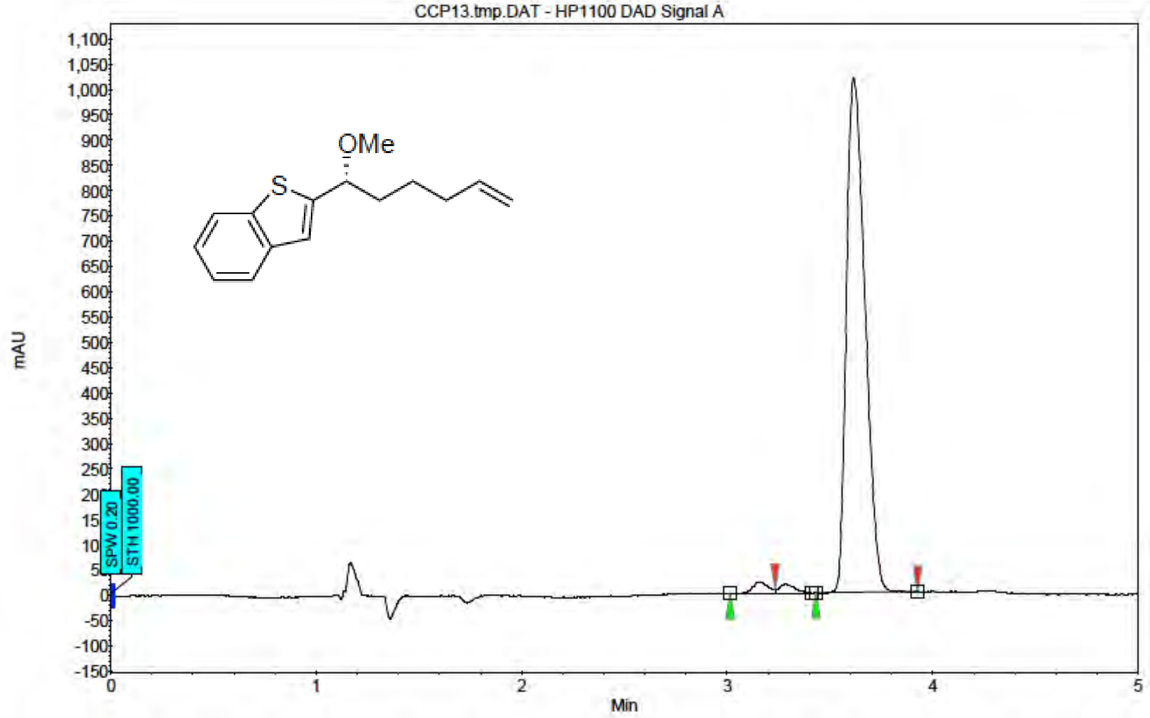
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 1.78 | 1.91 | 2.07 | 0.00 | 96.21 | 909.9 | 71.4 | 96.212 |
| 2 | UNKNOWN | 2.27 | 2.34 | 2.46 | 0.00 | 3.79 | 35.3 | 2.8 | 3.788 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 945.1 | 74.2 | 100.000 |



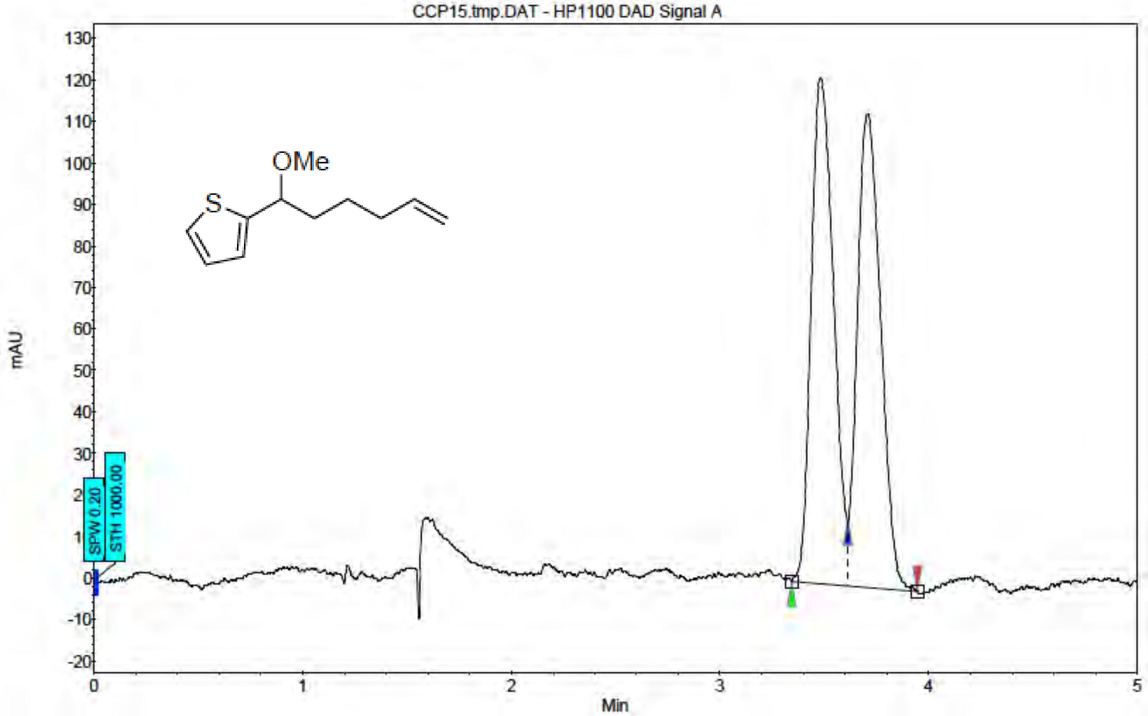


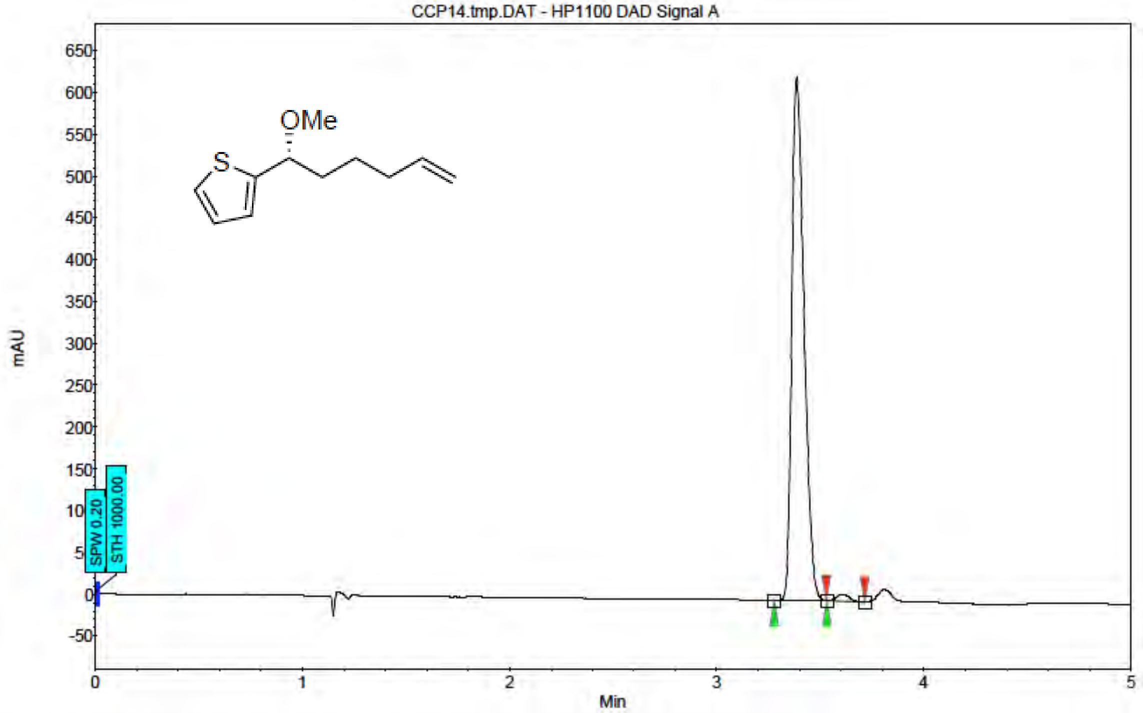
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 4.85 | 5.03 | 5.15 | 0.00 | 0.64 | 21.6 | 2.5 | 0.637 |
| 2 | UNKNOWN | 5.16 | 5.33 | 5.76 | 0.00 | 99.36 | 2105.2 | 384.1 | 99.363 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 2126.8 | 386.5 | 100.000 |



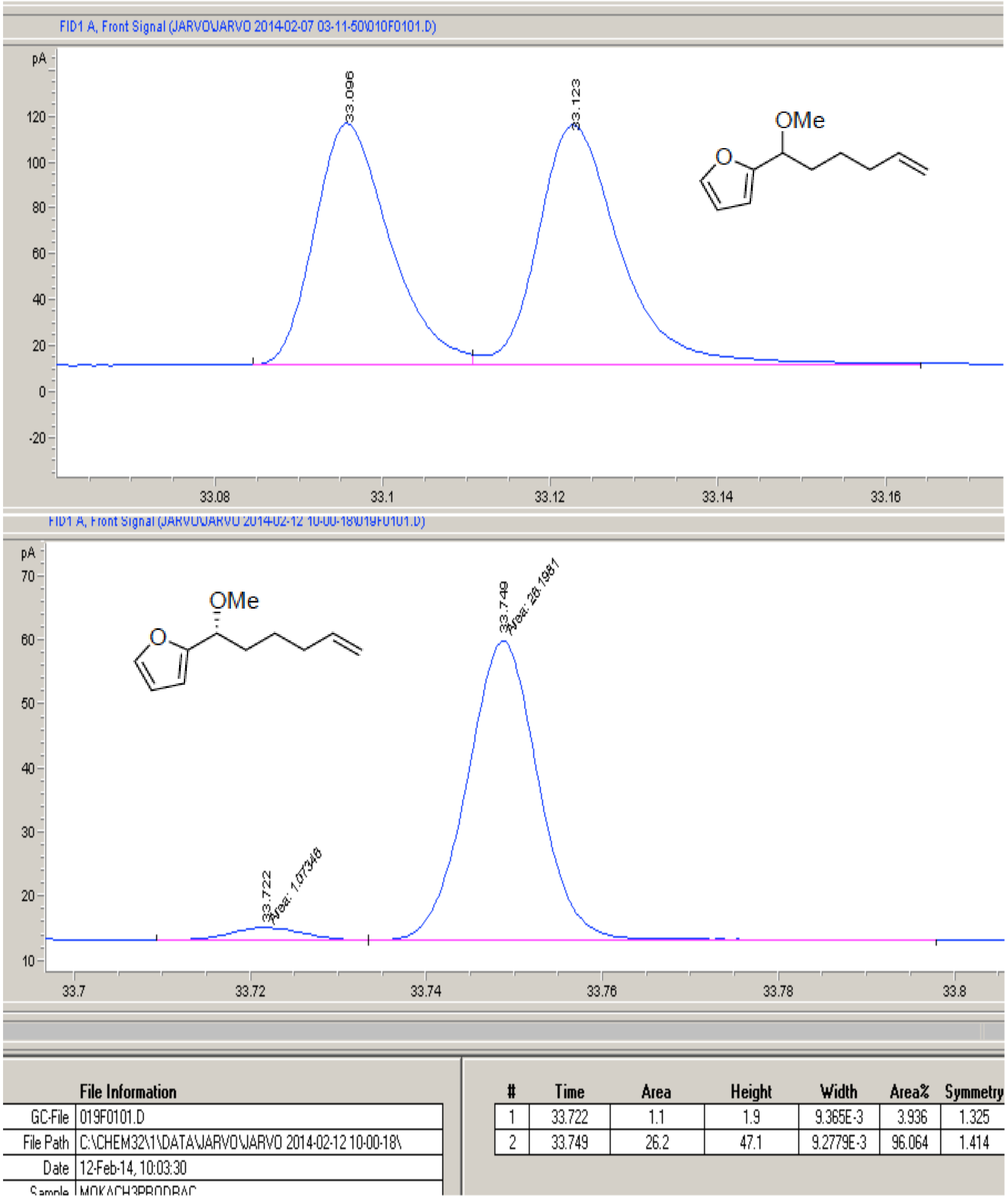


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 2 | UNKNOWN | 3.01 | 3.16 | 3.23 | 0.00 | 1.67 | 21.4 | 1.8 | 1.665 |
| 1 | UNKNOWN | 3.43 | 3.61 | 3.93 | 0.00 | 98.33 | 1016.6 | 106.5 | 98.335 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 1038.0 | 108.3 | 100.000 |



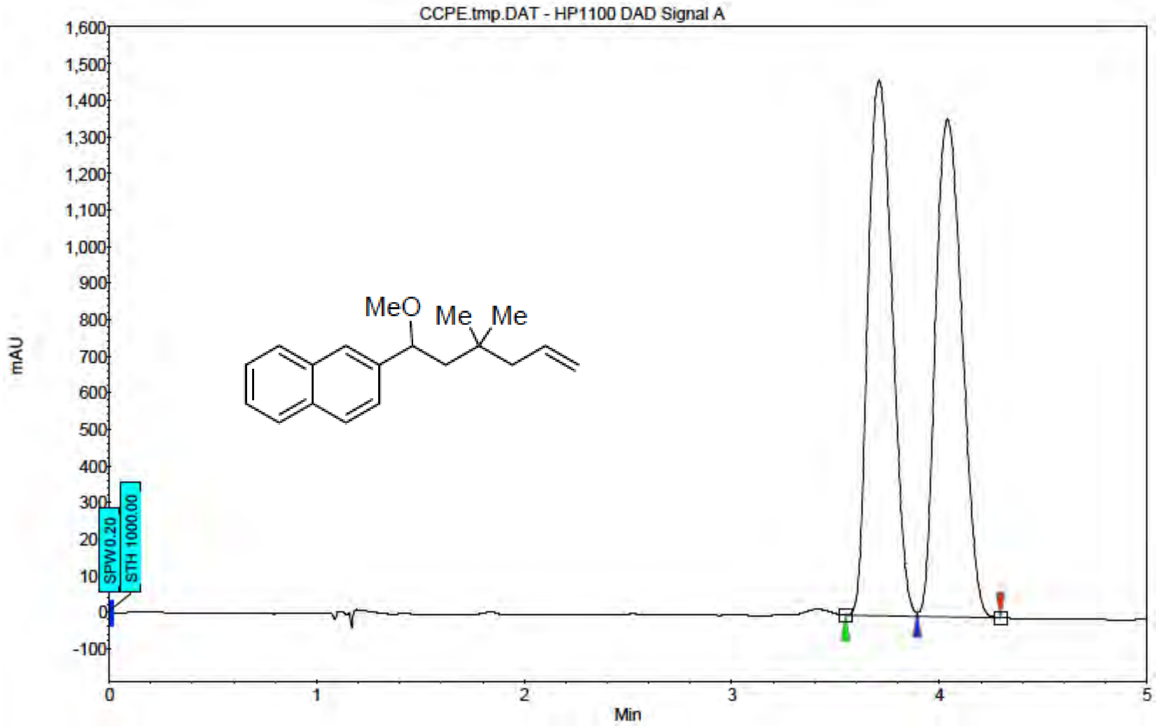


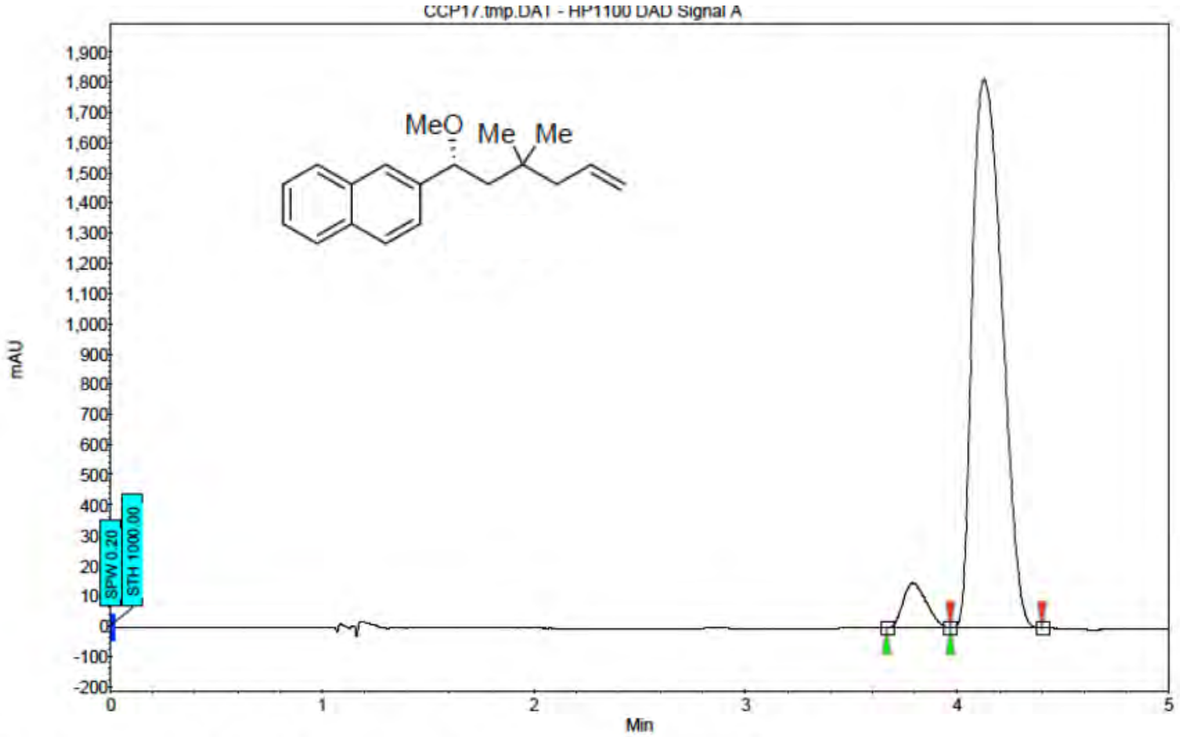
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 3.28 | 3.39 | 3.53 | 0.00 | 98.70 | 624.7 | 42.8 | 98.700 |
| 2 | UNKNOWN | 3.53 | 3.61 | 3.71 | 0.00 | 1.30 | 8.3 | 0.6 | 1.300 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 633.0 | 43.4 | 100.000 |



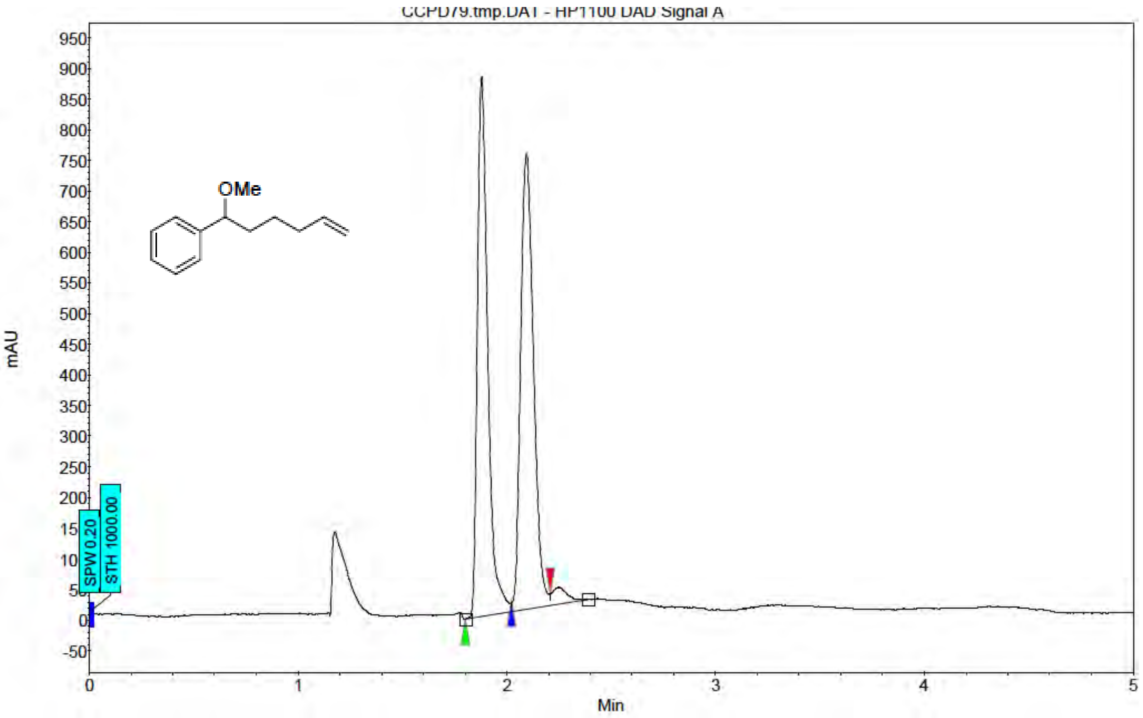
| File Information | |
|---|---|
| GC-File | 019F0101.D |
| File Path | C:\CHEM32\1\DATA\JARVO\JARVO 2014-02-12 10-00-18\ |
| Date | 12-Feb-14, 10:03:30 |
| Sample | MOKACH3PRODRAC |

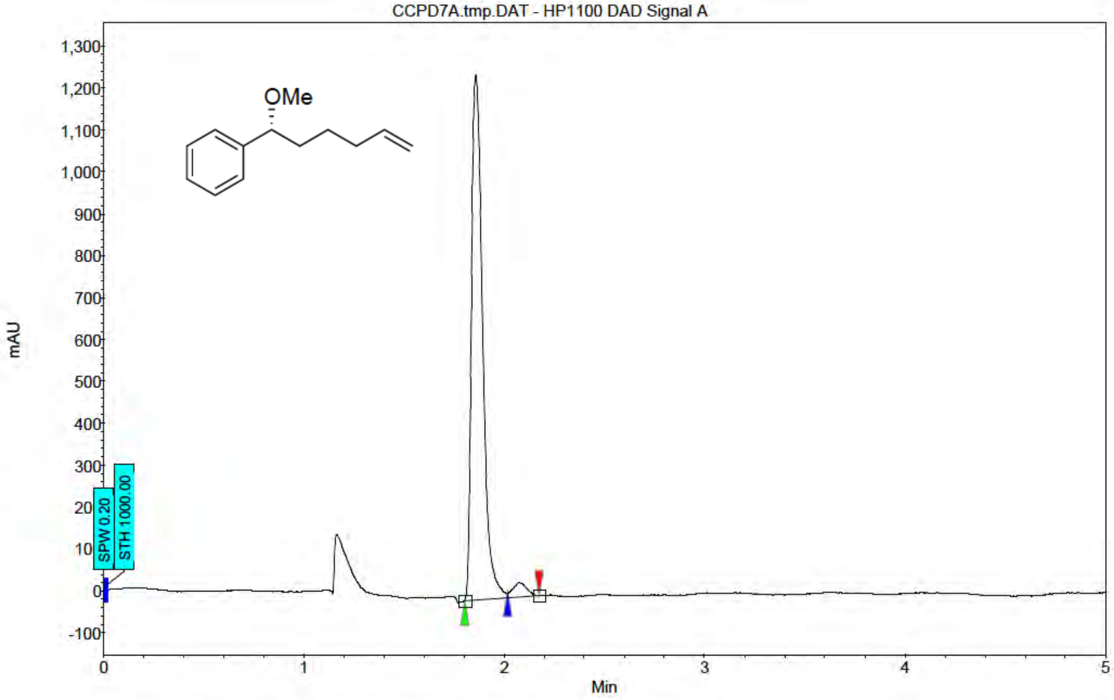
| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 33.722 | 1.1 | 1.9 | 9.365E-3 | 3.936 | 1.325 |
| 2 | 33.749 | 26.2 | 47.1 | 9.2779E-3 | 96.064 | 1.414 |



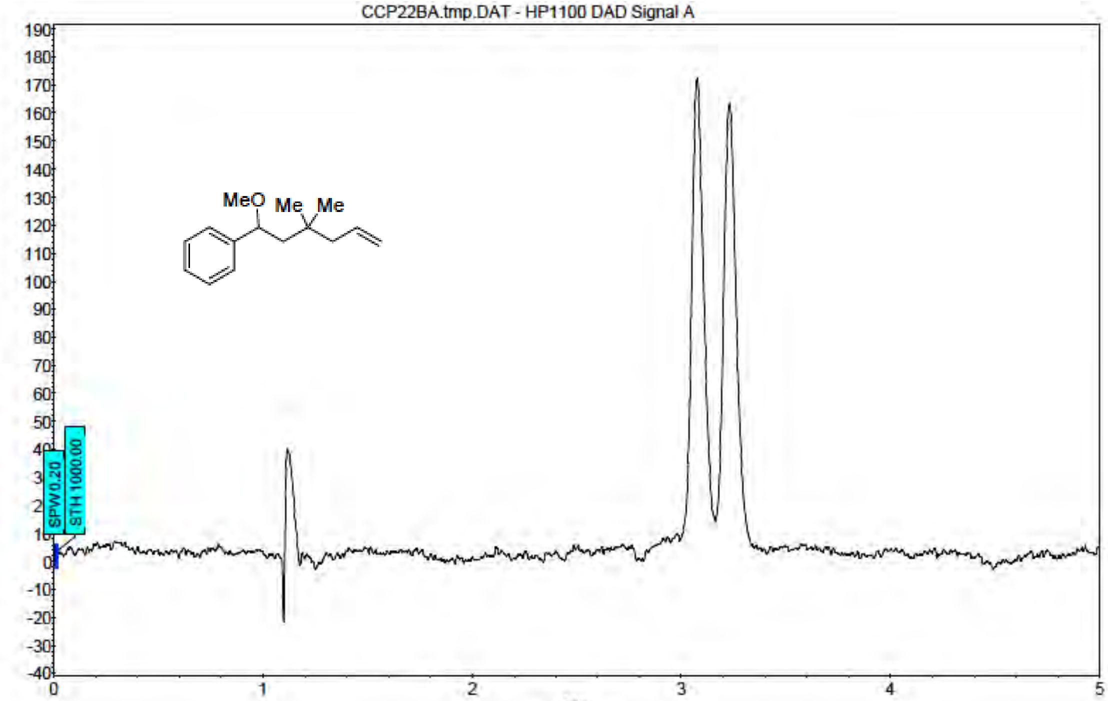


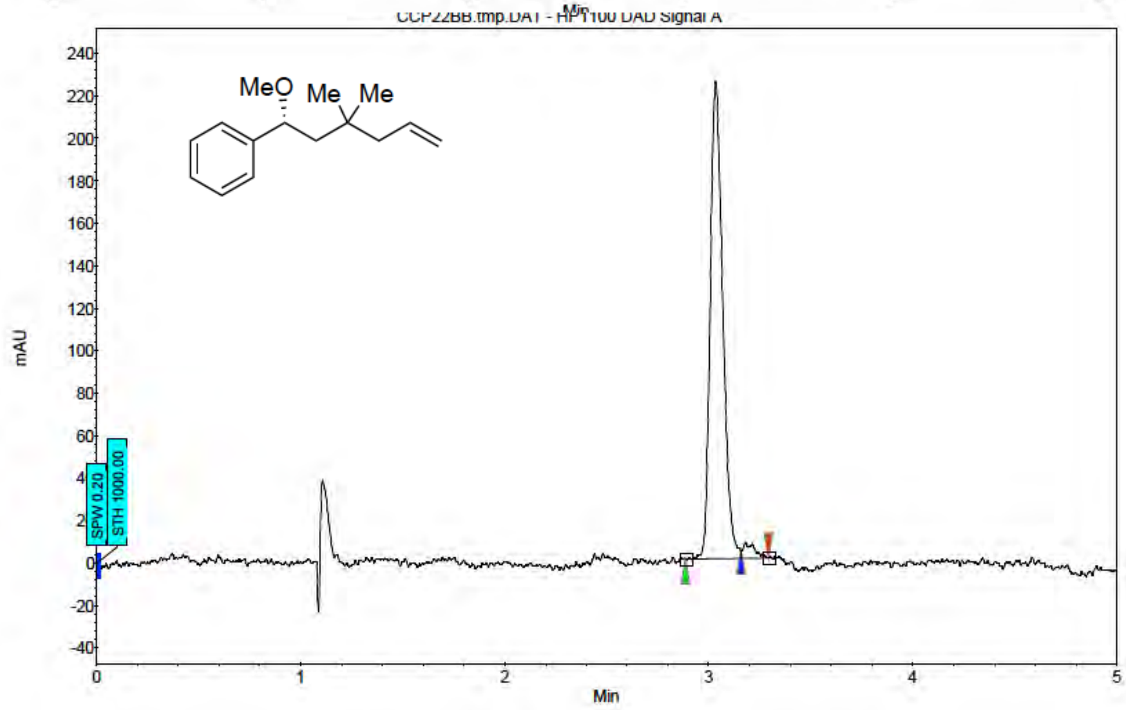
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 3.67 | 3.79 | 3.97 | 0.00 | 6.13 | 149.5 | 19.3 | 6.125 |
| 2 | UNKNOWN | 3.97 | 4.13 | 4.40 | 0.00 | 93.87 | 1815.0 | 295.1 | 93.875 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 1964.4 | 314.4 | 100.000 |



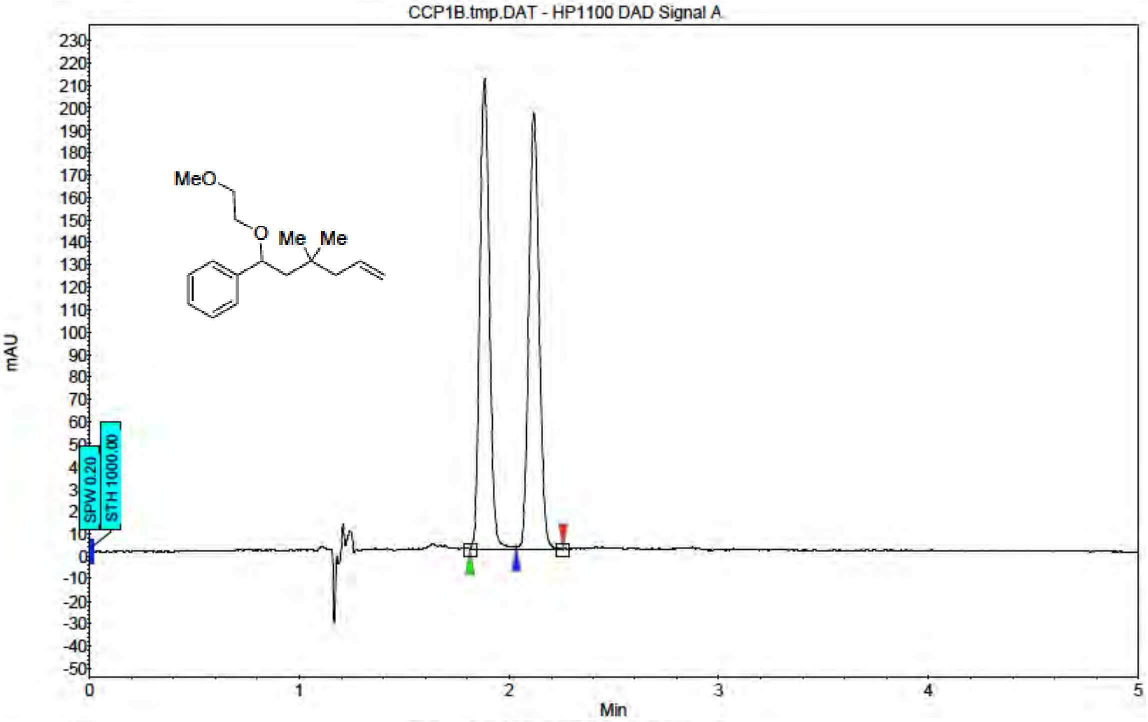


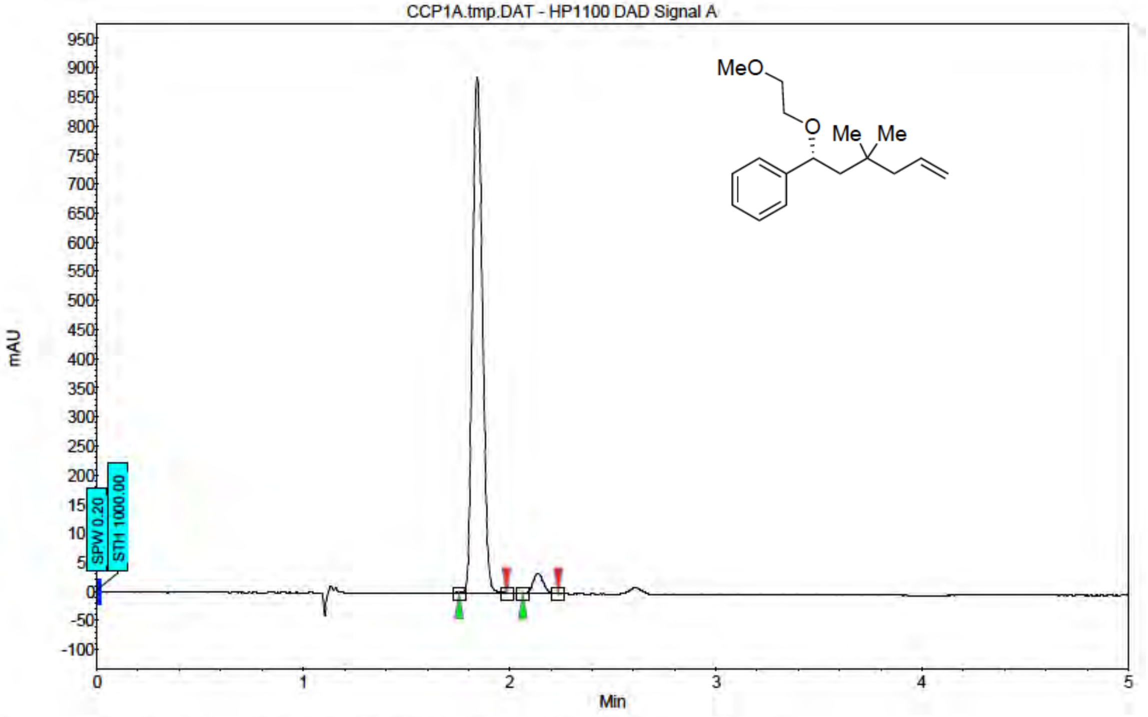
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 1.80 | 1.86 | 2.01 | 0.00 | 96.65 | 1252.1 | 80.4 | 96.654 |
| 2 | UNKNOWN | 2.01 | 2.07 | 2.17 | 0.00 | 3.35 | 34.3 | 2.8 | 3.346 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 1286.4 | 83.2 | 100.000 |



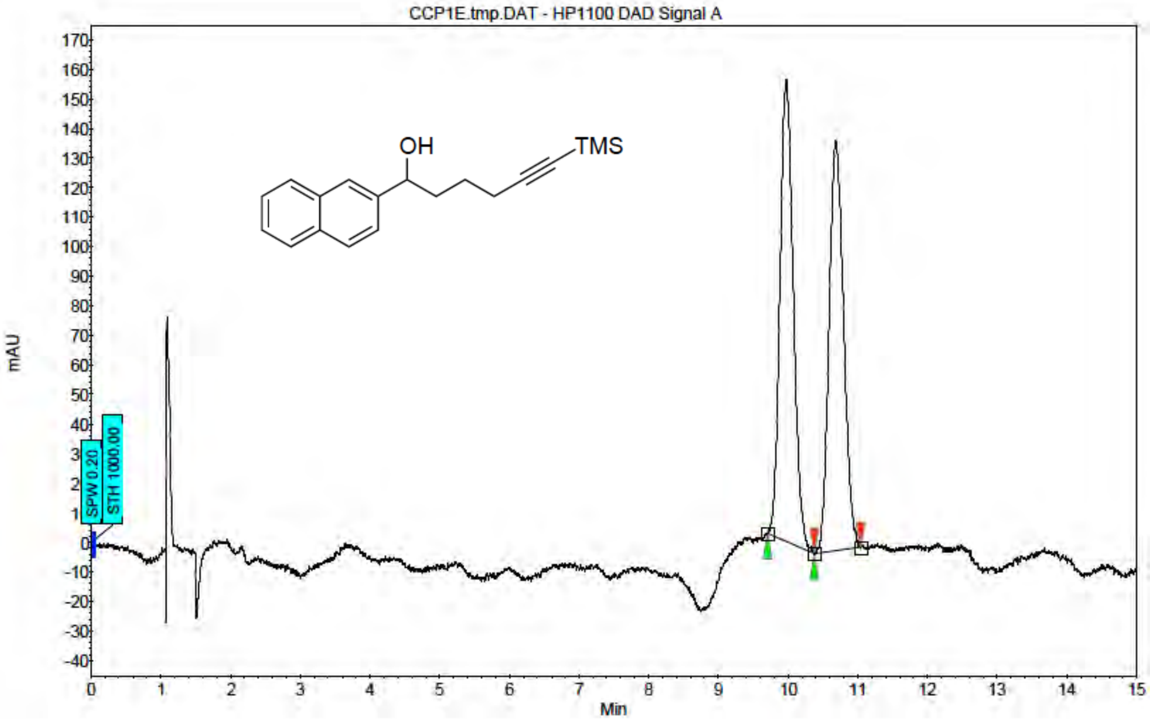


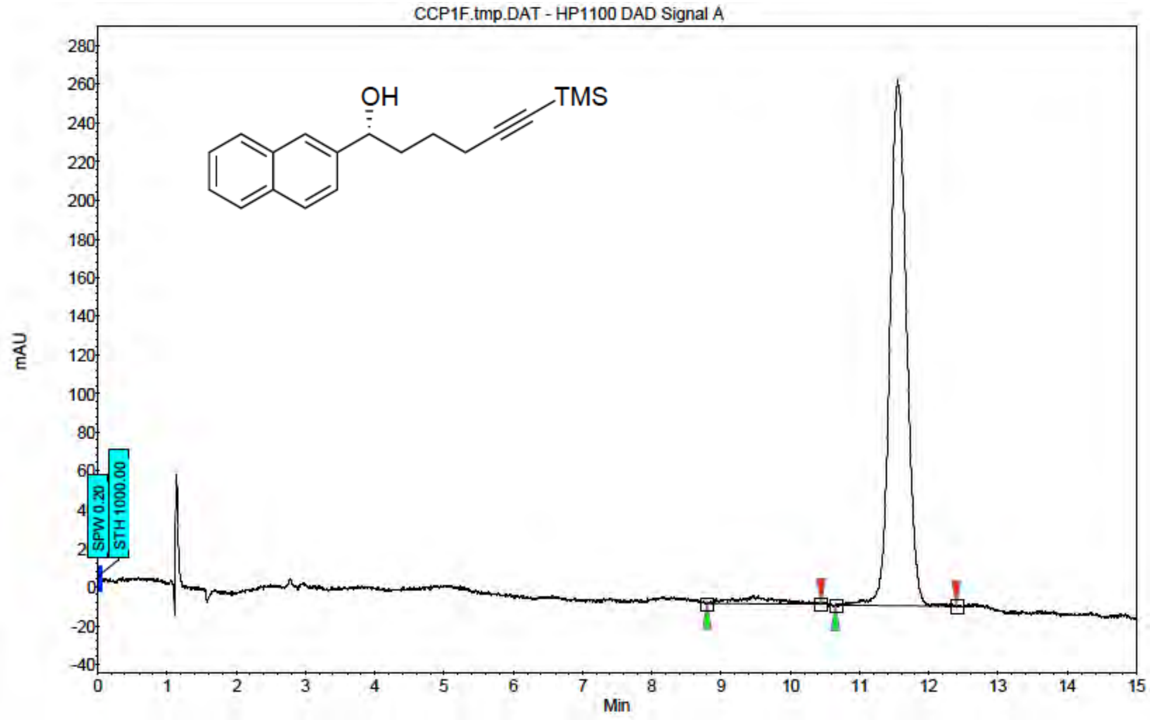
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 2.89 | 3.04 | 3.16 | 0.00 | 97.07 | 224.4 | 15.9 | 97.073 |
| 2 | UNKNOWN | 3.16 | 3.18 | 3.29 | 0.00 | 2.93 | 7.3 | 0.5 | 2.927 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 231.8 | 16.3 | 100.000 |



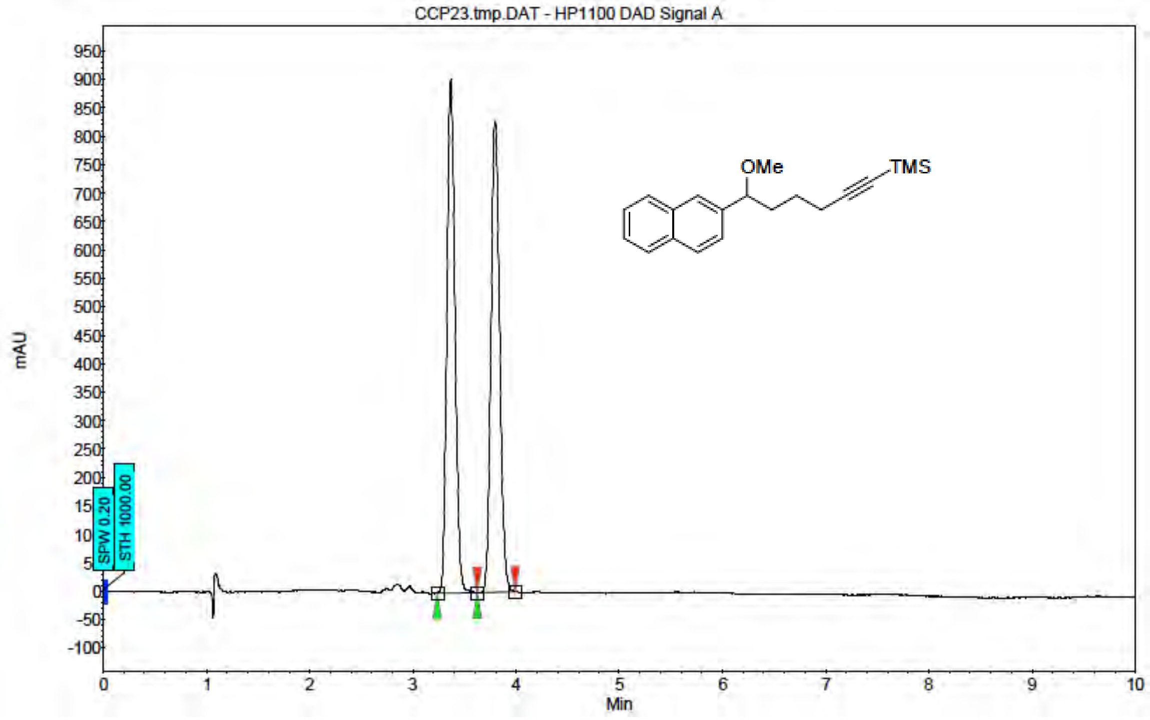


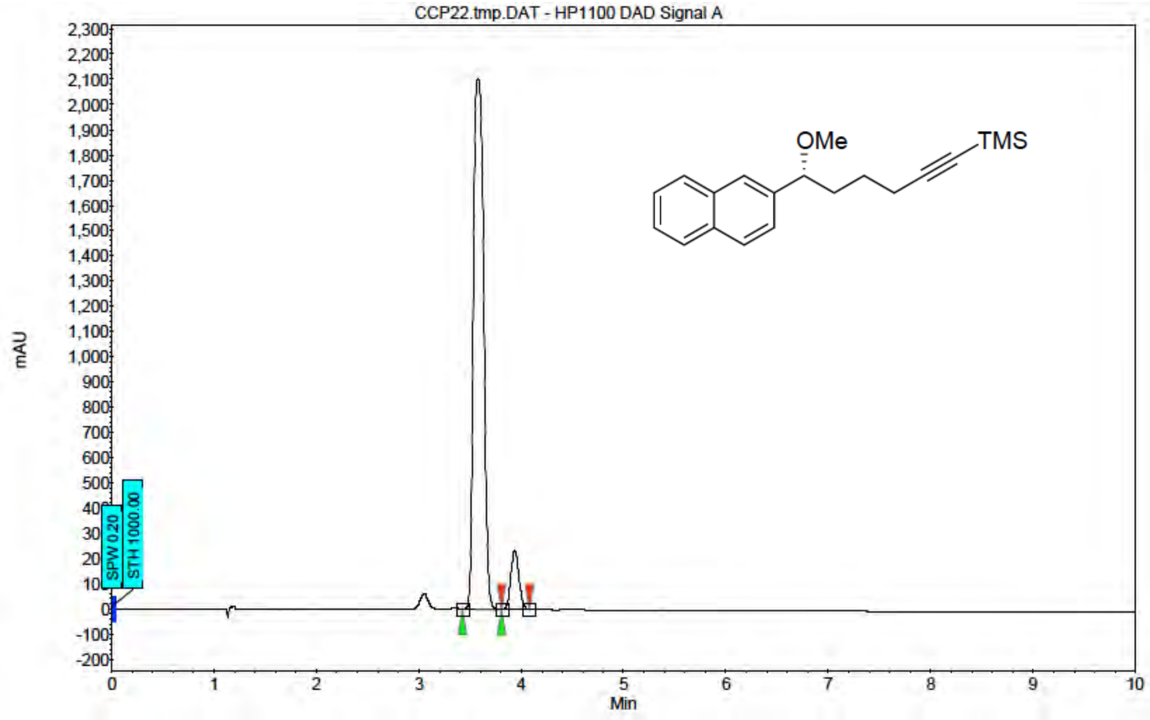
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 1.76 | 1.84 | 1.98 | 0.00 | 96.07 | 884.4 | 49.2 | 96.068 |
| 2 | UNKNOWN | 2.06 | 2.14 | 2.24 | 0.00 | 3.93 | 34.9 | 2.0 | 3.932 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 919.3 | 51.2 | 100.000 |



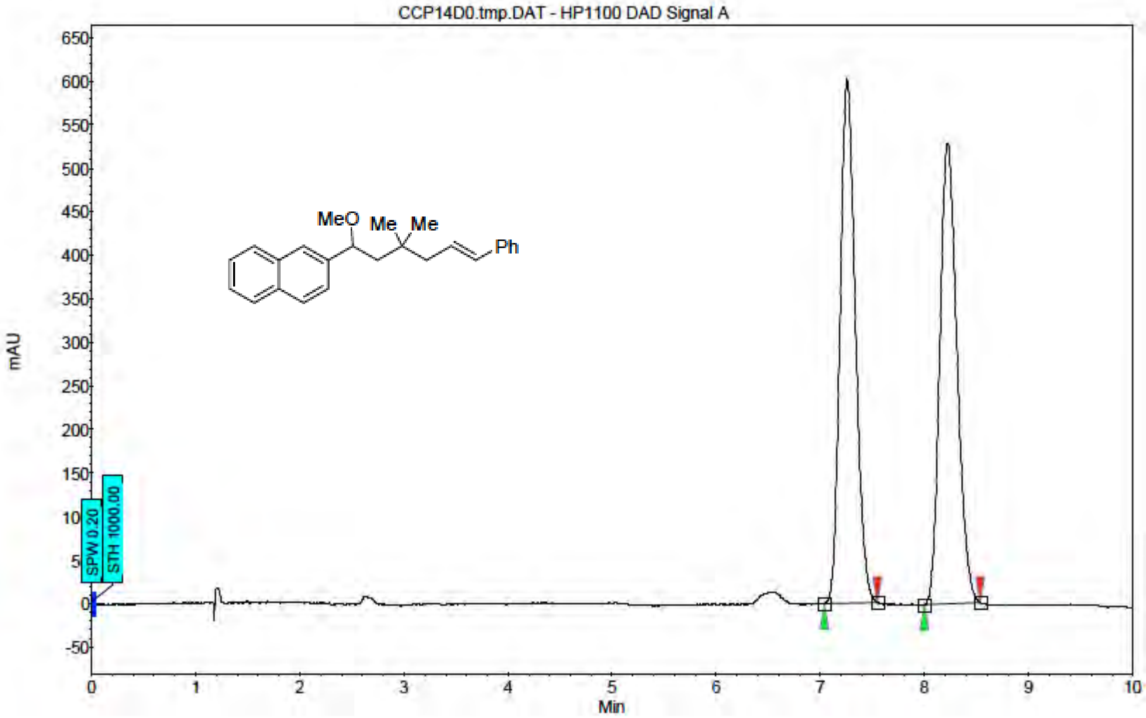


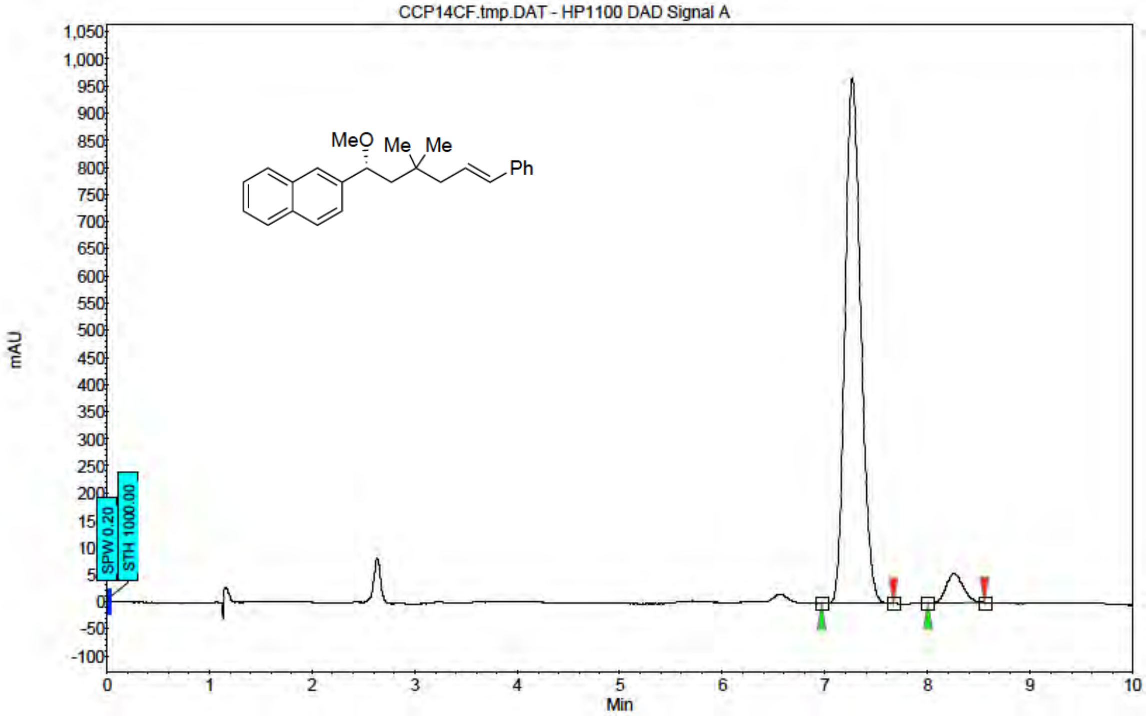
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 8.80 | 9.54 | 10.44 | 0.00 | 3.31 | 3.7 | 2.6 | 3.309 |
| 2 | UNKNOWN | 10.65 | 11.55 | 12.39 | 0.00 | 96.69 | 271.7 | 75.3 | 96.691 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 275.5 | 77.9 | 100.000 |



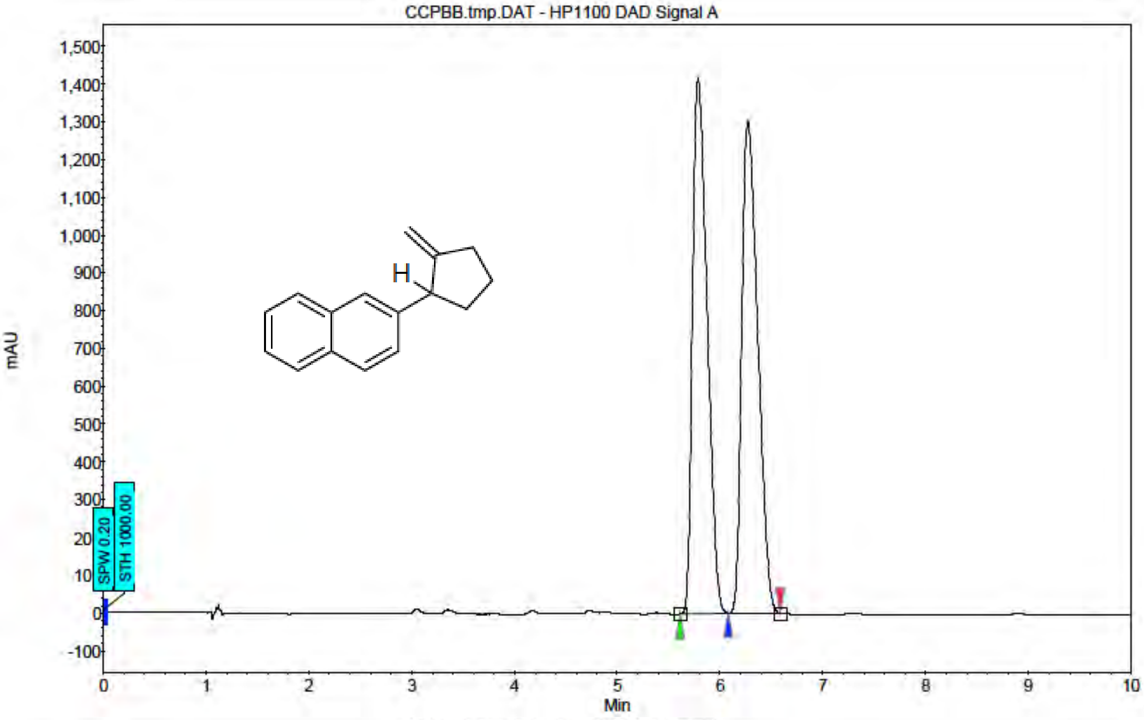


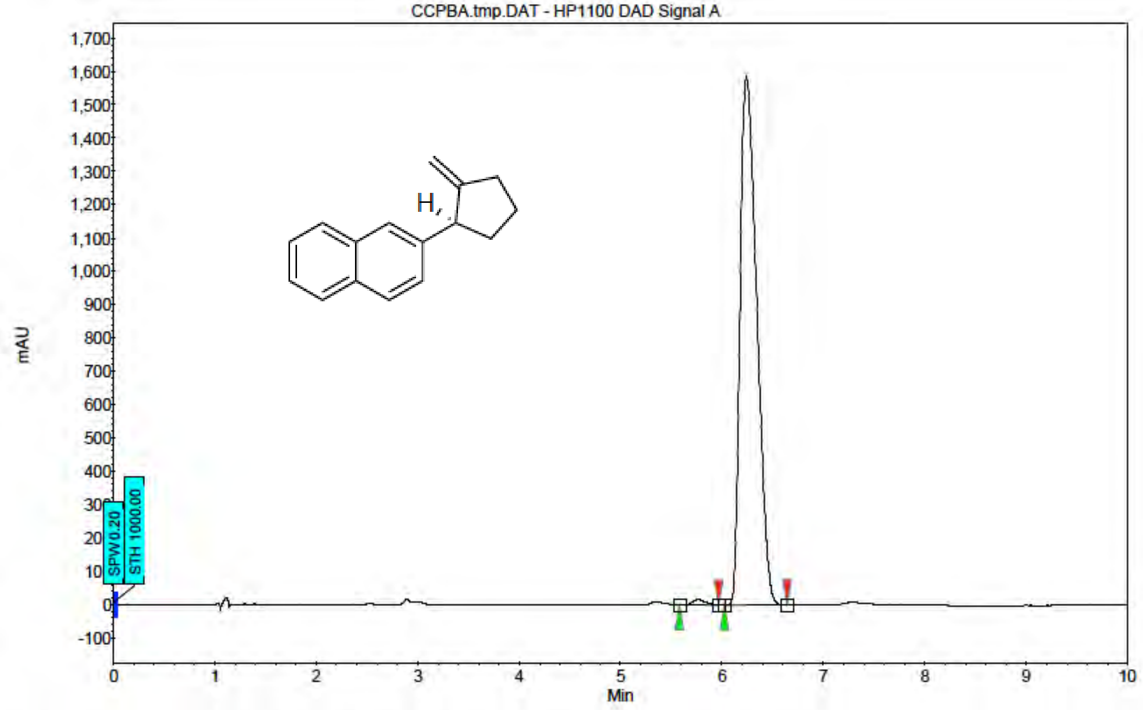
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 3.43 | 3.57 | 3.81 | 0.00 | 91.73 | 2101.7 | 240.9 | 91.735 |
| 2 | UNKNOWN | 3.81 | 3.94 | 4.08 | 0.00 | 8.27 | 237.0 | 21.7 | 8.265 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 2338.7 | 262.6 | 100.000 |



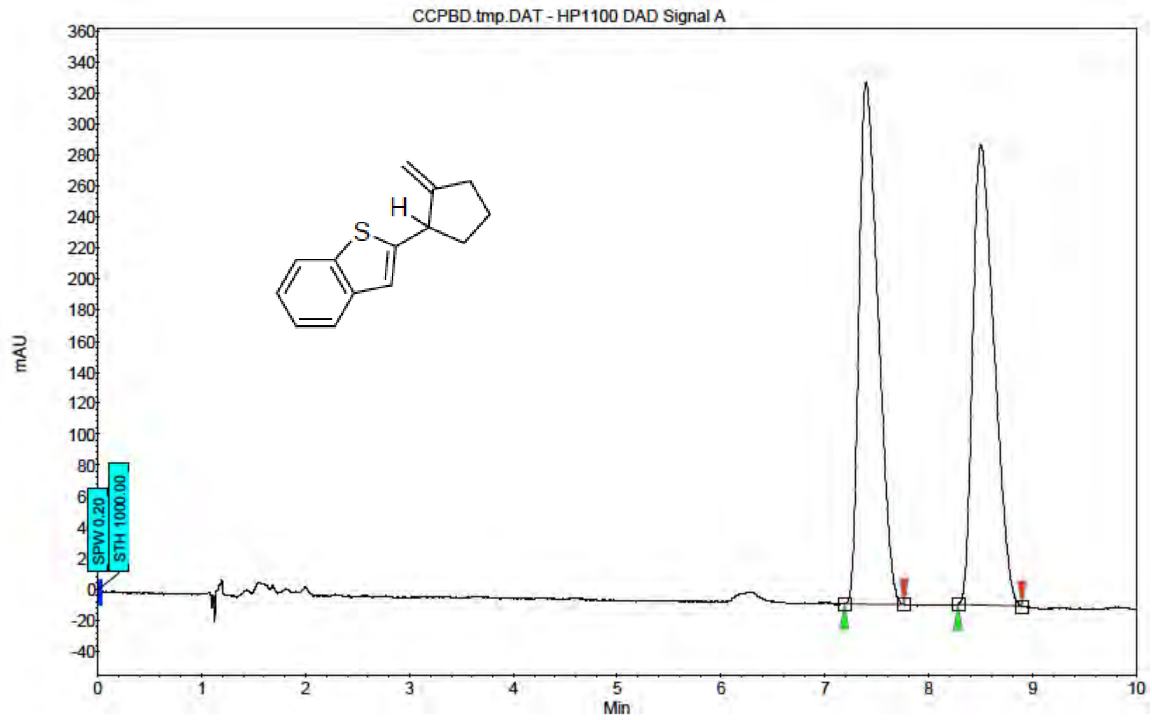


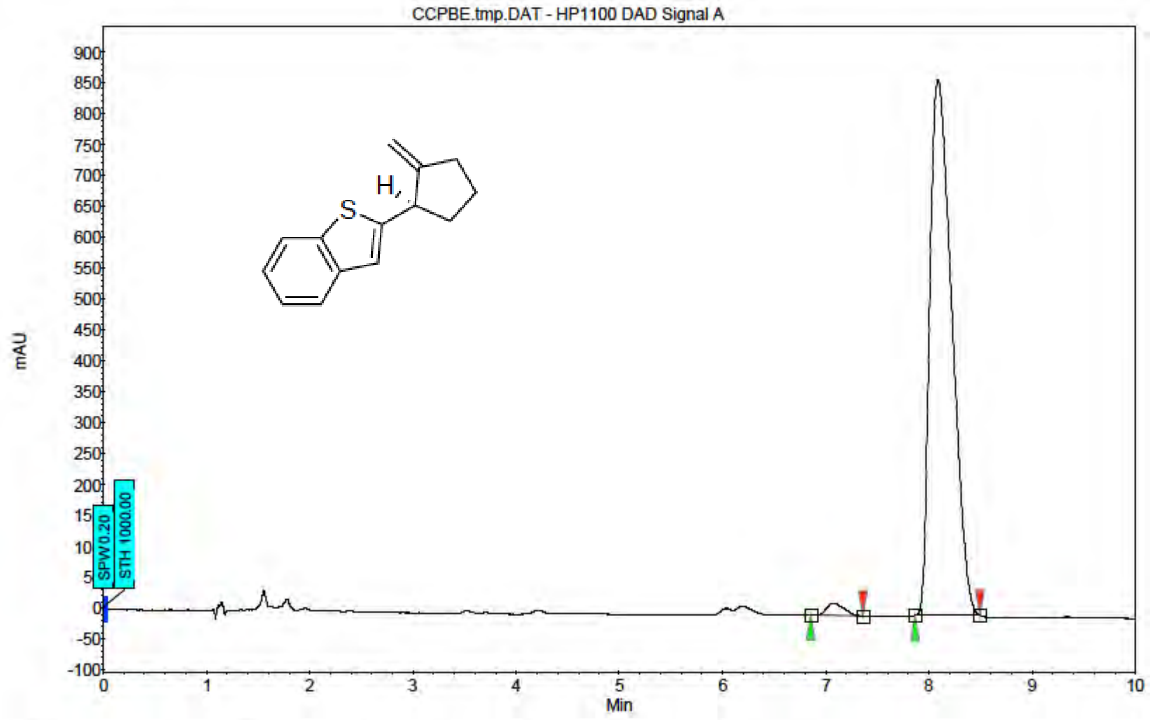
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 6.97 | 7.27 | 7.67 | 0.00 | 94.32 | 967.1 | 172.6 | 94.317 |
| 2 | UNKNOWN | 8.00 | 8.26 | 8.55 | 0.00 | 5.68 | 53.6 | 10.4 | 5.683 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 1020.7 | 183.0 | 100.000 |



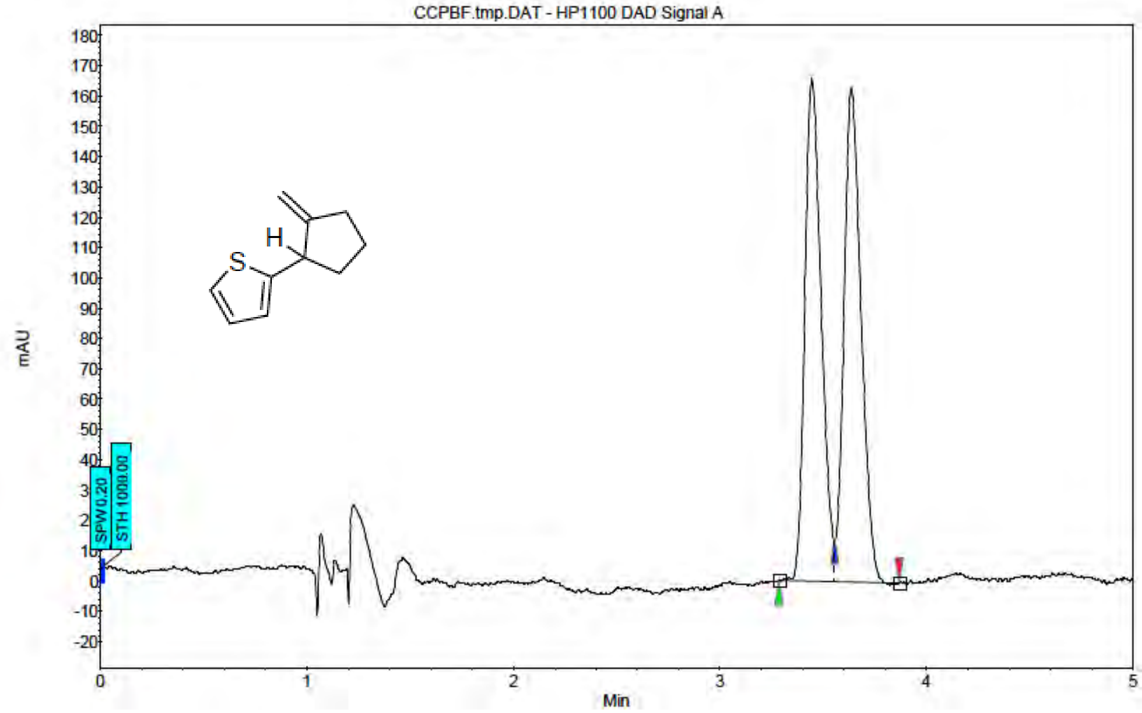


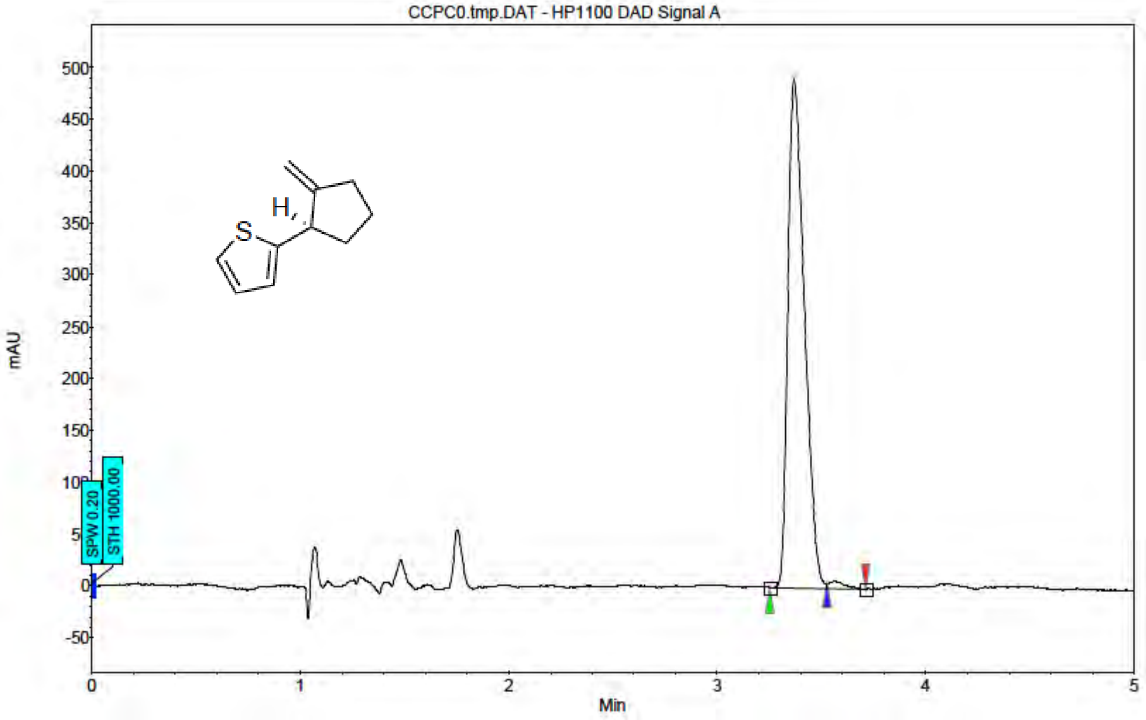
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 5.58 | 5.77 | 5.97 | 0.00 | 0.70 | 14.1 | 2.1 | 0.696 |
| 2 | UNKNOWN | 6.02 | 6.24 | 6.64 | 0.00 | 99.30 | 1585.0 | 301.4 | 99.304 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 1599.1 | 303.5 | 100.000 |



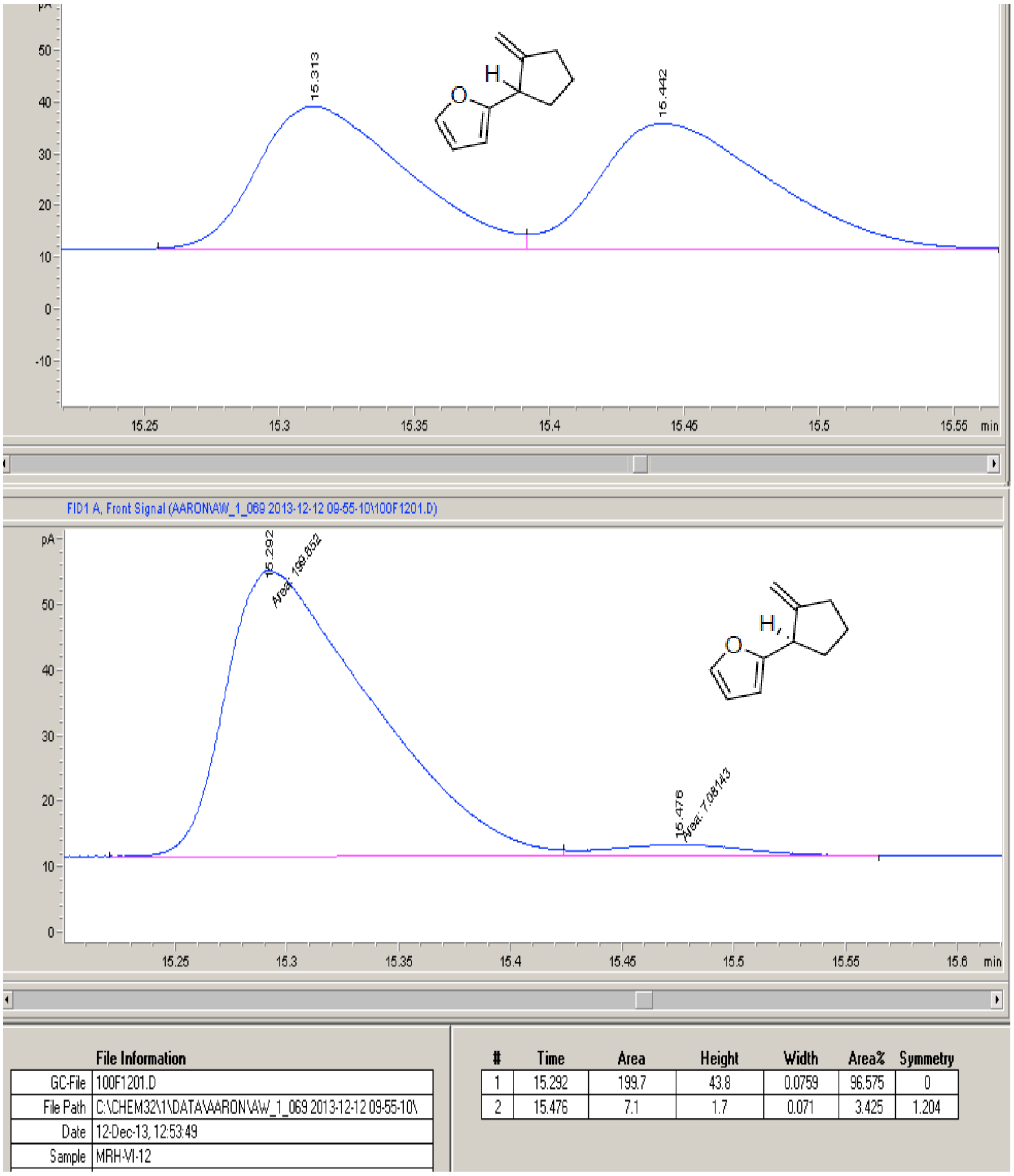


| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 2 | UNKNOWN | 6.85 | 7.08 | 7.36 | 0.00 | 1.75 | 19.5 | 3.8 | 1.746 |
| 1 | UNKNOWN | 7.87 | 8.09 | 8.49 | 0.00 | 98.25 | 865.4 | 213.2 | 98.254 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 885.0 | 217.0 | 100.000 |





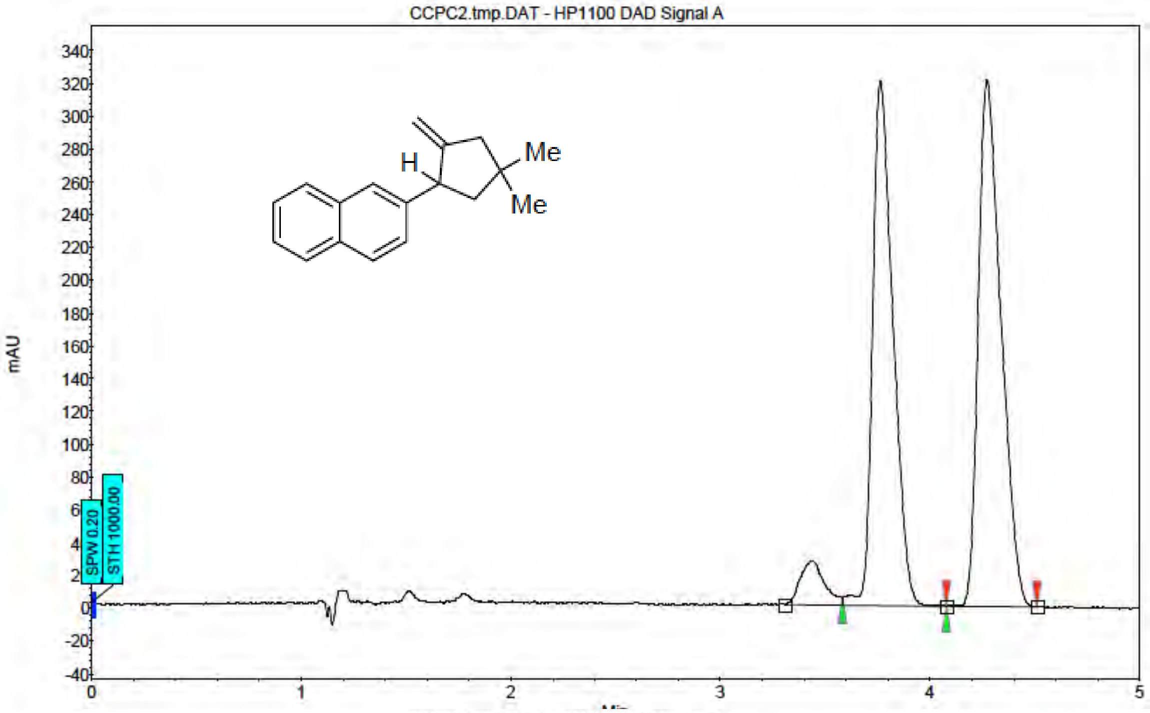
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 3.25 | 3.37 | 3.53 | 0.00 | 98.52 | 491.0 | 45.2 | 98.520 |
| 2 | UNKNOWN | 3.53 | 3.57 | 3.71 | 0.00 | 1.48 | 7.7 | 0.7 | 1.480 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 498.7 | 45.9 | 100.000 |

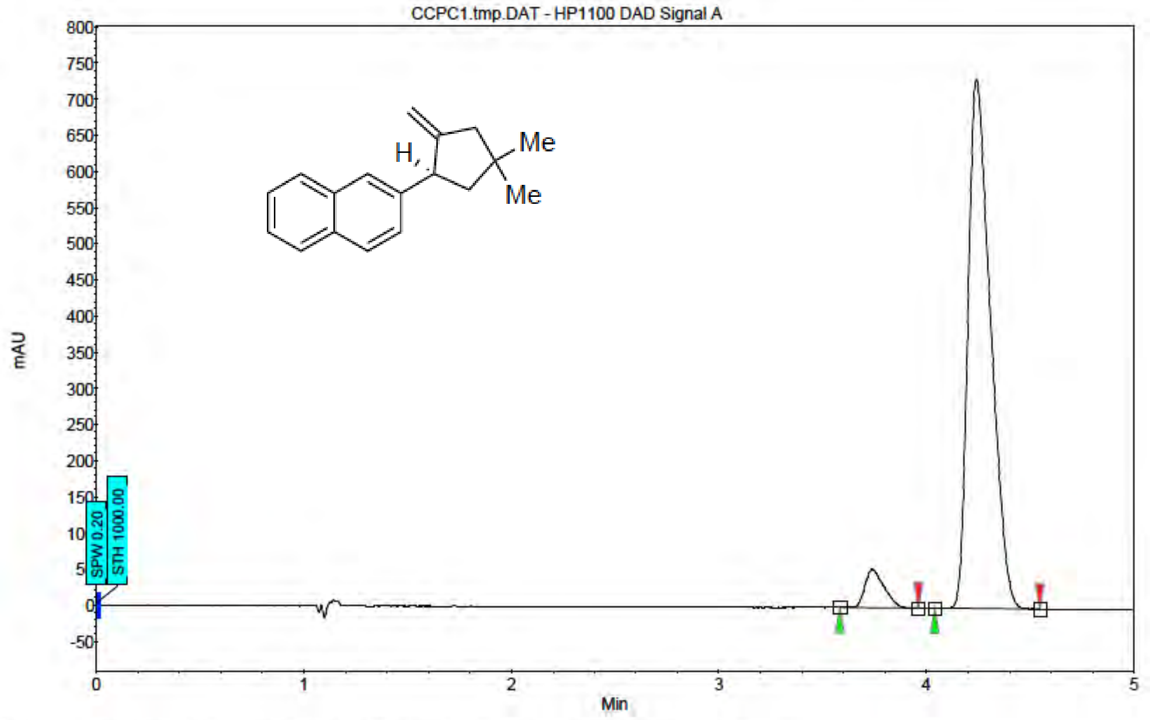


File Information

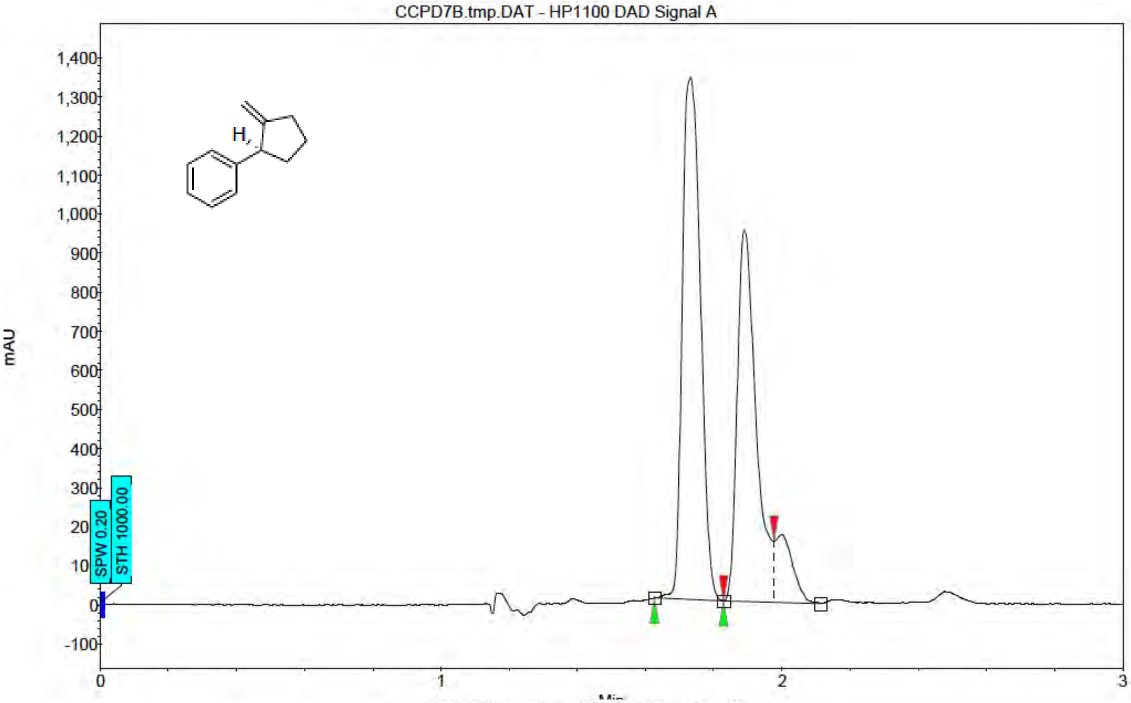
| | |
|---|---|
| GC-File | 100F1201.D |
| File Path | C:\CHEM32\1\DATA\AARON\AW_1_069 2013-12-12 09-55-10\ |
| Date | 12-Dec-13, 12:53:49 |
| Sample | MRH-VI-12 |

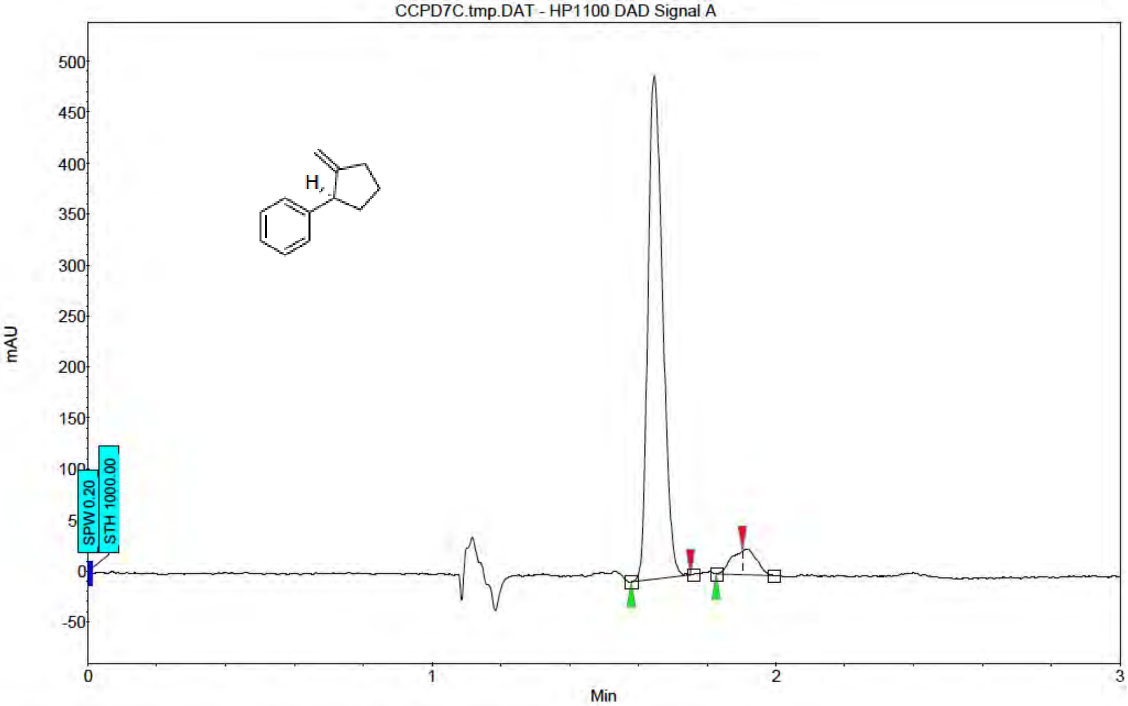
| # | Time | Area | Height | Width | Area% | Symmetry |
|---|---|---|---|---|---|---|
| 1 | 15.292 | 199.7 | 43.8 | 0.0759 | 96.575 | 0 |
| 2 | 15.476 | 7.1 | 1.7 | 0.071 | 3.425 | 1.204 |



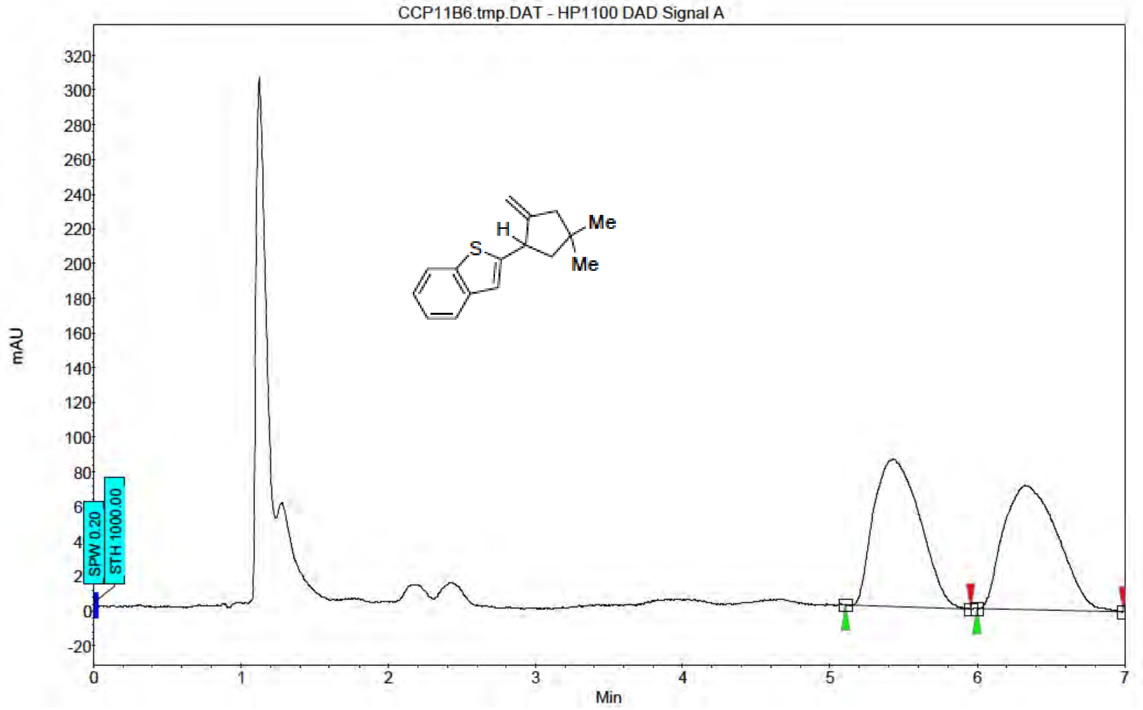


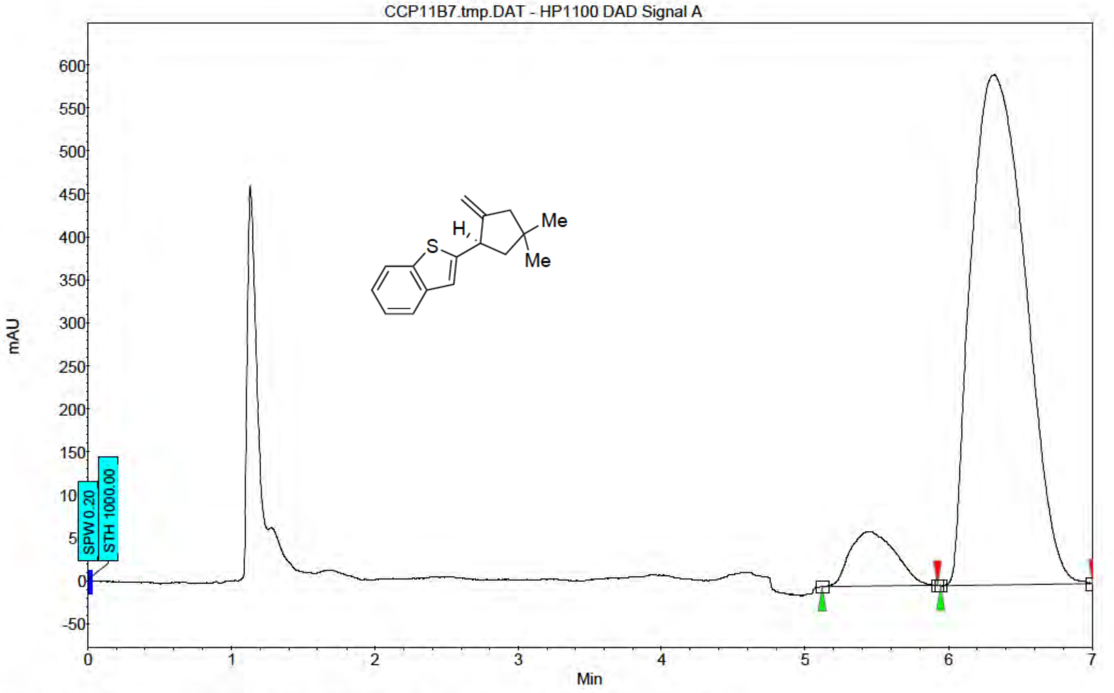
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 3.58 | 3.74 | 3.96 | 0.00 | 5.76 | 52.5 | 5.6 | 5.756 |
| 2 | UNKNOWN | 4.04 | 4.24 | 4.55 | 0.00 | 94.24 | 731.6 | 91.8 | 94.244 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 784.1 | 97.5 | 100.000 |



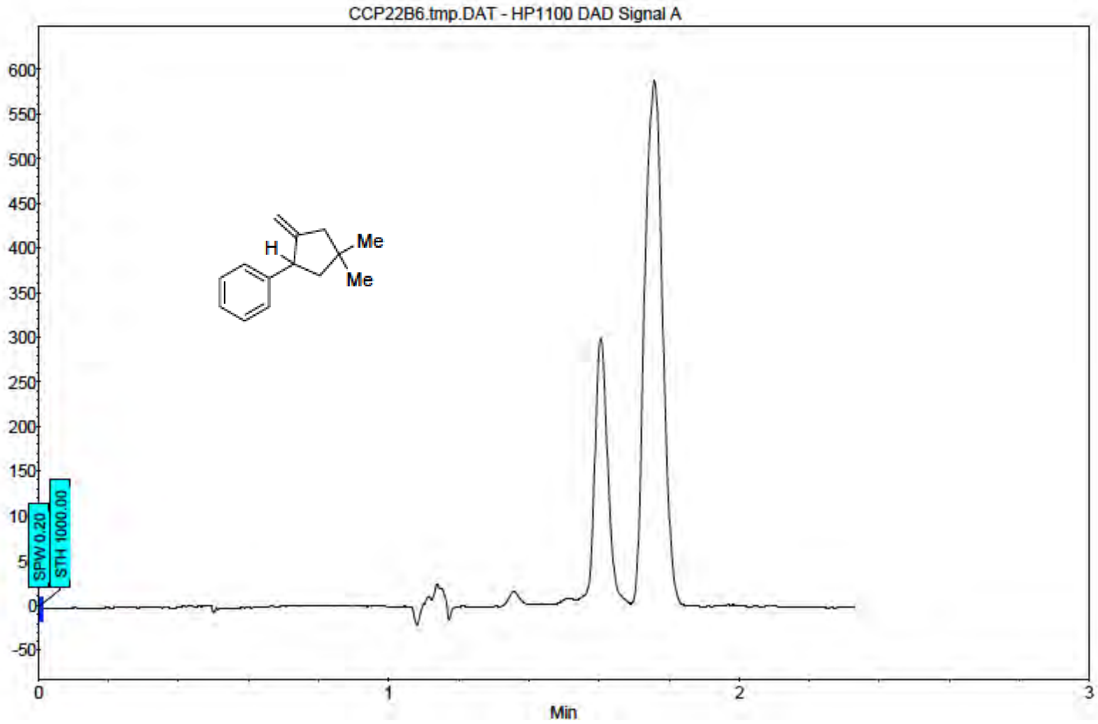


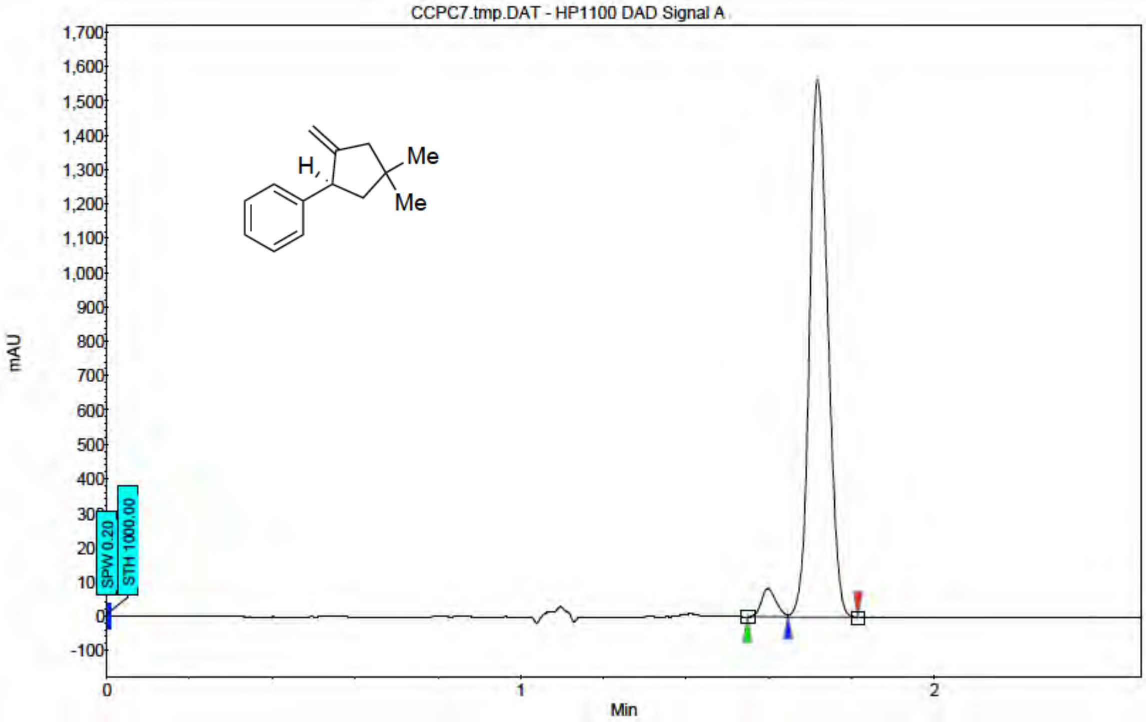
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 1.58 | 1.65 | 1.75 | 0.00 | 96.49 | 493.5 | 24.4 | 96.493 |
| 2 | UNKNOWN | 1.83 | 1.90 | 1.90 | 0.00 | 3.51 | 22.7 | 0.9 | 3.507 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 516.1 | 25.3 | 100.000 |



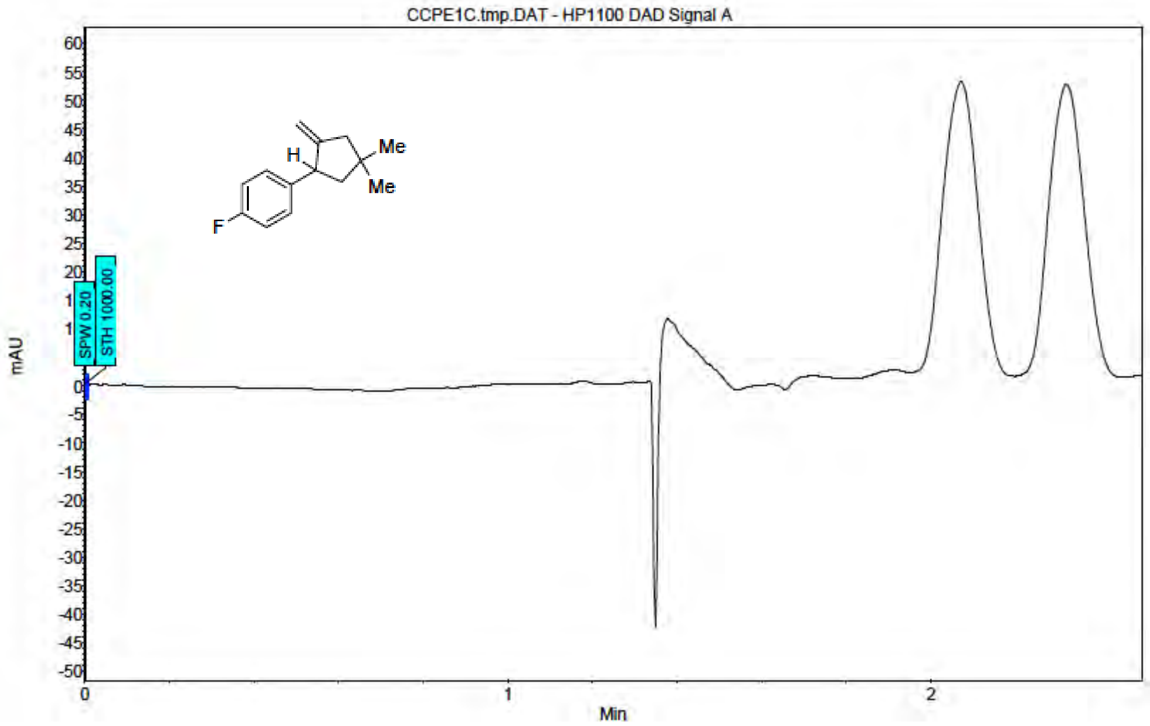


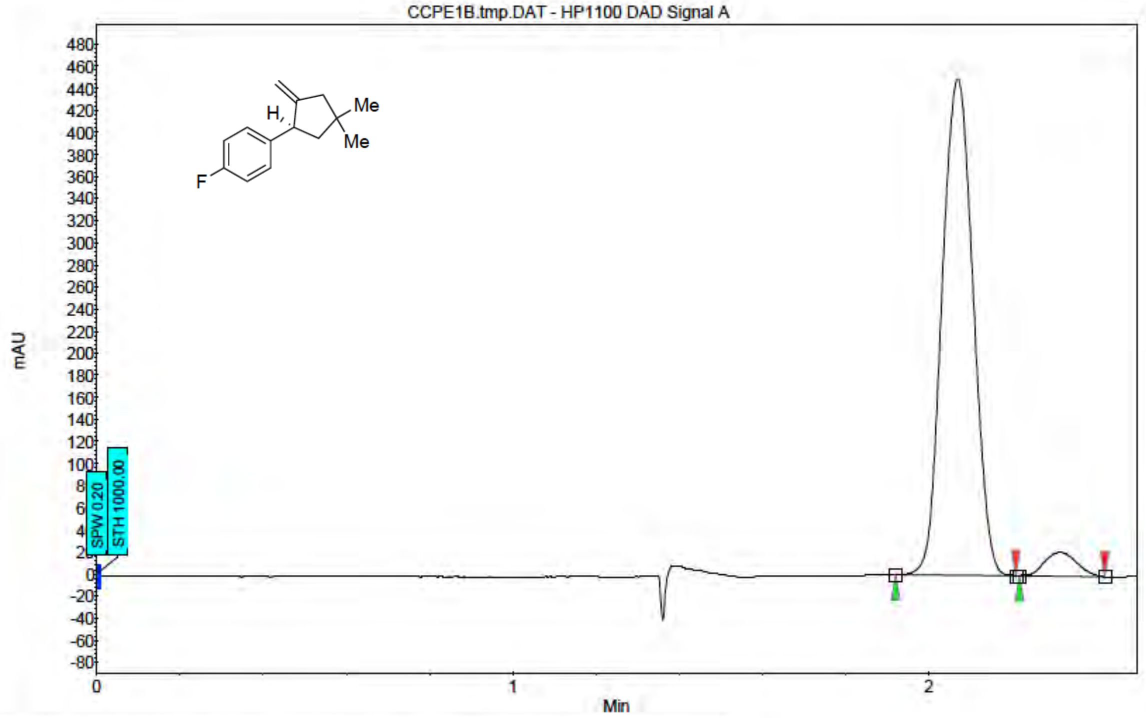
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 5.12 | 5.45 | 5.92 | 0.00 | 8.18 | 63.7 | 23.2 | 8.181 |
| 2 | UNKNOWN | 5.94 | 6.32 | 7.00 | 0.00 | 91.82 | 593.0 | 260.4 | 91.819 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 656.7 | 283.6 | 100.000 |



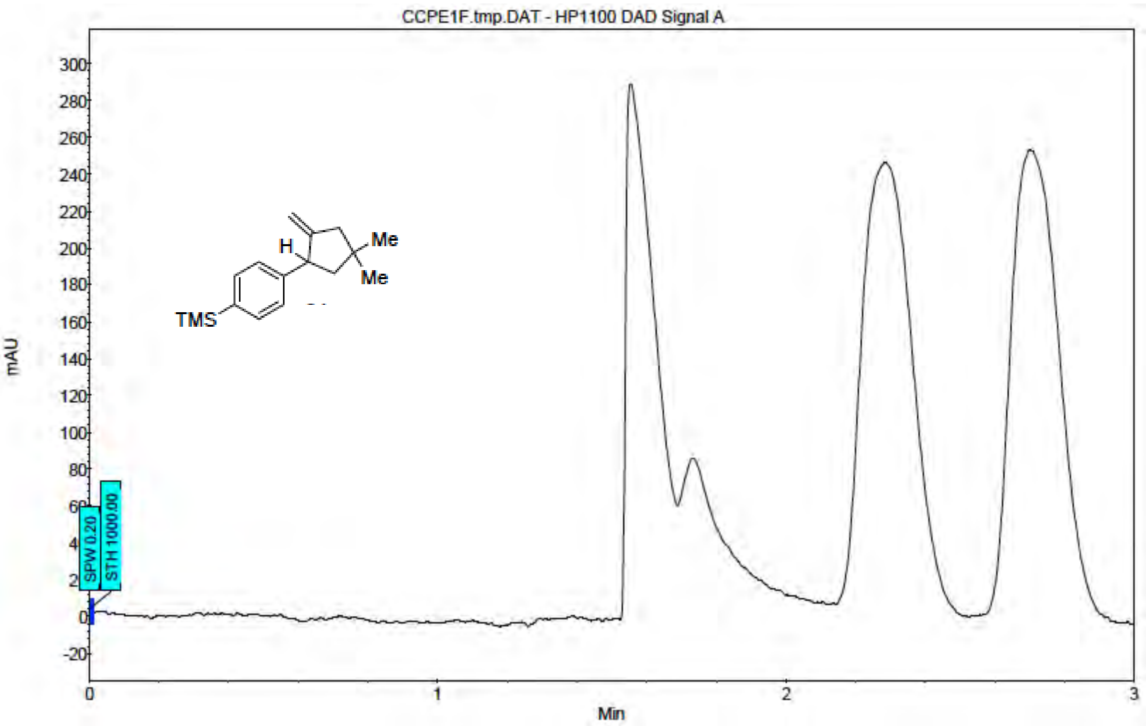


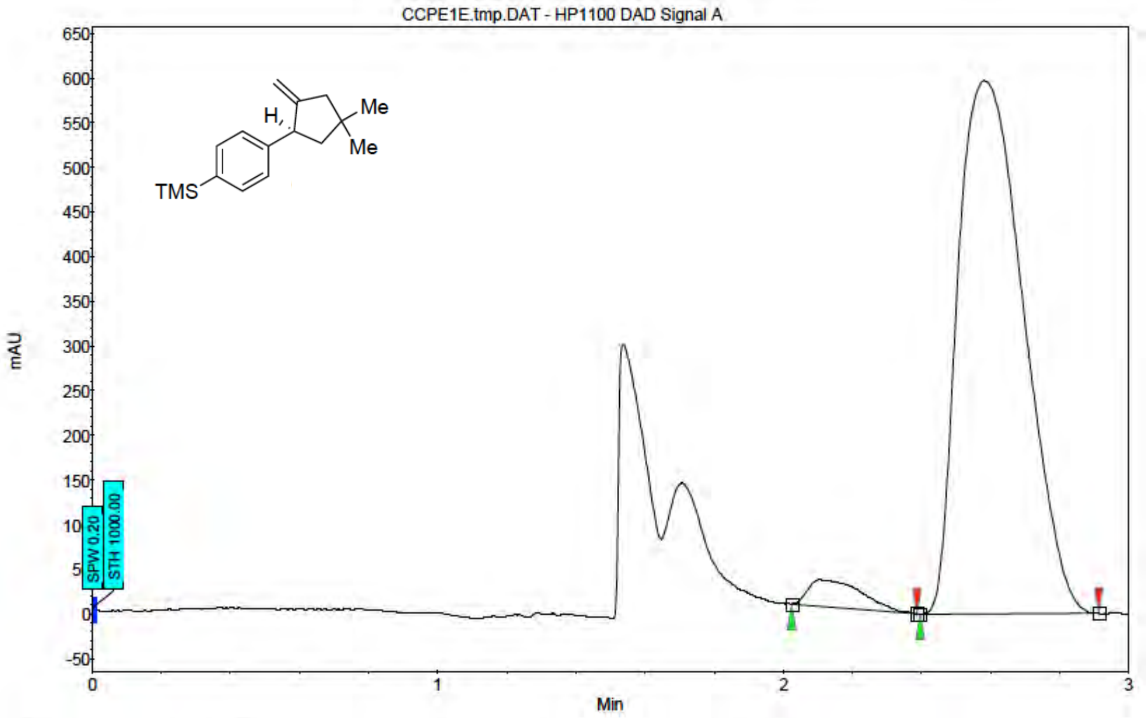
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 1.55 | 1.60 | 1.65 | 0.00 | 4.05 | 82.9 | 3.4 | 4.054 |
| 2 | UNKNOWN | 1.65 | 1.72 | 1.82 | 0.00 | 95.95 | 1563.6 | 80.0 | 95.946 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 1646.4 | 83.4 | 100.000 |



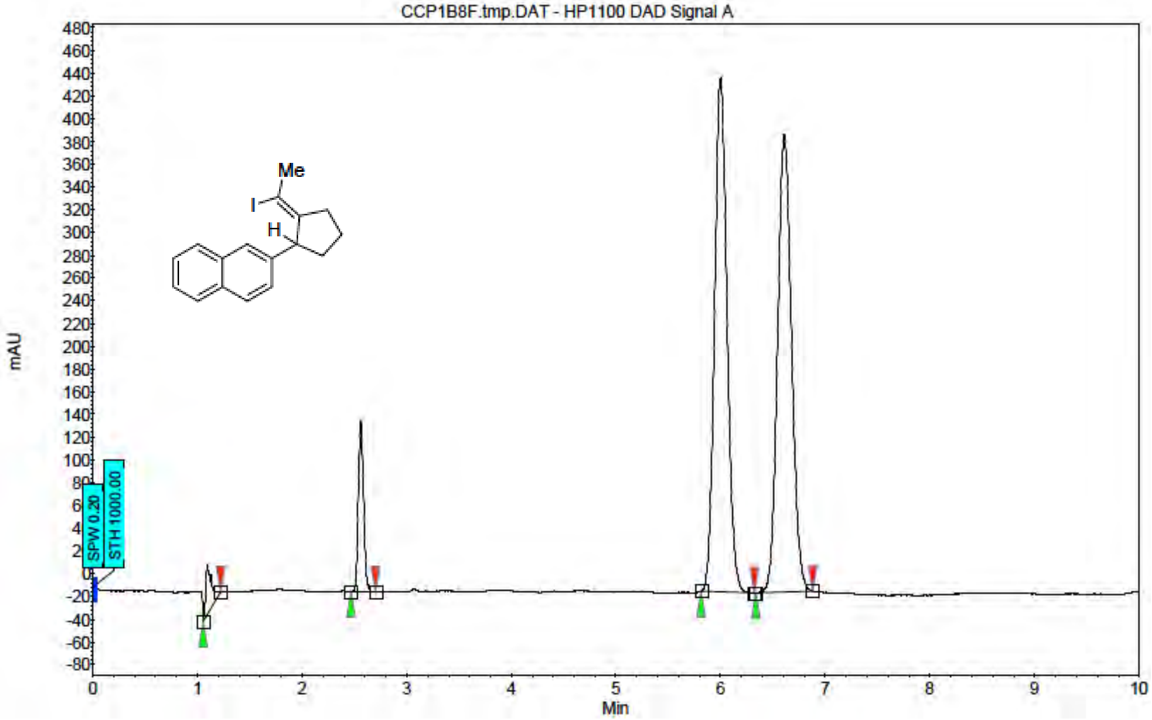


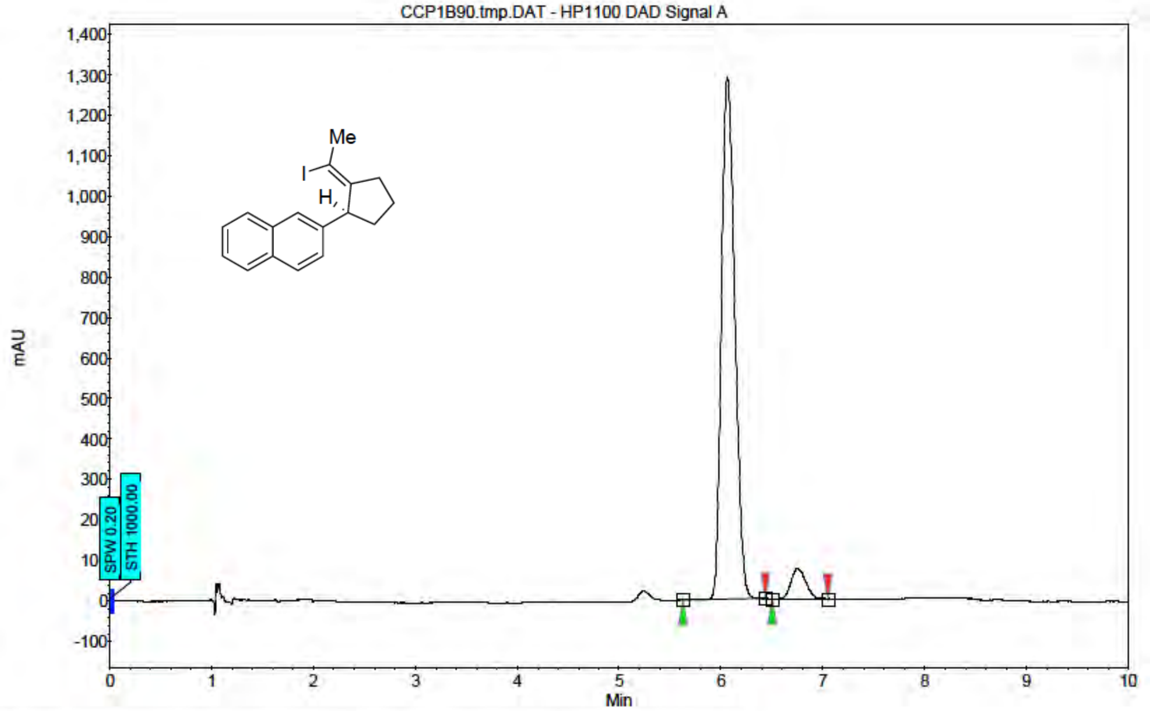
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 1.92 | 2.07 | 2.21 | 0.00 | 95.21 | 449.5 | 38.6 | 95.213 |
| 2 | UNKNOWN | 2.22 | 2.31 | 2.42 | 0.00 | 4.79 | 21.7 | 1.9 | 4.787 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 471.2 | 40.6 | 100.000 |



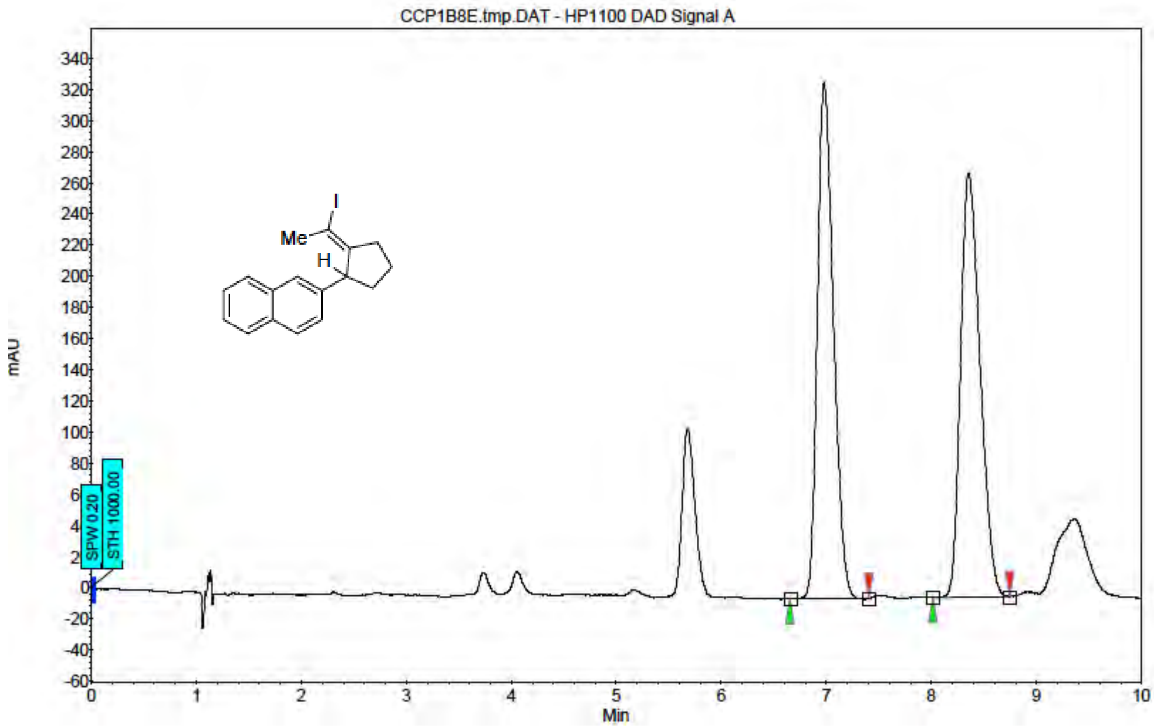


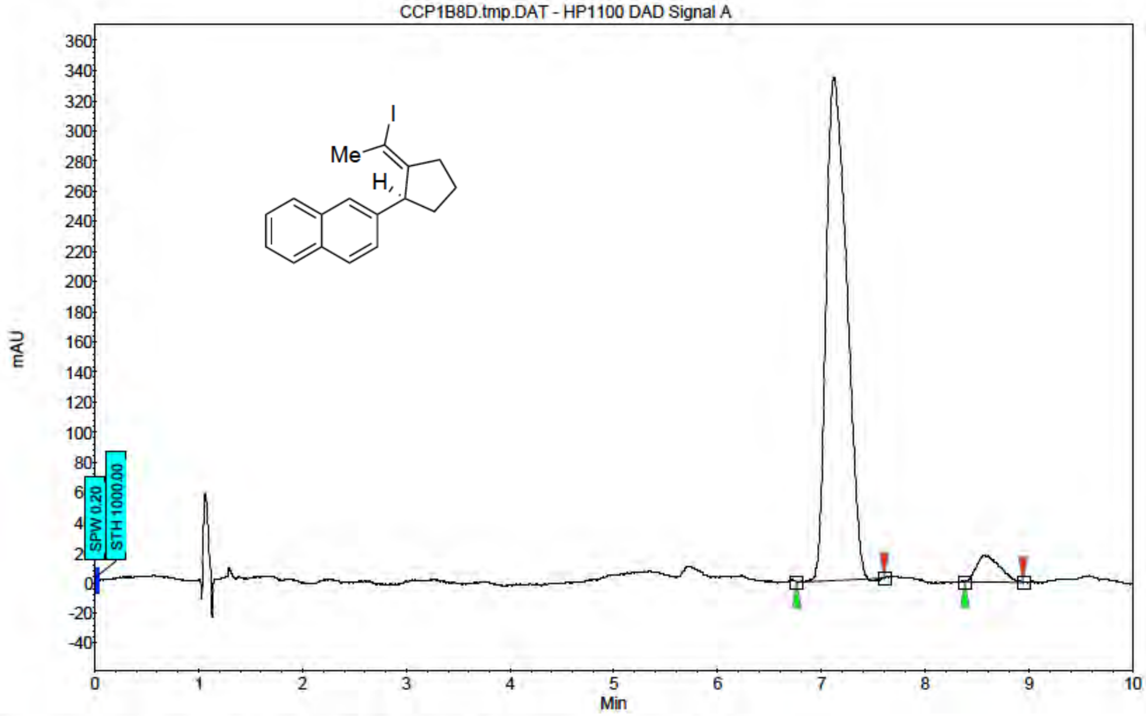
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 2.03 | 2.11 | 2.39 | 0.00 | 4.02 | 30.1 | 5.5 | 4.015 |
| 2 | UNKNOWN | 2.40 | 2.58 | 2.91 | 0.00 | 95.98 | 597.4 | 130.8 | 95.985 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 627.5 | 136.2 | 100.000 |



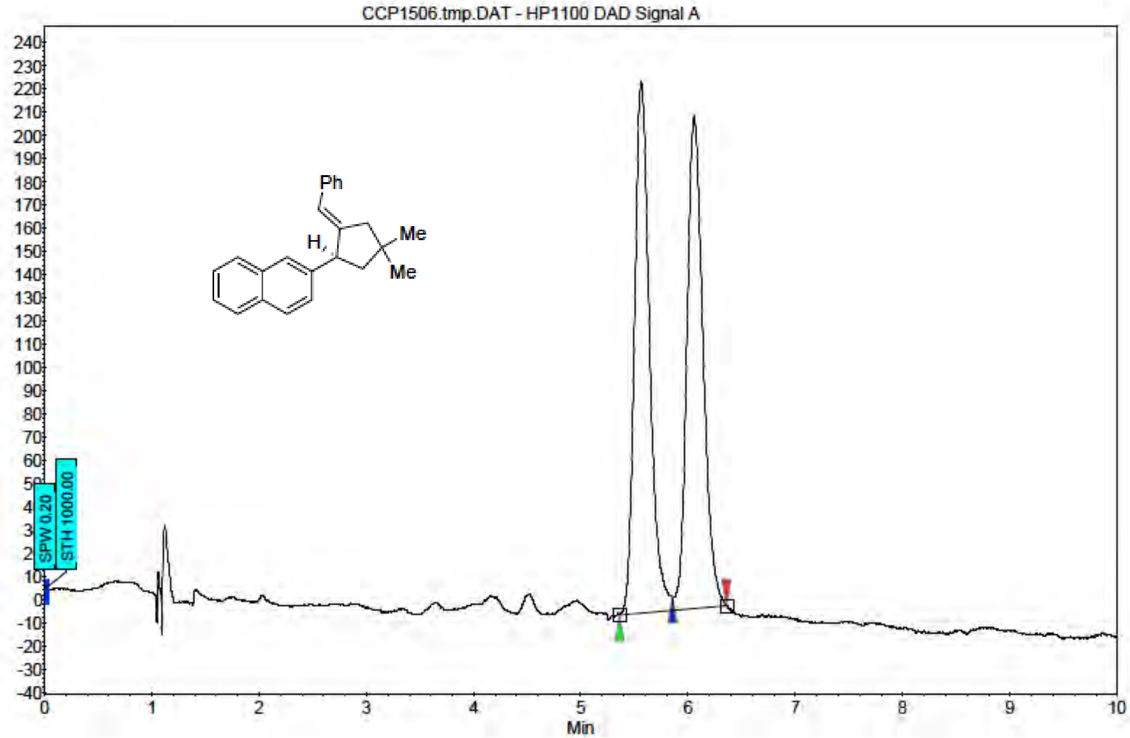


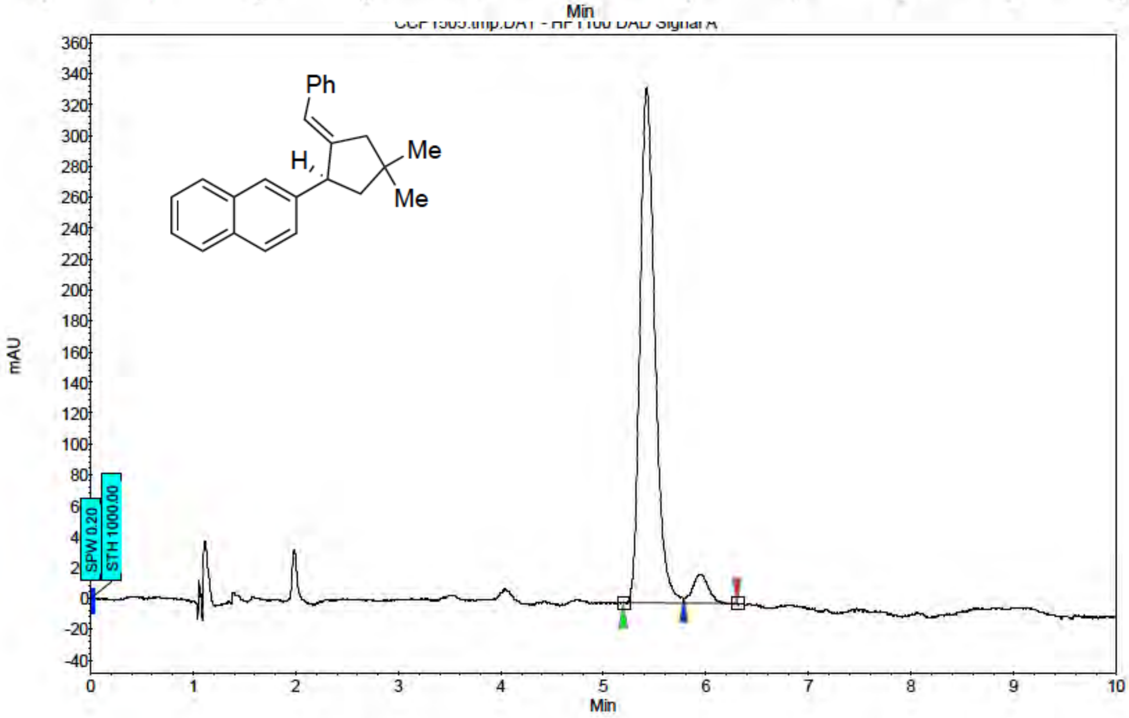
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 5.63 | 6.06 | 6.44 | 0.00 | 94.06 | 1287.8 | 195.2 | 94.062 |
| 2 | UNKNOWN | 6.50 | 6.75 | 7.05 | 0.00 | 5.94 | 74.4 | 12.3 | 5.938 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 1362.2 | 207.5 | 100.000 |



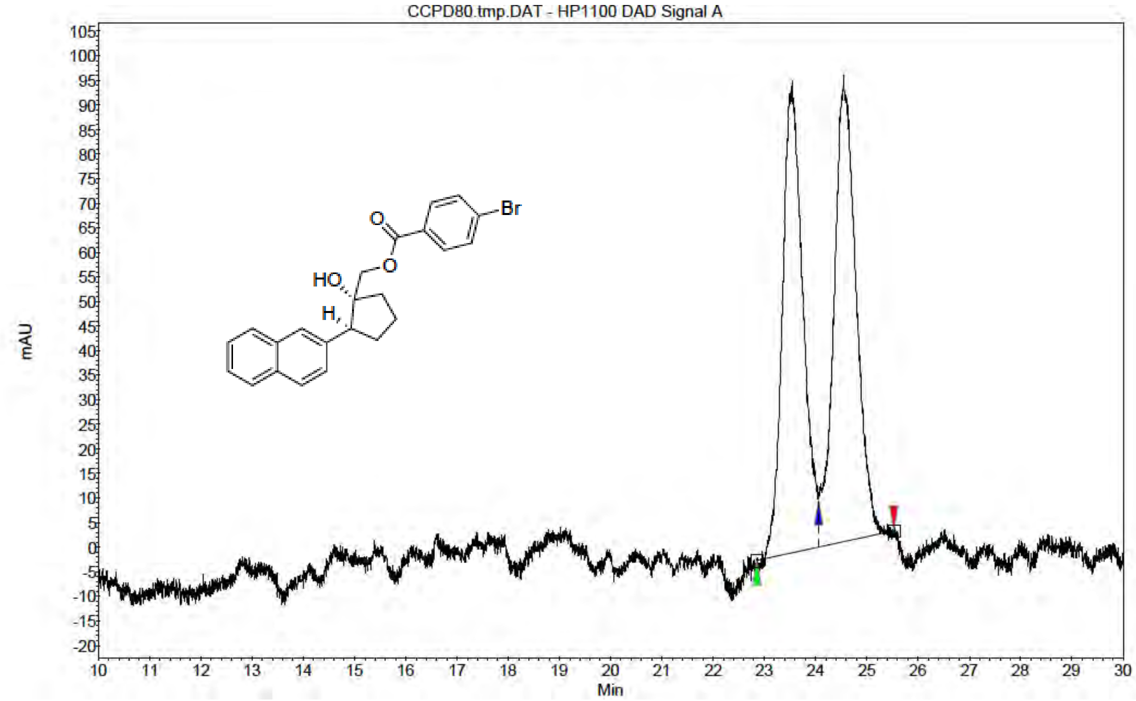


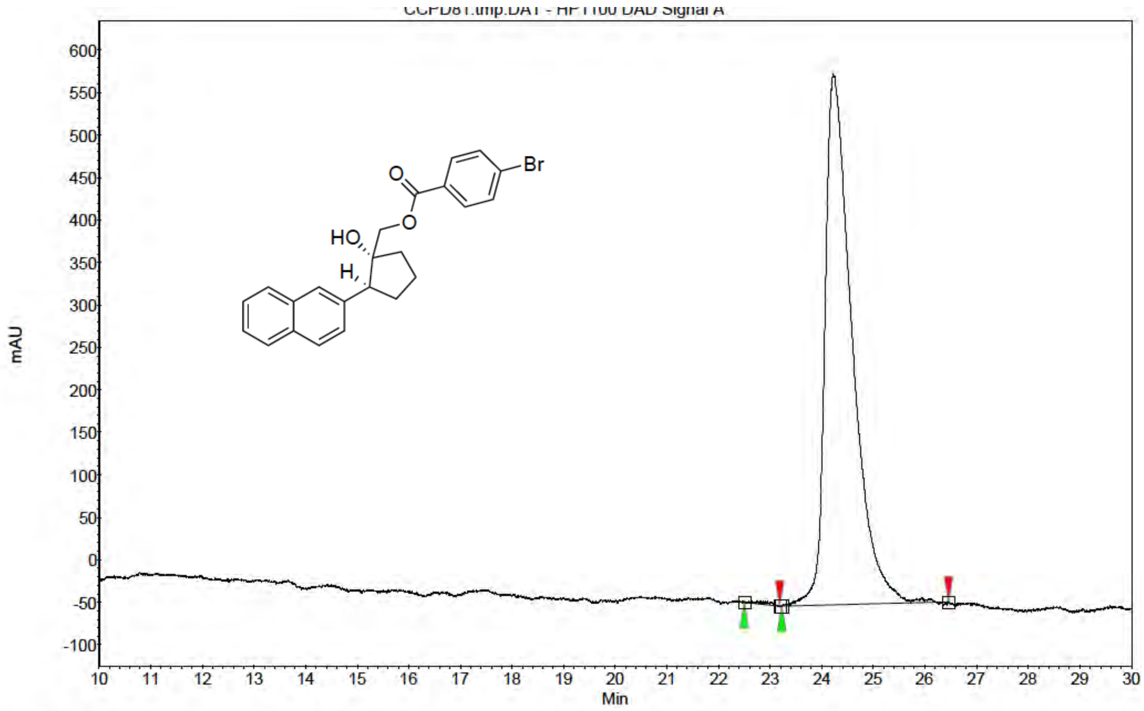
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 6.76 | 7.12 | 7.60 | 0.00 | 94.39 | 333.3 | 76.4 | 94.390 |
| 2 | UNKNOWN | 8.38 | 8.56 | 8.94 | 0.00 | 5.61 | 17.5 | 4.5 | 5.610 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 350.8 | 81.0 | 100.000 |



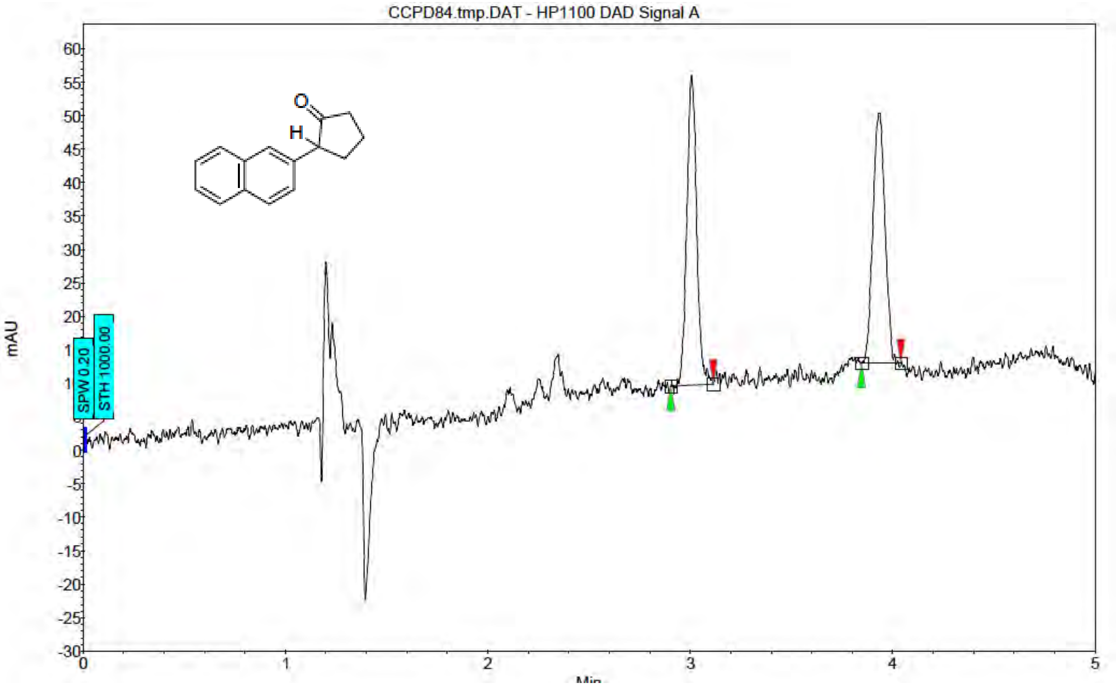


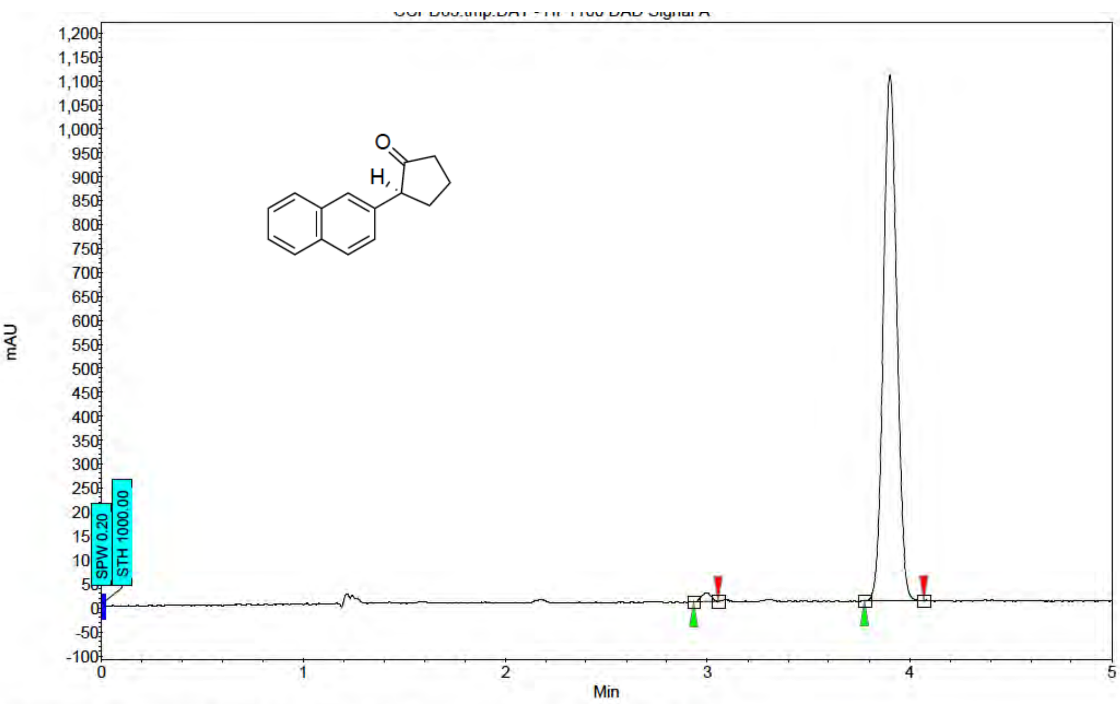
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 5.19 | 5.42 | 5.79 | 0.00 | 94.50 | 333.5 | 56.0 | 94.498 |
| 2 | UNKNOWN | 5.79 | 5.96 | 6.30 | 0.00 | 5.50 | 18.9 | 3.3 | 5.502 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 352.5 | 59.3 | 100.000 |



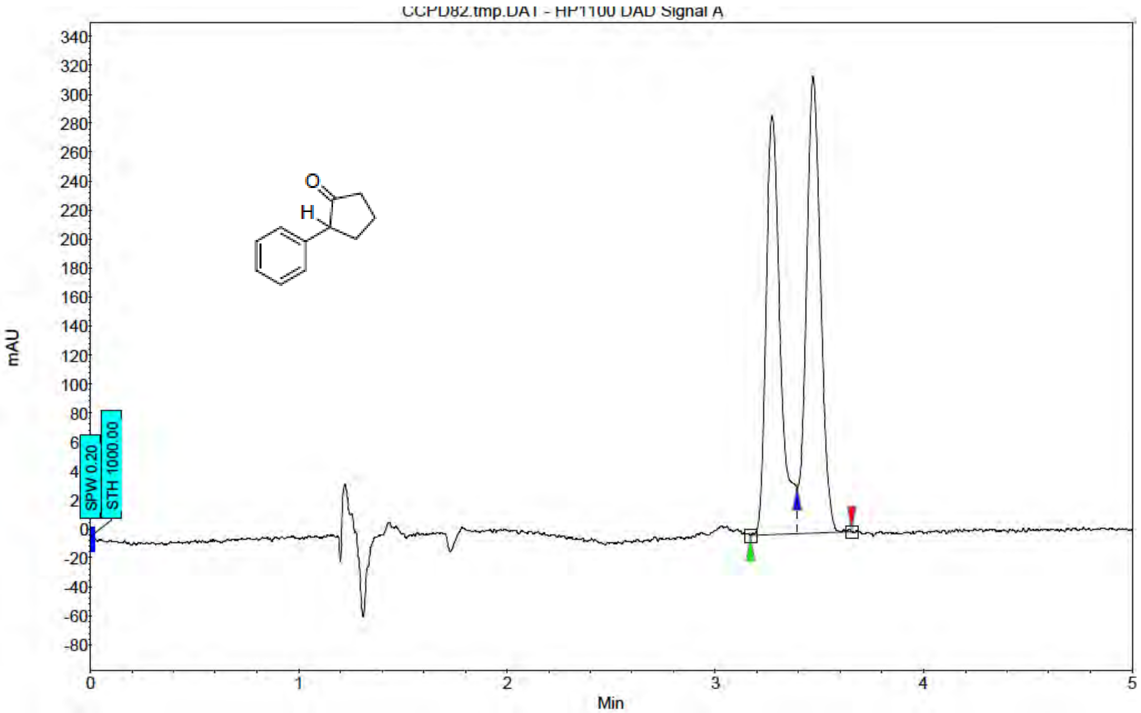


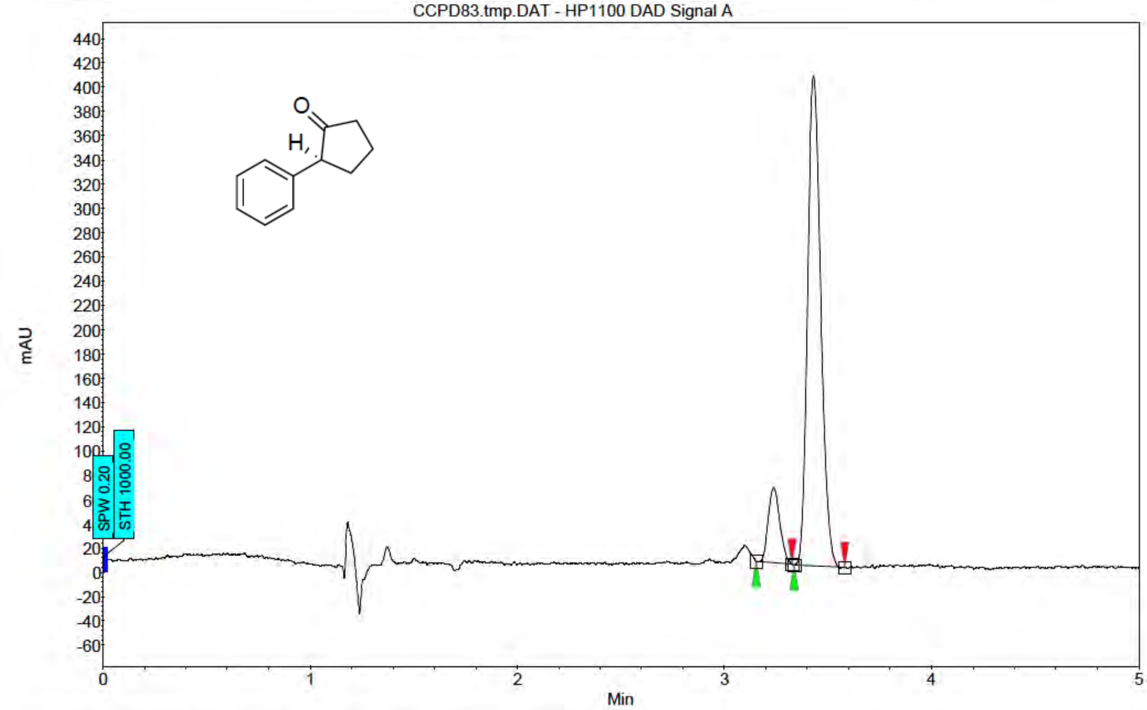
| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 2 | UNKNOWN | 22.51 | 22.96 | 23.18 | 0.00 | 0.28 | 4.0 | 1.1 | 0.277 |
| 1 | UNKNOWN | 23.23 | 24.23 | 26.46 | 0.00 | 99.72 | 624.2 | 380.6 | 99.723 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 628.2 | 381.7 | 100.000 |





| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 2 | UNKNOWN | 2.93 | 2.99 | 3.05 | 0.00 | 1.14 | 18.0 | 1.0 | 1.141 |
| 1 | UNKNOWN | 3.78 | 3.91 | 4.07 | 0.00 | 98.86 | 1096.7 | 85.6 | 98.859 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 1114.8 | 86.5 | 100.000 |





| Index | Name | Start | Time | End | RT Offset | Quantity | Height | Area | Area |
|---|---|---|---|---|---|---|---|---|---|
| | | [Min] | [Min] | [Min] | [Min] | [% Area] | [µV] | [µV.Min] | [%] |
| 1 | UNKNOWN | 3.15 | 3.24 | 3.33 | 0.00 | 11.78 | 61.5 | 4.0 | 11.780 |
| 2 | UNKNOWN | 3.34 | 3.43 | 3.58 | 0.00 | 88.22 | 403.6 | 29.7 | 88.220 |
| | | | | | | | | | |
| Total | | | | | | 100.00 | 465.2 | 33.7 | 100.000 |