UNIVERSITY OF CALIFORNIA,
IRVINE

Investigation of Silver-Catalyzed Propargylation Reactions and Nickel-Catalyzed Cross-Electrophile Couplings

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

by

Thomas Benjamin Donald Endean

Dissertation Committee:
Professor Elizabeth Jarvo, Chair
Professor Vy Dong
Professor Suzanne Blum

2018

DEDICATION

To

My wife, parents, family, and friends

in recognition of their unwavering support and love.

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I thank the American chemical Society for permission to include portions of Chapter 1 which was originally published in *Organic Letters*.

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Service

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DeGlopper, K. S.; Fodor, S. K.; **Endean, T. B. D.**; Johnson, J. B.; "Decarbonylative cross coupling of phthalimides with diorganozinc reagents—Efforts toward catalysis" *Polyhedron* **2016,** *114*, 393.

Presentations

Endean, T. B. D.; Osborne, C. A.; Jarvo, E. R. "Asymmetric Propargylation Reactions of Cyclic *N*-Sulfonyl Ketimines" 4-4-17, 253rd ACS National Meeting, San Francisco, CA (oral)

Endean, T. B. D.; Edwards, K. M. "Improving the safety culture of the University of California, Irvine through a graduate safety fellowship" 4-3-17, 253rd ACS National Meeting, San Francisco, CA (poster)

Endean, T. B. D.; Osborne, C. A.; Jarvo, E. R. "Enantioselective silver-catalyzed propargylation reactions of N-sulfonyl ketimines" 3-16-16, 251st ACS National Meeting, San Diego, CA (poster)

Endean, T. B. D.; Osborne, C. A.; Jarvo, E. R. "Enantioselective silver-catalyzed propargylation reactions of N-sulfonyl ketimines" 3-14-16, 251st ACS National Meeting, San Diego, CA (poster)

Endean, T. B. D.; Johnson, J. B. "Investigation of regioselectivity in the nickel-mediated decarbonylative cross-coupling of imides with organozinc reagents" 3-26-12, 243rd ACS National Meeting, San Diego, CA (poster)

Endean, T. B. D.; Johnson, J. B."Regioselectivity of Nickel-Mediated Decarbonylative Cross-Coupling of Cyclic Imides and Diorganozinc Reagents" 11-12-11, West Michigan Regional Undergraduate Science Research Conference, Grand Rapids, MI. (poster)

Endean, T. B. D.; Simmons, J.; Winton, V.; Johnson, J. B. "Nickel-Mediated Decarbonylative Coupling of Imides with Organozinc Reagents" 6-7-11 42nd National Organic Symposium, Princeton University, Princeton, NJ. (poster)

Endean, T. B. D.; Johnson, J. B"Regioselectivity of Nickel-Mediated Decarbonylative Cross-Coupling of Cyclic Imides and Diorganozinc Reagents" 7-22-11 Summer Undergraduate Research Symposium, Hope College, Holland, MI. (poster)

Endean, T. B. D.; Todd, D.; Johnson, J. B. "The Stereoselective Addition of a Gilman Reagent to an α,β-Unsaturated Ester" 4-15-11 Celebration of Undergraduate Research and Creative Performance, Hope College, Holland, MI (poster)

Endean, T. B. D.; Todd, D.; Johnson, J. B. "The Stereoselective Addition of a Gilman Reagent to an α,β-Unsaturated Ester" 7-30-10 Regional Chemistry REU Symposium, Hope College, Holland, MI. (poster)

Endean, T. B. D.; Todd, D.; Johnson, J. B. "The Stereoselective Addition of a Gilman Reagent to an α,β-Unsaturated Ester" 7-23-10 Summer Undergraduate Research Symposium, Hope College, Holland, MI. (poster)

Endean, T. B. D. "Nickel-Mediated Cross-Coupling: A Study in Regioselectivity" 5-25-11 Hope College Summer Research Seminar, Holland, MI (oral)

Endean, T. B. D. "The Asymmetric Addition of a Gilman Reagent to an α,β-unsaturated Ester" 6-9-10 Hope College Summer Research Seminar, Holland, MI (oral)

ABSTRACT OF THE DISSERTATION

Investigation of Silver-Catalyzed Propargylation Reactions and Nickel-Catalyzed Cross-Electrophile Couplings

By

Thomas Benjamin Donald Endean

Doctor of Philosophy in Chemistry

University of California, Irvine, 2018

Professor Elizabeth R. Jarvo, Chair

Metal-catalyzed reactions often allow access to reactivity that would be otherwise unavailable to researchers using more conventional synthetic methods. The Jarvo lab has worked to develop both stereoselective and stereospecific metal-catalyzed reactions that proceed with high stereochemical fidelity to produce synthetically useful products.

In Chapter 1 the enantioselective silver-catalyzed propargylation of *N*-sulfonylketimines is described. This reaction proceeds in high yield and excellent enantiomeric ratio and is compatible with a wide variety of diaryl and aryl-alkylketimines. The synthetic transformation of one of the homopropargylic products via Sonogashira cross-coupling proceeds with high stereochemical fidelity.

In Chapter 2 work towards a deeper understanding of the mechanism of a previously disclosed stereospecific nickel-catalyzed cross-electrophile coupling of 2-aryl-4-chlorotetrahydropyrans to form cyclopropanes is described. Experiments were performed to determine the overall rate law of the reaction as well as the kinetic order of each reagent participating in the rate-determining step of the reaction.

In Chapter 3 work towards a new stereospecific nickel-catalyzed cross-electrophile coupling is described. Utilizing a strained 2-aryl-oxetane scaffold with a pendant chloride the stereospecific cross-electrophile coupling to form cyclopropanes.

Chapter 1

Silver-Catalyzed Enantioselective Propargylation Reactions of N-Sulfonylketimines

1.1 Introduction:

Asymmetric addition reactions to carbonyl derivatives are important methods for synthesis. The addition of propargylic fragments to carbonyl derivatives is no exception. For example, in the synthesis of the monomeric unit of rhizopodin reported by Chakraborty and co-workers, an indium-catalyzed diastereoselective propargylation of an aldehyde was used to set a key propargylic alcohol stereocenter at the beginning of the synthesis.[1] In the synthesis of bongkrekic acid and isobongkrekic acid by Ley and co-workers, an indium-catalyzed asymmetric propargylation of an aldehyde was used to install a stereocenter, a Sonagashira reaction, and allow for the late stage installation of a Z alkene in a single step.[2] While they are the most common, aldehydes are certainly not the only important carbonyl-based electrophiles for asymmetric propargylation reactions in total synthesis. In 2013, Reeves and co-workers utilized an asymmetric propargylation reaction of a ketone on kilogram scale to install an important stereocenter and allow for elaboration of the propargyl fragment to a substituted 7-azaindole.[3]

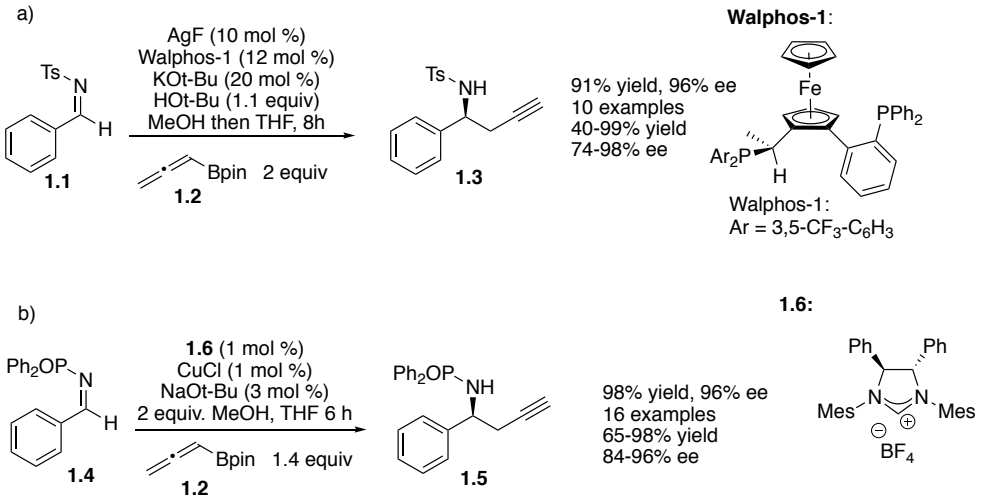
---

[1] Pulukuri, K. K.; Chakraborty, T. K. *Org. Lett.* **2012**, *14*, 2858.
[2] Francais, A.; Leyva, A.; Etxebarria-Jardi, G.; Ley, S. V. *Org. Lett.* **2010**, *12*, 340.
[3] Reeves, J. T. et. al. *J. Org. Chem.* **2013**, *78*, 3616

While aldehydes have been extensively studied as electrophiles in asymmetric propargylation reactions,[4,56,7,8] other carbonyl derivatives have seen less attention. Enantioselective propargylations of aldimines were first reported by the Jarvo group in 2011. They reported that a silver fluoride in the presence of a chiral Walphos ligand was effective in transforming tosyl-protected aldimines into homopropargylic amines in high yields and enantioselectivities (Scheme 1.1a).[9] In 2012 the Hoveyda group published conversion of *N*-phosphinoyl aldimines to homopropargylic amines using copper chloride in the presence of a chiral NHC ligand in high yields and enantioselectivities (Scheme 1.1b).[10] They utilized this protocol in the enantioselective synthesis of β-amino acid as well as the enantioselective synthesis of a fragment of an anti-cancer agent.

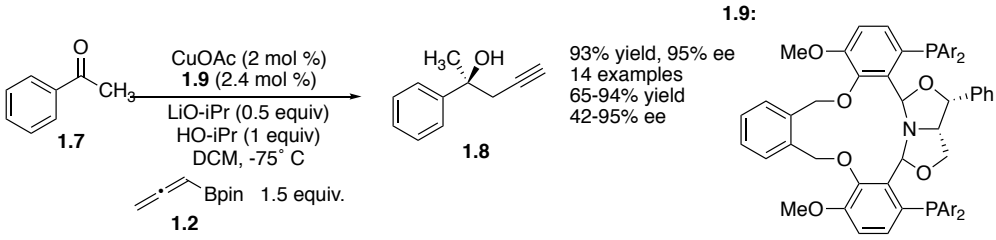
[4] Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7667.
[5] Fandrick, D. R; Fandrick, K. R.; Reeves, J. T.;Tan, Z.; Tang, W.; Capacci, A. G.; Rodriguez, S.; Song, J. J.; Lee, H.; Yee, N. K; Senanayake C. H. *J. Am. Chem. Soc.*, **2010**, *132*, 7600.
[6] Haddad, T. D.; Hirayama, L C.; Buckley, J. J.; Singaram, B. *J. Org. Chem.* **2012**, *77*, 889.
[7] Jain, P.; Wang, H.; Houk, K. N.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 1391.
[8] Reddy, L. R *Org. Lett.* **2012**, *14*, 1142.
[9] Wisniewska, H. M.; Jarvo E. R. *Chem. Sci.* **2011**, *2*, 807.
[10] Vieira, E. M.; Haeffner, F.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 6618.

Scheme 1.1: Enantioselective Propargylation Reactions of Aldimines



Enantioselective propargylation reactions of ketones have also been shown to be viable substrates for the addition of a propargylic fragment. In 2010, the Shibasaki group reported the first enantioselective propargylation of ketones (Scheme 1.2).[11] Utilizing copper acetate and a large chiral bidentate phosphine they were able to obtain homopropargylic alcohols in high yields and high enantioselectivities.

Scheme 1.2: First reported enantioselective propargylation reaction of ketones

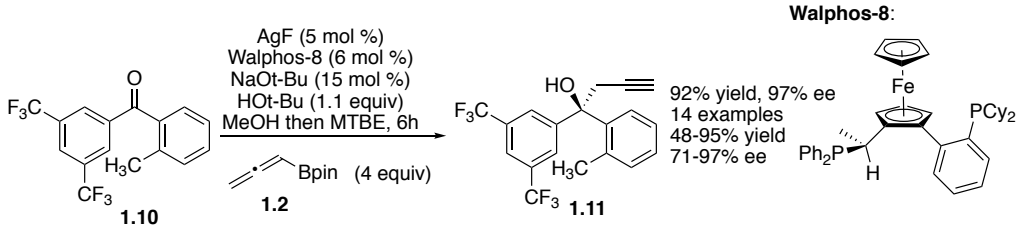


Asymmetric propargylation of diaryl ketones presents a particular challenge because of the similar steric environment of the two ketone substituents. In 2013 the Jarvo lab reported the silver catalyzed propargylation of pyruvates and ketones including five examples of

[11] Shi, S.-L.; Xu, L.-W.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 6638.

propargylation of diaryl ketones such as **1.10** (Scheme 3).[12] They found that in the case of the diaryl ketones an ortho group was required to be present on one of the arene rings to differentiate the *Re* and *Si* faces of the ketone.

Scheme 1.3: Enantioselective propargylation of diaryl ketones



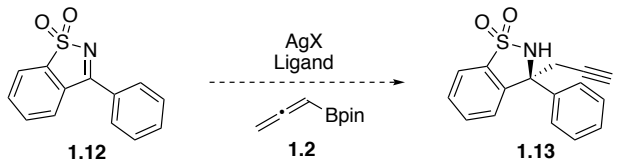
To date, the enantioselective propargylation of ketimines has not yet been reported. Ketimines have two major drawbacks as electrophiles. First, they are the least electrophilic of the series of aldehydes, ketones, aldimines, and ketimines making the addition step more difficult. Secondly, ketimines undergo E/Z isomerization very readily and when the substituents present a similar steric environment it is not possible to synthesize only one isomer. The first drawback can be overcome by employing longer reaction times as well as using more transmetallating reagent (*vide infra*). The second drawback can be overcome by utilizing cyclic ketimines where the protecting group on nitrogen is tethered to one of the ketimine substituents.

Cyclic *N*-sulfonyl ketimines have been utilized in asymmetric addition reactions for hydrogenation,[13] arylation,[14,15] alkenylation,[16] and allylation[17] but no methods for asymmetric propargylation have yet been reported. We hypothesized that using the same catalyst system that employed for the propargylation of aldimines and diaryl ketones, we could affect the

[12] Kohn, B. L.; Ichiishi, N.; Jarvo, E. R. *Angew. Chem. Int. Ed.*, **2013**, *52*, 4414.
[13] Yu, C. B.; Wang, D. W.; Zhou, Y. G. *J. Org. Chem.* **2009**, *74*, 5633.
[14] Nishimura, T.; Noishiki, A.; Tsui, G. C.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 5056.
[15] Jiang, C.; Lu, Y.; Hayashi, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 9936.
[16] Luo, Y.; Carnell, A. J.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, 5*1*, 6762.
[17] Luo, Y.; Hepburn, H. B.; Chotsaeng, N.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, 5*1*, 8309.

propargylation of cyclic *N*-sulfonyl ketimines in high enantioselectivities and yields (equation 1.1).

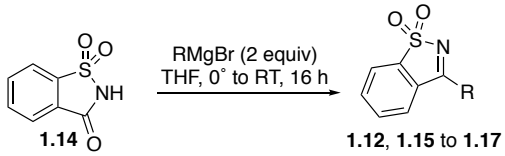
Equation 1.1: Proposed enantioselective propargylation of *N*-sulfonyl ketimines

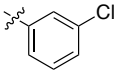
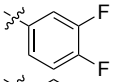
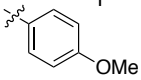


1.2 Results and discussion:

The *N*-sulfonyl ketimines such as **1.12** are readily synthesized by the addition of a Grignard reagent into saccharin. Four substrates were synthesized in order to test the reactivity and selectivity of the proposed reaction (Table 1.1).

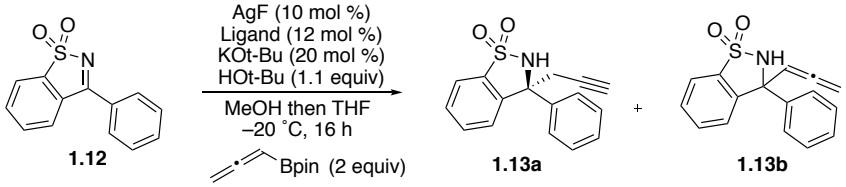
Table 1.1: Synthesis of *N*-sulfonyl ketimine starting materials



Entry	Product	R	% Yield
1	**1.12**		49
2	**1.15**		56
3	**1.16**		12
4	**1.17**		49

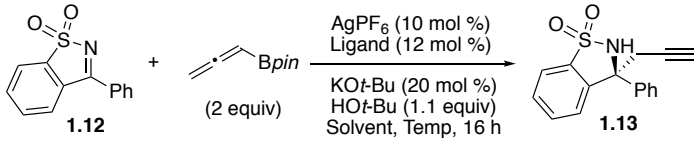
With these substrates in hand we began by determining whether or not enantioselective addition would be feasible. Ketimine **1.12** was used as a test case. Using the conditions that were previously reported by the Jarvo group,[9,12] we observed that moderate yields and good enantioselectivities of the desired product could be obtained (Scheme 1.4).

Scheme 1.4: Initial results using previously reported method



To further optimize the reaction we examined a variety of solvents and ligands. Previously Charlotte Osborne observed that the enantioselective propargylation of aldimines and ketimines could be effected in DMF instead of methanol then THF.[18] Using these reaction conditions we evaluated different temperatures and ligands (Table 1.2).

Table 1.2: Optimization of reaction conditions



Entry	Ligand	Solvent	Temperature	Yield (%)	er
1	Walphos-1	MeOH, then THF	–20˚ C	19	96:4
2	Walphos-1	MeOH, then THF	RT	26	95:5
3	Walphos-8	DMF	–20˚ C	35	76:24
4	Josiphos-6	DMF	–20˚ C	70	74:26
5	(S)-BINAP	DMF	–20˚ C	55	40:60
6	Walphos-1	DMF	–20˚ C	51	99:1
7	Walphos-1	DMF	4˚ C	54	99:1
8	Walphos-1	DMF	RT	57	98:2

Switching from silver fluoride to silver hexafluorophosphate gave a much less active catalyst in THF but it did impart higher enantioselectivities (92% ee compared to only 84% ee, Table 1.2, entry 1). It was found that Walphos-8 and Josiphos-6 gave good conversion but the enantioselectivities were found to be much lower than with Walphos-1 entries 3 and 4). Since ferrocene-based ligands are not only high molecular weight but also moderately expensive, (*S*)-

[18] Osborne, C. A.; Jarvo, E. R. *Unpublished Results.*

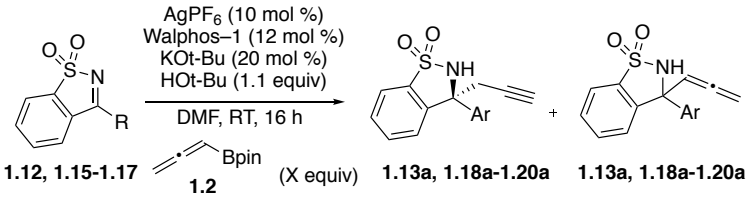
BINAP was also investigated to ensure that a readily available ligand was not overlooked. Unfortunately (*S*)-BINAP imparted the lowest enantioselectivity (entry 5). Walphos-1 in DMF was found to give the best selectivity and moderate yields (entry 6). When the temperature was raised from -20˚ C to 4˚ C a slight increase in yield was observed with no loss of enantioselectivity (entry 7). Further raising the temperature to room temperature lessened the enantioselectivity slightly and gave very similar yields (entry 8). Optimal temperature and solvent conditions therefore were determined to be Walphos-1 in DMF at room temperature.

Because ketimines are inherently less electrophilic than other carbonyl based electrophiles, the activation energy for addition reaction is higher slowing the reaction. In the presence of base the allenyl boronic pinacol ester decomposes into allene gas and a borate.[19] Due to this side reactivity more transmetallating reagent is required to increase the yield. Thus for most of the substrate scope four equivalents of boron reagent were added, two initially and two slowly over three hours. In the case of ketimine **1.17** it was observed that even upon the addition of four equivalents the conversion was still not optimal. Thus six total equivalents were added for this substrate.

As shown in Table 3, the reaction produces homopropargylic amine **1.13a** in high yields and high enantioselectivities. The reaction also tolerates halides (**1.18a**), which provide a handle for further functionalization, and these amines are also produced in high yields and specificities. Electron withdrawing (**1.19a**) and electron donating groups (**1.20a**) are tolerated as well though for electron donating groups, higher equivalencies of boronic ester are required to produce high yields.

[19] Kohn, B. L. Development of Nucleophilic Catalytic Organometallic Reactions. Ph.D. Dissertation, University of California, Irvine, Irvine, CA, 2012.

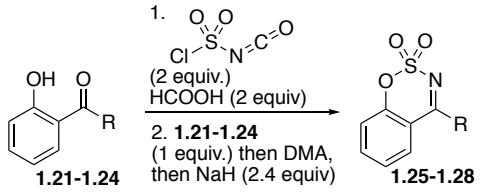
Table 1.3: Scope of *N*-sulfonyl ketimines



Entry	SM	Pdt	R	**1.2** Equiv.	% Yield **a**	%ee **a**	% Yield **b**
1	**1.12**	**1.13**	Ph	4	76	98	2
2	**1.15**	**1.18**	3-Cl-C_6H_4	4	84	92	16
3	**1.16**	**1.19**	3,4-F-C_6H_3	4	90	97	2
4	**1.17**	**1.20**	4-OMe-C_6H_4	6	77	96	<2

These sulfonyl protecting groups offer high reactivity and good selectivities but we wanted to expand the scope beyond these substrates. In the report by Hayashi,[14] most of the reactions were preformed using the cyclic *N*-sulfonyl ketimines but they have a single example with cyclic *N*-sulfamate ketimine. This sulfamate protecting group offers a new class of ketimine substrates to challenge the catalyst system. Using Hayashi's work as inspiration, we synthesized four substrates possessing this sulfamate protecting group (Table 1.4).

Table 1.4: Synthesis of sulfamate protected imines

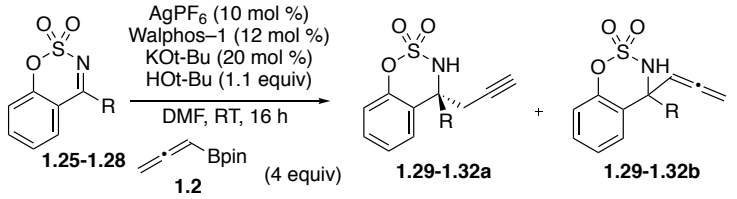


Entry	SM	Pdt	R	% Yield
1	**1.21**	**1.25**	H	38
2	**1.22**	**1.26**	Me	34
3	**1.23**	**1.27**	Et	50
4	**1.24**	**1.28**	Ph	23

With this new class of imine starting materials in hand we examined reactivity under standard conditions. We started with the aldimine **1.25** because it is the most electrophilic and would hopefully have the highest reactivity. When subjected to standard reaction conditions the aldimine showed the desired reactivity with a major side product being the allenylic amine **1.29b**

(Table 1.5, entry 1). This increase in the yield of the allene side product could be due to the increased electrophilicity of the aldimine causing more off cycle reactivity. Most of the sulfamate protected cyclic ketimines showed varying reactivity though they exhibited high good enantioselectivity.

Table 1.5: Scope of sulfamate protected ketimines



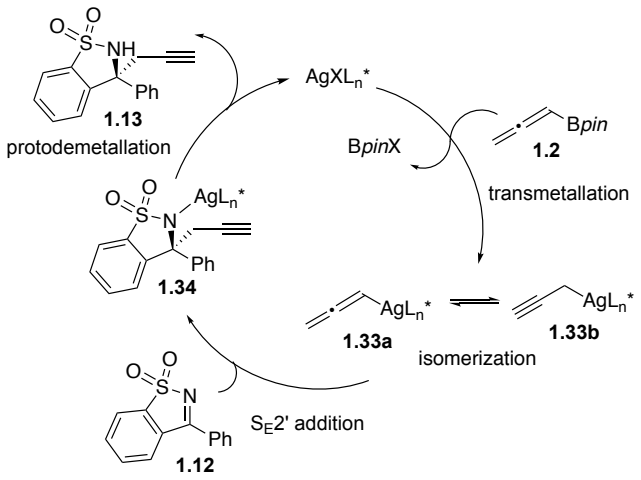
Entry	SM	Pdt	R	% Yield **a**	%ee **a**	% Yield **b**
1	**1.25**	**1.29**	H	54	96	23
2	**1.26**	**1.30**	Me	76	99	< 2
3	**1.27**	**1.31**	Et	51	98	< 2
4	**1.28**	**1.32**	Ph	0	N/A	0

It was found that the methyl sulfamate **1.26** showed the best reactivity with a 76% yield and 99% ee (entry 2). The reaction seemed to be very sensitive to steric bulk and as the steric bulk of the R group increased, reactivity decreased. The ethyl sulfamate **1.27** gave product in moderate yields and high selectivities (entry 3) but the phenyl sulfamate derivative **1.28** provided no product (entry 4). Expanding the protecting group from a sulfonyl to a sulfamate may have resulted in increased steric bulk around the ketimine slowing an already sluggish electrophile.

The allene side product is explained by the proposed operative reaction mechanism, outlined in Scheme 1.5. The mechanism begins with activation of the boron reagent **1.2** followed by a transmetallation to the silver catalyst **1.33**. The propargyl silver species **1.33b** and the allenyl silver species **1.33a** are in equilibrium. Allenyl silver complex **1.33a** is more stable and

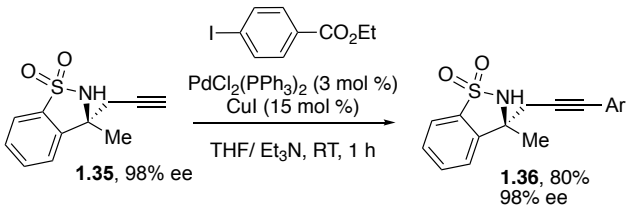
formed in higher concentration. Addition to the imine is proposed to happen through an S_E2' mechanism[20] and the desired product **1.13** is formed by protodemetallation of **1.34**.

Scheme 1.5: Proposed catalytic cycle



As highlighted in the introduction of this Chapter propargyl fragments are highly privileged synthons and have impressive synthetic utility. We wanted to showcase this utility and how they can be harnessed to effect further transformations. Sonagashira cross-coupling reactions are one of the many powerful reaction methodologies of alkynes. Sonagashira cross-coupling reaction of product **1.35** provided the product **1.36** in good yield (Equation 1.2).

Equation 1.2: Sonagashira cross-coupling reaction of **1.35**



1.3 Conclusion:

An asymmetric methodology for the enantioselective propargylation of *N*-sulfonyl ketimines with both five- and six-membered rings as the tethered protecting groups has been

[20] Fandrick, D. R.; Saha, J.; Fandrick, K. R.; Sanyal, S.; Ogikubo, J.; Lee, H.; Roschangar, F.; Song, J. J.; Senanayake, C. H. *Org. Lett.* **2011**, *13*, 5616.

developed. The sulfonyl protected ketimines derived from saccharine give high yields and excellent enantioselectivity. The sulfamate-protected substrates derived from 2′-hydroxyketones are more prone to influence from steric bulk and provide more modest yields. These however, still show promising reactivity and high enantioselectivities.

1.4 Experimental Details

All reactions were carried out under an atmosphere of N_2. All glassware was oven- or flame-dried prior to use. Tetrahydrofuran (THF), methanol (MeOH), and dimethylformamide (DMF) 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 organomagnesium reagents were determined by titration with iodine/LiCl.[21] ^{1}H NMR spectra were recorded on Bruker DRX-400 (400 MHz ^{1}H, 100 MHz ^{13}C, 376.5 MHz ^{19}F), GN-500 (500 MHz ^{1}H, 125.7 MHz ^{13}C), or CRYO-500 (500 MHz ^{1}H, 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), 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 (δ) relative to TMS 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 (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 F254 precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$ or *p*-anisaldehyde (PAA) solutions. Flash chromatography was performed using Silica Gel 60 (170-400 mesh) from Fisher Scientific and aluminum oxide,

[21] Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890.

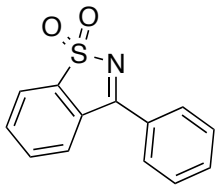
basic, Brockmann I, 50-200 μm from Acros Organics. Melting points (m.p.) were obtained using a Mel-Temp melting point apparatus and are uncorrected. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Automatic Polarimeter. SFC determinations of enantiopurity were performed on a Berger Analytical instrument using a Daicel™ Chiralpak® column (OD-H; 100 bar, 50 °C, 215 nm). High resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center. Allenyl boronic pinacol ester was prepared according to the procedure outlined by Yoshida and co-workers.[22] *tert*-Butyl alcohol was purchased from Fisher, distilled over CaH_2, and stored over activated 3Å mol sieves. All other chemicals were purchased commercially and used as received

Preparation of *N*-Sulfonyl Ketimines:

N-Sulfonyl ketimines **1.12**, **1.15**, **1.16**, and **1.17** were prepared according to a procedure outlined by Nishimura and Hayashi[23]

Representative Procedure for Arylation:

3-phenylbenzo[*d*]isothiazole 1,1-dioxide (**1.12**)

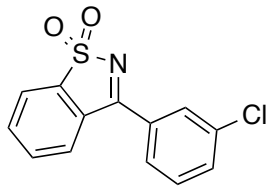


Magnesium turnings (0.438 g, 18.0 mmol, 3.00 equiv) were flame dried in a 25 mL round bottom flask under reduced pressure followed by addition of THF (9.5 mL) under an N_2 atmosphere. A small chip of iodine was added followed by a small portion of bromobenzene (1.27 mL, 12.0 mmol, 2.00 equiv) to initiate. This was followed by a dropwise addition of the

[22] K. Tonogaki, K.; Itami, K.; Yoshida, J. *J. Am. Chem. Soc.* **2006**, *128*, 1464–1465.
[23] Nishimura, T.; Noishiki, A.; Tsui, G. C.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 5056.

arylbromide to the reaction mixture in an ice bath. Upon completion of the addition of the arylbromide, the reaction flask was removed from the ice bath and stirred at room temperature for 2 h saccharin (1.10 g, 6.00 mmol, 1.00 equiv) was added to a 100 mL round bottom flask. The atmosphere was vacuum purged and filled with N_2 followed by addition of THF (50 mL). The Grignard reagent was added dropwise to the solution of saccharin in a 0˚ C ice bath. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with solid NH_4Cl (ca. 0.5 g) and the mixture was stirred at rt for 30 min. The organic mixture was passed through a short column of alumina with ethyl acetate as the eluent. The solvent was evaporated under reduced pressure to produce a yellow solid, which was recyrstalized from hot absolute ethanol and chloroform (1:1) to give **1.12** (0.715 g, 2.94 mmol, 49% yield) as an off-white solid. **m.p.** = 163–165 ˚C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (d, J = 7.5 Hz, 1 H), 7.98 (d, J = 7.3 Hz, 2 H), 7.91 (d, J = 7.3 Hz, 1 H), 7.80 (t, J = 7.3 Hz, 1 H), 7.75 (t, J = 7.3 Hz, 1 H), 7.71 (t, J = 7.5 Hz, 1 H), 7.62 (t, J = 7.6 Hz, 2 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.1, 141.2, 133.7, 133.5, 130.6, 130.5, 129.6, 129.3, 126.6, 123.2; **IR** (neat) 1599, 1532, 1333, 1172 cm^{-1}; **HRMS** (TOF MS CI+) m / z calcd for $C_{13}H_9NO_2S$ $(M + Na)^+$ 266.0252, found 266.0255.

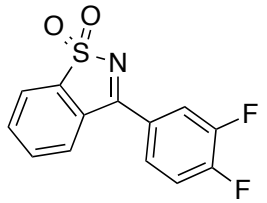
3-(3-chlorophenyl)benzo[*d*]isothiazole 1,1-dioxide (**1.15**)



Using representative procedure outlined above, the following amounts of reagents were used: magnesium turnings (0.219 g, 9.00 mmol, 2.00 equiv), 3-chlorobromobenzene (1.06 mL, 9.00

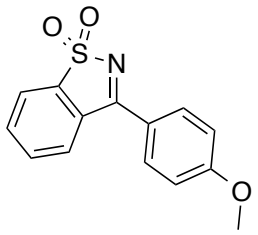
mmol, 2.00 equiv), saccharin (.824 g, 4.50 mmol, 1.00 equiv) to afford **1.15** as an off white solid (0.700 g, 56% yield). **m.p.** = 149–151 ˚C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (d, J = 7.2 Hz, 1 H), 7.96 (s, 1 H), 7.87 (t, J = 7.5 Hz, 2 H), 7.82 (t, J = 7.2 Hz, 1 H), 7.78 (t, J = 7.6 Hz, 1 H), 7.68 (d, J = 8.3 Hz, 1 H), 7.57 (t, J = 8.1 Hz, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 169.8, 141.0, 135.5, 133.8, 133.7, 133.4, 132.0, 130.6, 130.1, 129.4, 127.5, 126.3, 123.3 ; **IR** (neat) 1538, 1333, 1173 cm^{-1}; **HRMS** (TOF MS CI+) m / z calcd for $C_{13}H_8ClNO_2S$ $(M + Na)^+$ 299.9862, found 299.9863.

3-(3,4-difluorophenyl)benzo[*d*]isothiazole 1,1-dioxide (**1.16**)



Using representative procedure outlined above, the following amounts of reagents were used: magnesium turnings (0.437 g, 18.0 mmol, 2.57 equiv), 3,4–difluorobromobenzene (1.36 mL, 12.0 mmol, 1.71 equiv), saccharin (1.28 g, 7.00 mmol, 1.00 equiv) to afford **1.16** as a yellow solid (0.235 g, 12% yield). **m.p.** = 170–171 ˚C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, J = 7.5 Hz, 1 H), 7.76–7.89 (m, 5 H), 7.43 (q, J = 8.5 Hz, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.8, 1538. (dd, J = 258.9, 12.5 Hz), 150.8 (dd, J = 252.9, 13.4 Hz), 141.1, 133.9, 133.8, 129.9, 127.3 (dd, J = 6.0, 4.2 Hz), 126.6 (dd, J = 7.4, 3.7), 123.4, 119.1 (dd, J = 19.4, 1.4 Hz), 118.6 (d, J = 18.0 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –128.3– –128.4 (m, 1 F), –134.3 (dt, J = 20.7, 9.2 Hz); **IR** (neat) 1739, 1511, 1335, 1173 cm^{-1}; **HRMS** (TOF MS CI+) m / z calcd for $C_{13}H_7F_2NO_2S$ $(M + Na)^+$ 302.0063, found 302.0052.

3-(4-methoxyphenyl)benzo[*d*]isothiazole 1,1-dioxide (**1.17**)



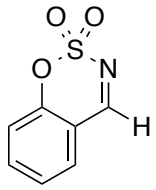
Using representative procedure outlined above, the following amounts of reagents were used: magnesium turnings (0.547 g, 22.5 mmol, 3.00 equiv), 4-bromoanisole (2.50 mL, 15.0 mmol, 2.00 equiv), saccharin (1.37 g, 7.50 mmol, 1.00 equiv) to afford **1.17** as a light green solid (1.00 g, 49%yield). **m.p.** = 205–206 ˚C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.02 (at, J = 7.1 Hz, 3 H), 7.96 (d, J = 7.3 Hz, 1 H), 7.76 (dt, J = 18.2, 7.5 Hz, 2 H), 7.10 (d, J = 8.7 Hz, 2 H), 3.94 (s, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.0, 164.2, 141.4, 133.5, 133.2, 132.0, 131.0, 126.6, 123.1, 122.9, 114.8, 55.7; **IR** (neat) 1599, 1503, 1316, 1254, 1159 cm^{-1}; **HRMS** (TOF MS CI+) m / z calcd for $C_{14}H_{11}NO_3S$ $(M + Na)^+$ 296.0357, found 296.0362.

Preparation of *N*-Sulfamate Imines:

N-Sulfonyl Ketimines **1.25**, **1.26**, **1.27**, and **1.28** were prepared according to a procedure outlined by Lu and Hayashi[24]

Representative Procedure for Condensation:

Benzo[e][1,2,3]oxathiazine 2,2-dioxide (**1.25**)

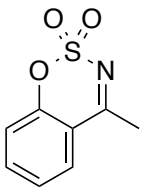


To flame dried 25 mL round bottom flask Chlorosulfonyl isocyanate (0.524 mL, 6.00 mmol, 2.00 equiv) was added. Anhydrous formic acid (0.226 mL, 6.00 mmol, 2.00 equiv) was added

[24] Jiang, C.; Lu, Y.; Hayashi, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 9936.

dropwise at 0 ˚C. Upon addition, a white solid formed and vigorous gas evolution was observed. The viscous mixture was stirred for 10 min, until gas evolution ceased. Neat salicylaldehyde (0.366 g, 3.00 mmol, 1.00 equiv) was added dropwise to the flask and the reaction mixture was stirred for 10 min. After the mixture was cooled to 0 ˚C, 10 mL of DMA (*N,N*-dimethyl-acetamide) was slowly added. The reaction mixture was warmed to room temperature and stirred for 10 min. Sodium hydride (86.4 mg, 3.60 mmol, 1.20 equiv) was added in portions. After stirring for 30 minutes another portion of sodium hydride (86.4 mg, 3.60 mmol, 1.20 equiv) was added. After stirring for 1 hr at room temperature, the reaction mixture was warmed to 50 ˚C and stirred overnight (12 h). The reaction mixture was quenched by the addition of H_2O and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (20% EtOAc/Hexanes to give compound **22** as a yellow solid (208 mg, 38% y). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.74 (s, 1 H), 7.83 (td, J = 8.0, 1.6 Hz, 1 H), 7.74 (dd, J = 7.7, 1.5 Hz, 1 H), 7.50 (t, J = 7.6 Hz, 1 H), 7.36 (d, J = 8.4 Hz, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.6, 154.3, 137.8, 126.2, 118.7, 115.4; **IR** (neat) 1600, 1559, 1373 cm^{-1}.

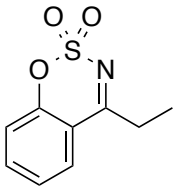
4-methylbenzo[e][1,2,3]oxathiazine 2,2-dioxide (**1.26**)



Using representative procedure outlined above, the following amounts of reagents were used: Chlorosulfonyl isocyanate (1.74 mL, 20.0 mmol, 2.00 equiv), anhydrous formic acid (0.750 mL,

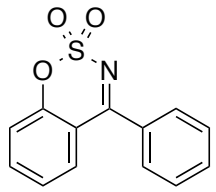
20.0 mmol, 2.00 equiv), 2-hydroxyacetophenone (1.20 mL, 10.0 mmol, 1.00 equiv), sodium hydride (0.576 g, 24.0 mmol, 2.4 equiv) to afford **24** as a light yellow solid (0.690 g, 34% y) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.87 (dd, J = 8.0, 1.2 Hz, 1 H), 7.78 (td, J = 7.6, 1.6 Hz, 2 H), 7.91 (d, J = 7.3 Hz, 1 H), 7.46 (t, J = 78.0 Hz, 1 H), 7.36 (d, J = 8.4 Hz, 1 H), 2.79 (s, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 177.3, 153.5, 137.1, 128.5, 125.9, 119.2, 116. 5, 23.8; **IR** (neat) 1594, 1556, 1367, 1324 cm^{-1}; HRMS (TOF MS ES+) m / z calcd for $C_8H_7NO_3S$ (M + Na)+ 220.0044, found 220.0046.

4-ethylbenzo[e][1,2,3]oxathiazine 2,2-dioxide (**1.27**)



Using representative procedure outlined above, the following amounts of reagents were used: Chlorosulfonyl isocyanate (1.74 mL, 20.0 mmol, 2.00 equiv), anhydrous formic acid (0.750 mL, 20.0 mmol, 2.00 equiv), 2-hydroxypropiophenone (1.74 mL, 10.0 mmol, 1.00 equiv), sodium hydride (0.576 g, 24.0 mmol, 2.4 equiv) to afford **26** as a light yellow solid (1.06 g, 50% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88 (dd, J = 8.2, 1.2 Hz, 1 H), 7.76 (td, J = 7.6, 1.6 Hz, 1 H), 7.45 (t, J = 7.5 Hz, 1 H), 7.36 (d, J = 8.3 Hz, 1 H), 3.17 (q, J = 7.3 Hz, 2 H), 1.42 (t, J = 7.3 Hz, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ180.8, 153.5, 136.8, 127.8, 125.9, 119.3, 116.2, 76.8, 29.4, 9.70; **IR** (neat) 1596, 1554, 1374, 1360 cm^{-1}; HRMS (TOF MS ES+) m / z calcd for $C_9H_9NO_3S$ (M + Na)+ 234.0201, found 234.0202.

4-phenylbenzo[e][1,2,3]oxathiazine 2,2-dioxide (**1.28**)



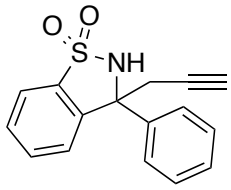
Using representative procedure outlined above, the following amounts of reagents were used: Chlorosulfonyl isocyanate (0.261 mL, 3.00 mmol, 2.00 equiv), anhydrous formic acid (0.113 mL, 3.00 mmol, 2.00 equiv), 2'-hydroxybenzophenone (.297 g, 1.50 mmol, 1.00 equiv), sodium hydride (86.4 mg, 3.60 mmol, 2.4 equiv) to afford **28** as a light tan solid (89.5 mg, 23% y) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80–7.84 (m, 3 H), 7.74 (aq, J = 7.5 Hz, 2 H), 7.63 (at, J = 7.8 Hz, 2 H), 7.43–7.48 (m, 2 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.51, 137.0, 133.8, 133.3, 131.9, 130.8, 129.0, 125.8, 119.6, 116.7; **IR** (neat) 1524, 1382, 1193 cm^{-1}.

Propargylation Reaction Conditions:

Initial conditions were reported by Wisniewska and co-workers.[25]

Representative Procedure for Additions:

3-phenyl-3-(prop-2-yn-1-yl)-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (**1.13a**)

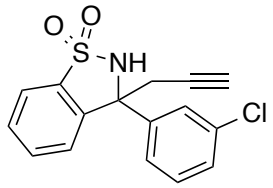


In the glovebox silver hexafluorophosphate (5.0 mg, 0.020 mmol, 10 mol %) and Walphos-1 (22.3 mg, 0.0240 mmol, 12.0 mol %) was added to an oven-dried conical vial. The vial was

[25] Wisniewska, H. M.; Jarvo E. R. *Chem. Sci.* **2011**, *2*, 807.

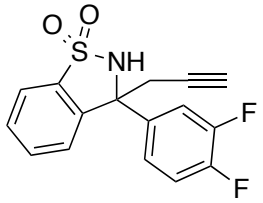
removed from the glovebox, placed under an atmosphere of N_2, and charged with DMF (0.40 mL). The reaction vial was placed in an oil bath at 70 ˚C. After stirring for 30 min, the vial was removed from the oil bath and allowed to cool to rt for 15 min. *tert*-Butanol (21 µl, 0.22 mmol, 1.1 equiv) was added via a syringe followed by the addition of ketimine **1.12** (48.6 mg, 0.200 mmol, 1.00 equiv) and potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv) under flow of N_2. The reaction mixture was stirred for 5 min to dissolve the imine. Allenyl boronic pinacol ester **1.2** was added in two equal portions. The first portion was added via syringe, then the second was added over 3 h via a syringe pump (144 µl, 0.800 mmol, 4.00 equiv). After stirring at rt for a total of 16 h, the reaction mixture was filtered through a short column of silica gel and rinsed with Et_2O (2 x 50 mL). The resulting organic solution was concentrated under reduced pressure and purified via flash chromatography (Benzene neat–5% TEA/Benzene) to remove the starting material then flash chromatography (10–20–30–40% EtOAc/Hexanes with 1% TEA) to give the desired amine **1.13a** as an off-white semi-solid (47.8 mg, 84% yield, 98% ee). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (d, J = 7.8 Hz, 1 H), 7.52–7.62 (m, 4 H), 7.31–7.41 (m, 4 H), 5.24 (br s, 1 H), 3.27 (qd, J = 9.2, 2.0 Hz, 2 H), 8.10 (s, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.4, 140.4, 135.0,133.4, 129.9, 129.1, 128.7, 126.6, 124.9, 121.4, 78.5, 73.3, 67.1, 31.3; **IR** (neat) 3286, 2924, 1714, 1293, 1166 cm^{-1}; **HRMS** (TOF MS CI+) m / z calcd for $C_{16}H_{13}NO_2S$ $(M + Na)^+$ 306.0565, found 306.0564. **SFC** analysis (OD-H, 10% *i*–PrOH, 3.0 mL/min): t_R (minor) = 11.84 minutes, t_R (major) = 14.13 minutes; **$[a]^{24}_D$** +41.5 (c 0.66, $CHCl_3$).

3-(3-chlorophenyl)-3-(prop-2-yn-1-yl)-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (**1.18a**)



Using representative procedure outlined above, the following amounts of reagents were used: silver hexafluorophosphate (5.0 mg, 0.020 mmol, 10 mol %), Walphos-1 (22.3 mg, 0.0240 mmol, 12.0 mol %), *tert*-Butanol (21 µl, 0.22 mmol, 1.1 equiv), ketimine **1.15** (55.5 mg, 0.200 mmol, 1.00 equiv), potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv), allenyl boronic pinacol ester **1.2** (144 µl, 0.800 mmol, 4.00 equiv) to afford amine **1.18a** as an off-white semi solid (48.9 mg, 76% yield, 92% ee). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (d, J = 6.6 Hz, 1 H), 7.53–7.66 (m, 3 H), 7.46 (d, J = 2.9 Hz, 1 H), 7.37 (d, J = 7.3 Hz, 1 H), 7.31 (br s, 2 H), 5.31 (br s, 1 H), 3.27 (q, J = 15.4 Hz, 2 H), 2.08 (s, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.5, 141.6, 135.0, 134.9, 130.3, 130.2, 128.9, 126.9, 124.9, 124.7, 121.6, 77.9, 66.6, 31.4; **IR** (neat) 3292, 2923, 2360, 1295, 1166 cm^{-1}; **HRMS** (TOF MS CI+) m / z calcd for $C_{16}H_{12}ClNO_2S$ $(M + Na)^+$ 340.0175, found 340.0183. **SFC** analysis (OD-H, 10% MeOH, 3.0 mL/min): t_R (minor) = 9.80 minutes, t_R (major) = 10.36 minutes; **[a]$^{26.6}_D$** +48.9 (c 0.95, $CHCl_3$).

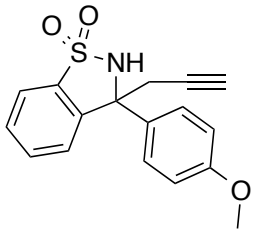
3-(3,4-difluorophenyl)-3-(prop-2-yn-1-yl)-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (**1.19a**)



Using representative procedure outlined above, the following amounts of reagents were used: silver hexafluorophosphate (5.0 mg, 0.020 mmol, 10 mol %), Walphos-1 (22.3 mg, 0.0240 mmol, 12.0 mol %), *tert*-Butanol (21 µl, 0.22 mmol, 1.1 equiv), ketimine **1.16** (55.9 mg, 0.200

mmol, 1.00 equiv), potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv), allenyl boronic pinacol ester **1.2** (144 µl, 0.800 mmol, 4.00 equiv) to afford amine **1.19a** as an off-white semi solid (58.0 mg, 90% yield, 97% ee). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, J = 7.7 Hz, 1 H) 7.62 (dt, J = 26.9,7.3 Hz, 2 H), 7.37–7.46 (m, 2 H), 7.30–7.34 (m, 1 H), 7.17 (q, J = 8.9 Hz, 1 H), 5.40 (br s, 1 H), 3.22 (q, J = 15.3 Hz, 2 H), 2.10 (s, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 151.3 (dd, J = 13.4, 7.7 Hz), 149.4 (dd, J = 13.0, 9.3 Hz), 141.5, 137.6 (t, J = 4.2 Hz), 135.0, 133.7, 130.3, 124.6, 122.9 (dd, J = 6.5, 3.7 Hz), 121.7, 117.8 (d, J = 17.6 Hz), 116.4 (d, J = 19.0 Hz), 77.8, 73.8, 66.2, 31.5; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –135.6 to –135.8 (m, 1 F), –137.6 to –137.7 (m, 1 F); **IR** (neat) 3281, 2924, 2360, 1519, 1284, 1168 cm^{-1}; **HRMS** (TOF MS CI+) m / z calcd for $C_{16}H_{11}F_2NO_2S$ $(M + Na)^+$ 342.0376, found 342.0372. **SFC** analysis (OD-H, 10% *i*–PrOH, 3.0 mL/min): t_R (major) = 8.47 minutes, t_R (minor) = 11.10 minutes; **$[a]^{25.7}_D$** +55.5 (c 0.78, $CHCl_3$).

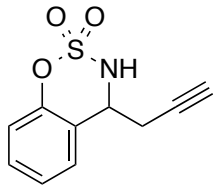
3-(4-methoxyphenyl)-3-(prop-2-yn-1-yl)-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (**1.20a**)



Using representative procedure outlined above, the following amounts of reagents were used: silver hexafluorophosphate (5.0 mg, 0.020 mmol, 10 mol %), Walphos-1 (22.3 mg, 0.0240 mmol, 12.0 mol %), *tert*-butanol (21 µl, 0.22 mmol, 1.1 equiv), ketimine **1.17** (49.9 mg, 0.200 mmol, 1.00 equiv), potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv), allenyl boronic pinacol ester **1.2** (216 µl, 1.20 mmol, 6.00 equiv) to afford amine **1.20a** as an off-white semi solid (38.5 mg, 61% yield, 96% ee). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (d, J = 7.3 Hz, 1 H), 7.58 (dt, J = 21.4, 7.6 Hz, 2 H), 7.44 (d, J = 8.4 Hz, 2 H), 7.35 (d, J = 7.5 Hz, 1 H), 6.89 (d, J =

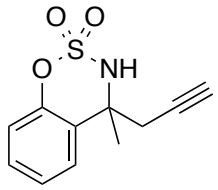
8.8 Hz, 2 H), 5.15 (br s, 1 H), 3.79 (s, 3 H), 3.24 (td, J = 17.5, 2.6 Hz, 2 H), 2.06 (t, J = 2.3 Hz, 1 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 159.8, 142.9, 135.1, 133.4, 132.3, 129.9, 128.0, 125.0, 121.4, 114.4, 78.7, 73.2, 66.8, 55.4, 31.4; **IR** (neat) 3273, 2923, 1512, 1293, 1164.36 cm^{-1}; **HRMS** (TOF MS CI+) m / z calcd for $C_{17}H_{15}NO_3S$ $(M + Na)^+$ 336.0670, found 336.0663. **SFC** analysis (OD-H, 10% *i*–PrOH, 3.0 mL/min): t_R (major) = 17.31 minutes, t_R (minor) = 22.94 minutes; **$[a]^{24.2}_D$** +33.0 (c 0.54, $CHCl_3$).

4-(prop-2-yn-1-yl)-3,4-dihydrobenzo[e][1,2,3]oxathiazine 2,2-dioxide (**1.29a**)



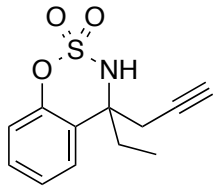
Using representative procedure outlined above, the following amounts of reagents were used: silver hexafluorophosphate (5.0 mg, 0.020 mmol, 10 mol %), Walphos-1 (22.3 mg, 0.0240 mmol, 12.0 mol %), *tert*-butanol (21 µl, 0.22 mmol, 1.1 equiv), aldimine **1.25** (36.6 mg, 0.200 mmol, 1.00 equiv), potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv), allenyl boronic pinacol ester **1.2** (144 µl, 0.800 mmol, 4.00 equiv) to afford amine **1.29a** as an off-white semi solid (24.1 mg, 54% yield, 96% ee). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (td, J = 8.2, 2.8 Hz, 1 H), 7.22–7.28 (m, 2 H), 7.06 (d, J = 8.6 Hz, 1 H), 4.96 (t, J = 5.0 Hz, 1 H), 3.14 (ddd, J = 17.4, 5.4, 2.5 Hz, 2 H), 2.98 (ddd, J = 17.7, 4.6, 2.4 Hz, 1 H), 2.20 (b s, 1 H), 2.09 (t, J = 2.6 Hz, 1 H), **^{13}C NMR** (125 MHz, $CDCl_3$) δ 151.7, 130.0, 126.3, 125.5, 120.6, 119.1, 77.8, 73.2, 55.4, 23.9; **IR** (neat) 3290, 1486, 1422, 1373.00cm^{-1}; **SFC** analysis (OD-H, 10% *i*–PrOH, 3.0 mL/min): t_R (minor) = 7.63 minutes, t_R (major) = 8.72 minutes;

4-methyl-4-(prop-2-yn-1-yl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (**1.30a**)



Using representative procedure outlined above, the following amounts of reagents were used: silver hexafluorophosphate (5.0 mg, 0.020 mmol, 10 mol %), Walphos-1 (22.3 mg, 0.0240 mmol, 12.0 mol %), *tert*-Butanol (21 µl, 0.22 mmol, 1.1 equiv), ketimine **1.26** (39.4 mg, 0.200 mmol, 1.00 equiv), potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv), allenyl boronic pinacol ester **1.2** (144 µl, 0.800 mmol, 4.00 equiv) to afford amine **1.30a** as an off-white semi solid (36.1 mg, 76% yield, 99% ee). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (td, J = 7.73, 2.5 Hz, 1 H), 7.21–7.27 (m, 2 H), 7.04 (d, J = 8.0 Hz, 1 H), 4.00 (br s, 1 H), 3.04 (dd, J = 17.2, 2.5 Hz, 1 H), 2.80 (dd, J = 17.2, 2.5 Hz, 1 H), 2.12 (t, J = 2.5 Hz, 1 H), 1.81 (s, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ150.1, 129.9, 126.4, 125.8, 125.5, 119.4, 76.8, 73.3, 61.7, 33.1, 28.5; **IR** (neat) 3273, 2923, 1512, 1293, 1164 cm^{-1}; **SFC** analysis (AD-H, 10% *i*–PrOH, 3.0 mL/min): t_R (minor) = 5.40 minutes, t_R (major) = 6.01 minutes;

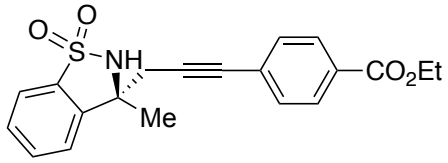
4-ethyl-4-(prop-2-yn-1-yl)-3,4-dihydrobenzo[*e*][1,2,3]oxathiazine 2,2-dioxide (**1.31a**)



Using representative procedure outlined above, the following amounts of reagents were used: silver hexafluorophosphate (5.0 mg, 0.020 mmol, 10 mol %), Walphos-1 (22.3 mg, 0.0240 mmol, 12.0 mol %), *tert*-butanol (21 µl, 0.22 mmol, 1.1 equiv), ketimine **1.27** (49.9 mg, 0.200 mmol, 1.00 equiv), potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv), allenyl boronic

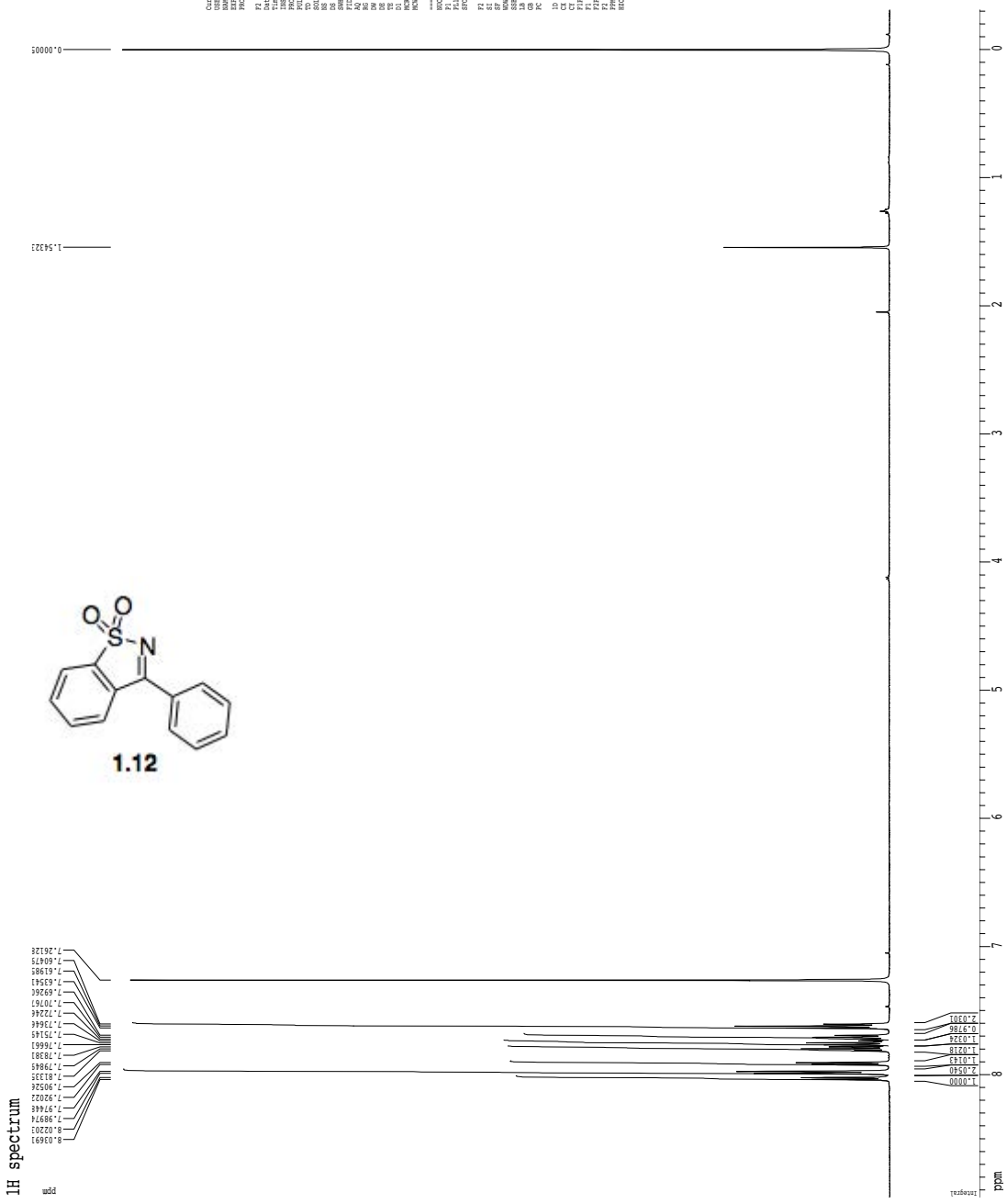
pinacol ester **1.2** (144 µl, 0.800 mmol, 4.00 equiv) to afford amine **1.31a** as an off-white semi solid (25.6 mg, 51% yield, 98% ee). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (td, J = 7.4, 2.4 Hz, 1 H), 7.22–7.28 (m, 2 H), 7.06 (d, J = 8.4 Hz, 1 H), 4.71 (b s, 1 H), 3.03 (dd, J = 17.5, 2.6 Hz, 1 H), 2.87 (dd, J = 17.9, 3.0 Hz, 1 H), 2.22 (sextet, J = 7.1 Hz, 1 H), 2.11 (t, J = 2.5 Hz, 1 H), 2.08 (sextet, J = 7.2 Hz, 1 H), 0.93 (t, J = 7.4 Hz, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 150.7, 129.8, 126.4, 125.8, 124.9, 119.4, 78.3, 73.3, 64.7, 32.8, 30.8, 7.8; **IR** (neat) 3294, 1485, 1417, 1364 cm^{-1}; **SFC** analysis (AD-H, 10% *i*–PrOH, 3.0 mL/min): t_R (minor) = 4.69 minutes, t_R (major) = 5.11 minutes.

Ethyl (R)-4-(3-(3-methyl-1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-3-yl)prop-1-yn-1-yl)benzoate (**1.36)**



Sultam **1.36** was prepared according to a modified procedure described by Hoppe and co-workers.10 To a flame-dried 7 mL reaction vial equipped with a N_2 line, substrate **1.35** (22.1 mg, 0.100 mmol, 1.00 equiv), bis(triphenylphosphine)palladium(II) dichloride (2.1 mg, 0.0030 mmol, 0.030 equiv), and copper(I) iodide (2.9 mg, 0.015, 0.15 equiv) was added anhydrous THF (0.7 mL) then anhydrous TEA (0.3 mL). Ethyl 4-iodobenzoate (37 µL, 0.20 mmol, 2.0 equiv) was added via syringe. After stirring 1 h at room temperature, the reaction mixture was quenched with 1 M HCl (2 mL), extracted with EtOAc (3 x 2 mL), rinsed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by flash column chromatography using 5– 30% EtOAc/hexanes (1% TEA) to afford the title compound as a yellow solid (29.8 mg, 0.0807 mmol, 80% yield, 98% ee). TLC R_f = 0.2 (20% EtOAc/hexanes, UV active, stains pink

with PAA); m.p. = 162–164 °C; ^{1}H NMR (500 MHz, CDCl3) δ 7.97 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 7.7 Hz, 1H), 7.67 (td, J = 7.7, 1.0 Hz, 1H), 7.57 (td, J = 7.7, 1.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 3H), 7.42 (d, J = 8.4, 2H), 4.83 (br s, 1H), 4.38 (q, J = 7.1 Hz, 2H), 3.08–3.00 (m, 2H), 1.82 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125.7 MHz, CDCl3) δ 166.0, 143.3, 135.7, 133.4, 131.6, 130.1, 129.8, 129.5, 127.1, 123.3, 121.5, 87.0, 83.9, 62.4, 61.2, 33.7, 27.2, 14.4; IR (neat) 3254, 2982, 1713, 1606, 1274, 1172 cm-1; HRMS (TOF MS ES+) m / z calcd for C20H19NO4S (M + Na)+ 392.0933, found 392.0932; [α]24D +8 (c 0.8, CDCl3); SFC analysis (OD-H, 20% IPA, 3.0 mL/min, 215 nm) indicated 99:1 er: t_R (minor) = 5.8 min, t_R (major) = 6.3 min.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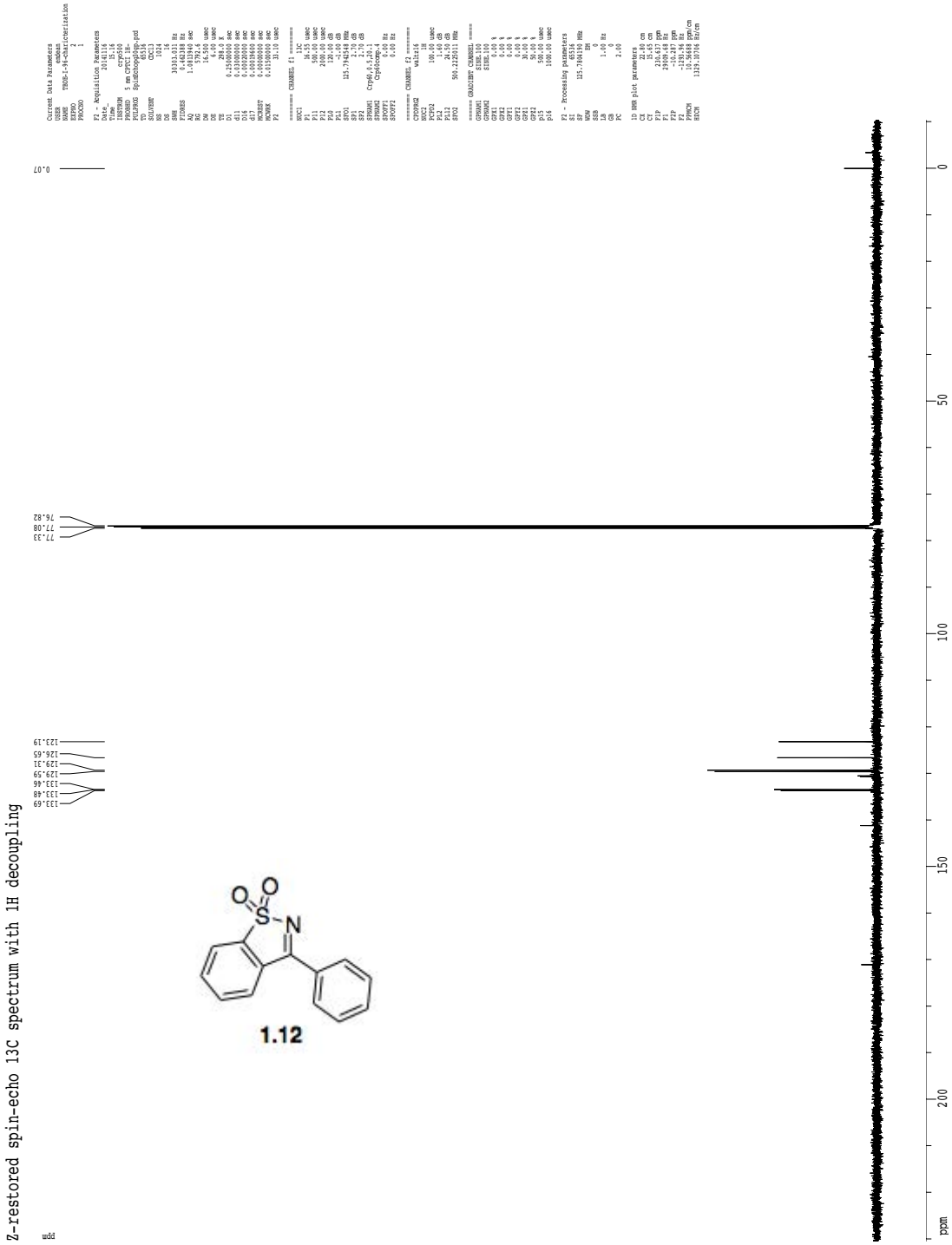
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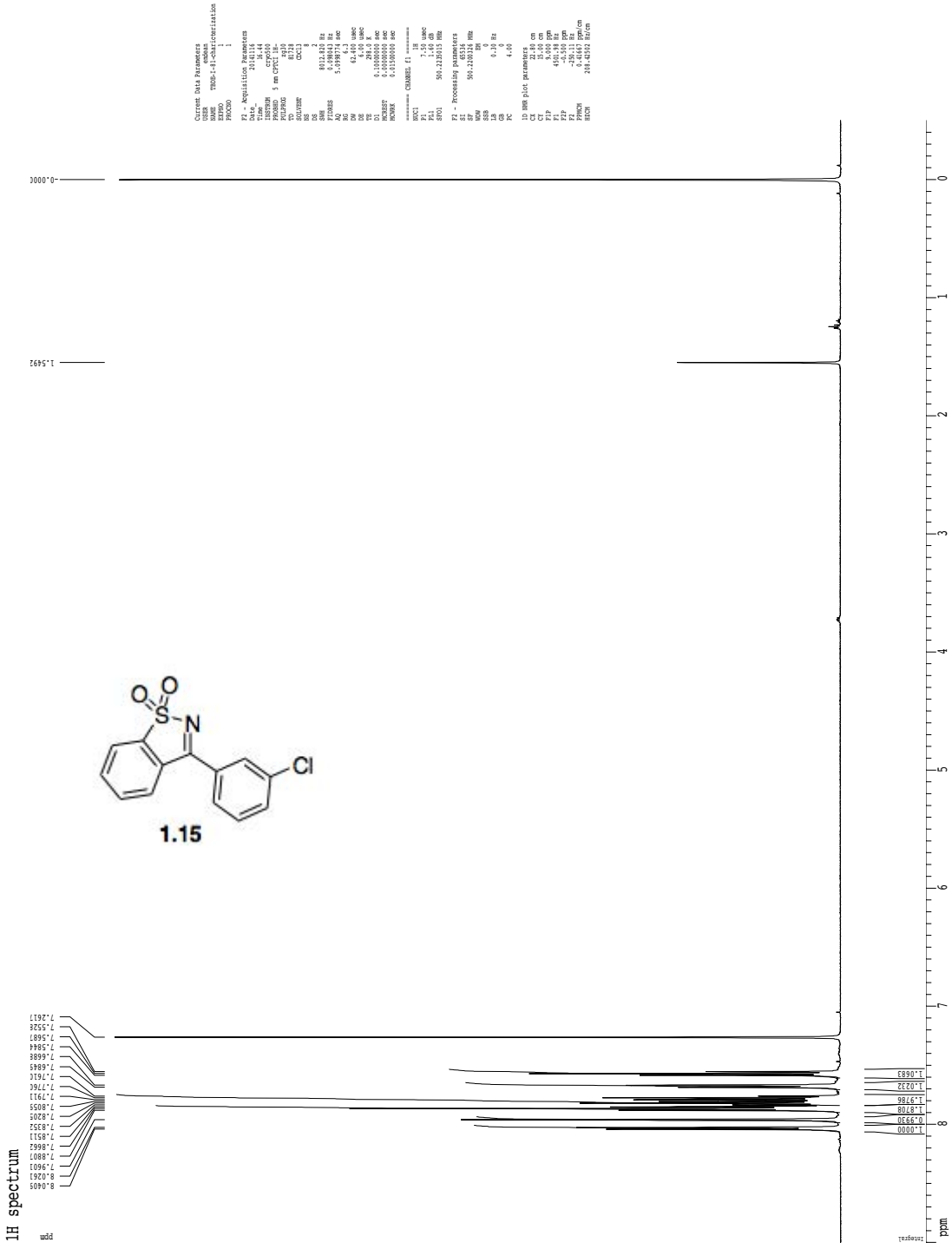
ppm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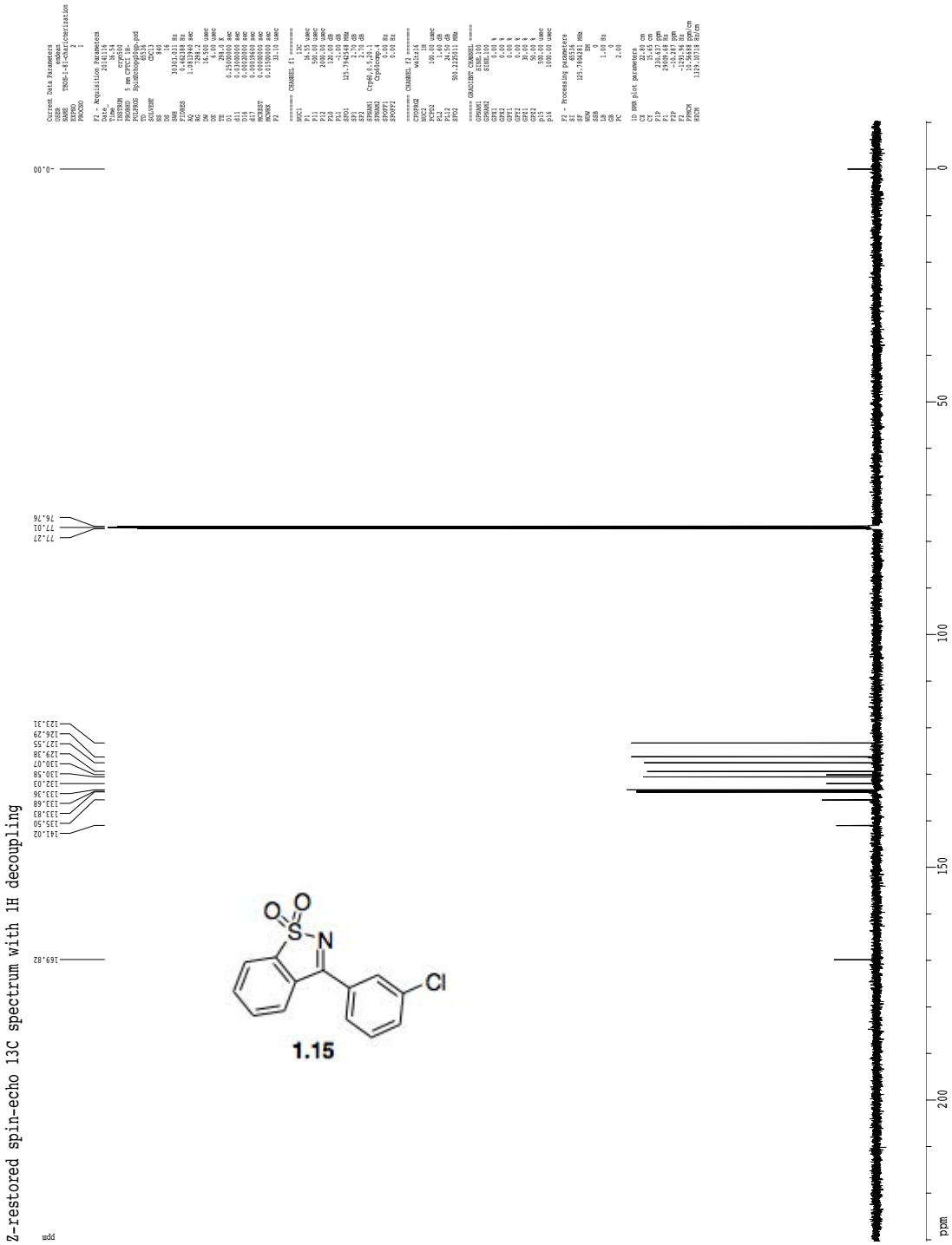
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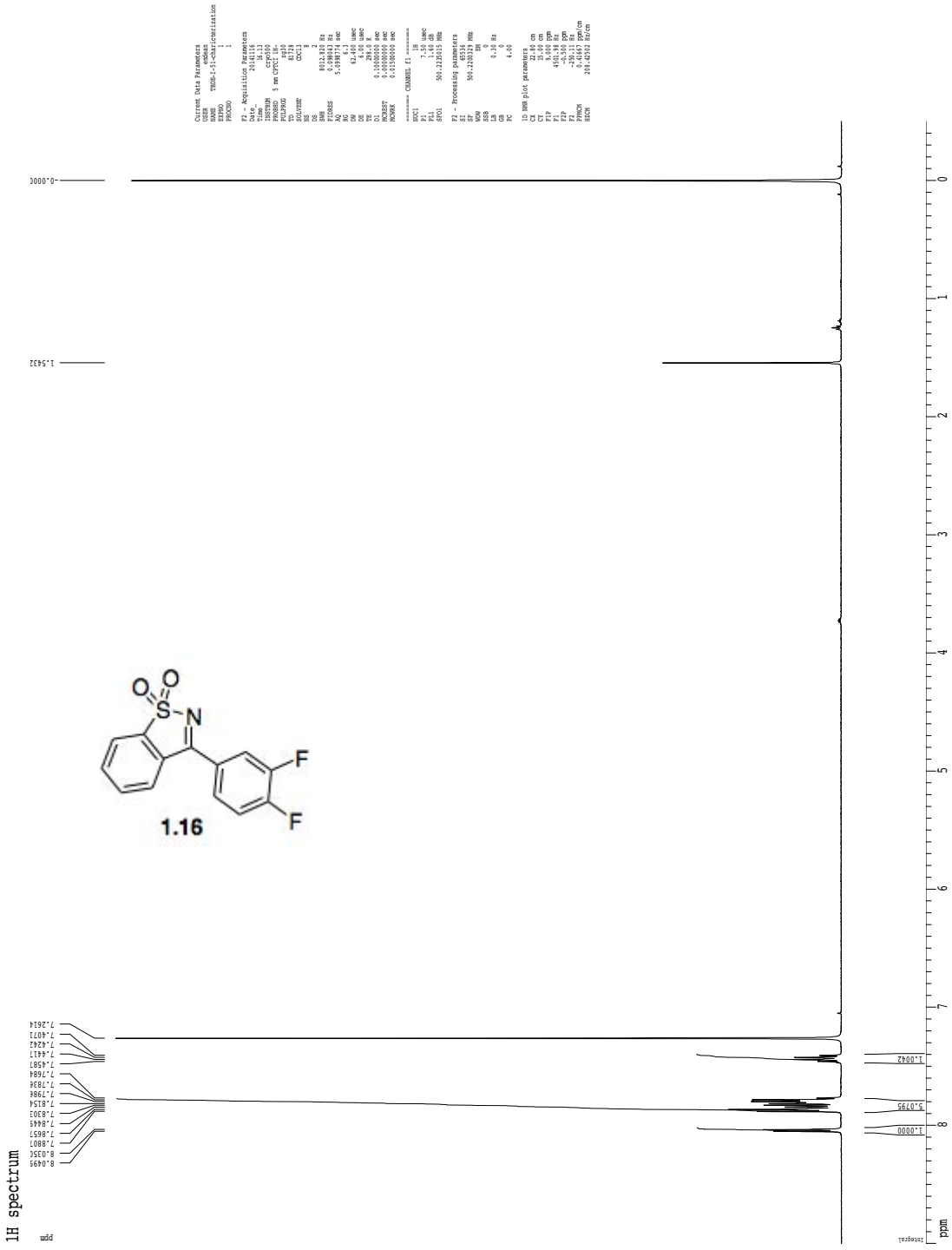
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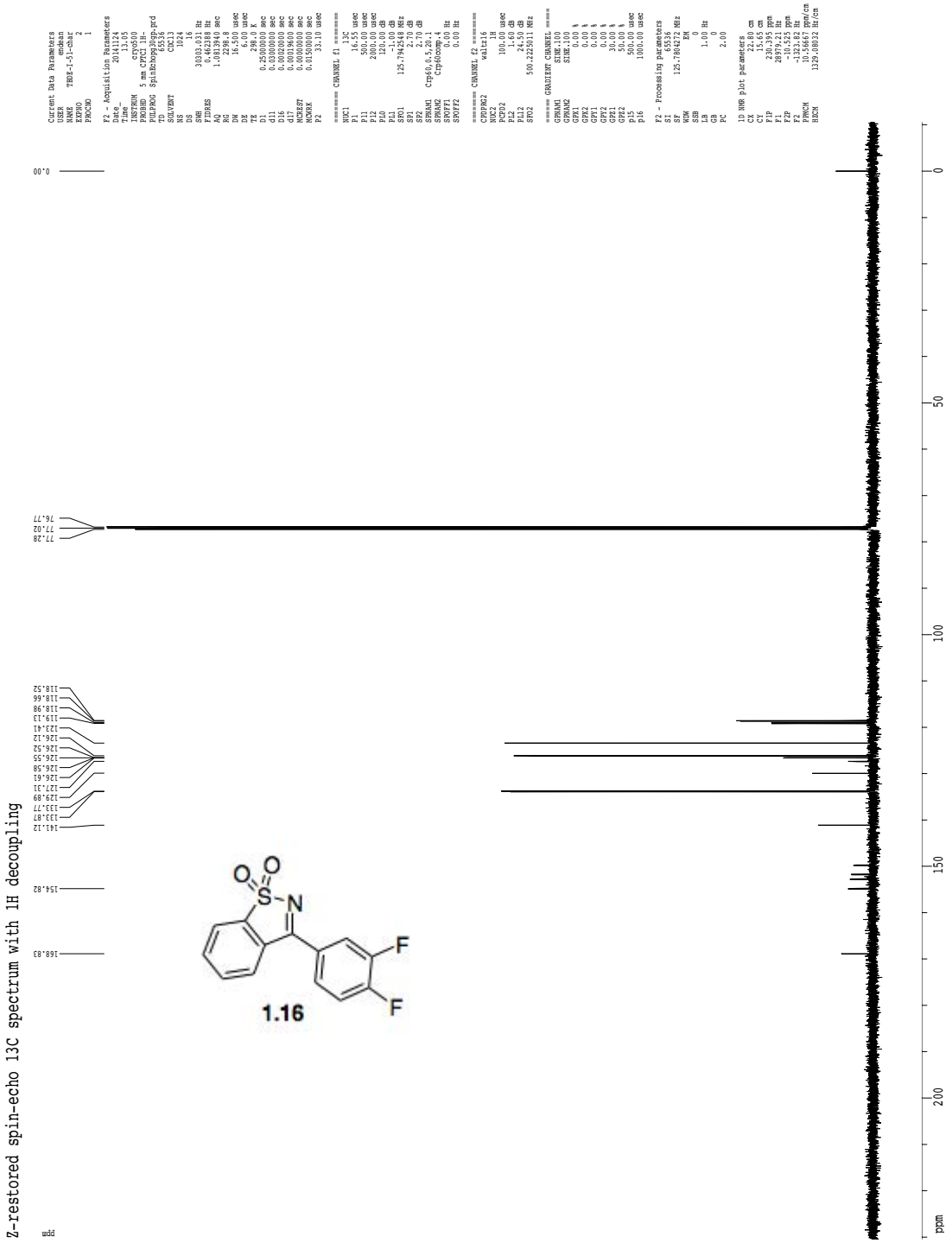
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150
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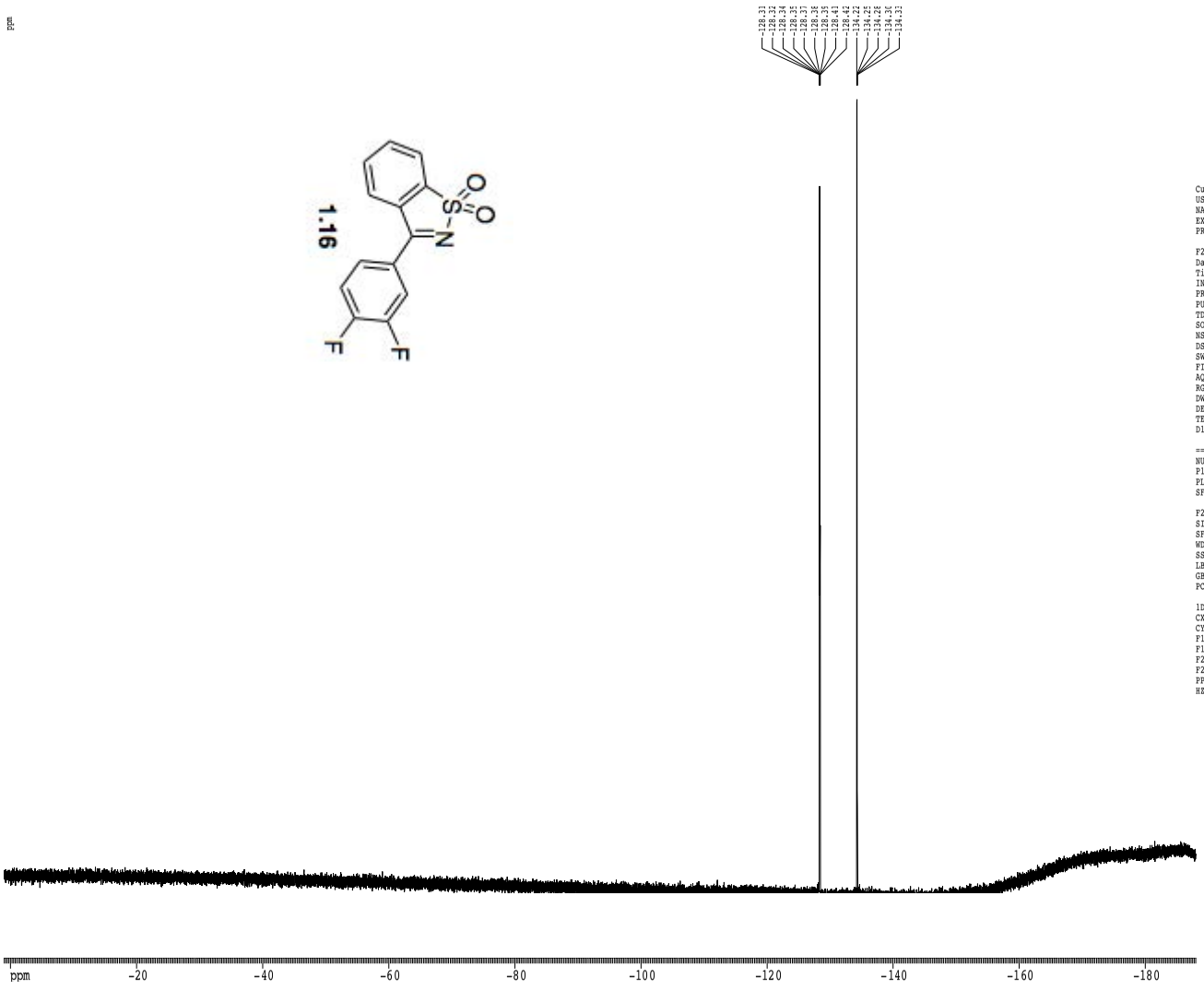
19F spectrum



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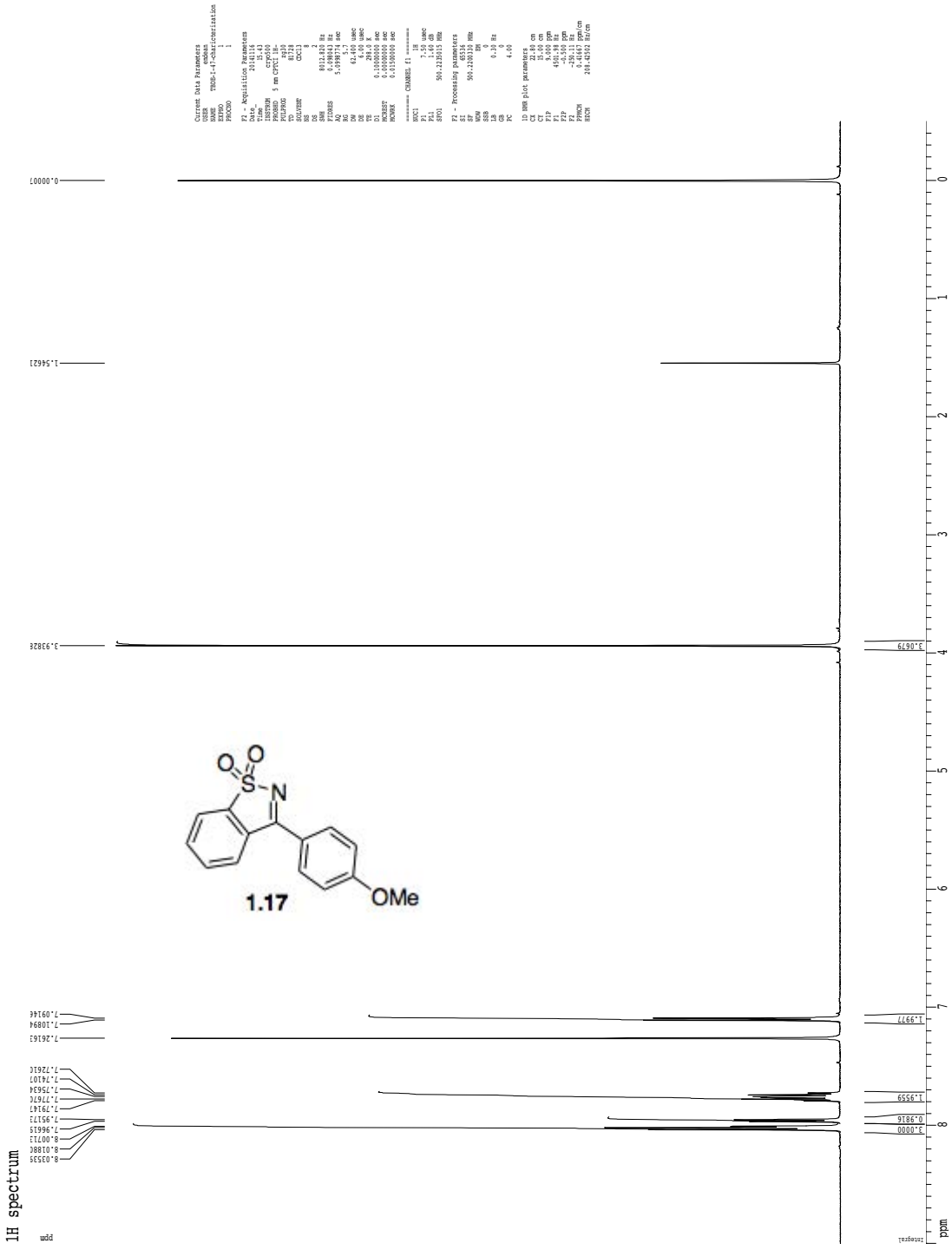
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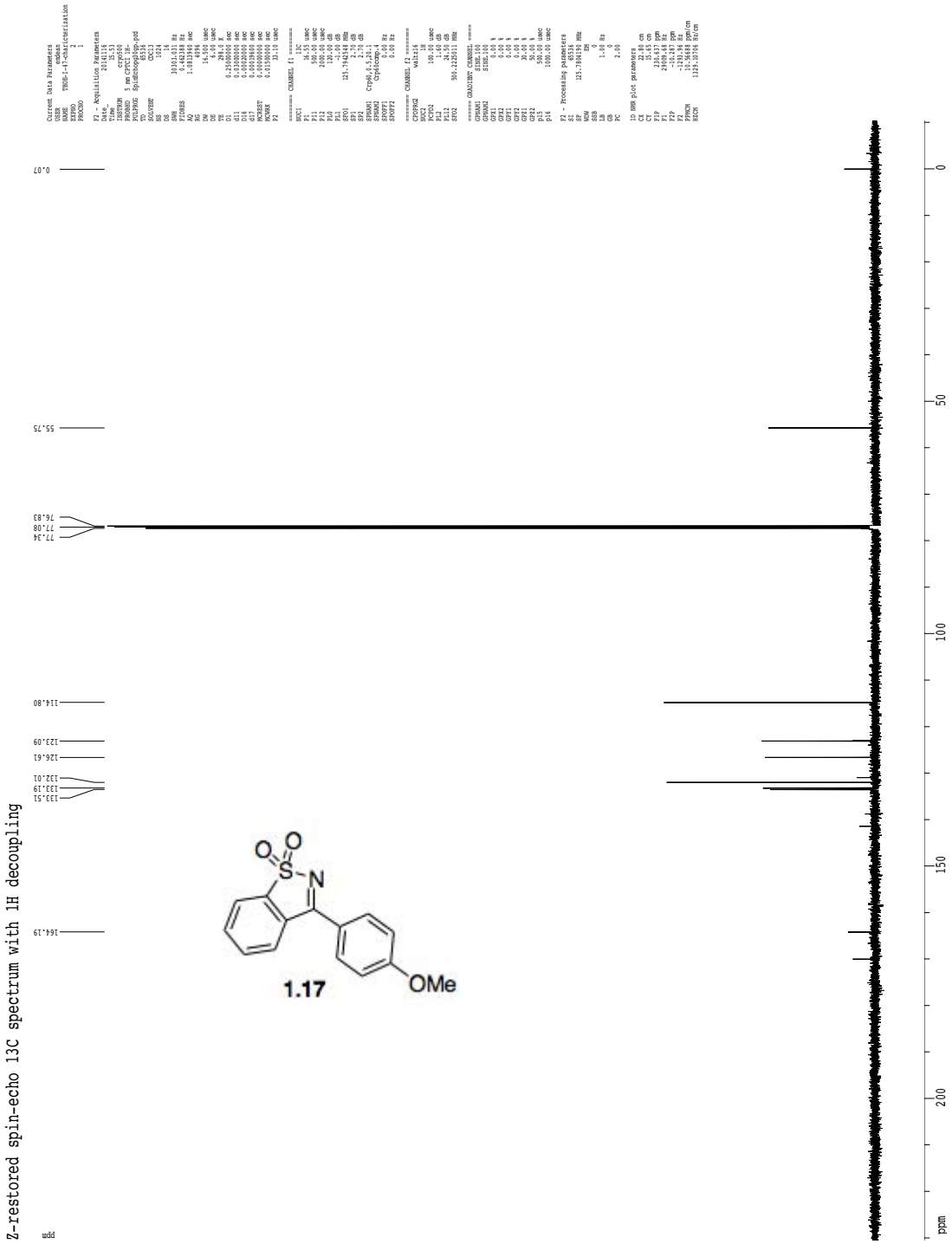
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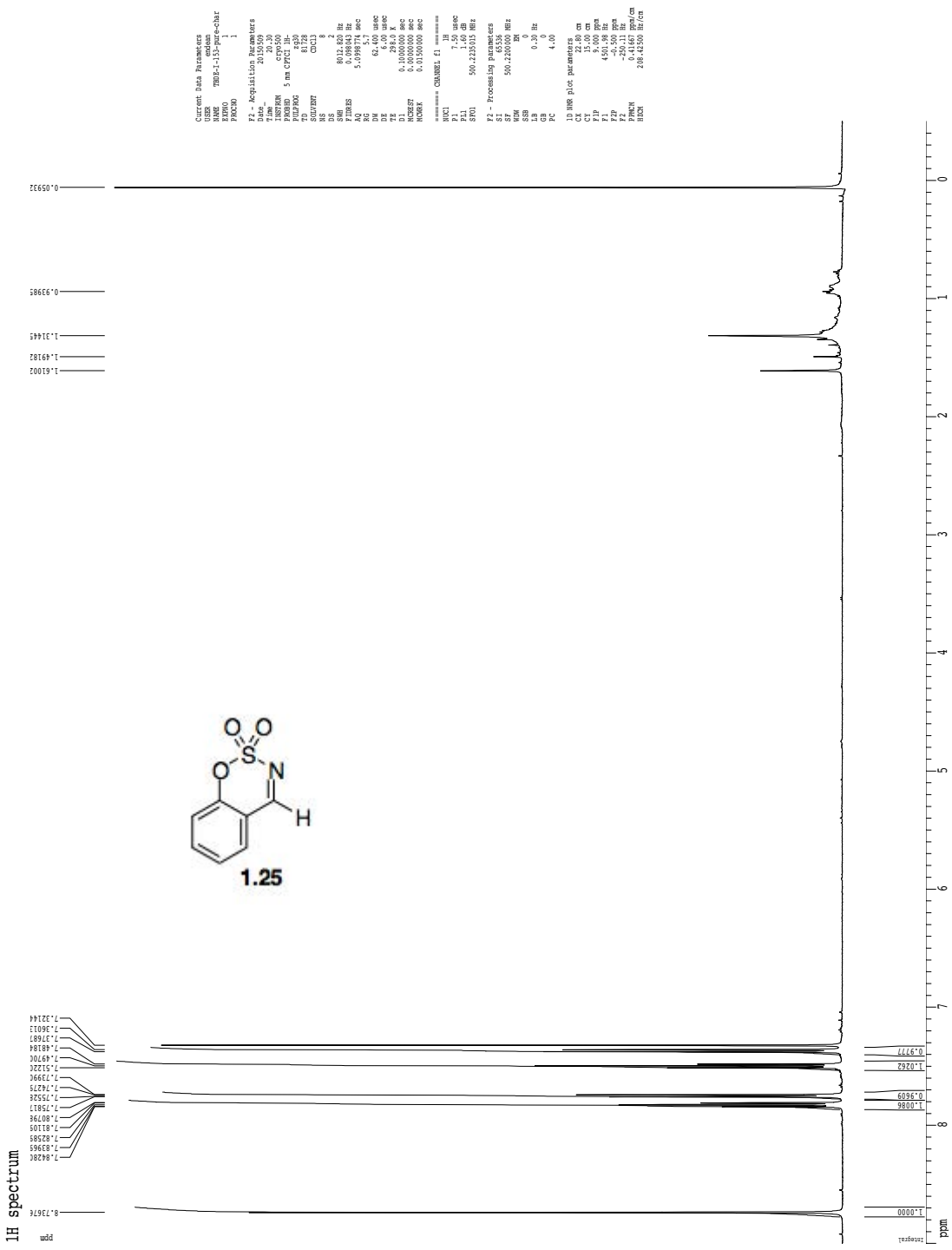
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Integral
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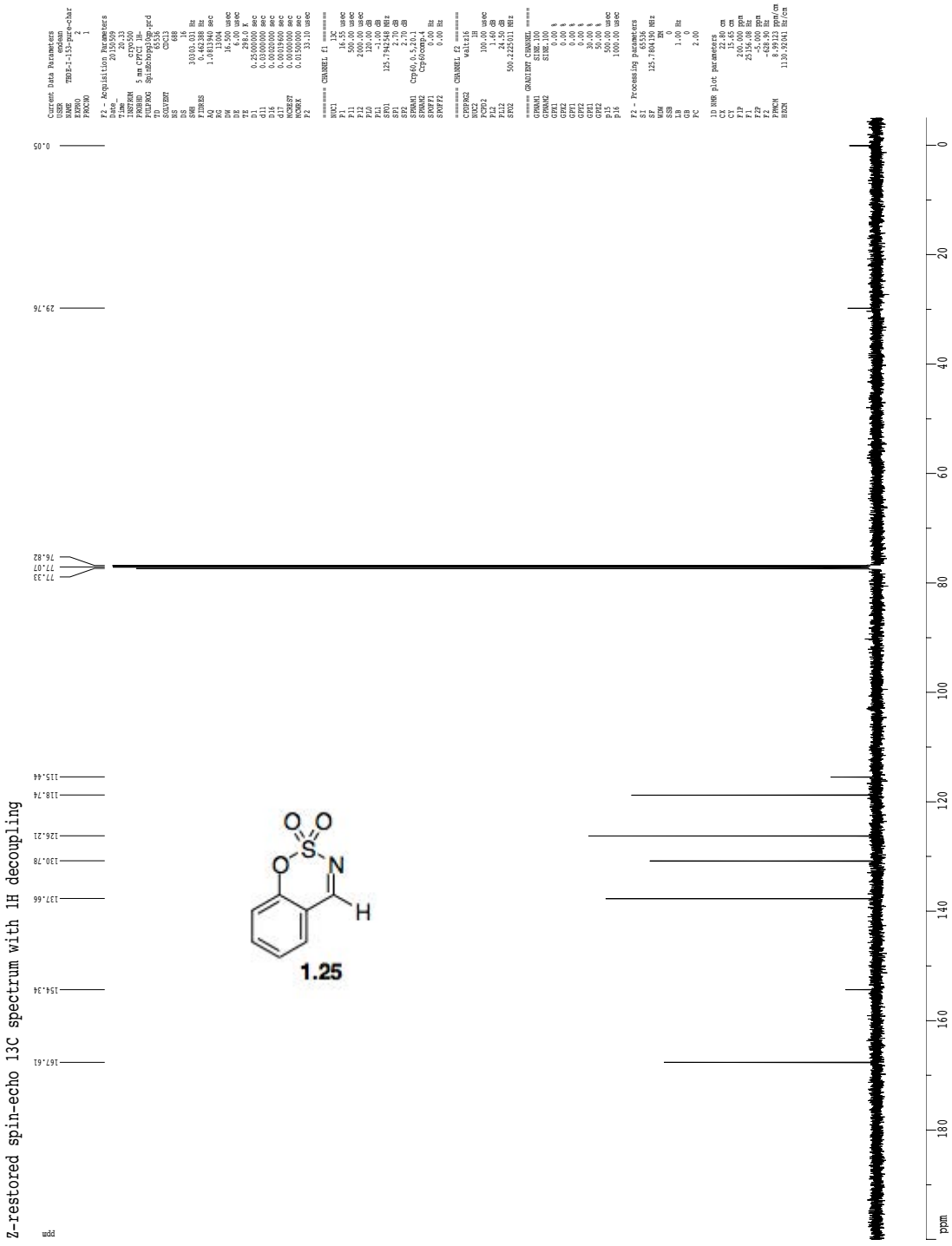
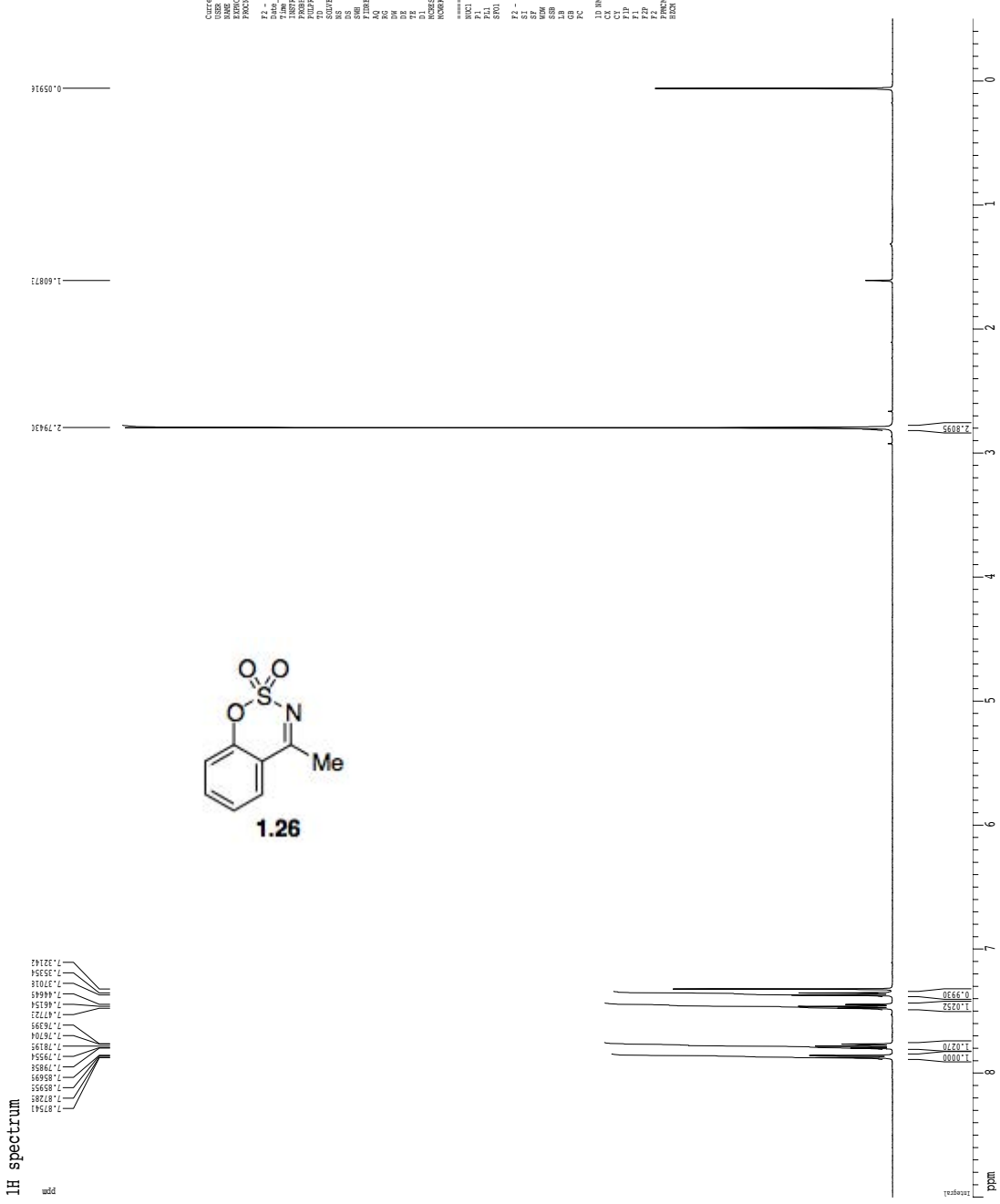
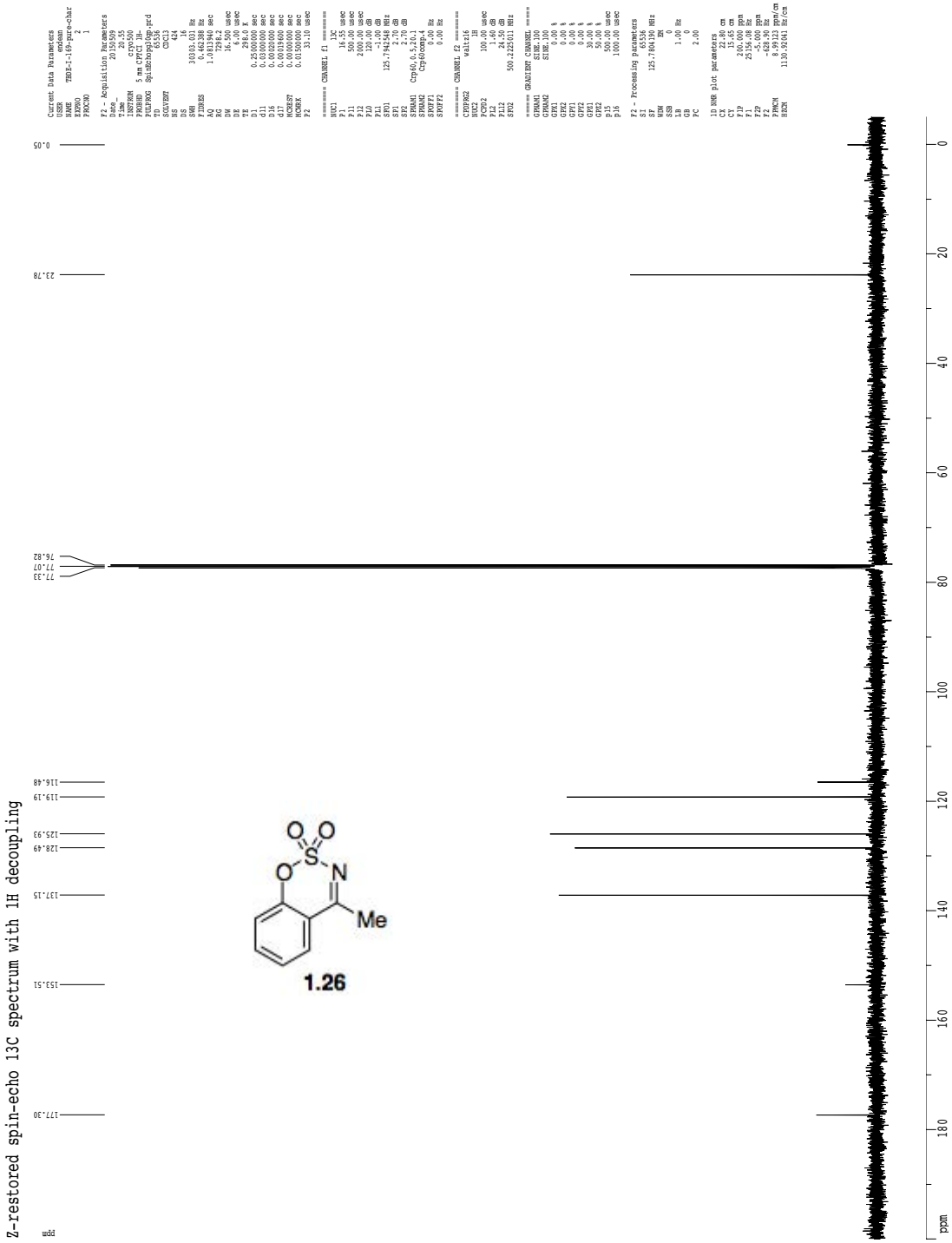
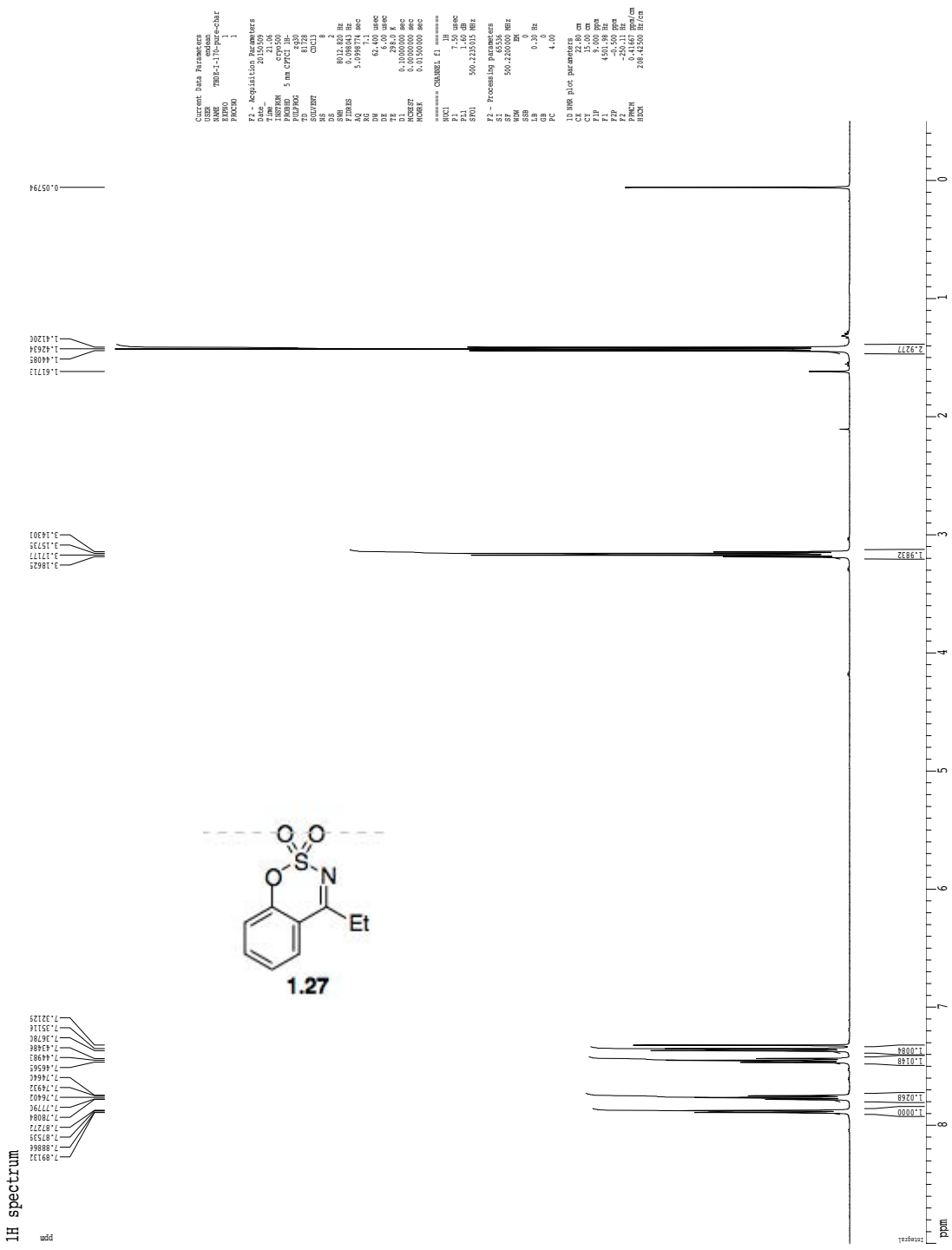
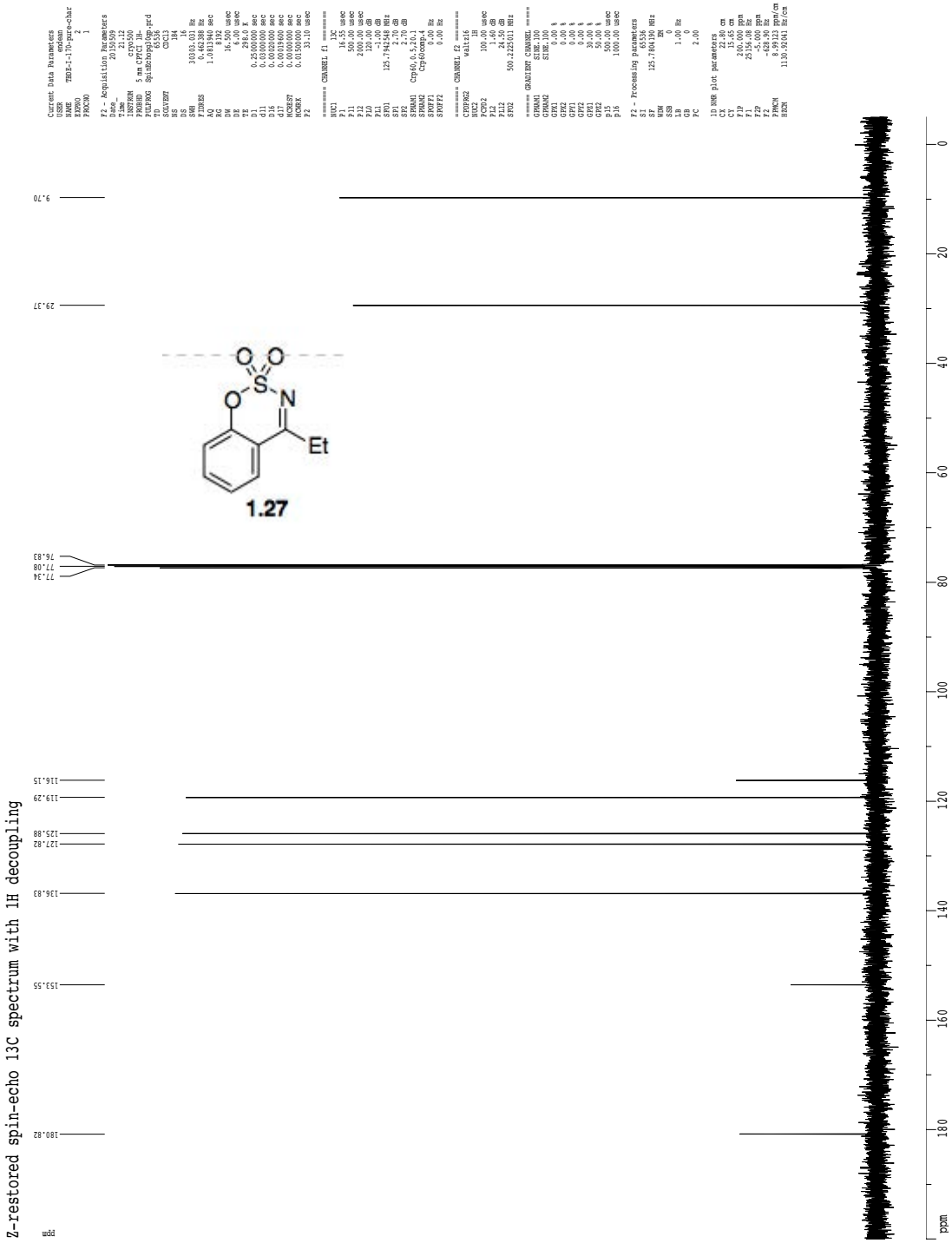

Z-restored spin-echo 13C spectrum with 1H decoupling
1.25
ppm


1H spectrum
ppm
Integral
0.05914
1.60872
2.79430
2.8095
0.9930
1.0252
1.0000
1.0270
7.87541
7.87281
7.85955
7.85695
7.79856
7.79554
7.78195
7.76704
7.76395
7.47321
7.46154
7.44645
7.37018
7.35354
7.32142
O
O
S
O
N
Me

1.26


Z-restored spin-echo 13C spectrum with 1H decoupling
1.26
Me
N
S
O
O
O
ppm


1H spectrum
Et
1.27


Z-restored spin-echo 13C spectrum with 1H decoupling
ppm
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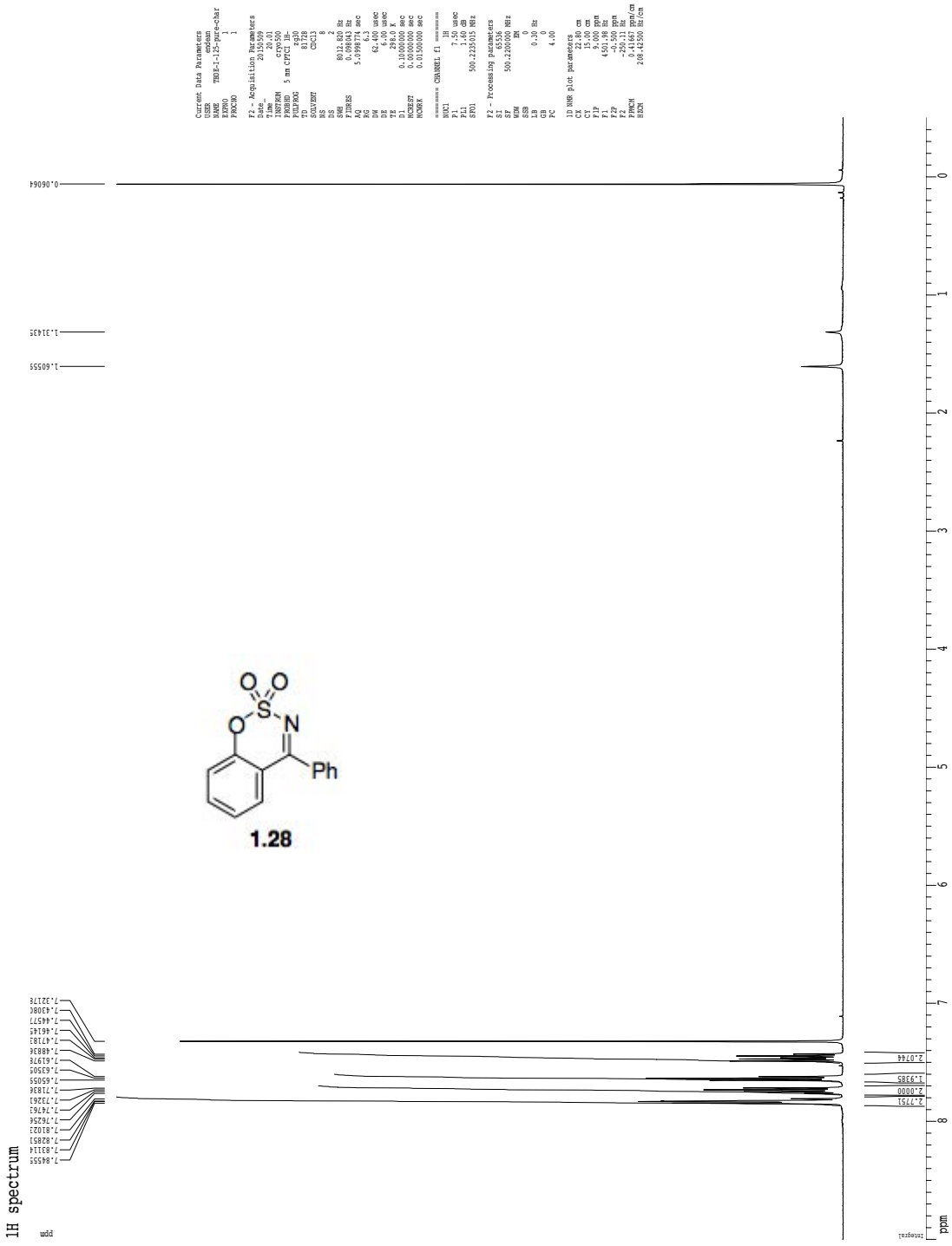
153.55
136.83
127.82
125.88
119.29
116.15
77.34
77.08
76.83
29.37
9.70
Et
1.27


1H spectrum
ppm
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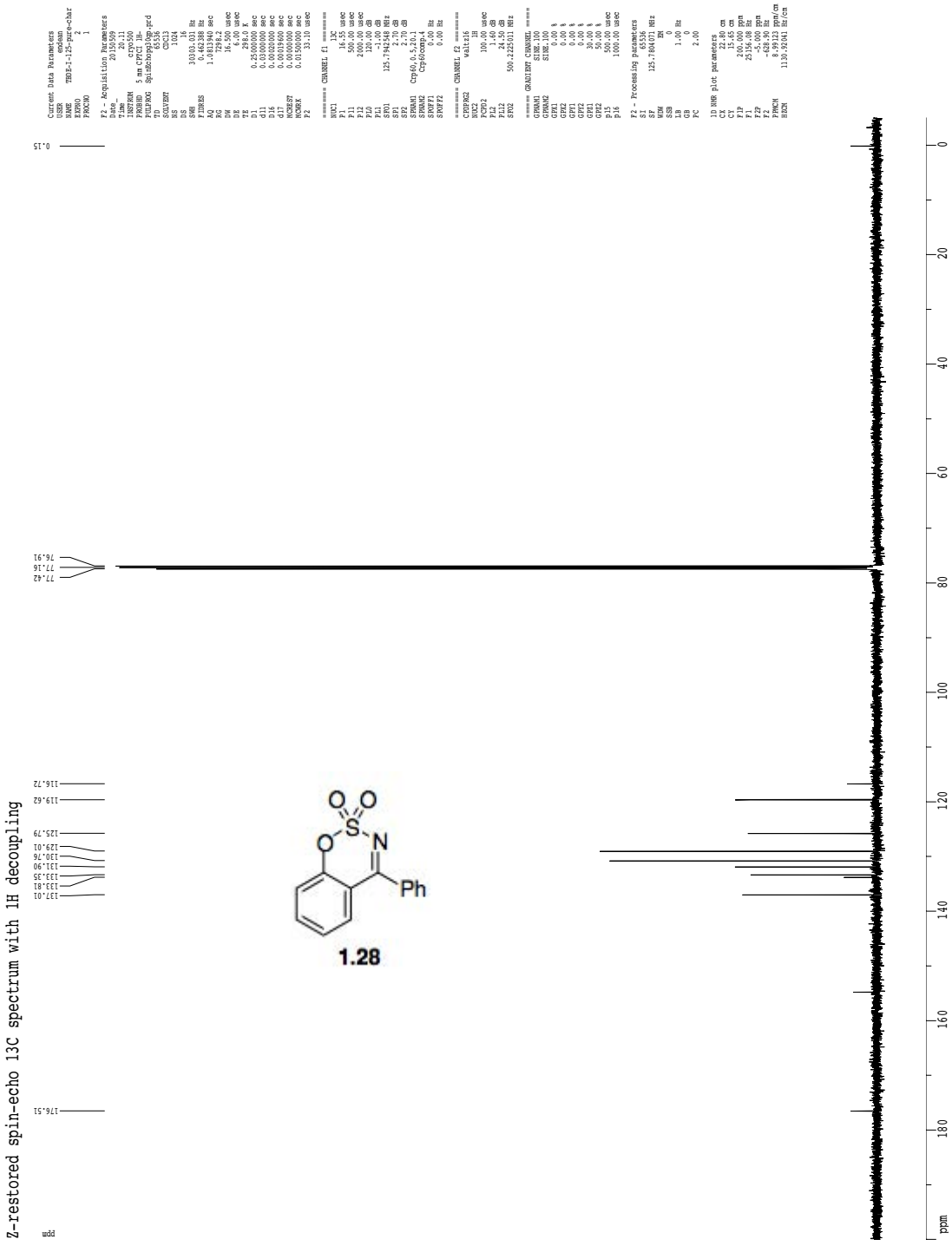
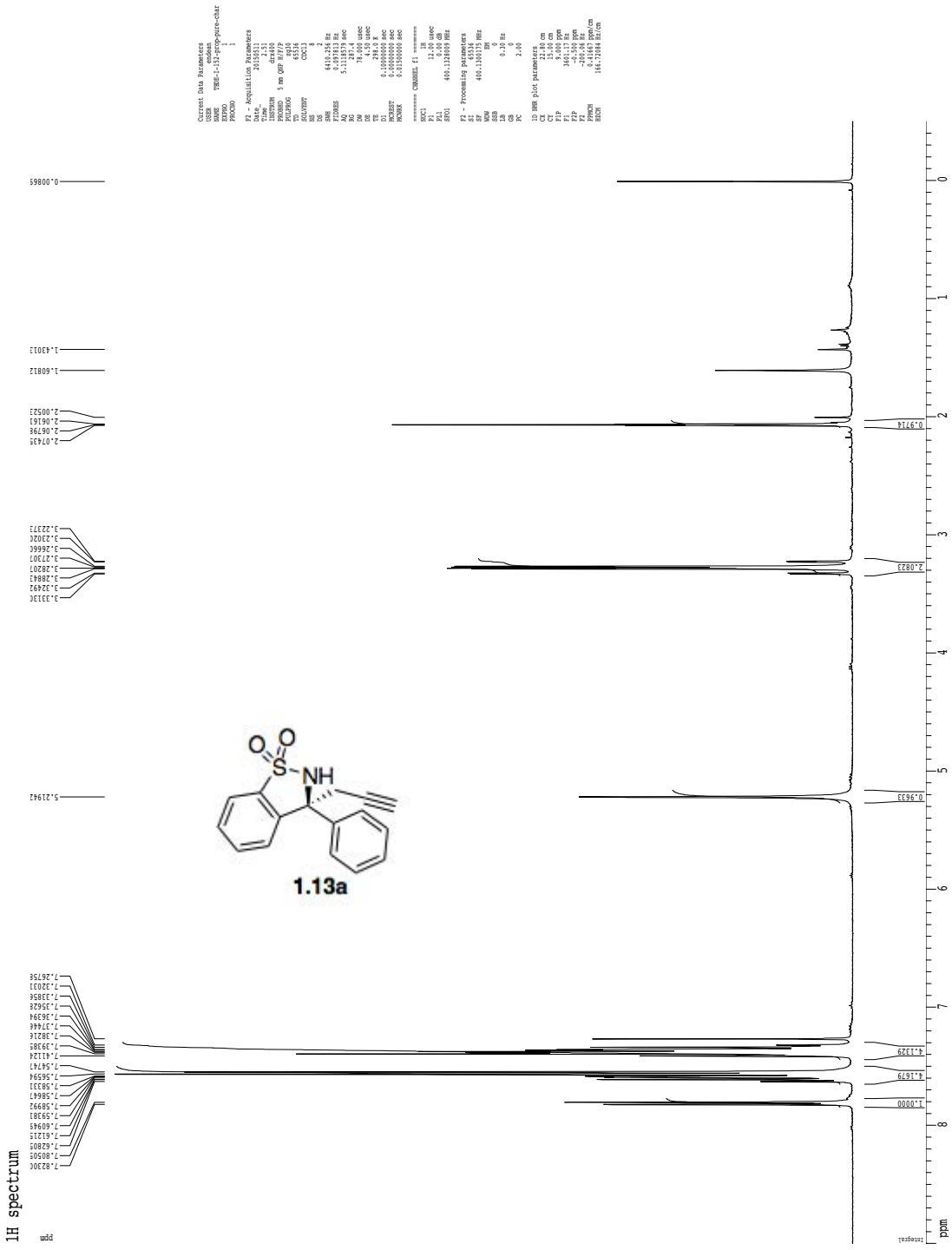
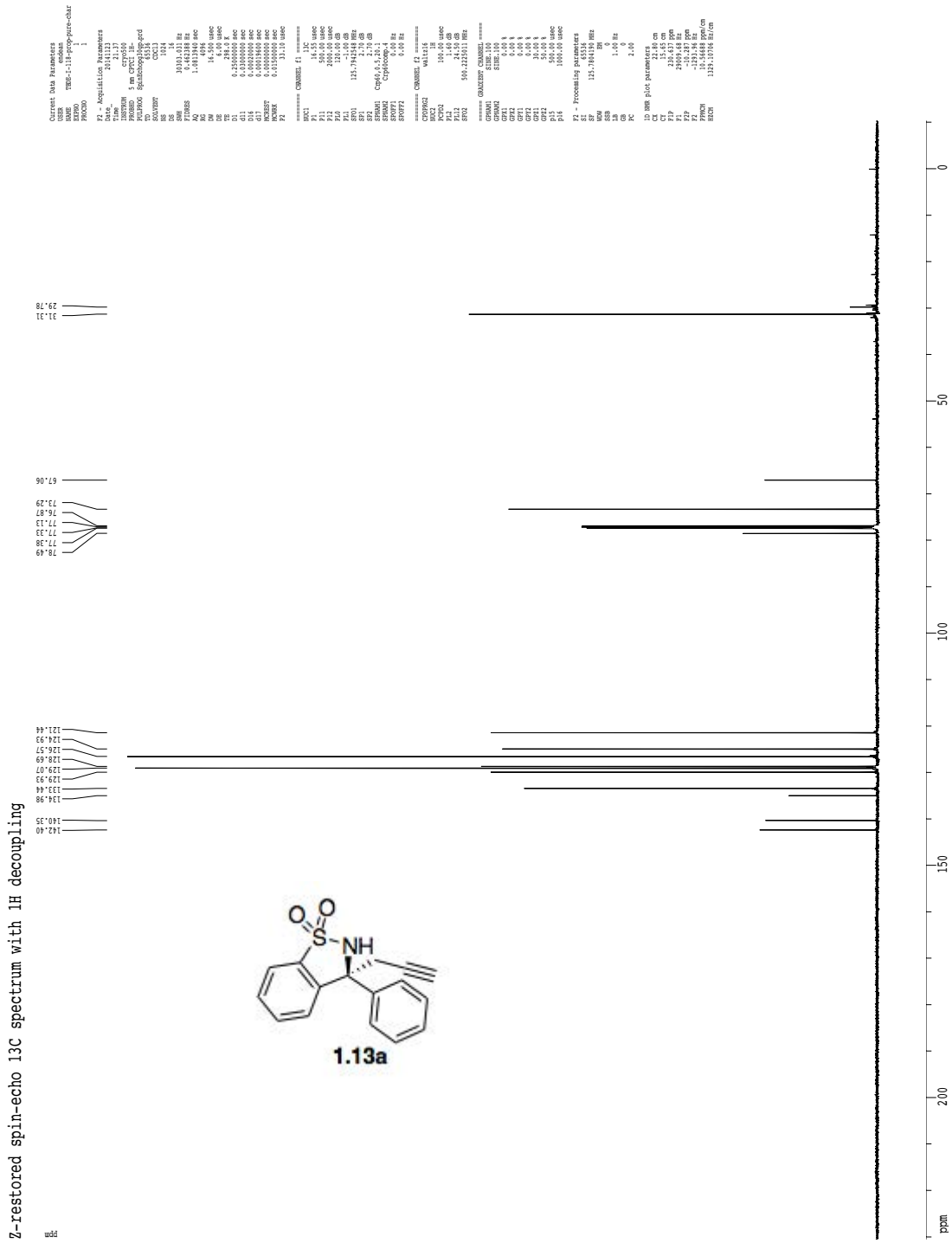
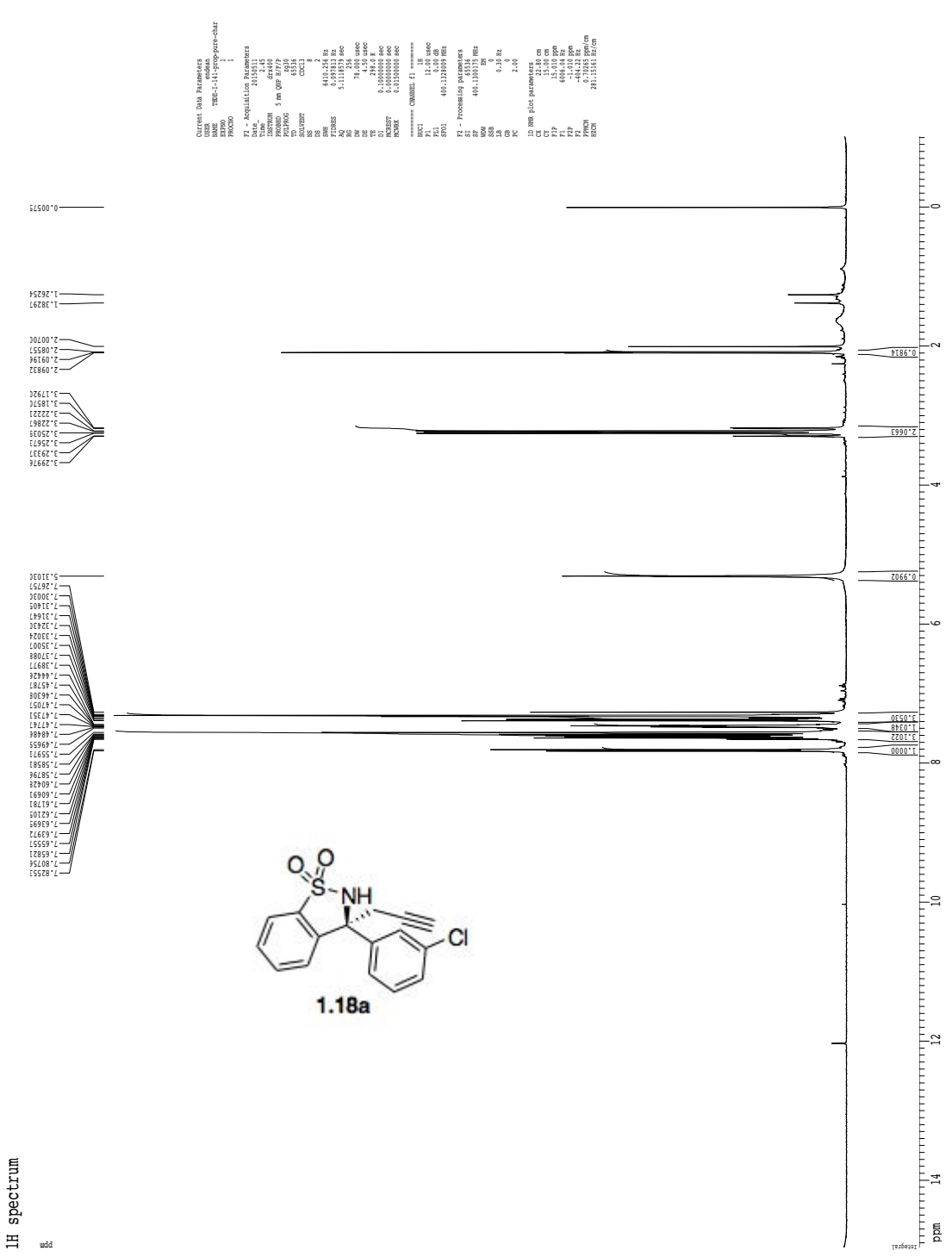
1.31435
1.60555
7.84555
7.83114
7.82851
7.81023
7.76256
7.74763
7.73261
7.71836
7.65055
7.63505
7.61978
7.48834
7.47181
7.46185
7.44571
7.43098
7.32178
2.07744
1.93785
2.00000
2.77751
Integral
O
O
S
O
N
Ph
1.28

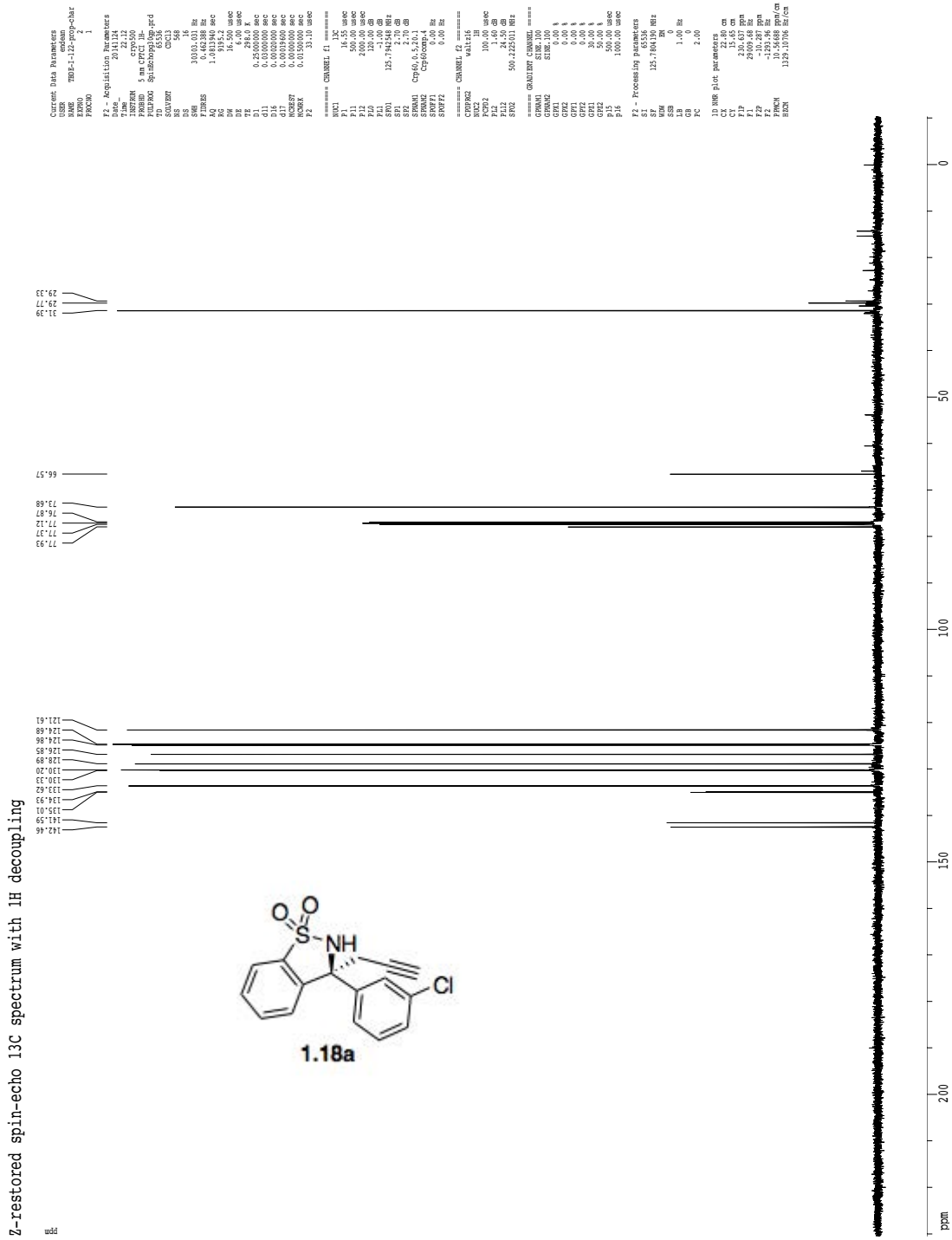

Z-restored spin-echo 13C spectrum with 1H decoupling
1.28
Ph
O
S
N
ppm


1H spectrum
1.13a

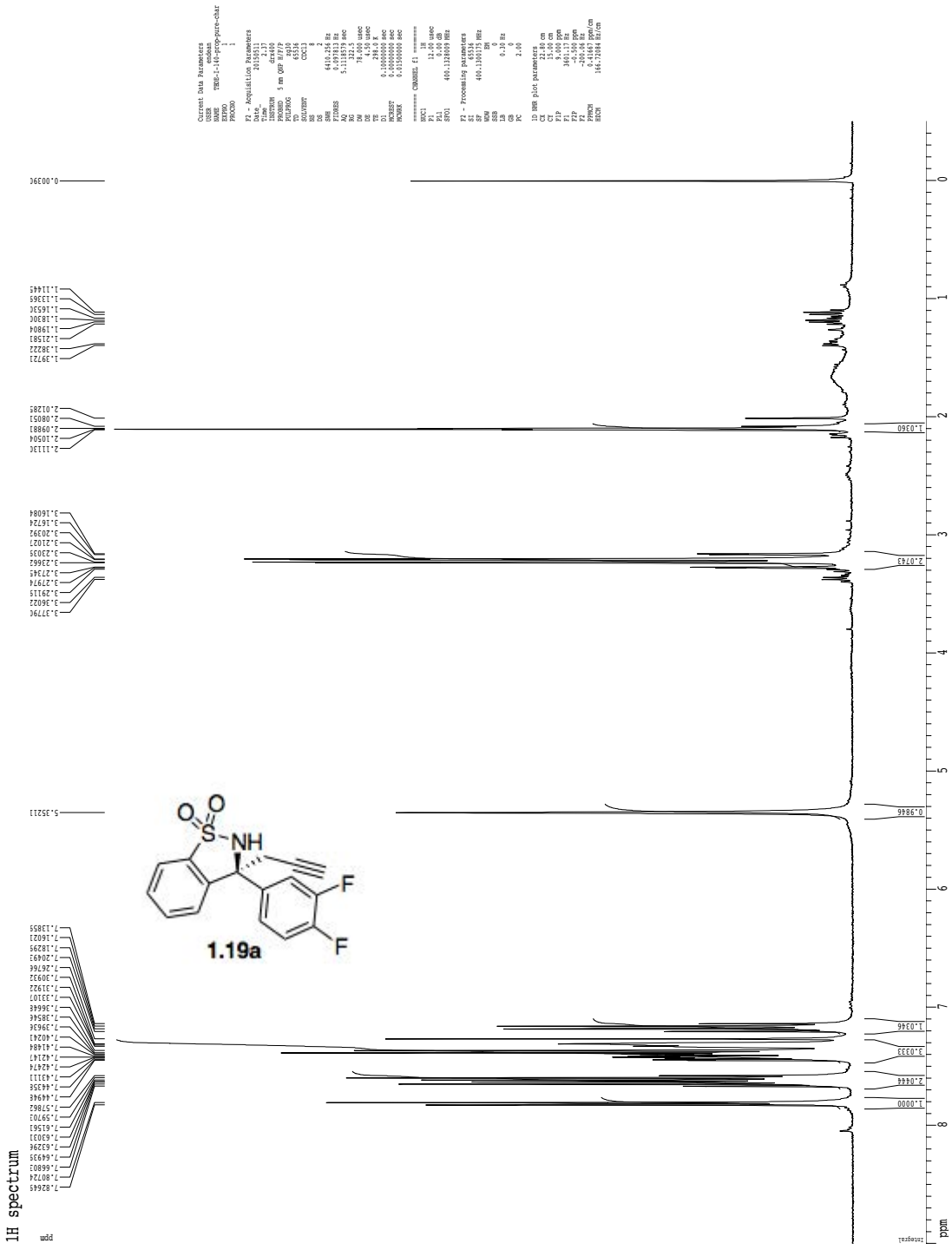

Z-restored spin-echo 13C spectrum with 1H decoupling
ppm
1.13a
31.31
29.78
67.06
73.29
76.87
77.13
77.33
77.38
78.49
121.44
124.93
126.57
128.69
129.07
129.93
133.44
134.98
140.35
142.40
0
50
100
150
200

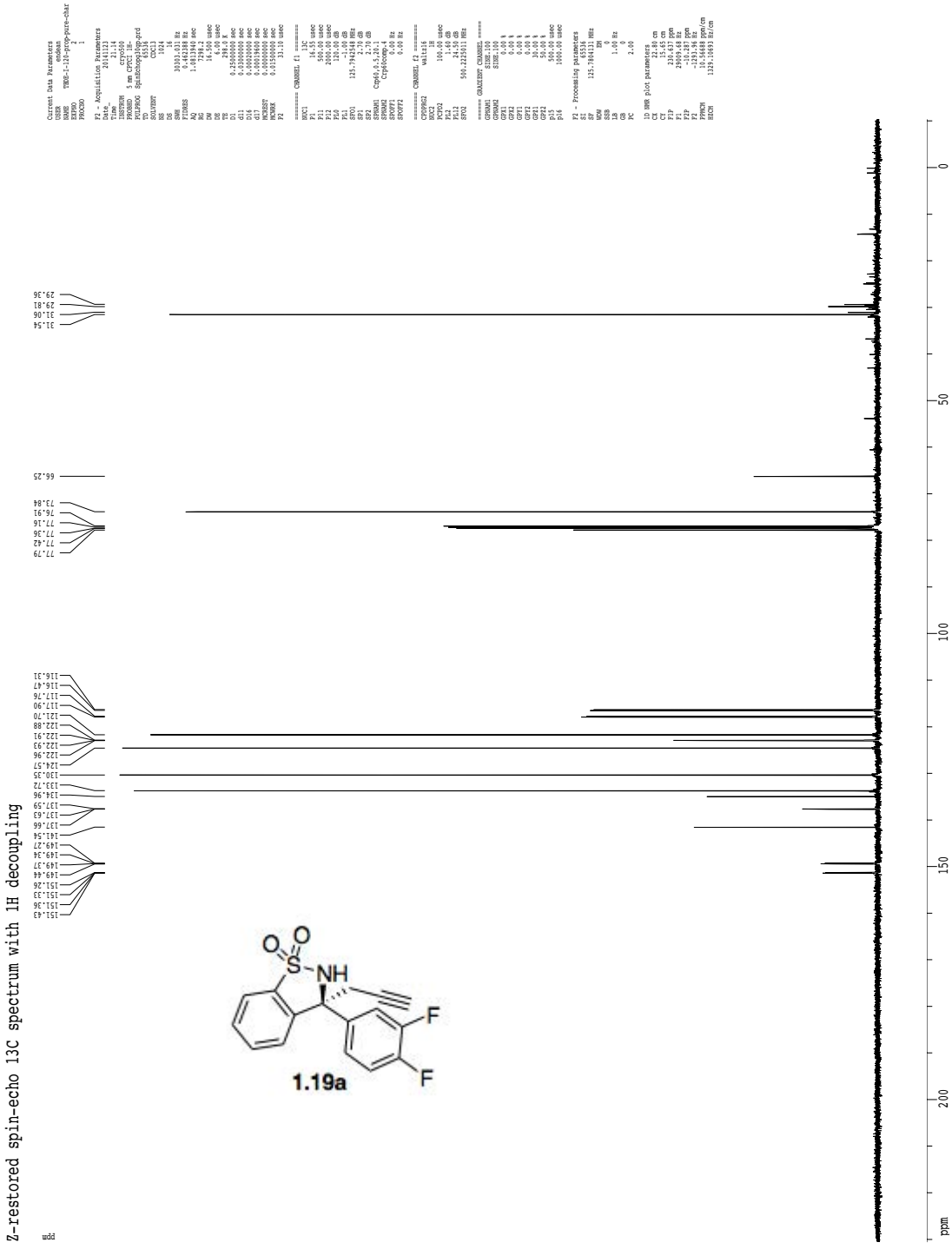

1H spectrum
1.18a
O
O
S
NH
Cl

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

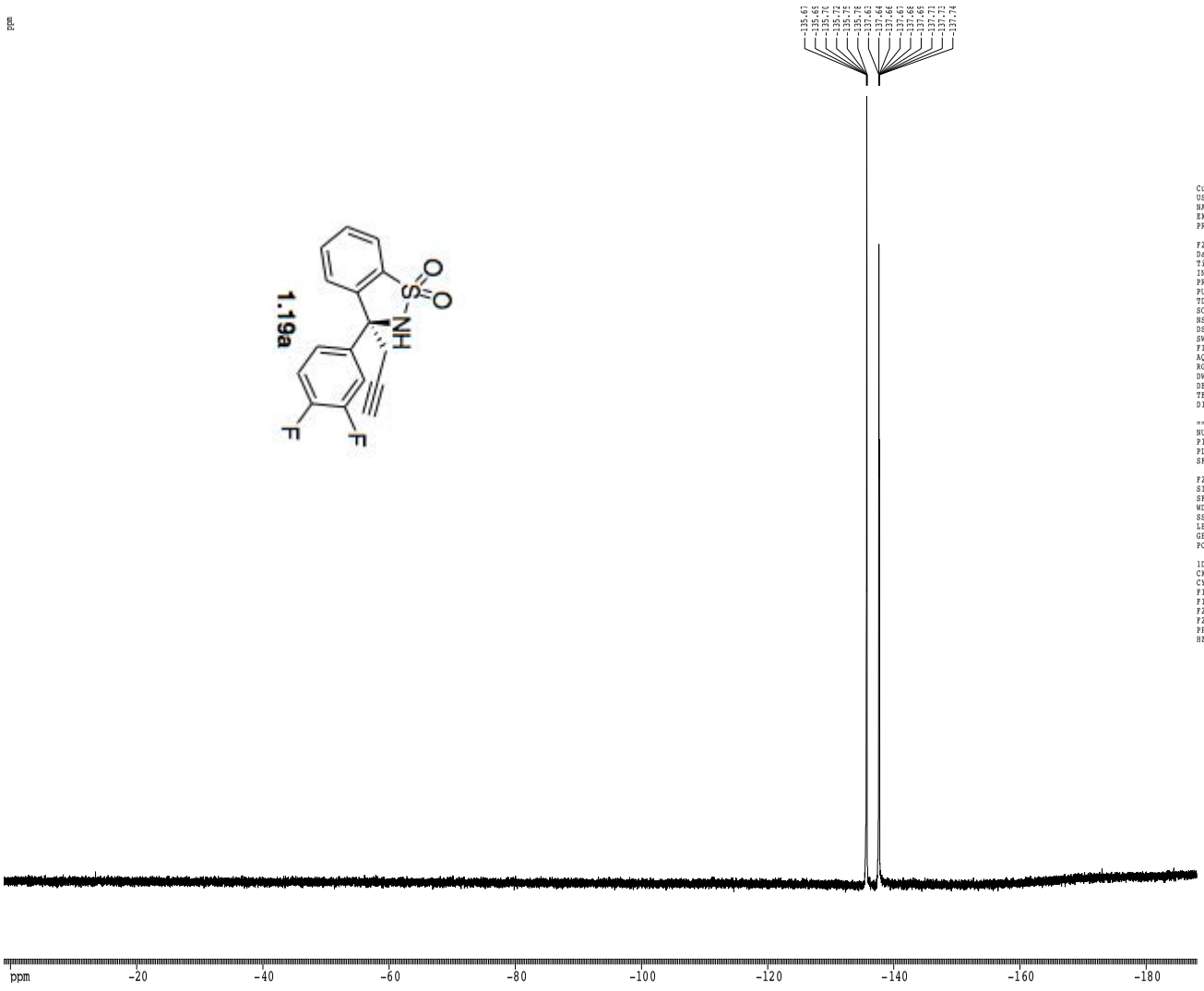


1.18a


1H spectrum
1.19a
ppm


Z-restored spin-echo 13C spectrum with 1H decoupling
1.19a
ppm

19F spectrum

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Current Data Parameters
USER                 endean
NAME       TBDE-I-120-prop-char
EXPNO                     3
PROCNO                    1

F2 - Acquisition Parameters
Date_              20141124
Time                  13.59
INSTRUM             drx400
PROBHD    5 mm QNP H/F/P
PULPROG           zgflqn30
TD                   65536
SOLVENT              CDCl3
NS                      48
DS                       2
SWH              75187.969 Hz
FIDRES               1.147277 Hz
AQ                0.4358644 sec
RG                    3251
DW                   6.650 usec
DE                   9.46 usec
TE                  297.9 K
D1               2.00000000 sec

======= CHANNEL f1 =======
NUC1                   19F
P1                   22.50 usec
PL1                  -6.00 dB
SFO1          376.4646491 MHz

F2 - Processing parameters
SI                   65536
SF            376.4984640 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                   22.80 cm
CY                   15.00 cm
F1P                1.000 ppm
F1                 376.50 Hz
F2P             -188.000 ppm
F2               -70781.71 Hz
PPMCM             8.28947 ppm/cm
HZCM           3120.97437 Hz/cm
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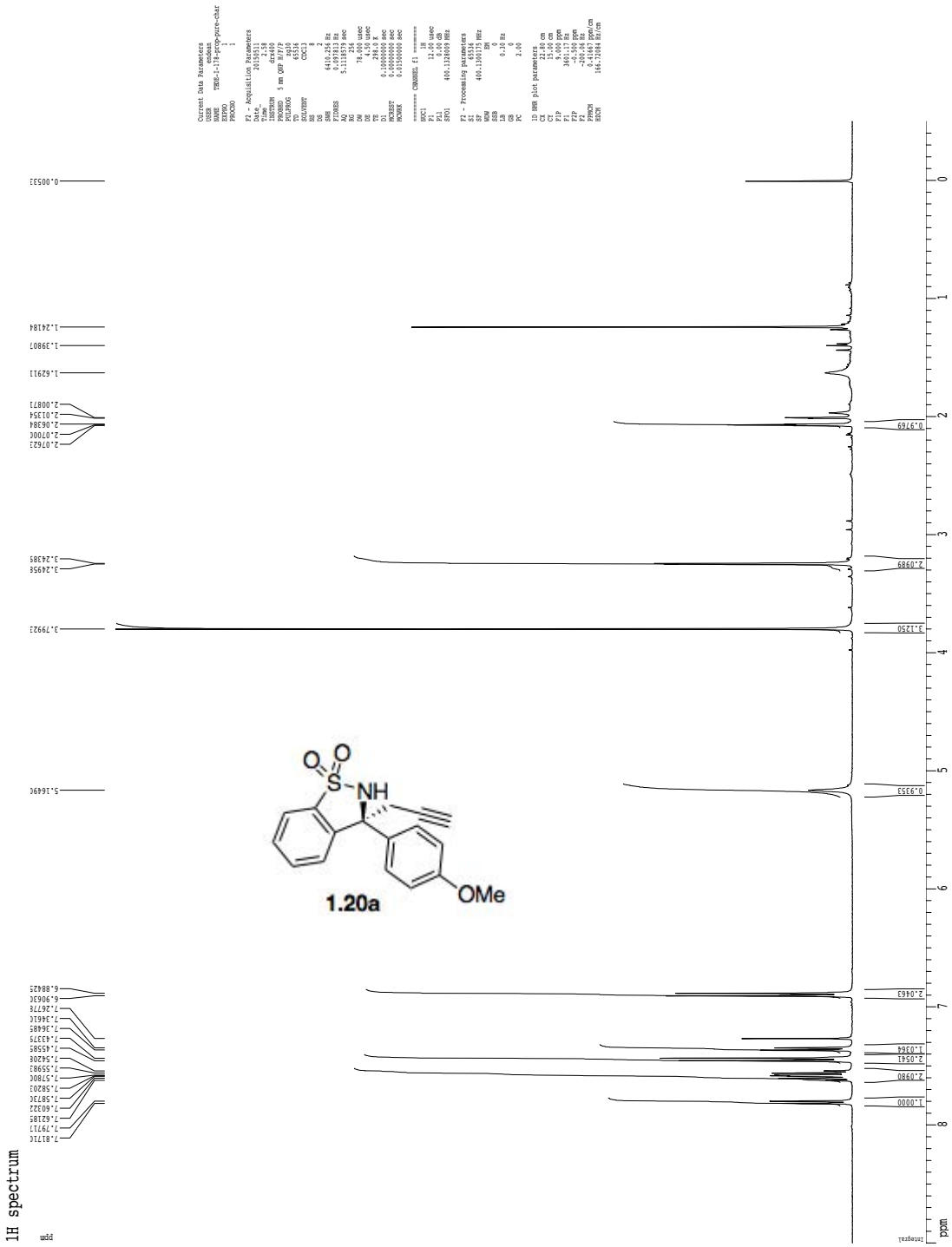
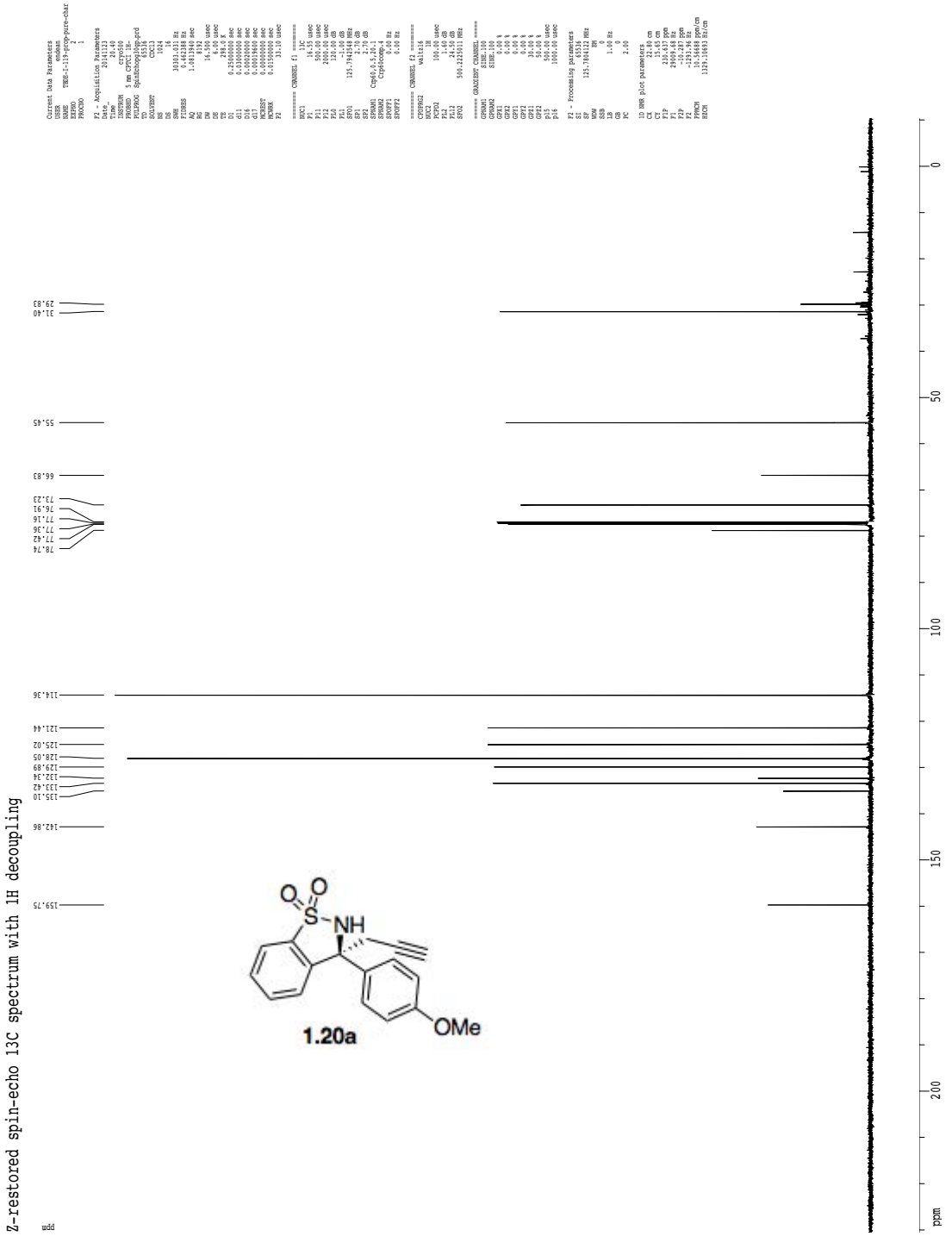
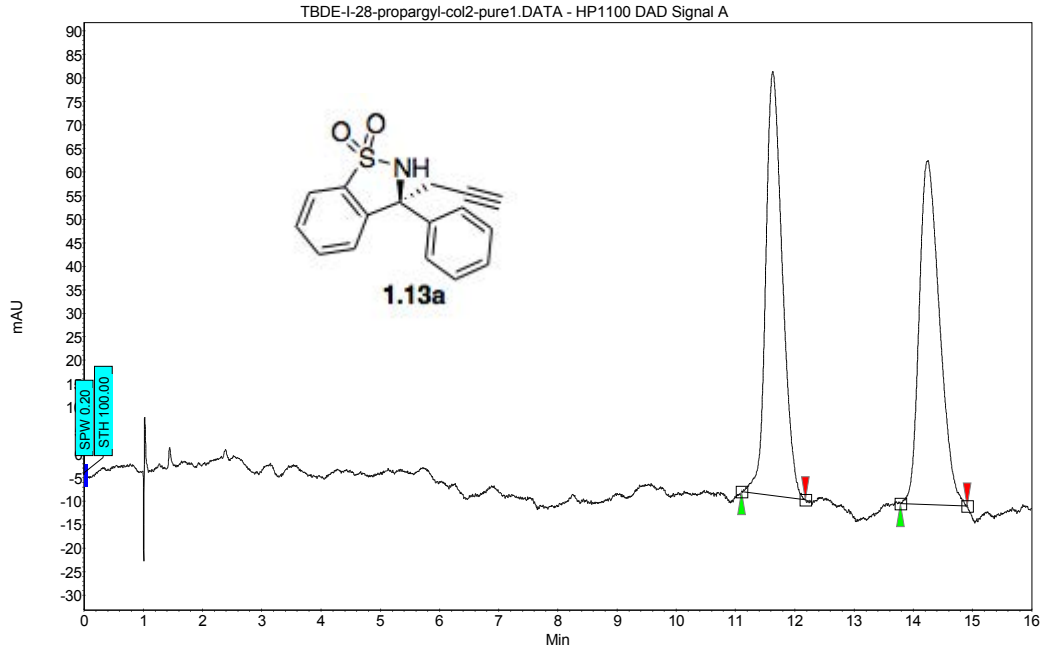

1H spectrum
1.20a
OMe
NH
ppm


Z-restored spin-echo 13C spectrum with 1H decoupling
ppm
159.75
142.86
135.10
133.42
132.34
129.89
128.05
125.02
121.44
114.36
78.74
77.42
77.36
77.16
76.91
73.23
66.83
55.45
31.40
29.83
0
50
100
150
200
ppm
O
O
S
NH
OMe
1.20a

Method Name:TBDE-propargyl-allenyl-mix
Run Name:TBDE-I-28-propargyl-col2-pure1

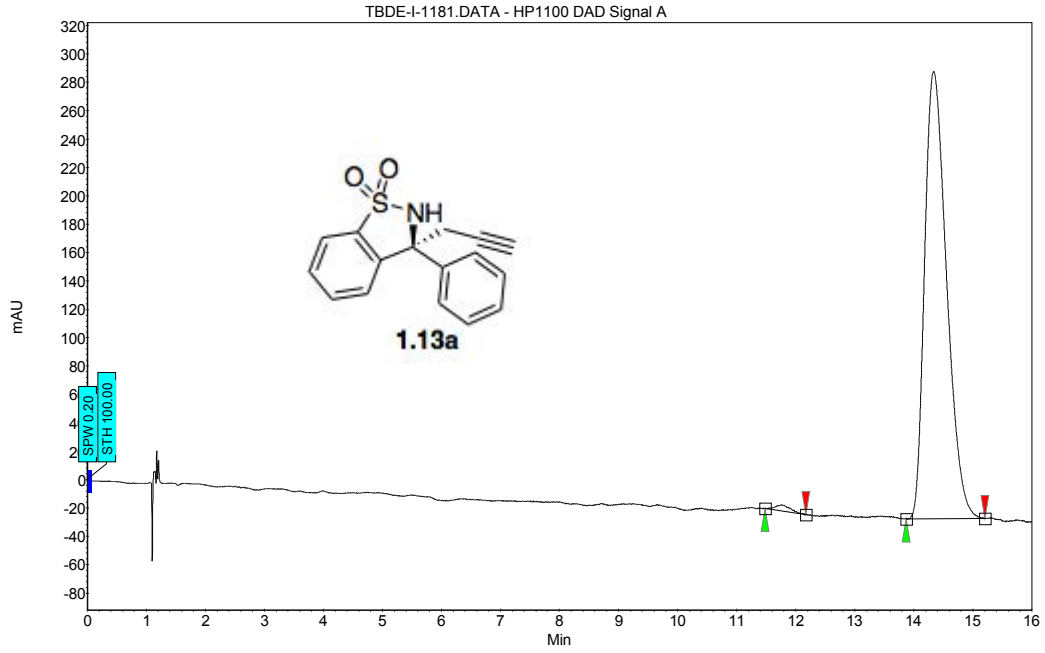
Date:11/25/2014
Time:10:22:39 PM



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	11.10	11.63	12.18	0.00	50.17	90.3	29.2	50.173
2	UNKNOWN	13.78	14.25	14.90	0.00	49.83	73.1	29.0	49.827
Total						100.00	163.4	58.3	100.000

Method Name:TBDE-propargyl-allenyl-mix
Run Name:TBDE-I-1181

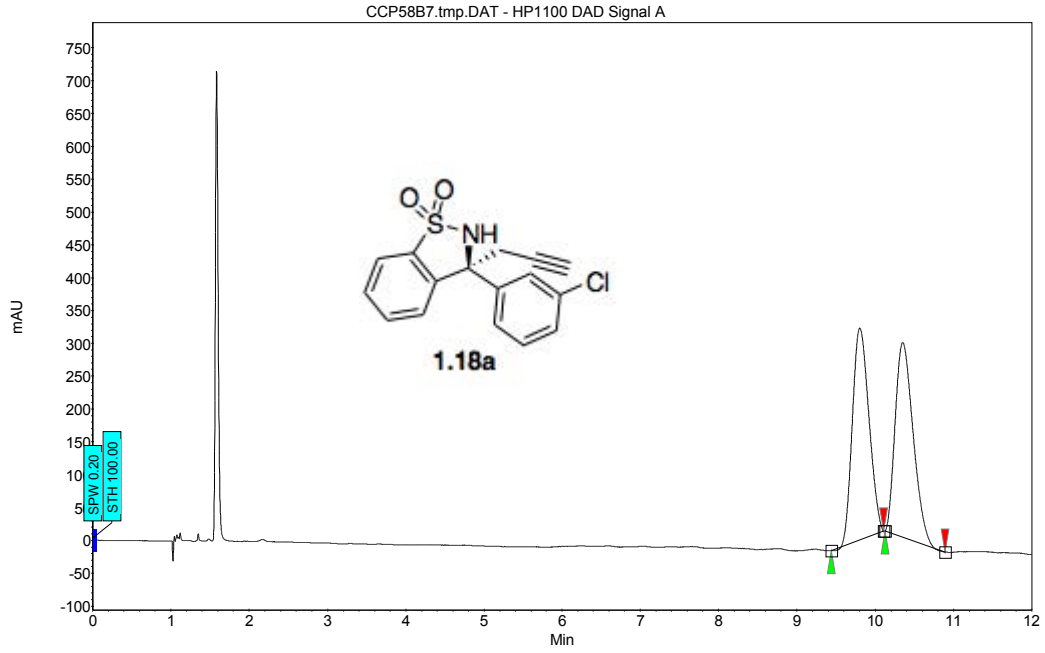
Date:11/25/2014
Time:10:24:19 PM



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	11.48	11.80	12.17	0.00	0.96	4.6	1.3	0.959
2	UNKNOWN	13.87	14.34	15.20	0.00	99.04	315.5	135.6	99.041
Total						100.00	320.1	136.9	100.000

Method Name:TBDE-propargyl-allenyl-mix-3-Cl-methanol
Run Name:TBDE-I-1214

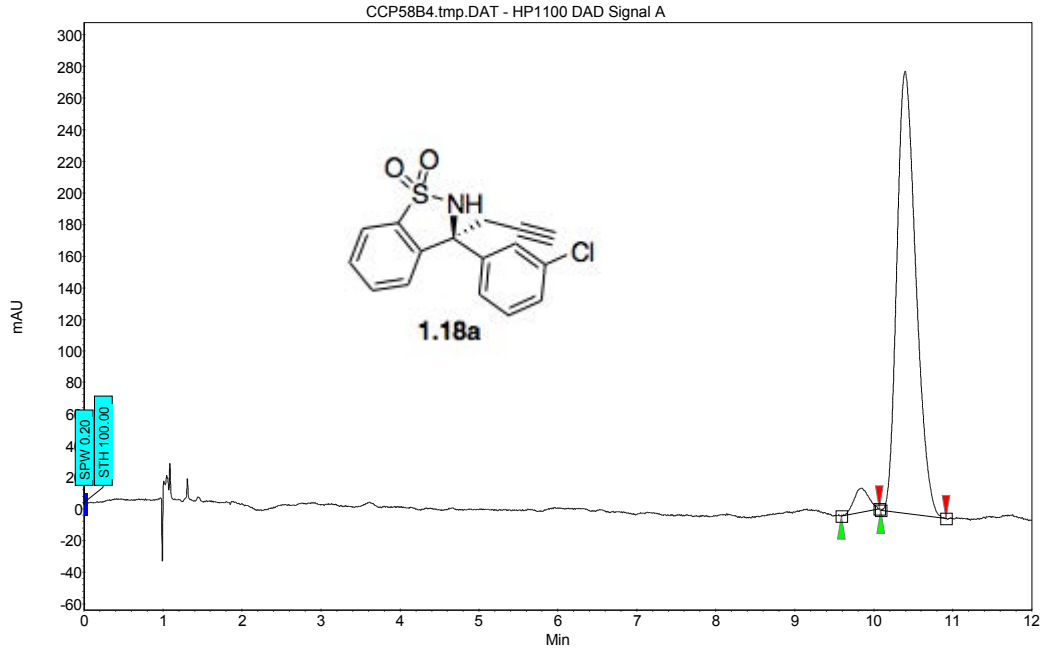
Date:11/25/2014
Time:6:43:38 PM



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	9.44	9.80	10.11	0.00	50.04	323.2	78.9	50.042
2	UNKNOWN	10.13	10.36	10.89	0.00	49.96	296.1	78.7	49.958
Total						100.00	619.2	157.6	100.000

Method Name:TBDE-propargyl-allenyl-mix-3-Cl-methanol
Run Name:TBDE-I-1222

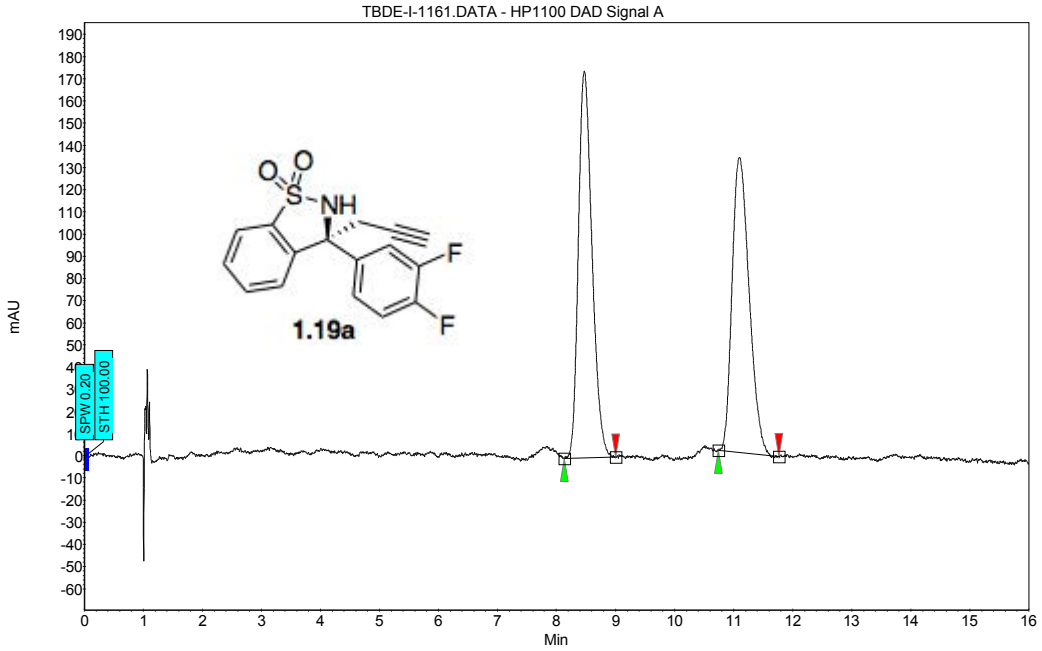
Date:11/25/2014
Time:6:40:49 PM



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	9.59	9.84	10.07	0.00	4.01	15.2	3.3	4.011
2	UNKNOWN	10.09	10.40	10.91	0.00	95.99	279.6	78.2	95.989
Total						100.00	294.8	81.4	100.000

Method Name:TBDE-propargyl-allenyl-mix
Run Name:TBDE-I-1161

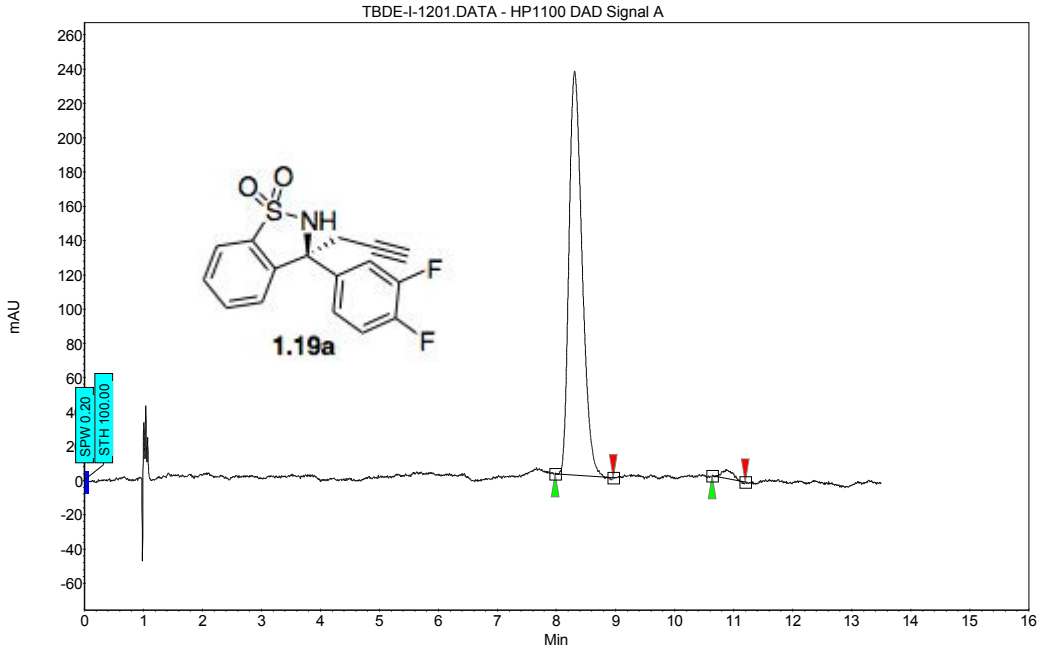
Date:11/25/2014
Time:10:26:03 PM



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	8.13	8.47	9.00	0.00	51.21	174.4	46.7	51.211
2	UNKNOWN	10.74	11.10	11.76	0.00	48.79	133.1	44.5	48.789
Total						100.00	307.5	91.1	100.000

Method Name:TBDE-propargyl-allenyl-mix
Run Name:TBDE-I-1201

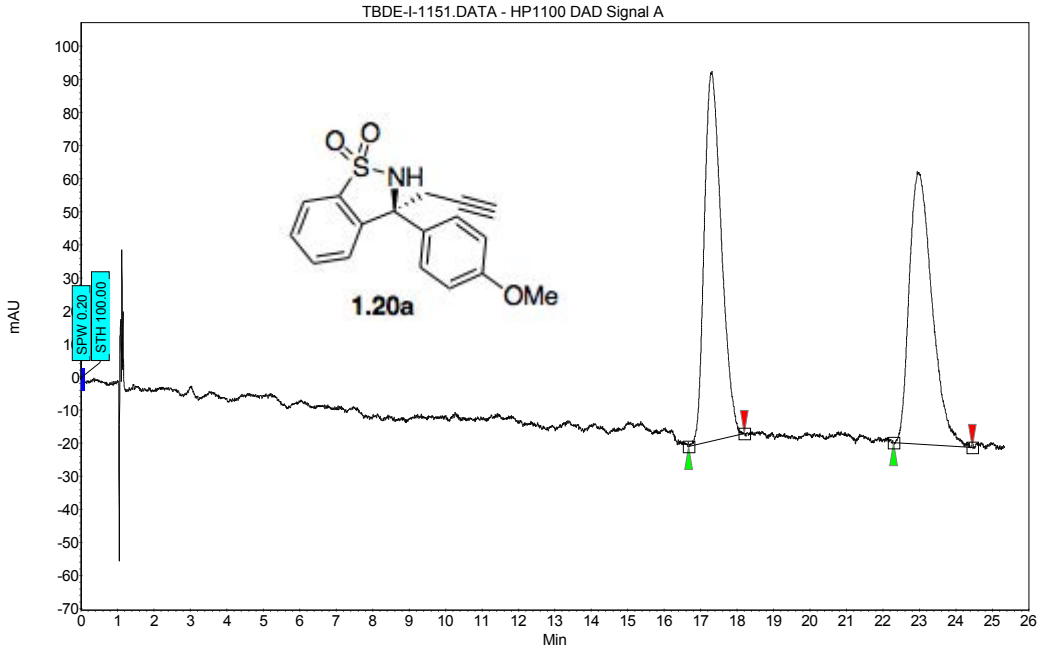
Date:11/25/2014
Time:4:26:19 PM



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	7.98	8.31	8.96	0.00	98.35	235.6	60.5	98.349
2	UNKNOWN	10.64	10.87	11.20	0.00	1.65	5.5	1.0	1.651
Total						100.00	241.1	61.5	100.000

Method Name:TBDE-propargyl-allenyl-mix
Run Name:TBDE-I-1151

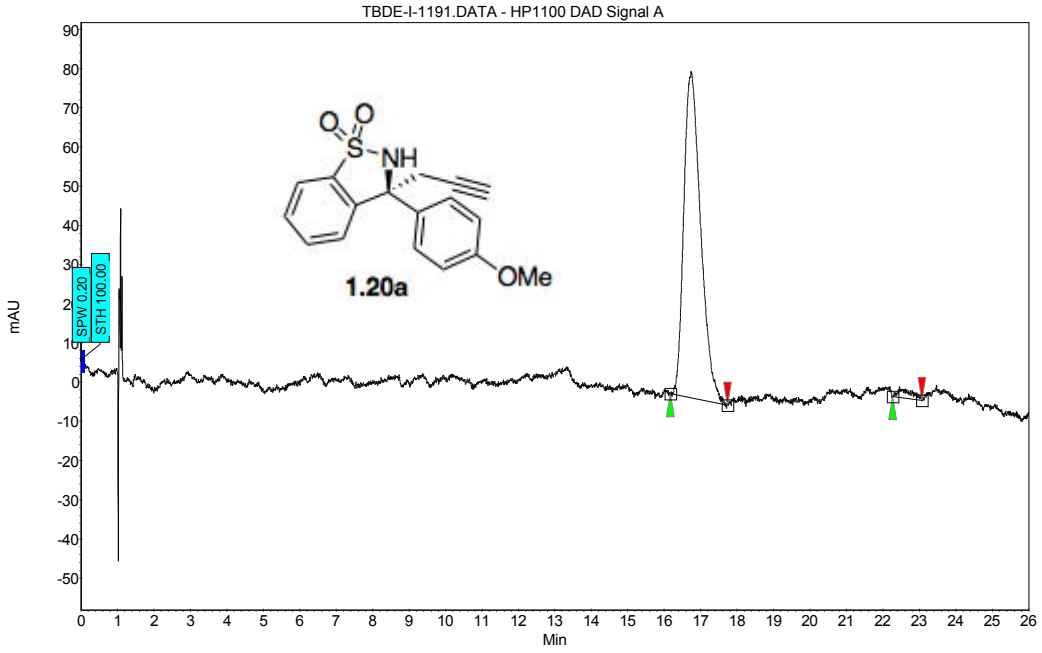
Date:5/11/2015
Time:1:55:28 PM



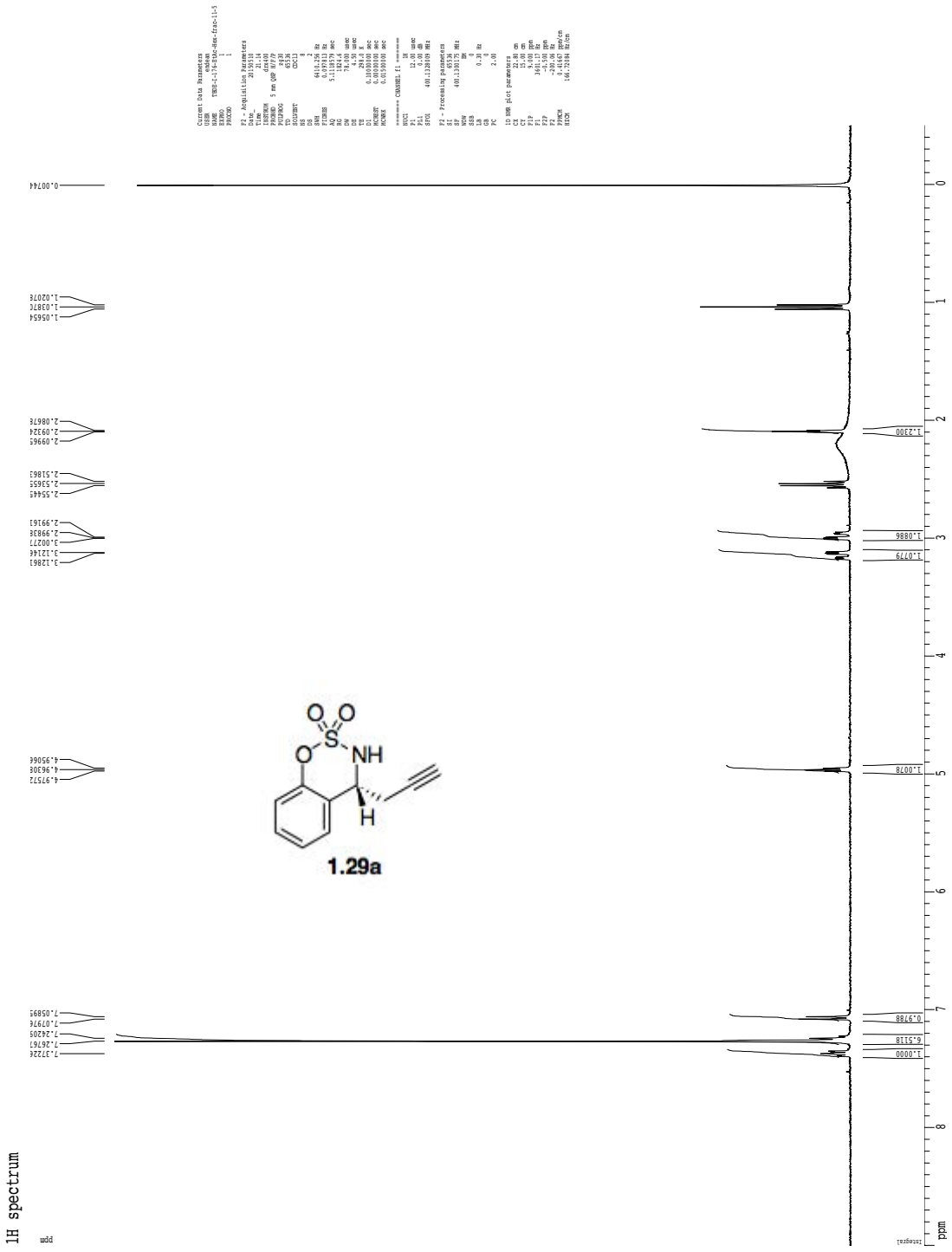
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	16.68	17.31	18.19	0.00	50.43	111.8	60.6	50.435
2	UNKNOWN	22.29	22.94	24.45	0.00	49.57	82.4	59.5	49.565
Total						100.00	194.2	120.1	100.000

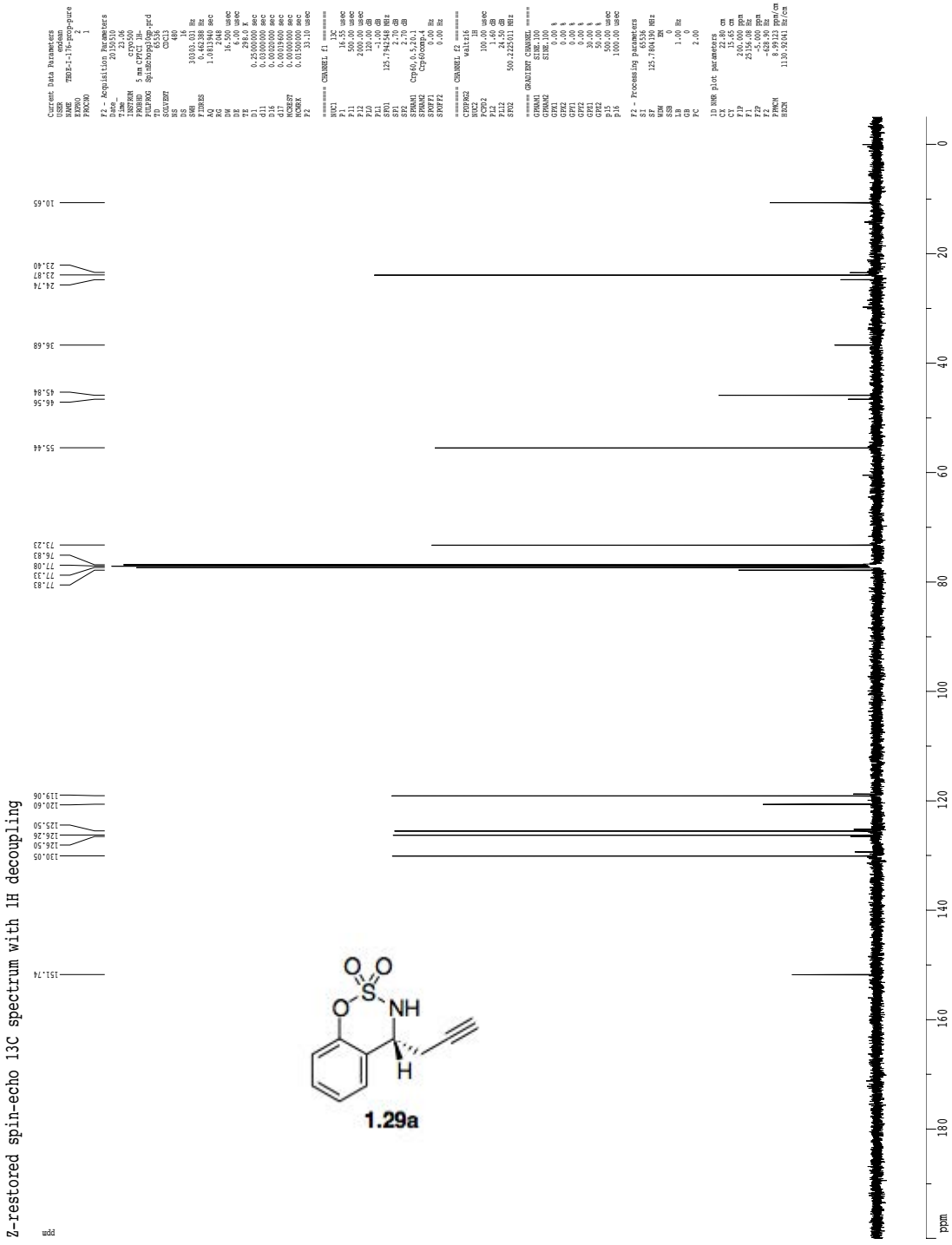
Method Name:TBDE-propargyl-allenyl-mix
Run Name:TBDE-I-1191

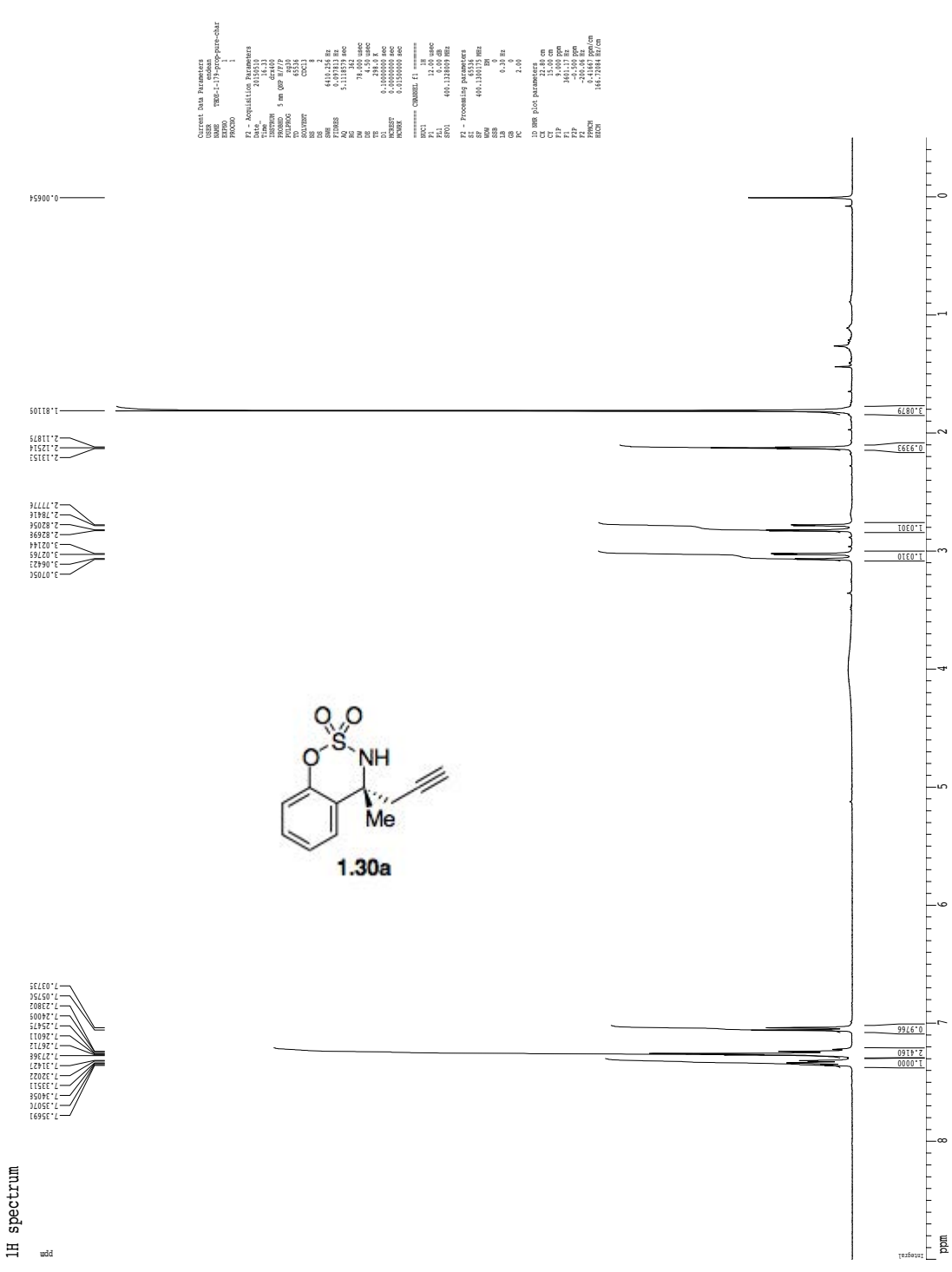
Date:11/25/2014
Time:10:26:36 PM

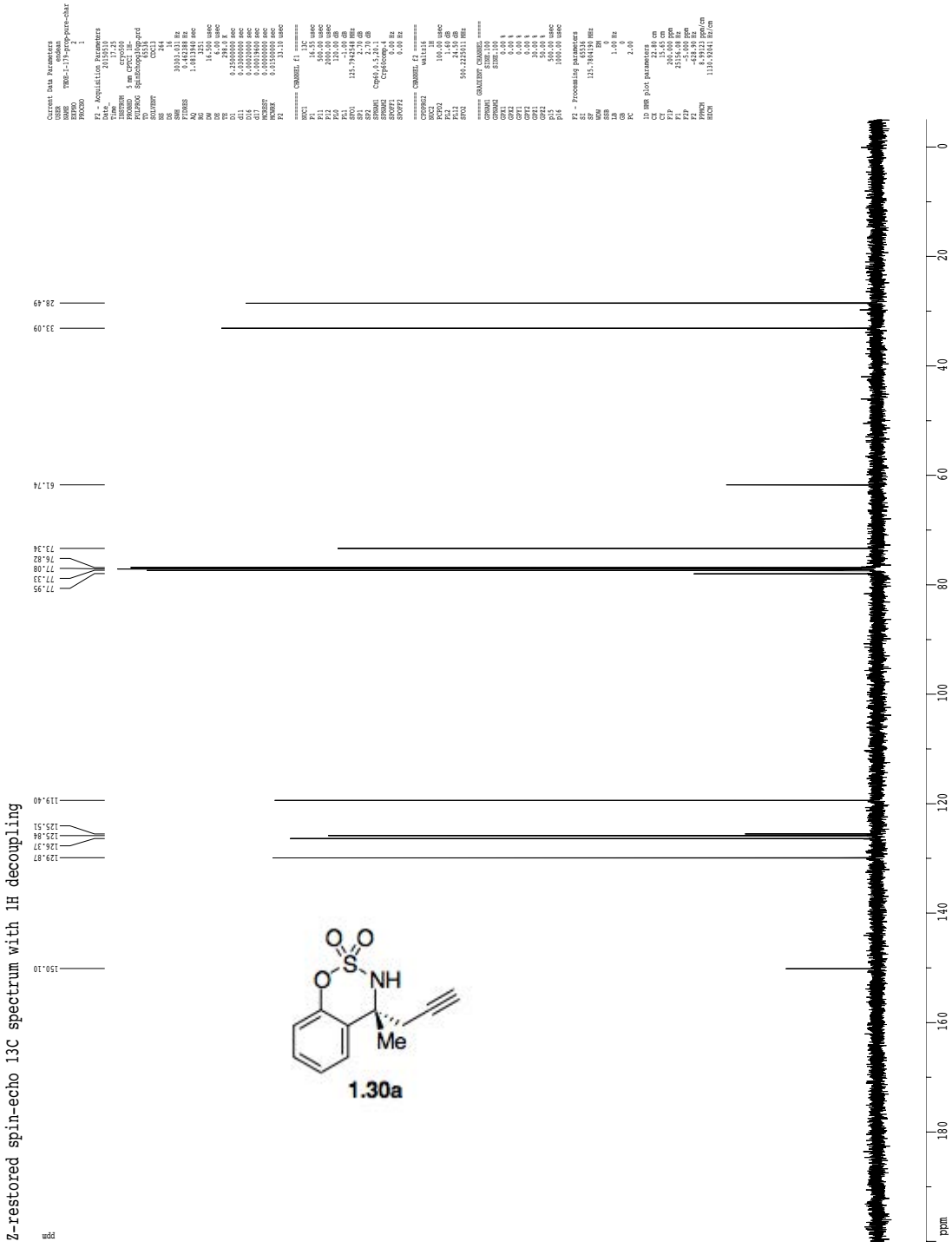


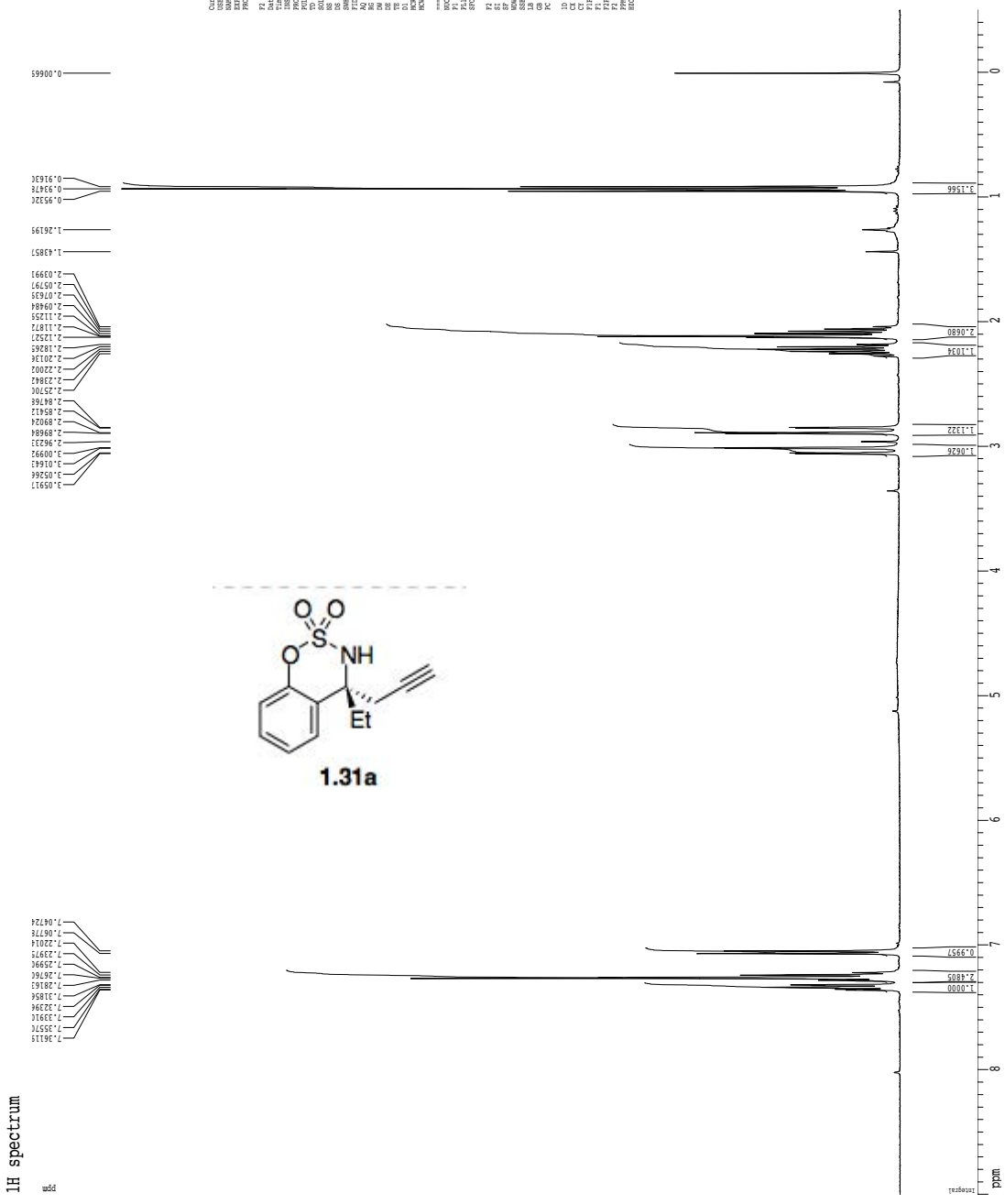
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	16.17	16.74	17.73	0.00	97.76	83.4	44.5	97.763
2	UNKNOWN	22.27	22.46	23.06	0.00	2.24	2.7	1.0	2.237
Total						100.00	86.1	45.6	100.000

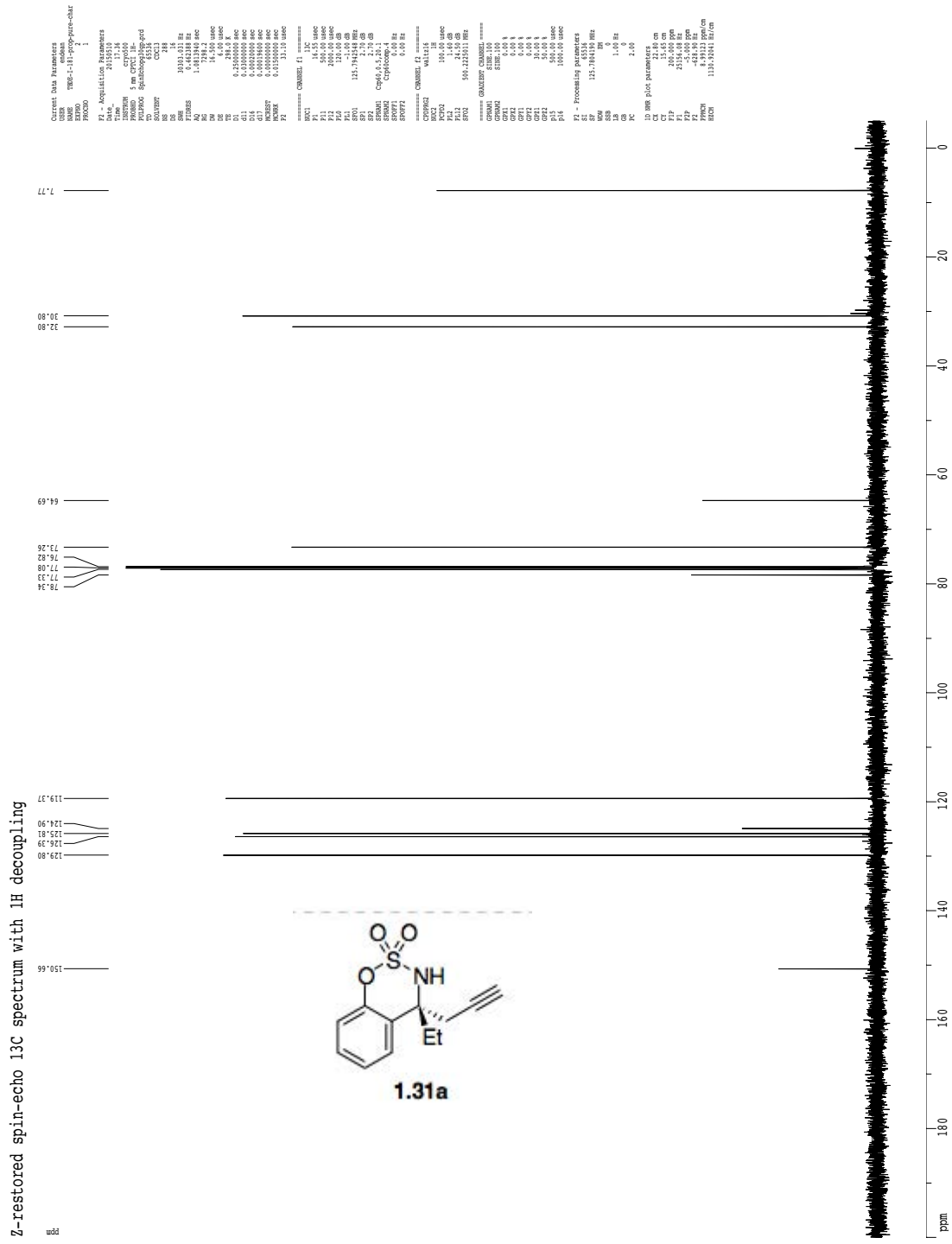

1H spectrum
ppm
1.29a


Z-restored spin-echo 13C spectrum with 1H decoupling
1.29a


1H spectrum
ppm
1.30a
Me
NH

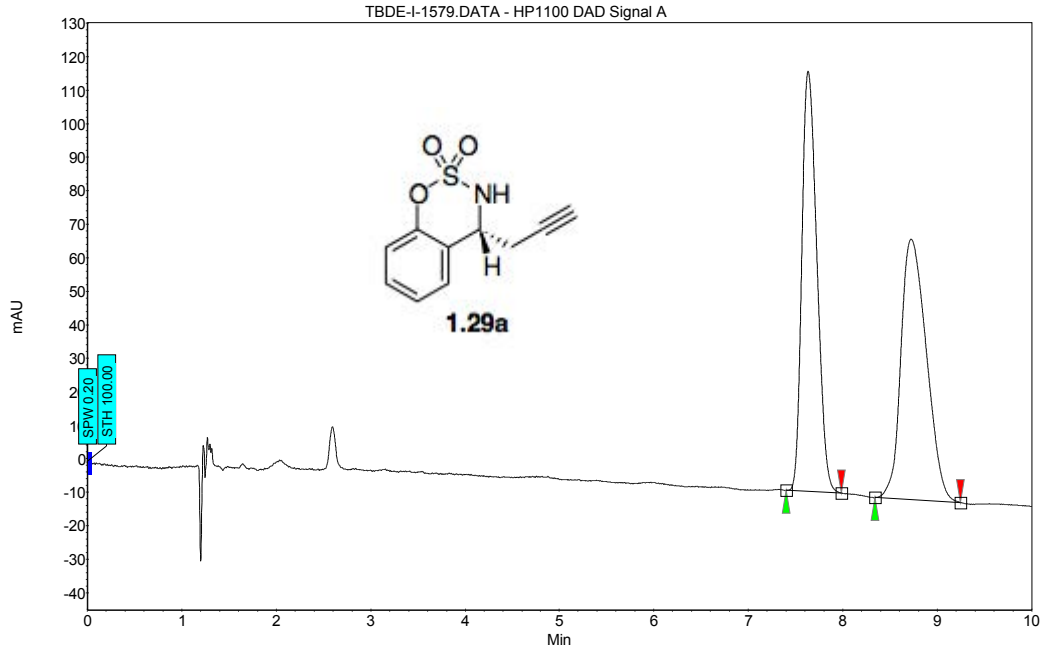

Z-restored spin-echo 13C spectrum with 1H decoupling
28.49
33.09
61.74
73.34
76.82
77.08
77.33
77.95
119.40
125.51
125.84
126.37
129.87
150.10
NH
Me
1.30a
ppm


1H spectrum
ppm
1.31a
O
S
NH
Et


Z-restored spin-echo 13C spectrum with 1H decoupling
ppm
77.77
30.80
32.80
64.69
73.26
76.82
77.08
77.33
78.34
119.37
124.90
125.81
126.39
129.80
150.66
O
O
S
O
NH
Et
1.31a
ppm

Method Name:TBDE-propargyl-allenyl-mix-6-mem-aldimine
Run Name:TBDE-I-1579

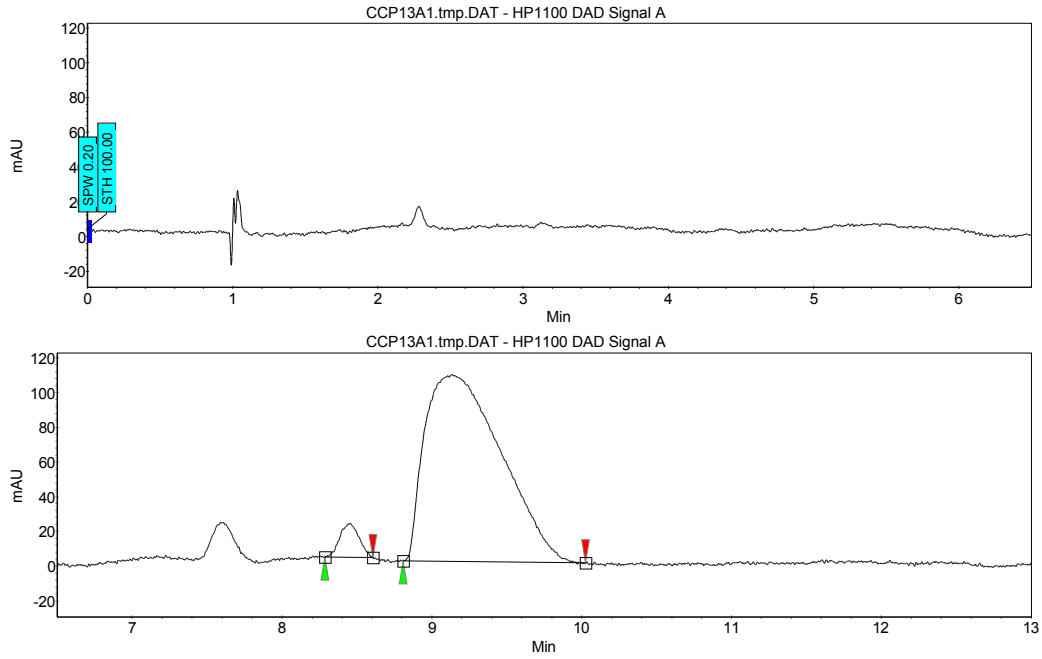
Date:5/11/2015
Time:9:17:05 AM



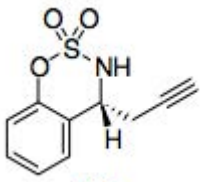
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	7.40	7.63	7.98	0.00	48.80	125.4	23.2	48.795
2	UNKNOWN	8.34	8.72	9.24	0.00	51.20	77.8	24.3	51.205
Total						100.00	203.2	47.5	100.000

Method Name:TBDE-propargyl-allenyl-mix-6-mem-aldimine
Run Name:TBDE-I-1761

Date:5/11/2015
Time:9:25:02 AM



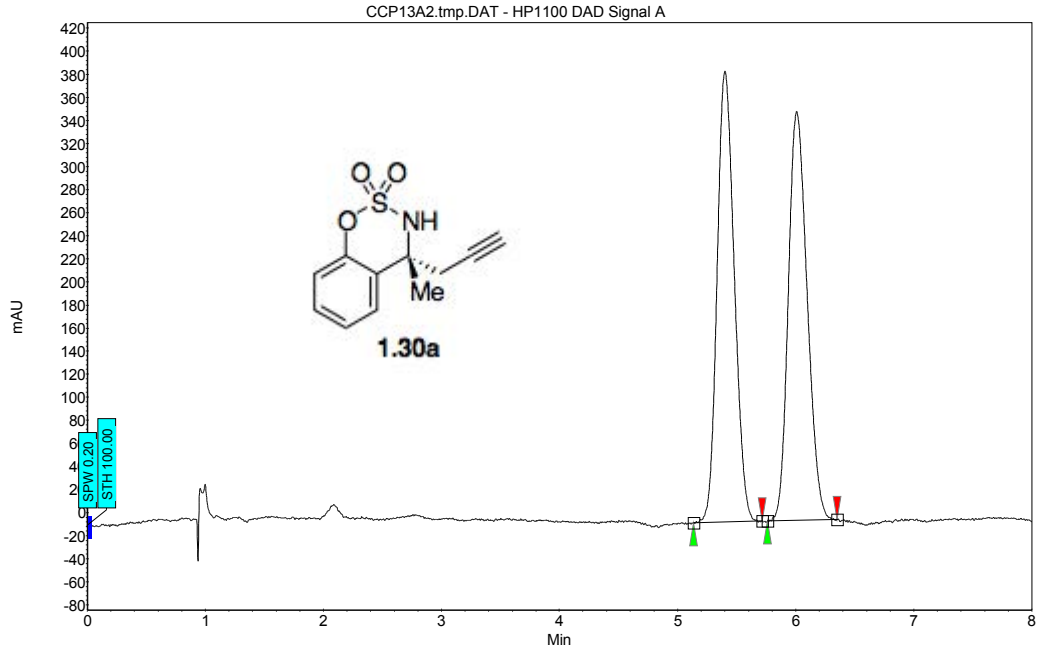
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	8.28	8.45	8.61	0.00	4.47	19.5	3.0	4.473
2	UNKNOWN	8.81	9.14	10.03	0.00	95.53	107.6	63.4	95.527
Total						100.00	127.1	66.4	100.000



1.29a

Method Name:TBDE-propargyl-allenyl-mix-6-mem-methylketimine
Run Name:TBDE-I-172-retry-adh1

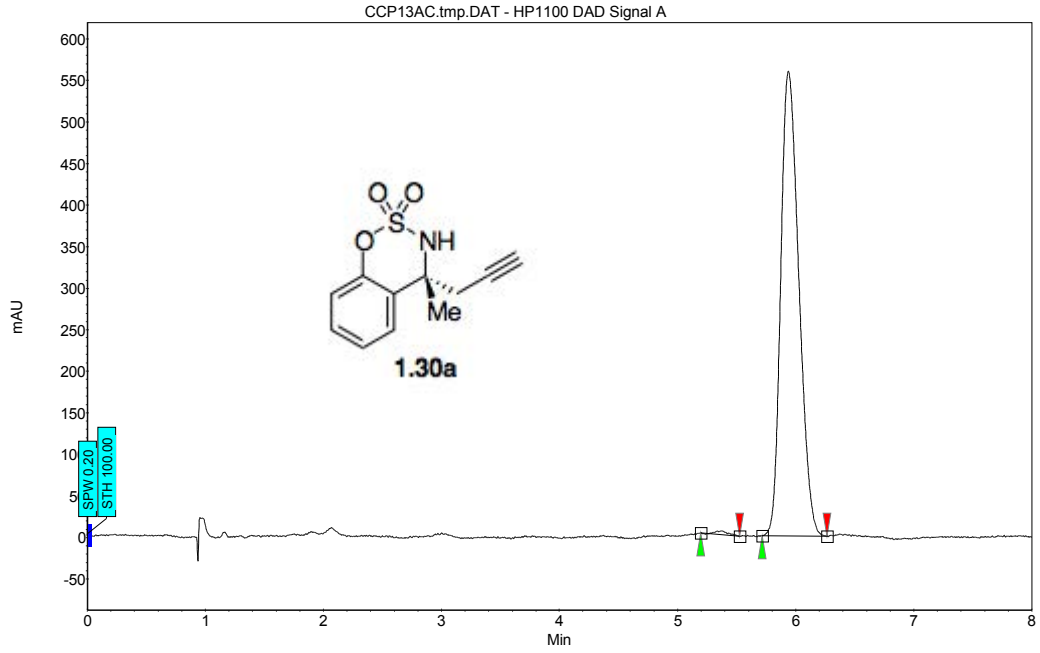
Date:5/11/2015
Time:9:28:13 AM



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	5.14	5.40	5.71	0.00	50.09	391.0	65.7	50.092
2	UNKNOWN	5.76	6.01	6.35	0.00	49.91	354.5	65.5	49.908
Total						100.00	745.5	131.3	100.000

Method Name:TBDE-propargyl-allenyl-mix-6-mem-methylketimine
Run Name:TBDE-I-1792

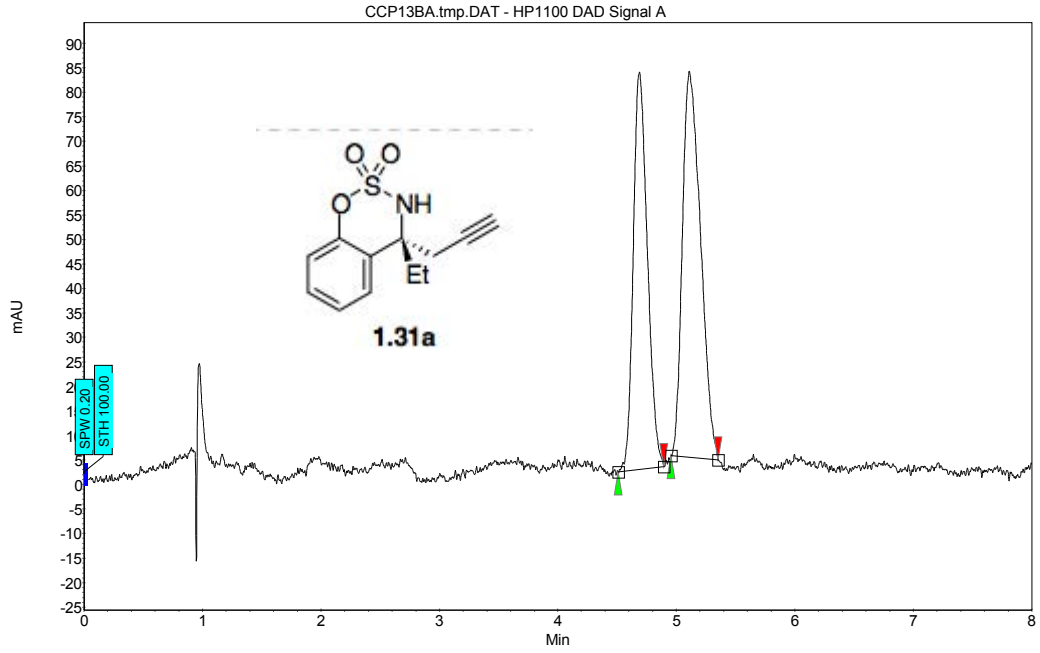
Date:5/11/2015
Time:9:32:46 AM



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	5.20	5.38	5.53	0.00	0.50	4.6	0.5	0.504
2	UNKNOWN	5.72	5.94	6.26	0.00	99.50	559.1	99.1	99.496
Total						100.00	563.7	99.6	100.000

Method Name:TBDE-propargyl-allenyl-mix-6-mem-methylketimine
Run Name:TBDE-I-1801

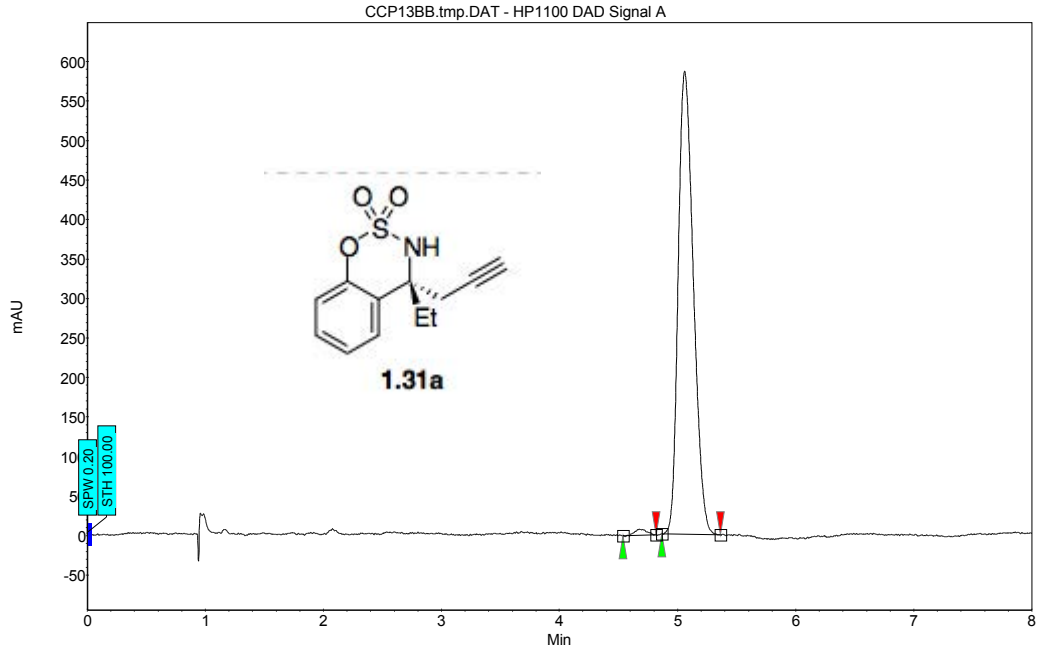
Date:5/11/2015
Time:9:45:46 AM



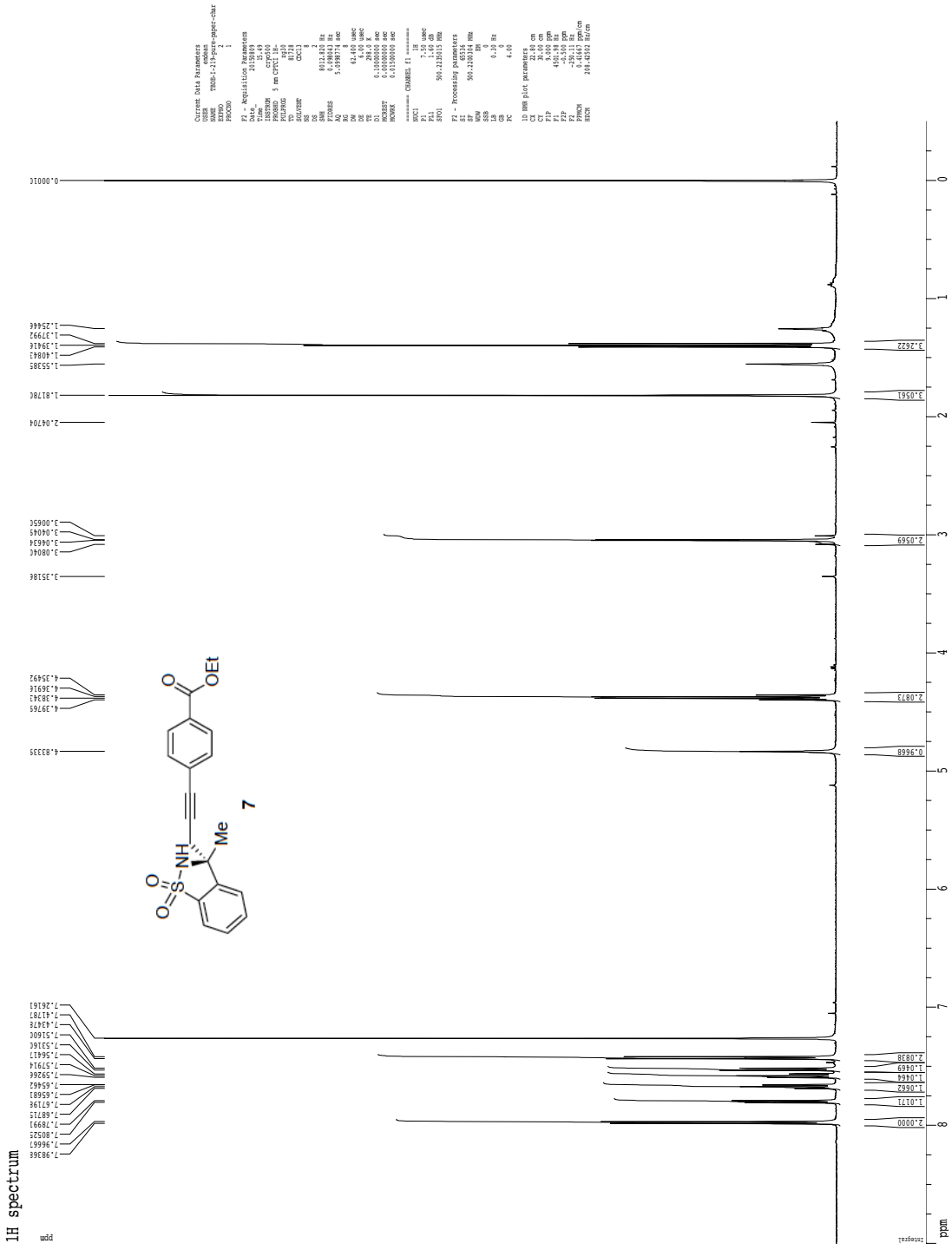
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	4.51	4.69	4.90	0.00	44.54	81.1	11.2	44.544
2	UNKNOWN	4.95	5.11	5.35	0.00	55.46	78.8	13.9	55.456
Total						100.00	159.8	25.2	100.000

Method Name:TBDE-propargyl-allenyl-mix-6-mem-methylketimine
Run Name:TBDE-I-1811

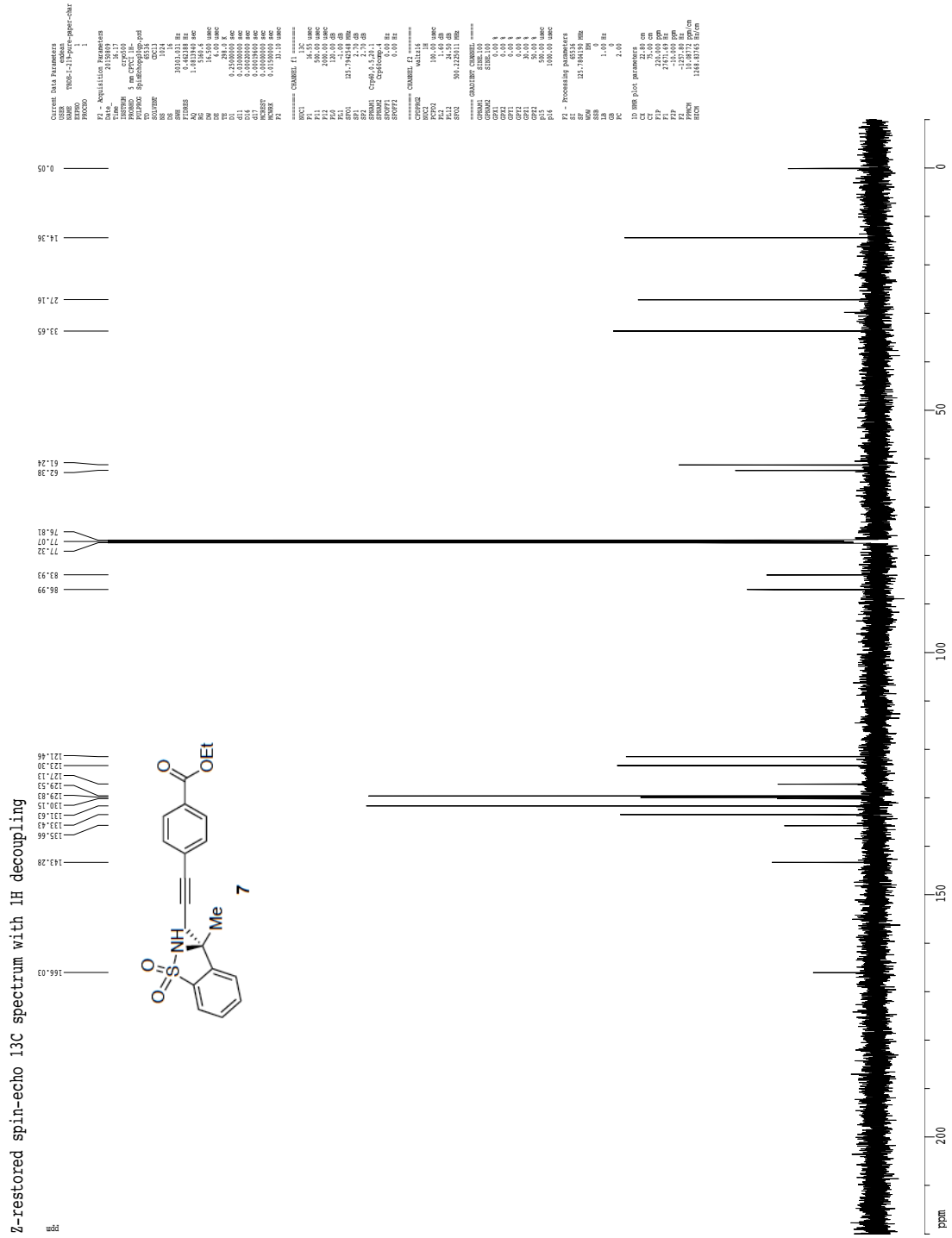
Date:5/11/2015
Time:9:52:47 AM

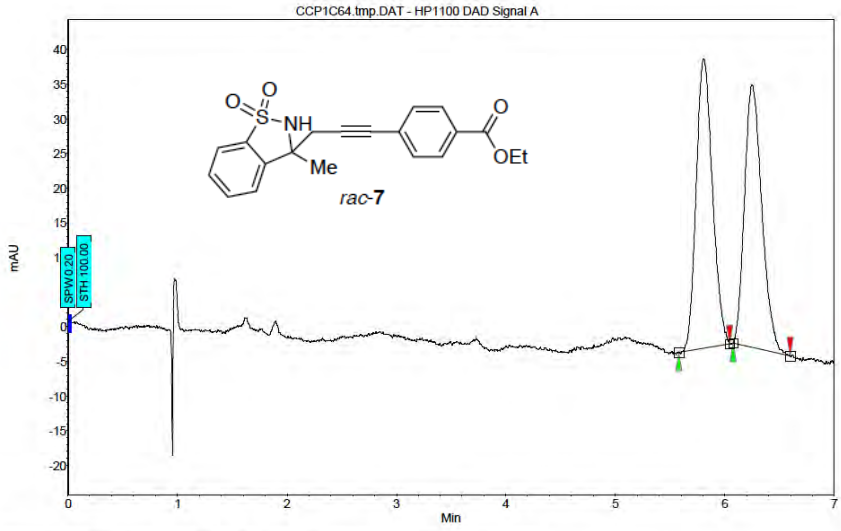


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	4.54	4.68	4.82	0.00	0.96	7.7	0.8	0.956
2	UNKNOWN	4.87	5.06	5.36	0.00	99.04	586.0	87.2	99.044
Total						100.00	593.8	88.1	100.000

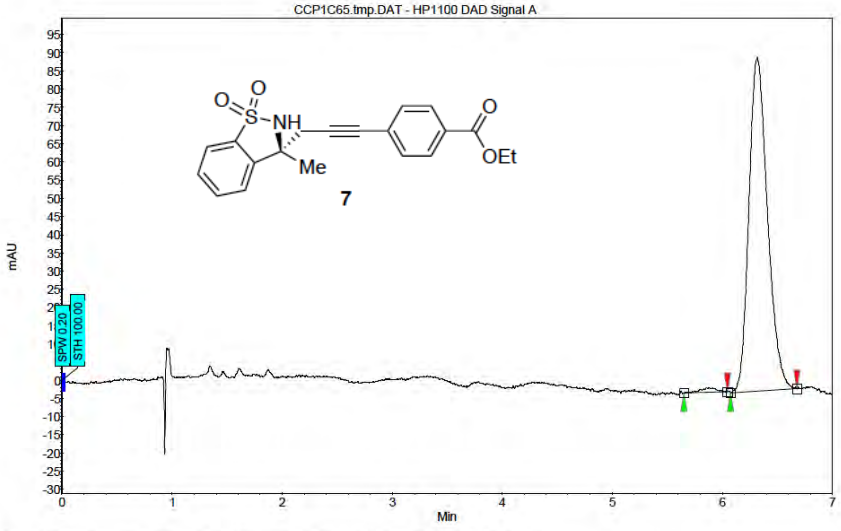

1H spectrum
OEt
O
NH
Me
7

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





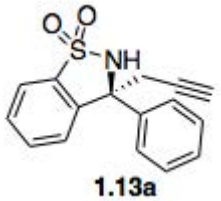
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	5.58	5.81	6.04	0.00	50.72	41.7	7.2	50.722
2	UNKNOWN	6.07	6.25	6.60	0.00	49.28	37.8	7.0	49.278
Total						100.00	79.5	14.1	100.000



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	5.65	5.86	6.04	0.00	1.09	1.3	0.2	1.091
2	UNKNOWN	6.07	6.32	6.68	0.00	98.91	91.6	17.9	98.909
Total						100.00	92.9	18.1	100.000

X-ray Data Collection, Structure Solution and Refinement for 1.13a:

CCDC 1405841



1.13a

A single crystal was grown from Et_2O with slow diffusion of pentanes at room temperature. A colorless crystal of approximate dimensions 0.250 x 0.196 x 0.182 mm was mounted on a glass fiber and transferred to a Bruker SMART APEX II diffractometer. The APEX2[1] program package was used to determine the unit-cell parameters and for data collection (60 sec/frame scan time for a sphere of diffraction data). The raw frame data was processed using SAINT[2] and SADABS[3] to yield the reflection data file. Subsequent calculations were carried out using the SHELXTL[4] program. The diffraction symmetry was 4/*m* and the systematic absences were consistent with the tetragonal space group $P4_3$ 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[5] 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}).

At convergence, wR2 = 0.0661 and Goof = 1.065 for 233 variables refined against 3225 data (0.74 Å), R1 = 0.0269 for those 3084 data with $I > 2.0\sigma(I)$. The absolute structure was assigned by refinement of the Flack parameter[6].

References.

1. APEX2 Version 2014.9-0, Bruker AXS, Inc.; Madison, WI 2014.

2. SAINT Version 8.34a, Bruker AXS, Inc.; Madison, WI 2013.

3. Sheldrick, G. M. SADABS, Version 2014/4, Bruker AXS, Inc.; Madison, WI 2014.

4. Sheldrick, G. M. SHELXTL, Version 2014/7, Bruker AXS, Inc.; Madison, WI 2014.

5. International Tables for Crystallography 1992, Vol. C., Dordrecht: Kluwer Academic Publishers.

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

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.

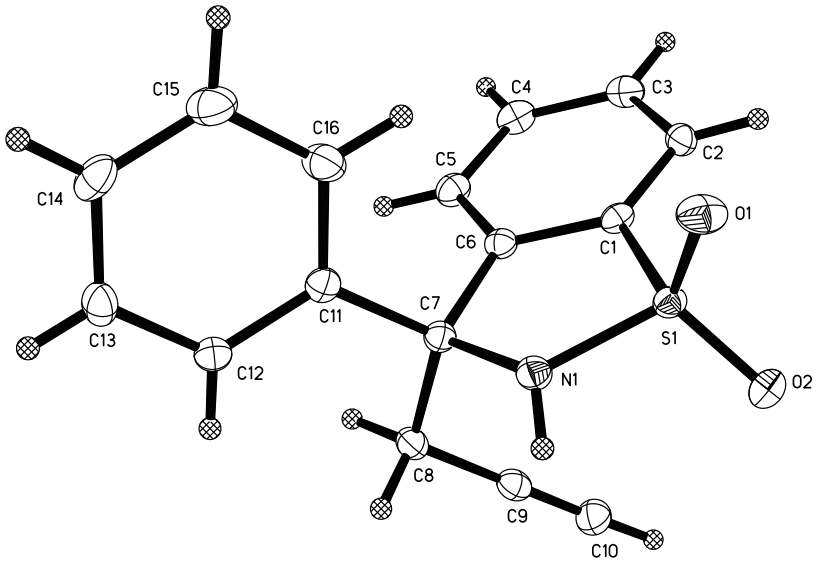

C15
C16
C14
C13
C12
C11
C4
C3
C5
C2
C6
C1
O1
C7
S1
N1
O2
C8
C9
C10

Table 1. Crystal data and structure refinement for erj21.

Identification code	erj21 (Thomas Endean)	
Empirical formula	$C_{16}H_{13}NO_2S$	
Formula weight	283.33	
Temperature	133(2) K	
Wavelength	0.71073 Å	
Crystal system	Tetragonal	
Space group	$P4_3$	
Unit cell dimensions	a = 10.7582(6) Å	a= 90°.
	b = 10.7582(6) Å	b= 90°.
	c = 11.4283(7) Å	g = 90°.
Volume	1322.70(17) $Å^3$	
Z	4	
Density (calculated)	1.423 Mg/m^3	
Absorption coefficient	0.245 mm^{-1}	
F(000)	592	
Crystal color	colorless	
Crystal size	0.250 x 0.196 x 0.182 mm^3	
Theta range for data collection	1.893 to 28.656°	
Index ranges	$-13 \le h \le 13$, $-14 \le k \le 14$, $-14 \le l \le 15$	
Reflections collected	15344	
Independent reflections	3225 [R(int) = 0.0270]	
Completeness to theta = 25.500°	100.0 %	
Absorption correction	Numerical	
Max. and min. transmission	1.0000 and 0.9257	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3225 / 1 / 233	
Goodness-of-fit on F^2	1.065	
Final R indices [I>2sigma(I) = 3084 data]	R1 = 0.0269, wR2 = 0.0645	
R indices (all data, 0.74 Å)	R1 = 0.0295, wR2 = 0.0661	

Absolute structure parameter	-0.04(3)
Largest diff. peak and hole	0.306 and -0.185 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for erj21. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	7902(1)	4294(1)	1443(1)	13(1)
O(1)	7584(2)	5501(1)	978(1)	21(1)
O(2)	8458(2)	4312(1)	2587(1)	20(1)
N(1)	6713(2)	3349(2)	1387(2)	15(1)
C(1)	8771(2)	3469(2)	396(2)	13(1)
C(2)	9948(2)	3779(2)	-26(2)	15(1)
C(3)	10465(2)	3013(2)	-878(2)	18(1)
C(4)	9807(2)	1980(2)	-1283(2)	18(1)
C(5)	8630(2)	1691(2)	-859(2)	17(1)
C(6)	8104(2)	2453(2)	-4(2)	14(1)
C(7)	6834(2)	2280(2)	570(2)	13(1)
C(8)	6822(2)	1046(2)	1277(2)	16(1)
C(9)	7837(2)	986(2)	2134(2)	16(1)
C(10)	8653(2)	950(2)	2833(2)	20(1)
C(11)	5777(2)	2333(2)	-340(2)	14(1)
C(12)	4743(2)	1553(2)	-280(2)	16(1)
C(13)	3790(2)	1650(2)	-1105(2)	20(1)
C(14)	3859(2)	2518(2)	-2002(2)	22(1)
C(15)	4885(2)	3302(2)	-2060(2)	24(1)
C(16)	5830(2)	3214(2)	-1232(2)	21(1)

Table 3. Bond lengths [Å] and angles [°] for erj21.

S(1)-O(2)	1.4373(16)
S(1)-O(1)	1.4446(15)
S(1)-N(1)	1.6351(17)
S(1)-C(1)	1.758(2)
N(1)-C(7)	1.487(3)
N(1)-H(1)	0.81(3)
C(1)-C(6)	1.386(3)
C(1)-C(2)	1.395(3)
C(2)-C(3)	1.392(3)
C(2)-H(2)	0.91(3)
C(3)-C(4)	1.396(3)
C(3)-H(3)	0.98(3)
C(4)-C(5)	1.391(3)
C(4)-H(4)	0.94(3)
C(5)-C(6)	1.395(3)
C(5)-H(5)	0.90(3)
C(6)-C(7)	1.527(3)
C(7)-C(11)	1.542(3)
C(7)-C(8)	1.554(3)
C(8)-C(9)	1.469(3)
C(8)-H(8A)	0.94(2)
C(8)-H(8B)	1.01(3)
C(9)-C(10)	1.187(3)
C(10)-H(10)	0.93(4)
C(11)-C(16)	1.393(3)
C(11)-C(12)	1.395(3)
C(12)-C(13)	1.397(3)
C(12)-H(12)	0.89(3)

C(13)-C(14)	1.388(3)
C(13)-H(13)	0.87(3)
C(14)-C(15)	1.391(3)
C(14)-H(14)	0.90(3)
C(15)-C(16)	1.392(3)
C(15)-H(15)	0.92(4)
C(16)-H(16)	0.95(3)

O(2)-S(1)-O(1)	114.86(10)
O(2)-S(1)-N(1)	111.71(10)
O(1)-S(1)-N(1)	111.03(10)
O(2)-S(1)-C(1)	113.88(9)
O(1)-S(1)-C(1)	109.23(9)
N(1)-S(1)-C(1)	94.34(9)
C(7)-N(1)-S(1)	115.92(13)
C(7)-N(1)-H(1)	116.9(19)
S(1)-N(1)-H(1)	112(2)
C(6)-C(1)-C(2)	122.99(19)
C(6)-C(1)-S(1)	110.32(15)
C(2)-C(1)-S(1)	126.66(16)
C(3)-C(2)-C(1)	117.60(19)
C(3)-C(2)-H(2)	118.0(16)
C(1)-C(2)-H(2)	124.4(16)
C(2)-C(3)-C(4)	120.00(19)
C(2)-C(3)-H(3)	119.5(16)
C(4)-C(3)-H(3)	120.5(16)
C(5)-C(4)-C(3)	121.6(2)
C(5)-C(4)-H(4)	119.2(19)
C(3)-C(4)-H(4)	119.2(19)
C(4)-C(5)-C(6)	118.9(2)

C(4)-C(5)-H(5)	121(2)
C(6)-C(5)-H(5)	120(2)
C(1)-C(6)-C(5)	118.95(18)
C(1)-C(6)-C(7)	114.70(17)
C(5)-C(6)-C(7)	126.34(18)
N(1)-C(7)-C(6)	104.68(15)
N(1)-C(7)-C(11)	109.29(16)
C(6)-C(7)-C(11)	111.43(16)
N(1)-C(7)-C(8)	109.52(16)
C(6)-C(7)-C(8)	109.54(16)
C(11)-C(7)-C(8)	112.11(16)
C(9)-C(8)-C(7)	112.23(17)
C(9)-C(8)-H(8A)	106.2(15)
C(7)-C(8)-H(8A)	111.0(14)
C(9)-C(8)-H(8B)	111.6(14)
C(7)-C(8)-H(8B)	109.0(14)
H(8A)-C(8)-H(8B)	106.7(19)
C(10)-C(9)-C(8)	179.2(2)
C(9)-C(10)-H(10)	178(2)
C(16)-C(11)-C(12)	118.56(19)
C(16)-C(11)-C(7)	119.24(18)
C(12)-C(11)-C(7)	122.16(19)
C(11)-C(12)-C(13)	120.5(2)
C(11)-C(12)-H(12)	121.3(17)
C(13)-C(12)-H(12)	118.2(17)
C(14)-C(13)-C(12)	120.6(2)
C(14)-C(13)-H(13)	119(2)
C(12)-C(13)-H(13)	120(2)
C(13)-C(14)-C(15)	119.1(2)
C(13)-C(14)-H(14)	121.6(18)

C(15)-C(14)-H(14)	119.3(18)
C(14)-C(15)-C(16)	120.4(2)
C(14)-C(15)-H(15)	124(2)
C(16)-C(15)-H(15)	116(2)
C(15)-C(16)-C(11)	120.9(2)
C(15)-C(16)-H(16)	120.1(16)
C(11)-C(16)-H(16)	119.0(16)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for erj21. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	16(1)	12(1)	12(1)	0(1)	0(1)	1(1)
O(1)	30(1)	14(1)	20(1)	2(1)	4(1)	5(1)
O(2)	22(1)	22(1)	14(1)	-2(1)	-3(1)	-2(1)
N(1)	15(1)	16(1)	14(1)	-2(1)	3(1)	-1(1)
C(1)	15(1)	14(1)	11(1)	0(1)	-1(1)	3(1)
C(2)	14(1)	16(1)	16(1)	2(1)	-3(1)	-1(1)
C(3)	12(1)	23(1)	18(1)	4(1)	1(1)	3(1)
C(4)	19(1)	20(1)	16(1)	0(1)	1(1)	6(1)
C(5)	20(1)	16(1)	15(1)	-1(1)	0(1)	2(1)
C(6)	13(1)	14(1)	13(1)	2(1)	-1(1)	1(1)
C(7)	13(1)	15(1)	13(1)	-1(1)	1(1)	0(1)
C(8)	15(1)	15(1)	17(1)	2(1)	0(1)	-2(1)
C(9)	18(1)	13(1)	18(1)	1(1)	2(1)	-1(1)
C(10)	22(1)	20(1)	19(1)	2(1)	-2(1)	-1(1)
C(11)	13(1)	17(1)	13(1)	-2(1)	2(1)	2(1)
C(12)	17(1)	18(1)	14(1)	0(1)	2(1)	0(1)
C(13)	13(1)	25(1)	20(1)	-4(1)	1(1)	-1(1)
C(14)	16(1)	32(1)	16(1)	-2(1)	-3(1)	6(1)
C(15)	22(1)	30(1)	21(1)	9(1)	0(1)	3(1)
C(16)	17(1)	24(1)	22(1)	6(1)	1(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for erj21.

	x	y	z	U(eq)
H(1)	6440(30)	3200(20)	2030(30)	20(7)
H(2)	10390(20)	4460(20)	210(20)	14(6)
H(3)	11290(30)	3210(20)	-1190(30)	22(7)
H(4)	10170(30)	1470(30)	-1850(30)	34(8)
H(5)	8220(30)	1010(30)	-1120(30)	34(8)
H(8A)	6080(20)	960(20)	1700(20)	11(6)
H(8B)	6850(20)	320(20)	710(20)	13(6)
H(10)	9310(30)	910(30)	3360(30)	46(9)
H(13)	3150(30)	1150(30)	-1080(30)	24(7)
H(14)	3250(30)	2590(30)	-2540(30)	23(7)
H(15)	5000(30)	3890(30)	-2640(30)	42(9)
H(16)	6510(30)	3780(30)	-1250(20)	22(7)
H(12)	4680(20)	970(30)	270(30)	20(6)

Table 6. Torsion angles [°] for erj21.

O(2)-S(1)-N(1)-C(7)	-117.33(15)
O(1)-S(1)-N(1)-C(7)	113.04(15)
C(1)-S(1)-N(1)-C(7)	0.52(16)
O(2)-S(1)-C(1)-C(6)	116.77(15)
O(1)-S(1)-C(1)-C(6)	-113.34(15)
N(1)-S(1)-C(1)-C(6)	0.71(16)
O(2)-S(1)-C(1)-C(2)	-65.2(2)
O(1)-S(1)-C(1)-C(2)	64.6(2)
N(1)-S(1)-C(1)-C(2)	178.70(19)
C(6)-C(1)-C(2)-C(3)	-0.8(3)
S(1)-C(1)-C(2)-C(3)	-178.56(16)
C(1)-C(2)-C(3)-C(4)	0.3(3)
C(2)-C(3)-C(4)-C(5)	0.2(3)
C(3)-C(4)-C(5)-C(6)	-0.3(3)
C(2)-C(1)-C(6)-C(5)	0.8(3)
S(1)-C(1)-C(6)-C(5)	178.84(15)
C(2)-C(1)-C(6)-C(7)	-179.80(18)
S(1)-C(1)-C(6)-C(7)	-1.7(2)
C(4)-C(5)-C(6)-C(1)	-0.2(3)
C(4)-C(5)-C(6)-C(7)	-179.56(19)
S(1)-N(1)-C(7)-C(6)	-1.5(2)
S(1)-N(1)-C(7)-C(11)	-120.91(16)
S(1)-N(1)-C(7)-C(8)	115.92(16)
C(1)-C(6)-C(7)-N(1)	2.0(2)
C(5)-C(6)-C(7)-N(1)	-178.63(19)
C(1)-C(6)-C(7)-C(11)	120.00(19)
C(5)-C(6)-C(7)-C(11)	-60.6(3)
C(1)-C(6)-C(7)-C(8)	-115.36(19)

C(5)-C(6)-C(7)-C(8)	64.0(3)
N(1)-C(7)-C(8)-C(9)	-59.2(2)
C(6)-C(7)-C(8)-C(9)	55.0(2)
C(11)-C(7)-C(8)-C(9)	179.28(17)
N(1)-C(7)-C(11)-C(16)	74.1(2)
C(6)-C(7)-C(11)-C(16)	-41.1(2)
C(8)-C(7)-C(11)-C(16)	-164.25(19)
N(1)-C(7)-C(11)-C(12)	-103.7(2)
C(6)-C(7)-C(11)-C(12)	141.10(19)
C(8)-C(7)-C(11)-C(12)	17.9(3)
C(16)-C(11)-C(12)-C(13)	0.6(3)
C(7)-C(11)-C(12)-C(13)	178.41(19)
C(11)-C(12)-C(13)-C(14)	0.4(3)
C(12)-C(13)-C(14)-C(15)	-0.8(3)
C(13)-C(14)-C(15)-C(16)	0.2(3)
C(14)-C(15)-C(16)-C(11)	0.8(4)
C(12)-C(11)-C(16)-C(15)	-1.2(3)
C(7)-C(11)-C(16)-C(15)	-179.1(2)

Table 7. Hydrogen bonds for erj21 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)

Chapter 2

Work Towards a Kinetic Understanding of a Nickel-Catalyzed Ring Contraction to Furnish Cyclopropanes

2.1 Introduction:

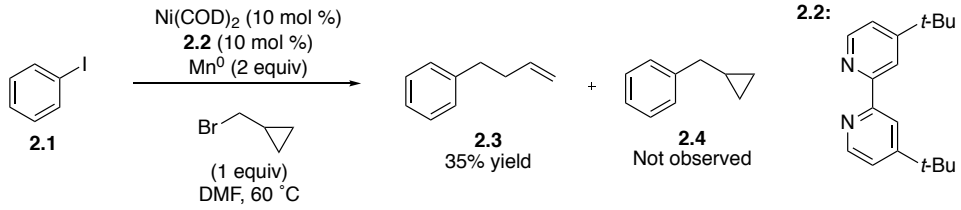
Nickel-catalyzed reductive cross-electrophile couplings have recently undergone rapid advances in both method development and mechanistic understanding.[1] With any reaction a deep understanding of the mechanism can allow for rational experimental design and expansion of reactivity. Cross-electrophile coupling reactions are no exception to this principle. Kinetic experiments are often used to analyze the reaction and determine the reaction order and identify the rate-determining step of the catalytic cycle. Utilizing this information can allow a researcher to develop catalysts that are better equipped to carry out the desired reactivity.

Various groups have investigated reaction mechanisms of cross electrophile couplings. The Weix group has reported[2] extensive kinetics studies on cross electrophile coupling reactions.[3] They have found that several of these reactions go through a radical polar crossover

[1] (a) Weix,D. *Acc. Chem. Res.* **2015**, *48*, 1767. (b) Knappke, E. I.; Grupe, G.; Gartner, D.; Corpet, M.; Gosmini, C.; Wangelin, A. J. V. *Chem. Eur. J.* **2014**, *20*, 6828. (c) Moragas, T.; Correa, A.; Martin, R.; *Chem. Eur. J.* **2014**, *20*, 8242.
[2] Ackerman, L. K. G.; Anka-Lufford, L. L.; Naodovic, M.; Weix, D. J. *Chem. Sci.* **2015**, *6*, 1115.
[3] Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192

mechanism where all four oxidation states of nickel from Ni^0 to Ni^{III} are present in the reaction. Though the all details of this mechanism are beyond the scope of this chapter, in Scheme 2.1 one of their experiments revealed that a carbon centered radical is produced at the alkyl bromide leadaing to only the formation of rearrangement product **2.3** while no non-rearranged product **2.4** was observed. The complexity of these reactions only further exemplifies the need to study them in further detail.

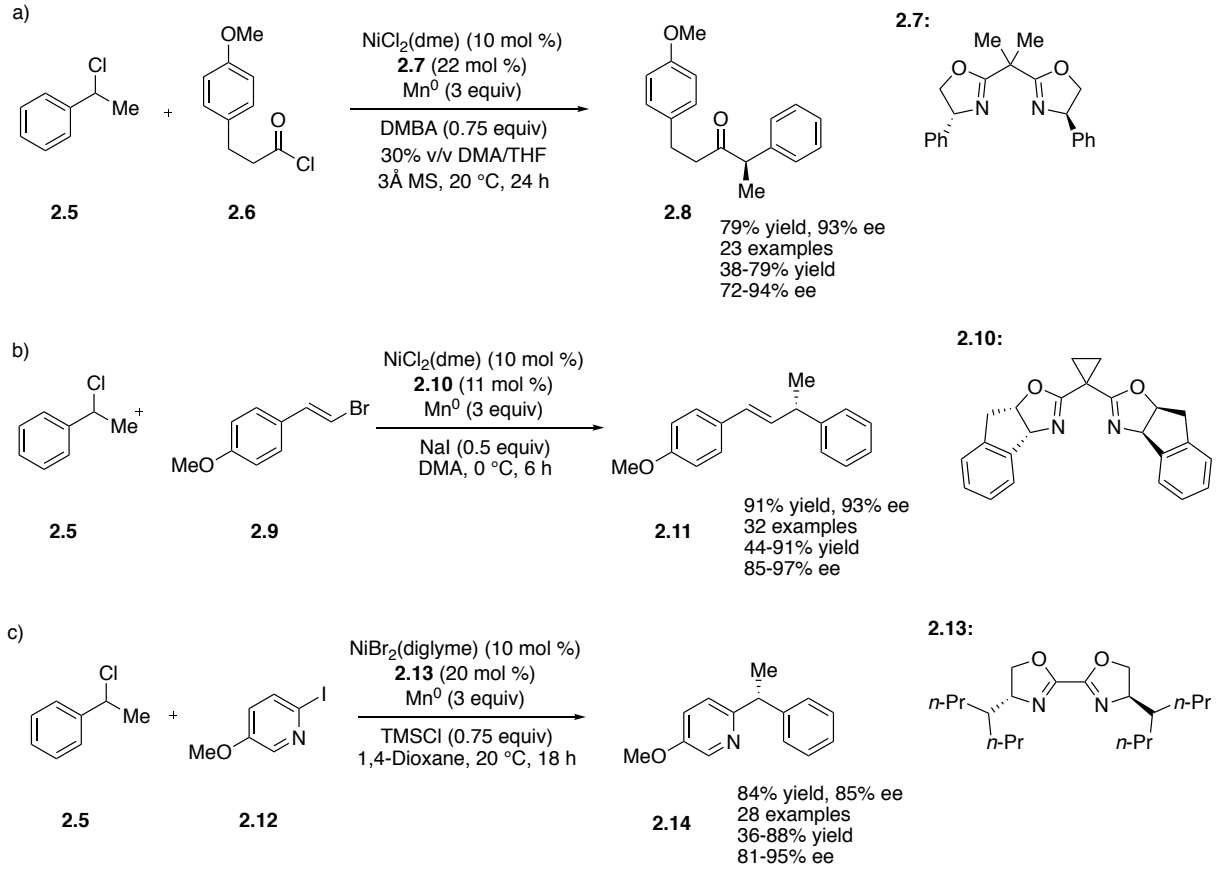
Scheme 2.1: Radical clock Experiment by the Weix group



The Riesman group also has shown many examples of nickel catalyzed reductive couplings of benzylic halides with acid chlorides (Scheme 2.2a),[4] vinyl bromides (Scheme 2.2b),[5] and heteroaromatic iodides (Scheme 2.2c)[6] that proceed through a radical pathway. These methods are stereoablative, with the ligand providing the source of enantioinduction.

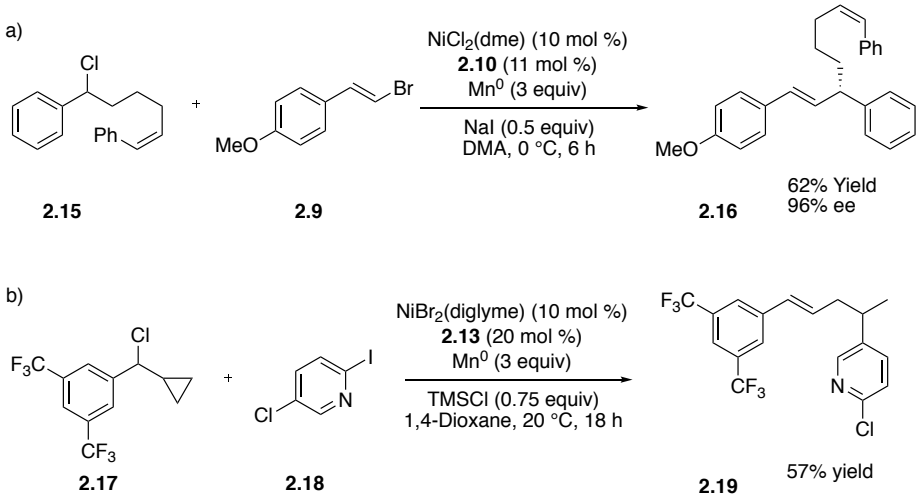
[4] Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7442.
[5] Cherney, A. H.; Reisman, S. E. *J. Am. Chem. Soc.* **2014**, *136*, 14365.
[6] Poremba, K. E.; Kadunce, N. T.; Suzuki, N.; Cherney, A. H.; Reisman, S. E. *J. Am. Chem. Soc.* **2017**, *139*, 5684.

Scheme 2.2: Cross electrophile couplings disclosed by the Riesman Group



As a part of this work the Reisman laboratory designed a few experiments to elucidate intermediates in the mechanism. For example in the reaction in Scheme 2.3a, a radical clock substrate with a pendent olefin poised for cyclization was synthesized as the benzylic halide partner and no cyclization or olefin isomerization was observed. On the other hand, in the reaction in Scheme 2.3b, a substrate with a cyclopropane radical clock was synthesized as the benzylic halide partner and in that case only the ring opened product **2.19** was observed. These two experiments show that the mechanisms of these cross-electrophile couplings are complex and not well understood.

Scheme 2.3: Radical clock experiments by the Reisman Group

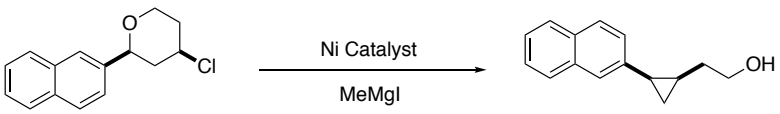


Recently the Jarvo group disclosed a stereospecific reductive ring contraction reaction to furnish arylcyclopropanes[7] or vinylcyclopropanes.[8] Because these ring contractions are highly stereospecific we would hypothesize that a radical chain mechanism is not in operation in this case. We instead propose a polar, two electron mechanism consistent with mechanisms that we propose for our stereospecific Kumada coupling reactions. In previous stereospecific cross couplings of benzylic ethers we propose oxidative addition as the rate-determining step and it generally proceeds with inversion at the benzylic center.[9] It has been shown however that this reductive ring contraction (Equation 2.1) proceeds with retention at the benzylic center and inversion at the halide.[7] While we have observed oxidative addition with retention,[10] this

[7] Tollefson, E. J.; Erickson, L. W.; Jarvo, E. R. *J. Am. Chem. Soc.* **2015**, *137*, 9760.
[8] Erickson, L. W.; Lucas, E. L.; Tollefson, E. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2016**, *138*, 14006.
[9] (a) Greene, M. A. Diastereoselective Synthesis of Seven-Membered Ring *trans*-Alkenes and Development of Stereospecific Nickel-Catalyzed Cross-Coupling Reactions. Ph.D. Dissertation, University of California, Irvine, Irvine, CA, 2013. (b) Tollefson, E. J.; Hanna, L. E.; Jarvo, E. R. *Acc. Chem. Res.* **2015**, *48*, 2344.
[10] Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303.

diversion from the general reactivity pattern provides for an interesting study of the reaction mechanism at work here.

Equation 2.1: Parent Reaction to be Investigated



2.20 **2.21**

One priority in any investigation of a reaction mechanism is to discern the rate law for the reaction being studied. The rate law describes the stoichiometry of all the reagents that are involved in the slow step of the reaction. The rate law can be defined in this situation as such shown in Equation 2.2. Our working hypothesis is that both the starting material (**2.20**) and the nickel catalyst will be first order (a and b = 1) and the Grignard reagent will be zero order (c = 0) for this reaction. We would also expect magnesium iodide to be non-zero and positive (d > 0) because previously we have observed a non-zero dependence on magnesium iodide.[9] This would mean that the slow step only involves one molecule of active catalyst and one molecule of starting material. This hypothesis is based on evidence that the rate-determining step for this reaction is the oxidative addition by the nickel catalyst into the benzylic carbon-oxygen bond.[11]

Equation 2.2: Rate Law for the Parent Reaction

$$\frac{d[\mathbf{2.20}]}{dt} = k[\mathbf{2.21}]^a[Ni]^b[MeMgI]^c[MgI_2]^d$$

Kinetics measurements were performed under pseudo-first-order conditions. Reaction progress was monitored by appearance of product **2.21**, which was determined by gas chromatography with dodecane as internal standard. Reactions were monitored to 20–40% completion where a plot of [**2.21**] vs. time provides a straight line, the slope of which is equal to

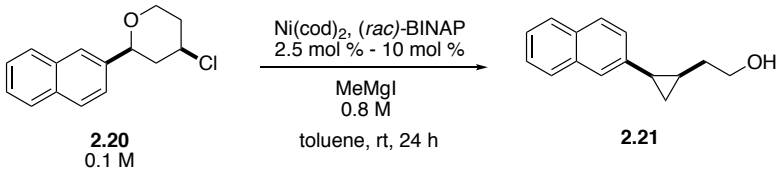
[11] Tollefson, E. J. Development of Stereospecific Nickel-Catalyzed Cross-Coupling Reactions. Ph.D. Dissertation, University of California, Irvine, Irvine, CA, 2016.

the initial rate of the reaction. Plotting this initial rate against the component of the reaction that is being varied will give data on the order of that component. If the slope of the line is zero the kinetic order of that component is zero. If the slope of the line is positive and linear the order of that component is first order. And finally if the slope of the line is positive and quadratic the order of that component is second order.

2.2 Results and Discussion:

Initial efforts for determining the rate law were focused on finding the order in the nickel catalyst. The order in nickel was investigated by running five simultaneous reactions at a one-millimole scale with different concentrations of nickel catalyst in triplicate (Equation 2.3).[12]

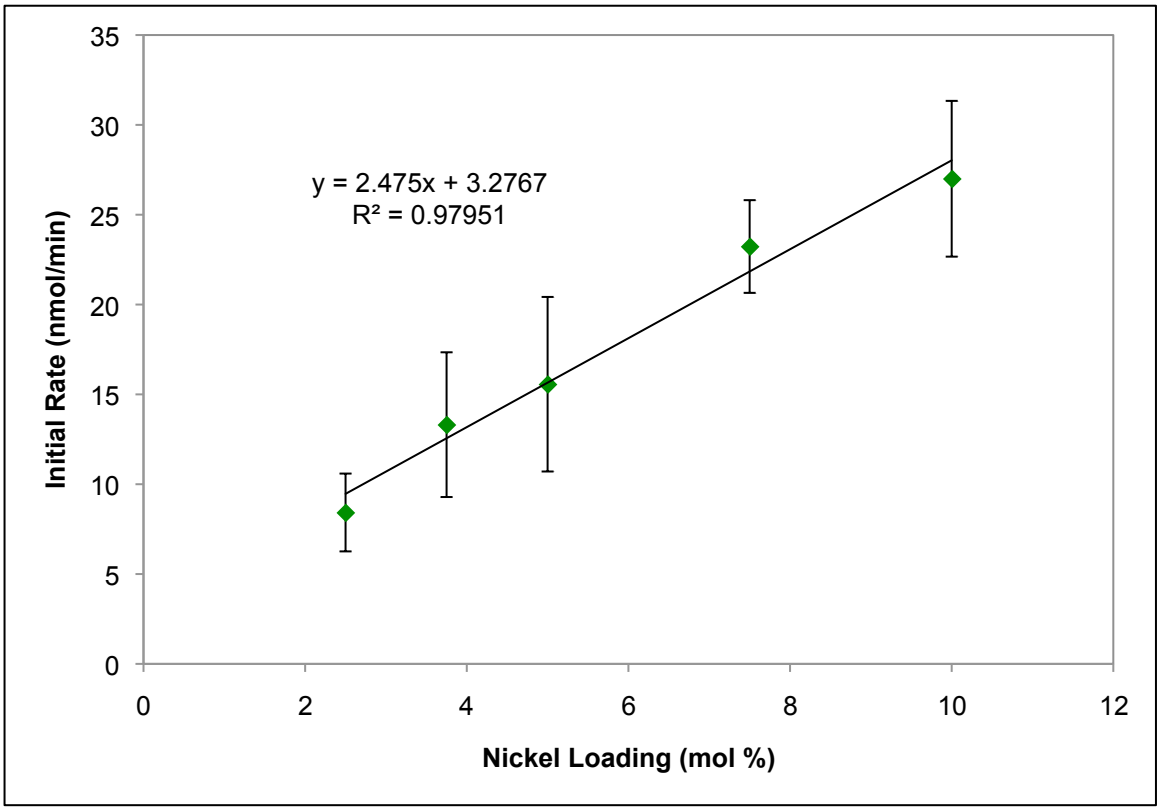
Equation 2.3: Initial Nickel Catalyst Analysis



The reaction was monitored by gas chromatography and the yield of product at various time points was calculated using an internal standard. This yield was then used to calculate the initial rate of the reaction. Plotting the initial rate of the reaction against the catalyst loading showed a linear relationship consistent with a first order dependence on nickel (Figure 2.1)

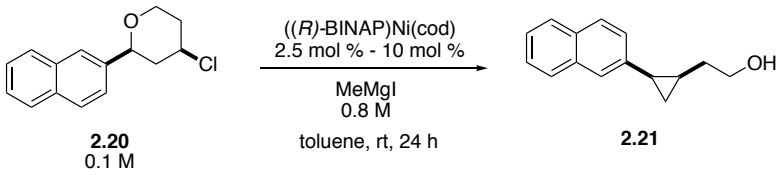
[12] $Ni(cod)_2$ was used as the pre-catalyst and *rac*-BINAP was used as the ligand in a 1:1 ratio

Figure 2.1: Plot Depicting Linear Dependence of Initial Rate on $[Ni]_{initial}$



While the trend here shows first order dependence on nickel but the error in the data is unacceptable to form an accurate picture of the true rate law. This error was attributed to the variability in weighing out separate nickel and ligand into each flask. To try to solve this problem utilization of a preformed nickel catalyst would be utilized (Equation 2.4).

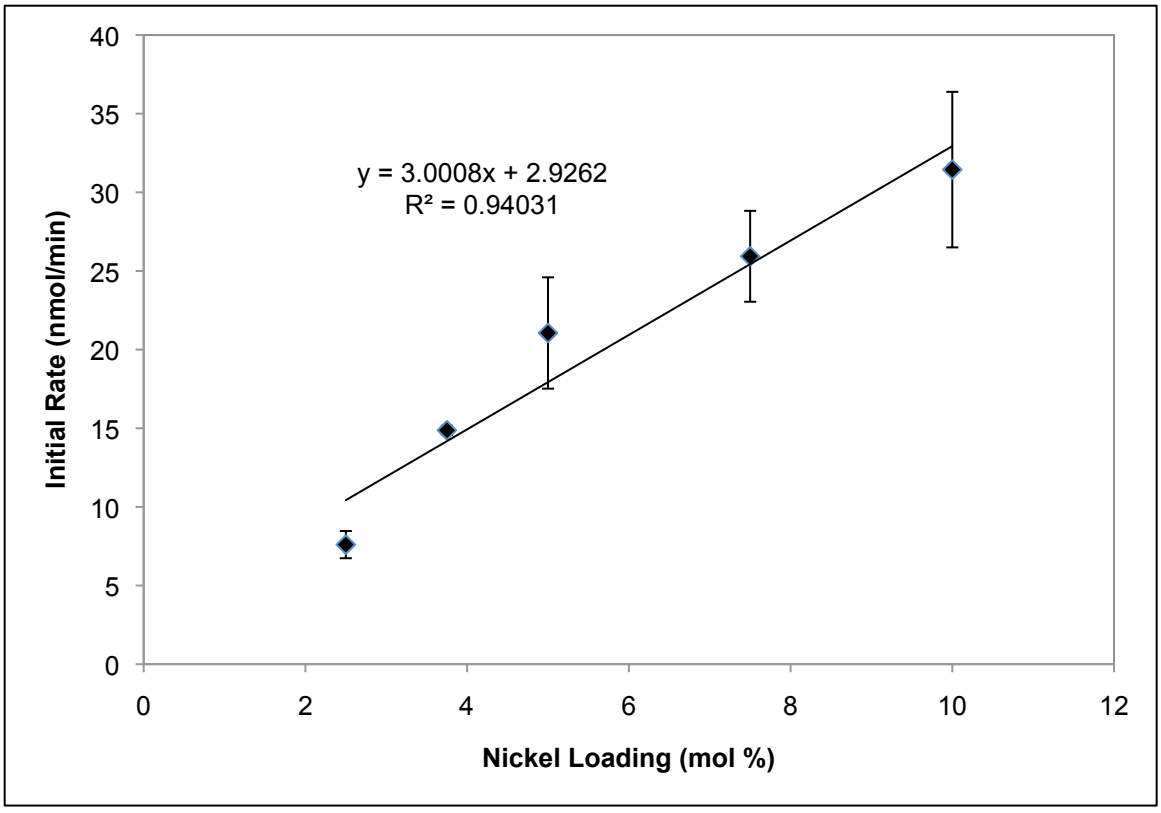
Equation 2.4: Preformed Nickel Catalyst Analysis



The trend with these data as well seemed to be close to linear but also looked as though it could be displaying saturation kinetics (Figure 2.2). The error bars for these data are also unacceptable for publication but they are not as wide as previous. The trend here is between

saturation kinetics and first order kinetics. Because the nickel loading is so low (2.5 mol% and 3.75 mol%) for the lowest two concentrations of nickel it is possible that quenching of the nickel by oxygen, water, or some other contaminant slowed these reactions giving the appearance of saturation kinetics. Also it has been shown that in the absence of cyclooctadiene, catalyst decomposition is rapid.[9] While there is still cyclooctadiene present in this reaction, the large excess of Grignard reagent could lead to catalyst decomposition. However, even with all of this taken into account, the error bars for the higher nickel loading reactions were too large to continue with this project.

Figure 2.2: Plot Depicting Linear Dependence of Initial Rate on Preformed $[Ni]_{initial}$



Concurrently with the investigation into the order with respect to nickel, the rate dependence on concentration of **2.20** was also being investigated. Investigation of the

dependence on substrate concentration proved to be even more irreproducible than the examination of the nickel catalyst. The same five reactions were performed with now varying concentrations of **2.20** (Equation 2.5). All three runs are shown on the same plot (Figure 2.3).

Equation 2.5: Substrate Analysis

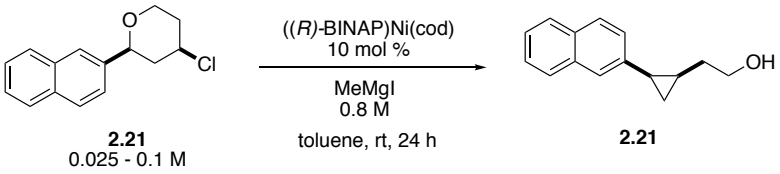
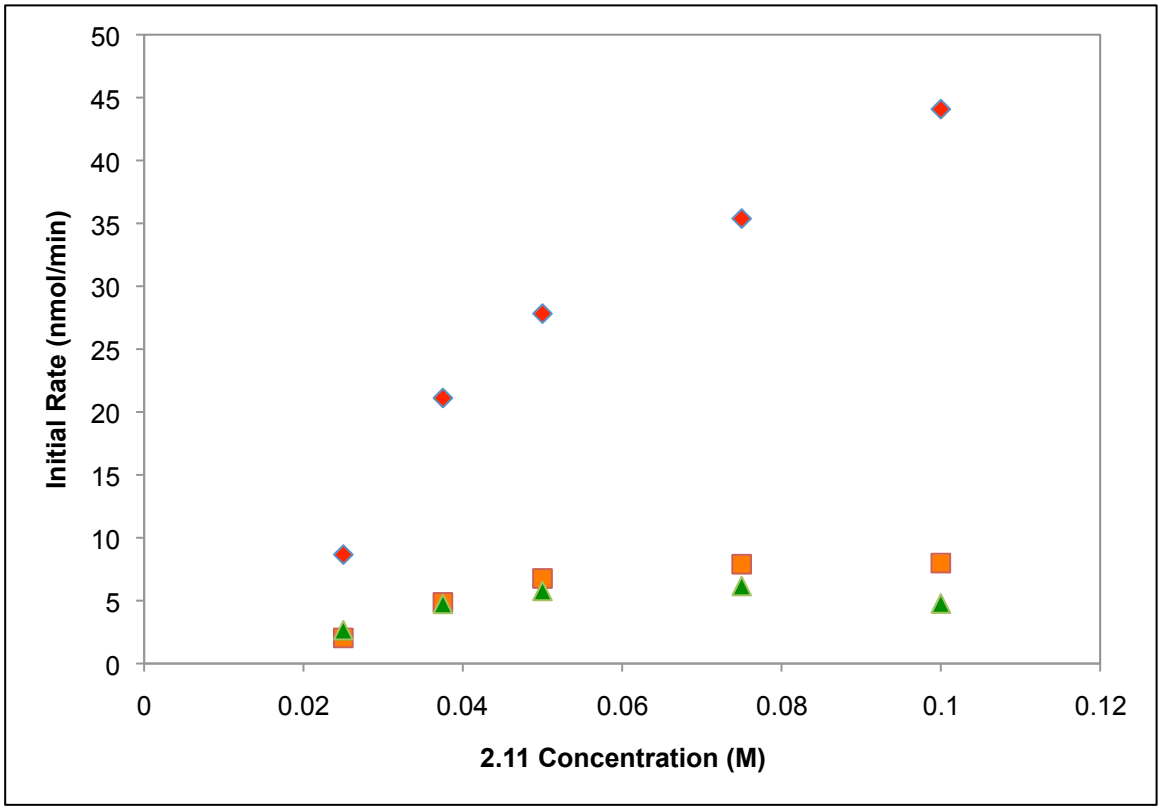


Figure 2.3: Plot Depicting Dependence of Initial Rate on [**2.20**]$_{initial}$



As can be seen here the diamond data show a positive relationship though the linearity of that relationship cannot be assigned unambiguously. The two other runs (triangles and squares) have a much smaller positive relationship with respect to substrate concentration. These

reactions did not achieve the high level of conversion that the first did. Due to this variability the order with respect to the substrate, **2.20**, could not be assigned unambiguously.

2.3 Conclusions:

Unfortunately due to irreproducibility and large error the rate law was not derived for this cross-electrophile coupling reaction. The trend from most of the data that was obtained seems to point to either our hypothesis being correct, that the reaction is first order in starting material and in catalyst, or that this reaction is subject to saturation kinetics. In the future if this question is revisited care must be taken to control for several experimental variables. One step to minimize experimental error would be to perform these reactions in a glove box and to investigate lowering the equivalents of methylmagnesium iodide to minimize catalyst decomposition while maintaining pseudo-first-order conditions.

2.4 Experimental Details:

General Procedures: All reactions were carried out under an atmosphere of N_2. All glassware was oven- or flame-dried prior to use. Ether (Et_2O) 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 organomagnesium reagents were determined by titration with iodine/LiCl.[13] ^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), 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 (δ) relative to TMS 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 (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 F254 precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$ or *p*-anisaldehyde (PAA) solutions. Flash chromatography was performed using Silica Gel 60 (170-400 mesh) from Fisher Scientific and aluminum oxide,

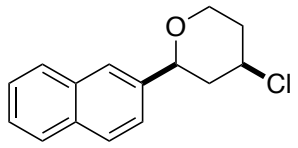
[13] Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890.

basic, Brockmann I, 50-200 μm from Acros Organics. Melting points (m.p.) were obtained using a Mel-Temp melting point apparatus and are uncorrected. High resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center.

Preparation of methylmagnesium iodide:

Under an N_2 atmosphere dry Et_2O (25 mL) to magnesium turnings (2.80 g, 115 mmol) in a 3-neck flask equipped with a reflux condenser and a Schlenk filtration apparatus. Freshly distilled iodomethane (5.00 mL, 80.3 mmol) was then added slowly (over 30 minutes) so as to maintain a gentle reflux. The mixture was stirred for two hours at room temperature then passed through a fritted Schlenk filter into a Schlenk flask under a N_2 atmosphere. The Schlenk flask was sealed and removed from the rest of the apparatus. The resulting Grignard reagent was typically between 2.5 and 3.5 M as titrated using Knochel's method.[13]

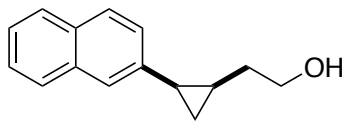
Synthesis of starting material:[7]



***cis-(±)*-4-chloro-2-(naphthalen-2-yl)tetrahydro-2*H*-pyran (2.20):** Zinc dichloride (1.9 g, 14 mmol, 1.1 equiv) was added to a flame-dried flask equipped with a stir bar and then flame-dried again under vacuum. *p*-Toluene sulfonic acid monohydrate (2.5 g, 13 mmol, 1.0 equiv) and anhydrous CH_2Cl_2 (100 mL) were added and the reaction mixture was set to stir at ambient temperature. To a separate flame-dried flask was added aldehyde 2-naphthaldehyde (2.1 g, 13 mmol, 1.0 equiv). Anhydrous CH_2Cl_2 (20 mL) and 3-buten-1-ol (1.3 mL, 15 mmol, 1.1 equiv)

were added and the mixture was stirred for 5 min at room temperature. The aldehyde solution was added to the $ZnCl_2$ solution and the reaction mixture was allowed to stir at room temperature for 18 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and was extracted with CH_2Cl_2 (x 3). 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 (10% EtOAc/hexanes) to afford the title compound as a white solid (2.6 g, 16 mmol, 80%, >20:1 cis:trans dr). The dr was determined based on the integration of the benzylic methines in the ^1H NMR spectrum. m.p. 62–64 °C; TLC R_f = 0.6 (20% EtOAc/hexanes); ^1H NMR (500 MHz, CDCl3) δ 7.85–7.80 (m, 4H), 7.49–7.44 (m, 3H), 4.50 (dd, J = 11.3, 2.0, 1H), 4.26–4.18 (m, 2H), 3.66 (td, J = 12.2, 2.1, 1H), 2.49–2.45 (m, 1H), 2.23–2.18 (m, 1H), 2.09–1.95 (m, 2H); ^{13}C NMR (125.7 MHz, CDCl3) δ 138.8, 133.4, 133.1, 128.4, 128.1, 127.8, 126.3, 126.1, 124.7, 124.0, 79.5, 67.6, 55.9, 44.7, 37.0; IR (neat) 3059, 2956, 2927, 2853, 1601, 1505, 1445 cm-1; HRMS (TOF MS ES+) m / z calcd for $C_{15}H_{15}ClONa$ (M + Na)+ 253.1205, found 253.1205.

General Procedure for Cross-Electrophile Coupling Reaction:[7]

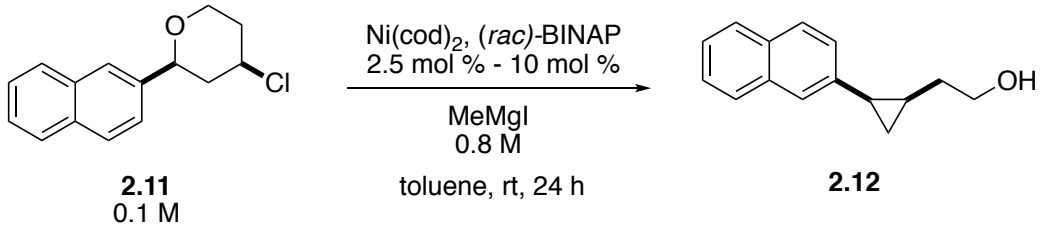


***cis-(±)-4-Chloro-2-(2-naphthyl)-tetrahydro-2H-pyran* (2.21):** In a glovebox, a flame-dried 7 mL vial equipped with a stir bar was charged with substrate **2.21** (49 mg, 0.20 mmol, 1.0 equiv, >20:1 cis:trans dr.) , $Ni(cod)_2$ (2.8 mg, 0.010 mmol, 5.0 mol %), rac-BINAP (6.9 mg, 0.011 mmol, 5.5 mol %) and PhMe (1.8 mL). Methylmagnesium iodide (0.16 mL, 0.42 mmol, 2.6 M in Et_2O, 2.1 equiv) was then added dropwise over a minute. After 24 h the reaction was removed from the glovebox, quenched with isopropyl alcohol, filtered through a plug of silica gel (neat

Et2O), and concentrated in vacuo. The compound was purified by flash column chromatography (20% EtOAc/hexanes) to yield the title compound as a pale tan oil (40. mg, 0.19 mmol, 94%, >20:1 cis:trans dr). The dr was determined based on the integration of the benzylic methines in the ^{1}H NMR spectrum. TLC R_f = 0.3 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80–7.73 (m, 3H), 7.56 (s, 1H), 7.46–7.36 (m, 3H), 3.57–3.52 (m, 2H), 2.30 (aq, J = 8.3, 1H), 1.43–1.38 (m, 1H), 1.27–1.19 (m, 3H), 1.12–1.07 (m, 1H), 0.90–0.86 (m, 1H); ^{13}C NMR (125.7 MHz, CDCl3) δ 136.9, 133.5, 132.2, 128.3, 127.7, 127.60, 127.57, 126.8, 126.1, 125.3, 63.0, 31.8, 20.9, 16.0, 9.4; IR (neat) 3328, 3052, 2999, 2928, 1721, 1631, 1600, 1505 cm-1; HRMS (TOF MS ES+) m / z calcd for $C_{15}H_{16}ONa$ (M + Na)+ 235.1099, found 235.1098.

Procedures for Kinetic Studies:

Description of conditions for determining order with respect to the nickel catalyst.



The protocol for the 10 mol % run exemplifies the experimental procedure for all kinetic experiments where the nickel catalyst and ligand are varied. All kinetics runs were performed in a nitrogen atmosphere on a Schlenk manifold. To a flame-dried 25 mL round bottom flask was added **2.20** (246 mg, 1.00 mmol, 1 equiv), $Ni(cod)_2$ (27.5 mg, 0.100 mmol, 10.0 mol %.), (*rac*)-BINAP (62.3 mg, 0.100 mmol, 10.0 mol %). To a separate flame-dried vial dodecane (0.227 mL, 1.00 mmol, 1 equiv) was added and diluted to 6.9 mL total volume with Toluene (6.7 mL). This stock solution of dodecane was added to the flask containing the catalyst system and **2.20** with a flame-dried Teflon coated stir bar. The reaction flask was sealed and removed from the

glovebox and placed on a Schlenk manifold under N_2 atmosphere. Methylmagneisum Iodide (3.1 mL, 8.0 mmol, 2.6 M in Et_2O) was added to the flask to reach a final volume of 10 mL at time equal zero. The reaction was monitored by removing 100 µL aliquots and quenching with 100 µL of isopropanol at the time periods shown in Table 2.1.

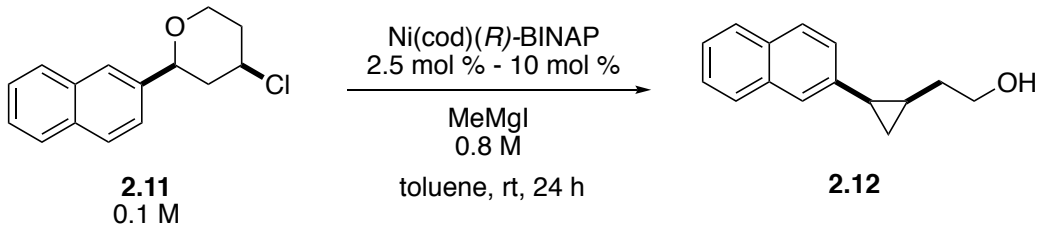
Table 2.1: *Nickel catalyst (10 mol %) reaction monitored by formation of product* ***2.21***

	Time (min)	µmol **2.21**	% Yield **2.21**
1	195	1.2	6.0
2	277	2.4	12.0
3	360	3.9	19.5
4	455	5.6	27.8
5	540	8.5	42.4

Table 2.2: *Summary of data for determination of order of nickel catalyst. Average and standard deviation is given which were used to create Figure 2.1*

	Initial Rate (nM/min)				
Catalyst Loading	Run 1	Run 2	Run 3	Average	Std Dev
10 mol %	31.9	23.6	25.5	27.0	4.3
7.5 mol %	20.4	25.4	23.9	23.2	2.6
5 mol %	20.4	10.7	15.7	15.6	4.9
3.75 mol %	9.8	17.7	12.4	13.3	4.0
2.5 mol %	10.8	8.1	6.5	8.4	2.2

Description of conditions for determining order with respect to the preformed nickel catalyst.



2.11
0.1 M

2.12

The protocol for the 10 mol % run exemplifies the experimental procedure for all kinetics runs where the nickel catalyst and ligand are varied. All kinetics runs were performed in a nitrogen atmosphere on a Schlenk manifold. To a flame-dried 25 mL round bottom flask was added **2.20** (246 mg, 1.00 mmol, 1 equiv) and Ni(cod)(*R*)-BINAP (79.0 mg, 0.100 mmol, 10.0 mol %). To a separate flame-dried vial dodecane (0.227 mL, 1.00 mmol, 1 equiv) was added and diluted to 6.9 mL total volume with toluene (6.7 mL). This stock solution of dodecane was added to the flask containing the catalyst system and **2.20** with a flame-dried Teflon coated stir bar. The reaction flask was sealed and removed from the glovebox and placed on a Schlenk manifold under N_2 atmosphere. Methyl Grignard reagent (3.1 mL, 8.0 mmol, 2.6 M in Et_2O) was added to the flask to reach a final volume of 10 mL at time equal zero. The reaction was monitored by removing 100 μL aliquots and quenching with 100 μL of isopropanol at the time periods shown in Table 2.3.

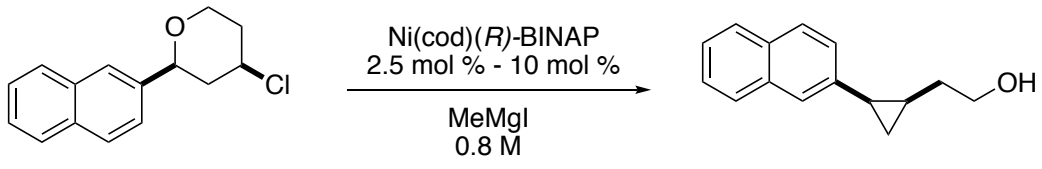
Table 2.3: *Preformed Nickel catalyst (10 mol %) reaction monitored by formation of product* ***2.21***

	Time (min)	μmol **2.21**	% Yield **2.21**
1	200	2.9	14.6
2	243	4.3	21.5
3	310	7.1	35.3
4	364	9.3	46.5
5	430	11.5	57.7
6	481	12.5	62.5

Table 2.4: *Summary of data for determination of order of nickel catalyst. Average and standard deviation is given which were used to create figure 2.2*

	Initial Rate (nM/min)				
Catalyst Loading	Run 1	Run 2	Run 3	Average	Std Dev
10 mol %	32.7	26.0	35.6	31.4	4.9
7.5 mol %	28.5	22.8	26.6	25.9	2.9
5 mol %	24.9	18.0	20.2	21.1	3.5
3.75 mol %	15.0	14.5	15.0	14.9	0.3
2.5 mol %	7.9	6.6	8.3	7.6	0.9

Description of conditions for determining order with respect to the preformed nickel catalyst.



2.11
0.1 M

2.12

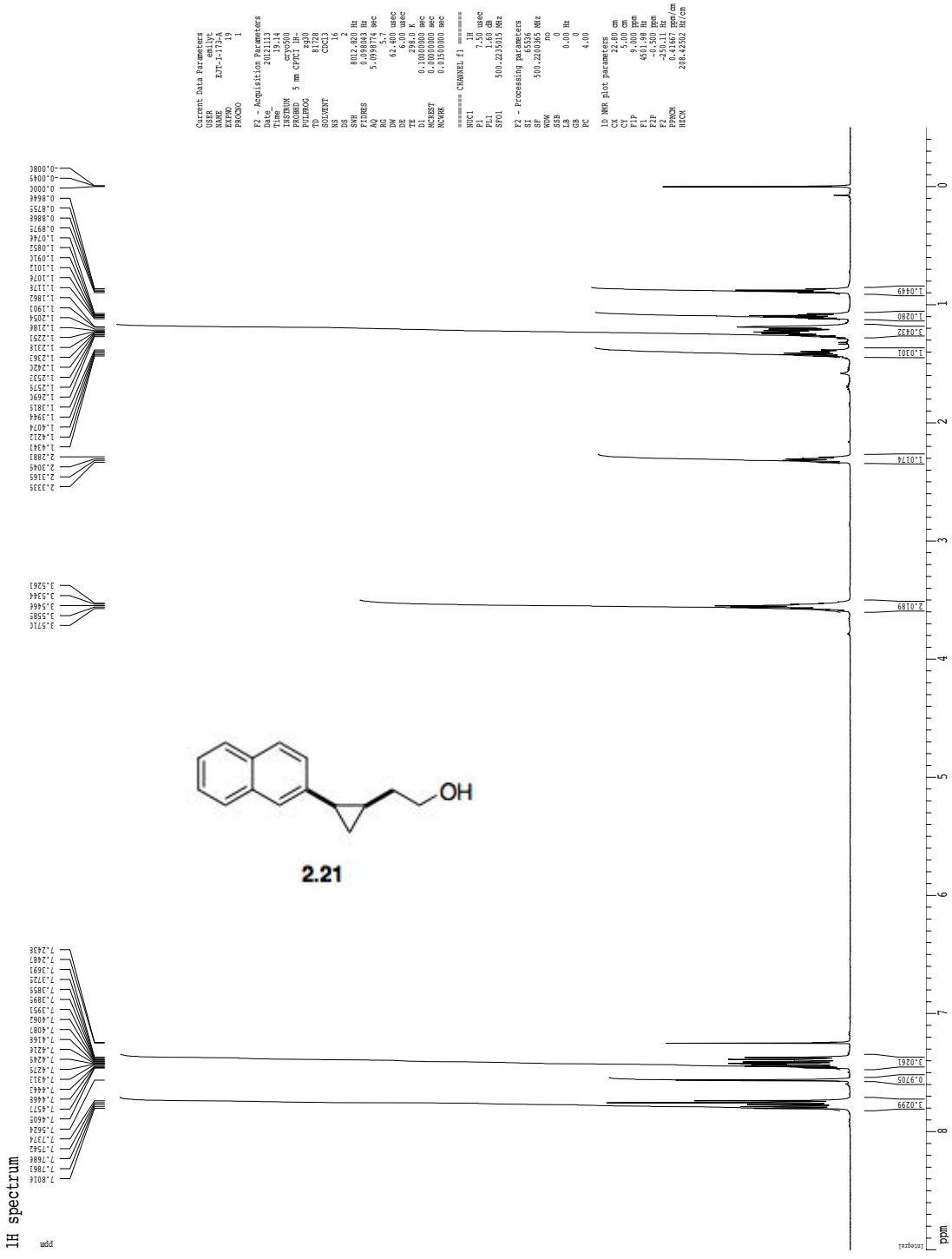
The protocol for the 0.1 M run exemplifies the experimental procedure for all kinetics runs where the nickel catalyst and ligand are varied. All kinetics runs were performed in a nitrogen atmosphere on a Schlenk manifold. To a flame-dried 25 mL round bottom flask was added **2.20** (246 mg, 1.00 mmol, 1 equiv) and Ni(cod)(*R*)-BINAP (79.0 mg, 0.100 mmol, 10.0 mol %). To a separate flame-dried vial dodecane (0.227 mL, 1.00 mmol, 1 equiv) was added and diluted to 6.9 mL total volume with Toluene (6.7 mL). This stock solution of dodecane was added to the flask containing the catalyst system and **2.20** with a flame-dried Teflon coated stir bar. The reaction flask was sealed and removed from the glove box and placed on a Schlenk manifold under N_2 atmosphere. Methyl Grignard reagent (3.1 mL, 8.0 mmol, 2.6 M in Et_2O) was added to the flask to reach a final volume of 10 mL at time equal zero. The reaction was monitored by removing 100 μL aliquots and quenching with 100 μL of isopropanol at the time periods shown in Table 2.5.

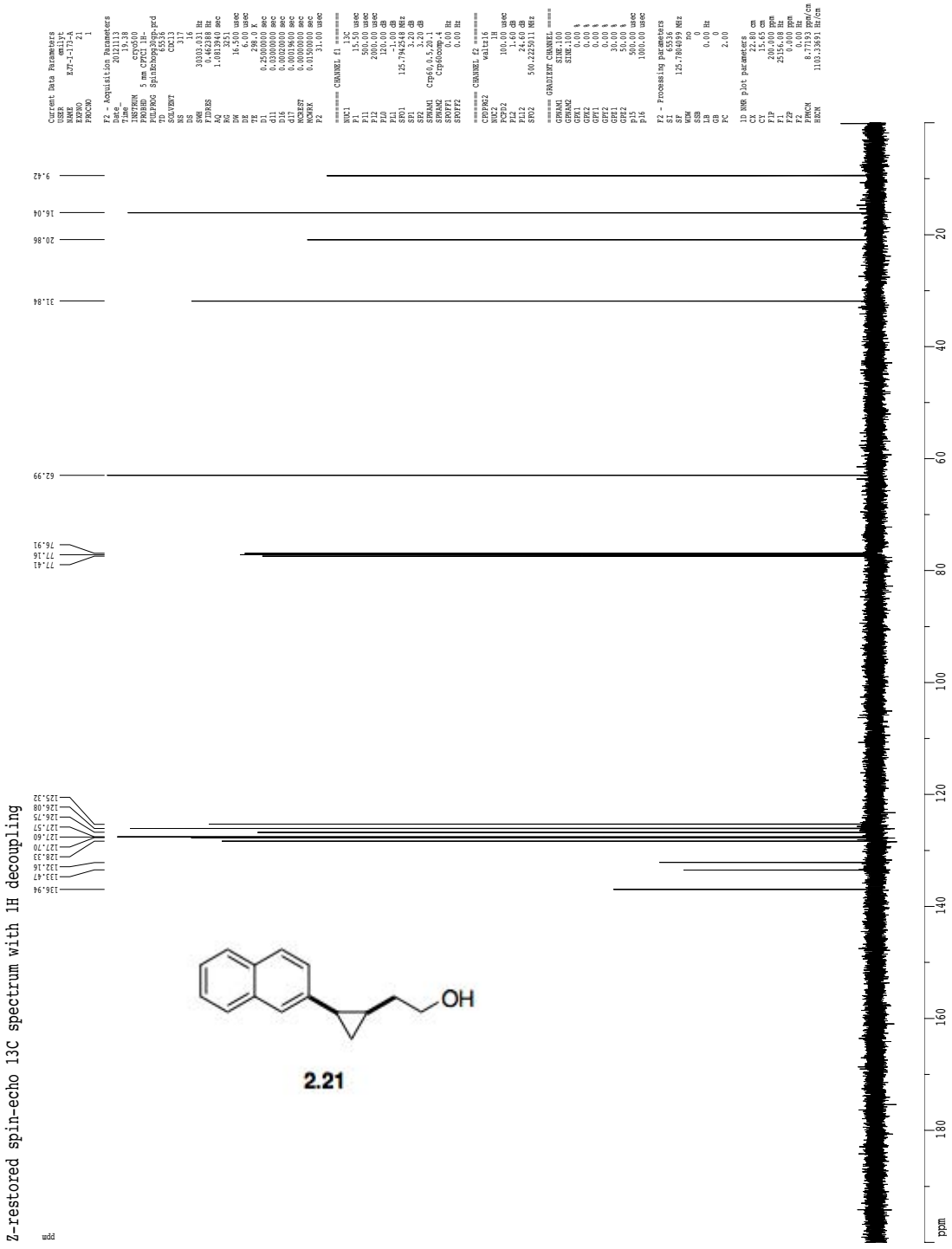
Table 2.5: *Substrate **2.20** (0.1 M) reaction monitored by formation of product **2.21***

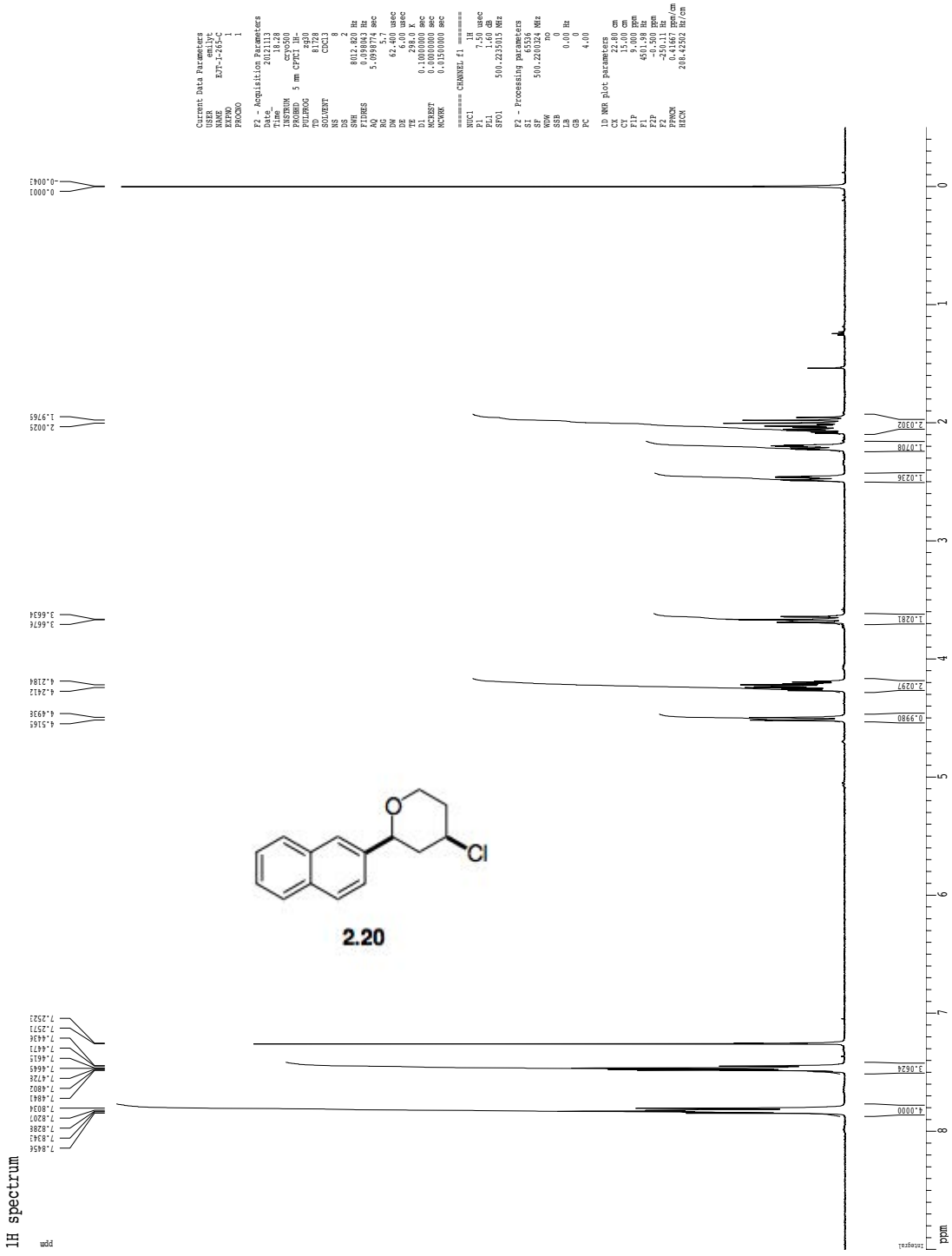
Time (min)	μmol **2.21**	% Yield **2.21**
349	0.7	3.4
448	1.2	6.1
497	1.3	6.6
540	1.5	7.6
601	2.0	10.0
658	2.5	12.6
720	2.6	12.9

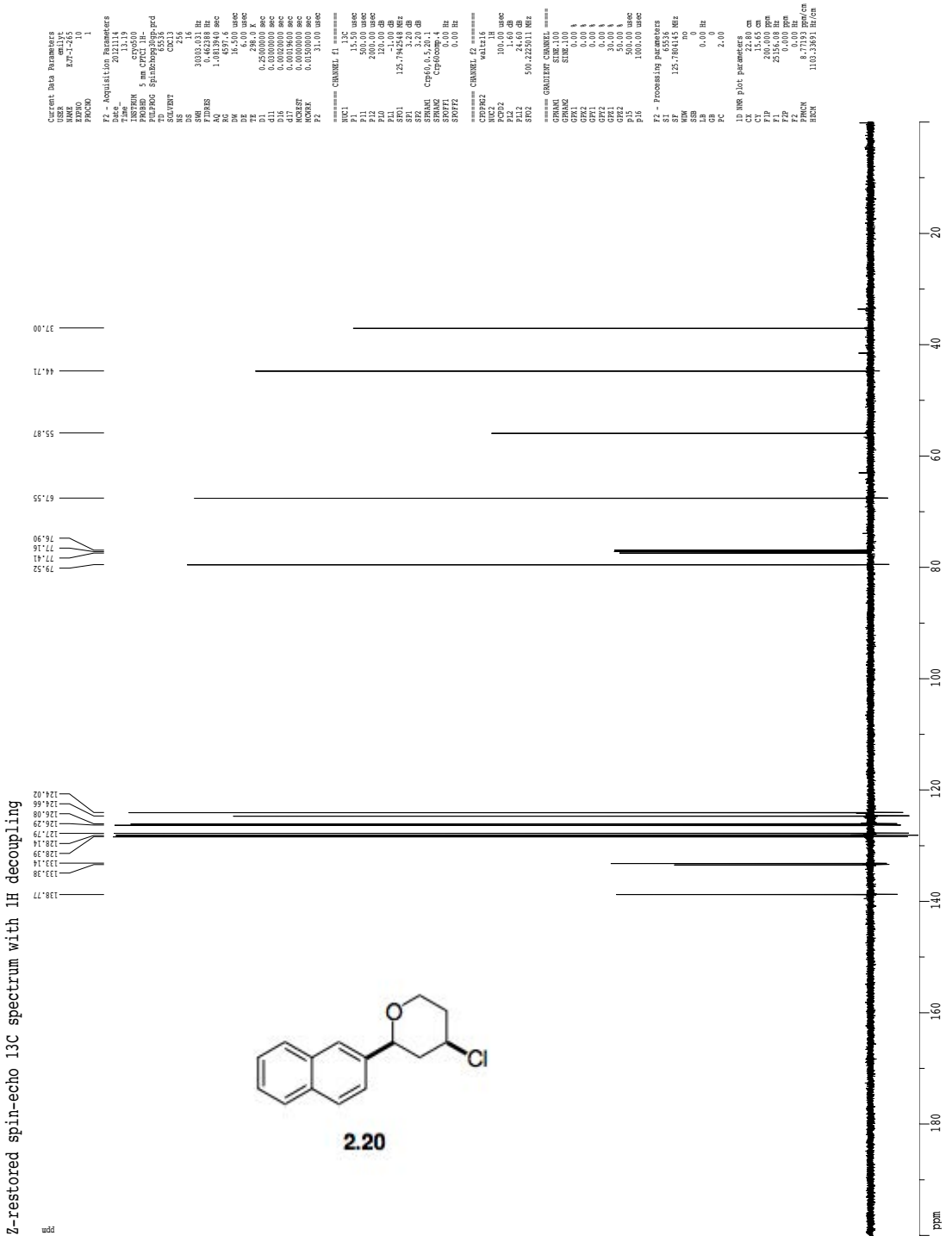
Table 2.6: *Summary of data for determination of order of nickel catalyst. Average and standard deviation is given which were used to create Figure 2.3*

	Initial Rate (nM/min)				
[2.21] (M)	Run 1	Run 2	Run 3	Average	Std Dev
0.1	44.1	8.0	4.8	18.9	21.8
0.075	35.4	7.9	6.2	16.5	16.4
0.05	27.8	6.8	5.8	13.5	12.5
0.0375	21.1	4.9	4.7	10.2	9.4
0.025	8.7	2.0	2.7	4.5	3.7


1H spectrum
OH
2.21


Z-restored spin-echo 13C spectrum with 1H decoupling
OH
2.21


1H spectrum
Current Data Parameters
USER emily
NAME EJT-2-215-C
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121113
Time 10.28
INSTRUM crys500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81920
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.822 Hz
FIDRES 0.098043 Hz
AQ 5.0990774 sec
RG 5.7
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 1.66 dB
SFO1 500.2239013 MHz
F2 - Processing parameters
SI 65536
SF 500.2200324 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 4.00
1D NMR plot parameters
CX 22.80 cm
CY 13.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42302 Hz/cm
0.0001
0.0043
1.9765
2.0025
3.6634
3.6674
4.2184
4.2412
4.4938
4.5165
7.2521
7.2571
7.4434
7.4471
7.4615
7.4649
7.4728
7.4802
7.4841
7.8034
7.8207
7.8288
7.8343
7.8454
2.0302
1.0708
1.0236
1.0281
2.0297
0.9980
3.0624
4.0000
Integral
ppm
2.20
Cl
O


Z-restored spin-echo 13C spectrum with 1H decoupling
2.20
Cl
O

Chapter 3

Work Towards a Stereospecific Intramolecular Cross-Electrophile Coupling of Oxetanes Bearing a Pendant Chloride to form Cyclopropanes

3.1 Introduction:

In recent years cross electrophile couplings have seen a resurgence in popularity. Cross electrophile couplings boast a wide array of benefits over traditional cross coupling reactions. One considerable benefits is the avoidance of preparing and handling organometallic reagents.[1] While many metal catalysts have been utilized in the development of these cross-electrophile couplings, nickel catalysts have been of particular interest in our lab and others. As discussed in the previous Chapter of this thesis, the Riesman and Weix labs have both shown impressive reductive cross electrophile couplings between different halide and pseudohalide electrophile partners.[2] All of these reactions however have been shown to proceed through a stereoablative radical pathway. While these stereoablative pathways provide stereoconvergent syntheses of

[1] Knappke, C. E. I.; Grupe, S.; Gartner, D.; Corpet, M.; Gosmini, C.; von Wangelin, A. J. *Chem. Eur. J.* **2014**, *20*, 6828.

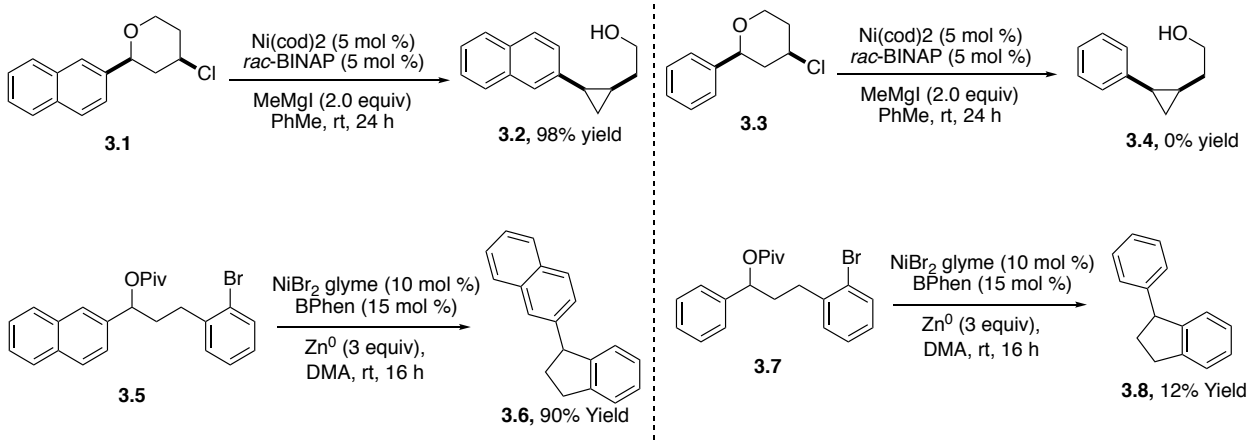
[2] (a) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. J. Am. Chem. Soc. 2013, 135, 7442. (b) Cherney, A. H.; Reisman, S. E. J. Am. Chem. Soc. 2014, 136, 14365. (c) Poremba, K. E.; Kadunce, N. T.; Suzuki, N.; Cherney, A. H.; Reisman, S. E. J. Am. Chem. Soc. **2017**, *139*, 5684. (d) Everson, D. A.; Shrestha, R.;. Weix, D. J.; *J Am Chem Soc* **2010**, *132*, 920. (e) Ackerman, L. K. G.; Anka-Lufford, L. L.; Naodovic, M.; Weix, D. J. *Chem. Sci.* **2015**, *6*, 1115.

compounds there is a complimentary stereospecific pathway for these cross electrophile couplings that can be investigated and would provide advantages in synthetic applications.

In 2015, our group disclosed a cross-electrophile coupling reaction to furnish cyclopropanes from 2-aryl-4-chlorotetrahydropyrans.[3] In this report enantioenriched benzylic ethers could be used as competent electrophilic partners for a cross-electrophile coupling in a stereospecific manner. Shortly after this report we also detailed a cross-electrophile coupling of 2-vinyl-4-halotetrahydropyrans to form cyclopropanes. This reaction was also stereospecific in nature and provided cyclopropanes in good to excellent yields. These results were exciting for our lab but one aspect that the Jarvo group has struggled with is utilizing substrates that include non-extended aromatic systems as the benzylic partner (Scheme 3.1).[3,4,5] The sluggishness of these simple benzylic substrates to engage our nickel catalyst is hypothesized to be due to the necessity to break aromaticity for oxidative addition to the benzylic carbon oxygen bond. Through substrate design we have shown that it is possible to overcome this limitation to our chemistry but this requires a specialized leaving group.[6] Another possible way to overcome this limitation would be to bias the substrate with an electrophile that has strain already present in the molecule to overcome the kinetic challenges of breaking aromaticity.

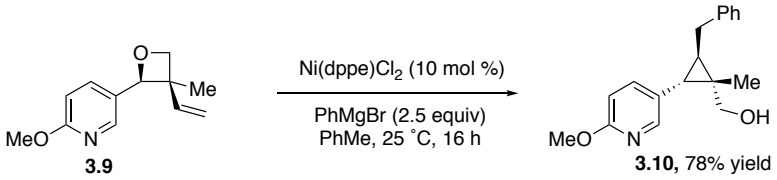
[3] Tollefson, E. J.; Erickson, L. W.; Jarvo, E. R.; *J. Am. Chem. Soc.* **2015**, *137*, 9760
[4] (a) Tollefson, E. J.; Hanna, L. E.; Jarvo, E. R. *Acc. Chem. Res.* **2015**, *48*, 2344. (b) Tollefson, E. J.; Jarvo, E. R. *Dissertation.*
[5] (a) Konev, M. O.; Hanna, L. E.; Jarvo, E. R. *Angew. Chem. Int. Ed.* **2016**, *55*, 6730. (b) Konev, M. O.; Jarvo, E. R. *Dissertation.*
[6] Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2002**, *14*, 4293

Scheme 3.1: *Jarvo group cross electrophile couplings with benzylic electrophiles*



We thought that we could use rational substrate design and attempt to use oxetanes with pendant alkyl chlorides as our test substrates. Epoxides have a rich history of being used as substrates for cyclopropanol synthesis.[7] Oxetanes on the other hand have not been used as often for cyclopropane synthesis. The Krische group has shown one example of using an oxetane bearing a vinyl group to form a cyclopropane through a Kumada-Heck type reaction (Scheme 3.2).[8] Using this result as inspiration we set out to synthesize oxetanes bearing pendent halogen electrophiles to probe the reactivity of this class of substrates.

Scheme 3.2: *Kumada-Heck type coupling of oxetane to form substituted cyclopropane*[8]

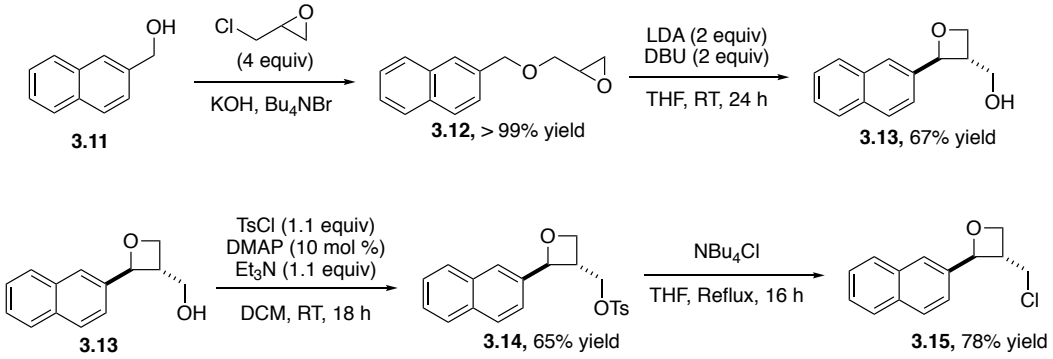


[7] For a discussion on the chemistry of cyclopropanols see: Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597.
[8] Guo, Y.-A.; Lee, L.; Krische, M. J. *Chem. Eur. J.* **2017**, *23*, 2557

3.2 Results and Discussion:

While the literature for the reactions for the synthesis of oxetanes is quite robust[9] the literature for the synthesis of 2,3-disubstituted oxetanes is not as full. We decided to tackle the substrate synthesis based on methods established by the Mordini group (Scheme 3.3). Etherification of commercially available 2-naphthalenemethanol with epichlorohydrin provided epoxy ether **3.12**. Utilizing the reaction conditions adapted from the Mordini laboratory we subjected this epoxy ether substrate to strongly basic conditions to effect a 4-exo-trig cyclization to form the desired oxetane. Straightforward functional group manipulation converted alcohol **3.13** to the more electrophilic chloride **3.15**.

Scheme 3.3: *Synthesis for oxetane* ***3.15***

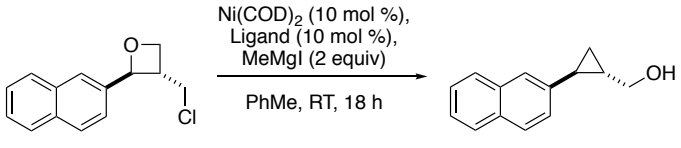


With this substrate in hand we moved on to optimization of XEC reaction conditions. We examined a series of ligands to identify the best catalyst system for the cross electrophile coupling (Table 3.1). We were excited to see that DPEPhos (entry 1) gave the desired product in high yield with no leftover starting material. Buchwald ligands were investigated but they showed only modest yields (entries 2 and 3). Generally, BINAP (entry 4) is an excellent ligand for our nickel catalyzed cross couplings but in this case we were surprised to see complete degradation of starting material with no product formation. CyDPEPhos was investigated due to

[9] Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F. *Chem. Rev.* **2016**, *116*, 12150

its similarity to DPEPhos but unfortunately the yield was not improvemed (entry 5). Various other phosphines were examined but none yielded better results than DPEPhos (entries 6-9). Finally, bidentate pyridine-based ligands (entries 10 and 11) as well as NHC ligands (entries 12 and 13) were examined but these yielded the poorest results overall of any ligand class.

Table 3.1: *Ligand Optimization Screen*



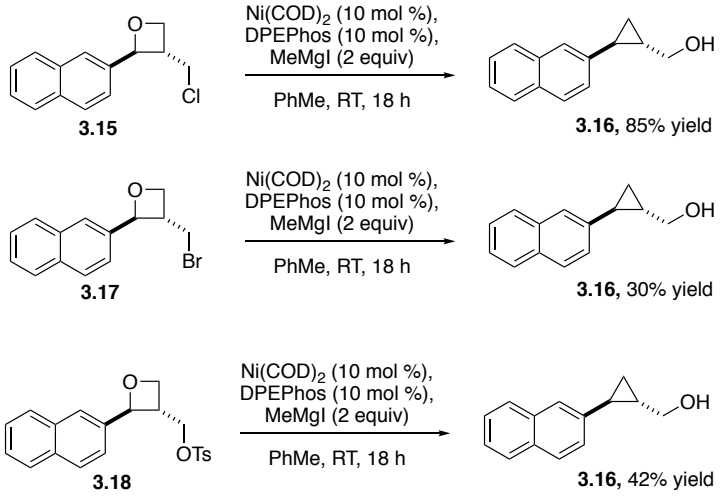
3.15 **3.16**

Entry	Ligand	% Product[a]	% Starting Material[a]
1	DPEPhos	85	0
2	CPhos	36	0
3	DavePhos	30	0
4	BINAP	0	0
5	CyDPEPhos	42	10
6	dppe	30	12
7	Dppf	60	0
8	PCy_3	0	10
9	PPh_3	65	0
10	Bipy	0	0
11	BPhen	22	0
12	IiPr	14	26
13	SIiPr	21	25

[a]Yield of product and starting material were base upon NMR integration against $PhSiMe_3$ as an internal standard

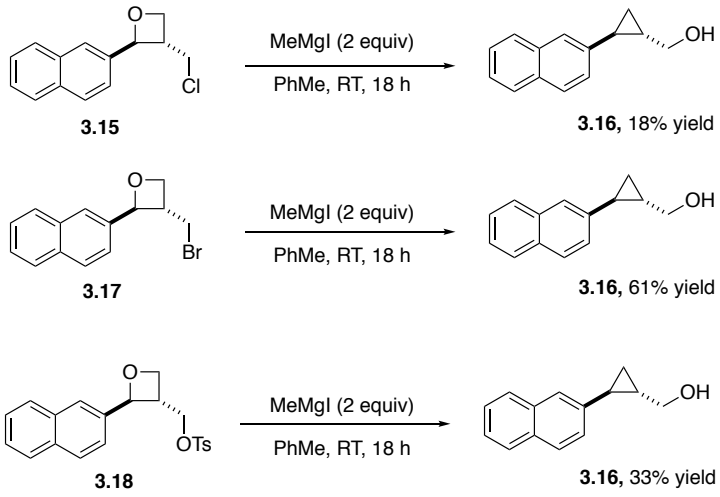
With the optimized conditions in hand we turned our attention to the leaving group identity. We examined the use of a chloride leaving group, a bromide leaving group, and a tosylate leaving group (Scheme 3.4). While the chloride still performed the best of the three we were interested to see that product was obtained with each of the other leaving groups in more modest yields.

Scheme 3.4: *Leaving group screen under catalytic conditions*



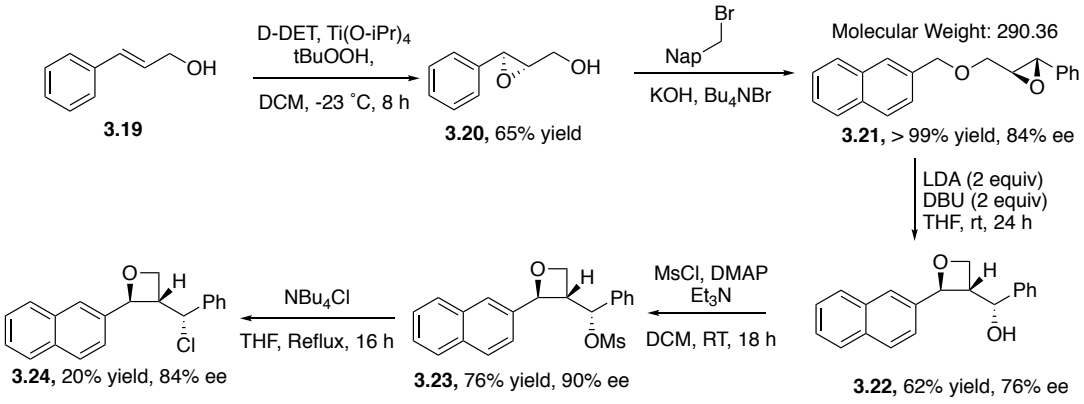
While these results demonstrate that the chloride leaving group and nickel/DPEPhos catalyst system are optimal for this substrate it still remained to be seen whether the reaction proceeded without a nickel catalyst. We performed the same experiment without adding catalyst to probe the background reactivity of these substrates. While chloride gave very low levels of background reactivity we were very surprised to see that the bromide and the tosylate both gave background reactivity that was higher than the chloride (Scheme 3.5).

Scheme 3.5: *Leaving group screen in the absence of nickel catalyst*



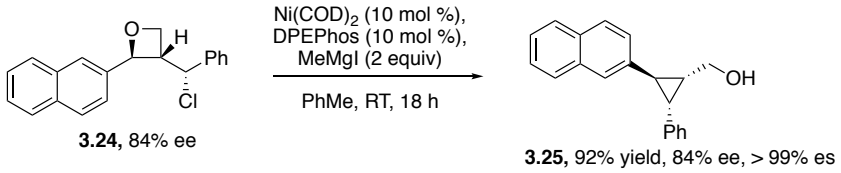
With this information in hand we wanted to test the stereospecificity of the reaction. To test this we synthesized another substrate bearing stereogenic centers at all points of interest in the reactivity pattern. The same basic synthetic plan from Scheme 3.2 was utilized. Starting from commercially available allylic alcohol **3.19** we first used a Sharpless epoxidation to afford an enantioenriched epoxide **3.20**. This epoxide was then reacted with a benzylic bromide to form the epoxy ether **3.21** that rearranged under strongly basic conditions. Functional group manipulation to the chloride was less successful in the displacement of the mesylate in this instance but the rest of the mass balance in this case was simply starting material that could be resubjected to the reaction conditions (Scheme 3.6).

Scheme 3.6: *Synthesis of stereoproof substrate*



With substrate **3.24** in hand we subjected it to the cross electrophile coupling conditions that had been previously identified. We were pleased to see that the reaction was in fact highly stereospecific and yielded product almost quantitatively (Scheme 3.7). Efforts to grow a single crystal of the starting material **3.24** and product **3.25** for X-ray crystallographic analysis are on going. Once absolute configuration is assigned we will have a greater understanding of the mechanism by which this reaction is taking place.

Scheme 3.7: *Cross electrophile coupling of stereoproof substrate*

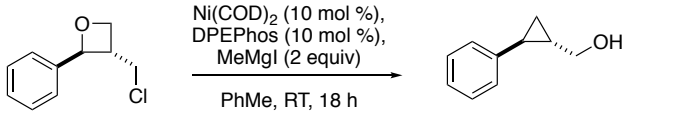


3.24, 84% ee

3.25, 92% yield, 84% ee, > 99% es

Finally we were interested in utilizing the strained oxetane ring to overcome the kinetic barrier of entry for non-extended aromatic systems for these cross electrophile couplings. We synthesized oxetane **3.26**, bearing a simple phenyl substituent in place of the naphthalene substituent. We were excited to see that this simple substrate underwent smooth intramolecular XEC to provide cyclopropane **3.27** (Scheme 3.8).

Scheme 3.8: *Cross electrophile coupling with non-extended aromatic substrate*



3.26, 4:1 dr

3.27, 80% yield, >20:1 dr

While the starting material was only 4:1 trans to cis it was interesting that the product was only one diastereomer. One explanation for this is that the trans diastereomer reacted productively to form trans product and the cis diastereomer reacted unproductively to give decomposition products. The other explanation is that the reaction is funneling towards the trans product preferentially. While the evidence of the stereospecificity of this reaction points towards the former, the latter cannot be ruled out without further experiments performed with each diastereomer individually.

3.3 Conclusions and Future Directions:

Disclosed in this Chapter is the beginning of a new method to transform oxetanes into cyclopropanes through a stereospecific cross electrophile coupling. We were pleased to discover that this reaction is both stereospecific as well as amenable to oxetanes bearing simple arene

substituents. Future directions for this methodology are very important. Currently only five substrates in total have been successfully synthesized and all have proven to be competent substrates for the cross electrophile coupling. The difficulty in synthesizing these substrates encourages us to look at alternative methods for synthesis of oxetanes bearing pendent alkyl chlorides.

3.4 Experimental Procedures:

General Procedures: All reactions were set up under an atmosphere of N_2. All glassware was either oven or flame-dried prior to use. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) and toluene (PhMe) were degassed with argon 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 were purchased "anhydrous" commercially, or purified as described (vide infra). Flash chromatography was performed using Silica Gel 60 (170-400 mesh) from Fisher Scientific. 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 *p*-anisaldehyde (PAA), cerium-ammonium-molybdate (CAM), or potassium permanganate ($KMnO_4$) solutions. Melting points (mp) were obtained using a Mel-Temp melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker GN-500 (500 MHz ^{1}H, 125.7 MHz ^{13}C), CRYO-500 (500 MHz ^{1}H, 125.7 MHz ^{13}C), DRX-400 (400 MHz ^{1}H, 100 MHz ^{13}C, 376.5 MHz ^{19}F) spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.00). Data is reported as follows: chemical shift, multiplicity [singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), pentet (p), doublet of doublets (dd), broad doublet of doublets (br dd), doublet of triplets (dt), doublet of quartets (dq), doublet of pentets (dp), doublet of doublet of doublets (ddd), doublet of triplet of doublets (dtd), doublet of doublet of doublets of doublets (dddd), triplet of doublets (td), triplet of triplets (tt), quartet of doublets (qd), apparent triplet (at), apparent pentet (ap), apparent sextet (as), apparent doublet of doublets (add), apparent pentet of doublets (apd), multiplet (m)], coupling constants [Hz], integration. Carbon chemical shifts are reported in ppm

(δ) relative to 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 Thermo Scientific Nicolet iS5 spectrometer with an iD5 ATR tip (neat) and are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center. Optical rotations were measured with a Rudolph Research Analytical Autopol III Automatic Polarimiter. SFC determinations of enantiopurity were performed on a Agilent Analytical instrument using a Daicel™ Chiralpak® column (AS-H, AD-H, OD-H, or OJ-H; 100 psi, 215 nm, 50 °C).

All Grignard reagents were titrated with iodine prior to use. All other reagents were purchased commercially and used as received.

Preparation of Starting Materials

Method A: Preparation of methylmagnesium iodide

Under an N_2 atmosphere dry Et_2O (25 mL) to magnesium turnings (2.80 g, 115 mmol) in a 3-neck flask equipped with a reflux condenser and a Schlenk filtration apparatus. Freshly distilled iodomethane (5.00 mL, 80.3 mmol) was then added slowly (over 30 minutes) so as to maintain a gentle reflux. The mixture was stirred for two hours at room temperature then passed through a fritted Schlenk filter into a Schlenk flask under a N_2 atmosphere. The Schlenk flask was sealed and removed from the rest of the apparatus. The resulting Grignard reagent was typically between 2.5 and 3.5 M as titrated using Knochel's method.[10]

Method B: Alkylation

[10] Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890.

Modified from a procedure reported by Fessner.[11] A mixture of KOH 50% aq. (50 mL), aryl halide (2.5 equiv) or epichlorohydrin (4 equiv) and tetrabutylammonium bromide (0.10 equiv) was stirred vigorously at 0 ˚C. To this mixture the alcohol (1.0 equiv) was slowly added. Reaction progress was monitored by TLC using $KMnO_4$ as the stain. After 24 h the reaction mixture was diluted with water (20 mL) and extracted three times with ether (25 mL). The organic phase was dried with $MgSO_4$ and concentrated in vacuo. The obtained crude product was purified by column chromatography.

Method C: Rearrangement of Epoxy Ethers

Modified from a procedure reported by Mordini. [12] To the flame-dried round-bottom flask equipped with the stir bar the *n*BuLi (2.0 equiv) was added under N_2. The precooled THF (10 mL) was added, followed by diidopropylamine (2.0 equiv). The reaction mixture was stirred at 0 ˚C for one hour after which time DBU (2.0 equiv) was added. In a separate flame-dried round-bottom flask the oxirane from Method B (1.0 equiv) was and dissolved in THF at 0 ˚C. The base mixture was added slowly at which time the reaction mixture darkened substantially. The mixture was allowed to react for 15 h at room temperature. The reaction was quenched with saturated ammonuium chloride (2 mL) and extracted twice with ether (20 mL). The organic layers were washed with saturated brine, dried with Na_2SO_4, concentrated in vacuo, and purified by column chromatography. Note: certain substrates require additional *n*BuLi to effect the transformation, and when extra equivalents are employed the reaction is stirred for 15 hours at -50 ˚C. See specific examples below.

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[11] Güclü D.; Rale M.; Fessner W.-D., *Eur. J. Org. Chem*. **2015**, *13*, 2960.
[12] Mordini A.; Bindi S.; Capperucci A.; Nistri D.; Reginato G.; Valacchi M., *J. Org. Chem.* **2001**, *66*, 3201.

Method D: Alcohol Mesylation/Tosylation

To the flame-dried round-bottom flask equipped with stir bar the alcohol from Method C (1.0 equiv) and 4-dimethylaminopyridine (0.10 equiv) was added. The flask was capped with rubber septum, evacuated and backfilled with N_2. Anhydrous DCM (10 mL) and triethylamine (1.5 equiv) was added to the reaction mixture. The reaction was allowed to stir for 10 minutes at 0 ^oC. Methanesulfonyl chloride (1.5 equiv) or *p*-toluenesulfonyl chloride (1.5 equiv) was added to the reaction mixture. The methanesulfonyl chloride solution was added via syringe to the reaction mixture and allowed to warm to ambient temperature. After stirring for 14 h, the reaction was quenched with $NaHCO_3$ and the organic layer was washed with water (10 mL). The organic layers were extracted three times with DCM (30 mL), washed with brine (10 mL), dried over $MgSO_4$, and concentrated on in vacuo. The crude product was purified by column chromatography.

Method E: Displacement of Mesylate/Tosylate with Chloride

Modified from a procedure reported by Cahiez.[13] To the flame-dried round-bottom flask equipped with stir bar the oxetane from Method D (1.0 equiv) in anhydrous THF (20 mL). Tetrabutylammonium chloride (2.0 equiv) was added and the reaction mixture was heated to reflux at 70 ^oC for 14 h. The reaction mixture was quenched with water (5.0 mL) and extracted twice with ethyl acetate (20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography.

[13] Cahiez, G.; Lefèvre, N.; Poizat, M.; Moyeux, A. *Synthesis* **2013**, *2*, 231.

Method F: General Cross-Electrophile Coupling Procedure

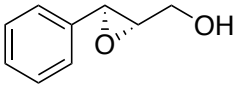
In a glovebox, a flame-dried 7 mL vial equipped with a stir bar was charged with $Ni(COD)_2$ (0.10 equiv) and DPEPhos (0.10 equiv). To the reaction suspension the anhydrous toluene (0.5 mL) was added, followed by the oxetane (1.0 equiv) and the Grignard solution (2.0 equiv, 2.8 M in ether). The reaction vial was capped with a screw-cap fitted with a septum and was stirred overnight in room temperature. After 18 h, the reaction was quenched with methanol, filtered through a plug of silica gel and washed with 100% ether and concentrated in vacuo. An NMR yield was obtained using internal standard, phenyltrimethylsilane. Purification was performed by column chromatography.

Method G: Sharpless Asymmetric Epoxidation of Allylic Alchols

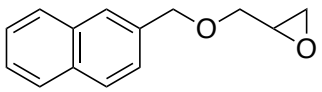
Modified from a procedure reported by Kumar.[14] To a flame dried round bottom flask was added activated powdered 4Å mol sieves (0.05 g per mmol of allylic alcohol) and DCM (0.5 M). The flask was cooled to –20 ˚C and the following were added sequentially: (+)–diisopropyltartrate (7.5 mol %), titanium(IV) isopropoxide (5 mol %), and *tert*–butyl hydroperoxide (2 equiv). The solution was stirred at –20 ˚C for 1 h and then a solution of allylic alcohol in DCM was added dropwise. After 3 h at –20 ˚C the reaction was quenched with 1 M KOH saturated with NaCl at –20 ˚C. After adding diethylether the cooling bath was allowed to warm to 10 ˚C and $MgSO_4$ and diatomaceous earth were added. After 15 min of stirring the reaction was allowed to settle and the slurry was filtered through a pad of diatomaceous earth and washed with diethyl ether. The organics were concentrated in vacuo and purified using column chromatography.

[14] Cherian, S. K.; Kumar, P. *Tetrahedron: Asymmetry* **2007**, *18*, 982

Characterization Data for Products:

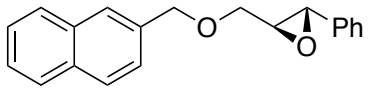


((2S,3S)-3-phenyloxiran-2-yl)methanol 3.20 was prepared according method G. The following amounts of reagents were used: activated powdered 4Å mol sieves (0.15 g), (+)–diisopropyltartrate (0.23 mmol, 47 µL, 7.5 mol %), titanium(IV) isopropoxide (0.15 mmol, 44 µL, 5.0 mol %), *tert*–butyl hydroperoxide (1.1 mL, 5.5 M in decane, 6.0 mmol, 2 equiv), cinnamyl alcohol (0.40 g, 3.0 mmol, 1.0 equiv). Purification by column chromatography afforded the product as a yellow oil (0.29 g, 65%). **TLC R_f** = 0.5 (20% EtOAc in hexanes). **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.36–7.21 (m, 5H), 4.05–3.96 (m, 1H), 3.92–3.88 (m, 1H), 3.80–3.72 (m, 1H), 3.23-3.19 (m, 1H), 2.68 (br s, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 136.7, 128.6, 128.4, 125.8, 62.7, 61.4, 55.8; $[\alpha]_{24}^{D}$ –95˚ (c 0.98, $CHCl_3$); **HRMS** (TOF MS ES+) m / z calcd for $C_9H_{10}O_2Na$ (M + Na)+ 173.0578, found 173.0574.

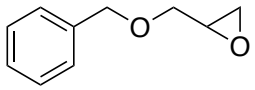


2-((naphthalen-2-ylmethoxy)methyl)oxirane 3.12 was prepared according to method B. The following amounts of reagents were used: 2-naphthalenemethanol (4.75 g, 30.0 mmol, 1 equiv), tetrabutylammonium bromide (0.967 g, 3.00 mmol, 0.100 equiv), epichlorohydrin (9.39 mL, 120 mmol, 4.00 equiv). Purification by column chromatography (10% ethyl acetate in hexane) afforded the title compound as a colorless oil (6.39 g, 99%). **TLC R_f** = 0.7 (20% EtOAc in hexanes). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.88–7.80 (m, 4H), 7.54–7.2046 (m, 1H), 4.76 (q, *J* = 12.2, 2H), 3.83 (dd, *J* = 2.9, 11.4, 1H), 3.49 (dd, *J* = 5.7, 11.4, 1H), 3.26–3.21 (m, 1H), 2.82 (t, *J* = 4.4 1H), 2.65 (dd, *J* = 2.6, 5.1, 1H), 0.97 (t, *J* = 7.2, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ

135.7, 133.5, 133.3, 128.5, 128.2, 128.0, 126.8, 126.4, 126.2, 126.0, 73.6, 71.1, 51.1, 44.5; **HRMS** (TOF MS ES+) m / z calcd for $C_{14}H_{14}O_2Na$ (M + Na)+ 237.0892, found 237.0899.

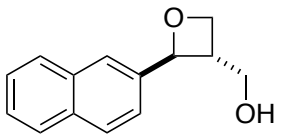


(2*S*,3*S*)-2-((naphthalen-2-ylmethoxy)methyl)-3-phenyloxirane 3.21 was prepared according to method B. The following amounts of reagents were used: epoxide **3.19** (1.50 g, 10.0 mmol, 1 equiv), tetrabutylammonium bromide (0.322 g, 1.00 mmol, 0.100 equiv), 2-(bromomethyl)naphthalene (5.28 g, 25.0 mmol, 2.50 equiv). Purification by column chromatography (10% ethyl acetate in hexane) afforded the title compound as a white solid (2.82g, 97%). **TLC R_f** = 0.7 (20% EtOAc in hexanes). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.88–7.81 (m, 4H), 7.53–7.45 (m, 3H), 7.38–7.27 (m, 5H), 4.85–4.76 (m, 2H), 3.91 (dd, *J* = 3.2, 11.6, 1H), 3.82 (d, *J* = 2.1, 1H), 3.69 (dd, *J* = 5.4, 11.6, 1H), 3.31–3.28 (m, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 137.1, 135.5, 133.5, 133.3, 128.7, 128.5, 128.1, 127.9, 126.8, 126.4, 126.2, 125.9, 123.6, 111.8, 73.8, 70.1, 61.4, 56.1; **SFC** analysis (AD-H, 10% IPA, 2.5 mL/min, 254 nm) indicated 92:8 er: t_R (minor) = 6.5 min, t_R (major) = 9.5 min; $[\alpha]_{24}^{D}$ –28˚ (c 1.13, $CHCl_3$); **HRMS** (TOF MS ES+) m / z calcd for $C_{20}H_{18}O_2Na$ (M + Na)+ 313.1205, found 313.1209.

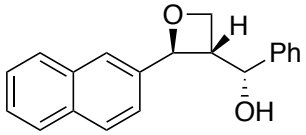


2-((Benzyloxy)methyl)oxirane 3.28 was prepared according to method B. The following amounts of reagents were used: benzyl alcohol (1.03 mL, 10.0 mmol, 1 equiv), tetrabutylammonium bromide (0.322 g, 1.00 mmol, 0.100 equiv), epichlorohydrin (3.13 mL, 40.0 mmol, 4.00 equiv). Purification by column chromatography (10% ethyl acetate in hexane)

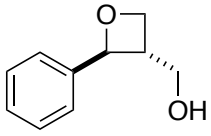
afforded the title compound as a colorless oil (1.55 g, 94%). **TLC R_f** = 0.7 (20% EtOAc in hexanes). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.39–7.27 (m, 5H), 4.60 (q, *J* = 12.0, 2H), 3.77 (dd, *J* = 3.2, 11.5, 1H), 3.46 (dd, *J* = 6.1, 11.2, 1H), 3.22–3.17 (m, 1H), 2.81 (t, *J* = 4.6, 1H), 2.63 (dd, *J* = 2.8, 5.2, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 138.1, 130.0, 128.7, 128.0, 73.6, 71.0, 51.1, 44.5; **HRMS** (TOF MS ES+) m / z calcd for $C_{10}H_{12}O_2Na$ (M + Na)+ 187.0735, found 187.0733.



***trans*-(2-(naphthalen-2-yl)oxetan-3-yl)methanol 3.13:** was prepared according to method C. The following amounts of reagents were used: *n*-butyllithium (2.0 mL, 2.5 M in hexanes , 5.0 mmol, 2.0 equiv), diisopropylamine (0.70 mL, 5.0 mmol, 2.0 equiv), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.75 mL, 5.0 mmol, 2.0 equiv), oxirane **3.12** (0.54 g, 2.5 mmol, 1.0 equiv). The resulting dark red suspension was allowed to stir overnight at room temperature. Purification by column chromatography (40% ethyl acetate in hexane) afforded the title compound as a yellow oil (0.32 g, 9:1 dr, 67%). **TLC R_f** = 0.4 (50% EtOAc in hexanes, stains blue with PAA). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.97–7.81 (m, 4H), 7.59–7.36 (m, 3H), 5.75 (d, *J* = 6.1, 1H), 4.83 (t, *J* = 8.3, 1H), 4.64 (t, *J* = 6.6, 1H), 4.07–3.97 (m, 2H), 3.19–3.09 (m, 1H), 1.65 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 140.2, 133.5, 133.3, 128.7, 128.3, 128.0, 126.5, 126.2, 124.1, 123.4, 85.8, 70.6, 63.9, 46.0. **HRMS** (TOF MS ES+) m / z calcd for $C_{15}H_{16}ONa$ (M + Na)+ 237.0892, found 237.0899.

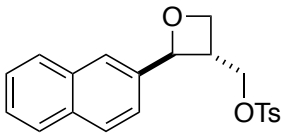


(*R*)-((2*S*,3*R*)-2-(naphthalen-2-yl)oxetan-3-yl)(phenyl)methanol 3.22: was prepared according to method C. The following amounts of reagents were used: *n*-butyllithium (2.0 mL, 2.5 M in hexanes, 5.0 mmol, 2.0 equiv), diisopropylamine (0.70 mL, 5.0 mmol, 2.0 equiv), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.75 mL, 5.0 mmol, 2.0 equiv), oxirane **3.21** (0.73 g, 2.5 mmol, 1.0 equiv). The resulting dark green suspension was allowed to stir overnight at room temperature. Purification by column chromatography (40% ethyl acetate in hexane) afforded the title compound as a yellow oil (0.45 g, 4:1 dr trans:cis, 62%). **TLC** $\mathbf{R_f}$ = 0.4 (50% EtOAc in hexanes, stains blue with PAA). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.83–7.70 (m, 4H), 7.48–7.43 (m, 2H), 7.38–7.27 (m, 4H), 7.23–7.19 (m, 2H), 5.10 (d, *J* = 8.7, 1H), 4.72–4.65 (m, 1H), 4.38 (dd, *J* = 6.2, 9.9, 1H), 4.20 (dd, *J* = 4.6, 10.7, 1H), 3.28 (dd, *J* = 5.5, 9.1, 1H), 1.97 (d, *J* = 5.4 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 139.0, 138.5, 129.2, 129.1, 128.5, 128.3, 128.2, 127.9, 127.5, 126.7, 126.3, 126.1, 124.9, 124.1, 87.7, 80.2, 75.1, 63.9. **SFC** analysis (AD-H, 10% IPA, 2.5 mL/min, 215 nm) indicated 88:12 er: t_R (trans major) = 17.2 min, t_R (trans minor) = 19.2 min, t_R (cis major) = 19.2 min, t_R (trans minor) = 20.7 min; $[\alpha]_{24}^{D}$ –71˚ (c 0.74, $CHCl_3$); **HRMS** (TOF MS ES+) m / z calcd for $C_{20}H_{18}O_2Na$ (M + Na)+ 313.1205, found 313.1209.

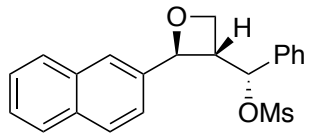


***trans*-(2-phenyloxetan-3-yl)methanol 3.29:** was prepared according to Method C. The following amounts of reagents were used: *n*-butyllithium (2.0 mL, 2.5 M in hexanes, 5.0 mmol, 2.0 equiv), diisopropylamine (0.70 mL, 5.0 mmol, 2.0 equiv), 1,8-diazabicyclo[5.4.0]undec-7-ene(0.75 mL, 5.0 mmol, 2.0 equiv), oxirane **3.28** (0.73 g, 2.5 mmol, 1.0 equiv). The resulting dark green suspension was cooled to -50 ˚C and 2.5 M *n*-butyllithium (2.0 mL, 5.0 mmol, 2.0

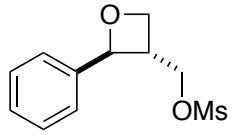
equiv) was added. The resulting dark brown solution was allowed to stir at -50 ˚C for 15 h. Purification by column chromatography (40% ethyl acetate in hexane) afforded the title compound as a colorless oil (0.21 g, 2:1 dr trans:cis 50%). **TLC R_f** = 0.5 (50% EtOAc in hexanes, stains blue with PAA). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.46–7.28 (m, 5H), 5.55 (d, *J* = 6.2, 1H), 4.72 (dd, *J* = 6.3, 8.3, 1H), 4.57 (t, *J* = 6.6, 1H), 3.95–3.86 (m, 2H), 3.59–3.46 (m, 1H), 3.08–2.99 (m, 1H), 2.22 (bs, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 142.8, 128.8, 128.1, 125.4, 85.7, 70.6, 63.3, 46.0; **HRMS** (TOF MS ES+) m / z calcd for $C_{15}H_{16}ONa$ (M + Na)+ 171.0786, found 171.0782.



***trans*-(2-(naphthalen-2-yl)oxetan-3-yl)methyl 4-methylbenzenesulfonate 3.14:** was prepared according to method D. The following amounts of reagents were used: alcohol **3.13** (1.07 g, 5.00 mmol, 1.00 equiv), 4-dimethylaminopyridine (61 mg, 0.50 mmol, 0.10 equiv), triethylamine (1.05 mL, 7.50 mmol, 1.50 equiv), methanesulfonyl chloride (0.76 g, 7.5 mmol, 1.5 equiv). Purification by column chromatography (30% ethyl acetate in hexane) afforded the title compound as a colorless oil (0.944 g, 65%). **TLC R_f** = 0.6 (40% EtOAc in hexanes). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.89–7.77 (m, 6H), 7.54–7.44 (m, 3H), 7.37–7.29 (m, 2H), 5.61 (d, *J* = 6.4, 1H), 4.75 (dd, *J* = 6.7, 8.4, 1H), 4.53 (t, *J* = 7.0, 1H), 4.44–4.32 (m, 2H), 3.29–3.19 (m, 1H), 2.45 (s, 3H), ; **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 145.4, 139.0, 133.4, 133.3, 133.0, 130.2, 128.9, 128.3, 128.2, 128.0, 126.6, 126.4, 124.3, 123.1, 85.1, 70.1, 69.8, 43.0, 21.9; **HRMS** (TOF MS ES+) m / z calcd for $C_{21}H_{20}O_4SNa$ (M + Na)+ 391.0980, found 391.0967.

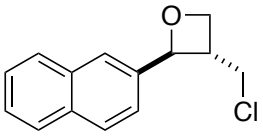


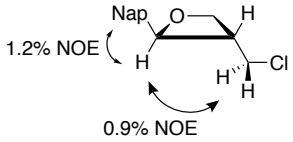
(R)-((2S,3S)-2-(naphthalen-2-yl)oxetan-3-yl)(phenyl)methyl methanesulfonate 3.23: was prepared according to method D. The following amounts of reagents were used: alcohol **3.22** (1.16 g, 4.00 mmol, 1.00 equiv), 4-dimethylaminopyridine (49 mg, 0.40 mmol, 0.10 equiv), triethylamine (0.84 mL, 6.0 mmol, 1.5 equiv), methanesulfonyl chloride (0.46 mL, 6.0 mmol, 1.5 equiv). Purification by column chromatography (30% ethyl acetate in hexane) afforded the title compound as a white solid (1.12 g, 76%). **TLC** $\mathbf{R_f}$ = 0.7 (40% EtOAc in hexanes). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.83–7.73 (m, 3H), 7.69 (s, 1H), 7.48–7.43 (m, 2H), 7.41–7.28 (m, 4H), 7.20 (d, *J* = 7.1, 1H), 5.42–5.39 (m, 1H), 5.05 (d, *J* = 8.7, 1H), 4.52 (dd, *J* = 2.8, 11.0, 1H), 4.42 (dd, *J* = 5.4, 11.0, 1H), 3.55 (dd, *J* = 4.8, 8.8, 1H), 2.82 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 137.2, 136.8, 133.3, 133.2, 129.2, 128.4, 128.1, 128.0, 127.9, 127.7, 126.3, 126.1, 125.1, 123.7, 87.6, 87.2, 73.1, 60.6, 38.4, **SFC** analysis (AD, 10% IPA, 2.5 mL/min, 210 nm) indicated 95:5 er: t_R (major) = 17.2 min, t_R (minor) = 19.2 min; $[\alpha]_{24}^{D}$ –76˚ (c 1.19, $CHCl_3$); **HRMS** (TOF MS ES+) m / z calcd for $C_{21}H_{20}O_4SNa$ (M + Na)+ 391.0980, found 391.0976.



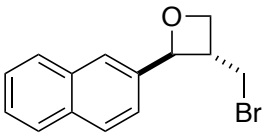
trans-(2-phenyloxetan-3-yl)methyl methanesulfonate 3.30: was prepared according to method D. The following amounts of reagents were used: alcohol **3.29** (0.575 g, 3.50 mmol, 1.00 equiv), 4-dimethylaminopyridine (43 mg, 0.35 mmol, 0.10 equiv), triethylamine (0.73 mL, 5.3 mmol, 1.5 equiv), methanesulfonyl chloride (0.41 mL, 5.3 mmol, 1.5 equiv). Purification by column chromatography (30% ethyl acetate in hexane) afforded the title compound as a white solid

(0.534 g, 2:1 dr trans:cis, 63%). **TLC R_f** = 0.7 (40% EtOAc in hexanes). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.45–7.29 (m, 5H), 5.57 (d, *J* = 6.2, 1H), 4.76 (t, *J* = 7.8, 1H), 4.59 (t, *J* = 7.0, 1H), 4.55–3.47 (m, 2H), 3.31–3.24 (m, 1H), 3.04 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 141.5, 128.8, 128.4, 125.3, 84.7, 69.5, 68.9, 43.0, 37.7; **HRMS** (TOF MS ES+) m / z calcd for $C_{11}H_{14}O_4SNa$ (M + Na)+ 265.0511, found 265.0522.



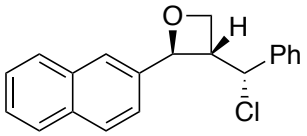


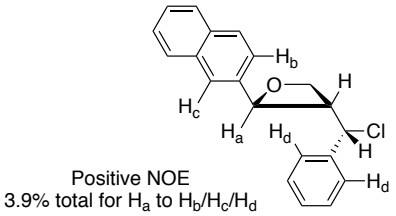
***trans*-3-(chloromethyl)-2-(naphthalen-2-yl)oxetane 3.14:** was prepared according to Method E. The following amounts of reagents were used: tosylate **3.14** (0.55 g, 1.5 mmol, 1.0 equiv) and tetrabutylammonium chloride (0.83 g, 3.0 mmol, 2.0 equiv). Purification by column chromatography (15% ethyl acetate in hexane) afforded the title compound as a yellow oil (0.5 g, 9:1 dr, 78%). **TLC R_f** = 0.5 (20% EtOAc in hexanes). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.96–7.79 (m, 4H), 7.62–7.37 (m, 3H), 5.71 (d, *J* = 6.2, 1H), 4.89–4.83 (m, 1H), 4.61 (t, *J* = 6.6, 1H), 3.97–3.85 (m, 2H), 3.34–3.23 (m, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 139.3, 133.5, 133.4, 128.8, 128.3, 128.0, 126.6, 126.4, 124.4, 123.4, 86.7, 71.5, 45.9, 45.6, ; **HRMS** (TOF MS ES+) m / z calcd for $C_{14}H_{13}ClONa$ (M + Na)+ 255.0553, found 255.0553.



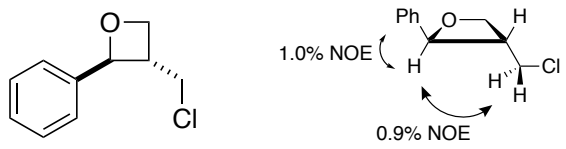
***trans*-3-(bromomethyl)-2-(naphthalen-2-yl)oxetane 3.17:** was prepared according to Method E. The following amounts of reagents were used: tosylate **3.14** (0.55 g, 1.5 mmol, 1.0 equiv) and tetrabutylammonium bromide (0.97 g, 3.0 mmol, 2.0 equiv). Purification by column

chromatography (15% ethyl acetate in hexane) afforded the title compound as a yellow oil (0.27 g, 4:1 dr, 65%). **TLC R_f** = 0.5 (20% EtOAc in hexanes). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.97–7.80 (m, 4H), 7.63–7.37 (m, 3H), 5.64 (d, *J* = 6.2, 1H), 4.88–4.82 (m, 1H), 4.55 (t, *J* = 6.6, 1H), 3.82–3.65 (m, 2H), 3.39–3.29 (m, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 139.2, 133.5, 128.8, 128.4, 128.1, 128.0, 126.6, 126.4, 124.6, 123.5, 87.7, 72.8, 46.0, 33.7; **HRMS** (TOF MS ES+) m / z calcd for $C_{14}H_{13}BrONa$ (M + Na)+ 299.0048, found 299.0038.

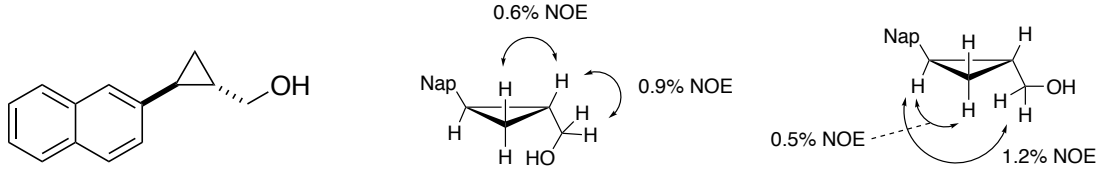




(2*S*,3*S*)-3-((I)-chloro(phenyl)methyl)-2-(naphthalen-2-yl)oxetane 3.24: was prepared according to Method E. The following amounts of reagents were used: mesylate **3.23** (1.11 g, 3.00 mmol, 1.00 equiv) and tetrabutylammonium chloride (1.67 g, 3.00 mmol, 2.00 equiv). Purification by column chromatography (15% ethyl acetate in hexane) afforded the title compound as a yellow solid (0.19 g, 20%). **TLC R_f** = 0.5 (20% EtOAc in hexanes). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.81–7.75 (m, 4H), 7.46–7.27 (m, 8H), 5.66 (d, *J* = 9.9, 1H), 4.80–4.72 (m, 2H), 3.12–3.02 (m, 1H), 4.42 (dd, *J* = 1.8, 10.2, 1H), 3.77 (dd, *J* = 5.0, 9.9, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 137.9, 135.3, 133.4, 133.3, 129.8, 128.6, 128.5, 128.2, 127.9, 126.3, 126.2, 125.6, 124.1, 82.8, 77.4, 76.8, 63.7, 58.6; **SFC** analysis (AD-H, 10% IPA, 2.5 mL/min, 254 nm) indicated 92:8 er: t_R (minor) = 11.4 min, t_R (major) = 16.2 min; $[\alpha]_{24}^{D}$ –156˚ (c 0.80, $CHCl_3$); **HRMS** (TOF MS ES+) m / z calcd for $C_{20}H_{17}ClONa$ (M + Na)+ 331.0865, found 331.0860.

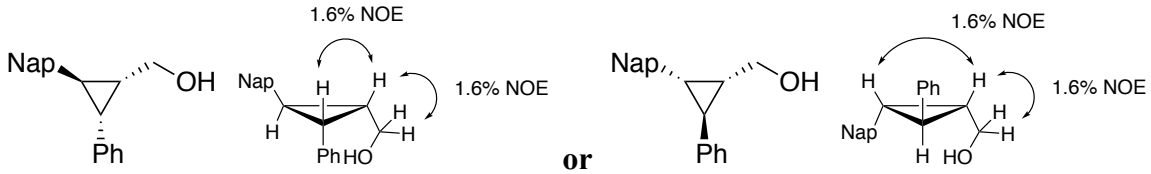


***trans*-3-(chloromethyl)-2-phenyloxetane 3.26:** was prepared according to Method E. The following amounts of reagents were used: mesylate **3.30** (0.726 g, 3.00 mmol, 1.00 equiv) and tetrabutylammonium chloride (1.67 g, 3.00 mmol, 2.00 equiv). Purification by column chromatography (15% ethyl acetate in hexane) afforded the title compound as a colorless oil (0.35 g, 4:1 dr trans:cis, 65%). **TLC R_f** = 0.5 (20% EtOAc in hexanes). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.49–7.30 (m, 5H), 5.54 (d, *J* = 6.4, 1H), 4.79 (dd, *J* = 6.6, 8.2, 1H), 4.55 (t, *J* = 6.6, 1H), 3.92–3.81 (m, 2H), 3.27–3.18 (m, 1H), 1.66–1.53 (m, 3H), 1.49–1.36 (m, 1H), 0.94 (t, *J* = 6.9, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 142.0, 128.8, 128.3, 125.5, 86.5, 71.4, 45.9, 45.5; **HRMS** (TOF MS ES+) m / z calcd for $C_{10}H_{11}ClONa$ (M + Na)+ 205.0396, found 205.0393.

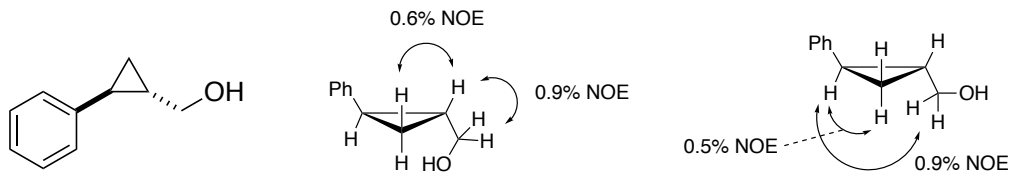


***trans*-2-(naphthalen-2-yl)cyclopropyl)methanol 3.16:** was prepared according to general cross-coupling procedure. The following amounts of reagents were used: $Ni(COD)_2$ (2.7 mg, 0.010 mmol, 0.10 equiv), DPEPhos (5.4 mg, 0.010 mmol, 0.10 equiv), oxetane **3.15** (23.2 mg, 0.100 mmol, 1.00 equiv), and MeMgI (80 μL, 0.20 mmol, 2.0 equiv, 2.5 M in Et_2O) in toluene (0.5 mL). The yield was determined to be 85% by NMR spectroscopy of the unpurified product by comparison to internal standard. Purification by flash chromatography (10% ethyl acetate in hexane) afforded the title compound as a colorless oil (14 mg, 72%). **TLC R_f** = 0.2 (20% EtOAc in hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.82–7.72 (m, 3H), 7.54 (s, 1H), 7.49–7.39 (m, 2H),

7.21 (d, *J* = 8.0, 1H), 3.73–3.64 (m, 2H), 2.04–1.98 (m, 1H), 1.70–1.52 (m, 2H), 1.13–1.06 (m, 1H), 1.05–0.98 (m, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 140.1, 133.7, 132.2, 128.2, 127.8, 127.5, 126.3, 125.3, 124.9, 124.3, 66.8, 25.5, 21.8, 14.0; **HRMS** (TOF MS ES+) m / z calcd for $C_{14}H_{14}ONa$ (M + Na)+ 221.0942, found 221.0949.



((1*R*,2*R*,3*R*)-2-(naphthalen-2-yl)-3-phenylcyclopropyl)methanol 3.25: was prepared according to general cross-coupling procedure. The following amounts of reagents were used: $Ni(COD)_2$ (2.7 mg, 0.010 mmol, 0.10 equiv), DPEPhos (5.4 mg, 0.010 mmol, 0.10 equiv), oxetane **3.24** (30.9 mg, 0.100 mmol, 1.00 equiv), and MeMgI (80 μL, 0.20 mmol, 2.0 equiv, 2.5 M in Et_2O) in toluene (0.5 mL). The yield was determined to be 96% by NMR spectroscopy of the unpurified product by comparison to internal standard. Purification by flash chromatography (10% ethyl acetate in hexane) afforded the title compound as a white solid (23 mg, 85%). **TLC** $\mathbf{R_f}$ = 0.4 (20% EtOAc in hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.85–7.76 (m, 3H), 7.69 (s, 1H), 7.51–7.32 (m, 7H), 7.30–7.24 (m, 1H), 3.73 (dd, *J* = 6.5, 12.0, 1H), 3.57 (dd, *J* = 8.3, 11.7, 1H), 2.76 (dd, *J* = 5.8, 9.2, 1H), 2.61 (t, *J* = 5.5, 1H), 2.08–1.99 (m, 1H), 1.27 (bs, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 139.0, 137.6, 133.6, 132.2, 128.9, 128.6, 128.2, 127.7, 127.4, 126.7, 126.3, 125.3, 125.2, 124.6, 62.2, 31.6, 31.2, 26.7; **SFC** analysis (AD-H, 10% IPA, 2.5 mL/min, 254 nm) indicated 92:8 er: t_R (minor) = 6.5 min, t_R (major) = 7.5 min; $[\alpha]_{24}^{D}$ –156˚ (c 0.47, $CHCl_3$); **HRMS** (TOF MS ES+) m / z calcd for $C_{20}H_{18}ONa$ (M + Na)+ 297.1255, found 297.1251.



***trans*-2-phenylcyclopropyl)methanol 3.27:** was prepared according to general cross-coupling procedure. The following amounts of reagents were used: $Ni(COD)_2$ (2.7 mg, 0.010 mmol, 0.10 equiv), DPEPhos (5.4 mg, 0.010 mmol, 0.10 equiv), oxetane **3.26** (18.2 mg, 0.100 mmol, 1.00 equiv), and MeMgI (80 μL, 0.20 mmol, 2.0 equiv, 2.5 M in Et_2O) in toluene (0.5 mL). The yield was determined to be 80% by NMR spectroscopy of the unpurified product by comparison to internal standard. Purification by flash chromatography (10% ethyl acetate in hexane) afforded the title compound as a white solid (10 mg, 65%). **TLC R_f** = 0.3 (20% EtOAc in hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.30–7.24 (m, 2H), 7.19–7.14 (m, 1H), 7.11–7.06 (m, 2H), 3.68–3.58 (m, 2H), 1.87–1.81 (m, 1H), 1.64 (bs, 1H), 1.51–1.43 (m, 1H), 1.01–0.89 (m, 2H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 142.7, 128.6, 126.1, 125.9, 66.8, 25.5, 21.5, 14.0; **HRMS** (TOF MS ES+) m / z calcd for $C_{10}H_{12}ONa$ (M + Na)+ 171.0786, found 171.0782.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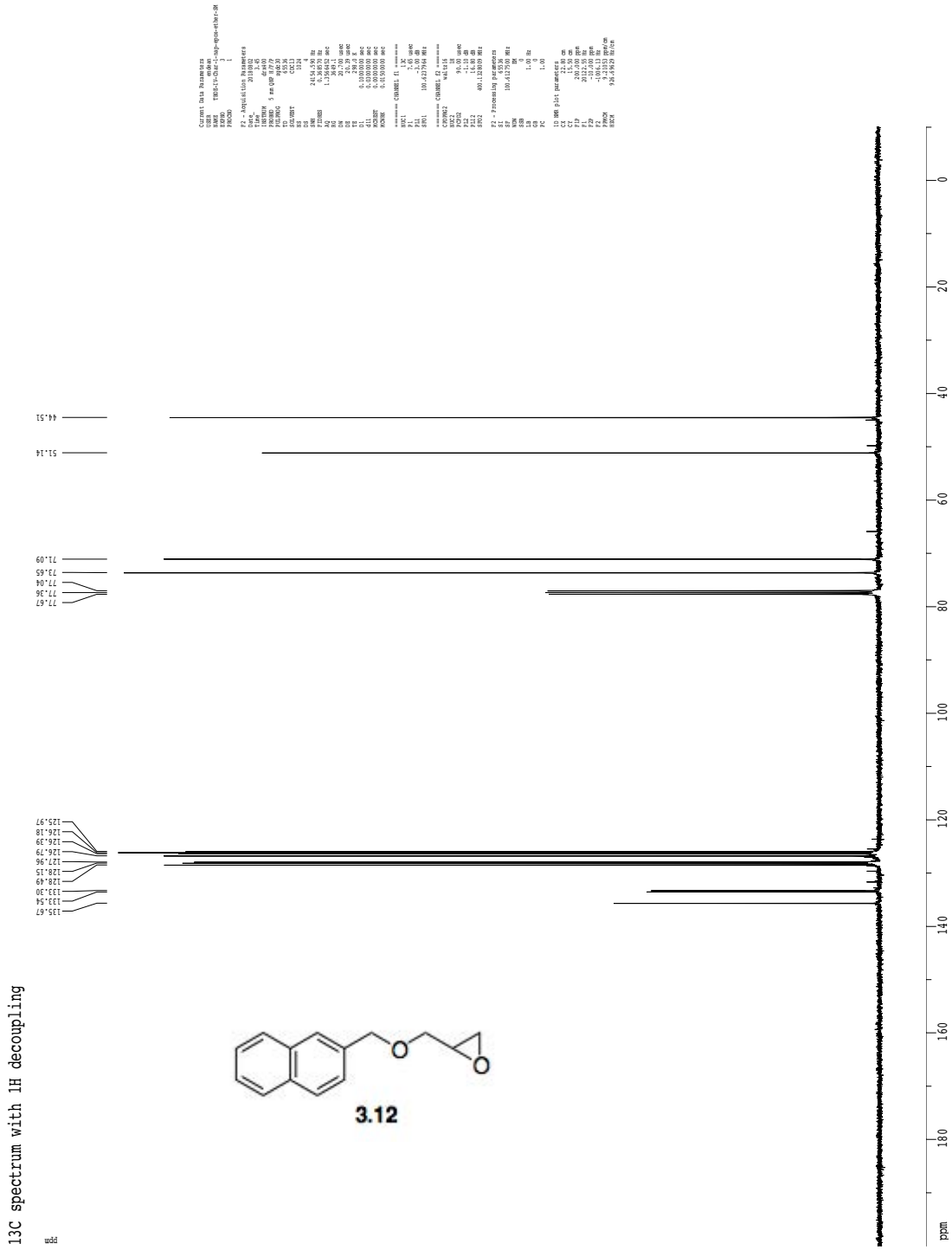
3.12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133.30
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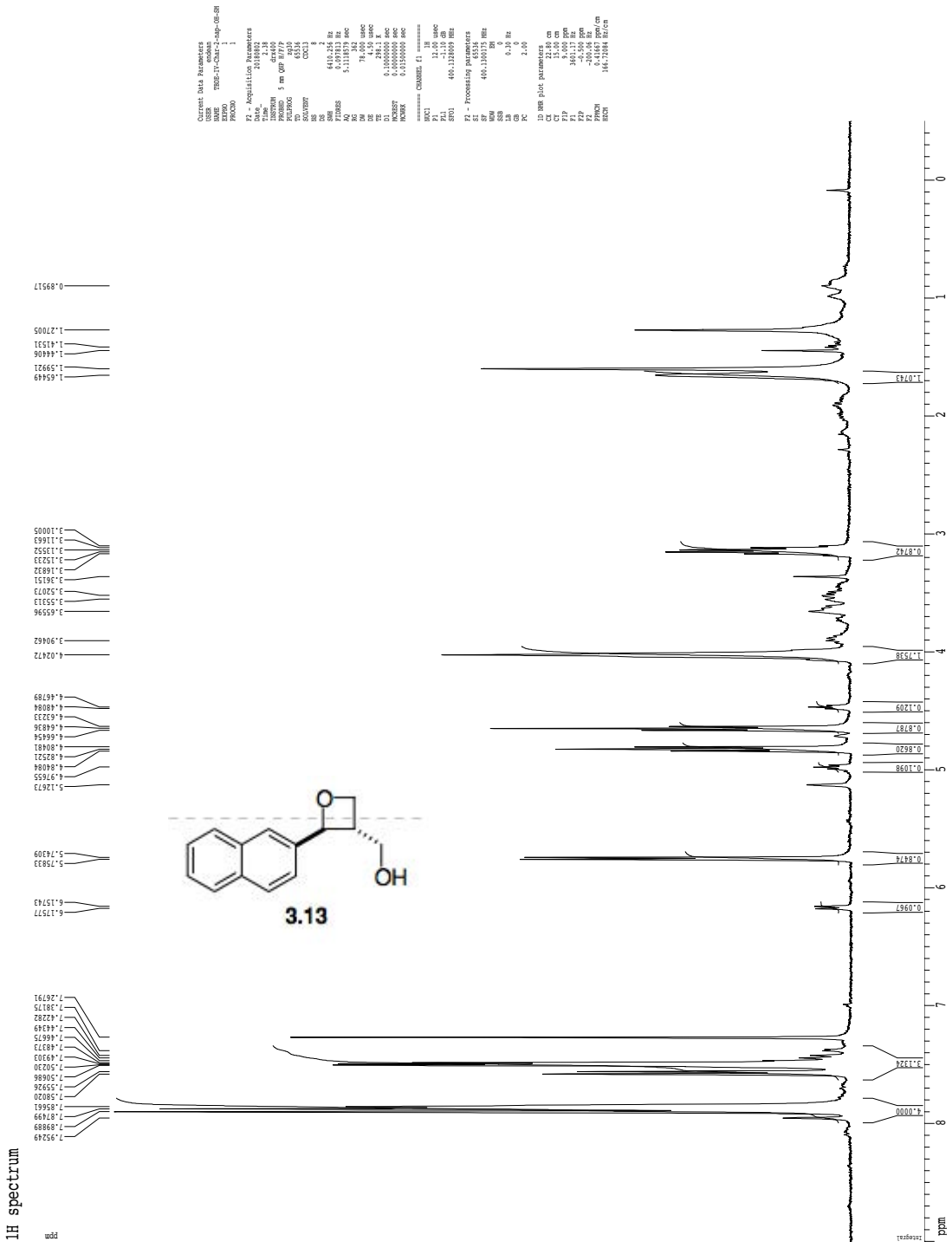
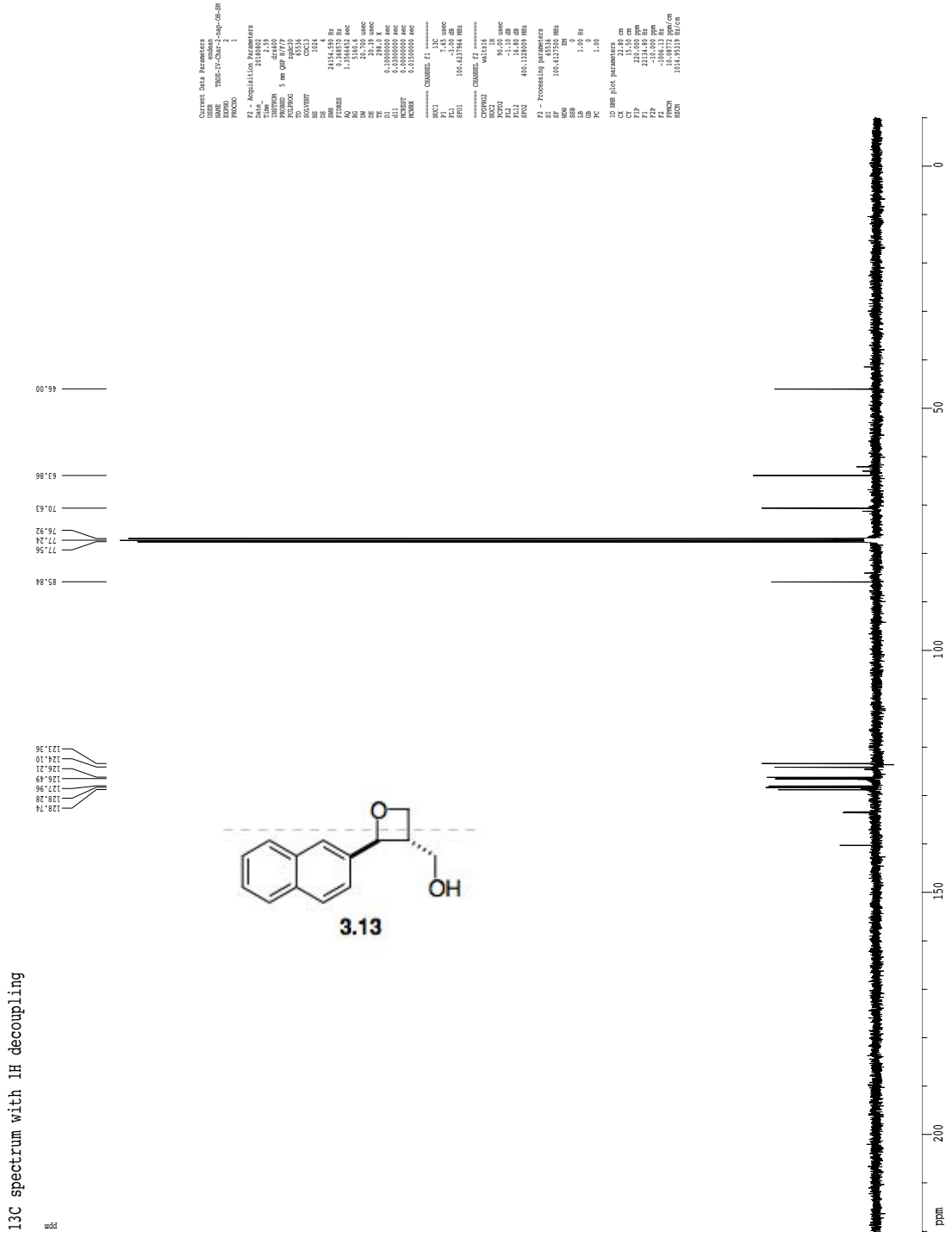
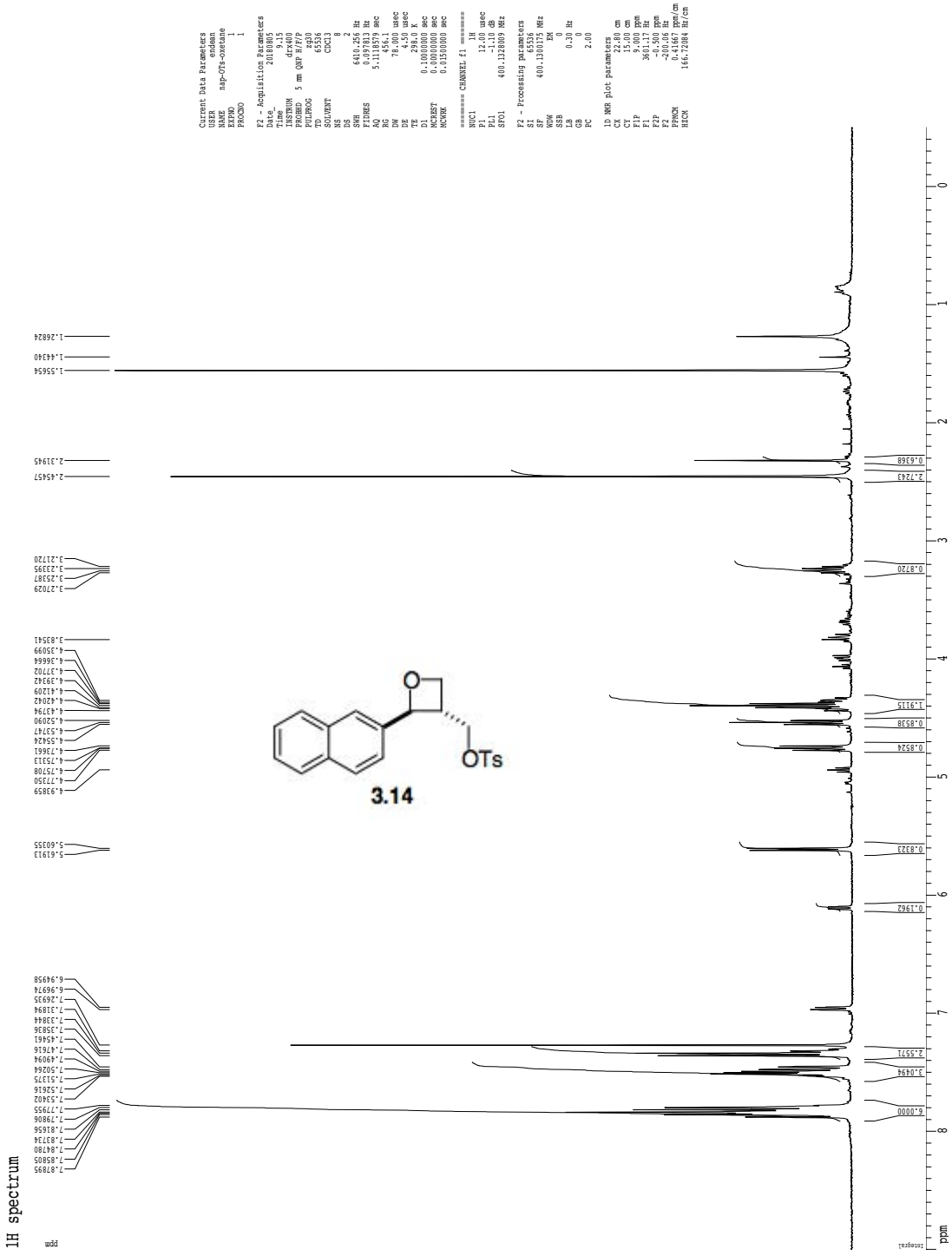
73.65
71.09
51.14
44.51
3.12


1H spectrum
3.13
OH
ppm



13C spectrum with 1H decoupling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FIDRES 0.097813 Hz
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RG 456.1
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DE 6.50 usec
TE 298.1 K
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MCREST 0.00000000 sec
MCWRK 0.01500000 sec
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PL1 -1.10 dB
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LB 0.30 Hz
GB 0
PC 2.00
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F2P -0.500 ppm
F2 -200.06 Hz
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HZCM 166.72084 Hz/cm
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1.44340
2.45457
0.63680
2.72430
0.87200
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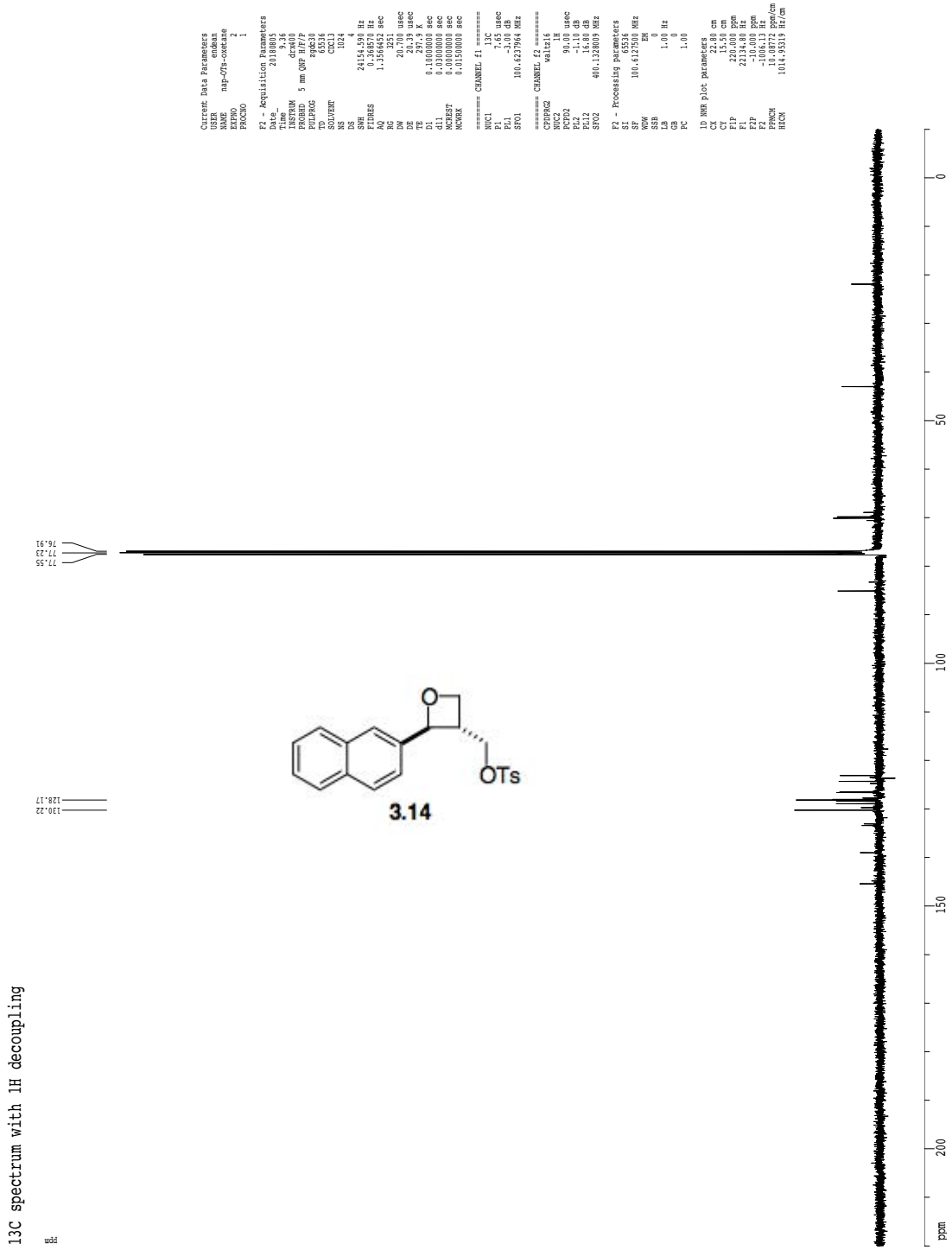
6.00000
OTs
3.14
ppm
Integral


13C spectrum with 1H decoupling
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PROCNO 1
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RG 203
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DE 20.39 usec
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PL1 -3.00 dB
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PCPD2 90.00 usec
PL2 -1.10 dB
PL12 16.40 dB
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76.91
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3.14
ppm
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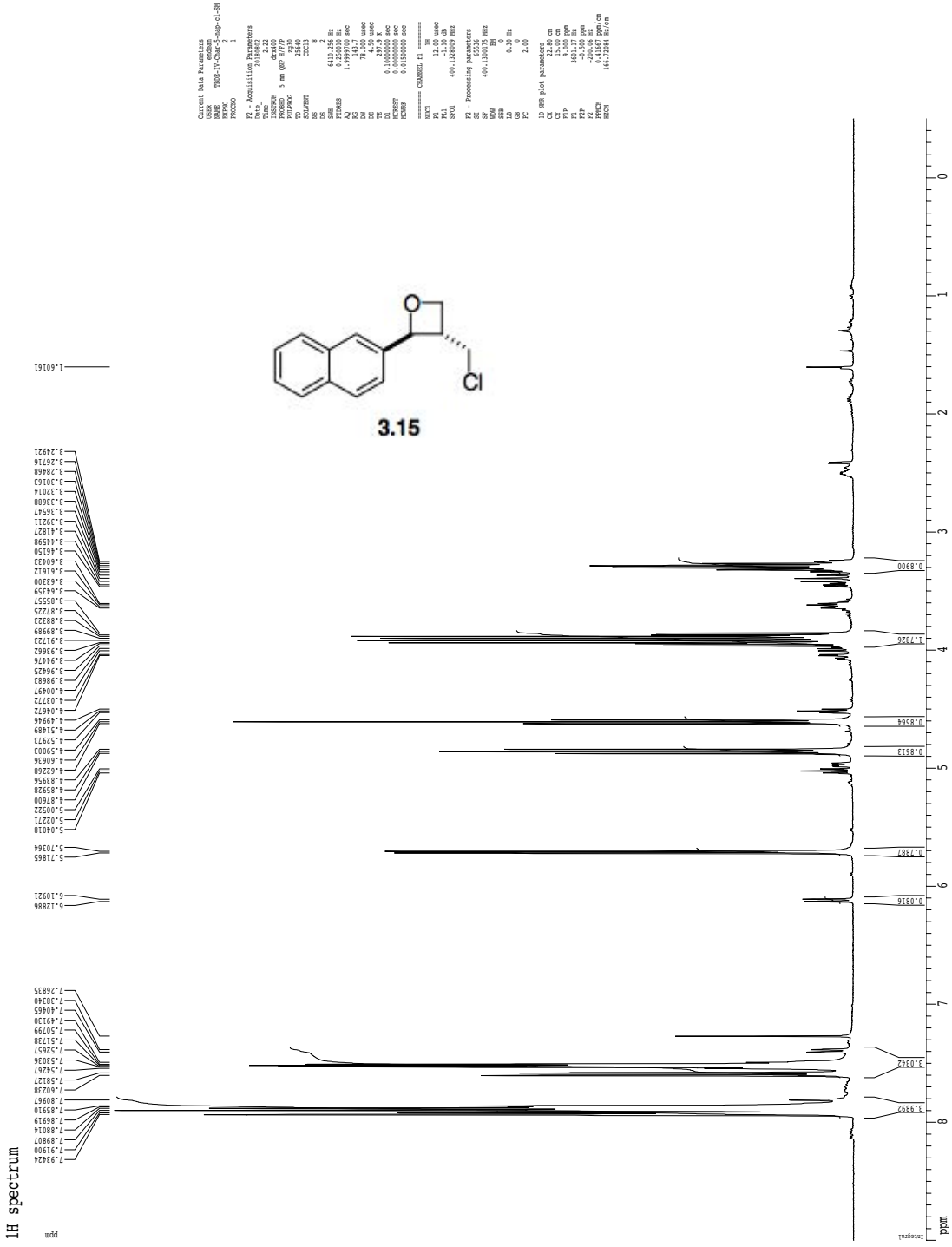
50
100
150
200
ppm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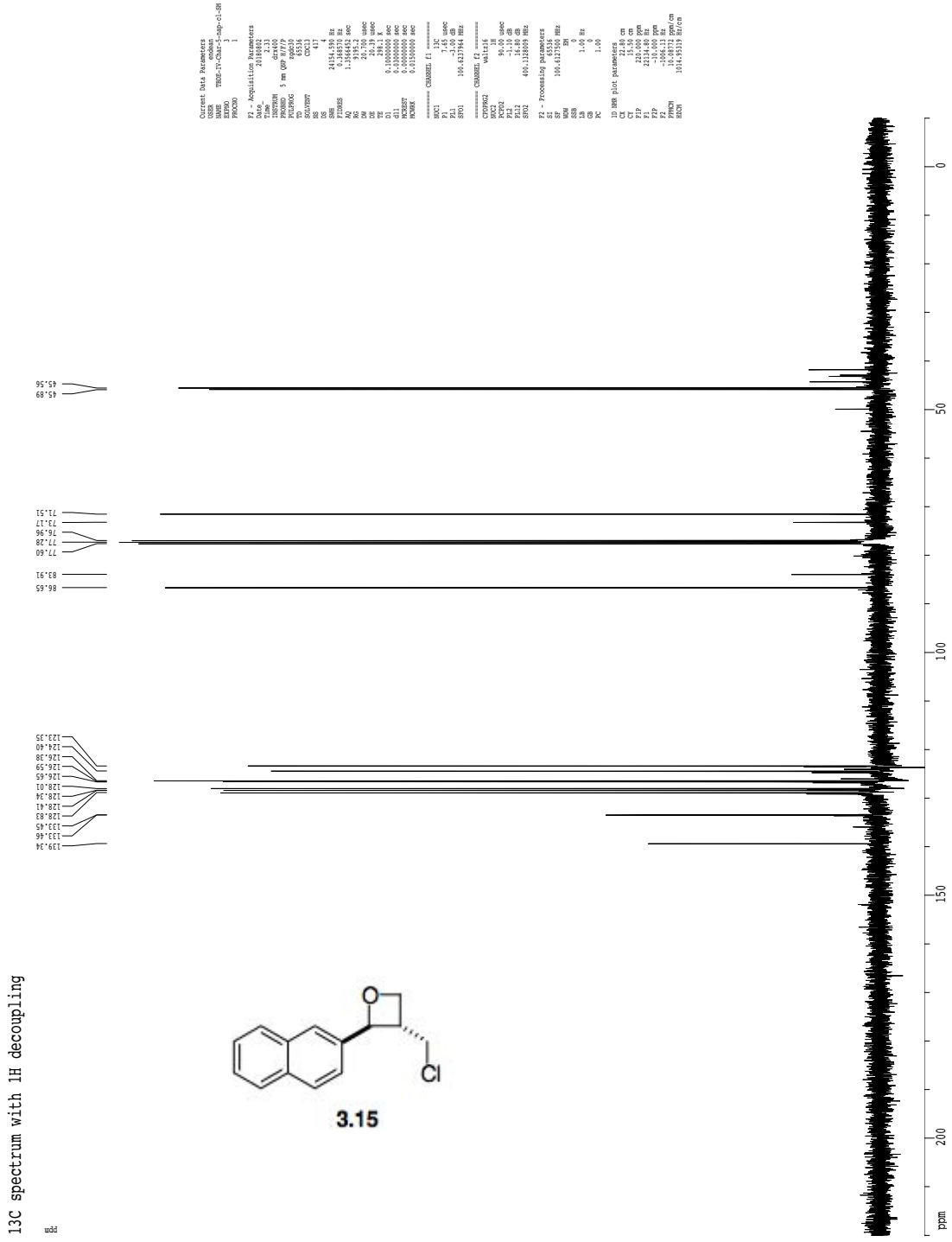
O
ppm


13C spectrum with 1H decoupling
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73.17
76.96
77.28
77.60
83.91
86.65
123.35
124.40
126.38
126.59
126.65
128.01
128.34
128.41
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133.46
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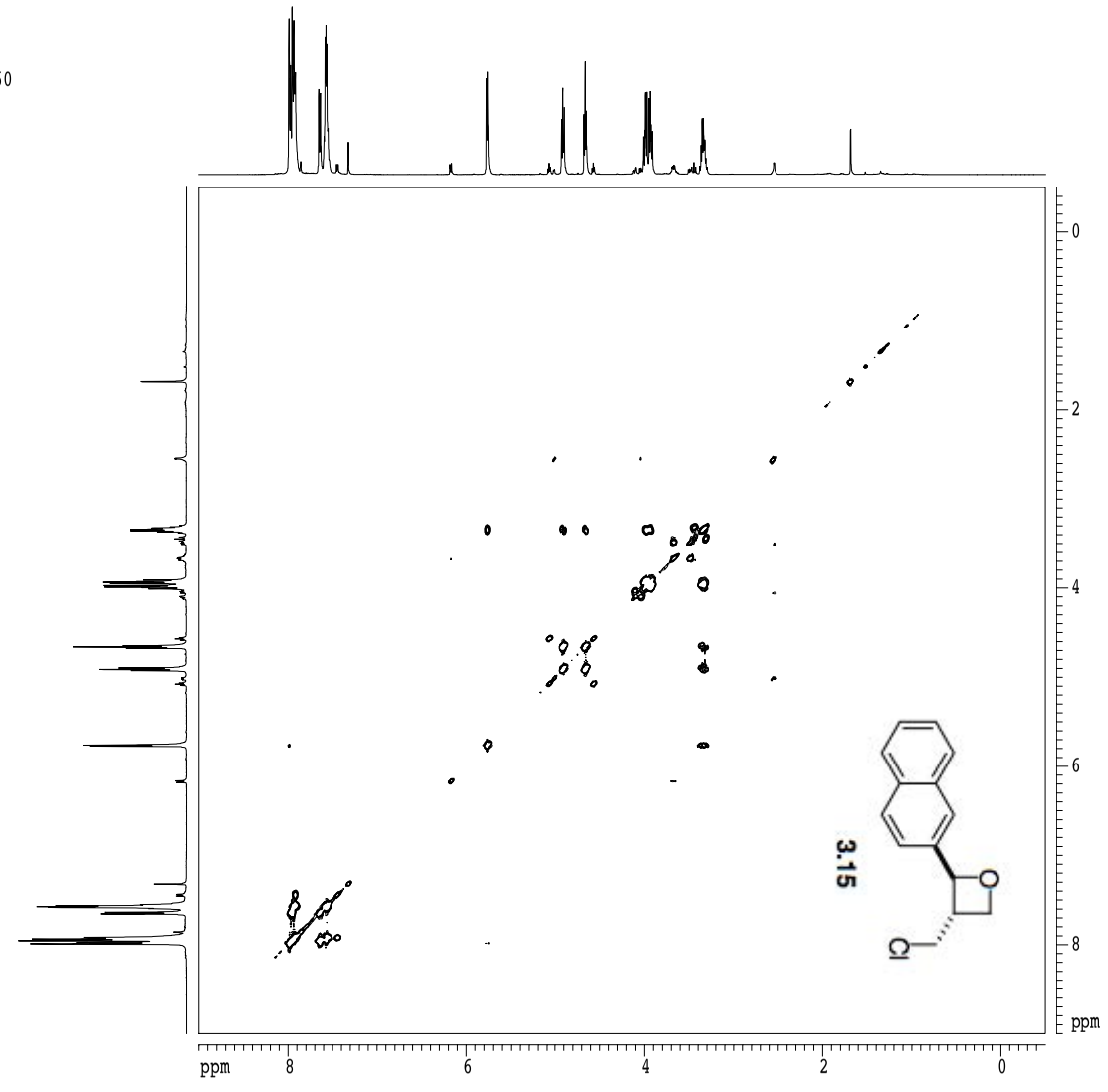
ppm
0
50
100
150
200

O
Cl

3.15

gcosy60

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  IN0               0.00012480 sec

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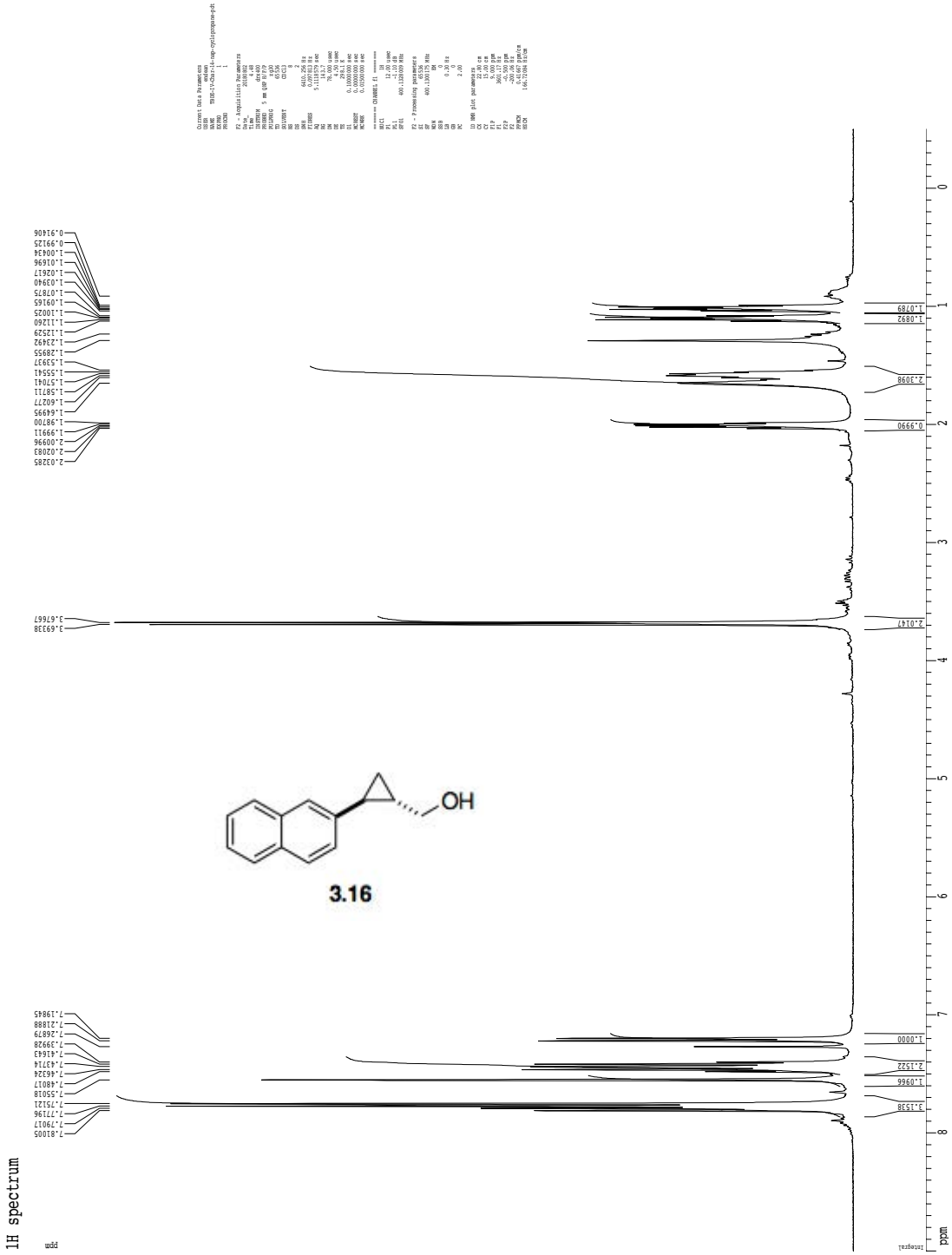
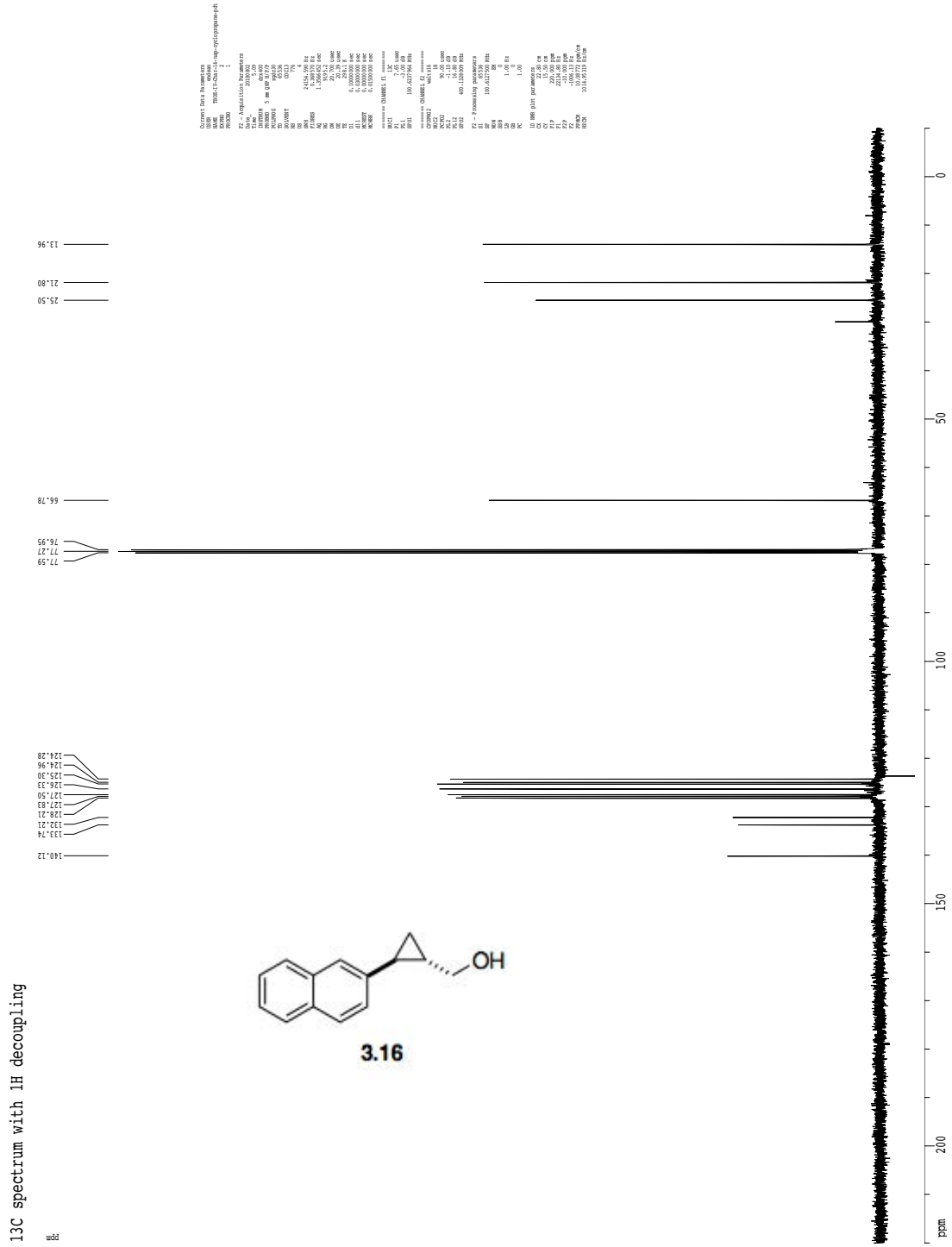
3.15
gmoe
ppm


1H spectrum
OH
3.16


13C spectrum with 1H decoupling
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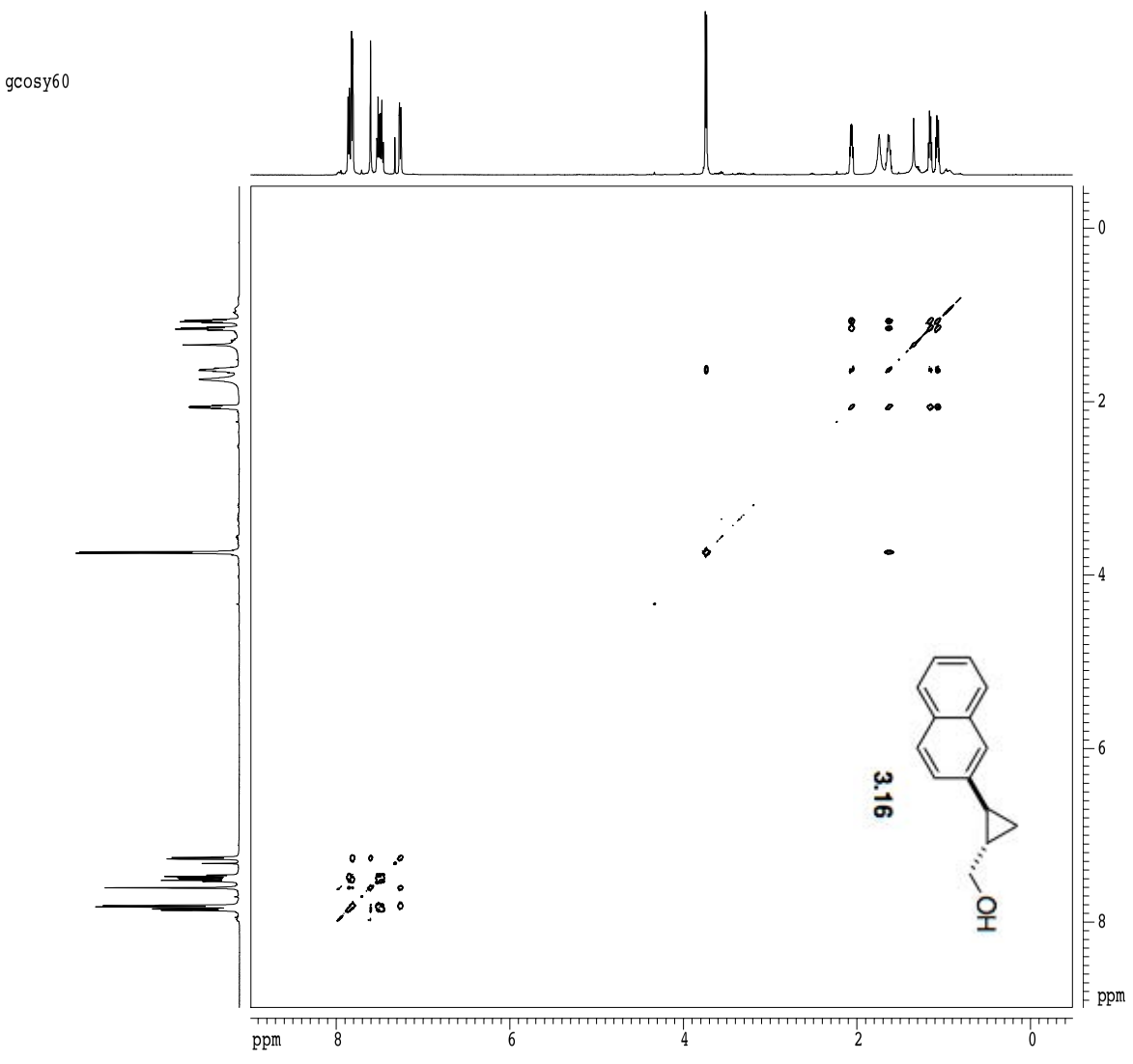
3.16
ppm

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  F1HZCM          315.65659 Hz/cm
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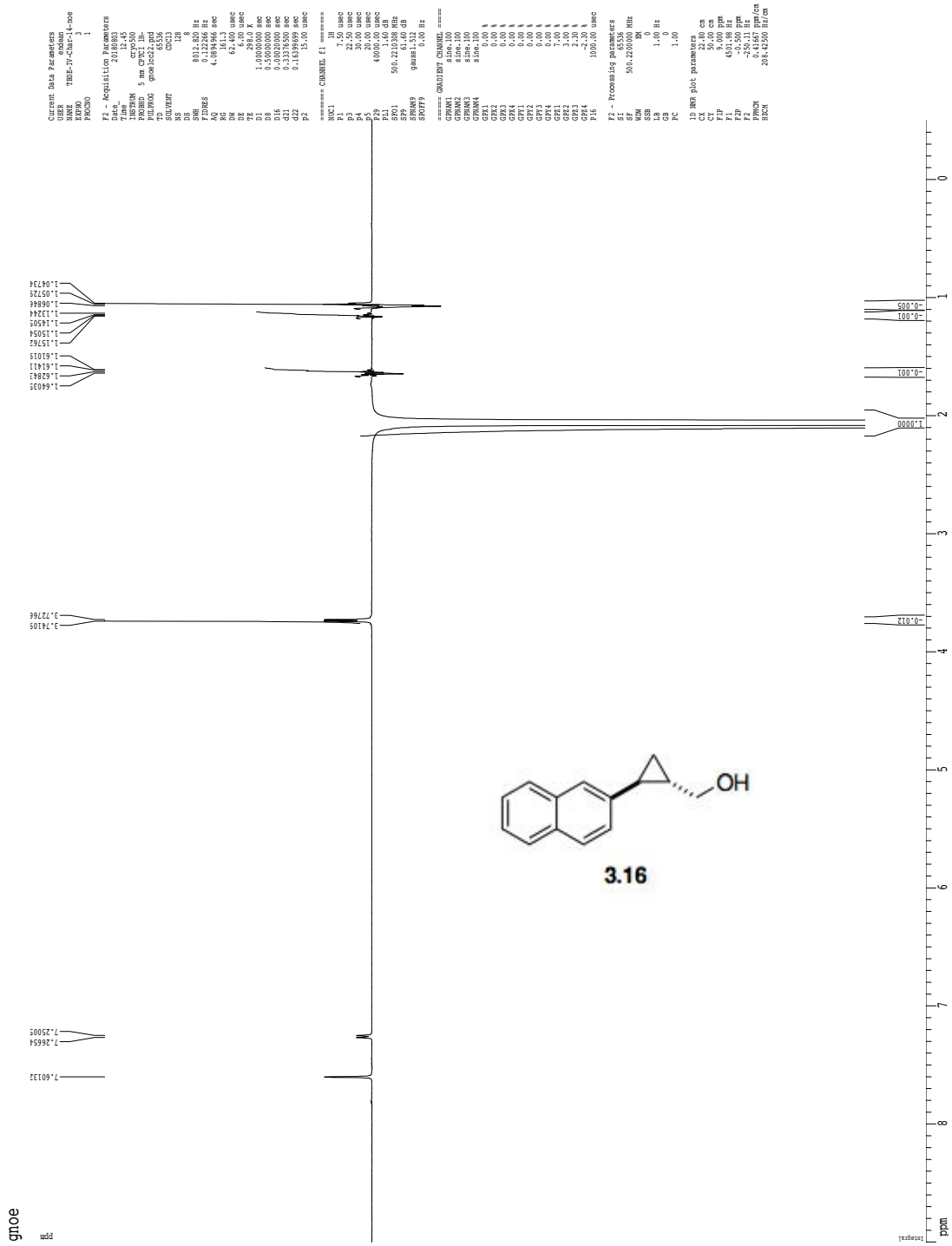
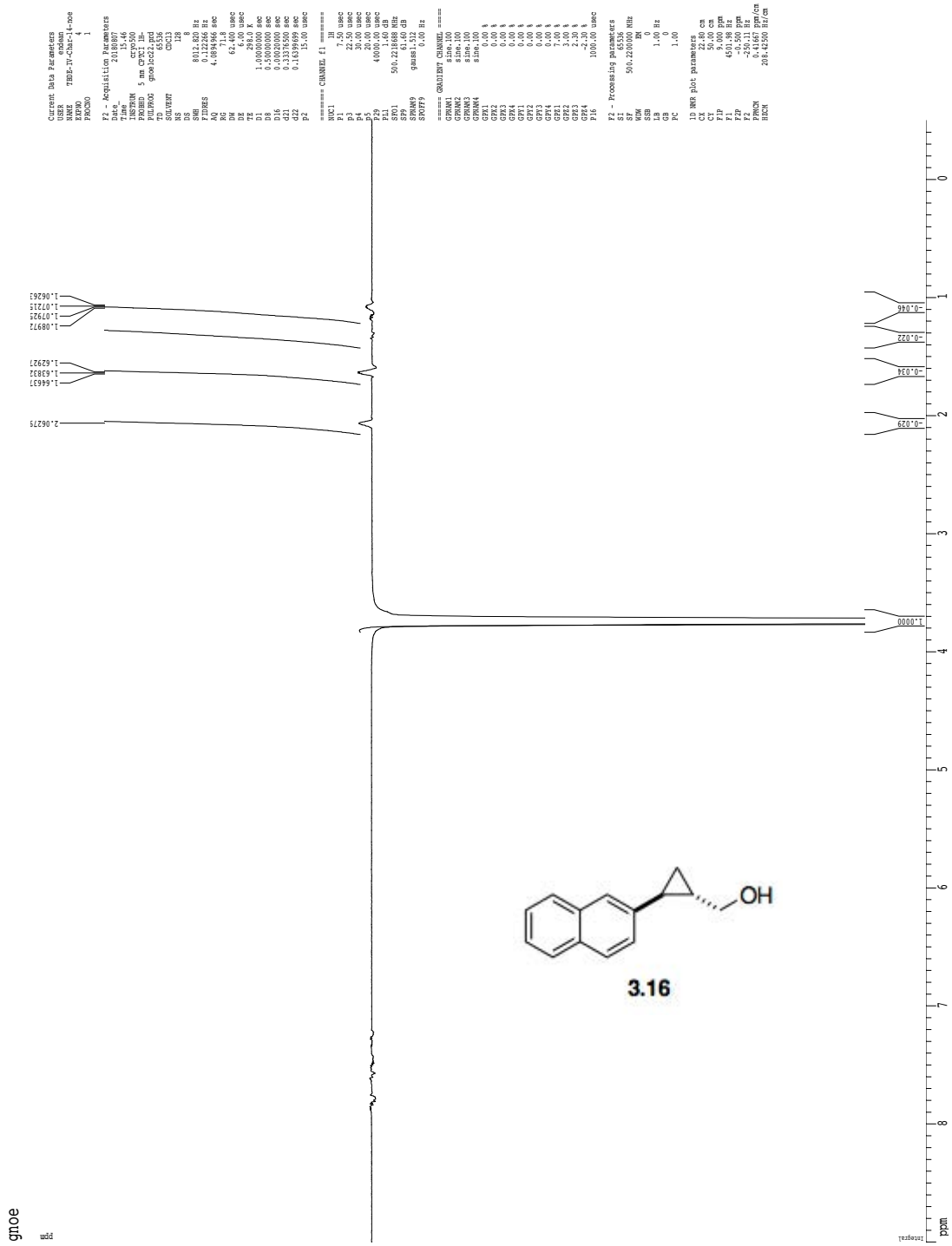
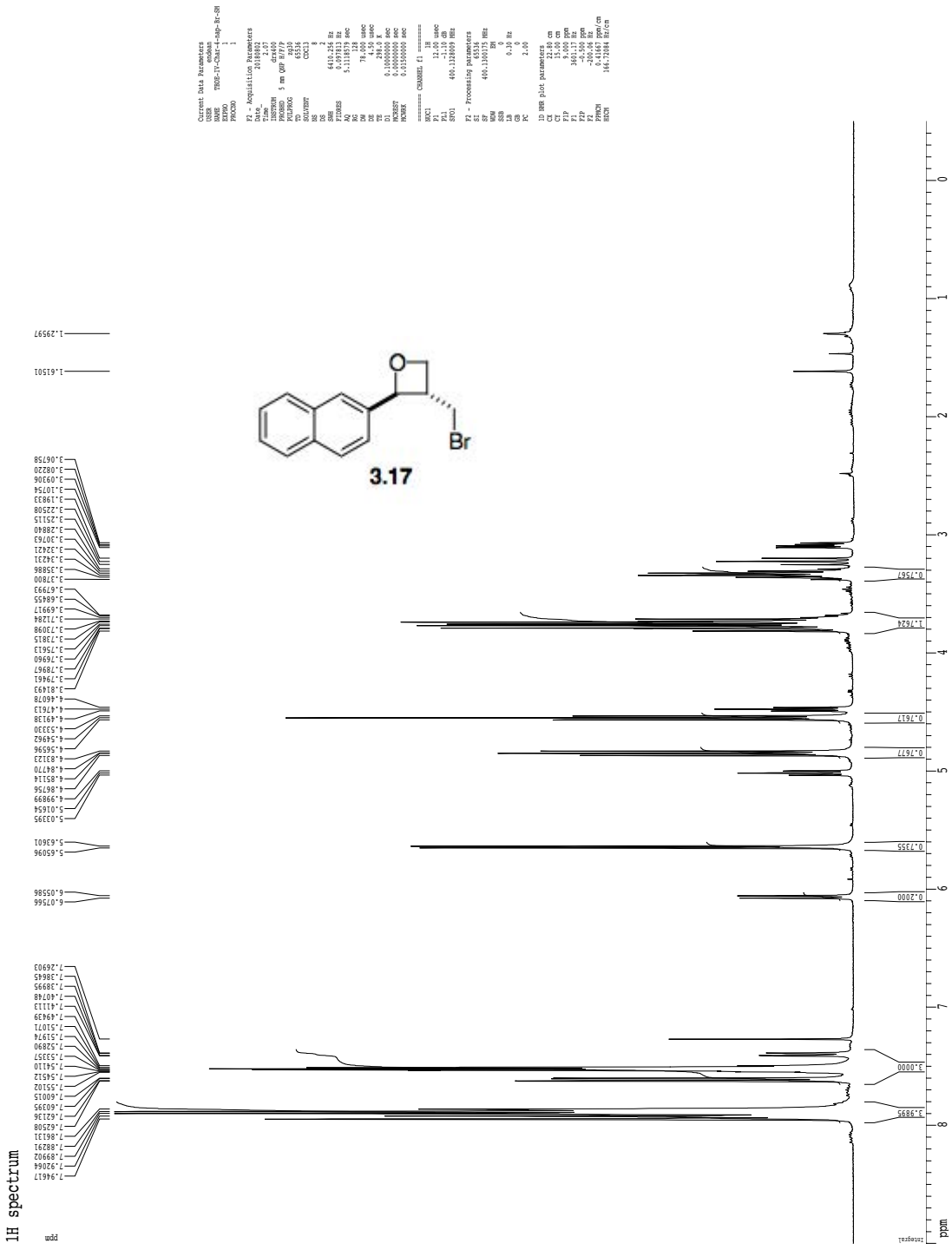
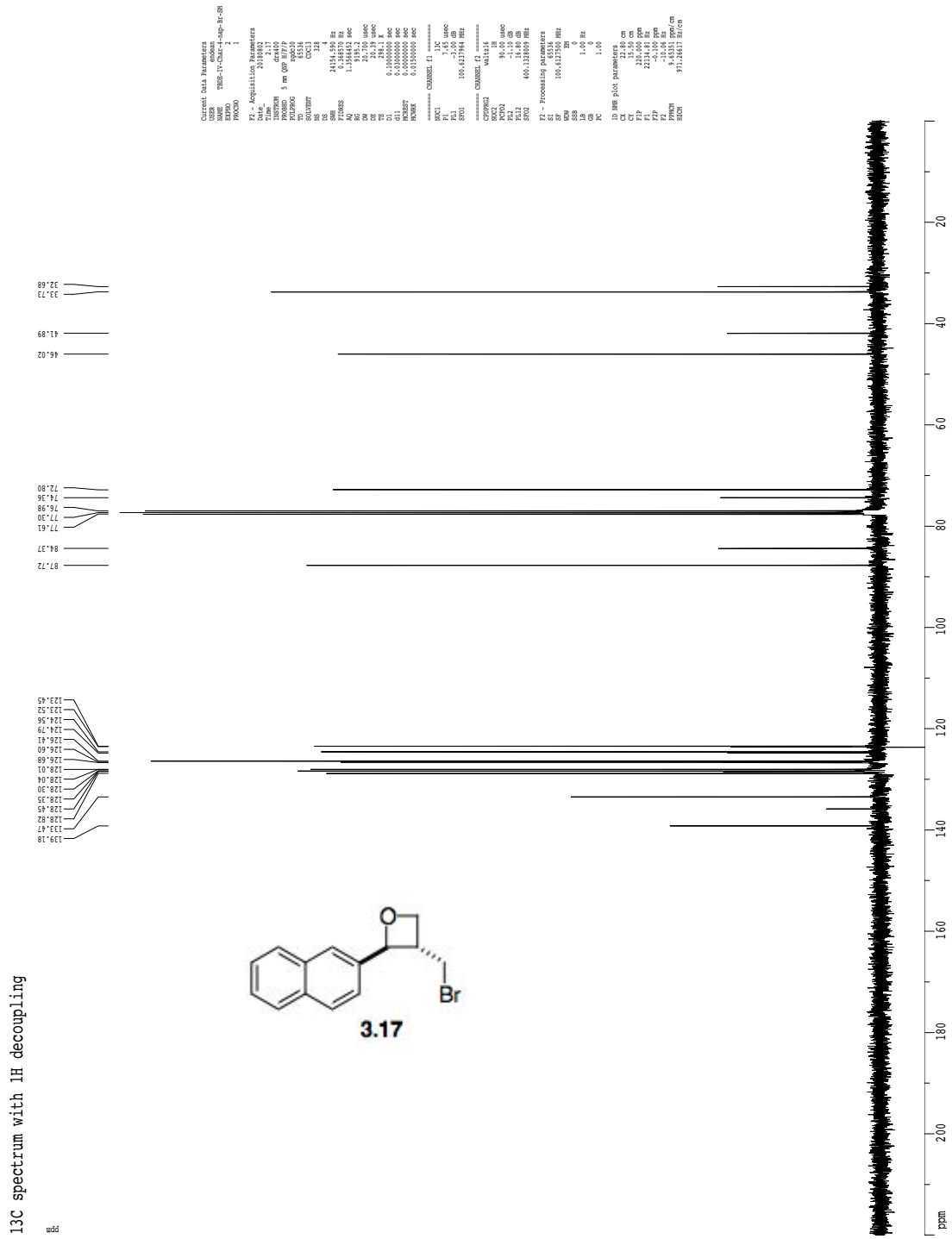
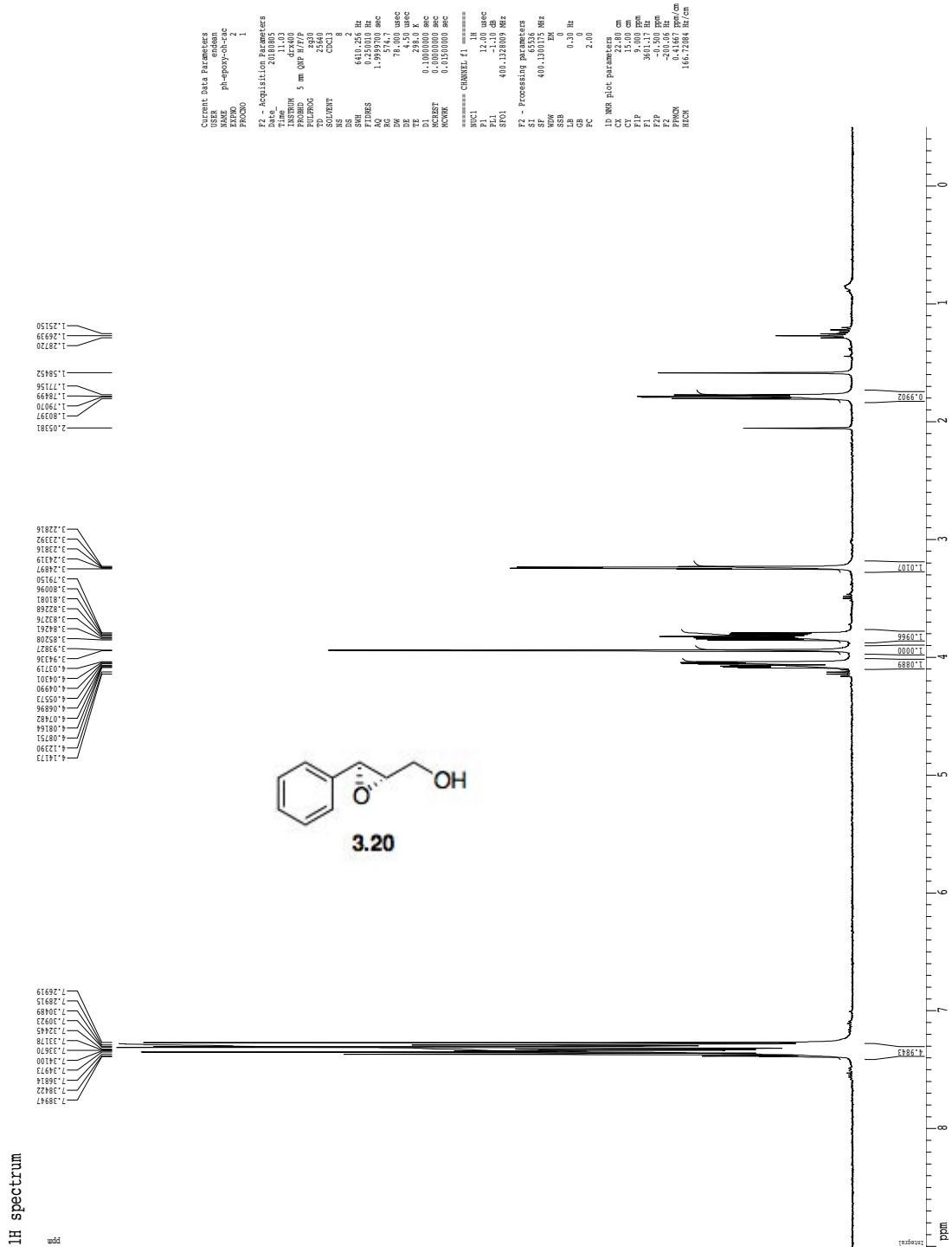

OH
3.16
gmoe
ppm

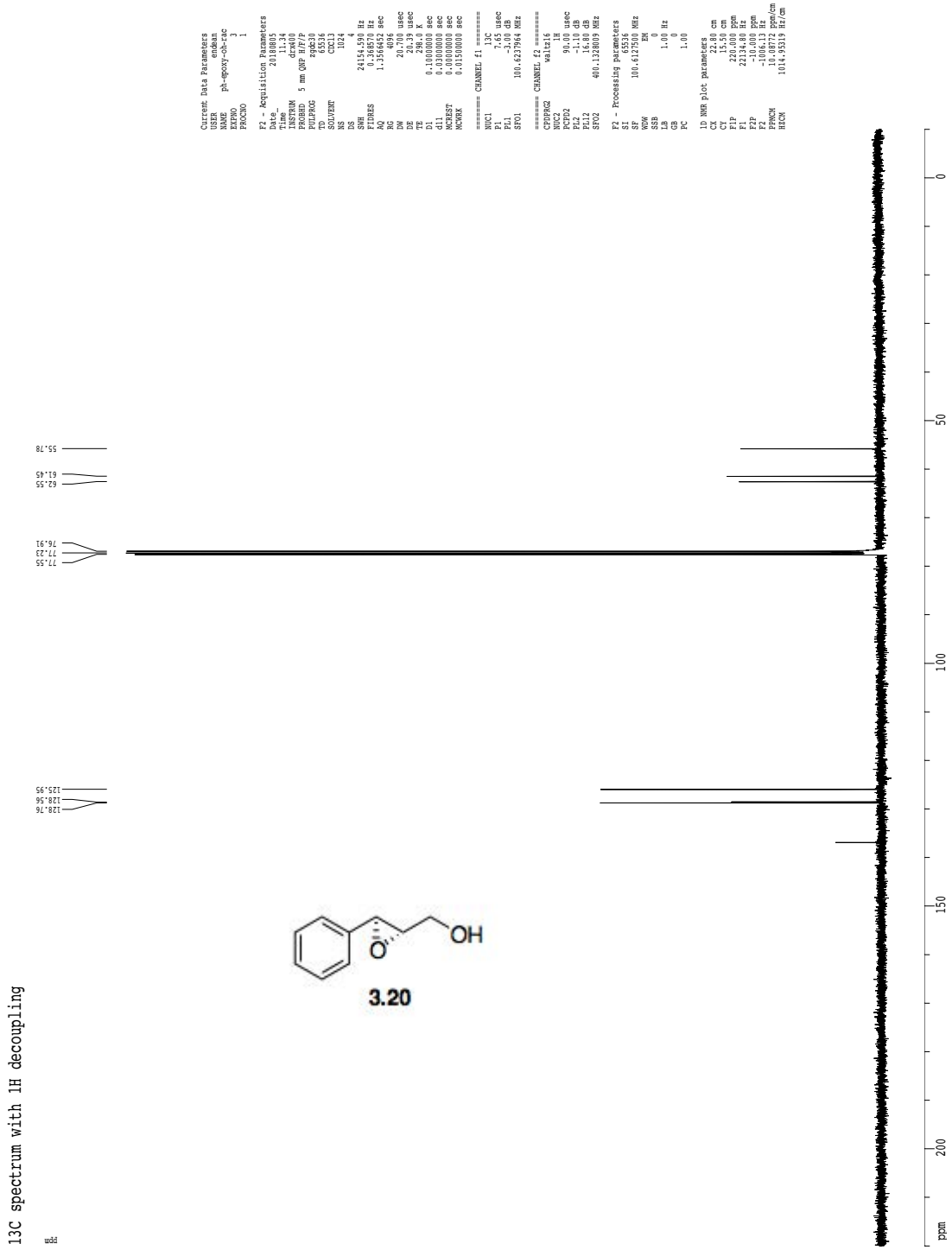

gmoe
ppm
1.0000
0.046
0.022
0.034
0.029
1.0672
1.0715
1.0793
1.0897
1.6467
1.6383
1.6292
2.0679
OH

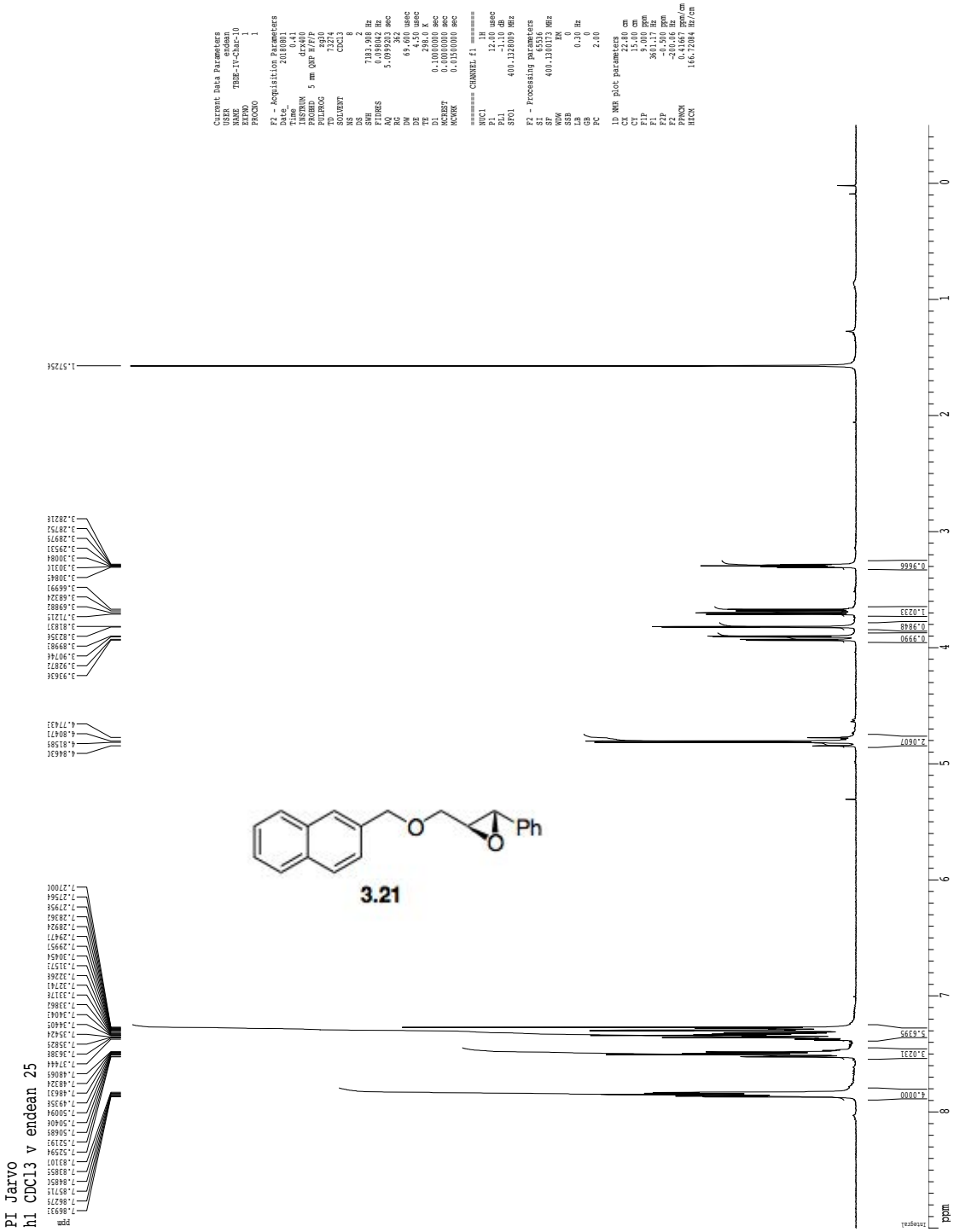
3.16


1H spectrum
3.17
Br
ppm


13C spectrum with 1H decoupling
Br
3.17
ppm


1H spectrum
Current data Parameters
USER endaan
NAME ph-epoxy-oh-cac
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20101015
Time 11.24 h
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 32464
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.197310 Hz
AQ 1.999700 sec
RG 574.7
DW 78.000 usec
DE 6.50 usec
TE 298.1 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 -1.10 dB
SFO1 400.1320009 MHz
F2 - Processing parameters
SI 65536
SF 400.1300175 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.51 Hz
F2P -0.501 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72084 Hz/cm
OH
3.20
ppm
Integral

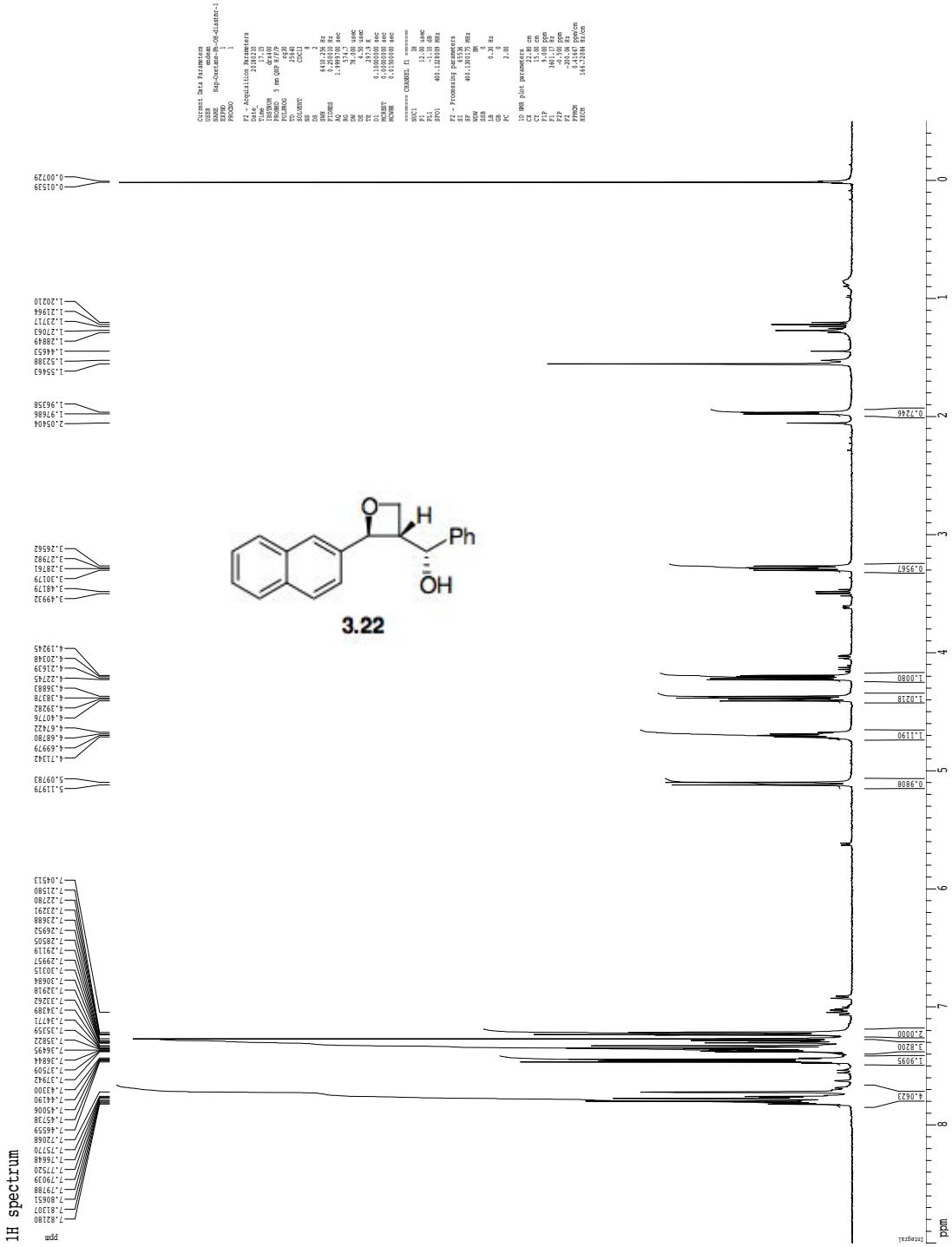

13C spectrum with 1H decoupling
wdd
Current Data Parameters
USER endaan
NAME ph-epoxy-oh-rac
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180815
Time 11.14
INSTRUM drx400
PROBHD 5 mm QNP H/P/P
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 24154.590 Hz
FIDRES 0.368570 Hz
AQ 1.3564432 sec
RG 406
DW 20.700 usec
DE 20.39 usec
TE 298.0 K
D1 0.11000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 7.45 usec
PL1 -3.00 dB
SFO1 100.6237964 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 -1.10 dB
PL12 16.40 dB
SFO2 400.1318019 MHz
F2 - Processing parameters
SI 65536
SF 100.6125010 MHz
WDW EM
SSB 1.00 Hz
LB 0
GB 1.00
PC
1D NMR plot parameters
CX 22.80 cm
CY 15.50 cm
F1P 220.000 ppm
F1 22134.40 Hz
F2P -1.100 ppm
F2 -106.13 Hz
PPMCM 10.08772 ppm/cm
HZCM 1014.95319 Hz/cm
55.78
61.65
62.55
76.91
77.23
77.55
125.95
128.56
128.76
OH
O
3.20
ppm
0
50
100
150
200

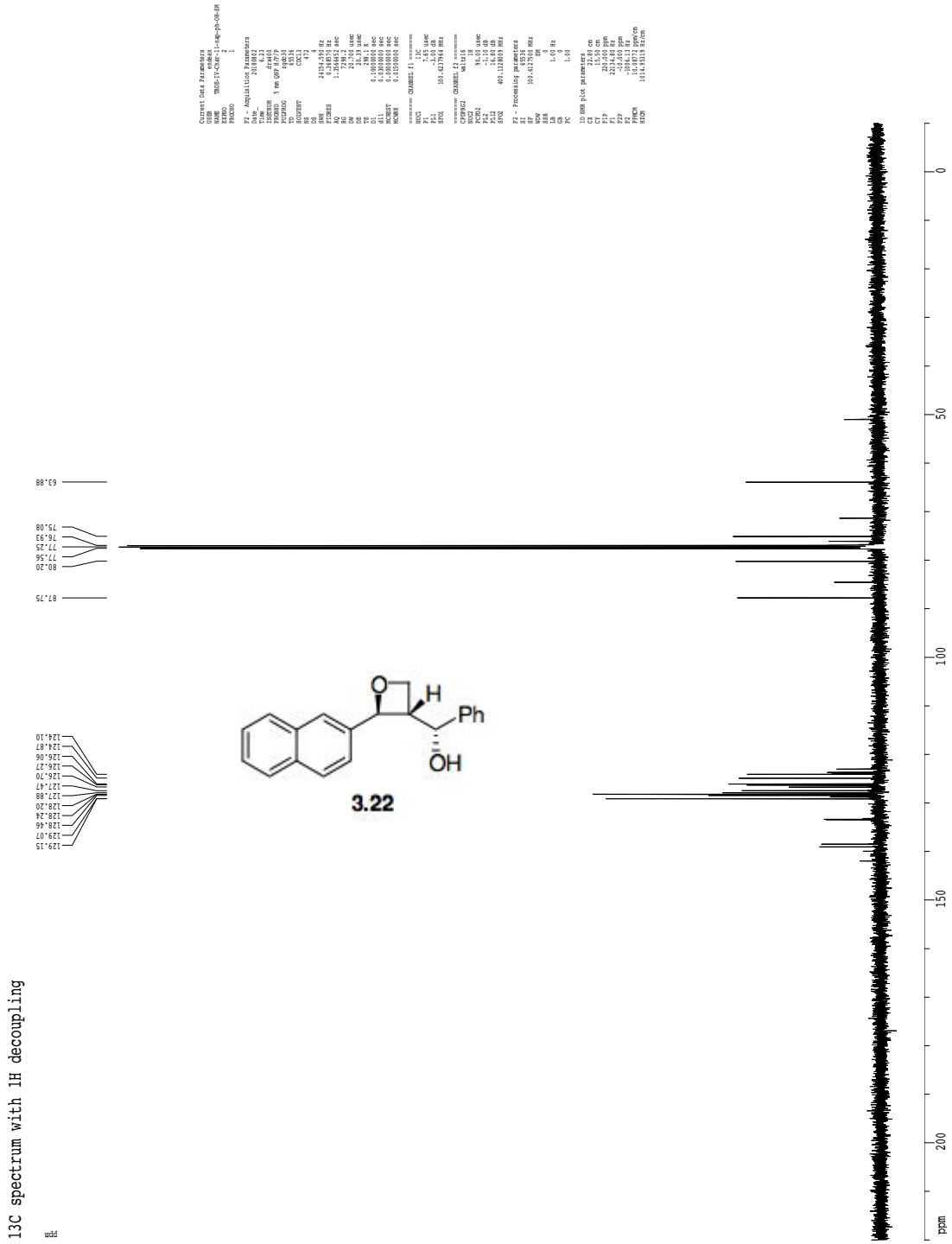

PI Jarvo
h1 CDCl3 v endean 25
Current data Parameters
USER endean
NAME TBDE-IV-Char-10
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20181001
Time 11.14
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 73724
SOLVENT CDCl3
NS 8
DS 2
SWH 7183.908 Hz
FIDRES 0.097543 Hz
AQ 5.099201 sec
RG 362
DW 69.600 usec
DE 6.50 usec
TE 293.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 -1.10 dB
SFO1 400.1320009 MHz
F2 - Processing parameters
SI 65536
SF 400.1300173 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.31 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72084 Hz/cm
1.57256
0.9666
1.0233
0.9848
0.9990
2.0607
5.6395
3.0231
4.0000
3.28218
3.28752
3.28975
3.29531
3.30064
3.30312
3.30845
3.66991
3.68324
3.69882
3.71215
3.81837
3.82356
3.89983
3.90746
3.92872
3.93634
4.77432
4.80471
4.81589
4.84634
7.27006
7.27564
7.27956
7.28362
7.28924
7.29671
7.29951
7.30454
7.31571
7.32268
7.32741
7.33178
7.33862
7.34641
7.34405
7.35424
7.35825
7.36388
7.37444
7.48065
7.48324
7.48631
7.49356
7.50094
7.50406
7.50689
7.52193
7.52594
7.83107
7.83855
7.84856
7.85715
7.86279
7.86931
ppm
Integral
ppm

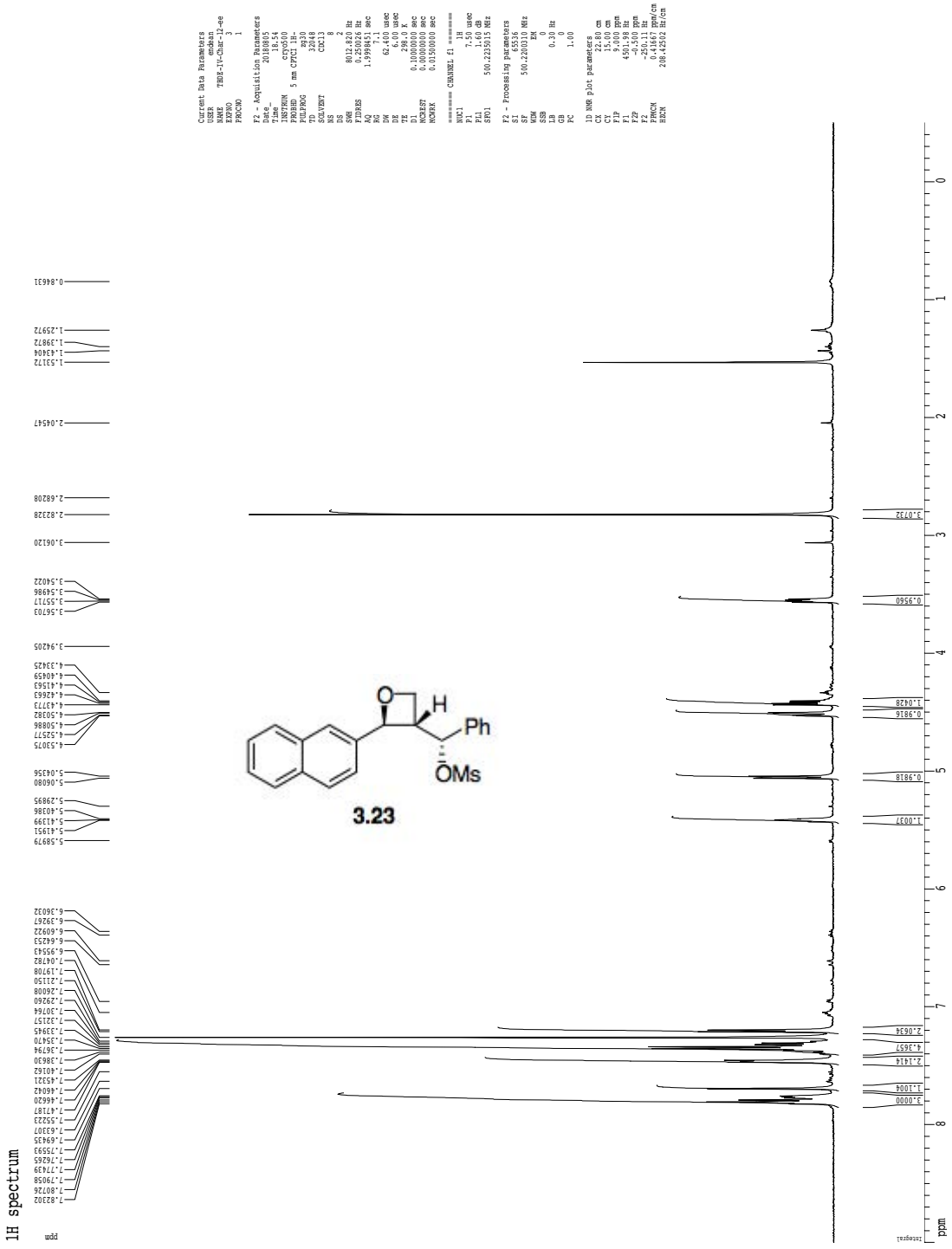
O
O
Ph

3.21

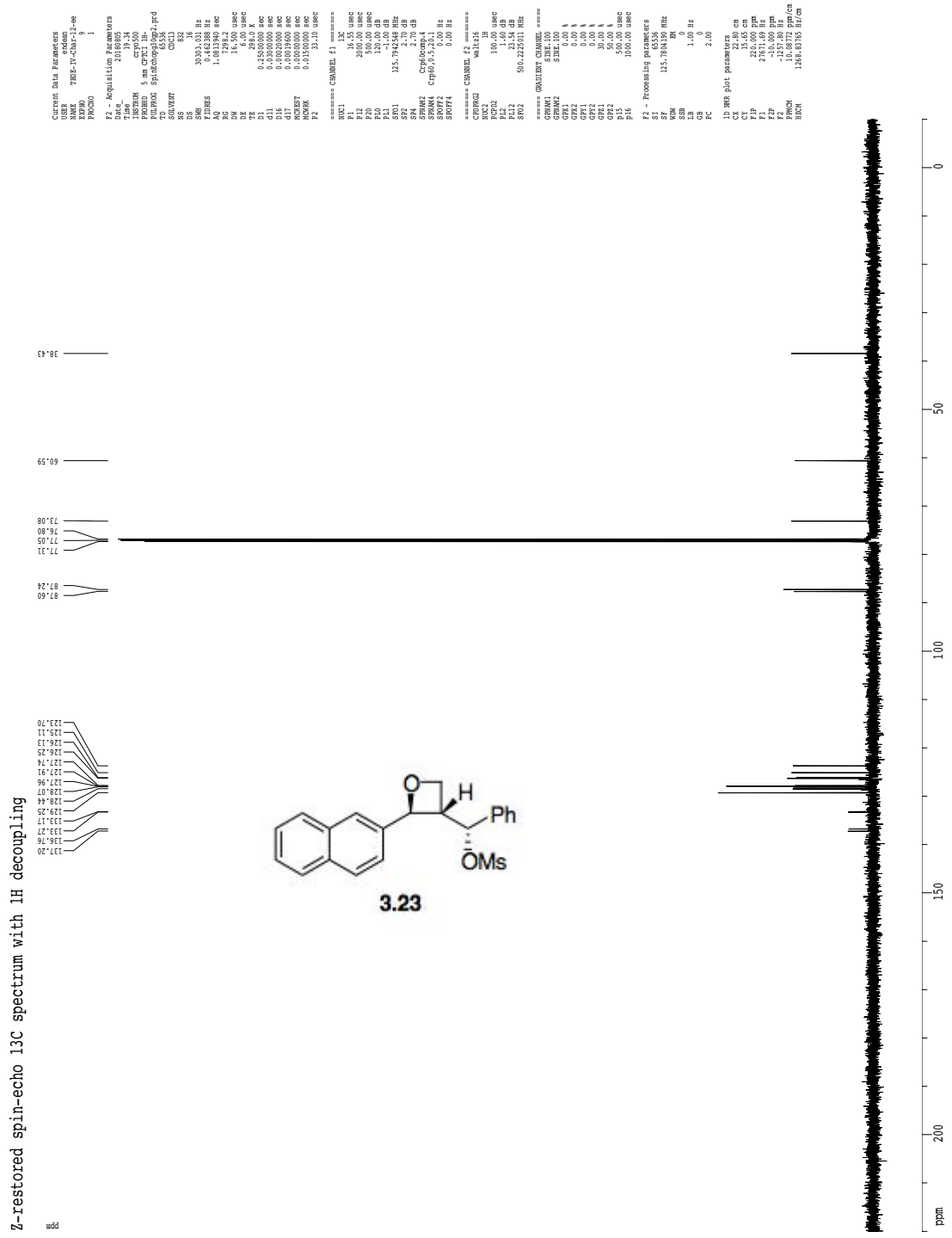

PI Jarvo
c13maxns=256 CDCl3 v endean 25
Current Data Parameters
USER endean
NAME TBDS-IV-Char-10
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190801
Time 6.40
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 24154.590 Hz
FIDRES 0.368570 Hz
AQ 1.3566443 sec
RG 181.75
DW 20.700 usec
DE 20.39 usec
TE 297.9 K
D1 0.11000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 7.60 usec
PL1 -3.00 dB
SFO1 100.6237964 MHz
======== CHANNEL f2 ========
CPDPRG2 mlev16
NUC2 1H
PCPD2 90.00 usec
PL2 -1.10 dB
PL12 16.40 dB
SFO2 400.1318019 MHz
F2 - Processing parameters
SI 65536
SF 100.6125759 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 22.80 cm
CY 15.50 cm
F1P 220.000 ppm
F1 22134.48 Hz
F2P -100.000 ppm
F2 -10061.13 Hz
PPMCM 10.08772 ppm/cm
HZCM 1014.95319 Hz/cm
O
O
Ph
3.21
56.14
61.41
70.13
73.75
76.91
77.23
77.55
125.94
126.17
126.37
126.82
127.93
128.12
128.49
128.71
135.54
ppm
0
50
100
150
200

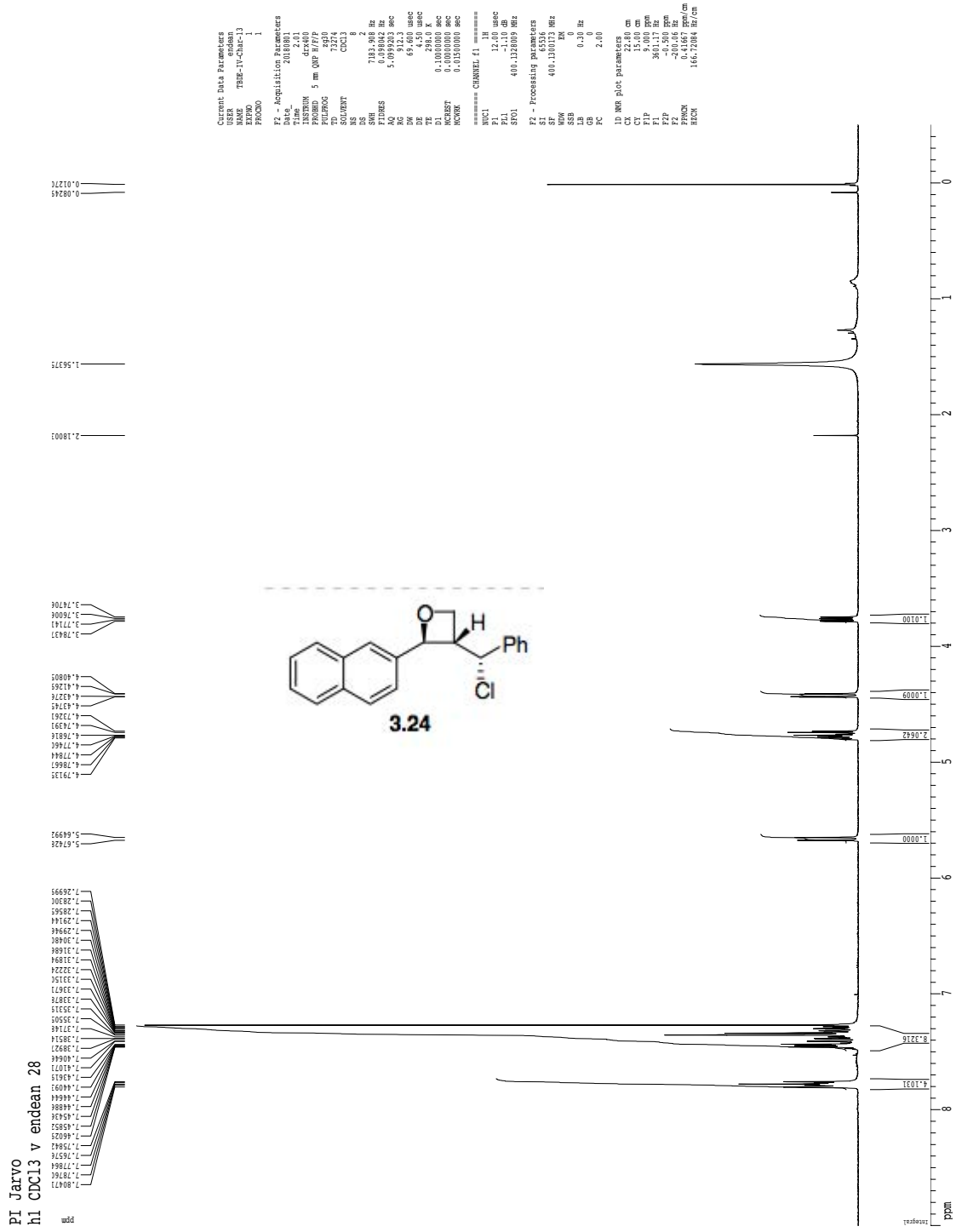

1H spectrum
ppm
Integral
O
H
Ph
OH
3.22


13C spectrum with 1H decoupling
ppm
63.88
75.08
76.93
77.25
77.56
80.20
87.75
124.10
124.87
126.06
126.27
126.70
127.47
127.88
128.20
128.24
128.66
129.07
129.15
O
H
Ph
OH
3.22
0
50
100
150
200

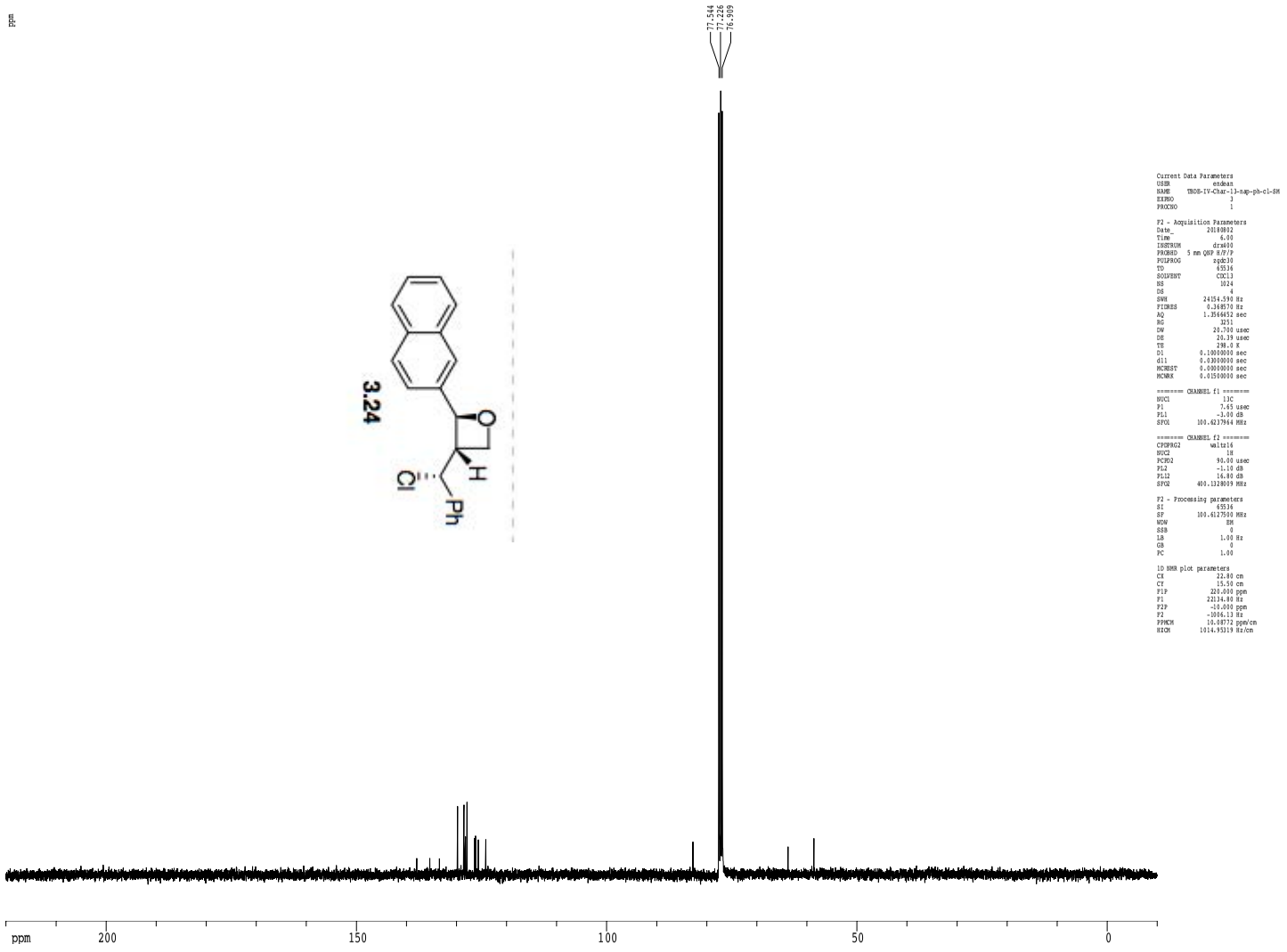

1H spectrum
Current Data Parameters
USER mndaan
NAME TBDR-IV-Char-2-ee
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180805
Time_ 18.54
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 32048
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.250026 Hz
AQ 1.9999451 sec
RG 1
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 2.0000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200110 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.300 ppm
F2 -150.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm
0.84631
1.25972
1.39872
1.43404
1.53172
2.04647
2.68208
2.82328
3.06120
3.54022
3.54986
3.55717
3.56703
3.94205
4.33425
4.40459
4.41563
4.42663
4.43773
4.50382
4.50886
4.52517
4.53075
5.04356
5.06080
5.29895
5.40386
5.41399
5.41951
5.58979
6.36032
6.39267
6.40922
6.44253
6.95543
7.04782
7.19708
7.21150
7.26008
7.29260
7.30164
7.32157
7.33945
7.35470
7.36794
7.38630
7.40162
7.44321
7.46042
7.46620
7.47187
7.52323
7.63307
7.69435
7.75593
7.76265
7.77439
7.79058
7.80726
7.82302
ppm
O
H
Ph
OMs
3.23
3.0732
0.9560
1.0428
0.9816
0.9818
1.0037
2.0634
4.3657
2.1414
1.1004
3.0000
Integral
ppm

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



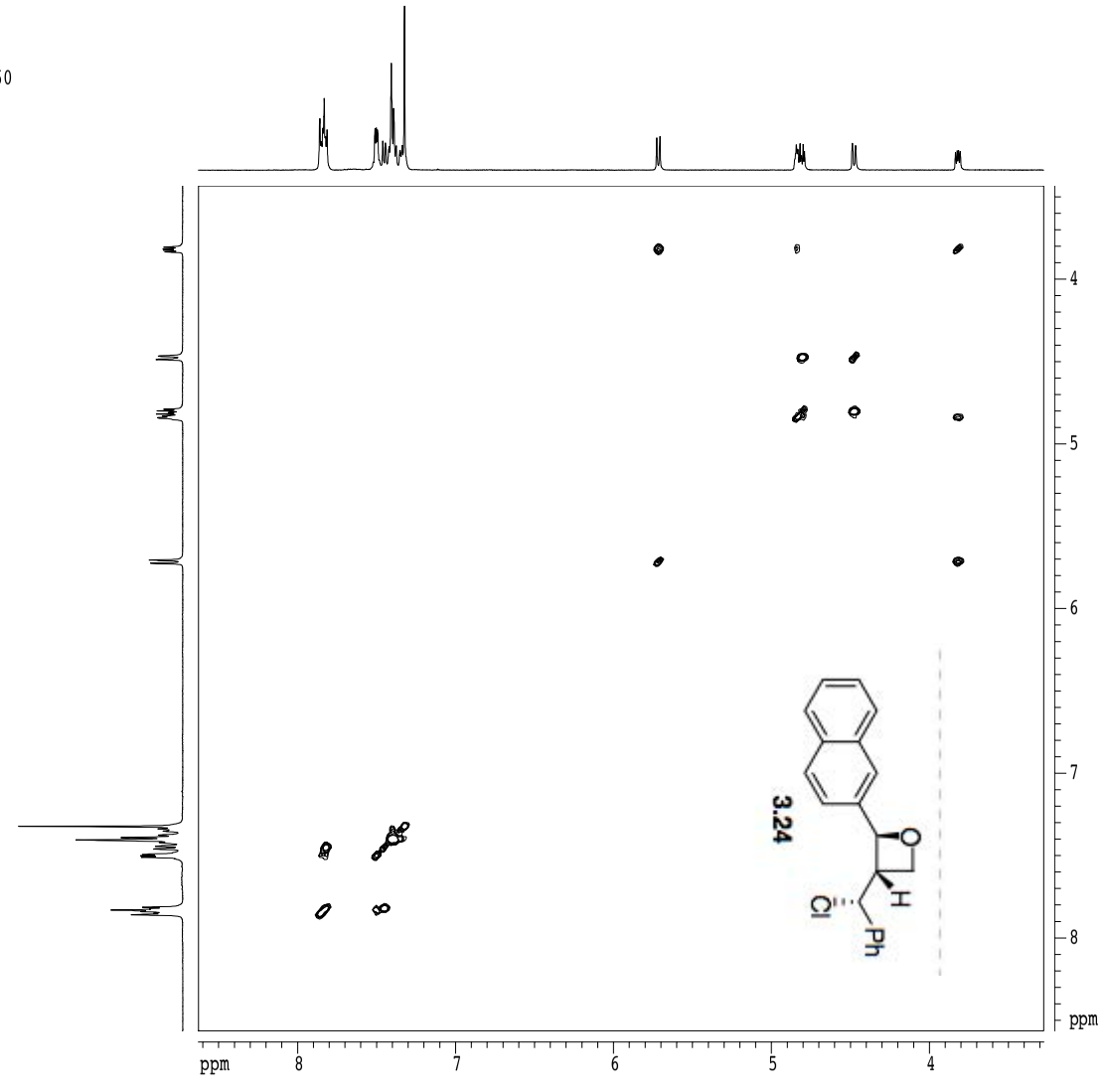

PI Jarvo
h1 CDCl3 v endean 28
Current data Parameters
USER endean
NAME TBDE-IV-Char-13
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20181001
Time 21.01
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 73724
SOLVENT CDCl3
NS 8
DS 2
SWH 7183.908 Hz
FIDRES 0.097483 Hz
AQ 5.1099203 sec
RG 912.3
DW 69.600 usec
DE 6.50 usec
TE 298.1 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 -1.10 dB
SFO1 400.1320009 MHz
F2 - Processing parameters
SI 65536
SF 400.1300172 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72084 Hz/cm
0.01276
0.08245
1.56375
2.18001
3.76437
3.77141
3.76006
3.74704
4.40805
4.41765
4.42745
4.42774
4.41765
4.72561
4.74391
4.76814
4.77466
4.77844
4.78661
4.79135
5.64992
5.67426
7.26995
7.28306
7.28565
7.29144
7.29946
7.30480
7.31686
7.31894
7.32224
7.33156
7.33671
7.33874
7.35319
7.35505
7.37148
7.38514
7.38927
7.40644
7.41073
7.43615
7.44093
7.44644
7.44886
7.45436
7.45852
7.46029
7.75842
7.76376
7.77844
7.78766
7.80471
1.0100
1.0009
2.0642
1.0000
8.3216
4.1031
3.24
O
H
Ph
Cl
ppm

13C spectrum with 1H decoupling

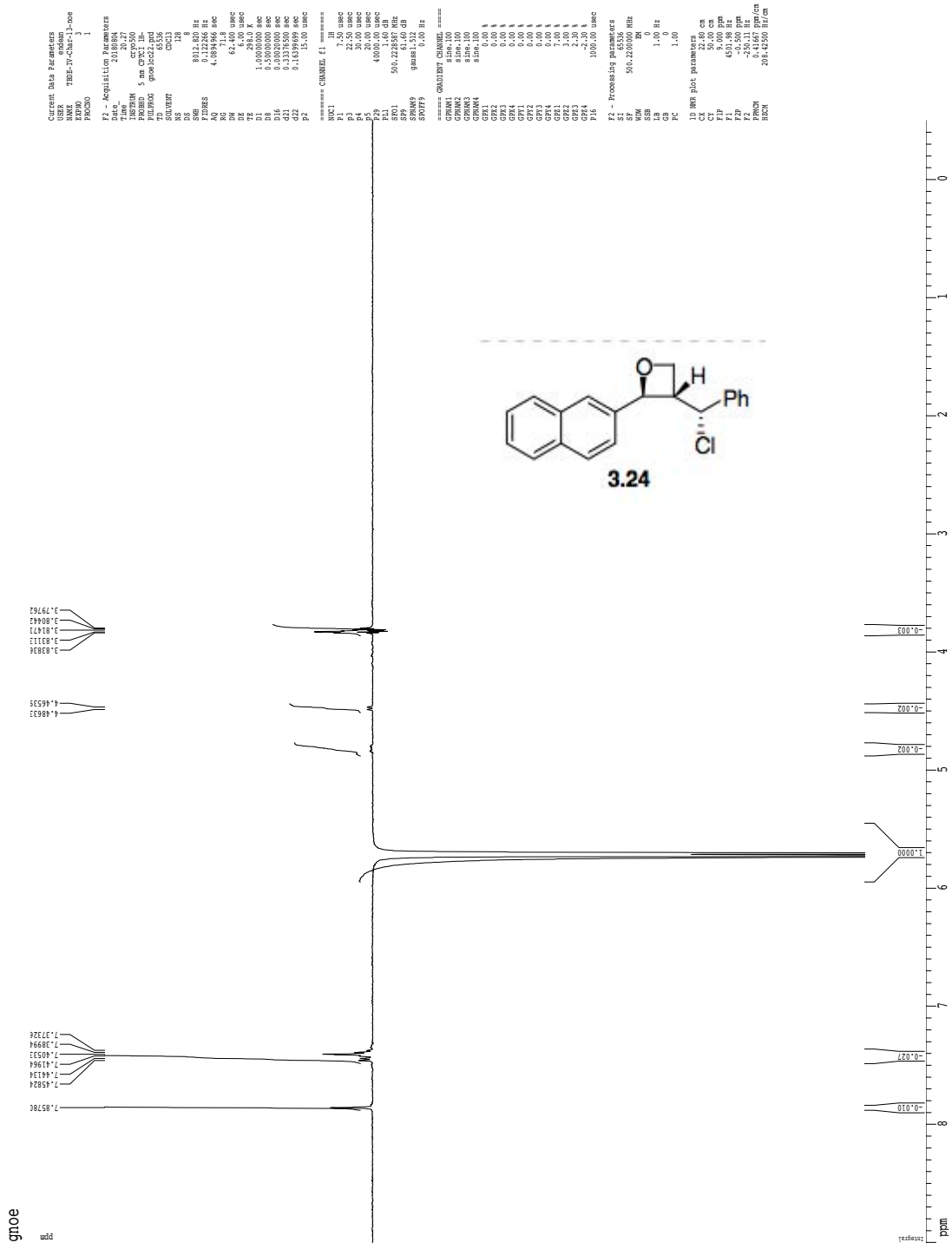


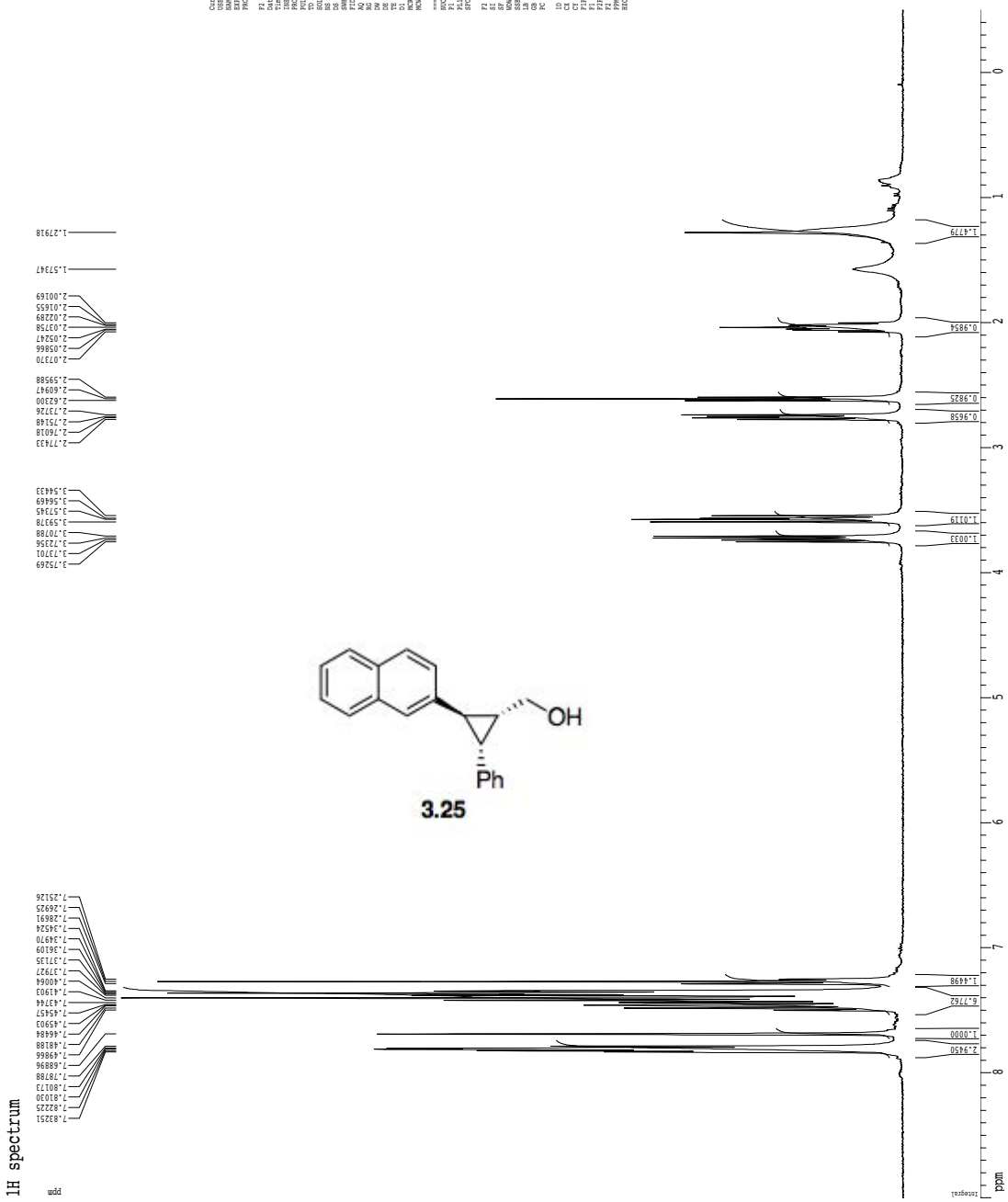

```
Current Data Parameters
USER            ezubkus
NAME      TBDB-IV-Char-13-nap-ph-cl-SM
EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters
Date_          20180612
Time              4.00
INSTRUM         drx400
PROBHD   5 mm QNP H/P/D
PULPROG         zgdc30
TD               65536
SOLVENT           CDCl3
NS                1024
DS                   4
SWH           24154.590 Hz
FIDRES        0.368570 Hz
AQ            1.3564452 sec
RG                3251
DW              20.700 usec
DE              20.39 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               7.45 usec
PL1             -3.00 dB
SFO1       100.6237964 MHz

======= CHANNEL f2 =======
CPDPRG2         waltz16
NUC2               1H
PCPD2           90.00 usec
PL2             -1.10 dB
PL12            16.80 dB
SFO2       400.1328009 MHz

F2 - Processing parameters
SI                65536
SF          100.6127500 MHz
WDW                 EM
SSB                 0
LB                1.00 Hz
GB                  0
PC                1.00

1D NMR plot parameters
CX               22.80 cm
CY               15.50 cm
F1P             220.000 ppm
F1             22134.80 Hz
F2P             -10.000 ppm
F2              -1006.13 Hz
PPMCM          10.08772 ppm/cm
HZCM         1014.93319 Hz/cm
```

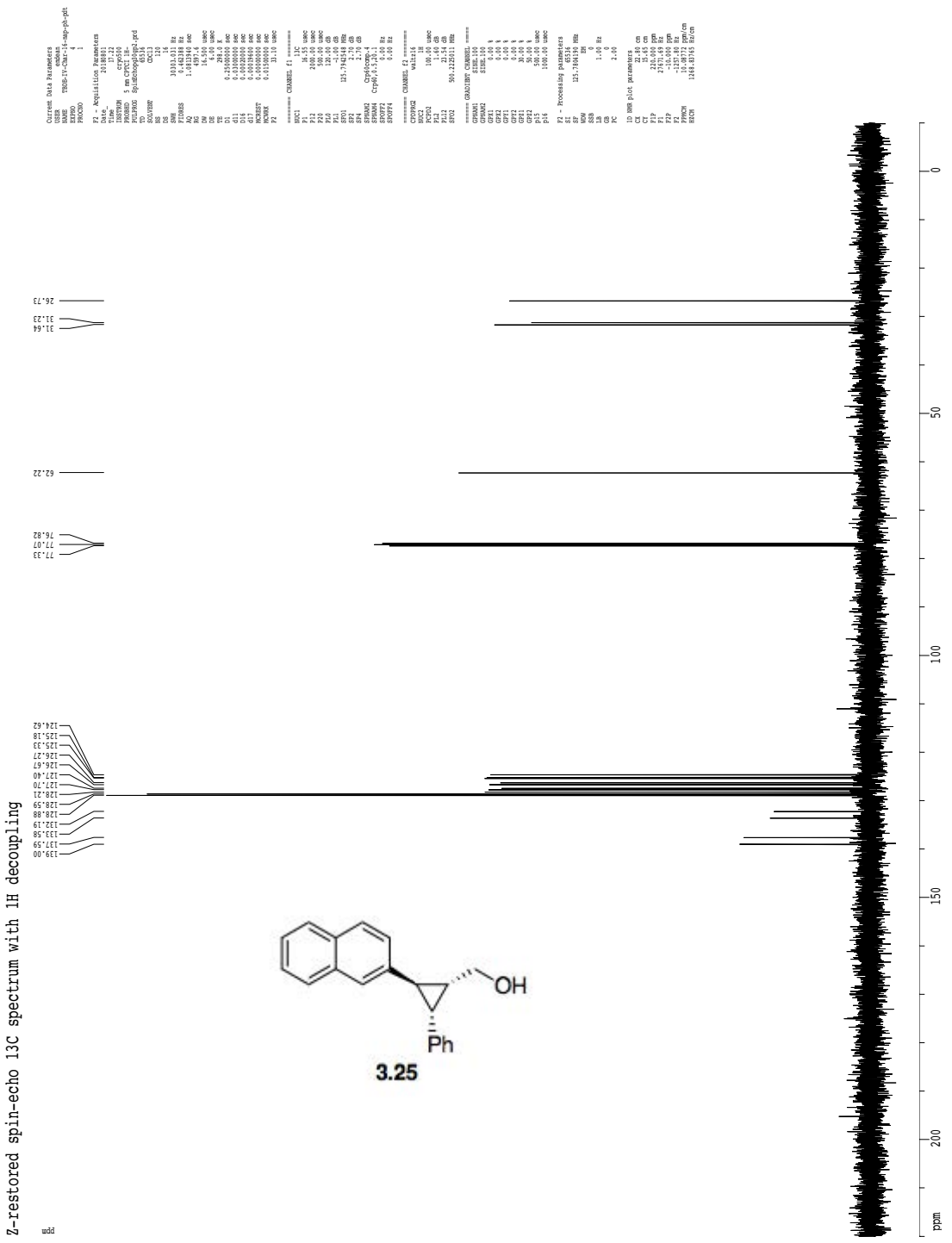
gcosy60



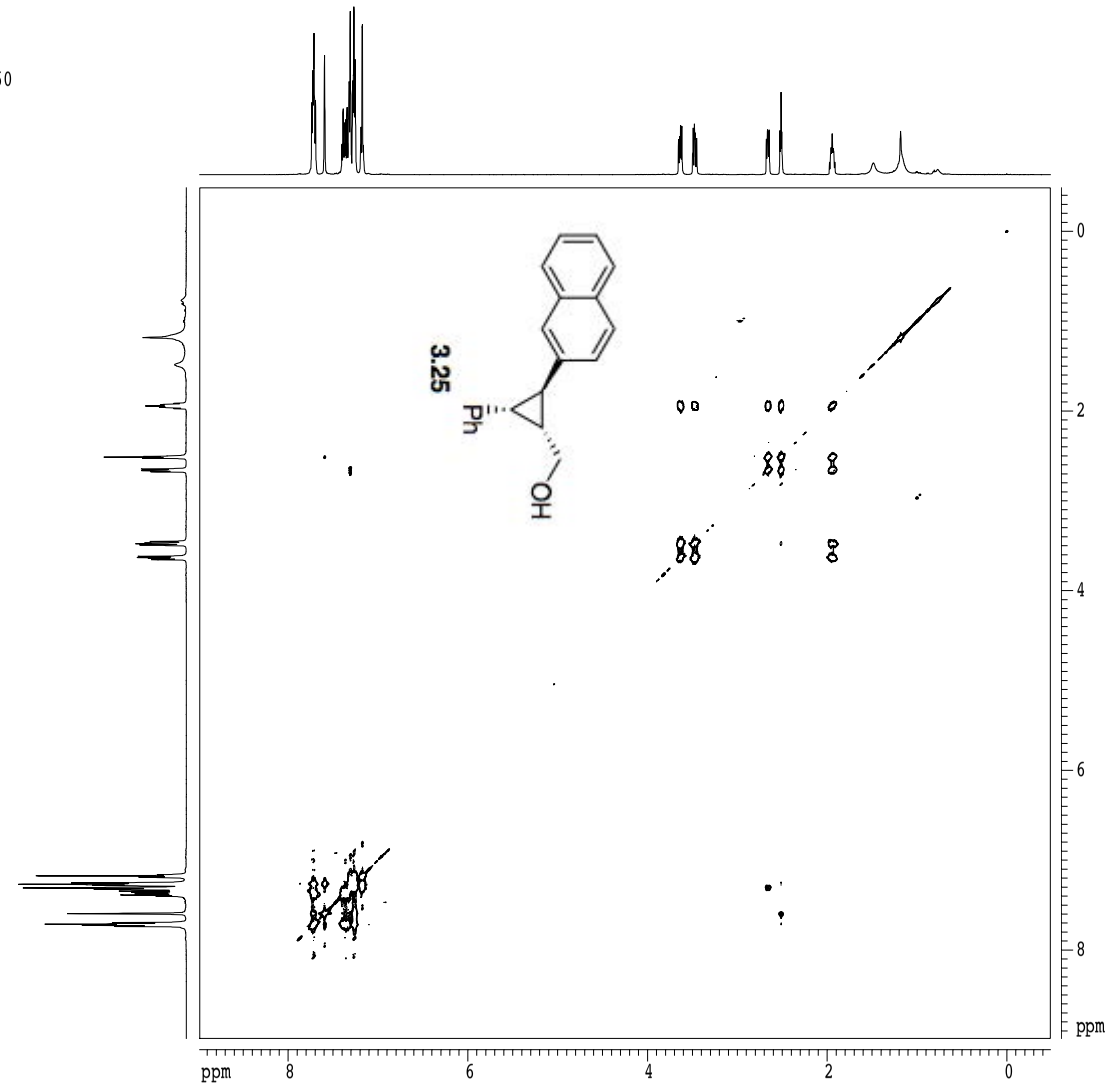

```
        Current Data Parameters
  USER              endean
NAME      TBDE-IV-Char-13-noe
  EXPNO                  2
  PROCNO                 1

      F2 - Acquisition Parameters
  Date_           20180804
  Time              19.59
  INSTRUM          cryo500
  PROBHD   5 mm CPTCI 1H-
  PULPROG     cosygp60.prd
  TD                  2048
  SOLVENT            CDCl3
  NS                     1
  DS                    16
  SWH             8012.820 Hz
  FIDRES          3.912510 Hz
  AQ              0.1278452 sec
  RG                1290.2
  DW                62.400 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            0.00012480 sec

      ======= CHANNEL f1 =======
  NUC1                  1H
  P1                  7.50 usec
  PL1                 1.60 dB
  SFO1         500.2235015 MHz

     ====== GRADIENT CHANNEL =====
  GPNAM1          sine.100
  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

      F1 - Acquisition parameters
  ND0                    1
  TD                   512
  SFO1           500.2235 MHz
  FIDRES         15.650040 Hz
  SW               16.018 ppm
  FnMODE                QF

      F2 - Processing parameters
  SI                  1024
  SF           500.2200000 MHz
  WDW                 SINE
  SSB                    0
  LB                  0.00 Hz
  GB                     0
  PC                  1.00

      F1 - Processing parameters
  SI                  1024
  MC2                   QF
  SF           500.2200000 MHz
  WDW                 SINE
  SSB                    0
  LB                  0.00 Hz
  GB                     0

      2D NMR plot parameters
  CX2                15.00 cm
  CX1                15.00 cm
  F2PLO               8.627 ppm
  F2LO             4315.34 Hz
  F2PHI               3.277 ppm
  F2HI             1639.19 Hz
  F1PLO               8.564 ppm
  F1LO             4284.04 Hz
  F1PHI               3.433 ppm
  F1HI             1717.44 Hz
  F2PPMCM          0.35666 ppm/cm
  F2HZCM         178.41046 Hz/cm
  F1PPMCM          0.34206 ppm/cm
  F1HZCM         171.10712 Hz/cm
```


3.24
gmoe
ppm


1H spectrum
OH
Ph
3.25

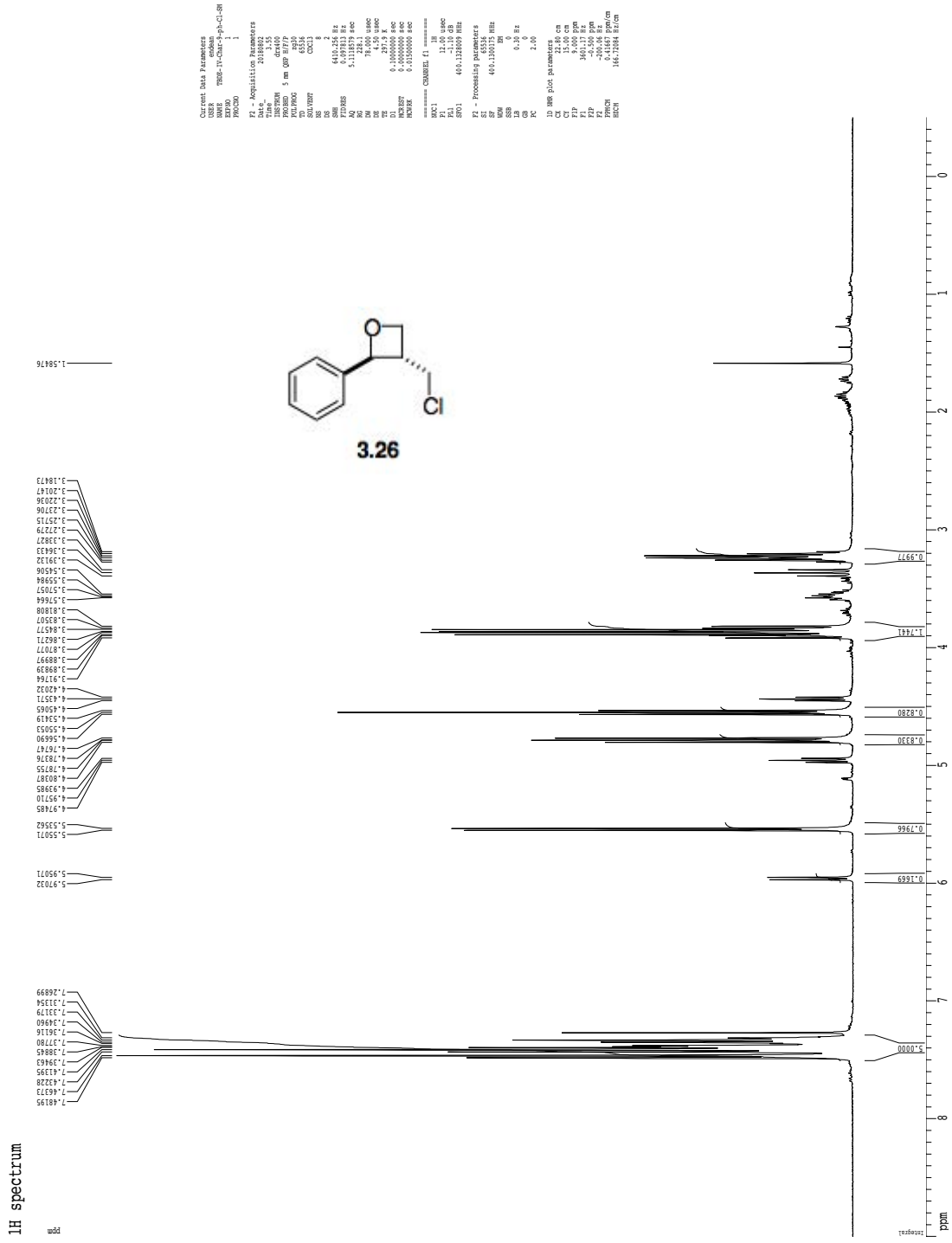

Z-restored spin-echo 13C spectrum with 1H decoupling
OH
Ph
3.25
ppm

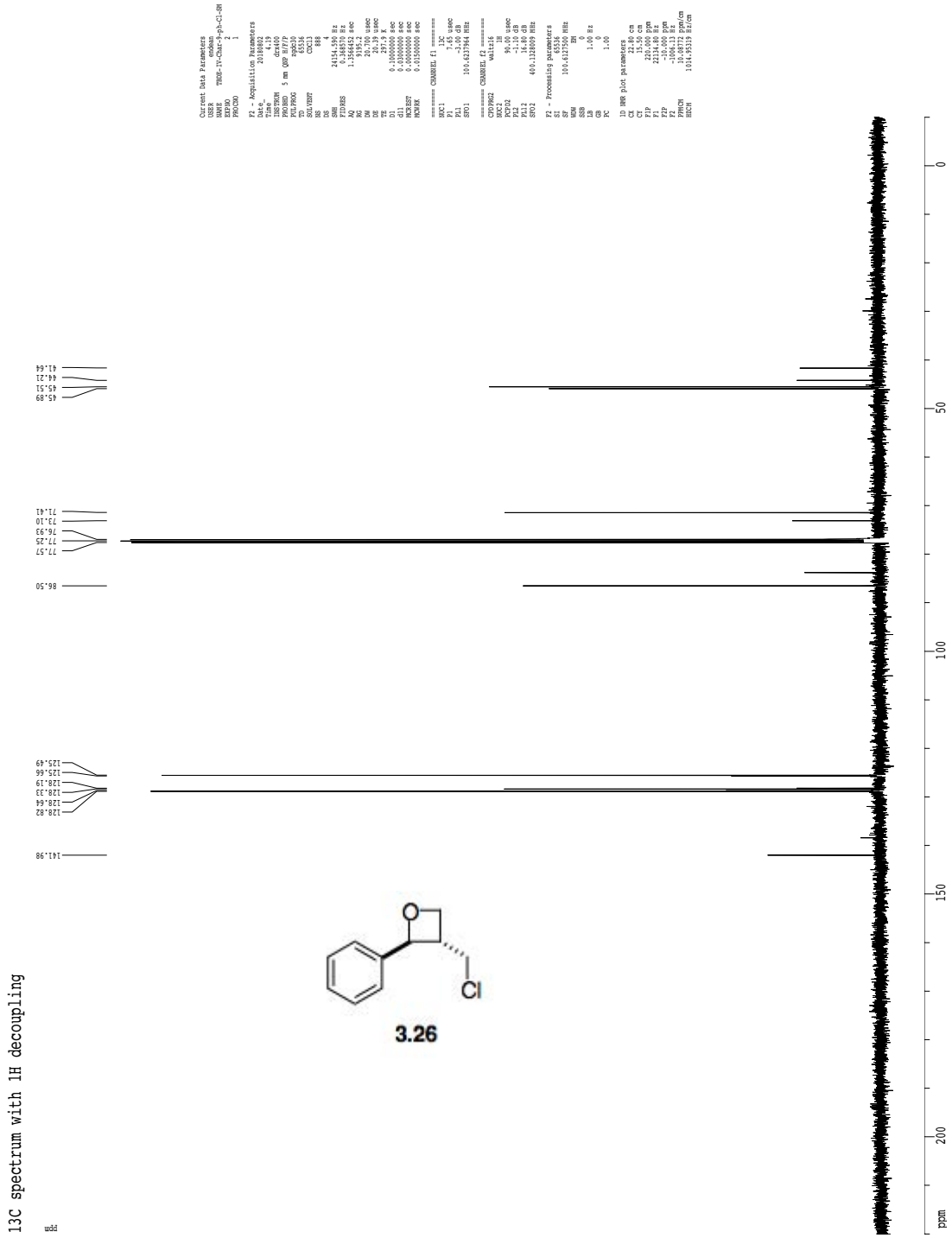
gcosy60



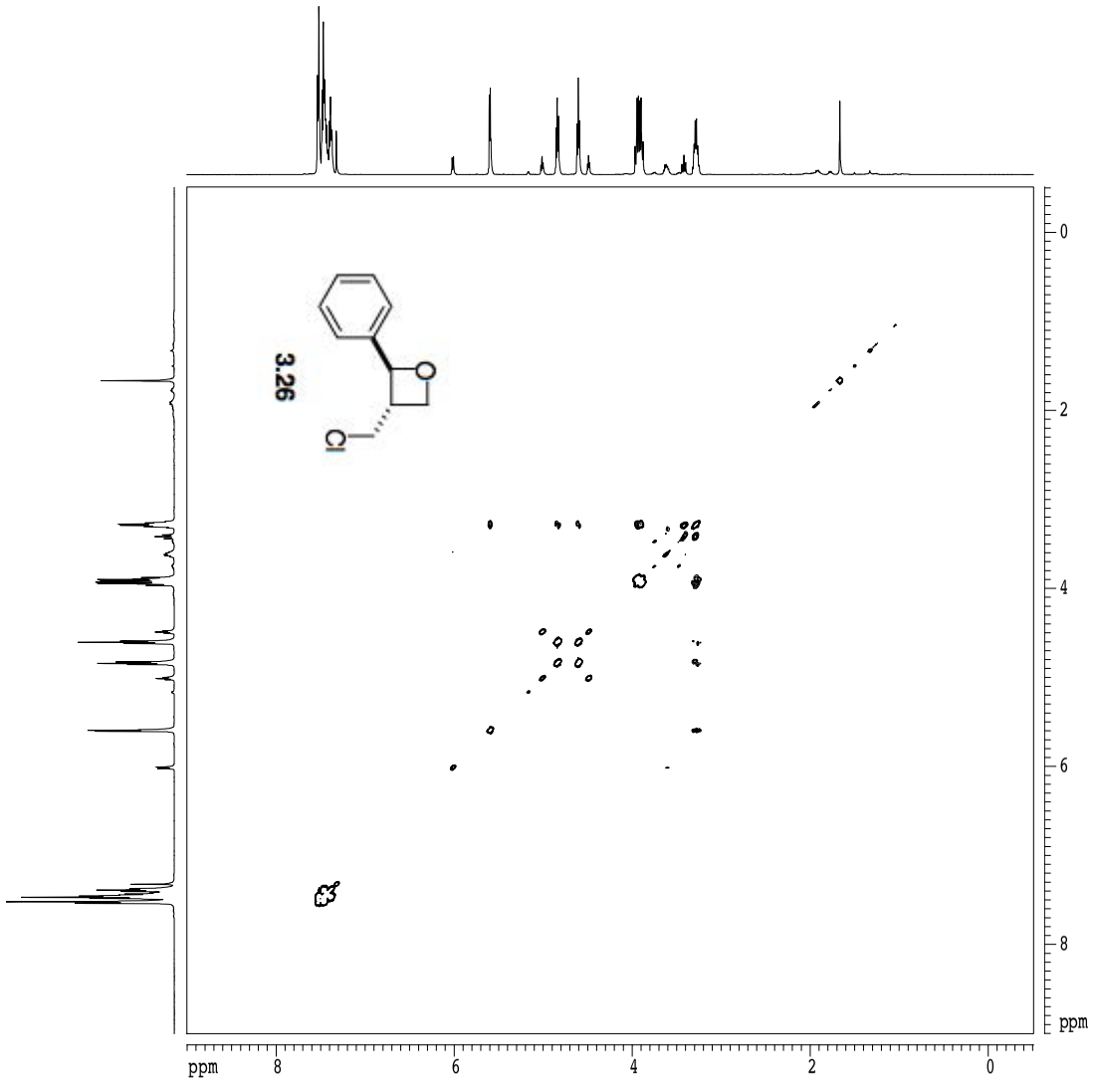

```
                Current Data Parameters
      USER                  endean
NAME      TBDE-IV-Char-16-nap-ph-pdt
      EXPNO                      3
      PROCNO                     1

           F2 - Acquisition Parameters
      Date_               20180801
      Time                   17.08
      INSTRUM              cryo500
      PROBHD    5 mm CPTCI 1H-
      PULPROG       cosygp60.prd
      TD                      2048
      SOLVENT                CDCl3
      NS                         1
      DS                        16
      SWH                4734.849 Hz
      FIDRES             2.311938 Hz
      AQ                 0.2163188 sec
      RG                       256
      DW                 105.600 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                0.00021120 sec

          ======== CHANNEL f1 =======
      NUC1                       1H
      P1                       7.50 usec
      PL1                      1.60 dB
      SFO1            500.2222002 MHz

         ====== GRADIENT CHANNEL =====
      GPNAM1               sine.100
      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

           F1 - Acquisition parameters
      ND0                        1
      TD                       512
      SFO1               500.2222 MHz
      FIDRES             9.247751 Hz
      SW                    9.465 ppm
      FnMODE                    QF

           F2 - Processing parameters
      SI                       1024
      SF              500.2200743 MHz
      WDW                      SINE
      SSB                         0
      LB                       0.00 Hz
      GB                          0
      PC                       1.00

           F1 - Processing parameters
      SI                       1024
      MC2                       QF
      SF              500.2200743 MHz
      WDW                      SINE
      SSB                         0
      LB                       0.00 Hz
      GB                          0

         2D NMR plot parameters
      CX2                     15.00 cm
      CX1                     15.00 cm
      F2PLO                    8.983 ppm
      F2LO                  4493.35 Hz
      F2PHI                   -0.483 ppm
      F2HI                  -241.49 Hz
      F1PLO                    8.983 ppm
      F1LO                  4493.35 Hz
      F1PHI                   -0.483 ppm
      F1HI                  -241.49 Hz
      F2PPMCM                0.63104 ppm/cm
      F2HZCM               315.65656 Hz/cm
      F1PPMCM                0.63104 ppm/cm
      F1HZCM               315.65656 Hz/cm
```


OH
Ph
3.25
gmoe
ppm


3.26
Cl
1H spectrum
ppm


13C spectrum with 1H decoupling
ppm
141.98
128.82
128.64
128.33
128.19
125.66
125.49
86.50
77.57
77.25
76.93
73.10
71.41
45.89
45.51
44.21
41.64
Cl
3.26
0
50
100
150
200

gcosy60



Current Data Parameters

USER	endean
NAME	TBDE-IV-Char-9-noe
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20180804
Time	13.09
INSTRUM	cryo500
PROBHD	5 mm CPTCI 1H-
PULPROG	cosygp60.prd
TD	2048
SOLVENT	CDCl3
NS	1
DS	16
SWH	8012.820 Hz
FIDRES	3.912510 Hz
AQ	0.1278452 sec
RG	256
DW	62.400 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	0.00012480 sec

======= CHANNEL f1 =======

NUC1	1H
P1	7.50 usec
PL1	1.60 dB
SFO1	500.2235015 MHz

====== GRADIENT CHANNEL =====

GPNAM1	sine.100
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

F1 - Acquisition parameters

ND0	1
TD	512
SFO1	500.2235 MHz
FIDRES	15.650040 Hz
SW	16.018 ppm
FnMODE	QF

F2 - Processing parameters

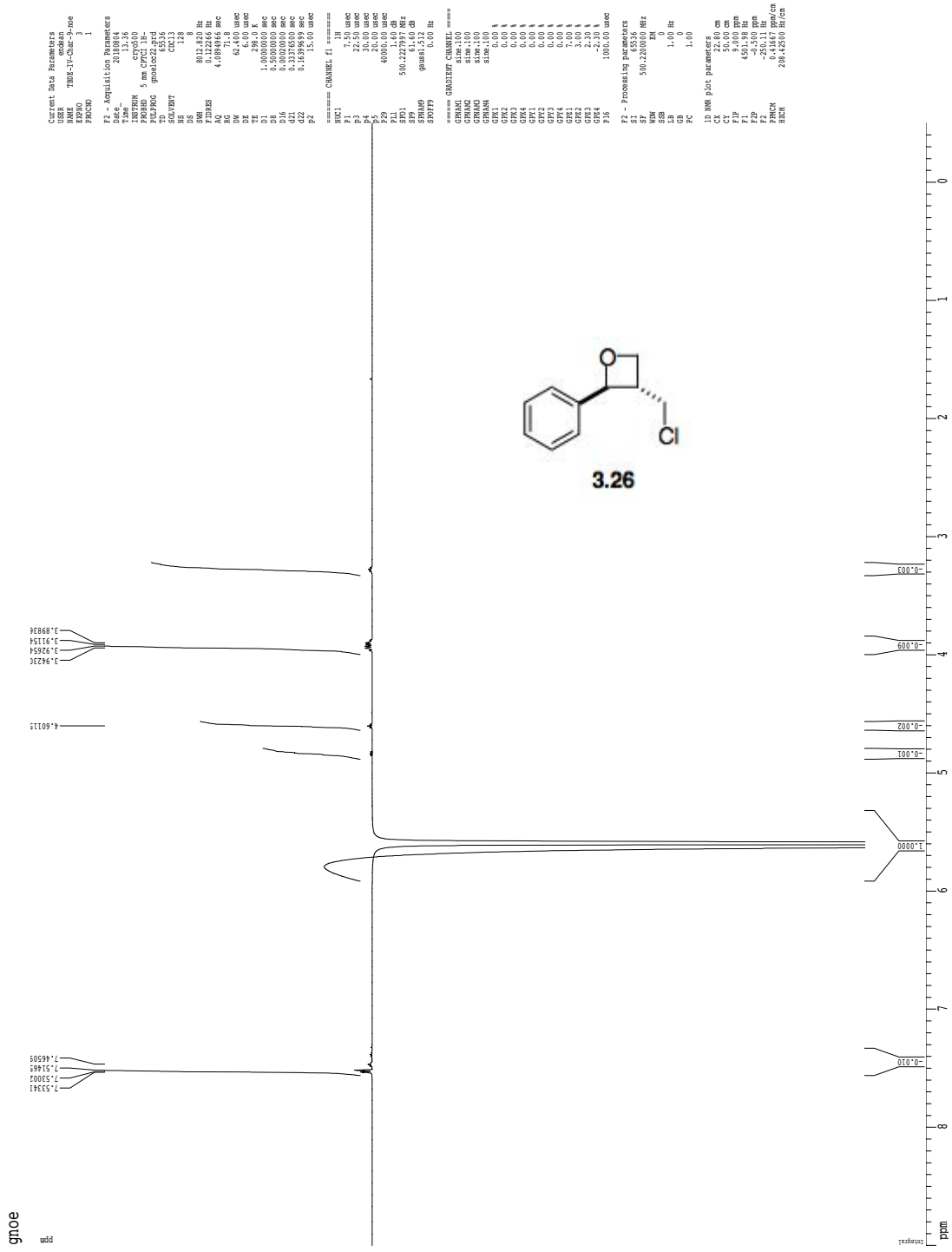
SI	1024
SF	500.2200000 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

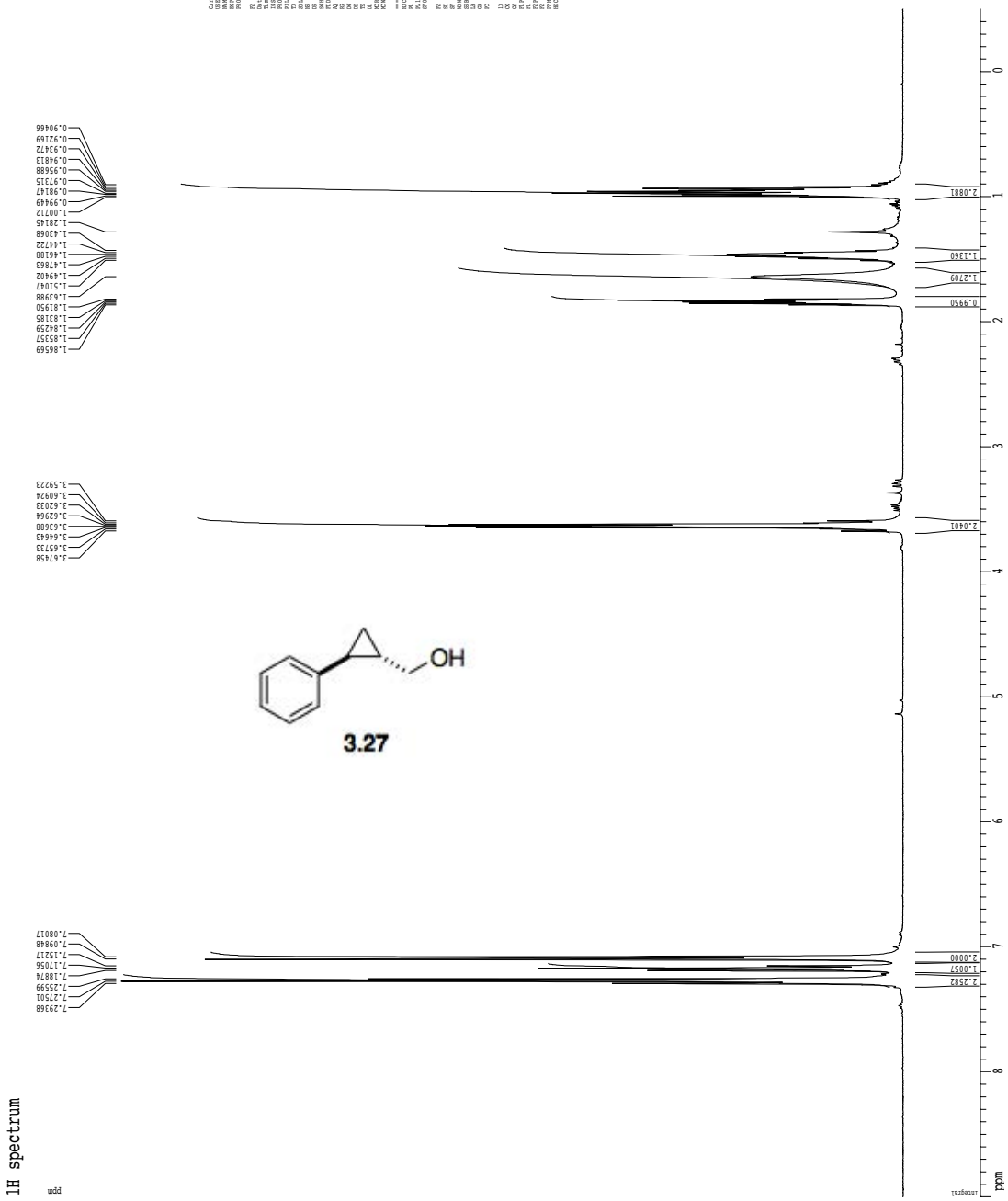
F1 - Processing parameters

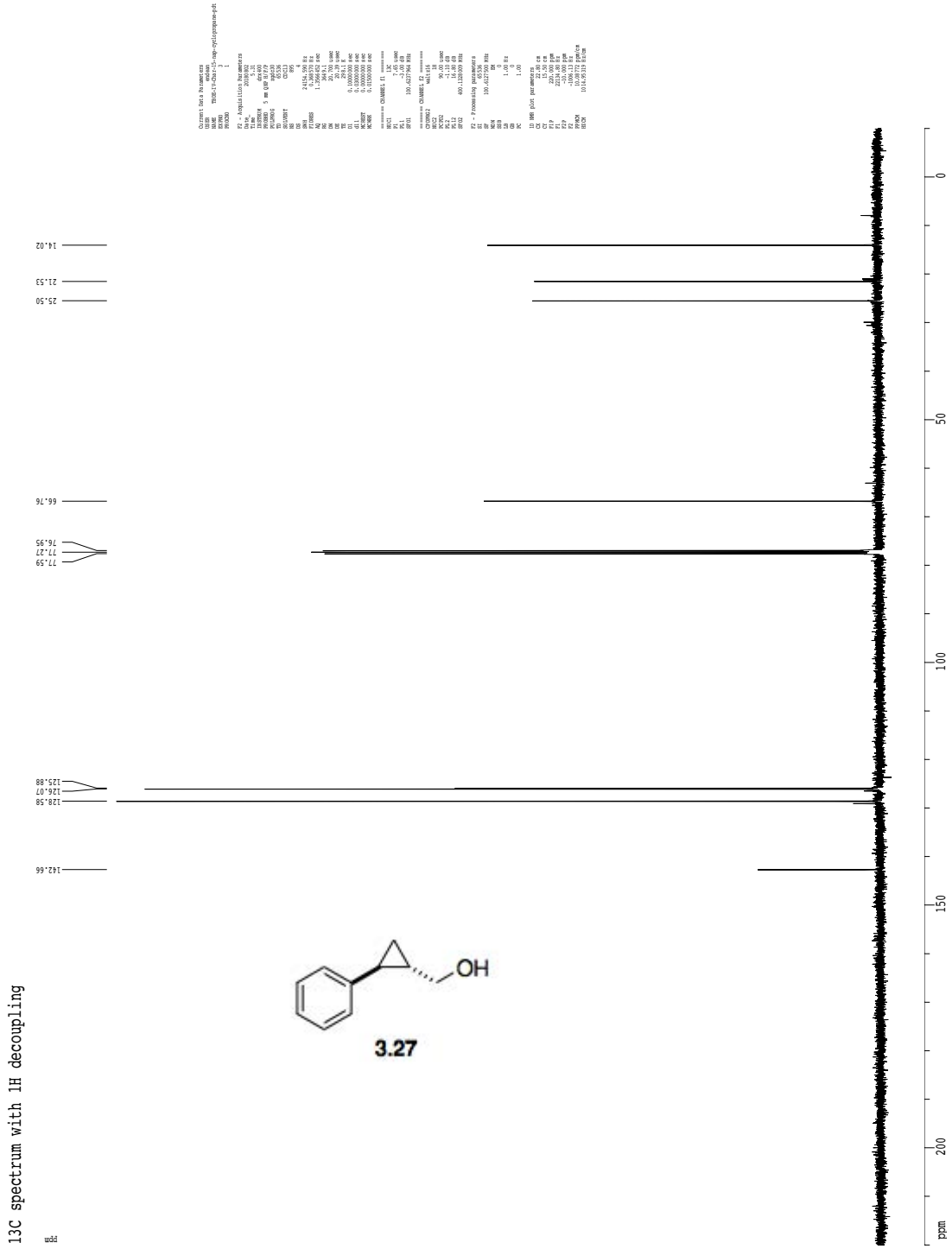
SI	1024
MC2	QF
SF	500.2200000 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

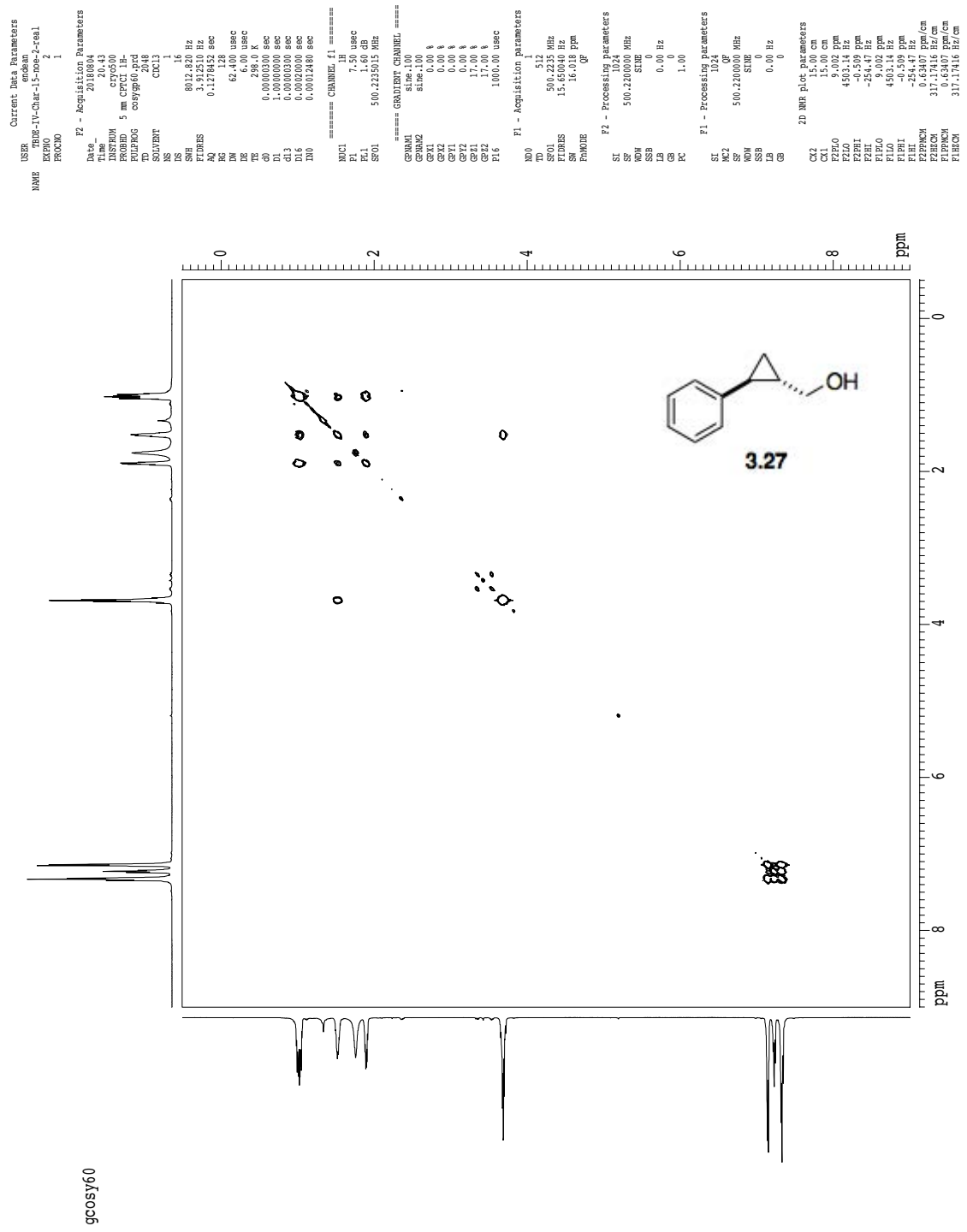
2D NMR plot parameters

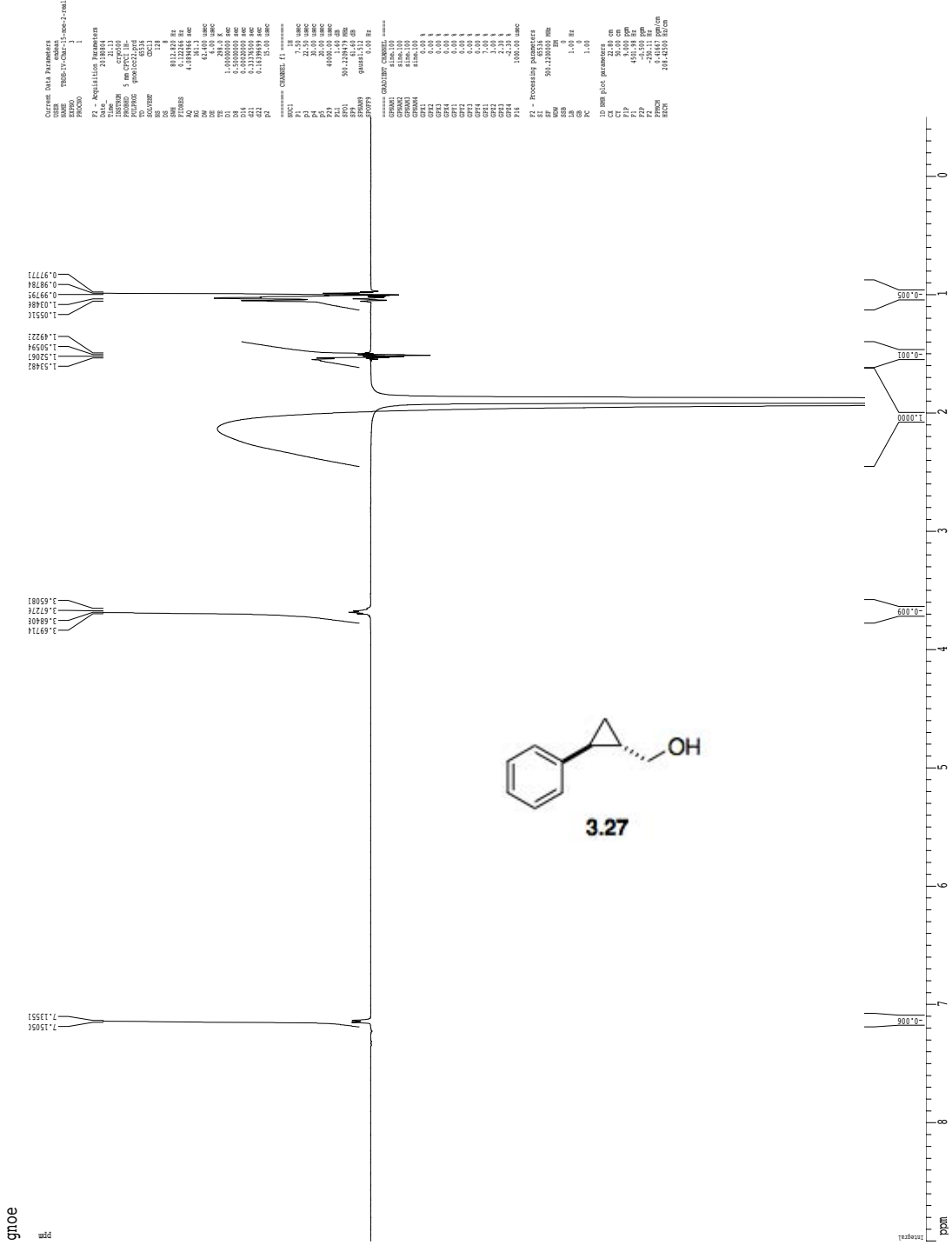
CX2	15.00 cm
CX1	15.00 cm
F2PLO	9.002 ppm
F2LO	4503.14 Hz
F2PHI	-0.509 ppm
F2HI	-254.47 Hz
F1PLO	9.002 ppm
F1LO	4503.14 Hz
F1PHI	-0.509 ppm
F1HI	-254.47 Hz
F2PPMCM	0.63407 ppm/cm
F2HZCM	317.17416 Hz/cm
F1PPMCM	0.63407 ppm/cm
F1HZCM	317.17416 Hz/cm

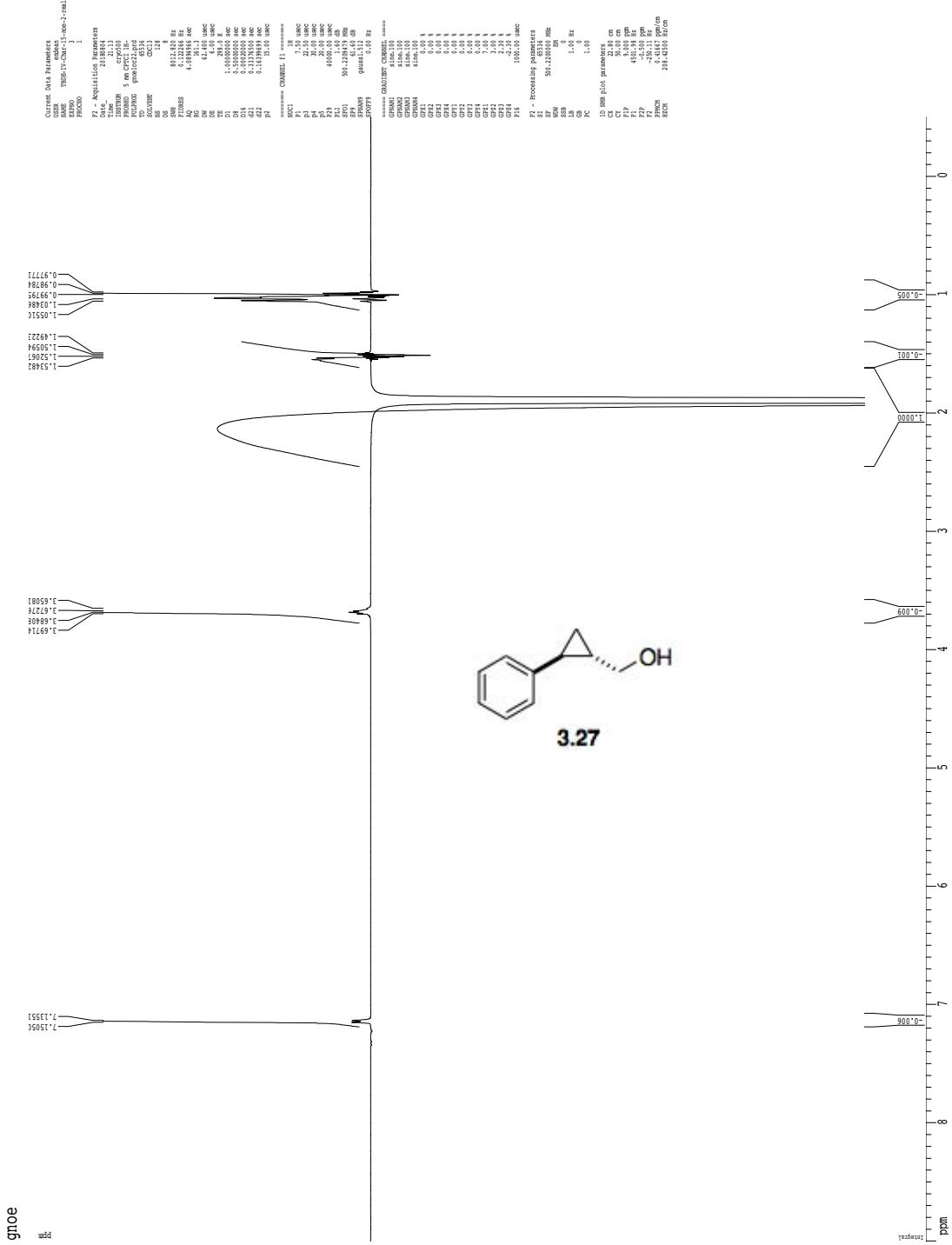

Current Data Parameters
USER
NAME
EXPNO
PROCNO
F2 - Acquisition Parameters
Date_
Time
INSTRUM
PROBHD
PULPROG
TD
SOLVENT
NS
DS
SWH
FIDRES
AQ
RG
DW
DE
TE
D1
D9
D16
d21
d22
p2
======== CHANNEL f1 ========
NUC1
P1
p3
p4
p5
P29
PL1
SFO1
SP9
SPNAM9
SPOFF9
==== GRADIENT CHANNEL ====
GPNAM1
GPNAM2
GPNAM3
GPNAM4
GPX1
GPX2
GPX3
GPX4
GPY1
GPY2
GPY3
GPY4
GPZ1
GPZ2
GPZ3
GPZ4
P16
F2 - Processing parameters
SI
SF
WDW
SSB
LB
GB
PC
1D NMR plot parameters
CX
CY
F1P
F1
F2P
F2
PPMCM
HZCM
7.53341
7.53002
7.51465
7.46505
4.60115
3.96236
3.92654
3.91154
3.89836
1.0000
0.010
0.009
0.003
0.002
0.001
ppm
gmoe
3.26
Cl

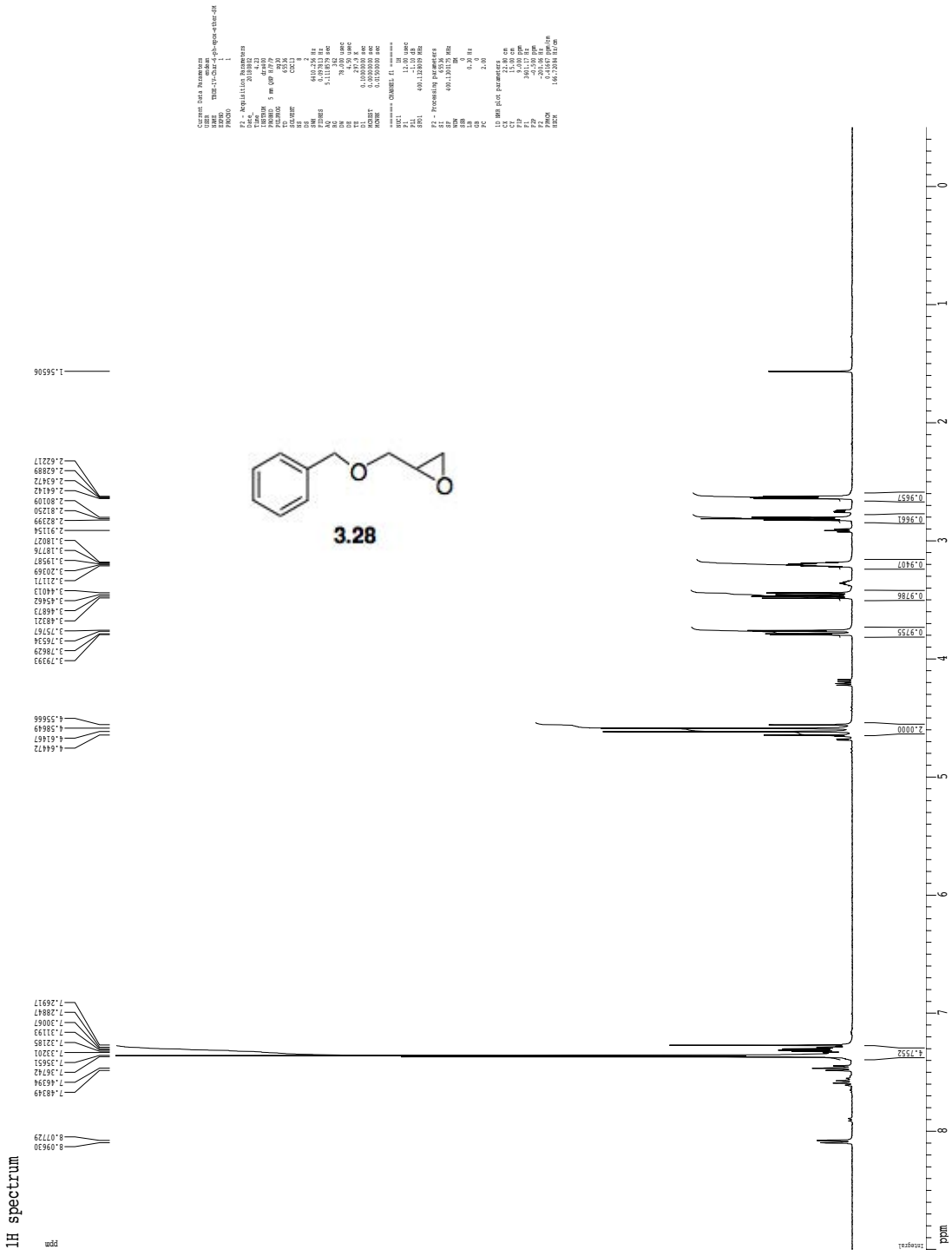

OH
3.27
1H spectrum
ppm

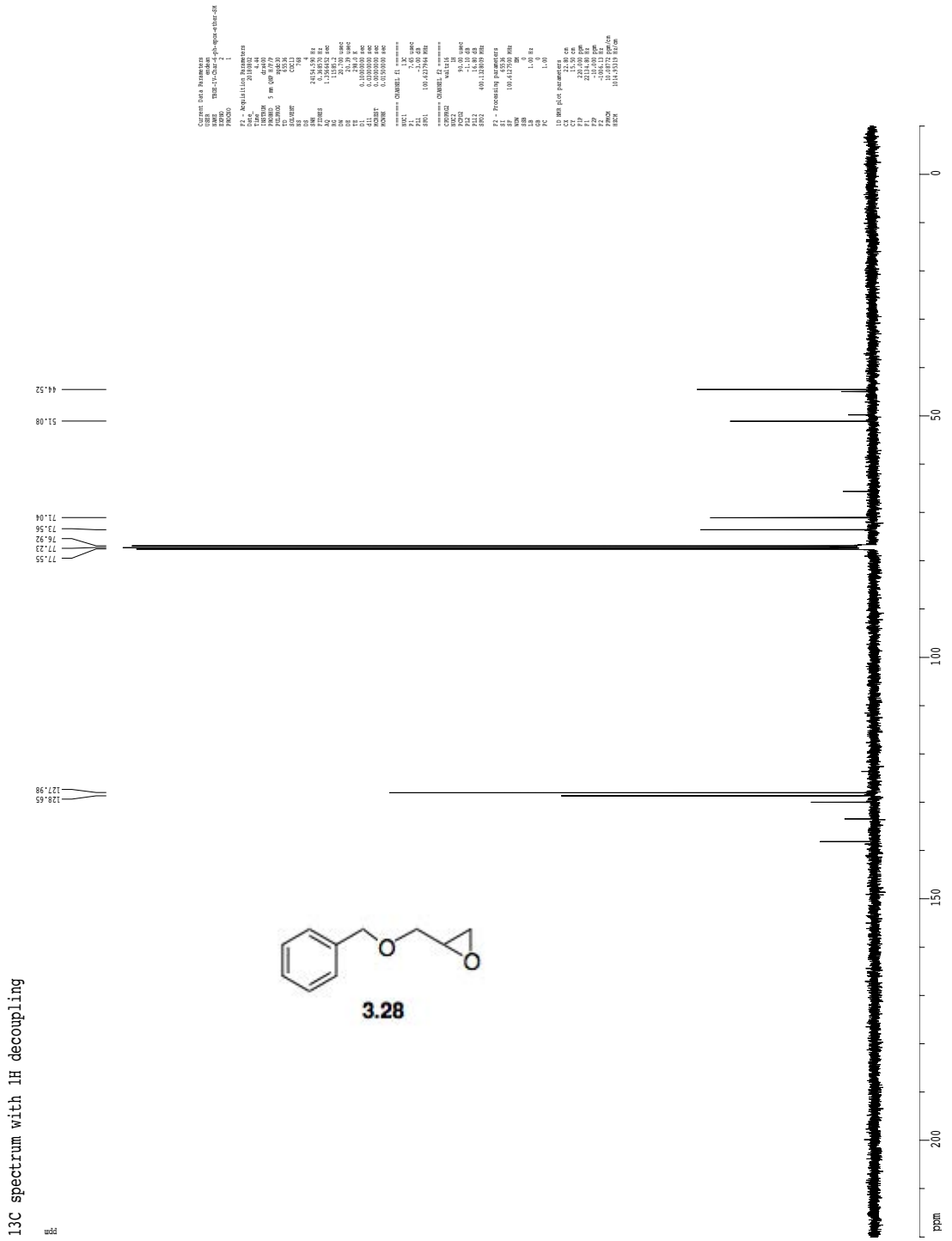

13C spectrum with 1H decoupling
ppm
142.66
128.58
126.07
125.88
77.59
77.27
76.95
66.76
25.50
21.53
14.02
OH
3.27


Current Data Parameters
endean
USER
TBDR-IV-Char-15-noe-2-real
NAME
EXPNO
2
PROCNO
1
F2 - Acquisition Parameters
20160804
Date_
20.43
Time
cryo500
INSTRUM
PROBHD 5 mm CPTCI 1H-
cosygp60.prd
PULPROG
2048
TD
CDCl3
SOLVENT
1
NS
16
DS
8012.820 Hz
SWH
0.1276452 sec
FIDRES
128
AQ
62.400 usec
RG
6.00 usec
DW
298.0 K
DE
0.00000300 sec
TE
1.00000000 sec
d0
0.00000300 sec
D1
0.00020000 sec
d13
0.00012480 sec
D16
1
IN0
====== CHANNEL f1 ======
NUC1
1H
7.50 usec
P1
1.60 dB
PL1
500.2235015 MHz
SFO1
===== GRADIENT CHANNEL =====
GPNAM1
sine.100
GPNAM2
sine.100
0.00 %
GPX1
0.00 %
GPX2
0.00 %
GPY1
0.00 %
GPY2
17.00 %
GPZ1
17.00 %
GPZ2
1000.00 usec
P16
F1 - Acquisition parameters
1
NDO
512
TD
500.2235 MHz
SFO1
15.650040 Hz
FIDRES
16.018 ppm
SW
QF
FnMODE
F2 - Processing parameters
1024
SI
500.2200000 MHz
SF
WDW
SINE
SSB
0.00 Hz
LB
0
GB
1.00
PC
F1 - Processing parameters
1024
SI
QF
MC2
500.2200000 MHz
SF
WDW
SINE
SSB
0
0.00 Hz
LB
GB
0
2D NMR plot parameters
15.00 cm
CX2
15.00 cm
CX1
4503.14 ppm
F2LO
-0.509 ppm
F2HI
4503.14 Hz
F1LO
-0.509 ppm
F1HI
-254.47 Hz
F1HI
0.63407 ppm/cm
F2PPMCM
317.17416 Hz/cm
F2HZCM
0.63407 ppm/cm
F1PPMCM
317.17416 Hz/cm
F1HZCM
OH
3.27
ppm
ppm
gcosy60

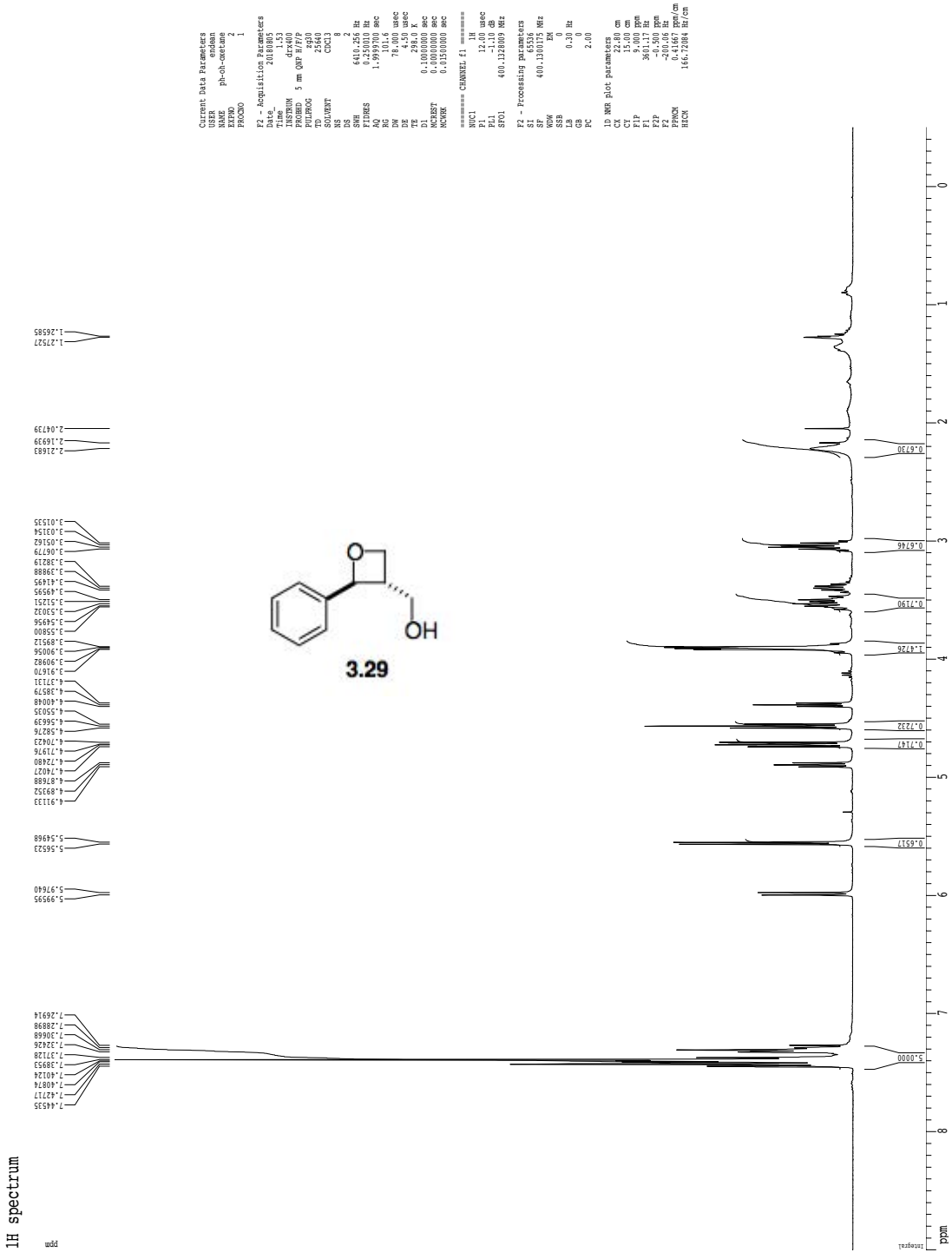

OH
3.27
gnoe
ppm


OH
3.27
gmoe
ppm

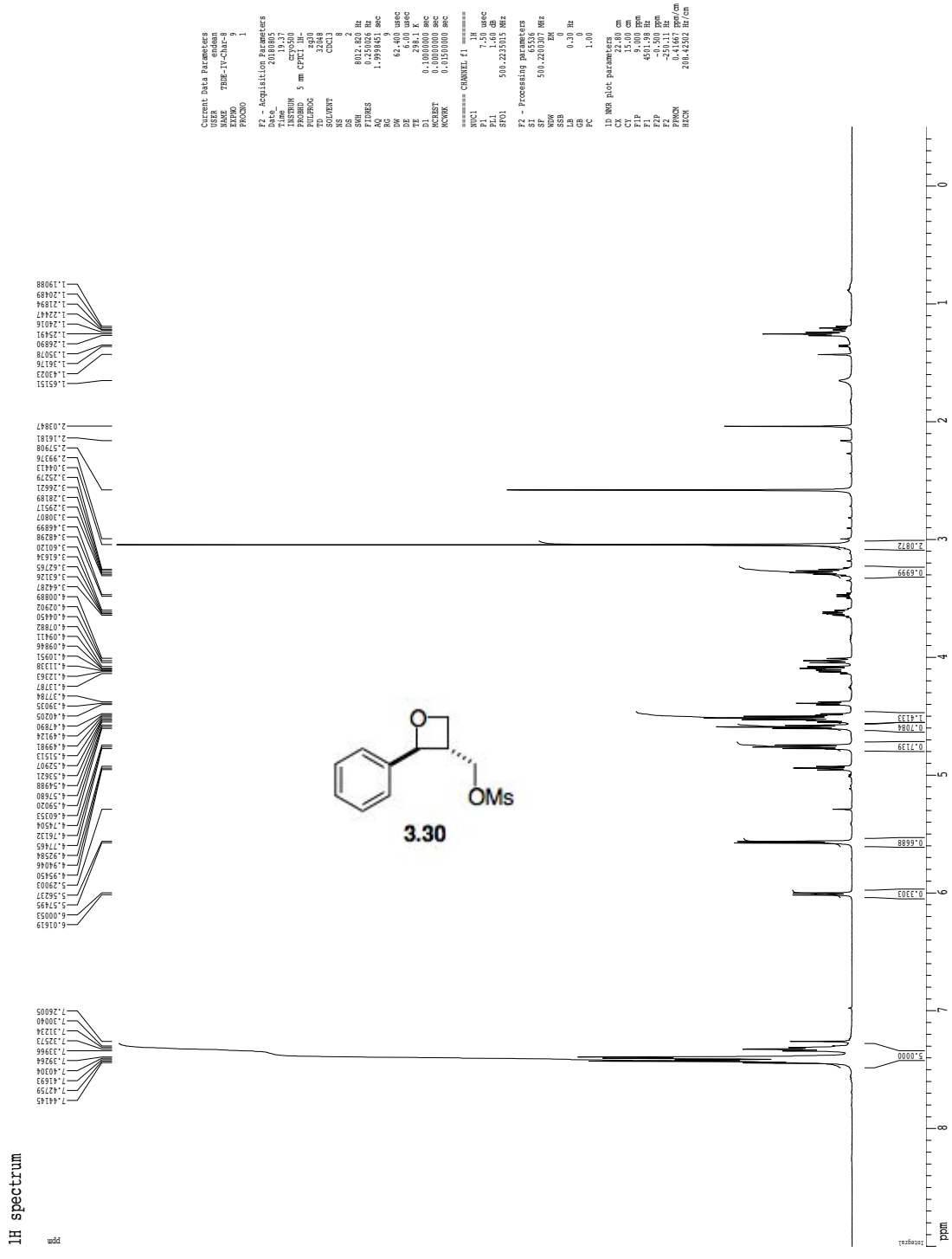

3.28
1H spectrum
ppm

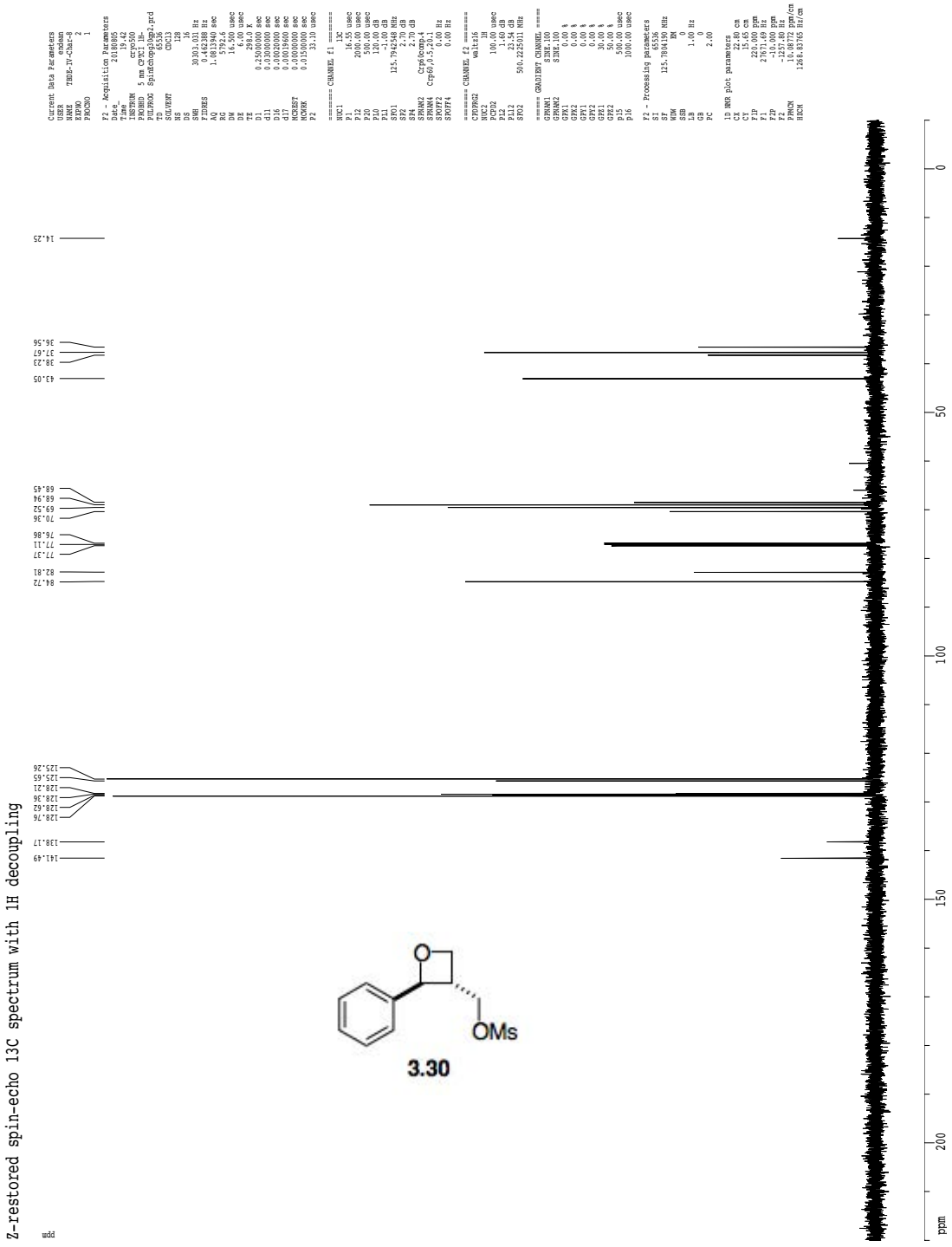

13C spectrum with 1H decoupling
ppm
127.98
128.65
44.52
51.08
71.04
73.56
76.92
77.23
77.55
0
50
100
150
200

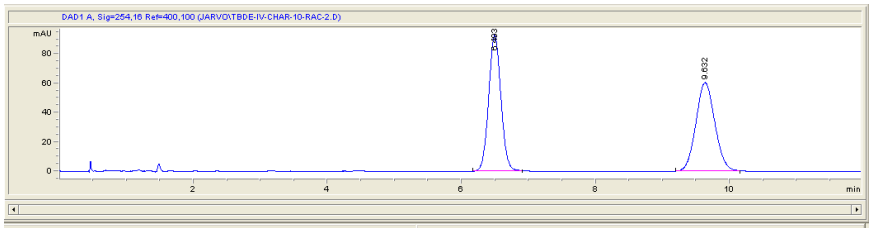
3.28


1H spectrum
Current Data Parameters
USER endaan
NAME ph-ch-cxetane
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20101015
Time 11.13
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.195710 Hz
AQ 1.4999700 sec
RG 101.6
DW 78.000 usec
DE 6.50 usec
TE 298.1 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 -1.10 dB
SFO1 400.1320009 MHz
F2 - Processing parameters
SI 65536
SF 400.1300175 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72084 Hz/cm
OH
3.29
ppm
Integral


13C spectrum with 1H decoupling
ppm
Current Data Parameters
USER endaan
NAME ph-oh-oxetane
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180815
Time 2.40
INSTRUM drx400
PROBHD 5 mm QNP H/P/P
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1014
DS 4
SWH 24154.590 Hz
FIDRES 0.368570 Hz
AQ 1.3566464 sec
RG 203.6
DW 20.700 usec
DE 20.39 usec
TE 297.9 K
D1 0.11000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 7.45 usec
PL1 -3.00 dB
SFO1 100.6237964 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 -1.10 dB
PL12 16.40 dB
SFO2 400.1318019 MHz
F2 - Processing parameters
SI 65536
SF 100.6125010 MHz
WDW EM
SSB 1.00 Hz
LB 0
GB 1.00
PC
1D NMR plot parameters
CX 22.80 cm
CY 15.50 cm
F1P 220.000 ppm
F1 22134.40 Hz
F2P -110.000 ppm
F2 -1006.13 Hz
PPMCM 10.08772 ppm/cm
HZCM 1014.95319 Hz/cm
41.24
45.98
62.02
63.57
70.63
71.45
76.98
77.30
77.61
83.95
85.75
125.42
125.50
128.02
128.09
128.71
128.77
142.79
OH
3.29
0
50
100
150
200
ppm

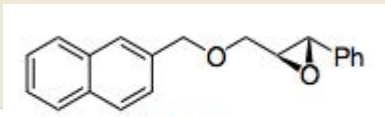

1H spectrum
OMs
3.30
ppm


Z-restored spin-echo 13C spectrum with 1H decoupling
OMs
3.30

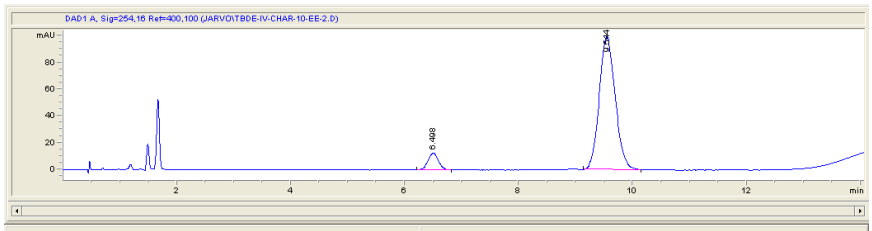


#	Time	Area	Height	Width	Area%	Symmetry
1	6.493	1182.2	92.8	0.1966	49.826	0.918
2	9.632	1190.5	60.5	0.3046	50.174	0.897

File Information	
LC-File	TBDE-IV-CHAR-10-RAC-2.D
File Path	C:\CHEM32\1\DATA\JARVO\
Date	05-Aug-18, 13:00:38
Sample	TBDE-IV-CHAR-10-RAC
Sample Info	AD-H, 10% i-PrOH, 2.5 mL/min, 44 C, 20 microL
Barcode	
Operator	TBDE
Method	NSZ_OJH_P.M
Analysis Time	11.96 min
Sampling Rate	0.0033 min (0.198 sec), 3589 datapoints

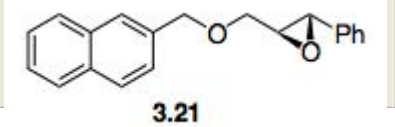


3.21

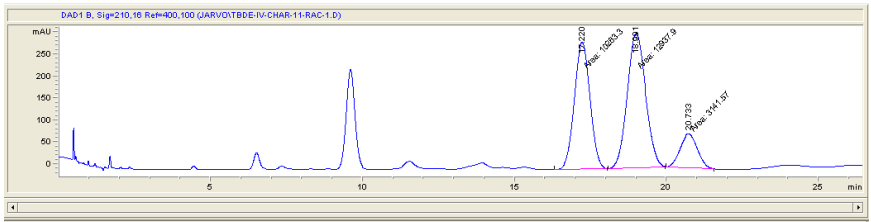


#	Time	Area	Height	Width	Area%	Symmetry
1	6.498	163.2	12.8	0.1935	7.752	0.974
2	9.544	1941.9	99.2	0.3033	92.248	0.852

File Information	
LC-File	TBDE-IV-CHAR-10-EE-2.D
File Path	C:\CHEM32\1\DATA\JARVO\
Date	05-Aug-18, 13:27:10
Sample	TBDE-IV-CHAR-10-EE
Sample Info	AD-H, 10% i-PrOH, 2.5 mL/min, 44 C, 20 microL
Barcode	
Operator	TBDE
Method	NSZ_OJH_P.M
Analysis Time	14.067 min
Sampling Rate	0.0033 min (0.198 sec), 4221 datapoints

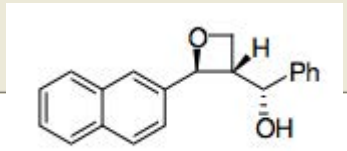


3.21

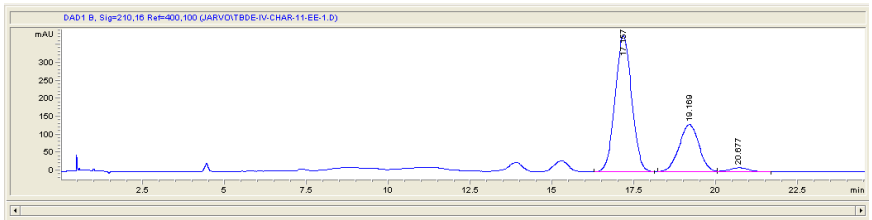


#	Time	Area	Height	Width	Area%	Symmetry
1	17.22	10263.3	290	0.5899	38.961	0.986
2	18.991	12937.9	306.3	0.7039	49.114	0.902
3	20.733	3141.6	78.4	0.6681	11.926	1.001

File Information	
LC-File	TBDE-IV-CHAR-11-RAC-1.D
File Path	C:\CHEM32\1\DATA\JARVO\
Date	05-Aug-18, 13:43:44
Sample	TBDE-IV-CHAR-11-RAC
Sample Info	AD-H, 10% i-PrOH, 2.5 mL/min, 44 C, 20 microL
Barcode	
Operator	TBDE
Method	NSZ_OJH_P.M
Analysis Time	26.45 min
Sampling Rate	0.0033 min (0.198 sec), 7936 datapoints

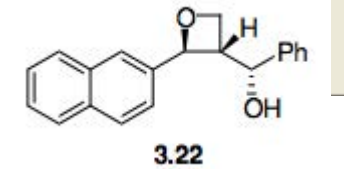


3.22

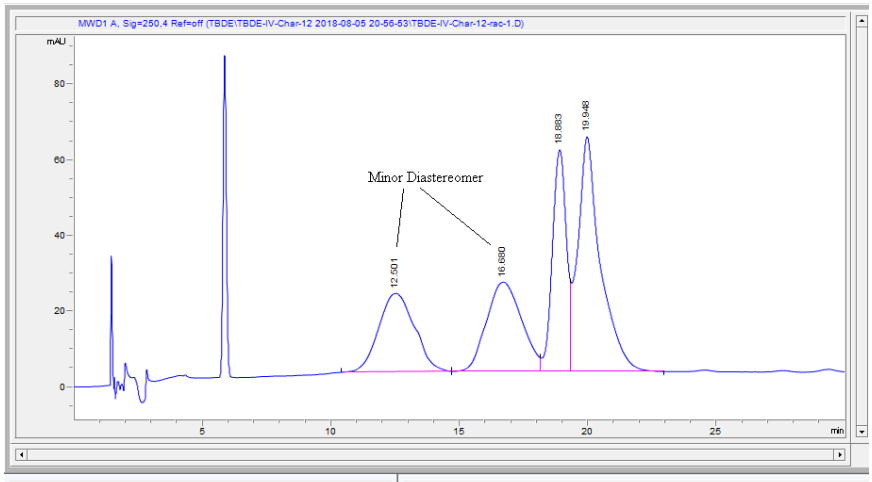


#	Time	Area	Height	Width	Area%	Symmetry
1	17.157	13326.2	377.8	0.5485	68.775	0.953
2	19.169	5562.9	131.5	0.6307	28.710	1.037
3	20.677	487.4	11.5	0.5024	2.515	0.961

File Information	
LC-File	TBDE-IV-CHAR-11-EE-1.D
File Path	C:\CHEM32\1\DATA\JARVO\
Date	05-Aug-18, 14:15:25
Sample	TBDE-IV-CHAR-11-EE
Sample Info	AD-H, 10% i-PrOH, 2.5 mL/min, 44 C, 20 microL
Barcode	
Operator	TBDE
Method	NSZ_OJH_P.M
Analysis Time	24.543 min
Sampling Rate	0.0033 min (0.198 sec), 7364 datapoints

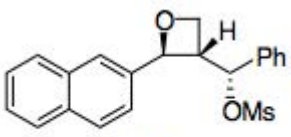


3.22

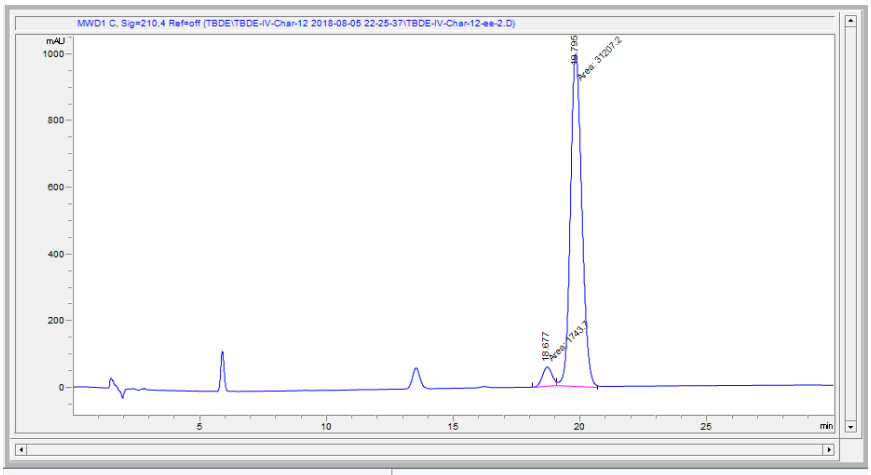


File Information	
LC-File	TBDE-IV-Char-12-rac-1.D
File Path	C:\Chem32\1\Data\TBDE\TBDE-IV-Char-12 2018-08-05 20-56-5
Date	05-Aug-18, 20:57:48
Sample	TBDE-IV-Char-12-rac-1
Sample Info	
Barcode	
Operator	SYSTEM
Method	Thom-TBDE-III-210.M
Reference	
Analysis Time	29.993 min
Sampling Rate	0.0067 min (0.402 sec), 4500 datapoints

#	Time	Type	Area	Height	Width	Area%	Sy
1	12.501	BB	2021.4	20.8	1.1824	19.596	
2	16.68	BV	2263.4	23.7	1.2156	21.941	
3	18.883	VV	2273.8	58.8	0.5991	22.042	
4	19.948	VB	3757.1	62.3	0.8321	36.421	

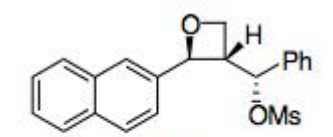


3.23

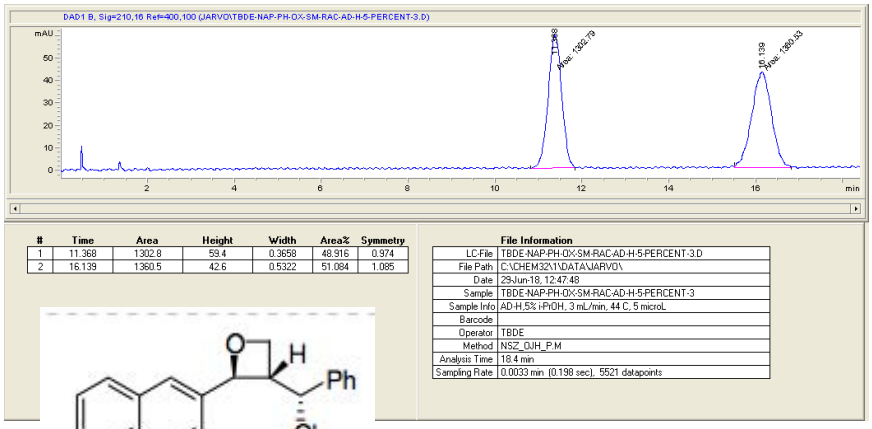


File Information	
LC-File	TBDE-IV-Char-12-ee-2.D
File Path	C:\Chem32\1\Data\TBDE\TBDE-IV-Char-12 2018-08-05 22-25-3
Date	05-Aug-18, 22:26:31
Sample	TBDE-IV-Char-12-ee-2
Sample Info	
Barcode	
Operator	SYSTEM
Method	Thom-TBDE-III-210.M
Reference	
Analysis Time	29.993 min
Sampling Rate	0.0067 min (0.402 sec), 4500 datapoints

#	Time	Area	Height	Width	Symmetry
1	18.677	1743.7	61	0.4764	1.007
2	19.795	31207.2	999.4	0.5204	0.819



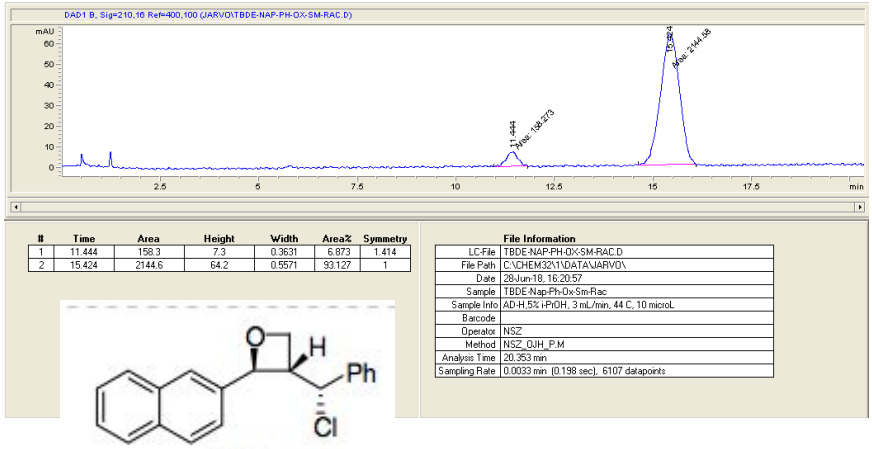
3.23



#	Time	Area	Height	Width	Area%	Symmetry
1	11.368	1302.8	59.4	0.3658	48.916	0.974
2	16.139	1360.5	42.6	0.5322	51.084	1.085

File Information	
LC-File	TBDE-NAP-PH-OX-SM-RAC-AD-H-5-PERCENT-3.D
File Path	C:\CHEM32\1\DATA\JARVO\
Date	29-Jun-18, 12:47:48
Sample	TBDE-NAP-PH-OX-SM-RAC-AD-H-5-PERCENT-3
Sample Info	AD-H,5% i-PrOH, 3 mL/min, 44 C, 5 microL
Barcode	
Operator	TBDE
Method	NSZ_OJH_P.M
Analysis Time	18.4 min
Sampling Rate	0.0033 min (0.198 sec), 5521 datapoints

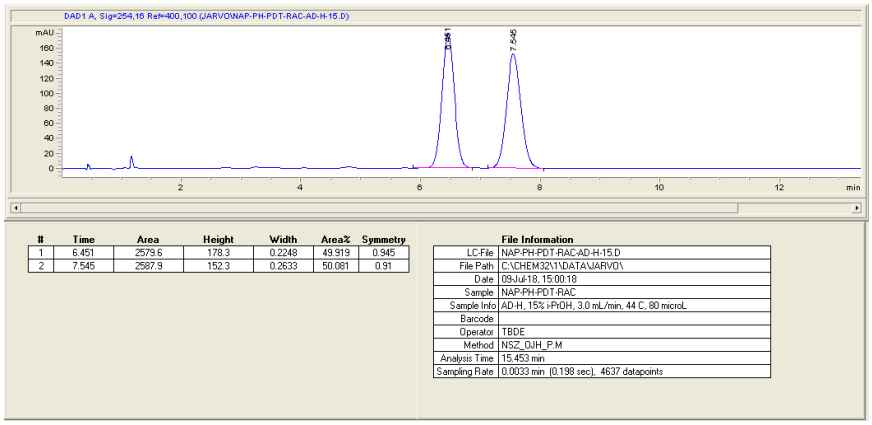
3.24



#	Time	Area	Height	Width	Area%	Symmetry
1	11.444	158.3	7.3	0.3631	6.873	1.414
2	15.424	2144.6	64.2	0.5571	93.127	1

File Information	
LC-File	TBDE-NAP-PH-OX-SM-RAC.D
File Path	C:\CHEM32\1\DATA\JARVO\
Date	28-Jun-18, 16:20:57
Sample	TBDE-Nap-Ph-Ox-Sm-Rac
Sample Info	AD-H,5% i-PrOH, 3 mL/min, 44 C, 10 microL
Barcode	
Operator	NSZ
Method	NSZ_OJH_P.M
Analysis Time	20.353 min
Sampling Rate	0.0033 min (0.198 sec), 6107 datapoints

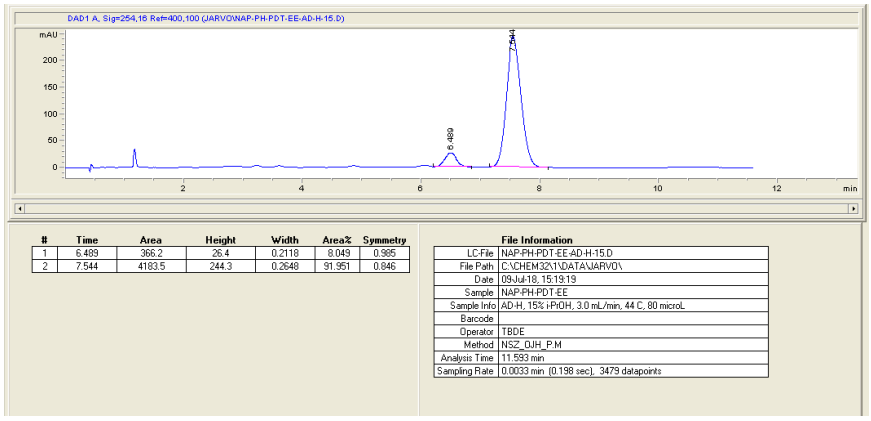
3.24



#	Time	Area	Height	Width	Area%	Symmetry
1	6.451	2579.6	178.3	0.2248	49.919	0.945
2	7.545	2587.9	152.3	0.2633	50.081	0.91

File Information

LC-File	NAP-PH-PDT-RAC-AD-H-15.D
File Path	C:\CHEM32\1\DATA\JARVO\
Date	09-Jul-18, 15:00:18
Sample	NAP-PH-PDT-RAC
Sample Info	AD-H, 15% i-PrOH, 3.0 mL/min, 44 C, 80 microL
Barcode	
Operator	TBDE
Method	NSZ_OJH_P.M
Analysis Time	15.453 min
Sampling Rate	0.0033 min (0.198 sec), 4637 datapoints



#	Time	Area	Height	Width	Area%	Symmetry
1	6.489	366.2	26.4	0.2118	8.049	0.985
2	7.544	4183.5	244.3	0.2648	91.951	0.846

File Information

LC-File	NAP-PH-PDT-EE-AD-H-15.D
File Path	C:\CHEM32\1\DATA\JARVO\
Date	09-Jul-18, 15:19:19
Sample	NAP-PH-PDT-EE
Sample Info	AD-H, 15% i-PrOH, 3.0 mL/min, 44 C, 80 microL
Barcode	
Operator	TBDE
Method	NSZ_OJH_P.M
Analysis Time	11.593 min
Sampling Rate	0.0033 min (0.198 sec), 3479 datapoints