UNIVERSITY OF CALIFORNIA

Santa Barbara

Stereoselective Construction of Carbon-Carbon Bonds and Application to the Scalable Total Synthesis of Xestospongin-type Natural Products

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

Maša Podunavac

Committee in charge:

Professor Armen Zakarian, Chair

Professor Javier Read de Alaniz

Professor Liming Zhang

Professor Gabriel Ménard

March 2021

The dissertation of Maša Podunavac is approved.

_____

Javier Read de Alaniz

_____

Liming Zhang

_____

Gabriel Ménard

_____

Armen Zakarian, Committee Chair

January 2021

Stereoselective Construction of Carbon-Carbon Bonds and Application to the Scalable Total Synthesis of Xestospongin-type Natural Products

by

Maša Podunavac

ACKNOWLEDGEMENTS

Firstly, I would like to express my sincere gratitude to my advisor Professor Armen Zakarian. Thank you for the continuous support, for your patience, motivation, enthusiasm, and immense knowledge. Your guidance helped me learn a tremendous amount and set me for success in my future endeavors. I could not have imagined having a better advisor and mentor for my graduate career than you!

I would also like to thank the rest of my thesis committee: Professor Javier Read de Alaniz, Professor Liming Zhang, and Professor Gabriel Ménard for their support and encouragement during this tenure.

There is no way to express how much it meant to me to have been a member of Zakarian Group. These brilliant friends and colleagues inspired me over the many years. Thank you for your energy, companionship, and scientific input. I would especially like to thank Dr. Jeffrey Jackson and Dr. Artur Mailyan for their mentorship that has not stopped even when they left the lab. I have grown so much as a chemist because of you two and I will always be grateful for your tutelage.

I am extremely grateful to Dr. Julio César Cárdenas for the collaboration and incredible learning opportunity I had during my visit to his lab at Universidad Mayor in Santiago, Chile.

Nobody has been more important to me in the pursuit of this journey than my family. I would like to thank my parents, Marina and Aleksandar, whose love and encouragement are with me every step of the way. Your endless love and unlimited support made all this possible. You are the ultimate role models! Mama i tata, volim vas mnogo! Finally, I am extremely grateful for my partner in crime, Tim Carroll. Thank you for being my rock and my home away from home.

CURRICULUM VITAE

Maša Podunavac
Santa Barbara, CA
podunavac.masa@gmail.com (805)-280-1770

EDUCATION

Ph.D. in Chemistry |University of California, Santa Barbara Sept 2015 – Jan 2021

B.S. in Chemistry, *Cum laude* | University of Arkansas–Fort Smith Aug 2011 – May 2015

RESEARCH EXPERIENCE

Graduate Research Assistant | UCSB Sept 2015 – Jan 2021

- Primary research advisor: Prof. Armen Zakarian

- **Scalable Synthesis of Xestospongin Type Natural Products**

Designed and implemented a modular approach for the assembly of the xestospongin carbon skeleton that is amenable to the preparation of a variety of analogues which have been used to interrogate the importance of inositol triphosphate (IP_3) mediated calcium signalling between the endoplasmic reticulum and the mitochondria. Currently scaling up the synthesis of desmethylxestospongin B (dmXeB) and its derivatives which are needed for *in vivo* experiments.

- **Stereodivergence in the Ireland-Claisen Rearrangement of α–Alkoxy Esters**

Conducted a systematic investigation into the Ireland-Claisen rearrangement of α-alkoxy esters. Our studies indicated that access to both diastereomeric rearrangement products can be achieved from the same starting material by simply switching the solvent and enolization reagent.

- **Enantioselective Alkylation of 2-Alkylpyridines Controlled by Organolithium Aggregation**

Conducted a systematic investigation into the enantioselective alkylation of 2-alkylpyridines. Our studies indicated that direct access to asymmetrically alkylated 2-alkylpyridines can be achieved by a simple protocol using chiral lithium amides as noncovalent stereodirecting auxiliaries.

Visiting Collaborative Researcher | Universidad Mayor, Chile Nov 2019 – Jan 2020

-Primary research advisor: Prof. Julio César Cárdenas

- **Cancer Metabolism**

Designed and performed *in vitro* Ca^{2+} signalling experiments that showed dmXeB is a potent inhibitor of IP_3 receptors making it a potential therapeutic target based on the

previously established hypothesis that in the absence of Ca^{2+}, cancer cells are unable to generate the building blocks needed to proliferate and maintain homeostasis. Additionally, we performed *in vivo* experiments that suggested dmXeB decreases metastasis of melanoma cells in mouse lungs.

RESEARCH PUBLICATIONS

[1] **Podunavac, M.**; Mailyan, A.; Jackson, J.J.; Lovy, A.; Farias, P.; Huerta, H.; Molgo, J.; Cárdenas, C.; Zakarian, A. "Scalable Total Synthesis, IP3R Inhibitory Activity of Desmethylxestospongin B, and Effect on Mitochondrial Function and Cancer Cell Survival." Submitted.

[2] Smith-Cortínez, N.; **Podunavac, M.**; Zakarian, A.; Cárdenas, C.; Faber, K. N. "Novel Inositol 1,4,5-Trisphosphate Receptor Inhibitor Antagonizes Hepatic Stellate Cell Activation: A Potential Drug to Treat Liver Fibrosis." Manuscript in preparation.

[3] Gladfelder, J.J.; Ghosh, S.; **Podunavac, M.**; Cook, A.W.; Ma Yun; Woltornist, R.A.; Keresztes, I.; Hayton, T.W.; Collum, D.B.; Zakarian, A. "Enantioselective Alkylation of 2-Alkylpyridines Controlled by Organolithium Aggregation." *J. Am. Chem. Soc.* **2019**, *141*, 15024-15028.

[4] **Podunavac, M.**; Lacharity, J.J.; Jones, K.E.; Zakarian, A. "Stereodivergence in the Ireland-Claisen Rearrangement of α-Alkoxy Esters." *Org. Lett.* **2018**, *20*, 4867–4870.

TECHNICAL SKILLS

• **Laboratory**: Multi-step synthesis (20-step synthesis experience), large scale synthesis (up to 150 g scale synthesis experience), anhydrous reactions, Schlenk line, purification methods (preparative HPLC, flash column chromatography, sublimation, distillation, recrystallization)
• **Instruments**: NMR (1D and 2D), HPLC, GC, ESI-MS, IR, polarimeter, glovebox
• **Software**: ChemDraw, MestReNova, Chemistry search engine (Reaxys, SciFinder), Microsoft Office

PRESENTATIONS

[1] **Podunavac, M.**; Zakarian, A. *Lunch & Learn*. UCSB. July 2019. (Oral presentation)
[2] **Podunavac, M.**; Zakarian, A. *The Chemical Student Seminar Series*. UCSB. March 2019. (Oral presentation)

INSTRUCTIONAL AND TEACHING EXPERIENCE

Undergraduate and Graduate Research Mentor | UCSB Sept 2016 – Jan 2021
Mentored and designed research projects for 3 different junior undergraduate researchers and trained 2 first-year graduate students in laboratory techniques and experimental design.

Organic Chemistry Lab I/II/III, Teaching Assistant | UCSB Sept 2015 – March 2019
Taught chemical instrumentation (NMR, FTIR, etc.) as well as organic laboratory techniques (chromatography, recrystallization, distillation, extractions, sublimations, etc.) twice a week to undergraduate students while enforcing laboratory safety.
Nominated for an Excellence in Teaching Award in the winter quarter of 2017.

HONORS AND AWARDS

- Winner of The Chemical Science Student Seminar (UCSB) 2019
- Mananya Tantiwiwat Award (UCSB) 2019
  - Awarded to the student with outstanding academic and life achievement
- Robert H. DeWolfe Graduate Teaching Award (UCSB) 2019
  - Received for my mentorship of undergraduate researchers in the Zakarian group
- Outstanding Service to the Department Award (UCSB) 2017, 2018, 2019
- Phillip Joshua Chase Mabe Memorial Fellowship (UCSB) 2018
  - Awarded to a student with great passion and intelligence in chemistry and biochemistry
- Academic Excellence Award in Chemistry (UAFS) 2015
- Division II Women's Tennis Team (UAFS) 2011 – 2015
  - Received full athletic scholarship

ABSTRACT

Stereoselective Construction of Carbon-Carbon Bonds and Application to the Scalable Total Synthesis of Xestospongin-type Natural Products

by

Maša Podunavac

Xestospongin type natural products (xestospongins and araguspongins) are a group of bis-1-oxaqunolizidine alkaloids isolated from Pacific sponge *Xestospongia* sp. They have been used to interrogate the importance of IP3 mediated calcium signaling between the endoplasmic reticulum and the mitochondria. It has been established that IP3R-mediated Ca^{2+} transfer to the mitochondria (MiU-IP3RCa) is essential to maintain homeostasis of the cell, and when inhibited, cell cycle and division are halted. Preliminary results show inhibition of MiU-IP3RCa with xestospongin B affects mitochondrial metabolism and reduces metastasis in cancer cells, without harming normal cells. However, an in-depth investigation into xestospongins activity has been limited by poor availability from natural resources. To provide material for further studies, a robust and scalable synthetic route was developed to access several members of the xestospongin family that delivers multimiligram quantities of the final products. The formation of xestostospongin 20-member macrocyclic core was based

on the early application of Ireland-Claisen rearrangement, macrolactamization, and a late-stage installation of the oxaquinolizidine units by lactam reduction. Importantly, the convergent strategy allowed the access to unsymmetrically oxidized xestospongins, such as desmethylxestospongin B that was used to investigate calcium signaling and its effect on mitochondrial metabolism in various cell types, including cancer cells.

The stereoselective construction of carbon-carbon bonds is a transformation that is of fundamental importance and a central goal of organic chemistry. Furthermore, Ireland–Claisen rearrangement is one of the most powerful synthetic methods for carbon-carbon bond formation. The utility of this method is underscored by the ease of preparation of the requisite allylic esters and the predictable stereochemical outcome of the reaction. It is generally presumed that only one diastereomer is accessible by the Ireland–Claisen rearrangement of α-alkoxy esters attributed to the overwhelming preference for the Z-enolate via chelation-controlled enolization. Our group has recently developed a procedure where selective E or Z-enolate formation was achieved from the same substrate, accessing both diasteromeric Ireland–Claisen products simply by the choice of base. In all cases, the use of $KN(SiMe_3)_2$ in toluene gave rearrangement products corresponding to a Z-enolate intermediate with excellent diastereoselectivity, presumably because of chelation control. On the other hand, chelation-controlled enolate formation could be overcome for most substrates through the use of lithium diisopropylamide (LDA) in tetrahydrofuran (THF). Furthermore, this method has been applied in the enantioselective total synthesis of the xestospongin type natural products.

The third chapter of this dissertation briefly focuses on enantioselective alkylation of 2-alkylpyridines controlled by organolithium aggregation. Our studies have shown that chiral pyridines can be accessed in high yields and enantioselectivity by a simple protocol using chiral lithium amides as noncovalent stereodirecting auxiliaries, which obviates the need for prefunctionalization or preactivation of the substrate. The alkylation is accomplished using chiral lithium amides as noncovalent stereodirecting auxiliaries. Crystallographic and solution NMR studies provide insight into the structure of well-defined chiral aggregates in which a lithium amide reagent directs asymmetric alkylation.

List of Figures

List of Schemes

List of Tables

TABLE OF CONTENTS

Chapter 1

Scalable Total Synthesis of Xestospongin-type Natural Products, IP_3R Inhibitory Activity of Desmethylxestospongin B, and Its Effect on Mitochondrial Function and Cancer Cell Survival

1.1. Introduction

1.1.1. Isolation and Biological Activity

Xestospongins, along with araguspongins, were first isolated from sponges of *Xestospongia sp*. found in various locations in the Pacific Ocean.[1] These metabolites are comprised of two oxaquinolizidine units tethered by saturated alkylidene chains to form a macrocyclic core. (**Figure 1**) While all of them have the set configuration at C2, C2', C10 and C10', they differ in variable oxidation and stereochemistry on C9, C9', C3 and C3'.[1]

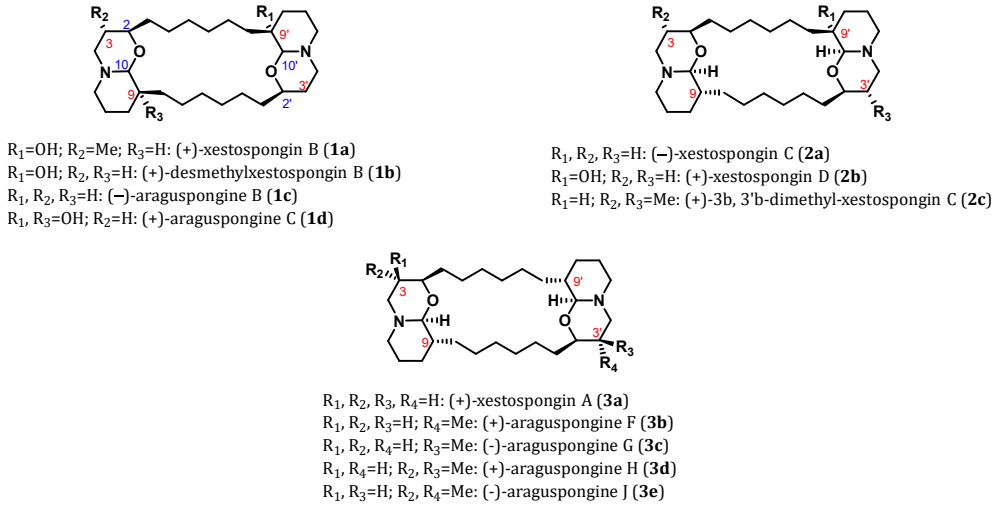


Figure 1. Xestospongin natural products.

While a range of biological activity was reported for xestospongins, we became intrigued by the mounting evidence for the unique ability of xestospongin B (**1a**, Xe B) to influence mitochondrial metabolism by modulating calcium signaling between the endoplasmic reticulum (ER) and mitochondria through the inhibition of inositol-1,4,5-

triphosphate receptors (IP3Rs).[2] The constitutive activity of IP3Rs is essential for cellular bioenergetics in a variety of cell types. Its inhibition disrupts the constitutive calcium transfer from ER to mitochondria causing a drop in mitochondrial respiration that generates a bioenergetic crisis characterized by AMPK and autophagy activation.[3] It has been shown that interruption of this communication leads to a selective, substantial cancer cell death leaving normal cells unaffected.[4]

1.1.2. The Mode of Action of Xestospongin B for IP3 Receptors

A hallmark feature of cancer cells is their ability to reprogram metabolism based on the environmental context to meet the bioenergetic and biosynthetic demands associated with rapid growth.[5,6] Increasing evidence indicates that, contrary to the Warburg seminal hypothesis,[7] most cancer cells rely on mitochondrial metabolism for ATP generation,[8,9,10,11] biosynthesis of metabolic intermediates necessary to produce lipids, proteins, and nucleic acids,[12] and for the generation of reactive oxygen species (ROS), which are required for optimal activation of signaling pathways needed for cell proliferation and metastasis.[13] Regarding the latter, little is known about the metabolic changes that occur during the different stages of the metastatic cascade, especially the role of mitochondrial metabolism.

Agonist-activation of IP3Rs at the ER enhances mitochondrial metabolism.[14,15,16] Calcium ions released by IP3Rs are taken up by the mitochondria Ca^{2+} uniporter (MCU),[17,18] stimulating the tricarboxylic acid (TCA) cycle dehydrogenases (PDH, α-KGDH and IDH),[19] as well as respiratory chain components to promote oxidative

phosphorylation (OXPHOS).[20,21] Cárdenas and co-workers previously established[22] that in the absence of agonist stimulation, low-level constitutive IP3R-mediated Ca^{2+} transfer to the mitochondria (MiU-IP3RCa) is essential to maintaining basal levels of OXPHOS and ATP production (**Figure 2a**) in a wide variety of cell types.[22,23] In the absence of MiU-IP3RCa induced by inhibition of the InsP3R or MCU, cells enter a bioenergetic stress characterized by a drop in the ATP levels, AMPK activation, and induction of an AMPK-dependent mTOR-independent autophagy (**Figure 2b**) as an essential survival mechanism.[22,23]

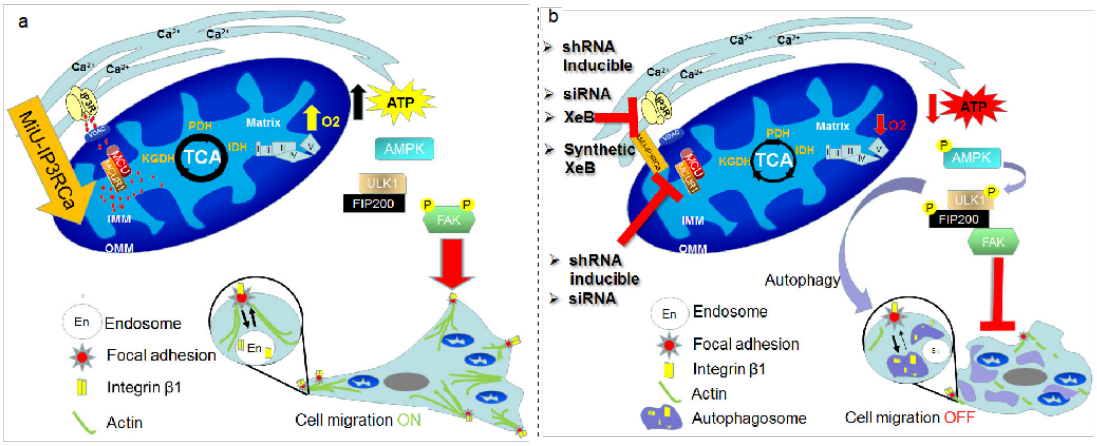


Figure 2 a. Constitutive IP3R-mediated Ca^{2+} transfer from the ER to the mitochondria (MiU-IP3RCa) sustains the activity of key dehydrogenases (PDH, IDH, KGDH) of the TCA cycle maintaining normal levels of ATP, with the concomitant inhibition of AMPK and autophagy, which allow FAK phosphorylation, integrin recycling and finally, migration**. b.** Lack of MiU-IP3RCa by inhibition of calcium release impairs the activity of the TCA cycle dehydrogenases, the levels of ATP drop, AMPK and autophagy are activated interfering with the activity of FAK and the recycling of integrins impairing migration.

In cancer, the expression of IP3Rs, in particular the IP3R-3 isoform, is up-regulated in: 1) glioblastoma,[24] 2) gastric,[25] 3) small and non-small lung,[26] and 4) colorectal cancers.[27] Importantly, the overexpression of IP3R-3 in gastric cancer was found in cell lines established from cells that invade to the peritonea, while the ones derived from primary tumor cells show normal levels of IP3R expression.[28] Similarly, in colorectal cancer IP3R-3 was found in the advancing margins of the tumors, which correlated with depth of invasion, lymph node metastasis, and liver metastasis.[27] In glioblastoma, the inhibition of IP3R with caffeine, a non-specific inhibitor of the IP3R, decreased migration in various *in vitro* assays and increased mean survival in a mouse xenograft model of glioblastoma.[24] In breast cancer, both estradiol and ATP-induced proliferation is mediated by the IP3R-3.[29,30] Moreover, the breast cancer metastasis suppressor 1 (BCMS1), a protein able to suppress formation of secondary tumor masses without blocking growth of neoplastic cells at orthotopic or subcutaneous sites, reduces IP3 signaling in the MDA-MB-435 cell line.[31] Clearly, IP3Rs are involved in cancer progression and metastasis; however, the mechanism behind their involvement has not been well understood. On the other hand, the role of MCU in cancer is just beginning to be explored. Various algorithms find that the expression of MCU correlates with a poor prognosis, invasive behavior and metastasis in breast cancer,[32,33] and the knockdown of MCU decreases cell migration through an unexplained mechanism,[33] supporting the concept that MiU-IP3RCa is essential in cancer. In 2016, Cárdenas determined that breast and prostate cancer cells, like normal cells, require IP3R-mediated constitutive Ca^{2+} transfer to the mitochondria for optimal

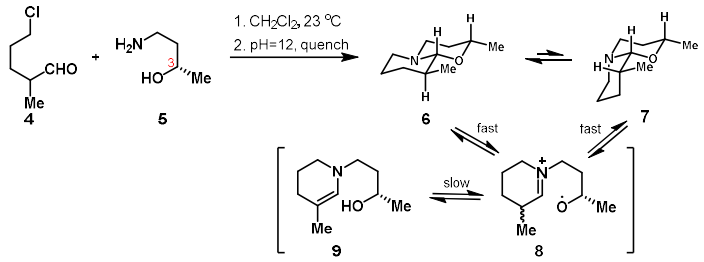
levels of ATP and NADH to support OXPHOS (Fig 2). Interruption of this communication, with Xe B or by knockdown of IP3R or MCU, elicits a selective, massive (60-70%) cancer cell death. Recently the survival of different cancer cell lines after the treatment with natural Xe B was determined, including their potential to grow, form colonies, and their ability to migrate in a transwell. No colonies were formed after 2 weeks and, migration was significantly reduced compared with untreated cells. Thus, it is hypothesized that without affecting normal cells, inhibition of constitutive IP3R-mediated Ca^{2+} uptake by mitochondria (MiU-IP3RCa) with xestospongin B (and possibly its derivatives) damages mitochondrial metabolism, reducing migration, invasion, and metastasis in breast cancer cells.

1.2. Previous Syntheses

1.2.1. Hoye's Synthesis of Xestospongin A[34]

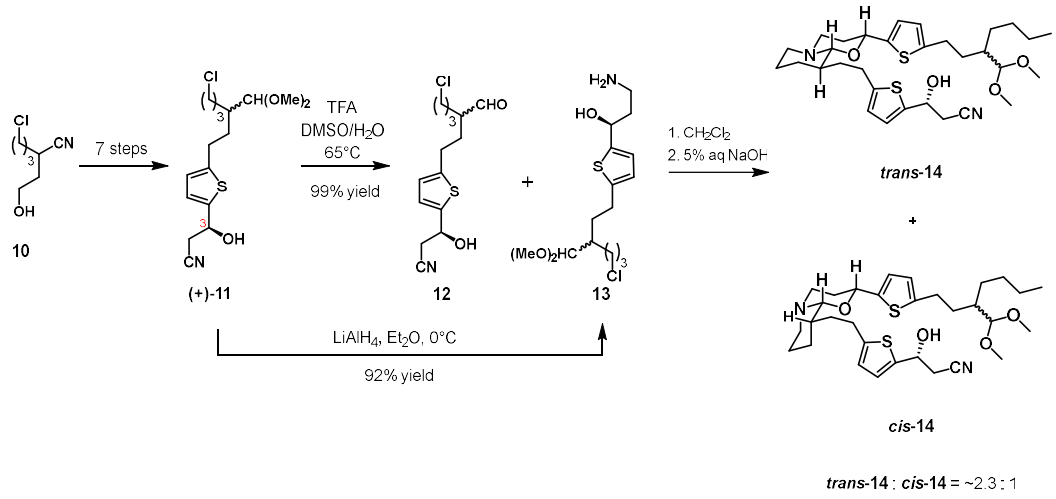
Hoye's strategy for the synthesis of (+)-Xe A (**3a**) involved dimerization protocol and taking advantage of its C2 symmetry. Extensive model studies suggested that the finest way to construct oxaquinolizidine rings is through the condensation between 5-haloaldehyde **4** and 1,3-amino alcohol **5** giving **6**.[35] This coupling thermodynamically favored formation of *trans* over *cis*-dimethylated oxaquinolizidines. due to fast reversible opening of **6** and **7** to the iminium ion **8**, and slower reversible proton transfer in **8** to form enamine **9** (Scheme 1).[35] Additionally the model studies suggested if the carbonyl stereocenter was set, it had ability to control all the relative and absolute stereocenters in Xe A through equilibrium.

Scheme 1. The macrocycle dimerization model study.



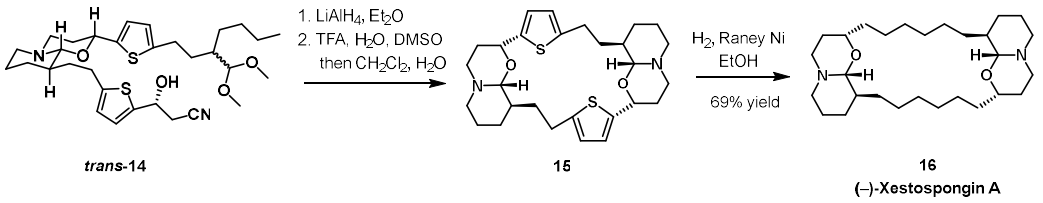
Racemic carbinol **11**, synthesized in 14% yield over 7 steps from alcohol **10**, underwent kinetic resolution to generate chiral acetate ester **(+)-11** (38%)[36] that has set configuration at C3 (Scheme 2). Although, thiophene was installed to ensure rigidity of the structure for the upcoming dimerization, Hoye and co-workers showed that this feature was not a critical requirement in the later publication.[34b] The key intermediate **(+)-11** was distributed divergently, with a part of it being hydrolyzed to the 5-haloaldehyde **12** (99%), and the remainder being reduced to 1,3-amino alcohol **13** (92%). Coupling of these two monomers **12** and **13** afforded a separable mixture of ***trans*-14** (42%) and ***cis*-14** (29%). Notably, it was possible to equilibrate *cis* isomer with the *trans* in the presence of a base such as triethylamine.

Scheme 2. Synthesis of key intermediate **(+)-11** and preparation for macrocyclization.



Protective groups were removed from ***trans*-14** in two consequent steps using $LiAlH_4$ (78%) and TFA followed by dilution in CH_2Cl_2 and water (Scheme 3). Subsequent elevation of the pH with 5% aqueous NaOH led to formation of C2-symmetric macrocyclic bis-thiophene **15** (70%). This set the stage for the last step Raney nickel reduction that removed both thiophene rings (69%) to afford **16**.

Scheme 3. Synthesis of xestospongin A.



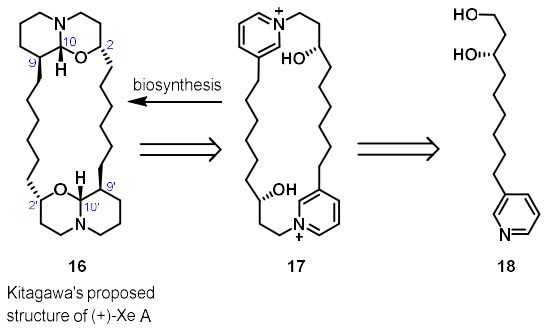
After completing the total synthesis of **16** and thereby assigning its absolute configuration, Hoye and coworkers proposed the configuration of natural xestospongin A to be 2*S*,9*S*,10*R*,2′*S*,9′*S*,10′*R* which later turned incorrect.

1.2.2. Baldwin's Synthesis of (−)-Xe A, (+)-Xe C and (+)-Ar B[37]

Baldwin and co-workers applied biomimetic dimerization strategy to the synthesis of (−)-Xe A (**16**), (+)-Xe C (**26**) and (+)-Ar B (**25**). Not only they were able to complete the synthesis of three natural products, but they also corrected the absolute configurations of natural (+)-Xe A (**3a**) (2*S*,9*S*,10*R*,2′*S*,9′*S*,10′*R)* that was proposed in previous publications.[1c, 34, 35]

They envisioned that xestospongins can be biosynthetically derived from bis-hydroxypyridinium dimer **17** (Scheme 4) based on the occurrence of the macrocyclic and polymeric 3-alkylpyridinium compounds among marine sponges.[38] The proposed dimer intermediate **17** could be prepared from monomer **18** which was the initial target of their synthesis.

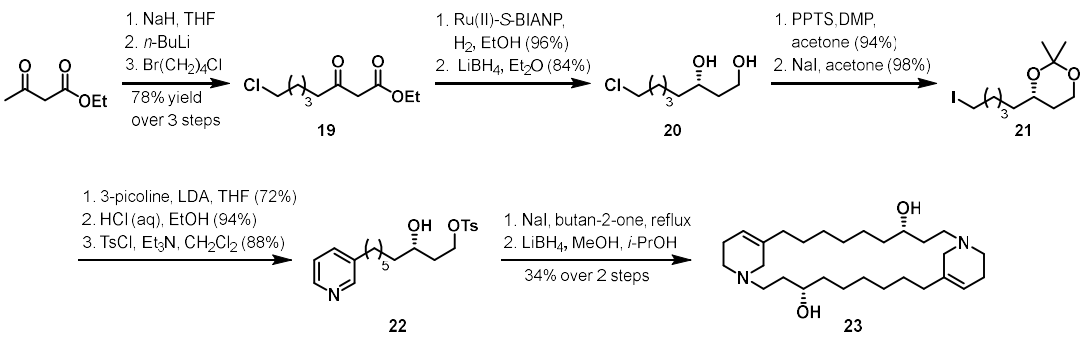
Scheme 4. Synthesis plan for (+)-Xe A.



The synthesis begun with advancement of ethyl acetate to ethyl 8-chloro-3-oxooctanone **20** in 3 steps (78%),[39,40] which upon Noyori hydrogenation with [Ru(II)-*S*-BINAP][41] (96% yield, ee 96%) and reduction by lithium borohydride provided diol **20** (84%) (Scheme 5). Treatment of **20** with pyridinium tosylate/2,2-dimethoxypropane/acetone (94%), followed by rection with sodium iodide in refluxing acetone afforded iodide **21** (98%). The monotosylated intermediate **22** was obtained after three-step refunctionalization of **21** that included treatment with lithiated 3-picoline[42] (72%), removal of acetonide with diluted hydrochloric acid in ethanol (94%) and finally selective tosylation (88%). The key dimerization step was accomplished by slow addition of a solution of **22** in butan-2-one to a refluxing solution of sodium iodide. Mixture of the products from macrocyclization step was reduced with lithium borohydride to provide tetrahydropyridine dimer **23** (34% over 2 steps).

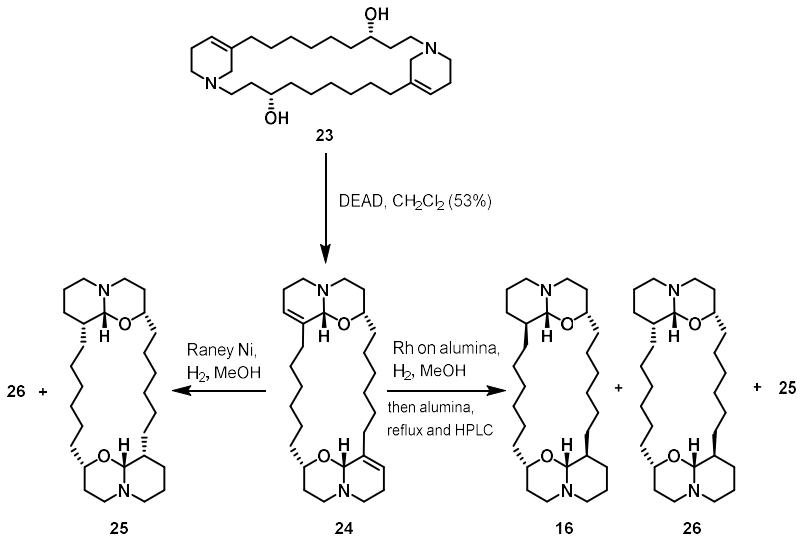
Reaction of **23** with diethyl azodicarboxylate[43] gave dehydro-bis-oxaquinolizidine **24** (53%) via iminium ion intermediate (Scheme 6). This set the stage for the final steps of the synthesis. A part of **24** was distributed to a hydrogenation with Raney nickel in methanol delivering araguspongine B[34,44] as a major product (**25**, 77%) and xestospongin C (**26,** 7%). The remaining amount of **24** was hydrogenated in the presence of rhodium on alumina[45] in methanol providing xestospongin A (**16,** 23%), xestospongin C (**26,** 17%) and araguspongine B (**25,** 9.5%) after HPLC separation.

Scheme 5. Synthesis of tetrahydropyridine dimer **23.**



Having established access to synthetic **16**, **25** and **26**, they proceeded to establish their absolute configurations. Previously both Kitagawa[1c] and Kobayashi[45] described **25** as (−)-Ar B, however Baldwin's synthetic **25** possessed specific rotation of $[\alpha]^{23}_{D}$ +10.7. Additionally, Baldwin's synthetic **16** had absolute rotation of $[\alpha]^{23}_{D}$ −9.5, and **26** of $[\alpha]^{23}_{D}$ +1.6. They were compared to the published values[34b] of $[\alpha]^{23}_{D}$ +8.9 and $[\alpha]^{23}_{D}$ −1.2 respectively suggesting both **16** and **25** were enantiomers of the originally assigned structures. Although these results are significantly different from those of Hoye and Kitigawa, Baldwin and coworker were certain about the stereochemistries of **16**, **25** and **26** because precursors **22** was previously derived from (*S*)-asparitic acid.[45]

Scheme 6. Synthesis of (+)-araguspongine B, (−)-xestospongin A and (+)-xestospongin C.



In conclusion, Baldwin and co-workers were able to use their biomimetic approach to derive (+)-araguspongine B (**25**), (−)-xestospongin A (**16**) and (+)-xestospongin C (**26**). Also, they were able to correct absolute configurations of (+) Xestospongin A (**3a**) as (2*R*,9*R*,10*S*,2′*R*,9′*R*,10′*S*), of (-)-Xestospongin C (**2a**) as (2*R*,9*S*,10*S*,2′*R*,9′*R*,10′*S*), and of (-)-Araguspongine B (**1c**) as (2*R*,9*S*,10*S*,2′*R*,9′*S*,10′*S*). (Scheme 6)

1.3. Motivation to Pursue a Synthesis of Desmethylxestospongin B

While xestospongin B (**1a**) is no longer available from the natural sources, total synthesis provides a feasible source of material. Previous syntheses in this area by Baldwin[37] and Hoye[34] are characterized by remarkable brevity and strategic elegance.

However, they were targeting C2-symmetrical, non-hydroxylated congeners which suggests that these dimerization approaches are not suitable for the access of unsymmetrical xestospongins such as Xe B.

The main goal of our study was to design a scalable and modular synthetic approach in order to access 1-oxaquinolizidine alkaloids which simplifying C2-symmetry is broken with variable substitution and stereochemistry at C9 and C9'. Instead of Xe B, we targeted desmethylxestospongin B (**1b,** dmXeB), a natural product within this family of metabolites, based on the premise that the 3'-methyl group has no effect on the IP3R inhibitory activity, and obviating the need to install it would simplify the development of a scalable synthesis. Once the access to dmXe B was established, we wanted to evaluate the effect of it on mitochondrial respiration in breast cancer cell lines, and the resultant selectivity in inducing cancer cell death leaving normal cells nearly unaffected.

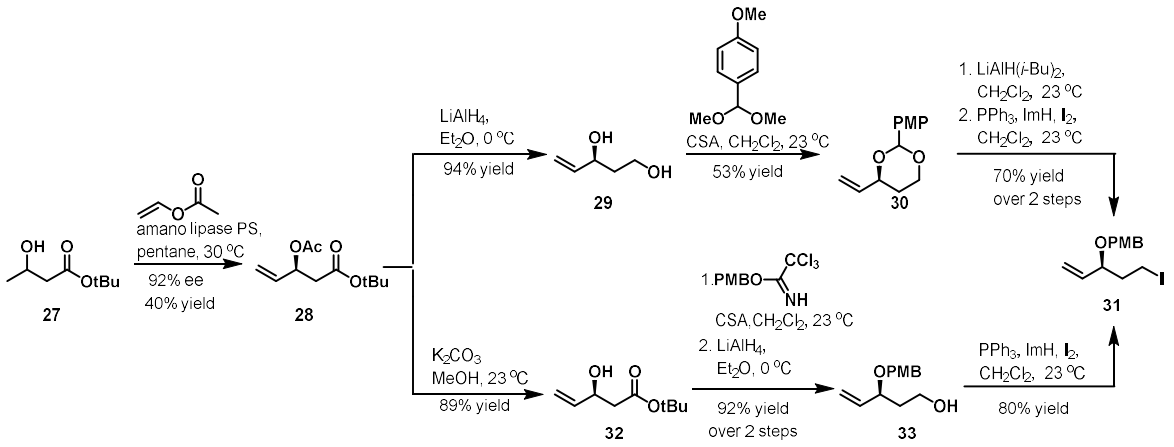
1.4. Scalable Total Synthesis of Desmethylxestospongin B

1.4.1. Early Strategies Towards the Scalable Total Synthesis of dmXe B

Our early synthetic strategy originally focused on preparation of iodide **31** from chiral allylic acetate **28** that was accessed by enzymatic kinetic resolution of **27**. Subsequent reduction $LiAlH_4$ to diol **29**, followed by acetal formation provided **30** in 53% yield. Finally, reduction with $LiAlH(i\text{-}Bu)_2$ and iodo-dehydroxylation afforded the chiral iodide **31** in 70% yield over 2 steps. However, our enthusiasm towards this

route was drastically reduced when purification of **30** turned out to be very challenging on scale due to formation of inseparable mixture with p-anisaldehyde.

Scheme 7. Attempted syntheses of **31.**

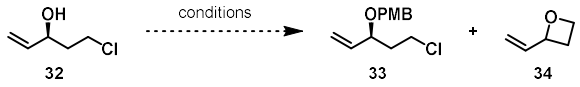


Alternatively, chiral allylic alcohol **32** was derived from acetate **28** in 89% yield. The crude para-methoxy benzyl ether was submitted to reduction with $LiAlH_4$ providing primary alcohol **32** in 92% yield over two steps. Finally, iodo-dehydroxylation of **32** afforded iodide **31** in 80% yield. This approach provided effortless isolation of the material unlike the previous route. Unfortunately, the downsides were the number of steps as well as a major loss of the material in the very first kinetic resolution step which motivated us to come up with a more efficient route.

We decided to use 1-chloro-3-butene served as the starting point for the 5-step synthesis of **31**. For this route, the development of electrophilic benzylation that was required due to the propensity of **32** to undergo intramolecular etherification during alkoxide formation. Formation of the vinyl oxetane **34** led to the low yield of **33** during

para-methoxy benzylations under well-established conditions such as the treatment with PMBCl and NaH or Ag_2O (Table 1, entries 1-4). Additionally, no reaction or low conversions were observed under a number of reaction conditions (Table 1, entries 5-7). After reductive para-methoxybenzylation (PMB) under electrophilic conditions that provided **33** in 72% yield and displacement of the chloro-group, iodide **31** was obtained.

Table 1. Optimization of synthesis of **33**.

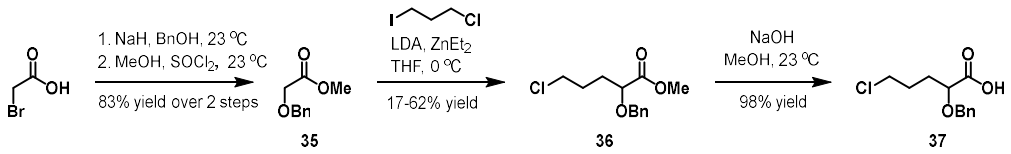


32 33 34

Entry	Reagents	Solvent	Temperature	Time	Result (XX)
1	PMBCl, NaH	THF	23 °C	24h	30% yield
2	PMBCl, NaH	THF	50 °C	3h	30% yield
3	PMBCl, Ag_2O	THF	65 °C	72h	50% yield
4	PMBCl, Ag_2O	MeCN	65 °C	72h	50% yield
5	PMBCl, Ag_2O	DMF	100 °C	15h	5% conversion
6	PMBCl, LiHMDS, TBAI	THF	23 °C	20h	no reaction
7	trichlorocarboximadate, CSA	CH_2Cl_2	23 °C	1h	50% conversion
8	p-anisaldehyde, $BF_3{\cdot}OEt_2$, Et_3SiH	CH_2Cl_2	-30 °C	1h	72% yield

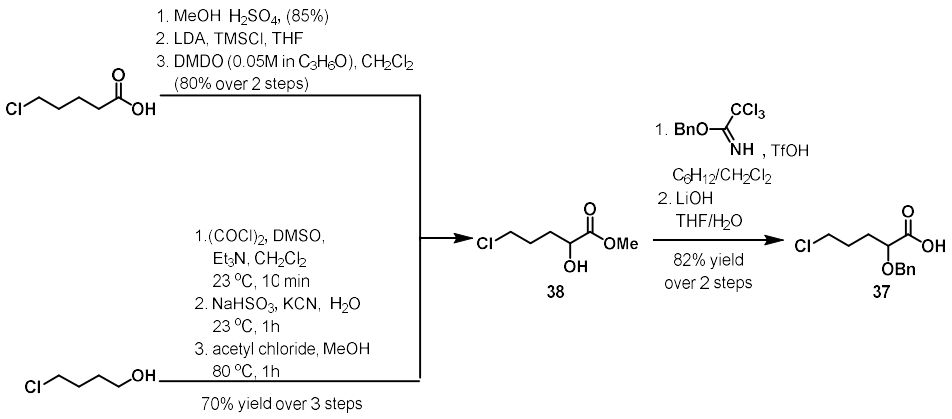
Another surprisingly challenging intermediate was α-benzyloxy acid **37**. The initial route was consisted of a 4-step synthesis with a key zinc enolate formation (Scheme 8). The issue arose when this reaction was performed on more than 4-gram scale. Isolated yield of methyl ester **36** dropped from previously observed 62% to 17% due to enolate decomposition and self-condensation.

Scheme 8. First-generation synthesis of **37**.



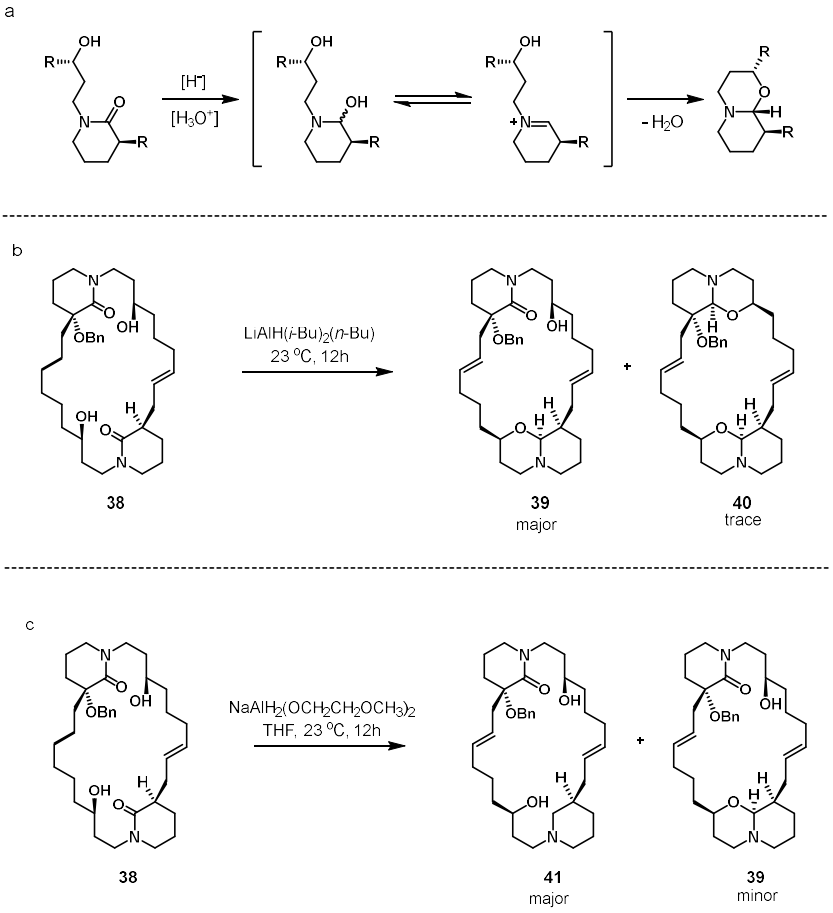
For the second route, 5-chlorovaleric acid served as a starting point (Scheme 9). Formation of silyl enol that was immediately treated with solution of DMDO in acetone provided α-hydroxy methyl ester **38** in 80% yield over 2 steps. Subsequent para-methoxy benzyl ether formation followed by ester hydrolysis afforded targeted acid **37** in 82% yield. Although we were optimistic about this route due to high yields and convenient isolation, it was not suitable for large scale synthesis due to limited amount of DMDO solution that could be generated in laboratory environment, as well as dioxiranes being potentially explosive. Thus, we decided to access methyl ester **38** via cyanohydrine in three steps from commercially available 4-chloro-1-butanol (Scheme 9). Although high yields were observed in these transformations, isolation of clean **37** was troublesome due to reaction with trichloroimidate forming inseparable mixture with byproducts.

Scheme 9. Alternative syntheses of **37**.



Formation of oxaquinolizidine rings was envisioned to be done using a selective reduction of a hydroxyl lactam to the hemiaminal, which would then cyclize to the oxaquinolizidine ring (Scheme 10a). It has been shown that tertiary amides can be selectively reduced to hemiaminals using nBuLi-DIBAL "ate" complex, and upon work up provide aldehydes in excellent yields.[35b, 46] Also, there has been couple examples of selectively reducing hydroxyl lactams with Red-Al.[47] Unfortunately, neither of the strategies showed promising results with our substrate. The crude mixtures of products were analyzed by ^{1}H NMR and mass spectroscopy. When **38** was treated with nBuLi-DIBAl "ate", formation of the mono reduction product **39** was detected as major, while there was only trace of desired product **40** (Scheme 10b). Surprisingly when **38** was submitted to the reaction with Red-Al, major product observed was overreduction to piperidine **41**, and minor was **39** (Scheme 10c).

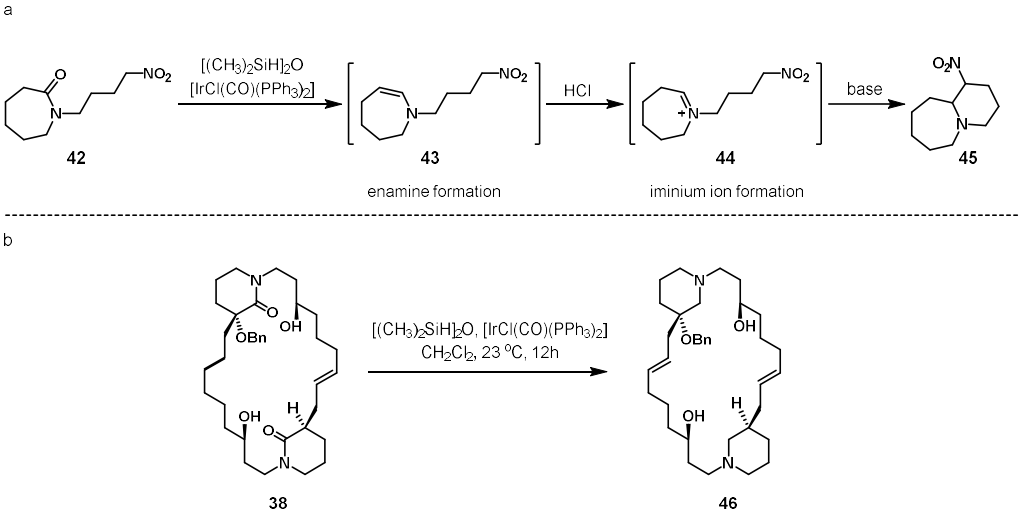
Scheme 10. a) Formation of bis-1-oxaquinolizidine rings via selective reduction of lactam. **b**) Attempted formation of bis-1-oxaquinolizidine rings using nBuLi-DIBAL "ate" complex. **c**) Attempted formation of bis-1-oxaquinolizidine rings using Red-Al.



Another strategy we tried was Dixon's well knows iridium catalyzed reactions. Dixon and coworkers[48] reported that the Vaska's complex $[IrCl(CO)(PPh_3)_2]$ catalyzes the partial reduction of amide **42** in the presence of syline to affords enamine **43** (Scheme 11a). Only upon acidic workup does **43** reprotonate to give the stable, water-soluble, iminium ion **44**. Upon addition of solid potassium carbonate, the resulting rise in pH to >10 facilitates smooth cyclization to **45**. Sadly, once **38** was

treated with Vaska's complex in the presence of syline, the only product found by mass spectral analysis was overreduction product of the amide to piperidine **46** (Scheme 11b).

Scheme 11. a) Iridium-catalyzed reductive cyclization. b) Attempted formation of bis-1-oxaquinolizidine rings using Iridium-catalyzed reductive cyclization.

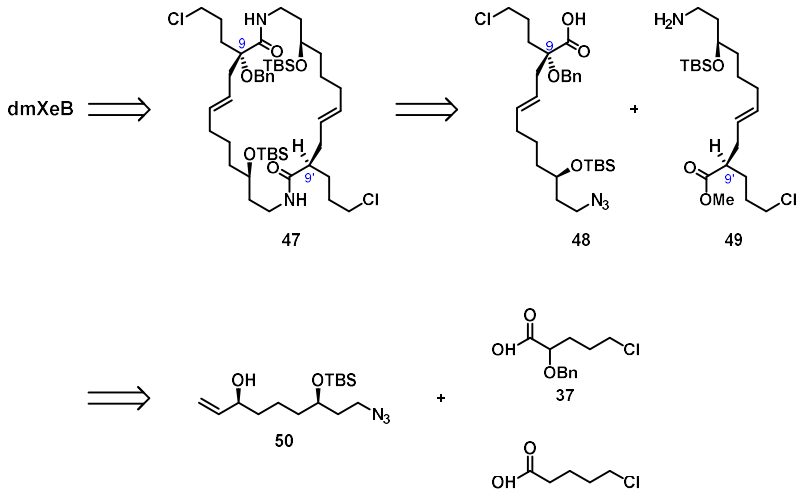


1.4.2. Synthesis plan

The synthesis design is depicted in Scheme 12. The final assembly of the 1-oxaquinolizidine units was envisioned to take place by intramolecular N-alkylation of the amide groups in macrocyclic bis(lactam) **47** followed by lactam semireduction and hemiaminal formation. The bis(lactam) was planned to arise from combining two ω-amino acid precursors **48** and **49** by sequential amide formation. These precursors will be prepared from a common starting material, azidoalcohol **50**. After its esterification with either 2-(benzyloxy)-5-chloropentanoic acid (**37**) or 5-chloropentanoic acid,

intermediates **48** and **49** will be accessed via Ireland-Claisen rearrangement to establish stereogenic centers at C9' and C9, respectively.

Scheme 12. Synthesis design for dmXe B.



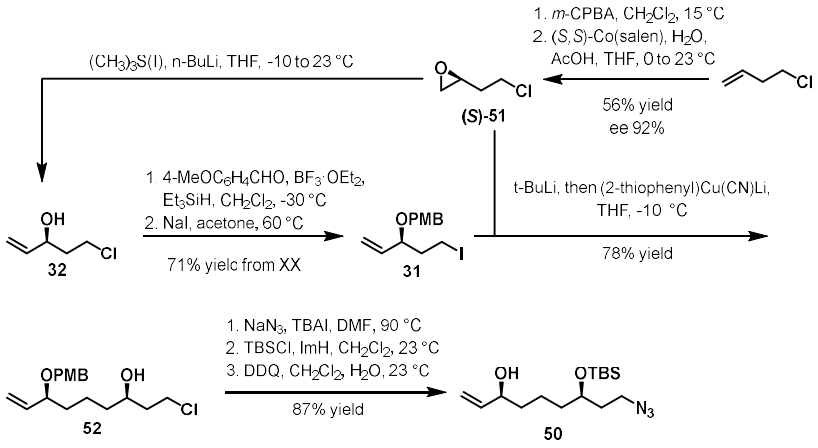
This synthesis design has the advantage of flexibility in accessing 1-oxaquinolizidine alkaloids with variable substitution at C9/9' (with or without OH groups), as well as variable stereochemistry at the same positions.

1.4.3. Synthesis of Common Intermediate Azido Alcohol 50

1-Chloro-3-butene served as the starting point for the synthesis of **50** (Scheme 13). Jacobsen hydrolytic kinetic resolution of 1-chlorobutene oxide, obtained by epoxidation with MCPBA, delivered **(*S*)-51** in 58% yield and 92% ee.[49] The epoxide **(*S*)-51** was distributed divergently, with part of it being advanced to allylic alcohol **32** with dimethylmethylenesulfur ylide.[50] As previously noted, the development of

electrophilic benzylation was required due to the propensity of **32** to undergo intramolecular etherification during alkoxide formation. After reductive para-methoxybenzylation (PMB) under electrophilic conditions and displacement of the chloro-group, iodide **31** was obtained in a 71% overall yield.[51] Cuprate coupling with the remainder of chloro epoxide **(*S*)-51** with the reagent formed from **31** was accomplished in 78% yield.[52] Subsequent substitution of chloride with sodium azide, O-silylation, and removal of the PMB group delivered 58.1 grams of **50** in 87% yield.

Scheme 13. Preparation of common azido alcohol intermediate **50**.

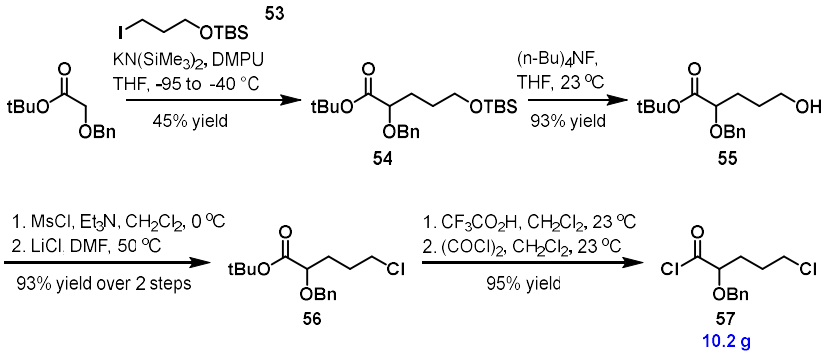


1.4.4. Synthesis of ω-Amino Acid Precursors 48 and 49

In order to access non-symmetrical congeners such as dmXe B possessing a C9 hydroxy group, the synthesis of an α-benzyloxy valeric acid **37** was required (Scheme 14). Due to the thermal instability of ester enolates generated from α-alkoxy esters, alkylation of t-butyl α-benzyloxyacetate with iodide **53** was accomplished at –95 °C in

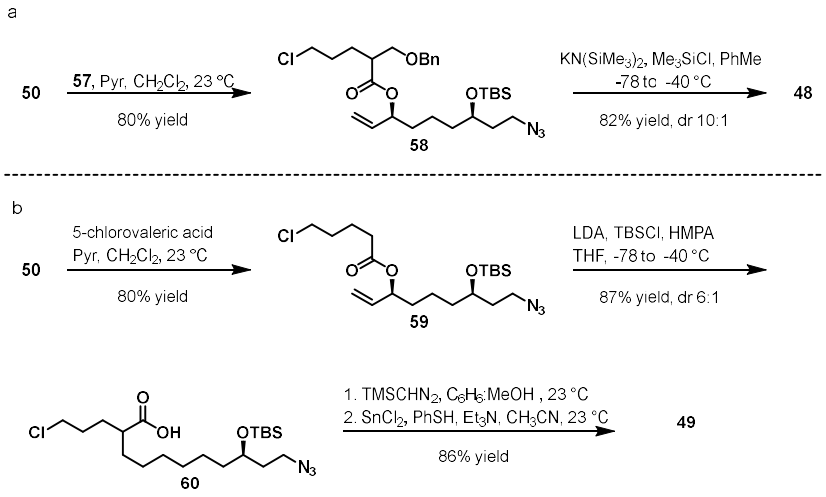
moderate yield of 45% under optimized reaction conditions. After desilylation, mesylation, and substitution with LiCl, ester **56** was obtained in 86% yield. Cleavage of the t-butyl ester and chlorodehydroxylation with oxalyl chloride completed the synthesis of acyl chloride **57** (93% yield, 10.2 grams).

Scheme 14. Preparation of early-stage intermediate **57**.



In preparation for the bis(macrolacram) assembly, the individual amino acid synthons were obtained by Ireland-Claisen rearrangement (ICR) of two esters prepared from allylic alcohol **50** (Scheme 15a and b).[53] Intermediate **48** was obtained from ester **58** (82% yield, dr 10:1) under reaction conditions developed specifically for α-alkoxy esters.[54] ICR of ester **59** gave rise to carboxylic acid **60** (87% yield, dr 6:1), which, after forming the methyl ester with Me_3SiCHN_2, was advanced to amino ester **49** by azide reduction with $SnCl_2$/PhSH (82% yield).[55]

Scheme 15. Preparation of fragments **48** and **49**.



1.4.5. Macrolactamization and Formation of Oxaquinolizidine Rings

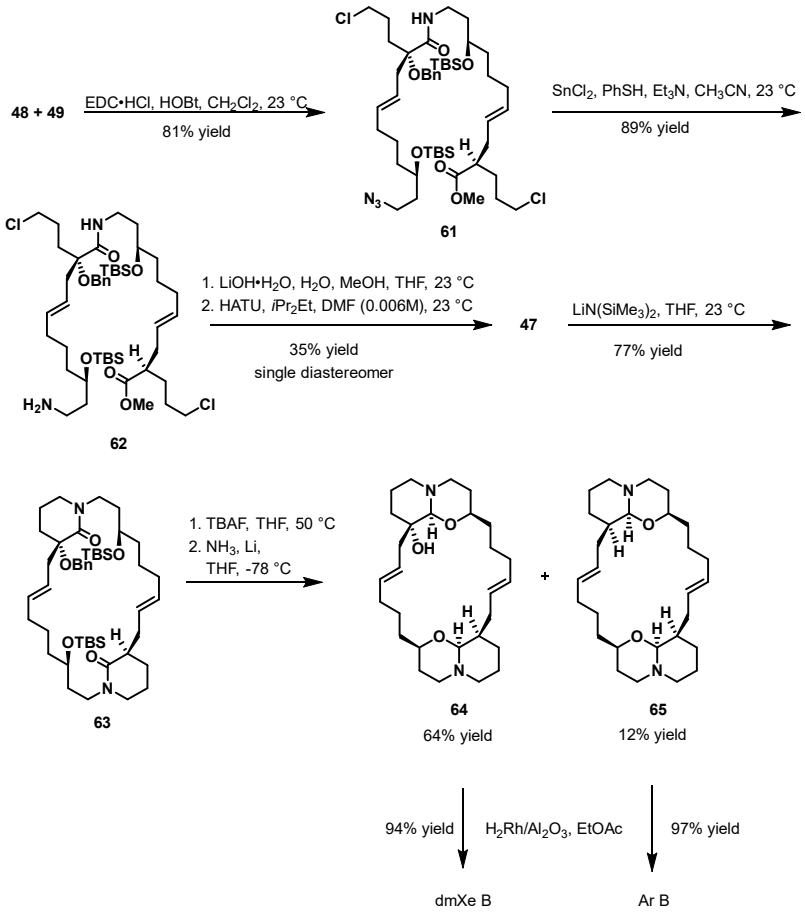
Fragment union was achieved by amide formation from acid **48** and amine **49**, followed by another azide reduction under the same conditions, ester hydrolysis, and macrolactamization (Scheme 16).[56] At this stage, the minor diastereomers formed during ICR were separable, and macrocyclic bis(lactam) **47** was isolated in 35% yield as a single diastereomer.

Completion of the synthesis follows a bidirectional strategy, starting with the formation of two valerolactam moieties by intramolecular N-alkylation of **47** ($LiN(SiMe_3)_2$, THF, 85% yield). Removal of the silyl groups preceded the crucial reductive 1-oxaquinolizidine formation with Li-NH3 reagent, which simultaneously accomplished O-debenzylation.[57] As previously stated, numerous alternative reagents attempted to achieve semireduction of the lactams (iBu$_2$AlH,[46] $NaAlH_2(OR)_2$,[47] $IrCl(CO)(PPh_3)_2$/$(HMe_2Si)_2O$),[48] consistently resulted in complete reduction to

piperidine. Partial α-dehydroxylation leading to a minor amount of **65** was also observed.

The final hydrogenation of the double bonds required optimization, as the typical conditions using Pd/C in various solvents proved inconsistent and occasionally resulted in an intractable mixture of products. However, hydrogenation of **64** and **65** with Rh/Al_2O_3 in ethyl acetate[58] reliably and cleanly delivered dmXe B (**1b,** 94% yield) and araguspongine B (**1c,** Ar B, 97% yield), respectively.

Scheme 16. Fragment union and completion of the synthesis.



1.5. IP3R Inhibitory Activity of dmXe B, and Effect on Mitochondrial Function and Cancer Cell Survival

Having established access to synthetic dmXe B, we proceeded to evaluate its effect on IP3R-mediated calcium release, mitochondrial respiration, and selective anticancer activity in breast cancer cell lines, and how it compares to Xe B isolated previously from a marine sponge. As shown in Figure 3a, 30 min incubation with either dmXe B or Xe B completely abolished IP3R calcium release induced by ATP in MDA-MB-231 cells. Subsequently, the normal cell line MCF10A and a cancer cell line MDA-MB-231 were treated with increasing concentrations of dmXe B and Xe B for 24 h, and oxygen consumption rates (OCR) were determined using Seahorse system. As shown in Figure 3b, both compounds decrease OCR similarly in a dose-dependent fashion. A similar effect was observed in a triple-negative cell line BT-549 and the luminal A MCF7 cell line (See Supporting Information).

We have also demonstrated that dmXe B induces selective cell death in breast cancer cell lines. Several breast cancer cell lines that represent heterogeneity of breast cancer and the normal cell line MCF10A were treated with different concentrations of either Xe B or dmXe B for 24 h and cell death was measured by propidium iodide incorporation through flow cytometry. As shown in Figure 3c, 7.5 μM Xe B induced a significant increase in cell death in MDA-MB-231 cells, without affecting the normal cell line MCF10A. At 10 μM, Xe B is still more effective in MDA-MB-231 cells, but some effects in MCF10A cells become measurable, indicating reduced selectivity. On the other hand, dmXe B in fact shows somewhat increase selectivity, inducing cell death in

MDA-MB-231 at 5 μM, which is sustained at 10 μM with no effect on normal MCF10 cells (Figure 3c). At 20 μM, MDA-MB-231 cells are still more sensitive, with almost 100% of the population dead, whereas MCF10A shows an initial increase in cell death. In cell lines representative of luminal A (MCF7) and luminal B (ZR75) breast cancer cell lines Xe B and dmXe B display selective cell death at concentrations between 5 and 10 μM. Similarly, to the observations with MDA-MB-231 cell line, dmXe B at 20 μM concentration caused an almost complete cell death in ZR75 and MCF7 cell lines, while also affecting the normal cell line MCF10A to a much lesser extent. The BT-549 cells are more resistant to both compounds, showing only selectivity at 7.5 μM. Finally, we determined whether dmXe B affected the ability of cancer cells to proliferate indefinitely (one of the hallmarks of cancer), as demonstrated previously for Xe B.[3] MDA-MB-231 cells were treated with either compound for 24 h and then one thousand cells were collected and reseeded. After one week, we evaluated colony formation and found that at 7.5 μM the synthetic dmXe B, similarly to natural Xe B, completely abolished this phenomenon (Figure 4).

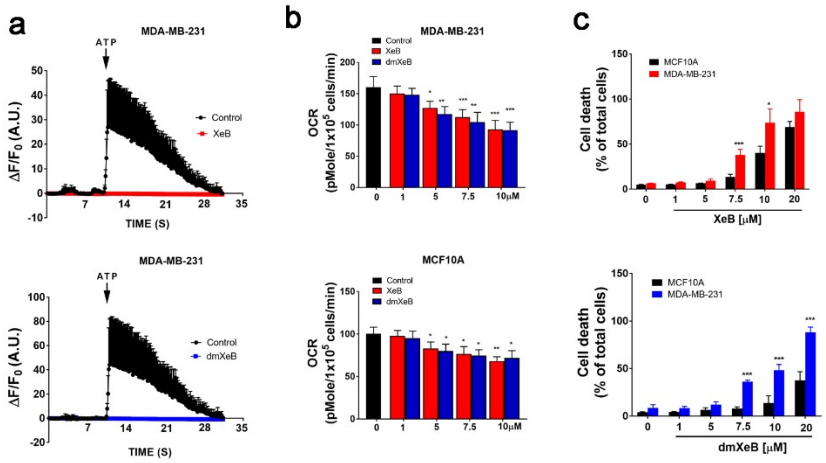


Figure 3. Average cytosolic calcium increases in response to ATP (100 μM) in MDA-MB-231 cells treated with ethanol (vehicle, control) or 5 μM Xe B (upper panel, red trace) or dmXe B (bottom panel, blue trace) for 1 h. Mean ± SEM of 3 independent experiments. In each experiment, 100 cells were analyzed. **b**. Basal oxygen consumption rate (OCR) of MDA-MB-231 (upper panel) and MCF10A (bottom panel) cells incubated for 24h with increasing concentration of either Xe B (red) or dmXe B (blue). The black bar represents cells basal OCR without treatment. Mean ± SEM of 3 independent experiments with 10 replicates each. *p < 0.05, **p < 0.01, ***p < 0.001 compared to respective control. **c**. MDA-MB-231 and MCF10A were treated with increasing concentrations of either Xe B (upper panel, red) or dmXe B (lower panel, blue) for 24 h and cell death was determined by propidium iodide incorporation by flow cytometry. Mean ± SEM of 3 independent experiments, each in triplicate. *p < 0.05, ***p < 0.001 compared to respective control.

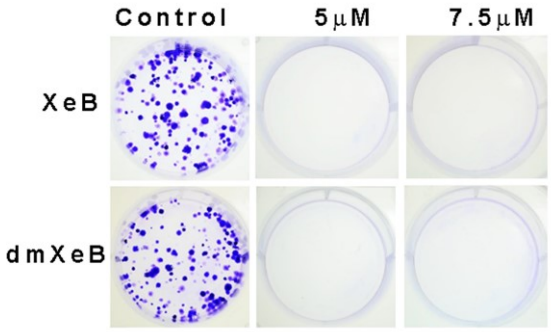
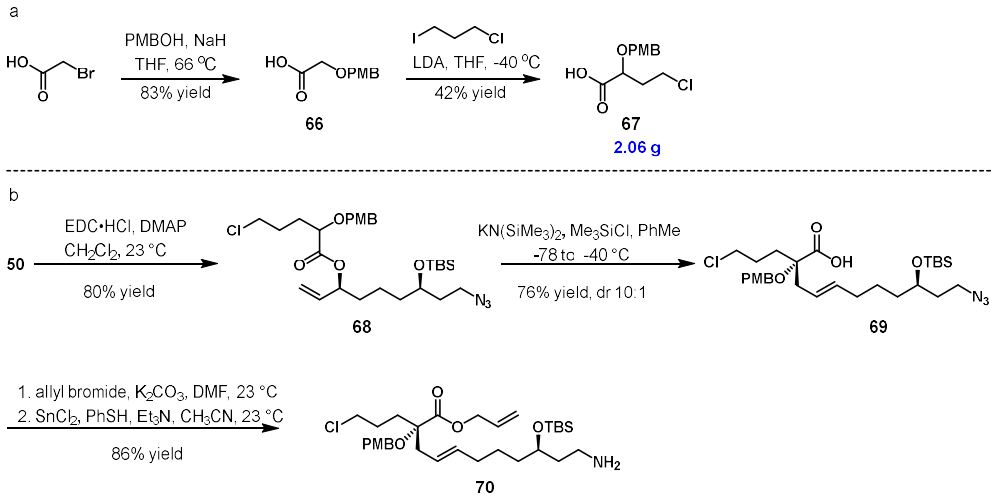


Figure 4. Representative plates of three different experiments with MDA-MB-231 cells treated with 7.5 μM of either Xe B (upper panel) or dmXe B (bottom panel).

1.6. Total Synthesis of Araguspongine C

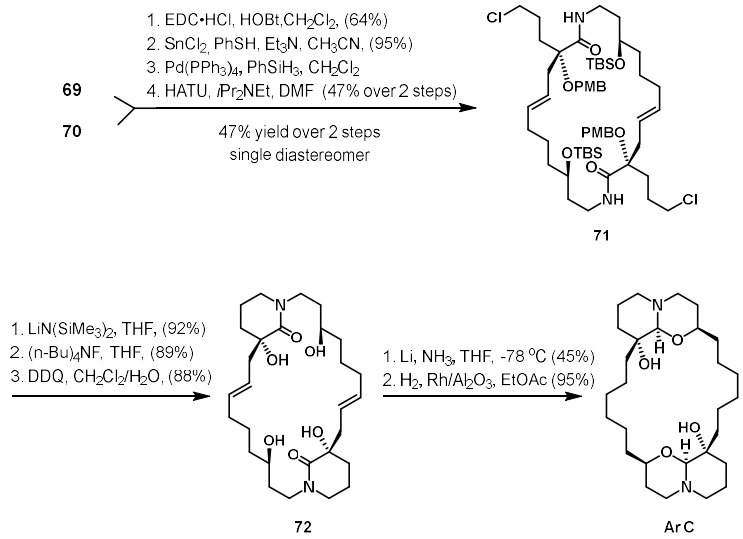
To further highlight the generality of the strategy, we completed the synthesis of bis-hydroxylated araguspongine C (**1d**), which has not been accessed previously by synthesis. In this case, we opted for p-methoxybenzyl (PMB) ether at C9/9' to test an alternative deprotection/reductive oxaquinolizine construction method. Alpha-alkoxy acid **67** was accessed in two steps from commercially available bromoacetic acid. (Sheme 17a) Ireland-Claisen rearrangement of ester **68** provided acid **69** in 76% yield and dr 10. It was treated with allyl bromide to utilized allyl ester in **70** to simplify access to the free acid, as the methyl ester proved resistant to hydrolysis (Scheme 17b).

Scheme 17. The synthesis of intermediates **67**, **69** and **70**.



Thus, after acid **69** and amine **70** were combined by amide formation, azide reduction, acid deallylation, and macrolactamization afforded bis-lactam **71** (Scheme 18). Six-membered lactam closure was accomplished with $LiN(SiMe_3)_2$ as previously, and removal of TBS and PMB groups delivered **72** in high yield. Finally, reduction of the lactam with Li-NH_3 and hydrogenation completed the synthesis of Ar C.

Scheme 18. The synthesis of araguspongine C (Ar C).

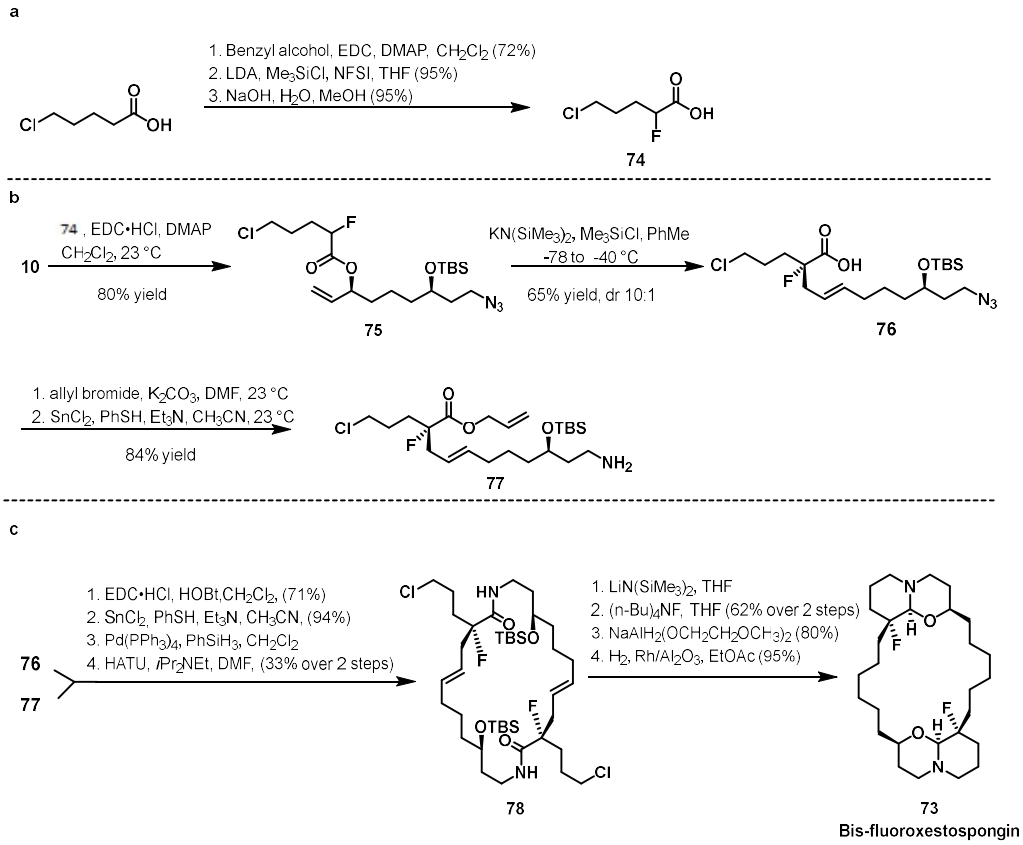


1.7. Total Synthesis of Bisfluoroxestospongin

In addition to the synthesis of three natural products (dmXe B, Ar B and Ar C), we completed the synthesis of bis-fluoroxestospongin (**73**) that has not been found in the nature. During the synthesis of dmXe B, we have noticed significant amount of epimerization of stereocenter C9 when lactam was reduced with Li-NH_3. We envisioned that substitution of hydrogens at C9 and 9' with similar in size fluoro-group could suppress epimerization of these stereocenters. As importantly, fluorine substitution is expected to impart unique physicochemical properties while maintaining nearly identical sterical makeup to the original natural product, with potentially beneficial impact on bioactivity.

Alpha fluoro-chlorovaleric acid **74** was accessed in three steps from commercially available 5-chlorovaleric acid. (Scheme 19a) Although synthesis of **73** was almost identical to previously made Ar C, including key steps such as Jacobsen's hydrolytic kinetic resolution and Ireland-Claisen rearrangement, major difference was method used to selectively reduce lactams. In this case we were able to form two bis-1-oxaquinolizidine rings with $NaAlH_2(OCH_2CH_2OCH_3)_2$ in high yields instead of applying previously used Li-NH_3 method. Formation of **78** set the stage for the last hydrogenation step that delivered bis-fluoro xestospongin **73** in 95% yield (Scheme 19b).

Scheme 19. The synthesis of bis-fluoroxestospongine **73**.



1.8. Conclusion

In summary, we developed a scalable synthesis of dmXe B, taking advantage of a convergent strategy allowing the preparation of xestospongins with variable stereochemistry and oxidation at C9/9'. The hallmarks of the strategy include a strategic application of ICR to achieve the desired makeup of the C9/9' stereocenters, assembly of the macrocyclic core by macrolactamization, and late-stage 1-oxaquinolizidine construction by amide reduction. Moreover, this synthesis represents a modular synthetic design in order to easily access other xestospongin derivatives

such as Ar C and non-natural products needed for SAR studies such as bis-fluoroxestospongin.

With dmXe B in hand, we established that it is an effective inhibitor of the constitutive ER-to-mitochondria calcium transfer, and subsequently confirmed its ability to induce selective cancer cell death in a variety of cell lines, including metastatic cancer, while leaving normal cells nearly unaffected. According to a recent study, these effects are associated with a drop in the mitochondrial activity of the calcium-sensitive α-ketoglutarate dehydrogenase, a key enzyme in oxidative phosphorylation and reductive carboxylation required for cancer cell survival.[59]

Chapter 2

Stereodivergence in the Ireland-Claisen Rearrangement of α-Alkoxy Esters

2.1. Introduction[i]

The Ireland–Claisen rearrangement has represented a powerful tool in chemical synthesis for over 40 years.[60] The utility of this method is underscored by the ease of preparation of the requisite allylic esters and the predictable stereochemical outcome of the reaction.[61] The stereochemistry of the alcohol fragment is reliably transferred to the α and β positions of the carboxylic acid product with high enantio- and diastereoselectivity, usually through a chairlike transition state, providing a streamlined approach to the construction of sterically congested vicinal stereocenters.[62] Furthermore, the carboxy group formed in the reaction can serve as an effective proxy to a wide variety of other functional groups.[63]

Efficient transmission of chirality during the Ireland–Claisen rearrangement is critically dependent on the stereoselective formation of an *E*- or *Z*-enolate. In the case of α-alkoxy esters, it is widely expected that formation of the *Z*-enolate is kinetically favored, because of chelation of the alkoxy and carbonyl oxygen atoms with the metal cation of the base. Indeed, selective *Z*-enolate formation in the Ireland–Claisen rearrangement of esters derived from glycolic and lactic acid has been observed in numerous cases.[64] Therefore, we were surprised to find a report from Langlois and co-workers that described selective *E*-enolate formation in the Ireland–Claisen rearrangement of an α-OPMB ester when LDA was used as the base in THF.[65] In this single reported example, rearrangement products were isolated as a 3 : 1 mixture of products arising from the *E*- and *Z*-enolates, respectively. This selectivity was reversed

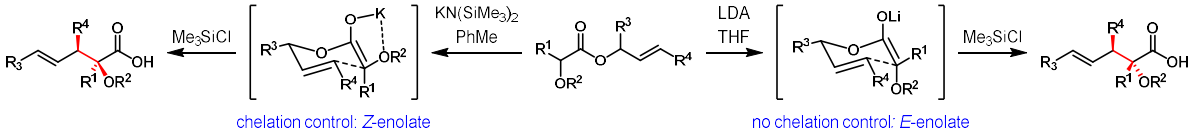
[i] Significant portions of this chapter were published in the journal *Organic Letters*.[54]

when Et_2O or toluene were used as the solvent, when HMPA was employed as an additive, or when $KN(SiMe_3)_2$ was used as the base.

To the best of our knowledge, this work represents the only case of nonchelation-controlled, *E*-selective enolization of an α-alkoxy ester. It is an important observation because it is generally presumed that only one diastereomer is accessible through the Ireland–Claisen rearrangement of α-alkoxy esters attributed to the overwhelming preference for the *Z*-enolate through chelation-controlled enolization.[66] Thus, no systematic studies on the divergence in the diastereoselectivity in the Ireland–Claisen rearrangement, based on the choice of the enolization reagent, has been reported for this class of substrates. If it is indeed possible to achieve selective *E*- or Z-enolate formation from the same substrate, facile access to both diasteromeric Ireland–Claisen products could be realized.

We became interested in exploring whether the effect of the base used for the enolization of α-alkoxy esters on the diastereochemical outcome of the Ireland–Claisen rearrangement is general. If so, practical levels of diastereomer ratios (dr) can be achieved for both isomers from the same substrate simply by the choice of base (Scheme 20). To this end, we prepared a library of these compounds to examine the effects of the reaction conditions and the structure of the ester on the diastereoselectivity of the rearrangement.

Scheme 20. Proposed stereodivergent access to both diastereomeric Ireland-Claisen rearrangement products from α-alkoxy esters.



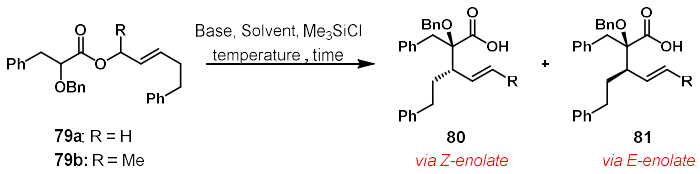
2.2. Substrate Scope

2.2.1. Optimization of Reaction Conditions

Using α-benzyloxy hydrocinnamates **79a** (R = H, Table 2) and **79b** (R = Me) as representative α–alkoxy esters, initial studies focused on identifying suitable reaction conditions capable of selectively delivering both diastereomeric products **80** and **81** based on the choice of base. The highest chelation-controlled Z-enolate formation of **79a** and **79b** was achieved upon treatment of $KN(SiMe_3)_2$ in toluene giving 88-90% yield as a 25:1 mixture of diastereomers favoring **80a** and **80b** (Table 2, entries 1 and 2). Notably, diastereoselectivity of the rearrangement product was lower with the change of solvent of the metal cation of the base (entries 3-6). Interestingly, an inversion in diastereoselectivity was observed with the use of LDA as a base (entries 7-11). Treatment with LDA in toluene delivered the rearrangement products in 34% yield as a 1:2.7 mixture of diastereomers favoring **81a** (entry 7). Although a slight decrease in stereoselectivity was observed when THF was used as a solvent, it provided **81a** in higher yield (entry 8). The remaining mass balance in this case was identified as a mixture of products arising from lithiation and subsequent silylation of

the allylic position alpha to the ester oxygen. Also, it was observed that addition of HMPA still maintains selectivity for the non-chelation controlled product 46a (entry 9). The use of esters that contained a methyl group in the allylic position prevented undesired lithiation. Treatment of **79b** with LDA in THF gave the *E*-enolization product **81b** in 80% yield as a 1:5 mixture of diastereomers (entry 10). Additionally, it was concluded that selectivity could be further improved to 1:9 by lowering deprotonation temperature to –100 °C (entry 11).

Table 2. Optimization experiments for the stereodivergent Ireland-Claisen rearrangement.



Entry	R	Base	Solvent	Temperature, deprotonation (°C)	Time, deprotonation (min.)	Ratio 83:84	Yield
1	H	$KN(SiMe_3)_2$	PhMe	-78	30	25:1	88
2	Me	$KN(SiMe_3)_2$	PhMe	-78	30	25:1	90
3	H	$KN(SiMe_3)_2$	THF	-78	30	6.7:1	46
4	H	$LiN(SiMe_3)_2$	PhMe	-78	30	5:1	90
5	H	$LiN(SiMe_3)_2$	THF	-78	30	11:1	77
6	H	$NaN(SiMe_3)_2$	PhMe	-78	30	4:1	74
7	H	LDA	PhMe	-78	30	1:2.7	34
8	H	LDA	THF	-78	internal quench	1:2	57
9	H	LDA	THF/HMPA	-100	internal quench	1:2.2	34
10	Me	LDA	THF	-78	internal quench	1:5	80
11	Me	LDA	THF	-100	internal quench	1:9	81

2.2.2. Application of Optimized Reaction Conditions to α-Alkoxy Esters

A series of α-alkoxy esters were prepared and subjected to the optimal [3,3] sigmatropic rearrangement protocols in the presence of bases $KN(SiMe_3)_2$ or LDA

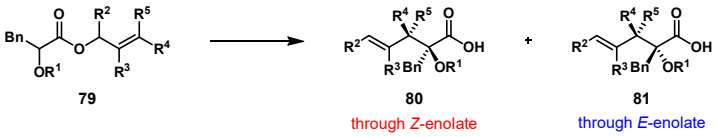
(Table 3). We began by screening a variety of α-alkoxy hydrocinnamic acid esters (**79**) bearing distinct R^2, R^3, and R^4 substituents, in addition to different R^1 alkoxy substituents. $KN(SiMe_3)_2$ as a base afforded acids *via Z*-enolate (**80c–j**) in moderate to excellent yields (79%–90%) with diastereoselectivities as high as 25:1. In all examples, a slight decrease in dr was observed when the alkoxy substituent R^1 was changed from Bn to a methyl group. It was found that the nature of the R^1 substituent had little effect on the reaction in terms of yield. In contrast, using LDA as the base gave rearrangement products *via E*-enolate (**81c–j**) in comparable yields (72%–92%), but with noticeably smaller dr (17:1 being the highest). As noted above, a substantial decrease in yield was observed for esters derived from primary alcohols compared with secondary (R^2 = H instead of Me) due to competitive lithiation of the allylic methylene group. Although yields were similar for acids with R^2 = Me, in most cases, α-benzyloxy esters gave products with higher dr.

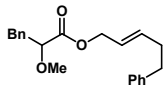
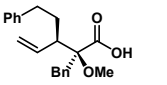
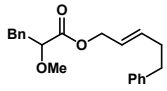
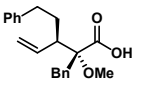
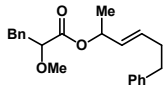
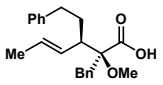
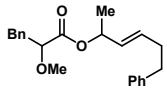
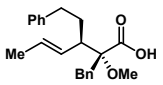
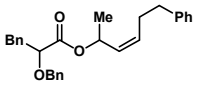
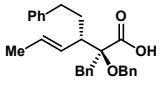
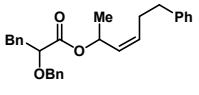
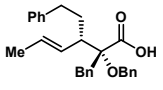
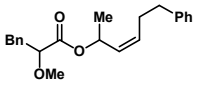
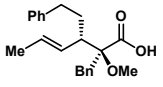
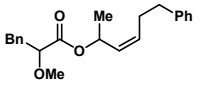
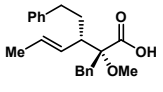
We then examined the Ireland–Claisen rearrangement of α–alkoxy propionic acid esters (**82a–j**, Table 4). Unlike α-alkoxy hydrocinnamic acid esters, the use of LDA as a base did not favor formation of *E*-enolate products **84a–j** in this class of substrates. Both bases gave the same major rearrangement products **83a–j**, corresponding to *Z*-enolate intermediates, in comparable yields, with $KN(SiMe_3)_2$ giving significantly higher dr. Surprisingly, higher dr is achieved when R^1 = Me, compared to R^1 = Bn, which is the opposite of what was observed for the esters in Table 6.

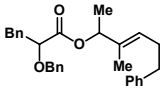
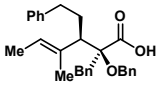
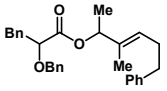
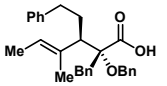
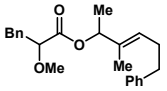
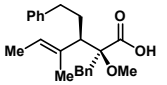
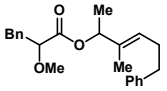
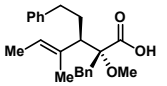
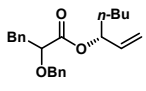
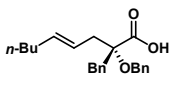
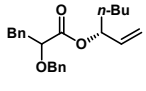
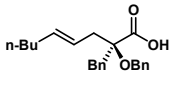
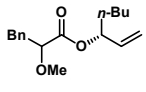
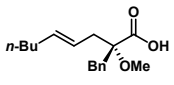
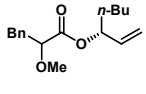
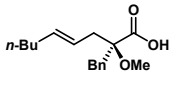
To gain insight into the structural constraints required to achieve selective *E*-enolization with LDA, we performed additional experiments, as summarized in Table 5.

The optimized conditions for the rearrangement were applied to α-alkoxy butyric acid esters **85a** and **b**. Remarkably, this simple one-carbon homologation of the carboxylic acid alkyl side chain, relative to the esters in Table 4, once again led to *E*-selective enolization when LDA was used as the base, although a much higher diastereomeric ratio was obtained for α-OBn substrate **85a** (1:6), relative to the corresponding α-OMe ester **85b** (1:1.1), as is consistent with our previous observations. α–Cyclopropyl substrate **85c** proved to be more resistant to *E*-enolization, with a modest diastereoselectivity of 1:1.1 favoring the *E*-enolate-derived product **87c** obtained when the rearrangement was performed using LDA as the base. These results seem to suggest that while *Z*-selective enolization and rearrangement is highly predictable and selective with $KN(SiMe_3)_2$, *E*-selective enolization for α-alkoxy esters is very sensitive to the structure of the alkyl side chains. In addition, greater selectivity is generally observed for larger alkoxy substituents (for example, for OBn versus OMe).

Table 3. Substrate scope for the α-alkoxy hydrocinnamic acid esters.[a]

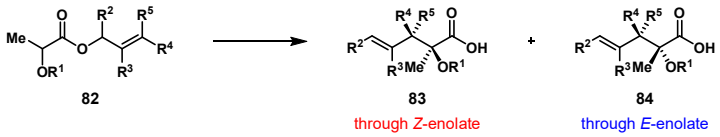


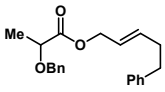
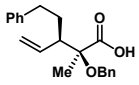
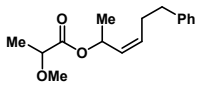
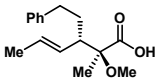
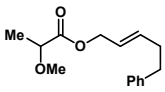
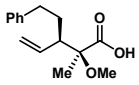
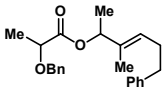
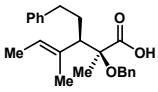
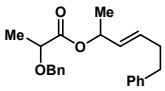
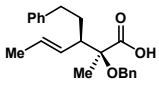
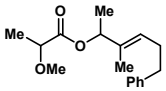
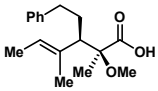
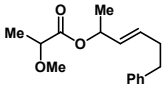
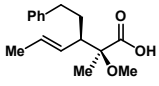
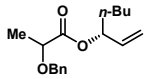
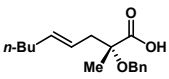
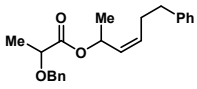
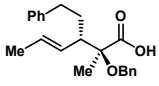
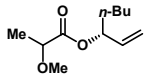
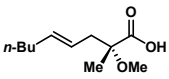
entry	substrate	base	major isomer	yield 80 : 81
1	 79c	$KN(SiMe_3)_2$	 80c	85% 14 : 1
2	 79c	LDA	 80c	45% 1 : 2
3	 79d	$KN(SiMe_3)_2$	 80d	82% 17 : 1
4	 79d	LDA	 81d	85% 1 : 5
5	 79e	$KN(SiMe_3)_2$	 80e	87% 25 : 1
6	 79e	LDA	 81e	79% 1 : 17
7	 79f	$KN(SiMe_3)_2$	 80f	90% 17 : 1
8	 79f	LDA	 81f	80% 1 : 8

entry	substrate	base	major isomer	yield 80 : 81
9	 79g	$KN(SiMe_3)_2$	 80g	79% 25 : 1
10	 79g	LDA	 81g	72% 1 :17
11	 79h	$KN(SiMe_3)_2$	 80h	80% 25 : 1
12	 79h	LDA	 81h	76% 1 : 6
13	 79i	$KN(SiMe_3)_2$	 80i	87% 10 : 1
14	 79i	LDA	 81i	73% 1 : 7
15	 79j	$KN(SiMe_3)_2$	 80j	87% 10 : 1
16	 79j	LDA	 81j	95% 1 : 7

[a]The substrate was treated with the indicated base at –78 °C ($KN(SiMe_3)_2$) or –100 °C (LDA). Internal quench with Me_3SiCl was used for LDA. Isomer ratio determined by ^1H NMR spectroscopy.

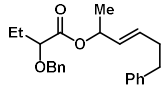
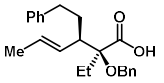
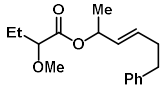
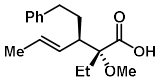
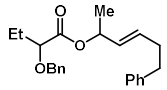
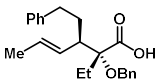
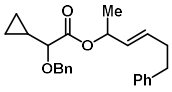
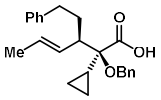
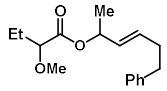
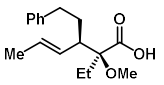
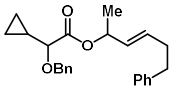
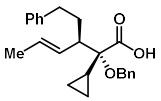
Table 4. Substrate scope for the α-alkoxy propionic acid esters.[a]



entry	substrate	base	major isomer	yield 86 : 87	entry	substrate	base	major isomer	yield 86 : 87
1		$KN(SiMe_3)_2$		94% 13 : 1	11		$KN(SiMe_3)_2$		82% 30 : 1
	82a		**83a**			**82f**		**83f**	
2	**82a**	LDA	**83a**	77% 2 : 1	12	**82f**	LDA	**84f**	83% 1 : 4
3		$KN(SiMe_3)_2$		81% 17 : 1	13		$KN(SiMe_3)_2$		72% 25 : 1
	82b		**83b**			**82g**		**83g**	
4	**82b**	LDA	**83b**	92% 5 : 1	14	**82g**	LDA	**83g**	78% 2 : 1
5		$KN(SiMe_3)_2$		82% 20 : 1	15		$KN(SiMe_3)_2$		64% 30 : 1
	82c		**83c**			**82h**		**83h**	
6	**82c**	LDA	**83c**	71% 2 : 1	16	**82h**	LDA	**83h**	82% 5 : 1
7		$KN(SiMe_3)_2$		85% 25 : 1	17		$KN(SiMe_3)_2$		88% 11 : 1
	82d		**83d**			**82i**		**83i**	
8	**82d**	LDA	**83d**	88% 6 : 1	18	**82i**	LDA	**83i**	85% 1.4 : 1
9		$KN(SiMe_3)_2$		81% 7 : 1	19		$KN(SiMe_3)_2$		72% 14 : 1
	82e		**83e**			**82j**		**83j**	
10	**82e**	LDA	**84e**	81% 1 : 2	20	**82j**	LDA	**83j**	91% 8 : 1

[a]The substrate was treated with the indicated base at –78 °C ($KN(SiMe_3)_2$) or –100 °C (LDA). Internal quench with Me_3SiCl was used for LDA. Isomer ratio determined by ^1H NMR spectroscopy.

Table 5. Additional substrate scope.[a]

entry	substrate	base	major isomer	yield 86 : 87	entry	substrate	base	major isomer	yield 86 : 87
1	 85a	$KN(SiMe_3)_2$	 86a	91% 25 : 1	4	 85b	LDA	 86b	94% 1 : 1.1
2	 85a	LDA	 87a	80% 1 : 6	5	 85c	$KN(SiMe_3)_2$	 86c	68% 7 : 1
3	 85b	$KN(SiMe_3)_2$	 86b	88% 25 : 1	6	 85c	LDA	 87c	68% 1 : 1.1

[a]The substrate was treated with the indicated base at –78 °C ($KN(SiMe_3)_2$) or –100 °C (LDA). Internal quench with Me_3SiCl was used for LDA. Isomer ratio determined by ^1H NMR spectroscopy.

2.3. Conclusion

In conclusion, we have conducted a detailed investigation into the Ireland-Claisen rearrangement of α-alkoxy esters.[54] Excellent chelation-controlled selectivity (dr > 10:1 in all cases) was observed when the reaction was performed using $KN(SiMe_3)_2$ in toluene for a broad range of substrates. Most importantly, non-chelation controlled enolization could be achieved in many cases through the use of LDA in THF with an internal Me_3SiCl quench. Both systems showed greater selectivity in the rearrangement of substrates with large α-alkyl chains on the ester and highly substituted double bonds. However, the selectivity patterns for non-chelation controlled enolization proved to be quite complex and were far more sensitive to the structure of the ester. α-Alkoxy propionate esters **82** proved to be the most challenging substrates for the LDA-THF system. In this series of esters, chelation controlled enolization was observed in all

cases using LDA in THF with very poor selectivity. Remarkably, a one-carbon homologation to the corresponding α–alkoxy butyric acid esters **85** proved to be enough of a structural change to allow for *E*-selective enolization when the LDA-THF system was employed. We have shown that, in many cases, both diastereomers of the Ireland-Claisen rearrangement products can be accessed from the same allylic ester simply by the choice of enolization reagent, which is a finding that will prove useful in future synthesis planning.

Chapter 3

Enantioselective Alkylation of 2-Alkylpyridines Controlled by Organolithium Aggregation

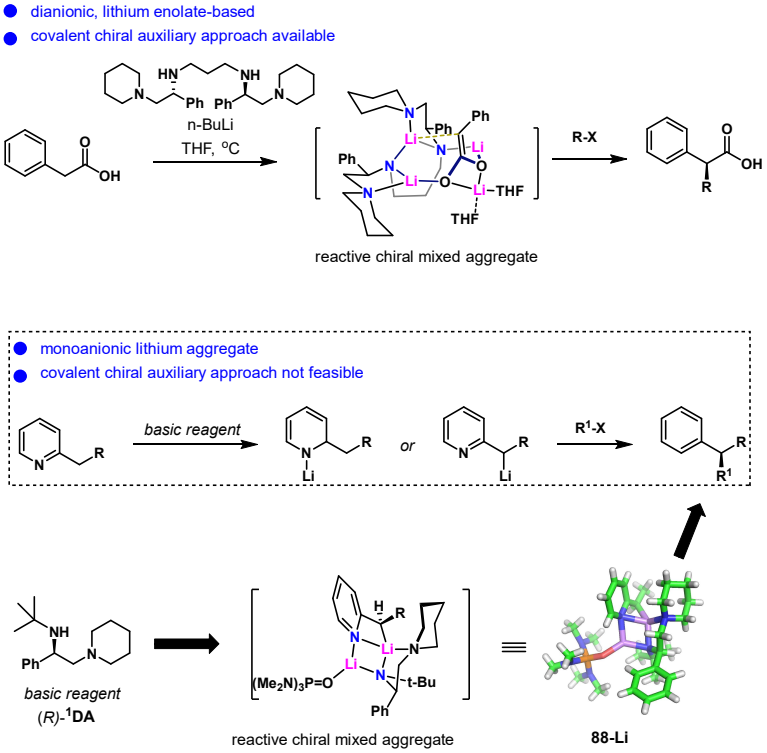
3.1. Introduction[ii]

Enantioselective alkylation is a fundamentally important transformation in organic synthesis. For enolate-based carbanions, asymmetric alkylations have been historically achieved using covalently attached chiral auxiliaries,[67,68,69,70] and these reactions have extensive applications in the synthesis of natural products and pharmaceuticals on scales spanning several orders of magnitude.[71,72] However, this strategy is not readily applicable to carbanions derived from noncarbonyl precursors. Building on discoveries by Shioiri[73] and subsequently Koga,[74] we previously demonstrated that chiral lithium amides (CLAs) function as noncovalent stereodirecting reagents enabling highly effective enantioselective transformations of dianionic enediolates derived directly from carboxylic acids.[75,76,77] The asymmetric alkylation is achieved by virtue of mixed aggregation[78] between the enediolate and CLA, providing the chiral environment for subsequent functionalization (Scheme 20).[79] CLAs derived from amines shown in Scheme 20 produce mixed aggregates with a broad range of organolithium reagents with a remarkably conserved threedimensional architecture.[80] Such well-defined aggregation suggests that CLAs can potentially direct the stereochemistry of alkylations for nonenolate monoanionic carbanions for which no covalent chiral auxiliary is feasible.[81,82]

We became interested in α-alkylation of 2-alkylpyridines for an initial examination of this approach. Pyridines bearing C2- alkyl substituents are privileged ligands in

asymmetric catalysis; however, their preparation often involves cumbersome multistep synthesis. Moreover, pyridines are the second most frequently occurring nitrogen-containing heterocycles in pharmaceuticals, with C-2 substitution appearing in more than 60%.[83] While several approaches have been developed to access chiral C2-substituted pyridines in some form,[84] each has its limitations in substrate scope profile, and no direct enantioselective alkylation has been reported.

Scheme 21. Chiral lithium amides in enolate alkylation versus alkylpyridine alkylation.



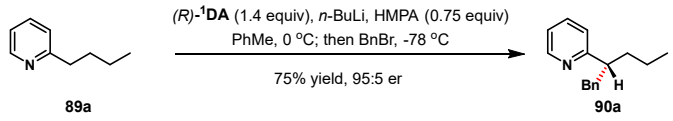
[ii] Significant portions of this chapter were published in the *Journal of the American Chemical Society*[85]

Herein, we report a general procedure for the direct asymmetric alkylation of C2-alkylpyridines.[85] This approach circumvents the need to incorporate a synthetic handle into the substrate or preactivate the pyridine nucleus prior to alkylation, thus offering an advantage over previously reported methods of accessing chiral pyridines.[86]

3.2. Optimization of Reaction Conditions

Diamine (*R*)-**1DA** showed excellent enantioselectivity in enediolate alkylation providing enantiomeric ratio as high as 87:13. Given the importance of additives for aggregation states of organolithium compounds,[87] we screened the effect of common lithium ligands. HMPA displayed an enhancement in both conversion (22% to 55%) and er (87:13 to 97:3). We found that in general, lithiation of **89a** was inhibited by lithium compounds, including *n*-BuLi itself. Toluene proved to be the optimal solvent; ethereal solvents (tetrahydrofuran, Et_2O, 1,4-dioxane, 1,2-dimethoxyethane) resulted in no enantioselectivity, while the use of hydrocarbon solvents (hexane, cyclohexane) encountered solubility problems. Highly reactive heteroaromatic benzylic bromides proved to be effective alkylating agents leading to er as high as 99:1.

Scheme 22. Optimal reaction conditions for benzylation of 2-butylpyridine.

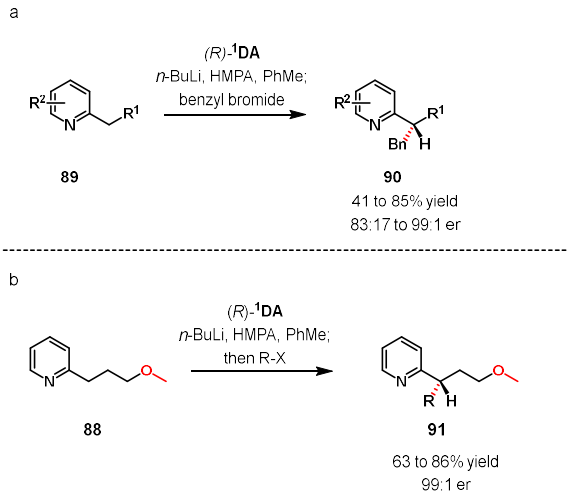


3.3. **Substrate scope**

The scope of 2-alkylpyridines was investigated by enantioselective benzylation employing the conditions developed for **89a** (Scheme 22 and 23a). Increasing the length of the alkyl chain produced results similar to those observed during benzylation of **89a**. Benzylation of 2-ethylpyridine occurred in similar yield (76%) but diminished er (85:15) compared to **90a**. When the stoichiometry of the chiral amine and HMPA was reduced, the reaction proceeded with greater er (92:8) and somewhat reduced yield (58%). When an ether or ketal are present at the γ-position, an exceptional increase in enantioselectivity is observed (up to 99:1 er). Notably, no enhancement was observed upon alkylation of the 1,3-dioxane in which no internal chelation by the γ-alkoxy group is feasible.

We explored this intriguing enhancement of enantioselectivity by the γ-alkoxy substituents in greater detail, testing additional electrophiles (Scheme 23b). Both methylation and alkylation with less reactive electrophiles occurred in 63-86% yield and excellent enantioselectivity (er 99:1). Additionally, we were able to reproduce excellent yield and er on a gram-scale, demonstrating the usefulness of this method for producing large quantities of chiral 2-alkylpyridines (see Supporting information).

Scheme 23. **a**. Enantioselective alkylation of 2-alkyl pyridines. **b**. Enantioselective alkylation of 2-(3-methoxy-1-propyl)pyridine (**88**).



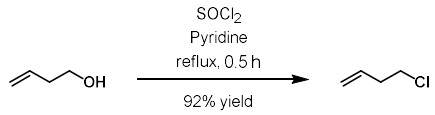
3.4. Conclusion

In summary, an operationally straightforward procedure for asymmetric alkylation of 2-alkylpyridines is described. The chiral amine reagent is readily available in bulk in two simple steps from styrene oxide, and can be readily recovered by aqueous pH-controlled extraction. This reaction validates CLAs as reagents for alkylation of nonenolate-derived organolithium reagents. Valuable insight into the mechanism of enantiocontrol were revealed by X-ray diffraction studies of mixed aggregate obtained by cocrystallization of (*R*)-**1DA** with **88** upon lithiation with *n*-BuLi. These structural studies provide a defined view of the intermediate aggregates involved in the alkylation reactions and allow for a structure-based design of new lithium amide reagents for expanded applications in the future.

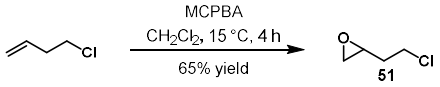
Experimental Procedures

General Information. All reactions were carried out under an inert atmosphere of dry argon in oven or flame-dried glassware unless the reaction procedure states otherwise. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone in a continuous still under an atmosphere of argon. Dichloromethane, di-iso-propylamine, triethylamine, and acetonitrile were distilled from calcium hydride in a continuous still under an atmosphere of argon. Reaction temperature was controlled by IKA ETS-D4 fuzzy thermo couples. Analytical normal-phase thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 F_{254} (EMD no. 5715-7) and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), and potassium permanganate staining. Normal-phase flash column chromatography was performed using 40-63 μm silica gel (EMD, Geduran, no. 1.11567.9026) as the stationary phase. Analytical reverse-phase thin-layer chromatography was performed using pre-coated TLC plates with Silica gel 60 RP-18 F_{254s} (Merck, no. 1.15685.0001). Reverse-phase flash column chromatography was performed using C_{18}-Reversed phase silica gel, fully end-capped (Fluka, no. 60756). Proton nuclear magnetic resonance spectra were recorded at 400, 500, and 600 MHz on Varian Unity Inova. Carbon nuclear magnetic resonance spectra were recorded at 101 MHz, 126 MHz, and 151 MHz on Varian Unity Inova, and Varian Unity Inova spectrometers. All chemical shifts were reported in δ units relative to tetramethylsilane. Optical rotations were measured on a Rudolph Autopol III polarimeter. High-resolution mass spectral data were obtained by the Mass Spectrometry laboratory at the University of California, Santa Barbara.

CHAPTER 1 EXPERIMENTAL PROCEDURES



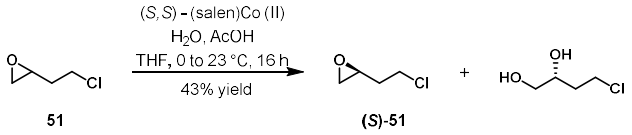
4-Chlorobut-1-ene: Prepared according to a modification of the literature procedure[88]: A mixture containing but-3-en-1-ol (83.65 g, 1.16 mol) and freshly distilled pyridine (0.50 mL, 6.50 mmol, 0.7 mol%) was cooled to 0 °C. After thionyl chloride (67.80 mL, 1.16 mol, 1.0 equiv) was added, reaction was heated at reflux for 0.5 h. The crude material was distilled under atmospheric pressure to afford 4-chlorobut-1-ene (96.57 g, 1.07 mol, 92% yield) as a clear liquid. ^{1}H and ^{13}C NMR spectral data matched that reported in the literature.[89]



2-(2-Chloroethyl)oxirane 51: 4-Chlorobut-1-ene (50 g, 0.55 mol) was dissolved in 135 mL of CH_2Cl_2 in a 1 L three neck flask equipped with a mechanical stirrer, reflux condenser and thermometer. After the mixture was cooled to 0 °C, MCPBA (75% wt, 140 g, 0.61 mol, 1.10 equiv) was added in 5 portions maintaining temperature below 10 °C. The mixture was warmed to 15 °C and stirred for 4 h. The white precipitate was removed by filtration and washed with 100 mL of cold CH_2Cl_2. The filtrate was placed in a freezer for 1 h and white solid was filtered and washed with 100 mL of cold dichoromethane again. The filtrate was cooled to 0 °C and dimethylsulfide (52 mL, 0.72 mol, 1.30 equiv) was added slowly. The mixture was allowed to warm to room temperature and stirred for 20 min. (Peroxide test showed the absence of peroxides.

The peroxide test: 1 mL of the mixture was added to a fresh solution of 100 mg of the sodium iodide dissolved in 1 mL of glacial acetic acid. The solution remained clear.) The mixture was washed with 3M aqueous NaOH (3x200 mL) and brine (300 mL), then dried with Na_2SO_4. The organic solvent was distilled off under atmospheric pressure and the crude residue was then distilled under reduced pressure (bp 52 °C/30 mmHg) to afford 2-(2-chloroethyl)oxirane (38.10 g, 0.358 mol, 65% yield) as a clear liquid.

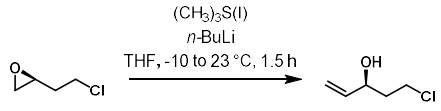
^{1}H NMR (600 MHz, $CDCl_3$) δ 3.69 – 3.64 (m, 2H), 3.10 (dtt, J = 6.7, 4.2, 2.1 Hz, 1H), 2.82 (dd, J = 4.9, 3.9 Hz, 1H), 2.56 (dd, J = 4.9, 2.6 Hz, 1H), 2.06 (dtd, J = 14.5, 7.4, 4.4 Hz, 1H), 1.93 (dq, J = 14.7, 5.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 49.64, 46.88, 41.15, 35.44. HRMS (TOF MS EI) calcd for C_4H_7ClO $[M]^+$ 106.0185, found 106.0184.



(*S*)-2-(2-Chloroethyl)oxirane (*S*)-51: Prepared according to a modification of the literature procedure[49]. 2-(2-chloroethyl)oxirane (165 g, 1.51 mol) was treated with (*S,S*)-(salen)Co (II) (4.56 g, 7.55 mmol, 0.005 equiv), AcOH (0.86 mL, 15.10 mmol, 0.01 equiv), and THF (15 mL). After the mixture was cooled to 0 °C, H_2O (15 mL, 0.83 mmol, 0.55 equiv) was added in one portion. The reaction was allowed to warm to room temperature and stir for 16 h. The (*S*)-2-(2-chloroethyl)oxirane and volatile materials were isolated by vacuum distillation at 0.2 mmHg into a cooled (–78 °C) receiving flask. The recovered epoxide was dried with Na_2SO_4 and washed with distilled CH_2Cl_2. Organic solvents were distilled off under atmospheric pressure and the crude residue

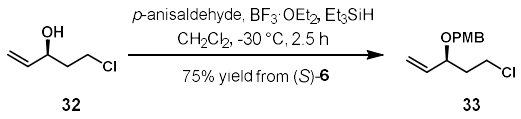
was then distilled under reduced pressure (bp 52 °C/30 mmHg) to afford (*S*)-2-(2-chloroethyl)oxirane (69 g, 0.648 mol, 43% yield) as a clear liquid.

$[\alpha]_D^{25}$ –31.1° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 3.69 – 3.64 (m, 2H), 3.10 (dtt, J = 6.7, 4.2, 2.1 Hz, 1H), 2.82 (dd, J = 4.9, 3.9 Hz, 1H), 2.56 (dd, J = 4.9, 2.6 Hz, 1H), 2.06 (dtd, J = 14.5, 7.4, 4.4 Hz, 1H), 1.93 (dq, J = 14.7, 5.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 49.64, 46.88, 41.15, 35.44. $[M]^+$ 106.0185, found 106.0184. Er was determined after derivatization to (–)-**33**.



(*S*)-51 32

(*S*)-5-Chloropent-1-en-3-ol 32: *n*-Butyllithium (2.50 M in hexanes, 273 mL, 0.681 mol, 2.90 equiv) was added to solution of trimethylsulfonium iodide (144 g, 0.70 mol, 3.0 equiv) in THF (1 L) at –30 °C under argon and the resulting solution was stirred for 30 min. A solution of epoxide **(*S*)-51** (25 g, 0.235 mol) in THF (175 mL) was then added and the mixture was allowed to warm to room temperature and stir for 1 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (100 mL) at 0 °C and then warmed to room temperature. It was extracted with Et_2O (3x800 mL). The combined organic layers were washed with brine (500 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. This yielded the alcohol **32** with minor impurities (29 g) as a pale-yellow liquid which was submitted to the next step without further purification.



(*S*)-Chloride 33: Boron trifluoride diethyl etherate (30.9 mL, 0.25 mol, 1.05 equiv) was added to the mixture of *p*-anisaldehyde (30.4 mL, 0.25 mol, 1.05 equiv) in CH_2Cl_2 (700 mL) under argon at –40 °C and the resulting solution was stirred for 5 min. A solution of crude alcohol **7** from the previous step (~29 g, ~0.235 mol) in CH_2Cl_2 (790 mL) was then added followed by triethylsilane (125.10 mL, 0.785 mol, 3.30 equiv) and the mixture turned orange. It was warmed to –30 °C and stirred for 2.5 h. The reaction mixture was quenched with H_2O (500 mL) and then warmed to room temperature. The layers were separated, and the organic layer was washed with saturated aqueous sodium bicarbonate, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (4% EtOAc in hexanes) to provide alkene **33** (42.85 g, 0.178 mol, 76% yield from epoxide **(*S*)-51**) as a pale-yellow oil after three reaction cycles with recovery of the starting material.

$[\alpha]_D^{25}$ –58.5° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 2H), 6.91 – 6.85 (m, 2H), 5.75 (ddd, J = 17.0, 10.3, 7.7 Hz, 1H), 5.33 – 5.24 (m, 2H), 4.54 (d, J = 11.2 Hz, 1H), 4.30 (d, J = 11.2 Hz, 1H), 3.99 (td, J = 8.0, 4.8 Hz, 1H), 3.81 (s, 3H), 3.68 (ddd, J = 10.7, 8.1, 6.1 Hz, 1H), 3.62 – 3.54 (m, 1H), 2.08 (ddt, J = 14.2, 8.4, 5.9 Hz, 1H), 1.91 (dddd, J = 14.4, 8.1, 6.5, 4.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.11, 137.91, 130.37, 129.32, 117.78, 113.73, 77.00, 70.08, 55.17, 41.27, 38.32. HRMS (TOF MS EI) calcd for $C_{13}H_{17}ClO_2$ $[M]^+$ 240.0917, found 240.0914. Er 96:4 (Chiralcel® OD-H; 0.5% i-

PrOH in hexanes; flow rate = 1.0 mL/min; detection at 220 nm; t_1 = 6.05 min (major); t_2 = 6.55 min (minor).

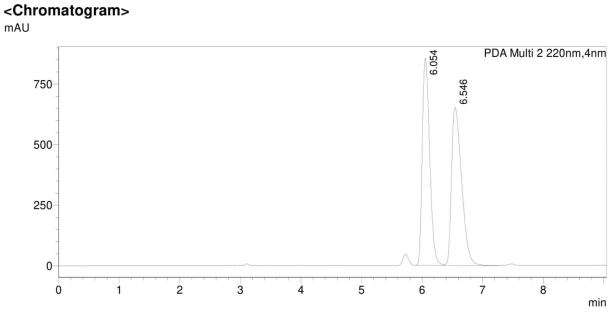
8/13/2020 1:56:47 PM Page 1 / 1

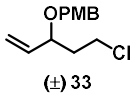
SHIMADZU LabSolutions Analysis Report

<Sample Information>

Sample Name	: mp-5-141-A-OD-2		
Sample ID	: mp-5-141-A-OD-2		
Data Filename	: mp-5-141-A-OD-2.lcd		
Method Filename	: YL 070520 method.lcm		
Batch Filename	:		
Vial #	: 1-1	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 8/13/2020 1:27:20 PM	Acquired by	: Masa Podunavac
Date Processed	: 8/13/2020 1:36:25 PM	Processed by	: Masa Podunavac

<Chromatogram>





(±) 33

<Peak Table>

PDA Ch2 220nm

Peak#	Ret. Time	Area	Height	Conc.	Area%
1	6.054	7272166	854354	49.060	49.060
2	6.546	7550963	652202	50.940	50.940
Total		14823129	1506556		100.000

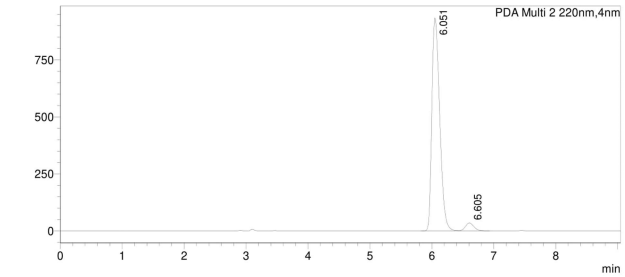
8/13/2020 1:54:41 PM Page 1 / 1

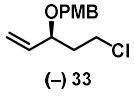
SHIMADZU LabSolutions Analysis Report

<Sample Information>

Sample Name	: mp-4-183-A-OD		
Sample ID	: mp-4-183-A-OD		
Data Filename	: mp-4-183-A-OD-2.lcd		
Method Filename	: YL 070520 method.lcm		
Batch Filename	:		
Vial #	: 1-1	Sample Type	: Unknown
Injection Volume	: 10 uL		
Date Acquired	: 8/13/2020 1:42:39 PM	Acquired by	: Masa Podunavac
Date Processed	: 8/13/2020 1:51:44 PM	Processed by	: Masa Podunavac

<Chromatogram>



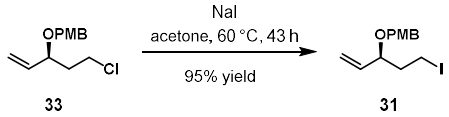


(–) 33

<Peak Table>

PDA Ch2 220nm

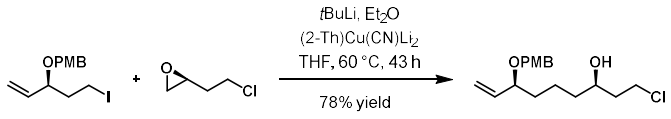
Peak#	Ret. Time	Area	Height	Conc.	Area%
1	6.051	8229242	933834	96.135	96.135
2	6.605	330890	34709	3.865	3.865
Total		8560131	968543		100.000



33 31

(*S*)-Iodide 31: Sodium iodide (57.2 g, 0.38 mol, 2.0 equiv) was added to the solution of chloride **33** (46 g, 0.19 mol) in dry acetone (190 mL) and the resulting solution was heated to 60 °C and stirred for 43 h. The reaction mixture was concentrated *in vacuo*. The residue was diluted with EtOAc (200 mL), washed with aqueous saturated sodium thiosulfate (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (4% EtOAc in hexanes) to provide iodide **31** (60.02 g, 0.181 mol, 95% yield) as a clear oil.

$[\alpha]_D^{25}$ –51.2° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 2H), 6.93 – 6.82 (m, 2H), 5.74 (ddd, J = 17.2, 10.3, 7.6 Hz, 1H), 5.36 – 5.26 (m, 2H), 4.54 (d, J = 11.1 Hz, 1H), 4.30 (d, J = 11.1 Hz, 1H), 3.88 (td, J = 7.8, 4.7 Hz, 1H), 3.81 (s, 3H), 3.32 – 3.19 (m, 2H), 2.11 (dddd, J = 15.0, 8.1, 7.0, 5.7 Hz, 1H), 2.02 – 1.95 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.11, 137.63, 130.33, 129.39, 117.88, 113.75, 79.79, 70.12, 55.21, 39.10, 2.41. HRMS (TOF MS EI) calcd for $C_{13}H_{17}IO_2$ $[M]^+$ 332.0273, found 332.0260.



31 (*S*)-51 52

Alcohol 52: Prepared according to a modification of the literature procedure[52]: *n*-Butyllithium (2.50 M in hexanes, 83.60 mL, 0.209 mol, 1.20 equiv) was added to a solution of thiophene (16.70 mL, 0.209 mol, 1.20 equiv) in THF (170 mL) was added at

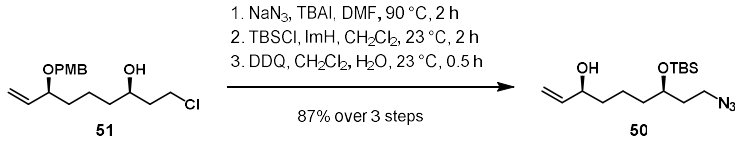
–78 °C. The temperature was slowly raised to 0 °C and the mixture was stirred for 30 min. Copper(I) cyanide (17 g, 0.190 mol, 1.10 equiv) was added to the mixture at –78°C and the reaction mixture was stirred for 30 min at 0 °C.

t-Buthyllithium (1.70 M in pentane, 223.50 mL, 0.380 mol, 2.20 equiv) was added to a solution of iodide **31** (63.10 g, 0.190 mol, 1.10 eq) in Et_2O (525 mL) at –78 °C and it was stirred for 1 h. The mixture was added via cannula to a solution of (2-Th)Cu(CN)Li_2 at –78 °C (105 mL wash with Et_2O) and the mixture was stirred for 30 min at 0 °C.

Previously cooled (–30 °C) solution of epoxide **(*S*)-51** (18.40 g, 0.173 mol) in THF (460 mL) was added via cannula to the cuprate at –78 °C and then stirred for 1 h at 0 °C. The reaction mixture was quenched with 500 mL of 90% NH_4Cl (satd)/10% NH_4OH (conc) solution, diluted with H_2O (500 mL) and let to stir for 3 h until two layers formed. The aqueous layer was extracted with EtOAc (3x500 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to afford alcohol **51** (42.0 g, 0.134 mol, 78% yield) as a clear oil.

$[\alpha]_D^{25}$ –44.7° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 2H), 6.91 – 6.83 (m, 2H), 5.73 (ddd, J = 17.1, 10.4, 7.8 Hz, 1H), 5.26 – 5.18 (m, 2H), 4.53 (d, J = 11.5 Hz, 1H), 4.27 (d, J = 11.5 Hz, 1H), 3.80 (s, 3H), 3.74 – 3.62 (m, 3H), 1.90 – 1.78 (m, 2H), 1.63 (m, 2H), 1.57 – 1.48 (m, 2H), 1.46 – 1.42 (m, 2H), 1.41 – 1.33 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.00, 138.88, 130.61, 129.34, 117.12, 113.68, 79.80, 69.62, 68.58,

55.19, 41.91, 39.68, 37.21, 35.18, 21.20. HRMS (TOF MS EI) calcd for $C_{17}H_{25}ClO_3$ $[M+Na]^+$ 335.1390, found 335.1392.



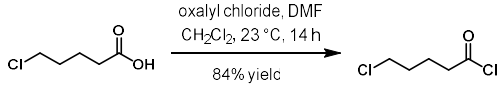
Azide 50: Sodium azide (15.20 g, 0.234 mol, 1.10 equiv) and tetrabutylammonium iodide (0.71 g, 1.92 mmol, 0.9 mol%) were added to the solution of chloride **51** (66.50 g, 0.213 mol) in DMF (133 mL) and the resulting solution was heated to 90 °C and stirred for 2 h. The reaction mixture was diluted with 20% EtOAc / 80% Hex solution (20 mL). The organic layer was washed with water (5 x 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The light-yellow oil residue was submitted to the next step without further purification.

The crude residue from the previous step was dissolved in CH_2Cl_2 (136 mL) and imidazole (43.50 g, 0.64 mol, 3.0 equiv) and *tert*-butyldimethylsilyl chloride (48.20 g, 0.320 mol, 1.50 equiv) were added at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 0.5 h. The mixture was diluted with CH_2Cl_2 (150 mL), and the organic layer was washed with water, then brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The light-yellow oil residue was submitted to the next step without further purification.

The crude material from the previous step was dissolved in 1:1 mixture of CH_2Cl_2 – water (700 mL), and DDQ (53.10 g, 0.234 mol, 1.10 equiv) was added. Reaction was let to stir for 0.5 h and then quenched by addition of 3M sodium sulfite in water (250 mL). The mixture was washed with saturated aqueous sodium bicarbonate (200 mL) and

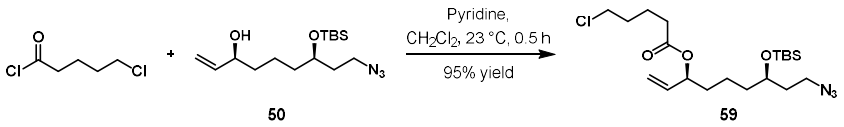
the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (100 % CH_2Cl_2 to 15% EtOAc-hexanes) to afford azide **50** (58.10 g, 0.185 mol, 87% yield over 3 steps) as a clear oil.

$[\alpha]_D^{25}$ –17.0° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 5.86 (ddd, J = 17.0, 10.4, 6.3 Hz, 1H), 5.22 (dt, J = 17.2, 1.4 Hz, 1H), 5.11 (dt, J = 10.4, 1.3 Hz, 1H), 4.10 (dt, J = 9.1, 4.6 Hz, 1H), 3.78 (dtd, J = 7.2, 5.7, 4.4 Hz, 1H), 3.41 – 3.29 (m, 2H), 1.77 – 1.64 (m, 2H), 1.56 – 1.45 (m, 4H), 1.45 – 1.39 (m, 1H), 1.35 (m, 1H), 0.88 (s, 9H), 0.05 (d, J = 1.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.09, 114.72, 73.06, 69.23, 47.96, 37.11, 36.96, 35.51, 25.81, 20.77, 18.00, -4.39, -4.72. HRMS (TOF MS EI) calcd for $C_{15}H_{31}N_3O_2Si$ $[M+Na]^+$ 336.2085, found 336.2085.



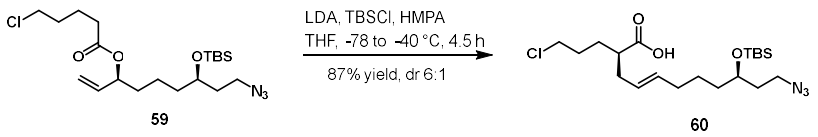
5-Chloropentanoyl chloride: Oxalyl chloride (8.80 mL, 0.103 mol, 1.10 equiv) was added to a solution of 5-chlorovaleric acid (11.0 mL, 94.16 mmol), dimethylformamide (10 μL), in CH_2Cl_2 (32 mL). The solution was stirred at room temperature for 14 h, and then concentrated *in vacuo*. The residue was purified by distillation under reduced pressure (bp 54 °C/2.50 mmHg) to afford 5-chloropentanoyl chloride (12.25 g, 79.02 mmol, 84% yield) as a pale-yellow liquid that was used immediately without further purification.

^1H NMR (500 MHz, C_6D_6) δ 3.45 (dd, J = 6.6, 5.5 Hz, 2H), 2.85 (t, J = 6.8 Hz, 2H), 1.83 – 1.70 (m, 4H).



Ester 59: 5-Chloropentanoyl chloride (6.10 mL, 47.22 mmol, 1.20 equiv) was added dropwise to the solution of alcohol **50** (12.30 g, 39.35 mmol) and pyridine (6.30 mL, 78.70 mmol, 2.0 eqiv) in CH_2Cl_2 (80 mL) at 0 °C. Reaction mixture was warmed up to room temperature after participate formed and reaction turned pink. The reaction mixture was stirred for 30 min, then diluted with CH_2Cl_2 (100 mL), and quenched with 1M aqueous HCl in water (30 mL). The organic layer was washed with water (100 mL), saturated aqueous sodium bicarbonate (100 mL), water again (100 mL), and finally with brine (100 mL). It was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc-hexanes) to afford ester **59** (16.10 g, 37.26 mmol, 95% yield) as a clear oil.

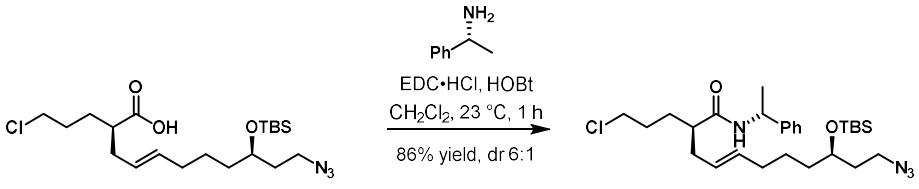
$[\alpha]_D^{25}$ –12.6° (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddd, J = 17.2, 10.5, 6.4 Hz, 1H), 5.28 – 5.22 (m, 2H), 5.17 (dt, J = 10.5, 1.2 Hz, 1H), 3.79 – 3.73 (m, 1H), 3.55 (t, J = 6.2 Hz, 2H), 3.40 – 3.29 (m, 2H), 2.36 (t, J = 7.0 Hz, 2H), 1.90 – 1.75 (m, 3H), 1.72 – 1.55 (m, 3H), 1.46 (ddd, J = 8.6, 7.2, 5.4 Hz, 2H), 1.42 – 1.27 (m, 1H), 0.88 (s, 8H), 0.05 (d, J = 4.6 Hz, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.33, 136.33, 116.85, 74.62, 69.14, 47.91, 44.40, 36.94, 35.62, 34.27, 33.61, 31.83, 25.80, 22.27, 20.61, 18.00, -4.41, -4.68. HRMS (TOF MS EI) calcd for $C_{20}H_{38}ClN_3O_3Si$ $[M+Na]^+$ 454.2269, found 454.2268.



Acid 60: *n*-Butyllithium (2.50M in hexanes, 21.80 ml, 54.62 mmol, 2.0 equiv) was added to a solution of diisopropylamine (8.30 mL, 59.26 mmol, 2.17 equiv) in THF (160 ml) at –78 °C, and the mixture was stirred for 20 min. The solution was cooled to –78 °C and a solution of ester **59** (11.80 g, 27.31 mmol) in THF (92 mL then 3 x 6.0 mL rinses) was added. The solution was stirred 0.5 h at –78 °C, when *tert*-butyldimethylsilyl chloride (9.60 g, 63.63 mmol, 2.33 equiv) followed by HMPA (48.20 mL, 15 %vol) were added. The solution was stirred 0.5 h at –78 °C, then 0.5 h at –40 °C, and finally 0.5 h at –15 °C. The reaction mixture was then poured into a separatory funnel containing 1M aqueous HCl (100 mL) and the layers were separated. The aqueous layer was extracted with hexanes (2 x 250 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The precooled solution of LiOH (1.64 g, 68.47 mmol, 2.50 equiv) in water (38 mL) was added to the mixture of the residue in THF (103 mL) at 0 °C. The mixture was stirred for 0.5 h and then diluted with EtOAc (200 mL) and washed with 1M aqueous HCl (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes) to give acid **60** (10.21 g, 23.63 mmol, 87% yield, dr 6:1) as a clear oil.

$[\alpha]_D^{25}$ –9.13° (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (dt, J = 14.9, 6.6 Hz, 1H), 5.41 – 5.31 (m, 1H), 3.83 – 3.72 (m, 1H), 3.54 (qd, J = 6.4, 5.4, 1.5 Hz, 2H), 3.40 – 3.28 (m, 2H), 2.44 (m, 1H), 2.36 (dt, J = 14.0, 7.1 Hz, 1H), 2.22 (dt, J = 13.7, 6.7 Hz, 1H), 1.99 (q, J = 6.9 Hz, 2H), 1.91 – 1.62 (m, 5H), 0.89 (s, 9H), 0.06 (d, J = 1.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.19, 133.18, 126.42, 69.24, 47.97, 44.82, 44.58, 36.64, 35.62, 34.96, 32.48, 30.15, 28.42, 25.83, 24.74, 18.03, -4.36, -4.69. HRMS (TOF MS EI) calcd for $C_{20}H_{38}ClN_3O_3Si$ $[M+Na]^+$ 454.2269, found 454.2271.

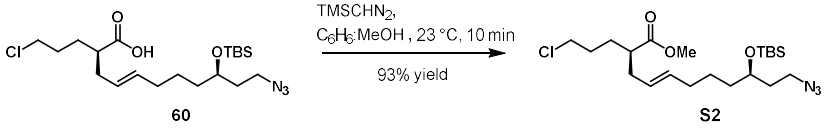
Determination of the diastereomer ratio for acid 60:



Amide S1: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (20 mg, 0.104 mmol, 1.5 equiv), (*R*)-(+)-alpha-methylbenzylamine (13 μL, 0.104 mmol, 1.5 equiv), and HOBt (14 mg, 0.104 mmol, 1.5 equiv) were added sequentially to a solution of acid **60** (30 mg, 0.069 mmol) in CH_2Cl_2 (0.40 mL). The solution was stirred at room temperature for 1h, then diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous sodium bicarbonate (5 mL) and brine (5 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **S1** (48 mg, 0.089 mmol, 86% yield, dr 6:1) as a clear oil.

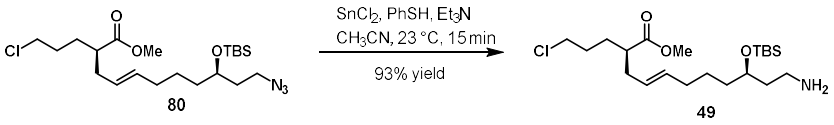
$[\alpha]_D^{25}$ +12.1° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.29 (overlapping m, 4.60H), 7.27 (t, J = 1.7 Hz, 0.5H), 5.64 (d, J = 7.9 Hz, 1H), 5.47 (dt, J = 14.2, 6.7 Hz,

0.17H), 5.44 – 5.37 (m, 1H), 5.35 (dd, J = 15.0, 7.3 Hz, 0.16H), 5.30 – 5.23 (m, 1H), 5.15 (overlapping h, J = 7.3 Hz, 1.16H), 3.74 (overlapping dtd, J = 7.1, 5.7, 4.3 Hz, 1.16H), 3.55 (overlapping dt, J = 10.8, 6.3 Hz, 1.16H), 3.52 – 3.43 (overlapping m, 1.32H), 3.38 – 3.29 (overlapping m, 2.32H), 2.28 (overlapping dt, J = 14.5, 7.5 Hz, 1.16H), 2.12 (overlapping dt, J = 13.3, 6.4 Hz, 1.16H), 2.08 – 2.02 (overlapping m, 1.16H), 1.98 (q, J = 7.3 Hz, 0.32H), 1.90 (q, J = 7.2 Hz, 2H), 1.84 – 1.78 (m, 1H), 1.77 – 1.59 (overlapping m, 5H), 1.49 (overlapping d, J = 6.9 Hz, 3.5H), 1.46 – 1.35 (overlapping m, 2.5H), 1.30 (overlapping p, J = 7.7 Hz, 2.16H), 0.88 (overlapping d, J = 2.2 Hz, 10.5H), 0.05 (overlapping d, J = 4.4 Hz, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.60, 143.10, 132.78, 132.73, 128.59, 128.52, 127.29, 127.23, 127.07, 126.12, 126.08, 69.13, 48.46, 48.35, 47.93, 47.39, 47.23, 44.79, 36.72, 36.67, 36.00, 35.53, 35.51, 32.54, 32.43, 30.40, 30.28, 29.57, 29.48, 25.80, 24.68, 24.61, 21.64, 17.98, -4.38, -4.74. HRMS (TOF MS EI) calcd for $C_{28}H_{47}ClN_4O_2Si$ $[M+Na]^+$ 557.3055, found 557.3051.



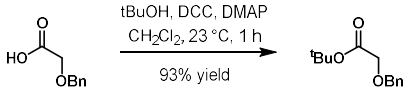
Methyl Ester S2: Trimethylsilyldiazomethane (3.30M in hexanes, 9.20 mL, 30.39 mmol, 1.30 equiv) was added to a solution of acid **60** (10.1 g, 23.38 mmol) in benzene (116 ml) and methanol (29 mL) at 0 °C. The mixture was warmed up to room temperature and stirred for 10 min. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (10% EtOAc-hexanes) to give ester **S2** (9.30 g, 20.85 mmol, 89% yield) as a clear oil.

$[\alpha]_D^{25}$ –13.3° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 5.44 (dtt, J = 14.8, 6.7, 1.3 Hz, 1H), 5.32 (dtt, J = 15.3, 7.0, 1.3 Hz, 1H), 3.76 (dtd, J = 7.2, 5.7, 4.4 Hz, 1H), 3.67 (s, 3H), 3.52 (td, J = 6.4, 3.0 Hz, 2H), 3.40 – 3.30 (m, 2H), 2.46 – 2.37 (m, 1H), 2.35 – 2.27 (m, 1H), 2.22 – 2.14 (m, 1H), 2.02 – 1.92 (m, 2H), 1.83 – 1.62 (m, 5H), 1.43 (dq, J = 10.1, 5.9 Hz, 1H), 1.38 – 1.31 (m, 1H), 0.88 (s, 8H), 0.05 (d, J = 2.1 Hz, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.62, 132.83, 126.64, 69.19, 51.42, 47.94, 44.99, 44.97, 44.56, 36.65, 35.61, 35.26, 32.49, 30.26, 28.78, 25.81, 24.75, 24.74, 18.00, -4.39, -4.72. HRMS (TOF MS EI) calcd for $C_{21}H_{42}ClN_3O_3Si$ $[M+H]^+$ 446.2527, found 44.2525.



Amine 49: Prepared according to a modification of the literature procedure[55]: thiophenol (8.20 mL, 80.70 mmol, 6.0 equiv) and triethylamine (8.40 mL, 60.52 mmol, 4.50 equiv) were added to a solution of anhydrous $SnCl_2$ (3.83 g, 20.17 mmol, 1.5 equiv) in acetonitrile (80 mL). The mixture turned bright yellow and was let to stir at room temperature for 15 min. Solution of azide **S2** (5.60 g, 12.50 mmol) in acetonitrile (46 mL then 3 x 3.0 mL rinses) was added and the mixture was stirred at room temperature for 15 min when it was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (20 mL) and washed with 2M aqueous NaOH (20 mL). The extract was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc-CH_2Cl_2 then 20% MeOH-1% NH_4OH-CH_2Cl_2) to afford amine **49** (4.89 g, 11.64 mmol, 93% yield) as a pale-yellow oil.

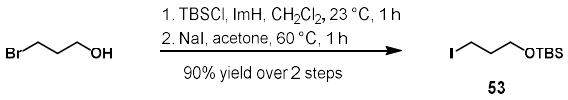
$[\alpha]_D^{25}$ –4.5° (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.44 (dt, J = 13.7, 6.6 Hz, 1H), 5.31 (dt, J = 14.7, 6.9 Hz, 1H), 3.74 (p, J = 5.7 Hz, 1H), 3.67 (s, 3H), 3.52 (t, J = 6.5 Hz, 2H), 2.77 (t, J = 7.4 Hz, 2H), 2.47 – 2.36 (m, 1H), 2.30 (dt, J = 14.4, 7.3 Hz, 1H), 2.17 (dt, J = 13.6, 6.6 Hz, 1H), 1.96 (q, J = 7.0 Hz, 2H), 1.84 – 1.63 (m, 6H), 1.59 (q, J = 6.8 Hz, 2H), 1.48 – 1.30 (m, 3H), 0.88 (s, 9H), 0.04 (d, J = 2.8 Hz, 6H). ^{13C} NMR (126 MHz, $CDCl_3$) δ 175.60, 132.88, 126.51, 70.25, 51.40, 44.95, 44.53, 36.60, 35.23, 32.50, 30.23, 28.74, 25.80, 24.88, 17.97, -4.46, -4.60. HRMS (TOF MS EI) calcd for $C_{21}H_{42}ClN_3O_3Si$ $[M+H]^+$ 420.2701, found 420.2702.



Benzyloxyacetic acid t-butylester: N,N′-Dicyclohexylcarbodiimide (45.0 g, 0.218 mol, 1.30 eq) was added to a solution of 2-(benzyloxy)acetic acid (28 g, 0.168 mol), 4-dimethylaminopyridine (2.26 g, 18.50 mmol, 0.11 equiv), *t*-butyl alcohol(31.90 mL, 0.336 mmol, 2 equiv)in CH_2Cl_2 (560 mL) at 0 °C. The mixture was warmed up to room temperature and stirred for 1 h. The white solid was filtered off, and the filtrate was washed with saturated sodium bicarbonate (50 mL), then brine (50 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was dissolved in 100 mL of Et_2O:hexanes (1:1) and it was stirred for 1 h at room temperature. Precipitate was filtered out and the filtrate was concentrated *in vacuo*. The crude residue was then distilled under reduced pressure (bp 100 °C/0.2 mmHg) to afford benzyloxyacetic acid t-butylester (34.81 g, 0.156 mol, 93% yield) as a clear liquid.

^1H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 5H), 7.32 – 7.28 (m, 1H), 4.63 (d, J = 1.2 Hz, 2H), 3.99 (d, J = 1.2 Hz, 2H), 1.49 (d, J = 1.4 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ

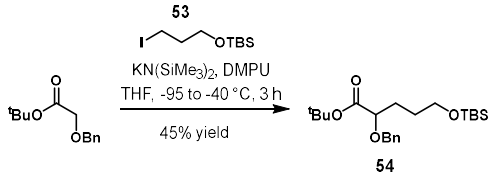
169.40, 137.25, 137.24, 128.29, 127.89, 127.75, 81.41, 73.05, 67.60, 27.98. HRMS (TOF MS EI) calcd for $C_{13}H_{18}O_3$ $[M+Na]^+$ 245.1154, found 245.1152.



53

Iodide 53: Imidazole (64.70 g, 0.950 mol, 2.20 equiv) and TBSCl (68.30 g, 0.453 mol, 1.05 equiv) were added to a precooled solution (0 °C) of 3-bromo-1-propanol (60.0 g, 0.432 mol) in CH_2Cl_2 (270 mL). The mixture was warmed up to room temperature and stirred for 1 h. It was washed with water (2 x 300 mL), then brine (200 mL) and the organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The clear liquid residue (123.0 g) was submitted to the next step without further purification.

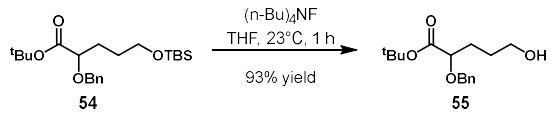
The crude material from the previous step was dissolved in dry acetone (432 mL), and sodium iodide (130 g, 0.864 mol, 2.0 equiv) was added. The resulting solution was heated to 60 °C and stirred for 1 h. The reaction mixture was concentrated *in vacuo*. The residue was diluted with EtOAc (200 mL), washed with aqueous saturated sodium thiosulfate (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by distillation under reduced pressure (bp 74 °C/0.2 mmHg) to afford **53** (116.8 g, 0.389 mol, 90% yield over 2 steps) as a pale-yellow liquid. ^1H and ^{13}C NMR spectral data matched that reported in the literature [90].



54

Ester 54: Precooled solution (–78 °C) of benzyloxyacetic acid t-butylester (24.20 g, 0.109 mol) in THF (175 mL) was added dropwise via cannula to the solution of $KN(SiMe_3)_2$ (47.84 g, 0.240 mol, 2.20 equiv), DMPU (18.50 mL, 5% v/v to THF) in THF (370 mL) at –95 °C. The reaction mixture was stirred for 0.5 h when precooled (–78 °C) neat iodide **53** (81.8 g, 0.273 mol, 2.50 equiv) was added dropwise. Reaction mixture was stirred for 0.5 h at –95 °C, then 0.5 h at –78 °C, and finally 2 h at –40 °C. The reaction mixture was quenched with an addition of sat. aq. NH_4Cl (100 mL) and warmed up to 0 °C. The product was extracted with EtOAc (3 x 300 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (5% EtOAc-hexanes) to give ester **54** (19.30 g, 48.91 mmol, 45% yield) as a clear oil.

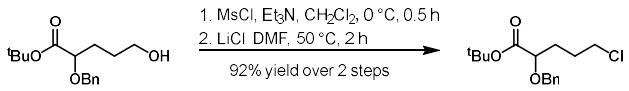
^1H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 4H), 7.30 – 7.27 (m, 1H), 4.70 (d, J = 11.6 Hz, 1H), 4.40 (d, J = 11.6 Hz, 1H), 3.82 (dd, J = 8.0, 4.7 Hz, 1H), 3.59 (t, J = 6.3 Hz, 2H), 1.83 (dddd, J = 14.5, 10.4, 6.1, 4.7 Hz, 1H), 1.79 – 1.72 (m, 1H), 1.71 – 1.63 (m, 1H), 1.60 (dtd, J = 13.4, 6.4, 3.7 Hz, 1H), 1.49 (s, 9H), 0.88 (d, J = 0.5 Hz, 9H), 0.03 (d, J = 0.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.02, 137.86, 128.30, 127.95, 127.67, 81.19, 78.28, 71.98, 62.57, 29.44, 28.49, 28.09, 25.92, 18.29, -5.34. HRMS (TOF MS EI) calcd for $C_{22}H_{38}O_4Si$ $[M+Na]^+$ 417.2437, found 417.2440.



Alcohol 55: Tetra-*n*-butylammonium fluoride (1M in THF, 74.0 mL, 73.37 mmol, 1.50 equiv) was added to a flask containing ester **54** (19.30 g, 48.91 mmol) at 0 °C. The

reaction mixture was warmed up to 23 °C for 1 h, then quenched with saturated aq. NH_4Cl (4 mL), and the mixture was extracted with CH_2Cl_2 (2 x 80 mL). The combined organic layers were washed with water (5 x 30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc-hexanes then 40% EtOAc-hexanes) to give alcohol **55** (12.81 g, 45.69 mmol, 93% yield) as clear liquid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 4H), 7.29 (t, J = 7.6 Hz, 1H), 4.72 (d, J = 11.4 Hz, 1H), 4.40 (dd, J = 11.4, 1.0 Hz, 1H), 3.85 (ddd, J = 7.8, 4.5, 1.1 Hz, 1H), 3.62 (dp, J = 8.7, 4.7 Hz, 2H), 1.94 – 1.76 (m, 2H), 1.76 – 1.63 (m, 2H), 1.49 (d, J = 1.2 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.78, 137.47, 128.37, 128.05, 127.83, 81.51, 78.30, 72.18, 62.35, 29.54, 28.62, 28.07. HRMS (TOF MS EI) calcd for $C_{16}H_{24}O_4$ $[M+Na]^+$ 303.1572, found 303.1574.

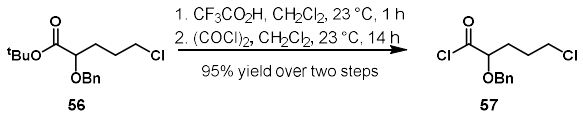


55 56

Chloride 56: Methanesulfonyl chloride (4.60 mL, 59.35 mmol, 1.30 equiv) was added to the solution of alcohol **55** (12.80 g, 45.66 mmol), triethylamine(16.60 mL, 0.119 mol, 2.60 equiv) in CH_2Cl_2 (114 mL) at 0 °C. Water (20 mL) was added to the reaction mixture after 0.5 h at 0 °C. The mixture was washed with water (2 x 50 mL), then 1M aqueous HCl (50 mL), then saturated aqueous sodium bicarbonate (50 mL), and finally with brine (50 mL). It was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The clear oil residue was submitted to the next step without further purification.

Lithium chloride (19.37 g, 0.457 mol, 10 equiv) was added to the solution of crude material from the previous step in DMF (46 mL). The reaction mixture was heated for 2 h at 50 °C. The mixture was diluted with EtOAc (80 mL), washed with water (4 x 150 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc-hexanes) to give chloride **56** (12.50 g, 41.83 mmol, 92% yield over two steps) as clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 4H), 7.32 – 7.28 (m, 1H), 4.72 (d, J = 11.5 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 3.83 (dd, J = 7.3, 3.4 Hz, 1H), 3.53 (t, J = 5.5 Hz, 2H), 1.97 – 1.78 (m, 4H), 1.50 (d, J = 0.9 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.44, 137.55, 128.29, 127.89, 127.72, 81.45, 77.51, 72.00, 44.56, 30.14, 28.34, 28.00. HRMS (TOF MS EI) calcd for $C_{22}H_{38}O_4Si$ $[M+H]^+$ 299.1336, found 299.1334.

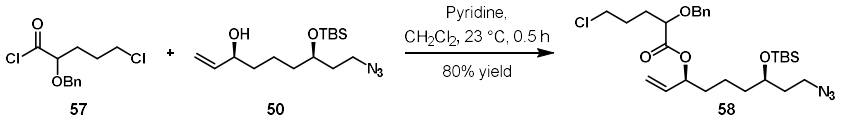


Acyl chloride 57: Ester **56** (12.50 g, 41.83 mmol) was dissolved in TFA (105 mL) and CH_2Cl_2 (210 mL), and the mixture and stirred for 1 h at 23 °C. The reaction mixture was concentrated *in vacuo*. The residue was diluted with toluene (30 mL) and concentrated *in vacuo*. This was repeated 3 times to provide the light-yellow oil residue (10.0 g) that was submitted to the next step without further purification.

Oxalyl chloride (3.50 mL, 41.20 mmol, 1 equiv) was added to a solution of the crude material from the previous step (10.0 g, 41.20 mmol), dimethylformamide (10 μL), in CH_2Cl_2 (14 mL). The solution was stirred at room temperature for 14 h, and then concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (15 mL) and concentrated

in vacuo. This was repeated 3 times to provide the light-yellow oil residue (10.24 g, 39.21 mmol, 95% yield) that was used immediately in the next step without further purification.

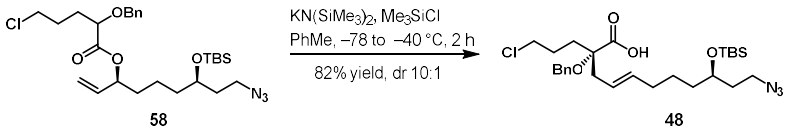
^{1}H NMR (500 MHz, C_6D_6) δ 7.16 – 6.98 (m, 5H), 4.45 (d, *J* = 11.1 Hz, 1H), 3.98 (dd, *J* = 11.4, 1.7 Hz, 1H), 3.79 (dt, *J* = 6.3, 2.7 Hz, 1H), 2.96 (td, *J* = 6.4, 2.4 Hz, 2H), 1.81 – 1.60 (m, 2H), 1.56 – 1.41 (m, 2H).



Ester 58: Acyl chloride **57** (11.90 g, 38.07 mmol) was added dropwise to the solution of alcohol **50** (10.24 g, 39.21 mmol, 1.03 equiv) and pyridine (15.40 mL, 0.190 mol, 5.0 eqiv) in CH_2Cl_2 (15.40 mL) at 0 °C. Reaction was warmed up to room temperature. After a participate formed the reaction turned pink. The mixture was stirred for 30 min, then diluted with CH_2Cl_2 (100 mL), and quenched with 1M aqueous HCl in water (30 mL). The organic layer was washed with water (100 mL), saturated aqueous sodium bicarbonate (100 mL), water again (100 mL), and finally with brine (100 mL). It was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc-hexanes) to afford ester **58** (16.32 g, 30.32 mmol, 80% yield) as a clear oil.

$[\alpha]_D^{25}$ –7.1˚ (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 4H), 7.32 – 7.28 (m, 1H), 5.78 (dddd, J = 17.3, 11.4, 10.6, 6.8 Hz, 1H), 5.37 – 5.25 (m, 2H), 5.22 (dq, J = 10.5, 1.3 Hz, 1H), 4.73 (dd, J = 11.6, 5.2 Hz, 1H), 4.39 (d, J = 11.6 Hz, 1H), 3.99 – 3.93 (m, 1H), 3.76 (ddt, J = 10.2, 6.9, 5.7 Hz, 1H), 3.52 (td, J = 5.9, 2.0 Hz, 2H), 3.39 – 3.28 (m,

2H), 2.00 – 1.84 (m, 3H), 1.74 – 1.58 (m, 3H), 1.51 – 1.45 (m, 2H), 1.43 – 1.27 (m, 1H), 0.88 (d, J = 2.7 Hz, 9H), 0.05 (dd, J = 5.6, 4.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.70, 171.50, 137.29, 137.28, 135.87, 135.77, 128.32, 127.88, 127.87, 127.82, 117.70, 117.32, 77.10, 75.38, 75.31, 72.13, 72.12, 69.02, 68.98, 47.81, 44.45, 36.82, 35.53, 35.45, 34.16, 30.77, 30.17, 30.12, 28.29, 28.26, 25.72, 20.53, 20.51, 17.92, 17.91, -4.45, -4.47, -4.77, -4.80. HRMS (TOF MS EI) calcd for $C_{27}H_{44}ClN_3O_4Si$ $[M+Na]^+$ 560.2687, found 560.2687.

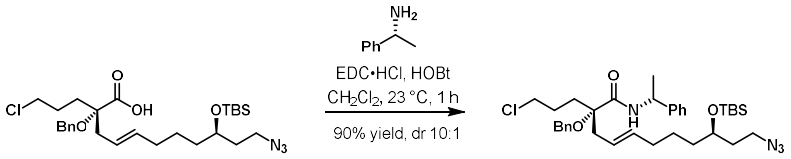


Carboxylic acid 48: Prepared according to a modification of the literature procedure[54]: Flame-dried 500 mL round bottom flask was brought into a nitrogen-filled glove box and charged with $KN(SiMe_3)_2$ (18.85 g, 94.49 mmol, 2.2 equiv). The flask was capped, removed from the glove box, attached to a Schlenk line, and backfilled with argon three times. Toluene (148 mL) was then added to the flask and the solution was cooled to –78 °C. A solution of ester **58** (23.12 g, 42.95 mmol) in PhMe (128 then 2 x 10 mL rinses) was added dropwise and the resulting solution was stirred 30 min. Chlorotrimethylsilane (10.90 mL, 9.33 g, 85.90 mmol, 2 equiv) was then added dropwise, and the solution was stirred 1h at –78 °C and 1h at –40 °C, The solution was then poured into a separatory funnel containing 1M aqueous HCl (100 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 80 mL), the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (30%

EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes) to give acid **48** (18.91 g, 35.14 mmol, 82% yield, dr 10:1) as a clear oil.

$[\alpha]_D^{25}$ –0.7° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 5H), 5.65 – 5.55 (m, 1H), 5.41 – 5.32 (m, 1H), 4.57 (d, J = 10.2 Hz, 1H), 4.50 (d, J = 10.2 Hz, 1H), 3.78 – 3.72 (m, 1H), 3.61 (dt, J = 11.1, 5.6 Hz, 1H), 3.50 (ddd, J = 10.8, 8.4, 4.9 Hz, 1H), 3.38 – 3.28 (m, 2H), 2.70 – 2.59 (m, 2H), 2.14 (ddd, J = 15.4, 12.0, 4.2 Hz, 1H), 2.06 – 1.97 (m, 3H), 1.87 (dddd, J = 19.4, 12.4, 8.6, 4.3 Hz, 1H), 1.82 – 1.73 (m, 1H), 1.71 – 1.63 (m, 2H), 1.46 – 1.32 (m, 4H), 0.88 (s, 9H), 0.05 (d, J = 5.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.99, 136.88, 135.52, 128.56, 128.12, 127.87, 122.58, 83.10, 69.19, 65.34, 47.92, 44.73, 37.96, 36.61, 35.61, 32.64, 31.77, 26.50, 25.81, 24.61, 18.01, -4.38, -4.70. HRMS (TOF MS EI) calcd for $C_{27}H_{44}ClN_3O_4Si$ $[M+Na]^+$ 560.2687, found 560.2686.

Determination of diastereomer ratio for carboxylic acid 48:

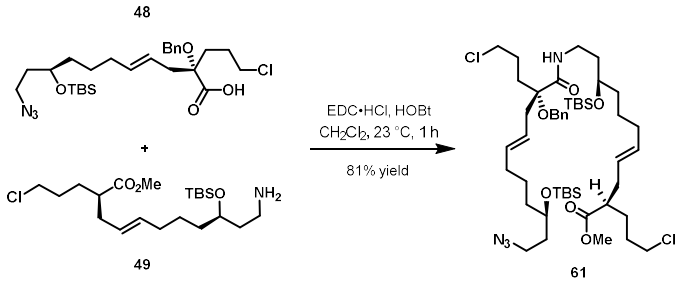


48 S3

Amide S3: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (21 mg, 0.111 mmol, 1.5 equiv), (*R*)-(+)-alpha-methylbenzylamine (14 µL, 0.111 mmol, 1.5 equiv), and HOBt (15 mg, 0.111 mmol, 1.5 equiv) were added sequentially to a solution of acid **48** (40 mg, 0.074 mmol) in CH_2Cl_2 (0.42 mL). The solution was stirred at room temperature for 1h, then diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous sodium bicarbonate (5 mL), brine (5 mL), dried over sodium sulfate, filtered, and concentrated

in vacuo. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **S3** (43 mg, 0.067 mmol, 90% yield, dr 10:1) as a clear oil.

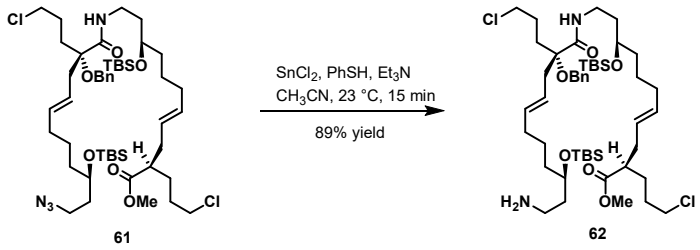
$[\alpha]_D^{25}$ –15.5° (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.27 (overlapping m, 11 H), 7.11 (overlapping d, J = 8.5 Hz, 1.10H), 5.55 (dt, J = 14.4, 7.1 Hz, 0.10H), 5.45 (dt, J = 14.1, 6.7 Hz, 1H), 5.37 (dt, J = 15.1, 7.3 Hz, 0.10H), 5.21 (dt, J = 14.8, 7.1 Hz, 1.10H), 5.13 (overlapping q, J = 7.4 Hz, 1.10H), 4.51 (overlapping d, J = 10.7 Hz, 1.10H), 4.45 (overlapping d, J = 10.7 Hz, 1.10H), 3.70 (overlapping dt, J = 10.7, 5.3 Hz, 1.10H), 3.60 (overlapping dt, J = 11.2, 5.8 Hz, 1.10H), 3.48 (overlapping ddd, J = 10.8, 8.3, 5.6 Hz, 1.10H), 3.41 – 3.24 (overlapping m, 2.20H), 2.62 (overlapping dd, J = 15.0, 6.5 Hz, 1.10H), 2.54 (overlapping dd, J = 14.9, 7.5 Hz, 1.10H), 2.01 (overlapping ddd, J = 9.5, 5.8, 3.3 Hz, 2.20H), 1.85 (overlapping p, J = 8.5, 7.8 Hz, 2.20H), 1.82 – 1.70 (overlapping m, 1.10H), 1.63 (overlapping dq, J = 11.6, 6.7 Hz, 2.20H), 1.45 (overlapping d, J = 7.0 Hz, 3.30H), 1.42 – 1.33 (overlapping m, 2.20H), 1.27 (overlapping h, J = 8.0, 7.4 Hz, 3.30H), 0.87 (overlapping s,9.90), 0.03 (overlapping d, J = 7.5 Hz, 6.60H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.69, 143.19, 137.79, 133.99, 128.51, 128.43, 127.67, 127.30, 127.14, 127.07, 125.96, 125.87, 123.59, 82.86, 69.06, 63.99, 48.28, 48.05, 47.87, 44.91, 37.99, 36.75, 36.68, 35.53, 35.47, 34.57, 32.72, 32.53, 31.68, 31.56, 31.49, 29.60, 26.58, 26.41, 25.76, 25.19, 24.63, 24.49, 22.56, 21.96, 17.94, 14.04, -4.41, -4.78. HRMS (TOF MS EI) calcd for $C_{35}H_{53}ClN_4O_3Si$ $[M+Na]^+$ 663.3473, found 663.3472.



Amide 61: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (3.76 g, 19.64 mmol, 1.5 equiv), amine **49** (5.0 g, 12.09 mmol, 1.0 equiv), and HOBt (2.67 g, 19.64 mmol, 1.5 equiv) were added sequentially to a solution of acid **48** (7.05 g, 12.09 mmol) in CH_2Cl_2 (75 mL). The solution was stirred at room temperature for 1h, then diluted with CH_2Cl_2 (25 mL) and washed with saturated aqueous sodium bicarbonate (50 mL), brine (50 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **61** (9.23 g, 9.82 mmol, 81% yield) as a clear oil.

$[\alpha]_D^{25}$ –11.1° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 5H), 6.85 (t, J = 6.0 Hz, 1H), 5.51 (dt, J = 15.0, 6.7 Hz, 1H), 5.42 (dtt, J = 13.3, 6.6, 1.2 Hz, 1H), 5.36 – 5.25 (m, 2H), 4.50 (d, J = 10.4 Hz, 1H), 4.42 (d, J = 10.4 Hz, 1H), 3.76 – 3.72 (m, 1H), 3.66 (overlapping m and s, 4H), 3.58 (dt, J = 11.5, 5.8 Hz, 1H), 3.51 (td, J = 6.4, 2.3 Hz, 2H), 3.45 (ddd, J = 10.7, 8.5, 5.6 Hz, 1H), 3.38 – 3.29 (m, 3H), 3.22 – 3.16 (m, 1H), 2.64 (dd, J = 15.0, 7.5 Hz, 1H), 2.55 (dd, J = 15.0, 7.5 Hz, 1H), 2.41 (tt, J = 8.1, 5.9 Hz, 1H), 2.33 – 2.27 (m, 1H), 2.20 – 2.13 (m, 1H), 2.02 – 1.91 (m, 6H), 1.82 – 1.60 (m, 9H), 1.53 (dtd, J = 13.1, 8.3, 6.0 Hz, 1H), 1.45 – 1.38 (m, 4H), 1.38 – 1.27 (m, 4H), 0.86 (d, J = 16.3 Hz, 18H), 0.04 (d, J = 6.5 Hz, 6H), -0.02 (d, J = 14.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.60, 172.46, 137.71, 133.83, 132.87, 128.44, 127.78, 127.76, 126.51, 123.84, 123.78, 82.92,

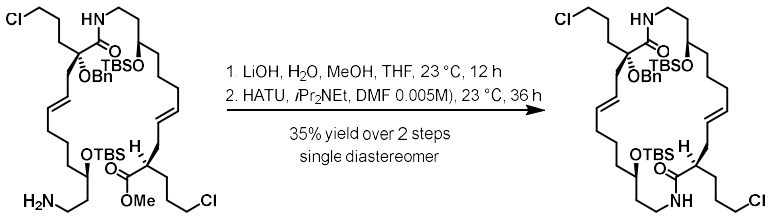
69.97, 69.88, 69.09, 64.04, 51.39, 47.90, 44.94, 44.89, 44.53, 38.07, 36.70, 36.65, 36.57, 35.73, 35.55, 35.24, 32.69, 32.51, 31.59, 30.24, 28.75, 26.71, 25.79, 24.81, 24.66, 17.96, -4.39, -4.44, -4.66, -4.75. HRMS (TOF MS EI) calcd for $C_{48}H_{84}Cl_2N_4O_6Si_2$ $[M+Na]^+$ 961.5204, found 961.5212.



Amine 62: Prepared according to a modification of the literature procedure[55]: thiophenol (4.50 mL, 44.04 mmol, 6.0 equiv) and triethylamine (4.60 mL, 33.03 mmol, 4.50 equiv) were added to a solution of anhydrous $SnCl_2$ (2.10 g, 11.01 mmol, 1.50 equiv) in acetonitrile (43 mL). The mixture turned bright yellow and was let to stir at room temperature for 15 min. Solution of azide **61** (6.90 g, 7.34 mmol) in acetonitrile (30 mL) was added and the mixture was stirred at room temperature for 15 min when it was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (30 mL) and washed with 2M aqueous NaOH (20 mL). It was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified using 3.5-inch silica plug (20% EtOAc-CH_2Cl_2 then 20% MeOH-1% NH_4OH-CH_2Cl_2) to afford amine **62** (5.97 g, 6.53 mmol, 89% yield) as a pale-yellow oil.

$[\alpha]_D^{25}$ –5.6˚ (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 4H), 6.85 (t, J = 6.0 Hz, 1H), 5.54 – 5.47 (m, 1H), 5.46 – 5.39 (m, 1H), 5.35 – 5.26 (m, 2H), 4.49 (d, J = 10.4 Hz, 1H), 4.41 (d, J = 10.4 Hz, 1H), 3.76 – 3.69 (m, 1H), 3.65 (s, 3H), 3.65 – 3.62 (m,

1H), 3.57 (dt, J = 11.5, 5.8 Hz, 1H), 3.51 (td, J = 6.4, 2.2 Hz, 2H), 3.45 (ddd, J = 10.7, 8.5, 5.6 Hz, 1H), 3.35 (ddt, J = 13.0, 8.6, 6.0 Hz, 1H), 3.22 – 3.13 (m, 1H), 2.80 (s, 2H), 2.66 – 2.60 (m, 1H), 2.54 (dd, J = 15.1, 7.5 Hz, 1H), 2.40 (tt, J = 8.0, 5.7 Hz, 1H), 2.30 (dt, J = 13.9, 7.4 Hz, 1H), 2.21 – 2.12 (m, 1H), 2.06 – 1.88 (m, 6H), 1.83 – 1.58 (m, 4H), 1.56 – 1.46 (m, 1H), 1.40 (ddd, J = 11.6, 6.0, 3.7 Hz, 4H), 1.36 – 1.22 (m, 4H), 0.85 (d, J = 14.9 Hz, 18H), 0.03 (d, J = 9.2 Hz, 6H), -0.02 (d, J = 15.0 Hz, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.60, 172.48, 137.71, 133.94, 132.87, 128.43, 127.77, 126.49, 123.74, 123.69, 82.91, 70.27, 69.86, 64.05, 51.40, 44.94, 44.89, 44.53, 38.08, 36.64, 36.55, 35.71, 35.23, 32.73, 32.50, 31.59, 30.23, 28.74, 26.70, 25.81, 25.79, 24.86, 24.81, 17.96, -4.43, -4.59, -4.66. HRMS (TOF MS EI) calcd for $C_{48}H_{86}Cl_2N_2O_6Si_2$ $[M+Na]^+$ 913.5480, found 913.5471.



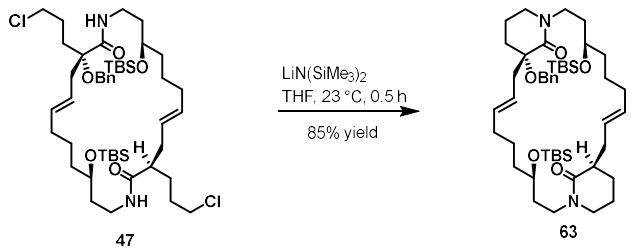
62 47

Macrocyclic bis-lactam 47: Lithium hydroxide (0.93 g, 22.21 mmol, 10 equiv) was added to a solution of ester **62** (2.0 g, 2.22 mmol) in MeOH (15 mL) and water (5 mL) at 0 °C. The mixture was warmed up to room temperature and THF (20 mL) was added. Reaction was cooled down back to 0 °C after 12 h, diluted with THF (20 mL) and quenched with 1M aqueous HCl (23 mL). The mixture was concentrated *in vacuo* and the residue was purified using 3.5 inch silica plug (20% MeOH-1% NH_4OH-CH_2Cl_2), concentrated *in vacuo* and submitted to the next step.

Amino acid from the previous step (6.36 g) was dissolved in anhydrous *N*,*N*-dimethylformamide (2.4 L) under argon. *N*,*N*-Diisopropylethylamine (4.90 mL, 28.28

mmol, 4.0 equiv) and HATU (4.0 g, 10.61 mmol, 1.5 equiv) were added, the mixture turned bright yellow and was let to stir at room temperature for 36 h. DMF was distilled off under reduced pressure (0.2 mmHg) into a receiving flask cooled to –78 °C. The residue was dissolved in EtOAc (30 mL) and washed with water (3x100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (40% EtOAc-hexanes) to give of macrolactam **47** (2.15 g, 2.44 mmol, 35% yield over two steps) as a single diastereomer, and as a white foam.

$[\alpha]_D^{25}$ +13.6° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 5H), 6.91 (dd, J = 7.9, 4.4 Hz, 1H), 6.25 (t, J = 4.9 Hz, 1H), 5.53 (dt, J = 15.2, 6.4 Hz, 1H), 5.43 (dt, J = 15.0, 6.4 Hz, 1H), 5.30 (dq, J = 15.0, 7.3 Hz, 2H), 4.49 (d, J = 10.5 Hz, 1H), 4.43 (d, J = 10.5 Hz, 1H), 3.87 – 3.79 (m, 1H), 3.73 (dq, J = 9.5, 5.2 Hz, 1H), 3.58 (dt, J = 11.1, 5.7 Hz, 1H), 3.55 – 3.41 (m, 3H), 3.36 (ddt, J = 14.2, 9.8, 5.1 Hz, 1H), 3.30 – 3.21 (m, 1H), 3.02 (ddt, J = 13.2, 8.8, 5.3 Hz, 1H), 2.56 (qd, J = 14.8, 7.0 Hz, 2H), 2.25 (ddd, J = 13.8, 10.6, 7.5 Hz, 1H), 2.10 (dt, J = 13.6, 5.1 Hz, 1H), 1.96 (dtd, J = 38.4, 14.4, 12.6, 6.1 Hz, 7H), 1.83 – 1.66 (m, 4H), 1.62 (ddq, J = 13.4, 9.2, 4.7 Hz, 1H), 1.58 – 1.26 (m, 7H), 0.86 (d, J = 18.6 Hz, 18H), 0.05 (s, 3H), 0.01 (d, J = 5.7 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.12, 172.24, 137.72, 133.59, 132.33, 128.40, 127.70, 127.68, 126.76, 123.37, 83.21, 71.38, 70.56, 63.88, 47.80, 47.78, 44.92, 44.71, 38.09, 37.47, 36.54, 36.29, 36.26, 36.20, 35.82, 34.57, 32.87, 32.64, 31.24, 30.60, 30.01, 26.61, 25.81, 25.79, 24.88, 24.46, 17.94, 17.87, -4.47, -4.62, -4.67. HRMS (TOF MS EI) calcd for $C_{47}H_{82}Cl_2N_2O_5Si_2$ $[M+Na]^+$ 903.5037, found 903.5037.

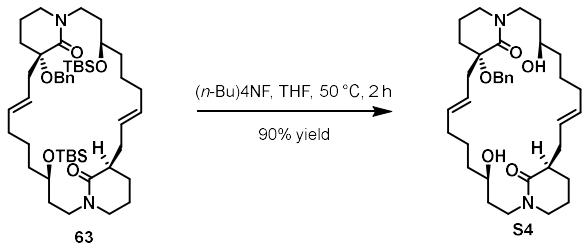


47 63

Bis-Lactam 63: Lithium bis(trimethylsilyl)amide (0.5M in THF, 5.25 mL, 2.63 mmol, 2.10 equiv) was added dropwise to a solution of macrocyclic bis-macrolactam **47** (1.10 g, 1.25 mmol) in anhydrous THF (6.20 mL) under argon. Saturated aq. NH_4Cl (6 mL) was added, and the mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc-hexanes) to give bis-lactam **63** (0.86 g, 1.06 mmol, 85% yield) as a white foam.

$[\alpha]_D^{25}$ +18.1° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 4H), 7.25 – 7.20 (m, 1H), 5.49 (ddt, J = 28.1, 15.3, 6.4 Hz, 2H), 5.40 (dt, J = 15.3, 6.7 Hz, 1H), 5.26 (ddd, J = 15.0, 8.1, 6.3 Hz, 1H), 4.67 (d, J = 11.6 Hz, 1H), 4.53 (d, J = 11.7 Hz, 1H), 3.79 (ddd, J = 13.1, 8.9, 6.3 Hz, 1H), 3.68 (dq, J = 11.9, 5.7 Hz, 2H), 3.43 (dt, J = 13.9, 7.1 Hz, 1H), 3.36 (dt, J = 13.6, 7.0 Hz, 1H), 3.29 (ddd, J = 11.9, 10.4, 4.9 Hz, 1H), 3.21 (dddd, J = 16.2, 11.9, 9.5, 4.6 Hz, 3H), 3.06 – 2.96 (m, 2H), 2.42 (dt, J = 13.2, 6.5 Hz, 1H), 2.37 – 2.27 (m, 2H), 2.20 (dd, J = 13.1, 8.2 Hz, 1H), 2.17 – 2.09 (m, 1H), 1.97 (tq, J = 8.2, 5.4, 4.5 Hz, 5H), 1.92 – 1.82 (m, 3H), 1.79 – 1.62 (m, 5H), 1.62 – 1.53 (m, 1H), 1.50 (ddd, J = 12.1, 9.4, 6.3 Hz, 1H), 1.40 (dddd, J = 20.9, 19.0, 11.4, 4.7 Hz, 6H), 1.32 – 1.23 (m, 1H), 0.88 (d, J = 1.1 Hz, 18H), 0.04 (d, J = 8.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.45, 168.13, 139.38, 134.43, 132.27, 128.00, 127.76, 127.25, 126.91, 124.91, 77.34, 70.51,

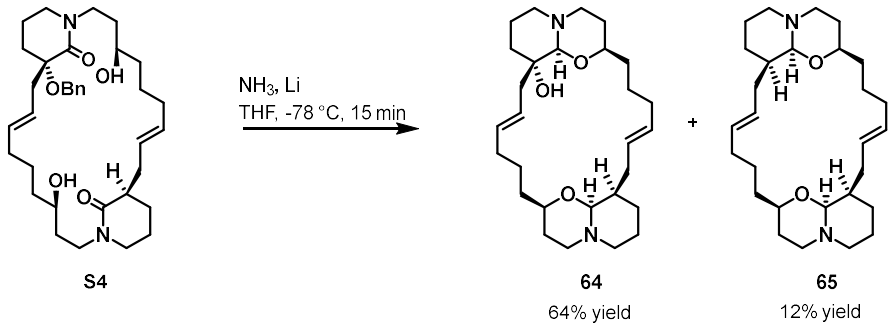
70.12, 65.76, 48.44, 48.05, 43.84, 43.81, 41.71, 38.80, 36.21, 35.55, 34.93, 33.93, 33.65, 32.46, 31.92, 26.37, 25.79, 25.02, 24.95, 22.06, 18.75, 17.96, -4.47, -4.52. HRMS (TOF MS EI) calcd for $C_{47}H_{80}N_2O_5Si_2$ $[M+Na]^+$ 831.5504, found 831.5507.



Macrocyclic diol S4: Tetra-*n*-butylammonium fluoride (1M in THF, 4.0 mL, 3.96 mmol, 4 equiv) was added to the flask with macrolactam **63** (0.80 g, 0.99 mmol) at 0 °C. The reaction mixture was heated to 50 °C for 2 h, when it was quenched with saturated aq. NH_4Cl (4 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with water (5 x 10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (30% acetone-hexanes to 50% acetone-hexanes) to give macrolactam **S4** (0.52 g, 0.891 mmol, 90% yield) as a white foam.

$[\alpha]_D^{25}$ +19.1˚ (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, J = 6.5 Hz, 4H), 7.20 (t, J = 6.7 Hz, 1H), 5.47 (dddt, J = 27.5, 22.0, 15.4, 6.3 Hz, 3H), 5.21 (ddd, J = 15.0, 8.8, 5.5 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 4.51 (d, J = 11.6 Hz, 1H), 3.82 (dt, J = 13.7, 6.9 Hz, 1H), 3.64 (ddd, J = 13.9, 9.9, 3.8 Hz, 1H), 3.54 (dq, J = 10.3, 6.0 Hz, 1H), 3.37 (qd, J = 10.3, 8.9, 4.2 Hz, 2H), 3.25 (td, J = 11.2, 9.4, 4.6 Hz, 2H), 3.21 – 3.16 (m, 2H), 3.11 (dd, J = 12.9, 5.4 Hz, 1H), 3.03 (dt, J = 13.3, 6.4 Hz, 1H), 2.33 (tq, J = 15.7, 6.7, 5.7 Hz, 3H), 2.13 (dq, J = 18.6, 7.1, 6.6 Hz, 1H), 2.07 – 1.98 (m, 4H), 1.91 (dddd, J = 28.1, 19.1, 10.6, 3.6 Hz, 5H),

1.75 (dd, J = 10.9, 4.8 Hz, 1H), 1.68 (dh, J = 13.8, 6.9 Hz, 3H), 1.59 (pd, J = 9.8, 4.0 Hz, 3H), 1.55 – 1.36 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.86, 168.62, 139.22, 134.54, 132.09, 128.02, 127.71, 127.18, 126.96, 124.64, 77.38, 77.20, 68.83, 66.68, 65.63, 48.48, 47.86, 44.43, 43.58, 41.73, 39.17, 35.85, 35.72, 35.08, 34.95, 34.64, 31.72, 31.64, 31.60, 26.60, 24.76, 24.49, 21.93, 18.55. HRMS (TOF MS EI) calcd for $C_{35}H_{52}N_2O_5$ $[M+Na]^+$ 603.3774, found 603.3779.

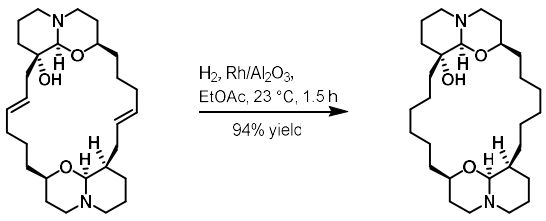


Bis-1-oxaquinolizidine 64 and 65: The outlet of the ammonia lecture bottle (anhydrous, ≥99.98%, Sigma Aldrich) was connected through a Teflon tube to a 25 mL round recovery flask with a glass stirring bar serving as a receiving vessel. The receiving flask was cooled to –78 °C and 5.0 mL of ammonia was condensed. Small pieces of lithium (46 mg, 6.63 mmol, 30 equiv) were added in portions and solution immediately turned deep blue. The mixture was stirred for 4 h at –40 °C, then cooled back to –78 °C. THF was added (2.50 mL), followed with macrocyclic diol **S4** (0.13 g, 0.221 mmol) in THF (2.50 mL). The reaction mixture stayed deep blue and was stirred for 15 min at –78 °C before it was quenched with solid NH_4Cl (2 g), diluted with THF (5.0 mL), warmed to room temperature. Water (3 mL) was carefully added and the solution was transferred to a separatory funnel containing 1M aqueous NaOH (7 mL), extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over

sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by reverse column chromatography (10% water-MeOH) to give **64** (65 mg, 0.140 mmol, 64% yield) and **65** (12 mg, 0.026 mmol, 12% yield) both as a clear oil.

64: $[\alpha]_D^{25}$ −5.8° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 5.55 (t, J = 4.3 Hz, 2H), 5.50 – 5.43 (m, 1H), 5.37 (ddd, J = 14.8, 9.0, 5.1 Hz, 1H), 4.20 (d, J = 3.3 Hz, 1H), 3.94 (s, 1H), 3.54 – 3.40 (m, 2H), 3.19 – 3.11 (m, 1H), 3.09 – 2.99 (m, 3H), 2.99 – 2.90 (m, 2H), 2.50 (s, 1H), 2.39 (dt, J = 10.7, 3.3 Hz, 1H), 2.36 – 2.30 (m, 2H), 2.16 – 2.01 (m, 4H), 1.96 – 1.84 (m, 3H), 1.82 – 1.23 (m, 19H), 1.08 – 0.97 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 134.26, 132.03, 127.48, 123.96, 87.43, 76.82, 76.54, 71.02, 52.67, 52.51, 45.19, 41.29, 40.40, 35.85, 35.66, 35.52, 32.30, 31.97, 26.19, 25.95, 25.68, 25.33, 25.26, 20.93. HRMS (TOF MS EI) calcd for $C_{28}H_{46}N_2O_3$ $[M+H]^+$ 459.3586, found 459.3586.

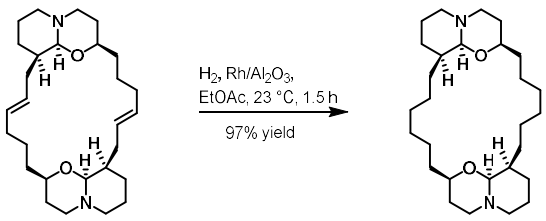
65: $[\alpha]_D^{25}$ -22.1° (*c* 0.50, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 5.52 – 5.43 (m, 2H), 5.35 (ddd, J = 14.8, 9.0, 5.1 Hz, 2H), 4.20 (d, J = 3.2 Hz, 2H), 3.45 (ddt, J = 14.7, 9.7, 2.8 Hz, 2H), 3.15 (td, J = 13.4, 3.5 Hz, 2H), 3.05 (ddd, J = 12.3, 10.6, 3.1 Hz, 2H), 2.94 (ddd, J = 13.7, 4.5, 1.6 Hz, 2H), 2.39 (dt, J = 10.8, 3.3 Hz, 2H), 2.20 – 2.01 (m, 4H), 1.89 (ddt, J = 31.9, 12.8, 5.5 Hz, 4H), 1.78 – 1.41 (m, 14H), 1.40 – 1.20 (m, 6H), 1.01 (dp, J = 13.2, 1.8 Hz, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 132.21, 127.34, 87.43, 76.50, 52.67, 45.17, 40.33, 32.08, 29.68, 26.18, 25.89, 25.41. HRMS (TOF MS EI) calcd for $C_{28}H_{46}N_2O_2$ $[M+H]^+$ 443.3629 found 443.3629.



64 (+)-dmXe B

(+)-Desmethylxestospongin B: Bis-1-oxaquinolizidine **64** (36 mg, 0.0785 mmol) was dissolved in dry EtOAc (3.60 mL), and 5 wt. % Rh/Al_2O_3 (18 mg) was added. The atmosphere in the flask was exchanged with hydrogen (a hydrogen balloon was inserted into the flask along with a hypodermic needle; the hypodermic needle was removed after 5 min). The solution was stirred for at room temperature for 1.5 h under a hydrogen atmosphere, then filtered through syringe filter (Acrodics, 13 mm, 0.2µm PFTE) and concentrated *in vacuo* to give (+)-desmethylxestospongin B (34.3 mg, 0.0741 mmol, 94% yield) as a white foam.

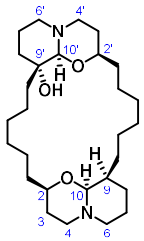
$[\alpha]_D^{25}$ +5.1˚ (*c* 0.40, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 4.28 (d, J = 3.2 Hz, 1H), 4.03 (s, 1H), 3.52 (dt, J = 22.1, 10.8 Hz, 2H), 3.17 (td, J = 14.0, 13.5, 3.5 Hz, 1H), 3.12 – 2.98 (m, 3H), 2.94 (ddd, J = 13.1, 7.4, 4.6 Hz, 2H), 2.45 (s, 1H), 2.39 (dd, J = 10.5, 3.6 Hz, 1H), 2.35 – 2.28 (m, 1H), 1.75 (dtt, J = 23.0, 11.5, 6.1 Hz, 3H), 1.69 (s, 1H), 1.62 – 1.45 (m, 9H), 1.44 – 1.22 (m, 16H), 1.20 – 1.06 (m, 6H), 1.05 – 0.97 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 90.32, 87.42, 76.40, 76.15, 70.72, 52.46, 52.40, 45.09, 44.20, 40.04, 38.45, 36.17, 36.07, 32.84, 32.19, 31.63, 31.50, 29.50, 29.41, 27.06, 26.13, 26.05, 25.95, 25.20, 24.81, 24.80, 22.65, 20.87. HRMS (TOF MS El) calcd for $C_{28}H_{50}N_2O_3$ $[M+H]^+$ 463.3900, found 463.3900.



65 (–)-Ar B

(−)-Araguspongine B: Bis-1-oxaquinolizidine **65** (16 mg, 0.0361 mmol) was dissolved in dry EtOAc (1.60 mL), and 5 wt. % Rh/Al_2O_3 (8 mg) was added. The atmosphere in the flask was exchanged with hydrogen (a hydrogen balloon was inserted into the flask along with a hypodermic needle; the hypodermic needle was removed after 5 min). The solution was stirred for at room temperature for 1.5 h under a hydrogen atmosphere, then filtered through syringe filter (Acrodics, 13 mm, 0.2µm PFTE) and concentrated *in vacuo* to give (−)-araguspongine B (15.6 mg, 0.0349 mmol, 97% yield) as a white solid.

$[\alpha]_D^{25}$ −12.5˚ (*c* 0.44, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 4.29 (d, J = 3.2 Hz, 2H), 3.52 (tt, J = 10.8, 2.3 Hz, 2H), 3.17 (td, J = 13.4, 3.5 Hz, 2H), 3.05 (ddd, J = 12.8, 10.8, 3.1 Hz, 2H), 2.95 (ddd, J = 13.8, 4.6, 1.6 Hz, 2H), 2.39 (dt, J = 10.9, 3.3 Hz, 2H), 1.78 – 1.70 (m, 2H), 1.67 (ddt, J = 16.1, 6.2, 3.7 Hz, 2H), 1.57 (ddt, J = 13.6, 9.2, 4.2 Hz, 8H), 1.47 (qd, J = 12.0, 4.4 Hz, 2H), 1.43 – 1.22 (m, 15H), 1.13 (dddd, J = 26.1, 18.2, 9.9, 4.0 Hz, 7H), 1.02 (ddt, J = 13.2, 3.6, 1.8 Hz, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 87.36, 75.96, 52.73, 45.17, 40.41, 36.22, 32.98, 31.74, 29.46, 27.32, 26.48, 26.24, 25.74, 24.74. HRMS (TOF MS El) calcd for $C_{28}H_{50}N_2O_2$ $[M+H]^+$ 447.3951, found 447.3944.



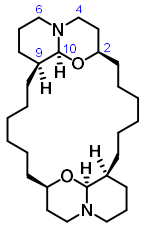
(+)-dmXe B

Table 6. Comparison of ^{1}H NMR Data for Natural[91] and Synthetic (+)-desmethylxestospongin B in C_6D_6.

Proton	Natural dmXeB (250 MHz)	Synthetic dmXeB (600 MHz)
H-2	3.40 (br t, J=10.8 Hz)	3.46 – 3.34 (m)
H-3α	0.65 (br d, J=13.5 Hz)	0.64 (dt, J = 13.5, 2.7 Hz)
H-4α	2.80 - 2.60 (m)	2.70 – 2.57 (m)
H-4β	2.95 - 2.80 (m)	2.95 – 2.83 (m)
H-6α	3.20 - 3.00 (m)	3.09 (td, J = 11.2, 5.2 Hz)
H-6β	2.33 (ddd, J=10.3, 2.3, 2.3 Hz)	2.33 (dd, J = 10.4, 3.6 Hz)
H-10	4.18 (s)	4.15 (s)
H-2’	3.40 (br t, J=10.8 Hz)	3.46 – 3.34 (m)
H-3’α	0.65 (br d, J=13.5 Hz)	0.70 (dt, J = 14.6, 2.8 Hz)
H-4’α	2.80 - 2.60 (m)	2.79 (ddd, J = 13.8, 4.6, 1.5 H)
H-4’β	2.95 - 2.80 (m)	2.95 – 2.83 (m)
H-6’α	3.30 - 2.90 (m)	3.09 (td, J = 11.2, 5.2 Hz)
H-6’β	2.09 (br d, J=10.2 Hz)	2.07 (dt, J = 10.9, 2.9 Hz)
H-10’	4.41 (br d, J=1.5 Hz)	4.38 (s)

Table 7. Comparison of ^{13}C NMR Data for Natural[91] and Synthetic (+)-desmethylxestospongin B in C_6D_6.

Carbon	Natural dmXeB (250 MHz)	Synthetic dmXeB (600 MHz)
C-2	76.5	76.7
C-4	52.7	53.0
C-6	45.6	45.9
C-9	70.7	71.0
C-10	91.2	91.4
C-2’	76.2	76.4
C-4’	53.0	53.3
C-6’	45.5	44.8
C-9’	40.7	40.9
C-10’	87.9	88.2



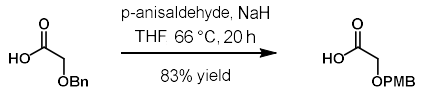
(–)-Ar B

Table 8. Comparison of ^{1}H NMR Data for Natural[1c] and Synthetic (−)-araguspongine B in $CDCl_3$.

Proton	Natural ArB (250 MHz)	Synthetic ArB (600 MHz)
H-2	3.53 (br t, J=11.0 Hz)	3.52 (tt, J = 10.8, 2.3 Hz)
H-4α	2.95 (ddd, J=13.7, 3.1, 1.5 Hz)	2.95 (ddd, J = 13.8, 4.6, 1.6 Hz)
H-4β	3.18 (ddd, J=13.7, 13.4, 3.1 Hz)	3.17 (td, J = 13.4, 3.5 Hz)
H-10	4.30 (d, J=2.8 Hz)	4.29 (d, J = 3.2 Hz)

Table 9. Comparison of ^{13}C NMR Data for Natural[1c] and Synthetic (−)-araguspongine B in $CDCl_3$.

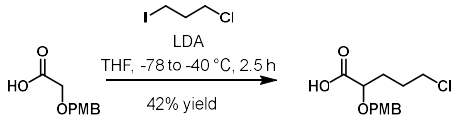
Carbon	Natural ArB (250 MHz)	Synthetic ArB (600 MHz)
C-2	76.0	75.96
C-4	52.8	52.73
C-6	45.3	45.17
C-9	40.5	40.41
C-10	87.5	87.36



66

2-((4-methoxybenzyl)oxy)acetic acid 66: Prepared according to a modification of the literature procedure[92]: Sodium hydride (1.54 g, 38.4 mmol, 2.4 equiv) was added in portions to a solution of bromoacetic acid (2.20 g, 16.0 mmol) and p-anisaldehyde (2.0 mL, 16.0 mmol) in THF (29 mL) at 0 °C under argon. The suspension was heated at reflux for 20 h when it was quenched with methanol (2 mL) and concentrated *in vacuo.* The residue was dissolved in Et_2O (10 mL) and washed with water (3 x 20 mL). The combined aqueous layers were acidified with 1 M HCl to pH=4, and the resulting solution was extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue afforded 2-((4-methoxybenzyl)oxy)acetic acid **66** (2.60 g, 13.25 mmol, 83% yield) as a clear oil that was used immediately without further purification.

^1H and ^{13}C NMR spectral data matched that reported in the literature.[9]

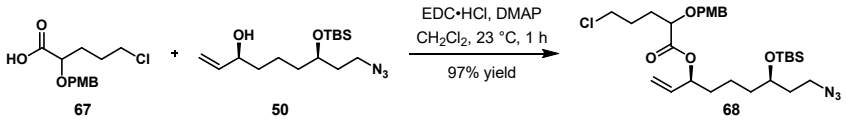


66 67

Acid 67: *n*-Butyllithium (2.40M in hexanes, 16.35 ml, 39.25 mmol, 2.20 equiv) was added to a solution of diisopropylamine (5.77 mL, 41.03 mmol, 2.30 equiv) in THF (53 ml) at –78 °C, and the mixture was stirred for 20 min. Solution of **66** (3.50 g, 17.84 mmol) in THF (30 mL then 3 x 2.0 mL rinses) was added. The solution was stirred 1 h at –78 °C, when 1-chloro-3-iodopropane (5.75 mL, 53.52 mmol, 3 equiv) was added. The solution was stirred 0.5 h at –78 °C, then 2 h at –40 °C. The reaction mixture was

then diluted with EtOAc (30 mL) and washed with 1M aqueous HCl (50 mL), brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (60% EtOAc-hexanes to 60% EtOAc-1% AcOH-hexanes) to give acid **67** (2.06 g, 7.55 mmol, 42% yield) as a clear oil.

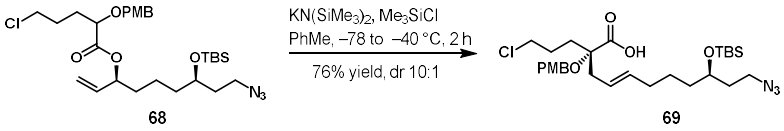
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.26 (s, 1H), 7.34 – 7.19 (m, 2H), 6.98 – 6.80 (m, 2H), 4.69 (d, J = 11.2 Hz, 1H), 4.41 (d, J = 11.3 Hz, 1H), 4.00 (dd, J = 7.2, 4.1 Hz, 1H), 3.81 (s, 3H), 3.55 – 3.41 (m, 2H), 2.07 – 1.74 (m, 4H).^{13}C NMR (126 MHz, $CDCl_3$) δ 178.02, 159.50, 129.80, 128.87, 113.88, 76.11, 72.14, 55.23, 44.38, 29.85, 28.16. HRMS (TOF MS EI) calcd for $C_{13}H_{17}ClO_4$ $[M+Na]^+$ 295.0708, found 295.0708.



Ester 68: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.47 g, 9.44 mmol, 2 equiv), was added to a solution of acid **67** (2.06 g, 7.55 mmol, 1.6 equiv) in CH_2Cl_2 (17 mL). A solution of alcohol **50** (1.50 g, 4.72 mmol) in CH_2Cl_2 (10 mL, then 3 x 1 mL rinses) was then added, followed by the addition of 4-dimethylaminopyridine (0.120 g, 0.944 mmol, 0.2 equiv). The solution was stirred at room temperature for 1 h, then diluted with additional CH_2Cl_2 (40 mL) and washed with brine (50 mL). The organic layer was dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (6% EtOAc-hexanes) to give ester **68** (2.60 g, 4.58 mmol, 97% yield) as a clear oil.

$[\alpha]_D^{25}$ –4.1° (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 2H), 6.96 – 6.78 (m, 2H), 5.79 (dddd, J = 17.2, 10.4, 8.0, 6.7 Hz, 1H), 5.36 – 5.25 (m, 2H), 5.23 (dt, J =

10.5, 1.1 Hz, 1H), 4.66 (dd, J = 11.3, 5.0 Hz, 1H), 4.33 (d, J = 11.2 Hz, 1H), 3.94 (dq, J = 5.3, 1.6 Hz, 1H), 3.81 (s, 3H), 3.77 (qd, J = 6.9, 3.5 Hz, 1H), 3.51 (td, J = 5.7, 1.9 Hz, 2H), 3.35 (tdt, J = 10.2, 7.3, 3.8 Hz, 2H), 2.00 – 1.80 (m, 4H), 1.73 – 1.58 (m, 4H), 1.53 – 1.44 (m, 2H), 1.37 (dttd, J = 20.9, 14.1, 10.5, 10.0, 7.0 Hz, 2H), 0.89 (d, J = 2.4 Hz, 9H), 0.06 (t, J = 4.0 Hz, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 171.67, 159.37, 135.93, 135.83, 129.62, 129.38, 129.36, 117.77, 117.38, 113.78, 75.39, 75.32, 71.82, 69.07, 69.04, 55.20, 47.87, 44.51, 36.88, 35.58, 35.51, 34.21, 30.22, 30.17, 28.37, 28.34, 25.78, 20.59, 20.57, 17.97, -4.39, -4.41, -4.62, -4.71, -4.74. HRMS (TOF MS EI) calcd for $C_{28}H_{46}ClN_3O_5Si$ $[M+Na]^+$ 590.2793, found 590.2793.

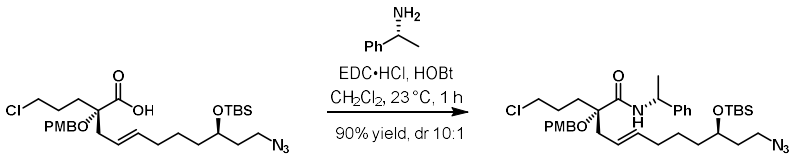


Carboxylic acid 69: Prepared according to a modification of the literature procedure[54]: flame-dried 100 mL round bottom flask was brought into a nitrogen-filled glove box and charged with $KN(SiMe_3)_2$ (2.00 g, 10.08 mmol, 2.2 equiv). The flask was capped, removed from the glove box, attached to a Schlenk line, and backfilled with argon three times. Toluene (16 mL) was then added to the flask and the solution was cooled to –78 °C. A solution of ester **68** (2.60 g, 4.58 mmol) in PhMe (14 mL then 2 x 1 mL rinses) was added dropwise and the resulting solution was stirred 30 min. Chlorotrimethylsilane (1.20 mL, 1.03 g, 9.16 mmol, 2 equiv) was then added dropwise, and the solution was stirred 1h at –78 °C and 1h at –40 °C, The solution was then poured into a separatory funnel containing 1M aqueous HCl (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 15 mL), the

combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes) to give acid **69** (1.98 g, 3.48 mmol, 76% yield, dr 10:1) as a clear oil.

$[\alpha]_D^{25}$ +0.2° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 6.94 – 6.88 (m, 2H), 5.60 (ddd, *J* = 15.0, 7.4, 6.1 Hz, 1H), 5.41 – 5.32 (m, 1H), 4.50 (d, *J* = 9.8 Hz, 1H), 4.42 (d, *J* = 9.8 Hz, 1H), 3.82 (s, 3H), 3.79 – 3.73 (m, 1H), 3.62 (dt, *J* = 11.0, 5.6 Hz, 1H), 3.50 (ddd, *J* = 10.8, 8.6, 4.9 Hz, 1H), 3.37 – 3.30 (m, 2H), 2.70 – 2.57 (m, 2H), 2.14 (ddd, *J* = 14.3, 11.9, 4.2 Hz, 1H), 2.06 – 1.96 (m, 3H), 1.86 (dddd, *J* = 20.2, 13.8, 7.2, 4.6 Hz, 1H), 1.81 – 1.72 (m, 1H), 1.72 – 1.63 (m, 2H), 1.47 – 1.33 (m, 4H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.57, 159.58, 135.49, 129.57, 128.85, 122.60, 113.99, 83.09, 69.19, 64.95, 55.27, 47.93, 44.71, 38.00, 36.62, 35.63, 32.64, 31.69, 26.52, 25.82, 24.63, 18.01, -4.38, -4.70. HRMS (TOF MS EI) calcd for $C_{28}H_{46}ClN_3O_5Si$ $[M+Na]^+$ 590.2793, found 590.2781.

Determination of diastereomer ratio for carboxylic acid 69:

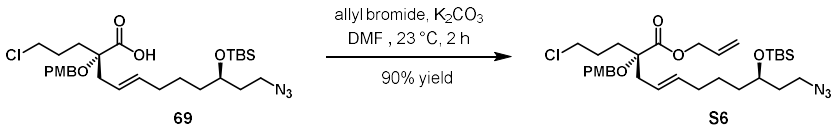


69 **S5**

Amide S5: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (10 mg, 0.053 mmol, 3 equiv), (*R*)-(+)-alpha-methylbenzylamine (7 μL, 0.058 mmol, 3 equiv), and HOBt (7 mg, 0.053 mmol, 3 equiv) were added sequentially to a solution of acid **69** (10 mg, 0.018 mmol) in CH_2Cl_2 (0.10 mL). The solution was stirred at room temperature for 1h, then

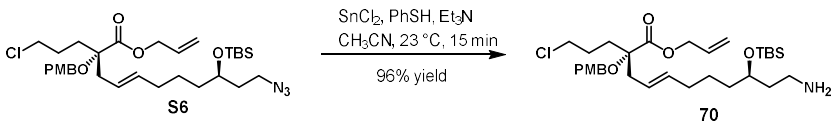
diluted with CH_2Cl_2 (2 mL) and saturated aqueous sodium bicarbonate (2 mL), brine (2 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **S5** (11 mg, 0.016 mmol, 90% yield, dr 10:1) as a clear oil.

$[\alpha]_D^{25}$ +14.5° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.17 (overlapping m, 11H), 7.09 (overlapping d, J = 8.5 Hz, 1H), 6.93 – 6.85 (overlapping m, 2.20H), 5.54 (dq, J = 15.0, 7.8, 7.3 Hz, 0.10H), 5.45 (dt, J = 15.2, 6.8 Hz, 1H), 5.26 – 5.17 (m, 1H), 5.17 – 5.06 (overlapping m, 1.10H), 4.43 (overlapping d, J = 10.1 Hz, 1.10H), 4.37 (overlapping d, J = 10.2 Hz, 1.10H), 3.82 (overlapping s, 3.30H), 3.77 – 3.67 (m, 1H), 3.61 (dt, J = 11.2, 5.8 Hz, 1H), 3.48 (overlapping ddd, J = 10.7, 8.4, 5.6 Hz, 1.10H), 3.39 – 3.23 (overlapping m, 2.20H), 2.66 – 2.57 (overlapping m, 1.10H), 2.53 (overlapping dd, J = 14.9, 7.4 Hz, 1.10H), 2.07 – 1.93 (overlapping m, 2.20H), 1.87 (overlapping q, J = 7.3 Hz, 2.20H), 1.82 (ddd, J = 11.0, 8.3, 5.4 Hz, 1H), 1.79 (overlapping s, 1.10H), 1.69 – 1.60 (m, 2H), 1.60 (overlapping s, 2.20H), 1.45 (overlapping d, J = 6.9 Hz, 3.30H), 1.41 – 1.33 (overlapping m, 2.20H), 1.32 – 1.23 (overlapping m, 3.30H), 0.87 (overlapping s, 9.90H), 0.04 (overlapping d, J = 7.8 Hz, 6.60H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.93, 159.28, 143.25, 134.02, 129.91, 129.03, 128.50, 127.15, 126.07, 125.07, 123.75, 113.92, 110.83, 82.82, 69.19, 64.16, 63.82, 55.28, 48.24, 48.12, 47.98, 45.04, 38.05, 36.80, 35.59, 32.65, 31.77, 29.69, 26.68, 25.85, 24.64, 22.00, 18.04, 17.90, 17.86, 11.85, 11.82, -4.32, -4.69. HRMS (TOF MS EI) calcd for $C_{36}H_{55}ClN_4O_4Si$ $[M+Na]^+$ 693.3579, found 693.3589.



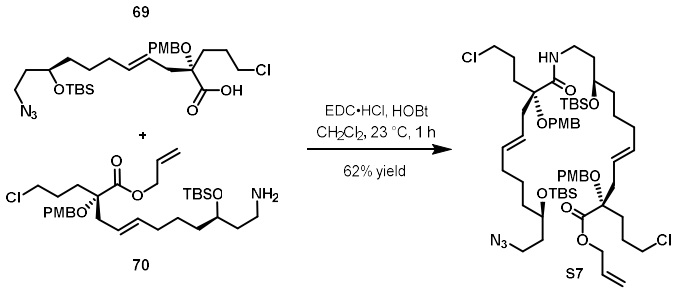
Allyl Ester S6: Potassium carbonate (0.20 g, 1.41 mmol, 1.10 equiv) was added to a solution of acid **69** (0.73 g, 1.28 mmol) and allyl bromide (0.33 mL, 3.84 mmol, 3 equiv) in DMF (2.60 mL). The solution was stirred at room temperature for 2 h, then diluted with water (5 mL) and hexanes (5 mL) and washed with 1M HCl (5 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc-hexanes) to give allyl ester **S6** (0.70 g, 1.15 mmol mmol, 90% yield) as a clear oil.

$[\alpha]_D^{25}$ –4.9° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 6.92 – 6.81 (m, 2H), 5.94 (ddt, *J* = 17.2, 10.4, 5.9 Hz, 1H), 5.57 – 5.49 (m, 1H), 5.42 – 5.33 (m, 2H), 5.27 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.65 (dt, *J* = 5.8, 1.4 Hz, 2H), 4.47 – 4.34 (m, 2H), 3.80 (s, 3H), 3.75 (ddd, *J* = 7.1, 6.0, 4.5 Hz, 1H), 3.59 – 3.45 (m, 2H), 3.33 (tt, *J* = 12.2, 6.8 Hz, 2H), 2.65 – 2.52 (m, 2H), 2.03 – 1.94 (m, 4H), 1.93 – 1.85 (m, 1H), 1.82 – 1.73 (m, 1H), 1.73 – 1.61 (m, 2H), 1.44 (dq, *J* = 9.7, 5.7 Hz, 2H), 1.40 – 1.31 (m, 2H), 0.88 (s, 9H), 0.05 (d, *J* = 2.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.77, 159.07, 134.59, 131.81, 130.31, 129.07, 123.54, 118.78, 113.64, 82.18, 69.15, 65.96, 65.45, 55.16, 47.88, 45.06, 37.72, 36.67, 35.60, 32.64, 31.87, 26.40, 25.78, 24.70, 17.96, -4.41, -4.74. HRMS (TOF MS EI) calcd for $C_{31}H_{50}ClN_3O_5Si$ $[M+Na]^+$ 630.3106, found 630.3096.



Amine 70: Prepared according to a modification of the literature procedure[55]: thiophenol (0.70 mL, 6.90 mmol, 6.0 equiv) and triethylamine (0.72 mL, 5.17 mmol, 4.50 equiv) were added to a solution of anhydrous $SnCl_2$ (0.33 g, 1.72 mmol, 1.5 equiv) in acetonitrile (7 mL). The mixture turned bright yellow and was let to stir at room temperature for 15 min. Solution of azide **S6** (0.70 g, 1.15 mmol) in acetonitrile (3 mL then 3 x 0.5 mL rinses) was added and the mixture was stirred at room temperature for 15 min when it was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (15 mL) and washed with 2M aqueous NaOH (10 mL). The extract was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc-CH_2Cl_2 then 20% MeOH-1% NH_4OH-CH_2Cl_2) to afford amine **70** (0.64 g, 1.10 mmol, 96% yield) as a pale-yellow oil.

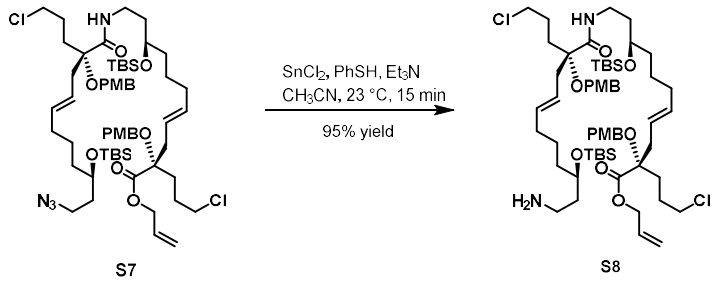
$[\alpha]_D^{25}$ –1.9° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 6.90 – 6.81 (m, 2H), 5.94 (ddt, J = 17.1, 10.4, 5.8 Hz, 1H), 5.52 (dt, J = 13.4, 3.8 Hz, 1H), 5.41 – 5.33 (m, 2H), 5.27 (dq, J = 10.4, 1.3 Hz, 1H), 4.65 (dt, J = 5.9, 1.3 Hz, 2H), 4.48 – 4.35 (m, 2H), 3.80 (s, 3H), 3.73 (q, J = 5.7 Hz, 1H), 3.58 – 3.46 (m, 2H), 2.84 – 2.69 (m, 2H), 2.64 – 2.53 (m, 2H), 2.18 – 2.03 (m, 2H), 1.99 (tdd, J = 10.5, 7.8, 5.5 Hz, 4H), 1.92 – 1.84 (m, 1H), 1.76 (dddd, J = 19.7, 12.4, 9.2, 5.6 Hz, 1H), 1.59 (qd, J = 7.0, 6.0, 1.4 Hz, 2H), 1.47 – 1.29 (m, 4H), 0.88 (s, 9H), 0.04 (d, J = 5.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.81, 159.05, 134.78, 131.80, 130.32, 129.08, 123.35, 118.81, 113.64, 82.18, 70.36, 65.97, 65.46, 55.18, 45.08, 40.07, 38.46, 37.71, 36.75, 32.72, 31.88, 26.41, 25.82, 24.90, 17.98, -4.42, -4.57. HRMS (TOF MS EI) calcd for $C_{31}H_{52}ClNO_5Si$ $[M+H]^+$ 582.2381, found 582.3386.



Amide S7: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.21 g, 1.34 mmol, 1.5 equiv), amine **70** (0.52 g, 0.89 mmol, 1 equiv), and HOBt (0.18 g, 1.34 mmol, 1.5 equiv) were added sequentially to a solution of acid **69** (0.51 g, 0.89 mmol) in CH_2Cl_2 (5 mL). The solution was stirred at room temperature for 1h, then diluted with CH_2Cl_2 (3 mL) and washed with saturated aqueous sodium bicarbonate (5 mL), brine (5 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **S7** (0.62 g, 0.547 mmol, 62% yield) as a clear oil.

$[\alpha]_D^{25}$ –6.8° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.25 (d, J = 8.8 Hz, 2H), 6.87 (ddd, J = 16.8, 9.4, 7.3 Hz, 5H), 5.93 (ddt, J = 16.5, 10.4, 5.8 Hz, 1H), 5.51 (dq, J = 12.5, 6.3 Hz, 2H), 5.43 – 5.29 (m, 3H), 5.28 – 5.23 (m, 1H), 4.64 (dt, J = 5.8, 1.4 Hz, 2H), 4.47 – 4.30 (m, 4H), 3.81 (s, 3H), 3.79 (s, 3H), 3.75 (dt, J = 10.6, 5.2 Hz, 1H), 3.65 (tq, J = 10.8, 5.7, 4.6 Hz, 1H), 3.61 – 3.42 (m, 4H), 3.38 – 3.29 (m, 3H), 3.17 (tt, J = 13.6, 6.2 Hz, 1H), 2.71 – 2.49 (m, 4H), 1.96 (dp, J = 14.2, 5.7, 5.0 Hz, 8H), 1.89 (tt, J = 11.3, 5.6 Hz, 1H), 1.76 (dtd, J = 19.3, 7.4, 3.7 Hz, 2H), 1.72 – 1.59 (m, 4H), 1.59 – 1.48 (m, 1H), 1.42 (qd, J = 7.3, 4.1 Hz, 4H), 1.39 – 1.29 (m, 4H), 0.86 (d, J = 18.9 Hz, 18H), 0.05 (d, J = 5.4 Hz, 6H), -0.02 (d, J = 14.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.83, 172.58, 159.31, 159.08, 134.73, 133.76, 131.83, 130.34, 129.83, 129.40, 129.12, 123.90, 123.43,

118.83, 113.85, 113.67, 82.79, 82.20, 69.89, 69.14, 66.00, 65.48, 63.72, 55.22, 55.21, 47.93, 45.10, 44.95, 38.08, 37.73, 36.73, 36.60, 35.71, 35.59, 32.77, 32.71, 31.88, 31.59, 29.63, 26.73, 26.43, 25.81, 24.86, 24.71, 17.98, -4.36, -4.41, -4.64, -4.73. HRMS (TOF MS EI) calcd for $C_{59}H_{96}Cl_2N_4O_9Si_2$ $[M+Na]^+$ 1153.5991, found 1153.6012.

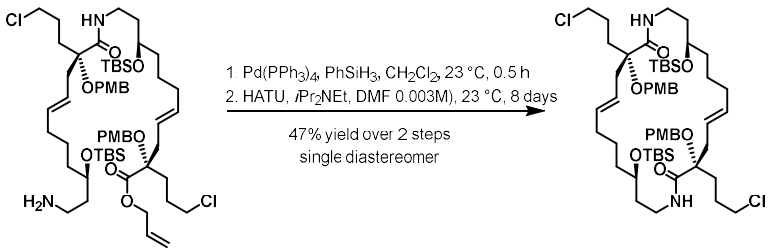


S7 S8

Amine S8: Prepared according to a modification of the literature procedure[55]: thiophenol (0.40 mL, 3.92 mmol, 6.0 equiv) and triethylamine (0.41 mL, 2.94 mmol, 4.50 equiv) were added to a solution of anhydrous $SnCl_2$ (0.19 g, 0.98 mmol, 1.50 equiv) in acetonitrile (4 mL). The mixture turned bright yellow and was let to stir at room temperature for 15 min. Solution of azide **S7** (0.74 g, 0.65 mmol) in acetonitrile (2.5 mL) was added and the mixture was stirred at room temperature for 15 min when it was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (5 mL) and washed with 2M aqueous NaOH (5 mL). It was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc-CH_2Cl_2 then 20% MeOH-1% NH_4OH-CH_2Cl_2) to afford amine **S8** (0.69 g, 0.62 mmol, 95% yield) as a pale-yellow oil.

$[\alpha]_D^{25}$ –5.7° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.18 (m, 4H), 6.95 – 6.78 (m, 5H), 5.99 – 5.88 (m, 1H), 5.51 (dt, J = 14.4, 6.9 Hz, 2H), 5.42 – 5.27 (m, 3H), 5.27 – 5.22 (m, 1H), 4.69 – 4.60 (m, 2H), 4.48 – 4.29 (m, 4H), 4.11 – 3.87 (m, 2H), 3.80

(two singlets, 6H), 3.73 (p, J = 5.8 Hz, 1H), 3.64 (h, J = 6.1 Hz, 1H), 3.60 – 3.40 (m, 4H), 3.38 – 3.28 (m, 1H), 3.20 – 3.09 (m, 1H), 2.79 (q, J = 6.8 Hz, 2H), 2.67 – 2.48 (m, 4H), 2.06 – 1.82 (m, 10H), 1.82 – 1.57 (m, 8H), 1.51 (ddt, J = 12.6, 9.7, 6.4 Hz, 2H), 1.42 (h, J = 5.4 Hz, 4H), 1.37 – 1.19 (m, 14H), 1.08 – 1.01 (m, 1H), 0.96 (dd, J = 6.7, 1.5 Hz, 1H), 0.91 – 0.80 (m, 18H), 0.04 (dd, J = 7.1, 1.5 Hz, 6H), -0.02 (dd, J = 15.5, 1.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.85, 172.60, 159.32, 159.10, 134.76, 133.88, 131.84, 130.36, 129.87, 129.43, 129.14, 123.85, 123.44, 118.84, 113.87, 113.68, 82.80, 82.22, 70.39, 69.89, 66.02, 65.50, 63.76, 55.24, 55.22, 45.11, 44.96, 38.11, 37.97, 37.75, 36.74, 36.69, 36.62, 35.71, 34.63, 34.48, 32.79, 31.90, 31.62, 31.54, 29.02, 26.76, 26.45, 25.85, 25.83, 25.24, 24.95, 24.89, 22.61, 20.66, 18.72, 18.00, 14.07, 11.38, -4.39, -4.57, -4.62. HRMS (TOF MS EI) calcd for $C_{59}H_{98}Cl_2N_2O_9Si_2$ $[M+H]^+$ 1105.6266, found 1105.6281.

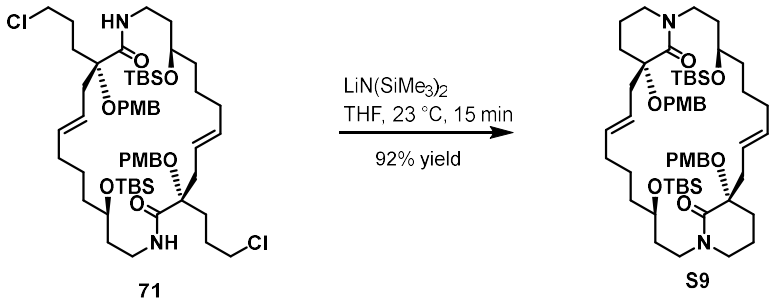


S8 71

Macrocyclic bis-lactam 71: Tetrakis(triphenylphosphine)-palladium(0) (22 mg, 0.019 mmol, 0.03 equiv) was added to a solution of amine **S8** (0.69 g, 0.62 mmol) and phenylsilane (0.31 mL, 0.27 g, 2.50 mmol, 4 equiv) in CH_2Cl_2 (3.10 mL). The mixture was stirred at room temperature for 30 min when it was concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc-Hex then 20% MeOH-1% NH_4OH-CH_2Cl_2), concentrated *in vacuo* and submitted to the next step.

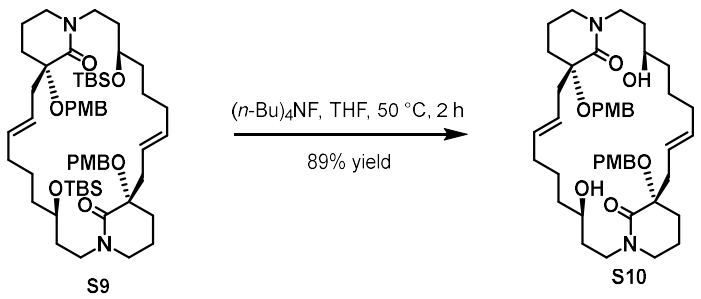
Amino acid from the previous step (0.70 g) was dissolved in anhydrous *N*,*N*-dimethylformamide (208 mL) under argon. *N*,*N*-Diisopropylethylamine (0.43 mL, 2.50 mmol, 4.0 equiv) and HATU (0.36 g, 0.94 mmol, 1.5 equiv) were added, the mixture turned bright yellow and was let to stir at room temperature for 8 days. DMF was distilled off under reduced pressure (0.2 mmHg) into a receiving flask cooled to –78 °C. The residue was dissolved in EtOAc (10 mL) and washed with water (3x50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc-hexanes) to give of macrolactam **71** (0.31 g, 0.29 mmol, 47% yield over two steps) as a single diastereomer, and as a white foam.

$[\alpha]_D^{25}$ +11.6° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 5H), 6.93 (dd, J = 7.8, 4.5 Hz, 2H), 6.90 – 6.76 (m, 4H), 5.50 (dt, J = 15.2, 6.5 Hz, 2H), 5.28 (dt, J = 14.8, 6.9 Hz, 2H), 4.43 (d, J = 10.1 Hz, 2H), 4.36 (d, J = 10.1 Hz, 2H), 3.74 (s, 6H), 3.70 (dq, J = 9.7, 5.4 Hz, 2H), 3.60 (dt, J = 11.1, 5.8 Hz, 2H), 3.51 – 3.37 (m, 4H), 3.05 – 2.90 (m, 2H), 2.55 (qd, J = 14.7, 7.1 Hz, 4H), 2.08 – 1.96 (m, 4H), 1.92 (q, J = 7.3 Hz, 4H), 1.78 (tdd, J = 14.0, 9.8, 4.7 Hz, 2H), 1.70 (ddt, J = 19.5, 11.3, 5.6 Hz, 3H), 1.63 – 1.53 (m, 2H), 1.46 – 1.20 (m, 11H), 0.84 (s, 18H), 0.01 (d, J = 6.7 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.47, 159.21, 133.90, 129.93, 129.42, 129.28, 123.42, 113.84, 83.12, 70.33, 63.53, 55.17, 45.09, 38.22, 37.44, 36.68, 36.23, 33.02, 31.34, 26.75, 25.85, 24.58, 18.02, -4.42, -4.57. HRMS (TOF MS EI) calcd for $C_{56}H_{92}Cl_2N_2O_8Si_2$ $[M+Na]^+$ 1069.5667, found 1069.5673.



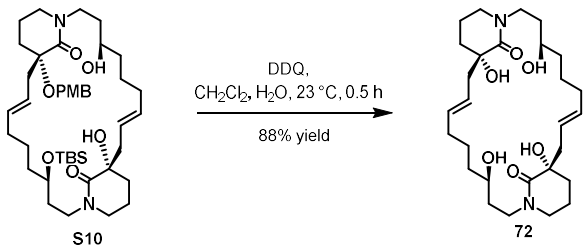
Bis-Lactam S9: Lithium bis(trimethylsilyl)amide (0.5M in THF, 1.20 mL, 0.59 mmol, 2.20 equiv) was added dropwise to a solution of macrocyclic bis-macrolactam **71** (0.28 g, 0.27 mmol) in anhydrous THF (1.30 mL) that was heated at reflux under argon. After 15 min, saturated aq. NH_4Cl (1 mL) was added, and the mixture was extracted with EtOAc (2 x 4 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc-hexanes) to give bis-lactam **S9** (0.24 g, 0.25 mmol, 92% yield) as a white foam.

$[\alpha]_D^{25}$ +1.01˚ (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 – 7.15 (m, 5H), 6.89 – 6.69 (m, 4H), 5.55 (dt, J = 15.4, 6.6 Hz, 2H), 5.37 – 5.18 (m, 2H), 4.60 (d, J = 11.1 Hz, 2H), 4.46 (d, J = 11.1 Hz, 2H), 3.77 (overlapping m and s, 8H), 3.65 (h, J = 6.3, 5.9 Hz, 2H), 3.28 – 3.13 (m, 4H), 3.12 – 2.96 (m, 4H), 2.15 (td, J = 14.6, 13.9, 7.4 Hz, 4H), 2.07 – 1.77 (m, 8H), 1.77 – 1.52 (m, 8H), 1.47 – 1.29 (m, 6H), 0.89 (s, 18H), 0.05 (d, J = 9.0 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13C NMR (126 MHz, cdcl3) δ 168.23, 158.73, 134.43, 131.53, 128.89, 124.87, 113.52, 77.42, 70.15, 65.58, 55.16, 48.35, 43.59, 38.89, 35.70, 33.47, 32.33, 32.00, 25.81, 25.20, 18.85, 18.00, -4.43. HRMS (TOF MS EI) calcd for $C_{56}H_{90}N_2O_8Si_2$ $[M+Na]^+$ 997.6133, found 997.6152.



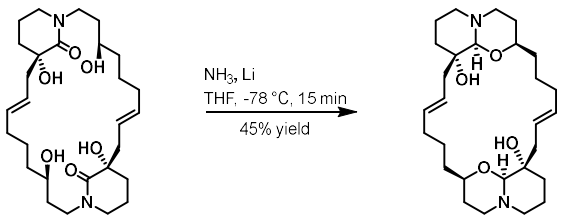
Macrocyclic diol S10: Tetra-n-butylammonium fluoride (1M in THF, 0.62 mL, 0.62 mmol, 4 equiv) was added to the flask with macrolactam **S9** (0.15 g, 0.15 mmol) at 0 °C. The reaction mixture was heated to 50 °C for 2 h, when it was quenched with saturated aq. NH_4Cl (1 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 x 2 mL). The combined organic layers were washed with water (5 x 2 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (40% acetone-hexanes to 50% acetone-hexanes) to give macrocyclic diol **S10** (0.10 g, 0.14 mmol, 89% yield) as a white foam.

$[\alpha]_D^{25}$ −10.9° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.22 (d, J = 8.3 Hz, 5H), 6.83 (d, J = 8.3 Hz, 4H), 5.59 (dt, J = 15.5, 5.8 Hz, 2H), 5.27 (dq, J = 15.3, 7.4, 6.7 Hz, 2H), 4.59 (d, J = 11.1 Hz, 2H), 4.45 (d, J = 11.0 Hz, 2H), 4.06 (ddd, J = 14.0, 9.5, 4.0 Hz, 2H), 3.77 (s, 6H), 3.48 (t, J = 7.5 Hz, 2H), 3.43 – 3.24 (m, 4H), 3.13 (td, J = 12.5, 10.7, 5.7 Hz, 4H), 2.87 (dt, J = 14.0, 5.3 Hz, 2H), 2.20 – 2.00 (m, 6H), 1.92 (dtt, J = 18.7, 13.5, 4.9 Hz, 6H), 1.82 – 1.64 (m, 6H), 1.64 – 1.51 (m, 4H), 1.46 (qt, J = 15.8, 7.7 Hz, 2H), 1.28 (dtd, J = 21.5, 12.3, 10.9, 6.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.81, 158.76, 134.64, 131.35, 128.80, 124.32, 113.57, 77.40, 68.74, 65.41, 55.19, 48.28, 44.19, 39.10, 36.60, 35.03, 32.04, 31.77, 25.07, 18.44. HRMS (TOF MS EI) calcd for $C_{44}H_{62}N_2O_8$ $[M+Na]^+$ 769.4404, found 769.4413.



Tetrahydroxy macrocycle 72: Macrocyclic diol **S10** (0.10 g, 0.134 mmol) was dissolved in 10:1 mixture of CH_2Cl_2 – water (2.40 mL), and DDQ (76 mg, 0.34 mol, 2.50 equiv) was added. Reaction was let to stir for 0.5 h. The mixture was diluted with CH_2Cl_2 (2 mL), washed with 1:1 mixture of saturated aqueous sodium bicarbonate-brine (2 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (100% acetone-hexanes to 10 % MeOH-CH_2Cl_2) to afford tetrahydroxy macrocycle **72** (60 mg, 0.118 mol, 88% yield) as a clear oil.

$[\alpha]_D^{25}$ −11° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.48 (dt, J = 15.2, 6.6 Hz, 2H), 5.36 (dt, J = 15.1, 7.3 Hz, 2H), 3.61 (s, 2H), 3.50 (q, J = 7.3, 6.5 Hz, 4H), 3.41 – 3.31 (m, 2H), 3.27 (dt, J = 9.4, 4.4 Hz, 4H), 2.42 – 2.28 (m, 4H), 2.03 (h, J = 8.0, 7.3 Hz, 4H), 1.98 – 1.88 (m, 4H), 1.84 (tt, J = 11.0, 6.8 Hz, 4H), 1.74 – 1.64 (m, 2H), 1.58 – 1.39 (m, 10H). ^{13}C NMR (126 MHz, CDCl3) δ 173.67, 134.74, 124.57, 72.33, 67.55, 48.31, 44.34, 43.59, 35.31, 34.66, 32.70, 31.58, 24.39, 19.34. HRMS (TOF MS EI) calcd for $C_{28}H_{46}N_2O_6$ $[M+Na]^+$ 529.3254, found 529.3246.

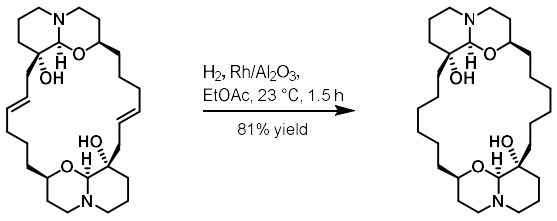


72 S11

Bis-1-oxaquinolizidine S11: The outlet of the ammonia lecture bottle (anhydrous, ≥99.98%, Sigma Aldrich) was connected through a Teflon tube to a 25 mL round recovery flask with a glass stirring bar serving as a receiving vessel. The receiving flask was cooled to –78 °C and 2.0 mL of ammonia was condensed. Small pieces of lithium (20 mg, 2.88 mmol, 27 equiv) were added in portions and solution immediately turned deep blue. The mixture was stirred for 1 h at –40 °C, then cooled back to –78 °C. THF was added (1 mL), followed with tetrahydroxy macrocycle **72** (55 mg, 0.11 mmol) in THF (1 mL). The reaction mixture stayed deep blue and was stirred for 15 min at –78 °C before it was quenched with solid NH_4Cl (0.5 g), diluted with THF (3 mL), warmed to room temperature. Water (1 mL) was carefully added, and the solution was transferred to a separatory funnel containing 1M aqueous NaOH (2 mL), extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by reverse column chromatography (10% water-MeOH) to give **S11** (28 mg, 0.059 mmol, 45% yield) as a white foam.

$[\alpha]_D^{25}$ +8.9° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 5.65 – 5.43 (m, 4H), 3.93 (s, 2H), 3.54 – 3.44 (m, 2H), 3.13 – 2.90 (m, 6H), 2.58 – 2.47 (m, 2H), 2.38 – 2.26 (m, 2H), 2.14 – 2.00 (m, 4H), 1.98 – 1.86 (m, 2H), 1.75 (tdd, J = 17.4, 10.3, 3.5 Hz, 4H), 1.69 –

1.58 (m, 4H), 1.57 – 1.45 (m, 8H), 1.44 – 1.37 (m, 2H), 1.34 – 1.25 (m, 2H), 1.06 (d, J = 13.7 Hz, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 134.14, 124.14, 76.91, 71.01, 52.52, 41.24, 40.31, 35.73, 32.23, 31.93, 28.75, 25.63, 25.24, 20.95. HRMS (TOF MS EI) calcd for $C_{28}H_{46}N_2O_4$ $[M+H]^+$ 475.3536, found 475.3527.

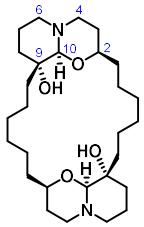


40 (+)-Ar C

(+)-Araguspongine C: Bis-1-oxaquinolizidine **S11** (25 mg, 0.053 mmol) was dissolved in dry EtOAc (2.5 mL), and 5 wt. % Rh/Al_2O_3 (12 mg) was added. The atmosphere in the flask was exchanged with hydrogen (a hydrogen balloon was inserted into the flask along with a hypodermic needle; the hypodermic needle was removed after 5 min). The solution was stirred for at room temperature for 1 h under a hydrogen atmosphere, then filtered through syringe filter (Acrodics, 13 mm, 0.2μm PFTE) and concentrated *in vacuo* to give (+)-araguspongine C (20 mg, 0.043 mmol, 81% yield) as a white foam.

$[\alpha]_D^{25}$ +25.2° (*c* 0.32, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.05 (s, 2H), 3.55 (tt, J = 10.9, 2.2 Hz, 2H), 3.16 – 3.07 (m, 2H), 3.03 (ddd, J = 13.4, 10.6, 2.9 Hz, 2H), 2.97 (ddd, J = 13.8, 4.7, 1.5 Hz, 2H), 2.51 (s, 1H), 2.37 – 2.29 (m, 2H), 1.77 (dtdd, J = 13.0, 11.2, 9.1, 4.5 Hz, 4H), 1.64 – 1.58 (m, 2H), 1.53 (dddd, J = 17.3, 14.7, 9.6, 5.5 Hz, 6H), 1.45 – 1.34 (m, 6H), 1.33 – 1.24 (m, 8H), 1.20 (tdd, J = 12.5, 9.3, 2.7 Hz, 2H), 1.17 – 1.08 (m, 2H), 1.10 – 0.97 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 90.33, 76.49, 70.75, 52.51, 44.24,

38.48, 36.28, 32.28, 31.48, 29.60, 26.00, 24.95, 22.58, 20.91. HRMS (TOF MS El) calcd for $C_{28}H_{50}N_2O_4$ $[M+H]^+$ 479.3849, found 479.3847.



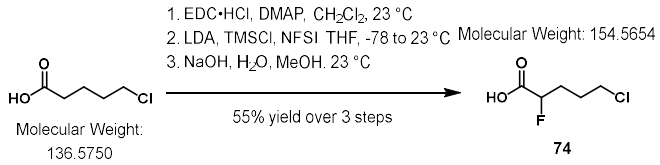
(+)-Ar C

Table 10. Comparison of ^{1}H NMR Data for Natural[1c] and Synthetic (+)-araguspongine C in $CDCl_3$.

Proton	Natural ArC (250 MHz)	Synthetic ArC (600 MHz)
H-2	3.56 (br t, J=10.7 Hz)	3.55 (tt, J = 10.9, 2.2 Hz)
H-4α	2.97 (br dd, J=13.7, 3.4 Hz)	2.97 (ddd, J = 13.8, 4.7, 1.5 Hz)
H-4β	3.11 (br t, J=13.7 Hz)	3.16 – 3.07 (m)
H-6α	2.34 (br d, J=10.0)	2.37 – 2.29 (m)
H-6β	3.03 (ddd, J=10.0, 10.0, 3.1 Hz)	3.03 (ddd, J = 13.4, 10.6, 2.9 Hz)
H-7β	1.72 (m)	1.77 (dtdd, J = 13.0, 11.2, 9.1, 4.5 Hz)
H-10	4.06 (s)	4.05 (s)

Table 11. Comparison of ^{13}C NMR Data for Natural[1c] and Synthetic (+)-araguspongine C in $CDCl_3$.

Carbon	Natural ArC (250 MHz)	Synthetic ArC (600 MHz)
C-2	76.5	76.49
C-4	52.6	52.51
C-6	44.3	45.24
C-9	70.8	70.75
C-10	90.4	90.33

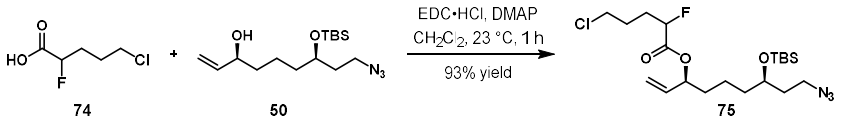


Acid 74: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.37 g, 8.80 mol, 1.30 equiv), was added to a solution of 5-chlorovaleric acid (0.92 g, 6.77 mmol) in CH_2Cl_2 (80 mL). Benzyl alcohol (1.47 g, 13.56 mmol, 2 equiv) was then added, followed by the addition of 4-dimethylaminopyridine (0.12 g, 0.97 mmol, 0.11 equiv). The solution was stirred at room temperature for 1 h, then diluted with additional CH_2Cl_2 (30 mL) and washed with brine (50 mL). The organic layer was dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified using 4-inch silica plug (5% EtOAc-Hex), concentrated *in vacuo* and submitted to the next step.

n-BuLi (2.46 M in hexanes, 6.00 ml, 14.89 mmol, 2.2 equiv) was added to a solution of diisopropylamine (2.30 mL, 16.25 mmol, 2.4 equiv) in THF (20 ml) at –78 °C, and the mixture was stirred for 20 min. Ester from the previous step in THF (5 mL) was added. The solution was stirred for 30 min, when freshly distilled chlorotrimethylsilane (2. 57 mL, 20.31 mmol, 3.0 equiv) was added. After additional 30 min, NFSI (8.54 g, 27.08 mmol, 4 equiv) in THF (5 mL) was added and the solution was stirred for 1 h at –78 °C, 1h at 0 °C and 12 h at room temperature. The solution was then quenched with saturated aqueous ammonium chloride (5 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL), and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue

was purified by using 4-inch silica plug (4% EtOAc-Hex), concentrated *in vacuo* and submitted to the next step.

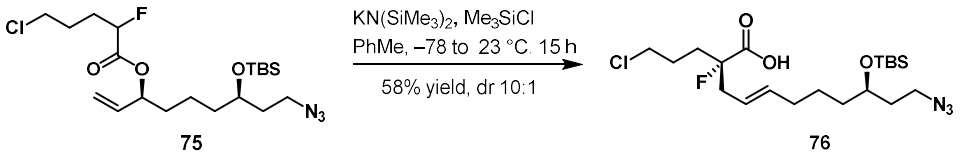
Sodium hydroxide (1.08 g, 27.08 mmol, 4 equiv) in H_2O (9 mL) was added to a solution of α-fluorobenzyl ester from the previous step in MeOH (45 mL) at 0 °C. The reaction was warmed up to room temperature and stirred for 1 h. The resultant mixture was evaporated, diluted with H_2O, pH=11, and washed with Et_2O (3 x 10 mL). The aqueous layer was acidified with 1 M HCl until pH=2 and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. This yielded the acid **74** (3.72 g, 24.09 mmol, 55% yield over 3 steps) which was submitted to the next step without further purification. ^{1}H NMR spectral data matched those reported by Wolff and coworkers.[93]



Ester 75: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (2.51 g, 16.18 mmol, 2 equiv), was added to a solution of acid **74** (2.0 g, 12.94 mmol, 1.6 equiv) in CH_2Cl_2 (30 mL). A solution of alcohol **50** (2.54 g, 8.09 mmol) in CH_2Cl_2 (15 mL, then 3 x 2 mL rinses) was then added, followed by the addition of 4-dimethylaminopyridine (0.20 g, 1.62 mmol, 0.2 equiv). The solution was stirred at room temperature for 1 h, then diluted with additional CH_2Cl_2 (20 mL) and washed with brine (50 mL). The organic layer was dried with sodium sulfate, filtered, and concentrated *in vacuo*. The

residue was purified by column chromatography (10% EtOAc-hexanes) to give ester **75** (3.38 g, 7.51 mmol, 93% yield) as a clear oil.

$[\alpha]_D^{25}$ –4.1° (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (dddd, J = 17.3, 10.5, 6.8, 2.7 Hz, 1H), 5.05 (td, J = 6.7, 4.2 Hz, 1H), 5.00 (dd, J = 17.2, 1.3 Hz, 1H), 4.96 – 4.90 (m, 1H), 4.64 (dddd, J = 49.0, 7.3, 4.2, 1.1 Hz, 1H), 3.52 – 3.45 (m, 1H), 3.29 (td, J = 6.2, 3.1 Hz, 2H), 3.11 – 2.99 (m, 2H), 1.90 – 1.58 (m, 4H), 1.47 – 1.29 (m, 4H), 1.23 – 1.15 (m, 2H), 1.14 – 0.97 (m, 2H), 0.59 (s, 9H), -0.24 (d, J = 4.8 Hz, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 168.64, 168.63, 168.46, 168.44, 135.34, 117.84, 117.81, 88.89, 88.79, 87.41, 87.32, 76.04, 76.00, 68.95, 47.76, 43.99, 43.98, 36.72, 35.50, 35.46, 34.02, 34.00, 29.75, 29.71, 29.59, 29.54, 27.38, 27.35, 27.32, 27.30, 25.69, 20.41, 17.88, -4.52, -4.54, -4.79, -4.81. ^{19}F NMR (376 MHz, $CDCl_3$) δ –191.80 – –192.16 (m). HRMS (TOF MS EI) calcd for $C_{20}H_{37}ClFN_3O_3Si$ $[M+Na]^+$ 472.2174, found 472.2175.

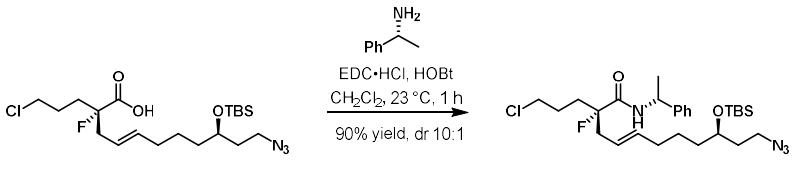


Carboxylic acid 76: Prepared according to a modification of the literature procedure[54]: Flame-dried 50 mL round bottom flask was brought into a nitrogen-filled glove box and charged with $KN(SiMe_3)_2$ (0.98 g, 4.89 mmol, 2.2 equiv). The flask was capped, removed from the glove box, attached to a Schlenk line, and backfilled with argon three times. Toluene (7.5 mL) was then added to the flask and the solution was cooled to –78 °C. A solution of ester **75** (1.0 g, 2.22 mmol) in PhMe (4.5 mL then 2 x 1 mL rinses) was added dropwise and the resulting solution was stirred 30 min.

Chlorotrimethylsilane (0.56 mL, 0.48 g, 4.44 mmol, 2 equiv) was then added dropwise, and the solution was stirred 1h at –78 °C, 2h at –40 °C, and then let stir for 12 h and warm up to room temperature. The solution was then poured into a separatory funnel containing 1M aqueous HCl (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL), the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes) to give acid **76** (0.58 g, 1.29 mmol, 58% yield, dr 10:1) as a pale yellow oil.

$[\alpha]_D^{25}$ –2.1˚ (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 5.58 (dt, J = 15.1, 6.7 Hz, 1H), 5.45 – 5.34 (m, 1H), 3.82 – 3.69 (m, 1H), 3.60 – 3.50 (m, 2H), 3.41 – 3.25 (m, 2H), 2.59 (dtd, J = 32.5, 14.6, 7.1 Hz, 2H), 2.01 (qd, J = 12.6, 11.6, 5.5 Hz, 5H), 1.81 (dddd, J = 14.4, 11.5, 8.4, 5.1 Hz, 1H), 1.73 – 1.63 (m, 2H), 1.49 – 1.30 (m, 4H), 0.88 (s, 9H), 0.06 (d, J = 2.1 Hz, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 136.36, 121.58, 121.55, 69.31, 47.93, 44.37, 40.40, 40.23, 36.47, 35.60, 33.96, 33.78, 32.50, 26.46, 26.43, 25.83, 24.58, 18.04, -4.38, -4.68. ^{19}F NMR (376 MHz, $CDCl_3$) δ -164.95 (s). HRMS (TOF MS EI) calcd for $C_{20}H_{37}ClFN_3O_3Si$ $[M+Na]^+$ 472.2174, found 472.2191.

Determination of diastereomer ratio for carboxylic acid 76:

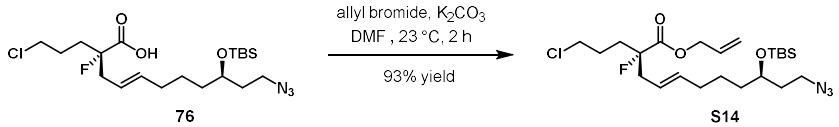


76 S13

Amide S13: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (12 mg, 0.066 mmol, 3 equiv), (*R*)-(+)-alpha-methylbenzylamine (10 μL, 0.066 mmol, 3 equiv), and HOBt (10 mg, 0.066 mmol, 3 equiv) were added sequentially to a solution of acid **76** (10 mg, 0.022 mmol) in CH_2Cl_2 (0.20 mL). The solution was stirred at room temperature for 1h, then diluted with CH_2Cl_2 (2 mL) and washed with saturated aqueous sodium bicarbonate (2 mL) and brine (2 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **S13** (11 mg, 0.020 mmol, 90% yield, dr 10:1) as a clear oil.

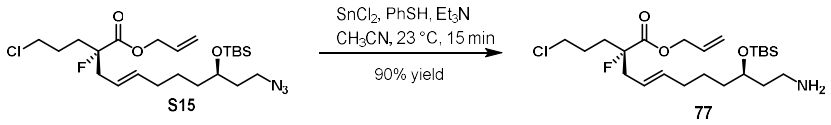
$[\alpha]_D^{25}$ +16.9° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.20 (overlapping m, 5.5H), 6.58 (dd, J = 8.3, 5.8 Hz, 1H), 5.55 (s, 0.10H), 5.47 (dt, J = 15.2, 6.7 Hz, 1H), 5.42 – 5.35 (m, 0.10H), 5.31 – 5.21 (m, 1H), 5.18 – 5.08 (overlapping m, 1.10H), 3.82 – 3.64 (overlapping m, 1.10H), 3.58 – 3.47 (overlapping m, 2.10H), 3.43 (dt, J = 8.9, 6.6 Hz, 0.10H), 3.39 – 3.25 (overlapping m, 2.20H), 2.65 – 2.50 (overlapping m, 1.10H), 2.43 (overlapping ddd, J = 17.1, 14.5, 7.4 Hz, 1H), 2.18 – 2.01 (overlapping m, 1.20H), 2.01 – 1.86 (overlapping m, 4.30H), 1.86 – 1.74 (overlapping m, 1.20H), 1.74 – 1.56 (overlapping m, 2.20H), 1.52 (overlapping d, J = 6.9 Hz, 3.30H), 1.47 – 1.36 (overlapping m, 2.20H), 1.36 – 1.24 (overlapping m, 2.20H), 0.88 (overlapping s, 9.90H), 0.05 (overlapping d, J = 4.4 Hz, 6.60H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.06, 169.90, 142.61, 135.57, 128.61, 127.42, 126.09, 122.10, 122.07, 100.50, 98.99, 69.15, 48.28, 47.95, 44.47, 40.52, 40.35, 36.66, 35.53, 34.16, 33.98, 32.48, 26.52, 26.49, 25.82,

24.44, 21.75, 18.01, -4.37, -4.71. ^{19}F NMR (376 MHz, $CDCl_3$) δ −164.93 - −167.98 (m). HRMS (TOF MS EI) calcd for $C_{28}H_{46}ClFN_4O_2Si$ [M+Na]$^+$ 575.2960, found 575.2966.



Allyl Ester S14: Potassium carbonate (0.12 g, 0.86 mmol, 1.10 equiv) was added to a solution of acid **76** (0.32 g, 0.70 mmol) and allyl bromide (0.20 mL, 2.33 mmol, 3.3 equiv) in DMF (1.60 mL). The solution was stirred at room temperature for 2 h, then diluted with water (3 mL) and hexanes (5 mL) and washed with 1M HCl (5 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc-hexanes) to give allyl ester **S14** (0.32 g, 0.65 mmol mmol, 93% yield) as a clear oil.

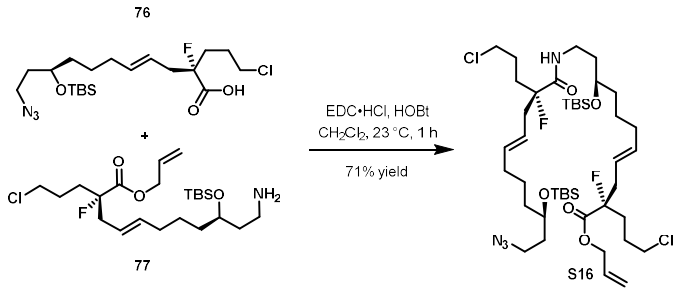
$[\alpha]_D^{25}$ −8.8° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.91 (ddt, J = 17.2, 10.4, 5.9 Hz, 1H), 5.52 (dt, J = 15.1, 6.7 Hz, 1H), 5.44 – 5.32 (m, 2H), 5.28 (dq, J = 10.4, 1.2 Hz, 1H), 4.66 (dq, J = 5.9, 1.2 Hz, 2H), 3.75 (ddd, J = 7.1, 5.9, 4.5 Hz, 1H), 3.58 – 3.47 (m, 2H), 3.41 – 3.23 (m, 2H), 2.65 – 2.41 (m, 2H), 2.09 – 1.89 (m, 5H), 1.82 – 1.55 (m, 3H), 1.49 – 1.29 (m, 4H), 0.88 (s, 9H), 0.05 (d, J = 2.9 Hz, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 170.58, 170.37, 135.78, 131.37, 121.97, 121.94, 119.24, 97.70, 96.19, 69.19, 65.95, 47.96, 44.49, 40.68, 40.50, 36.67, 35.64, 34.23, 34.05, 32.57, 26.53, 26.50, 25.82, 24.59, 18.02, -4.38, -4.70. ^{19}F NMR (376 MHz, $CDCl_3$) δ -165.20 (dddd, J = 30.3, 26.3, 17.7, 13.3 Hz). HRMS (TOF MS EI) calcd for $C_{23}H_{41}ClFN_3O_3Si$ [M+Na]$^+$ 512.2487, found 512.2479.



Amine 77: Prepared according to a modification of the literature procedure[55]: thiophenol (0.40 mL, 3.92 mmol, 6.0 equiv) and triethylamine (0.41 mL, 2.94 mmol, 4.50 equiv) were added to a solution of anhydrous $SnCl_2$ (0.19 g, 0.98 mmol, 1.5 equiv) in acetonitrile (4 mL). The mixture turned bright yellow and was let to stir at room temperature for 15 min. Solution of azide **S15** (0.32 g, 0.65 mmol) in acetonitrile (1.5 mL then 2 x 0.5 mL rinses) was added and the mixture was stirred at room temperature for 15 min when it was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (10 mL) and washed with 2M aqueous NaOH (10 mL). The extract was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc-CH_2Cl_2 then 20% MeOH-1% NH_4OH-CH_2Cl_2) to afford amine **77** (0.27 g, 0.58 mmol, 90% yield) as a pale-yellow oil.

$[\alpha]_D^{25}$ –3.5° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 5.99 – 5.80 (m, 1H), 5.51 (dt, J = 14.1, 6.7 Hz, 1H), 5.43 – 5.31 (m, 2H), 5.27 (d, J = 10.4 Hz, 1H), 4.77 – 4.49 (m, 2H), 3.74 (p, J = 5.3 Hz, 1H), 3.60 – 3.42 (m, 2H), 3.01 – 2.88 (m, 2H), 2.80 (s, 2H), 2.54 (dqd, J = 21.5, 14.7, 7.2 Hz, 2H), 2.11 – 1.88 (m, 5H), 1.80 – 1.68 (m, 1H), 1.66 – 1.55 (m, 2H), 1.49 – 1.29 (m, 4H), 0.87 (s, 9H), 0.03 (d, J = 5.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.59, 170.38, 135.90, 131.36, 121.83, 121.80, 119.24, 97.70, 96.19, 70.42, 65.94, 44.48, 40.67, 40.49, 36.67, 34.19, 34.02, 32.61, 26.52, 26.49, 25.86, 24.75, 18.02, -4.41, -

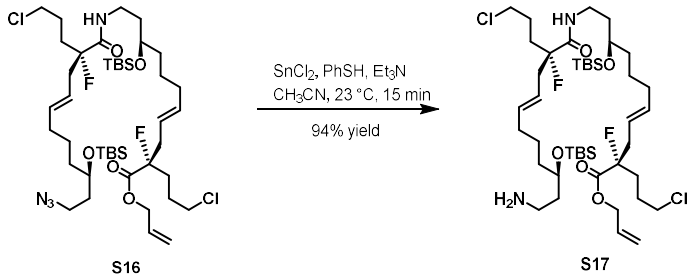
4.53. ^{19}F NMR (376 MHz, $CDCl_3$) δ -163.37 – -167.61 (m). HRMS (TOF MS EI) calcd for $C_{23}H_{43}ClFNO_3Si$ $[M+H]^+$ 464.2685, found 464.2687.



Amide S16: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.16 g, 0.840 mmol, 1.5 equiv), amine **77** (0.26 g, 0.56 mmol, 1 equiv), and HOBt (0.11 g, 0.84 mmol, 1.5 equiv) were added sequentially to a solution of acid **76** (0.25 g, 0.56 mmol) in CH_2Cl_2 (3.20 mL). The solution was stirred at room temperature for 1h, then diluted with CH_2Cl_2 (3 mL), washed with saturated aqueous sodium bicarbonate (5 mL), and brine (5 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **S16** (0.36 g, 0.40 mmol, 71% yield) as a clear oil.

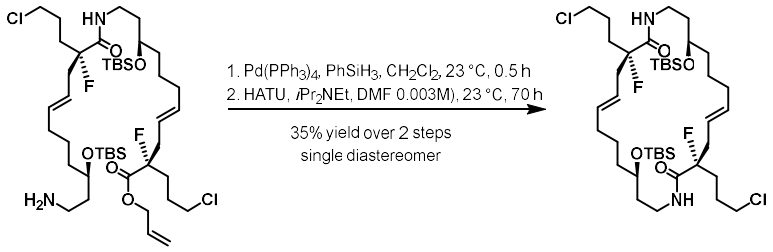
$[\alpha]_D^{25}$ –12.4° (*c* 1.00, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.68 (q, J = 5.5 Hz, 1H), 5.91 (ddt, J = 16.3, 10.4, 5.9 Hz, 1H), 5.52 (dtd, J = 13.8, 6.8, 2.5 Hz, 2H), 5.44 – 5.32 (m, 3H), 5.32 – 5.21 (m, 1H), 4.66 (dq, J = 6.0, 1.2 Hz, 2H), 3.76 (dq, J = 8.0, 5.7 Hz, 2H), 3.60 – 3.42 (m, 4H), 3.42 – 3.20 (m, 4H), 2.52 (ddtd, J = 41.7, 21.8, 14.1, 7.2 Hz, 4H), 2.13 – 1.80 (m, 11H), 1.80 – 1.54 (m, 7H), 1.52 – 1.28 (m, 8H), 0.88 (d, J = 6.2 Hz, 18H), 0.05 (dd, J = 6.4, 2.9 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.97, 170.81, 170.56, 170.36, 135.70, 135.37, 131.36, 122.31, 122.29, 122.00, 121.97, 119.24, 100.44, 98.94, 97.66,

96.16, 70.73, 69.17, 65.94, 47.97, 44.48, 40.66, 40.48, 40.31, 36.68, 36.20, 35.84, 35.60, 35.52, 34.21, 34.04, 33.84, 33.67, 32.61, 32.56, 26.62, 26.59, 26.52, 26.49, 25.86, 25.82, 24.86, 24.58, 18.07, 18.02, -4.36, -4.46, -4.56, -4.70. ^{19}F NMR (376 MHz, $CDCl_3$) δ -164.95 (s). HRMS (TOF MS EI) calcd for $C_{43}H_{78}Cl_2F_2N_4O_5Si_2$ $[M+Na]^+$ 917.4753, found 917.4762.



Amine S17: Prepared according to a modification of the literature procedure[55]: thiophenol (0.24 mL,2.38 mmol, 6.0 equiv) and triethylamine (0.25 mL, 1.78 mmol, 4.50 equiv) were added to a solution of anhydrous $SnCl_2$ (0.10 g, 0.55 mmol, 1.50 equiv) in acetonitrile (3 mL). The mixture turned bright yellow and was let to stir at room temperature for 15 min. Solution of azide **S16** (0.36 g, 0.40 mmol) in acetonitrile (1 mL) was added and the mixture was stirred at room temperature for 15 min when it was concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 (4 mL) and washed with 2M aqueous NaOH (4 mL). It was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc-CH_2Cl_2 then 20% MeOH-1% NH_4OH-CH_2Cl_2) to afford amine **S17** (0.33 g, 0.37 mmol, 94% yield) as a pale-yellow oil.

$[\alpha]_D^{25}$ –8.6° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 6.70 (q, J = 5.5 Hz, 1H), 5.89 (ddt, J = 16.6, 10.5, 5.9 Hz, 1H), 5.50 (dt, J = 15.3, 6.1 Hz, 2H), 5.40 – 5.30 (m, 3H), 5.25 (d, J = 10.4 Hz, 1H), 4.64 (d, J = 5.9 Hz, 2H), 3.74 (h, J = 4.4, 3.1 Hz, 2H), 3.63 (s, 2H), 3.50 (dp, J = 23.0, 6.3, 5.6 Hz, 4H), 3.32 (ddp, J = 19.5, 13.5, 6.4 Hz, 2H), 2.81 (p, J = 6.8, 6.3 Hz, 2H), 2.64 – 2.33 (m, 4H), 2.13 – 1.78 (m, 12H), 1.65 (dddd, J = 54.0, 20.5, 13.2, 6.4 Hz, 7H), 1.37 (dddd, J = 44.7, 15.0, 11.1, 7.1 Hz, 9H), 0.86 (d, J = 7.6 Hz, 18H), 0.03 (dd, J = 7.4, 4.2 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.95, 170.78, 170.52, 170.31, 135.66, 135.42, 131.32, 122.20, 122.17, 121.95, 121.92, 119.20, 100.38, 98.88, 97.62, 96.11, 70.67, 70.32, 65.90, 44.43, 40.61, 40.44, 40.27, 38.79, 38.14, 36.56, 36.16, 35.80, 35.50, 34.16, 33.99, 33.77, 33.59, 32.59, 32.52, 26.58, 26.56, 26.48, 26.45, 25.82, 24.81, 24.70, 18.03, 17.98, -4.44, -4.49, -4.56, -4.59.^{19}F NMR (376 MHz, $CDCl_3$) δ -165.21 (dddd, J = 30.4, 26.3, 17.7, 13.2 Hz), -165.67 (ttd, J = 32.7, 18.1, 8.4 Hz). HRMS (TOF MS EI) calcd for $C_{43}H_{80}Cl_2F_2N_2O_5Si_2$ $[M+H]^+$ 869.5029, found 869.5026.



S17 78

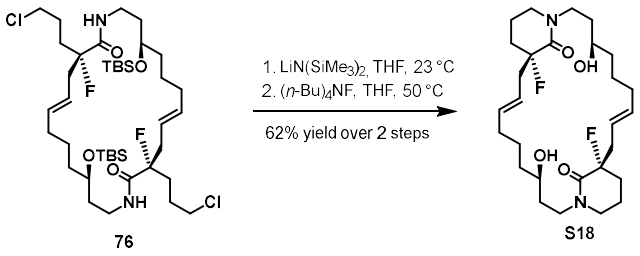
Macrocyclic bis-lactam 78: Tetrakis(triphenylphosphine)-palladium(0) (13 mg, 0.011 mmol, 0.03 equiv) was added to a solution of amine **S17** (0.33 g, 0.37 mmol) and phenylsilane (0.18 mL, 0.16 g, 1.49 mmol, 4 equiv) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 30 min when it was concentrated *in vacuo*. The

residue was purified by column chromatography (20% EtOAc-Hex then 20% MeOH-1% NH_4OH-CH_2Cl_2), concentrated *in vacuo* and submitted to the next step.

Amino acid from the previous step (0.36 g) was dissolved in anhydrous *N*,*N*-dimethylformamide (125 mL) under argon. *N*,*N*-Diisopropylethylamine (0.26 mL, 1.49 mmol, 4 equiv) and HATU (0.21 g, 0.56 mmol, 1.5 equiv) were added, the mixture turned bright yellow and was let to stir at room temperature for 70 h. DMF was distilled off under reduced pressure (0.2 mmHg) into a receiving flask cooled to –78 °C. The residue was dissolved in EtOAc (10 mL) and washed with water (3x50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc-hexanes then 40% EtOAc-hexanes) to give of macrolactam **78** (0.11 g, 0.13 mmol, 35% yield over two steps) as a single diastereomer, and as a white foam.

$[\alpha]_D^{25}$ +14.4° (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.07 (q, J = 5.1 Hz, 2H), 5.51 (dt, J = 13.9, 6.4 Hz, 2H), 5.36 – 5.25 (m, 2H), 3.89 – 3.76 (m, 2H), 3.60 – 3.39 (m, 6H), 3.21 (dq, J = 11.3, 5.4 Hz, 2H), 2.58 (ddd, J = 39.3, 14.3, 8.1 Hz, 2H), 2.38 (ddd, J = 15.2, 9.9, 6.2 Hz, 2H), 2.14 – 2.02 (m, 2H), 1.97 (q, J = 7.3 Hz, 4H), 1.87 (tt, J = 13.5, 7.1 Hz, 4H), 1.82 – 1.66 (m, 4H), 1.64 – 1.55 (m, 2H), 1.50 (ddt, J = 15.6, 10.8, 5.6 Hz, 2H), 1.47 – 1.35 (m, 2H), 1.34 – 1.26 (m, 4H), 0.90 (d, J = 1.5 Hz, 18H), 0.07 (t, J = 1.8 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.53, 170.36, 134.83, 122.28, 122.26, 100.78, 99.27, 71.65, 44.55, 40.65, 40.48, 36.21, 36.12, 34.71, 34.53, 34.39, 32.88, 29.67, 26.59, 26.57, 25.85, 24.81, 18.09, -4.59, -4.61.^{19}F NMR (376 MHz, $CDCl_3$) δ -166.43 – -167.09

(m). HRMS (TOF MS EI) calcd for $C_{40}H_{74}Cl_2F_2N_2O_4Si_2$ $[M+Na]^+$ 833.4532, found 833.4545.

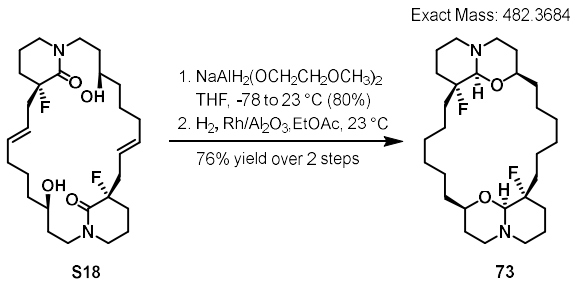


76 S18

Macrocyclic diol S18: Lithium bis(trimethylsilyl)amide (0.5M in THF, 0.75 mL, 0.38 mmol, 3.40 equiv) was added dropwise to a solution of macrocyclic bis-macrolactam **76** (90 mg, 0.11 mmol) in anhydrous THF (0.55 mL) that was heated at reflux under argon. After 15 min, saturated aq. NH_4Cl (0.5 mL) was added, and the mixture was extracted with EtOAc (2 x 2 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was submitted to the next step.

Tetra-n-butylammonium fluoride (1M in THF, 0.45 mL, 0.44 mmol, 4 equiv) was added to the flask with the residue from the previous step at 0 °C. The reaction mixture was heated to 50 °C for 2 h, when it was quenched with saturated aq. NH_4Cl (0.5 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 x 2 mL). The combined organic layers were washed with water (5 x 1 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (40% acetone-hexanes to 50% acetone-hexanes) to give macrocyclic diol **S18** (35 mg, 0.069 mmol, 62% yield over 2 steps) as a white foam.

$[\alpha]_D^{25}$ +31.1° (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 5.55 (dt, J = 15.3, 6.4 Hz, 2H), 5.37 – 5.17 (m, 2H), 3.58 – 3.39 (m, 6H), 3.28 (ddt, J = 36.1, 12.1, 4.4 Hz, 6H), 2.80 (ddd, J = 19.0, 13.1, 6.0 Hz, 2H), 2.42 (dt, J = 13.2, 8.9 Hz, 2H), 2.11 – 1.88 (m, 10H), 1.78 (ddt, J = 12.5, 7.7, 3.7 Hz, 2H), 1.74 – 1.44 (m, 10H), 1.37 (ddt, J = 13.2, 8.3, 4.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.56, 167.38, 135.85, 123.06, 122.98, 93.38, 91.99, 67.51, 48.16, 44.18, 40.31, 40.11, 35.19, 34.79, 31.75, 31.57, 31.48, 24.26, 18.76, 18.74, 18.00. ^{19}F NMR (376 MHz, $CDCl_3$) δ -143.70 (d, J = 26.3 Hz). HRMS (TOF MS EI) calcd for $C_{28}H_{44}F_2N_2O_4$ $[M+Na]^+$ 511.3269, found 511.3278.



Bis-fluoroxestospongin 73: Red-Al (0.30 mL,65% solution in toluene) was added to solution of **S18** (28 mg, 0.055 mmol) in THF (1.20 mL) at –78 °C. The solution was let to stir for 30 min at –78 °C, then 1 h at 0 °C, and finally 30 min at room temperature when it was quenched with dry MeOH (0.10 mL) followed by saturated solution of Rochelle's salt in water (0.10 mL). The mixture was let to stir for 30 min at room temperature and then extracted with EtOAc (3 x 2 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified using 1-inch reverse phase silica plug (10% water-MeOH), concentrated *in vacuo* and submitted to the next step.

Bis-1-oxaquinolizidine from the previous step (21 mg) was dissolved in dry EtOAc (1.0 mL), and 5 wt. % Rh/Al_2O_3 (10 mg) was added. The atmosphere in the flask was exchanged with hydrogen (a hydrogen balloon was inserted into the flask along with a hypodermic needle; the hypodermic needle was removed after 5 min). The solution was stirred for at room temperature for 1 h under a hydrogen atmosphere, then filtered through syringe filter (Acrodics, 13 mm, 0.2μm PFTE) and concentrated *in vacuo* to give bis-fluoroxestospongin **73** (20 mg, 0.041 mmol, 76% yield over 2 steps) as a white foam.

$[\alpha]_D^{25}$ +31.1° (*c* 0.5, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 4.33 (d, J = 6.5 Hz, 1H), 3.58 (tt, J = 10.9, 2.3 Hz, 1H), 3.20 (td, J = 13.6, 3.5 Hz, 1H), 3.08 – 2.93 (m, 2H), 2.52 – 2.35 (m, 1H), 1.89 (qt, J = 10.4, 2.4 Hz, 1H), 1.81 – 0.94 (m, 14H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -161.96 – -166.20 (m). ^{13}C NMR (126 MHz, CDCl3) δ 94.37, 93.03, 87.45, 87.21, 52.13, 44.27, 38.07, 37.90, 36.31, 31.31, 31.00, 30.83, 29.54, 26.05, 24.92, 22.39, 22.38, 20.98. HRMS (TOF MS El) calcd for $C_{28}H_{48}F_2N_2O_2$ $[M+H]^+$ 483.3684, found 483.3686.

BIOLOGICAL STUDIES SECTION

Material and Methods

Reagents

Oligomycin A, FCCP, Rotenone, and Antimycin A used to obtain the bioenergetic profiles were purchased from Sigma-Aldrich Corp. (St. Louis, MO, USA) as well as ATP.

The Xestospongine B (Xe B), extracted and purified from the *Xestospongia exigua* marine sponge, was provided by Dr. Jordi Molgo (France).

Cell Culture

Breast cell line MCF10A was maintained in DMEM/F12 supplemented with 5% (v/v) horse serum, 10 μg/ml insulin, 20 ng/ml EGF, 100 ng/ml cholera toxin and 0.5 μg/ml hydrocortisone. MCF7, MDA-MB-231, ZR75-1 and BT549 cell lines were maintained in DMEM supplemented with 10% (v/v) FBS (Hyclone, Logan, UT, USA). All cells were grown in the presence of 100 U/ml penicillin,100 μg/ml streptomycin and 0.25 μg/ ml fungizone (Gibco) at 37 ˚C (95%/5% air/CO2).

Cytoplasmic Ca^{2+} Measurement

Imaging of cytoplasmic Ca^{2+} signals was accomplished by confocal microscopy using a Nikon A1R confocal microscope equipped with Perfect Focus in a Tokai Hit incubation chamber. Cells were loaded with freshly prepared Fluo-4 (5 μM) and imaged at 37 °C and 5% CO_2. After 10 seconds of basal $[Ca^{2+}]_c$ measurement, ATP-Mg (100 μM) was added, and images were recorded every 3 s at 488 nm using a 20X objective. Images were analyzed and quantified using ImageJ (NIH).

Cellular Oxygen Consumption in Real Time

Oxygen consumption rate (OCR) as measurements of oxidative phosphorylation (OXPHOS) was measured at 37 °C using an XFe96 extracellular analyzer (Agilent, USA).

1.5 x 10^4 cells per well were seeded onto poly-lysine (Sigma-Aldrich, USA) pre-treated plates and allowed to attach for 24 h. When indicated, MCF10A and MDA-MB-231 cells were exposed to increasing concentration of either Xe B or dmXe B for 24 h and then loaded into the analyzer in fresh un-buffered Seahorse media, and basal OCR was determined. Sequential injections of 1 μM oligomycin, 250 nM FCCP and 1 μM rotenone/antimycin A were used to reveal different parameters of cellular respiration. The data were normalized for protein concentration by lysing samples after each experiment.

Cell Viability

Cell death was determined by propidium iodide (PI) incorporation (Molecular Probes) through flow cytometry. The culture medium from each well was collected in an Eppendorf tube to preserve dead cells present in the medium. Then, the plates were washed with PBS and the cells detached and collected in the respective Eppendorf tubes. The tubes were centrifuged at 2,500 rpm for 5 min at 4 °C and the supernatant was discarded. The cells pellet was resuspended in a PI solution (5 mg/mL) in 1X PBS and transferred to BD cytometer tubes. Fluorescence was detected using a BD FACSaria III flow cytometer.

Colony Formation Assay

Briefly, MDA-MB-231 cells were treated with 7.5 μM of either Xe B or dmXe B for 24 h. Then, the cells were trypsinized and counted. One thousand cells were seeded and

left undisturbed for 1 week. Finally, colonies obtained were fixed and stained with 6% glutaraldehyde and 0.5% crystal violet, analyzed and counted.

Analysis and Statistics

All statistical analyses were performed using Graph Pad Prism 4.03 (GraphPad Software, San Diego, California, USA). The data are expressed as mean ± SEM of three or more independent experiments, each one performed in technical triplicate. Statistical analysis was performed using unpaired t-tests, one-way ANOVA with Bonferroni's post-test for pairwise comparisons or two-way ANOVA. The data were considered statistically significant at the 95% level ($p < 0.05$).

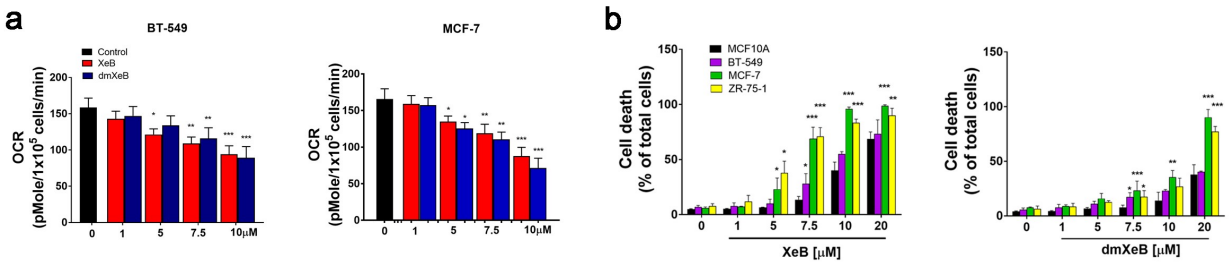
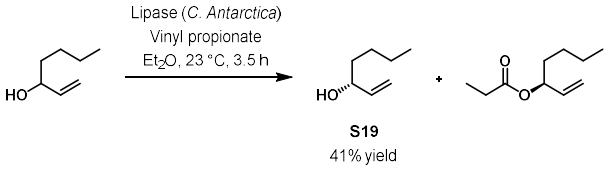
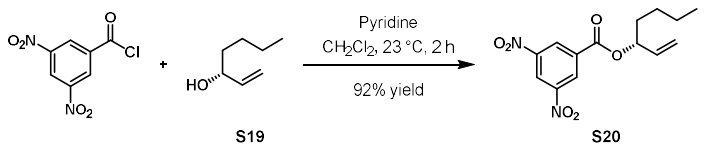


Figure 5. a. Basal oxygen consumption rate (OCR) of BT-549 (left panel) and MCF7 (right panel) cells incubated for 24 h with increasing concentration of either Xe B (red) or dmXe B (blue). The black bar represents cells basal OCR without treatment. Mean ± SEM of 3 independent experiments with 10 replicates each. *p < 0.05, **p < 0.01, ***p < 0.001 compared to respective control. **b.** MCF10A (black), BT-549 (purple), MCF7 (green) and ZR-75-1 (yellow) were treated with increasing concentrations of either Xe B (lef panel) or dmXe B (right panel) for 24 h and cell death was determined by propidium iodide incorporation by flow cytometer. Mean ± SEM of 3 independent experiments, each in triplicate. *p < 0.05, ***p < 0.001 compared to respective control.



(*R*)-Hept-1-en-3-ol (S19): Prepared according to a modification of the procedure outlined by Shaw and coworkers:[94] Acrylic supported lipase (*C. Antarctica*, 1.25 g) was added to a vigorously stirring solution of (±)-hept-1-en-3-ol (2.5 g, 21.9 mmol) in Et_2O (75 mL) and vinyl propionate (25 mL, 23.0 g, 229 mmol, 10.5 equiv.). Aliquots of the reaction (~0.4 mL) were removed approximately every 30 min. and analyzed by ^1H NMR to monitor conversion, and once the reaction had reached 50% consumption of the racemic alcohol (3.5 h), the reaction mixture was filtered through Celite (rinsing with Et_2O). The mixture was carefully concentrated on a rotary evaporator (the bath temperature was set to 20 °C with a pressure between 80 – 120 mmHg), and purified by column chromatography (3% Et_2O/ hexanes to 20% Et_2O/ hexanes). Concentration of initial fractions gave a mixture of (*S*)-hept-1-en-3-yl propionate and vinyl propionate which was not purified further. Concentration of later fractions (again on a rotary evaporator rotary with a bath temperature of 20 °C and a pressure between 80 – 120 mmHg) delivered the desired (*R*)-hept-1-en-3-ol **S19** as a clear oil (1.03 g, 8.96 mmol, 41% yield). ^1H and ^{13}C NMR spectral data and optical rotation matched that reported by Shaw.[94]

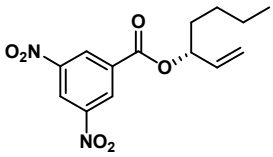


(*R*)-Hept-1-en-3-yl 3,5,-dinitrobenzoate (S20): 3,5-Dinitrobenzoyl chloride (48 mg, 0.210 mmol, 1.2 equiv) was added in one portion to a solution of alcohol **S19** (20 mg, 0.175 mmol) and pyridine (42 μL, 42 mg, 0.25 mmol, 3 equiv) in CH_2Cl_2 (2.0 mL). A white precipitate formed immediately. The solution was stirred for 2 h, then the mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (10 mL). The organic layer was dried over sodium sulfate, filtered, concentrated *in vacuo*, and purified by flash chromatography (5% Et_2O - hexanes) to give ester **S20** as a white solid (50 mg, 0.161 mmol, 92% yield). ^1H and ^{13}C NMR spectral data and optical rotation matched those reported by Shaw.[94] ee: 96% [Chiralcel ® OD-H; 5% *i*-PrOH/ hexanes, flow rate = 1 mg/ mL, detection at 210 nm; t_1= 13.6 min (major), t_1= 18.4 min (minor)].

==== Shimadzu LCsolution Analysis Report ====

C:\LabSolutions\Data\Project1\JJL-2-285-a1.lcd

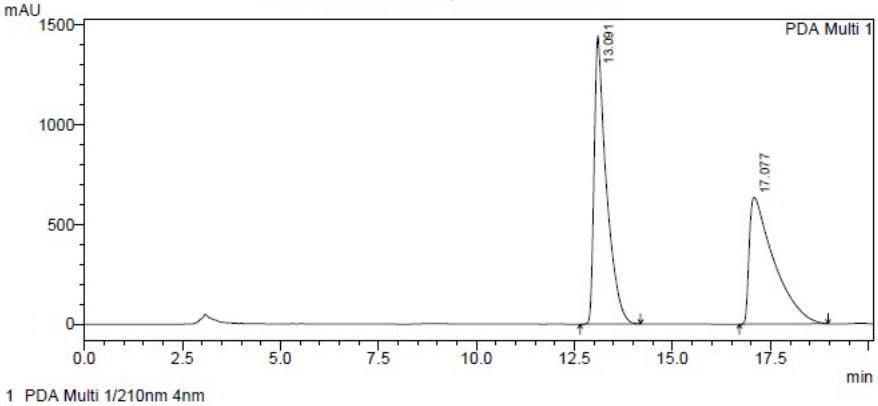
Acquired by	: Jacob L
Sample Name	: JJL-2-285-a
Sample ID	: JJL-2-285-a
Vail #	:
Injection Volume	: 10 uL
Data File Name	: JJL-2-285-a1.lcd
Method File Name	: brad.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 6/21/2017 2:43:34 PM
Data Processed	: 6/21/2017 3:03:42 PM



(±)

<Chromatogram>

C:\LabSolutions\Data\Project1\JJL-2-285-a1.lcd



1 PDA Multi 1/210nm 4nm

PeakTable

PDA Ch2

PeakTable

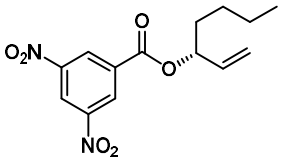
PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.091	31311646	1445237	52.911	69.449
2	17.077	27866351	635769	47.089	30.551
Total		59177997	2081006	100.000	100.000

==== Shimadzu LCsolution Analysis Report ====

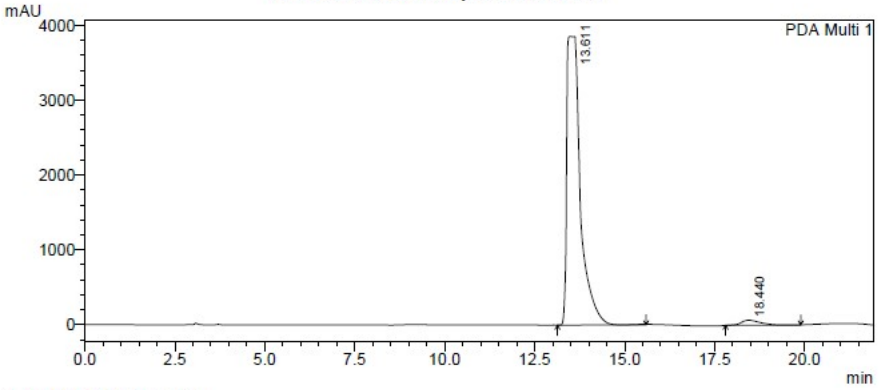
C:\LabSolutions\Data\Project1\JJL-2-291.lcd

Acquired by	: Jacob L
Sample Name	: JJL-2-291-a
Sample ID	: JJL-2-291-a
Vail #	:
Injection Volume	: 10 uL
Data File Name	: JJL-2-291.lcd
Method File Name	: brad.lcm
Batch File Name	:
Report File Name	: Default.lcr
Data Acquired	: 6/26/2017 8:22:10 AM
Data Processed	: 6/26/2017 8:44:07 AM



<Chromatogram>

C:\LabSolutions\Data\Project1\JJL-2-291.lcd



1 PDA Multi 1/210nm 4nm

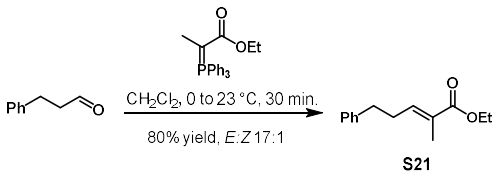
PeakTable

PDA Ch2

PeakTable

PDA Ch1 210nm 4nm

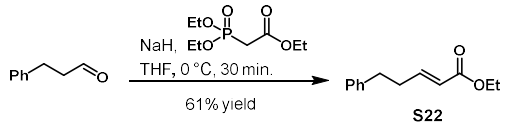
Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.611	101242167	3854607	97.775	98.347
2	18.440	2303916	64768	2.225	1.653
Total		103546083	3919375	100.000	100.000



S21

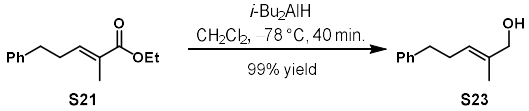
Ethyl (*E*)-2-methyl-5-phenylpent-2-enoate (S21): A solution of ethyl 2-(triphenylphosphoranylidene)propionate[95] (3.86 g, 10.7 mmol, 1.4 equiv) in CH_2Cl_2 (37 mL) was cooled to 0 °C. Hydrocinnamaldehyde (0.98 mL, 1.00 g, 7.45 mmol) was then added dropwise. The resulting solution was warmed to room temperature and stirred 30 min. The reaction mixture was then concentrated *in vacuo* and pentanes (40 mL)

were added. The solids were removed by filtration and the filtrate was concentrated *in vacuo*. This process was then repeated. The residue was purified by column chromatography (5% Et_2O - hexanes) to afford **S21** as a clear oil (1.30 g, 5.96 mmol, 80% yield, *E:Z* 17:1). ^1H and ^{13}C NMR spectral data matched those reported in the literature.[96]



S22

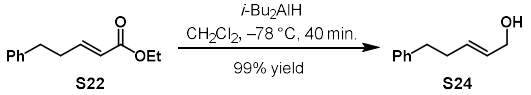
Ethyl (E)-5-phenylpent-2-enoate (S22): Ethyl 2-(diethoxyphosphoryl)acetate (10.0 g, 44.72 mmol, 1.2 equiv) was added to a suspension of NaH (1.64 g, 41.0 mmol, 1.1 equiv) in THF (70 mL) dropwise over 10 min at 0 °C. The reaction mixture was let to stir until no NaH remained in the mixture. Hydrocinnamaldehyde (5.1 mL, 5.0 g, 37.26 mmol, 1 equiv) in THF (55 mL) was then added dropwise. The resulting solution was stirred for 30 min at 0 °C. The reaction was quenched with NH_4Cl (50 mL), warmed up to room temperature, and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Ester **S22** was isolated after column chromatography (4% EtOAc-hexanes) as a clear oil (4.62 g, 22.6 mmol, 61% yield). ^1H and ^{13}C NMR spectral data matched those reported in the literature.[97]



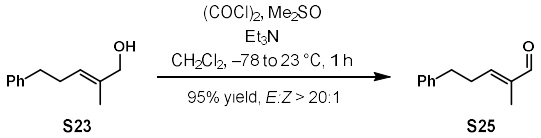
S21 S23

(*E*)-2-Methyl-5-phenylpent-2-en-1-ol (S23): A solution of **S21** (5.18 g, 23.7 mmol) in CH_2Cl_2 (180 mL) in a 3-neck 1 L round bottom flask fitted with an addition

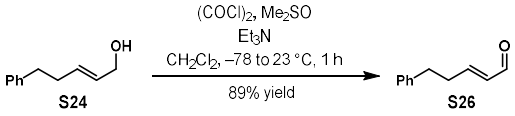
funnel was cooled to −78 °C. *i*-Bu_2AlH (12.7 mL, 10.11 g, 71.1 mmol, 3 equiv) was added to the addition funnel followed by CH_2Cl_2 (75 mL). The *i*-Bu_2AlH solution was then added to the reaction mixture dropwise over 40 min. The reaction mixture was then quenched by the dropwise addition of MeOH (6 mL) and stirred for 5 min. A saturated aqueous solution of sodium potassium tartrate (300 mL) was then added, the mixture was allowed to warm to room temperature and stirred vigorously for 2.5 h. The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 150 mL). The combined organic extracts were then washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Alcohol **S23** (4.15 g, 23.5 mmol, 99% yield) was obtained as a clear oil and submitted to the next step without further purification. ^{1}H NMR spectral data matched those reported in the literature.[98]



(*E*)-5-Phenylpent-2-en-1-ol (S24): Following the procedure outlined above, ester **S22** (14.5 g, 70.8 mmmol) in CH_2Cl_2 (250 mL) was treated with a solution of *i*-Bu_2AlH (26.8 mL, 21.4 g, 150 mmol, 2.1 equiv) in CH_2Cl_2 (100 mL) to afford alcohol **S24** (11.49 g, 70.8 mmol, 99% yield) as a clear oil which was submitted to the next step without further purification. ^{1}H NMR spectral data matched those reported in the literature.[99]

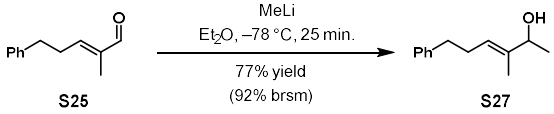


(*E*)-2-Methyl-5-phenylpent-2-enal (S25): A solution of oxalyl chloride (4.03 mL, 5.97 g, 47.0 mmol, 2 equiv) in CH_2Cl_2 (235 mL) was cooled to −78 °C. Dimethyl sulfoxide (3.67 mL, 4.04 g, 51.7 mmol, 2.2 equiv) was then added dropwise over approximately 7 minutes, and the resulting solution was stirred 20 min. A solution of alcohol **S23** (4.14 g, 23.5 mmol) in CH_2Cl_2 (23 mL, then 3 x 4 mL rinses) was added dropwise over 10 min. Triethylamine was then added (13.1 mL, 9.51 g, 93.6 mmol, 4 equiv), the cooling bath was removed, and the mixture was stirred 10 min. The reaction mixture was then poured into water (400 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 200 mL). The combined organic extracts were washed with saturated aqueous ammonium chloride, brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (15% Et_2O- hexanes) to afford **S25** as a clear oil (3.89 g, 22.3 mmol, 95% yield, *E:Z* > 20:1). *Note: the α,β–unsaturated aldehyde **S25** is unstable and should be submitted to the next step immediately*. ^1H NMR spectral data matched those reported in the literature.[98]

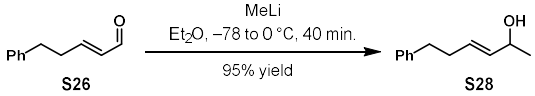


(*E*)-5-Phenylpent-2-enal (S26): Prepared according to the procedure outlined above using oxalyl chloride (5.82 mL, 8.61 g, 67.8 mmol, 2 equiv) in CH_2Cl_2 (300 mL) with dimethyl sulfoxide (5.30 mL, 5.83 g, 74.6 mmol, 2.2 equiv), followed by addition of alcohol **S24** (5.5 g, 33.9 mmol) in CH_2Cl_2 (28 mL, then 3 x 4 mL rinses), and subsequent addition of triethylamine (18.9 mL, 13.7, 0.136 mol, 4 equiv). Aldehyde **S26** (4.86 g,

30.3 mmol, 89% yield) was isolated after column chromatography (15% Et_2O-hexanes) as a clear oil. *Note: the α,β–unsaturated aldehyde **S26** is unstable and should be submitted to the next step immediately*. ^1H NMR spectral data matched those reported in the literature.[100]

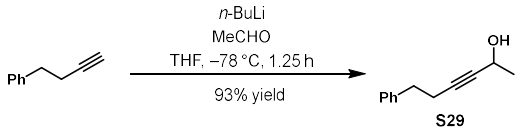


(*E*)-3-Methyl-6-phenylhex-3-en-2-ol (S27): Methyllithium (1.6 M in Et_2O, 15.3 mL, 24.6 mmol, 1.1 equiv) was added dropwise to a solution of aldehyde **S25** (3.89 g, 22.3 mmol) in Et_2O (75 mL) at −78 °C. The resulting solution was stirred 25 min, then quenched by the dropwise addition of saturated aqueous ammonium chloride (100 mL). The mixture was warmed to room temperature and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 50 mL), the combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (25% EtOAc-hexanes) to give recovered aldehyde **S25** (eluted first, 0.582 g, 3.34 mmol, 15%) and the desired alcohol **S27** (3.28 g, 17.2 mmol, 77% yield) as a clear oil. ^1H and ^{13}C NMR spectral data matched those reported in the literature.[101]

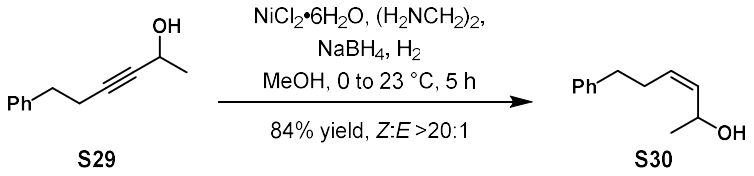


(*E*)-6-Phenylhex-3-en-2-ol (S28): Methyllithium (1.6 M in Et_2O, 21 mL, 33.3 mmol, 1.1 equiv) was added dropwise to a solution of aldehyde **S26** (4.86 g, 30.3 mmol) in Et_2O (100 mL) at −78 °C. The resulting solution was stirred 10 min, then

warmed to 0 °C and stirred an additional 30 min. The reaction was then quenched by the dropwise addition of saturated aqueous ammonium chloride (125 mL). The mixture was warmed to room temperature and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 75 mL), the combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (25% EtOAc-hexanes) to give alcohol **S28** (5.06 g, 28.7 mmol, 95% yield) as a clear oil. ^1H and ^{13}C NMR spectral data matched those reported in the literature.[102]

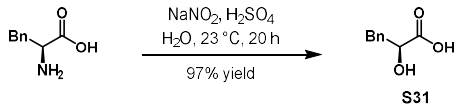


6-Phenylhex-3-yn-2-ol (S29): *n*-BuLi (2.35 M in hexanes, 8.00 mL, 18.8 mmol, 1.1 equiv) was added dropwise to a solution of 4-phenyl-1-butyne (2.23 g, 17.1 mmol) in THF (18 mL) at −78 °C and the resulting solution was stirred 30 min. A solution of freshly distilled acetaldehyde (1.44 mL, 1.13 g, 25.7 mmol, 1.5 equiv) in THF (9 mL) was then added dropwise via cannula and the mixture was stirred 45 min. at −78 °C. The reaction was then quenched by the dropwise addition of saturated aqueous ammonium chloride (50 mL), warmed to room temperature, and the layers separated. The aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc-hexanes) to afford alcohol **S29** (2.77 g, 15.9 mmol, 93% yield) as a clear oil. ^1H NMR spectral data matched those reported in the literature.[103]



S29 S30

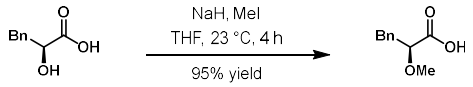
(*Z*)-6-Phenylhex-3-en-2-ol (S30): Following a modification of the procedure outlined by Gansäuer and co-workers:[104] Sodium borohydride (0.148 g, 3.92 mmol, 0.25 equiv) was added to a solution of $NiCl_2 \cdot 6H_2O$ (0.931 g, 3.92 mmol, 0.25 equiv) in MeOH (27 mL) at 0 °C. The solution immediately turned black and vigorous gas evolution was observed, along with the formation of black solids which broke into smaller pieces with vigorous stirring. The ice bath was removed, and the solution was stirred 5 min before ethylene diamine (0.52 mL, 0.472 g, 7.85 mmol, 0.5 equiv) was added (the solution turned purple), followed by a solution of alcohol **S29** (2.73 g, 15.7 mmol) in MeOH (6 mL, then 3 x 1 mL rinses). The atmosphere in the flask was exchanged with hydrogen (a hydrogen balloon was inserted into the flask along with a hypodermic needle; the hypodermic needle was removed after 10 min). The solution was stirred an additional 5 h under a hydrogen atmosphere, then filtered through Celite and concentrated *in vacuo*. The residue was purified by column chromatography (25% EtOAc-hexanes) to give alcohol **S30** (2.33 g, 13.2 mmol, 84% yield, *Z*:*E* >20:1) as a clear oil. ^{1}H and ^{13}C NMR spectral data matched those reported in the literature.[102]



S31

(*S*)-2-Hydroxy-3-phenylpropionic acid (S31): Prepared according to a modification of the procedure outlined by Castanet and coworkers:[105] L-Phenylalanine

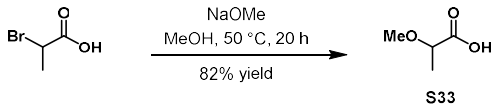
(2.0 g, 12.11 mmol) was dissolved in 1 M H_2SO_4 (24.2 mL). The solution was cooled to 0 °C and sodium nitrite (5.00 g, 72.6 mmol, 6 equiv) in H_2O (14.5 mL) was added slowly over 30 min. The reaction mixture was stirred at 0 °C for 2 h, then warmed to room temperature and stirred for another 20 h. The mixture was diluted with EtOAc (30 mL) and layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. This yielded the hydroxy acid **S31** (1.95 g, 11.7 mmol, 97% yield) as a white solid which was submitted to the next step without further purification. ^{1}H NMR spectral data matched those reported by Castanet.[iii]



S31 S32

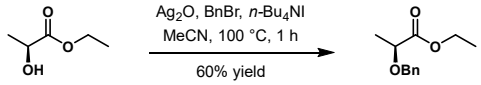
(*S*)-2-Methoxy-3-phenylpropionic acid (S32): Prepared according to a modification of the procedure outlined by Hsin and coworkers:[106] Solution of **S31** (4.64 g, 27.9 mmol) in THF (25 mL) was added to a stirred solution of NaH (5.36 g, 0.134 mol, 4.8 equiv) in THF (92 mL) at room temperature. The reaction mixture was stirred for 10 min before iodomethane (3.48 mL, 12.0 mmol, 2 equiv) was added. The reaction was stirred at room temperature for 5 h, when 1 M aqueous HCl was added until pH=1 and the resultant mixture was concentrated. The residue was treated with additional 1 M aqueous HCl (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. This yielded the acid **S32** (4.76 g, 26.4 mmol, 95% yield) which

was submitted to the next step without further purification. ^{1}H NMR spectral data matched those reported by Hsin.[2]



S33

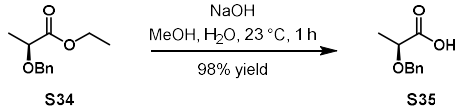
2-Methoxypropionic acid (S33): Prepared according to a modification of the procedure outlined by Hamon and coworkers:[107] Sodium methoxide (4.38M in MeOH, 25.8 mL, 0.113 mol, 2.75 equiv) was added to a solution of 2-bromopropionic acid (6.3 g, 41.2 mmol) in MeOH under argon. The reaction was stirred at 50 °C for 20 h and the resultant mixture was concentrated yielding a white salt. Concentrated HCl (2 mL) and 1 M HCl (5 mL) were added to dissolve all salts. This mixture was evaporated and Et_2O was added. The organic mixture was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to yield the acid **S33** (3.5 g, 33.6 mmol, 82% yield), which was submitted to the next step without further purification. ^{1}H NMR spectral data matched those reported by Bales and coworkers.[108]



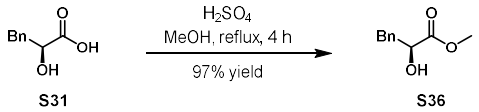
S34

Ethyl (*S*)-2-benzyloxypropionate (S34): (-)-Ethyl L-lactate (1.00 g, 8.45 mmol) was dissolved in MeCN (34 mL). Benzyl bromide (2 mL, 16.8 mmol, 2 equiv), Ag_2O (2.05 g, 8.85 mmol, 1.05 equiv.), and *n*-Bu_4NI (0.62 g, 1.69 mmol, 0.2 equiv) were added to the mixture. The reaction was stirred at 100°C for 1h. The resulting mixture was filtered through Celite with DCM and concentrated *in vacuo*. The resulting oil was diluted with H_2O and EtOAc, filtered, and the layers were separated. The aqueous layer

was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (4% EtOAc-hexanes) to afford **S34** (1.04 g, 5.00 mmol, 60% yield). Spectral data matched those reported by Kunishima and coworkers.[109]

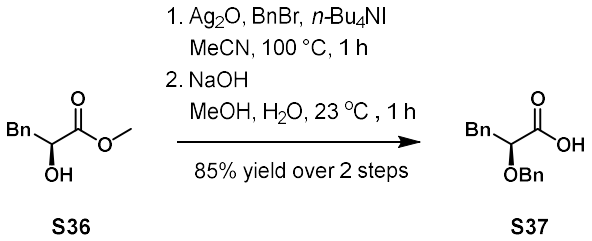


(*S*)-2-Benzyloxypropionic acid (S35): Sodium hydroxide (0.77 g, 19.2 mmol, 4 equiv) in H_2O (20 mL) was added to a solution of ester **S34** (1.00 g, 4.80 mmol) in MeOH (110 mL) at 0 °C. The reaction was warmed up to room temperature and stirred for 1 h. The resultant mixture was evaporated, diluted with H_2O, pH=11, and washed with Et_2O (3 x 10 mL). The aqueous layer was acidified with 1 M HCl until pH=2 and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. This yielded the acid **S35** (0.85 g, 4.71 mmol, 98% yield) which was submitted to the next step without further purification. ^{1}H NMR spectral data matched those reported by Matsuda and coworkers.[110]



Methyl (*S*)-2-hydroxy-3-phenylpropionate (S36): Sulfuric acid, 98% (0.14 mL, 0.1 equiv) was added to a solution of hydroxy acid **S31** (4.53 g, 27.2 mmol) in MeOH (34 mL). The reaction was heated at reflux for 4 h. The resultant mixture was concentrated and then diluted with EtOAc. The organic layer was washed with sodium

bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. This yielded the methyl ester **S36** (4.76 g, 26.4 mmol, 97% yield), which was submitted to the next step without further purification. ^{1}H NMR spectral data matched those reported by Li and coworkers.[111]

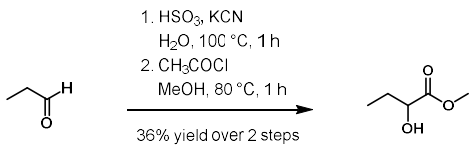


S36 **S37**

(*S*)-2-Benzyloxy-3-phenylpropionic acid (S37): Ester **S36** (3.06 g, 17.0 mmol) was dissolved in MeCN (68 mL). Benzyl bromide (4.0 mL, 34.0 mmol, 2 equiv), Ag_2O (4.14 g, 17.9 mmol, 1.05 equiv), and *n*-Bu_4NI (6.3 g, 17.0 mmol, 1 equiv) were added to the mixture. The reaction was stirred at 100 °C for 1 h. The resulting mixture was filtered through Celite with DCM and concentrated *in vacuo*. The resulting oil was diluted with H_2O and DCM, filtered, and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (4% EtOAc-hexanes) to afford the mixture of the methyl ester and the benzyl ester that was submitted to the next step without further purification.

Sodium hydroxide (2.27 g, 56.8 mmol, 4 equiv) in H_2O (19 mL) was added to a solution of the esters in MeOH (47 mL) at 0 °C. The reaction was warmed up to room temperature and stirred for 1 h. The resultant mixture was concentrated, diluted with H_2O and washed with Et_2O (3 x 10 mL). The aqueous layer was acidified with 1 M HCl until pH=1 and extracted with Et_2O (3 x 10 mL). The combined organic layers were

dried over magnesium sulfate, filtered, and concentrated *in vacuo*. This yielded acid **S37** (3.67 g, 14.3 mmol, 85% yield over 2 steps) which was submitted to the next step without further purification. ^{1}H NMR spectral data matched those reported by Zhang and coworkers.[112]

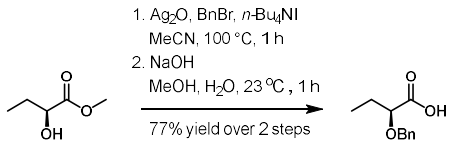


S38

Methyl 2-hydroxybutanoate (S38): A solution of $NaHSO_3$ (3.7 g, 35.97 mmol, 2.2 equiv) in H_2O (13 mL) was added to propanaldehyde (0.95 g, 16.35 mmol, 1 equiv) at room temperature. The reaction mixture was stirred for 1 h, then the mixture was cooled to 0 ˚C, and a solution of KCN (2.34 g, 35.97 mmol, 2.2 equiv) in H_2O (9 mL) was added dropwise. After stirring for 10 min at 0 ˚C, the reaction mixture was warmed to room temperature and stirred for 1 h. The resulting mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting 2-hydroxybutanenitrile was submitted to the next step without further purification.

Acetyl chloride (9.20 mL, 0.129 mmol, 10 equiv) was added dropwise to MeOH (26 mL) at -20 ˚C, and the mixture wasstirred for 10 min. Then, the mixture was added to propionyl cyanide (1.1 g, 12.9 mmol, 1 equiv) in MeOH (17 mL) dropwise at -20 ˚C. Mixture was warmed to room temperature, and then heated at reflux for 1 h. MeOH was evaporated *in vacuo*, and the residue was diluted with Et_2O (10 mL) and washed with sat. $NaHCO_3$ twice. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. This yielded ester **S38** (0.70 g, 5.93 mmol, 36% yield over 2

steps) which was submitted to the next step without further purification. ^{1}H NMR spectral data matched those reported by Miller and Kolasa. [113]

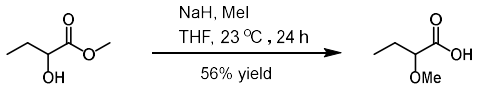


S38 S39

2-(Benzyloxy)butanoic acid (S39): Ester **S38** (0.32 g, 2.69 mmol, 1 equiv) was dissolved in MeCN (10.8 mL). Benzyl bromide (0.64 mL, 5.38 mmol, 2 equiv), Ag_2O (0.65 g, 2.82 mmol, 1.05 equiv), and *n*-Bu_4NI (0.99 g, 2.69 mmol, 1 equiv) were added to the mixture. The reaction was stirred at 100 °C for 1 h. The resulting mixture was filtered through Celite with CH_2Cl_2 and concentrated *in vacuo*. The resulting oil was diluted with H_2O and CH_2Cl_2, filtered, and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (4% EtOAc-hexanes) to afford the mixture of the methyl ester and the benzyl ester that was submitted to the next step without further purification.

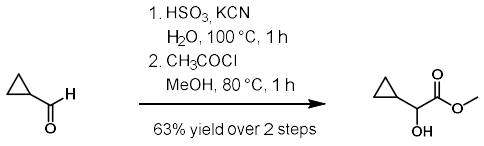
Sodium hydroxide (0.20 g, 8.00 mmol, 4 equiv) in H_2O (2.50 mL) was added to a solution of the esters in MeOH (13 mL) at 0 °C. The reaction was warmed up to room temperature and stirred for 1 h. The resultant mixture was concentrared, diluted with H_2O and washed with Et_2O (3 x 10 mL). The aqueous layer was acidified with 1 M HCl until pH=1 and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. This yielded acid **S39** (0.31 g, 2.60 mmol, 77% yield over 2 steps) which was submitted to the next step

without further purification. ^{1}H NMR spectral data matched those reported by Selfridge and Feldman.[114]



S38 S40

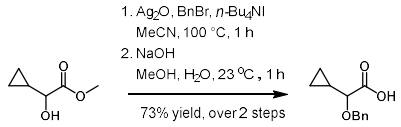
2-Methoxybutanoic acid (S40): The solution of **S38** (0.50 g, 4.24 mmol, 1 equiv) in THF (3 mL) was added dropwise to a suspension of NaH (0.81g, 20.3 mmol, 4.8 equiv) in THF (14 mL). The reaction was stirred for 10 min at room temperature, then MeI (1.20g, 8.48 mmol, 2 equiv) was added. It was stirred for 24 h at room temperature, then quenched with water (5 mL) at 0 ˚C and the mixture was concentrated *in vacuo*. The resulting liquid was washed with Et_2O (3 x 10 mL). The aqueous layer was acidified with 1 M HCl until pH=1 and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. This yielded acid **S40** (0.28 g, 2.37 mmol, 56% yield) which was submitted to the next step without further purification. ^{1}H NMR spectral data matched those reported by Steckel and Reeve.[115]



S41

Methyl 2-cyclopropyl-2-hydroxyacetate (S41): Solution of $NaHSO_3$ (4.2 g, 40.06 mmol, 2.2 equiv) in H_2O (15 mL) was added to cyclopropanecarbaldehyde (1.28 g, 18.21 mmol, 1 equiv) at room temperature. The reaction mixture was stirred for 1 h, then cooled to 0 ˚C, and a solution of KCN (2.61 g, 40.06 mmol, 2.2 equiv) in H_2O (10

mL) was added dropwise. After stirring for 10 min at 0 ˚C, the reaction mixture was warmed to the room temperature and stirred for 1 h. The resulting mixture was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. This yielded 2-cyclopropyl-2-hydroxyacetonitrile which was submitted to the next step without further purification. Acetyl chloride (12 mL, 170 mmol, 10 equiv) was added dropwise to MeOH (36 mL) at -20 ˚C, and the mixture was stirred for 10 min. Then, the mixture was added to 2-cyclopropyl-2-hydroxyacetonitrile (1.65 g, 17 mmol, 1 equiv) in MeOH (20 mL) dropwise at -20 ˚C. Mixture was warmed to room temperature, and then heated at reflux for 1 h. MeOH was evaporated *in vacuo*, and the residue was diluted with Et_2O (10 mL) and washed with sat. $NaHCO_3$ twice. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. This yielded ester **S41** (1.50 g, 11.5 mmol, 63% yield over 2 steps) which was submitted to the next step without further purification. ^1H NMR spectral data matched those reported by Walton and coworkers.[116]



S41 S42

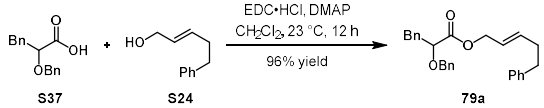
2-Benzyloxy-2-cyclopropylacetic acid (42): Ester **S41** (0.32 g, 2.46 mmol, 1 equiv) was dissolved in MeCN (10 mL). Benzyl bromide (0.58 mL, 4.93 mmol, 2 equiv), Ag_2O (0.60 g, 2.59 mmol, 1.05 equiv), and *n*-Bu_4NI (0.90 g, 2.46 mmol, 1 equiv) were added to the mixture. The reaction mixture was stirred at 100 °C for 1 h. The resulting mixture was filtered through Celite with CH_2Cl_2 and concentrated *in vacuo*. The

resulting oil was diluted with H_2O and CH_2Cl_2, filtered, and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The mixture of methyl ester and benzyl ester was submitted to the next step without further purification.

Sodium hydroxide (0.55 g, 13.71 mmol, 4 equiv) in H_2O (5 mL) was added to a solution of esters in MeOH (11.5 mL) at 0 °C. The reaction was warmed up to room temperature and stirred for 1 h. The resultant mixture was evaporated, diluted with H_2O and washed with Et_2O (3 x 10 mL). The aqueous layer was acidified with 1 M HCl until pH=1 and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. This yielded acid **S42** (0.37 g, 1.79 mmol, 73% yield over 2 steps) which was submitted to the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, J = 3.6, 1.2 Hz, 4H), 7.33 – 7.29 (m, 1H), 4.72 (dd, J = 11.7, 4.8 Hz, 1H), 4.62 – 4.51 (m, 1H), 3.52 – 3.42 (m, 1H), 1.26 – 1.15 (m, 1H), 0.71 – 0.59 (m, 2H), 0.55 – 0.51 (m, 1H), 0.48 – 0.37 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.55, 137.03, 128.40, 128.25, 127.96, 127.94, 80.42, 71.90, 13.34, 3.76, 1.98. HRMS (ESI) calcd for $C_{12}H_{15}O_3$ $[M + H]^+$ 207.1016, found 207.1010.

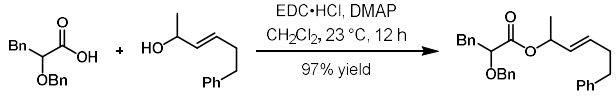
GENERAL PROCEDURE I:



S37 S24 79a

(*E*)-5-Phenylpent-2-en-1-yl 2-(benzyloxy)-3-phenylpropanoate (79a): EDC·HCl (1.53 g, 8.00 mmol, 2 equiv), was added to a solution of acid **S37** (1.50 g, 6.00 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL). A solution of alcohol **S24** (0.649 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (4 mL, then 3 x 1 mL rinses) was then added, followed by the addition of 4-dimethylaminopyridine (0.147 g, 1.20 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, then diluted with additional CH_2Cl_2 (100 mL) and washed with brine (100 mL). The organic layer was dried with sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (3% EtOAc-hexanes) to give ester **79a** (1.53 g, 3.82 mmol, 96% yield) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 10H), 7.30 (td, J = 5.6, 2.7 Hz, 5H), 5.91 (dtt, J = 14.7, 6.7, 1.3 Hz, 1H), 5.66 (dtt, J = 15.7, 6.5, 1.5 Hz, 1H), 4.80 (d, J = 11.9 Hz, 1H), 4.72 – 4.63 (m, 2H), 4.49 (d, J = 11.9 Hz, 1H), 4.27 (dd, J = 8.2, 5.0 Hz, 1H), 3.26 – 3.11 (m, 2H), 2.82 (dd, J = 8.8, 6.8 Hz, 2H), 2.50 (tdd, J = 7.9, 6.7, 1.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.62, 141.18, 137.18, 136.84, 135.51, 129.33, 128.19, 128.16, 128.06, 128.05, 127.61, 127.47, 126.42, 125.75, 123.92, 79.02, 72.16, 65.18, 39.13, 35.03, 33.75. HRMS (ESI) calcd for $C_{27}H_{29}O_3$ $[M + H]^+$ 401.2111, found 401.2106.

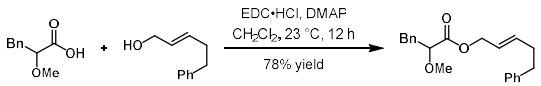


S37 S28 79b

(*E*)-5-Phenylpent-2-en-1-yl 2-(benzyloxy)-3-phenylpropanoate (79b): The title compound was prepared according to General Procedure I using EDC·HCl (1.53 g, 8.00i mmol, 2 equiv), acid **S37** (1.54 g, 6.00 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL), followed by addition of alcohol **S28** (0.705 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (3 mL, then

3 x 1 mL rinses) and 4-dimethylaminopyridine (0.147 g, 1.20 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **79b** was isolated after column chromatography (3% EtOAc-hexanes) as a clear oil (1.61 g, 3.88 mmol, 97% yield, inconsequential mixture of diastereomers).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.21 (m, 10H), 7.17 (tdt, J = 5.1, 3.5, 1.5 Hz, 5H), 5.72 (ddd, J = 21.6, 15.1, 6.8 Hz, 1H), 5.50 – 5.27 (m, 2H), 4.65 (overlapping doublets, J = 11.8, 6.8 Hz, 1H), 4.35 (d, J = 11.8 Hz, 1H), 4.09 (ddd, J = 8.0, 5.2, 2.7 Hz, 1H), 3.11 – 2.94 (m, 2H), 2.68 (dt, J = 10.8, 7.8 Hz, 2H), 2.34 (dtd, J = 15.9, 9.1, 8.6, 4.2 Hz, 2H), 1.27 (d, J = 6.2 Hz, 1.30H (minor diastereomer)), 1.21 (d, J = 6.4 Hz, 1.70H (major diastereomer)). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.35, 171.33, 141.47, 141.46, 137.40, 137.05, 137.02, 132.68, 132.57, 129.79, 129.69, 129.53, 129.52, 128.39, 128.38, 128.28, 128.23, 128.19, 128.18, 127.79, 127.78, 127.63, 127.62, 126.55, 126.53, 125.86, 79.29, 79.27, 72.26, 71.76, 71.71, 39.25, 39.21, 35.34, 35.32, 33.90, 33.88, 20.34, 20.21. HRMS (ESI) calcd for $C_{28}H_{31}O_3$ $[M + H]^+$ 415.2268, found 415.2270.

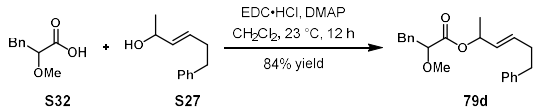


S34 S24 79c

(*E*)-5-Phenylpent-2-en-1-yl 2-methoxy-3-phenylpropanoate (79c): The title compound was prepared according to General Procedure I using EDC·HCl (1.53 g, 8.00 mmol, 2 equiv), acid **S34** (1.08 g, 6.00 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL), followed by addition of alcohol **S24** (0.649 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (3 mL, then 3 x 1 mL rinses) and 4-dimethylaminopyridine (0.147 g, 1.20 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **79c** was isolated after column

chromatography (5% EtOAc-hexanes) as a clear oil (1.01 g, 3.11 mmol, 78% yield, inconsequential mixture of diastereomers).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 6.95 (m, 10H), 5.86 – 5.69 (m, 1H), 5.54 (dddd, J = 13.1, 7.9, 6.5, 1.4 Hz, 1H), 4.56 (dd, J = 6.6, 1.2 Hz, 2H), 3.97 (ddd, J = 7.7, 5.3, 1.2 Hz, 1H), 3.35 (d, J = 0.8 Hz, 3H), 3.02 (t, J = 6.3 Hz, 1H), 2.70 (t, J = 7.8 Hz, 2H), 2.38 (q, J = 7.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.68, 141.27, 136.81, 135.70, 129.24, 128.26, 128.22, 128.17, 126.53, 125.80, 123.93, 81.59, 65.29, 58.12, 39.02, 35.08, 33.81. HRMS (ESI) calcd for $C_{21}H_{25}O_3$ $[M + H]^+$ 325.1798, found 325.1789.

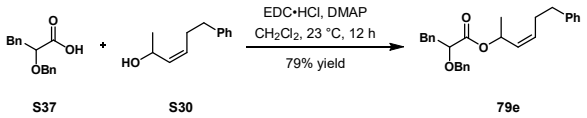


S32 S27 79d

(*E*)-6-Phenylhex-3-en-2-yl 2-methoxy-3-phenylpropanoate (79d): The title compound was prepared according to General Procedure I using EDC·HCl (1.15 g, 6.00 mmol, 1.5 equiv), acid **S32** (0.721 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (20 mL), followed by addition of alcohol **S27** (0.740 g, 4.2 mmol, 1.05 equiv) in CH_2Cl_2 (4 mL, then 3 x 1 mL rinses) and 4-dimethylaminopyridine (0.147 g, 1.20 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **79d** was isolated after column chromatography (5% EtOAc-hexanes) as a clear oil (1.13 g, 3.34 mmol, 84% yield, inconsequential ~2:1 mixture of diastereomers).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.12 (m, 10H), 5.78 – 5.64 (m, 1H), 5.50 – 5.29 (m, 2H), 3.93 (ddd, J = 7.2, 5.7, 1.4 Hz, 1H), 3.34 (s, J = 4.1, 1.4 Hz, 3H), 3.00 (td, J = 7.4, 6.5, 3.6 Hz, 2H), 2.68 (q, J = 6.9, 6.3 Hz, 2H), 2.43 – 2.21 (m, 2H), 1.30 – 1.25 (m, 1H (minor diastereomer), 1.20 (dd, J = 6.4, 1.5 Hz, 2H (major diastereomer)). ^{13}C NMR

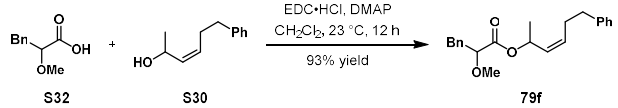
(126 MHz, $CDCl_3$) δ 171.26, 141.45, 141.44, 136.93, 136.90, 132.69, 132.59, 129.76, 129.65, 129.37, 129.36, 128.37, 128.30, 128.26, 128.22, 128.21, 126.58, 126.56, 125.83, 81.76, 81.74, 71.72, 71.66, 58.09, 58.08, 39.07, 39.03, 35.29, 35.29, 33.85, 33.84, 20.30, 20.14. HRMS (ESI) calcd for $C_{22}H_{27}O_3$ $[M + H]^+$ 339.1955, found 339.1963.



(*Z*)-6-Phenylhex-3-en-2-yl 2-(benzyloxy)-3-phenylpropanoate (79e): The title compound was prepared according to General Procedure I using EDC·HCl (0.882 g, 4.60 mmol, 1.5 equiv), acid **S37** (0.749 g, 3.10 mmol, 1 equiv) in CH_2Cl_2 (14 mL), followed by addition of alcohol **S30** (0.545 g, 3.10 mmol, 1 equiv) in CH_2Cl_2 (3 mL, then 3 x 1 mL rinses) and 4-dimethylaminopyridine (0.110 g, 0.930 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **79e** was isolated after column chromatography (6% EtOAc-hexanes) as a clear oil (1.02 g, 2.46 mmol, 79% yield, inconsequential mixture of diastereomers).

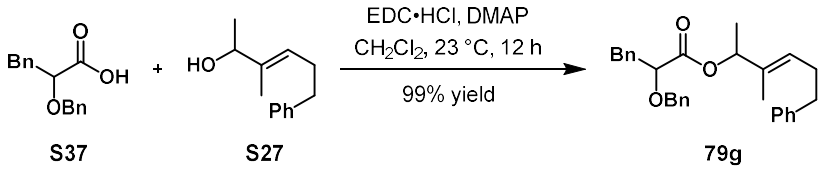
^1H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.11 (m, 15H), 5.68 – 5.60 (m, 1H), 5.53 (tt, J = 10.2, 7.5 Hz, 1H), 5.33 (dddt, J = 25.5, 10.7, 9.1, 1.6 Hz, 1H), 4.64 (dd, J = 11.8, 3.3 Hz, 1H), 4.33 (d, J = 11.8 Hz, 1H), 4.07 (dd, J = 8.2, 5.1 Hz, 1H), 3.08 – 2.95 (m, 2H), 2.75 (ddd, J = 14.2, 8.4, 6.3 Hz, 1H), 2.64 (dtd, J = 13.5, 7.8, 5.3 Hz, 1H), 2.55 – 2.39 (m, 2H), 1.15 (d, J = 6.4 Hz, 1.30H (minor diastereomer)), 1.09 (d, J = 6.4 Hz, 1.70H (major distereomer)). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.29, 171.27, 141.37, 141.36, 137.40, 137.38, 137.08, 137.01, 132.16, 132.15, 129.52, 129.52, 129.50, 129.44, 128.51, 128.49, 128.29, 128.28, 128.22, 128.21, 128.18, 128.16, 127.77, 127.76, 127.61, 127.60, 126.54,

126.51, 125.90, 125.89, 79.24, 79.22, 72.23, 72.21, 67.58, 39.24, 39.19, 35.58, 35.57, 29.56, 29.53, 20.62, 20.52. HRMS (ESI) calcd for $C_{27}H_{29}O_3$ $[M + H]^+$ 401.2195, found 401.2183.



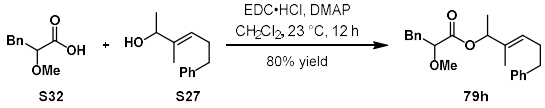
(*Z*)-6-Phenylhex-3-en-2-yl 2-methoxy-3-phenylpropanoate (79f): The title compound was prepared according to General Procedure I using EDC·HCl (1.15 g, 6.00 mmol, 1.5 equiv), acid **S32** (0.811 g, 4.50 mmol, 1.5 equiv) in CH_2Cl_2 (15 mL), followed by addition of alcohol **S30** (0.529 g, 3.00 mmol, 1 equiv) in CH_2Cl_2 (2 mL, then 3 x 0.75 mL rinses) and 4-dimethylaminopyridine (0.110 g, 0.900 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **79f** was isolated after column chromatography (5% EtOAc-hexanes) as a clear oil (0.942 g, 2.78 mmol, 93% yield, inconsequential 1:1 mixture of diastereomers).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 4H), 7.24 – 7.21 (m, 3H), 7.19 (d, J = 7.5 Hz, 3H), 5.67 – 5.60 (m, 1H), 5.52 (ttd, J = 10.8, 7.5, 1.0 Hz, 1H), 5.33 (dddt, J = 30.6, 10.7, 9.1, 1.5 Hz, 1H), 3.91 (ddd, J = 7.1, 5.4, 1.7 Hz, 1H), 3.33 (overlapping singlets, 3H), 3.01 – 2.95 (m, 2H), 2.74 (ddd, J = 14.3, 8.5, 6.3 Hz, 1H), 2.63 (dtd, J = 13.3, 7.8, 5.0 Hz, 1H), 2.54 – 2.40 (m, 2H), 1.15 (d, J = 6.5 Hz, 1.5H), 1.08 (d, J = 6.4 Hz, 1.5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.23, 171.22, 141.36, 136.96, 136.89, 132.17, 129.46, 129.36, 129.35, 129.34, 128.49, 128.47, 128.27, 128.25, 128.23, 128.21, 126.57, 126.55, 125.88, 125.87, 81.73, 81.71, 67.54, 67.53, 58.09, 58.06, 39.06, 39.01, 35.54, 29.52, 29.49, 20.58, 20.46. HRMS (ESI) calcd for $C_{22}H_{27}O_3$ $[M + H]^+$ 339.1955, found 339.1965.



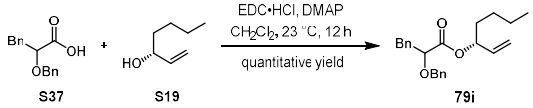
(*E*)-3-Methyl-6-phenylhex-3-en-2-yl 2-(benzyloxy)-3-phenylpropanoate (79g): The title compound was prepared according to General Procedure I using EDC·HCl (1.04 g, 5.44 mmol, 2 equiv), acid **S37** (0.662 g, 4.08 mmol, 1.5 equiv) in CH_2Cl_2 (16 mL), followed by addition of alcohol **S27** (0.520 g, 2.74 mmol, 1 equiv) in CH_2Cl_2 (2 mL, then 3 x 1 mL rinses) and 4-dimethylaminopyridine (0.147 g, 1.20 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **79g** was isolated after column chromatography (5% EtOAc-hexanes) as a clear oil (1.17 g, 2.73 mmol, 99% yield, inconsequential mixture of diastereomers).

^{1}H NMR (500 MHz, $CHCl_3$) δ 7.31 – 7.21 (m, 10H), 7.20 – 7.13 (m, 5H), 5.51 (tq, J = 7.1, 1.2 Hz, 1H), 5.32 (dq, J = 17.0, 6.5 Hz, 1H), 4.67 (overlapping doublets, J = 11.8, 9.2 Hz, 1H), 4.35 (dd, J = 11.9, 1.5 Hz, 1H), 4.11 (ddd, J = 8.4, 5.2, 2.0 Hz, 1H), 3.11 – 2.96 (m, 2H), 2.66 (q, J = 7.8 Hz, 2H), 2.35 (qd, J = 8.1, 7.7, 3.5 Hz, 2H), 1.53 (d, J = 1.2 Hz, 2H (major diastereomer)), 1.50 (d, J = 1.2 Hz, 1H (minor diastereomer)), 1.28 (d, J = 6.6 Hz, 1H (minor diastereomer)), 1.21 (d, J = 6.5 Hz, 2H (major diastereomer)). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.30, 141.75, 137.45, 137.43, 137.12, 137.07, 134.66, 134.53, 129.49, 129.48, 128.42, 128.23, 128.21, 128.19, 127.76, 127.71, 127.62, 127.59, 126.83, 126.53, 126.52, 126.51, 125.79, 79.32, 79.22, 76.09, 75.99, 72.25, 72.20, 39.27, 39.23, 35.48, 35.45, 29.46, 19.05, 18.91, 11.89, 11.80. HRMS (ESI) calcd for $C_{29}H_{33}O_3$ $[M + H]^+$ 429.2424, found 429.2437.



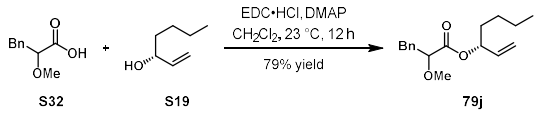
(*E*)-3-Methyl-6-phenylhex-3-en-2-yl 2-methoxy-3-phenylpropanoate (79h): The title compound was prepared according to General Procedure I using EDC·HCl (1.15 g, 6.00 mmol, 1.5 equiv), acid **S32** (0.721 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (20 mL), followed by addition of alcohol **S27** (0.761 g, 4.00 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL, then 3 x 1 mL rinses) and 4-dimethylaminopyridine (0.147 g, 1.20 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **79h** was isolated after column chromatography (5% EtOAc-hexanes) as a clear oil (1.13 g, 3.34 mmol, 80% yield, inconsequential ~3:1 mixture of diastereomers).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.14 (m, 10H), 5.49 (t, J = 7.2 Hz, 1H), 5.30 (dq, J = 13.1, 6.6 Hz, 1H), 3.97 – 3.81 (m, 1H), 3.34 (s, 3H), 3.00 (d, J = 6.6 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H), 2.33 (qd, J = 7.4, 2.7 Hz, 2H), 1.51 (d, J = 1.3 Hz, 3H), 1.28 (d, J = 6.5 Hz, 0.8H (minor diastereomer)), 1.19 (d, J = 6.5 Hz, 2.2H (major diastereomer). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.23, 141.73, 137.02, 136.95, 134.62, 134.49, 130.00, 129.32, 129.29, 128.41, 128.31, 128.23, 128.21, 128.10, 126.83, 126.56, 126.53, 126.50, 125.77, 81.79, 81.74, 76.03, 75.90, 58.13, 58.05, 39.10, 39.07, 35.44, 35.43, 29.41, 19.02, 18.83, 11.84, 11.73. HRMS (ESI) calcd for $C_{23}H_{29}O_3$ $[M + H]^+$ 353.2111, found 353.2118.



(*R*)-Hept-1-en-3-yl 2-(benzyloxy)-3-phenylpropanoate (79i): The title compound was prepared according to General Procedure I using EDC·HCl (0.740 g, 3.86 mmol, 2 equiv), acid **S37** (0.741 g, 2.90 mmol, 1.5 equiv) in CH_2Cl_2 (14 mL), followed by addition of alcohol **S19** (0.221 g, 1.93 mmol, 1 equiv) in CH_2Cl_2 (2 mL, then 2 x 1 mL rinses) and 4-dimethylaminopyridine (70.7 mg, 0.579 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **79i** was isolated after column chromatography (4% EtOAc-hexanes) as a clear oil (0.679 g, 1.93 mmol, quantitative yield, inconsequential mixture of diastereomers).

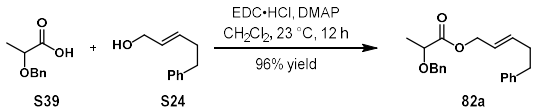
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 8H), 7.15 (dd, J = 7.2, 2.4 Hz, 2H), 5.74 (overlapping multiplets, J = 29.1, 17.2, 10.5, 6.6 Hz, 1H), 5.33 – 5.09 (m, 3H), 4.67 (overlapping doublets, J = 11.8, 2.8 Hz, 1H), 4.36 (dd, J = 11.8, 1.4 Hz, 1H), 4.13 (ddd, J = 8.2, 5.0, 3.2 Hz, 1H), 3.12 – 2.98 (m, 2H), 1.65 – 1.54 (m, 2H), 1.35 – 1.17 (m, 4H), 0.89 (overlapping triplets, J = 12.5, 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.46, 171.43, 137.36, 137.04, 137.03, 136.25, 136.12, 129.52, 129.50, 128.23, 128.22, 128.20, 127.76, 127.75, 127.63, 126.58, 126.56, 117.20, 117.00, 79.32, 79.25, 75.58, 75.56, 72.27, 72.25, 39.31, 39.24, 33.82, 33.75, 27.14, 27.08, 22.38, 22.36, 13.93, 13.89. HRMS (ESI) calcd for $C_{23}H_{29}O_3$ $[M + H]^+$ 353.2111, found 353.2103.



(*R*)-Hept-1-en-3-yl 2-methoxy-3-phenylpropanoate (79j): The title compound was prepared according to General Procedure I using EDC·HCl (1.15 g, 6.00

mmol, 1.5 equiv), acid **S32** (0.721 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (20 mL), followed by addition of alcohol **S19** (0.460 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (4 mL, then 3 x 1 mL rinses) and 4-dimethylaminopyridine (0.147 g, 1.20 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **79j** was isolated after column chromatography (5% EtOAc-hexanes) as a clear oil (0.872 g, 3.15 mmol, 79% yield, inconsequential mixture of diastereomers).

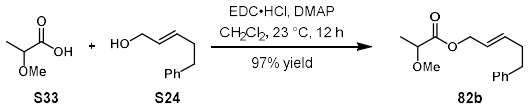
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.15 (m, 5H), 5.77 (ddd, J = 17.2, 10.5, 6.6 Hz, 1H), 5.35 – 5.21 (m, 2H), 5.17 (dt, J = 10.5, 1.2 Hz, 1H), 3.97 (dd, J = 7.8, 5.5 Hz, 1H), 3.35 (s, 3H), 3.02 (t, J = 6.3 Hz, 2H), 1.67 – 1.46 (m, 2H), 1.36 – 1.24 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.38, 136.90, 136.20, 129.41, 129.33, 129.30, 128.24, 128.23, 126.59, 116.99, 81.87, 75.49, 58.13, 39.15, 33.76, 33.66, 27.09, 27.01, 22.30, 13.83. HRMS (ESI) calcd for $C_{17}H_{25}O_3$ $[M + H]^+$ 277.1798, found 277.1804.



S39 S24 82a

(*E*)-5-Phenylpent-2-en-1-yl 2-(benzyloxy)propanoate (82a): The title compound was prepared according to General Procedure I using EDC·HCl (1.72 g, 9.00 mmol, 2 equiv), acid **S39** (1.08 g, 6.80 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL), followed by addition of alcohol **S24** (1.08 g, 6.80 mmol, 1 equiv) in CH_2Cl_2 (3 mL, then 3 x 1 mL rinses) and 4-dimethylaminopyridine (0.165 g, 1.35 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **82a** was isolated after column chromatography (3% EtOAc-hexanes) as a clear oil (1.40 g, 4.31 mmol, 96% yield).

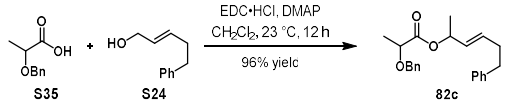
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 4H), 7.31 – 7.25 (m, 3H), 7.22 – 7.09 (m, 3H), 5.88 – 5.78 (m, 1H), 5.61 (dtt, J = 15.5, 6.5, 1.5 Hz, 1H), 4.69 (d, J = 11.6 Hz, 1H), 4.63 – 4.56 (m, 2H), 4.45 (d, J = 11.6 Hz, 1H), 4.06 (q, J = 6.8 Hz, 1H), 2.71 (dd, J = 8.9, 6.7 Hz, 2H), 2.39 (tdd, J = 7.8, 6.7, 1.3 Hz, 2H), 1.44 (m, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.92, 141.35, 137.54, 135.67, 128.34, 128.33, 128.28, 127.90, 127.75, 125.87, 124.13, 74.01, 71.93, 65.30, 35.21, 33.91, 18.65. HRMS (ESI) calcd for $C_{21}H_{25}O_3$ $[M + H]^+$ 325.1798, found 325.1791.



S33 S24 82b

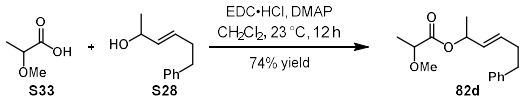
(*E*)-5-Phenylpent-2-en-1-yl 2-methoxypropanoate (82b): The title compound was prepared according to General Procedure I using EDC·HCl (1.53 g, 8.00 mmol, 2 equiv), acid **S33** (0.625 g, 6.00 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL), followed by addition of alcohol **S24** (0.649 g, 4.00 mmol) in CH_2Cl_2 (4 mL, then 3 x 1 mL rinses) and 4-dimethylaminopyridine (0.147 g, 1.20 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **82b** was isolated after column chromatography (5% EtOAc-hexanes) as a clear oil (0.959 g, 3.86 mmol, 97% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.21 (m, 2H), 7.23 – 7.05 (m, 3H), 5.92 – 5.73 (m, 1H), 5.61 (dtt, J = 15.6, 6.5, 1.4 Hz, 1H), 4.69 – 4.34 (m, 2H), 3.87 (q, J = 6.8 Hz, 1H), 3.39 (s, 3H), 2.71 (dd, J = 8.8, 6.7 Hz, 2H), 2.39 (tdd, J = 7.8, 6.5, 1.3 Hz, 2H), 1.40 (d, J = 6.9 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 172.70, 141.24, 135.62, 128.24, 128.17, 125.76, 124.01, 76.23, 65.20, 57.48, 35.08, 33.79, 18.25. HRMS (ESI) calcd for $C_{15}H_{21}O_3$ $[M + H]^+$ 249.1485, found 249.1491.



(*E*)-6-Phenylhex-3-en-2-yl 2-(benzyloxy)propanoate (82c): The title compound was prepared according to General Procedure I using EDC·HCl (1.53 g, 8.00 mmol, 2 equiv), acid **S35** (1.08 g, 6.00 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL), followed by addition of alcohol **S24** (0.705 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (3 mL, then 3 x 1 mL rinses) and 4-dimethylaminopyridine (0.147 g, 1.20 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **82c** was isolated after column chromatography (5% EtOAc-hexanes) as a clear oil (1.30 g, 3.84 mmol, 96% yield, inconsequential mixture of diastereomers).

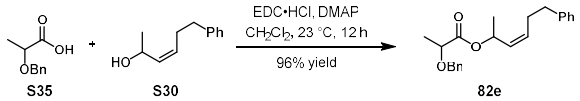
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (m, 4H), 7.31 – 7.25 (m, 3H), 7.20 – 7.13 (m, 3H), 5.81 – 5.74 (m, 1H), 5.50 (dddt, J = 15.2, 13.6, 6.8, 1.4 Hz, 1H), 5.43 – 5.37 (m, 1H), 4.68 (dd, J = 11.6, 8.1 Hz, 1H), 4.43 (d, J = 11.6 Hz, 1H), 4.02 (qd, J = 6.9, 4.2 Hz, 1H), 2.69 (q, J = 8.1 Hz, 2H), 2.39 – 2.31 (m, 2H), 1.42 (t, J = 7.1 Hz, 3H), 1.31 (dd, J = 6.4, 4.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.38, 172.37, 141.41, 141.38, 137.60, 132.60, 132.47, 129.80, 129.77, 128.34, 128.30, 128.22, 128.21, 127.88, 127.70, 125.80, 125.79, 74.10, 74.09, 71.82, 71.51, 71.48, 35.31, 35.29, 33.86, 33.83, 20.33, 20.26, 18.58, 18.56. HRMS (ESI) calcd for $C_{22}H_{27}O_3$ $[M + H]^+$ 339.1955, found 339.1947.



(*E*)-6-Phenylhex-3-en-2-yl 2-methoxypropanoate (82d): The title compound was prepared according to General Procedure I using EDC·HCl (1.15 g, 6.00 mmol, 1.5

equiv), acid **S33** (0.416 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (20 mL), followed by addition of alcohol **S28** (0.705 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (4 mL, then 3 x 1 mL rinses) and 4-dimethylaminopyridine (0.147 g, 1.20 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **82d** was isolated after column chromatography (5% EtOAc-hexanes) as a clear oil (0.780 g, 2.97 mmol, 74% yield, inconsequential mixture of diastereomers).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.23 – 7.08 (m, 3H), 5.76 (dtdd, J = 15.3, 6.7, 3.1, 1.0 Hz, 1H), 5.49 (dddt, J = 15.4, 11.4, 6.9, 1.4 Hz, 1H), 5.39 (td, J = 6.9, 3.0 Hz, 1H), 3.89 – 3.72 (m, 1H), 3.37 (d, J = 3.6 Hz, 3H), 2.69 (td, J = 7.8, 2.6 Hz, 2H), 2.35 (tdd, J = 8.7, 5.7, 1.8 Hz, 2H), 1.37 (t, J = 6.7 Hz, 3H), 1.31 (dd, J = 6.4, 4.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.28, 141.41, 141.38, 132.62, 132.53, 129.76, 129.74, 128.35, 128.21, 125.79, 76.41, 71.50, 71.47, 57.48, 35.28, 33.83, 33.80, 20.30, 20.21, 18.29. HRMS (ESI) calcd for $C_{16}H_{23}O_3$ $[M + H]^+$ 263.1642, found 263.1651.



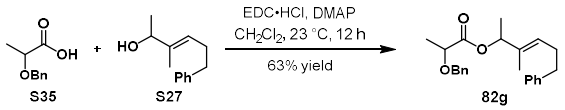
(*Z*)-6-Phenylhex-3-en-2-yl 2-(benzyloxy)propanoate (82e): The title compound was prepared according to General Procedure I using EDC·HCl (0.860 g, 6.00 mmol, 2 equiv), acid **S35** (0.811 g, 4.50 mmol, 1.5 equiv) in CH_2Cl_2 (16 mL), followed by addition of alcohol **S30** (0.529 g, 3.00 mmol, 1 equiv) in CH_2Cl_2 (3 mL, then 3 x 1 mL rinses) and 4-dimethylaminopyridine (0.110 g, 0.90 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **82e** was isolated after column chromatography (5% EtOAc-hexanes) as a clear oil (0.970 g, 2.87 mmol, 96% yield, inconsequential mixture of diastereomers).

^{1}H NMR (500 MHz, $CHCl_3$) δ 7.37 – 7.32 (m, 4H), 7.30 – 7.26 (m, 3H), 7.22 – 7.15 (m, 3H), 5.67 (dqdd, J = 9.2, 6.4, 2.8, 1.0 Hz, 1H), 5.55 (dtdd, J = 10.8, 7.4, 4.8, 1.0 Hz, 1H), 5.39 (tdt, J = 10.8, 9.0, 1.5 Hz, 1H), 4.68 (dd, J = 11.6, 2.8 Hz, 1H), 4.42 (dd, J = 11.6, 2.5 Hz, 1H), 4.00 (qd, J = 6.8, 1.0 Hz, 1H), 2.75 (ddd, J = 14.2, 8.4, 6.2 Hz, 1H), 2.65 (dtd, J = 13.5, 7.8, 5.5 Hz, 1H), 2.57 – 2.43 (m, 2H), 1.41 (dd, J = 6.8, 4.1 Hz, 3H), 1.18 (dd, J = 6.4, 1.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.40, 172.36, 141.35, 141.34, 137.61, 132.21, 132.16, 129.54, 129.49, 128.48, 128.47, 128.33, 128.26, 128.26, 127.90, 127.89, 127.72, 125.88, 125.87, 74.09, 74.06, 71.86, 71.83, 67.43, 67.40, 35.57, 35.56, 29.57, 29.54, 20.60, 20.58, 18.58, 18.57. HRMS (ESI) calcd for $C_{22}H_{27}O_3$ $[M + H]^+$ 339.1955, found 339.1960.

(*Z*)-6-Phenylhex-3-en-2-yl 2-methoxypropanoate (82f): The title compound was prepared according to General Procedure I using EDC·HCl (1.15 g, 6.00 mmol, 1.5 equiv), acid **S33** (0.468 g, 4.50 mmol, 1.5 equiv) in CH_2Cl_2 (15 mL), followed by addition of alcohol **S30** (0.529 g, 3.00 mmol, 1 equiv) in CH_2Cl_2 (2 mL, then 3 x 0.75 mL rinses) and 4-dimethylaminopyridine (0.110 g, 0.900 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **82f** was isolated after column chromatography (5% EtOAc-hexanes) as a clear oil (0.747 g, 2.85 mmol, 95% yield, inconsequential mixture of diastereomers).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 2H), 7.21 – 7.15 (m, 3H), 5.66 (dqdd, J = 9.0, 6.4, 3.9, 1.0 Hz, 1H), 5.57 – 5.50 (m, 1H), 5.38 (tdt, J = 10.9, 9.0, 1.5 Hz, 1H), 3.81

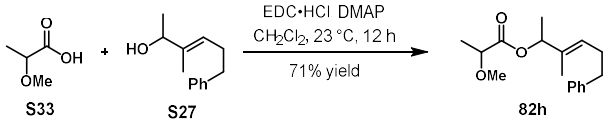
(qd, J = 6.9, 1.1 Hz, 1H), 3.37 (overlapping singlets, 3H), 2.74 (ddd, J = 14.3, 8.5, 6.3 Hz, 1H), 2.64 (dtd, J = 13.4, 7.7, 3.8 Hz, 1H), 2.56 – 2.39 (m, 2H), 1.36 (overlapping doublets, J = 6.8, 4.8 Hz, 3H), 1.18 (overlapping doublets, J = 6.4, 3.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.21, 141.29, 141.28, 132.20, 132.15, 129.43, 129.36, 128.42, 128.41, 128.20, 125.81, 125.80, 76.36, 76.33, 67.32, 67.31, 57.42, 35.48, 29.49, 29.47, 20.51, 20.47, 18.23. HRMS (ESI) calcd for $C_{16}H_{23}O_3$ $[M + H]^+$ 263.1642, found 263.1636.



(*E*)-3-Methyl-6-phenylhex-3-en-2-yl 2-(benzyloxy)propanoate (82g): The title compound was prepared according to General Procedure I using EDC·HCl (1.53 g, 8.00 mmol, 2 equiv), acid **S35** (1.08 g, 6.00 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL), followed by addition of alcohol **S27** (0.761 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (3 mL, then 3 x 1 mL rinses) and 4-dimethylaminopyridine (0.147 g, 1.20 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **82g** was isolated after column chromatography (3% EtOAc-hexanes) as a clear oil (0.890 g, 2.53 mmol, 63% yield, inconsequential mixture of diastereomers).

^{1}H NMR (500 MHz,$CDCl_3$) δ 7.38 – 7.32 (m, 4H), 7.31 – 7.24 (m, 3H), 7.17 (tt, J = 6.4, 2.2 Hz, 3H), 5.53 (tp, J = 7.3, 1.4 Hz, 1H), 5.34 (qd, J = 6.5, 2.5 Hz, 1H), 4.69 (dd, J = 11.6, 1.7 Hz, 1H), 4.43 (dd, J = 11.6, 2.3 Hz, 1H), 4.03 (q, J = 6.9 Hz, 1H), 2.66 (q, J = 7.4 Hz, 2H), 2.40 – 2.28 (m, 2H), 1.56 (ddd, J = 5.6, 1.5, 0.9 Hz, 3H), 1.42 (dd, J = 6.9, 5.3 Hz, 3H), 1.31 (dd, J = 6.5, 3.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.34, 141.72, 141.70, 137.65, 137.63, 134.70, 134.62, 128.39, 128.32, 128.32, 128.19, 128.19, 127.87, 127.83,

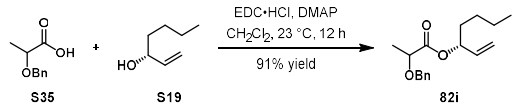
127.71, 127.69, 126.62, 126.40, 125.75, 125.74, 75.79, 75.72, 74.10, 74.08, 71.82, 35.46, 35.43, 29.44, 29.43, 19.05, 18.99, 18.63, 18.61, 11.89, 11.83. HRMS (ESI) calcd for $C_{23}H_{29}O_3$ $[M + H]^+$ 353.2111, found 353.2105.



S33 S27 82h

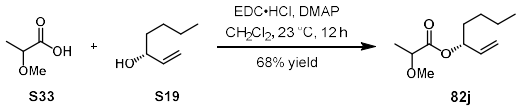
(*E*)-3-Methyl-6-phenylhex-3-en-2-yl 2-methoxypropanoate (82h): The title compound was prepared according to General Procedure I using EDC·HCl (1.15 g, 6.00 mmol, 1.5 equiv), acid **S33** (0.416 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (20 mL), followed by addition of alcohol **S27** (0.761 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (4 mL, then 3 x 1 mL rinses) and 4-dimethylaminopyridine (0.147 g, 1.20 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **82h** was isolated after column chromatography (5% EtOAc-hexanes) as a clear oil (0.786 g, 2.84 mmol, 71% yield, inconsequential mixture of diastereomers).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 2H), 7.23 – 7.11 (m, 3H), 5.51 (ddt, J = 8.4, 7.2, 1.3 Hz, 1H), 5.33 (q, J = 6.5 Hz, 1H), 3.84 (qd, J = 6.9, 1.0 Hz, 1H), 3.38 (s, 3H), 2.66 (t, J = 7.6 Hz, 2H), 2.40 – 2.26 (m, 2H), 1.56 – 1.53 (overlapping singlets, 3H), 1.37 (overlapping doublets, J = 7.1 Hz, 3H), 1.30 (overlapping doublets, J = 6.5, 4.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.27, 141.73, 141.72, 134.67, 134.60, 128.40, 128.19, 126.61, 126.40, 125.75, 125.74, 76.47, 76.42, 75.74, 75.67, 57.55, 57.51, 35.44, 35.42, 29.42, 29.41, 19.03, 18.93, 18.38, 18.34, 11.87, 11.81. HRMS (ESI) calcd for $C_{17}H_{25}O_3$ $[M + H]^+$ 277.1798, found 277.1791.



(*R*)-Hept-1-en-3-yl 2-(benzyloxy)propanoate (82i): The title compound was prepared according to General Procedure I using EDC·HCl (1.53 g, 8.00 mmol, 2 equiv), acid **S35** (1.08 g, 6.00 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL), followed by addition of alcohol **S19** (0.460 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (3 mL, then 3 x 1 mL rinses) and 4-dimethylaminopyridine (0.147 g, 1.20 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **82i** was isolated after column chromatography (5% EtOAc-hexanes) as a clear oil (1.01 g, 3.65 mmol, 91% yield, inconsequential mixture of diastereomers).

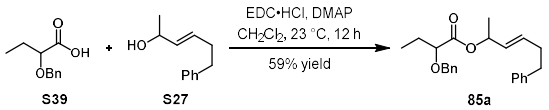
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 4H), 7.31 – 7.27 (m, 1H), 5.81 (ddd, J = 17.1, 10.5, 6.5 Hz, 1H), 5.35 – 5.30 (m, 1H), 5.27 (dt, J = 17.2, 1.3 Hz, 1H), 5.19 (dt, J = 10.5, 1.2 Hz, 1H), 4.71 (d, J = 11.6 Hz, 1H), 4.44 (d, J = 11.6 Hz, 1H), 4.06 (q, J = 6.9 Hz, 1H), 1.72 – 1.59 (m, 1H), 1.45 (d, J = 6.8 Hz, 3H), 1.36 – 1.28 (m, 3H), 0.93 – 0.84 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.40, 137.51, 136.25, 128.26, 127.79, 127.66, 116.69, 75.13, 74.01, 71.80, 33.74, 27.09, 22.25, 18.64, 13.80. HRMS (ESI) calcd for $C_{17}H_{25}O_3$ $[M + H]^+$ 277.1798, found 277.1805.



(*R*)-Hept-1-en-3-yl 2-methoxypropanoate (82j): The title compound was prepared according to General Procedure I using EDC·HCl (1.15 g, 6.00 mmol, 1.5 equiv), acid **S33** (0.416 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (20 mL), followed by addition

of alcohol **S19** (0.460 g, 4.00 mmol, 1 equiv) in CH_2Cl_2 (4 mL, then 3 x 1 mL rinses) and 4-dimethylaminopyridine (0.147 g, 1.20 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **82j** was isolated after column chromatography (5% EtOAc-hexanes) as a clear oil (0.541 g, 2.70 mmol, 68% yield, inconsequential mixture of diastereomers).

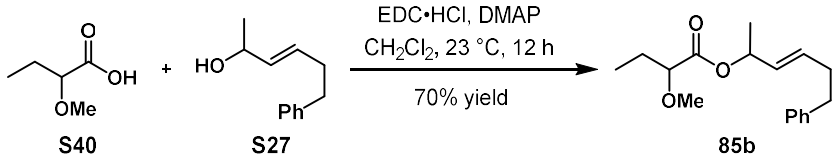
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (dddd, J = 17.2, 10.6, 6.5, 5.8 Hz, 1H), 5.31 (dtd, J = 7.4, 6.1, 4.6 Hz, 1H), 5.26 (dq, J = 17.3, 1.4 Hz, 1H), 5.17 (dt, J = 10.5, 1.3 Hz, 1H), 3.87 (q, J = 6.9 Hz, 1H), 3.39 (two singlets, J = 1.5 Hz, 3H), 1.71 – 1.64 (m, 1H), 1.64 – 1.57 (m, 1H), 1.40 (overlapping doublets, J = 6.8, 3.8 Hz, 3H), 1.35 – 1.26 (m, 2H), 0.92 – 0.87 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.39, 136.28, 136.20, 116.99, 116.80, 76.50, 76.49, 75.21, 75.20, 57.59, 57.51, 33.80, 33.76, 27.14, 27.14, 22.32, 22.30, 18.45, 18.36, 13.85, 13.85. HRMS (ESI) calcd for $C_{11}H_{21}O_3$ $[M + H]^+$ 201.1485, found 201.1489.



S39 S27 85a

(E)-6-Phenylhex-3-en-2-yl 2-(benzyloxy)butanoate (85a): The title compound was prepared according to General Procedure I using EDC·HCl (0.46 g, 2.40 mmol, 2 equiv), acid **S39** (2.60 g, 1.60 mmol, 1 equiv) in CH_2Cl_2 (6.5 mL), followed by addition of alcohol **S27** (0.28 g, 1.60 mmol, 1 equiv) in CH_2Cl_2 (2 mL, then 3 x 0.5 mL rinses) and 4-dimethylaminopyridine (0.147 g, 1.20 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **85a** was isolated after column chromatography (3% EtOAc-hexanes) as a clear oil (0.33 g, 0.94 mmol, 59% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 4H), 7.31 – 7.25 (m, 3H), 7.21 – 7.11 (m, 3H), 5.77 (dtd, J = 14.6, 6.7, 1.1 Hz, 1H), 5.41 (pd, J = 6.3, 3.7 Hz, 1H), 4.69 (dd, J = 11.7, 7.5 Hz, 1H), 4.40 (dd, J = 11.7, 1.3 Hz, 1H), 3.84 (ddd, J = 7.2, 5.3, 4.2 Hz, 1H), 2.69 (q, J = 8.1 Hz, 2H), 2.36 (tt, J = 7.8, 5.7 Hz, 2H), 1.79 (dtd, J = 13.6, 7.4, 6.0 Hz, 2H), 1.31 (dd, J = 6.4, 2.8 Hz, 3H), 0.97 (td, J = 7.4, 4.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.89, 171.85, 141.37, 141.34, 137.66, 132.62, 132.40, 129.83, 129.80, 128.31, 128.30, 128.23, 128.19, 128.18, 127.86, 127.63, 125.77, 125.76, 79.27, 72.00, 71.39, 71.34, 35.29, 35.27, 33.83, 33.80, 26.11, 26.09, 20.34, 20.28, 9.61. HRMS (ESI) calcd for $C_{23}H_{29}O_3$ $[M + H]^+$ 353.2111, found 353.2120.

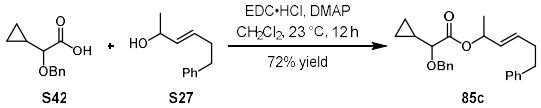


S40 S27 85b

(E)-6-Phenylhex-3-en-2-yl 2-methoxybutanoate (85b): The title compound was prepared according to General Procedure I using EDC·HCl (0.68 g, 3.56 mmol, 1.5 equiv), acid **S40** (0.28 g, 2.37 mmol, 1 equiv) in CH_2Cl_2 (10 mL), followed by addition of alcohol **S27** (0.42 g, 2.37 mmol, 1 equiv) in CH_2Cl_2 (6.5 mL, then 3 x 0.5 mL rinses) and 4-dimethylaminopyridine (87 mg g, 0.711 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **85b** was isolated after column chromatography (3% EtOAc-hexanes) as a clear oil (0.46 g, 1.66 mmol, 70% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.22 – 7.11 (m, 3H), 5.83 – 5.68 (m, 1H), 5.50 (dddt, J = 15.4, 11.0, 6.9, 1.5 Hz, 1H), 5.41 (td, J = 6.6, 4.5 Hz, 1H), 3.66 (ddd, J = 6.9, 5.2, 3.5 Hz, 1H), 3.37 (dd, J = 4.5, 1.2 Hz, 3H), 2.69 (td, J = 7.8, 3.3 Hz, 2H), 2.43 – 2.25 (m, 2H), 1.85 – 1.60 (m, 2H), 1.31 (dd, J = 6.4, 4.2 Hz, 3H), 1.03 – 0.85 (m,

3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.87, 141.50, 141.47, 132.75, 132.57, 129.91, 129.88, 128.41, 128.28, 125.86, 125.85, 81.82, 71.49, 71.44, 57.90, 35.37, 33.91, 33.88, 25.98, 25.97, 20.43, 20.35, 9.42. HRMS (ESI) calcd for $C_{17}H_{25}O_3$ $[M + H]^+$ 277.1798, found 277.1791.



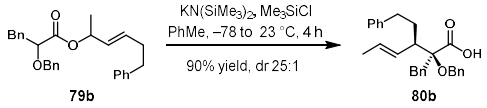
S42 S27 85c

(E)-6-Phenylhex-3-en-2-yl 2-(benzyloxy)-2-cyclopropylacetate (85c): The title compound was prepared according to General Procedure I using EDC·HCl (0.38 g, 2.00 mmol, 2 equiv), acid **S42** (0.31 g, 1.50 mmol, 1.5 equiv) in CH_2Cl_2 (3.5 mL), followed by addition of alcohol **S27** (0.18 g, 1.0 mmol, 1 equiv) in CH_2Cl_2 (2 mL, then 3 x 0.5 mL rinses) and 4-dimethylaminopyridine (36 mg g, 0.30 mmol, 0.3 equiv). The solution was stirred at room temperature for 12 h, and ester **85c** was isolated after column chromatography (3% EtOAc-hexanes) as a clear oil (0.26 g, 0.716 mmol, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 4H), 7.31 – 7.21 (m, 3H), 7.20 – 7.12 (m, 3H), 5.84 – 5.71 (m, 1H), 5.54 – 5.45 (m, 1H), 5.45 – 5.36 (m, 1H), 4.67 (dd, J = 11.8, 6.3 Hz, 1H), 4.41 (d, J = 11.8 Hz, 1H), 3.34 (d, J = 8.0 Hz, 1H), 2.69 (q, J = 8.3 Hz, 2H), 2.36 (dq, J = 14.6, 7.8, 6.8 Hz, 2H).1.32 (dd, J = 6.4, 1.7 Hz, 3H), 1.22 – 1.11 (m, 1H), 0.64 – 0.58 (m, 1H), 0.56 – 0.47 (m, 1H), 0.44 (ddd, J = 10.4, 9.4, 4.9 Hz, 1H), 0.41 – 0.33 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.20, 171.18, 141.40, 141.39, 137.52, 132.33, 132.29, 129.85, 129.83, 128.33, 128.32, 128.26, 128.20, 128.19, 127.87, 127.68, 125.78,

125.76, 81.21, 71.57, 71.39, 71.37, 35.33, 33.86, 33.83, 20.38, 20.30, 13.43, 13.41, 3.58, 3.55, 1.84, 1.77. HRMS (ESI) calcd for $C_{24}H_{29}O_3$ $[M + H]^+$ 365.2111, found 365.2123.

REPRESENTATIVE IRELAND-CLAISEN REARRANGEMENTS ON 1 MMOL SCALE:

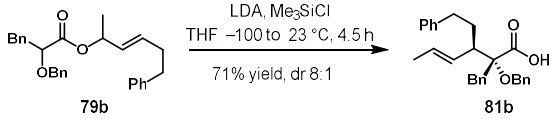


79b 80b

Carboxylic acid 80b: A flame-dried 25 mL round bottom flask was brought into a nitrogen-filled glove box and charged with $KN(SiMe_3)_2$ (0.439 g, 2.20 mmol, 2.2 equiv). The flask was capped, removed from the glove box, attached to a Schlenk line, and backfilled with argon three times. PhMe (3.40 mL) was then added to the flask and the solution was cooled to –78 °C. A solution of ester **79b** (0.415 g, 1.00 mmol) in PhMe (1.9 mL then 3 x 0.5 mL rinses) was added dropwise and the resulting solution was stirred 30 min. Chlorotrimethylsilane (254 μL, 0.217 g, 2.00 mmol, 2 equiv) was then added dropwise, and the solution was stirred 1 h at –78 °C, 1 h at –40 °C, and 1 h at room temperature. The solution was then poured into a separatory funnel containing 1 M HCl (40 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 40 mL), the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column

chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes) to give acid **80b** (0.372 g, 0.897 mmol, 90% yield, dr 25:1) as a clear oil.

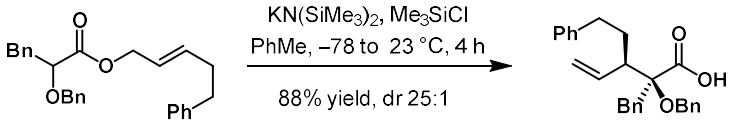
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.15 (m, 13H), 7.10 (dd, J = 6.7, 2.8 Hz, 2H), 5.70 (dq, J = 15.3, 6.5 Hz, 1H), 5.42 (ddq, J = 15.0, 9.8, 1.6 Hz, 1H), 4.76 – 4.65 (m, 2H), 3.40 (d, J = 14.9 Hz, 1H), 3.19 (d, J = 14.9 Hz, 1H), 2.84 – 2.71 (m, 2H), 2.49 (ddd, J = 13.9, 9.7, 7.2 Hz, 1H), 2.02 – 1.93 (m, 1H), 1.93 – 1.86 (m, 1H), 1.83 (dd, J = 6.5, 1.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.83, 141.73, 136.88, 135.38, 131.04, 129.90, 128.79, 128.74, 128.45, 128.43, 128.40, 128.37, 128.33, 127.92, 127.57, 127.45, 126.86, 125.85, 86.22, 74.24, 65.86, 49.40, 38.76, 33.96, 31.42, 18.20. HRMS (ESI) calcd for $C_{28}H_{31}O_3$ $[M + H]^+$ 415.2268, found 415.2274.



Carboxylic acid 81b: *n*-BuLi (2.40 M in hexanes, 1.00 ml, 2.40 mmol, 2.4 equiv) was added to a solution of diisopropylamine (370 µL, 2.60 mmol, 2.6 equiv) in THF (6.0 ml) at –78 °C, and the mixture was stirred for 20 min. The solution was cooled to –100 °C and freshly distilled chlorotrimethylsilane (320 µL, 0.272 g, 2.50 mmol, 2.5 equiv) was added followed by the dropwise addition of a solution of ester **79b** (0.415 g, 1.00 mmol) in THF (2.5 mL then 3 x 0.5 mL rinses). The solution was stirred 1 h at –100 °C, 1 h at –78 °C, 1 h at –40 °C, and 1 h at room temperature. The solution was then poured into a separatory funnel containing 1 M HCl (40 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 40 mL), the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*.

The residue was purified by column chromatography (30% EtOAc- inhexanes to 1% AcOH, 30% EtOAc in hexanes) to give acid **81b** (0.294 g, 0.710 mmol, 71% yield, dr 7 : 1)

^{1}H NMR (500 MHz, CDCl3) δ 9.46 (brs, 1H), 7.35 – 7.15 (m, 15H), 7.10 – 7.05 (m, 0.23H), 6.94 – 6.87 (m, 2H), 5.77 – 5.64 (m, 2.12H), 5.40 (ddq, *J* = 15.0, 9.9, 1.6 Hz, 0.11H), 4.74 – 4.66 (m, 0.22H), 4.50 (d, *J* = 10.2 Hz, 1H), 4.01 (d, *J* = 10.3 Hz, 1H), 3.49 (d, *J* = 15.2 Hz, 1H), 3.40 (d, *J* = 15.0 Hz, 0.1H), 3.18 (d, *J* = 15.0 Hz, 0.1.24H), 2.96 (d, *J* = 15.2 Hz, 1H), 2.78 (ddd, *J* = 12.8, 7.0, 4.7 Hz, 1H), 2.55 (ddd, *J* = 11.3, 8.6, 2.1 Hz, 1H), 2.50 – 2.41 (m, 1H), 1.93 (dddd, *J* = 13.3, 9.4, 7.3, 2.1 Hz, 1H), 1.87 (d, *J* = 4.9 Hz, 3H), 1.83 (dd, *J* = 6.5, 1.6 Hz, 0.32H), 1.53 (dddd, *J* = 13.4, 11.8, 7.0, 4.9 Hz, 1H). ^{13}C NMR (126 MHz, CDCl3) δ 172.62, 141.75, 136.31, 135.45, 135.37, 131.01, 130.06, 129.89, 129.70, 129.47, 128.77, 128.41, 128.38, 128.31, 128.00, 127.90, 127.55, 127.43, 126.84, 126.77, 125.98, 125.83, 86.21, 85.63, 65.83, 64.05, 49.38, 46.92, 39.56, 38.74, 33.94, 32.66, 31.41, 30.28, 29.65, 18.18, 18.04. HRMS (ESI) calcd for $C_{28}H_{31}O_3$ $[M + H]^+$ 415.2268, found 415.2259.



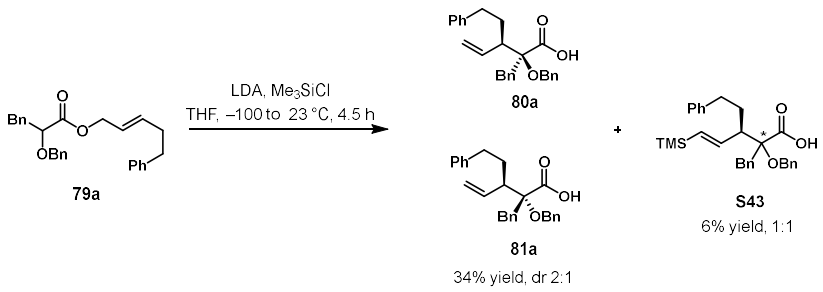
79a 80a

GENERAL PROCEDURE II:

Carboxylic acid 80a: A flame-dried 10 mL round bottom flask was brought into a nitrogen-filled glove box and charged with $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv). The flask was capped, removed from the glove box, attached to a Schlenk line,

and backfilled with argon three times. PhMe (0.85 mL) was then added to the flask and the solution was cooled to –78 °C. A solution of ester **79a** (0.100 g, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) was added dropwise and the resulting solution was stirred 30 min. Chlorotrimethylsilane (63 μL, 54 mg, 0.500 mmol, 2 equiv) was then added dropwise, and the solution was stirred 1 h at –78 °C, 1 h at –40 °C, and 1 h at room temperature. The solution was then poured into a separatory funnel containing 1 M HCl (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL), the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes) to give acid **80a** (88 mg, 0.220 mmol, 88% yield, dr 25:1) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.15 (m, 13H), 7.10 (dt, J = 7.2, 2.1 Hz, 2H), 5.82 (dt, J = 17.0, 10.0 Hz, 1H), 5.41 (dd, J = 10.2, 1.6 Hz, 1H), 5.36 – 5.24 (m, 1H), 4.78 – 4.62 (m, 2H), 3.42 (d, J = 14.9 Hz, 1H), 3.21 (d, J = 14.9 Hz, 1H), 2.81 (dtd, J = 24.2, 10.3, 9.9, 3.7 Hz, 2H), 2.49 (ddd, J = 13.9, 9.7, 7.2 Hz, 1H), 2.06 – 1.96 (m, 1H), 1.91 (ddt, J = 13.8, 9.5, 5.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.76, 141.57, 136.97, 136.82, 136.17, 135.26, 129.93, 129.73, 128.81, 128.46, 128.40, 128.38, 128.34, 128.09, 127.95, 127.58, 127.47, 126.92, 126.88, 126.08, 125.92, 120.24, 119.43, 85.93, 65.98, 64.14, 50.44, 48.15, 39.51, 38.70, 33.82, 32.53, 31.03, 29.93, 29.68. HRMS (ESI) calcd for $C_{27}H_{29}O_3$ $[M + H]^+$ 401.2111, found 401.2109.

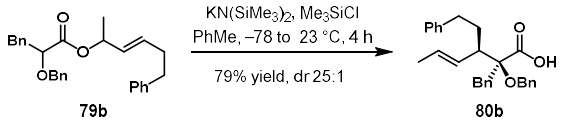


GENERAL PROCEDURE III:

Carboxylic acids 80a, 81a, and S43: *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) was added to a solution of diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) at –78 °C, and the mixture was stirred for 20 min. The solution was cooled to –100 °C and freshly distilled chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) was added followed by the dropwise addition of a solution of ester **79a** (0.100 g, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). The solution was stirred 1 h at –100 °C, 1 h at –78 °C, 1 h at –40 °C, and 1 h at room temperature. The solution was then poured into a separatory funnel containing 1 M HCl (10 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL), the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes) to give 41 mg of a mixture of acids **80a**, **81a (**34% yield) and **S43** (6% yield, dr 1:1) in a ratio of ~4:2:1.

Data for the mixture: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.13 (m, 31H), 6.95 – 6.87 (m, 3H), 6.24 (dd, J = 18.5, 9.0 Hz, 0.49H), 6.10 (dt, J = 17.1, 9.8 Hz, 1H), 5.90 (d, J = 18.5 Hz, 0.58H), 5.81 (dt, J = 17.0, 10.0 Hz, 045H), 5.40 (ddd, J = 12.0, 10.1, 1.7 Hz,

1.49H), 5.29 (ddd, J = 17.1, 11.7, 1.7 Hz, 1.49H), 4.71 (q, J = 10.3 Hz, 1H), 4.52 (dd, J = 10.2, 8.0 Hz, 1.59H), 4.04 (dd, J = 10.2, 6.3 Hz, 1.57H), 3.49 (d, J = 15.3 Hz, 1H), 3.43 (dd, J = 15.1, 5.3 Hz, 1H), 3.21 (d, J = 14.9 Hz, 0.50H), 3.00 (dd, J = 15.3, 7.5 Hz, 1.73H), 2.79 (dddd, J = 26.1, 12.7, 9.0, 6.6 Hz, 2.83H), 2.65 – 2.55 (m, 1.69H), 2.53 – 2.38 (m, 2.25H), 2.01 – 1.87 (m, 2H), 1.57 (dddd, J = 13.4, 11.9, 7.0, 4.9 Hz, 1H), 0.19 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.59, 144.33, 141.61, 141.57, 136.95, 136.50, 136.34, 136.23, 136.15, 135.38, 135.25, 130.16, 129.93, 129.76, 129.73, 129.52, 128.81, 128.48, 128.46, 128.45, 128.44, 128.43, 128.42, 128.41, 128.38, 128.09, 128.05, 127.95, 127.58, 127.47, 126.93, 126.88, 126.86, 126.08, 126.05, 125.93, 120.26, 119.44, 85.94, 85.25, 77.25, 77.00, 76.75, 66.00, 64.19, 64.15, 50.94, 50.44, 48.15, 39.55, 39.51, 38.82, 38.71, 33.82, 32.63, 32.53, 31.04, 29.93, 29.77, -1.13. HRMS (ESI) calcd for $C_{27}H_{29}O_3$ $[M + H]^+$ 401.2111, found 401.2121 and $C_{20}H_{37}O_3Si$ $[M + H]^+$ 473.2506, found 473.2515.

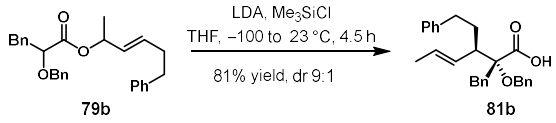


79b 80b

Carboxylic acid 80b: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL), **79b** (0.104 g, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 μL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **80b** (82 mg, 0.198 mmol, 79% yield, dr 25:1) was isolated as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.15 (m, 13H), 7.10 (dd, J = 6.7, 2.8 Hz, 2H), 5.70 (dq, J = 15.3, 6.5 Hz, 1H), 5.42 (ddq, J = 15.0, 9.8, 1.6 Hz, 1H), 4.76 – 4.65 (m, 2H),

3.40 (d, J = 14.9 Hz, 1H), 3.19 (d, J = 14.9 Hz, 1H), 2.84 – 2.71 (m, 2H), 2.49 (ddd, J = 13.9, 9.7, 7.2 Hz, 1H), 2.02 – 1.93 (m, 1H), 1.93 – 1.86 (m, 1H), 1.83 (dd, J = 6.5, 1.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.83, 141.73, 136.88, 135.38, 131.04, 129.90, 128.79, 128.74, 128.45, 128.43, 128.40, 128.37, 128.33, 127.92, 127.57, 127.45, 126.86, 125.85, 86.22, 74.24, 65.86, 49.40, 38.76, 33.96, 31.42, 18.20. HRMS (ESI) calcd for $C_{28}H_{31}O_3$ $[M + H]^+$ 415.2268, found 415.2274.

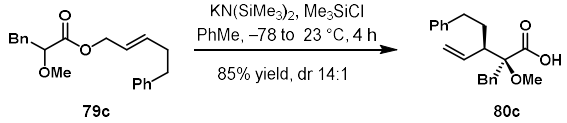


79b 81b

Carboxylic acid 81b: The title compound was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv), diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml), chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **79b** (0.104 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **81b** (84 mg, 0.203 mmol, 81% yield, dr 9:1) was isolated as a clear oil.

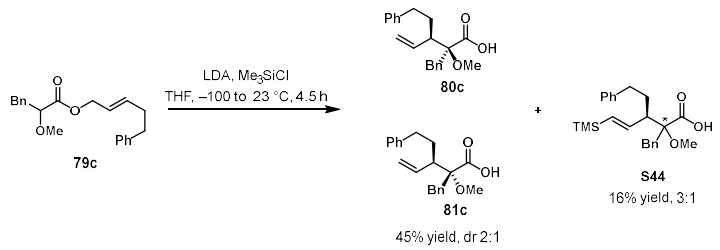
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.46 (brs, 1H), 7.35 – 7.15 (m, 15H), 7.10 – 7.05 (m, 0.23H), 6.94 – 6.87 (m, 2H), 5.77 – 5.64 (m, 2.12H), 5.40 (ddq, J = 15.0, 9.9, 1.6 Hz, 0.11H), 4.74 – 4.66 (m, 0.22H), 4.50 (d, J = 10.2 Hz, 1H), 4.01 (d, J = 10.3 Hz, 1H), 3.49 (d, J = 15.2 Hz, 1H), 3.40 (d, J = 15.0 Hz, 0.1H), 3.18 (d, J = 15.0 Hz, 0.1.24H), 2.96 (d, J = 15.2 Hz, 1H), 2.78 (ddd, J = 12.8, 7.0, 4.7 Hz, 1H), 2.55 (ddd, J = 11.3, 8.6, 2.1 Hz, 1H), 2.50 – 2.41 (m, 1H), 1.93 (dddd, J = 13.3, 9.4, 7.3, 2.1 Hz, 1H), 1.87 (d, J = 4.9 Hz, 3H), 1.83 (dd, J = 6.5, 1.6 Hz, 0.32H), 1.53 (dddd, J = 13.4, 11.8, 7.0, 4.9 Hz, 1H). ^{13}C NMR

(126 MHz, $CDCl_3$) δ 172.62, 141.75, 136.31, 135.45, 135.37, 131.01, 130.06, 129.89, 129.70, 129.47, 128.77, 128.41, 128.38, 128.31, 128.00, 127.90, 127.55, 127.43, 126.84, 126.77, 125.98, 125.83, 86.21, 85.63, 65.83, 64.05, 49.38, 46.92, 39.56, 38.74, 33.94, 32.66, 31.41, 30.28, 29.65, 18.18, 18.04. HRMS (ESI) calcd for $C_{28}H_{31}O_3$ $[M + H]^+$ 415.2268, found 415.2259.



Carboxylic acid 80c: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **79c** (81 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 µL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **80c** (69 mg, 0.212 mmol, 85% yield) was isolated as a white solid.

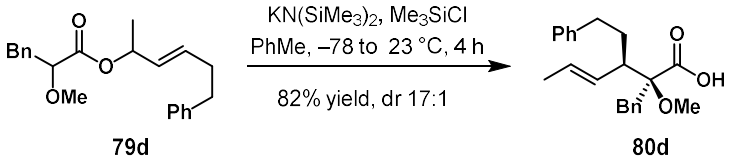
^1H NMR (500 MHz, $CDCl_3$) δ 7.44 – 6.76 (m, 11H), 5.73 (dt, J = 16.9, 10.0 Hz, 1H), 5.36 (dd, J = 10.3, 1.7 Hz, 1H), 5.25 (dd, J = 17.0, 1.7 Hz, 1H), 3.48 (s, 3H), 3.28 – 3.15 (m, 1H), 3.08 (d, J = 14.9 Hz, 1H), 2.74 (tdd, J = 10.5, 7.8, 3.8 Hz, 2H), 2.46 (ddd, J = 13.8, 9.9, 7.1 Hz, 1H), 1.87 (tddd, J = 24.3, 15.4, 8.7, 3.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.52, 141.61, 136.12, 135.31, 129.82, 128.41, 128.34, 128.33, 126.83, 125.89, 120.10, 85.98, 51.85, 37.43, 33.80, 30.95. HRMS (ESI) calcd for $C_{21}H_{25}O_3$ $[M + H]^+$ 325.1798, found 325.1797.



Carboxylic acids 80c, 81c, and S44: The title mixture was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **79c** (81 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), 54 mg of the mixture of acid **80c**, **81c** (45% calc. yield, dr 2:1) and trimethylsilyl acid **S44** (16% calc. yield, dr 3:1) was isolated.

Data for the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.16 (m, 19H), 7.15 – 7.12 (m, 3H), 6.23 (dd, J = 18.5, 9.0 Hz, 0.4H), 6.08 (dt, J = 17.1, 9.9 Hz, 1H), 5.92 – 5.81 (m, 0.67H), 5.78 – 5.69 (m, 0.53H), 5.36 (ddd, J = 10.0, 8.0, 1.8 Hz, 1.48H), 5.23 (ddd, J = 17.1, 15.2, 1.8 Hz, 1.54H), 3.49 (s, 1.36H), 3.47 (s, 0.35H), 3.31 (s, 0.48H), 3.28 (s, 0.52H), 3.25 (d, J = 2.6 Hz, 0.42H), 3.22 (d, J = 2.4 Hz, 0.54H), 3.18 (overlapping singlets, 4.24H), 2.87 (d, J = 6.5 Hz, 0.76H), 2.84 (d, J = 6.5 Hz, 0.68H), 2.82 – 2.65 (m, 3H), 2.51 – 2.37 (m, 3.60H), 1.96 – 1.79 (m, 2.73H), 1.58 – 1.46 (m, 1.54H), 0.18 (s, 3.87H), 0.14 (s, 1.14H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.97, 172.91, 144.76, 141.96, 141.89, 141.86, 137.33, 136.54, 136.48, 135.85, 135.73, 135.68, 130.18, 130.06, 130.04, 129.00, 128.76, 128.71, 128.68, 128.67, 128.64, 128.62, 127.16, 127.15, 127.10, 127.07, 126.33, 126.30, 126.22, 120.41, 119.55, 86.35, 86.31, 85.50, 52.84, 52.24, 50.60, 50.28, 50.09, 47.84,

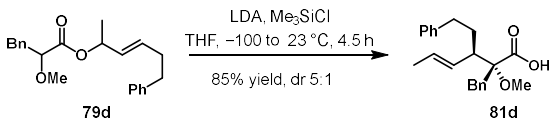
38.75, 38.66, 37.79, 34.15, 33.20, 33.13, 31.31, 31.04, 30.15, 29.97, -0.81, -0.88. HRMS (ESI) calcd for $C_{21}H_{25}O_3$ [M + H]$^+$ 325.1798, found 325.1808 and $C_{21}H_{25}O_3Si$ [M + H]$^+$ 397.2193, found 397.2182.



79d 80d

Carboxylic acid 80d: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **79d** (0.85 g, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 µL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **80d** (70 mg, 0.206 mmol, 82% yield, dr 17:1) was isolated as a yellow oil.

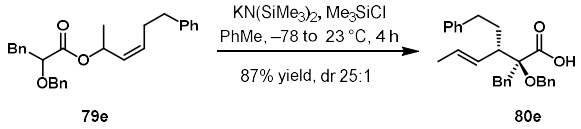
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.39 (brs, 1H), 7.35 – 7.00 (m, 10H), 5.65 (dq, J = 15.1, 6.4 Hz, 1H), 5.33 (ddt, J = 15.2, 9.9, 1.7 Hz, 1H), 3.48 (s, 3H), 3.18 (d, J = 14.8 Hz, 1H), 3.05 (dd, J = 14.9, 1.7 Hz, 1H), 2.71 (dtd, J = 23.6, 10.1, 4.1 Hz, 2H), 2.44 (ddd, J = 13.8, 9.9, 7.1 Hz, 1H), 1.97 – 1.63 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.66, 141.80, 135.49, 130.83, 129.80, 128.76, 128.39, 128.28, 128.28, 126.75, 125.80, 86.25, 51.82, 48.90, 37.55, 33.93, 31.35, 18.15. HRMS (ESI) calcd for $C_{22}H_{27}O_3$ [M + H]$^+$ 339.1955, found 339.1948.



79d 81d

Carboxylic acid 81d: The title compound was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 μL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 μL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **79d** (85 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **81d** (72 mg, 0.212 mmol, 85% yield, dr 5:1) was isolated as a clear oil.

Data for the mixture of diastereomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.27 (overlapping multiplets, 2.61H), 7.27 – 7.23 (overlapping multiplets, 2.64H), 7.22 – 7.16 (overlapping multiplets, 5.21H), 7.14 – 7.11 (m, 2H), 5.73 – 5.56 (overlapping multiplets, 2.22H), 5.37 – 5.30 (m, 0.22H), 3.48 (s, 0.57H), 3.29 (d, J = 15.1 Hz, 1H), 3.16 [overlapping singlet (major) and doublet (minor), 3.20H], 3.06 (d, J = 14.9 Hz, 0.22H), 2.82 (d, J = 15.1 Hz, 1H), 2.80 – 2.65 (overlapping multiplets, 1.40H), 2.48 – 2.35 (overlapping multiplets, 2.40H), 1.82 [overlapping multiplet (major), and two doublets (major and minor), 4.96H), 1.48 (dddd, J = 13.0, 11.6, 7.9, 4.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.46, 172.47, 141.80, 141.71, 135.59, 135.47, 130.89, 129.84, 129.80, 129.68, 129.49, 128.75, 128.65, 128.40, 128.33, 128.30, 128.27, 126.77, 126.69, 125.91, 125.81, 86.29, 85.59, 51.80, 49.65, 48.92, 46.27, 38.44, 37.55, 33.95, 32.93, 31.36, 30.20, 18.17, 18.01. HRMS (ESI) calcd for $C_{22}H_{27}O_3$ $[M + H]^+$ 339.1955, found 339.1966.

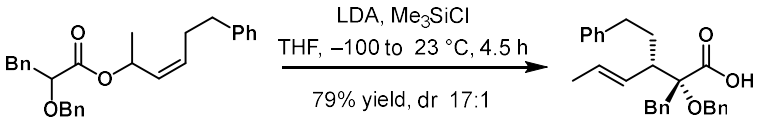


79e 80e

Carboxylic acid 80e: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **79e** (0.104 g, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 µL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **80e** (90 mg, 0.217 mmol, 87% yield, dr 25:1) was isolated as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.48 (brs, 1H), 7.37 – 7.16 (m, 13H), 6.92 (dd, J = 7.3, 2.2 Hz, 2H), 5.78 – 5.63 (m, 2H), 4.52 (d, J = 10.2 Hz, 1H), 4.02 (d, J = 10.2 Hz, 1H), 3.51 (d, J = 15.3 Hz, 1H), 2.98 (d, J = 15.3 Hz, 1H), 2.90 – 2.75 (m, 1H), 2.57 (ddd, J = 11.2, 8.6, 2.0 Hz, 1H), 2.47 (ddd, J = 13.6, 9.5, 7.0 Hz, 1H), 1.95 (dddd, J = 13.3, 9.4, 7.2, 2.0 Hz, 1H), 1.89 (d, J = 5.2 Hz, 3H), 1.55 (dddd, J = 13.3, 11.8, 7.0, 4.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.59, 141.75, 136.30, 135.45, 130.06, 129.70, 129.47, 128.77, 128.41, 128.38, 128.38, 128.01, 127.55, 126.78, 125.98, 85.63, 64.04, 46.92, 39.57, 32.66, 30.29, 18.04. HRMS (ESI) calcd for $C_{27}H_{29}O_3$ $[M + H]^+$ 401.2195, found 401.2202.

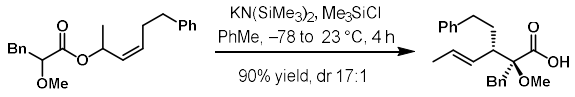


79e 81e

Carboxylic acid 81e: The title compound was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv.) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **79e** (0.104 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography

(30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **81e** (82 mg, 0.199 mmol, 79% yield, dr 17:1) was isolated as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.16 (m, 13H), 7.12 (dd, J = 7.1, 2.5 Hz, 2H), 5.71 (dq, J = 15.2, 6.4 Hz, 1H), 5.43 (ddd, J = 15.1, 9.9, 1.9 Hz, 1H), 4.80 – 4.65 (m, 2H), 3.40 (d, J = 14.9 Hz, 1H), 3.20 (d, J = 14.9 Hz, 1H), 2.82 – 2.75 (m, 2H), 2.50 (ddd, J = 13.8, 9.7, 7.2 Hz, 1H), 2.02 – 1.95 (m, 1H), 1.90 (ddt, J = 13.2, 9.2, 6.1 Hz, 1H), 1.84 (dd, J = 6.4, 1.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.06, 141.74, 136.97, 135.42, 130.97, 129.92, 129.72, 128.78, 128.76, 128.44, 128.37, 128.34, 128.32, 128.00, 127.88, 127.55, 127.42, 126.83, 125.84, 86.19, 85.62, 65.91, 49.39, 39.54, 38.81, 33.95, 32.69, 31.44, 30.29, 18.19, 18.05. HRMS (ESI) calcd for $C_{27}H_{29}O_3$ $[M + H]^+$ 401.2195, found 401.2184.

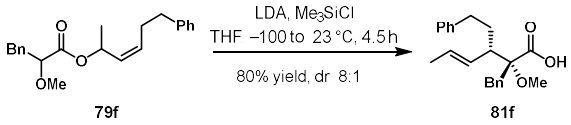


79f 80f

Carboxylic acid 80f: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **79f** (85 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 µL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **81f** (77 mg, 0.227 mmol, 90% yield, dr 17:1) was isolated as a clear oil.

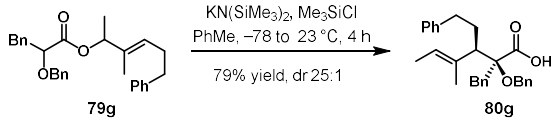
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.11 (m, 10H), 5.72 – 5.57 (m, 2H), 3.28 (d, J = 15.1 Hz, 1H), 3.16 (s, 3H), 2.82 (dd, J = 15.1, 1.8 Hz, 1H), 2.77 (ddd, J = 13.4, 8.2, 4.9 Hz, 1H), 2.48 – 2.36 (m, 2H), 1.90 – 1.74 (m, 4H), 1.47 (dddd, J = 13.0, 11.6, 7.9, 4.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.56, 141.71, 135.60, 129.81, 129.68, 129.50,

128.63, 128.31, 128.24, 126.66, 125.89, 85.55, 49.65, 46.27, 38.39, 32.92, 30.17, 17.98. HRMS (ESI) calcd for $C_{22}H_{27}O_3$ $[M + H]^+$ 339.1955, found 339.1969.



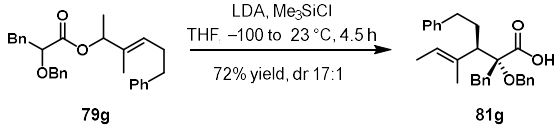
Carboxylic acid 81f: The title compound was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **79f** (85 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **81f** (68 mg, 0.201 mmol, 80% yield, dr 8:1) was isolated as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 5H), 7.25 – 7.16 (m, 6.22H), 7.15 – 7.12 (m, 0.36H), 5.65 (overlapping multiplets, 1.24H), 5.34 (ddq, J = 15.0, 9.8, 1.6 Hz, 1H), 3.48 (s, 3H), 3.29 (d, J = 15.1 Hz, 0.13H), 3.20 (s, 0.35H), 3.17 (d, J = 5.0 Hz, 1H), 3.06 (d, J = 14.9 Hz, 11H), 2.83 (d, J = 15.1 Hz, 0.12H), 2.77 – 2.66 (overlapping multiplets, 2.H), 2.48 – 2.39 (overlapping multiplets, 1.24H), 1.91 – 1.82 (m, 1.63iH), 1.81 (overlapping dd, J = 6.4, 1.6 Hz, 3.32H), 1.52 – 1.45 (m, 0.14H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.63, 141.81, 141.72, 135.60, 135.49, 130.86, 129.81, 129.69, 129.50, 128.76, 128.65, 128.40, 128.29, 128.27, 128.21, 126.76, 126.68, 125.91, 125.81, 86.28, 85.57, 51.84, 49.67, 48.93, 46.30, 38.42, 37.57, 33.95, 32.94, 31.37, 30.19, 18.16, 18.01. HRMS (ESI) calcd for $C_{22}H_{27}O_3$ $[M + H]^+$ 339.1955, found 339.1964.



Carboxylic acid 80g: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **79g** (0.107 g, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 µL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **80g** (84 mg, 0.196 mmol, 79% yield, dr 25:1) was isolated as a clear oil.

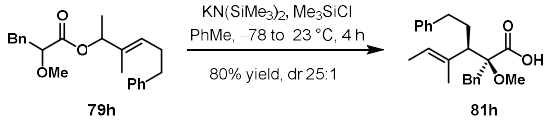
^{1}H NMR (500 MHz, Chloroform-d) δ 7.35 – 7.14 (m, 13H), 7.09 (dd, J = 7.3, 2.3 Hz, 2H), 5.50 (td, J = 6.7, 4.7 Hz, 1H), 4.76 (d, J = 10.3 Hz, 1H), 4.63 (d, J = 10.3 Hz, 1H), 3.53 (d, J = 14.9 Hz, 1H), 3.07 (d, J = 14.9 Hz, 1H), 2.78 (dd, J = 11.8, 2.8 Hz, 1H), 2.69 (ddd, J = 13.9, 9.4, 4.7 Hz, 1H), 2.46 – 2.33 (m, 1H), 2.22 (dddd, J = 13.9, 11.7, 9.2, 4.7 Hz, 1H), 2.08 – 1.95 (m, 1H), 1.70 (d, J = 5.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.38, 172.37, 141.41, 141.38, 137.60, 132.60, 132.47, 129.80, 129.77, 128.34, 128.30, 128.25, 128.22, 128.21, 127.88, 127.70, 125.80, 125.79, 74.10, 74.09, 71.82, 71.51, 71.48, 35.31, 35.29, 33.86, 33.83, 20.33, 20.26, 18.58, 18.56. HRMS (ESI) calcd for $C_{29}H_{33}O_3$ $[M + H]^+$ 429.2424, found 429.2434.



Carboxylic acid 81g: The title compound was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition

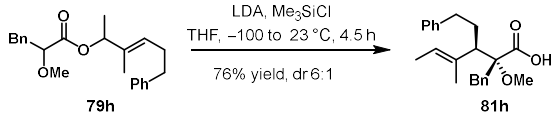
of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **79g** (0.107 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **81g** (77 mg, 0.180 mmol, 72% yield, dr 17:1) was isolated as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1H NMR (500 MHz, Chloroform-d) δ 7.36 – 7.14 (m, 15H), 7.02 – 6.96 (m, 2H), 5.59 – 5.47 (m, 1H), 4.56 (d, J = 10.5 Hz, 1H), 4.22 (d, J = 10.5 Hz, 1H), 3.38 (d, J = 15.4 Hz, 1H), 3.15 (d, J = 15.3 Hz, 1H), 2.66 (q, J = 6.8, 6.2 Hz, 2H), 2.31 (dt, J = 13.6, 8.3 Hz, 1H), 1.94 (td, J = 8.0, 5.6 Hz, 2H), 1.80 (d, J = 1.4 Hz, 3H), 1.75 (dd, J = 6.7, 1.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.86, 141.91, 136.84, 135.78, 132.76, 129.91, 129.86, 128.66, 128.49, 128.36, 128.35, 128.33, 128.29, 127.87, 127.72, 127.50, 127.47, 127.14, 126.84, 126.70, 125.93, 125.80, 86.48, 74.23, 65.00, 52.70, 39.04, 34.14, 33.33, 29.72, 28.44, 13.66, 13.50, 13.12. HRMS (ESI) calcd for $C_{29}H_{33}O_3$ [M + H]$^+$ 429.2424, found 429.2431.



Carboxylic acid 81h: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **79h** (88 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 µL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **81h** (71 mg, 0.201 mmol, 80% yield, dr 25:1) was isolated as a white solid.

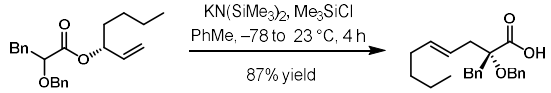
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.06 (m, 10H), 5.52 – 5.24 (m, 1H), 3.40 (m, 4H), 2.91 (d, J = 14.8 Hz, 1H), 2.63 (ddd, J = 19.5, 10.6, 3.9 Hz, 2H), 2.35 (ddd, J = 13.8, 9.3, 7.4 Hz, 1H), 2.24 – 2.08 (m, 1H), 1.97 (dddd, J = 13.3, 9.9, 7.3, 2.8 Hz, 1H), 1.68 (dt, J = 6.6, 1.2 Hz, 3H), 1.64 (q, J = 1.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.33, 141.97, 135.57, 132.59, 129.83, 128.43, 128.24, 126.71, 125.73, 125.22, 85.41, 54.11, 51.53, 38.81, 34.11, 29.67, 13.48, 13.36. HRMS (ESI) calcd for $C_{23}H_{29}O_3$ $[M + H]^+$ 353.2111, found 353.2103.



Carboxylic acid 81h: The title compound was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 μL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 μL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **79h** (88 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **81h** (67 mg, 0.190 mmol, 76% yield, dr 6:1) was isolated as a clear oil.

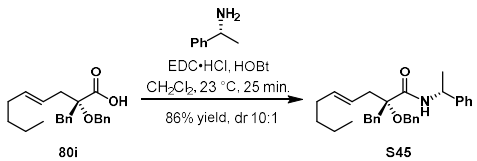
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (overlapping m, 2.60H), 7.24 – 7.11 (overlapping m, 9.61H), 5.52 – 5.40 (overlapping m, 1.17H), 3.40 (s, 0.43H), 3.22 (s, 3H), 3.14 (d, J = 15.1 Hz, 1H), 2.96 (d, J = 15.2 Hz, 1H), 2.89 (d, J = 14.9 Hz, 0.17H), 2.65 (overlapping ddd, J = 13.4, 8.3, 5.0 Hz, 1.33H), 2.52 (dd, J = 11.8, 3.4 Hz, 1H), 2.32 (overlapping dt, J = 13.7, 8.3 Hz, 1.18H), 1.91 – 1.80 (overlapping m, 2.34H), 1.77 (p, J = 1.1 Hz, 3H), 1.72 (dt, J = 6.7, 1.2 Hz, 3H), 1.68 (dd, J = 6.6, 1.2 Hz, 0.54H, CH_3, minor

isomer), 1.63 (d, J = 1.3 Hz, 0.52H, CH_3, minor isomer). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.35, 141.97, 141.84, 135.85, 135.50, 132.67, 129.82, 129.80, 128.55, 128.45, 128.27, 128.26, 128.22, 126.97, 126.75, 126.60, 125.89, 125.76, 125.24, 86.44, 85.41, 54.08, 51.98, 51.43, 50.59, 38.76, 37.96, 34.12, 33.50, 29.68, 28.39, 13.62, 13.51, 13.08. HRMS (ESI) calcd for $C_{23}H_{29}O_3$ $[M + H]^+$ 353.2111, found 353.2101.



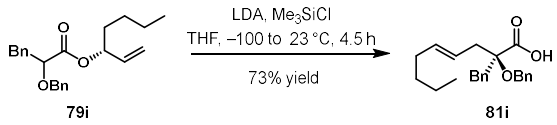
Carboxylic acid 80i: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **79i** (88 mg, 0.250 mmol) in PhMe (0.55 mL then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 μL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **80i** (77 mg, 0.218 mmol, 87% yield) was isolated as a clear oil.

$[\alpha]_D^{25}$ +21.0 (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 3H), 7.32 – 7.21 (m, 7H), 5.67 (dt, J = 15.3, 6.9 Hz, 1H), 5.46 – 5.36 (m, 1H), 4.75 (d, J = 10.2 Hz, 1H), 4.67 (d, J = 10.2 Hz, 1H), 3.29 (d, J = 14.6 Hz, 1H), 3.21 (d, J = 14.6 Hz, 1H), 2.87 – 2.68 (m, 2H), 2.05 (q, J = 6.9 Hz, 2H), 1.43 – 1.23 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.36, 136.80, 136.20, 135.14, 129.99, 128.47, 128.35, 128.02, 127.70, 127.00, 122.12, 84.41, 65.43, 40.64, 37.92, 32.35, 31.38, 22.14, 13.88. HRMS (ESI) calcd for $C_{23}H_{29}O_3$ $[M + H]^+$ 353.2111, found 353.2116.



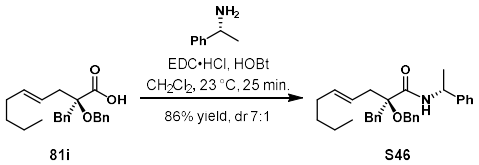
Amide S45 from the $KN(SiMe_3)_2$ reaction: EDC·HCl (43 mg, 0.225 mmol, 1.5 equiv), (*R*)-(+)-alpha-methylbenzylamine (29 μL, 27 mg, 0.225 mmol, 1.5 equiv), and HOBt (31 mg, 0.225 mmol, 1.5 equiv) were added sequentially to a solution of acid **80i** (53 mg, 0.150 mmol) in CH_2Cl_2 (1 mL). The solution was stirred at room temperature for 25 min, then diluted with CH_2Cl_2 (10 mL) and washed with 1 M HCl (10 mL), water (10 mL), saturated aqueous sodium bicarbonate (10 mL), brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **S45** (59 mg, 0.129 mmol, 86% yield, dr 10:1) as a clear oil.

$[\alpha]_D^{25}$ +1.62 (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 4H), 7.22 – 7.13 (m, 6H), 7.10 (d, J = 4.3 Hz, 4H), 5.62 (dtt, J = 14.9, 6.8, 1.3 Hz, 1H), 5.46 – 5.34 (m, 1H), 5.09 – 4.95 (m, 1H), 4.76 (d, J = 10.9 Hz, 1H), 4.65 (d, J = 10.9 Hz, 1H), 3.24 (d, J = 14.4 Hz, 1H), 3.10 (d, J = 14.4 Hz, 1H), 2.94 – 2.78 (m, 1H), 2.73 – 2.62 (m, 1H), 2.01 (q, J = 7.0 Hz, 2H), 1.40 – 1.23 (m, 8H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.63, 143.78, 138.32, 136.82, 135.08, 130.64, 130.56, 128.76, 128.73, 128.66, 128.35, 128.29, 127.89, 127.46, 127.33, 126.82, 126.40, 126.30, 123.69, 84.48, 64.77, 48.23, 41.15, 38.30, 32.68, 31.83, 31.70, 30.06, 22.59, 21.81, 14.26. HRMS (ESI) calcd for $C_{31}H_{38}NO_2$ $[M + H]^+$ 456.2897, found 456.2910.



Carboxylic acid 81i: The title compound was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **79i** (88 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **81i** (64 mg, 0.182 mmol, 73% yield) was isolated as a clear oil.

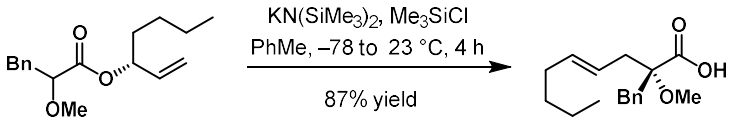
$[\alpha]_D^{25}$ –22.0 (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 3H), 7.32 – 7.21 (m, 7H), 5.67 (dt, J = 15.3, 6.9 Hz, 1H), 5.46 – 5.36 (m, 1H), 4.75 (d, J = 10.2 Hz, 1H), 4.67 (d, J = 10.2 Hz, 1H), 3.29 (d, J = 14.6 Hz, 1H), 3.21 (d, J = 14.6 Hz, 1H), 2.87 – 2.68 (m, 2H), 2.05 (q, J = 6.9 Hz, 2H), 1.43 – 1.23 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.36, 136.80, 136.20, 135.14, 129.99, 128.47, 128.35, 128.02, 127.70, 127.00, 122.12, 84.41, 65.43, 40.64, 37.92, 32.35, 31.38, 22.14, 13.88. HRMS (ESI) calcd for $C_{23}H_{29}O_3$ $[M + H]^+$ 353.2111, found 353.2103.



Amide S46 from the LDA reaction: EDC·HCl (43 mg, 0.225 mmol, 1.5 equiv), (*R*)-(+)-alpha-methylbenzylamine (29 µL, 27 mg, 0.225 mmol, 1.5 equiv), and HOBt (31 mg, 0.225 mmol, 1.5 equiv) were added sequentially to a solution of acid **81i** (53 mg,

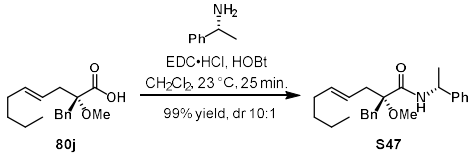
0.150 mmol) in CH_2Cl_2 (1 mL). The solution was stirred at room temperature for 25 min, then diluted with CH_2Cl_2 (10 mL) and washed with 1 M HCl (10 mL), water (10 mL), saturated aqueous sodium bicarbonate (10 mL), brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **S46**(59 mg, 0.129 mmol, 86% yield, dr 7:1) as a clear oil.

$[\alpha]_D^{25}$ –1.52 (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.13 (overlapping multiplets, 17H), 7.09 (d, J = 4.3 Hz, 0.33H), 6.91 – 6.87 (m, 0.19H), 6.82 (d, J = 8.4 Hz, 0.08H), 6.70 (d, J = 8.4 Hz, 1H), 5.66 – 5.51 (overlapping multiplets, 1.10H), 5.39 (dt, J = 14.8, 7.1 Hz, 0.10H), 5.29 (dddt, J = 15.4, 7.8, 6.3, 1.5 Hz, 1H), 5.00 (overlapping multiplets, 1.10H), 4.74 (overlapping doublets, J = 10.9 Hz, 1.10H), 4.64 (d, J = 10.8 Hz, 0.11H), 4.59 (d, J = 10.9 Hz, 1H), 3.23 (d, J = 14.4 Hz, 0.10H), 3.21 – 3.12 (m, 2H), 3.10 (d, J = 14.4 Hz, 0.11H), 2.87 – 2.80 (overlapping multiplets, 1.10H), 2.71 – 2.64 (overlapping multiplets, 1.10H), 2.01 (q, J = 7.0 Hz, 0.20H), 1.90 (t, J = 6.9 Hz, 2H), 1.37 (d, J = 6.9 Hz, 0.33H), 1.30 – 1.19 (overlapping multiplets, 5.50H), 1.08 (d, J = 6.9 Hz, 3H), 0.84 (overlapping triplets, J = 7.1, 6.2, 2.6 Hz, 3.36H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.29, 142.77, 137.94, 136.17, 134.68, 130.26, 130.19, 128.39, 128.37, 128.29, 127.98, 127.92, 127.53, 127.11, 127.09, 126.80, 126.30, 126.03, 125.93, 123.27, 84.22, 64.28, 47.85, 40.19, 38.44, 32.39, 31.46, 22.20, 21.80, 13.92. HRMS (ESI) calcd for $C_{30}H_{38}NO_2$ $[M + H]^+$ 456.2897, found 456.2890.



Carboxylic acid 80j: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **79j** (69 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 µL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **80j** (60 mg, 0.217 mmol, 87% yield) was isolated as a clear oil.

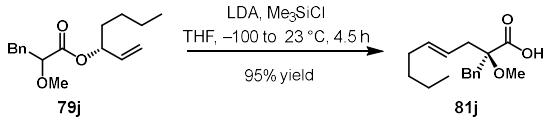
$[\alpha]_D^{25}$ + 2.0 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.09 (m, 5H), 5.60 (dtt, J = 15.1, 6.9, 1.3 Hz, 1H), 5.40 – 5.19 (m, 1H), 3.47 (s, 3H), 3.23 – 2.97 (m, 2H), 2.66 (dd, J = 15.0, 6.9 Hz, 1H), 2.58 (dd, J = 15.0, 7.2 Hz, 1H), 2.02 (q, J = 6.9 Hz, 2H), 1.39 – 1.22 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.73, 135.94, 135.28, 129.90, 128.25, 126.85, 122.12, 84.27, 50.92, 39.66, 37.18, 32.29, 31.36, 22.07, 13.84. HRMS (ESI) calcd for $C_{17}H_{25}O_3$ $[M + H]^+$ 277.1798, found 277.1890.



Amide S47 from the $KN(SiMe_3)_2$ reaction: EDC·HCl (31 mg, 0.162 mmol, 1.5 equiv), (R)-(+)-alpha-methylbenzylamine (21 µL, 20 mg, 0.162 mmol, 1.5 equiv), and HOBt (22 mg, 0.162 mmol, 1.5 equiv) were added sequentially to a solution of acid **80j** (30 mg, 0.108 mmol) in CH_2Cl_2 (0.82 mL). The solution was stirred at room temperature for 25 min, then diluted with CH_2Cl_2 (10 mL) and washed with 1 M HCl

(10 mL), water (10 mL), saturated aqueous sodium bicarbonate (10 mL), brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **S47** (40 mg, 0.107 mmol, 99% yield, dr 7:1) as a clear oil.

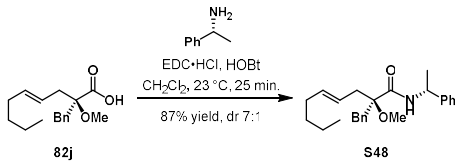
$[\alpha]_D^{25}$ +18.1 (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.05 (m, 8H), 6.91 – 6.85 (m, 2H), 6.77 (d, J = 8.3 Hz, 1H), 5.67 – 5.55 (m, 1H), 5.38 – 5.27 (m, 1H), 5.05 – 4.92 (m, 1H), 3.41 (s, 3H), 3.09 (d, J = 14.3 Hz, 1H), 2.96 (d, J = 14.3 Hz, 1H), 2.75 – 2.67 (m, 1H), 2.54 (dd, J = 14.9, 7.2 Hz, 1H), 2.02 (q, J = 7.0 Hz, 2H), 1.40 (d, J = 6.9 Hz, 3H), 1.38 – 1.28 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.29, 142.67, 136.39, 134.42, 130.08, 130.02, 128.24, 127.95, 127.87, 126.78, 126.20, 126.19, 123.25, 86.13, 84.02, 50.14, 49.83, 47.85, 47.65, 39.14, 37.74, 37.34, 32.35, 31.46, 22.14, 21.43, 18.57, 17.62, 13.91. HRMS (ESI) calcd for $C_{25}H_{34}NO_2$ $[M + H]^+$ 380.2584, found 380.2598.



79j 81j

Carboxylic acid 81j: The title compound was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **79j** (69 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **3i** (66 mg, 0.238 mmol, 95% yield) was isolated as a clear oil.

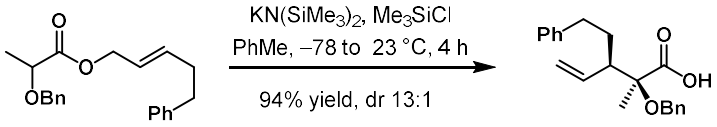
$[\alpha]_D^{25}$ –3.12 (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.26 (dd, J = 8.1, 6.4 Hz, 2H), 7.24 – 7.20 (m, 1H), 7.20 – 7.16 (m, 2H), 5.59 (dtt, J = 15.1, 6.8, 1.3 Hz, 1H), 5.32 (dtt, J = 15.5, 7.1, 1.4 Hz, 1H), 3.45 (s, 3H), 3.12 – 3.02 (m, 2H), 2.64 (ddd, J = 15.2, 6.9, 1.4 Hz, 1H), 2.59 – 2.51 (m, 1H), 2.05 – 1.97 (m, 2H), 1.36 – 1.22 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.90, 136.07, 135.20, 129.88, 128.32, 126.92, 122.00, 84.48, 50.77, 39.62, 37.40, 32.30, 31.37, 22.09, 13.87. HRMS (ESI) calcd for $C_{17}H_{25}O_3$ $[M + H]^+$ 277.1798, found 277.1805.



Amide S48 from the LDA reaction: EDC·HCl (43 mg, 0.225 mmol, 1.5 equiv), (R)-(+)-alpha-methylbenzylamine (29 µL, 27 mg, 0.225 mmol, 1.5 equiv), and HOBt (31 mg, 0.225 mmol, 1.5 equiv) were added sequentially to a solution of acid **82j** (41 mg, 0.150 mmol) in CH_2Cl_2 (1 mL). The solution was stirred at room temperature for 25 min, then diluted with CH_2Cl_2 (10 mL) and washed with 1 M HCl (10 mL), water (10 mL), saturated aqueous sodium bicarbonate (10 mL), brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **S48** (46 mg, 0.121 mmol, 87% yield, dr 7:1) as a clear oil.

$[\alpha]_D^{25}$ +27.4 (*c* 1.00, $CHCl_3$). ^1H NMR (500 MHz, Chloroform-d) δ 7.28 (ddt, J = 8.2, 7.0, 2.7 Hz, 4H), 7.25 – 7.19 (m, 6H), 7.16 – 7.11 (m, 0H), 7.10 – 7.06 (m, 0H), 6.90 –

6.84 (m, 0H), 6.77 (d, J = 8.6 Hz, 0H), 6.68 (d, J = 8.5 Hz, 1H), 5.65 – 5.57 (m, 0.14H), 5.56 – 5.47 (m, 1H), 5.35 – 5.28 (m, 0.14H), 5.26 – 5.14 (m, 1H), 5.03 – 4.90 (m, 1.11H), 3.42 (s, 0.45H), 3.40 (s, 3H), 3.07 (overlapping doublets, 1.14H), 3.00 (overlapping doublets, 1.13H), 2.73 (overlapping doublets, 1.13H), 2.53 (overlapping doublets, 1.13H), 2.03 (q, J = 7.0 Hz, 0.28H), 1.92 (q, J = 6.9 Hz, 2H), 1.40 (d, J = 7.0 Hz, 0.48H), 1.27 (td, J = 4.5, 2.4 Hz, 5H), 1.10 (d, J = 6.9 Hz, 3H), 0.90 (t, J = 7.0 Hz, 0.43H), 0.86 (td, J = 6.0, 5.1, 3.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.37, 143.54, 136.78, 136.56, 134.55, 134.52, 130.26, 130.23, 128.50, 128.39, 128.10, 128.02, 127.10, 126.92, 126.50, 126.34, 126.26, 123.46, 84.17, 84.10, 50.06, 49.99, 47.81, 39.74, 39.32, 37.93, 37.55, 32.51, 32.43, 31.63, 31.47, 29.83, 22.34, 22.31, 21.60, 21.32, 14.06. HRMS (ESI) calcd for $C_{25}H_{34}NO_2$ $[M + H]^+$ 380.2584, found 380.2590.

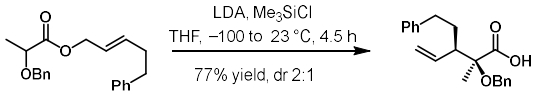


82a 83a

Carboxylic acid 83a: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **82a** (81 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 μL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83a** (76 mg, 0.234 mmol, 94% yield, dr 13:1) was isolated as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 4H), 7.21 – 7.12 (m, 3H), 7.09 – 7.02 (m, 3H), 5.61 (dt, J = 17.1, 10.0 Hz, 1H), 5.16 (dd, J = 10.2, 1.9 Hz, 1H), 5.07 (dd, J = 17.1, 1.9 Hz, 1H), 4.48 – 4.39 (q, 2H), 2.61 (ddd, J = 14.6, 10.3, 4ll.7 Hz, 1H), 2.42 (ddd, J =

12.0, 9.9, 2.6 Hz, 1H), 2.35 (ddt, J = 13.4, 9.0, 6.7 Hz, 1H), 1.85 (dddd, J = 13.2, 9.9, 6.9, 2.6 Hz, 1H), 1.68 (dtd, J = 13.3, 10.5, 4.7 Hz, 1H), 1.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.38, 142.11, 142.01, 138.41, 137.22, 136.58, 128.58, 128.47, 128.40, 128.35, 128.31, 127.54, 127.46, 127.38, 125.87, 125.78, 119.46, 118.69, 82.61, 66.83, 66.18, 52.37, 33.67, 33.41, 30.30, 29.74, 19.75, 18.63. HRMS (ESI) calcd for $C_{21}H_{25}O_3$ [M + H]$^+$ 325.1798, found 325.1807.

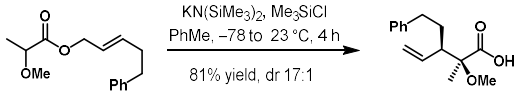


82a 83a

Carboxylic acid 83a: The title compound was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 μL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 μL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **82a** (81 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83a** with its diastereomer (62 mg, 0.192 mmol, 77% yield, dr 2:1) was isolated as a clear oil.

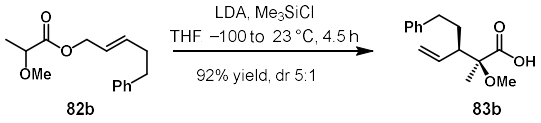
Data for the mixture of diastereomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (overlapping dd, J = 5.8, 3.0 Hz, 5H), 7.42 – 7.33 (overlapping m, 6H), 7.29 – 7.23 (overlapping m, 4H), 5.97 (dt, J = 17.1, 9.9 Hz, 0.55H), 5.80 (dt, J = 17.1, 10.0 Hz, 1H), 5.35 (overlapping ddd, J = 15.8, 10.2, 1.9 Hz, 1.51H), 5.25 (overlapping td, J = 16.6, 16.1, 1.9 Hz, 1.49H), 4.67 – 4.57 (overlapping singlet (major) and doublet (minor) , 2.40H), 4.45 (d, J = 10.9 Hz, 0.50H), 2.82 (overlapping dddd, J = 18.8, 14.6, 9.8, 4.8 Hz, 0.62H), 2.60 (ddd, J = 11.9, 9.9, 2.6 Hz, 1H), 2.58 – 2.48 (m, 2H), 2.17 – 2.10 (m, 0.52H), 2.03

(dddd, J = 13.2, 10.0, 7.0, 2.6 Hz, 1H), 1.88 (tdd, J = 10.8, 8.6, 4.8 Hz, 1H), 1.74 – 1.68 (m, 0.57H), 1.62 (s, 1.40H), 1.59 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.52, 142.04, 141.92, 138.24, 137.85, 137.12, 136.47, 129.31, 128.82, 128.79, 128.55, 128.51, 128.48, 128.45, 128.43, 128.40, 128.37, 128.34, 128.27, 127.71, 127.55, 127.47, 127.44, 127.35, 125.85, 125.74, 119.48, 118.74, 82.62, 82.47, 77.25, 77.00, 76.75, 66.80, 66.02, 52.27, 51.24, 33.63, 33.30, 30.29, 29.74, 19.83, 18.62. HRMS (ESI) calcd for $C_{21}H_{25}O_3$ $[M + H]^+$ 325.1798, found 325.1790.



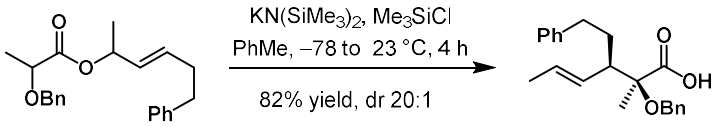
Carboxylic acid 83b: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **82b** (62 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 µL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83b** (50 mg, 0.203 mmol, 81% yield, dr 17:1) was isolated as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, J = 7.5 Hz, 2H), 7.20 – 7.05 (m, 3H), 5.63 (dt, J = 17.1, 10.0 Hz, 1H), 5.24 (dd, J = 10.1, 1.9 Hz, 1H), 5.14 (dd, J = 17.1, 2.0 Hz, 1H), 3.32 (s, 3H), 2.69 (ddd, J = 14.7, 10.6, 4.7 Hz, 1H), 2.48 – 2.34 (m, 2H), 1.92 – 1.81 (m, 1H), 1.67 (dtd, J = 13.4, 10.8, 4.7 Hz, 1H), 1.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.85, 142.07, 136.42, 128.37, 128.24, 125.71, 119.34, 82.48, 52.29, 52.06, 33.67, 30.13, 17.27. HRMS (ESI) calcd for $C_{15}H_{21}O_3$ $[M + H]^+$ 249.1485, found 249.1477.



Carboxylic acid 83b: The title compound was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **82b** (62 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83b** with its diastereomer (57 mg, 0.229 mmol, 92% yield, dr 5:1) was isolated as a clear oil.

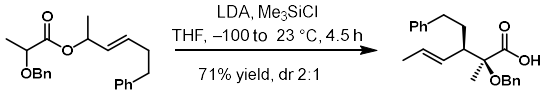
Data for the mixture of diastereomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 – 7.22 (overlapping multiplets, 2.38H), 7.18 – 7.11 (overlapping multiplets, 3.56H), 5.86 – 5.73 (m, 0.19H), 5.63 (dt, J = 17.1, 10.0 Hz, 1H), 5.23 (overlapping doublets, J = 12.8, 10.2, 1.9 Hz, 1.19H), 5.13 (overlapping doublets, J = 19.4, 17.0, 1.9 Hz, 1.18H), 3.32 (s, 3H), 3.25 (s, 0.58H), 2.70 (overlapping tdd, J = 14.8, 10.0, 4.9 Hz, 1.19H), 2.43 (overlapping multiplets, 2.18H), 2.33 (ddd, J = 11.9, 9.7, 2.5 Hz, 0.20H), 1.98 – 1.82 (overlapping multiplets, 1.19H), 1.67 (ddt, J = 13.3, 10.8, 5.3 Hz, 1H), 1.55 (dddd, J = 13.7, 11.3, 9.4, 4.7 Hz, 0.20H), 1.40 (s, 0.53H), 1.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.74, 143.87, 142.06, 141.91, 137.01, 136.41, 136.22, 128.46, 128.37, 128.28, 128.23, 125.79, 125.71, 119.33, 118.60, 82.47, 82.19, 54.64, 52.29, 52.06, 51.45, 50.88, 33.68, 33.39, 30.13, 29.84, 29.68, 18.61, 17.28. HRMS (ESI) calcd for $C_{15}H_{21}O_3$ $[M + H]^+$ 249.1485, found 249.1475.



82c 83c

Carboxylic acid 83c: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **82c** (85 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 µL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83c** (69 mg, 0.204 mmol, 82% yield, dr 20:1) was isolated as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.24 (m, 7H), 7.19 (td, J = 6.3, 1.7 Hz, 3H), 5.61 (dq, J = 15.4, 6.4 Hz, 1H), 5.35 (ddt, J = 15.3, 9.6, 1.7 Hz, 1H), 4.56 (s, 2H), 2.73 (ddd, J = 14.6, 10.4, 4.8 Hz, 1H), 2.48 (tdd, J = 17.0, 9.9, 4.7 Hz, 2H), 2.01 – 1.90 (m, 1H), 1.77 (dd, J = 6.4, 1.7 Hz, 3H), 1.49 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.43, 142.26, 138.42, 130.02, 129.07, 128.41, 128.27, 128.21, 127.45, 127.30, 125.65, 82.93, 66.72, 51.07, 33.76, 30.60, 18.38, 18.08. HRMS (ESI) calcd for $C_{22}H_{27}O_3$ $[M + H]^+$ 339.1955, found 339.1962.

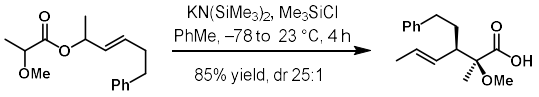


82c 83c

Carboxylic acid 83c: The title mixture was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **82c** (85 mg,

0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **5c** with its diastereomer (60 mg, 0.178 mmol, 71% yield, dr 2:1) was isolated as a clear oil.

Data for the mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 5H), 7.34 – 7.24 (m, 7H), 7.23 – 7.15 (m, 4H), 5.65 – 5.46 (overlapping multiplets, 2.26H), 5.33 (ddq, J = 15.0, 9.7, 1.6 Hz, 1H), 4.53 (overlapping singlet and doublet, J = 17.8 Hz, 2.59H), 4.38 (d, J = 10.9 Hz, 0.6H), 2.73 (overlapping dd, J = 18.3, 14.6, 9.8, 4.8 Hz, 1.62H), 2.53 – 2.34 (overlapping multiplets, 2.55H), 2.38 (ddd, J = 11.4, 9.1, 2.4 Hz, 0.71H), 2.08 – 2.00 (m, 0.58H), 1.99 – 1.89 (m, 1H), 1.76 (td, J = 6.1, 1.4 Hz, 6H), 1.60 (dddd, J = 13.6, 11.4, 9.1, 4.9 Hz, 0.77H), 1.52 (s, 1.76H), 1.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.06, 142.26, 142.13, 138.37, 138.04, 130.06, 129.66, 129.36, 129.05, 128.53, 128.41, 128.36, 128.32, 128.29, 128.28, 128.21, 127.62, 127.47, 127.40, 127.31, 125.75, 125.65, 82.96, 82.73, 66.73, 65.99, 51.04, 50.20, 33.77, 33.46, 30.62, 30.13, 19.83, 18.40, 18.08, 18.01. HRMS (ESI) calcd for $C_{22}H_{27}O_3$ $[M + H]^+$ 339.1955, found 339.1960.

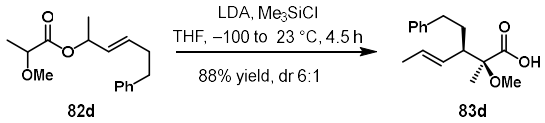


82d 83d

Carboxylic acid 83d: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **82d** (66 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 µL, 54 mg, 0.500 mmol, 2 equiv). After column

chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83d** (56 mg, 0.213 mmol, 85% yield, dr 25:1) was isolated as a clear oil.

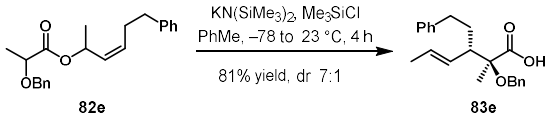
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 2H), 7.19 – 7.13 (m, 3H), 5.56 (dq, J = 15.2, 6.4 Hz, 1H), 5.28 – 5.18 (m, 1H), 3.32 (s, 3H), 2.67 (ddd, J = 13.8, 10.6, 4.7 Hz, 1H), 2.48 – 2.31 (m, 2H), 1.84 (dddd, J = 13.2, 10.6, 6.7, 2.5 Hz, 1H), 1.63 (dtd, J = 13.2, 10.8, 4.8 Hz, 1H), 1.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.05, 142.27, 129.98, 128.96, 128.36, 128.19, 125.63, 82.86, 52.26, 50.84, 33.82, 30.47, 18.04, 17.07. HRMS (ESI) calcd for $C_{16}H_{23}O_3$ $[M + H]^+$ 263.1642, found 263.1633.



Carboxylic acid 83d: The title mixture was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **82d** (66 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83d** (58 mg, 0.219 mmol, 88% yield, dr 6:1) was isolated as a clear oil.

Data for the mixture of diastereomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (overlapping dd, J = 8.6, 6.8 Hz, 2.34H), 7.16 (overlapping td, J = 6.7, 1.6 Hz, 3.50H), 5.54 (overlapping ddq, J = 21.5, 15.1, 6.3 Hz, 1.17H), 5.46 – 5.38 (m, 0.17H), 5.24 (ddq, J = 15.0, 9.6, 1.6 Hz, 1H), 3.31 (s, 3H), 3.23 (s, 0.51H), 2.82 – 2.59 (overlapping multiplets, 1.17H), 2.46 – 2.33 (overlapping multiplets, 2.16H), 2.27 (ddd, J = 11.7, 9.5, 2.5 Hz,

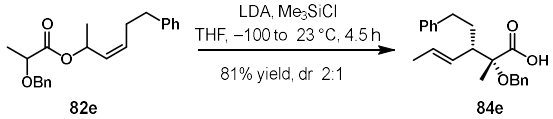
0.17H), 1.94 – 1.81 (overlapping multiplets, 1.17H), 1.73 (overlapping doublets, J = 6.2, 1.6 Hz, 3.50H), 1.63 (dtd, J = 13.2, 10.8, 4.8 Hz, 1H), 1.54 – 1.48 (m, 0.18H), 1.38 (s, 0.51H), 1.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.71, 142.27, 142.11, 130.00, 129.54, 129.27, 128.94, 128.46, 128.37, 128.24, 128.20, 125.72, 125.64, 82.87, 82.50, 52.26, 51.39, 50.82, 49.68, 33.83, 33.52, 30.50, 30.07, 18.73, 18.05, 17.98, 17.11. HRMS (ESI) calcd for $C_{16}H_{23}O_3$ $[M + H]^+$ 263.1642, found 263.1654.



Carboxylic acid 83e: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **82e** (85 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 μL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83e** (69 mg, 0.204 mmol, 81% yield, dr 7:1) was isolated as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.28 (overlapping multiplets, 8H), 7.22 – 7.17 (overlapping multiplets, 3.38H), 5.58 (overlapping multiplets, 1.15H), 5.55 – 5.47 (m, 1H), 5.39 – 5.28 (m, 0.14H), 4.59 – 4.51 [overlapping singlet (minor) and doublet(major), 1.28H], 4.38 (d, J = 10.9 Hz, 1H), 2.75 (overlapping multiplets, 1.14H), 2.52 – 2.42 (overlapping multiplets, 1.14H), 2.38 (m, 1.28H), 2.09 – 2.01 (m, 1H), 1.94 (dtd, J = 13.1, 7.2, 6.8, 3.7 Hz, 0.15H), 1.80 – 1.75 (overlapping doublets, 3.42H), 1.60 (dddd, J = 13.5, 11.3, 9.1, 4.9 Hz, 1H), 1.52 (s, 3H), 1.49 (s, 0.40H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.31, 142.25, 142.13, 138.38, 138.05, 130.03, 129.66, 129.33, 129.05,

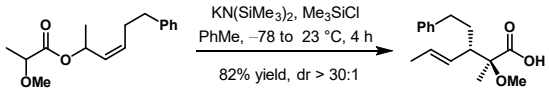
128.52, 128.41, 128.34, 128.27, 128.21, 127.60, 127.46, 127.39, 127.30, 125.74, 125.64, 82.94, 82.72, 66.71, 65.99, 51.04, 50.21, 33.76, 33.46, 30.60, 30.13, 19.81, 18.40, 18.08, 18.01. HRMS (ESI) calcd for $C_{22}H_{27}O_3$ $[M + H]^+$ 339.1955, found 339.1948.



Carboxylic acid 84e: The title mixture was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **82e** (85 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30%EtOAc-hexanes), acid **84e** with its diastereomer (69 mg, 0.204 mmol, 81% yield, dr 2:1) was isolated as a clear oil.

Data for the mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.24 (m, 12H), 7.23 – 7.15 (m, 5H), 5.64 – 5.47 (overlapping multiplets, 2.55H), 5.33 (ddq, J = 15.0, 9.7, 1.6 Hz, 0.55H), 4.57 – 4.50 (overlapping singlet (minor) and doublet (major), 2.10H), 4.38 (d, J = 10.9 Hz, 1H), 2.79 – 2.68 (overlapping multiplets, 2.55H), 2.52 – 2.42 (m, 2H), 2.38 (ddd, J = 11.4, 9.1, 2.5 Hz, 1H), 2.09 – 2.00 (m, 1H), 1.98 – 1.90 (m, 0.55H), 1.77 (overlapping triplets, J = 6.1, 1.4 Hz, 4.64H), 1.60 (dddd, J = 13.6, 11.4, 9.1, 4.8 Hz, 1.10H), 1.52 (s, 3H), 1.48 (s, 1.63H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.06, 142.25, 142.13, 138.34, 137.99, 130.15, 130.07, 129.64, 129.37, 129.03, 128.53, 128.46, 128.42, 128.36, 128.30, 128.28, 128.21, 127.63, 127.48, 127.41, 127.31, 125.76, 125.65,

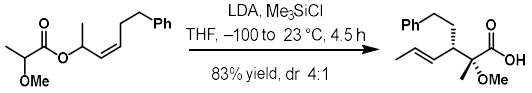
82.96, 82.74, 66.73, 65.97, 51.03, 50.12, 33.77, 33.45, 30.62, 30.14, 19.84, 18.41, 18.08, 18.01. HRMS (ESI) calcd for $C_{22}H_{27}O_3$ $[M + H]^+$ 339.1955, found 339.1962.



82f 83f

Carboxylic acid 83f: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **82f** (66 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 µL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83f** (54 mg, 0.207 mmol, 82% yield) was isolated as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 7.19 – 7.13 (m, 3H), 5.52 (dq, J = 15.1, 6.1 Hz, 1H), 5.42 (ddd, J = 15.2, 9.4, 1.7 Hz, 1H), 3.22 (s, 3H), 2.70 (ddd, J = 14.0, 9.5, 4.8 Hz, 1H), 2.39 (ddd, J = 13.7, 9.2, 7.7 Hz, 1H), 2.25 (ddd, J = 11.7, 9.3, 2.4 Hz, 1H), 1.90 (dddd, J = 12.6, 9.8, 7.7, 2.3 Hz, 1H), 1.74 (dd, J = 6.2, 1.4 Hz, 3H), 1.49 (dddd, J = 13.6, 11.4, 9.3, 4.8 Hz, 1H), 1.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.18, 142.11, 129.54, 129.26, 128.46, 128.24, 125.71, 82.48, 51.36, 49.62, 33.50, 30.05, 18.73, 17.97. HRMS (ESI) calcd for $C_{16}H_{23}O_3$ $[M + H]^+$ 263.1642, found 263.1652.

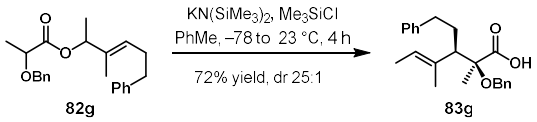


82f 84f

Carboxylic acid 84f: The title mixture was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition

of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **82f** (66 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **84f** with its diastereomer (55 mg, 0.208 mmol, 83% yield, dr 4:1) was isolated as a clear oil.

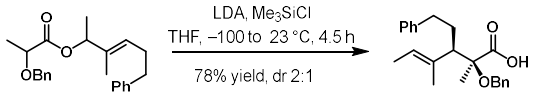
Data for the mixture of diastereomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 - 7.23 (overlapping multiplets, 3H), 7.19 - 7.13 (overlapping multiplets, 4H), 5.58 – 5.47 (overlapping multiplets, 1.25H), 5.45 – 5.38 (m, 1H), 5.23 (ddq, J = 15.0, 9.6, 1.6 Hz, 0.23H), 3.30 (s, 0.66H), 3.22 (s, 3H), 2.69 (ddt, J = 16.0, 11.1, 5.6 Hz, 1.23H), 2.44 – 2.34 (overlapping multiplets, 1.49H), 2.26 (ddd, J = 11.7, 9.5, 2.5 Hz, 1H), 1.93 – 1.86 (m, 1H), 1.86 – 1.80 (m, 0.24H), 1.72 (overlapping dd, J = 6.0, 1.6 Hz, 3.67H), 1.62 (dtd, J = 13.2, 10.9, 4.8 Hz, 0.23H), 1.49 (dddd, J = 13.5, 11.2, 9.4, 4.8 Hz, 1H), 1.37 (s, 3H), 1.35 (s, 0.69H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.24, 142.26, 142.11, 142.10, 129.98, 129.54, 129.25, 128.94, 128.45, 128.36, 128.23, 128.18, 125.70, 125.62, 82.84, 82.48, 52.25, 51.39, 50.81, 49.67, 33.82, 33.51, 30.49, 30.06, 18.71, 18.04, 17.97, 17.11. HRMS (ESI) calcd for $C_{16}H_{23}O_3$ $[M + H]^+$ 263.1642, found 263.1633.



Carboxylic acid 83g: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **82g** (88 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 µL, 54 mg, 0.500 mmol, 2 equiv). After column

chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83g** (63 mg, 0.179 mmol, 72% yield, dr 25:1) was isolated as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 4H), 7.32 – 7.28 (m, 1H), 7.28 – 7.23 (m, 2H), 7.19 – 7.14 (m, 3H), 5.44 (h, J = 4.7 Hz, 1H), 4.54 (q, 2H), 2.56 (ddd, J = 14.6, 10.4, 4.6 Hz, 1H), 2.49 (dd, J = 11.8, 3.0 Hz, 1H), 2.38 (ddd, J = 13.9, 10.1, 6.9 Hz, 1H), 2.15 – 2.05 (m, 1H), 1.82 (dddd, J = 13.8, 10.3, 7.0, 3.1 Hz, 1H), 1.68 (overlapping doublet and singlet, J = 5.2 Hz, 6H), 1.49 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.89, 142.36, 138.43, 132.85, 130.17, 128.38, 128.28, 128.18, 127.43, 127.42, 125.75, 125.63, 83.13, 66.64, 56.72, 33.93, 28.61, 19.81, 13.42, 13.35. HRMS (ESI) calcd for $C_{23}H_{29}O_3$ [M + H]$^+$ 353.2111, found 353.2102.

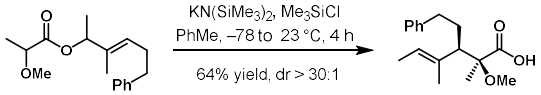


82g 83g

Carboxylic acid 83g: The mixture was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **82g** (88 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83g** with its diastereomer (69 mg, 0.196 mmol, 78% yield, dr 2:1) was isolated as a clear oil.

Data for the mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 6H), 7.33 – 7.24 (m, 5H), 7.21 – 7.14 (m,4H), 5.48 – 5.35 (overlapping multiplets, 1.49H), 4.56 (overlapping doublets, J = 11.0 Hz, 1.45H), 4.51 (d, J = 10.9 Hz, 1H), 4.45

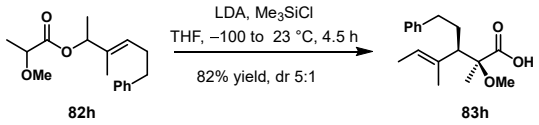
(d, J = 11.0 Hz, 0.50H), 2.64 – 2.52 (overlapping multiplets, 1.58H), 2.48 (dd, J = 11.8, 3.1 Hz, 1H), 2.43 – 2.32 (m, 2H), 2.10 (dddd, J = 13.5, 11.6, 10.1, 4.6 Hz, 1H), 2.05 – 1.99 (m, 0.44H), 1.99 – 1.90 (m, 0.52H), 1.86 – 1.77 (m, 1H), 1.74 – 1.71 (m, 1.53H), 1.68 (t, J = 2.8 Hz, 6H), 1.63 (dd, J = 6.7, 1.2 Hz, 1.58H), 1.55 (s, 1.47H), 1.49 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.21, 179.52, 142.44, 142.36, 141.98, 138.63, 138.50, 134.39, 132.87, 130.15, 129.63, 128.42, 128.37, 128.25, 128.23, 128.21, 128.16, 127.41, 127.37, 127.33, 127.31, 125.73, 125.69, 125.61, 124.80, 84.14, 83.07, 66.93, 66.61, 57.04, 56.73, 33.94, 33.83, 28.59, 27.59, 19.87, 19.84, 13.53, 13.42, 13.37, 13.35. HRMS (ESI) calcd for $C_{23}H_{29}O_3$ $[M + H]^+$ 353.2111, found 353.2106.



Carboxylic acid 83h: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **82h** (69 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 µL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83h** (45 mg, 0.161 mmol, 64% yield, dr > 30:1) was isolated as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 2H), 7.19 – 7.10 (m, 3H), 5.39 (q, J = 6.4 Hz, 1H), 3.30 (s, 3H), 2.52 (ddd, J = 14.7, 10.6, 4.6 Hz, 1H), 2.43 – 2.30 (m, 2H), 1.99 (dddd, J = 13.3, 11.7, 10.2, 4.7 Hz, 1H), 1.71 (tdt, J = 10.0, 6.6, 2.9 Hz, 1H), 1.68 – 1.55 (m, 6H), 1.35 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.54, 142.36, 132.80, 128.34,

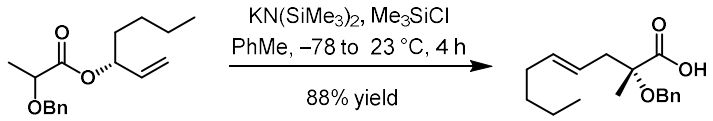
128.16, 125.61, 83.05, 56.47, 51.96, 33.94, 28.52, 18.55, 13.39, 13.10. HRMS (ESI) calcd for $C_{17}H_{25}O_3$ $[M + H]^+$ 277.1798, found 277.1806.



82h 83h

Carboxylic acid 83h: The title mixture was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **82h** (69 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83h** with its diastereomer (57 mg, 0.206 mmol, 82% yield, dr 5:1) was isolated as a clear oil.

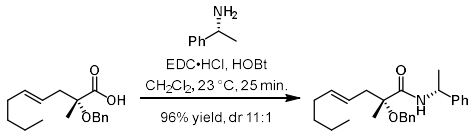
Data for the mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.24 (overlapping multiplets, 2.47H), 7.22 – 7.14 (overlapping multiplets, 3.62H), 5.44 – 5.32 (overlapping quartets, 1.20H), 3.31 (s, 3H), 3.28 (s, 0.60H), 2.54 (overlapping ddd, J = 18.5, 9.4, 4.1 Hz, 1.20H), 2.44 – 2.30 (overlapping multiplets, 2.41H), 2.01 (dddd, J = 13.5, 11.9, 10.3, 4.7 Hz, 1H), 1.93 – 1.85 (m, 0.40H), 1.74 (overlapping tdt, J = 13.7, 10.2, 6.8, 3.1 Hz, 1.20H), 1.69 (t, J = 1.2 Hz, 0.57H), 1.66 (overlapping singlets, 6H), 1.62 (dd, J = 6.7, 1.2 Hz, 0.63H), 1.43 (s, 0.58H), 1.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.81, 178.98, 142.44, 142.35, 134.16, 132.82, 128.36, 128.32, 128.21, 128.14, 125.67, 125.59, 125.58, 124.75, 83.88, 83.01, 56.61, 56.50, 52.20, 51.94, 33.94, 33.86, 28.49, 27.72, 18.85, 18.55, 13.38, 13.10. HRMS (ESI) calcd for $C_{17}H_{25}O_3$ $[M + H]^+$ 277.1798, found 277.1790.



82i 83i

Carboxylic acid 83i: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **82i** (69 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 µL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83i** (61 mg, 0.220 mmol, 88% yield) was isolated as a clear oil.

$[\alpha]_D^{25}$ + 5.4 (*c* 1.0, $CHCl_3$).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.27 (m, 5H), 5.68 – 5.49 (m, 1H), 5.49 – 5.36 (m, 1H), 4.55 (d, J = 2.1 Hz, 2H), 2.69 – 2.44 (m, 2H), 2.03 (q, J = 6.9 Hz, 2H), 1.53 (s, 3H), 1.41 – 1.20 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.40, 137.87, 135.56, 128.35, 127.65, 123.00, 122.91, 80.58, 66.39, 40.78, 32.26, 31.45, 22.09, 21.31, 13.86. HRMS (ESI) calcd for $C_{17}H_{25}O_3$ $[M + H]^+$ 277.1798, found 277.1788.

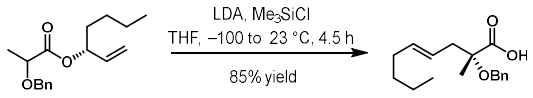


83i S49

Amide S49 from the $KN(SiMe_3)_2$ reaction: EDC·HCl (31 mg, 0.162 mmol, 1.5 equiv), (*R*)-(+)-alpha-methylbenzylamine (21 µL, 20 mg, 0.162 mmol, 1.5 equiv), and HOBt (30 mg, 0.162 mmol, 1.5 equiv) were added sequentially to a solution of acid **83i** (30 mg, 0.108 mmol) in CH_2Cl_2 (0.82 mL). The solution was stirred at room temperature for 25 min, then diluted with CH_2Cl_2 (10 mL) and washed with 1 M HCl

(10 mL), water (10 mL), saturated aqueous sodium bicarbonate (10 mL), brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **S49** (39 mg, 0.102 mmol, 96% yield, dr 11:1) as a clear oil.

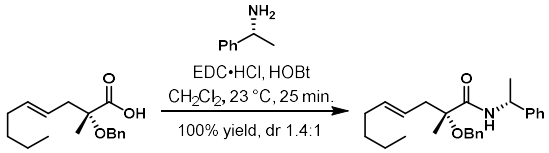
$[\alpha]_D^{25}$ +1.40 (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 5H), 7.28 – 7.22 (m, 6H), 6.98 (d, J = 8.5 Hz, 1H), 5.61 – 5.52 (m, 1H), 5.48 – 5.34 (m, 1H), 5.20 – 5.08 (m, 1H), 4.52 (d, J = 11.0 Hz, 1H), 4.39 (d, J = 11.0 Hz, 1H), 2.60 (ddd, J = 14.4, 7.0, 1.2 Hz, 1H), 2.54 – 2.45 (m, 1H), 2.03 (q, J = 6.9 Hz, 2H), 1.52 – 1.37 (m, 6H), 1.39 – 1.25 (m, 3H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.20, 143.28, 138.21, 134.54, 128.60, 128.49, 128.45, 128.42, 127.57, 127.28, 127.24, 127.19, 126.04, 126.00, 123.73, 81.19, 65.34, 48.29, 40.56, 32.33, 31.52, 22.18, 22.03, 21.36, 13.91. HRMS (ESI) calcd for $C_{25}H_{34}NO_2$ $[M + H]^+$ 380.2584, found 380.2591.



82i 83i

Carboxylic acid 83i with LDA: The title compound was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **82i** (69 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83i** (59 mg, 0.213 mmol, 85% yield) was isolated as a clear oil.

$[\alpha]_D^{25}$ -0.289 (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 4H), 7.33 – 7.28 (m, 1H), 5.63 – 5.55 (m, 1H), 5.47 – 5.39 (m, 1H), 4.58 – 4.52 (m, 2H), 2.68 – 2.51 (m, 2H), 2.08 – 1.98 (m, 2H), 1.53 (s, 3H), 1.38 – 1.25 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.92, 137.78, 135.62, 128.39, 127.75, 127.67, 122.85, 80.65, 66.34, 40.67, 32.27, 31.46, 22.11, 21.35, 13.88. HRMS (ESI) calcd for $C_{17}H_{25}O_3$ $[M + H]^+$ 277.1798, found 277.1792.

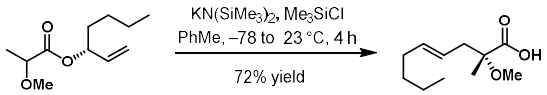


83i **S49**

Amide S49 from the LDA reaction: EDC·HCl (43 mg, 0.225 mmol, 1.5 equiv), (R)-(+)-alpha-methylbenzylamine (29 μL, 27 mg, 0.225 mmol, 1.5 equiv), and HOBt (31 mg, 0.225 mmol, 1.5 equiv) were added sequentially to a solution of acid **83i** (41 mg, 0.150 mmol) in CH_2Cl_2 (1 mL). The solution was stirred at room temperature for 25 min, then diluted with CH_2Cl_2 (10 mL) and washed with 1 M HCl (10 mL), water (10 mL), saturated aqueous sodium bicarbonate (10 mL), brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **S49** (57 mg, 0.150 mmol, 100% yield, dr 1.4:1) as a clear oil.

$[\alpha]_D^{25}$ +1.40 (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.28 (overlapping multiplets, 10H), 7.28 – 7.22 (overlapping multiplets, 7.31H), 6.98 (overlapping dd, J = 12.6, 8.4 Hz, 1.5H), 5.55 (dtt, J = 14.7, 6.6, 1.3 Hz, 1H), 5.50 – 5.38 (overlapping multiplets, 1.73H), 5.30 – 5.23 (m, 0.73H), 5.11 (overlapping ddt, J = 9.8, 7.0, 4.9 Hz,

1.73H), 4.52 (overlapping doublets, J = 11.0, 7.0 Hz, 1.72H), 4.46 (d, J = 11.0 Hz, 0.74H), 4.38 (d, J = 11.0 Hz, 1H), 2.63 – 2.54 (overlapping multiplets, 1.72H), 2.53 – 2.43 (overlapping multiplets, 1.73H), 2.02 (q, J = 6.9 Hz, 2H), 1.90 (q, J = 6.8 Hz, 1.5H), 1.49 (s, 2.18H), 1.47 – 1.42 [overlapping singlet (major) and two triplets (minor and major), 8.07H], 1.38 – 1.28 (overlapping multiplets, 4.29H), 1.28 – 1.19 (overlapping multiplets, 5.24H), 0.91 – 0.82 (overlapping multiplets, 5.17H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.30, 173.17, 143.36, 143.28, 138.31, 138.20, 134.52, 128.59, 128.48, 128.44, 128.40, 127.58, 127.56, 127.27, 127.22, 127.18, 127.10, 126.03, 125.99, 123.73, 123.62, 81.19, 81.09, 65.33, 65.17, 48.27, 48.22, 40.56, 40.16, 32.33, 32.23, 31.51, 31.39, 29.67, 22.18, 22.17, 22.02, 21.95, 21.65, 21.35, 13.91, 13.89. HRMS (ESI) calcd for $C_{25}H_{34}NO_2$ $[M + H]^+$ 380.2584, found 380.2595.

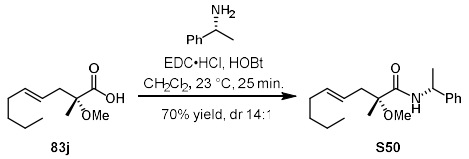


82j 83j

Carboxylic acid 83j with $KN(SiMe_3)_2$: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **82j** (50 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 µL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83j** (36 mg, 0.180 mmol, 72% yield) was isolated as a clear oil.

$[\alpha]_D^{25}$ + 46.1 (*c* 1.0, $CHCl_3$).^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 – 5.47 (m, 1H), 5.33 (dt, J = 14.8, 7.2 Hz, 1H), 3.34 (s, 3H), 2.47 (qd, J = 14.5, 7.1 Hz, 2H), 2.00 (q, J = 6.9 Hz, 2H), 1.41 (s, 3H), 1.36 – 1.24 (m, 4H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$)

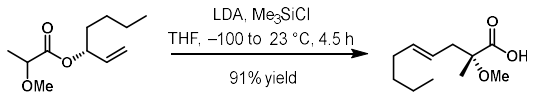
δ 177.77, 135.55, 122.72, 80.46, 51.51, 40.01, 32.25, 31.44, 22.09, 20.51, 13.85. HRMS (ESI) calcd for $C_{11}H_{21}O_3$ $[M + H]^+$ 201.1485, found 201.1480.



83j S50

Amide S50 from the $KN(SiMe_3)_2$ reaction: EDC·HCl (43 mg, 0.225 mmol, 1.5 equiv), (R)-(+)-alpha-methylbenzylamine (29 µL, 27 mg, 0.225 mmol, 1.5 equiv), and HOBt (31 mg, 0.225 mmol, 1.5 equiv) were added sequentially to a solution of acid **83j** (30 mg, 0.150 mmol) in CH_2Cl_2 (1 mL). The solution was stirred at room temperature for 25 min, then diluted with CH_2Cl_2 (10 mL) and washed with 1 M HCl (10 mL), water (10 mL), saturated aqueous sodium bicarbonate (10 mL), brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **S50** (32 mg, 0.105 mmol, 70% yield, dr 14:1) as a clear oil.

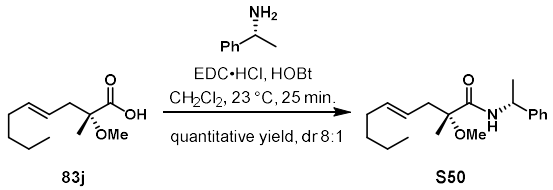
$[\alpha]_D^{25}$ + 33.9 (*c* 1.0, $CHCl_3$).^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (dtt, J = 14.7, 6.6, 1.3 Hz, 1H), 5.32 (dtt, J = 15.5, 7.1, 1.4 Hz, 1H), 5.09 (dt, J = 8.5, 6.7 Hz, 1H), 3.24 (s, 2H), 2.52 – 2.46 (m, 1H), 2.41 – 2.36 (m, 1H), 2.01 (q, J = 6.7 Hz, 2H), 1.47 (d, J = 6.9 Hz, 3H), 1.38 – 1.21 (m, 8H), 0.89 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.22, 143.36, 134.27, 128.58, 127.17, 126.10, 123.72, 80.72, 50.43, 48.17, 39.38, 32.31, 31.50, 22.16, 21.94, 20.80, 13.91. HRMS (ESI) calcd for $C_{19}H_{30}NO_2$ $[M + H]^+$ 304.2271, found 304.2262.



82j 83j

Carboxylic acid 83j with LDA: The title compound was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **82j** (50 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **83j** (46 mg, 0.228 mmol, 91% yield) was isolated as a clear oil.

$[\alpha]_D^{25}$ -1.52 (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CHCDl_3$) δ 5.52 (dtt, J = 15.0, 6.8, 1.3 Hz, 1H), 5.38 – 5.31 (m, 1H), 3.33 (s, 3H), 2.55 – 2.38 (m, 2H), 2.03 – 1.95 (m, 2H), 1.40 (s, 3H), 1.36 – 1.22 (m, 3H), 0.86 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.80, 135.53, 122.72, 80.41, 51.52, 40.04, 32.25, 31.44, 22.09, 20.51, 13.85. HRMS (ESI) calcd for $C_{11}H_{21}O_3$ $[M + H]^+$ 201.1485, found 201.1489.

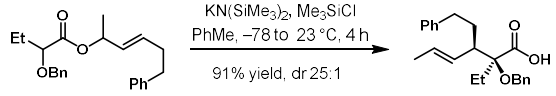


83j S50

Amide S50 from the LDA reaction: EDC·HCl (43 mg, 0.225 mmol, 1.5 equiv), (R)-(+)-alpha-methylbenzylamine (29 µL, 27 mg, 0.225 mmol, 1.5 equiv), and HOBt (31 mg, 0.225 mmol, 1.5 equiv) were added sequentially to a solution of acid **83j** (30 mg, 0.150 mmol) in CH_2Cl_2 (1 mL). The solution was stirred at room temperature for 25 min, then diluted with CH_2Cl_2 (10 mL) and washed with 1 M HCl (10 mL), water (10

mL), saturated aqueous sodium bicarbonate (10 mL), brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc-hexanes) to give amide **S50** (45 mg, 0.150 mmol, quantitative yield, dr 8:1) as a clear oil.

$[\alpha]_D^{25}$ +34.1 (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.28 (overlapping multiplets, 4.51H), 7.28 – 7.22 (overlapping multiplets, 1.13H), 6.92 (d, J = 8.6 Hz, 1H), 5.51 (dtt, J = 14.9, 6.8, 1.3 Hz, 1H), 5.41 (dtt, J = 14.8, 6.7, 1.4 Hz, 0.13H), 5.32 (dtt, J = 15.6, 7.1, 1.4 Hz, 1H), 5.17 (dtt, J = 15.5, 7.1, 1.5 Hz, 0.13H), 5.09 (overlapping dt, J = 8.6, 6.8 Hz, 1.13H), 3.26 (s, 0.40H), 3.24 (s, 3H), 2.52 – 2.47 (overlapping multiplets, 1.12H), 2.39 (overlapping dddd, J = 15.9, 8.5, 2.3, 1.2 Hz, 1.14H), 2.01 (q, J = 6.8 Hz, 2H), 1.88 (q, J = 6.6 Hz, 0.25H), 1.48 (overlapping doublets, J = 12.1, 6.9 Hz, 3.40H), 1.36 (s, 0.39H), 1.34 – 1.23 [overlapping singlet (major) and multiplets (minor and major), 7.55H), 0.93 – 0.83 (overlapping triplets, J = 7.1 Hz, 3.43H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.20, 143.35, 134.24, 134.21, 128.66, 128.56, 128.45, 127.15, 127.08, 126.15, 126.07, 123.71, 123.60, 80.70, 50.41, 50.32, 48.16, 48.08, 39.37, 39.30, 32.40, 32.29, 32.19, 31.49, 31.34, 29.65, 22.15, 21.93, 21.81, 20.87, 20.79, 13.90. HRMS (ESI) calcd for $C_{19}H_{30}NO_2$ $[M + H]^+$ 304.2271, found 304.2279.

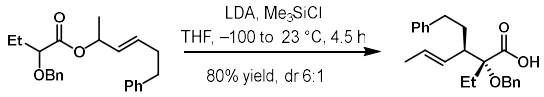


85a 86a

Carboxylic acid 86a: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **85a** (88 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL

rinses) and chlorotrimethylsilane (63 μL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **86a** (80 mg, 0.227 mmol, 91% yield, dr 25:1) was isolated as a clear oil.

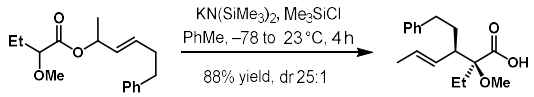
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 7H), 7.22 – 7.15 (m, 3H), 5.72 – 5.53 (m, 1H), 5.35 (ddq, J = 15.0, 9.7, 1.6 Hz, 1H), 4.64 (d, J = 10.5 Hz, 1H), 4.48 (d, J = 10.5 Hz, 1H), 2.75 (ddd, J = 14.3, 9.1, 5.6 Hz, 1H), 2.63 (td, J = 9.9, 3.9 Hz, 1H), 2.46 (ddd, J = 13.9, 9.5, 7.5 Hz, 1H), 1.99 (ddt, J = 37.1, 14.8, 7.4 Hz, 2H), 1.89 – 1.74 (m, 5H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.42, 141.95, 137.32, 130.37, 129.70, 129.48, 129.10, 128.75, 128.64, 128.61, 128.49, 128.41, 128.33, 128.05, 127.81, 127.62, 125.94, 125.82, 86.35, 65.53, 64.11, 48.81, 46.64, 33.94, 32.98, 31.43, 30.47, 26.11, 25.58, 18.19, 18.04, 8.14, 7.76. HRMS (ESI) calcd for $C_{23}H_{29}O_3$ $[M + H]^+$ 353.2111, found 353.2101.



85a 87a

Carboxylic acid 87a: The title compound was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 μL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 μL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **85a** (69 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **87a** (65 mg, 0.199 mmol, 80% yield, dr 6:1) was isolated as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.10 (overlapping m, 11.7H), 5.63 – 5.49 (m, 2H), 4.61 (d, J = 10.4 Hz, 0.16H), 4.44 (d, J = 10.4 Hz, 0.16H), 4.25 (d, J = 10.2 Hz, 1H), 4.03 (d, J = 10.2 Hz, 1H), 2.74 (overlapping ddd, J = 13.1, 7.9, 4.8 Hz, 1.17H), 2.51 – 2.32 (overlapping m, 2.17H), 2.08 (dt, J = 15.2, 7.5 Hz, 1H), 2.04 – 1.90 (overlapping m, 1.38H), 1.81 – 1.66 (overlapping m, 5.8H), 1.55 – 1.41 (overlapping m, 1.32iH), 0.96 – 0.79 (overlapping m, 3.43H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.98, 141.90, 136.73, 131.81, 131.40, 130.43, 129.62, 129.48, 129.01, 128.72, 128.62, 128.44, 128.37, 128.34, 128.29, 128.27, 128.23, 128.17, 128.09, 127.80, 127.62, 125.91, 125.79, 125.64, 86.42, 86.01, 65.42, 63.99, 52.13, 51.88, 48.76, 46.52, 45.14, 44.68, 34.84, 34.26, 33.89, 33.54, 32.90, 31.37, 30.44, 26.11, 25.44, 23.25, 22.97, 18.15, 17.99, 17.94, 12.05, 11.91, 8.07, 7.75. HRMS (ESI) calcd for $C_{23}H_{29}O_3$ $[M + H]^+$ 353.2111, found 353.2104.

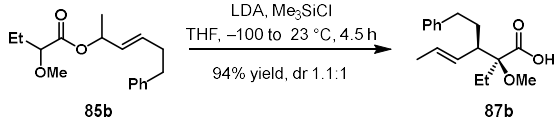


85b 86b

Carboxylic acid 86b: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **85b** (69 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 μL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **86b** (60 mg, 0.219 mmol, 88% yield, dr 25:1) was isolated as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (tt, J = 7.2, 1.7 Hz, 2H), 7.22 – 7.09 (m, 3H), 5.61 – 5.51 (m, 1H), 5.24 (ddq, J = 15.0, 9.8, 1.6 Hz, 1H), 3.33 (s, 3H), 2.69 (ddd, J = 14.4, 9.1, 5.9 Hz, 1H), 1.89 (dq, J = 14.9, 7.5 Hz, 1H), 1.82 – 1.71 (m, 6H), 0.83 (t, J = 7.4 Hz,

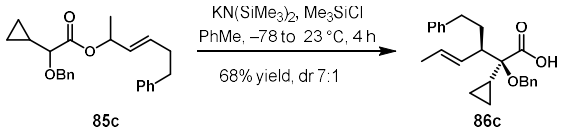
3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.35, 141.93, 130.04, 129.56, 129.12, 129.02, 128.56, 128.35, 128.23, 128.20, 125.77, 125.68, 85.81, 50.97, 49.14, 48.27, 45.99, 33.84, 33.02, 31.20, 30.19, 29.63, 25.36, 24.64, 18.07, 17.90, 7.79, 7.47. HRMS (ESI) calcd for $C_{17}H_{25}O_3$ $[M + H]^+$ 277.1798, found 277.1807.



Carboxylic acid 87b: The title compound was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 μL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 μL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **85b** (69 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **87b** with its diastereomer (65 mg, 0.235 mmol, 94% yield, dr 1.1:1) was isolated as a clear oil.

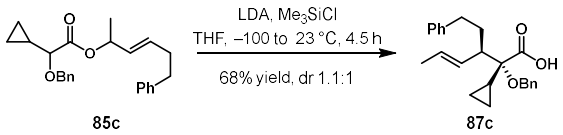
Data for the mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 5H), 7.22 – 7.10 (m, 6H), 5.61 – 5.44 (m, 3H), 5.24 (ddq, J = 15.0, 9.9, 1.7 Hz, 1H), 3.33 (s, 3H), 3.05 (s, 3H), 2.82 – 2.62 (m, 2H), 2.49 (dt, J = 10.0, 5.0 Hz, 1H), 2.39 (dq, J = 13.7, 8.4 Hz, 2H), 2.24 (ddd, J = 11.4, 7.3, 2.4 Hz, 1H), 2.02 – 1.84 (m, 3H), 1.82 – 1.70 (m, 8H), 1.58 (dt, J = 14.8, 7.3 Hz, 1H), 1.41 (dddd, J = 13.1, 11.5, 8.1, 4.8 Hz, 1H), 0.84 (d, J = 7.3 Hz, 3H), 0.82 – 0.71 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.26, 173.38, 141.93, 141.85, 130.07, 129.56, 129.14, 129.02, 128.57, 128.36, 128.24, 128.21, 125.78, 125.69, 85.84, 85.29, 50.97, 49.14, 48.28, 45.98, 33.85, 33.02, 31.20, 30.19, 25.38,

24.64, 18.08, 17.91, 7.79, 7.49. HRMS (ESI) calcd for $C_{17}H_{25}O_3$ $[M + H]^+$ 277.1798, found 277.1804.



Carboxylic acid 86c: The title compound was prepared according to General Procedure II using $KN(SiMe_3)_2$ (0.110 g, 0.550 mmol, 2.2 equiv) in PhMe (0.85 mL) followed by addition of ester **85c** (91 mg, 0.250 mmol) in PhMe (0.55 then 3 x 0.1 mL rinses) and chlorotrimethylsilane (63 μL, 54 mg, 0.500 mmol, 2 equiv). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **86c** (62 mg, 0.170 mmol, 68% yield, dr 7:1) was isolated as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 4.4 Hz, 3.8H), 7.34 – 7.23 (m, 3.8H), 7.21 – 7.09 (m, 3H), 5.70 – 5.52 (m, 1.15H), 5.44 (ddd, J = 15.3, 9.6, 1.9 Hz, 1H), 4.88 – 4.69 (m, 2H), 4.57 (d, J = 11.1 Hz, 0.10H), 2.71 (ddd, J = 14.6, 10.2, 4.9 Hz, 1.12H), 2.63 (ddd, J = 11.6, 9.6, 2.5 Hz, 1H), 2.43 (ddd, J = 13.9, 9.9, 7.0 Hz, 1H), 1.96 – 1.84 (m, 1H), 1.81 – 1.73 (m, 3H), 1.72 (dd, J = 6.1, 1.3 Hz, 0.35H), 1.15 (tt, J = 8.6, 5.6 Hz, 1.13H), 0.85 (dq, J = 10.3, 5.3 Hz, 1.13H), 0.71 – 0.62 (m, 1H), 0.55 (dq, J = 9.4, 4.4, 3.8 Hz, 1.12H), 0.47 (dq, J = 10.8, 5.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.39, 142.33, 138.83, 130.13, 129.70, 129.55, 128.98, 128.62, 128.50, 128.41, 128.37, 128.33, 128.32, 128.24, 127.59, 127.48, 127.43, 127.29, 125.78, 125.67, 86.21, 66.54, 66.00, 50.70, 49.98, 33.89, 33.46, 31.58, 30.19, 18.20, 18.05, 14.71, 14.60, 4.19, 3.98, 1.83. HRMS (ESI) calcd for $C_{24}H_{29}O_3$ $[M + H]^+$ 365.2111, found 365.2105.



85c 87c

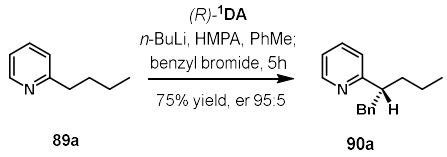
Carboxylic acid 87c: The title compound was prepared according to General Procedure III using *n*-BuLi (2.30 M in hexanes, 0.260 ml, 0.600 mmol, 2.4 equiv) and diisopropylamine (91 µL, 0.650 mmol, 2.6 equiv) in THF (1.50 ml) followed by addition of chlorotrimethylsilane (79 µL, 68 mg, 0.625 mmol, 2.5 equiv) and ester **85c** (91 mg, 0.250 mmol) in THF (0.7 mL then 3 x 0.1 mL rinses). After column chromatography (30% EtOAc-hexanes to 1% AcOH in 30% EtOAc-hexanes), acid **87c** (62 mg, 0.170 mmol, 68% yield, dr 1.1:1) was isolated as a clear oil.

Data for the mixture of diastereomers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 – 8.08 (m, 1H), 7.63 (td, J = 7.3, 1.3 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.39 – 7.23 (m, 14H), 7.22 – 7.12 (m, 7H), 5.68 – 5.49 (m, 3H), 5.48 – 5.39 (m, 1H), 4.81 (s, 2H), 4.77 (d, J = 11.1 Hz, 1H), 4.58 (d, J = 11.2 Hz, 1H), 2.82 – 2.69 (m, 2H), 2.64 (ddd, J = 11.5, 9.6, 2.6 Hz, 1H), 2.55 (ddd, J = 11.5, 9.2, 2.5 Hz, 1H), 2.50 – 2.39 (m, 2H), 2.19 – 2.02 (m, 1H), 1.90 (dtd, J = 13.8, 10.4, 4.9 Hz, 1H), 1.77 (dd, J = 6.4, 1.6 Hz, 3H), 1.76 – 1.68 (m, 3H), 1.22 – 1.11 (m, 2H), 0.92 – 0.78 (m, 2H), 0.72 – 0.60 (m, 2H), 0.60 – 0.43 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.94, 142.30, 142.28, 138.75, 138.42, 133.82, 130.17, 130.05, 129.69, 129.50, 129.16, 128.98, 128.58, 128.47, 128.46, 128.38, 128.33, 128.28, 128.20, 127.58, 127.45, 127.41, 127.26, 125.74, 125.71, 125.63, 86.32, 86.21, 66.50, 65.93, 50.67, 49.90, 33.86, 33.42, 31.53, 30.18, 29.69, 18.15, 18.02, 14.68, 14.55, 4.14, 3.89, 2.72, 1.84. HRMS (ESI) calcd for $C_{24}H_{29}O_3$ $[M + H]^+$ 365.2111, found 365.2103.

Determination of the Relative Stereochemistry of the Ireland-Claisen Rearrangement Products:

The relative stereochemistry of compounds **80h** and **81h** was determined through X-ray crystallography. The relative stereochemistry of all other products was inferred by correlation to this data. This crystal structures can be obtained from the Cambridge Crystallographic Data Centre (CCDC 1853280 and 1853281) free of charge at www.cdc.cam.ac.u/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk.

CHAPTER 3 EXPERIMENTAL PROCEDURES



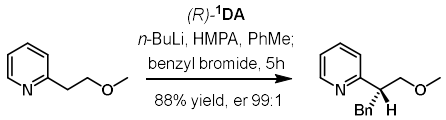
GENERAL PROCEDURE IV:

(*S*)-2-(Pentan-2-yl)pyridine (90a). A round bottom flask equipped with a stir bar was flame dried under vacuum and cooled under an atmosphere of dry argon. (*R*)-**1DA** (0.160 g, 0.616 mmol, 1.4 equiv) is added and the flask is backfilled with argon three times. 2-Butylpyridine **89a** (60 mg, 0.44 mmol) and HMPA (0.516 mL, 0.639 M in toluene, 0.33 mmol, 0.75 equiv) were added by syringe and dissolved in toluene (4.6 ml). The solution was cooled to 0 °C and *n*-BuLi (0.422 mL, 2.5 M in hexanes, 1.065 mmol, 2.4 equiv) was added dropwise. The solution was stirred for 15 min, then cooled to −78 °C and stirred for an additional 15 min. benzyl bromide (78 µL, 0.66 mmol, 1.5 equiv) was added at −78 °C, and the solution was stirred at this temperature for 5 h. Upon completion, the reaction was quenched with 300 µL of methanol at −78 °C and the solution was stirred for 15 min before being brought to room temperature. The reaction was diluted with deionized H_2O (5 mL) and EtOAc (2 mL) and transferred to a separatory funnel. The aqueous layer was extracted 3 times with EtOAc (5 mL). Combined organic layers were rinsed with a 10 mL portion of deionized H_2O containing 0.552 mmol of HCl to recover (*R*)-**1DA.** Organic layers were rinsed with brine, dried over anhydrous Na_2SO_4, concentrated, and the crude extract is purified by column chromatography on silica gel (1-2% EtOAc in hexane) to afford **90a** (75 mg,

0.33 mmol, 75% yield) was obtained as a colorless oil after purification by column chromatography on silica gel (2% EtOAc in hexane). Er: 95:5 (Chiralcel® OD-H; 2% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 254 nm; t_2 = 11.88 min (major); t_1 = 10.98 min).

$[\alpha]_D^{25}$ – 90.8° (*c* 1.25, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.58 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.48 (td, *J* = 7.6, 1.9, Hz, 1H), 7.20–7.15 (m, 2H), 7.14–7.09 (m, 1H), 7.08-7.05 (m, 1H), 7.04–7.00 (m, 2H), 6.92 (dt, *J* = 7.8, 1.0 Hz, 1H), 3.07–2.97 (m, 2H), 2.94 (m, 1H), 1.82-1.76 (m, 1H), 1.69-1.62 (m, 1H), 1.22–1.08 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 164.3, 149.4, 140.7, 135.8, 129.1, 128.0, 125.7, 123.2, 121.1, 49.7, 42.2, 37.0, 20.7, 14.1. HRMS (TOF MS EI) calcd for $C_{16}H_{19}N$ $[M]^+$ 225.1517, found 225.1520.

REPRESENTATIVE ALKYLATION OF 2-ALKYL PYRIDINES ON GRAM-SCALE:



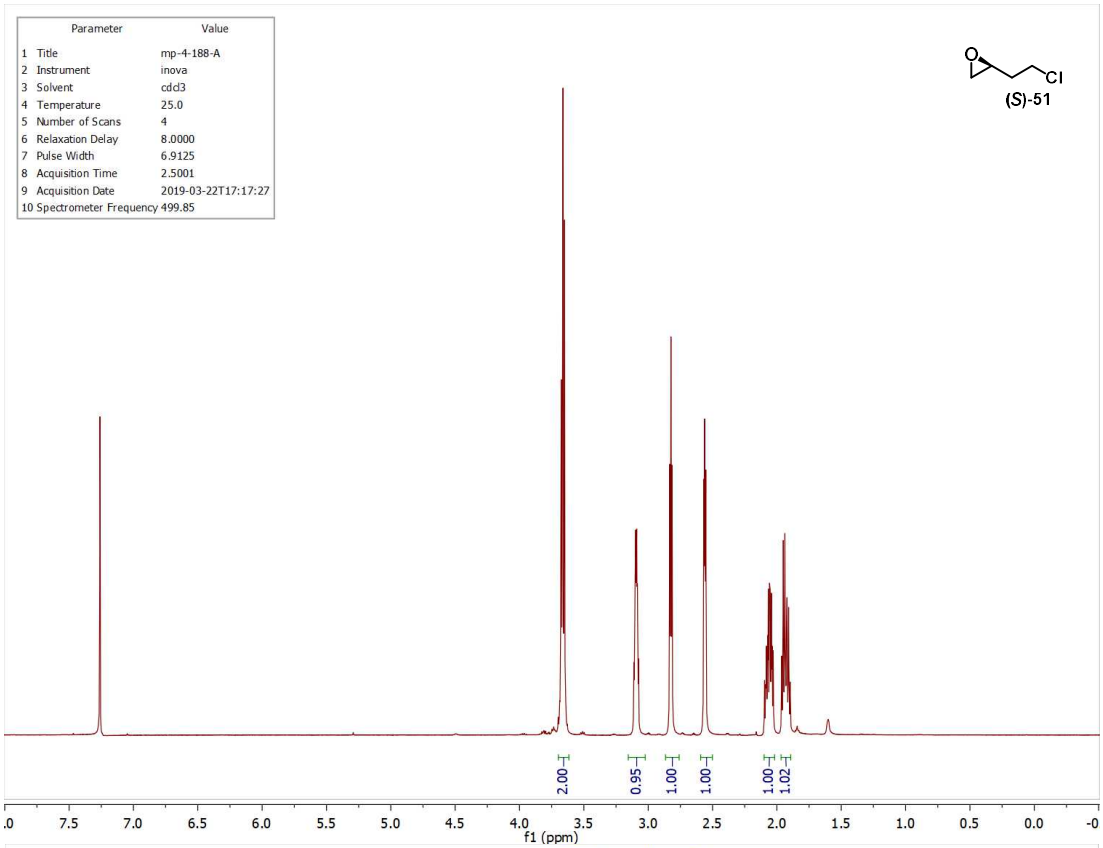
88 91a

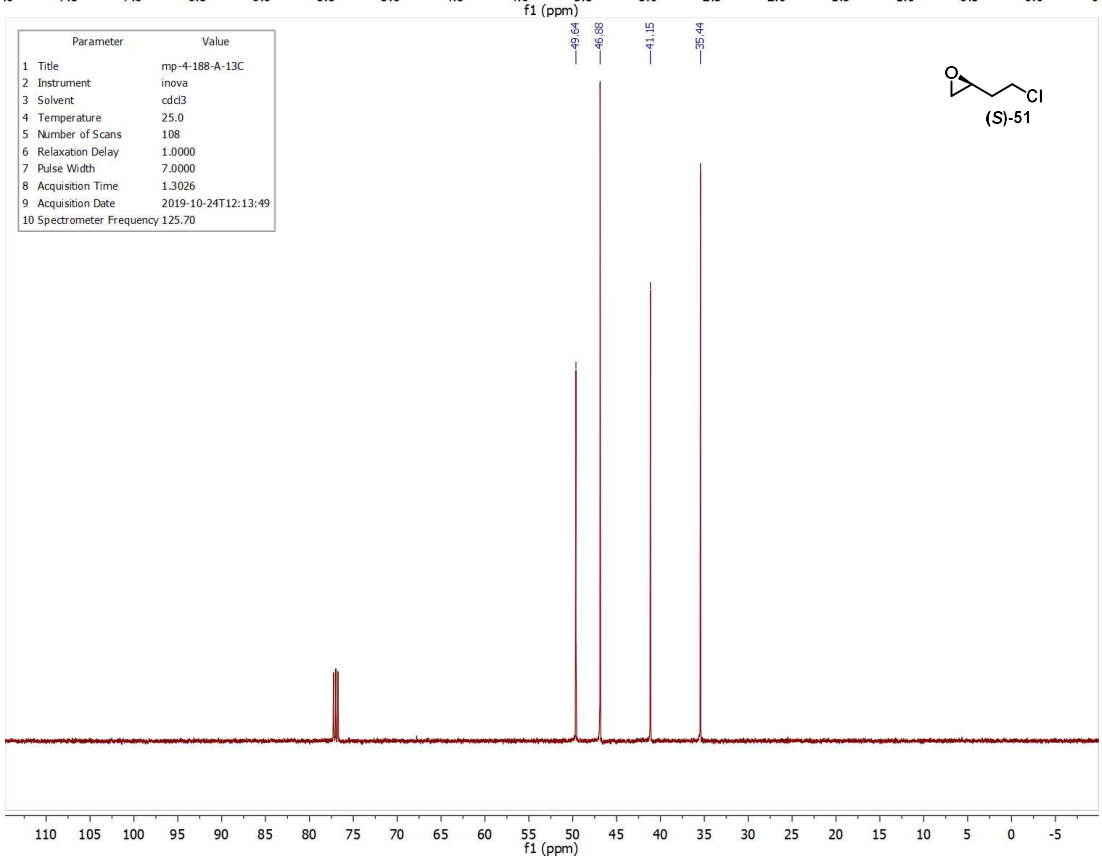
(*S*)-2-(4-Methoxy-1-phenylbutan-2-yl)pyridine (91a). The title compound was prepared according to **general procedure IV** using 2-(3-methoxypropyl) pyridine (**88**) (1.50 g, 9.92 mmol), HMPA (1.30 mL, 0.639M in toluene, 7.44 mmol, 0.75 equiv), and (*R*)-**1DA** (3.62 g, 13.89 mmol, 1.4 equiv), *n*-BuLi (9.52 mL, 2.5 M in hexanes, 23.81 mmol, 2.4 equiv) in toluene (11.1 ml) followed by addition of benzyl bromide (1.41 mL, 11.90 mmol, 1.2 equiv) at –78 °C. The reaction was quenched after 2 h and product **91a**

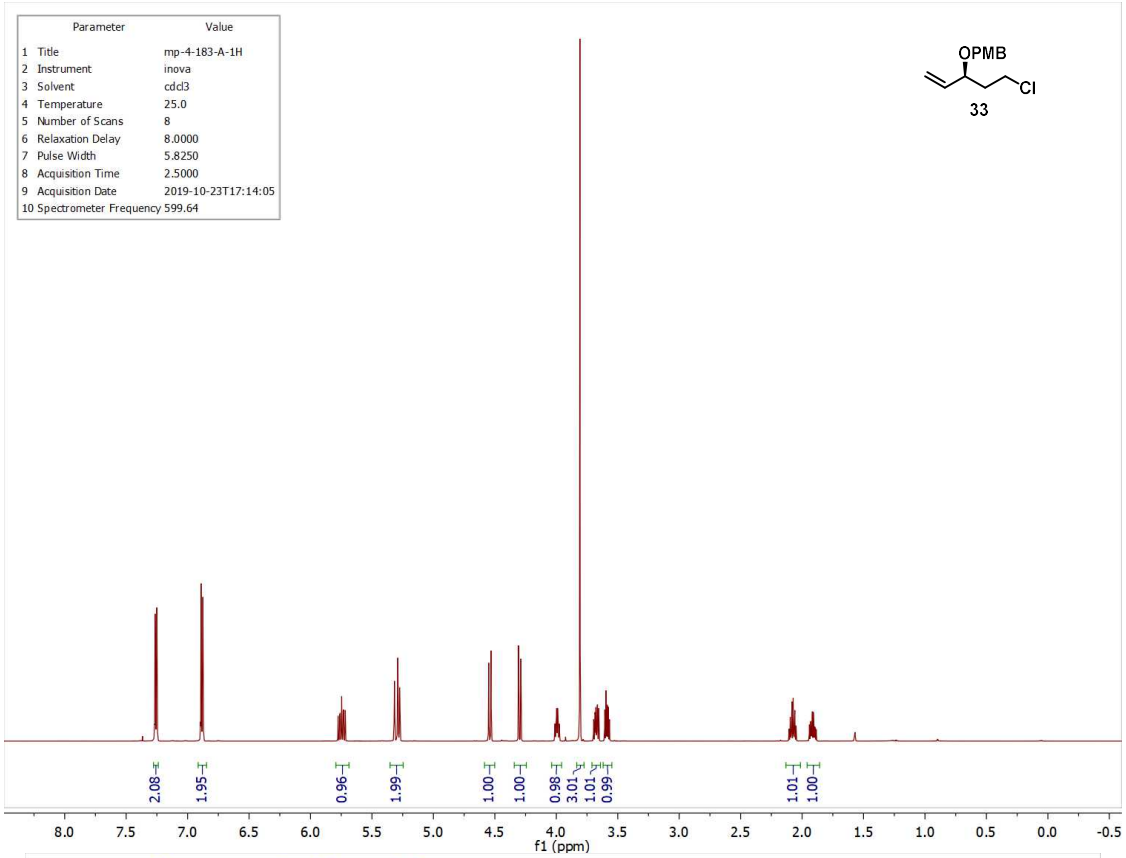
(2.10g, 08.70 mmol, 88% yield) was obtained after purification by column chromatography on silica gel (3% EtOAc in hexane). Er: 99:1 (Chiralcel® AD-H; 2% *i*-PrOH in hexanes; flow rate = 1.0 mL/min; detection at 254 nm; t_2 = 8.14 min (major); t_1 = 7.23 min).

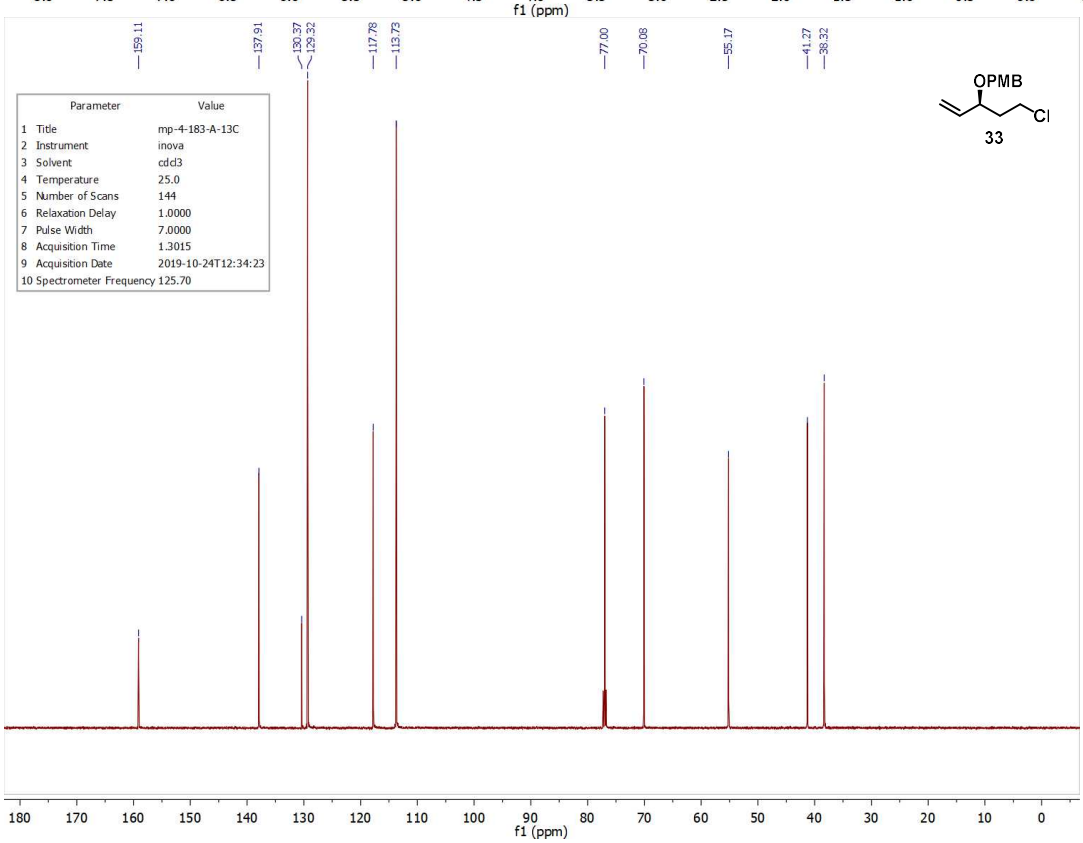
$[\alpha]_D^{25}$ – 81.7° (*c* 1.15, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.59 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.48 (td, *J* = 7.6, 1.8 Hz, 1H), 7.19-7.15 (m, 2H), 7.12-7.10 (m, 1H), 7.09-7.06 (m, 1H), 7.02 (m, 2H), 6.92 (dt, *J* = 7.8, 1.0 Hz, 1H), 3.28-3.23(m, 1H), 3.20 (s, 3H), 3.20-3.16 (m, 1H), 3.15-3.10 (m, 1H), 3.07-3.04 (m, 1H), 2.97-2.93 (m, 1H), 2.11-1.97 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 163.5, 149.4, 140.3, 135.9, 129.1, 128.0, 125.8, 123.6, 121.3, 70.6, 58.4, 46.2, 42.1, 34.4. HRMS (TOF MS EI) calcd for $C_{16}H_{19}NO$ $[M]^+$ 241.1467, found 241.1464.

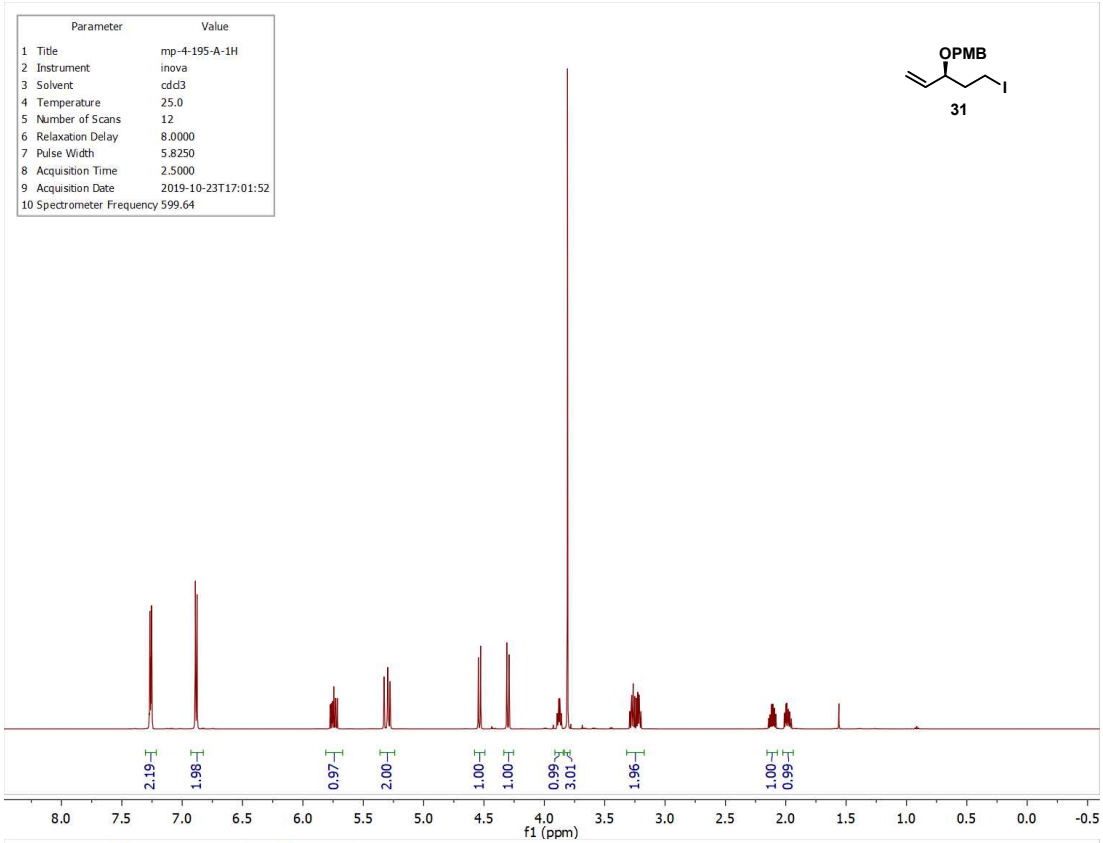
^{1}H NMR, ^{13}C NMR and ^{19}F NMR Spectra

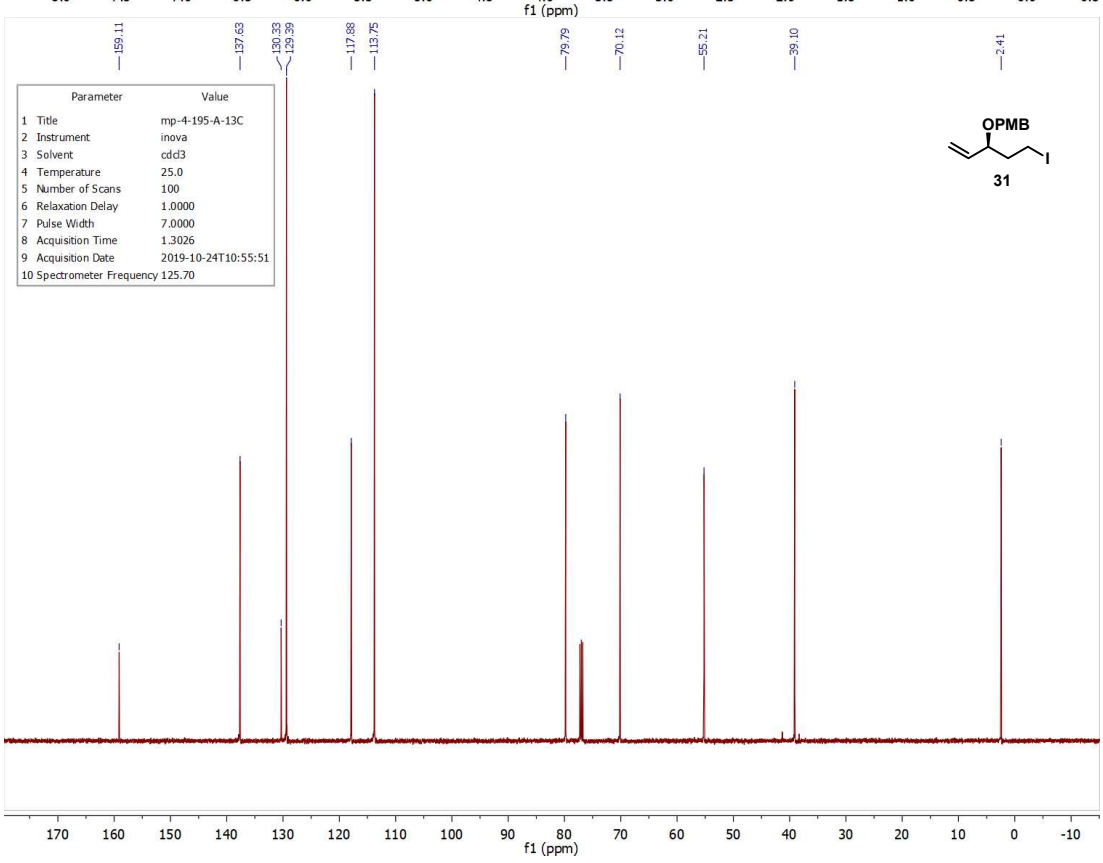

Parameter Value
1 Title mp-4-188-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 4
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2019-03-22T17:17:27
10 Spectrometer Frequency 499.85
(S)-51
2.00
0.95
1.00
1.00
1.00
1.02
f1 (ppm)

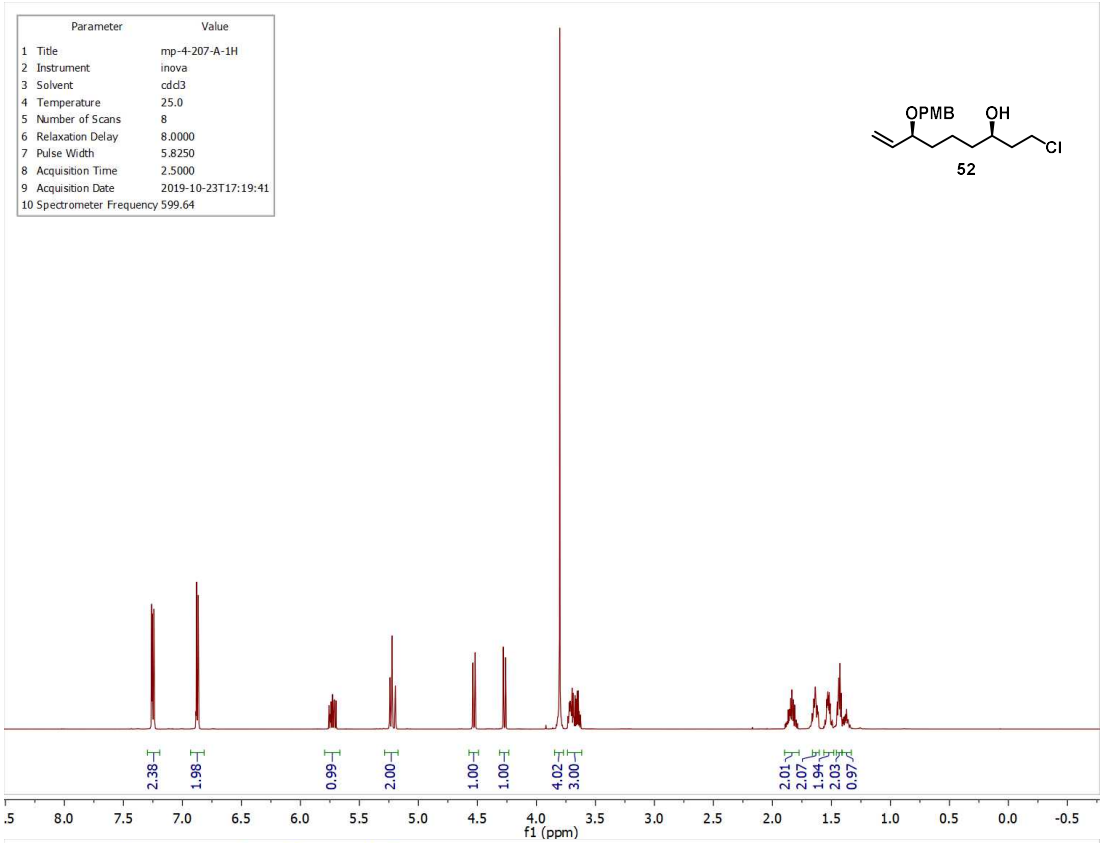

Parameter Value
1 Title mp-4-188-A-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 108
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2019-10-24T12:13:49
10 Spectrometer Frequency 125.70
49.64
46.88
41.15
35.44
(S)-51
f1 (ppm)

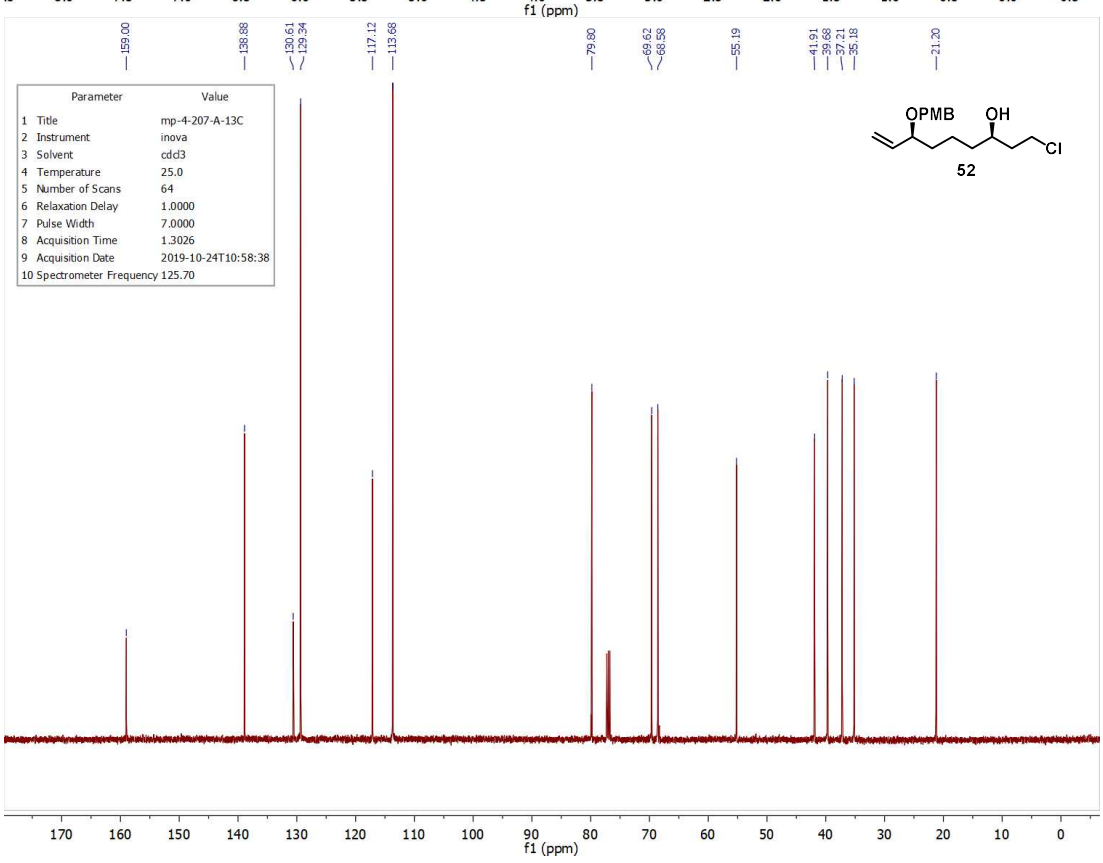

Parameter Value
1 Title mp-4-183-A-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 5.8250
8 Acquisition Time 2.5000
9 Acquisition Date 2019-10-23T17:14:05
10 Spectrometer Frequency 599.64
OPMB
Cl
33
2.08
1.95
0.96
1.99
1.00
1.00
0.98
3.01
1.01
0.99
1.01
1.00
f1 (ppm)

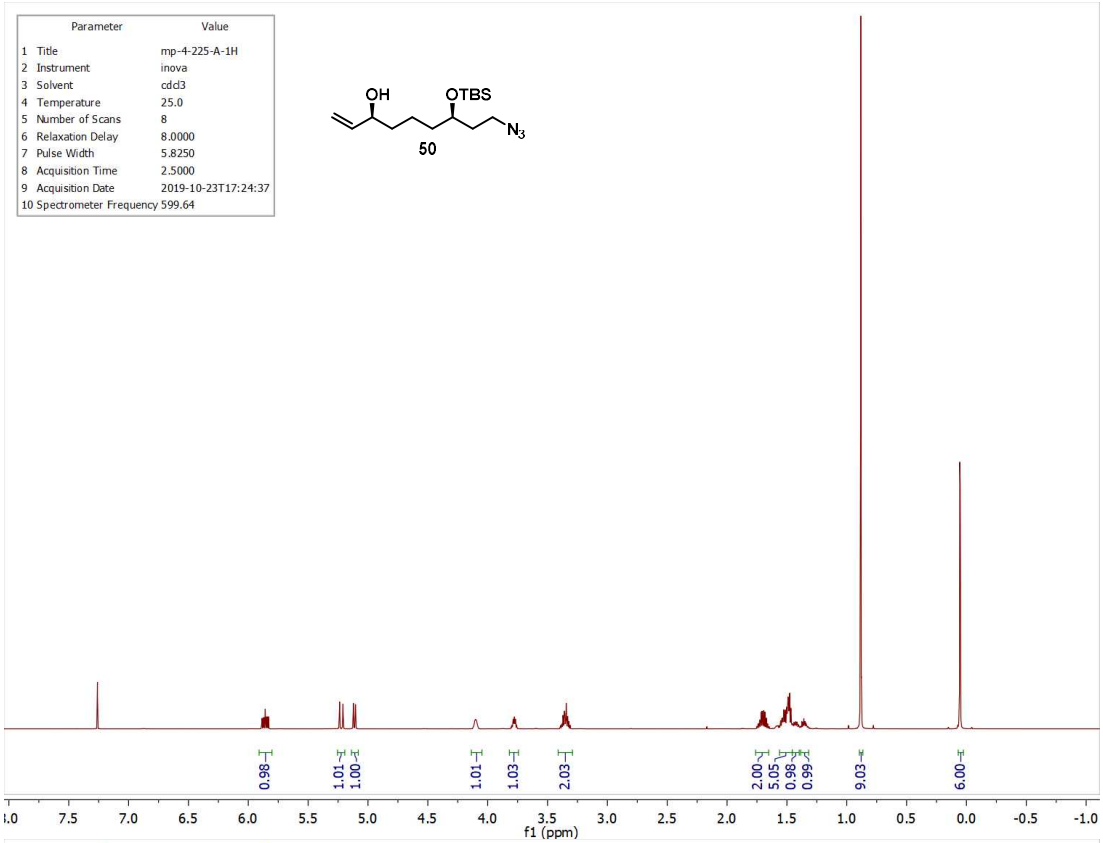

159.11
137.91
130.37
129.32
117.78
113.73
77.00
70.08
55.17
41.27
38.32
Parameter Value
1 Title mp-4-183-A-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 144
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3015
9 Acquisition Date 2019-10-24T12:34:23
10 Spectrometer Frequency 125.70
OPMB
Cl
33
f1 (ppm)

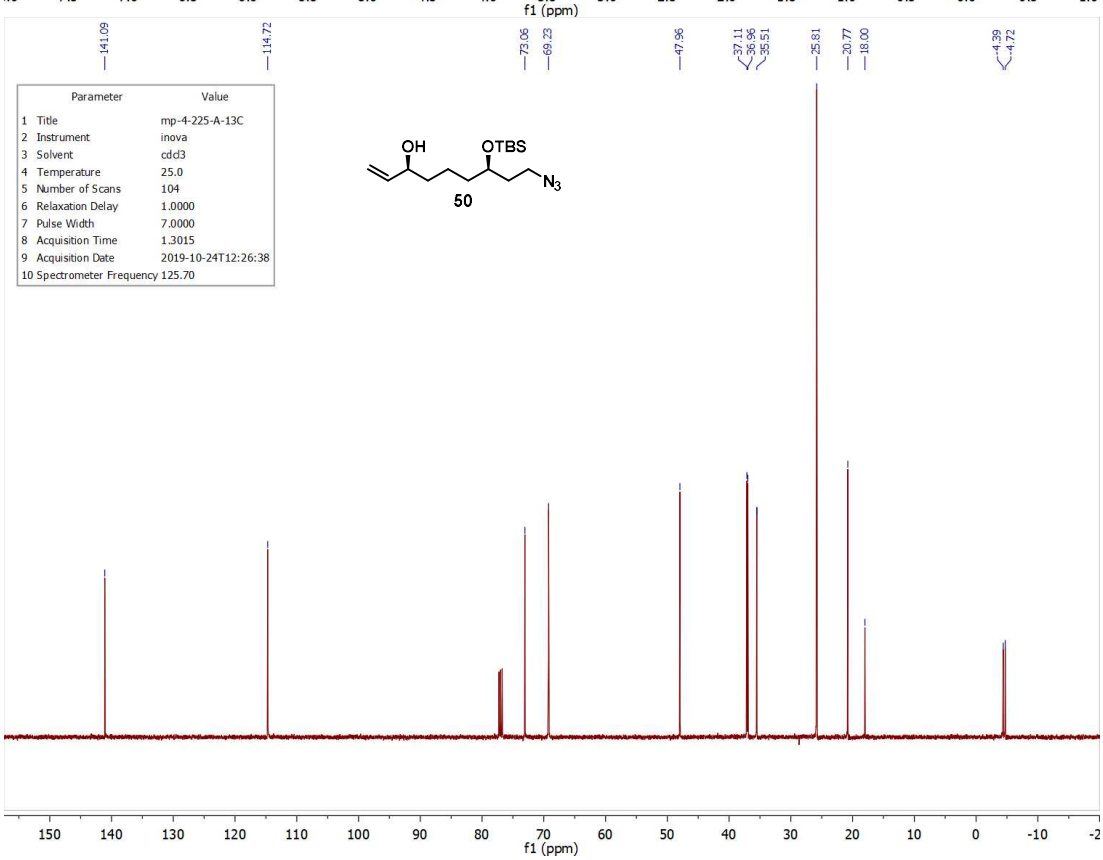

Parameter Value
1 Title mp-4-195-A-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 5.8250
8 Acquisition Time 2.5000
9 Acquisition Date 2019-10-23T17:01:52
10 Spectrometer Frequency 599.64
OPMB
31
2.19
1.98
0.97
2.00
1.00
1.00
0.99
3.01
1.96
1.00
0.99
f1 (ppm)


159.11
137.63
130.33
129.39
117.88
113.75
79.79
70.12
55.21
39.10
2.41
Parameter Value
1 Title mp-4-195-A-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 100
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2019-10-24T10:55:51
10 Spectrometer Frequency 125.70
OPMB
31
f1 (ppm)

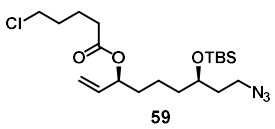

Parameter Value
1 Title mp-4-207-A-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 5.8250
8 Acquisition Time 2.5000
9 Acquisition Date 2019-10-23T17:19:41
10 Spectrometer Frequency 599.64
OPMB
OH
Cl
52
2.38
1.98
0.99
2.00
1.00
1.00
4.02
3.00
2.01
2.07
1.94
2.03
0.97
f1 (ppm)


159.00
138.88
130.61
129.34
117.12
113.68
79.80
69.62
68.58
55.19
41.91
39.68
37.71
35.18
21.20
Parameter Value
1 Title mp-4-207-A-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 64
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2019-10-24T10:58:38
10 Spectrometer Frequency 125.70
OPMB
OH
Cl
52
f1 (ppm)

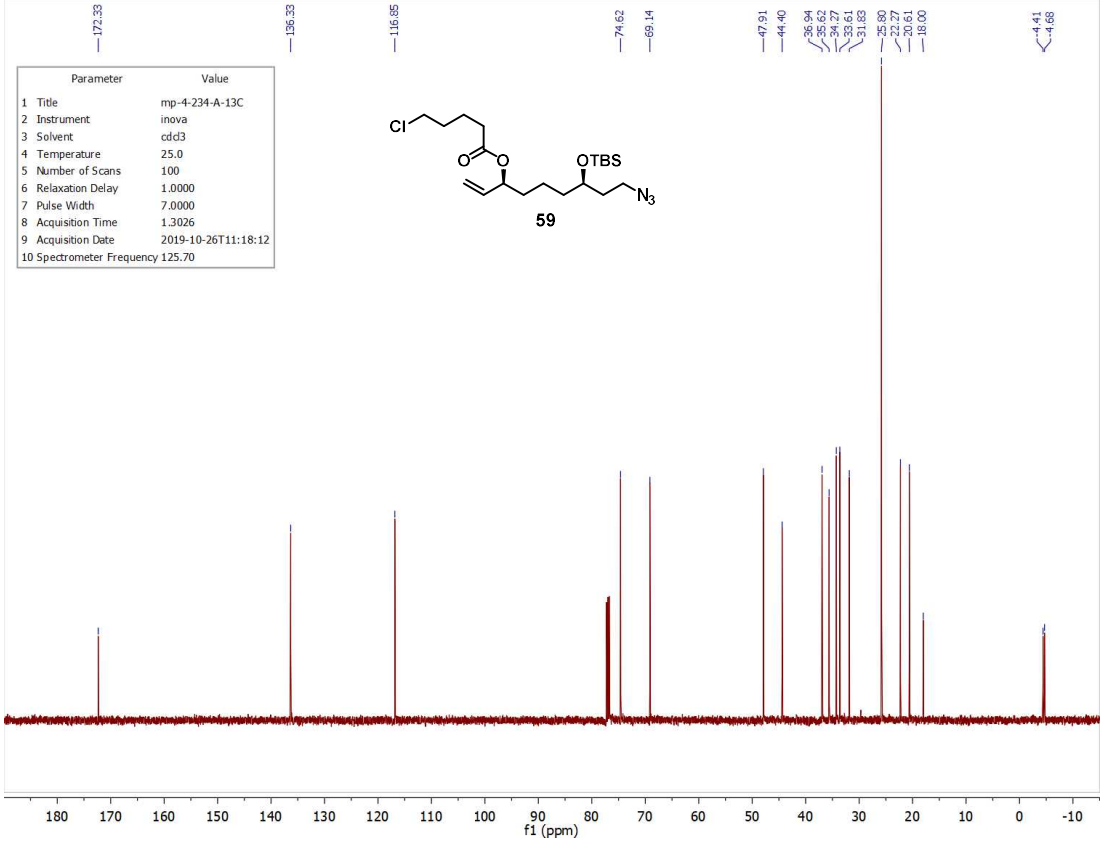

Parameter Value
1 Title mp-4-225-A-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 5.8250
8 Acquisition Time 2.5000
9 Acquisition Date 2019-10-23T17:24:37
10 Spectrometer Frequency 599.64
OH
OTBS
N3
50
0.98
1.01
1.00
1.01
1.03
2.03
2.00
5.05
0.98
0.99
9.03
6.00
f1 (ppm)


141.09
114.72
73.06
69.23
47.96
37.11
36.96
35.51
25.81
20.77
18.00
14.39
14.72
Parameter Value
1 Title mp-4-225-A-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 104
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3015
9 Acquisition Date 2019-10-24T12:26:38
10 Spectrometer Frequency 125.70
OH
OTBS
N3
50
f1 (ppm)

Parameter	Value
1 Title	mp-4-234-A-1H
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	12
6 Relaxation Delay	8.0000
7 Pulse Width	6.2500
8 Acquisition Time	2.5001
9 Acquisition Date	2019-10-26T11:08:03
10 Spectrometer Frequency	499.85



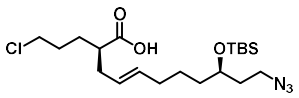
59



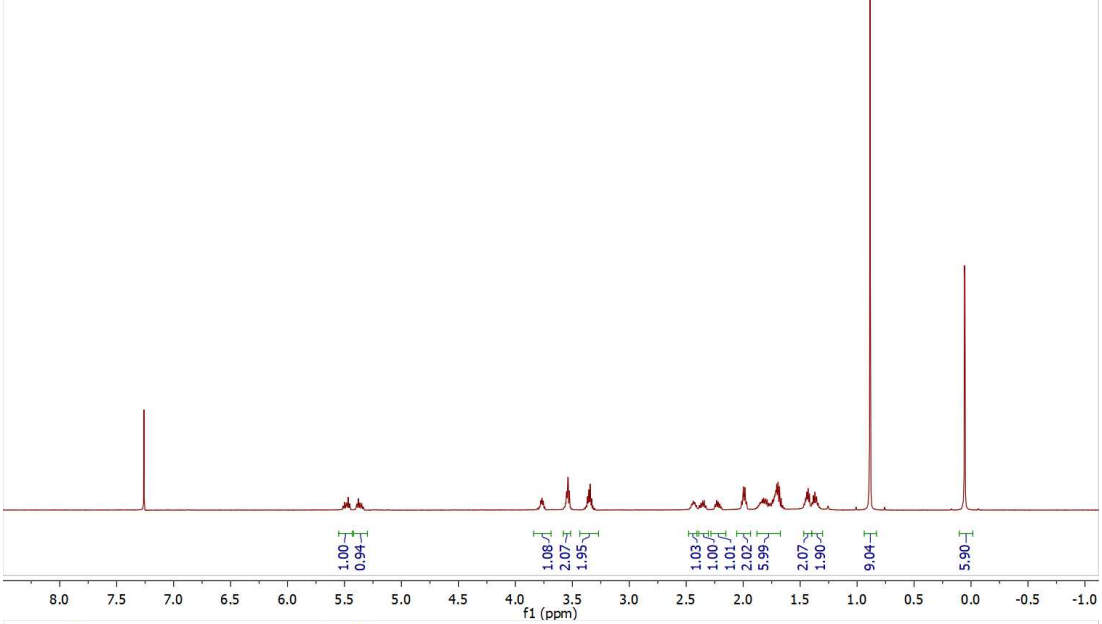
Parameter	Value
1 Title	mp-4-234-A-13C
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	100
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2019-10-26T11:18:12
10 Spectrometer Frequency	125.70

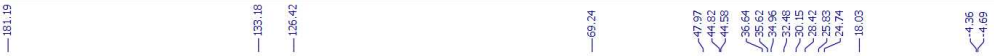
59

Parameter	Value
1 Title	mp-4-087-A-1H
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.2500
8 Acquisition Time	2.5001
9 Acquisition Date	2019-10-26T11:22:20
10 Spectrometer Frequency	499.85

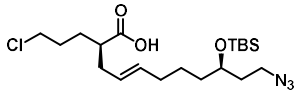


60

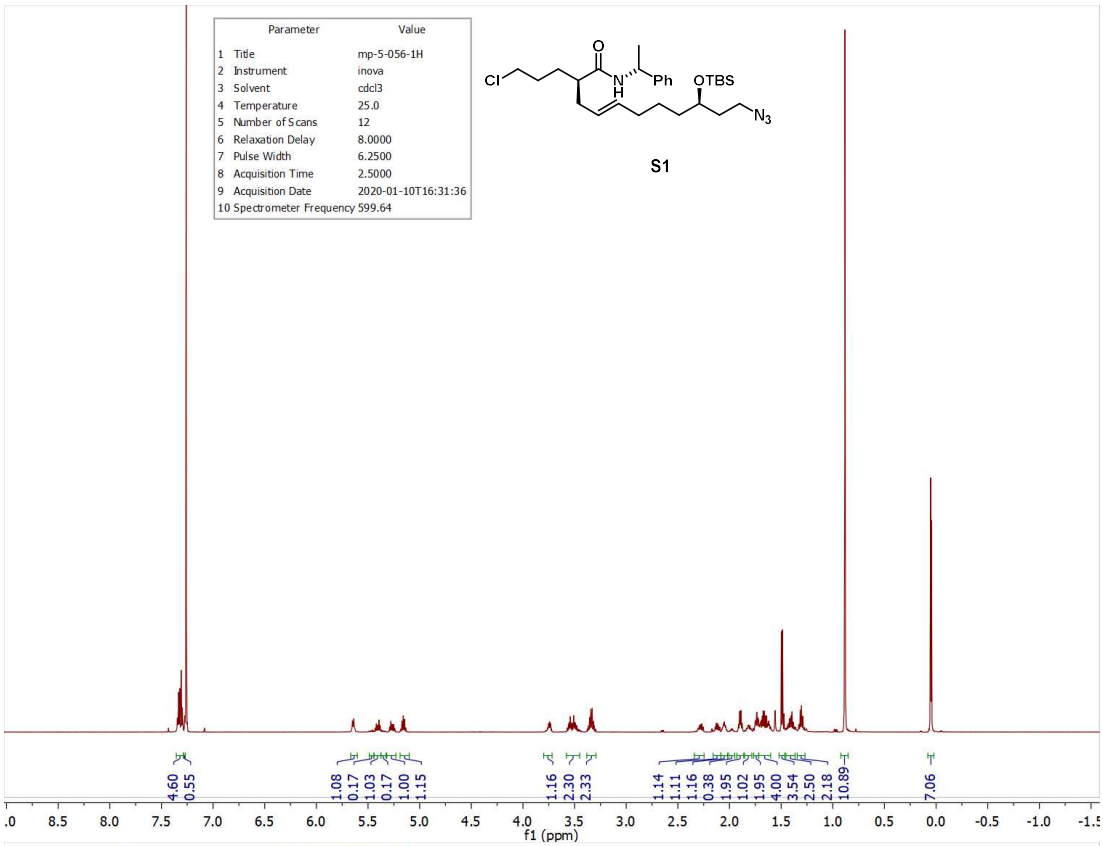


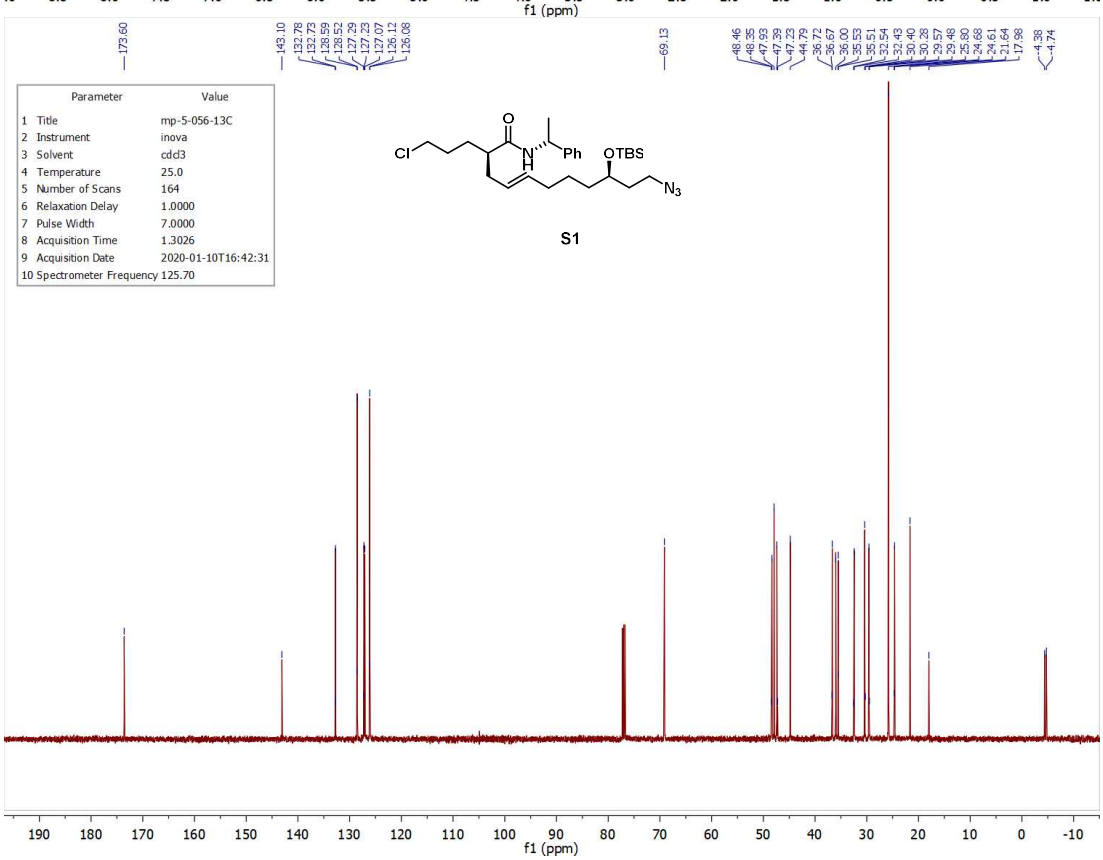


Parameter	Value
1 Title	mp-4-087-A-13C
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	1016
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2019-10-28T18:21:10
10 Spectrometer Frequency	125.70

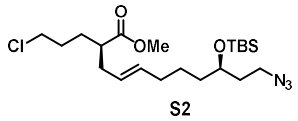


60

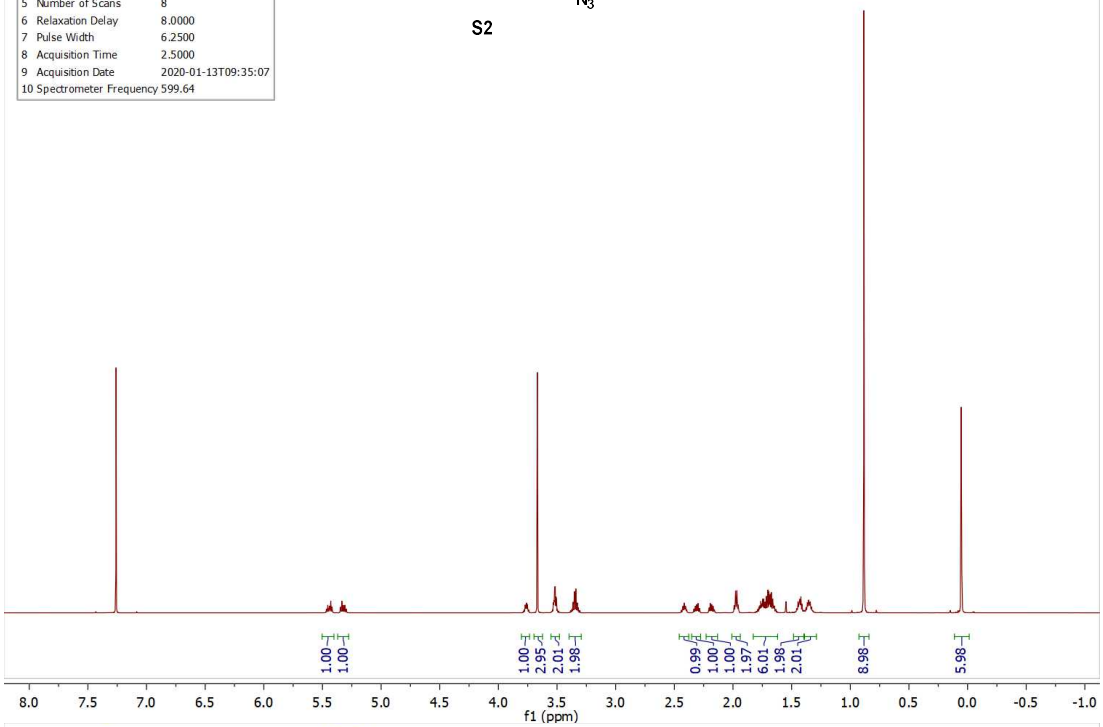

Parameter Value
1 Title mp-5-056-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.2500
8 Acquisition Time 2.5000
9 Acquisition Date 2020-01-10T16:31:36
10 Spectrometer Frequency 599.64
Cl
O
N
H
Ph
OTBS
N3
S1
4.60 0.55 1.08 0.17 1.03 0.17 1.00 1.15 1.16 2.30 2.33 1.14 1.11 1.16 0.38 1.95 1.02 1.95 4.00 3.54 2.50 2.18 10.89 7.06
f1 (ppm)

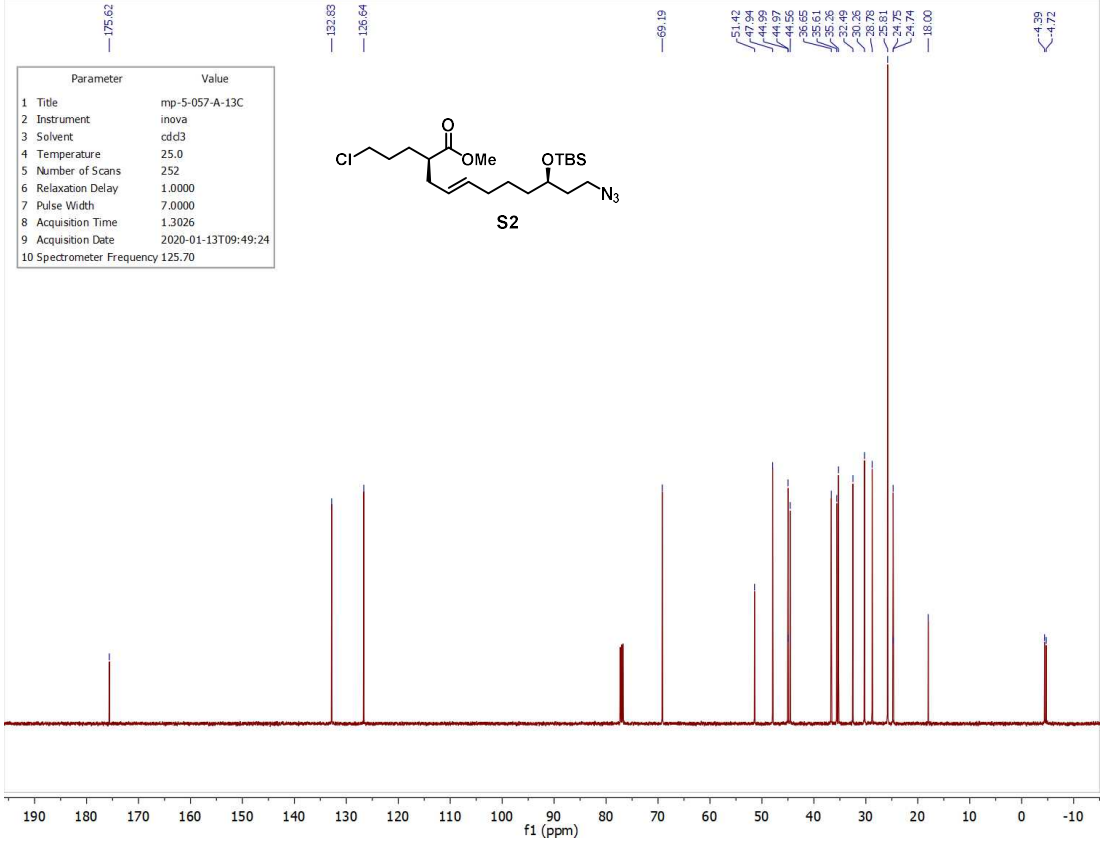

173.60 143.10 132.78 132.73 128.59 128.52 127.29 127.23 127.07 126.12 126.08 69.13 48.46 48.35 47.93 47.39 47.23 44.79 36.72 36.67 36.00 35.53 35.51 32.54 32.43 30.48 30.28 29.97 29.48 25.80 24.68 24.61 21.64 17.98 -4.38 -4.74
Parameter Value
1 Title mp-5-056-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 164
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-01-10T16:42:31
10 Spectrometer Frequency 125.70
Cl
O
N
H
Ph
OTBS
N3
S1
f1 (ppm)

Parameter	Value
1 Title	mp-5-057-A-1H
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.2500
8 Acquisition Time	2.5000
9 Acquisition Date	2020-01-13T09:35:07
10 Spectrometer Frequency	599.64



S2

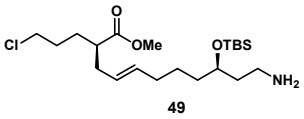




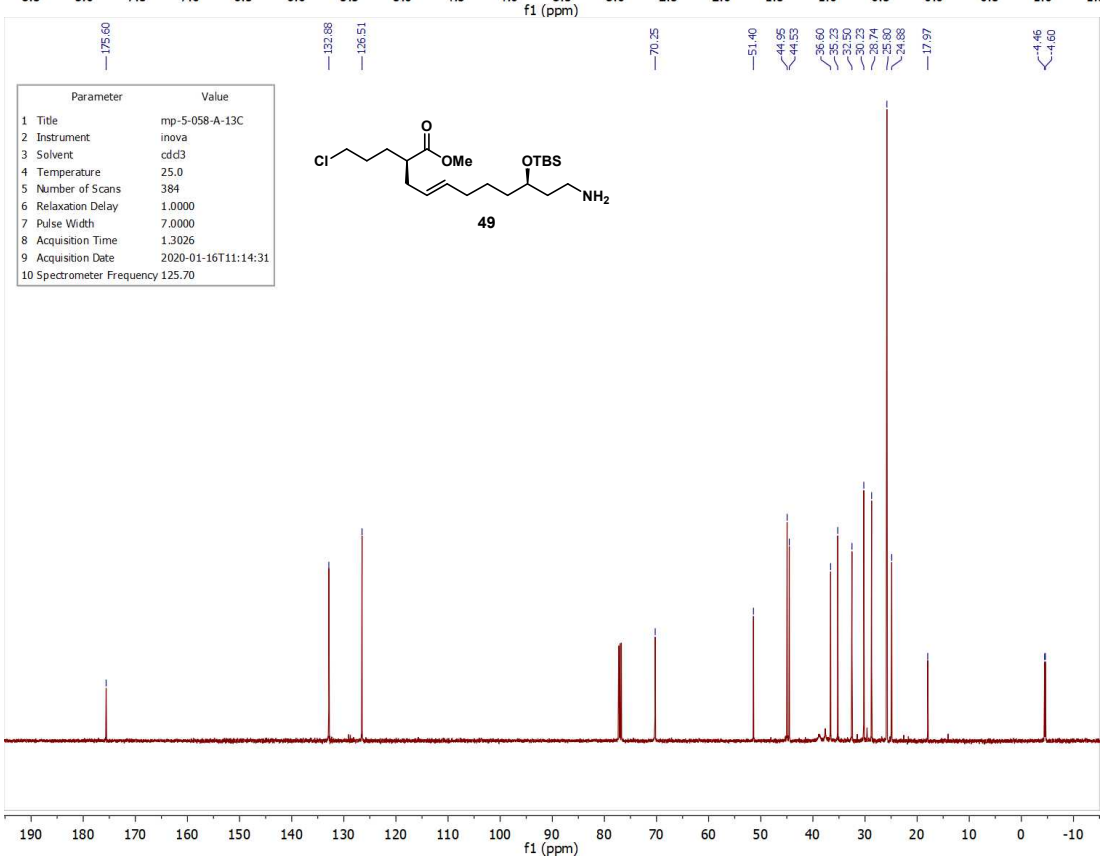
Parameter	Value
1 Title	mp-5-057-A-13C
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	252
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2020-01-13T09:49:24
10 Spectrometer Frequency	125.70

S2

Parameter	Value
1 Title	mp-4-247-A-1H
2 Instrument	vnmrs
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	12
6 Relaxation Delay	8.0000
7 Pulse Width	9.1625
8 Acquisition Time	2.5001
9 Acquisition Date	2019-08-01T12:38:08
10 Spectrometer Frequency	399.78



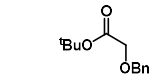
49



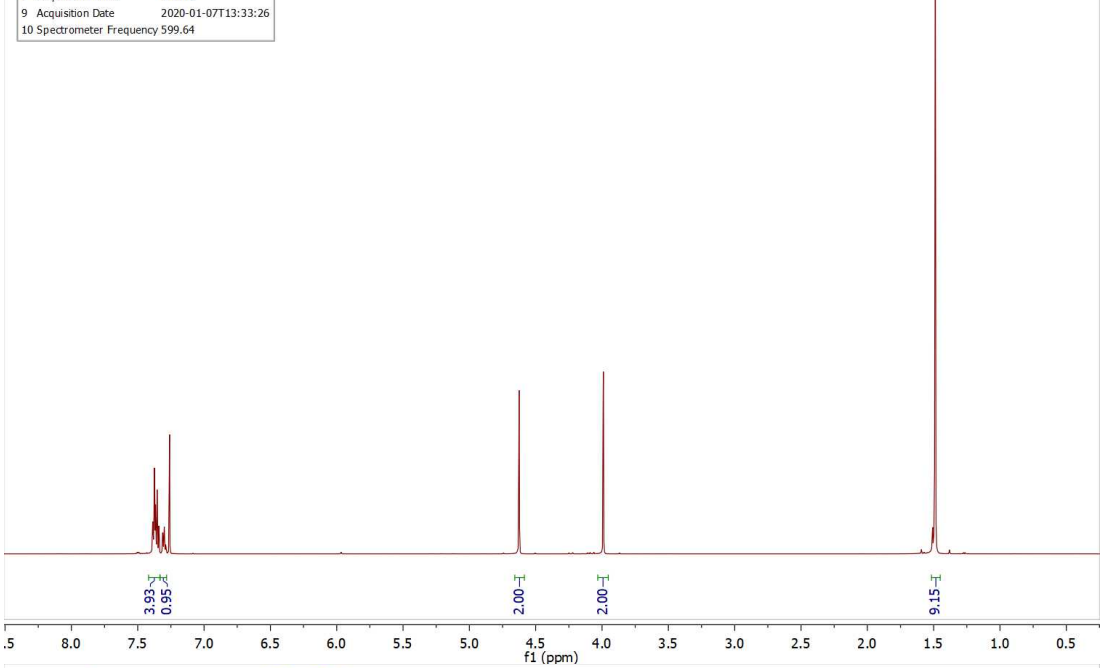
Parameter	Value
1 Title	mp-5-058-A-13C
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	384
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2020-01-16T11:14:31
10 Spectrometer Frequency	125.70

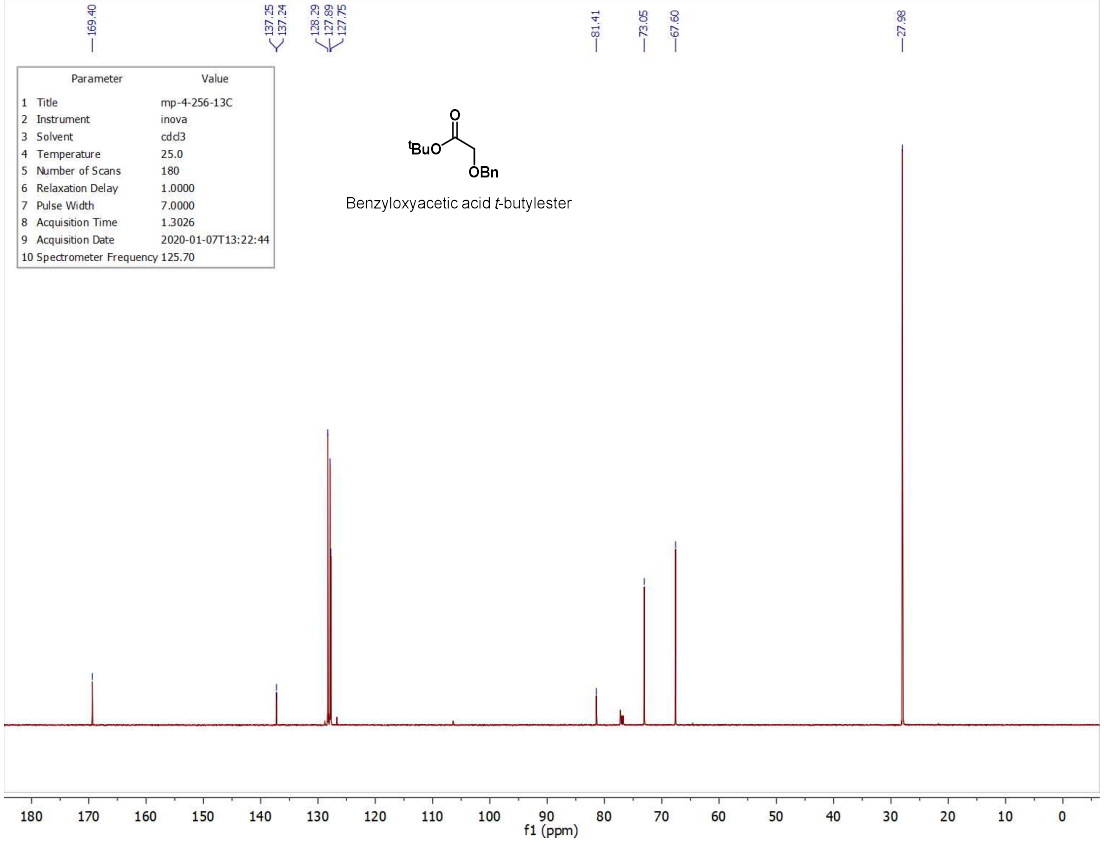
49

Parameter	Value
1 Title	mp-4-256-1H
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	20
6 Relaxation Delay	8.0000
7 Pulse Width	6.2500
8 Acquisition Time	2.5000
9 Acquisition Date	2020-01-07T13:33:26
10 Spectrometer Frequency	599.64



Benzyloxyacetic acid *t*-butylester

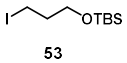




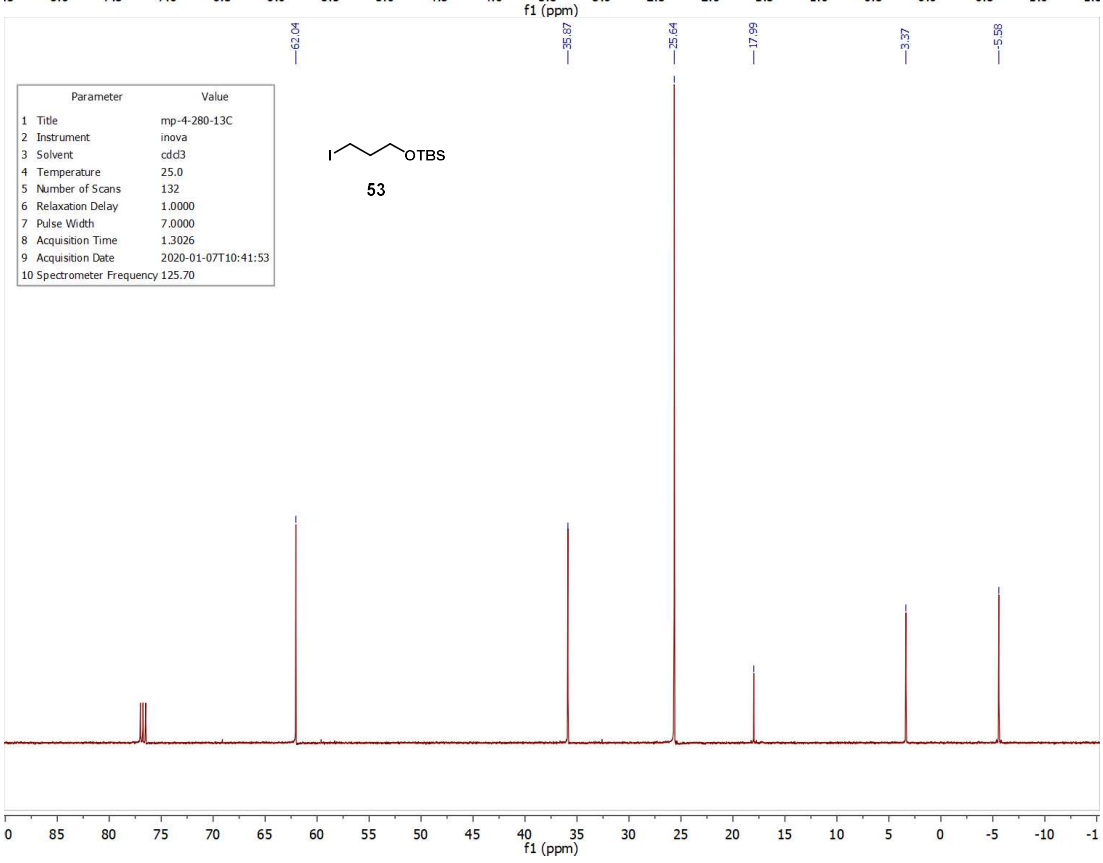
Parameter	Value
1 Title	mp-4-256-13C
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	180
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2020-01-07T13:22:44
10 Spectrometer Frequency	125.70

Benzyloxyacetic acid *t*-butylester

	Parameter	Value
1	Title	mp-4-280-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	6.2500
8	Acquisition Time	2.5000
9	Acquisition Date	2020-01-07T10:11:39
10	Spectrometer Frequency	599.64

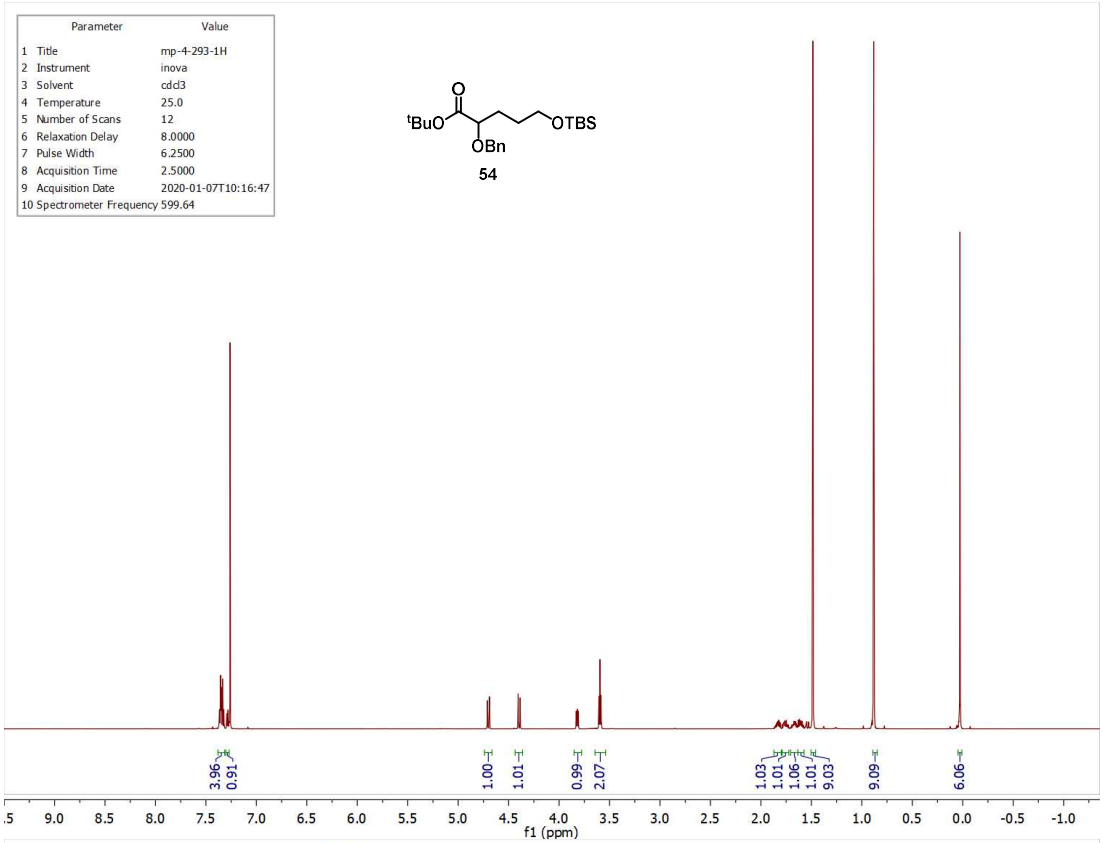


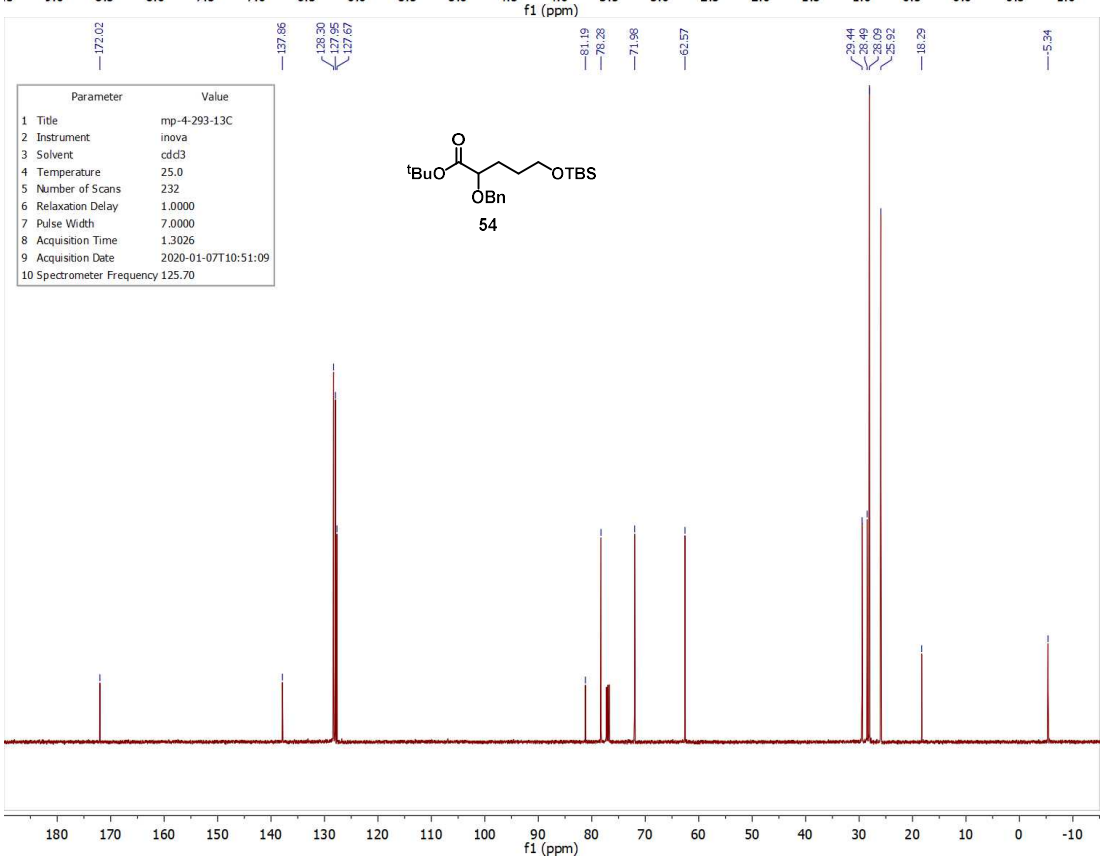
53



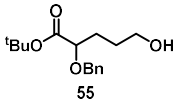
	Parameter	Value
1	Title	mp-4-280-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	132
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-01-07T10:41:53
10	Spectrometer Frequency	125.70

53

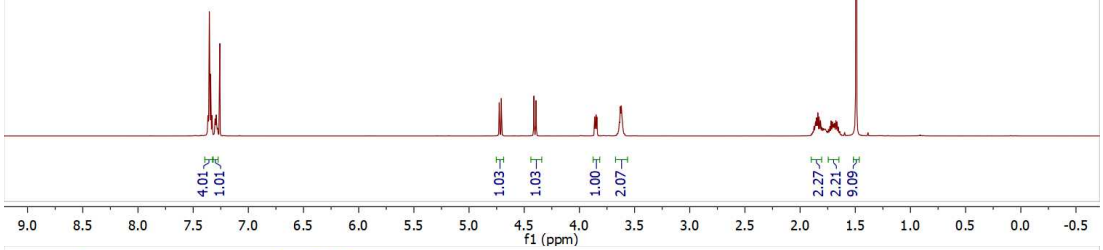

Parameter Value
1 Title mp-4-293-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.2500
8 Acquisition Time 2.5000
9 Acquisition Date 2020-01-07T10:16:47
10 Spectrometer Frequency 599.64
tBuO
OBn
OTBS
54
3.96
0.91
1.00
1.01
0.99
2.07
1.03
1.01
1.06
1.01
9.03
9.09
6.06
f1 (ppm)

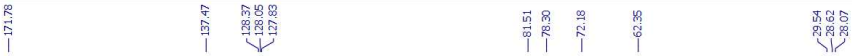

172.02
137.86
128.30
127.95
127.67
81.19
78.28
71.98
62.57
29.44
28.49
28.09
25.92
18.29
-5.34
Parameter Value
1 Title mp-4-293-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 232
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-01-07T10:51:09
10 Spectrometer Frequency 125.70
tBuO
OBn
OTBS
54
f1 (ppm)

Parameter	Value
1 Title	mp-4-295-1H
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.2500
8 Acquisition Time	2.5000
9 Acquisition Date	2020-01-07T10:22:39
10 Spectrometer Frequency	599.64

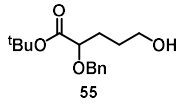


55



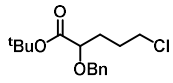


Parameter	Value
1 Title	mp-4-295-13C
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	204
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2020-01-07T13:11:32
10 Spectrometer Frequency	125.70

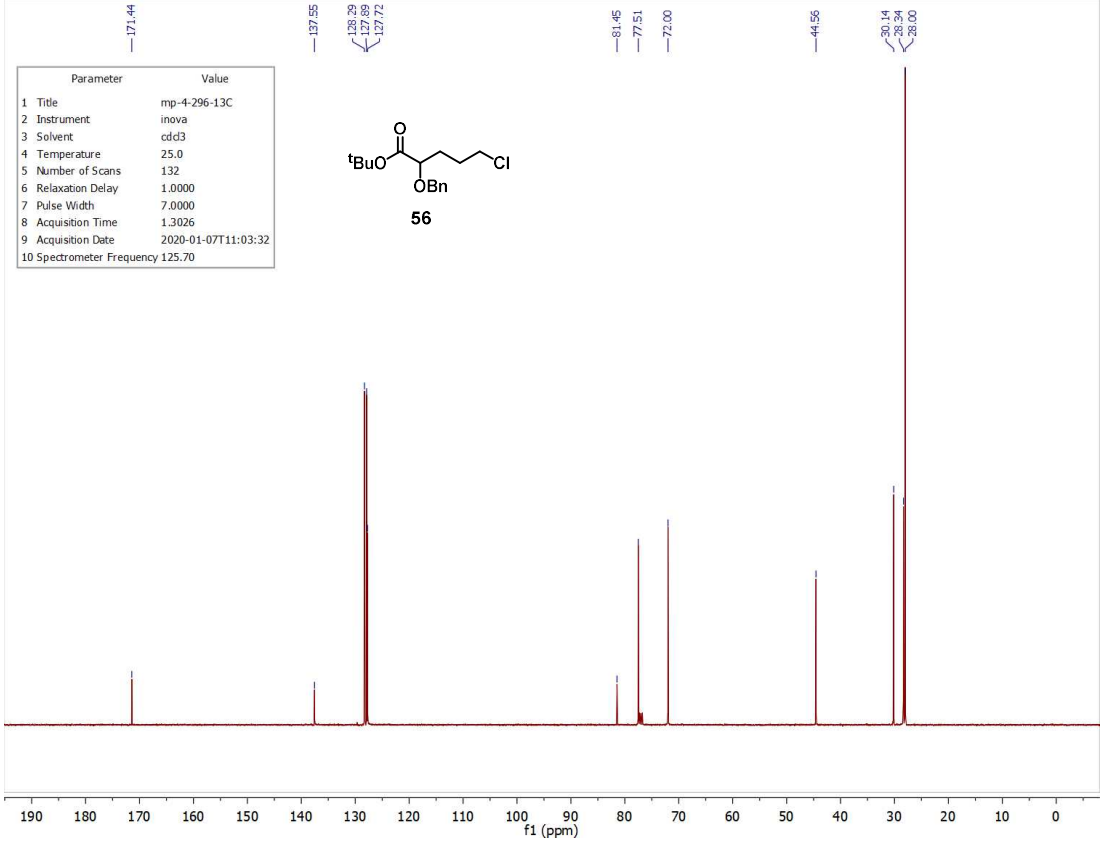


55

	Parameter	Value
1	Title	mp-4-296-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	24
6	Relaxation Delay	8.0000
7	Pulse Width	6.2500
8	Acquisition Time	2.5000
9	Acquisition Date	2020-01-07T10:27:50
10	Spectrometer Frequency	599.64

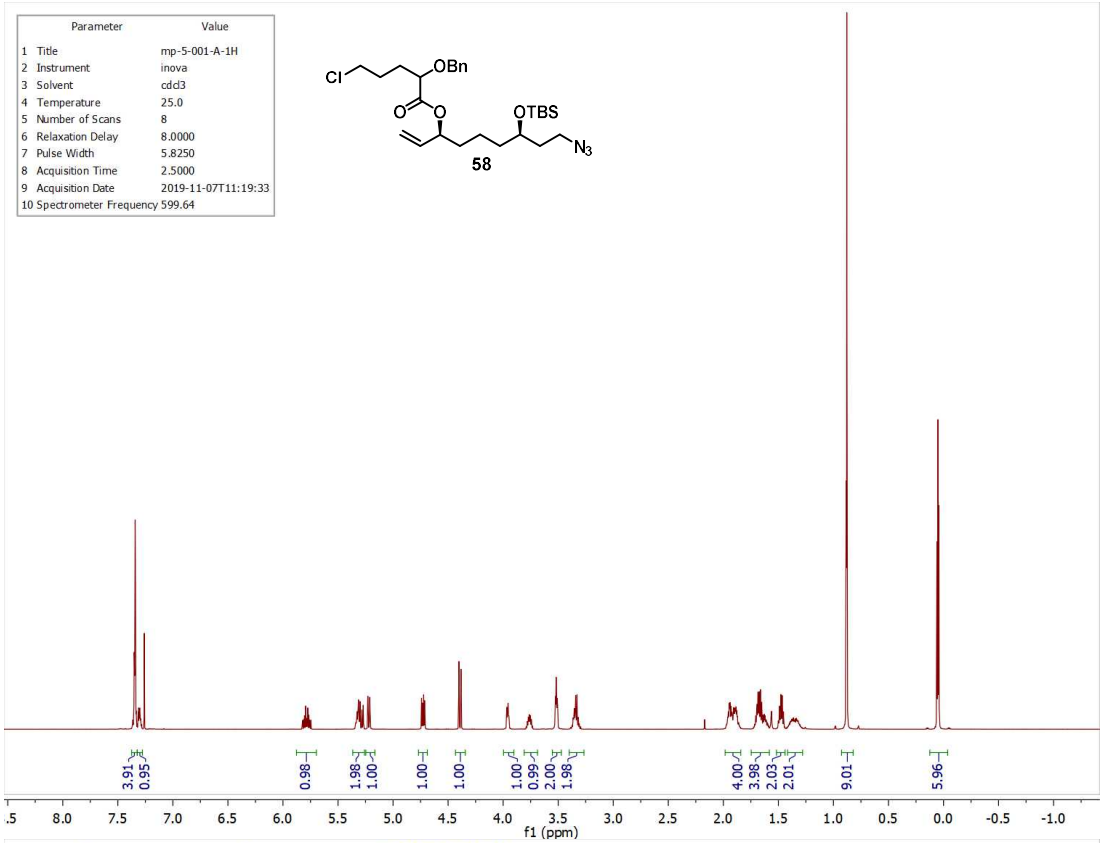


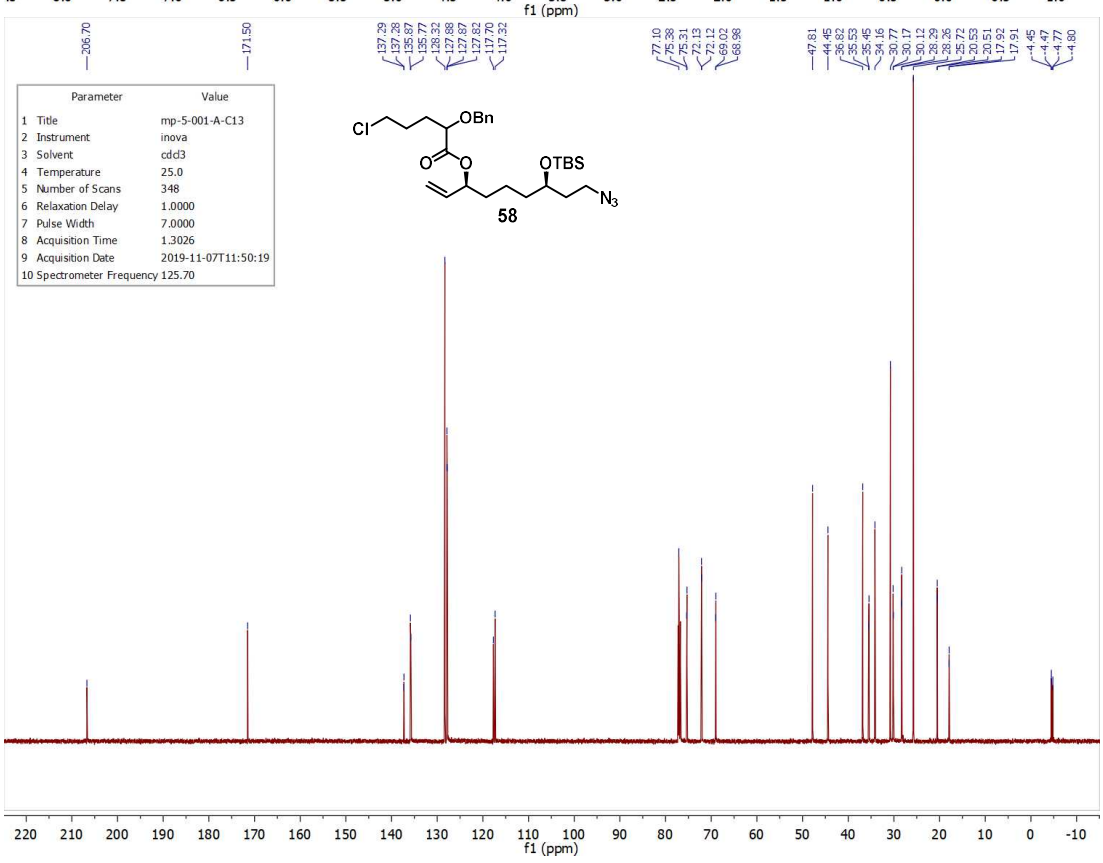
56



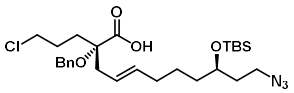
	Parameter	Value
1	Title	mp-4-296-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	132
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-01-07T11:03:32
10	Spectrometer Frequency	125.70

56

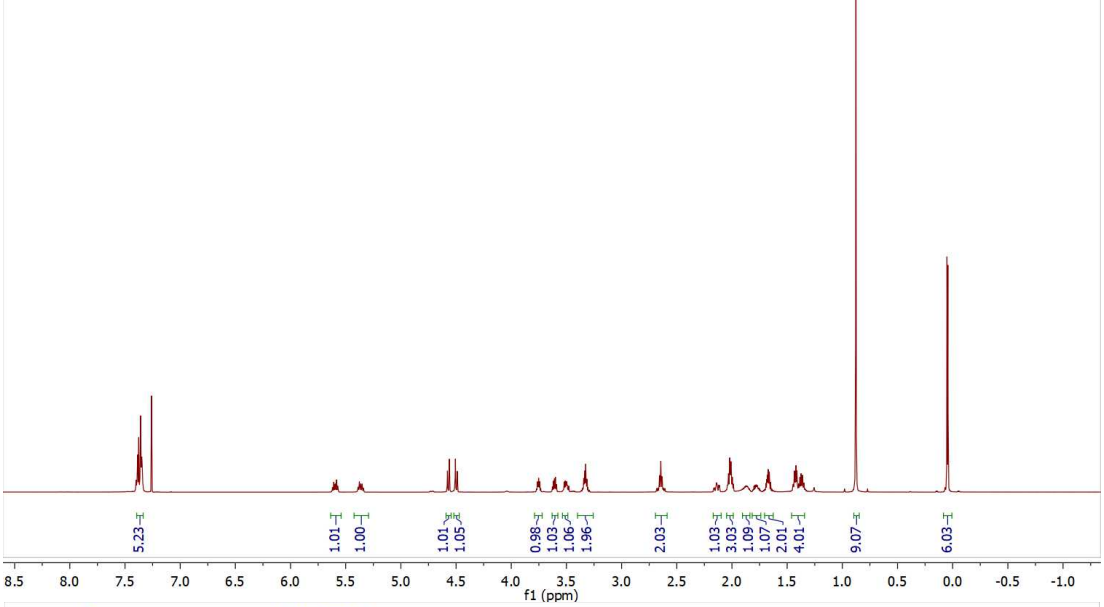

Parameter Value
1 Title mp-5-001-A-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 5.8250
8 Acquisition Time 2.5000
9 Acquisition Date 2019-11-07T11:19:33
10 Spectrometer Frequency 599.64
Cl
OBn
O
O
OTBS
N3
58
3.91
0.95
0.98
1.98
1.00
1.00
1.00
1.00
0.99
2.00
1.98
4.00
3.98
2.03
2.01
9.01
5.96
f1 (ppm)

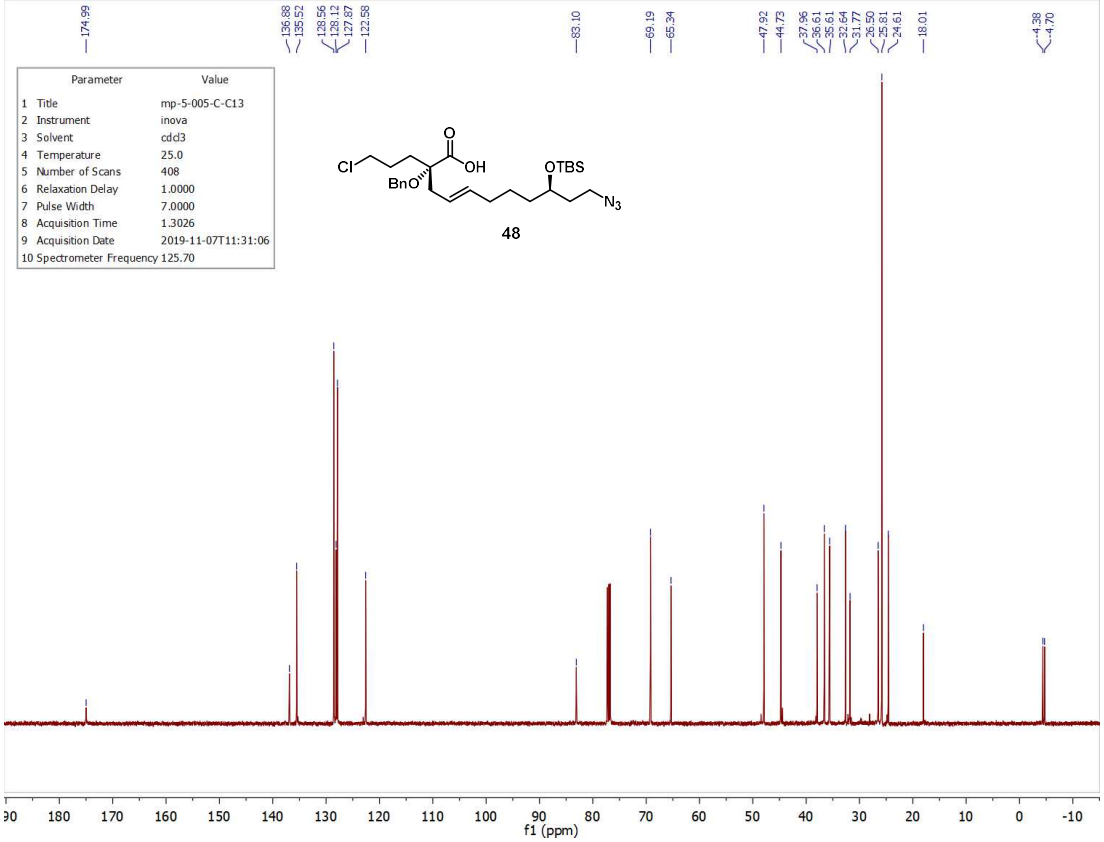

206.70
171.50
137.29
137.28
135.87
135.77
128.32
127.88
127.87
127.82
117.70
117.32
77.10
75.38
75.31
72.13
72.12
69.02
68.98
47.81
44.45
36.82
35.53
35.45
34.16
30.77
30.17
30.12
28.29
28.26
25.72
20.53
20.51
17.92
17.91
-4.45
-4.47
-4.77
-4.80
Parameter Value
1 Title mp-5-001-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 348
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2019-11-07T11:50:19
10 Spectrometer Frequency 125.70
Cl
OBn
O
O
OTBS
N3
58
f1 (ppm)

Parameter	Value
1 Title	mp-5-005-C-1H
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	5.8250
8 Acquisition Time	2.5000
9 Acquisition Date	2019-11-07T11:14:34
10 Spectrometer Frequency	599.64



48

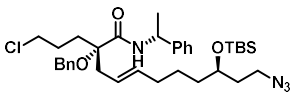




Parameter	Value
1 Title	mp-5-005-C-C13
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	408
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2019-11-07T11:31:06
10 Spectrometer Frequency	125.70

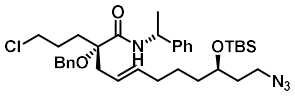
48

Parameter	Value
1 Title	mp-5-003-A-1H
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	12
6 Relaxation Delay	8.0000
7 Pulse Width	6.2500
8 Acquisition Time	2.5001
9 Acquisition Date	2020-01-03T17:49:07
10 Spectrometer Frequency	499.85

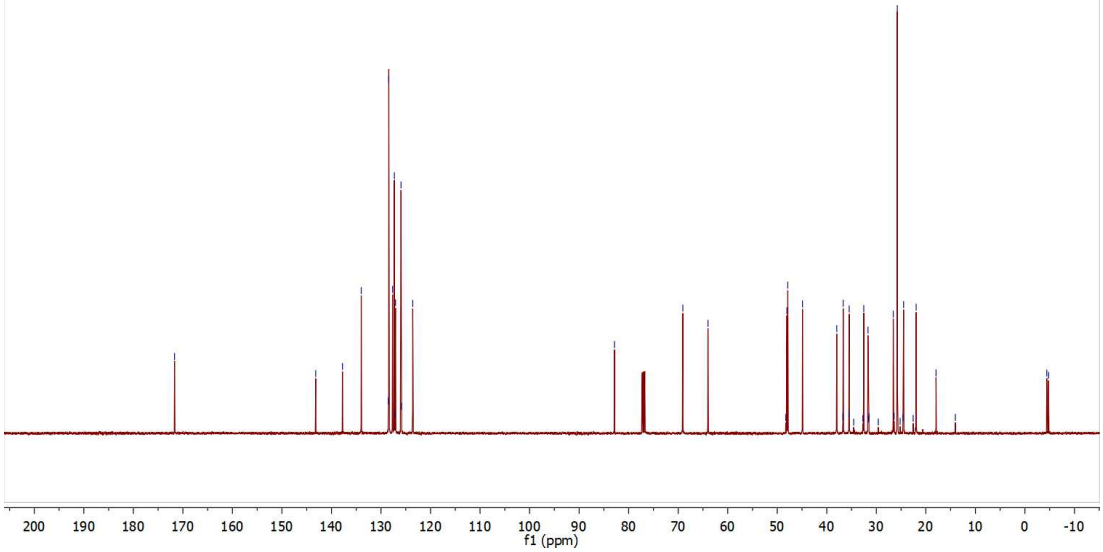


S3

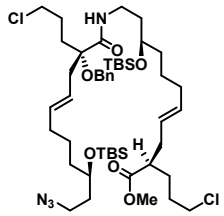
Parameter	Value
1 Title	mp-5-003-A-13C
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	216
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2020-01-03T17:55:31
10 Spectrometer Frequency	125.70



S3

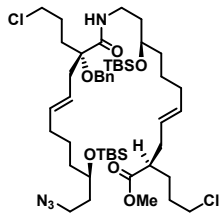


Parameter	Value
1 Title	mp-5-004-A-1H
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.2500
8 Acquisition Time	2.5000
9 Acquisition Date	2020-01-18T13:13:13
10 Spectrometer Frequency	599.64



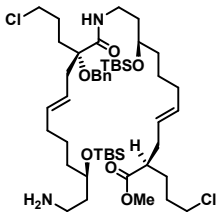
61

Parameter	Value
1 Title	mp-5-004-A-13C
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	352
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2020-01-18T13:20:31
10 Spectrometer Frequency	125.70

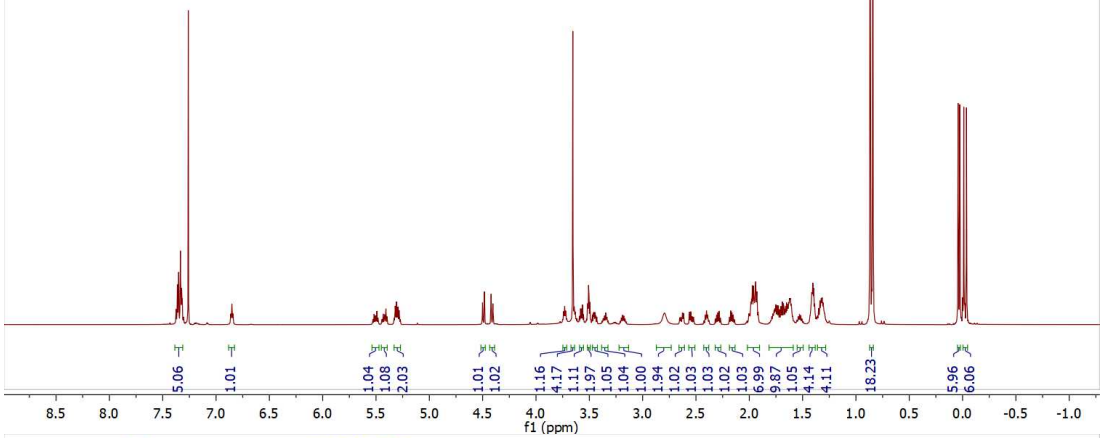


61

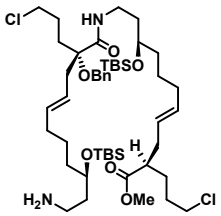
Parameter	Value
1 Title	mp-5-059-A-1H
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	20
6 Relaxation Delay	8.0000
7 Pulse Width	6.2500
8 Acquisition Time	2.5000
9 Acquisition Date	2020-01-21T11:03:44
10 Spectrometer Frequency	599.64



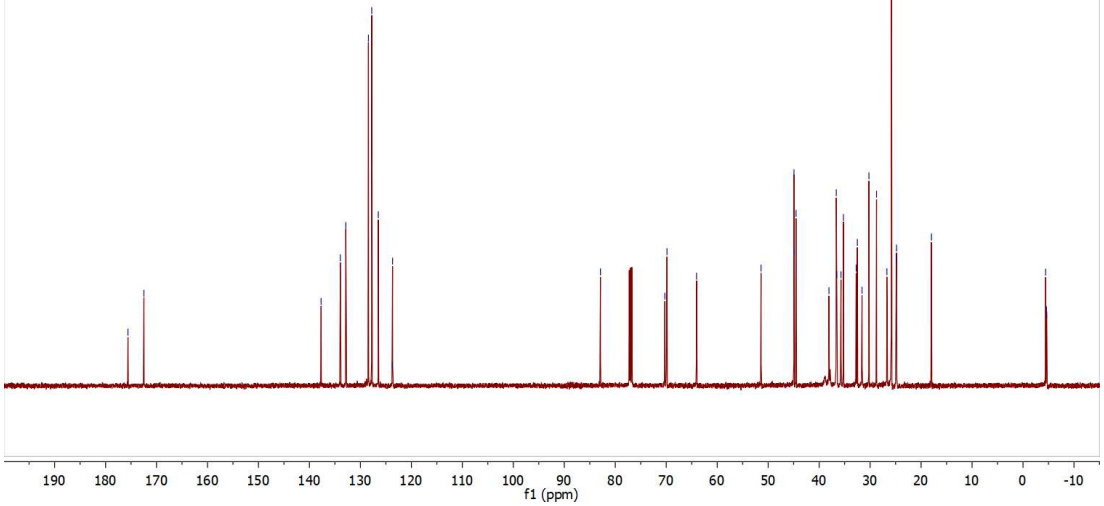
62



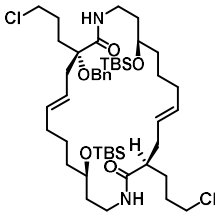
Parameter	Value
1 Title	mp-5-059-A-13C
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	368
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2020-01-21T11:13:48
10 Spectrometer Frequency	125.70



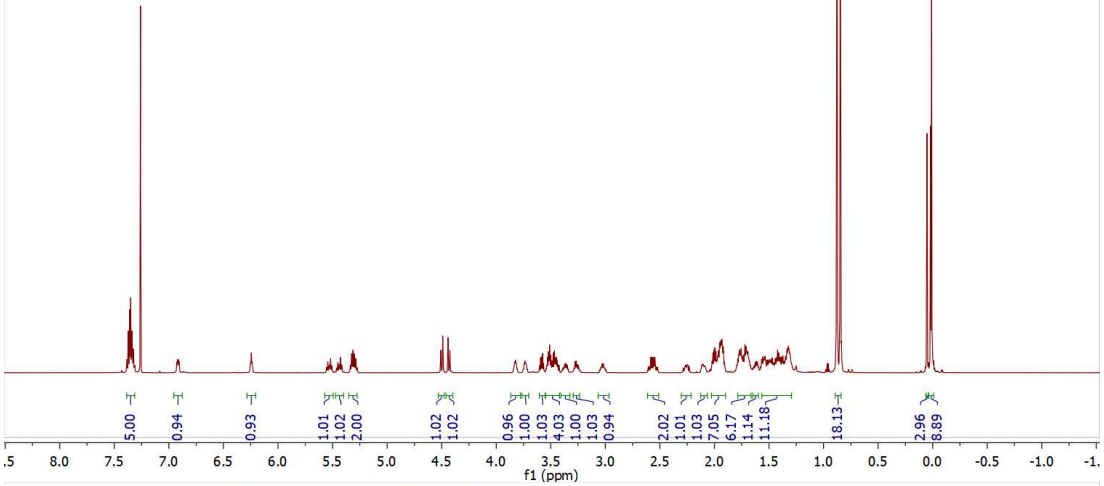
62



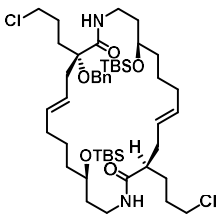
	Parameter	Value
1	Title	mp-5-091-B-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	6.2500
8	Acquisition Time	2.5000
9	Acquisition Date	2020-06-30T17:31:56
10	Spectrometer Frequency	599.64



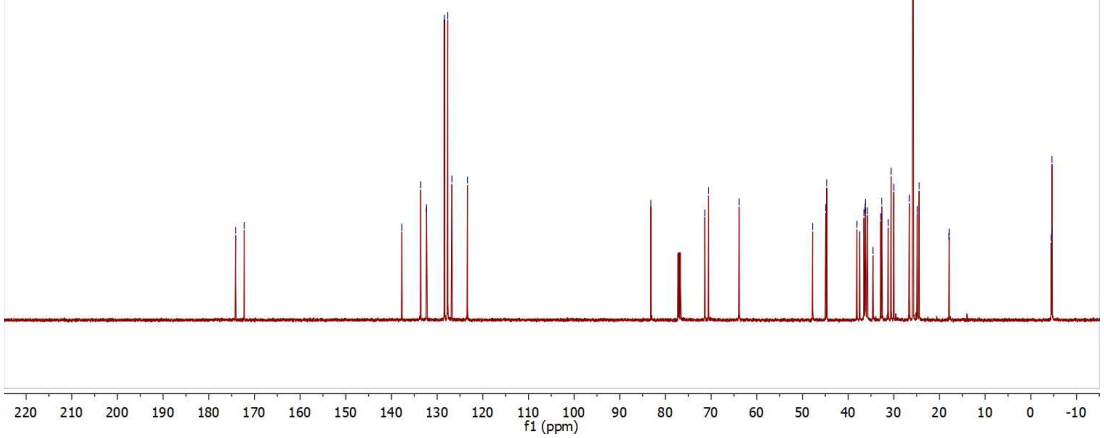
47



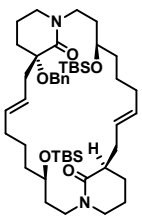
	Parameter	Value
1	Title	mp-5-091-B-C13
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	364
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-06-30T17:23:12
10	Spectrometer Frequency	125.70



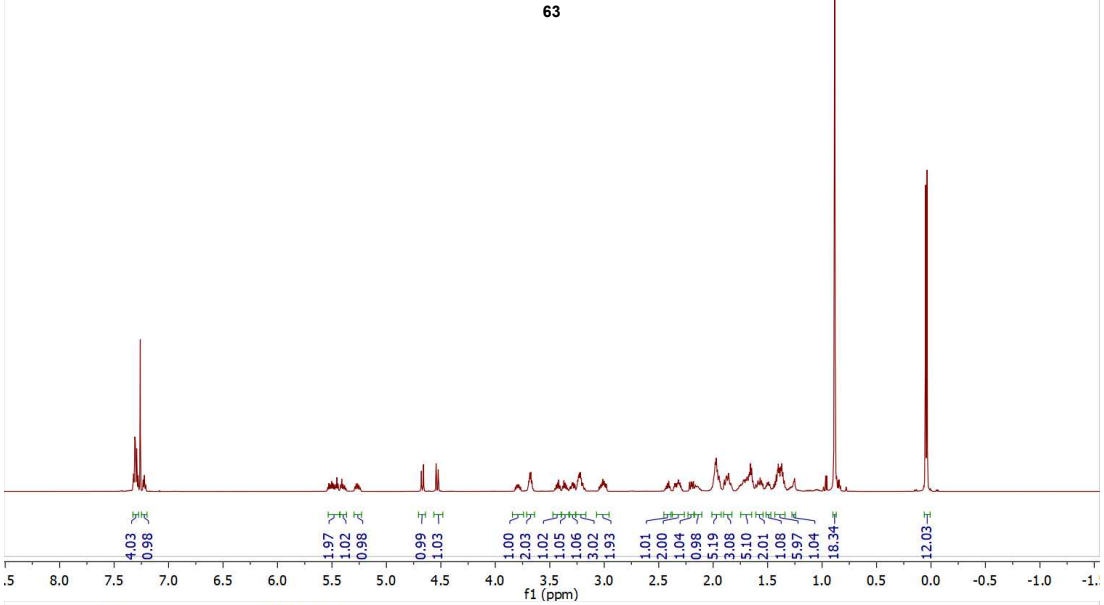
47



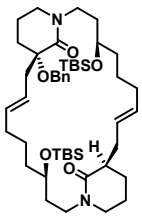
Parameter	Value
1 Title	mp-5-092-A-1H
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.2500
8 Acquisition Time	2.5000
9 Acquisition Date	2020-07-03T20:22:48
10 Spectrometer Frequency	599.64



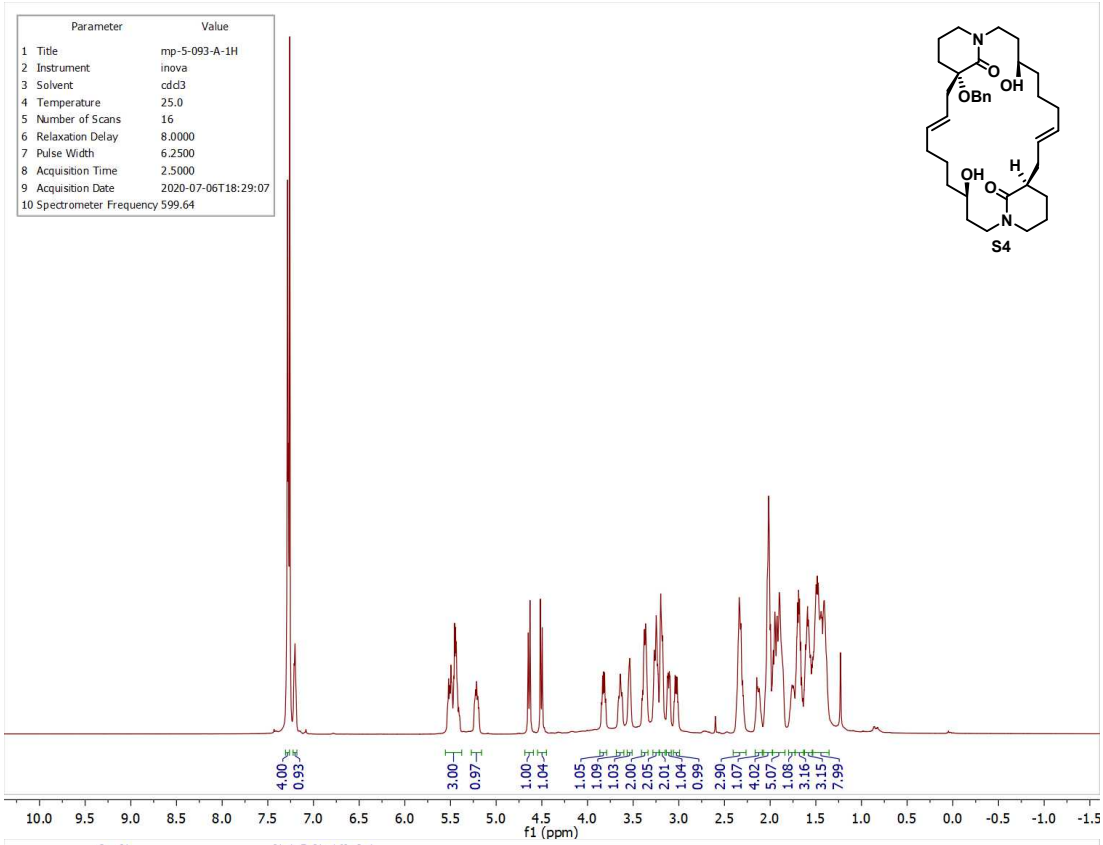
63

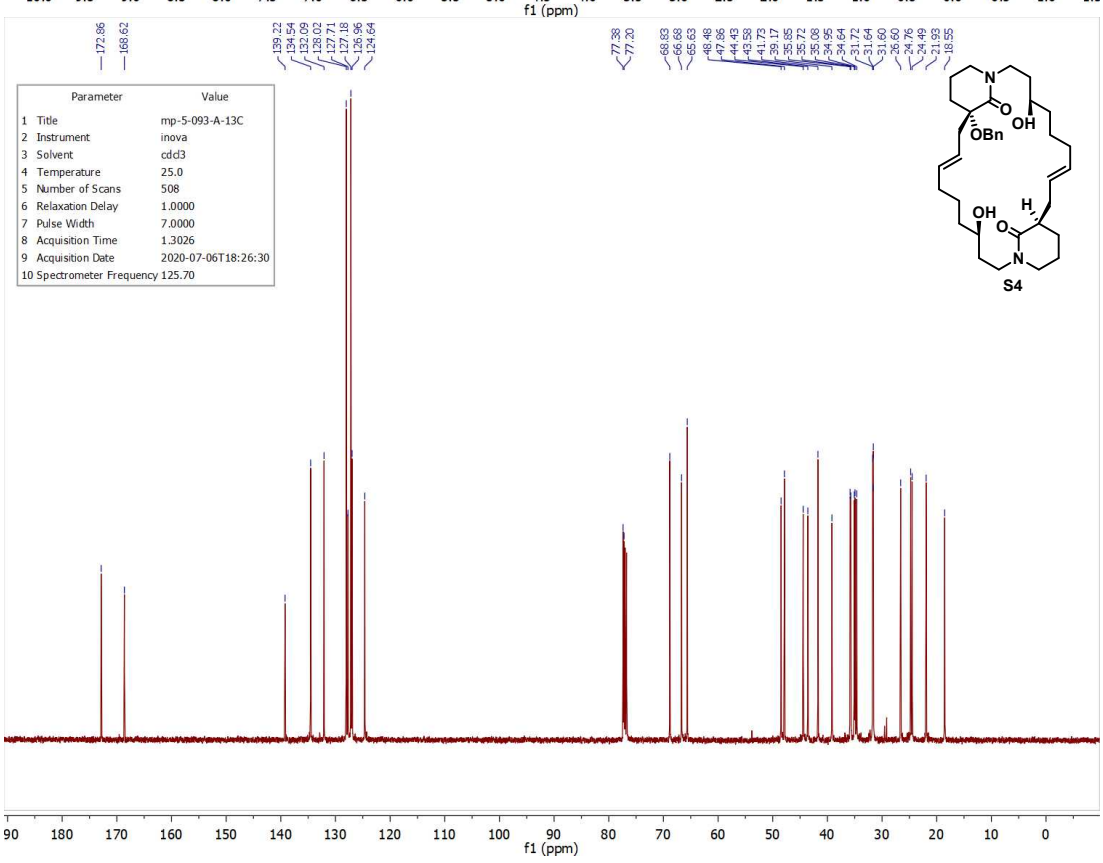


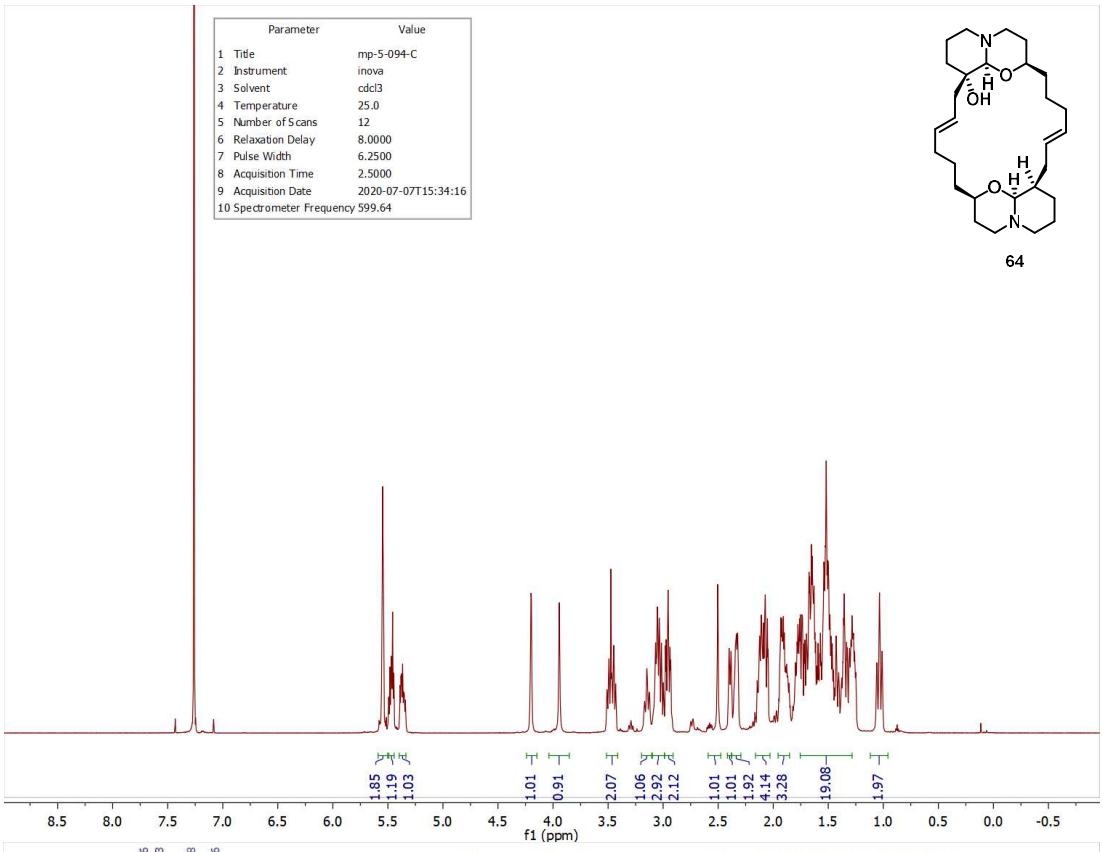
Parameter	Value
1 Title	mp-5-092-A-C13
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	308
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2020-07-03T20:20:02
10 Spectrometer Frequency	125.70

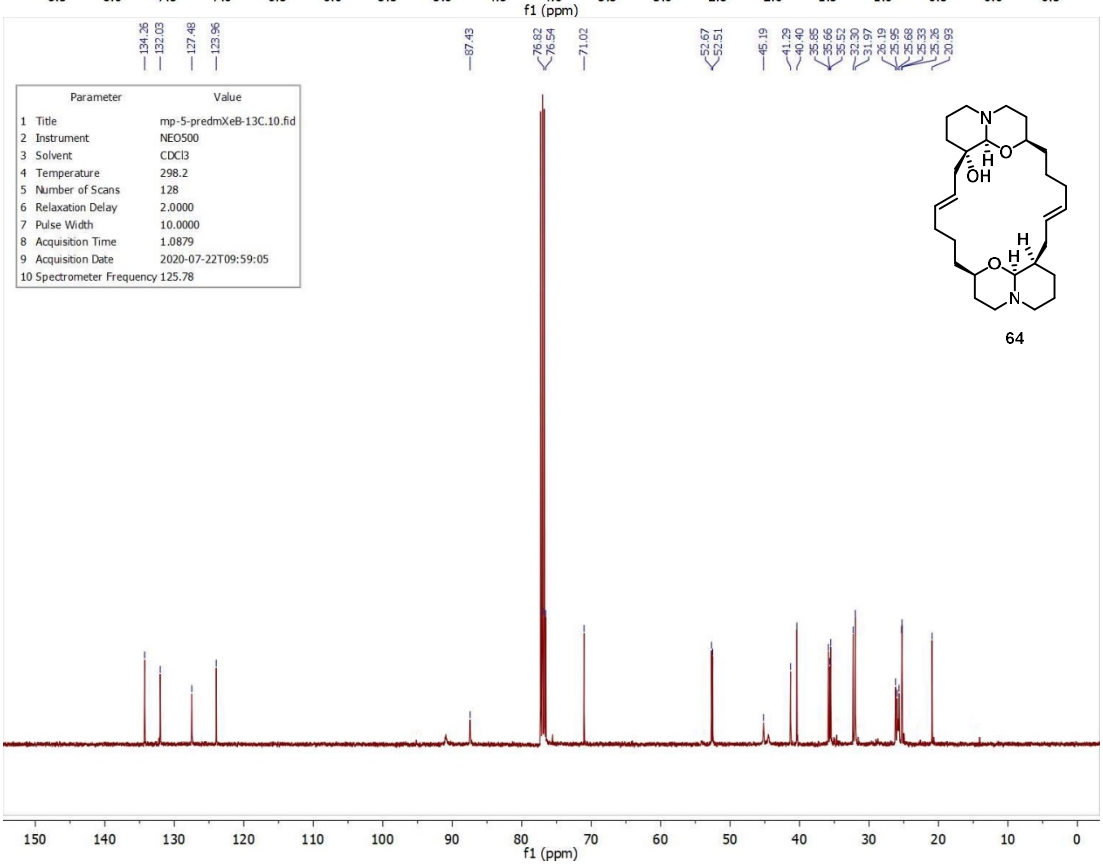


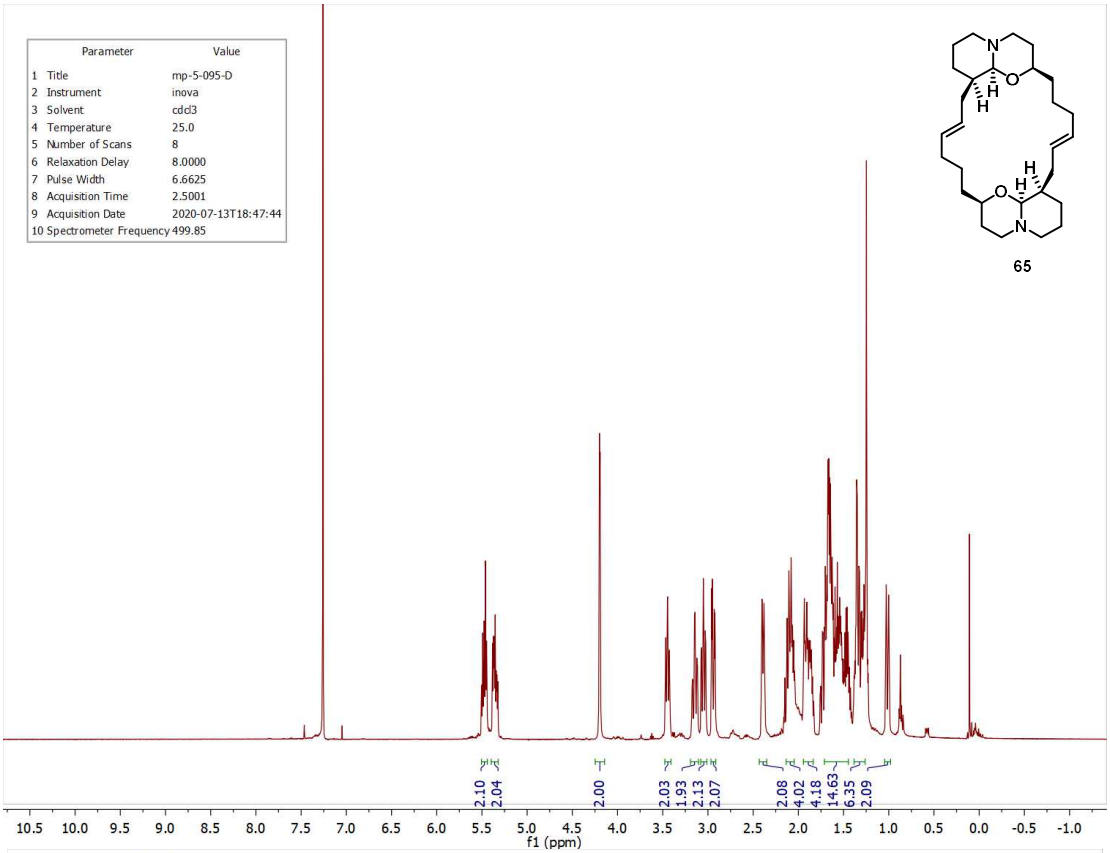
63

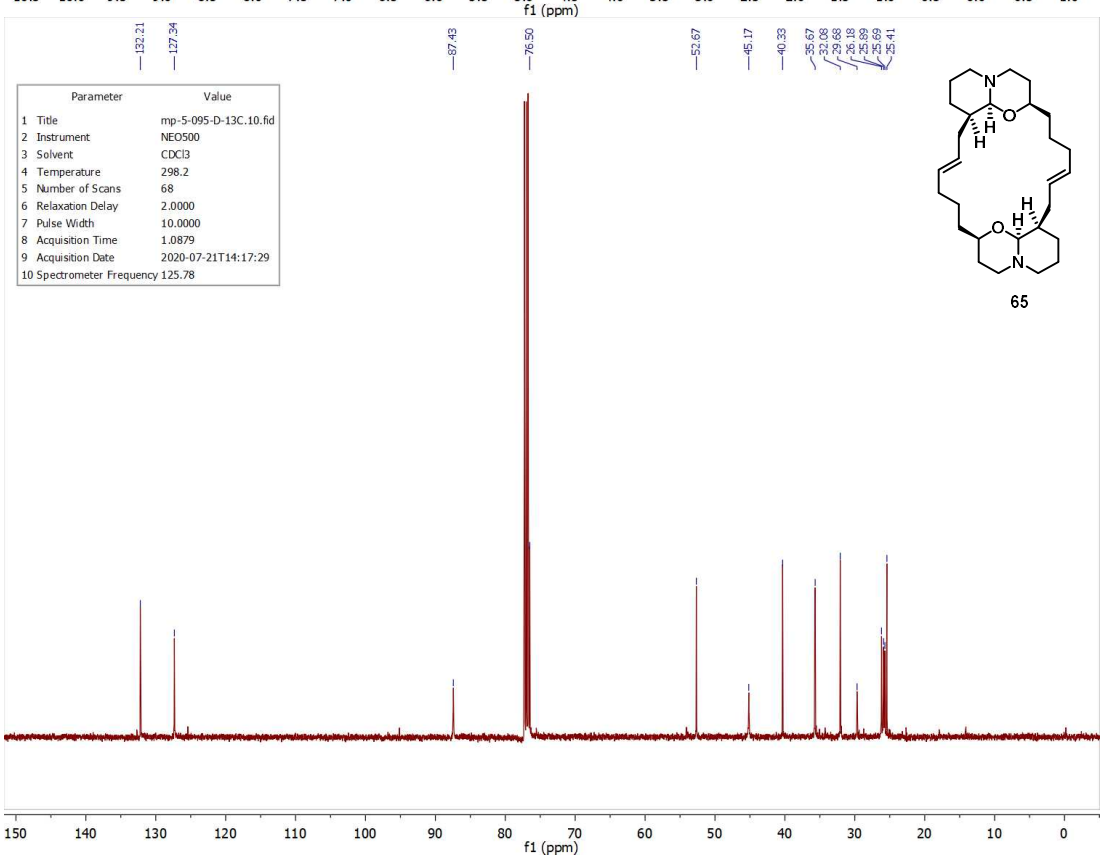

Parameter Value
1 Title mp-5-093-A-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Pulse Width 6.2500
8 Acquisition Time 2.5000
9 Acquisition Date 2020-07-06T18:29:07
10 Spectrometer Frequency 599.64
OBn
OH
OH
H
S4
4.00 0.93 3.00 0.97 1.00 1.04 1.05 1.09 1.03 2.00 2.05 2.01 1.04 0.99 2.90 1.07 4.02 5.07 1.08 3.16 3.15 7.99
f1 (ppm)

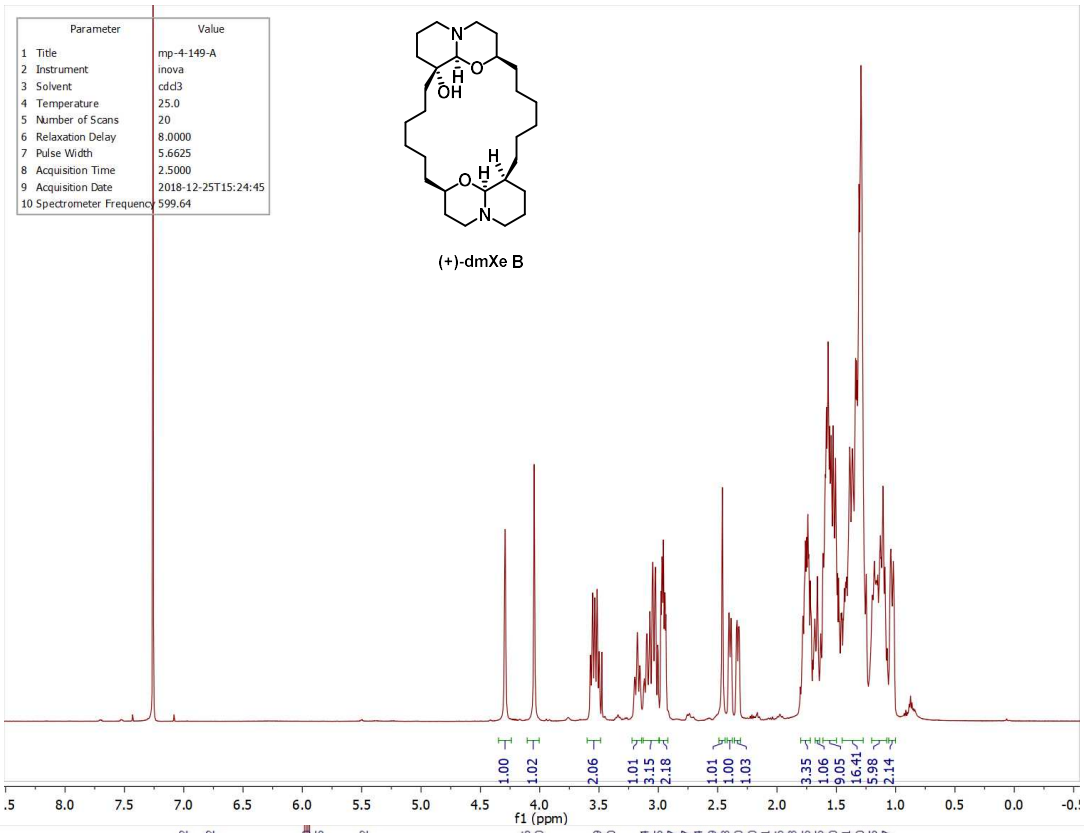

172.86 168.62 139.22 134.54 132.09 128.02 127.71 127.18 126.96 124.64 77.38 77.20 68.83 66.68 65.63 48.48 47.86 44.43 43.58 41.73 39.17 35.85 35.72 35.08 34.95 34.64 31.72 31.64 31.60 26.60 24.76 24.49 21.93 18.55
Parameter Value
1 Title mp-5-093-A-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 508
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-07-06T18:26:30
10 Spectrometer Frequency 125.70
OBn
OH
OH
H
S4
f1 (ppm)

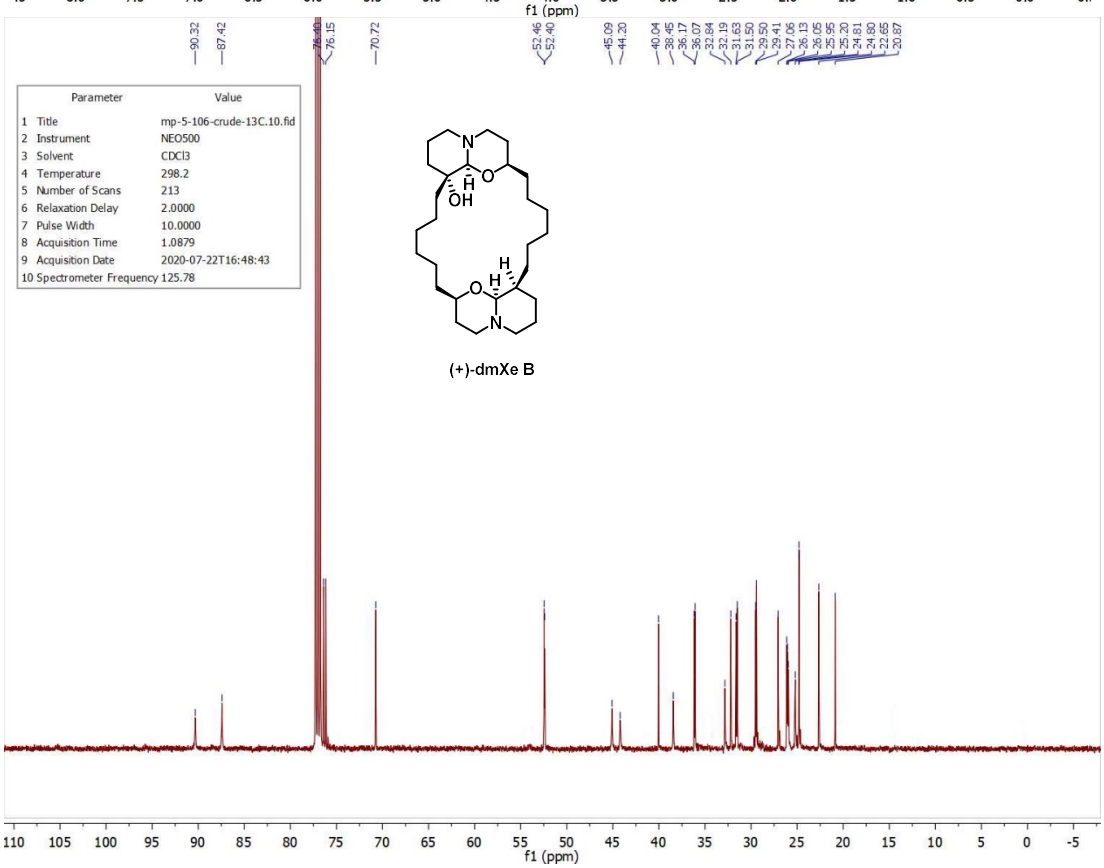

Parameter Value
1 Title mp-5-094-C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.2500
8 Acquisition Time 2.5000
9 Acquisition Date 2020-07-07T15:34:16
10 Spectrometer Frequency 599.64
64
1.85 1.19 1.03 1.01 0.91 2.07 1.06 2.92 2.12 1.01 1.01 1.92 4.14 3.28 19.08 1.97
f1 (ppm)

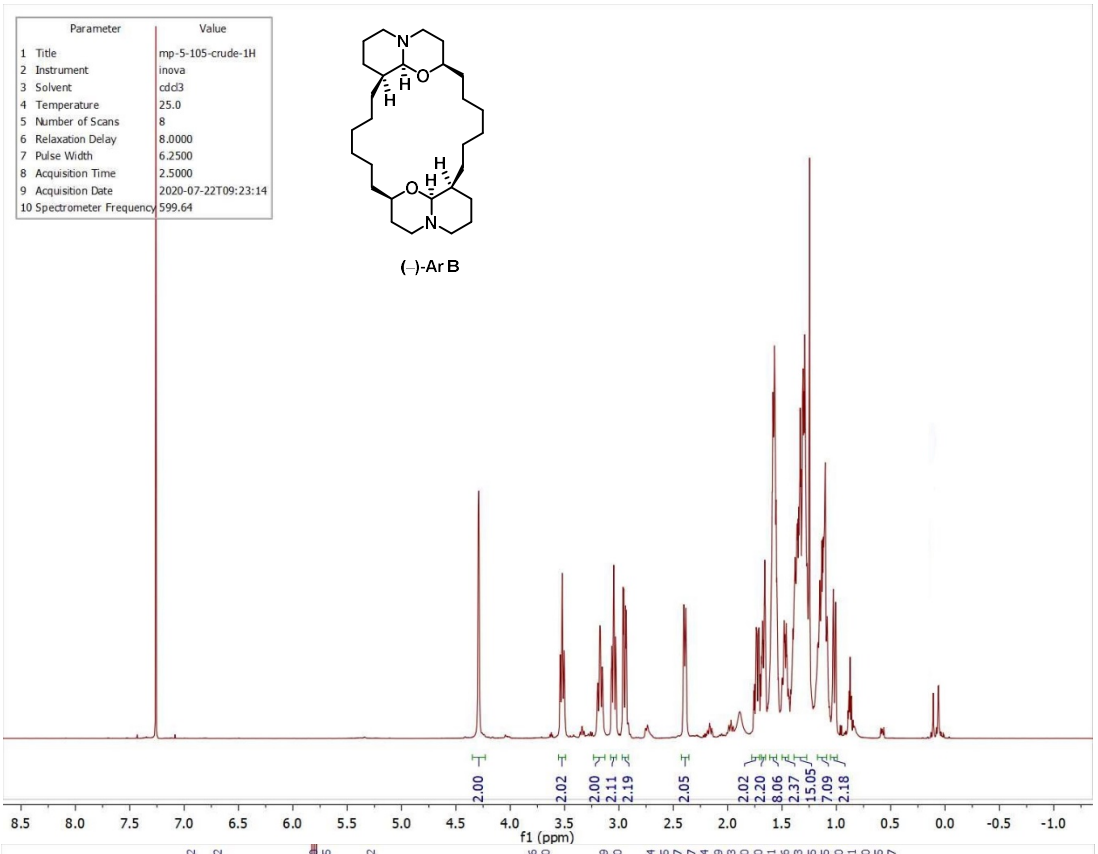

134.26 132.03 127.48 123.96 87.43 76.82 76.54 71.02 52.67 52.51 45.19 41.29 40.40 35.85 35.66 35.52 31.30 31.07 26.19 25.95 25.68 25.33 25.26 20.93
Parameter Value
1 Title mp-5-predmXeB-13C.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 128
6 Relaxation Delay 2.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.0879
9 Acquisition Date 2020-07-22T09:59:05
10 Spectrometer Frequency 125.78
64
f1 (ppm)

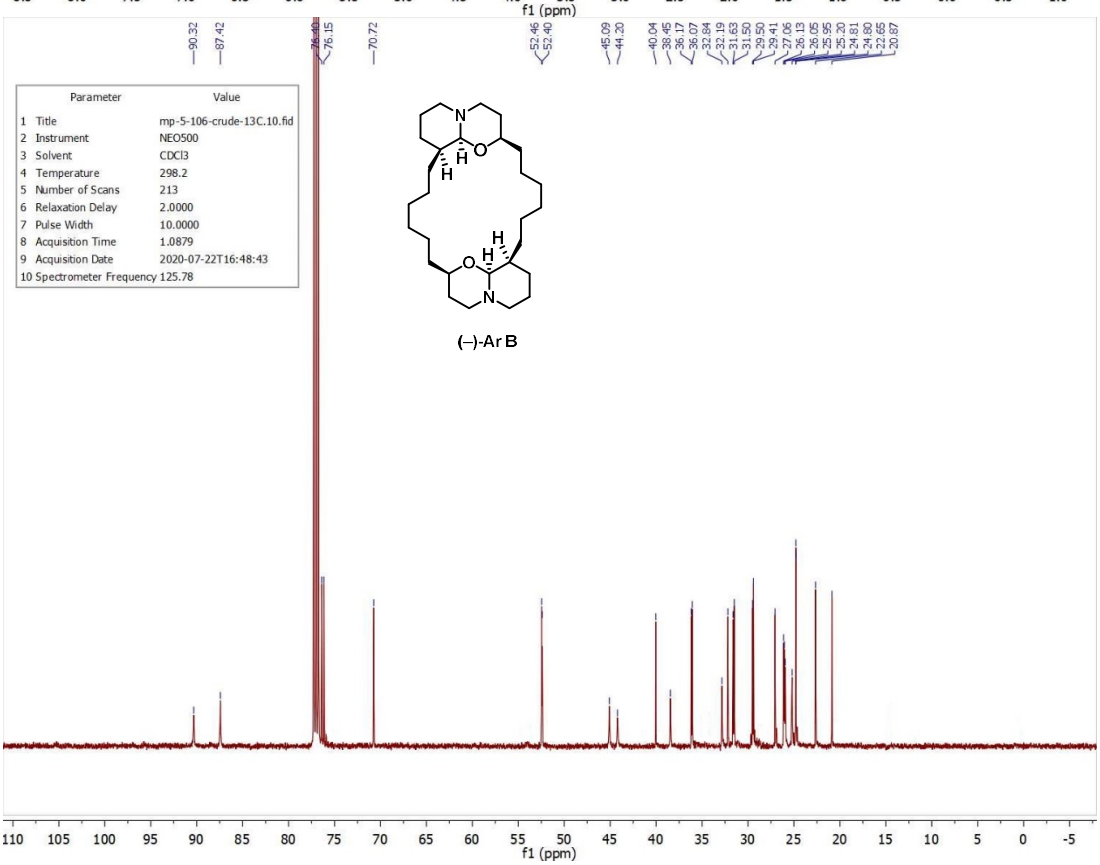

Parameter Value
1 Title mp-5-095-D
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.6625
8 Acquisition Time 2.5001
9 Acquisition Date 2020-07-13T18:47:44
10 Spectrometer Frequency 499.85
65
2.10 2.04 2.00 2.03 1.93 2.13 2.07 2.08 4.02 4.18 14.63 6.35 2.09
f1 (ppm)

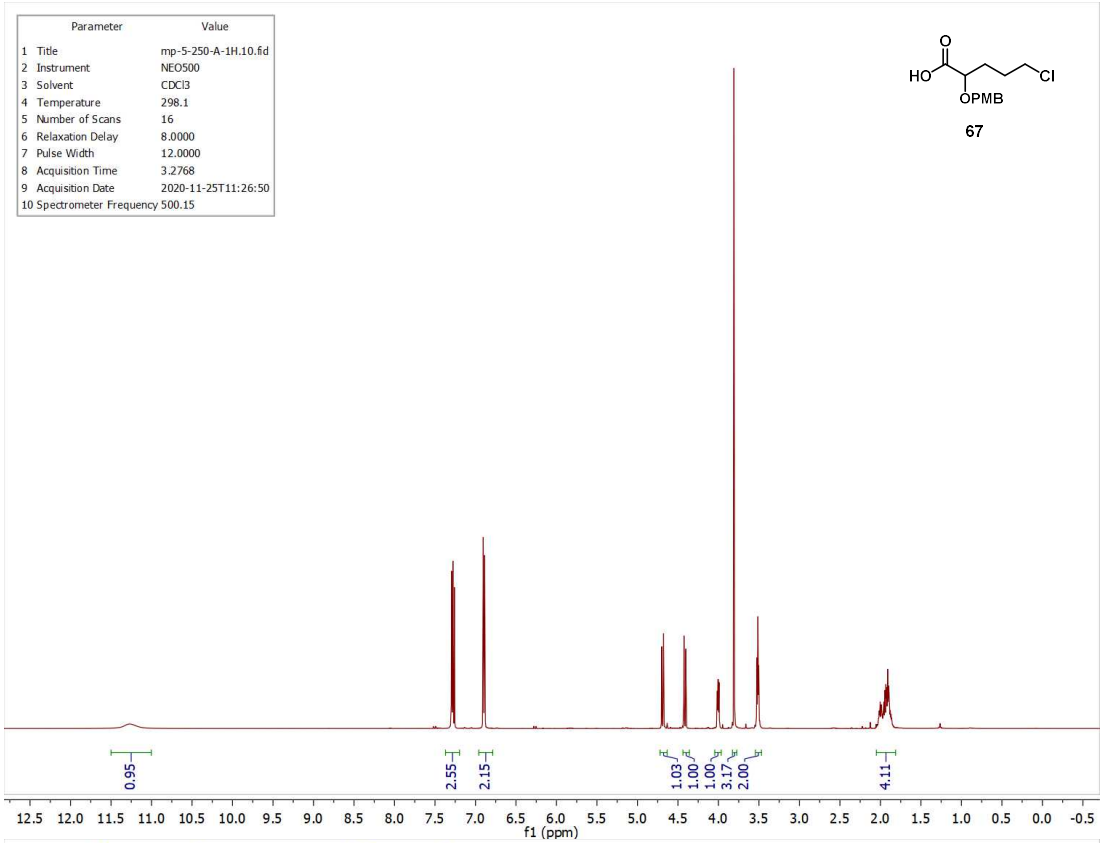

132.21 127.34 87.43 76.50 52.67 45.17 40.33 35.67 32.08 29.68 26.18 25.89 25.69 25.41
Parameter Value
1 Title mp-5-095-D-13C.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 68
6 Relaxation Delay 2.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.0879
9 Acquisition Date 2020-07-21T14:17:29
10 Spectrometer Frequency 125.78
65
f1 (ppm)

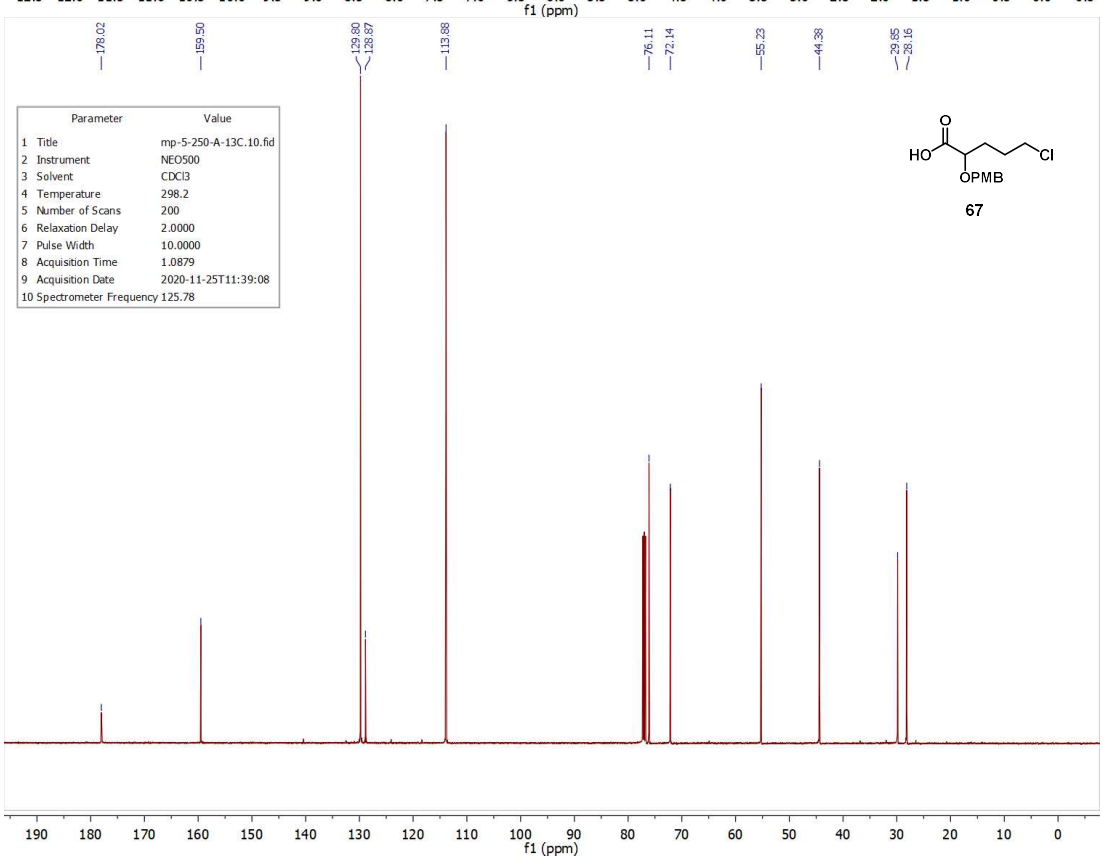

Parameter Value
1 Title mp-4-149-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 20
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2018-12-25T15:24:45
10 Spectrometer Frequency 599.64
(+)-dmXe B
1.00 1.02 2.06 1.01 3.15 2.18 1.01 1.00 1.03 3.35 1.06 9.05 16.41 5.98 2.14
f1 (ppm)

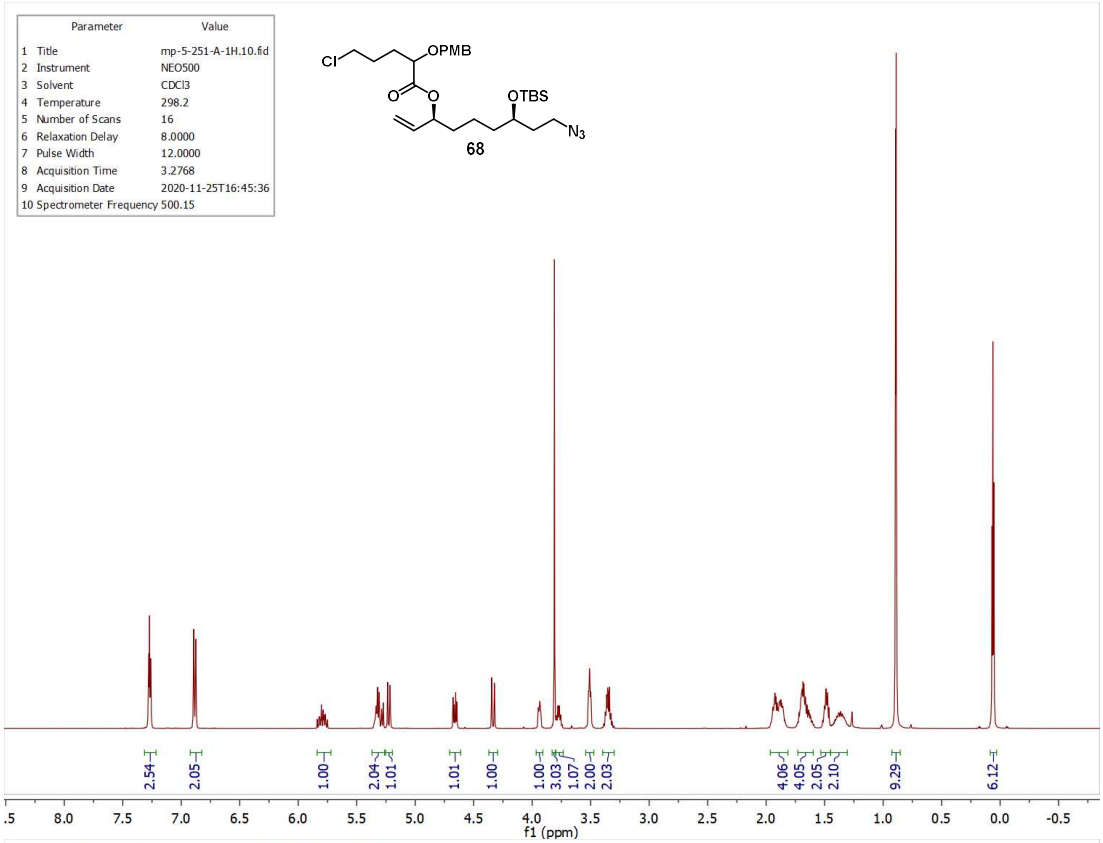

90.32 87.42 76.15 70.72 52.46 52.40 45.09 44.30 40.04 38.45 36.17 36.07 32.84 32.19 31.63 31.50 29.50 29.41 27.06 26.13 26.05 25.95 25.20 24.81 24.80 22.65 20.87
Parameter Value
1 Title mp-5-106-crude-13C.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 213
6 Relaxation Delay 2.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.0879
9 Acquisition Date 2020-07-22T16:48:43
10 Spectrometer Frequency 125.78
(+)-dmXe B
f1 (ppm)

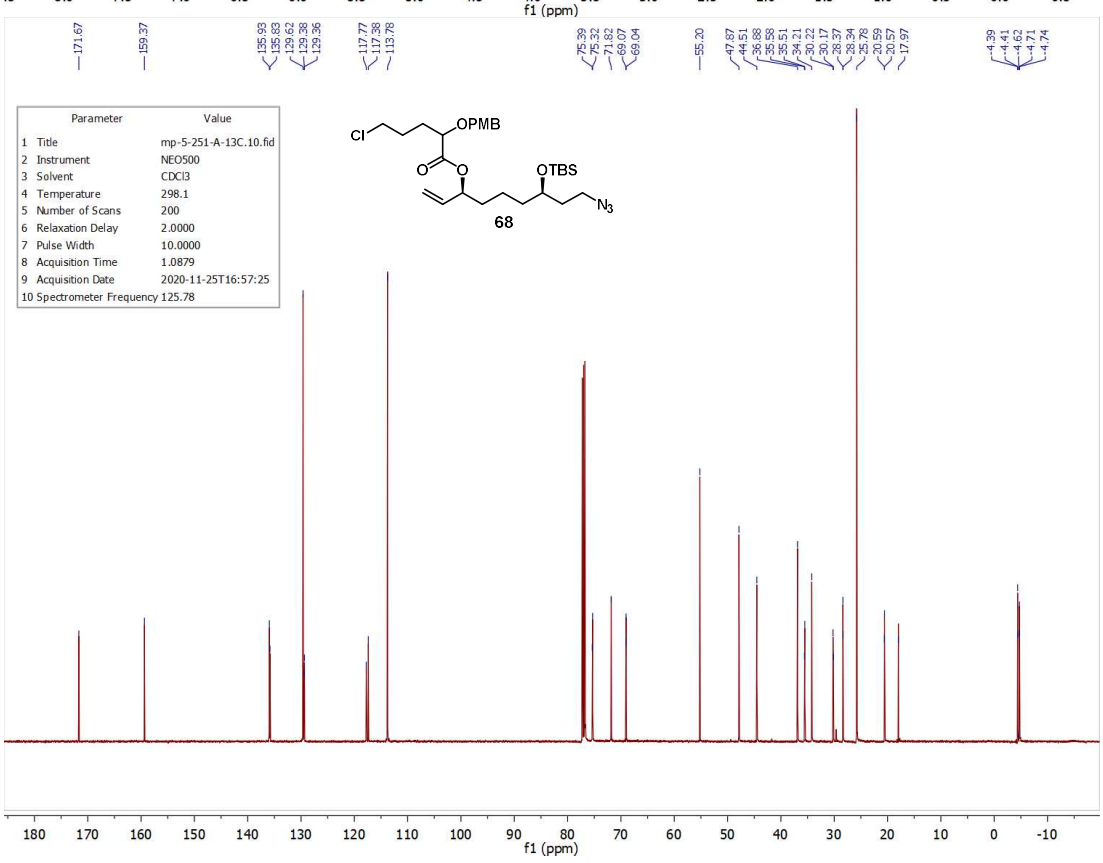

Parameter Value
1 Title mp-5-105-crude-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.2500
8 Acquisition Time 2.5000
9 Acquisition Date 2020-07-22T09:23:14
10 Spectrometer Frequency 599.64
(–)-ArB
2.00 2.02 2.00 2.11 2.19 2.05 2.02 2.20 8.06 2.37 15.05 7.09 2.18
f1 (ppm)


90.32 87.42 76.40 76.15 70.72 52.46 52.40 45.09 44.20 40.04 38.45 36.17 36.07 32.84 32.19 31.63 31.50 29.50 29.41 27.06 26.13 26.05 25.95 25.20 24.81 24.60 22.65 20.87
Parameter Value
1 Title mp-5-106-crude-13C.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 213
6 Relaxation Delay 2.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.0879
9 Acquisition Date 2020-07-22T16:48:43
10 Spectrometer Frequency 125.78
(–)-ArB
f1 (ppm)

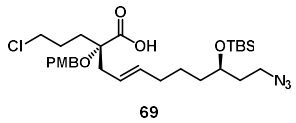

Parameter Value
1 Title mp-5-250-A-1H.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.1
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Pulse Width 12.0000
8 Acquisition Time 3.2768
9 Acquisition Date 2020-11-25T11:26:50
10 Spectrometer Frequency 500.15
HO
O
OPMB
Cl
67
0.95
2.55
2.15
1.03
1.00
1.00
3.17
2.00
4.11
f1 (ppm)


178.02
159.50
129.80
128.87
113.88
76.11
72.14
55.23
44.38
29.85
28.16
Parameter Value
1 Title mp-5-250-A-13C.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 200
6 Relaxation Delay 2.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.0879
9 Acquisition Date 2020-11-25T11:39:08
10 Spectrometer Frequency 125.78
HO
O
OPMB
Cl
67
f1 (ppm)

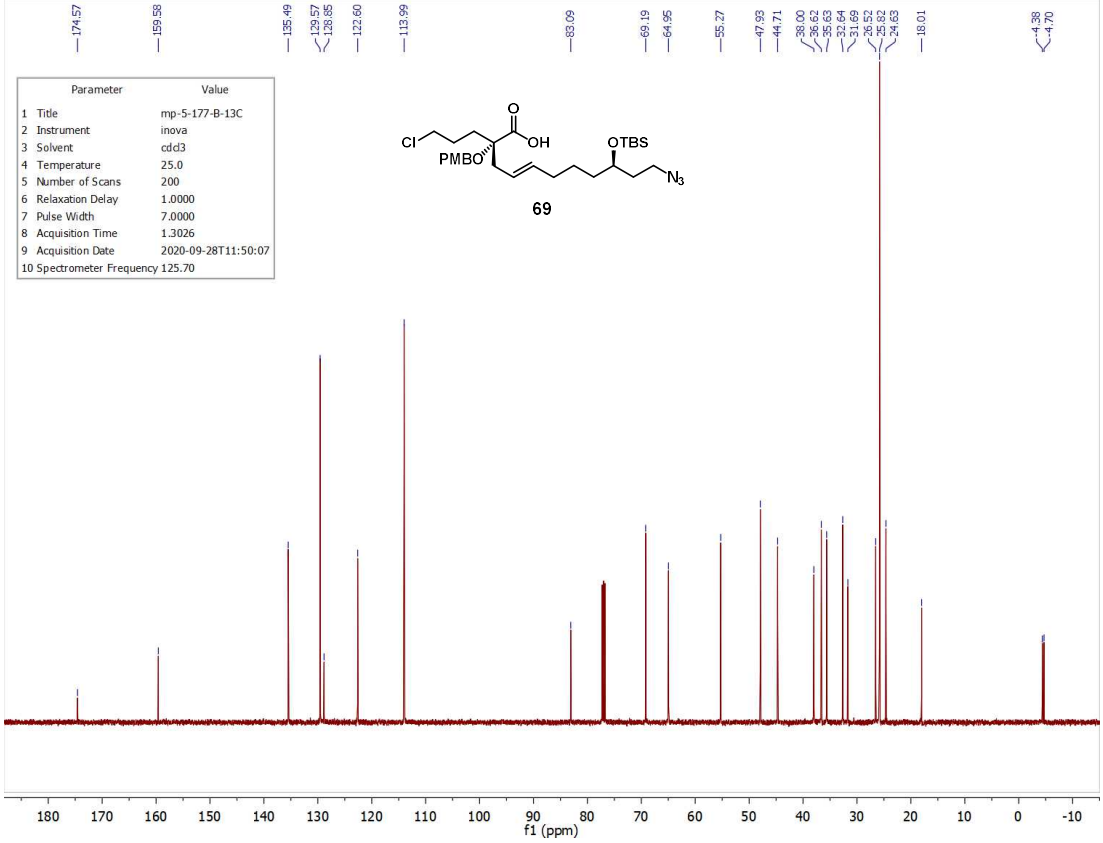

Parameter Value
1 Title mp-5-251-A-1H.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Pulse Width 12.0000
8 Acquisition Time 3.2768
9 Acquisition Date 2020-11-25T16:45:36
10 Spectrometer Frequency 500.15
Cl
OPMB
O
O
OTBS
N3
68
2.54
2.05
1.00
2.04
1.01
1.01
1.00
1.00
3.03
1.07
2.00
2.03
4.06
4.05
2.05
2.10
9.29
6.12
f1 (ppm)


171.67
159.37
135.93
135.83
129.62
129.38
129.36
117.77
117.38
113.78
75.39
75.32
71.82
69.07
69.04
55.20
47.67
44.51
36.88
35.51
34.21
30.22
30.17
28.37
28.34
25.78
20.59
20.57
17.97
4.39
4.41
4.62
4.71
4.74
Parameter Value
1 Title mp-5-251-A-13C.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.1
5 Number of Scans 200
6 Relaxation Delay 2.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.0879
9 Acquisition Date 2020-11-25T16:57:25
10 Spectrometer Frequency 125.78
Cl
OPMB
O
O
OTBS
N3
68
f1 (ppm)

	Parameter	Value
1	Title	mp-5-177-B-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	6.0375
8	Acquisition Time	2.5000
9	Acquisition Date	2020-09-28T11:28:01
10	Spectrometer Frequency	599.64



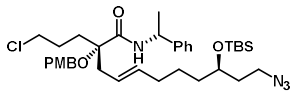
69



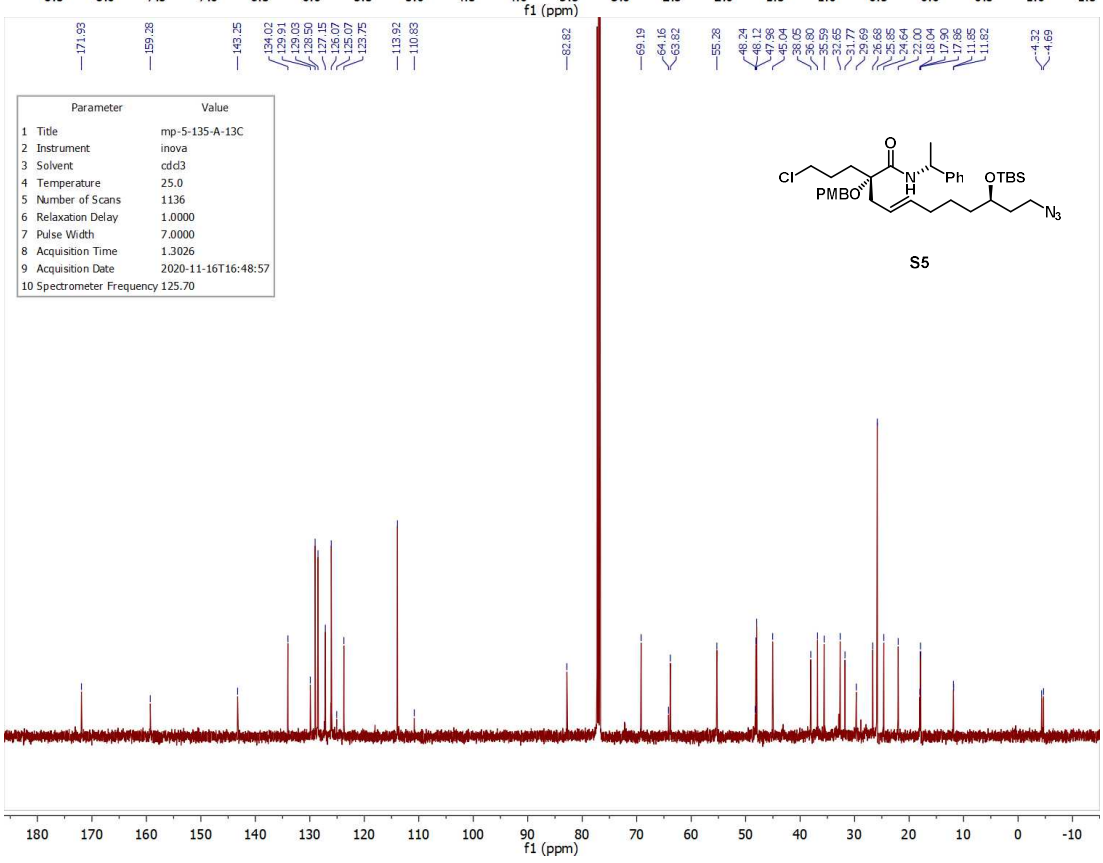
	Parameter	Value
1	Title	mp-5-177-B-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	200
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-09-28T11:50:07
10	Spectrometer Frequency	125.70

69

Parameter	Value
1 Title	mp-5-178-A
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.2500
8 Acquisition Time	2.5000
9 Acquisition Date	2020-09-01T16:00:41
10 Spectrometer Frequency	599.64

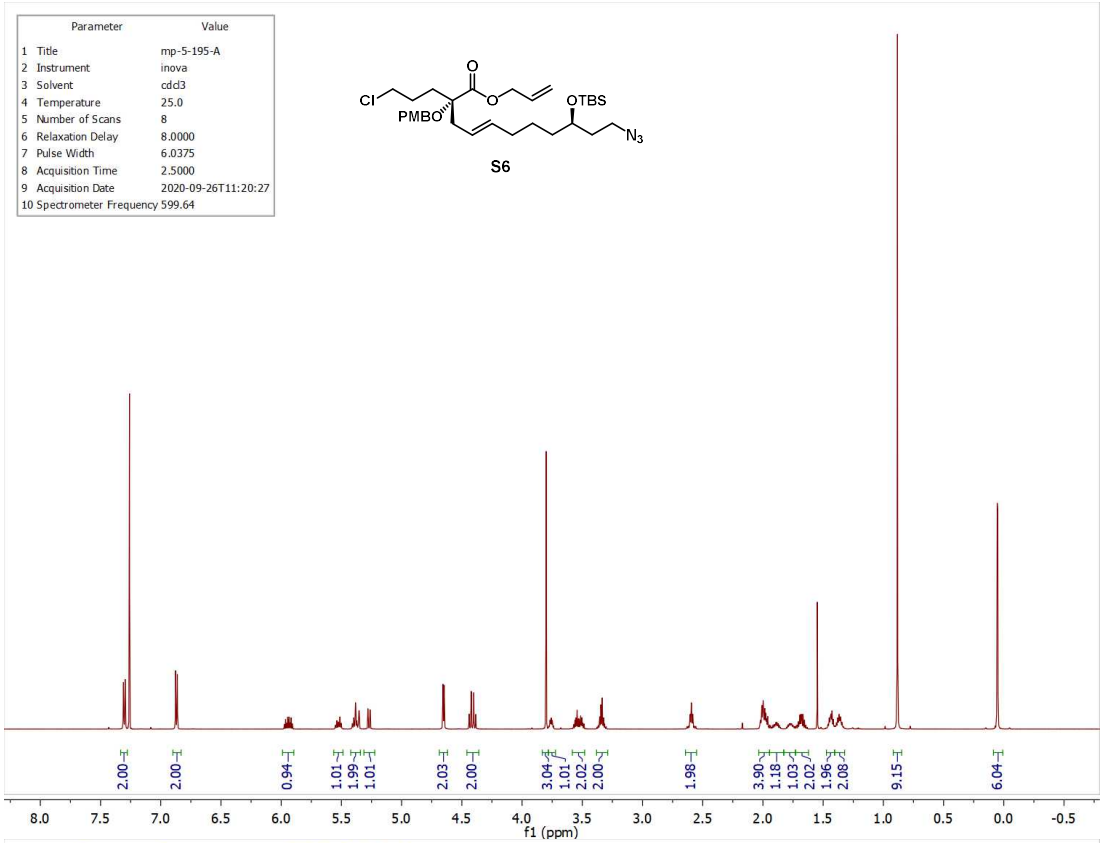


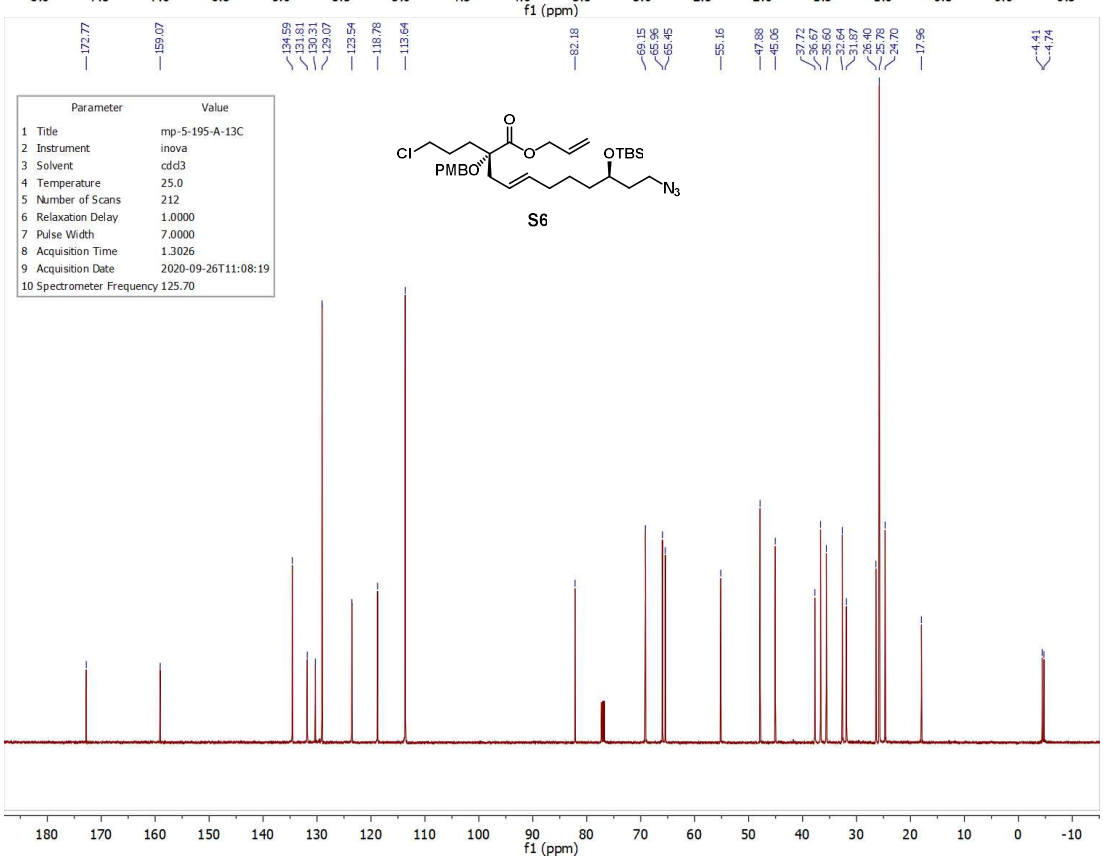
S5



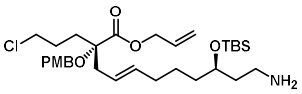
Parameter	Value
1 Title	mp-5-135-A-13C
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	1136
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2020-11-16T16:48:57
10 Spectrometer Frequency	125.70

S5

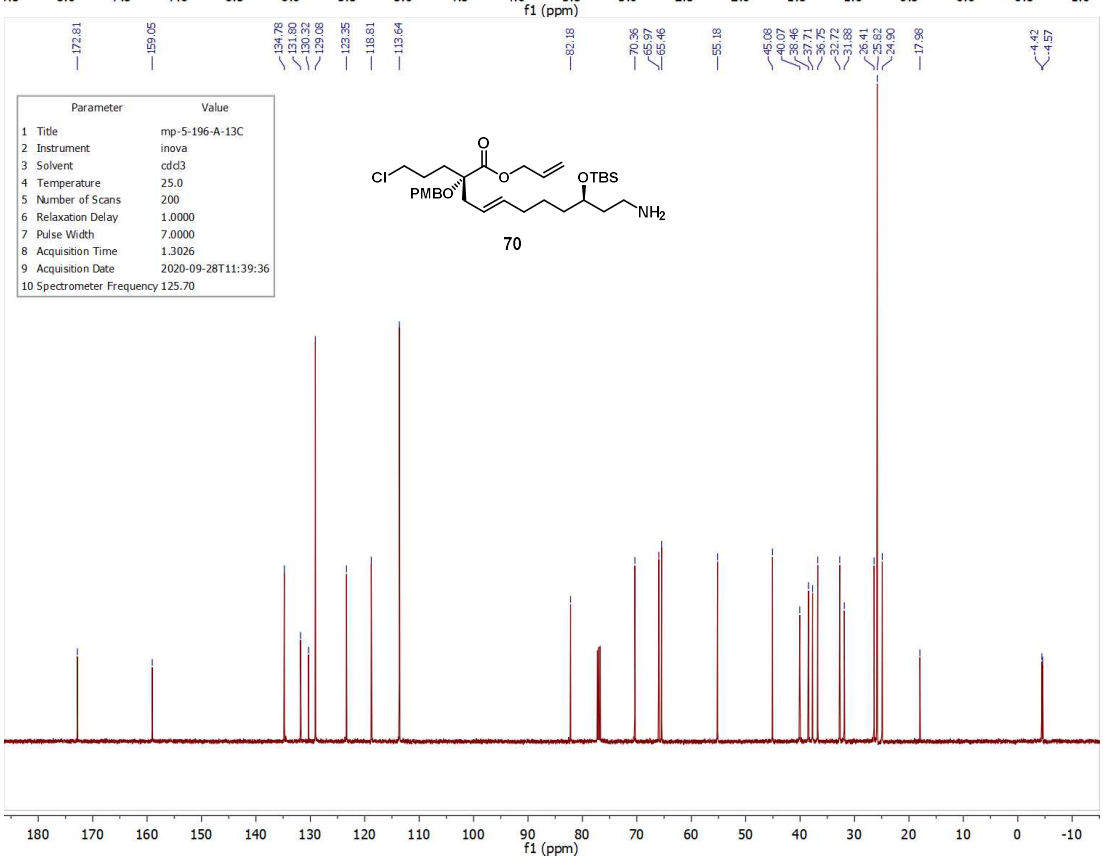

Parameter Value
1 Title mp-5-195-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.0375
8 Acquisition Time 2.5000
9 Acquisition Date 2020-09-26T11:20:27
10 Spectrometer Frequency 599.64
Cl
PMBO
O
O
OTBS
N3
S6
2.00 2.00 0.94 1.01 1.99 1.01 2.03 2.00 3.04 1.01 2.02 2.00 1.98 3.90 1.18 1.03 2.02 1.96 2.08 9.15 6.04
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


172.77 159.07 134.59 131.81 130.31 129.07 123.54 118.78 113.64 82.18 69.15 65.96 65.45 55.16 47.88 45.06 37.72 36.67 35.60 33.64 31.67 26.40 25.78 24.70 17.96 -4.41 -4.74
Parameter Value
1 Title mp-5-195-A-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 212
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-09-26T11:08:19
10 Spectrometer Frequency 125.70
Cl
PMBO
O
O
OTBS
N3
S6
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Parameter	Value
1 Title	mp-5-196-A
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.0375
8 Acquisition Time	2.5000
9 Acquisition Date	2020-09-28T11:33:27
10 Spectrometer Frequency	599.64



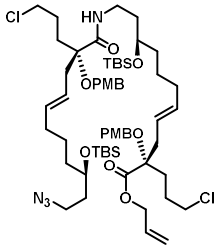
70



Parameter	Value
1 Title	mp-5-196-A-13C
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	200
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2020-09-28T11:39:36
10 Spectrometer Frequency	125.70

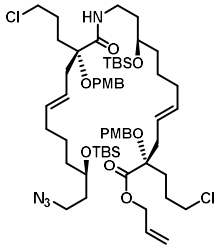
70

	Parameter	Value
1	Title	mp-5-197-A-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	6.0375
8	Acquisition Time	2.5000
9	Acquisition Date	2020-10-06T10:15:19
10	Spectrometer Frequency	599.64



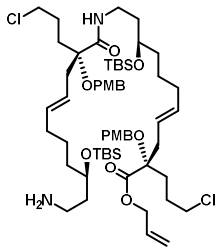
S7

	Parameter	Value
1	Title	mp-5-197-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	252
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-10-06T10:23:30
10	Spectrometer Frequency	125.70

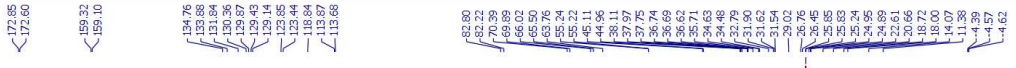


S7

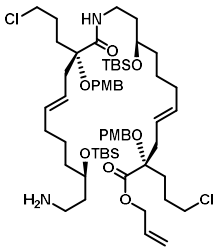
	Parameter	Value
1	Title	mp-5-187-A-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	12
6	Relaxation Delay	8.0000
7	Pulse Width	6.2500
8	Acquisition Time	2.5000
9	Acquisition Date	2020-09-15T18:20:56
10	Spectrometer Frequency	599.64



S8

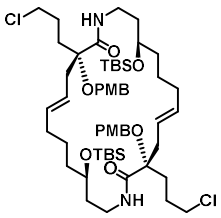


	Parameter	Value
1	Title	mp-5-187-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	368
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-09-15T18:29:47
10	Spectrometer Frequency	125.70

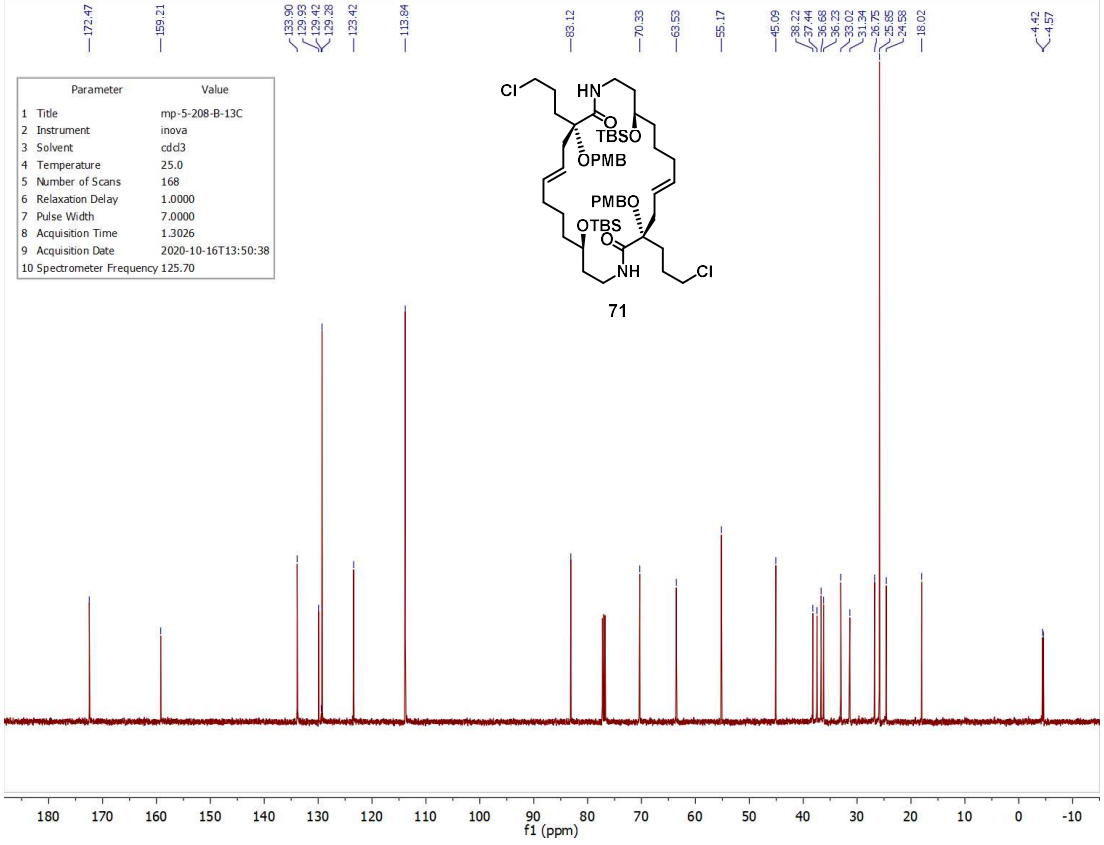


S8

Parameter	Value
1 Title	mp-5-189-A
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	12
6 Relaxation Delay	8.0000
7 Pulse Width	6.0375
8 Acquisition Time	2.5000
9 Acquisition Date	2020-09-21T14:49:25
10 Spectrometer Frequency	599.64



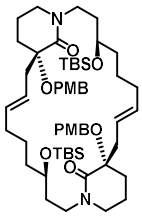
71



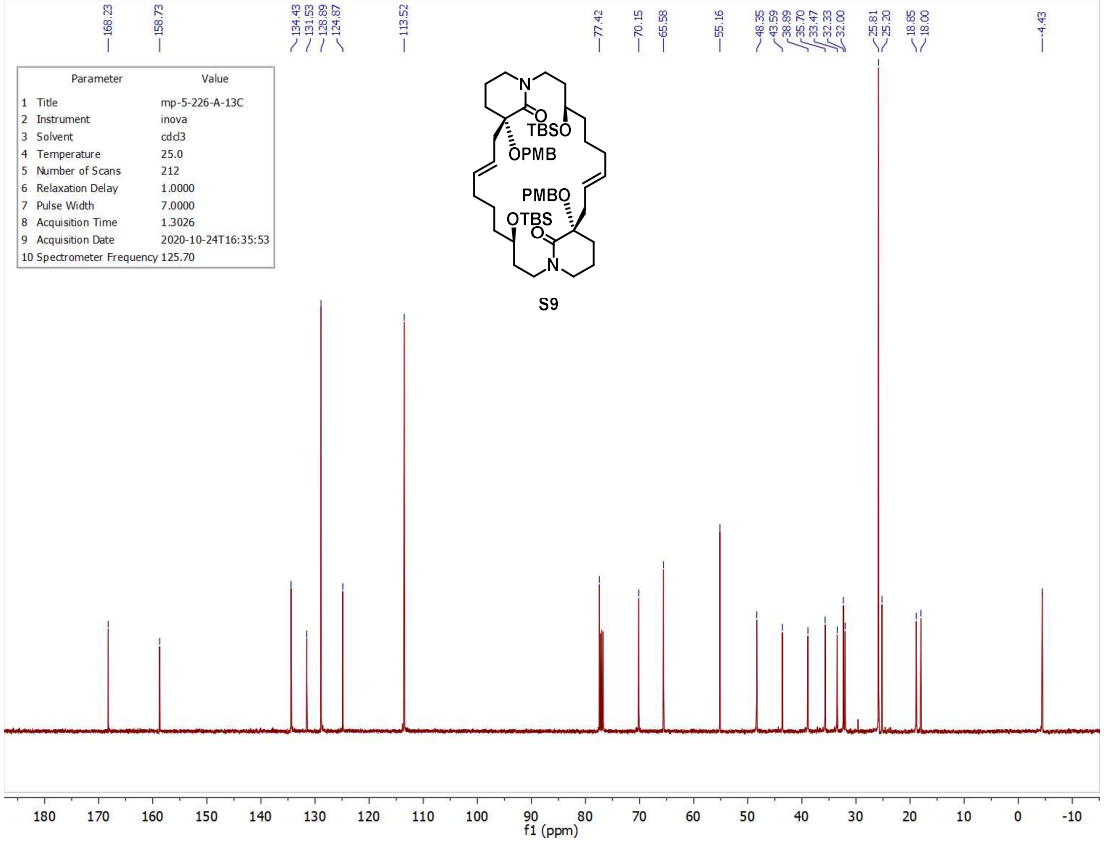
Parameter	Value
1 Title	mp-5-208-B-13C
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	168
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2020-10-16T13:50:38
10 Spectrometer Frequency	125.70

71

	Parameter	Value
1	Title	mp-5-226-A-1H
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	12
6	Relaxation Delay	12.0000
7	Pulse Width	6.6625
8	Acquisition Time	2.5001
9	Acquisition Date	2020-10-24T16:28:45
10	Spectrometer Frequency	499.85

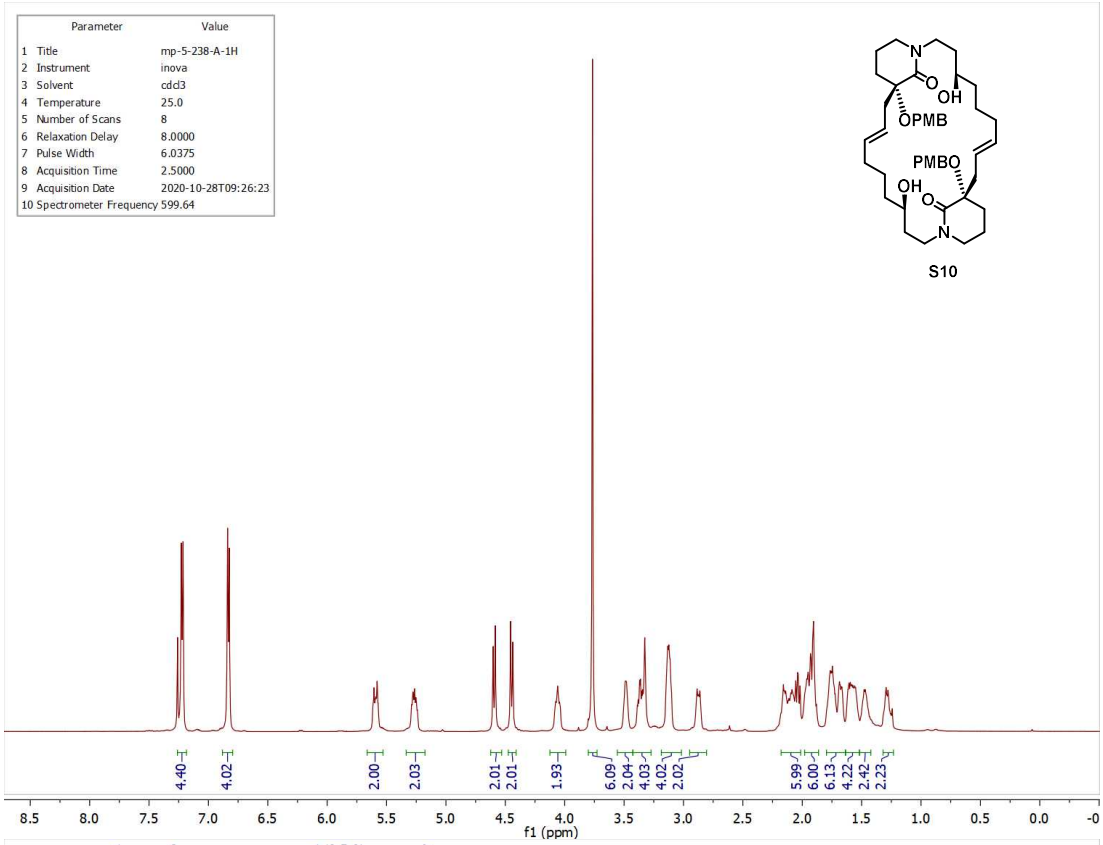


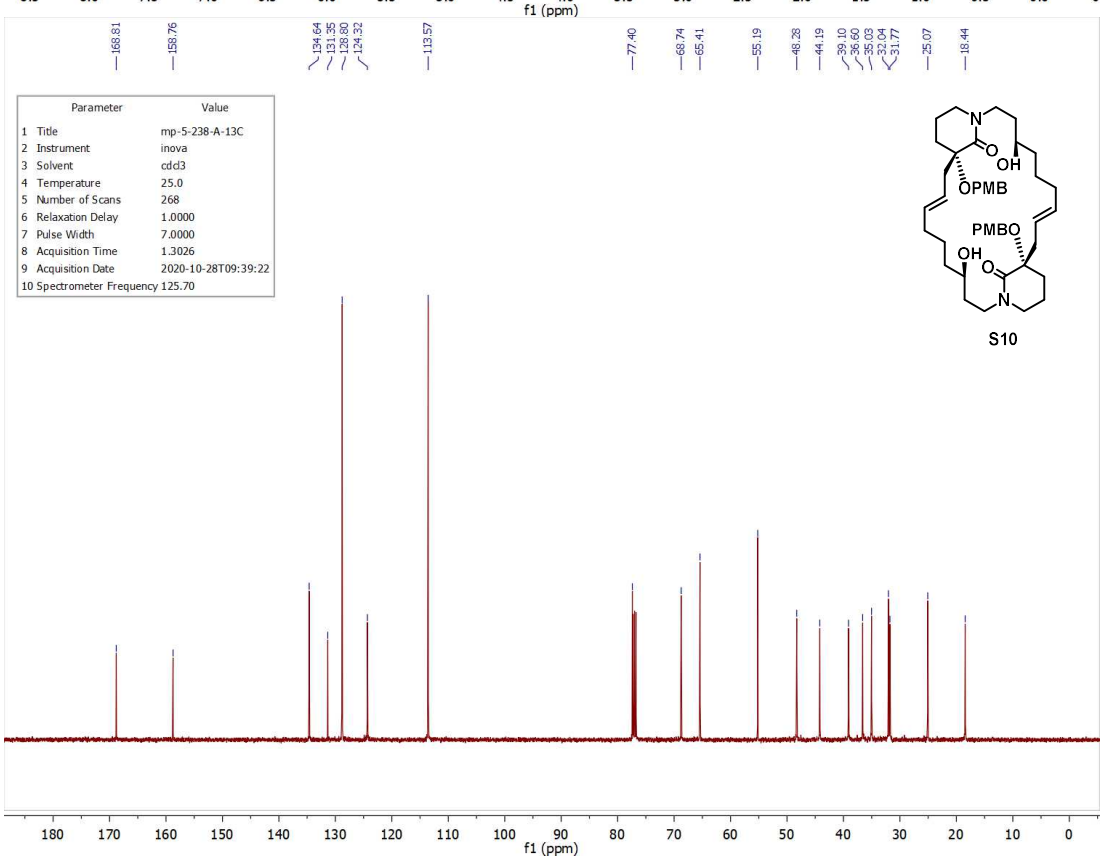
S9



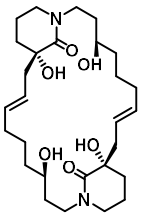
	Parameter	Value
1	Title	mp-5-226-A-13C
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	212
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2020-10-24T16:35:53
10	Spectrometer Frequency	125.70

S9

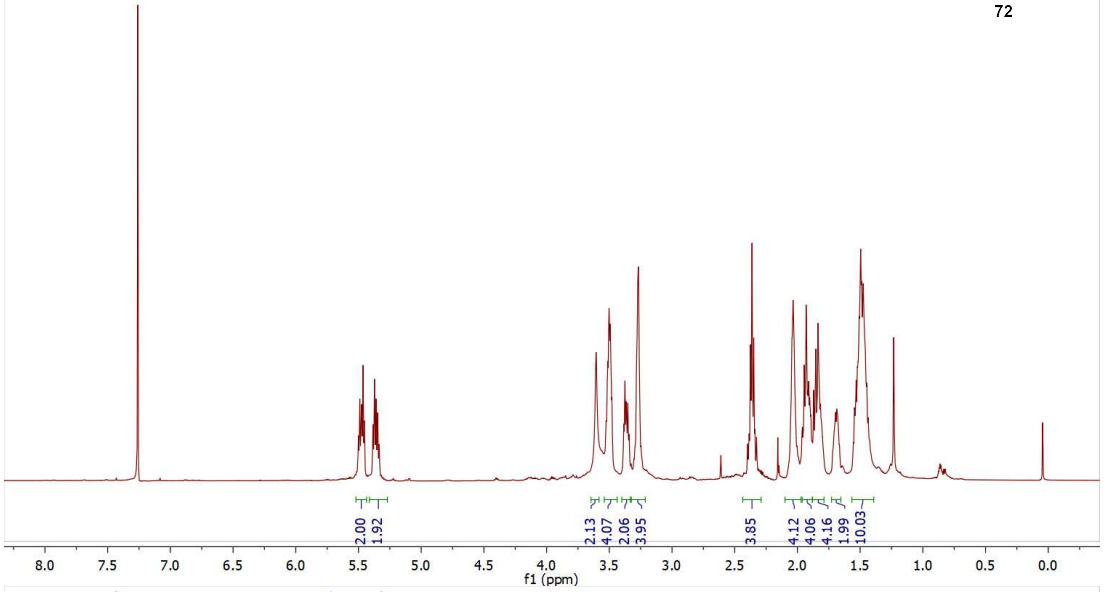

Parameter Value
1 Title mp-5-238-A-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.0375
8 Acquisition Time 2.5000
9 Acquisition Date 2020-10-28T09:26:23
10 Spectrometer Frequency 599.64
OH
OPMB
PMBO
OH
S10
4.40 4.02 2.00 2.03 2.01 2.01 1.93 6.09 2.04 4.03 4.02 2.02 5.99 6.00 6.13 4.22 2.42 2.23
f1 (ppm)

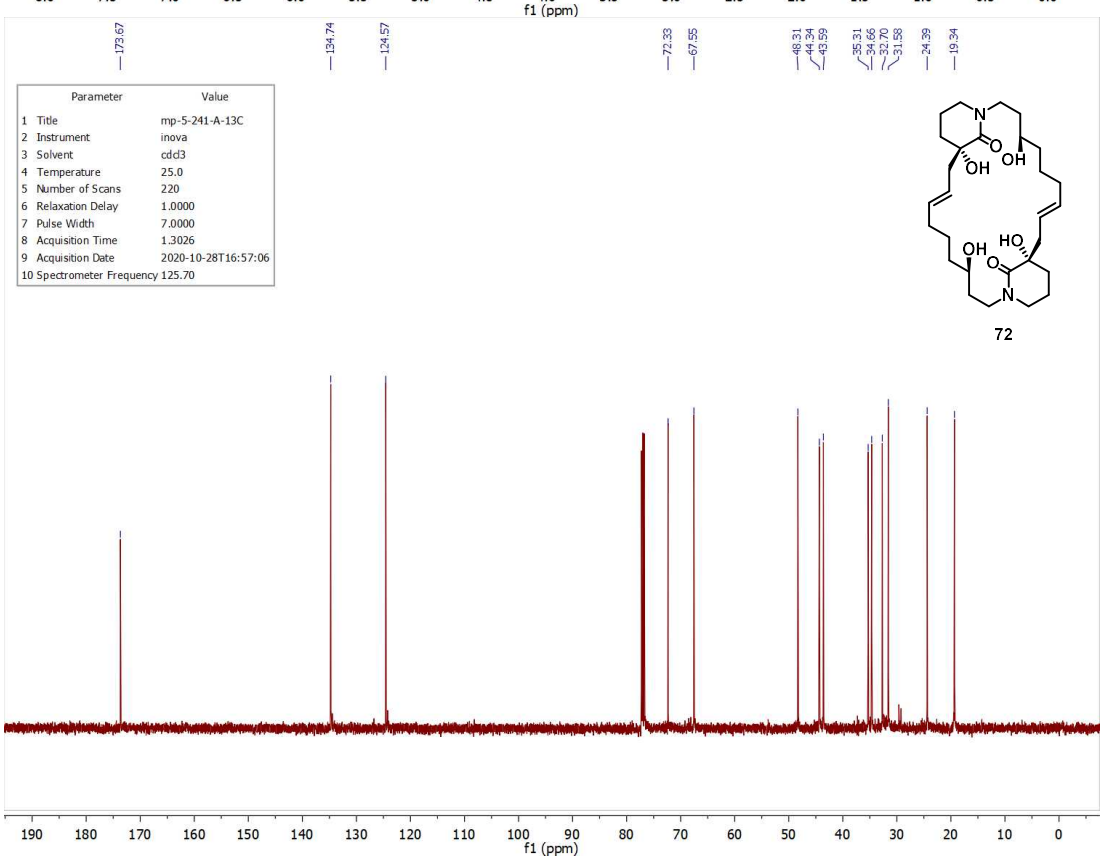

168.81 158.76 134.64 131.35 128.80 124.32 113.57 77.40 68.74 65.41 55.19 48.28 44.19 39.10 36.60 35.03 32.04 31.77 25.07 18.44
Parameter Value
1 Title mp-5-238-A-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 268
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-10-28T09:39:22
10 Spectrometer Frequency 125.70
OH
OPMB
PMBO
OH
S10
f1 (ppm)

Parameter	Value
1 Title	mp-5-241-A-1H
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	12
6 Relaxation Delay	8.0000
7 Pulse Width	6.0375
8 Acquisition Time	2.5000
9 Acquisition Date	2020-10-28T16:43:37
10 Spectrometer Frequency	599.64



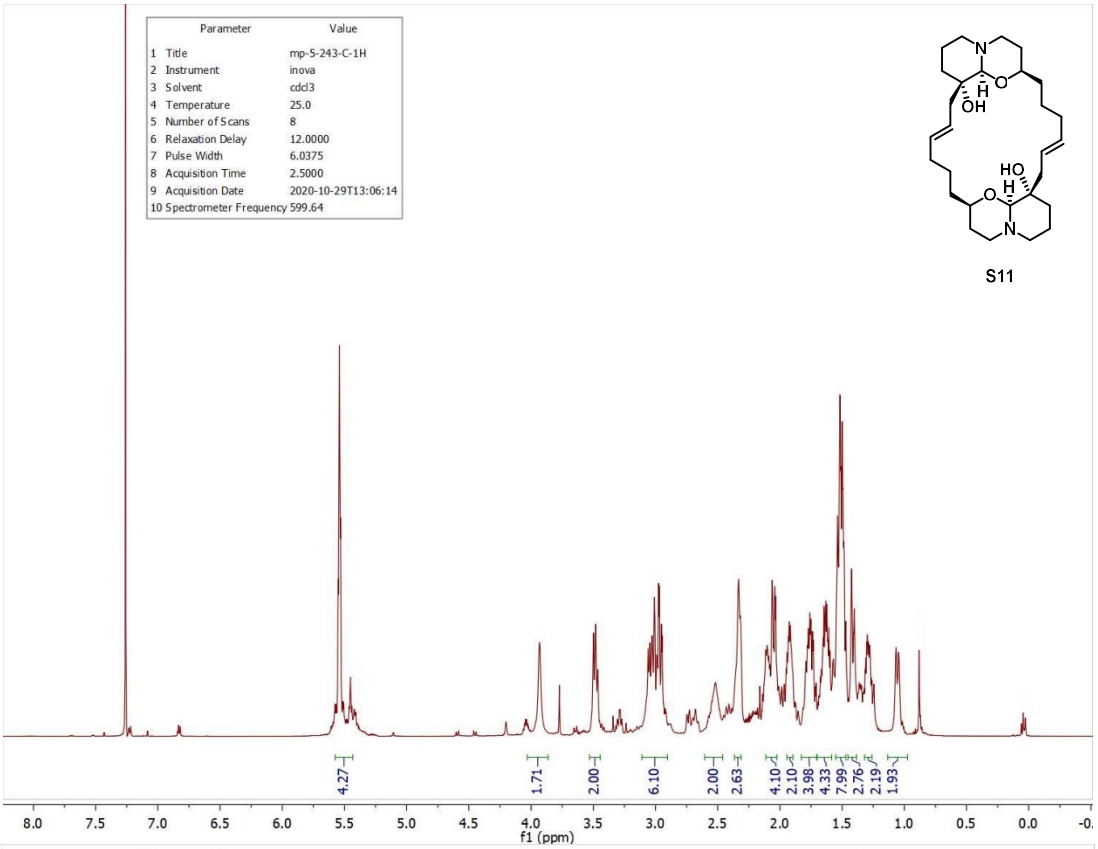
72

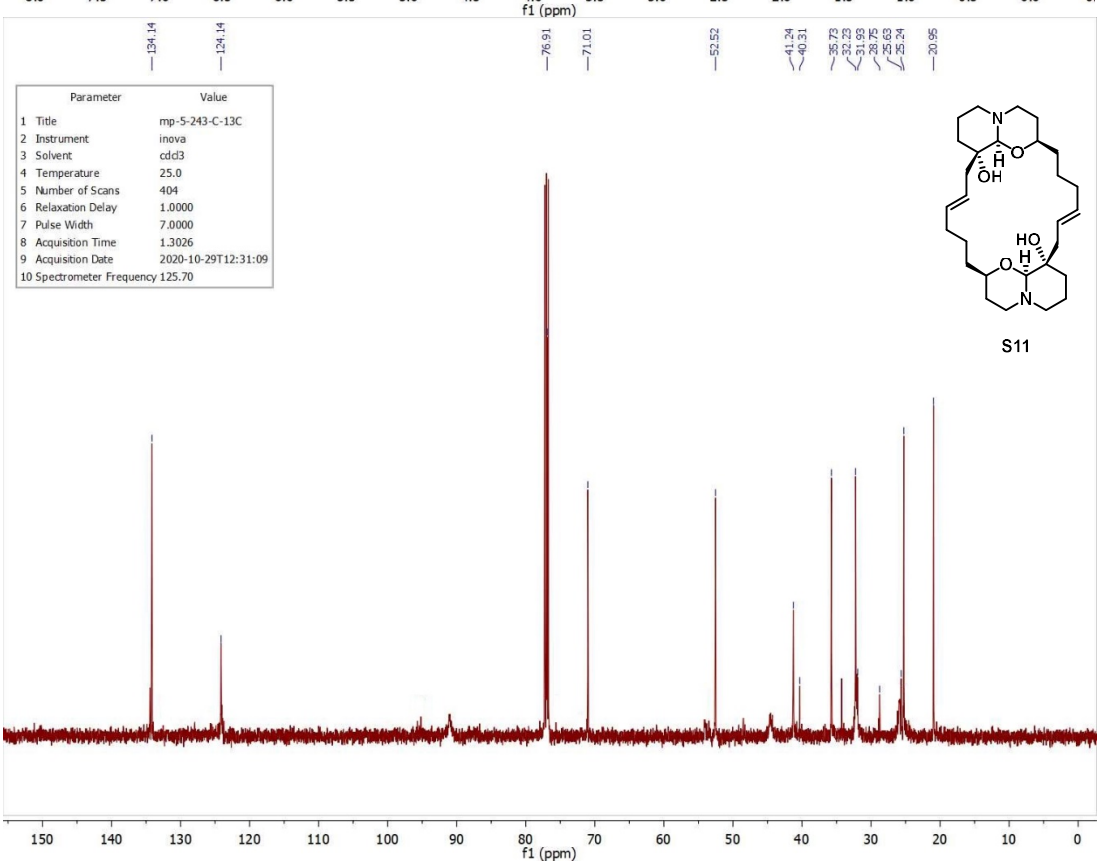


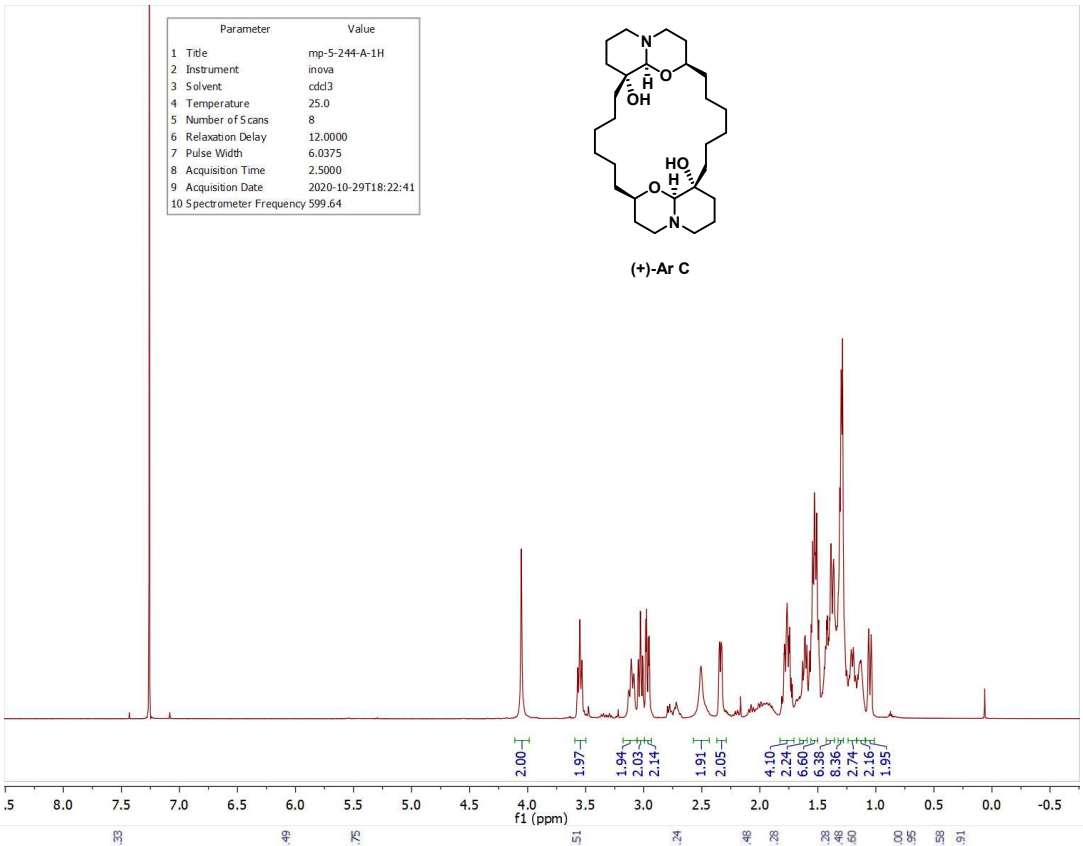


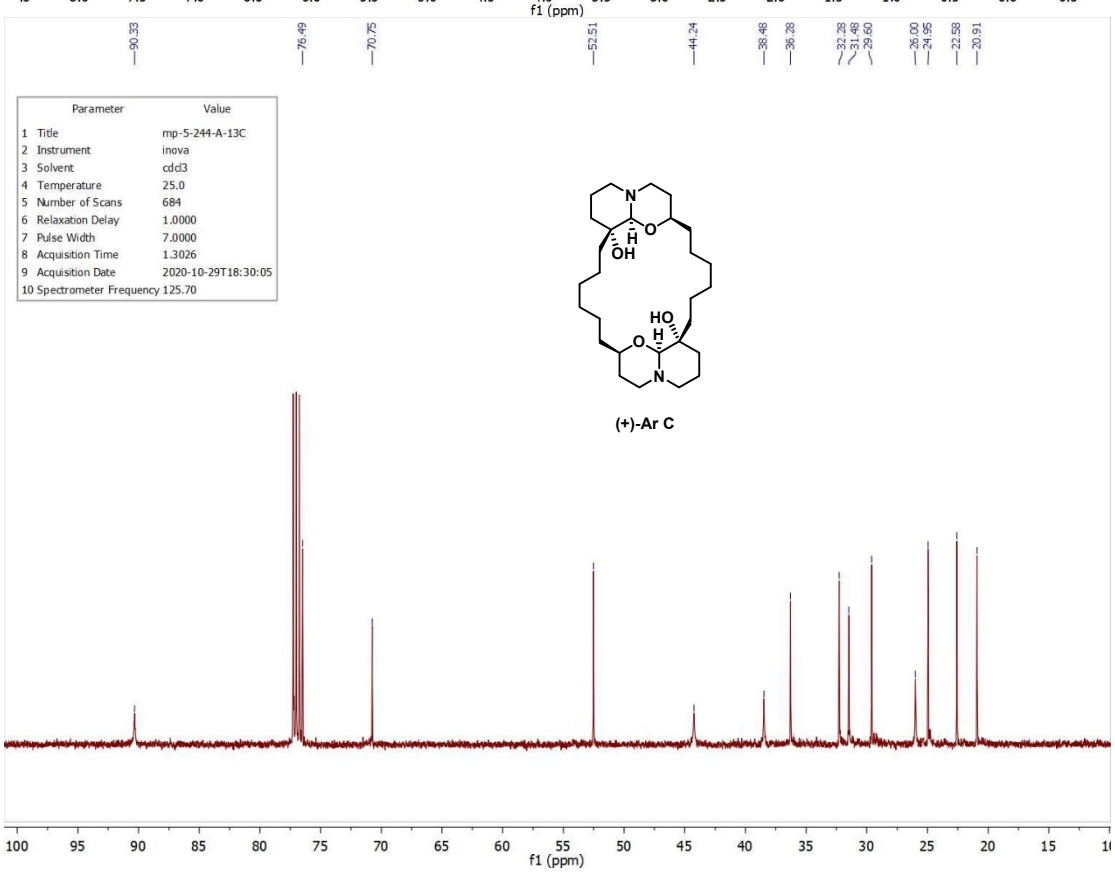
Parameter	Value
1 Title	mp-5-241-A-13C
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	220
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2020-10-28T16:57:06
10 Spectrometer Frequency	125.70

72

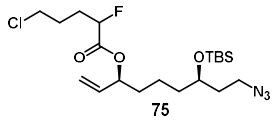

Parameter Value
1 Title mp-5-243-C-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 12.0000
7 Pulse Width 6.0375
8 Acquisition Time 2.5000
9 Acquisition Date 2020-10-29T13:06:14
10 Spectrometer Frequency 599.64
S11
4.27
1.71
2.00
6.10
2.00
2.63
4.10
2.10
3.98
4.33
7.99
2.76
2.19
1.93
f1 (ppm)


134.14
124.14
76.91
71.01
52.52
41.24
40.31
35.73
32.23
31.93
28.75
25.63
25.24
20.95
Parameter Value
1 Title mp-5-243-C-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 404
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-10-29T12:31:09
10 Spectrometer Frequency 125.70
S11
f1 (ppm)


Parameter Value
1 Title mp-5-244-A-1H
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 12.0000
7 Pulse Width 6.0375
8 Acquisition Time 2.5000
9 Acquisition Date 2020-10-29T18:22:41
10 Spectrometer Frequency 599.64
(+)-Ar C
2.00 1.97 1.94 2.03 2.14 1.91 2.05 4.10 2.24 6.60 6.38 8.36 2.74 2.16 1.95
f1 (ppm)

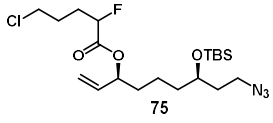

90.33 76.49 70.75 52.51 44.24 38.48 36.28 32.28 31.48 29.60 26.00 24.95 22.58 20.91
Parameter Value
1 Title mp-5-244-A-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 684
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-10-29T18:30:05
10 Spectrometer Frequency 125.70
(+)-Ar C
f1 (ppm)

Parameter	Value
1 Title	mp-5-176-A-1H.10.fid
2 Instrument	NEO500
3 Solvent	CDCl3
4 Temperature	298.2
5 Number of Scans	16
6 Relaxation Delay	8.0000
7 Pulse Width	12.0000
8 Acquisition Time	3.2768
9 Acquisition Date	2020-11-24T14:19:14
10 Spectrometer Frequency	500.15



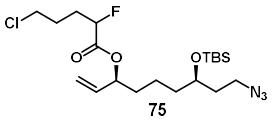
75

Parameter	Value
1 Title	mp-5-176-A-13C.10.fid
2 Instrument	NEO500
3 Solvent	CDCl3
4 Temperature	298.1
5 Number of Scans	200
6 Relaxation Delay	2.0000
7 Pulse Width	10.0000
8 Acquisition Time	1.0879
9 Acquisition Date	2020-11-24T14:32:08
10 Spectrometer Frequency	125.78

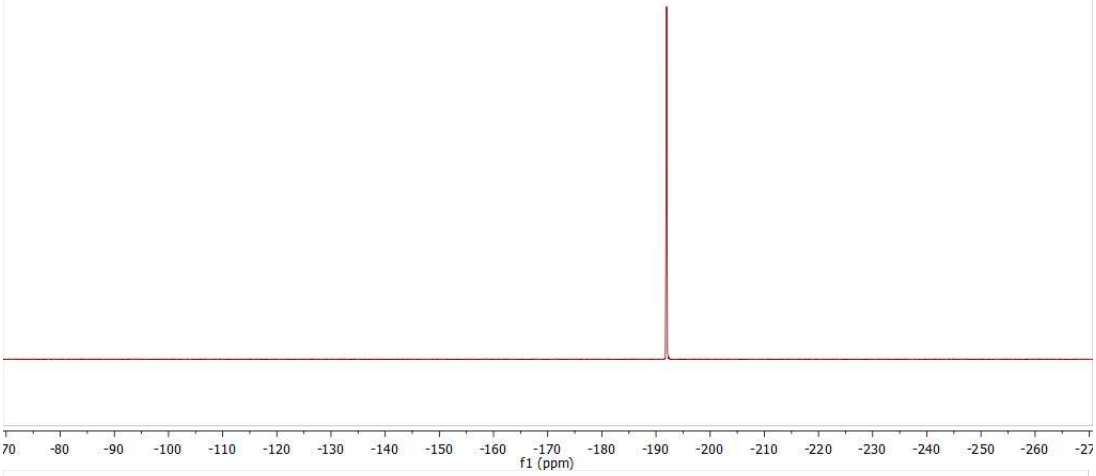


75

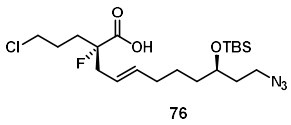
	Parameter	Value
1	Title	mp-5-176-A-F19.1.fid
2	Instrument	spect
3	Solvent	CDCl3
4	Temperature	298.1
5	Number of Scans	16
6	Relaxation Delay	1.0000
7	Pulse Width	18.0000
8	Acquisition Time	2.3599
9	Acquisition Date	2020-11-24T13:47:32
10	Spectrometer Frequency	376.43



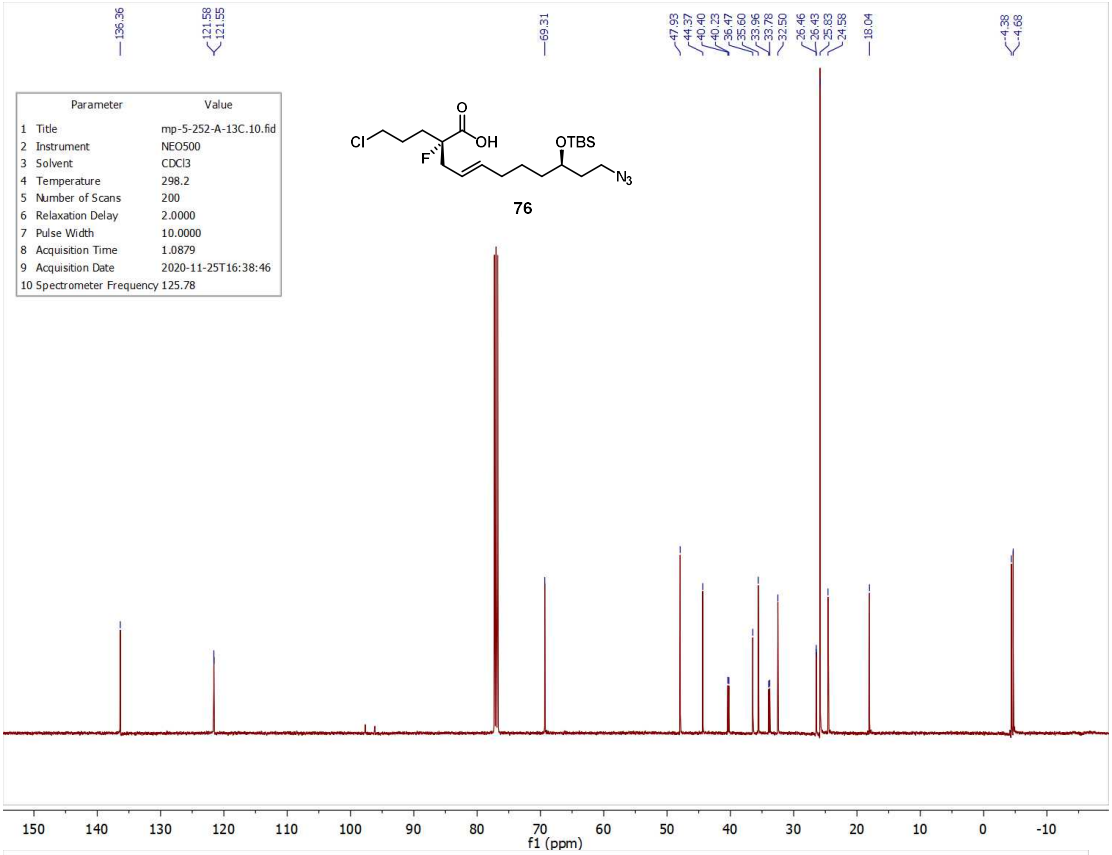
75

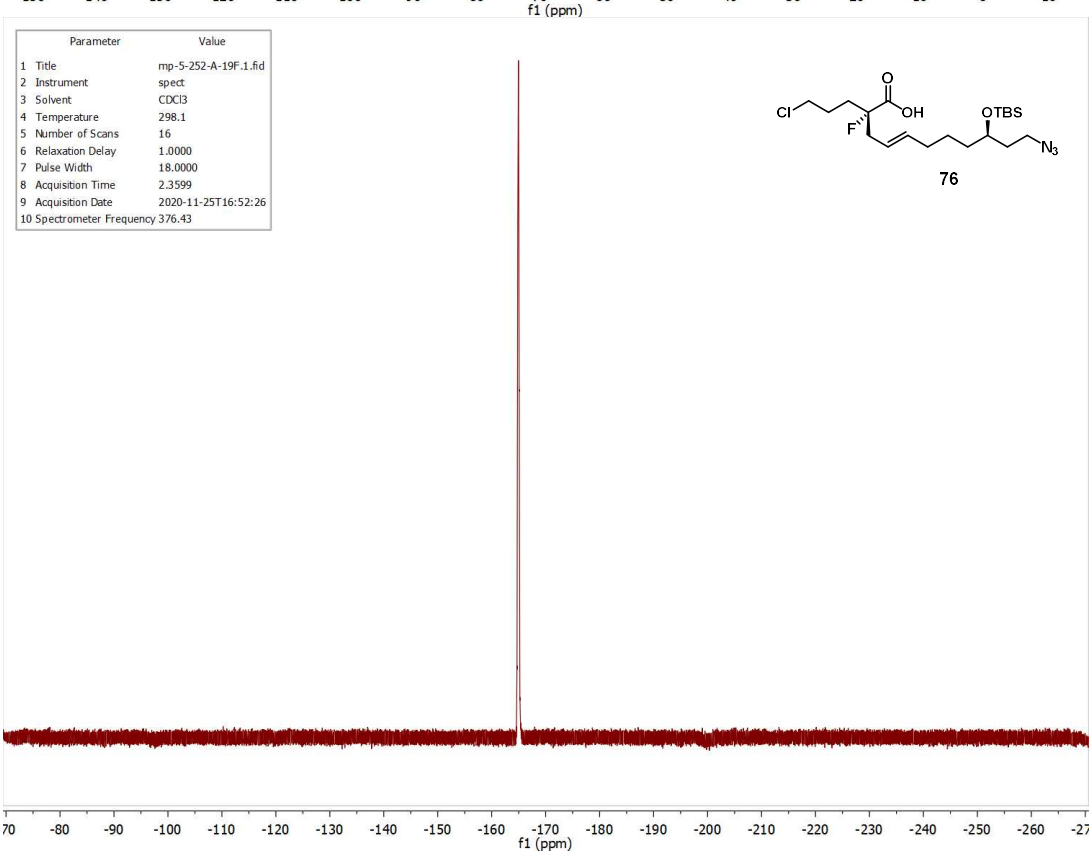


	Parameter	Value
1	Title	mp-5-252-A-1H.10.fid
2	Instrument	NEO500
3	Solvent	CDCl3
4	Temperature	298.1
5	Number of Scans	16
6	Relaxation Delay	8.0000
7	Pulse Width	12.0000
8	Acquisition Time	3.2768
9	Acquisition Date	2020-11-25T16:27:08
10	Spectrometer Frequency	500.15

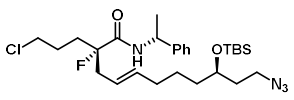


76

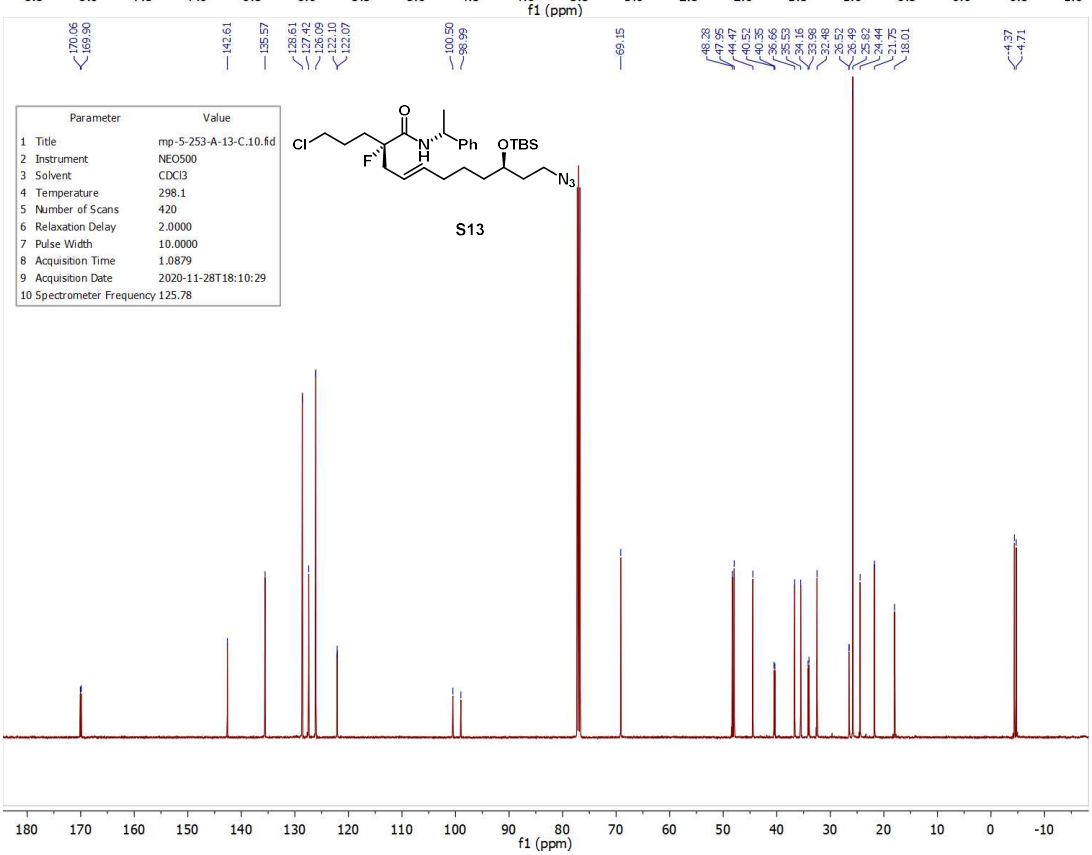

136.96
121.58
121.55
69.31
47.93
44.37
40.40
40.23
36.47
35.60
33.96
33.78
32.50
26.46
26.43
25.83
24.58
18.04
4.38
4.68
Parameter Value
1 Title mp-5-252-A-13C.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 200
6 Relaxation Delay 2.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.0879
9 Acquisition Date 2020-11-25T16:38:46
10 Spectrometer Frequency 125.78
Cl
O
OH
F
OTBS
N3
76
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Parameter Value
1 Title mp-5-252-A-19F.1.fid
2 Instrument spect
3 Solvent CDCl3
4 Temperature 298.1
5 Number of Scans 16
6 Relaxation Delay 1.0000
7 Pulse Width 18.0000
8 Acquisition Time 2.3599
9 Acquisition Date 2020-11-25T16:52:26
10 Spectrometer Frequency 376.43
Cl
O
OH
F
OTBS
N3
76
70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -27
f1 (ppm)

Parameter	Value
1 Title	mp-5-253-A-1H.10.fid
2 Instrument	NEO500
3 Solvent	CDCl3
4 Temperature	298.2
5 Number of Scans	16
6 Relaxation Delay	8.0000
7 Pulse Width	12.0000
8 Acquisition Time	3.2768
9 Acquisition Date	2020-11-28T17:46:30
10 Spectrometer Frequency	500.15



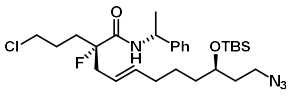
S13



Parameter	Value
1 Title	mp-5-253-A-13-C.10.fid
2 Instrument	NEO500
3 Solvent	CDCl3
4 Temperature	298.1
5 Number of Scans	420
6 Relaxation Delay	2.0000
7 Pulse Width	10.0000
8 Acquisition Time	1.0879
9 Acquisition Date	2020-11-28T18:10:29
10 Spectrometer Frequency	125.78

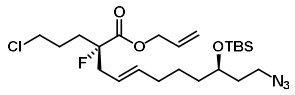
S13

Parameter	Value
1 Title	mp-5-253-A-19F.1.fid
2 Instrument	spect
3 Solvent	CDCl3
4 Temperature	298.1
5 Number of Scans	16
6 Relaxation Delay	1.0000
7 Pulse Width	18.0000
8 Acquisition Time	2.3599
9 Acquisition Date	2020-11-28T17:31:55
10 Spectrometer Frequency	376.43

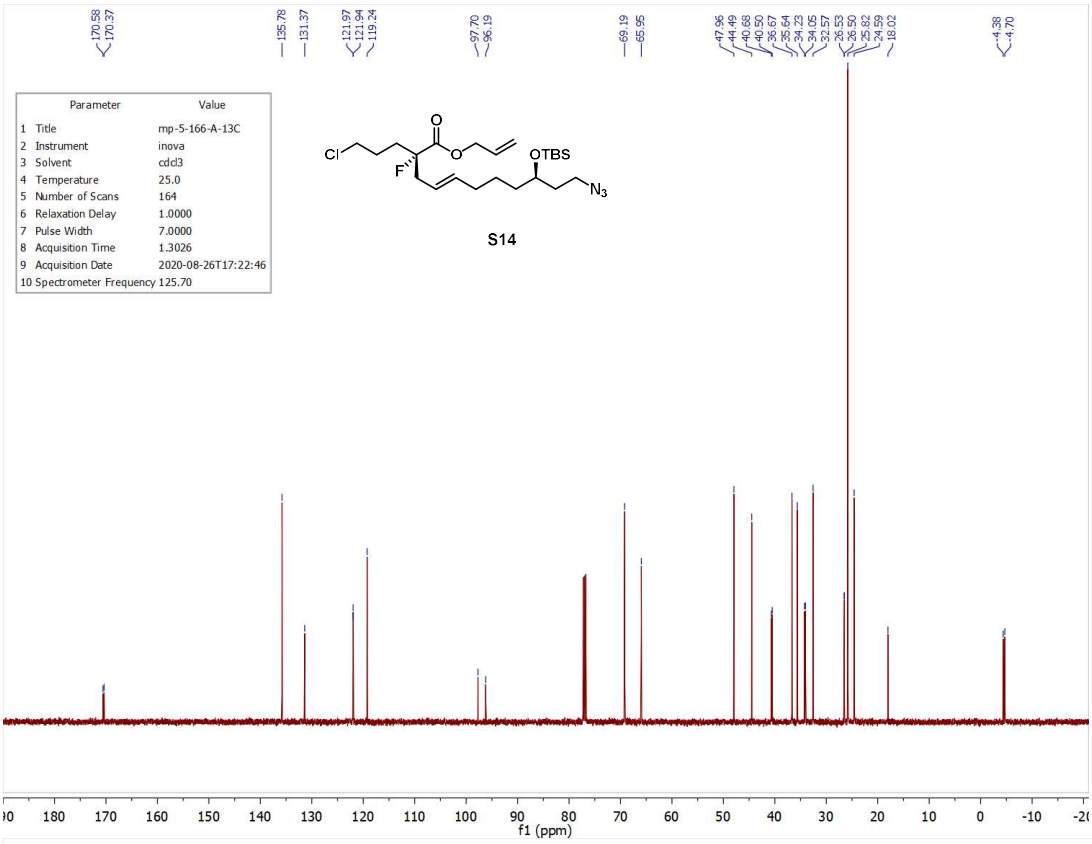


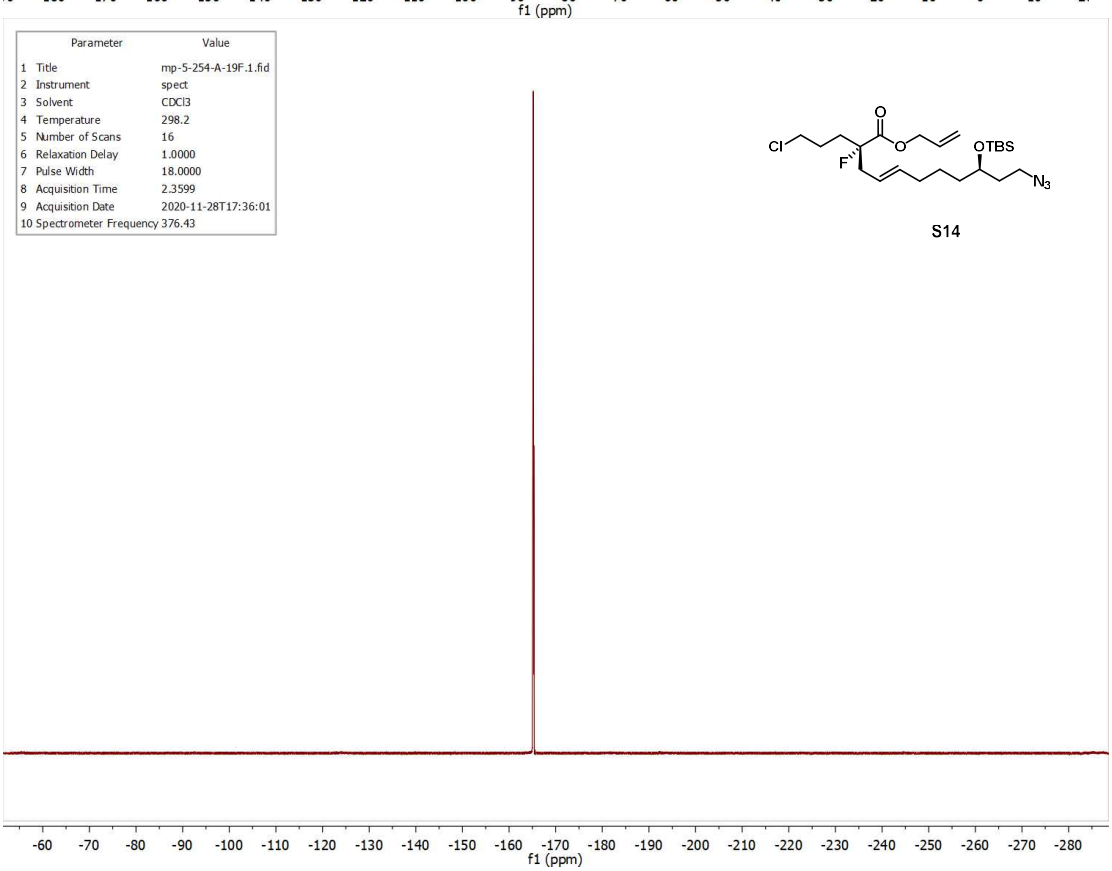
S13

Parameter	Value
1 Title	mp-5-166-A-1H
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	12
6 Relaxation Delay	8.0000
7 Pulse Width	6.2500
8 Acquisition Time	2.5000
9 Acquisition Date	2020-08-26T17:07:46
10 Spectrometer Frequency	599.64

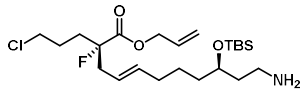


S14

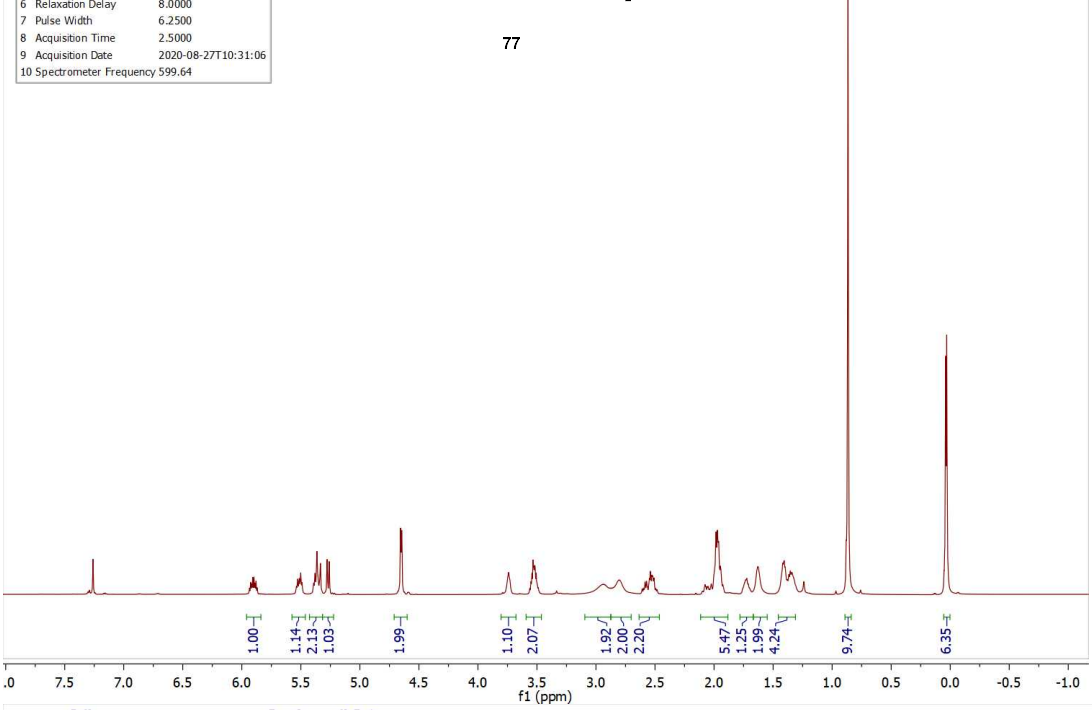

170.58
170.37
135.78
131.37
121.97
121.94
119.24
97.70
96.19
69.19
65.95
47.96
44.49
40.68
40.50
36.67
35.64
34.23
34.05
32.57
26.53
26.50
25.82
24.59
18.02
14.38
4.70
Parameter Value
1 Title mp-5-166-A-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 164
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-08-26T17:22:46
10 Spectrometer Frequency 125.70
Cl
F
O
OTBS
N3
S14
f1 (ppm)

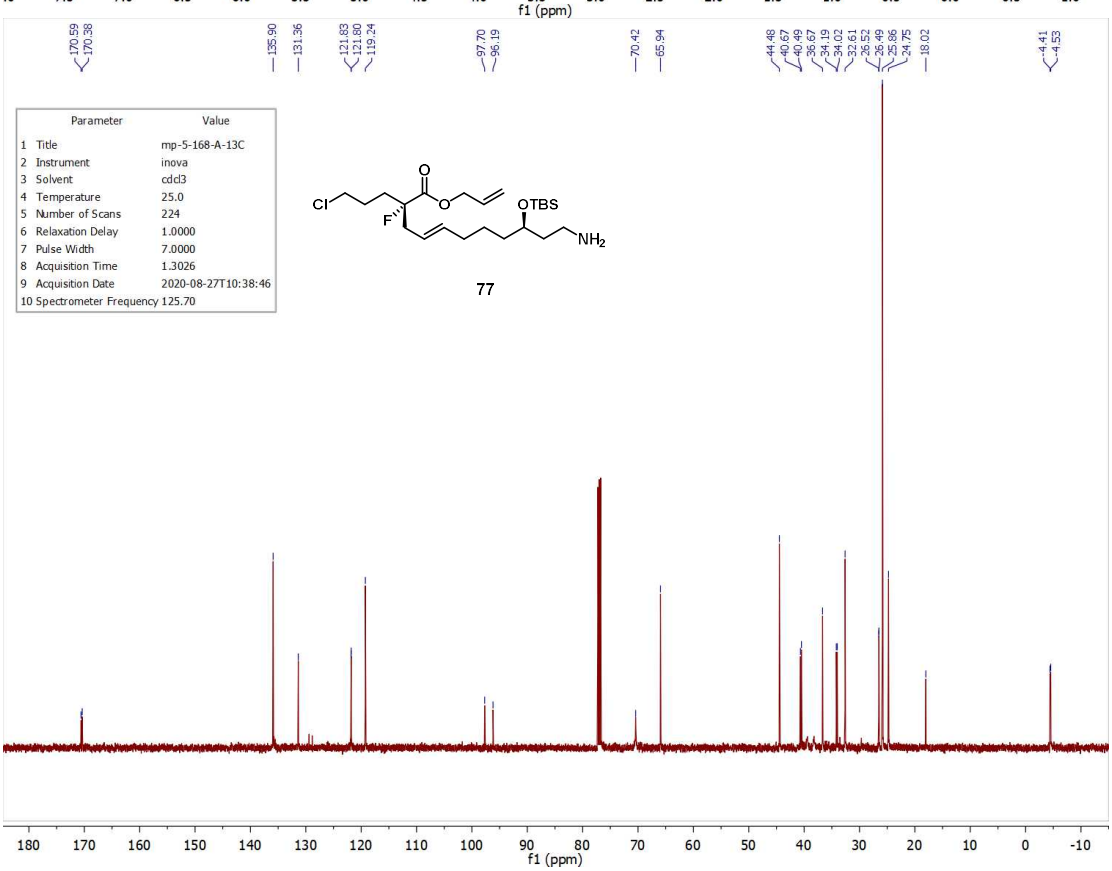

Parameter Value
1 Title mp-5-254-A-19F.1.fid
2 Instrument spect
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 16
6 Relaxation Delay 1.0000
7 Pulse Width 18.0000
8 Acquisition Time 2.3599
9 Acquisition Date 2020-11-28T17:36:01
10 Spectrometer Frequency 376.43
Cl
F
O
OTBS
N3
S14
f1 (ppm)

Parameter	Value
1 Title	mp-5-168-A
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	12
6 Relaxation Delay	8.0000
7 Pulse Width	6.2500
8 Acquisition Time	2.5000
9 Acquisition Date	2020-08-27T10:31:06
10 Spectrometer Frequency	599.64



77

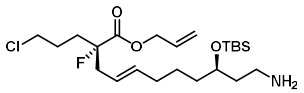




Parameter	Value
1 Title	mp-5-168-A-13C
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	224
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2020-08-27T10:38:46
10 Spectrometer Frequency	125.70

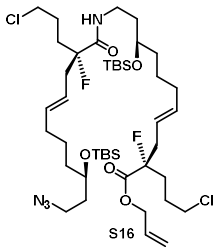
77

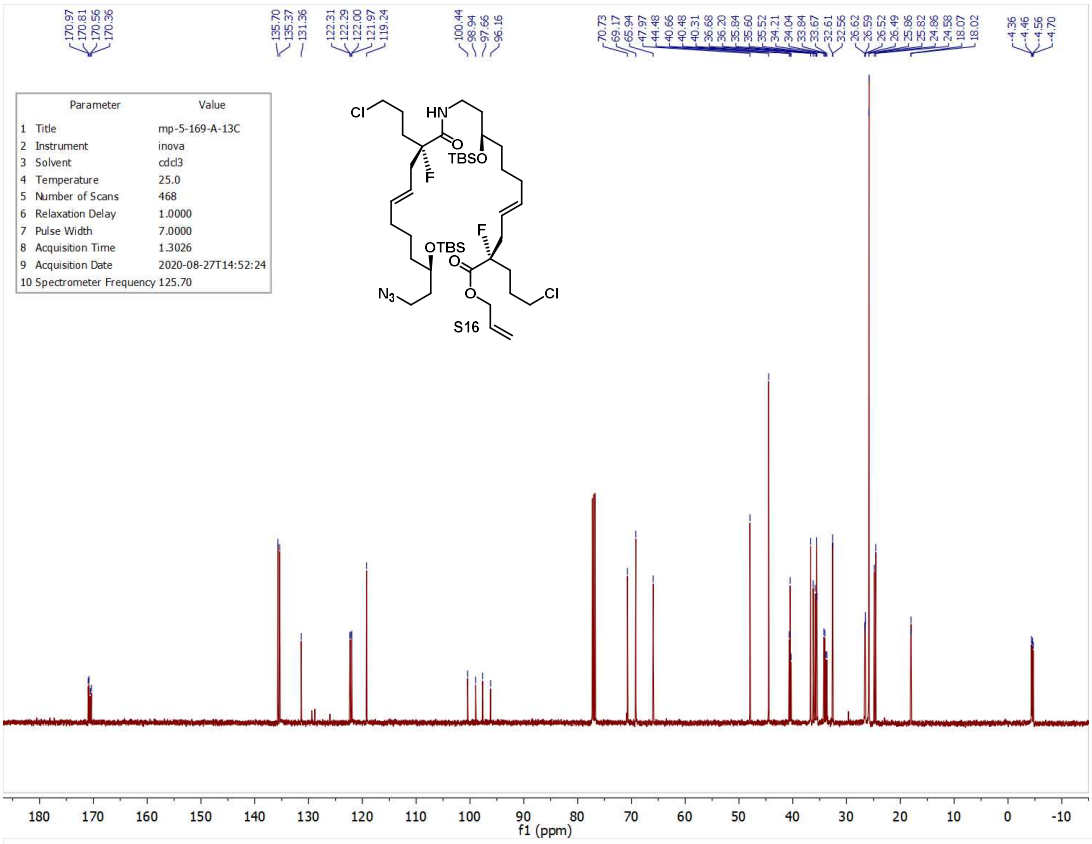
Parameter	Value
1 Title	mp-5-257-A-19F.1.fid
2 Instrument	spect
3 Solvent	CDCl3
4 Temperature	298.2
5 Number of Scans	16
6 Relaxation Delay	1.0000
7 Pulse Width	18.0000
8 Acquisition Time	2.3599
9 Acquisition Date	2020-12-03T13:10:10
10 Spectrometer Frequency	376.43

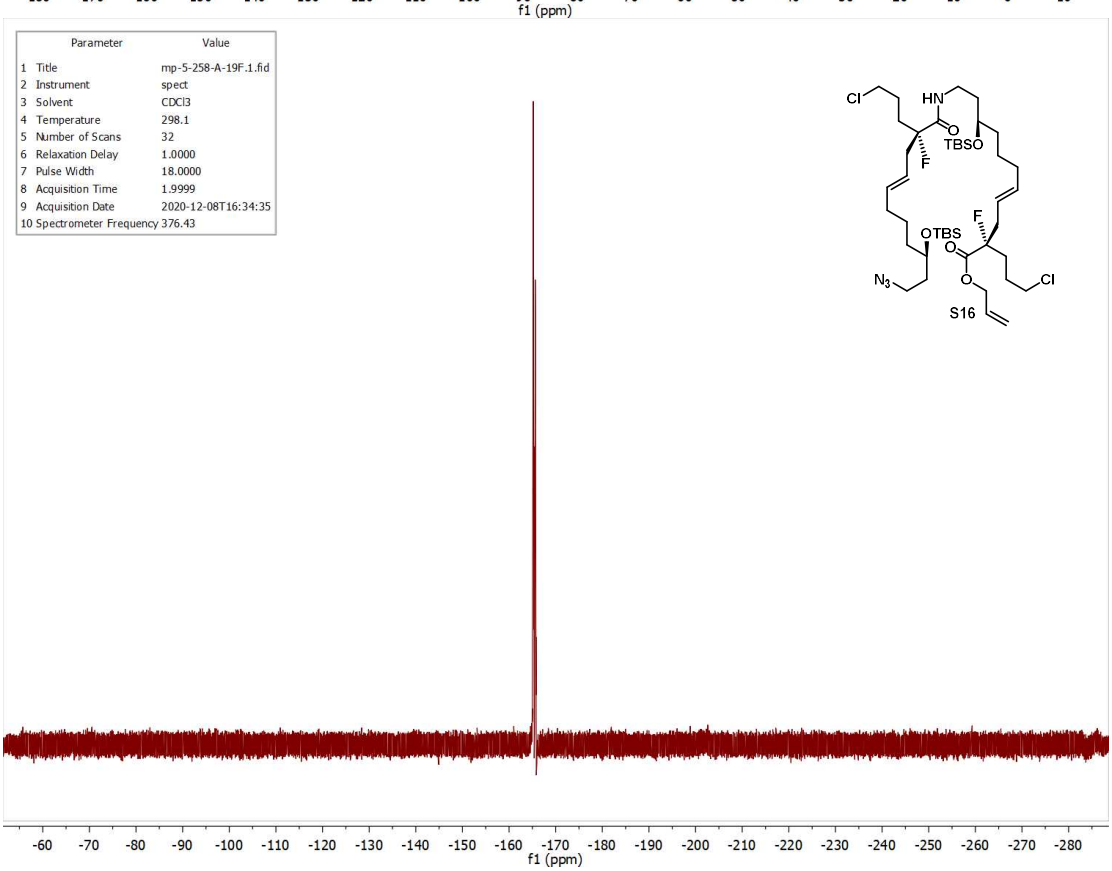


77

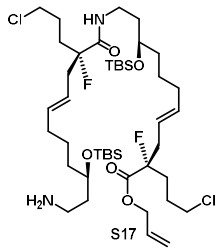
Parameter	Value
1 Title	mp-5-169-A
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	12
6 Relaxation Delay	8.0000
7 Pulse Width	6.6625
8 Acquisition Time	2.5001
9 Acquisition Date	2020-08-27T14:47:18
10 Spectrometer Frequency	499.85



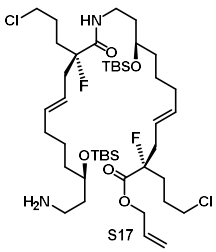

Parameter Value
1 Title mp-5-169-A-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 468
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2020-08-27T14:52:24
10 Spectrometer Frequency 125.70
Cl
HN
O
TBSO
F
F
OTBS
O
N3
O
Cl
S16
f1 (ppm)


Parameter Value
1 Title mp-5-258-A-19F.1.fid
2 Instrument spect
3 Solvent CDCl3
4 Temperature 298.1
5 Number of Scans 32
6 Relaxation Delay 1.0000
7 Pulse Width 18.0000
8 Acquisition Time 1.9999
9 Acquisition Date 2020-12-08T16:34:35
10 Spectrometer Frequency 376.43
Cl
HN
O
TBSO
F
F
OTBS
O
N3
O
Cl
S16
f1 (ppm)

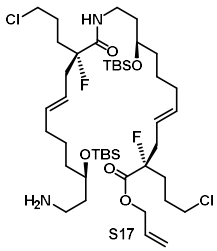
Parameter	Value
1 Title	mp-5-259-B-1H
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.6625
8 Acquisition Time	2.5001
9 Acquisition Date	2020-12-05T10:32:11
10 Spectrometer Frequency	499.85

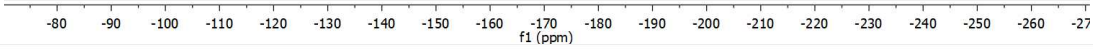


Parameter	Value
1 Title	mp-5-259-B-13C
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	208
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2020-12-05T10:43:07
10 Spectrometer Frequency	125.70

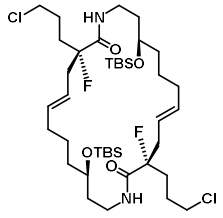


Parameter	Value
1 Title	mp-5-259-B-19F.1.fid
2 Instrument	spect
3 Solvent	CDCl3
4 Temperature	298.1
5 Number of Scans	70
6 Relaxation Delay	1.0000
7 Pulse Width	18.0000
8 Acquisition Time	2.3599
9 Acquisition Date	2020-12-05T11:01:18
10 Spectrometer Frequency	376.43

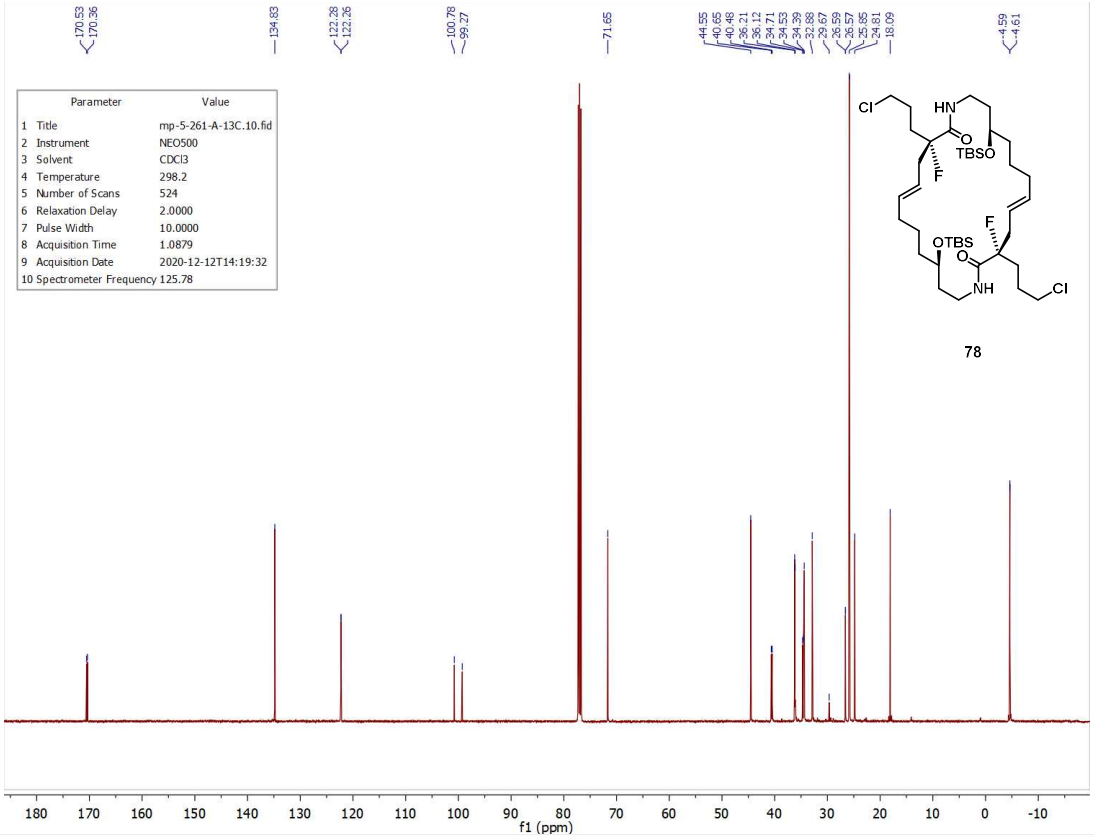


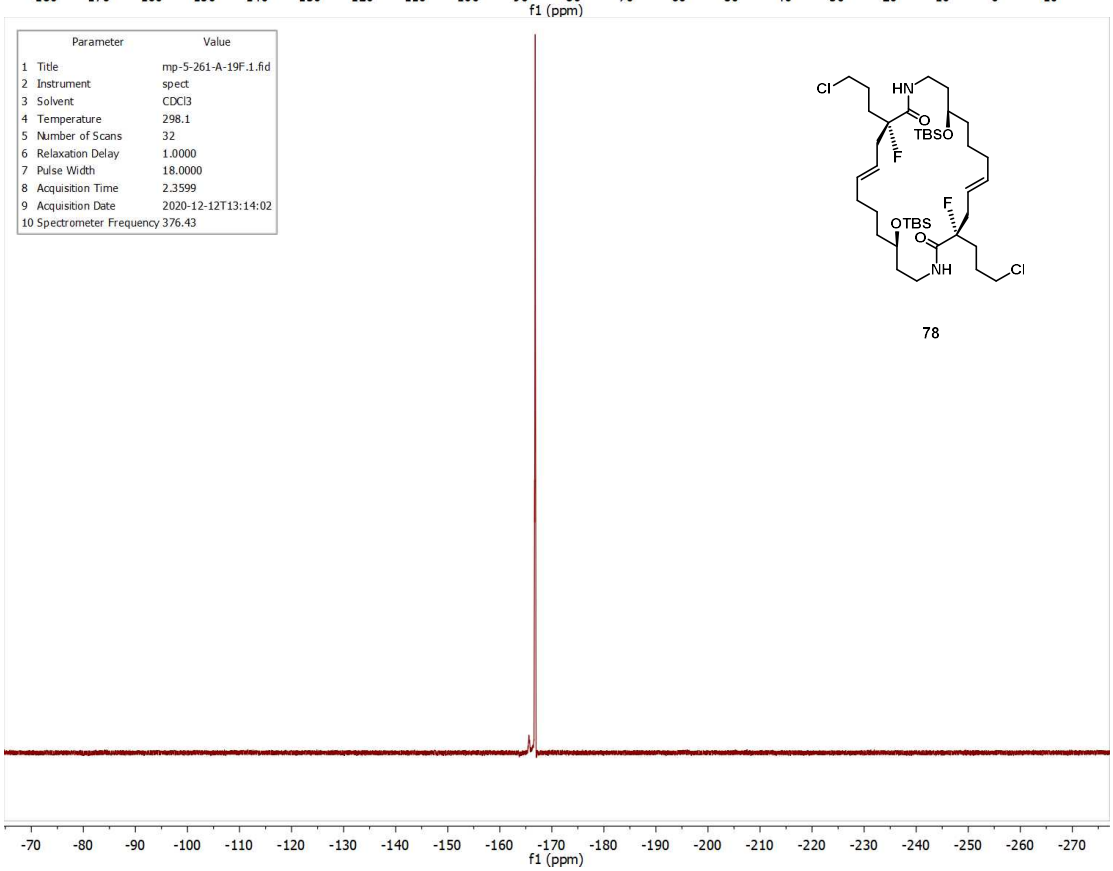


Parameter	Value
1 Title	mp-5-261-A-1H
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.0375
8 Acquisition Time	2.5000
9 Acquisition Date	2020-12-12T13:03:12
10 Spectrometer Frequency	599.64

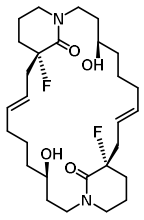


78

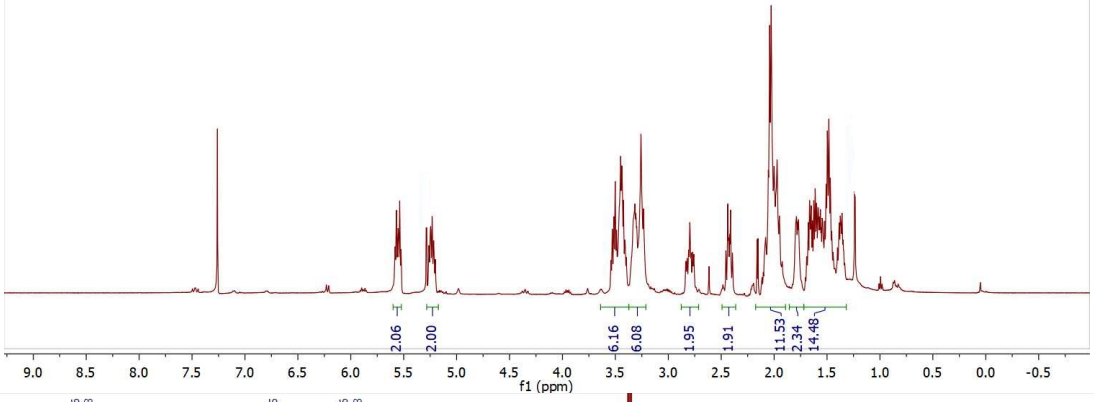

170.53
170.36
134.83
122.28
122.26
100.78
99.27
71.65
44.55
40.65
40.48
36.21
36.12
34.71
34.53
34.39
32.68
29.67
28.59
26.57
26.35
24.81
18.09
14.59
14.61
Parameter Value
1 Title mp-5-261-A-13C.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 524
6 Relaxation Delay 2.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.0879
9 Acquisition Date 2020-12-12T14:19:32
10 Spectrometer Frequency 125.78
Cl
HN
O
TBSO
F
F
OTBS
O
NH
Cl
78
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

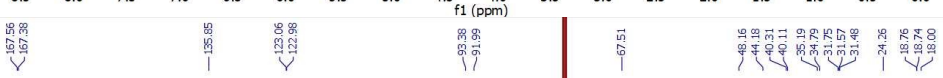

Parameter Value
1 Title mp-5-261-A-19F.1.fid
2 Instrument spect
3 Solvent CDCl3
4 Temperature 298.1
5 Number of Scans 32
6 Relaxation Delay 1.0000
7 Pulse Width 18.0000
8 Acquisition Time 2.3599
9 Acquisition Date 2020-12-12T13:14:02
10 Spectrometer Frequency 376.43
Cl
HN
O
TBSO
F
F
OTBS
O
NH
Cl
78
-70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270
f1 (ppm)

	Parameter	Value
1	Title	mp-5-223-A
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	25.0
5	Number of Scans	12
6	Relaxation Delay	8.0000
7	Pulse Width	6.6625
8	Acquisition Time	2.5001
9	Acquisition Date	2020-10-19T11:25:06
10	Spectrometer Frequency	499.85

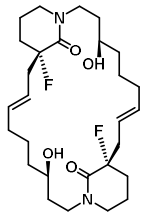


S18

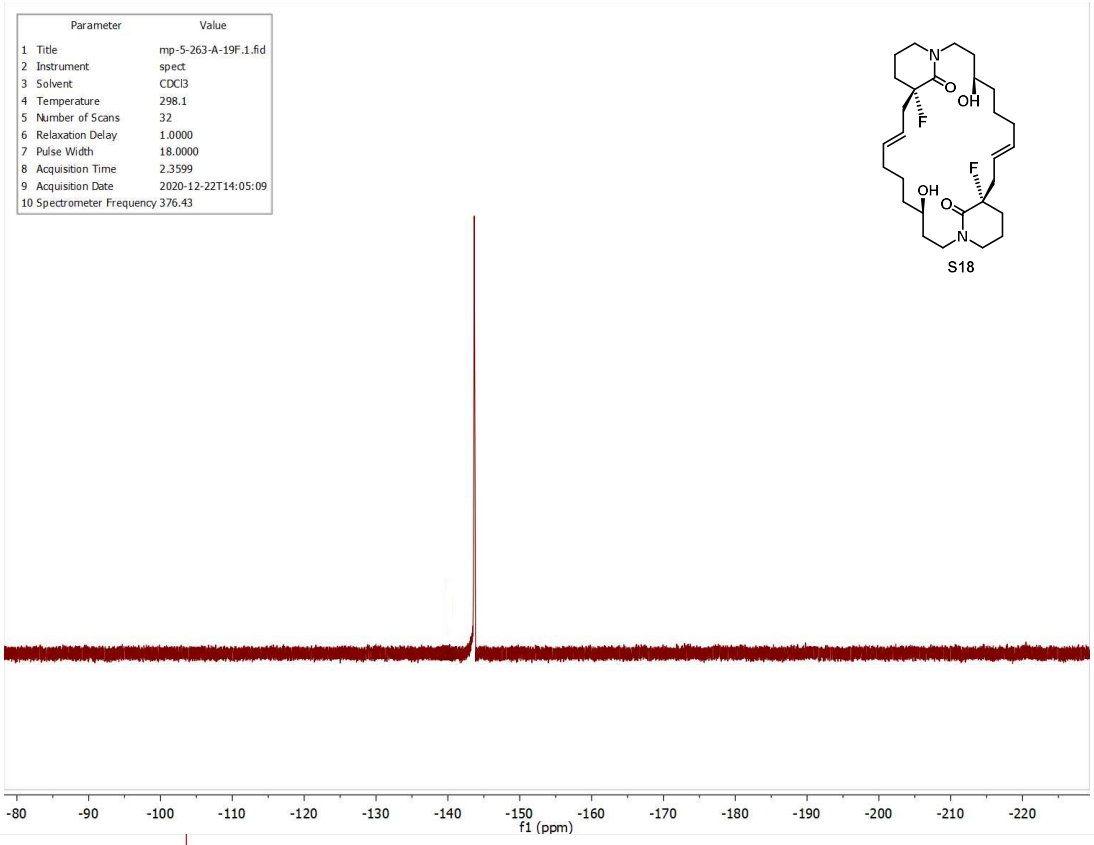


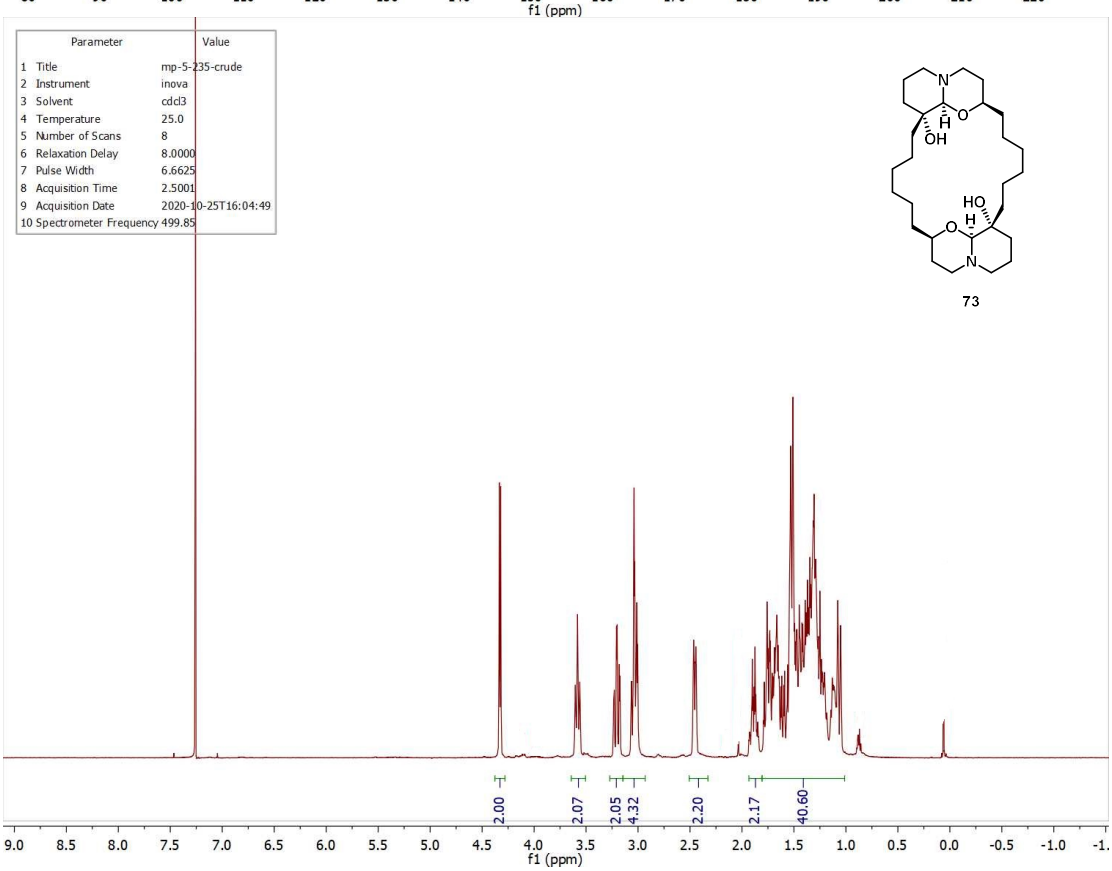


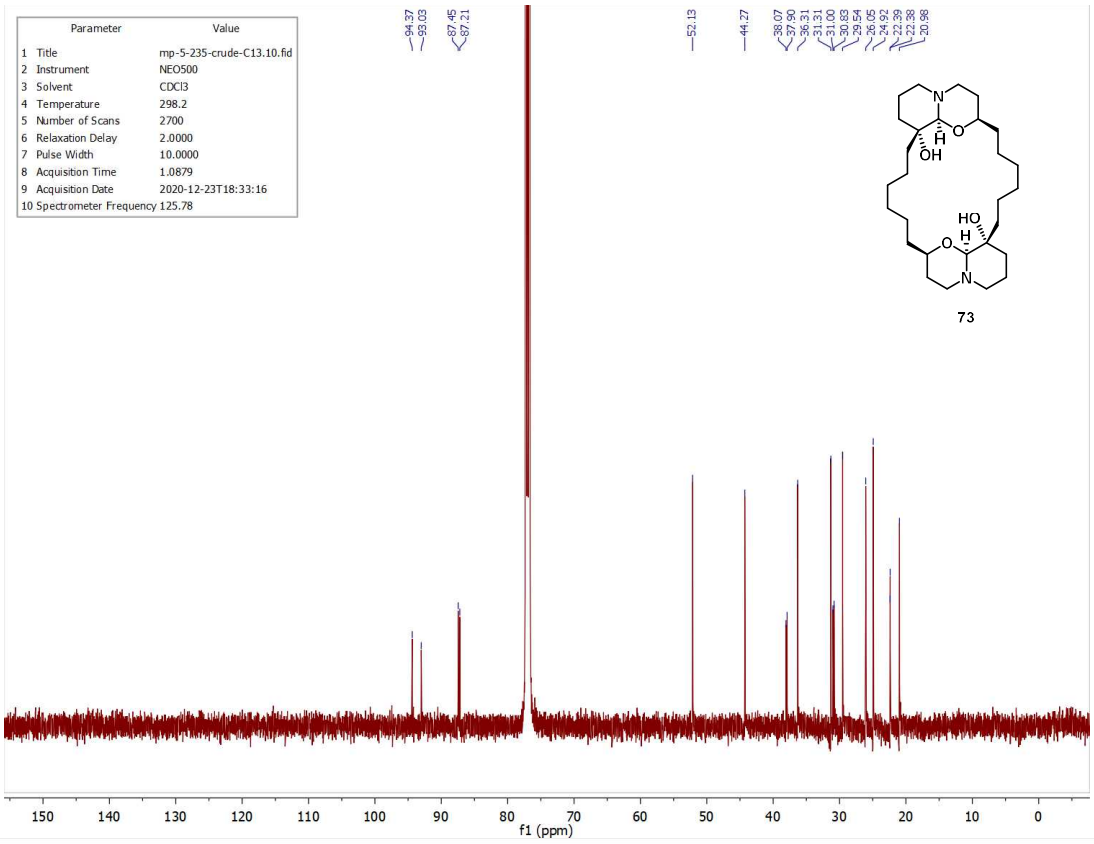
	Parameter	Value
1	Title	mp-5-263-A-13C.10.fid
2	Instrument	NEO500
3	Solvent	CDCl3
4	Temperature	298.2
5	Number of Scans	1800
6	Relaxation Delay	2.0000
7	Pulse Width	10.0000
8	Acquisition Time	1.0879
9	Acquisition Date	2020-12-22T15:46:57
10	Spectrometer Frequency	125.78

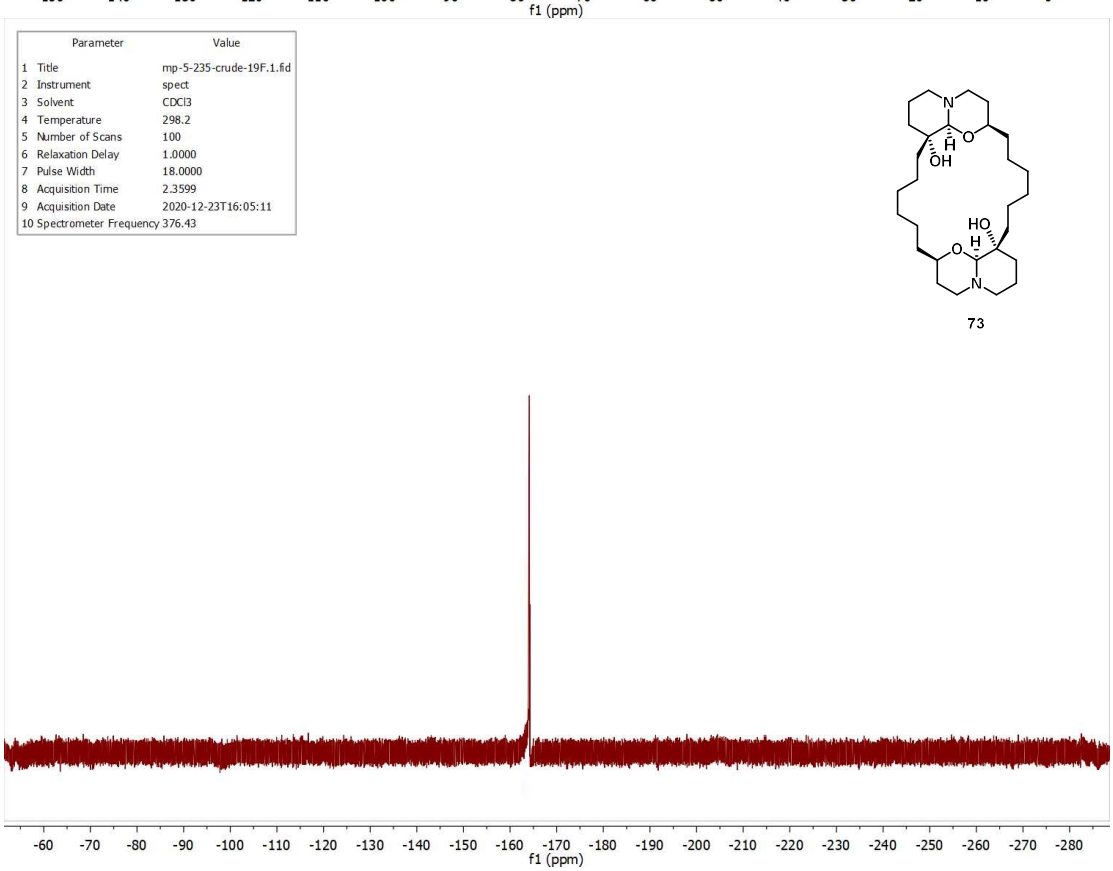


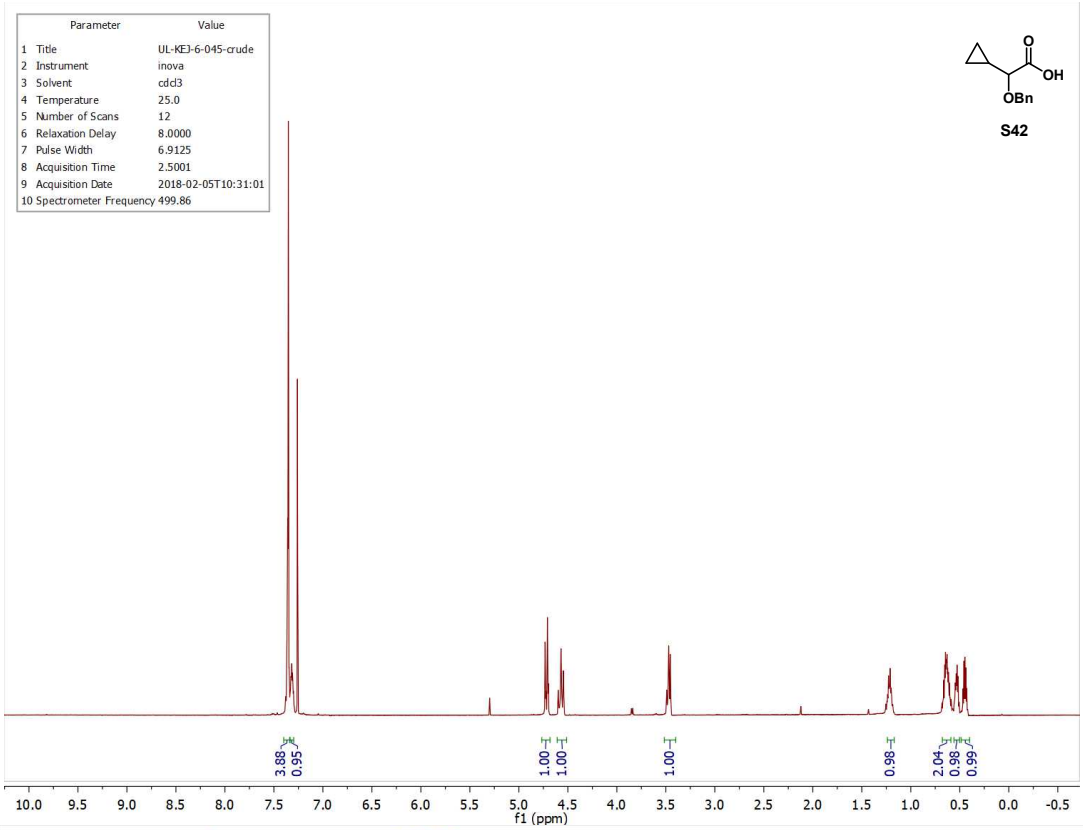
S18

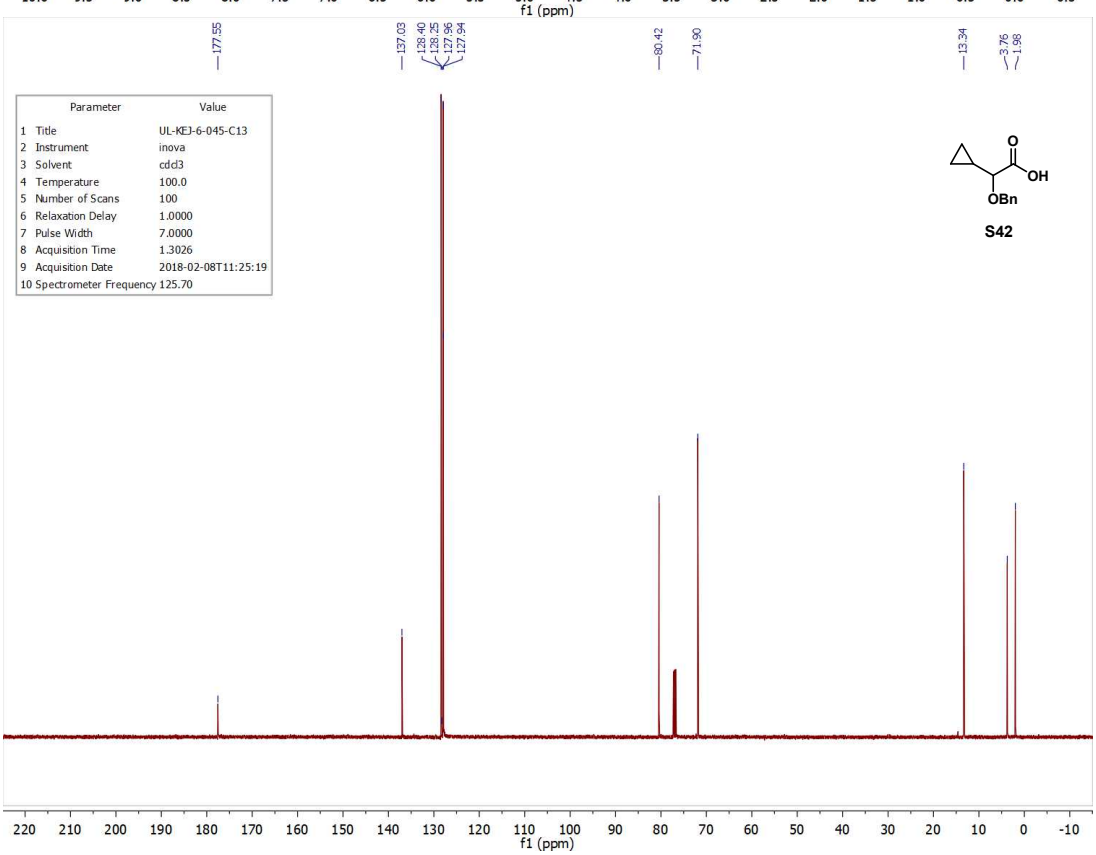

Parameter Value
1 Title mp-5-263-A-19F.1.fid
2 Instrument spect
3 Solvent CDCl3
4 Temperature 298.1
5 Number of Scans 32
6 Relaxation Delay 1.0000
7 Pulse Width 18.0000
8 Acquisition Time 2.3599
9 Acquisition Date 2020-12-22T14:05:09
10 Spectrometer Frequency 376.43
S18
-80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

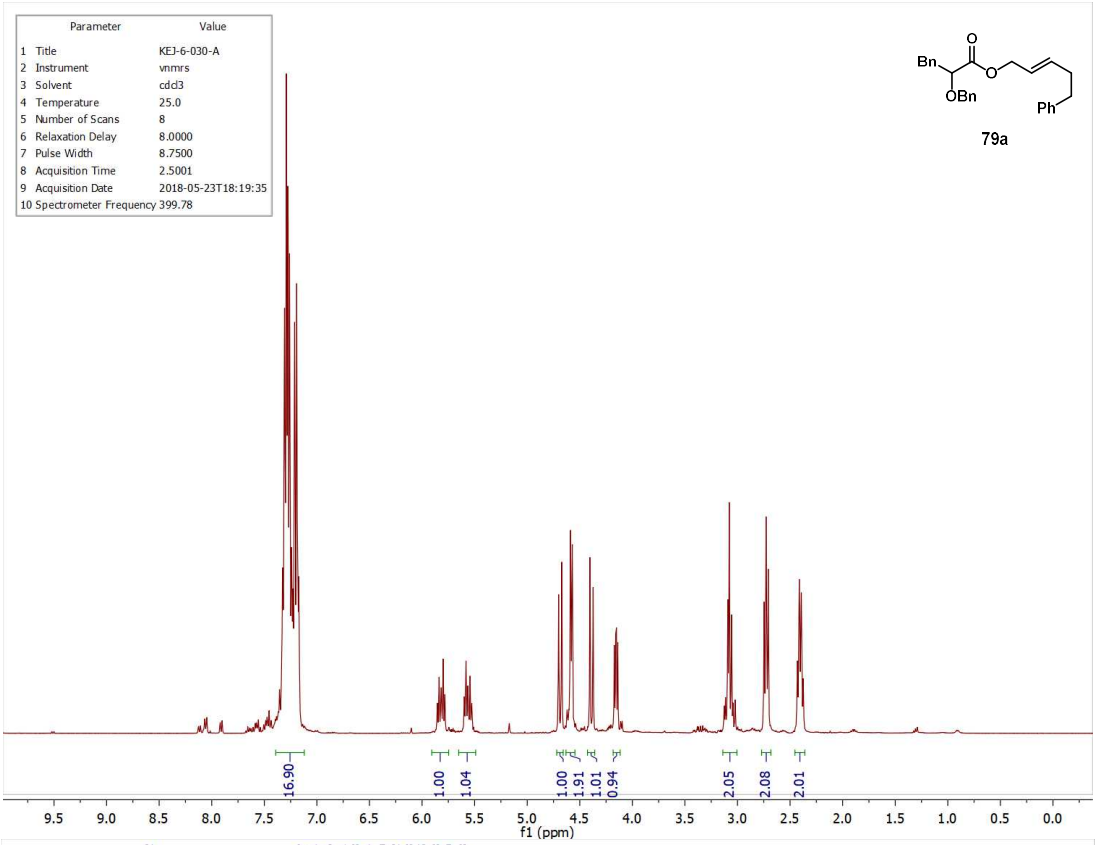

Parameter Value
1 Title mp-5-235-crude
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.6625
8 Acquisition Time 2.5001
9 Acquisition Date 2020-10-25T16:04:49
10 Spectrometer Frequency 499.85
73
2.00 2.07 2.05 4.32 2.20 2.17 40.60
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

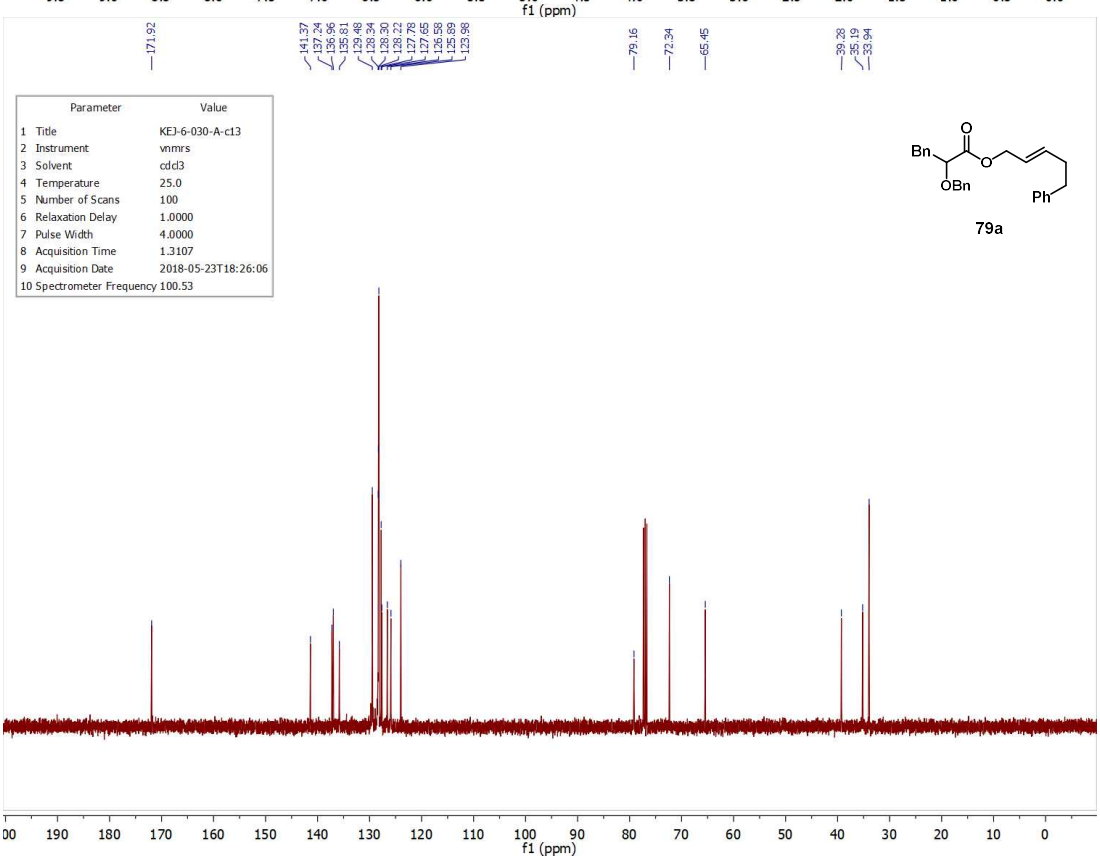

Parameter Value
1 Title mp-5-235-crude-C13.10.fid
2 Instrument NEO500
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 2700
6 Relaxation Delay 2.0000
7 Pulse Width 10.0000
8 Acquisition Time 1.0879
9 Acquisition Date 2020-12-23T18:33:16
10 Spectrometer Frequency 125.78
94.37
93.03
87.45
87.21
52.13
44.27
38.07
37.90
36.31
31.31
31.00
30.83
29.54
26.05
24.92
22.39
22.38
20.98
73
f1 (ppm)

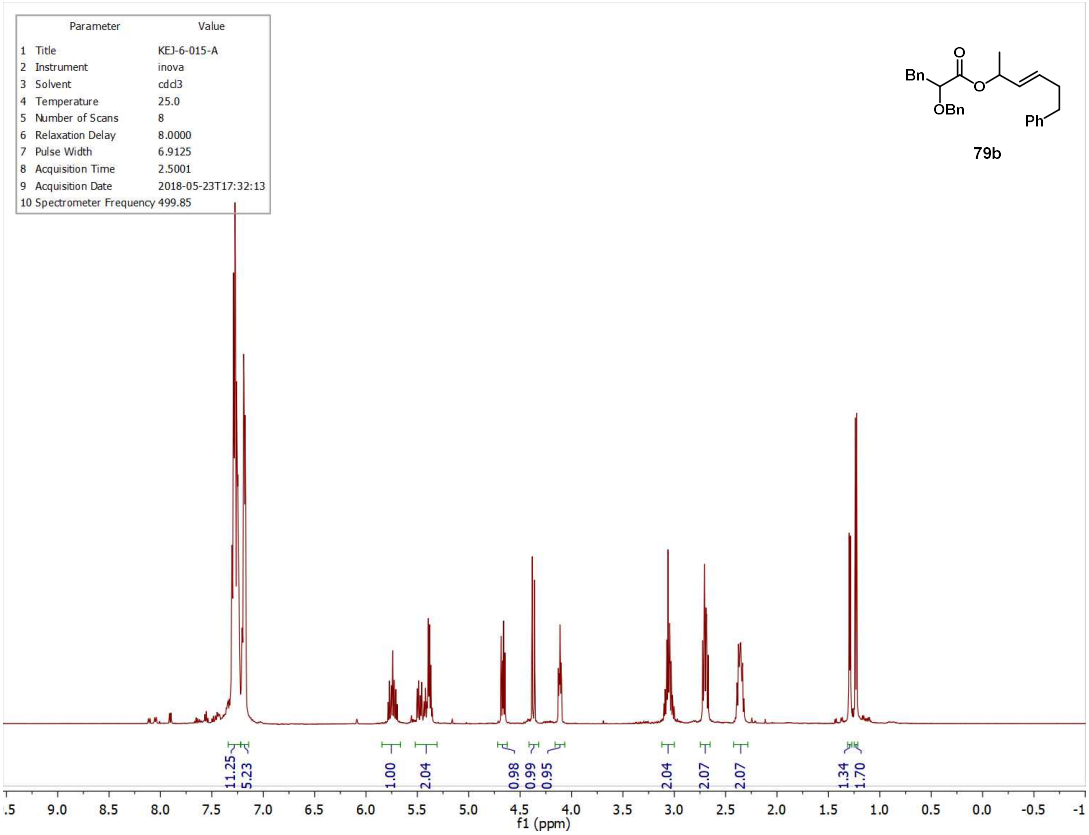

Parameter Value
1 Title mp-5-235-crude-19F.1.fid
2 Instrument spect
3 Solvent CDCl3
4 Temperature 298.2
5 Number of Scans 100
6 Relaxation Delay 1.0000
7 Pulse Width 18.0000
8 Acquisition Time 2.3599
9 Acquisition Date 2020-12-23T16:05:11
10 Spectrometer Frequency 376.43
73
f1 (ppm)

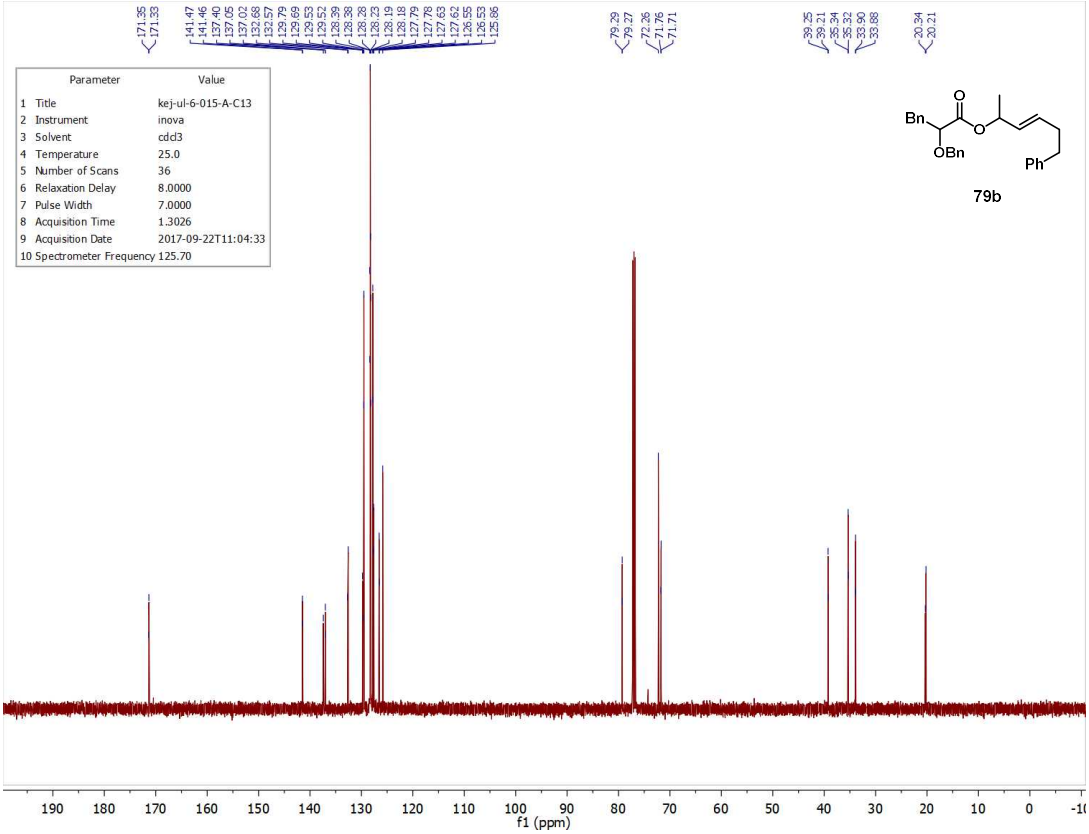

Parameter Value
1 Title UL-KEJ-6-045-crude
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2018-02-05T10:31:01
10 Spectrometer Frequency 499.86
OH
OBn
S42
3.88
0.95
1.00
1.00
1.00
0.98
2.04
0.98
0.99
f1 (ppm)


177.55
137.03
128.40
128.25
127.96
127.94
80.42
71.90
13.34
3.76
1.98
Parameter Value
1 Title UL-KEJ-6-045-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 100.0
5 Number of Scans 100
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2018-02-08T11:25:19
10 Spectrometer Frequency 125.70
OH
OBn
S42
f1 (ppm)

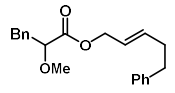

Parameter Value
1 Title KEJ-6-030-A
2 Instrument vnmrs
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 8.7500
8 Acquisition Time 2.5001
9 Acquisition Date 2018-05-23T18:19:35
10 Spectrometer Frequency 399.78
Bn
OBn
O
O
Ph
79a
16.90
1.00
1.04
1.00
1.91
1.01
0.94
2.05
2.08
2.01
f1 (ppm)


171.92
141.37
137.24
136.96
135.81
129.48
128.34
128.30
128.22
127.78
127.65
126.58
125.89
123.98
79.16
72.34
65.45
39.28
35.19
33.94
Parameter Value
1 Title KEJ-6-030-A-c13
2 Instrument vnmrs
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 100
6 Relaxation Delay 1.0000
7 Pulse Width 4.0000
8 Acquisition Time 1.3107
9 Acquisition Date 2018-05-23T18:26:06
10 Spectrometer Frequency 100.53
Bn
OBn
O
O
Ph
79a
f1 (ppm)

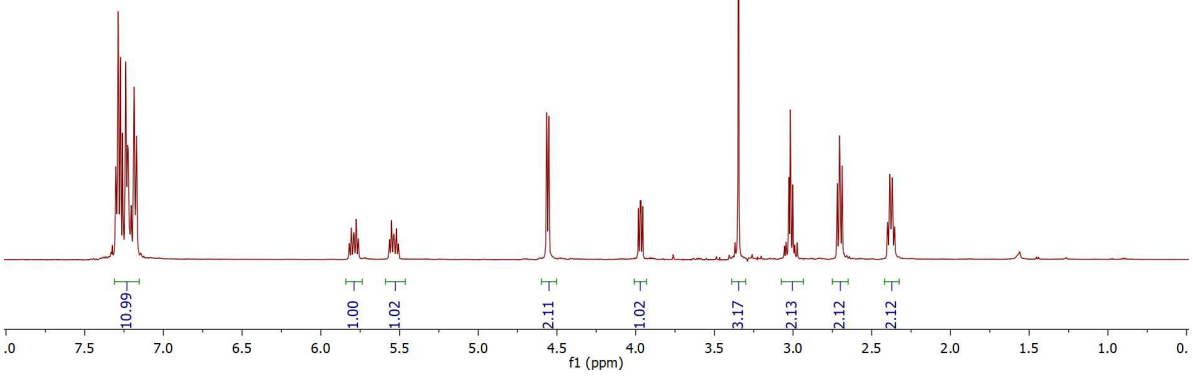

Parameter Value
1 Title KEJ-6-015-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2018-05-23T17:32:13
10 Spectrometer Frequency 499.85
Bn
OBn
O
O
Ph
79b
11.25
5.23
1.00
2.04
0.98
0.99
0.95
2.04
2.07
2.07
1.34
1.70
f1 (ppm)


171.35
171.33
141.47
141.46
137.40
137.05
137.02
132.68
132.57
129.79
129.69
129.53
129.52
128.39
128.38
128.28
128.23
128.19
128.18
127.79
127.78
127.63
127.62
126.55
126.53
125.86
79.29
79.27
72.26
71.76
71.71
39.25
39.21
35.34
35.32
33.96
33.88
20.34
20.21
Parameter Value
1 Title kej-ul-6-015-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 36
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-09-22T11:04:33
10 Spectrometer Frequency 125.70
Bn
OBn
O
O
Ph
79b
f1 (ppm)

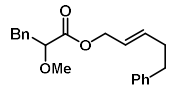
Parameter	Value
1 Title	JJL-3-065-a
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	8.3250
8 Acquisition Time	2.5001
9 Acquisition Date	2017-11-01T10:13:16
10 Spectrometer Frequency	499.86



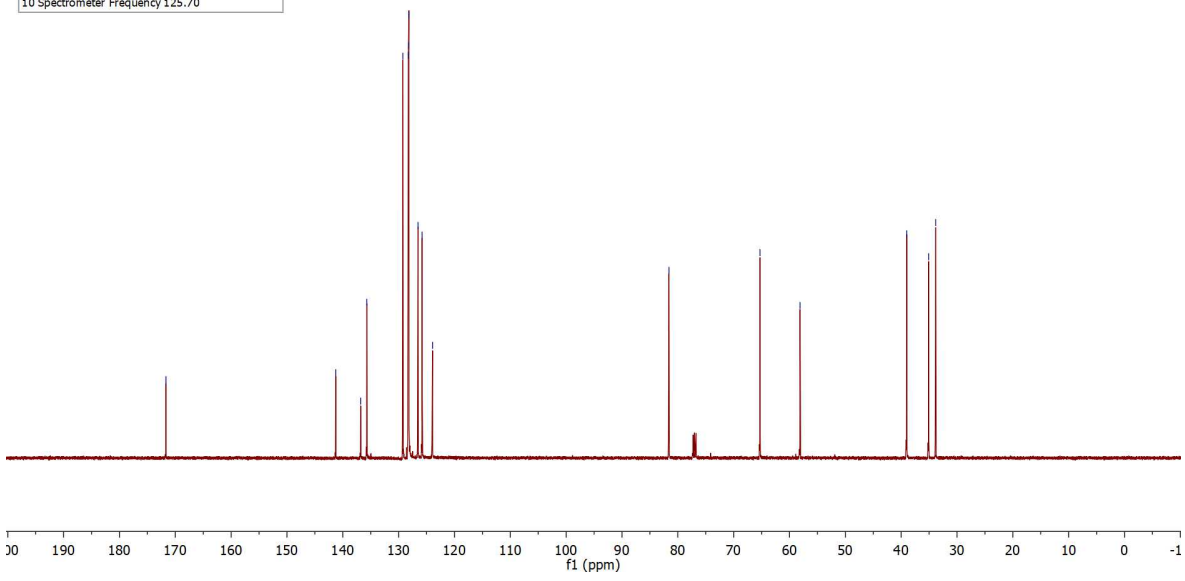
79c



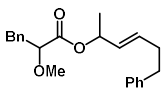
Parameter	Value
1 Title	JJL-3-065-13CNMR
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	84
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-11-04T14:50:49
10 Spectrometer Frequency	125.70



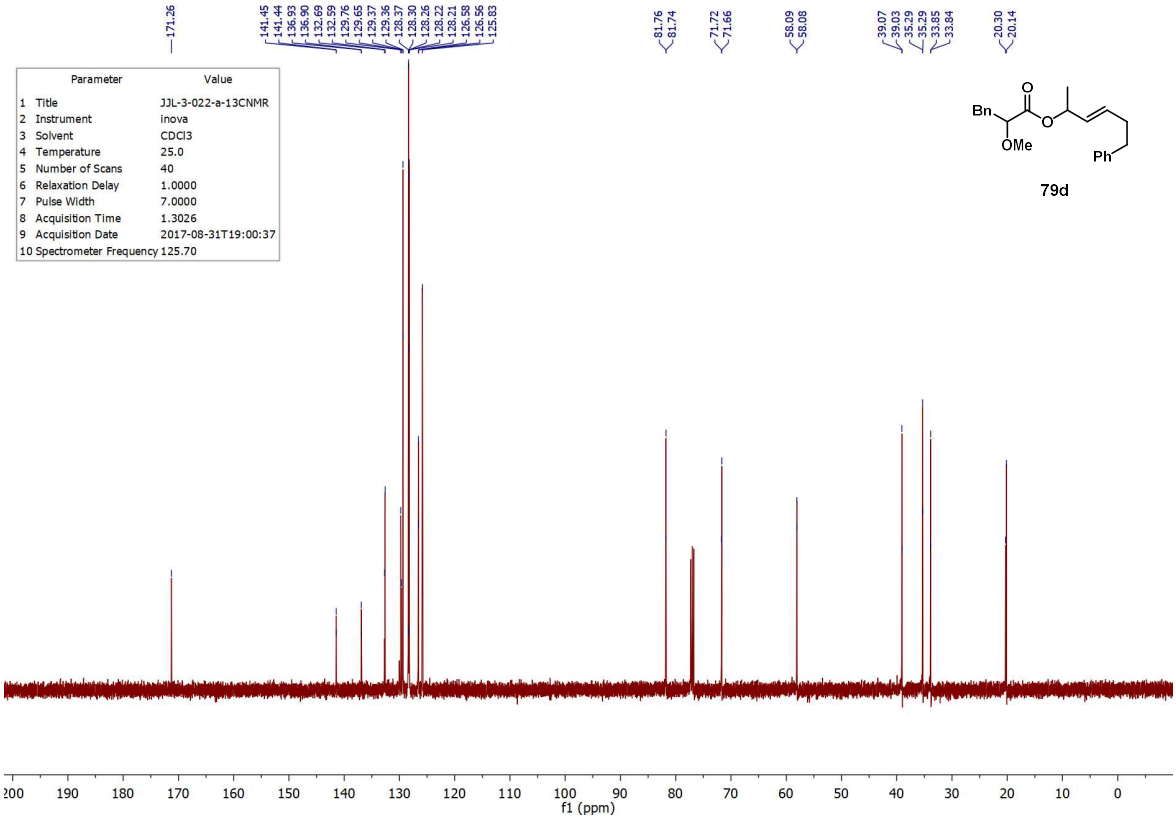
79c



Parameter	Value
1 Title	JJL-3-022-a
2 Instrument	inova
3 Solvent	CDCl3
4 Temperature	22.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	8.3250
8 Acquisition Time	2.5001
9 Acquisition Date	2017-08-22T14:50:50
10 Spectrometer Frequency	499.86

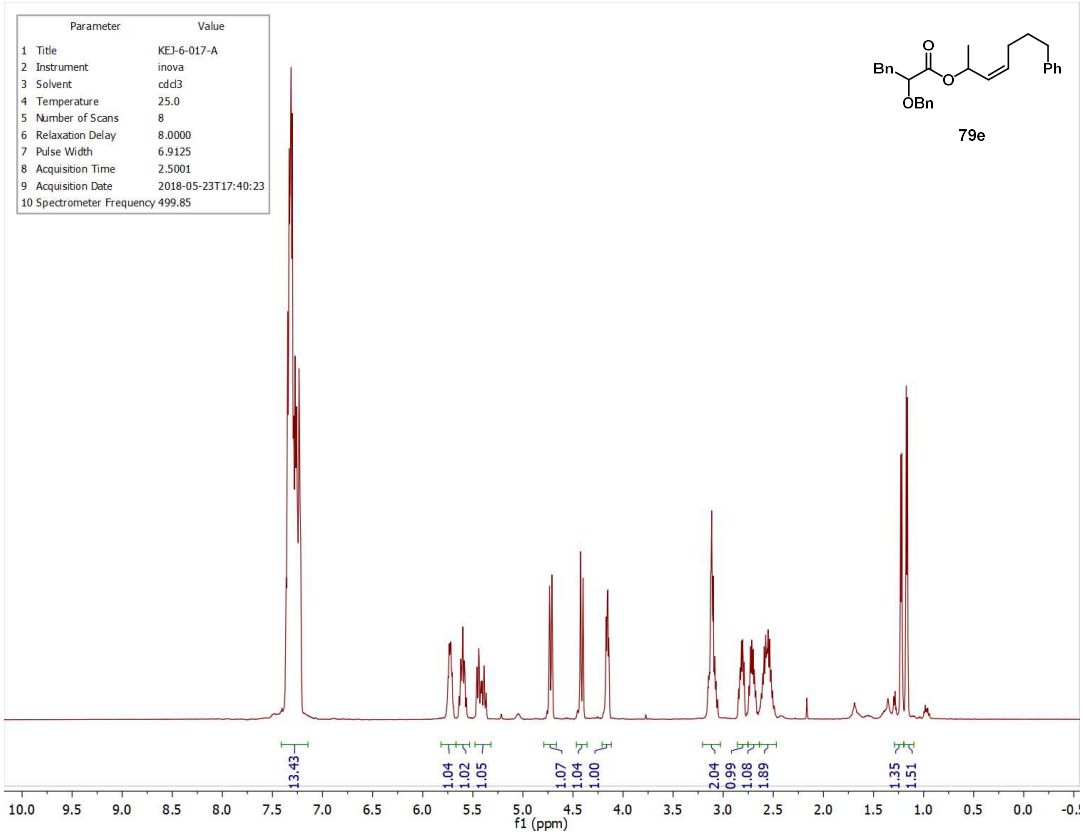


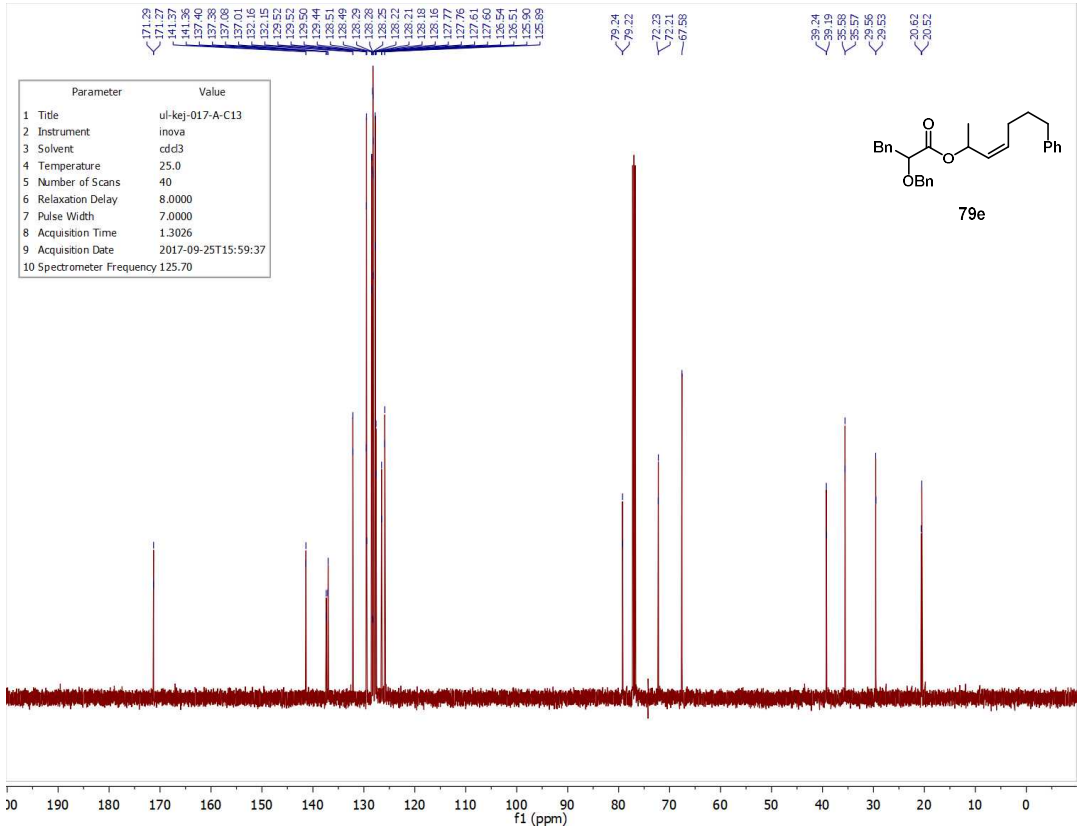
79d



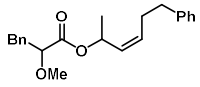
Parameter	Value
1 Title	JJL-3-022-a-13CNMR
2 Instrument	inova
3 Solvent	CDCl3
4 Temperature	25.0
5 Number of Scans	40
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-08-31T19:00:37
10 Spectrometer Frequency	125.70

79d

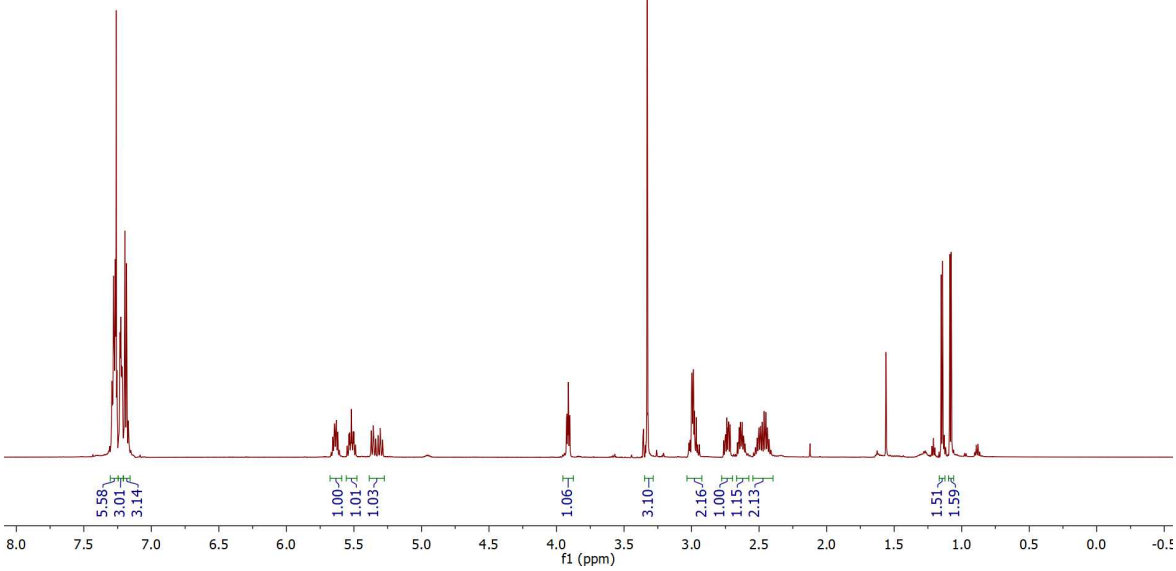

Parameter Value
1 Title KEJ-6-017-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2018-05-23T17:40:23
10 Spectrometer Frequency 499.85
Bn
OBn
Ph
79e
13.43
1.04
1.02
1.05
1.07
1.04
1.00
2.04
0.99
1.08
1.89
1.35
1.51
f1 (ppm)


Parameter Value
1 Title ul-kej-017-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 40
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-09-25T15:59:37
10 Spectrometer Frequency 125.70
Bn
OBn
Ph
79e
f1 (ppm)

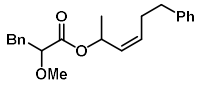
Parameter	Value
1 Title	JJL-3-042-a
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	5.6625
8 Acquisition Time	2.5000
9 Acquisition Date	2017-11-14T11:25:28
10 Spectrometer Frequency	599.64



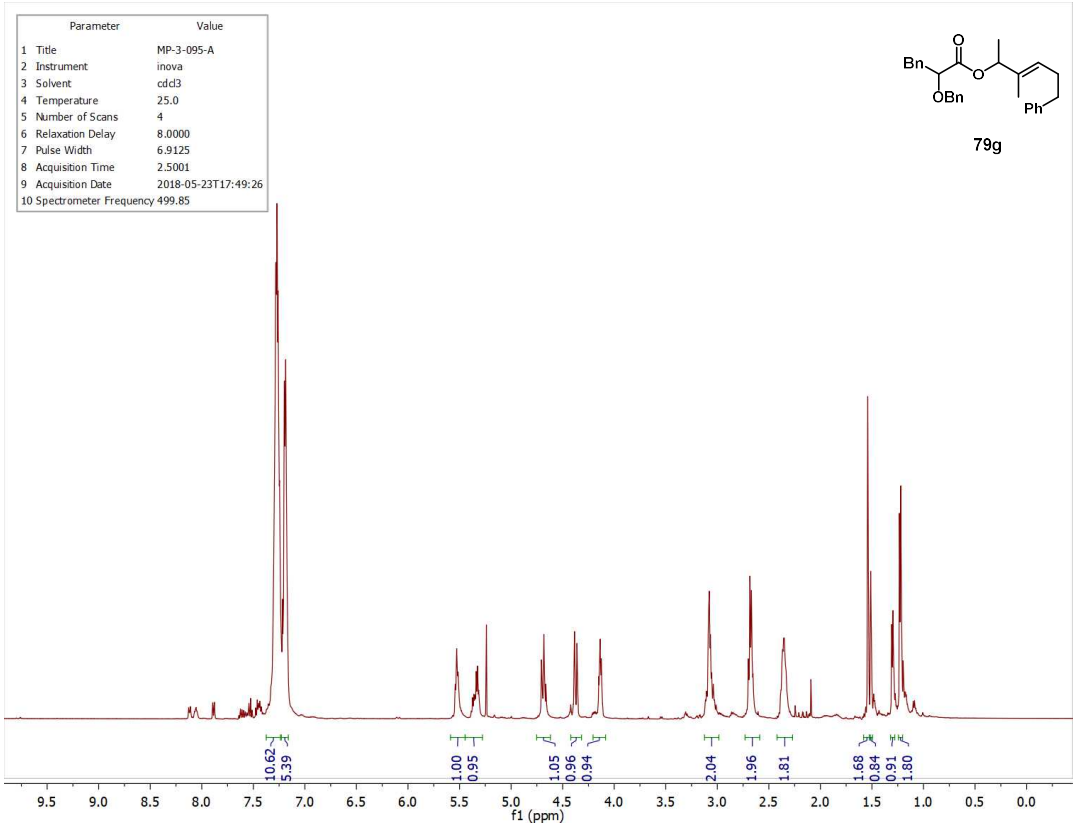
79f

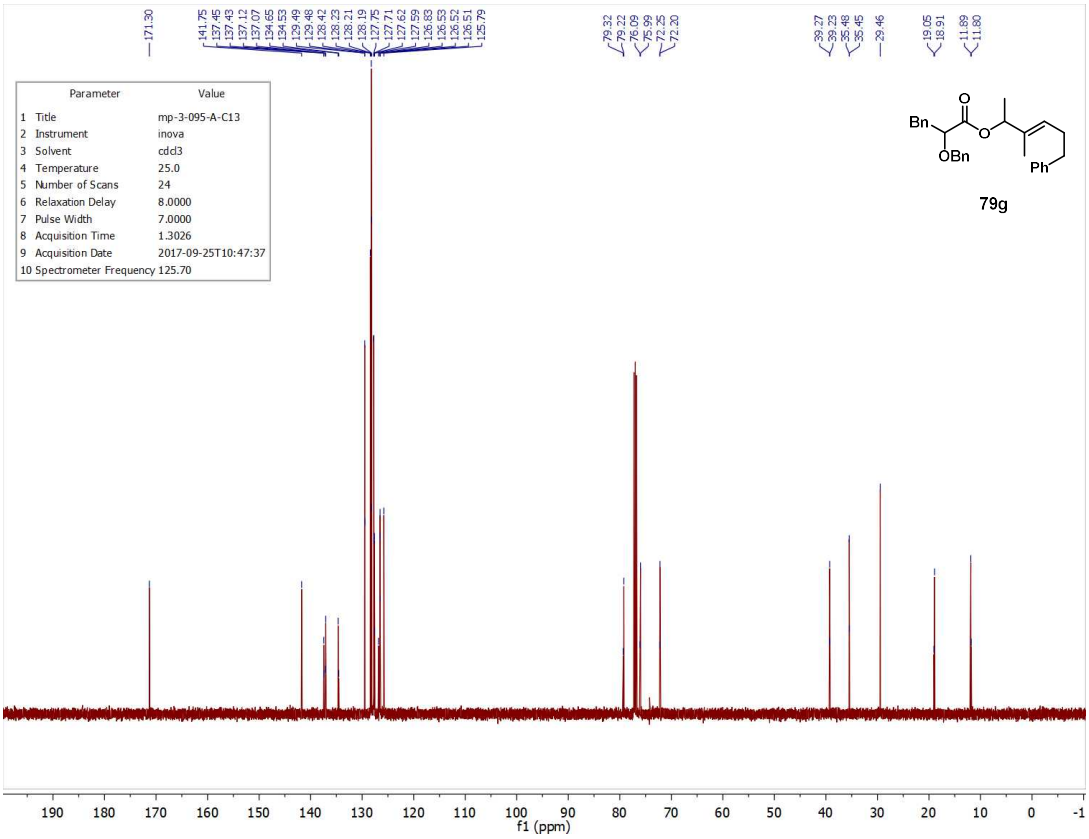


Parameter	Value
1 Title	JJL-3-042-13CNMR
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	384
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-11-04T14:20:25
10 Spectrometer Frequency	125.70

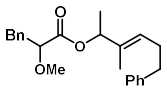


79f


Parameter Value
1 Title MP-3-095-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 4
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2018-05-23T17:49:26
10 Spectrometer Frequency 499.85
Bn
OBn
O
O
Ph
79g
10.62
5.39
1.00
0.95
1.05
0.96
0.94
2.04
1.96
1.81
1.68
0.84
0.91
1.80
f1 (ppm)

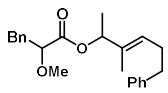

171.30
141.75
137.45
137.43
137.12
137.07
134.65
134.53
129.49
129.48
128.42
128.23
128.21
128.19
127.75
127.71
127.62
127.39
126.83
126.53
126.51
125.79
79.32
79.22
76.09
75.99
72.25
72.20
39.27
39.23
35.48
35.45
29.46
19.05
18.91
11.89
11.80
Parameter Value
1 Title mp-3-095-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 24
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-09-25T10:47:37
10 Spectrometer Frequency 125.70
Bn
OBn
O
O
Ph
79g
f1 (ppm)

Parameter	Value
1 Title	JJL-3-025-b
2 Instrument	inova
3 Solvent	CDCl3
4 Temperature	22.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	8.3250
8 Acquisition Time	2.5001
9 Acquisition Date	2017-08-24T18:37:08
10 Spectrometer Frequency	499.86

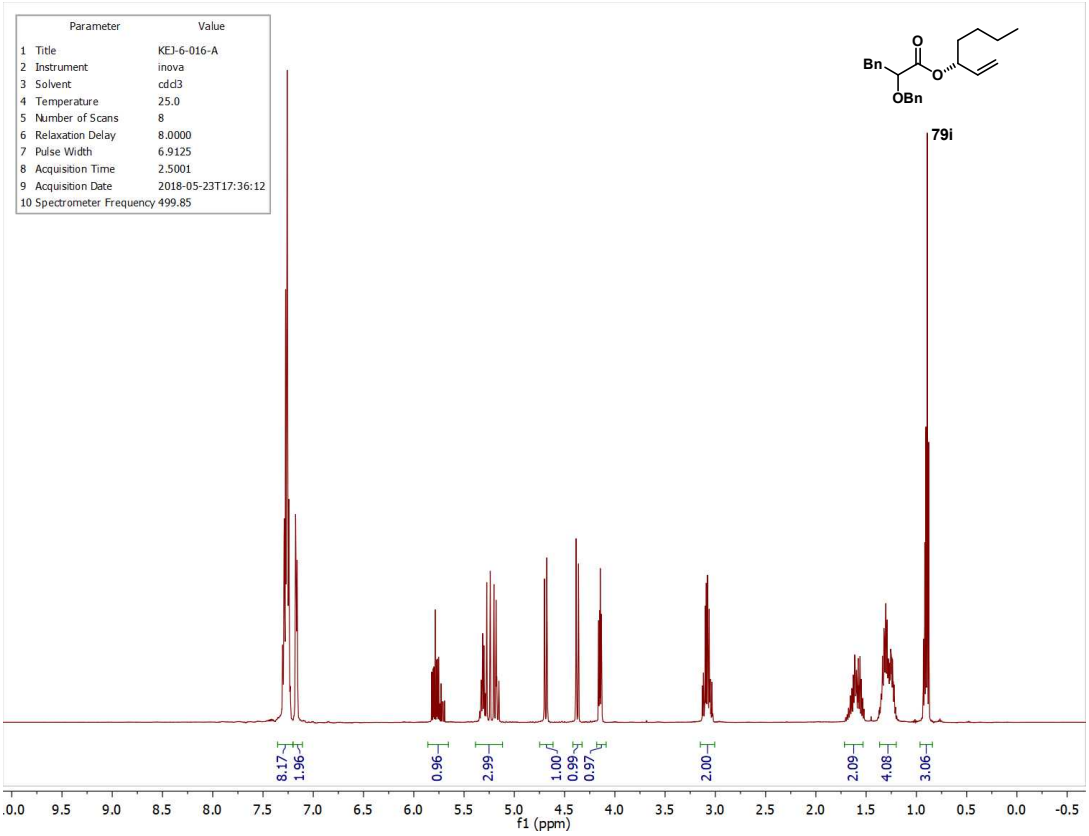


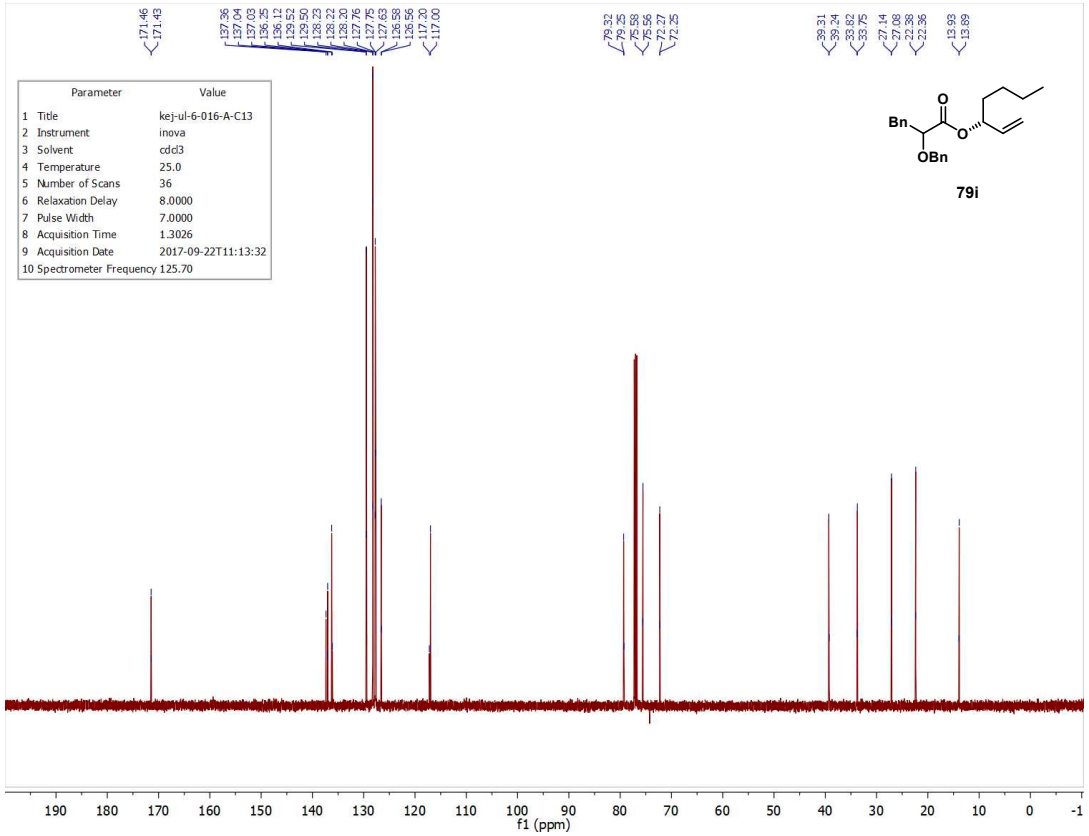
79h

Parameter	Value
1 Title	JJL-3-025-a-13CNMR
2 Instrument	inova
3 Solvent	CDCl3
4 Temperature	25.0
5 Number of Scans	80
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-08-31T19:04:18
10 Spectrometer Frequency	125.70

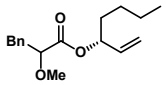


79h


Parameter Value
1 Title KEJ-6-016-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2018-05-23T17:36:12
10 Spectrometer Frequency 499.85
Bn
O
OBn
79i
8.17
1.96
0.96
2.99
1.00
0.99
0.97
2.00
2.09
4.08
3.06
f1 (ppm)

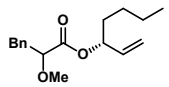

171.46
171.43
137.36
137.04
137.03
136.25
136.12
129.52
129.50
128.23
128.22
128.20
127.76
127.75
127.63
126.58
126.56
117.20
117.00
79.32
79.25
75.58
75.56
72.27
72.25
39.31
39.24
33.82
33.75
27.14
27.08
22.38
22.36
13.93
13.89
Parameter Value
1 Title kej-ul-6-016-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 36
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-09-22T11:13:32
10 Spectrometer Frequency 125.70
Bn
O
OBn
79i
f1 (ppm)

Parameter	Value
1 Title	JJL-3-026-a
2 Instrument	inova
3 Solvent	CDCl3
4 Temperature	22.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	8.3250
8 Acquisition Time	2.5001
9 Acquisition Date	2017-08-24T18:41:03
10 Spectrometer Frequency	499.86

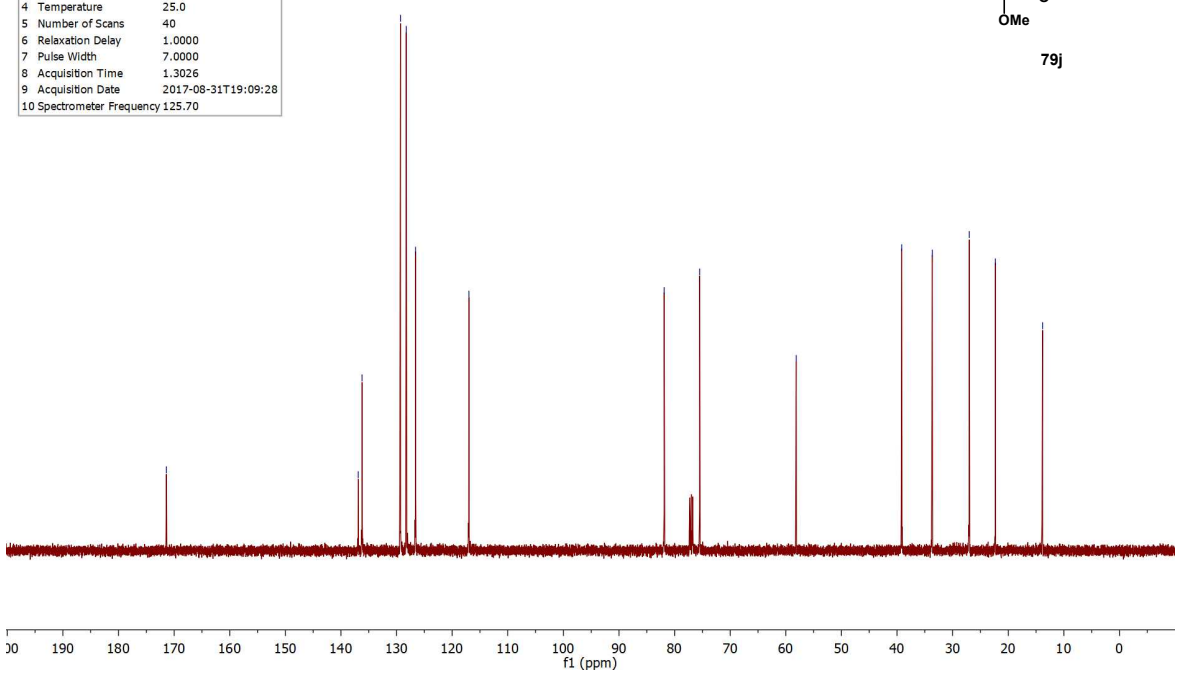


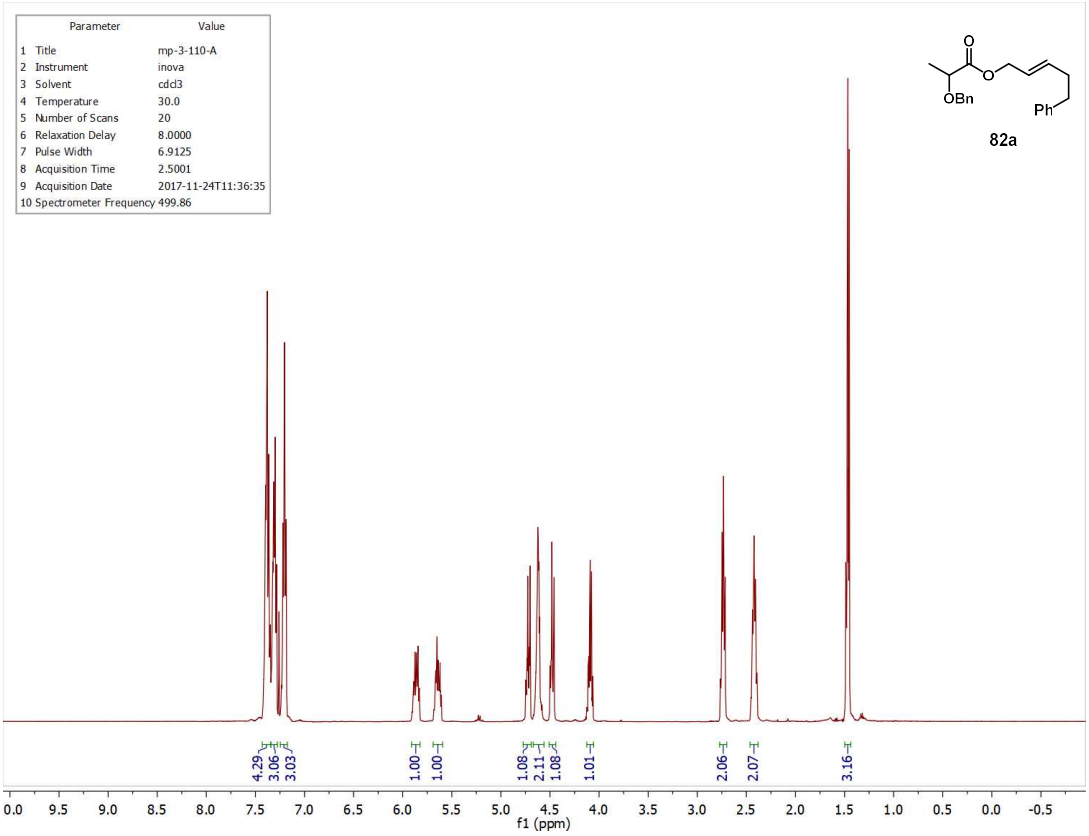
79j

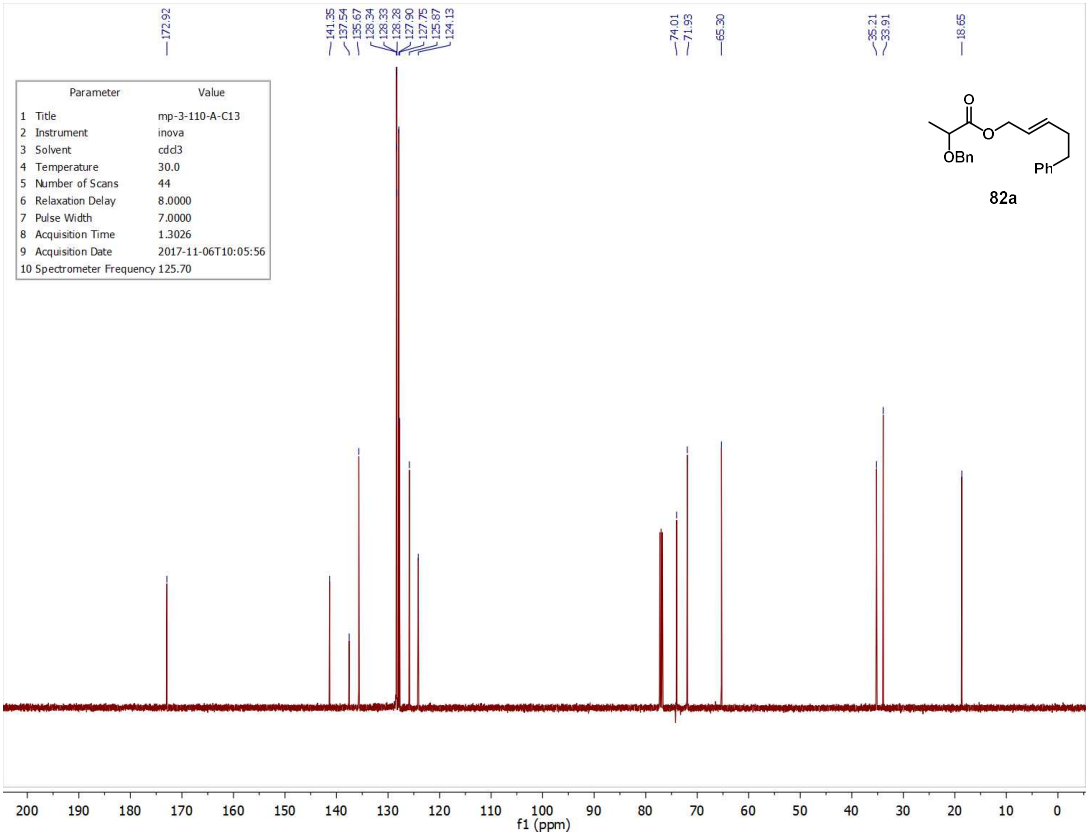
Parameter	Value
1 Title	JJL-3-026-a-13CNMR
2 Instrument	inova
3 Solvent	CDCl3
4 Temperature	25.0
5 Number of Scans	40
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-08-31T19:09:28
10 Spectrometer Frequency	125.70



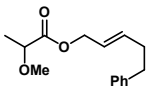
79j



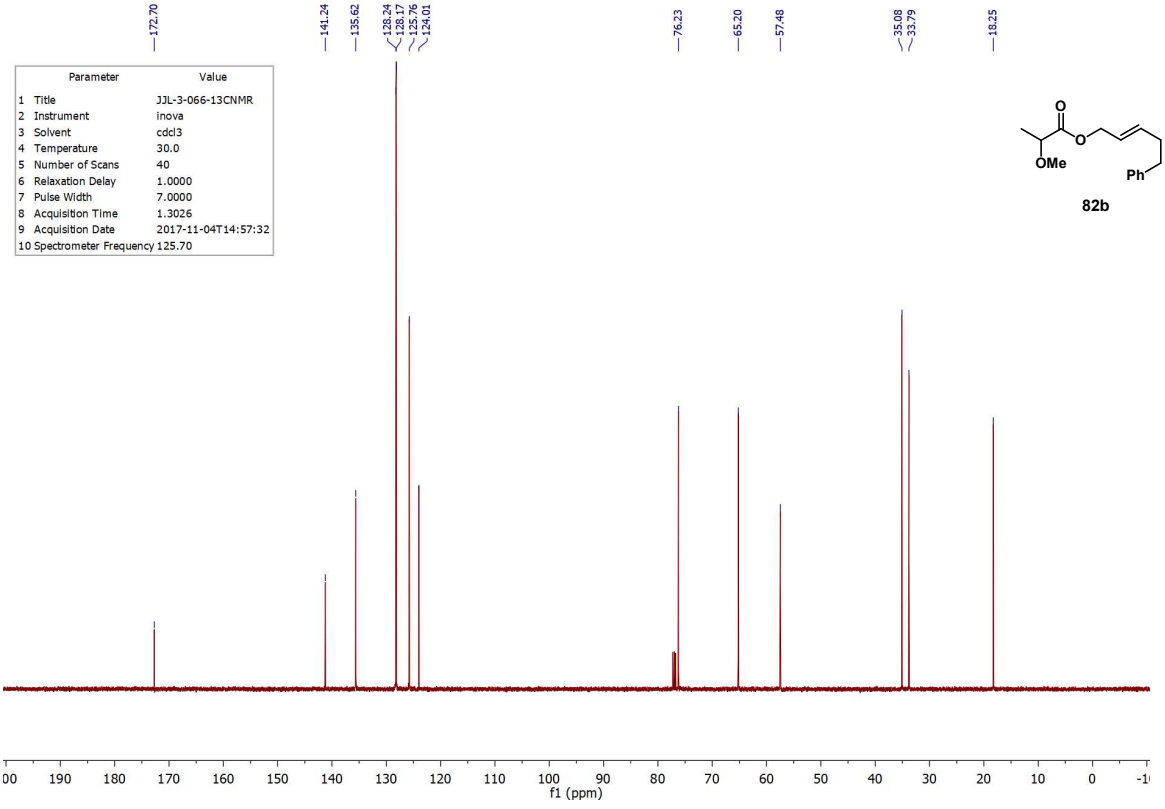

Parameter Value
1 Title mp-3-110-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 20
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-24T11:36:35
10 Spectrometer Frequency 499.86
OBn
Ph
82a
4.29
3.06
3.03
1.00
1.00
1.08
2.11
1.08
1.01
2.06
2.07
3.16
f1 (ppm)


172.92
141.35
137.54
135.67
128.34
128.33
128.28
127.90
127.75
125.87
124.13
74.01
71.93
65.30
35.21
33.91
18.65
Parameter Value
1 Title mp-3-110-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 44
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-06T10:05:56
10 Spectrometer Frequency 125.70
OBn
Ph
82a
f1 (ppm)

Parameter	Value
1 Title	JJL-3-066-a
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	8.3250
8 Acquisition Time	2.5001
9 Acquisition Date	2017-11-01T10:18:02
10 Spectrometer Frequency	499.86

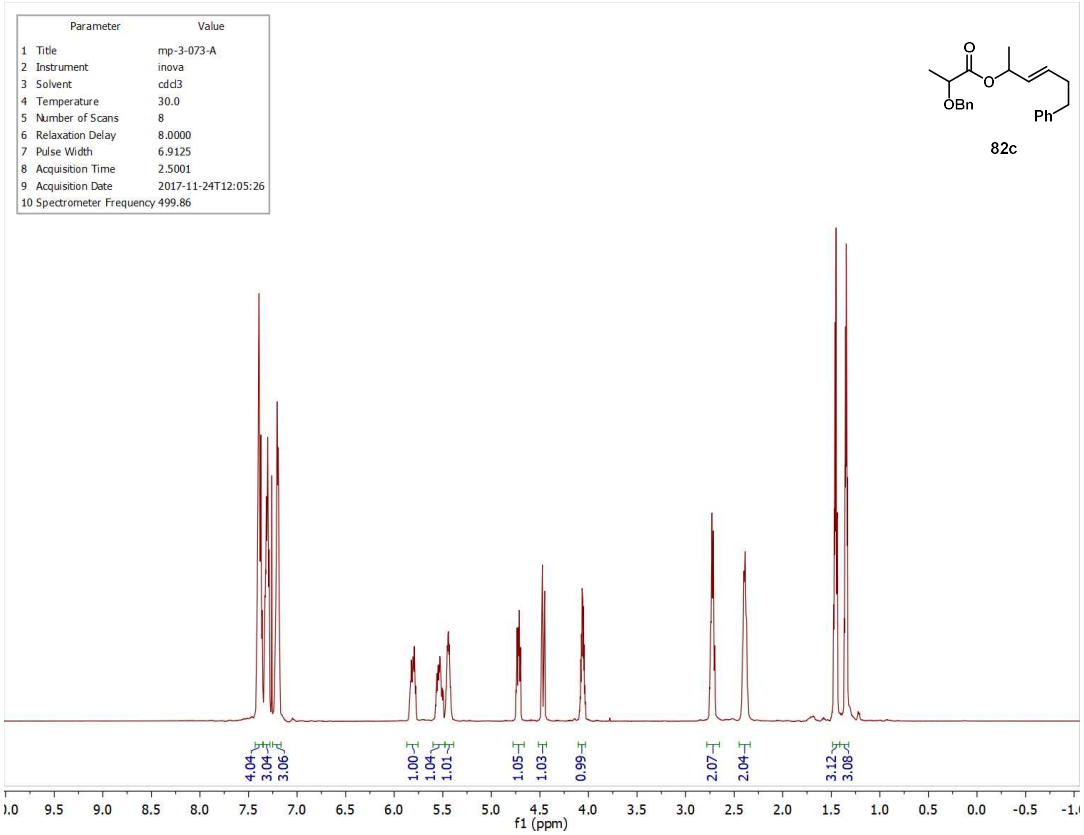


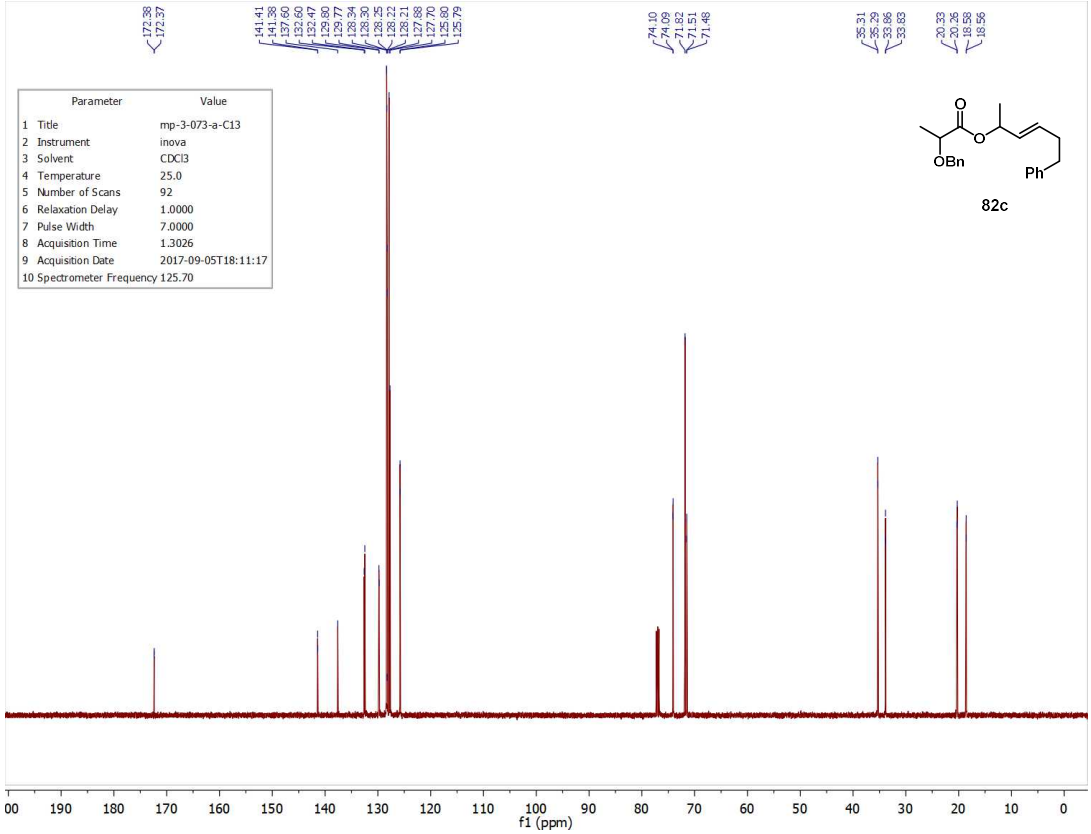
82b



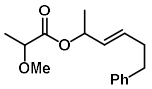
Parameter	Value
1 Title	JJL-3-066-13CNMR
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	40
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-11-04T14:57:32
10 Spectrometer Frequency	125.70

82b

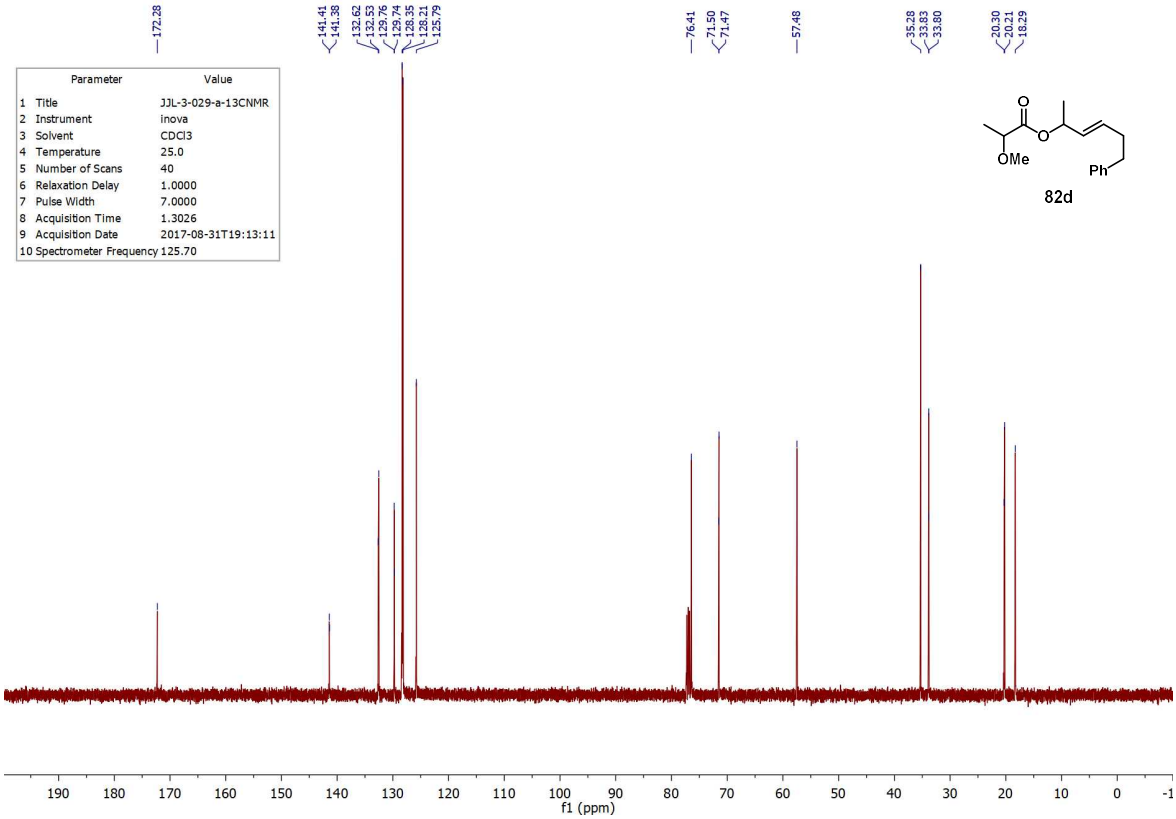

Parameter Value
1 Title mp-3-073-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-24T12:05:26
10 Spectrometer Frequency 499.86
OBn
Ph
82c
4.04
3.04
3.06
1.00
1.04
1.01
1.05
1.03
0.99
2.07
2.04
3.12
3.08
f1 (ppm)


172.38
172.37
141.41
141.38
137.60
132.60
132.47
129.80
129.77
128.34
128.30
128.25
128.22
128.21
127.88
127.70
125.80
125.79
74.10
74.09
71.82
71.51
71.48
35.31
35.29
33.86
33.83
20.33
20.26
18.58
18.56
Parameter Value
1 Title mp-3-073-a-C13
2 Instrument inova
3 Solvent CDCl3
4 Temperature 25.0
5 Number of Scans 92
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-09-05T18:11:17
10 Spectrometer Frequency 125.70
OBn
Ph
82c
f1 (ppm)

	Parameter	Value
1	Title	JJL-3-029-a
2	Instrument	inova
3	Solvent	CDCl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	8.3250
8	Acquisition Time	2.5001
9	Acquisition Date	2017-08-26T11:59:33
10	Spectrometer Frequency	499.86

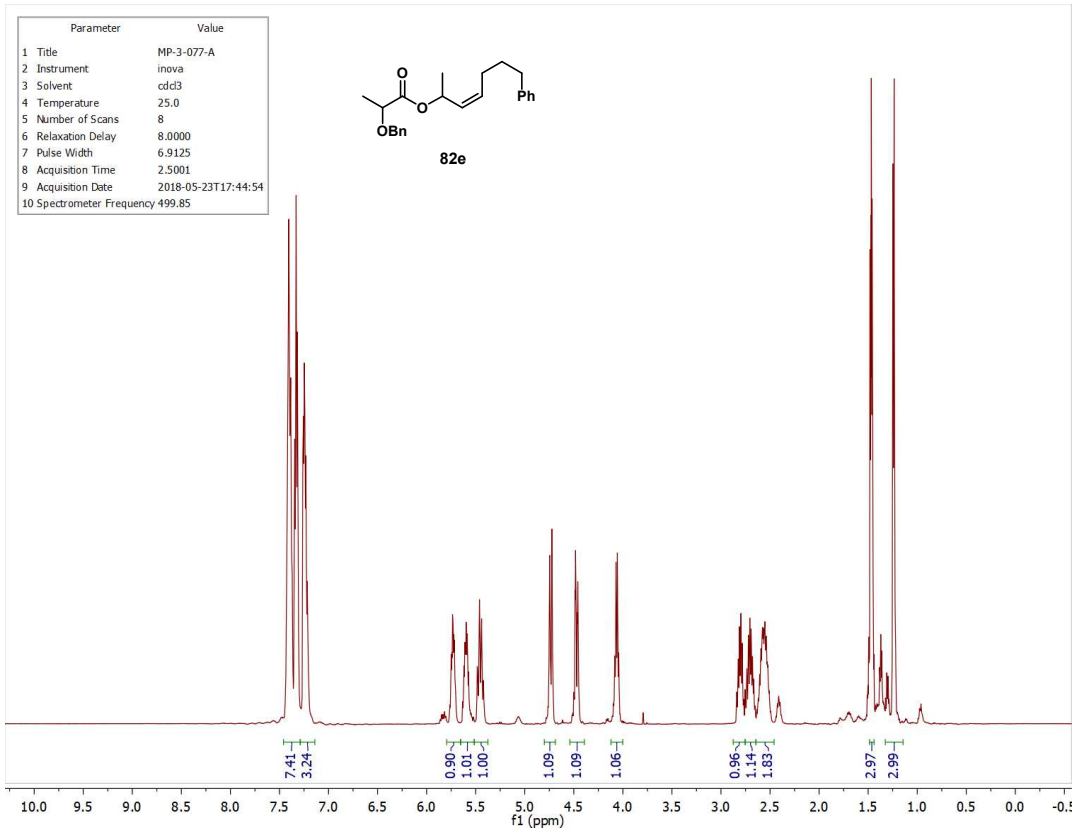


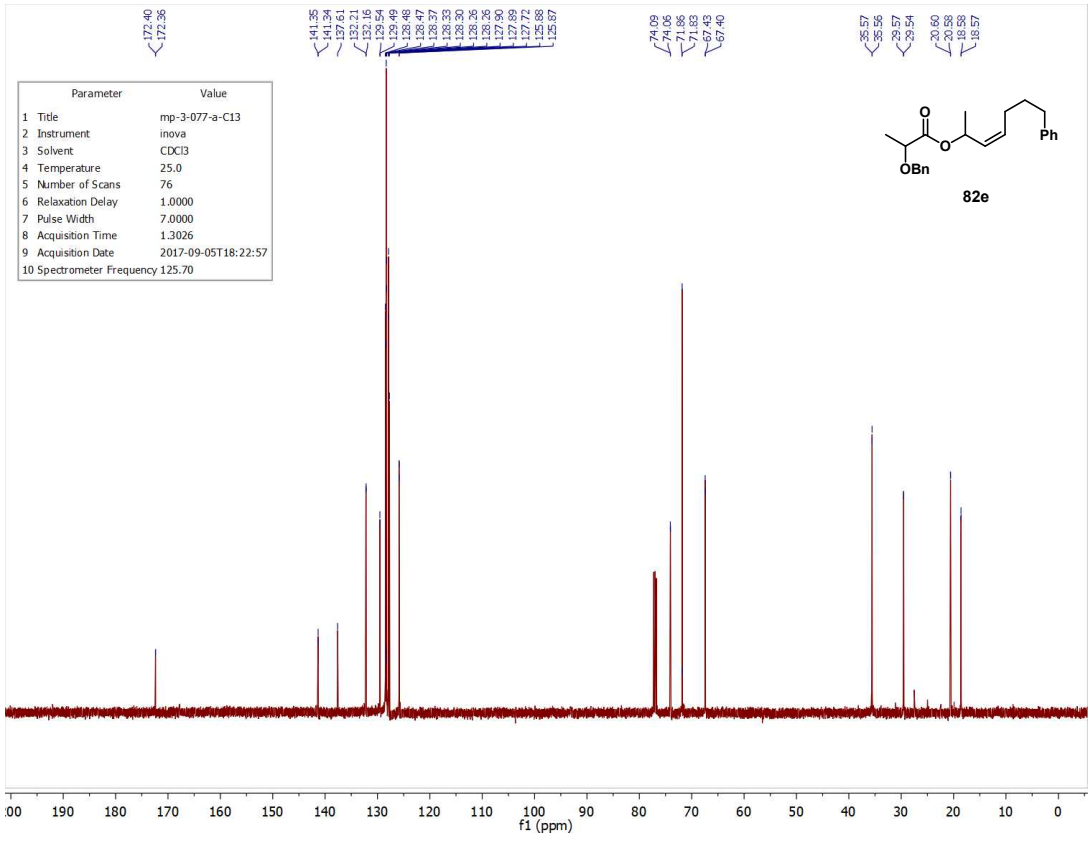
82d



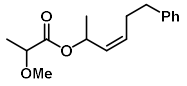
	Parameter	Value
1	Title	JJL-3-029-a-13CNMR
2	Instrument	inova
3	Solvent	CDCl3
4	Temperature	25.0
5	Number of Scans	40
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2017-08-31T19:13:11
10	Spectrometer Frequency	125.70

82d

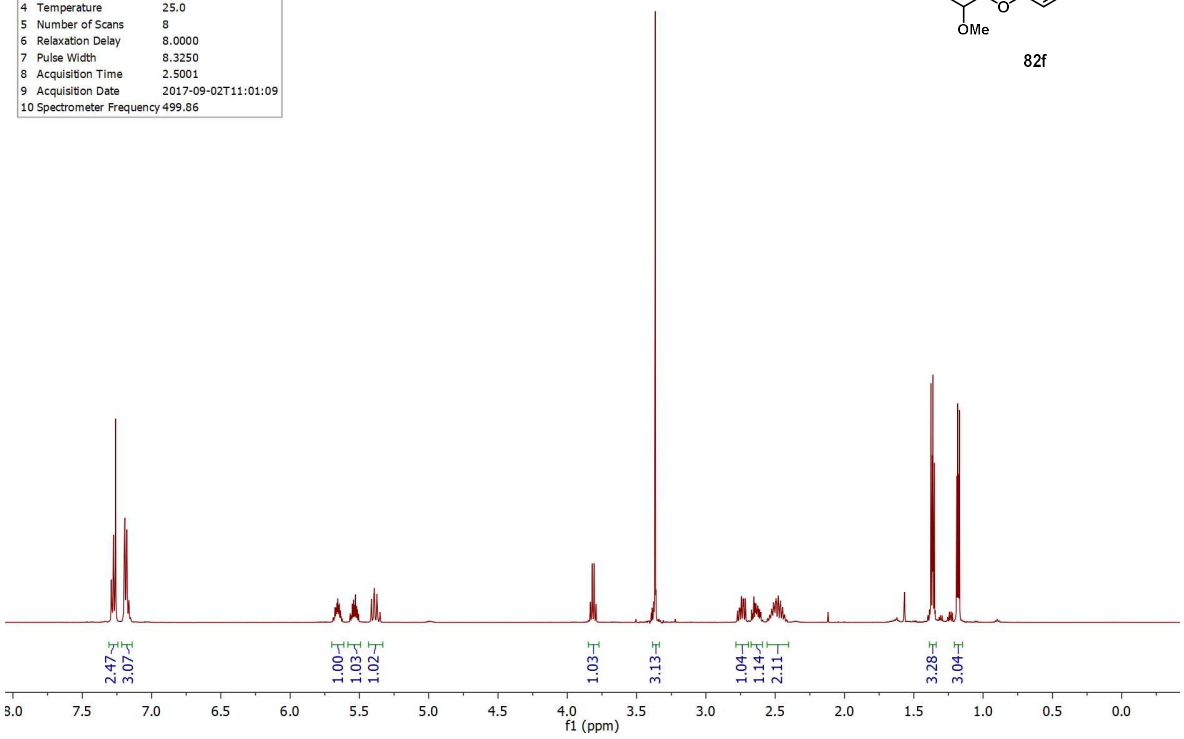

Parameter Value
1 Title MP-3-077-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2018-05-23T17:44:54
10 Spectrometer Frequency 499.85
O
O
OBn
Ph
82e
7.41
3.24
0.90
1.01
1.00
1.09
1.09
1.06
0.96
1.14
1.83
2.97
2.99
f1 (ppm)

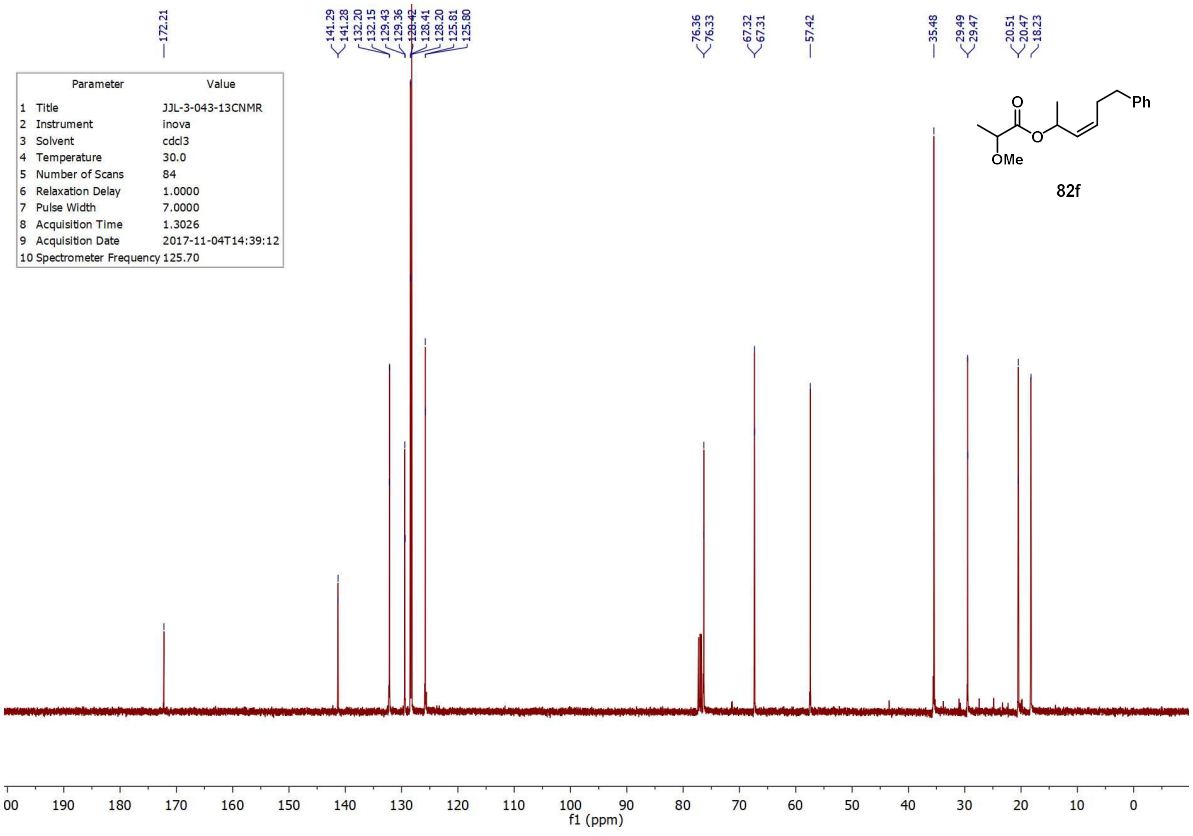

172.40
172.36
141.35
141.34
137.61
132.21
132.16
129.54
129.49
128.48
128.47
128.37
128.33
128.30
128.26
128.25
127.90
127.89
127.72
125.88
125.87
74.09
74.06
71.86
71.83
67.43
67.40
35.57
35.56
29.57
29.54
20.60
20.58
18.58
18.57
Parameter Value
1 Title mp-3-077-a-C13
2 Instrument inova
3 Solvent CDCl3
4 Temperature 25.0
5 Number of Scans 76
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-09-05T18:22:57
10 Spectrometer Frequency 125.70
O
O
OBn
Ph
82e
f1 (ppm)

	Parameter	Value
1	Title	JJL-3-043-a
2	Instrument	inova
3	Solvent	CDCl3
4	Temperature	25.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	8.3250
8	Acquisition Time	2.5001
9	Acquisition Date	2017-09-02T11:01:09
10	Spectrometer Frequency	499.86



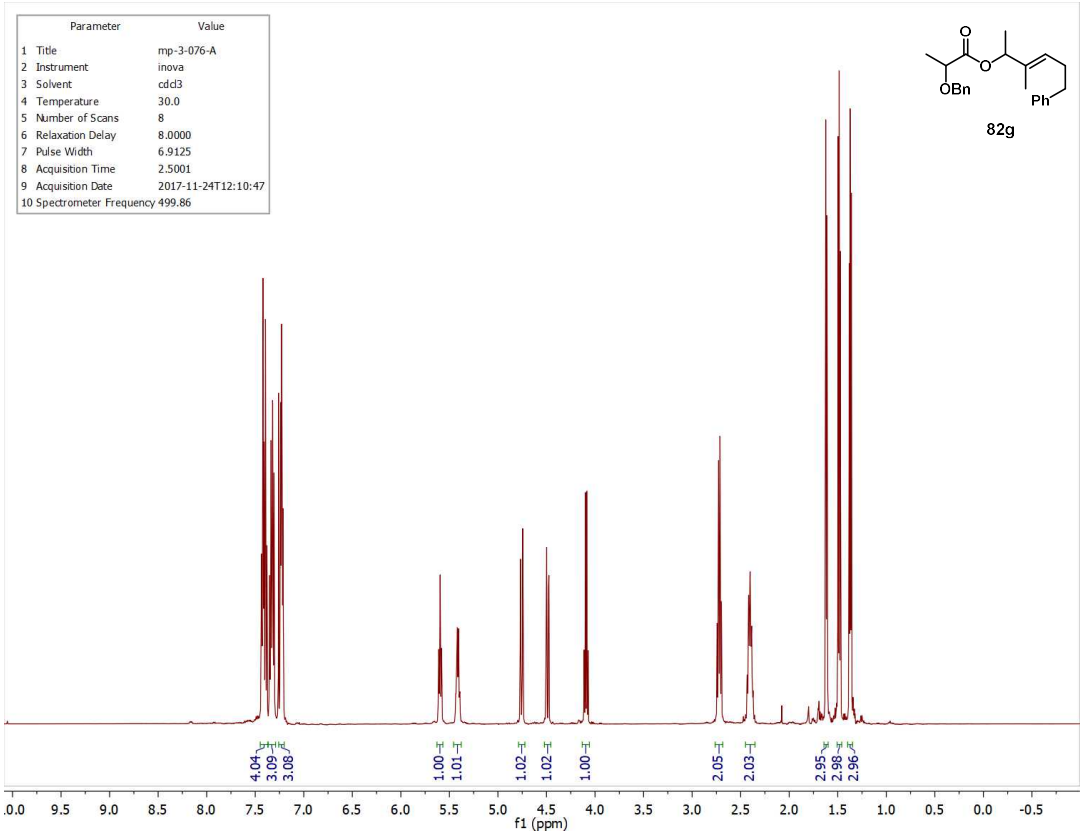
82f

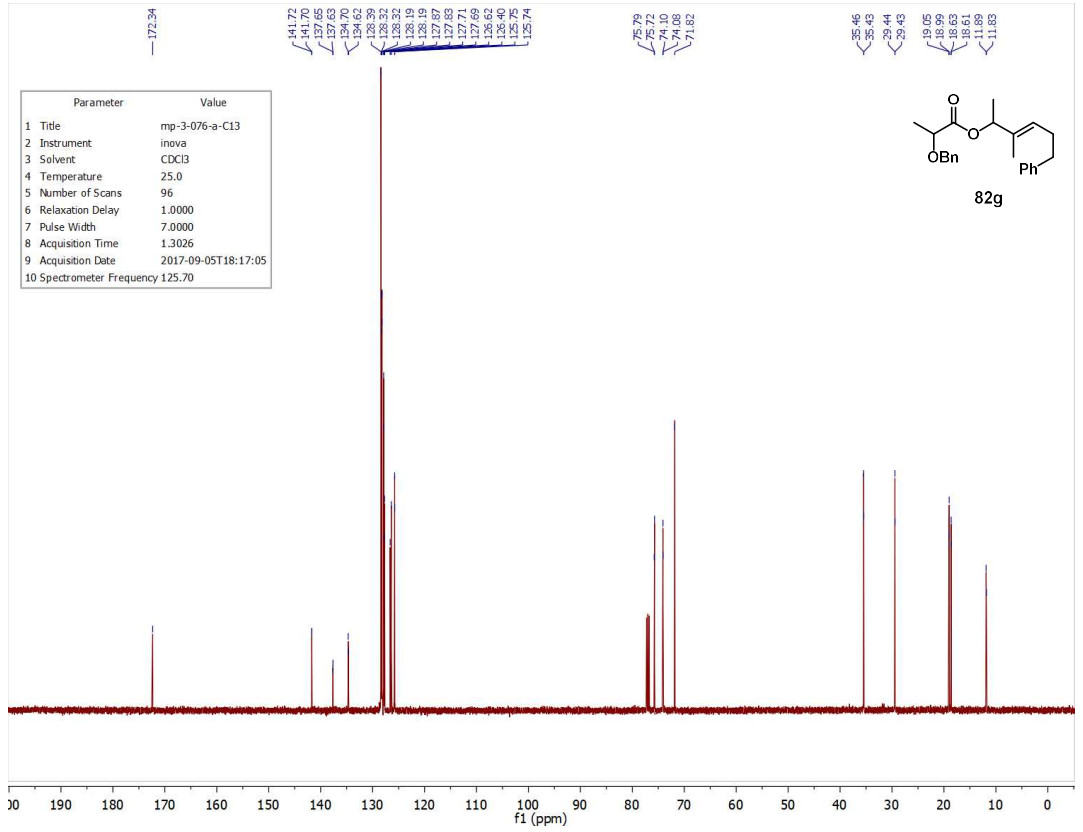




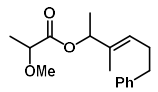
	Parameter	Value
1	Title	JJL-3-043-13CNMR
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	30.0
5	Number of Scans	84
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2017-11-04T14:39:12
10	Spectrometer Frequency	125.70

82f


Parameter Value
1 Title mp-3-076-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-24T12:10:47
10 Spectrometer Frequency 499.86
OBn
Ph
82g
4.04
3.09
3.08
1.00
1.01
1.02
1.02
1.00
2.05
2.03
2.95
2.98
2.96
f1 (ppm)

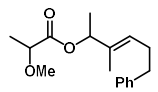

172.34
141.72
141.70
137.65
137.63
134.70
134.62
128.39
128.32
128.32
128.19
128.19
127.87
127.83
127.71
127.69
126.62
126.40
125.75
125.74
75.79
75.72
74.10
74.08
71.82
35.46
35.43
29.44
29.43
19.05
18.99
18.63
18.61
11.89
11.83
Parameter Value
1 Title mp-3-076-a-C13
2 Instrument inova
3 Solvent CDCl3
4 Temperature 25.0
5 Number of Scans 96
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-09-05T18:17:05
10 Spectrometer Frequency 125.70
OBn
Ph
82g
f1 (ppm)

Parameter	Value
1 Title	JJL-3-030-a
2 Instrument	inova
3 Solvent	CDCl3
4 Temperature	25.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	8.3250
8 Acquisition Time	2.5001
9 Acquisition Date	2017-08-26T12:03:31
10 Spectrometer Frequency	499.86

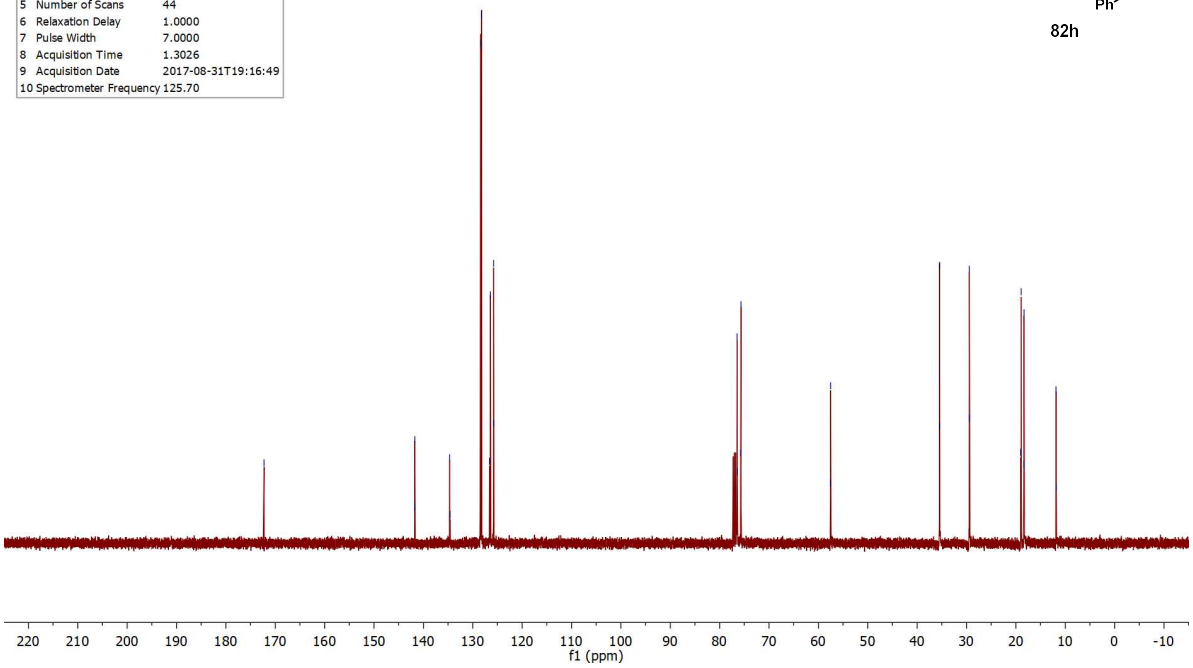


82h

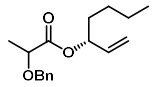
Parameter	Value
1 Title	JJL-3-030-a-13CNMR
2 Instrument	inova
3 Solvent	CDCl3
4 Temperature	25.0
5 Number of Scans	44
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-08-31T19:16:49
10 Spectrometer Frequency	125.70



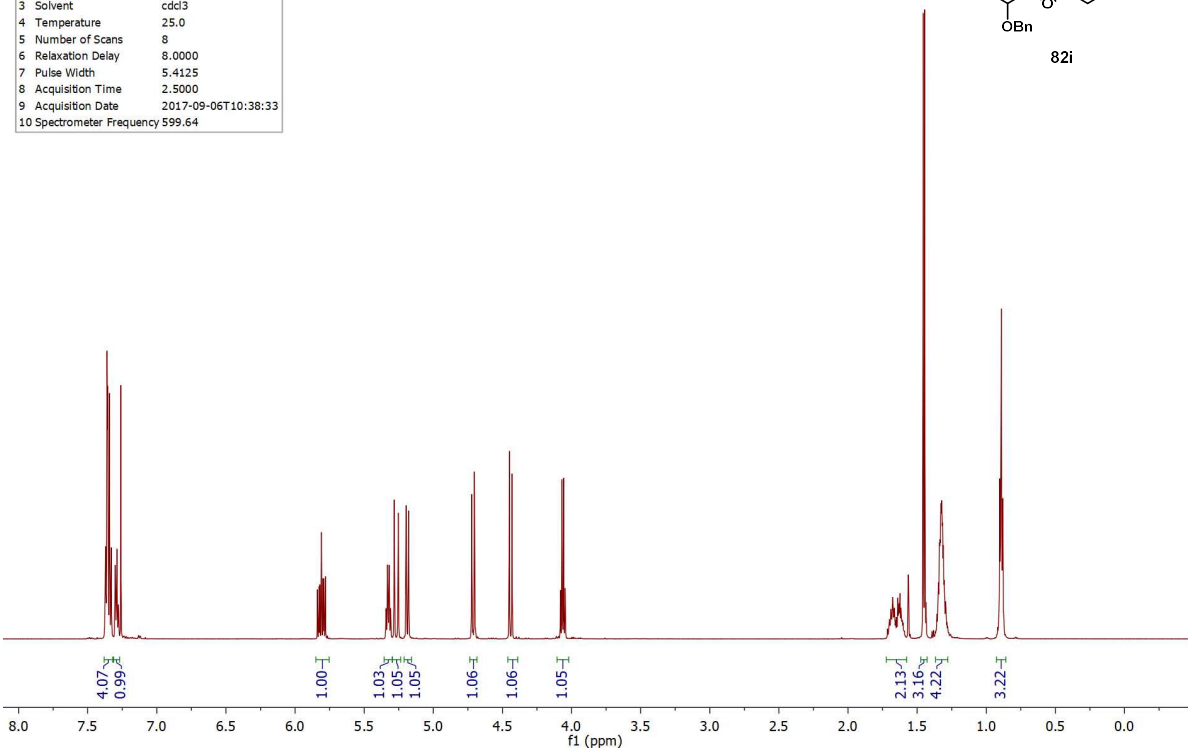
82h



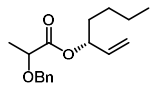
Parameter	Value
1 Title	JJL-3-052-a
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	5.4125
8 Acquisition Time	2.5000
9 Acquisition Date	2017-09-06T10:38:33
10 Spectrometer Frequency	599.64



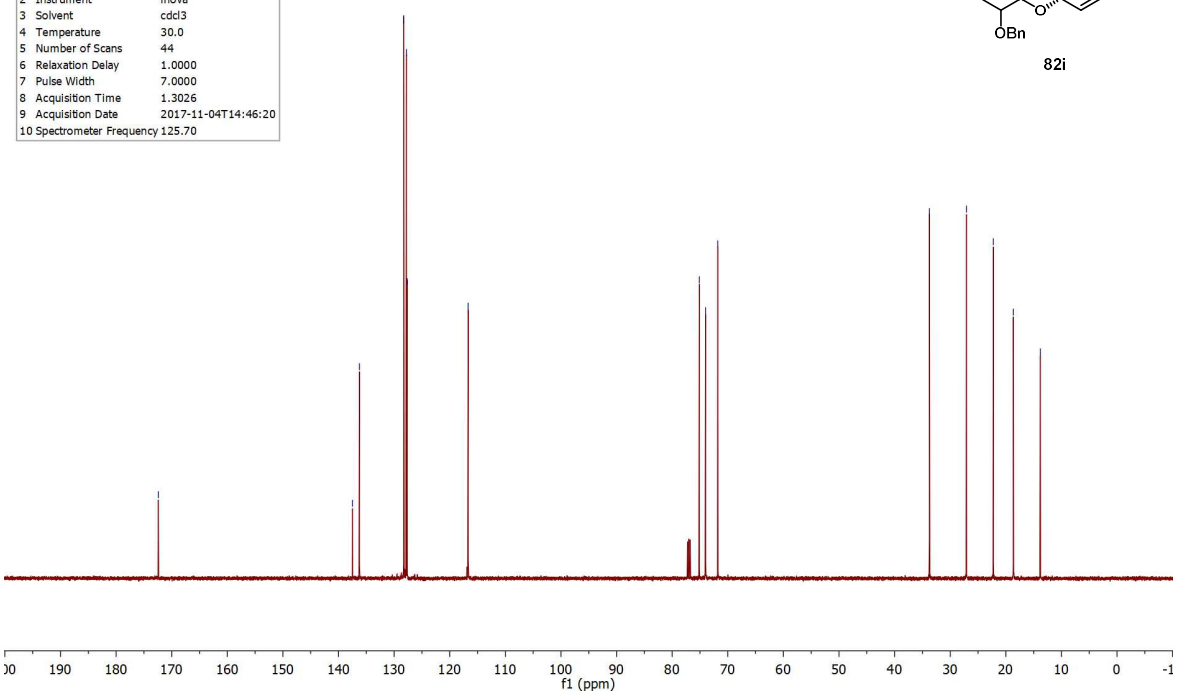
82i



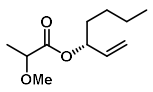
Parameter	Value
1 Title	JJL-3-052-13CNMR
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	44
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-11-04T14:46:20
10 Spectrometer Frequency	125.70



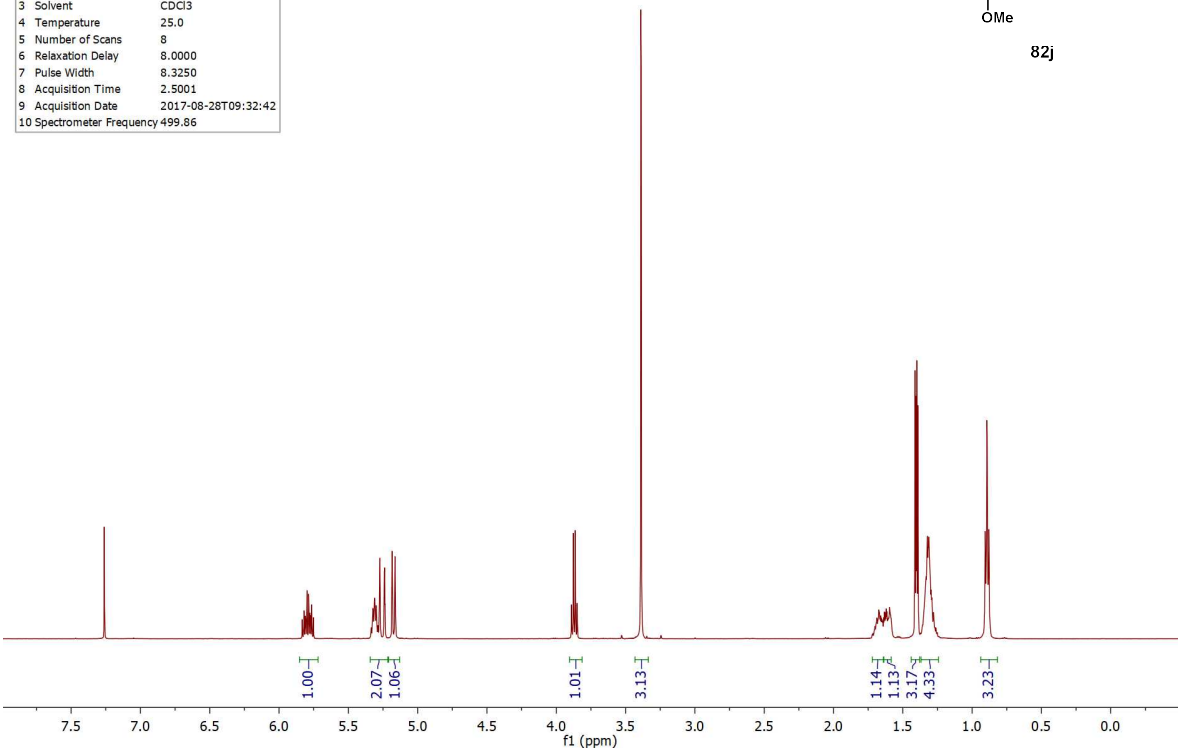
82i



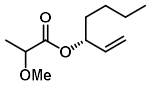
Parameter	Value
1 Title	JJL-3-035-a
2 Instrument	inova
3 Solvent	CDCl3
4 Temperature	25.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	8.3250
8 Acquisition Time	2.5001
9 Acquisition Date	2017-08-28T09:32:42
10 Spectrometer Frequency	499.86



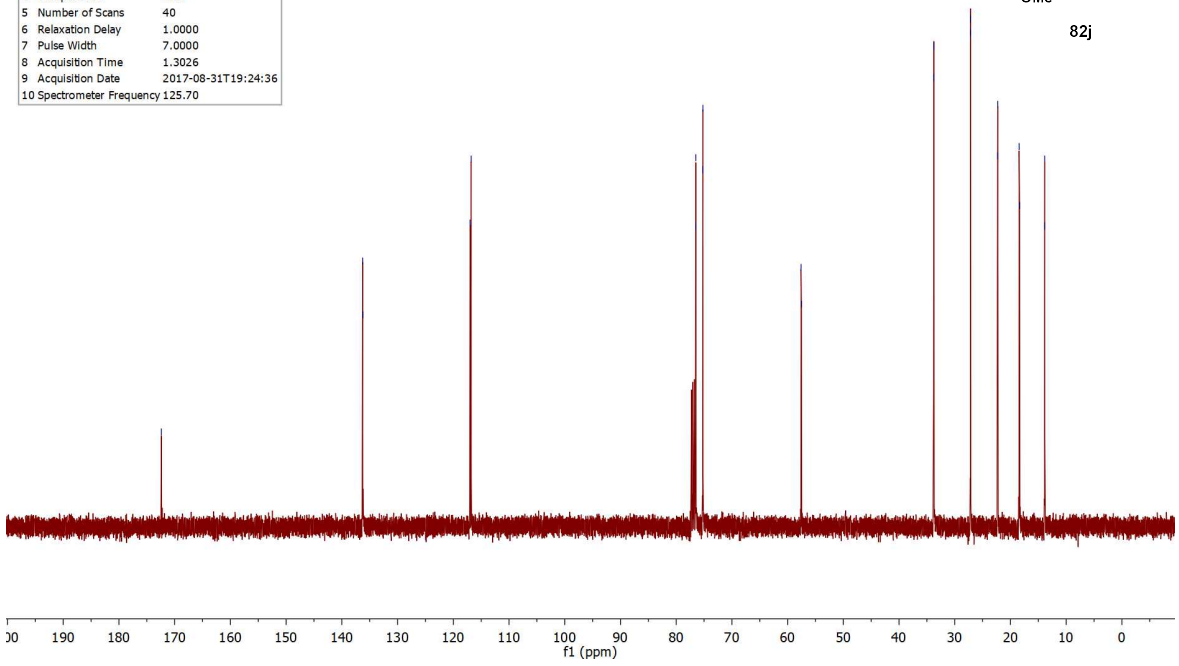
82j

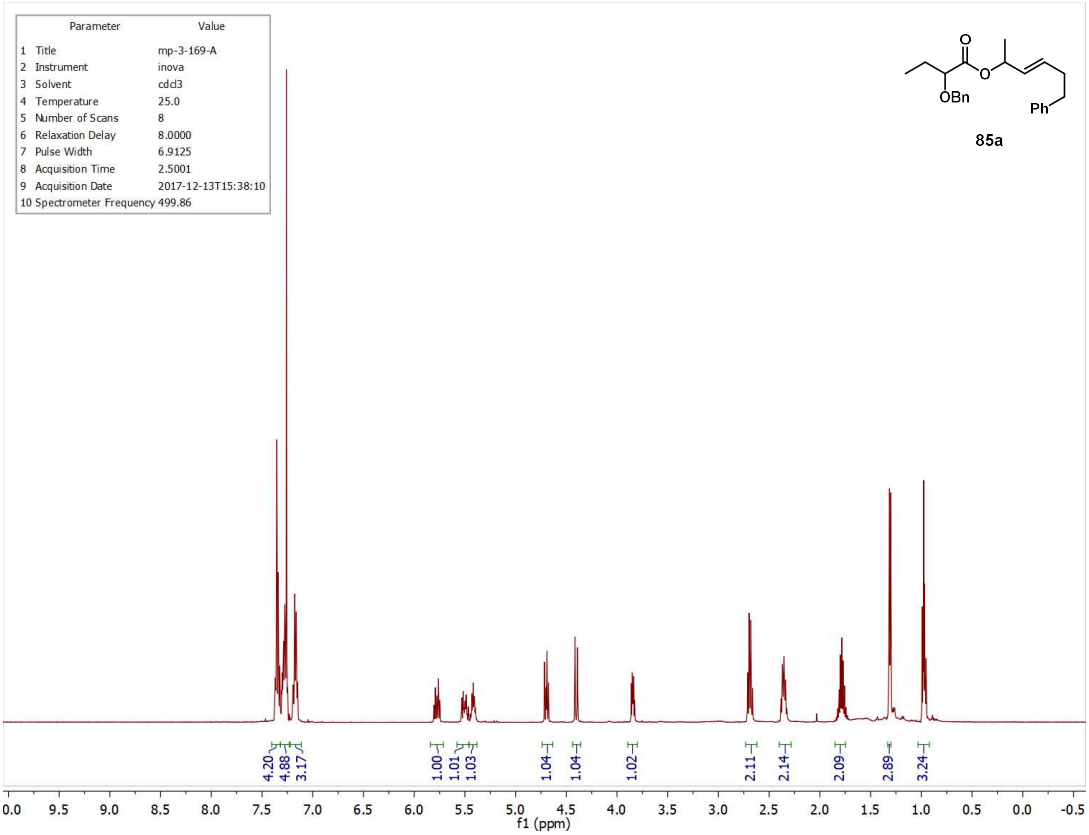


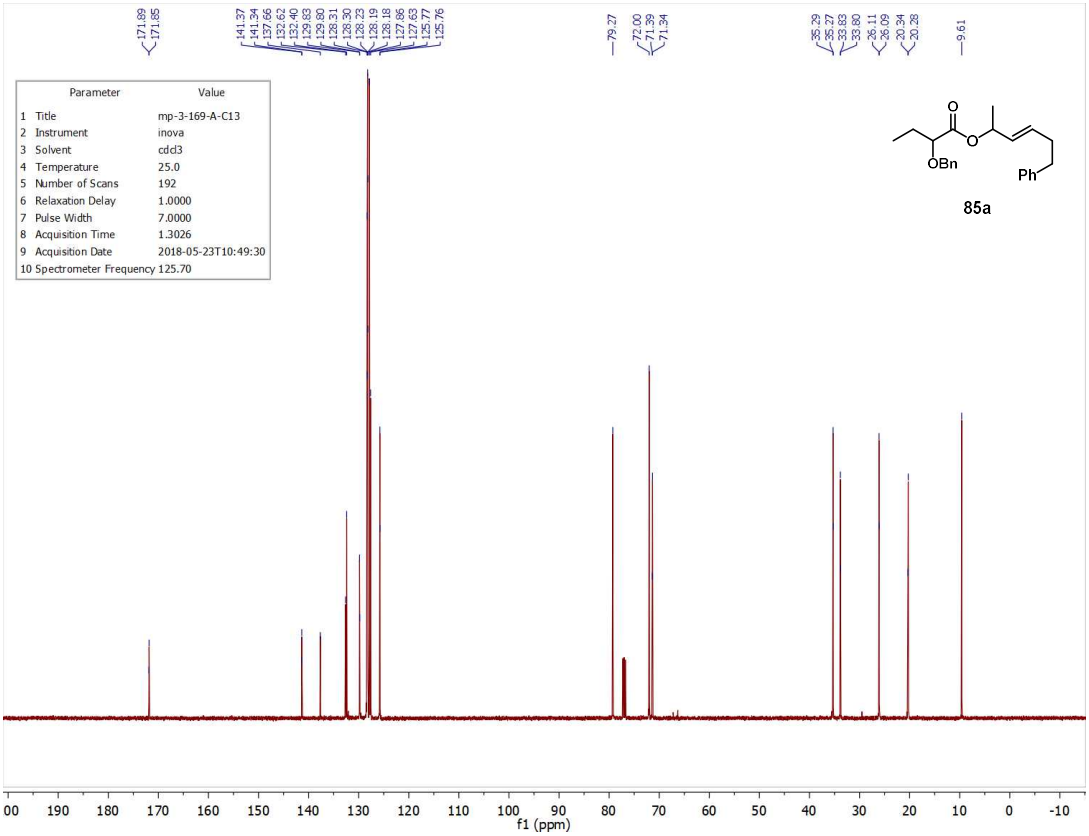
Parameter	Value
1 Title	JJL-3-035-a-13CNMR
2 Instrument	inova
3 Solvent	CDCl3
4 Temperature	25.0
5 Number of Scans	40
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-08-31T19:24:36
10 Spectrometer Frequency	125.70

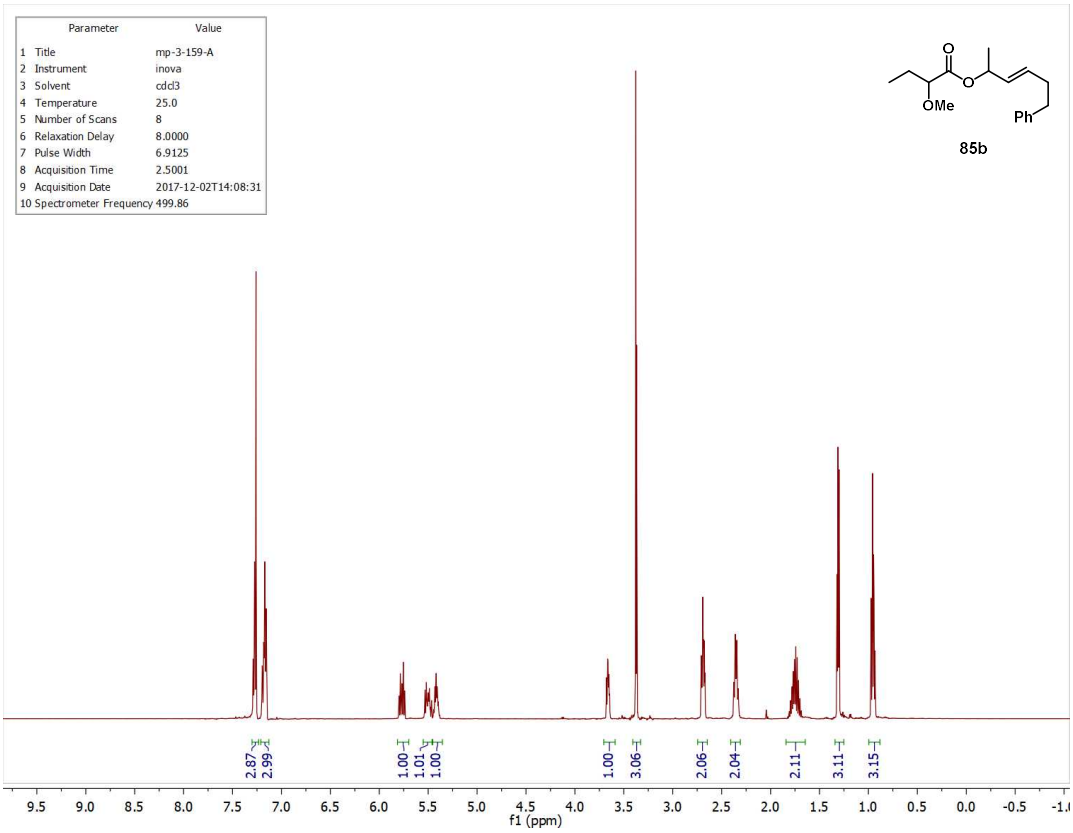


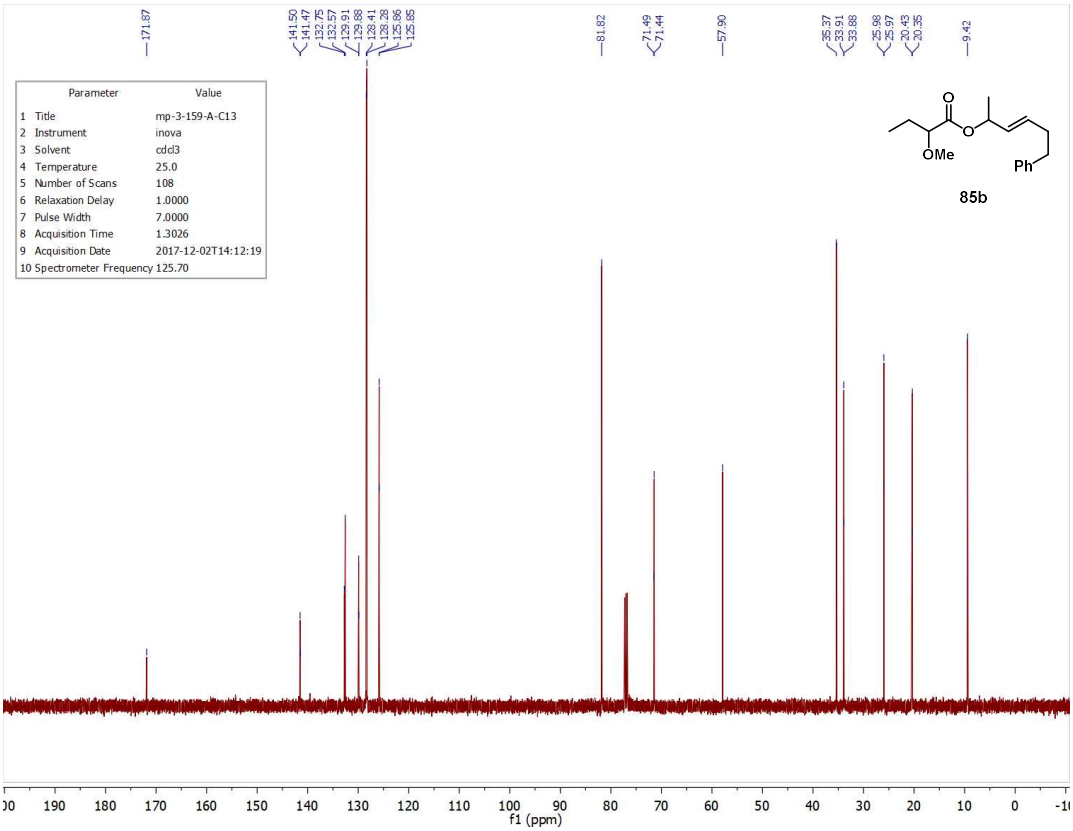
82j

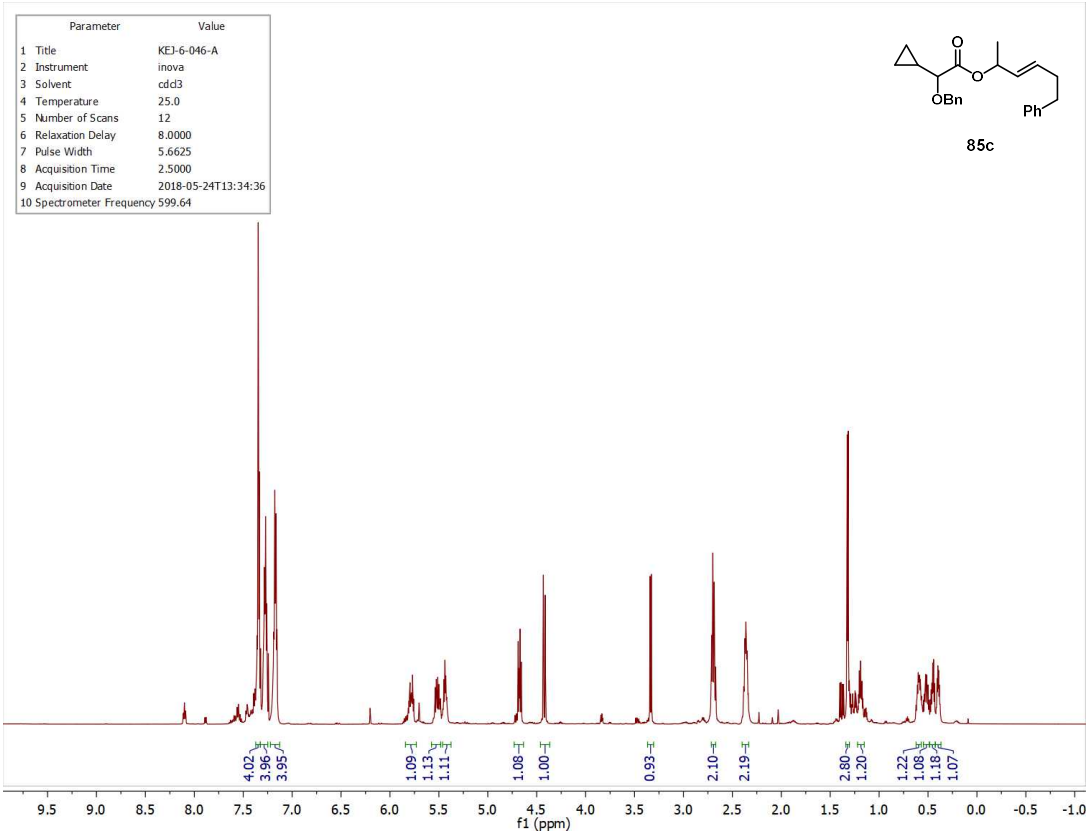


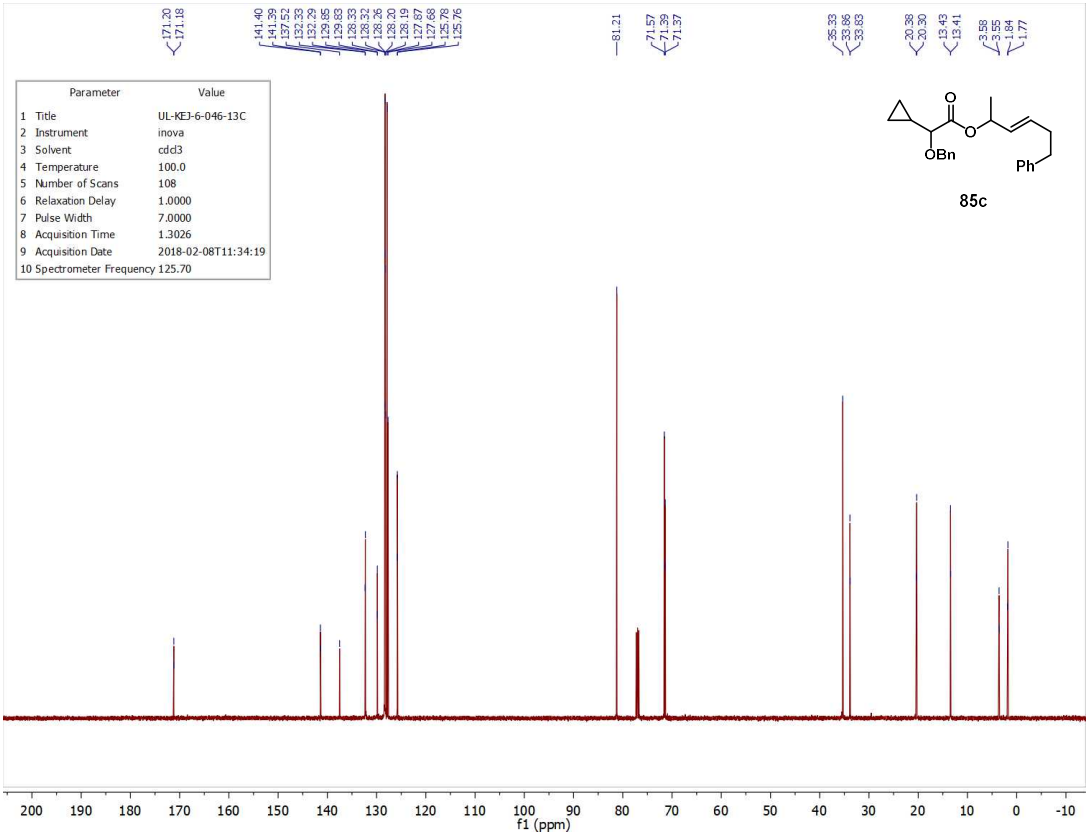

Parameter Value
1 Title mp-3-169-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-12-13T15:38:10
10 Spectrometer Frequency 499.86
OBn
Ph
85a
4.20
4.88
3.17
1.00
1.01
1.03
1.04
1.04
1.02
2.11
2.14
2.09
2.89
3.24
f1 (ppm)

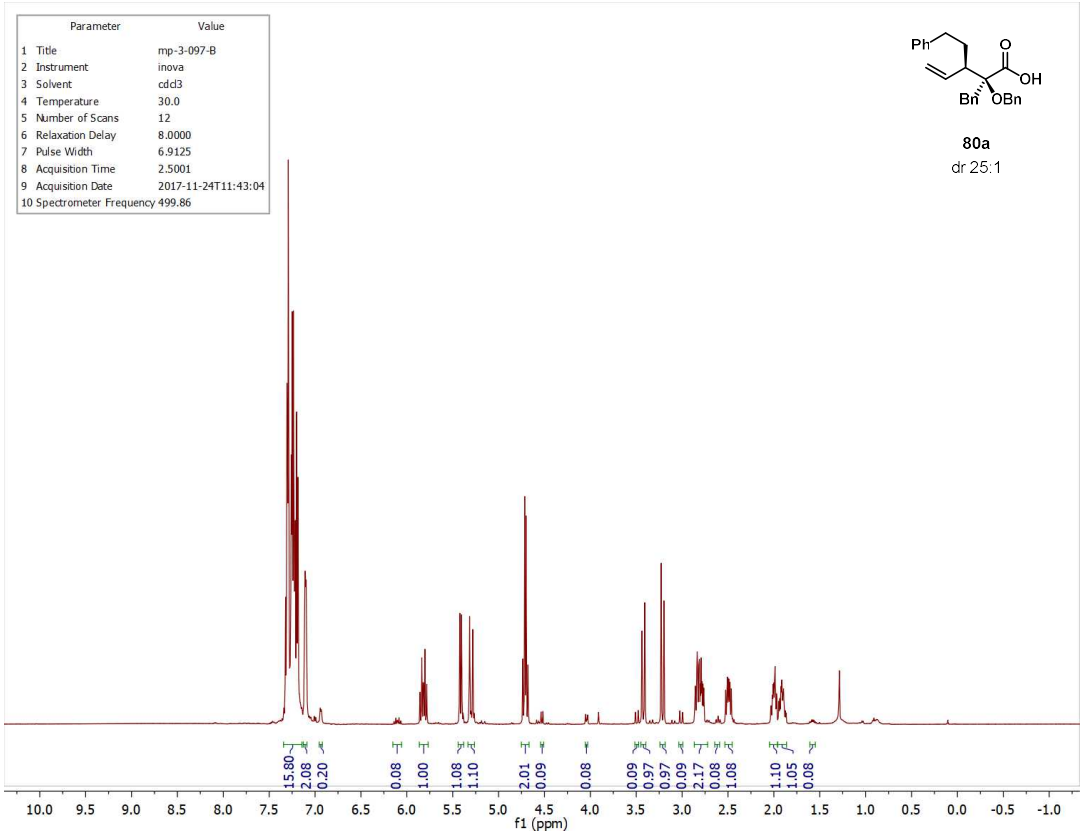

171.89
171.85
141.37
141.34
137.66
132.62
132.40
129.83
129.80
128.31
128.30
128.23
128.19
128.18
127.85
127.63
125.77
125.76
79.27
72.00
71.39
71.34
35.29
35.27
33.83
33.80
26.11
26.09
20.34
20.28
9.61
Parameter Value
1 Title mp-3-169-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 192
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2018-05-23T10:49:30
10 Spectrometer Frequency 125.70
OBn
Ph
85a
f1 (ppm)

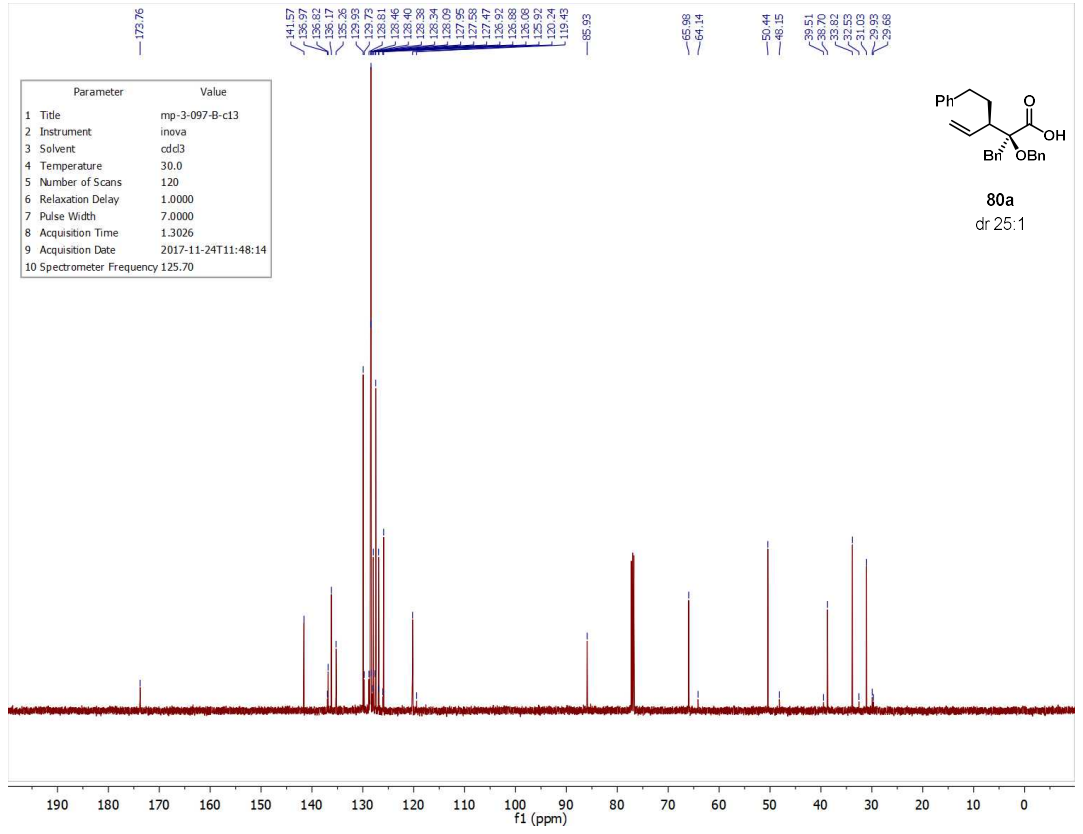

Parameter Value
1 Title mp-3-159-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-12-02T14:08:31
10 Spectrometer Frequency 499.86
OMe
Ph
85b
2.87
2.99
1.00
1.01
1.00
1.00
3.06
2.06
2.04
2.11
3.11
3.15
f1 (ppm)

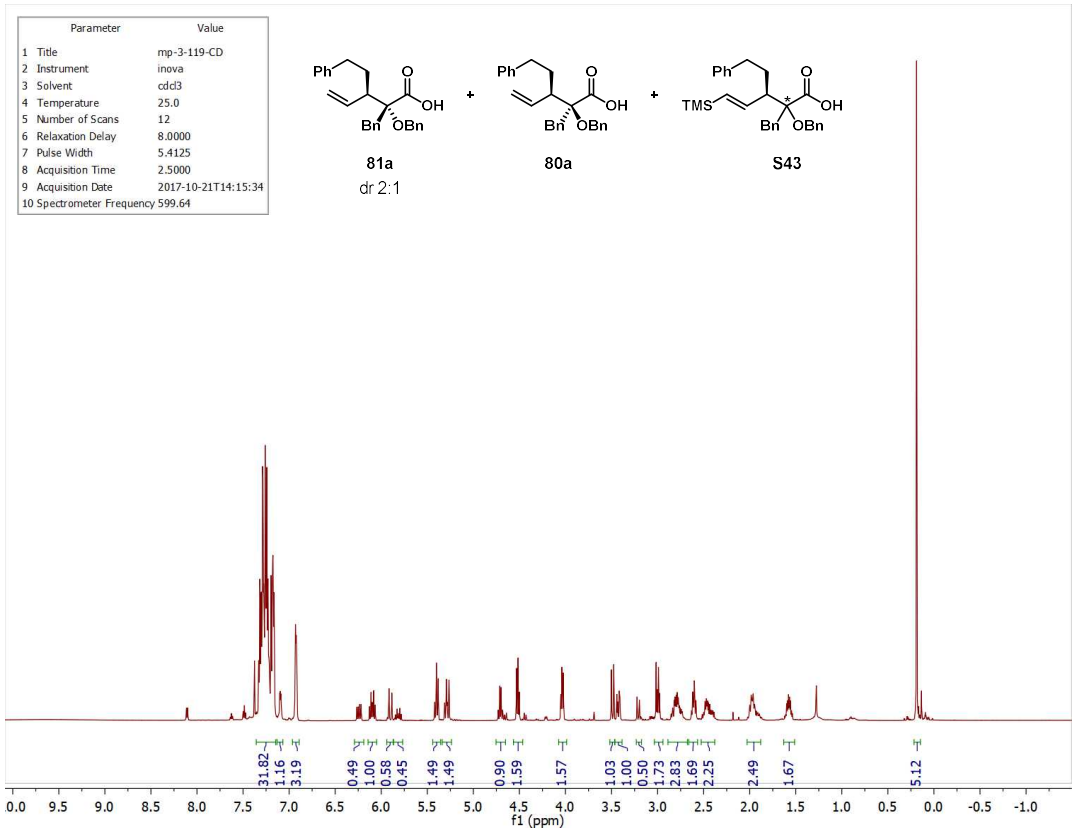

171.87
141.50
141.47
132.75
132.57
129.91
129.88
128.41
128.28
125.86
125.85
81.82
71.49
71.44
57.90
35.37
33.91
33.88
25.98
25.97
20.43
20.35
9.42
Parameter Value
1 Title mp-3-159-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 108
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-12-02T14:12:19
10 Spectrometer Frequency 125.70
OMe
Ph
85b
f1 (ppm)

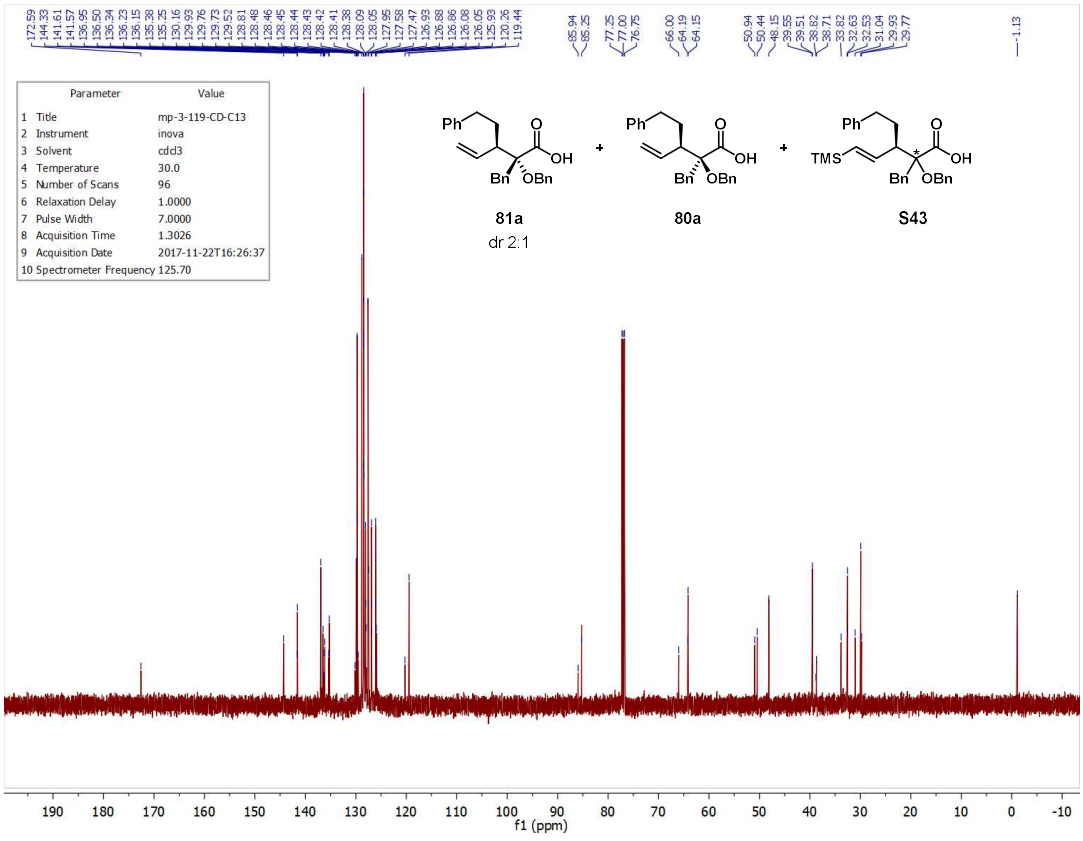

Parameter Value
1 Title KEJ-6-046-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2018-05-24T13:34:36
10 Spectrometer Frequency 599.64
OBn
Ph
85c
4.02 3.96 3.95 1.09 1.13 1.11 1.08 1.00 0.93 2.10 2.19 2.80 1.20 1.22 1.08 1.18 1.07
f1 (ppm)

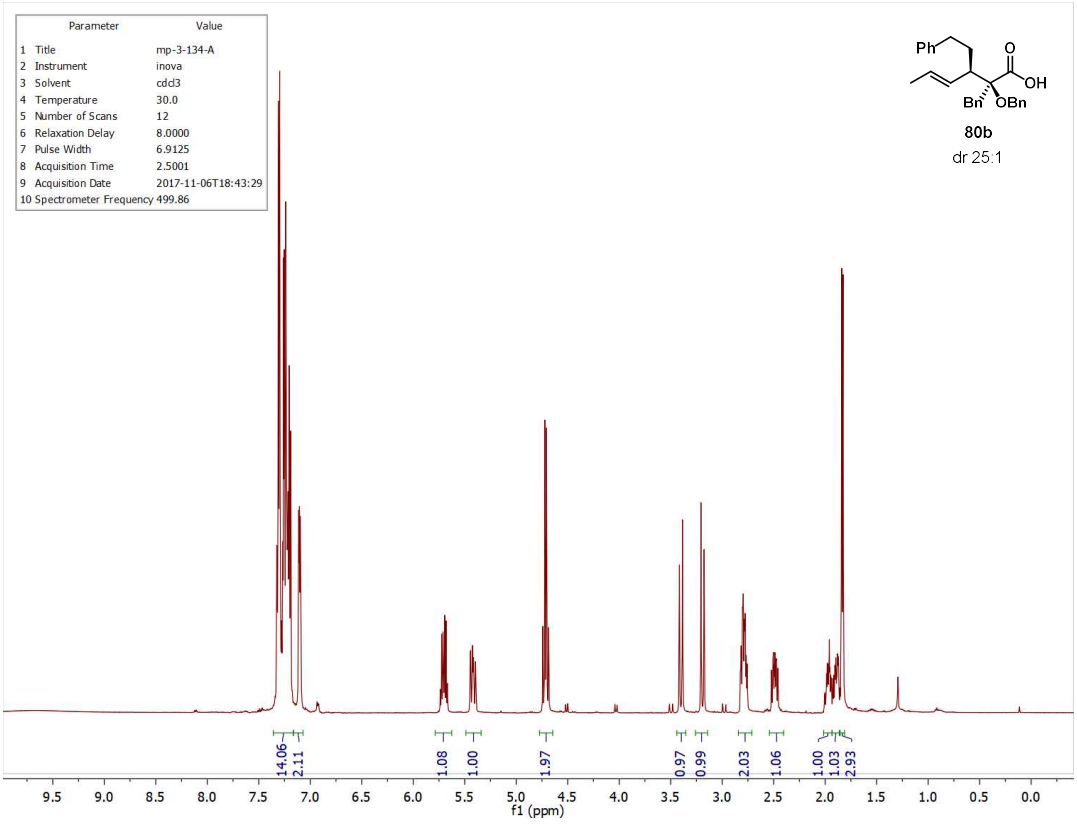

171.20 171.18 141.40 141.39 137.52 132.33 132.29 129.85 129.83 128.33 128.32 128.26 128.20 128.19 127.87 127.68 125.78 125.76 81.21 71.57 71.39 71.37 35.33 33.86 33.83 20.38 20.30 13.43 13.41 3.58 3.55 1.84 1.77
Parameter Value
1 Title UL-KEJ-6-046-13C
2 Instrument inova
3 Solvent cdcl3
4 Temperature 100.0
5 Number of Scans 108
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2018-02-08T11:34:19
10 Spectrometer Frequency 125.70
OBn
Ph
85c
f1 (ppm)

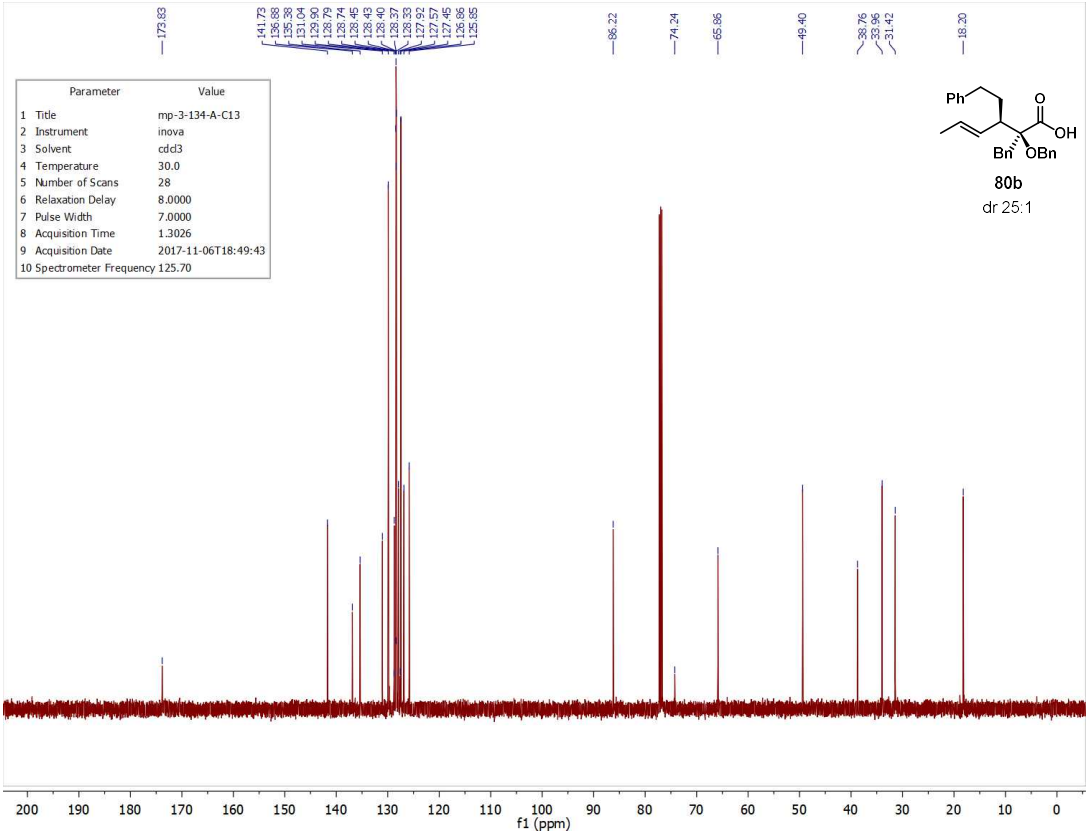

Parameter Value
1 Title mp-3-097-B
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-24T11:43:04
10 Spectrometer Frequency 499.86
Ph
O
OH
Bn
OBn
80a
dr 25:1
15.80 2.08 0.20 0.08 1.00 1.08 1.10 2.01 0.09 0.08 0.09 0.97 0.97 0.09 2.17 0.08 1.08 1.10 1.05 0.08
f1 (ppm)

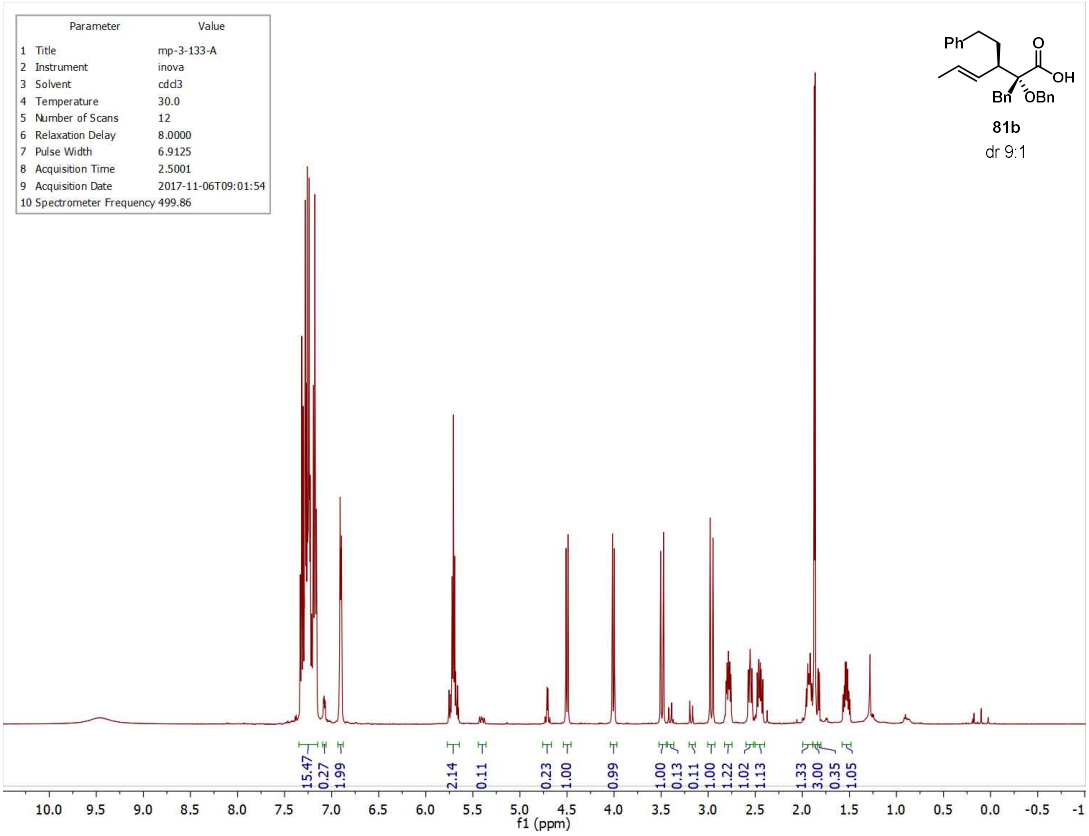

173.76
141.57 136.97 136.82 136.17 135.26 129.93 129.73 128.81 128.46 128.40 128.38 128.34 128.09 127.95 127.58 127.47 126.92 126.88 126.08 125.92 120.24 119.45
85.93
65.98 64.14
50.44 48.15
39.51 38.70 33.82 32.53 31.03 29.93 29.68
Parameter Value
1 Title mp-3-097-B-c13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 120
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-24T11:48:14
10 Spectrometer Frequency 125.70
Ph
O
OH
Bn
OBn
80a
dr 25:1
f1 (ppm)

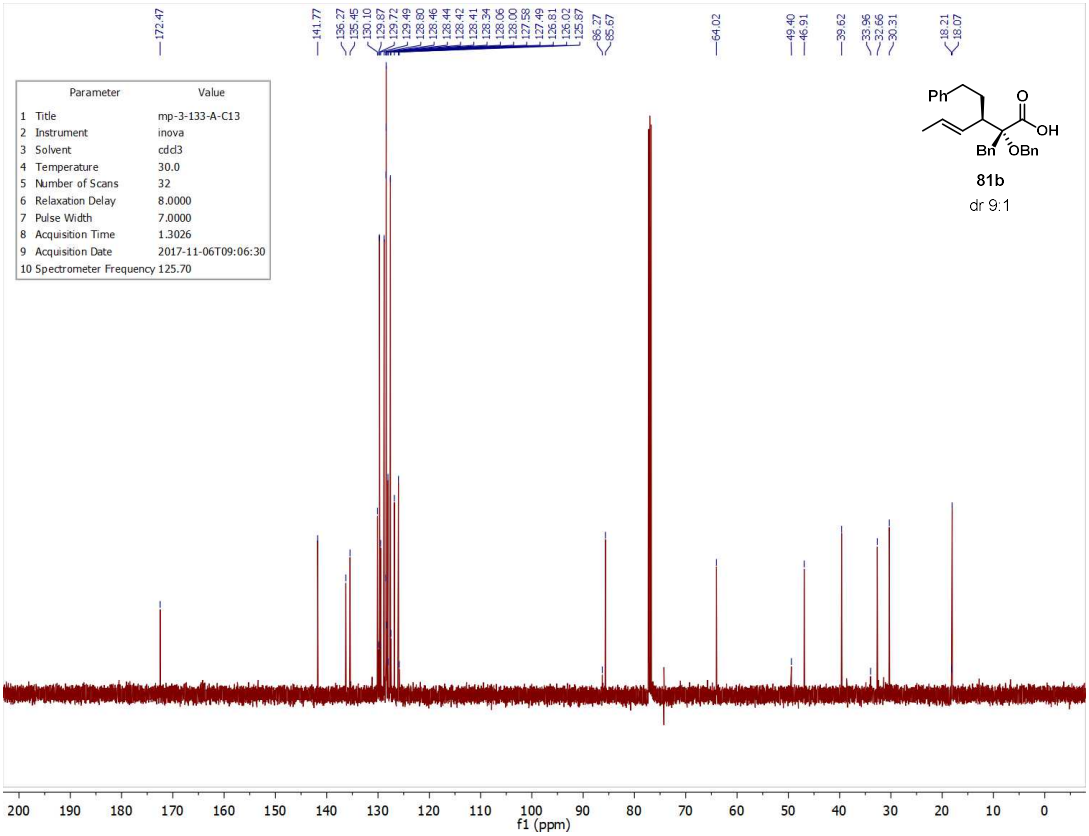

Parameter Value
1 Title mp-3-119-CD
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 5.4125
8 Acquisition Time 2.5000
9 Acquisition Date 2017-10-21T14:15:34
10 Spectrometer Frequency 599.64
81a
dr 2:1
80a
S43
31.82 1.16 3.19 0.49 1.00 0.58 0.45 1.49 1.49 0.90 1.59 1.57 1.03 1.00 0.50 1.73 2.83 1.69 2.25 2.49 1.67 5.12
f1 (ppm)


Parameter Value
1 Title mp-3-119-CD-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 96
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-22T16:26:37
10 Spectrometer Frequency 125.70
81a
dr 2:1
80a
S43
f1 (ppm)

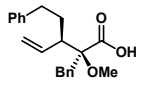

Parameter Value
1 Title mp-3-134-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-06T18:43:29
10 Spectrometer Frequency 499.86
Ph
O
OH
Bn
OBn
80b
dr 25:1
14.06
2.11
1.08
1.00
1.97
0.97
0.99
2.03
1.06
1.00
1.03
2.93
f1 (ppm)


173.63
141.73
136.88
135.38
131.04
129.90
128.79
128.74
128.45
128.43
128.40
128.37
128.33
127.92
127.57
127.45
126.86
125.85
86.22
74.24
65.86
49.40
38.76
38.45
31.42
18.20
Parameter Value
1 Title mp-3-134-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 28
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-06T18:49:43
10 Spectrometer Frequency 125.70
Ph
O
OH
Bn
OBn
80b
dr 25:1
f1 (ppm)

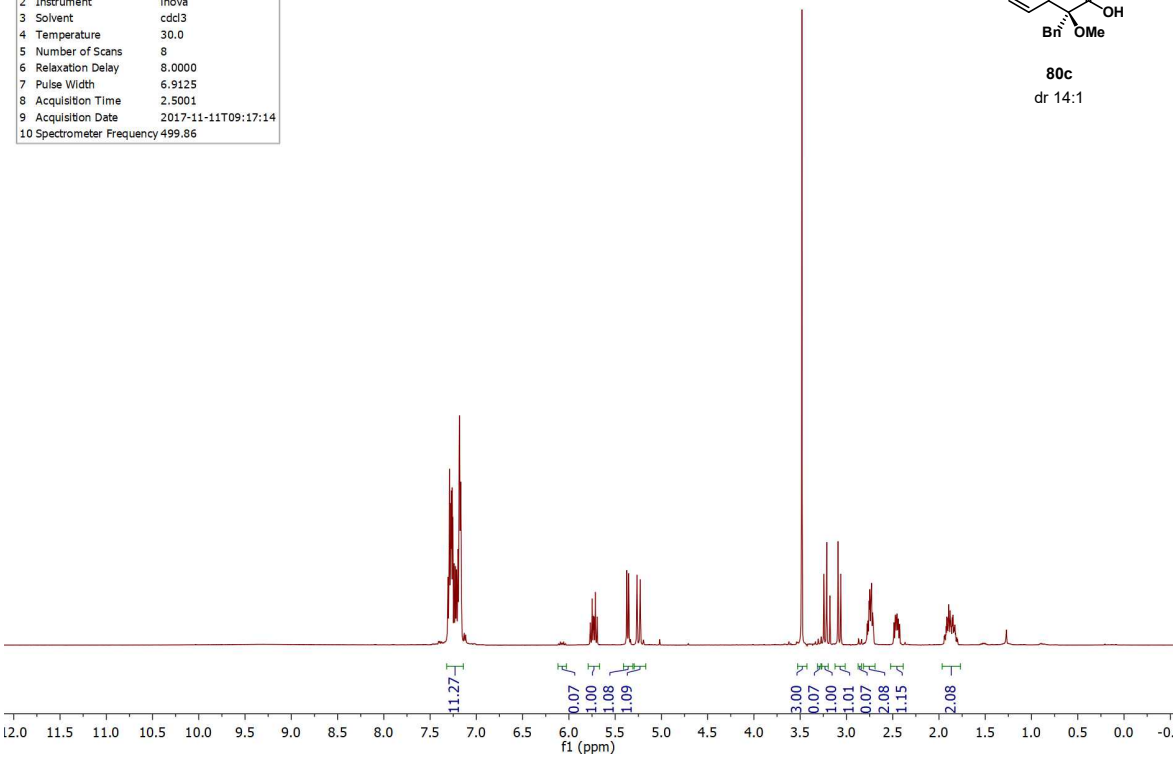

Parameter Value
1 Title mp-3-133-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-06T09:01:54
10 Spectrometer Frequency 499.86
Ph
O
OH
Bn
OBn
81b
dr 9:1
15.47 0.27 1.99 2.14 0.11 0.23 1.00 0.99 1.00 0.13 0.11 1.00 1.22 1.02 1.13 1.33 3.00 0.35 1.05
f1 (ppm)

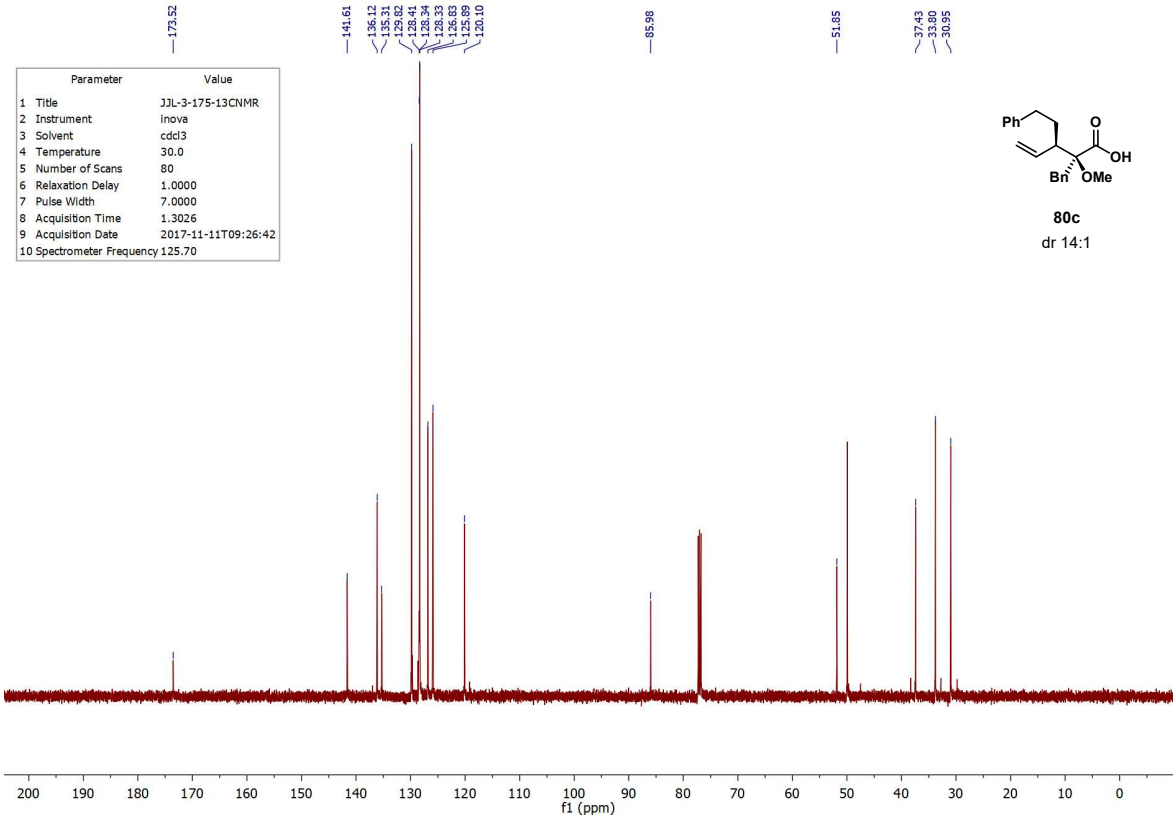

172.47
141.77
136.27
135.45
130.10
129.87
129.72
129.49
128.80
128.46
128.44
128.42
128.41
128.34
128.06
128.00
127.58
127.49
126.81
126.02
125.67
86.27
65.67
64.02
49.40
46.91
39.62
33.96
32.66
30.31
18.21
18.07
Parameter Value
1 Title mp-3-133-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 32
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-06T09:06:30
10 Spectrometer Frequency 125.70
Ph
O
OH
Bn
OBn
81b
dr 9:1
f1 (ppm)

Parameter	Value
1 Title	JJL-3-175-b
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.9125
8 Acquisition Time	2.5001
9 Acquisition Date	2017-11-11T09:17:14
10 Spectrometer Frequency	499.86



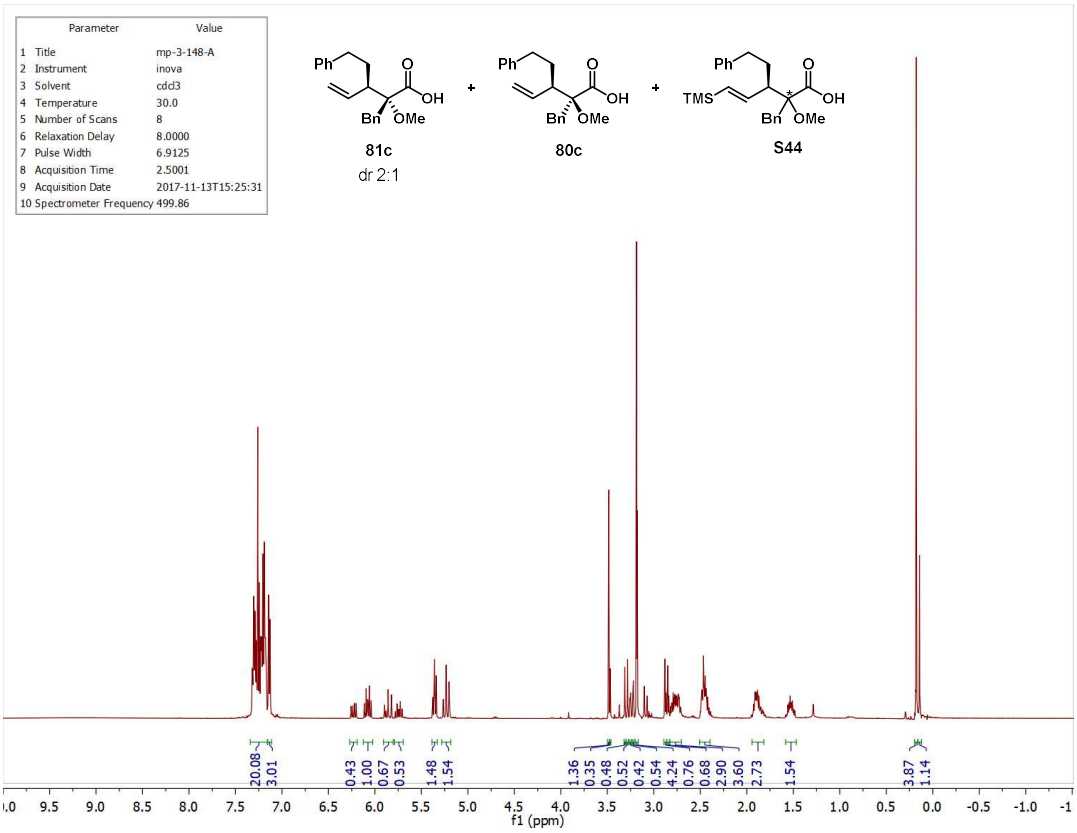
80c
dr 14:1

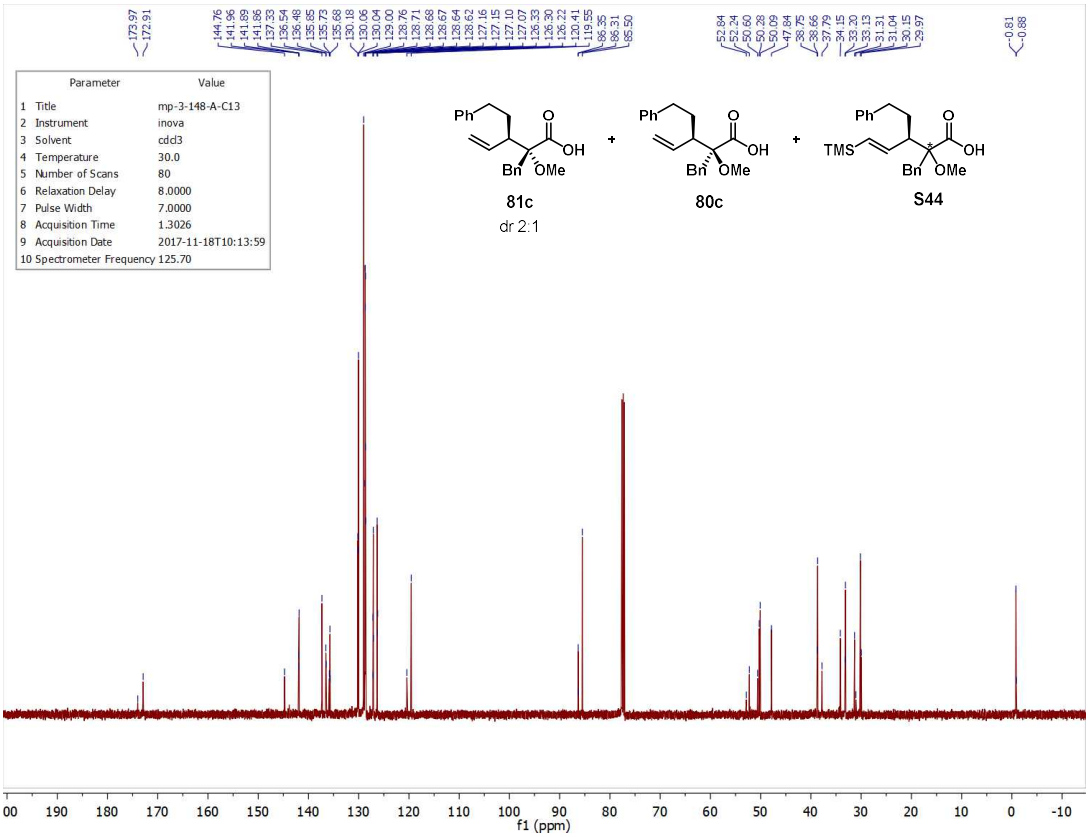




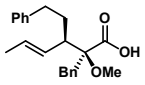
Parameter	Value
1 Title	JJL-3-175-13CNMR
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	80
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-11-11T09:26:42
10 Spectrometer Frequency	125.70

80c
dr 14:1


Parameter Value
1 Title mp-3-148-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-13T15:25:31
10 Spectrometer Frequency 499.86
81c
dr 2:1
80c
S44
f1 (ppm)

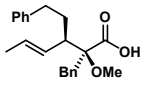

Parameter Value
1 Title mp-3-148-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 80
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-18T10:13:59
10 Spectrometer Frequency 125.70
81c
dr 2:1
80c
S44
f1 (ppm)

Parameter	Value
1 Title	JJL-3-157-b
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.9125
8 Acquisition Time	2.5001
9 Acquisition Date	2017-11-10T08:20:03
10 Spectrometer Frequency	499.86

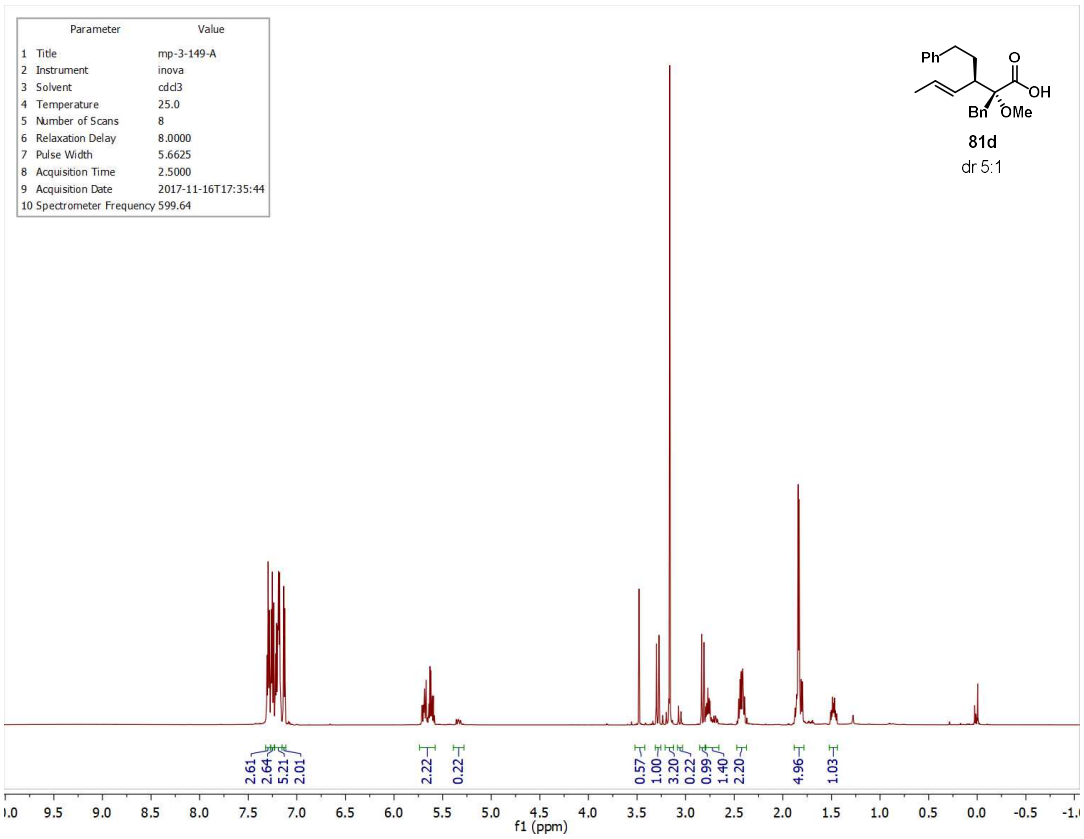


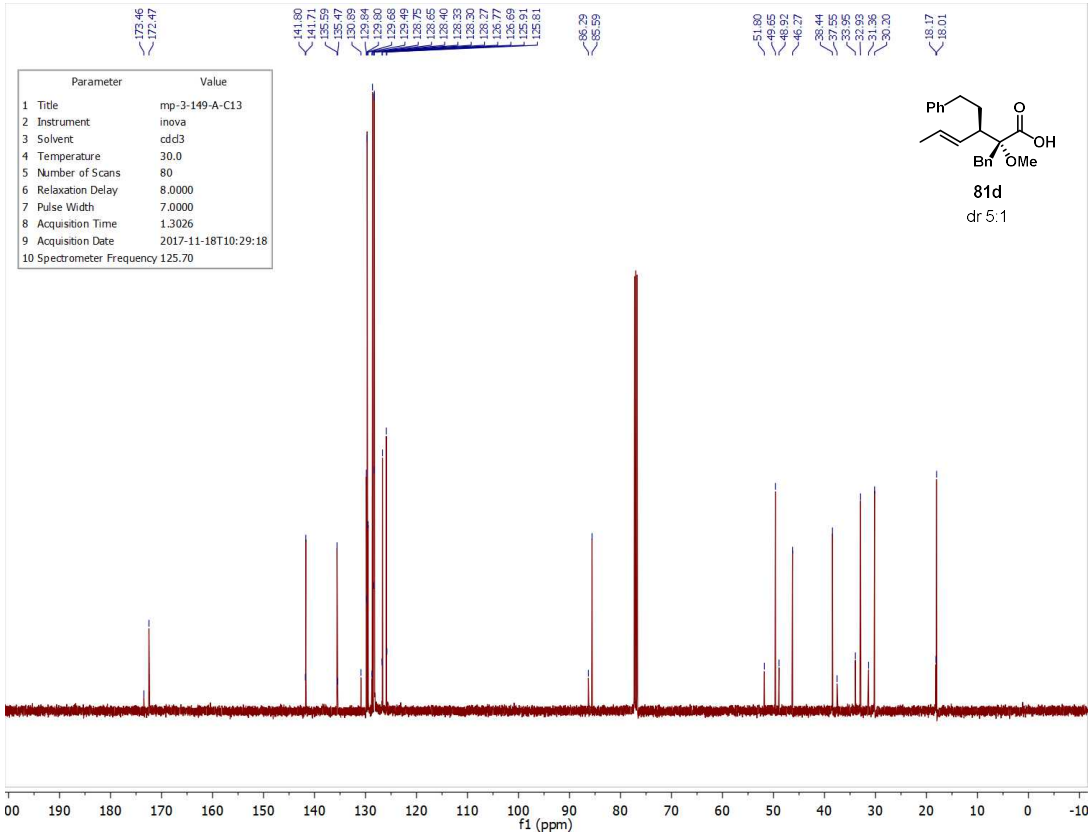
80d
dr 17:1

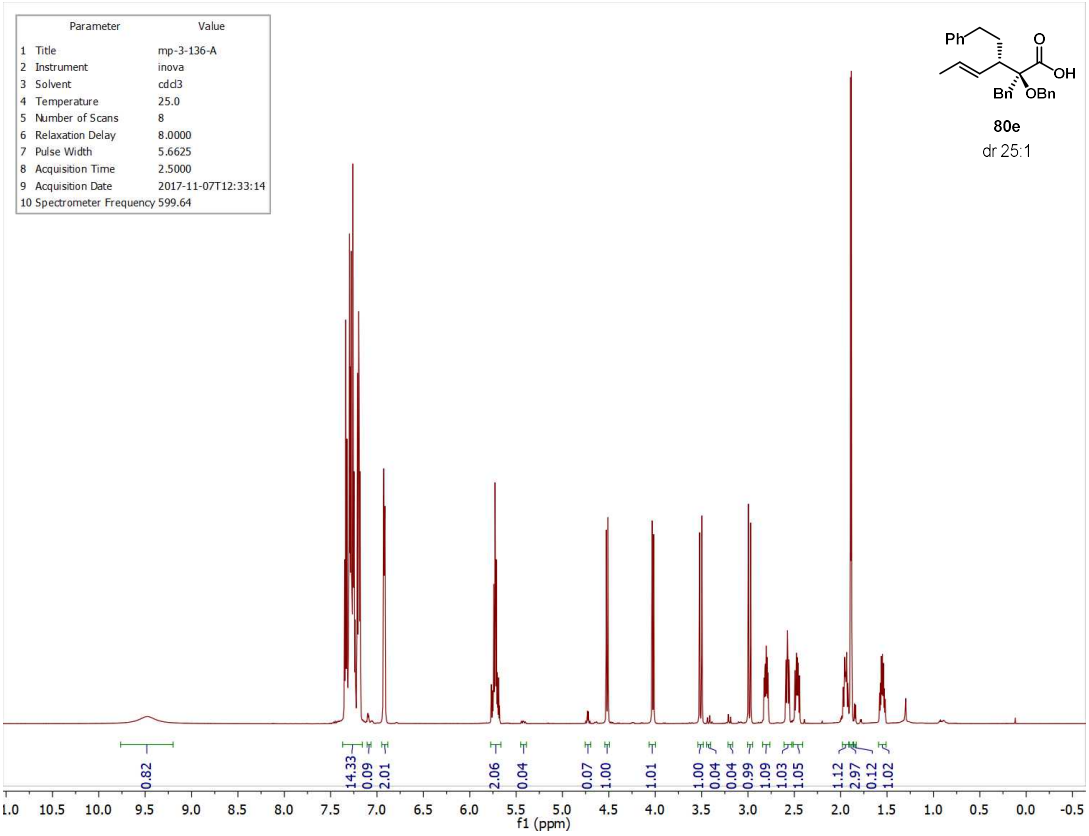
Parameter	Value
1 Title	JJL-3-157-13CNMR
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	104
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-11-10T08:39:51
10 Spectrometer Frequency	125.70

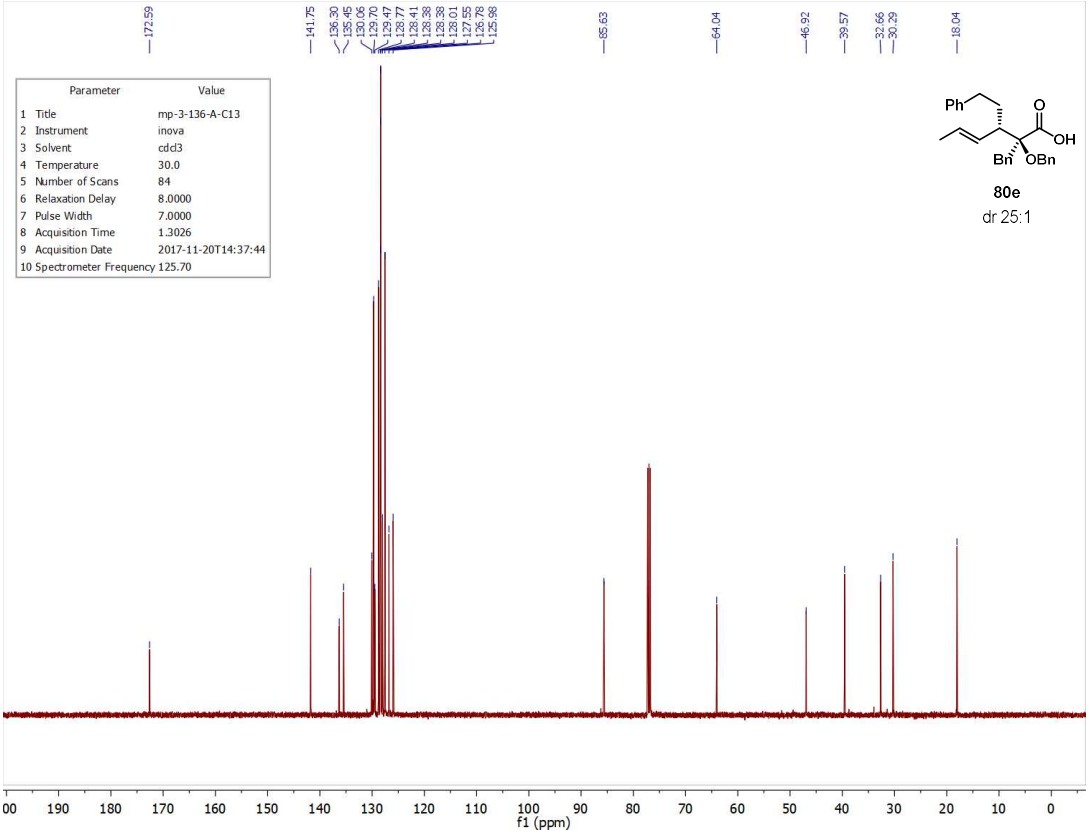


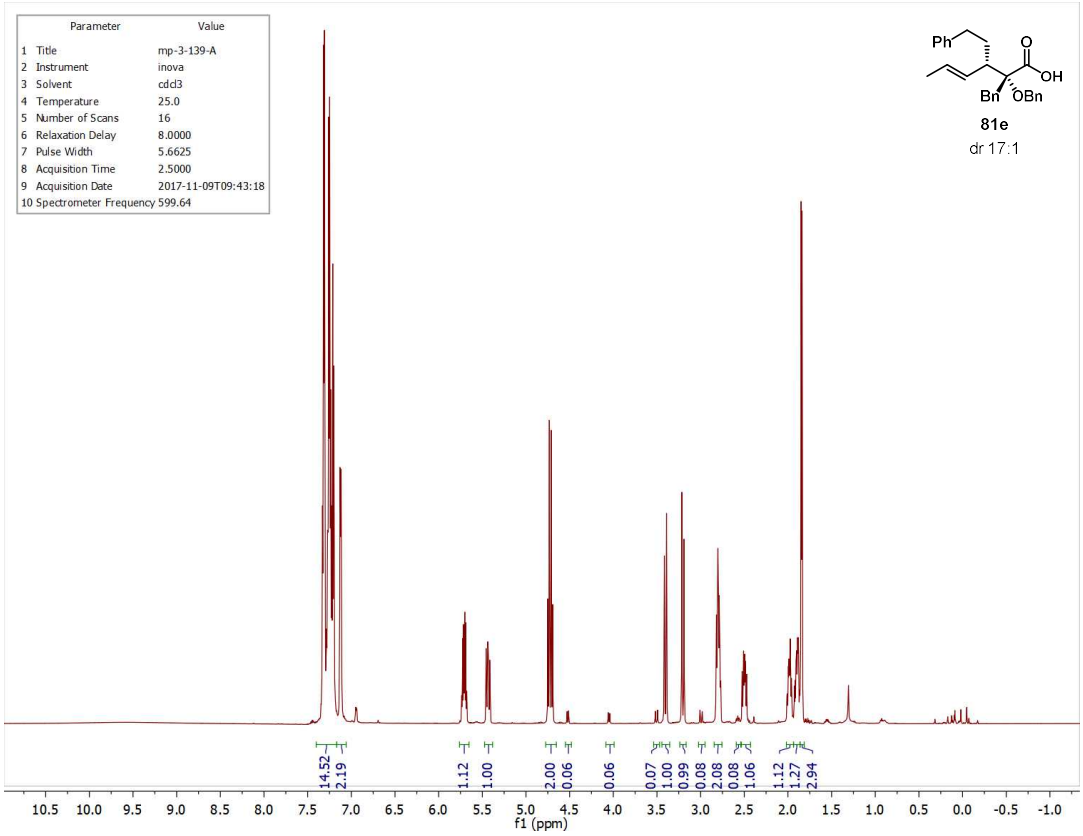
80d
dr 17:1

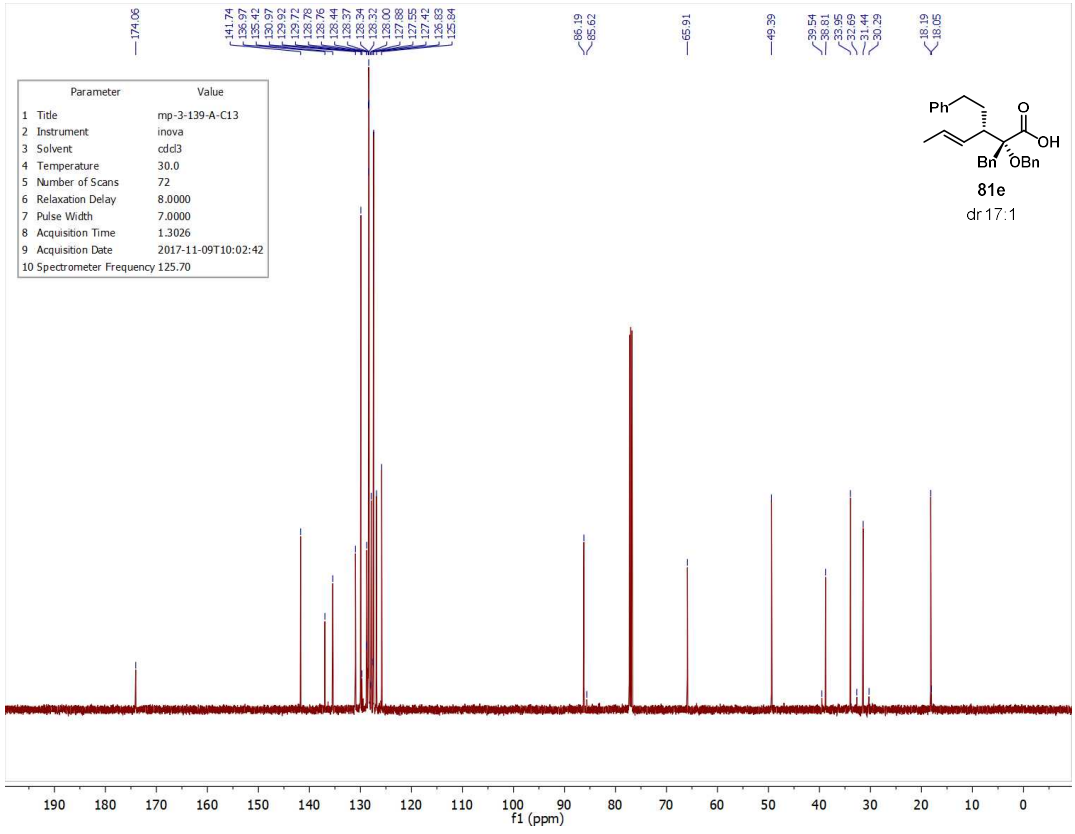

Parameter Value
1 Title mp-3-149-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2017-11-16T17:35:44
10 Spectrometer Frequency 599.64
Ph
O
OH
Bn
OMe
81d
dr 5:1
2.61
2.64
5.21
2.01
2.22
0.22
0.57
1.00
3.20
0.22
0.99
1.40
2.20
4.96
1.03
f1 (ppm)


173.46
172.47
141.80
141.71
135.59
135.47
130.89
129.84
129.80
129.68
129.49
128.75
128.65
128.40
128.33
128.30
128.27
126.77
126.69
125.91
125.81
86.29
85.59
51.80
49.65
48.92
46.27
38.44
37.55
33.95
32.93
31.36
30.20
18.17
18.01
Parameter Value
1 Title mp-3-149-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 80
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-18T10:29:18
10 Spectrometer Frequency 125.70
Ph
O
OH
Bn
OMe
81d
dr 5:1
f1 (ppm)

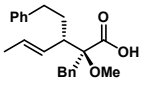

Parameter Value
1 Title mp-3-136-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2017-11-07T12:33:14
10 Spectrometer Frequency 599.64
Ph
O
OH
Bn
OBn
80e
dr 25:1
0.82
14.33
0.09
2.01
2.06
0.04
0.07
1.00
1.01
1.00
0.04
0.04
0.99
1.09
1.03
1.05
1.12
2.97
0.12
1.02
f1 (ppm)


172.59
141.75
136.30
135.45
130.06
129.70
129.47
128.77
128.41
128.38
128.01
127.55
126.78
125.98
85.63
64.04
46.92
39.57
32.66
30.29
18.04
Parameter Value
1 Title mp-3-136-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 84
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-20T14:37:44
10 Spectrometer Frequency 125.70
Ph
O
OH
Bn
OBn
80e
dr 25:1
f1 (ppm)

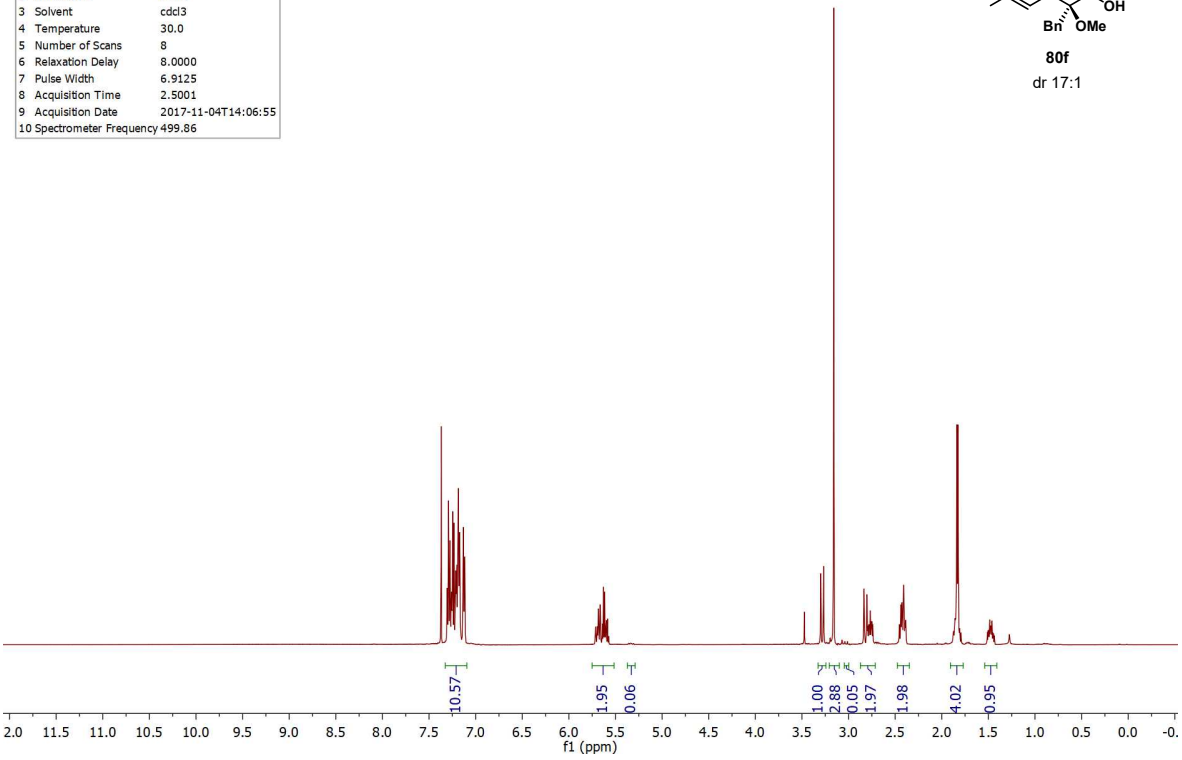

Parameter Value
1 Title mp-3-139-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2017-11-09T09:43:18
10 Spectrometer Frequency 599.64
Ph
O
OH
Bn
OBn
81e
dr 17:1
14.52
2.19
1.12
1.00
2.00
0.06
0.06
0.07
1.00
0.99
0.08
2.08
0.08
1.06
1.12
1.27
2.94
f1 (ppm)


174.06
141.74
136.97
135.42
130.97
129.92
129.72
128.76
128.76
128.44
128.37
128.34
128.32
128.00
127.88
127.55
127.42
126.83
125.84
86.19
85.62
65.91
49.39
39.54
38.81
33.95
32.69
31.44
30.29
18.19
18.05
Parameter Value
1 Title mp-3-139-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 72
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-09T10:02:42
10 Spectrometer Frequency 125.70
Ph
O
OH
Bn
OBn
81e
dr 17:1
f1 (ppm)

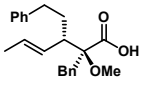
Parameter	Value
1 Title	JJL-3-159-b
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.9125
8 Acquisition Time	2.5001
9 Acquisition Date	2017-11-04T14:06:55
10 Spectrometer Frequency	499.86



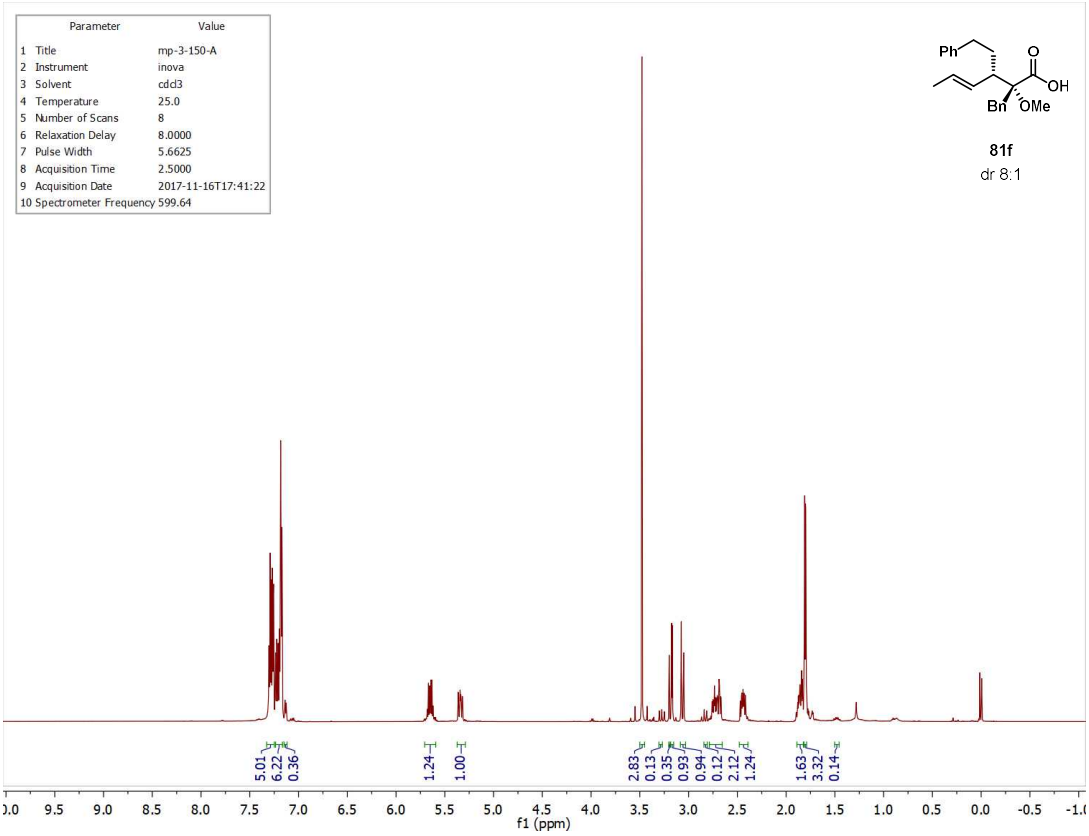
80f
dr 17:1

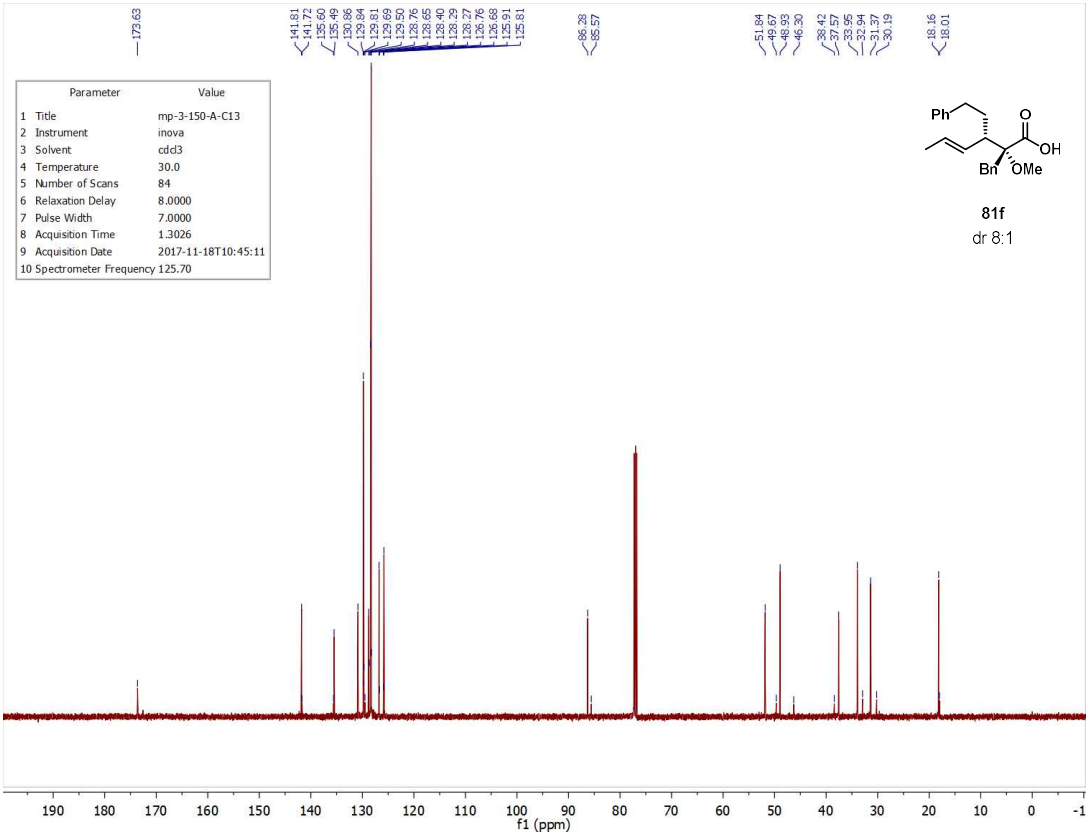


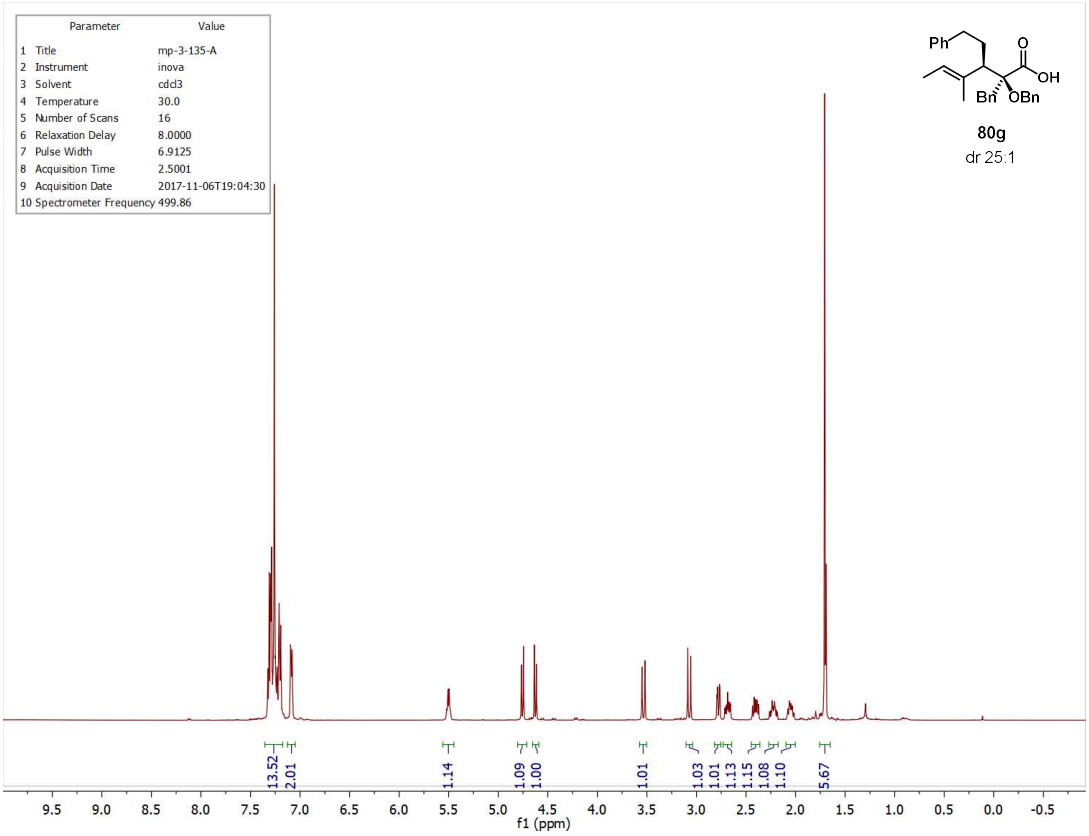
Parameter	Value
1 Title	JJL-3-159-13CNMR
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	92
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-11-04T15:13:38
10 Spectrometer Frequency	125.70

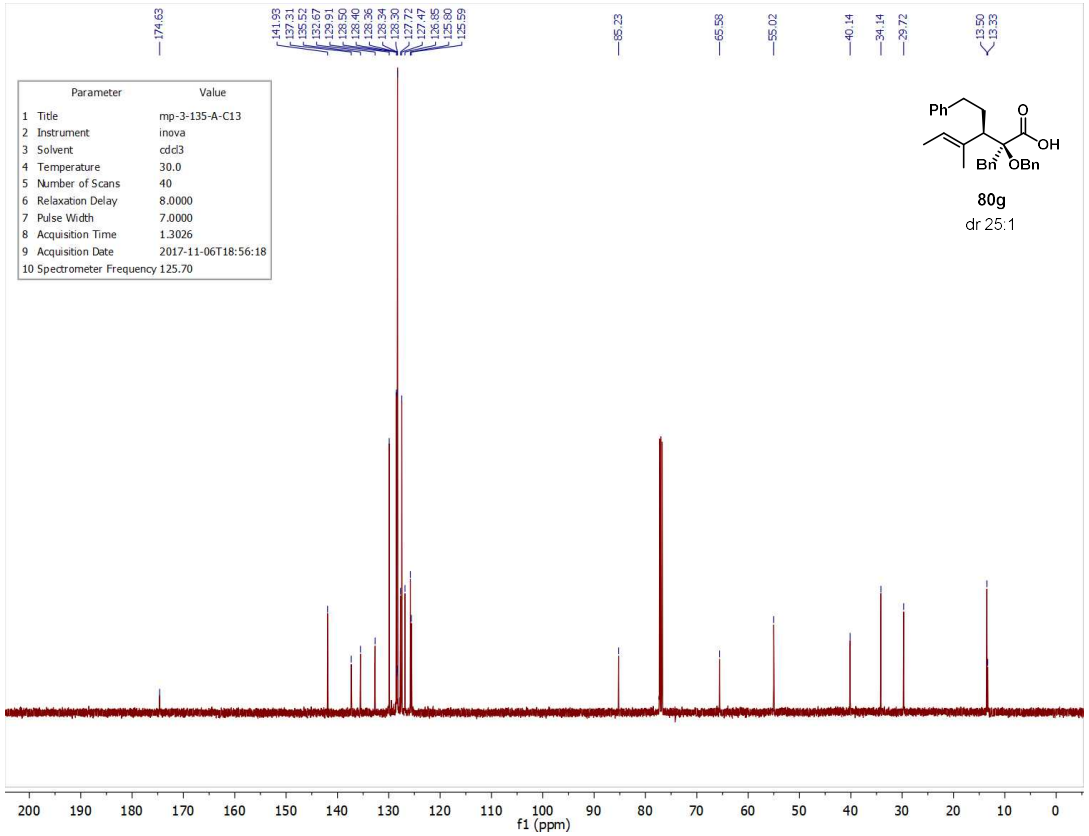


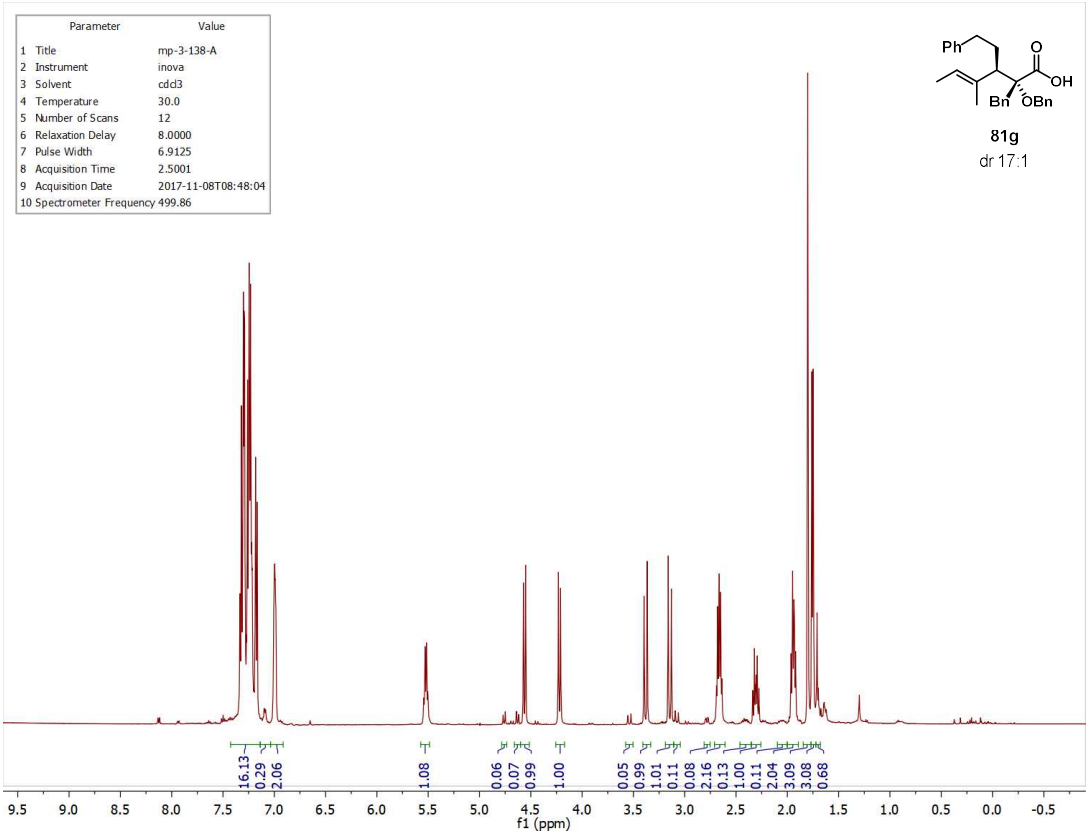
80f
dr 17:1

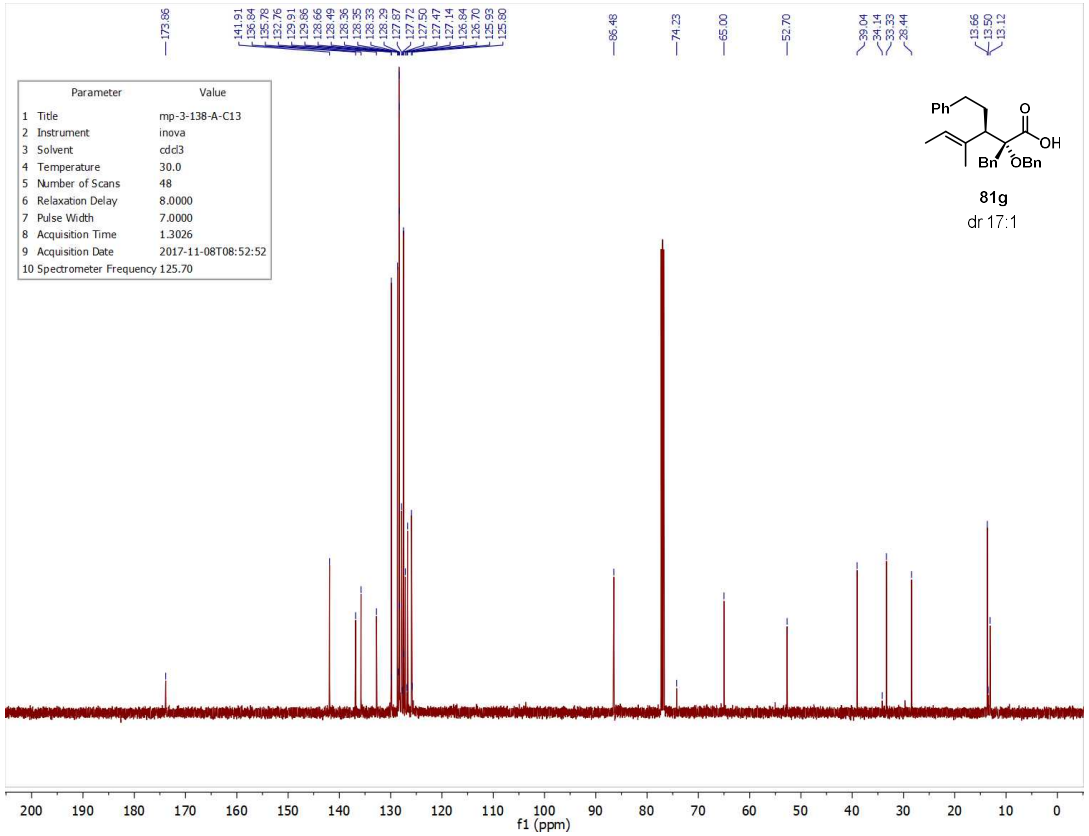

Parameter Value
1 Title mp-3-150-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2017-11-16T17:41:22
10 Spectrometer Frequency 599.64
Ph
O
OH
Bn
OMe
81f
dr 8:1
5.01
6.22
0.36
1.24
1.00
2.83
0.13
0.35
0.93
0.94
0.12
2.12
1.24
1.63
3.32
0.14
f1 (ppm)


173.63
141.81
141.72
135.60
135.49
130.86
129.84
129.81
129.69
129.53
128.76
128.65
128.40
128.29
128.27
126.76
126.68
125.91
125.81
86.28
85.57
51.84
49.67
48.93
46.30
38.42
37.57
33.55
33.34
31.37
30.19
18.16
18.01
Parameter Value
1 Title mp-3-150-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 84
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-18T10:45:11
10 Spectrometer Frequency 125.70
Ph
O
OH
Bn
OMe
81f
dr 8:1
f1 (ppm)

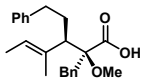

Parameter Value
1 Title mp-3-135-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-06T19:04:30
10 Spectrometer Frequency 499.86
Ph
O
OH
Bn
OBn
80g
dr 25:1
13.52
2.01
1.14
1.09
1.00
1.01
1.03
1.01
1.13
1.15
1.08
1.10
5.67
f1 (ppm)


174.63
141.93
137.31
135.52
132.67
129.91
128.50
128.40
128.36
128.34
128.30
127.72
127.47
126.85
125.80
125.59
85.23
65.58
55.02
40.14
34.14
29.72
13.50
13.33
Parameter Value
1 Title mp-3-135-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 40
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-06T18:56:18
10 Spectrometer Frequency 125.70
Ph
O
OH
Bn
OBn
80g
dr 25:1
f1 (ppm)


Parameter Value
1 Title mp-3-138-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-08T08:48:04
10 Spectrometer Frequency 499.86
Ph
O
OH
Bn
OBn
81g
dr 17:1
16.13 0.29 2.06 1.08 0.06 0.07 0.99 1.00 0.05 0.99 1.01 0.11 0.08 2.16 0.13 1.00 0.11 2.04 3.09 3.08 0.68
f1 (ppm)

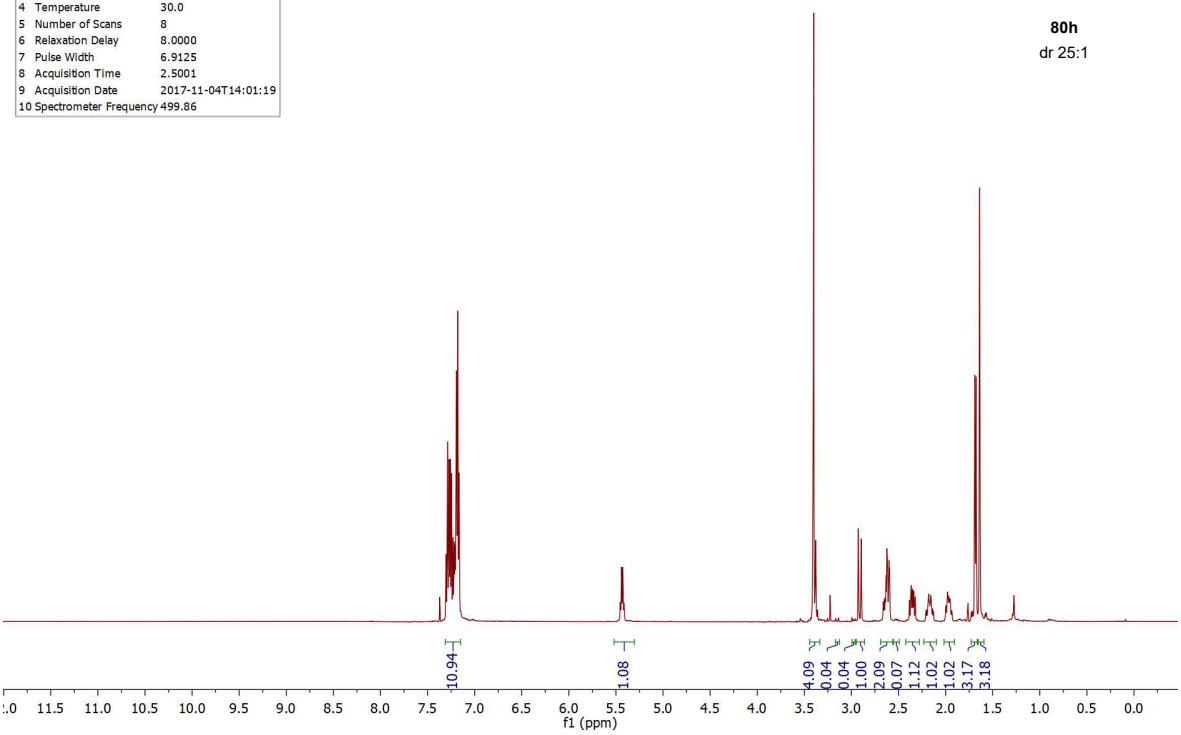

173.86
141.91 136.84 135.78 132.76 129.91 129.86 128.66 128.49 128.36 128.35 128.33 128.29 127.87 127.72 127.50 127.47 127.14 126.84 126.70 125.93 125.80
86.48
74.23
65.00
52.70
39.04 34.14 33.33 28.44
13.66 13.50 13.12
Parameter Value
1 Title mp-3-138-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 48
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-08T08:52:52
10 Spectrometer Frequency 125.70
Ph
O
OH
Bn
OBn
81g
dr 17:1
f1 (ppm)

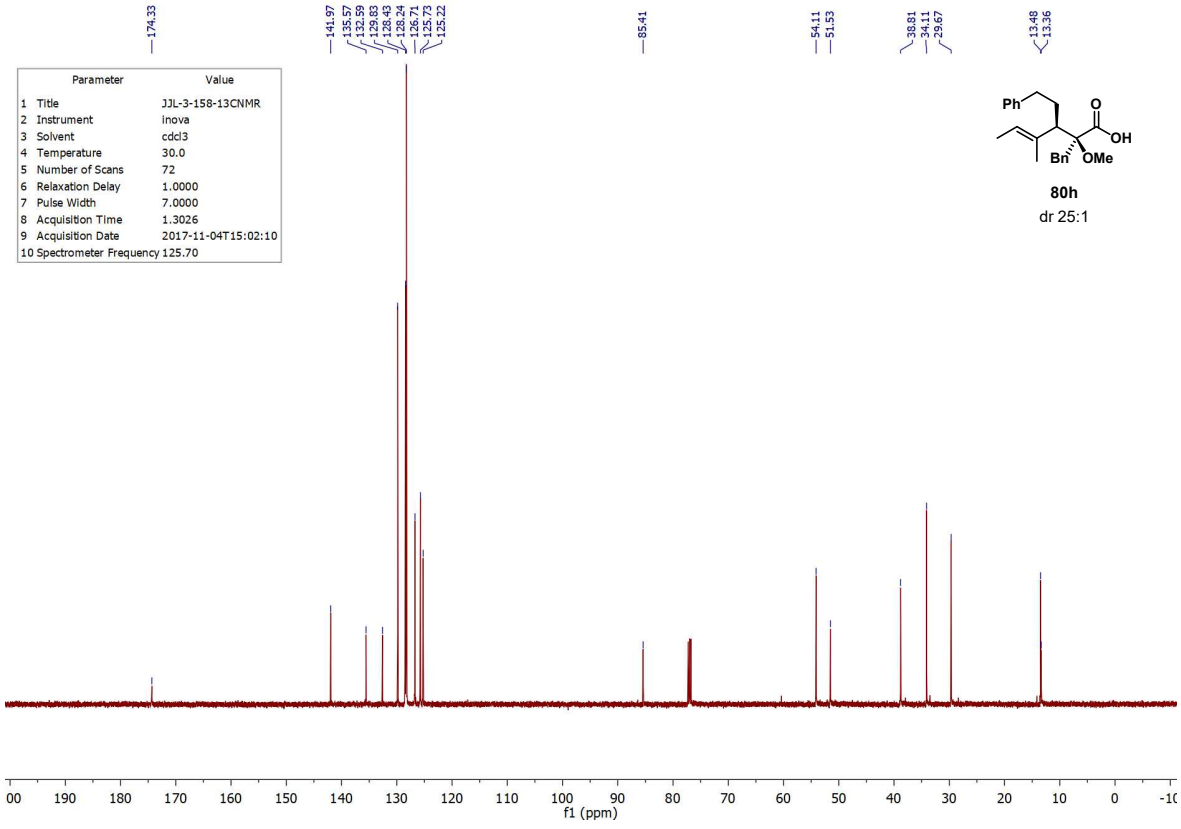
	Parameter	Value
1	Title	JJL-3-158-b
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	30.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	6.9125
8	Acquisition Time	2.5001
9	Acquisition Date	2017-11-04T14:01:19
10	Spectrometer Frequency	499.86



80h

dr 25:1

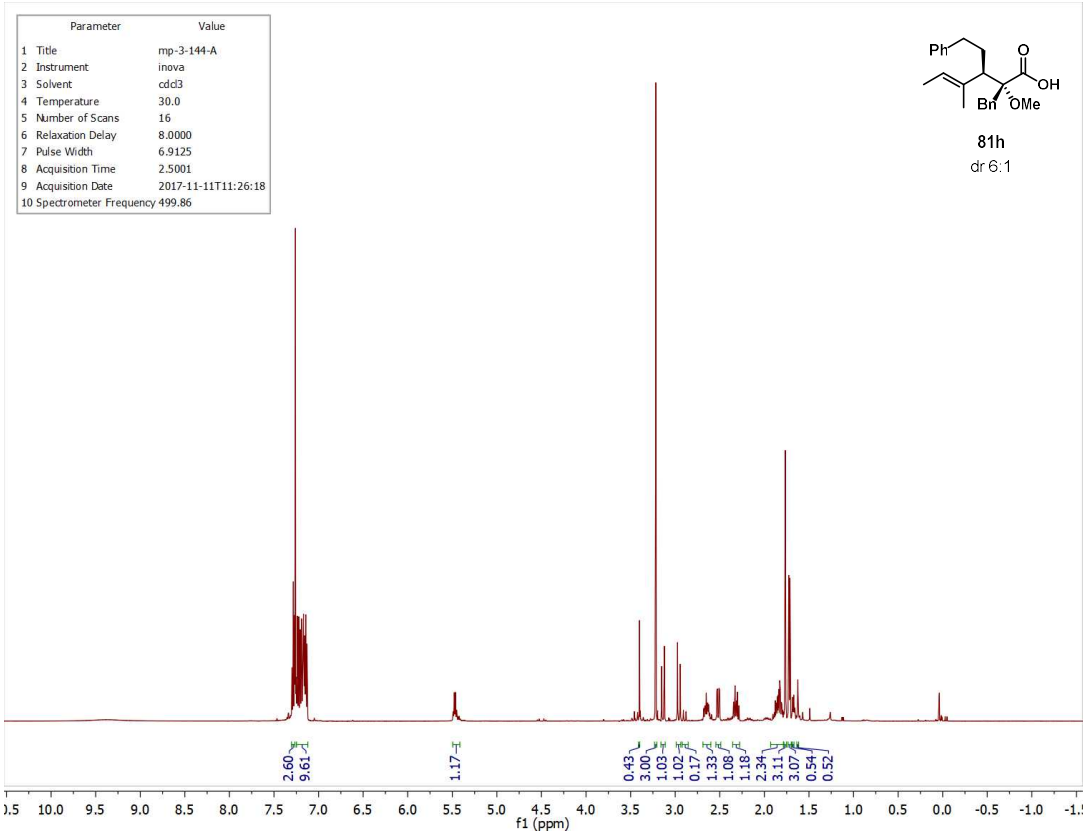


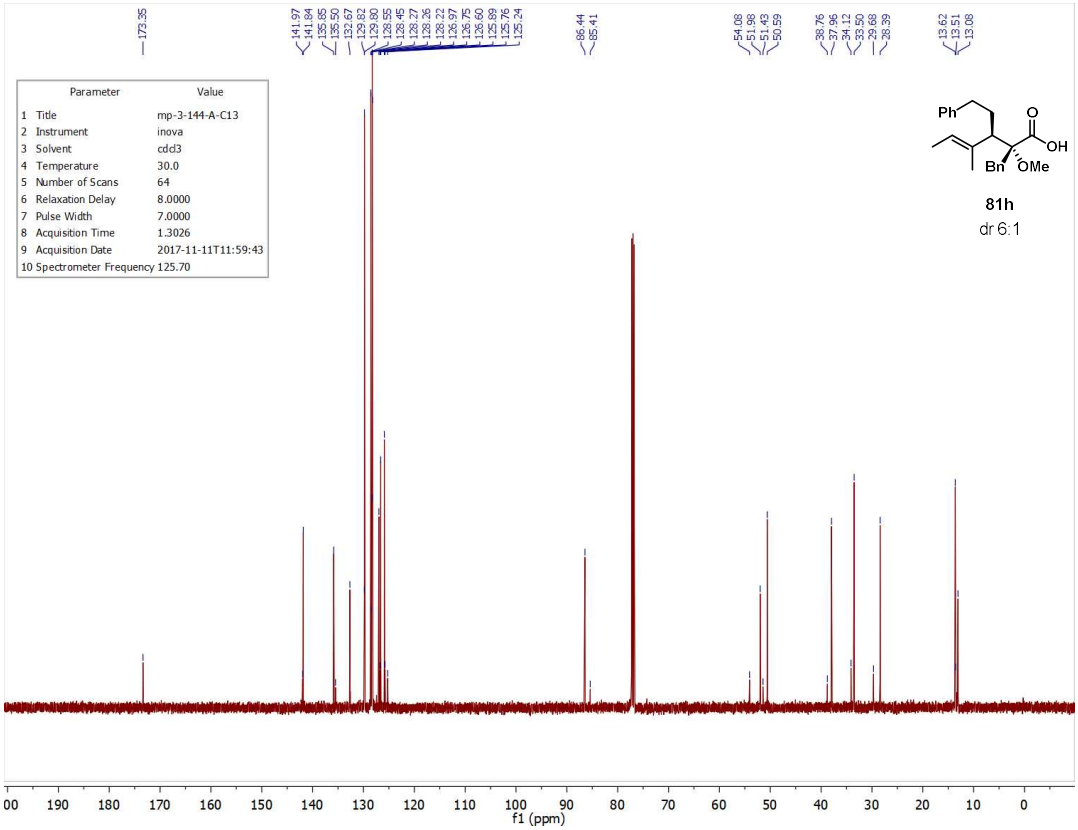


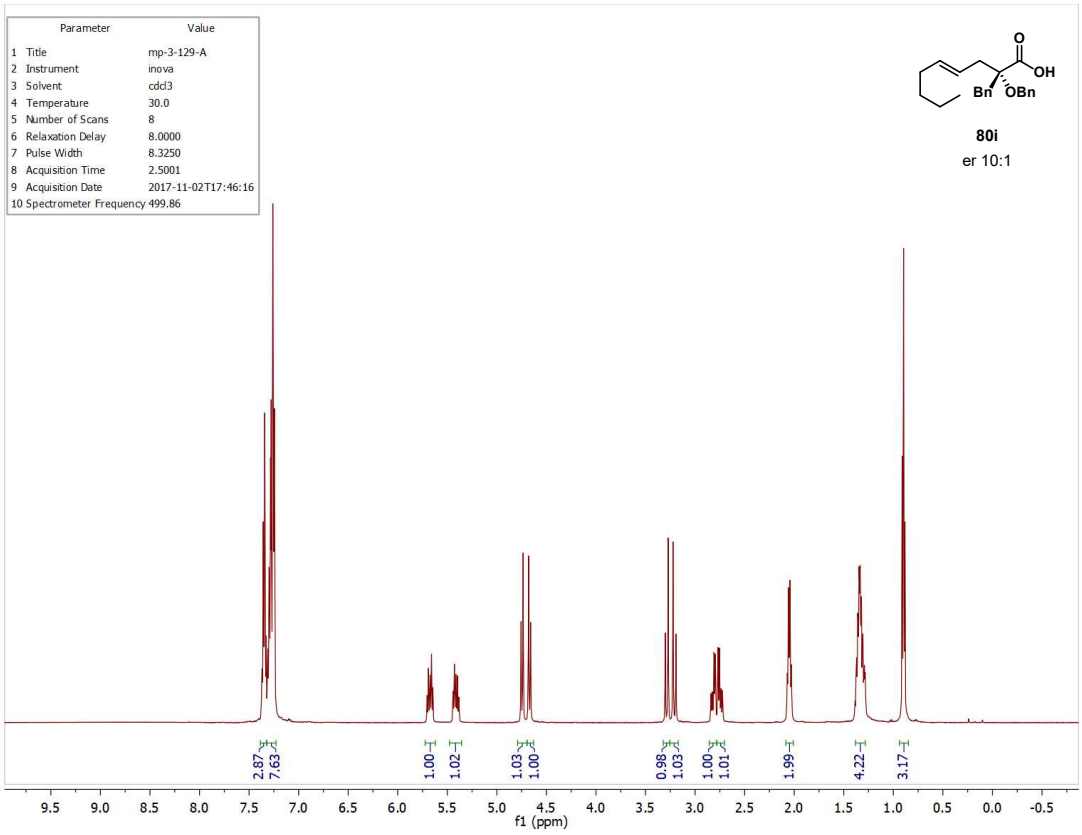
	Parameter	Value
1	Title	JJL-3-158-13CNMR
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	30.0
5	Number of Scans	72
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2017-11-04T15:02:10
10	Spectrometer Frequency	125.70

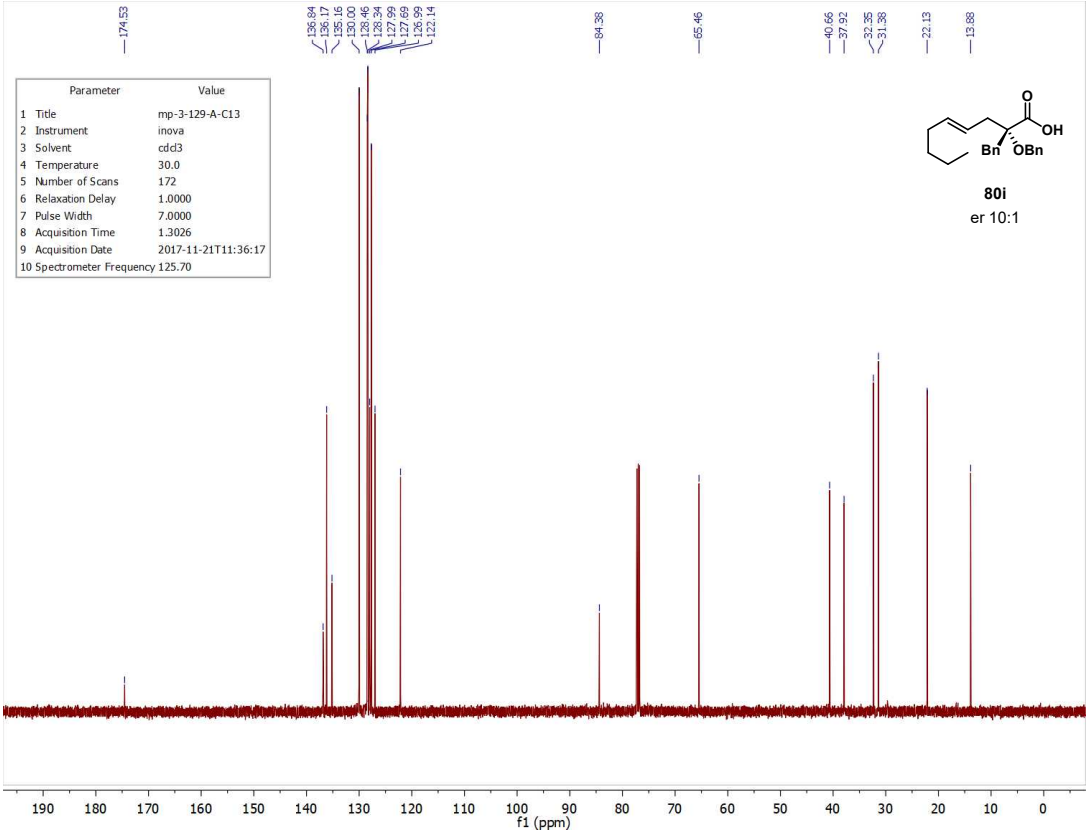
80h

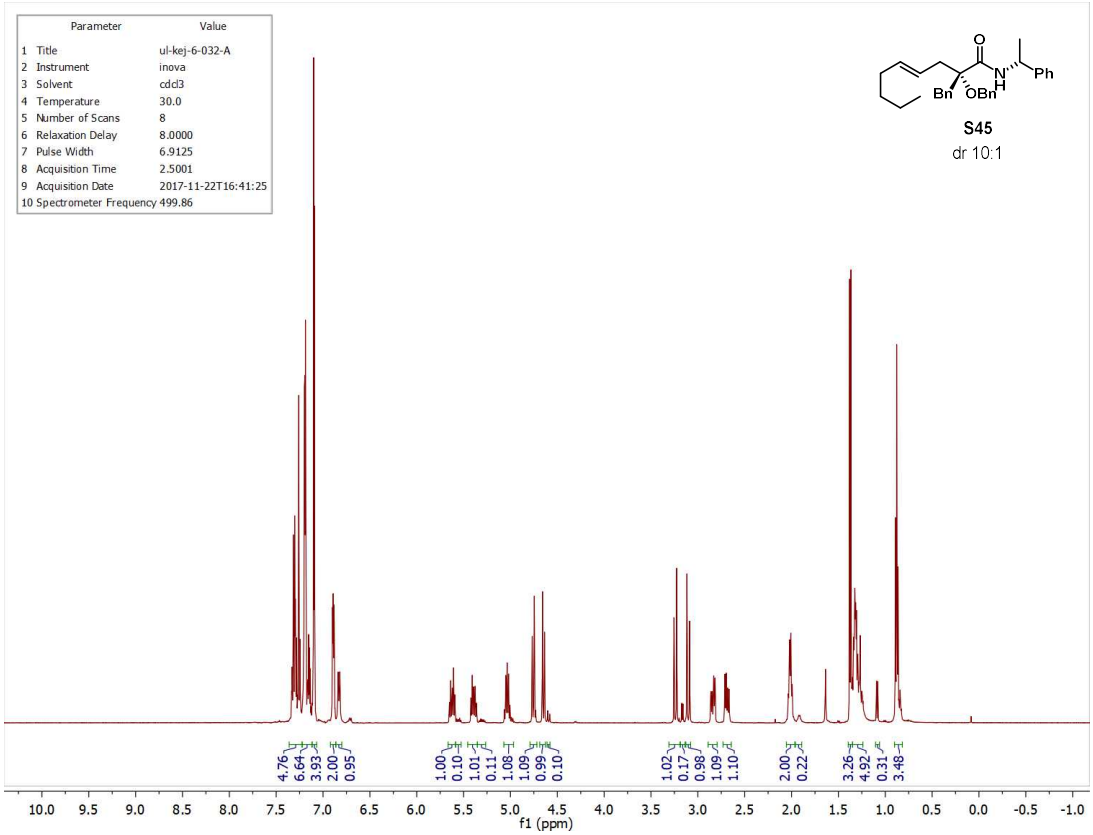
dr 25:1

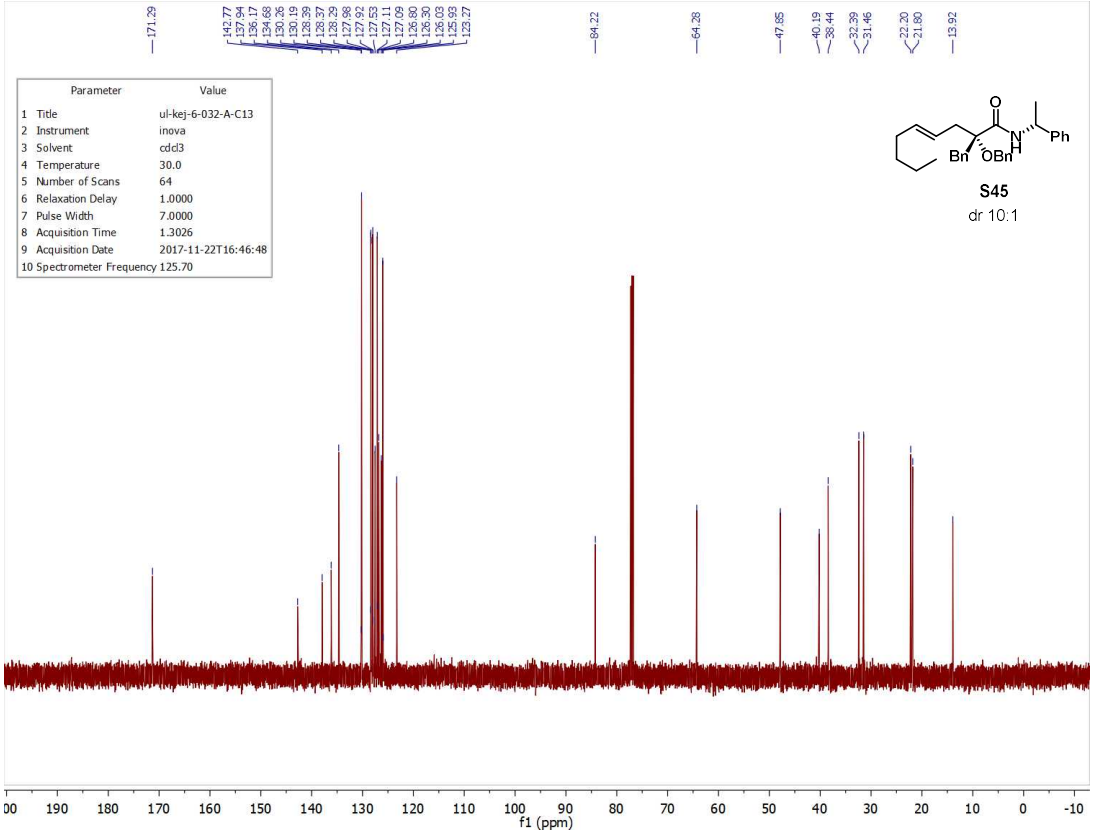

Parameter Value
1 Title mp-3-144-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-11T11:26:18
10 Spectrometer Frequency 499.86
Ph
O
OH
Bn
OMe
81h
dr 6:1
2.60
9.61
1.17
0.43
3.00
1.03
1.02
0.17
1.33
1.08
1.18
2.34
3.11
3.07
0.54
0.52
f1 (ppm)

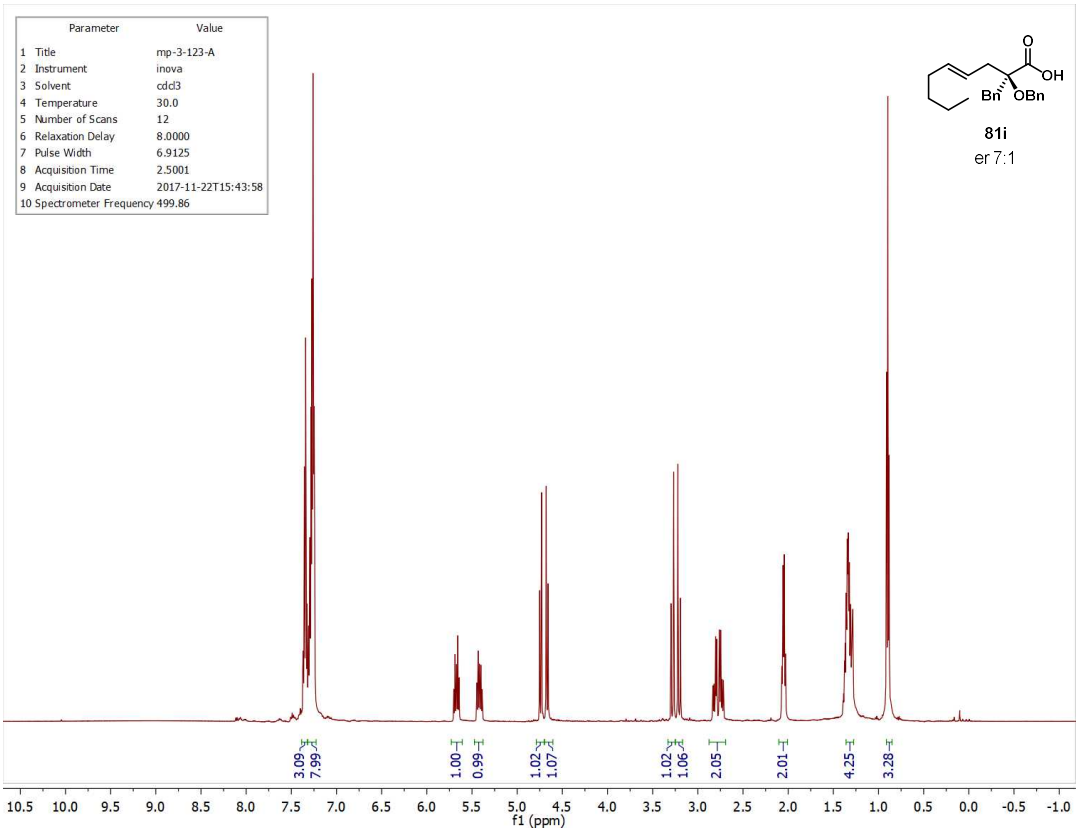

173.35
141.97
141.84
135.85
135.50
132.67
129.82
129.80
128.55
128.45
128.27
128.26
128.22
126.97
126.75
126.60
125.89
125.76
125.24
86.44
85.41
54.08
51.98
51.43
50.59
38.76
37.96
34.12
33.50
29.68
28.39
13.62
13.51
13.08
Parameter Value
1 Title mp-3-144-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 64
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-11T11:59:43
10 Spectrometer Frequency 125.70
Ph
O
OH
Bn
OMe
81h
dr 6:1
f1 (ppm)

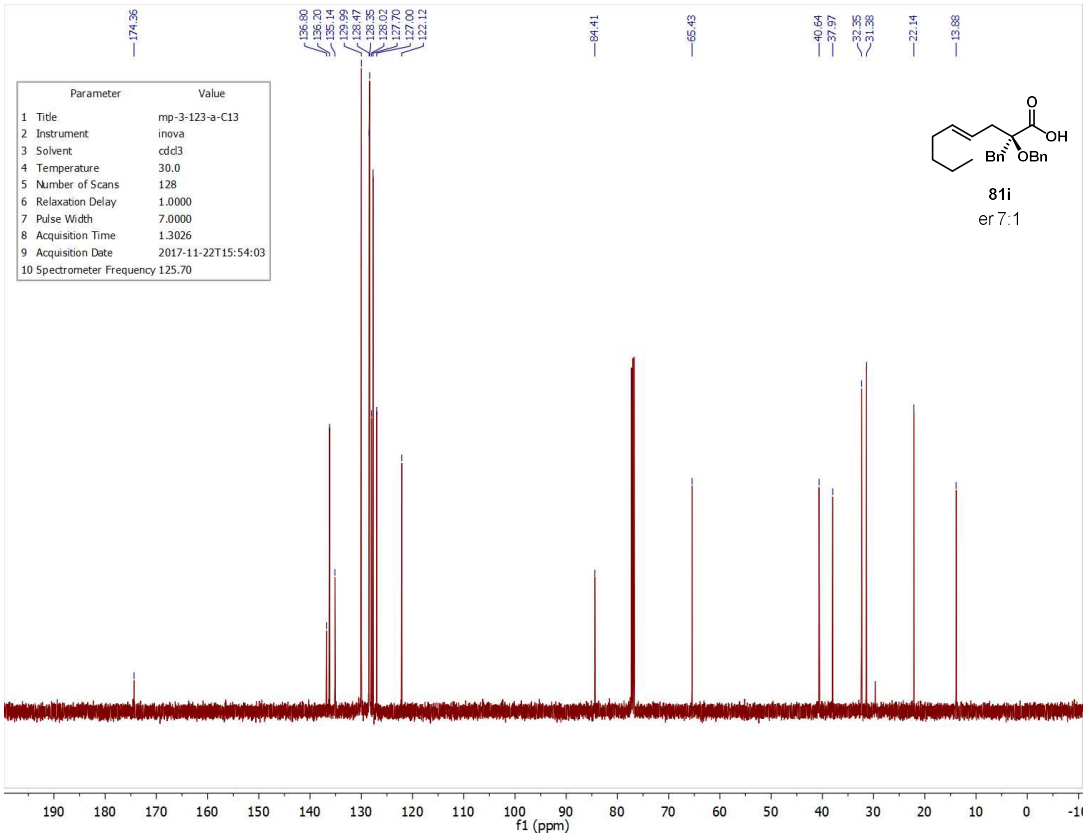

Parameter Value
1 Title mp-3-129-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 8.3250
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-02T17:46:16
10 Spectrometer Frequency 499.86
O
OH
Bn OBn
80i
er 10:1
2.87
7.63
1.00
1.02
1.03
1.00
0.98
1.03
1.00
1.01
1.99
4.22
3.17
f1 (ppm)

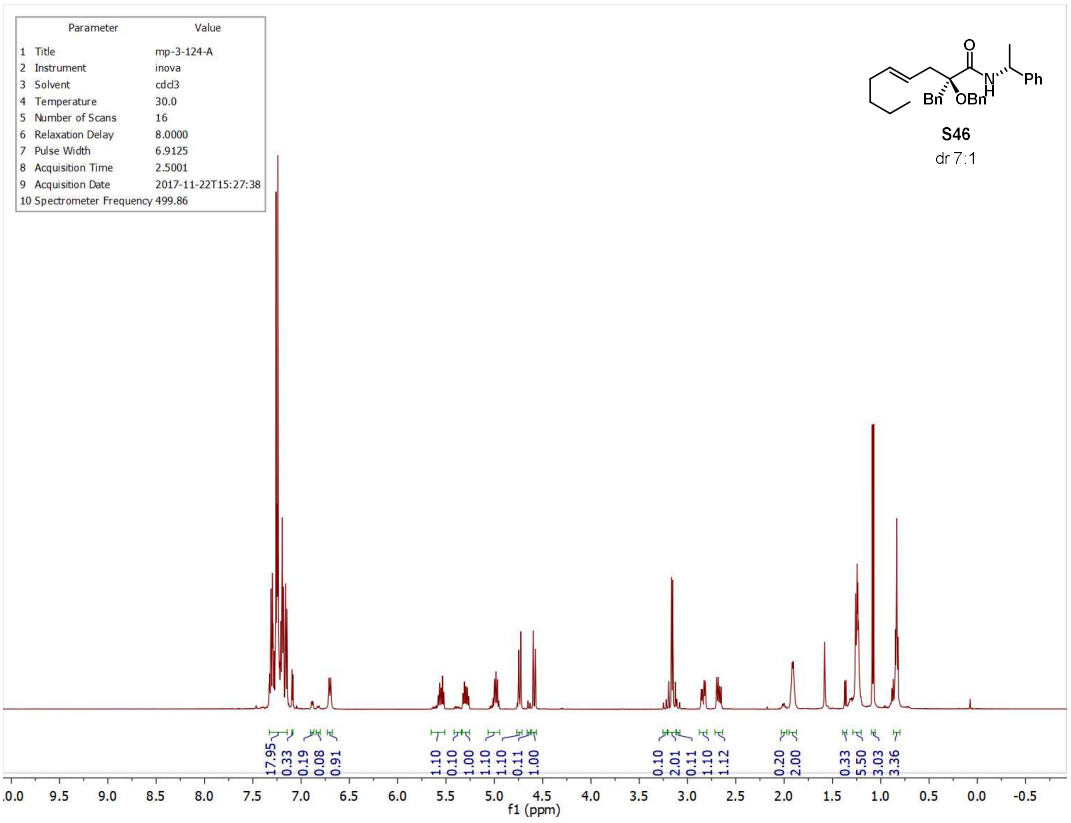

174.53
136.84
136.17
135.16
130.00
128.46
128.34
127.99
127.69
126.99
122.14
84.38
65.46
40.66
37.92
32.35
31.38
22.13
13.88
Parameter Value
1 Title mp-3-129-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 172
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-21T11:36:17
10 Spectrometer Frequency 125.70
O
OH
Bn OBn
80i
er 10:1
f1 (ppm)

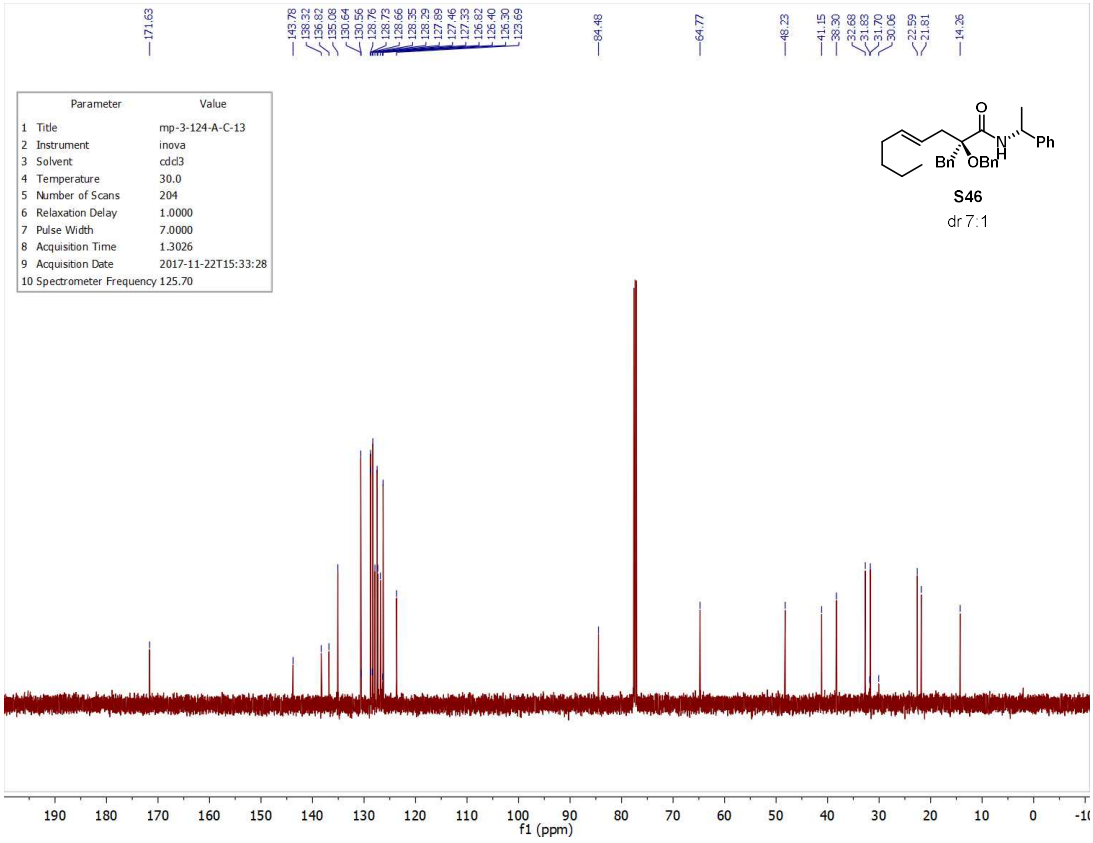

Parameter Value
1 Title ul-kej-6-032-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-22T16:41:25
10 Spectrometer Frequency 499.86
S45
dr 10:1
f1 (ppm)


Parameter Value
1 Title ul-kej-6-032-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 64
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-22T16:46:48
10 Spectrometer Frequency 125.70
S45
dr 10:1
f1 (ppm)

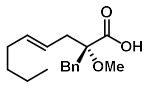

Parameter Value
1 Title mp-3-123-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-22T15:43:58
10 Spectrometer Frequency 499.86
OH
Bn OBn
81i
er 7:1
3.09
7.99
1.00
0.99
1.02
1.07
1.02
1.06
2.05
2.01
4.25
3.28
f1 (ppm)


174.36
136.80
136.20
135.14
129.99
128.47
128.35
128.02
127.70
127.00
122.12
84.41
65.43
40.64
37.97
32.35
31.38
22.14
13.88
Parameter Value
1 Title mp-3-123-a-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 128
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-22T15:54:03
10 Spectrometer Frequency 125.70
OH
Bn OBn
81i
er 7:1
f1 (ppm)


Parameter Value
1 Title mp-3-124-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-22T15:27:38
10 Spectrometer Frequency 499.86
Bn OBn
Ph
S46
dr 7:1
17.95 0.33 0.19 0.08 0.91 1.10 0.10 1.00 1.10 0.11 1.00 0.10 2.01 0.11 1.10 1.12 0.20 2.00 0.33 5.50 3.03 3.36
f1 (ppm)

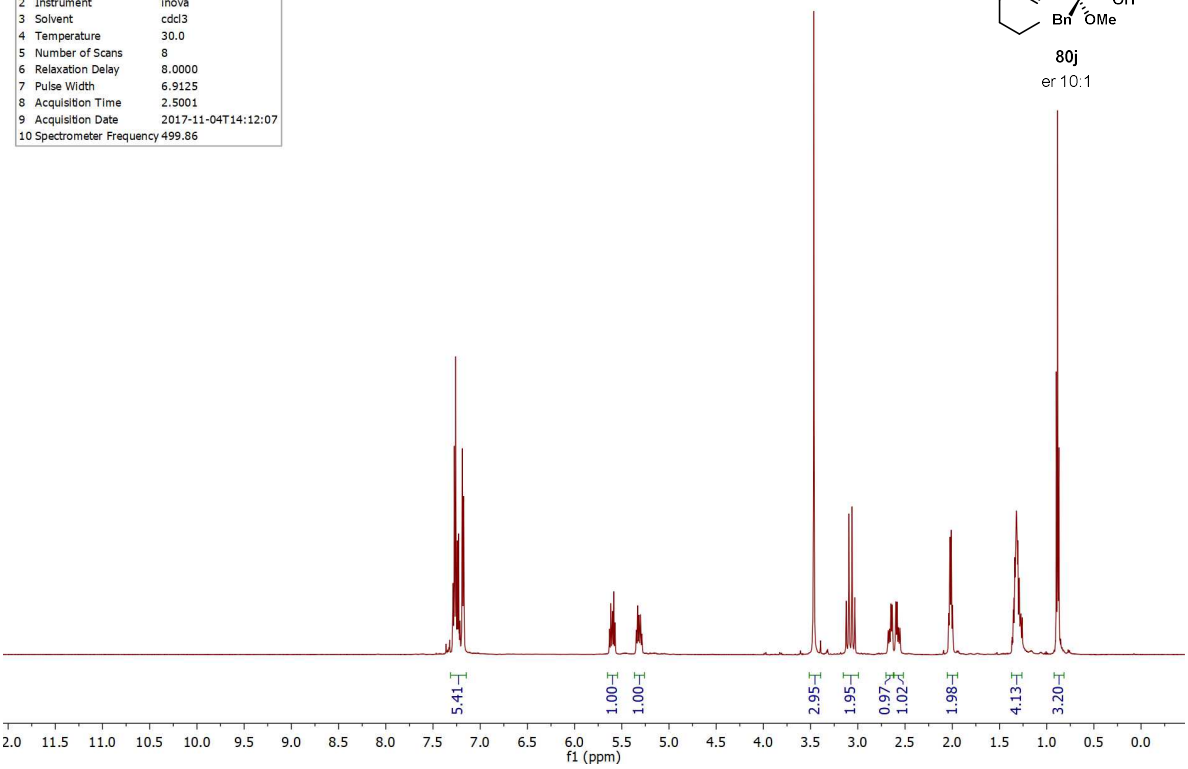

171.63
143.78 138.32 136.82 135.08 130.64 130.56 128.76 128.73 128.66 128.35 128.29 127.89 127.46 127.33 126.82 126.40 126.30 123.69
84.48
64.77
48.23
41.15 38.30 32.68 31.83 31.70 30.06
22.59 21.81
14.26
Parameter Value
1 Title mp-3-124-A-C-13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 204
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-22T15:33:28
10 Spectrometer Frequency 125.70
Bn OBn
Ph
S46
dr 7:1
f1 (ppm)

Parameter	Value
1 Title	JJL-3-161-b
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.9125
8 Acquisition Time	2.5001
9 Acquisition Date	2017-11-04T14:12:07
10 Spectrometer Frequency	499.86

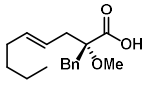


80j

er 10:1



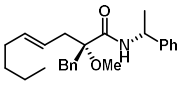
Parameter	Value
1 Title	JJL-3-161-13CNMR
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	80
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-11-04T15:21:32
10 Spectrometer Frequency	125.70



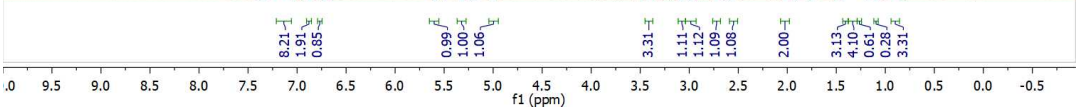
80j

er 10:1

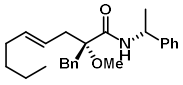
Parameter	Value
1 Title	UL-KEJ-6-035-a
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.9125
8 Acquisition Time	2.5001
9 Acquisition Date	2017-11-15T13:34:05
10 Spectrometer Frequency	499.86



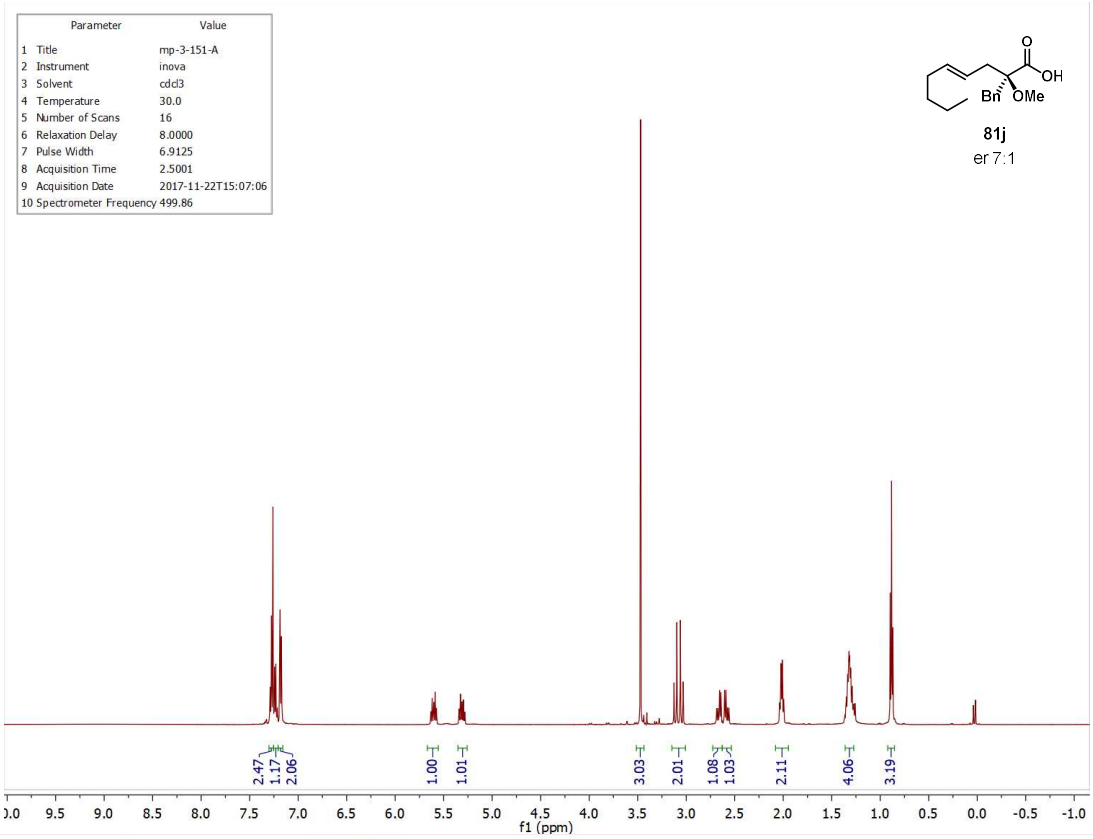
S47
dr 10:1

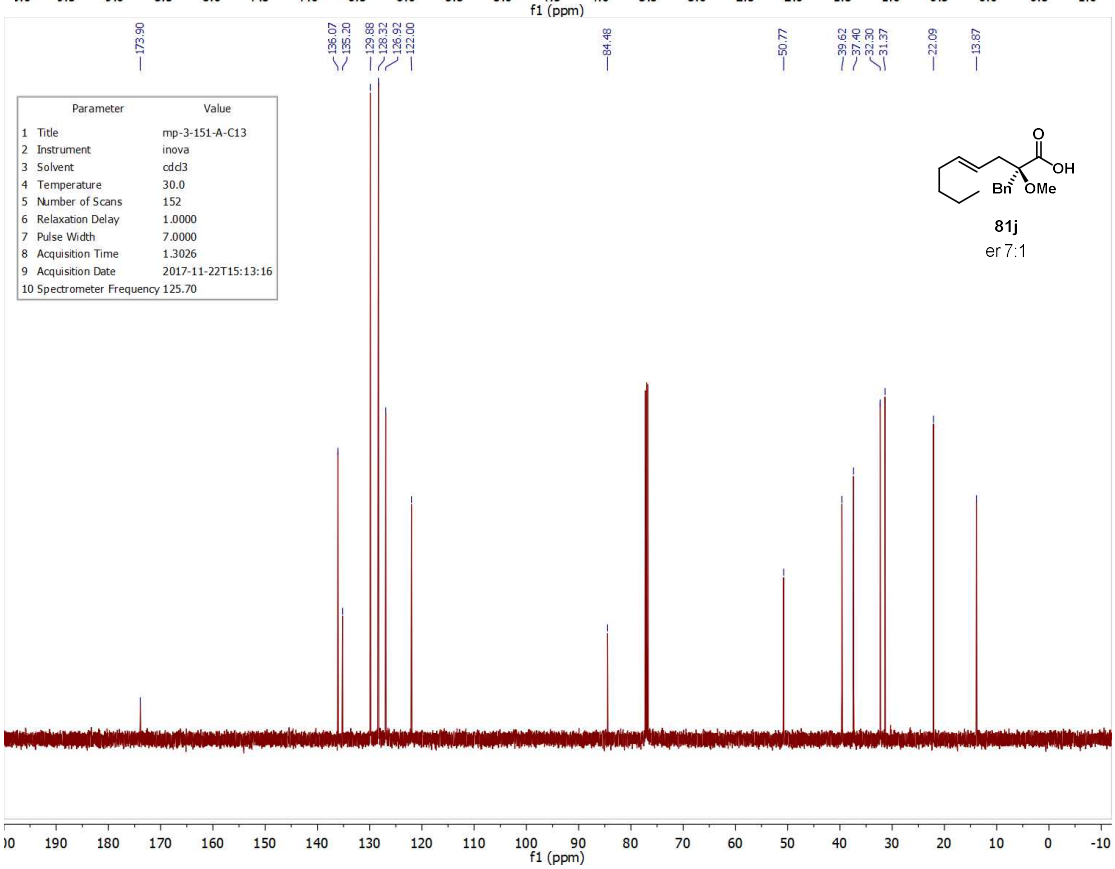


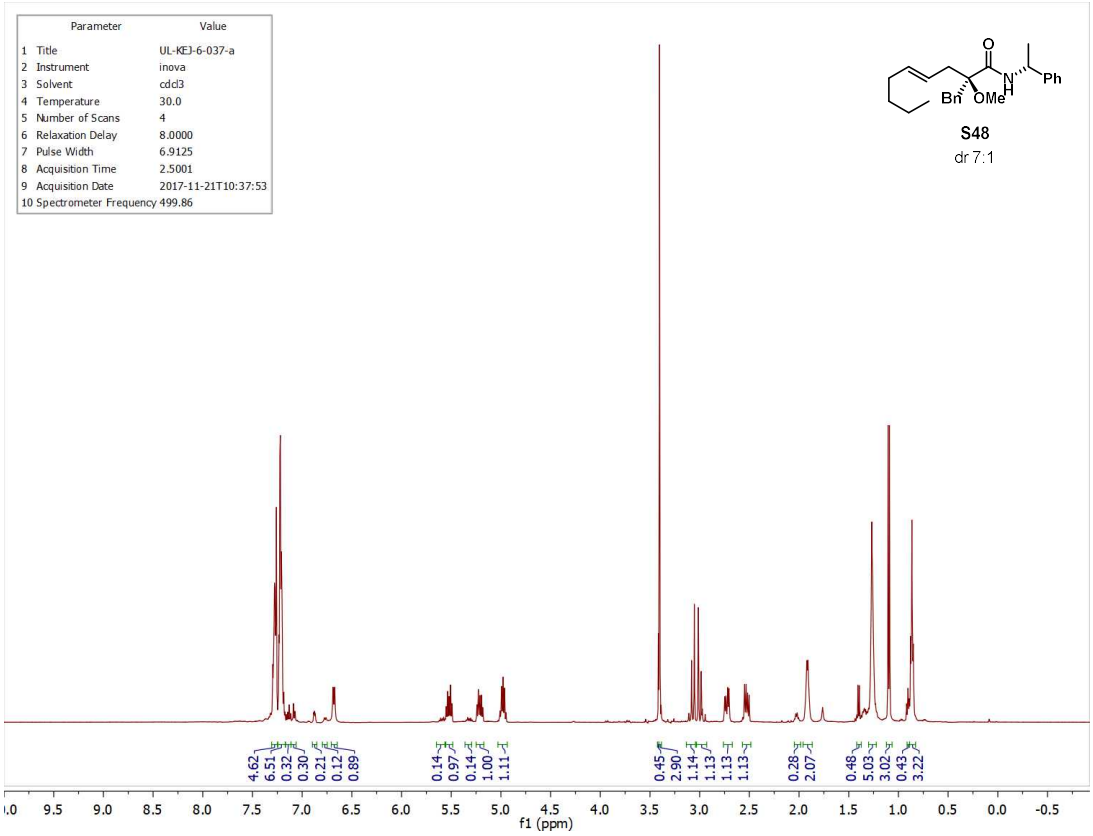
Parameter	Value
1 Title	KEJ-6-035-13CNMR
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	25.0
5 Number of Scans	200
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2018-04-30T17:50:22
10 Spectrometer Frequency	125.70

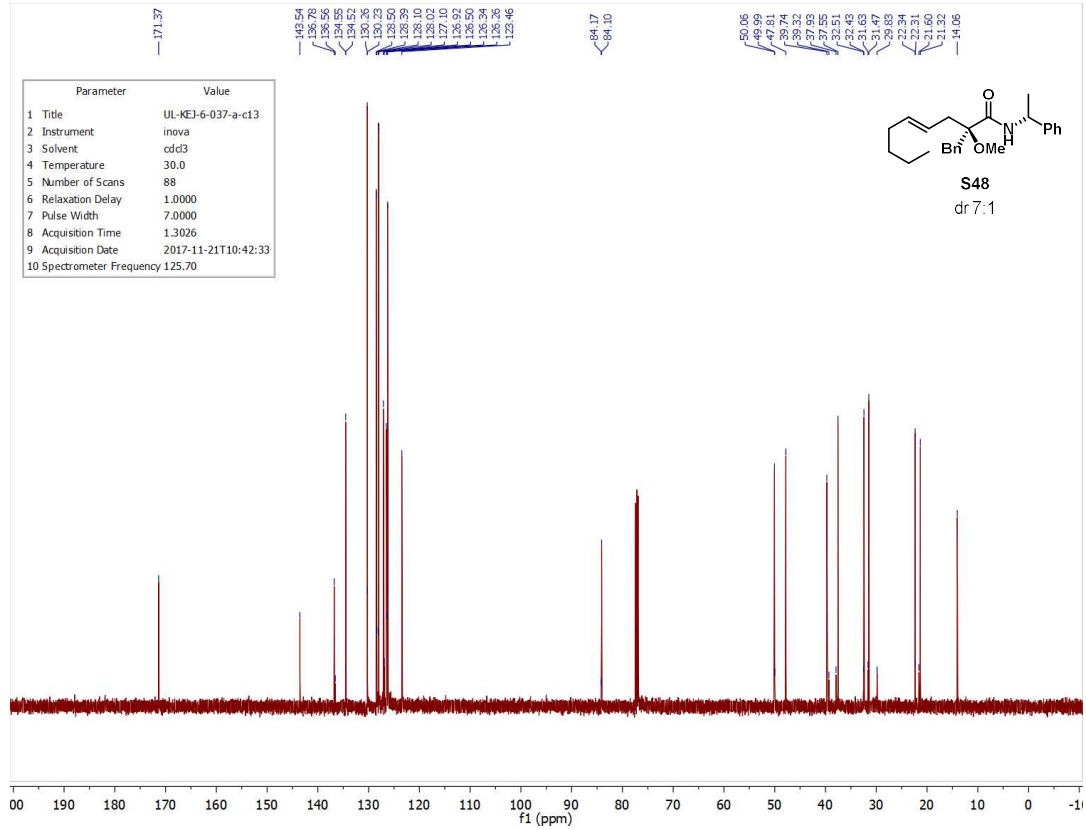


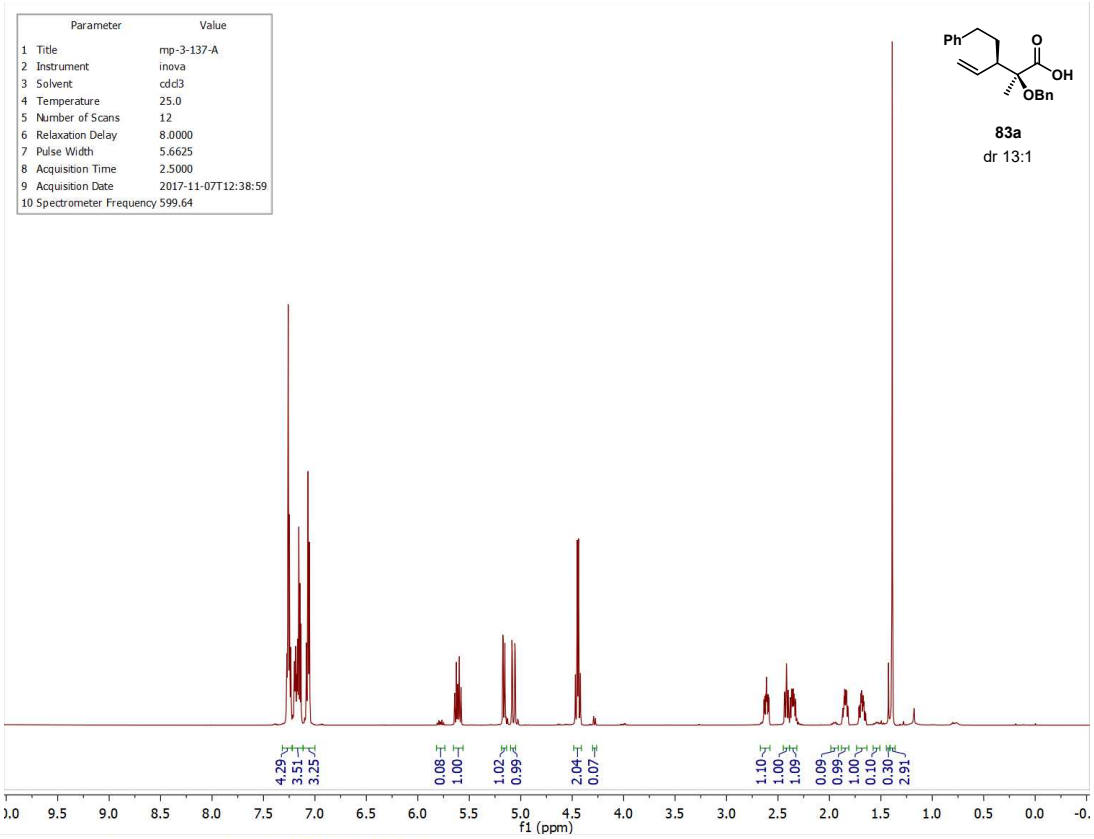
S47
dr 10:1

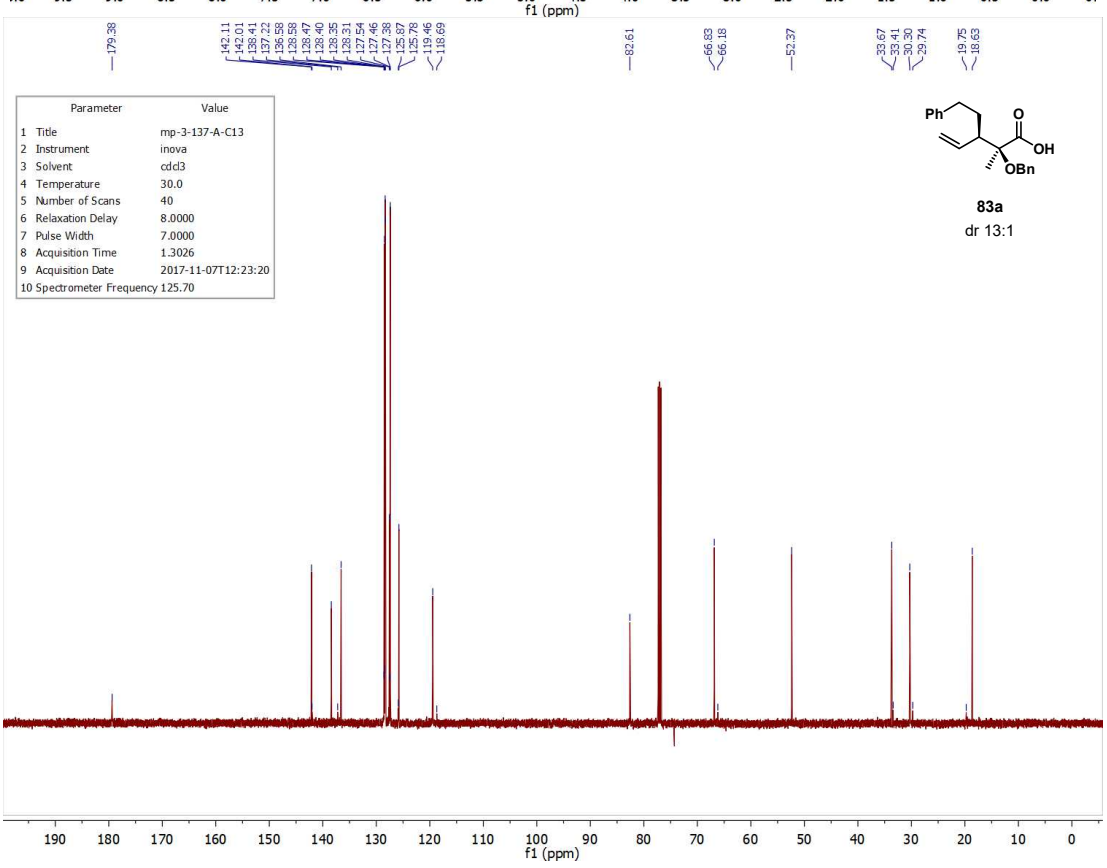

Parameter Value
1 Title mp-3-151-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-22T15:07:06
10 Spectrometer Frequency 499.86
OH
Bn OMe
81j
er 7:1
2.47
1.17
2.06
1.00
1.01
3.03
2.01
1.08
1.03
2.11
4.06
3.19
f1 (ppm)

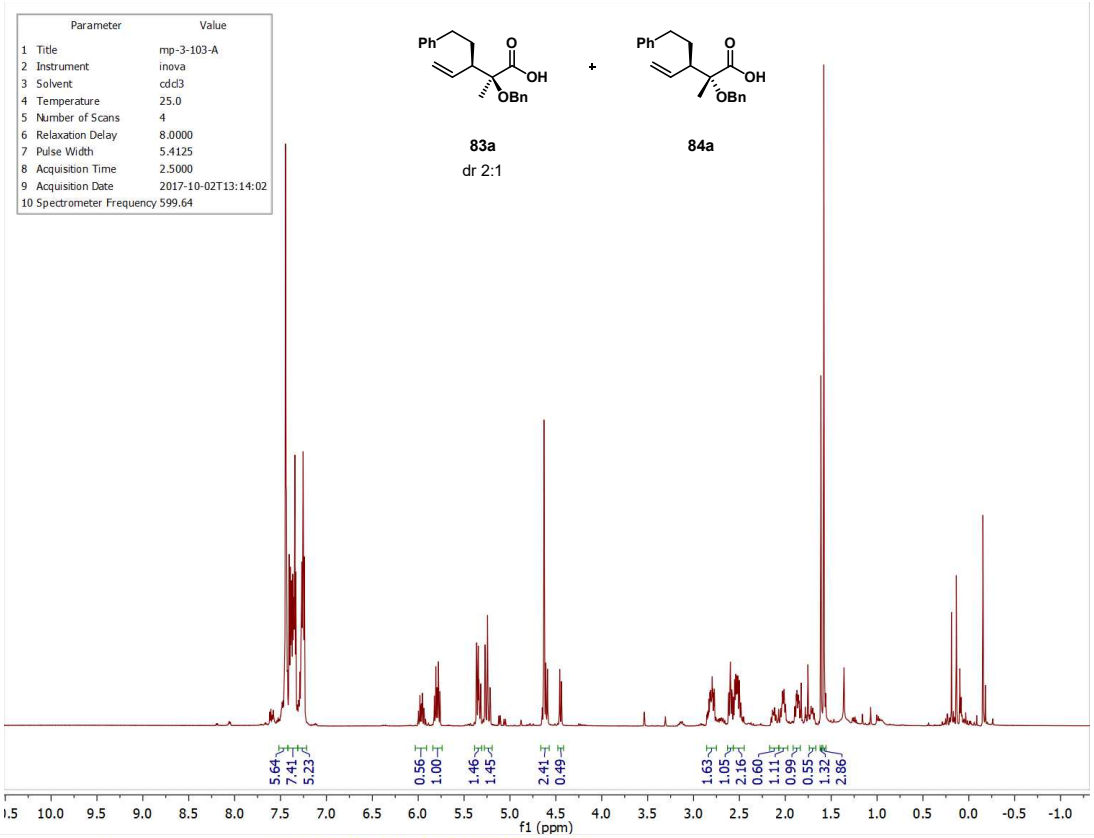

173.90
136.07
135.20
129.88
128.32
126.92
122.00
84.48
50.77
39.62
37.40
32.30
31.37
22.09
13.87
Parameter Value
1 Title mp-3-151-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 152
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-22T15:13:16
10 Spectrometer Frequency 125.70
OH
Bn OMe
81j
er 7:1
f1 (ppm)

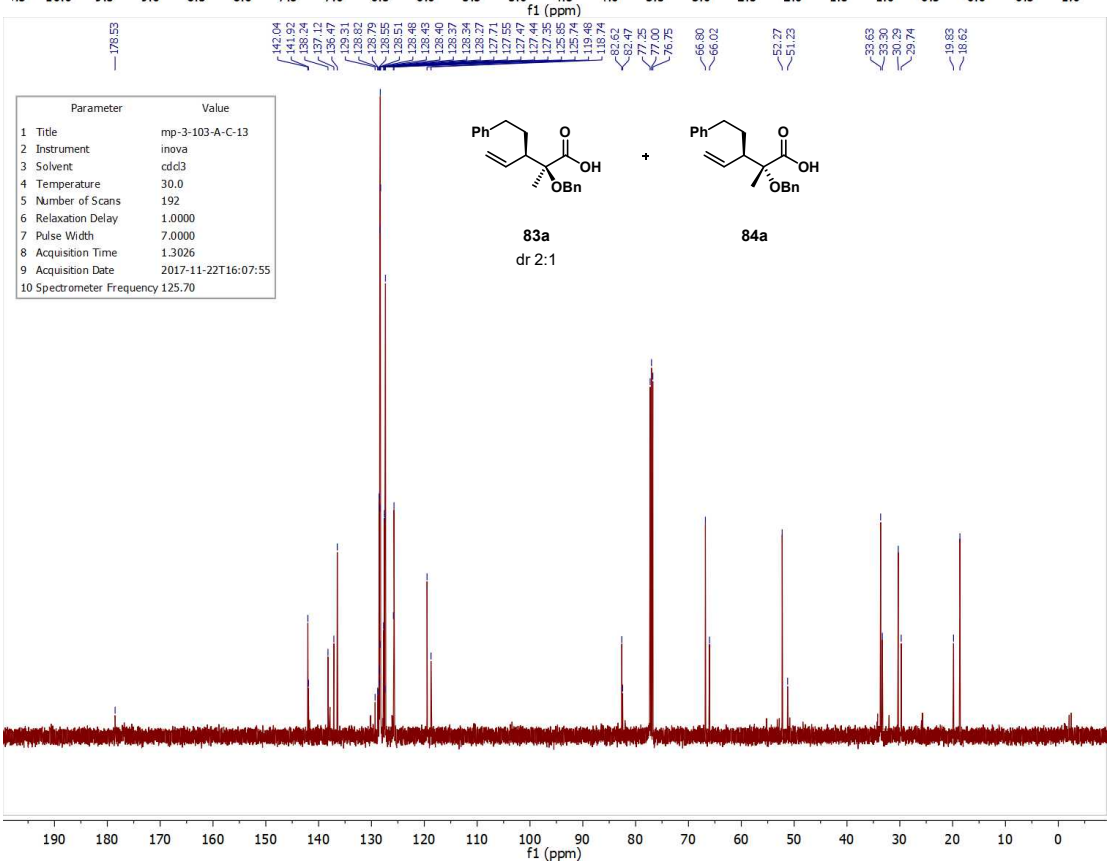

Parameter Value
1 Title UL-KEJ-6-037-a
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 4
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-21T10:37:53
10 Spectrometer Frequency 499.86
Bn OMe
Ph
S48
dr 7:1
4.62 6.51 0.32 0.30 0.21 0.12 0.89 0.14 0.97 0.14 1.00 1.11 0.45 2.90 1.14 1.13 1.13 1.13 0.28 2.07 0.48 5.03 3.02 0.43 3.22
f1 (ppm)


171.37
143.54 136.78 136.56 134.55 134.52 130.26 130.23 128.50 128.39 128.10 128.02 127.10 126.92 126.50 126.34 126.26 123.46
84.17 84.10
50.06 49.99 47.81 39.74 39.32 37.93 37.55 32.51 32.43 31.63 31.47 29.83 22.34 22.31 21.60 21.32 14.06
Parameter Value
1 Title UL-KEJ-6-037-a-c13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 88
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-21T10:42:33
10 Spectrometer Frequency 125.70
Bn OMe
Ph
S48
dr 7:1
f1 (ppm)

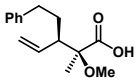

Parameter Value
1 Title mp-3-137-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2017-11-07T12:38:59
10 Spectrometer Frequency 599.64
Ph
O
OH
OBn
83a
dr 13:1
4.29 3.51 3.25 0.08 1.00 1.02 0.99 2.04 0.07 1.10 1.00 1.09 0.09 0.99 1.00 0.10 0.30 2.91
f1 (ppm)


179.38
142.11 142.01 136.41 137.22 136.58 128.58 128.47 128.40 128.35 128.31 127.54 127.46 127.38 125.87 125.78 119.46 118.69
82.61
66.83 66.18
52.37
33.67 33.41 30.30 29.74
19.75 18.63
Parameter Value
1 Title mp-3-137-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 40
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-07T12:23:20
10 Spectrometer Frequency 125.70
Ph
O
OH
OBn
83a
dr 13:1
f1 (ppm)

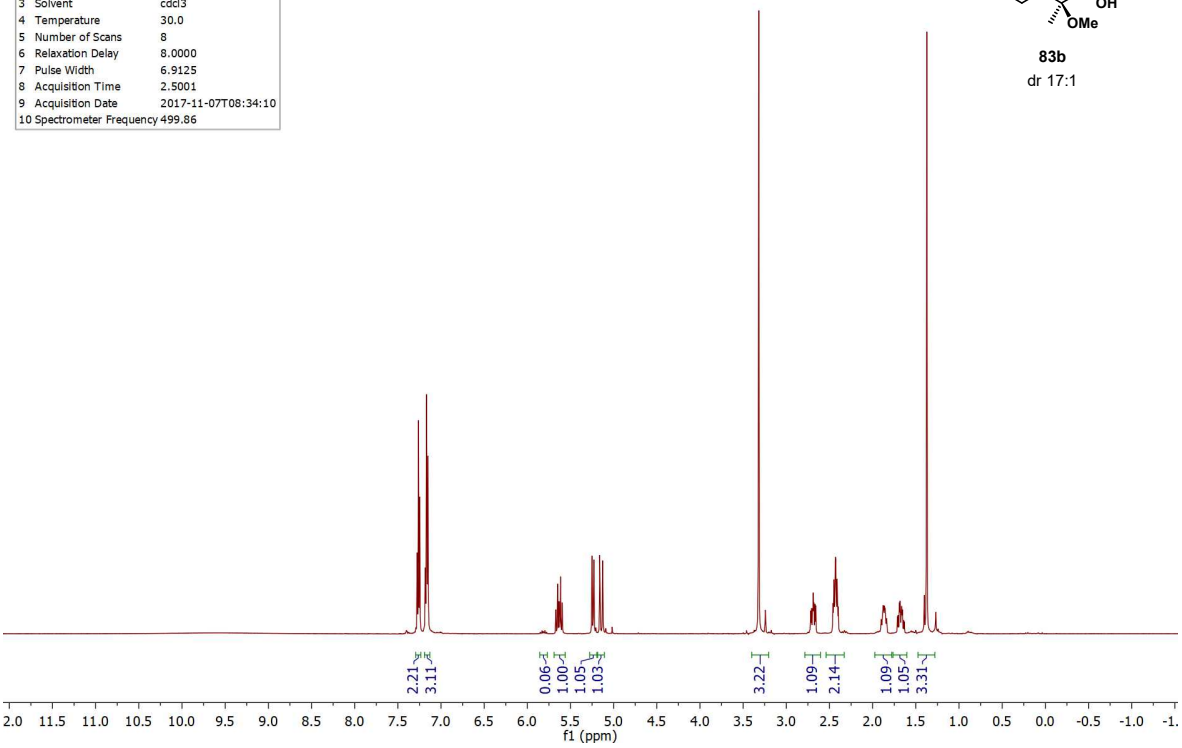

Parameter Value
1 Title mp-3-103-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 4
6 Relaxation Delay 8.0000
7 Pulse Width 5.4125
8 Acquisition Time 2.5000
9 Acquisition Date 2017-10-02T13:14:02
10 Spectrometer Frequency 599.64
Ph
O
OH
OBn
83a
dr 2:1
84a
5.64
7.41
5.23
0.56
1.00
1.46
1.45
2.41
0.49
1.63
1.05
2.16
0.60
1.11
0.99
0.55
1.32
2.86
f1 (ppm)

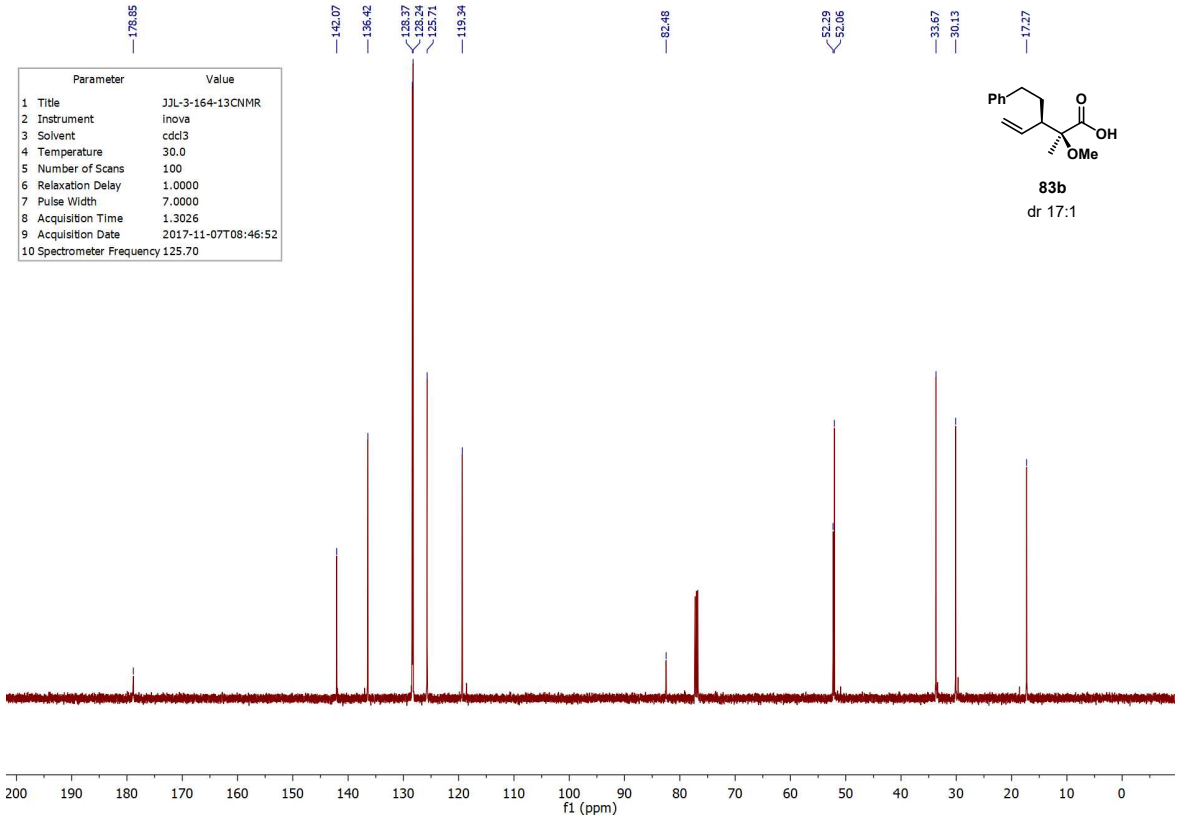

178.53
142.04
141.92
138.24
137.12
136.47
129.31
128.82
128.79
128.55
128.51
128.48
128.43
128.40
128.37
128.34
128.27
127.71
127.51
127.47
127.44
127.35
125.85
125.74
119.48
118.74
82.62
82.47
77.25
77.00
76.75
66.80
66.02
52.27
51.23
33.63
33.30
30.29
29.74
19.83
18.62
Parameter Value
1 Title mp-3-103-A-C-13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 192
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-22T16:07:55
10 Spectrometer Frequency 125.70
Ph
O
OH
OBn
83a
dr 2:1
84a
f1 (ppm)

Parameter	Value
1 Title	JJL-3-164-b
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.9125
8 Acquisition Time	2.5001
9 Acquisition Date	2017-11-07T08:34:10
10 Spectrometer Frequency	499.86



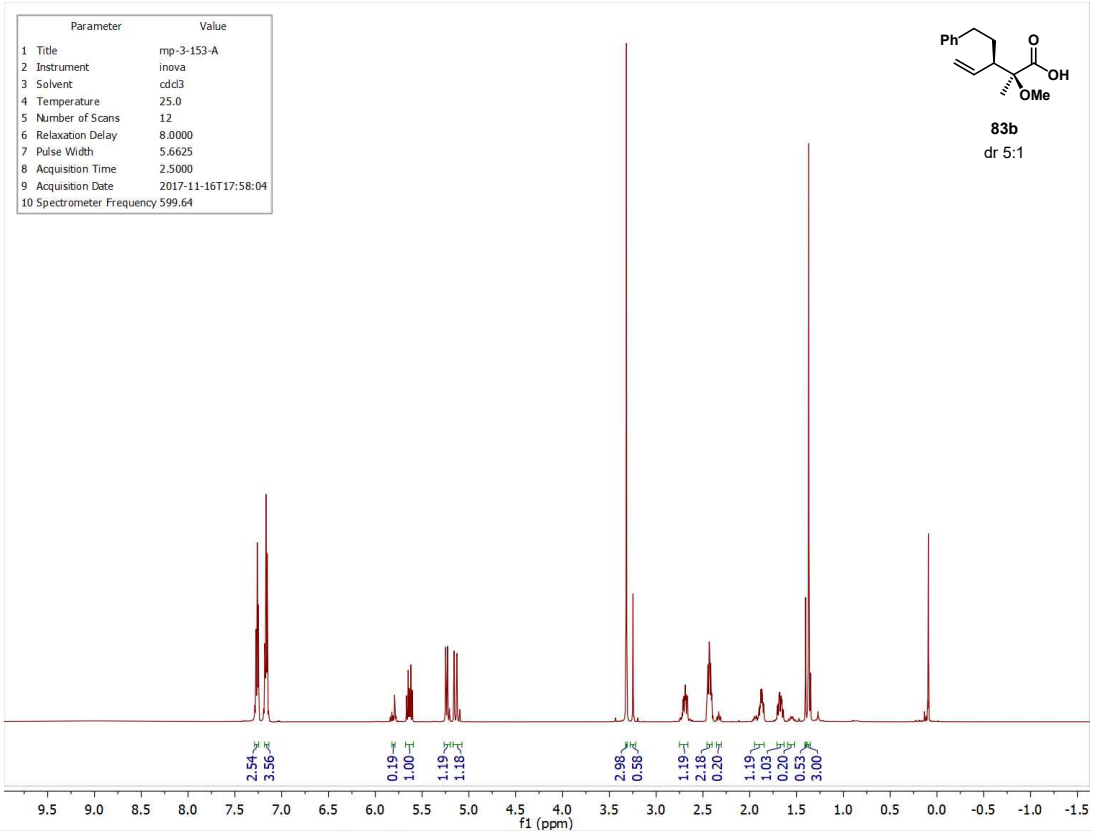
83b
dr 17:1

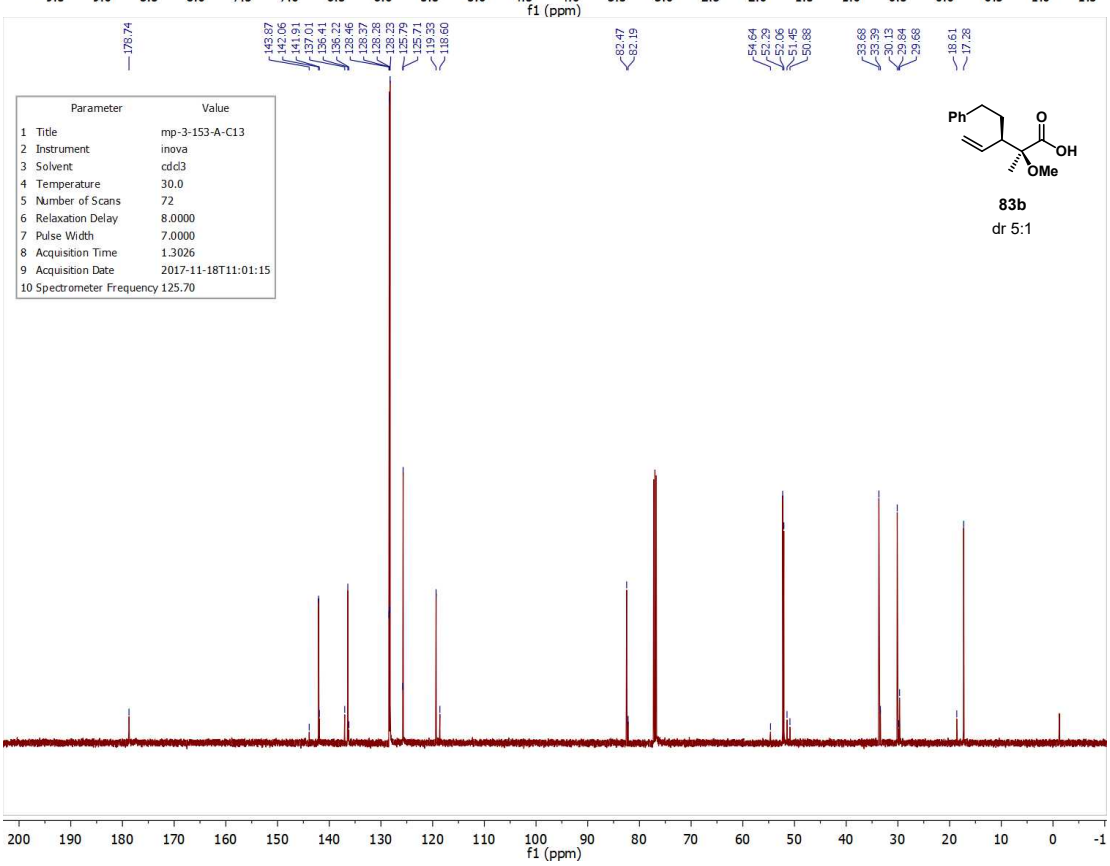


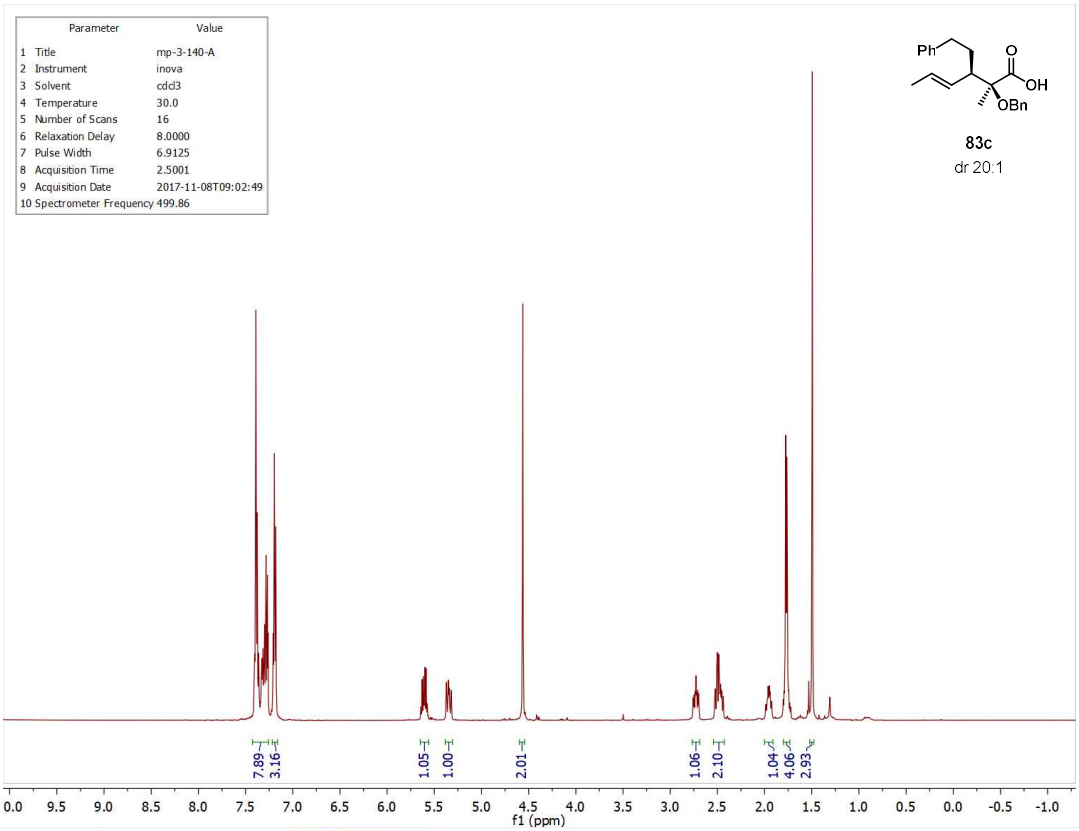


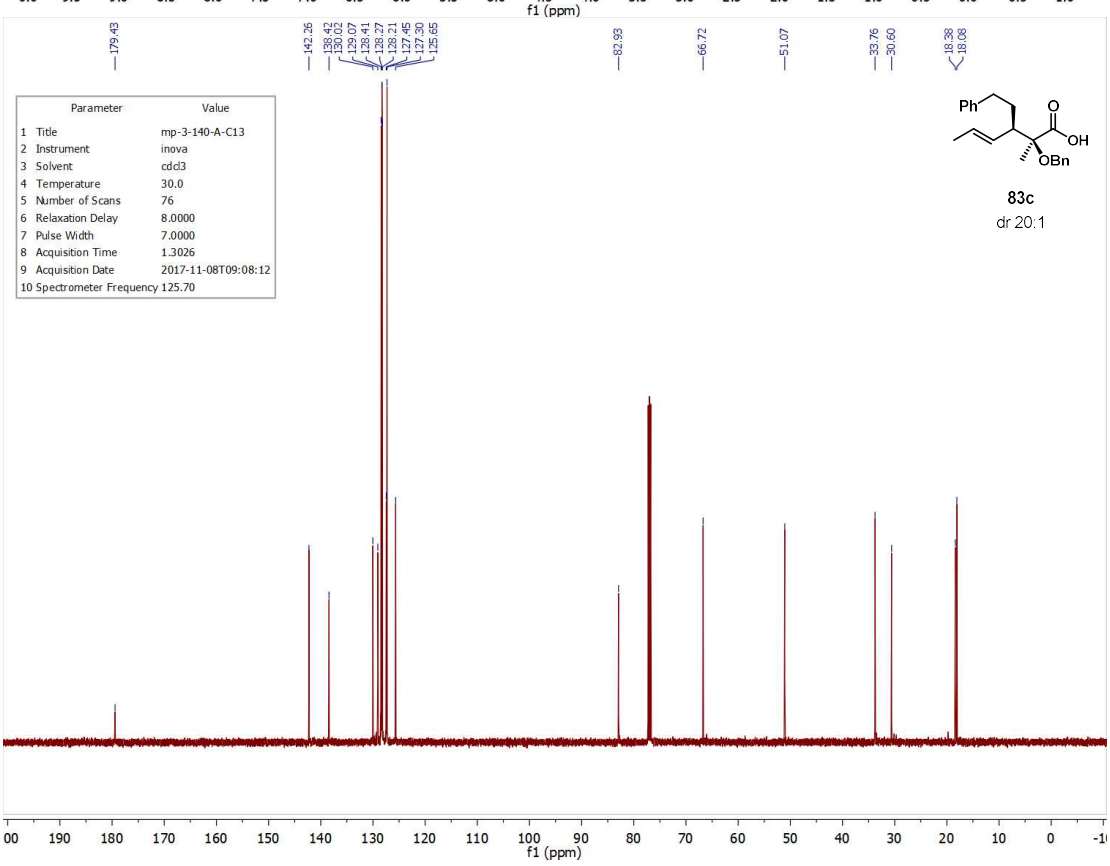
Parameter	Value
1 Title	JJL-3-164-13CNMR
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	100
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-11-07T08:46:52
10 Spectrometer Frequency	125.70

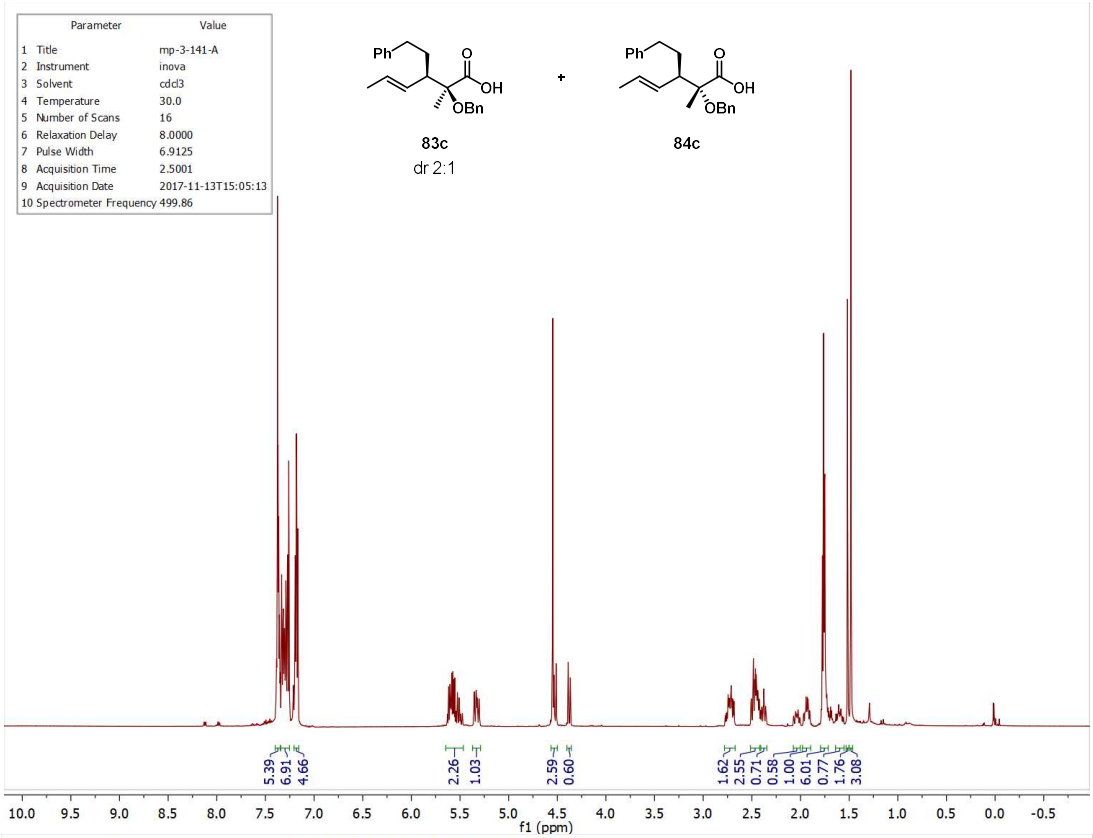
83b
dr 17:1

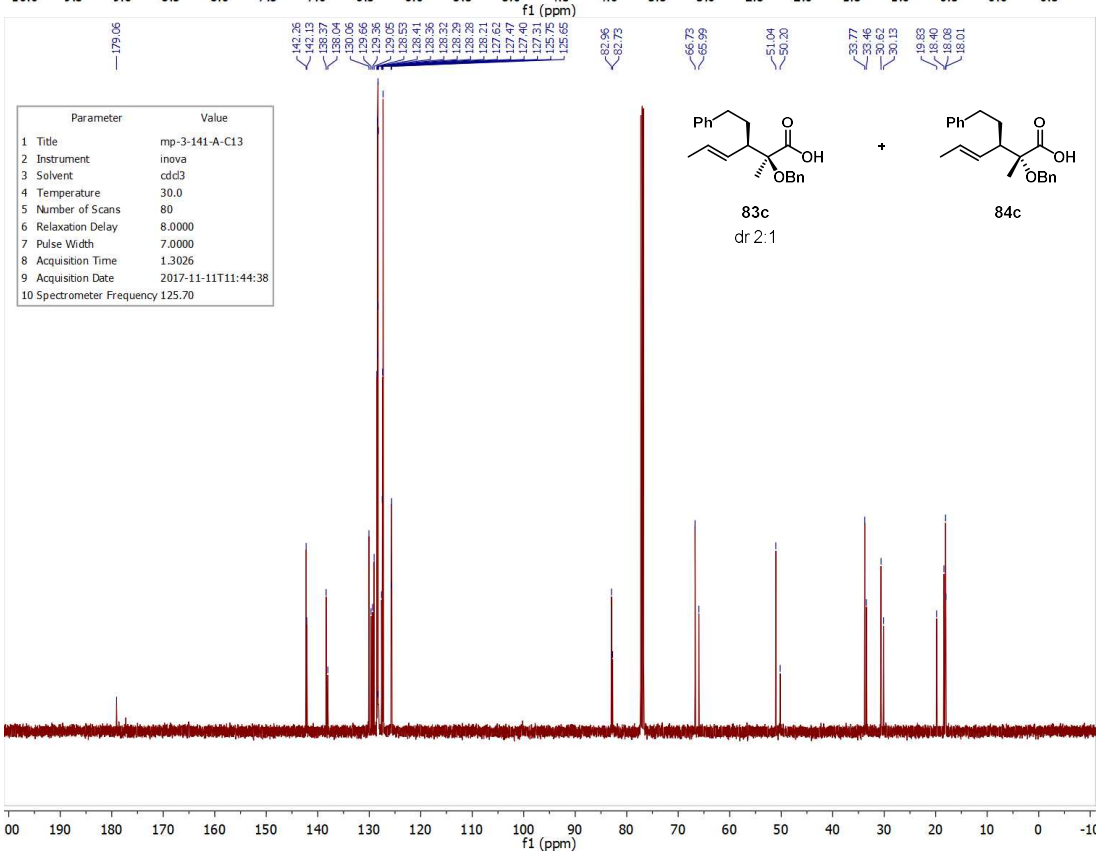

Parameter Value
1 Title mp-3-153-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2017-11-16T17:58:04
10 Spectrometer Frequency 599.64
Ph
O
OH
OMe
83b
dr 5:1
2.54 3.56 0.19 1.00 1.19 1.18 2.98 0.58 1.19 2.18 0.20 1.19 1.03 0.20 0.53 3.00
f1 (ppm)


178.74
143.87 142.06 141.91 137.01 136.41 136.22 128.46 128.37 128.28 128.23 125.79 125.71 119.33 118.60
83.47 82.19
54.64 52.29 52.06 51.45 50.88
33.68 33.39 30.13 29.84 29.68
18.61 17.28
Parameter Value
1 Title mp-3-153-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 72
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-18T11:01:15
10 Spectrometer Frequency 125.70
Ph
O
OH
OMe
83b
dr 5:1
f1 (ppm)

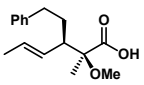

Parameter Value
1 Title mp-3-140-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-08T09:02:49
10 Spectrometer Frequency 499.86
Ph
O
OH
OBn
83c
dr 20:1
7.89
3.16
1.05
1.00
2.01
1.06
2.10
1.04
4.06
2.93
f1 (ppm)


179.43
142.26
138.42
130.02
129.07
128.41
128.27
128.21
127.45
127.30
125.65
82.93
66.72
51.07
33.76
30.60
18.38
18.08
Parameter Value
1 Title mp-3-140-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 76
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-08T09:08:12
10 Spectrometer Frequency 125.70
Ph
O
OH
OBn
83c
dr 20:1
f1 (ppm)

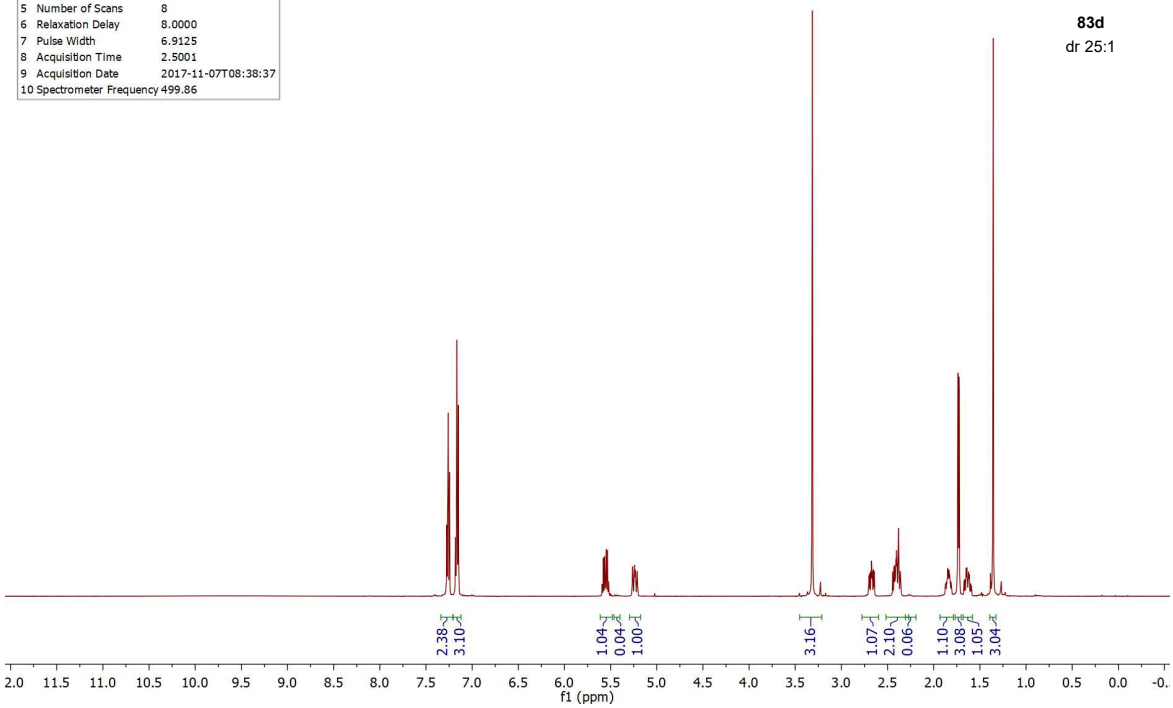

Parameter Value
1 Title mp-3-141-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-13T15:05:13
10 Spectrometer Frequency 499.86
Ph
O
OH
OBn
83c
dr 2:1
84c
5.39
6.91
4.66
2.26
1.03
2.59
0.60
1.62
2.55
0.71
0.58
1.00
6.01
0.77
1.76
3.08
f1 (ppm)

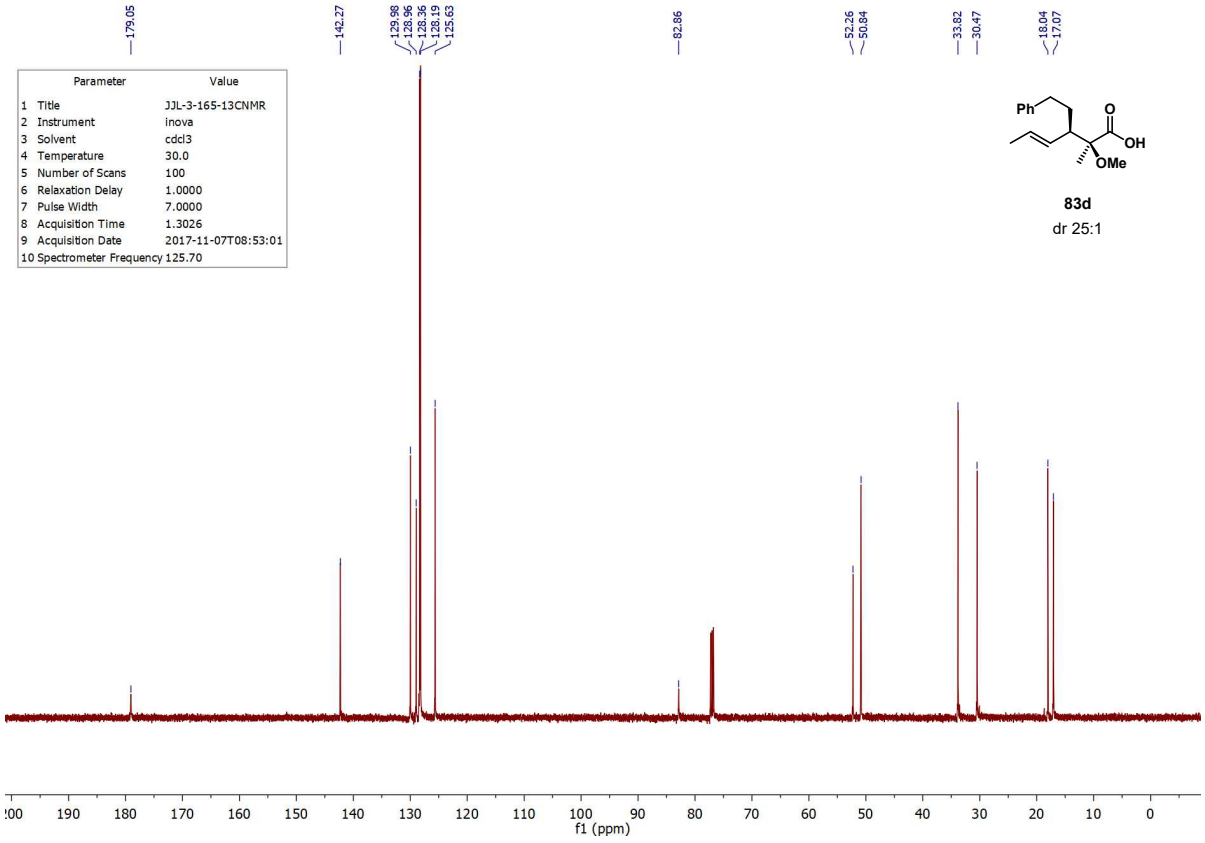

179.06
142.26
142.13
138.37
138.04
130.06
129.66
129.35
129.05
128.53
128.41
128.36
128.32
128.29
128.28
128.21
127.62
127.47
127.40
127.31
125.75
125.65
82.96
82.73
66.73
65.99
51.04
50.20
33.77
33.46
30.62
30.13
19.83
18.40
18.08
18.01
Parameter Value
1 Title mp-3-141-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 80
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-11T11:44:38
10 Spectrometer Frequency 125.70
Ph
O
OH
OBn
83c
dr 2:1
84c
f1 (ppm)

Parameter	Value
1 Title	JJL-3-165-b
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.9125
8 Acquisition Time	2.5001
9 Acquisition Date	2017-11-07T08:38:37
10 Spectrometer Frequency	499.86



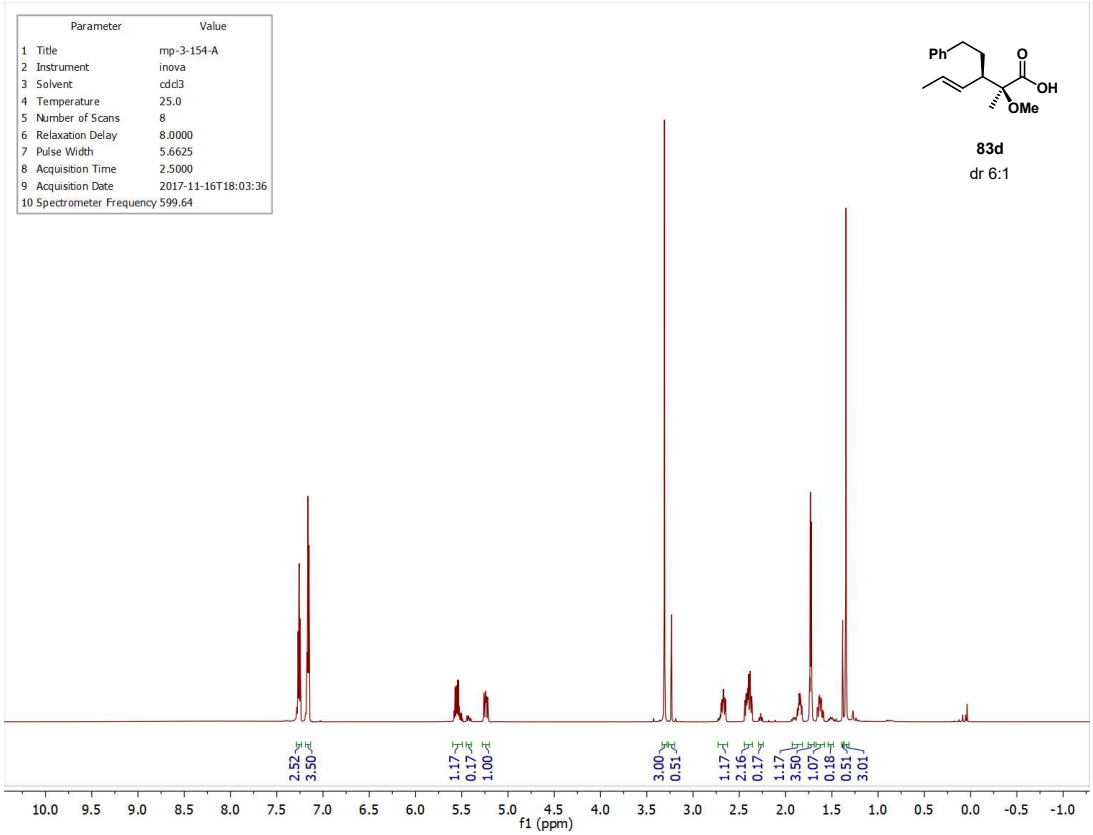
83d
dr 25:1

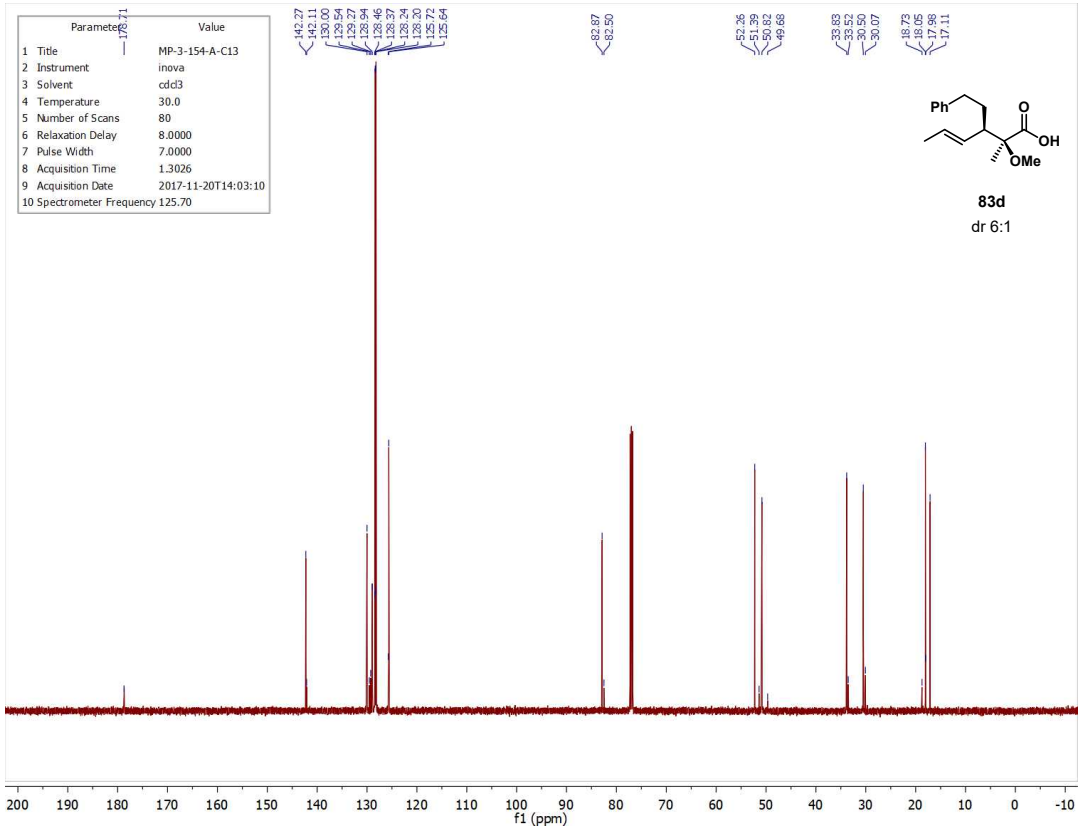


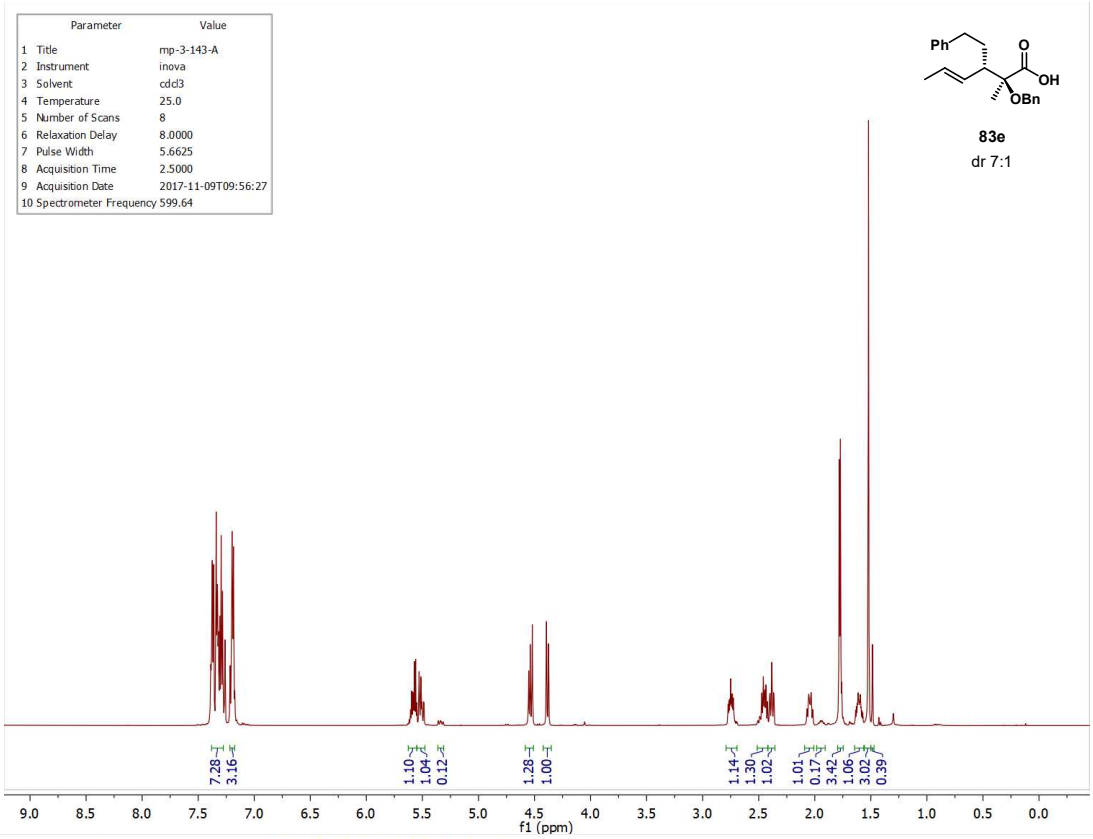


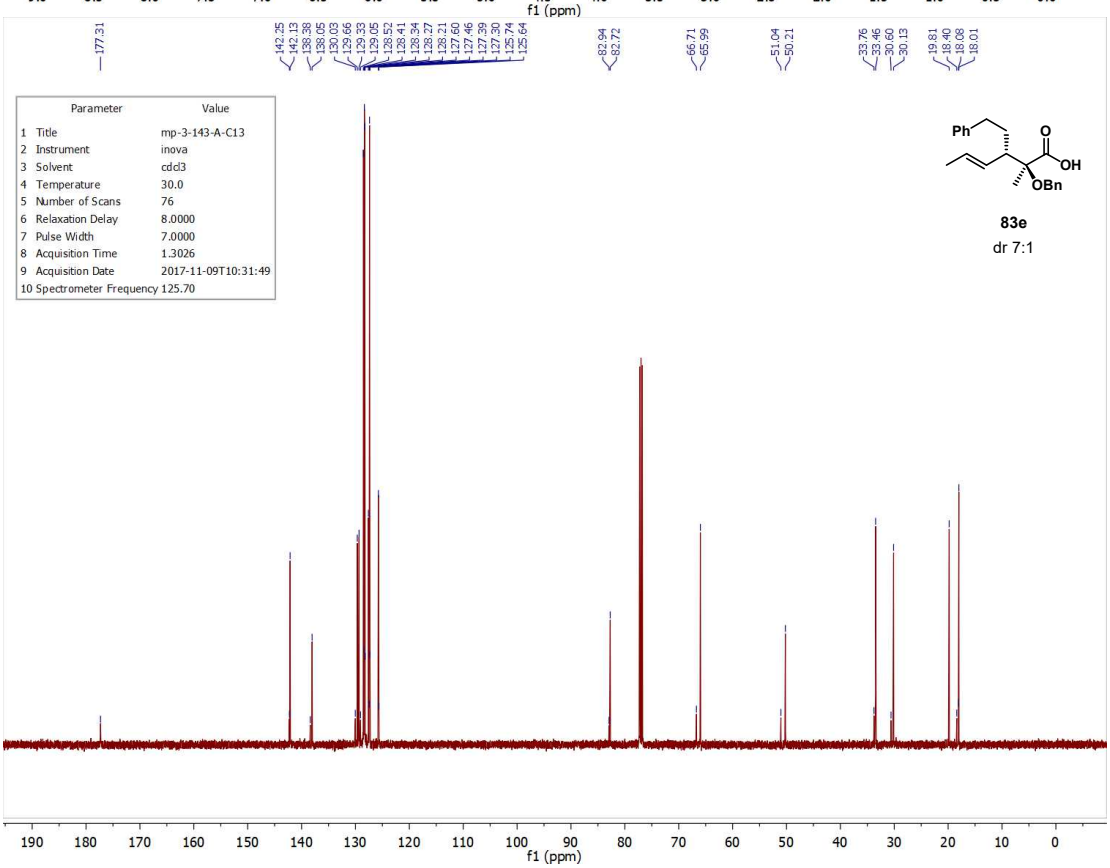
Parameter	Value
1 Title	JJL-3-165-13CNMR
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	100
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-11-07T08:53:01
10 Spectrometer Frequency	125.70

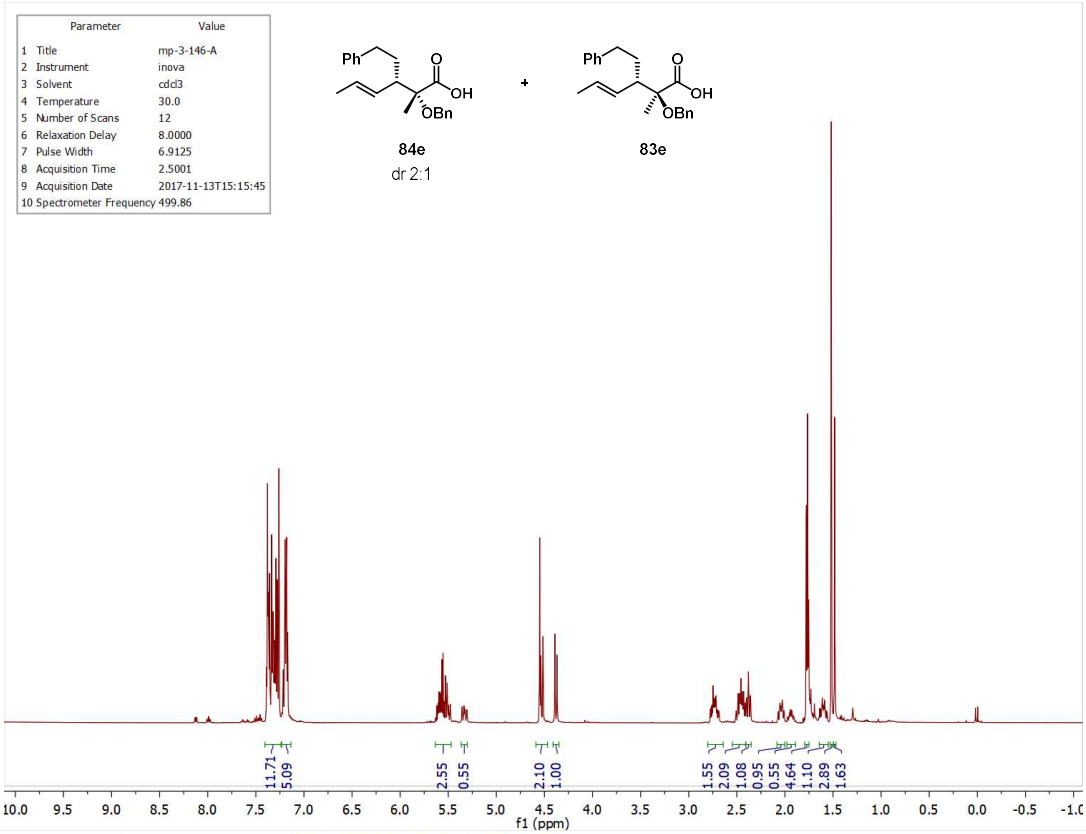
83d
dr 25:1

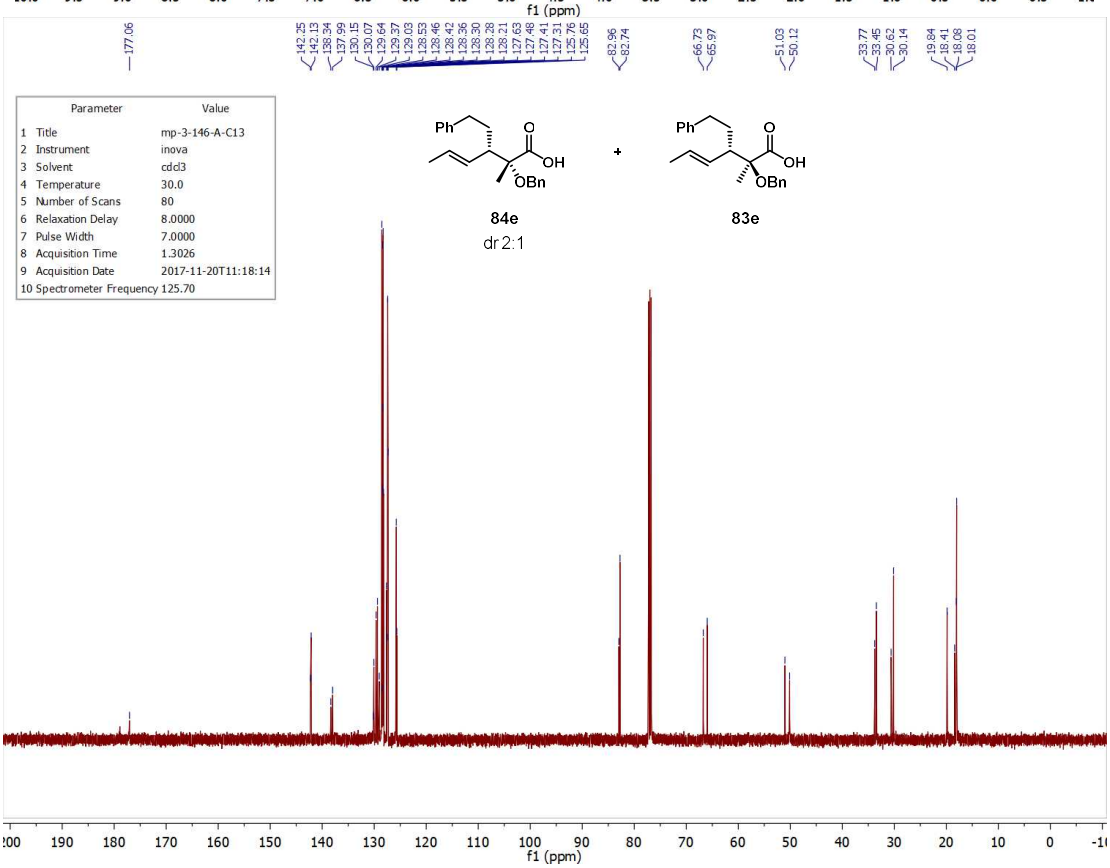

Parameter Value
1 Title mp-3-154-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2017-11-16T18:03:36
10 Spectrometer Frequency 599.64
Ph
O
OH
OMe
83d
dr 6:1
2.52
3.50
1.17
0.17
1.00
3.00
0.51
1.17
2.16
0.17
1.17
3.50
1.07
0.18
0.51
3.01
f1 (ppm)


Parameter Value
1 Title MP-3-154-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 80
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-20T14:03:10
10 Spectrometer Frequency 125.70
178.71
142.27
142.11
130.00
129.54
129.27
128.94
128.46
128.37
128.24
128.20
125.72
125.64
82.87
82.50
52.26
51.39
50.82
49.68
33.83
33.52
30.50
30.07
18.73
18.05
17.98
17.11
Ph
O
OH
OMe
83d
dr 6:1
f1 (ppm)

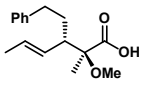

Parameter Value
1 Title mp-3-143-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2017-11-09T09:56:27
10 Spectrometer Frequency 599.64
Ph
O
OH
OBn
83e
dr 7:1
7.28
3.16
1.10
1.04
0.12
1.28
1.00
1.14
1.30
1.02
1.01
0.17
3.42
1.06
3.02
0.39
f1 (ppm)


177.31
142.25
142.13
138.38
138.05
130.03
129.66
129.33
129.05
128.52
128.41
128.34
128.27
128.21
127.60
127.46
127.39
127.30
125.74
125.64
82.94
82.72
66.71
65.99
51.04
50.21
33.76
33.46
30.60
30.13
19.81
18.40
18.08
18.01
Parameter Value
1 Title mp-3-143-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 76
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-09T10:31:49
10 Spectrometer Frequency 125.70
Ph
O
OH
OBn
83e
dr 7:1
f1 (ppm)


Parameter Value
1 Title mp-3-146-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-13T15:15:45
10 Spectrometer Frequency 499.86
Ph
O
OH
OBn
84e
dr 2:1
83e
11.71
5.09
2.55
0.55
2.10
1.00
1.55
2.09
1.08
0.95
0.55
4.64
1.10
2.89
1.63
f1 (ppm)

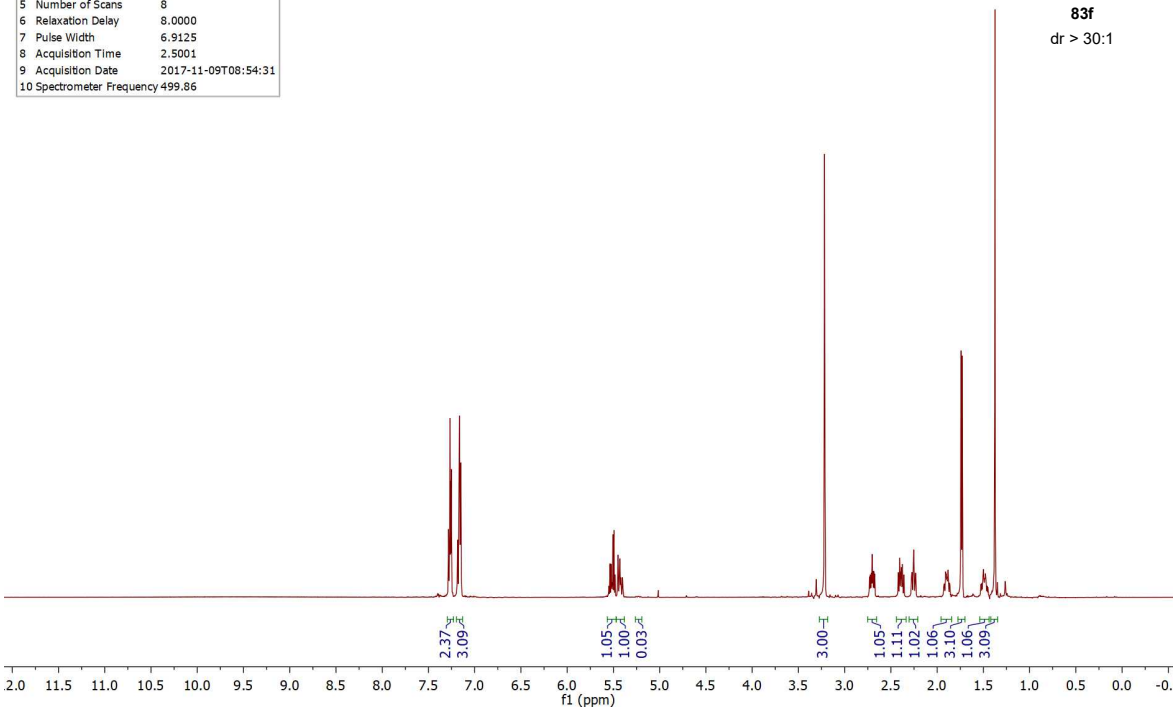

177.06
142.25
142.13
138.34
137.99
130.15
130.07
129.64
129.57
129.03
128.53
128.46
128.42
128.36
128.30
128.28
128.21
127.63
127.48
127.41
127.31
125.76
125.65
82.96
82.74
66.73
65.97
51.03
50.12
33.77
33.45
30.62
30.14
19.84
18.41
18.08
18.01
Parameter Value
1 Title mp-3-146-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 80
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-20T11:18:14
10 Spectrometer Frequency 125.70
Ph
O
OH
OBn
84e
dr 2:1
83e
f1 (ppm)

	Parameter	Value
1	Title	JJL-3-171-b
2	Instrument	inova
3	Solvent	cdcl3
4	Temperature	30.0
5	Number of Scans	8
6	Relaxation Delay	8.0000
7	Pulse Width	6.9125
8	Acquisition Time	2.5001
9	Acquisition Date	2017-11-09T08:54:31
10	Spectrometer Frequency	499.86

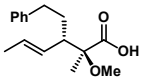


83f

dr > 30:1

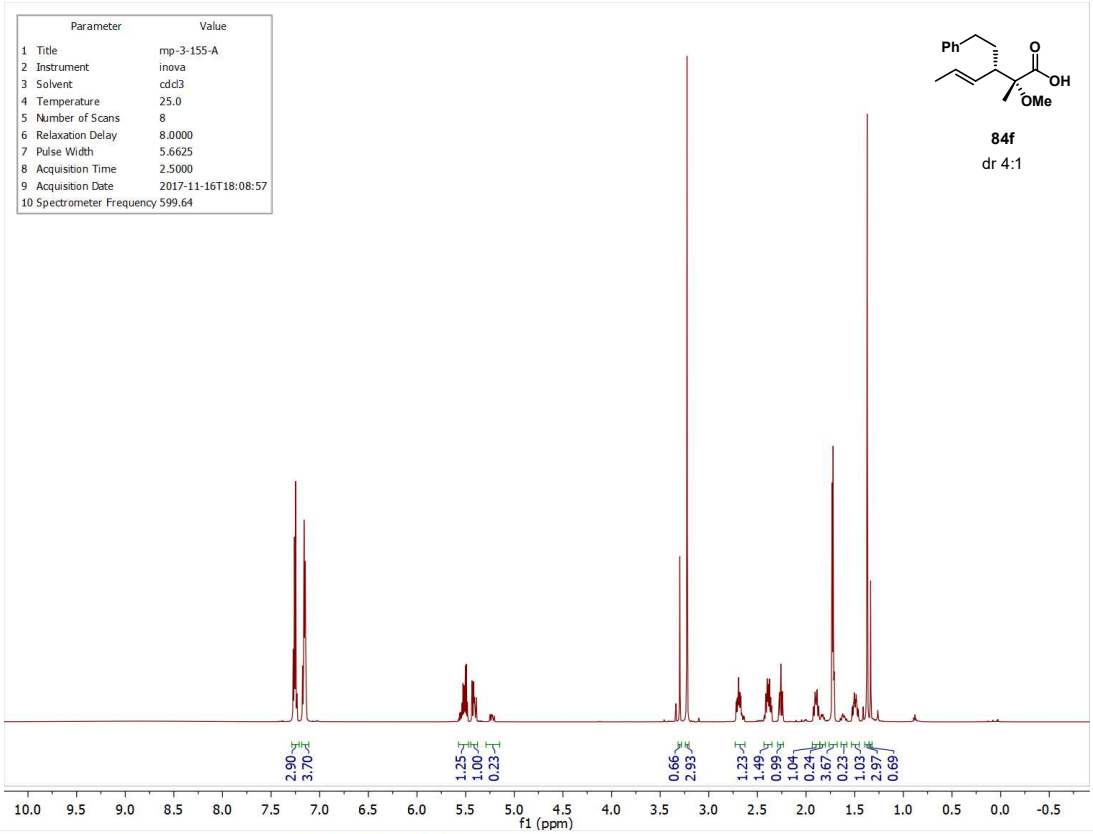


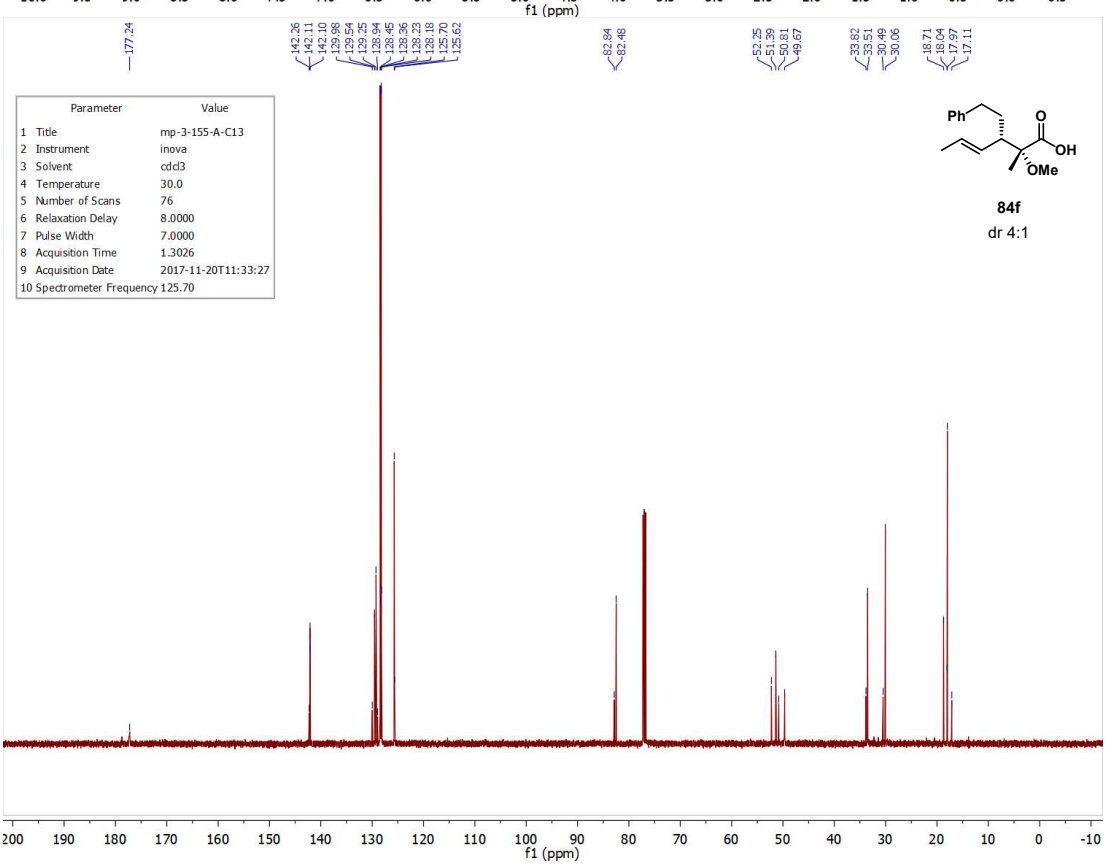
	Parameter	Value
1	Title	JJL-3-171-13CNMR
2	Instrument	inova
3	Solvent	d2o
4	Temperature	30.0
5	Number of Scans	80
6	Relaxation Delay	1.0000
7	Pulse Width	7.0000
8	Acquisition Time	1.3026
9	Acquisition Date	2017-11-09T09:33:30
10	Spectrometer Frequency	125.70

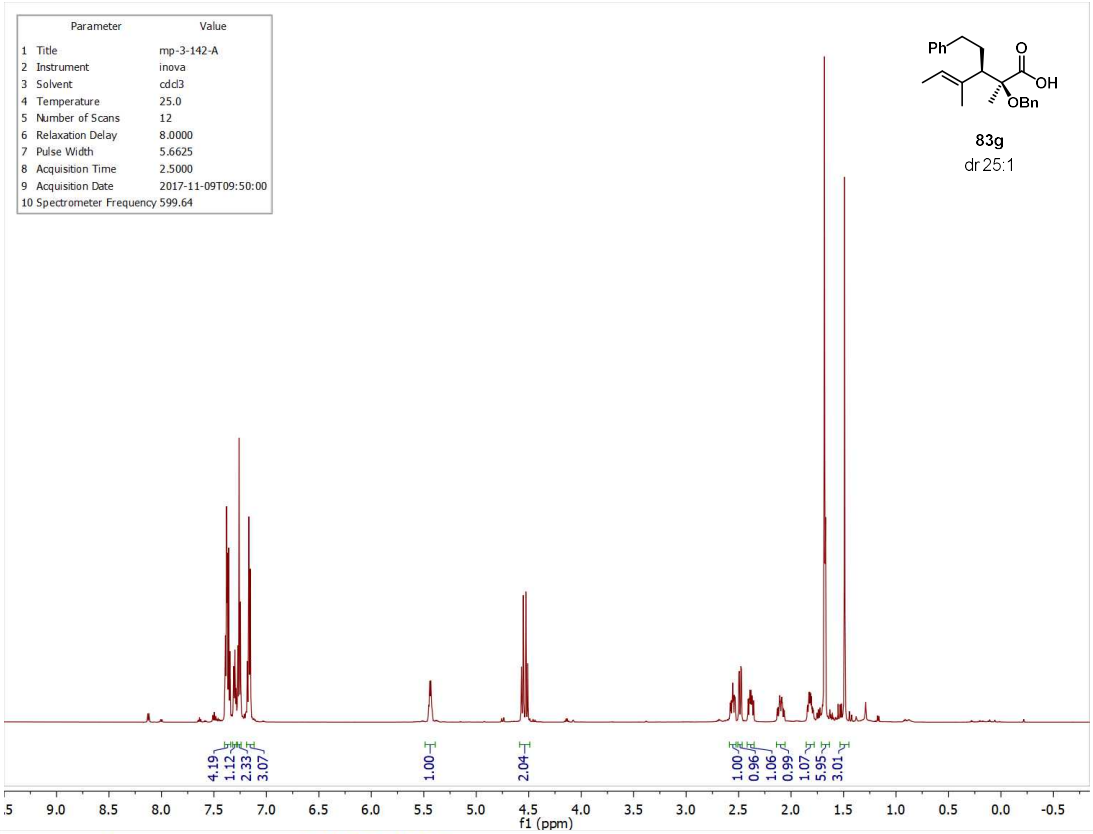


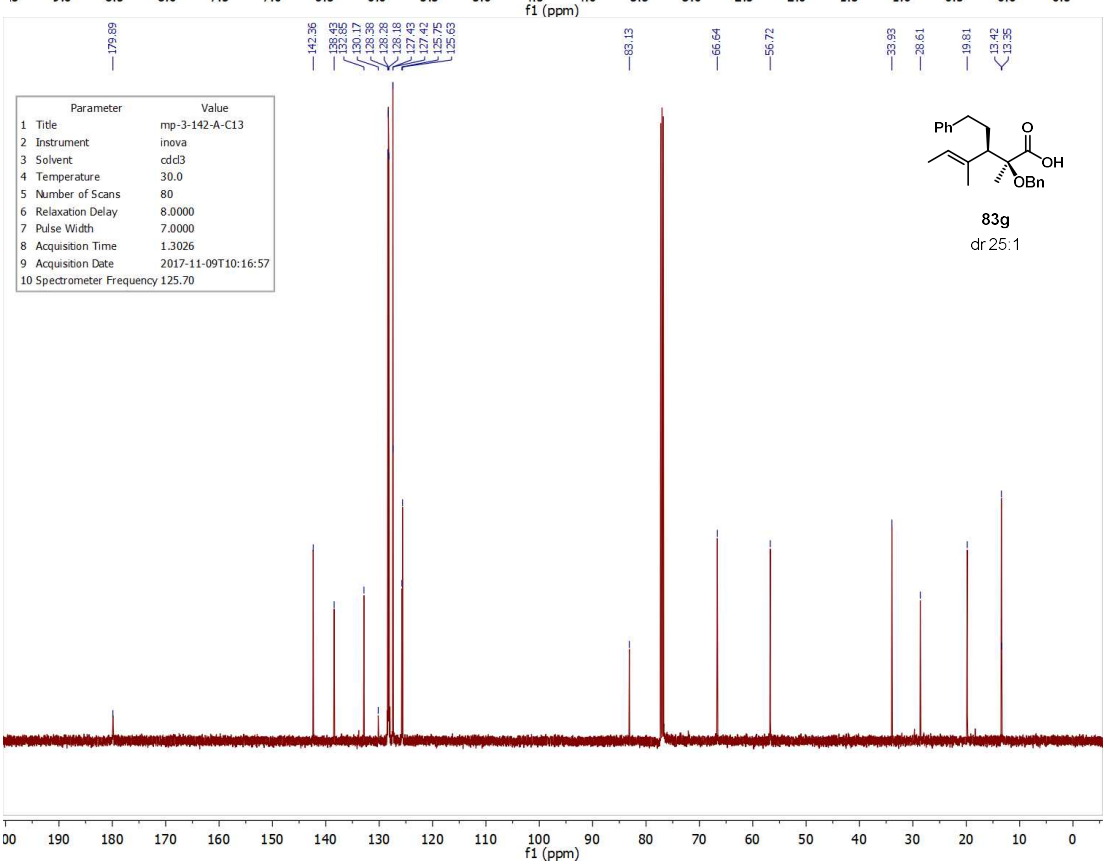
83f

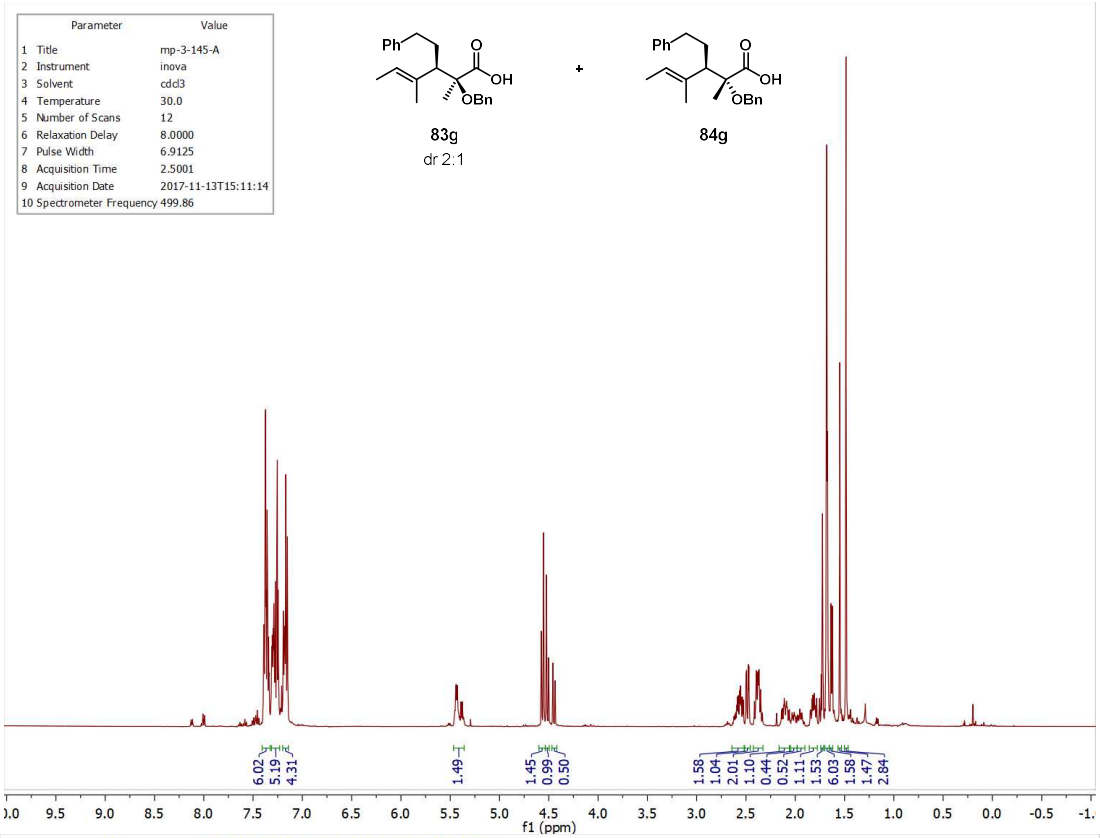
dr > 30:1

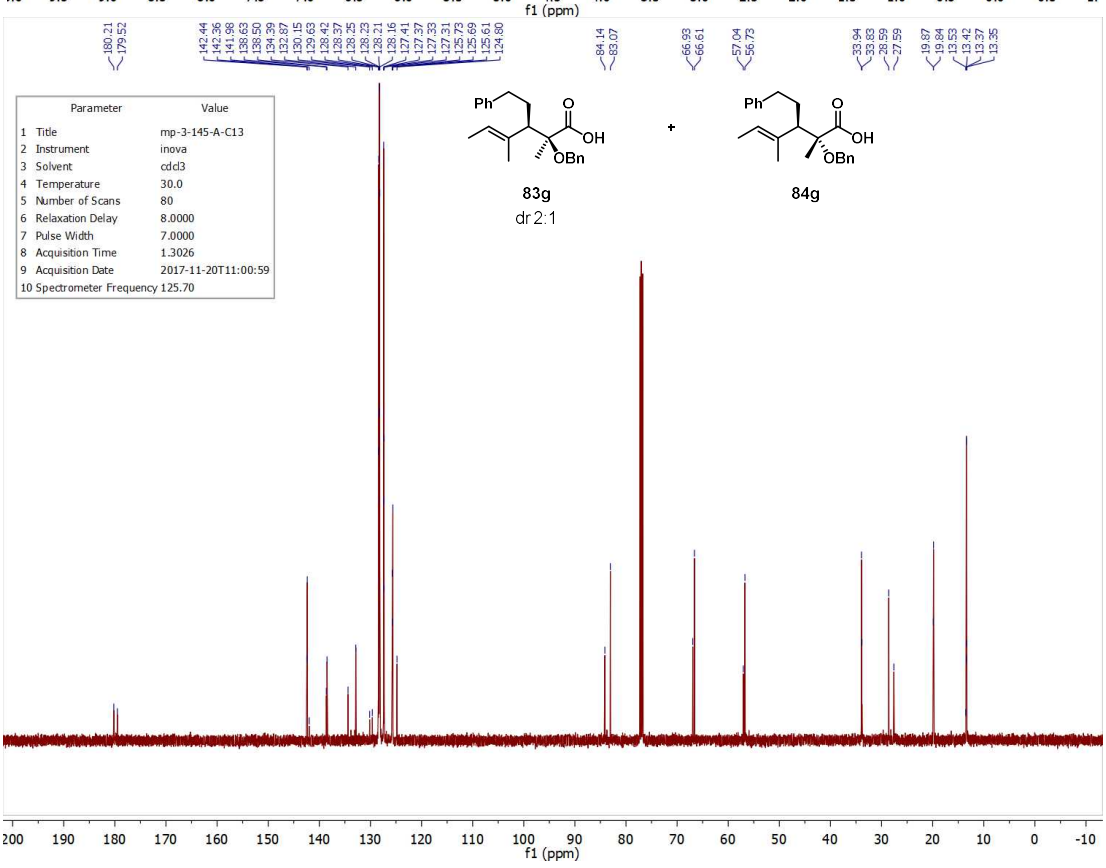

Parameter Value
1 Title mp-3-155-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2017-11-16T18:08:57
10 Spectrometer Frequency 599.64
Ph
O
OH
OMe
84f
dr 4:1
2.90
3.70
1.25
1.00
0.23
0.66
2.93
1.23
1.49
0.99
1.04
0.24
3.67
0.23
1.03
2.97
0.69
f1 (ppm)


177.24
142.26
142.11
142.10
129.98
129.54
129.25
128.94
128.45
128.36
128.23
128.18
125.70
125.62
82.84
82.48
52.25
51.39
50.81
49.67
33.82
33.51
30.49
30.06
18.71
18.64
17.97
17.11
Parameter Value
1 Title mp-3-155-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 76
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-20T11:33:27
10 Spectrometer Frequency 125.70
Ph
O
OH
OMe
84f
dr 4:1
f1 (ppm)

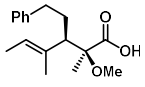

Parameter Value
1 Title mp-3-142-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2017-11-09T09:50:00
10 Spectrometer Frequency 599.64
Ph
O
OH
OBn
83g
dr 25:1
4.19
1.12
2.33
3.07
1.00
2.04
1.00
0.96
1.06
0.99
1.07
5.95
3.01
f1 (ppm)


179.89
142.36
138.43
132.85
130.17
128.38
128.28
128.18
127.43
127.42
125.75
125.63
83.13
66.64
56.72
33.93
28.61
19.81
13.42
13.35
Parameter Value
1 Title mp-3-142-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 80
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-09T10:16:57
10 Spectrometer Frequency 125.70
Ph
O
OH
OBn
83g
dr 25:1
f1 (ppm)

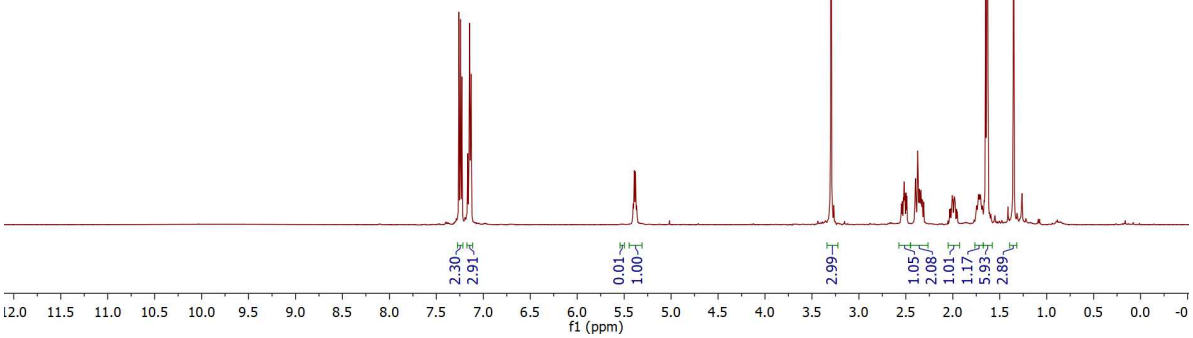

Parameter Value
1 Title mp-3-145-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-13T15:11:14
10 Spectrometer Frequency 499.86
Ph
O
OH
OBn
83g
dr 2:1
84g
6.02
5.19
4.31
1.49
1.45
0.99
0.50
1.58
1.04
2.01
1.10
0.44
0.52
1.11
1.53
6.03
1.58
1.47
2.84
f1 (ppm)


180.21
179.52
142.44
142.36
141.98
138.63
138.50
134.39
132.87
130.15
129.63
128.42
128.37
128.33
128.21
128.16
127.41
127.37
127.33
127.31
125.73
125.69
125.61
124.80
84.14
83.07
66.93
66.61
57.04
56.73
38.94
38.83
38.59
27.59
19.87
19.84
13.53
13.42
13.37
13.35
Parameter Value
1 Title mp-3-145-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 80
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-20T11:00:59
10 Spectrometer Frequency 125.70
Ph
O
OH
OBn
83g
dr 2:1
84g
f1 (ppm)

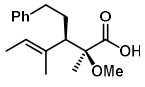
Parameter	Value
1 Title	JJL-3-166-b
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.9125
8 Acquisition Time	2.5001
9 Acquisition Date	2017-11-09T08:42:23
10 Spectrometer Frequency	499.86



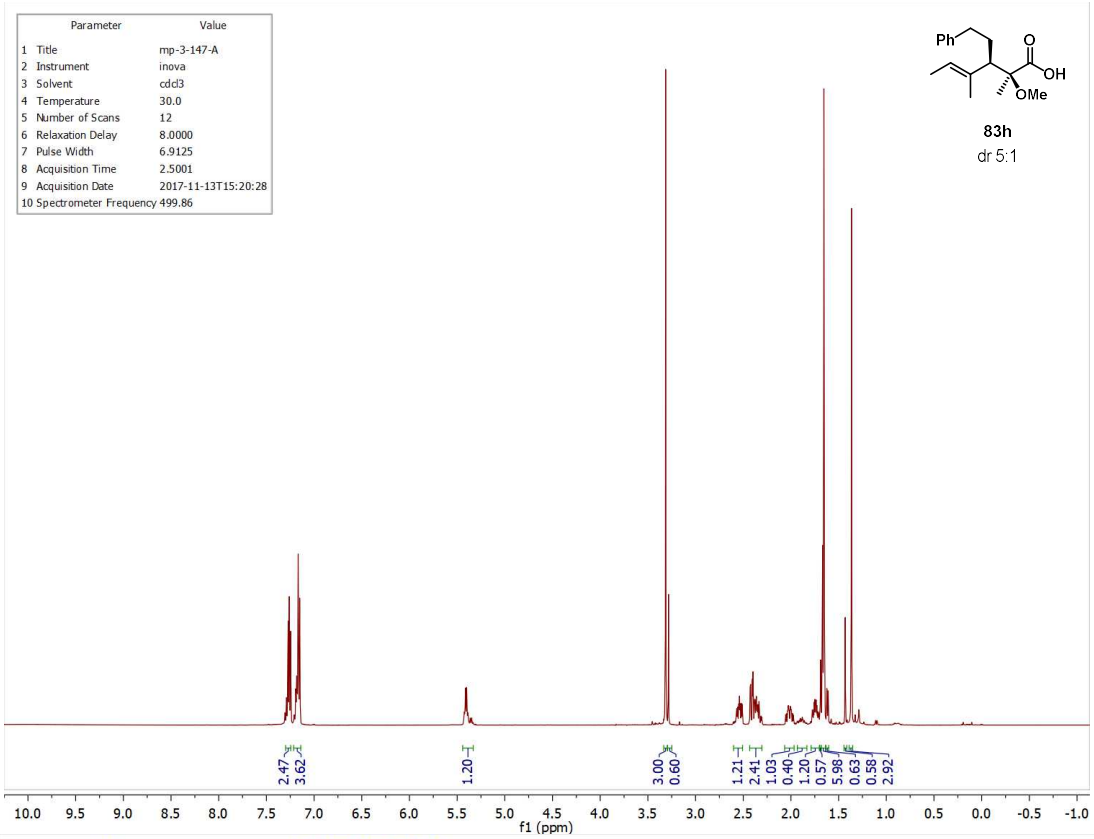
83h
dr 30:1

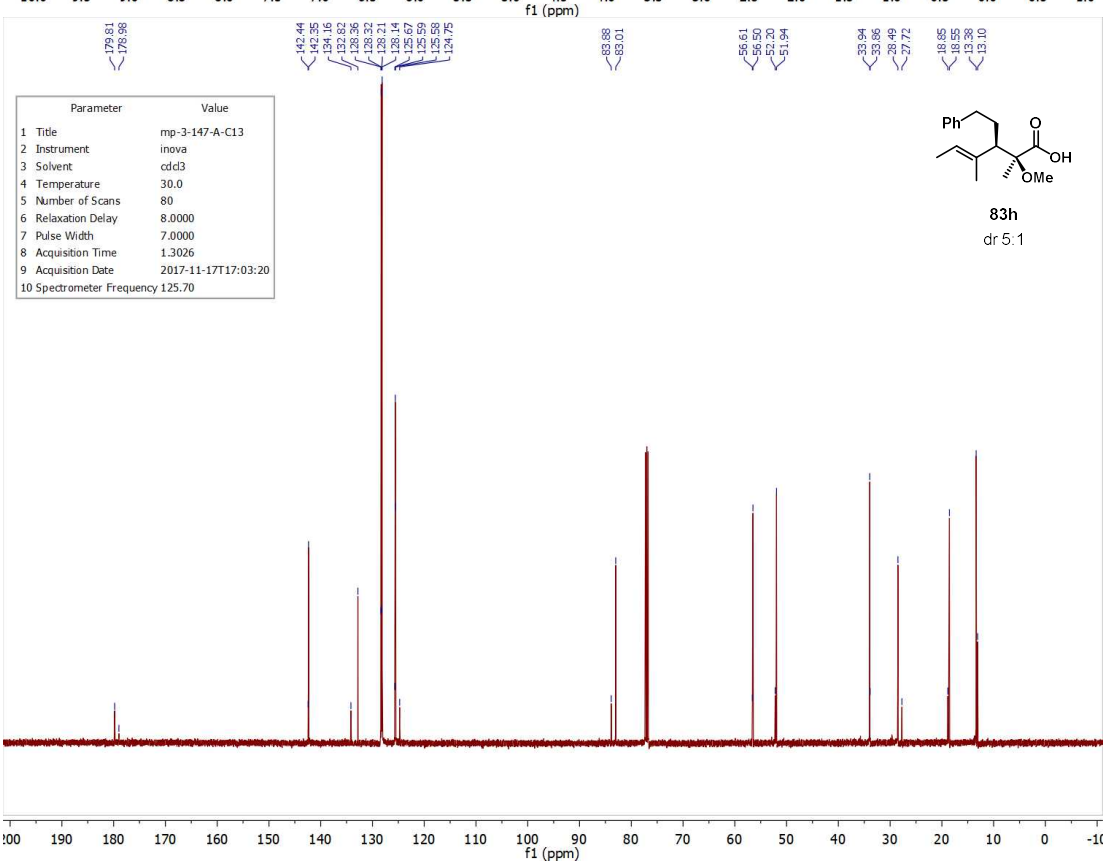


Parameter	Value
1 Title	JJL-3-166-13CNMR
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	84
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-11-09T09:22:00
10 Spectrometer Frequency	125.70

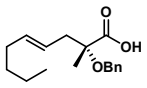


83h
dr 30:1

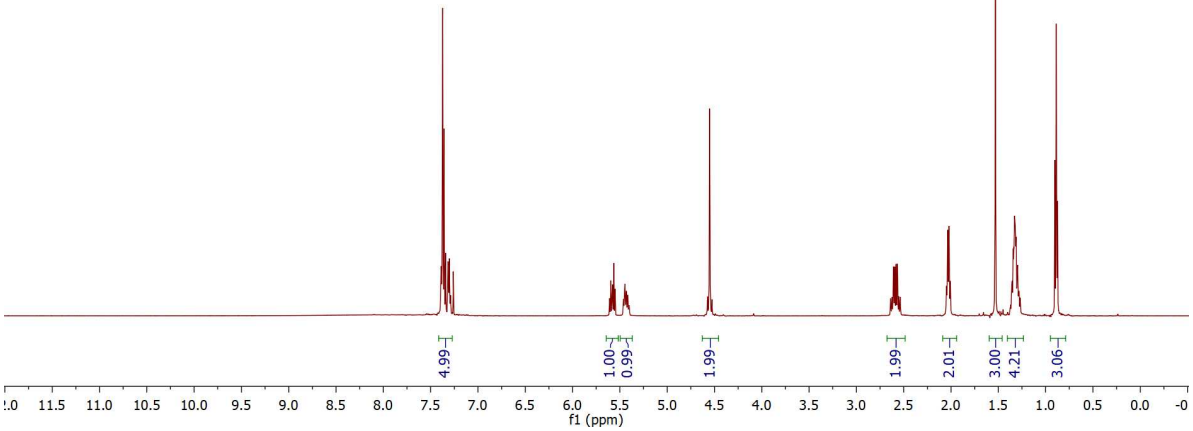

Parameter Value
1 Title mp-3-147-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-13T15:20:28
10 Spectrometer Frequency 499.86
Ph
O
OH
OMe
83h
dr 5:1
2.47 3.62 1.20 3.00 0.60 1.21 2.41 1.03 0.40 1.20 0.57 5.98 0.63 0.58 2.92
f1 (ppm)


179.81 178.98 142.44 142.35 134.16 132.82 128.36 128.32 128.21 126.14 125.67 125.59 125.58 124.75 83.88 83.01 56.61 56.50 52.20 51.94 33.94 33.86 28.49 27.72 18.85 18.55 13.38 13.10
Parameter Value
1 Title mp-3-147-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 80
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-17T17:03:20
10 Spectrometer Frequency 125.70
Ph
O
OH
OMe
83h
dr 5:1
f1 (ppm)

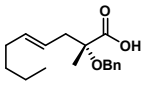
Parameter	Value
1 Title	JJL-3-162-b
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.9125
8 Acquisition Time	2.5001
9 Acquisition Date	2017-11-04T14:17:18
10 Spectrometer Frequency	499.86



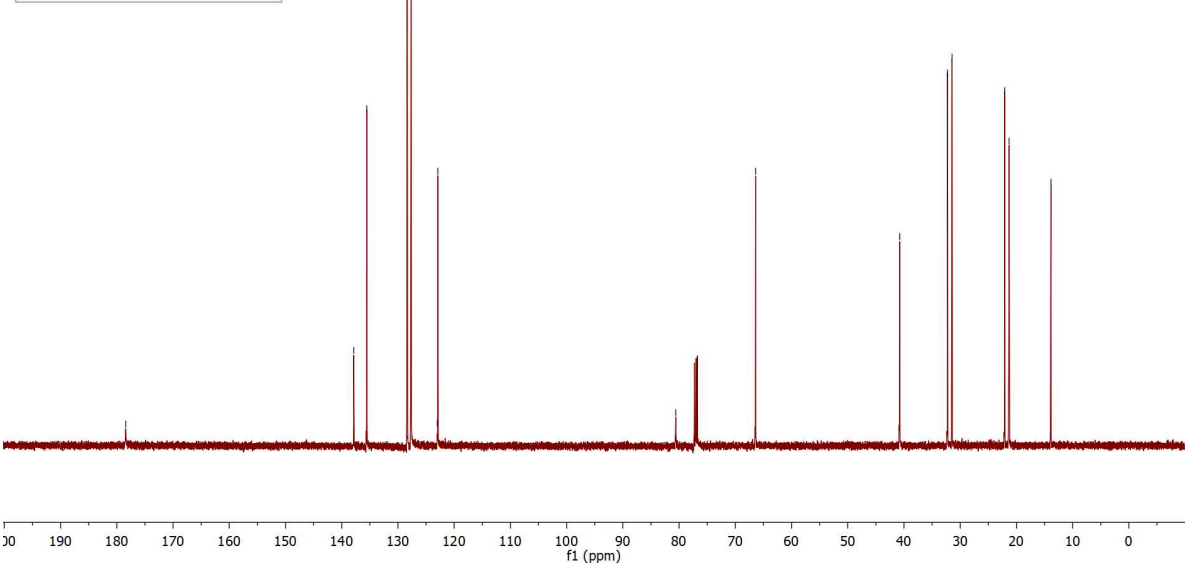
83i
er 11:1

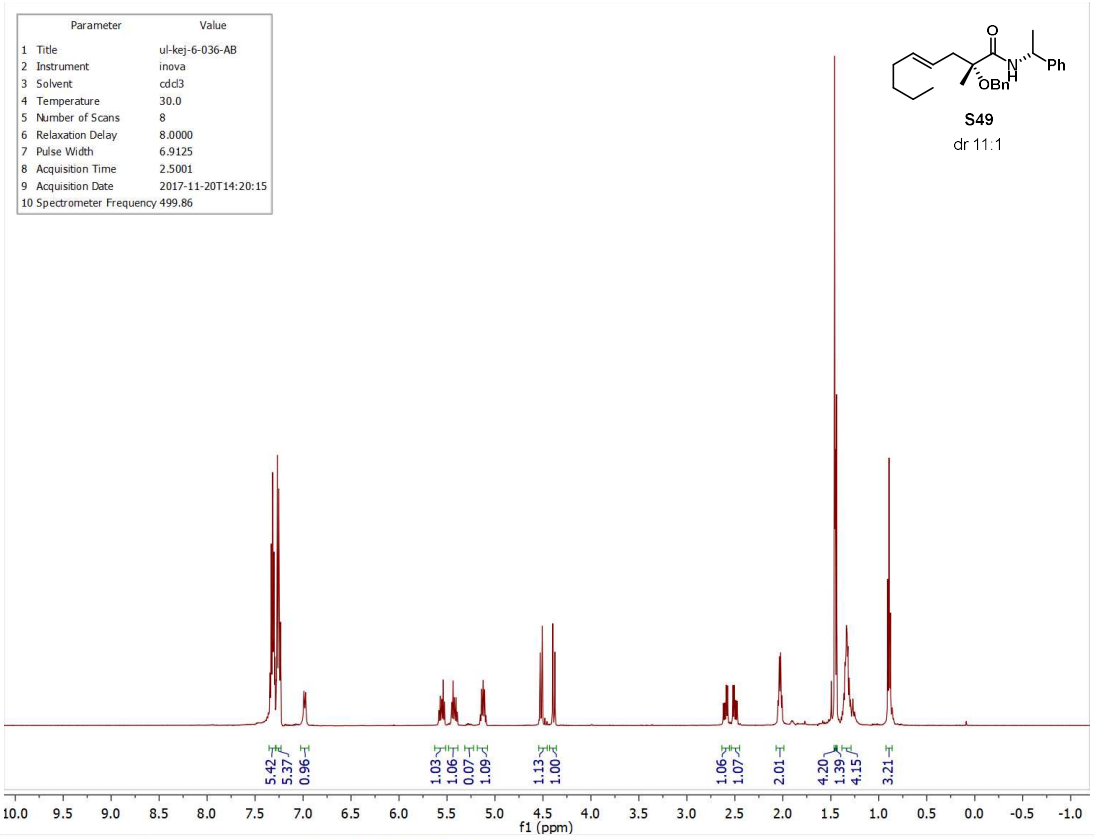


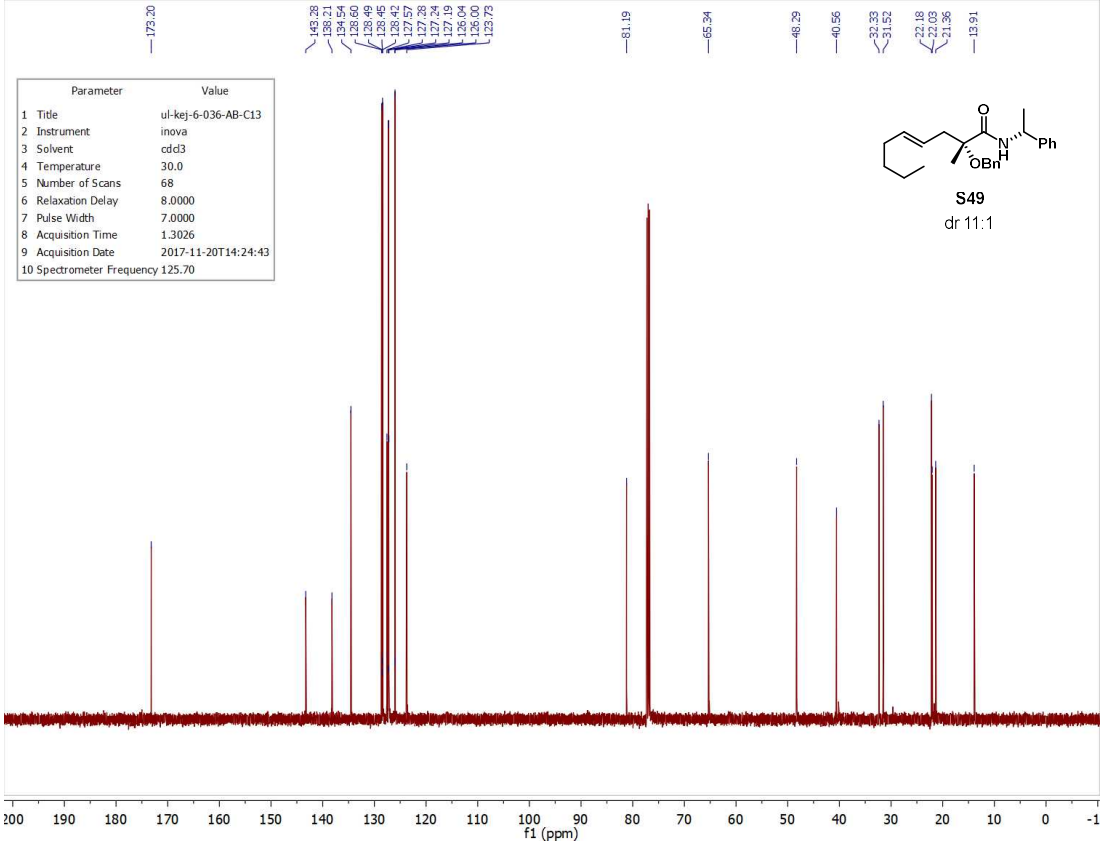
Parameter	Value
1 Title	JJL-3-162-13CNMR
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	80
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-11-04T15:27:24
10 Spectrometer Frequency	125.70

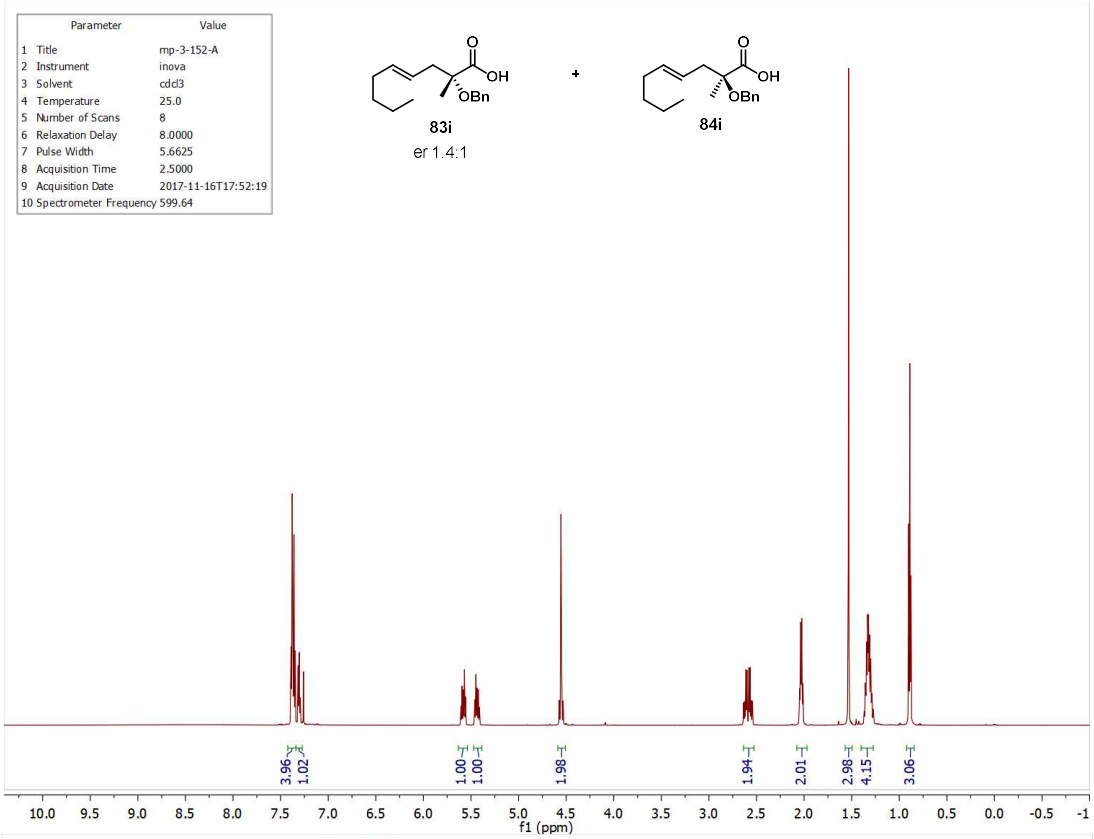


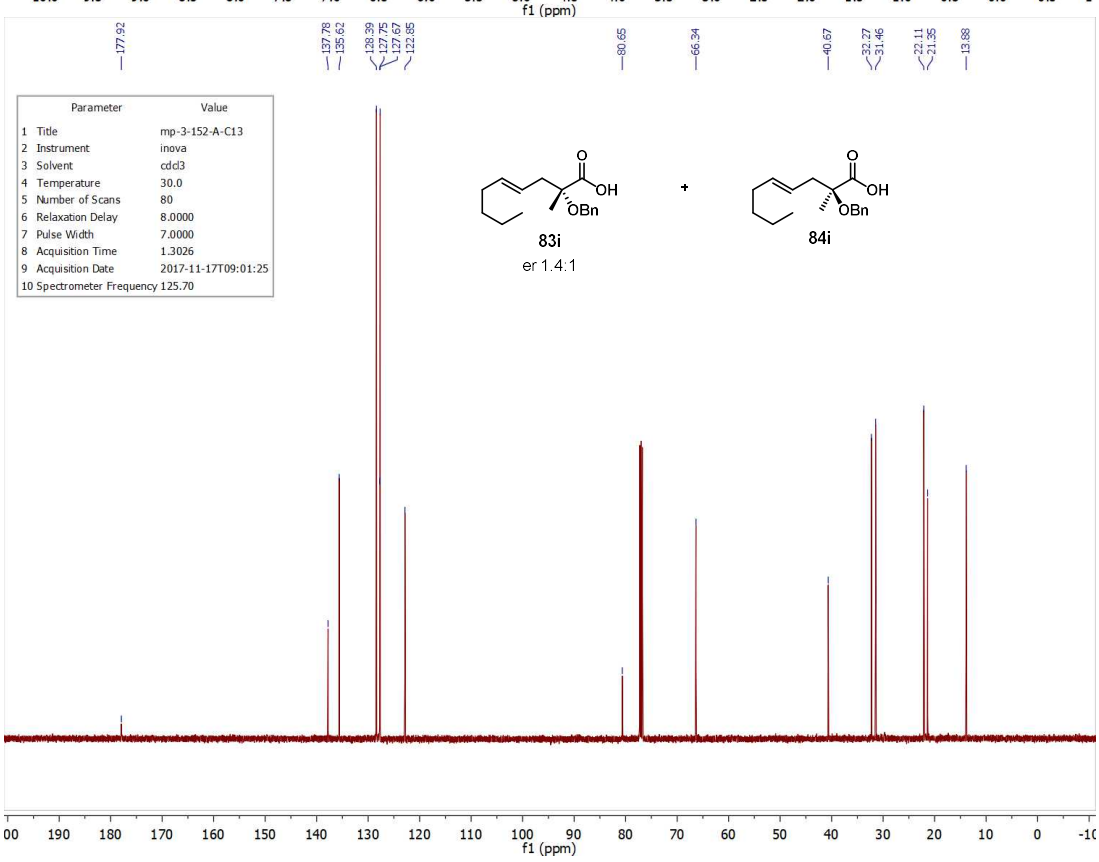
83i
er 11:1

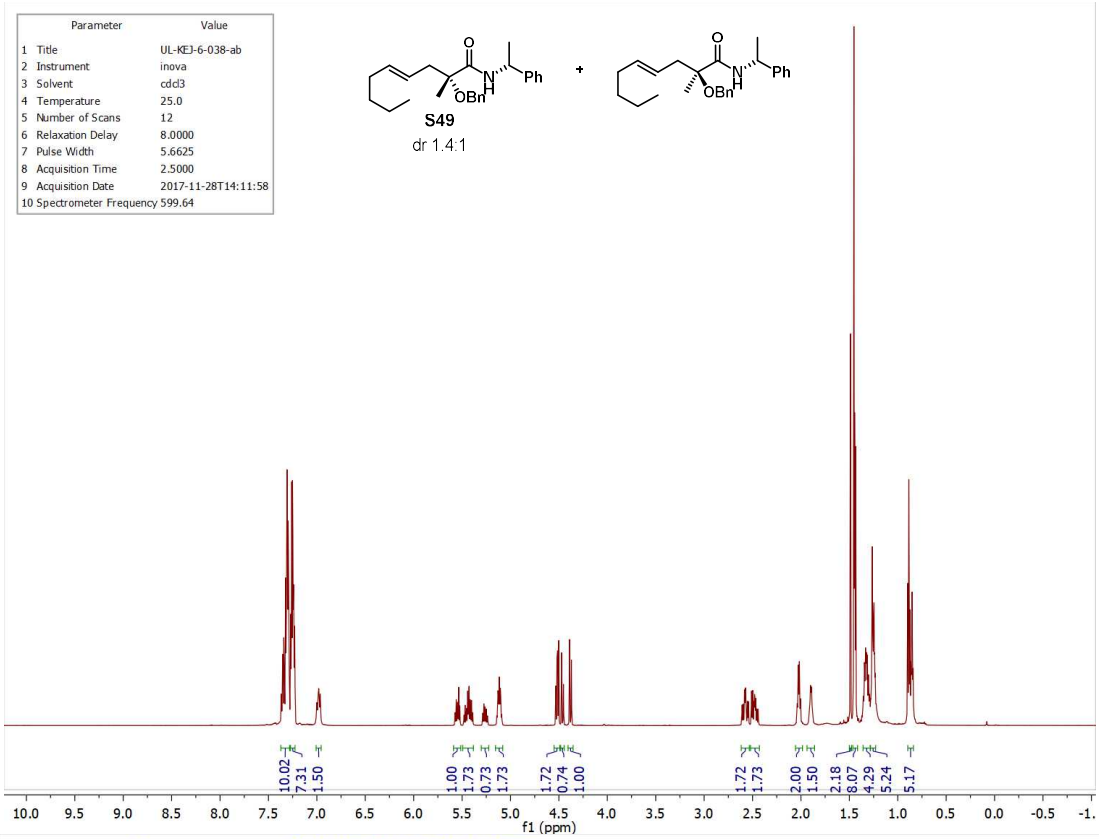


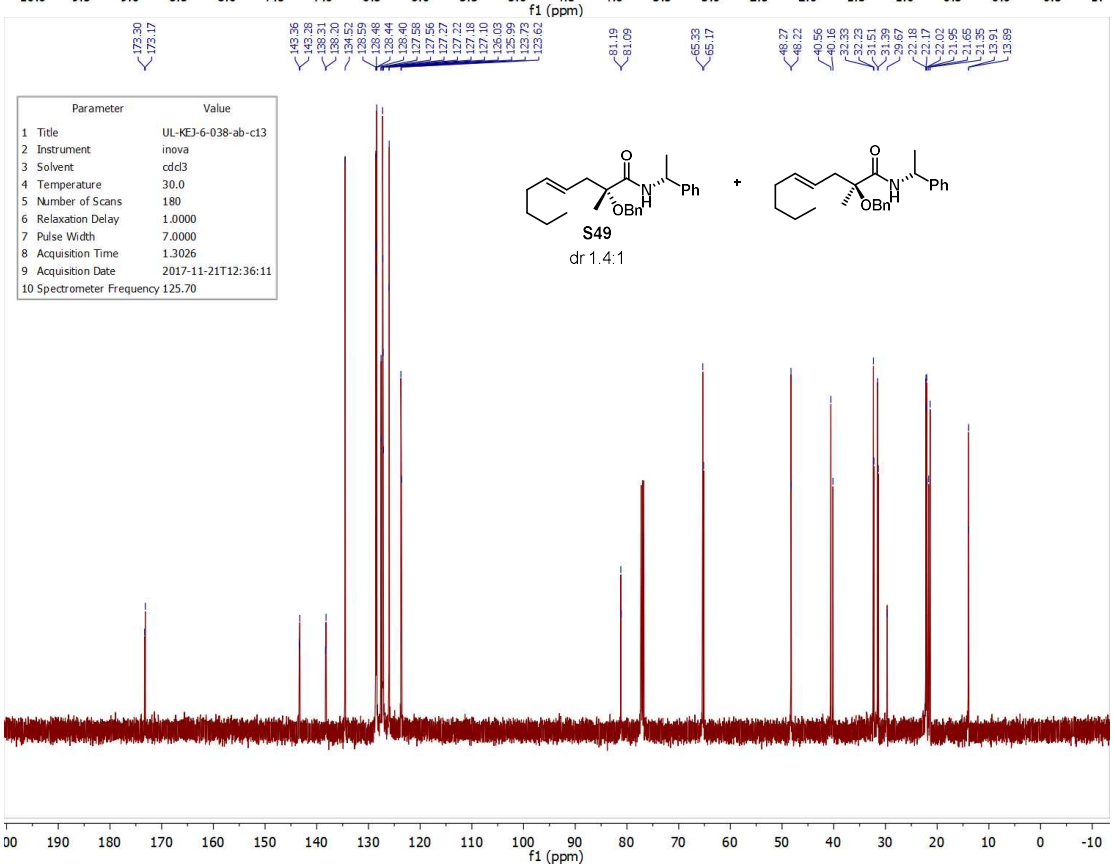

Parameter Value
1 Title ul-kej-6-036-AB
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-11-20T14:20:15
10 Spectrometer Frequency 499.86
S49
dr 11:1
5.42
5.37
0.96
1.03
1.06
0.07
1.09
1.13
1.00
1.06
1.07
2.01
4.20
1.39
4.15
3.21
f1 (ppm)


173.20
143.28
138.21
134.54
128.60
128.49
128.45
128.42
127.57
127.28
127.14
126.04
126.00
123.73
81.19
65.34
48.29
40.56
32.33
31.52
22.18
22.03
21.36
13.91
Parameter Value
1 Title ul-kej-6-036-AB-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 68
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-20T14:24:43
10 Spectrometer Frequency 125.70
S49
dr 11:1
f1 (ppm)

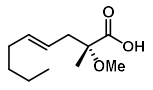

Parameter Value
1 Title mp-3-152-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2017-11-16T17:52:19
10 Spectrometer Frequency 599.64
OH
OBn
83i
er 1.4:1
84i
3.96
1.02
1.00
1.00
1.98
1.94
2.01
2.98
4.15
3.06
f1 (ppm)


177.92
137.78
135.62
128.39
127.75
127.67
122.85
80.65
66.34
40.67
32.27
31.46
22.11
21.35
13.88
Parameter Value
1 Title mp-3-152-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 80
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-17T09:01:25
10 Spectrometer Frequency 125.70
OH
OBn
83i
er 1.4:1
84i
f1 (ppm)

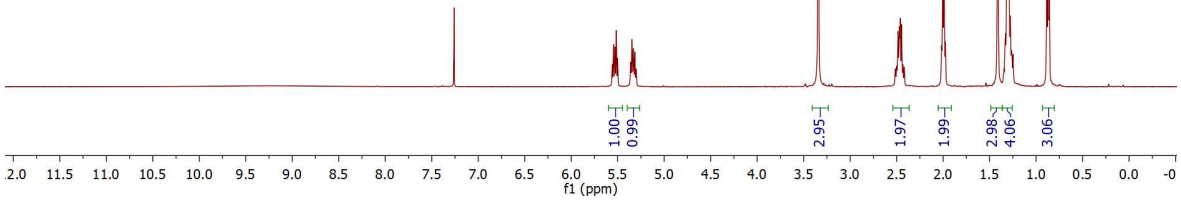

Parameter Value
1 Title UL-KEJ-6-038-ab
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2017-11-28T14:11:58
10 Spectrometer Frequency 599.64
S49
dr 1.4:1
10.02 7.31 1.50 1.00 1.73 0.73 1.73 1.72 0.74 1.00 1.72 1.73 2.00 1.50 2.18 8.07 4.29 5.24 5.17
f1 (ppm)


173.30 173.17 143.36 143.28 138.31 138.20 134.52 128.59 128.48 128.44 128.40 127.58 127.56 127.27 127.22 127.18 127.10 126.03 125.99 123.73 123.62 81.19 81.09 65.33 65.17 48.27 48.22 40.56 40.16 32.33 32.23 31.51 31.39 29.67 22.18 22.17 22.02 21.95 21.65 21.35 13.91 13.89
Parameter Value
1 Title UL-KEJ-6-038-ab-c13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 180
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-21T12:36:11
10 Spectrometer Frequency 125.70
S49
dr 1.4:1
f1 (ppm)

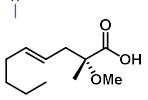
Parameter	Value
1 Title	JJL-3-167-b
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.9125
8 Acquisition Time	2.5001
9 Acquisition Date	2017-11-09T08:47:25
10 Spectrometer Frequency	499.86



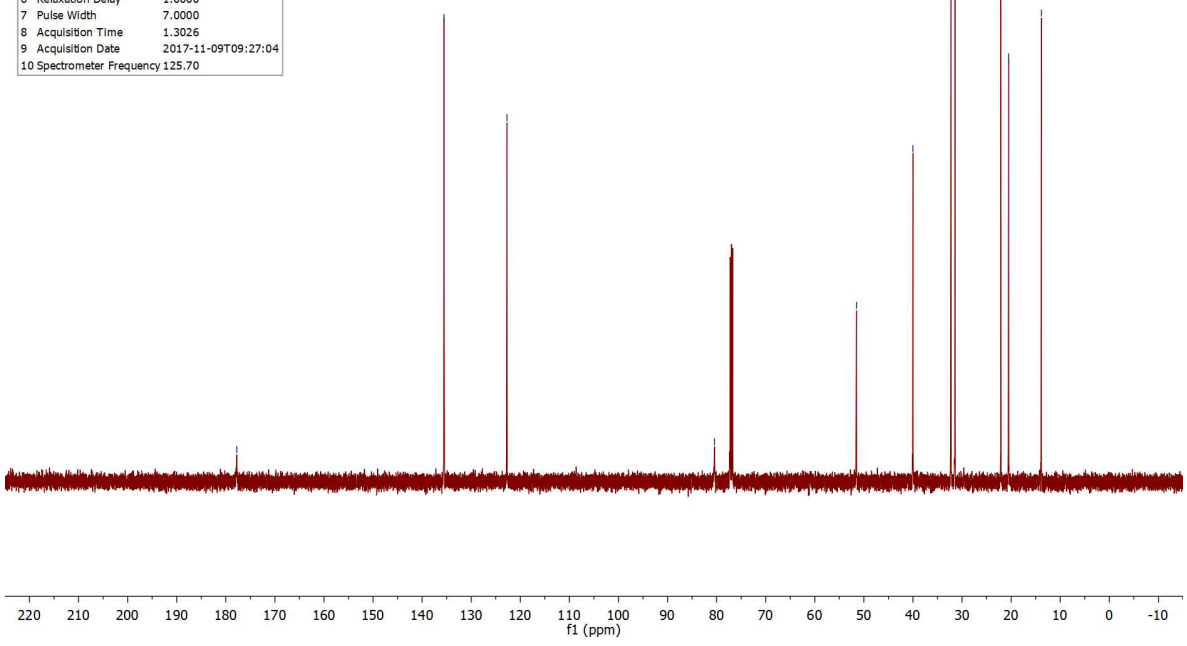
83j
er 14:1



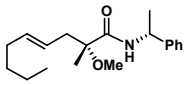
Parameter	Value
1 Title	JJL-3-167-13CNMR
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	100
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-11-09T09:27:04
10 Spectrometer Frequency	125.70



83j
er 14:1

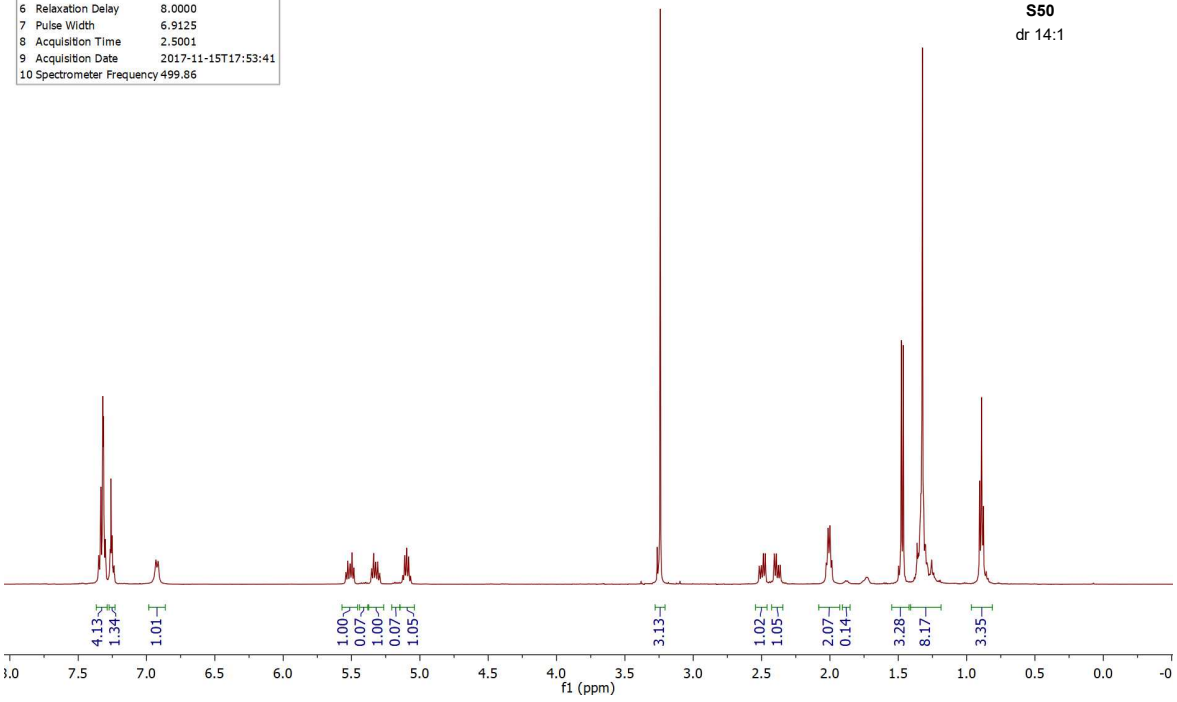


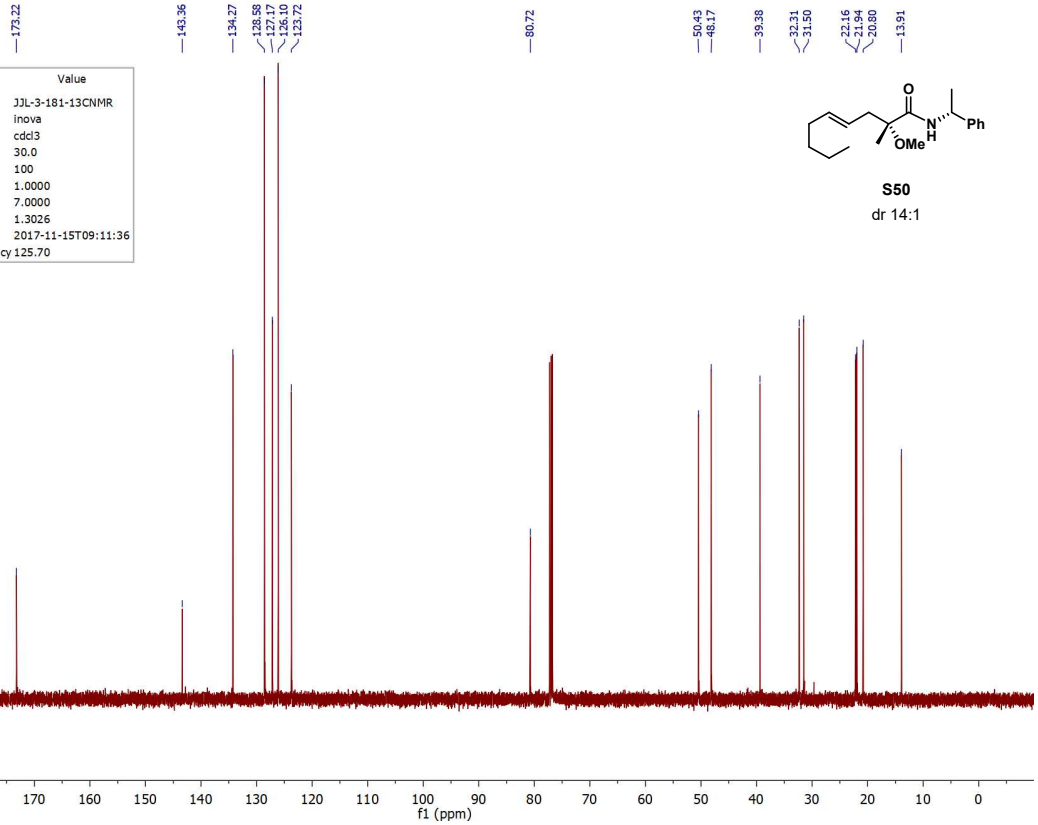
Parameter	Value
1 Title	JJL-3-181-a
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	8
6 Relaxation Delay	8.0000
7 Pulse Width	6.9125
8 Acquisition Time	2.5001
9 Acquisition Date	2017-11-15T17:53:41
10 Spectrometer Frequency	499.86



S50

dr 14:1

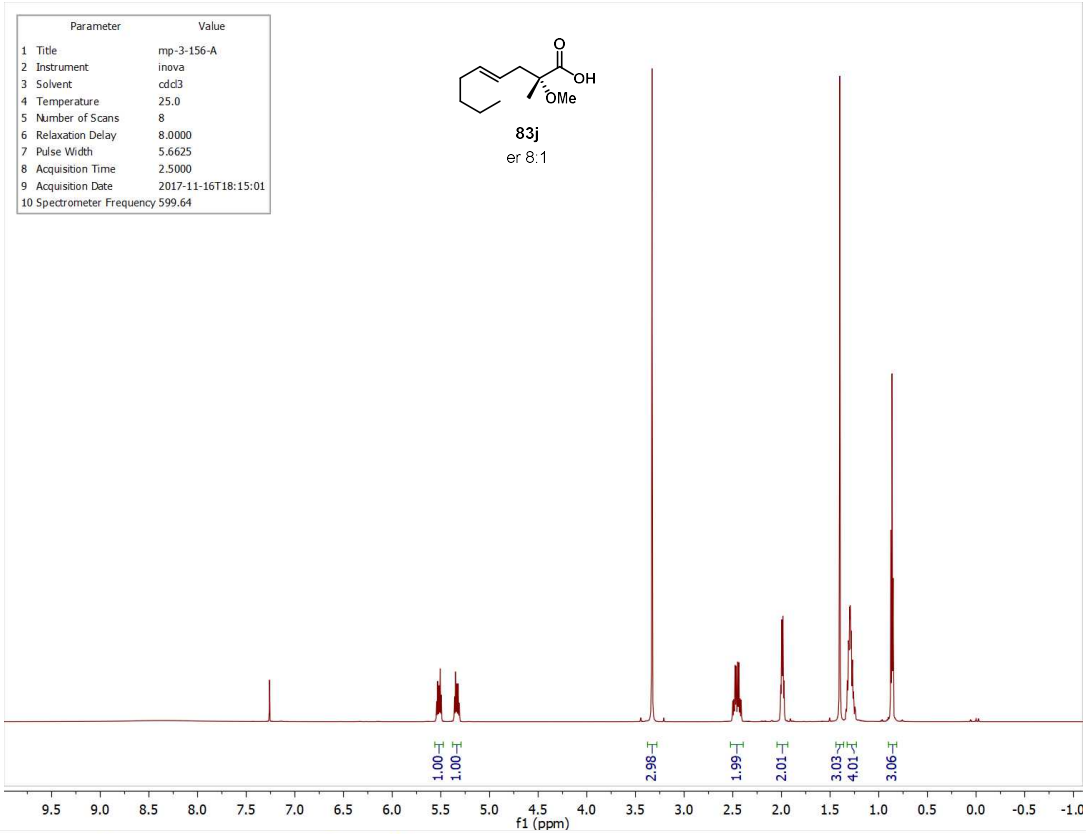


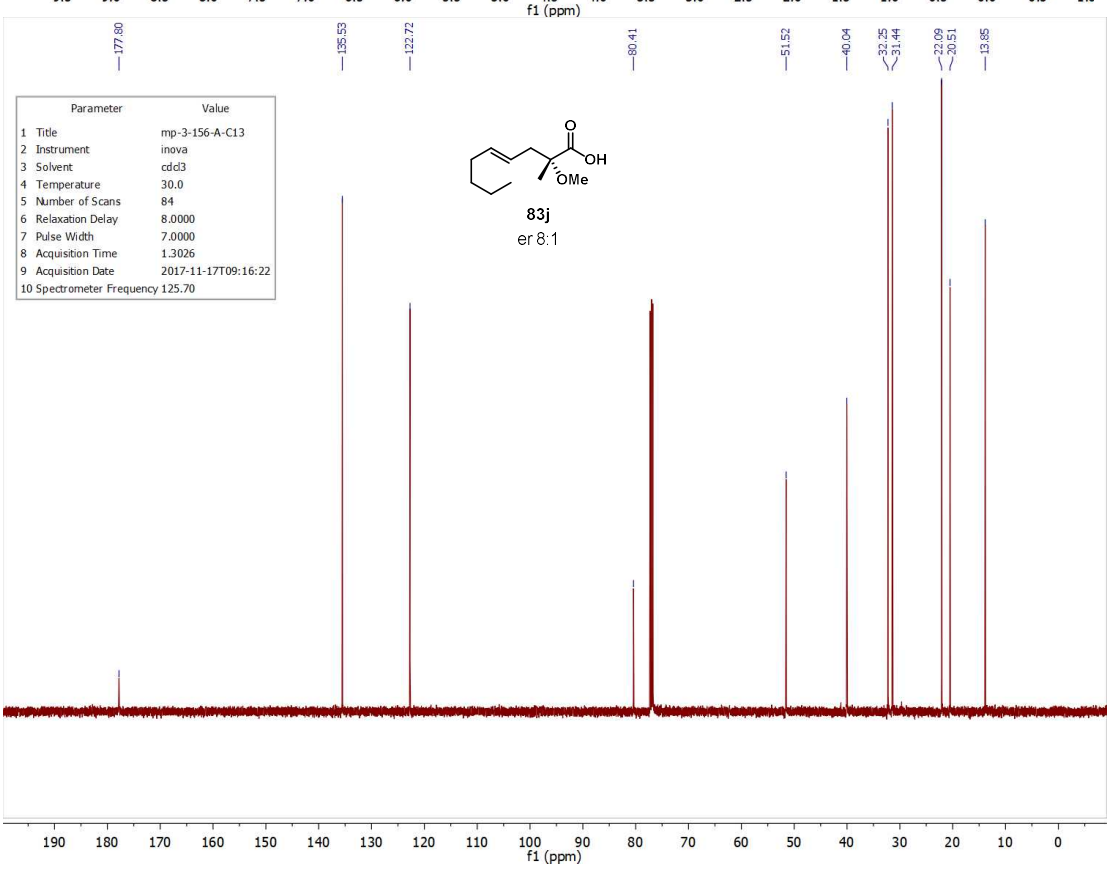


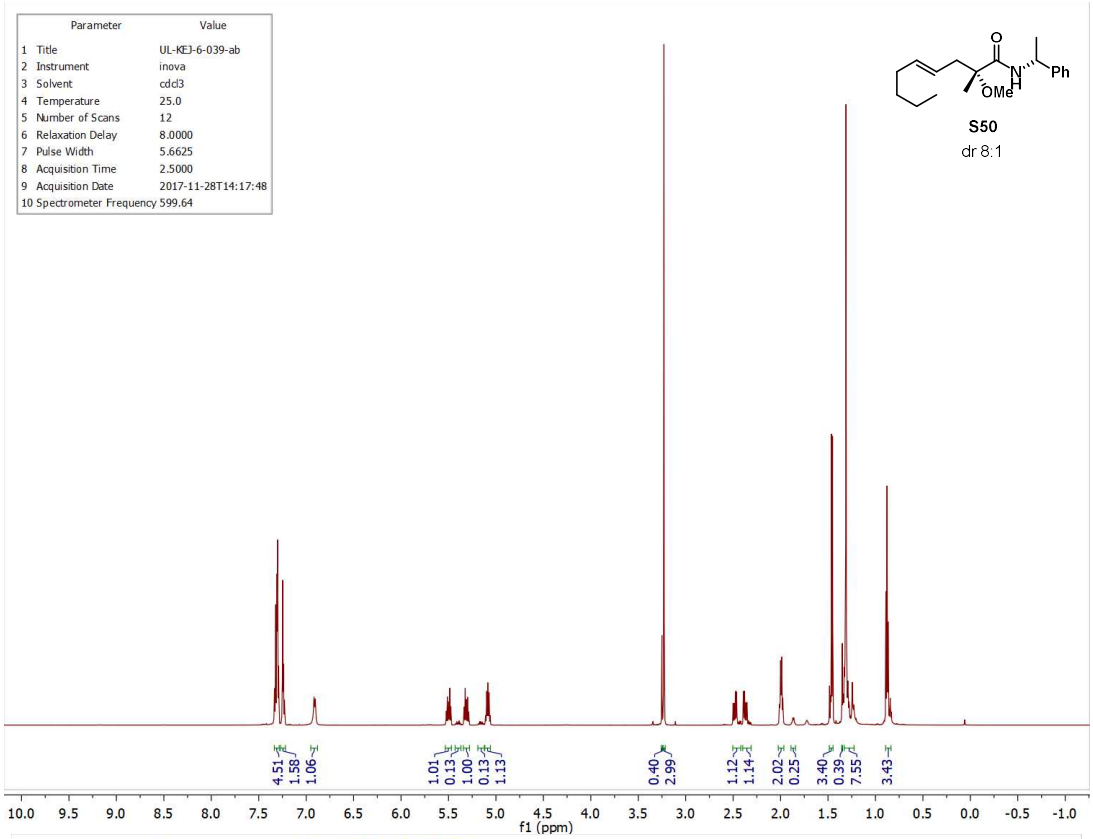
Parameter	Value
1 Title	JJL-3-181-13CNMR
2 Instrument	inova
3 Solvent	cdcl3
4 Temperature	30.0
5 Number of Scans	100
6 Relaxation Delay	1.0000
7 Pulse Width	7.0000
8 Acquisition Time	1.3026
9 Acquisition Date	2017-11-15T09:11:36
10 Spectrometer Frequency	125.70

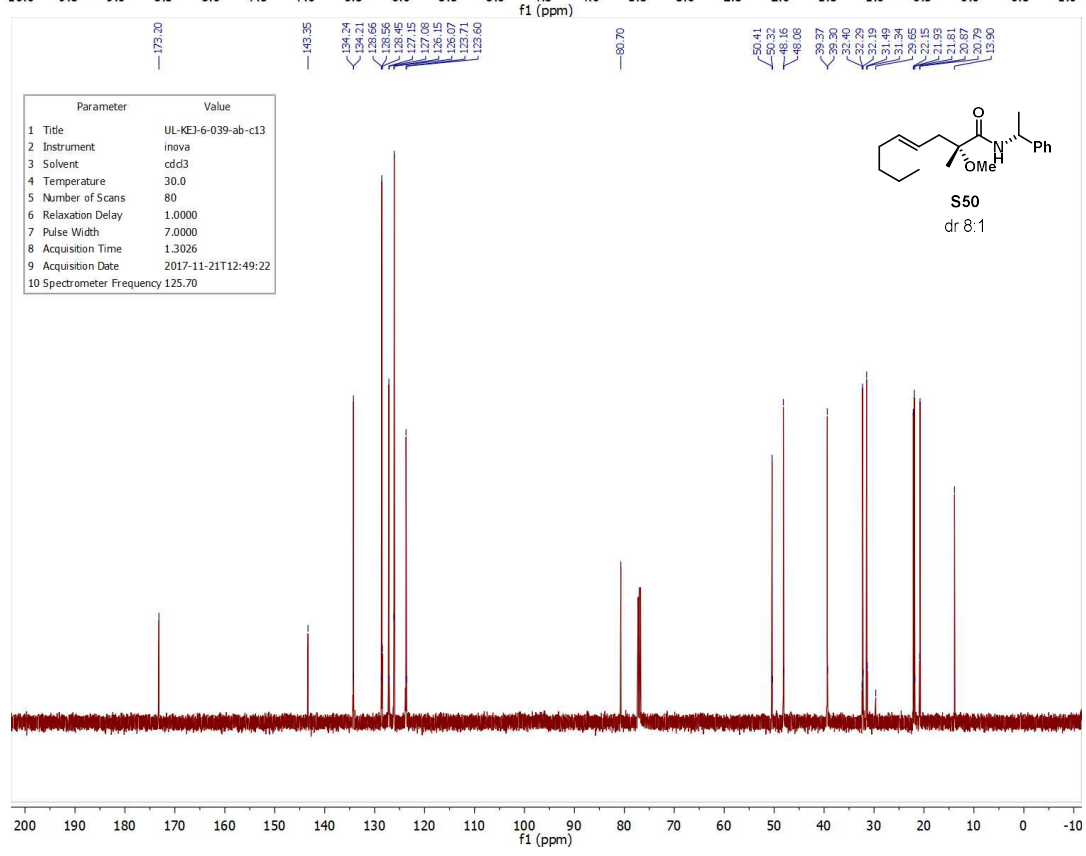
S50

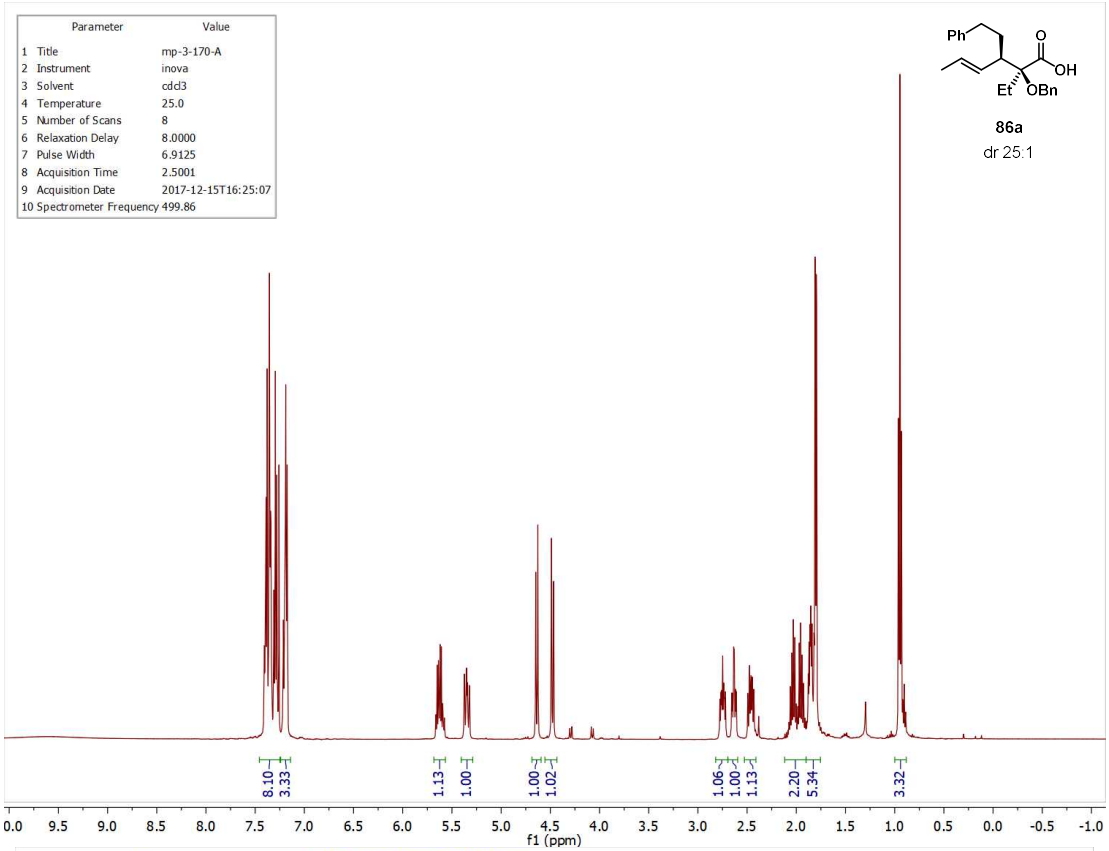
dr 14:1

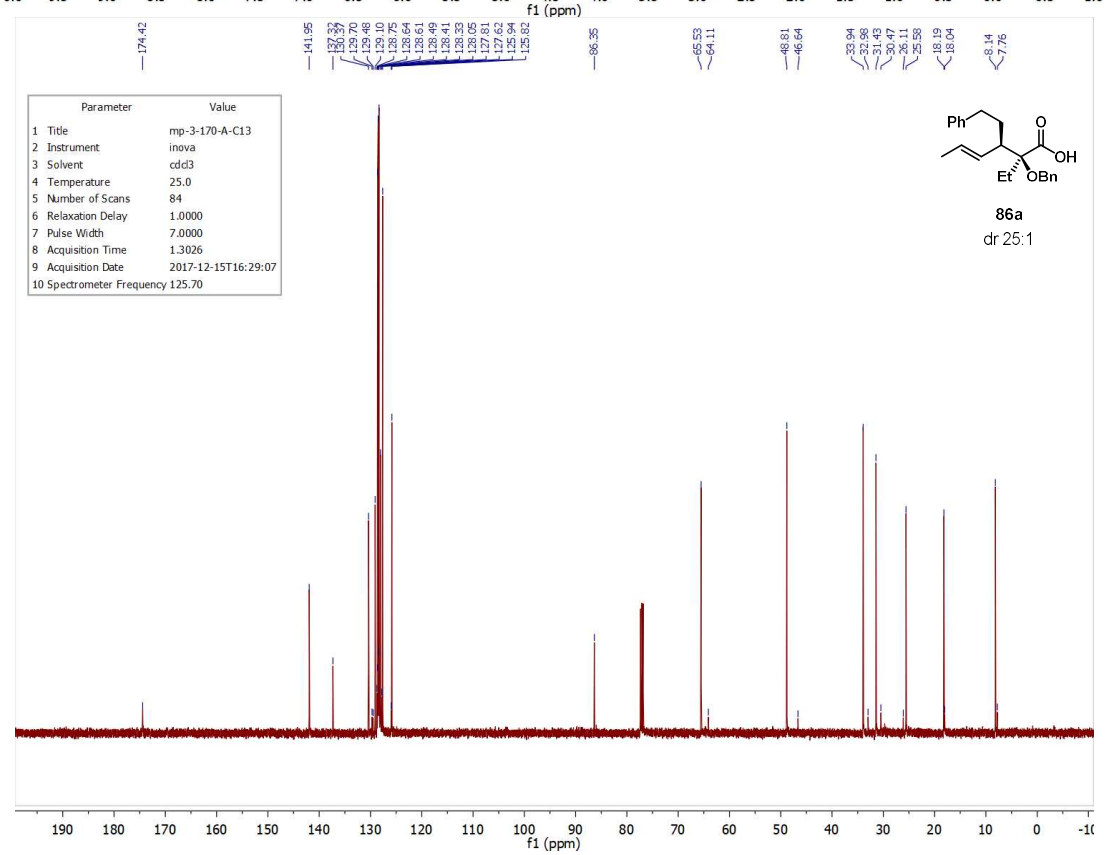

Parameter Value
1 Title mp-3-156-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2017-11-16T18:15:01
10 Spectrometer Frequency 599.64
OH
OMe
83j
er 8:1
1.00
1.00
2.98
1.99
2.01
3.03
4.01
3.06
f1 (ppm)

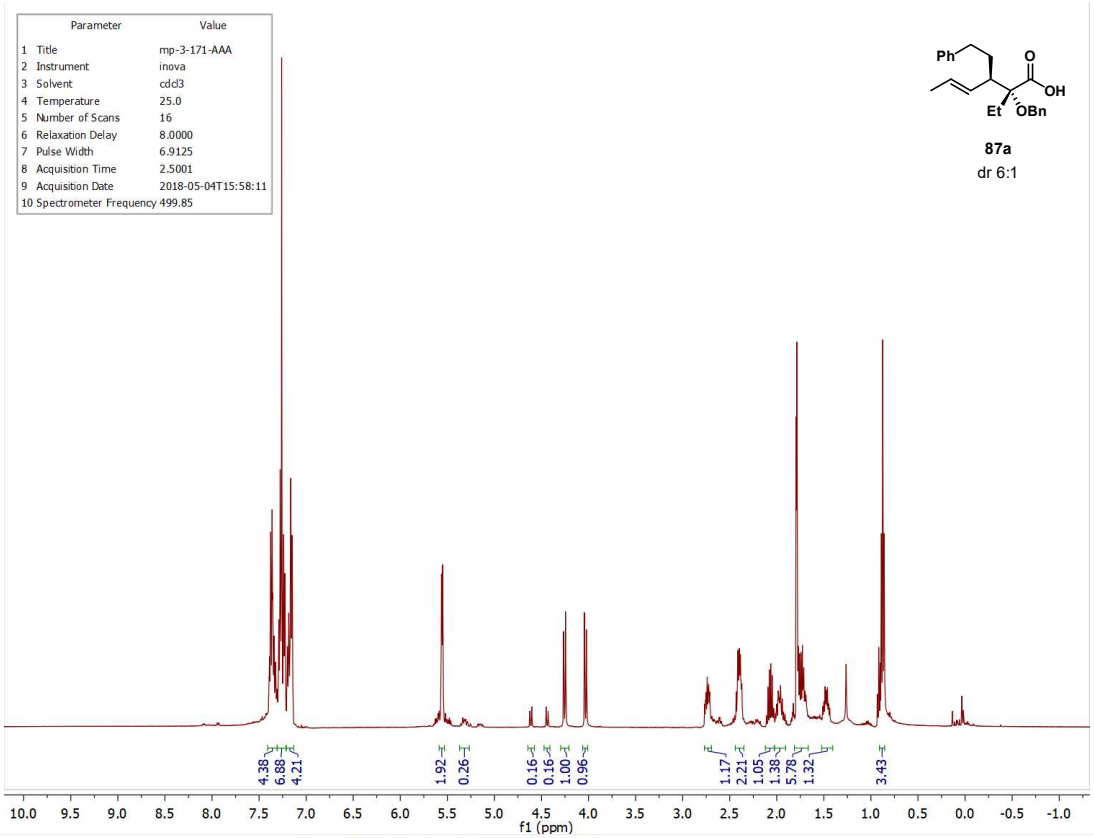

177.80
135.53
122.72
80.41
51.52
40.04
32.25
31.44
22.09
20.51
13.85
Parameter Value
1 Title mp-3-156-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 84
6 Relaxation Delay 8.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-17T09:16:22
10 Spectrometer Frequency 125.70
OH
OMe
83j
er 8:1
f1 (ppm)

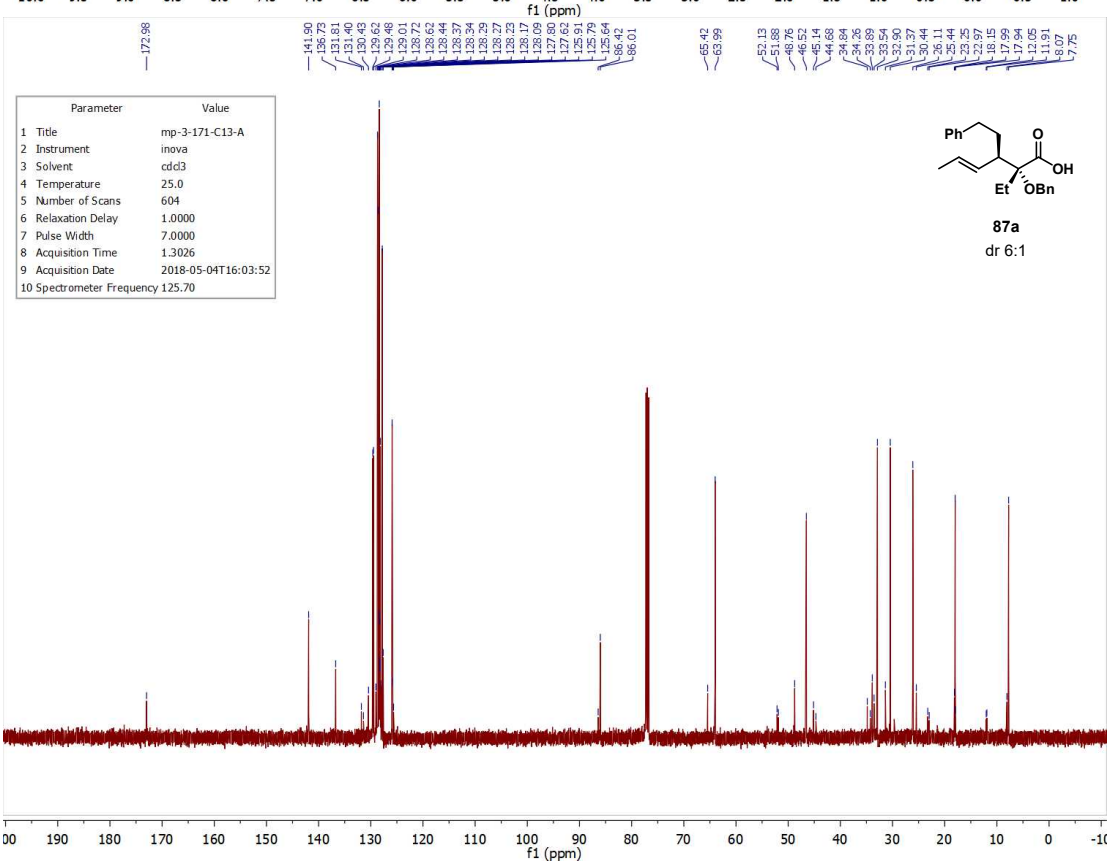

Parameter Value
1 Title UL-KEJ-6-039-ab
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2017-11-28T14:17:48
10 Spectrometer Frequency 599.64
S50
dr 8:1
4.51 1.58 1.06 1.01 0.13 1.00 0.13 1.13 0.40 2.99 1.12 1.14 2.02 0.25 3.40 0.39 7.55 3.43
f1 (ppm)

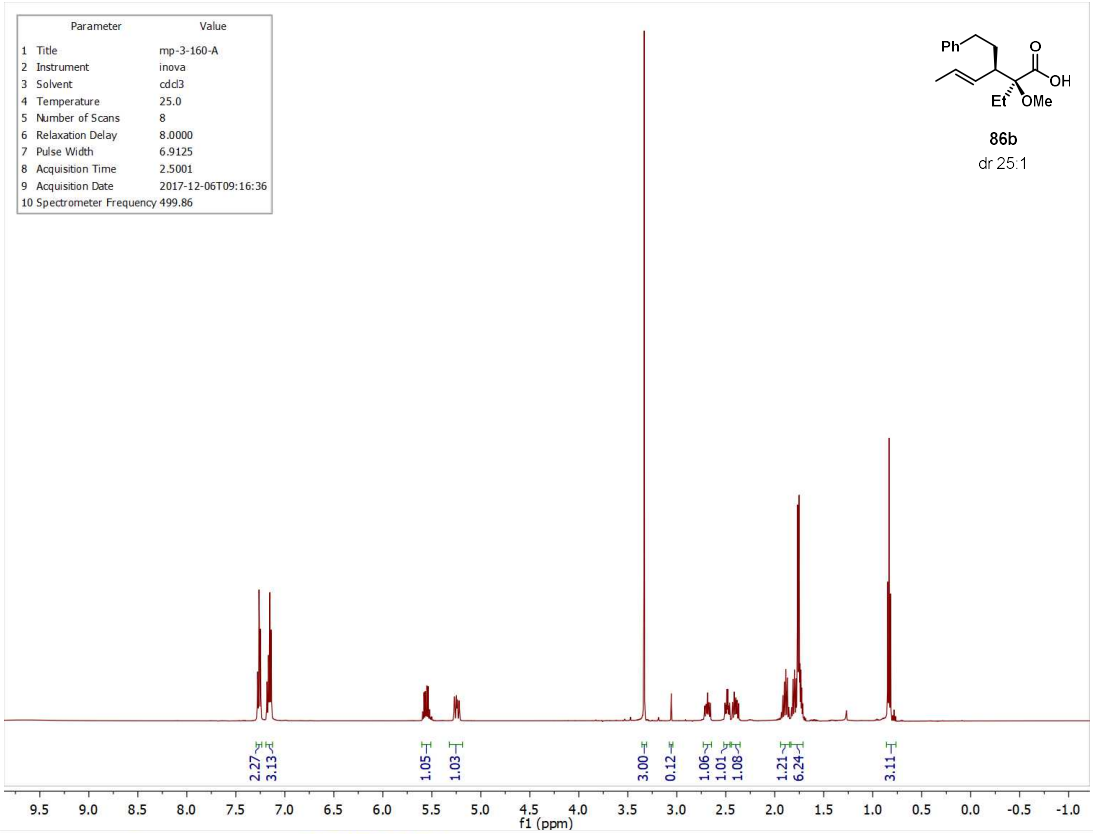

173.20 143.35 134.24 134.21 128.66 128.56 128.45 127.15 127.08 126.15 126.07 123.71 123.60 80.70 50.41 50.32 48.16 48.08 39.37 39.30 32.40 32.29 32.19 31.49 31.34 29.65 22.15 21.93 21.81 20.87 20.79 13.90
Parameter Value
1 Title UL-KEJ-6-039-ab-c13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 30.0
5 Number of Scans 80
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-11-21T12:49:22
10 Spectrometer Frequency 125.70
S50
dr 8:1
f1 (ppm)

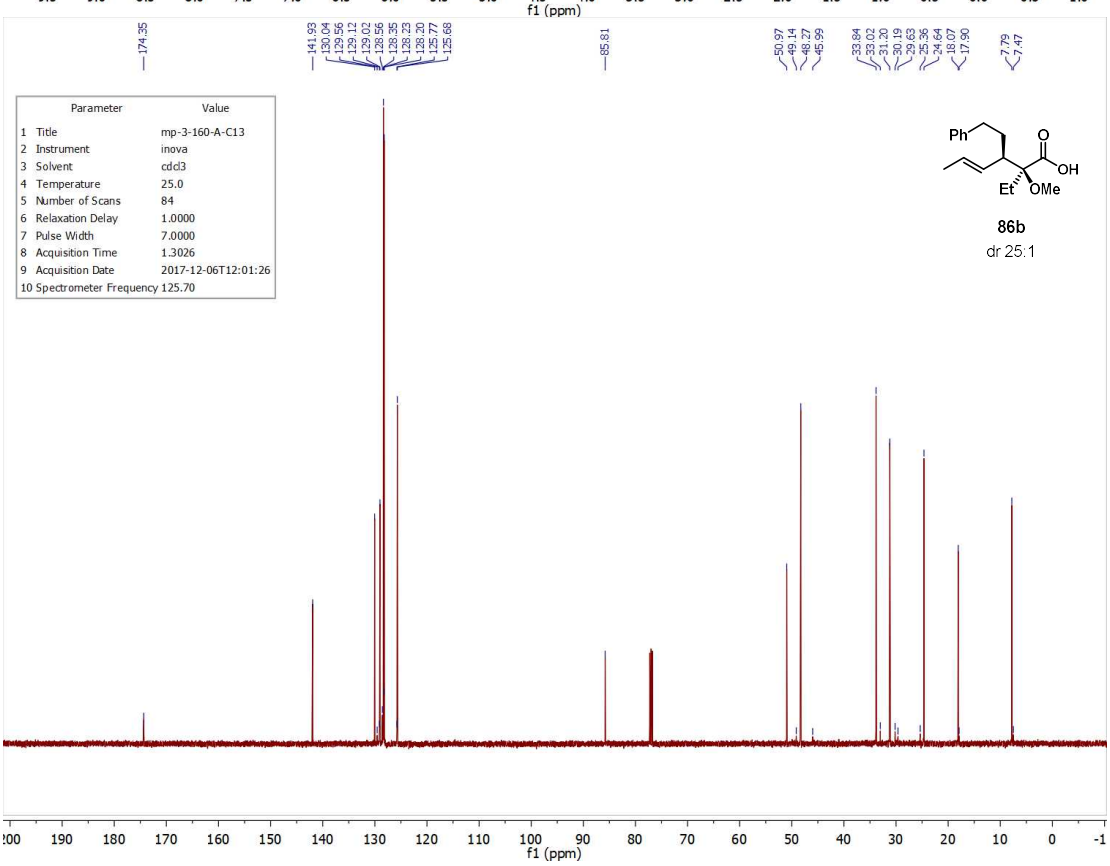

Parameter Value
1 Title mp-3-170-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-12-15T16:25:07
10 Spectrometer Frequency 499.86
Ph
O
OH
Et
OBn
86a
dr 25:1
8.10
3.33
1.13
1.00
1.00
1.02
1.06
1.00
1.13
2.20
5.34
3.32
f1 (ppm)

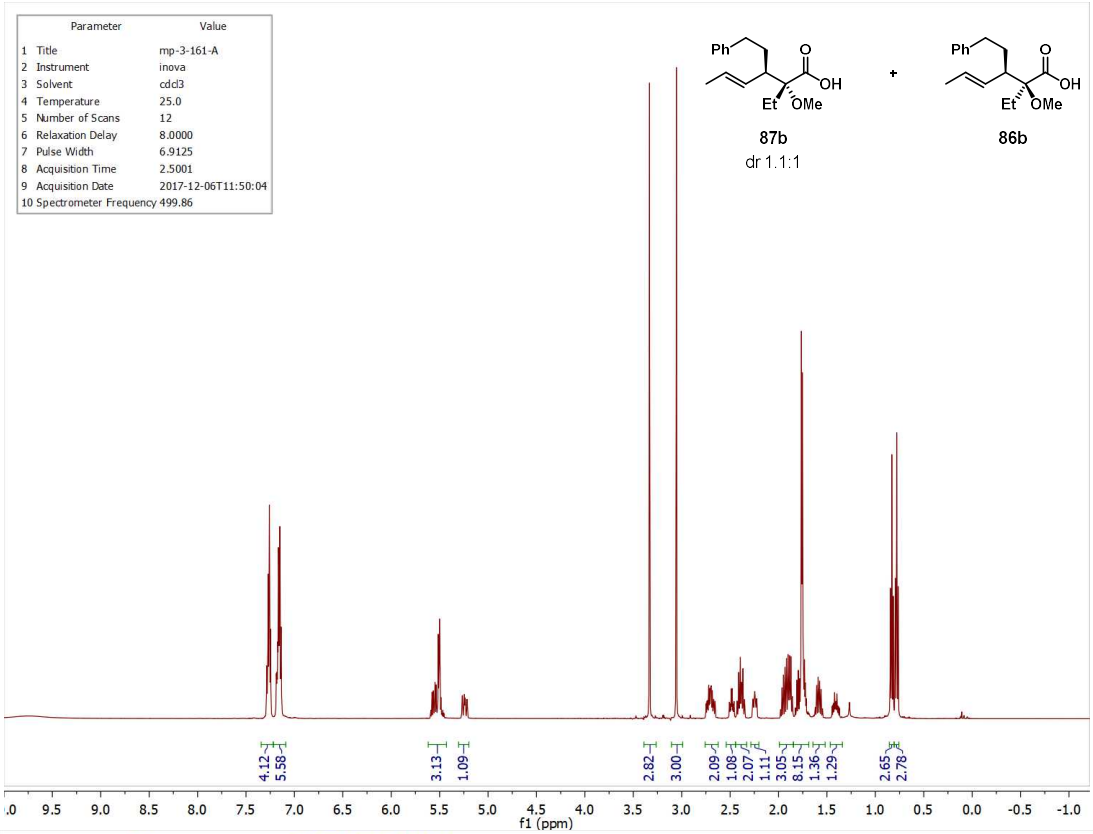

174.42
141.95
137.32
130.37
129.48
129.10
128.75
128.64
128.61
128.49
128.41
128.33
128.05
127.81
127.62
125.94
125.82
86.35
65.53
64.11
48.81
46.64
33.94
32.98
31.43
30.47
26.11
25.58
18.19
18.04
8.14
7.76
Parameter Value
1 Title mp-3-170-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 84
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-12-15T16:29:07
10 Spectrometer Frequency 125.70
Ph
O
OH
Et
OBn
86a
dr 25:1
f1 (ppm)

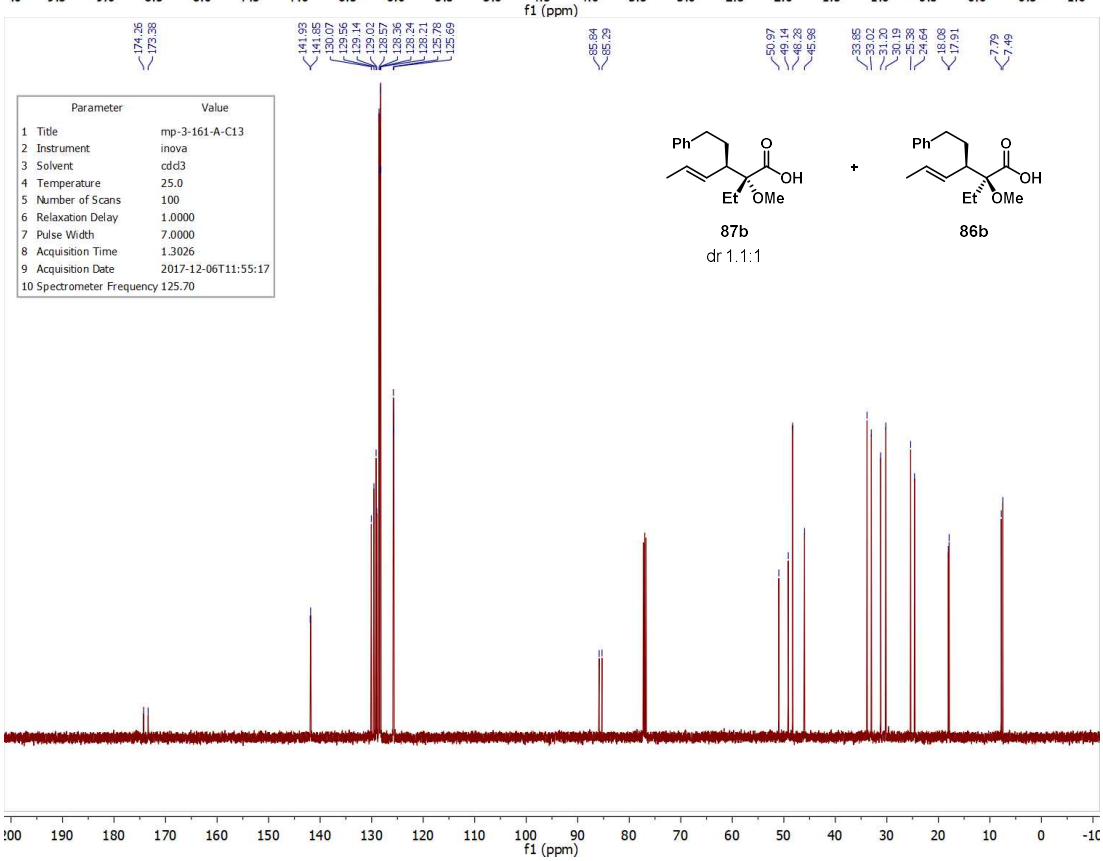

Parameter Value
1 Title mp-3-171-AAA
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 16
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2018-05-04T15:58:11
10 Spectrometer Frequency 499.85
Ph
O
OH
Et
OBn
87a
dr 6:1
4.38
6.68
4.21
1.92
0.26
0.16
0.16
1.00
0.96
1.17
2.21
1.05
1.38
5.78
1.32
3.43
f1 (ppm)

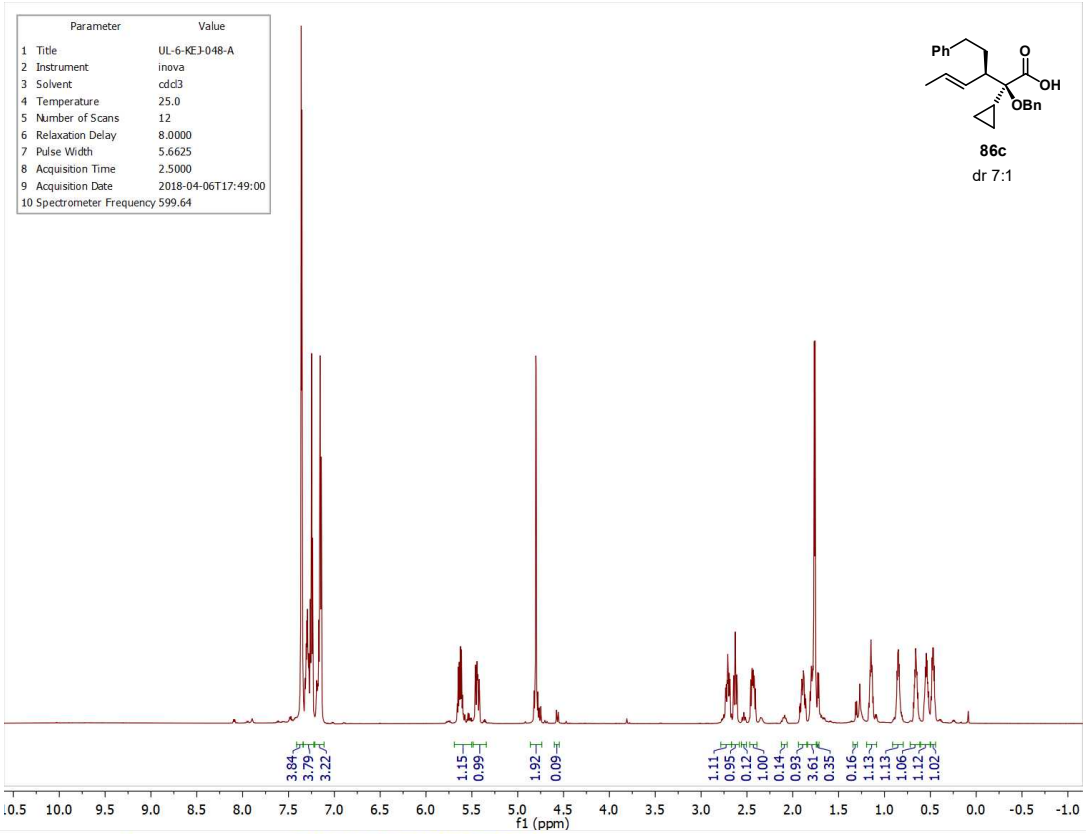

172.98
141.90
136.73
131.81
131.40
130.43
129.62
129.48
129.01
128.72
128.62
128.44
128.37
128.34
128.29
128.27
128.23
128.17
128.09
127.80
127.62
125.91
125.79
125.64
86.42
86.01
65.42
63.99
52.13
51.88
48.76
46.52
45.14
44.68
34.84
34.26
33.89
33.54
32.90
31.37
30.44
26.11
25.44
23.25
22.97
18.15
17.99
17.94
12.05
11.91
8.07
7.75
Parameter Value
1 Title mp-3-171-C13-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 604
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2018-05-04T16:03:52
10 Spectrometer Frequency 125.70
Ph
O
OH
Et
OBn
87a
dr 6:1
f1 (ppm)

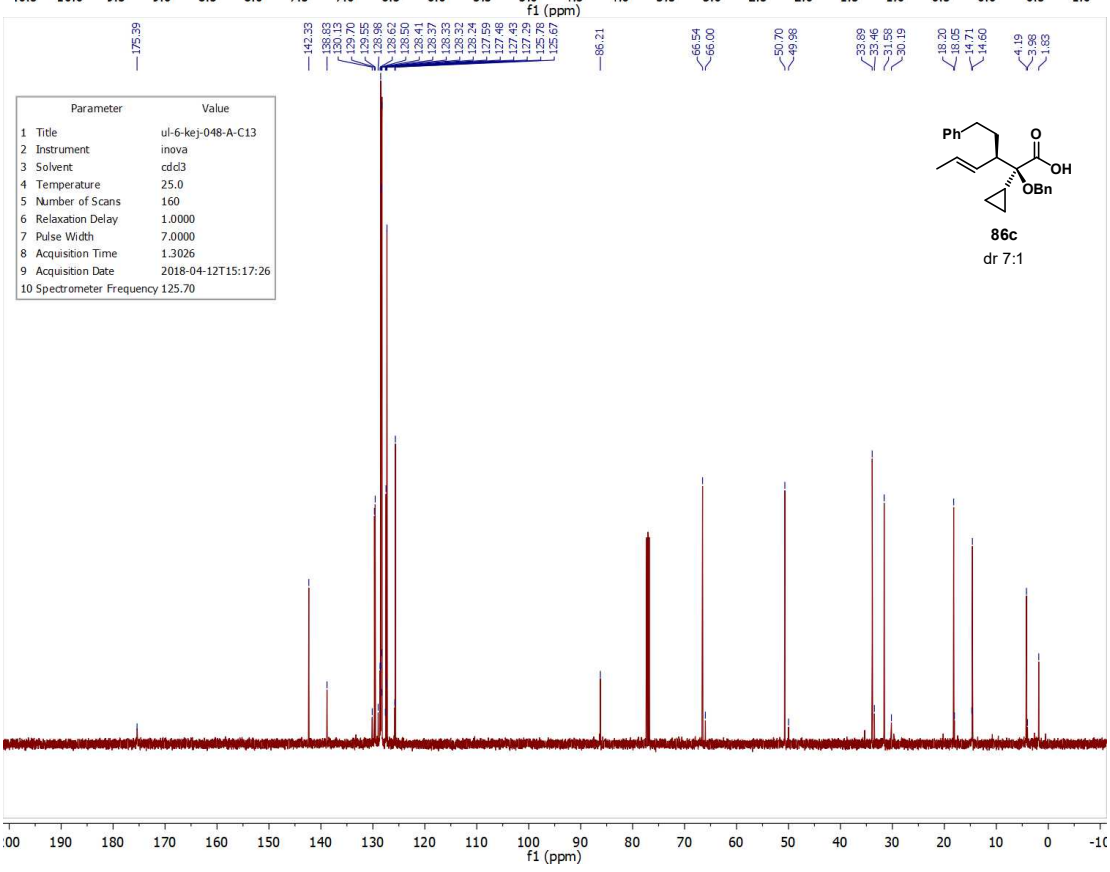

Parameter Value
1 Title mp-3-160-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 8
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-12-06T09:16:36
10 Spectrometer Frequency 499.86
Ph
O
OH
Et
OMe
86b
dr 25:1
2.27
3.13
1.05
1.03
3.00
0.12
1.06
1.01
1.08
1.21
6.24
3.11
f1 (ppm)

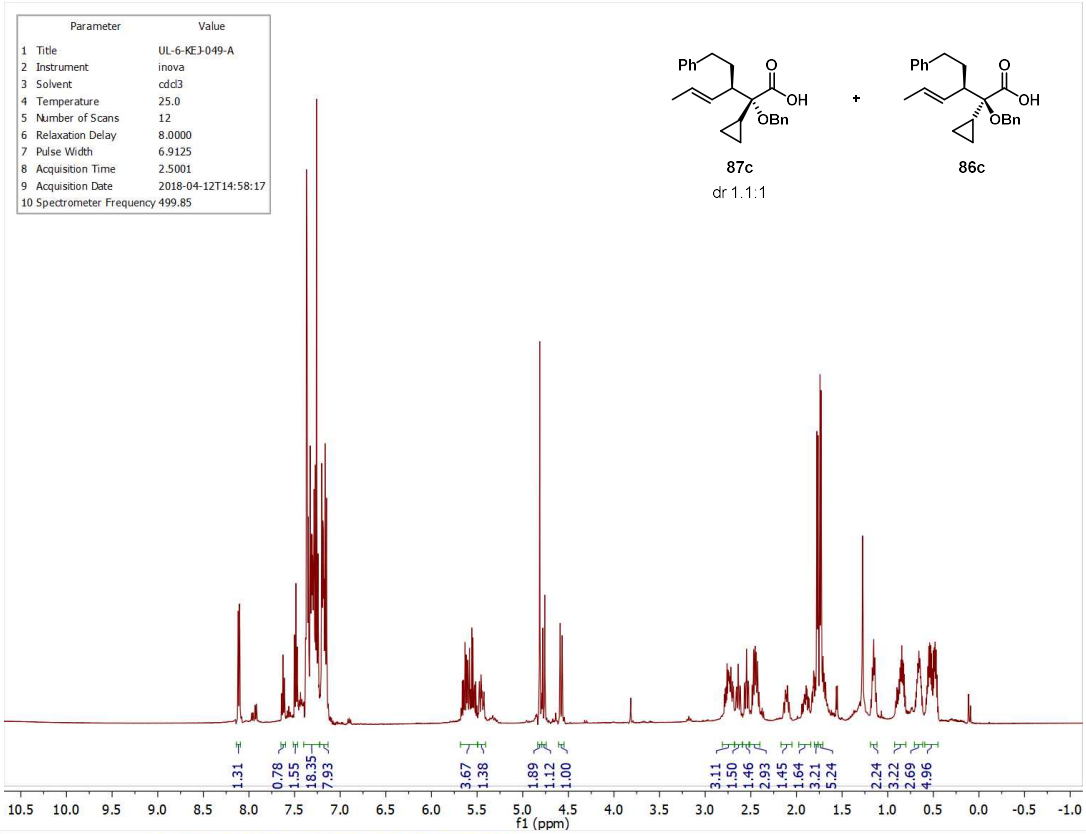

174.35
141.93
130.04
129.56
129.12
129.02
128.56
128.35
128.23
128.20
125.77
125.68
85.81
50.97
49.14
48.27
45.99
33.84
33.02
31.20
30.19
29.63
25.36
24.64
18.07
17.90
7.79
7.47
Parameter Value
1 Title mp-3-160-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 84
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-12-06T12:01:26
10 Spectrometer Frequency 125.70
Ph
O
OH
Et
OMe
86b
dr 25:1
f1 (ppm)

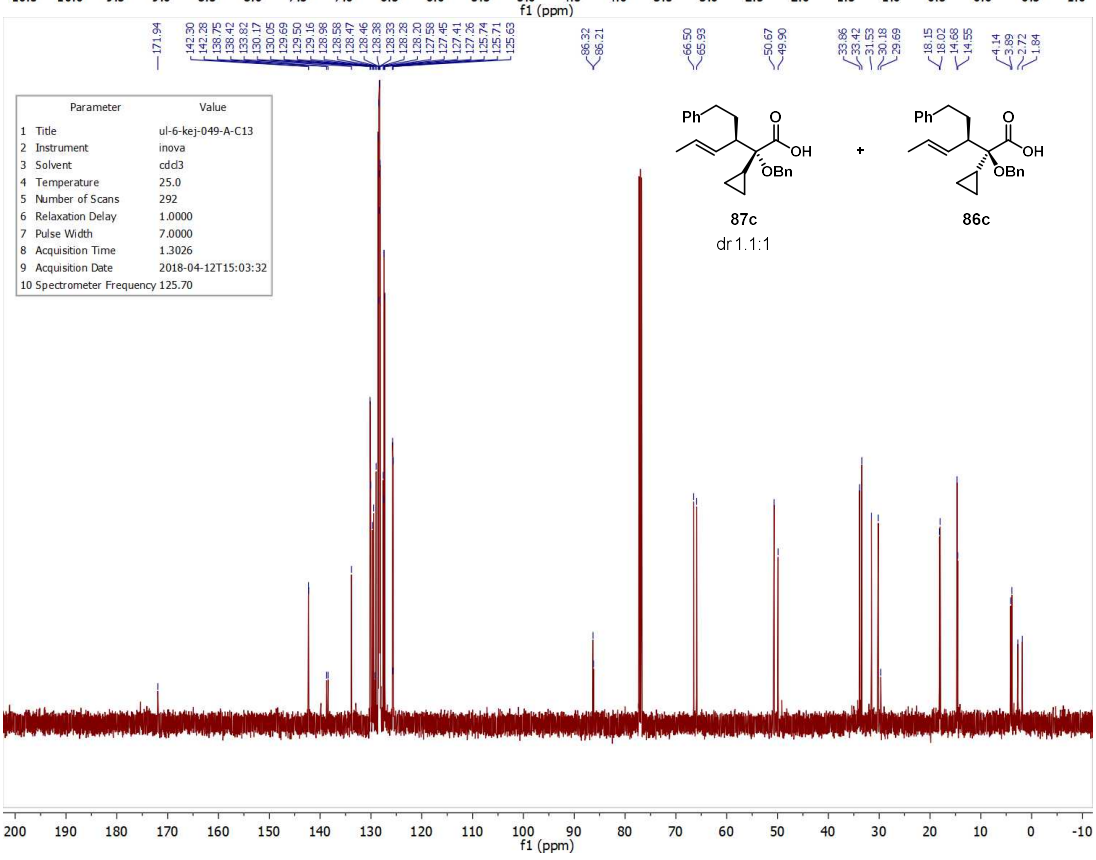

Parameter Value
1 Title mp-3-161-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2017-12-06T11:50:04
10 Spectrometer Frequency 499.86
Ph
O
OH
Et
OMe
87b
dr 1.1:1
86b
4.12
5.58
3.13
1.09
2.82
3.00
2.09
1.08
2.07
1.11
3.05
8.15
1.36
1.29
2.65
2.78
f1 (ppm)

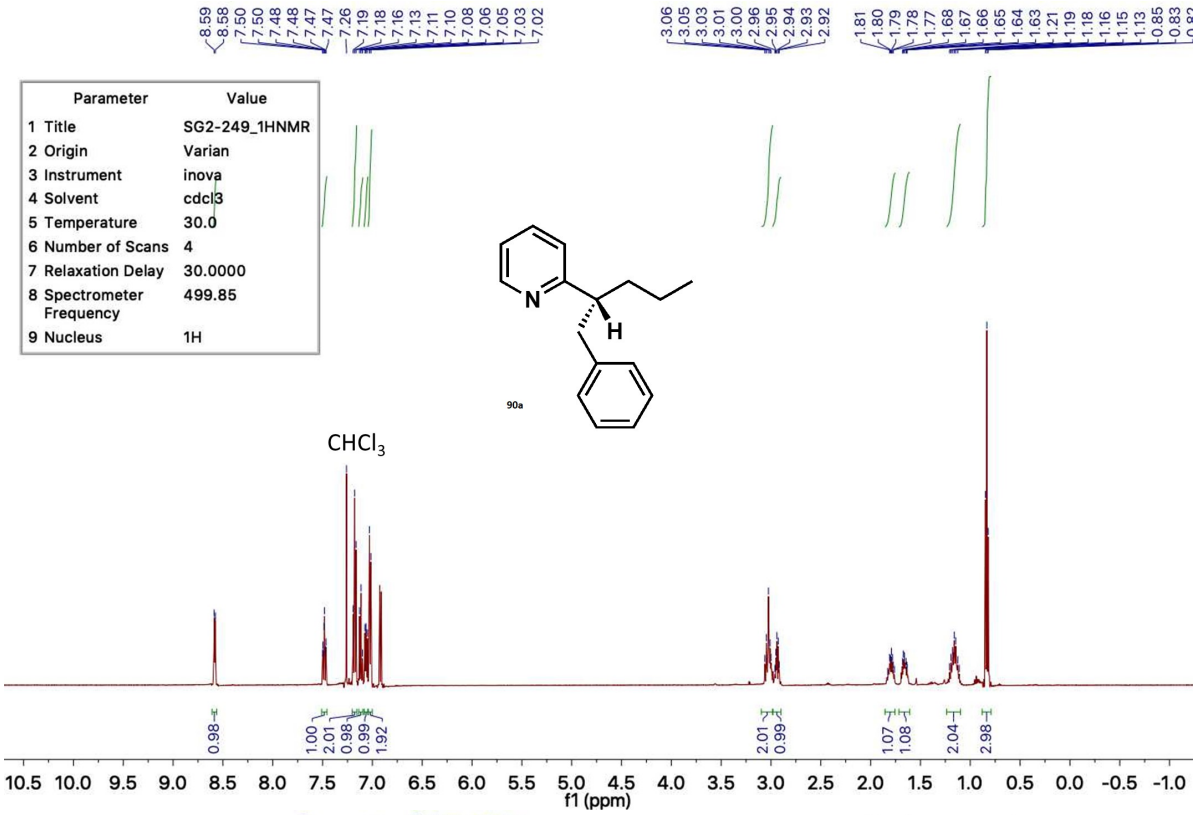

174.26
173.38
141.93
141.85
130.07
129.56
129.14
129.02
128.57
128.36
128.24
128.21
125.78
125.69
85.84
85.29
50.97
49.14
48.28
45.98
39.85
33.02
31.20
30.19
25.38
24.64
18.08
17.91
7.79
7.49
Parameter Value
1 Title mp-3-161-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 100
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2017-12-06T11:55:17
10 Spectrometer Frequency 125.70
Ph
O
OH
Et
OMe
87b
dr 1.1:1
86b
f1 (ppm)

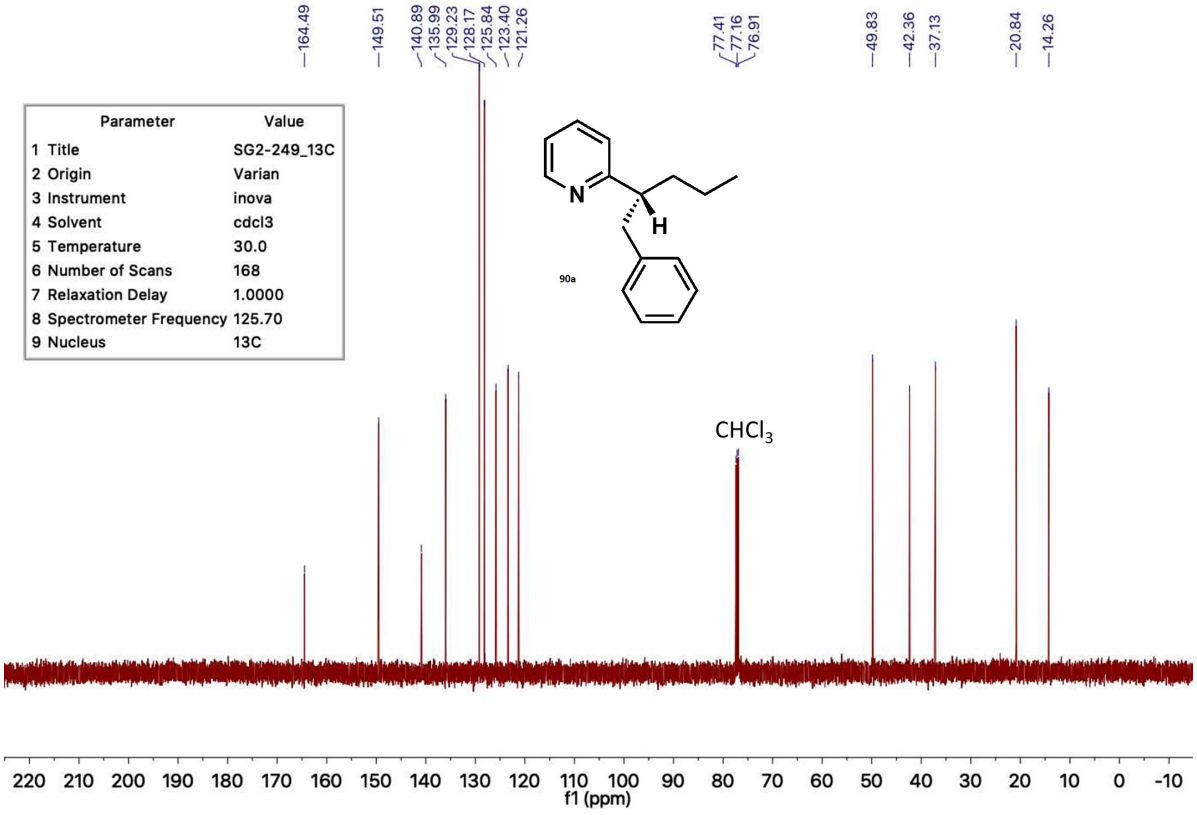

Parameter Value
1 Title UL-6-KEJ-048-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 5.6625
8 Acquisition Time 2.5000
9 Acquisition Date 2018-04-06T17:49:00
10 Spectrometer Frequency 599.64
Ph
O
OH
OBn
86c
dr 7:1
3.84 3.79 3.22 1.15 0.99 1.92 0.09 1.11 0.95 0.12 1.00 0.14 0.93 3.61 0.35 0.16 1.13 1.13 1.06 1.12 1.02
f1 (ppm)

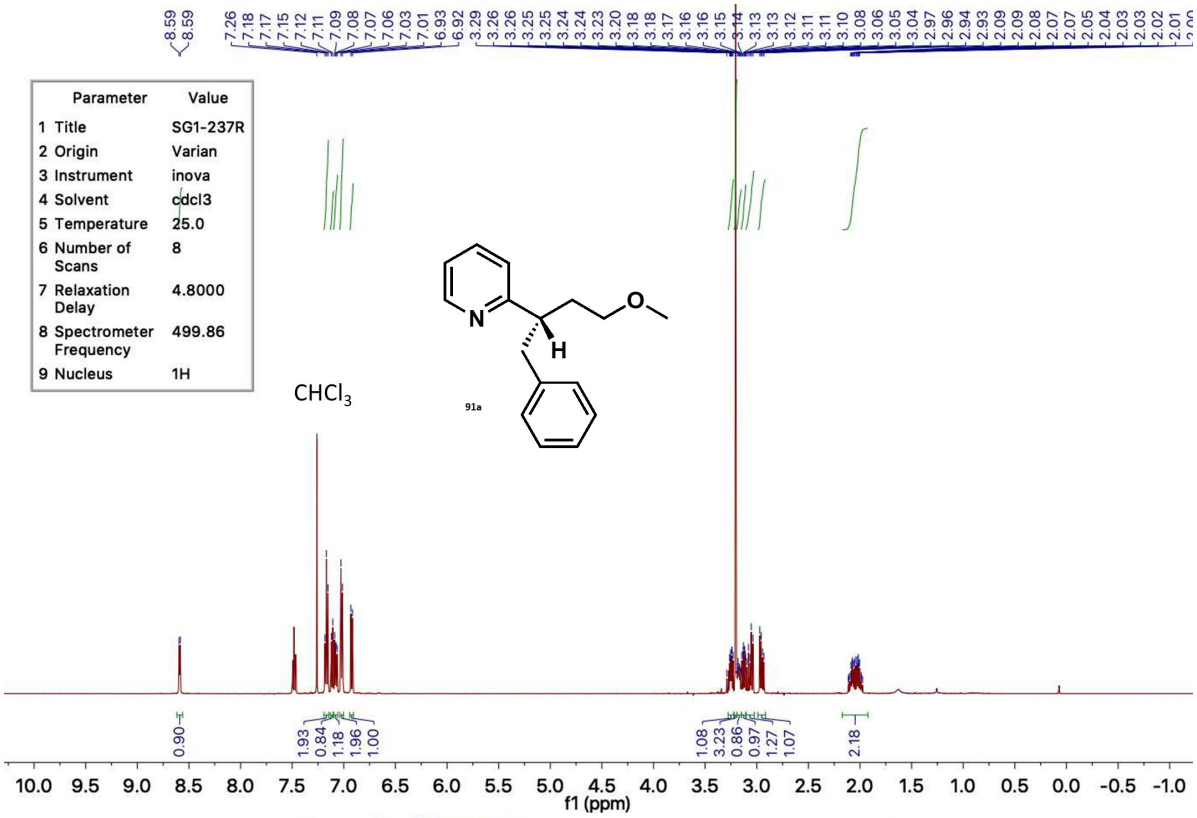

175.39
142.33 138.83 130.13 129.70 129.55 128.98 128.62 128.50 128.41 128.37 128.33 128.32 128.24 127.59 127.48 127.43 127.29 125.78 125.67
86.21
66.54 66.00
50.70 49.98
33.89 33.46 31.58 30.19
18.20 18.05 14.71 14.60
4.19 3.98 1.83
Parameter Value
1 Title ul-6-kej-048-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 160
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2018-04-12T15:17:26
10 Spectrometer Frequency 125.70
Ph
O
OH
OBn
86c
dr 7:1
f1 (ppm)

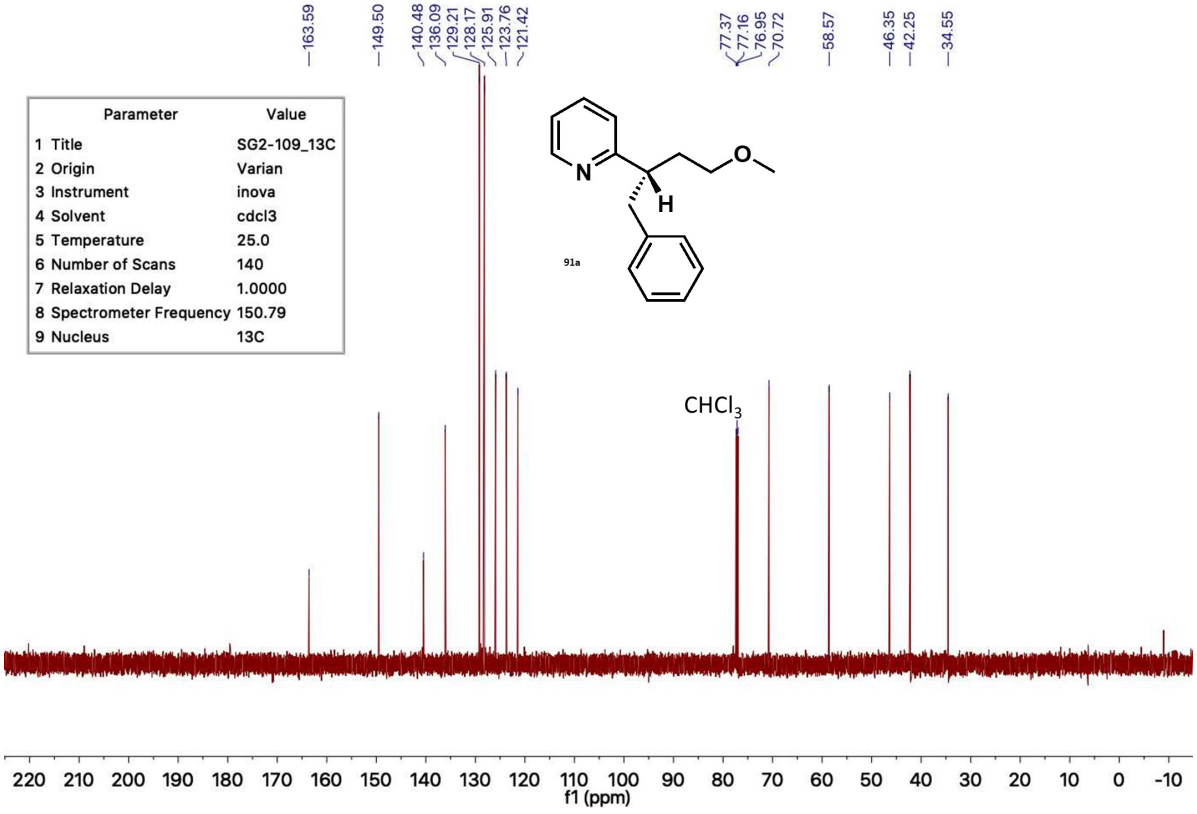

Parameter Value
1 Title UL-6-KEJ-049-A
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 12
6 Relaxation Delay 8.0000
7 Pulse Width 6.9125
8 Acquisition Time 2.5001
9 Acquisition Date 2018-04-12T14:58:17
10 Spectrometer Frequency 499.85
Ph
O
OH
OBn
87c
dr 1.1:1
86c
1.31
0.78
1.55
18.35
7.93
3.67
1.38
1.89
1.12
1.00
3.11
1.50
1.46
2.93
1.45
1.64
3.21
5.24
2.24
3.22
2.69
4.96
f1 (ppm)


171.94
142.30
142.28
138.75
138.42
133.82
130.17
130.05
129.69
129.50
129.16
128.98
128.58
128.47
128.46
128.38
128.33
128.28
128.20
128.00
127.58
127.45
127.41
127.26
125.74
125.71
125.63
86.32
86.21
66.50
65.93
50.67
49.90
33.86
33.42
31.53
30.18
29.69
18.15
18.02
14.68
14.55
4.14
3.89
2.72
1.84
Parameter Value
1 Title ul-6-kej-049-A-C13
2 Instrument inova
3 Solvent cdcl3
4 Temperature 25.0
5 Number of Scans 292
6 Relaxation Delay 1.0000
7 Pulse Width 7.0000
8 Acquisition Time 1.3026
9 Acquisition Date 2018-04-12T15:03:32
10 Spectrometer Frequency 125.70
Ph
O
OH
OBn
87c
dr 1.1:1
86c
f1 (ppm)


Parameter Value
1 Title SG2-249_1HNMR
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 30.0
6 Number of Scans 4
7 Relaxation Delay 30.0000
8 Spectrometer Frequency 499.85
9 Nucleus 1H
CHCl3
f1 (ppm)


Parameter Value
1 Title SG2-249_13C
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 30.0
6 Number of Scans 168
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 125.70
9 Nucleus 13C
CHCl3
f1 (ppm)


Parameter Value
1 Title SG1-237R
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 8
7 Relaxation Delay 4.8000
8 Spectrometer Frequency 499.86
9 Nucleus 1H
CHCl3
91a
f1 (ppm)


Parameter Value
1 Title SG2-109_13C
2 Origin Varian
3 Instrument inova
4 Solvent cdcl3
5 Temperature 25.0
6 Number of Scans 140
7 Relaxation Delay 1.0000
8 Spectrometer Frequency 150.79
9 Nucleus 13C
CHCl3
91a
f1 (ppm)

References

[1] a) Nakagawa, M.; Endo, M.; N. Tanaka, N.; Gen-Pei, L. *Tetrahedron Lett.* **1984**, *25*, 3227-3230. b) Moon, S.-S.; MacMillan, J. B.; Olmstead, M. M.; Ta, T. A.; Pessah, I. N.; Molinski, T. F. *J. Nat. Prod.* **2002**, *65*, 249-254. c) Kobayashi, M; Kawazoe, K.; Kitagawa, I. *Chem. Pharm. Bull.* **1989**, *37*, 1676-1678 . d) Reddy, M. V. R.; Faulkner, D. J. *Nat. Prod. Lett.* **1997**, *11*, 53-59. e) Venkateswarlu, Y. ; Reddy, M. V. R. ; Rao, J. V. *J. Nat. Prod*. **1994**, *57*, 1283-1285.

[2] a) Gafni, J.; Munsch, J. A.; Lam, T. H. ; Catlin, M. C. ; Costa, L. G.; Molinski, T. F.; Pessah, I. N. *Neuron* **1997**, *19*, 723-733. b) Jaimovich, E. ; Mattei, C. ; Liberona, J. L.; Cárdenas, C.; Estrada, M.; Barbier, J.; Debitus, C.; Laurent, D.; Molgo, J. *FEBS Lett.* **2005**, *579*, 2051-2057.

[3] Cárdenas, C.; Muller, M.; McNeal, A.; Lovy, A.; Jaňa, F.; Bustos, G.; Smith, N.; Molgo, J.; Diehl, A.; Ridky, T. W.; Foskett. J.K. *Cell Rep*. **2016**, *14*, 2313-2324.

[4] Baldwin, J. E.; Melman, A.; Lee, V.; Firkin, C. R.; Whitehead, R. C. *J. Am. Chem. Soc.* **1998**, *120*, 8559-8560.

[5] Jones, R. G., Thompson, C. B. *Genes Dev.* **2009**, *23*, 537-548.

[6] Boroughs, L. K. and R. J. DeBerardinis. *Nat. Cell Biol.* **2015**, *17*, 351-359.

[7] Warburg, O. *Science* **1956**, *123*, 309-314.

[8] Fan, Y.; Dickman, K. G.; Zong, W. X. *J. Biol. Chem.* **2010**, *285*, 7324-7333.

[9] W. H. Koppenol, W. H.; Bounds, P. L.; Dang, C. V. *Nat. Rev. Cancer* **2011**, *11*, 325-337.

[10] Moreno-Sanchez, R.; Marín-Hernández A.; Saavedra, E.; Pardo. J. P.; Ralph, S. J.; Rodríguez-Enríquez, S. *Int. J. Biochem. Cell Biol.* **2014**, *50*, 10-23.

[11] Porporato, P. E.; Payen, V. L.; Pérez-Escuredo, J.; De Saedeleer, C. J.; Danhier, P.; Copetti, T.; Dhup, S.; Tardy, M.; Vazeille, T.; Bouzin, C.; Feron, O.; Michiels, C.; Gallez, B.; Sonveaux, P. *Cell Rep.* **2014**, *8*, 754-766.

[12] Deberardinis, R. J.; Sayed, N.; Ditsworth, D.; Thompson, C. B.*Curr. Opin. Genet. Dev.* **2008**, *18*, 54-61.

[13] Weinberg, F.; Hamanaka, R.; Wheaton, W. W.; Weinberg, S.; Joseph, J.; Lopez, M.; Kalyanaraman, B.; Multu, G. M.; Budinger., G. R. S.; Chandel, N. S.; *Proc. Natl. Acad. Sci.* **2010**, *107*, 8788-8793.

[14] Rizzuto, R.; Pinton, P.; Carrintgton, W.; Fay, F. S.; Fogarty, K. E.; Lifshitz, L. M.; Tuft, R. A.; Pozzan, T. *Science* **1998**, *280*, 1763-1766.

[15] Robb-Gaspers, L. D.; Butnett, P.; Rutter, G. A.; Denton, R. M.; Rizzuto, R.; Thomas, A. P. *EMBO J.* **1998**, *17*, 4987-5000.

[16] Spät, A.; Szanda, G.; Csordás, G.; Hajnóczky, G. C*ell Calcium* **2008**, *44*, 51-63.

[17] J. M. Baughman, J. M.; Perrochi, F.; Gitigis, H. S.; Plovanich, M.; Blecher-Timme, C. A.; Sancak, Y.; Bao, R.; Strittmatter, L.; Goldberger, O.; Bogorad, R. L.; Koteliansky, V.; Mootha, V. K. *Nature* **2011**, *476*, 341-345.

[18] De Stefani, D.; Raffaello, A.; Teardo, E.; Szabò, I.; Rizzuto, R. *Nature* **2011**, *476*, 336-340.

[19] McCormack J. G. and Denton R. M. *Biochem. J.* **1979**, *180*, 533-544.

[20] Murphy, A. N.; Kelleher, J. K.; Fiskum, G. et al. *J. Biol. Chem.* **1990**, *265*, 10527-10534.

[21] Territo, P.R.; Mootha, V. K.; Balaban, R. S.. *Am. J. Physiol. Cell Physiol.* **2000**, *278*, C423-435.

[22] Cárdenas, C.; Miller, R. A.; Smith, I.; Bui, T.; Molgó, J.; Müller, M.; Vais, H.; Cheung, K. H.; Yang, J.; Parker, I.; Thompson, C. B.; Birnbaum, M. J.; Hallows, K. R.; Foskett, J. K. *Cell* **2010**, *142*, 270-283.

[23] Mallilankaraman, K.; Cárdenas, C.; Doonan, P. J.; Chandramoorthy, H. C.; Irrinki, K. M.; Golenár, T.; Csordás, G.; Madireddi, P.; Yang, J.; Müller, M.; Miller, R.; Kolesar, J. E.; Molgó, J.; Kaufman, B.; Hajnóczky, G.; Foskett, J. K.; Madesh, M. *Nat. Cell Biol*. **2012**, *14*, 1336-1343.

[24] S. S. Kang, et al. *Cancer Res.* **2010**, *70*, 1173-1183.

[25] Sakakura, C.; Hagiwara, A.; Fukuda, K.; Shimomura, K.; Takagi, T.; Kin, S.; Nakase, Y.; Fujiyama, J.; Mikoshiba, K.; Okazaki, Y.; Yamagishi, H. *Anticancer Res*. **2003**, *23*, 3691-3697.

[26] Bergner, A.; Kellner, J.; Tufman, A.; Huber, R. M. *J. Exp. Clin. Cancer Res.* **2009**, *28*, 25.

[27] Shibao, K.; Fiedler, M. J.; Nagata, J.; Minagawa, N.; Hirata, K.; Nakayama, Y.; Iwakiri, Y.; Nathanson, M. H.; Yamaguchi, K..*Cell Calcium* **2010**, *48*, 315-323.

[28] Sakakura, C.; Hagiwara, A.; Fukuda, K.; Shimomura, K.; Takagi, T.; Kin, S.; Nakase, Y.; Fujiyama, J.; Mikoshiba, K.; Okazaki, Y.; Yamagishi, H. *Anticancer Res.* **2003**, *23*, 3691-3697.

[29] Szatkowski, C. Parys, J. B.; Ouadid-Ahidouch ,H.; Matifat, F. *Mol. Cancer* **2010**, *9*, 156.

[30] Mound, A.; Parys, J. B.; Ouadid-Ahidouch ,H.; Matifat, F. *Eur. J. Cancer* **2013**, *49*, 3738-3751.

[31] DeWald, D. B.; Torabinejad, J.; Samant, R. S.; Johnston, D.; Erin, N.; Shope, J. C.; Xie, Y.; Welch, D. R. *Cancer Res.* **2005**, *65*, 713-717.

[32] Hall, D.; Wu, Y.; Domann, F.; Spitz, D.; Anderson, M. *PLoS One* **2014**, *9*, e96866.

[33] Tang, S.; Wang, X.; Shen, Q.; Yang, X.; Yu, C.; Cai, C.; Cai, G.; Meng, X.; Zou, F. *Biochem. Biophys. Res. Commun.* **2015**, *458*, 186-193.

[34] a) Hoye, T.R.; North, J. T.; Yao, L. J. *J. Am. Chem. Soc.* **1994**, *116*, 2617-2618. b) Hoye, T. R.; Ye, Z.; Yao, L. J.; North, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 12074-12081.

[35] a) Hoye, T. R.; North, J. T. *Tetrahedron Lett.* **1990**,*31*,4281. (b) Ahn, K. H.; Lee, S. J. T*etrahedron Lett*. **1992**, *33*, 507. (c) Borjesson, L.; Welch, C. J. *Tetrahedron* **1992**, *48*, 6325.

[36] (a) Alcohol (+)-XX represents a pair of diastereomers epimeric at the center a to the acetal [C(10)] but of a single configuration at C(3). The “stereogenic purity" of the carbinol center was found to be >95% “ee" by ^{1}H and, ^{19}F NMR analysis of the corresponding Mosher ester derivatives, and the configuration was determined to be *R*. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *93*, 512. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

[37] Baldwin, J. E.; Melman, A.; Lee, V.; Firkin, C. R.; Whitehead, R. C. *J. Am. Chem. Soc.* **1998**, *120*, 8559-8560.

[38] For example, see: Sepcic, K.; Guella, G.; Mancini, I.; Pietra, F.; Dalla Serra, M.; Menestrina, G.; Tubbs, K.; Macek, P.; Turk, T. *J. Nat. Prod.* **1997**, *60*, 991-996 and references therein.

[39] Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc*. **1974**, *96*, 1082-1087.

[40] Lambert, P. H.; Vaultier, M.; Carrie´, R. *J. Org. Chem*. **1985**, *50*, 5352-5356.

[41] (a) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163-4166. (b) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1993**, *71*, 1-13.

[42] Kaiser, E. M.; Petty, J. D. *Synthesis* 1975, 705-706.

[43] Smissman, E. E.; Makriyannis, A. *J. Org. Chem*. **1973**, *38*, 1652-1657.

[44] Kobayashi, M.; Miyamoto, Y.; Aoki, S.; Murakami, N.; Kitagawa, I.; In, Y.; Ishida, T. *Heterocycles* **1998**, *47*, 195-203.

[45] Firkin, C. R. D. Phil. Thesis, University of Oxford, **1997**.

[46] Kim, S.; Ahn, K.H. *J. Org. Chem.* **1984**, *49*, 17-17-1724.

[47] a) Roussi, F.; Quirion, J.-C.; Tomas, A.; Husson, H.-P. *Tetrahedron* **1998**, *54*, 10363-10378. b) Amat, M. ; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919-1928.

[48] a) Gergory, A. W.; Chambers, A.; Hawkins, A.; Jakubec, P.; Dixon, D. J. *Chem.-Eur. J.* **2015**, *21*, 111-114. b) Tan, P. W.; Seayad, J.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2016**, *55*, 13436-13440.

[49] Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 1307-1315.

[50] Alcaraz, L.; Hartnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D. S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449–5452

[51] Morimoto, Y.; Iwahashi, M.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35,* 904-906.

[52] Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437-447.

[53] a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877. b) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Chem. Soc. Rev.* **2009**, *38*, 2133-3148.

[54] Podunavac, M.; Lacharity, J. J.; Jones, K. E.; Zakarian, A. *Org. Lett.* **2018**, *20*, 4867-4870.

[55] Bartra, M.; Romea, P.; Urpi, F.; Vilarrasa, J. *Tetrahedron*, **1990**, *46*, 587-594.

[56] El-Faham, A.; Albericio, F. *Chem. Rev.* 2011, *111*, 6557-6602.

[57] a) Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 17270-17271. b) Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2478-2479.

[58] a) Berkowitz, W. F.; Choudhry, S. C.; Hrabie, J. A. *J. Org. Chem.* **1982**, *47*, 824-829. b) Golan, O.; Goren, Z.; Biali, S. E. *J. Am. Chem. Soc.* **1990**, *112*, 9300-9307.

[59] Cárdenas, C.; Lovy, A.; Silva-Pavez, E.; Urra, F.; Mizzoni, C.; Ahumada-Castro, U.; Bustos, G.; Jaña, F.; Cruz, P.; Farias, P.; Mendoza, E.; Huerta, H.; Murgas, P.; Hunter, M.; Rios, M.; Cerda, O.; Georgakoudi, I.; Zakarian, A.; Molgó, J.; Fosket, J. K. *Sci. Signaling* **2020**, *13*, doi: 10.1126/scisignal.aay1212.

[60] (a) Ireland, R.E.; Muller, R.H. *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877. (c) Ireland, R.E.; Wipf, P.; Armstrong III, J.D. *J. Org. Chem.* **1991**, *56*, 650–657. (d) Ireland, R.E.; Wipf, P.; Xiang, J.N. *J. Org. Chem.* **1991**, *56*, 3572–3582.

[61] (a) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Chem. Soc. Rev.* **2009**, *38*, 3133–3148. (b) Castro, A.M.M. *Chem. Rev.* **2004**, *104*, 2939–3002. (c) Chai, Y.; Hong, S.-P.; Lindsay, H.A.; McFarland, C.; McIntosh, M.C. *Tetrahedron* **2002**, *58*, 2905–2928.

[62] (a) Kuilya, T. K.; Goswami, R. K. *Org. Lett.* **2017**, *19*, 2366–2369. (b) Stivala, C.; Zakarian, A. *J. Am. Chem. Soc.* **2008**, *130*, 3774–3776. (c) Xiao, Q.; Jackson, J. J.; Basak, A.; Bowler, J. M.; Miller, B. G.; Zakarian, A. *Nat. Chem.* **2013**, *5*, 410–416. (d) He, C.; Zhu, C.; Dai, Z.; Tseng, C.-C.; Ding, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 13256–13260.

[63] (a) Kobayashi, H.; Eickhoff, J. A.; Zakarian, A. *J. Org. Chem.* **2015**, *80*, 9989–9999. (b) Jackson, J. J.; Kobayashi, H.; Steffens, S.; Zakarian, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 9971–9975. (c) Cannon, J. S. *Org. Lett.* **2018**, *20*, 3883–3887. (d) Ref. **Error! Bookmark not defined.**. (e) Jamison, C. R.; Overman, L. E. *Acc. Chem. Res.* **2016**, 49, 1578–1586.

[64] (a) Moore, J. T.; Hanhan, N. V.; Mahoney, M. E.; Cramer, S. P.; Shaw, J. T. *Org. Lett.* **2013**, *15*, 5615–5617. (b) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221–5228. (c) Sato, T.; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 729–730. (d) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941–3945. (d) Whitesell, J. K.; Helbling, A. M. *J. Org. Chem.* **1980**, *45*, 4135–4139.

[65] Picoul, W.; Urchegui, R.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 4797–4800.

[66] (a) Feldman, K. S.; Selfridge, B. R. *Tetrahedron Lett.* **2012**, 53, 825–828. (b) Yang, Y.; Fu, X.; Chen, J.; Zhai, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 9825–9828. (c) Gilbert, J. C.; Selliah, R. D. *J. Org. Chem.* **1993**, *58*, 6255–6265.

[67] Evans, D. A., Helmchen, G., Rüping, M. In *Asymmetric Synthesis—The Essentials*; Christmann, M., Bräse, S., Eds.; Wiley-VCH: Weinheim, Germany, **2007**; pp 3– 9.

[68] Morales, M. R.; Mellem, K. T.; Myers, A. G. Pseudoephenamine: a practical chiral auxiliary for asymmetric synthesis. *Angew. Chem., Int. Ed.* **2012**, *51*, 4568– 4571, DOI: 10.1002/anie.201200370.

[69] Roose, G. *Key Chiral Auxiliary Applications*; Academic Press: Boston, MA, **2014**.

[70] Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley: New York, **1995**.

[71] Dugger, R. W.; Ragan, J. A.; Ripin, D. H. B. Survey of GMP bulk reactions run in a research facility between **1985** and **2002**. *Org. Process Res. Dev.* **2005**, *9*, 253– 258.

[72] Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734– 2793.

[73] Ando, A.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1987**, 656– 658.

[74] Matsuo, J.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 2122– 2124.

[75] Stivala, C. E.; Zakarian, A. *J. Am. Chem. Soc.* **2011**, *133*, 11936– 11939.

[76] Lu, P.; Jackson, J. J.; Eickhoff, J. A.; Zakarian, A. *J. Am. Chem. Soc.* **2015**, *137*, 656– 659.

[77] Yu, K.; Lu, P.; Jackson, J. J.; Nguyen, T.; Alvarado, J.; Stivala, C. E.; Ma, Y.; Mack, K. A.; Hayton, T. W.; Collum, D. B.; Zakarian, A. *J. Am. Chem. Soc.* **2017**, *139*, 527– 533.

[78] Reich, H. J. *Chem. Rev.* **2013**, *113*, 7130– 7178.

[79] Ma, Y.; Stivala, C. E.; Wright, A. M.; Hayton, T.; Liang, J.; Keresztes, I.; Lobkovsky, E.; Collum, D. B.; Zakarian, A. *J. Am. Chem. Soc.* **2013**, *135*, 16853– 16864.

[80] Ma, Y.; Mack, K. A.; Liang, J.; Keresztes, I.; Collum, D. B.; Zakarian, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 10093– 10097.

[81] Asymmetric alkylation of typical enolates mediated by CLAs:Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829– 8830.

[82] Frizzle, M. J.; Nani, R. R.; Martinelli, M. J.; Moniz, G. A. *Tetrahedron Lett.* **2011**, *52*, 5613– 5616.

[83] Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257– 10274.

[84] a) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 12056– 12057. b) Yin, Y.; Dai, Y.; Jia, H.; Li, J.; Bu, L.; Qiao, B.; Zhao, X.; Jiang, Z. *J. Am. Chem. Soc.* **2018**, *140*, 6083– 6087. c) Meazza, M.; Tur, F.; Hammer, N.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2017**, *56*, 1634– 1638. d) Saxena, A.; Choi, B.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 8428– 8431. e) Best, D.; Kujawa, S.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 18193– 18196. f) Izquierdo, J.; Landa, A.; Bastida, I.; Lopez, R.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2016**, *138*, 3282– 3285. g) Yu, S.; Sang, H. L.; Ge, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 15896– 15900. h) Yang, H.; Wang, E.; Yang, P.; Lv, H.; Zhang, X. *Org. Lett.* **2017**, *19*, 5062– 5065.

[85] Gladfelder, J.J.; Ghosh, S.; Podunavac, M.; Cook, A. W.; Ma, Y.; Woltornist, R. A.; Keresztes, I.; Hayton, T. W.; Collum, D. B.; Zakarian, A. *J. Am. Chem. Soc.* **2019** *141*, 15024-15028.

[86] a) Yin, Y.; Dai, Y.; Jia, H.; Li, J.; Bu, L.; Qiao, B.; Zhao, X.; Jiang, Z. *J. Am. Chem. Soc.* **2018**, *140*, 6083– 6087. b) Meazza, M.; Tur, F.; Hammer, N.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2017**, *56*, 1634– 1638. c) Saxena, A.; Choi, B.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 8428– 8431. d) Best, D.; Kujawa, S.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 18193– 18196. e) Izquierdo, J.; Landa, A.; Bastida, I.; Lopez, R.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2016**, *138*, 3282– 3285. f) Yu, S.; Sang, H. L.; Ge, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 15896– 15900. g) Yang, H.; Wang, E.; Yang, P.; Lv, H.; Zhang, X. *Org. Lett.* **2017**, *19*, 5062– 5065. h) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem.* **2010**, *45*, 3245– 3264.

[87] Reich, H. J. *Chem. Rev.* **2013**, *113*, 7130– 7178.

[88]Mazur, R. H.; Roberts, J. D. *J. Am. Chem. Soc.* **1951**, *73*, 2509-2520.

[89] Schmidt, T.;Kirschning, A.; *Angew. Chem. Int. Ed.* **2012**, *51*, 1063– 1066.

[90] Nomura, T.; Yokoshima, S.; Fokuyama, T. *Org. Lett.* **2018**, *20*, 119–121.

[91] Quirion, J-C.; Sevenet, T.; Husson, H.-P.; Weniger, B.; Debitus, C. J. *Nat. Prod.* **1992**, *55*, 1505-1508.

[92] Stockley, M.; Clegg, W.; Fontana, G.; Golding, B. T.; Martin, N.; Rigoreau, L. J. M.; Smith, G. C. M.; Griffin, R. J. *Bioorganic Med. Chem. Lett*. **2001**, *11*, 2837-2841.

[93] Jens Wolff, J.; Frenking, G.; Harms, K. *Chemische Berichte*, 1991, *124*, 551-561. doi: 10.1002/cber.19911240322

[94] Moore, J.T.; Hanhan, N.V.; Mahoney, M.E.; Cramer, S.P.; Shaw, J.T. *Org. Lett*. **2013**, *15*, 5615-5617.

[95] Prepared according to the procedure outlined by Denmark and co-workers: Denmark, S.E.; Kobayashi, T.; Regens, C.S. *Tetrahedron* **2010**, *66*, 4745-4759.

[96] Leung, P.S.W.; Teng, Y.; Toy, P.H. *Org. Lett.* **2010**, *12*, 4996-4999.

[97] Race, N. J.; Bower, J. F. *Org. Lett.*, **2013**, 15, 4616–4619.

[98] Browder, C.C.; Marmasäter, F.P.; West, F.G. *Org. Lett.* **2001**, *3*, 3033-3035.

[99] Chen, Y.G.; Shuai, B.; Ma, C.; Zhang, X.J.; Fang, P.; Mei, T.S. *Org. Lett.* **2017**, *19*, 2969-2972.

[100] Schmidt, A.; Hilt, G. *Org. Lett.* **2013**, *15*, 2708-2711.

[101] Lindstadt, R.T.H.; Peterson, C.A.; Jette, C.I.; Boskovic, Z.V.; Lipshutz, B.H. *Org. Lett.* **2017**, *19*, 328-331.

[102] Li, X.; Jiang, H.; Uffman, E.W.; Guo, L.; Zhang, Y.; Yang, X.; Birman, V.B. *J. Org. Chem.* **2012**, *77*, 1722-1737.

[103] Lifchits, O.; Mahlau, M.; Reisinger, C.M.; Lee, A.; Farès, C.; Polyak, I.; Gopakumar, G.; Thiel, W.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 6677-6693.

[104] Gansäuer, A.; Fan, C.A.; Keller, F.; Keil, J. *J. Am. Chem. Soc.* **2007**, *129*, 3483-3485.

[105] Guyon, H.; Boussonnière, A.; Castanet, A. *J. Org. Chem.*, **2017**, 82, 4949-4957.

[106] Hsin, L. W.; Chang, L. T.; Rothman, R. B.; Dersch, C. M.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.*, **2008**, 51, 2795-2806.

[107] Hamon, David, P. G.; Trenerry, C. V., *Aust. J. Chem*., **1980**, 33, 809-821.

[108] Bales, B. C.; Horner, J. H.; Huang, X.; Newcomb, M.; Crich, D.; Greenberg M. M.; *J. Am. Chem. Soc*., **2001**, *123*, 3623-3629

[109] Fujita, H.; Kakuyama, S.; Kunishima, M. *Eur. J. Med. Chem.*, **2017**, 4, 833-839.

[110] Casalme, L. O.; Yamauchi, A.; Sato, A.; Petitbois, J. G.; Nogata, Y.; Yoshimura, E.; Okino, T.; Umezawa, T.; Matsuda, F. *Org. Biomol. Chem.*, **2017**, 15, 1140-1150.

[111] Ji, Y.; Xue, P.; Ma, D.; Li, Xue.; Gu, P.; Li, R. *Tetrahedron Lett.* **2015,** 56, 192-194.

[112] Yao, L.; Wen, J.; Liu, S.; Tan, R.; Wood, N. M.; Chen, W.; Zhang, S.; Zhang, X. *Chem. Commun.* **2016,** 52, 2273-2276.

[113] Kolasa, T.; Miller, M. J. *J. Org. Chem.*, **1987**, 52, 4978–4984.

[114] Fedman, K. S.; Selfridge, B. R. *Tetrahedron Lett.*, **2012**, 53, 825-828.

[115] Reeve, W.; Steckel, T. F. *Can. J. Chem.*, **1980**, 58, 2784-2788.

[116] Laurie, D.; Lucas, E.; Nonhebel, D. C.; Suckling, C. J.; Walton, J. C. *Tetrahedron*, **1986**, 42, 1035-1045.