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Progress Toward the Total Synthesis of Lyconadin A

Yu Zhang
Brigham Young University - Provo

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Yu Zhang

A dissertation submitted to the faculty of
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Doctor of Philosophy

Steven L.Castle, Chair
Merrit B. Andrus
Paul B. Savage
Young W. Ham
Allen R. Buskirk

Department of Chemistry and Biochemistry

Brigham Young University

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ABSTRACT

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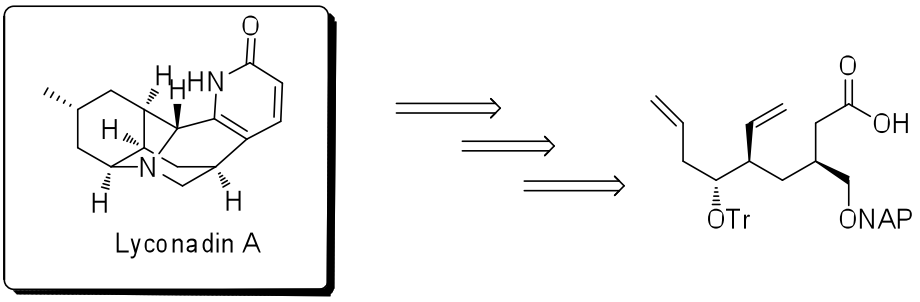

Lyconadin A is a pentacyclic *Lycopodium* alkaloid isolated from the club moss *Lycopodium* complanatum with antitumor properties. We have developed a novel 7-*exo*/6-*exo* acyl radical cascade cyclization as a method of making the bicyclo[5.4.0]undecane ring system of lyconadin A. The model products are *trans*-fused ring systems, while a *cis*-fused ring system is needed in lyconadin A. We have discovered a method to convert the *trans*-fused model cascade cyclization product into the desired *cis* isomer. Based on Donohoe's pyridone synthesis, we developed a method for the construction of 5-alkyl and 3,5-dialkyl-6-carbomethoxy-2-pyridones, the former of which is a subunit of lyconadin A. An intramolecular Reformatsky reaction is a key step in this process. We have proceeded with our total synthesis, in which we generated an epoxide by Shi asymmetric epoxidation and regioselectively opened epoxide rings. We have prepared carboxylic acid **197**.

Keywords: radical cyclization, pyridone, lyconadin A

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Most of all I want to express my appreciation to my husband, Zhaofan, and my parents, Rongbang and Zhilan, for their love. It is to them that I dedicate this dissertation.

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Chapter 1. Introduction

1.1 *Lycopodium* Alkaloids

The genus *Lycopodium* consists of low, evergreen, coarse moss–like plants, which are commonly known as club mosses. They are non–flowering plants and reproduce via spores rather than seeds. The name club mosses originates from the fact that the strobili look like club–shaped growths at the tips of the moss-like branches.[1] *Lycopodium* species produce a lot of structurally diverse alkaloids with quinolizine, pyridine or *α*–pyridone type skeletons.

In 1881, Bödeker made the first investigations on *Lycopodium* alkaloids.[2] He isolated lycopodine from *Lycopodium complanatum*. In 1938, Achmatowicz and Uzieblo gave the correct molecular formula for lycopodine.[3] Since the 1940s, W. A. Ayer's group has explored the isolation, structural determination, biogenesis, and chemical synthesis of *Lycopodium* alkaloids.[4] During the period of 1986-1990, some *Lycopodium* alkaloids were found to possess potent acetylcholinesterase inhibition activity.[5,6] Chinese scientists Liu and co-workers isolated huperzine A from the Chinese herb Qian Ceng Ta. Huperzine A has been shown to be the most potent, reversible inhibitor of acetylcholine esterase. It can increase efficiency for learning and memory and it shows promise in the treatment of Alzheimer's disease and myasthenia gravis

disease, which is a chronic disease characterised by fluctuating levels of muscle weakness.[7,8,9] So far, over 200 *Lycopodium* alkaloids have been characterized from 54 species of *Lycopodium.*

Lycopodium alkaloids can be separated into four classes according to their structures: The lycopodine class, alkaloids possessing the lycopodane skeleton; the lycodine class, the dinitrogenous alkaloids which contain a pyridine or pyridine ring; the fawcettimine class, those containing a five-membered B ring; and a miscellaneous class, alcoloids possessing unique frameworks distinct from the traditional structural class.[10] Lycopodine, lycodine, fawcettimine and phlegmarine are representative compounds for these classes (Figure 1).[4]

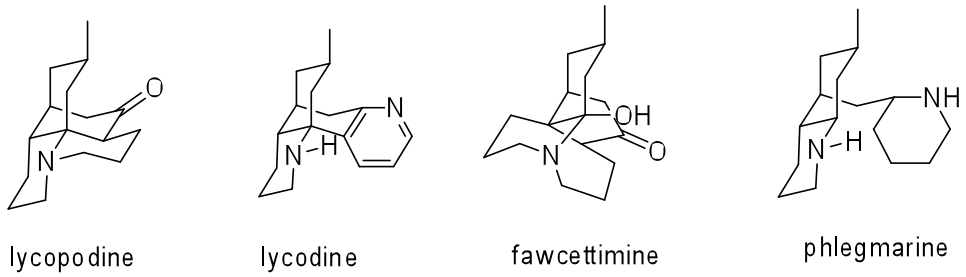


Figure 1. Representative Compounds of the Four Major Classes of Lycopodium Alkaloids

Lycopodium alkaloids have wonderful bioactivities. Nevertheless, these plants are not abundant. They grow very slowly, and are only found in special places. They have not been cultivated successfully. Tissue culture also appears to be very difficult. Thus, very few biosynthetic studies have been performed with *Lycopodium* alkaloids. [11,12,13,14] However, total synthesis can provide material for investigation of the biological properties of *Lycopodium* alkaloids. Moreover, the complex structures provide a significant challenge to synthetic chemists.

1.2 Lyconadin A

The alkaloid lyconadin A is a member of the *Lycopodium* alkaloid family which belongs to the miscellaneous class (Figure 2). It was isolated by Kobayashi and co-workers from the club moss *Lycopodium complanatum*.[15] It possesses a unique molecular skeleton consisting of an *α*-pyridone ring as well as one five-membered and three six-membered rings. It contains six stereocenters. In addition to its novel structure, lyconadin A exhibits modest in vitro cytotoxity against murine lymphoma L 1210 cells (IC_{50} = 0.46 μg/mL) and human epidermoid carcinoma KB cells (IC_{50} = 1.70μg/mL).[15] This unprecedented framework and biological activity make it a challenging and attractive target for total synthesis.

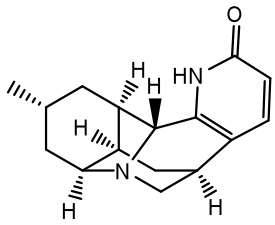


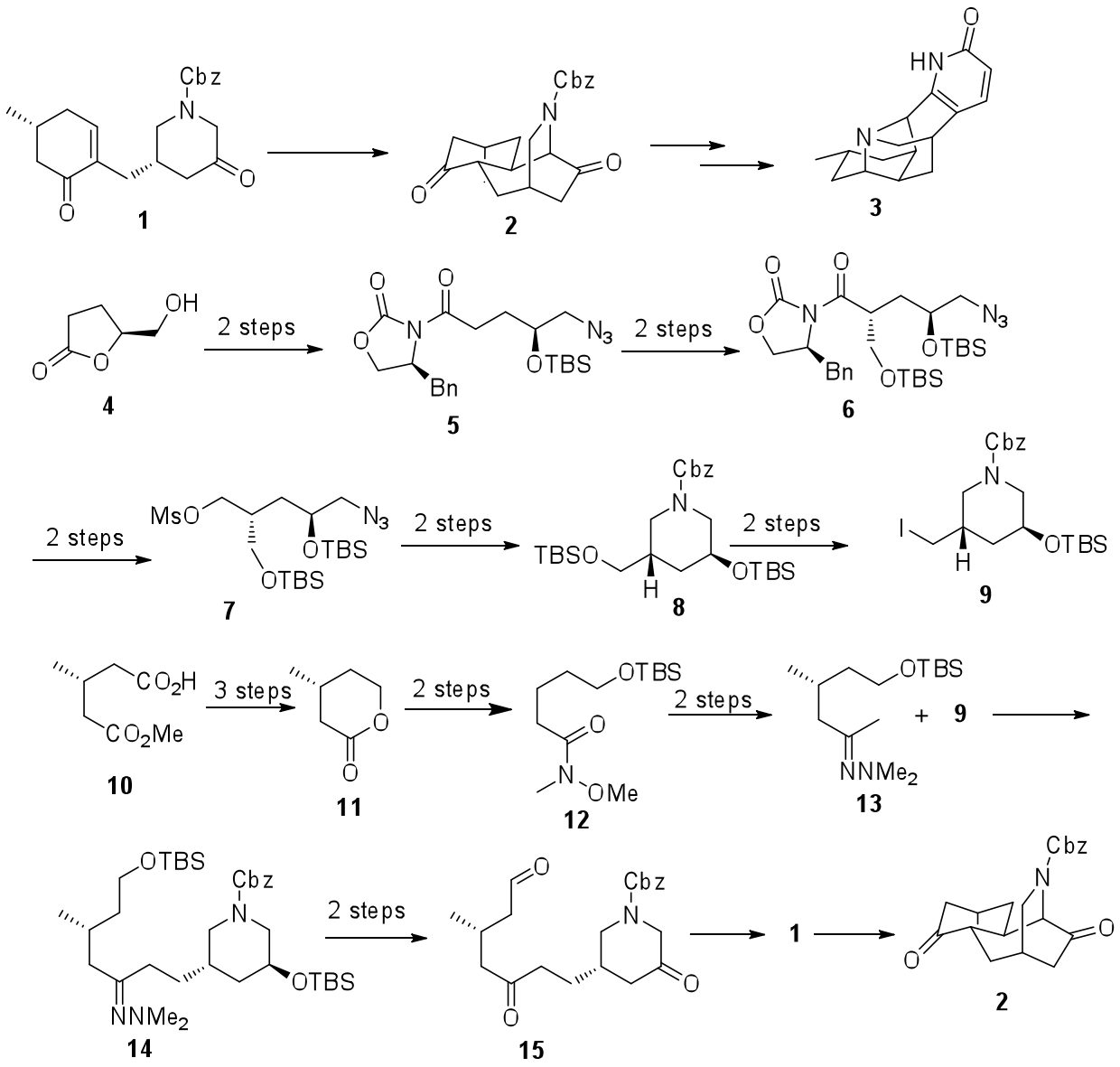
Figure 2. Lyconadin A

1.3 Total Synthesis

Lyconadin A possesses an unprecedented pentacyclic ring system, with an *α*-pyridone ring fused to a tetracyclic core. The tightly functionalized structure containing four adjacent stereocenters makes lyconadin A a challenging synthetic target. The first total synthesis of (+)-lyconadin A was reported by Smith in 2007.[16] Sarpong finished a total synthesis of racemic lyconadin A in 2008[17] and an enantioselective synthesis in 2009.[18]

In Smith's synthesis, the pentacyclic sketon of lyconadin A was constructed by the key intermediate enone **1** (Scheme 1), which was mainly installed by the coupling of iodide **9** with

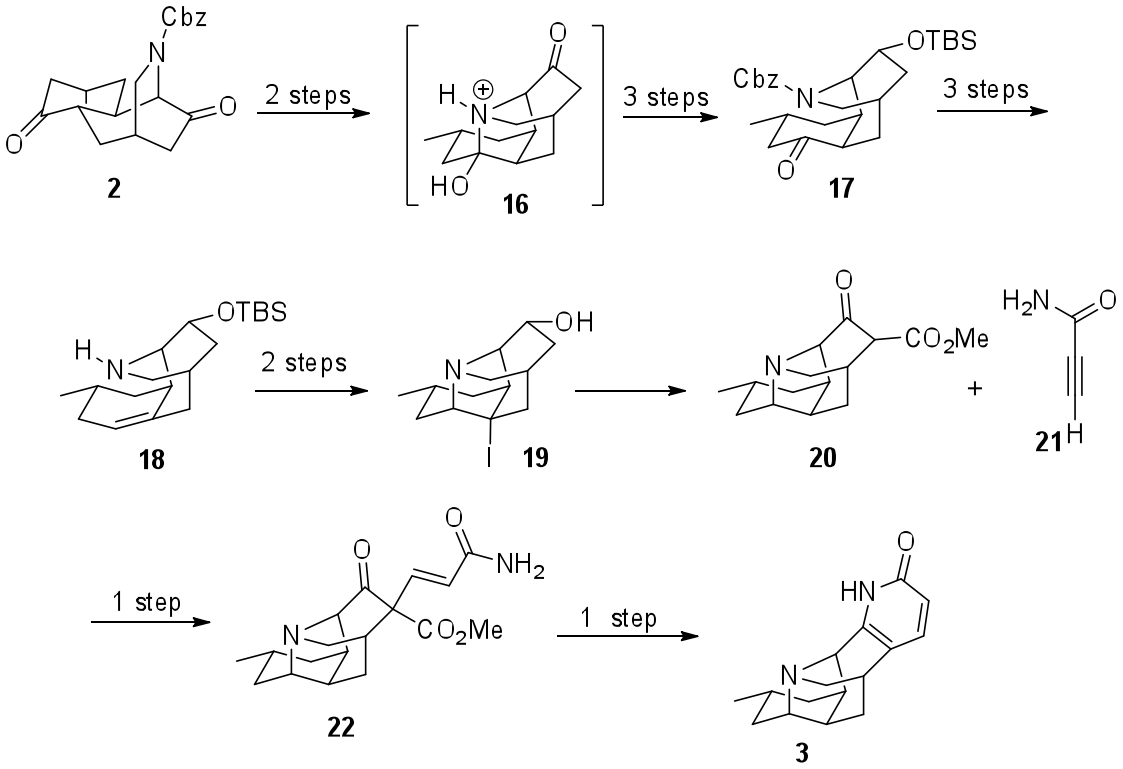
hydrazone **13** and resultant intramolecular aldol condensation of **15**. The iodide **9** was prepared from the commercially available enantiomerically pure lactone **4**. Then, they introduced the L-Phe oxazolidinone chiral auxiliary to enable diastereoselective hydroxymethylation. Then, TBS protection, removal of chiral auxiliary, cyclization and iodination provided iodide **9**. The enantiomerically pure secondary methyl substituent of **15** derived from the monoester **10**. Lactone formation followed by opening of lactone with $HCONHCH_3 \cdot HCl$ afforded, after protection, Weinreb amide **12**. Alkylation of the derived hydrazone **13**, after deprotection, led to **15**. Under the acidic condition, the intromolecular aldol condensation and Michael addition gave the trans-fused bicyclic diketone **2**.



Scheme 1. Smith's Synthesis of Diketone **2**

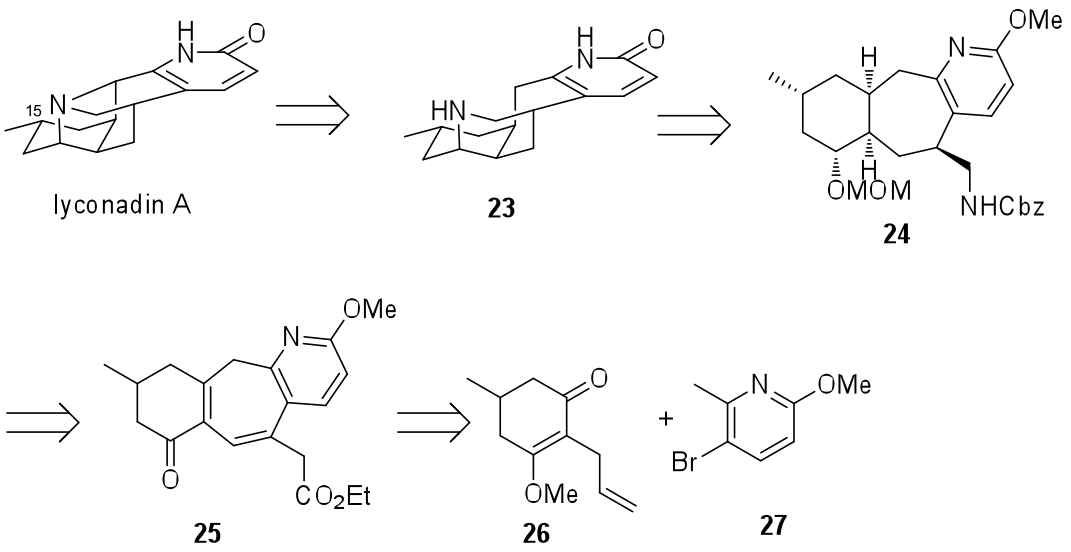
Lyconadin A possesses a *cis*-fused ring system. So, it was necessary to epimerize **2** to the *cis* ring fusion **16** (Scheme 2). Smith and Beshore tried to dehydrate the tertiary alcohol of **16**, but failed because of Bredt's rule. Then, they cleaved the C-N bond by selective reduction followed by protection to deliver **17**. Later, the C-N bond was reinstalled by exposure of **18** to NIS to lead

to **19**. Michael addition followed by cyclocondensation to provide **3** (+)-lyconadin A. Smith and Beshore finished the total synthesis in 28 steps and 2.2% overall yield.



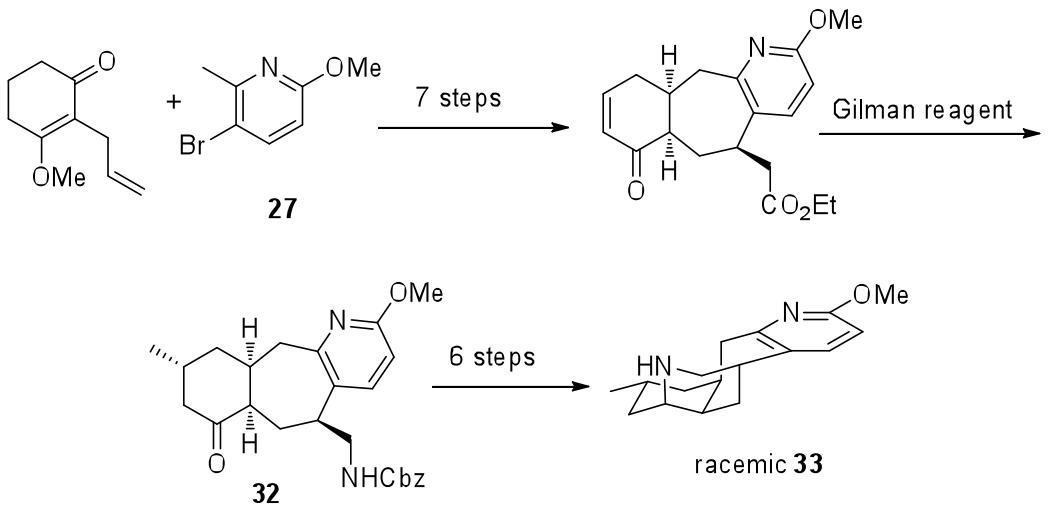
Scheme 2. Synthesis of (+)-Lyconadin A

The Sarpong group postulated that the majority of miscellaneous *Lycopodium* alkaloids could originate synthetically from a common precursor related to the tetracyclic core of **23** (Scheme 3). They sought to highlight a unified approach to the miscellaneous group of *Lycopodium* alkaloids by designing the synthesis of lyconadin A. A key result was that they developed a simple C-N bond formation reaction to make the pentacyclic core of lyconadins.



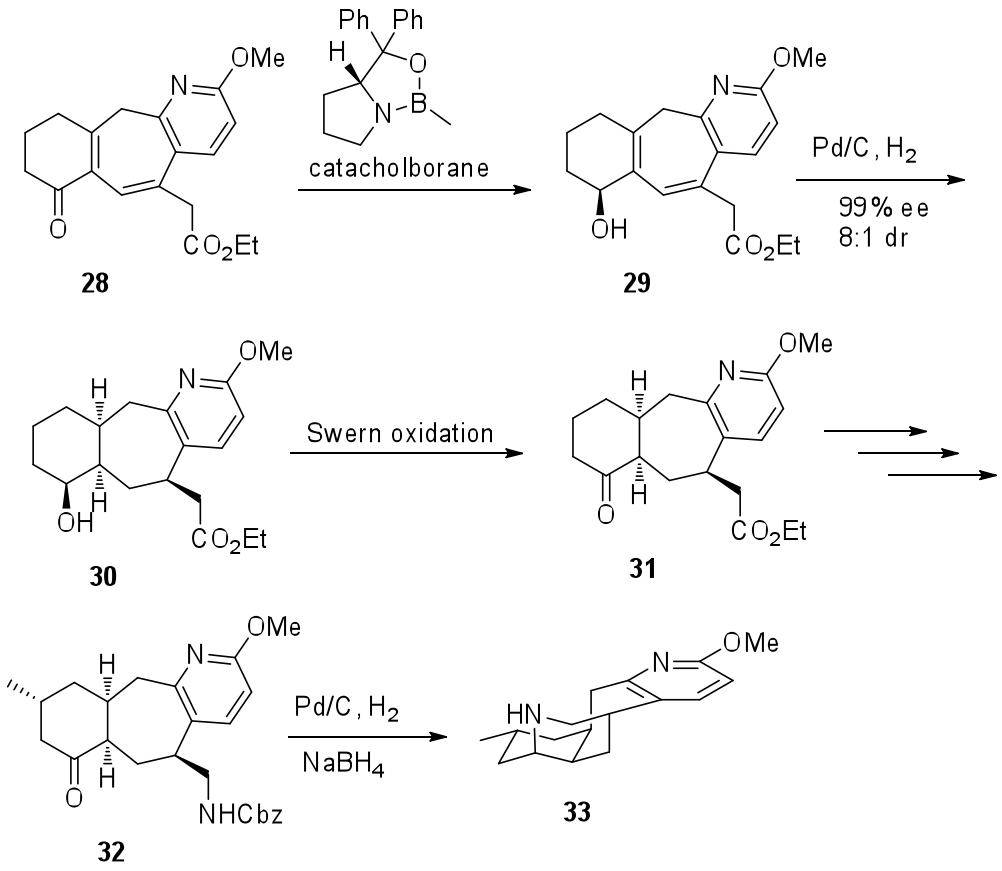
Scheme 3. Retrosynthesis of Lyconadin A in Sarpong Group

In the racemic total synthesis of lyconadin A published in 2008 by Sarpong group, they coupled enone **26** with bromopicoline derivative **27** in a Stork–Danheiser sequence. Unfortunately, after cross-metathesis, intramolecular Heck reaction, Luche reduction, and hydrogenation, they obtained a diastereomer of **23** with an axial methyl group. They turned to react a derivative of **26**, without the methyl group, with **27**, and at the late stage conjugate addition of a Gilman reagent to the enone provided the desired stereochemistry at C15 (Scheme 4). Hydrogenation provided racemic **33**.



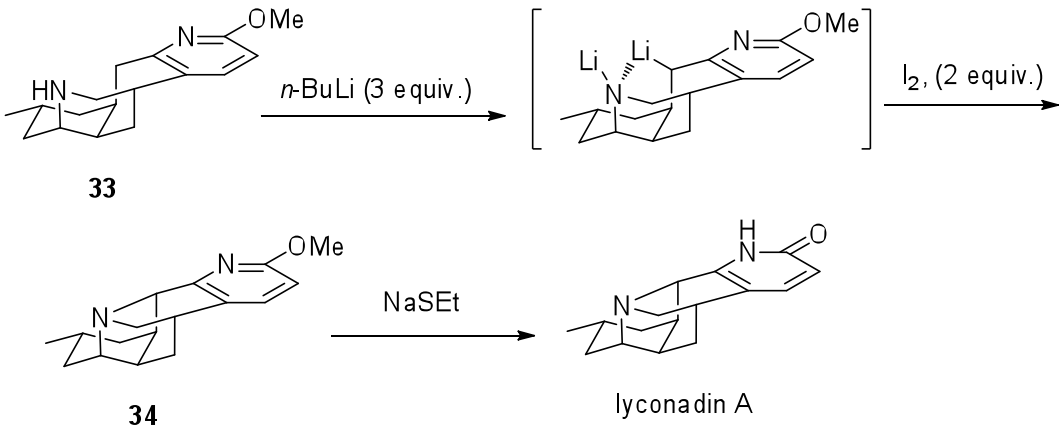
Scheme 4. Synthesis of Racemic **33**

In their enatioselective total synthesis of lyconadin A, Sarpong and co-workers created a temporary stereocenter, and used this stereocenter to control further asymmetric chemistry (Scheme 5). The chiral secondary hydroxyl group in **29** was formed by CBS reduction in high yield and enantiomeric excess. This hydroxyl group directed hydrogenation of both double bonds to generate **30** with three required stereocenters in excellent diastereometric excess. Then, the hydroxyl group was oxidized back to ketone **31**. After similar sequences, **31** was converted into enantioselective **33** in 99% ee.



Scheme 5. Synthesis of **33**

The intermediate **33** is close to the target, but it lacks a key C-N bond. Apparently, it also lacks a functional group with which to build this bond. Sarpong and co-workers tried a lot of name reactions to install this group, and no good result was achieved. Later, they used excess base to form a chelated dianionic bridged intermediate (Scheme 6). The lyconadin A skeleton was completed by treatment with I_2. Demethylation of **34** provided enantiopure (+)-lyconadin A.



Scheme 6. Synthesis of (+)-lyconadin A

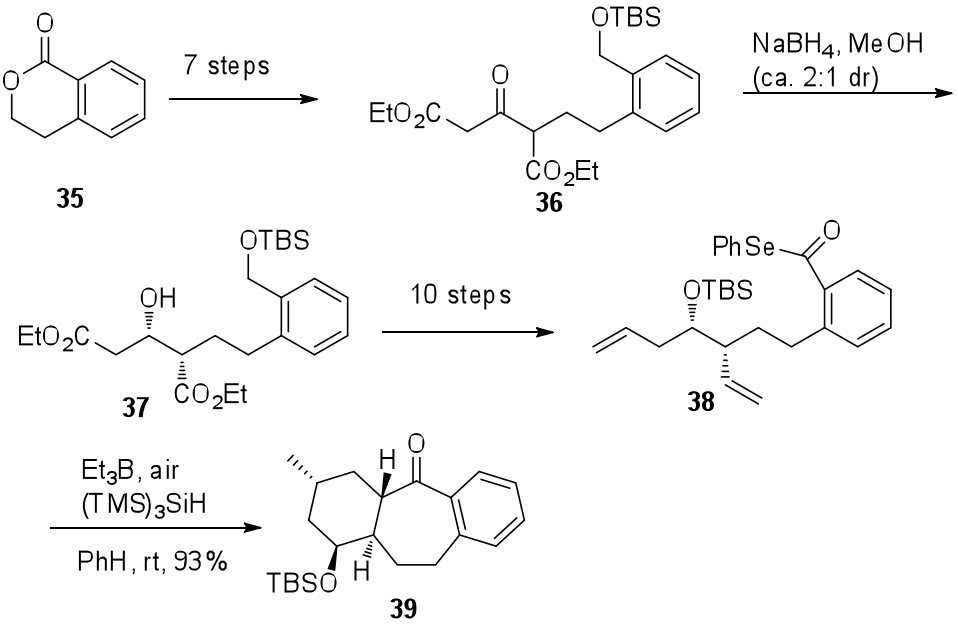
Sarpong and co-worker finished the total synthesis of racemic lyconadin A in 18 steps with 10% overall yield, and enantiopure (+)-lyconadin A in 17 steps with 6.5% overall yield.

1.4 Seth Grant's work on Acyl Radical Cascade Cyclization

Lyconadin A possesses a bicyclo[5.4.0]undecane ring system fused to a pyridone ring. An efficient approach to installing this framework involves building two rings in a single reaction. A radical reaction is suitable for this purpose. The radical reactions which lead to seven-membered rings are rare and only applied to special substates.[20] The rate of 7-*exo* radical cyclization is slow, so the short-lived alkyl radical is not very useful.[21] However, Boger demonstrated that acyl radicals can participate in 7-*exo*-*trig* cyclizations as long as an aromatic ring is present in the tether between the radical and the acceptor.[22] Evans, Bonjoch, and Ryu disclosed various 7-*exo* acyl radical reactions.[23] Nevertheless, there are no examples of cascade reactions that invole a 7-*exo* acyl radical cyclization before the work of Seth Grant in our group.[24]

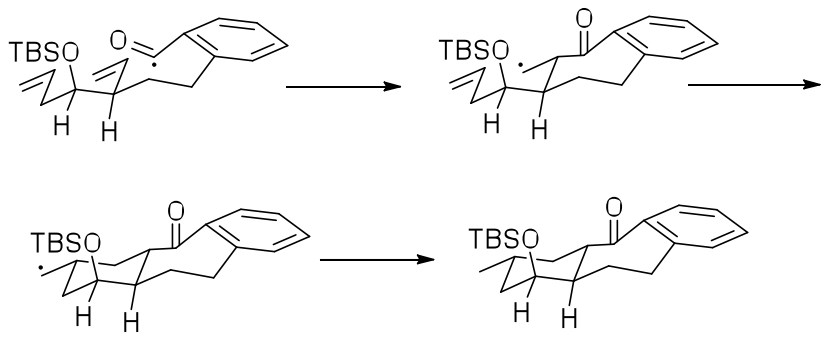
To study the feasibility and stereoselectivity of an acyl radical cyclization which could be used in the total synthesis of lyconadin A, Seth first performed a tandem 7-*exo*-6-*exo* reaction with model substrate **38** (Scheme 7). He used a phenyl-tethered phenyl selenoester as his

cyclization substrate to mimic the 2-pyridone moiety of lyconadin A. He started his synthesis from 1-isochromanone **35**, and got diester **36** via 7 steps. Reduction of **36** with $NaBH_4$ was modestly *syn* selective and provided **37** as a mixture of diastereomers. After 10 steps, the precursor of tadem 7-*exo*-6-*exo* cyclization, phenyl selenoester **38**, was achieved. Treatment of **38** with Et_3B, air, and tris(trimethylsilyl)silane provided tricyclic **39** in excellent yield as a single diastereomer.



Scheme 7. Synthesis of **39**

The *trans* ring fusion and relative configuration of **39** were determined by both 1D and 2D NMR experiments. The stereochemistry of the radical reaction is consistent with cyclization via chairlike or pseudochairlike transition states (Scheme 8).



Scheme 8. Proposed Stereochemistry of the Acyl Radical Cascade Cyclization

1.5 References

1. Kobayashi, J.; Morita, H. *The Alkaloids* **2005**, *61*, 1.

2. Bödeker, K. *Justus Liebigs Ann. Chem*. **1881**, *208*, 363.

3. Achmatowicz, O.; Uzieblo, W. *Rocz. Chem*. **1938**, *18*, 88.

4. Ma, X.; Gang, D. R. *Nat. Prod. Rep*. **2004**, *21*, 752.

5. Tang, X. C.; Han, Y. F.; Chen, X. P.; Zhu, X. D. *Acta Pharmacol. Sin.* **1986**, *7*, 507.

6. Tang, X. C.; Sarno, P. D.; Sugaya, K.; Giacobini, E. J. *Neurosci. Res.* **1989**, *24*, 276.

7. Kozikoski, A. P.; Tüeckmantel, W. *Acc.Chem. Res.* **1999**, *32*, 641.

8. Bai, D. L.; Tang, X. C.; He, X. C. *Curr. Med. Chem*. **2000**, *7*, 355.

9. Tan, C. H.; Zhu, D. Y. *Zhongguo Tianran Yaowu* **2003**, *1*, 1.

10. Ma, X.; Gang, D. R. *Nat. Prod. Rep*. **2004**, *21*, 752.

11. Freeberg, J. A.; Wetmore, R. H. *Phytomorphology* **1957**, *7*, 204.

12. Freeberg, J. A.; Wetmore, R. H. *Phytomorphology* **1967**, *17*, 78.

13. Dwyer, T.; Waegel, A. S. *Acta Hortic* **2004**, *631*, 181.

14. Yang, H.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc*. **2008**, *130*, 9238.

15. Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. *J. Org. Chem***. 2001**, *66*, 5901.

16. Beshore, D. C.; Smith, A. B. *J. Am. Chem. Soc.* **2007**, *129*, 4148.

17. Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc*. **2008**, *130*, 7222.

18. West, S.; Bisai, A.; Lim, A. D.; Narayan, R. R.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 11187.

20. Lang, S.; Corr, M.; Muir, N.; Khan, T. A.; Murphy, J. A.; Payne, A. H.; Williams, A. C. *Tetrahedron Lett*. **2005**, *46*, 4027.

21. (a) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991. (b) Boger, D. L. *Israel J. Chem.* **1997**, *37*, 119.

22. Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1988**, *53*, 3377.

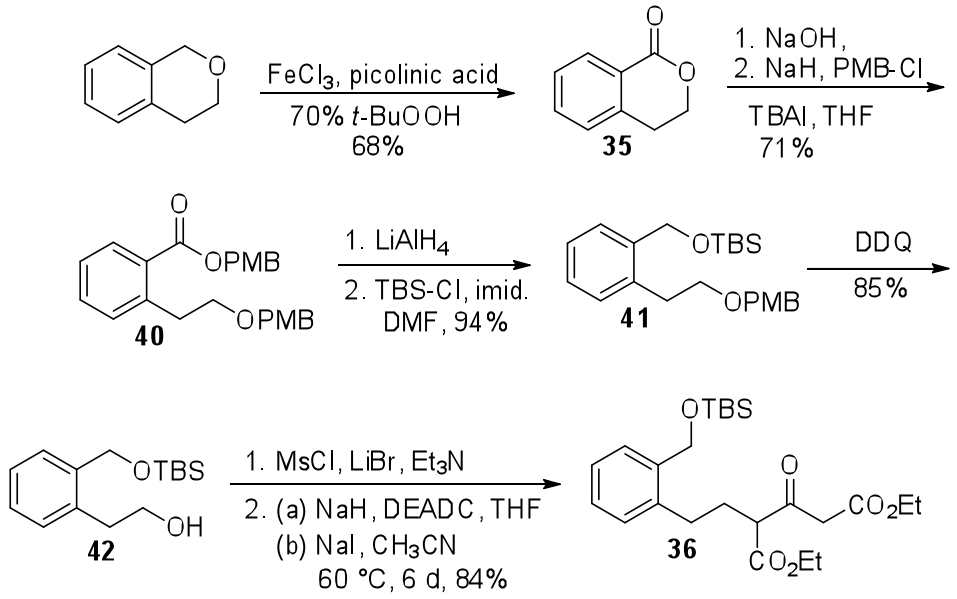
Chapter 2. Model Studies Towards Acyl Radical Cascade

Cyclization and Conversion to *cis*-Fusion

In our group, Seth Grant demonstrated the first example of a 7-*exo*-6-*exo* acyl radical cascade reaction. In this reaction, two new C-C bonds and two stereocenters are formed in a highly regio- and stereoselective fashion. The relative configurations of the products are consistent with cyclization occurring via chairlike or pseudochairlike transition states. This acyl radical cascade cyclization should be useful in the preparation of the bicyclo[5.4.0]undecane ring system and could be employed in the total synthesis of lyconadin A. To determine if the bulky TBS group has some effect on the diastereoselectivity, we removed the TBS group from Seth's substrate, and performed the cyclization with the free alcohol. We also studies the role of OTBS configuration by cyclization with the diastereomer of Seth's substrate. In addition, we developed a method to epimerize the model products to *cis* –fused isomers, which is needed in lyconadin A.

2.1. Alkylation

The synthesis of the diester **36** was developed by Seth Grant, [1] and is shown in Scheme 1. Commercially available isochroman was oxidized into lactone **35**, which was hydrolyzed under basic conditions. Protection of both alcohol and carboxylic acid functionalities of the resulting hydroxy acid with PMB-Cl provided **40**. Reduction of **40** with LAH followed by treatment of the resultant alcohol with TBS-Cl afforded differentially protected diol **41**. The PMB group was then removed under oxidative conditions to afford alcohol **42**, which was converted into a bromide in excellent yield. Alkylation of diethyl acetonedicarboxylate (DEADC) by this bromide delivered ketone **36**.

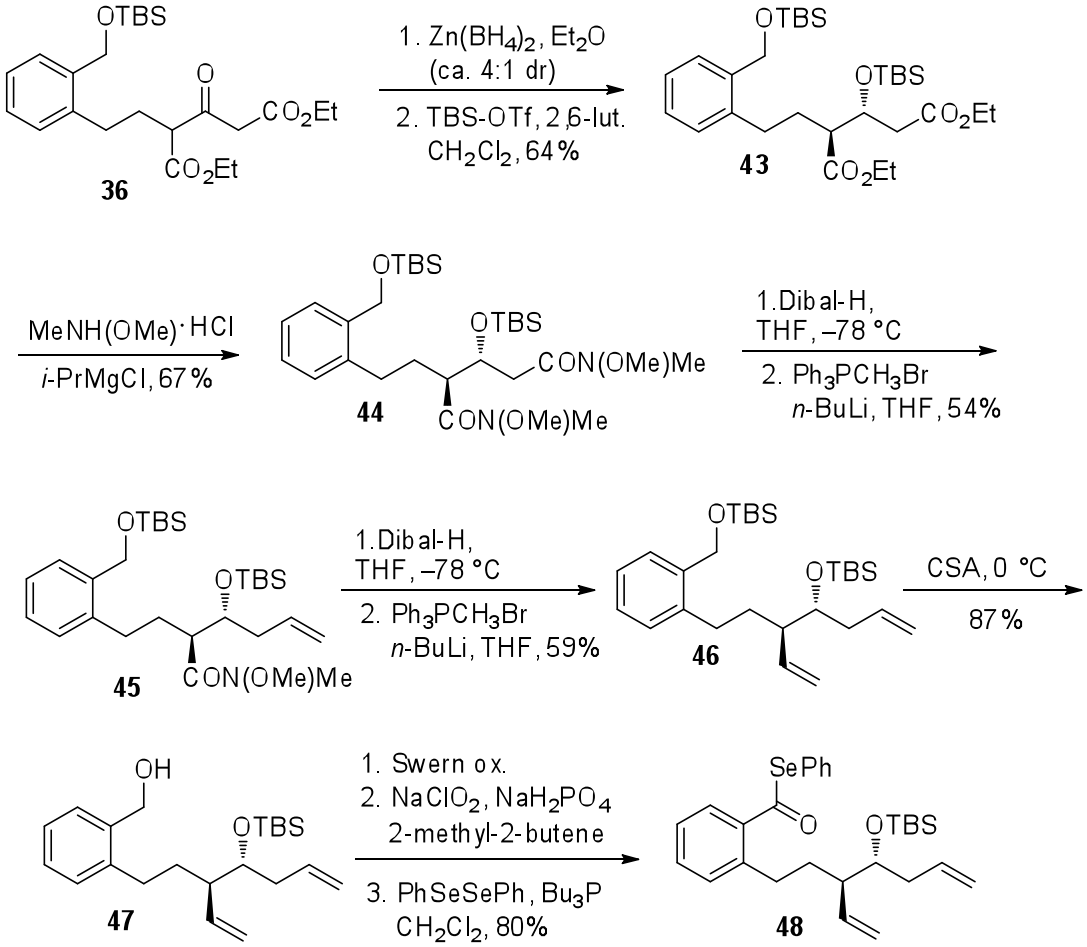


Scheme 1. Synthesis of Ketone **36**

2.2 Synthesis of the Phenyl Selenoester

Based on Seth Grant's work, we were able to access phenyl selenoester **48**, the diastereomer of **38,** by simply changing the conditions for reduction of ketone **36**. Reduction of **36** with

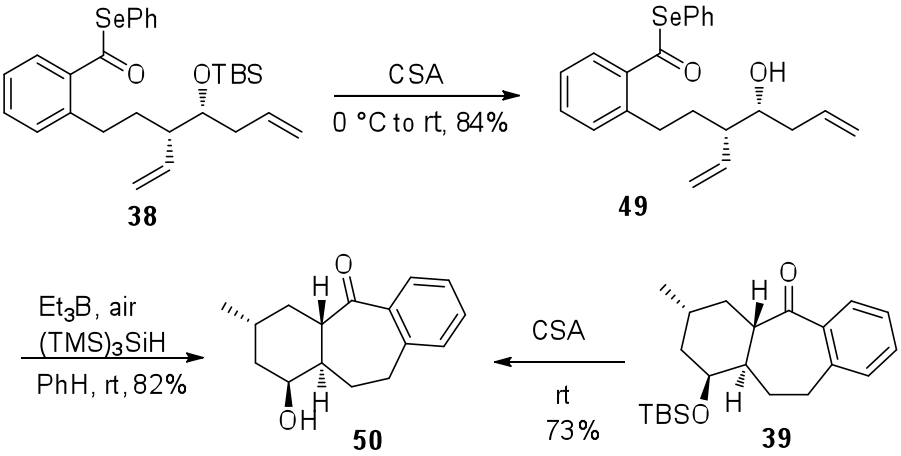
freshly prepared $Zn(BH_4)_2$[2] followed by TBS protection provided *anti* isomer **43** in 4:1 dr (Scheme 2). Conversion of both ester moieties into Weinreb amides provided **44**. Due to significant differences in the reduction rates of the two amides, the reduction–Wittig olefination sequence was conducted twice. Treatment of **44** with Dibal-H followed by Wittig reaction afforded monoalkene **45**, which was subjected to further Dibal-H reduction and Wittig reaction to produce **46**. Selective cleavage of the primary benzylic silyl ether mediated by CSA delivered **47**. Swern oxidation, further oxidation of the resultant aldehyde, and phenyl selenoesterification provided **48** in good yield.



Scheme 2. Synthesis of Phenyl Selenoester **48**

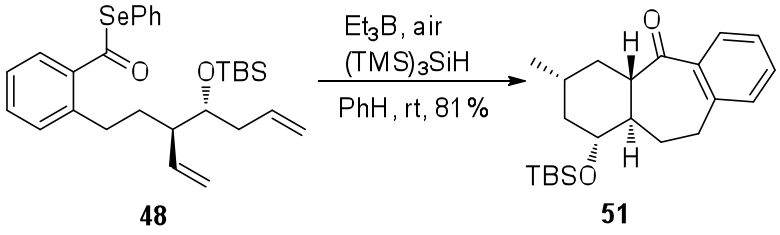
2.3 Acyl Radical Cascade Cyclization

To probe the role of the OTBS group in the stereoselectivity of the radical cyclization, we generated free alcohol **49** from **38** via treatment with CSA (Scheme 3). Cyclization of **49** delivered alcohol **50** as a single diastereomer which has the same structure as that obtained from deprotection of **39**. Accordingly, the bulky TBS group is not required to achieve stereoselectivity in this process.



Scheme 3. Tandem Cyclization of Alcohol **49**

Treatment of **48** with Et_3B, air, and tris(trimethylsilyl)silane provided tricycle **51** in good yield as a single diastereomer (Scheme 4).



Scheme 4. Tandem 7-*exo*-6-*exo* Cyclization of **48**

To determine the relative configuration of all the stereocenters of **51**, we performed NMR analysis (^1H, ^{13}C, COSY, NOE). From the 1H NMR of **51**, the coupling constant between the

proton 10 and proton 15 is 9.0 Hz or 13.0 Hz, which indicates a *trans* ring configuration. Furthermore, when the proton 13 was irradiated, the signal at proton 11 was enhanced. This suggests that the relative stereochemistry of the OTBS group and methyl group are *cis*. Irradiation of the proton 10 did not lead to an enhancement in the signal at proton 11. This indicates that proton 10 and proton 11 are *trans* to each other. Based on these results, the stereochemistry of **51** is derived as shown in Figure 1. Thus, based the cyclizations of **38** and **48**, it is clear that this 7-*exo*-6-*exo* cascade radical cyclization occurs with excellent diastereoselectivity regardless of the relative configuration of the OTBS group.

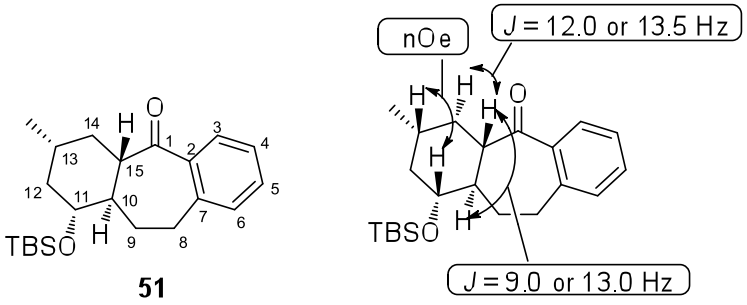
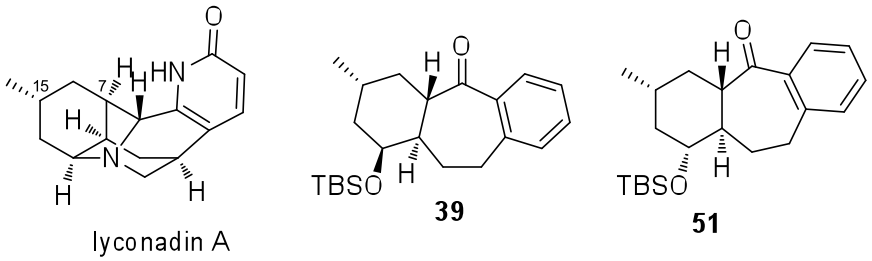


Figure 1. Stereochemistry of Compound **51**

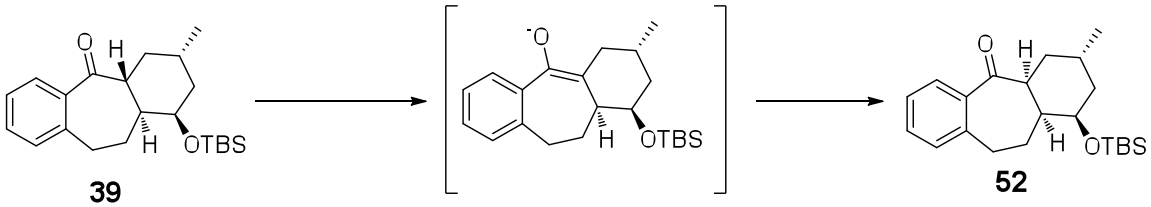
2.4 Epimerization

Comparing the structures of our obtained model compounds **39** and **51** with targeted lyconadin A, we could find that the cyclization installed the correct stereochemistry at C15 but not at C7 (Scheme 5).



Scheme 5. Structure Comparison

In order to develop a method for building *cis*-fused lyconadin A, We explored the conversion of the *trans*-fused model cascade cyclization product into the desired *cis* isomer. Since C7 is adjacent to a carbonyl, it may be epimerized via a kinetically controlled protonation (Scheme 6). Thus, treatment of the enolate derived from **39** with BHT or other bulky hydrogen source should result in formation of *cis*-fused isomer **52**. Because OTBS group is more bulky than methyl group, it will shield the top face of **39**. So the enolate will be expected to attack the the proton source, especially a bulky one, from the bottom face to obtain *cis*-fused isomer **52**.

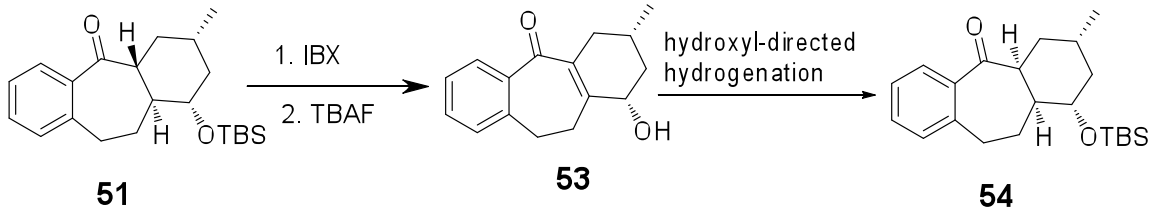


Scheme 6. Proposed Kinetically Controlled Protonation

To generate the enolate, *t*-BuLi[3] was chosen as a base for this reaction. We treated **39** with *t*-BuLi at –78 °C. After 10 seconds, we quenched the reaction with a solution of butylated hydroxytoluene (BHT) in THF. Unfortunately, we only recovered the starting material. Then, we tried to quench the reaction at –78 °C after 3 minutes, 10 minutes, 30 minutes and 1 hour respectively, but we still recovered starting material. To make sure that the enolate was formed after treating with *t*-BuLi, we quenched the reaction with D_2O. The ^1H NMR and mass spectrum

showed that the deutarated compound of **39** was obtained. Thus the enolate was formed in this reaction. Other hydrogen sources, *t*-BuOH and triphenylacetic acid, were tried to replace BHT respectively. However, only starting material was recovered. Then other bases, *n*-BuLi and LDA, were tried respectively. The resulting enolate was treated with BHT, *t*-BuOH, and triphenyl acedic acid respectively. Unfortunately, we still recovered all the starting material.

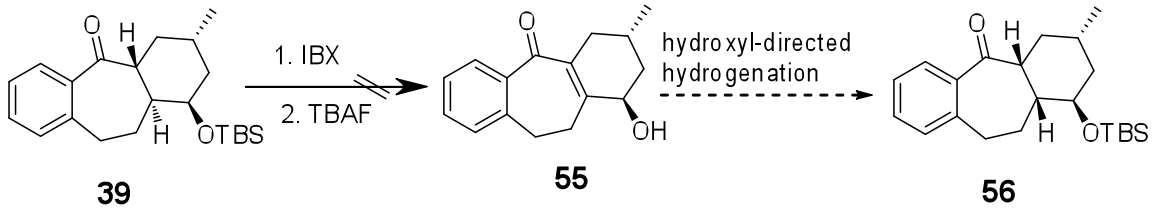
Then, we turned to an alternative sequence (Scheme 7). Oxidation of of **51** according to the protocol of Nicolaou-Baran[4] or Saegusa[5] and resulting silyl ether deprotection should afford enone **53**. With enone in hand, hydroxyl-directed hydrogenation would result in the desired *cis*-fused product **54**.



51 **53** **54**

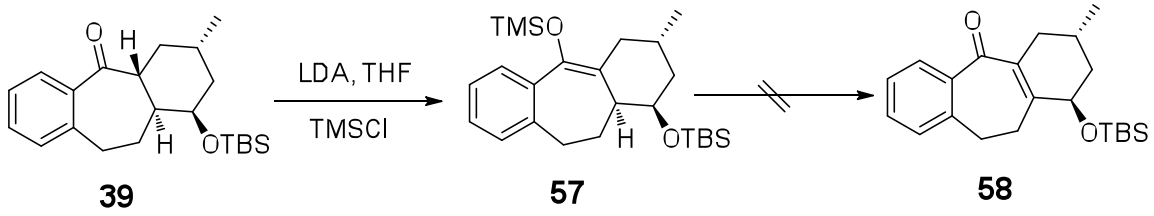
Scheme 7. Planned Epimerization of **51**

Due to the ready availability of **39**, we tried to oxidize **39** with IBX in DMSO at 70 °C, but failed to get the enone **55**, and only recovered starting material (Scheme 8). We changed to the mixed solvent system of DMSO and toluene, and still no reaction was observed. Then, a catalytic amount of *p*-TsOH was added, and the mixture was heated to 85 °C. Unfortunately, only TBS deprotected by-product was provided. Later, IBX·MPO as an oxidant was used in DMSO and CH_2Cl_2 at room temperature.[6] However, only starting material was recovered.



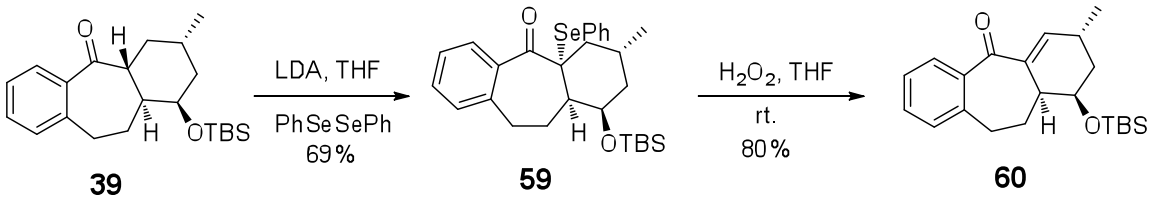
Scheme 8. Attempted Epimerization of **39**

Oxidation of a silyl enol ether is a mild condition for the synthesis of an enone (Scheme 9). Treatment of ketone **39** with LDA followed by adding TMS-Cl at –78 °C provided silyl enol ether **57**. Then, oxidation of **57** was attempted with both IBX·MPO[7] and $Pd(OAc)_2$.[8] Unfortunately, no enone formation was detected, and only sily enol ether **57** was obtained.



Scheme 9. Attempted Enone **58** Formation

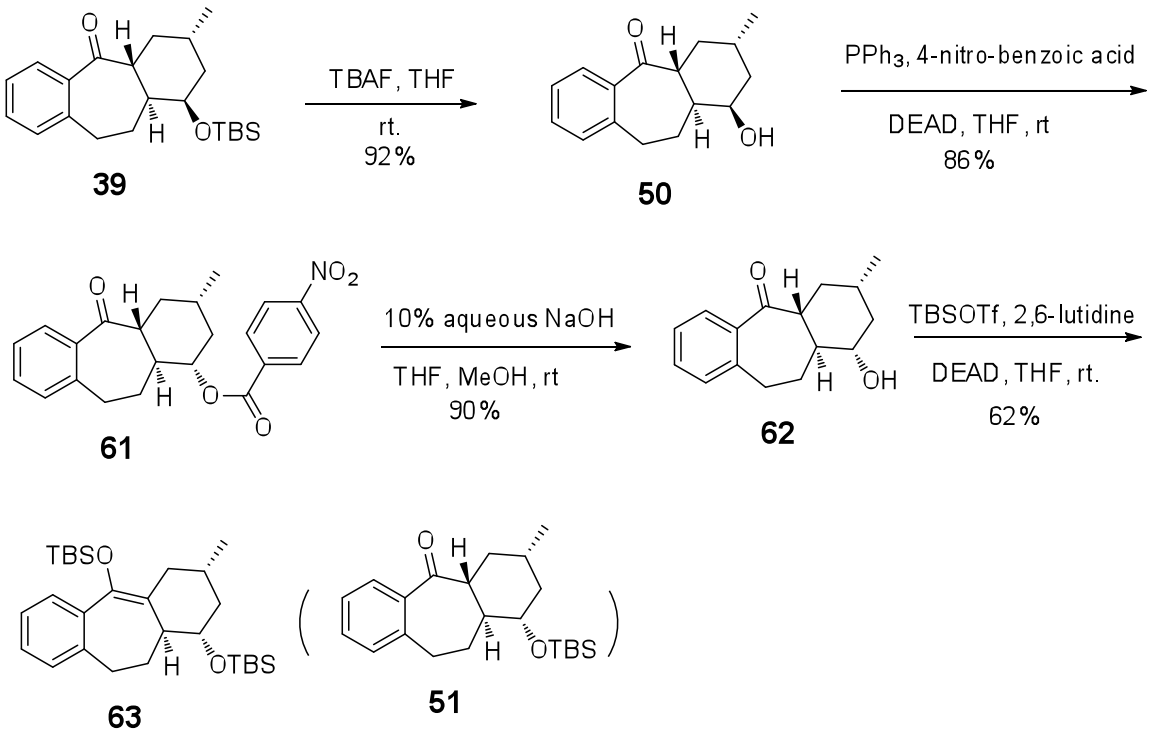
Because phenyl selenide can be oxidized to enone by H_2O_2,[9] we converted **39** to selenide **59** (scheme 10). Fortunately, oxidation of **59** with H_2O_2 provided enone **60.**



Scheme 10. Enone **60** Formation

Based on this result, we believed that this procedure would work for substrate **51**. Due to the ready availability of **39**, We tried to epimerize the stereocenter of OTBS group in **39** by Mitsunobu reaction,[10] then followed the procedure shown in Scheme 10. In the real total

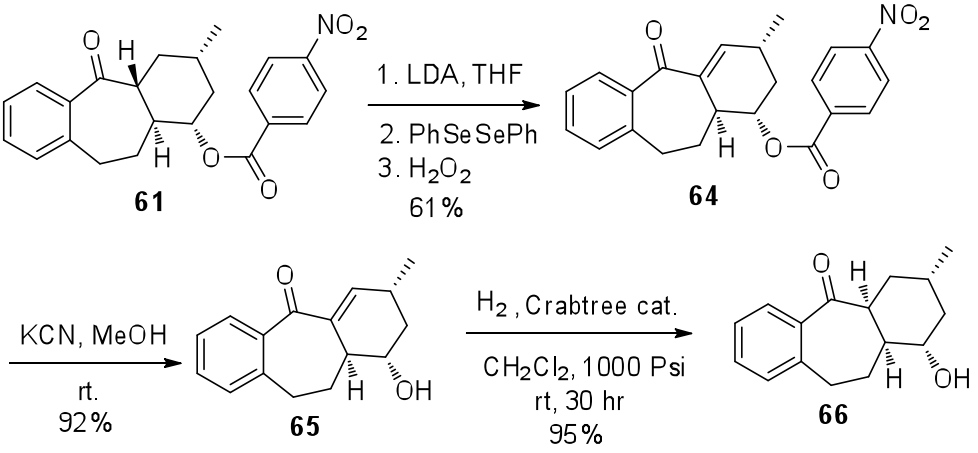
synthesis of lyconadin A, we will not need to do this, because we would obtain a substrate with **51**- type stereochemistry. Treatment of **39** with TBAF provided alcohol **50**, which was exposed to Mitsunobu conditions to afford **61** (Scheme 11). Hydrolysis of **61** under basic conditions delievered alcohol **62**. Unfortunately, TBS protection of **62** led to **63**, rather than **51**.



Scheme 11. Tried Epimerization of **39**

Finally, we got the epimerized product via the following route (Scheme 12). Enone formation followed by hydrolysis afforded enone **65**. With enone **65** in hand, we tried hydrogenation directed by cationic rhodium catalyst with 1000 Psi of H_2.[11] Unfortunately, only starting material was recovered. Later, the Crabtree catalyst was applied, and stirred for 48 hours at room temperature.[12] Fortunately, desired product **66** was obtained. We compared the mass spectrum and ^{1}H NMR of **66** with those of **62**. We found they have the same mass spectrum, but

they have different ^{1}H NMR spectrum. So, we successfully epimerized the proton adjacent to the carbonyl in the model compound **39**.



Scheme 12. Epimerization of **50**

Based on the successful protocol for epimerization of the model product, we could use our acyl radical tandem cyclization to make lyconadin A.

2.5 References

1. Grant, S. W.; Zhu, K.; Zhang, Y. *Org. Lett*. **2006**, *8*, 1867.

2. Overman, L. E.; Angle, S. R. *J. Org. Chem*. **1985**, *50*, 4021.

3. Magnus, P.; Matthews, K. S. *J. Am. Chem. Soc*. **2005**, *127*, 12476.

4. Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. L. *J. Am. Chem. Soc*. **2002**, *124*, 2245.

5. Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem*. **1978**, *43*, 1011.

6. Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem. Int. Ed*. **2002**, *41*, 993.

7. Snyder, S. A.; Corey, E. J. *J. Am. Chem. Soc*. **2006**, *128*, 740.

8. Hu, X.; Tu, Y. Q.; Zhang, E.; Gao, S.; Wang, S.; Wang, A.; Fan, C.; Wang, M. *Org. Let*. **2006**, *8*, 1823.

9. Clive, D. L. J.; Tao, Y.; Khodabocus, A.; Wu, Y.; Angoh, G.; Bennett, S. M.; Boddy, C. N.; Bordeleau, L.; Kellner, D. *J. Am. Chem. Soc*. **1994**, *116*, 11275.

10. Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem.Soc*. **2000**, *122*, 4583.

11. Evans, D. A.; Morrissey, M. M. *J. Am. Chem.. Soc.* **1984**, *106*, 3866.

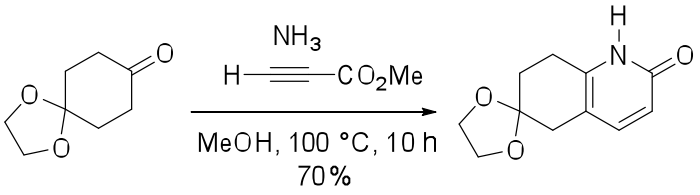
12. Crabtree, R. H.; Davis, M. W. *J. Org. Chem*. **1986**, *51*, 2655.

Chapter 3. Model Pyridone Synthesis Studies

Many biologically active natural products possess a 2-pyridone ring system.[1] As a result, numerous annulation methods have been developed to install this ring.[2] We are interested in synthesizing lyconadin A, which contains a 2-pyridone ring moiety. In our total synthesis, we plan to install the pyridone moiety at an early stage. Thus, it is necessary to develop a new protocol to prepare a pyridone system with an alkyl group at C-5 and a carboxy group at C-6.

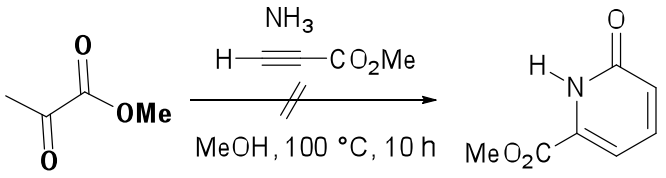
3.1 Kozikowski Synthesis

In 1990, Kozikowski and co-workers developed a 2-pyridone synthesis by condensation of ketone, methyl propiolate and ammonia in one pot (Scheme 1).[3] This method results in the formation of 5,6-disubstituted 2-pyridone. Unfortunately, it only can be used with symmetrical ketones and ketones which can only form a single enamine. As a member of the latter category, an α-keto ester, if subjected to the Kozikowski pyridone annulation, would afford a 6-carboxy-substituted 2-pyridone.



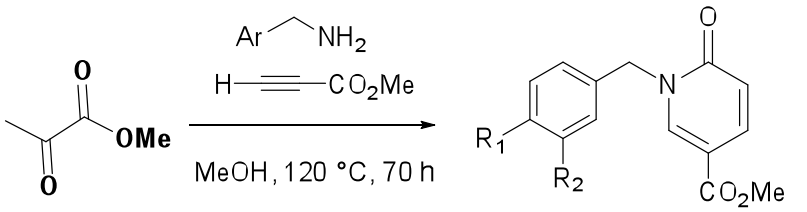
Scheme 1. Kozikowski Pyridone Synthesis

In order to overcome the problem of regioselectivity in enamine formation, we selected methyl pyruvate as the ketone component in the Kozikowski pyridone synthesis (Scheme 2). This reaction was conducted in a sealed tube. Unfortunately, reaction with ammonia failed to give any pyridone product.



Scheme 2. Attempted Kozikowski Pyridone Annulation

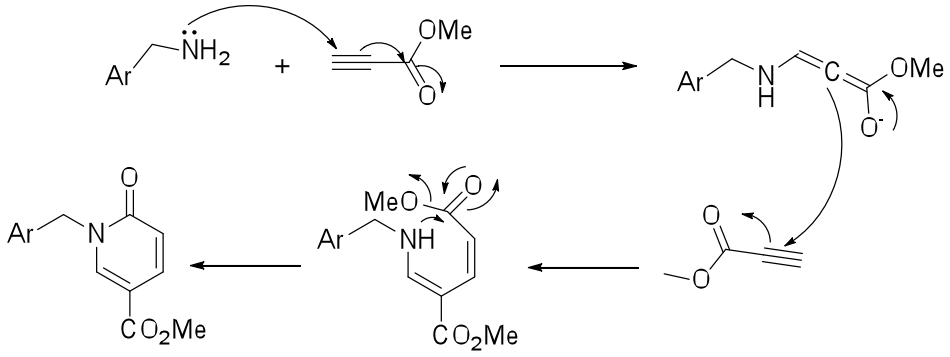
Then, we employed benzylamines to replace ammonia (Scheme 3). In these cases, we were able to obtain pyridones **67**, **68,** and **69**. However, ^{1}H NMR spectra revealed that the methyl ester group was located on C-5 rather than C-6.



67. $R_1 = R_2 = H$, 73%
68. $R_1 = OMe$, $R_2 = H$, 73%
69. $R_1 = R_2 = OMe$, 79%

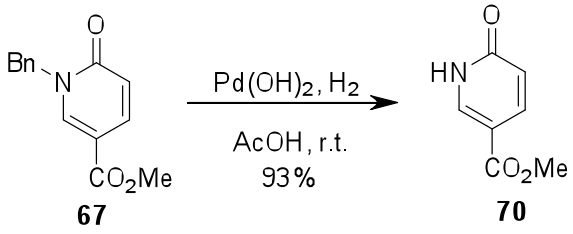
Scheme 3. Attempted Kozikowski Pyridone Annulation

The proposed mechanism for the formation of **67**–**69** is shown in Scheme 4. It involves Michael addition of the amine to methyl propiolate to form an allenolate. Then, a second Michael addition of the allenolate to another molecule of methyl propiolate occurred. Lactamization afforded 2-pyridone. Apparently, the α-keto ester was not participating in this reaction. To confirm this hypothesis, the reaction was carried out with ethyl pyruvate in EtOH. A pyridone with a methyl ester was obtained, and none of the corresponding ethyl ester was detected.



Scheme 4. Proposed Mechanism of Pyridone Regioisomer Formation

Because there is no substituent on the N atom of lyconadin A, we would face the removal of the N atom substituent at some point in the total synthesis. With the regioisomeric pyridone in hand, we tried to deprotect the Bn, PMB, and 3,4-DMB groups (Table 1 and Table 2). Exposure of **67** to $Pd(OH)_2$ and H_2 under acidic conditions provided **70**.[4]



Scheme 5. Benzyl Deprotection of **67**

Table 1 shows the conditions we examined for PMB deprotection of **68**. When this compound was subjected to $AlCl_3$ in anisole, only starting material was recovered.[5] CAN made most of the starting material decompose.[6] Fortunately, treatment of **68** with DDQ delivered **70** in good yield.[7]

Conditions:	Results
1. $AlCl_3$, anisole rt.	No Reaction
2. $(NH_4)_2Ce(NO_3)_6$,CH_3CN:H_2O = 2:1	SM. disappeared, small amount of product obtained
3. DDQ ,CH_2Cl_2, H_2O , rt.	76%

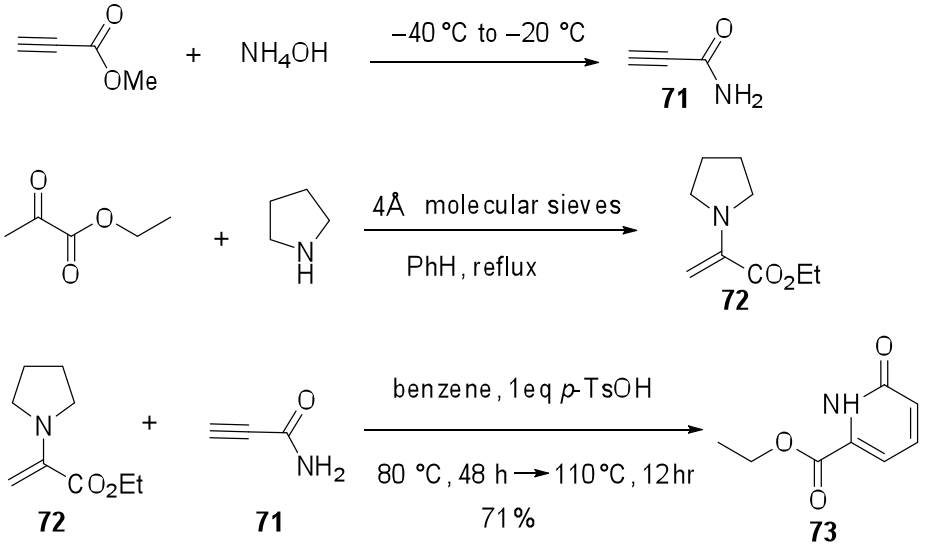
Table 1. PMB Deprotection of **68**

The conditions used to attempt 3,4-DMB deprotection of **69** are shown in Table 2. Under acidic conditions, **69** was untouched.[8] DDQ did not work for this reaction. Fortunately, CAN in CH_3CN and H_2O resulted in the formation of **70** in 78% yield.

Conditions:	Results
1. TFA, CH_2Cl_2 ,rt.	No Reaction
2. TFA, CH_2Cl_2, anisole, rt	No Reaction
3. TFA, anisole, concd. H_2SO_4 ,rt.	No Reaction
4. DDQ ,CH_2Cl_2, H_2O , rt.	No Reaction
5. $(NH_4)_2Ce(NO_3)_6$,CH_3CN:H_2O = 2:1, rt.	78%

Table 2. 3,4-DMB Deprotection of **69**

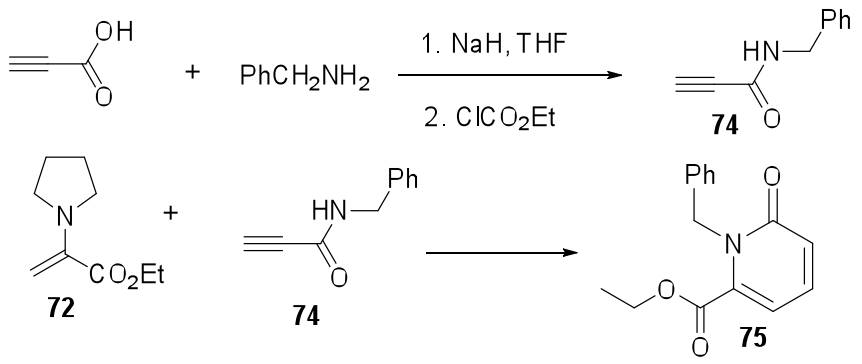
To improve the reactivity of the α-keto ester , we formed the nucleophilic pyrrolidine enamine **72** and reacted it with propiolamide **71** (Table 3).[9,10,11] After some experimentation, we found that annulation of enamine **72** and propioamide **71** proceeded in the presence of toluenesulfonic acid, providing 2-pyridone **73**.



conditions:	results
1. benzene, reflux	got two intermediates
2. DBU, benzene, reflux	No product, no intermediates
3. DABCO, benzene, reflux	No product, no intermediates
4. i) dioxane, reflux ii) H_2O, reflux	No product, no intermediates
5.(i) benzene, 80 °C, 48h (ii) 1eq *p*-TSOH,110°C	low
6. enamine : propiolamide = 2 : 1	very low
7. benzene, 1eq *p*-TsOH, 80 °C, 48 →110°C, 12hr	71%
8. benzene, 0.1eq *p*-TSOH, 80 °C, 40h →110°C	Yield is lower than 7
9. benzene, 1eq PPTS, 80 °C, 40h →110°C	66%
10. benzene, 1eq *DBU*, 80 °C, 40 h→110°C	No product.

Table 3. Modified Kozikowski Pyridone Annulation.

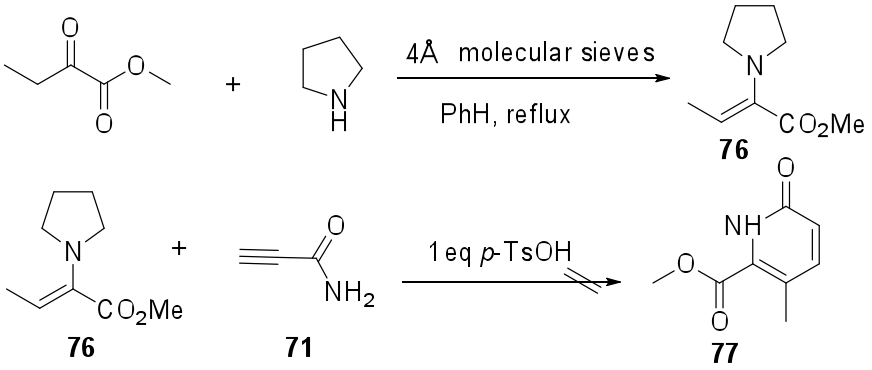
However, when we replaced the propiolamide **71** with benzyl propiolamide **74**, we could only obtain a 20% yield of pyridone **75** (Table 4).



tried conditions:	results
1. benzene, 1 eq *p*-TSOH, 80 °C, 48 h, 110°C, 12 h	20%
2. benzene, 0.1 eq *p*-TSOH, 80 °C, 48 h, 110°C, 12 h	14%
3. benzene, 1 eq PPTS, 80 °C, 48 h, 110°C, 12 h	17%
4. benzene, 0.1 eq PPTS, 80 °C, 48 h, 110°C, 12 h	10%
5. (i). benzene, 80 °C, 48 h (ii) 1 eq *p*-TSOH, 110°C, 12 h	6%
6. benzene, DBU, 80 °C, 48 h	no product

Table 4. Attempted Pyridone Annulation.

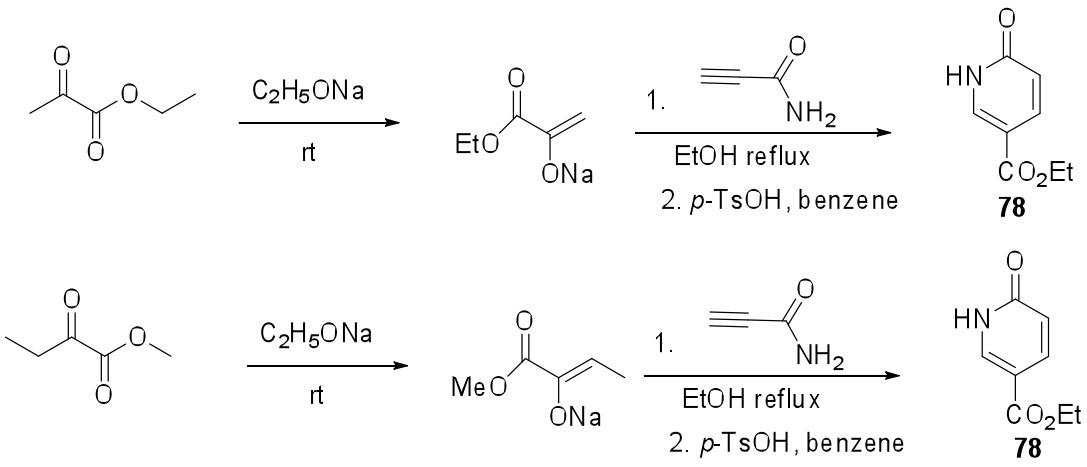
Then we replaced the ethyl pyruvate with a more hindered α-keto ester. We tried many solvents, such as DMF, CH_3CN, toluene, DMSO, triflorotoluene, dioxane, CCl_4, $CHCl_3$, and benzene in the presence of toluenesulfonic acid. However, the reaction did not occur (Scheme 6).



Scheme 6. Attempted Pyridone Annulation.

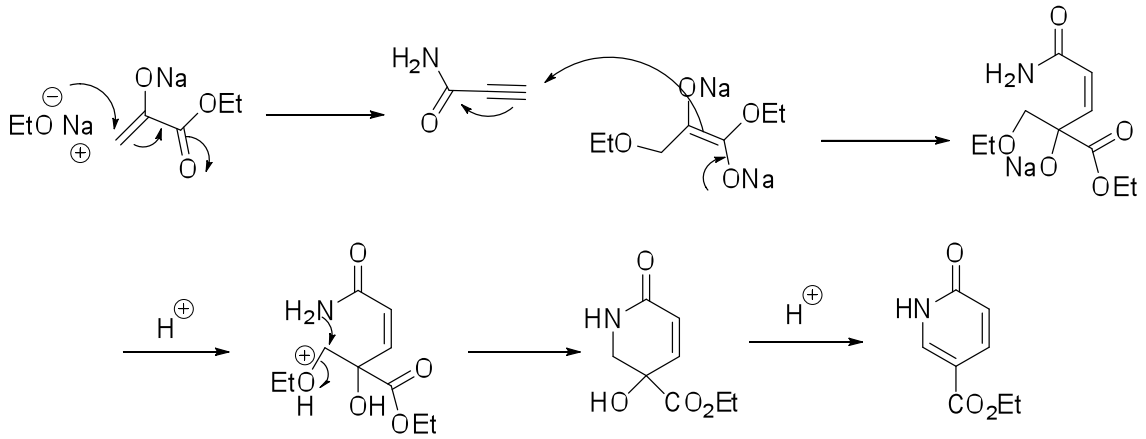
Apparently, the increased steric hindrance of these substrates prevented the reaction.

Then, we tried to make the enolate of the α-keto ester. Surprisingly, reaction of the enolate with propioamide provided undesired product **78** (Scheme 7).[12,13]



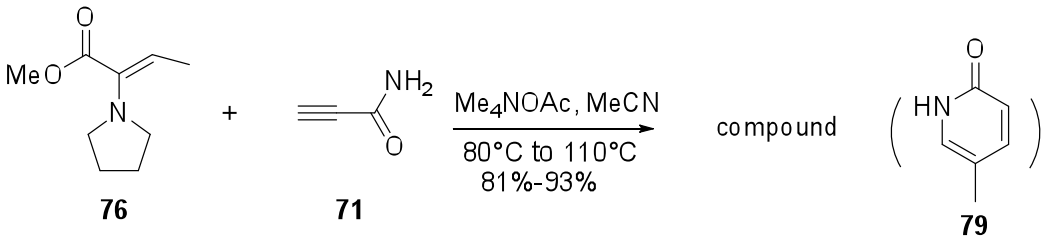
Scheme 7. Attempted Pyridone Annulation.

The following is the proposed mechanism (Scheme 8). It involves Michael addition of the sodium ethoxide to the enolate of the α-keto ester followed by a second Michael addition to form an α,β-unsaturated amide. Then, the dihydropyridone formation followed by elimination provides 2-pyridone.



Scheme 8. Proposed Mechanism of Pyridone Annulation

We tried the reaction with Me_4NOAc, and got an undentified compound in 81–93% yield (Scheme 9). Initially, we thought it was **79**, since the undentified compound has the same mass spectrum as that of the compound **79** and it possesses the following ^{1}H NMR peaks: δ 8.17 (d, *J* = 3 Hz, 1H), 7.58 (dd, *J* = 3 Hz, 9.8 Hz, 1H), 6.57 (d, *J* = 9.5 Hz, 1H), 5.64 (br s, 1H), 3.61 (s, 3H). However, we compared the ^{1}H NMR of this compound with the reported ^{1}H NMR data of **79**.[14] They do not match.

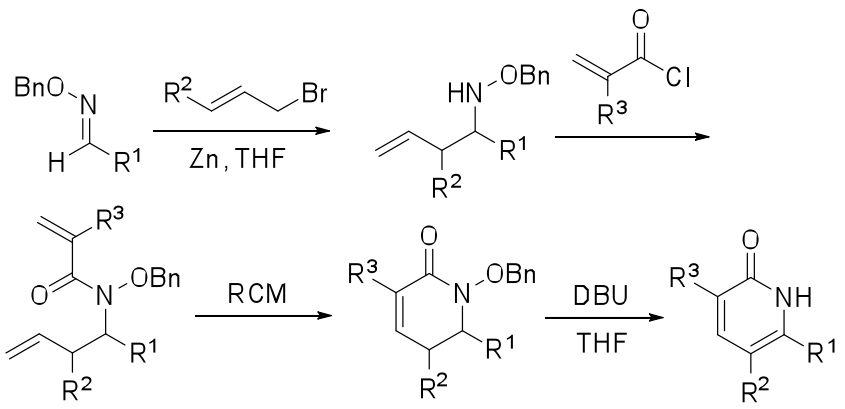


Scheme 9. Attempted Pyridone Annulation.

Thus, the modified Kozikowski pyridone annulation was unsuitable for our case.

3.2 H–W–E Reaction for the RCM

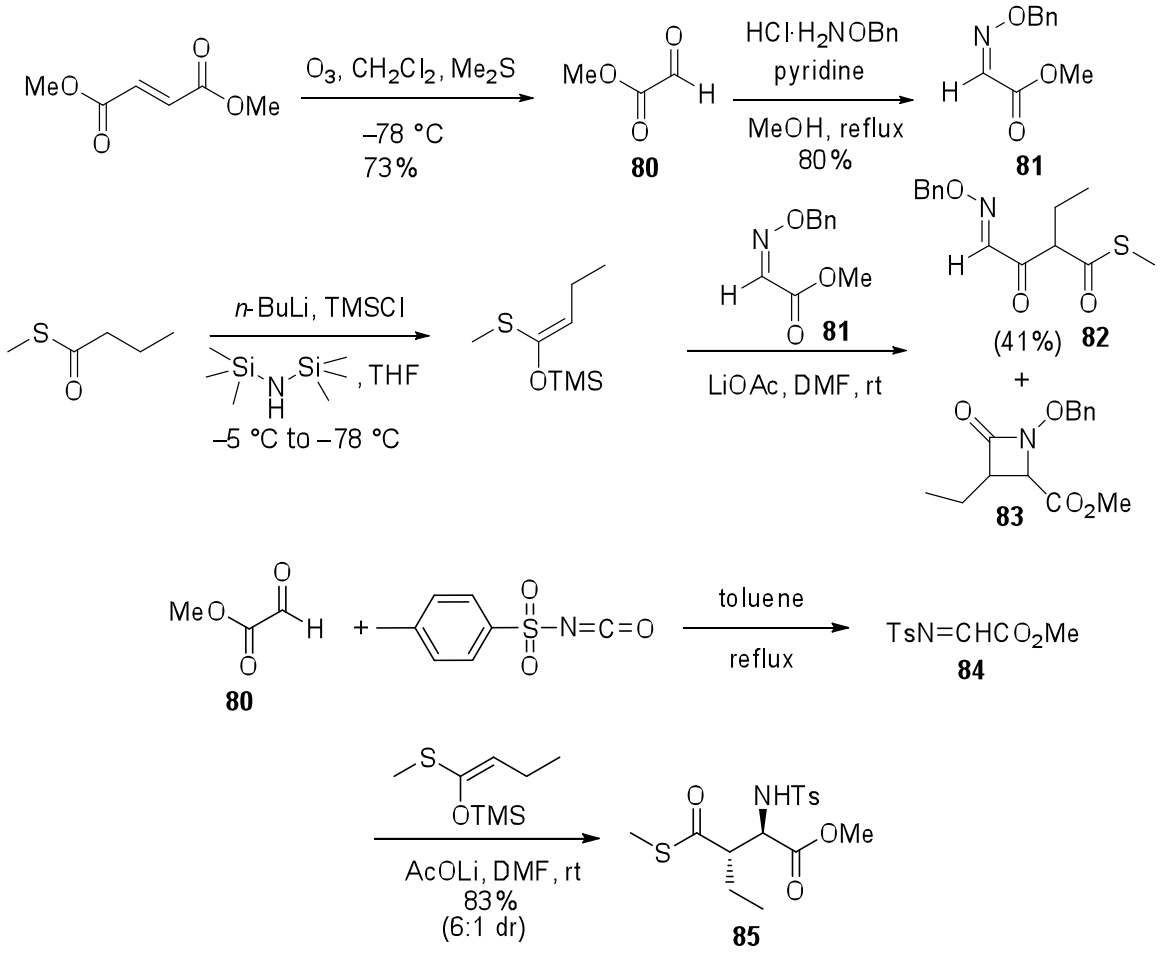
In 2008, Donohoe and co-workers developed a novel pyridone synthesis strategy, which can provide a wide variety of substituted pyridones including 5-alkyl-6-carboxypyridones.[15] This process is summarized in Scheme 10. They employ ring-closing metathesis to form a dihydropyridone. Then, elimination generates the pyridone. However, ring-closing metathesis could not be used in our case, because the substrate required for the total synthesis of lyconadin A would possess additional double bonds for use in the radical cascade cyclization. Thus, we tried to develop a pyridone annulation method based on the Donohoe strategy. We would employ a different reaction in the cyclization step.



Scheme 10. Donohoe Pyridone Annulation

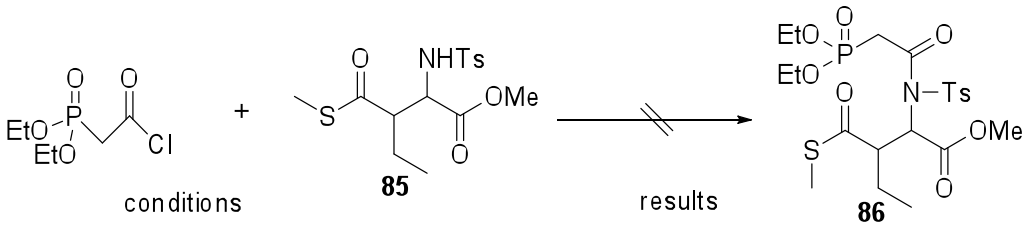
We attempted to substitute an intramolecular Horner–Wadsworth–Emmons reaction for the ring-closing metathesis. The electron-deficient methyl ester group, which is needed in our total synthesis, was installed at C-6 to make the α-proton more acidic and help the base-induced aromatization. We started our model study from dimethyl malonate. Ozonolysis of dimethyl malonate provided aldehyde **80**, which was converted into oxime **81** by treatment with H_2NOBn (Scheme 11).[15] We tried a Mannich reaction of oxime **81** with a silyl enol ether catalyzed by a Lewis acid, such as $Cu(OTf)_2$, $Zn(OTf)_2$, or Cu(OTf), but only recovered starting material.[16] The OBn group is an electron-donating group, which lowers the electrophilicity of oxime **81**. The protocol mediated by the Lewis base LiOAc provided Claisen adduct **82** as the major product in modest yield, and β-lactam **83** was a minor product of this reaction.[17] In this reaction, the OBn group increases the nucleophilicity of **81**, and under the basic conditions, the by-product **83** is generated. Then, we changed the OBn group into a Ts group, which is an electron-withdrawing group. Thermal [2+2] cycloaddition of *p*-toluenesulfonylisocyanate and methyl glyoxylate **80** followed by loss of CO_2 afforded tosylimine **84**.[18] The Lewis-base- catalyzed reaction between trimethylsilyl enol ether and tosyl imine **84** led to Mannich adduct **85** in good yield as a ca. 6:1 mixture of diastereomers. The Lewis acid $Cu(OTf)_2$ did not work in this reaction. The major

isomer was assumed to possess the *anti* configuration according to the acyclic transition state proposed by Mukaiyama and co-workers for the Mannich reaction.[17]Because both stereocenters would be destroyed later in the synthesis, the mixture was carried forward without separation.



Scheme 11. Synthesis of Tosylamine **85**.

To prepare the precursor **86** of Horner–Wadsworth–Emmons reaction, we tried acylation reactions between acyl chloride and tosylamine **85** in different conditions, however we were unable to obtain desired product (Table 5).



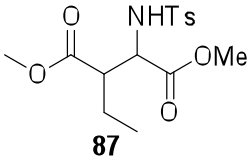
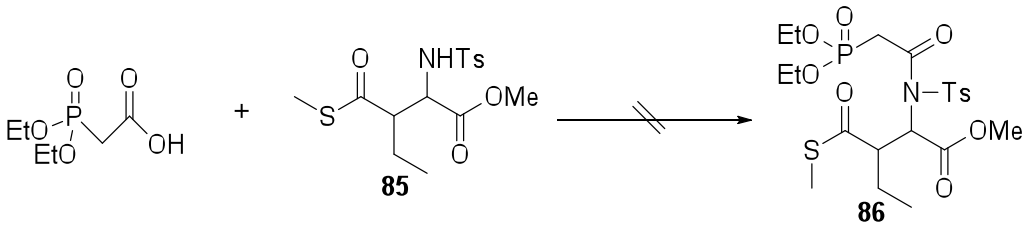
conditions	results
Et_3N, CH_2Cl_2, rt	recovered SM
Et_3N, DMAP, CH_2Cl_2, 0°C to rt	recovered SM
toluene, reflux	SM + decomposed
NaH, THF, rt	recovered SM
Na, MeOH, DMF, rt	 **87**
imidazole, DMF, rt	recovered SM
toluene, DMAP, reflux	decomposed no product
DMAP, DMF, 80 to 125 °C	decomposed no product

Table 5. Attempted Synthesis of Horner–Wadsworth–Emmons Cyclization Substrate

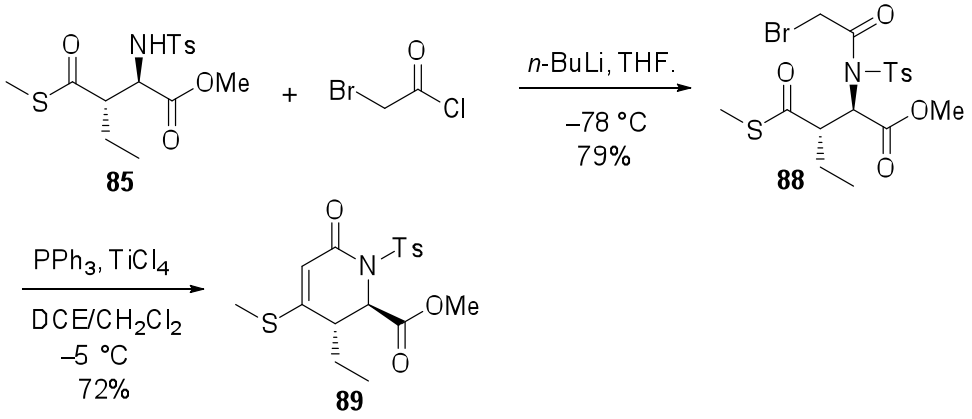
Then, we turned to reactions between carboxylic acid and tosylamine **85** (Scheme 12). We tried conditions of DCC and PPY, carbonyl diimidazole, and N-methyl-2-chloropyridine salt.[19] Unfortunately, we only recovered starting material. Apparently, the tosylamine is not nucleophilic enough to react with inductively deactivated acid chlorides. In this case, Horner–Wadsworth–Emmons reaction is not feasible.



Scheme 12. Attempted Synthesis of Horner–Wadsworth–Emmons Cyclization Substrate

3.3 Reformatsky Reaction for the RCM

It seemed that a Reformatsky reaction might meet our needs. We hoped to perform the metal-induced intramolecular reaction of an α-halocarbonyl with the thioester in our substrate. A bromide is commonly used in the Reformatsky reaction. We tried the reaction of tosylamine **85** with bromoacetyl chloride in pyridine, but only starting material was returned. The reaction of tosylamine **85**, bromoacetyl chloride, and DMAP in CH_2Cl_2/DMF did not work either.[20] Then, NaH in benzene was tried in this reaction. We only obtained a trace amount of product. Eventually, acylation of **85** with bromoacetyl chloride was successful when we treated **85** with *n*-BuLi in THF, affording bromide **88** in good yield (Scheme 13). With the bromide **88** in hand, we tried to selectively reduce the thioester moiety in **88** to aldehyde. Unfortunately, we were unable to obtain aldehyde, as exposure to Raney Ni[22] or Lindlar catalyst/Et_3SiH[23] resulted in debromination. Similar results were obtained with the chlorinated analogue of **88**.



Scheme 13. Intramolecular Reformatsky-type Condensation.

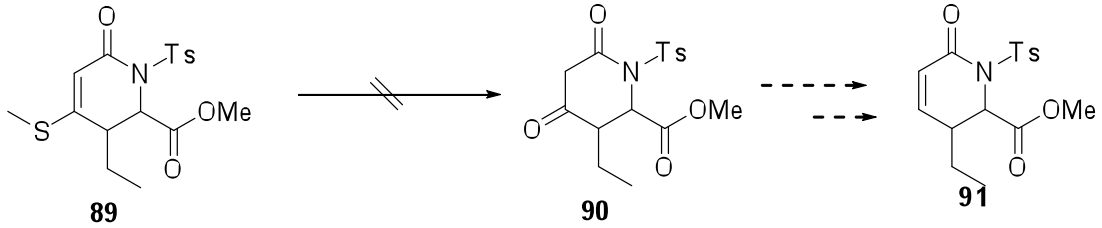
Reformatsky reactions employing thioesters as eletrophiles are unknown.[24] However, we were encouraged by some examples of Reformatsky reactions with species such as *N*-acyloxazolidinones,[25] *N*-acylpyrazoles,[26] and lactones.[27] We determined to directly attempt the cyclization of **88**. SmI_2 is typically used in intramolecular Reformatsky reactions.[28] However, the

reaction of **88** under these conditions led to debromination. Then, we discovered the work of Hashimoto and co-workers.[29] They combined PPh_3 and $TiCl_4$ to generate an enolate from an α-bromothioester, which underwent both self-condensations and crossed-Claisen-type reactions to provide various types of β-ketothioester adducts. Bromo tosylamide **88** was subjected to Hashimoto protocol. Fortunately, the cyclized product was achieved. Interestingly, a vinylogous thiocarbamate was formed rather than the corresponding Dieckmann-type product. This reaction is very sensitive to moisture, which led to the formation of debrominated starting material.

3.4 Pyridone Synthesis

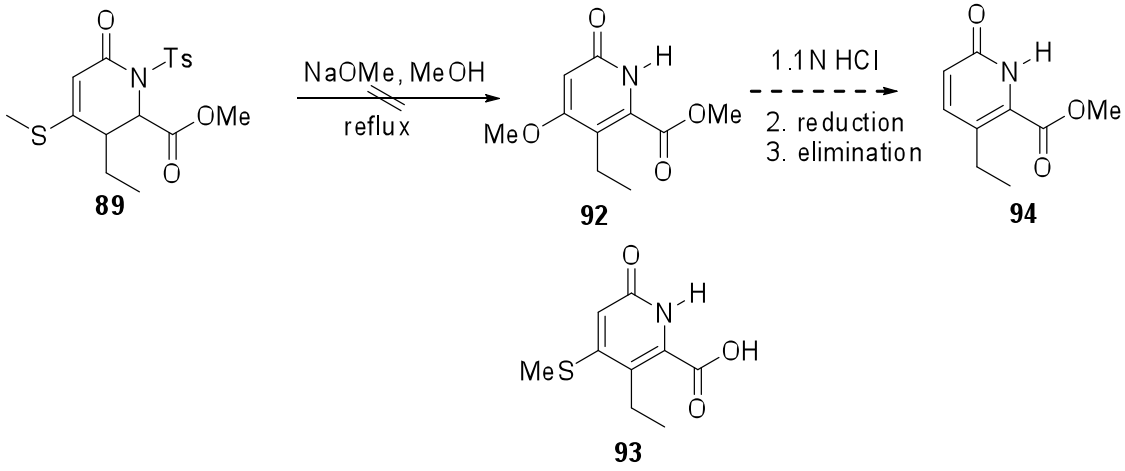
Elimination and desulfurization of **89** were needed to prepare the 2-pyridone. In principle, these two steps could be carried out in either order. However, we failed to remove the sulfide from **89**. Among numerous desulfurizing reagents, nickel reagents occupy an important position. $NiCl_2/NaBH_4$[30]and Ra(Ni)[31] led to over-reduction to the saturated derivative. NiCRA's and NiCRA-bPy's are effective desulfurization reagents for aromatic sulfoxides or vinyl thioethers. We tried these reactions with different ratios of reagents and different temperatures, but we only obtained elimination product, pyridone, rather than desulfurization product.[32]

Hydrolysis of vinyl thioether catalyzed by acid/Lewis acid is a good method to prepare a ketone. If ketone **90** is achieved, then reduction followed by elimination would provide desired dihydropyridone **91** (Scheme 14). We tried to form ketone **90** by treatment of **89** with $HgCl_2$,[33] HCl,[34] $TiCl_4$,[35] $AgNO_3$,[36] but only recovered starting material.



Scheme 14. Proposed Pathway to the Synthesis of **91**

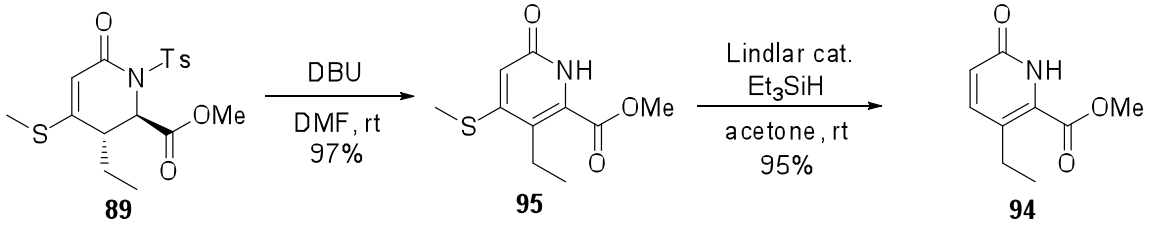
Treatment of vinylogous thiocarbamate **89** with NaOMe should provide vinylogous carbamate **92**.[37] Then hydrolysis under acidic conditions followed by reduction and elimination will also achieve our desulfurization goal (Scheme 15). We tried to treat **89** with NaOMe, but we got carboxylic acid **93** rather than **92**. Hydrolysis of the thioether did not happen. Under basic conditions, elimination occurred first, and generated aromatic pyridone thioether **93**. It is too difficult to substitute SMe for OMe on an aromatic ring.



Scheme 15. Proposed Pathway to the Synthesis of **91**

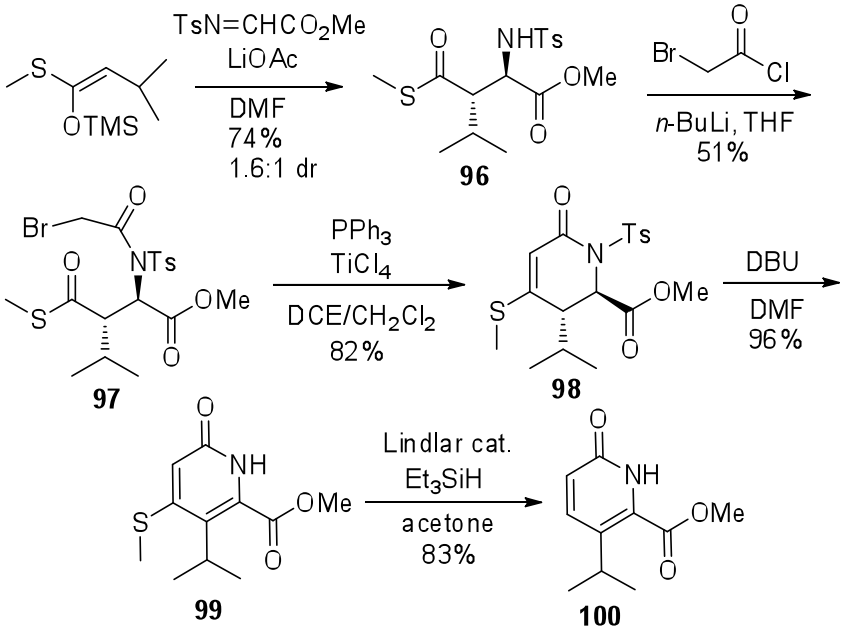
Due to the problems encountered in the desulfurization of **89**, we decided to perform the elimination step first. Thus, treatment of **89** with DBU in DMF provided pyridone **95** in excellent yield (Scheme 16). Pyridone **95** was subjected to Lindlar catalyst and Et_3SiH in acetone at room

temperature to afford **94** in 95% yield.[38] The combination of Lindlar catalyst and Et_3SiH selectively cleaved the vinyl sulfide without reducing the pyridone.



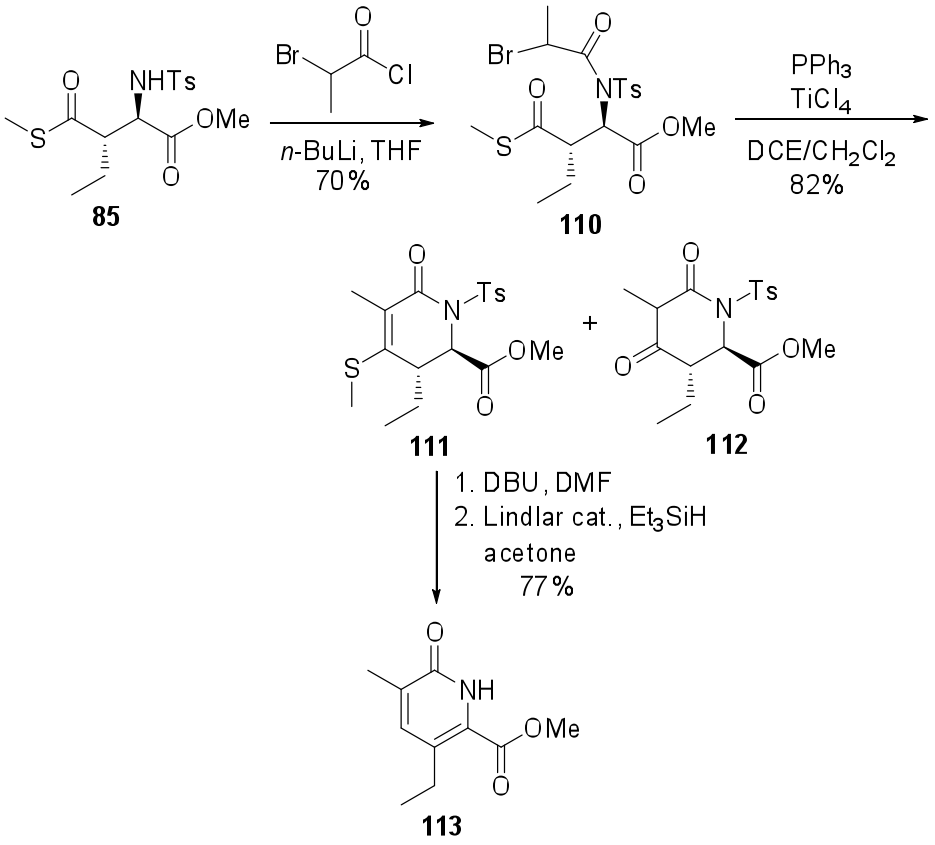
Scheme 16. Synthesis of Pyridone **94**.

We had developed a novel method to generate the 5-alkyl-6-carbomethoxy-2-pyridone nucleus. To explore the scope of the annulation method, we used a larger group at C-5 (Scheme 17). The Mannich reaction between silyl ketene thioacetal and tosylimine was less selective (1.6:1) than the corresponding reaction shown in Scheme 13. Acylation of the tosylamine **96** provided **97** in lower yield. Cyclization, elimination, and desulfurization proceeded smoothly, providing isopropyl-substituted pyridone **100** in good yield.



Scheme 17. Synthesis of Isopropyl-substituted Pyridone **100**.

We also synthesized 3,5-dialkyl-substituted pyridone **113** via this protocol, as outlined in Scheme 18. Cyclization of **110** afforded a 1:2.4 mixture of vinyl sulfide **111** and ketone **112** in 80% overall yield. So, the substitutent on the enolate intermediate has effect on the product distribution of the cyclization. In theory, we can convert compound **112** into **113** by means of a sequence of ketone reduction, mesylation (or halogenation) of the resulting alcohol, and elimination.



Scheme 18. Synthesis of Dialkyl-substituted Pyridone **113**.

In conclusion, inspired by Donohoe's pyridone synthesis, we developed a method for the construction of 5-alkyl and 3,5-dialkyl-6-carbomethoxy-2-pyridone, which is an important moiety of lyconadin A. We employed the Mannich reaction to make a tosylamine. Acylation of

the resulting tosylamine generated the cyclization substrate. We used intramolecular Reformatsky-type reaction to construct the 6-membered ring. The typical cyclization products were vinylogous thiocarbamates (i. e. **89**, **98**, and **111**), but in one case the Dieckmann-type product was also formed (**112**). Elimination and desulfurization delievered the desired pyridones. We believe that this new method could be used in the synthesis of complex molecules such as lyconadin A.

3.5 References

1. (a) Du, W. *Tetrahedron* **2003**, *59*, 8649. (b) Jiang, H.; Luo, X.; Bai, D. *Curr. Med. Chem.* **2003**, *10*, 2231. (c) Misra, R.; Pandey, R. C.; Silverton, J. V. *J. Am. Chem. Soc.* **1982**, *104*, 4478.

2. Torres, M.; Gil, S.; Parra, M. *Curr. Org. Chem*. **2005**, *9*, 1757.

3. Kozikowski, A. P.; Reddy, E. R.; Miller, C. P. *J. Chem. Soc. Perkin. Trans. 1* **1990**, 195.

4. Lin, C. H.; Tsai, M. R.; Wang, Y. S.; Chang, N. C. *J. Org. Chem*. **2003**, *68*, 5688.

5. Akiyama, T.; Takesue, Y.; Kumegawa, M.; Nishimoto, H.; Ozaki, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2266.

6. Torii, S.; Tanaka, H.; Inokuchi, T.; Nakane, S.; Akada, M.; Saito, N.; Sirakawa, T. *J. Org. Chem*. **1982**, *47*, 1647.

7. Grunder-Klotz, E.; Ehrhardt, J. *Tetrahedron Lett*. **1991**, *32*, 751.

8. Wood, J. I.; Stoltz, B. M.; Dietrich, H.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc*. **1997**, *119*, 9641.

9. Camps, P.; Muñoz-Torreo, D.; Simon, M. *Syn. Commun.* **2001**, *31*, 3507.

10. Elad, D.; Ginsburg, D. *J. Chem. Soc*. **1953**, 4137.

11. Xia, Y.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1989**, *111*, 4116.

12. Marvel, C. S.; Dreger, E. E. *Org. Syn.* Coll. Vol. *1*, 238.

13. Melius, P.; Marshall, D. L. *J. Med. Chem.* **1967**, *10*, 1157.

14. *Bell, C. L.; Egan, R. S.; Bauer, L. J. Heterocycl. Chem*. **1965**, *2*, 420.

15. Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Org. Lett*. **2008**, *10*, 285.

16. (a) Salter, M. M.; Kobayashi, J.; Shimizu, Y.; Kobayashi, S. *Org. Lett*. **2006**, *8*, 3533.

(b) Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc*. **2003**, *125*, 2507.

17. Fujisawa, H.; Takahashi, E.; Mukaiyama, T. *Chem. Eur. J.* **2006**, *12*, 5082.

18. Hamley, P.; Holmes, A. B.; Kee, A.; Ladduwaherry, T.; Smith, D. F. *Synlett.* **1991**, *1*,

19. (a) Teichert, A.; Jantos, K.; Harms, K.; Studer, A. *Org. Lett.* **2004**, *6*, 3477. (b) Gheorghe, A.; Quiclet-sire, B.; Vila, X.; Zard, S. Z. *Org. Ltt.* **2005**, *7*, 1653.

(c) Raghavan, S.; Rajender, A. *Tetrahedron* **2004**, *60*, 5059. (d) Jung, M. E.; Rhee, H. *J. Org. Chem*. **1994**, *59*, 4719. (e) Cheeseman, G. W. H.; Varvounis, G. *J. of Heterocycl. Chem*. **1988**, *25*, 431. (f) Davis, F. A.; Song, M. *Org. Lett*. **2007**, *9*, 2413. (g) Gheorghe, A.; Quiclet-Sire, B.; Vila, X.; Zard, S. Z. *Tetrahedron* **2007**, *63*, 7187. (h) Okada, Y.; Minami, T.; Miyamoto, M.; Otaguro, T.; Sawasaki, S.; Chikawa, *J. Heteroatom Chemistry* **1995**, *6*, 195.

20. Ozaki, S.; Matsushita, H.; Emoto, M.; Ohmori, H. *Chem. Pharm. Bull.* **1995**, *43*, 32.

21. Nagashima, H.; Isono, Y.; Iwamatsu, S. *J. Org. Chem*. **2001**, *66*, 315.

22. Rosen, S; Shahak, I.; Bergmann, E. D. *Tetrahedron* **1973**, *29*, 2327.

23. Evans, D. A.; Black, W. C. *J. Am. Chem. Soc*. **1993**, *115*, 4497.

24. Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325.

25. Kashima, C.; Huang, X. C.; Harada, Y.; Hosomi, A. *J. Org. Chem.* **1993**, *58*, 793.

26. Kashima, C.; Kita, I.; Takahashi, K.; Hosomi, A. *J. Heterocycl. Chem*. **1995**, *32*, 723.

27. Wang, M. –X.; Liu, Y.; Gao, H. –Y.; Zhang, Y.; Yu, C. –Y.; Huang, Z. –T.; Fleet, G. W. *J. Org. Chem*. **2003**, *68*, 3281.

28. Reddy, P. P.; Yen, K. –F.; Uang, B. –J. *J. Org. Chem*. **2002**, *67*, 1034.

29. Hashimoto, Y.; Konishi, S. *Synlett*. **2004**, 1264.

30. Hatanaka, M.; Himeda, Y.; Tanaka, Y.; Ueda, I. *Tetrahedron Lett*. **1995**, *36*, 3211.

31. Yoo, K. H.; Choi, E. B.; Lee, H. K.; Yeon, G. H.; Yang, H. C.; Pak, C. S. *Synthesis* **2006**, 1599.

32. Becker, S.; Fort, Y.; Caubère, P. *J. Org. Chem*. **1990**, *55*, 6194.

33. Manjunatha, S. G.; Chittari, P.; Rajappa, S. *Helvetia Chimica Acta* **1991**, *74*, 1071.

34. Kizil, M.; Murphy, J. A. *J. Chem. Soc., Chem. Commun*. **1991**, 1409.

35. Wilson, S. R.; Georgiadis, G. M.; Khatri, H. N.; Bartmess, J. E. *J. Am. Chem. Soc*. **1980**, *102*, 3577.

36. Corey, E. J.; Erickson, B. W.; Noyory, R. *J. Am. Chem. Soc.* **1971**, *93*, 1724.

37. Desmaeele, D.; Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292.

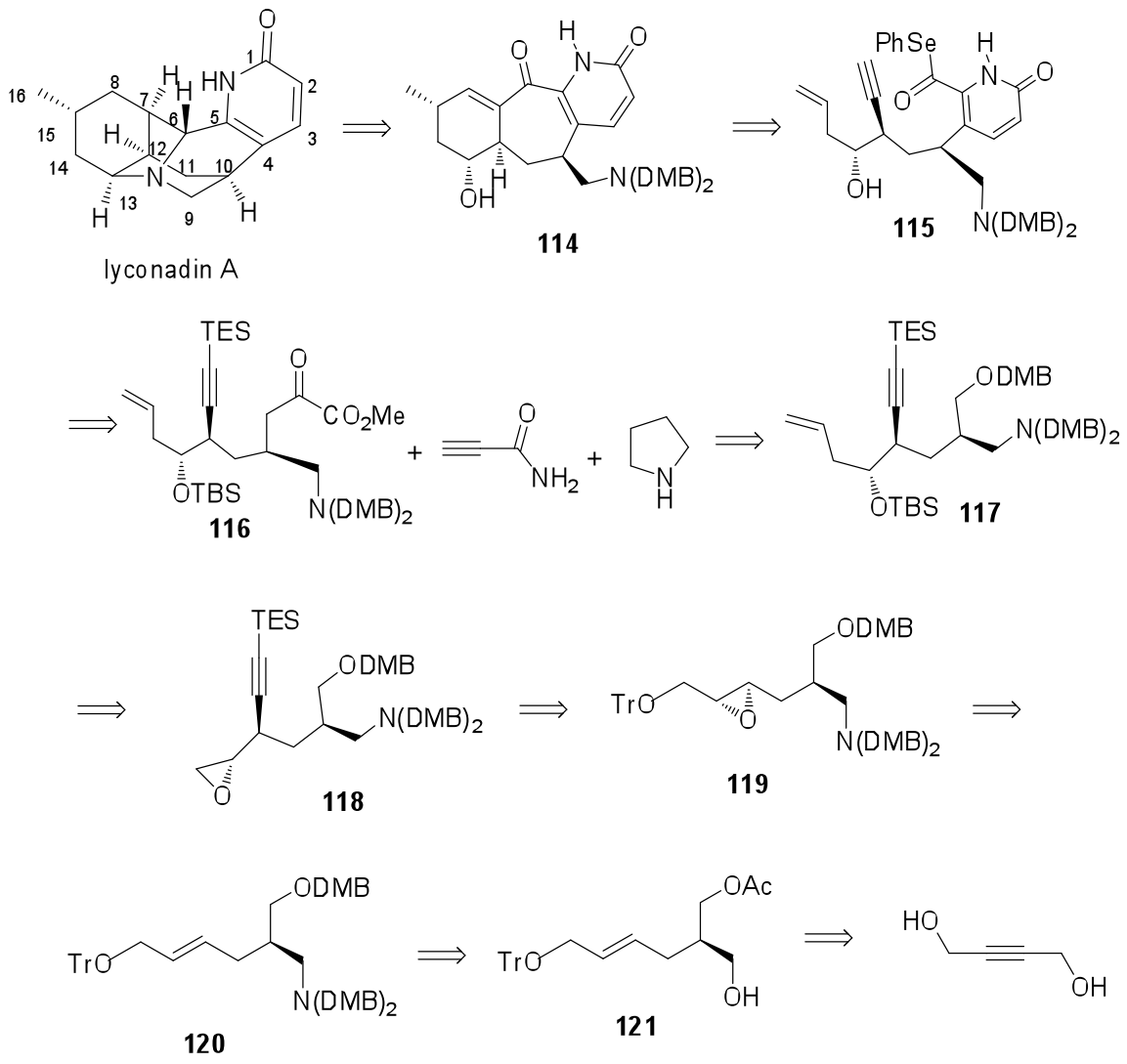
38. Evans, D. A.; Black, W. C. *J. Am. Chem. Soc*. **1993**, *115*, 4497.

Chapter 4. Attempted Synthetic Approaches to Lyconadin A.

Our model studies towards the acyl radical cascade cyclization have given us confidence that a tandem 7-*exo*/6-*exo* cyclization can be used to install the central portion of lyconadin A. In addition, we were exploring the modified Kozikowski pyridone annulation, which involved the condensation of pyrrolidine enamine and propiolamide in the presence of toluenesulfonic acid, and we found that the desired 2-pyridone **73** was provided. Before we probed the scope of this pyridone annulation, we assumed that this strategy could be used in the total synthesis of lyconadin A. Based on these two model studies, we started our total synthesis of lyconadin A.

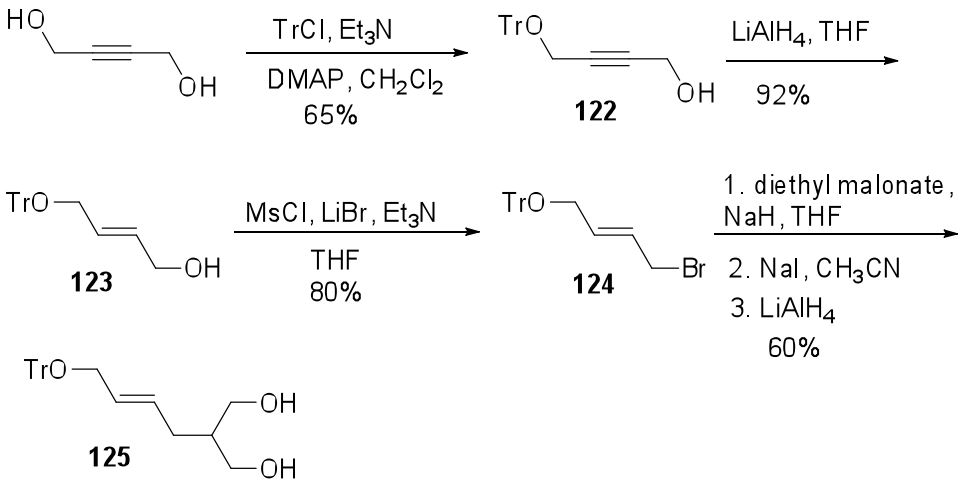
4.1 Enzymatic Approach

The retrosynthesis of lyconadin A is shown in Scheme 1. Cleavage of the C6–N and C13–N bonds and protection of the resulting primary amine will provide tricyclic compound **114**. Then, disconnection of the C8–C15 and C6–C7 bonds in **114** will afford ene-yne **115**, the precursor of a radical cascade cyclization. The compound **115** could be derived from α-keto ester **116** via condensation of pyrrolidine enamine of **116** and propiolamide. Removal of α-keto ester from **116** will form intermediate **117**, which could be obtained by regioselective ring opening of epoxide **118**. Scission of alkyne from **118** will result in epoxide **119**, which can be generated from alkene **120** by means of the Shi asymmetric epoxidation.[1] The alkene **120** could be synthesized from alkene **121**. The alkene **121** will be obtained by an enzymatic desymmetrization of a diol,[2] which can be prepared from 2-butyne-1,4-diol.



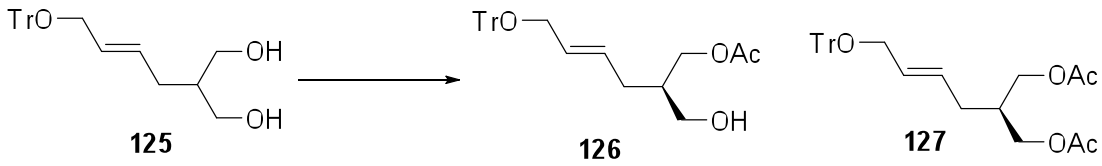
Scheme 1. Retrosynthesis of Lyconadin A

We started our total synthesis with 2-butyne-1,4-diol (Scheme 2). Tritylation of 2-butyne-1,4-diol with 1 equiv. of TrCl and 1.1 equiv. of Et_3N provided alkyne **122**. Reduction of **122** with $LiAlH_4$ provided alkene **123**. Bromination of **123** led to bromide **124**. Alkylation of **124** with diethyl malonate followed by reduction with LAH afforded diol **125**.



Scheme 2. Synthesis of Diol **125**

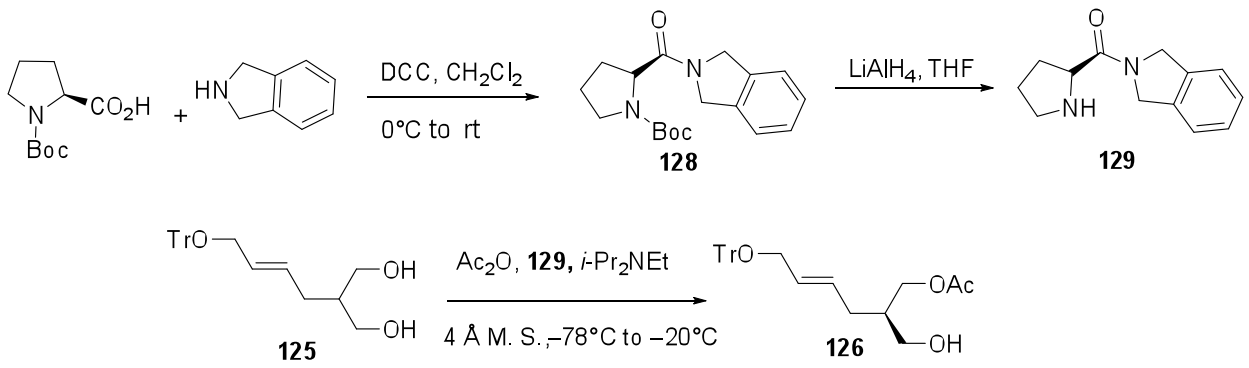
The preparation of chiral building blocks can be accomplished using chemical or enzymatic methodologies. In particular, the asymmetrization of 1,3-propanediols using lipases has been extensively studied.[2] 1,3-Diol **125** was asymmetrized by enantioselective acetylation in organic solvent catalyzed by a lipase. We tried a series of reactions catalyzed by different lipases (Table 1). Treatment of **125** with PSPL or CAL B led to diacetate **127**.[3,4] The acetylation catalyzed by PCL led to higher ee in 1,4-dioxane/THF than in THF.[4] A long stirring time was helpful to increase the ee value, but the highest we obtained is 70% ee with stirring for one week. PPL only delivered poor ee.[5] For the reaction catalyzed by ANL, the ee value changed with time. It increased first and then decreased. The best result we obtained is 84% ee.



Conditions	Results
PSPL, 4Å M.S., vinyl acetate, 35 °C or rt	obtained **127**
PCL, vinyl acetate, 1,4–dioxane:THF=5:1, 0 °C	81%, 70% ee
PCL, vinyl acetate, THF, 0 °C	56%, 55% ee
PPL, vinyl acetate, 30°C	86%, 26% ee
PFL, vinyl acetate, 30°C	90%, 64% ee
ANL, vinyl acetate, 30°C	91%, 84% ee
CAL B, vinyl acetate, 4 Å M. S., rt	obtained **127**

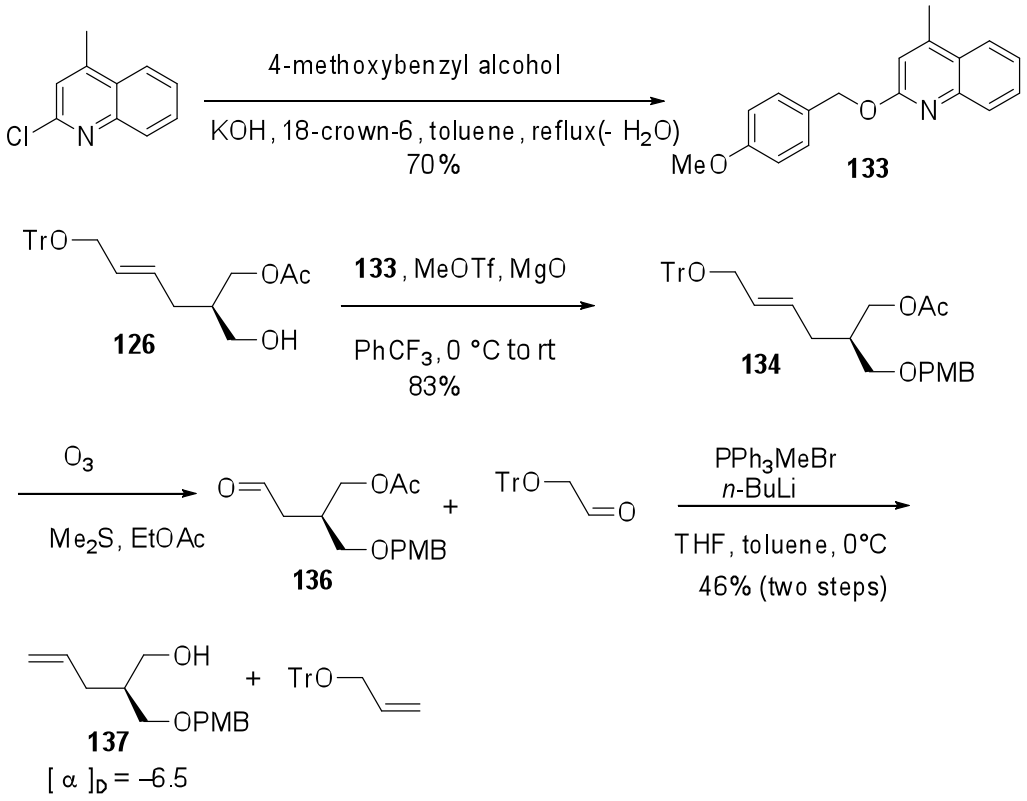
Table 1. Lipase Catalyzed Desymmetrization

In 2002, Oriyama and co-workers developed a promising catalyst for asymmetrization of symmetrical 1,3-diol.[6] This is the first example of non-enzymatic catalytic asymmetrization of *meso*-1,3-propanediol. It involves the reaction of a 1,3-diol with benzoyl chloride or derivatives catalyzed by a chiral 1,2-diamine derived from (S)-proline to provide highly enantiomerically enriched 3-acyloxy alcohol. We tried this reaction with acetic anhydride as acylating agent catalyzed by 1,2-diamine **129** (Scheme 3). Unfortunately, it afforded the monoacetate **126** as a racemic mixture.



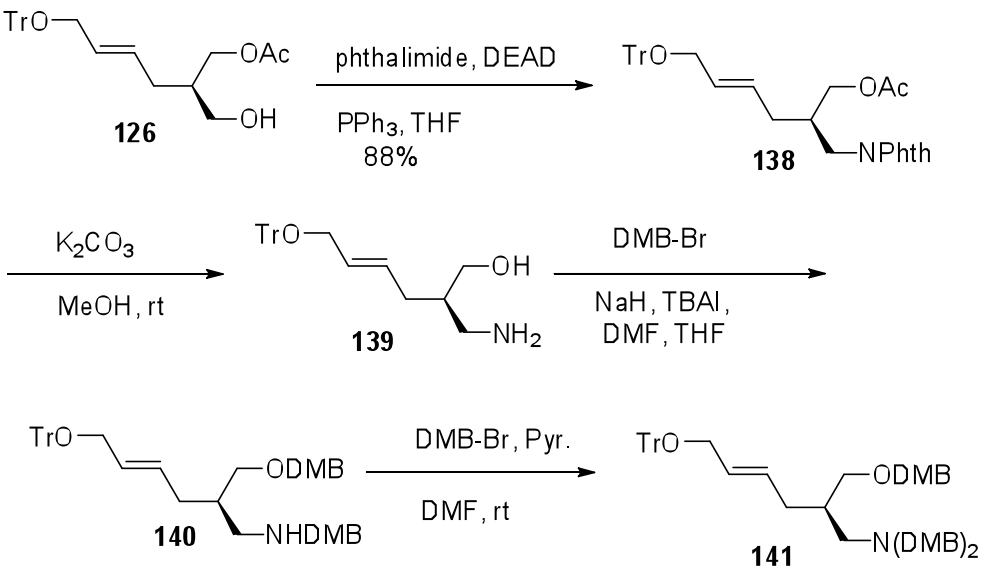
Scheme 3. Asymmetrization With Organic Catalyst **129**

In order to determine the absolute configuration of monoacetate **126**, we converted **126** to known compound **137**. Protection of **126** as a PMB ether under basic conditions led to acetate hydrolysis. So, Dudley's reagent **133,** which forms PMB ethers under mild conditions, was employed. Treatment of alcohol **126** with **133** provided PMB ether **134** (Scheme 4).[7] Ozonolysis followed by Wittig reaction of the resulting aldehyde **136** delievered alkene **137**, which possesses identical rotation to that reported in the literature. The standard rotation is –13.8 (*c* 1.2, $CHCl_3$), and we got –6.5. So, we obtained the desired enantiomer in the desymmetrization step.



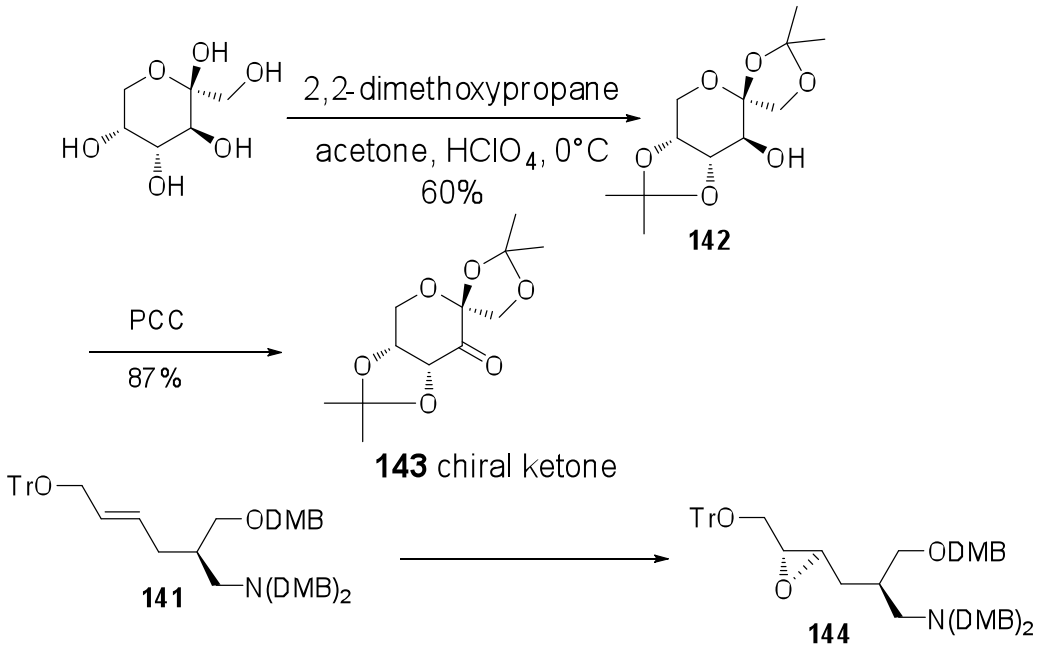
Scheme 4. Attempt to Determine the Configuration of Monoacetate **126**

We converted monoacetate **126** to secondary amine **138** via a Mitsunobu reaction (Scheme 5).[8] Then, treatment of **138** with K_2CO_3 afforded hydroxy amine **139**. 3,4-DMB protection of **139** with 3,4-DMB-Br led to compound **140**,[9] which was further protected with 3,4-DMB group to provide secondary amine **141**.



Scheme 5. Synthesis of Secondary Amine **141**

The Shi epoxidation is an asymmetric epoxidation of an olefin with oxone and a fructose-derived catalyst.[10] This procedure generates epoxides with high ee from *trans*-disubstituted alkenes and trisubstituted alkenes. In addition, the reagents are cheap. We are greatly attracted by this protocol and planned to employ this method in our synthesis by constructing epoxide **144**. The chiral ketone **143** was prepared via protection of D-fructose with acetone followed by PCC oxidation of the resulting ketal **142** (Scheme 6). We tried the epoxidation with mCPBA first.[11] We found that there is no diastereoselectivity, and we got a 1:1 ratio of diastereomers. We tried three Shi epoxidation conditions. The conditions shown in entries 1 and 2 only led to recovered starting material. For entry 3, if the reaction was carried out at 0 °C, we only obtained a very small amount of product, and recovered most of the starting material.[12] When the reaction was performed at 4–5 °C (*i. e.* ice water bath), desired product was achieved in 45 % yield with 43 % starting material recovered.

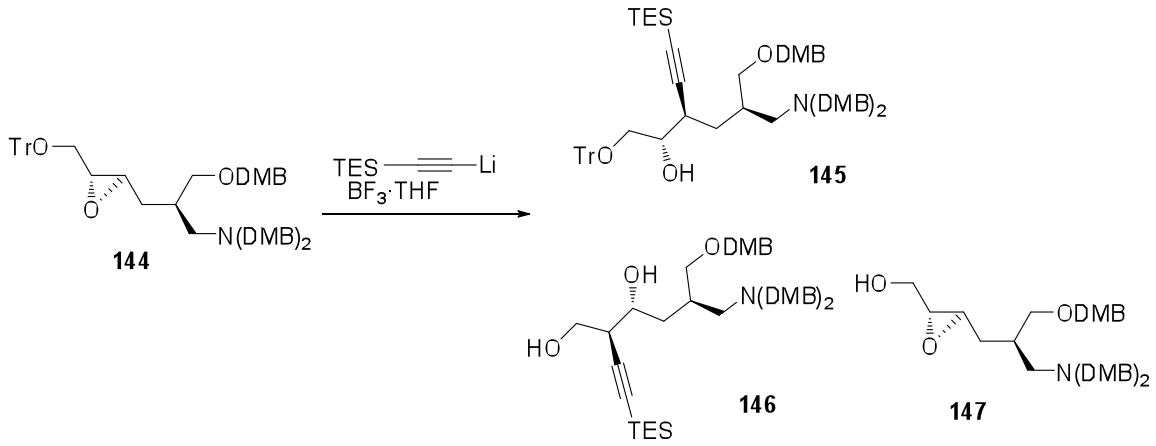


Conditions	results
1. chiral ketone oxone/4x10^{-4}M Na_2EDTA-1.47M KOH CH_3CN, dimethoxymethane K_2CO_3-CH_3COOH Bu_4NHSO_4, 0°C	recovered all SM
2. chiral ketone H_2O_2, CH_3CN, K_2CO_3 4x10^{-4} M EDTA, 0°C	recovered all SM
3. chiral ketone 0.05M $Na_2B_4O_7.10H_2O$ in 4x10^{-4} M Na_2EDTA CH_3CN, Bu_4NHSO_4, K_2CO_3 in H_2O oxone in 4x10^{-4} M Na_2EDTA ice-water bath	45%, 95% *de*, 43% SM

Scheme 6. Synthesis of Epoxide **144**

With epoxide **144** in hand, we hoped to open the epoxide ring by treatment with an alkynyllithium reagent (Scheme 7). In theory, because the trityl group is bulky, the alkynyl group will attack the epoxide from the less hindered position to provide product **145**. Unfortunately, when we performed the reaction with lithium reagent catalyzed by $BF_3{\cdot}O(C_2H_5)_2$, or $BF_3{\cdot}$THF at

–78 °C, we only obtained a small amount of detritylation product **147**, and recovered most of the starting material.[13,14] If we allowed the reaction to warm to rt and stir at rt, we obtained a mixture of **144**, **146** and **147**. The trityl group is sensitive to Lewis acids, and it is removed before the alkynyl group attacks the epoxide. The $HOCH_2$ group is less hindered. Thus, the alkynyl group attacks from the less hindered side to afford undesired product **146**. So this synthetic route is not feasible.

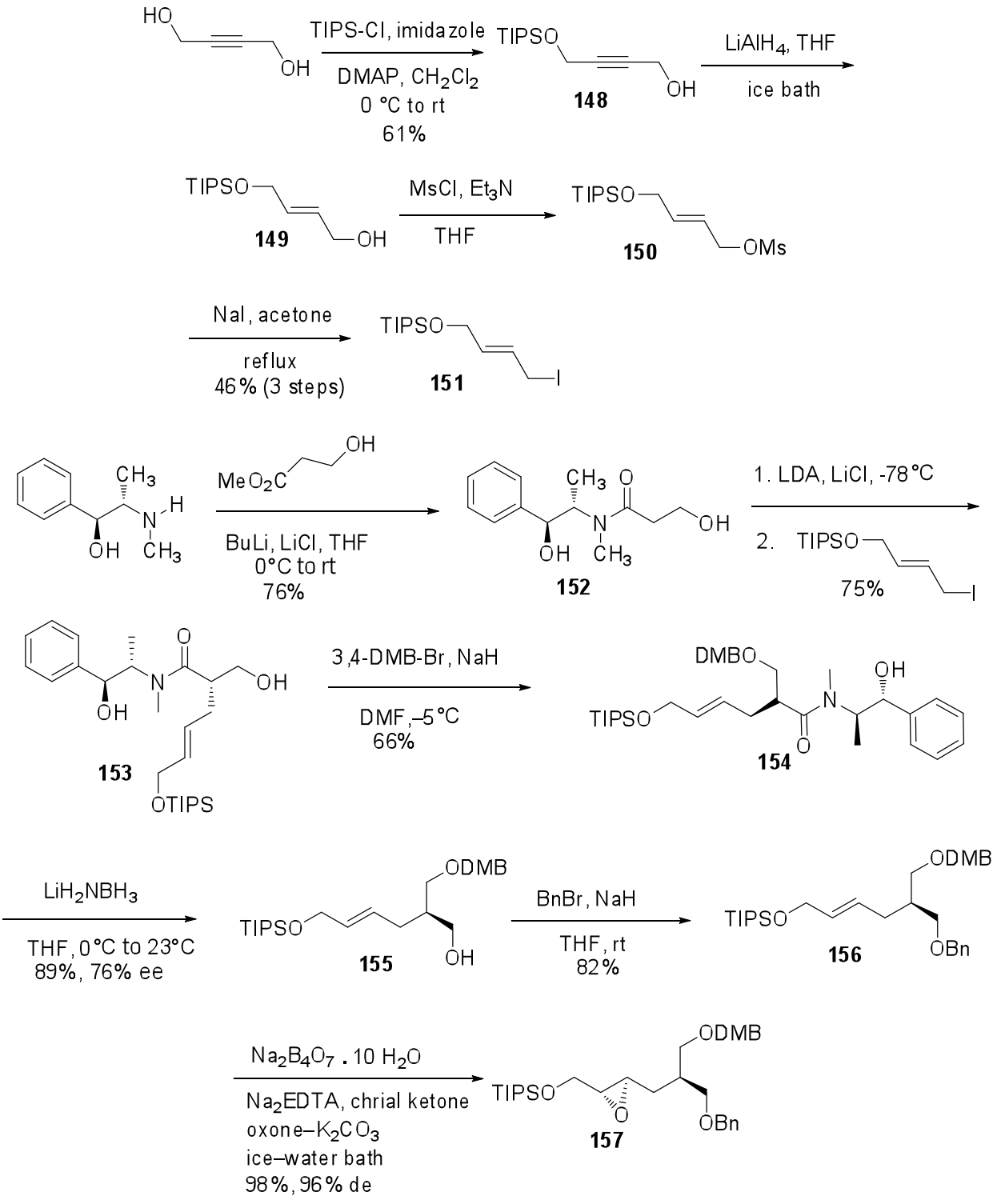


Scheme 7. Ring Opening of Epoxide **144**

4.2. One Carbon Short Chiral Auxiliary-Mediated Approach

Based on the drawbacks of the previous route (ee value is difficult to control and Tr group is labile), we turned to another route to construct the building block. We introduced the chiral auxiliary pseudoephedrine to control diastereoselectivity and switched the Tr group to a TIPS group. We started our total synthesis with 2-butyne-1,4-diol (Scheme 8). Protection of 2-butyne-1,4-diol with a TIPS group provided alkyne **148**. Reduction of **148** with $LiAlH_4$ provided alkene **149**. Mesylation of crude **149** followed by iodination of the resulting meyslate **150** afforded iodide **151**. Treatment of (1S, 2S)-(+)-pseudoephedrine with methyl-3-hydroxy propanoate provided **152**. Myers asymmetric alkylation followed by protection of primary alcohol **153** with

3,4-DMB group afforded **154**. Removal of chiral auxiliary formed alcohol **155** with 76% ee. Benzylation with BnBr resulted in **156**. Shi epoxidation of **156** led to **157** in excellent yield with 96% de.



Scheme 8. Synthesis of Epoxide **153**

While we were working on this synthetic approach, we were also conducting the

model studies towards 2-pyridone synthesis. Based on the results of these studies, we recognized the benefit of having one more carbon on the chain of **152**. So, we halted work on this route.

4.3 References

1. Tu, Y.; Frohn, M.; Wang, Z.; Shi, Y. *Org. Syntheses* Vol. 80, 1.

2. Banfi, L.; Guanti, G.; Mugnoli, A.; Riva, R. *Tetrahedron:Asymmetry* **1998**, *9*, 2481.

3. Kastrinsky, D. B.; Boger, D. L. *J. Org. Chem*. **2004**, *69*, 2284.

4. Baldisserotto, A.; Marastoni, M.; Gavioli, R.; Tomatis, R. *Bioorganic & Medicinal Chemistry Letters* **2003**, *13*, 1966.

5. *Neri, C.; Williams, J. M. Adv. Synth. Catal*. **2003**, *345*, 835.

6. Oriyama, T.; Taguchi, H.; Terakado, D.; Sano, T. *Chemistry Letters* **2002**, *31*, 26.

7. Nwoye, E.; Dudley, G. B. *Chem. Commun*. **2007**, 1436.

8. Kordes, M.; Brands, M.; Es-Sayed, M.; Meijere, A. *Eur. J. Org. Chem*. **2005**, 3008.

9. Mootoo, D. R.; Fraser-Reid, B. *Tetrahedron* **1990**, *46*, 185.

10. Tu, Y.; Frohn, M.; Wang, Z.; Shi, Y. *Org. Syntheses* Vol. 80, 1.

11. Fristruo, P.; Dideriksen, B. B.; Tanner, D.; Norrby, P. *J. Am. Chem. Soc*. **2005**, *127*, 13672.

12. Wang, Z.; Tu, Y.; Frohn, M.; Zhang, J.; Shi, Y. *J. Am. Chem. Soc*. **1997**, *119*, 11224.

13. Kane, V. V.; Singh, V.; Martin, A.; Doyle, D. L. *Tetrahedron* **1983**, *39*, 345.

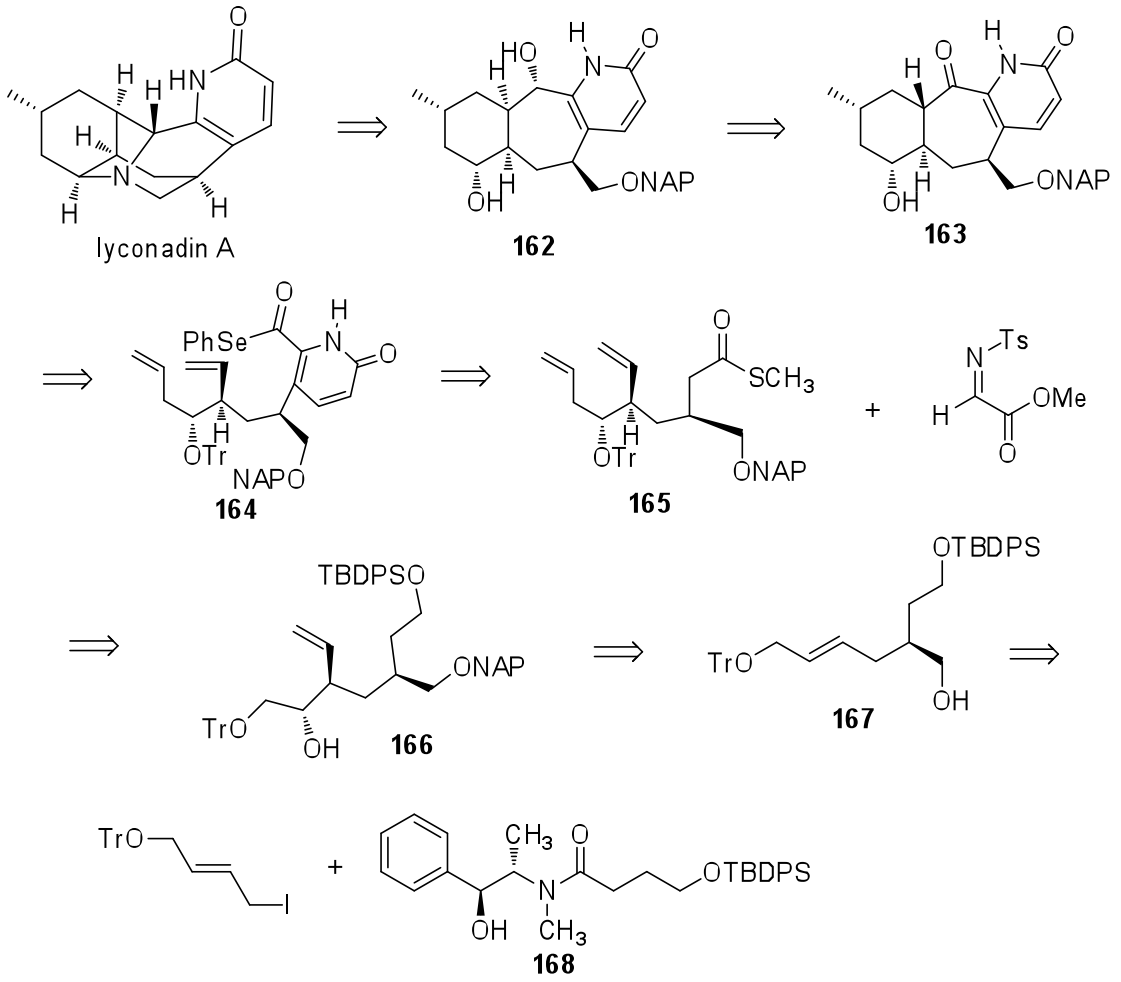
14. Ritschel, J.; Sasse, F.; Maier, M. E. *Eur. J. Org. Chem*. **2007**, 78.

Chapter 5. Progress Towards Total Synthesis of Lyconadin A

When we explored the scope of the modified Kozikowski pyridone annulation, which involved the condensation of pyrrolidine enamine and propiolamide in the presence of toluenesulfonic acid, we found that the increased steric hindrance on pyrrolidine enamine prevents the reaction. Then, we successfully developed a method for the construction of 5-alkyl and 3,5-dialkyl-6-carbomethoxy-2-pyridones based on Donohoe's pyridone synthesis. We plan to use this pyridone annulation protocol in our total synthesis of lyconadin A. The synthetic route shown in Scheme 9 of Chapter 4 was designed for the pyridone synthesis based on modified the Kozikowski protocol. We made a small change to that route to match our modified Donohoe's pyridone synthesis by adding one more carbon on the chain of **152**.

5.1. Retrosynthesis

Scheme 1 shows our current retrosynthetic strategy of lyconadin A. We will epimerize the stereocenter adjacent to the carbonyl group in compound **163** to generate *cis*-fused compound **162** via the directed hydrogenation method we tried in the model product. The tricyclic intermediate **163** would be derived from compound **164** by means of a tandem 7-*exo*/6-*exo* radical cyclization. The thioester **165** could be converted into pyridone **164** via the strategy developed by us. The thioester **165** could be prepared from **166** via a sequence of reactions. Compound **166** could be prepared from alkene **167** by epoxide formation, followed by ring opening. We introduced chiral auxiliary pseudoephedrine to control the stereochemistry of compound **167**.

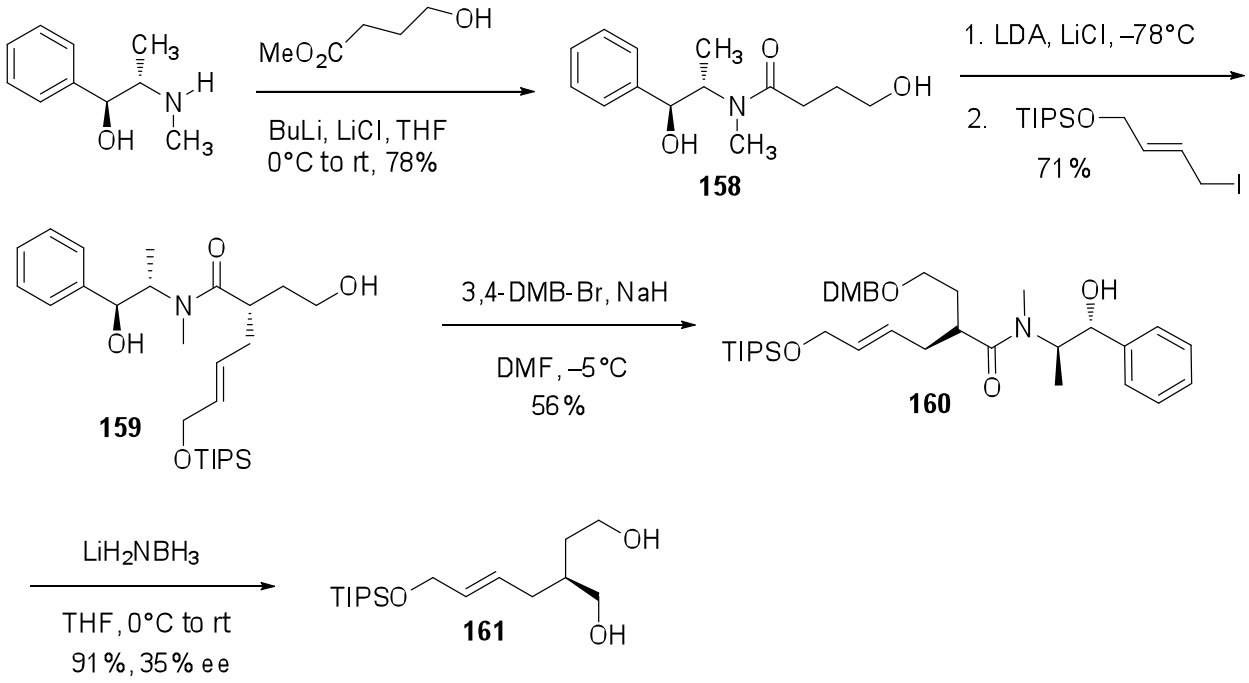


Scheme 1. Current Retrosynthesis of Lyconadin A

5.2. First Attempt to the Synthesis of the Precursor of Epoxidation

Treatment of (1*S*, 2*S*) -(+)-pseudoephedrine with methyl-4-hydroxy butanoate provided **158** (Scheme 2). Myers asymmetric alkylation followed by protection of the resulting primary alcohol **159** with a 3,4-dimethoxybenzyl (DMB) group afforded **160**.[1] Removal of the chiral auxiliary by treatment with borane–ammonia formed undesired diol **161**.[2] In this reaction, lithium coordinated with both oxygen of alcohol and ODMB to form a 7-membered ring. H^- then attacked the CH_2 of DMB group to provide diol **161** in 35% ee. In the alkylation step, the lithium

apparently coordinated with the free primary alcohol of **158** along with the secondary alcohol and the carbonyl. This lowers the diastereoselectivity of alkylation.

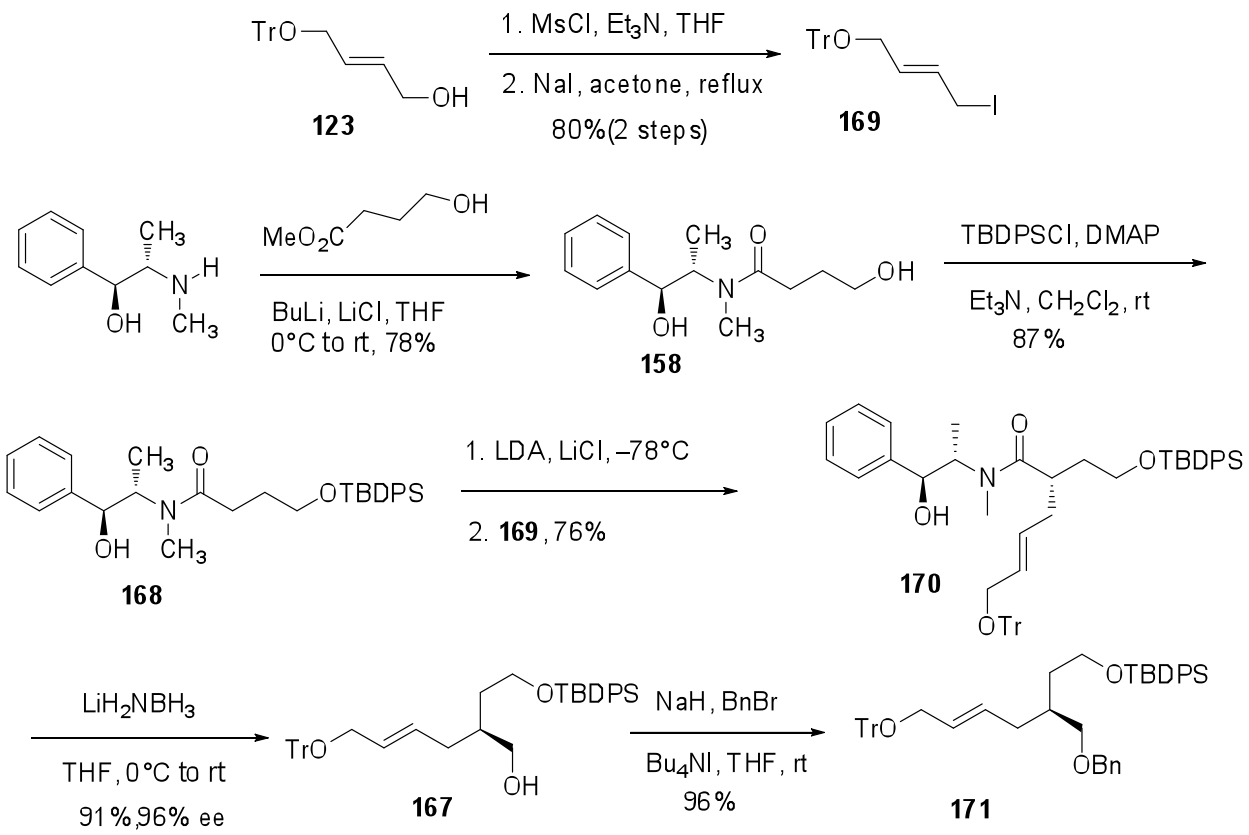


Scheme 2. Failed Synthesis of DMB Ether

5.3. Second Attempt to the Synthesis of the Precursor of Epoxidation

To avoid coordination, we protected primary alcohol **158** with a bulky TBDPS group before alkylation. To control the regioselectivity of ring-opening in a later step, we installed a Tr group in place of the TIPS group.

Treatment of pseudoephedrine with methyl 4-hydroxyl butanoate provided amide **158** (Scheme 3). Then, we protected the hydroxyl group with a bulky TBDPS group to prevent lithium coordination. Asymmetric alkylation of **168** provided **170**. Removal of the chiral auxiliary in **170** generated alcohol **167** in 91% yield and 96% ee. Benzylation of **167** afforded **171** in excellent yield.



Scheme 3. Synthesis of Compound **171**

5.4. Shi-Epoxidation

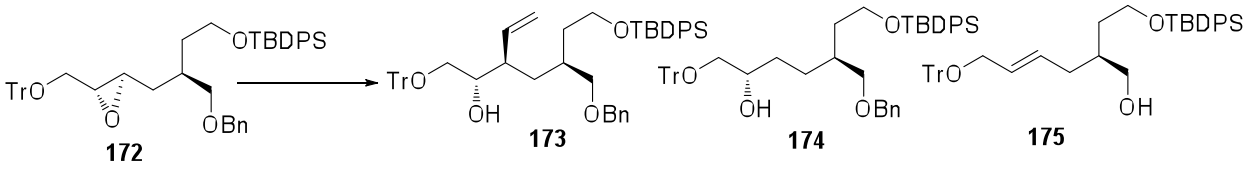
The Shi epoxidation[3] is highly pH dependent. Generally, higher pH results in more rapid autodecomposition of oxone, which leads to the decrease of epoxidation efficiency. However, at lower pH, the chiral ketone decomposed very rapidly. The epoxidation is typically carried out around pH 10.5. Our substrate **171** is sterically hindered. So, it reacted slowly under Shi epoxidation conditions. Therefore, we added chiral ketone and oxone– KOH once more after 4 hours of reaction time. Shi epoxidation of alkene **171** conducted in this way provided epoxide **172** in 63% yield with 96% de, and recovered starting material in 15% yield (Table 1, entry 3). The stereochemistry of epoxidation is based on the spiro transition state proposed by Shi and co-workers. We tried other Shi epoxidation conditions, but they did not work (entries 1 and 2).

conditions	results
1. 30% H_2O_2, CH_3CN/dimethoxy methane chiral ketone, 2M K_2CO_3, $4x10^{-4}$ M EDTA	trace of product
2. $Na_2B_4O_7.10H_2O$, Na_2EDTA, Bu_4NHSO_4, CH_3CN, chiral ketone, oxone, K_2CO_3	recovered SM
3. oxone/$4x10^{-4}$ M Na_2EDTA, 1.47 M KOH, Bu_4NHSO_4, chiral ketone, K_2CO_3+CH_3COOH, DMM/ CH_3CN, 4°C	63%, 96% de recovered 15% SM

Table 1. Synthesis of Epoxide **172**

5.5. Ring Opening Reaction

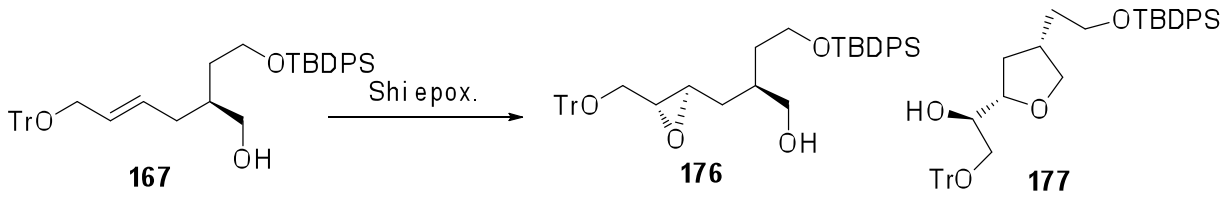
The regioselective ring-opening of epoxides by Grignard reagents has been restricted mostly to unhindered epoxides and those activated by an adjacent vinyl or aryl group. Disubstituted epoxides present regioselectivity problems and due to Lewis acid (magnesium halide salts), the formation of side products (rearrangement, elimination, reduction, etc.) may be observed.[4] In our substrate **172**, a bulky Tr group is installed to control the regiochemistry. In this epoxide ring-opening reaction, since Tr group is bulky, the vinyl group should attack the less hindered carbon. We tried a series of copper salts in different ratios of Et_2O/THF (Table 2). However, all the results were poor. We recovered starting material or got a trace of product along with major elimination and reduction side products.



conditions	results
MgBr, CuI, Me_2S, THF, ice-bath	trace of product
MgBr, $CeCl_3$, THF, –78°C to rt	recovered SM
MgBr, CuI, Et_2O, THF,–78 °C to rt	trace of product
MgBr, CuI, Et_2O/ THF= 7/1,–20 °C to rt	trace of product
MgBr, CuI, Et_2O/ THF= 7/1, 30°C	decomposed
(2-thienyl)Cu(CN)Li_2, THF/Et_2O=3/5	recovered SM
(2-thienyl)Cu(CN)Li_2, THF/Et_2O=3/5, BF_3.Et_2O	recovered SM
Cu(CN)Li	recovered SM
Cu(CN)Li, BF_3.Et_2O	decomposed
MgBr,CuBr.SMe_2, SMe_2, Et_2O/THF	trace of product

Table 2. Attempted Ring Opening of Compound **172**

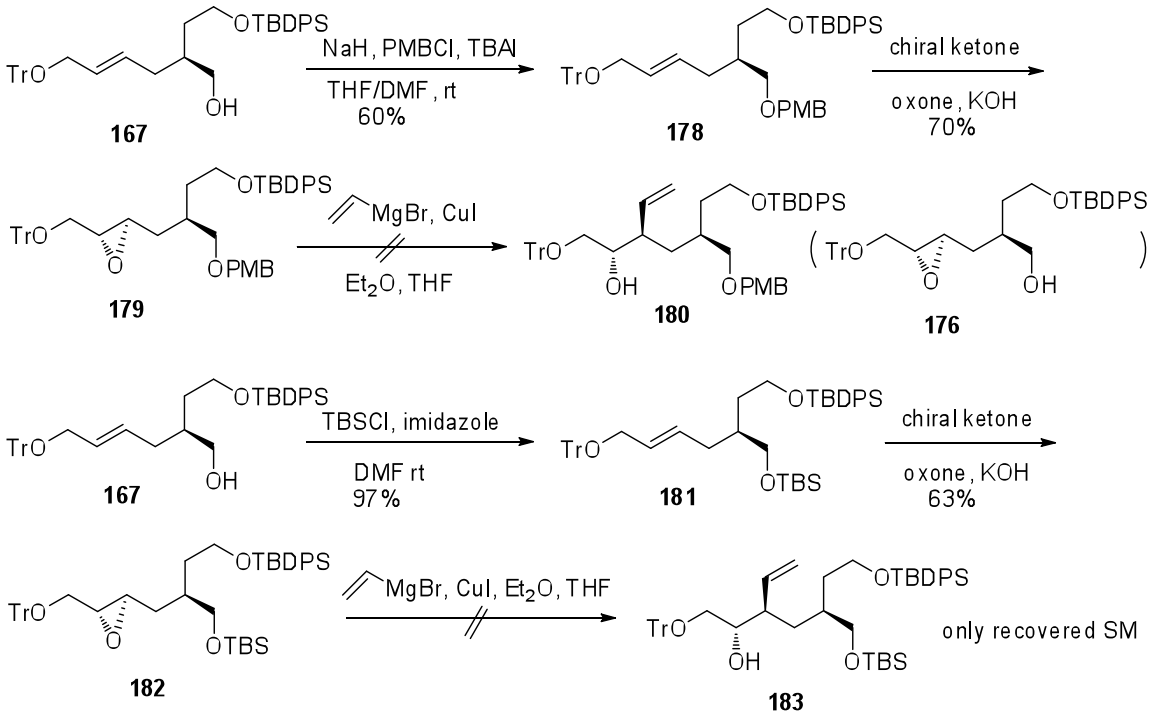
Prieto's work[4] manifests that the copper-catalyzed Grignard cleavage of hindered epoxide does tolerate a free hydroxyl group. In order to decrease the hindrance of epoxide, we planned to perform the ring-opening reaction with epoxide **176** with free hydroxyl group. Unfortunately, in the epoxidation step, we got cyclized compound **177,** rather than epoxide **176** (Table 3).



Conditions	result
1 $Na_2B_4O_7.10H_2O$, Na_2EDTA, Bu_4NHSO_4, CH_3CN, chiral ketone, oxone, K_2CO_3	recovered SM
2. oxone/$4x10^{-4}$ M Na_2EDTA, 1.47 M KOH, Bu_4NHSO_4, chiral ketone, K_2CO_3+CH_3COOH, DMM/ CH_3CN, 4°C	recovered SM
3. oxone/$4x10^{-4}$ M Na_2EDTA, 1.47 M KOH, Bu_4NHSO_4, chiral ketone, K_2CO_3+CH_3COOH, DMM/ CH_3CN, rt	obtained mostly **177**

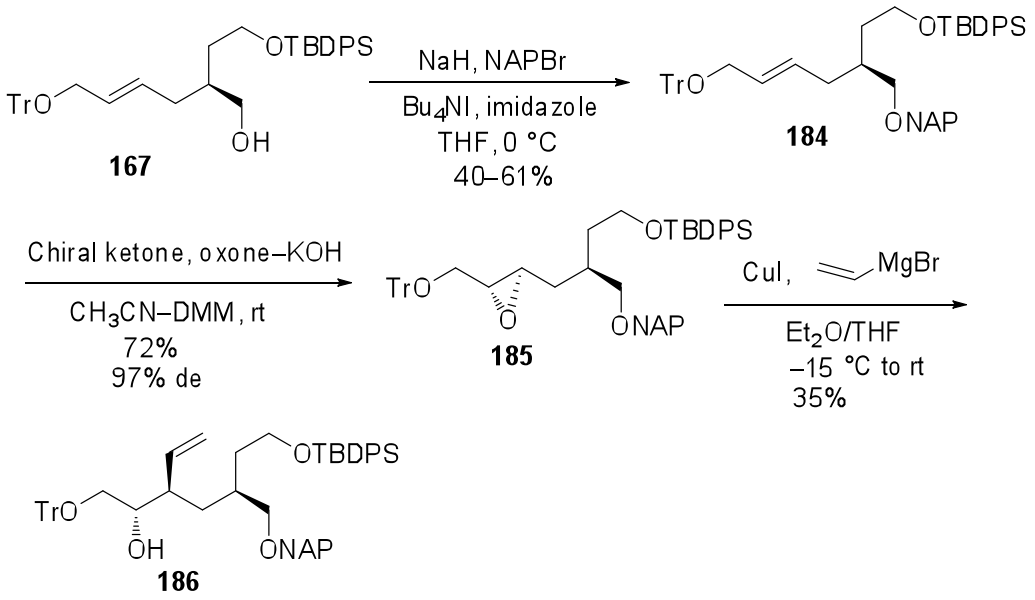
Table 3. Attempted Epoxide **176** Formation

Then, we protected the alcohol **167** with PMB and TBS respectively (Scheme 4). Shi epoxidation afforded desired epoxides **179** and **182** respectively. However, the ring-opening of epoxide **179** only resulted in decomposed compound **176**, and ring-opening of epoxide **182** only afforded recovered starting material.



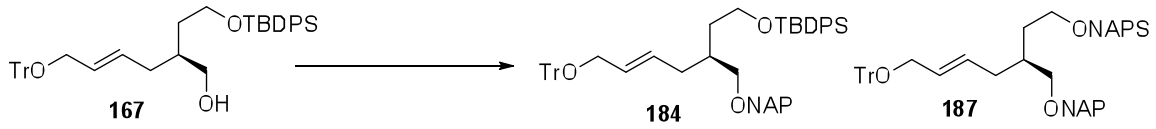
Scheme 4. Attempted Ring Opening of Epoxide **179** and **182**

Then, we protected **167** with a 2-naphthylmethyl (NAP) group to form **184** (Scheme 5)**.** Shi epoxidation of compound **184** afforded epoxide **185** with 97% de. We tried the ring opening reaction by treating the epoxide **185** with Lewis acid CuI at first, and we obtained compound **186** in 35% yield.[5] We believe that we could improve the yield of ring opening reaction by optimization.



Scheme 5. Synthesis of Compound **186**

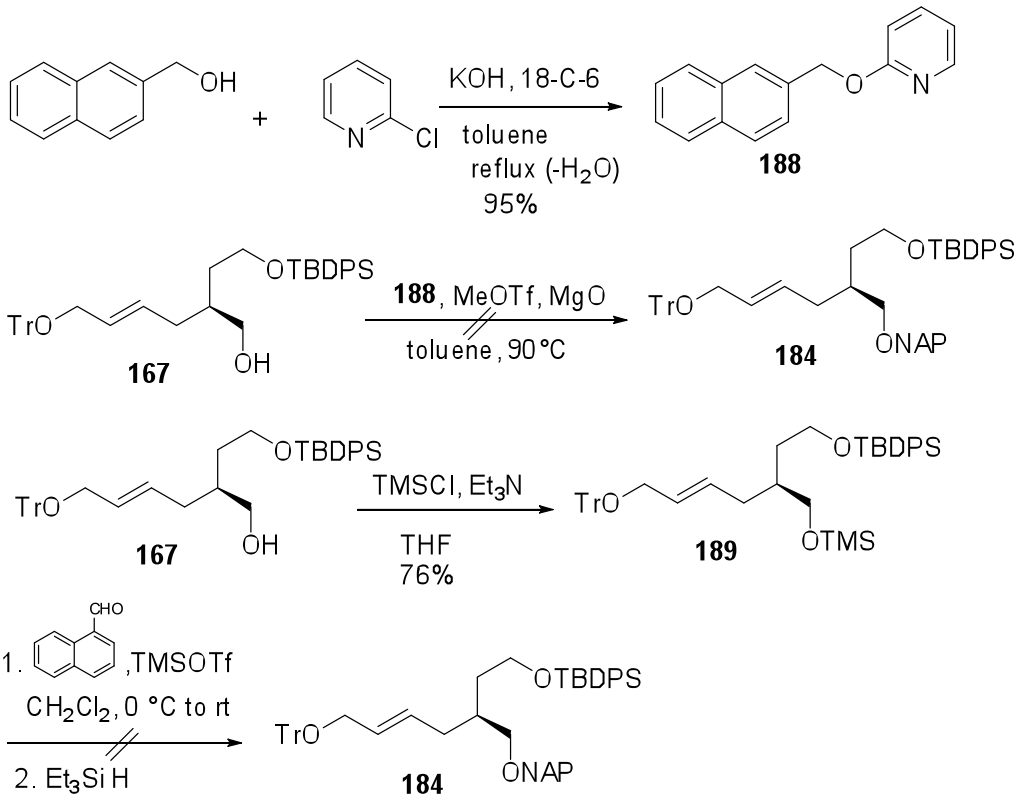
The NAP protection was challenging, because the TBDPS group and the Tr group are sensitive to base and acid respectively. NaH and NAPBr delivered product **184** and di-NAP **187** by-product (Table 4). In the presence of imidazole, there was no di-NAP **187** by-product formed. However, the TBDPS group migration by-product was formed. Pyridine, BuLi, or Bu_2SnO at room temperature with NAPBr resulted in recovered starting material.[6]



Conditions	Results
1.4 eq NaH, NAPBr, THF/DMF, rt	most of **187**
1.4 eq NaH, NAPBr, Bu_4NI, THF/DMF, 0°C	**184**:**187** = 1:1
0.86 eq NaH, NAPBr, Bu_4NI, THF/DMF, – 5°C	**184**:**187** = 1:1
0.86 eq NaH, NAPBr, Bu_4NI, THF, – 5°C	most of SM + **184**:**187** = 1:1
NAPBr, Ag_2O, DMF	decomposed
NAPBr, Pyr. rt	recovered SM
NAPBr, BuLi, THF, –78 °C to 5°C	recovered SM
Bu_4NHSO_4, 50% KOH, NAPBr, benzene	most of diol+ **187**
NAPBr, NaH, $CuCl_2$, TBAI, THF	decomposed
Bu_2SnO, NAPBr, TBAI, CSF, toluene, DMF, rt	recovered SM
Bu_2SnO, NAPBr, TBAI, CSF, toluene, DMF, 95 °C	decomposed
NAPBr, NaH, imidazole, TBAI, THF/DMF = 4/1, 0 °C migration	41–62% **184**+ TBDPS

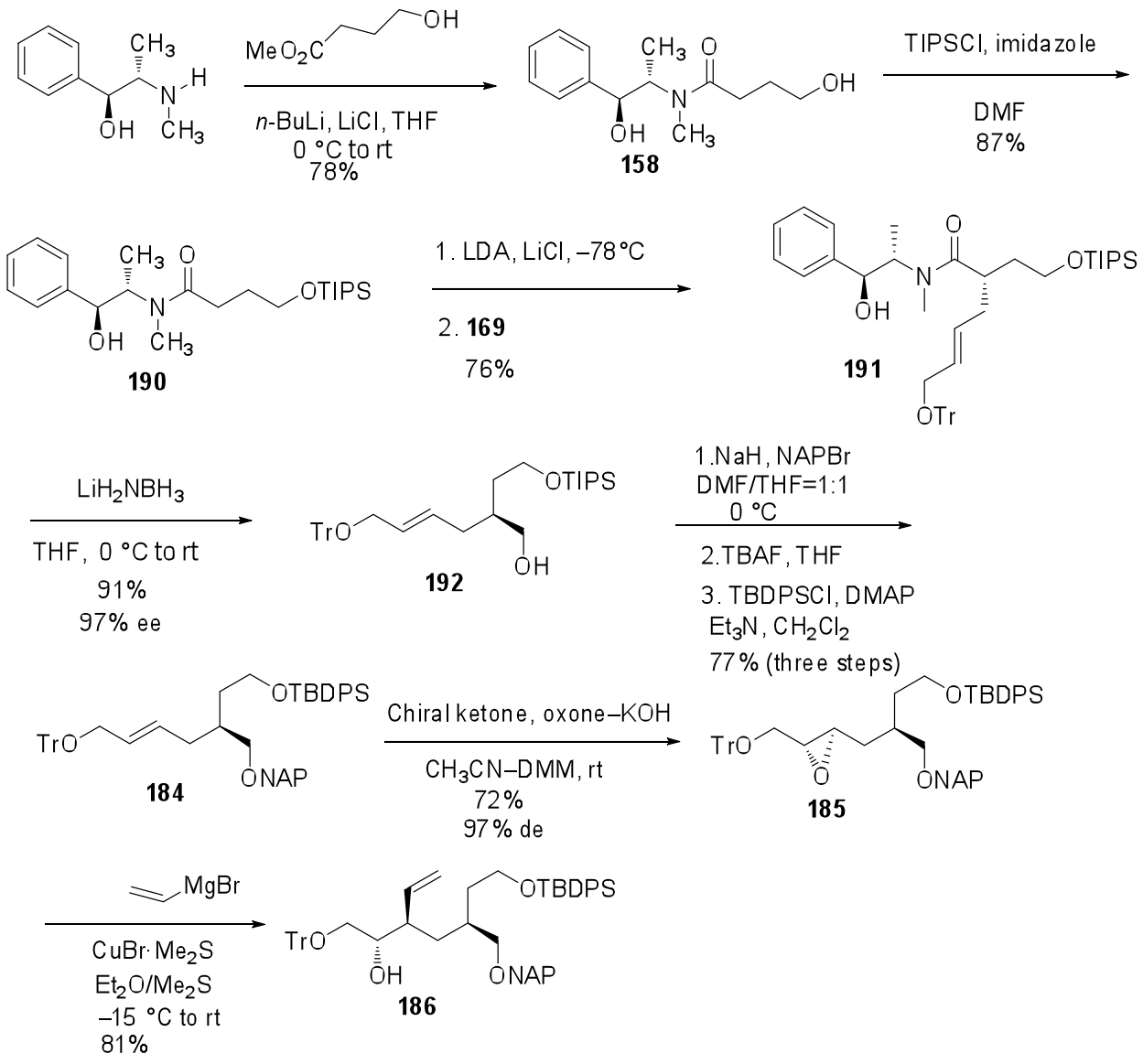
Table 4. Attempted NAP Protection of Compound **167**

We also tried some mild conditions (Scheme 6). 2-Benzyloxy-1-methylpyridinium triflate is a novel benzylation reagent for alcohols.[7] No acidic or basic promoters are needed for benzyl transfer, which occurs upon warming in the presence of the alcohol substrate under mild conditions. However, in our case, triflated salt of compound **188** led to a mixture of product **184**, di-NAP **187**, TBDPS migration by-product, and other by-products. We also tried a TMSOTf-catalyzed benzyl ether synthesis from aldehyde and TMS ether **189** via triethylsilane-reduction.[8] Unfortunately, it delivered decomposed by-products.



Scheme 6. Attempts to Synthesize Compound **184**

Based on all our attempted reactions, we realized that the TBDPS group in our substrate is very sensitive to base and easy to migrate. Because a TIPS group is more stable to base and less likely to migrate than a TBDPS group, the TBDPS group was switched to a TIPS group in the alkylation substrate (Scheme 7). We tried the ring opening of the derivative of epoxide **185** with TIPS group rather than TBDPS group. However, we only recovered starting material. Thus, after the NAP protection of alcohol **192**, we cleaved the TIPS group, and reprotected with TBDPS group. The overall yield of these three steps was 77%. Then, we optimized the ring opening reaction. This reaction is very sensitive to moisture and air, and a more concentrated solution is also helpful to improve the yield. Because our substrate **185** is more hindered, stirring at room temperature after adding all the starting materials is necessary.

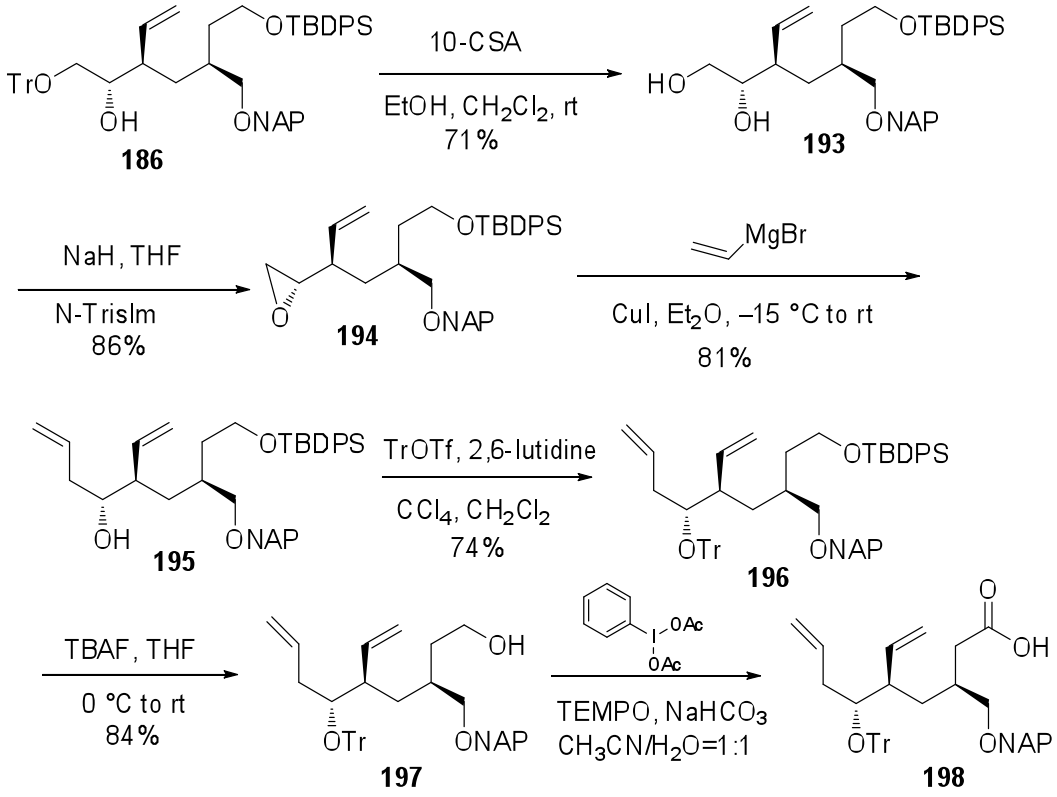


Scheme 7. Synthesis of Compound **186**

5.6. Synthesis of Carboxylic Acid

Compound **186** was subjected to CSA to lead to diol **193** (Scheme 8).[9] This reaction could not be stirred for more than 4 hour, since the NAP group would be cleaved by CSA after a long time. Diol **193** was exposed to 1-(2,4,6-triisopropylbenzenesulfonyl) imidazole to form epoxide **194**.[10] Ring opening of epoxide **194** delivered alcohol **195**. Initially, we protected the alcohol **195**

with a TBS group. Unfortunately, in a later step, we were unable to selectively remove the TBDPS group without touching the TBS group. So, we protected the alcohol **195** with a Tr group to provide compound **196**.[11] Treatment of **196** with TBAF afforded primary alcohol **197**, which was oxidized to carboxylic acid **198**.[12]



Scheme 8. Synthesis of Carboxylic Acid **198**

5.7 References

1. Myers, A. G.; Yang, B. H.; Chen, H.; Mckinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc*. **1997**, *119*, 6496.

2. *Myers, A. G.; Yang, B. H.; Chen, H. Org. Synth*. Vol. *77*, 29.

3. Tu, Y.; Frohn, M.; Wang, Z.; Shi, Y. *Org. Synth*. Vol. *80*, 1.

4. Rodriguez, D.; Mulero, M.; Prieto, J. *J. Org. Chem*. **2006**, *71*, 5826.

5. Nicolaou, K. C.; Daines, R. A.; Uenishi, R. A.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc*. **1988**, *110*, 4672.

6. (a) Letsinger, R. L.; Finna, J. L. *J. Am. Chem. Soc*. **1975**, *97*, 7197. (b) Hijfte, L. V.; Little, R. D. *J. Org. Chem*. **1985**, *50*, 3940. (c) Amin, M. N.; Ishiwata, A.; Ito, Y. *Carbohydrate Research* **2006**, *341*, 1922. (d) Fuwa, H.; Fujikawa, S.; Tachibana, K.; Takakura, H.; Sasaki, M. *Tetrahedron Lett*. **2004**, *45*, 4795. (e) Freedman, H. H.; Dubois, R. A. *Tetrahedron Lett*. **1975**, *16*, 3251. (f) Classon, B.; Garegg, P. J.; Oscarson, S. Tiden, A. *Carbohydrate Research* **1991**, *216*, 187. (g) Hoshi, H.; Ohnuma, T.; Aburaki, S.; Konishi, M.; Oki, T. *Tetrahedron Lett.* **1993**, *34*, 1047. (h) Wei, A.; Kishi, Y. *J. Org. Chem.* **1994**, *59*, 88. (i) Liao, W.; Locke, R. D.; Matta, K. *Chem. Commun*. **2000**, *5*, 369.

7. Poon, K. W.; Albiniak, P. A.; Dudley, G. B. *Org. Synth*. **2007**, *84*, 295.

8. Hatakeyama, S.; Mori, H.; Kitano, K.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1994**. *35*, 4367.

9. Tortosa, M.; Yakelis, N. A.; Roush, W. R. *J. Am. Chem. Soc*. **2008**, *130*, 2722.

10. Smith, A. B.; Kim, D. *Org. Lett*. **2007**, *9*, 3311.

11. (a) Forbus, T. R.; Martin, J. C. *J. Org. Chem*. **1979**, *44*, 313. (b) Zimmerman, S. C.; Zeng, Z.; Wu, W.; Reichert, D. E. *J. Am. Chem. Soc*. **1991**, *113*, 183.

12. Epp, J. B.; Widlanski, T. S. *J. Org. Chem*. **1999**, *64*, 293.

Chapter 6. Conclusion and Future Work

6.1. Conclusion

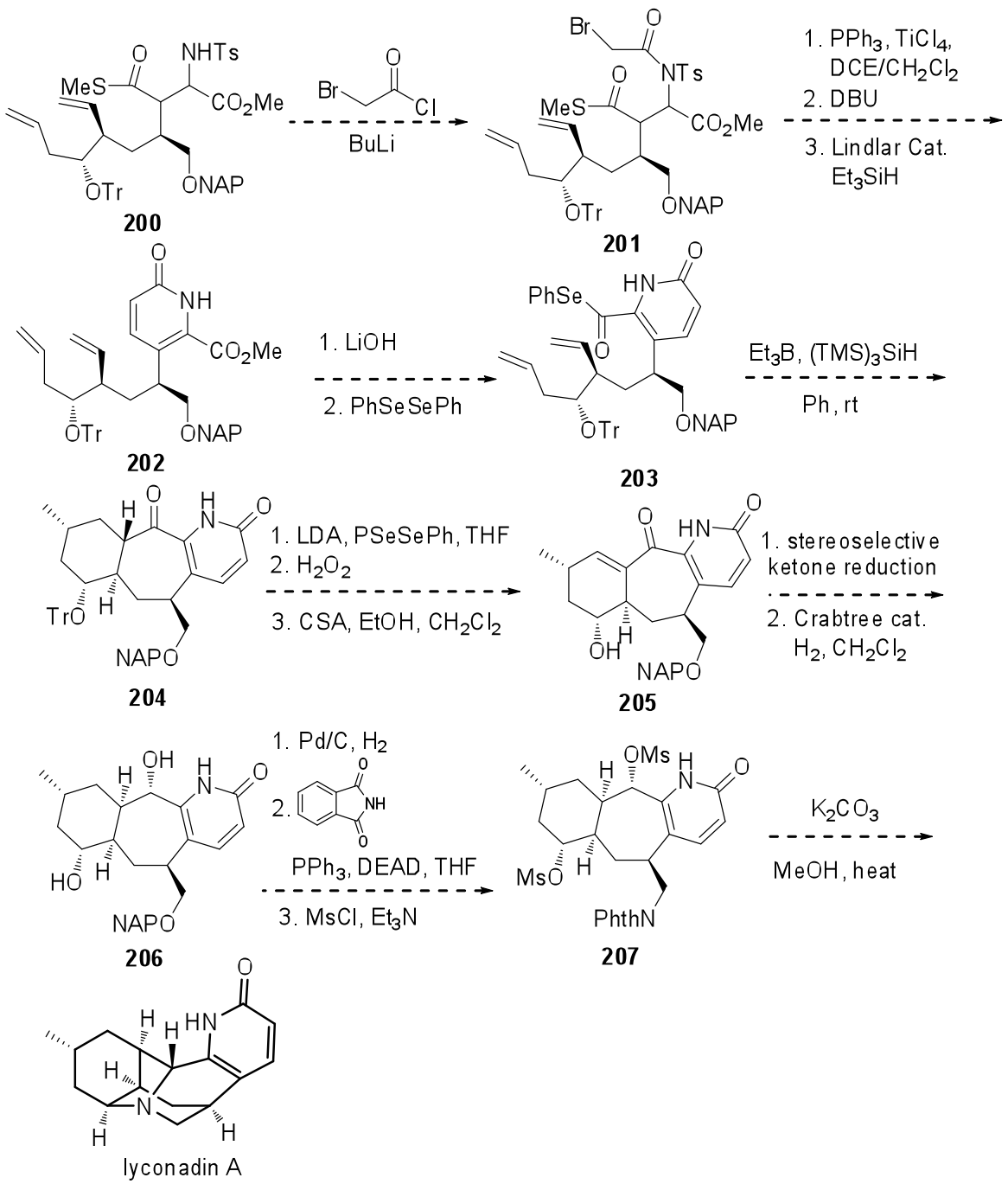
In our group, Seth Grant developed a novel 7-*exo*/6-*exo* acyl radical cascade cyclization as a method of making the bicyclo[5.4.0]undecane ring system of lyconadin A, and he obtained *trans*-fused product in high yield as a single diastereomer. To explore the origin of stereochemistry, we performed the radical cascade cyclization with a free alcohol derived from Seth's precursor of cyclization. An alcohol was obtained as a single diastereomer which has the same stereochemistry as Seth's cyclization product. In addition, a cyclization of a diastereomeric substrate also afforded a single diastereomer. These experiments prove that the 7-*exo*/6-*exo* cascade radical cyclization happens with excellent diastereoselectivity. The stereochemistry is consistent with chairlike or pseudochairlike transition states. The model products are *trans*-fused ring systems, while a *cis*-fused ring system is needed in lyconadin A. We have discovered a method to convert *trans*-fused model cascade cyclization product into the desired *cis* isomer.

Based on Donohoe's pyridone synthesis, we developed a method for the construction of 5-alkyl and 3,5-dialkyl-6-carbomethoxy-2-pyridones, the former of which is an important moiety of lyconadin A. An intramolecular Reformatsky reaction is a key step in this process. We believe that this new method could be used in the total synthesis of lyconadin A.

We have proceeded with our total synthesis, in which we generated an epoxide by Shi asymmetric epoxidation and regioselectively opened epoxide rings. So far, we have prepared carboxylic acid **197**.

6.2. Future Work

Our future work is shown in Scheme 1. The carboxylic acid **198** will be converted into thioester **199**,[1] which we will use to install pyridone **202** by means of the pyridone synthesis developed by us.[2] Mannich reaction of thioester and tosylimine will provide tosylamine **200**. Acylation of tosylamine **200** with bromoacetyl chloride will give tosylamide **201**. Reformatsky reaction, elimination, and desulfurization will result in pyridone **202**. Ester hydrolysis and phenyl selenoesterification will deliver phenyl selenoester **203**, the precursor of tandem radical cyclization. We will perform tandem 7-*exo*/6-*exo* radical cyclization to convert **203** to tricyclic compound **204**.[3] Then, we will epimerize the stereocenter adjacent to the carbonyl group in compound **204** via the method employed in the model system. The phenyl selenide formation, oxidation, and the Tr deprotection will afford enone **205**. Stereoselective reduction of ketone **205** followed by hydrogenation directed by hydroxyl group will lead to compound **206**. The NAP deprotection, Mitsunobu reaction of the resulting alcohol,[4] and mesylation will generate compound **207**. According to our experience, K_2CO_3 can cleave a Phth group in methanol at rt. Treatment of **207** with K_2CO_3 in methanol will afford lyconadin A.



Scheme 1. Future Work

6.3. References

1. Wyk, M. V.; Strauss, E. *Chem. Commun*. **2007**, 398.

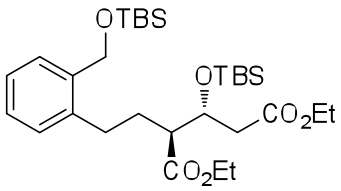
2. Zhang, Y.; Loertscher, B. M.; Castle, S. L. *Tetrahedron* **2009**, *65*, 6584.

3. Grant, S. W.; Zhu, K.; Zhang, Y.; Castle, S. L. *Org. Lett*. **2006**, *8*, 1867.

4. Kordes, M.; Brands, M.; Es–Sayed, M.; Meijere, A. *Eur. J. Org. Chem*. **2005**, 3008.

Chapter 7 Experimental Information

Benzene, dimethylformamide, methanol, methylene chloride, tetrahydrofuran, and toluene were dried by passage through a solvent drying system containing cylinders of activated alumina. Flash chromatography was carried out using 60–230 mesh silica gel. ^{1}H NMR spectra were acquired on 300 or 500 MHz spectrometers with chloroform (7.27 ppm) or pyridine (8.74 ppm) as internal references. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), br s (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz). ^{13}C NMR spectra were acquired on spectrometers operating at 75 or 125 MHz with chloroform (77.23 ppm) or pyridine (149.80) as internal references. Infrared spectra were obtained on an FT-IR spectrometer. Mass spectral data were obtained using ESI techniques.

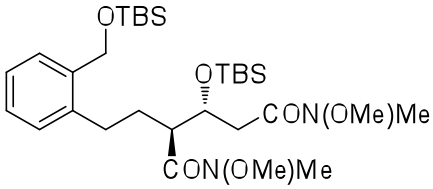


***anti*-Diethyl 3-(*tert*-butyldimethylsilyloxy)-2-(2-((*tert*-butyldimethylsilyloxy) methyl)phenethyl)pentanedioate (43).** Freshly prepared $Zn(BH_4)_2$[1] (0.10 M in ether, 50 mL, 4.99 mmol) was added dropwise at 0 °C under Ar to a stirred solution of **36** (1.50 g, 3.33 mmol)

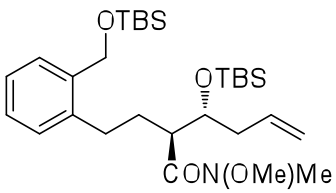
[1] Gensler, W. J.; Johnson, F.; Sloan, A. D. B. *J. Am. Chem. Soc.* **1960**, *82*, 6074.

in anhydrous Et_2O (68 mL). The resulting solution was stirred for 10 min at 0 °C, and then treated with sat aq NH_4Cl (1 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo.

To a solution of the crude alcohol in anhydrous CH_2Cl_2 (16.6 mL) at 0 °C under Ar was added 2,6-lutidine (1.16 mL, 1.07 g, 9.98 mmol). The solution was stirred at 0 °C for 5 min, then treated dropwise with TBS-OTf (1.53 mL, 1.76 g, 6.66 mmol). The resultant mixture was stirred for 16 h, then treated with sat aq $NaHCO_3$ (18 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 5% EtOAc in hexanes elution) afforded **43** (1.215 g, 2.14 mmol, 64%, ca. 4:1 mixture of diastereomers) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46–7.42 (m, 1H), 7.23–7.20 (m, 2H), 7.15–7.12 (m, 1H), 4.75 and 4.74 (2s, 2H), 4.44–4.36 (m, 1H), 4.22–4.08 (m, 4H), 2.69–2.61 (m, 2H), 2.59–2.44 (m, 3H), 1.98–1.71 (m, 2H), 1.31 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H), 0.95 (s, 9H), 0.85 (s, 9H), 0.11 and 0.10 (2s, 6H) 0.06 and 0.02 (2s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 173.7 and 173.3, 171.9 and 171.7, 139.0 and 138.9, 138.6 and 138.6, 129.1 and 129.0, 127.3 and 127.2, 127.1, 126.4, 70.8 and 70.4, 63.0 and 62.8, 60.7 and 60.6, 52.2 and 51.8. 40.0 and 39.8, 30.6 and 30.5, 29.4, 27.9, 26.2 (3C), 25.9 (3C), 18.6, 18.2 and 18.1, 14.5, 14.4, –4.5, –4.7, –5.0 (2C); IR (film) ν_{max} 2955, 2929, 2896, 2856, 1736, 1471, 1463, 1376, 1254, 1182, 1081, 836, 776 cm^{-1}; HRMS (ESI) *m/z* 567.3534 (MH^+, $C_{30}H_{54}O_6Si_2H$ requires, 567.3531).



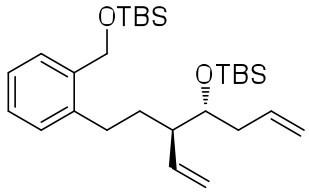
***anti*-3-(*tert*-Butyldimethylsilyloxy)-2-(2-((*tert*-butyldimethylsilyloxy)methyl)-phenethyl)-N^1,N^5-dimethoxy-N^1,N^5-dimethylpentanediamide (44).** To a stirred suspension of MeNH(OMe)•HCl (106 mg, 1.09 mmol) in anhydrous THF (2.0 mL) at –10 °C (ice/acetone bath) under Ar was added *i*-PrMgCl (2.0 M in THF, 1.1 mL, 2.2 mmol) dropwise. The mixture was stirred for 10 min at –10 °C, then treated with a solution of diester **43** (244 mg, 0.43 mmol) in anhydrous THF (0.8 mL + 0.4 mL rinse). The resultant mixture was allowed to warm to rt and stir under Ar for 26 h, then treated with sat aq NH_4Cl (5 mL) and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 2.5 × 23 cm, 2% MeOH in CH_2Cl_2 elution) afforded bis-Weinreb amide **44** (172 mg, 0.287 mmol, 67%) as an orange oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44–7.42 (m, 1H), 7.21–7.15 (m, 3H), 4.74 (s, 2H), 4.53–4.49 (m, 1H), 3.67 (s, 3H), 3.63 (s, 3H), 3.20 (s, 3H), 3.16–3.13 (m, 1H), 3.15 (s, 3H), 2.77 (m, 1H), 2.66–2.52 (m, 3H), 2.05–1.99 (m, 1H), 1.88–1.83 (m, 1H), 0.94 (s, 9H), 0.86 (s, 9H), 0.10 (s, 6H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.0, 172.3, 139.1, 139.0, 128.9, 127.2, 127.0, 126.2, 70.5, 62.9, 61.5, 61.3, 47.0, 38.1, 32.3 (2C), 30.2, 28.7, 26.2 (3C), 26.2 (3C), 18.6, 18.2, –4.5 (2C), –5.0 (2C); IR (film) ν_{max} 2929, 2894, 2856, 1665, 1462, 1413, 1385, 1360, 1254, 939, 812 cm^{-1}; HRMS (ESI) *m/z* 619.3564 (MNa^+, $C_{30}H_{56}N_2O_6Si_2Na$ requires 619.3569).



***anti*-3-(*tert*-Butyldimethylsilyloxy)-2-(2-((*tert*-butyldimethylsilyloxy)methyl) phenethyl)-*N*-methoxy-*N*-methylhex-5-enamide (45).** To a solution of bis-Weinreb amide **44** (184 mg, 0.31 mmol) in anhydrous THF (1.8 mL) at –78 °C under Ar was added DIBAL (1.0 M in THF, 1.23 mL, 1.23 mmol) dropwise, and the solution was stirred at –78 °C under Ar for 2.0 h, then treated with sat aq potassium sodium tartrate (5.0 mL). The mixture was allowed to warm to rt and stirred vigorously at rt for 1.0 h, then extracted with CH_2Cl_2 (4 × 4 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude monoaldehyde (192 mg).

To a suspension of methyltriphenylphosphonium bromide (359 mg, 1.01 mmol) in anhydrous THF (2.0 mL) under Ar was added *n*-BuLi (1.6 M in hexanes, 0.54 mL, 0.86 mmol) dropwise, and the yellow solution was stirred at rt for 10 min then cooled to –78 °C. A solution of the crude monoaldehyde (192 mg) in anhydrous THF (0.4 mL + 2 × 0.3 mL rinses) was then added dropwise, and the mixture was allowed to warm to rt and stir under Ar for 18.5 h. The reaction was quenched with sat aq NH_4Cl (3 mL), and the mixture was extracted with EtOAc (4 × 3 mL). The combined organic layers were washed with brine (7 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 2.5 × 22 cm, 0.5% MeOH in CH_2Cl_2 elution) to afford **45** (90 mg, 0.17 mmol, 54%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44 (t, *J* = 5.0 Hz, 1H), 7.21–7.14 (m, 3H), 5.86–5.78 (m, 1H), 5.04–5.00 (m, 2H), 4.75 (d, *J* = 13.0 Hz, 1H), 4.71 (d, *J* = 13.5 Hz, 1H), 4.02 (dt, *J* = 4.0, 6.5 Hz, 1H), 3.59 (s, 3H), 3.19 (s, 3H), 3.00 (br s, 1H), 2.63–2.49 (m, 2H), 2.37–2.23 (m, 2H), 2.00–1.94 (m, 2H), 0.95 (s, 9H), 0.89 (s, 9H), 0.10 (s, 6H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.6, 139.1 (2C), 135.0, 128.7, 127.1, 126.9, 126.1, 117.4, 73.0, 62.9, 61.3, 46.3, 40.8, 32.5, 29.9, 29.0, 26.2 (3C), 26.2 (3C), 18.6, 18.3, –3.9, –4.2, –5.0 (2C); IR

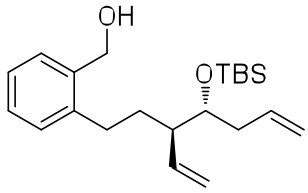
(film) ν_{max} 2928, 2856, 1663, 1471, 1384, 1254, 1078, 837, 775 cm^{-1}; HRMS (ESI) *m/z* 558.3417 (MNa^+, $C_{29}H_{53}NO_4Si_2Na$ requires 558.3405).



***anti*-4-(*tert*-Butyldimethylsilyloxy)-3-(2-((*tert*-butyldimethylsilyloxy)methyl) phenethyl)-1,6-heptadiene (46).** To a solution of Weinreb amide **45** (131 mg, 0.24 mmol) in anhydrous THF (1.3 mL) at –78 °C under Ar was added DIBAL (1.0 M in THF, 1.22 mL, 1.22 mmol) dropwise, and the resulting solution was stirred at –78 °C under Ar for 6 h, then poured into a stirred solution of sat aq potassium sodium tartrate (5.0 mL). The quenched mixture was stirred vigorously at rt for 2.5 h, then diluted with H_2O (2.0 mL) and extracted with CH_2Cl_2 (4 × 4 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude aldehyde, which was combined with another portion of the identical aldehyde (43 mg, 0.09 mmol).

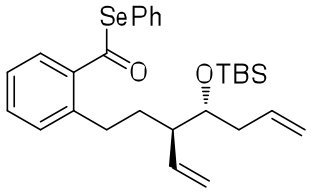
To a suspension of methyltriphenylphosphonium bromide (523 mg, 1.55 mmol) in anhydrous THF (1.4 mL) under Ar was added *n*-BuLi (1.4 M in hexanes, 1.0 mL, 1.4 mmol) dropwise. The red solution was stirred at rt for 10 min, cooled to –78 °C, and then added dropwise via syringe to a solution of the aldehyde (149 mg) in anhydrous THF (1.0 mL) at –78 °C. The resulting solution was allowed to warm to rt and stir under Ar for 18 h, then poured into sat aq NH_4Cl (5 mL). The mixture was extracted with EtOAc (4 × 3 mL), and the combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, 2.5 × 20 cm, 2% Et_2O in hexanes elution) to afford diene **46** (91 mg, 0.19 mmol, 59%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.45–7.43 (t, J = 4.5 Hz,

1H), 7.21–7.18 (m, 2H), 7.16–7.14 (m, 1H), 5.85–5.70 (m, 2H), 5.17 (dd, J = 2.0, 10.0 Hz, 1H), 5.11–5.00 (m, 3H), 4.73 (s, 2H), 3.64 (q, J = 5.5 Hz, 1H), 2.69–2.63 (m, 1H), 2.45–2.38 (m, 1H), 2.29–2.18 (m, 3H), 1.88–1.81 (m, 1H), 1.51–1.43 (m, 1H), 0.96 (s, 9H), 0.89 (s, 9H), 0.11 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.0, 139.9, 138.9, 135.5, 128.9, 127.2, 127.1, 126.0, 117.1, 116.8, 75.3, 63.0, 49.6, 39.2, 30.5, 30.2, 26.2 (3C), 26.2 (3C), 18.7, 18.4, –3.9, –4.2, –5.0 (2C); IR (film) ν_{max} 3072, 2954, 2928, 2856, 1471, 1462, 1434, 1254, 1072, 1004, 913, 836, 774 cm^{-1}; HRMS (ESI) *m/z* 492.3708 (MNH_4^+, $C_{28}H_{50}O_2Si_2NH_4$ requires 492.3687).



(2-(*anti*-4-(*tert*-Butyldimethylsilyloxy)-3-vinylhept-6-enyl)phenyl)methanol (47) To a solution of **46** (87 mg, 0.18 mmol) in CH_2Cl_2 (1.9 mL) at 0 °C under Ar was added a solution of (1*S*)-(+)-(10)-camphorsulfonic acid (9.3 mg, 0.04 mmol) in MeOH (1.9 mL). The mixture was stirred at 0 °C under Ar for 1 h and 40 min, then poured into sat aq $NaHCO_3$ (3 mL) and diluted with CH_2Cl_2 and H_2O (1 mL each). The organic phase was collected and the aqueous phase extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo, then purified by flash chromatography (SiO_2, 1.5 × 16.5 cm, 7% EtOAc in hexanes elution) to afford benzyl alcohol **47** (57 mg, 0.16 mmol, 87%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39–7.37 (m, 1H), 7.27–7.19 (m, 3H), 5.85–5.69 (m, 2H), 5.16 (dd, J = 2.0, 10.0 Hz, 1H), 5.10–5.00 (m, 3H), 4.74–4.69 (m, 2H), 3.64 (q, J = 5.5 Hz, 1H), 2.77–2.71 (m, 1H), 2.53–2.47 (m, 1H), 2.29–2.18 (m, 3H), 1.92–1.85(m, 1H), 1.53–1.45 (m, 2H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.0, 140.0, 138.5, 135.4, 129.6,

128.4, 128.2, 126.4, 117.1, 116.9, 75.2, 63.3, 49.5, 39.3, 31.1, 30.4, 26.2 (3C), 18.4, –3.9, –4.2; IR (film) ν_{max} 3327(br), 3074, 2954, 2928, 2856, 1639, 1471, 1462, 1255, 1065, 1004, 913, 836, 774 cm^{-1}; HRMS (ESI) *m/z* 383.2357 (MNa^+, $C_{22}H_{36}O_2SiNa$ requires 383.2376).

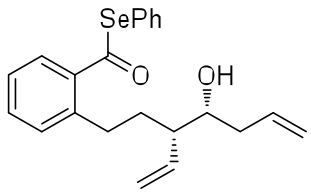


***Se*-Phenyl 2-(*anti*-4-(*tert*-butyldimethylsilyloxy)-3-vinylhept-6-enyl)benzoselenoate (48).** To a solution of oxalyl chloride (51 μL, 74 mg, 0.58 mmol) in anhydrous CH_2Cl_2 (1.0 mL) at –78 °C under Ar was added a solution of DMSO (80 μL, 88 mg, 1.13 mmol) in anhydrous CH_2Cl_2 (0.6 mL) dropwise. The resultant solution was stirred at –78 °C under Ar for 15 min, then treated with a solution of benzyl alcohol **47** (66 mg, 0.18 mmol) in anhydrous CH_2Cl_2 (0.5 mL + 2 × 0.5 mL rinses). The resulting solution stirred at –78 °C under Ar for 80 min. A solution of Et_3N (260 μL, 189 mg, 1.87 mmol) in anhydrous CH_2Cl_2 (0.6 mL) was then added, and stirring continued as the mixture warmed from –78 to 10 °C over 2.5 h. The reaction was then quenched with sat aq $NaHCO_3$ (3 mL). The organic phase was collected and the aqueous phase extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give the aldehyde (67 mg).

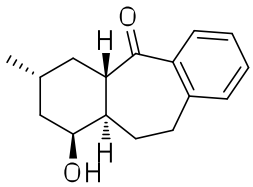
To a solution of the crude aldehyde in *t*-BuOH (2.0 mL) and H_2O (0.5 mL) was added successively 2-methyl-2-butene (0.24 mL, 156 mg, 2.23 mmol), NaH_2PO_4 (28 mg, 0.24 mmol), and NaOClO (102 mg, 1.13 mmol). The orange solution was stirred at rt under Ar for 13 h and 45 min, after which it had faded to a clear solution. It was then treated with sat aq NH_4Cl (3 mL)

and extracted with CH_2Cl_2 (4 × 3 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give the benzoic acid (71 mg).

To a solution of the crude acid in anhydrous CH_2Cl_2 (1.8 mL) under Ar was added PhSeSePh (1.0 M solution in CH_2Cl_2, 0.28 mL, 0.28 mmol) and Bu_3P (0.11 mL, 86 mg, 0.43 mmol) dropwise. The orange solution was stirred at rt under Ar for 5 h and 40 min, after which TLC analysis indicated incomplete conversion. Additional PhSeSePh (1.0 M solution in CH_2Cl_2, 0.15 mL, 0.15 mmol) and Bu_3P (75 μL, 62 mg, 0.30 mmol) were added, and the solution was stirred at rt under Ar for an additional 2.5 h, then treated with sat aq NH_4Cl (3 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 2.5 × 28 cm, 1% Et_2O in hexanes elution) afforded phenyl selenoester **48** (74.4 mg, 0.147 mmol, 80%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.61–7.59 (m, 2H), 7.46–7.43 (m, 4H), 7.32 (dt, *J* = 1.0, 7.5 Hz, 1H), 7.28–7.26 (m, 1H), 5.80–5.68 (m, 2H), 5.11 (dd, *J* = 2.0, 10.0 Hz, 1H), 5.06–4.96 (m, 3H), 3.61 (q, *J* = 5.5 Hz, 1H), 2.89–2.83 (m, 1H), 2.69–2.63 (m, 1H), 2.25–2.14 (m, 3H), 1.86–1.80 (m, 1H), 1.56–1.48 (m, 1H), 0.87 (s, 9H), 0.02 (s, 3H), –0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.6, 141.0, 139.8, 139.0, 136.2 (2C), 135.7, 132.1, 131.2, 129.6 (2C), 129.1, 128.7, 127.5, 126.2, 117.0, 116.7, 75.4, 49.2, 39.0, 31.6, 31.2, 26.2 (3C), 18.4, –4.0, –4.2; IR (film) ν_{max} 3073, 2953, 2927, 2855, 1703, 1639, 1570, 1476, 1438, 1254, 1183, 1065, 912, 835, 736 cm^{-1}; HRMS (ESI) *m/z* 532.2192 (MNH_4^+, $C_{28}H_{38}O_2SeSiNH_4$ requires 532.2144).

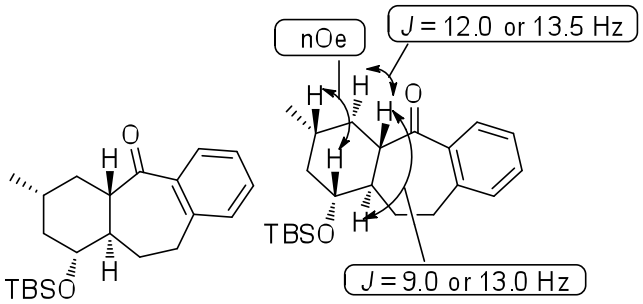


***Se*-Phenyl 2-(*syn*-4-hydroxy-3-vinylhept-6-enyl)benzoselenoate (49).** A solution of **38** (10 mg, 0.019 mmol) in anhydrous CH_2Cl_2 (0.4 mL) at 0 °C under Ar was treated with a solution of (1*S*)-(+)-(10)-camphorsulfonic acid (9 mg, 0.039 mmol) in CH_3OH (0.4 mL). The resulting mixture was allowed to warm to rt and stir under Ar for 12 h. It was then poured into sat aq $NaHCO_3$ (0.3 mL), diluted with CH_2Cl_2 and H_2O (ca. 0.1 mL each), and extracted with CH_2Cl_2 (4 × 1 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 7% EtOAc in hexanes elution) gave **49** (6.5 mg, 0.016 mmol, 84%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.61–7.59 (m, 2H), 7.47–7.43 (m, 4H), 7.33 (dt, *J* = 1.0, 7.5 Hz, 1H), 7.28 (d, *J* = 7.0 Hz, 1H), 5.86–5.70 (m, 2H), 5.23 (dd, *J* = 2.0, 10.5 Hz, 1H), 5.15–5.08 (m, 3H), 3.60–3.57 (m, 1H), 2.85–2.72 (m, 2H), 2.31–2.26 (m, 1H), 2.19–2.09 (m, 2H), 1.86–1.79 (m, 1H), 1.68–1.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.0, 140.8, 138.9, 138.4, 136.3 (2C), 135.4, 132.3, 131.3, 129.7 (2C), 129.3, 128.9, 127.4, 126.4, 118.5, 117.9, 72.6, 49.8, 39.6, 33.2, 31.7; IR(film) ν_{max} 3444, 2925, 1700, 1639, 1477, 1438, 1184, 885, 738 cm^{-1}; HRMS (ESI) *m/z* 401.1017 (MH^+, $C_{22}H_{24}O_2SeH$ requires 401.1014).



Tricycle 50. Phenyl selenoester **49** (7.5 mg, 0.019 mmol) was dried azeotropically with anhydrous benzene (2 × 2.0 mL) then dissolved in anhydrous benzene (6.4 mL) in a 3-necked round-bottom flask under an atmosphere of dry air. $(TMS)_3SiH$ (18.2 μL, 0.0591 mmol) and Et_3B (1.0 M in hexane, 54 μL, 0.054 mmol) were added to the mixture, and additional Et_3B (1.0 M in hexane, 536 μL, 0.536 mmol) was then added slowly by syringe pump over 4 h while a

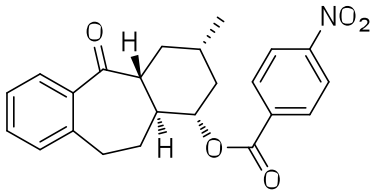
continuous flow of compressed air was passed over the reaction. TLC analysis indicated incomplete conversion, so additional $(TMS)_3SiH$ (54 uL, 0.0591 mmol) was added, and another portion of Et_3B (1.0 M in hexane, 536 μL, 0.536 mmol) was added by syringe pump over 40 min while a constant supply at air was still passed over the reaction. Following the addition the reaction was stirred for an additional 3h, then concentrated in vacuo. Flash chromatography (SiO_2, 1.5% ether in hexanes elution) afforded **50** (3.8 mg, 0.016 mmol, 82%) as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.33 (dt, *J* = 1.0, 7.0 Hz, 1H), 7.27–7.23 (m, 2H), 7.19–7.14 (m, 1H), 4.12 (br s, 1H), 2.84–2.74 (m, 3H), 2.54–2.45 (m, 2H), 2.10–2.04 (m, 1H), 1.94–1.89 (m, 1H), 1.76–1.63 (m, 3H), 1.45–1.39 (m, 1H), 1.26 (br s, 1H), 0.93 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125MHz) δ 211.8, 142.8, 137.8, 130.0, 129.8, 126.4, 123.7, 75.8, 50.7, 48.7, 42.7, 40.8, 34.8, 32.6, 30.6, 15.9; IR (film) ν_{max} 3445 (br), 2924, 1693, 1456, 1286, 1266, 1101, 1023, 758 cm^{-1}; HRMS (ESI) *m/z* 245.1538 (MH^+, $C_{16}H_{20}O_2H$ requires 245.1536).



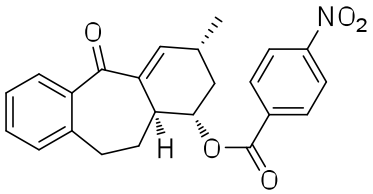
Tricycle 51. Phenyl selenoester **48** (5.0 mg, 0.0097 mmol) was dried azeotropically with anhydrous benzene (2 × 2.0 mL), then dissolved in anhydrous benzene (2.0 mL) in a 3-necked round-bottom flask under an atmosphere of dry air. $(TMS)_3SiH$ (6.0 μL, 0.0195 mmol) and Et_3B (1.0 M in hexane, 18 μL, 0.018 mmol) were added to the mixture, and additional Et_3B (1.0 M in hexane, 177 μL, 0.177 mmol) was then added slowly by syringe pump over 1.5 h while a continuous flow of compressed air was passed over the reaction. The mixture was stirred

vigorously throughout the addition time. TLC analysis indicated incomplete conversion, so additional $(TMS)_3SiH$ (6.0 uL, 0.0195 mmol) was added, and another portion of Et_3B (1.0 M in hexane, 177 μL, 0.177 mmol) was added by syringe pump over 15 min while the reaction was still stirring vigorously under air. Following the addition, the reaction was stirred for an additional 3 h, then concentrated in vacuo. Flash chromatography (SiO_2, 1.5% ether in hexanes elution) afforded **51** (2.8 mg, 0.0079 mmol, 81%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 (dt, *J* = 1.5, 7.5 Hz, 1H), 7.23 (dt, *J* = 1.0, 7.5 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 3.59 (dt, *J* = 6.0, 8.5 Hz, 1H), 2.79–2.74 (m, 2H), 2.69 (ddd, *J* = 3.0, 9.5, 14.0 Hz, 1H), 2.57 (dd, *J* = 12.0, 13.5 Hz, 1H), 2.15 (tdd, *J* = 3.5, 9.0, 13.0 Hz, 1H), 2.09–2.02 (m, 1H), 1.90–1.85 (m, 1H), 1.84–1.79 (m, 1H), 1.59–1.53 (m, 1H), 1.34–1.24 (m, 2H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.0, 142.6, 138.1, 129.9, 129.6, 126.3, 123.5, 70.2, 54.5, 49.0, 42.1, 40.6, 34.1, 33.6, 32.9, 26.1 (3C), 18.2, 16.1, –4.5, –4.2; IR (film) ν_{max} 3348(br), 2954, 2926, 2855, 1700, 1598, 1471, 1360, 1287, 1125, 1090, 868, 775 cm^{-1}; HRMS (ESI) *m/z* 381.2216 (MNa^+, $C_{22}H_{34}O_2SiNa$ requires 381.2220).

2D ^{1}H–^{1}H COSY NMR ($CDCl_3$, 500 MHz) 3.59/1.84–1.79 (m, H-11/H-12), 3.59/1.59–1.53 (w, H-11/H-9), 3.59/1.34–1.24 (m, H-11/H-12), 2.79–2.74/2.57 (s, H-15/H-14$_{ax}$), 2.79–2.74/2.15 (s, H-15/H-10), 2.79–2.74/1.90–1.85 (w, H-15/H-14$_{eq}$), 2.79–2.74/1.34–1.24 (w, H-8/H-9), 2.69/1.34–1.24 (m, H-8/H-9), 2.57/1.90–1.85 (s, H-14$_{ax}$/H-14$_{eq}$), 2.15/1.34–1.24 (m, H-10/H-9), 2.09–2.02/1.90–1.85 (w, H-13/H-14$_{eq}$), 2.09–2.02/1.84–1.79 (w, H-13/H-12), 2.09–2.02/1.34–1.24 (m, H-13/H-12), 2.09–2.02/0.94 (s, H-13/H-16), 1.84–1.79/1.34–1.24 (s, H-12/H-12), 1.59–1.53/1.34–1.24 (m, H-9/H-9); 1D nOe NMR ($CDCl_3$, 500 MHz) Irradiation of the signal at 2.09–2.02 led to an enhancement in the signal at 3.59 (H-13/H-11).

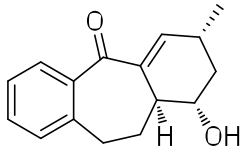


(1S, 3S, 4aR, 11aS)-3-methyl-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1H-dibenzo[a,d][7]annulen-1-yl 4-nitrobenzoate (61) To a stirred solution of alcohol **50** (3.8 mg, 0.0156 mmol) in THF (0.35 mL) at 0°C under Ar was added PPh_3 (16.4 mg, 0.0625 mmol) followed by 4-nitrobenzoic acid (10.7 mg, 0.0640 mmol). Then, DEAD (10 μL, 0.0656 mmol) was added dropwise. The resultant mixture was stirred at –5 °C under Ar for 5 h. The reaction was quenched by the addition of 1 N HCl (0.17 mL). The mixture was extracted with Et_2O (3 × 1 mL), and the combined organic layers were washed with brine (0.3 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 20% EtOAc in hexanes elution) afforded **61** (5.3mg, 0.0135 mmol, 86%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (d, J = 9 Hz, 2H), 8.19 (d, J = 9 Hz, 2H), 5.01 (q, J = 6 Hz, 1H), 2.95–2.67 (m, 4H), 2.33–2.16 (m, 4H), 2.11–2.04 (m, 2H), 1.62–1.53 (m, 1H), 1.07 (d, J = 7.2 Hz, 3H); HRMS (ESI) *m/z* 411.19134 (MNH_4^+, $C_{23}H_{23}NO_5NH_4^+$ requires 411.19145).



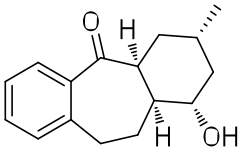
(1S**,3R,11aS)-3-methyl-5-oxo-2,3,5,10,11,11a-hexahydro-1H-dibenzo[a,d][7]annulen-1-yl 4-nitrobenzoate (64)** A solution of **61** (6 mg, 0.0153 mmol) in THF (0.2 mL) was added dropwise to freshly prepared solution of LDA (0.23 M, 0.82 mL, 0.189 mmol) at -78 °C under

Ar. The resultant mixture was stirred at –78 °C under Ar for 1 h. A precooled solution of PhSeSePh (9.5 mg, 0.0304 mmol) in dry THF (2 × 0.1 mL) was added. The resultant mixture was stirred at –78 °C under Ar for 1 h. Then, it was warmed to –20 °C and stirred for another 1 h till Starting material was all consumed. The reaction was quenched by the addition of saturated NH_4Cl (0.2 mL). The mixture was extracted with EtOAc (3 × 1.2 mL), and the combined organic layers were washed with brine (0.4 mL), dried (Na_2SO_4), and concentrated in vacuo. H_2O_2 (30%, 0.2 mL) was added to the crude product in THF (0.4 mL) at 0 °C. The resultant mixture was stirred at rt for 12 h. The reaction was quenched by the addition of brine (0.4 mL). The mixture was extracted with EtOAc (3 × 1 mL), and the combined organic layers were washed with brine (1 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 10% EtOAc in hexanes elution) afforded **64 (**3.7 mg, 0.00945 mmol, 63%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.24 (d, *J* = 7 Hz, 2H), 8.07 (d, *J* = 7 Hz, 2H), 7.65–7.06 (m, 4H), 5.26 (br s, 1H), 3.03–3.05 (m, 1H), 2.81 (t, *J* = 7.5 Hz, 2H), 2.55–2.50 (m, 1H), 2.20–2.16 (m, 1H), 1.76–1.47 (m, 2H), 1.38–1.26 (m, 2H), 1.21–1.19 (d, *J* = 8 Hz, 3H); HRMS (ESI) *m/z* 414.12955 (MNa^+, $C_{23}H_{21}NO_5Na^+$ requires 414.13119).

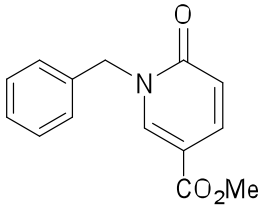


1S,3R,11aS)-1-hydroxy-3-methyl-2,3,11,11a-tetrahydro-1H-dibenzo[a,d][7]annulen-5(10H)-one (65) A solution of **64** (5 mg, 0.0128 mmol) in MeOH (20 mL) at rt was treated with KCN (0.416 mg, 0.00639 mmol). The resultant mixture was stirred at rt for 5 h. The solvent was removed in vacuo. The crude mixture was washed with brine (0.5 mL), and extracted with

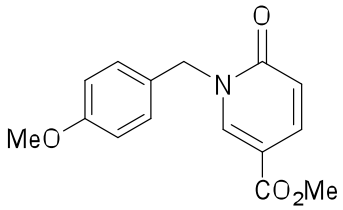
EtOAc (3 × 1 mL). The combined organic layers were washed with brine (0.5 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 35% EtOAc in hexanes elution) afforded **65** (2.9 mg, 0.0118 mmol, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44–7.18 (m, 4H), 5.35 (br s, 1H), 2.98–2.97 (m, 1H), 2.83–2.81 (t, *J* = 7 Hz, 2H), 2.63–2.60 (m, 1H), 2.25–2.18 (m, 1H), 1.72–1.56 (m, 2H), 1.50–1.37 (m, 2H), 1.34 (d, *J* = 7 Hz, 3H); HRMS (ESI) *m/z* 243.13786 (MH^+, $C_{16}H_{18}O_2H^+$ requires 243.13796).



(1S,3S,4aS,11aS)-1-hydroxy-3-methyl-2,3,4,4a,11,11a-hexahydro-1H-dibenzo[a,d][7]annulen-5(10H)-one (66) A solution of alcohol **65** (1 mg, 0.00413 mmol) in anhydrous THF (1 mL) was added a trace amount of Crabtree catalyst . Then, put the reaction vial in a hydrogenator, which was pressure-flushed with hydrogen for three times and pressurized to 1000 Psi. The resultant mixture was stirred at rt for 2 days. The catalyst was removed by filtration. The residue was purified by flash chromatography (SiO_2, 35% EtOAc in hexanes elution) to afford **66** (0.96 mg, 0.00392 mmol, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61–7.15 (m, 4H), 3.27–3.29 (m, 1H), 3.14 (t, *J* = 7 Hz, 2H), 2.94–2.86 (m, 1H), 2.36–2.32 (m, 1H), 1.98–1.96 (m, 1H), 1.83–1.78 (m, 3H), 1.68–1.65 (m, 1H), 1.25–1.21 (m, 2H), 1.23 (d, *J* = 7.6 Hz, 3H); HRMS (ESI) *m/z* 245.15291 (MH^+, $C_{16}H_{20}O_2H^+$ requires 245.15361).

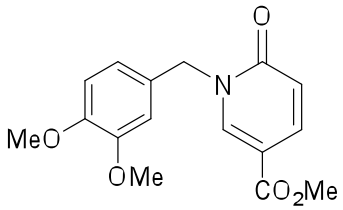


Methyl 1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxylate (67) To a solution of methyl pyruvate (17.5 μL, 19.4 mg, 0.190 mmol) and methyl propiolate (32.0 μL, 32.2 mg, 0.383 mmol) in MeOH (0.6 mL) was added benzylamine (41.5 μL, 40.7 mg, 0.380 mmol). The reaction vessel was sealed, and the mixture was heated at 120 °C for 2 d. After cooling to rt, the mixture was concentrated in vacuo. Flash chromatography (SiO_2, 25% EtOAc in hexanes elution) afforded **67** (33.9 mg, 0.139 mmol, 73%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (d, *J* = 3.0 Hz, 1H), 7.84 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.38–7.32 (m, 5H), 6.58 (d, *J* = 9.5 Hz, 1H), 5.17 (s, 2H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.9, 162.7, 142.9, 138.7, 135.7, 129.3 (2C), 128.6, 128.4 (2C), 120.3, 110.2, 52.9, 52.3; IR (film) ν_{max} 2951, 1719, 1666, 1612, 1542, 1496, 1446, 1300, 1151 cm^{-1}; HRMS (ESI) *m/z* 266.07975 (MNa^+, $C_{14}H_{13}NO_3Na^+$ requires 266.07876).



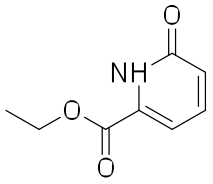
Methyl 1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (68) To a solution of methyl pyruvate (17.5 μL, 19.4 mg, 0.190 mmol) and methyl propiolate (31.8 μL, 31.9 mg,

0.380 mmol) in MeOH (0.6 mL) was added *p*-methoxybenzylamine (49.3 μL, 52.1 mg, 0.380 mmol). The reaction vessel was sealed, and the mixture was heated at 120 °C for 2 d. After cooling to rt, the mixture was concentrated in vacuo. Flash chromatography (SiO_2, 25% EtOAc in hexanes elution) afforded **68** (38.0 mg, 0.139 mmol, 73%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (d, *J* = 2.5 Hz, 1H), 7.81 (dd, *J* = 9.8, 2.8 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.56 (d, *J* = 9.5 Hz, 1H), 5.09 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.9, 162.7, 159.9, 142.7, 138.6, 130.1 (2C), 127.8, 120.2, 114.6 (2C), 110.1, 55.5, 52.5, 52.3; IR (film) ν_{max} 2953, 2838, 1716, 1612, 1544, 1515, 1396, 1297, 1114 cm^{-1}; HRMS (ESI) *m/z* 274.10674 (MH^+, $C_{15}H_{15}NO_4H^+$ requires 274.10738).



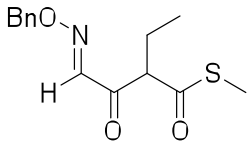
Methyl 1-(3,4-dimethoxybenzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (69) To a solution of methyl pyruvate (17.5 μL, 19.4 mg, 0.190 mmol) and methyl propiolate (31.8 μL, 31.9 mg, 0.380 mmol) in MeOH (0.6 mL) was added 3,4-dimethoxybenzylamine (56.4 μL, 63.5 mg, 0.380 mmol). The reaction vessel was sealed, and the mixture was heated at 120 °C for 2 d. After cooling to rt, the mixture was concentrated in vacuo. Flash chromatography (SiO_2, 25% EtOAc in hexanes elution) afforded **69** (45.4 mg, 0.150 mmol, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (d, *J* = 2.5 Hz, 1H), 7.83 (dd, *J* = 10.0, 2.5 Hz, 1H), 6.91–6.89 (m, 2H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.58 (d, *J* = 9.5 Hz, 1H), 5.10 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.9, 162.8, 149.6, 149.5, 142.6, 138.7, 128.2, 121.2, 120.2, 111.9, 111.5, 110.2, 56.22, 56.16, 52.7, 52.3; IR (film) ν_{max} 1718, 1667, 1517,

1446, 1301, 1263, 1239 cm^{-1}; HRMS (ESI) *m/z* 304.11635 (MH^+, $C_{16}H_{17}NO_5H^+$ requires 304.11795).

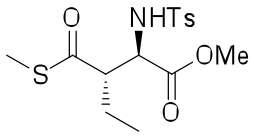


73

Ethyl 6-oxo-1,6-dihydropyridine-2-carboxylate (73) A mixture of ethyl pyruvate (21 μL, 22 mg, 0.19 mmol), 4 Å MS (66.2 mg), pyrrolidine (19.5 μL, 16.9 mg, 0.238 mmol) and anhydrous benzene (2.0 mL) was refluxed at 80 °C for 5 h. The mixture was allowed to cool to rt and was then filtered under Ar. The solution of crude enamine was placed in a sealable tube and treated with propiolamide[23] (33 mg, 0.48 mmol) followed by *p*-TsOH (36 mg, 0.21 mmol). The vessel was sealed, and the resulting mixture was stirred at 80 °C for 48 h, then at 110 °C for 12 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (SiO_2, 4% MeOH in EtOAc elution), affording **73** (22.5 mg, 0.135 mmol, 71%) as a white solid: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.73 (br s, 1H), 7.46 (dd, *J* = 9.2, 6.8 Hz, 1H), 6.98 (dd, *J* = 7.0, 1.0 Hz, 1H), 6.81 (dd, *J* = 9.5, 1.0 Hz, 1H), 4.42 (q, *J* = 7.0 Hz, 2H), 1.41 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.3, 160.1, 140.0, 133.9, 127.3, 109.4, 63.1, 14.4; IR (film) ν_{max} 2979, 1726, 1661, 1610, 1472, 1349, 1284, 1164, 1022 cm^{-1}; HRMS (ESI) *m/z* 190.04838 (MNa^+, $C_8H_9NO_3Na^+$ requires 190.04746).

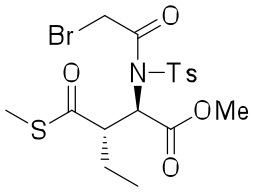


***S*-methyl 4-(benzyloxyimino)-2-ethyl-3-oxobutanethioate (82**) *n*-BuLi (1.6 M in hexane, 567 μL, 0.907 mmol) was added to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (198 μL, 153 mg, 0.950 mmol) in anhydrous THF (2.0 mL) at –5 °C under Ar. The resulting mixture was stirred at –5 °C for 30 min, cooled to –78 °C, and treated with a solution of *S*-methyl butanethioate (101 μL, 97.5 mg, 0.825 mmol) in anhydrous THF (590 μL). The mixture was then stirred at –78 °C for 30 min, treated with TMSCl (121 μL, 104 mg, 0.953 mmol), stirred at –78 °C for 1 h, allowed to warm to rt, and stirred at rt for 15 min. The solvent was removed in vacuo, the residue was suspended in hexane, and crude silyl ketene thioacetal was obtained by filtration. The crude silyl ketene thioacetal was then dissolved in anhydrous DMF (650 μL), and this solution was added to a stirred solution of LiOAc (3.9 mg, 0.059 mmol) in anhydrous DMF (880 μL) at rt under Ar. Next, a solution of methyl 2-(benzyloxyimino)acetate (**81,** 113.8 mg, 0.589 mmol) in anhydrous DMF (650 μL) was added to the mixture, and it was stirred at rt under Ar for 6 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (0.2 mL), and the mixture was extracted with EtOAc (3 × 1 mL). The combined organic layers were washed with brine (0.3 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 20% EtOAc in hexanes elution) afforded **82** (67.4 mg, 0.241 mmol, 41%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (s, 1H), 7.40–7.36 (m, 5H), 5.31 (s, 2H), 4.47 (t, J = 7.2 Hz, 1H), 2.28 (s, 3H), 1.99–1.92 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.5, 192.3, 147.6, 142.8, 136.2, 129.0 (2C), 128.8 (2C), 78.6, 63.0, 23.0, 19.5, 12.1; IR (film) ν_{max} 2968, 2932, 1748, 1705, 1678, 1583, 1367, 1340, 1269, 1181, 1009 cm^{-1}; HRMS (ESI) *m/z* 280.10158 (MH^+, $C_{14}H_{17}NO_3SH^+$ requires 280.10019). Additionally, an undetermined amount of β-lactam **83** (identified by HRMS) could be obtained contaminated with recovered **81**.



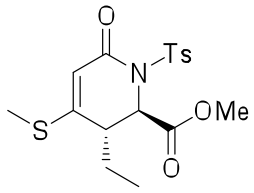
Methyl 2-(4-methylphenylsulfonamido)-3-(methylthiocarbonyl)pentanoate (85) *n*-BuLi (1.6 M in hexane, 690 μL, 1.1 mmol) was added to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (240 μL, 186 mg, 1.15 mmol) in anhydrous THF (4.3 mL) at –5 °C under Ar. The resulting mixture was stirred at –5 °C for 30 min, cooled to –78 °C, and treated with a solution of *S*-methyl butanethioate (120 μL, 118 mg, 0.998 mmol) in anhydrous THF (810 μL). The mixture was then stirred at –78 °C for 30 min, treated with TMSCl (146 μL, 125 mg, 1.15 mmol), stirred at –78 °C for 1 h, allowed to warm to rt, and stirred at rt for 15 min. The solvent was removed in vacuo, the residue was suspended in hexane, and crude silyl ketene thioacetal was obtained by filtration. The crude silyl ketene thioacetal was then dissolved in anhydrous DMF (1.0 mL), and this solution was added to a stirred solution of LiOAc (4.2 mg, 0.0643 mmol) in anhydrous DMF (0.84 mL) at rt under Ar. Next, a solution of methyl 2-(tosylimino)acetate (**84**, 156 mg, 0.647 mmol) in anhydrous DMF (1.0 mL) was added to the mixture, and the resulting mixture was stirred at rt under Ar for 6 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (0.2 mL), and the mixture was extracted with EtOAc (3 × 1 mL). The combined organic layers were washed with brine (0.3 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 20% EtOAc in hexanes elution) afforded **11** (193 mg, 0.537 mmol, 83%) as a white solid that was a 6:1 mixture of diastereomers favoring the *anti* isomer (data for major isomer): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 9.0 Hz, 2H), 5.56 (d, J = 11.0 Hz, 1H), 4.15 (dd, J = 10.2, 4.8 Hz, 1H), 3.46 (s, 3H), 3.00–

2.96 (m, 1H), 2.41 (s, 3H), 2.25 (s, 3H), 1.89–1.80 (m, 1H), 1.72–1.63 (m, 1H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.2, 170.7, 143.8, 137.4, 129.7 (2C), 127.5 (2C), 56.8, 56.5, 52.8, 23.0, 21.8, 12.0, 11.8; IR (film) ν_{max} 3279, 2966, 1744, 1674, 1598, 1435, 1385, 1165 cm^{-1}; HRMS (ESI) *m/z* 360.09427 (MH^+, $C_{15}H_{21}NO_5S_2H^+$ requires 360.09339).

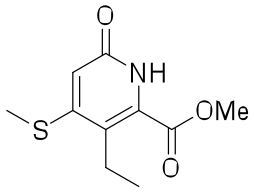


Methyl 2-(2-bromo-*N*-tosylacetamido)-3-(methylthiocarbonyl)pentanoate (88) A solution of **85** (100 mg, 0.278 mmol) in anhydrous THF (3.0 mL) at –78 °C under Ar was treated with *n*-BuLi (1.6 M in hexane, 180 μL, 0.289 mmol), stirred at –78 °C for 10 min and at rt for 5 min, then recooled to –78 °C. Bromoacetyl chloride (25.5 μL, 48.8 mg, 0.310 mmol) was added, and the resulting mixture was stirred at –78 °C under Ar for 30 min, warmed to rt, and stirred for 12 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (0.5 mL), and the mixture was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (0.5 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 8% EtOAc in hexanes elution) afforded **88** (106 mg, 0.221 mmol, 79%) as a colorless oil that was a 6:1 mixture of diastereomers favoring the *anti* isomer (data for major isomer): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 5.46 (d, J = 10.0 Hz, 1H), 4.56 (d, J = 13.0 Hz, 1H), 4.18 (d, J = 13.5 Hz, 1H), 3.56 (s, 3H), 3.54–3.51 (m, 1H), 2.49 (s, 3H), 2.39 (s, 3H), 1.60–1.54 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.9, 168.7, 166.5, 146.4, 135.2, 130.3 (2C), 128.8 (2C), 62.5, 53.7, 52.8, 29.2, 23.7, 22.0, 12.1, 11.8; IR

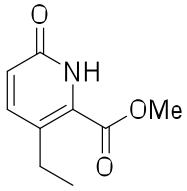
(film) ν_{max} 2958, 1747, 1682, 1596, 1436, 1369, 1023 cm^{-1}; HRMS (ESI) *m/z* 501.99658 (MNa^+, $C_{17}H_{22}NO_6BrS_2Na^+$ requires 501.99641).



Methyl 3-ethyl-4-(methylthio)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridine-2-carboxylate (89) A solution of **88** (28.1 mg, 0.0585 mmol) in anhydrous 1,2-dichloroethane (810 μL) at –20 °C under Ar was treated with $TiCl_4$ (1.0 M in CH_2Cl_2, 87 μL, 0.087 mmol) followed by a solution of PPh_3 (22 mg, 0.0839 mmol) in anhydrous CH_2Cl_2 (270 μL). The resultant mixture was stirred at –5 °C under Ar for 16 h. The reaction was quenched by the addition of H_2O (100 μL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 1 mL), and the combined organic layers were washed with brine (0.3 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 15% EtOAc in hexanes elution) afforded **89** (16.2 mg, 0.0422 mmol, 72%) as a colorless oil that was a 6:1 mixture of diastereomers favoring the *anti* isomer (data for major isomer): ^1H NMR ($CDCl_3$, 500 MHz) δ 7.94 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 5.46 (d, J = 2.5 Hz, 1H), 5.39 (d, J = 5.0 Hz, 1H), 3.59 (s, 3H), 3.17–3.13 (m, 1H), 2.43 (s, 3H), 2.24 (s, 3H), 2.14–2.09 (m, 1H), 1.69–1.63 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.6, 161.7, 161.0, 145.0, 135.8, 129.6 (2C), 129.3 (2C), 112.6, 58.5, 52.7, 45.2, 21.9, 21.1, 14.9, 12.4; IR (film) ν_{max} 2924, 2853, 1747, 1682, 1532, 1260, 1167, 1087 cm^{-1}; HRMS (ESI) *m/z* 406.07600 (MNa^+, $C_{17}H_{21}NO_5S_2Na^+$ requires 406.07534).

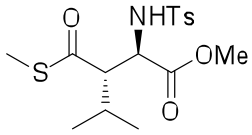


Methyl 3-ethyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-2-carboxylate (95) A solution of **89** (33 mg, 0.086 mmol) in DMF (3.0 mL) at rt was treated with DBU (193 μL, 197 mg, 1.29 mmol). The resulting mixture was stirred at rt for 6 h, treated with H_2O (0.5 mL) and sat. aq. NH_4Cl (0.5 mL), and extracted with EtOAc (3 × 1 mL). The combined organic layers were washed with brine (0.3 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 3% MeOH in CH_2Cl_2 elution) afforded **95** (19 mg, 0.084 mmol, 97%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.50 (br s, 1H), 6.41 (s, 1H), 3.97 (s, 3H), 2.93 (q, J = 7.3 Hz, 2H), 2.43 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.8, 160.0, 157.9, 128.3, 126.3, 117.2, 53.5, 21.3, 15.0, 14.2; IR (film) ν_{max} 2965, 2930, 1739, 1641, 1527, 1423, 1343, 1280, 1229, 1109, 1055, 927 cm^{-1}; HRMS (ESI) *m/z* 228.06996 (MH^+, $C_{10}H_{13}NO_3SH^+$ requires 228.06889).



Methyl 3-ethyl-6-oxo-1,6-dihydropyridine-2-carboxylate (94) To a vigorously stirred mixture of **95** (20.6 mg, 0.0906 mmol) and Lindlar catalyst (606.6 mg) in acetone (4.0 mL) at rt under Ar was added Et_3SiH (214.5 μL, 156 mg, 1.34 mmol) dropwise. The resulting mixture was stirred at rt for 4 h, filtered through a plug of Celite (washed with 7 × 3.5 mL acetone), and

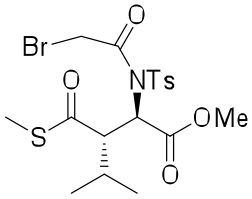
concentrated in vacuo. Flash chromatography (SiO_2, 4% MeOH in CH_2Cl_2 elution) afforded **94** (15.6 mg, 0.0861 mmol, 95%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.51 (br s, 1H), 7.34 (d, *J* = 9.0 Hz, 1H), 6.76 (d, *J* = 9.5 Hz, 1H), 3.97 (s, 3H), 2.84 (q, *J* = 7.5 Hz, 2H), 1.18 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.9, 161.4, 144.6, 128.9, 128.1, 127.3, 53.4, 25.0, 15.2; IR (film) ν_{max} 2968, 1736, 1662, 1605, 1437, 1324, 1282, 1234, 1099 cm^{-1}; HRMS (ESI) *m/z* 182.08252 (MH^+, $C_9H_{11}NO_3H^+$ requires 182.08117).



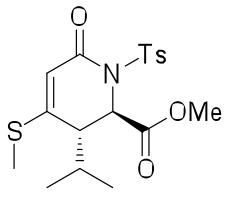
Methyl 4-methyl 2-(4-methylphenylsulfonamido)-3-(methylthiocarbonyl)pentanoate (96)

Following the procedure detailed for the synthesis of **85**, but using *n*-BuLi (1.6 M in hexane, 3.40 mL, 5.5 mmol), 1,1,1,3,3,3-hexamethyldisilazane (1.20 mL, 930 mg, 5.75 mmol), anhydrous THF (12 mL), *S*-methyl 3-methylbutanethioate (661.2 mg, 5.00 mmol), anhydrous THF (3.5 mL), TMSCl (750 μL, 625 mg, 5.75 mmol), anhydrous DMF (4.5 mL), LiOAc (66.0 mg, 1.00 mmol), **84** (1.207 g, 5.00 mmol), and anhydrous DMF (3.5 mL) afforded **96** (1.382 g, 3.70 mmol mmol, 74%) as a white solid that was a 1.6:1 mixture of diastereomers favoring the *anti* isomer. The isomers could be separated for characterization purposes. For *anti*-**96**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 5.42 (d, *J* = 9.0 Hz, 1H), 4.16 (dd, *J* = 8.8, 5.8 Hz, 1H), 3.48 (s, 3H), 2.71 (dd, *J* = 8.0, 6.0 Hz, 1H), 2.40 (s, 3H), 2.25 (s, 3H), 2.24–2.18 (m, 1H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.5, 170.5, 144.1, 136.7, 129.9 (2C), 127.6 (2C), 64.6, 55.5, 52.8, 28.0, 21.8, 21.1, 20.0, 12.2; IR (film) ν_{max} 3279, 2957, 1741, 1674, 1455, 1432, 1339, 1312, 1200, 1164, 1093 cm^{-1}; HRMS (ESI) *m/z* 374.10872 (MH^+, $C_{16}H_{23}NO_5S_2H^+$ requires 374.10904).

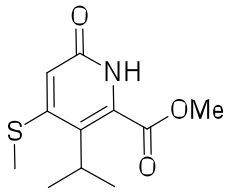
For *syn*-**96**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 7.5 Hz, 2H), 5.62 (d, *J* = 10.5 Hz, 1H), 4.27 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.40 (s, 3H), 2.64 (dd, *J* = 9.5, 4.0 Hz, 1H), 2.40 (s, 3H), 2.24 (s, 3H), 2.22–2.16 (m, 1H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.1, 170.5, 143.7, 137.5, 129.7 (2C), 127.4 (2C), 61.6, 55.9, 52.6, 28.1, 21.7, 20.9, 19.9, 12.1; IR (film) ν_{max} 3342, 2965, 1745, 1670, 1342, 1168, 1143, 1093 cm^{-1}; HRMS (ESI) *m/z* 374.10852 (MH^+, $C_{16}H_{23}NO_5S_2H^+$ requires 374.10904).



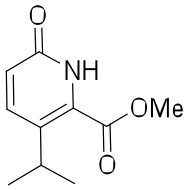
Methyl 2-(2-bromo-*N*-tosylacetamido)-4-methyl-3-(methylthiocarbonyl)pentanoate (19) Following the procedure detailed for the synthesis of **88**, but using **96** (448.2 mg, 1.20 mmol), anhydrous THF (3.0 mL), *n*-BuLi (1.6 M in hexane, 1.1 mL, 1.8 mmol), and bromoacetyl chloride (400 μL, 756 mg, 4.80 mmol) afforded **97** (304.8 mg, 0.616 mmol, 51%) as a colorless oil that was a 1.6:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz, data for major isomer) δ 7.97 (d, *J* = 7.0 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 5.34 (d, *J* = 7.0 Hz, 1H), 4.53 (d, *J* = 14.5 Hz, 1H), 4.06 (d, *J* = 13.5 Hz, 1H), 3.59 (s, 3H), 3.56–3.51 (m, 1H), 2.47 (s, 3H), 2.36 (s, 3H), 2.28–2.17 (m, 1H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 3H); HRMS (ESI) *m/z* 494.03259 (MH^+, $C_{18}H_{24}BrNO_6S_2H^+$ requires 494.03012).



Methyl 3-isopropyl-4-(methylthio)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridine-2-carboxylate (98) Following the procedure detailed for the synthesis of **89**, but using **97** (19.7 mg, 0.0398 mmol), anhydrous 1,2-dichloroethane (540 μL), $TiCl_4$ (1.0 M in CH_2Cl_2, 61 μL, 0.061 mmol), PPh_3 (16 mg, 0.061 mmol), and anhydrous CH_2Cl_2 (180 μL) afforded **98** (13 mg, 0.033 mmol, 82%) as a colorless oil that was a ca. 3:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 500 MHz, data for major isomer) δ 8.00 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 9.0 Hz, 2H), 5.43 (s, 1H), 5.41 (d, *J* = 2.0 Hz, 1H), 3.68 (s, 3H), 2.73 (dd, *J* = 7.0, 2.0 Hz, 1H), 2.44 (s, 3H), 2.28 (s, 3H), 2.07–2.00 (m, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz, data for major isomer) δ 170.6, 161.3, 160.2, 145.0, 132.4, 130.0 (2C), 129.1 (2C), 112.2, 58.8, 53.2, 49.7, 31.5, 21.9, 21.3, 20.3, 15.0; IR (film) ν_{max} 2961, 1749, 1683, 1352, 1167 cm^{-1}; HRMS (ESI) *m/z* 398.10827 (MH^+, $C_{18}H_{23}NO_5S_2H^+$ requires 398.10904).

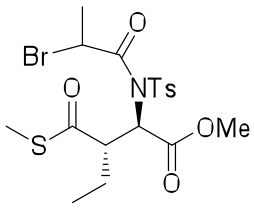


Methyl 3-isopropyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-2-carboxylate (99) Following the procedure detailed for the synthesis of **95**, but using **98** (26 mg, 0.065 mmol), DMF (2.2 mL), and DBU (147 μL, 149 mg, 0.981 mmol) afforded **99** (15.2 mg, 0.063 mmol, 96%) as a colorless film: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.80 (br s, 1H), 6.38 (s, 1H), 3.96 (s, 3H), 2.43 (s, 3H), 2.06–1.99 (m, 1H), 1.35 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.7, 173.0, 159.8, 139.0, 130.2, 116.4, 53.5, 28.2, 20.6 (2C), 15.7; IR (film) ν_{max} 2925, 1737, 1650, 1461 cm^{-1}; HRMS (ESI) *m/z* 242.08599 (MH^+, $C_{11}H_{15}NO_3SH^+$ requires 242.08454).



Methyl 3-isopropyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-2-carboxylate (100)

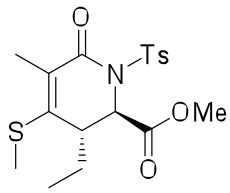
Following the procedure detailed for the synthesis of **94**, but using **99** (10 mg, 0.041 mmol), Lindlar catalyst (300 mg), acetone (2.0 mL), and Et_3SiH (98 μL, 71 mg, 0.61 mmol) afforded **100** (6.7 mg, 0.034 mmol, 83%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.28 (br s, 1H), 7.54 (d, J = 10.0 Hz, 1H), 6.80 (d, J = 9.5 Hz, 1H), 3.97 (s, 3H), 2.06–1.96 (m, 1H), 1.19 (d, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1, 159.4, 145.3, 131.2, 128.7, 127.2, 52.9, 27.2, 22.9 (2C); IR (film) ν_{max} 2973, 1696, 1668, 1378 cm^{-1}; HRMS (ESI) *m/z* 196.09627 (MH^+, $C_{10}H_{13}NO_3H^+$ requires 196.09682).



Methyl 2-(2-bromo-*N*-tosylpropanamido)-3-(methylthiocarbonyl)pentanoate (110)

Following the procedure detailed for the synthesis of **88**, but using **85** (584.5 mg, 1.63 mmol), anhydrous THF (8.0 mL), *n*-BuLi (1.6 M in hexane, 1.50 mL, 2.40 mmol), and 2-bromopropanoyl chloride (1.111 g, 6.50 mmol) afforded **110** (561 mg, 1.13 mmol, 70%) as a colorless oil that was a mixture of diastereomers at the bromo-bearing carbon: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 5.77–5.72 (m, 1H), 4.14–4.10 (m, 1H), 3.58 (s, 3H), 2.77–2.72 (m, 1H), 2.40 (s, 3H), 2.08 (s, 3H), 1.63–1.54 (m, 1H), 1.48–1.40

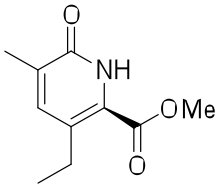
(m, 1H), 1.27–1.19 (m, 3H), 0.88–0.81 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.7, 175.7, 172.3, 143.3, 139.2, 129.6 (2C), 127.4 (2C), 60.6, 51.8, 50.4, 31.7, 23.7, 22.3, 21.7, 17.8, 14.0, 11.9; IR (film) ν_{max} 2960, 1738, 1435, 1336, 1161 cm^{-1}; HRMS (ESI) *m/z* 494.02870 (MH^+, $C_{18}H_{24}BrNO_6S_2H^+$ requires 494.03012).



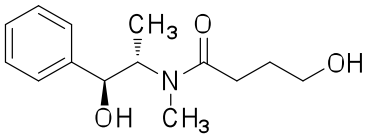
Methyl 3-ethyl-5-methyl-4-(methylthio)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridine-2-carboxylate (111) Following the procedure detailed for the synthesis of **89**, but using **110** (43 mg, 0.0870 mmol), anhydrous 1,2-dichloroethane (1.2 mL), $TiCl_4$ (1.0 M in CH_2Cl_2, 140 μL, 0.140 mmol), PPh_3 (34 mg, 0.13 mmol), and anhydrous CH_2Cl_2 (400 μL) afforded **111** (8.1 mg, 0.020 mmol, 24%) as a colorless film that was a ca. 1.1:1 mixture of diastereomers, and ketone **112** (18 mg, 0.049 mmol, 56%) as a colorless film. for **111**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 and 7.74 (2d, *J* = 8.5 Hz, 2H), 7.31–7.27 (m, 2H), 6.00 and 5.57 (2d, *J* = 9.0 and 10.0 Hz, 1H), 3.65 and 3.66 (2s, 3H), 2.98–2.94 and 2.86–2.82 (2m, 1H), 2.43 and 2.42 (2s, 3H), 2.18 (s, 3H), 1.73–1.64 and 1.85–1.79 (2m, 1H), 1.57 (s, 3H), 1.53–1.46 and 1.43–1.38 (2m, 1H), 0.92 and 0.99 (2t, *J* = 7.5 Hz, 3H); HRMS (ESI) *m/z* 398.10839 (MH^+, $C_{18}H_{23}NO_5S_2H^+$ requires 398.10904).

For **112**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 5.45 (s, 1H), 3.80 (s, 3H), 3.16 (q, *J* = 7.5 Hz, 1H), 2.73 (sextet, *J* = 7.3 Hz, 1H), 2.47–2.40 (m, 1H), 2.44 (s, 3H), 2.36 (sextet, *J* = 7.2 Hz, 1H), 1.38 (d, *J* = 7.0 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C

NMR ($CDCl_3$, 125 MHz) δ 170.9, 169.5, 145.4, 135.4, 132.9, 129.7 (2C), 129.4 (2C), 61.3, 53.3, 42.0, 25.2, 21.9, 18.5, 14.6, 12.5; IR (film) ν_{max} 2931, 1749, 1708, 1359, 1171, 1087 cm^{-1}; HRMS (ESI) *m/z* 368.11745 (MH^+, $C_{17}H_{21}NO_6SH^+$ requires 368.11623).

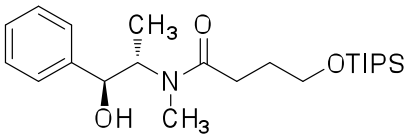


Methyl 3-ethyl-5-methyl-6-oxo-1,6-dihydropyridine-2-carboxylate (113) Following the procedure detailed for the synthesis of **95**, but using **111** (3.7 mg, 0.0093 mmol), DMF (1.1 mL), and DBU (71 μL, 72 mg, 0.47 mmol) afforded the vinyl sulfide intermediate, which was reduced according to the procedure detailed for the synthesis of **94**, but using Lindlar catalyst (230 mg), acetone (1.5 mL), and Et_3SiH (75 μL, 55 mg, 0.47 mmol), affording **113** (1.4 mg, 0.0072 mmol, 77%) as a white film: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.36 (br s, 1H), 7.20 (s, 1H), 3.95 (s, 3H), 2.82 (q, *J* = 7.5 Hz, 2H), 2.21 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); HRMS (ESI) *m/z* 218.06491 (MNa^+, $C_{10}H_{13}NO_3Na^+$ requires 218.07876).



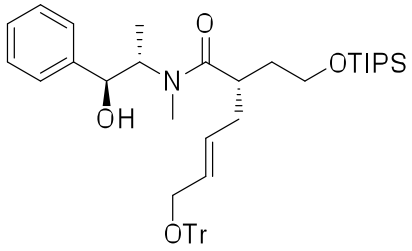
4-hydroxy-N-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N-methylbutanamide (158) A solution of *n*-BuLi (1.6 M in hexane, 227 mL, 363.108 mmol) was added to an ice-cooled suspension of LiCl (17.9575 g, 423.626 mmol) and (1S, 2S)-(+)-pseudoephedrine (20 g, 121.036 mmol) in THF (710 mL), and the suspension was stirred at 0 °C for 30 min. Then, methyl-4-hydroxy butanoate (crude, 121.036 mmol) was added to the suspension. The mixture was

warmed to rt and stirred at rt for overnight. The reaction was quenched by the addition of 0.5 N NaOH (460 mL). The solvent was removed in vacuo. The residue was extracted with 10% MeOH-CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 10% MeOH in CH_2Cl_2 elution) afforded **158** (23.7 g, 94.408 mmol, 54%) as a brown oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.12–6.99 (m, 5H), 4.79 (br s, 1H), 4.39 (br s, 1H), 4.29 (d, *J* = 8 Hz, 2H), 3.31–3.26 (m, 2H), 2.67 (q, *J* = 7 Hz, 1H), 2.61 and 2.59 (2s, 3H), 2.39–2.05 (m, 2H), 1.60–1.49 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 2H), 0.71–0.69 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.0 and 174.5, 142.4 and 142.2, 128.5 (2C) and 128.3 (2C), 128.0 and 127.6, 127.1 (2C) and 126.9 (2C), 75.4 and 74.9, 61.6 and 61.6, 58.4 and 46.4, 31.1 and 30.2, 28.1 and 27.8, 21.2 and 15.6, 14.37 and 9.6; IR (film) ν_{max} 3376, 2937, 1614, 1482, 1453, 1407, 1049; HRMS (ESI) *m/z* 274.14082 (MNa^+, $C_{14}H_{21}NO_3Na^+$ requires 274.14136).



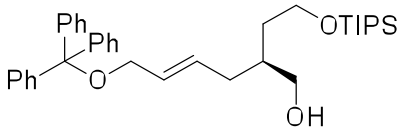
N-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N-methyl-4-((triisopropylsilyl)oxy)butanamide (190) A solution of **158** (9.5 g, 37.8 mmol) in anhydrous DMF (50 mL) at rt was treated with imidazole (6.4 g, 94.6 mmol). The resultant mixture was stirred at at rt for 36 h. The reaction was quenched by the addition of brine (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 5% MeOH in CH_2Cl_2 elution) afforded **190** (13.41 g, 32.87 mmol, 87%) as a yellow oil: ^{1}H NMR

($CDCl_3$, 500 MHz) δ 7.27–7.15 (m, 5H), 4.47–4.45 (m, 2H), 3.63–3.61 (m, 2H), 2.80–2.79 (m, 1H), 2.75 and 2.74 (2s, 3H), 2.48–2.38 (m, 1H), 2.32–2.29 (m, 1H), 1.78–1.69 (m, 2H), 1.04–0.86 (m, 24H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.4 and 174.0, 142.7 and 142.7, 128.3 (2C) and 128.1 (2C), 127.7(2C) and 127.3 (2C), 127.0 and 126.7, 75.6 and 75.1, 62.8 and 62.4, 58.3 and 56.2, 31.5 and 30.6, 30.2 and 30.0, 28.7 and 28.3, 18.1 (6C), 15.4 and 14.2, 12.0 (12C); IR (film) ν_{max} 3388, 2942, 2865, 1623, 1463, 1405, 1105, 1067; HRMS (ESI) *m/z* 430.27546 (MNa^+, $C_{23}H_{41}NO_3SiNa^+$ requires 430.27479).



(S,E)-N-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N-methyl-2-(2-((triisopropylsilyl)oxy)ethyl)-6-(trityloxy)hex-4-enamide (191) A solution of *n*-BuLi (1.6 M in hexane, 68 mL, 109.08 mmol) was added to a suspension of LiCl (flamed dried) (13.34 g, 314.64 mmol) and *i*-Pr_2NH (16.7 mL, 118 mmol) in THF (126 mL) at –78 °C under Ar. The suspension was stirred at –78 °C under Ar for 10 minutes. The resulting suspension was warmed to 0 °C briefly for 5 min and then it was cooled to –78 °C. An ice-cooled solution of **190** (21.35 g, 52.44 mmol) in THF (64 mL) was added. The mixture was stirred at –78 °C for 1 h, at 0 °C for 15 min, and at rt for 5 min. The mixture was cooled to 0 °C. The iodide (25.4 g, 57.69 mmol) was added to the reaction mixture. The resultant mixture was stirred at 0 °C under Ar for 18 h. The reaction was quenched by the addition of half-sat. NH_4Cl (35 mL) solution, extracted with

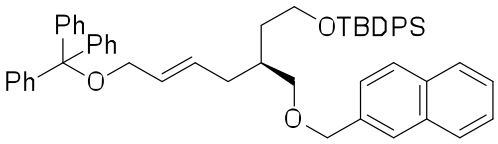
EtOAc (3 × 40 mL). Flash chromatography (SiO_2: 1% MeOH in CH_2Cl_2) provided **191** (18.36 g, 39.86 mmol, 76 %) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50–7.48 (m, 3H), 7.38–7.20 (m, 7H), 5.74–5.60 (m, 2H), 4.65–4.62 (m, 1H), 4.48 (br s, 1H), 3.81–3.77 (m, 2H), 3.69–3.65 (m, 1H), 3.60–3.52 (m, 2H), 3.13–3.09 (m, 1H), 2.97 and 2.95 (2s, 3H), 2.42–2.36 (m, 1H), 2.25–2.20 (m, 1H), 1.93–1.86 (m, 1H), 1.78–1.69 (m, 1H), 1.17–1.05 (m, 24H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.0 and 176.9, 144.6 (3C) and 144.5 (3C), 142.9 and 142.0, 131.1 and 129.6, 129.0 (2C), 128.9 (2C) and 128.8 (2C), 128.6 (4C), 128.5 (12C), 128.0 (12C), 127.7 and 126.6, 127.2 (6C), 76.4 and 75.7, 65.2 and 64.9, 61.2 and 61.1, 61.0 and 60.8, 38.6 and 37.5, 36.1 and 35.5, 35.7 and 31.9, 27.7 and 27.3, 18.4 (2C), 16.2 and 14.9, 14.7 (3C) and 14.5 (3C), 12.5 (6C) and 12.2 (6C); IR (film) ν_{max} 3388, 2942, 2865, 1623, 1463, 1405, 1366, 1105; HRMS (ESI) *m/z* 742.42604 (MNa^+, $C_{46}H_{61}NO_4SiNa^+$ requires 742.42621).



(S,E)-2-(2-((triisopropylsilyl)oxy)ethyl)-6-(trityloxy)hex-4-en-1-ol (192) To a flamed dried round bottom flask, THF (200 mL) was added under Ar. The flask was cooled to –78 °C. *i*-Pr_2NH (10.3 mL, 72.97 mmol) and *n*-BuLi (1.6 M in hexanes, 42 mL, 467.76 mmol) were added to the reaction flask respectively. The resultant reaction mixture was stirred at –78 °C for 10 min. Then, it was stirred at 0 °C for 5 min and cooled to –78 °C. Borane-ammonia complex (90%, 2.38 g, 69.50 mmol) was added to the reaction mixture in one portion. The reaction mixture was warmed to 0 °C, and stirred at 0 °C for 20 min. Then, it was warmed to rt, and stirred at rt for 20 min. The resultant reaction mixture was cooled to 0 °C. A solution of **191** (12.5 g, 17.37 mmol)

in THF (127 mL) was added to the reaction mixture dropwise. The reaction was stirred at rt for 50 min. Then it was cooled to 0 °C, and quenched with sat. NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 20% EtOAc in hexanes elution) afforded **192** (8.83 g, 15.81 mmol, 93%) as a colorless oil:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55 (d, *J* = 7 Hz, 6H), 7.36 (t, *J* = 7.5 Hz, 6 H), 7.28 (t, *J* = 7 Hz, 3H), 5.84–5.78 (m, 1H), 5.74–5.69 (m, 1H), 3.97–3.93 (m, 1H), 3.86–3.81 (m, 1H), 3.75–3.69 (m, 1H), 3.66 (d, *J* = 5.5 Hz, 2H), 3.60–3.56 (m, 1H), 3.49 (br s, 1H), 2.63–2.21 (m, 1H), 2.17–2.09 (m, 1H), 1.88–1.84 (m, 1H), 1.82–1.76 (m, 1H), 1.69–1.63 (m, 1H), 1.18–1.16 (m, 21H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.6, 130.8, 129.0 (6C), 128.1 (6C), 127.2 (3C), 87.1, 66.2, 65.2, 62.5, 39.9, 35.6, 35.3, 18.4, 18.3 (6C), 12.2 (3C); IR (film) ν_{max} 3415, 2941, 2865, 1490, 1448, 1381, 1098, 1055; HRMS (ESI) *m/z* 576.38523 (MNH_4^+, $C_{36}H_{50}O_3SiNa^+$ requires 576.38675).



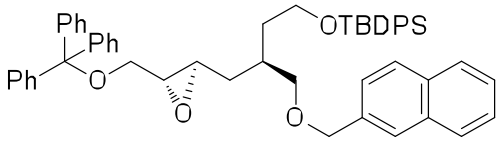
(S,E)-tert-butyl((3-((naphthalen-2-ylmethoxy)methyl)-7-(trityloxy)hept-5-en-1-yl)oxy)diphenylsilane (184) A solution of **192** (500 mg, 0.895 mmol) in anhydrous DMF/THF (1:1) (20 mL) at 0 °C under Ar was treated with NaH (60%, 72 mg, 1.79 mmol) followed by NAPBr (297 mg, 1.34 mmol). The resultant mixture was stirred at 0 °C under Ar for 12 h. The reaction was quenched by the addition of sat. NH_4Cl (6 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine (5 mL), dried

(Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 2% EtOAc in hexanes elution) afforded triether product (557 mg, 0.797 mmol, 89%) as as a colorless oil.

A solution of the obtained triether (557 mg, 0.797 mmol) in anhydrous THF (15 mL) at 0 °C under Ar was treated with TBAF (1.0 M in THF, 1.8 mL, 1.79 mmol). The resultant mixture was warmed to rt and stirred at rt under Ar for 8 h. The reaction was quenched by the addition of sat. NH_4Cl (4 mL). The aqueous layer was extracted with EtOAc (3 × 8 mL), and the combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 35% EtOAc in hexanes elution) afforded alcohol (411 mg, 0.757 mmol, 95%) as a colorless oil.

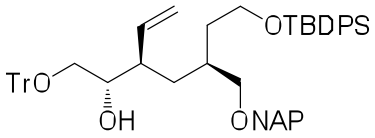
A solution of the obtained alcohol (411 mg, 0.757 mmol) in anhydrous 1,2-dichloroethane (6 mL)) at 0 °C under Ar was treated with Et_3N (0.15 mL, 0.109 g, 1.074 mmol, DMAP (22 mg, 0.179 mmol), and TBDPS-Cl (0.26 mL, 0.275 g, 0.984 mmol). The resultant mixture was stirred at rt under Ar for 24 h. The reaction was quenched by the addition of sat. NH_4Cl (3 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with brine (4 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 2% EtOAc in hexanes elution) afforded **184** (411.8 mg, 0.527 mmol, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85–7.76 (m, 4H), 7.67–7.65 (m, 4H), 7.48–7.21 (m, 24H), 5.71–5.66 (m, 1H), 5.64–5.59 (m, 1H), 4.64 (s, 2H), 3.76 (dt, *J* = 1 Hz, 6.8 Hz, 2H), 3.54 (d, *J* = 5Hz, 2H), 3.45–3.38 (m, 2H), 2.27–2.23 (m, 1H), 2.18–2.14 (m, 1H), 2.02–1.98 (m, 1H), 1.71–1.63 (m, 2H), 1.07 (s, 9H); 144.5 (3C), 136.3, 135.7 (2C), 134.1, 133.4, 133.0, 130.6, 130.4, 129.7 (2C), 128.8 (4C), 128.7, 128.2, 128.2, 128.0, 127.9 (4C), 127.8, 127.7 (6C), 127.0 (6C), 126.3, 126.1, 125.8 (3C), 73.2, 73.0, 65.1, 62.2, 60.5, 35.5, 34.6, 34.1, 27.0 (3C), 19.3; IR (film)

ν_{max} 3055, 2929, 2856, 1489, 1448, 1428, 1372, 1265, 1110; HRMS (ESI) *m/z* 798.43376 (MNH_4^+, $C_{54}H_{56}O_3SiNa^+$ requires 798.43370).



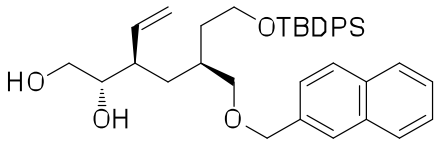
tert-butyl((R)-4-(naphthalen-2-ylmethoxy)-3-(((2R,3R)-3-((trityloxy)methyl)oxiran-2-yl)methyl)butoxy)diphenylsilane (185) The alkene **184** (0.1286 g, 0.2006 mmol) was dissolved in DMM/CH_3CN (2:1, 1.86 mL). Then, the K_2CO_3-CH_3COOH (1.12 mL) buffer solution, Bu_4NHSO_4 (1.5 mg, 0.0044 mmol), chiral ketone (52 mg, 0.2006 mmol) were added respectively. A solution of oxone (0.1612 g, 0.3009 mmol) in aqueous 4×10^{-4} Na_2EDTA solution (0.62 mL) and 1.47 M KOH aqueous solution (0.62 mL) were added slowly at the same rate. The resulting suspension was stirred at rt for 5 hr. Added chiral ketone (52 mg, 0.2006 mmol) once more. Then A solution of oxone (0.1612 g, 0.3009 mmol) in aqueous 4×10^{-4} Na_2EDTA solution (0.62 mL) and 1.47 M KOH aqueous solution (0.62 mL) were added slowly at the same rate again. The resultant suspension was stirred at rt for 4 h. The solution was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with brine (3 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1% EtOAc in hexanes elution) afforded **185** (115 mg, 0.144 mmol, 72%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.83–7.71 (m, 4H), 7.65–7.62 (m, 4H), 7.48–7.44 (m, 8H), 7.41–7.21 (m, 16H), 4.60 (s, 2H), 3.72 (t, *J* = 6.5 Hz, 2H), 3.45 (d, *J* = 5.5 Hz, 2H), 3.23 (, dd, *J* = 3.5 Hz, 10 Hz, 1H), 3.09 (dd, *J* = 6 Hz, 11 Hz, 1H), 2.90–2.88 (m, 1H), 2.82–2.81 (m, 1H), 2.13–2.08 (m, 1H), 1.71–1.56 (m, 4H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.9 (3C), 136.0, 135.5 (2C), 133.8,

133.2, 132.9, 129.6 (2C), 128.7 (4C), 128.1 (4C), 127.9, 127.8 (6C), 127.7, 127.6 (6C), 127.0 (3C), 126.2, 126.0, 125.7, 125.7, 73.1, 73.1, 64.7, 61.8, 57.2, 55.0, 34.2, 34.1, 33.8, 26.9 (3C), 19.2, –0.002; IR (film) ν_{max} 2928, 1448, 1427, 1110, 744; HRMS (ESI) *m/z* 814.43165 (MNH_4^+, $C54H_{56}O_4SiNH_4^+$ requires 814.42861).

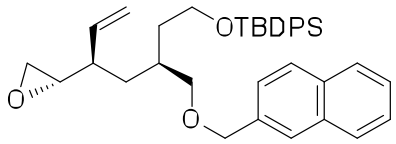


2S,3R,5S)-7-((tert-butyldiphenylsilyl)oxy)-5-((naphthalen-2-ylmethoxy)methyl)-1-(trityloxy)-3-vinylheptan-2-ol (186) To a mixture of CuBr·Me_2S (23.2 mg, 0.1129 mmol) and Me_2S (51 μL) in Et_2O (0.51 mL) was added vinyl magnesium bromide (1 M in THF, 0.34 mL, 0.3387 mmol) at –15 °C. The resultant mixture was stirred at at –15 °C for 30 min. Then, it was warmed to 0 °C, and stirred at 0 °C for 30 min. The epoxide **185** (45 mg, 0.05645 mmol) in Et_2O (0.2 mL) was added to the reaction mixture. The resultant mixture was warmed to rt and stirred at rt for 18 h. The reaction was quenched by the addition of brine (0.5 mL). The mixture was extracted with EtOAc (3 × 3 mL), and the combined organic layers were washed with brine (1 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 5% EtOAc in hexanes elution) afforded **186** (37.8 mg, 0.04572 mmol, 81%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84–7.65 (m, 8H), 7.50–7.43 (m, 9H), 7.41–7.23 (m, 15H), 5.77 (dt, *J* = 2 Hz, 8.8 Hz, 1H), 5.31 (dd, *J* = 1.5 Hz, 17.5 Hz, 1H), 5.18 (dq, *J* = 1.5 Hz, 7.3 Hz, 1H), 4.58 (s, 2H), 3.73–3.67 (m, 2H), 3.38–3.30 (m, 2H), 3.11–3.10 (m, 1H), 3.04 (t, *J* = 8 Hz, 1H), 2.36 (d, *J* = 5.5 Hz, 1H), 1.75–1.73 (m, 1H), 1.62–1.52 (m, 3H), 1.44–1.37 (m, 1H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.0 (3C), 142.0, 136.4, 135.8 (2C), 134.3, 133.5, 133.2, 129.7

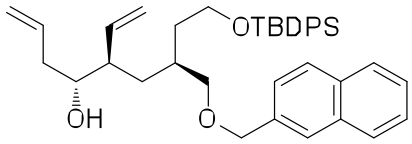
(2C), 129.0 (4C), 128.2 (2C), 128.0 (4C), 127.9 (6C), 127.8 (6C), 127.3 (2C), 126.4, 126.2, 125.9 (3C), 114.2, 75.5, 73.6, 73.5, 73.3, 69.7, 62.3, 35.6, 35.0, 34.8, 34.7, 27.1 (3C), 19.4; IR (film) ν_{max} 3056, 2929, 2857, 1599, 1489, 1448, 1427, 1088, 1032; HRMS (ESI) *m/z* 842.45747 (MNH_4^+, $C_{56}H_{60}O_4SiNH_4$ requires 842.45991).



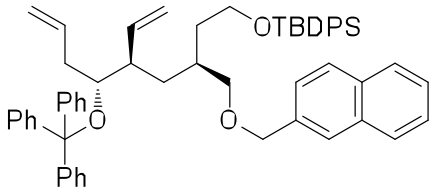
(2S,3R,5S)-7-((tert-butyldiphenylsilyl)oxy)-5-((naphthalen-2-ylmethoxy)methyl)-3-vinylheptane-1,2-diol (193) 10-CSA (1.8 mg, 0.00728 mmol) was added to a solution of **186** (10 mg, 0.012129 mmol) in EtOH/CH_2Cl_2 (2:1, 1.6 mL) at rt. The reaction mixture was stirred for 4 h. The reaction was quenched by the addition of solid $NaHCO_3$, filtered and concentrated. Flash chromatography (SiO_2, 30% EtOAc in hexanes elution) provided **193** (5.02 mg, 0.00861 mmol, 71%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86–7.75 (m, 4H), 7.7.68–7.66 (m, 4H), 7.50–7.48 (m, 2H), 7.45–7.41 (m, 3H), 7.39–7.37 (m, 4H), 5.73 (dd, *J* = 11 Hz, 17 Hz, 1H), 5.33 (dd, *J* = 5 Hz, 17 Hz, 1H), 5.24 (d, *J* = 10.5 Hz, 1H), 4.61 (s, 2H), 3.74–3.70 (m, 2H), 3.45–3.40 (m, 4H), 3.37–3.34 (m, 1H), 1.87–1.85 (m, 1H), 1.64–1.54 (m, 3H), 1.47–1.42 (m, 2H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.7, 140.6, 135.6 (2C), 134.0, 133.3, 129.6 (4C), 128.1, 127.9, 127.9, 127.7 (4C), 127.6 (4C), 126.3, 126.1, 125.8, 125.8, 125.8, 115.3, 73.1, 68.9, 68.8, 62.0, 62.0, 35.4, 35.2, 34.5, 34.0 33.8, 26.9 (3C), 19.2; IR (film) ν_{max} 3418, 2930, 2857, 1471, 1427, 1389, 1110; HRMS (ESI) *m/z* 605.30492 (MNa^+, $C_{37}H_{46}O_4SiNa^+$ requires 605.30576).



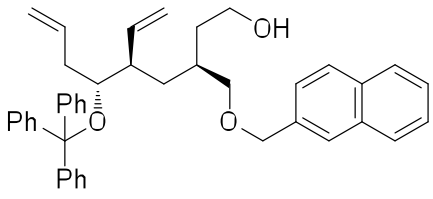
tert-butyl(((3S,5R)-3-((naphthalen-2-ylmethoxy)methyl)-5-((S)-oxiran-2-yl)hept-6-en-1-yl)oxy)diphenylsilane (194) To a solution of **193** (4 mg, 0.00686 mmol) in THF (0.3 mL) at 0 °C was added NaH (0.8 mg, 0.0206mmol). The resultant reaction mixture was warmed to rt and stirred at rt for 30 min. Then, it was cooled to 0 °C. *N*-(2,4,6-Triisopropyl benzenesulfonyl)imidazole (2.5 mg, 0.00755 mmol) was added in one portion. The reaction mixture was allowed to warm to rt and stirred at rt for 2 h. The reaction was quenched with sat. NH_4Cl (0.2 mL), extracted with EtOAc (3 × 0.5 mL). The combined organic layers were washed with brine (0.5 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 6% EtOAc in hexanes elution) afforded **193** (2.7 mg, 70%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86–7.75 (m, 3H), 7.68–7.66 (m, 4H), 7.49 (t, *J* = 4.5 Hz, 2H), 7.45–7.43 (m, 3H), 7.38 (t, *J* = 7 Hz, 4H), 5.77–5.71 (m, 1H), 5.33 (d, *J* = 17.5 Hz, 1H), 5.20 (d, *J* = 10.5 Hz, 1H), 4.62 (s, 2H), 3.75–3.71 (m, 3H), 3.44–3.35 (m, 3H), 2.77 (t, *J* = 5 Hz, 1H), 2.66–2.65 (m, 1H), 1.89–1.87 (m, 1H), 1.75–1.52 (m, 3H), 1.51–1.44 (m ,1H), 1.06 (s, 9H); 137.5, 137.5, 135.6 (2C), 134.0, 133.3, 132.9, 129.6 (4C), 128.1, 127.9, 127.7, 127.6 (4C), 126.2, 126.1, 125.8, 125.7 (2C), 116.5, 73.1, 73.0, 73.0, 62.0, 55.0, 54.9, 35.2, 35.1, 34.4, 26.9 (3C), 19.2; IR (film) ν_{max} 2929, 2856, 2359, 1472, 1428, 1362, 1111; HRMS (ESI) *m/z* 582.34114 (MNH_4^+, $C_{37}H_{44}O_3SiNH_4$ requires 582.33980).



(4R,5R,7S)-9-((tert-butyldiphenylsilyl)oxy)-7-((naphthalen-2-ylmethoxy)methyl)-5-vinylnon-1-en-4-ol (195) To a mixture of CuI (7.6 mg, 0.04 mmol) in Et_2O (1.2 mL) was added vinyl magnesium bromide (0.12 mL, 0.12 mmol) at –15 °C under Ar. The resultant mixture was stirred at at –15 °C for 30 min. Then, it was warmed to 0 °C, and stirred at 0 °C for 30 min. The epoxide **194** (11.3 mg, 0.02 mmol) in Et_2O (0.3 mL) was added to the reaction mixture. The resultant mixture was warmed to rt and stirred at rt for 18 h. The reaction was quenched by the addition of brine (1 mL). The mixture was extracted with EtOAc (3 × 3 mL), and the combined organic layers were washed with brine (1 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 8% EtOAc in hexanes elution) provided **195** as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83–7.71 (m, 4H), 7.66–7.64 (m, 4H), 7.47–7.33 (m, 9H), 5.80–5.72 (m, 1H), 5.41 (t, *J* = 15 Hz, 1H), 5.03–4.93 (m, 4H), 4.60 (s, 2H), 4.01 (d, *J* = 4.5 Hz, 1H), 3.73–3.69 (m, 2H), 3.44–3.41 (m, 1H), 3.37–3.34 (m, 1H), 2.75 (t, *J* = 7 Hz, 2H), 2.07 (t, *J* = 8.5 Hz, 1H), 1.68–1.59 (m, 2H), 1.52–1.39 (m, 1H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.4, 136.9, 136.1, 135.6 (2C), 134.0, 133.3, 132.9, 129.6 (4C), 128.1, 127.9, 127.7, 127.6 (4C), 126.3, 126.0, 125.8, 125.7 (2C), 123.7, 114.8, 73.2, 73.0, 67.1, 62.1, 35.3, 34.4, 31.8, 30.4 (3C), 26.9, 25.3, 19.2; IR (film) ν_{max} 3069, 2929, 2856, 2359, 1636, 1589, 1471, 1427, 1110; HRMS (ESI) *m/z* 610.37184 (MNH_4^+, $C_{39}H_{48}O_3SiNa^+$ requires 610.37110).

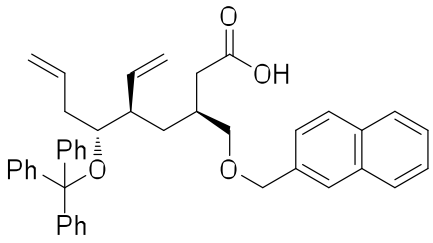


tert-butyl(((3S,5R,6R)-3-((naphthalen-2-ylmethoxy)methyl)-6-(trityloxy)-5-vinylnon-8-en-1-yl)oxy)diphenylsilane (196) A solution of **195** (3 mg, 0.00516 mmol) in anhydrous 1,2-dichloroethane (0.4 mL) at 0 °C under Ar was treated with 2,6-lutidine (3 μL, 0.32 mg, 0.0253 mmol) followed by TrOTf (crude, 0.01265 mmol) in anhydrous CCl_4 (0.4 mL). The resultant mixture was warmed to rt and stirred at rt for 12 h. The reaction was quenched by the addition of sat. NH_4Cl (0.5 mL). The layers were separated. The aqueous layer was extracted with EtOAc (3 × 1 mL), and the combined organic layers were washed with brine (0.3 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 8% EtOAc in hexanes elution) afforded **89** (3.13 mg, 0.00374 mmol, 74%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.82–7.64 (m, 5H), 7.47 (d, *J* = 7.5 Hz, 4H), 7.40–7.15 (m, 23H), 5.83–5.78 (m, 1H), 5.57–5.54 (m, 1H), 5.03 (dd, *J* = 2 Hz, 17 Hz, 2H), 4.68 (dd, *J* = 1.5 Hz, 10.5 Hz, 2H), 4.55 (s, 2H), 3.71–3.64 (m, 2H), 3.69–3.63 (m, 2H), 3.51 (br s, 1H), 3.56–3.29 (m, 2H), 2.80 (t, *J* = 6.5 Hz, 2H), 2.05 (t, *J* = 8.5 Hz, 1H), 1.78–1.73 (m, 1H), 1.67–1.56 (m, 2H), 1.48–1.30 (m, 2H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.3 (3C), 138.2, 135.6 (2C), 129.5 (2), 129.5, 129.3, 128.8, 128.7 (4C), 128.3 (2C), 128.0, 127.9, 127.7 (4C), 127.7, 127.6 (6C), 127.3, 126.9 (6C), 126.3, 126.2, 126.0, 125.7 (2C), 123.3 (3C), 114.6, 73.1, 73.1, 67.5, 62.2, 35.5, 34.5, 31.8, 30.6, 26.9, 26.9 (3C), 25.9, 19.2; IR (film) ν_{max} 3478, 2929, 2856, 2360, 1698, 1597, 1490, 1446, 1332, 1157, 1088; HRMS (ESI) *m/z* 857.43633 (MNa^+, $C_{58}H_{62}O_3SiNa^+$ requires 857.43604).



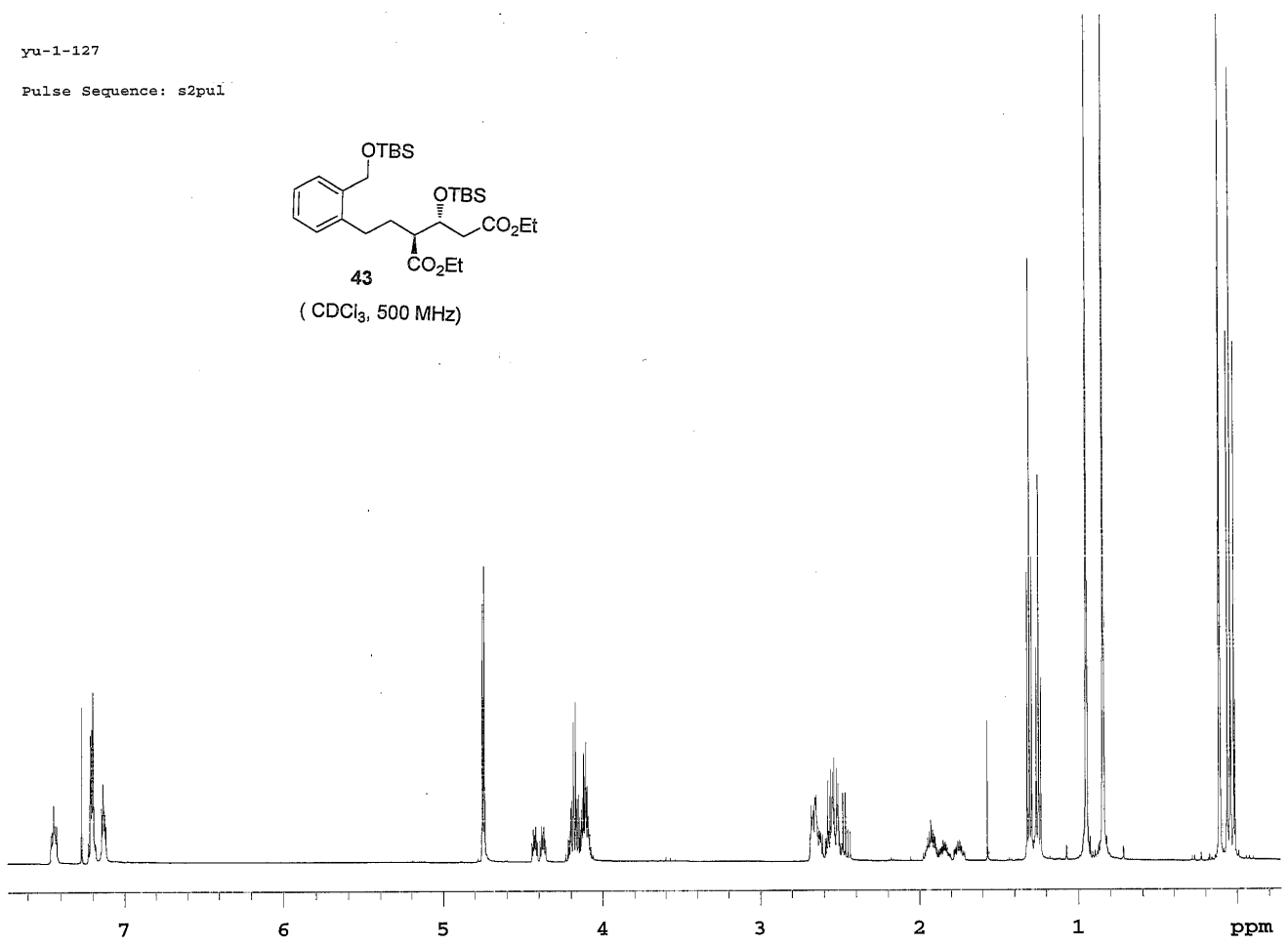
(3S,5R,6R)-3-((naphthalen-2-ylmethoxy)methyl)-6-(trityloxy)-5-vinylnon-8-en-1-ol (198)

A solution of **196** (8 mg, 0.0096 mmol) in anhydrous THF (1 mL) at 0 °C under Ar was treated with TBAF (1.0 M in THF, 0.11 mL, 0.11 mmol). The resultant mixture was warmed to rt and stirred at rt under Ar for 8 h. The reaction was quenched by the addition of sat. NH_4Cl (4 mL). The aqueous layer was extracted with EtOAc (3 × 1 mL), and the combined organic layers were washed with brine (0.5 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 25% EtOAc in hexanes elution) afforded alcohol **197**(4.8 mg, 0.00806 mmol, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85–7.73 (m, 4H), 7.50–7.38 (m, 9H), 7.28–7.22 (m, 9H), 5.84–5.54 (m, 1H), 5.06 (t, *J* = 7 Hz, 1H), 5.02–4.94 (m, 4H), 3.68–3.63 (m, 1H), 3.59–3.55 (m, 1H), 3.52 (br s, 1H), 3.45 (dd, *J* = 3.5 Hz, 8.8 Hz, 1H), 3.36–3.32 (m, 1H), 2.80 (t, J = 6.5 Hz, 1H), 2.62–2.58 (m, 1H), 2.11–2.06 (m, 2H), 1.71–1.63 (m, 2H), 1.58–1.53 (m, 1H), 1.35–1.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.3 (3C), 137.8, 137.0, 135.3, 133.2, 133.0, 128.7 (6C), 128.3, 127.9, 127.7 (6C), 127.7, 126.9 (3C), 126.6, 126.1, 125.9, 125.8, 123.8, 114.7, 73.9, 73.5, 67.5, 61.1, 36.6, 36.2, 31.8, 30.6, 29.7, 25.9; IR (film) ν_{max} 3630, 3058, 2924, 2854, 2192, 1638, 1600, 1448, 1030; HRMS (ESI) *m/z* 619.31684 (MNa^+, $C_{42}H_{44}O_3Na^+$ requires 619.31827).



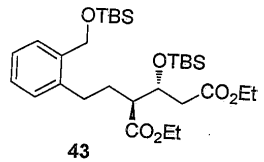
(3S,5R,6R)-3-((naphthalen-2-ylmethoxy)methyl)-6-(trityloxy)-5-vinylnon-8-enoic acid (198) BAIB (3.6 mg, 0.01106 mmol), TEMPO (0.2 mg, 0.001 mmol), $NaHCO_3$ (0.4 mg, 0.005

mmol) and alcohol **197** (3 mg, 0.005 mmol) were combined in a vial at 0 °C, and to this mixture was added 0.4 mL of a 1:1 acetonitrile–water solution. The reaction mixture was stirred at 0 °C for 3 h. The reaction was filtered and triturated with diethyl ether to remove the catalytic amount of TEMPO and reaction byproducts. Then the crude product was used directly for the next step. HRMS (ESI) *m/z* 633.29427 (MNa^+, $C_{42}H_{42}O_4Na^+$ requires 633.29753).


yu-1-127
Pulse Sequence: s2pul
OTBS
OTBS
CO2Et
CO2Et
43
(CDCl3, 500 MHz)
7
6
5
4
3
2
1
ppm

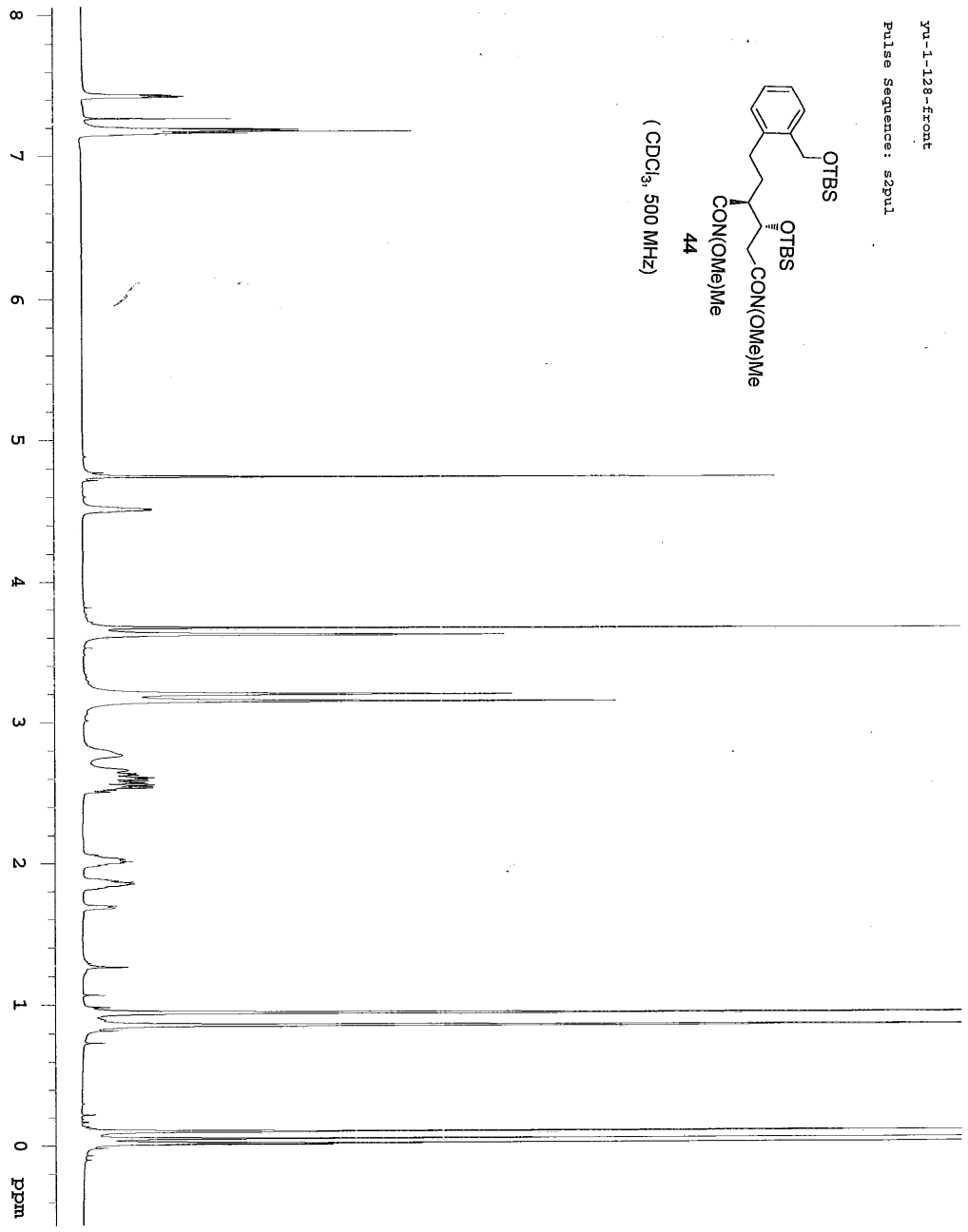
yu-1-127

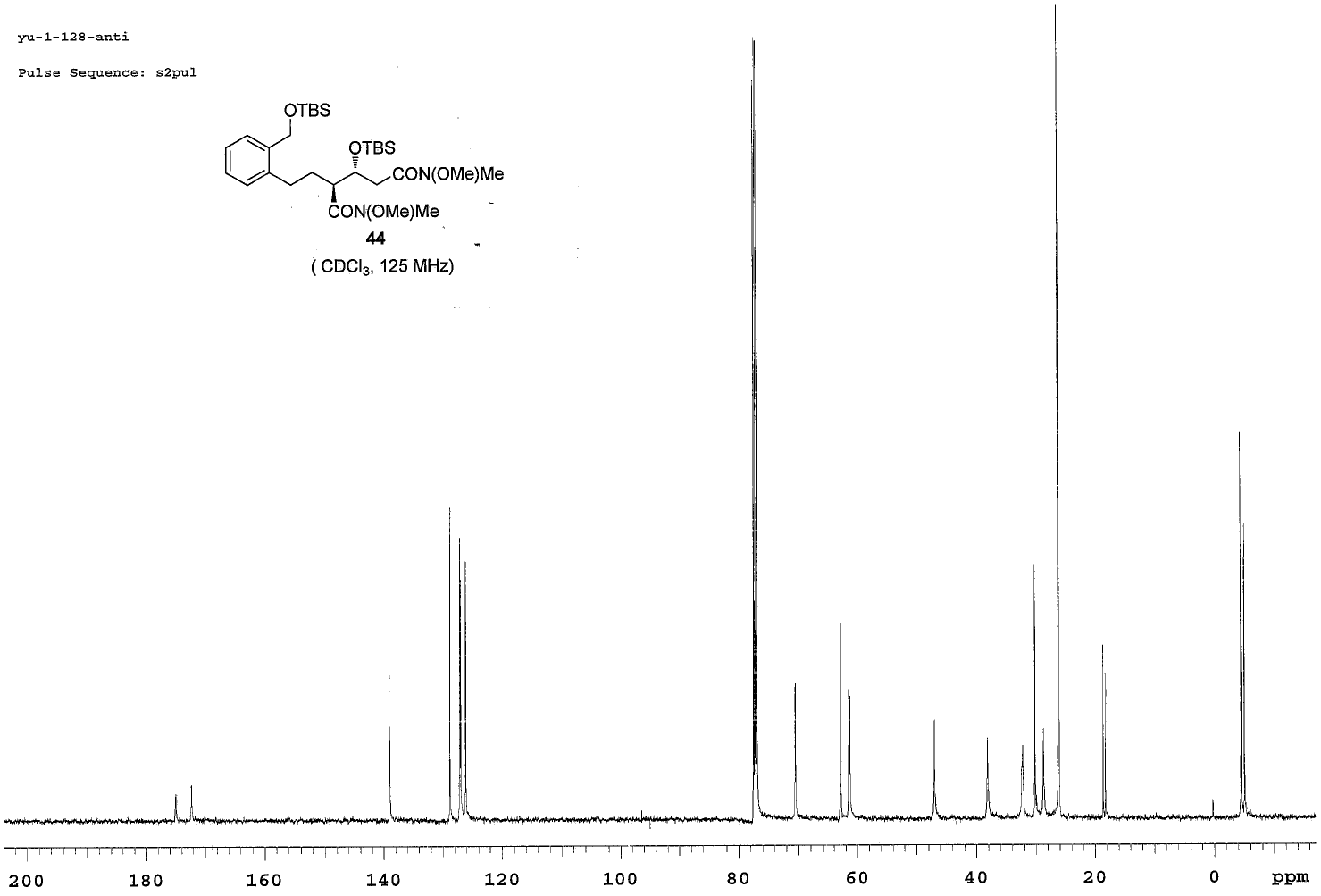
Pulse Sequence: s2pul

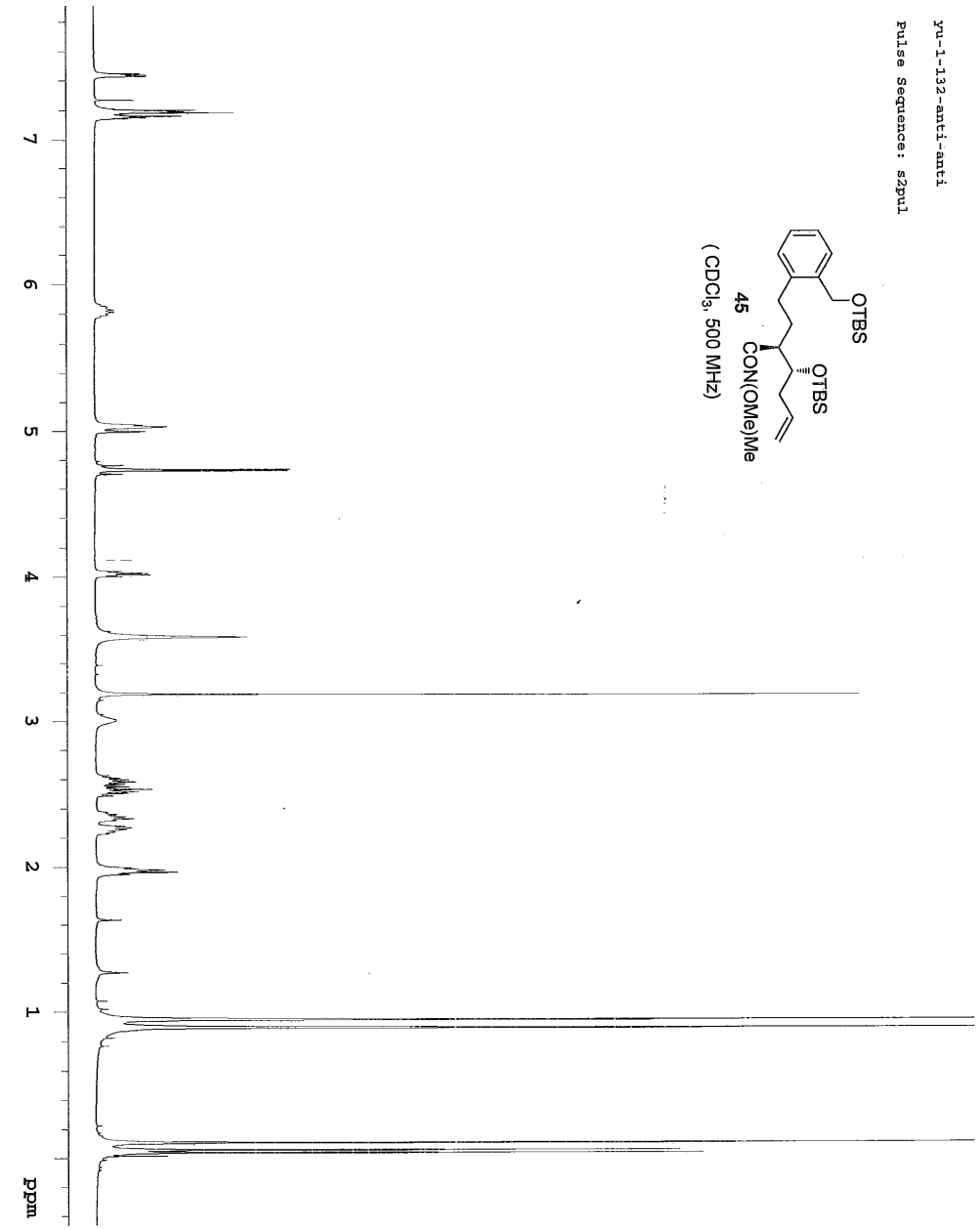


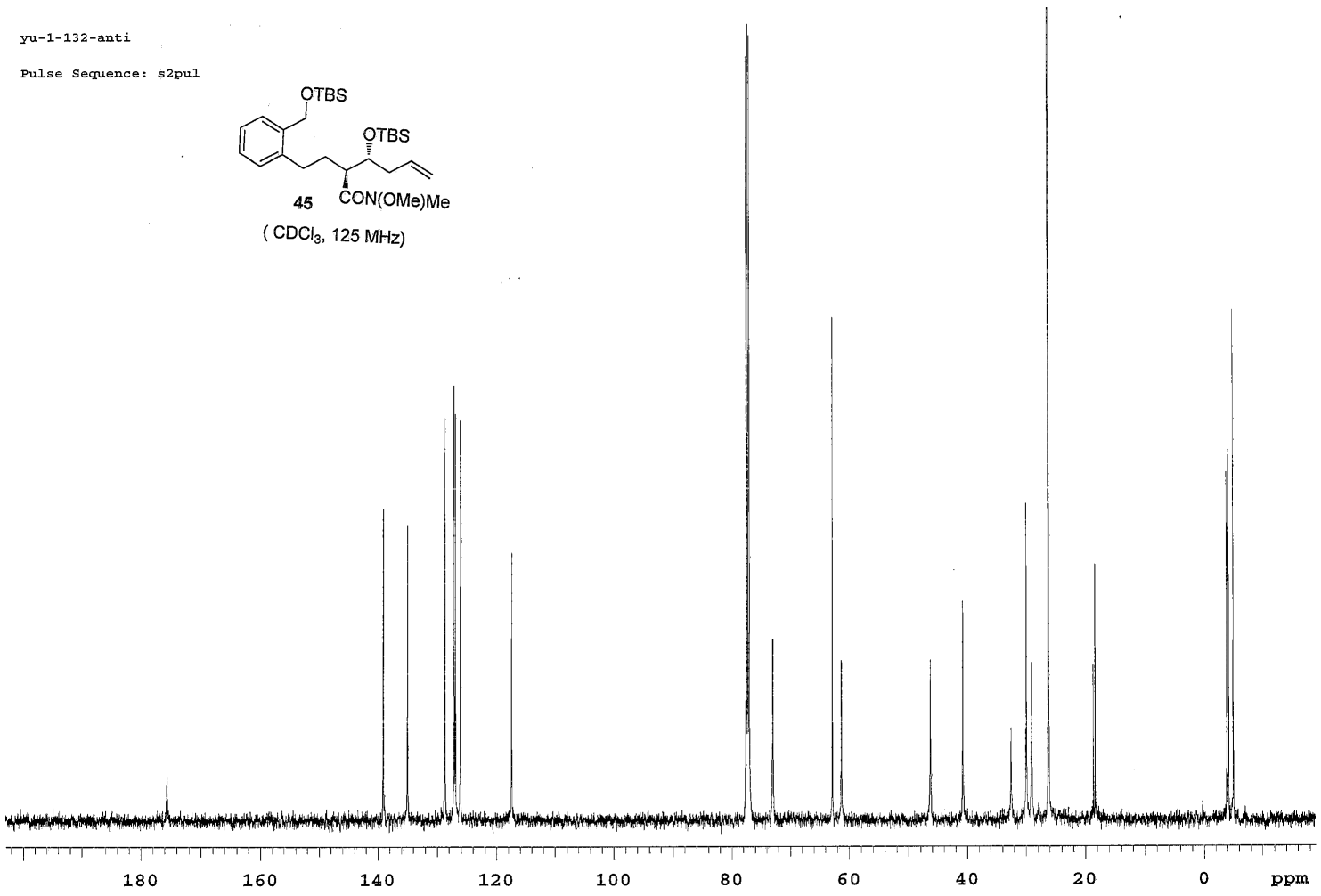
43

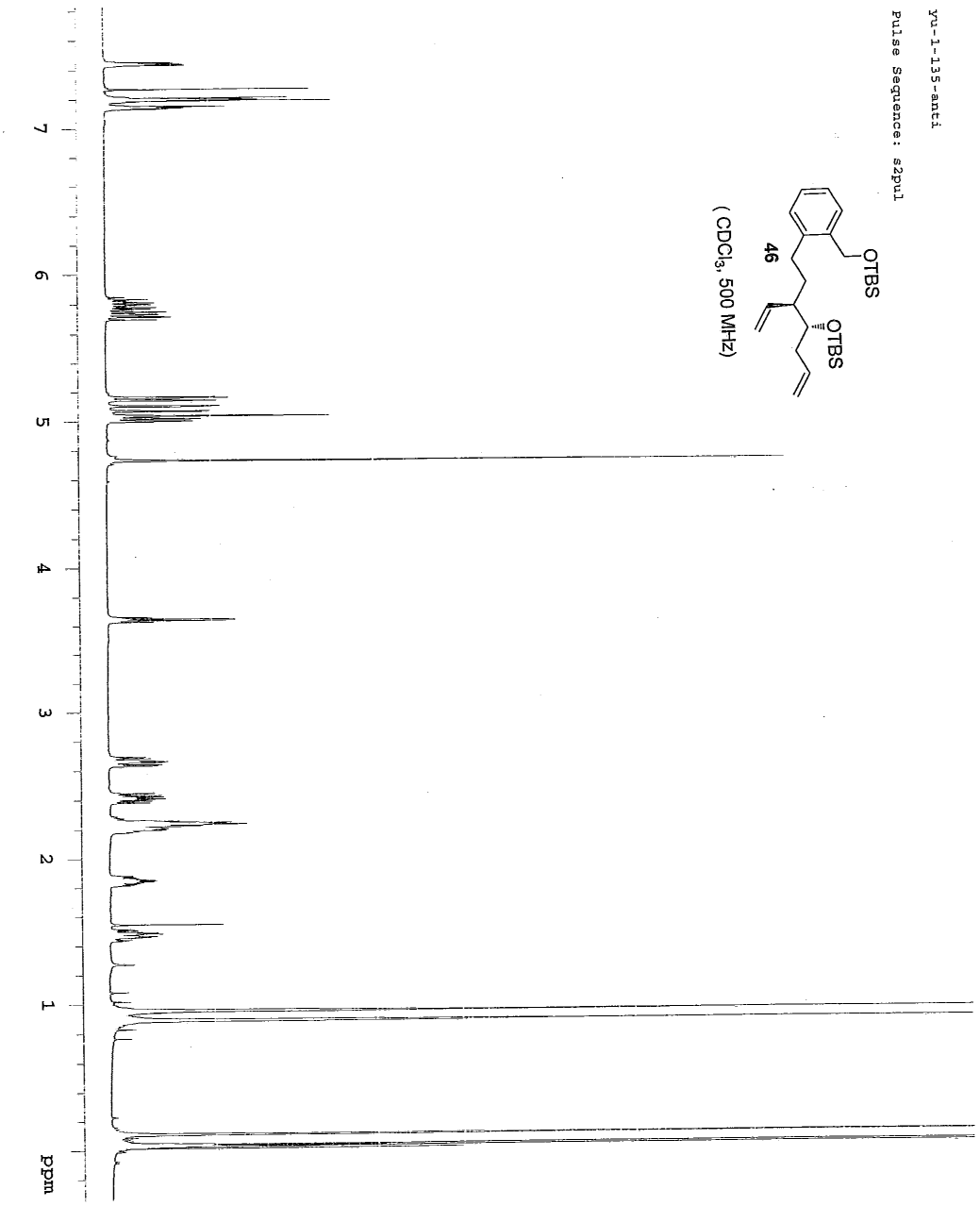
($CDCl_3$, 125 MHz)


yu-1-128-front
Pulse Sequence: s2pul
OTBS
OTBS
CON(OMe)Me
CON(OMe)Me
44
(CDCl3, 500 MHz)
8
7
6
5
4
3
2
1
0
ppm


yu-1-128-anti
Pulse Sequence: s2pul
OTBS
OTBS
CON(OMe)Me
CON(OMe)Me
44
(CDCl3, 125 MHz)
200
180
160
140
120
100
80
60
40
20
0
ppm

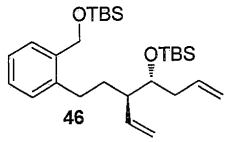

yu-1-132-anti-anti
Pulse Sequence: s2pul
OTBS
OTBS
45 CON(OMe)Me
(CDCl3, 500 MHz)
7
6
5
4
3
2
1
ppm


yu-1-132-anti
Pulse Sequence: s2pul
OTBS
OTBS
45
CON(OMe)Me
(CDCl3, 125 MHz)
180
160
140
120
100
80
60
40
20
0
ppm


yu-1-135-anti
Pulse Sequence: s2pul
OTBS
OTBS
46
(CDCl3, 500 MHz)
7
6
5
4
3
2
1
ppm

yu-1-135-anti

Pulse Sequence: s2pul

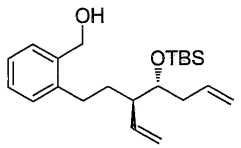


46

($CDCl_3$, 125 MHz)

yu-1-136

Pulse Sequence: s2pul

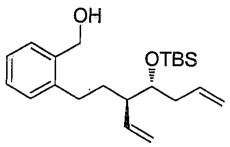


47

($CDCl_3$, 500 MHz)

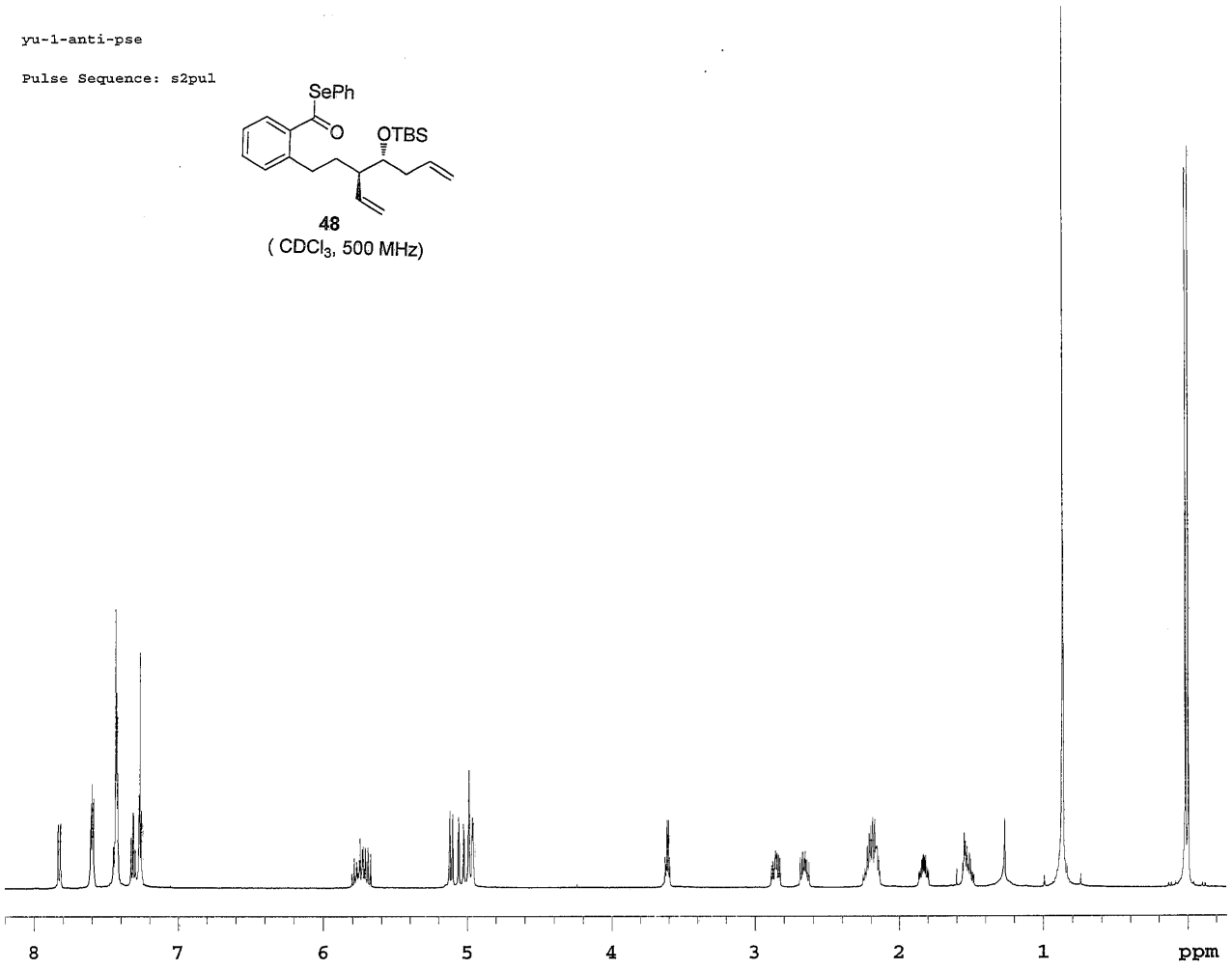
yu-1-136

Pulse Sequence: s2pul



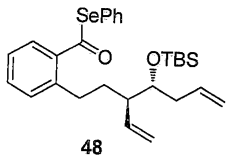
47

($CDCl_3$, 125 MHz)


yu-1-anti-pse
Pulse Sequence: s2pul
SePh
O
OTBS
48
(CDCl3, 500 MHz)
8
7
6
5
4
3
2
1
ppm

yu-anti-pse

Pulse Sequence: s2pul

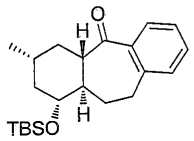


48

($CDCl_3$, 125 MHz)

yu-1-111-anticascade-2

Pulse Sequence: s2pul

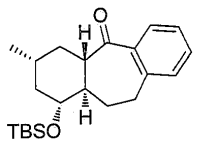


51

($CDCl_3$, 500 MHz)

yu-1-111

Pulse Sequence: s2pul

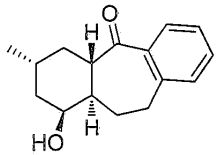


51

($CDCl_3$, 125 MHz)

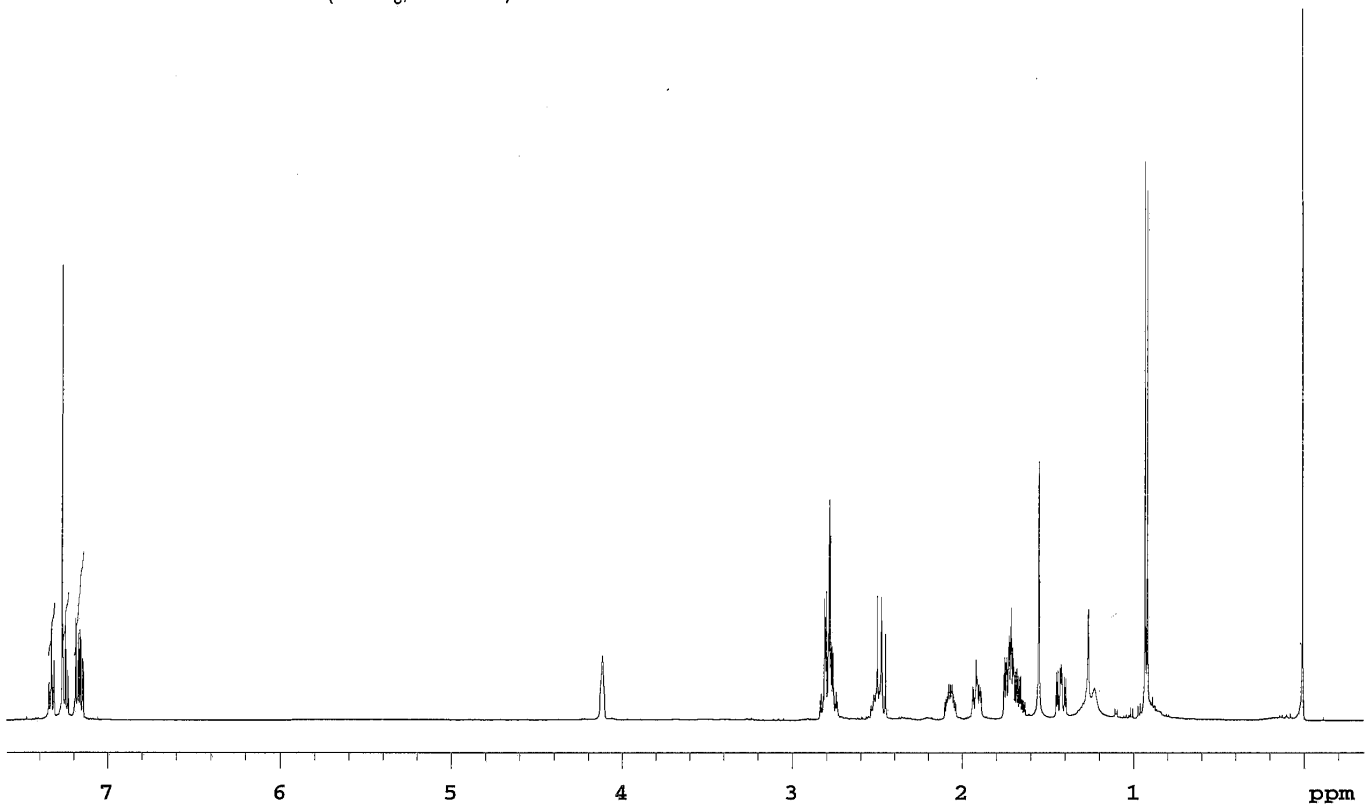
yu-1-118

Pulse Sequence: s2pul



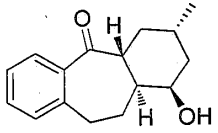
51

($CDCl_3$, 500 MHz)



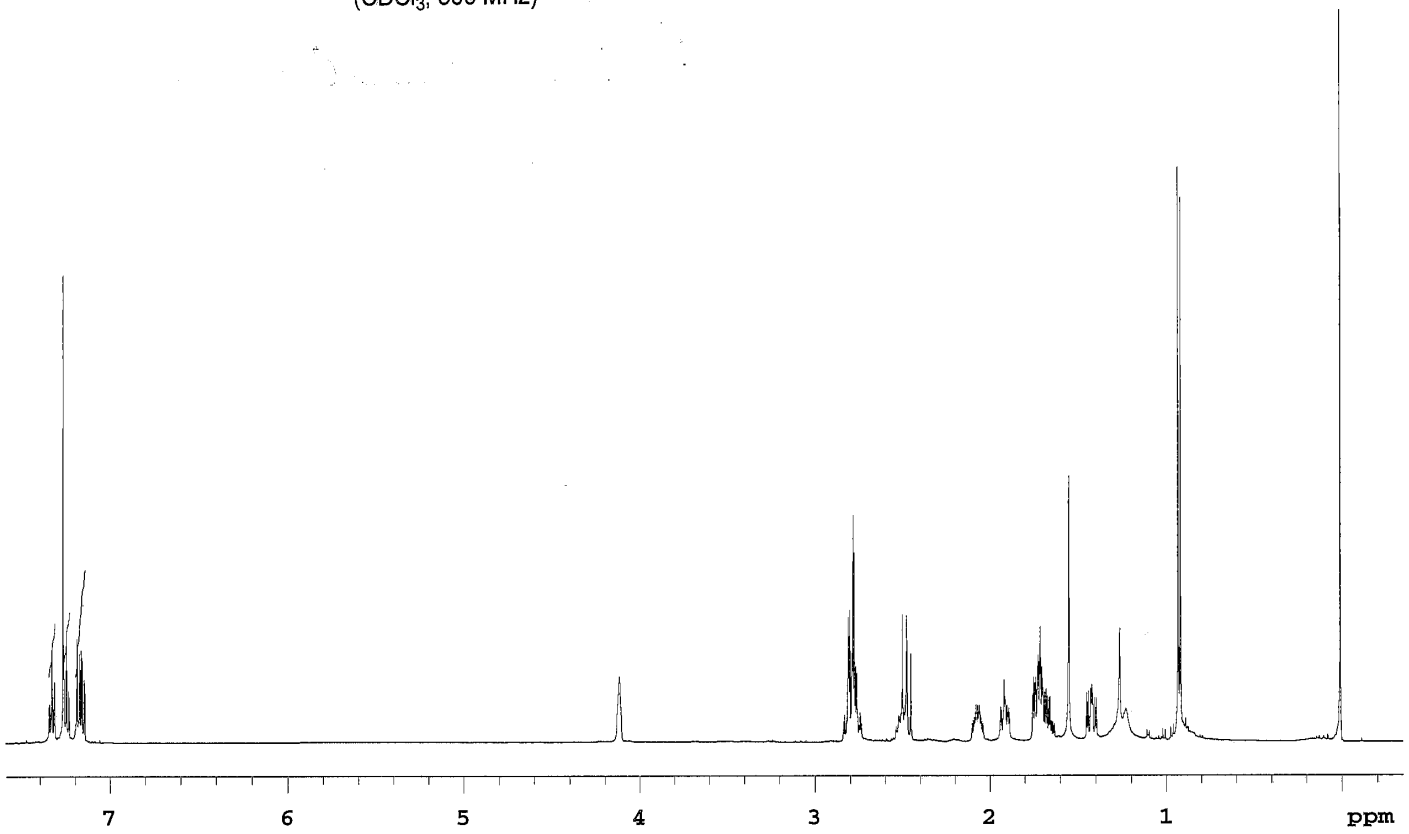
yu-1-118

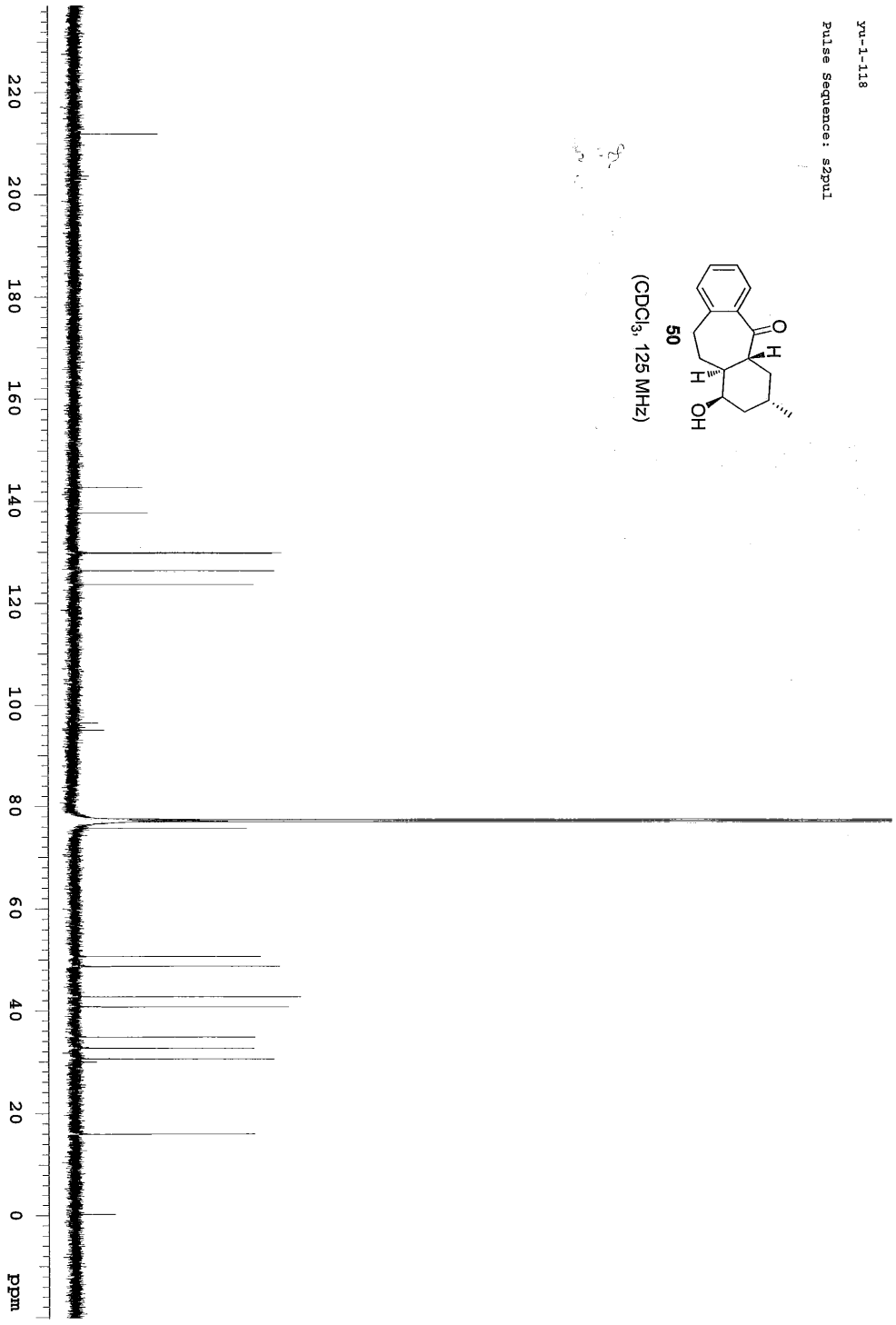
Pulse Sequence: s2pul



50

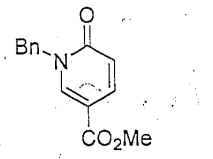
($CDCl_3$, 500 MHz)




yu-1-118
Pulse Sequence: s2pul
O
H
H
OH
50
(CDCl3, 125 MHz)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

yu-1-179

Pulse Sequence: s2pul

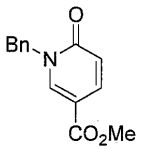


67

($CDCl_3$, 500 MHz)

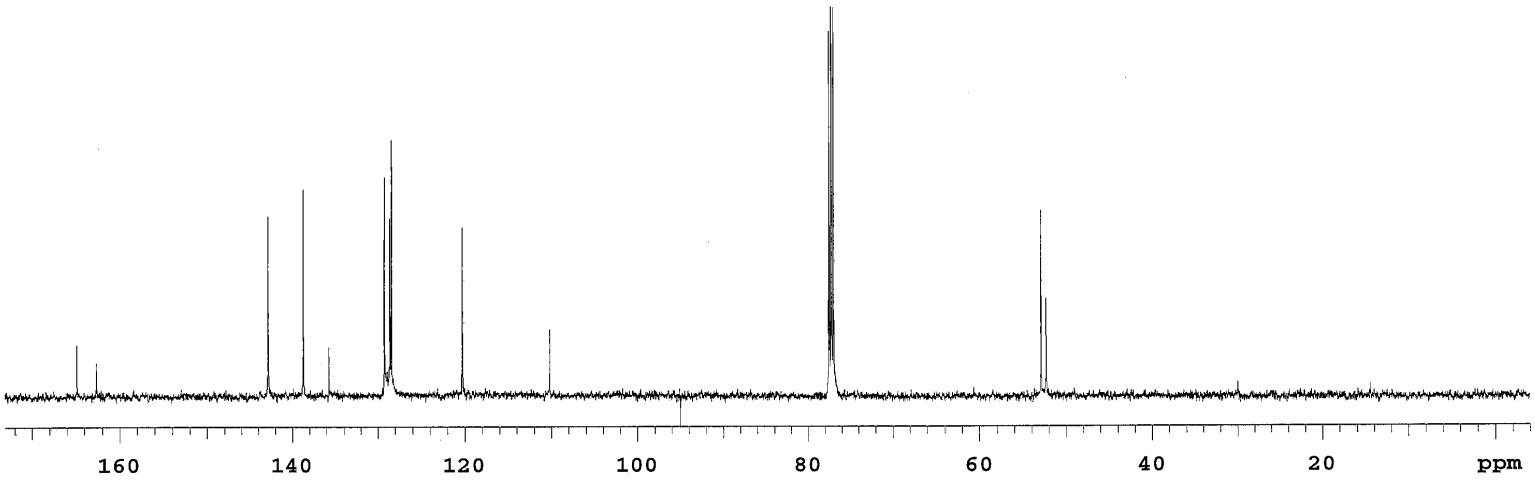
yu-1-179

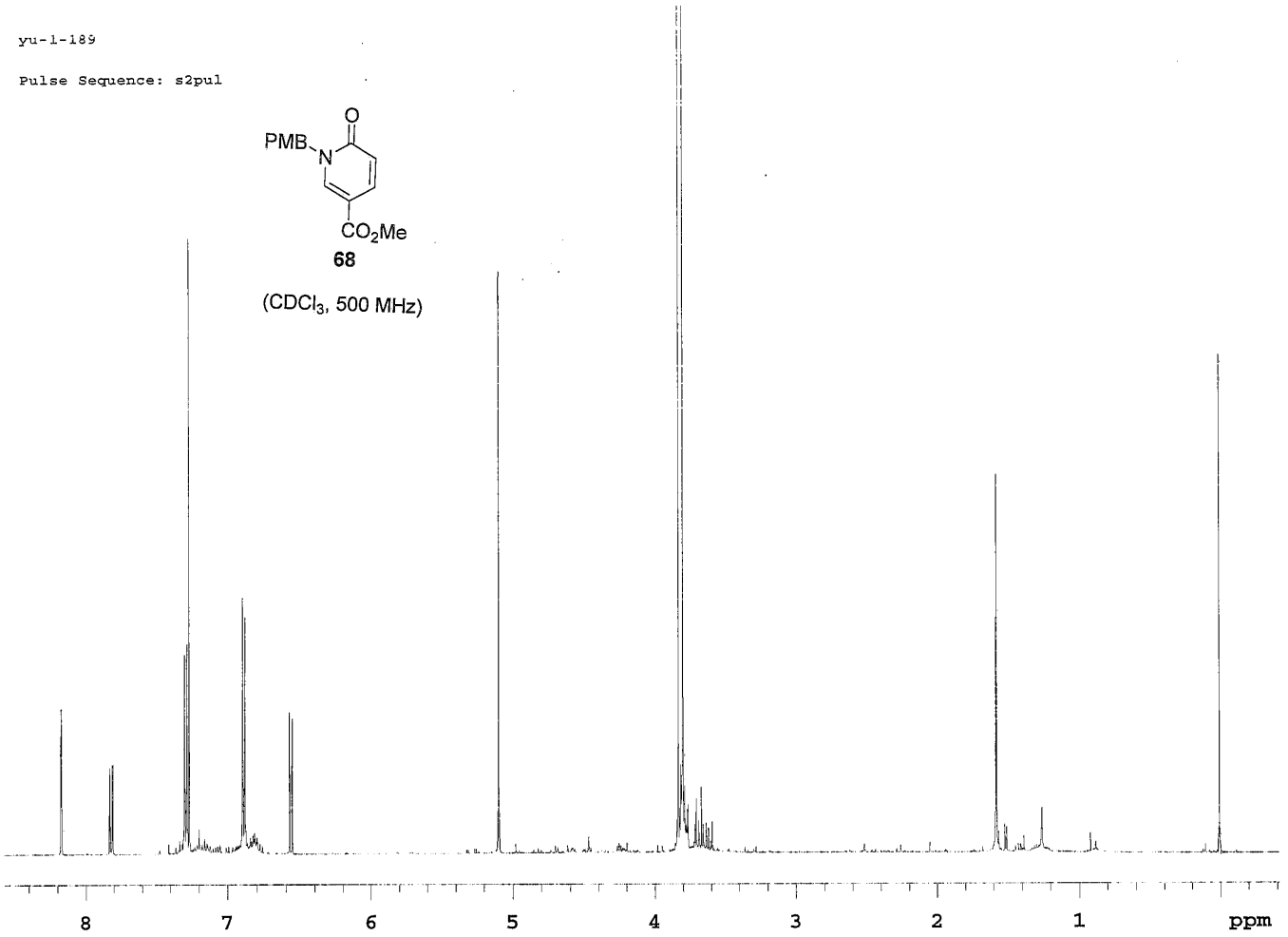
Pulse Sequence: s2pul

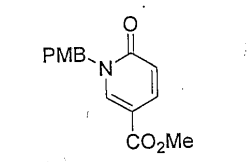


67

($CDCl_3$, 125 MHz)

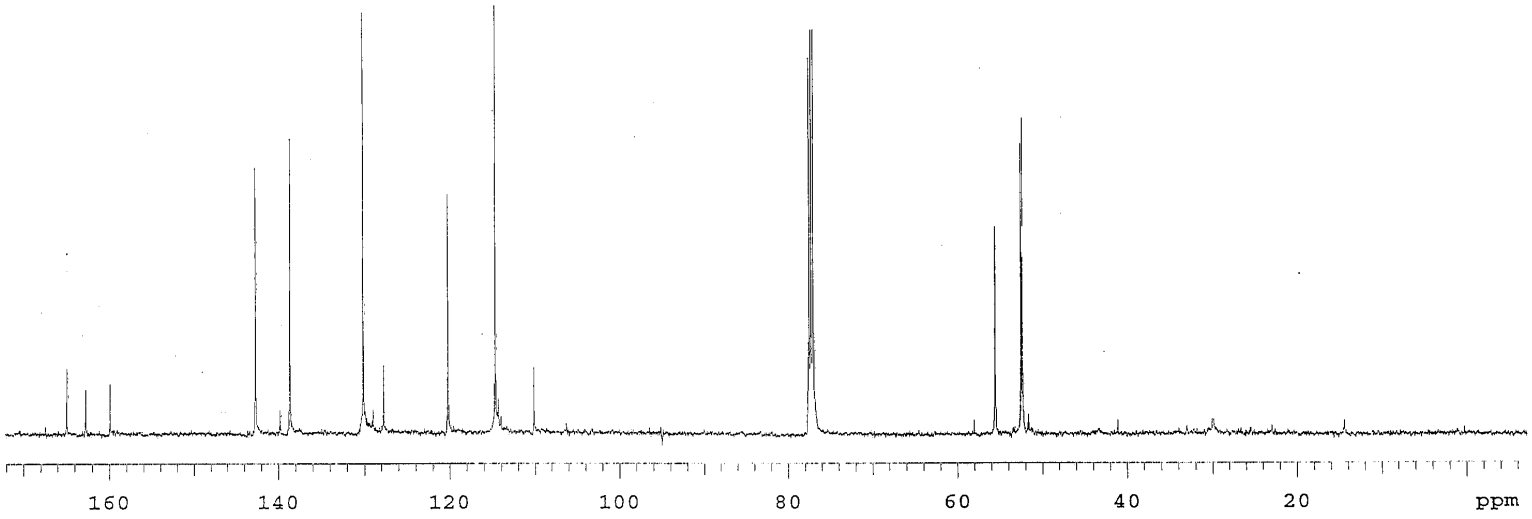


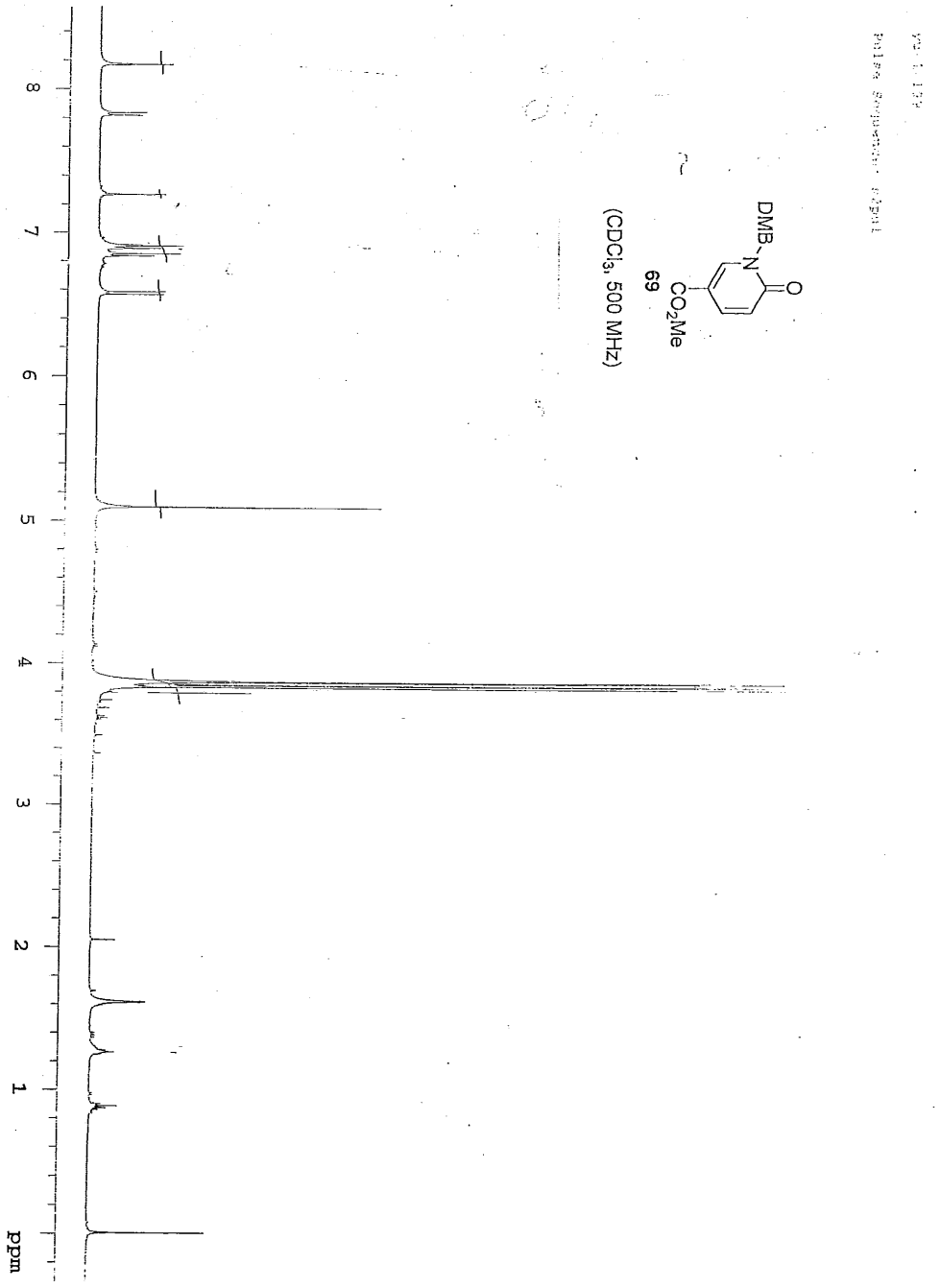

yu-1-189
Pulse Sequence: s2pul
PMB
N
O
CO2Me
68
(CDCl3, 500 MHz)
8
7
6
5
4
3
2
1
ppm

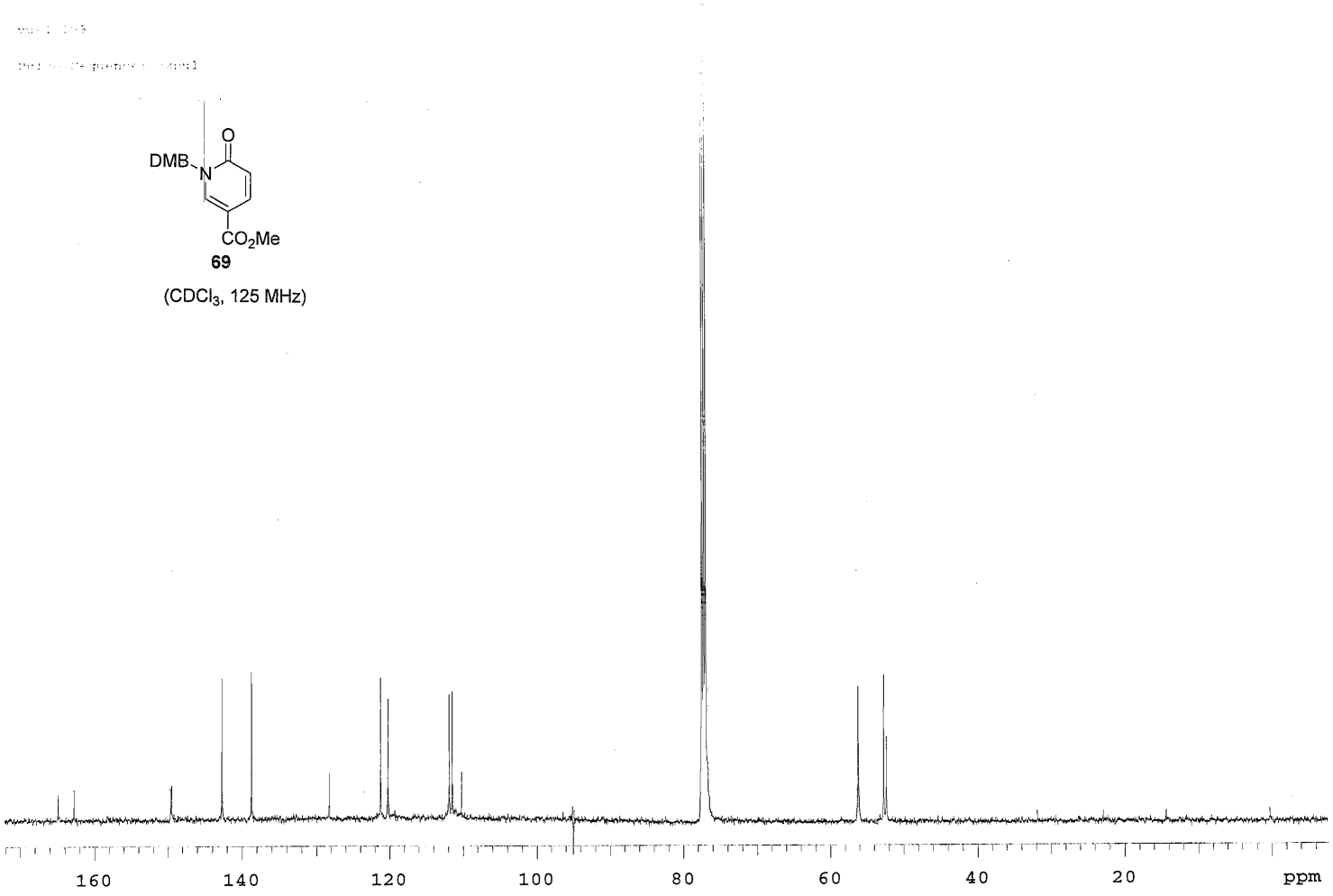


68

($CDCl_3$, 125 MHz)

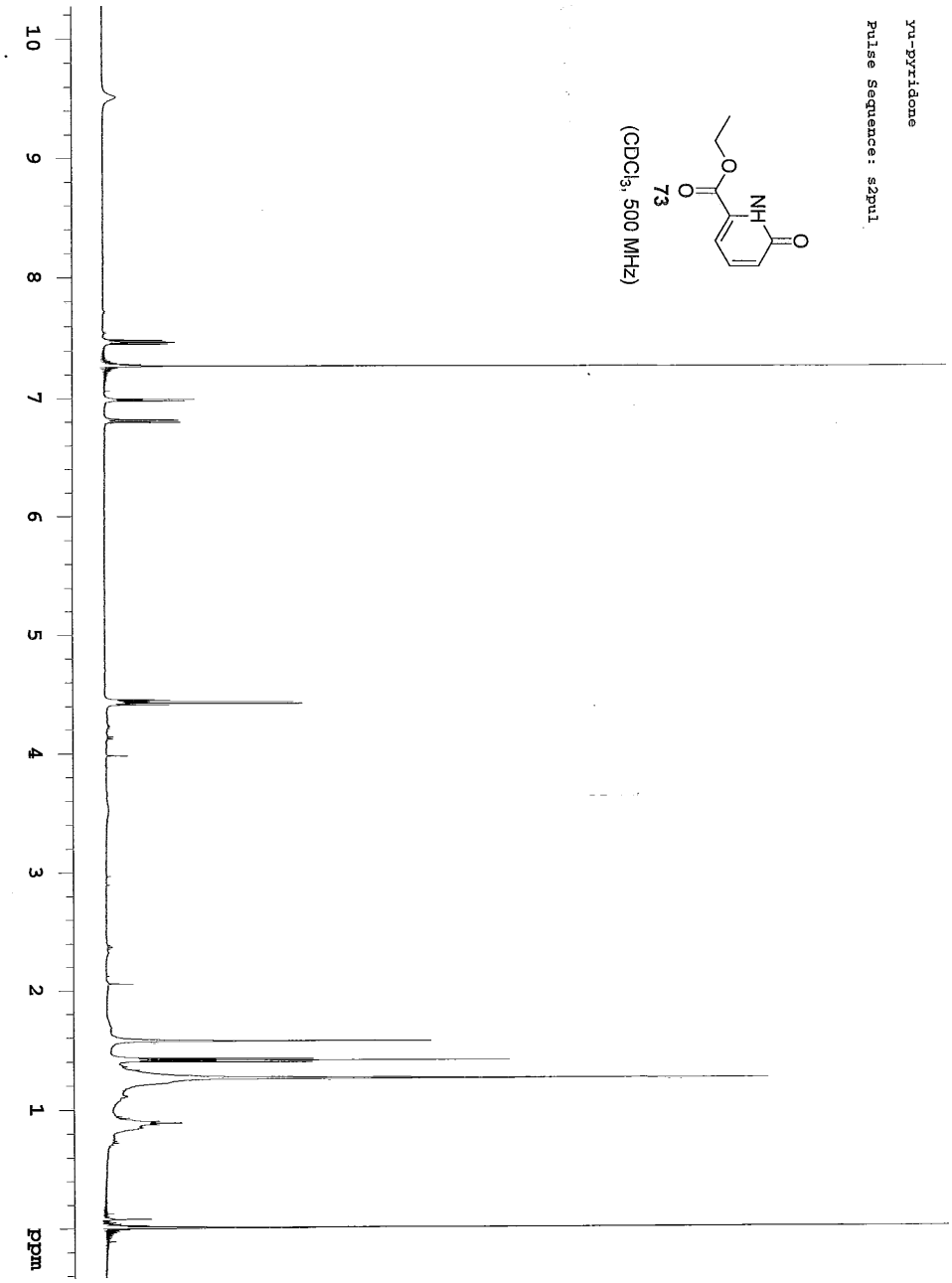



DMB
N
O
CO2Me
69
(CDCl3, 500 MHz)
8
7
6
5
4
3
2
1
ppm



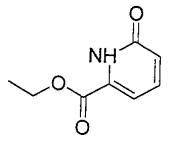
69

($CDCl_3$, 125 MHz)


yu-pyridone
Pulse Sequence: s2pul
NH
O
O
O
73
(CDCl3, 500 MHz)
10
9
8
7
6
5
4
3
2
1
ppm

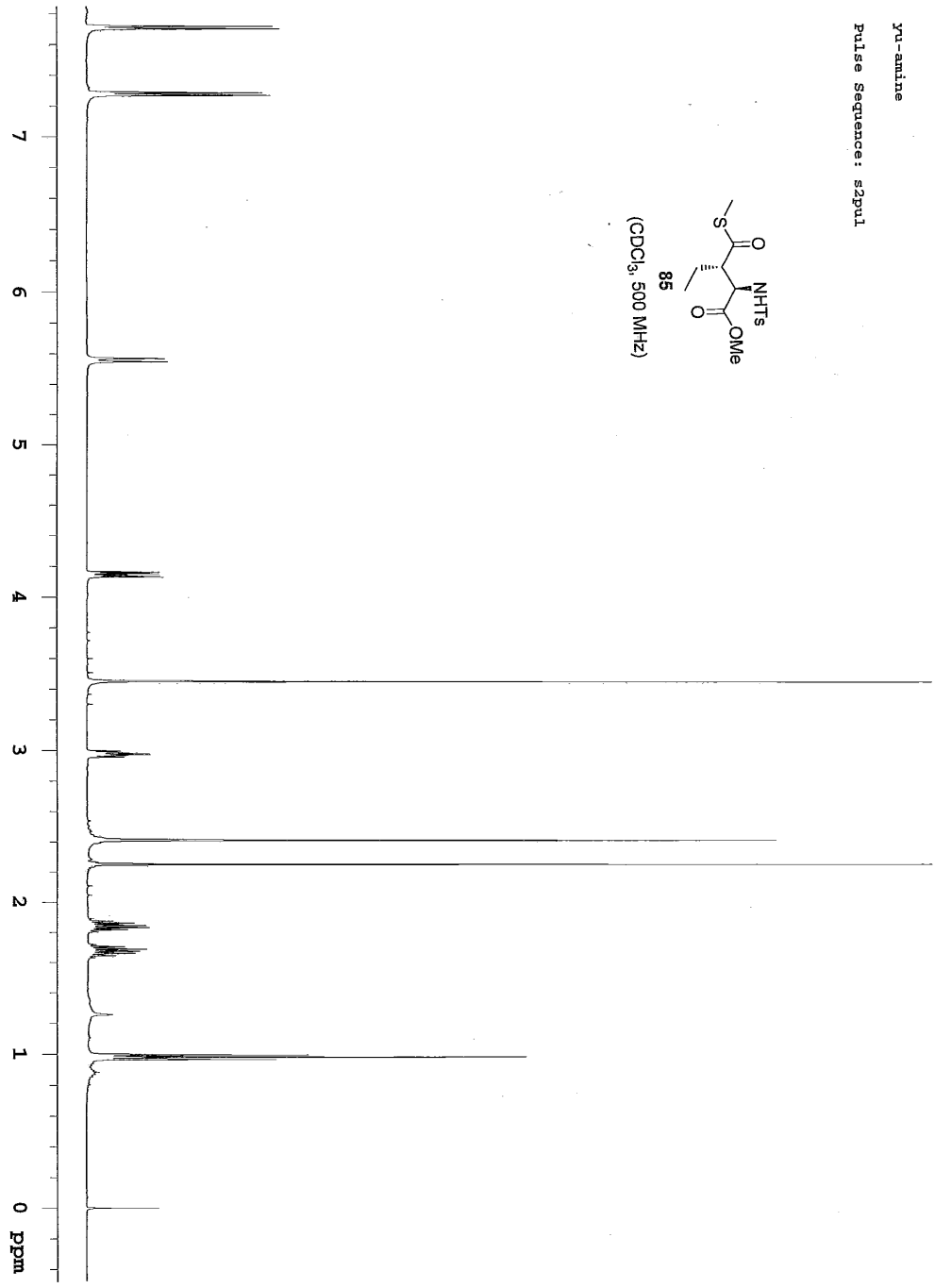
yu-pyridone

Pulse Sequence: s2pul



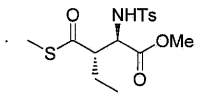
73

($CDCl_3$, 125 MHz)


yu-amine
Pulse Sequence: s2pul
NHTs
OMe
85
(CDCl3, 500 MHz)
7
6
5
4
3
2
1
0 ppm

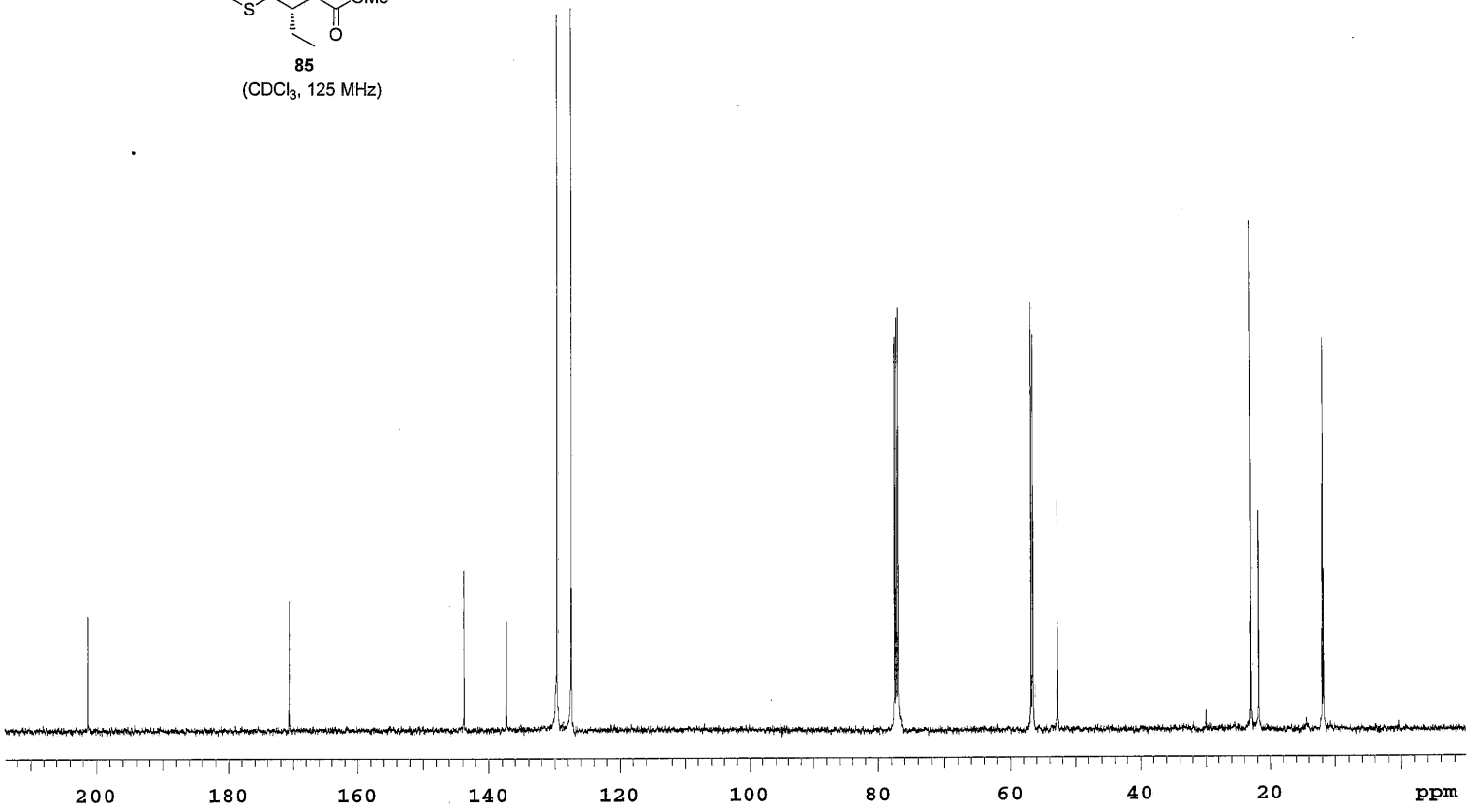
yu-amine

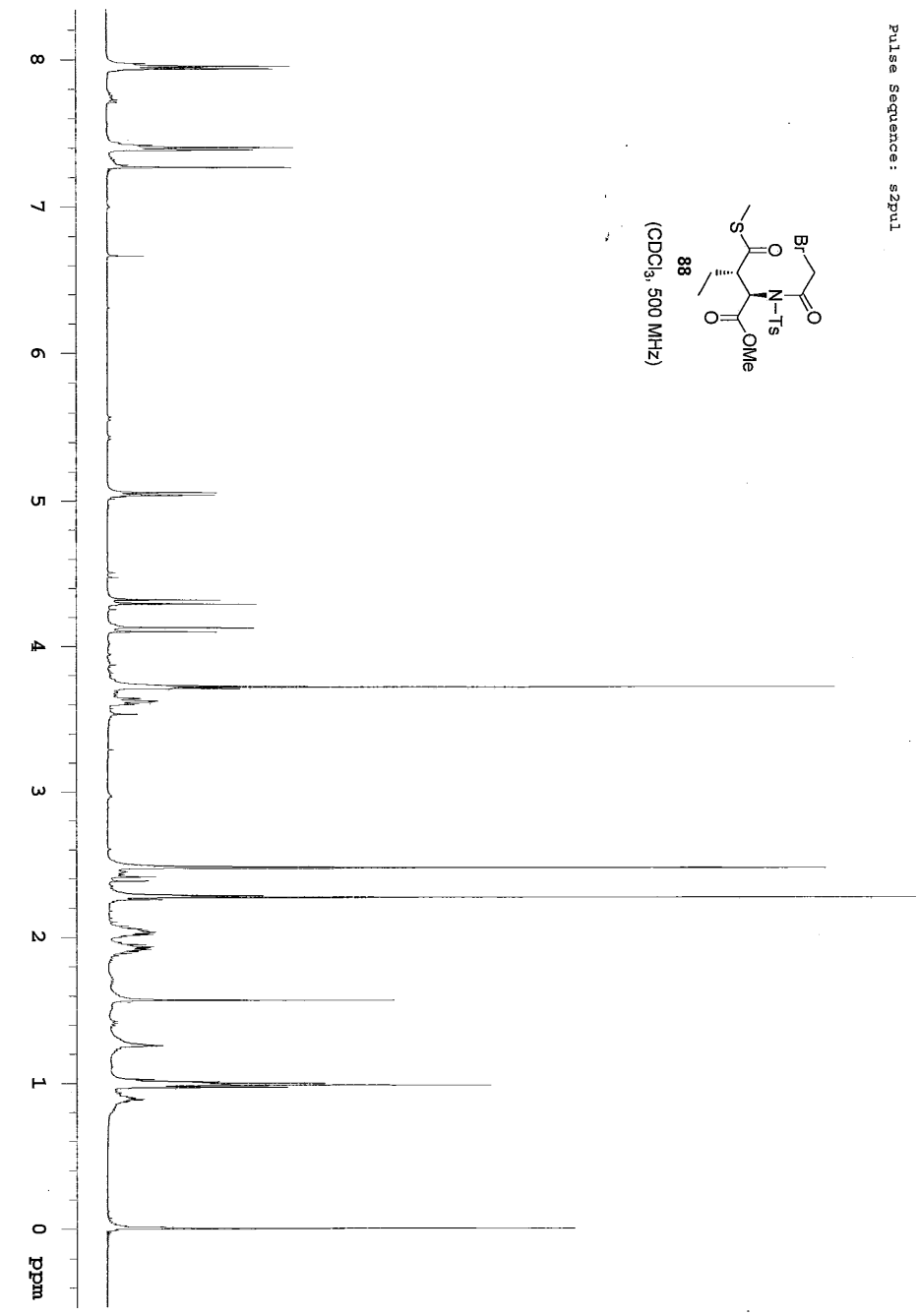
Pulse Sequence: s2pul

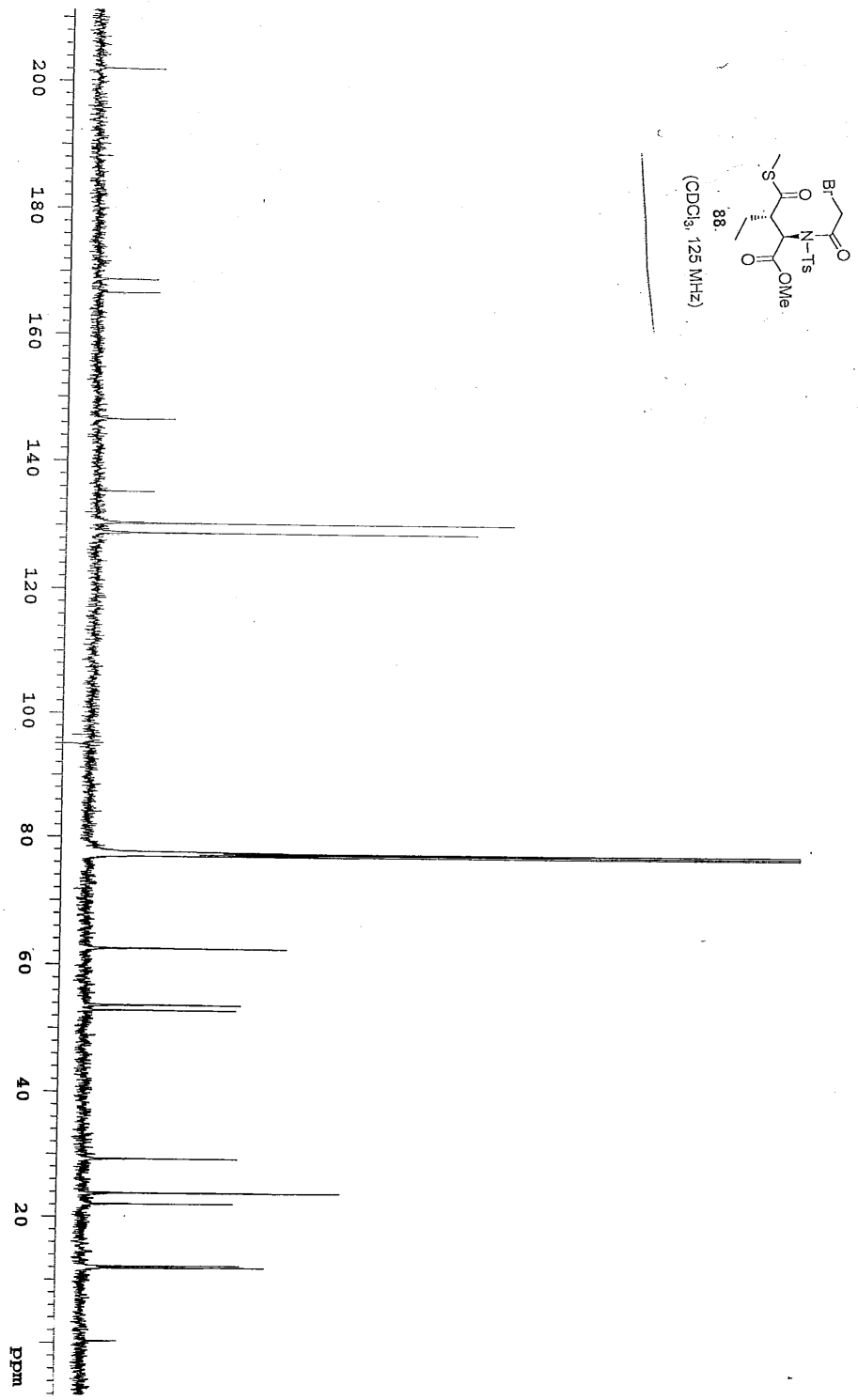


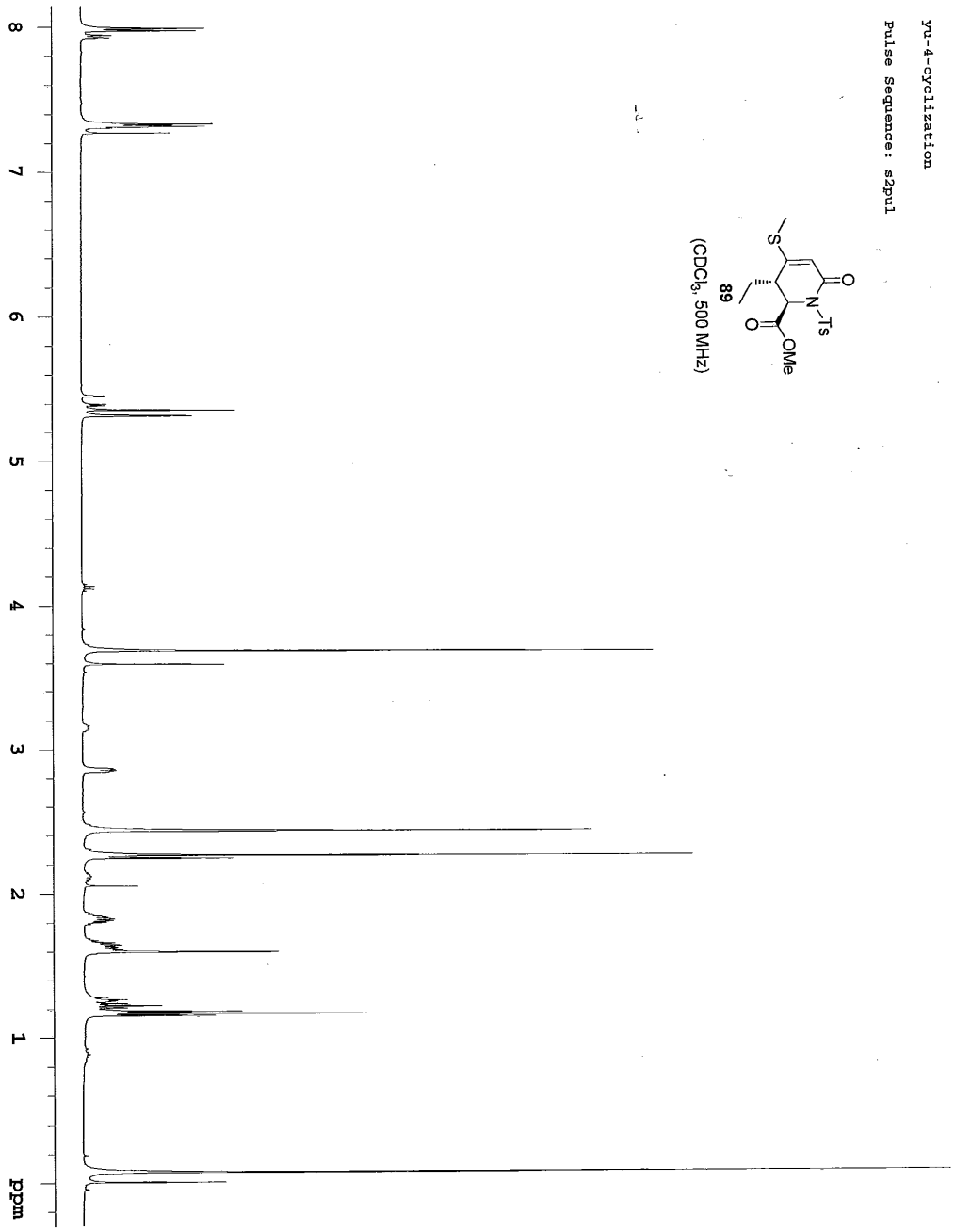
85

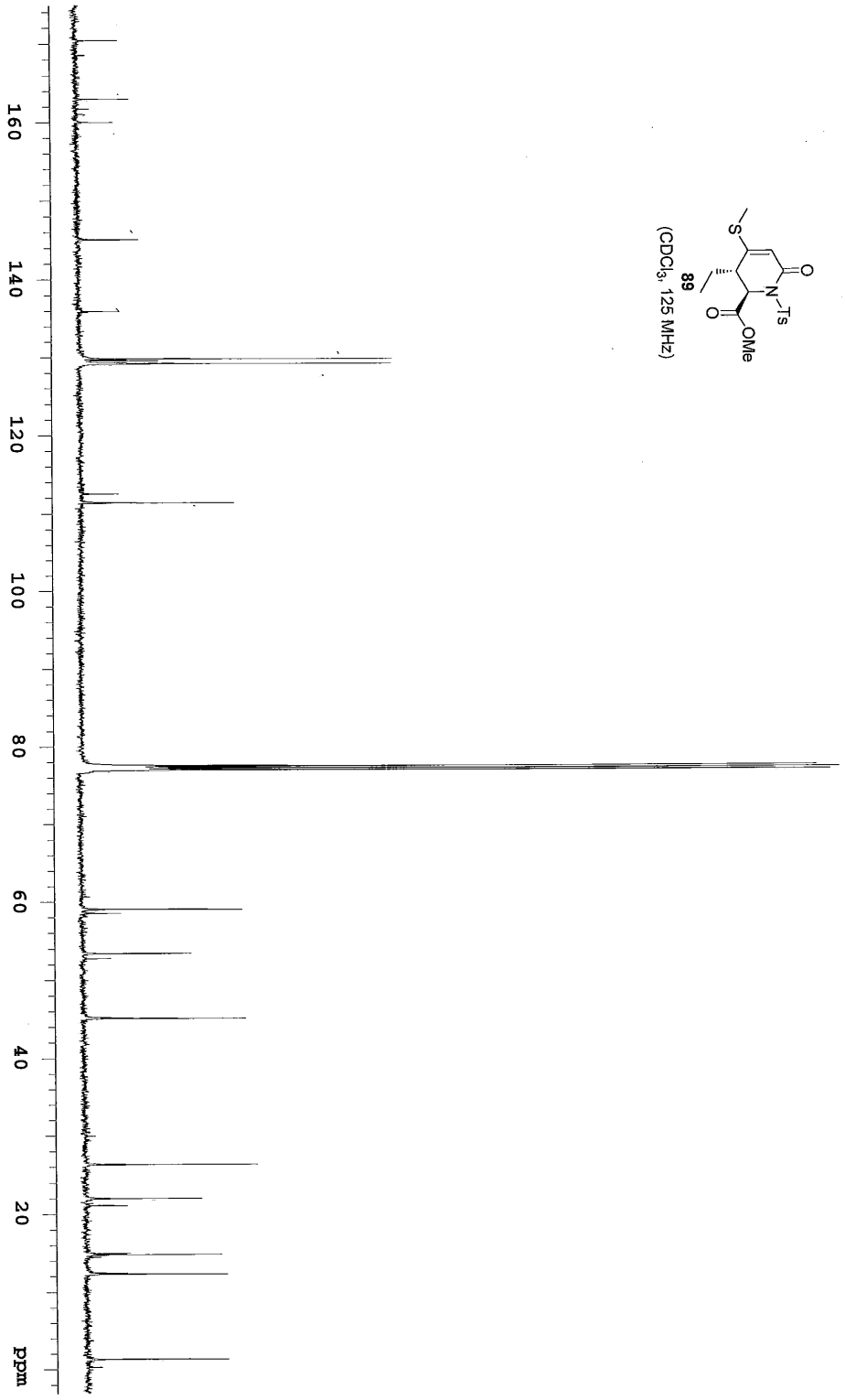
($CDCl_3$, 125 MHz)

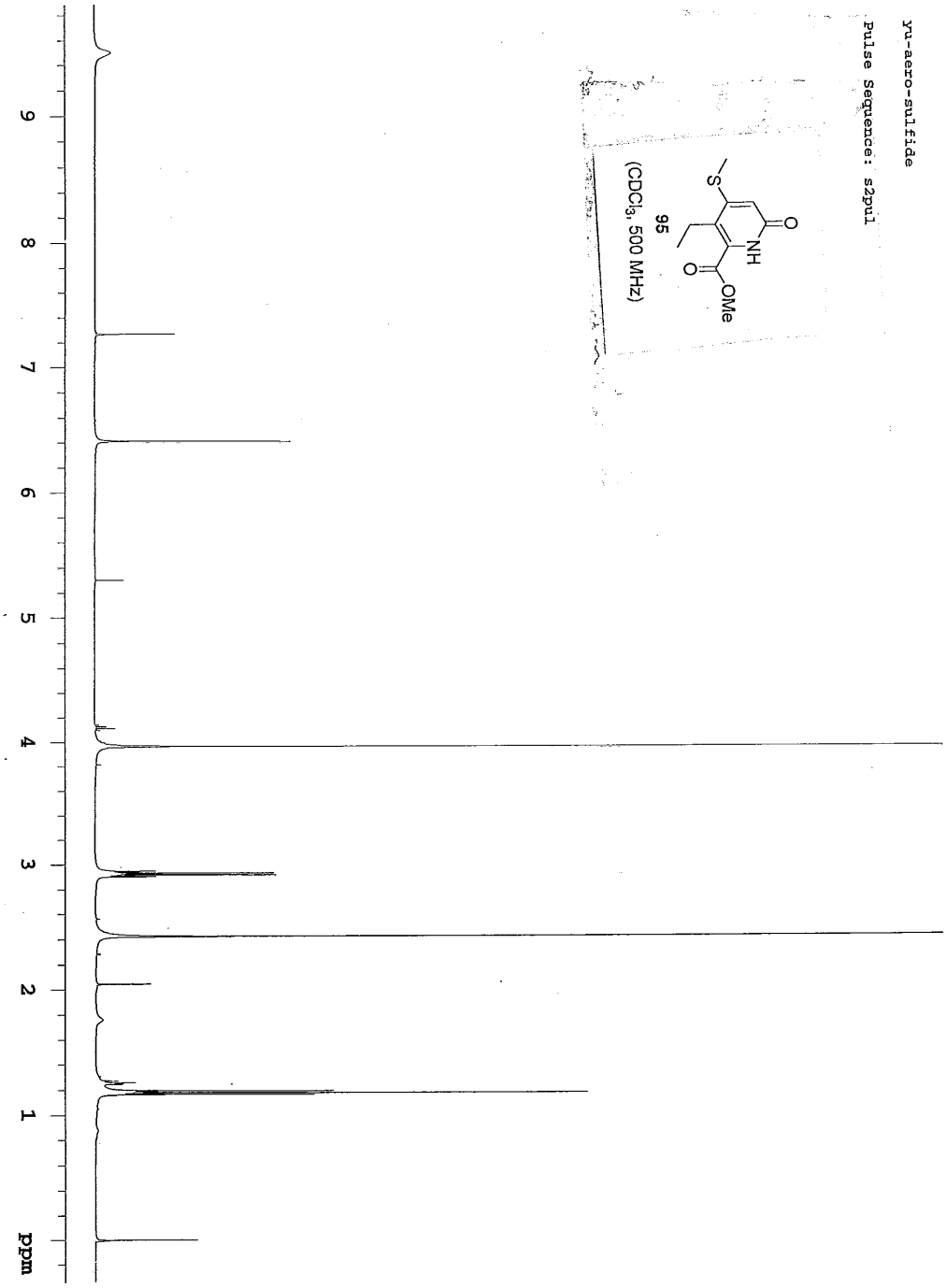



yu-3-216
Pulse Sequence: s2pul
88
(CDCl3, 500 MHz)
Br
O
N–Ts
O
OMe
S
O
8
7
6
5
4
3
2
1
0 ppm


yu-bromide
Pulse Sequence: s2pul
88.
(CDCl3, 125 MHz)
200
180
160
140
120
100
80
60
40
20
ppm

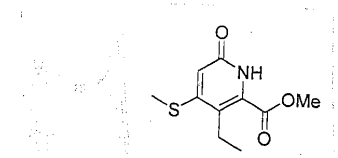

yu-4-cyclization
Pulse Sequence: s2pul
89
(CDCl3, 500 MHz)
OMe
Ts
ppm
8
7
6
5
4
3
2
1


yu-3-cyclization
Pulse Sequence: s2pul
89
(CDCl3, 125 MHz)
160
140
120
100
80
60
40
20
ppm


yu-aero-sulfide
Pulse Sequence: s2pul
95
(CDCl3, 500 MHz)
S
NH
O
O
OMe
9
8
7
6
5
4
3
2
1
ppm

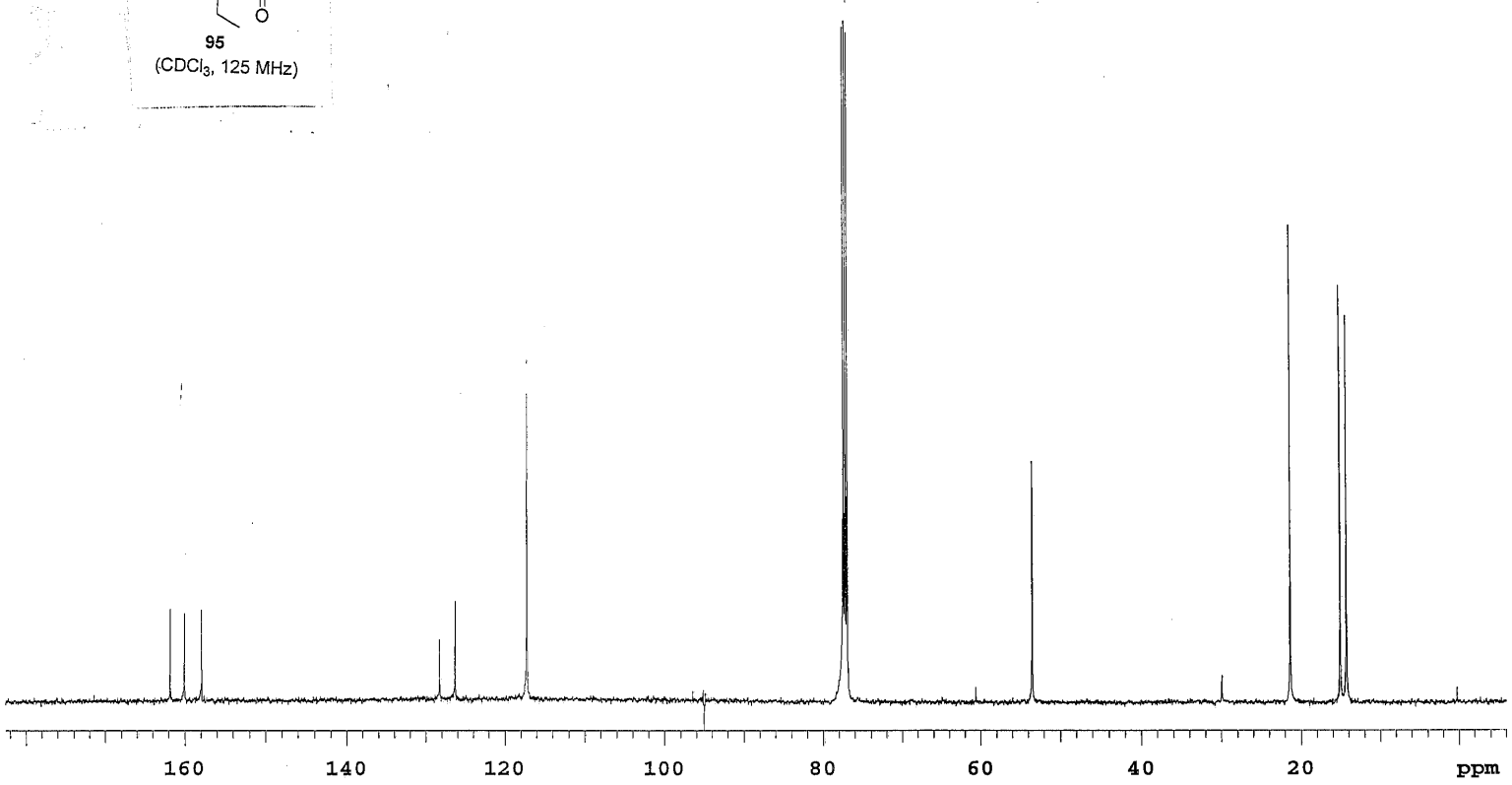
yu-areo-sulfife

Pulse Sequence: s2pul



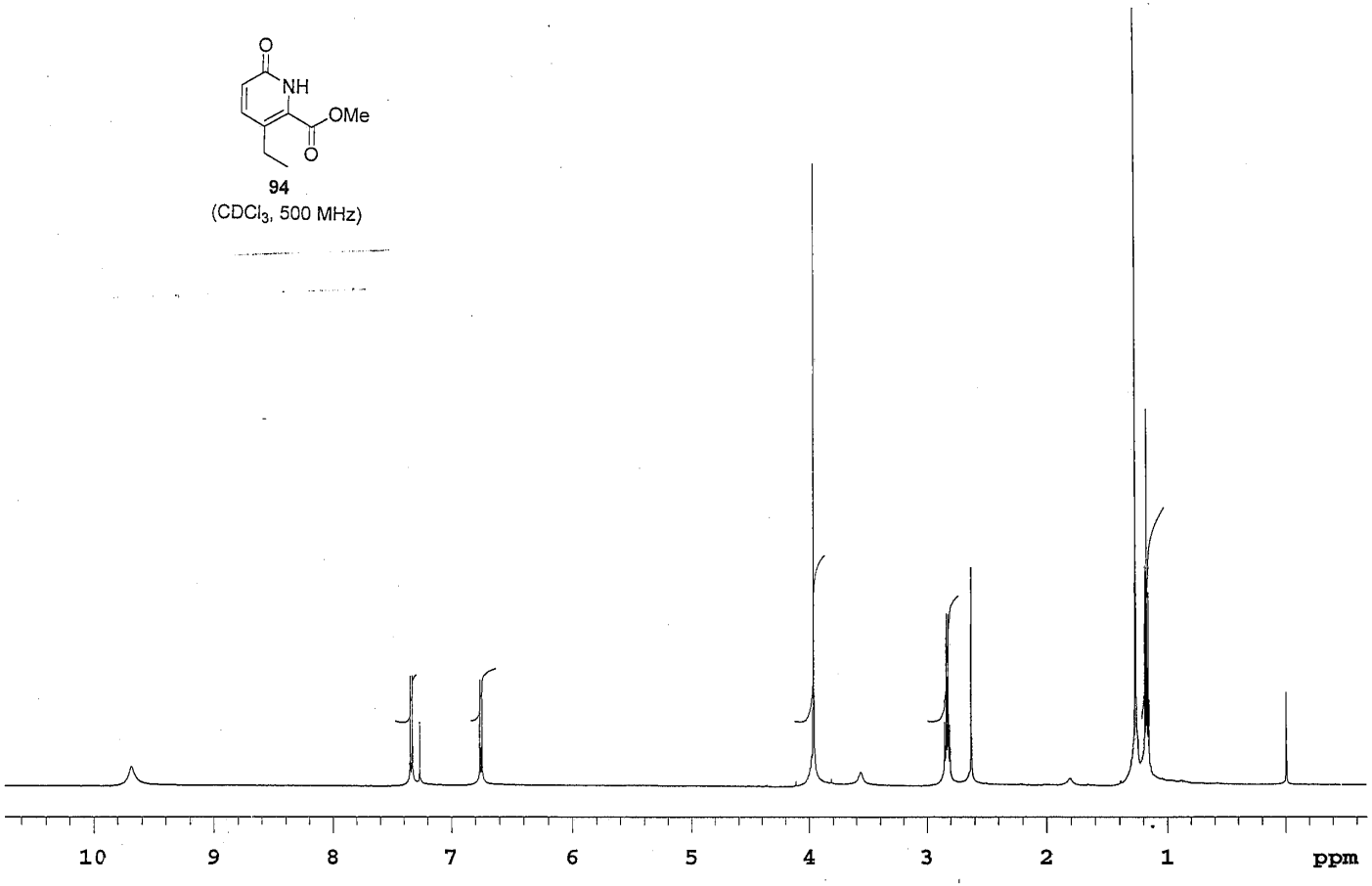
95

($CDCl_3$, 125 MHz)



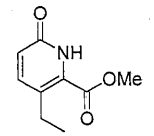
yu-final

Pulse Sequence: s2pul



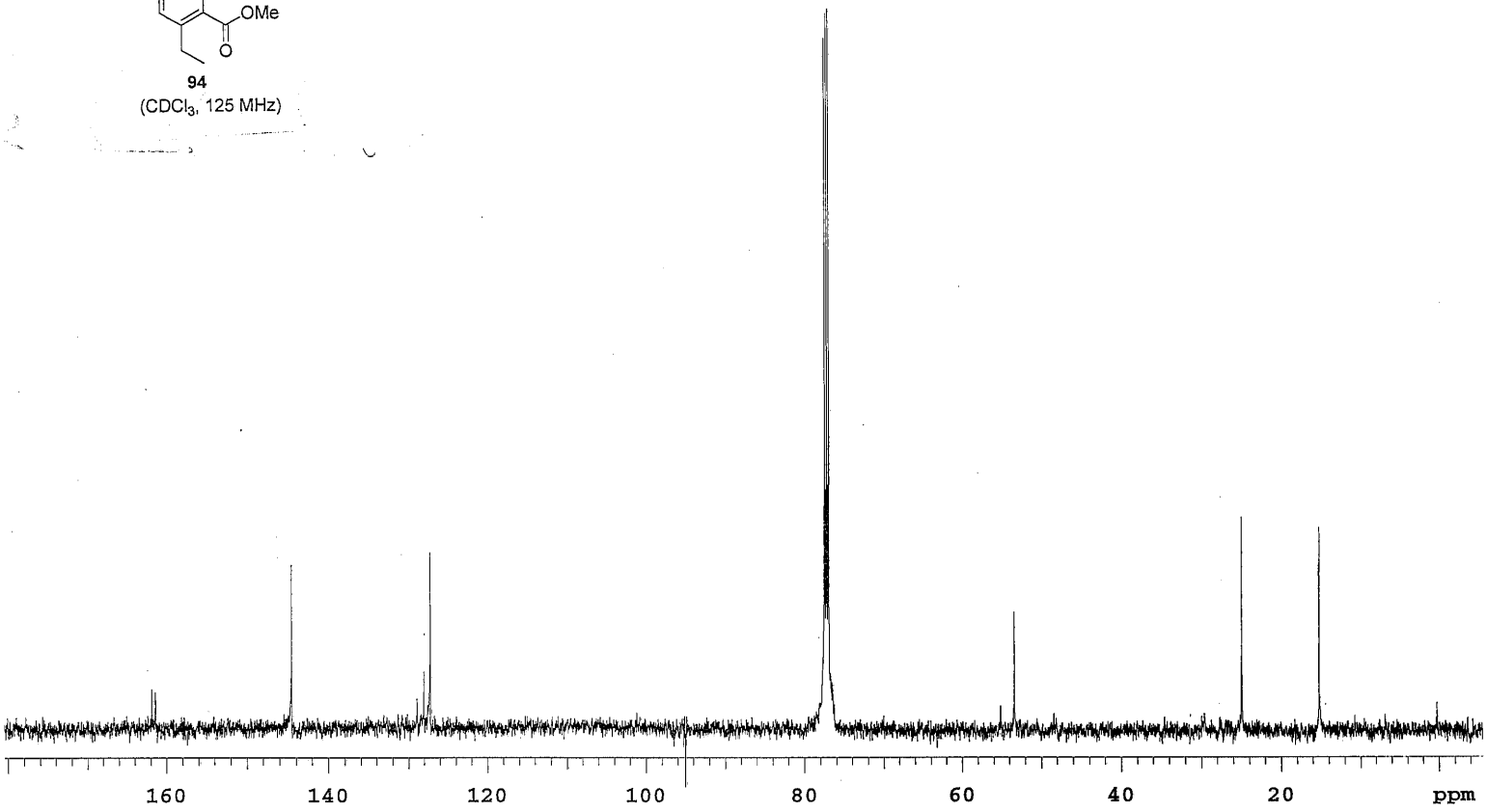
yu-pyridone

Pulse Sequence: s2pul



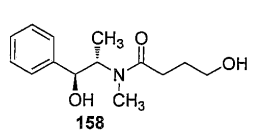
94

($CDCl_3$, 125 MHz)



yu-4-269

Pulse Sequence: s2pul

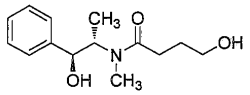


158

($CDCl_3$, 500 MHz)

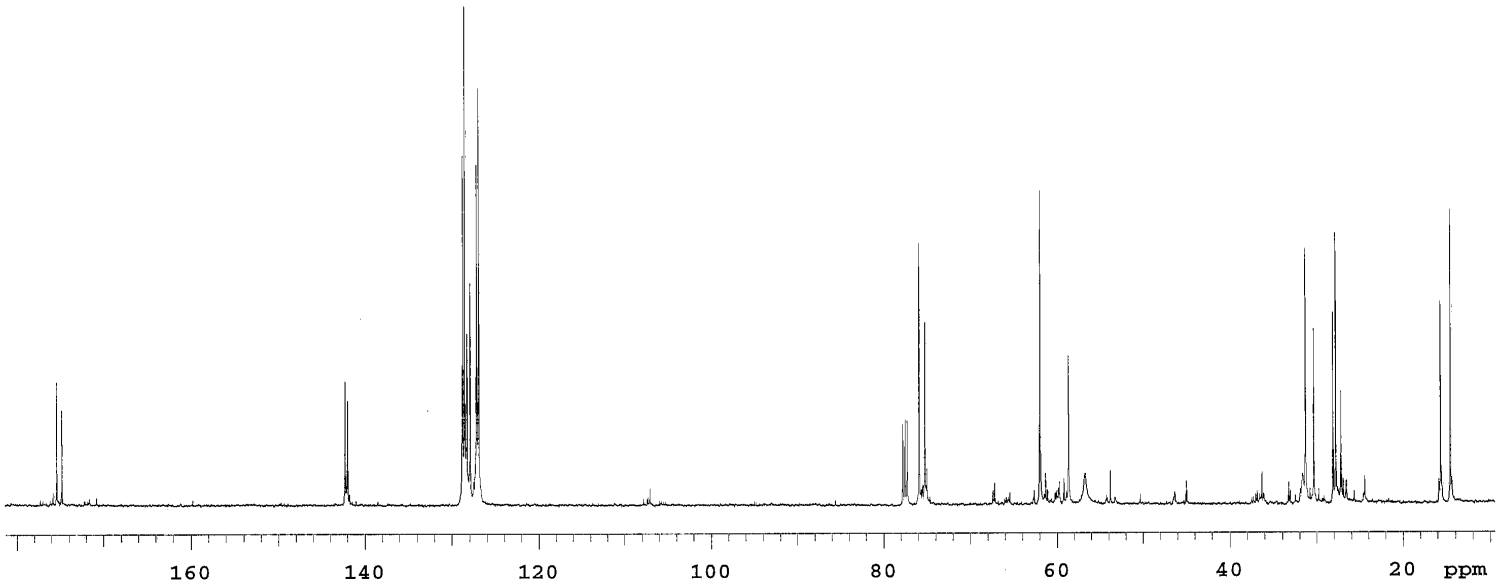
yu-3-157

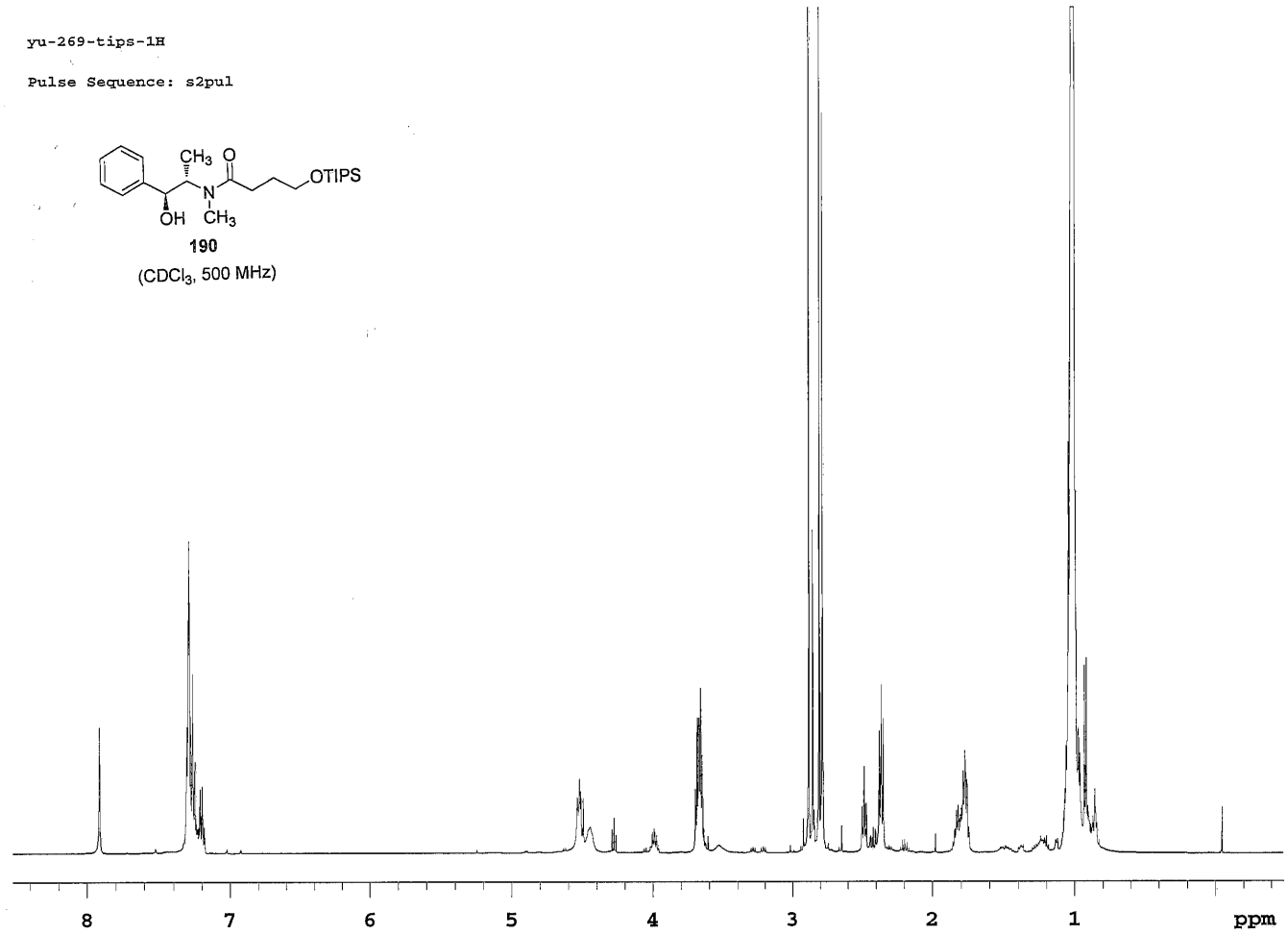
Pulse Sequence: s2pul

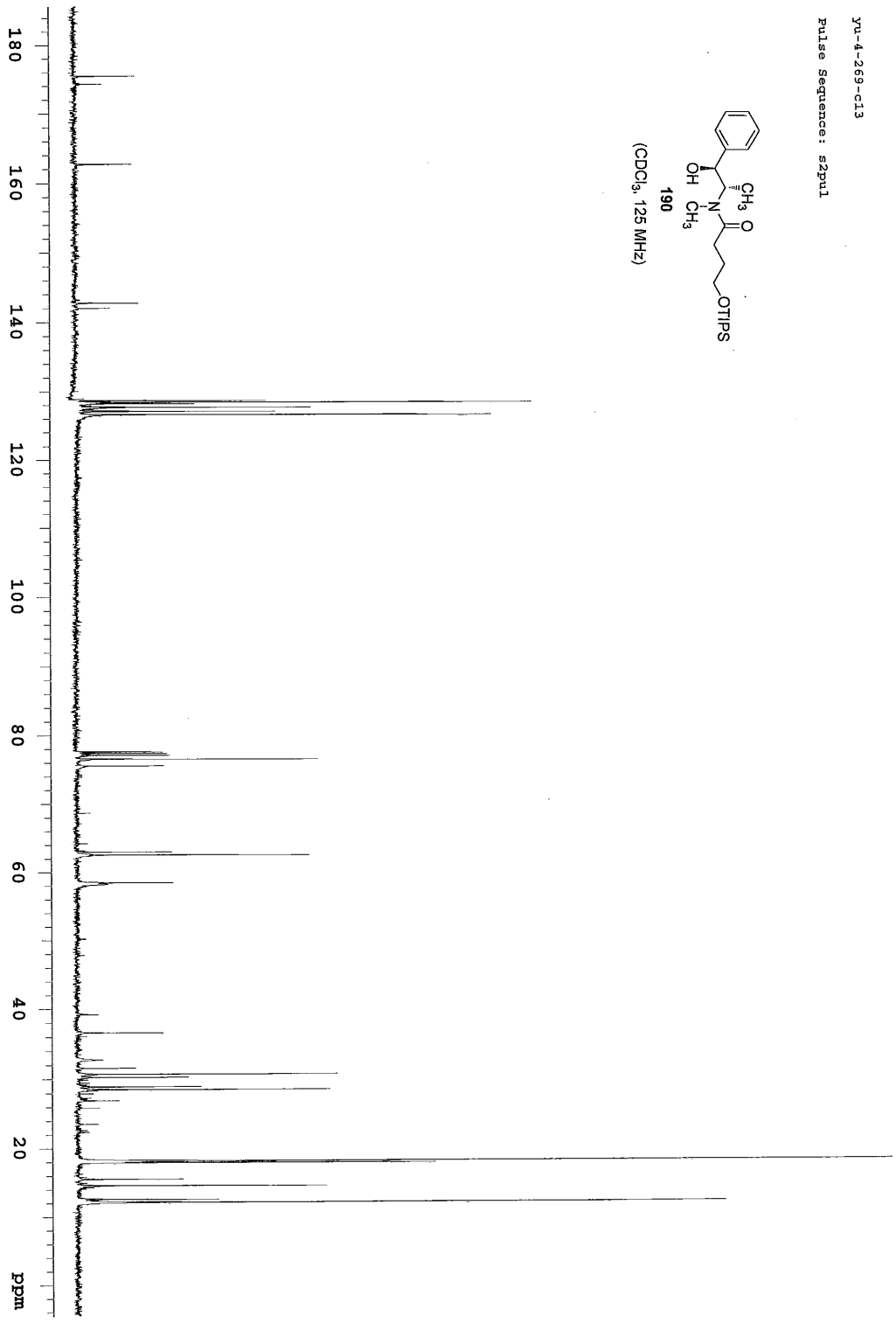


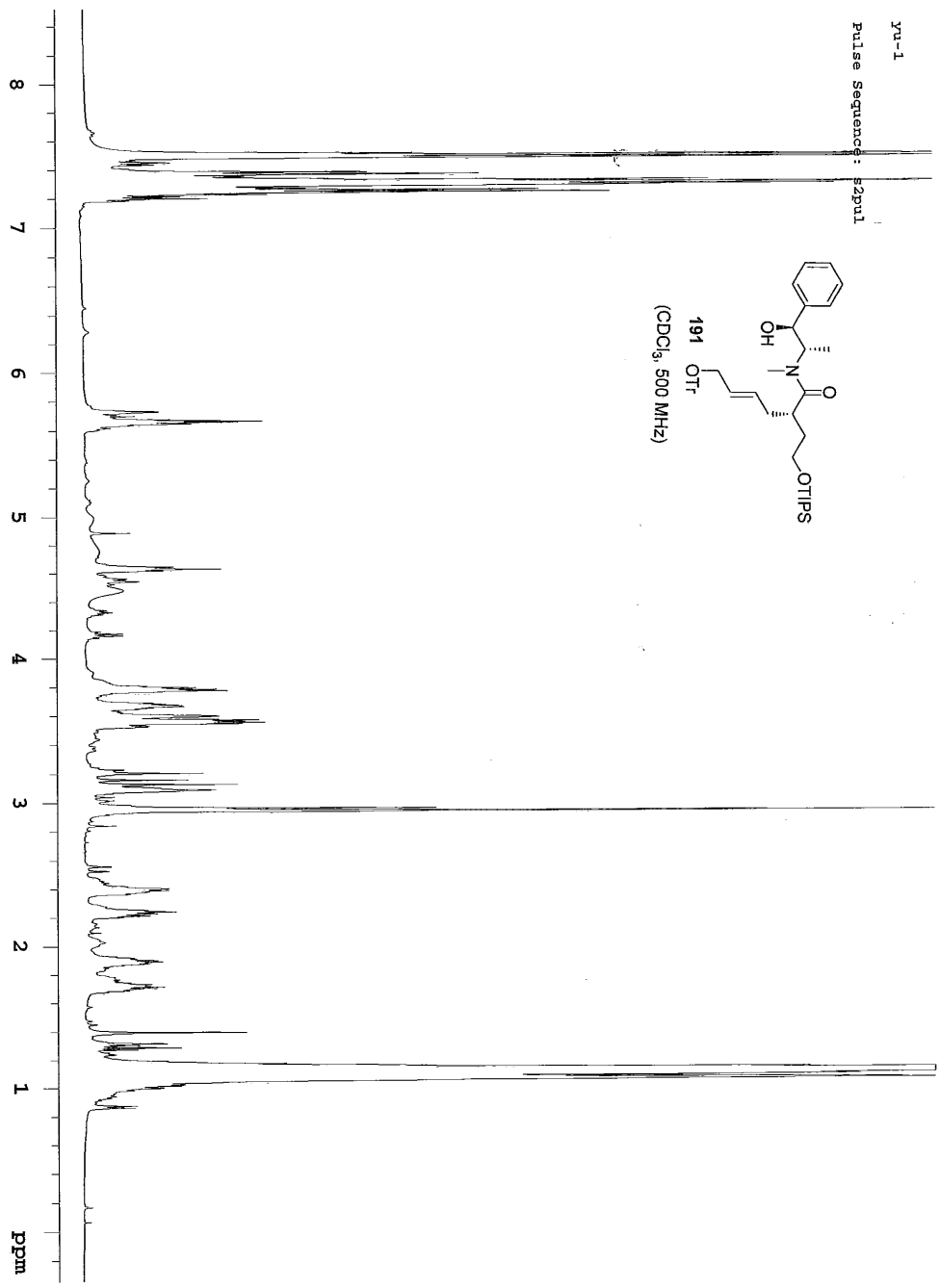
158

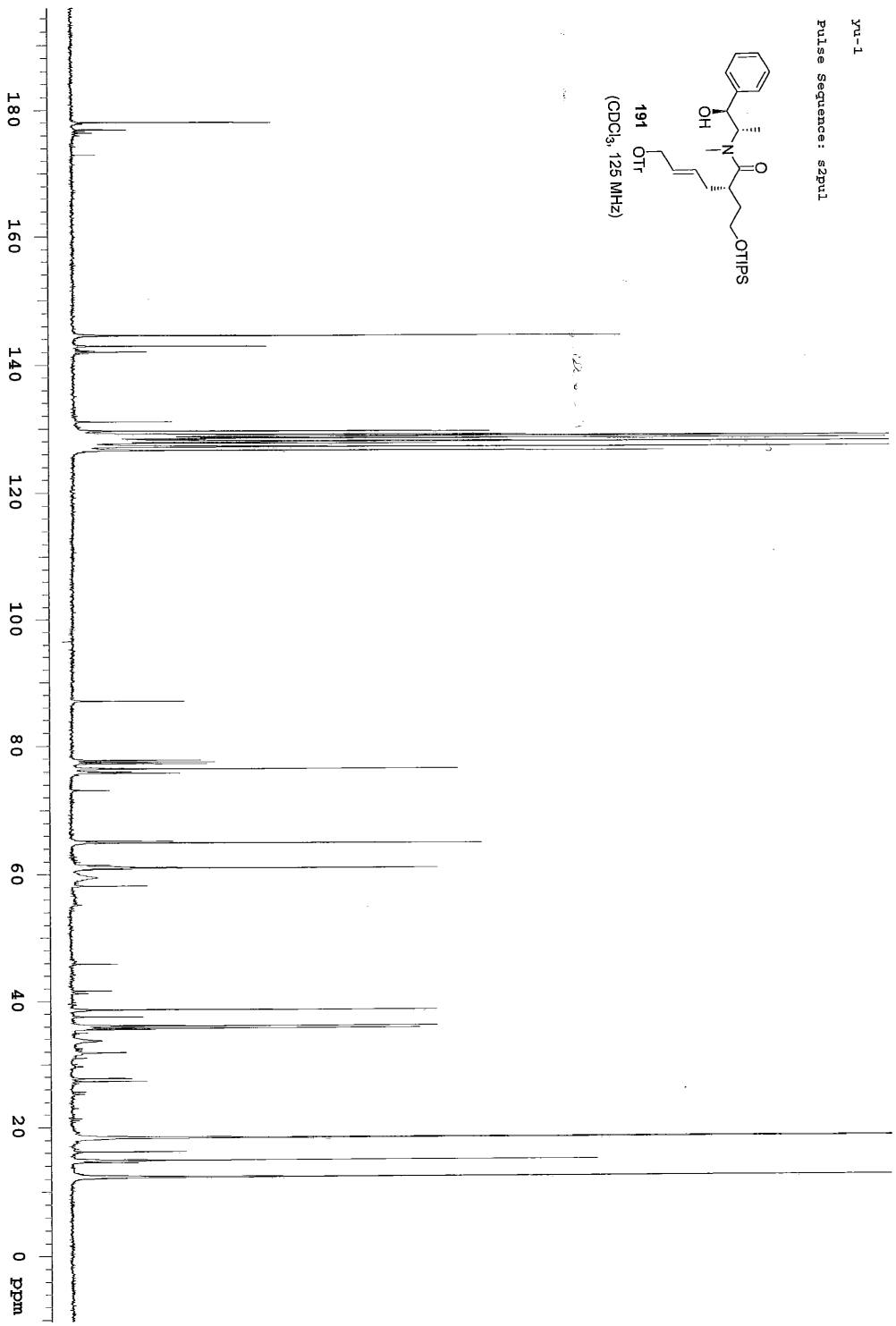
($CDCl_3$, 125 MHz)

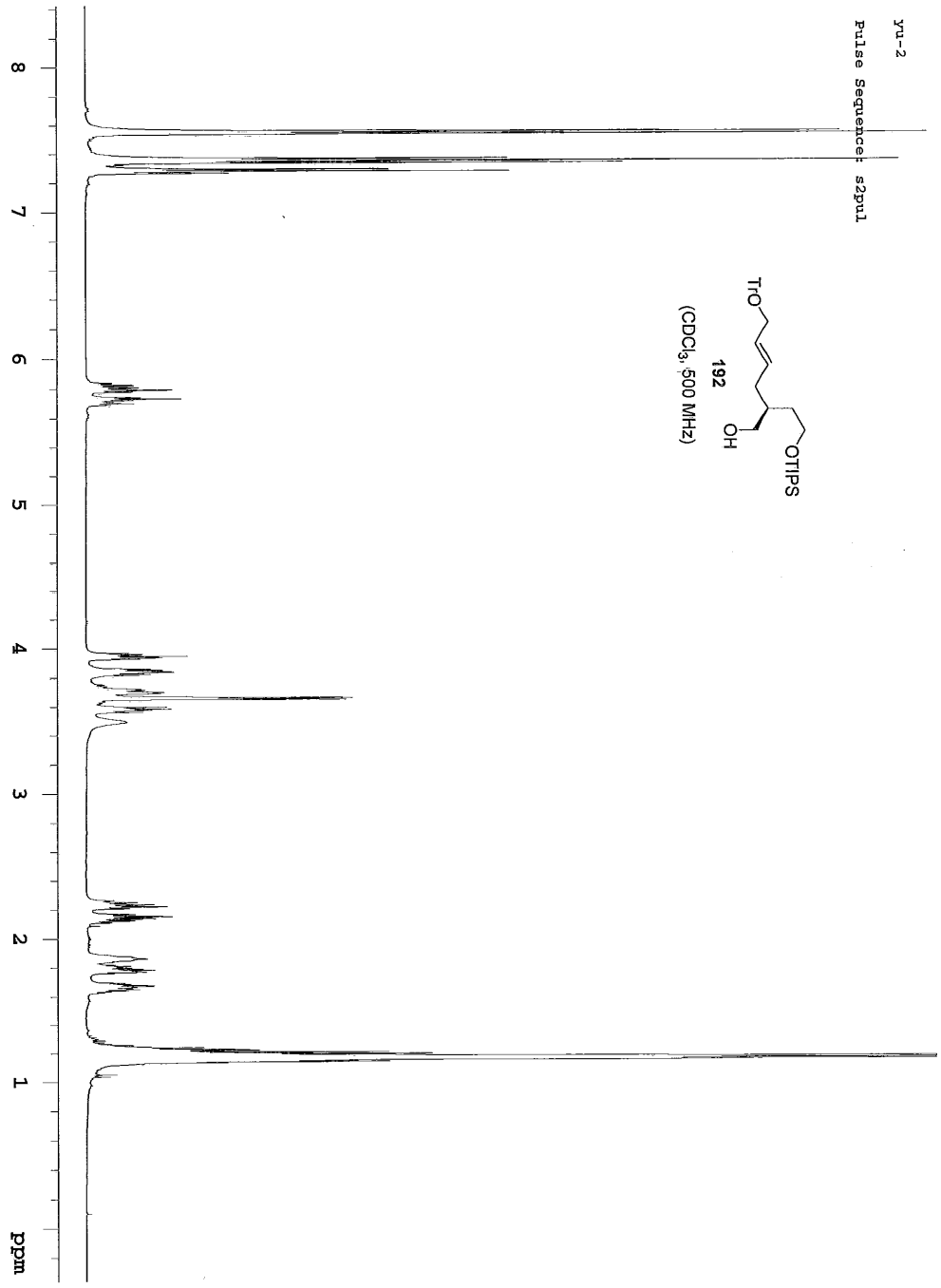


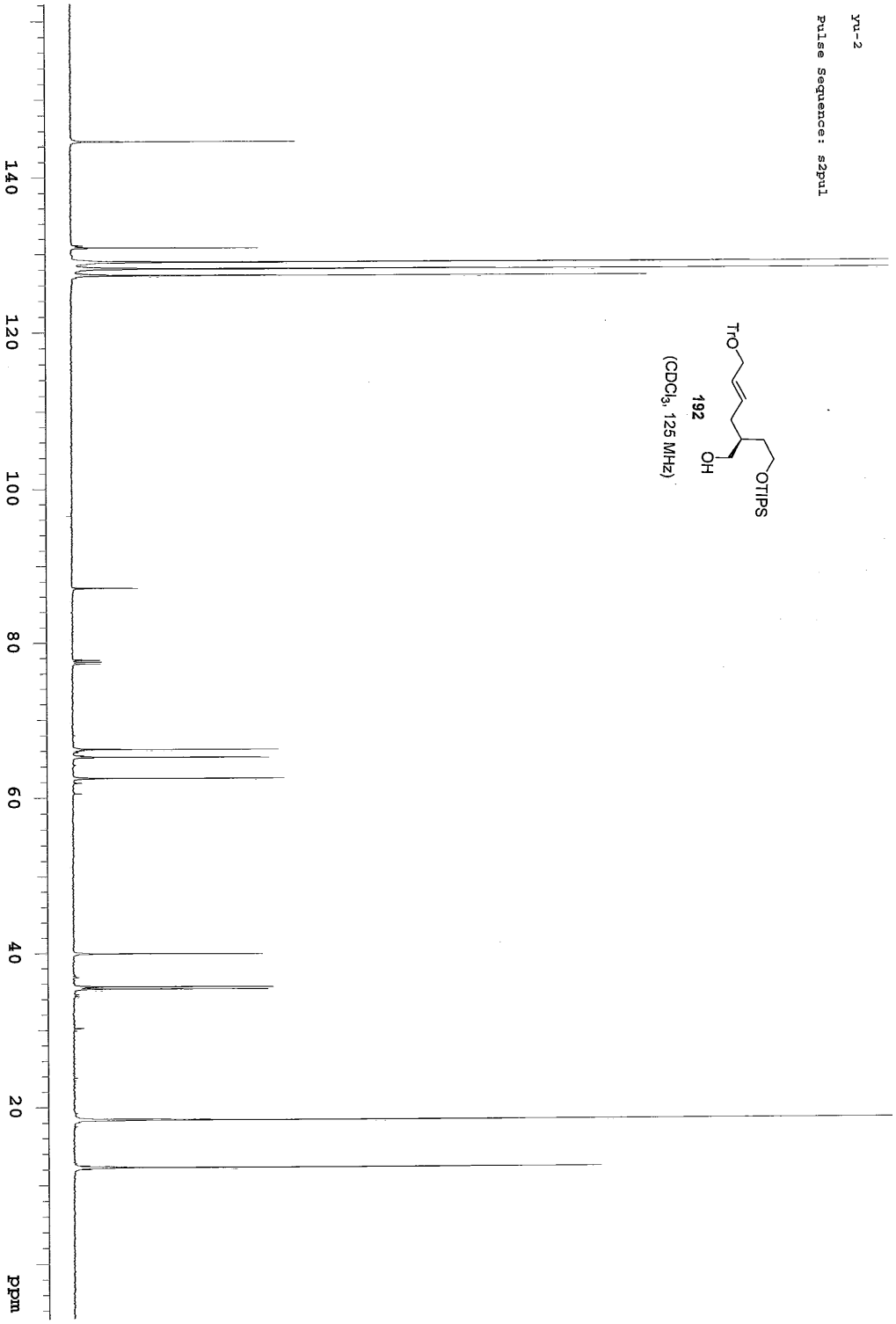

yu-269-tips-1H
Pulse Sequence: s2pul
CH3
O
OTIPS
N
OH
CH3
190
(CDCl3, 500 MHz)
8
7
6
5
4
3
2
1
ppm

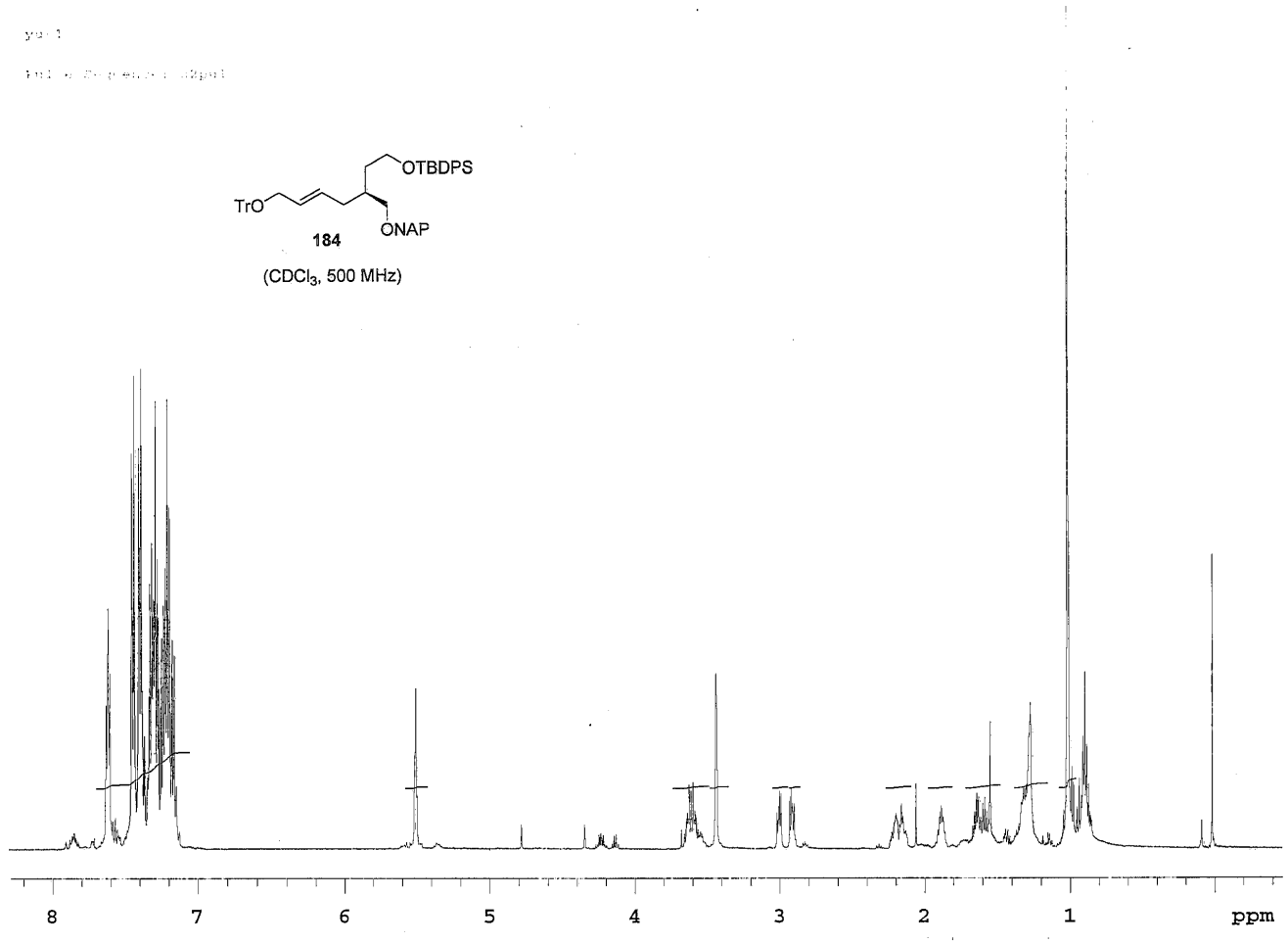

yu-4-269-c13
Pulse Sequence: s2pul
OH
CH3
N
CH3
O
OTIPS
190
(CDCl3, 125 MHz)
180
160
140
120
100
80
60
40
20
ppm

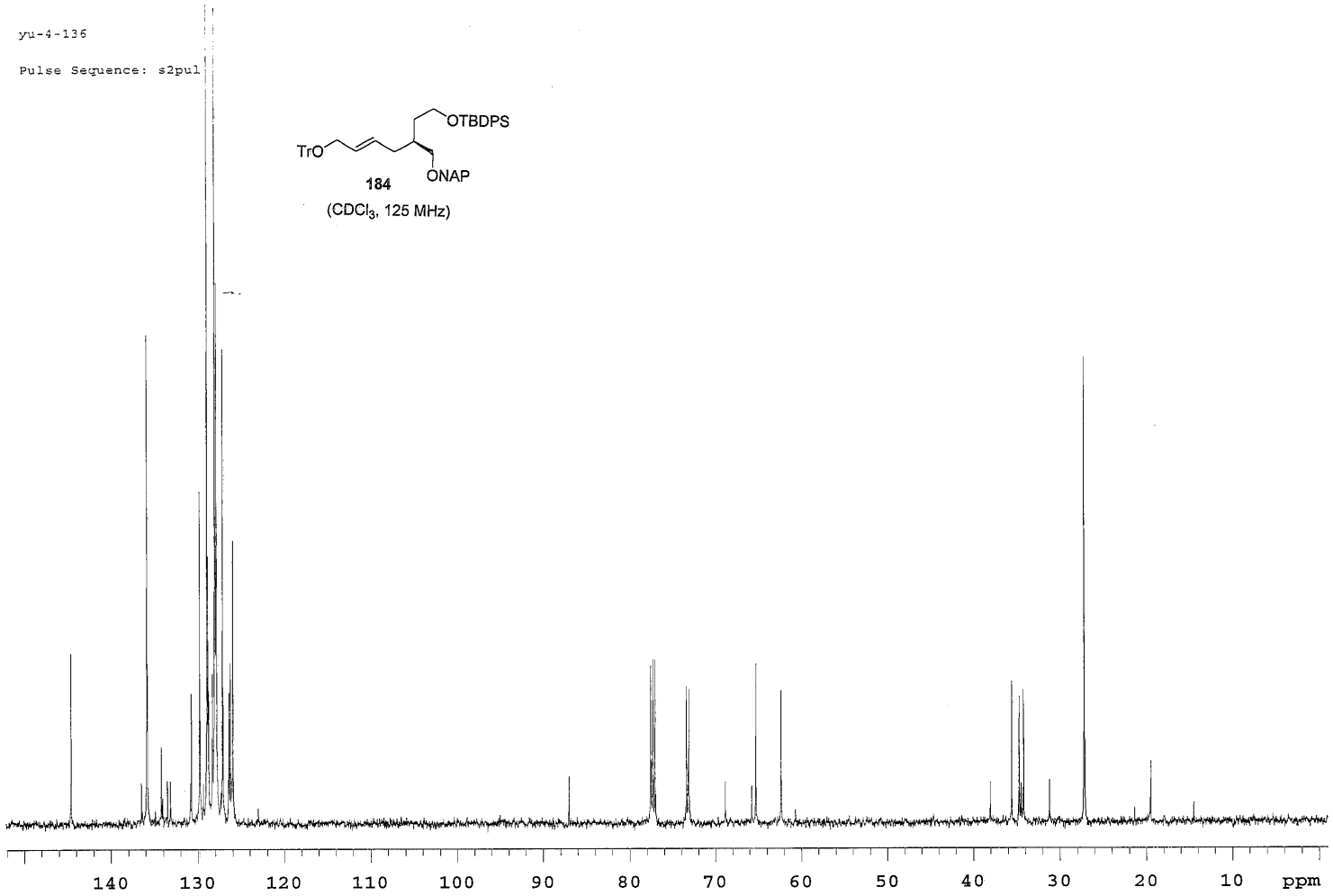

yu-1
Pulse Sequence: s2pul
OH
N
O
OTIPS
191
OTr
(CDCl3, 500 MHz)
8
7
6
5
4
3
2
1
ppm

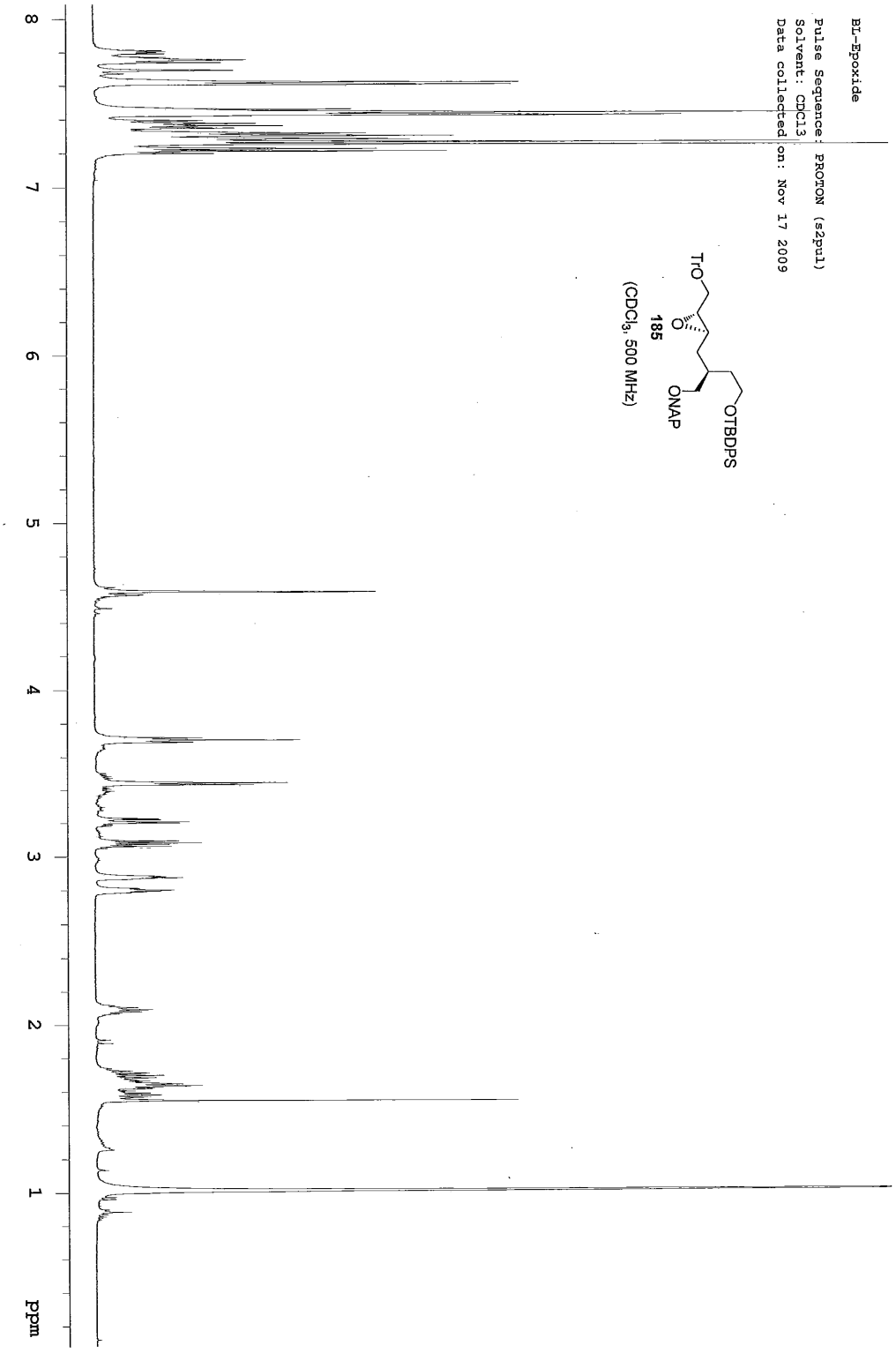

yu-1
Pulse Sequence: s2pul
OH
N
O
OTIPS
191 OTr
(CDCl3, 125 MHz)
180
160
140
120
100
80
60
40
20
0 ppm

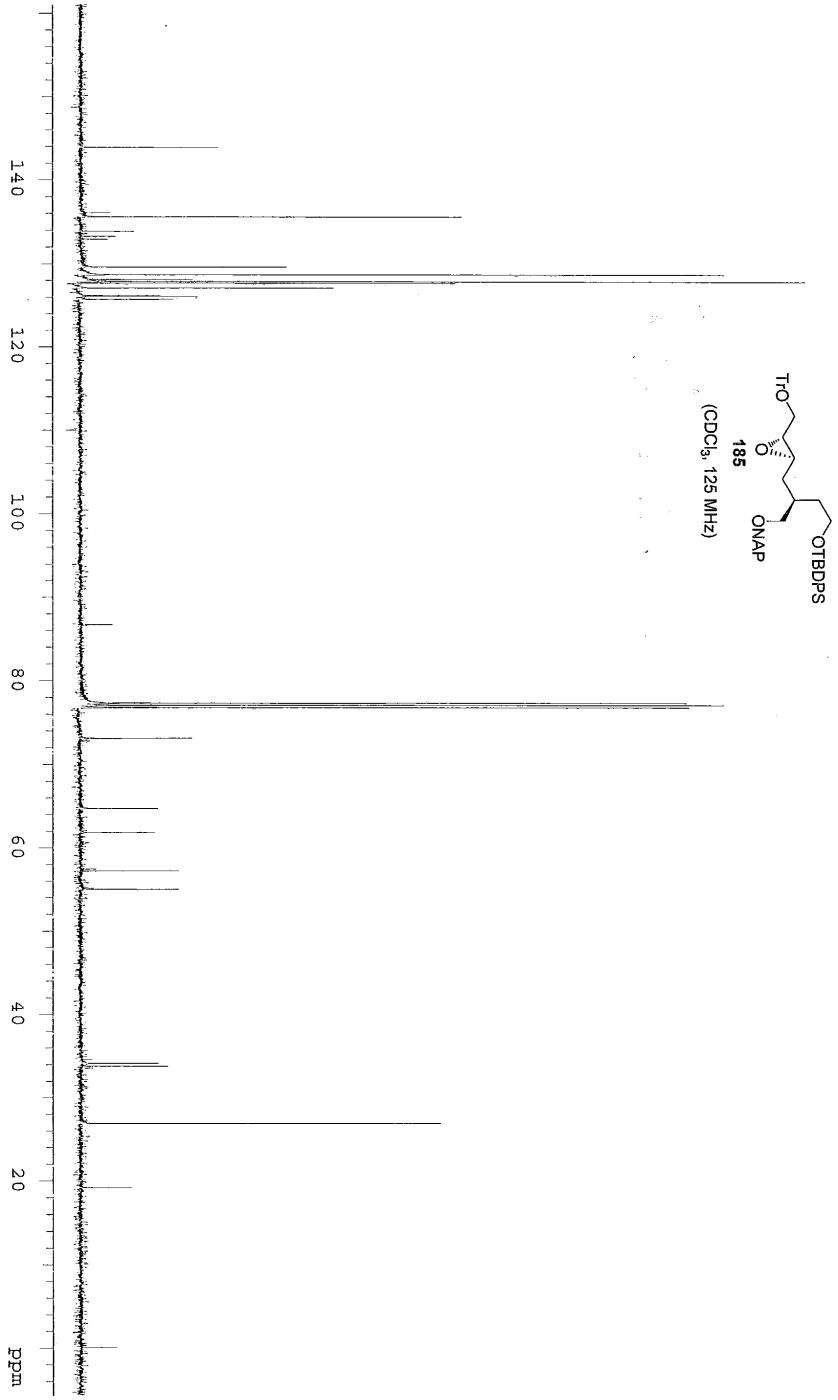

yu-2
Pulse Sequence: s2pul
TrO
OH
OTIPS
192
(CDCl3, 500 MHz)
8
7
6
5
4
3
2
1
ppm


yu-2
Pulse Sequence: s2pul
TrO
OTIPS
OH
192
(CDCl3, 125 MHz)
140
120
100
80
60
40
20
ppm


OTBDPS
TrO
ONAP
184
(CDCl3, 500 MHz)
8
7
6
5
4
3
2
1
ppm

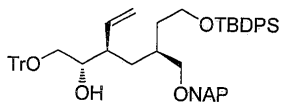

yu-4-136
Pulse Sequence: s2pul
TrO
OTBDPS
ONAP
184
(CDCl3, 125 MHz)
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


BI-Epoxide
Pulse Sequence: PROTON (s2pul)
Solvent: CDCl3
Data collected on: Nov 17 2009
TrO
O
ONAP
OTBDPS
185
(CDCl3, 500 MHz)
8
7
6
5
4
3
2
1
ppm


TrO
O
ONAP
OTBDPS
185
(CDCl3, 125 MHz)
140
120
100
80
60
40
20
ppm

yu-opening-1

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 4 2009

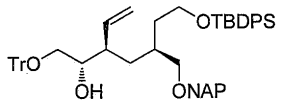


186

($CDCl_3$, 500 MHz)

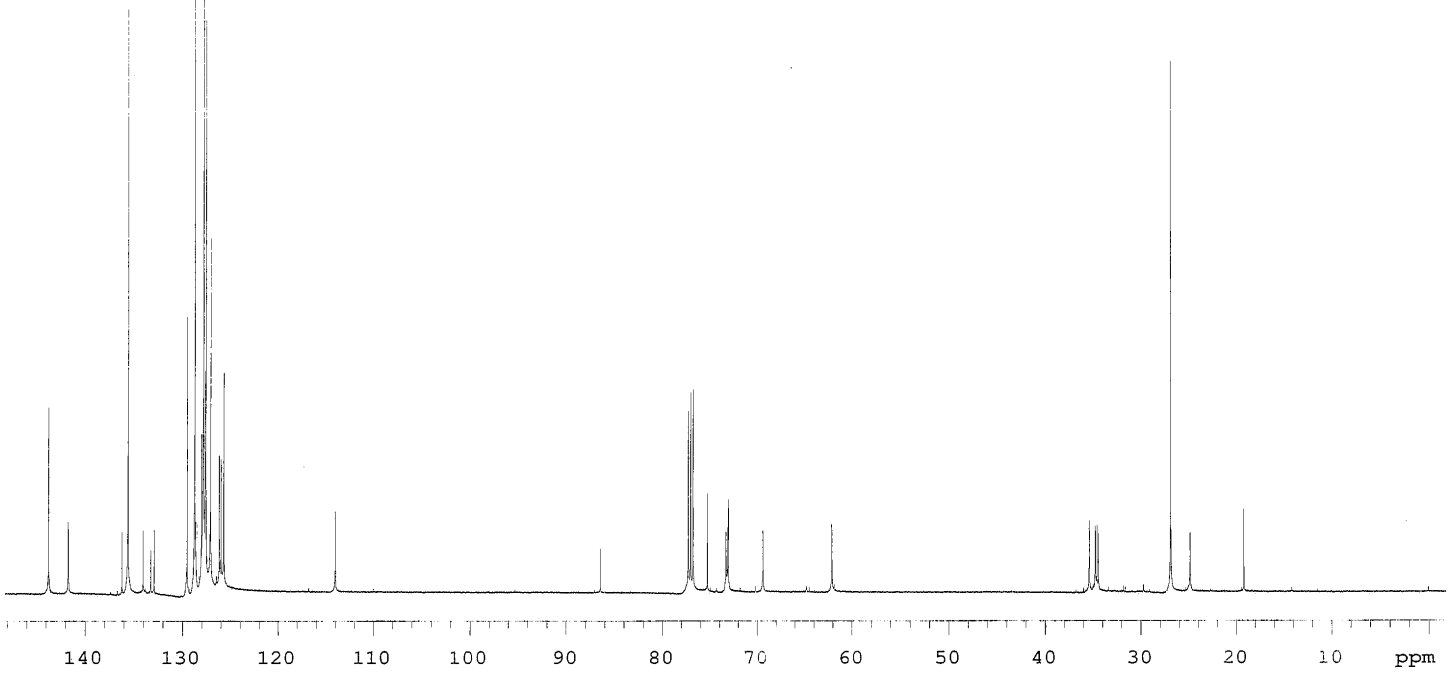
yu-ringopening-c13pure

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 4 2009



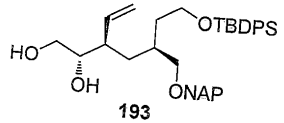
186

($CDCl_3$, 125 MHz)



yu-diol

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 12 2009

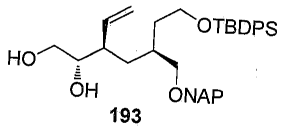


193

($CDCl_3$, 500 MHz)

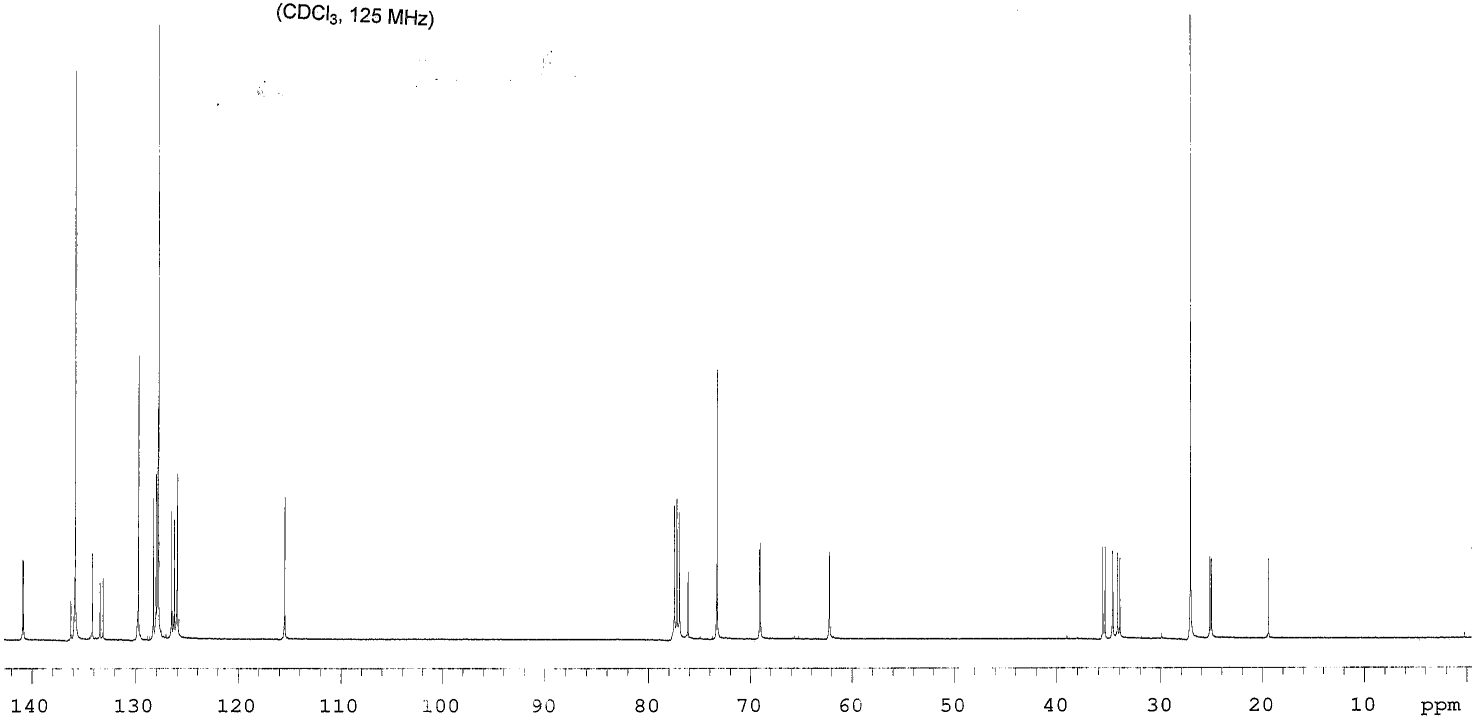
yu-diol-cl3pure

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 12 2009



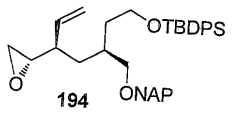
193

($CDCl_3$, 125 MHz)



yu-epoxide

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 4 2009

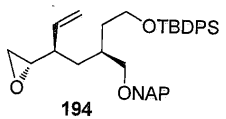


194

($CDCl_3$, 500 MHz)

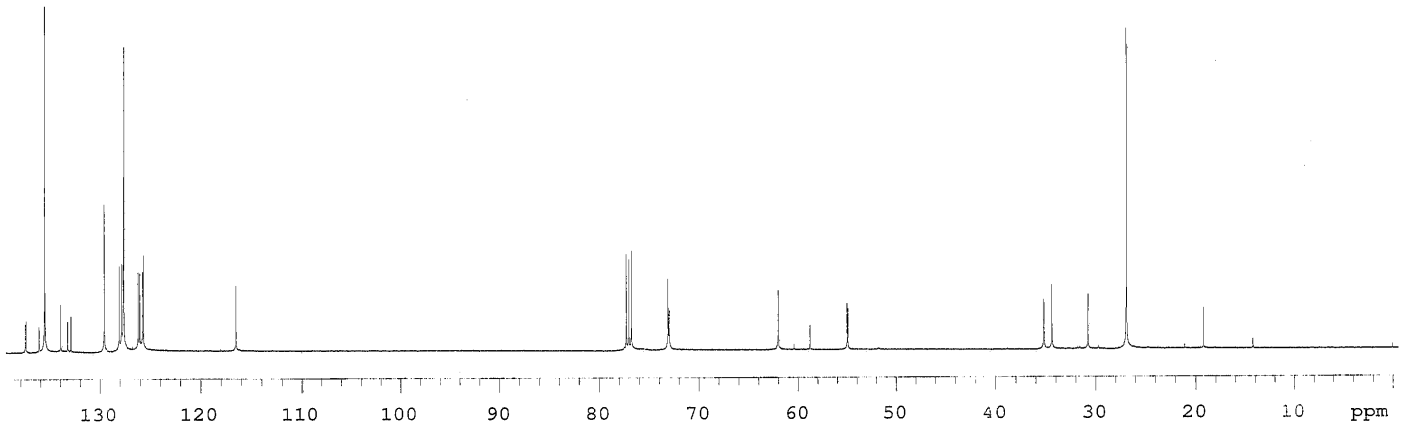
yu-epoxide-c13

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 4 2009



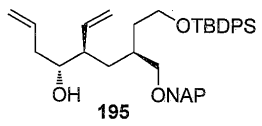
194

($CDCl_3$, 125 MHz)



yu-diene-1

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 5 2009

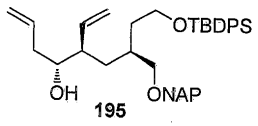


195

($CDCl_3$, 500 MHz)

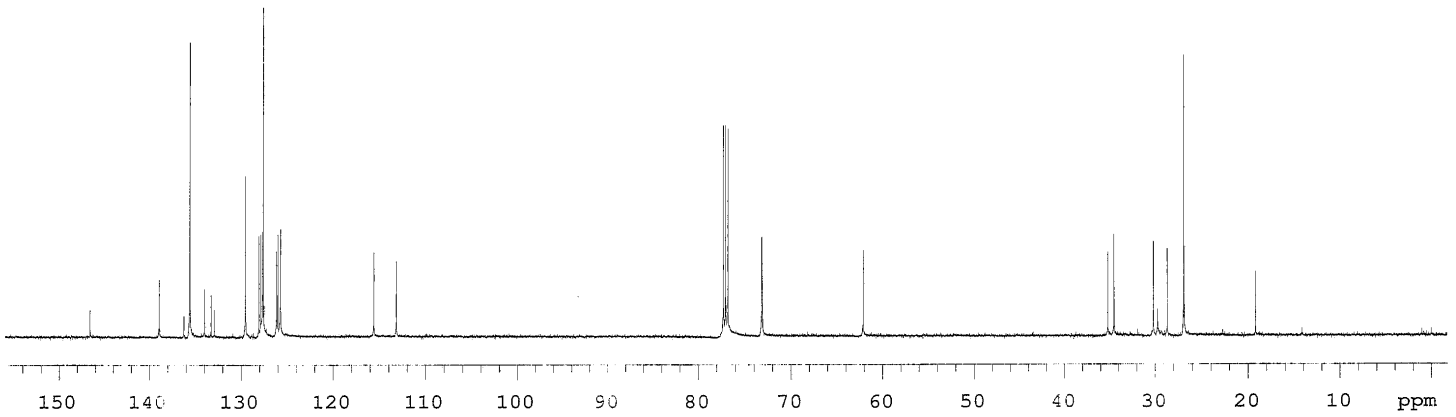
yu-1

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 8 2009



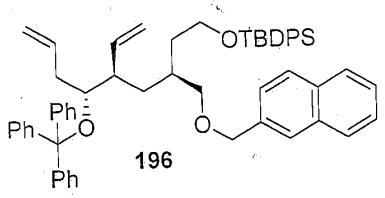
195

($CDCl_3$, 125 MHz)



yu-tr-2

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 27 2009

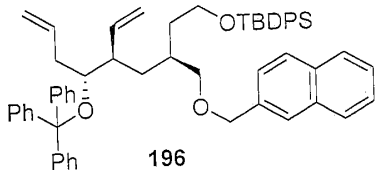


196

($CDCl_3$, 500 MHz)

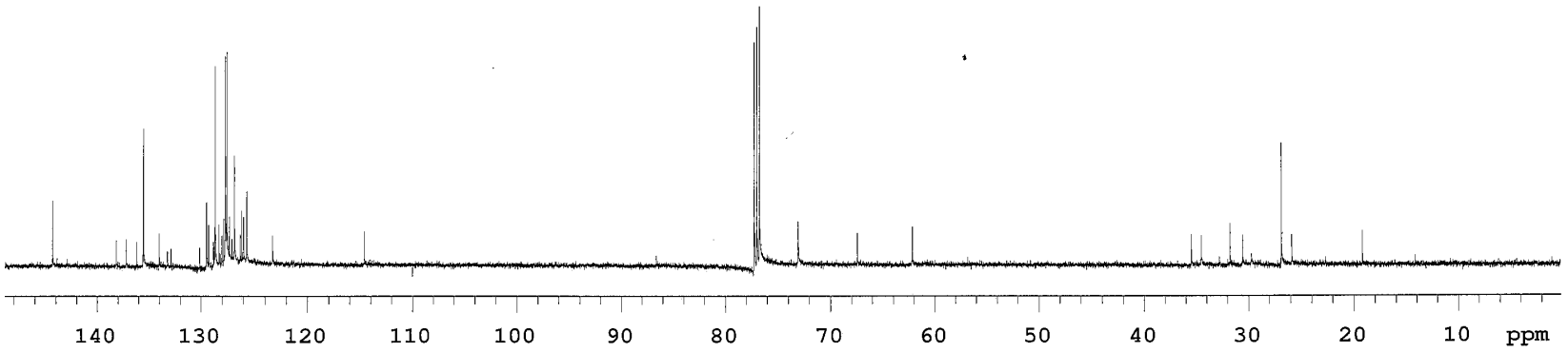
yu-tr-protection

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 27 2009



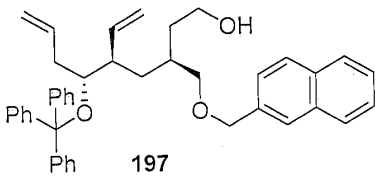
196

($CDCl_3$, 125 MHz)



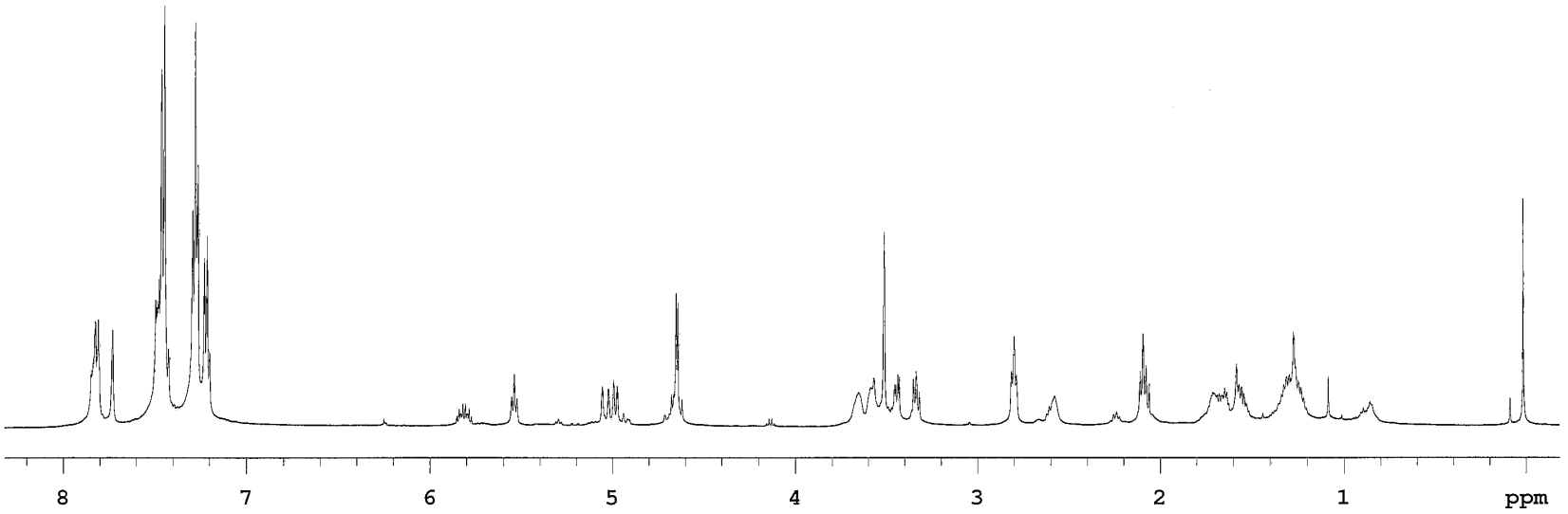
yu-alcihol-beforeacid

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Nov 28 2009



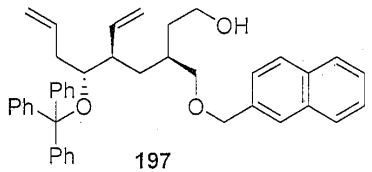
197

($CDCl_3$, 500 MHz)



yu-alcohol-beforeacid

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Nov 28 2009



197

($CDCl_3$, 125 MHz)