2013-07-18

Studies Toward the Synthesis of Lyconadin A and Cranomycin

Brad M. Loertscher
Brigham Young University - Provo

Studies Toward the Synthesis of Lyconadin A and Cranomycin

Brad M. Loertscher

A dissertation submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Steven L. Castle, Chair
Merritt B. Andrus
Paul B. Savage
Joshua L. Price
Roger G. Harrison

Department of Chemistry and Biochemistry

Brigham Young University

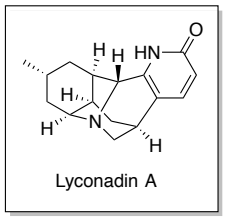
August 2013

ABSTRACT

Studies Toward the Total Synthesis
of Lyconadin A and
Cranomycin

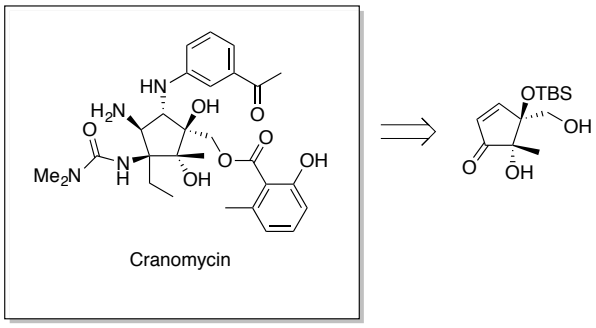
Brad M. Loertscher
Department of Chemistry and Biochemistry, BYU
Doctor of Philosophy

Lyconadin A is a pentacyclic *Lycopodium* alkaloid isolated from the club moss *Lycopodium companatum* with anticancer activity. Our approach sought to incorporate a 7-*exo*–6-*exo* acyl radical cyclization cascade to access the bicyclo[5.4.0]undecane framework of lyconadin A. Our studies created methodology for the synthesis of 5-alkyl and 3,5-dialkyl-6-carbomethoxy-2-pyridones and sterically demanding epoxide substrates. These epoxide substrates underwent an unanticipated Payne rearrangement.



Lyconadin A

Cranomycin is a potent antibiotic with antiprotozoal activity. Structurally it is a cyclopentane ring system with substitution at each carbon in the ring. Another interesting structural aspect is the existence of three contiguous quaternary stereocenters including two tertiary alcohols and a *tert*-alkylamine. Our strategy led to the development of a highly diastereoselective synthesis of vicinal tertiary diol systems. We have successfully synthesized the cyclopentenone system shown above, from which we hope to assemble cranomycin.



Cranomycin

Keywords: epoxidation, pyridone synthesis, lyconadin A, tandem radical cyclization, tethered radical vinylation, Grignard addition, cranomycin

ACKNOWLEDGEMENTS

There have been many who have supported me in my research endeavors. First and foremost, I would like to thank my wife, Angela. She has shown remarkable understanding of my long hours and my anxiety at stressful times.

I would also like to thank my parents for teaching me the value of hard work.

I would like to thank Dr. Steven Castle for allowing me to join his research group. He has encouraged me when plans fail and works tirelessly to find solutions to difficult problems.

I have had the privilege to work with some great individuals in the Castle group, only a few of which I can thank here. Yu Zhang did much of the early studies for lyconadin A. I would like to thank Nathan Wilde, Phil Young, Patrick Evans, and Ankur Jalan for their contributions to this work.

I would also like to thank members of my committee: Dr. Andrus, Dr. Savage, Dr. Price, and Dr. Harrison for their guidance and suggestions.

Finally, I would like to thank Brigham Young University Department of Chemistry and Biochemistry for a fantastic opportunity to pursue a Ph.D. For financial support I would like to acknowledge the Roland K. Robins fellowship, the BYU Cancer Research Center, and BYU Graduate Studies.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

Chapter 1. Lyconadin A Introduction

1.1 *Lycopodium* Alkaloids

The genus *Lycopodium* is a diverse group of moss-like plants that produce a wide variety of alkaloids. *Lycopodium* species are non-flowering and reproduce with spores instead of seeds. They grow cone-shaped strobili at the tips of their branches, which give them a club shape and the moniker club mosses.[1]

Bödeker was the first to isolate a *Lycopodium* alkaloid and named it lycopodine in 1881.[2] He reported a specious molecular formula, which was corrected in 1938 by Achmatowicz and Uzieblo, upon isolation of two novel alkaloids (clavatine and clavatoxine).[3] Since 1940, Ayer and co-workers gave considerable attention to isolation, structural determination, biogenesis, and chemical synthesis of *Lycopodium* alkaloids.[4] In the late 1980s it was shown that some *Lyopodium* alkaloids have potent acetylcholine esterase inhibition activity.[5] Of particular note was huperzine A, a potential treatment for Alzhiemer's disease and myasthenia gravis.[6] This promising bioactivity has encouraged further study of the isolation and synthesis of *Lycopodium* alkaloids.

To date, over 200 *Lycopodium* alkaloids have been discovered.[1,4] The *Lycopodium* alkaloids are divided into four classes, each named after specific *Lycopodium* alkaloids except for the miscellaneous class. The lycopodine class is characterized by the lycopodane skeleton (Figure 1.1). The lycodine class is comprised of dinitrogen alkaloids that contain a pyridine or pyridone ring. The fawcettimine class contains a tetracyclic skeleton including a five-membered ring, two six-membered rings, and a seven-membered ring. The fourth class is a miscellaneous

group (represented by phlegmarine) consisting of alkaloids that are structurally distinct from the other classes.[4]

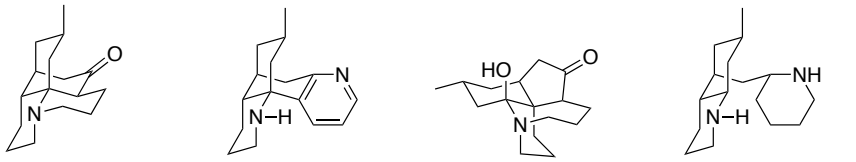


Figure 1.1. Representative compounds of the major classes of lycopodium alkaloids.

Despite the promising activity of *Lycopodium* alkaloids, very few biological studies have been performed. *Lycopodium* species are scarce and grow slowly in specific locales. They have not been successfully cultivated and even tissue culture has proven difficult. Fortunately, total synthesis can provide these alkaloids in amounts needed for further biological evaluation.[7–9] Total synthesis of these diverse compounds pushes the limits of synthetic chemistry and can lead to development of useful methodology.

1.2 Lyconadin A

Lyconadin A (**1**, Figure 1.2) is a *Lycopodium* alkaloid of the miscellaneous class that was isolated in 2001 by Kobayashi and co-workers from the club moss *Lycopodium complanatum*.[10] Lyconadins B–F (**2–6**) have also been isolated and characterized.[11] Each is a pentacyclic dinitrogenous alkaloid that bears either a δ-lactam or an α-pyridone ring, except in the case of lyconadin F, which has an open-chain amide in place of the pyridone. Other noteworthy structural features include a *cis*-fused bicyclo[5.4.0]undecane system and six stereocenters, four of which are contiguous. The bicyclo[5.4.0]undecane system observed in lyconadins A, B, C, and F is presumably derived by rearrangement of the phlegmarine skeleton.[11c] Lyconadins D and E lack the bicyclo[5.4.0]undecane skeleton and do not bear a strong resemblance with the other members of the lyconadin family.

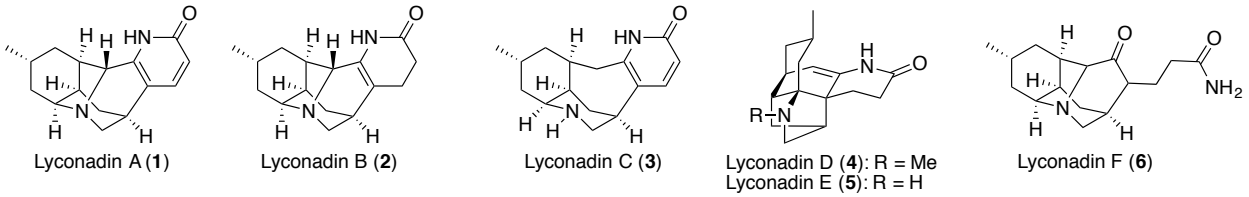


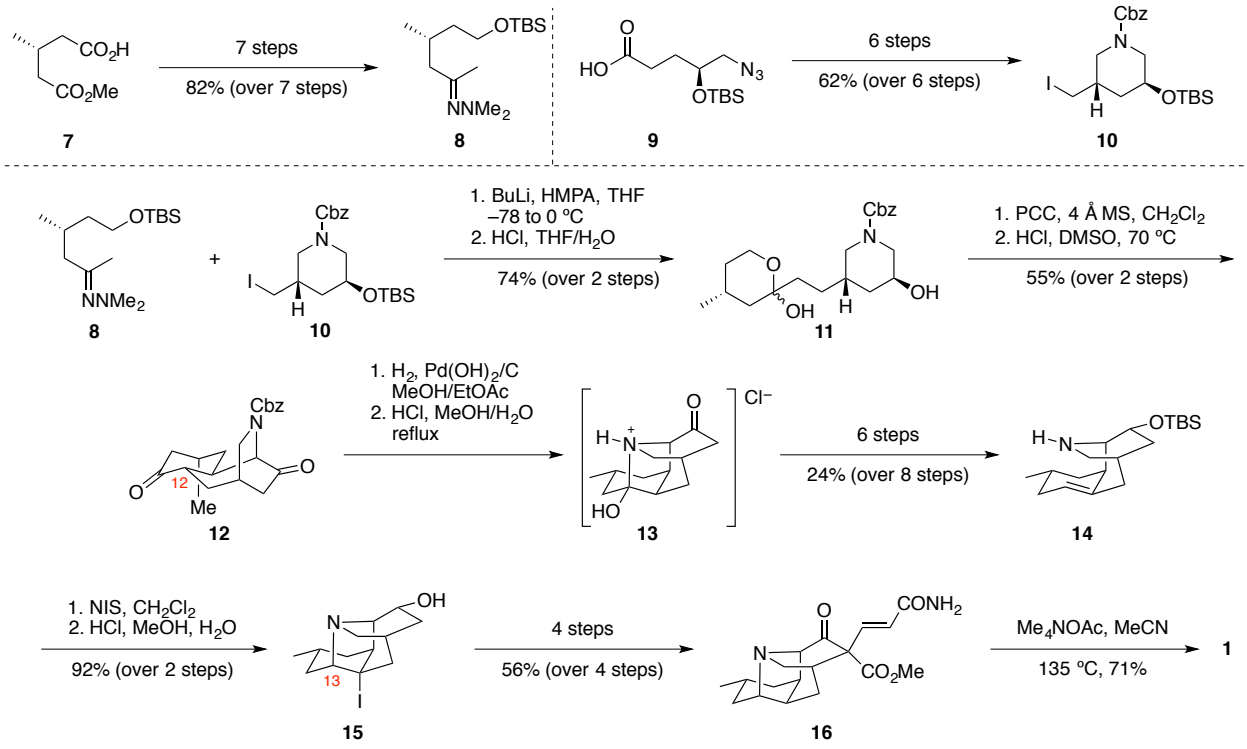
Figure 1.2. Lyconadins A–F.

Biological screening revealed cytoxicity of **1** against murine lymphoma L1210 and human epidermoid carcinoma KB cells (IC_{50} = 0.46 μg/mL and 1.7 μg/mL, respectively).[10] Additionally, **1** promotes nerve growth factor biosynthesis in 1321N1 human astrocytoma cells.[11a] In light of these useful biological properties and the intriguing chemical structure, lyconadin A has received considerable attention from synthetic chemists. The Smith,[12] Sarpong,[13] and Fukuyama[14] groups have each completed the total synthesis of lyconadin A. A brief summary of these syntheses and model studies towards the synthesis of **1** from our research group will be described below.[15]

1.3 Smith Group Synthesis

The key steps of Smith and Beshore's total synthesis of lyconadin A are summarized in Scheme 1.1.[12] The first transformation was the union of hydrazone **8** and iodide **10** (prepared respectively from known monoester **7** and from known acid **9**)[16], which was accomplished by treatment of **8** with butyllithium in the presence of hexamehtylphosphoramide (HMPA) and addition of iodide **10** followed by acidic cleavage of the silyl ethers and hydrolysis of the hydrazone to afford **11** as a mixture of diastereomers. Oxidation and acid-promoted Michael addition delivered diketone **12**, which contained the undesired stereochemistry at C-12, prompting removal of the Cbz group and epimerization to afford hydrochloride salt **13**. Attempts to remove the hydroxyl group via reductive amination failed, presumably because the required iminium ion would be too strained due to its inclusion in a bridged polycyclic ring system. To

circumvent this issue, Smith and Beshore converted **13** into olefin **14** by a six-step sequence of routine manipulations. The desired C–N bond at C-13 was formed via iodoamination. A four-step sequence (oxidation, β-ketoester formation, dehalogenation, and alkylation) was followed by pyridone annulation to afford lyconadin A (**1**). The synthesis was accomplished in 34 steps with 27 steps in the longest linear sequence from commercially available starting materials with an overall yield of 1.4%.

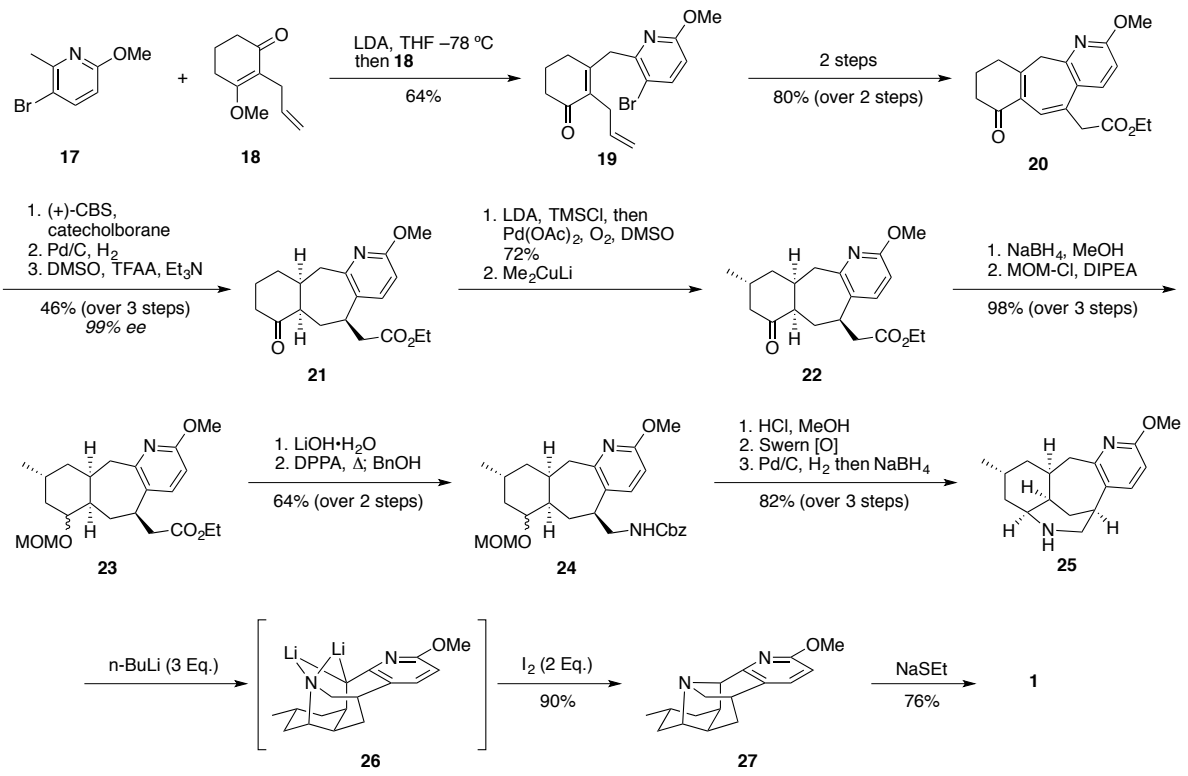


Scheme 1.1. Smith and Beshore's total synthesis of lyconadin A.

1.4 Sarpong Group Synthesis

The synthesis of lyconadin A by Sarpong and co-workers contained some interesting transformations. Sarpong and co-workers began with the pyridone ring intact, masked as the 2-methoxy pyridine derivative **17** (prepared from 2-methoxy-6-methylpyridine and *N*,*N*-dibromodimethylhydantoin (DBDMH) in 97% yield, see Scheme 1.2).[13] The union of **17** with vinylogous ester **18** was achieved by a Stork–Danheiser reaction in 64% yield, then tricyclic

ketone **20** was constructed via cross-metathesis and a subsequent intramolecular Heck reaction. The ketone was selectively reduced to direct the hydrogenation of the 7-membered ring. Afterwards, the alcohol was reoxidized, delivering ketone **21**. Saegusa–Ito oxidation[17] followed by 1,4-addition with Me_2CuLi afforded ketone **22**. To avoid epimerization, the ketone was reduced and protected to furnish ester **23**. Saponifcation and a subsequent Curtius rearrangement delivered carbamate **24**. MOM deprotection was followed by oxidation, hydrogenolysis, and reductive amination to construct tetracycle **25**. At this point, Sarpong and co-workers attempted several oxidative coupling conditions, all of which formed a complex mixture. Finally, they found that treatment of **25** with n-BuLi formed lithium dianion **26** which was oxidized by iodine to deliver desired pentacyclic intermediate **27**.[13b] Cleavage of the methyl ether with NaSEt afforded lyconadin A in 18 steps and 5.8% overall yield from commercially available starting materials. Despite some inefficiency caused by two necessary reduction/oxidation sequences, this is a particularly powerful method for accessing several miscellaneous *Lycopodium* alkaloids.

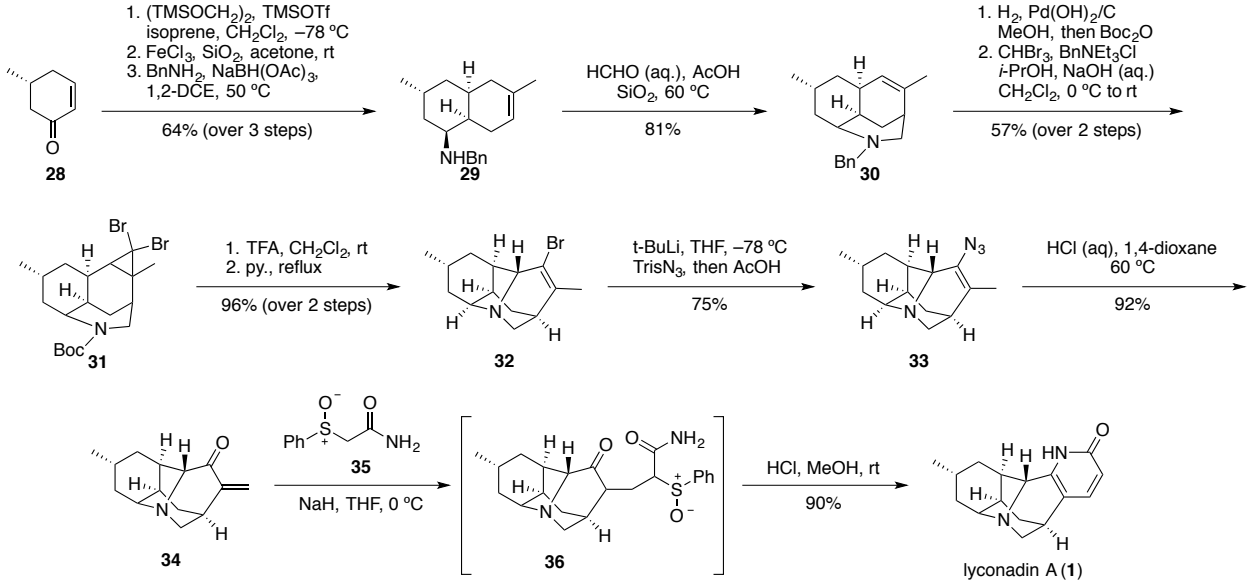


Scheme 1.2. Synthesis of lyconadin A by Sarpong and co-workers.

1.5 Fukuyama Group Synthesis

Fukuyama and co-workers have reported the most recent total synthesis of lyconadin A.[14] They began with known enone **28**, which is prepared from (+)-pulegone in 65% yield over 4 steps (Scheme 1.3).[18] A one-pot acetal formation/Diels-Alder process[20] is followed by acetal cleavage and reductive amination with benzyl amine to selectively deliver amine **29**. Tricycle **30** was constructed via an aza-Prins reaction. For synthetic convenience, the *N*-benzyl group was swapped for an *N*-Boc group and subsequent cyclopropanation afforded dihalide **31**. *N*-Boc cleavage was followed by refluxing in pyridine to deliver tetracycle **32**, which contains the entire lyconadin A skeleton except for the pyridone moiety. Lithium-halogen exchange and treatment with trisyl azide and acetic acid converted halide **32** into azide **33**. Release of molecular nitrogen was promoted under acidic conditions to afford enone **34**. Michael addition of the enolate generated from sulfoxide **35** produced compound **36**, which furnished lyconadin A (**1**) upon

treatment with methanolic HCl. The Fukuyama synthesis of lyconadin A is the shortest to date being 15 steps from (+)-pulegone in 12% overall yield.



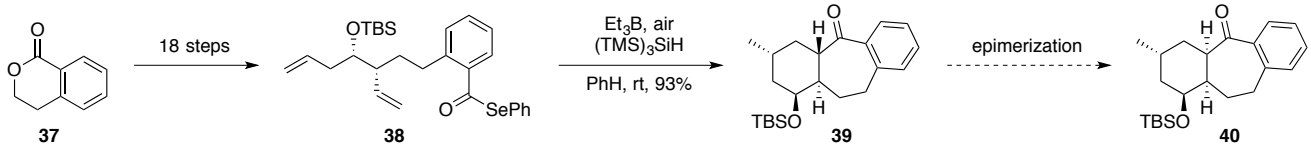
Scheme 1.3. Total synthesis of lyconadin A by Fukuyama and co-workers.

1.6 Radical Cyclization Cascade and Epimerization Model Studies

While analyzing the structure of lyconadin A, we realized that the bicyclo[5.4.0]undecane system could potentially be constructed via a 7-*exo*–6-*exo* radical cyclization cascade. Typically 7-exo radical cyclization is slow[20] and only proceeds in special cases.[21] However, Boger and co-workers demonstrated that tethering acyl radicals to an aromatic ring allows 7-*exo* cyclizations to proceed.[22] Evans,[23] Bonjoch,[24] and Ryu[25] have also discovered other useful 7-*exo* radical cyclizations. To our knowledge there were no examples of cascade reactions that incorporated 7-*exo* acyl radical cyclizations prior to our model studies.

To learn whether a tandem 7-*exo*–6-*exo* radical cyclization was feasible, we prepared diene **38** from 1-isochromanone **37** in 18 steps (Scheme 1.4).[26] Gratifyingly, treatment of the phenyl selenoester generated an acyl radical that afforded tricycle **39** as a single isomer. The use of tris(trimethylsilyl)silane (TTMSS) is crucial for this transformation, presumably because the

hydrogen atom transfer from this reagent is slower than that from Bu_3SnH. 7-exo-5-*exo* tandem cyclizations are also possible. Further investigations revealed that the *trans*-fused ring system is formed exclusively, regardless of the configuration or the size of the secondary alcohol. This prompted us to investigate suitable epimerization conditions to construct the *cis*-fused system (**39** → **40**).

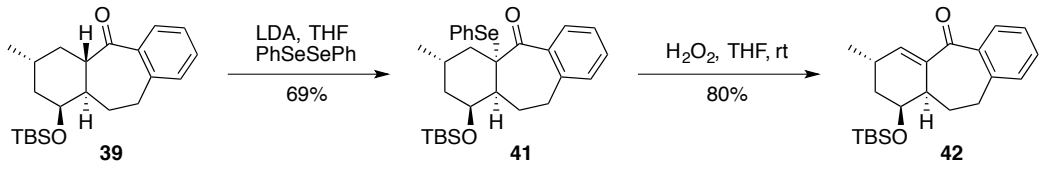


37 **38** **39** **40**

Scheme 1.4. Model study of the 7-*exo*–6-*exo* radical cyclization cascade.

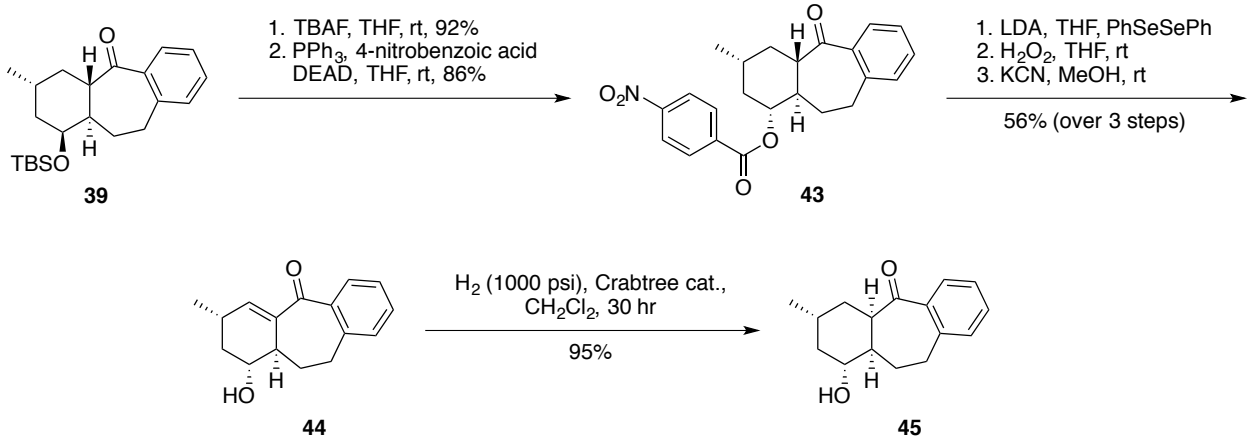
Initially, we sought to exploit the presence of the carbonyl for the epimerization via kinetically controlled protonation of the enolate by a hindered proton source such as butylated hydroxytoluene (BHT). Unfortunately, this only resulted in recovery of starting material. Quenching of the enolate with D_2O incorporated deuterium in the *trans*-fused ring system, suggesting that the enolate was generated, but protonation only favors the *trans*-fused product. We then explored a hydroxyl-directed hydrogenation of an enone as an alternative.

Attempts to oxidize **39** to the enone directly via treatment with IBX[27] and IBX•MPO[28] gave no reaction, even at elevated temperatures. Treatment of ketone **39** with LDA and TMS-Cl successfully formed the silyl enol ether but the attempted oxidation of the intermediate with IBX•MPO[29] or $Pd(OAc)_2$[17,30] was unsuccessful. Fortunately, quenching of the enolate of **39** with diphenyldiselenide formed selenide **41** in moderate yield (Scheme 1.5). The selenide was then oxidized by H_2O_2 to generate enone **42**.



Scheme 1.5. Successful formation of enone **42.**

In order to direct hydrogenation to the correct face of the alkene we needed to invert the configuration of the silyl ether. This inversion would be unnecessary for our lyconadin A synthesis since we would design it to have the correct configuration of the silyl ether prior to the radical cyclization step (see Chapter 2). Desilylation and subsequent Mitsunobu reaction afforded *p*-nitrobenzoate **43** (Scheme 1.6). Enone formation was followed by KCN-catalyzed transesterification to afford alcohol **44**. Hydrogenation with cationic rhodium failed, but was successful when Crabtree's catalyst was implemented, delivering *cis*-fused bicycle **45**. Thus, we felt confident that we would be able to epimerize the *trans*-fused ring system in the total synthesis of lyconadin A.

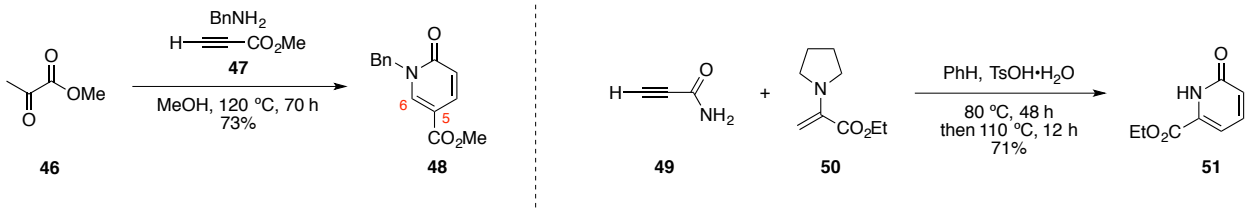


Scheme 1.6. Epimerization of bicyclo[5.4.0]undecane skeleton in the model system.

1.7 Pyridone Annulation Model Study

Another important process for our lyconadin A synthesis was the pyridone annulation sequence. I played a minor role in this study, although most of this work was performed by Yu Zhang.[31] Initially, we tried to adapt the Kozikowski pyridone annulation protocol which entails

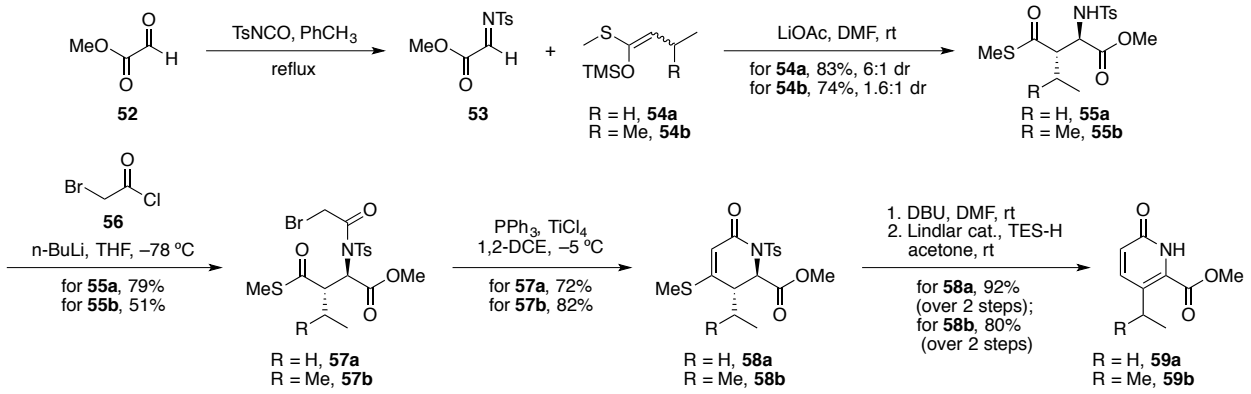
condensation of a ketone, methyl propiolate, and ammonia[33] to a model system matching the lyconadin A substitution pattern. However, attempted use of benzylamine instead of ammonia and of methyl pyruvate (**46**) as the ketone resulted in the methyl ester being placed at C-5 of the pyridone rather than the desired C-6 position (see **48**, Scheme 1.7). This presumably occurs because methyl pyruvate does not participate in the reaction. To circumvent this issue, we preformed propiolamide **49** and pyrrolidine enamine **50** and heated them in the presence of *p*-toluenesulfonic acid to deliver pyridone **51**. Unfortunately, attempts to employ substituted pyrrolidine enamines instead of **50** failed to give any product.



Scheme 1.7. Early pyridone annulation attempts.

Upon failure to adapt the Kozikowski protocol, we found that Donohoe had also developed a useful pyridone annulation sequence.[33] Donohoe's protocol would need to be altered, since it employs ring closing metathesis (RCM), an unsuitable transformation for our lyconadin A synthesis (see Chapter 2). To this end, we prepared methyl glyoxylate (**52**) via ozonolysis of dimethyl maleate[32] and converted it to tosylimine **53** by reaction with tosyl isocyanate.[34] A Mannich reaction of this imine with silyl ketene thioacetal **54a** (prepared from *S*-methyl thiobutanoate by treatment with LiHMDS and TMS-Cl) afforded tosylamide **55a** in high yield and in 6:1 dr.[31] We also explored the Mannich reaction with **54b**, which proceeded with a modest decrease in yield and an appreciable drop in diastereoselectivity. The decrease in dr is irrelevant, as these stereocenters will be destroyed later in the pyridone annulation. Acylation of **55a** proceeded smoothly but the same transformation was sluggish for **55b**. Cyclization was achieved

by a Reformatsky-type condensation, a transformation inspired by a Claisen-type condensation reported Hashimoto and co-workers.[35] Elimination of the tosyl group[33] and subsequent desulfurization with Lindlar's catalyst and triethylsilane[36] afforded pyridones **59a** and **59b**.



Scheme 1.8. Successful pyridone annulation sequence.

With a viable route to access an appropriately substituted pyridone moiety, we were confident we could proceed with our synthesis of lyconadin A. Our efforts toward this endeavor will be explained in Chapter 2.

1.8 References

(1) For recent reviews of Lycopodium alkaloids see (a) Kobayashi, J.; Morita, H. *The Alkaloids Chem. Biol.* **2005**, *61*, 1–57. (b) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679–729.

(2) Bödeker, K. *Justus Liebigs Ann. Chem.* **1881**, *208*, 363–367.

(3) Achmatowicz, O.; Uzieblo, W. *Rocz. Chem.* **1938**, *18*, 88–95.

(4) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772.

(5) (a) Tang, X. C.; Han, Y. F.; Chen, X. P.; Zhu, X. D. *Acta Pharmacol. Sin.* **1986**, *7*, 507–511. (b) Tang, X. C.; Sarno, P. D.; Sugay, K.; Giacobini, E. J. *Neurosci. Res.* **1989**, *24*, 276–285.

(6) (a) Kozikowski, A. P.; Tüeckmantel, W. *Acc. Chem. Res.* **1999**, *32*, 641–650. (b) Bai, D. L.; Tang, X. C.; He, X. C. *Curr. Med. Chem.* **2000**, *7*, 355–374. (c) Tan, C. H.; Zhu, D. Y. *Zhongguo Tianran Yaowu* **2003**, *1*, 1–7.

(7) (a) Freeberg, J. A.; Wetmore, R. H. *Phytomorphology* **1957**, *7*, 204–217. (b) Freeberg, J. A.; Wetmore, R. H. *Phytomorphology* **1967**, *17*, 78–91.

(8) Dwyer, T.; Waegel, A. S. *Acta Hortic.* **2004**, *631*, 181–185.

(9) Yang, H.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2008**, *130*, 9238–9239.

(10) Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. *J. Org. Chem.* **2001**, *66*, 5901–5904.

(11) (a) Ishiuchi, K.; Kubota, T.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Bioorg. Med. Chem.* **2006**, *14*, 5995–6000. (b) Ishiuchi, K.; Kubota, T.; Ishiyama, H.; Hayashi, S.; Shibata, T.; Kobayashi, J. *Tetrahedron Lett.* **2011**, *52*, 289–292. (c) Ishiuchi, K.; Kubota, T.; Ishiyama, H.; Hayashi, S.; Shibata, T.; Mori, K.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Bioorg. Med. Chem.* **2011**, *19*, 749–753.

(12) (a) Beshore, D. C.; Smith, A. B., III *J. Am. Chem. Soc.* **2007**, *129*, 4148–4149. (b) Beshore, D. C.; Smith, A. B., III *J. Am. Chem. Soc.* **2008**, *130*, 13778–13689.

(13) (a) Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc.* **2008**, *130*, 7222–7223. (b) West, S. P.; Bisai, A.; Lim, A. D.; Narayan, R. R.; Sarpong, R. *J. Am. Chem. Soc.*, **2009**, *131*, 11187–11194.

(14) (a) Nishimura, T.; Unni, A. K.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 418–419. (b) Nishimura, T.; Unni, A. K.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2013**, *135*, 3243–3247.

(15) For a more detailed account on pyridone annulation attempts, see Zhang, Y. Progress Towards Total Synthesis of Lyconadin A. PhD. Dissertation, Brigham Young University, 2010.

(16) Acid **9** was prepared from (4S)-4,5-dihydroxy-valeric acid-γ-lactone in 62% yield over 2 steps. See Kottirsch, G.; Metternich, R. Eur. Patent EP 0 560 730 B1, 1996.

(17) Ito, Y.; Hirao, T.; Saegusa, T. J. *J. Org. Chem.* **1978**, *43*, 1011–1013.

(18) Fleming, I.; Maiti, P.; Ramarao, C. *Org. Biomol. Chem.* **2003**, *1*, 3989–4004.

(19) (a) Nilsson, B. L.; Overman, L. E.; Read de Alaniz, J.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 11297–11299. (b) Altman, R. A.; Nilsson, B. L.; Overman, L. E.; Read de Alaniz, J.; Rohde, J. M.; Taupin, V. *J. Org. Chem.* **2010**, *75*, 7519–7534.

(20) (a) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991–2070. (b) Boger, D. L.; *Israel J. Chem.* **1997**, *37*, 119–129.

(21) Lang, S.; Corr, M.; Muir, N.; Khan, T. A.; Murphy, J. A.; Payne, A. H.; Williams, A. C.; *Tetrahedron Lett.* **2005**, *46*, 4027–4030.

(22) Boger, D. L.; Matvink, R. J. *J. Org. Chem.* **1988**, *53*, 3377–3379.

(23) (a) Evans, P A.; Roseman, J. D. *J. Org. Chem.* **1996**, *61*, 2252–2253. (b) Evans, P. A.; Raina, S. Ahsan, K. *Chem. Commun.* **2001**, 2504–2505. (c) Evans, P. A.; Manangan, T.; Rheingold, A. L. *J. Am. Chem. Soc.* **2000**, *122*, 11009–11010. (d) Evans, P. A.; Manangan, T. *Tetrahedron Lett.* **1997**, *38*, 8165–8168. Evans, P. A.; Manangan, T. *J. Org. Chem.* **2000**, *65*, 4523–4528.

(24) (a) Quirante, J.; Vila, X.; Escolano, C.; Bonjoch, J. *J. Org. Chem.* **2002**, *67*, 2323–2328. (b) Quirante, J.; Escolano, C.; Bonjoch, J. *Synlett* **1997**, 179–180.

(25) (a) Ryu, I.; Miyazato, H.; Kuriyama, H.; Matsu, K.; Tojino, M.; Fukuyama, T.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2003**, *125*, 5632–5633. (b) Tojino, M.; Otsuka, M.; Fukuyama, T.; Matsubara, H.; Schiesser, C. H.; Kuriyama, H.; Miyazato, H.; Minakata, S.; Komatsu, M.; Ryu, I. *Org. Biomol. Chem.* **2003**, *1*, 4262–4267.

(26) Grant, S. W.; Zhu, K.; Zhang, Y.; Castle, S. L. *Org. Lett.* **2006**, *8*, 1867–1870.

(27) Nicolaou, K. C; Montagnon, T.; Baran, P. S.; Zhong, Y. L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.

(28) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 993–996.

(29) Snyder, S. A.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 740–742.

(30) Hu, X.; Tu, Y. Q.; Zhang, E.; Gao, S.; Wang, S.; Wang, A.; Fan, C.; Wang, M. *Org. Lett.* **2006**, *8*, 1823–1825.

(31) For a more detailed account on the pyridone annulation attempts see the dissertation of Yu Zhang (ref. 15) and Zhang, Y.; Loertscher, B. M.; Castle, S. L. *Tetrahedron* **2009**, *65*, 6584–6590.

(32) Kozikowski, A. P.; Reddy, E. R.; Miller, C. P.; *J. Chem. Soc. Perkin. Trans. 1* **1990**, 195–197.

(33) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Org. Lett.*, **2008**, *10*, 285–288.

(34) Hamley, P.; Holmes, A. B.; Kee, A.; Ladduwahetty, T.; Smith, D. F. *Synlett* **1991**, 29–30.

(35) Hashimoto, Y.; Konishi, S.; Kikuchi, S. *Synlett* **2004**, 1264–1266.

(36) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513.

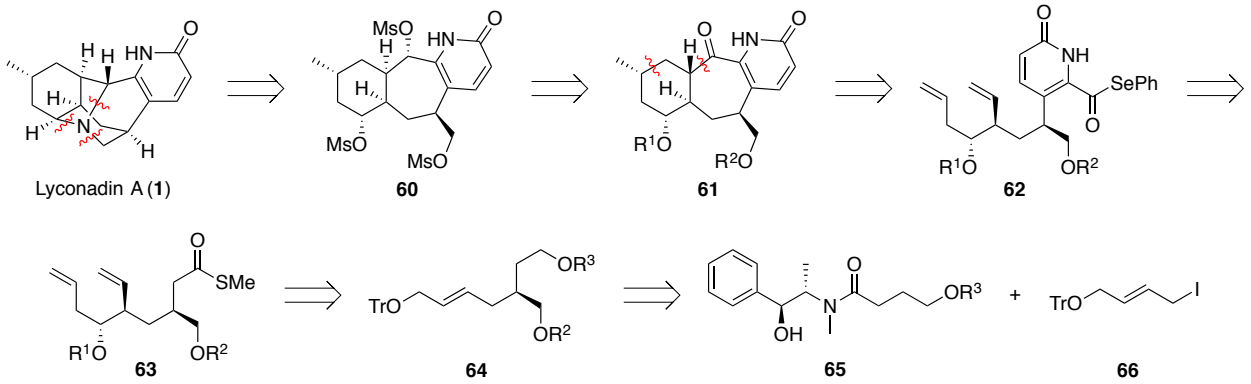
Chapter 2. Synthetic Strategies Toward Lyconadin A

2.1 Introduction

In the synthesis of lyconadin A, we sought to apply our model studies of 7-*exo*–6-*exo* tandem radcial cyclization and pyridone annulation. This chapter includes discussion of our overall strategy, retrosynthetic analysis, and our attempts to follow that plan.

2.2 Retrosynthesis

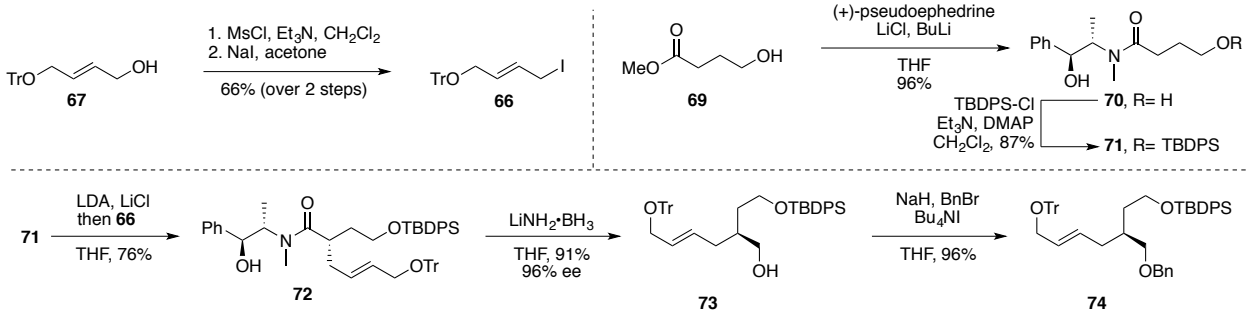
Our retrosynthetic analysis of lyconadin A (**1**) is shown in Scheme 2.1. Trialkylation of ammonia with trimesylate **60** would form the pentacyclic structure of lyconadin A. Alternatively, this process could be performed sequentially. Mesylate **60** could be derived by the epimerization of tricycle **61** via the protocol discussed in Chapter 1. Generation of an acyl radical from phenylselenoester **62** should construct tricycle **61** via 7-*exo*-6-*exo* tandem radical cyclization (see Section 1.6).[1] In turn, pyridone **62** could be furnished from thioester **63** by our pyridone annulation sequence (see Section 1.7).[2] Thioester **63** could be afforded from olefin **64** via epoxidation and two consecutive regioselective epoxide openings with a vinyl nucleophile. We thought that the Shi protocol for asymmetric epoxidation by fructose-derived ketones would be suitable for alkene **64**.[3,4] In theory, the ring opening reaction would be directed by the bulky trityl group.[5] Subsequent detritylation and dehydration of the resulting diol would form a monosubstituted epoxide, which could be opened with a vinyl nucleophile to form the diene moiety of **63**. Olefin **64** would be formed selectively by the union of (+)-pseudoephedrine amide **65** and iodide **66** and routine functional group manipulations.



Scheme 2.1 Retrosynthesis of lyconadin A.

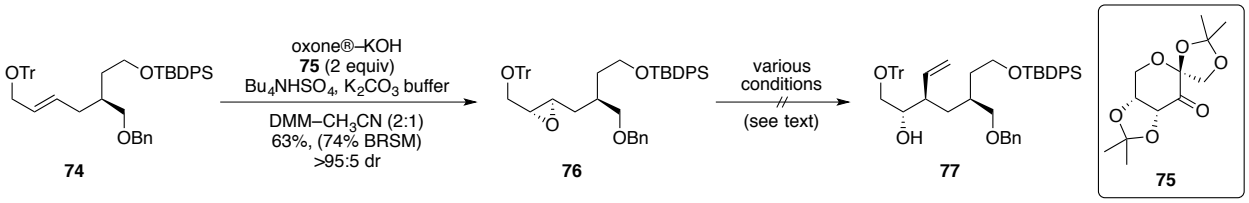
2.3 Sequential Epoxide Opening Route

A number of protecting group sets were investigated and these are discussed in greater detail elsewhere.[6] Prior to my involvment in the project, we were targeting an olefin of type **64** with benzyl and TBDPS ethers as protecting groups. First, allylic iodide **66** was prepared from known alcohol **67**[7] via mesylation and subsequent iodination (Scheme 2.2). Methyl γ-hydroxybutyrate (**69**)[8] was then united with (+)-pseudoephedrine to afford amide **70** in high yield. TBDPS protection delivered amide **71**. Alkylation of **71** with **66** according to the Myers protocol[9] delivered **72** in high yield. Reductive cleavage of the chiral auxiliary with lithium amidotrihydroborate[10] afforded alcohol **73** in 96% *ee* according to HPLC analysis. The configuration of **73** was assumed to be consistent with other Myers alkylation reactions.[9] Benzylation furnished triether **74**.

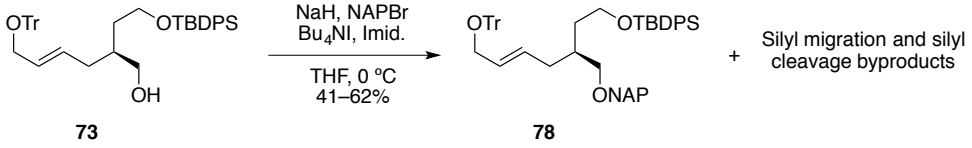


Scheme 2.2 Synthesis of triether **74**.

Asmymmetric epoxidation of **74** was slow and required excess amounts of ketone **75**,[11] presumably because decomposition of the ketone was more rapid than epoxidation of the olefin (Scheme 2.3). The epoxide configuration was assigned based on the spiro transition state proposed by Shi and co-workers.[11] Attempted ring openings of epoxide **76** either resulted in recovery of starting material or debenzylation byproducts. This prompted us to replace the benzyl ether with a more robust protecting group: 2-naphthylmethyl (NAP). Unfortunately, NAP protection of **73** produced triether **78** in varying yields, with byproducts derived from silyl migration and/or silyl ether cleavage.



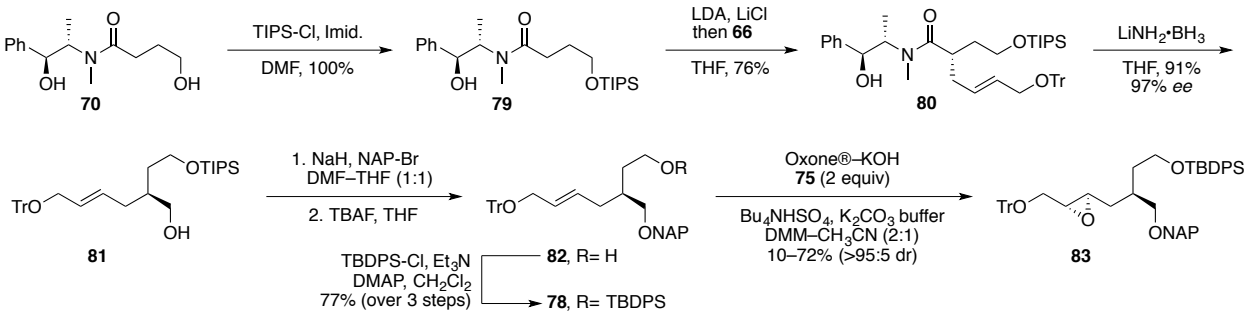
Scheme 2.3. Synthesis and attempted ring opening of **77**.



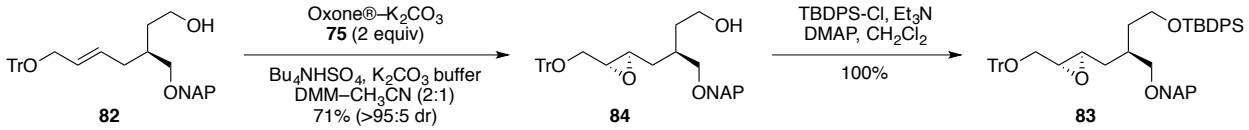
Scheme 2.4. Attempted protection of **73** and silyl cleavage/migration.

Hoping that a more robust TIPS ether would be less prone to silyl migration, we synthesized amide **79** from **70**. Fortunately, the yield of the Myers alkylation was unaffected by this minor alteration to the substrate. Removal of the chiral auxiliary showed that the enantioselectivity of the alkylation was also unaffected. Gratifyingly, NAP protection proceeded without detrimental silyl migration and/or cleavage. Shi epoxidation of this triether substrate was low-yielding (*ca.* 8%), and the ring opening of that epoxide did not proceed, so the TIPS moiety was swapped for a TBDPS group to afford triether **78**. Epoxidation of alkene **78** did proceed, albeit in varying yields. We posited that the unreliable epoxidation outcome was caused by the

substrate's poor solubility in the reaction medium. Thus, epoxidation of alcohol **82** afforded epoxy alcohol **84** in a reproducible yield and subsequent TBDPS protection proceeded without intramolecular opening of the epoxide to afford epoxide **83**. Attempts to decrease the amount of ketone resulted in lower yields (30–40% at 30 mol% loading), suggesting that the organocatalyst still fails to turn over in the reaction conditions despite the decreased steric hindrance of **82**.



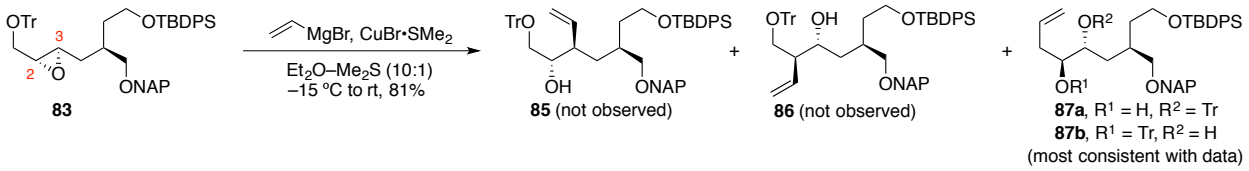
Scheme 2.5. Successful incorporation of NAP ether in epoxide **83**.



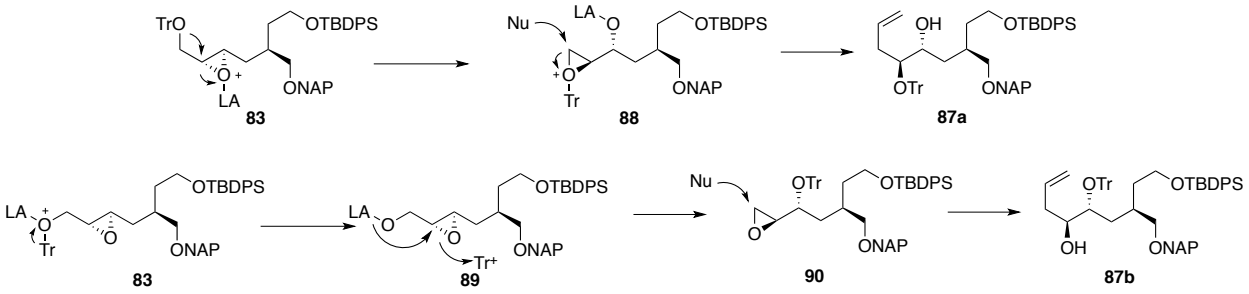
Scheme 2.6. Alternative synthesis of epoxide **83**.

With epoxide **83** in hand, we proceeded with epoxide opening. Exploration of many copper(I) salts led to the discovery that CuBr•SMe_2[12] was most suitable for epoxide opening (Scheme 2.7). Initially, we believed that epoxide **83** had opened to deliver alcohol **85**. However, closer inspection of the spectral data led us to realize that an additional proton signal was found in the 1–2 ppm range and a signal was missing from the 3–5 ppm range. These data are also inconsistent with the other possible regioisomer (**86**). The product was later determined to be alcohol **87a** or **87b**, by continuing with our planned synthetic route (vide infra). This unanticipated product is presumably formed by Payne rearrangement of **83**. It is interesting to note that the trityl group is retained in this transformation. The rearrangement probably occurs because both C-2 and C-3 are too hindered for nucleophilic attack. Two possible mechanisms for

the formation of **87** are shown in Scheme 2.8. Lewis acid activation is followed by attack of the oxygen attached to the trityl group to form a highly reactive cationic oxirane species (**88**). Ring opening of **88** then should deliver alcohol **87a**. Alternatively, the trityl group could migrate to the epoxide[13] to afford epoxonium ion **89**. The Payne rearrangement could then occur and the resultant epoxide would then open to afford **87b**. Due to the limited amount of **87** that we had available after prolonged storage, we were unable to further characterize it and cannot assign the position the trityl group without ambiguity.



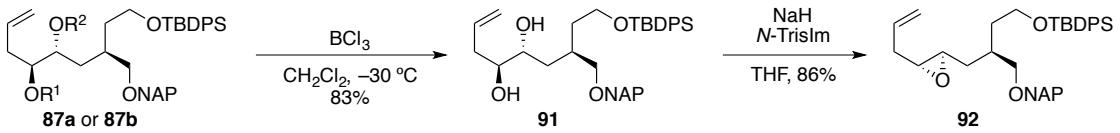
Scheme 2.7. Possible outcomes for epoxide opening of **83**.



Scheme 2.8 Plausible mechanisms for Payne rearrangement of epoxide **83**.

For further evidence of formation of **87a** or **87b**, we decided to proceed with our plan to remove the trityl group and dehydrate the resultant diol. We reasoned that if the desired product (**85**) had formed, we should observe 3 proton signals in the NMR in the 2–3 ppm range as is consistent with mono-substituted oxiranes. The Payne rearrangement product (**87**) would only have 2 proton signals in the 2–3 ppm range, which would be consistent with a disubstituted epoxide. The undesired regioisomer (**86**) would form an oxetane and would be spectroscopically distinguishable from the epoxides formed from **85** and **87**.

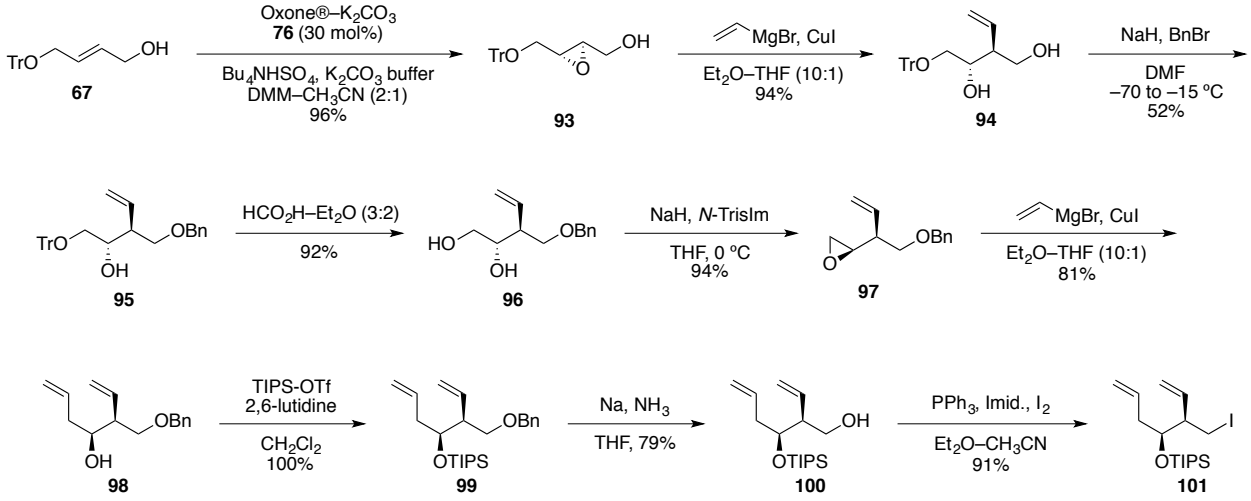
Detritylation of the epoxide opening product (**87a** or **87b**) was accomplished with BCl_3 at –30 ºC.[14] Once again, data were not consistent for the diols that would be formed upon detritylation of **85** and **86**, but fit well with diol **91**. Treatment of diol **91** with NaH and 1-(2,4,6-triisopropylbenzenesulfonyl)imidazole (*N*-TrisIm) afforded a disubstituted epoxide as a single diastereomer.[15] We have assigned the configuration for the epoxide as **92**, since the bulky sulfonyl group is more likely to attach at the less hindered alcohol. The discovery of the unanticipated Payne rearrangement prompted us to investigate an alternative route to thioester **63**.



Scheme 2.9. Epoxide formation from undesired ring opening product **89**.

2.4 Simpler Epoxidation, Ring Opening Route

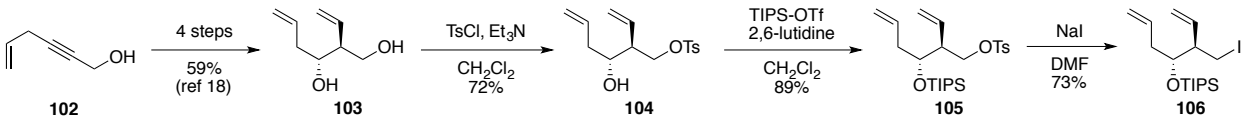
We decided to pursue a simpler substrate for the epoxidation. Epoxidation of **67** proceeded smoothly with catalytic loading of **75**. Encouraged by this result, we continued with CuI-mediated ring opening in a mixed Et_2O–THF solvent system to deliver diol **94** as a single isomer.[16] Monobenzylation of **94** furnished alcohol **95**, which was detritylated to afford diol **96**. Dehydration afforded epoxide **97**, unfortunately with inversion of the secondary alcohol (see Section 2.5). Epoxide opening of **97** and subsequent TIPS protection afforded **99**. Debenzylation under Birch conditions released primary alcohol **100**, which was converted to iodide **101** via Appel substitution. Myers alkylation attempts exhausted our supply of iodide **101**. The lengthy synthesis of iodide **101** prompted us to find a shorter route.



Scheme 2.10. Synthesis of iodide **101**.

2.5 Shorter Iodide Synthesis and Myers Alkylation

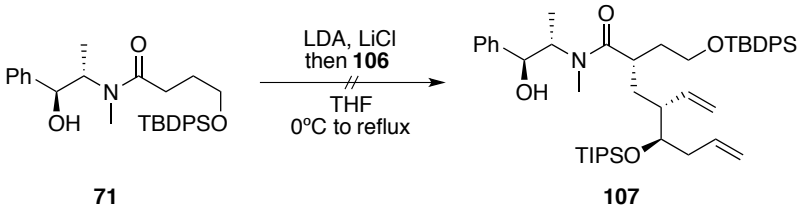
Fortunately, we found a useful precedent beginning with hex-5-en-2-yn-1-ol[17] (**102**, Scheme 2.11). Alkyne **102** is reduced by lithium aluminum hydride, epoxidized by the Sharpless protocol, and opened with good regioselectivity.[18] The mixture of diols is treated with sodium periodate to ease separation of the regioisomers affording diol **103**. Monotosylation and silylation delivered diene **105**, which underwent substitution with NaI at reflux to afford iodide **106**. Comparison of **106** with **101** showed that these two compounds were diastereomers. The inversion probably occurred in the dehydrative epoxide formation (**95** → **96**). This reaction sequence was easily increased to gram-scale, facilitating the synthesis of iodide **106**.



Scheme 2.11. Shorter synthesis of desired iodide **106**.

With a good supply of iodide **106** available, we decided to attempt the Myers alkylation. Unfortunately, all attempts have only resulted in recovery of starting material even when the reaction mixture is refluxed. Presumably the difficulty of this transformation is caused by the

combination of a bulky enolate and a sterically demanding iodide. Perhaps replacement of the TIPS group with a smaller TBS group would allow the transformation to occur. Another possibility is to run the reaction in 2-methyltetrohydrofuran to allow a higher reflux temperature. Unfortunately, our research focus has shifted to another project and we have not been able to explore the alkylation further at this point in time.



71 107

Scheme 2.12 Attempted Myers' alkylation with iodide **106**.

2.6 Conclusion

Our attempted synthesis of lyconadin A pushed the limits of the Shi epoxidation, requiring superstoichiometric quantitites of the chiral ketone. Ring opening of these epoxides also demonstrates the limitation of epoxide ring opening reactions, which led us to seek an alternative route in our lyconadin A synthesis. While we have not successfully worked through these challenges, knowing the limits of epoxidation and ring opening will be helpful to others.

2.7 References

(1) Grant, S. W.; Zhu, K.; Zhang, Y.; Castle, S. L. *Org. Lett.* **2006**, *8*, 1867–1870.

(2) See Chapter 1 and Loertscher, B. M.; Castle, S. L. *Tetrahedron* **2009**, *65*, 6584–6590.

(3) (a) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488–496. (b) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979–2000.

(4) (a) Wong, O. A.; Shi, Y. *Top. Curr. Chem.* **2010**, *291*, 201–232. (b) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958–3987.

(5) (a) Taber, D. F.; Green, J. H.; Geremia, J. M. *J. Org. Chem.* **1997**, *62*, 9342–9344. (b) Yang, C.-G.; Wang, J.; Jiang, B. *Tetrahedron Lett.* **2002**, *43*, 1063–1066. (c) Watanabe, B.; Yamamoto, S.; Sasaki, K.; Nakagawa, Y.; Miyagawa, H. *Tetrahedron Lett.* **2004**, *45*, 2767–2769. (d) Roulland, E.; Ermolenko, M. S. *Org. Lett.* **2005**, *7*, 2225–2228.

(6) For greater detail on other attempted routes see (a) Zhang, Y. Progress Towards Total Synthesis of Lyconadin A. PhD. Dissertation, Brigham Young University, 2010. (b) Loertscher, B. M.; Zhang, Y.; Castle, S. L. *Beilstein J. Org. Chem.* **2013**, *9*, 1179–1184.

(7) Hernandez, A.-I.; Balzarini, J.; Karlsson, A.; Camarasa, M.-J.; Perez-Perez, M.-J. *J. Med. Chem.* **2002**, *45*, 4254–4263

(8) Gannett, P. M.; Nagel, D. L.; Reilly, P. J.; Lawson, T.; Sharpe, J.; Toth, B. *J. Org. Chem.* **1988**, *53*, 1064–1071.

(9) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.

(10) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623–3626.

(11) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235.

(12) Marfat, A.; McGuirk, P. R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888–3901.

(13) (a) Bartlett, P. A.; Green, F. R. III *J. Am. Chem. Soc.* **1978**, *100*, 4585–865. (b) Cabral, N. L. D.; Thiessen, L. J. H.; Doboszewksi, B. *Nucloesides, Nucleotides Nucleic Acids* **2008**, *27*, 931–948.

(14) Jones, G. B.; Hynd, G.; Wright, J. M.; Sharma, A. *J. Org. Chem.* **2000**, *65*, 263–265.

(15) Smith, A. B., III; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783–786.

(16) Tius, M. A.; Fauq, A. H. *J. Org. Chem.* **1983**, *48*, 4131–4132.

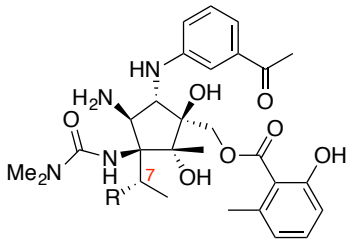
(17) Hex-5-en-2-yn-1-ol is commercially available but is more economically prepared from propargyl alcohol and allyl bromide in quantitative yield in water under basic conditions. See Bieber, L. W.; da Silva M. F. *Tetrahedron Lett.* **2007**, *48*, 7088–7090.

(18) Ma, S.; Ni, B. *Chem.—Eur. J.* **2004**, *10*, 3286–3300.

Chapter 3. Cranomycin Introduction

3.1 Introduction

Cranomycin (**108**, Figure 3.1) is an aminocyclitol antibiotic isolated in 1964 from a culture broth of *Streptomyces* SE-801.[1,2] Later, it was isolated from two other *Streptomyces* species and named PD 113,618[3] and 7-deoxypactamycin.[4] The latter name refers to its structural relationship with pactamycin (**109**),[5–8] which exhibits broad spectrum cytotoxicity.[8,9] The cyclopentane core of cranomycin is densely functionalized, bearing substituents at every carbon atom. Other interesting features of **108** include three contiguous quaternary stereocenters consisting of a *tert*-alkylamine and two tertiary alcohols.



Cranomycin (**108**), R = H
Pactamycin (**109**), R = OH

Figure 3.1 Structures of cranomycin and pactamycin.

Pactamycin inhibits protein synthesis by interaction with rRNA.[10] Given its structural similarity to pactamycin, cranomycin is likely to have a similar mode of action. Recent biological studies have shown that **108** is active against *Trypanosoma brucei brucei* (IC_{50} = 0.9 nM) and *Plasmodium falciparum* (IC_{50} = 0.4 nM), the protozoa that respectively cause African sleeping sickness and malaria.[11] Pactamycin is also active against these diseases but has an 8-fold decrease in its antitrypanosomal activity and a 40-fold decrease in its antimalarial activity. While **108** and **109** are excluded from clinical use because of their cytotoxicity, they can serve as lead structures for the development of new therapies for sleeping sickness and malaria. In fact,

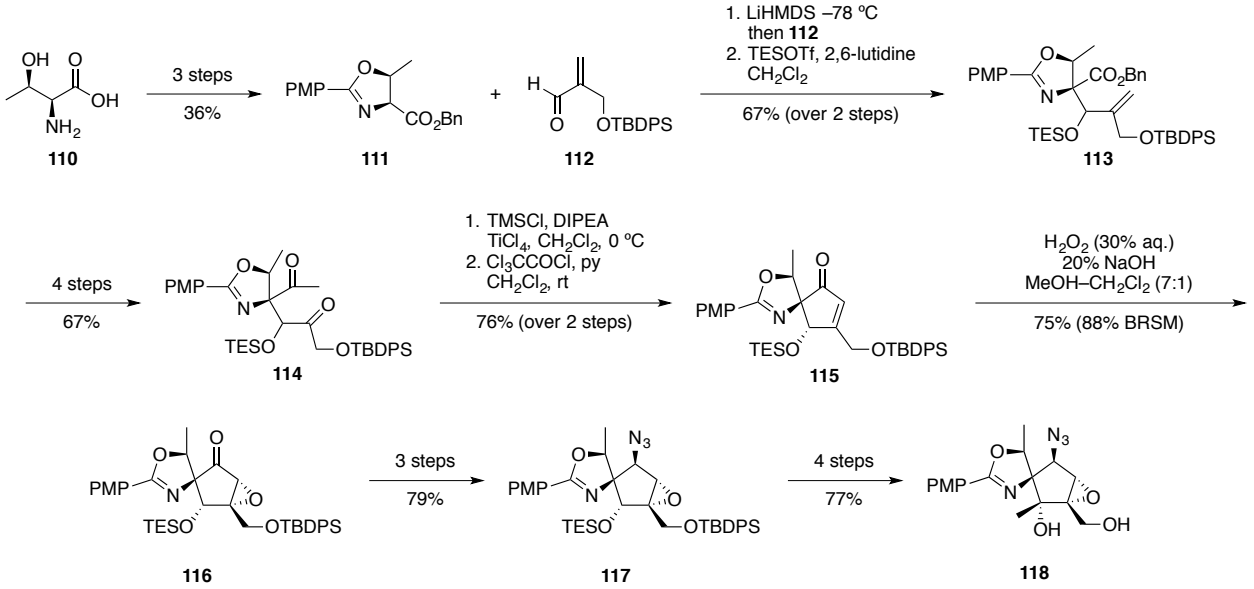
Mahmud and co-workers have demonstrated that the 7-demethyl congener of **108** (produced via biosynthetic and genetic engineering techniques) conserves antimalarial activity but has decreased cytotoxicity.[12] An efficient total synthesis of **108** would complement Mahmud's work by providing access to other cranomycin analogs. Methodology developed in the synthesis of **108** would also be valuable to others who seek to synthesize compounds with many functional groups in a congested system. Thus, cranomycin is an ideal target for total synthesis.

No synthetic studies targeting cranomycin directly have been published, but many groups have proposed synthetic routes toward pactamycin. Progress has been reported by the Isobe,[13] Knapp,[14] and Looper[15] groups. Hanessian and co-workers were the first to successfully construct **109** from threonine in 34 steps.[16] Earlier this year, Johnson and co-workers disclosed a much shorter synthesis of **109**.[17] This chapter will summarize these two ground-breaking syntheses and discuss some of the attempts by groups mentioned above.

3.2 Hanessian Group Synthesis

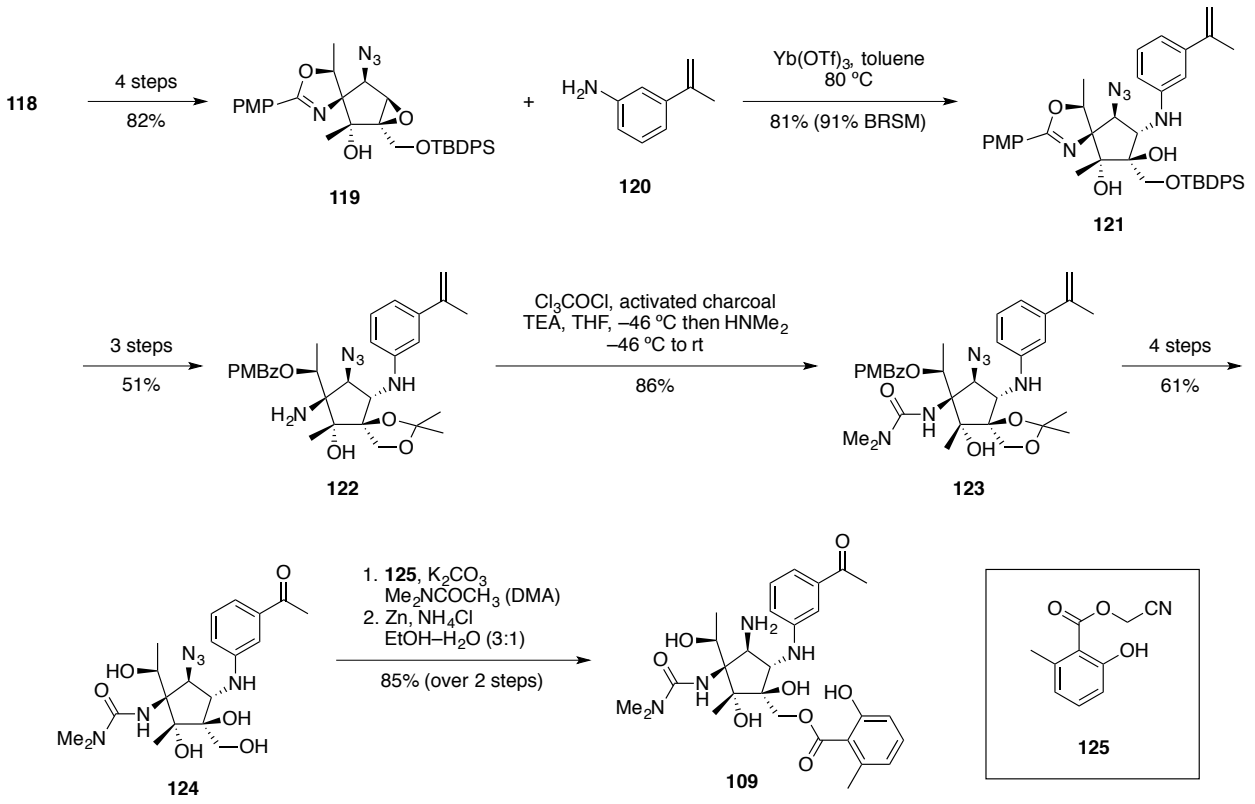
Hanessian and co-workers began the synthesis of pactamycin with L-threonine (**110**, Scheme 3.1) by formation of oxazoline **111**.[18] Condensation of the enolate generated from **111** with acrolein **112** was followed by TES protection to afford **113**. Reduction of the benzyl ester to an aldehyde, methylation, oxidation, and ozonolysis furnished γ-diketone **114**. A Mukaiyama-type intramolecular aldol reaction and subsequent dehydration provided enone **115**. Epoxidation proceeded efficiently, giving α-epoxide **116**. Attempts to prepare the desired β-epoxide were successful, but this configuration led to decomposition in subsequent steps. Thus, they proceeded with epoxide **116**, seeking to invert the configuration of the epoxide at a later stage. Luche reduction, triflation, and S_N2 displacement delivered azide **117**. Selective cleavage of the TES

ether, oxidation, methylation, and desilylation afforded epoxy diol **118**. At this stage, they were ready to invert the configuration of the epoxide.



Scheme 3.1 Synthesis of epoxide **118**.

The inversion of the epoxide was accomplished by Lewis-acid promoted Payne rearrangement of **118** to create a transient terminal epoxide intermediate which is opened by addition of acetic acid (Scheme 3.2). Acetate removal, silylation, and dehydrative epoxide formation afforded **119**, an intermediate whose crystal structure allowed unambiguous assignment of all stereocenters. $Yb(OTf)_3$-mediated ring opening with aniline **120** delivered intermediate **121** in high yield. Oxazoline cleavage, desilylation, and acetonide formation allowed successful carbamoylation of the *tert*-alkylamine. Without the acetonide in place the tertiary hydroxyl group on the β-face of the cyclopentane ring interfered with carbamoylation, forming a bridged carbamate. Removal of the *p*-methoxybenzoyl (PMBz) group, dihydroxylation, oxidative cleavage, and acetonide removal released tetraol **124**. Ketene esterification of **124** with **125** and subsequent reduction afforded pactamycin. Despite the length of this synthesis, it is achieved in notably high overall yield (0.8% over 34 steps).

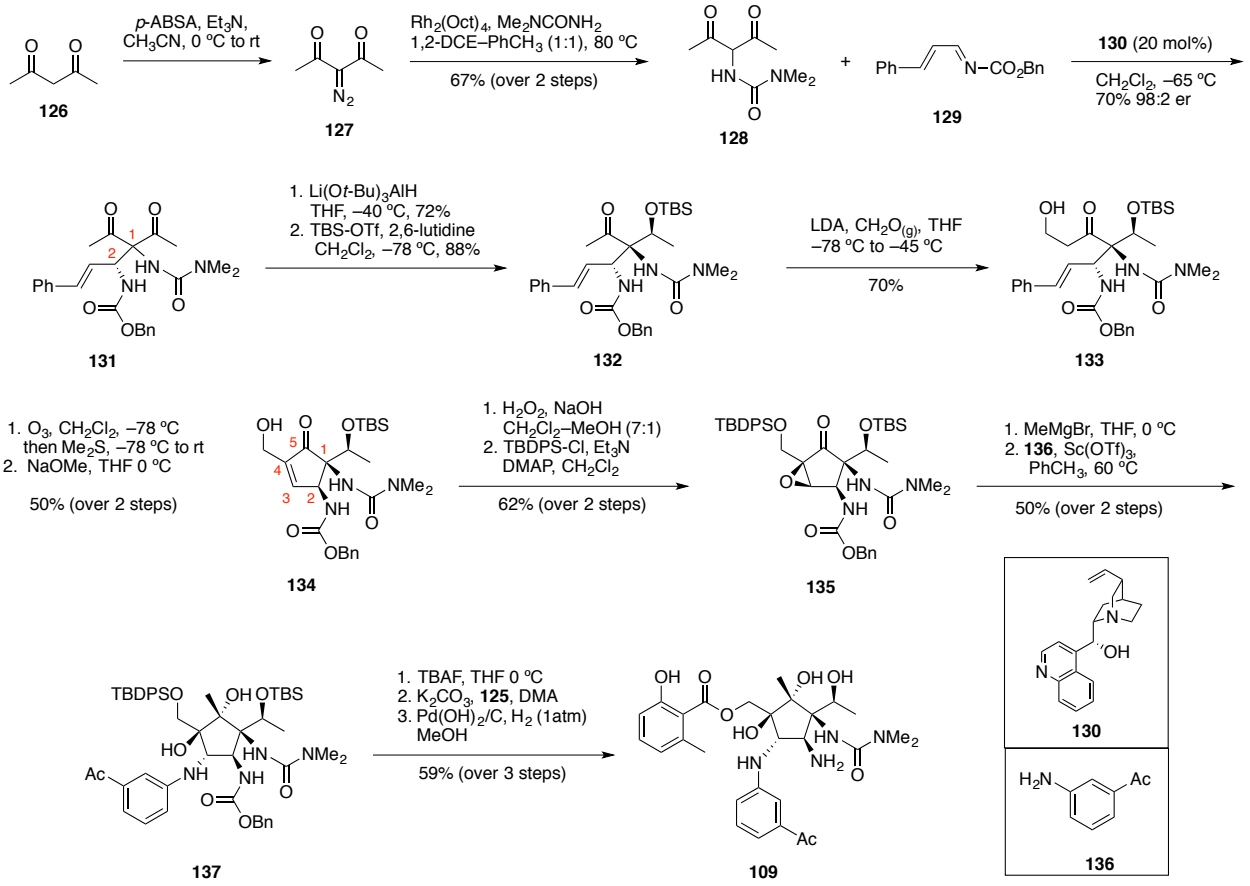


Scheme 3.2 Completion of total synthesis of pactamycin by Hanessian and co-workers.

3.3 Johnson Group Synthesis

Johnson and co-workers recently published the total synthesis of pactamycin.[17] This synthesis differs significantly from their previous approach which required a late stage installation of the amino group at C-2, a transformation that they were unable to accomplish.[19] This prompted them to install the amino group at an early stage. The *N*,*N*-dimethyl urea moiety was introduced by formation of the diazo compound **127** derived from acetylacetone (**126**) and trapping of the Rh carbenoid with Me_2NCONH_2. An intramolecular Mannich reaction between **128** and imine **129** was mediated by cinchonidine (**130**) to afford **131** in 70% yield and high ee. Fortunately, monoreduction of **131** by lithium tri(*tert*-butoxy)aluminum hydride (LTBA) proceeded with great selectivity in >10:1 ratio favoring **132** over the three other diastereomers, a notable transformation. Formylation, ozonolysis and intramolecular aldol condensation afforded

enone **134**. Fortunately, the intramolecular aldol reaction proceeded by epimerization at C-2. Epoxidation was followed by silylation to afford **135**. The remaining steps and intermediates share some similarities with the Hanessian synthesis of pactamycin. Grignard addition and $Sc(OTf)_3$-mediated epoxide opening with 3-acetylanaline furnished **137**. The synthesis was completed by desilylation, ketene esterification, and hydrogenation. Thus, total synthesis of pactamycin was achieved in 17 steps with an overall yield of 1.9%.

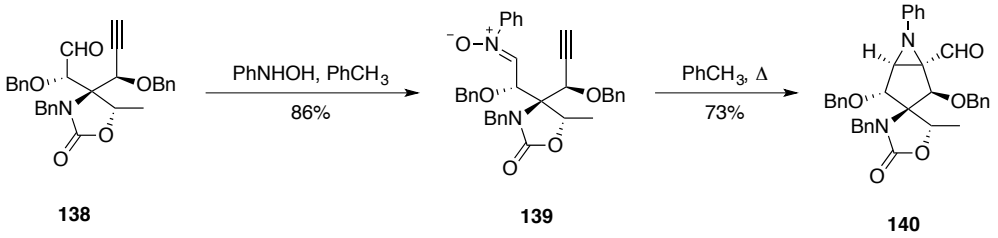


Scheme 3.3 Johnson synthesis of pactamycin.

3.4 Other Synthesis Attempts

Besides these completed syntheses of pactamycin, several research groups have tried their hand at the synthesis of **110**. The attempts by the Isobe, Knapp, and Looper groups are described below.

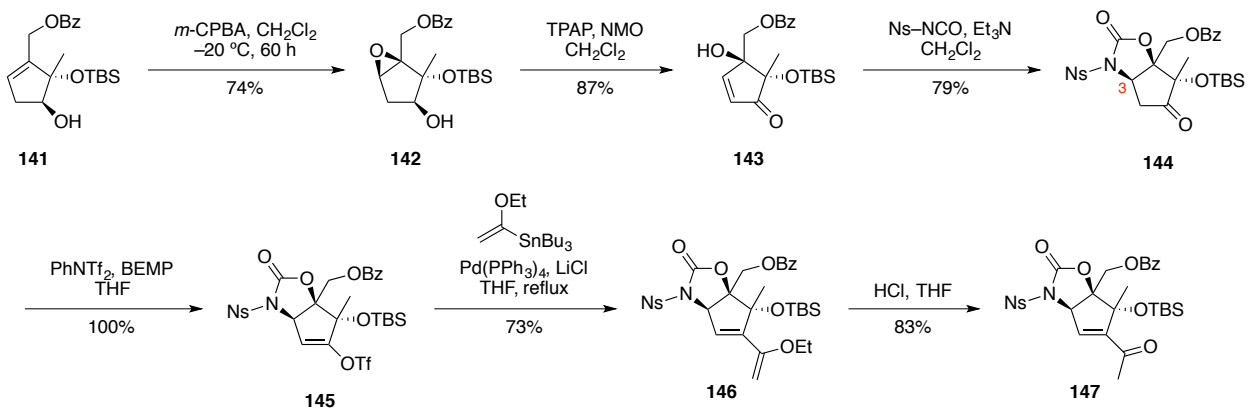
Isobe and co-workers attempted to synthesize the pactamycin from glucose-derived aldehyde **138**.[13b] Reaction of **138** with *N*-phenylhydroxylamine produced dipole **139**, which upon refluxing formed aziridine **140**. This intermediate presumably forms via Baldwin rearrangement of the isoxazoline formed by [3+2]-dipolar cycloaddition. Unfortunately, later steps revealed that the configuration of the aziridine was reversed from what is required to synthesize pactamycin.



138 **139** **140**

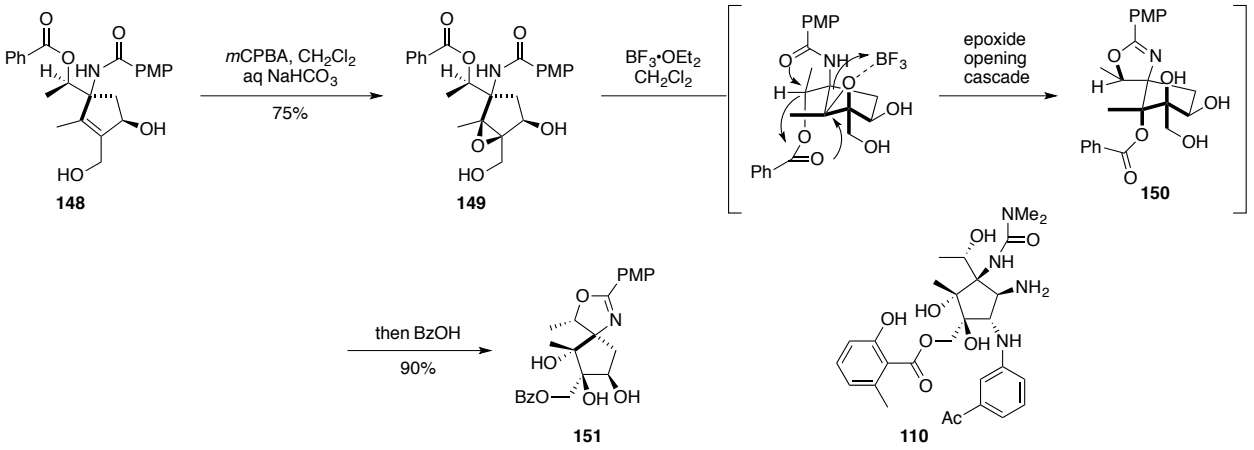
Scheme 3.4 Isobe synthesis of pactamycin core.

Knapp and co-workers performed epoxidation on advanced intermediate **141** (prepared from 2-methylcyclopent-2-en-1-one in 10 steps).[14] Ley–Griffith oxidation formed enone **143**. Reaction of the tertiary alcohol with 2-nitrobenzenesulfonate afforded oxazolidinone **144**. This transformation established a C–N bond at C-3 with a configuration opposite what is required for pactamycin. Knapp asserts that this nitrogen is bound for C-2, but does not elaborate how it would be shifted to that position. They proceeded by formation of triflate **145**. Stille cross-coupling and enol ether hydrolysis then delivered ketone **147**, the oxygenated core of pactamycin. Knapp and co-workers also performed model studies for installation of the C-1 amino group. As it has been several years since the Knapp group has reported on the synthesis of **147**, it is unclear if those model studies were adaptable for further elaboration to the natural product.



Scheme 3.5 Knapp synthesis of oxygenated pactamycin core.

Looper's approach to pactamycin involves epoxide opening of **149** mediated by BF_3•OEt_2.[15] Lewis-acid activation of the epoxide is presumably followed by intramolecular attack of the adjacent benzoyl group. The nearby PMP-amide carbonyl oxygen displaces the benzoyl group to form oxazoline **150**. Acyl migration then delivers **151**. This interesting transformation allows access to a highly advanced intermediate in the pactamycin synthesis in only 14 steps from L-threonine.



Scheme 3.6 Looper epoxide opening strategy for pactamycin.

3.5 Conclusion

Pactamycin and cranomycin are powerful antibiotic compounds with complex structures. We have discussed several approaches for the synthesis of pactamycin. To our knowledge, no

synthetic approaches that target cranomycin directly have been disclosed. Our strategy toward cranomycin will be discussed in Chapters 4 and 5.

3.6 References

(1) Kondo, S.; Shiumura, M.; Sezaki, M.; Sato, K.; Hara, T. *J. Antibiot. Ser. A.* **1964**, *17*, 230–233.

(2) Hara, T.; Niida, T.; Sato, K.; Kondo, S.; Noguchi, T.; Kohmoto, K. *J. Antibiot. Ser. A.* **1964**, *17*, 266.

(3) Hurley, T. R.; Smitka, T. A.; Wilton, J. H.; Bunge, R. H.; Hokanson, G. C.; French, J. C. *J. Antibiot.* **1986**, *39*, 1086–1091.

(4) Dobashi, K.; Isshiki, K.; Sawa, T.; Obata, T.; Hamada, M.; Naganawa, H.; Takita, T.; Takeuchi, T.; Umezawa, H. Bei, H.; Zhu, B.; Tong, C.; Xu, W. *J. Antibiot.* **1986**, *39*, 1779–1783.

(5) Argoudelis, A. D.; Jahnke, H. K.; Fox, J. A. *Antimicrob. Agents Chemother* **1962**, 191–167.

(6) Wiley, P. F.; Jahnke, H. K.; MacKellar, F.; Kelly, R. B.; Argoudelis, A. D. *J. Org. Chem.* **1970**, *35,* 1420–1425.

(7) Duchamp, D. J. *Abstracts, American Crystallographic Association Winter Meeting*, Albuquerque, NM, **1972**, 23.

(8) Bhuyan, B. K.; Dietz, A.; Smith, C. G. *Antimicrob. Agents Chemother.* **1962**, 184–190.

(9) White, F. R. *Canc. Chemother. Rep. 1* **1962**, *24*, 75–78.

(10) Mankin, A. S. *J. Mol. Biol.* **1997**, *274*, 8–15.

(11) (a) Otoguro, K.; Iwatsuki, M.; Ishiyama, A.; Namatame, M.; Nishimura-Tukashima, A.; Shibahara, S.; Kondo, S.; Yamada, H.; Omura, S. *J. Antibiot.* **2010**, *63*, 381–384. (b) Iwatsuki, M.; Nishihara-Tsukashima, A.; Ishiyama, A.; Namatame1, M.; Watanabe, Y.;

Handasah, S.; Pranamuda, H.; Marwoto, B.; Matsumoto, A.; Takahashi, Y.; Otoguro, K.; Ōmura, S. *J. Antibiot.* **2012**, *65*, 169–171.

(12) (a) Lu, W.; Roongsawang, N.; Mahmud, T. *Chem. Biol.* **2011**, *18*, 425–431. (b) Almabruk, K. H.; Lu, W.; Li, Y.; Aburgreen, M.; Kelly, J. X.; Mahmud, T. *Org. Lett.* **2013**, *15*, 1678–1681.

(13) (a) Tsujimoto, T.; Nishikawa, T.; Urabe, D.; Isobe, M. *Synlett* **2005**, 433–436. (b) Matsumoto, N.; Tsujimoto, T. Nakazak, A.; Isobe, M.; Nashikawa, T. *RSC Adv.* **2012**, *2*, 9448–9462.

(14) Knapp, S.; Yu, Y. *Org. Lett.* **2007**, *9*, 1359–1362.

(15) Haussner, T. J.; Looper, R. E. *Org. Lett.* **2012**, *14*, 3632–3635.

(16) (a) Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Lecomte, F.; DelValle, J. R.; Zhang, J.; Deschênes-Simard, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 3497–3500. (b) Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Deschênes-Simard, B. *J. Org. Chem.* **2012**, *77*, 9458–9472.

(17) Malinowski, J. T.; Sharpe, R. J.; Johnson, J. S. *Science*, **2013**, *340*, 180–182.

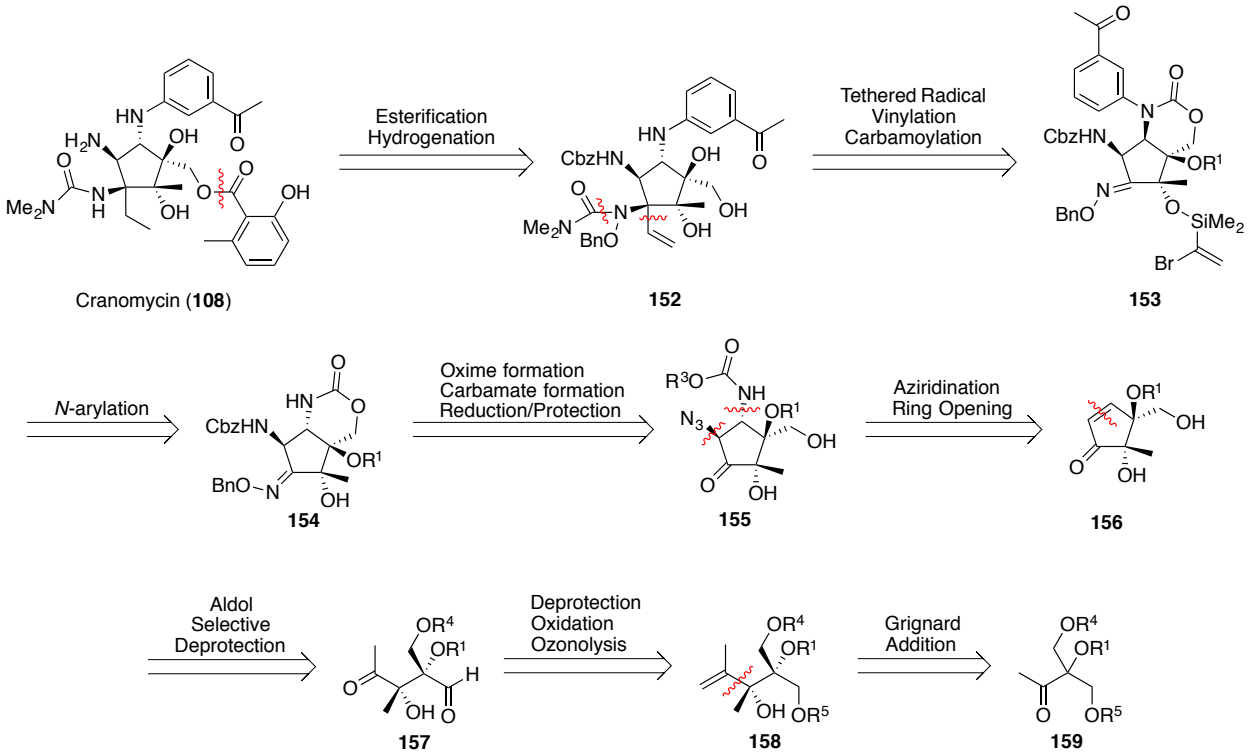
(18) (a) Reddy, L. R.; Fournier, J.-F.; Reddy, B. V. S.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 8974–8976. (b) Soukup, M.; Wipf, E. H.; Leuenberger, H. G. *Helv. Chim. Acta* **1987**, *70*, 232–236.

(19) Malinowski, J. T.; McCarver, S. J.; Johnson, J. S. *Org. Lett.* **2012**, *14*, 2878–2881.

Chapter 4. Early Cranomycin Studies

4.1 Retrosynthesis

In our retrosynthetic analysis of cranomycin (**109**, Scheme 4.1), we thought that a late stage ketene esterification[1] of triol **152** followed by hydrogenation with Raney nickel[2] would afford the natural product. Inspired by the work of Friestad and co-workers,[3] we would construct **152** via tethered radical vinylation of bromovinylsilane **153** and proceed with urea formation and carbamate hydrolysis. *N*-arylation[4] of cyclic carbamate **154** would deliver **153**. Carbamate **155** could be converted to **154** by oxime formation, intramolecular transesterification of the carbamate, azide reduction and Cbz protection. We considered tethered aminohydroxylation (TA) as a method to install a C–N bond at C-3,[5] but model studies (vide infra) discouraged us from pursuing this route. We also contemplated intramolecular aza-Michael addition for installation of the arylamino group at C-3,[6] but this provides the additional challenge of electrophilic amination at C-2, which proved difficult for Johnson and co-workers.[7] We finally decided that stereoselective aziridination[8] of enone **156** and subsequent opening with azide[8b] would be a suitable strategy. Enone **156** would be constructed via an intramolecular aldol cyclization of γ-ketoaldehyde **157**, which would be prepared from **158** through routine functional group manipulations. Triether **158** could be furnished by 1,2-addition to ketone **159**. We envisioned that judicious selection of protecting groups would control the diastereoselectivity of the Grignard addition. It was especially important for us to use orthogonal protecting groups to allow selective deprotection of the primary alcohols at various stages of the synthesis (e.g. **158** → **157** and **157** → **156**). We thought 1,3-dihdyroxyacetone dimer would be an appropriate starting material to access ketones of type **159**.[9]



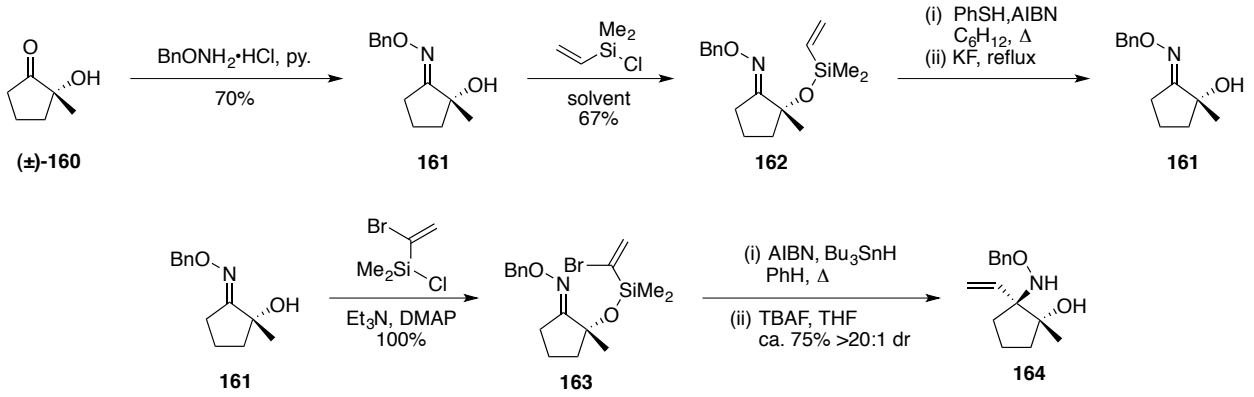
Scheme 4.1 Retrosynthetic analysis of cranomycin.

This chapter will discuss model studies of the tethered radical vinylation, *N*-arylation, and aziridination, as well as our preliminary results from an early tethered aminohydroxylation model. An early synthetic route to ketones of type **159** will also be included.

4.2 Tethered Radical Vinylation Model

The crucial tethered radical vinylation step was a top priority for our model studies. We thought that an *O*-benzyloxime ether would be an appropriate radical acceptor, although related work employed hydrazones as the radical acceptors. Radical addition to an *O*-benzyloxime acceptor has the added benefit of forming a nucleophilic *N*-benzyloxy amino group which would allow selective formation of the *N*,*N*-dimethylurea moiety. Perusal of the literature led us to α-hydroxy ketone **160**,[10] which we easily converted to oxime **161** (see Scheme 4.2). Reaction of

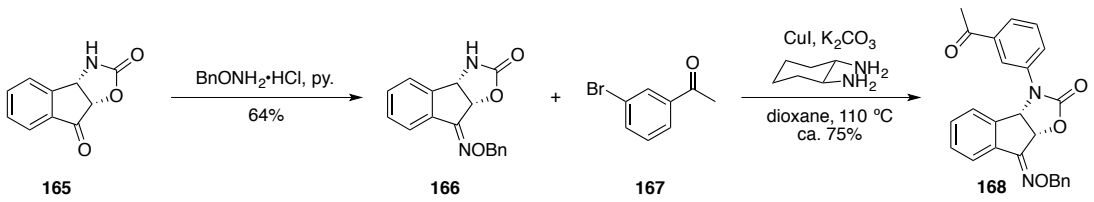
161 with chlorodimethylvinylsilane provided silyl ether **162**. Unsurprisingly, treatment of **162** with PhSH and AIBN in cyclohexane at elevated temperatures failed to deliver any of the desired vinylation product, presumably because the ketoxime radical acceptor is less electrophilic than the hydrazones used by Friestad and co-workers. Treatment of the crude mixture with KF returned oxime **161**. Fortunately, Friestad and co-workers had also employed a bromovinylsilane tether in cases where the vinylsilane failed.[3b] Installation of the bromovinylsilane tether proceeded smoothly to afford **163**. In this case the radical cyclization proceeded to completion and subsequent desilylation afforded amino alcohol **164**. This study suggests that we could use a tethered radical vinylation approach to install the *tert*-alkylamine of cranomycin.



Scheme 4.2 Tethered radical vinylation model study.

4.3 *N*-Arylation Model

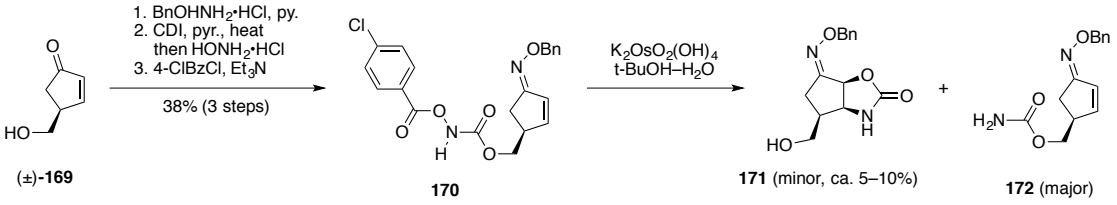
Our strategy requires *N*-arylation in the presence of an oxime ether. We were uncertain if this group would survive the transformation. We synthesized known oxazolidinone **165**[11] and converted it into oxime ether **166** (see Scheme 4.3). Gratifyingly, *N*-arylation with 3'-bromoacetophenone (**167**) using Trehan's protocol proceeded smoothly to afford **168** without any evident cleavage of the oxime ether. This allows us to differentiate the carbonyl of the cyclopentanone ring and the acetophenone moiety without using additional protecting groups. If necessary, other ligands[12] could be explored for the *N*-arylation process in the total synthesis.



Scheme 4.3 *N*-arylation model study.

4.4 Tethered Aminohydroxylation Model

We were concerned that an oxime ether would not survive aminohydroxylation. As a tethered aminohydroxylation model study, we synthesized enone **169**[13] and converted it to carbamate **170** in 3 steps.[14] Treatment of **170** with potassium osmate did not cleave the oxime ether and did deliver the desired oxazolidinone (**171**) in low yield, however the majority of the product is derived from N-O cleavage, suggesting that the TA reaction is slow. This could potentially be remedied by modifiying the leaving group, but we decided to pursue a different approach.

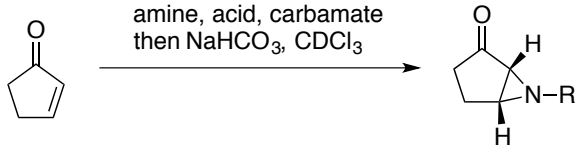


Scheme 4.4 Tethered aminohydroxylation model study.

4.5 Aziridination Model

It occurred to us that an aza-Michael ring closure (AZA-MIRC) would be a suitable method for installation of the C-2 and C-3 amino groups. We found an AZA-MIRC protocol for acyclic enones that is followed by a ring opening protocol to prepare oxazolidinones in a formal aminohydroxylation.[13] It was unclear if this process was suitable for cyclic systems, so we performed the reaction on 2-cyclopenten-1-one (**173**). The AZA-MIRC reaction failed and further exploration led us to a process that employs chiral amine salt catalysts.[8] We would be

relying on substrate control for diastereoselectivity, so we explored a racemic AZA-MIRC process with butylamine or pyrrolidine in combination with benzoic acid (see Table 4.1). Butylamine failed to deliver any product, but results were much better when pyrroldine was employed for the reaction. We also explored several carbamates, and found that TrocNHOMs (entries 6 and 7) gave the best results. We also found that AcOH could be used instead of benzoic acid, although the conversion appeared to be slower in this case.

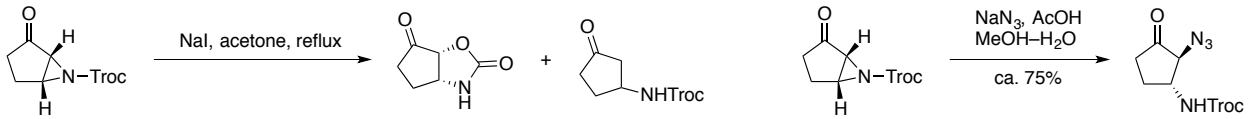


173 **174**

Entry	amine (20 mol%)	acid (30 mol%)	carbamate (1.1 Equiv.)	Result
1	$BuNH_2$	$PhCO_2H$	BocNHOTs	N.R.
2	pyrrolidine	$PhCO_2H$	BocNHOTs	7.1% yield
3	$BuNH_2$	$PhCO_2H$	CbzNHOMs	N.R.
4	pyrrolidine	$PhCO_2H$	CbzNHOMs	trace **174**
5	$BuNH_2$	$PhCO_2H$	TrocNHOMs	N.R.
6	**pyrrolidine**	**$PhCO_2H$**	**TrocNHOMs**	**73% yield**
7	pyrrolidine	CH_3CO_2H	TrocNHOMs	48% yield

Table 4.1 AZA-MIRC model study.

As a continuation of the model study, we first explored the conversion of aziridine **174** to oxazolidinone **175** by treatment with iodide (see Scheme 4.5). Unfortunately, this resulted in reduction at C-2 to afford carbamate **176**. However, ring opening with azide under acidic conditions proceeded smoothly to afford **177**, providing us with a method to install the C-2 and C-3 amino groups of cranomycin.

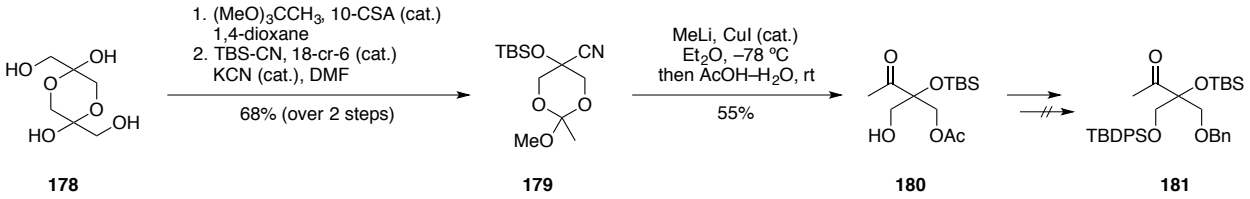


174 **175** (not observed) **176** (observed) **174** **177**

Scheme 4.5 Aziridine opening in model system.

4.6 Early Synthetic Route to Methyl Ketone

We initially began our synthesis of cranomycin by targeting a ketone of type **159**. To this end, we converted 1,3-dihydroxyacetone dimer (**178**, Scheme 4.6) into cyanohydrin **179** using Giese's protocol.[9a] Methylation and subsequent acidic hydrolysis of the orthoester delivered ketone **180**. We were able to protect the primary alcohol of **180** successfully with either a TBDPS or benzyl group, but we were unable to realize the transformation to **181** by this methodology. We explored hydrolysis of cyanohydrin **179** and attempted differentiation of the primary alcohols, but we were unable to methylate the resultant cyanohydrin, presumably due to steric hindrance from the adjacent TBS group. This required us to modify our strategy to access ketones of type **159**. Our successful route will be discussed in Chapter 5.



Scheme 4.6 Attempted synthesis of ketone of type **159**.

4.7 Conclusion

We performed a series of model studies to assess the feasibility of late stage transformations in our proposed cranomycin synthesis. After some experimentation, we were able to determine suitable conditions for key transformations, increasing our confidence that we would be able to synthesize cranomycin. A detailed account of our progress on the cranomycin synthesis will be discussed in Chapter 5.

4.8 References

(1) (a) Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Lecomte, F.; DelValle, J. R.; Zhang, J.; Deschênes-Simard, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 3497–3500. (b)

Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Deschênes-Simard, B. *J. Org. Chem.* **2012**, *77*, 9458–9472.

(2) (a) Chiara, J. L.; Destabel, C.; Gallego, P.; Marco-Contelles, J. *J. Org. Chem.* **1996**, *61*, 359–360. (b) Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755–11772.

(3) (a) Friestad, G. K.; Massari, S. E. *J. Org. Chem.* **2004**, *69*, 863–875. (b) Friestad, G. K.; Jiant, T.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 3964–3972.

(4) Mallesham, B.; Rajesh, B. M.; Reddy, P. R.; Srinivas, D.; Trehan, S. *Org. Lett.* **2003**, *5*, 963–965.

(5) (a) Donohoe, T. J.; Bataille, C. J. R.; Gattrell, W.; Kloesges, J.; Rossignol, E. *Org. Lett.* **20**

(6) (a) Kang, Q.; Zhang, Y. Org. Biomol. Chem. **2011**, *9*, 6715–6720 (b) Donohoe, T. J.; Chughtai, M. J.; Klauber, D. J.; Griffin, D.; Campbell, A. D. *J. Am. Chem. Soc.* **2006**, *128*, 2514–2515.

(7) Malinowski, J. T.; McCarver, S. J.; Johnson, J. S. *Org. Lett.* **2012**, *14*, 2878–2881.

(8) (a) De Vincentiis, F.; Bencivenni, G.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Galzerano, P.; Melchiorre, P. *Chem. Asian J.* **2010**, *5*, 1652–1656. (b) Menjo, Y.; Hamajima, A.; Sesaki, N.; Hamada, Y. *Org. Lett.* **2011**, *13*, 5744–5747.

(9) (a) Peukart, S.; Giese, B. *J. Org. Chem.* **1998**, *63*, 9045–9051. (b) Müller, S. N.; Batra, R.; Senn M.; Giese, B.; Kisel, M.; Shadyro, O. *J. Am. Chem. Soc.* **1997**, *119*, 2795–2803.

(10) Yamamoto, Y.; Matsumi, D. *Chem. Commun.* **1998**, 875–876.

(11) Kim, E. J.; An, K. M.; Ko, S. Y.; *Bull. Korean Chem. Soc.* **2006**, *27*, 2019–2022.

(12) (a) Phillips, D. P.; Zhu, X.-F.; Lau, T. L.; He, X.; Yang, K.; Liu, H. *Tetrahedron Lett.* **2009**, *50*, 7293–7296. (b) Chen, Y.-J.; Chen, H.-H. *Org. Lett.* **2006**, *8*, 5609–5612. (c) Morán-

Ramallal, R.; Liz, R.; Gotor, V. *Org. Lett.* **2008**, *10*, 1935–1938. (d) Mino, T.; Harada, Y.; Shindo, H.; Sakamoto, M.; Fujita, T. *Synlett* **2008**, 614–620. (e) Nandakumar, M. V. *Adv. Synth. Catal.* **2004**, *346*, 954–958.

(13) Hudon, J.; Cernak, T. A.; Ashenhurst, J. A.; Gleason, J. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 8885–8888.

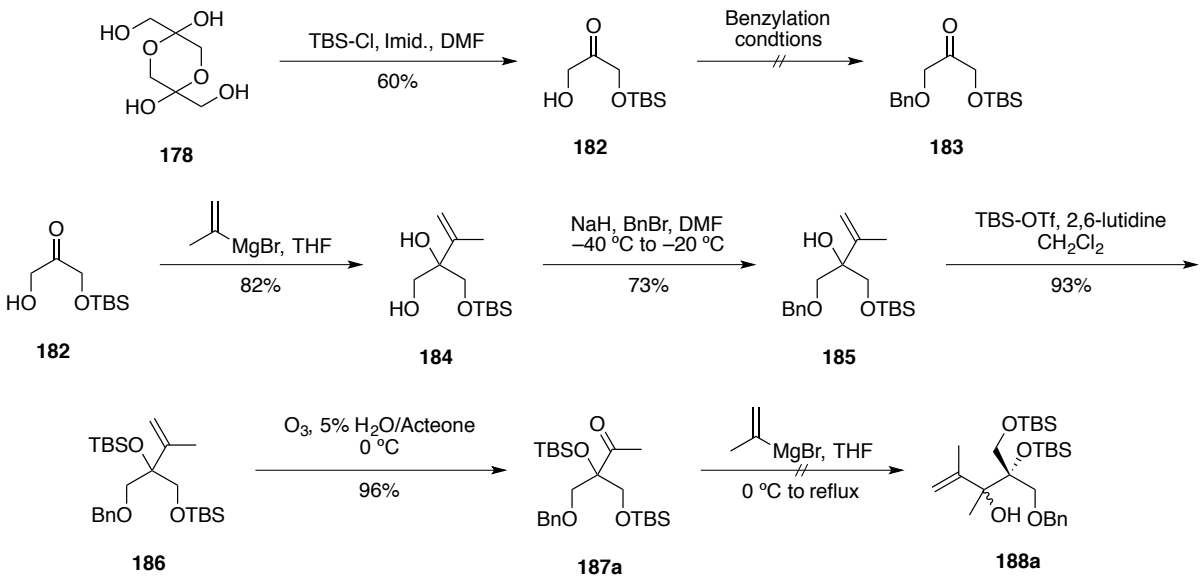
(14) We would like to acknowledge Braden Leigh for perfoming this reaction sequence.

Chapter 5. Progress Towards the Total Synthesis of Cranomycin

With our model studies complete, we were able to pursue the total synthesis of cranomycin. As mentioned in Chapter 4, we were unable to adapt Giese's protocol for the synthesis of ketone **181**. We decided to pursue an alternative method to access this key compound. This chapter contains an account of the successful synthesis of several ketone intermediates. It also includes a summary of the progress that we have currently made towards the synthesis of cranomycin.

5.1 Successful Synthesis of Ketone Substrates

We examined a different strategy to access the hindered methyl ketone substrate. We began with monosilylation of **178** to afford hydroxyketone **182** according to a known procedure.[1] Then, we explored several benzylation conditions including benzyl 2,2,2-trichloroacetimidate (Bn-TCAI)/TfOH,[2] AgO/BnBr,[3] and the Dudley benzylation protocol.[4] None of these transformations were successful, instead resulting in desilylation. Fortunately, Grignard addition to **182** delivered **184** in good yield. After much experimentation, we found that monobenzylation of diol **184** worked best when performed in DMF that was warmed from –40 ºC to –20 ºC. Silylation and ozonolysis then afforded ketone **187a**. We then attempted Grignard addition to **187a**, but the reaction only returned starting material even when refluxed for several hours, an unsurprising result considering the congestion around the carbonyl. Clearly, we needed to use an additive to allow the Grignard reaction to proceed.

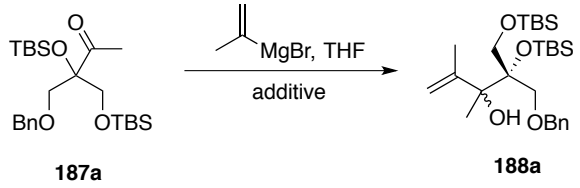


178 **182** **183** **182** **184** **185** **186** **187a** **188a**

Scheme 5.1 Synthesis of ketone **187a** and attempted Grignard addition.

5.2 Grignard Additions

Since it has been shown to improve the outcome of 1,2-additions for sterically demanding ketone substrates, we attempted the Grignard addition with $CeCl_3$.[5] However, the transformation was unsuccessful. We also found examples that used $ZnCl_2$[6] and homogeneous lanthanide additives.[7] $ZnCl_2$ allowed a trace amount of conversion, but the reaction appeared to stall after a few hours. $CeCl_3$•2LiCl (prepared in our lab), improved the yield of the transformation somewhat. Fortunately, use of $LaCl_3$•2LiCl (commercially available as a solution in THF) allowed the reaction to proceed to completion, affording adduct **188a** in good yield.

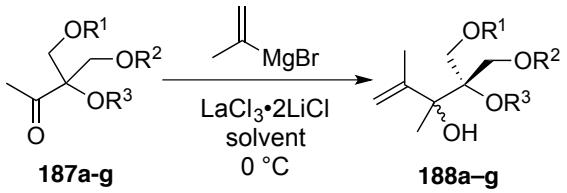


187a **188a**

Entry	Additive	Yield	dr
1	$CeCl_3$	0%	N.A.
2	$ZnCl_2$, LiCl, $TMSCH_2MgBr$	trace	N.A.
3	$CeCl_3$•2LiCl	13% (by NMR)	2:1
4	$LaCl_3$•2LiCl	94%	2:1

Table 5.1 Grignard addition with additives.

Seeking to improve the diastereoselectivity of the reaction, we prepared ketones **187b–g** (Table 5.2).[8] Changing protecting groups alone did not have a significant impact on the diastereomeric ratio (dr) of products formed, except in the case of ketone **187f**. We found that running the reaction in a 1:1 mixture of CH_2Cl_2–THF improved dr in all cases except for ketone **187b**. Since the synthesis of **187a** was most convenient, we explored further dilution of the reaction mixture with CH_2Cl_2 and found that a 15:1 mixture delivered adduct **188a** with excellent dr.



187a-g **188a–g**

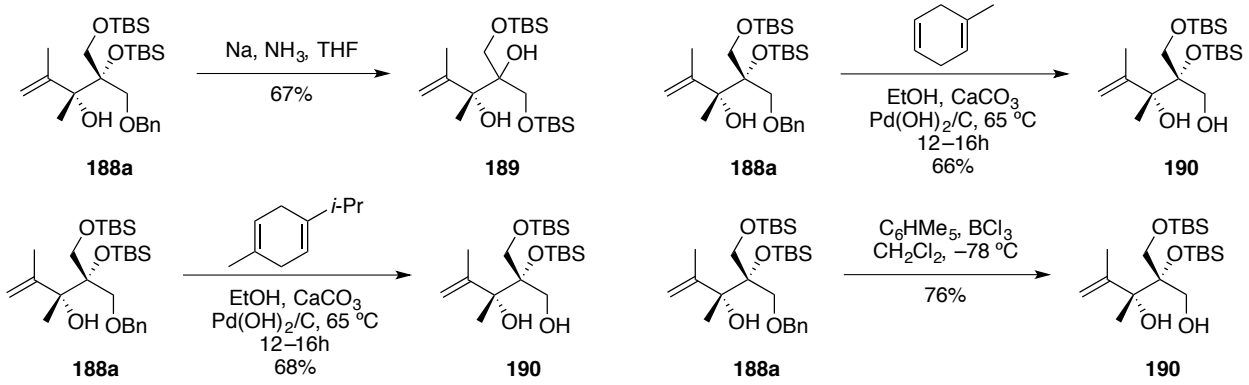
Entry	ketone	solvent	R^1	R^2	R^3	yield (%)	dr
1	**187a**	THF	Bn	TBS	TBS	90%	2:1
2	**187a**	CH_2Cl_2–THF (1:1)				89%	5.8:1
3	**187a**	CH_2Cl_2–THF (15:1)				93%	>20:1
4	**187b**	THF	Bn	TBS	MOM	75%	1.5:1
5	**187b**	CH_2Cl_2–THF (1:1)				74%	1.6:1
6	**187c**	THF	Bn	TBS	TES	80%	2:1
7	**187c**	CH_2Cl_2–THF (1:1)				76%	7.7:1
8	**187d**	THF	Bn	TBDPS	TBS	<10% (NMR)	1:1
9	**187d**	CH_2Cl_2–THF (1:1)				98%	10:1
10	**187e**	THF	MOM	TBS	TBS	95%	1.4:1
11	**187e**	CH_2Cl_2–THF (1:1)				90%	5.1:1
12	**187f**	THF	MOM	TBDPS	TBS	96%	7:1
13	**187f**	CH_2Cl_2–THF (3:1)				96%	19:1
14	**187g**	THF	BOM	TBDPS	TBS	42%	1.2:1
15	**187g**	CH_2Cl_2–THF (1:1)				91%	>20:1

Table 5.2 Optimization of Grignard reaction for improved dr.

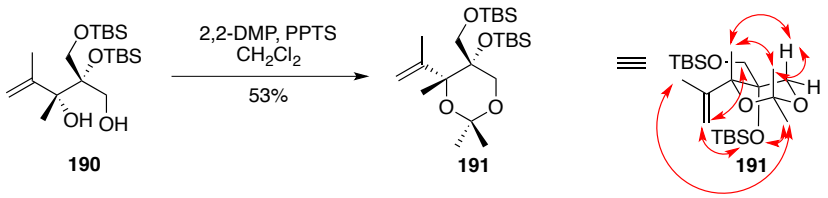
To determine the relative configuration of **188a**, we decided to selectively cleave the benzyl ether. When we explored debenzylation with Na/NH_3, **189** was formed via silyl migration with no trace of the desired product (see Scheme 5.2). Debenzylation by transfer hydrogenolysis mediated by $Pd(OH)_2$ in the presence of $CaCO_3$ and 1-methyl-1,4-cyclohexadiene[10] gave a significantly higher yield, although silyl migration still occurred occasionally. Diol **190** was

easily converted to acetonide **191** to assign the relative configuration of the vicinal tertiary diol (see Scheme 5.3).

With the relative configuration of **188a** assigned, we turned our attention to the removal of the benzyl group. Although the benzyl ether was already successfully removed via transfer hydrogenolysis, the process is not well-suited for large scale reactions because of the use of excess $Pd(OH)_2$ and 1-methyl-1,4-cyclohexadiene as the costly hydrogen source. Therefore, the more economical γ-terpinene was explored as the hydrogen source in transfer hydrogenolysis. Gratifyingly, conversion to diol **190** was successful even with a decreased loading of $Pd(OH)_2$ (see Scheme 5.6). However, this reaction suffered from poor reproducibility, giving the silyl migration for reasons that are not currently understood by our group. Fortunately, debenzylation with pentamethybenzene as a cation scavenger and BCl_3 as a Lewis acid[9] gave more consistent results.

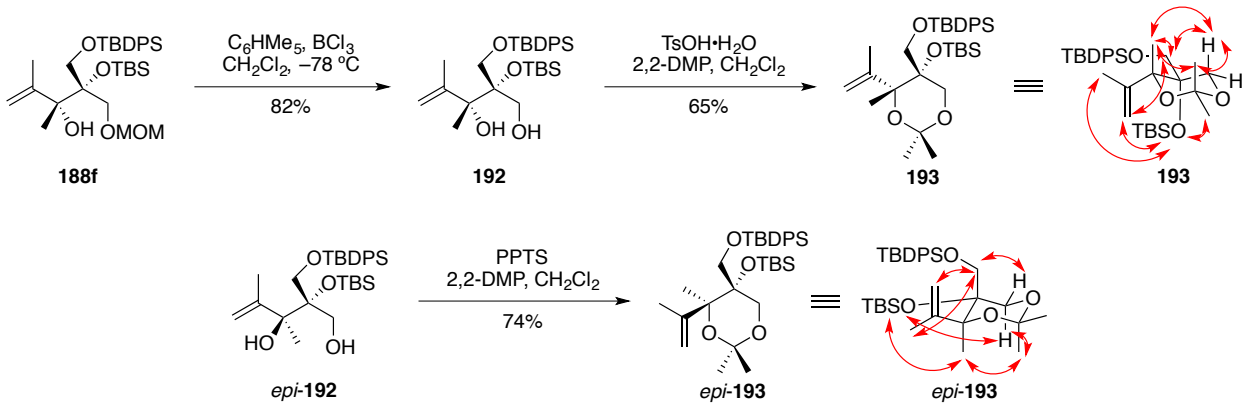


Scheme 5.2 Debenzylation reactions of **188a**.



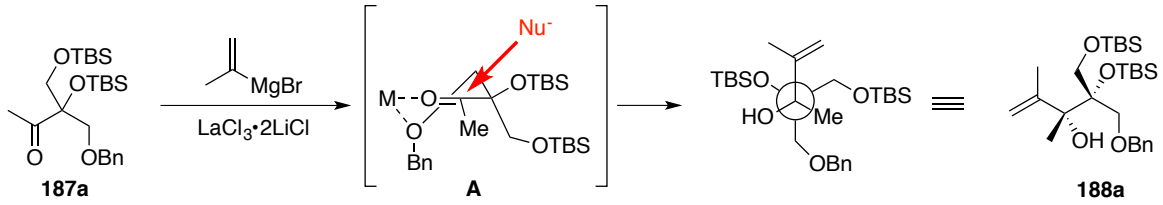
Scheme 5.3 Assignment of relative configuration.

We also performed a similar reaction sequence with both isomers of **188f** (Scheme 5.4). After considerable experimentation, we found that BCl_3 in the presence of pentamethylbenzene effected the MOM deprotection in high yield.[9] Diols **192** and *epi*-**192** were converted into acetonides **193** and *epi*-**193**. NOESY spectra of these compounds confirmed that the diastereoselectivity for $LaCl_3$•2LiCl-promoted 1,2-addition to **187f** was similar to that for addition to **187a**.



Scheme 5.4. Assignment of relative configuration of **188f**.

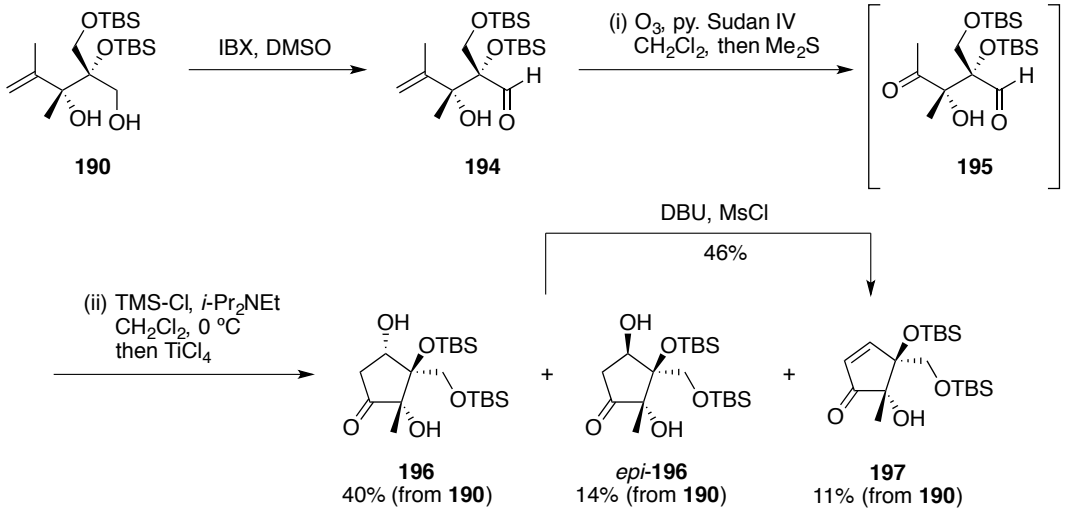
Improved selectivity by dilution with CH_2Cl_2 suggests that chelation control[11] may be involved. A rationale for the observed diastereoselectivity is shown in Scheme 5.5. Nucleophilic addition occurs on the less-hindered face of 1,3-chelate **A** to deliver **188a**. When THF is employed as the only solvent in the reaction, a less-selective non-chelated addition process may become competitive due to disruption of **A** by THF. The presence of two chelating groups in **187b** allows a competitive 1,2-chelated intermediate, which may explain why good selectivity was not achieved even when the reaction was run in CH_2Cl_2–THF mixtures.



Scheme 5.5. Rationale for stereocontrol.

5.3 Intramolecular Aldol Reaction

Oxidation of **190** was cleanly performed by treatment with IBX in DMSO. Ozonolysis originally resulted in decomposition of **194**. We found that stirring olefin **194** under a stream of ozone rather than bubbling ozone directly into the solution prevented the formation of undesired byproducts. We attempted several conditions for the intramolecular aldol reaction. Basic conditions (NaOH, NaOMe, KO*t*-Bu, etc.) caused unproductive decomposition of **195**. A Mukaiyama-type cyclization[12] afforded **196** and *epi*-**196** as well as a minor amount of enone **197**. The transformation worked best when reaction time was short (*ca*. 5 min), as prolonged reaction times resulted in lower yields. The NOESY spectra of **196**, *epi*-**196**, and **197** provided further evidence of the relative configuration of the tertiary diol centers (see Figure 5.1). The mixture of **196** and *epi*-**196** was converted to **197** by DBU/MsCl.



Scheme 5.6. Synthesis of enone **197**.

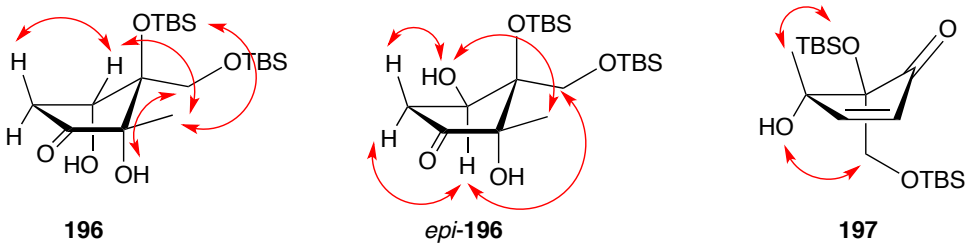
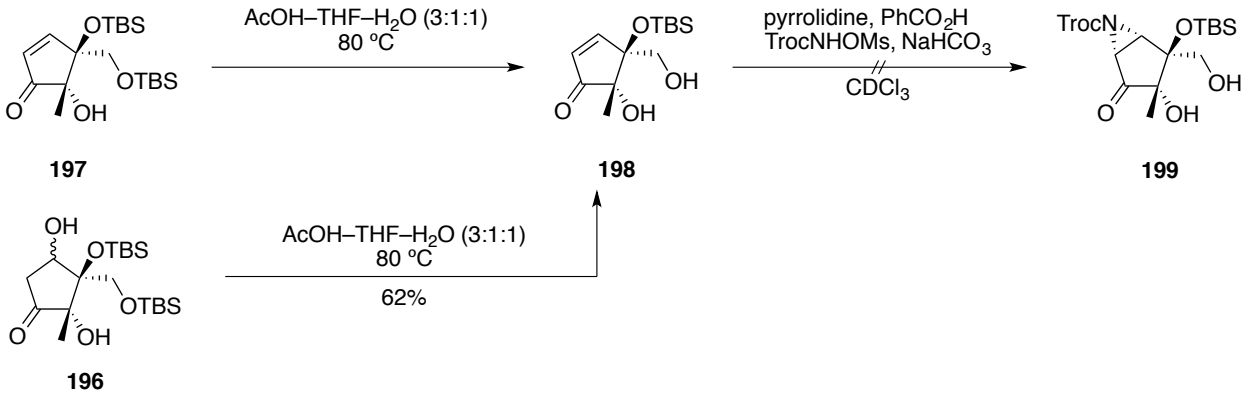


Figure 5.1. Diagnostic nOes of aldol products.

Somewhat disappointed by the low yield for dehydration of **196** to **197**, we tried other conditions including Et_3N/TsCl, which was sluggish and required excess TsCl to proceed to completion, which complicated purification. Employing MsCl in combination with Et_3N led to significant amounts of unidentified byproducts. Since DBU/MsCl gave the best result, we decided to carry on with those conditions for the time being.

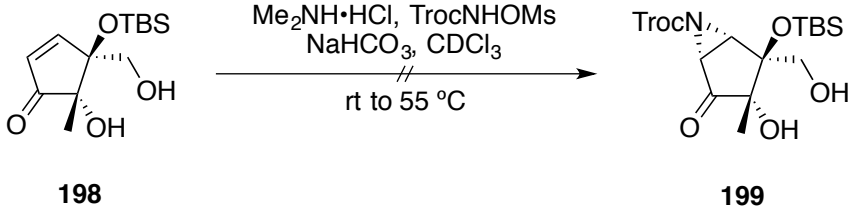
5.4 Desilylation and Aziridination

In order to ensure good diastereoselectivity for the aziridination reaction and to facilitate further steps in the synthesis, removal of the primary TBS protecting group is required. HF•py,[13] 10-CSA,[14] PPTS,[15] TsOH•H_2O,[16] $NaIO_4$,[17] and $CeCl_3$•$7H_2O/I_2$[18] all failed to deliver the desired product. NH_4F[19] effected the transformation, but delivered a complex mixture of products. Fortunately, stirring **197** in AcOH–THF–H_2O (3:1:1) at 80 ºC[20] cleanly afforded **198**. Our initial attempts to purify **196** on silica gel failed, but we found that it was stable to Florisil®. When applied to diol **196** these same conditions were able to dehydrate and selectively remove the primary TBS group in a single step. We attempted aziridination on crude **198** by the conditions found in our model study (see Chapter 4.5), but the reaction failed to proceed. We realized that we would need to consider alternative conditions for aziridination of **198**.



Scheme 5.7 Selective desilylation and attempted aziridination conditions.

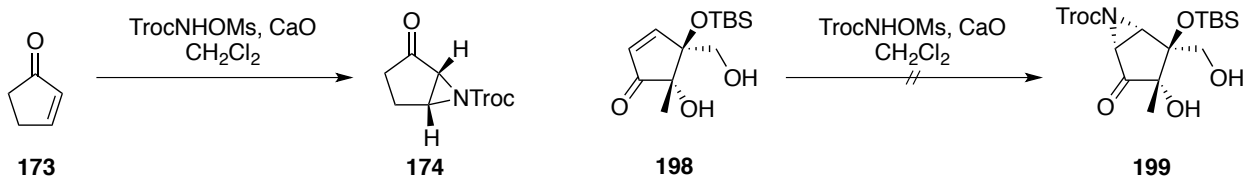
We posited that increased steric demand of **198** could prevent aziridination by (1) blocking iminium ion formation or (2) blocking Michael-addition. Using a smaller ammonium salt should allow the iminium ion formation. Increased reaction temperature should allow the Michael-addition to occur as well, so long as the carbamate did not decompose in the process. These conditions were run on the model substrate first to ensure that they were viable for the transformation. We found that Me_2NH•HCl was a suitable salt for the transformation. We then set up the reaction with **198** and ran it from rt up to 55 ºC in 10 degreee increments and monitored the reaction by NMR (Scheme 5.8). This reaction has not afforded any aziridine.



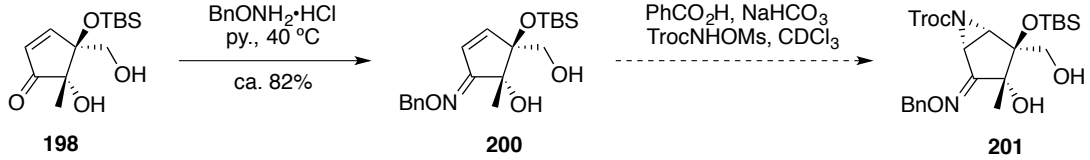
Scheme 5.8 Aziridination with Me_2NH•HCl.

As we searched in the literature, we found that nitrenes have successfully been used for aziridination of enones.[21] While aziridination was successful on the model compound it was not effective when the same conditions were applied to **198**. We then found that Lebel and colleagues employed copper(II) catalysts for toxyloxycarbamates tethered to allylic alcohols.[22] We converted the ketone to oxime **200** by heating enone **198** in pyridine with $BnONH_2$•HCl

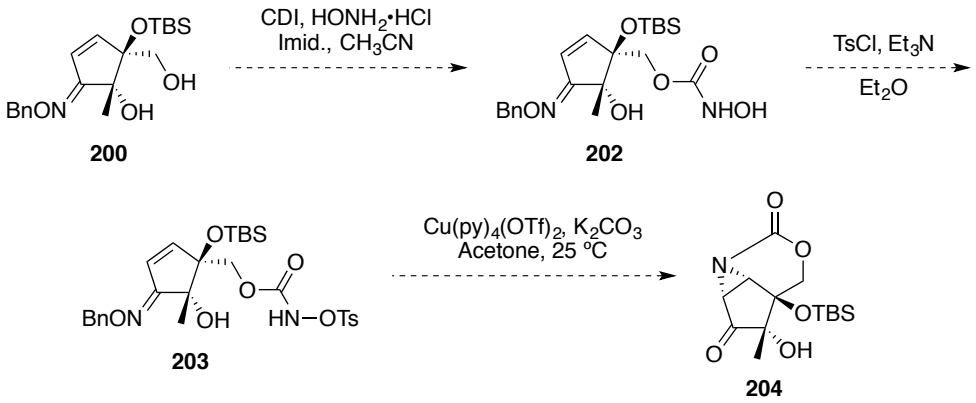
(Scheme 5.10). At this stage we have two possible pathways to pursue. We can attempt to protonate the oxime to allow it to undergo an AZA-MIRC reaction (see Scheme 5.10), or we can pursue Lebel's intramolecular aziridination conditions (see Scheme 5.11).



Scheme 5.9 Nitrene-mediated aziridination of model substrate and attempted aziridination of **198**.



Scheme 5.10 Attempted aziridination of oxime **200**.



Scheme 5.11 Alternative aziridination protocol.

5.5 Conclusion

Our strategy for the cranomycin synthesis has allowed us to construct enone **198**, the core structure of cranomycin. We are currently pursuing studies to form C–N bonds at C-2 and C-3, which should bring us closer to completing the first total synthesis of cranomycin.

5.6 References

(1) Bálinta, J.; Egria, G.; Kolberta, A.; Dianóczkyb, C.; Fogassya, E.; Novákb, L.; Poppec, L. *Tetrahedron: Asymmetry* **1999**, *10*, 4017–4028.

(2) Tang, G.; Tian, H.; Ma, D. *Tetrahedron* **2004**, *60*, 10547–10552.

(3) Matsutani, H.; Ichikawa, S.; Yaruva, J. Kusumoto, T.; Hiyama, T. *J. Am. Chem. Soc.* **1997**, *119*, 4541–4542.

(4) Poon, K. W. C.; Dudley, G. B. *J. Org. Chem.* **2006**, *71*, 3923–2927.

(5) (a) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398. (b) Bartoli, G.; Marcantoni, E.; Marcolini, M.; Sambri, L. *Chem. Rev.* **2010**, *110*, 6104–6143.

(6) M. Hatano, O. Ito, S. Suzuki, K. Ishihara, *J. Org. Chem.*, **2010**, *75*, 5008-5016.

(7) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 497–500.

(8) See supporting information of Loertscher, B. M.; Young, P. R.; Evans, P. R.; Castle, S. L. *Org. Lett.* **2013**, *15*, 1930–1933.

(9) Okano, K.; Okuyama, K.-i.; Fukuyama, T.; Tokuyama, H. *Synlett* **2008**, 1977–1980.

(10) Smith, A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Boldi, A. M.; Murase, N.; Moser, W. H.; Brook, C. S.; Bennett, C. S.; Nakayama, K.; Sobukawa, M.; Trout, R. E. L. *Tetrahedron* **2009**, *65*, 6470–6488.

(11) (a) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4019–4026. (b) Still, W. C.; Schneider, J. A. *Tetrahedron Lett*. **1980**, *21*, 1035–1038. (c) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729–732. (d) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* **1986**, *108*, 3847–3849. Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**,

110, 2506–2526. (f) Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*; Wiley-VCH: Weinheim, 2009; pp 29–37.

(12) (a) Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Lecomte, F.; DelValle, J. R.; Zhang, J.; Deschênes-Simard, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 3497–3500. (b) Hanessian, S.; Vakiti, R. R.; Dorich, S.; Banerjee, S.; Deschênes-Simard, B. *J. Org. Chem.* **2012**, *77*, 9458–9472.

(13) Gao, D.; O'Doherty, G. A. *Org. Lett.* **2010**, *12*, 4752–3755.

(14) Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *J. Am. Chem. Soc.* **2005**, *127*, 848–849.

(15) Ghosh, A. K.; Gong, K. *Org. Lett.* **2007**, *9*, 1437–1440.

(16) Reddy, C. R.; Dharmapuri, G.; Rao, N. N. *Org. Lett.* **2009**, *11*, 5730–5733.

(17) Li, J.; Menche, D. *Synthesis* **2009**, 1904–1908.

(18) Bartoli, G.; Bosco, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Synlett* **1998**, 209–211

(19) Ohyoshi, T.; Miyazawa, Y.; Aoki, K.; Ohmura, S.; Asuma, Y.; Hayakawa, I.; Kigoshi, H. **2011**, *13*, 2160–2163.

(20) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.

(21) (a) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Synthesis* **2001,** 1975–1978. (b) Fioravanti, S.; Mascia, M. G.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Eur. J. Org. Chem.* **2002,** 4071–4074. (c) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *J. Org. Chem.* **2002,** *67,* 4972–4974. (d Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Eur. J. Org. Chem.* **2003,** 4549–4552. (e) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Synlett* **2004,** 1083–1085.

(22) Lebel, H.; Lectard, S.; Parmentier, M. *Org. Lett*. **2007**, *9*, 4797–4800.

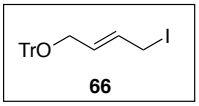
(23) Qin, L.; Zhou, Z.; Wei, J.; Yan, T.; Wen, H. *Synth. Commun.* **2010**, *40*, 642–646.

Chapter 6. Experimental Section

6.1 General Experimental Details.

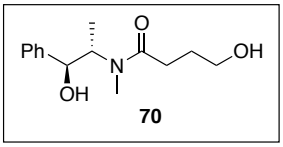
Dichloromethane, dimethylformamide, dimethylsulfoxide, pyridine, tetrahydrofuran, benzene, toluene, and triethylamine were dried by passage through a solvent drying system containing cylinders of activated alumina.[1] Other solvents and reagents were purchased from commercial vendors and used without purification. Flash chromatography was carried out using 60–230 mesh silica gel. ^{1}H NMR spectra were acquired on a 500 MHz spectrometer with chloroform (7.27 ppm) as internal reference. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), br s (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz). ^{13}C NMR spectra were acquired on a spectrometer operating at 125 MHz with chloroform (77.23 ppm) as internal reference. Infrared spectra were obtained on an FT-IR spectrometer. Mass spectral data were obtained using ESI techniques.

6.2 Experimental procedures and spectral data.



(*E*)-(((4-iodobut-2-en-1-yl)oxy)methanetriyl)tribenzene (66). Triethylamine (5.40 mL, 3.94 g, 39.0 mmol) and methanesulfonyl chloride (1.50 mL, 2.22 g, 19.4 mmol) were added successively to a solution of alcohol **67**[2] (4.2904 g, 13.9847 mmol) in anhydrous THF (100 mL) at 0 ºC under Ar. The resultant mixture was warmed to rt and stirred for 4 h. The reaction was quenched with H_2O (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. **NOTE:** *The procedure below was performed in the dark as the product is light sensitive.* The

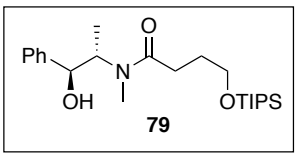
crude mesylate was dissolved in acetone (100 mL) and treated with NaI (5.7464 g, 38.337 mmol). The resultant mixture was refluxed under Ar for 18 h **in the dark**. The reaction was quenched by the addition of H_2O (50 mL), and the volatiles were removed *in vacuo*. The remaining aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (500 mL of SiO_2, 0–2% EtOAc in hexanes gradient elution) afforded iodide **66** (4.0037 g, 9.0927 mmol, 70%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46–7.42 (m, 6H), 7.31 (t, *J* = 7.6 Hz, 6H), 7.26–7.23 (m, 3H), 6.12–6.05 (m, 1H), 5.80 (dt, *J* = 15.2, 4.9 Hz, 1H), 3.91 (d, *J* = 7.8 Hz, 2H), 3.62 (d, *J* = 4.4 Hz, 2H); HRMS (ESI) *m/z* 441.0732 (MH^+, $C_{23}H_{21}OIH^+$ requires 441.0710).



70

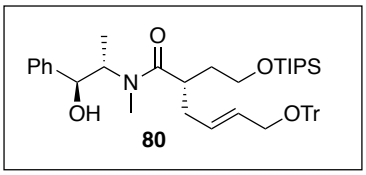
4-Hydroxy-N-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N-methylbutanamide (70). A solution of n-BuLi (1.6 M in hexane, 2.10 mL, 3.36 mmol) was added to an ice-cooled suspension of LiCl (810.7 mg, 19.12 mmol) and (1S,2S)-(+)-pseudoephedrine (1.0534 g, 6.3754 mmol) in anhydrous THF (40 mL), and the suspension was stirred at 0 °C under Ar for 30 min. Then, a solution of methyl 4-hydroxybutanoate[3] (**69**, 1.5062 g, 12.750 mmol) in anhydrous THF (8 mL) was added to the mixture, and it was warmed to rt and stirred under Ar for 3 h. The reaction was quenched by the addition of 0.5 N NaOH (20 mL), and the volatiles were removed *in vacuo*. The residue was extracted with CHCl3–iPrOH 3:1 (4 × 25 mL), and the combined organic layers were washed with brine (100 mL), dried (Na2SO4), and concentrated *in vacuo*. Flash chromatography (200 mL of SiO2, 3–10% MeOH in CH2Cl2 gradient elution) afforded **70** (1.5416 g, 6.1338 mmol, 96%) as a brown oil: ^{1}H NMR (CDCl3, 500 MHz, mixture of rotamers, data for major rotamer) δ 7.41–7.28 (m, 5H), 4.59 (dd, J = 13.8, 7.8 Hz, 1H), 4.54 (br s, 1H), 3.74– 3.66 (m, 3H), 2.88 (s, 3H), 2.60 (br s, 1H), 2.55–2.41 (m, 2H),

1.93–1.88 (m, 2H), 1.09 (d, J =6.7 Hz, 3H); ^{13}C NMR (CDCl3, 125 MHz, mixture of rotamers, data for major rotamer) δ173.8, 142.2, 127.5 (2C), 126.7, 126.1 (2C), 75.0, 61.9, 57.7, 29.7, 27.8, 26.4, 13.6; IR (film) ν_{max} 3376, 2937, 1614, 1482, 1453, 1407, 1049 cm^{-1}; HRMS (ESI) m/z 274.14082 (MNa+, $C_{14}H_{21}NO_3Na$+ requires 274.14136).



79

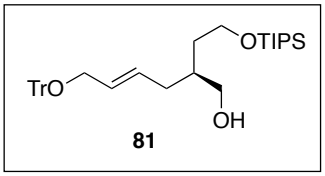
***N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-4-(triisopropylsilyloxy) butanamide (79).** A solution of **70** (294.5 mg, 1.172 mmol) in anhydrous DMF (1.6 mL) at rt under Ar was treated with imidazole (199.4 mg, 2.929 mmol) and TIPS-Cl (390 μL, 351 mg, 1.82 mmol). The resultant mixture was stirred at rt for 24 h, and the reaction was quenched by the addition of brine (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (50 mL of SiO_2, 5% MeOH in CH_2Cl_2 elution) afforded **79** (477.7 mg, 1.172 mmol, quant.) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz, mixture of rotamers) δ 7.37–7.29 (m, 5H), 4.59–4.54 (m, 2H), 4.50 (br s, 1H), 3.75–3.69 (m, 3H), 2.93 (s, 3H), 2.36 (m, 2H), 1.86–1.73 (m, 4H), 1.06–0.96 (m, 24H); ^{13}C NMR ($CDCl_3$, 125 MHz, mixture of rotamers) δ 175.3, 142.6, 128.3 (2C), 127.6, 126.5 (2C), 76.4, 62.4, 58.3, 30.6, 28.4, 26.8, 18.0 (6C), 14.4, 12.0 (3C); IR (film) ν_{max} 3388, 2942, 2865, 1623, 1463, 1405, 1105, 1067 cm^{-1}; HRMS (ESI) *m/z* 430.27546 (MNa^+, $C_{23}H_{41}NO_3SiNa^+$ requires 430.27479).



80

(*S*,*E*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*-methyl-2-(2-(triisopropylsilyloxy)ethyl)-6-(trityloxy)hex-4-enamide (80). A solution of *n*-BuLi (1.6 M in hexane, 1.50 mL, 2.41 mmol) was added to a suspension of LiCl (flame-dried, 294.9 mg,

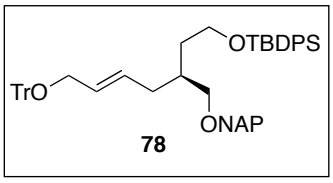
6.9558 mmol) and *i*-Pr_2NH (370 μL, 263.9 g, 2.6084 mmol) in anhydrous THF (2.8 mL) at –78 °C under Ar. The resulting suspension was stirred at –78 °C under Ar for 10 minutes, then warmed to 0 °C, stirred for 5 min, cooled to –78 °C, and treated with an ice-cooled solution of **79** (472.6 mg, 1.1593 mmol) in anhydrous THF (1.4 mL). The mixture was stirred at –78 °C under Ar for 1 h, at 0 °C for 15 min, and at rt for 5 min. It was then cooled to 0 °C and treated with allylic iodide **66** (578.9 mg, 1.3147 mmol). The resultant mixture was stirred at 0 °C under Ar for 2.5 h. The reaction was quenched by the addition of sat aq NH_4Cl (18 mL) and H_2O (18 mL), and the mixture was extracted with EtOAc (3 × 40 mL). Flash chromatography (SiO_2, 1% MeOH in CH_2Cl_2 elution) afforded **80** (609.1 mg, 0.8459 mmol, 73%) as a white solid: ^1H NMR ($CDCl_3$, 500 MHz, mixture of rotamers) δ 7.45–7.41 (m, 3H), 7.38–7.20 (m, 17H), 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, 21H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.0, 144.5 (3C), 142.9, 131.1, 129.1 (2C), 128.9 (2C), 128.6, 128.5 (6C), 128.0 (6C), 127.7, 127.2 (3C), 87.0, 76.4, 64.9, 61.1, 60.8, 58.1, 38.6, 36.1, 35.7, 18.4 (6C), 14.9, 12.3 (3C); IR (film) ν_{max} 3388, 2942, 2865, 1623, 1463, 1405, 1366, 1105 cm^{-1}; HRMS (ESI) *m/z* 742.42604 (MNa^+, $C_{46}H_{61}NO_4SiNa^+$ requires 742.42621).



81

(*S*,*E*)-2-(2-(Triisopropylsilyloxy)ethyl)-6-(trityloxy)hex-4-en-1-ol (81). A flame-dried round bottom flask containing anhydrous THF (200 mL) at –78 °C under Ar was treated with *i*-Pr_2NH (10.3 mL, 7.44 g, 72.97 mmol) followed by *n*-BuLi (1.6 M in hexanes, 42.0 mL, 67.2 mmol). The resultant mixture was stirred at –78 °C for 10 min, at 0 °C for 5 min,

and then cooled to –78 °C. Borane–ammonia complex (90%, 2.38 g, 69.4 mmol) was added to the mixture in one portion, and it was stirred at 0 °C for 20 min, then at rt for 20 min. The mixture was then cooled to 0 °C and treated dropwise with a solution of **80** (12.5 g, 17.4 mmol) in anhydrous THF (127 mL). The resulting mixture was stirred at rt under Ar for 50 min, then cooled to 0 °C and treated with sat aq. 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 **81** (8.83 g, 15.8 mmol, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55 (d, *J* = 7.0 Hz, 6H), 7.36 (t, *J* = 7.5 Hz, 6H), 7.28 (t, *J* = 7.0 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 (3C), 130.8, 129.0 (7C), 128.1 (6C), 127.2 (3C), 87.1, 66.2, 65.2, 62.5, 39.9, 35.6, 35.3, 18.3 (6C), 12.2 (3C); IR (film) ν_{max} 3415, 2941, 2865, 1490, 1448, 1381, 1098, 1055 cm^{-1}; HRMS (ESI) *m/z* 576.38523 ($M(NH_4)^+$, $C_{36}H_{50}O_3SiNH_4^+$ requires 576.38675).



78

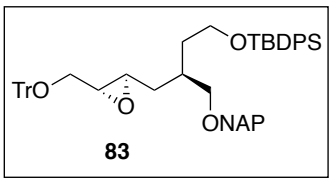
(*S*,*E*)-*tert*-Butyl((3-((naphthalen-2-ylmethoxy)methyl)-7-(trityloxy)hept-5-en-1-yl)oxy)diphenylsilane (78). A solution of **81** (500 mg, 0.895 mmol) in anhydrous DMF–THF 1:1 (20 mL) at 0 °C under Ar was treated with NaH (60% dispersion in mineral oil, 72.0 mg, 1.80 mmol) followed by 2-(bromomethyl)naphthalene (297 mg, 1.34 mmol). The resultant mixture was stirred at 0 °C under Ar for 12 h, then treated with sat aq NH_4Cl (6 mL) and extracted with EtOAc (3 × 10 mL). 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 the triether (557 mg, 0.797 mmol, 89%) 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, 1.80 mL, 1.80 mmol). The resultant mixture was stirred at rt under Ar for 8 h. then treated with sat aq NH_4Cl (4 mL) and extracted with EtOAc (3 × 8 mL). 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 **82** (411 mg, 0.757 mmol, 95%) as a colorless oil.

A solution of **82** (411 mg, 0.757 mmol) in anhydrous CH_2Cl_2 (6 mL) at 0 °C under Ar was treated with Et_3N (150 μL, 109 mg, 1.08 mmol), DMAP (22.0 mg, 0.180 mmol), and TBDPS-Cl (260 μL, 275 mg, 1.00 mmol). The resultant mixture was stirred at rt under Ar for 24 h. The reaction was quenched by the addition of sat aq NH_4Cl (3 mL), and the layers were separated. 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 **78** (411.8 mg, 0.527 mmol, 70% 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 = 6.6, 1.5 Hz, 2H), 3.54 (d, J = 5.0 Hz, 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, 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 cm^{-1}; HRMS (ESI) *m/z*

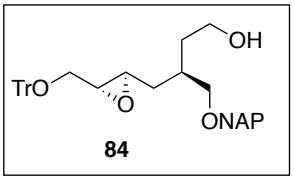
798.43376 ($M(NH_4)^+$, $C_{54}H_{56}O_3SiNH_4^+$ requires 798.43370). **79** was obtained in 94% *ee* as analysed by HPLC (Chiralcel OD-H, 99.2:0.8 hexane:*i*-PrOH 1 mL/min; t_R = 6.7 min (major), 7.9 min (minor)).



83

***tert*-Butyl((*R*)-4-(naphthalen-2-ylmethoxy)-3-(((2*R*,3*R*)-3-(trityloxymethyl)oxiran-2-yl)methyl)butoxy)diphenylsilane (83).** A solution of alkene **78** (128.6 mg, 0.1646 mmol) in dimethoxymethane/CH_3CN (2:1, 1.86 mL) was treated sequentially with a K_2CO_3–CH_3COOH buffer solution (1.12 mL), Bu_4NHSO_4 (1.5 mg, 0.0044 mmol), and ketone **76** (52.0 mg, 0.201 mmol). A solution of Oxone® (161.2 mg, 0.2622 mmol) in 4×10^{-4} M aq Na_2EDTA (0.62 mL) and a 1.47 M aq KOH solution (0.62 mL) were added simultaneously and dropwise to this mixture at the same rate. The resulting suspension was stirred at rt for 5 hr, and an additional quantity of ketone **75** (52.0 mg, 0.201 mmol) was added. Then, a solution of oxone® (161.2 g, 0.2622 mmol) in 4×10^{-4} M aq Na_2EDTA (0.62 mL) and a 1.47 M aq KOH solution (0.62 mL) were once again added simultaneously and dropwise to this mixture at the same rate. The resulting suspension was stirred at rt for 4 h and then extracted with EtOAc (3 × 5 mL). 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 **83** (115.0 mg, 0.144 mmol, 72%) as a colorless oil: ^{1}H 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* = 10.0, 3.5 Hz, 1H), 3.09 (dd, *J* = 11.0, 6.0 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, 125.75, 125.67, 86.7, 73.10, 73.08, 64.7, 61.8, 57.2, 55.0, 34.2, 34.1, 33.8, 26.9 (3C), 19.2; IR (film) ν_{max} 2928, 1448, 1427, 1110 cm^{-1}; HRMS (ESI) *m/z* 814.43165 ($M(NH_4)^+$, $C_{54}H_{56}O_4SiNH_4^+$ requires 814.42861).

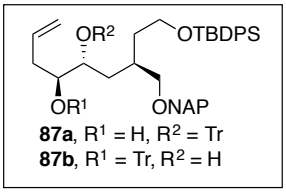


84

(*R*)-4-(Naphthalen-2-ylmethoxy)-3-(((2*R*,3*R*)-3-(trityloxymethyl)oxiran-2-yl)methyl)butan-1-ol (84). A solution of Oxone® (260.8 mg, 0.4242 mmol) in 4×10^{-4} M aq Na_2EDTA (1.5 mL) and a solution of K_2CO_3 (246.4 mg, 1.7829 mmol) in H_2O (1.5 mL) were added simultaneously and dropwise by syringe pump over 6 h to a suspension of alcohol **82** (166.8 mg, 0.3073 mmol), ketone **75** (159.1 mg, 0.6160 mmol), and Bu_4NHSO_4 (2.3 mg, 0.0068 mmol) in dimethoxymethane–CH_3CN (2:1, 3.1 mL) and K_2CO_3–AcOH buffer[3] (2.1 mL) at rt in an open flask. The resultant mixture was stirred at 0 ºC for an additional 2 h then was diluted with H_2O (20 mL) and extracted with 5% MeOH in CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (40 mL of SiO_2, 20% EtOAc in hexanes elution) afforded epoxide **84** (121.6 mg, 0.2176 mmol, 71%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.84–7.79 (m, 4H), 7.48–7.42 (m, 8H), 7.32–7.20 (m, 10H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 3.74–3.64 (m, 2H), 3.58 (dd, *J* = 9.5, 5.0 Hz, 1H), 3.46 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.22 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.16 (dd, *J* = 10.5, 5.5 Hz, 1H), 2.91–2.88 (m, 1H), 2.85 (dt, *J* = 5.5, 2.5 Hz, 1H), 2.38 (br s, 1H), 2.09–2.02 (m, 1H), 1.79–1.58 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.8 (3C), 135.3, 133.2, 133.0, 128.6 (6C), 128.3, 127.9, 127.8 (6C),

127.7, 127.1 (3C), 126.6, 126.1, 125.9, 125.7, 86.8, 73.8, 73.5, 64.5, 60.9, 57.1, 55.0, 35.7, 34.7, 24.3; HRMS (ESI) *m/z* 559.2822 (MH^+, $C_{38}H_{38}O_4H^+$ requires 559.2843).

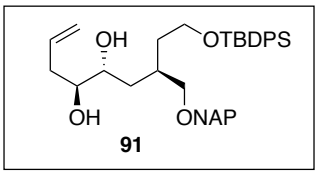
***tert*-Butyl((*R*)-4-(naphthalen-2-ylmethoxy)-3-(((2*R*,3*R*)-3-(trityloxymethyl)oxiran-2-yl)methyl)butoxy)diphenylsilane (83, prepared from 84).** Et_3N (210 μL, 152 mg, 1.51 mmol), DMAP (25.8 mg, 0.211 mmol), and TBDPS-Cl (360 μL, 381 mg, 1.38 mmol) were added successively to a solution of epoxy alcohol **84** (589.4 mg, 1.0549 mmol) in anhydrous CH_2Cl_2 (10.5 mL) at 0 ºC under N_2. The resultant mixture was stirred at rt for 18 h. The reaction was quenched by the addition of H_2O (20 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (100 mL of SiO_2, 1–2% EtOAc in hexanes gradient elution) afforded epoxide **83** (840.9 mg, 1.0549 mmol, quant.) as a colorless oil. Spectral data were identical to those reported above in the preparation of **83** from **78**.



87a, R^1 = H, R^2 = Tr
87b, R^1 = Tr, R^2 = H

(4S,5R,7R)-9-(tert-Butyldiphenylsilyloxy)-7-((naphthalen-2-ylmethoxy)methyl)-5- (trityloxy)non-1-en-4-ol (87a or 87b). A mixture of CuBr•Me_2S (23.2 mg, 0.113 mmol) and Me_2S (51 μL) in anhydrous Et_2O (0.51 mL) at –15 °C under Ar was treated with vinylmagnesium bromide (1.0 M in THF, 0.34 mL, 0.34 mmol). The resultant mixture was stirred at –15 °C for 30 min and at 0 °C for 30 min. A solution of epoxide **83** (45.0 mg, 0.0565 mmol) in anhydrous Et_2O (200 mL) was added dropwise to the mixture. The resultant mixture was warmed to rt and stirred under Ar 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

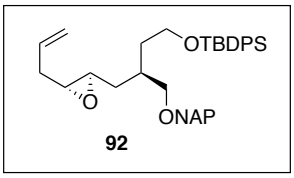
vacuo. Flash chromatography (SiO_2, 5% EtOAc in hexanes elution) afforded **87** (37.8 mg, 0.0458 mmol, 81%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.84–7.65 (m, 8H), 7.50–7.43 (m, 9H), 7.41–7.23 (m, 15H), 5.77 (ddd, *J* = 17.4 Hz, 10.7 Hz, 8.8 Hz, 1H), 5.31 (ddd, *J* = 17.4 Hz, 5.4 Hz, 1.5 Hz, 1H), 5.18 (ddd, *J* = 10.7 Hz, 6.3 Hz, 1.5 Hz, 1H), 4.58 (s, 2H), 3.73–3.67 (m, 2H), 3.38– 3.30 (m, 2H), 3.10 (dd, *J* = 8.5 Hz, 1.5 Hz, 1H), 3.04 (t, *J* = 8.1 Hz, 1H), 2.36 (d, *J* = 5.9 Hz, 1H), 1.75–1.73 (m, 1H), 1.62–1.52 (m, 3H), 1.44–1.38 (m, 1H), 1.37–1.27 (m, 2H), 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 cm^{-1}; HRMS (ESI) m/z 842.45747 ($M(NH_4)^+$, $C_{56}H_{60}O_4SiNH_4^+$ requires 842.45991).



91

(4S,5R,7R)-9-(tert-Butyldiphenylsilyloxy)-7-((naphthalen-2-ylmethoxy)methyl)non-1- ene-4,5-diol (91). A solution of BCl_3 (1.0 M in CH_2Cl_2, 65 μL, 0.065 mmol) was added dropwise to a solution of alcohol **87a** or **87b** (54.9 mg, 0.0665 mmol) in anhydrous CH_2Cl_2 (2.0 mL) at –35 ºC under Ar. The resultant mixture was stirred at –35 °C for 30 min, and the reaction was quenched by the addition of MeOH (2.0 mL). The suspension was poured into sat aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (10 mL of SiO_2, 20% EtOAc in hexanes elution) afforded diol **91** (32.1 mg, 0.0551 mmol, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86–7.75 (m, 4H), 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* = 17.1

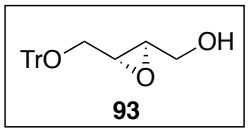
Hz, 10.7 Hz, 1H), 5.33 (dd, *J* = 17.1 Hz, 5.1 Hz, 1H), 5.24 (dd, *J* = 10.7 Hz, 1.1 Hz, 1H), 4.61 (s, 2H), 3.74–3.70 (m, 2H), 3.45–3.40 (m, 3H), 3.35 (dd, *J* = 9.3 Hz, 6.3 Hz, 1H), 2.30 (d, *J* = 19.5 Hz, 1H), 1.87–1.85 (m, 2H), 1.64–1.54 (m, 3H), 1.47– 1.42 (m, 3H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.6, 136.0, 135.6 (4C), 134.0 (2C), 133.3, 133.0, 129.6 (2C), 128.1, 127.9, 127.7, 127.6 (4C), 126.3, 126.1, 125.83, 125.78, 115.3, 76.0, 73.1, 68.9, 68.8, 62.0, 35.4, 34.5, 34.0, 26.9 (3C), 25.0, 19.2; IR (film) ν_{max} 3418, 2930, 2857,1471, 1427, 1389, 1110 cm^{-1}; HRMS (ESI) m/z 605.30492 (MNa+, $C_{37}H_{46}O_4SiNa^+$ requires 605.30576).



92

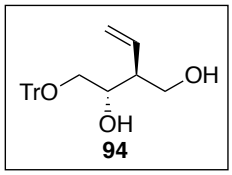
((R)-4-((2R,3R)-3-Allyloxiran-2-yl)-3-((naphthalen-2-ylmethoxy)methyl)butoxy)(tert- butyl)diphenylsilane (92). A solution of **91** (13.5 mg, 0.0232 mmol) in anhydrous THF (1.0 mL) at 0 °C under Ar was treated with NaH (60% dispersion in mineral oil, 1.9 mg, 0.0475 mmol). The resultant mixture was stirred at rt for 30 min, then cooled to 0 °C and treated with 2,4,6-triisopropylbenzenesulfonyl imidazole (8.5 mg, 0.0254 mmol). The mixture was stirred at rt for 2 h, treated with sat aq NH_4Cl (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO2, 6% EtOAc in hexanes elution) afforded **92** (11.3 mg, 0.0200 mmol, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86–7.75 (m, 4H), 7.68–7.66 (m, 4H), 7.49 (t, *J* = 4.5 Hz, 2H), 7.45–7.43 (m, 3H), 7.38 (t, *J* = 7.0 Hz, 4H), 5.77–5.71 (ddd, *J* = 17.5 Hz, 10.8 Hz, 3.3 Hz, 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, 2H), 3.44–3.35 (m, 2H), 2.77 (dd, *J* = 7.3 Hz, 5.3 Hz, 1H), 2.66–2.65 (m, 1H), 1.89–1.87 (m, 1H), 1.75– 1.52 (m, 4H), 1.51–1.44 (m, 1H), 1.30–1.26 (m, 1H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.54, 137.47, 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, 73.03, 72.96, 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 cm^{-1}; HRMS (ESI) m/z 582.3411 $(M(NH_4)^+$, $C_{37}H_{44}O_3SiNH_4^+$ requires 582.3398).



93

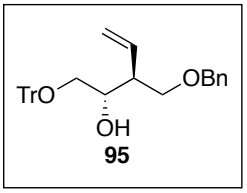
((2R,3R)-3-((trityloxy)methyl)oxiran-2-yl)methanol (93). A solution of Oxone® (1.8690 g, 3.0401 mmol) in 4×10^{-4} M Na_2EDTA (11.2 mL) and a solution of K_2CO_3 (1.7659 g, 12.7552 mmol) in H_2O (11.2 mL) were added simultaneously and dropwise by syringe pump over 4.5 h to a solution of alcohol **67** (679.4 mg, 2.0562 mmol), ketone **75** (170.7 mg, 0.6609 mmol), Bu_4NHSO_4 (13.5 mg, 0.0397 mmol) in DMM–CH_3CN (2:1, 22.3 mL) and K_2CO_3–AcOH buffer[3] (14.9 mL). The resultant mixture was stirred for an additional 30 min then H_2O (20 mL) and EtOAc (20 mL) were added. The aqueous layer was extracted with EtOAc (3 × 40 mL). Combined extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (SiO_2, 5–20% EtOAc in hexanes gradient elution) afforded of epoxy alcohol **93** (683.4 mg, 1.9727 mmol, 96%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.47–7.43 (m, 6H), 7.32–7.28 (m, 6H), 7.27–7.22 (m, 3H), 3.97–3.91 (m, 1H), 3.67–3.61 (m, 1H), 3.38 (dd, J = 10.5 Hz, 2.5 Hz, 1H), 3.23–3.16 (m, 2H), 3.13–3.11 (m, 1H), 1.49–1.46 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.7 (3C), 128.6 (6C), 127.9 (6C), 127.1 (3C), 87.0, 63.6, 61.2, 55.8, 54.4; HRMS (ESI) m/z 364.1912 $(M(NH_4)^+$, $C_{23}H_{22}O_3NH_4^+$ requires 364.1907).



94

(2S,3S)-4-(trityloxy)-2-vinylbutane-1,3-diol (94). A solution of vinylmagnesium bromide (0.8 M in THF, 9.5 mL, 7.600 mmol) was added to a suspension of

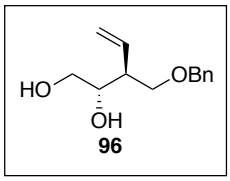
CuI (25.8 mg, 0.1430 mmol) in anhydrous Et_2O (80 mL) at –10 ºC under Ar and the resultant mixture was immediately cooled to –25 ºC. Epoxide **93** (880.4 mg, 2.5414 mmol) was added as a solution in anhydrous Et_2O (15 mL) via cannula. The resultant mixture was stirred at –25 ºC for 18 h then was quenched with basified NH_4Cl (pH 8.5, 20 mL) and extracted with EtOAc (3 × 100 mL). Combined extracts were washed with brine (3 × 50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (150 mL of SiO_2, 10–30% EtOAc in hexanes gradient elution) afforded diol **94** (894.1 mg, 2.3876 mmol, 94%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 7.43–7.40 (m, 6H), 7.33–7.28 (m, 6H), 7.27–7.23 (m, 3H), 5.46 (ddd, *J* = 17.3 Hz, 10.3 Hz, 8.6 Hz, 1H), 5.07–5.02 (m, 2H), 3.82–3.74 (m, 2H), 3.65–3.60 (m, 1H), 3.30 (dd, *J* = 9.7 Hz, 3.2 Hz, 1H), 3.13 (dd, *J* = 9.7 Hz, 6.9 Hz, 1H), 2.71 (d, *J* = 4.2 Hz, 1H), 2.59 (dd, *J* = 6.9 Hz, 5.3 Hz, 1H), 2.43–2.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.7 (3C), 135.1, 128.6 (6C), 127.9 (6C), 127.2 (3C), 118.4, 87.0, 73.5, 66.0, 65.2, 48.7; HRMS (ESI) m/z 392.2223 ($M(NH_4)^+$, $C_{25}H_{26}O_3NH_4^+$ requires 392.2220).



95

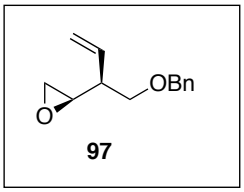
(2S,3S)-3-((benzyloxy)methyl)-1-(trityloxy)pent-4-en-2-ol (95). NaH (60% dispersion in mineral oil, 92.7 mg, 2.3175 mmol) was added to a solution of diol **94** (434.1 mg, 1.1592 mmol) in anhydrous DMF (12 mL) at 0 ºC under Ar. The resultant mixture was cooled to –70 ºC and BnBr (150 μL, 218.1 mg, 1.2629 mmol) was added. The mixture was stirred for 30 min at –70 ºC then was warmed to –15 ºC over 3 h. The reaction was quenched with sat aq NH_4Cl (10 mL) and extracted with Et_2O (3 × 15 mL). Combined extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (75 mL of SiO_2, 2–5% EtOAc in hexanes gradient elution) afforded alcohol **95** (279.7 mg,

0.6020 mmol, 52%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45–7.42 (m, 6H), 7.33–7.21 (m, 14H), 5.66 (ddd, *J* = 17.3 Hz, 10.3 Hz, 8.7 Hz, 1H), 5.05 (d, *J* = 17.3 Hz, 1H), 5.00 (dd, *J* = 10.4 Hz, 1.3 Hz, 1H), 4.44 (s, 2H), 3.87–3.81 (m, 1H), 3.61–3.54 (m, 2H), 3.23 (dd, *J* = 9.6 Hz, 4.0 Hz, 1H), 3.13 (dd, *J* = 9.6 Hz, 6.2 Hz, 1H), 2.96 (d, *J* = 4.9 Hz, 1H), 2.62–2.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.9 (3C), 138.0, 136.2, 128.7 (6C), 128.4, 127.8 (8C), 127.6 (3C), 127.0 (2C), 117.2, 86.6, 73.3, 72.2, 71.5, 65.8, 46.7; HRMS (ESI) m/z 482.2660 ($M(NH_4)^+$, $C_{32}H_{32}O_3NH_4^+$ requires 482.2690).



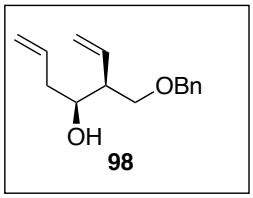
96

(2S,3S)-3-((benzyloxy)methyl)pent-4-ene-1,2-diol (96). Formic acid (3 mL) was added to a solution of alcohol **95** (200.0 mg, 0.4305 mmol) in anhydrous Et_2O (2 mL) at rt. The resultant mixture was stirred for 5 min then washed with saturated aq $NaHCO_3$ (100 mL). The aqueous layer was extracted with Et_2O (3 × 15 mL). Combined extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (20 mL of SiO_2, 20–50% EtOAc in hexanes gradient elution) afforded diol **96** (88.2 mg, 0.3968 mmol, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.29 (m, 5H), 5.70–5.61 (m, 1H), 5.17 (d, *J* = 16.8 Hz, 1H), 5.15 (d, *J* = 10.0 Hz, 1H), 4.55 (s, 2H), 3.82–3.76 (m, 1H), 3.68–3.63 (m, 3H), 3.60 (br s, 1H), 3.53 (dd, *J* = 11.4 Hz, 5.9 Hz, 1H), 2.63–2.53 (m, 1H), 2.29 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.4, 134.9, 128.6 (2C), 128.0, 127.7 (2C), 118.2, 74.2, 73.6, 72.8, 64.9, 46.4; HRMS (ESI) m/z 223.1335 (MH^+, $C_{13}H_{18}O_3H^+$ requires 223.1329).



97

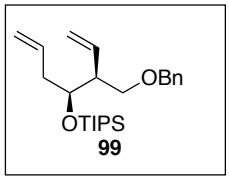
(R)-2-((S)-1-(benzyloxy)but-3-en-2-yl)oxirane (97). NaH (60% dispersion in mineral oil, 49.1 mg, 1.2282 mg) was added to a solution of diol **96** (91.0 mg, 0.4094 mmol) in anhydrous THF (4 mL) at 0 ºC. The resultant suspension was warmed to rt and stirred for 30 min. 2,4,6-triisopropylbenzenesulfonyl imidazole (150.6 mg, 0.4503 mmol) was added neat and the resultant mixture was stirred for 2.5 h at rt. The reaction was quenched with sat aq NH_4Cl (10 mL) and extracted with EtOAc (3 × 15 mL). Combined extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (25 mL of SiO_2, 0 –2% Et_2O in hexanes) afforded epoxide **97** (78.4 mg, 0.3838 mmol, 94%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.27 (m, 5H), 5.83 (ddd, *J* = 17.5 Hz, 10.3 Hz, 7.3 Hz, 1H), 5.19 (d, *J* = 10.8 Hz, 1H), 5.16 (d, *J* = 3.4 Hz, 1H), 4.57 (d, *J* = 12.4 Hz, 1H), 4.54 (d, *J* = 12.4 Hz, 1H), 3.63 (d, *J* = 5.5 Hz, 2H), 3.05–3.02 (m, 1H), 2.78 (t, *J* = 4.4 Hz, 1H), 2.59–2.56 (m, 1H), 2.28–2.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.3, 134.9, 128.4 (2C), 127.6 (3C), 117.4, 73.2, 70.9, 52.5, 46.4, 46.0; HRMS (ESI) m/z 205.1589 (MH^+, $C_{13}H_{16}O_2H^+$ requires 205.1223).



98

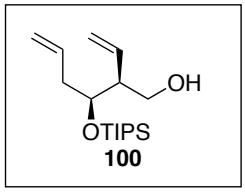
(3S,4S)-3-((benzyloxy)methyl)hepta-1,6-dien-4-ol (98). A solution of vinylmagnesium bromide (0.8 M in THF, 950 μL) was added to a suspension of CuI (21.7 mg, 0.1139 mmol) in anhydrous Et_2O (7.0 mL) at –10 ºC under Ar. The resultant mixture was immediately cooled to –25 ºC and a solution of epoxide **97** (77.5 mg, 0.3794 mmol) in anhydrous Et_2O (1.5 mL) was added. The resultant mixture was stirred at –25 ºC for 1.5 h. The reaction was quenched with basified NH_4Cl solution (pH 8.5 (10 mL) and extracted with EtOAc (3 × 10 mL).

Combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (15 mL of SiO_2, 0–5% EtOAc in hexanes gradient elution) afforded alcohol **98** (71.7 mg, 0.3086 mmol, 81%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39–7.27 (m, 5H), 5.93–5.84 (m, 1H), 5.75–5.66 (m, 1H), 5.21–5.08 (m, 4H), 4.53 (s, 2H), 3.80–3.75 (m, 1H), 3.71–3.59 (m, 2H), 3.17–3.13 (m, 1H), 2.51–2.43 (m, 1H), 2.38–2.32 (m, 1H), 2.19–2.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.7, 136.0, 135.1, 128.5 (2C), 127.8, 127.7 (2C), 117.7, 117.4, 73.5, 73.0, 72.7, 49.1, 39.6; HRMS (ESI) m/z 233.1531 (MH^+, $C_{15}H_{20}O_2H^+$ requires 233.1536).

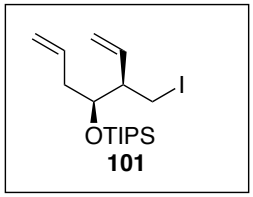


99

(((3S,4S)-3-((benzyloxy)methyl)hepta-1,6-dien-4-yl)oxy)triisopropylsilane (99). To a solution of alcohol **98** (71.0 mg, 0.3056 mmol) in anhydrous CH_2Cl_2 (5 mL) at rt under Ar was added 2,6-lutidine (70 μL, 64.4 mg, 0.6010 mmol) and TIPS-OTf (120 μL, 136.3 mg, 0.4449 mmol). The resultant mixture stirred at rt for 4h. The reaction was quenche with saturated aq NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (20 mL of SiO_2, 0–2% EtOAc in hexanes) afforded diether **99** (118.7 mg, 0.3054 mmol, 100%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.30 (m, 5H), 5.94–5.79 (m, 2H), 5.13–5.00 (m, 4H), 4.43 (d, J = 12.2 Hz, 1H), 4.47 (d, J = 12.2 Hz, 1H), 3.97 (dd, J = 11.2 Hz, 5.1 Hz, 1H) 3.67–3.53 (m, 2H), 2.67–2.60 (m, 1H), 2.37–2.22 (m, 2H), 1.05 (m, 21H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.6, 137.8, 135.1, 128.2 (2C), 127.5 (2C), 127.4, 117.0, 116.4, 73.0, 72.9, 70.1, 48.8, 39.2, 18.20 (6C), 12.83 (3C); HRMS (ESI) m/z 406.3153 ($M(NH_4)^+$, $C_{24}H_{40}O_2NH_4^+$ requires 406.3136).

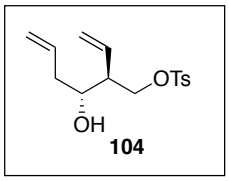


(2S,3S)-3-((triisopropylsilyl)oxy)-2-vinylhex-5-en-1-ol (100). Na metal (36.0 mg, 1.5659 mmol) was added to a 3-neck flask containing liquid NH_3 (*ca.* 20 mL) under Ar at –78 ºC. The solution became dark blue. A solution of diether **99** (86.9 mg, 0.2236 mmol) in anhydrous THF (2.5 mL) was added and the resultant mixture was stirred at –78 ºC for 1 h. The reaction was quenched by addition of MeOH (5 mL) and NH_3 was evaporated under a stream of N_2 as the solution warmed to rt. The resultant mixture was partitioned in a sep funnel with H_2O (15 mL) and extracted with EtOAc (3 × 10 mL). Combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (10 mL of SiO_2, 0–1% EtOAc in hexanes) afforded alcohol **100** (53.0 mg, 0.1775 mmol, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 125 MHz) δ 5.97–5.87 (m, 1H), 5.68–5.59 (m, 1H), 5.15–5.07 (m, 4H), 3.92 (dd, *J* = 10.0 Hz, 4.2 Hz, 1H), 3.85–3.80 (m, 3H), 2.39–2.31 (m, 2H), 2.19–2.12 (m, 1H), 1.09–1.05 (m, 21H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 135.8, 135.3, 117.7, 117.0, 74.0, 67.3, 50.8, 39.8, 17.9 (6C), 11.7 (3C); HRMS (ESI) m/z 299.2378 (MH^+, $C_{17}H_{34}O_2SiH^+$ requires 299.2401).



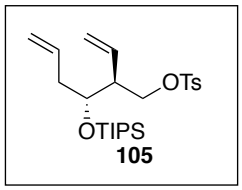
(((3R,4S)-3-(iodomethyl)hepta-1,6-dien-4-yl)oxy)triisopropylsilane (101). Triphenylphosphine (34.1 mg, 0.1300 mmol), imidazole (17.7 mg, 0.2600 mmol) and I_2 (33.0 mg, 0.1300 mmol) were added successively to a solution of alcohol **100** (13.6 mg, 0.0456 mmol) in anhydrous Et_2O–CH_3CN (3:1, 1.0 mL) under Ar at rt and the resultant mixture was stirred for 5 h. The reaction was quenched with saturated aq $Na_2S_2O_3$ (1 mL) and extracted with Et_2O (3 × 10 mL). Combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *n*

vacuo. Flash chromatography (10 mL of SiO_2, 100% hexanes elution) afforded iodide **101** (17.0 mg, 0.0416 mmol, 91%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.84–5.75 (m, 1H), 5.64 (ddd, *J* = 17.2 Hz, 10.3 Hz, 8.4 Hz, 1H), 5.25 (dd, *J* = 10.4 Hz, 1.8 Hz, 1H), 5.19 (ddd, *J* = 17.2 Hz, 1.8 Hz, 0.7 Hz, 1H), 5.14–5.08 (m, 2H), 4.70 (td, *J* = 7.6 Hz, 2.6 Hz, 1H), 3.69–3.61 (m, 2H), 2.80–2.73 (m, 1H), 2.65–2.58 (m, 1H), 1.79–1.73 (m, 1H), 1.08–1.05 (m, 21H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.8, 136.7, 118.8, 117.3, 66.6, 51.0, 43.1, 39.6, 18.0 (6C), 12.0 (3C); HRMS (ESI) m/z 409.1475 (MH^+, $C_{17}H_{33}IO_2SiH^+$ requires 409.1418).

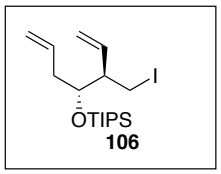


104

(2S,3R)-3-hydroxy-2-vinylhex-5-en-1-yl 4-methylbenzenesulfonate (104). A solution of TsCl (987.8 mg, 5.1812 mmol) in anhydrous CH_2Cl_2 (5.2 mL) was added over 5 h via syringe pump to a solution of diol **103**[4] (614.0 mg, 4.3179 mmol) and anhydrous Et_3N (900 μL, 653.4 mg, 6.4572 mmol) in anhydrous CH_2Cl_2 (22 mL) at 10 ºC under Ar. The resultant mixture was stirred at 10 ºC for an additional 17 h. The reaction was quenched with ice-cold H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 30 mL). Combined extracts were dried (Na_2SO_4) and concentratred *in vacuo*. Flash chromatography (160 mL of SiO_2, 10–15% EtOAc in hexanes) afforded tosylate **104** (923.1 mg, 3.1145 mmol, 72%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 5.82–5.72 (m, 1H), 5.69–5.59 (m, 1H), 5.19–5.09 (m, 4H), 4.25 (dd, *J* = 9.6 Hz, 6.0 Hz, 1H), 4.16 (dd, *J* = 9.6 Hz, 4.0 Hz, 1H), 3.65 (td, *J* = 8.3 Hz, 3.1 Hz, 1H), 2.45 (s, 3H), 2.42–2.32 (m, 2H), 2.10–2.02 (m, 1H), 1.76 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.8, 134.6, 134.1, 132.8, 129.8 (2C), 128.0 (2C), 119.2, 118.9, 70.7, 69.3, 49.2, 39.3, 21.6; HRMS (ESI) m/z 297.1164 (MH^+, $C_{15}H_{20}O_4SH^+$ requires 297.1155).

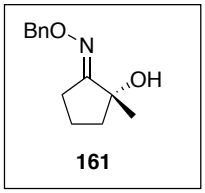


(2S,3R)-3-((triisopropylsilyl)oxy)-2-vinylhex-5-en-1-yl 4-methylbenzenesulfonate (105). To a solution of alcohol **104** (92.2 mg, 0.3111 mmol) in anhydrous CH_2Cl_2 (4.0 mL) under N_2 at rt was successively added 2,6-lutidine (70 μL, 66.7 mg, 0.6221 mmol) and TIPS-OTf (120 μL, 136.3 mg, 0.4449 mmol). The mixture stirred for 5 h then additional 2,6-lutidine (40 μL, 36.8 mg, 0.3434 mmol) and TIPS-OTf (40 μL, 45.5 mg, 0.1483 mmol) were added. After stirring an additional 2 h the reaction was quenched with saturated aq NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). Combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (30 mL of SiO_2, 0–5% EtOAc in hexanes) afforded diene **105** (125.2 mg, 0.2765 mmol, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 5.78–5.69 (m, 1H), 5.65 (ddd, J = 17.4 Hz, 10.3 Hz, 8.4 Hz, 1H), 5.12–4.99 (m, 4H), 4.23 (dd, J = 9.6 Hz, 5.2 Hz, 1H), 4.07 (dd, J = 9.6 Hz, 7.8 Hz, 1H), 3.90 (dd, J = 11.2 Hz, 5.4 Hz, 1H), 2.60–2.54 (m, 1H), 2.45 (s, 3H), 2.27 (t, J = 6.5 Hz, 2H), 1.05 (s, 21H); HRMS (ESI) m/z 470.2786 $(M(NH_4)^+$, $C_{24}H_{40}O_4SSiNH_4^+$ requires 470.2755).



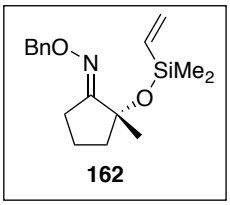
(((3R,4R)-3-(iodomethyl)hepta-1,6-dien-4-yl)oxy)triisopropylsilane (106). NaI (114.0 mg, 0.7606 mmol) was added to a stirring solution of tosylate **105** (125.2 mg, 0.2765 mmol) in anhydrous DMF (2.0 mL) under Ar. The mixture was heated and stirred at 80 ºC for 6 h. The mixture was cooled to rt, diluted with ice-cold H_2 (5 mL) and extracted with hexanes (3 × 10 mL). Combined extracts were washed with saturated aq $Na_2S_2O_3$ (3 × 10 mL), dried (Na_2SO_4),

and concentrated *in vacuo* to obtain iodide **106** (82.1 mg, 0.2010 mmol, 73%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.89–5.80 (m, 1H), 5.72 (ddd, *J* = 17.3 Hz, 10.3 Hz, 8.5 Hz, 1H), 5.18 (dd, *J* = 10.4 Hz, 1.1 Hz, 1H), 5.13–5.05 (m, 3H), 4.00–3.96 (m, 1H), 3.43 (dd, *J* = 9.8 Hz, 4.6 Hz, 1H), (dd, *J* = 9.6 Hz, 4.6 Hz, 1H); 2.53–2.46 (m, 1H), 2.40–2.28 (m, 2H), 1.09 (s, 21H); HRMS (ESI) m/z 409.1479 (MH^+, $C_{17}H_{33}IO_2SiH^+$ requires 409.1418).



161

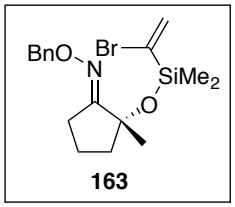
2-hydroxy-2-methylcyclopentan-1-one O-benzyl oxime (161). To a solution of hydroxyketone **160**[5] (46.3 mg, 0.4059 mmol) in anhydrous pyridine (2.5 mL) at rt under Ar was added $BnONH_2$•HCl. The mixture stirred at rt for 1 h, then was diluted with 10% HCl (5 mL) and was extracted with Et_2O (3 × 10 mL). Combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (12 mL of SiO_2, 2–6% EtOAc in hexanes gradient elution) afforded oxime **161** (69.8 mg, 0.3185 mmol, 78%), a yellow oil as a mixture of diastereomers. Data for major isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.34 (m, 5H), 5.11 (d, *J* = 12.2 Hz, 1H), 5.09 (d, *J* = 12.2 Hz, 1H), 2.68–2.59 (m, 1H), 2.48–2.39 (m, 1H), 2.15 (br s, 1H), 2.03–1.84 (m, 2H), 1.79–1.64 (m, 2H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.0, 138.1, 128.5 (2C), 128.2 (2C), 127.9, 77.4, 76.1, 40.6, 26.6, 26.0, 20.5; HRMS (ESI) m/z 220.1367 (MH^+, $C_{13}H_{17}NO_2H^+$ requires 220.1332).



162

2-((dimethyl(vinyl)silyl)oxy)-2-methylcyclopentan-1-one O-benzyl oxime (162). A solution of alcohol **161** (64.7 mg, 0.2953 mmol) in anhydrous CH_2Cl_2 (2.0 mL) at 0 ºC under Ar was treated successively with Et_3N (60 μL, 43.6 mg, 0.4305 mmol) and

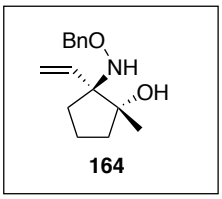
chlorodimethylvinylsilane (50 μL, 44.2 mg, 0.3663 mmol). The resultant mixture was stirred at rt for 4 h. The reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). Combined extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (10 mL of SiO_2, 0–2% EtOAc in hexanes gradient elution) afforded silyl ether **162** (59.6 mg, 0.1964 mmol, 67%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.28 (m, 5H), 6.08 (dd, J = 20.4 Hz, 14.8 Hz, 1H), 5.88 (dd, J = 14.8 Hz, 3.9 Hz, 1H), 5.65 (dd, J = 20.3 Hz, 3.9 Hz, 1H), 5.12 (d, J = 12.0 Hz, 1H), 5.08 (d, J = 12.0 Hz, 1H), 2.53–2.45 (m, 1H), 2.41–2.33 (m, 1H), 1.96–1.78 (m, 2H), 1.68–1.60 (m, 1H), 1.57–1.49 (m, 1H), 1.43 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.2, 139.5, 138.3, 131.5, 128.3 (2C), 128.2 (2C), 127.6, 79.8, 75.9, 42.7, 26.8, 25.0, 20.3, 0.0, –0.1; HRMS (ESI) m/z 321.1964 ($M(NH_4)^+$, $C_{17}H_{25}NO_2SiNH_4^+$ requires 321.1993).



163

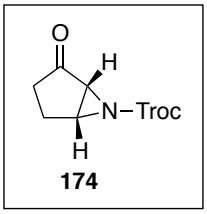
2-(((1-bromovinyl)dimethylsilyl)oxy)-2-methylcyclopentan-1-one O-benzyl oxime (163). A solution of alcohol **161** (129.8 mg, 0.5923 mmol) in anhydrous benzene (3.0 mL) at 0 ºC under Ar was treated successively with Et_3N (100 μL, 72.6 mg, 0.7175 mmol), DMAP (7.2 mg, 0.0592 mmol), and (1-bromovinyl)chlorodimethylsilane solution (*ca*. 43 wt% in benzene, 330 μL, 141.9 mg, 0.7111 mmol). The resultant mixture was allowed to warm to rt as it stirred for 16 h. The resultant mixture was filtered through a silica gel plug and the filter cake was rinsed with hexanes–EtOAc (5:1, 20 mL). The filtrate was washed with brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford **163** (216.4 mg, 0.5923 mmol, 100%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.29 (m, 5H), 6.24 (d, J = 1.6 Hz, 1H), 6.19 (d, J = 1.6 Hz, 1H), 5.11 (d, J = 12.2 Hz, 1H), 5.06 (d, J = 12.2 Hz, 1H), 2.58–

2.50 (m, 1H), 2.43–2.33 (m, 1H), 2.02–1.86 (m, 2H), 1.72–1.63 (m, 1H), 1.62–1.54 (m, 1H), 1.46 (s, 3H), 0.24 (s, 3H), 0.19 (s, 3H); HRMS (ESI) m/z 399.1085 $(M(NH_4)^+$, $C_{17}H_{24}BrNO_2SiNH_4^+$ requires 399.1098).



164

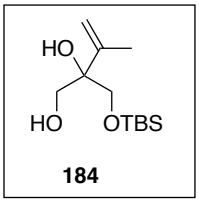
(1R*,2S*)-2-((benzyloxy)amino)-1-methyl-2-vinylcyclopentan-1-ol (164). A solution of vinylsilane **163** (142.1 mg, 0.3889 mmol) in anhydrous benzene (20 mL) was deoxygenated by bubbling N_2 through it for 30 min. The solution was heated to reflux and a deoxygenated solution of AIBN (31.9 mg, 0.1943 mmol) and Bu_3SnH (130 μL, 142.7 mg, 0.4904 mmol) in benzene (5 mL) was added by syringe pump over 10 h. The reaction was refluxed an additional 10 h, at which point TLC confirmed consumption of the starting material. A solution of TBAF was added and reflux continued an additional 4 h. The reaction mixture was filtered through a silica gel plug and the filtrate was concentrated *in vacuo*. Flash chromatography (30 mL of SiO_2, 5–10% EtOAc in hexanes gradient elution) afforded alcohol **164** (75.0 mg, 0.3032 mmol, 78%) contaminated with some tin components. Data for **164**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39–7.28 (m, 5H), 6.05 (dd, J = 17.7 Hz, 11.1 H, 1H), 5.47 (br s, 1H), 5.39 (dd, J = 11.1 H, 1.2 Hz, 1H), 5.35 (dd, J = 17.7 Hz, 1.1 Hz, 1H), 5.10 (br s, 1H) 4.71 (d, J = 11.7 Hz, 1H), 4.67 (d, J = 11.7 Hz, 1H), 2.08–1.59 (m, 6H), 1.43 (s, 3H); HRMS (ESI) *m/z* 265.1930 $(M(NH_4)^+$, $C_{15}H_{21}NO_2NH_4^+$ requires 265.1911).



174

2,2,2-trichloroethyl (1R*,5R*)-2-oxo-6-azabicyclo[3.1.0]hexane-6-carboxylate (174). 2-Cyclopentene-1-one (**173**, 25 μL, 24.5 mg, 0.2984 mmol) was added to a

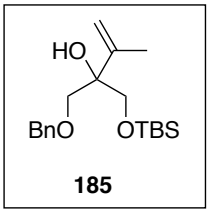
solution of pyrroldine (5 μL, 4.26 mg, 0.0600 mmol) and benzoic acid (11.1 mg, 0.0910 mmol) in $CDCl_3$ (1.0 mL) at rt under air. The resultant mixture became pink in color as it stirred for 30 min, then TrocNHOMs (86.1 mg, 0.3005 mmol) was added. After stirring an additional 10 min, $NaHCO_3$ (51.6 mg, 0.6142 mmol) was added and the resultant mixture was stirred for 36 h. The mixture was filtered through a medium glass frit and concentrated *in vacuo*. Flash chromatography (10 mL of SiO_2, 20% EtOAc in hexanes elution) afforded aziridine **174** (59.7 mg, 0.2191 mmol, 73%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.77 (d, J = 12.0 Hz, 1H), 4.70 (d, J = 12.0 Hz, 1H), 3.53 (t, J = 2.9 Hz, 1H), 3.15 (d, J = 3.2 Hz, 1H), 2.55–2.47 (m, 1H), 2.22–1.99 (m, 3H); HRMS (ESI) *m/z* 271.9614 (MH^+, $C_8H_8Cl_3NO_3H^+$ requires 271.9643).



184

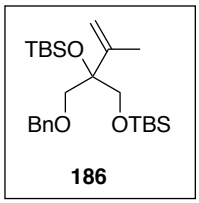
2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-methylbut-3-ene-1,2-diol (184). A solution of isopropenylmagnesium bromide (0.57 M in THF, 4.3 mL, 2.5 mmol) was added to a solution of hydroxyketone **182** (145.7 mg, 0.7130 mmol) in anhydrous THF (5 mL) at –78 ºC under Ar. The resultant mixture was stirred at –78 ºC for 1h and at rt for 1 h. The reaction was quenched with sat aq NH_4Cl (10 mL) and extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (25 mL of SiO_2, 5–15% EtOAc in hexanes gradient elution) afforded diol **184** (143.5 g, 0.5823 mmol, 82% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.05 (s, 1H), 4.99 (t, J = 1.4 Hz, 1H), 3.76 (d, J = 9.9 Hz, 1H), 3.68 (dd, J = 11.2, 5.4 Hz, 1H), 3.64 (d, J = 9.9 Hz, 1H), 3.57 (d, J = 11.2, 7.0 Hz, 1H), 2.99 (s, 1H), 2.22 (t, J = 6.4 Hz, 1H), 1.77 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.0, 112.4, 76.8, 67.0, 66.1, 25.8

(3C), 19.4, 18.2, –5.54, –5.55; IR (film) ν_{max} 3418, 2929, 2858, 1644, 1471, 1256, 1092, 1428, 1113, 1092 cm^{-1}; HRMS (ESI) *m/z* 247.1707 (MH^+, $C_{12}H_{26}O_3SiH^+$ requires 247.1724).



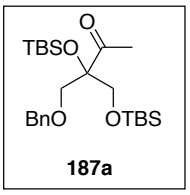
185

1-(Benzyloxy)-2-((*tert*-butyldimethylsilyloxy)methyl)-3-methylbut-3-en-2-ol (185). NaH (60% dispersion in mineral oil, 18.0 mg, 0.450 mmol) was added to a solution of diol **184** (54.1 mg, 0.220 mmol) in anhydrous DMF (2 mL) at –40 ºC under Ar. The resultant mixture was stirred at –40 ºC for 1 h, then treated dropwise with benzyl bromide (26.0 μL, 37.4 mg, 0.219 mmol) and stirred at –20 ºC for 18 h. The reaction was quenched with sat aq NH_4Cl (5 mL), diluted with H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with cold Et_2O (3 × 15 mL), and the combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (10 mL of SiO_2, 5% EtOAc in hexanes elution) afforded **185** (53.7 mg, 0.160 mmol, 73%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.26 (m, 5H), 5.10 (s, 1H), 4.97 (s, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.56 (d, *J* = 12.1 Hz, 1H), 3.70 (d, *J* = 9.7 Hz, 1H), 3.62 (d, *J* = 9.7 Hz, 1H), 3.55 (d, *J* = 9.4 Hz, 1H), 3.52 (d, *J* = 9.4 Hz, 1H), 2.79 (s, 1H), 1.80 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.9, 138.2, 128.3 (2C), 127.7 (2C), 127.6, 112.2, 76.5, 73.6, 72.8, 66.0, 25.8 (3C), 19.7, 18.2, –5.48, –5.50; IR (film) ν_{max} 3419, 2928, 2857, 1673, 1497, 1387, 1257, 1093 cm^{-1}; HRMS (ESI) *m/z* 337.2139 (MH^+, $C_{19}H_{32}O_3SiH^+$ requires 337.2193).



186

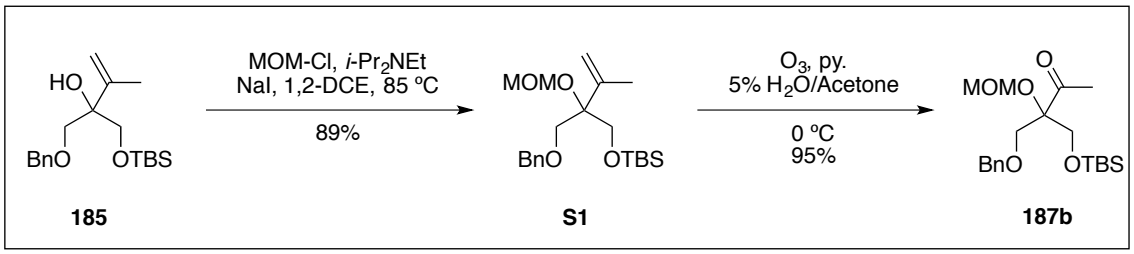
5-((Benzyloxy)methyl)-2,2,3,3,8,8,9,9-octamethyl-5-(prop-1-en-2-yl)-4,7-dioxa-3,8-disiladecane (186). 2,6-Lutidine (180 μL, 166 mg, 1.55 mmol) and TBS-OTf (180 μL, 207 mg, 0.784 mmol) were added successively to a solution of alcohol **185** (106.2 mg, 0.3156 mmol) in anhydrous CH_2Cl_2 (3.2 mL) at rt under Ar. The resulting mixture was stirred for 18 h, then treated with sat aq NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (25 mL of SiO_2, 2–3% Et_2O in hexanes gradient elution) afforded triether **186** (133.0 mg, 0.2950 mmol, 93%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.25 (m, 5H), 5.00 (s, 1H), 4.91 (s, 1H), 4.59 (d, J = 12.2 Hz, 1H), 4.56 (d, J = 12.2 Hz, 1H), 3.66 (d, J = 9.8 Hz, 1H), 3.61 (d, J = 9.8 Hz, 1H), 3.58 (s, 2H), 1.78 (s, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.0, 138.3, 128.2 (2C), 127.7 (2C), 127.4, 112.0, 79.8, 73.4, 72.7, 66.6, 26.0 (3C), 25.9 (3C), 20.0, 18.7, 18.3, –2.7, –2.8, –5.55, –5.56; IR (film) ν_{max} 3090, 3032, 2928, 2885, 2856, 1644 cm^{-1}; HRMS (ESI) *m/z* 451.3080 (MH^+, $C_{25}H_{46}O_3Si_2H^+$ requires 451.3058).



187a

4-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-3-((*tert*-butyldimethylsilyloxy) methyl) butan-2-one (187). A stream of ozone was bubbled into a solution of alkene **186** (1.1172 g, 2.4782 mmol) and 1 drop of Sudan IV (concentrated solution in CH_2Cl_2) in 5% H_2O/acetone (50 mL) at 0 ºC until the solution became colorless. The mixture was purged with Ar for 5 min then was dilted with H_2O (50 mL) an extracted with EtOAc (3 × 100 mL).

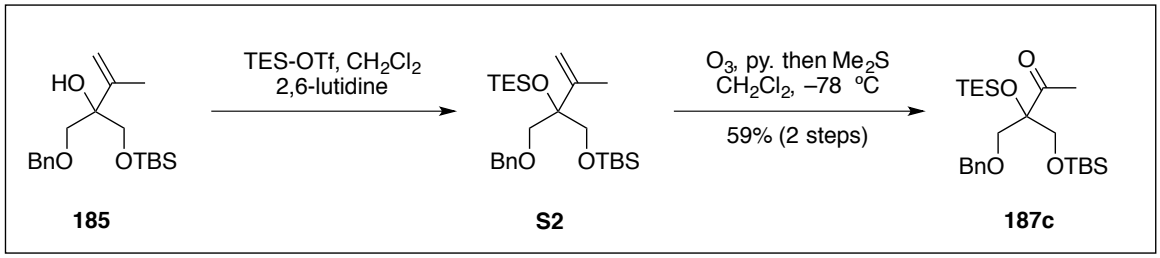
Combined extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (120 mL of SiO_2, 2–3% EtOAc in hexanes gradient elution) afforded ketone **187a** (1.0799 g, 2.3850 mmol, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.25 (m, 5H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 3.78 (d, *J* = 10.1 Hz, 1H), 3.68 (d, *J* = 10.1 Hz, 1H), 3.63 (d, *J* = 9.5 Hz, 1H), 3.56 (d, *J* = 9.5 Hz, 1H), 2.25 (s, 3H), 0.92 (s, 9H), 0.87 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.0, 137.8, 128.3 (2C), 127.7 (2C), 127.6, 85.4, 73.5, 72.6, 66.3, 27.7, 25.9 (3C), 25.8 (3C), 18.6, 18.3, –2.9, –3.0, –5.6, –5.7; IR (film) ν_{max} 2955, 2929, 2857, 1721, 1472, 1253, 1111 cm^{-1}; HRMS (ESI) *m/z* 453.2815 (MH^+, $C_{24}H_{44}O_4Si_2H^+$ requires 453.2851).



5-((Benzyloxy)methyl)-8,8,9,9-tetramethyl-5-(prop-1-en-2-yl)-2,4,7-trioxa-8-siladecane (S1). Sodium iodide (4.8 mg, 0.032 mmol), *N,N*-diisopropylethylamine (130 μL, 96.5 mg, 0.746 mmol), and chloromethyl methyl ether (25.0 μL, 26.5 mg, 0.329 mmol) were added successively to a solution of alcohol **185** (48.5 mg, 0.144 mmol) in 1,2-dichloroethane (2.0 mL). The resulting mixture was stirred at 85 ºC for 5 d. The reaction was quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat aq $Na_2S_2O_3$ (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (10 mL of SiO_2, 2% Et_2O in hexanes elution) afforded triether **S1** (48.7 mg, 0.128 mmol, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.25 (m, 5H), 5.10 (s, 1H), 5.01 (s, 1H), 4.74 (d, *J* = 6.7 Hz, 1H), 4.69 (d, *J* = 6.7 Hz, 1H), 4.59 (d, *J* = 12.1 Hz, 1H), 4.54 (d, *J* = 12.1 Hz, 1H), 3.91 (d, *J* =

9.8 Hz, 1H), 3.77–3.70 (m, 2H) 3.69 (d, J = 9.5 Hz, 1H), 3.41 (s, 3H), 1.77 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.1, 138.5, 128.2 (2C), 127.6 (2C), 127.4, 114.9, 91.9, 81.9, 73.5, 70.3, 63.8, 55.9, 25.8 (3C), 19.3, 18.2, –5.5, –5.6; IR (film) ν_{max} 3090, 3066, 3031, 2954, 2928, 2885, 2856, 1644, 1497, 1472, 1107, 1034 cm^{-1}; HRMS (ESI) *m/z* 398.2685 ($M(NH_4)^+$, $C_{21}H_{36}O_4SiNH_4^+$ requires 398.2721).

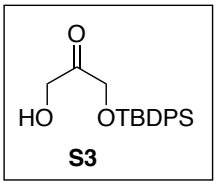
4-(Benzyloxy)-3-((*tert*-butyldimethylsilyloxy)methyl)-3-(methoxymethoxy)butan-2-one (187b). A solution of triether **S1** (408.3 mg, 1.073 mmol) and pyridine (170 μL, 167 mg, 2.11 mmol) in acetone–H_2O (95:5, 10 mL) at 0 ºC was treated with a drop of Sudan IV (saturated solution in acetone), and ozone was bubbled through until the pink solution became colorless. It was purged with Ar for 5 min, and then diluted with EtOAc (15 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (25 mL of SiO_2, 2–3% Et_2O in hexanes gradient elution) afforded ketone **2d** (391.5 mg, 1.023 mmol, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.28 (m, 5H), 4.87 (d, J = 6.9 Hz, 1H), 4.82 (d, J = 6.9 Hz, 1H), 4.50 (s, 2H), 3.90 (d, J = 10.4 Hz, 1H), 3.85 (d, J = 10.4 Hz, 1H), 3.76 (d, J = 10.1 Hz, 1H), 3.70 (d, J = 10.1 Hz, 1H), 3.41 (s, 3H), 2.25 (s, 3H), 0.85 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.7, 137.8, 128.3 (2C), 127.69 (2C), 127.68, 92.7, 85.8, 73.6, 69.1, 63.2, 56.2, 26.9, 25.7 (3C), 18.1, –5.74, –5.75; IR (film) ν_{max} 2929, 2886, 2857, 1722, 1472, 1409, 1389, 1256, 1109, 1035 cm^{-1}; HRMS (ESI) *m/z* 400.2514 ($M(NH_4)^+$, $C_{20}H_{34}O_5SiNH_4^+$ requires 400.2546).



6-(Benzyloxymethyl)-8,8-diethyl-2,2,3,3-tetramethyl-6-(prop-1-en-2-yl)-4,7-dioxa-3,8-disiladecane (S2). 2,6-Lutidine (210 μL, 194 mg, 1.81 mmol) and TES-OTf (240 μL, 281 mg, 1.06 mmol) were added successively to a solution of alcohol **185** (237.8 mg, 0.7066 mmol) in anhydrous CH_2Cl_2 (7.0 mL) at 0 ºC under Ar. The resultant mixture was warmed to rt and stirred for 2 h. The reaction was quenched with sat aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Crude **S2** (318.5 mg, 0.7065 mmol, quant.) was used directly in the next reaction without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.32 (m, 5H), 4.99 (s, 1H), 4.90 (s, 1H), 4.52 (s, 2H), 3.65 (d, J = 9.8 Hz, 1H), 3.61–3.54 (m, 3H), 1.77 (s, 3H), 0.91 (t, J = 7.8 Hz, 9H), 0.88 (s, 9H), 0.59 (q, J = 7.8 Hz, 6H), 0.034 (s, 3H), 0.029 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.1, 138.4, 128.1 (2C), 127.8 (2C), 127.4, 111.9, 79.7, 73.4, 72.8, 66.7, 30.9, 25.9 (3C), 19.9, 7.2 (3C), 6.5 (3C), –5.53, –5.55; IR (film) ν_{max} 2954, 2930, 2875, 1455, 1255, 1098, 1007 cm^{-1}; HRMS (ESI) *m/z* 468.3482 ($M(NH_4)^+$, $C_{25}H_{46}O_3Si_2NH_4^+$ requires 468.3324).

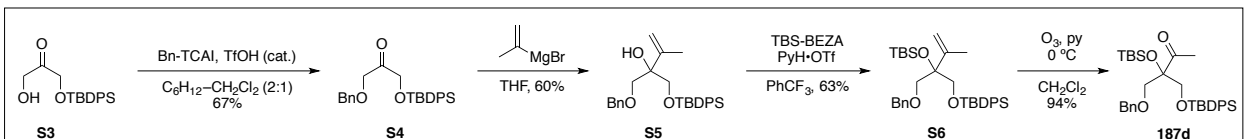
4-(Benzyloxy)-3-((*tert*-butyldimethylsilyloxy)methyl)-3-(triethylsilyloxy)butan-2-one (187c). A solution of alkene **S2** (318.5 mg, 0.7065 mmol) and anhydrous pyridine (110 μL, 108 mg, 1.37 mmol) in anhydrous CH_2Cl_2 (7.0 mL) at –78 ºC was treated with a drop of Sudan IV (saturated solution in CH_2Cl_2), and ozone was bubbled through until the solution became colorless. It was purged with Ar for 5 min, then treated with Me_2S (570 μL, 482 mg, 7.76 mmol).

The resultant mixture was stirred at –78 ºC for 30 min and at rt for 18 h. Flash chromatography (35 mL of SiO_2, 2–3% EtOAc in hexanes gradient elution) afforded ketone **187c** (187.8 mg, 0.4148 mmol, 59%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.25 (m, 5H), 4.48 (d, J = 11.9 Hz, 1H), 4.44 (d, J = 11.9 Hz, 1H), 3.76 (d, J = 10.1 Hz, 1H), 3.66 (d, J = 10.1 Hz, 1H), 3.61 (d, J = 9.5 Hz, 1H), 3.54 (d, J = 9.5 Hz, 1H), 2.23 (s, 3H), 0.94 (t, J = 7.9 Hz, 9H), 0.86 (s, 9H), 0.63 (q, J = 8.0 Hz, 6H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 211.8, 137.8, 128.3 (2C), 127.7 (2C), 127.6, 85.0, 73.5, 72.5, 66.4, 27.1, 25.8 (3C), 18.3, 7.1 (3C), 6.4 (3C), –5.60, –5.65; IR (film) ν_{max} 3065, 3032, 2955, 2876, 1721, 1462, 1415, 1361, 1349, 1254, 1190, 1112 cm^{-1}; HRMS (ESI) *m/z* 453.2863 (MH^+, $C_{24}H_{44}O_4Si_2H^+$ requires 453.2851).



S3

1-(*tert*-Butyldiphenylsilyloxy)-3-hydroxypropan-2-one (S3). TBDPS-Cl (6.80 mL, 7.19 g, 26.2 mmol) was added by syringe pump (0.6 mL/h) to a solution of dihydroxyacetone dimer (7.0312 g, 78.1 mmol) and imidazole (2.6775 g, 39.3 mmol) in anhydrous DMF (90 mL) at rt under Ar. The resultant mixture was stirred at rt for 18 h. The reaction was quenched with H_2O (100 mL) and extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with brine (3 × 100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (1000 mL of SiO_2, 5–15% EtOAc in hexanes gradient elution) afforded hydroxyketone **S3**[6] (7.3227 g, 22.3 mmol, 85%) as a colorless, viscous oil.



Scheme S4. Synthesis of ketone **2e**.

1-(Benzyloxy)-3-(*tert*-butyldiphenylsilyloxy)propan-2-one (S4). Triflic acid (3.0 μL, 5.1 mg, 0.034 mmol), was added to a solution of hydroxyketone **S3** (77.4 mg, 0.236 mmol) and benzyl 2,2,2-trichloroacetimidate (87.0 μL, 118 mg, 0.468 mmol) in anhydrous cyclohexane–CH_2Cl_2 (2:1, 2.4 mL) at 0 ºC under Ar. The resultant mixture was warmed to rt and stirred for 18 h. The mixture was filtered, washed with saturated aqueous $NaHCO_3$ (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (10 mL of SiO_2, 5–10% EtOAc in hexanes gradient elution) afforded ketone **S4** (66.4 mg, 0.159 mmol, 67%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61 (d, J = 7.0 Hz, 4H), 7.46–7.29 (m, 11H), 4.54 (s, 2H), 4.34 (s, 2H), 4.33 (s, 2H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.7, 137.1, 135.5 (4C), 134.8 (2C), 130.0 (2C), 128.5 (2C), 128.0 (2C), 127.9 (4C), 127.7, 73.4, 73.2, 68.7, 26.7 (3C), 19.2; IR (film) ν_{max} 3070, 2931, 2857, 1740, 1428, 1114 cm^{-1}; HRMS (ESI) *m/z* 436.2245 ($M(NH_4)^+$, $C_{26}H_{30}O_3SiNH_4^+$ requires 436.2302).

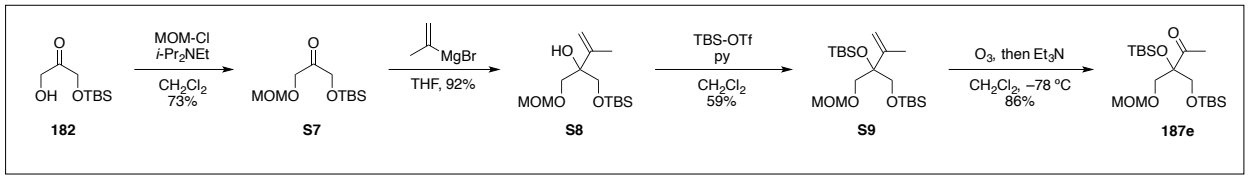
1-(Benzyloxy)-2-((*tert*-butyldiphenylsilyloxy)methyl)-3-methylbut-3-en-2-ol (S5). A solution of isopropenylmagnesium bromide (0.57 M in THF, 950 μL, 0.542 mmol) was added to a solution of ketone **S4** (66.4 mg, 0.159 mmol) in anhydrous THF (2 mL) at –78 ºC under Ar. The resultant mixture was stirred at –78 ºC for 1 h and at rt for 1.5 h. The reaction was quenched with sat aq NH_4Cl (10 mL) and extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (20 mL of SiO_2, 1–6% Et_2O in hexanes gradient elution) afforded alcohol **S5** (44.1 mg, 0.0957 mmol, 60%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66–7.63 (m, 4H), 7.48–7.28 (m, 11H), 5.10 (s, 1H), 4.98 (t, J = 2.0 Hz, 1H), 4.59 (d, J = 12.2 Hz, 1H), 4.57 (d, J = 12.2 Hz, 1H), 3.75 (d, J = 9.8 Hz, 1H), 3.67 (d, J = 9.8 Hz, 1H), 3.64 (d, J = 9.3 Hz, 1H), 3.56 (d, J = 9.3 Hz, 1H), 2.81 (s, 1H), 1.74 (s, 3H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ

145.7, 138.1, 135.72 (2C), 135.68 (2C), 133.14, 133.10, 129.82, 129.80, 128.4 (2C), 127.77 (2C), 127.76 (2C), 127.72 (2C), 127.66, 112.5, 76.9, 73.6, 72.8, 66.6, 26.9 (3C), 19.6, 19.4; IR (film) ν_{max} 3558, 3070, 3049, 2930, 2857, 1589, 1471, 1454, 1428, 1113 cm^{-1}; HRMS (ESI) *m/z* 478.2799 ($M(NH_4)^+$, $C_{29}H_{36}O_3SiNH_4^+$ requires 478.2772).

5-(Benzyloxymethyl)-2,2,3,3,9,9-hexamethyl-8,8-diphenyl-5-(prop-1-en-2-yl)-4,7-dioxa-3,8-disiladecane (S6). A solution of alcohol **S5** (145.9 mg, 0.3167 mmol), TBDMS-BEZA[7] (496.0 mg, 1.592 mmol), and PyH•OTf (14.8 mg, 0.0646 mmol) in benzotrifluoride (3.2 mL) was stirred at 100 ºC under Ar for 3 d. The mixture was filtered through cotton (rinsed with 20 mL of EtOAc), and the filtrate was concentrated *in vacuo*. Flash chromatography (20 mL of SiO_2, 1–2% EtOAc in hexanes gradient elution) afforded triether **S6** (114.5 mg, 0.1992 mmol, 63%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (d, *J* = 7.0 Hz, 2H), 7.64 (d, *J* = 6.8 Hz, 2H), 7.44–7.28 (m, 11H), 5.04 (s, 1H), 4.95 (s, 1H), 4.55 (d, *J* = 12.5 Hz, 1H), 4.52 (d, *J* = 12.5 Hz, 1H), 3.81 (d, *J* = 9.3 Hz, 1H), 3.75 (d, *J* = 9.6 Hz, 1H), 3.69 (d, *J* = 9.3 Hz, 1H), 3.56 (d, *J* = 9.6 Hz, 1H), 1.72 (s, 3H), 1.04 (s, 9H), 0.85 (s, 9H), 0.02 (s, 3H), –0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.7, 138.2, 135.74 (2C), 135.71 (2C), 133.51, 133.47, 129.52, 129.50, 128.2 (2C), 127.9 (2C), 127.53 (2C), 127.52 (2C), 127.4, 112.4, 79.8, 73.5, 72.7, 66.9, 26.8 (3C), 26.0 (3C), 19.9, 19.2, 18.7, –2.6, –2.9; IR (film) ν_{max} 2955, 2929, 2856, 1472, 1251, 1113 cm^{-1}; HRMS (ESI) *m/z* 592.3665 ($M(NH_4)^+$, $C_{35}H_{50}O_3Si_2NH_4^+$ requires 592.3637).

4-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl) butan-2-one (187d). A stream of O_3 gas was bubbled into A solution of alkene **S6** (112.0 mg, 0.1948 mmol) and pyridine (40.0 μL, 39.3 mg, 0.497 mmol) in anhydrous CH_2Cl_2 (1.9 mL) at –78 °C was treated with a drop of Sudan IV (saturated solution in CH_2Cl_2), and ozone was bubbled through until the solution became colorless. It was purged with Ar for 5 min and treated

with Et_3N (270 μL, 196 mg, 1.94 mmol). The resultant mixture was warmed to rt, stirred for 1 h, and concentrated *in vacuo*. Flash chromatography (20 mL of SiO_2, 2–3% EtOAc in hexanes gradient elution) afforded ketone **2e** (105.5 mg, 0.1829 mmol, 94%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (d, J = 6.7 Hz, 2H), 7.59 (d, J = 6.7 Hz, 2H), 7.44–7.22 (m, 11H), 4.43 (s, 2H), 3.86 (d, J = 10.0 Hz, 1H), 3.65 (s, 2H), 3.62 (d, J = 10.0 Hz, 1H), 2.25 (s, 3H), 1.02 (s, 9H), 0.89 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.8, 137.7, 135.74 (2C), 135.73 (2C), 132.9, 132.8, 129.74, 129.70, 128.2 (2C), 127.7 (2C), 127.6 (4C), 127.5, 85.0, 73.5, 72.2, 66.8, 27.1, 26.8 (3C), 25.9 (3C), 19.1, 18.6, –2.8, –3.1; IR (film) ν_{max} 3071, 2955, 2930, 2892, 2857, 1721, 1472, 1428, 1253, 1114, 1028 cm^{-1}; HRMS (ESI) *m/z* 594.3425 ($M(NH_4)^+$, $C_{34}H_{48}O_4Si_2NH_4^+$ requires 594.3429).



1-(*tert*-Butyldimethylsilyloxy)-3-methoxymethoxypropan-2-one (S7). *N,N*-diisopropylethylamine (2.30 mL, 1.71 g, 13.2 mmol) and chloromethyl methyl ether (430 μL, 455.8 mg, 5.661 mmol) were added successively and dropwise to a solution of hydroxyketone **182** (897.9 mg, 4.394 mmol) in anhydrous CH_2Cl_2 (10 mL) at rt under Ar. The resultant mixture was stirred at rt for 18 h, then quenched with sat aq NH_4Cl (5 mL), diluted with H_2O (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (100 mL of SiO_2, 2.5–7.5% EtOAc in hexanes gradient elution) afforded ketone **S7** (790.8 mg, 3.184 mmol, 72%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.69 (s, 2H), 4.44 (s, 2H), 4.31 (s, 2H), 3.39 (s, 3H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.0, 96.5, 70.5, 68.2, 55.7, 25.7 (3C),

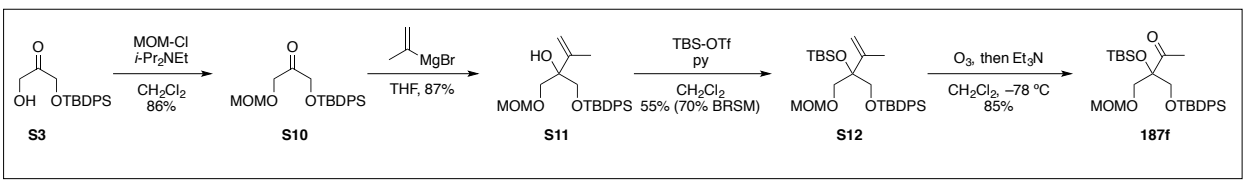
18.2, –5.6 (2C); IR (film) ν_{max} 2954, 2930, 2894, 2857, 1741, 1254, 1153, 1007, 1063 cm^{-1}; HRMS (ESI) *m/z* 266.1755 ($M(NH_4)^+$, $C_{11}H_{24}O_4SiNH_4^+$ requires 266.1782).

9,9,10,10-Tetramethyl-6-(prop-1-en-2-yl)-2,4,8-trioxa-9-silaundecan-6-ol (S8). A solution of isopropenylmagnesium bromide (0.57 M in THF, 5.40 mL, 3.08 mmol) was added to a solution of ketone **S7** (224.0 mg, 0.9018 mmol) in anhydrous THF (10 mL) at –78 ºC under Ar. The resultant mixture was stirred at –78 ºC for 30 min, then warmed to rt and stirred for an additional 2 h. The reaction was quenched with sat aq NH_4Cl (10 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (30 mL of SiO_2, 2–6% EtOAc in hexanes gradient elution) afforded alcohol **S8** (242.1 mg, 0.8335 mmol, 92%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 5.11 (s, 1H), 5.00 (s, 1H), 4.63 (s, 2H), 3.71 (d, *J* = 9.9 Hz, 1H), 3.69 (s, 2H), 3.65 (d, *J* = 9.9 Hz, 1H), 3.33 (s, 3H), 2.93 (s, 1H), 1.75 (s, 3H), 1.06 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.8, 112.2, 96.9, 76.3, 70.9, 66.1, 55.2, 25.7 (3C), 19.5, 18.1, –5.60, –5.62; IR (film) ν_{max} 3465, 2954, 2930, 2885, 2858, 1645, 1472, 1254, 1111, 1046 cm^{-1}; HRMS (ESI) *m/z* 291.2006 (MH^+, $C_{14}H_{30}O_4SiH^+$ requires 291.1986).

6-(*tert*-Butyldimethylsilyloxy)-9,9,10,10-tetramethyl-6-(prop-1-en-2-yl)-2,4,8-trioxa-9-silaundecane (S9). Pyridine (180 μL, 177 mg, 2.23 mmol) and TBS-OTf (250 μL, 288 mg, 1.09 mmol) were added successively to a solution of alcohol **S8** (216.1 mg, 0.7440 mmol) in anhydrous CH_2Cl_2 (7.4 mL) at 0 ºC under Ar. The resulting mixture was stirred at 0 °C to rt for 18 h, then treated with sat aq NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (20 mL of SiO_2, 1–2% EtOAc in hexanes gradient elution) afforded triether **S9** (177.8 mg, 0.4393 mmol, 59%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 5.00 (s, 1H), 4.92 (s, 1H),

4.64 (d, J = 6.7 Hz, 1H), 4.62 (d, J = 6.7 Hz, 1H), 3.67 (d, J = 9.5 Hz, 1H), 3.65 (d, J = 9.7 Hz, 1H), 3.63 (d, J = 9.5 Hz, 1H), 3.61 (d, J = 9.7 Hz, 1H), 3.37 (s, 3H), 1.79 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 6H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.7, 112.1, 97.1, 79.6, 70.3, 66.2, 55.5, 26.0 (3C), 25.9 (3C), 19.7, 18.7, 18.3, –2.6, –2.7, –5.5, –5.6; IR (film) ν_{max} 2955, 2929, 2857, 1472, 1252, 1111, 1049 cm^{-1}; HRMS (ESI) *m/z* 405.2881 (MH^+, $C_{20}H_{44}O_4Si_2H^+$ requires 405.2851).

3,4-bis((*tert*-Butyldimethylsilyl)oxy)-3-((methoxymethoxy)methyl)butan-2-one (187e). A solution of alkene **S9** (184.4 mg, 0.4556 mmol) in anhydrous CH_2Cl_2 (4.6 mL) was treated with a drop of Sudan IV (saturated solution in CH_2Cl_2), and ozone was bubbled through until the solution became colorless. It was purged with Ar for 5 min, then treated dropwise with Et_3N (640 μL, 465 mg, 4.59 mmol). The resulting orange solution was warmed to rt, stirred for 1 h, and concentrated *in vacuo*. Flash chromatography (20 mL of SiO_2, 2–3% EtOAc in hexanes gradient elution) afforded ketone **187e** (158.3 mg, 0.3892 mmol, 85%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.56 (s, 2H), 3.76 (d, J = 10.1 Hz, 1H), 3.70 (d, J = 9.7 Hz, 1H), 3.67 (d, J = 10.1 Hz, 1H), 3.56 (d, J = 9.7 Hz, 1H), 3.31 (s, 3H), 2.26 (s, 3H), 0.93 (s, 9H), 0.88 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 211.8, 96.9, 85.4, 70.4, 66.3, 55.5, 27.7, 25.9 (3C), 25.8 (3C), 18.6, 18.3, –2.8, –2.9, –5.6, –5.7; IR (film) ν_{max} 2954, 2929, 2885, 2858, 1723, 1472, 1254, 1153, 1114, 1049 cm^{-1}; HRMS (ESI) *m/z* 407.2611 (MH^+, $C_{19}H_{42}O_5Si_2H^+$ requires 407.2644).



1-(*tert*-Butyldiphenylsilyloxy)-3-methoxymethoxypropan-2-one (S10). *N,N*-Diisopropylethylamine (11.9 mL, 8.83 g, 68.3 mmol) and chloromethyl methyl ether (3.10 mL, 3.29 g, 40.8 mmol) were added successively to a solution of hydroxyketone **S3 (**4.481 g, 13.6 mmol) in anhydrous CH_2Cl_2 (70 mL) at rt under Ar. The resultant mixture was stirred at rt for 18 h. The reaction was quenched with sat aq NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (150 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (60 mL of SiO_2, 2–6% EtOAc in hexanes gradient elution) afforded ketone **S10** (4.37 g, 11.7 mmol, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64 (dd, *J* = 7.9, 1.3 Hz, 4H), 7.49–7.38 (m, 6H), 4.65 (s, 2H), 4.47 (s, 2H), 4.32 (s, 2H), 3.35 (s, 3H), 1.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.4, 135.5 (4C), 132.3 (2C), 130.1 (2C), 127.9 (4C), 96.5, 70.5, 68.7, 55.7, 26.7 (3C), 19.2; IR (film) ν_{max} 3071, 3050, 2932, 2892, 2858, 1740, 1589, 1472, 1428, 1152, 1113, 1061 cm^{-1}; HRMS (ESI) *m/z* 390.2106 ($M(NH_4)^+$, $C_{21}H_{28}O_4SiNH_4^+$ requires 390.2095).

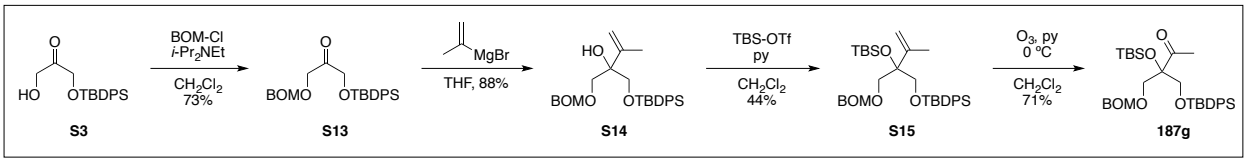
10,10-dimethyl-9,9-diphenyl-6-(prop-1-en-2-yl)-2,4,8-trioxa-9-silaundecan-6-ol (S11). A solution of isopropenylmagnesium bromide (0.57 M in THF, 30.0 mL, 17.1 mmol) was added to a solution of ketone **S10** (3.0792 g, 8.27 mmol) in anhydrous THF (25 mL) at –78 ºC under Ar. The resultant mixture was stirred at –78 ºC for 30 min, allowed to warm to rt, and stirred at rt for 1 h. The reaction was quenched with sat aq NH_4Cl (30 mL), diluted with H_2O (30 mL), and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (300 mL of SiO_2, 4–6% EtOAc in hexanes gradient elution) afforded alcohol **S11** (2.9687 g, 7.16 mmol, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67–7.63 (m, 4H), 7.45–7.36 (m, 6H), 5.11 (s, 1H), 5.00 (s, 1H), 4.63 (s, 2H), 3.71 (d, *J* = 9.9 Hz, 1H), 3.69 (s, 2H), 3.65 (d, *J* = 9.9 Hz, 1H), 3.33 (s,

3H), 2.93 (s, 1H), 1.75 (s, 3H) 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.6, 135.7 (2C), 135.6 (2C), 133.03, 132.96, 129.79, 129.78, 127.7 (4C), 112.6, 97.1, 76.7, 71.1, 66.6, 55.4, 26.8 (3C), 19.5, 19.3; IR (film) ν_{max} 3562, 3450, 3071, 2931, 2858, 1472, 1428, 1113, 1045 cm^{-1}; HRMS (ESI) *m/z* 432.2582 ($M(NH_4)^+$, $C_{24}H_{34}O_4SiNH_4^+$ requires 432.2565).

6-(*tert*-Butyldimethylsilyloxy)-10,10-dimethyl-9,9-diphenyl-6-(prop-1-en-2-yl)-2,4,8-trioxa-9-silaundecane (S12). Pyridine (570 μL, 560 mg, 7.08 mmol) and TBS-OTf (1.48 mL, 1.70 g, 6.44 mmol) were added successively to a solution of alcohol **S11** (2.0053 g, 4.84 mmol) in anhydrous CH_2Cl_2 (20 mL). The resultant mixture was stirred at rt under Ar for 3 d. The reaction was quenched with sat aq NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (200 mL of SiO_2, 2–10% EtOAc in hexanes gradient elution) afforded triether **7** (1.4148 g, 2.68 mmol, 55%) and recovered alcohol **S12** (432.4 mg, 1.04 mmol, 22%) as colorless oils. For **7**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.69 (dd, *J* = 7.9, 1.2 Hz, 2H), 7.47–7.38 (m, 6H), 5.07 (s, 1H), 4.98 (s, 1H), 4.66 (s, 2H), 3.87 (d, *J* = 9.9 Hz, 1H), 3.77 (d, *J* = 9.9 Hz, 1H), 3.76 (d, *J* =9.8 Hz, 1H), 3.62 (d, *J* = 9.8 Hz, 1H), 3.39 (s, 3H), 1.74 (s, 3H), 1.09 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.4, 135.8 (4C), 133.44, 133.42, 129.64, 129.62, 127.60 (2C), 127.58 (2C), 112.6, 97.2, 79.7, 70.4, 66.7, 55.7, 26.9 (3C), 26.1 (3C), 19.9, 19.3, 18.7, –2.4, –2.7; IR (film) ν_{max} 3072, 2930, 2857, 1472, 1428, 1251, 1113, 1048 cm^{-1}; HRMS (ESI) *m/z* 546.3427 ($M(NH_4)^+$, $C_{30}H_{48}O_4Si_2NH_4^+$ requires 546.3429).

3-((*tert*-Butyldimethylsilyl)oxy)-4-((*tert*-butyldiphenylsilyl)oxy)-3-((methoxymethoxy)methyl)butan-2-one (187f). A stream of ozone was bubbled into a solution of alkene **S12** (759.5 mg, 1.436 mmol) in anhydrous CH_2Cl_2 (10 mL) at –78 ºC until the solution

became blue in color. The solution was purged with Ar for 5 min, then treated with Et_3N (2.0 mL, 1.4520 g, 14.349 mmol). The resultant mixture was stirred at –78 ºC for 10 min, allowed to warm to rt, stirred at rt for 1 h, and concentrated *in vacuo*. Flash chromatography (80 mL of SiO_2, 2–3% EtOAc in hexanes gradient elution) afforded ketone **187f** (649.9 mg, 1.224 mmol, 85%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.60 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.45–7.35 (m, 6H), 4.53 (d, *J* = 6.5 Hz, 1H), 4.51, (d, *J* = 6.5 Hz, 1H), 3.80 (d, *J* = 10.2 Hz, 1H), 3.75 (d, *J* = 10.1 Hz, 1H), 3.61 (d, *J* = 10.2 Hz, 1H), 3.58 (d, *J* = 10.1 Hz, 1H) 3.28 (s, 3H), 2.24 (s, 3H), 1.03 (s, 9H), 0.91 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.9, 135.8 (4C), 132.8, 132.7, 129.79, 129.77, 127.66 (2C), 127.65 (2C), 96.9, 85.2, 70.0, 67.1, 55.6, 27.5, 26.8 (3C), 25.9 (3C), 19.1, 18.6, –2.7, –2.9; IR (film) ν_{max} 3072, 3050, 2930, 2858, 1722, 1472, 1428, 1114, 1048 cm^{-1}; HRMS (ESI) *m/z* 531.2957 (MH^+, $C_{29}H_{46}O_5Si_2H^+$ requires 531.2957).



10,10-Dimethyl-1,9,9-triphenyl-2,4,8-trioxa-9-silaundecan-6-one (S13). *N,N*-diisopropylethylamine (810 μL, 601 mg, 4.65 mmol) and benzyl chloromethyl ether (400 μL, 450 mg, 2.88 mmol) were added successively and dropwise to a solution of hydroxyketone **4** (304.4 mg, 0.9267 mmol) in anhydrous CH_2Cl_2 (9.3 mL) at rt under Ar. The resultant mixture was stirred at rt for 24 h. The reaction was quenched with sat aq NH_4Cl (5 mL), diluted with H_2O (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (80 mL of SiO_2, 2–10% EtOAc in hexanes gradient elution) afforded ketone **S13** (303.7 mg, 0.6770 mmol, 73%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (d, *J* = 6.9 Hz, 4H), 7.47–7.28 (m,

11H), 4.80 (s, 2H), 4.60 (s, 2H), 4.52 (s, 2H), 4.30 (s, 2H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.4, 137.5, 135.5 (4C), 132.3 (2C), 130.1 (2C), 128.5 (2C), 127.93 (4C), 127.90 (2C), 127.8, 94.7, 70.7, 69.9, 68.7, 26.7 (3C), 19.2; IR (film) ν_{max} 3070, 2931, 2890, 2858, 1740, 1454, 1167, 1113, 1028 cm^{-1}; HRMS (ESI) *m/z* 466.2351 ($M(NH_4)^+$, $C_{27}H_{32}O_4SiNH_4^+$ requires 466.2408).

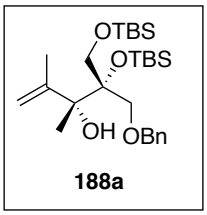
10,10-Dimethyl-1,9,9-triphenyl-6-(prop-1-en-2-yl)-2,4,8-trioxa-9-silaundecan-6-ol (S14). A solution of ketone **S13** (117.3 mg, 0.2615 mmol) in anhydrous THF (2.6 mL) was added to a solution of isopropenylmagnesium bromide (0.57 M in THF, 1.1 mL, 0.6270 mmol) at 0 ºC under Ar. The resultant mixture was warmed to rt and stirred for 30 min. The reaction was quenched with sat aq NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (20 mL of SiO_2, 2–6% EtOAc in hexanes gradient elution) afforded alcohol **S14** (113.0 mg, 0.2303 mmol, 88%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (d, *J* = 6.8 Hz, 4H), 7.47–7.27 (m, 11H), 5.15 (s, 1H), 5.03 (s, 1H), 4.80 (d, *J* = 7.2 Hz, 1H), 4.79 (d, *J* = 7.2 Hz, 1H), 4.60 (d, *J* = 11.0 Hz, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 3.77 (s, 2H), 3.75 (d, *J* = 9.9 Hz, 1H), 3.69 (d, *J* = 9.9 Hz, 1H), 2.94 (s, 1H), 1.78 (s, 3H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.7, 137.7, 135.7 (2C), 135.6 (2C), 133.1, 133.0, 129.81, 129.80, 128.4 (2C), 127.9 (2C), 127.74 (4C), 127.72, 112.7, 95.3, 76.8, 71.3, 69.6, 66.8, 26.9 (3C), 19.6, 19.3; IR (film) ν_{max} 3452, 2070, 2931, 2858, 1645, 1265, 1471, 1428, 1113, 1044 cm^{-1}; HRMS (ESI) *m/z* 508.2904 ($M(NH_4)^+$, $C_{30}H_{38}O_4SiNH_4^+$ requires 508.2878).

6-(*tert*-Butyldimethylsilyloxy)-10,10-dimethyl-1,9,9-triphenyl-6-(prop-1-en-2-yl)-2,4,8-trioxa-9-silaundecane (S15). Anhydrous pyridine (80.0 μL, 78.6 mg, 0.993 mmol) and TBS-OTf (80.0 μL, 92.1 mg, 0.348 mmol) were added successively and dropwise to a solution of

alcohol **S14** (59.8 mg, 0.1219 mmol) in anhydrous CH_2Cl_2 (600 μL) at rt under Ar. The resultant mixture was stirred at rt under Ar for 18 h. The reaction was quenched with sat aq NH_4Cl (2 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (10 mL of SiO_2, 2–4% EtOAc in hexanes gradient elution) afforded triether **S15** (32.3 mg, 0.05339 mmol, 44%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (d, *J* = 6.8 Hz, 2H), 7.65 (d, *J* = 6.8 Hz, 2H), 7.44–7.28 (m, 11H), 5.04 (s, 1H), 4.95 (s, 1H), 4.76 (d, *J* = 7.4 Hz, 1H), 4.75 (d, *J* = 7.4 Hz, 1H), 4.61 (d, *J* = 11.9 Hz, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 3.87 (d, *J* = 9.9 Hz, 1H), 3.82 (d, *J* = 9.9 Hz, 1H), 3.72 (d, *J* = 9.8 Hz, 1H), 3.59 (d, *J* = 9.8 Hz, 1H), 1.71 (s, 3H), 1.04 (s, 9H), 0.85 (s, 9H), 0.032 (s, 3H), 0.026 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.4, 137.9, 135.75 (2C), 135.74 (2C), 133.4 (2C), 129.6 (2C), 128.4 (2C), 127.8 (2C), 127.6 (2C), 127.5 (3C), 112.6, 95.3, 79.8, 70.8, 69.6, 66.9, 26.9 (3C), 26.0 (3C), 19.9, 19.3, 18.7, –2.4, –2.7; IR (film) ν_{max} 3071, 2930, 2886, 2857, 1590, 1472, 1428, 1251, 1113 cm^{-1}; HRMS (ESI) *m/z* 622.3771 ($M(NH_4)^+$, $C_{36}H_{52}O_4Si_2NH_4^+$ requires 622.3742).

4-(Benzyloxymethoxy)-3-(*tert*-butyldimethylsilyloxy)-3-((*tert*-butyldiphenylsilyloxy) methyl)butan-2-one (187g). A solution of alkene **S15** (37.4 mg, 0.0618 mmol) and anhydrous pyridine (20.0 μL, 19.6 mg, 0.248 mmol) in anhydrous CH_2Cl_2 (620 μL) at –78 ºC was treated with a drop of Sudan IV (saturated solution in CH_2Cl_2), and ozone was bubbled through until the solution became colorless. It was purged with Ar for 5 min and treated with Et_3N (90.0 μL, 65.3 mg, 0.645 mmol). The resultant mixture was warmed to rt, stirred for 1 h, and concentrated *in vacuo*. Flash chromatography (5 mL of SiO_2, 2–3% EtOAc in hexanes gradient elution) afforded ketone **187g** (26.5 mg, 0.0437 mmol, 71%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.61 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.46–7.28 (m, 11H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.64 (d, *J* = 6.7 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 3.86 (d, *J* =

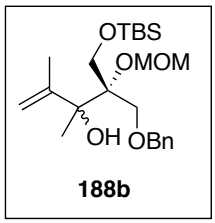
10.1 Hz, 1H), 3.82 (d, J = 10.2 Hz, 1H), 3.65 (d, J = 10.1 Hz, 1H), 3.64 (d, J = 10.2 Hz, 1H), 2.26 (s, 3H), 1.05 (s, 9H), 0.92 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.8, 137.6, 135.8 (4C), 132.8, 132.7, 129.81, 129.79, 128.4 (2C), 128.0 (2C), 127.8, 127.69 (2C), 127.67 (2C), 94.8, 85.3, 70.3, 69.5, 67.2, 27.5, 26.8 (3C), 26.0 (3C), 19.2, 18.6, –2.7, –2.9; IR (film) ν_{max} 3071, 2930, 2885, 2857, 1720, 1472, 1428, 1114, 1048 cm^{-1}; (ESI) *m/z* 624.3516 ($M(NH_4)^+$, $C_{35}H_{50}O_5Si_2NH_4^+$ requires 624.3535).



188a

(3R*,4S*)-5-(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,3-dimethylpent-1-en-3-ol (188a). A solution of $LaCl_3$•2LiCl (0.59 M in THF, 24.7 mL, 14.5730 mmol) was added to a solution of ketone **187a** (1.32 g, 2.9153 mmol) in anhydrous CH_2Cl_2 (600 mL) at 0 ºC and the solution became cloudy. The mixture was stirred at 0 ºC for 10 min. A solution of isopropenylmagnesium bromide (0.57 M in THF, 15.4 mL, 8.7780 mmol) was added dropwise and the resultant mixture was stirred at 0 ºC for 2 h. The reaction was quenched with saturated aq NH_4Cl (50 mL) and volatiles were removed by rotary evaporation. The aqueous layer was extracted with EtOAc (3 × 125 mL). Combined extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford **188a** in >20:1 dr as evidenced by ^{1}H NMR. Flash chromatography (150 mL of SiO_2, 2% EtOAc in hexanes) afforded alcohol **188a** (1.3470 g, 2.7220 mmol, 93%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.28 (m, 5H), 5.09 (d, J = 1.6 Hz, 1H), 4.97 (d, J = 6.7 Hz, 1H), 4.96 (s, 1H), 4.95 (s, 1H), 4.88 (d, J = 6.7 Hz, 1H), 4.47 (s, 2H), 4.13 (d, J = 10.6 Hz, 1H), 4.06 (d, J = 10.6 Hz, 1H), 3.88 (s, 2H), 3.37 (s, 3H), 1.90 (s, 3H), 1.41 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.3, 137.8, 128.3 (2C), 127.63 (2C), 127.61,

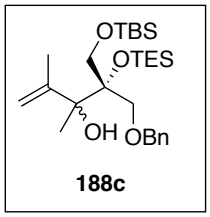
112.3, 92.9, 81.0, 78.8, 73.8, 70.6, 62.8, 56.0, 25.8 (3C), 23.3, 21.6, 18.1, –5.7, –5.8; Data for minor isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.28 (m, 5H), 5.11 (d, J = 1.6 Hz, 1H), 4.97 (s, 1H), 4.96 (d, J = 6.6 Hz, 1H), 4.88 (d, J = 6.6 Hz, 1H), 4.63 (s, 1H), 4.53 (d, J = 11.8 Hz, 1H), 4.51 (d, J = 11.8 Hz, 1H), 4.07 (d, J = 10.2 Hz, 1H), 4.05 (d, J = 9.5 Hz, 1H), 3.97 (d, J = 10.2 Hz, 1H), 3.87 (d, J = 9.5 Hz, 1H), 3.37 (s, 3H), 1.91 (s, 3H), 1.36 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.6, 137.9, 128.3 (2C), 127.7 (2C), 127.6, 112.2, 92.9, 80.6, 79.2, 73.8, 70.0, 63.5, 56.0, 25.7 (3C), 23.0, 21.7, 18.0, –5.81, –5.85; IR (film) ν_{max} 3467, 2928, 2856, 1472, 1254, 1070, 1023 cm^{-1}; HRMS (ESI) *m/z* 425.2719 (MH^+, $C_{23}H_{40}O_5SiH^+$ requires 425.2719).



188b

5-(Benzyloxy)-4-((*tert*-butyldimethylsilyloxy)methyl)-4-(methoxymethoxy)-2,3-dimethylpent-1-en-3-ol (188b). A solution of $LaCl_3$•2LiCl (0.59 M in THF, 160 μL, 0.0944 mmol) was added to a solution of ketone **187b** (7.3 mg, 0.0191 mmol) in anhydrous CH_2Cl_2 (260 μL) at 0 ºC under Ar, and the resultant mixture was stirred for 10 min. A solution of isopropenylmagnesium bromide (0.57 M in THF, 100 μL, 0.0570 mmol) was then added, and the mixture was stirred at 0 ºC for 1 h. The reaction was quenched with sat aq NH_4Cl (2 mL), diluted with H_2O (2 mL), and extracted with CH_2Cl_2 (5 × 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford crude **188b** in 1.6:1 dr as evidenced by ^{1}H NMR. Flash chromatography (2 mL of SiO_2, 2% EtOAc in hexanes elution) afforded **188b** (6.0 mg, 0.0141 mmol, 74%) as a 2.3:1 mixture of diastereomers that was a colorless oil. Data for major isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.28 (m, 5H), 5.09 (d, J = 1.6 Hz, 1H), 4.97 (d, J = 6.7 Hz, 1H), 4.96 (s, 1H), 4.95 (s, 1H), 4.88 (d, J = 6.7 Hz, 1H), 4.47 (s, 2H), 4.13 (d, J =

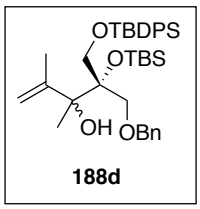
10.6 Hz, 1H), 4.06 (d, J = 10.6 Hz, 1H), 3.88 (s, 2H), 3.37 (s, 3H), 1.90 (s, 3H), 1.41 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.3, 137.8, 128.3 (2C), 127.63 (2C), 127.61, 112.3, 92.9, 81.0, 78.8, 73.8, 70.6, 62.8, 56.0, 25.8 (3C), 23.3, 21.6, 18.1, –5.7, –5.8; Data for minor isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37–7.28 (m, 5H), 5.11 (d, J = 1.6 Hz, 1H), 4.97 (s, 1H), 4.96 (d, J = 6.6 Hz, 1H), 4.88 (d, J = 6.6 Hz, 1H), 4.63 (s, 1H), 4.53 (d, J = 11.8 Hz, 1H), 4.51 (d, J = 11.8 Hz, 1H), 4.07 (d, J = 10.2 Hz, 1H), 4.05 (d, J = 9.5 Hz, 1H), 3.97 (d, J = 10.2 Hz, 1H), 3.87 (d, J = 9.5 Hz, 1H), 3.37 (s, 3H), 1.91 (s, 3H), 1.36 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.6, 137.9, 128.3 (2C), 127.7 (2C), 127.6, 112.2, 92.9, 80.6, 79.2, 73.8, 70.0, 63.5, 56.0, 25.7 (3C), 23.0, 21.7, 18.0, –5.81, –5.85; IR (film) ν_{max} 3467, 2928, 2856, 1472, 1254, 1070, 1023 cm^{-1}; HRMS (ESI) *m/z* 425.2719 (MH^+, $C_{23}H_{40}O_5SiH^+$ requires 425.2719).



188c

5-(Benzyloxy)-4-((*tert*-butyldimethylsilyloxy)methyl)-2,3-dimethyl-4-(triethylsilyloxy)pent-1-en-3-ol (188c). A solution of $LaCl_3$•2LiCl (0.59 M in THF, 160 μL, 0.0944 mmol) was added to a solution of ketone **187c** (8.3 mg, 0.0183 mmol) in anhydrous CH_2Cl_2 (260 μL) at 0 ºC under Ar, and the resultant mixture was stirred for 10 min. A solution of isopropenylmagnesium bromide (0.57 M in THF, 100 μL, 0.0570 mmol) was then added, and the mixture was stirred at 0 ºC for 1 h. The reaction was quenched with sat aq NH_4Cl (2 mL), diluted with H_2O (2 mL), and extracted with CH_2Cl_2 (5 × 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford crude **188c** in 7.7:1 dr as evidenced by ^{1}H NMR. Flash chromatography (2 mL of SiO_2, 2% EtOAc in hexanes elution) afforded pure **188c** (6.9 mg, 0.0139 mmol, 76%) as a mixture of diastereomers that was a colorless oil. Data for

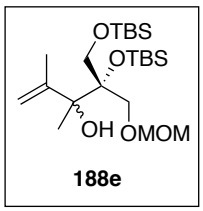
major isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.29 (m, 5H), 5.07 (s, 1H), 4.92 (s, 1H), 4.48 (d, J = 11.2 Hz, 1H), 4.41 (d, J = 11.2 Hz, 1H), 4.40 (s, 1H), 3.90 (d, J = 9.9 Hz, 1H), 3.84 (d, J = 9.9 Hz, 1H), 3.78 (d, J = 9.2 Hz, 1H), 3.63 (d, J = 9.2 Hz, 1H), 1.86 (s, 3H), 1.38 (s, 3H), 0.93–0.87 (m, 18H), 0.63–0.56 (m, 6H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.2, 137.6, 128.3 (2C), 128.1 (2C), 127.7, 112.0, 79.2, 79.1, 73.7, 70.9, 63.8, 25.9 (3C), 23.2, 21.8, 18.3, 7.1 (3C), 6.4 (3C), –5.6, –5.7; IR (film) ν_{max} 3481, 2954, 2876, 1472, 1256, 1131, 1071 cm^{-1}; HRMS (ESI) *m/z* 495.3324 (MH^+, $C_{27}H_{50}O_4Si_2H^+$ requires 495.3320).



188d

5-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-4-((*tert*-butyldiphenylsilyloxy) methyl)-2,3-dimethylpent-1-en-3-ol (188d). A solution of $LaCl_3$•2LiCl (0.59 M in THF, 110 μL, 0.0649 mmol) was added to a solution of ketone **187d** (7.4 mg, 0.0128 mmol) in anhydrous CH_2Cl_2 (180 μL) at 0 ºC under Ar, and the resultant mixture was stirred for 10 min. A solution of isopropenylmagnesium bromide (0.57 M in THF, 70 μL, 0.040 mmol) was then added, and the mixture was stirred at 0 ºC for 1 h. The reaction was quenched with sat aq NH_4Cl (2 mL), diluted with H_2O (2 mL), and extracted with CH_2Cl_2 (5 × 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford crude **188d** in 10:1 dr as evidenced by ^{1}H NMR. Flash chromatography (2 mL of SiO_2, 2% EtOAc in hexanes elution) afforded pure **188d** (7.8 mg, 0.0126 mmol, 98%) as a mixture of diastereomers that was a colorless oil. Data for major isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (dd, J = 8.1, 1.3 Hz, 2H), 7.64 (dd, J = 7.9, 1.2 Hz, 2H), 7.45–7.20 (m, 11H), 5.21 (d, J = 2.3 Hz, 1H), 4.93 (s, 1H), 4.92 (d, J = 0.9 Hz, 1H), 4.47 (d, J = 10.7 Hz, 1H), 4.42 (d, J = 10.7 Hz, 1H), 4.07 (d, J = 10.1 Hz, 1H), 3.89 (d, J = 10.0 Hz, 1H), 3.70 (d, J = 10.0 Hz, 1H), 3.58 (d, J = 10.1 Hz, 1H), 1.86 (s, 3H), 1.41 (s, 3H), 1.08 (s,

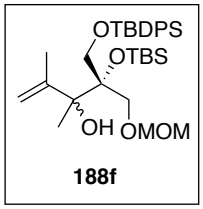
9H), 0.78 (s, 9H), –0.02 (s, 3H), –0.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.4, 137.5, 135.9 (2C), 135.7 (2C), 132.2, 131.9, 130.0, 129.6, 128.7 (2C), 128.2 (2C), 127.8 (2C), 127.7, 127.6 (2C), 112.4, 79.31, 79.28, 74.0, 71.6, 64.5, 26.8 (3C), 26.1 (3C), 24.0, 21.8, 19.1, 18.7, –2.2, –3.0; IR (film) ν_{max} 3467, 2954, 2929, 2857, 1472, 1428, 1253, 1114, 1071 cm^{-1}; HRMS (ESI) *m/z* 619.3645 (MH^+, $C_{37}H_{54}O_4Si_2H^+$ requires 619.3633).



188e

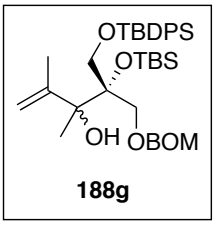
4,5-bis(*tert*-butyldimethylsilyloxy)-4-((methoxymethoxy)methyl)-2,3-dimethylpent-1-en-3-ol (188e). A solution of $LaCl_3$•2LiCl (0.59 M in THF, 250 μL, 0.148 mmol, 4.9 equiv) was added to a solution of ketone **187e** (12.2 mg, 0.0300 mmol) in anhydrous CH_2Cl_2 (410 μL) at 0 ºC under Ar, and the resultant mixture was stirred for 10 min. A solution of isopropenylmagnesium bromide (0.57 M in THF, 160 μL, 0.0912 mmol, 3.0 equiv) was then added, and the mixture was stirred at 0 ºC for 1 h. The reaction was quenched with sat aq NH_4Cl (2 mL), diluted with H_2O (2 mL), and extracted with CH_2Cl_2 (5 × 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford crude **188e** in 5.1:1 dr as evidenced by ^{1}H NMR. Flash chromatography (2 mL of SiO_2, 2% EtOAc in hexanes elution) afforded pure **188e** (12.1 mg, 0.0269 mmol, 90%) as a mixture of diastereomers that was a colorless oil. Data for major isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.12 (s, 1H), 4.90 (s, 1H), 4.63 (d, *J* = 6.6 Hz, 1H), 4.62 (d, *J* = 6.6 Hz, 1H), 4.51 (s, 1H), 3.91 (d, *J* = 10.3 Hz, 1H), 3.90 (d, *J* = 9.8 Hz, 1H), 3.78 (d, *J* = 9.8 Hz, 1H), 3.54 (d, *J* = 10.4 Hz, 1H), 3.38 (s, 3H), 1.85 (s, 3H), 1.40 (s, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.4, 112.5, 97.4, 79.6, 79.0, 69.0, 63.7, 55.9, 26.2 (3C), 25.8 (3C),

23.9, 21.7, 18.8, 18.2, –2.0, –2.6, –5.7, –5.8; IR (film) ν_{max} 3467, 2929, 2857, 1472, 1388, 1254, 1045 cm^{-1}; HRMS (ESI) *m/z* 449.3098 (MH^+, $C_{22}H_{48}O_5Si_2H^+$ requires 449.3113).



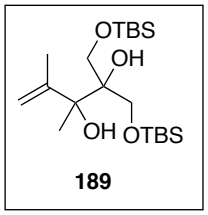
188f

(3*R,4*S**)-4-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-4-((methoxymethoxy)methyl)-2,3-dimethylpent-1-en-3-ol (188f)**. A solution of $LaCl_3$•2LiCl (0.59 M in THF, 1.8 mL, 1.06 mmol) was added to a solution of ketone **187f** (112.5 mg, 0.212 mmol) in anhydrous CH_2Cl_2 (1.1 mL) at 0 ºC under Ar. The resultant mixture was stirred at 0 ºC for 15 min, then treated with a solution of isopropenylmagnesium bromide (0.57 M in THF, 1.10 mL, 0.627 mmol). The resultant mixture was stirred at 0 ºC for 1 h, then treated with sat aq NH_4Cl (10 mL), diluted with H_2O (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford crude **3a** in 19:1 dr as evidenced by ^1H NMR. Flash chromatography (15 mL of SiO_2, 2% EtOAc in hexanes elution) afforded alcohol **188f** (116.0 mg, 0.203 mmol, 96%) as a white solid: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.72–7.66 (m, 4H), 7.49–7.37 (m, 6H), 5.20 (s, 1H), 4.91 (s, 1H), 4.78 (s, 1H), 4.55 (d, *J* = 6.2 Hz, 1H), 4.49 (d, *J* = 6.2 Hz, 1H), 4.03 (d, *J* = 10.7 Hz, 1H), 3.88 (d, *J* = 9.9 Hz, 1H), 3.73 (d, *J* = 9.9 Hz, 1H), 3.57 (d, *J* = 10.7 Hz, 1H), 3.30 (s, 3H), 1.84 (s, 3H), 1.42 (s, 3H), 1.10 (s, 9H), 0.78 (s, 9H), –0.04 (s, 3H), –0.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.1, 135.83 (2C), 135.75 (2C), 132.2, 131.9, 130.1, 130.0, 127.8 (2C), 127.7 (2C), 112.6, 97.5, 79.4, 79.1, 69.2, 64.3, 56.0, 26.9 (3C), 26.1 (3C), 24.1, 21.7, 19.1, 18.7, –2.2, –2.8; IR (film) ν_{max} 3471, 2930, 2888, 2857, 1472, 1428, 1249, 1114, 1045 cm^{-1}; HRMS (ESI) *m/z* 573.3395 (MH^+, $C_{32}H_{52}O_5Si_2H^+$ requires 573.3426).



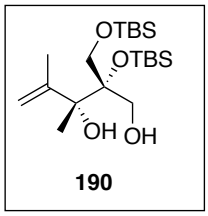
188g

5-(Benzyloxymethoxy)-4-(*tert*-butyldimethylsilyloxy)-4-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-dimethylpent-1-en-3-ol (188g). A solution of $LaCl_3$•2LiCl (0.59 M in THF, 260 μL, 0.153 mmol) was added to a solution of ketone **187g** (18.9 mg, 0.0311 mmol) in anhydrous CH_2Cl_2 (260 μL) at 0 ºC under Ar, and the resultant mixture was stirred for 10 min. A solution of isopropenylmagnesium bromide (0.57 M in THF, 160 μL, 0.0912 mmol) was then added, and the mixture was stirred at 0 ºC for 1 h. The reaction was quenched with sat aq NH_4Cl (2 mL), diluted with H_2O (2 mL), and extracted with CH_2Cl_2 (5 × 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford crude **188g** in >19:1 dr as evidenced by ^1H NMR. Flash chromatography (2 mL of SiO_2, 1–4% Et_2O in hexanes gradient elution) afforded pure **188g** (18.4 mg, 0.0284 mmol, 91%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.71–7.66 (m, 4H), 7.48–7.27 (m, 11H), 5.20 (d, *J* = 1.5 Hz, 1H), 4.91 (s, 1H), 4.76 (s, 1H), 4.67 (d, *J* = 6.5 Hz, 1H), 4.61 (d, *J* = 6.5 Hz, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.10 (d, *J* = 10.6 Hz, 1H), 3.90 (d, *J* = 9.9 Hz, 1H), 3.76 (d, *J* = 9.9 Hz, 1H), 3.65 (d, *J* = 10.6 Hz, 1H), 1.84 (s, 3H), 1.42 (s, 3H), 1.09 (s, 9H), 0.78 (s, 9H), –0.03 (s, 3H), –0.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.1, 137.7, 135.82 (2C), 135.75 (2C), 132.2, 132.0, 130.05, 130.00, 128.4 (2C), 127.8 (2C), 127.74 (2C), 127.72 (2C), 127.7, 112.6, 95.5, 79.5, 79.1, 69.8, 69.6, 64.5, 27.0 (3C), 26.1 (3C), 24.2, 21.7, 19.1, 18.7, –2.1, –2.7; IR (film) ν_{max} 3471, 2930, 2886, 2858, 1472, 1428, 1114, 1047 cm^{-1}; HRMS (ESI) *m/z* 671.3593 (MNa^+, $C_{38}H_{56}O_5Si_2Na^+$ requires 671.3558).



189

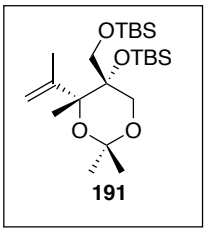
1-((*tert*-butyldimethylsilyl)oxy)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,4-dimethylpent-4-ene-2,3-diol (189). Ammonia (*ca*. 10 mL) was condensed into a 3-neck flask equipped with a stir bar at –78 ºC. Sodium metal (67.0, 2.9143 mmol) was added and stirred until the solution became dark blue. A solution of alcohol **188a** (28.3 mg, 0.0572 mmol) in anhydrous THF (200 µL) was added and the resultant mixture was stirred at –78 ºC for 1 h. MeOH (10 mL) was added and the ammonia was removed *in vacuo*. Flash chromatography (5 mL of SiO_2, 1–4% EtOAc in hexanes gradient elution) afforded diol **189** (15.5 mg, 0.03830 mmol, 67%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.08 (d, J = 1.3 Hz, 1H), 4.93 (t, J = 1.7 Hz, 1H), 4.08 (s, 1H), 3.84 (d, J = 9.8 Hz, 1H), 3.68 (d, J = 9.8 Hz, 1H), 3.64 (s, 2H), 2.97 (s, 1H), 1.89 (d, J = 0.7 Hz, 3H), 1.36 (s, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.5, 111.4, 78.8, 74.2, 64.0, 62.3, 25.81 (3C), 25.78 (3C), 22.6, 20.9, 18.1, 18.0, –5.5, –5.61, –5.63, –5.8; IR (film) ν_{max} 3494, 2955, 2885, 2858, 2741, 2712, 1639, 1471, 1390, 1362, 1331, 1255, 1191, 1082; HRMS (ESI) *m/z* 405.2869 (MH^+, $C_{20}H_{44}O_4Si_2H^+$ requires 405.2851).



190

(2S*,3R*)-2-((*tert*-butyldimethylsilyl)oxy)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3,4-dimethylpent-4-ene-1,3-diol (190). A solution of BCl_3 (1.0 M in CH_2Cl_2, 250 µL, 0.2500 mmol) was added to a solution of triether **188a** (105.1 mg, 0.2124 mmol), in anhydrous CH_2Cl_2 (2.1 mL) at –78 ºC under Ar over 10 min by syringe pump. The resultant mixture was

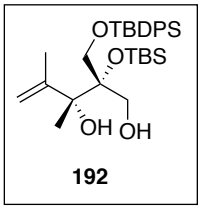
stirred at –78 ºC for 30 min then diluted with THF (1.0 mL) and saturated aq $NaHCO_3$ (250 μL). The mixture was stirred at –78 ºC for 5 min, at 0 ºC for 10 min, and at rt for 10 min then extracted with CH_2Cl_2 (3 × 10 mL). Combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (10 mL of SiO_2, 0–5% EtOAc in hexanes gradient elution) afforded diol **190** (65.5 mg, 0.1618 mmol, 76%) as a yellow solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.11 (s, 1H), 4.96 (s, 1H), 4.01 (s, 1H), 3.89–3.82 (m, 3H), 3.71 (d, *J* = 10.3 Hz, 1H), 2.42 (t, *J* = 6.0 Hz, 1H), 1.87 (s, 6H), 1.42 (s, 6H), 0.91 (s, 9H), 0.90 (s, 9H), 0.17 (s, 3H), 0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.9, 112.7, 80.3, 79.2, 66.5, 65.2, 26.2, 25.8, 23.9, 21.6, 18.7 (3C), 18.2 (3C), –2.1, –2.5, –5.70, –5.74; IR (film) ν_{max} 3384, 2954, 2930, 2892, 2857, 1471, 1254, 1093; HRMS (ESI) *m/z* 405.2867 (MH^+, $C_{20}H_{44}O_4Si_2H^+$ requires 405.2851).



191

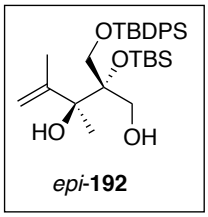
***tert*-butyl(((4R*,5S*)-5-((tert-butyldimethylsilyl)oxy)-2,2,4-trimethyl-4-(prop-1-en-2-yl)-1,3-dioxan-5-yl)methoxy)dimethylsilane (191).** A solution of diol **190** (24.0 mg, 0.0593 mmol), 2,2-dimethoxypropane (70 μL, 59.4 mg, 0.5706 mmol), and PPTS (1.5 mg, 0.0060 mmol) in anhydrous CH_2Cl_2 (1.2 mL) was stirred at rt under Ar for 18 h. Solid $NaHCO_3$ (10 mg) was added and the mixture was filtered through celite. The filtrate was concentrated *in vacuo*. Flash chromatography (3 mL of SiO_2, 1% EtOAc in hexanes elution) afforded acetonide **191** (13.9 mg, 0.0313 mmol, 53%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.27 (d, *J* = 1.7 Hz, 1H), 4.92 (s, 1H), 3.99 (d, *J* = 11.8 Hz, 1H), 3.97 (d, *J* = 10.4 Hz, 1H), 3.87 (d, *J* = 11.8 Hz, 1H), 3.67 (d, *J* = 10.4 Hz, 1H), 1.82 (s, 3H), 1.49 (s, 3H), 1.44 (s, 3H), 1.36 (s, 3H), 0.93 (s, 9H), 0.85 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.3,

112.6, 98.9, 81.0, 76.4, 66.0, 62.1, 27.8, 26.8, 26.0 (6C), 23.5, 21.6, 18.7, 18.5, –2.34, –2.35, –5.43, –5.44; 2D $^{1}H–^{13}C$ HSQC NMR ($CDCl_3$, 500 MHz) δ 5.27/112.6, 4.92/112.6, 3.99/62.1, 3.97/66.0, 3.87/62.1, 3.67/66.0, 1.82/21.6, 1.49/26.8, 1.44/27.8, 1.36/23.5, 0.93/26.0, 0.85/26.0, 0.17/–2.34, 0.13/–2.35, 0.10/–5.43, 0.10/–5.44; 2D $^{1}H–^{13}C$ HMBC NMR ($CDCl_3$, 500 MHz) δ 5.27/81.0, 5.27/21.6, 4.92/81.0, 4.92/21.6, 3.99/98.9, 3.99/81.0, 3.99/62.1, 3.97/62.1, 3.87/98.9, 3.87/81.0, 3.87/66.0, 3.87/62.1, 3.67/81.0, 3.67/62.1, 1.82/148.3, 1.82/112.6, 1.82/81.0, 1.49/98.9, 1.49/27.8, 1.44/98.9, 1.44/26.8, 1.36/148.3, 1.36/81.0, 1.36/76.4, 0.93/26.0, 0.93/18.5, 0.85/26.0, 0.85/18.7; NOE NMR ($CDCl_3$, 500 MHz): irradiation of the signal at 5.27 enhanced the signals at 4.92 (s), 3.97 (w), 3.87 (m), 3.67 (w), 1.49 (w), 1.36 (m), 0.85 (w), 0.17 (w); irradiation of the signal at 4.92 enhanced the signals at 5.27 (s), 1.82 (m), and 0.85 (w); irradiation of the signal at 3.99 enhanced the signals at 3.87 (s), 1.44 (w), and 1.35 (w); irradiation of the signal at 3.97 enhanced the signals at 3.67 (s), 1.82 (w), 1.44 (w), 1.36 (m), 0.93 (w), 0.85 (w), and 0.10 (w); irradiation of the signal at 3.87 enhanced the signals at 3.99 (s), 3.67 (w), 1.49 (m), 0.93 (w), 0.85 (w), 0.17 (w), 0.13 (w); irradiation of the signal at 3.67 enhanced the signals at 3.97 (s), 1.82 (w), 1.36 (m), 0.93 (w), 0.85 (w), 0.17 (w), 0.13 (w), and 0.10 (w); irradiation of the signal at 1.82 enhanced the signals at 5.27 (w), 4.92 (s), 3.97 (w), 3.67 (m), 1.49 (m), 1.36 (s), 0.93 (w), 0.85 (m), 0.17 (w), 0.13 (w), and 0.10 (w); irradiation of the signal at 1.49 enhanced the signals at 3.87 (m), 1.82 (m), 1.44 (m), 0.85 (w), and 0.17 (w); irradiation of the signal at 3.99 enhanced the signals at 3.99 (m), 1.49 (s), 1.36 (s), 0.93 (w), 0.85 (w), and 0.10 (w); irradiation of the signal at 1.36 enhanced the signals at 3.99 (w), 3.97 (m), 3.67 (m), 1.82 (m), and 1.44 (m); HRMS (ESI) *m/z* 445.3159 (MH^+, $C_{23}H_{48}O_4Si_2H^+$ requires 445.3164).



192

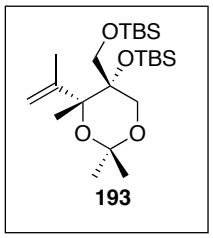
(2*S,3*R**)-2-(*tert*-Butyldimethylsilyloxy)-2-((*tert*-butyldiphenylsilyloxy) methyl)-3,4-dimethylpent-4-ene-1,3-diol (192).** A solution of BCl_3 (1.0 M in CH_2Cl_2, 40 μL, 0.040 mmol) was added to a solution of triether **188f** (22.7 mg, 0.0396 mmol) and pentamethylbenzene (29.6 mg, 0.200 mmol) in anhydrous CH_2Cl_2 (800 μL) at –78 ºC under Ar. The resultant mixture was stirred for 1 h at –78 ºC, then the reaction was quenched with sat aq $NaHCO_3$ (2 mL), diluted with H_2O (1 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (6 mL of SiO_2, 0–4% EtOAc in hexanes gradient elution) afforded diol **192** (17.1 mg, 0.0323 mmol, 82%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70–7.64 (m, 4H), 7.50–7.39 (m, 6H), 5.15 (d, *J* = 1.5 Hz, 1H), 4.96 (s, 1H), 4.19 (s, 1H), 3.90 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.86 (d, *J* = 10.4 Hz, 1H), 3.80 (dd, *J* = 12.0, 6.7 Hz, 1H), 3.58 (d, *J* = 10.4 Hz, 1H), 2.13 (t, *J* = 6.3 Hz, 1H), 1.86 (s, 3H), 1.45 (s, 3H), 1.10 (s, 9H), 0.80 (s, 9H), 0.02 (s, 3H), –0.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.9, 135.8 (2C), 135.7 (2C), 132.2, 132.0, 130.2, 130.1, 128.0 (2C), 127.9 (2C), 112.7, 80.2, 79.3, 66.9, 65.0, 26.9 (3C), 26.1 (3C), 24.1, 21.5, 19.1, 18.6, –2.3, –2.8; IR (film) ν_{max} 3467, 3072, 3052, 2954, 2930, 2858, 1472, 1428, 1252, 1114 cm^{-1}; HRMS (ESI) *m/z* 529.3161 (MH^+, $C_{30}H_{48}O_4Si_2H^+$ requires 529.3164).



epi-192

(2*S,3*R**)-2-(*tert*-butyldimethylsilyloxy)-2-((*tert*-butyldiphenylsilyloxy) methyl)-3,4-dimethylpent-4-ene-1,3-diol (*epi*-192).** Prepared from a mixture of **188f** and *epi*-

188f (1:2.8 dr, 78.4 mg, 0.137 mmol) using the same procedure outlined for the synthesis of **192**. Afforded diol *epi*-**192** (41.7 mg, 0.0788 mmol, 58%) as a colorless oil and **192** (15.0 mg, 0.0284 mmol, 21%) as white film. Data for *epi*-**192**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.65 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.49–7.39 (m, 6H), 5.08 (s, 1H), 4.94 (t, *J* = 1.4 Hz, 1H), 3.97 (dd, *J* = 12.0, 5.8 Hz, 1H), 3.86 (d, *J* = 10.3 Hz, 1H), 3.82 (dd, *J* = 12.0, 7.3 Hz, 1H), 3.71 (s, 1H), 3.60 (d, *J* = 10.3 Hz, 1H), 2.05 (dd, *J* = 7.3, 5.8 Hz, 1H), 1.82 (d, *J* = 0.5 Hz, 3H), 1.34 (s, 3H), 1.10 (s, 9H), 0.85 (s, 9H), 0.06 (s, 3H), –0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.0, 135.8 (2C), 135.7 (2C), 132.23, 132.21, 130.2, 130.1, 128.0 (2C), 127.9 (2C), 112.5, 80.5, 79.9, 66.9, 64.3, 27.0 (3C), 26.1 (3C), 23.0, 21.6, 19.1, 18.8, –2.3, –2.6; IR (film) ν_{max} 3423, 3072, 3052, 2958, 2931, 2893, 2857, 1472, 1428, 1251, 1114 cm^{-1}; HRMS (ESI) *m/z* 529.3173 (MH^+, $C_{30}H_{48}O_4Si_2H^+$ requires 529.3164).

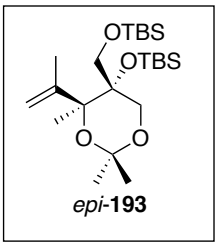


193

***tert*-Butyl(((4*R**,5*S**)-5-(*tert*-butyldimethylsilyloxy)-2,2,4-trimethyl-4-(prop-1-en-2-yl)-1,3-dioxan-5-yl)methoxy)diphenylsilane (193)**. A solution of diol **192** (5.4 mg, 0.010 mmol), 2,2-dimethoxypropane (20.0 μL, 17.0 mg, 0.163 mmol), and TsOH•H_2O (0.4 mg, 0.002 mmol) in CH_2Cl_2 (1.0 mL) was stirred at rt for 1 h. The reaction was quenched with solid $NaHCO_3$ (10 mg) and then filtered through Celite (1.0 mL, rinsed with 10 mL of CH_2Cl_2). The filtrate was concentrated *in vacuo*. Flash chromatography (1.0 mL of SiO_2, 0–3% EtOAc in hexanes gradient elution) afforded acetonide **193** (3.8 mg, 0.0067 mmol, 65%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.66 (d, *J* = 7.8 Hz, 2H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.47–7.37 (m, 6H), 4.93 (s, 1H), 4.81 (s, 1H), 4.19 (d, *J* = 12.7 Hz, 1H), 3.86 (d, *J* = 10.9 Hz, 1H), 3.67 (d, *J* =

12.7 Hz, 1H), 3.48 (d, J = 10.9 Hz, 1H), 1.75 (s, 3H), 1.44 (s, 6H), 1.41 (s, 3H), 1.09 (s, 9H), 0.76 (s, 9H), 0.08 (s, 3H), –0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.4, 135.81 (2C), 135.80 (2C), 132.90, 132.86, 129.9, 129.8, 127.7 (4C), 111.3, 98.3, 81.8, 75.5, 67.1, 62.8, 29.6, 27.0 (3C), 25.9 (3C), 25.8, 25.2, 22.1, 19.2, 18.5, –2.4, –2.5; 2D ^{1}H–^{13}C HSQC NMR ($CDCl_3$, 500 MHz) δ 7.66–7.64/135.81, 7.66–7.64/135.80, 7.47–7.39/129.9, 7.47–7.39/129.8, 7.44–7.37/127.7, 4.93/111.3, 4.81/111.3, 4.19/62.8, 3.86/67.1, 3.67/62.8, 3.48/67.1, 1.75/22.1, 1.44/29.6, 1.44/25.8, 1.41/25.2, 1.09/27.0, 0.76/25.9, 0.08/–2.5, –0.09/–2.4; 2D ^{1}H–^{13}C HMBC NMR ($CDCl_3$, 500 MHz) δ 7.66–7.64/135.81, 7.66–7.64/135.80, 7.66–7.64/132.90, 7.66–7.64/132.86, 7.66–7.64/129.9, 7.66–7.64/129.8, 7.47–7.39/135.81, 7.47–7.39/135.80, 7.44–7.37/132.90, 7.44–7.37/132.86, 7.44–7.37/132.90, 7.44–7.37/127.7, 4.93/149.4, 4.93/81.8, 4.93/22.1, 4.81/81.8, 4.81/22.1, 4.19/98.3, 3.86/62.8, 3.67/98.3, 3.67/81.8, 3.67/75.5, 3.48/81.8, 3.48/75.5, 3.48/62.8, 1.75/149.4, 1.75/111.3, 1.75/81.8, 1.44/149.4, 1.44/98.3, 1.44/29.7, 1.44/25.8, 1.41/81.8, 1.41/75.5, 1.09/27.0, 1.09/19.2, 0.76/25.8, 0.76/18.5, 0.08/18.5, 0.08/–2.4, –0.09/18.5, –0.09/–2.5; NOE NMR ($CDCl_3$, 500 MHz): irradiation of the signal at 4.93 enhanced the signals at 4.81 (s), 3.86 (m), 3.67 (w), 3.48 (w), 1.75 (w), 1.44 (w), 1.41 (s), 0.76 (w), and 0.08 (w); irradiation of the signal at 4.81 enhanced the signals at 4.93 (s), 1.75 (s), and 0.76 (w); irradiation of the signal at 4.19 enhanced the signals at 7.66 (w), 3.86 (w), 3.67 (s), 3.48 (w), 1.44 (s), 1.41 (m), and 1.09 (w); irradiation of the signal at 3.86 enhanced the signals at 7.66 (m), 4.93 (s), 4.19 (w), 3.48 (s), 1.75 (m), 1.41 (m), 1.09 (w), and 0.76 (w); irradiation of the signal at 3.67 enhanced the signals at 7.64 (w), 4.93 (w), 4.19 (s), 3.48 (w), 1.41 (w), 1.09 (w), 0.76 (w), 0.08 (w), and –0.09 (m); irradiation of the signal at 3.48 enhanced the signals at 7.64 (m), 4.93 (w), 4.19 (w), 3.86 (s), 3.67 (m), 1.75 (m), 1.41 (w), 1.09 (w), 0.76 (m), 0.08 (w), and –0.09 (m); irradiation of the signal at 1.75 enhanced the signals at 4.81 (s), 3.86 (m), 3.48 (m), 1.44 (w),

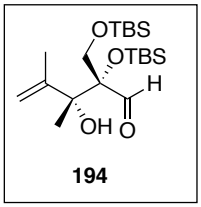
1.41 (m), 0.75 (m), 0.08 (w), –0.09 (w); irradiation of the signal at 1.44 enhanced the signal at 4.19 (m); irradiation of the signal at 1.41 enhanced the signals at 4.93 (s), 4.19 (m), 3.87 (m), 1.75 (m), 1.44 (m), 1.09 (w); IR (film) ν_{max} 3077, 3052, 2958, 2930, 2893, 2857, 1472, 1428, 1378, 1246, 1190, 1159, 1113, 1072 cm^{-1}; HRMS (ESI) *m/z* 569.3472 (MH^+, $C_{33}H_{52}O_4Si_2H^+$ requires 569.3477).



epi-**193**

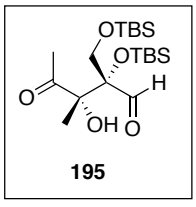
***tert*-Butyl(((4*S**,5*S**)-5-(*tert*-butyldimethylsilyloxy)-2,2,4-trimethyl-4-(prop-1-en-2-yl)-1,3-dioxan-5-yl)methoxy)diphenylsilane (*epi*-193)**. A solution of *epi*-**192** (41.7 mg, 0.0788 mmol), 2,2-dimethoxypropane (100 μL, 84.7 mg, 0.813 mmol), and PPTS (2.3 mg, 0.0092 mmol) in anhydrous CH_2Cl_2 (1.0 mL) at rt under Ar was stirred for 24 h. The reaction was quenched with solid $NaHCO_3$ (20 mg) and then filtered through Celite (1.0 mL, rinsed with 10 mL of CH_2Cl_2). The filtrate was concentrated *in vacuo*. Flash chromatography (4 mL of SiO_2, 0–3% EtOAc in hexanes gradient elution) afforded acetonide *epi*-**193** (33.1 mg, 0.0582 mmol, 74%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.73 (d, *J* = 6.8 Hz, 2H), 7.69 (d, *J* = 6.8 Hz, 2H), 7.44–7.32 (m, 6H), 4.89 (d, *J* = 1.8 Hz, 1H), 4.64 (s, 1H), 4.22 (d, *J* = 10.9 Hz, 1H), 3.97 (d, *J* = 11.1 Hz, 1H), 3.73 (d, *J* = 10.9 Hz, 1H), 3.38 (d, *J* = 11.1 Hz, 1H), 1.70 (s, 3H), 1.53 (s, 3H), 1.48 (s, 3H), 1.22 (s, 3H), 1.10 (s, 9H), 0.89 (s, 9H), 0.23 (s, 3H), 0.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.3, 136.3 (2C), 135.9 (2C), 133.7, 133.0, 129.48, 129.45, 127.40 (2C), 127.36 (2C), 111.9, 98.2, 80.4, 74.6, 66.1, 59.3, 30.8, 27.2 (3C), 25.9 (3C), 24.5, 22.8, 21.0, 19.2, 18.6, –1.6, –2.3; 2D ^1H–^{13}C HSQC NMR ($CDCl_3$, 500 MHz) δ 7.73/136.3, 7.69/135.9, 7.44–7.36/129.48, 7.44–7.36/129.45, 7.41–7.32/127.40, 7.41–7.32/127.36,

4.89/111.9, 4.64/111.9, 4.22/59.3, 3.97/66.1, 3.73/59.3, 3.38/66.1, 1.70/21.0, 1.53/24.5, 1.48/22.8, 1.22/30.8, 1.10/27.2, 0.89/25.9, 0.23/–1.6, 0.11/–2.3; 2D $^{1}H–^{13}C$ HMBC NMR ($CDCl_3$, 500 MHz) δ 7.73/136.3, 7.73/129.45, 7.69/135.9, 7.69/129.48, 7.44–7.36/136.3, 7.41–7.32/133.0, 7.41–7.32/127.40, 7.41–7.32/127.36, 4.89/146.3, 4.89/80.4, 4.89/21.0, 4.64/80.4, 4.64/21.0, 4.22/98.2, 4.22/80.4, 4.22/74.6, 4.22/66.1, 3.97/80.4, 3.73/80.4, 3.73/74.6, 3.73/66.1, 3.38/74.6, 3.38/59.3, 1.70/146.3, 1.70/111.9, 1.70/80.4, 1.53/98.2, 1.53/30.8, 1.48/146.3, 1.48/80.4, 1.48/74.6, 1.22/98.2, 1.22/24.5, 1.10/27.2, 1.10/19.2, 0.89/25.9, 0.89/18.6, 0.23/18.6, 0.23/–2.3, 0.11/18.6, 0.11/–1.6; NOE NMR ($CDCl_3$, 500 MHz): irradiation of the signal at 4.89 enhanced the signals at 4.64 (s), 3.97 (m), 3.38 (w), 1.48 (m), 1.22 (m), and 0.89 (w); irradiation of the signal at 4.64 enhanced the signals at 4.89 (s), 3.97 (w), 3.38 (w), and 1.70 (m); irradiation of the signal at 4.22 enhanced the signals at 7.73 (w), 7.69 (w), 3.97 (w), 3.73 (s), 1.10 (w), 0.23 (m), and 0.11 (w); irradiation of the signal at 3.97 enhanced the signals at 7.73 (m), 7.69 (w), 4.89 (m), 4.22 (w), 3.38 (s), 1.22 (w), and 1.10 (w); irradiation of the signal at 3.73 enhanced the signals at 4.22 (s), 1.53 (s), 1.48 (s), 0.89 (w), and 0.23 (m); irradiation of the signal at 3.38 enhanced the signals at 7.73 (w), 7.69 (m), 4.89 (w), 4.64 (w), 4.22 (w), 3.97 (s), 1.70 (s), 1.10 (w), 0.89 (w), 0.11 (m); irradiation of the signal at 1.70 enhanced the signals at 4.64 (m), 3.38 (m), 1.48 (m), 0.89 (w), and 0.11 (w); irradiation of the signal at 1.53 enhanced the signals at 3.73 (m), 1.48 (m), and 1.22 (m); irradiation of the signal at 1.48 enhanced the signals at 4.89 (w) 3.73 (m), 1.70 (m), 1.53 (m), 0.89 (w), and 0.23 (w); irradiation of the signal at 1.22 enhanced the signal at 1.53 (m); IR (film) ν_{max} 3073, 3052, 2999, 2956, 2931, 2885, 2858, 1473, 1428, 1245, 1198, 1113, 1051 cm^{-1}; HRMS (ESI) *m/z* 569.3472 (MH^+, $C_{33}H_{52}O_4Si_2H^+$ requires 569.3477).



194

(2S*,3R*)-2-((tert-butyldimethylsilyl)oxy)-2-(((tert-butyldimethylsilyl)oxy) methyl)-3-hydroxy-3,4-dimethylpent-4-enal (194). 2-Iodoxybenzoic acid (87.2 mg, 0.3114 mmol) was added to a solution of diol **190** (41.7 mg, 0.1030 mmol) in anhydrous DMSO (3 mL) at rt under Ar. The resultant mixture was stirred for 18 h then was diluted with EtOAc (10 mL) and washed with H_2O (4 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford crude **194** (*ca*. 41.5 mg, 0.1030 mmol) as a colorless oil. The crude material was used directly without further purification. Data for **194**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.88 (s, 1H), 5.07 (s, 1H), 4.97 (s, 1H), 4.13 (d, *J* = 10.5 Hz, 1H), 3.87 (s, 1H), 3.76 (d, *J* = 10.5 Hz, 1H), 1.80 (s, 3H), 1.41 (s, 3H), 0.90 (s, 18H), 0.18 (s, 3H), 0.11 (s, 3H), 0.09 (s, 6H); ^{13}C NMR (125 MHz) δ 203.6, 147.3, 113.8, 85.0, 78.7, 65.8, 26.1 (3C), 25.8 (3C), 23.7, 21.0, 18.8, 18.4, –2.6, –2.8, –5.69, –5.70; IR (film) ν_{max} 3476, 2955, 2930, 2885, 2857, 1737, 1471, 1362, 1255, 1099; HRMS (ESI) *m/z* 403.2720 (MH^+, $C_{20}H_{42}O_4Si_2H^+$ requires 403.2694).

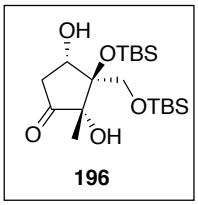


195

(2S*,3S*)-2-((tert-butyldimethylsilyl)oxy)-2-(((tert-butyldimethylsilyl)oxy) methyl)-3-hydroxy-3-methyl-4-oxopentanal (195). A solution of aldehyde **194** (*ca.* 41.5 mg, 0.1030 mmol), pyridine (20 μL, 19.6 mg, 0.2473 mmol), and Sudan IV (1 drop of saturated solution in CH_2Cl_2) in anhydrous CH_2Cl_2 (5.0 mL) at –78 ºC was stirred under a stream of ozone gas until the indicator was discharged. The solution was purged with Ar for 5 min, treated with Me_2S (820 μL, 693.7 mg, 11.1656 mmol). The resultant mixture was allowed to warm slowly to rt as it stirred for 18 h. The resultant solution was concentrated *in vacuo* to afford γ-ketoaldehyde

195 (*ca*. 41.7 mg, 0.1030 mmol) as a yellow oil, which was used directly without further purification. Data for **195**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.75 (s, 1H), 4.23 (d, J = 10.5 Hz, 1H), 3.80 (d, J = 10.5 Hz, 1H), 2.63 (s, 1H), 2.29 (s, 3H), 1.32 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.19 (s, 3H), 0.10 (s, 3H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 210.8, 202.1, 85.4, 82.9, 65.1, 26.6, 25.96 (3C), 25.91 (3C), 21.3, 18.7, 18.5, –2.76, –2.81, –5.7 (2C); HRMS (ESI) *m/z* 405.2482 (MH^+, $C_{19}H_{40}O_5Si_2H^+$ requires 405.2487).

Intramolecular Aldol Cyclization. To a solution of azeotropically dried γ-ketoaldehyde **195** (*ca*. 41.7 mg, 0.1030 mmol) in anhydrous CH_2Cl_2 (5.0 mL) at 0 ºC under Ar was added *N,N*-diisopropylethylamine (50 μL, 37.1 mg, 0.2870 mmol) and freshly distilled TMS-Cl (7.0 μL, 6.0 mg, 0.0554 mmol). The resultant mixture was stirred at 0 ºC for 5 min. A solution of $TiCl_4$ (1.0 M in CH_2Cl_2, 100 μL, 0.100 mmol) was added rapidly (<5 seconds) and the solution was stirred for 2 min at 0 ºC. The reaction was quenched with H_2O (5 mL), stirred vigorously for 10 min. and extracted with CH_2Cl_2 (3 × 5 mL). Combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (6 mL of SiO_2, 1–10% EtOAc in hexanes) afforded enone **197** (4.4 mg, 0.0114 mmol, 11%), diol **196** (14.1 mg, 0.0347 mmol, 30%) and diol *epi*-**196** (4.8 mg, 0.0120 mmol, 14%).

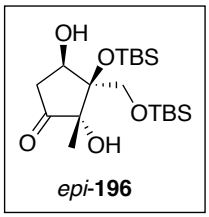


196

Data for **(2S*,3R*,4S*)-3-((tert-butyldimethylsilyl)oxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-2,4-dihydroxy-2-methylcyclopentan-1-one (196):** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.40–4.34 (m, 1H), 4.01 (d, J = 9.9 Hz, 1H), 3.92 (d, J = 9.9 Hz, 1H), 3.04 (s, 1H), 2.88 (dd, J = 19.4 Hz, 8.9 Hz, 1H) 2.46, (d, J = 2.5 Hz, 1H), 2.34 (dd, J = 19.4 Hz, 4.6 Hz, 1H), 1.21 (s, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.17 (s, 6H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C

NMR ($CDCl_3$, 125 MHz) δ 213.0, 84.5, 81.1, 73.5, 62.5, 43.0, 25.82 (3C), 25.76 (3C), 18.6, 18.4, 18.2, –2.5, –2.6, –5.8 (2C); 2D $^1H–^{13}C$ HSQC NMR ($CDCl_3$, 500 MHz) δ 4.40–4.34/73.5, 4.01/62.5, 3.92/62.5, 2.88/43.0, 2.34/43.0, 1.21/18.6, 0.90/25.82, 0.86/25.76, 0.17/–2.5, 0.17/–2.6,

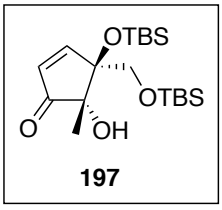
0.11/–5.8, 0.09/–5.8; NOE NMR ($CDCl_3$, 500 MHz): irradiation of the signal at 4.40–4.34 enhanced the signals at 4.01 (w), 3.92 (w), 2.88 (s), 2.46 (w), 2.34 (w), 1.21 (m), 0.90 (w), 0.86 (w), and 0.17 (m); irradiation of the signal at 4.01 enhanced the signals at 3.92 (s), 3.04 (m), 1.21 (w), 0.90 (w), 0.86 (w), 0.17 (m), 0.11 (m), and 0.9 (m); irradiation of the signal at 3.92 enhanced the signals at 4.01 (s), 1.21 (m), 0.90 (w), 0.86 (w), 0.17 (m), 0.11 (w), and 0.09 (w); irradiation of the signal at 2.88 enhanced the signals at 4.40–4.34 (s), 2.34 (s), 1.21 (m), and 0.86 (m); irradiation of the signal at 2.34 enhanced the signals at 4.40–4.34 (w) and 2.88 (s); irradiation of the signal at 1.21 enhanced the signals at 4.40–4.34 (m), 0.86 (w), and 0.17 (w); IR (film) ν_{max} 3444, 2955, 2930, 2886, 2858, 1755, 1472, 1468, 1389, 1361, 1254, 1158, 1097; HRMS (ESI) *m/z* 405.2510 (MH^+, $C_{19}H_{40}O_5Si_2H^+$ requires 405.2487).



epi-**196**

Data for **(2S*,3R*,4R*)-3-((tert-butyldimethylsilyl)oxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-2,4-dihydroxy-2-methylcyclopentan-1-one (*epi*-196)**: ^1H NMR ($CDCl_3$, 500 MHz) δ 4.27–4.23 (m, 1H), 4.01 (d, *J* = 8.6 Hz, 1H), 3.55 (d, *J* = 8.6 Hz, 1H), 2.88 (s, 1H), 2.713 (dd, *J* = 19.4 Hz, 1H), 2.710 (s, 1H), 2.50 (dd, *J* = 19.4 Hz, 2.3 Hz, 1H), 1.31 (s, 3H), 0.94 (s, 9H), 0.86 (s, 9H), 0.26 (s, 3H), 0.18 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.1, 82.3, 79.7, 70.7, 66.1, 42.7, 26.0 (3C), 25.7 (3C), 21.1, 18.6, 18.2, –1.7, –2.4, –5.89, –5.92; 2D $^1H–^{13}C$ HSQC NMR ($CDCl_3$, 500 MHz) δ 4.27–4.23/70.7, 4.01/66.1, 3.55/66.1,

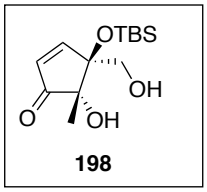
2.713/42.7, 2.50/42.7, 1.31/21.1, 0.94/26.0, 0.86/25.7, 0.26/–2.4, 0.18/–1.7, 0.05/–5.89, 0.03/–5.92; NOE NMR ($CDCl_3$, 500 MHz): irradiation of the signal at 4.27–4.23 enhanced the signals at 4.01 (w), 3.55 (s), 2.88 (s), 2.713 (m), 2.50 (w), 1.31 (w), 0.94 (w), 0.86 (w), 0.18 (w), 0.05 (w), and 0.03 (w); irradiation of the signal at 4.01 enhanced the signals at 4.27–4.23 (w), 3.55 (s), 2.710 (m), 1.31 (w), 0.94 (w), 0.86 (w), 0.26 (m), 0.18 (m), 0.05 (w), and 0.03 (w); irradiation of the signal at 3.55 enhanced the signals at 4.27–4.23 (s), 4.01 (s), 2.88 (w), 2.710 (w), 1.31 (w), 0.94 (w), 0.86 (w), 0.26 (w), 0.18 (m), 0.05 (w), and 0.03 (w); irradiation of the signal at 2.88 enhanced the signals at 4.27–4.23 (m), 3.55 (w), 2.710 (m, inverted), 2.50 (w), 1.31 (m), 0.94 (m), 0.26 (w), and 0.18 (w); irradiation of the signal at 2.713 enhanced the signals at 4.27–4.23 (s), 2.50 (s), and 0.86 (w); irradiation of the signal at 2.50 enhanced the signals at 4.27–4.23 (m), 2.88 (m), 2.713 (s), 1.31 (m), and 0.94 (w); irradiation of the signal at 1.31 enhanced the signals at 2.88 (m), 2.710 (m), 0.94 (w), and 0.26 (w); IR (film) ν_{max} 3446, 2954, 2930, 2885, 2858, 1755, 1472, 1389, 1362, 1255, 1138, 1094; HRMS (ESI) *m/z* 405.2522 (MH^+, $C_{19}H_{40}O_5Si_2H^+$ requires 405.2487).



197

Data for **(4S,5S)-4-((tert-butyldimethylsilyl)oxy)-4-(((tert-butyldimethylsilyl)oxy)methyl)-5-hydroxy-5-methylcyclopent-2-en-1-one (197):** ^1H NMR ($CDCl_3$, 500 MHz) δ 7.19 (d, *J* = 6.5 Hz, 1H), 6.36 (d, *J* = 6.5 Hz, 1H), 3.89 (d, *J* = 9.3 Hz, 1H), 3.59 (d, *J* = 9.3 Hz, 1H), 3.12 (s, 1H), 1.25 (s, 3H), 0.91 (s, 9H), 0.82 (s, 9H), 0.19 (s, 3H), 0.15 (s, 3H), 0.03 (s, 3H), –0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.3, 158.7, 132.6, 84.4, 82.7, 65.5, 25.7 (3C), 25.6 (3C), 22.0, 18.3, 18.0, –2.0, –2.3, –5.6, –5.7; 2D ^1H–^{13}C HSQC NMR ($CDCl_3$, 500 MHz) δ 7.19/158.7, 6.36/132.6, 3.89/65.5, 3.59/65.5, 1.25/22.0, 0.91/25.7, 0.82/25.6, 0.19/–2.0,

0.15/–2.3, 0.03/–5.7, –0.02/–5.6; NOE NMR ($CDCl_3$, 500 MHz): irradiation of the signal at 7.19 enhanced the signals at 6.36 (s), 3.59 (m), 1.25 (w), 0.91 (w), 0.82 (w), 0.19 (m), 0.15 (m), 0.03 (w), and –0.02 (w); irradiation of the signal at 6.36 enhanced the signals at 7.19 (s), 1.25 (w), 0.91 (w), 0.82 (w), 0.19 (w), 0.15 (w), 0.03 (w), and –0.02 (w); irradiation of the signal at 3.89 enhanced the signals at 3.59 (s), 3.12 (m), 1.25 (w), 0.91 (m), 0.82 (m), 0.19 (m), 0.15 (w), 0.03 (m), and –0.02 (w); irradiation of the signal at 3.59 enhanced the signals at 3.89 (s), 0.91 (w), 0.82 (w), 0.19 (m), 0.15 (w), 0.03 (w), and –0.02 (w); irradiation of the signal at 1.25 enhanced the signals at 7.19 (m), 6.36 (m), 3.89 (m), 3.59 (w), 3.12 (s), 0.91 (s), 0.82 (w), 0.19 (m), 0.15 (s), 0.03 (w), and –0.02 (w); IR (film) ν_{max} 2337, 2924, 2853, 1733, 1463, 1258, 1129; HRMS (ESI) *m/z* 387.2407 (MH^+, $C_{19}H_{38}O_4Si_2H^+$ requires 387.2381).



198

(4S*,5S*)-4-((tert-butyldimethylsilyl)oxy)-5-hydroxy-4-(hydroxymethyl)-5-methylcyclopent-2-en-1-one (198). A solution of diol **196** (2.9:1 dr, 17.9 mg, 0.0442 mmol) in AcOH–THF–H_2O (3:1:1, 5 mL) was stirred at 80 ºC for 3 days. The reaction was cooled to rt, diluted with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). Combined extracts were washed with saturated aq $NaHCO_3$ (2 × 30 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (1.5 mL of Florisil®, 5–15% EtOAc in hexanes) afforded **198** (7.5 mg, 0.0275 mmol, 62%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31 (d, *J* = 6.2 Hz, 1H), 6.39 (d, *J* = 6.2 Hz, 1H), 3.90 (d, *J* = 11.2 Hz, 1H), 3.57 (d, *J* = 11.2 Hz, 1H), 2.88 (br s, 1H), 2.02 (br s, 1H), 1.25 (s, 3H), 0.91 (s, 9H), 0.21 (s, 3H), 0.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.8, 160.9, 131.8, 84.4, 82.9, 67.0, 25.7 (3C), 23.3, 18.4, –2.2, –2.4; IR (film) ν_{max} 3419, 2928, 2856, 1716, 1463, 1361, 1255, 1132; HRMS (ESI) *m/z* 273.1554 (MH^+, $C_{13}H_{24}O_4SiH^+$ requires 273.1517.

6.3 References

(1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

(2) Hernandez, A.-I.; Balzarini, J.; Karlsson, A.; Camarasa, M.-J.; Perez-Perez, M.-J. *J. Med. Chem.* **2002**, *45*, 4254–4263

(3) Wang, Z.-X.; Shu, L.; Frohn, M.; Tu, Y.; Shi, Y. *Org. Syn.* **2009**, *Coll. Vol. 11*, 183–188.

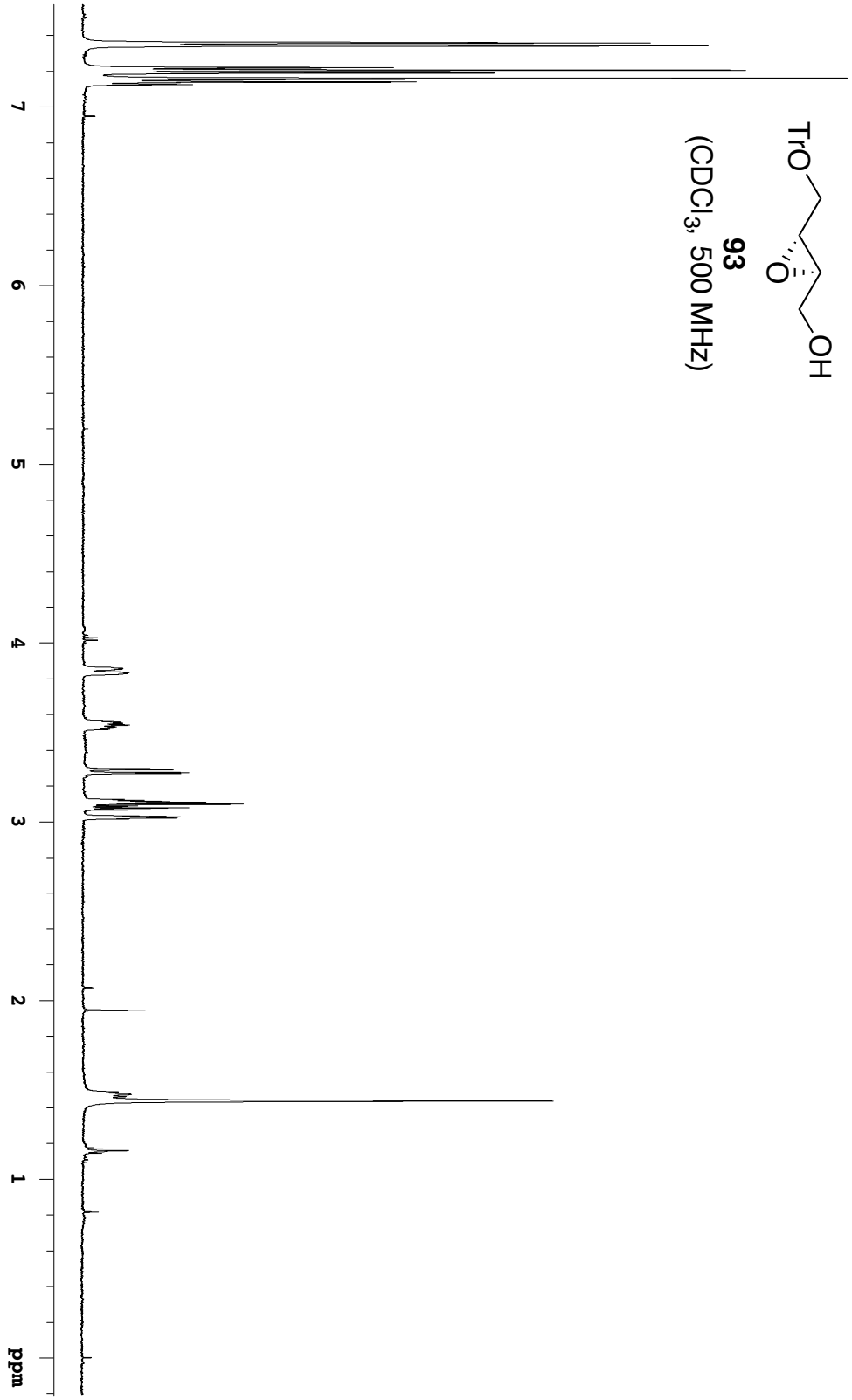
(4) Ma, S.; Ni, B. *Chem.—Eur. J.* **2004**, *10*, 3286–3300.

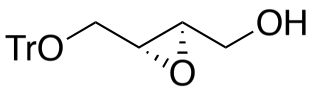
(5) Yamamoto, Y.; Matsumi, D. *Chem. Commun.* **1998**, 875–876.

(6) Sharma, R.; Lee, J.; Wang, S.; Milne, G. W. A.; Lewin, N. E.; Blumberg, P. M.; Marquez, V. E. *J. Med. Chem.* **1996**, *39*, 19–28.

(7) Misaki, T.; Kurihar, M.; Tanabe, Y. *Chem. Commun.* **2001**, 2478.

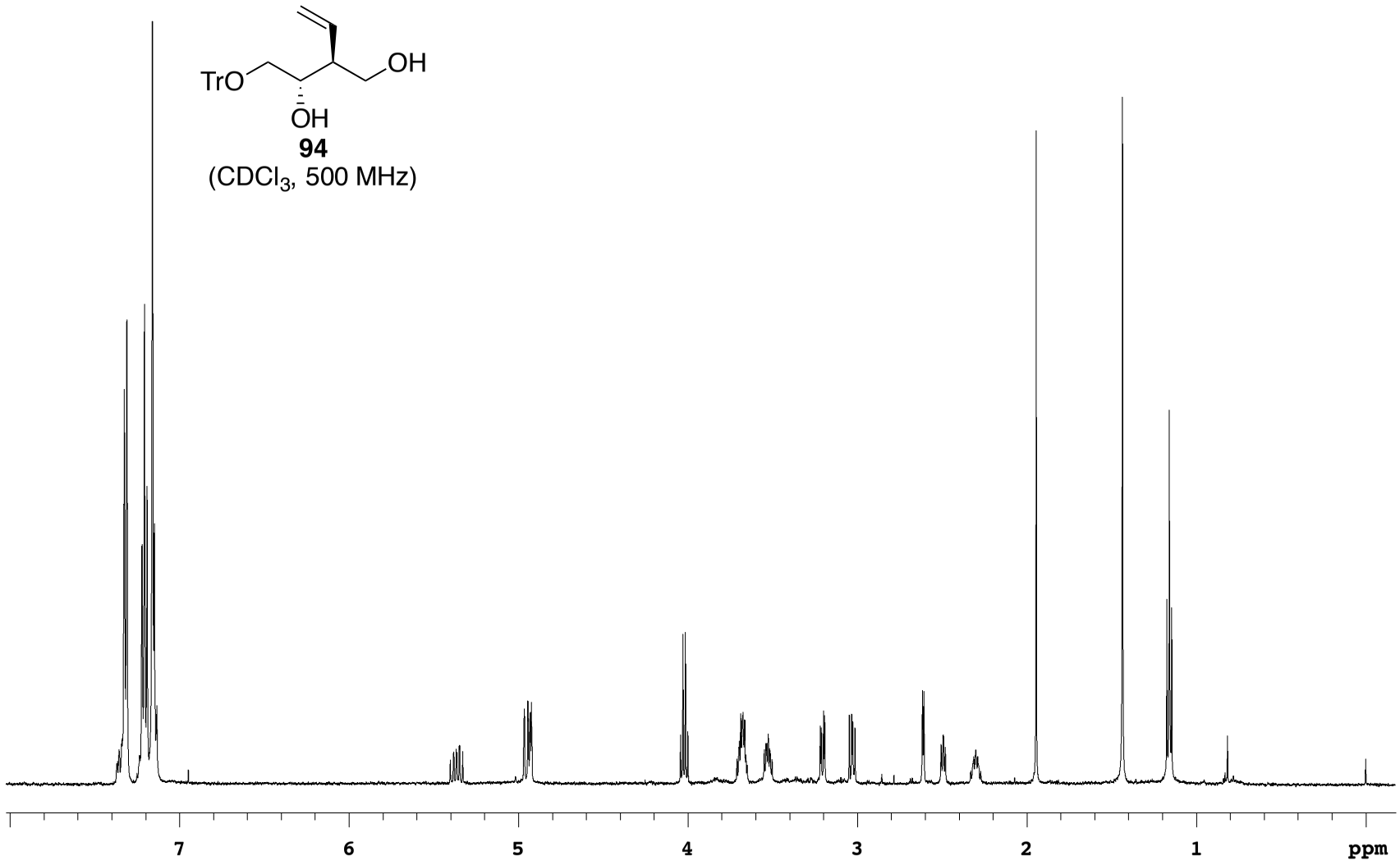
6.4 Spectra

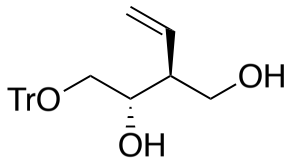




93

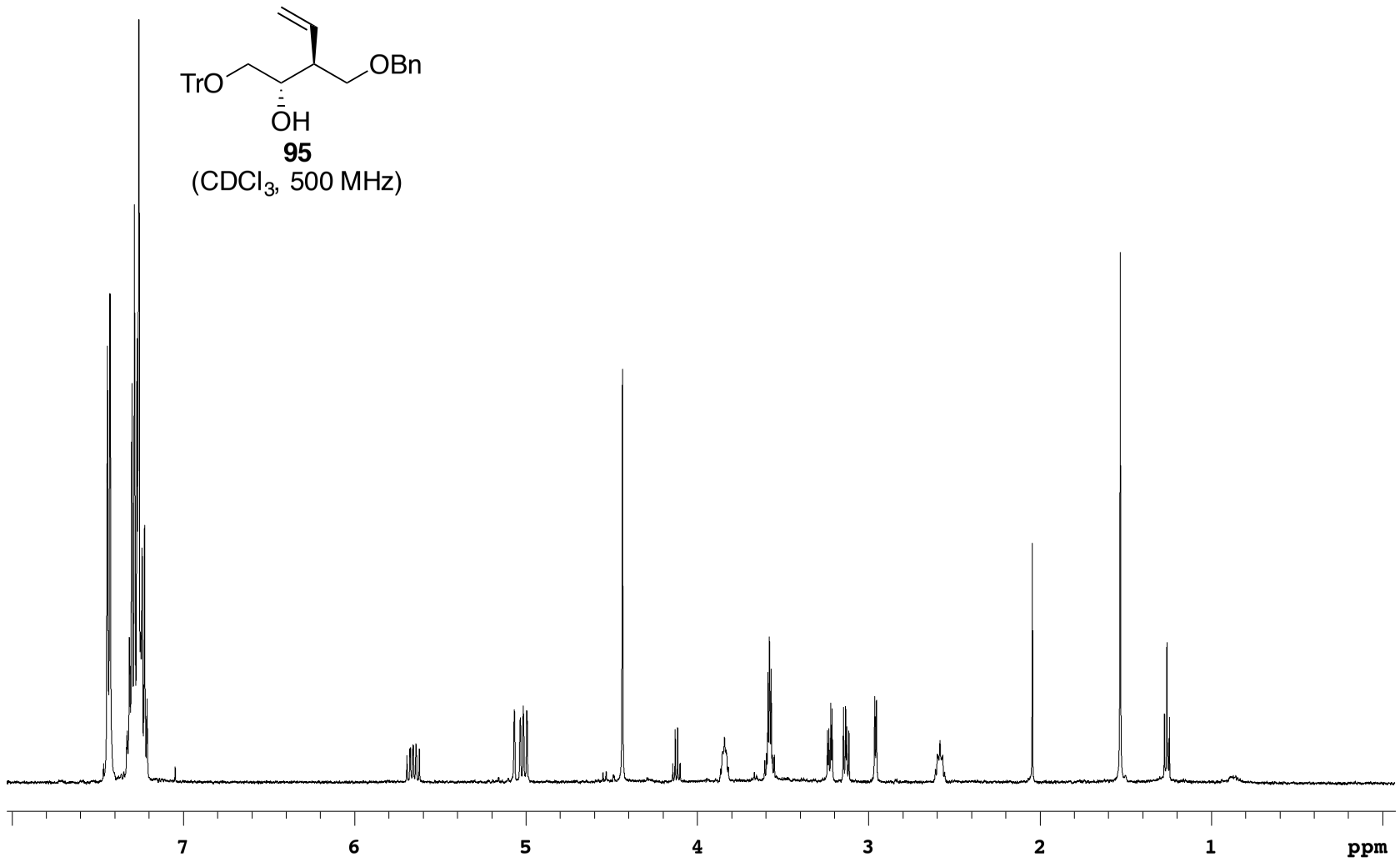
($CDCl_3$, 125 MHz)

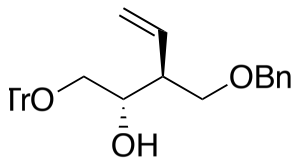

TrO
OH
OH
94
(CDCl3, 500 MHz)
7
6
5
4
3
2
1
ppm



94

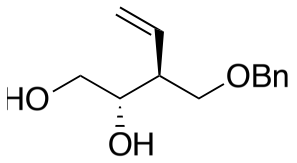
($CDCl_3$, 125 MHz)


TrO
OBn
OH
95
(CDCl3, 500 MHz)
7
6
5
4
3
2
1
ppm



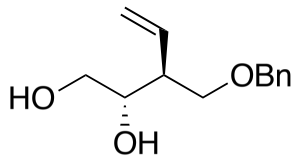
95

($CDCl_3$, 125 MHz)



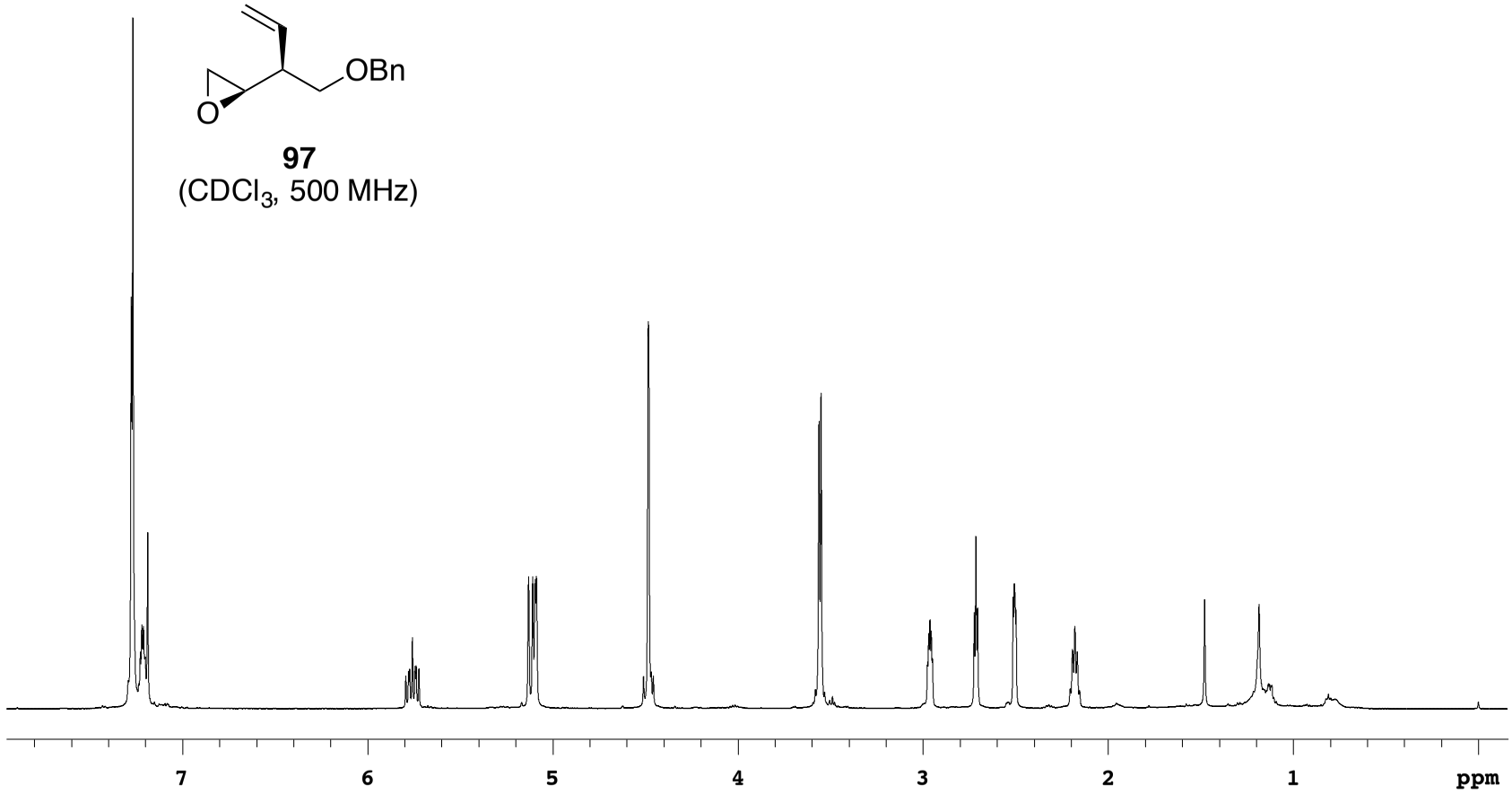
96

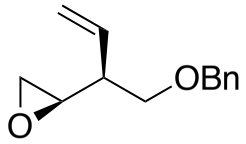
($CDCl_3$, 500 MHz)



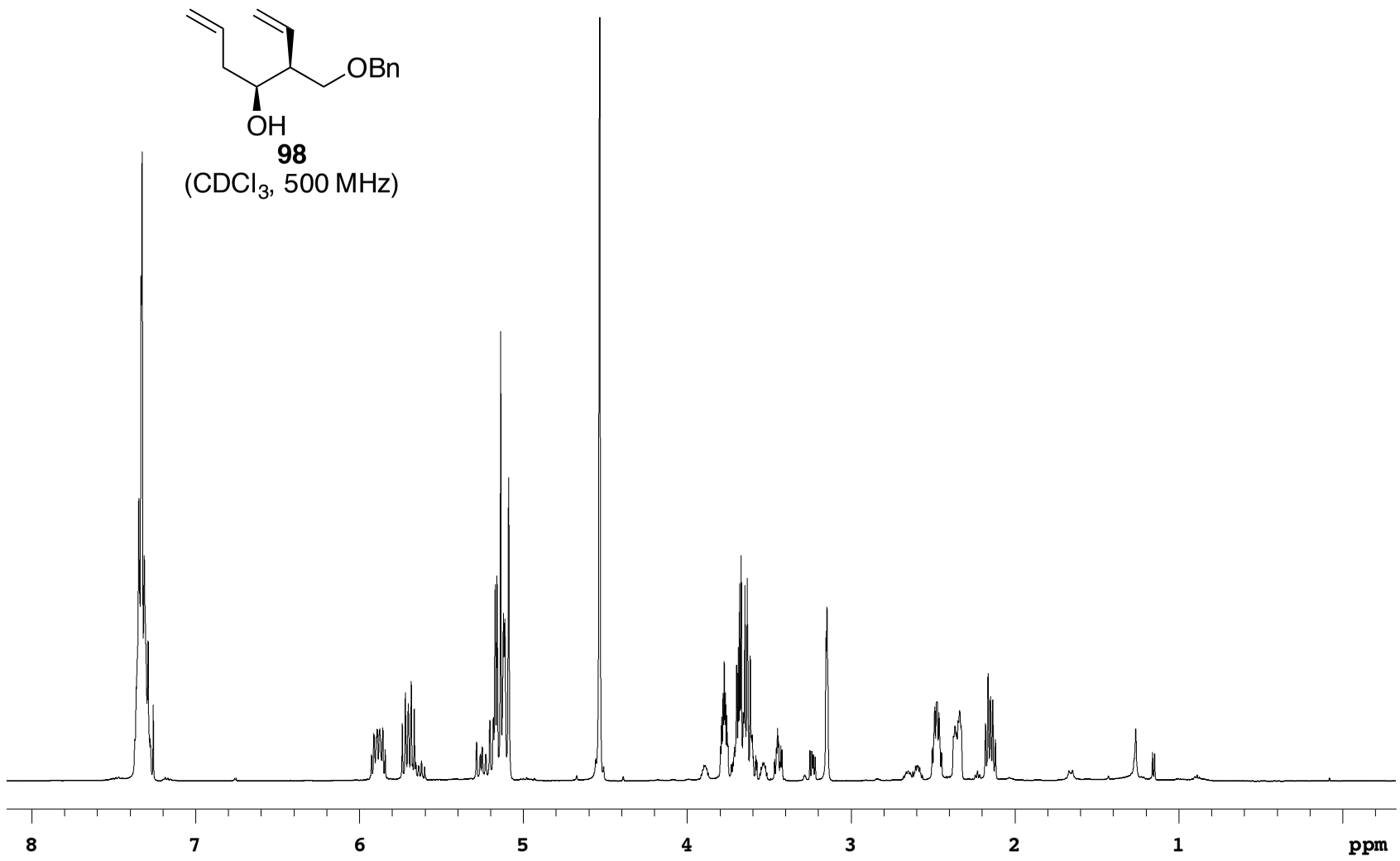
96

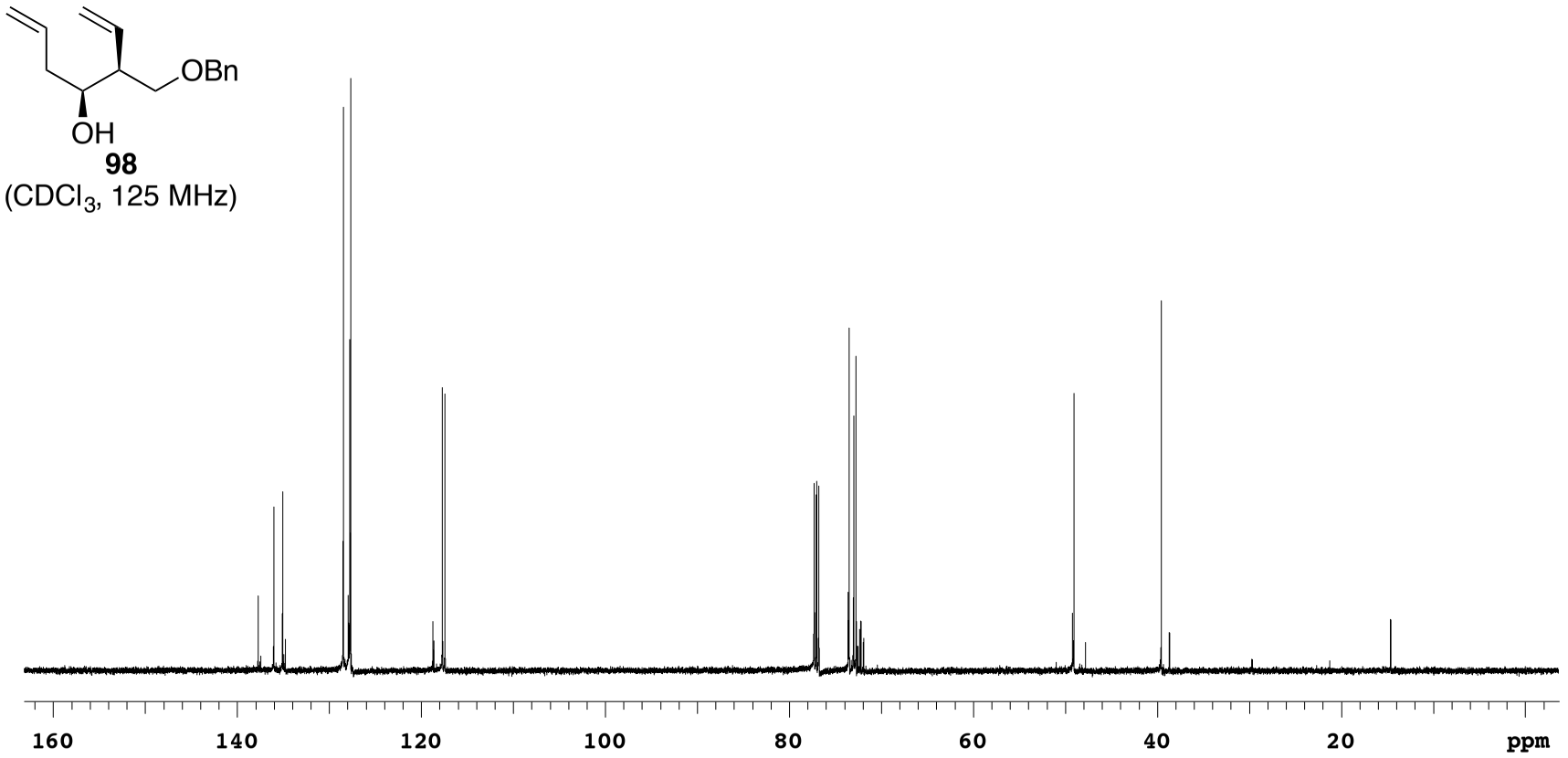
($CDCl_3$, 125 MHz)

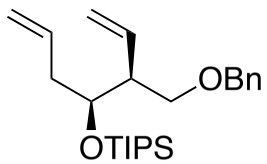

OBn
O
97
(CDCl3, 500 MHz)
7
6
5
4
3
2
1
ppm



97
($CDCl_3$, 125 MHz)

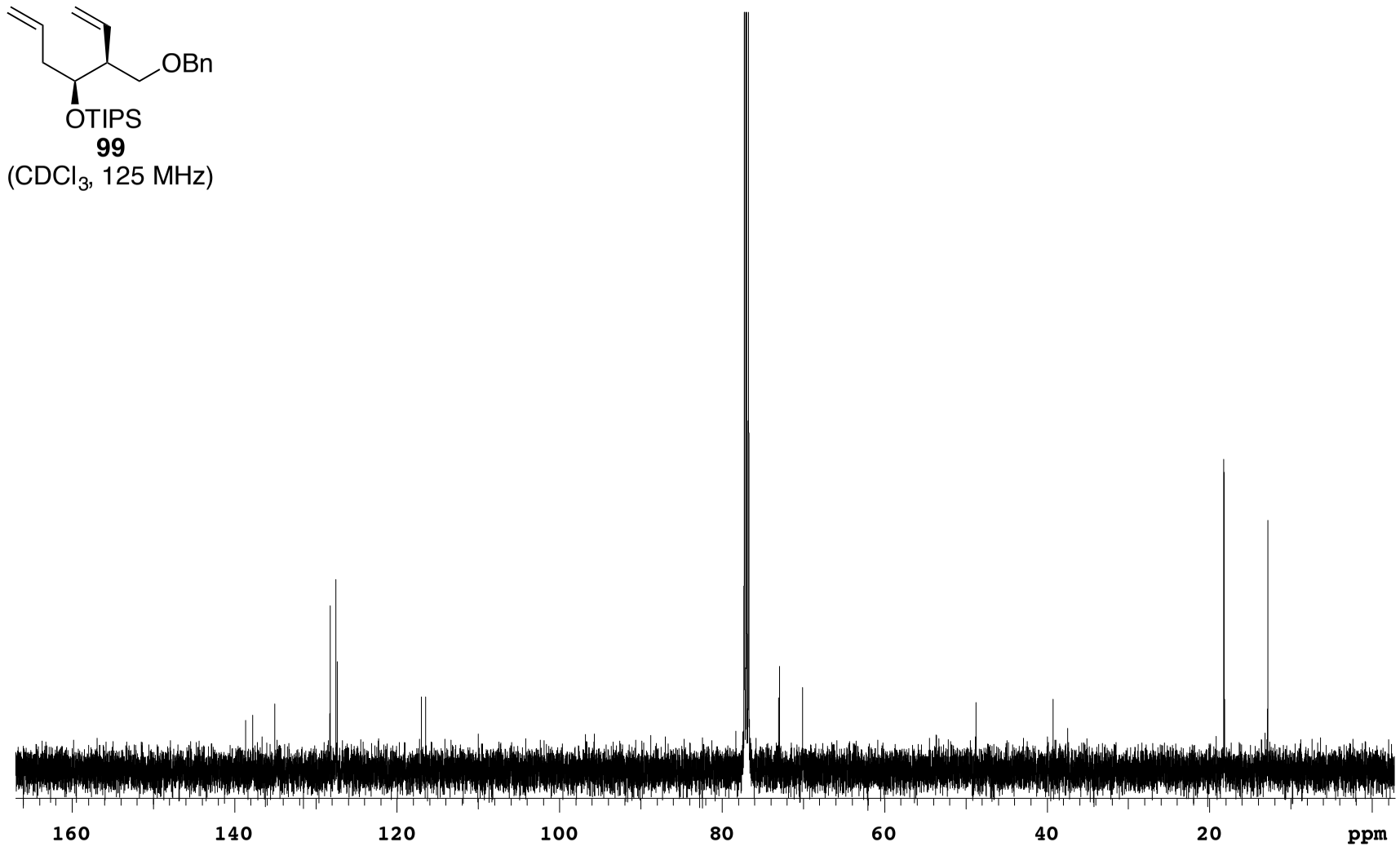

OBn
OH
98
(CDCl3, 500 MHz)
8
7
6
5
4
3
2
1
ppm

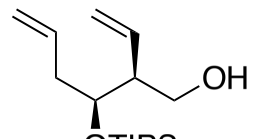

OBn
OH
98
(CDCl3, 125 MHz)
160
140
120
100
80
60
40
20
ppm



99

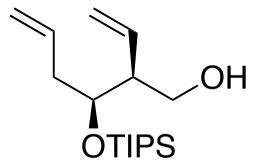
($CDCl_3$, 500 MHz)


OBn
OTIPS
99
(CDCl3, 125 MHz)
160
140
120
100
80
60
40
20
ppm



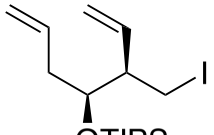
100

($CDCl_3$, 500 MHz)



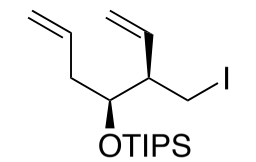
100

($CDCl_3$, 125 MHz)



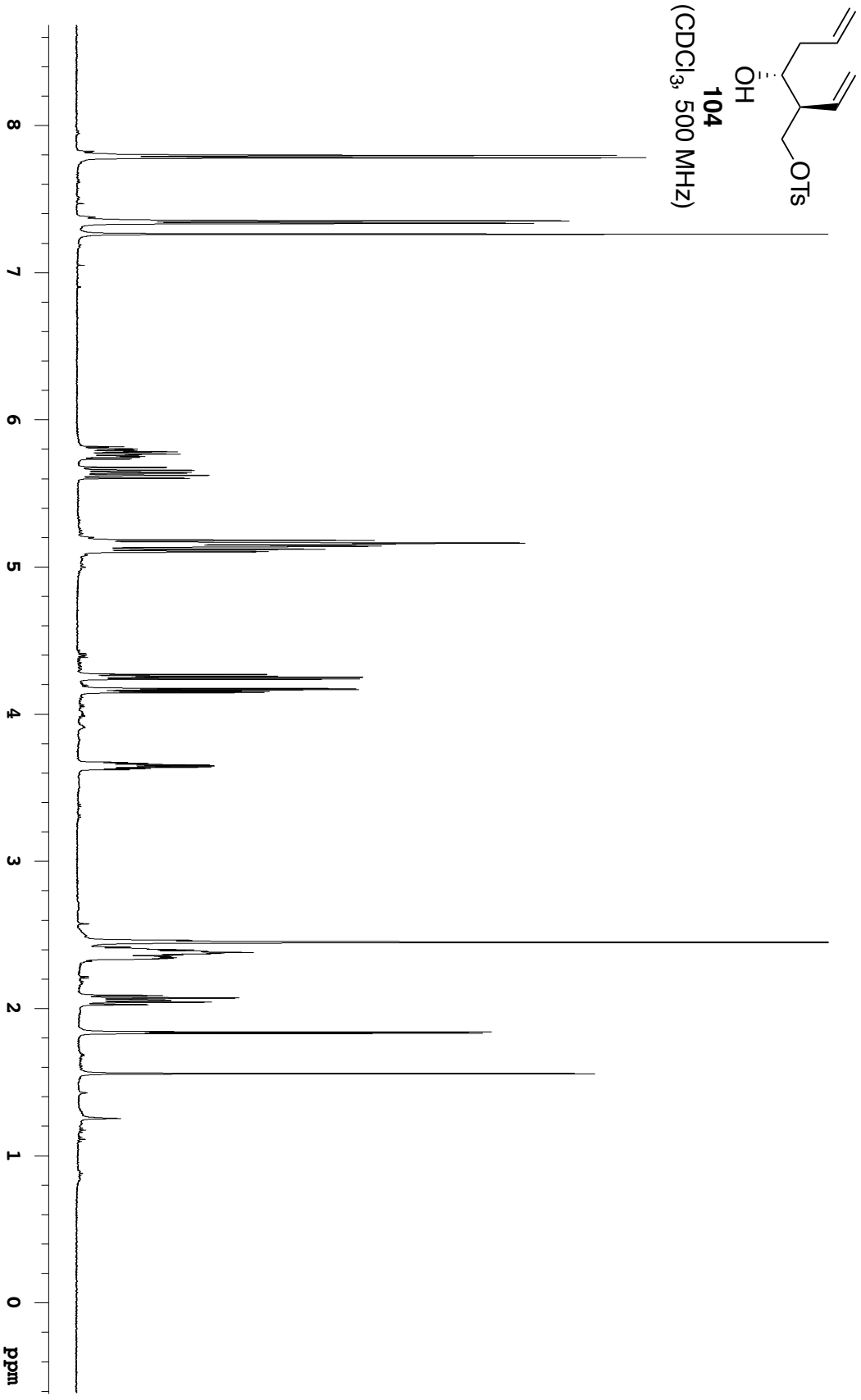
101

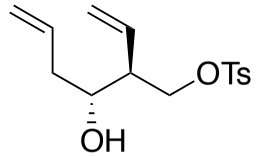
($CDCl_3$, 500 MHz)



101

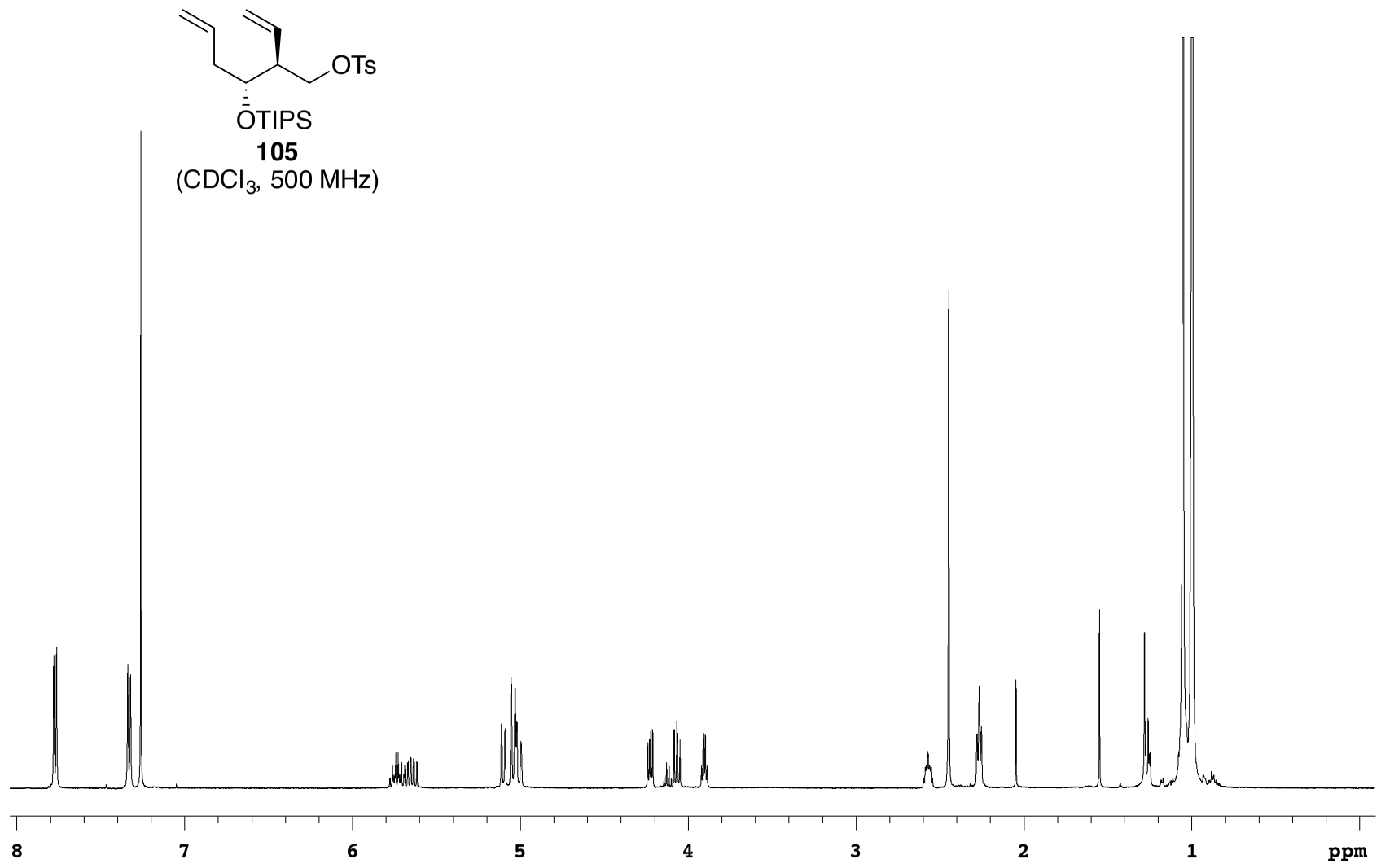
($CDCl_3$, 125 MHz)

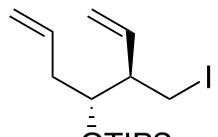

OTs
OH
104
(CDCl3, 500 MHz)
8
7
6
5
4
3
2
1
0
ppm



104

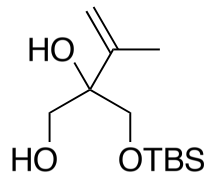
($CDCl_3$, 125 MHz)


OTs
OTIPS
105
(CDCl3, 500 MHz)
8
7
6
5
4
3
2
1
ppm

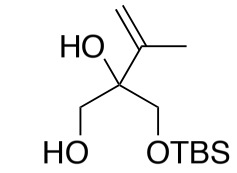


105

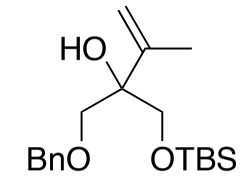
($CDCl_3$, 500 MHz)



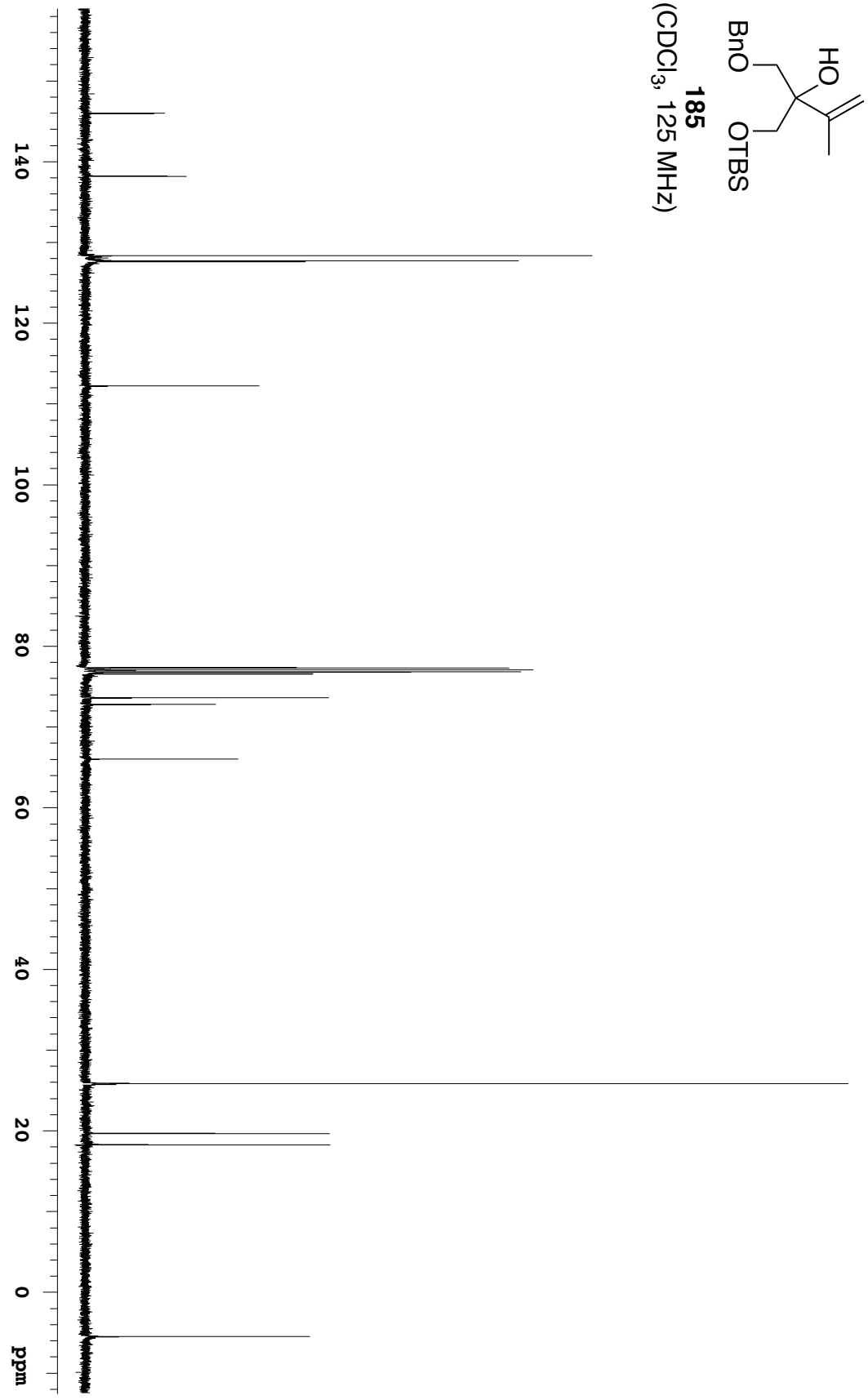
184
($CDCl_3$, 500 MHz)

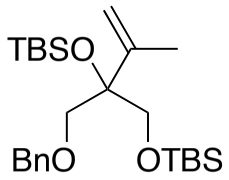


184
($CDCl_3$, 125 MHz)

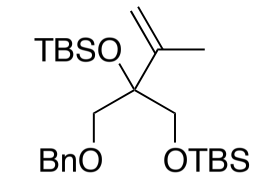


185
($CDCl_3$, 500 MHz)

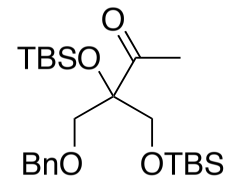

HO
BnO
OTBS
185
(CDCl3, 125 MHz)
140
120
100
80
60
40
20
0
ppm



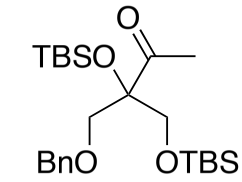
186
($CDCl_3$, 500 MHz)



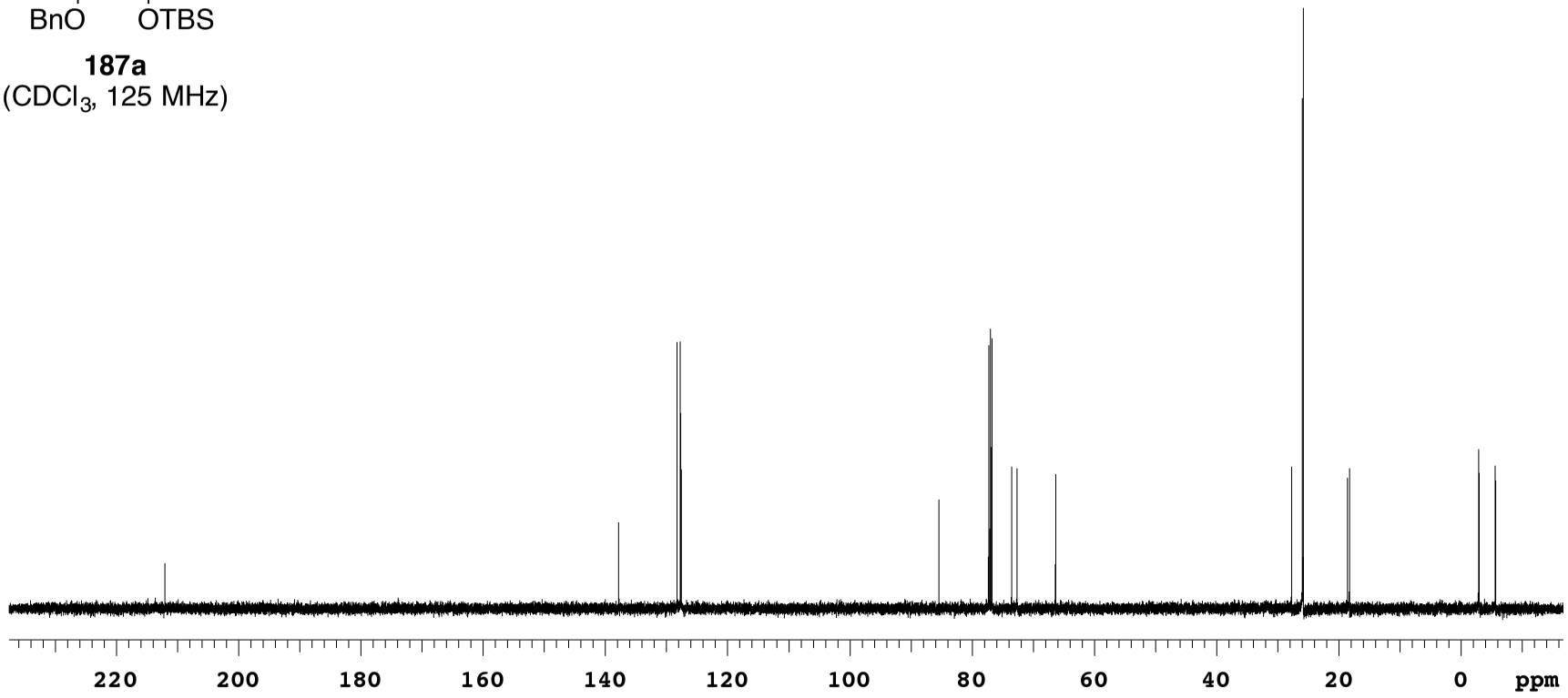
186
($CDCl_3$, 125 MHz)

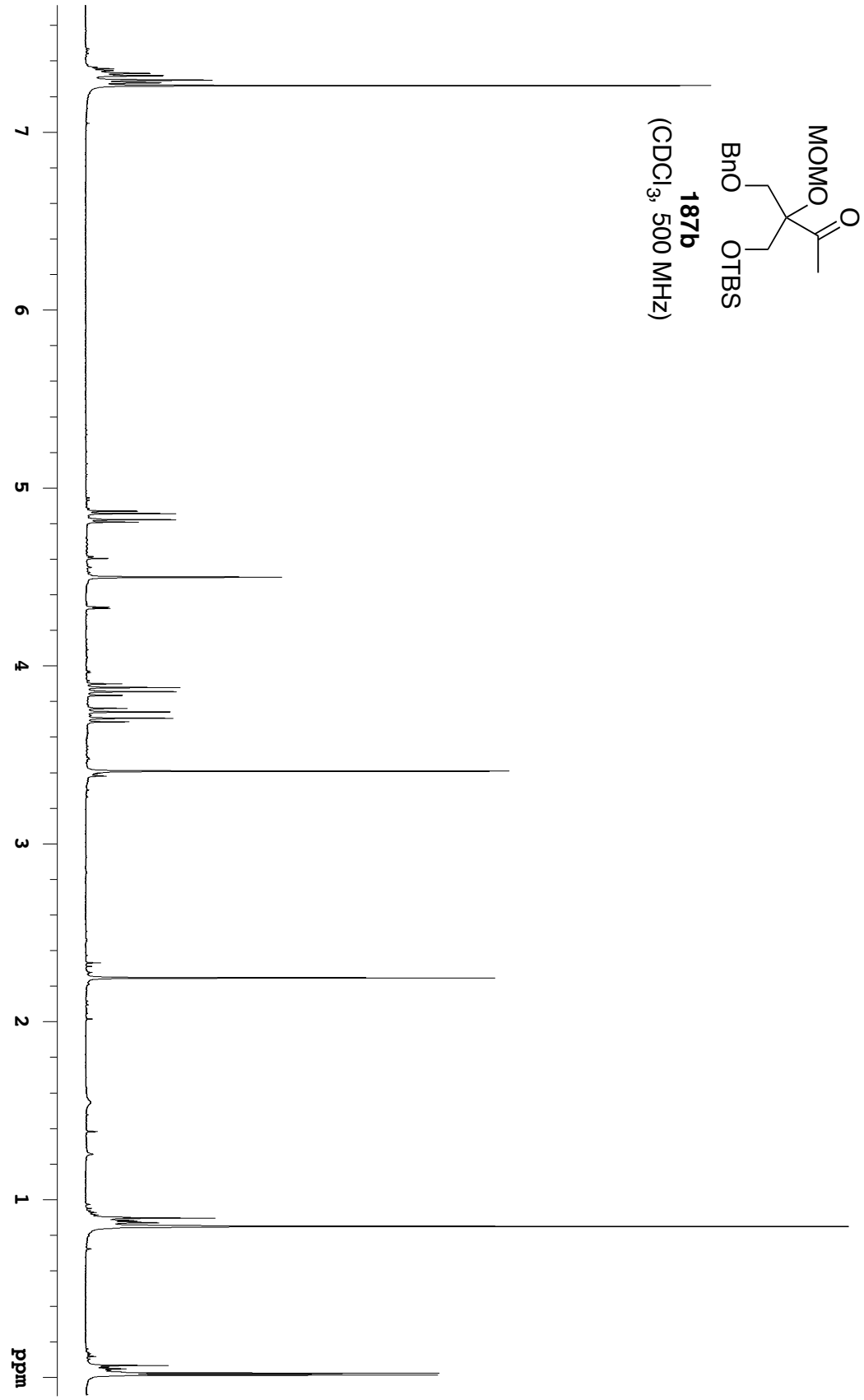


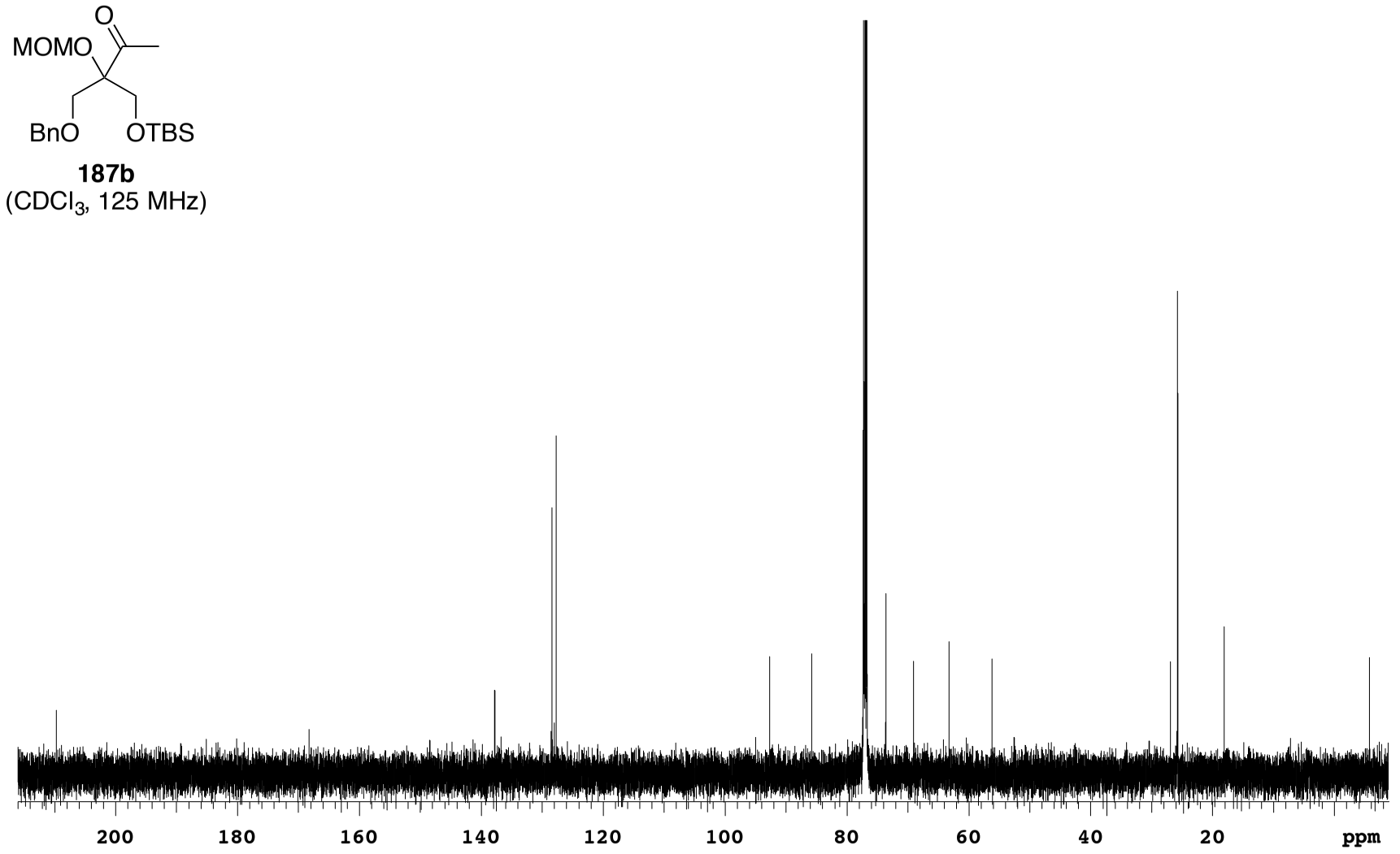
187a
($CDCl_3$, 500 MHz)



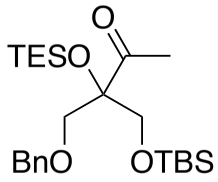
187a
($CDCl_3$, 125 MHz)



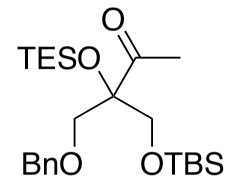

MOMO
O
BnO
OTBS
187b
(CDCl3, 500 MHz)
7
6
5
4
3
2
1
ppm



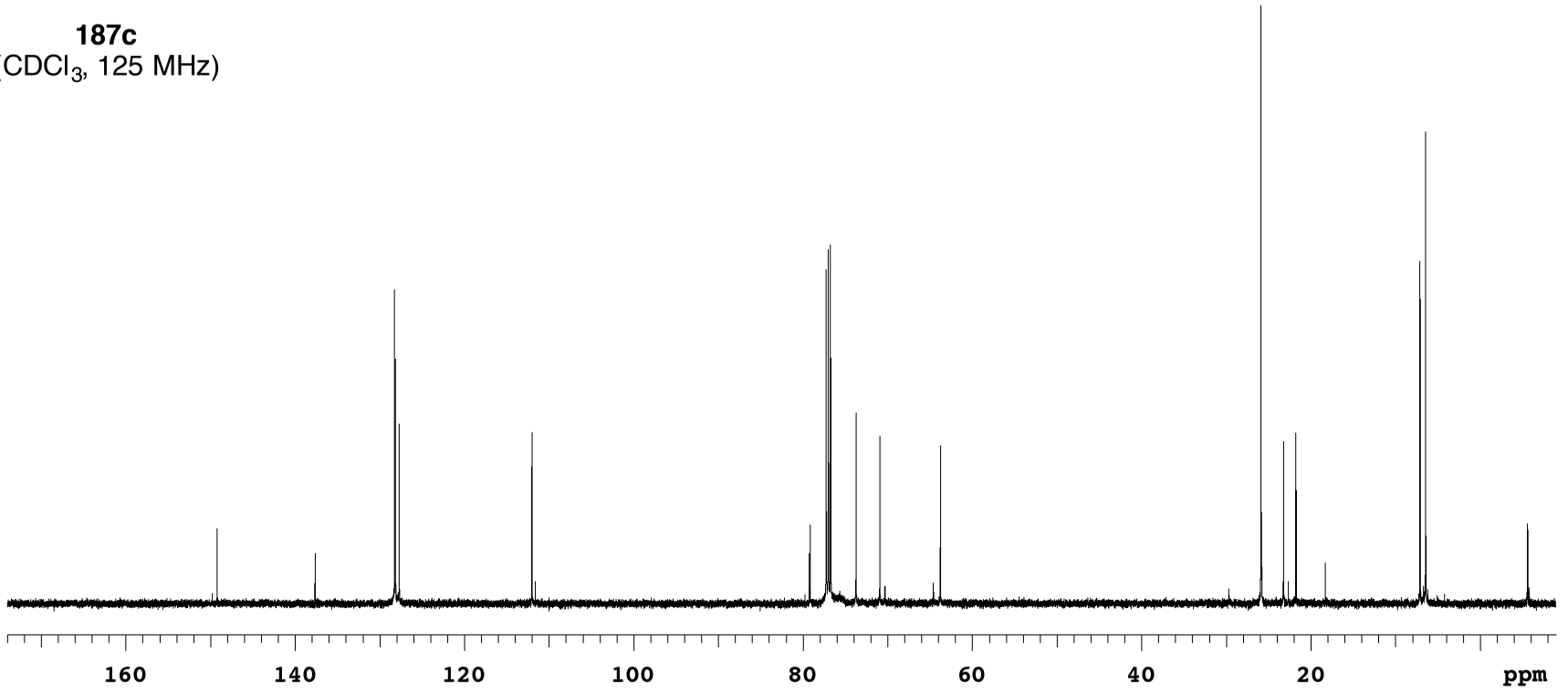
187b
($CDCl_3$, 125 MHz)

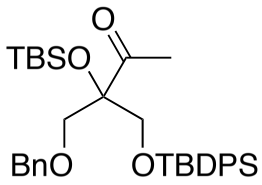


187c
($CDCl_3$, 500 MHz)

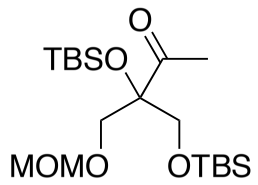


187c
($CDCl_3$, 125 MHz)

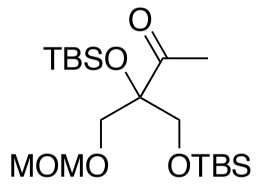




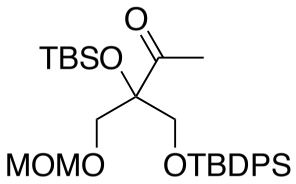
187d
($CDCl_3$, 500 MHz)



187e
($CDCl_3$, 500 MHz)

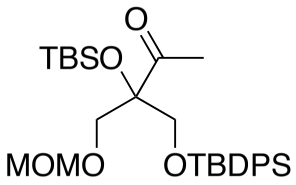


187e
($CDCl_3$, 125 MHz)

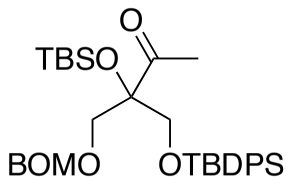


187f

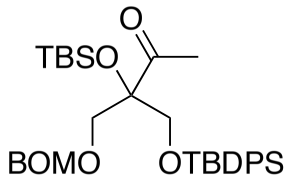
($CDCl_3$, 500 MHz)



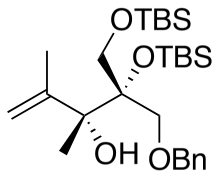
187f
($CDCl_3$, 125 MHz)



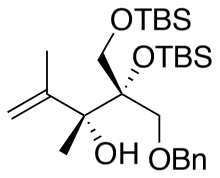
187g
($CDCl_3$, 500 MHz)



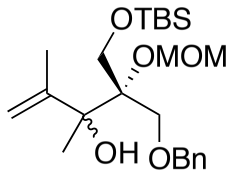
187g
($CDCl_3$, 125 MHz)



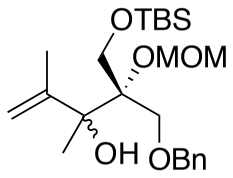
188a
($CDCl_3$, 500 MHz)



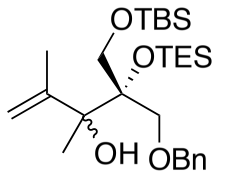
188a
($CDCl_3$, 125 MHz)



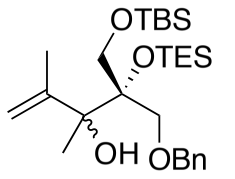
188b
($CDCl_3$, 500 MHz)



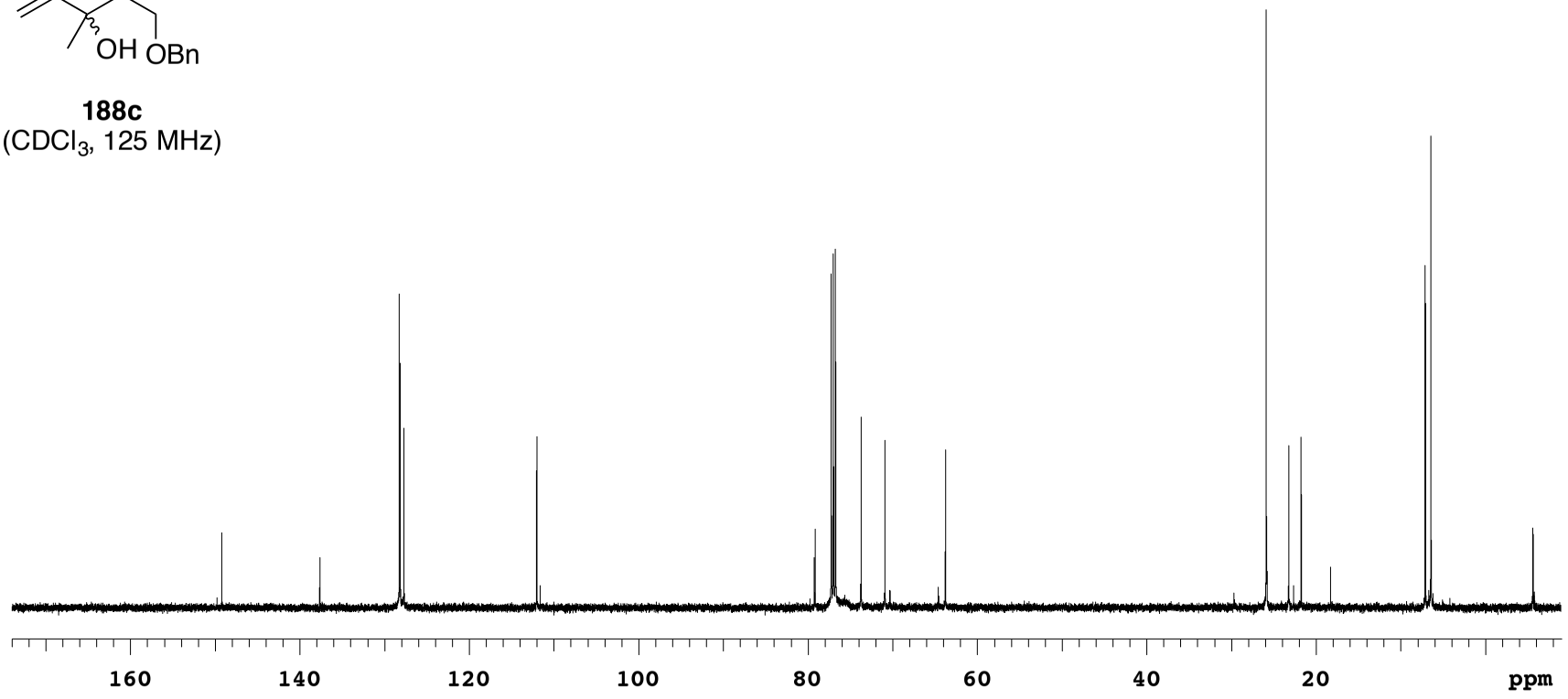
188b
($CDCl_3$, 125 MHz)

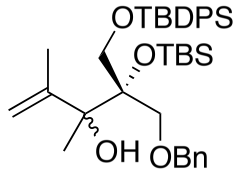


188c
($CDCl_3$, 500 MHz)

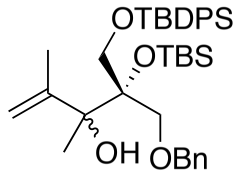


188c
($CDCl_3$, 125 MHz)

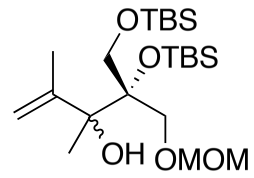




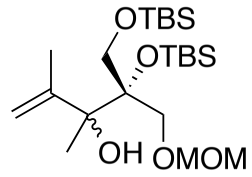
188d
($CDCl_3$, 500 MHz)



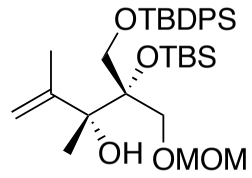
188d
($CDCl_3$, 125 MHz)



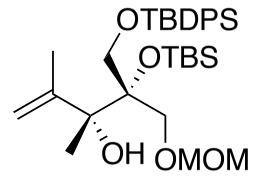
188e
($CDCl_3$, 500 MHz)



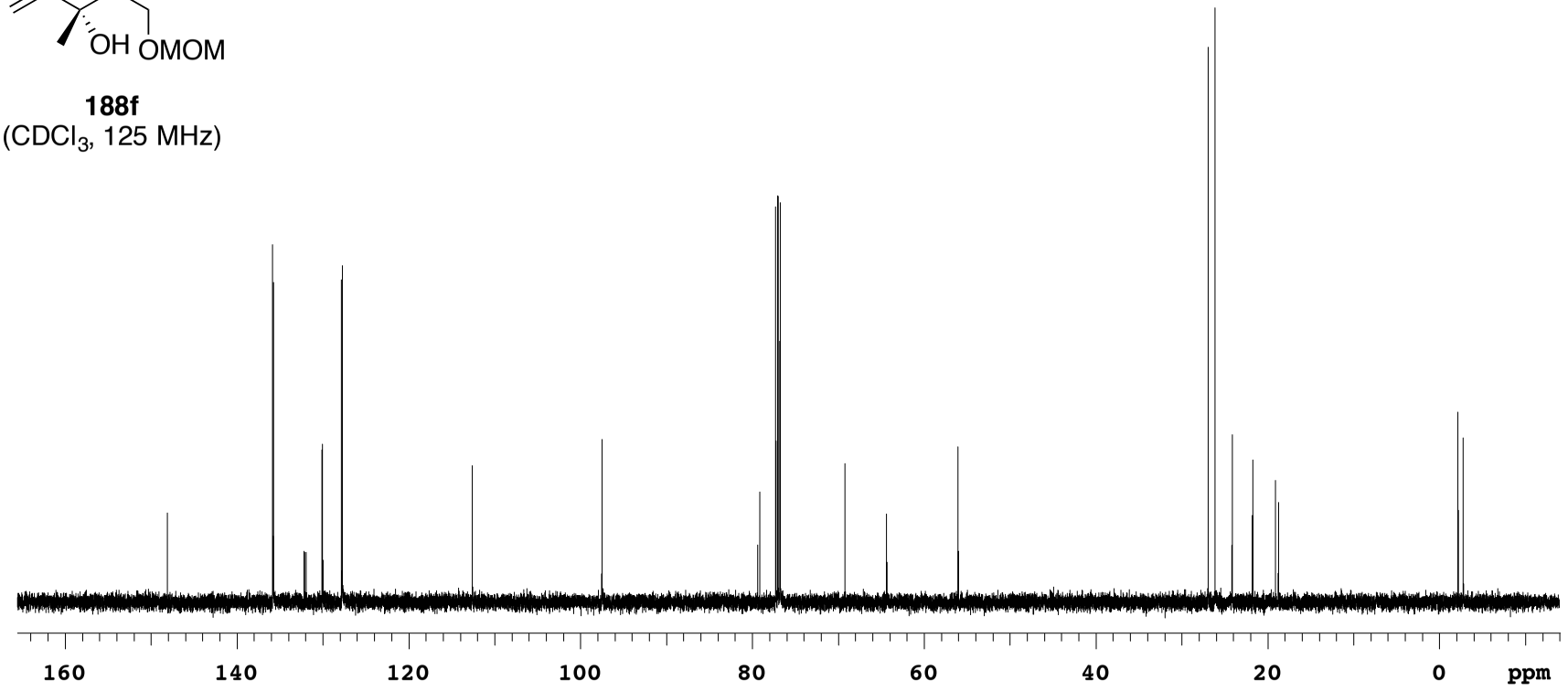
188e
($CDCl_3$, 125 MHz)

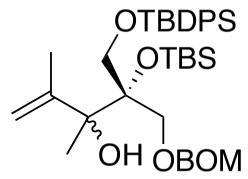


188f
($CDCl_3$, 500 MHz)

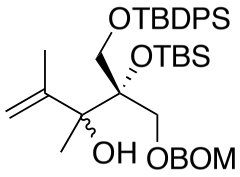


188f
($CDCl_3$, 125 MHz)

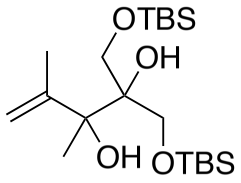




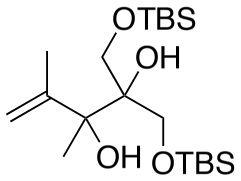
188g
($CDCl_3$, 500 MHz)



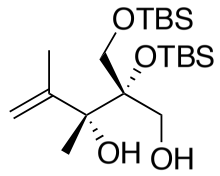
188g
($CDCl_3$, 125 MHz)



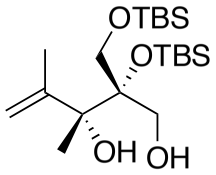
189
($CDCl_3$, 500 MHz)



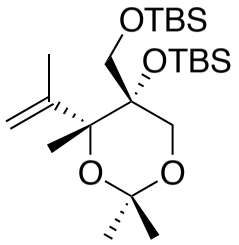
189
($CDCl_3$, 125 MHz)



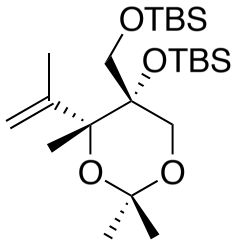
190
($CDCl_3$, 500 MHz)



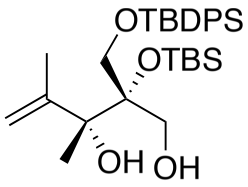
190
($CDCl_3$, 125 MHz)



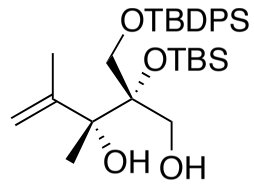
191
($CDCl_3$, 500 MHz)



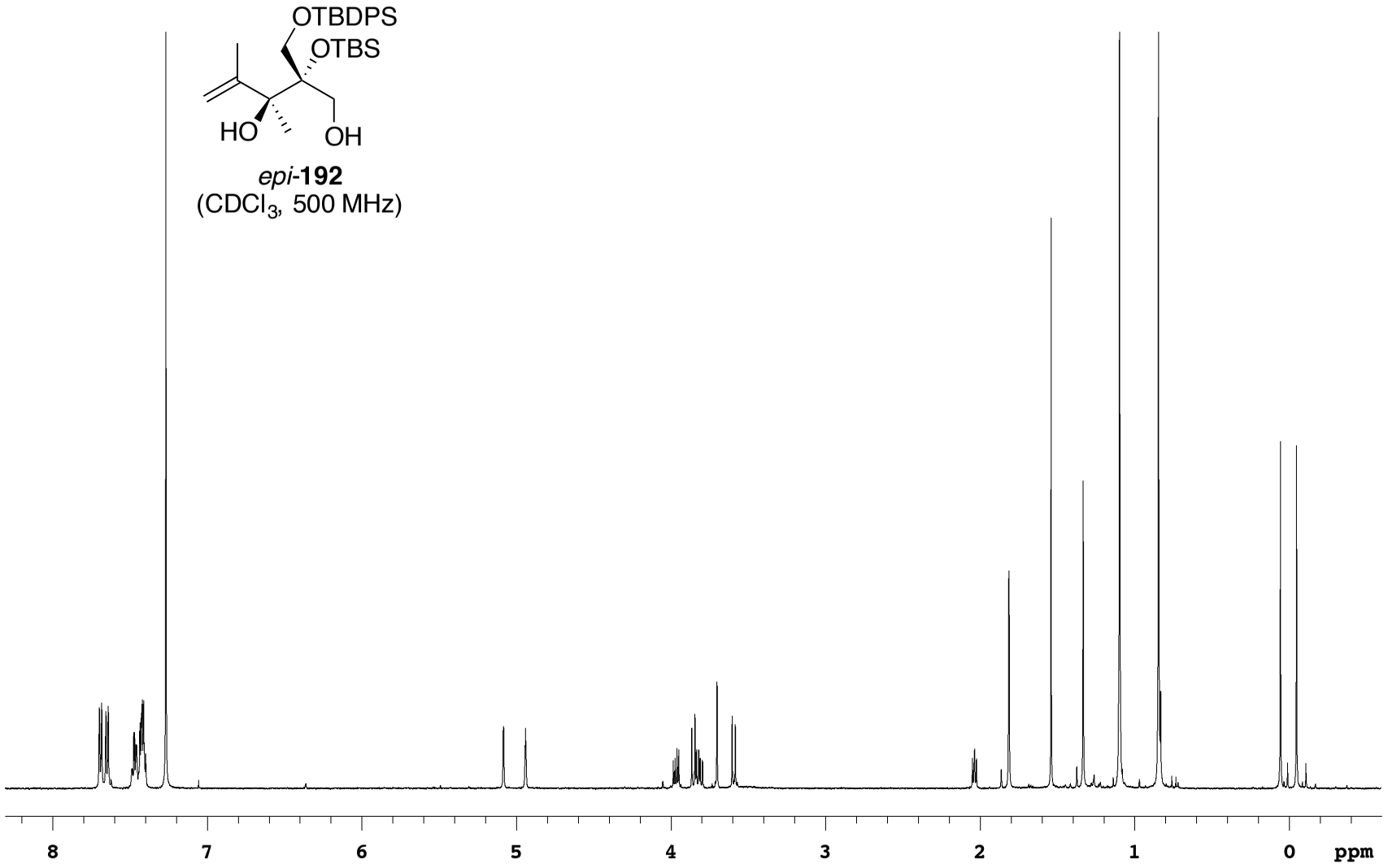
191
($CDCl_3$, 125 MHz)

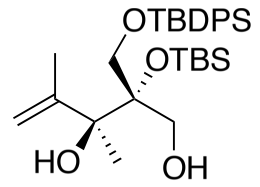


192
($CDCl_3$, 500 MHz)

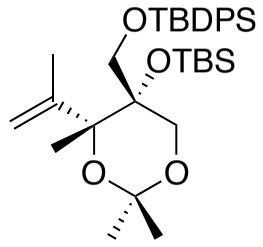


192
($CDCl_3$, 125 MHz)

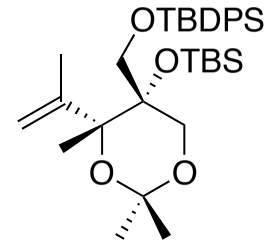

OTBDPS
OTBS
HO
OH
epi-192
(CDCl3, 500 MHz)
8
7
6
5
4
3
2
1
0
ppm



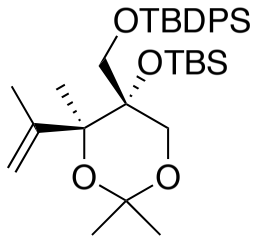
epi-**192**
($CDCl_3$, 125 MHz)



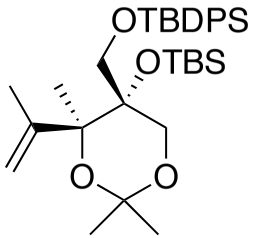
193
($CDCl_3$, 500 MHz)



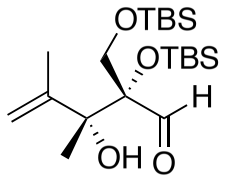
193
($CDCl_3$, 125 MHz)



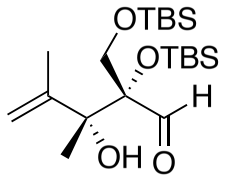
epi-**193**
(500 MHz, $CDCl_3$)



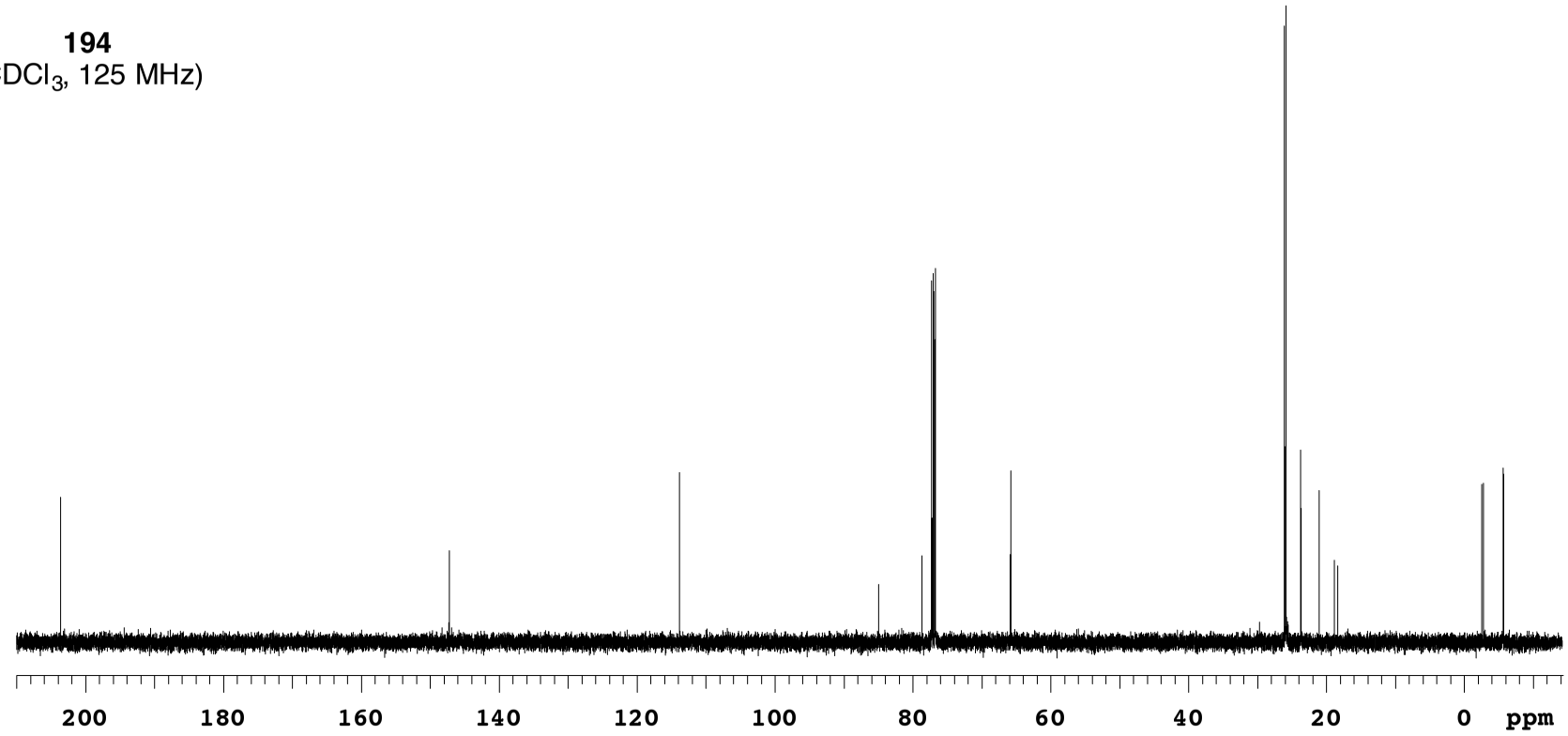
epi-**193**
(125 MHz, $CDCl_3$)

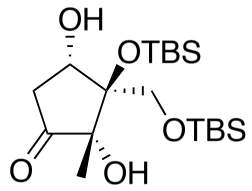


194
($CDCl_3$, 500 MHz)

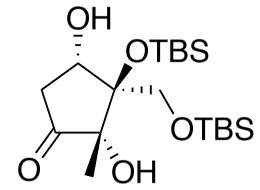


194
($CDCl_3$, 125 MHz)

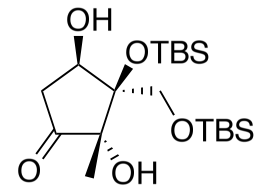




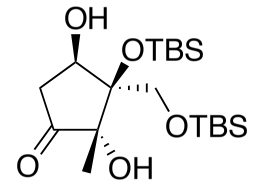
196
($CDCl_3$, 500 MHz)



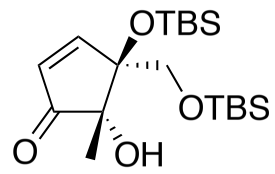
196
($CDCl_3$, 125 MHz)



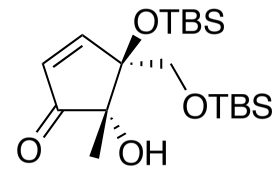
epi-**196**
($CDCl_3$, 500 MHz)



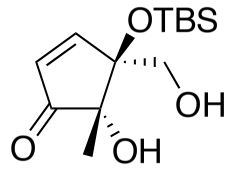
epi-**196**
($CDCl_3$, 125 MHz)



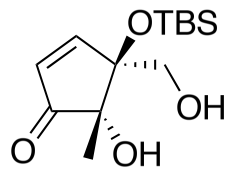
197
($CDCl_3$, 500 MHz)



197
($CDCl_3$, 125 MHz)



198
($CDCl_3$, 500 MHz)



198
($CDCl_3$, 125 MHz)