Studies Directed Towards the Total Synthesis of (+)-Sieboldine A

by

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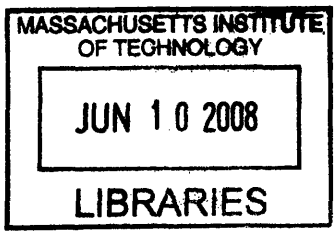

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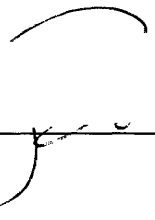

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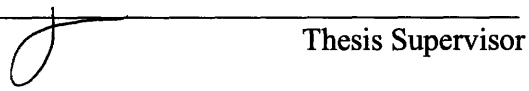

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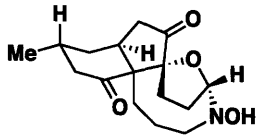
To Eleanor and my family

Studies Directed Towards the Total Synthesis of Sieboldine A

by

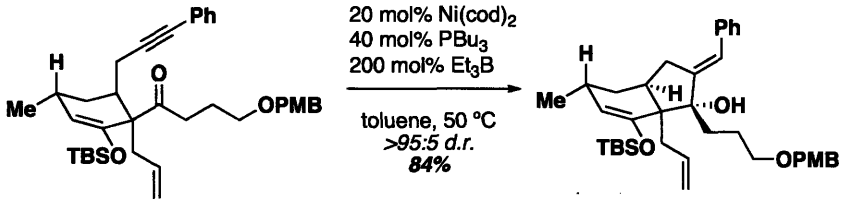
Victor S. Gehling

Abstract

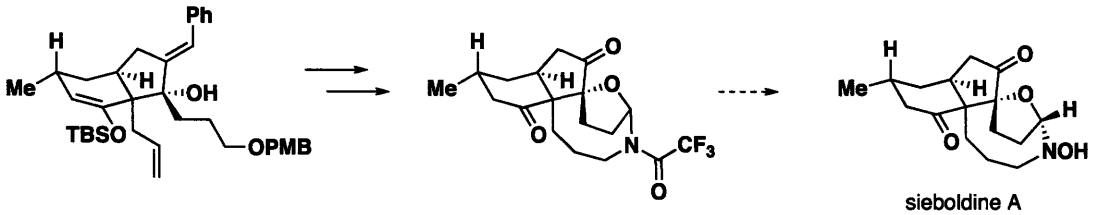


sieboldine A

Progress towards the total synthesis of sieboldine A is described. This synthetic approach uses a nickel-catalyzed alkyne-ketone reductive cyclization to form the hydrindane core of the natural product in good yield and with excellent diastereoselectivity about the newly formed tertiary allylic alcohol.



The hydrindane product from this reductive cyclization can be transformed into the tetracyclic *N,O*-acetal which is two steps removed from the natural product **1**. Efforts directed towards completion of the synthesis of **1** via a direct late-stage amine oxidation are presented.



sieboldine A

Thesis Supervisor: Timothy F. Jamison
Title: Associate Professor of Chemistry

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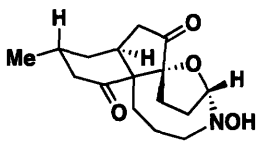
Abbreviations

Ac	acetyl
Alloc	allyl carbamate
Boc	*tert*-butyl carbamate
BSA	*bis*-trimethylsilylacetamide
°C	degree celcius
cod	cyclooctadiene
DDQ	2,3-dichloro-5,6-dicyanoquinone
DEAD	diethyl azodicarboxamide
DMF	N,N'-dimethylformamide
DMDO	dimethyldioxirane
DMSO	dimethylsulfoxide
Et	ethyl
g	gram
gCOSY	gradient correlation spectroscopy
HMBC	heteronuclear multiple bond correlation spectroscopy
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence spectroscopy
Hz	hertz
IR	infrared
KAPA	potassium aminoproprylamide
KHMDS	potassium hexamethyldisilazane
L	liter
LDA	lithium disopropylamide
m	milli
mol	mole
μ	micro
M	molar
Me	methyl
MHz	megahertz
Ms	methanesulfonyl
NMO	N-methyl morpholine N-oxide
Ph	phenyl
PMB	*para*-methoxy benzyl
PPTS	pyridinium-*para*-toluenesulfonate
Py	pyridine
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyl dimethyl silyl
THF	tetrahydrofuran
TMS	trimethylsilyl

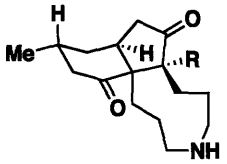
Introduction

The Lycopodium alkaloids are a large group of natural products characterized by their compact polycyclic frameworks. These alkaloids derive their name from the *Lycopodium* species of plants from which they were originally isolated. This group of natural products is divided into four distinct structural classes (Figure 1). Hydrindane containing natural products, such as sieboldine A (**1**), alopecuridine (**2a**), and fawcettimine (**2b**), are classified in the fawcettimine group of the Lycopodium alkaloids, whereas natural products that contain a pyridine or pyridone ring, such as huperzine A (**3**), are classified in the lycodine group. Furthermore, alkaloids that contain four interconnected 6-membered rings, such as lycopodine (**4**), are members of the lycopodine group. Finally, the natural products that are devoid of one of the aforementioned structural features are members of the miscellaneous class of Lycopodium alkaloids, such as phlegmarine (**5**).[1]

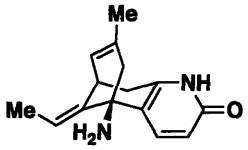
Figure 1. Representative Lycopodium Alkaloids.



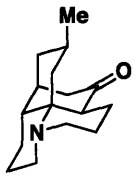
sieboldine A (**1**)
fawcettimine class



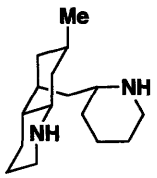
R = OH alopecuridine (**2a**)
R = H fawcettimine (**2b**)
fawcettimine class



huperzine A (**3**)
lycodine class



lycopodine (**4**)
lycopodine class



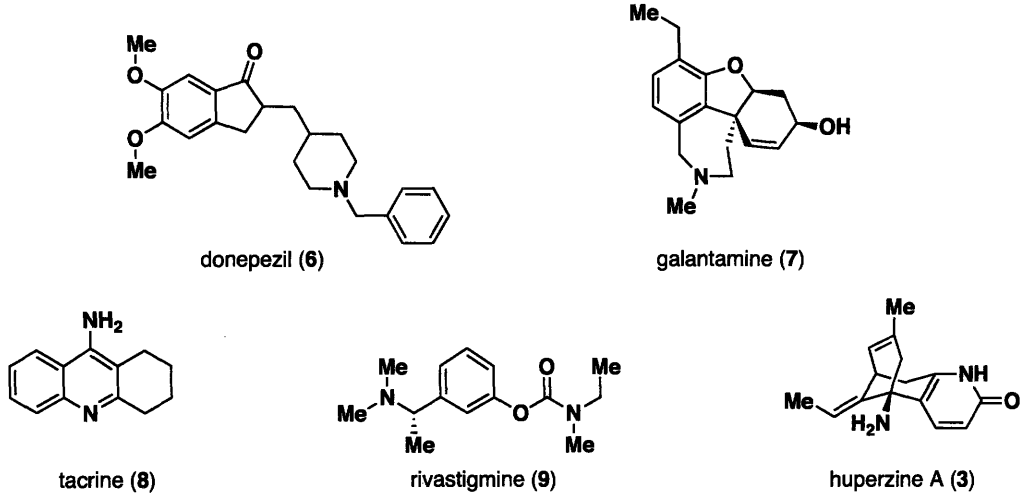
phlegmarine (**5**)
miscellaneous class

[1] Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752-772.

Along with their complex structures, the Lycopodium alkaloids often have interesting biological activities, and plants or plant extracts containing these alkaloids have been used in traditional Chinese medicine.[1] Recently, these alkaloids have received increased attention from practitioners of Western medicine as treatments for a variety of human diseases.[2]

In particular, huperzine A (**3**) has been the subject of many studies because of its acetylcholinesterase inhibition activity.[3] This activity has current relevance because acetylcholinesterase inhibitors are used in the treatment of Alzheimer's disease, myasthenia gravis, and some dementias. In general these diseases are associated with low levels of acetylcholine in the central nervous system and/or in the peripheral nervous system.

Figure 2. Acetylcholinesterase Inhibitors.



[2] For recent investigation into the biological properties of Huperzine A, see: Peng, Y.; Lee, D. W. C.; Jiang, L.; Ma, Z.; Schachter, S. C.; Lemere, C. A. *Neuroscience* **2007**, *150*, 386-395.

[3] Tang, X. -C.; Han, Y. –F.; Chen, X. –P.; Zhu, X. –D. *Acta Pharmacologica Sinica* **1986**, *7*, 507-511.

Acetylcholinesterase inhibitors help treat these conditions by increasing the lifetime of acetylcholine through inhibition of the enzyme responsible for its breakdown. Huperzine A compares favorably with the currently prescribed drugs tacrine,[4] donepezil,[5] rivastigmine,[6] and galantamine[7] in terms of activity, bioavailability, half-life, and selectivity towards acetylcholinesterase. In clinical trials it has been shown to have beneficial effects on cognitive function and memory in patients with Alzheimer's disease. In fact, huperzine A has been approved for treatment of Alzheimer's disease in China and is currently in phase II clinical trials in the US.[8]

These findings have spurred increased attention from both the synthetic organic chemistry community and the natural products community, culminating in several recent total syntheses[9] and renewed interest in the isolation and characterization of novel Lycopodium alkaloid structures.[10]

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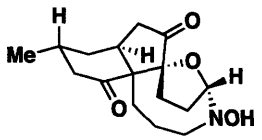
[4] Marketed by Sciele Pharmaceuticals.
[5] Marketed by Eisai Pharmaceuticals.
[6] Marketed by Novartis Pharmaceuticals.
[7] Marketed by Janssen Pharmaceuticals.
[8] For details, see: http://www.alzforum.org/drg/drc/detail.asp?id=53.
[9] For recent syntheses of Lycopodium alkaloids, see: a) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7671-7637. b)Kozaka, T.; Miyakoshi, N.; Mukai, C. *J. Org. Chem.* **2007**, *72*, 10147-10154. c) Lucey, C.; Kelly, S. A.; Mann, J. *Org. Biomol. Chem.* **2007**, *5*, 301-306. d) Shigeyama, T.; Katakawa, K.; Kogure, N.; Kitajima, M.; Takayama, H. *Org. Lett.* **2007**, *9*, 4069-4072. e) Evans, D. A.; Scheerer, J. R. *Angew. Chem. Int. Ed.* **2005**, *44*, 6038-6042.
[10] For examples of recently isolated lycopodium alkaloids, see: a) Choo, C. Y.; Hirasawa, Y.; Karimata, C.; Koyama, K.; Sekiguchi, M.; Kobayashi, J.–I.; Morita, H. *Bioorg. Med. Chem.* **2007**, *15*, 1703-1707. b) Wang, H.–B.; Tan, C.–H.; Tan, J.–J.; Gao, M.–Y.; Li, Y.–M.; Jiang, S.–H.; Zhu, D.–Y. *Helv.Chim. Acta* **2007**, *90*, 153-157. c) Katakawa, K.; Nozoe, A.; Kogure, N.; Kitajima, M.; Hosokawa, M.; Takayama, H. *J. Nat. Prod.* **2007**, *70*, 1024-1028. d) Koyama, K.; Hirasawa, Y.; Kobayashi, J.–I.; Morita, H. *Bioorg. Med. Chem.* **2007**, *15*, 7803-7808.

Figure 3. Sieboldine A.



sieboldine A (**1**)

In 2003, Kobayashi and coworkers reported the isolation of a novel alkaloid from the club moss *Lycopodium sieboldii* that was subsequently named sieboldine A (**1**) (Figure 3). NMR and X-ray studies established that **1** has a unique tetracyclic structure containing a cyclohexanone, a cyclopentanone, a tetrahydrofuran, and an *aza*-cyclononane ring. In addition, sieboldine A (**1**) has modest biological activity that includes cytotoxicity to murine lymphoma L1210 cells and inhibitory activity against acetylcholinesterase (AchE).[11]

As one of its structural components, **1** contains an α-hydroxy ketone that features a tertiary alcohol vicinal to an all-carbon quaternary stereocenter. This substructure is a challenging motif, and one that might be well suited for assembly using nickel-catalyzed reductive coupling chemistry developed in our laboratories.

Transition metal-catalyzed carbon–carbon bond-forming reactions have become very powerful methods in synthetic organic chemistry because of their high efficiency and functional group tolerance. To this end the Jamison group and several others have investigated the nickel-catalyzed reactions of alkynes with a variety of electrophiles.[12] These reactions provide access to synthetically useful functional groups such as allylic

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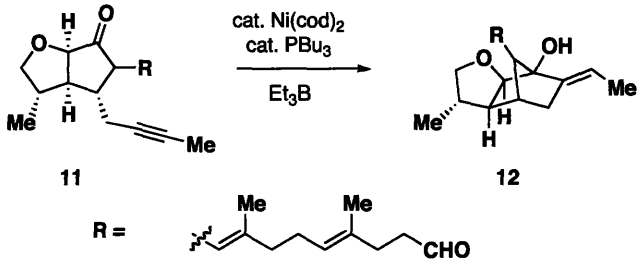
[11] Hirasawa, Y.; Morita, H.; Shiro, M.; Kobayashi, J.–I. *Org. Lett.* **2003**, *5*, 3991-3993.
[12] For a recent review of nickel catalyzed reductive couplings, see: Montgomery, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3890-3908.

alcohols,[13] allylic amines,[14] and homoallylic alcohols.[15] The versatility and functional group tolerance of these reductive coupling reactions have been featured as key steps in the synthesis of several complex natural products such as amphidinolide T1,[16] amphidinolide T4,[17] and (–)-gloeosporone.[18]

Figure 4.



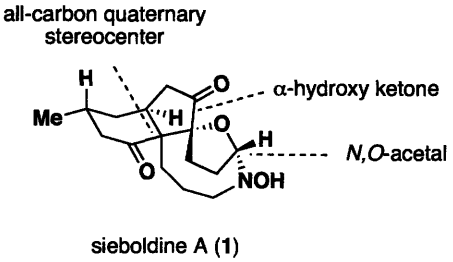
At the outset of this project the sole example of a nickel-catalyzed alkyne-ketone reductive cyclization reaction was observed in the course of the total synthesis of (–)-terpestacin (Figure 4).[19] In this example, reaction between the cyclopentanone and the alkyne was observed in the presence of a pendant aldehyde. This reactivity was unexpected, as ketones had not previously been observed to react under nickel-catalyzed reductive cyclization conditions even when present in large excess.[20] The increased reactivity of the ketone observed in this substrate may be the result of the proximity of the alkyne and ketone functional groups. This example served as a starting point for the total synthesis of **1**.

---

[13] From aldehydes: a) Huang, W. S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221-4223. b) From ketones: Miller, K. M.; Jamison, T.F. *Org. Lett.* **2000**, *7*, 3077-3080.
[14] Patel, S.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2003**, *42*, 1364-1366.
[15] Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076-8077.
[16] Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 998-999.
[17] Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 4297-4307.
[18] Trenkle, J. D. Ph. D. Thesis, Massachusetts Institue of Technology, 2007.
[19] Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 10682-10691.
[20] Coupling reactions run in acetone show no trace of acetone coupling products.

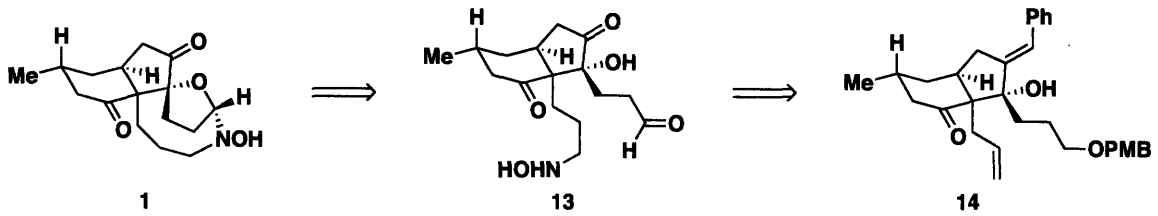
Retrosynthetic Analysis and Structural Considerations

Figure 5. Structural Considerations.



The total synthesis of sieboldine A was initiated with the purpose of investigating a novel nickel-catalyzed alkyne-ketone reductive cyclization for assembly of the hydrindane core of **1**. Besides the construction of the hydrindane core, the unique molecular framework of **1** presented three significant synthetic challenges (Figure 5). These challenges included: (i) construction of an all-carbon quaternary stereogenic center, (ii) formation of an α-hydroxy ketone (containing a tertiary alcohol vicinal to the all-carbon quaternary stereocenter), and (iii) assembly of a hydroxylamine-containing *N,O*-acetal, which closes the polycyclic framework of **1**.

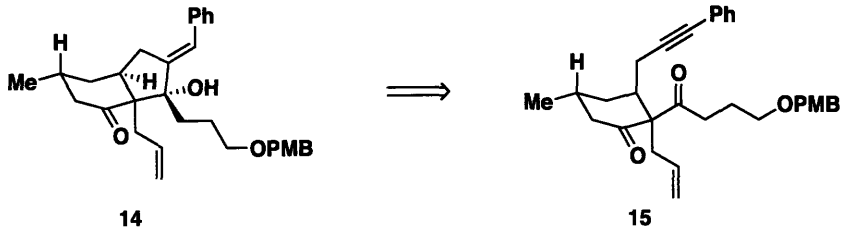
Figure 6. Retrosynthetic Analysis.



Our retrosynthetic analysis starts from sieboldine A (**1**) via opening of the *N,O*-acetal to afford hydroxylamine **13** (Figure 6). This retrosynthetic hydrolysis reveals the alcohol, aldehyde, and hydroxylamine components that make up the *N,O*-acetal and provides inspiration for a condensation strategy to assemble the 9-membered ring in **1**.

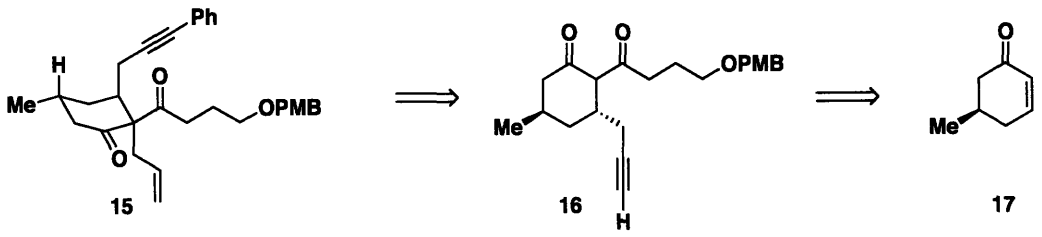
Further simplification of **13** via standard functional group manipulations and oxidation state adjustments affords cyclohexanone **14**, where the α-hydroxy ketone is masked as an allylic alcohol.

Figure 7. Disconnection of the Hydrindane Core.



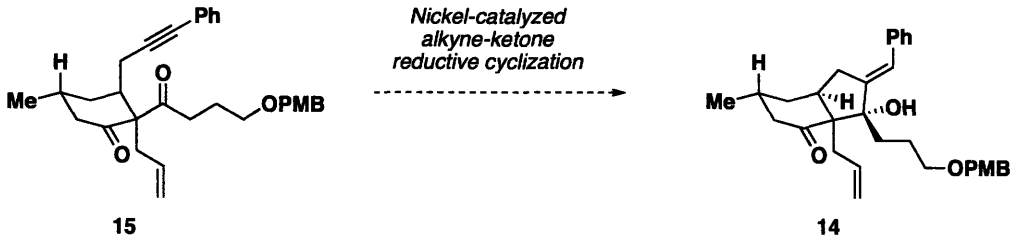
Application of the nickel-catalyzed alkyne-ketone reductive cyclization disconnection to hydrindane **14** opens the bicyclic system to afford diketone **15** (Figure 7). This transformation reveals the alkyne and ketone functional groups that are required for the reductive cyclization and identifies cyclohexanone **15** as an important intermediate towards the total synthesis of sieboldine A (**1**).

Figure 8. Retrosynthetic Analysis.



Simplification of alkyne **15** can be accomplished by disconnection of the allyl group at the all-carbon quaternary center to afford 1,3-diketone **16**. The 1,3-diketone **16** can be simplified into enone **17** by application of a conjugate addition/aldol/oxidation strategy to afford 5-methyl-cyclopent-2-en-1-one (**17**) as the starting material.

Figure 9. Proposed Synthesis of the Hydrindane Core.

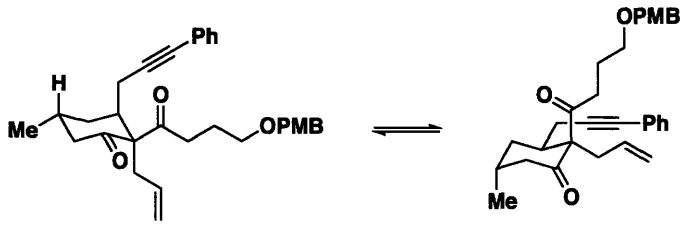


15 14

This synthetic approach hinges upon a successful intramolecular alkyne-ketone reductive coupling of diketone **15** to form hydrindane **14**. The cyclization must differentiate the two carbonyl groups in **15**, as only reaction at the exocyclic carbonyl will afford the hydrindane **14**. In addition to differentiating the two reaction sites, this reaction must differentiate between the two faces, *Re* and *Si*, of the carbonyl as only reaction on the *Si* face will afford the desired diastereomer about the allylic alcohol.

It was initially proposed that the site selectivity of the nickel-catalyzed alkyne-ketone reductive cyclization reaction would be controlled by the conformation of diketone **15** (Figure 10).

Figure 10. Chair Conformations of Diketone 15.



15a 15b

Diketone **15** is expected to have two major conformers in solution, conformer **15a** and conformer **15b**. In conformer **15a** the propargyl group and the allyl group are in axial positions and the methyl group and the exocyclic carbonyl group are in equatorial positions. If the nickel-catalyzed reductive cyclization reaction were to take place from

conformer **15a** this conformation would allow the propargyl group to interact with either of the carbonyl groups present in **15** and a mixture of cyclization products could be expected.[21]

The situation is different in conformer **15b** as in this conformation the methyl group and the exocyclic carbonyl group take up axial positions and the propargyl group and the allyl group take up equatorial positions. With the propargyl group in the equatorial position it can only interact with the exocyclic carbonyl group and this would lead to a site selective reaction.[22] Based upon published *A* values for the different substituents on the cyclohexyl ring, **15b** is expected to be the dominant conformer in solution and should be favored by 0.6 to 1.6 kcal/mol.[23,24] If reaction occurs through these conformers with similar rates selectivity for reaction with the exocyclic carbonyl would be predicted.

Modeling the diastereoselectivity of this reaction is another challenge as this is dependent upon which face of the carbonyl group, *Re* or *Si*, reacts under these conditions. However, some insight can be gained by analysis of the catalytic cycle of the alkyne-ketone reductive cyclization (Figure 11).

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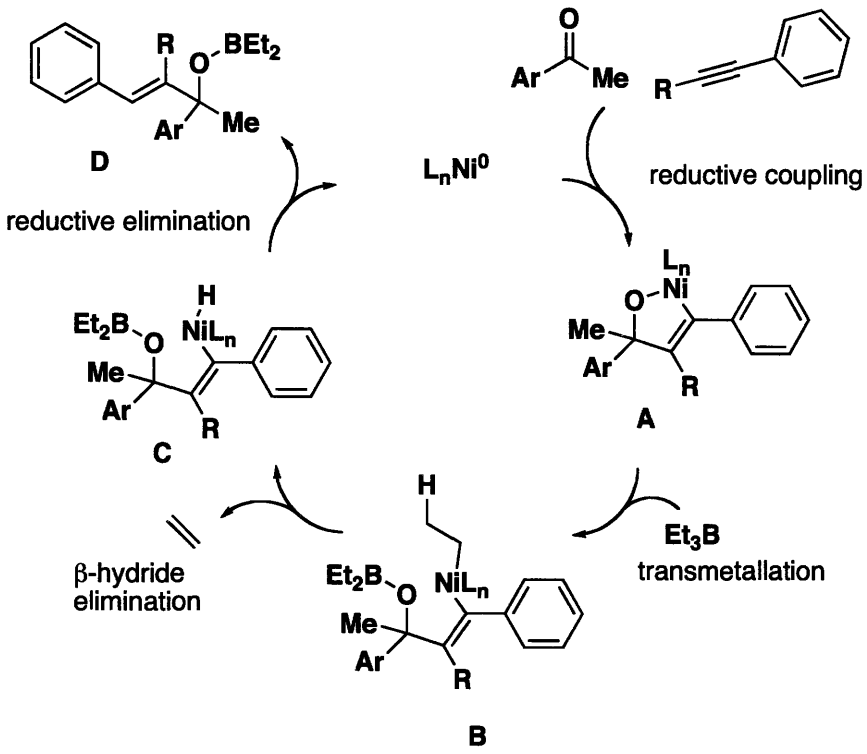
[21] This analysis assumes that the reaction proceeds through a low energy chair conformation and not another conformation.

[22] If reaction of one conformer is much more rapid than the other a Curtin-Hammett situation could be imagined and high selectivity for reaction from the higher energy conformer **15a** could be observed.

[23] Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York 1994.

[24] For this calculation the reported *A* values for the methyl and allyl groups were used and approximate values were used for the exocyclic carbonyl (approximated as CH_3CO) and the propargyl group (approximated as CH_2CN).

Figure 11. Proposed Catalytic Cycle.



Initially the nickel(0) catalyst binds the alkyne and the ketone. This complexation is followed by a reductive coupling to afford oxametallocyclopentene intermediate **A**.[25] Formation of intermediate **A** is followed by transmetallation with Et_3B to afford ethyl-nickel complex **B**. Intermediate **B** then undergoes a β-hydride elimination to release ethylene and form nickel-hydride **C**. From this nickel-hydride species a reductive elimination releases the product **D**, as a borinate ester, and regenerates the nickel(0) catalyst.

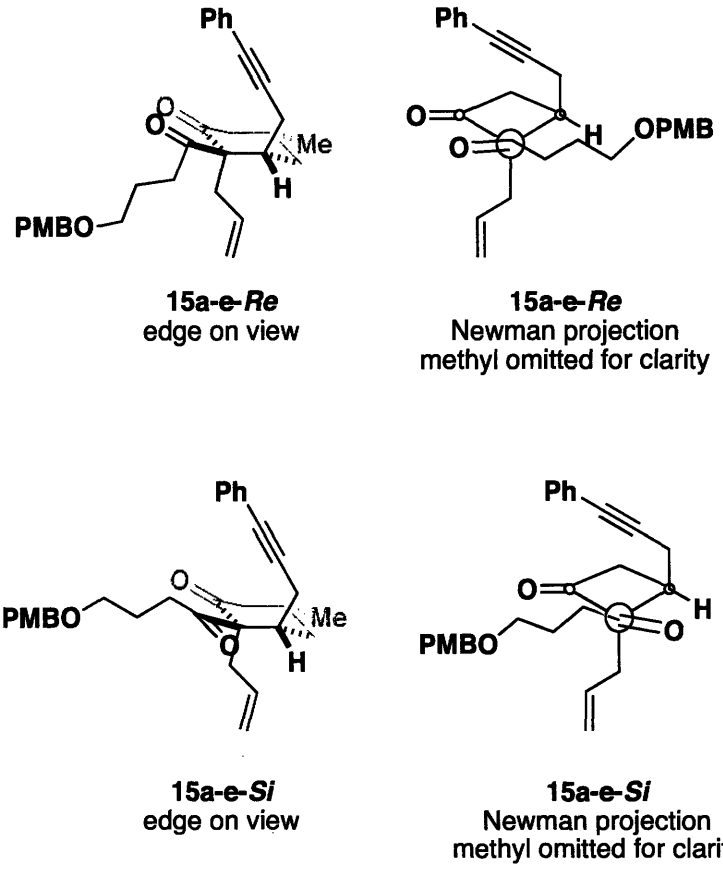
Inspection of this catalytic cycle reveals that formation of the oxametallacyclopentene intermediate determines the diastereoselectivity about the

[25] For a recent crystal structure of a related oxametallacyclopentene, see: Ogoshi, S.; Arai, T.; Ohashi, M.; Kurosawa, H. *Chem. Commun.* **2008**, 1347-1349.

tertiary allylic alcohol. In the formation of this intermediate it is possible to predict the selectivity for the reaction considering two limiting cases, reaction through an early, reagent-like transition state and reaction through a late, product-like transition state.

To predict the facial selectivity for an early, reagent-like transition state it is useful to analyze the interactions that are important in the starting material, because these interactions will be present in the transition state. This analysis considers only steric interactions and electronic factors such as dipole-dipole interactions are omitted. Analysis for reaction from both **15a** and **15b** is presented.

Figure 12. Early Transition States From 15a.



15a-e-*Re*
edge on view

15a-e-*Re*
Newman projection
methyl omitted for clarity

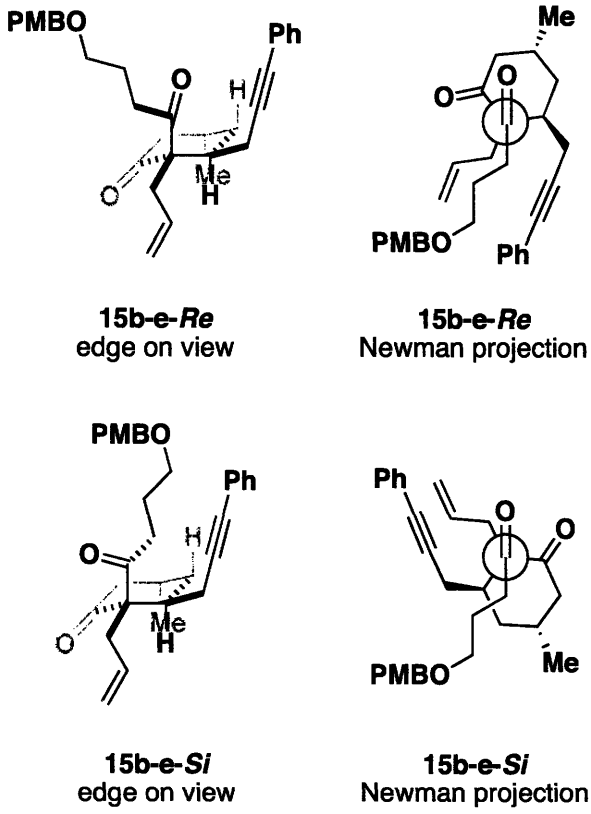
15a-e-*Si*
edge on view

15a-e-*Si*
Newman projection
methyl omitted for clarity

For conformer **15a** two transition states, **15a-e-*Re*** and **15a-e-*Si***, can be proposed. In these two transition states the exocyclic carbonyl is positioned to allow approach of the

alkyne-nickel complex along the Bürgi-Dunitz trajectory. As a consequence of this required trajectory, in **15a-e-*Re*** the exocyclic carbonyl aligns with the cyclic carbonyl. In **15a-e-*Si*** the exocyclic carbonyl aligns *anti* to the ring carbonyl. This forces the alkyl group of the exocyclic carbonyl to eclipse the ring carbonyl. On the basis of these interactions, **15a-e-*Re*** should be the more accessible transition state. This would result in reductive cyclization onto the *Re* face of the exocyclic carbonyl group and formation of the undesired diastereomer about the tertiary allylic alcohol.

Figure 13. Early Transition States from 15b.



15b-e-*Re*
edge on view

15b-e-*Re*
Newman projection

15b-e-*Si*
edge on view

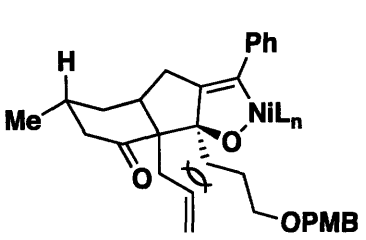
15b-e-*Si*
Newman projection

From conformer **15b** two reagent-like transition states can be proposed, **15b-e-*Re*** and **15b-e-*Si***. These transition states allow approach of the nickel-alkyne complex along the Bürgi-Dunitz angle just as in **15a**. In **15b-e-*Re*** the exocyclic carbonyl is rotated so that the C–O bond is placed over the ring. This forces the alkyl group to eclipse the allyl

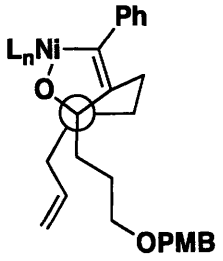
group. In **15b-e-*Si*** the carbonyl is rotated so that the alkyl group is placed over the ring and the carbonyl group eclipses the allyl group. With the eclipsed alkyl groups in **15b-e-*Re*** it would be more difficult to access this transition state than **15-e-*Si***. Thus, if the reaction occurs through conformer **15b** reaction on the *Si* face of the exocyclic carbonyl is predicted and would afford the desired diastereomer about the tertiary allylic alcohol.

In contrast, if the reaction occurs via a late transition state we should consider transition states similar to the oxametallacycle intermediate. Examining the important interactions in the oxametallacycle intermediates can then be used to predict the diastereoselectivity of the reductive cyclization.

Figure 14. Late Transition States from 15a.

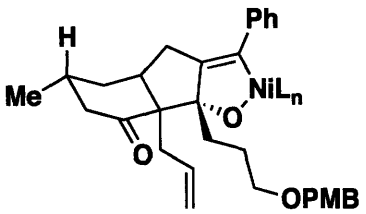


15a-l-*Re*

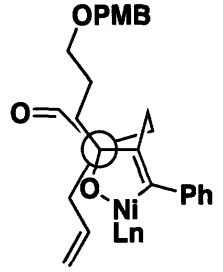


15a-l-*Re*

Newman projection
cyclohexyl ommitted for clarity



15a-l-*Si*



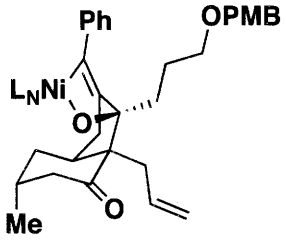
15a-l-*Si*

Newman projection
cyclohexyl ommitted for clarity

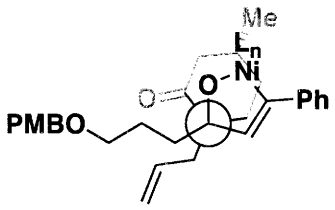
In a late transition state **15a** would afford two oxametallocyclopentene transition states arising from attack at the *Re* and the *Si* face of the exocyclic carbonyl to generate

15a-l-*Re* and **15a-l-*Si*** (Figure 15). In **15a-l-*Re*** the alkyl chain of the carbonyl eclipses the allyl group and engenders a severe steric interaction that should be significant in the transition state. In **15a-l-*Si*** the oxygen in the oxametalocyclopentene is placed near the allyl group. Since **15a-l-*Si*** is devoid of significant steric interactions, it should be a more accessible transition state than **15a-l-*Re***. As a consequence of the accessibility of **15a-l-*Re*** if the reaction were to occur from conformer **15a** through a late transition state, reaction at the *Si* face of the carbonyl would be predicted. This would afford the desired diastereomer about the tertiary allylic alcohol.

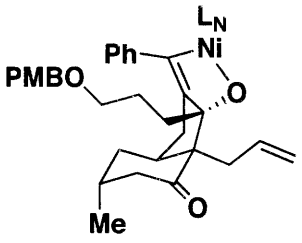
Figure 15. Late Transition States from 15b.



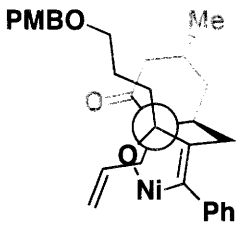
15b-l-*Re*



15b-l-*Re*
Newman projection



15b-l-*Si*



15b-l-*Si*
Newman projection

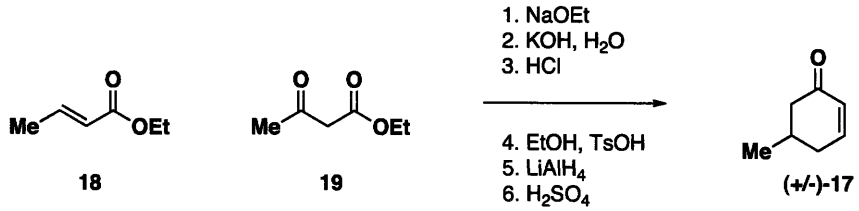
Reaction through **15b** would afford two oxametallocyclopentene transition states, from attack at the *Re* and the *Si* face of the acyclic carbonyl to generate intermediates **15b-l-*Re*** and **15b-l-*Si*** (Figure 15). In **15b-l-*Re*** the alkyl chain of the acyclic carbonyl is very nearly eclipsed with the allyl group and engenders a severe steric interaction that

should be significant in the transition state. In **15b-l-*Si***, the oxygen in the oxametallacyclopentene is placed near the allyl group. This forces the alkyl group out over the cyclohexyl ring and would encounter significant steric interactions. While not as clearly differentiated, in this analysis the most accessible transition state for **15b** would be reaction through **15-l-*Si***. Therefore regardless of chair conformation, **15a** or **15b,** a late transition state would predict formation of the desired diastereomer about the allylic alcohol.

To summarize, if the nickel-catalyzed alkyne-ketone reductive coupling occurs through an early transition state the undesired diastereomer about the allylic alcohol would be expected to be the major product. In contrast, if the reaction involves a late transition state, the desired diastereomer about the tertiary alcohol should be formed and could be elaborated towards the total synthesis of **1**. To answer some of these questions and test these predictions the synthesis of diketone **15** was initiated.

Results and Discussion

Scheme 1.



Our studies directed towards towards the total synthesis of sieboldine A (**1**) began from (±)-5-methyl-cyclohex-2-en-1-one (**17**), which was readily obtained from ethyl crotonate (**18**) and ethyl acetoacetate (**19**) following literature procedures.[26] With a reliable and scalable synthesis of enone **17** in hand a tandem conjugate propargylation-aldol reaction was investigated.

A. Tandem Approach to β-Hydroxy Ketone

Tandem reactions are powerful methods in synthetic organic chemistry due to the rapid increase in molecular complexity that can be achieved by coupling two or more discrete bond-forming reactions. Of these methods the tandem conjugate addition-aldol reaction is particularly useful as it allows for the formation of two new carbon-carbon bonds and up to three new stereogenic centers. A wide variety of substrates participate in this process,[27] providing valuable products that have been used in a number of total syntheses.[28] The most widely encountered form of this reaction employs alkyl or alkenyl

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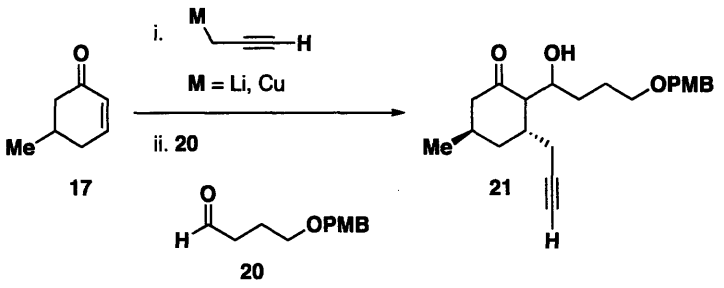
[26] a) Musser, A. K.; Fuchs, P. L. *J. Org. Chem.* **1982**, *47*, 3121-3131. b) Majetch, G.; Lowery, D.; Khetani, V.; Song, J.-S.; Hull, K.; Ringold, C. *J. Org. Chem.* **1991**, *56*, 3988-4001.

[27] Hosomi, A.; Yanagi, T.; Hojo, M. *Tetrahedron Lett.* **1991**, *32*, 2371-2374.

[28] For examples of a tandem conjugate addition-aldol reaction, see: a.) Arnold, L. A.; Naasz, R.; Minnaard, J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841-5842. b.) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718-4726.

copper species for the conjugate addition and generation of the enolate used in the subsequent aldol addition.[29]

Scheme 2.

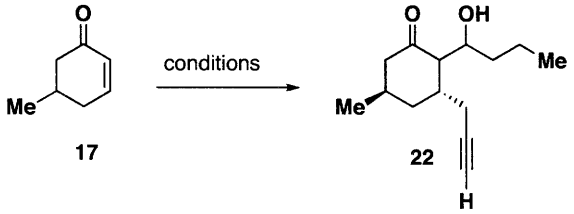


Application of this approach to the synthesis of β-hydroxy ketone **21** requires that the propargyl copper reagent undergo a selective propargyl addition to enone **17**. Use of propargyl copper reagents for conjugate addition reactions are difficult and have encountered two main problems, i) low reactivity of the propargyl copper species and ii) low selectivity for propargyl versus allenyl addition products.

To overcome these problems several strategies have been taken, including attempts to bias the propargyl copper species for a selective addition and/or the use of alternative propargyl metal species. Despite the concerns over the tandem conjugate addition-aldol reaction investigation into this reaction sequence was explored, as this reaction to would provide rapid access to β-hydroxy ketone **21**.

[29] For reviews of organocopper tandem reactions, see: a.) Taylor, R. J. K. *Synthesis* **1985**, 364-392. b.) Heng, K. K.; Smith, R. J. *Tetrahedron* **1979**, *35*, 425-435.

Table 1. Tandem Conjugate Propargylation-Aldol Reaction.



17 22

Entry	Conditions	Result
1	$CuBr_2 \cdot SMe_2$, TMS-propargyllithium; butyraldehyde	Complex mixture
2	HMPA, TIPS-propargyllithium; butyraldehyde	No reaction
3	TBSOTf, In^0, SMe_2, Propargylbromide	Trace[a]

[a] Silyl enol ether is the desired product.

Investigation into the tandem conjugate propargylation-aldol reaction began with the conditions listed in Table 1. A propargyl copper species (Table 1, entry 1) provided complex mixtures of products after reaction with enone **17** potentially due to competing propargyl and allenyl conjugate addition products.[30] Alternative propargyl metal reagents, including a propargyl lithium species[31] (Table 1, entry 2) and a propargyl indium species[32] (Table 1, entry 3) were also ineffective for this transformation.

An alternative to nucleophilic propargyl metal species are allenyl metal reagents that undergo a S_E2' reaction to afford propargylated products. In the presence of a Lewis acid promoter, allenylstannanes are reported to undergo a conjugate propargylation reaction with a variety of cyclohexenenone substrates to provide β-propargylated cyclohexanones (Scheme 3).[33]

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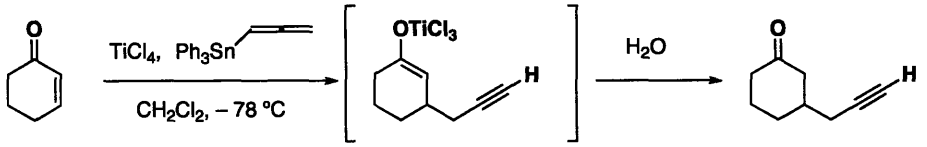
[30] For an example of competing propargyl and allenyl conjugate addition of propargyl copper species, see: Ganem, B. *Tetrahedron Lett.* **1974**, *51/52*, 4467-4470.
[31] Corey, E. J.; Rücker, C. *Tetrahedron Lett.* **1982**, *23*, 719-722.
[32] Lee, K.; Kim, H.; Miura, T.; Kiyota, K.; Kusama, H.; Kim, S.; Isawa, N.; Lee, P. H. *J. Am. Chem. Soc.* **2003**, *125*, 9682-9688.
[33] Haruta, J.-I.; Nishi, K.; Matsuda, S.; Akai, S.; Tamura, Y.; Kita, Y. *J. Org. Chem.* **1990**, *55*, 4853-4859.

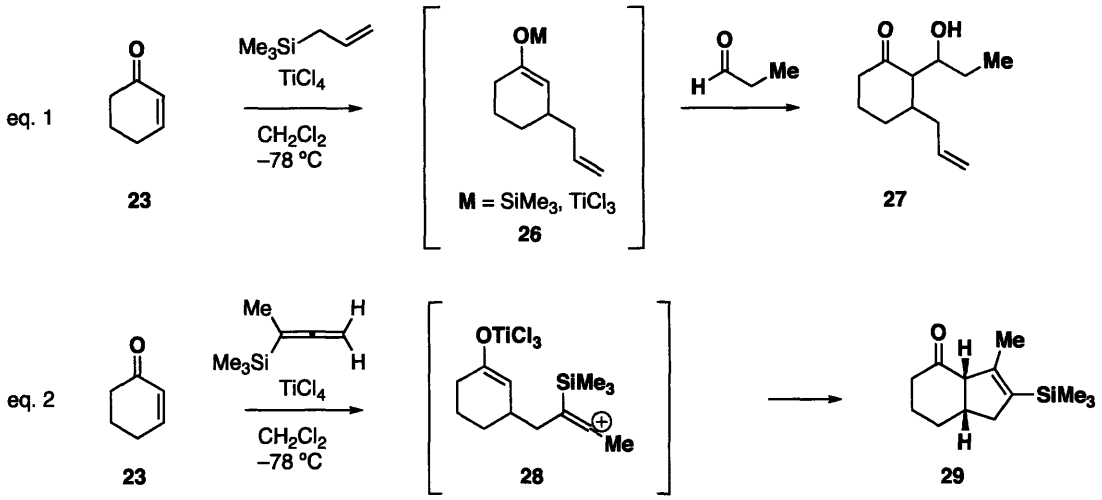
Scheme 3.



23 24 25

Presumably this reaction generates an intermediate titanium enolate, such as **24**, that should be a competent nucleophile for aldol addition. While no tandem conjugate addition-aldol reactions have been reported for allenylstannanes, similar tandem processes with ally and allenylsilanes are known (Scheme 4).

Scheme 4. Tandem Reactions of Silanes.

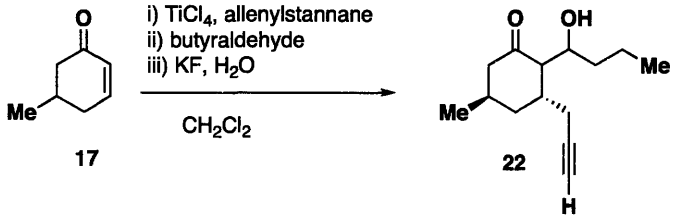


With allylsilanes the initial conjugate addition affords an enolate species and this enolate has been added to a variety of electrophiles including aldehydes, acetals, and alkyl halides to afford α-functionalized products (Scheme 4, equation 1).[34] Allenylsilanes also perform a similar conjugate addition reaction to afford an enolate, however in this instance intramolecular reaction with a vinyl cation that results from a 1,2-silyl migration affords trimethylsilylcyclopentenes (Scheme 4, eq. 2).[35] Since similar

[34] Hosomi, A.; Hashimoto, H.; Kobayashi, H.; Sakurai, H. *Chem. Lett.* **1979**, 245-248.
[35] Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935-947.

tandem transformations are known with other S_E2' nucleophiles investigation into the tandem reaction of allenylstannanes began.

Table 2. Allenylstannane Propargylation Reactions.



Entry	Allenylstannane	Temperature (°C)	Result
1	tributylallenylstannane	-40	Complex mixture
2	triphenylallenylstannane	-78 → -40	**22**, 15% yield[a]
3	triphenylallenylstannane	-78 → -20	**22**, ~ 30% yield[a]

[a] Product contaminated with tin byproducts.

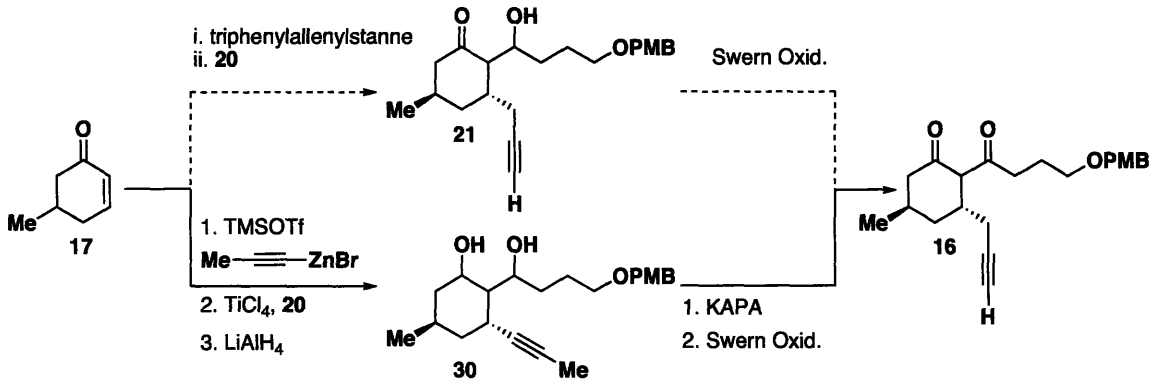
Initial propargylation reactions with tributylallenylstannane (Table 2, entry 1) resulted in a variety of decomposition products derived from enone **17**. The analogous triphenylallenylstannane reagent (Table 2, entries 2 and 3) afforded small amounts of the desired product. Attempts to improve the reaction efficiency by varying temperature, stoichiometry, and reaction time proved ineffective, as only minor improvements in yield were observed. It was unclear whether an inefficient S_E2' reaction or the subsequent aldol reaction was leading to the poor yield in these reaction attempts.

Several factors may contribute to the poor efficiency of this tandem conjugate propargylation-aldol reaction with allenylstannanes. The initial conjugate addition reaction generates a titanium enolate and also generates triphenyltin chloride as a byproduct. The tin chloride may react with the enolate species to afford the corresponding tin enolate. Tin enolates have different reactivity profiles than the

corresponding titanium enolates and generally require an added promoter to afford efficient aldol reactions.[36] The prevalence of both titanium and tin enolates in the reaction mixture could lead to poor reactivity in the aldol addition. Ultimately, the tandem conjugate propargylation-aldol reaction was abandoned due to its poor efficiency in producing the desired β-hydroxy ketone.

B. Conjugate Propynylation

Scheme 5.



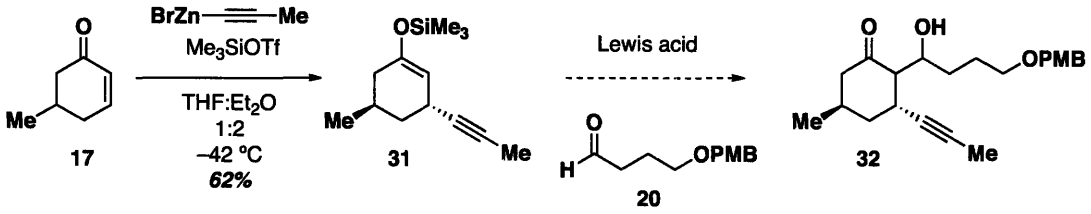
Without direct access to β-hydroxy ketone **21**, alternative means of installing the propargyl group were investigated. The most direct approach used a conjugate propynylation followed by an alkyne isomerization to install the propargyl group. This approach would require three additional transformations to access diketone **16** when compared to the tandem reaction approach but would rely upon well-established synthetic methods.

To begin, the conjugate propynylation of enone **17** was pursued. Standard organocuprate chemistry cannot be used to install the propynyl group due to the strength

[36] Yanagisawa, A.; Kimura, K.; Nakatsuka, Y.; Yamamoto, H. *Synlett* **1998**, 958-959.

of the copper-alkyne bond.[37] Methods that rely upon the use of alkynyl aluminum[38] or alkynyl zinc[39] species with Lewis acid promoters are effective for this transformation and allow access to β-alkynylated cyclohexanones. In addition, with the appropriate choice of Lewis acid promoter the resultant enolate may be trapped as an enol ether providing the means to perform a regiospecific functionalization via the aldol reaction.

Scheme 6.



Treatment of enone **17** with propynyl zinc bromide and trimethylsilyl trifluoromethanesulfonate resulted in conjugate propynylation to afford silyl enol ether **31** in good yield. With access to silyl enol ether **31**, investigation into its reactivity in the Mukaiyama aldol reaction was pursued. [40] Treating silyl enol ether **31** with variety of promoters resulted in low isolated yields of β-hydroxy ketone **32** and instead led to hydrolysis of the silyl enol ether. The difficulty associated with the Mukaiyama aldol reaction led to the investigation of alternative methods for generation of β-hydroxy ketone **32**.

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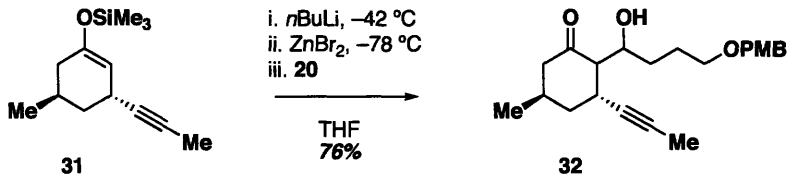
[37] a) House, H. O.; Fisher, W. F. *J. Org. Chem.* **1969**, *34*, 3615-3618. b) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210-7211.
[38] Kim, S.; Park, J. H. *Synlett* **1995**, 163-164.
[39] Kim, S.; Lee, J. M. *Tetrahedron Lett.* **1990**, *52*, 7627-7630.
[40] Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503-7509.

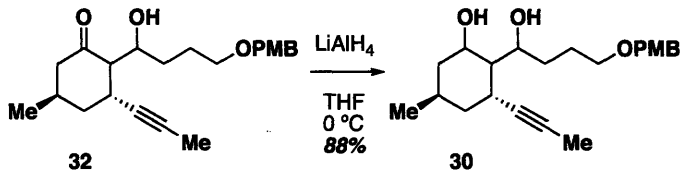
Generation of enolates from silyl enol ethers can be accomplished by nucleophilic cleavage of the silyl enol ether with a potassium alkoxide[41] or an alkyl lithium reagent.[42] Cleavage of silyl enol ethers with these reagents provide the corresponding potassium or lithium enolates which can be used in a variety of subsequent transformations, including aldol reactions.[43]

Scheme 7.



Treatment of silyl enol ether **31** with *n*-butyllithium cleaved the silyl enol ether to generate the corresponding lithium enolate. Transmetallation of the lithium enolate to the zinc enolate[44] followed by addition of aldehyde **20** resulted in an aldol reaction to provide β-hydroxy ketone **32** in good yield as a mixture of diastereomers. With access to β-hydroxy ketone **32**, attention turned to base-mediated isomerization of the internal alkyne to the terminal position.

Scheme 8.

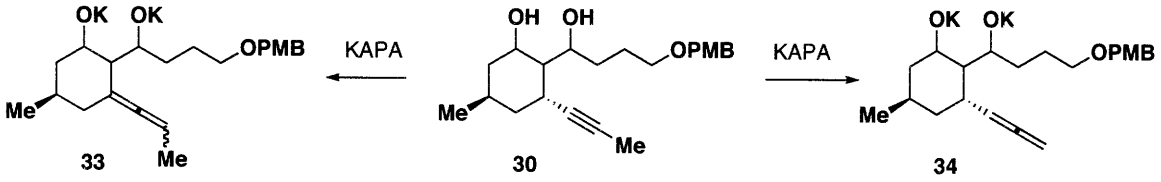


[41] Yu, W.; Jin, Z. *Tetrahedron Lett.* **2001**, *42*, 369-372.
[42] Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464-4465.
[43] For an example of the use of nucleophilic cleavage of silyl enol ethers in natural products total syntheses, see: Sakai, M.; Sasaki, M.; Tanino, K.; Miyashita, M. *Tetrahedron Lett.* **2002**, *43*, 1705-1708.
[44] House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310-3324.

Before exploration of the alkyne isomerization reaction, reduction of β-hydroxy ketone **32** with $LiAlH_4$ was performed to afford diol **30** as a mixture of diastereomers. This reduction was performed to prevent base-mediated decomposition of **32** as the majority of alkyne isomerization methods rely upon strongly basic conditions to promote the reaction.

The most commonly employed reagent for isomerization reactions of internal alkynes to terminal alkynes is potassium aminopropylamide (KAPA).[45] The mechanism of this transformation involves initial propargylic deprotonation followed by a reprotonation step to afford an allenyl intermediate. The allenyl intermediate undergoes a similar deprotonation/reprotonation step to afford the terminal alkyne, which gets irreversibly deprotonated to afford the potassium acetylide.

Scheme 9.

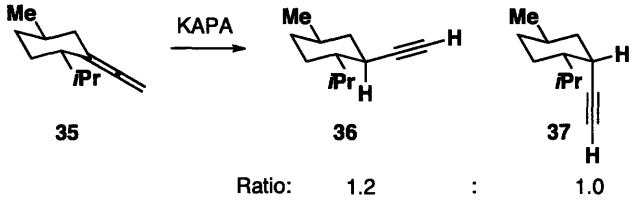


One concern with the isomerization step is the competition between deprotonation at the propargylic methyl group, to afford allene **34**, and deprotonation at the ring junction to afford allene **33** (Scheme 9). Formation of allene **33** has the potential to epimerize the stereocenter at the ring junction. Deprotonation at the propargylic methyl group should be favored because of its larger number of propargylic hydrogen atoms (3

[45] Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891-892.

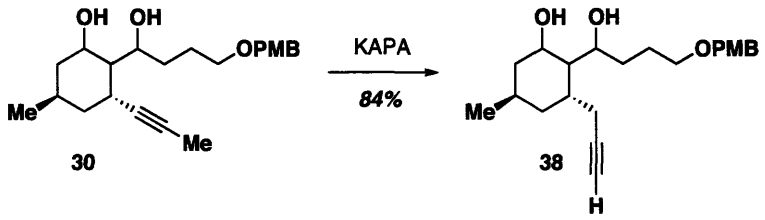
vs 1), its increased acidity relative to the ring junction hydrogen atom, and its relative accessibility compared to the ring junction.

Scheme 10.



While formation of allene **33** is a concern, studies on isomerization reactions with exocyclic allenes[46] suggest that there will be low selectivity for formation of the equatorial versus the axial alkyne product (Scheme 10, **36** vs. **37**). If a small amount of allene **33** is formed, half will be epimerized and the remainder will return to **30**. Considering this it was reasoned that little epimerization would occur in the isomerization reaction.

Scheme 11.



With these concerns in mind, isomerization of diol **30** was pursued. Initially isomerization of diol **30** was a difficult transformation plagued with inconsistent conversion of the starting material and often required multiple reaction attempts for complete isomerization. Full conversion could be obtained by increasing the amount of KAPA used in the isomerization reaction. Under these conditions the isomerization

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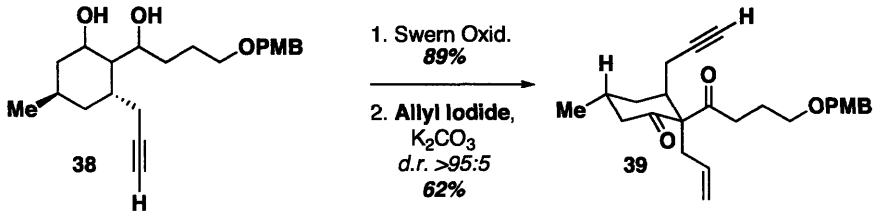
[46] Spence, J. D.; Wyatt, J. K.; Bender, D. M.; Moss, D. K.; Nantz, M. H. *J. Org. Chem.* **1996**, *61*, 4014-4021.

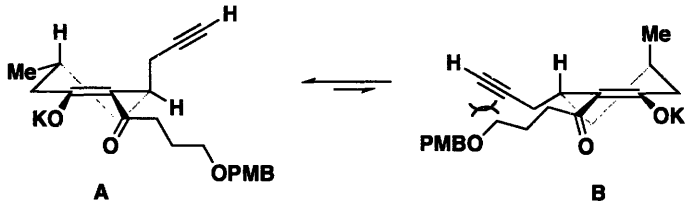
afforded good yields of diol **38**. Unfortunately, at this time it was difficult to determine whether any epimerization at the ring junction had occurred.

Scheme 12.



Subsequent Swern oxidation of diol **38** followed by alkylation of the resulting 1,3-diketone assembled cyclohexanone **39** in good yield and with excellent diastereoselectivity. Notable, is that only two reaction products could be isolated from the alkylation, the desired product **39** and an *O*-alkylation product.[47]

Figure 16. Rationale for observed diastereoselectivity.

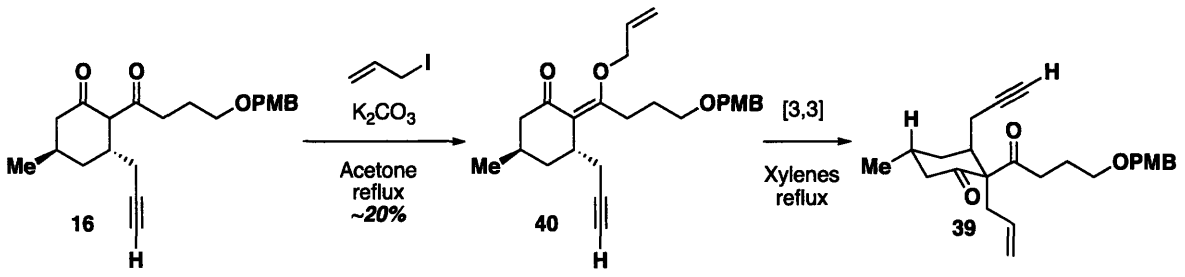


The diastereoselectivity of the alkylation reaction can be rationalized by examining the two enolate conformations **A** and **B** (Figure 16). In conformer **B** there is $A^{1,2}$ strain between the exocyclic carbonyl and the propargyl group which occupies a pseudo equatorial position. Conformer **A** is free of this allylic strain and is the dominant conformer in solution. Reaction occurs through conformer **A** where the propargyl group occupies a pseudo axial position and sterically hinders the top face of the enolate. Due to this steric shielding by the propargyl group, the allyl electrophile approaches from the

[47] *O*-alkylation and *C*-alkylation account for ~ 80-85% of the mass. No other alkylation products are observed in the crude reaction mixture.

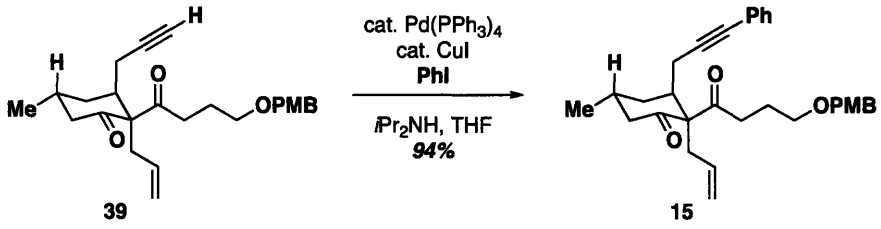
bottom face of the enolate and sets the desired *syn* relationship between the propargyl group and the exocyclic carbonyl.[48] In addition to a direct alkylation, there is an alternative reaction pathway available for formation of diketone **39**; *O*-alkylation followed by a Claisen rearrangement.

Scheme 13.



Isolation of the *O*-alkylation product **40** and subsequent Claisen rearrangement required much higher temperatures than those reached in the alkylation reaction. The diastereoselectivity of the Claisen rearrangement was much lower, ~3:1, than that observed in the alkylation. Due to these observations it seems reasonable to assume that the major reaction pathway for formation of **39** is by a direct alkylation.

Scheme 14.



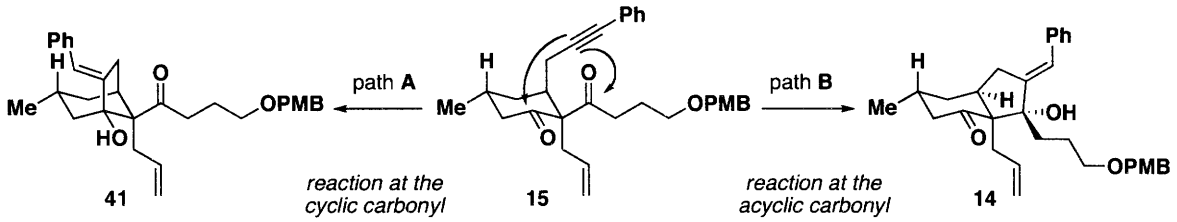
Sonogashira reaction of terminal alkyne **39** with iodobenzene afforded reductive cyclization substrate **15** in good yield (Scheme 14).

---

[48] For similar selectivity with 2,3 substituted cyclohexanones, see: Boeckman, R. K. *J. Org. Chem.* **1973**, *38*, 4450-4452.

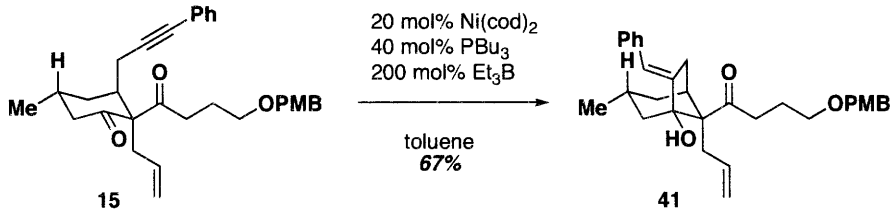
C. Initial Reductive Cyclization

Figure 17. Reductive Cyclization Site Selectivity.



With an efficient route to diketone **15** (7 steps, 18% overall yield), investigation of the reductive cyclization reaction could begin. These studies were directed towards exploration of the site-selectivity (Figure 17, path A vs. path B) and the diastereoselectivity of the nickel-catalyzed alkyne-ketone reductive cyclization of diketone **15**.

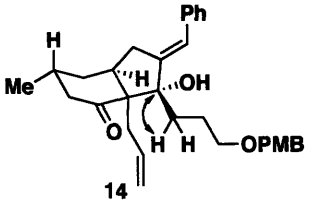
Scheme 15.



To answer these questions diketone **15** was treated with the nickel-catalyzed reductive cyclization conditions shown (Scheme 15). Purification of the reaction mixture afforded a single reductive coupling product.[49] However, conclusive identification of the product as compound **14** or compound **41** could not be accomplished with simple (^{1}H, ^{13}C, IR) spectroscopic techniques.

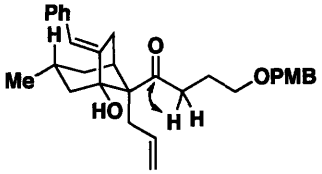
[49] As determined by ^{1}H, ^{13}C, IR, HRMS.

Figure 18. Structure Determination.



14

characteristic HMBC crosspeak
not observed



41

characteristic HMBC crosspeak
observed

Differentiation of the two possible reductive coupling products, **14** and **41**, was accomplished with the use of gCOSY and HMBC spectra. The HMBC spectrum of the reductive coupling product showed a signal from a carbonyl carbon to hydrogen atoms that were located on the alkyl sidechain of the exocyclic carbonyl in diketone **15**. This observation is consistent only with the structure of bicycle **41**.

Formation of bicycle **41** from reaction with the ring carbonyl group suggested that the reaction was occurring though conformer **15a**, where the propargyl group occupies an axial position (Figure 10). Since it was expected that reaction at either carbonyl could be obtained through conformer **15a**, studies aimed at altering the site selectivity of the reductive cyclization were performed. However, in all cases the sole reductive coupling product was bicycle **41** resulting from reaction at the ring carbonyl. The consistent, and apparently exclusive, reactivity of this carbonyl group under the reductive cyclization conditions led to the investigation of strategies aimed at differentiating the two carbonyl functional groups in **15**.

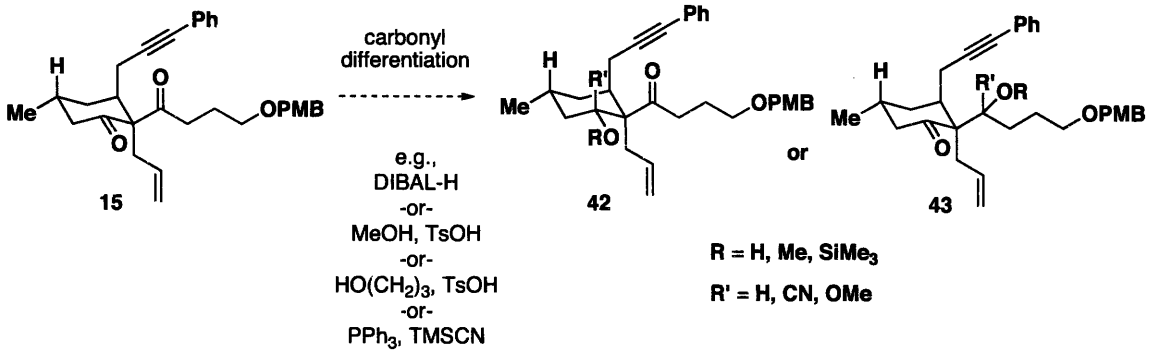
D. Carbonyl Differentiation

Most carbonyl differentiation methods, such as ketal formation, reduction, and cyanohydrin formation, rely upon large electronic or steric differences to provide the

basis for selectivity.[50] In diketone **15**, both carbonyl functional groups have similar steric and electronic characteristics, and it follows that differentiation of the two carbonyl groups could pose a significant challenge.

Ideally, the differentiation reaction would occur with complete selectivity for the cyclic carbonyl to afford compounds of general structure **42**. These compounds could be directly screened in the reductive cyclization without the need for further transformations (Scheme 16). Less desirable is a selective reaction with the acyclic carbonyl to afford compounds such as **43**. While still useful these compounds would require subsequent transformations before they could be screened in the reductive cyclization reaction.

Scheme 16.



Initially, a variety of nucleophilic differentiation methods were investigated, such as ketal formation, reduction, and cyanohydrin formation. These methods were unable to differentiate the two carbonyl groups of **15** and led to either intractable reaction mixtures or recovery of unreacted starting material. An alternative strategy to these intermolecular differentiation methods is an intramolecular approach.

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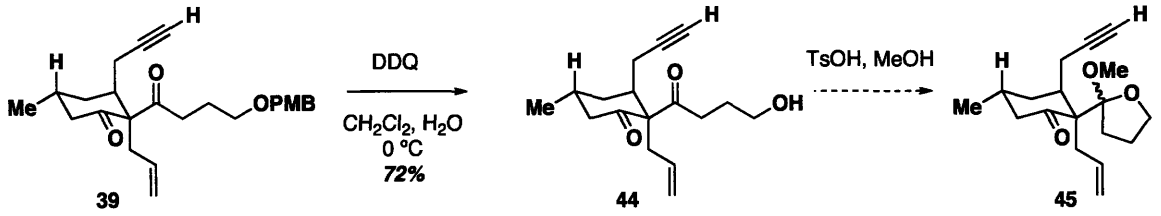
[50] For differentiation between carbonyl groups, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; and references therein.

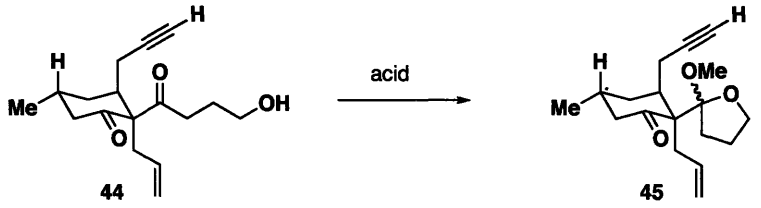
Investigation into the intramolecular differentiation strategy began with oxidative deprotection of the PMB ether to afford diol **44** (Scheme 17). It was envisioned that upon treatment of diol **44** with Lewis or Brønsted acidic conditions that an intramolecular ketal formation would occur. Selectivity would be based upon the formation of the 5-membered ring versus a 7-membered ring and should allow access to ketal **45**.

Scheme 17



While intramolecular ketal formation may allow differentiation of the two carbonyl groups in **39** it does have some limitations. The first is that the ketal product **45** may be formed as a mixture of diastereomers. While the diastereomers would not be a problem in the long term, due to eventual deprotection of the ketal, they will make analysis of the crude reaction mixture more difficult. Another problem is that the ketal product would require at least three further transformations before it could be investigated in the reductive cyclization reaction. Despite these limitations the intramolecular ketal formation was pursued, as it appeared to allow for differentiation of the two carbonyl groups.

Table 3: Intramolecular Ketal Formation



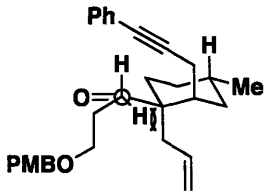
44 45

Entry	Acid	Result
1	HCl, MeOH, 65 °C	Decomposition
2	PPTS, MeOH, C_6H_6, 80 °C	No reaction
3	BF_3•OEt_2, $MeOSiMe_3$, – 78 °C	"
4	TsOH, C_6H_6, 80 °C	Decomposition
5	BF_3•OEt_2, – 78 °C	No reaction

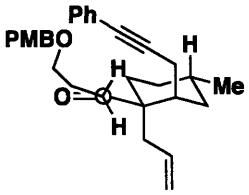
Treatment of diol **44** under a variety of reaction conditions did not lead to isolation of the desired methyl ketal **45**. Several reaction conditions using strong acids and heating (Table 3, entries 1 and 3) resulted in decomposition of the starting material. Milder acids resulted in no reaction. Attempts at hemiacetal formation (Table 3, entries 4 and 5) were also unsuccessful. Since both intramolecular and intermolecular methods were ineffective for the differentiation of the two carbonyl groups in diketone **15**, more unconventional methods were investigated. In particular a selective enolization strategy appeared attractive.

For enolate formation to occur an α-hydrogen atom must be aligned with the π-system of the carbonyl. This orientation increases the acidity of that hydrogen atom and allows formation of the enolate. For deprotonation of the hydrogen atoms α to the exocyclic carbonyl group, the ground state, with the alkyl chain eclipsed with the carbonyl group, must rotate to align the hydrogen atom with the π system of the carbonyl (Figure 19).

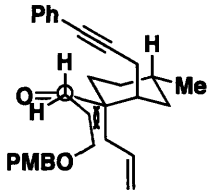
Figure 19. Conformations of 39.



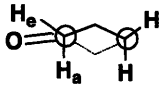
Orientation for formation of *Z*-enol ether *(cyclic carbonyl ommitted)*



Ground State *alkyl-chain eclipsed with carbonyl*



Orientation for formation of *E*-enol ether *(cyclic carbonyl ommitted)*



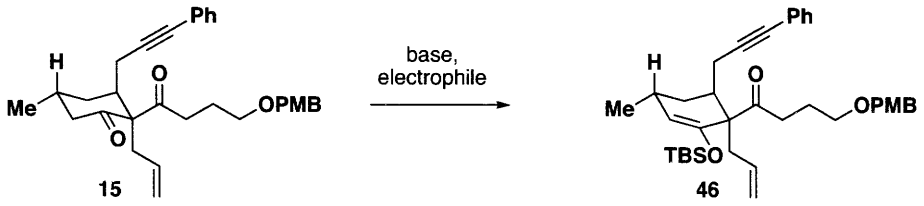
Cyclic Carbonyl *(substituents ommitted)*

If the alkyl chain rotates to allow formation of the *E*-enolate the alkyl chain encounters a steric interaction with the substituents at the quaternary center. If the alkyl chain rotates towards to allow formation of the *Z*-enolate a hydrogen atom encounters a steric interaction with the quaternary stereocenter. These interactions destabilize the transition states for formation of an enolate from the exocyclic carbonyl.

In the ground state of the cyclic carbonyl the axial hydrogen is aligned with π system of the ring carbonyl as is required for enolate formation. [51] Since the hydrogen atoms α to the exocyclic carbonyl are destabilized in the orientations required for enolate formation and the axial hydrogen atom α to the cyclic carbonyl does not encounter these interactions, a selective enolization reaction may be possible. [52,53]

[51] Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269-6278.
[52] For an example of differentiation of carbonyl by selective enolization, see: Paquette, L. A.; Zhao, M.; Friedrich, D. *Tetrahedron Lett.* **1992**, *33*, 7311-7314.
[53] This analysis assumes a kinetically controlled deprotonation.

Table 4. Selective Enolization Studies.



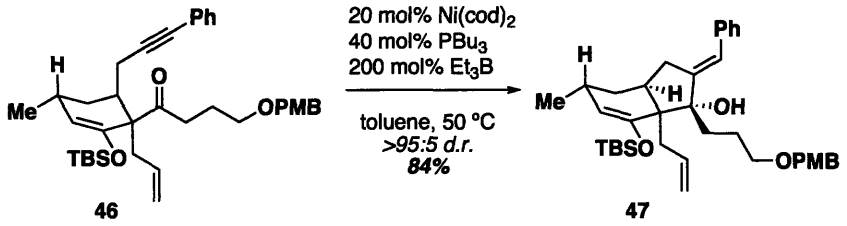
Entry	Base	Electrophile	Yield 46
1	LDA	Ac_2O	no reaction
2	KH	TBSCl	trace
3	KHMDS	TBSCl	15%
4	TBSOTf	TBSCl	90%

Investigation into the selective enolization strategy began by treatment of **15** with LDA and Ac_2O, in an attempt to form an enol acetate, and resulted in isolation of starting material from the reaction mixture (Table 4, entry 1). Use of KH and TBSCl was also ineffective leading to a very low conversion at room temperature. However, use of KHMDS and TBSCl resulted in isolation of the desired silyl enol ether **46**, albeit in low yield. Switching to soft enolization conditions (Table 4, entry 4) afforded silyl enol ether **46** in good yield and provided a high yielding method for differentiation of the two carbonyl groups in diketone **15**.

E. Reductive Cyclization

With an effective way of differentiating the two carbonyl groups in **15**, attention turned to exploration of the reactivity and diastereoselectivity of silyl enol ether **46** under nickel-catalyzed reductive cyclization conditions.

Scheme 18.



Treatment of **46** with $Ni(cod)_2$, PBu_3, and Et_3B at room temperature led to complete recovery of starting material. Interestingly the alkyne in **46** did not undergo commonly observed side reactions, including cyclotrimerization, oligomerization, or reduction.[54] This pointed to a congested steric environment about the alkyne. In an effort to overcome the steric hindrance heating of the reaction mixture was investigated. At elevated temperatures silyl enol ether **46** underwent a smooth reductive cyclization reaction to afford bicycle **47** in good yield and with excellent diastereoselectivity.[55,56]

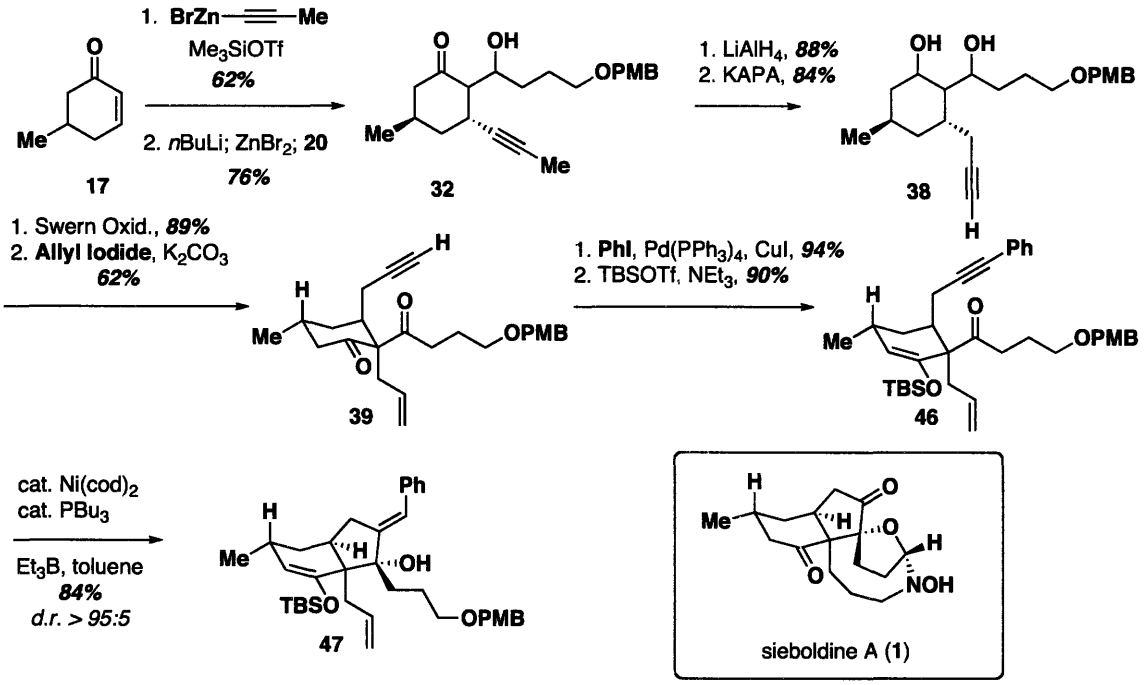
Figure 20. Rationale for Observed Diastereoselectivity.

The high diastereoselectivity for formation of the allylic alcohol can be rationalized by assuming a late transition state structure and examining two diastereomeric oxametallacycles, ***Re*** and ***Si*** (Figure 20).[57] Reaction with the *Re* face of the carbonyl affords oxametallacycle ***Re*** and results in a severe steric interaction between

[54] Many nickel-mediated side reactions of alkynes require the binding of two alkynes at the same time.
[55] Diastereoselectivity confirmed by NOESY.
[56] Lower catalyst loadings may be used but lead to slightly lower yields of **47**.
[57] This analysis assumes the reaction is kinetically controlled, i.e. formation of ***Re*** and ***Si*** is irreversible, and that this occurs through a late transition state.

the allyl group and the alkyl side chain of the carbonyl. Reaction with the Si face of the carbonyl affords oxanickelacycle ***Si*** and results in the placement of the oxygen atom *syn* to the allyl group. Reaction occurs through the more accessible transition state to afford bicycle **47** with the observed diastereoselectivity.

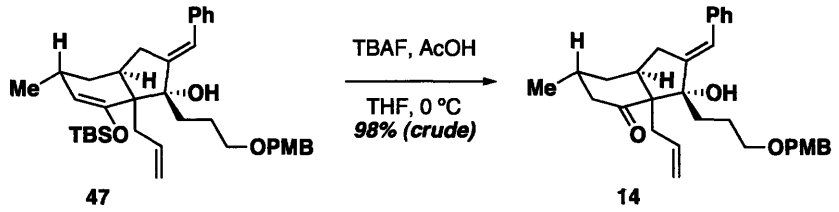
Scheme 19.



With use of the alkyne-ketone reductive cyclization, bicycle **47** has been constructed over 9 steps in 14% overall yield (Scheme 20). The synthesis of **47** has installed several of the notable features of sieboldine A (**1**), including the all-carbon quaternary stereocenter, the tertiary alcohol, and the hydrindane ring system. With many of the key features already installed the focus turned to assembly of the final two rings in sieboldine A (**1**).

F. Deprotection of 47 and Instability of β-Hydroxy Ketone 14.

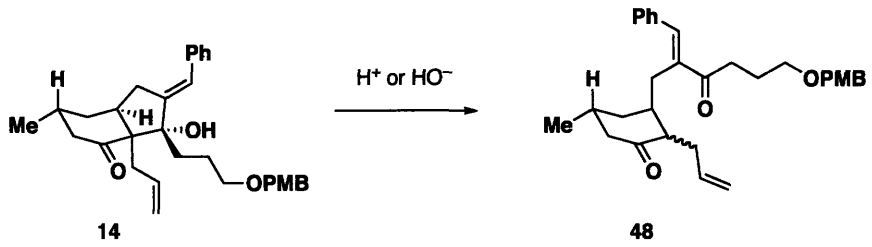
Scheme 20.



47 14

From the reductive coupling product **47** deprotection of the silyl enol ether allowed access to β-hydroxy ketone **14**. However, β-hydroxy ketone **14** was prone to decomposition reactions under acidic and basic conditions.

Scheme 21.

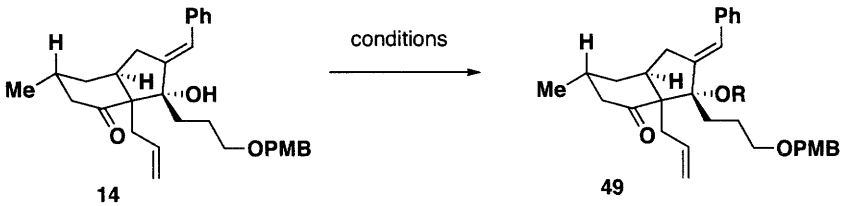


14 48

The major decomposition pathway of β-hydroxy ketone **14** is likely a retro-aldol reaction to form an enone such as **48**. This decomposition reaction readily occurred upon treatment with tertiary amine bases or upon exposure to silica gel. The instability of β-hydroxy ketone **14** made subsequent functionalization difficult and investigation into more robust synthetic intermediates was pursued.

To increase the stability of β-hydroxy ketone **14** attempts to protect the tertiary alcohol were pursued. Due to its sensitivity to both acidic and basic conditions the protection conditions were limited to those occurring under neutral conditions.

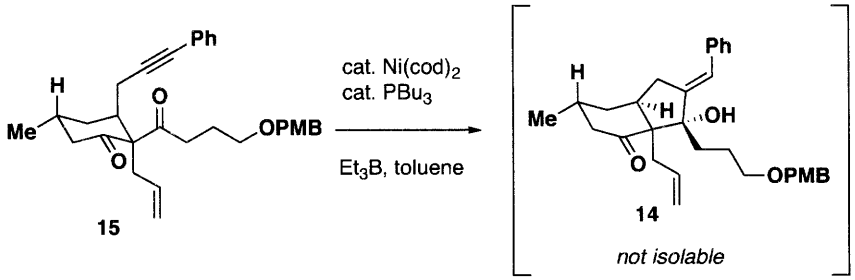
Table 5. Protection of β-Hydroxy Ketone 14



Entry	Conditions	Result
1	Ac_2O, DMAP, NEt_3	Decomposition
2	Ac_2O, DMSO	No reaction
3	TMSCN, DCE, 40 °C	No reaction
4	TMSCN (neat), 100 °C	50% **49**, R = $SiMe_3$

β-Hydroxy ketone **14** was treated with the conditions indicated in table 5. Exposure of **14** to tertiary amine bases resulted in decomposition of the starting material, likely via the retro aldol reaction. Less basic conditions resulted in recovery of starting ketone **14** unchanged (Table 5, entries 2 and 3). Forcing conditions with TMSCN lead to successful protection as the silyl ether (table 5, entry 4).[58] While this method allowed access to the silylated product **49** in small quantities the toxicity of the reagents required for this protection led us to pursue other avenues.

Scheme 22.



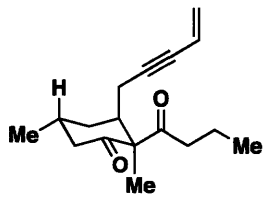
[58] For use of TMSCN in the protection of a base sensitive compound, see: Corey, E. J.; Wu, Y. –J. *J. Am. Chem. Soc.* **1993**, *115*, 8871-8872.

While the sensitivity of β-hydroxy ketone **14** was an unexpected problem it may explain the site selectivity observed in the reductive cyclization of diketone **15** (Scheme 23). Reaction at the cyclic carbonyl of **15** affords the bicyclic compound **41**, which was isolated and characterized (Scheme 15). In contrast, reaction at the exocyclic carbonyl would afford the sensitive β-hydroxy ketone **14** which may decompose under the reaction conditions or upon workup and isolation. Thus the apparent site-selectivity may be a consequence of the sensitivity of β-hydroxy ketone **14** and its selective destruction under the reaction conditions.[59]

G. Tertiary Alcohol Protection

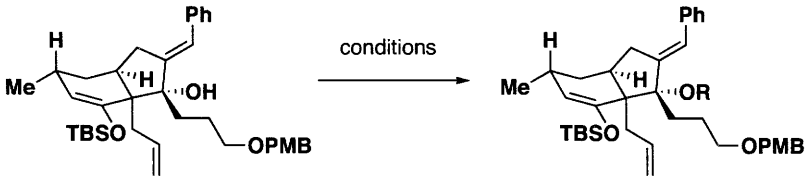
In order to circumvent the decomposition reactions of β-hydroxy ketone **14**, a strategy involving protection of the tertiary alcohol of **47**, followed by subsequent functional group transformations was pursued.

59



In model reactions with a substrate containing a 1,3-enyne component the crude reaction mixture displayed two peaks corresponding to reductive coupling products. Additionally, GC/MS trace also showed the presence of two reductive coupling products. However, only one product could be isolated from the reaction mixture and it corresponded to reaction at the ring carbonyl.

Table 6. Protection of Allylic Alcohol 47.



47 50

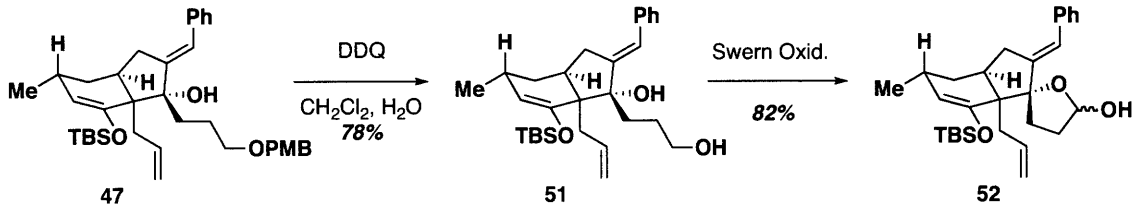
Entry	Conditions	Result
1	Ac_2O, DMAP, NEt_3, C_6H_6, 80 °C	No reaction
2	TBSOTf, NEt_3	No reaction
3	TMSOTf, NEt_3	No reaction
4	PMBCl, NaH, TBAI	Decomposition
5	BSA, DMF, 70 °C	No reaction
6	KOH, DMSO, MeI	62 % **50**, **R = Me**

The tertiary allylic alcohol of **47** could not be protected under a variety of intermolecular reaction conditions (Table 4, entries 1-5). This is likely the result of the severely congested environment about the allylic alcohol of **47**. The only successful protection of **47** was accomplished upon treatment with iodomethane in DMSO to form methyl ether **50** (Table 4, entry 6). While this product was potentially useful for spectroscopic studies, it was not synthetically useful due to the harsh reaction conditions required to remove this protecting group.[60]

In an attempt to circumvent some of the difficulties encountered with the intermolecular protection of **47** an intramolecular protection strategy was pursued. It was reasoned that an intramolecular protection would be less sensitive to the steric environment about the alcohol and would allow for protection of the tertiary alcohol **47**.

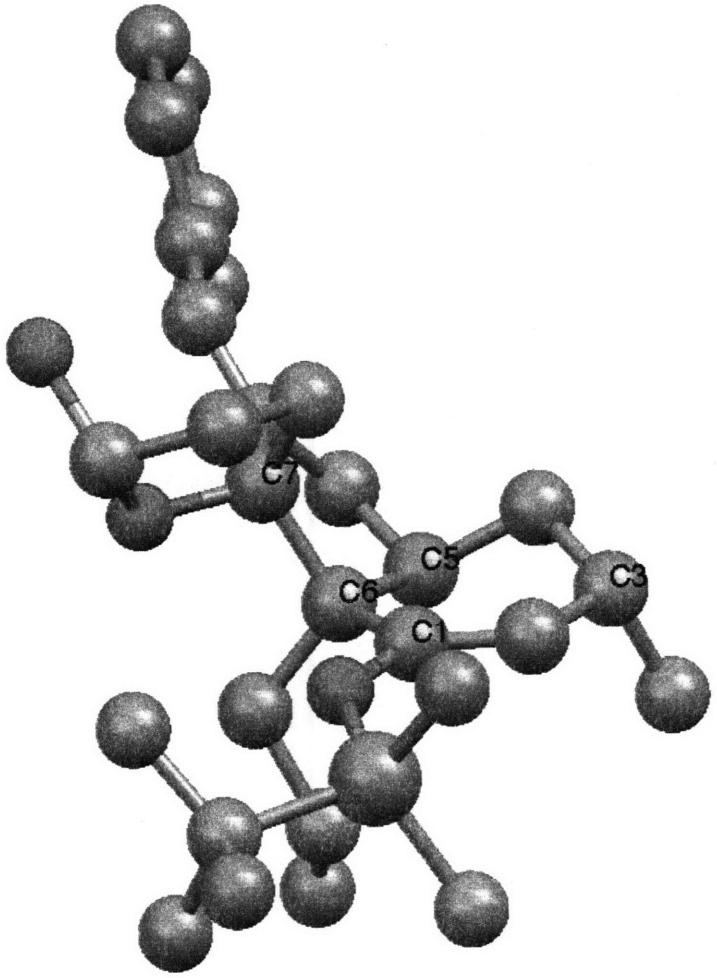
[60] Methyl ether **50** was formed for subsequent NOESY studies.

Scheme 23.

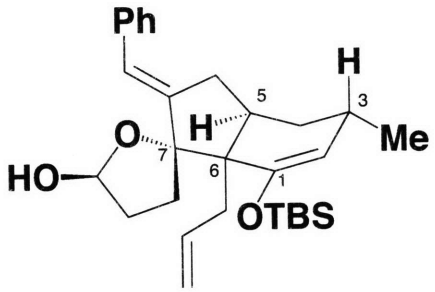


Pursuit of the intramolecular protection strategy began with an oxidative deprotection of the PMB ether of **47** to afford diol **51** in good yield. Subsequent Swern oxidation of diol **51** afforded hemiacetal **52**. Fortuitously, hemiacetal **52** was a crystalline solid and an X-ray crystal structure confirmed the relative stereochemistry shown (Figure 21).

Figure 21. Confirmation of Relative Stereochemistry.

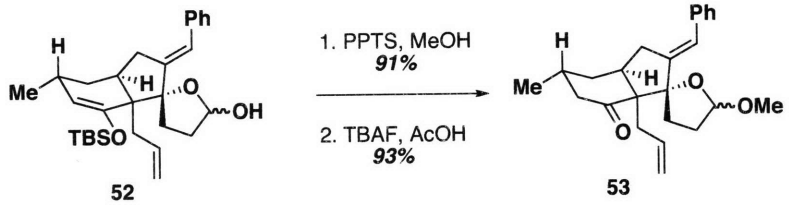


X-ray structure of **52**



(+/–)-52

Scheme 24.

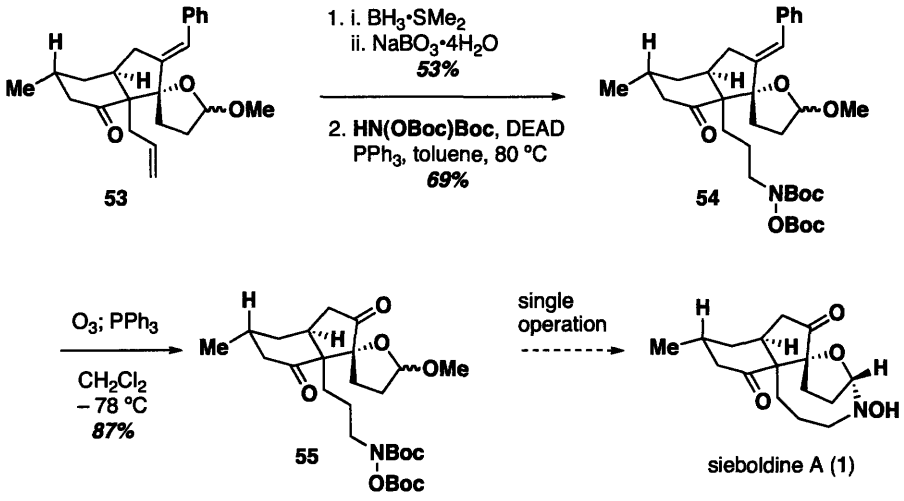


Treatment of hemiacetal **52** with MeOH and PPTS afforded a methyl acetal, which was subsequently treated with buffered TBAF to afford the cyclohexanone **53** (Scheme 25). This four-step process accomplished protection of the hindered tertiary

alcohol of **47**, formation of the THF ring in **1**, and afforded the cyclohexanone substrate used in subsequent transformations.

H. Synthesis of Diketone 55

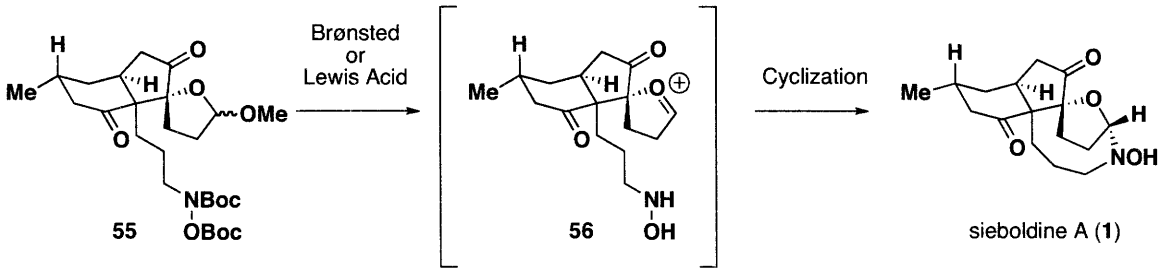
Scheme 25.



Functionalization of the terminal olefin of **53** via a hydroboration/oxidation sequence afforded a primary alcohol, which was treated with the commercially available Boc protected hydroxylamine reagent under Mitsunobu conditions.[61] This afforded the desired hydroxylamine compound **54**, which was treated with ozone to oxidatively cleave the aryl-substituted olefin and form diketone **55** in good yield.

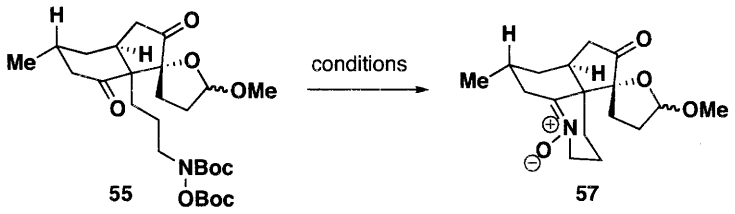
[61] For Mitsunobu reactions with protected hydroxylamines, see: Knight, D. W.; Leese, M. P. *Tetrahedron Lett.* **2001**, *42*, 2593-2595.

Figure 22. Proposed Ring Formation.



Diketone **55** possesses all of the necessary functional groups to form **1**. It was envisioned that treatment of **55** with Lewis or Brønsted acids would remove the Boc groups from the hydroxylamine, thereby freeing the hydroxylamine to react with oxocarbenium ion **56** generated from the methyl acetal under acidic reaction conditions (Figure 22). If successful, this reaction would assemble a 9-membered ring and complete the total synthesis of **1**.

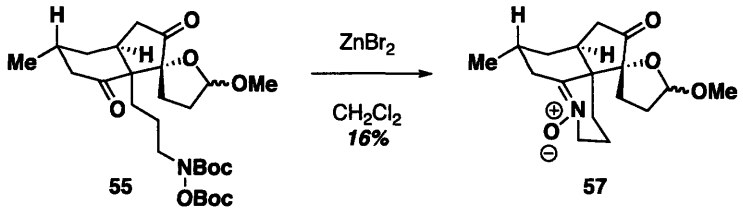
Table 7. Condensation Attempts.



Entry	Conditions	Result
1	AcCl, MeOH	Decomposition
2	TFA, CH_2Cl_2	"
3	TMSI, CH_2Cl_2	"
4	CAN, MeCN	No reaction
5	$ZnBr_2$, CH_2Cl_2	16% **57**

Treatment of diketone **55** with a variety of Brønsted and Lewis acids resulted in complete destruction of the starting material (Table 4, entries 1-4). In only one case was successful Boc deprotection observed (Table 4, entry 5). Unfortunately, under these conditions the freed hydroxylamine cyclized onto the cyclohexanone to form nitrone **57**.

Scheme 26.

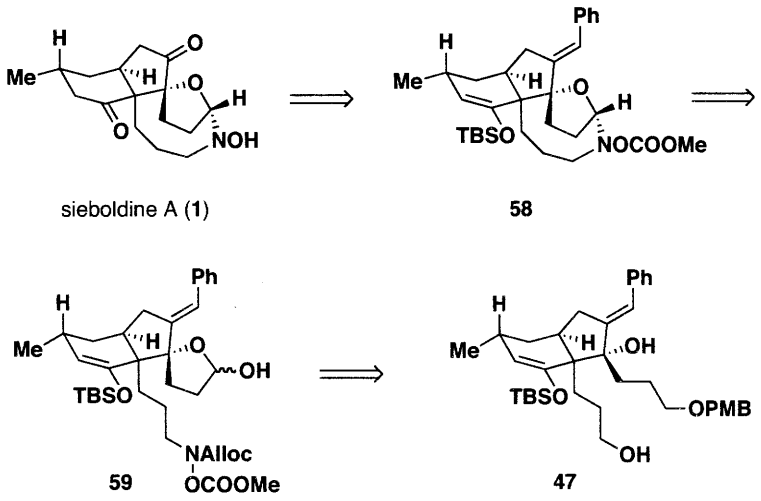


In retrospect nitrone formation should have been a larger concern as formation of a 6-membered ring should be much more facile than formation of a 9-membered ring. Isolation and characterization of nitrone **57** conclusively demonstrated that an alternative ring-closing strategy was required to complete the total synthesis of sieboldine A (**1**).

I. Synthesis of Alloc Derivatives

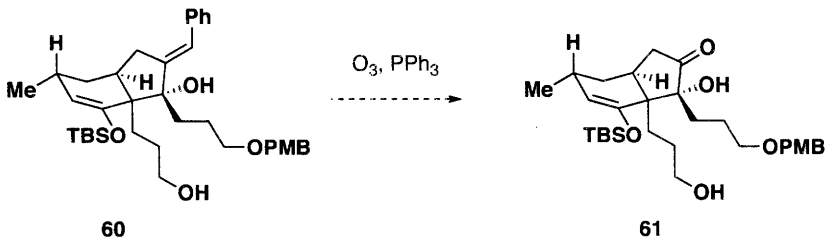
From the cyclization studies with diketone **55** three main problems were identified, they are i) condensation of the hydroxylamine with the cyclohexanone, ii) low reactivity of the methyl acetal, and iii) difficulty in removing the Boc groups from the hydroxylamine.

Figure 23. Revised Synthetic Plan.



These problems were addressed by targeting hydroxylamine **59** as the ring-forming substrate. With the cyclohexanone protected as a silyl enol ether, nitrone formation cannot occur. Additionally, with the silyl enol ether in place a hemiacetal can be used as the electrophile in ring-closing reactions and should be much more reactive than the methyl acetal. Finally, replacing the Boc protecting groups with readily removable and differentiable protecting groups should allow for facile access to a variety of ring-closing substrates.

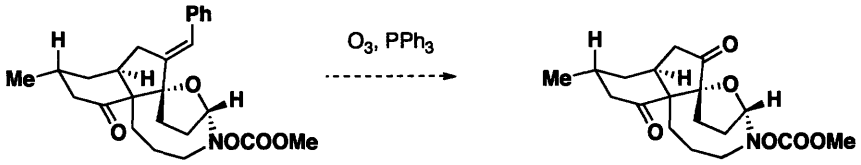
Figure 24. Selective Oxidative Cleavage of Alkene 60



The one complication of targeting hydroxylamine **59** is that oxidative cleavage of the aryl-substituted olefin becomes more challenging. Due to the Alloc protecting group, the

olefin must be cleaved before introduction of the protected hydroxylamine. This would require a selective oxidation of the aryl-substituted olefin in the presence of the silyl enol ether (Figure 24). This reaction was expected to be difficult due to the presence of an electron rich silyl enol ether which should react more readily than the aryl-substituted olefin under the oxidative cleavage conditions.

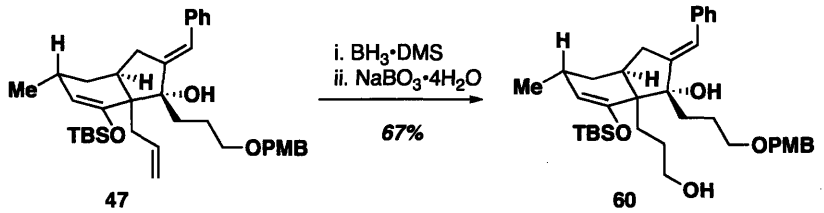
Figure 25. Selective Oxidative Cleavage of Alkene 58.



58 62

If the oxidative cleavage of **60** to **61** is difficult, the aryl-substituted olefin could be cleaved after formation of the nine-membered ring (Figure 25). This would also be a challenging transformation as oxidative cleavage after ring formation must be selective for reaction with the aryl-substituted olefin in the presence of a secondary hydroxylamine. In an effort to determine whether the aryl-substituted olefin could be cleaved in the presence of a silyl enol ether studies on this oxidative cleavage were performed.

Scheme 27.

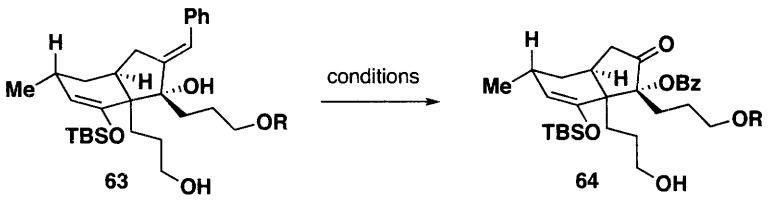


47 60

These studies began from the reductive cyclization product **47**. From **47** a chemoselective hydroboration afforded primary alcohol **60** after oxidative workup. The

selectivity of this hydroboration was surprising given that it reacted preferentially with the terminal olefin, which is less electron-rich than the silyl enol ether. Presumably, this is a result of the steric hindrance about the silyl enol ether.

Table 8. Oxidative Cleavage.



Entry	R	Conditions	Result
1	Ac	1% Pyridine, O_3; PPh_3	No enol ether present
2	PMB	$(C_{16}H_{33})NMe_3MnO_4$, CH_2Cl_2	No reaction
3	PMB	OsO_4, Pyridine, NMO, tBuOH, H_2O, THF	No reaction
4	Ac	$RuCl_3 \cdot H_2O$, $NaIO_4$	No reaction
5	PMB	$KMnO_4$, THF, H_2O	Trace **64**

Primary alcohol **63** was subjected to the oxidative cleavage conditions indicated. Ozone, in the presence of pyridine, reacted preferentially with the silyl enol ether.[62] OsO_4-mediated dihydroxylation conditions were unsuccessful as both the aryl substituted olefin and the silyl enol ether proved unreactive under catalytic or stochiometric metal loading. Even RuO_4, a very reactive oxidant, failed to react with either olefin in **63** and resulted in isolation of starting material.

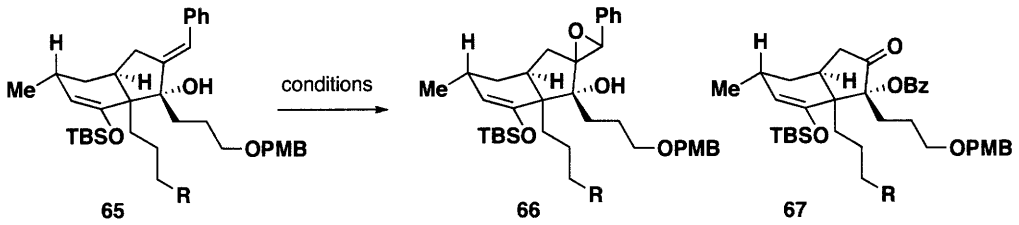
Permanganate reactions were probed next. Cetyltrimethylammonium permanganate is reported to be selective for the oxidative cleavage of aryl-substituted olefins in the presence of alcohols and non-conjugated olefins,[63] but this reagent did not

[62] Slomp, G.; Johnson, J. L. *J. Am .Chem. Soc.* **1958**, *80*, 915-921.
[63] Rathore, R.; Chandrasekara, S. *J. Chem. Res.* **1986**, 458-459.

react with alcohol **63**. Finally, alcohol **63** was treated with $KMnO_4$ and a trace amount of diketone **64** was isolated. This product results from cleavage of the aryl-substituted olefin and transfer of the aryl group to the tertiary alcohol as a benzoate. Unfortunately, optimization of this oxidative cleavage reaction could not be achieved.

The steric environment about the aryl-substituted olefin likely contributes to its low reactivity with these oxidants. One other possible explanation for the difficulty encountered in the oxidative cleavage of the aryl-substituted olefin of **63** is that the primary alcohol participates in undesired oxidation reactions and/or sequesters the oxidant in some way. To test this hypothesis studies upon compounds without the free primary alcohol were pursued.

Table 9. Oxidative Cleavage



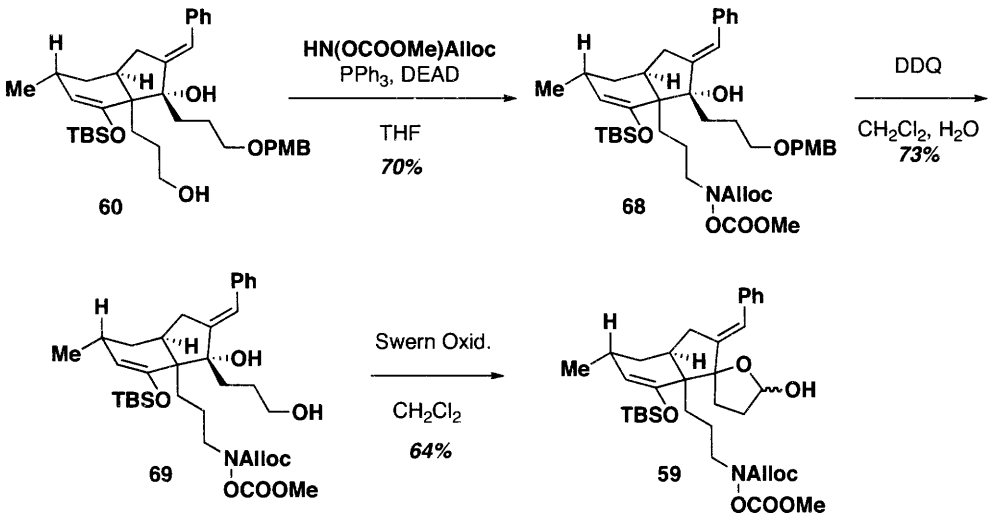
65 66 67

Entry	R	Conditions	Result
1	OAc	$KMnO_4$, THF, H_2O	No Reaction
2	N_3	$RuCl_3 \cdot H_2O$, Oxone, $NaHCO_3$ CH_3CN, H_2O	No Reaction
3	N_3	$RuCl_3 \cdot H_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O	No Reaction
4	N_3	$RuCl_3 \cdot H_2O$, $NaIO_4$, $CHCl_3$, CH_3CN, H_2O 50 °C	20% **66**

Treatment of **65** with $KMnO_4$ resulted in recovery of starting material. RuO_4-catalyzed oxidative cleavage conditions at room temperature showed low reactivity to both the aryl-substituted olefin and the silyl enol ether. Under forcing conditions RuO_4

did oxidize the aryl-substituted olefin, however instead of cleaving the olefin to provide **67** it afforded a product tentatively assigned as epoxide **66**.[64] After these extensive screens, efficient and selective oxidative cleavage of the aryl-substituted olefin remained elusive. Despite concerns about when and how the oxidative cleavage of the aryl-substituted olefin could be accomplished investigation into the Alloc protecting group strategy continued.

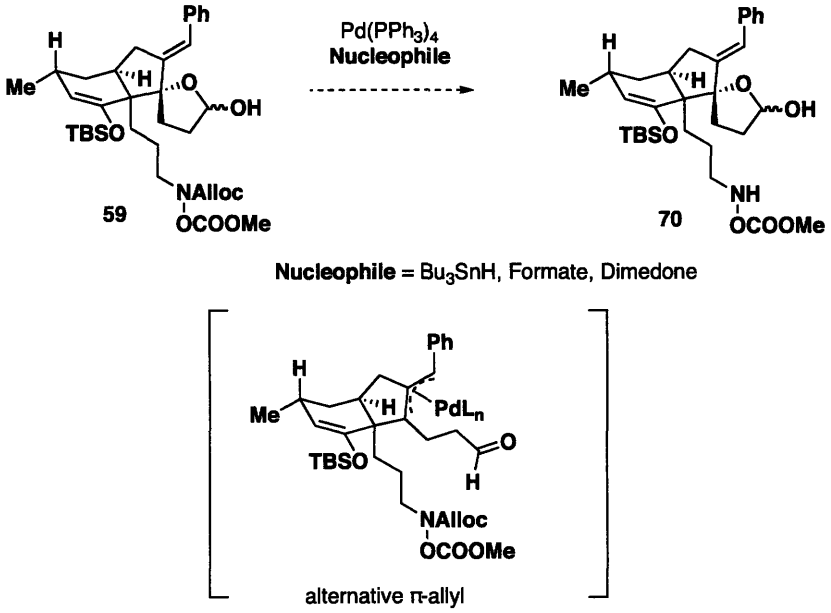
Scheme 28.



From primary alcohol **60** a Mitsunobu reaction installed the protected hydroxylamine derivative to afford compound **68**. Subsequent oxidative deprotection of the PMB ether afforded diol **69**, which was oxidized to afford hemiacetal **59**.

[64] RuO_4 is reported to epoxidize sterically hindered olefins. For an example, see: Kametani, T.; Katoh, T.; Tsubuki, M.; Honda, T. *Chem. Lett.* **1985**, 485-488.

Scheme 29.



At this point removal of the Alloc group was required so that formation of the 9-membered ring could be investigated. Treatment of hemiacetal **59** with standard Alloc deprotection conditions resulted in isolation of only trace amounts of the deprotected product **70**. The difficulty in removing the Alloc group was ascribed to the formation of an alternative π-allyl species between the hemiacetal and the aryl-substituted olefin.[65] Formation of this alternative π-allyl species destroys the tertiary allylic alcohol that had been installed in the reductive cyclization. Without access to hydroxylamine **70**, investigation into formation of the 9-membered ring could not be pursued, and our attention turned to alternative synthetic strategies.

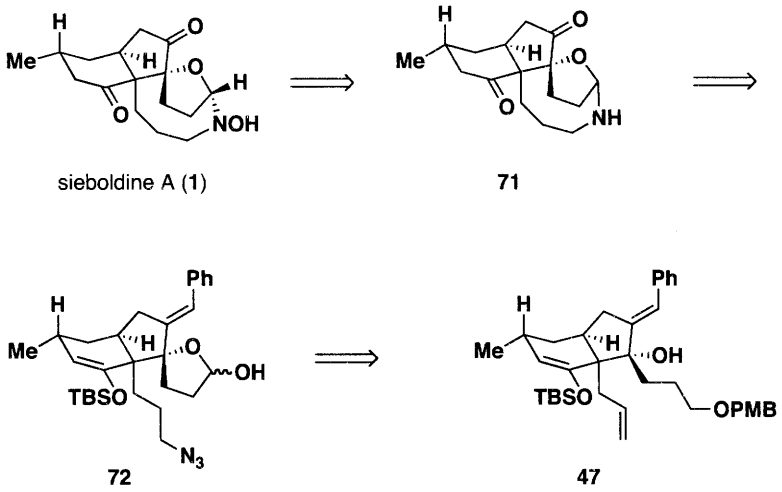
J. Staudinger aza-Wittig Approach

The problems with deprotecting the Alloc group of **59** resulted in a significant redesign of the synthesis. While the silyl enol ether and hemiacetal functional groups of

[65] This assertion is supported by the observation that diol **69**, without the hemiacetal present, undergoes facile Alloc deprotection.

the new target were kept intact, the hydroxylamine portion of the molecule was replaced with an azide (Figure 26). Substitution of the hydroxylamine moiety with an azide reduces the number of protecting group manipulations and allows the use of an alternative ring-closing strategy, the Staudinger *aza*-Wittig reaction.[66]

Figure 26. Staudinger *aza*-Wittig Approach



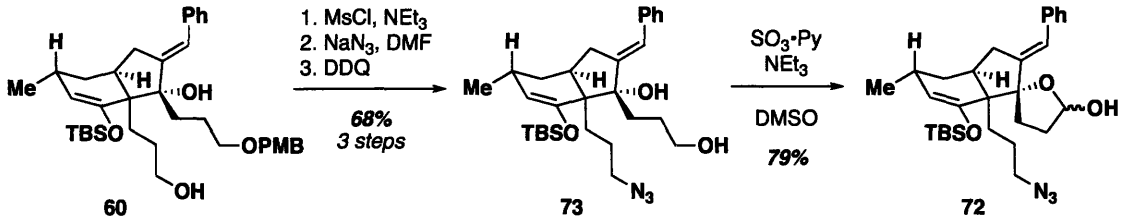
While the azide simplifies the synthesis in some aspects, the main complication of pursuing a Staudinger *aza*-Wittig approach is that the nitrogen atom is no longer in the same oxidation state in *N,O*-acetal **71** as it is in sieboldine A (**1**). Substituting an azide for the hydroxylamine would require the use of a selective, late-stage oxidation of *N,O*-acetal **71** to a hydroxylamine containing *N,*O-acetal for completion of the total synthesis of sieboldine A (**1**).

[66] For recent reviews of this reaction, see: a) Palacios, F. P.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. *Tetrahedron* **2007**, *63*, 523-575. b) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197-1218.

Figure 27. Proposed Amine Oxidation.

While a variety of oxidation methods are reported to allow formation of hydroxylamines from secondary amines, including oxidation with DMDO,[67] Davis' reagent,[68] Oxone/silica,[69] and benzoyl peroxide,[70] these methods generally rely upon strict control of the oxidant stoichiometry to prevent over-oxidation of the amine. Additionally, these methods are reported for oxidations of dialkyl amines, and it is unclear how an *N,O*-acetal will behave under the same oxidation conditions. Despite concerns about the final oxidation step, this strategy was pursued because it appeared to allow the most straightforward access to the natural product **1**.

Scheme 30.



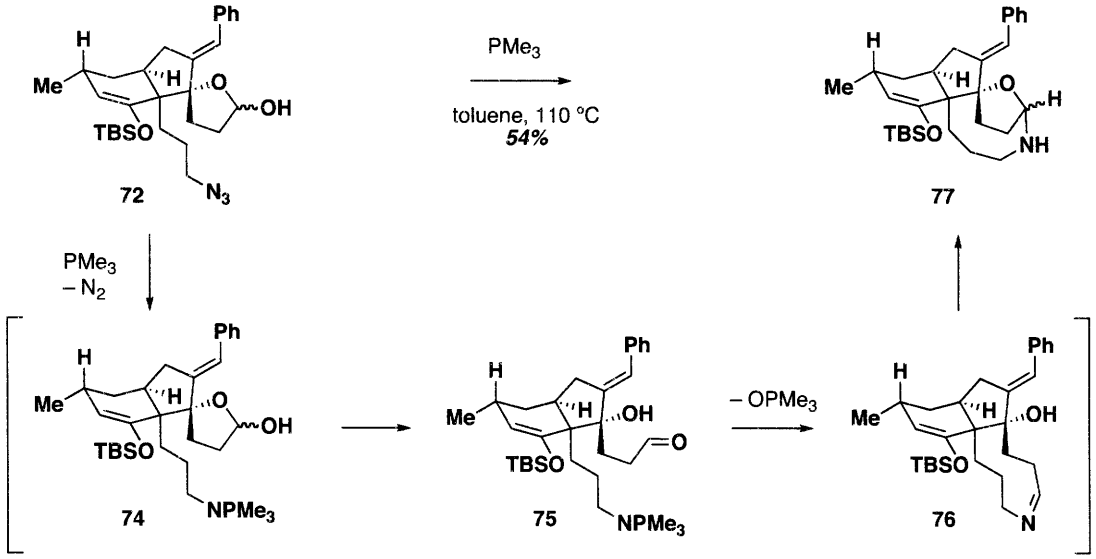
Starting from primary alcohol **60**, mesylation followed by sodium azide displacement, and oxidative deprotection of the PMB ether affords diol **73** in good yield

[67] a) Murray, R. W.; Singh, M. *Synthetic Commun.* **1989**, *19*, 3509-3522. b) Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 1981-1983.
[68] Zajac, W. W.; Walters, T. R.; Darcy, M. G. *J. Org. Chem.* **1988**, *53*, 5856-5860.
[69] Fields, J. D.; Kropp, P. J. *J. Org. Chem.* **2000**, *65*, 5937-5941.
[70] Biloski, A. J.; Ganem, B. *Synthesis* **1983**, 537-538.

over three steps. Oxidation of diol **73** under Parikh-Doering conditions resulted in clean conversion of the diol into hemiacetal **72**.[71]

Investigation into the intramolecular Staudinger *aza*-Wittig reaction began by treatment of azide **72** with triphenylphosphine. At room temperature no reaction was observed between the azide and triphenylphosphine, but upon heating slow disappearance of the starting material was observed. Presumably, the phosphine was reducing the azide to form an iminophosphorane. However, upon prolonged heating the iminophosphorane generated from triphenylphosphine and azide **72** slowly decomposed without any observed *aza*-Wittig reaction.

Scheme 31.

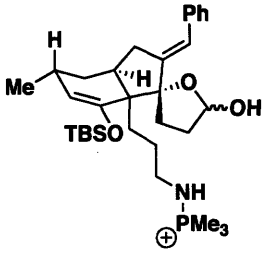


Other phosphines are capable of participating in the Staudinger *aza*-Wittig reaction, and a report comparing the reactivity of different phosphines[72] suggested that small electron rich phosphines would be more reactive in both initial formation of the iminophosphorane and in the subsequent *aza*-Wittig reaction. To this end, azide **72** was

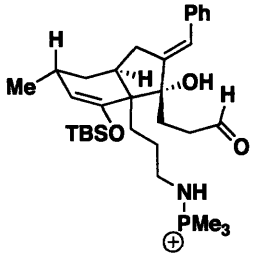
[71] Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.
[72] Boezio, A. A.; Solberghe, G.; Lauzon, C.; Charette, A. B. *J. Org. Chem.* **2003**, *68*, 3241-3245.

treated with trimethylphosphine in refluxing toluene and afforded the tetracyclic *N,O*-acetal **77** in modest yield (Scheme 31).

Figure 28. Aminophosphonium Salts



78



79

In an attempt to gain further understanding of the *aza*-Wittig reaction of **72** simple ^{31}P NMR experiments were conducted. These experiments showed that initial reduction of the azide with PMe_3 required heating to approximately 50 °C. Interestingly, a ^{31}P NMR signal was not observed for the intermediate iminophosphorane (-10 to 0 ppm)[73] or oxazaphosphetane (-55 to -35 ppm).[74] Instead, signals were observed between 30 and 40 ppm and most closely correspond to the chemical shifts of aminophosphonium salts (30 to 45pppm).[70] Aminophosphonium salts, such as **78** or **79**, result from protonation of the iminophosphorane (Figure 28). Attempts to regenerate the iminophosphorane from the presumed aminophosphonium salt were pursued by addition of an external base. However these attempts directed towards regeneration of the iminophosphorane intermediate did not provide better results.

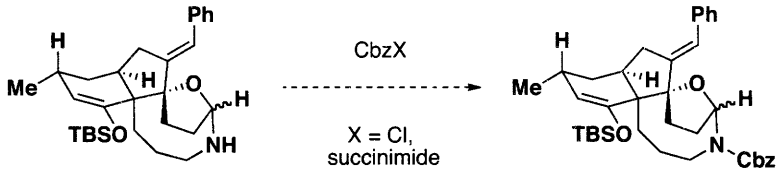
Assuming that the proton source for formation of the aminophosphonium intermediate was derived from the hemiacetal, treatment of hemiacetal **72** with strong base before addition of trimethylphosphine was explored. This reaction did not lead to an

---

[73] Johnson, A. W. *Ylides and Imines of Phosphorous;* Wiley: New York, 1993.
[74] Sheldrick, W. S.; Schomburg, D.; Schmidpeter, A.; von Criegern, T. *Chem. Ber.* **1980**, *113*, 55-69.

improvement of the yield of the Staudinger *aza*-Wittig reaction and additional attempts to improve the chemical yield of this ring-forming step were unsuccessful. Eventually, it was decided that the modest yield of this reaction was acceptable in light of the challenges involved in construction of medium-sized rings and the complexity of the system.

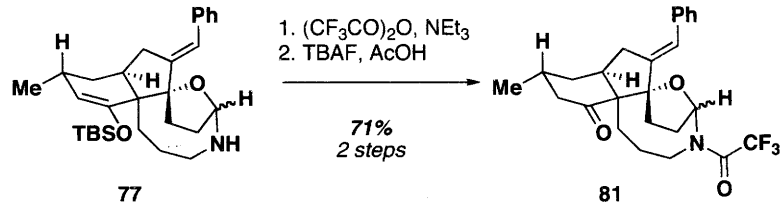
Scheme 32.



77 80

To continue protection of *N,O*-acetal was necessary. Initially Cbz protection of *N,O*-acetal **77** as was pursued. However, with several reagents and reaction conditions the Cbz protected *N,O*-acetal **80** was not isolated. The low reactivity of *N,O*-acetal **77** with the Cbz donors was unexpected and suggested that the nitrogen of the *N,O*-acetal was a poor nucleophile. This may be attributed to its steric hindrance and the donation of electron density into the *N,O*-acetal. Due to the reduced nucleophilicity of **77** more electrophilic acylating reagents were explored.

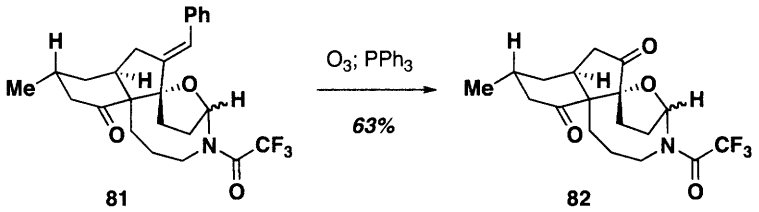
Scheme 33.



77 81

Protection of the tetracyclic *N,O*-acetal could be accomplished with trifluoroacetic acid anhydride and triethylamine to afford a trifluoroacetamide product. Subsequent deprotection of the silyl enol ether afforded cyclohexanone **81**.

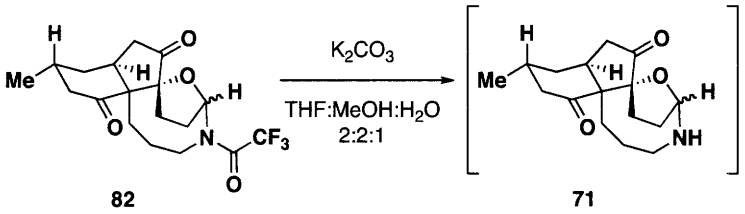
Scheme 34.



Oxidative cleavage of the aryl-substituted olefin of **81** proceeded smoothly to afford diketone **82**. This diketone is a deprotection step and an amine oxidation step removed from sieboldine A (**1**).

K. Amine Oxidation Studies

Table 10

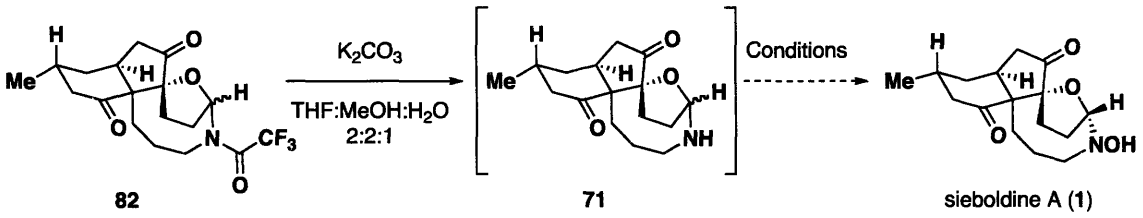


Entry	Conditions	Result
1	$Ba(OH)_2$	Decomposition
2	$NaBH_4$	"
3	K_2CO_3, MeOH, THF	"
4	K_2CO_3, MeOH, THF, H_2O (1:1:1)	slow, inconsistent conversion
5	K_2CO_3, MeOH, THF, H_2O (2:2:1)	consistent formation of **71** over 1 h

Deprotection of the trifluoroacetamide was much more difficult than initially anticipated. Treatment of trlfluoroacetamide **82** with several conditions resulted in decomposition of the substrate. After several attempts, deprotection of

trifluoroacetamide **82** could be consistently acheived by treatment with K_2CO_3 in THF/MeOH/H_2O (2:2:1) (Table 10). Free *N,O*-acetal **71** was used in the subsequent oxidation studies without purification due to concerns about its stability.[75]

Table 11. Amine Oxidation Studies.



82 71 sieboldine A (1)

Entry	Conditions	Result
1	DMDO	Decomposition
2	Davis's Reagent	"
3	Oxone, SiO_2	"
4	*m*CPBA	"
5	MTO, UHP	"
6	Benzoyl Peroxide	No Reaction

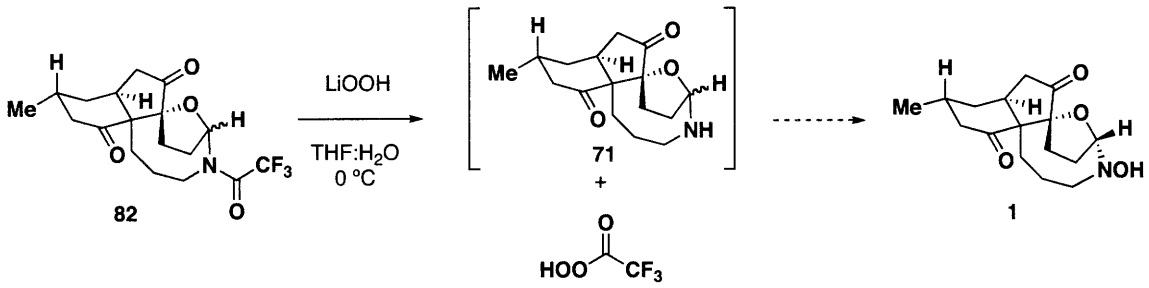
Treatment of the unpurified *N,O*-acetal **71** with several different oxidants afforded a variety of unidentifiable oxidation products (Table 7, entries, 1, 2-7). Attempts at the direct oxidation with DMDO, Davis' reagent, methyltrioxorhenium/urea hydrogen peroxide, and Oxone/silica resulted in destruction of the starting *N,O*-acetal. Treatment of *N,O*-acetal with *m*CPBA, in an attempt to oxidize directly to the nitrone, also resulted in destruction of the starting material.

An attempt at a one-step deprotection/oxidation with LiOOH was also pursued. This attempt relied upon the *in situ* generation of trifluoroperacetic acid (TFPAA) for oxidation of the *N,O*-acetal. This was an attractive approach because exactly one

[75] Studies with model *N,O*-acetals showed them to be very sensitive to purification on silica gel and alumina resulting in hydrolysis of the *N,O*-acetal

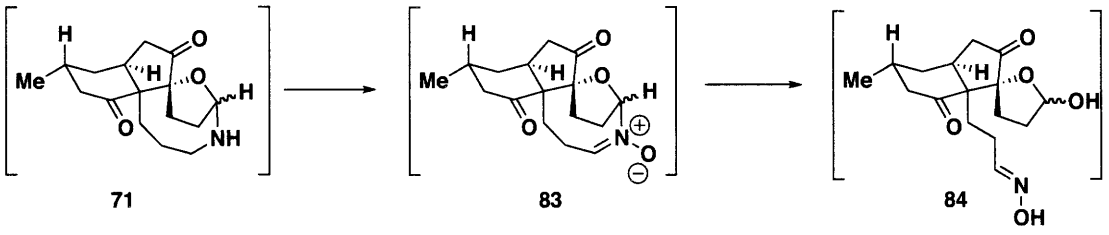
equivalent of TFPAA would be generated from the deprotection of trifluoroacetamide **82**. It was reasoned that with an exactly stoichiometric amount of TFPAA, a selective oxidation would occur to afford sieboldine A (**1**).

Scheme 35.



Unfortunately, this reaction did not result in isolation of the natural product **1**. Instead, treatment of **82** with LiOOH afforded an unidentifiable mixture of oxidation products. While exactly 1 equivalent of TFPAA would be formed in this reaction an excess of hydrogen peroxide was present. Hydrogen peroxide may have led to additional oxidation events as this reagent is known to oxidize amines.

Figure 29.

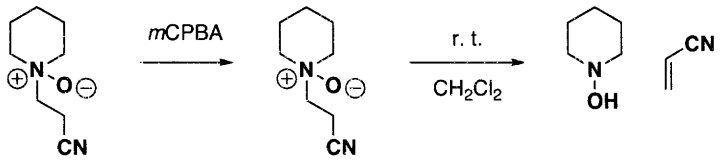


The destruction of *N,O*-acetal **71** under these conditions may be due to over-oxidation to form nitrone **83**. If nitrone **83** were formed a variety of different reactions could occur. In particular, a hydrolysis reaction either upon workup or under the reaction conditions would afford the oxime **84**. Other nucleophiles could also react with nitrone **83** such as *N,O*-acetal **71** thereby providing an oxidative dimer. Unfortunately, none of

the oxidation products could be isolated and characterized and the reactivity of *N,O*-acetal **71** under these oxidation conditions is still unknown. Due to the difficulty with the direct oxidation of *N,O*-acetal **71** to sieboldine A (**1**) investigation into alternative amine oxidation strategies were pursued.

One possible strategy towards the total synthesis of **1** could rely upon formation of the hydroxylamine by a Cope elimination.[76] In this reaction an amine *N*-oxide undergoes a thermal elimination to afford a secondary hydroxylamine and an olefin. The elimination occurs intramolecularly with the amine *N*-oxide acting as base and proceeds through a 5-membered ring transition state. In the classic reaction, selectivity between elimination of different substituents is determined by the number of β-hydrogen atoms.

Figure 30.



85 **86** **87**

More recent studies have focused upon the use of β-electron withdrawing groups. This allows the elimination to occur at lower temperatures and provides selectivity for elimination of the substituent substituted with the β-electron withdrawing group (Figure 24).[77] The Cope strategy is an attractive approach because it avoids the difficult problem of a selective amine oxidation reaction. The oxidation required for the Cope elimination is from tertiary amine to amine *N*-oxide, a process that is not plagued by the same over-oxidation concerns as the direct oxidation approach.

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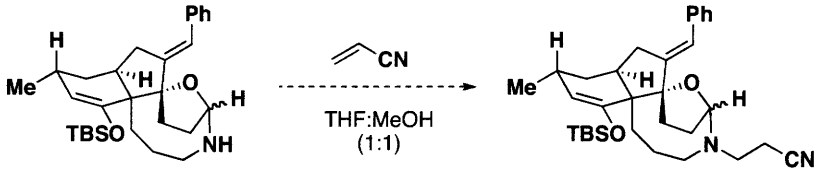
[76] Cope, A. C.; Foster, T. T.; Towle, P. H. *J. Am. Chem. Soc.* **1949**, *71*, 3929-3935.
[77] O'Neil, I. A.; Cleator, E.; Tapolczay, D. J. *Tetrahedron Lett.* **2001**, *42*, 8247-8249.

The Cope elimination requires a tertiary amine substrate and the first attempts to access tertiary amine substrates began with *N,O*-acetal **77** (Scheme 36). It was envisioned that an *aza*-Michael reaction of *N,O*-acetal **77** and acrylonitrile would afford tertiary amine **88**. Subsequent oxidation would afford the the *N*-oxide for the Cope elimination.

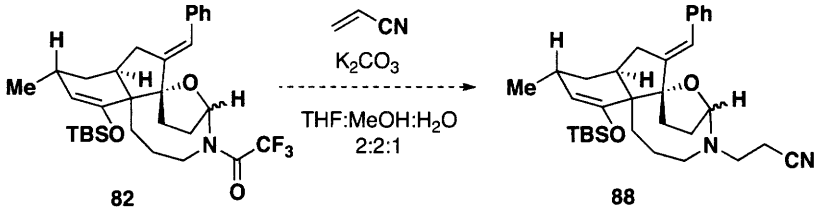
Scheme 36.



77 **88**

Unfortunately, *N,O*-acetal **77** failed to react with acrylonitrile under the reaction conditions.[78] The poor reactivity of this system is likely due to the reduced nucleophilicity of the nitrogen atom due to donation of electron density into the C–O σ* orbital and the steric environment about the *N,O*-acetal.

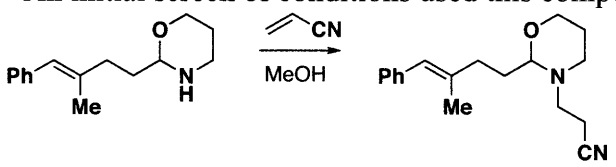
Scheme 37.



82 **88**

Another attempt at formation of the tertiary amine entailed treatment of **82** with the deprotection conditions in the presence of acrylonitrile. Unfortunately, this did not

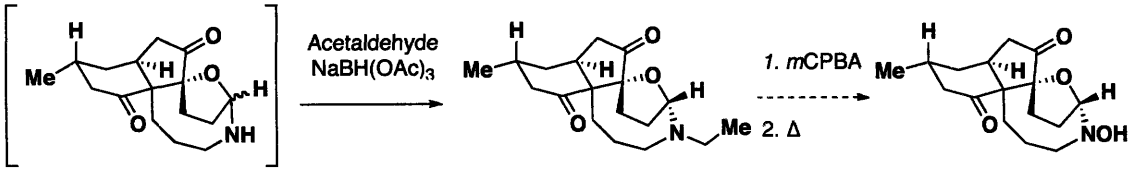
[78]An initial screen of conditions used this compound as a model for **77**:



result in the formation of the desired tertiary amine **89** and instead resulted in decomposition of the *N,O*-acetal. With the *aza*-Michael ineffective alternative methods for tertiary amine synthesis were investigated.

The next strategy investigated for tertiary amine synthesis was reductive amination. While this method could not allow access to the β-cyano amines, it should allow access to a variety of tertiary amine substrates.

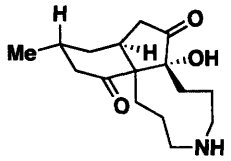
Scheme 38.



71 90 sieboldine A (1)

Treatment of **71** with acetaldehyde and sodium triacetoxyborohydride afforded tertiary amine **90**.[79] From tertiary amine **90** oxidation of the amine to the *N*-oxide was attempted with *m*CPBA. While consumption of starting material was observed it was not possible to determine whether formation of the amine *N*-oxide had occurred. The difficulty encountered in the amine oxidation of *N,O*-acetal **71** led to exploration of alternative targets that could be constructed with a nickel-catalyzed alkyne ketone reductive cyclization.

Figure 31. Alopecuridine.



alopecuridine (**2a**)

[79] Tentatively characterized by ^{1}H NMR.

Among the Lycopodium alkaloids, alopecuridine (**2a**) is an attractive target displaying similar structural characteristics to sieboldine A (**1**), including the hydrindane core, the all-carbon quaternary center, and the α-hydroxy ketone motif, but without the hydroxylamine containing *N,O*-acetal (Figure 31).

Figure 32. Keto-amine and Carbinolamine Forms of Alopecuridine.

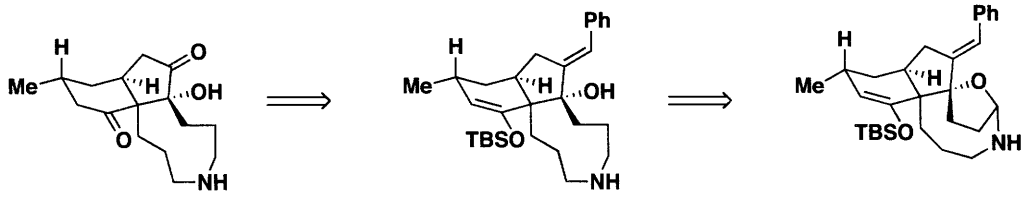
alopecuridine (**2a**)
keto-amine form

alopecuridine (**2a'**)
carbinolamine form

Alopecuridine was first isolated in 1967 by Ayer and coworkers from *Lycopodium alopecuroides*.[80] Initially only a basic outline of the structural features of **2a** were reported due to some unusual characteristics noted in its IR spectra. A subsequent X-ray structure confirmed the structure shown in Figure 32.[81] The IR characteristics of this compound were explained by the formation of an equilibrium mixture of the keto-amine (**2a**) and carbinolamine (**2a'**) forms of alopecuridine wherein the secondary amine adds to the cyclohexanone (Figure 32). Two retrosynthetic analyses were considered for **2a**, both intercepting intermediates formed in the studies directed towards the total synthesis of **1.**

[80] Ayer, W. A.; Altenkirk, B.; Valverde-Lopez, S.; Douglas, B.; Raffauf, R. F.; Weisbach, J. A. *Can. J. Chem.* **1968**, *46*, 15-20.
[81] Ayer, W. A.; Altenkirk, B.; Fukuzawa, Y. *Tetrahedron*, **1974**, *30*, 4213-4214.

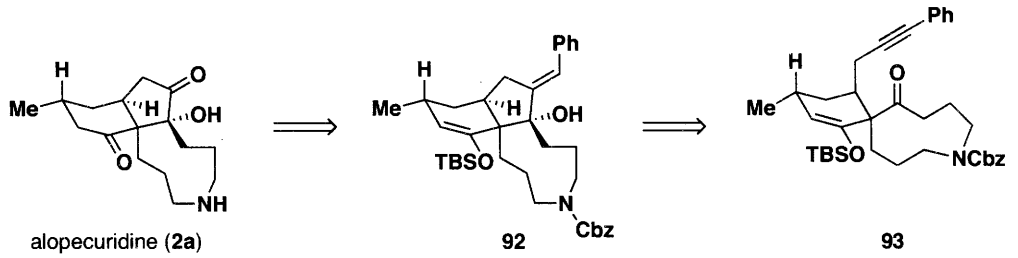
Figure 33. Retrosynthetic Analysis



alopecuridine (**2a**) **91** **77**

The first retrosynthetic analysis led to the notion of preparing alopecuridine (**2a**) via oxidation state adjustments and functional group manipulations of tricyclic amine **91**. Amine **91** could be accessed from tetracycle **77** via reduction of the *N,O*-acetal. This approach is attractive as it intercepts an advanced intermediate already prepared (**77**).

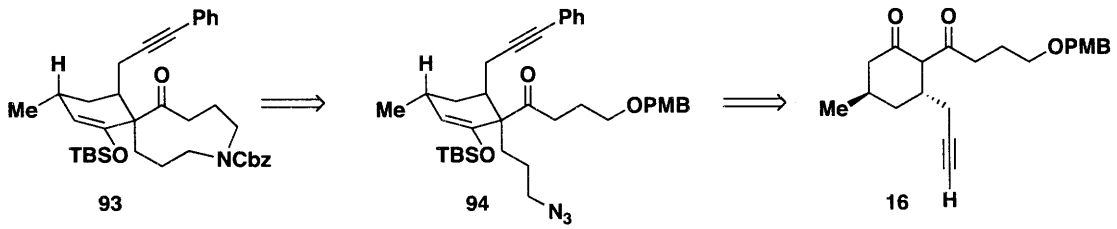
Figure 34. Retrosynthetic Analysis.



alopecuridine (**2a**) **92** **93**

An alternative retrosynthesis of **2a** is shown in figure 34. Starting from **2a**, oxidation state adjustments and functional group manipulations would suggest tricycle **92** as a logical precursor. The hydrindane core of **92** could in turn be constructed from precursor **93**, a novel substrate for the nickel-catalyzed alkyne-ketone reductive cyclization.

Figure 35. Retrosynthetic Analysis.

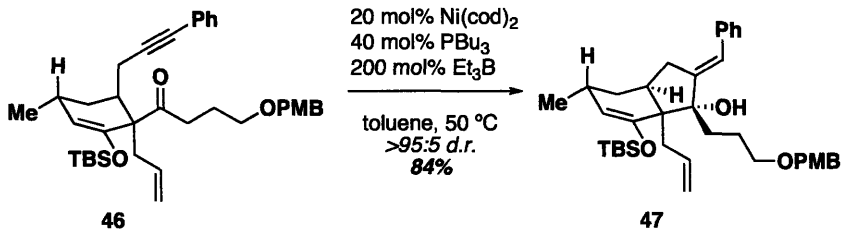


93 **94** **16**

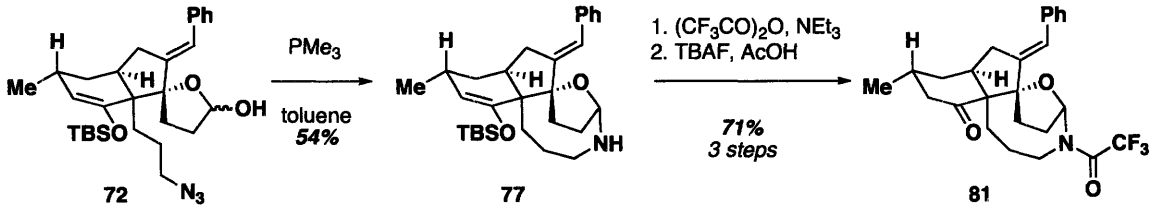
Ketone **93** could be prepared from **16** by way of a cyclization reaction and other functional group manipulations reminiscent of those already performed on closely related compounds.

This second approach is interesting as it relies upon formation of the *aza*-cyclononane before the nickel-catalyzed alkyne-ketone reductive cyclization. Investigation into the synthesis of alopecuridine (**2a**) is currently ongoing and will be reported in due course.

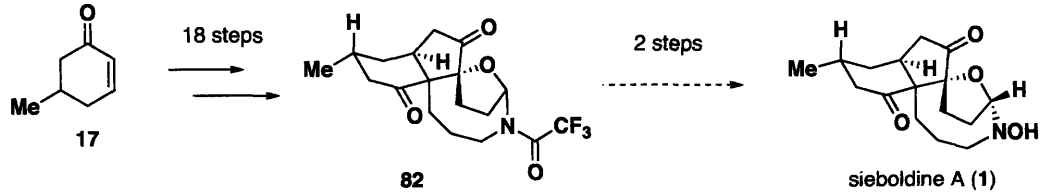
Conclusion



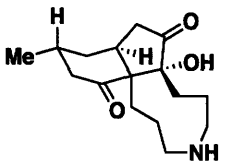
A nickel-catalyzed alkyne-ketone reductive cyclization was employed to assemble the hydrindane core of **1**. Treatment of ketone **46** with reductive cyclization conditions resulted in formation of bicycle **47** with high yield and high diastereoselectivity. This reaction assembles the vicinal quaternary stereogenic centers of **1**.



Subsequent elaboration of **47** allows access to hemiacetal **72**. Treatment of hemiacetal **72** with trimethylphosphine results in an intramolecular Staudinger *aza*-Wittig reaction to afford the tetracyclic *N,O*-acetal shown. This *N,O*-acetal was then protected and the silyl enol ether removed to afford tetracyclic cyclohexanone **81**.



These two steps allow access to the tetracyclic diketone **82**. This intermediate contains the tetracyclic structure of the natural product and is a trifluoroacetamide deprotection and an amine oxidation removed from sieboldine A (**1**). Overall, tetracyclic diketone **82** is assembled over 18 steps and in 1% yield from enone **17**.



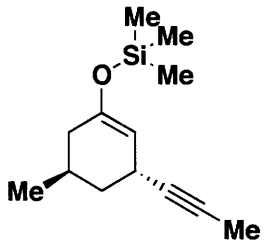
alopecuridine (**2a**)

Studies directed towards the application of a nickel-catalyzed alkyne-ketone reductive cyclization towards the synthesis of alopecuridine are currently under investigation.

Experimental Section:

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of inert gas (Ar, N_2) with rigid exclusion of moisture from reagents and glassware. Dichloromethane and toluene were distilled from calcium hydride. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from a blue solution of benzophenone ketyl. Diisopropylamine (iPr$_2$NH) and 1,3-diaminopropylamine (APA) were distilled from calcium hydride and stored over potassium hydroxide. Trifluoroacetic anhydride ($(CF_3CO)_2O$) was distilled from phosphorous pentoxide. All other reagents were used as received from commercial supplier. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was visualized by UV lamp (254 nm), ethanolic phosphomolybdic acid (PMA) or cerium molybdate (CAM). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on a Varian Mercury 300 MHz spectrometer, Bruker Avance 400 MHz spectrometer, a Varian Inova 500 MHz spectrometer, or a Bruker Avance 600 MHz spectrometer. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm) or benzene (7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d= doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{19}F NMR

spectra are reported in ppm from an external standard of trifluoroacetic acid (-76.55 ppm). Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) or C_6D_6 (128.4 ppm). Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High resolution mass spectra (HR-MS) were obtained on a Bruker Daltronics ApexIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Melting points were recorded on a Mel-Temp II melting point apparatus.



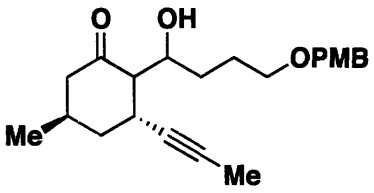
(±)-Trimethyl((3*R*, 5*R*)-5-methyl-3-(prop-1-ynyl)cyclohex-1-enyloxy)silane (31): To a round-bottomed flask at –42 °C was condensed propyne (2.5 mL, 46 mmol) followed by slow addition of Et_2O (91 mL) down the sides of the flask. To this solution was added *n*BuLi (18 mL, 2.5 M, 46 mmol) and a solution of anhydrous $ZnBr_2$ (10 g, 46 mmol) in THF (46 mL). The alkynyl zinc solution was warmed to room temperature and stirred 10 min before being cooled to –42 °C and addition of **17** (4.0 g, 36 mmol) and TMSOTf (8.2 mL, 46 mmol). The solution was stirred at –42 °C for 15 min before quenching with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous was extracted with hexane. The organic layers were combined, washed with water, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was distilled at reduced pressure (2 torr, 90 °C) to yield 4.9 g (62%) of **31**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (dd, J = 4.9, 1.8 Hz, 1H), 3.12 (m, 1H), 2.12-2.01 (m, 2H), 1.77 (d, J = 2.4 Hz, 3H), 1.69-1.58 (m, 2H), 1.31 (ddd, J = 12.7, 10.6, 5.6 Hz, 1H), 0.97 (d, J = 6.5 Hz, 3H), 0.18 (s, 9H)

^{13}C NMR (100 mHz, $CDCl_3$) δ 150.9, 104.8, 82.8, 75.3, 38.3, 36.9, 26.1, 26.1, 21.3, 3.8, 0.5

IR (thin film NaCl): 2957, 1667, 1457, 1370, 1304, 1253, 1197, 899, 845, 755, 684 cm^{-1}

HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{22}OSiNa$, 245.1332; found 245.1339.



(±)-(3*R*,5*R*)-2-(1-Hydroxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-3-(prop-1-ynyl) cyclohexanone (32): To a round-bottomed flask equipped was added **31** (4.9 g, 22 mmol) and THF (90 mL) before cooling to –42 °C and addition of *n*BuLi (9.2 mL, 2.5 M, 23 mmol). This solution was stirred at – 42 °C for 4 h before cooling to –78 °C and addition of a solution $ZnBr_2$ (2.5 g, 11 mmol) in THF (20 mL). This solution was stirred for 1 hour at –78 °C before addition of **20** and stirred for 1 hour at –78 °C before quenching with saturated aqueous NH_4Cl. The layers were separated and extracted with EtOAc. The organic layers were combined, washed with water, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue

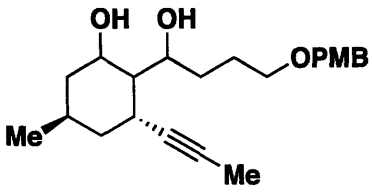
was purified by silica gel chromatography (15% EtOAc/hex - 50% EtOAc/hex) to yield 6.0 g (76%) of **32** as a mixture of diastereomers.

^{1}H NMR (500MHz, $CDCl_3$, major diastereomer) δ 7.24 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.44 (d, J = 11.5 Hz, 1H), 4.41 (d, J = 11.5 Hz, 1H), 3.90-3.84 (m, 1H), 3.78 (s, 3H), 3.49-3.43 (m, 2H), 3.05 (d, J = 8.7 Hz, 1H), 3.02-2.96 (m, 1H), 2.44 (dd, J = 13.2, 5.2 Hz, 1H), 2.38-2.31 (m, 2H), 2.13 (dd, J = 13.1, 7.4 Hz, 1H), 1.89-1.6 (m, 6H), 1.75 (d, J = 2.3 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$, major diastereomer) δ 212.5, 159.3, 130.4, 129.5, 113.9, 80.3, 78.7, 72.8, 71.4, 70.1, 60.0, 55.4, 49.0, 36.7, 33.4, 30.7, 30.4, 26.6, 20.3, 3.7

IR (thin film NaCl): 3419, 2952, 2868, 1709, 1612, 1513, 1456, 1363, 1302, 1248, 1174, 1095, 1035, 820 cm^{-1}

HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{30}O_4Na$, 381.2036; found 381.2030.



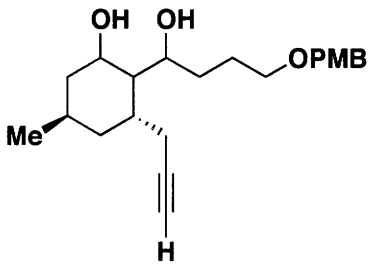
(±)-(3*R*,5*R*)-2-(1-Hydroxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-3-(prop-1-ynyl) cyclohexanol (30): To a round-bottomed flask was added $LiAlH_4$ (513 mg, 14 mmol) and THF (50 mL). This suspension was cooled to 0 °C and a THF (20 mL) solution of **32** (2.4 g, 6.7 mmol) was added dropwise and stirred with warming to room temperature overnight. After stirring overnight the reaction was cooled to 0 °C and carefully quenched with 0.51 mL H_2O, followed by 0.51 mL 15% (w/w) NaOH solution, and an additional 1.0 mL H_2O. The resulting precipitate was removed by filtration and the filtrate concentrated. The crude residue was purified by silica gel chromatography (40%) to yield 2.1 g (88%) **30** as a mixture of diastereomers.

^{1}NMR (500 MHz, $CDCl_3$, major diastereomer) δ 7.25 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.47 (d, J = 11.6 Hz, 1H), 4.44 (d, J = 11.6 Hz, 1H), 4.39-4.28 (m, 2H), 4.28-4.24 (m, 1H), 4.12-4.05 (m, 1H), 3.81 (s, 3H), 3.50 (t, J = 5.6 Hz, 2H), 2.87-2.81 (m, 1H), 1.99-1.91 (m, 1H), 1.82-1.65 (m, 5H), 1.78 (d, J = 2.4 Hz, 3H), 1.60-1.40 (m, 3H), 1.32-1.21 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$, major diastereomer) δ 159.4, 130.0, 129.6, 129.6, 114.0, 113.9, 82.0, 77.4, 77.2, 73.0, 70.4, 55.4, 48.0, 39.2, 33.0, 27.5, 26.0, 21.9, 21.8, 3.7

IR (thin film NaCl): 3334, 2921, 2857, 1612, 1586, 1513, 1456, 1362, 1302, 1248, 1173, 1096, 1036, 820 cm^{-1}

HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{32}O_4Na$, 383.2193; found 383.2183.



(±)-(3*S*,5*R*)-2-(1-Hydroxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-3-(prop-2-ynyl) cyclohexanol (38): To a round-bottomeded flask at 0 °C charged with KAPA[1] solution (71 mL, 1.3 M, 92 mmol) was added **30** (2.1 g, 5.9 mmol) as a solution in THF (10 mL). The reaction was stirred for 2 h while warming from 0 °C to room temperature. After 2 h, the solution was cooled to 0 °C and quenched with H_2O. The aqueous layer was extracted with EtOAc and the combined organics were washed with 1 M HCl, H_2O, and brine before being dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 20% EtOAc/hec -60% EtOAc/hex) to yield 1.8 g (84%) of **38**.

^1H NMR (500 MHz, $CDCl_3$, major diastereomer) δ 7.25 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.47 (d, J = 11.6 Hz, 1H), 4.45 (d, J = 11.6 Hz, 1H), 4.40-4.24 (m, 2H), 4.13-4.07 (m, 1H), 4.04-3.99 (m, 1H), 3.80 (s, 3H), 3.55-3.47 (m, 2H), 2.34 (ddd, J =

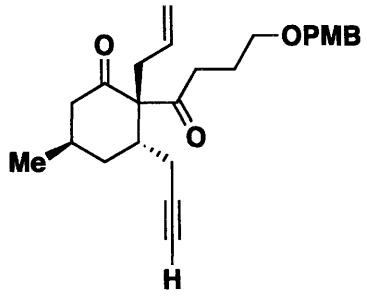
[1] Abrams, S. R.; Shaw, A. C. *Organic Syntheses* **1988**, *66*, 127-129.

16.9, 7.1, 2.6 Hz, 1H), 2.25 (ddd, J = 16.9, 6.2, 2.6 Hz, 1H), 2.19-2.12 (m, 1H), 1.98 (t, J = 2.6 Hz, 1H), 1.83-1.67 (m, 6H), 1.64-1.46 (m, 3H), 1.30-1.23 (m, 1H), 1.05 (d, J = 6.8 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$, major diastereomer) δ 159.4, 130.0, 129.7, 114.0, 114.0, 83.1, 73.0, 71.5, 70.5, 70.0, 69.5, 55.4, 46.3, 39.4, 35.3, 33.2, 26.9, 26.3, 22.8, 22.1

IR (thin film NaCl): 3340, 3296, 2927, 2869, 2115, 1613, 1586, 1513, 1457, 1362, 1302, 1248, 1174, 1096, 1034, 820, 637 cm^{-1}

HRMS ESI (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{32}O_4Na$, 383.2193; found 383.2203.



(±)-(*2S*, *3S*, *5R*)-2-Allyl-(4-(4-methoxybenzyloxy)butanoyl)-5-methyl-3-(prop-2-ynyl) cyclohexanone (39): To a round-bottomed flask was added oxalyl chloride (6.0 mL, 70 mmol) and CH_2Cl_2 (120 mL) before cooling to –78 °C. To this solution was added DMSO (9.9 mL, 140 mmol) dropwise over 5 min and the solution stirred for 15 min before dropwise addition of **38** (5.0 g, 14 mmol) as a solution CH_2Cl_2 (20 mL). The resulting solution was stirred for 15 min at –78 °C before addition of triethylamine (39 mL, 280 mmol) and removal of the cold bath. After warming to room temperature the

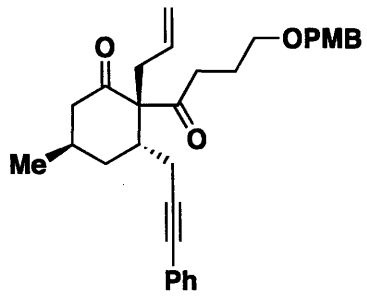
solution was poured into water and extracted with ether. The combined organics were washed with water and brine before being dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel chromatography (gradient, 10% EtOAc/hex to 20% EtOAc/hex) to afford 4.4 g (89%) of the 1,3-diketone as a mixture of tautomers. To a round-bottomed flask was added potassium carbonate (6.8 g, 50 mmol), acetone (125 mL), and the 1,3-diketone (4.4 g, 12 mmol). The reaction flask was fitted with a reflux condenser before heating to reflux. After reaching reflux, allyl iodide (1.4 mL, 16 mmol) was added and the reaction was stirred overnight before being cooled to room temperature, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 3% EtOAc/hex to 8% EtOAc/hex) to yield 3.0 g (62%) of **39**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.69-5.57 (m, 1H), 5.16 (d, J = 7.2 Hz, 1H), 5.13 (s, 1H), 4.39 (s, 2H), 3.81 (s, 3H), 3.39 (t, J = 6.1 Hz, 2H), 3.15 (ddt, J = 14.0, 5.5, 1.6 Hz, 1H), 2.59-2.17 (m, 10H), 1.97 (t, J = 2.7 Hz, 1H), 1.92-1.79 (m, 3H), 0.98 (d, J = 6.7 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 208.9, 208.2, 159.3, 132.8, 130.6, 129.5, 119.6, 113.9, 83.3, 72.7, 69.8, 69.6, 68.9, 55.5, 47.2, 38.0, 37.3, 36.6, 32.8, 28.9, 23.8, 20.5, 19.8

IR (thin film NaCl): 3289, 2925, 2852, 2117, 1694, 1611, 1585, 1511, 1245

HRMS ESI (*m/z*): $[M+Na]^+$ Calcd for $C_{25}H_{32}O_4Na$, 419.2193; found 419.2192.



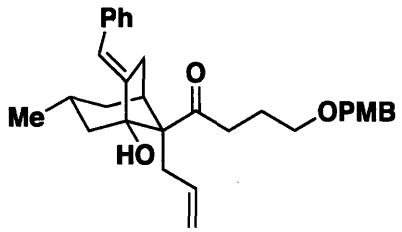
(±)-(2*S*,3*S*,5*R*)-2-Allyl-2-(4-(4-methoxybenzyloxy)butanoyl)-5-methyl-3-(3-phenylprop-2-ynyl)cyclohexanone (15): To a round-bottomed flask was added $Pd(PPh_3)_4$ (0.45 g, 0.39 mmol), CuI (150 mg, 0.77 mmol), and $i Pr_2NH$ (38 mL). The solution was cooled to 0 °C before addition of iodobenzene (1.3 mL, 12 mmol) and stirred 5 min before dropwise addition of a solution of **39** (3.0 g, 7.7 mmol) in THF (15 mL). Reaction stirred with warming from 0 °C to room temperature overnight before being diluted with ether and addition of saturated aqueous NH_4Cl. The layers were separated and the aqueous extracted with Et_2O. The combined organics were washed with NH_4Cl, H_2O, and brine before being dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 5% EtOAc/hex to 10% EtOAc/hex) to yield 3.4 g (94%) of **15**.

^1H NMR (600 MHz, $CDCl_3$) δ 7.40-7.37 (m, 2H), 7.30-7.27 (m, 3H), 7.24 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.70-5.62 (m, 1H), 5.18 (d, J = 17.7 Hz, 1H) 5.15 (d, J = 11.4, 1H), 4.39 (s, 2H), 3.81 (s, 3H), 3.41 (t, J = 6.1 Hz, 2H), 3.16 (dd, J = 13.9, 5.6 Hz, 1H), 2.63-2.45 (m, 6H), 2.44-2.38 (m, 1H), 2.36-2.23 (m, 3H), 1.92 (dt, J = 13.4, 5.3 Hz, 1H), 1.86-1.78 (m, 2H), 1.01 (d, J = 6.8 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 209.0, 208.5, 159.3, 132.8, 131.7, 130.6, 129.5, 128.4, 127.9, 123.9, 119.6, 114.0, 88.9, 82.0, 72.7, 69.7, 68.9, 55.5, 47.3, 38.4, 37.7, 36.9, 33.2, 28.9, 23.8, 21.0, 20.7

IR (thin film NaCl): 2955, 2927, 2857, 1685, 1612, 1512, 1247, 1098, 1034 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{31}H_{36}O_4Na$, 495.25058; found 495.24512.



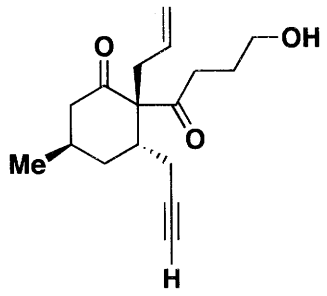
(±)-1-((1*S*,3*R*,5*S*,8*R*,*E*)-8-Allyl-7-benzylidene-1-hydroxy-3-methylbicyclo[3.2.1]octan-8-yl)-4-(4-methoxybenzyloxy)butan-1-one (41): To a round-bottomed flask in a glovebox was added $Ni(cod)_2$ (11 mg, 0.040 mmol) and PBu_3 (21 μL, 0.084 mmol). This flask was removed from the glovebox before addition of BEt_3 (65 μL, 0.45 mmol) and toluene (3 mL). To this yellow catalyst solution was added a solution of **15** in toluene (2 mL) over 5 min. The reaction was stirred overnight before opening to air and stirring for 45 min. The reaction was filtered and concentrated under reduced pressure and the crude residue was purified by silica gel chromatography (gradient, 5% EtOAc/hex to 10% EtOAc/hex) to afford 70 mg (67%) of **41**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.30 (m, 4H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.19 (t, *J* = 7.0 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.51 (s, 1H), 6.04-5.97 (m, 1H), 5.05 (d, *J* = 17.0 Hz, 1H), 5.03 (d, *J* = 9.5 Hz, 1H), 4.85 (s, 1H), 4.38 (d, *J* = 11.6 Hz, 1H), 4.35 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 3H), 3.38 (t, *J* = 6.0 Hz, 2H), 2.79 (dd, *J* = 14.8, 6.1 Hz, 1H), 2.63 (dt, *J* = 7.1, 2.8 Hz, 2H), 2.60-2.53 (m, 3H), 2.49 (dd, *J* = 14.9, 8.8 Hz, 1H), 1.85-1.70 (m, 4H), 1.59-1.49 (m, 3H), 0.94 (d, *J* = 6.0 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.4, 159.3, 147.4, 138.0, 134.2, 130.6, 129.4, 128.5, 128.5, 126.4, 120.2, 117.4, 113.9, 82.9, 72.6, 69.0, 62.6, 55.5, 44.1, 37.6, 34.9, 34.4, 34.3, 34.2, 25.4, 23.5, 21.5

IR (thin film NaCl): 3468, 2928, 2863, 1688, 1613, 1513, 1446, 1360, 1301, 1248, 1174, 1096, 1035, 916, 820, 755, 695 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{31}H_{38}O_4Na$, 497. 2657; found 497.2662.



(±)-(2*S*,3*S*,5*R*)-2-Allyl-2-(4-hydroxybutanoyl)-5-methyl-3-(prop-2-ynyl)cyclohexanone (44): To a round-bottomed flask was added **39** (59 mg, 0.15 mmol), CH_2Cl_2 (5 mL), and pH 7.0 buffer (0.5 mL), before cooling to 0 °C. To the

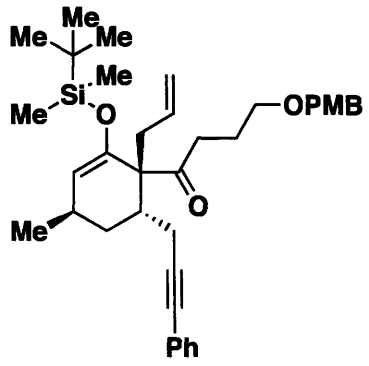
solution was added DDQ (43 mg, 0.19 mmol) and the reaction stirred at 0 °C for 1.25 h before addition of a saturated aqueous solution of $NaHCO_3$. The reaction mixture was then extracted with EtOAc, washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 10% EtOAc/hex to 20% EtOAc/hex) to afford 30 mg of **44** (72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (m, 1H), 5.17 (d, *J* = 9.0 Hz, 1H), 5.14 (s, 1H), 3.61 (m, 2H), 3.15 (dd, *J* = 14.0, 5.7 Hz, 1H), 2.56-2.18 (m, 10H), 2.0-1.97 (m, 1H), 1.92-1.84 (m, 1H), 1.78 (p, *J* = 6.8 Hz, 2H), 1.67-1.62 (m, 1H), 1.00 (d, *J* = 6.6 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 209.0, 132.5, 119.8, 83.2, 69.8, 69.7, 62.1, 47.3, 38.2, 37.5, 37.0, 32.8, 28.9, 26.6, 20.7, 19.8

IR (thin film NaCl): 3400, 3291, 2956, 2928, 2874, 2117, 1694, 1437, 1383, 1221, 1056, 1018, 921 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{17}H_{24}O_3Na$, 299.16177; found 299.16120.



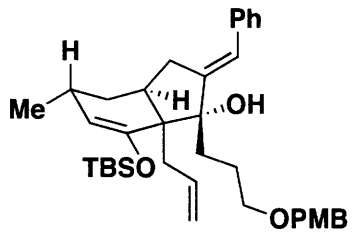
(±)-1-((1*R*, 4*R*, 6*S*)-1-Allyl-2-(*tert*-butyldimethylsilyloxy)-4-methyl-6-(3-phenylprop-2-ynyl)cyclohex-2-enyl)-4-(4-methoxybenzyloxybutan-1-one (46): To a round-bottomed flask was added **15** (3.4 g, 7.2 mmol), dichloromethane (36 mL), and triethylamine (6.0 mL, 43 mmol) before cooling to 0 °C. To this solution was added TBSOTf (8.3 mL, 36 mmol) and the reaction stirred at 0 °C for 3 h before being quenched by addition of a saturated aqueous solution of $NaHCO_3$. The aqueous was extracted with dichloromethane and the combined organics were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10% Et_2O/pentanes) to yield 3.8 g (90%) of **46**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39-7.37 (m, 2H), 7.29-7.26 (m, 3H), 7.24 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.60 (m, 1H), 5.15 (d, J = 23.3 Hz, 1H), 5.14 (s, 1H), 5.06 (d, J = 5.7 Hz, 1H), 4.40 (s, 2H), 3.81 (s, 3H), 3.43 (t, J = 6.2 Hz, 2H), 2.75 (ddd, J = 18.7, 8.3, 5.8 Hz, 1H), 2.70-2.62 (m, 2H), 2.57 (dd, J = 16.8, 3.9 Hz, 1H), 2.56-2.48 (m, 2H), 2.24-2.18 (m, 1H), 1.97 (dd, J = 16.8, 10.2 Hz, 1H), 1.91-1.76 (m, 4H), 1.06 (d, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.21 (s, 3H), 0.19 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1, 159.3, 149.3, 135.0, 131.7, 130.8, 129.5, 128.4, 127.8, 124.1, 118.7, 113.9, 111.3, 89.2, 81.9, 72.6, 69.3, 59.2, 55.5, 38.7, 36.0, 34.2, 31.6, 27.7, 25.7, 23.9, 22.0, 21.6, 18.2, -4.6, -4.9

IR (thin film NaCl): 2930, 1703, 1660, 1613, 1513, 1490, 1250, 1196, 1100, 1038, 839 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{37}H_{50}O_4SiNa$, 609.3371; found 609.3372.



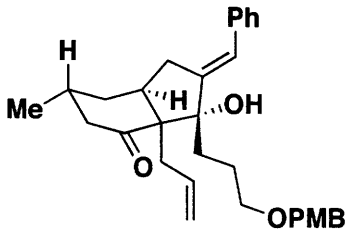
(±)-(1*S*,3a*S*,5*R*,7a*S*,*E*)-7a-Allyl-2-benzylidene-7-(*tert*-butyldimethylsilyloxy)-1-(3-(4-methoxybenzyloxy)propyl)-5-methyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-1-ol (47): To a round-bottomed flask in a glovebox was added $Ni(cod)_2$ (116 mg, 0.422 mmol) and PBu_3 (210 μL, 0.842 mmol). The flask was removed from the glovebox before addition of triethylborane (610 μL, 4.20 mmol) and toluene (21 mL). The solution was heated to 50 °C in an oil bath before dropwise addition of **46** (1.23 g, 2.10 mmol) as a solution in toluene (21 mL). The reaction was stirred at 50 °C for 6 h before cooling to room temperature and opening to air. Reaction stirred open to air 45 min before being filtered through celite and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (3% EtOAc/hex) to afford 1.03 g (84%) of **47**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.31 (m, 4H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.23-7.19 (m, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.44 (s, 1H), 5.68-5.60 (m, 1H), 5.01 (d, *J* = 10.4 Hz, 1H), 4.99 (d, *J* = 6.2 Hz, 1H), 4.94 (d, *J* = 16.9 Hz, 1H), 4.41 (s, 2H), 3.81 (s, 3H), 3.46-3.41 (m, 2H), 2.96 (dd, *J* = 18.8, 9.8 Hz, 1H), 2.80 (dd, *J* = 13.9, 4.9 Hz, 1H), 2.39-2.33 (m, 1H), 2.33-2.26 (m, 1H), 2.23 (s, 1H), 2.14 (dt, *J* = 17.6, 3.6 Hz, 1H), 1.88-1.80 (m, 1H), 1.77-1.63 (m, 5H), 1.55 (dd, *J* = 13.3, 6.4 Hz, 1H), 0.98 (d, *J* = 7.1 Hz, 3H), 0.96 (s, 9H), 0.25 (s, 3H), 0.22 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 150.8, 145.0, 137.9, 136.5, 131.0, 129.4, 129.1, 128.3, 126.3, 121.9, 117.5, 113.9, 110.3, 84.0, 72.4, 70.7, 55.5, 52.3, 37.9, 36.5, 35.6, 33.4, 32.7, 29.0, 26.1, 23.8, 21.9, 18.2, -4.0, -4.6

IR (thin film NaCl): 3578, 2929, 2857, 1654, 1612, 1512, 1463, 1362, 1248, 1177, 1036, 827 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{37}H_{52}O_4SiNa$, 611.3527; found 611.3525.



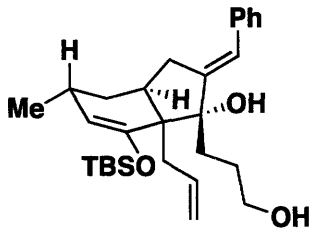
(±)-(3*S*,3a*S*,6*R*,7a*S*,*E*)-3a-Allyl-2-benzylidene-3-hydroxy-3-(3-(4-methoxybenzyloxy) propyl)-6-methylhexahydro-1*H*-inden-4(2*H*)-one (14): To a round-bottomed flask was added **47** (23 mg, 0.039 mmol) and THF (0.78 mL) before cooling to 0 °C. To this solution was added a pre-mixed solution of AcOH and TBAF (85 μL of a solution consisting of 180 μL AcOH and 2.0 mL of a 1.0 M TBAF solution in THF). The reaction was stirred at 0 °C for 15 min before addition of H_2O. The reaction was extracted with Et_2O, washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 18 mg (98%) of **14**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.33 (m, 2H), 7.31-7.29 (m, 2H), 7.25-7.22 (m, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.49 (s, 1H), 5.64-5.57 (m, 1H), 5.03-4.97 (m, 2H), 4.41 (d, *J* = 11.8 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 3.81 (s, 3H), 3.40 (t, *J* = 6.0 Hz, 2H), 2.97-2.90 (m, 2H), 2.55 (s, 1H), 2.50-2.42 (m, 2H), 2.24 (dd, *J* = 7.2, 2.9 Hz, 1H), 2.22-2.17 (m, 1H), 2.06 (dd, *J* = 17.9, 6.9 Hz, 1H), 1.85 (dd, *J* = 13.3, 8.8 Hz, 1H), 1.81-1.73 (m, 3H), 1.72-1.57 (m, 2H), 1.49-1.44 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3, 159.3, 143.6, 137.5, 134.9, 130.6, 129.5, 129.5, 129.1, 128.4, 126.7, 122.8, 118.9, 113.9, 84.7, 72.6, 70.0, 60.1, 55.5, 49.8, 41.9, 37.6, 35.7, 33.3, 27.3, 23.7, 21.3

IR (thin film NaCl): 3451, 2925, 1683, 1611, 1512, 1247 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{31}H_{38}O_4Na$, 497.2662; found 497.2648.



(±)-(1*S*, 3a*S*, 5*R*, 7a*S*, *E*)-7a-Allyl-2-benzylidene-7-(*tert*-butyldimethylsilyloxy)-1-(3-hydroxypropyl)-5-methyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-1-ol (51): To a round-bottomed flask was added **47** (218 mg, 0.370 mmol), CH_2Cl_2 (7.9 mL), and H_2O (0.79 mL) before the reaction was cooled to 0 °C. and addition of DDQ (223 mg, 0.982 mmol). The reaction was stirred at 0 °C for 1 hour before addition of saturated aqueous $NaHCO_3$. The reaction was extracted with CH_2Cl_2 and the organics were washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 5% EtOAC/hex to 10% EtOAc/hex) to yield 136 mg (78%) of **51**.

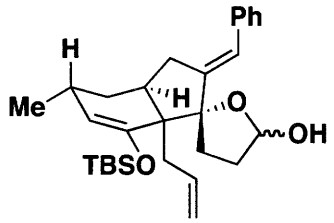
^1H NMR (600 MHz, $CDCl_3$) δ 7.37-7.34 (m, 4H), 7.25-7.20 (m, 1H), 6.45 (s, 1H), 5.69-5.61 (m, 1H), 5.02 (d, J = 12.7 Hz, 1H), 5.01 (d, J = 6.4 Hz, 1H), 4.95 (d, J = 17.0 Hz, 1H), 3.64 (t, J = 6.0 Hz, 2H), 2.99 (dd, J = 17.5, 9.8 Hz, 1H), 2.79 (dd, J = 13.9, 4.9 Hz,

1H), 2.39-2.28 (m, 2H), 2.33 (s, 1H), 2.17 (dt, J = 17.6, 3.8 Hz, 1H), 1.85-1.59 (m, 7H), 1.57 (dd, J = 12.9, 6.2 Hz, 1H), 1.00-0.96 (m, 12H), 0.28 (s, 3H), 0.24 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 144.9, 137.8, 136.4, 129.1, 128.4, 126.4, 122.2, 117.6, 110.4, 84.0, 63.8, 52.2, 37.9, 36.4, 35.6, 33.4, 32.6, 29.0, 27.0, 26.1, 21.9, 18.2, -4.0, -4.6

IR (thin film NaCl): 3579, 3357, 2953, 2929, 2859, 1658, 1462, 1471, 1257, 1180, 838 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{29}H_{44}O_3Na$, 491. 2952; found 491.2966.



(±)-(1'*S*,3a'*S*,5'*R*,7a'*S*,*E*)-7a'-Allyl-2'-benzylidene-7'-(*tert*-butyldimethylsilyloxy)-5'-methyl-2',3',3a',4,4',5,5',7a'-octahydro-3*H*-spiro[furan-2,1'-inden]-5-ol (52): To a round-bottomed flask was added CH_2Cl_2 (10 mL) and oxalyl chloride (26 μL, 0.30 mmol) before being cooled to –78 °C. To this solution was added DMSO (34 μL, 0.48 mmol) and the solution stirred for 15 min before addition of **51** (113 mg, 0.24 mmol) as a solution in CH_2Cl_2 (2 mL). The solution was stirred an additional 15 min at –78 °C before addition of NEt_3 (100 μL, 0.72 mmol), removal of the cold bath, and warming to

room temperature. The reaction was poured into H_2O, extracted with Et_2O, washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (2% EtOAc/hex to 5% EtOAc/hex) to afford 92 mg (82%) **52**.

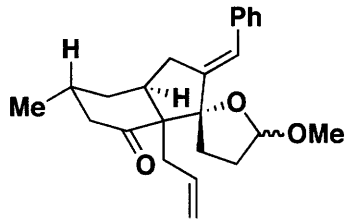
^{1}H NMR (500 MHz, $CDCl_3$, * denotes minor diastereomer) δ 7.40-7.32 (m, 4H), 7.20 (t, J = 7.1 Hz, 1H), 6.79 (s, 1H), 6.28* (s, 1H), 5.69-5.56 (m, 2H), 5.15* (d, J = 5.5 Hz, 1H), 5.50-4.98 (m, 2H), 4.97-4.94 (m, 1H), 3.65* (d, J = 7.7 Hz, 1H), 3.01 (d, J = 4.5 Hz, 1H), 3.00-2.87 (m, 2H), 2.50-2.43 (m, 1H), 2.38-2.27 (m, 2.H), 2.27-2.16 (m, 2H), 2.01 (s, 1H), 1.97 (dd, J = 12.3, 7.4 Hz, 1H), 1.93-1.86 (m, 1H), 1.77 (dd, J = 14.1, 10.0 Hz, 1H), 1.70-1.61 (m, 1H), 1.50-1.44* (m, 1H), 1.39 (dd, J = 13.3, 3.4 Hz, 1H), 1.02* (d, J = 7.0 Hz, 1H), 0.98 (d, J = 7.3 Hz, 3H), 0.95 (s, 9H), 0.27* (s, 3H), 0.26* (s, 3H), 0.22 (s, 3H), 0.21 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 150.3, 149.3, 147.0, 138.2, 137.7, 136.5, 136.0, 129.0, 129.0, 128.4, 128.4, 126.5, 126.4, 122.6, 121.1, 117.5, 117.0, 115.0, 111.5, 99.1, 99.1, 96.0, 95.2, 52.2, 52.1, 36.9, 36.5, 35.8, 35.2, 34.9, 34.0, 33.8, 33.1, 33.1, 33.0, 32.5, 32.4, 28.6, 28.5, 26.6, 26.1, 22.5, 22.0, 18.9, 18.5, -3.8, -3.9, -4.0, -4.8

IR (thin film NaCl): 3387, 2955, 2930, 2860, 1648, 1470, 1352, 1257, 1183, 1166, 1133, 907, 731 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{29}H_{42}O_3SiNa$, 489.2795; found 489.2800.

MP (from $CDCl_3$) 103-108 °C



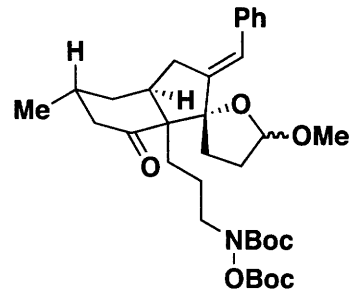
(±)-(1'*S*, 3a'*S*, 5'*R*, 7a'*S*, *E*)-7a'-Allyl-2'-benzylidene-5-methoxy-5'-methyloctahydro-3*H*-spiro[furan-2,1'-inden]-7'(7a'*H*)-one (53): To a round-bottomed flask were added **52** (53 mg, 0.11 mmol), benzene (2.3 mL), and anhydrous methanol (0.46 mL) before addition of PPTS (2.8 mg, 0.011 mmol). The solution was stirred overnight at room temperature before addition of a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous extracted with Et_2O. The combined organics were washed with water and brine before being dried over anhydrous Na_2SO_4. The solution was filtered and concentrated under reduced pressure to yield the crude residue which was purified by silica gel chromatography (hexanes to 10% EtOAc/hexanes) to afford 50 mg (91%) of the methyl acetal as a mixture of diastereomers about the acetal carbon ~3:1. To a round-bottomed flask was added the methyl acetal (50 mg, 0.10 mmol), THF (5.0 mL) and the solution cooled to 0 °C. To this flask was added pre-mixed solution of TBAF and AcOH (210 μL of solution composed of 180 μL AcOH and 2.0 mL of a 1.0 M TBAF solution in THF). The reaction was stirred at room temperature for 45 min before quenching with saturated aqueous $NaHCO_3$. The reaction was extracted with Et_2O, washed with H_2O, brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 35 mg (93%) of **53**.

^{1}H NMR (600 MHz, $CDCl_3$, * denotes minor diastereomer) δ 7.35-7.30 (m, 4H), 7.23-7.18 (m, 1H), 6.57 (t, *J* = 2.5 Hz, 1H), 6.31* (t, *J* = 2.5 Hz, 1H), 5.80-5.72* (m, 1H), 5.71-5.64 (m, 1H), 5.09 (dd, *J* = 16.9, 1.8 Hz, 1H), 5.06 (dd, *J* = 5.0, 1.8 Hz, 1H), 5.04-5.00 (m, 1H), 3.43* (s, 3H), 3.29 (s, 3H), 2.96-2.90* (m, 1H), 2.88 (ddd, *J* = 17.4, 9.3, 2.4 Hz, 1H), 2.81 (dd, *J* = 14.8, 7.3 Hz, 1H), 2.74-2.66 (m, 1H), 2.52 (dt, *J* = 14.2, 8.9 Hz, 1H), 2.42-2.10 (m, 9H), 2.06-1.94 (m, 3H), 1.80 (dt, *J* = 14.2, 4.2 Hz, 1H), 1.74-1.65 (m, 1H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.99* (d, *J* = 6.6 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.8, 212.7, 145.4, 144.9, 138.3, 137.5, 135.1, 134.9, 129.1, 129.0, 128.4, 128.3, 126.8, 126.5, 122.5, 120.9, 118.1, 117.9, 105.0, 104.3, 96.8, 95.4, 62.5, 61.8, 55.1, 54.6, 49.6, 49.1, 41.5, 41.2, 36.9, 36.5, 34.6, 33.8, 33.6, 33.6, 33.1, 32.7, 31.8, 29.9, 29.7, 29.6, 29.1, 29.0, 22.2, 22.0

IR (thin film NaCl): 2952, 2922, 1705, 1560, 1492, 1447, 1367, 1212, 1102, 1036, 985, 955, 917, 752, 695 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{24}H_{30}O_3Na$, 389.2087; found 389.2087.



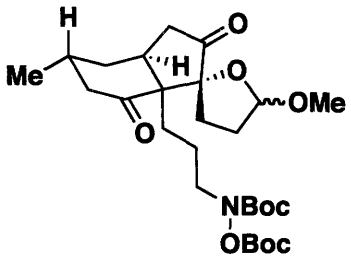
(±)-*tert*-Butyl-3-((1'*S*,3a'*S*,5'*R*,7a'*S*,*E*)-2'-benzylidene-5-methoxy-5'-methyl-7'-oxodecahydro-3*H*-spiro[furan-2,1'-indene]-7a'-yl)propyl(*tert*-butoxycarbonyloxy) carbamate (54): To a round-bottomed flask was added **53** (35 mg, 0.074 mmol), THF (0.73 mL) before addition of BH_3•SMe_2 (37 μL of a 2.0 M THF solution, 0.074 mmol). Reaction stirred at room temperature for 4.25 h before addition of $NaBO_3$•$4H_2O$ (31 mg, 0.20 mmol) and H_2O (0.73 mL). The solution was stirred at room temperature overnight before extracting with EtOAc. The combined organics were washed with H_20, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude residue. The crude residue was purified by silica gel chromatography (40% EtOAC/hex to 50% EtOAc/hex) to afford 15 mg (53%) of the primary alcohol and 7.0 mg (27%) of recovered **32**. To a round-bottomed flask was added the hydroboration product (15 mg, 0.039 mmol), PPh_3 (39 mg, 0.15 mmol), HN(OBoc)Boc (37 mg, 0.16 mmol) and toluene (3.9 mL) before addition of DEAD (28 μL, 0.18 mmol). The reaction was heated to 80 °C for 3 h. After 3 h the reaction was cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 2% EtOAc/hex to 20% EtOAc/hex) to afford 16 mg (69%) of **54**.

^{1}H NMR (600 MHz, $CDCl_3$, * denotes minor diastereomer) δ 7.34-7.28 (m, 4H), 7.22-7.17 (m, 1H), 6.55 (s, 1H), 6.32* (s, 1H), 5.06 (d, *J* = 4.9 Hz, 1H), 4.99* (d, *J* = 5.0 Hz, 1H), 3.64-3.48 (m, 2H), 3.41* (s, 3H), 3.26 (s, 3H), 2.90* (dd, *J* = 17.6, 9.7 Hz, 1H), 2.85 (dd, *J* = 17.4, 9.3, 1H), 2.71-2.62 (m, 1H), 2.60-2.48 (m, 1H), 2.43-1.94 (m, 10H), 1.83-1.60 (m, 5H), 1.53 (s, 9H), 1.49 (s, 9H), 1.01 (d, *J* = 6.3 Hz, 3H), 1.00-0.98* (m, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 213.4, 155.2, 155.1, 152.4, 145.4, 145.3, 138.3, 137.6, 129.1, 128.9, 128.3, 128.3, 126.7, 126.5, 122.3, 121.0, 104.8, 104.5, 96.7, 95.3, 94.9, 85.0, 84.8, 82.5, 82.4, 62.3, 62.0, 55.3, 54.5, 51.0, 49.0, 49.0, 43.1, 42.4, 37.7, 36.8, 33.9, 33.8, 33.5, 33.0, 32.8, 29.7, 29.3, 29.3, 28.7, 28.3, 27.8, 23.4, 22.3, 22.1

IR (thin film NaCl): 2954, 2980, 2929, 1783, 1706, 1599, 1576, 1457, 1395, 1370, 1275, 1255, 1149, 1133, 1035, 985, 955, 916, 835, 753, 733, 696, 648 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{34}H_{49}NO_8Na$, 622.3350; found 622.3335.



(±)-*tert*-Butyl *tert*-butoxycarbonyloxy(3-((1'*R*,3a'*S*,5'*R*,7a'*S*)-5-methoxy-5'-methyl-2',7'-dioxodecahydro-3*H*-spiro[furan-2,1'-indene]-7a'-yl)propyl)carbamate (55): To a round-bottomed flask was added **33** (25 mg, 0.041 mmol), CH_2Cl_2 (4.1 mL), and

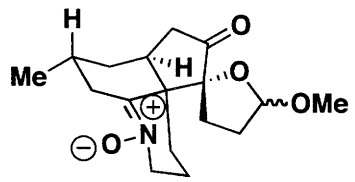
cooled to – 78 °C before passing a stream of ozone through solution until the blue color remains. Argon was bubbled through the blue solution to remove any dissolved ozone before addition of PPh_3 (22 mg, 0.082 mmol) and removal of the cold bath. The reaction was warmed to room temperature over 2 h and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 10% EtOAc/hex to 20% EtOAc/hex) to yield 19 mg of **55** (87%)

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.01 (d, *J* = 4.9 Hz, 1H), 3.65-3.54 (m, 2H), 3.17 (s, 3H), 2.88-2.83 (m, 1H), 2.50 (dd, *J* = 19.5, 9.3 Hz, 1H), 2.41 (t, *J* = 12.4 Hz, 1H), 2.17 (dd, *J* = 11.9, 2.6 Hz, 1H), 2.13-2.00 (m, 1H), 1.94 (dd, *J* = 19.5, 11.1 Hz, 1H), 1.91-1.86 (m, 1H), 1.85-1.78 (m, 1H), 1.74-1.69 (m, 1H), 1,65-1.54 (m, 2H), 1.53 (s, 9H), 1.49 (s, 1H), 1.46-1.36 (m, 2H), 1.08 (d, *J* = 6.4 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 210.1, 155.3, 152.4, 105.1, 90.5, 85.2, 82.8, 62.1, 54.7, 50.8, 47.9, 41.5, 36.6, 33.7, 32.1, 31.6, 28.3, 27.8, 26.6, 24.3, 23.4, 22.4

IR (thin film NaCl): 2930, 1783, 1760, 1702, 1458, 1395, 1369, 1245, 1148, 1106, 1035, 977, 949, 852, 761 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{27}H_{43}NO_9Na$, 548.2830; found 548.2835.



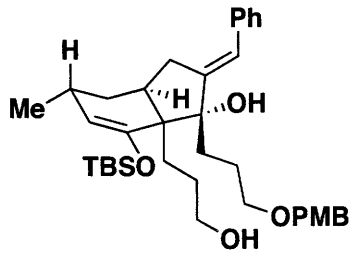
(±)-(2'*R*,4[1]*R*,7a*S*,9*R*)-5'-Methoxy-9-methyl-6-oxo-3,4,4',5',6,7,7a,8,9,10-decahydro-2*H*,3'*H*-spiro[cyclopenta[*e*]quinoline-5,2'-furan] 1-oxide (57): To a round-bottomed flask was added **55** (6.5 mg, 0.012 mmol), CH_2Cl_2 (1.2 mL), and anhydrous $ZnBr_2$ (11 mg, 0.049 mmol). Reaction stirred at room temperature for 5 h before addition of saturated aqueous solution of $NaHCO_3$. The reaction was extracted with EtOAc, washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 60% EtOAc/hex to 5% MeOH/$CHCl_3$) to afford 0.6 mg (16%) **57**.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.07 (dd, *J* = 5.2, 2.5 Hz, 1H), 3.93 (m, 2H), 3.34 (s, 3H), 3.16 (dd, *J* = 18.7, 6.5 Hz, 1H), 2.96 (dd, *J* = 17.9, 10.8 Hz, 1H), 2.47 (dt, *J* = 13.4, 4.7 Hz, 1H), 2.38 (dt, *J* = 10.8, 2.3 Hz, 1H), 2.27-2.21 (m, 2H), 2.14 (dd, *J* = 17.9, 2.3 Hz, 1H), 2.12-1.88 (m, 5H), 1.78 (ddd, *J* = 13.1, 9.1, 5.3 Hz, 1H), 1.63-1.53 (m, 2H), 1.41 (ddd, *J* = 13.9, 9.3, 5.7 Hz, 1H), 1.01 (d, *J* = 6.7 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.5, 149.3, 106.4, 91.7, 57.9, 55.6, 48.1, 40.3, 38.6, 36.7, 33.6, 32.7, 30.1, 29.2, 25.5, 22.0, 20.5

IR (thin film NaCl): 3387, 2953, 1750, 1457, 1214, 1104, 1034, 949 cm^{-1}

HRMS ESI (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{26}NO_4$, 308.1856; found 308.1955.



(±)-(1*S*,3a*S*,5*R*,7a*S*,*E*)-2-Benzylidene-7-(*tert*-butyldimethylsilyloxy)-7a-(3-hydroxypropyl)-1-(3-(4-methoxybenzyloxy)propyl)-5-methyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-1-ol (60): To a round-bottomed flask were added **47** (1.7 g, 2.9 mmol), THF (58 mL), and BH_3•DMS (2.9 mL of a 2.0 M solution in THF, 5.8 mmol). This solution was stirred at room temperature for 30 min before addition of $NaBO_3$•$4H_2O$ (2.7 g, 17 mmol) and H_2O (58 mL). The reaction was stirred overnight before separating the layers and extracting with EtOAc. The combined organic layers were washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (gradient, 10% EtOAc/hex to 20% EtOAc/hex) to yield 1.2 g (67%) of **60**.

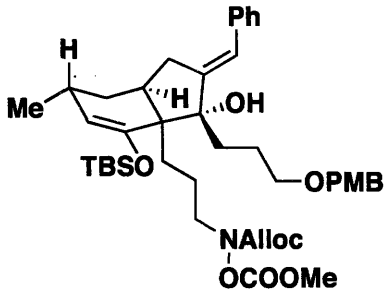
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.29 (m, 4H), 7.26-7.18 (m, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.43 (s, 1H), 4.99 (d, *J* = 6.0 Hz, 1H), 4.41 (s, 2H), 3.81 (s, 3H), 3.63-3.53 (m, 2H), 3.43 (t, *J* = 5.9 Hz, 2H), 2.97 (dd, *J* = 17.3, 9.7 Hz, 1H), 2.42-2.35 (m, 1H), 2.29-2.23 (m, 1H), 2.22 (s, 1H), 2.15 (dt, *J* = 17.6, 3.7 Hz, 1H), 1.99 (dt, *J* = 13.0, 3.7 Hz, 1H), 1.88-1.63 (m, 5H), 1.58 (dd, *J* = 13.2, 6.2 Hz, 1H), 1.54-1.45 (m, 1H), 1.41-1.32 (m,

1H), 1.30-1.25 (m, 1H), 1.06 (dt, J = 12.9, 4.6 Hz, 1H), 1.02 (d, J = 7.1 Hz, 3H), 0.95 (s, 9H), 0.24 (s, 3H), 0.22 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 151.0, 144.9, 137.8, 131.0, 129.4, 129.1, 128.3, 126.4, 121.9, 113.9, 110.2, 84.0, 72.4, 70.7, 63.9, 55.5, 52.2, 36.6, 35.7, 33.6, 33.5, 28.8, 28.8, 28.3, 26.0, 23.8, 22.1, 18.2, -4.1, -4.6

IR (thin film NaCl): 3583, 3399, 2929, 2857, 1656, 1612, 1463, 1363, 1248, 1172, 1099, 1036, 837 cm^{-1}

HRMS ESI (*m/z*): [M+ Na]$^+$ calcd for $C_{37}H_{54}O_5SiNa$, 629.3633; found 629.3645.



(±)-Allyl 3-((3*S*,3a*S*,6*R*,7a*S*,*E*)-2-benzylidene-4-(*tert*-butyldimethylsilyloxy)-3-hydroxy-3-(3-(4-methoxybenzyloxy)propyl)-6-methyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-3a-yl)propyl(methoxycarbonyloxy)carbamate (68): To a round-bottomed flask was added **60** (45 mg, 0.075 mmol), PPh_3 (34 mg, 0.13 mmol), HN(OCOOMe)Alloc (26 mg, 0.15 mmol), and toluene (1.5 mL). To this solution was added DEAD (24 μL, 0.15 mmol) and the reaction stirred for 1 hour at room temperature. The reaction mixture was

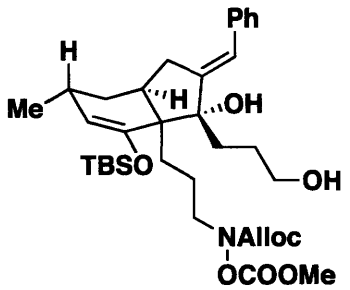
loaded directly onto silica gel and purified by silica gel chromatography (10% EtOAc/hex) to yield 40 mg (70%) of **68**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.28 (m, 4H), 7.26-7.18 (m, 3H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.42 (s, 1H), 5.88 (m, 1H), 5.28 (d, *J* = 17.2 Hz, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 4.98 (d, *J* = 6.0 Hz, 1H), 4.62 (m, 2H), 4.40 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.55 (m, 2H), 3.43 (t, *J* = 6.0 Hz, 2H), 2.96 (dd, *J* = 17.4, 9.6 Hz, 1H), 2.37 (m, 1H), 2.25-2.18 (m, 1H), 2.19 (s, 1H), 2.14 (dt, *J* = 17.7, 3.7 Hz, 1H), 1.95 (dt, *J* = 13.1, 3.7 Hz, 1H), 1.87-1.78 (m, 1H), 1.76-1.70 (m, 1H), 1.69-1.62 (m, 2H), 1.60-1.53 (m, 2H), 1.47-1.31 (m, 1H), 1.01 (dt, *J* = 13.2, 4.6 Hz, 1H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.94 (s, 9H), 0.23 (s, 3H), 0.20 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 155.4, 155.0, 150.8, 144.7, 137.8, 132.0, 130.9, 129.4, 129.1, 128.3, 126.4, 122.0, 118.5, 113.9, 110.4, 83.9, 72.4, 70.7, 67.3, 56.2, 55.5, 52.3, 51.5, 36.6, 35.7, 33.6, 33.5, 29.5, 28.8, 26.0, 23.8, 22.5, 22.0, 18.2, -4.1, -4.9

IR (thin film NaCl): 3583, 2928, 1793, 1734, 1653, 1457, 1247, 1202, 839 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{43}H_{61}NO_9SiNa$, 786.4008; found 786.4025.



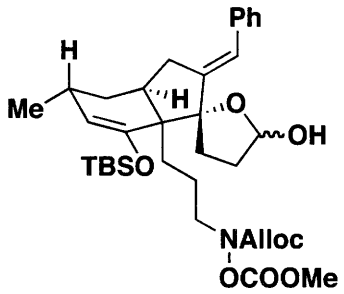
(±)-Allyl-3-((3*S*,3a*S*,6*R*,7a*S*,*E*)-2-benzylidene-4-(*tert*-butyldimethylsilyloxy)-3-hydroxy-3-(3-hydroxypropyl)-6-methyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-3a-yl)propyl(methoxycarbonyloxy)carbamate (69): To a round-bottomed flask was added **68** (40 mg, 0.052 mmol), CH_2Cl_2 (1.0 mL), and H_2O (52 μL), before cooling to 0 °C. To the solution was added DDQ (15 mg, 0.065 mmol) and the reaction stirred at 0 °C for 2 h before addition of a saturated aqueous solution of $NaHCO_3$. The reaction mixture was then extracted with CH_2Cl_2, washed brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 10% EtOAc/hex to 15% EtOAc/hex) to afford 25 mg (73%) of **69**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.31 (m, 4H), 7.23-7.19 (m, 1H), 6.43 (s, 1H), 5.87 (m, 1H), 5.28 (d, *J* = 17.2 Hz, 1H), 5.20 (d, *J* = 10.5 Hz, 1H), 5.00 (d, *J* = 6.1 Hz, 1H), 4.62 (m, 2H), 3.83 (s, 3H), 3.63 (t, *J* = 5.8 Hz, 2H), 3.60-3.53 (m, 2H), 2.99 (dd, *J* = 17.3, 9.4 Hz, 1H), 2.37 (m, 1H), 2.28-2.13 (m, 3H), 1.94 (dt, *J* = 13.1, 3.7 Hz, 1H), 1.83-1.64 (m, 4H), 1.64-1.52 (m, 3H), 1.48-1.38 (m, 1H), 1.03 (dt, *J* = 13.1, 4.6 Hz, 1H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.96 (s, 9H), 0.26 (s, 3H), 0.22 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 155.0, 150.6, 144.6, 137.6, 132.0, 129.1, 128.4, 126.5, 122.2, 118.5, 110.5, 83.9, 67.3, 63.8, 56.2, 52.3, 51.5, 36.5, 35.7, 33.5, 33.5, 29.5, 28.8, 26.9, 26.0, 22.5, 22.0, 18.2, -4.1, -4.9

IR (thin film NaCl): 3584, 2928, 2857, 1795, 1725, 1653, 1441, 1376, 1240, 1202, 1141, 931, 839 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{35}H_{53}NO_8SiNa$, 666.3433; found 666.3409.



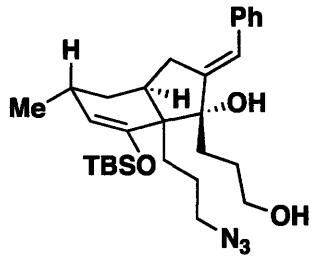
(±)-Allyl 3-((1'*S*,3a'*S*,5'*R*,7a'*S*,*E*)-2'-benzylidene-7'-(*tert*-butyldimethylsilyloxy)-5-hydroxy-5'-methyl-2',3',3a',4,4',5,5',7a'-octahydro-3*H*-spiro[furan-2,1'-indene]-7a'-yl)propyl(methoxycarbonyloxy)carbamate (59): To a round-bottomed flask was added CH_2Cl_2 (0.5 mL) and oxalyl chloride (3 μL, 0.035 mmol) before being cooled to –78 °C. To this solution was added DMSO (5 μL, 0.071 mmol) and the solution stirred for 15 min before addition of **69** (8.9 mg, 0.014 mmol) as a solution in CH_2Cl_2 (0.5 mL). The solution was stirred an additional 15 min at –78 °C before addition of NEt_3 (20 μL, 0.14 mmol), removal of the cold bath, and warming to room temperature and addition of H_2O. The reaction was extracted with Et_2O, washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10% EtOAc/hex to 20% EtOAc/hex) to afford 5.7 mg (64%) of **59**.

^{1}H NMR (500 MHz, $CDCl_3$, * denotes minor diastereomer) δ 7.37-7.30 (m, 4H), 7.24-7.18 (m, 1H), 6.74 (s, 1H), 6.25* (s, 1H), 5.92-5.84 (m, 1H), 5.62-5.58 (m, 1H), 5.29 (dd, J = 17.2, 1.4 Hz, 1H), 5.21 (dd, J = 10.5, 1.2 Hz, 1H), 5.10* (d, J = 5.2 Hz, 1H), 4.94 (d, J = 5.2 Hz, 1H), 4,67-4.58 (m, 3H), 3.84 (s, 3H), 3.61-3.52 (m, 2H), 3.46* (d, J = 7.5 Hz, 1H), 2.97 (dd, J = 17.3, 9.3 Hz, 1H), 2.92* (dd, J = 18.0, 9.6 Hz, 1H), 2.74 (d, J = 4.8 Hz, 1H), 2.45-2.38 (m, 1H), 2.36-2.13 (m, 4H), 2.11-1.98 (m, 2H), 1.96-1.84 (m, 2H), 1.79-1.63 (m, 2H), 1.48-1.38 (m, 2H), 1.21-1.14 (m, 1H), 1.02* (d, J = 7.0 Hz, 3H), 0.99 (d, J =7.1 Hz, 3H), 0.98* (s, 9H), 0.94 (s, 9H), 0.25* (s, 3H), 0.23* (s, 3H), 0.21 (s, 3H), 0.20 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 155.0, 155.0, 150.3, 150.3, 148.8, 146.5, 138.0, 137.5, 132.0, 132.0, 129.0, 129.0, 128.4, 128.4, 126.6, 126.4, 122.2, 120.9, 118.5, 118.5, 114.8, 111.6, 99.1, 99.0, 95.8, 95.4, 67.4, 67.3, 56.2, 56.2, 52.3, 52.2, 51.4, 51.4, 35.7, 35.4, 35.2, 33.9, 33.8, 33.7, 33.6, 33.1, 32.6, 32.1, 28.8, 28.3, 28.3, 28.1, 26.5, 26.3, 26.0, 22.6, 22.5, 22.4, 22.1, 18.9, 18.4, -3.9, -4.0, -4.3, -5.1

IR (thin film NaCl): 3460, 2956, 2859, 1796, 1726, 1650, 1600, 1441, 1405, 1362, 1239, 1193, 1140, 1046, 992, 931, 838, 778, 754, 696, 669 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{35}H_{51}NO_8SiNa$, 664.3276; found 664.3269.



(±)-(1*S*,3a*S*,5*R*,7a*S*,*E*)-7a-(3-Azidopropyl)-2-benzylidene-7-(*tert*-butyldimethylsilyloxy)-1-(3-hydroxypropyl)-5-methyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-1-ol (73): To a round-bottomed flask was added **60** (697 mg, 1.15 mmol), CH_2Cl_2 (5.8 mL), and NEt_3 (320 μL, 2.30 mmol). This solution was cooled to 0 °C before addition of MsCl (107 μL, 1.38 mmol) and stirred at 0 °C for 20 min before addition of H_2O. The layers were separated before the aqueous was extracted with Et_2O and the combined organics washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mesylate was added to a round-bottomed flask before addition of DMF (7.7 mL) and NaN_3 (224 mg, 3.45 mmol). The reaction was heated to 50 °C overnight before cooling to room temperature. After cooling to room temperature the reaction was diluted with H_2O, extracted with Et_2O, washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude azide. To a round-bottomed flask was added the crude azide, CH_2Cl_2 (23 mL), and H_2O (1.2 mL), before cooling to 0 °C. To the solution was added DDQ (654 mg, 2.08 mmol) and the reaction stirred at 0 °C for 1 hour before addition of a saturated aqueous solution of $NaHCO_3$. The reaction mixture was then extracted with CH_2Cl_2, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography

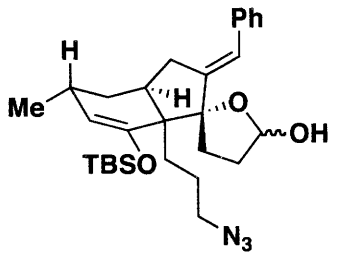
(gradient, 5% EtOAc/hex to 10% EtOAc/hex) to afford 401 mg (68% yield over the three steps) of **73**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.31 (m, 4H), 7.24-7.20 (m, 1H), 6.44 (s, 1H), 5.01 (d, *J* = 6.1 Hz, 1H), 3.63 (m, 2H), 3.21 (t, *J* = 7.2 Hz, 2H), 3.00 (dd, *J* = 17.0, 9.3 Hz, 1H), 2.43-2.35 (m, 1H), 2.28 (s, 1H), 2.26-2.15 (m, 2H), 2.01 (dt, *J* = 13.1, 3.8 Hz, 1H), 1.82-1.33 (m, 9H), 1.07 (dt, *J* = 13.1, 4.5 Hz, 1H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.97 (s, 9H), 0.28 (s, 3H), 0.24 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 144.5, 137.6, 129.1, 128.4, 126.5, 122.2, 110.4, 84.0, 63.8, 52.3, 52.2, 36.6, 35.6, 33.6, 33.5, 30.0, 28.8, 26.9, 26.0, 24.6, 22.0, 18.2, -4.1, -4.6

IR (thin film NaCl): 3583, 3353, 2929, 2859, 2095, 1654, 1463, 1363, 1260, 1172, 837 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{29}H_{45}N_3O_3SiNa$, 534.3122; found 534.3115.



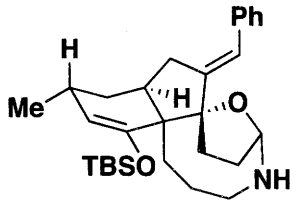
(±)-(1'*S*,3a'*S*,5'*R*,7a'*S*,*E*)-7a'-(3-Azidopropyl)-2'-benzylidene-7'-(*tert*-butyldimethylsilyloxy)-5'-methyl-2',3',3a',4,4',5,5',7a'-octahydro-3*H*-spiro[furan-2,1'-inden]-5-ol (72): To a round-bottomed flask was added **73** (240 mg, 0.469 mmol), DMSO (9.4 mL), NEt_3 (390 μL, 2.82 mmol) before addition of solid SO_3•Py (224 mg, 1.41 mmol). The reaction was stirred at room temperature for 1 hour before addition of water and extracting with EtOAc. The combined organics were washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 5% EtOAc/hex to 10% EtOAc/hex) to afford 188 mg (79%) of **72**.

^{1}H NMR (500 MHz, $CDCl_3$, * denotes minor diastereomer) δ 7.37-7.30 (m, 4H), 7.24-7.19 (m, 1H), 6.76 (s, 1H), 6.26* (s, 1H), 5.63-5.59 (m, 1H), 5.12* (d, J = 5.3 Hz, 1H), 4.96 (d, J = 5.2 Hz, 1H), 3.42* (d, J = 7.5 Hz, 1H), 3.29-3.22 (m, 1H), 3.21-3.09 (m, 1H), 2.98 (ddd, J =17.6, 8.9, 2.2 Hz, 1H), 2.93* (ddd, J = 17.6, 9.4, 2.0 Hz, 1H), 2.77 (d, J = 4.8 Hz, 1H), 2.45-2.02 (m, 6H), 1.98-1.85 (m, 2H), 1.79-1.64 (m, 2H), 1.60-1.36 (m, 4H), 1.22 (dt, J = 13.0, 4.5 Hz, 1H), 1.09* (dd, J = 13.0, 4.3 Hz, 1H), 1.04* (d, J = 7.0 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H), 0.99* (s, 9H), 0.95 (s, 9H), 0.27* (s, 3H), 0.26* (s, 3H), 0.23 (s, 3H), 0.22 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 150.2, 148.7, 146.4, 138.0, 137.5, 129.0, 129.0, 128.4, 128.4, 126.6, 126.4, 122.3, 121.0, 114.8, 111.6, 99.1, 99.0, 95.8, 95.4, 52.3, 52.2, 52.1, 35.7, 35.5, 35.2, 34.0, 33.9, 33.8, 33.7, 33.1, 32.6, 32.2, 29.2, 28.5, 28.3, 26.6, 26.0, 24.7, 24.6, 22.5, 22.1, 18.9, 18.4, -3.8, -4.0, -4.1, -4.8

IR (thin film NaCl) 3584, 3424, 2955, 2930, 2850, 2095, 1650, 1600, 1464, 1363, 1260, 1177, 1109, 1046, 991, 932, 918, 837, 777, 754, 695 cm^{-1}

HRMS ESI (*m/z*): $[M+ Na]^+$ calcd for $C_{29}H_{43}N_3O_3SiNa$, 532.2966; found 532.2962.



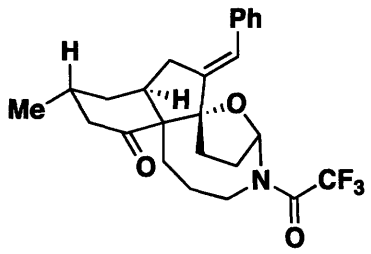
Tetracyclic diene (77): To a round-bottomed flask was added **72** (127 mg, 0.25 mmol), toluene (25 mL), and PMe_3 (0.74 mL of a 1.0 M solution in toluene, 0.74 mmol) before heating to reflux for 5 h. Reaction cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (wash silica with 1% NEt_3/3% EtOAC/hex, followed by purification by silica gel chromatography (3% EtOAC/Hex) to afford 61 mg (54%) of **77**.

^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 9.1 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.12 (s, 1H), 4.72 (d, *J* = 6.4 Hz, 1H), 4.56 (s, 1H), 3.05 (t, *J* = 10.6 Hz, 1H), 3.00-2.92 (m, 1H), 2.77-2.71 (m, 1H), 2.62-2.56 (m, 1H), 2.34-2.18 (m, 3H), 2.09 (dd, *J* = 12.8, 6.0 Hz, 1H), 2.05-1.98 (m, 1H), 1.93-1.84 (m, 1H), 1.77 (dd, *J* = 11.3, 6.3 Hz, 1H), 1.73-1.63 (m, 1H), 1.45-1.13 (m, 5H), 1.01 (s, 9H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.21 (s, 3H), 0.19 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 147.3, 138.2, 129.1, 126.3, 118.0, 113.3, 96.9, 89.5, 51.1, 46.1, 41.3, 35.2, 33.9, 33.2, 29.0, 27.5, 26.7, 26.3, 25.1, 22.8, 18.7, -3.7, -4.7

IR (thin film NaCl): 2954, 2927, 2856, 1649, 1471, 1362, 1253, 1174, 1122, 1009, 990, 955, 914, 830, 778, 734, 695 cm^{-1}

HRMS ESI (*m/z*): $[M+ H]^+$ calcd for $C_{29}H_{44}NO_2Si$, 466.3136; found 466.3127.



Tetracyclic cyclohexanone (81): To a round-bottomed flask was added the **77** (77 mg, 0.17 mmol), CH_2Cl_2 (3.3 mL), and NEt_3 (46 μL, 0.33 mmol) before being cooled to 0 °C and addition of freshly distilled $(CF_3CO)_2O$ (28 μL, 0.20 mmol). The reaction was stirred for 45 min at 0 °C before addition of saturated aqueous solution of $NaHCO_3$. The reaction solution was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (3% EtOAC/hex) to afford the trifluoroacetamide product. To a round bottom flask was added the trifluoroacetamide and THF before the reaction was cooled to 0 °C and addition of AcOH (21 μL, 0.38 mmol) and TBAF (0.25 mL of a 1.0 M solution in THF, 0.25 mmol). Stir at 0 °C for 1 hour before addition of a saturated aqueous solution of $NaHCO_3$. The reaction was extracted with EtOAc, washed with H_2O, brine,

dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 15% EtOAc/hex to 20% EtOAc/hex) to afford 52 mg (71% over the two steps) of **81**.

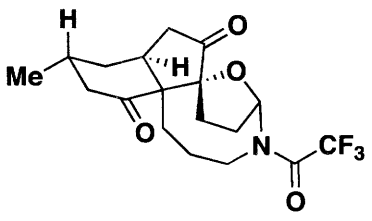
^{1}H NMR (500 MHz, $CDCl_3$, * denotes minor diastereomer) δ 7.38-7.28 (m, 4H), 7.25 (t, J = 7.3 Hz, 1H), 6.40* (s, 1H), 6.38 (s, 1H), 5.53 (t, J = 7.0 Hz, 1H), 3.54-3.44 (m, 2H), 2.85 (dd, J = 17.4, 9.4 Hz, 1H), 2.74-2.65 (m, 2H), 2.49-2.38 (m, 1H), 2.36-2.25 (m, 2H), 2.23-1.93 (m, 6H), 1.91-1.83 (m, 2H), 1.78 (d, J = 14.0 Hz, 1H), 1.73-1.65 (m, 2H), 1.08 (d, J = 5.8 Hz, 3H), 1.02 (d, J = 6.4 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9, 212.6, 143.9, 137.1, 129.2, 128.9, 128.5, 128.5, 127.2, 122.3, 117.8, 115.0, 94.1, 93.3, 83.4, 62.1, 61.9, 60.6, 48.4, 43.2, 36.8, 33.1, 32.5, 30.6, 30.2, 29.9, 28.2, 27.8, 24.9, 23.8, 22.3, 21.8, 14.4

^{19}F NMR (500 MHz, $CDCl_3$) δ -71.7, -72.6

IR (thin film NaCl): 2956, 2925, 1700, 1653, 1457, 1225, 1199, 1144, 1044, 1000, 913, 734, 694 cm^{-1}

HRMS ESI (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{29}F_3NO_3$, 448.2094; found 448.2104.



Tetracyclic diketone (82): To a round-bottomed flask at -78 °C charged with **81** (44 mg, 0.098 mmol) and CH_2Cl_2 (9.8 mL) was bubbled a stream of O_3 until the solution turned blue. Argon was then bubbled through the solution to remove any remaining dissolved O_3 before addition of PPh_3 (51 mg, 0.19 mmol). The cold bath was removed and the solution was allowed to warm to room temperature over 2 h before the solution was concentrated under reduced pressure. The resulting crude residue was purified by silica gel chromatography (gadient, 15% EtOAc/hex to 25% EtOAc/hex) to afford 23 mg (63%) of **82**.

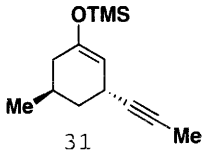
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (dd, *J* = 9.3, 4.9 Hz, 1H), 3.65-3.56 (m, 1H), 3.34-3.26 (m, 1H), 2.81-2.74 (m, 1H), 2.74-2.65 (m, 1H), 2.47 (dd, *J* =19.5, 8.5 Hz, 1H), 2.42 (t, *J* =12.4 Hz, 1H), 2.31-2.21 (m, 4H), 2.16-2.06 (m, 1H), 2.05-1.94 (m, 2H), 1.87-1.66 (m, 4H), 1.47-1.39 (m, 1H), 1.11 (d, *J* = 1.4 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, peaks due to trifluoroacetamide not observed) δ 213.1, 209.4, 87.3, 84.9, 61.7, 47.9, 42.7, 42.6, 36.3, 32.5, 31.3, 30.5, 26.9, 25.2, 23.9, 22.3

^{19}F NMR (300 MHz, $CDCl_3$) δ -71.5, -72.6

IR (thin film NaCl): 2959, 1752, 1701, 1653, 1559, 1457, 1196, 1147, 1033, 909, 735 cm^1

HRMS ESI (*m/z*): $[M+ H]^+$ calcd for $C_{18}H_{23}F_3NO_4$, 374.1574; found 374.1561.



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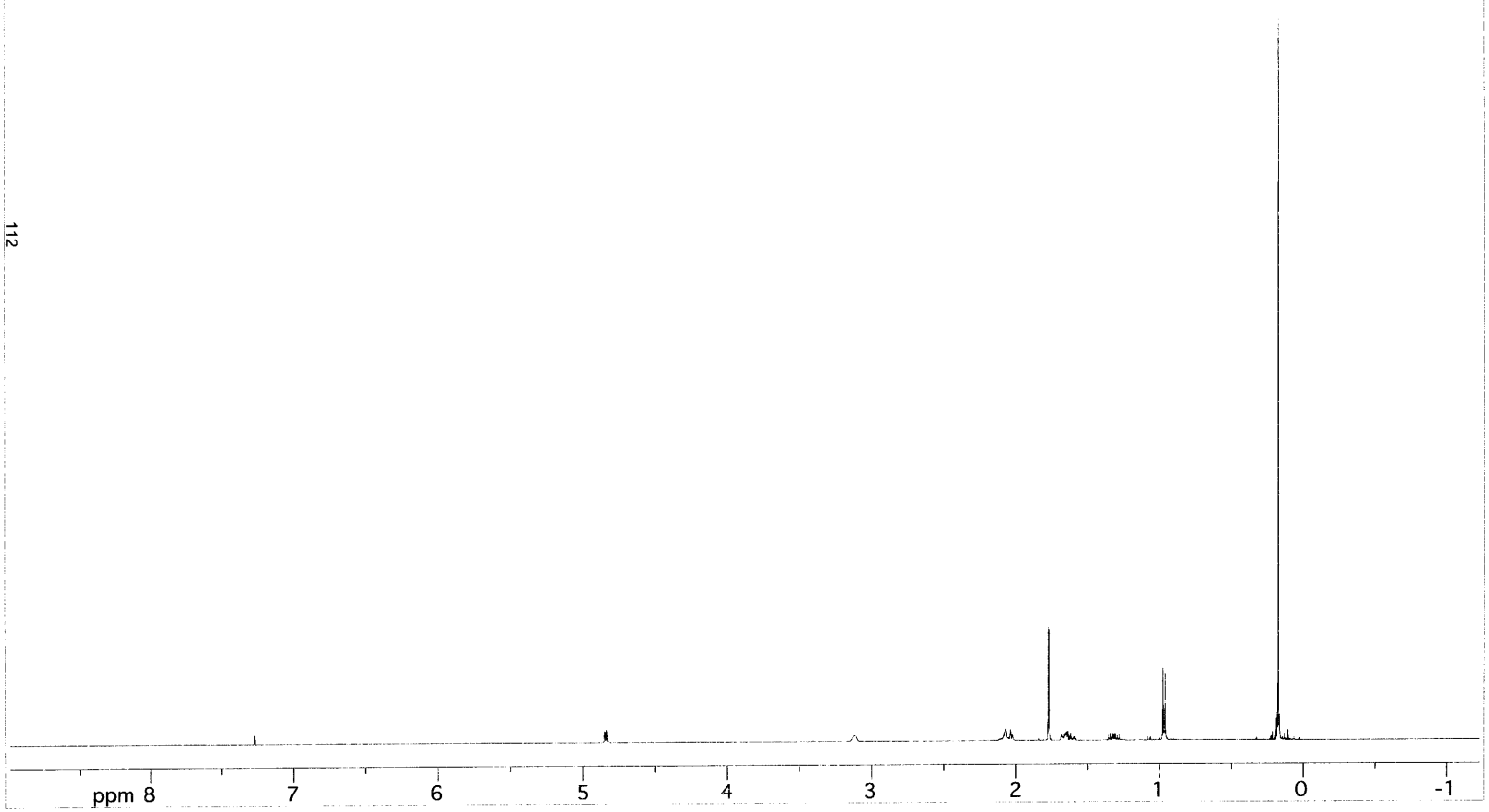

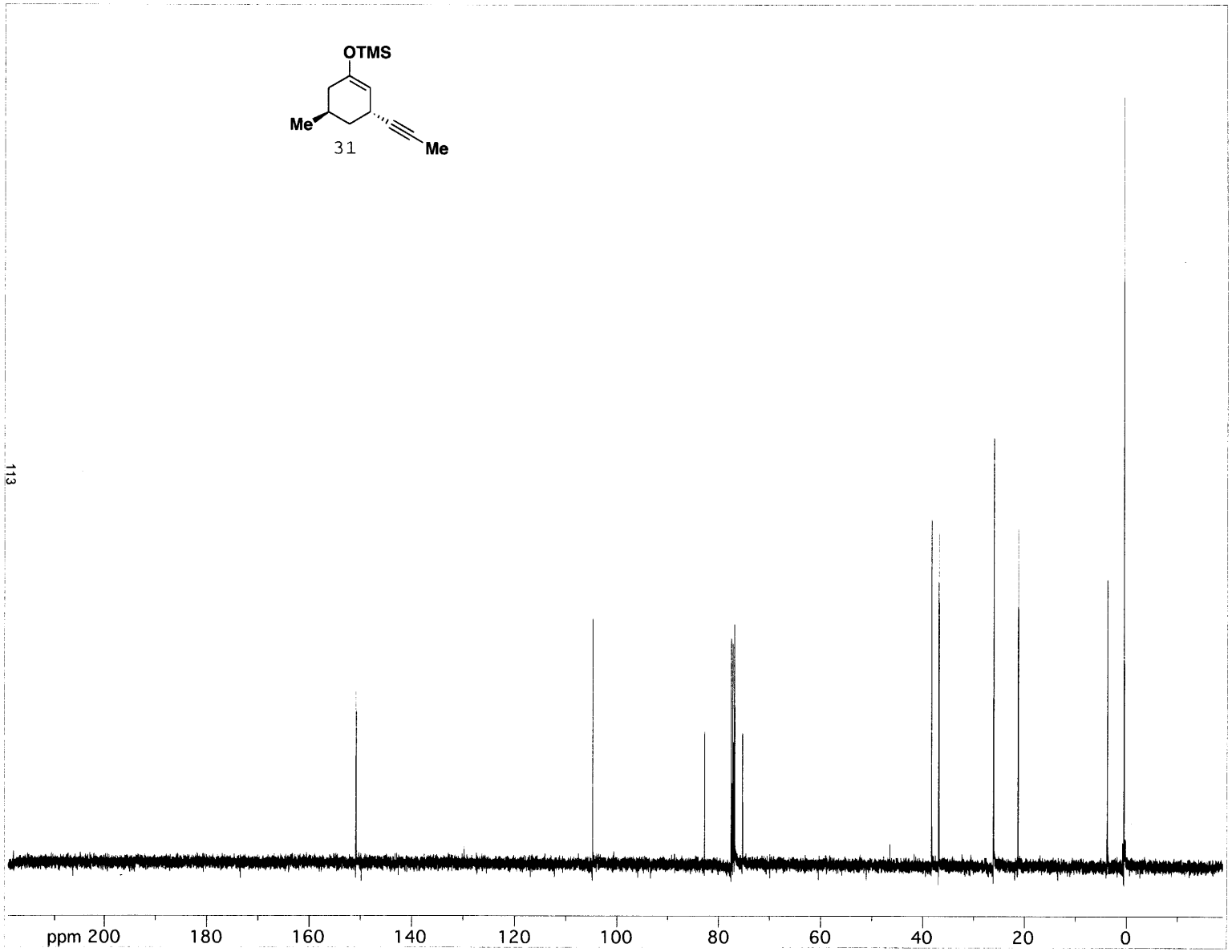
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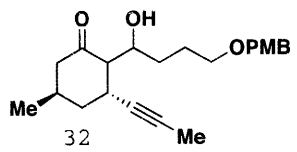

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114

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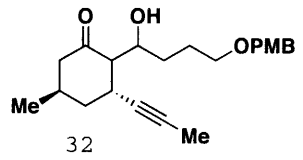

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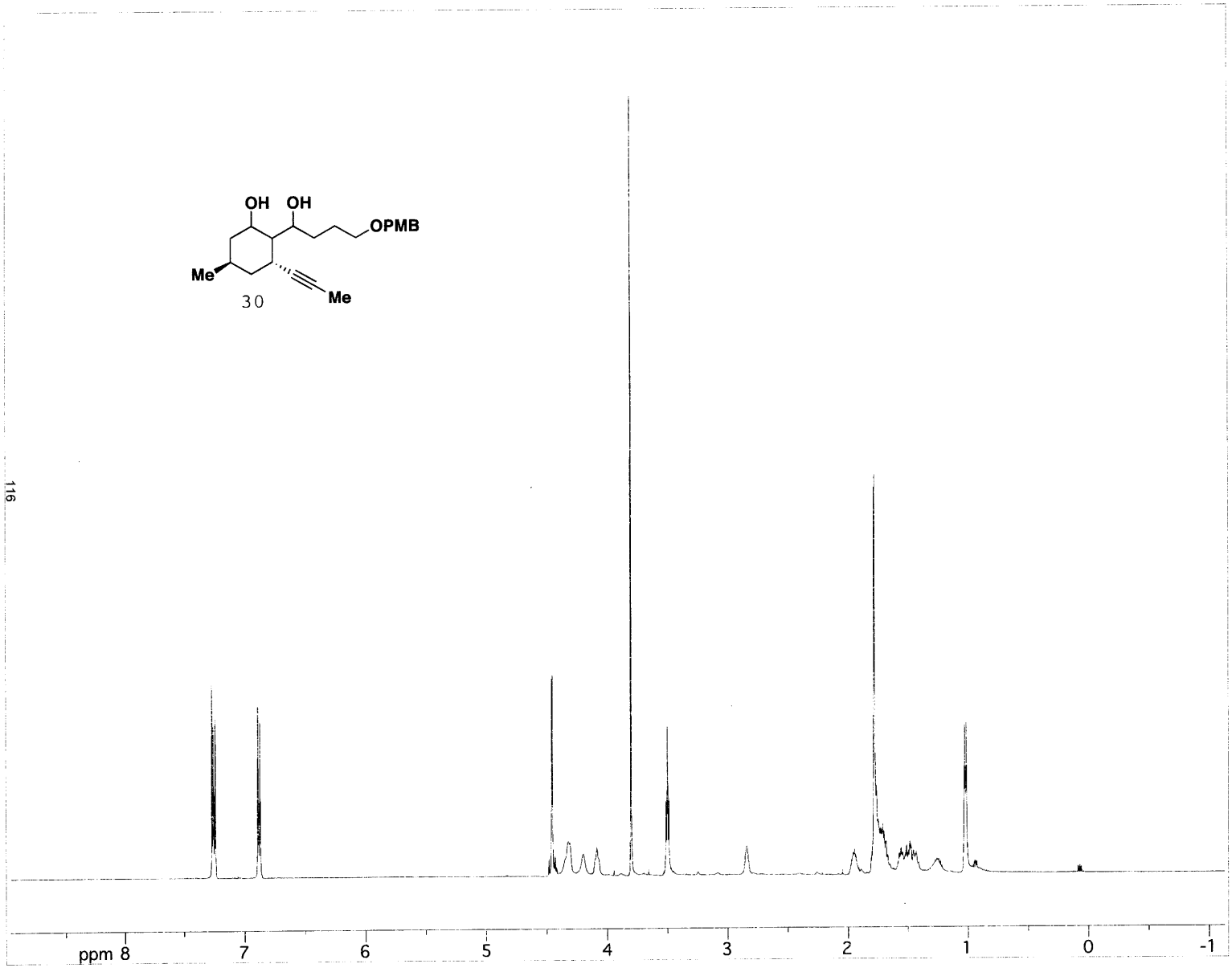
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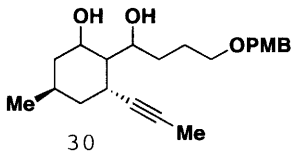

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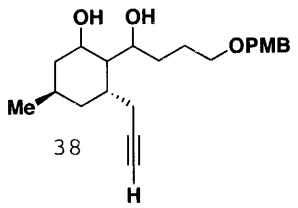

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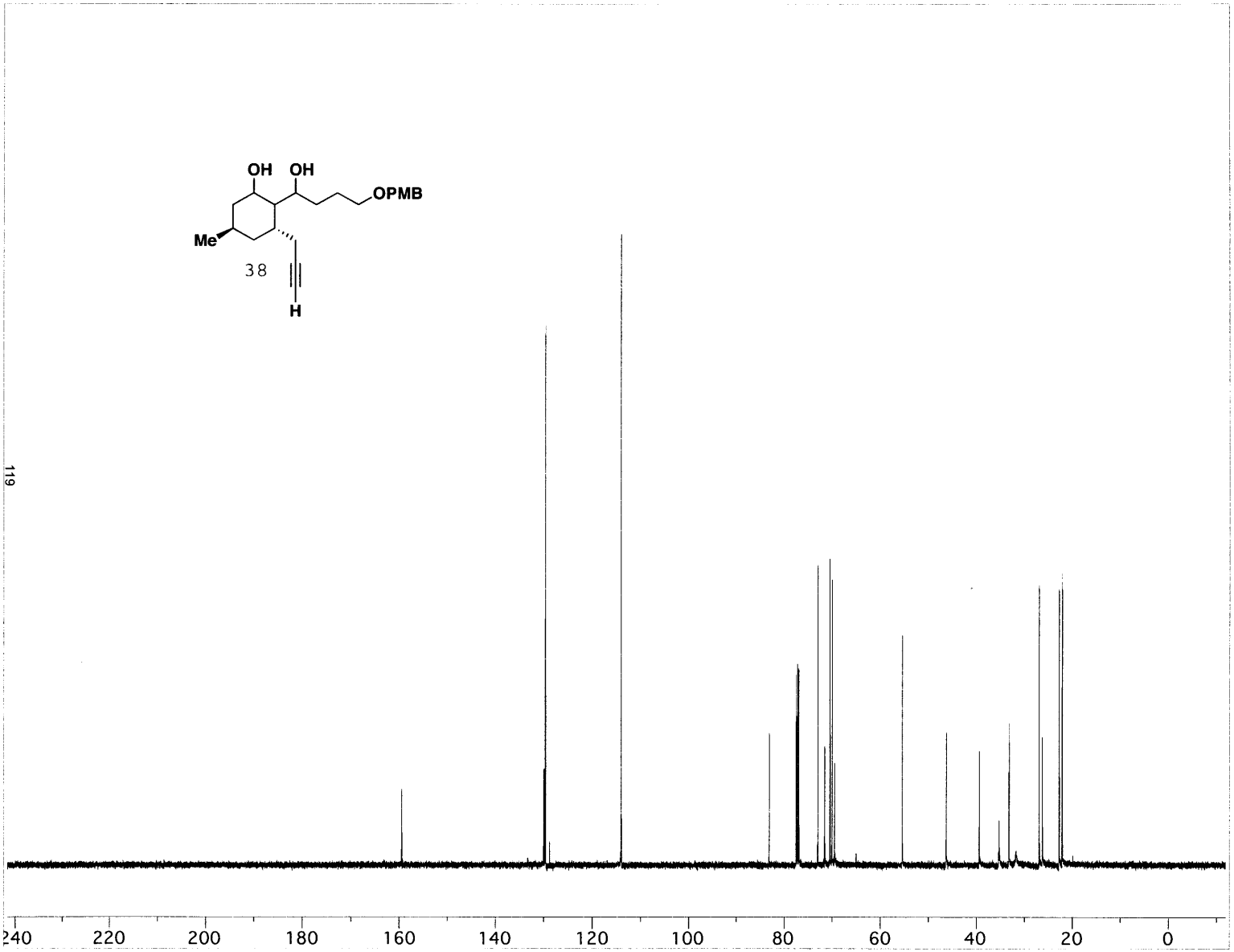
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OPMB
Me
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20
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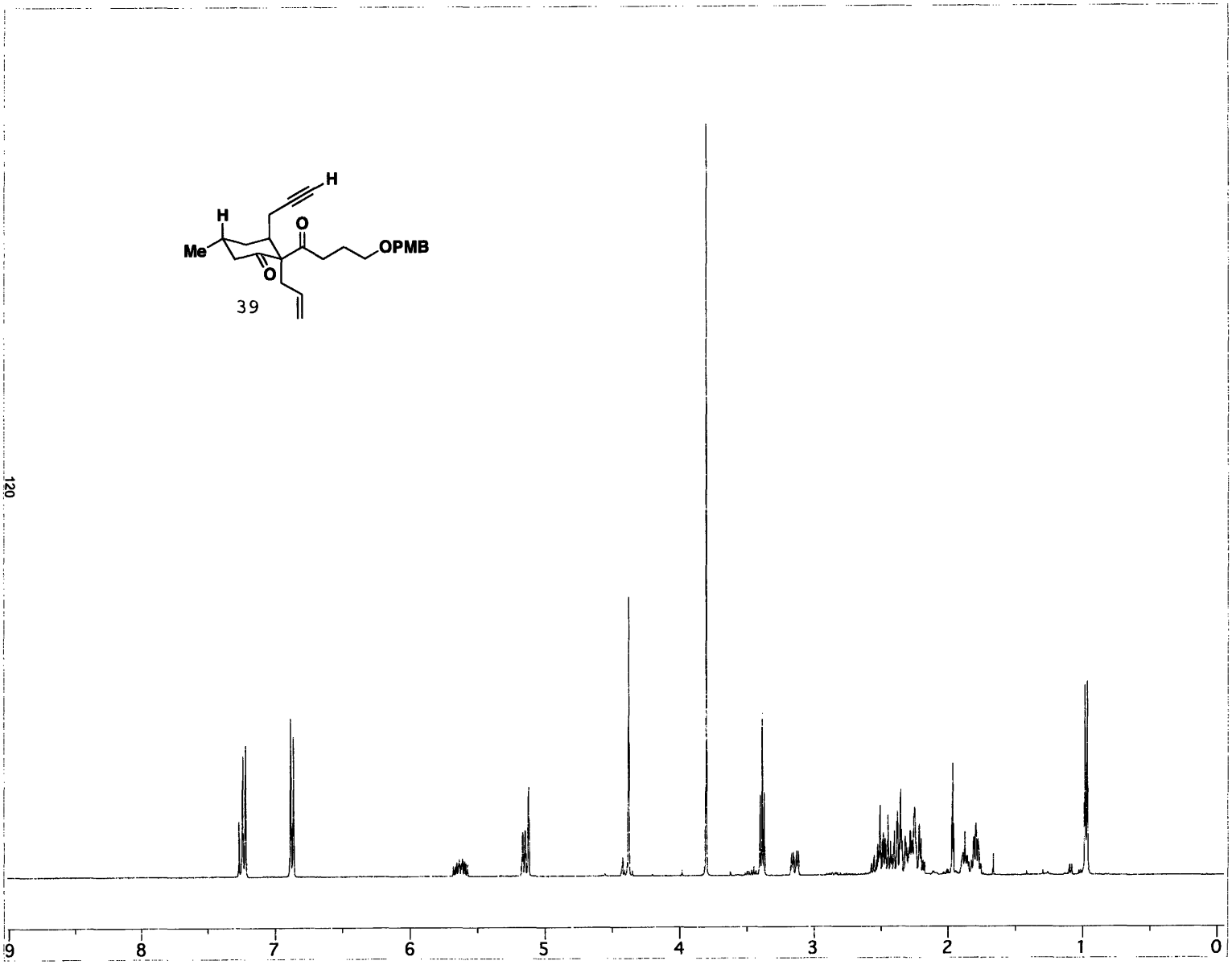
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O
OPMB
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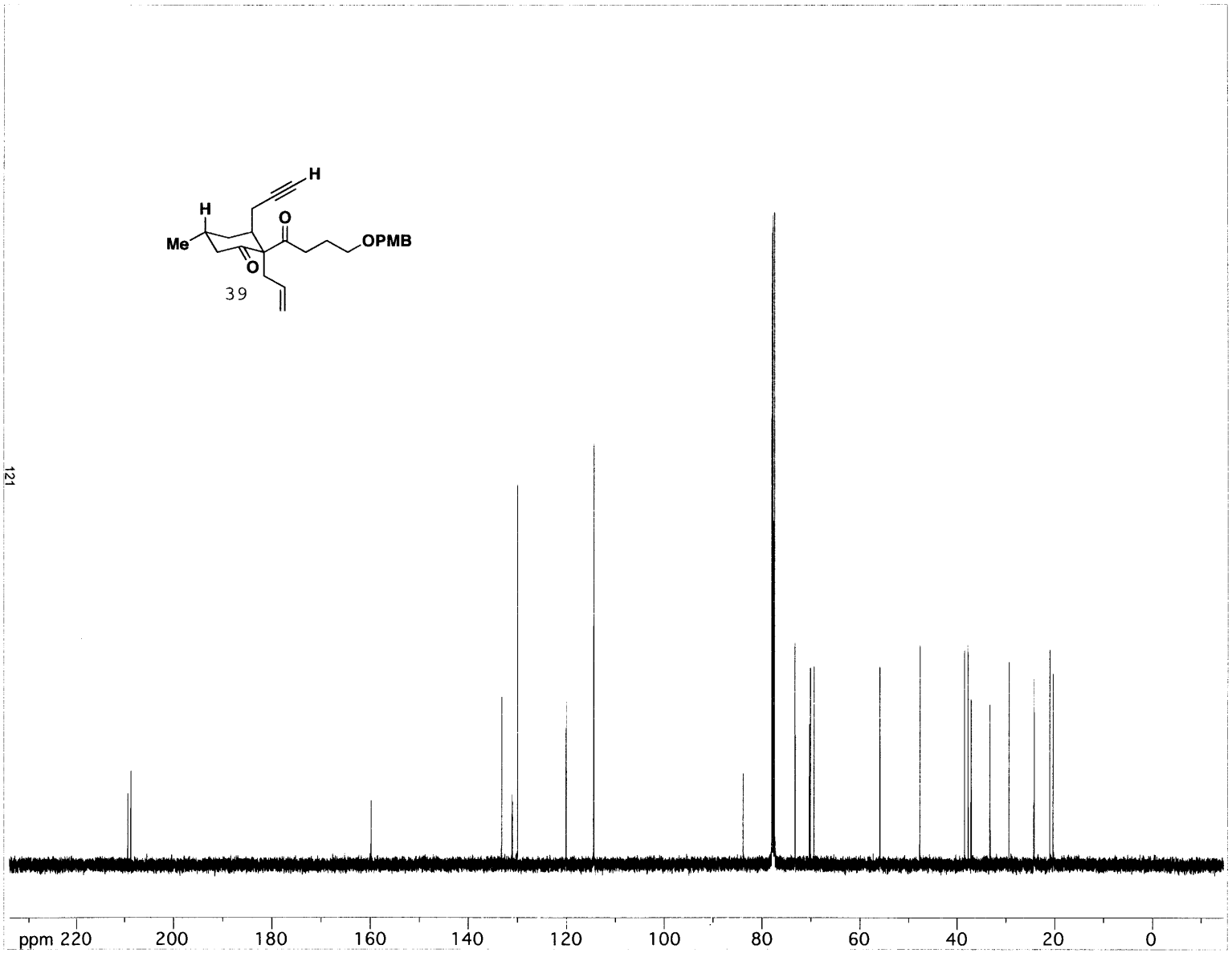
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Me
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OPMB
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20
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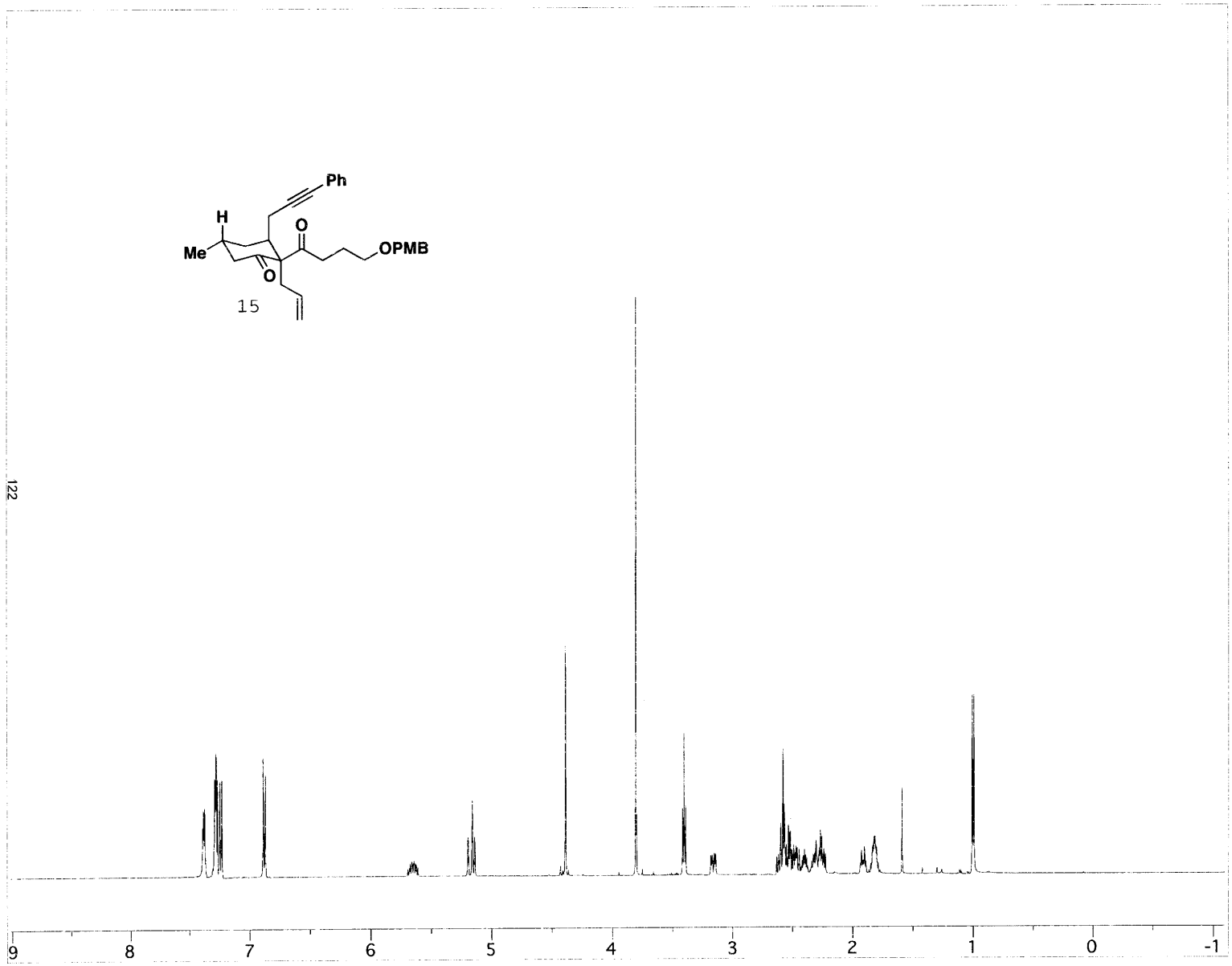
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OPMB
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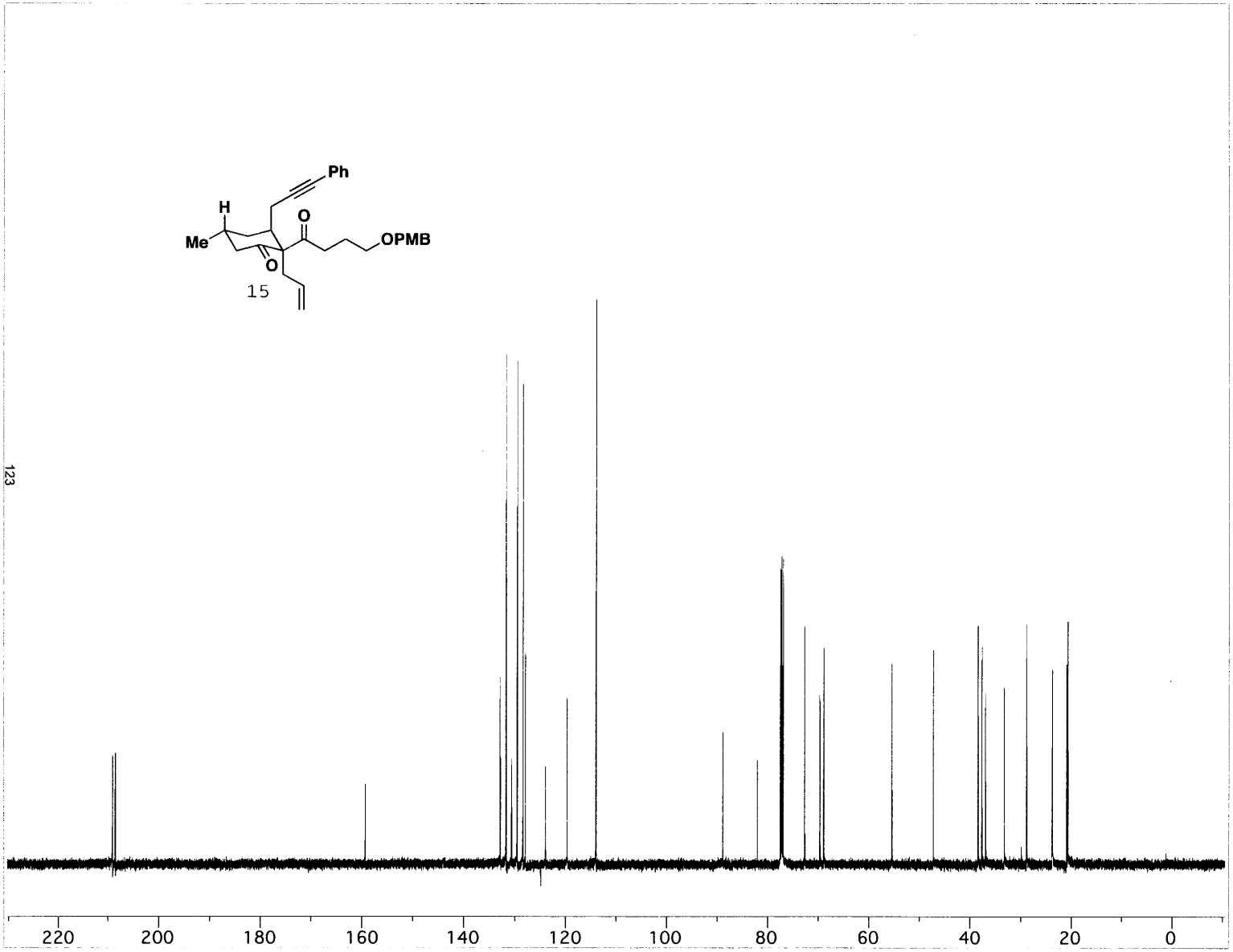
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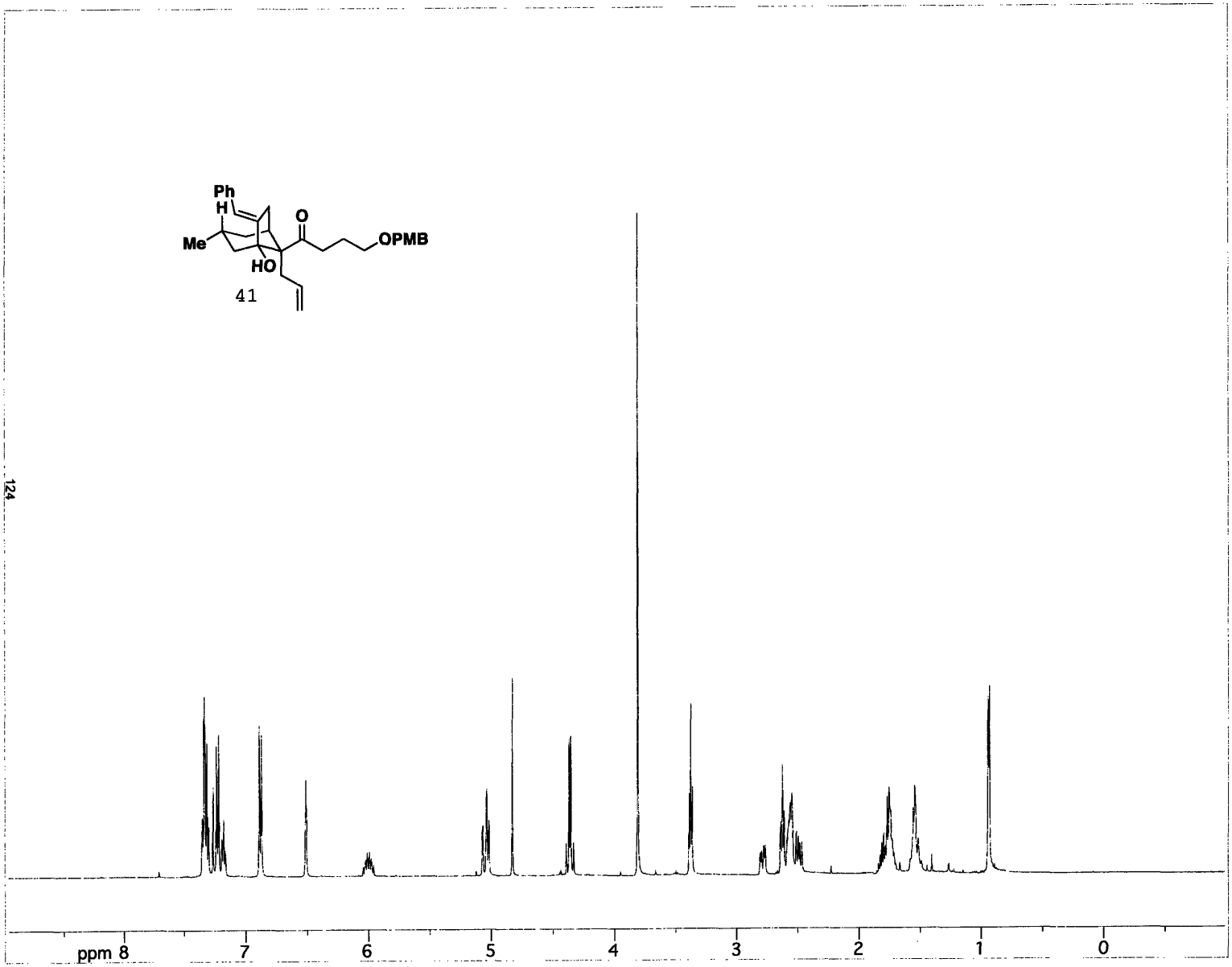
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Me
OPMB
HO
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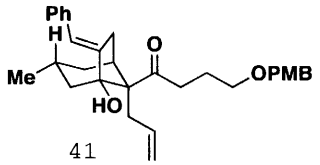
124
ppm 8
7
6
5
4
3
2
1
0



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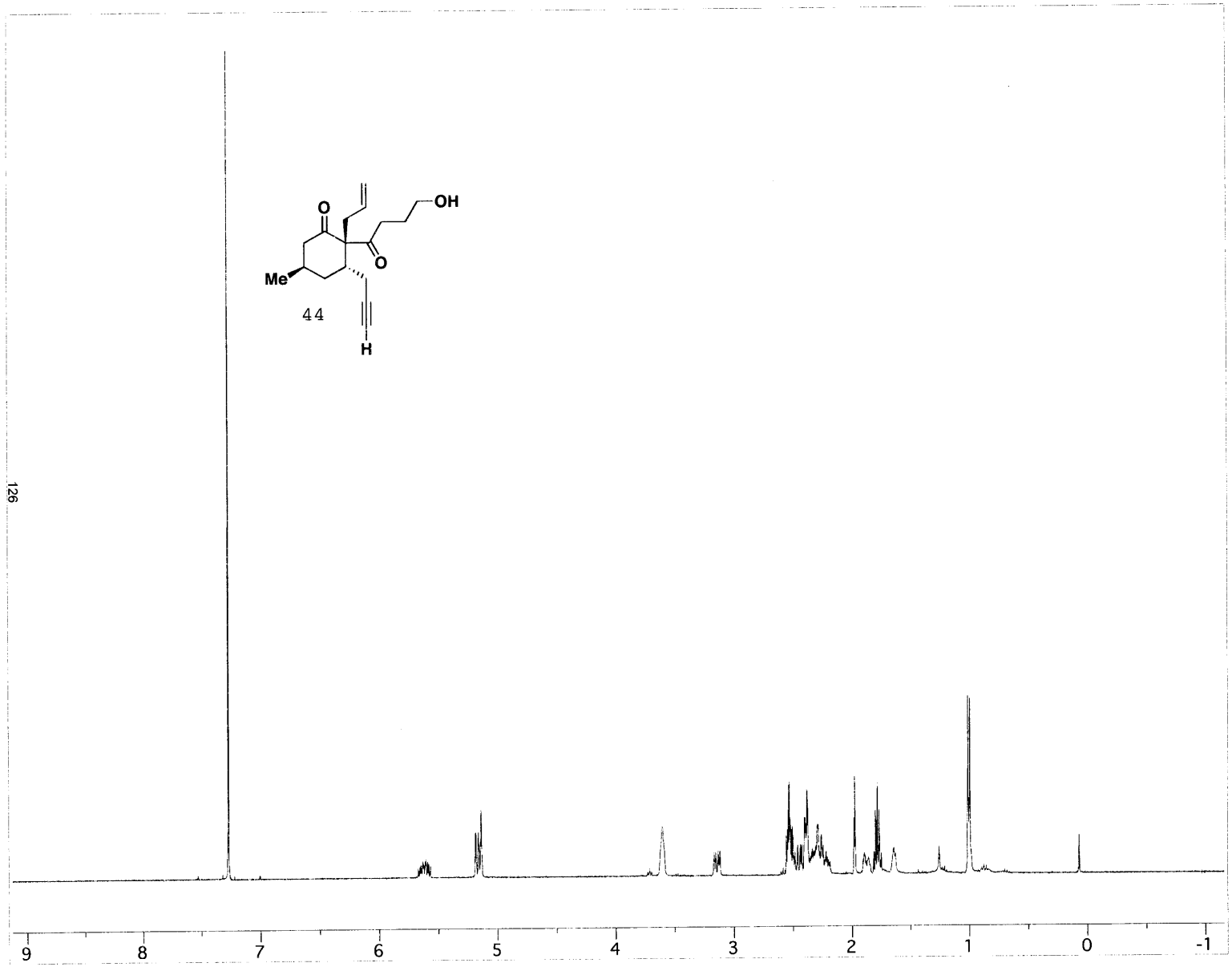
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Me
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6
5
4
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2
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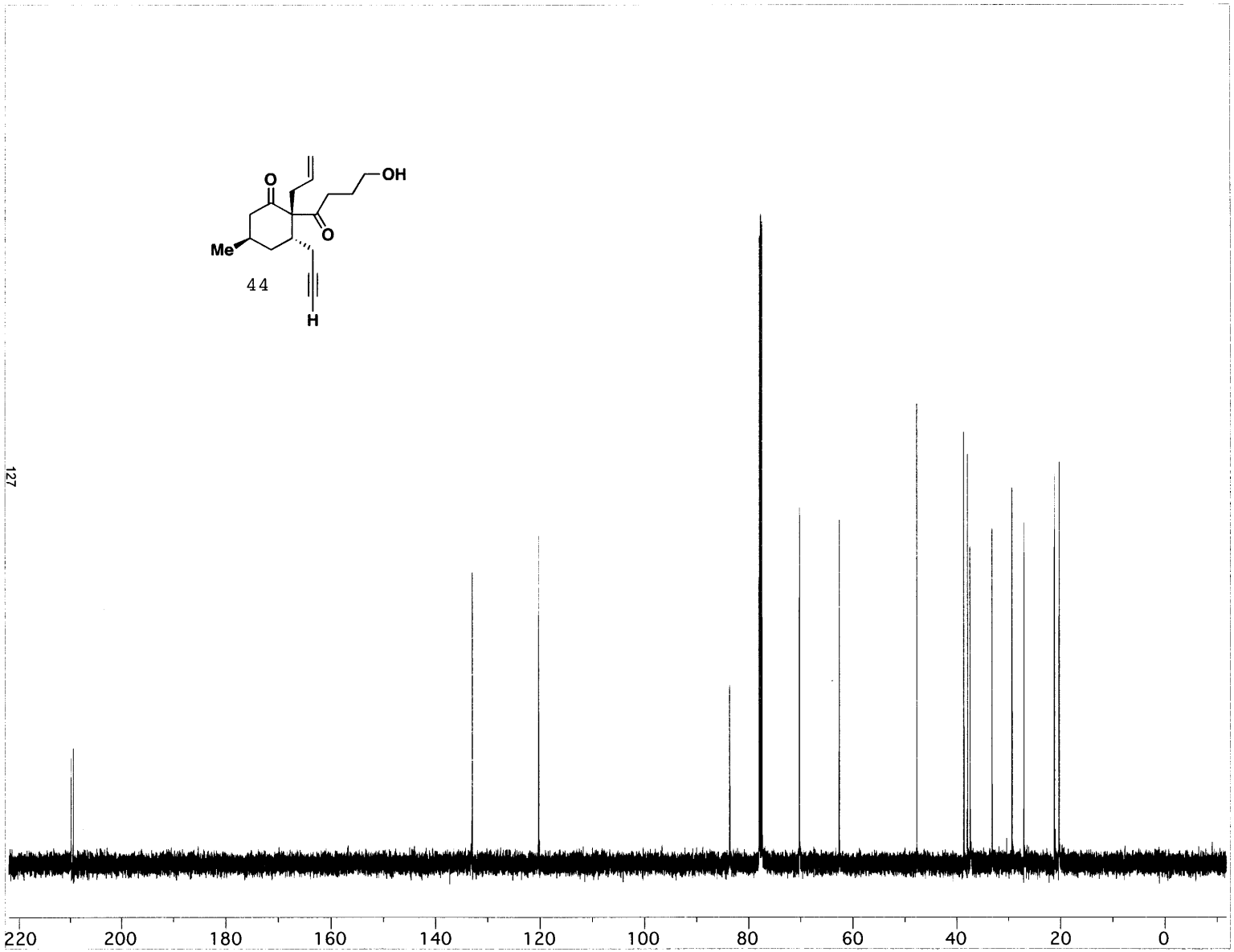
0
-1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Me
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44
127
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140
120
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20
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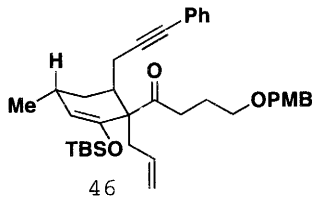

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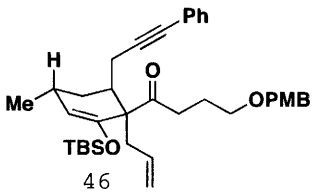
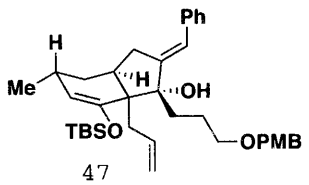

Ph
H
O
Me
OPMB
TBSO

46

129
ppm 220
200
180
160
140
120
100
80
60
40
20
0



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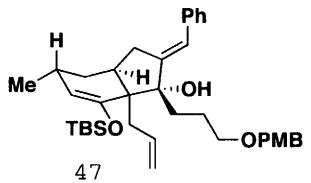

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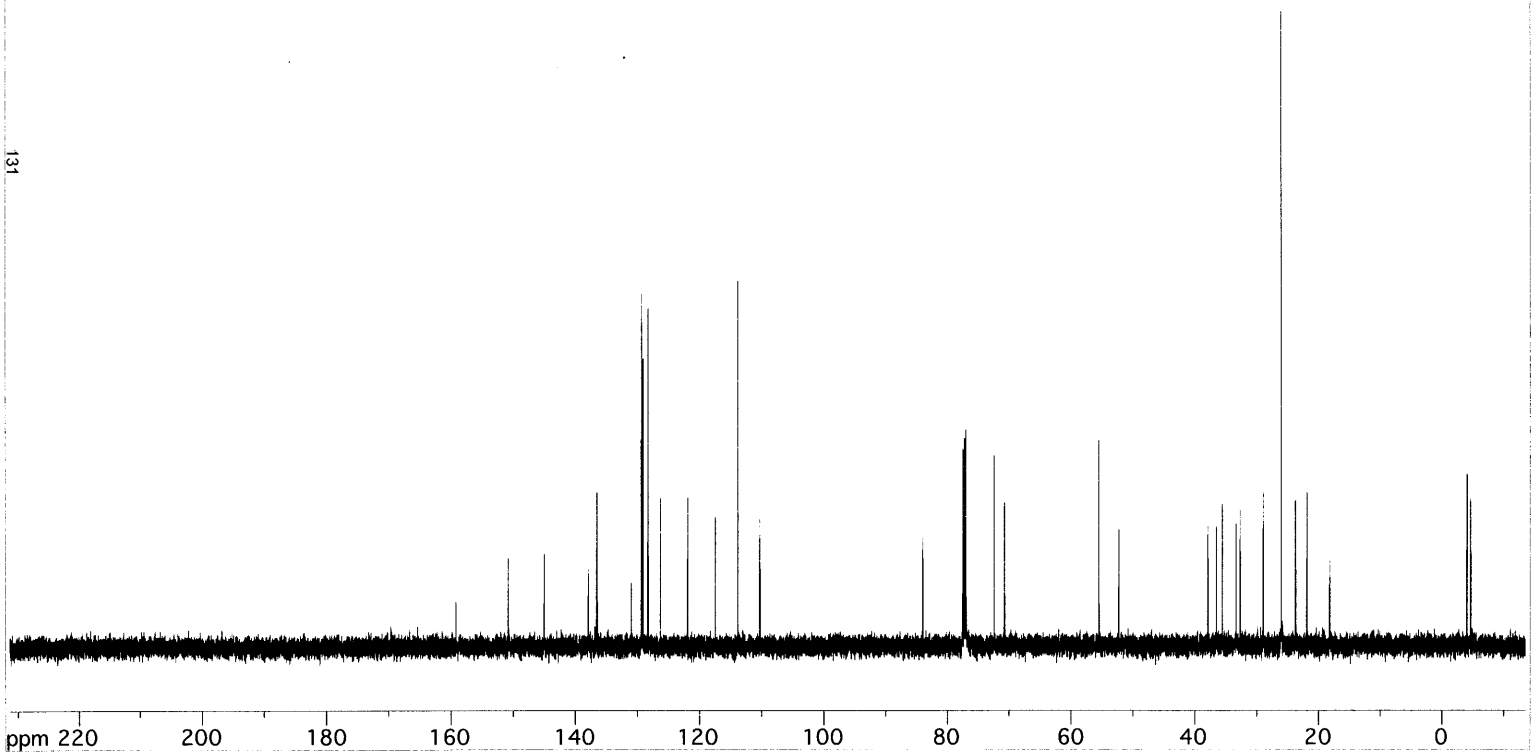

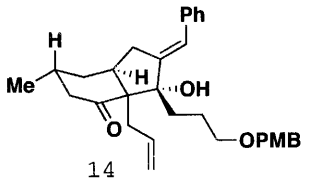

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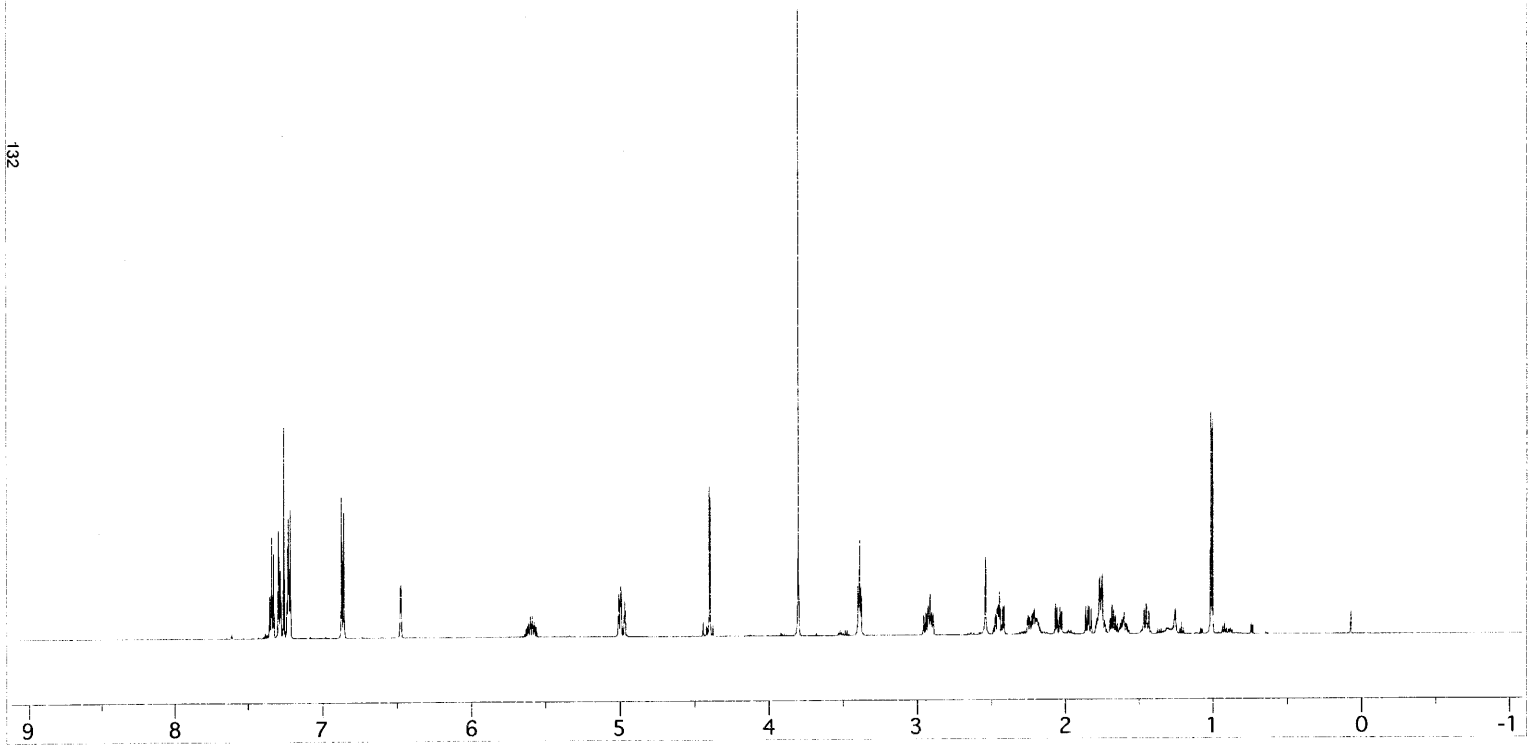

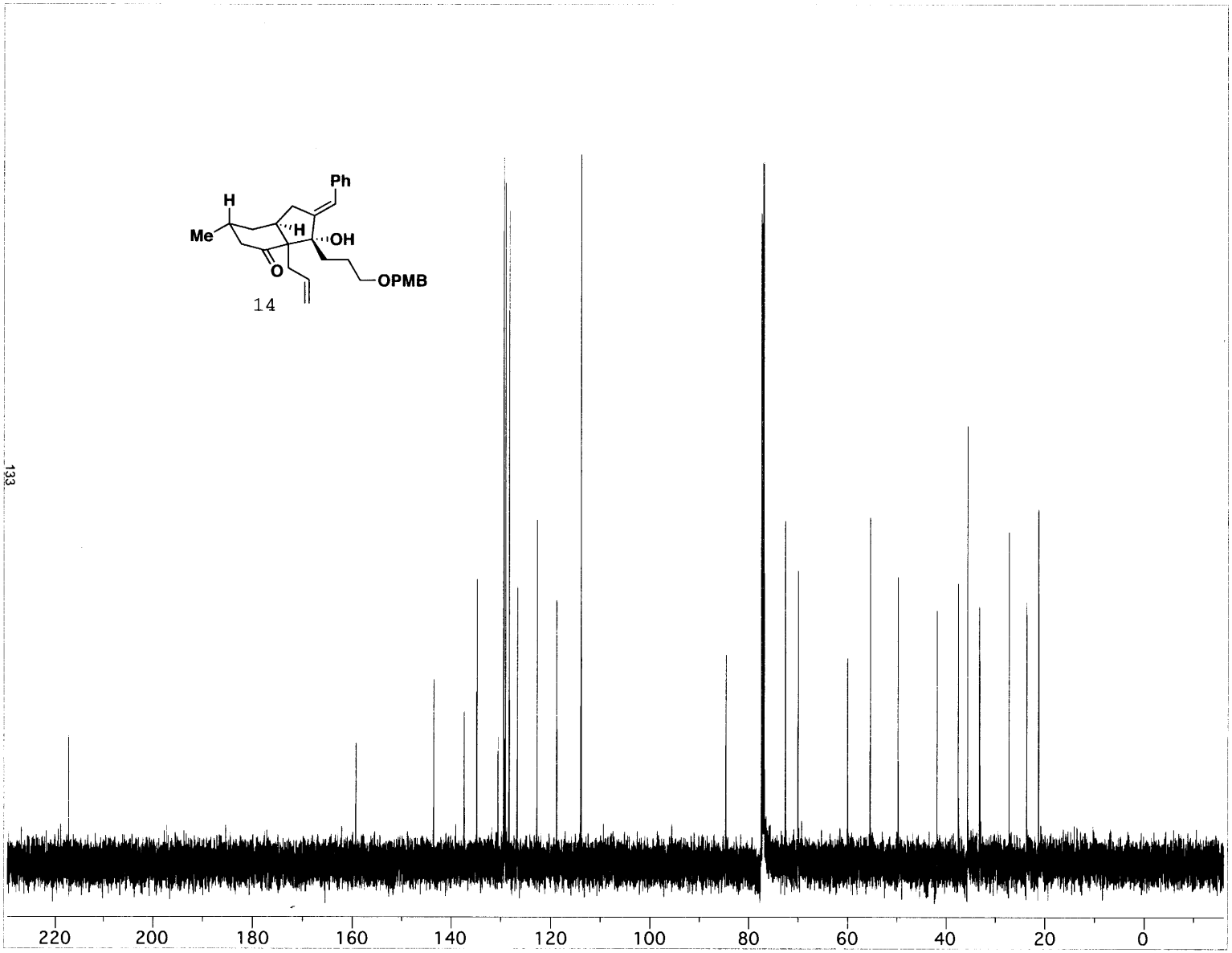
Ph
H
Me
H
OH
O
OPMB
14
133
220
200
180
160
140
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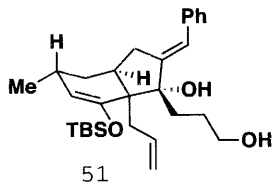
20
0



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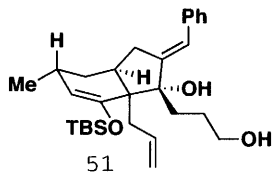

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135

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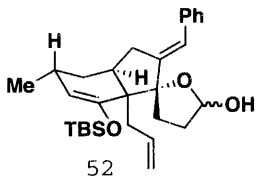

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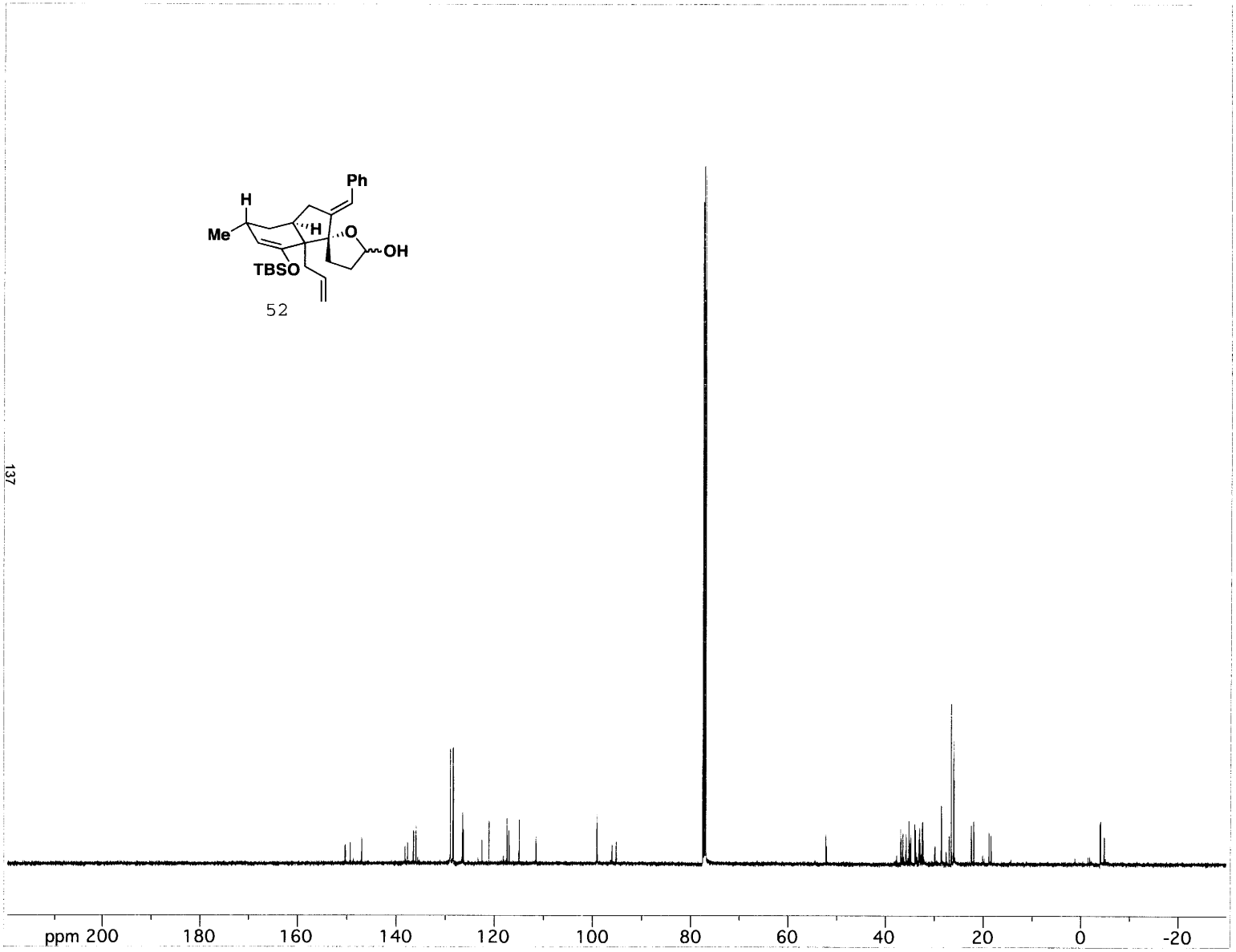
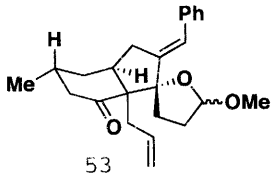

Ph
H
Me
H
O
OH
TBSO
52
137
ppm 200
180
160
140
120
100
80
60
40
20
0
-20



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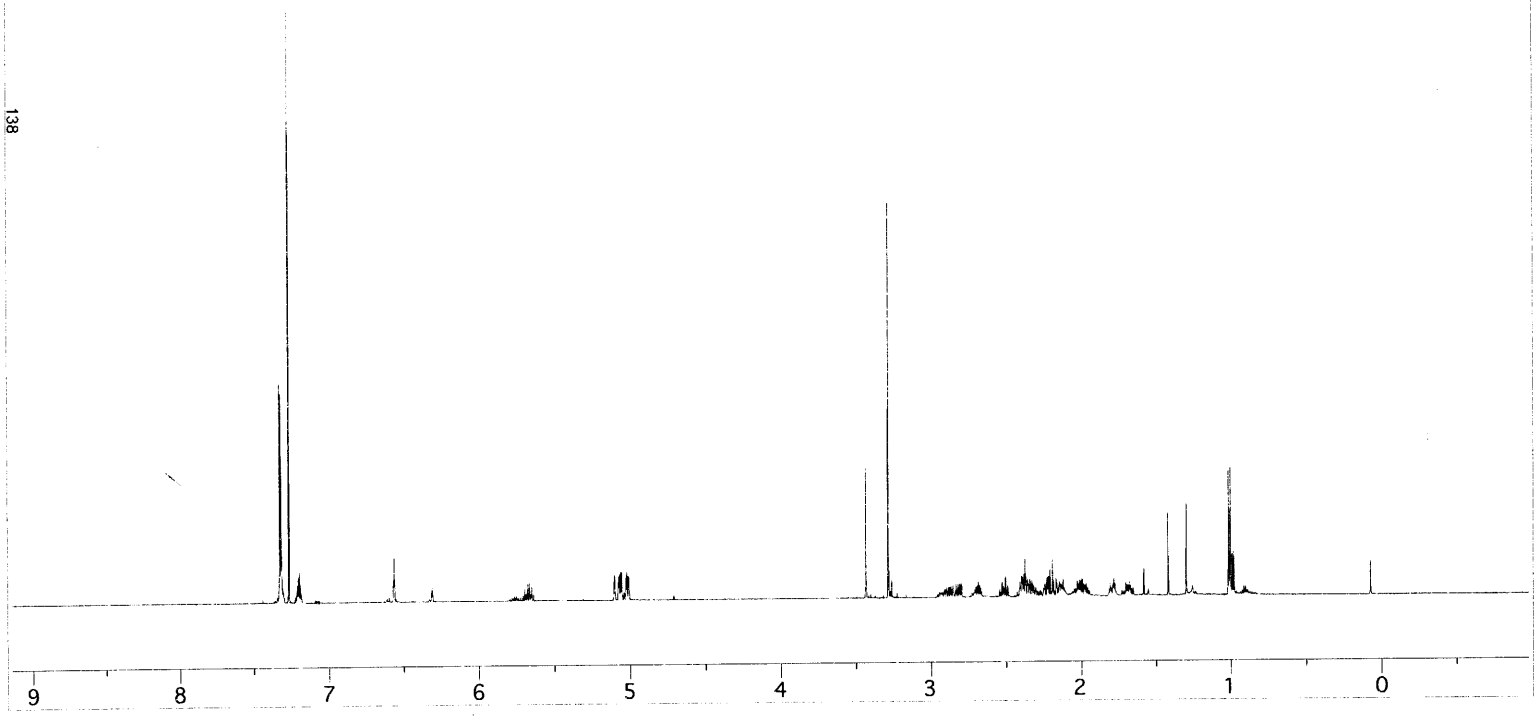

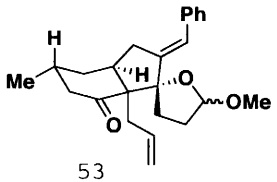

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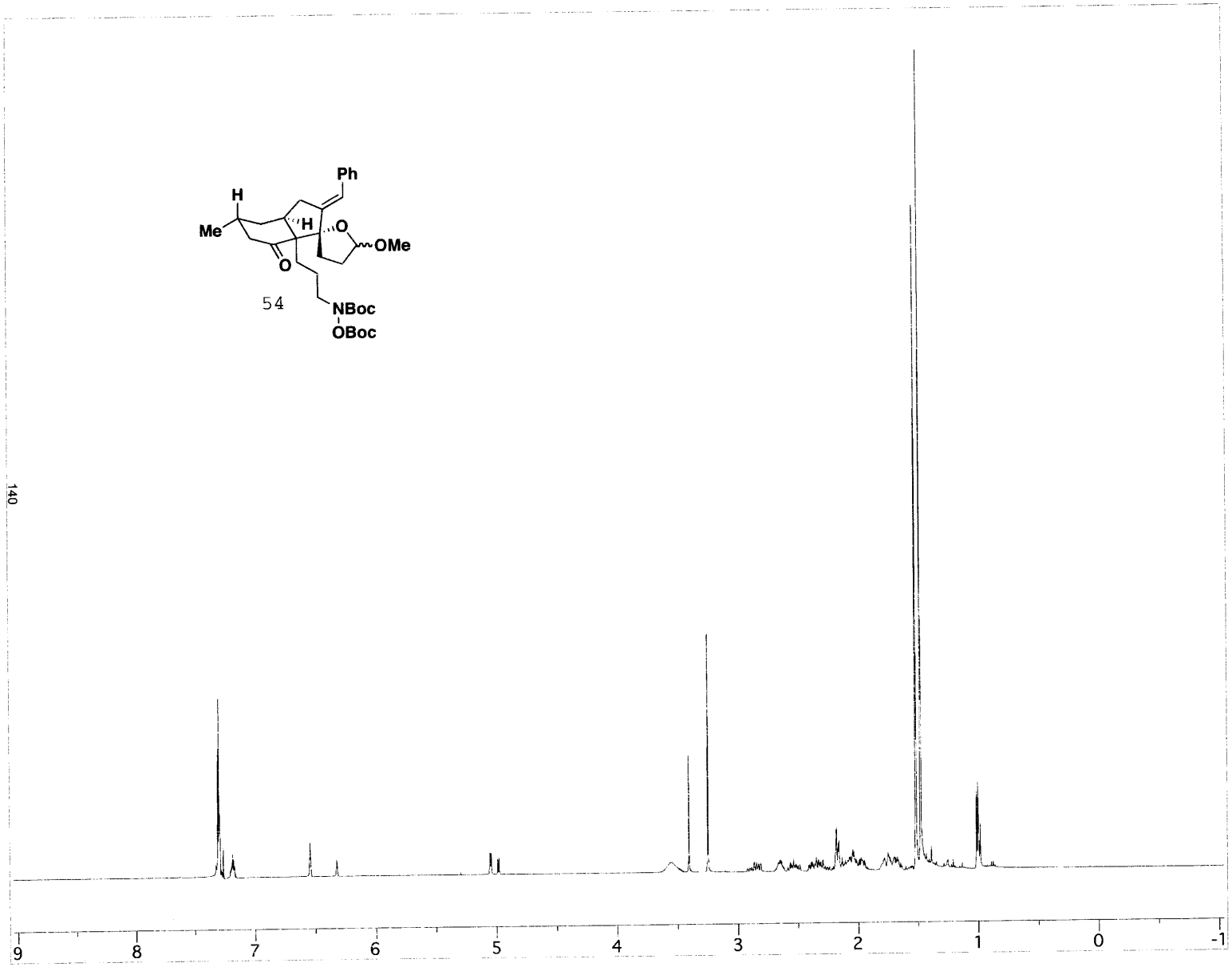
139

ppm 200 180 160 140 120 100 80 60 40 20 0 -20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Me
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OMe
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NBoc
OBoc
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6
5
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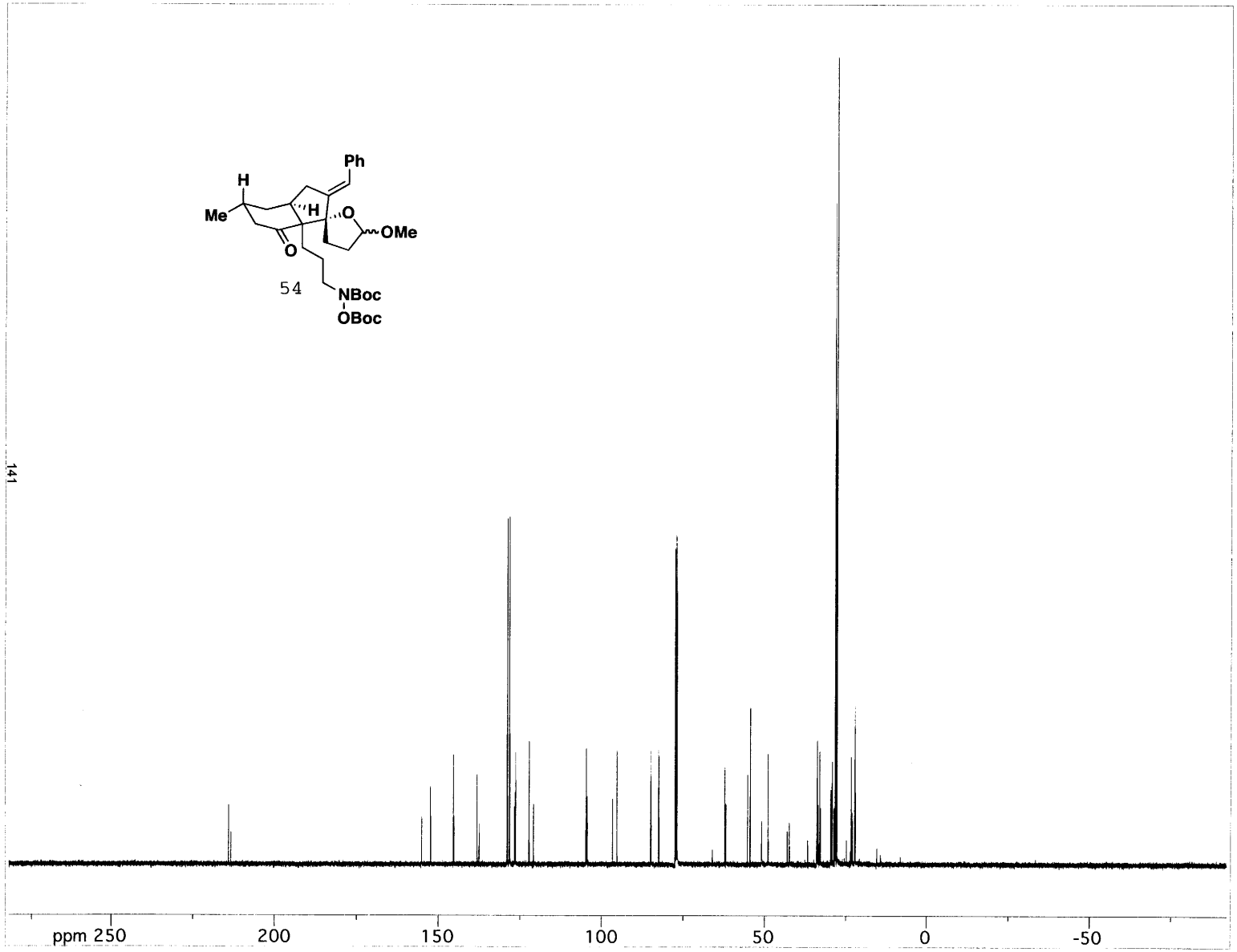
2
1
0
-1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Me
H
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OMe
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NBoc
OBoc
141
ppm 250
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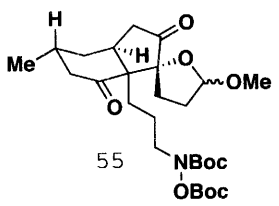
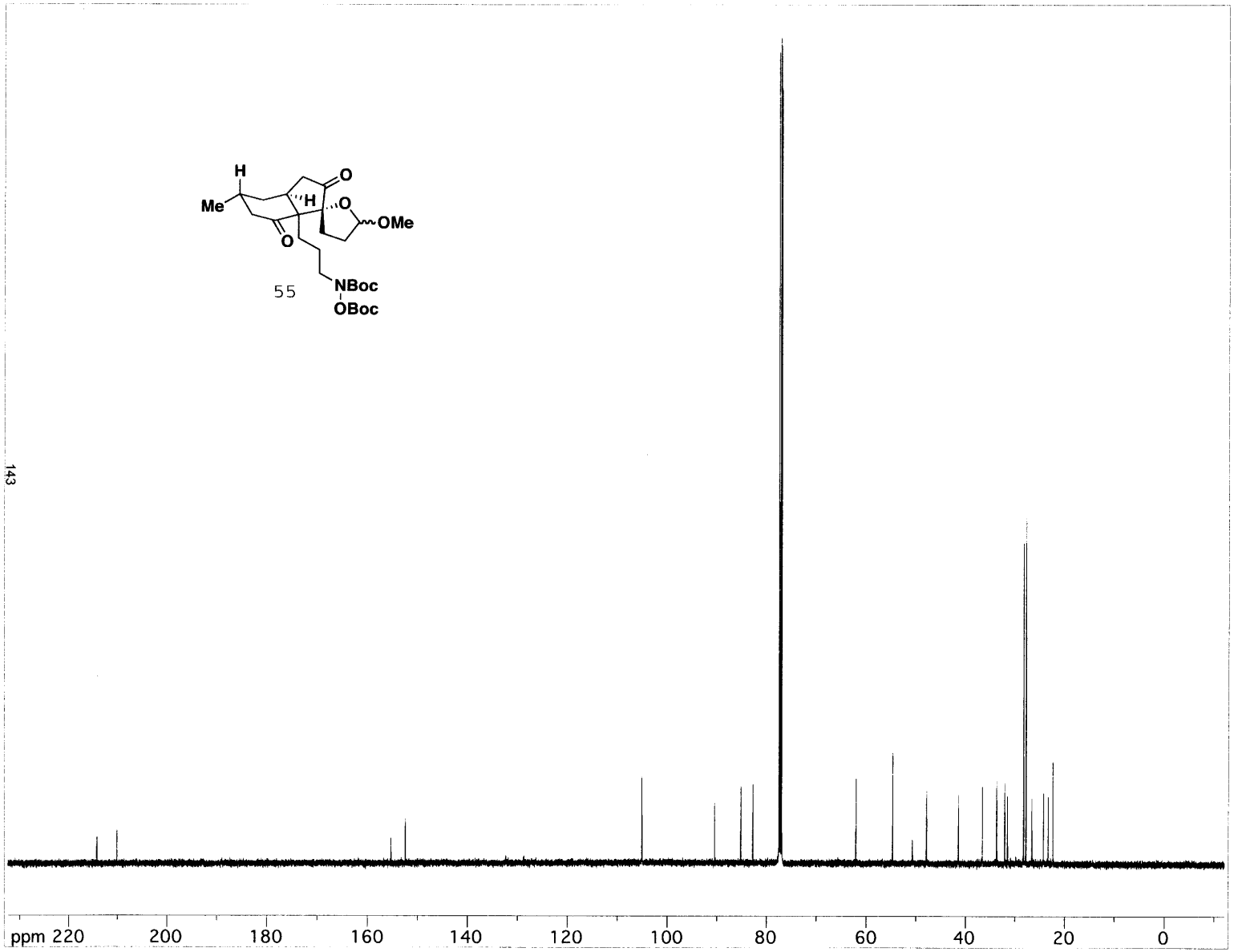
150
100
50
0
-50



55

142

ppm 8 7 6 5 4 3 2 1 0 -1


H
Me
O
H
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OMe
O
NBoc
OBoc
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ppm 220
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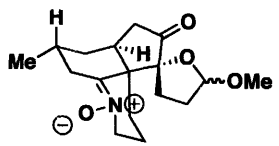
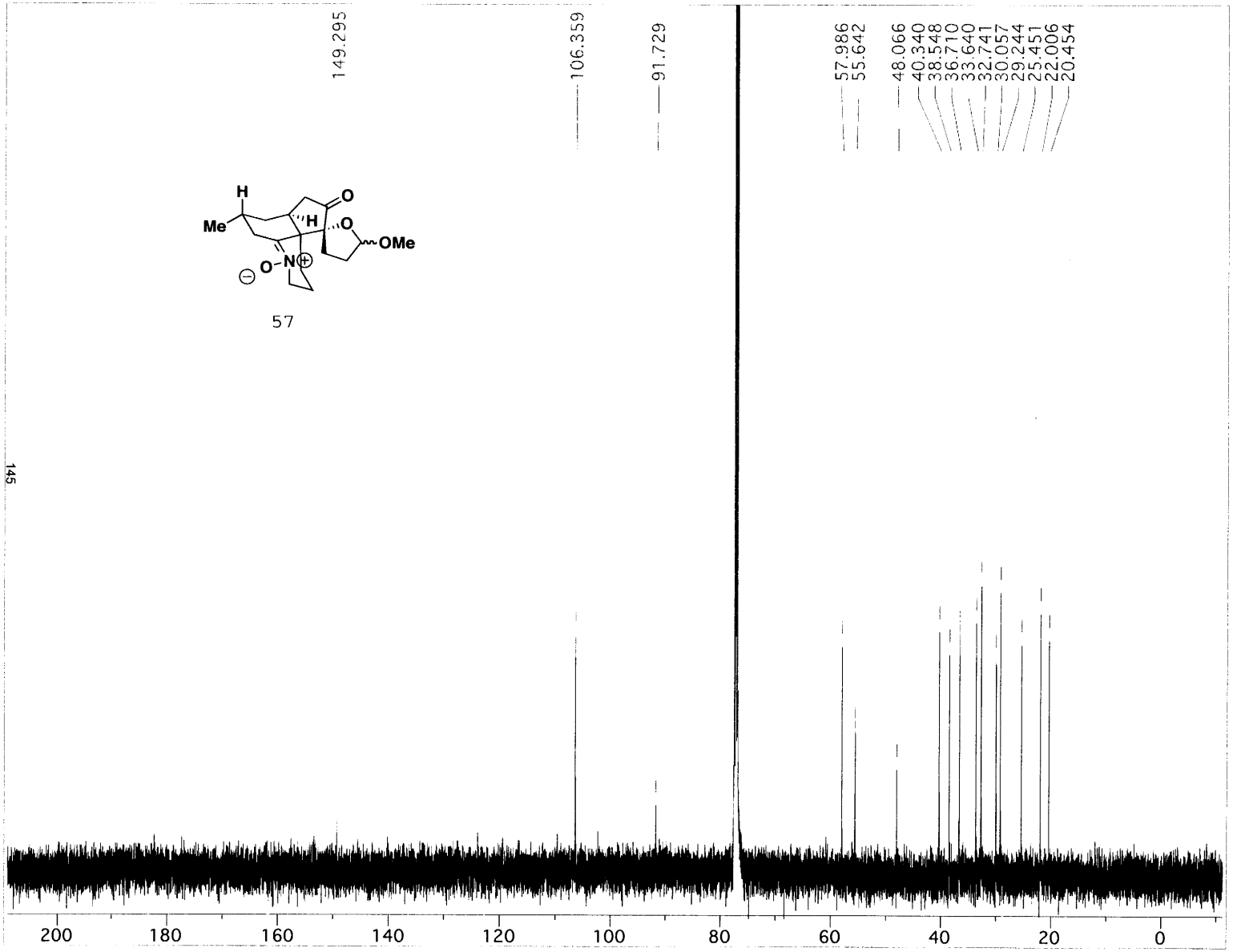
60
40
20
0



57

144

9 8 7 6 5 4 3 2 1 0 -1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38.548
36.710
33.640
32.741
30.057
29.244
25.451
22.006
20.454
H
Me
H
O
O
OMe
O-N⊕
⊖
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120
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40
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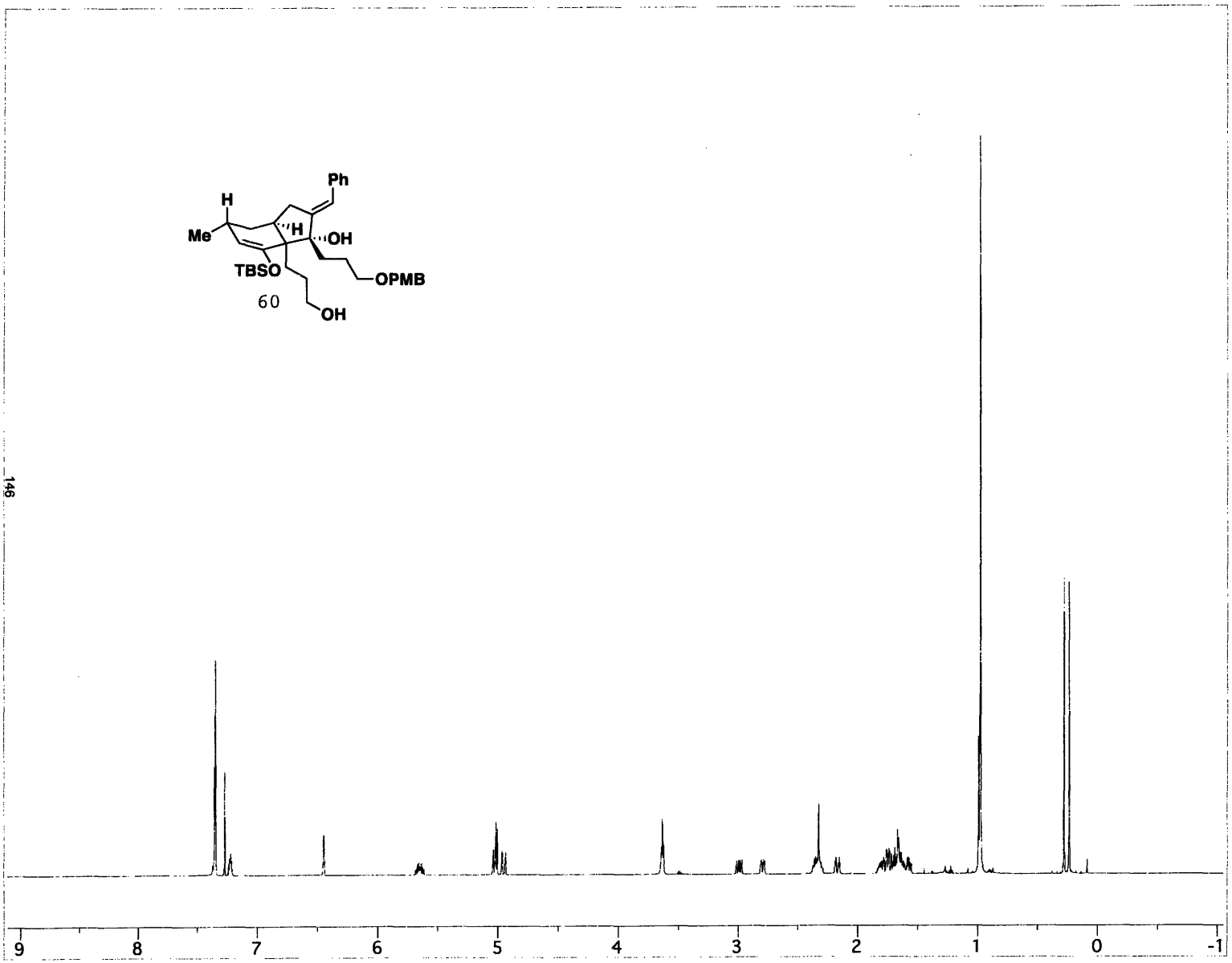
0

57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OH
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OPMB
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OH
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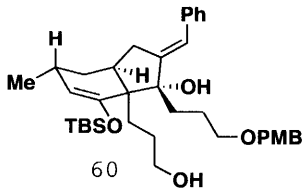
2
1
0
-1



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147

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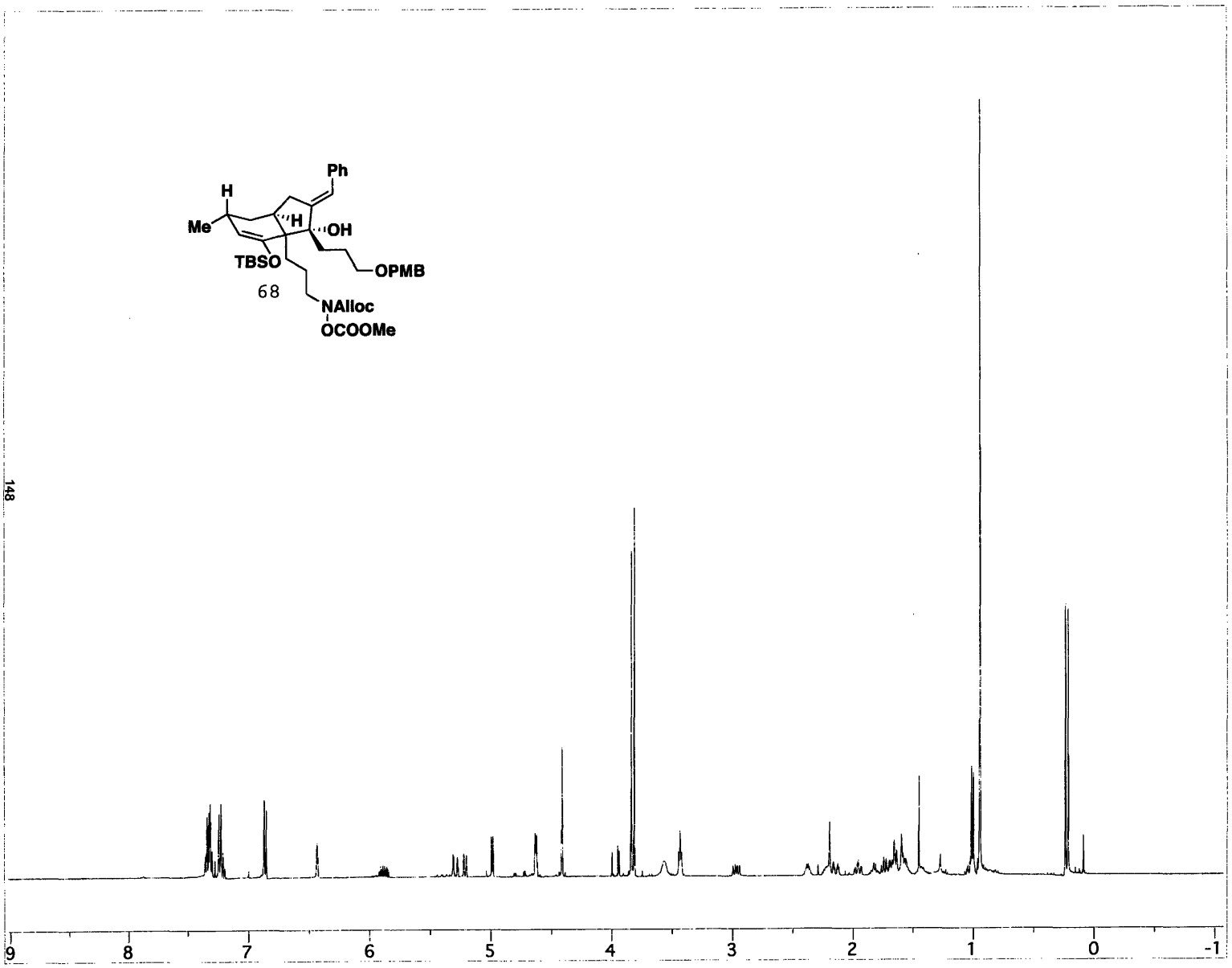
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OPMB
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NAlloc
OCOOMe
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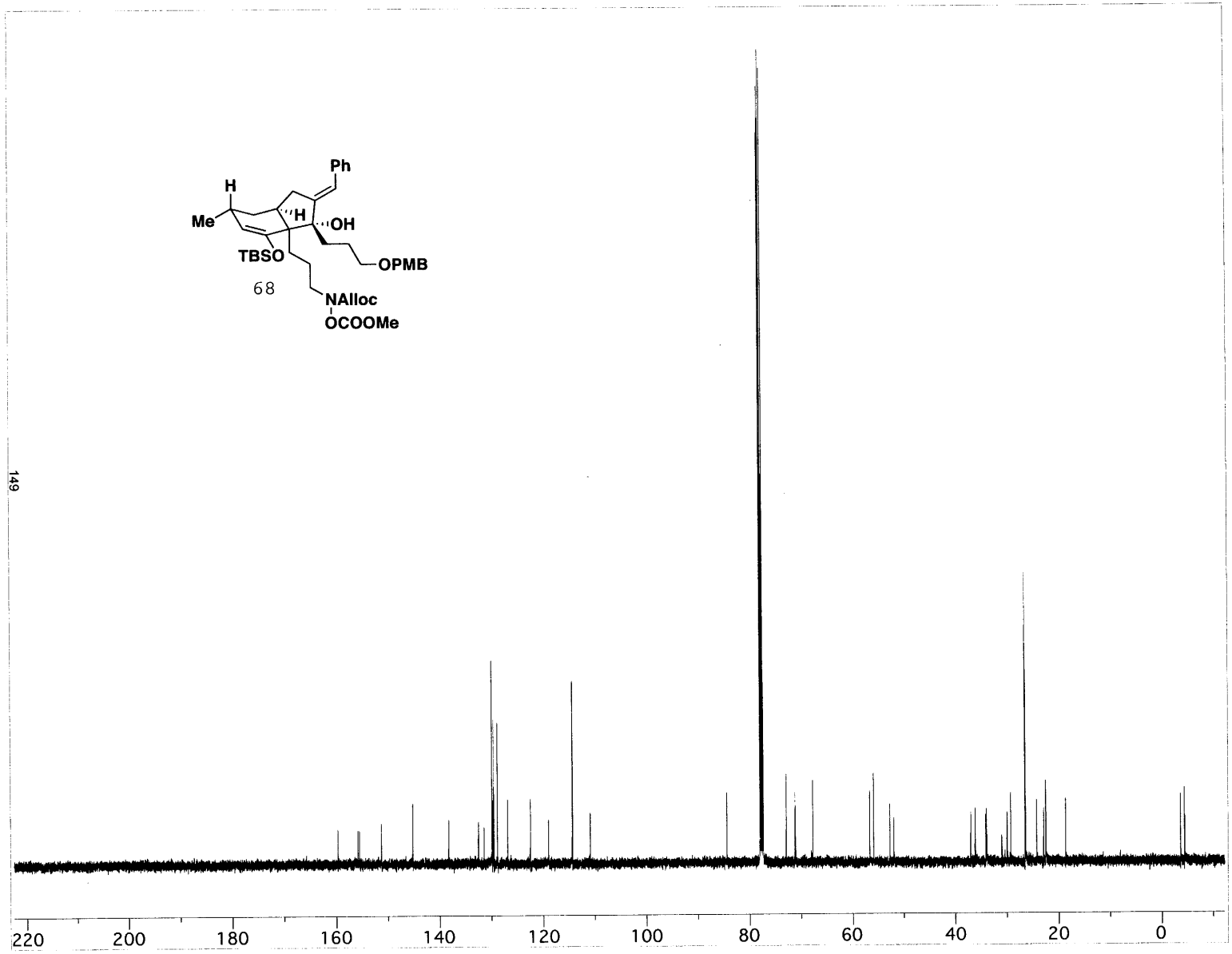
-1


Ph
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Me
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OH
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OCOOMe
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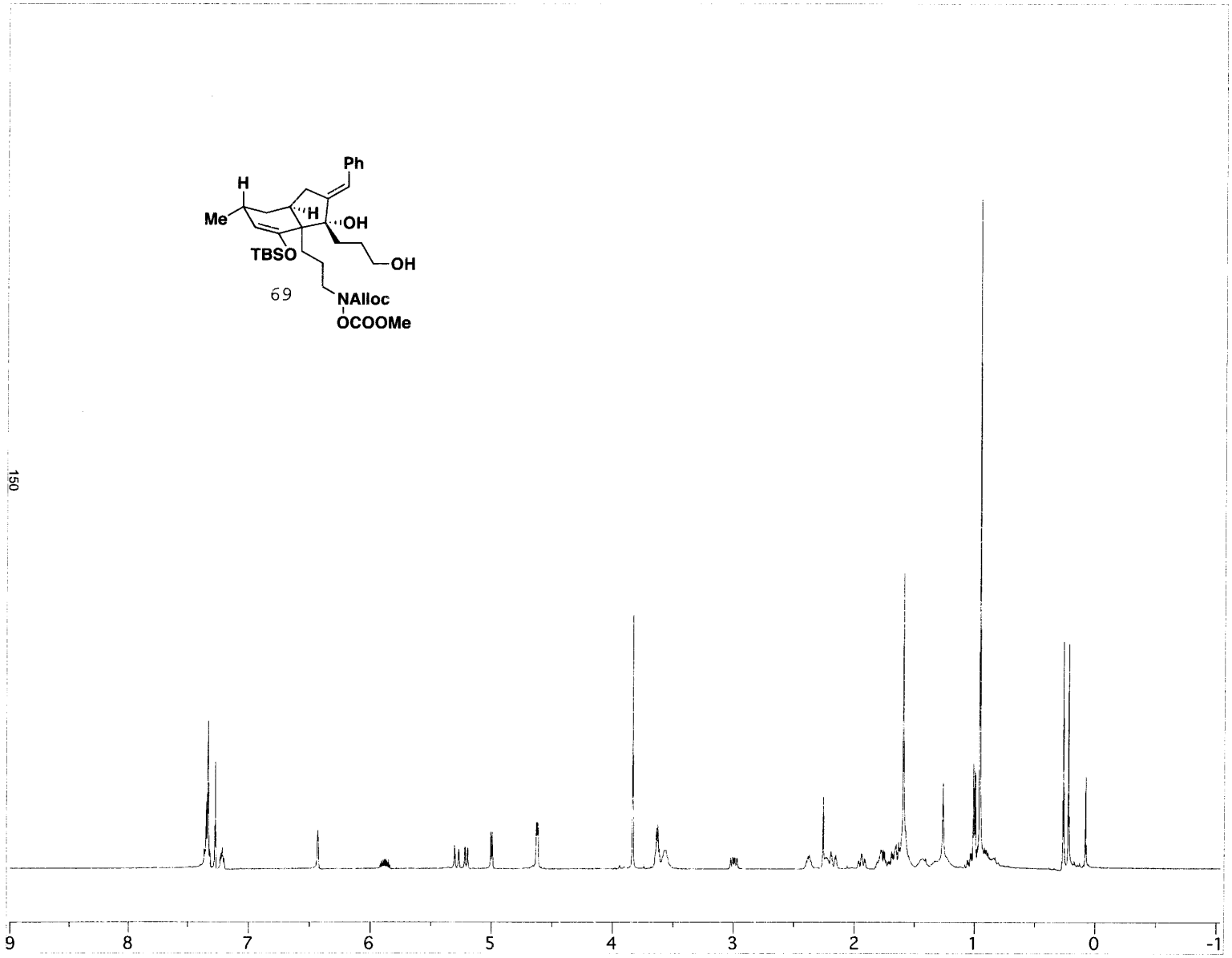
20
0


Ph
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Me
H
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TBSO
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OCOOMe
150
9
8
7
6
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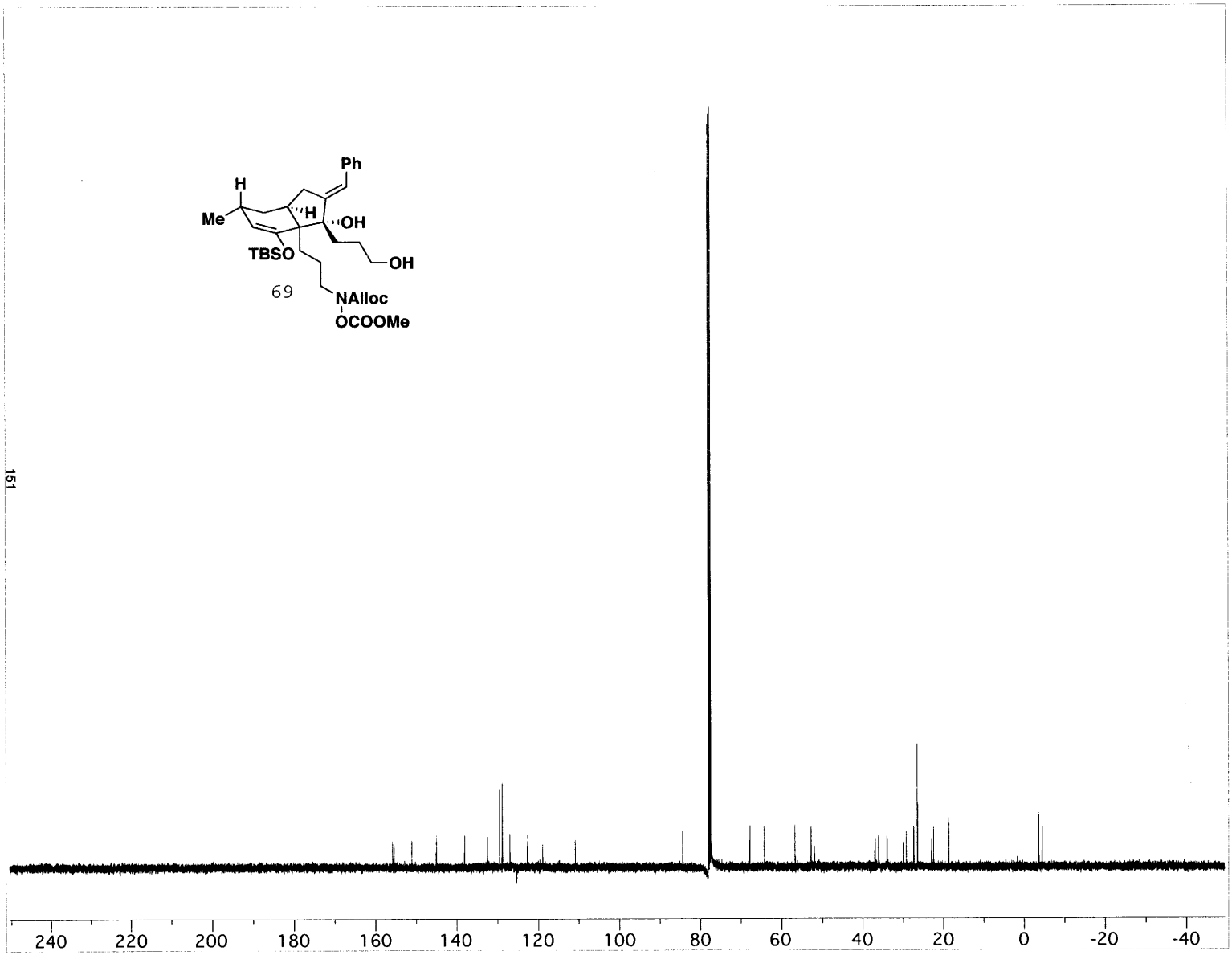
2
1
0
-1


Ph
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Me
H
OH
TBSO
OH
69
NAlloc
OCOOMe
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240
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200
180
160
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100
80
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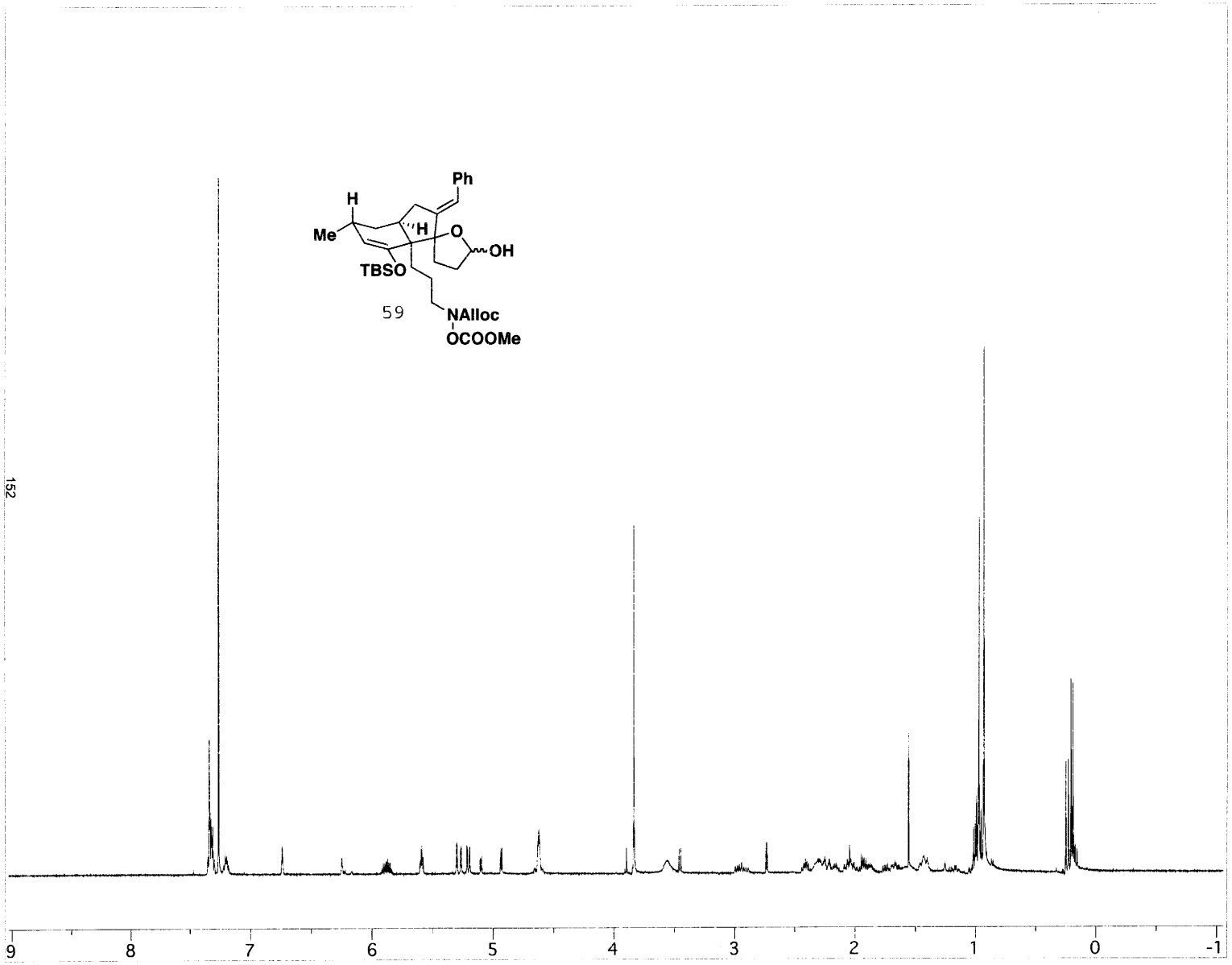
0
-20
-40


Ph
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Me
H
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OCOOMe
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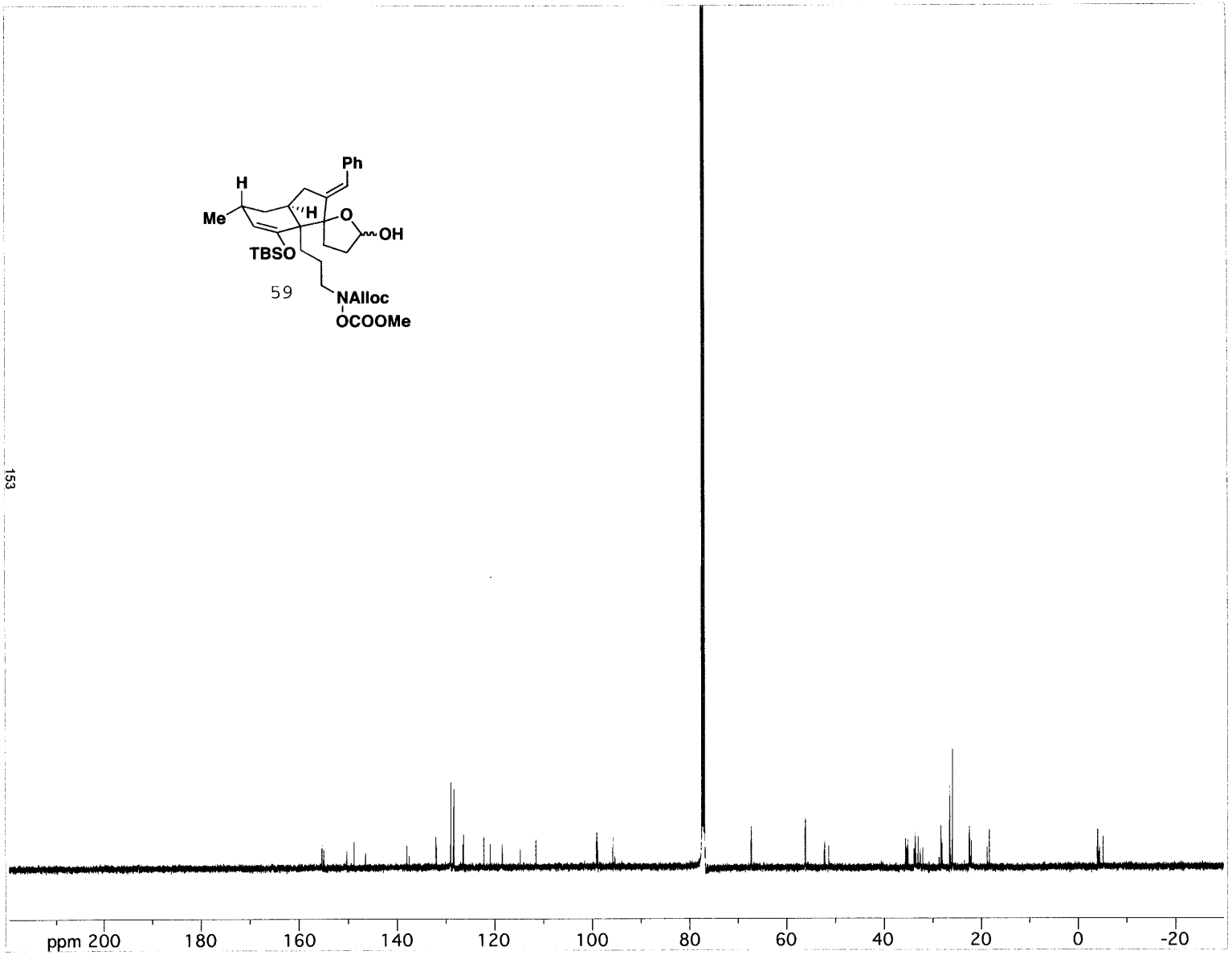
-1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Me
H
O
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TBSO
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OCOOMe
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100
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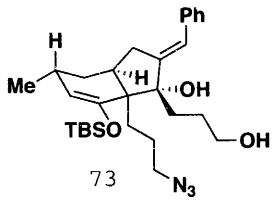
20
0
-20



73

154

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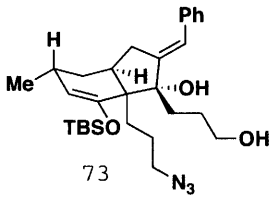
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Me
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TBSO
OH
N3

73

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ppm 220
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140
120
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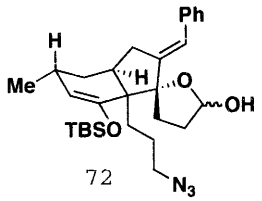
60
40
20
0



72

156

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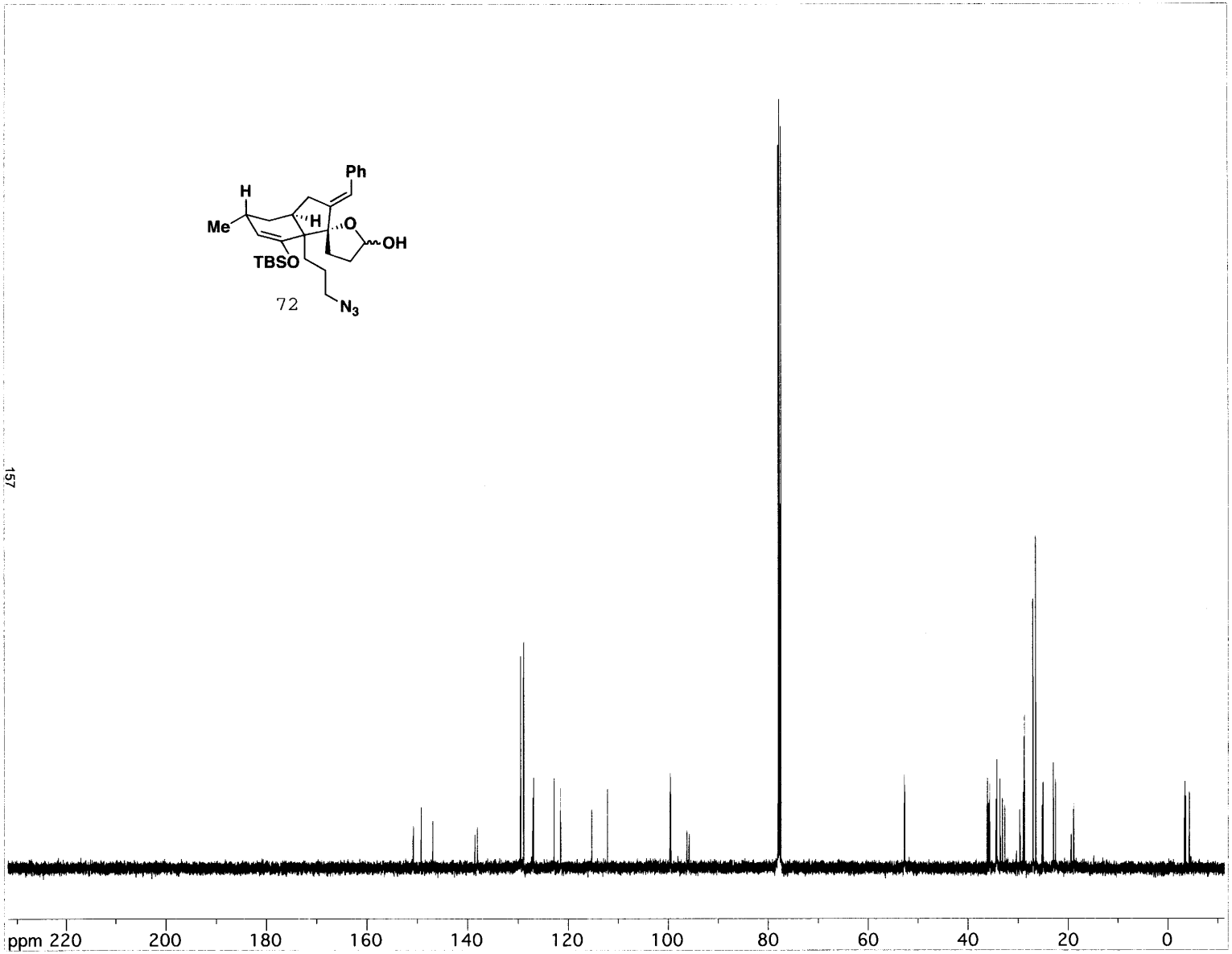
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O
OH
TBSO
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N3
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ppm 220
200
180
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140
120
100
80
60
40
20
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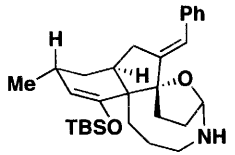

77

158

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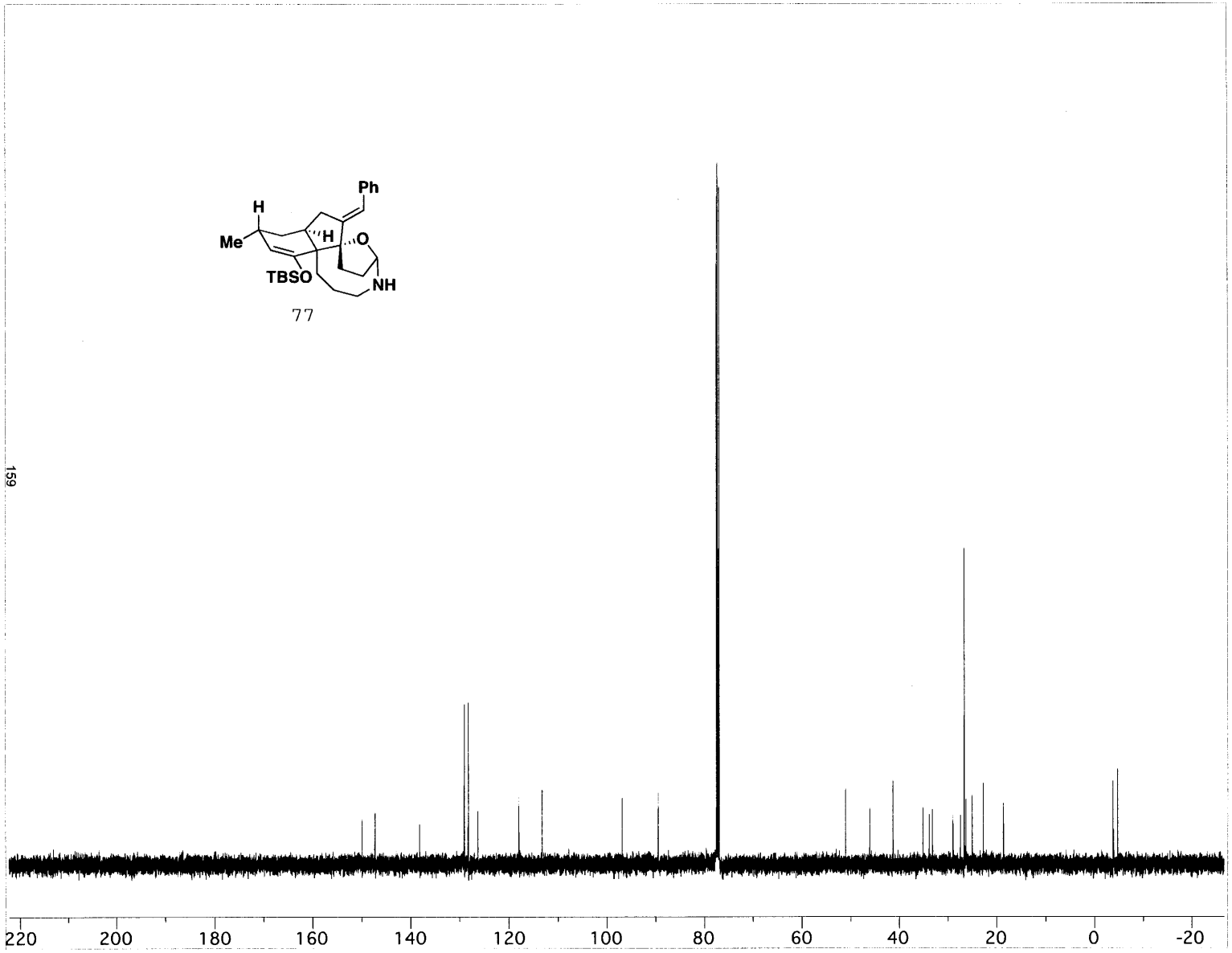
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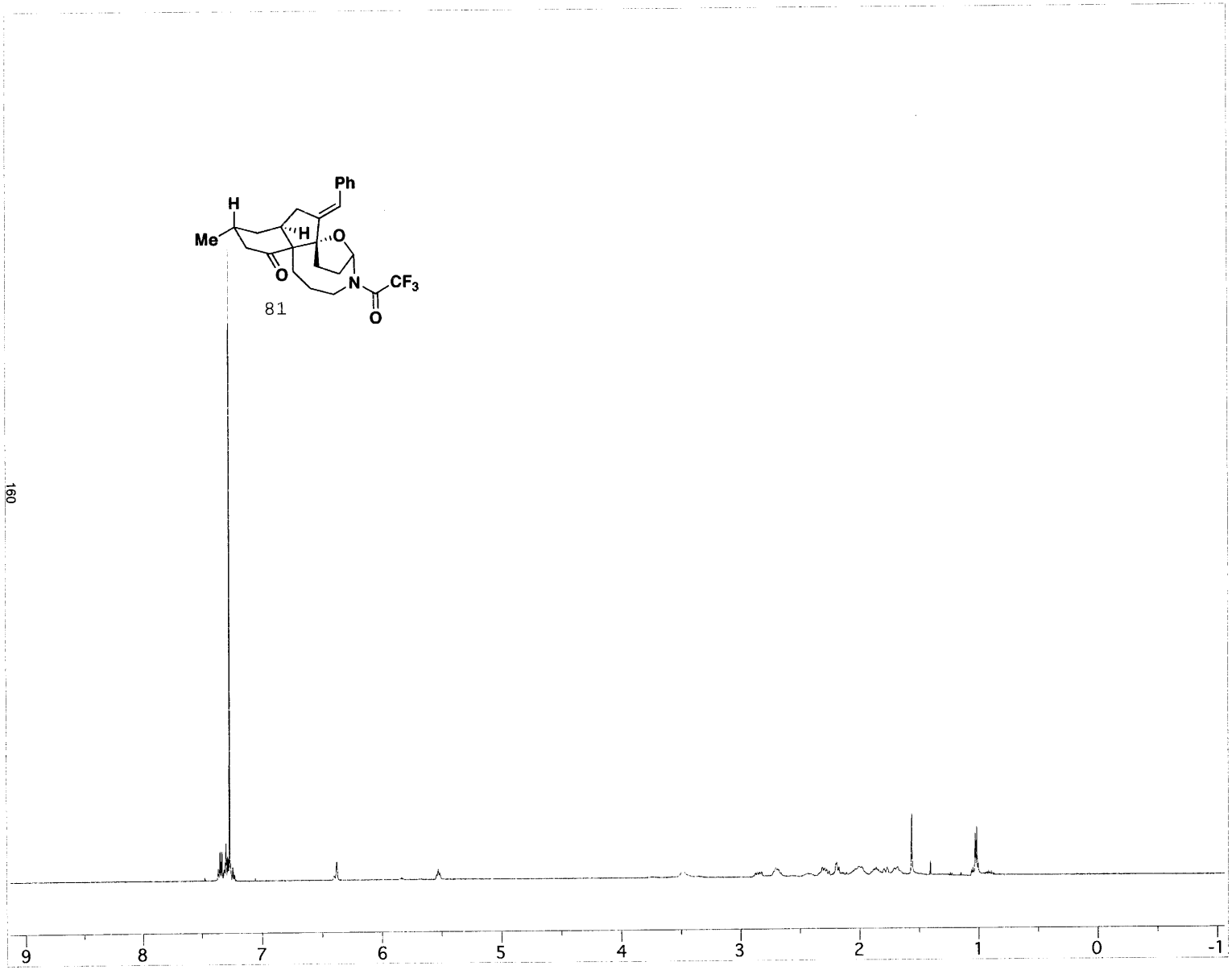
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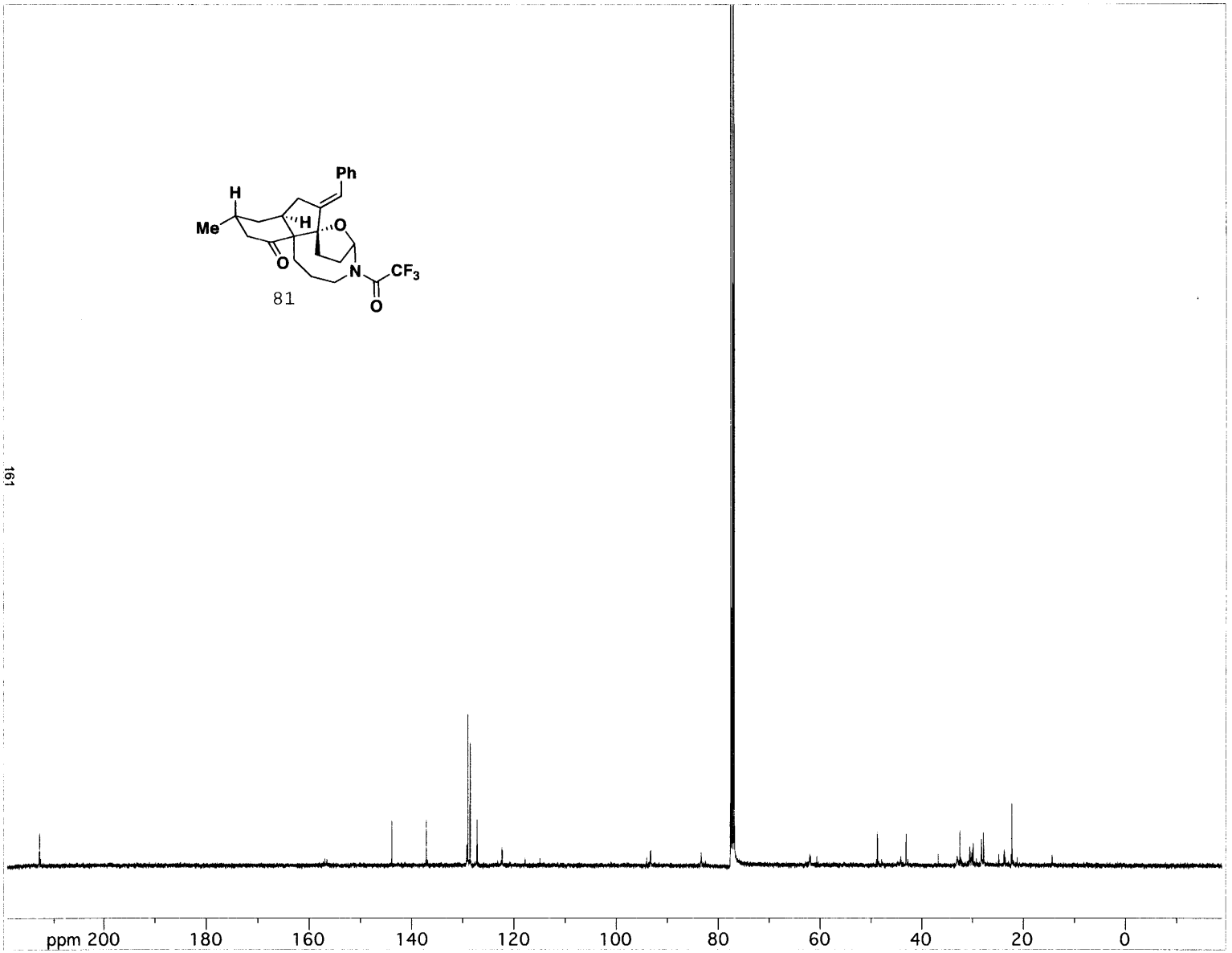
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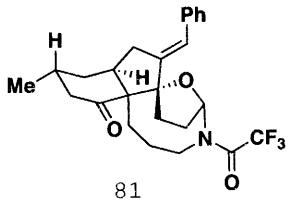
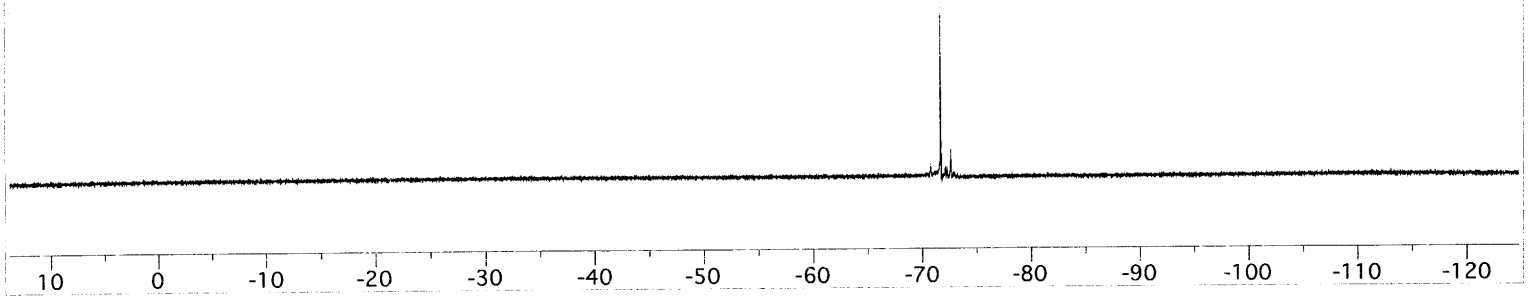
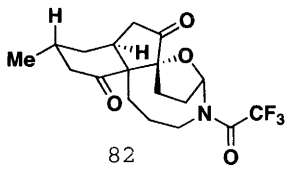


81

19F





82

163

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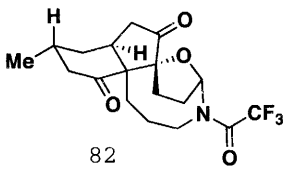

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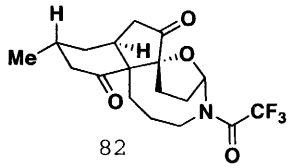

82
19F

165

ppm 150 100 50 0 -50 -100 -150

Curriculum Vitae

Education:

2003-2008 Ph.D. Candidate
Department of Chemistry
Massachusetts Institute of Technology, Cambridge, MA
Research Advisor: Professor Timothy F. Jamison

Studies directed towards the total synthesis of sieboldine A

1999-2003 B.S. Chemistry
College of Chemistry
University of California, Berkeley, Berkeley, CA

Research and Teaching Experience:

2003-2008 Graduate Research Assistant with Professor Timothy F. Jamison
Massachusetts Institute of Technology, Cambridge, MA

2003-2005 Teaching Assistant/Head Teaching Assistant

2002 Intern
Sunesis Pharmaceuticals, South San Fransisco, CA

2001 Undergraduate Research Assistant with Professor John Ellman
University of California, Berkeley, Berkeley, CA

2000-2001 Undergraduate Research Assistnat with Professor Sung-Ho Kim
University of California, Berkeley, Berkeley, CA

Honors and Awards:

2007 AstraZeneca Graduate Fellowship in Organic Chemistry
2007 Morse Travel Grant, Massachusetts Institute of Technology
2003 Graduated with Honors, University of California, Berkeley

Publications and Presentations:

Gehling, V. S.; Jamison, T. F. "Studies Directed Towards the Total Synthesis of (+)-Sieboldine A." *234th ACS National Meeting*, Boston, MA, August 2007.

Gehling, V. S.; Jamison, T. F. "Studies Directed Towards the Total Synthesis of (+)-Sieboldine A." *56th Natural Products Gordon Research Conference*, Tilton, NH, July 2007.