STUDIES TOWARD THE TOTAL SYNTHESIS OF GLYCINOECLEPIN A

by

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Lastly, I would like to thank my family for their support throughout my entire life. I would like to present my most sincere gratitude to my parents. If it were not for them, there would not have been today for me. As I was growing up, they have always emphasized the importance of good education and they have worked hard to ensure that their children would have good education, the privilege they did not have, and for that I would like to dedicate this thesis to them.

To My Parents,

for Their Love and Support

Studies Toward the Total Synthesis of Glycinoeclepin A

by

Charnsak Thongsornkleeb

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requirements for the Degree of Doctor of Philosophy

ABSTRACT

Studies directed toward the synthesis of the A-ring portion of glycinoeclepin A are described. The enantioselective synthesis of key diketone intermediate **128** in four steps from 2,2-dimethyl-1,3-cyclohexanedione (**5**) has been accomplished via the acid-catalyzed intramolecular Michael cyclization of an enone generated in situ from **132**. In the course of these studies, a new method for the preparation of the highly reactive α-alkynyl acroleins was developed. Several methods for the further elaborations of diketone **128** to the key enyne intermediate **95** were investigated and the best route developed to date involves the conversion of the methyl ketone to a vinyl triflate (**177**) followed by Sonogashira coupling. In addition, the conversion of diketone **128** to the vinyl halide **258** via a Shapiro strategy was achieved and model studies were carried out on the synthesis of vinylallene by coupling cuprate derivatives of this intermediate with propargyl alcohol derivatives.

Thesis Supervisor: Rick L. Danheiser

Title: Professor of Chemistry

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Part I

Introduction and Background

Chapter 1

Glycinoeclepin A: Background and Significance

Heterodera glycines Ichinohe: The Soybean Cyst Nematode

Nematodes are elongated worms of the phylum Nematoda found in the soil and water[1] and are the most abundant animals on earth. For example, it is estimated that there can be five billion nematodes in the upper three inches of an acre of soil. At least 32 species of these organisms are parasitic to a number of plants and animals. Nematodes infect many of the plants and animals on which humans depend for food, and therefore are a serious contributing cause to the global problem of starvation and food shortage.

Nematodes of the genus *Heterodera* have been particularly serious pests because they feed on a number of economically significant crops. The cyst nematodes take their name from the cyst that acts as a protective shell for their larvae allowing them to survive adverse environmental conditions and remain a viable threat in the soil for a number of years.[2] In general, the cyst nematodes have a limited number of host plants and this specificity is thought to be due to the fact that the larvae are hatched upon the release of a key stimulant from the host plant. This insight into the nematode life cycle was first realized in 1922 when Baunacke found that extracts from potatoes could stimulate the emergence of larvae from the cysts of the potato cyst nematode.[3]

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[1] (a) Perry, R. N., Wright, D. J., Eds. *The Physiology and Biochemistry of Free-living and Plant-parasitic Nematodes*; CAB International: New York, 1998. (b) Chitwood, B. G.; Chitwood, M. B. *Introduction to Nematology*; University Park Press: Baltimore, 1974. (c) Decker, H. *Plant Nematodes and Their Control (Phytonematology)* (translated from Russian); Amerind: New Delhi, 1980; p 128.

[2] Whitehead, A. G. In *Cyst Nematodes*; NATO ASI Series A, Vol 121; Lamberti, F. and Taylor, C. E., Eds.; Plenum: New York, 1985; p 413.

[3] Baunacke, W. E. *Arb. Biol. Bund Anst. Land-u. Forstw.* **1922**, *11*, 185.

The soybean cyst nematode (*Heterodera glycines* Ichinohe) has attracted considerable attention because it parasitizes a number of economically important plants such as soybeans (*Glycine max*), kidney beans (*Phaseolus vulgaris*), and adzuki beans (*Phaseolus angularis*). This nematode causes *daizu iwo byo* ("yellow dwarf disease") in soybean plants which leads to severe inhibition in growth and fewer production of flowers and seeds. The leaves of infected plants also lack pigments and drop early. In addition to attacking the plant's cells and blocking its vital transport channels, the nematode also renders the plants susceptible to viruses, bacteria, and fungi. *H. glycines* is widespread in Japan, the United States, Canada, and South America, and accounts for most of the $2.5 billion in crops lost each year to nematodes.[4] In the United States alone, it costs soybean producers more than $1 billion in crop losses annually.[5] Soybeans are one of the most important crops in the United States and rank third in total area planted. There is also concern that other crops, such as kidney beans, could be affected by the soybean cyst nematode in an economically significant way.

A wide range of toxic chemicals such as halogenated aliphatic hydrocarbons (e.g., methyl bromide) and carbamates (e.g., aldicarb) have traditionally been employed as a standard practice in the agricultural industry to control and kill many types of pests.[2,6] However, since it is estimated that only 0.1% of the pesticide applied to crops actually affects the pest, many of these toxic substances are applied in relatively high concentrations, which together with their chemical stability, has caused these materials to accumulate in the environment. Furthermore, as pests

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[4] (a) Sasser, J. N.; Frackman, D. W. In *Vistas on Nematology*; Veech, J. A.; Dickson, D. W., Eds.; Society of Nematologists, Inc.: Hyattsville, 1987. (b) Noel, G. R. In *Biology and Management of the Soybean Cyst Nematode*; Riggs, R. D.; Wrather, J. A.; APS Press: St. Paul, MN, 1992.

[5] Illinois SCN Coalition. http://scn.cropsci.uiuc.edu/impact.html (Accessed Nov. 2005)

[6] (a) Atkinson, H. J.; Lilley, C. J.; Urwin, P. E.; McPherson, M. J. Engineering Resistance to Plant-parasitic Nematodes. In *The Physiology and Biochemistry of Free-living and Plant-parasitic Nematodes*; Perry, R. N., Wright, D. J., Eds. CAB International: New York, 1998; pp 381-413. (b) Illinois SCN Coalition. http://scn.cropsci.uiuc.edu/manage7.html (Accessed Nov 2005)

develop resistance to these chemicals, their effectiveness is deteriorating. Thus, new strategies to control agricultural pests are needed in response to these limitations.

Currently, the main strategy employed to fight the soybean cyst nematode involves the use of crop rotation and nematode-resistant varieties of soybean. Non-host crops, such as corn, cereals and forage grasses are used to break the host crop cycle in conjunction with the use of nematode-resistant varieties of soybean. This strategy offers the best management of the soybean cyst nematode.[6b] Unfortunately, the resistant varieties are not resistant to all soybean cyst nematode species, and continued use can lead to an increase in the population of soybean cyst nematode species which the crop has no resistance to.

Alternative Approaches to Pest Control

The application of a combination of different approaches to the problem of pest control, commonly referred to as integrated pest management (IPM), has gained favor as an alternative to the large-scale use of toxic pesticides.[7] Among the strategies employed in IPM are the uses of pest predators such as parasites, bacteria, and viruses, together with chemical control. This latter category involves the use of rationally designed synthetic pest control agents as well as behavior-modifying substances, known as semiochemicals.

Semiochemicals are usually highly selective and highly active substances.[8] They can be categorized as pheromones and allelochemicals. Pheromones are substances used by members of a species to communicate with each other. A common use of these compounds in pest control is the employment of sex pheromones to attract insects into traps containing insecticides.

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[7] For example, see: Bellus, D. *Chimia* **1991**, *45*, 154.

[8] For overviews, see: (a) *Semiochemicals, Their Role in Pest Control*; Nordlung, D. A., Jones, R. L., Lewis, W. J., Eds.; John Wiley & Sons: New York, 1981. (b) *Semiochemicals in Pest and Weed Control*; Petroski, R. J., Tellez, M. R., Behle, R. W., Eds.; American Chemical Society: Washington, DC, 2005.

Allelochemicals are substances produced by one species with an effect on a different species. There are two classes of allelochemicals: allomones and kairomones. With allomones, the effect is favorable to the emitter, but not to the receiving species (e.g., plant defense agents such as azadirachtin[9]). Kairomones, however, produce a favorable effect to the receiving species, but not to the emitter. Semiochemicals typically exhibit high levels of activity in the environment, and are usually species-specific. Since both pheromones and kairomones are generally not toxic to pests, they are more likely to not be toxic towards the ecosystem as compared to classical pesticides. This makes semiochemicals attractive candidates as pest control agents.

In the battle against the soybean cyst nematode, a strategy involving kairomones or pheromones could be extremely effective. The high selectivity and activity of these compounds could allow for the elimination of this pest using a minimal amount of the substances without harmful effects to the environment.

Isolation and Biological Activity of Glycinoeclepin A

It is best to understand the biological activity of glycinoeclepin A and its potential use as a pest control agent by considering the life cycle of *H. glycines*. The life of cyst nematodes begins when the eggs hatch into larvae and migrate into the host plant.[10] Glandular secretions from the larvae cause the surrounding cells in the vascular cylinder tissue to swell. These cells provide the nourishment for the developing nematode during its four-week life cycle. Following fertilization, the female fills with eggs and dies. Its body becomes a cyst which protects the eggs

[9] Azadirachtin is a natural product found in the seeds of the neem tree and used in India to control insects. Scientists believe the neem tree produces azadirachtin as a deterrent to insect attacks.

[10] Opperman, C. H.; Dong, K.; Chang, S. In *Advances in Molecular Plant Nematology*; NATO ASI Series A, Vol 268; Lamberti, F., De Giorgi, C., Bird, D. M., Eds.; Plenum: New York, 1985; p 65.

from adverse conditions until the optimal factors for hatching are present. These protected nematodes can survive in harsh conditions for approximately three to four years.

In 1966, Tsutsumi and Sakurai showed that, as is the case with the potato cyst nematode (vide supra), host plant extracts are potent stimulants for the hatching of the larvae of the soybean cyst nematode.[11] This exciting discovery offered the possibility of a potential means to control the hatching of this agricultural pest, and prompted the search for the exact nature of the compound. In 1967, Tadashi Masamune undertook the task of isolating and identifying this important compound.[12]

Fifteen years later, in 1982, Masamune and co-workers reported the first isolation of 50 μg of the *p*-bromophenacyl ester (*p*-BPE) of a substance that stimulated the hatching of the soybean cyst nematode.[13] The source of the sample was a 113-kg sample of dried and powdered kidney bean roots collected from a 1-hectare field. Through extensive extractions and purifications, fractions were obtained and tested for bioactivity. When the 50-μg sample[14] isolated was tested for the hatching rate of the nematode eggs, it was found to stimulate hatching, in vitro, at a level of 10^{-11} to 10^{-12} g/mL! Mass spectrometry established the molecular formula, and ^{1}H NMR revealed the types of oxygen functionality in the sample. The minuscule amount of the compound first isolated was not adequate to assign the structure of this fascinating compound, designated as glycinoeclepin A, and a larger amount of sample was required.

The structure of glycinoeclepin A (**1**) was firmly established in 1987. Over 1,000 kg of dried and powdered kidney bean roots were harvested from a 10-hectare field. Extractions and

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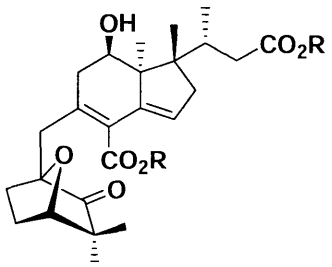
[11] Tsusumi, M.; Sakurai, K. *Jpn. J. Appl. Ent. Zool.* **1966**, *10*, 129.
[12] Masamune, T. In *Natural Product and Biological Activities; A Naito Foundation Symposium*; University of Tokyo Press; Elsevier: New York, 1986; p 25.
[13] Masamune, T.; Anetai, M.; Takasugi, M.; Katsui, N. *Nature* **1982**, *297*, 495.
[14] Sample was isolated as its *p*-BPE and hydrolyzed before testing.

purification led to 1.25 mg of glycinoeclepin A as its *p*-bromophenacyl ester (*p*-BPE) (**2**).[15] This sample was characterized using several spectroscopic methods (including mass spectrometry and various NMR techniques) and was assigned the structure shown below.[15a,16] The assignment was confirmed by X-ray analysis of a single crystal of glycinoeclepin A *p*-BPE.[16] The hydrolysis of glycinoeclepin A *p*-BPE-derivative (**2**) afforded the natural compound (**1**) which was found to be active, in vitro, at the 10^{-12} g/mL level.



R = H Glycinoeclepin A (**1**)
R = $CH_2COC_6H_4$*p*-Br (**2**)

Potential Use of Glycinoeclepin A as a Pest-Control Agent

Researchers found that exposure of the cysts to a solution of glycinoeclepin A stimulated the hatching of the larvae. It was observed from bioassays that the larvae which emerge from cysts treated with glycinoeclepin A are active, whereas the larvae from untreated cysts are less active and appeared in smaller numbers. This finding suggests the idea that hatching is the result of the active motion of the larvae and that glycinoeclepin A stimulates the larvae's motor nervous system.[12]

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[15] (a) Fukuzawa, A.; Furusaki, A.; Ikura, M.; Masamune, T. *J. Chem. Soc. Chem. Commun.* **1985**, 222. (b) Masamune, T.; Anetai, M.; Fukuzawa, A.; Takasugi, M.; Matsue, H.; Kobayashi, K.; Ueno, S.; Katsui, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 981.

[16] (a) Masamune, T.; Fukuzawa, A.; Furuzaki, A.; Ikura, M.; Matsue, H.; Kaneko, T.; Abiko, A.; Sakamoto, N.; Tanimoto, N.; Murai, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1001. (b) Takasugi, M.; Fukuzawa, A.; Masamune, T. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 416.

The ability of glycinoeclepin A to stimulate the hatching of the soybean cyst nematode has led to great interest in its potential use as a pest control agent. One could envision that the application of glycinoeclepin A on the fields in the spring, before the soybeans are planted, or in the fall after the harvest, should cause the larvae to hatch from the cysts. Since no host plant would be present, the nematodes would have no source of nourishment, and would then die and not reproduce. The protocol for field applications and environmental impacts of glycinoeclepin A still need to be studied. However, the possibility exists that glycinoeclepin A could be used as an *environmentally benign* agent for nematode control.

A major obstacle to implementing this strategy that needs to be addressed is the lack of a suitable source of **1**. Nature does not appear to be a feasible source of material, but chemical synthesis could provide the quantities necessary for testing and, eventually, application of the compound. It should therefore be of no surprise that the combination of the potential utility of this molecule as a nematode control agent and its challenging molecular skeleton have made it an interesting target for total synthesis. Work in this area has resulted in three total syntheses, a biomimetic synthesis of a close analog (vide infra), and several papers on synthetic approaches[17] and structure-activity relationships of analogs.[18]

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[17] (a) For synthetic approaches to the D-Ring side chain, see: Okawara, H.; Nii, Y.; Miwa, A.; Sakakibara, M. *Tetrahedron Lett.* **1987**, *28*, 2597. (b) Kraus, G. A.; Choudhury, P. K. *Eur. J. Org. Chem.* **2004**, 2193.

[18] For a summary, see: Martin, M. W. Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, February 2000 and references cited therein.

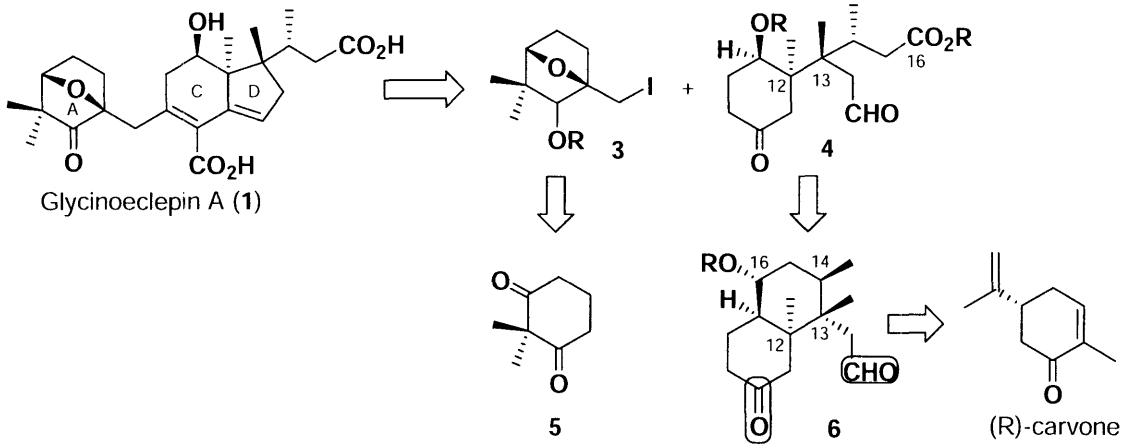
Previous Syntheses of Glycinoeclepin A

Murai Synthesis

The first total synthesis of glycinoeclepin A was reported in 1988 by Murai and coworkers at Hokkaido University.[19] While it is noteworthy for being the first total synthesis of this challenging molecule, the route is not very efficient (35 steps in the longest linear sequence plus 7 steps for other fragments) and few measures were taken to control the stereoselectivity of key steps. Thus the synthesis is not sufficiently practical in accessing significant quantities of glycinoeclepin A.

The Murai synthesis of **1** involved the disconnection of the molecule to the A-ring precursor **3** and the CD-ring precursor **4** as shown below (Scheme 1). Murai planned to join the two fragments together via an alkylation. Subsequent intramolecular aldol reaction between the C-ring ketone and the side chain aldehyde would yield the five-membered D-ring.

Scheme 1

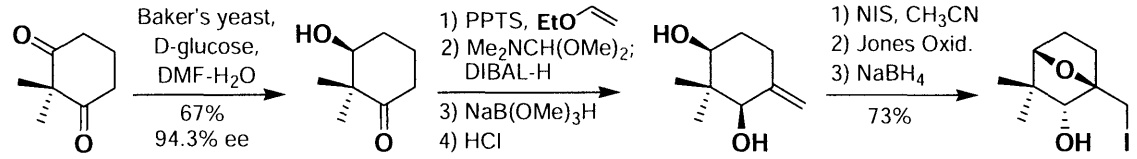


[19] (a) Murai, A.; Tanimoto, N.; Sakamoto, N.; Masamune, T. *J. Am. Chem. Soc.* **1988**, *110*, 1985. (b) Murai, A. *Pure Appl. Chem.* **1989**, *61*, 393.

Compound **3** would be derived from the dimethyl cyclohexanedione **5**. The CD-ring fragment **4** would be obtained from the bicyclic intermediate **6** by deprotection of the C-16 alcohol and oxidation to the corresponding ketone. Baeyer-Villiger oxidation followed by hydrolysis of the resulting lactone would then furnish **4**. Bicyclic compound **6** would be synthesized from (*R*)-(−)-carvone via a sequence involving methyl cuprate addition and trapping of the enolate (to attach substituents at C-13 and C-14), Robinson annulation, and Nagata hydrocyanation (to introduce the C-12 methyl group).

Enzymatic reduction of diketone **5** with Baker's yeast provided alcohol **7**[20] with high enantioselectivity. Protection of alcohol **7** as an acetal, α-methylenation, reduction of the ketone, and deprotection of the alcohol provided diol **8**. Iodoetherification of **8** with NIS was used as the key step in the next three-step sequence to yield the oxabicyclic system **9**.

Scheme 2



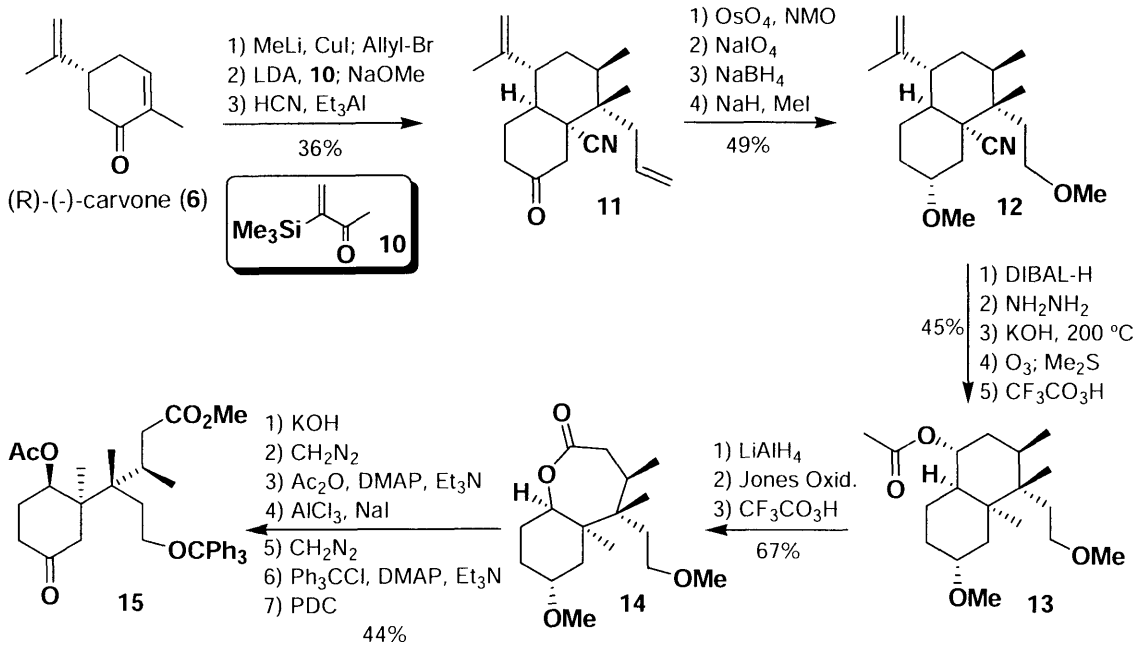
5 **7** **8** **9**

As shown in Scheme 3, the synthesis of the key intermediate **15** commenced with stereoselective methyl cuprate addition to *R*-(−)-carvone, followed by trapping of the resulting enolate with allyl bromide. Subsequent Robinson annulation with **10** and hydrocyanation provided the desired *cis*-fused β-cyano ketone **11** in 63% (shown), accompanied by 30% of the *trans*-fused isomer. Conversion to lactone **14** was achieved by a series of functional group manipulations. Oxidative cleavage of the allyl side chain in **11**, followed by reduction and protection afforded **12**. Reduction of the nitrile to a methyl group, oxidative degradation of the

[20] (a) *Organic Syntheses*; Wiley & Sons: New York, 1993; Collect. Vol. VIII, 312. (b) Mori K.; Mori, H. *Tetrahedron*, **1985**, *41*, 5487. (c) Mori, K.; Watanabe, H. *Tetrahedron*, **1986**, *42*, 273.

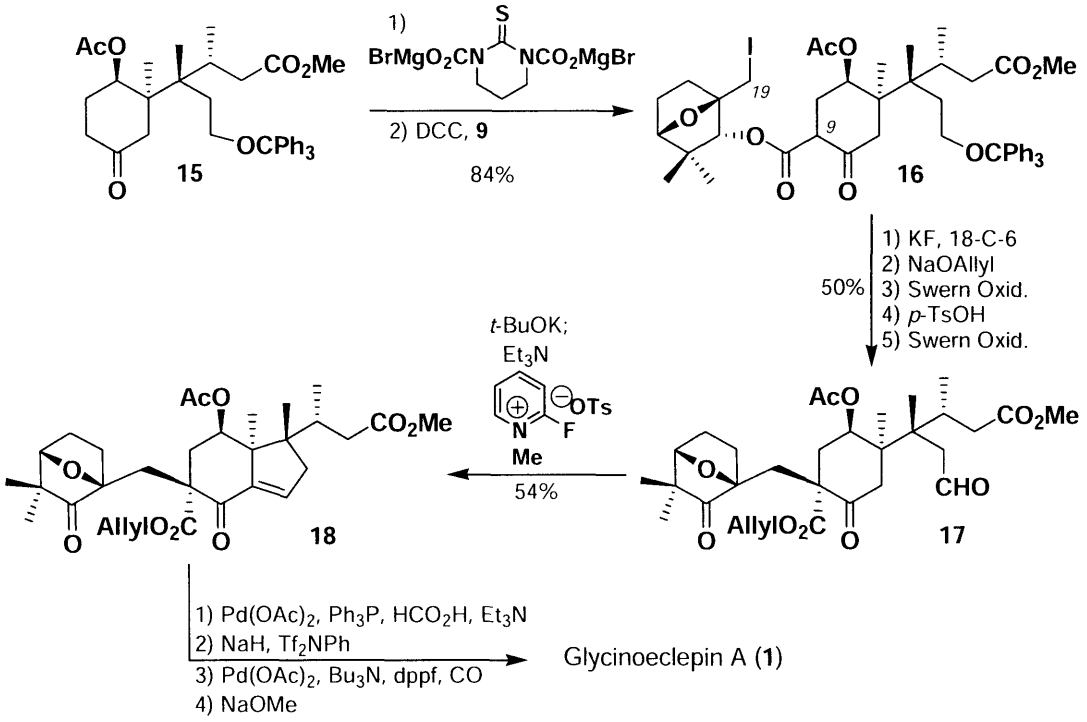
isopropenyl side chain, and Baeyer-Villiger oxidation finally furnished **14**. Lactone hydrolysis and several functional group manipulations yielded ketone **15**.

Scheme 3



Initial attempts to perform an alkylation of **15** with **9** met with failure. A successful alkylation was, however, realized when this process was performed in an *intramolecular* fashion. Thus fragments **15** and **9** were first joined together as the ester **16** (Scheme 4). Subsequent treatment with KF in the presence of 18-crown-6 effected the coupling of C-9 and C-19 to provide the desired intermediate spirolactone in good yield. However, the authors did not address the issue of stereoselectivity of this process. Allyl ester formation, Swern oxidation, deprotection, and another Swern oxidation then provided **17**. Aldol condensation between the C-ring ketone and the aldehyde side chain in **17** was the next key step employed to form the D-ring. Final conversion to glycinoeclepin A was achieved in four steps via enol triflate formation and subsequent palladium-promoted carboxylation and deprotection.

Scheme 4



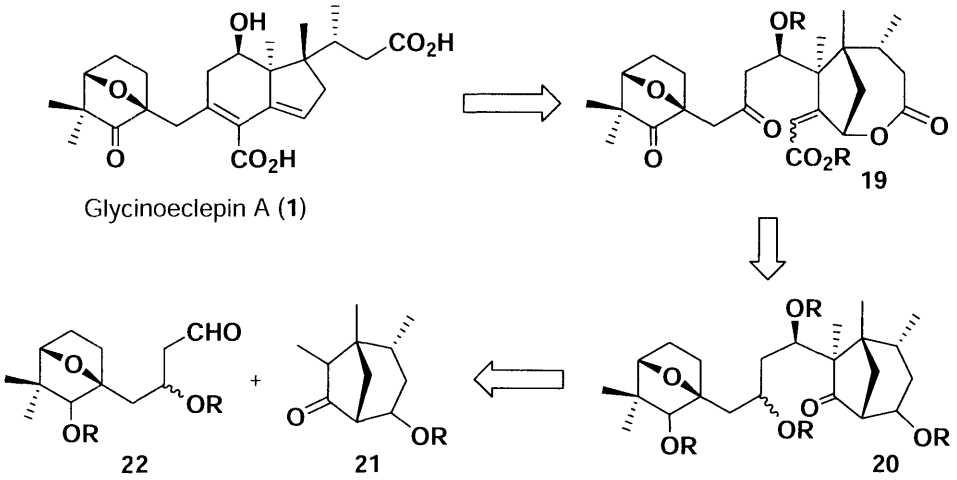
Mori Synthesis

In 1989, Mori and Watanabe completed the second total synthesis of glycinoeclepin A.[21] Like the previous Murai synthesis, this route is rather lengthy (38 steps in the longest linear sequence plus 14 steps for other fragments) and does not provide a practical route to the natural product. In an approach similar to the first synthesis, Mori disconnected the target into A-ring and CD-ring fragments. While the construction of A-ring fragment is almost identical to that of the Murai group, their strategy for the construction of the CD-ring is very different. In the Mori synthesis, an aldol reaction was used to join the A-ring fragment **22** with the CD-ring precursor

[21] (a) Mori, K.; Watanabe, H. *Pure Appl. Chem.* **1989**, *61*, 543. (b) Watanabe, H.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, *12*, 2919.

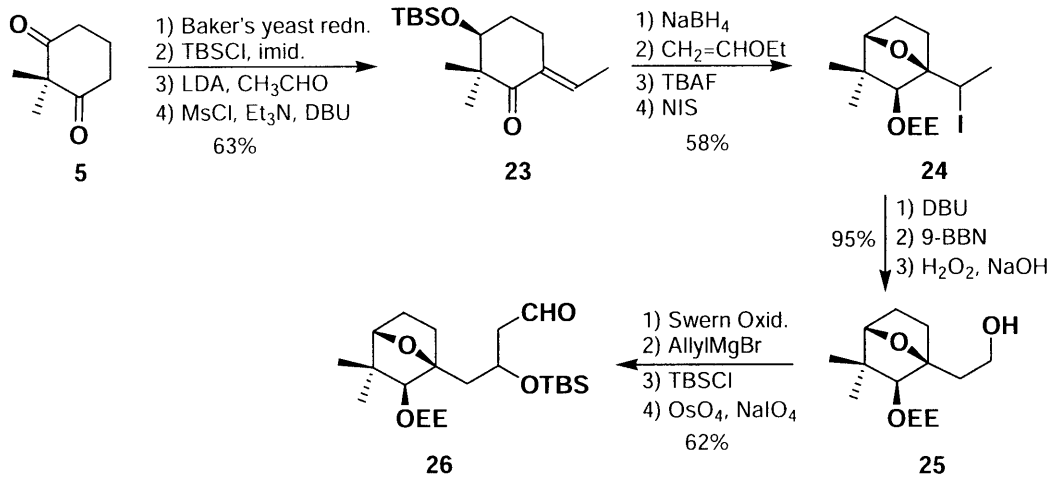
21, generating the requisite alcohol stereoisomer **20**. It was envisioned that subsequent intramolecular reaction of **19** would generate the C-ring of glycinoeclepin A.

Scheme 5



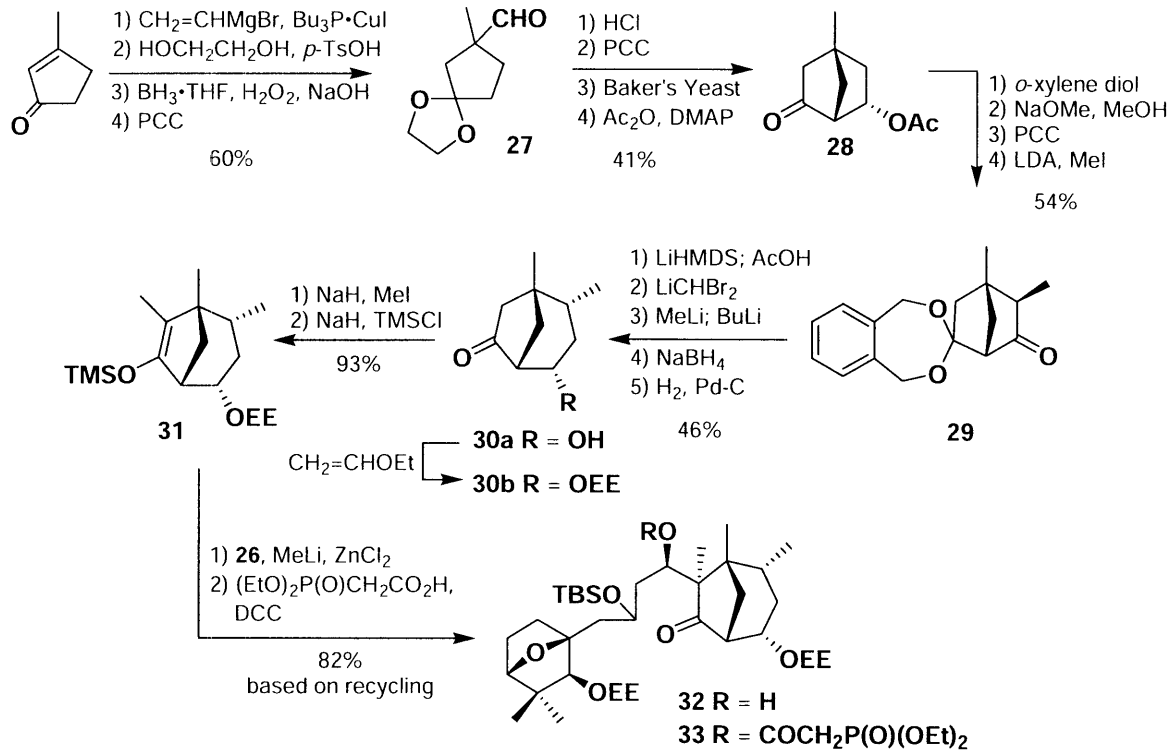
Mori's synthesis of the oxabicyclic A-ring fragment is outlined below. In an approach similar to the first synthesis, enzymatic reduction of **5** with Baker's yeast, followed by a series of protection-deprotection and functional group manipulations, including the NIS-promoted iodoetherification, gave **24** in 37% overall yield from **5**. Iodide **24** was elaborated to the desired A-ring fragment **26** via the addition of a three carbon unit to **25** and subsequent oxidative cleavage of the terminal olefin.

Scheme 6



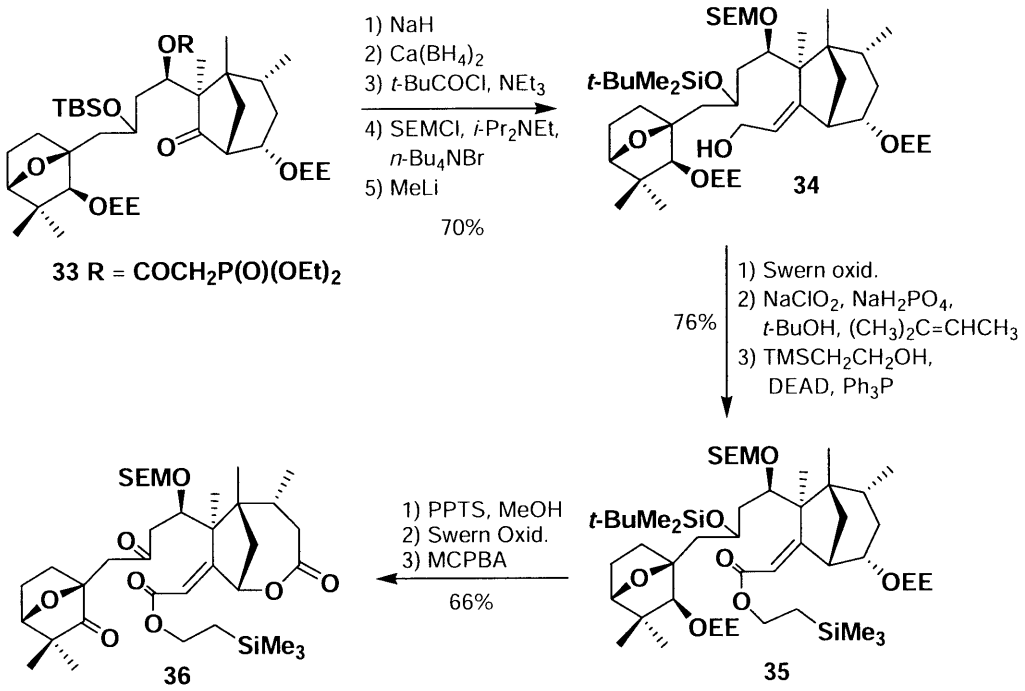
As outlined in the Scheme 7, the CD-ring precursor **30a** was obtained in 17 steps from 3-methylcyclopentenone. Vinyl cuprate addition, protection of the carbonyl group, hydroboration, and oxidation gave aldehyde **27**. Deprotection of the ketone and intramolecular aldol cyclization followed by a Baker's yeast reduction and protection of the resulting alcohol afforded ketone **28**, whose enantiomeric excess was enhanced to 100% by recrystallization. A series of functional group manipulations and an alkylation then gave ketone **29**. Subsequent synthetic operations highlighted by a deprotonation/kinetic protonation to epimerize the methyl group in **29** followed by a ring expansion via treatment with lithiodibromomethane followed by the addition of 1 equivalent of MeLi and 1 equivalent of *n*-BuLi furnished the keto-alcohol **30a**.

Scheme 7



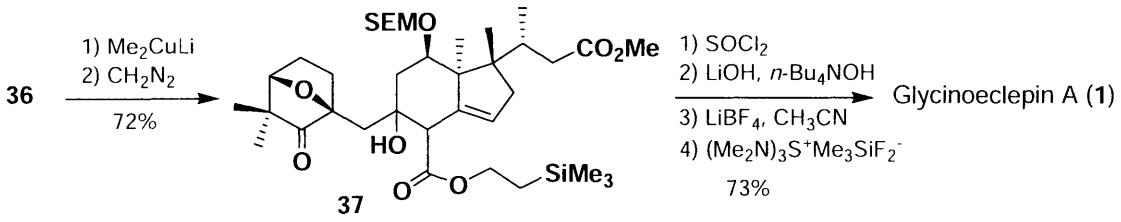
Aldol reaction between the A-ring fragment **26** and CD-ring fragment **30b** was accomplished via the silyl enol ether (**31**) to give **32** in 62% yield as well as significant amounts of the recovered substrates **26** and **30b** (42% of each). Recycling of these compounds afforded **32** in a total yield of 82% (Scheme 7). Intramolecular olefination of **32** and a series of functional group manipulations and Baeyer-Villiger oxidation afforded lactone **36**.

Scheme 8



Synthesis of glycinoeclepin A was then accomplished in six steps, starting with intramolecular reductive cyclization by treatment of **36** with lithium dimethyl cuprate and esterification of the resulting carboxylic acid with diazomethane to give **37**. Dehydration and a series of deprotections then afforded the natural product.

Scheme 9

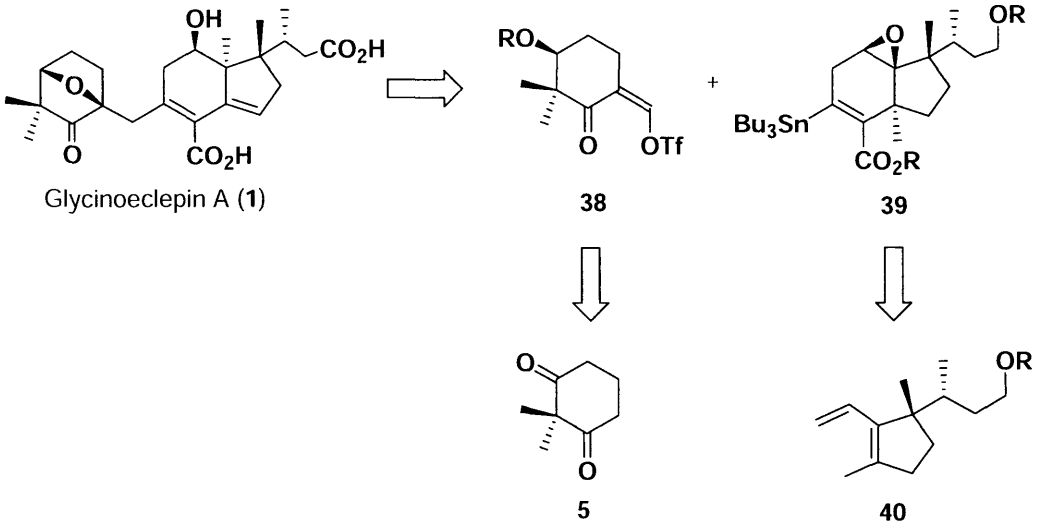


Corey Synthesis

The third total synthesis of glycinoeclepin A was completed by Corey and Houpis in 1990.[22] This synthesis is by far the most efficient to date (28 steps in the longest linear sequence plus 7 steps for other fragments). However, its length also precludes it from being considered practical enough to obtain useful quantities of glycinoeclepin A. A key step in the Corey synthesis is the coupling of the A-ring fragment **38** and CD-ring fragment **39** via a Stille coupling. Methyl group migration with concomitant epoxide opening then generates the required CD-ring system. The A-ring precursor **38** is derived from dione **5** while the tricyclic system **39** is available from diene **40** by a Diels-Alder reaction. Diene **40** is, in turn, accessible from 2-methylcyclopentanone (**42**).

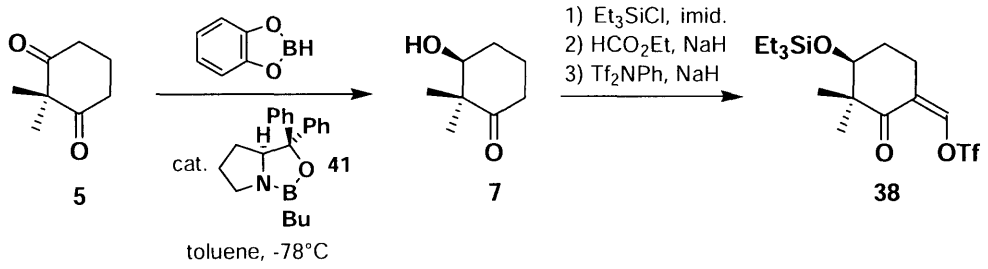
[22] Corey, E. J.; Houpis, I. N. *J. Am. Chem. Soc.* **1990**, *112*, 8997.

Scheme 10



The Corey synthesis of oxabicylic ring precursor **38** is shown below. Starting from diketone **5**, enantioselective reduction with either Baker's yeast or catecholborane in the presence of oxazaborolidine **41** and *n*-butylboronic acid afforded keto alcohol **7**. Silylation of the alcohol, formylation, and enol triflate formation yielded A-ring precursor **38**.

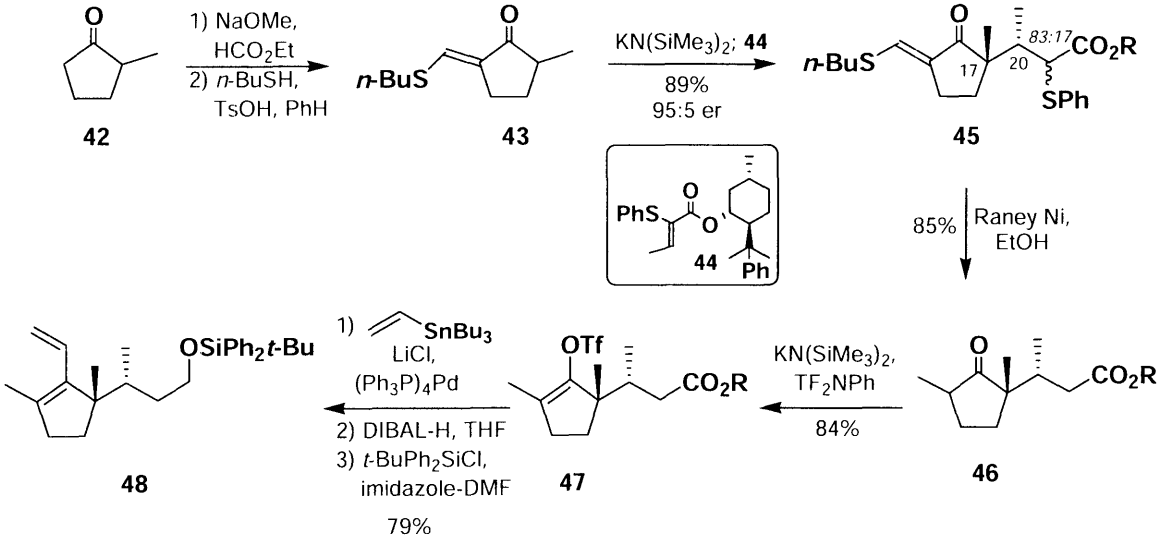
Scheme 11



The construction of the CD-ring fragment **39** commenced with the conversion of 2-methylcyclopentanone to compound **43**. Enantioselective addition of the potassium enolate of **43** to the (−)-8-phenylmenthol ester of (*Z*)-2-(phenylthio)crotonic acid gave cyclopentanone **45** (95:5 er; 83:17 dr for C17-C20). Separation of the major diastereomer of **45** by silica gel chromatography, reduction of the thiomethylene group, and enol triflate formation yielded **47**.

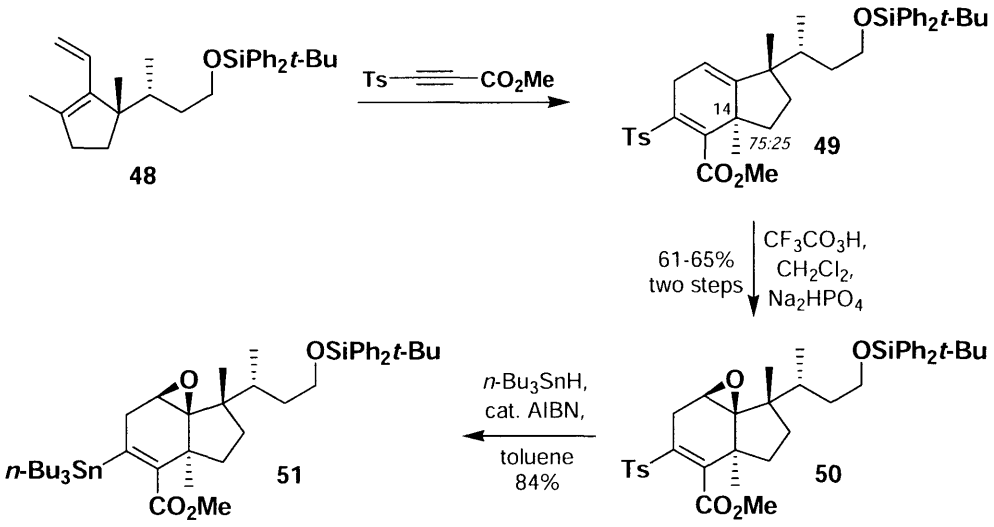
Stille coupling with vinyltributyltin, reduction of the side chain ester, and protection of the resulting alcohol afforded diene **48**.

Scheme 12



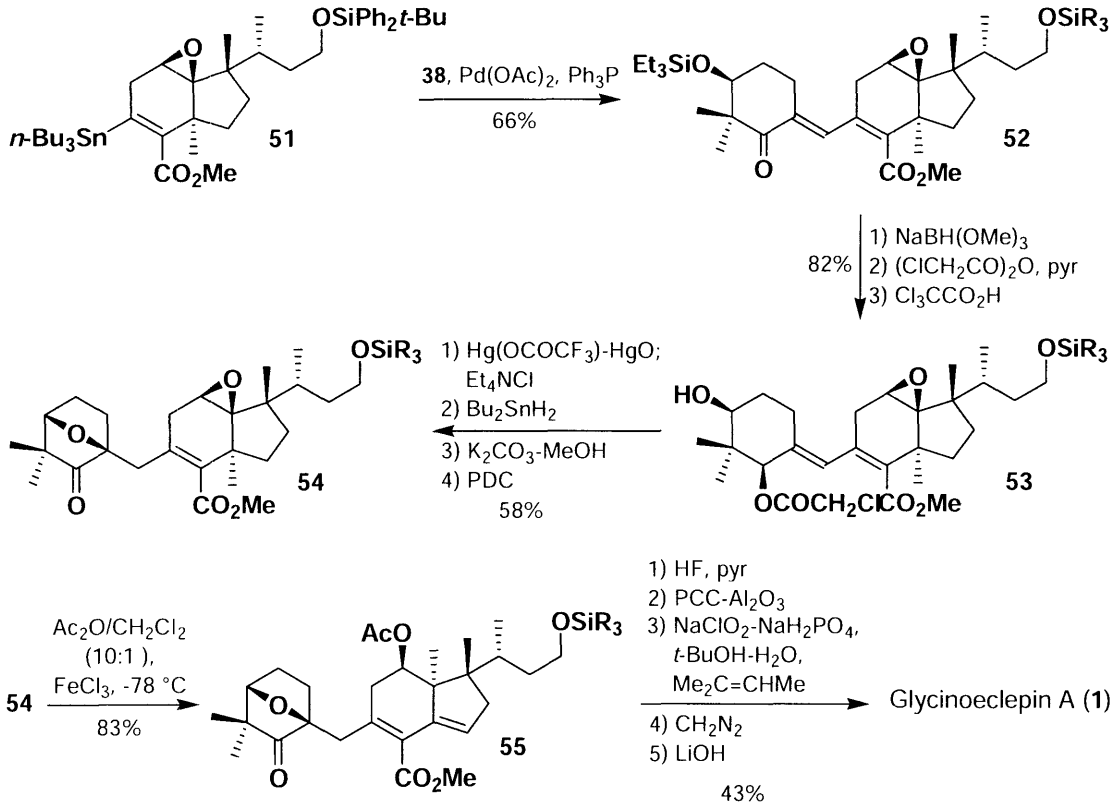
Completion of the CD-ring fragment proceeded in three steps. A Diels-Alder reaction of diene **48** and 3-(*p*-toluenesulfonyl)propiolic acid methyl ester completed the CD-ring skeleton and afforded **49** (75:25 dr at C-14). Epoxidation of the mixture of diastereomers at the trisubstituted double bond, separation of the major adduct **50** by silica gel chromatography, and introduction of the tributylstannyl group yielded **51**, the substrate for the key Stille reaction.

Scheme 13



Palladium-catalyzed Stille coupling of stannane **51** with enol triflate **38** yielded the tetracyclic intermediate **52**. Reduction of the ketone, protection of the alcohol, and removal of the triethylsilyl group gave **53**. An oxymercuration-demercuration reaction followed by deprotection and oxidation of the resulting oxabicyclic ring alcohol afforded compound **54**. Ferric chloride-induced epoxide opening/methyl group migration followed by a series of functional group manipulations then completed the synthesis of glycinoeclepin A.

Scheme 14

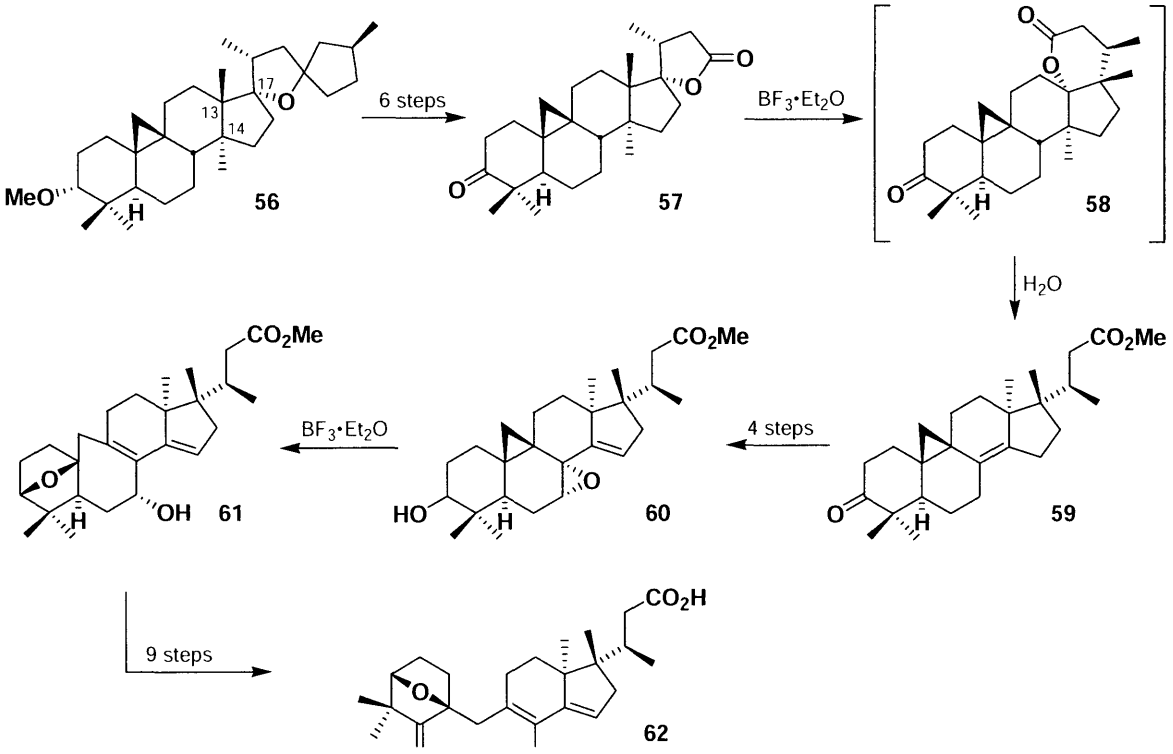


Corey Biomimetic Synthesis

Corey has also completed a biomimetic synthesis of a close derivative of glycinoeclepin A.[23] In this chemical emulation of the natural biosynthesis, Corey was able to convert the naturally occurring spirolactone abietospiran (**56**) into 12-desoxyglycinoeclepin (**62**) in just over 20 steps.

[23] Corey, E. J.; Hong, B.-C. *J. Am. Chem. Soc.* **1994**, *116*, 3149.

Scheme 15



The conversion of **57** to **59** is particularly noteworthy. Treatment of **57** with $BF_3{\cdot}OEt_2$ at 0 °C, followed by slow treatment with water affected sequential double methyl group migration resulted in **59** which possesses the fully-substituted D-ring of glycinoeclepin A. Later in the synthesis, Corey employed $BF_3{\cdot}OEt_2$ for the closure of the oxabicyclic A-ring with concomitant cyclopropane ring opening to afford **61**.

Summary

More work needs to be done in order to fully understand the biological functions and environmental effects of glycinoeclepin A. The lack of an ample source of the compound in nature and the lengthy synthetic routes to the natural product in the laboratory greatly impedes the progress of the research in this area. A more practical and efficient chemical synthesis of this

compound is needed in order to provide a sufficient and reliable source of material for future studies.

Chapter 2

Approaches to the Synthesis of the A-Ring of Glycinoeclepin A

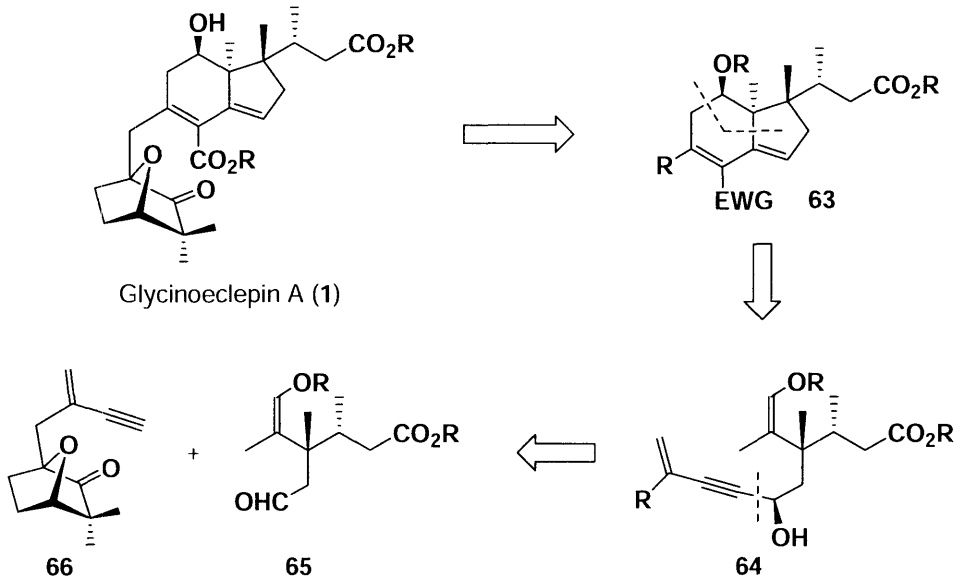
The goal of our research has been to develop a *practical* and *efficient* total synthesis of glycinoeclepin A. Chemical synthesis could provide sufficient quantities of the natural product for further testing and studies on its biological and environmental effects, and would also allow for the possibility of generating a variety of analogs. This chapter will highlight our retrosynthetic analysis and provide an overview of previous research conducted in the Danheiser group.

Retrosynthetic Analysis

We consider a synthetic route to a complex natural product to be practical when it consists of 20 or fewer steps in the longest linear sequence. In order to achieve such efficiency, synthetic convergence is the essential principle. In a disconnection similar to that used in the previous total syntheses (vide supra), we envisioned dividing the target molecule into two roughly equal-sized fragments, **65** and **66**. The core hydrindane system in the CD-ring (**63**) would be assembled via an asymmetric inverse electron-demand intramolecular vinylallene [4 + 2] cycloaddition.[24] The latent vinylallene is envisioned to be derived in situ from propargyl alcohol **64**, which, in turn, should be available from an asymmetric addition of A-ring fragment **66** to the CD-ring precursor **65**.

[24] (a) Huboux, A. H. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June 1995. (b) Martin, M. W. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, February 2000. (c) Okamura, W. H.; Curtin, M. L. *Synlett* **1990**, 1.

Scheme 16



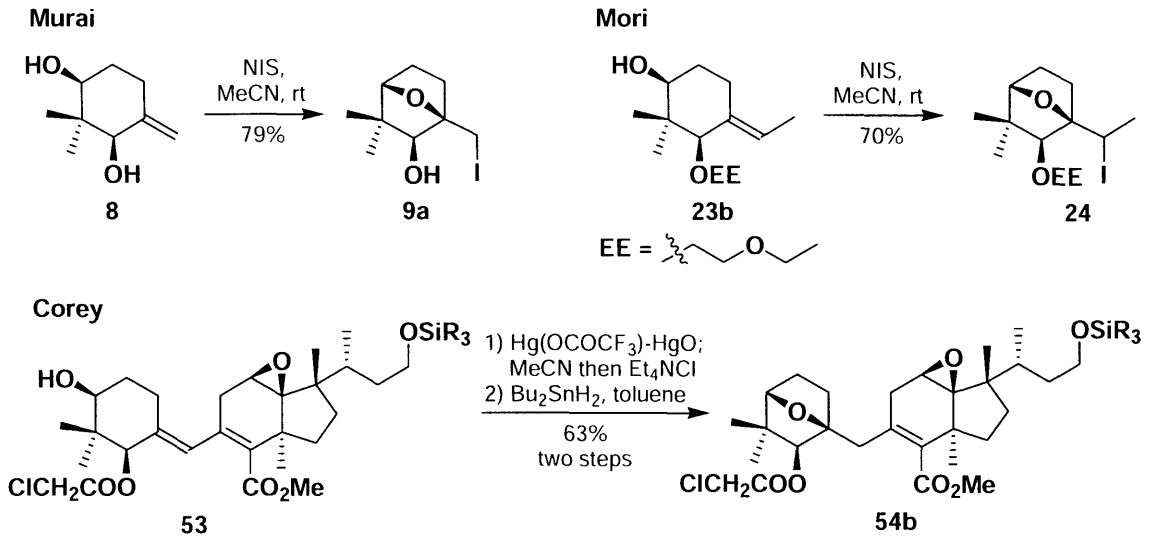
Aldehyde **65**, precursor to the CD-ring system, has been synthesized in a stereoselective manner via a ten-step route by our former group members.[24] In the following section, previous synthetic studies toward the construction of A-ring enyne **66** will be presented.

A prominent feature embedded in A-ring enyne fragment **66** is the 7-oxabicyclo[2.2.1]heptane substructure, which is also found in a number of natural products.[25] Chapter 1 outlined three previous total syntheses of glycinoeclepin A. The strategies used previously in constructing the 7-oxabicyclo[2.2.1]heptane skeleton were similar – transannular-cyclization of the hydroxyl group onto the nascent carbocation generated by reaction of an alkene with either "I^+" (the Murai[19] and Mori[21] syntheses) or by Hg(II) (the Corey[22] synthesis). In the first two syntheses, where the reagent used was *N*-iodosuccinimide (NIS), the initially obtained alkyl iodide product was further elaborated later in the synthesis. In Corey's synthesis, Hg(II)-mediated reaction product was reduced with Bu_2SnH_2.

---

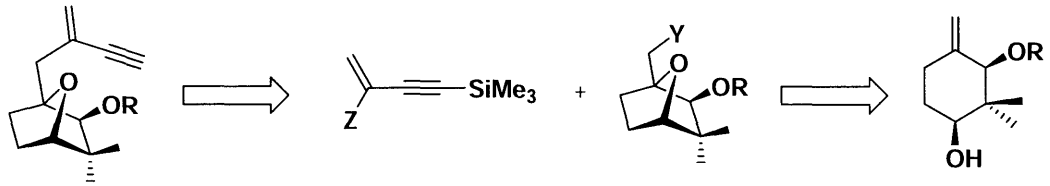
[25] For recent reviews, see: (a) Lautens, M.; Chiu, P. *Topics. Curr. Chem.* **1997**, *190*, 1. (b) Vogel, P.; Cossy, J.; Plumet, J.; Arjona, O. *Tetrahedron* **1999**, *55*, 12521. (c) For a general overview, see: Diffendal, J. M. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, September 2002.

Scheme 17



In our original plan, we envisioned a similar strategy for constructing the bicyclic system in **66** or in the related system **67** with the carbonyl masked as a protected alcohol. We also planned to utilize cross-coupling methodology to install the requisite enyne moiety after formation of the oxabicyclic ring as outlined below.

Scheme 18



68a Z = MgCl, ZnCl
68b Z = $SnBu_3$
68c Z = Cl, Br, I

69a Y = I
69b Y = PdL_n
69c Y = HgCl

A number of routes to access enyne **67** were considered including, in particular the possibility of coupling enynylzinc **68a** with alkyl iodide **69a**. One concern regarding this approach was the possible difficulty in coupling a neopentyl-type alkyl halide such as **69a** since this type of substrate is very sterically hindered. However, this problem has been addressed in

the procedures reported by Scott and coworkers.[26] Their method involves nickel-catalyzed coupling of organozinc compounds with neopentyl iodides, which could prove to be an appropriate tactic for our substrates.

Other possible methods for assembling enyne **67** involve other palladium-catalyzed cross-coupling reactions of appropriate starting materials, for example, the enynylstannane, **68b** with a halide such as **69a** or an organomercury compound such as **69c**. While the intermediate in this approach would be an alkylpalladium compound **69b**, it cannot undergo β-hydride elimination. We also considered the possibility of generating the bicyclic enyne **67** via an oxypalladation reaction of alcohol **8** followed by trapping of the resulting organopalladium intermediate with a vinyl metal species such as stannane **68b**. A concern we had about working with compounds of the type **69** where X is Hg, Pd, or Zn is the stability of these species since they could potentially eliminate the β-alkoxy group to relieve ring strain and regenerate compound **8**. Having identified a number of alternative procedures to construct key intermediate **67**, we focused our efforts on testing the feasibility of each strategy.

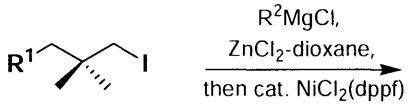
Cross-Coupling Strategies I: Nickel-Catalyzed Coupling

The cross-coupling of neopentyl-type alkyl halides, such as **69a**, is a particularly difficult synthetic problem since the steric hindrance around the electrophilic carbon bearing the halogen atom may render it unreactive toward oxidative addition with the transition metal catalyst. Nonetheless, we believed that by employing the method reported by Scott and coworkers, the cross-coupling of neopentyl-type iodides **69a** with enynyl metal species **68a** might be feasible.[26] As shown in the scheme below, Scott found that when a mixture of neopentyl iodides **70a** and

[26] (a) Yuan, K.; Scott, W. J. *Tetrahedron Lett.* **1991**, *32*, 189. (b) Park, K.; Yuan, K.: Scott, W. J. *J. Org. Chem.* **1993**, *58*, 4866.

70b and $NiCl_2$(dppf) was treated with various organozinc reagents, the desired adducts **71a-e** were obtained in high yield. Unfortunately, the desired product is not formed when vinyl Grignard reagent (Scheme 19, **71f**) is employed; only the reduction product **71** (R^1 = Ph, R^2 = H) is formed in this case.[26a] It was our hope that enynylzinc compounds might prove to be more reactive than simple vinyl derivatives, or that modified conditions could be developed under which the desired coupling would occur.

Scheme 19



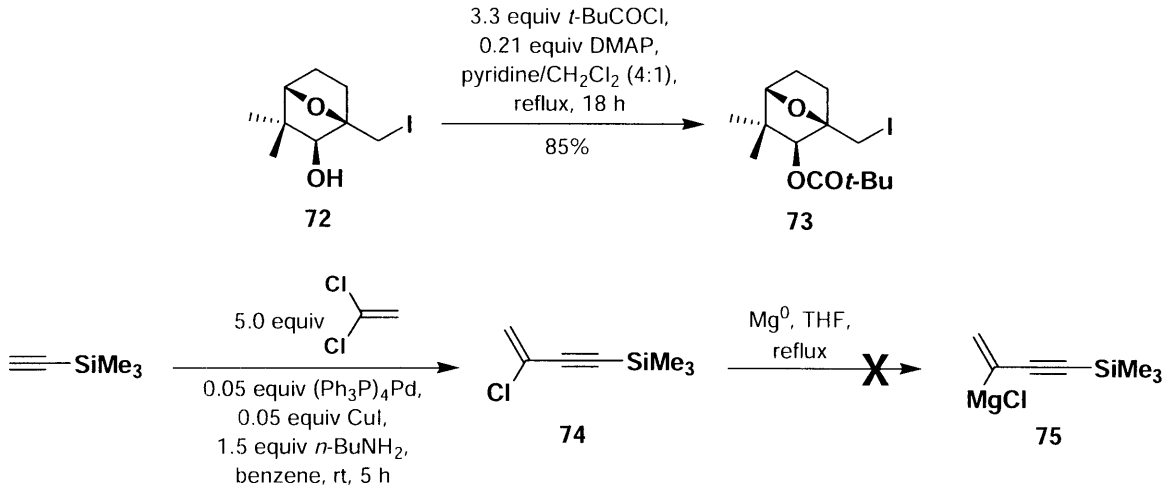
70a R^1 = **Ph**
70b R^1 = ***t*-Bu**

71a R^1 = **Ph**	R^2 = **Me**	83%
71b R^1 = **Ph**	R^2 = **Ph**	81%
71c R^1 = **Ph**	R^2 = ***o*-tol**	83%
71d R^1 = ***t*-Bu**	R^2 = **Ph**	72%
71e R^1 = ***t*-Bu**	R^2 = ***o*-tol**	73%
71f R^1 = ***t*-Bu**	R^2 = **vinyl**	0%

Initial experiments were conducted with iodide **73** and vinylmagnesium chloride **75**.[27] Chloroenyne **74** is available from the cross-coupling of 1,1-dichloroethylene with trimethylsilylacetylene, a procedure which has been previously reported.[28] Iodide **73** can be synthesized from alcohol **72**, an intermediate in Murai's glycinoeclepin A synthesis (vide supra). Unfortunately, all attempts to convert chloride **74** to the corresponding Grignard reagent **75** were unsuccessful. Attempts using activated magnesium turnings[29] or Riecke magnesium both afforded only recovered starting material. Vinyl chlorides are known to be poor substrates for Grignard formation, and for this reason the corresponding bromides are usually employed.

[27] For a discussion of this key transformation, see reference 24(b).
[28] Ratovelomanana, V.; Hammoud, A.; Linstrumelle, G. *Tetrahedron Lett.* **1987**, *28*, 1649.
[29] Magnesium turnings were activated by treatment with 1,2-dibromoethane or by heating under vacuum.

Scheme 20



However, the bromide derivative, corresponding to **74** was not investigated for several reasons. First, 1,1-dibromoethylene is not commercially available and its synthesis is not trivial.[30] Furthermore, we were concerned that the dibromide might not undergo selective coupling to give only the desired monosubstituted enyne corresponding to **74**.[31] These factors, combined with Scott's report that he was unable to effect coupling with vinyl substrates (e.g., **70b** → **71f**), persuaded us to explore alternative strategies.

Cross-Coupling Strategies II: Palladium-Catalyzed Coupling

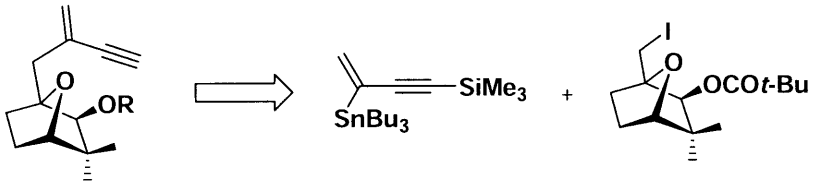
Next, we considered the use of a palladium-catalyzed cross-coupling process for constructing A-ring intermediate **67**. We initially envisioned employing a Stille coupling of iodide **73** with vinylstannane **76**. Stille couplings of alkyl iodides generally suffer β-hydride elimination during the catalytic cycle as transmetalation cannot compete with rapid olefin

[30] The best synthesis of 1,1-dibromoethylene is that reported by Bergman, involving bromination of vinyl bromide to afford 1,1,2-tribromoethylene, followed by treatment with base to effect elimination and provide the desired product as a highly reactive oil. See: Jacobsen, E. N.; Bergman, R. G. *J. Am. Chem. Soc.* **1985**, *107*, 2023.

[31] Linstrumelle has only reported this selective reaction for chlorides (see reference 28). We were concerned that the more reactive dibromide would afford the bis(trimethylsilylacetylene) derivative.

formation.[32] However, since our *neopentyl*-like iodide **73** cannot undergo β-hydride elimination, we speculated that it might be possible to effect the desired coupling reaction. However, in his preliminary investigations of Stille couplings with neopentyl iodide and phenyltrimethylstannane, Matthew Martin recovered both starting materials with only a trace amount (if any) of the desired neopentylbenzene. Consequently, we decided to explore alternative strategies.

Scheme 21



67 **76** **73**

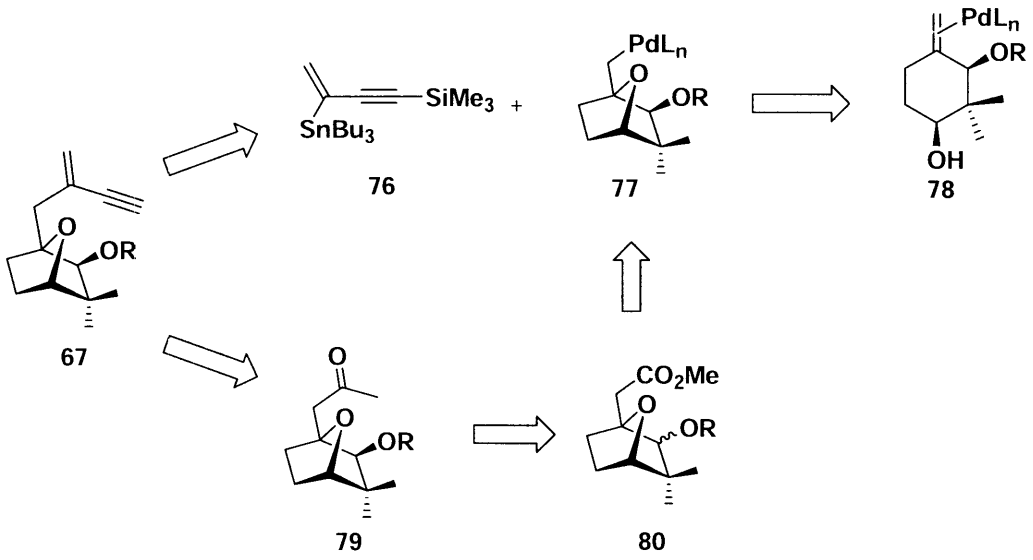
We next decided to focus our efforts on an interesting cross-coupling strategy based on intramolecular oxypalladation.[33] As shown in the retrosynthesis scheme below, treatment of our intermediate **8** with Pd(II) is anticipated to produce palladium-alkene complex **78**. Subsequent nucleophilic addition of the hydroxyl group would afford oxabicylic alkylpalladium species **77**. From this intermediate, a variety of options are available. The most straightforward and convergent route would be an in situ Stille coupling of this species with vinylstannane **76** to provide adduct **67**. Alternatively, bicyclic intermediate **80** could be generated by trapping intermediate **77** with carbon monoxide in the presence of methanol. Methyl ester **80** could then be transformed to **79**, followed by conversion to the corresponding vinyl triflate and Sonogashira

[32] Collman, J.P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.

[33] For reviews, see: (a) Semmelhack, M. F.; Kim, C.; Zang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure Appl. Chem.* **1990**, *62*, 2035. (b) Hosokawa, T.; Murahashi, S.-I. *Acc. Chem. Res.* **1990**, *23*, 49. (c) Hosokawa, T.; Murahashi, S.-I. *Heterocycles* **1992**, *33*, 1079. (c) Hosokawa, T.; Murahashi, S.-I. *J. Synth. Org. Chem., Jpn.* **1995**, *53*, 1009. (d) Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 63. (e) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285.

coupling[34] with trimethylsilylacetylene to afford the desired enyne **67**.

Scheme 22



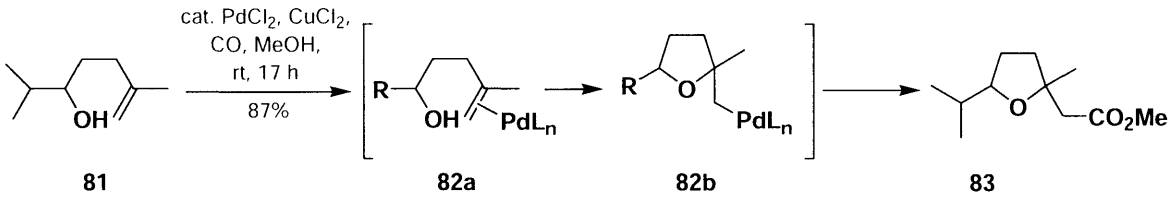
Encouraging precedent for the oxypalladation strategy is available in Semmelhack's work on the syntheses of tetrahydrofurans and tetrahydropyrans via the oxypalladation–carbonylation sequence of simple alkenyl alcohols.[35] For example, treatment of alcohol **81** with cupric chloride and palladium(II) chloride in methanol under an atmosphere of carbon monoxide provides alkenylpalladium intermediate **82a** and subsequently **82b**. Ester **83** then forms via subsequent CO insertion. The example shown below was particularly applicable to our work as it involves the formation of the quaternary center and provides ester **83** which corresponds to potentially useful intermediate ester **80**.

---

[34] For recent reviews on palladium-catalyzed alkynylations, see: (a) Sonogashira, K. Sonogashira Alkyne Synthesis. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; Wiley-Interscience: New York, 2002; Vol. I, p 493. (b) Negishi, E.; Xu, C. Palladium-Catalyzed Alkynylation with Alkynylmetals and Alkynyl Electrophiles. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; Wiley-Interscience: New York, 2002; Vol. I, p 531. (c) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.

[35] Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496.

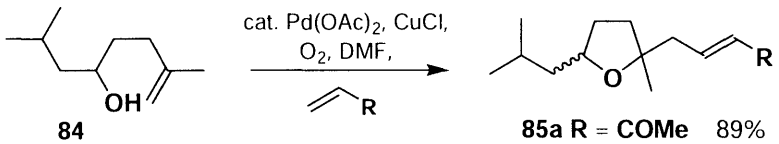
Scheme 23



81 **82a** **82b** **83**

In addition to Semmelhack's tandem oxypalladation–carbonylation, a tandem oxypalladation–vinylation procedure has also been reported.[36] In this reaction, the intermediate alkenylpalladium species is trapped with an alkene and undergoes an in situ Heck reaction to provide a substituted tetrahydrofuran. The process is limited to substrates which cannot undergo β-hydride elimination.

Scheme 24



84

85a R = COMe 89%
85b R = CO_2Me 82%
85c R = Ph 85%

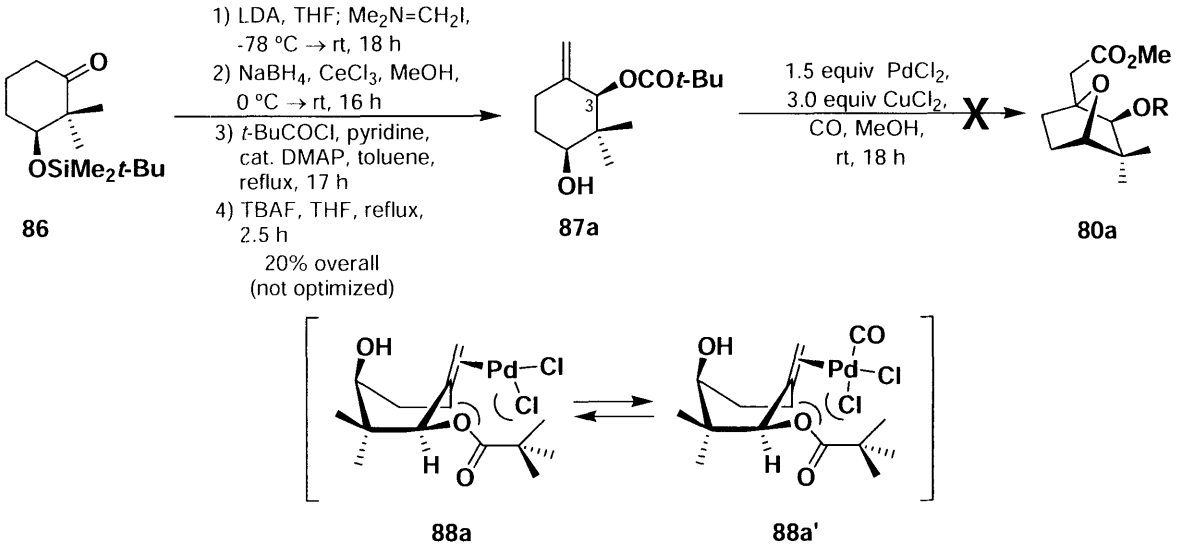
This particular method was of interest to us since it is directly related to our convergent Stille strategy. It was our hope that substitution of the alkene with a vinylstannane could effect a tandem oxypalladation–Stille coupling.

Martin's initial experiments using Semmelhack's conditions were performed with alcohol **87a** which was synthesized in three steps from silyl ether **86**.[37] A solution of **87a** in methanol was treated with palladium(II) chloride and cupric chloride and stirred at room temperature for 18 h under an atmosphere of carbon monoxide; however, in the event we found that no reaction took place. Heating the reaction mixture to 60 °C did not promote the reaction. The scheme

[36] Semmelhack, M. F.; Epa, W. R. *Tetrahedron Lett.* **1993**, *34*, 7205.
[37] Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 273.

below illustrates the presumed conformations of intermediate **88a** and **88a′** which are involved in the formation of the oxabicyclic ring system.[38] In this conformation, a potential steric interaction between the ligands on the palladium and the pivaloyl-protected alcohol is present, and this interaction may have prevented the reaction from taking place.

Scheme 25

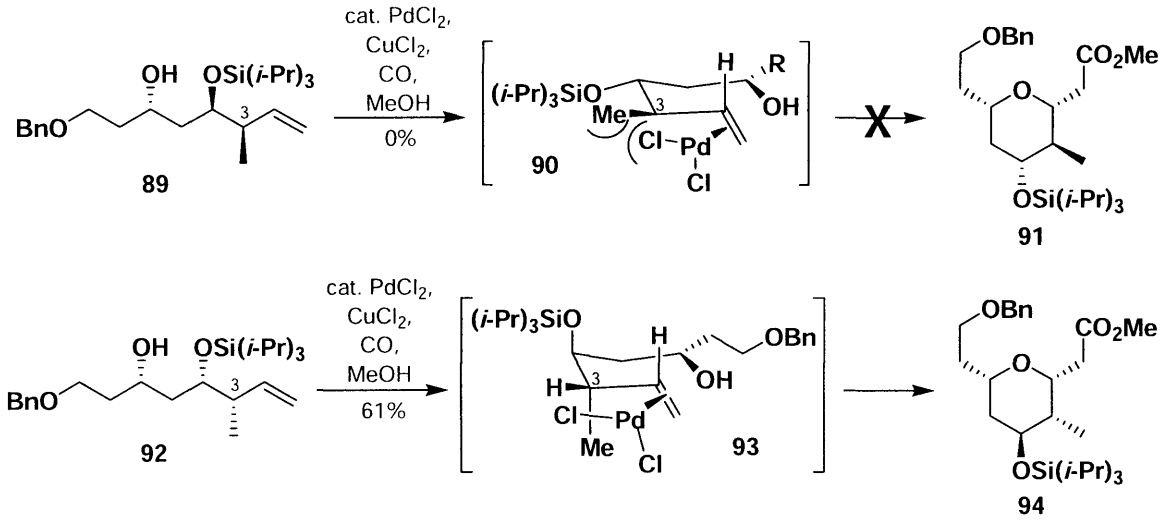


White has also reported similar results.[39] In his work on the tandem oxypalladation-carbonylation of 6-hydroxy-1-octenes, White has shown that yields of the products were dependent upon the configuration of substituents in the starting materials. Specifically, attempted reaction of alkoxy alcohol **89** results in no reaction, while **92** affords a 61% yield of the desired adduct even though the other product (**91**) in which all substituents are equatorial should be more stable than **94** (two axial substituents). White rationalized these results by considering the structure of the presumed intermediates **90** and **93.** In intermediate **90**, there is the possibility of a severe steric interaction between the ligands on palladium and the C-3 methyl group, which is in a pseudo-equatorial position. However, this interaction is absent in

[38] It is not clear if the cyclization proceeds via tri- or tetra-coordinate palladium.
[39] White, J. D.; Hong, J.; Robarge, L. A. *Tetrahedron Lett.* **1999**, *40*, 1463.

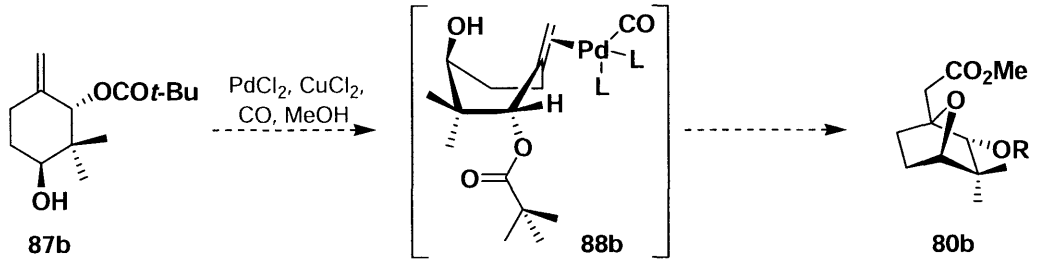
intermediate **93**.

Scheme 26



Presumably, this steric interaction in our substrate (as in **88a**) could be overcome by inverting the configuration of the pivaloyl-bearing carbon (C-3 in **87b**). The steric interaction seen in **88a** would be minimized or absent and reaction should afford the desired product **80b**. However, the uncertainty of finding a suitable reducing agent and lack of progress in synthesizing the A-ring combined with a desire to test the key alkynylation and rearrangement-cycloaddition steps on the actual substrates led us to temporarily abandon the investigation of the cross-coupling strategy.

Scheme 27



The First-Generation Synthesis of the A-Ring Enyne

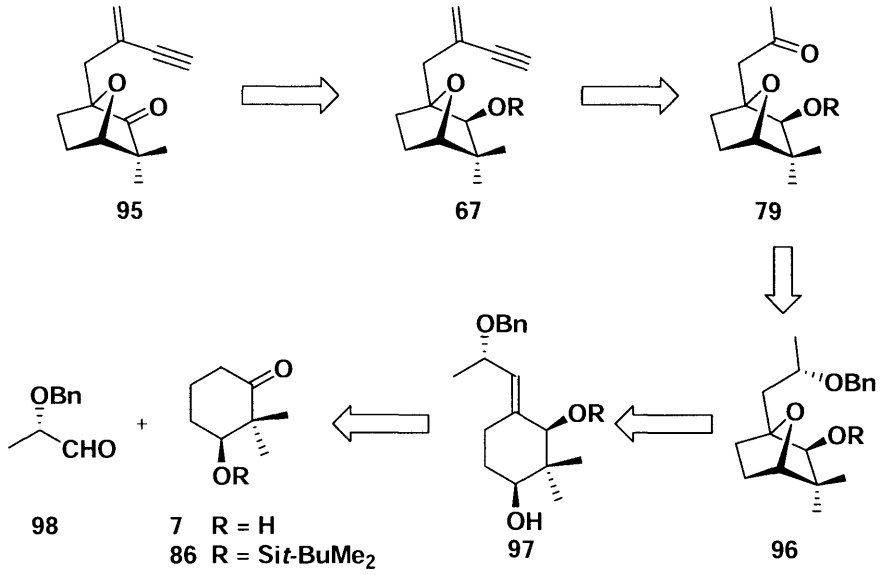
Since we abandoned the cross-coupling route to the A-ring enyne, we set out to find another efficient route to access material for the key vinylallene cycloaddition.

Dr. Christophe Mellon developed the retrosynthetic plan shown in the scheme below which led to our successful "first-generation" synthesis of A-ring enyne **95**. The actual target molecule for this synthetic strategy was protected alcohol **67**. We envisioned that deprotection of the alcohol and oxidation to the ketone would take place after the key rearrangement-cycloaddition step, concurrent with other functional group transformations required for completion of the synthesis.

According to this strategy, we planned to install the enyne moiety via a Sonogashira coupling of the vinyl triflate generated from ketone **79** with trimethylsilylacetylene. A key oxymercuration–demercuration protocol was planned for conversion of intermediate **97** to the oxabicyclic intermediate **96**. Key intermediate **97** could, in turn, be assembled via an aldol reaction between cyclic ketone **86** and an aldehyde containing a masked carbonyl group in the α-position. This masked carbonyl would be unmasked after the oxymercuration–demercuration sequence to provide methyl ketone **79**. The known β-alkoxy aldehyde **98** was selected because it is readily available in 3 steps from commercially available ethyl lactate according to the protocol reported by Heathcock.[40]

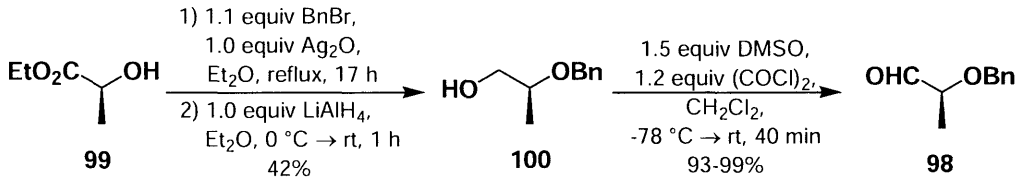
[40] Takai, K.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 3247.

Scheme 28



Thus, protection of alcohol **99** as the benzyl ether using silver(II) oxide-promoted etherification with benzyl bromide, followed by reduction of the ester to the alcohol with lithium aluminum hydride, afforded **100** in 42% yield over two steps. Swern oxidation proceeded in excellent yield to afford aldehyde **98** necessary for the aldol reaction.

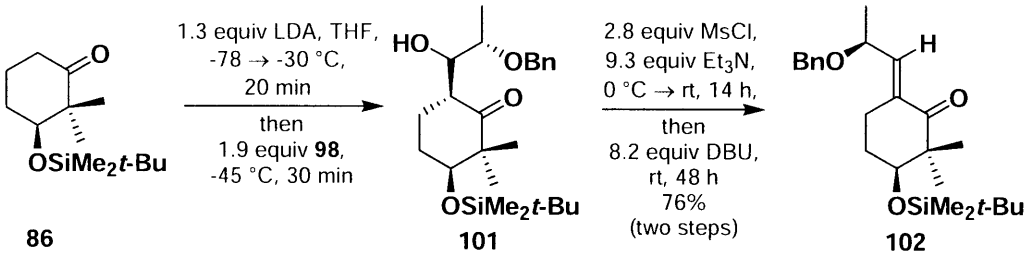
Scheme 29



Aldol reaction between aldehyde **98** and ketone **86** (available in one step from alcohol **7**) followed by in situ dehydration of the aldol adduct afforded a mixture of products from which enone **102** could be isolated in 36% yield. Optimal conditions for this sequence of reactions was later developed by Dr. Yoshinori Ikeura. By performing this sequence of reactions in two separate steps (i.e. aldol reaction followed by formation of the corresponding mesylate and DBU-assisted elimination) the yield of enone **102** could be improved to 76% over two steps.

Under these optimized conditions, enone **102** was formed exclusively as the (*E*)-isomer as determined by ^{1}H NMR analysis.[41]

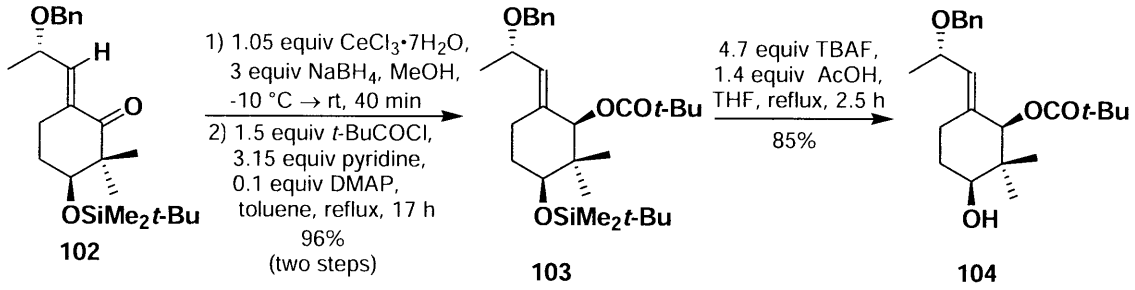
Scheme 30



86 **101** **102**

Enone **102** was next converted to alcohol **104** by a three-step sequence. Reduction of the ketone carbonyl was accomplished following the Luche protocol[42] to yield the expected allyl alcohol. Protection of the alcohol by esterification with pivaloyl chloride afforded **103** in 96% yield over two steps. Cleavage of the silyl ether with TBAF and acetic acid in refluxing THF then gave the 4-alkylidenecyclohexanol **104** in 85% yield.

Scheme 31



102 **103** **104**

As outlined below, intramolecular oxymercuration with mercury(II) oxide and mercury(II) trifluoroacetate followed by in situ demercuration of the organomercurial intermediate with sodium borohydride provided the desired oxabicyclic compound **105** in 83%

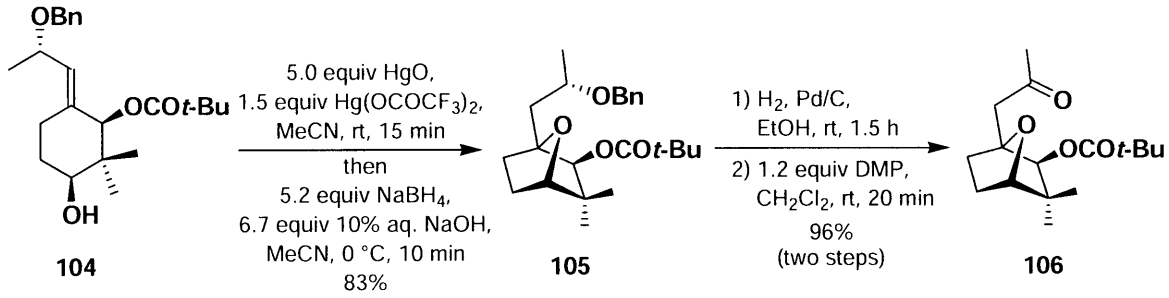
---

[41] In preliminary experiments, a mixture of (*E*)- and (*Z*)-isomers was obtained. ^{1}H NMR analysis of the two isomers revealed that the C-7 vinyl protons appear at 6.4 ppm and 5.6 ppm for the major and minor isomers, respectively. The downfield shift for the vinyl proton in the major isomer results from its orientation in the deshielding region of the adjacent carbonyl group. The major isomer was therefore assigned the (*E*)-configuration.

[42] (a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

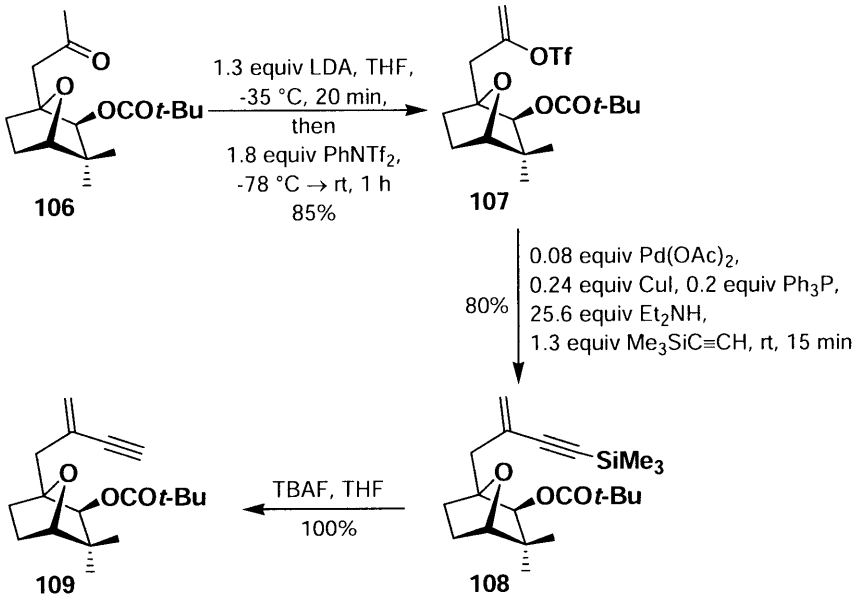
yield. Debenzylation and Dess–Martin oxidation of the resulting alcohol then provided ketone **106** in excellent yield.

Scheme 32



Formation of vinyl triflate **107** and Sonogashira coupling with trimethylsilylacetylene then afforded the desired silyl enyne **108**. Desilylation of **108** under standard conditions with TBAF in THF furnished enyne **109** in quantitative yield. This compound (**109**) was used in initial studies of the tandem propargylic rearrangement-intramolecular vinylallene Diels–Alder reaction.

Scheme 33



Summary

The three published synthetic routes for construction of the A-ring portion of glycinoeclepin A laid the groundwork for our attempts in synthesizing this fragment. Subsequent efforts by Dr. Christophe Mellon and Dr. Yoshinori Ikeura in our group have resulted in the development of a 12-step route to this required fragment for our initial studies in our key tandem propargylic rearrangement–vinylallene cycloaddition. Our first-generation route employed oxymercuration–demercuration methodology as the key step in building the oxabicyclic core.

The next part of this thesis will detail the results of a collaborative effort by former group member Jason Diffendal and myself to develop a more efficient route to the A-ring enyne fragment which involves a novel acid-catalyzed transannular Michael addition. The post-cyclization manipulations of functional groups to access the enyne and our initial studies of alternative routes for the construction of the CD-ring system of glycinoeclepin A will also be presented.

Part II

Results and Discussion

Chapter 1

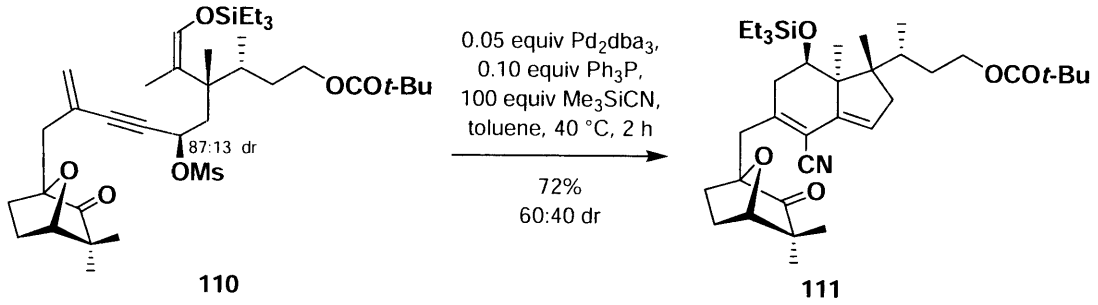
New Approaches to the Synthesis of an A-Ring Intermediate

Although the 13-step route to A-ring enyne **109** developed previously in our lab supplied us with materials for the study of the key tandem propargylic rearrangement–intramolecular vinylallene Diels–Alder reaction, the synthesis was rather lengthy and was not regarded as efficient enough for our total synthesis. Therefore, the development of a more practical synthesis of A-ring enyne **109** was desirable. A number of alternatives were envisioned to construct A-ring fragment **109** more efficiently. These included streamlining the "first-generation" route and changing some of the tactics employed in the original approach (vide infra).

A Modified Rearrangement–Cycloaddition Strategy: The Need for a Different A-Ring Intermediate

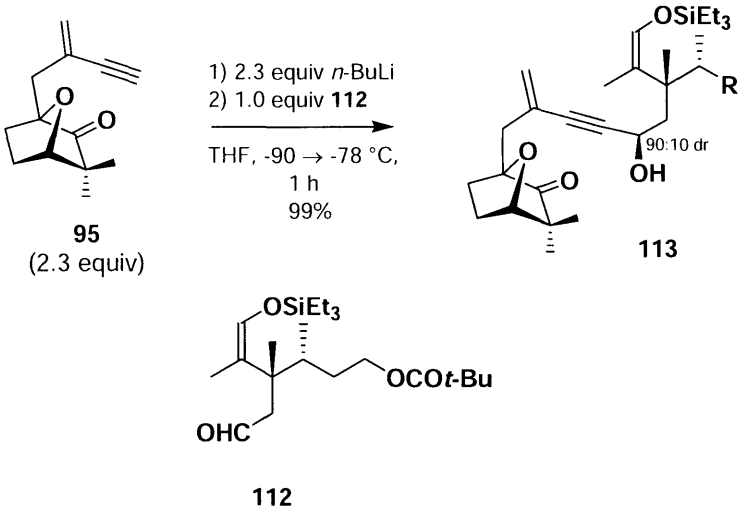
As shown in Scheme 34, considerable experimentation in our studies of the propargylic rearrangement–cycloaddition reaction has led to the optimal conditions for this step which involved using mesylate **110**. Additional studies are planned to further improve the stereoselectivity of this reaction.

Scheme 34



These studies on the key rearrangement–cycloaddition step identified the propargylic alcohol **113**, the precursor to mesylate **110**, as our key A-ring intermediate. Alcohol **113** could be obtained with good diastereoselectivity via a substrate-controlled addition of the lithium acetylide derived from ketone **95** to aldehyde **112**. Upon purification of alcohol **113**, excess enyne **95** could also be recovered in 95% yield. In model studies, we had previously developed a reagent-controlled addition procedure for this step based on the Corey asymmetric alkynylation reaction.[43] Thus it is likely that an even better ratio of isomers could be achieved if desired in this step by employing double asymmetric synthesis.

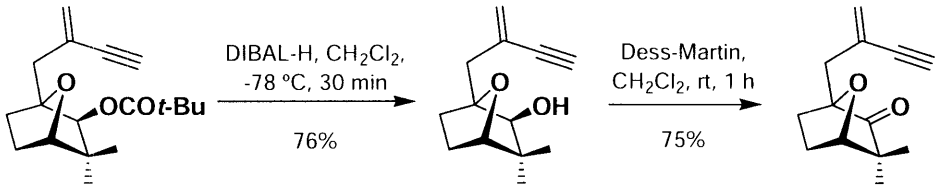
Scheme 35



In our previous studies, ketone **95** was obtained from intermediate **109** by the two-step sequence shown in Scheme 36. This route was only used because at the time, a considerable supply of **109** was in hand. Overall, the preparation of enyne **95** by this approach entailed 13 steps beginning with ketone **86**. A shorter route was clearly needed.

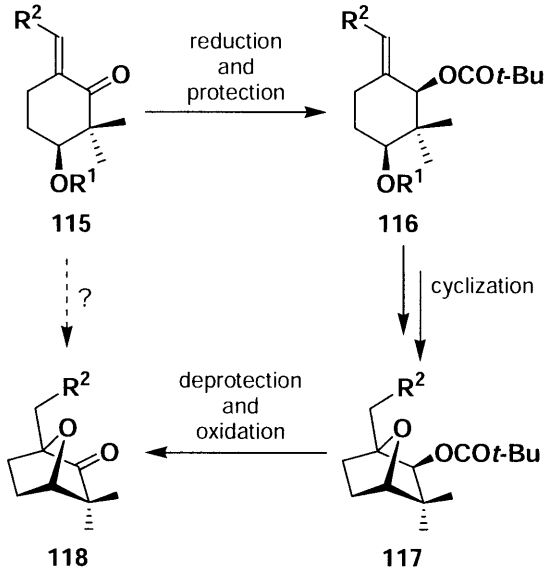
[43] Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151.

Scheme 36



As shown in Scheme 37, a new strategy was required to access a ketone of type **118** by bypassing the total of four unnecessary steps before and after cyclization.[44]

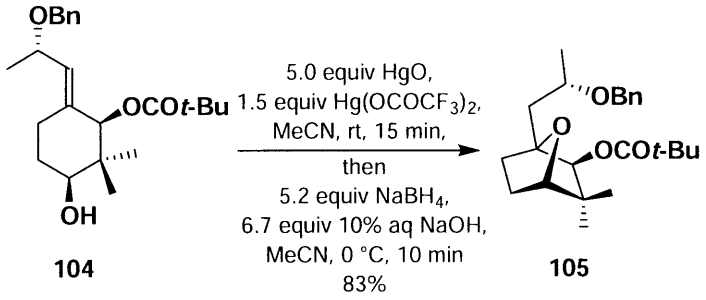
Scheme 37



The new plan for the construction of the oxabicyclic system of **118** called for a direct and efficient cyclization of an α,β-unsaturated ketone intermediate of type **115** (R^1 = H). Our previous cyclization of a related alcohol **104** had been promoted by a Hg(II) salt in an electrophilic cyclization process (Scheme 38).

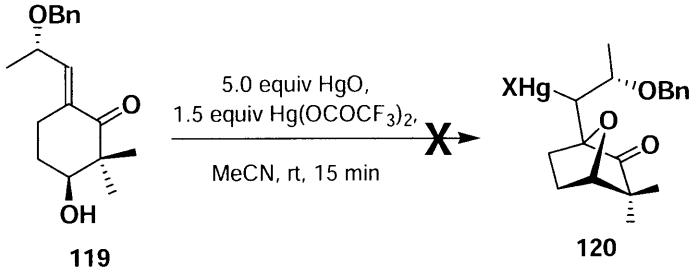
[44] For a detailed discussion, see p 177, Diffendal, J. M. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, September 2002 (reference 25(c)).

Scheme 38



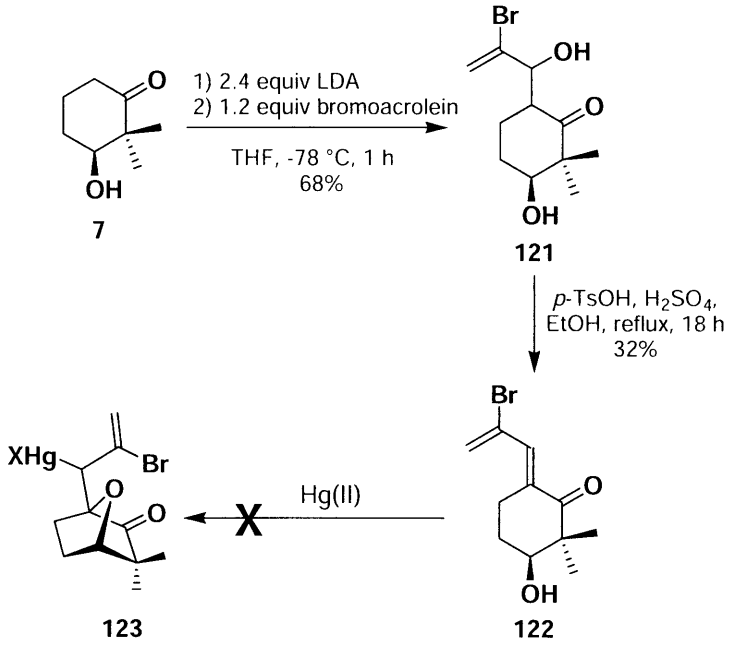
However, it was found that this process could not be performed successfully with enone **119**, presumably due to the electron-withdrawing effect of the carbonyl group (Scheme 39). Other electrophiles, such as Br_2, I_2, and NIS also failed to promote the desired transformation, with only starting material recovered in each case.

Scheme 39



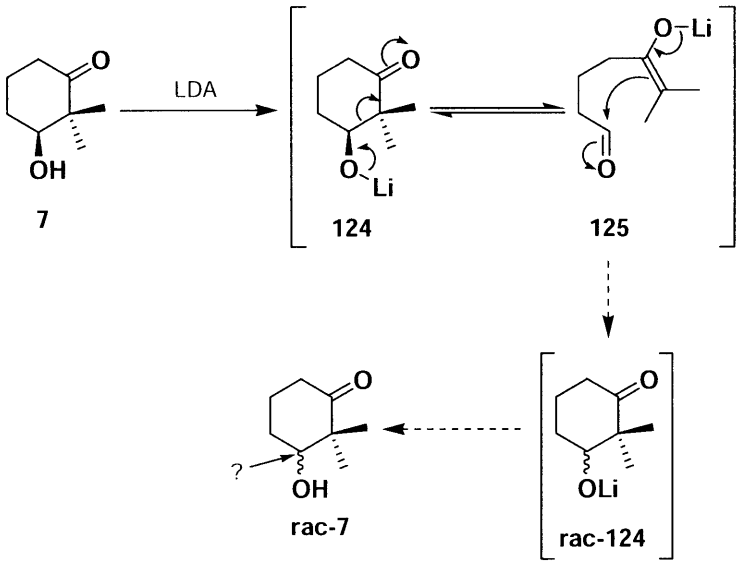
Former group member Dr. Hiroshi Shinokubo studied the oxymercuration reaction of bromo enone **122** and found that the desired cyclization does not take place. However, in these studies he discovered that alcohol **121**, the precursor to **122**, could be synthesized via an aldol reaction of β-ketol **7** with bromoacrolein in 68% yield (Scheme 40).

Scheme 40



This result was significant since no products resulting from retro-aldol reaction of the lithium salt of alcohol **7** were observed as byproducts of this reaction. This indicated that the hydroxyl group in alcohol **7** might not need protection during the aldol condensation step. However, the absence of acyclic cleavage products did not mean that the retro-aldol reaction did not occur since it was possible that retro-aldol cleavage could have occurred to give enolate **125**, which then recyclized in a non-selective fashion to produce **rac-124**, thus compromising the stereochemical integrity of the starting material, alcohol **7** (Scheme 41).

Scheme 41



As the aldol reaction of alcohol **7** would later become a method we relied on in our construction of the oxabicyclic system (vide infra), we decided to investigate the stereochemical integrity issue to ensure that the stereochemistry of alcohol **7** was preserved after aldol reaction. Toward this end, the enantiomerically enriched alcohol **7** was first converted to the corresponding α-methoxy-α-trifluoromethylphenylacetate ester **126** (MTPA, "Mosher's" ester[45,46]), the diastereomeric ratio of which was measured by GC analysis[47] to be >99:1. Alcohol **7** was next subjected to 1.1 and 2.2 equiv of LDA and the crude alcohol was recovered and converted to the corresponding MTPA ester (**126**). In both cases, the diastereomeric ratio as determined by GC analysis was found to be ca. 99:1. On this basis, we concluded that the retro-aldol process did not occur to any appreciable extent during the reaction. This investigation is summarized in Scheme 42.

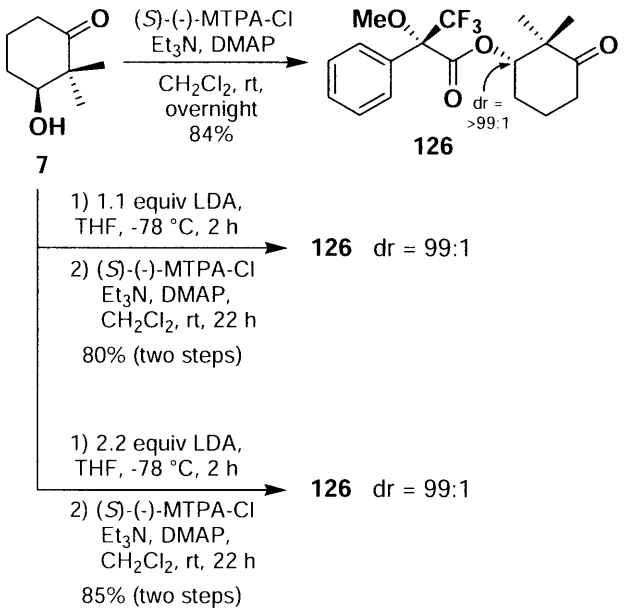
---

[45] (*S*)-(-)-MTPA acid was first converted to the corresponding acid chloride by treatment with $(COCl)_2$/DMF in hexane at room temperature for 1 h.

[46] Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.*, **1969**, *34*, 2543.

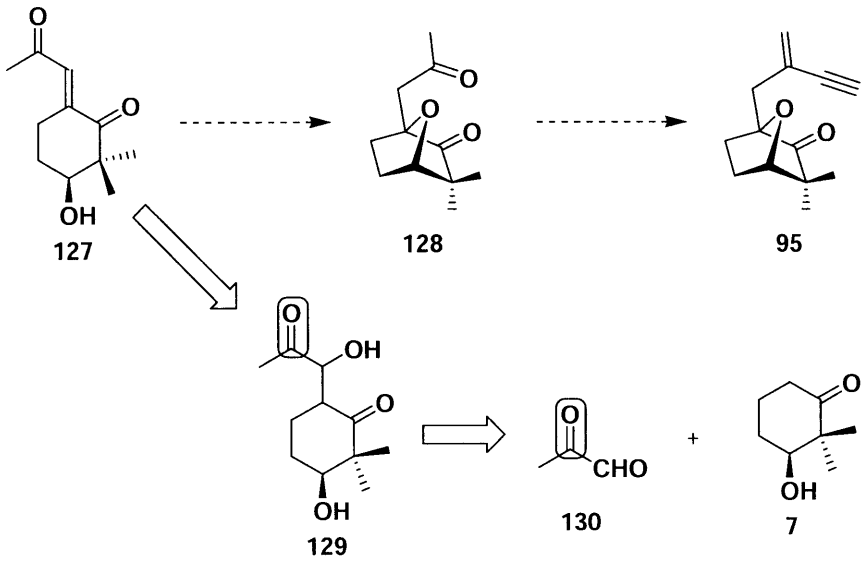
[47] HP-5 (Crosslinked 5% PH ME Siloxane) column; Length: 30 m; Inner diameter: 0.32 mm. Initial temperature: 50 °C hold for 2 min, then increase at a rate 10 °C /min to 150 °C, then increase at a rate 20 °C /min to 230 °C and hold at 230 °C for 10 min.

Scheme 42



Further consideration of cyclization strategies for the construction of the oxabicyclic A-ring intermediate led us to the plan outlined in Scheme 43 involving cyclization of enedione **127**. In contrast to the previously investigated electrophilic cyclization approaches, this cyclization strategy utilizes a nucleophilic conjugate addition of the hydroxyl group to the α,β-unsaturated diketone.

Scheme 43



The 1,4-addition of heteroatom nucleophiles to α,β-unsaturated carbonyl compounds is well-known in the literature.[48] A number of examples of the addition of oxygen nucleophiles to α,β-unsaturated enones have been reported.[49] Recent examples include base-[50a], acid-[50b], phosphine-[50c], and rhodium-catalyzed[50d] processes. In addition, the conjugate addition of heteroatom nucleophiles to quinones and related species are well documented.[51] Several examples in the literature demonstrate the feasibility of 1,4-additions of alcohols to enediones.[52]

As illustrated in Scheme 43, we hoped that this approach would overcome the difficulties encountered previously with electrophilic cyclizations involving enones. Cyclization of alcohol

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[48] For an overview of 1,4-additions of oxygen nucleophiles, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: New York, 1992. (b) Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Org. React.* **1995**, *47*, 315.

[49] Berkessel, A. In *Methoden der Organischen Chemie (Houben-Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: New York, 1995; Vol. E21e, p 4818.

[50] (a) Dumez, E.; Rodriguez, J.; Dulcère, J.-P. *J. Chem. Soc. Chem. Commun.* **1997**, 1831. (b) Wabnitz, T. C.; Spencer, J. B. *Org. Lett.* **2003**, *5*, 2141. (c) Kisanga, P. B.; Ilankumaran, P.; Fetterly, B. M.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 3555. (d) Farnworth, M. V.; Cross, M. J.; Louie, J., *Tetrahedron Lett.* **2004**, *45*, 7441.

[51] Ulrich, H.; Richter, R. In *Methoden der Organischen Chemie (Houben-Weyl)*, 4th ed.; Müller, E., Ed.; Verlag: Stuttgart, 1977; Vol. VII/3a, p 660.

[52] (a) Burke, S. D.; Letourneau, J. J.; Matulenko, M. A. *Tetrahedron Lett.* **1999**, *40*, 9. (b) Smith, A. B.; Fukui, M. *J. Am. Chem. Soc.* **1987**, *109*, 1269. (c) Sachchar, S. P.; Tripathi, N. N.; Singh, A. K. *Indian J. Chem., Sect. B.* **1987**, *26*, 493.

127 should furnish the oxabicyclic ketone **128**, which we envisioned could be elaborated further to enyne **95** by employing a strategy analogous to that used in the first generation route to this compound (i.e., vinyl triflate formation, Sonogashira coupling, and desilylation; Scheme 33, p 46).

As outlined in Scheme 43, we planned to access enedione **127** through diol **129**, which should be available via an aldol reaction between alcohol **7** and aldehyde **130** with a masked ketone carbonyl group. In our initial studies, we used a racemic mixture of alcohol **7** (**rac-7**) because it is more convenient to prepare, and enantiomeric enrichment is not required for studies of the subsequent transformations. We initially focused our attention on the use of methacrolein as the aldehyde intermediate **130**. Aldol reaction of **rac-7** with methacrolein furnished diol **131**. Ozonolysis of **131** to unmask the carbonyl group provided diol **132**. A close examination of each of the ^{1}H NMR spectra of **131** and **132** revealed a mixture of at least two different diastereomers. No attempt was made to assign the relative stereochemistry of either **131** or **132** since the new stereocenters will be lost during the formation of enedione **127**.

The aldol reaction typically proceeds in 80-90% yield without complete conversion of alcohol **rac-7**, which is difficult to separate from product **131**. Therefore, the crude product from the first step is subjected to ozonolysis to afford diol **132** in 52-56% yield over two steps[53] and **rac-7** can be recovered during the purification process (Scheme 44). It should be noted that at least 3.0 equiv of LDA and 2.0 equiv of methacrolein are necessary for the good overall yield of compound **132**.

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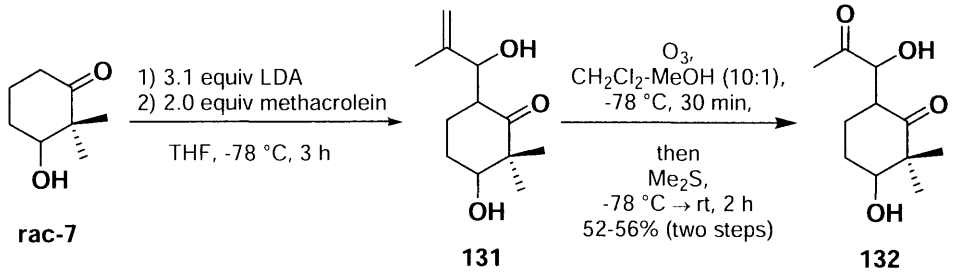
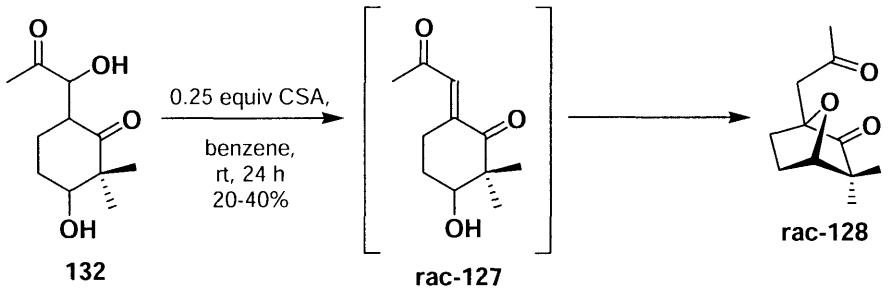
[53] Jason Diffendal reported to have obtained diol **132** in 65% yield over two steps from **rac-7**, see pp 269-271, Diffendal, J. M. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, September 2002 (reference 25(c)).

Scheme 44



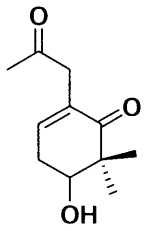
Exploratory work by Jason Diffendal on the elimination and cyclization of **132** led to the important discovery that treatment of **132** with camphorsulfonic acid in benzene at room temperature leads directly to the desired dione **128**, presumably via the intermediacy of enedione **127**.

Scheme 45

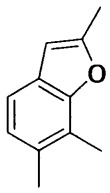


Upon careful purification of the reaction mixture, byproducts **133** and **134** were also isolated in varying amounts depending upon the reaction conditions (e.g., type and amount of acid, solvent, concentration, and temperature).[54] These two byproducts were characterized by NMR and IR analyses.

[54] For a complete account, including mechanistic studies, see pp 185-192, Diffendal, J. M. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, September 2002 (reference 25(c)).



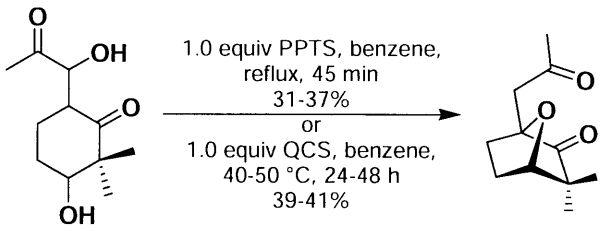
133



134

After extensive optimization work, it was found that the highest and most consistent yields are obtained when starting material **132** is added to a *solution*[55] of 1.0 equiv of pyridinium *p*-toluenesulfonate (PPTS) or quinolinium camphorsulfonate (QCS) in benzene such that the concentration of substrate in the reaction solution is maintained at 0.03-0.05 M. In the case of PPTS, the reaction is heated at reflux for 45 min to 1 h, whereas in the case of QCS, the reaction is heated at 40-50 °C for 24-48 h. In addition, when QCS is employed as the acid catalyst the reaction generally appears cleaner by TLC and crude product is easier to purify. The optimal conditions are summarized in Scheme 46.

Scheme 46



132

rac-128

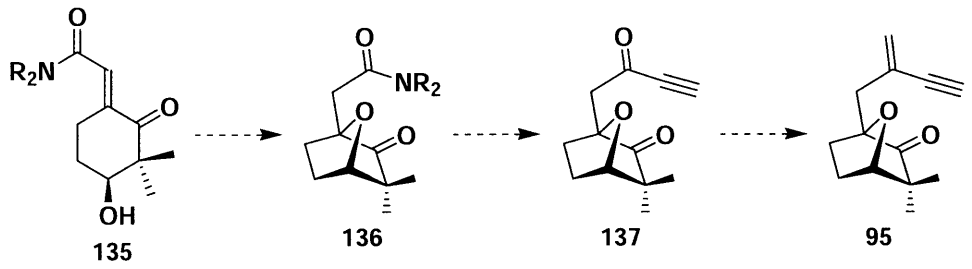
Alternative Approaches to A-ring Enyne 95

Concurrent with our studies of routes based on bicyclic dione **128**, we also investigated alternative strategies involving other precursors to the desired enyne. For example, we hypothesized that the use of amide **136** instead of methyl ketone **128** could eliminate the need to

[55] Note that the acid should be added to benzene and heated at reflux to obtain a homogeneous solution before the substrate is added. See Experimental Section for more details.

form the corresponding vinyl triflate, as addition of lithium acetylide to amide **136** could provide ynone **137**, which could then be olefinated[56] under a variety of conditions.

Scheme 47



The aforementioned amide strategy was examined using glyoxylic amide **141** (Scheme 48),[57] which was expected to function similarly to a Weinreb amide[58] for acetylide addition. We first planned to access amide **141** via a two-step procedure beginning with fumaryl chloride, as shown in Scheme 48. Addition of fumaryl chloride to excess morpholine provides the corresponding bis-amide (**139**). Subsequent ozonolysis did not provide amide **141** under the reaction condition; instead hemiacetal **140** was obtained in 68% overall yield.[59] In the case of **140**, the equilibrium lies on the side of the hemiacetal as is often the case for 1,2-dicarbonyl compounds.

---

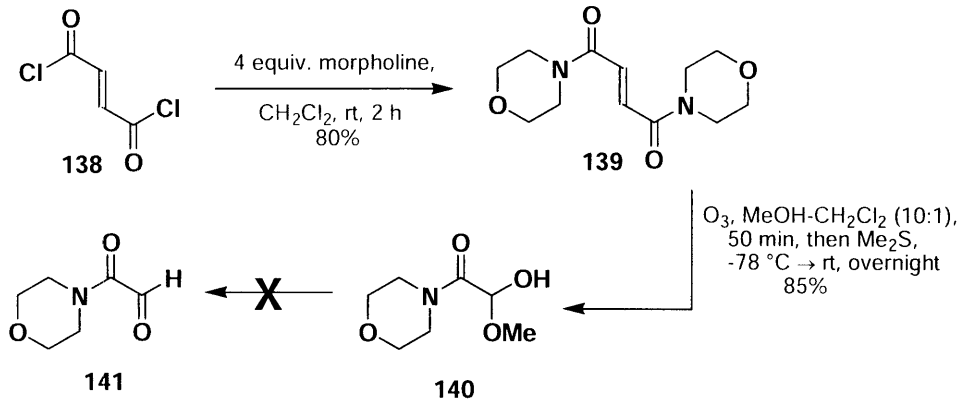
[56] For an example of the construction of an enyne via olefination of an ynone, see: Hoffmann, H. M. R.; Krumwiede, D.; Mucha, B.; Oehlerking, H. H.; Prahst, G. W. *Tetrahedron* **1993**, *49*, 8999.

[57] For a recent example of the use of glyoxylic amide derivatives as electrophiles, see: Kiegiel, K.; Jurczak, J. *Tetrahedron Lett.* **1999**, *40*, 2009.

[58] Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

[59] For a recent example of the synthesis of the hemiacetal of a glyoxylic amide derivative, see: (a) Bauer, T.; Jezewski, A.; Chapuis, C.; Jurczak, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1385. (b) Meester, W. J. N.; van Dijk, R.; van Maarseveen, J. H.; Rutjes, F. P. J. T.; Hermkens, P. H. H.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2909. (c) Parhi, A. K.; Franck, R. W. *Org. Lett.* **2004**, *6*, 3063.

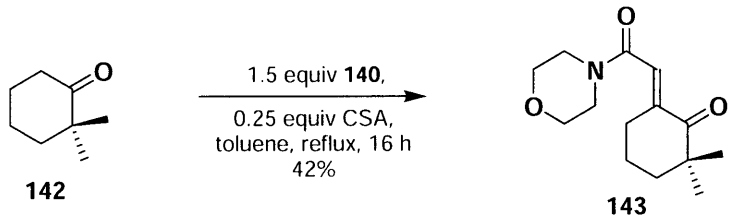
Scheme 48



When we attempted ozonolysis of bis-amide **139** without methanol in order to prevent the formation of hemiacetal **140**, a complex mixture of compounds was obtained. Analysis of the mixture by ^{1}H NMR indicated that the mixture contained an aldehyde, presumably the desired amide **141**, in relatively small amount compared to other products. We also studied the use of hemiacetal **140** as a precursor to amide **141**. When hemiacetal **140** was subjected to heat under vacuum or azeotropic conditions in benzene to remove methanol from the molecule, only the starting material was recovered. Catalytic sodium hydride and 4-Å molecular sieves were also utilized to facilitate the process but none of the desired amide **141** could be efficiently produced and only the starting material was recovered. The resistance to form amide **141** was probably due to the higher stability of hemiacetal **140**.

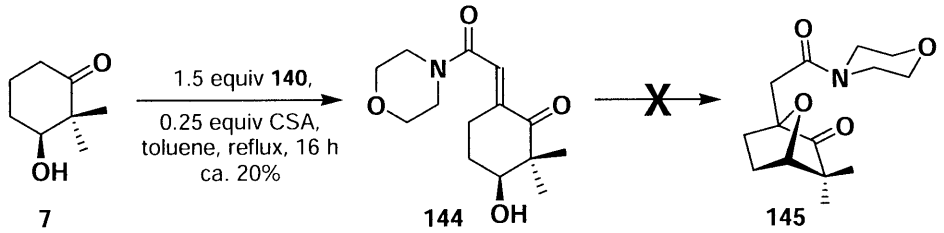
Since we could synthesize hemiacetal **140** in good yield, we decided to examine an alternative approach based on the acid-catalyzed aldol reaction of the hemiacetal. A model reaction using cyclic ketone **142** afforded the aldol condensation product **143** in 42% yield (Scheme 49). We hoped that acid-catalyzed condensation of **140** with keto alcohol **7** would produce intermediate **144** that would then cyclize to furnish bicyclic amide **145** directly.

Scheme 49

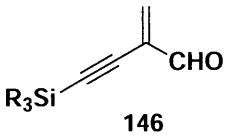


As shown in Scheme 50, aldol condensation of alcohol **7** with hemiacetal **140** afforded **144** in disappointingly low yield. No cyclization product **145** was observed, and subsequent attempts to effect the cyclization to afford bicyclic amide **145** met with failure. Apparently, the amide functionality, which is not as electron-withdrawing as a ketone, is not sufficiently electrophilic for the desired conjugate addition.

Scheme 50

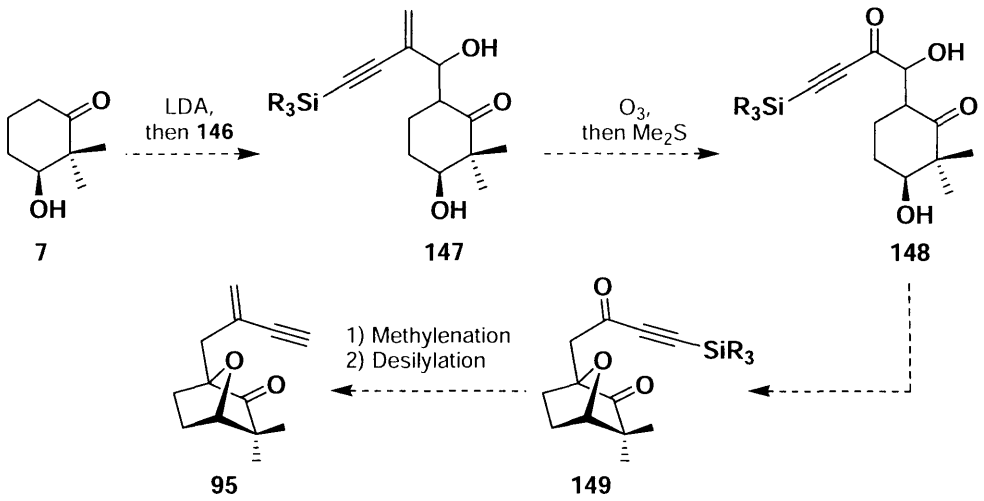


Based on the results described above, we decided to abandon the strategy employing amide **136** (Scheme 47) or **145** (Scheme 50), and chose to investigate an alternative route to prepare enyne **95**. We planned to maintain our aldol and acid-catalyzed nucleophilic 1,4-addition strategies to construct the A-ring enyne (starting from alcohol **7**), but to use an aldehyde of type **146** for the key aldol reaction. This strategy would be more convergent than our previous route based on methacrolein and would avoid possible regiochemical complications in the proposed conversion of intermediate diketone **128** to enyne **95** (Scheme 43).



We anticipated that there might be other advantages in utilizing aldehydes of type **146** (2-alkynyl-α,β-unsaturated aldehydes or α-alkynyl acroleins) in place of methacrolein. Aldehyde **146** should be more electrophilic than methacrolein, and the aldol reaction with hydroxyl ketone **7** might proceed to completion using this more reactive aldehyde. In addition, ozonolysis of diol **147** would provide ynone **148**, which should be more reactive than methyl ketone **132** (Scheme 46) in the acid-catalyzed 1,4-addition, perhaps allowing milder reaction conditions. Methylenation of ynone **149** would then afford the desired A-ring enyne **95** without the need for additional steps and without any regiochemical ambiguity.

Scheme 51



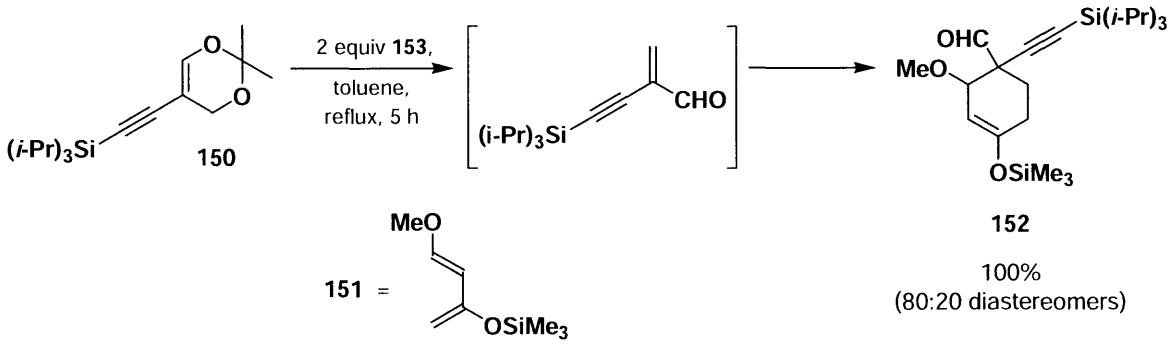
2-Alkynyl-α,β-Unsaturated Aldehydes

Having identified aldehydes of type **146** for our aldol reaction, we then started an investigation of methods for the efficient preparation of such compounds. Remarkably, only one example of the isolation and characterization of an aldehyde of this class had previously been

reported in the literature.[60] Acrolein derivatives of this type are expected to undergo facile dimerization via hetero Diels–Alder cycloaddition[61] and also should be especially susceptible to polymerization via radical pathways and in the presence of nucleophiles. In addition to their potential utility in our proposed aldol strategy for the construction of enyne **95**, the multiple functional groups embedded in these compounds suggest that they should serve as valuable synthetic building blocks in a number of applications. Unfortunately, their anticipated sensitivity limits the range of methods potentially applicable for their preparations, and to date their synthetic utility remains unrealized.

In 2000, Funk and coworkers described an ingenious method for the in situ generation of sensitive 2-substituted acroleins involving the thermal [4+2] cycloreversion of 5-substituted 4*H*-1,3-dioxins.[62] Funk found that the attempted application of this protocol to the preparation of a 2-alkynyl acrolein derivatives led only to the isolation of the corresponding hetero Diels–Alder dimer, but the unstable aldehyde could be trapped in situ by including excess Danishefsky's diene in the reaction mixture for the thermolysis step (Scheme 52).

Scheme 52



[60] Dreiding has reported that vapor phase pyrolysis of propargyl propiolate at 500 °C affords a complex mixture of products from which 2-ethynylpropenal was isolated in 12% yield. See: Bilinski, V.; Dreiding, A. S.; Hollenstein, H. *Helv. Chim. Acta* **1983**, *66*, 2322.

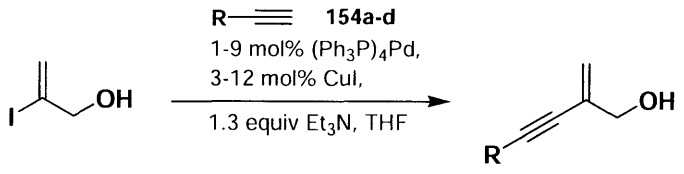
[61] For the dimerization of 2-substituted acroleins, see: (a) Schulz, H.; Wagner, H. *Angew. Chem.* **1950**, *29*, 105. (b) Laitalainen, T.; Kuronen, P.; Hesso, A. *Org. Prep. Proc. Int.* **1993**, *25*, 597. (c) Keiko, N. A.; Voronkov, M. G. *Russ. Chem. Rev.* **1993**, *62*, 751.

[62] Fearnley, S. P.; Funk, R. L.; Gregg, R. J. *Tetrahedron* **2000**, *56*, 10275.

Unfortunately, these conditions are not compatible with our projected use of 2-alkynyl aldehydes in an aldol reaction at low temperature with lithium enolates. The elevated temperatures required in the Funk protocol, as well as the fact that one equivalent of acetone is generated as a byproduct of the retro Diels–Alder reaction, obviously set severe constraints on the range of applications possible for 2-alkynyl acroleins produced under these conditions. We therefore undertook an investigation of alternative methods for the preparation of these α,β-unsaturated aldehydes that would be compatible with a broader spectrum of subsequent transformations.[63]

As shown in Scheme 53, Sonogashira coupling of 2-iodo-2-propenol, available by reaction of propargyl alcohol with chlorotrimethylsilane and sodium iodide,[64] with a wide range of acetylenes was expected to provide convenient access to enynyl alcohols of type **155**,[65] which would then be oxidized to furnish the desired aldehydes. Utilizing a standard Swern oxidation protocol afforded the desired aldehyde in clean conversion (as observed by TLC). However, upon aqueous workup, the sensitive product was found to readily decompose providing the unstable acroleins in poor yield due to their propensity to undergo Diels–Alder dimerization and polymerization (vide supra).

Scheme 53



153

154a R = $SiMe_3$
154b R = $Si(i\text{-}Pr)_3$
154c R = *n*-Bu
154d R = Ph

155a 96%[65]
155b 56%
155c 79%
155d 70%

[63] Thongsornkleeb, C.; Danheiser, R. L. *J. Org. Chem.* **2005**, *70*, 2364.
[64] Kamiya, N.; Chikami, Y.; Ishii, Y *Synlett* **1990**, 675.
[65] Compound **155a** has been previously synthesized using Sonogashira methodology, see: Nicolaou, K. C.; Koide, K. *Tetrahedron Lett.* **1997**, *38*, 3667.

Success was finally achieved by employing a modified Dess–Martin oxidation[66,67] protocol which avoids an aqueous workup procedure. Wavrin and Viala recently introduced the stratagem of precipitating the iodinane byproducts of Dess–Martin oxidations by diluting with pentane in connection with their synthesis of sensitive β,γ-unsaturated acyclic aldehydes.[68] We found that the synthesis of 2-alkynyl acrolein derivatives of type **146** could be achieved in good yields with a modified variant of the Dess–Martin reaction as described below.

Oxidation is first carried out using 1.1-1.3 equivalents of Dess–Martin periodinane in CH_2Cl_2 at 0 °C. The reaction mixture is then cooled to −78 °C and diluted with an equal volume of pentane as described by Wavrin and Viala to precipitate the iodinane byproducts. We then found that the addition of excess poly(4-vinylpyridine) (PVP) can serve to sequester the acetic acid generated in the reaction. The reaction is next filtered through a jacketed plug of silica gel cooled at −78 °C using a positive pressure of argon. The solution obtained is concentrated with the aid of toluene (ca. 5 mL) to a small volume (ca. 2 mL) to remove remaining traces of acetic acid via azeotropic distillation. Since the rate of dimerization increases with concentration and temperature, it is important not to concentrate the aldehyde product completely at room temperature. Final concentration to dryness is conducted at 0.05 mmHg and at −78 °C. The desired aldehydes are obtained in 41-78% overall yield and >95% purity as indicated by IR and ^{1}H NMR analysis.

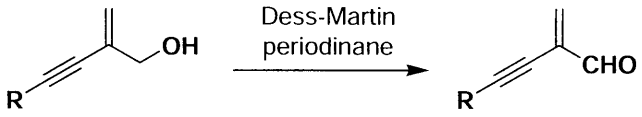
---

[66] (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

[67] For a recent review on the use of Dess-Martin periodinane and related compounds in organic synthesis, see: Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111 and references cited therein.

[68] Wavrin, L.; Viala, J. *Synthesis* **2002**, 326.

Scheme 54

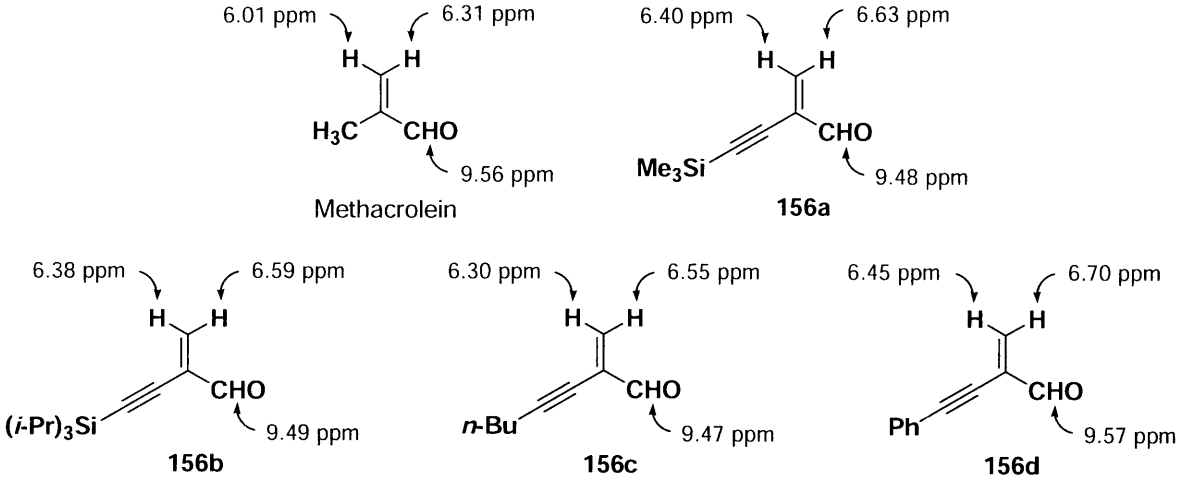


155a R = $SiMe_3$
155b R = $Si(i\text{-}Pr)_3$
155c R = *n*-Bu
155d R = Ph

156a 52-53%
156b 78%
156c 59%
156d 41%

^{1}H NMR spectra of the aldehydes **156a-d** show a characteristic pattern for this type of compounds. The chemical shifts of vinyl and aldehyde protons are found to be more downfield in **156d** than in **156a-c** probably due to the electron withdrawing effect of the phenyl group. IR spectra of these aldehydes also match the typical value at ca. 1700 cm^{-1} for the carbonyl group of the α,β-unsaturated aldehydes. ^{1}H NMR chemical shifts of the vinyl and aldehyde protons of **156a-d** are summarized in the scheme below together with methacrolein.

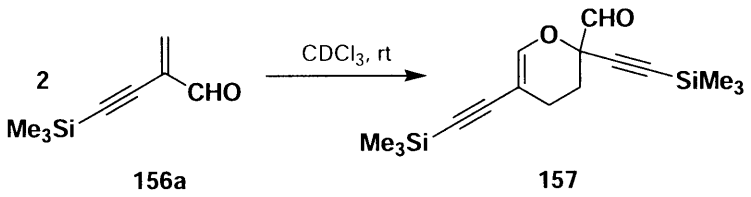
Scheme 55



As expected, the 2-alkynylpropenals **156a-d** readily undergo dimerization via hetero Diels–Alder cycloaddition. For example, aldehyde **156a** dimerizes to give aldehyde **157** when standing at room temperature as a solution in $CDCl_3$. ^{1}H NMR spectra of this solution (0.4 M) containing 1 equiv (0.26 mmol) of 4-isopropylbenzaldehyde as the internal standard, were

recorded over several hours and the yields observed for **156a** and **157** are summarized in Table 1. Initially, aldehyde **156a** was converted to give dimer **157**. After 16 h, accumulation of dimer **157** seemed to stop while aldehyde **156a** was still decomposing. Decomposition of aldehyde **156a** was complete after 260 h.

Scheme 56



156a **157**

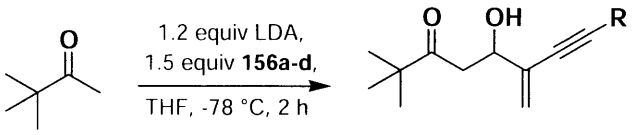
Table 1 Progress of Reaction **156a** → **157**[a]

Time (h)	Yield of **156a** (%)	Yield of **157** (%)
0	65	4
2	45	10
16	20	25
26	16	30
41	9	31
119	3	31
261	0	31

[a]Yields of **156a** and **157** were measured against 1 equiv of 4-isopropylbenzaldehyde (internal standard)

The 2-alkynyl-α,β-unsaturated aldehydes produced in this fashion can be taken up in other solvents and employed in a broad range of subsequent transformations. As aldehydes **156a-d** can undergo undesired side reactions upon standing at room temperature, these compounds should be prepared freshly before use. The aldehydes should be taken up in the reaction solvent and stored at low temperature (i.e., −78 °C) until ready for use in the subsequent reaction. When these precautions are followed, aldol condensation of aldehydes **156a-d** with the lithium enolate derivative of pinacolone provides with desired β-hydroxy ketones in good to excellent yield (Scheme 57).

Scheme 57

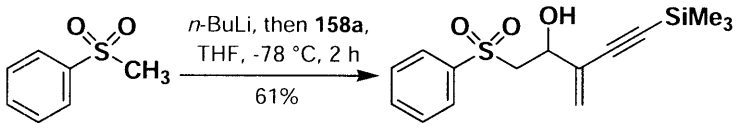


158a-d

158a	R = $SiMe_3$	94%
158b	R = $Si(i\text{-}Pr)_3$	70%
158c	R = *n*-Bu	70%
158d	R = Ph	71%

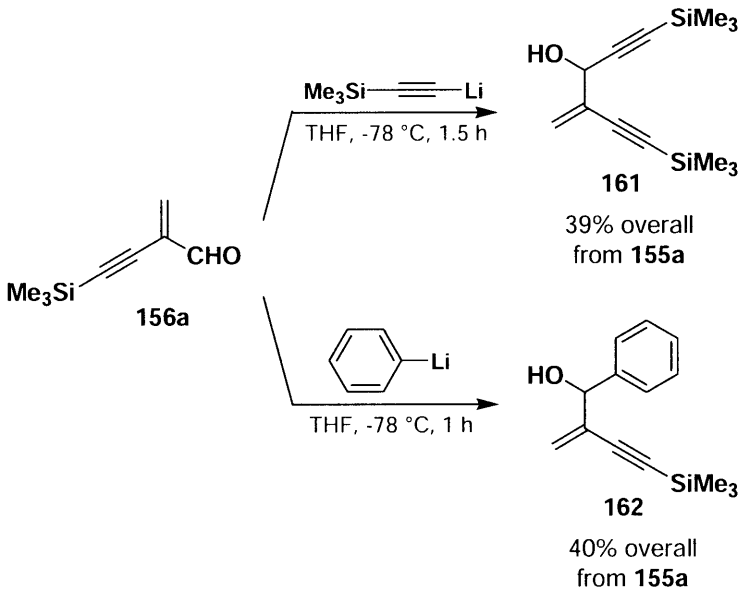
In a similar manner, addition of the lithium derivative of methyl phenyl sulfone proceeds smoothly to afford the β-hydroxy sulfone **160** in 61% yield (Scheme 58). For addition of organolithium compounds, we found that when organolithium reagents were added to the solution of the aldehyde **156a**, yields of **161** and **162** were low and reactions were not very clean. However, the reaction proceeds more smoothly when an inverse addition technique is employed. Thus addition of −78 °C solution of aldehyde **156a** to −78 °C solutions of both phenyllithium and lithium trimethylsilylacetylide furnishes the expected enynyl alcohols in good overall yield from **155a**, the precursor to the alkynyl acrolein (Scheme 59).

Scheme 58



159 160

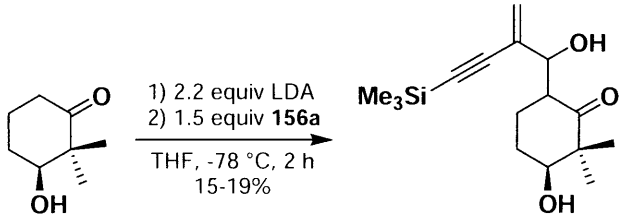
Scheme 59



In summary, the combination of Sonogashira coupling and Dess–Martin oxidation provides a convenient method for the preparation of a wide range of 2-alkynyl acroleins. Critical to the success of this procedure is the use of the a modified workup procedure for the oxidation step, in which byproducts are separated by precipitation with pentane, trapping with poly(4-vinylpyridine), and azeotropic distillation with toluene.

Having developed a method to efficiently generate aldehyde **156a**, we next investigated the aldol reaction with keto alcohol **7**. Under the same conditions used for our previous aldol reaction with methacrolein (Scheme 43), reaction of ketone **7** with aldehyde **156a** afforded enyne **163** in only 15-19% yield as a mixture of diastereomers. The reaction mixture was also not very clean as observed by TLC.

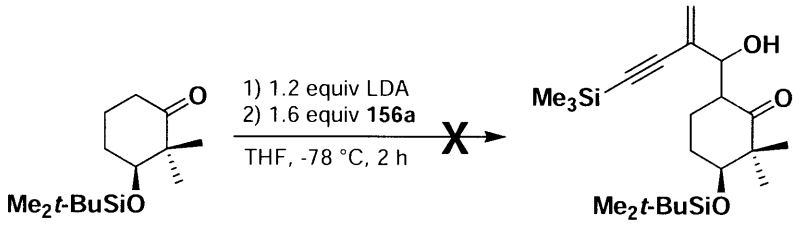
Scheme 60



7 **163**

We speculated that perhaps the free hydroxyl group of keto alcohol **7** may have an adverse effect when more electrophilic aldehydes such as **156a** are used as the aldol reaction partner. We decided to protect the hydroxyl group as the *t*-butyldimethylsilyl (TBDMS) ether (ketone **86**) which was used in the aldol reaction with **156a**. However, we found that the reaction did not proceed and most of starting material **86** was recovered.

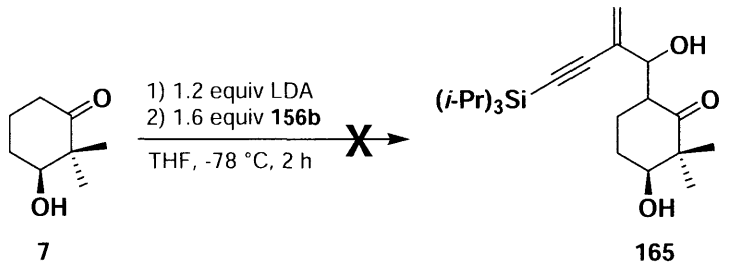
Scheme 61



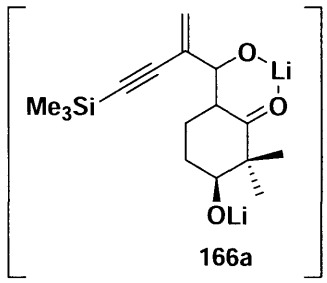
86 **164**

In addition, we attempted the aldol reaction employing keto alcohol **7** and aldehyde **156b** as aldol reaction partners hoping that this aldehyde would react more smoothly than **156a**. Unfortunately, we obtained an inferior result as compared to aldehyde **156a** – most of the starting material keto alcohol **7** was recovered.

Scheme 62

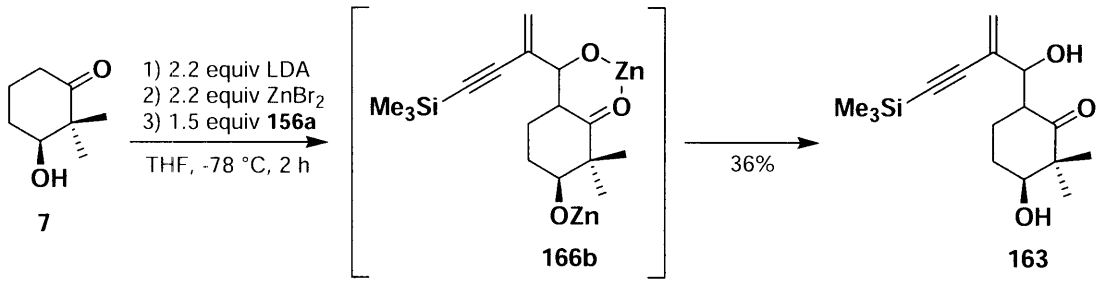


When we monitored the progress of these reactions by TLC, we noticed that in all cases, the reaction never went to completion and starting material keto alcohol **7** was always recovered. We suspected that under the basic reaction conditions, aldehyde **156a** may have rapidly decomposed. In addition, some of the aldolate intermediate (**166a**) may have undergone a retro aldol reaction to yield back both starting materials and deteriorate the overall yield of keto alcohol **163**.



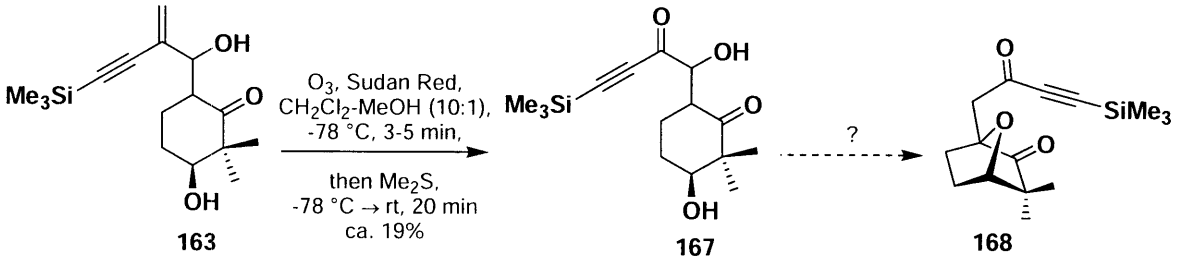
We hypothesized that by switching the counterion from lithium to zinc, the resulting aldolate intermediate (**166b**) would be held together through a stronger chelate and the retro-aldol would be minimized. We put this hypothesis to test by adding a solution of $ZnBr_2$ in THF to the lithium enolate of ketone **7** before addition of aldehyde **156a**. As shown in Scheme 63, the reaction afforded enyne **163** in an improved, but still low, yield.

Scheme 63



Uncertain about whether or not to invest more efforts to optimize the aldol reaction, we examined the ozonolysis of enyne **163**. We found that ozonolysis proceeds to afford impure ynone **167** in low yield, ca. 19%. We also found that upon purification, ynone **167** obtained rapidly decomposes to multiple products as observed by TLC. This result cast doubts on whether or not we would ultimately be able to effect the cyclization of ynone **167** to bicyclic ynone **168** even if we could prepare it efficiently (Scheme 61). For this reason, we decided to abandon the strategy employing aldehyde **156a** as an aldol partner, and to refocus our attention on bicyclic dione **rac-128** or **128**, a product we could synthesize in modest but consistent yield from methyl ketone **132** (Scheme 46).

Scheme 64



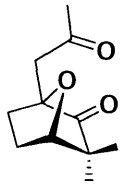
In the next chapter, the results of our attempts to convert bicyclic dione **128** to enyne **95** will be presented. In addition, preliminary results on the development of alternative approach to the hydrindane core structure of glycinoeclepin A (i.e., structure **63**, Scheme 16, p 33) via a different vinylallene intermediate, will be discussed.

Chapter 2

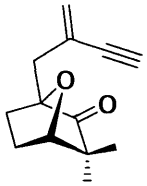
Synthetic Elaboration of the A-Ring Bicyclic Diketone

Introduction

The next focus of our efforts was the elaboration of dione **128** to enyne **95** and related intermediates that would be employed in the synthesis of glycinoeclepin A.



128

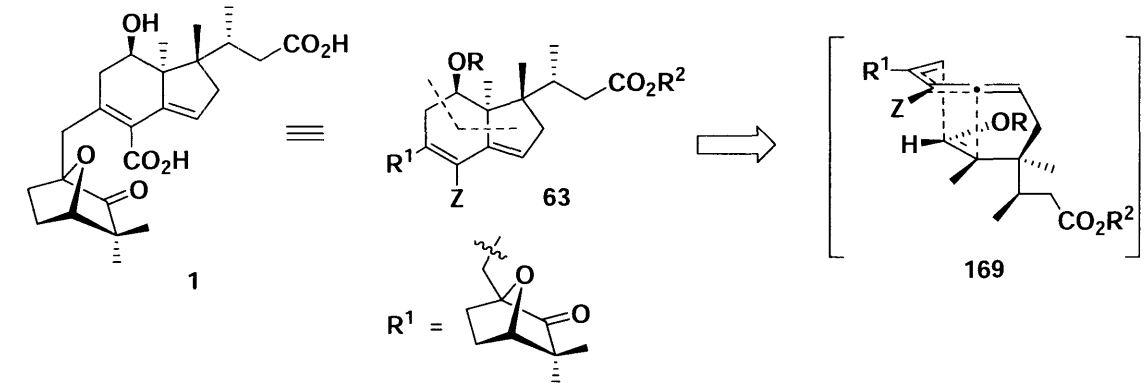


95

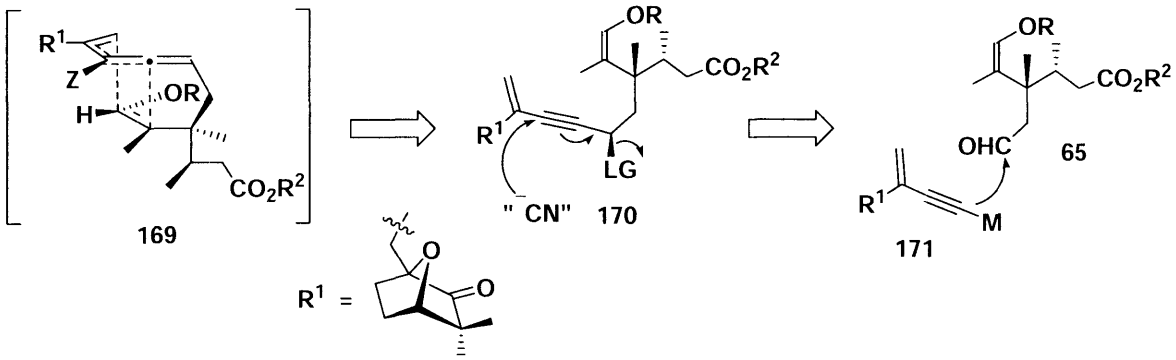
As discussed previously (see pp 32-33) and as shown in Scheme 65, our disconnection of the hydrindane core structure (**63**) involved an inverse-electron demand Diels–Alder reaction of vinylallene **169**. As illustrated in Scheme 66, our plan for the generation of this vinylallene intermediate involved propargylic alcohol derivatives of type **170**. In model studies, several methods for the conversion of **170** to the desired vinylallenes were developed. For example, one approach was based on the palladium-catalyzed cyanation strategy reported by Y. Tsuji and coworkers[69] involving the palladium-catalyzed reaction of Me_3SiCN with allyl carbonates and acetates. Application of this strategy requires the addition of metal acetylides (**171**) to the previously synthesized aldehyde **65**,[24b] followed by conversion of the resulting propargyl alcohol to either carbonate or acetate.

[69] (a) Tsuji, Y.; Yamada, N.; Tanaka, S. *J. Org. Chem.* **1993**, *58*, 16. (b) Tsuji, Y.; Kusui, T.; Kojima, T.; Sugiura, Y.; Yamada, N.; Tanaka, S.; Ebihara, M.; Kawamura, T. *Organometallics* **1998**, *17*, 4835.

Scheme 65

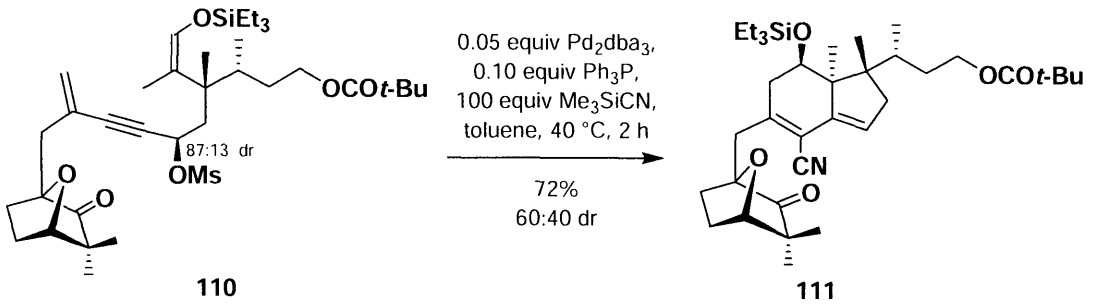


Scheme 66



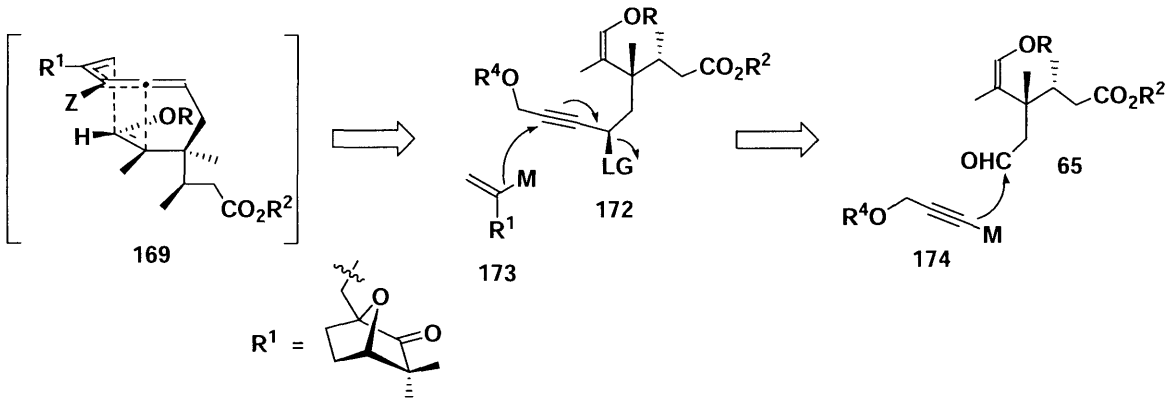
As shown here in Scheme 67 (identical to Scheme 34, p 49), former group members have shown that desired key intermediate **111** can be prepared from mesylate **110**. As mentioned earlier, double asymmetric synthesis could be employed in the metal acetylide addition of enynyl metal **171** to aldehyde **65** to achieve even better diastereoselectivity in the product, which is critical to the success of subsequent cycloaddition.

Scheme 67



In a slightly different strategy to access vinylallene **169**, we considered coupling reactions of vinylmetal species (**173**) with compounds of type **172** (Scheme 68). The propargyl compound **172** could, in turn, be obtained via a reagent-controlled addition of alkynyl metal **174** to aldehyde **65**.

Scheme 68

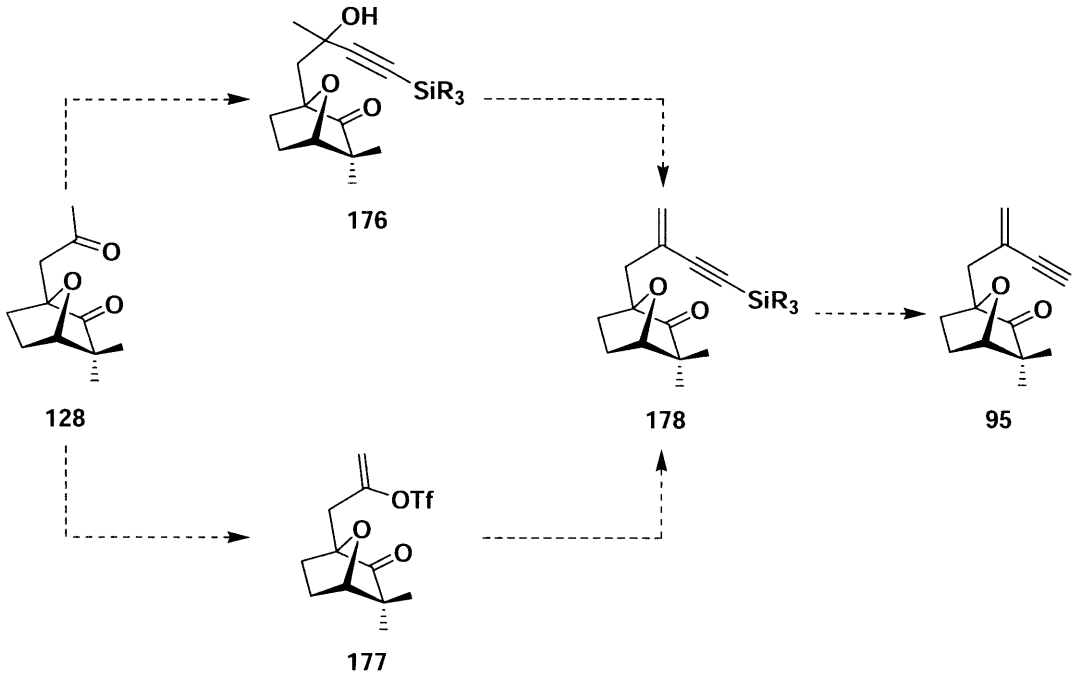


Synthetic Elaborations of Dione 128 to Enyne 95

As shown in Scheme 69, several schemes were considered for elaborating the enyne moiety in **95** beginning with dione **128**. One approach involved nucleophilic addition of metal acetylide to the methyl ketone in **128** followed by elimination, while another approach was based on Sonogashira coupling of vinyl triflate **177** with a trialkylsilyl acetylene. Propargyl alcohol **176** could be elaborated to enyne **178** via a variety of methods available for elimination of

alcohols. We mainly considered base-induced elimination of a leaving group formed in situ from alcohol **176** and Tsuji's palladium-catalyzed elimination of the corresponding carbonate derivatives.

Scheme 69



Synthesis of Enyne 95 via Elimination of Alcohol 176

Base-Induced E2 Elimination

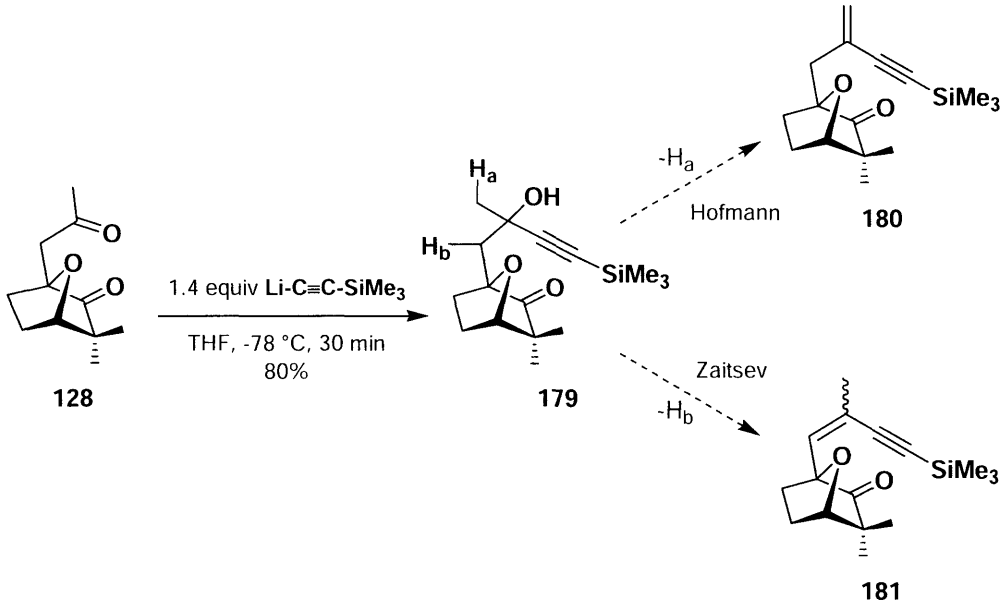
The requisite substrate for our elimination[70] studies was synthesized via an addition of metal trimethylsilyl acetylide to the methyl ketone carbonyl group of **128**. We planned to utilize either lithium or cerium[71] acetylide for this step. Lithium acetylide addition to ketone **128**

[70] For an overview of elimination reactions, see: March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; p 982.

[71] For review of organocerium compounds, see: Liu, H.-J.; Shia, K.-S.; Shang, X.; Zhu, B.-Y. *Tetrahedron*, **1999**, *55*, 3803.

proceeded uneventfully to afford propargyl alcohol **179** in good yield as a mixture of diastereomers (Scheme 70). We expected our elimination strategy to be somewhat problematic due to a potential competition between E1 and E2 processes. In E1 elimination, the process is expected to give mainly the more substituted (Zaitsev) alkenes (i.e., **181**). To obtain the desired less-substituted (Hofmann) alkene (i.e., **180**), we have to rely on E2 pathway. We hypothesized that the abstraction of H_b by base is more difficult due to steric hindrance of the neopentyl-like center and thus Hofmann alkene **180** might be favored under the proper conditions.

Scheme 70

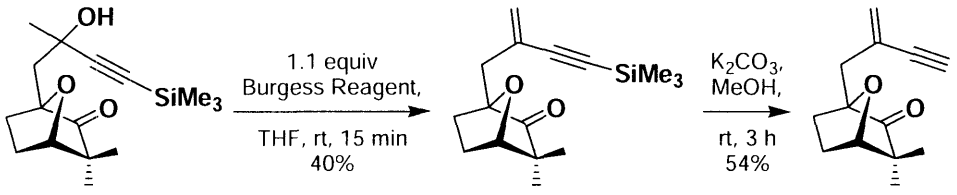


Jason Diffendal performed initial experiments on the elimination reaction of alcohol **179** utilizing the Burgess reagent[72] and found that the crude product consisted of a mixture of enynes in statistical distribution (i.e., **180**/**181** = ca. 60:40) by ^{1}H NMR analysis. Separation of enynes **180** and **181** by conventional column chromatography was not possible and the separation of pure enyne **180** was only achieved by preparative HPLC to afford the desired enyne in 40%

[72] *Organic Syntheses*; Wiley & Sons: New York, 1988; Collect. Vol. VI, 788.

yield. Subsequent desilylation of enyne **180** was achieved with catalytic potassium carbonate in methanol to furnish enyne **95** in 54% yield (Scheme 71).

Scheme 71



179 **180** **95**

We studied a variety of base-induced elimination conditions and the results are summarized in Table 2. In general, we transformed the hydroxyl group of propargyl alcohol **179** to a labile leaving group followed by in situ elimination with bases. We found that the reaction proceeded best when thionyl chloride and pyridine was employed (entry 3) to give a clean and complete conversion with a 79:21 mixture of **180/181**.

Initially, we conducted the elimination of alcohol **179** with $SOCl_2$/pyridine at room temperature. We speculated that by lowering the temperature of the reaction, the ratio of **180/181** could be improved. Following the initial result, we conducted the reaction at lower temperatures, 0 °C and −78 °C. However, even at lower temperatures, the elimination still yielded **180/181** in the same ratio as room temperature. A variety of bases were also studied. Pyridine was replaced with other bases such as DABCO, Et_3N, DBU, 2,6-lutidine, and 2,4,6-collidine, all of which provided inferior results to pyridine in terms of both byproduct formation and the ratio of **180/181**.

Other attempts were made to affect the desired regioselective elimination. Installation of a mesylate leaving group at low temperature (−78 °C) followed by in situ elimination with bulky bases (entries 1 and 6-8) resulted in incomplete conversions and yielded several products as seen on TLC. A potent oxophilic reagent, triphenylphosphonium anhydride trifluoromethane-

sulfonate[73] (entry 5), was found to completely convert alcohol **179** to enynes at low temperature. The enyne products were found to be unstable under the reaction conditions and decomposed upon warming. When the reaction was stopped at 0 °C, enynes were isolated in low yield (32%) as a 62:38 mixture of **180/181** (Table 2). Utilization of transition metal salts adsorbed on silica gel[74] (entries 9 and 10) as dehydrating agents also proved unsuccessful as these reagents either effected no reaction or resulted in low **180/181** ratios.

Table 2 Investigation of Elimination Conditions: **179** → **180** + **181**

Entry	Reagents/Conditions	Temperature, Time	Conversion	Ratio **180/181**
1	MsCl/Et_3N, CH_2Cl_2	0 °C → rt, 4 h	Incomplete	60:40[a]
2	TsCl/Et_3N, CH_2Cl_2	rt, 72 h	No reaction	N/A
3	$SOCl_2$/pyridine, CH_2Cl_2	rt, overnight	Complete	79:21[b,c]
4	$POCl_3$/DMF, CH_2Cl_2	rt, 48 h	Complete	54:46[d]
5	Ph_3PO[73]/Tf_2O, CH_2Cl_2	0 °C, <10 min	Complete	62:38
6	MsCl, *n*-BuLi, THF, then LDA	−78 °C, 3.75 h	Incomplete	N/A[e]
7	MsCl, *n*-BuLi, THF, then LiO*t*-Bu	−78 °C, 2 h	Incomplete	N/A[e]
8	MsCl, *n*-BuLi, THF, then KO*t*-Bu	−78 °C, 1 h, then rt 1 h	Incomplete	N/A[e]
9	$FeCl_3 \cdot SiO_2$,[74a] toluene	rt, 35 min	No reaction	N/A
10	$CuSO_4 \cdot SiO_2$,[74b] toluene	rt, 20 h	Complete	55:45[f]

[a]Several combinations of bases (Et_3N, DBU, DABCO) and solvents (CH_2Cl_2, benzene) were attempted and the best result is shown. [b]Several combinations of bases (pyridine, DBU, Et_3N, DABCO, 2,6-lutidine, 2,4,6-collidine) and solvents (CH_2Cl_2, benzene) were attempted and the best result is shown. [c]The reactions were conducted at several temperatures (−78 °C, 0 °C, and rt), all of which yielded the same ratio. Reaction was not purified for yield. [d]The enyne was presumably obtained via elimination of HCl from the corresponding propargyl chloride intermediate. [e]Mixture of several compounds was observed. [f]Reaction was heated at reflux. Reaction did not occur in CH_2Cl_2 at rt.

After several unsuccessful attempts to utilize the base-induced elimination strategy to furnish enyne **180** in satisfactory yield and regioselectivity, we decided to investigate a different strategy, specifically a palladium-catalyzed elimination of the methyl carbonate derivative of alcohol **179**.

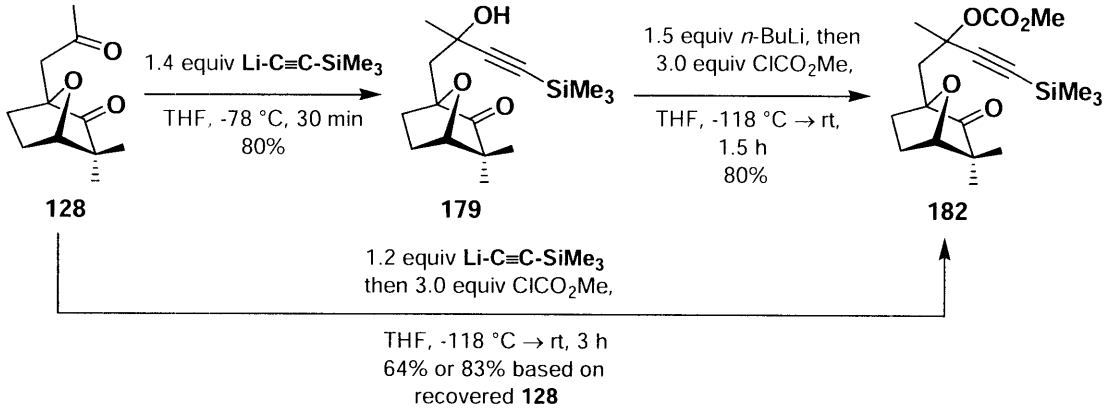
[73] (a) Hendrickson, J. B.; Hussoin, M. S. *J. Org. Chem.* **1987**, *52*, 4137. (b) Hendrickson, J. B.; Hussoin, M. S. *J. Org. Chem.* **1989**, *54*, 1144.

[74] (a) Keinan E.; Mazur Y. *J. Org. Chem.* **1978**, *43*, 1020. (b) Nishiguchi T.; Machida N.; Yamamoto E. *Tetrahedron Lett.* **1987**, *28*, 4565.

Pd(0)-Catalyzed Elimination of Propargyl Carbonate

Tsuji and coworkers reported a strategy specifically for the synthesis of enynes based on the palladium-catalyzed elimination of propargyl carbonates[75] and we next examined the application of this method for the preparation of **95**. As illustrated in Scheme 72, methyl propargyl carbonate **182** can be prepared easily from propargyl alcohol **179** in good yield. Compound **182** can also be prepared in one pot from bicyclic diketone **128** in fair yield (64%) over two steps. When the reaction was performed at −78 °C, a significant amount of byproducts were observed, complicating the purification of the desired carbonate **182**. This problem was alleviated when the reaction was first carried out at lower temperature (−118 °C) and allowed to warm to room temperature over 1.5-3 h.

Scheme 72

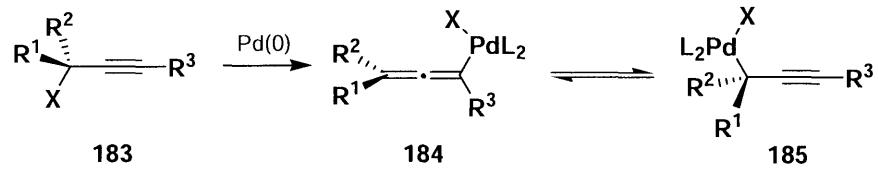


[75] Mandai, T.; Matsumoto, T.; Tsujiguchi, Y.; Matsuoka, S.; Tsuji, J. *J. Organomet. Chem.* **1994**, *473*, 343.

Pd(0)-Catalyzed Reactions of Propargyl Compounds: An Overview

Tsuji has described a number of reactions of propargyl alcohol derivatives catalyzed by palladium(0)[75,76] Pd(0) catalysts react with the propargyl compounds in an S_N2' fashion with high *anti* stereoselectivity[77] to give allenylpalladium **184** as shown in Scheme 73. It is believed that allenylpalladium **184** is in equilibrium with its isomeric propargylpalladium **185** through the [1,3] shift of the palladium moiety. The position of the equilibrium between the two species depends on the relative size of the substituents R^1, R^2, and R^3.[76a,77b] When R^3 is relatively small, allenyl species **184** predominates. However, if R^3 is bulky, then propargylpalladium **185** becomes the predominant species.

Scheme 73



R^1, R^2, R^3 = alkyl, aryl
X = halides, acetate, carbonates

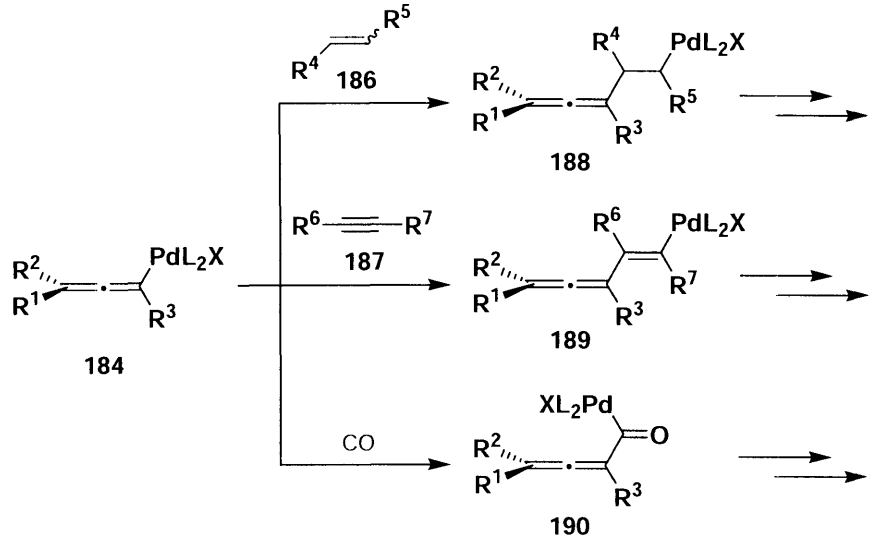
Three types of reactions are known for allenyl species **184**: insertion, transmetallation and nucleophilic addition. As illustrated in Scheme 74, *insertion* of allenylpalladium **184** into alkenes (**186**), alkynes (**187**) and carbon monoxide proceed to afford intermediates **188**, **189** and **190**, respectively.

---

[76] (a) Mandai, T.; Tsujiguchi, Y.; Matsuoka, S.; Tsuji, J. *Tetrahedron Lett.* **1993**, *34*, 7615. (b) Tsuji, J.; Mandai, T. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2589. (c)Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; John Wiley & Sons, Ltd.: Chichester, 2004; p 543.

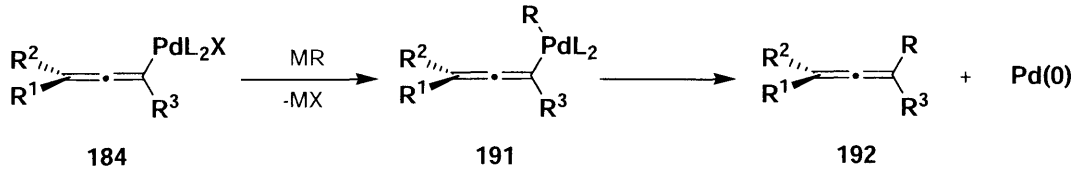
[77] (a) Elsevier, C. J.; Stehouwar, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem.* **1983**, *48*, 1103. (b) Elsevier, C. J.; Kleijn, H.; Boersma, J.; Vermeer, P. *Organometallics* **1986**, *5*, 716.

Scheme 74



In the second type of reaction, *transmetallation* of allenylpalladium **184** with an organometallic compound generates organopalladium intermediate **191**. Subsequent reductive elimination generates allene **192** and regenerates Pd(0) (Scheme 75).

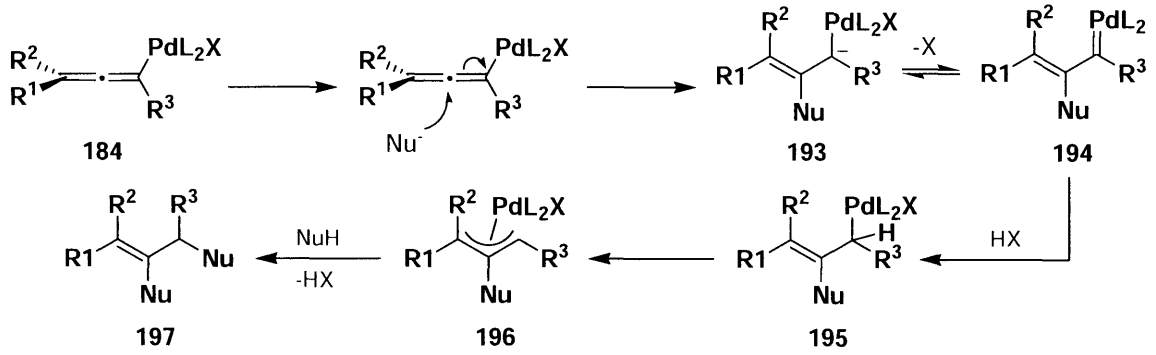
Scheme 75



M = Mg, Zn, B, Si, Cu
R = aryl, alkenyl, alkynyl, H

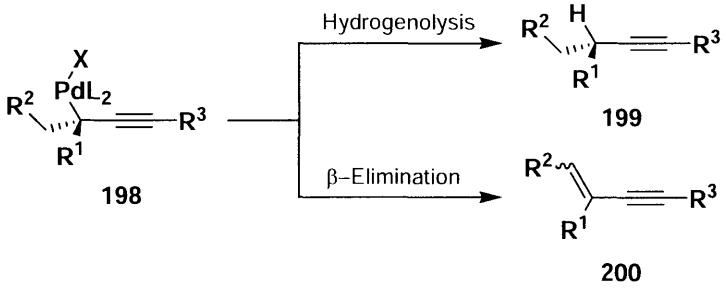
The third type of reaction of allenylpalladium **184** involves a *nucleophilic addition* to the sp-carbon center of the allene to generate the palladium-carbene complex (**193**). Upon addition of HX (present in the reaction), palladium π-allyl complex **196** is formed. Subsequent reaction with another nucleophile leads to the formation of alkene **197** (Scheme 76).

Scheme 76



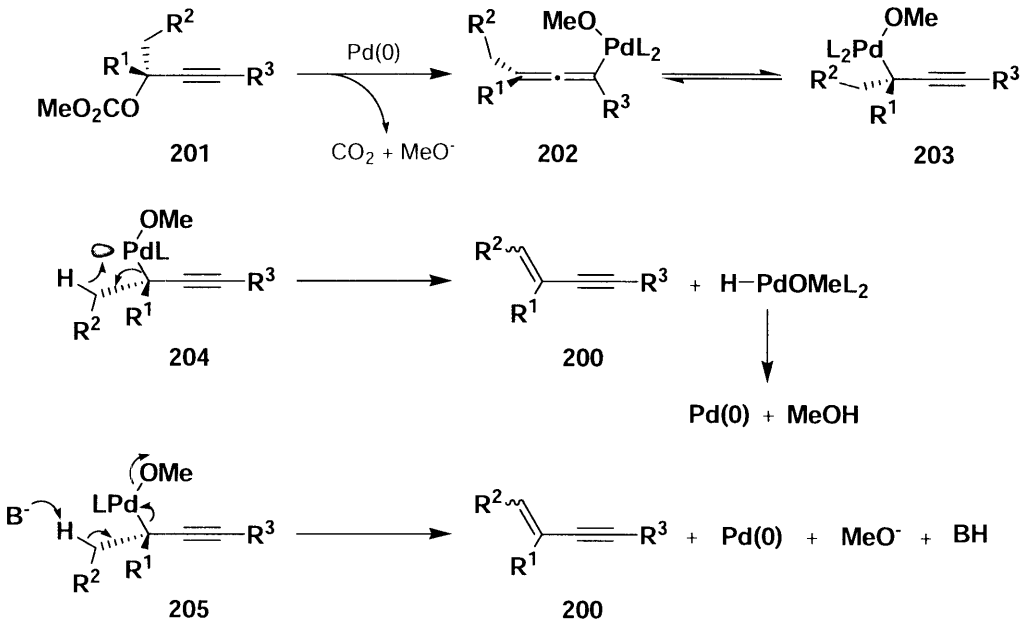
For propargylpalladium intermediate **185** (redrawn as **198**, Scheme 77), two types of reaction have been reported. Hydrogenolysis of intermediate **198** leads to alkyne **199**, while β-elimination affords enyne **200**. The latter process is the reaction of interest to us.

Scheme 77



The mechanism of β-elimination is shown in Scheme 78. Anti S_N2' addition of the palladium catalyst to propargyl carbonate **201** yields allenylpalladium **202** with an expulsion of CO_2 and methoxide anion, which becomes coordinated to palladium. As mentioned earlier, this intermediate is believed to be in equilibrium with propargylpalladium intermediate **203**.

Scheme 78



Two mechanisms are possible for the β-elimination of propargylpalladium **203**. In **204**, a hydrogen atom from adjacent C-H bond can transfer to an available orbital of palladium center (β-H elimination), resulting in the expulsion of HPdOMe, which reductively eliminates MeOH to regenerate Pd(0). In **205**, a proton is abstracted from adjacent C-H bond by a base. Methoxide anion generated from the first step could serve as the base in the abstraction of the proton in this process.

The extensive list of examples provided by Tsuji,[75,76a] encouraged us to explore this possibility. The method is reported to work well with both cyclic and acyclic methyl carbonates. A wide range of secondary and tertiary propargyl carbonates were reported to undergo the reaction to give good to excellent yields of enynes. Among many examples, particularly noteworthy are cases where regiochemistry in the β-H elimination becomes an issue. Tsuji and coworkers found that by switching between monodentate and bidentate ligands in conjunction with Pd(0) catalysts, regioselective β-H elimination could be effected.

Three catalyst systems were reported in their regioselective transformation of secondary and tertiary propargyl carbonate to give enynes. These systems are:

A-1 $Pd_2(dba)_3$ (0.025 equiv), dppf (0.05 equiv)

A-2 $Pd_2(dba)_3$ (0.05 equiv), dppf (0.10 equiv)

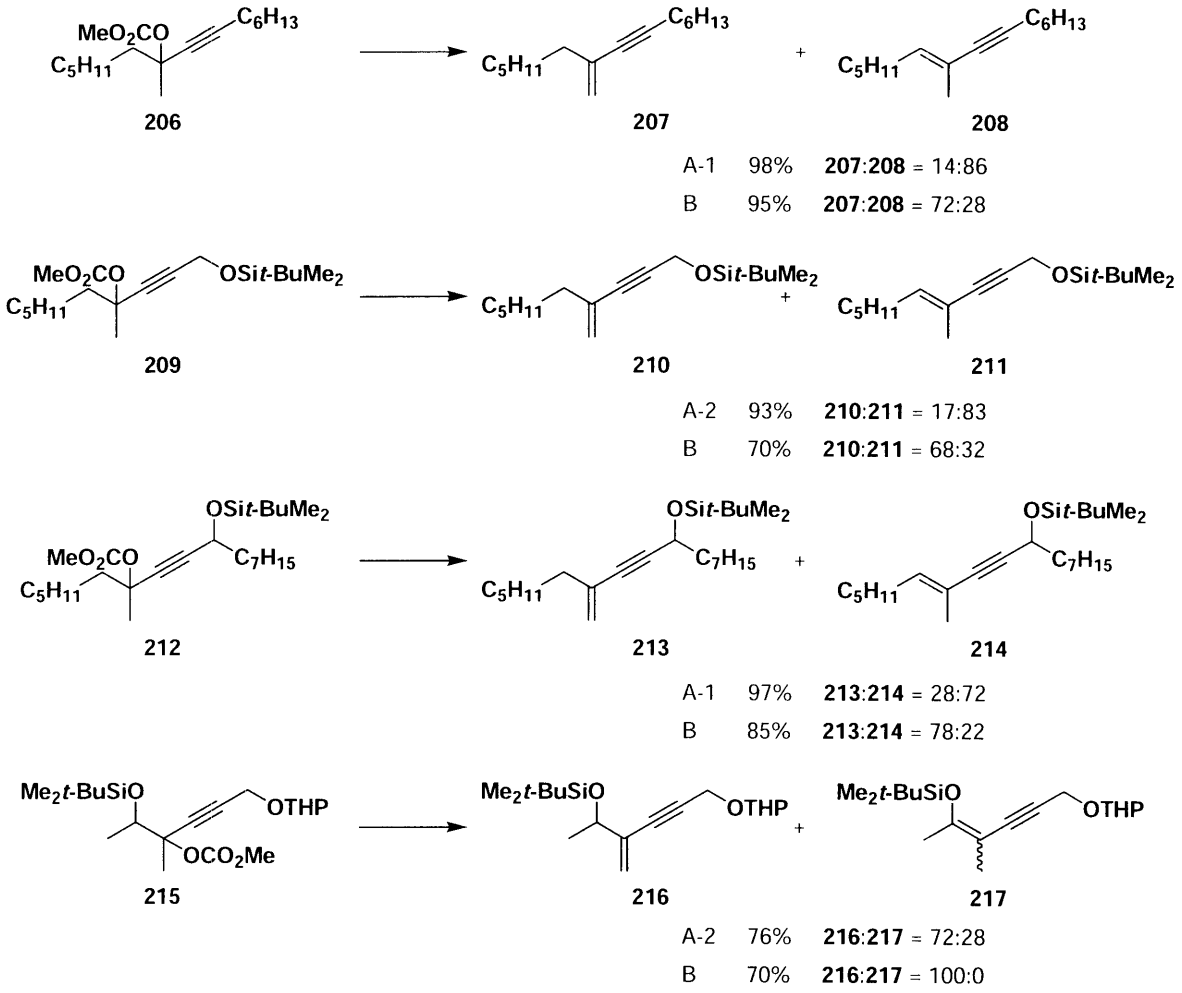
B $Pd(OAc)_2$ (0.10 equiv), Ph_3P (0.30 equiv)

dba = *trans,trans*-dibenzylideneacetone

dppf = 1,1′-bis(diisopropylphosphino)ferrocene

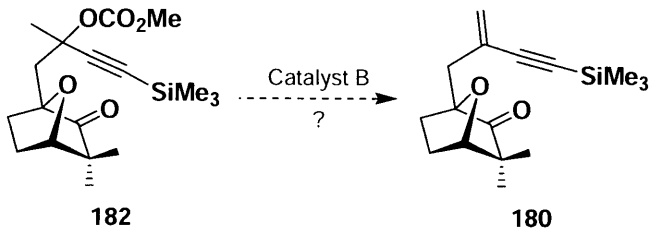
Selected examples from Tsuji's work are outlined in Scheme 79.[75] When methyl carbonate **206** was subjected to catalyst system A-1 for 2.5 h, enynes **207** and **208** were obtained in a combined yield of 98% with selectivity shown to be in favor of **208**, the more highly-substituted alkene. But when carbonate **206** was subjected to condition B for 1 h, both enynes **207** and **208** were obtained in 95% yield, but this time with reverse selectivity in favor of enyne **207**. Similarly, when carbonates **209** and **212** were subjected to conditions A-1 and A-2, respectively, the more highly-substituted alkenes **211** and **214** were favored. One particularly noteworthy example is in the case of carbonate **215**, with an adjacent *t*-butyldimethylsilyl ether functionality. When carbonate **215** was subjected to both A-2 (for 3 h) and B (for 4 h) catalyst systems, 1,1-disubsituted enyne **216** is favored in both cases, and with the B catalyst system the less-substituted enyne **216** was the sole product.

Scheme 79



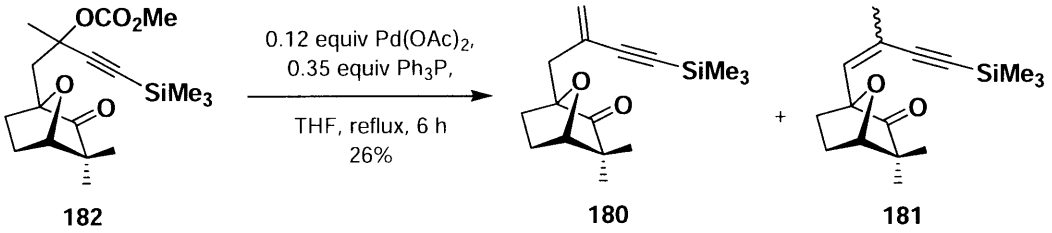
We planned to apply catalyst system B to our carbonate substrate **182**, which contains nearby ether oxygen, and hoped that the less-substituted alkene **180** would be favored as the product.

Scheme 80



We first subjected carbonate **182** to 0.12 equiv of $Pd(OAc)_2$ and 0.35 equiv of Ph_3P in refluxing THF for 6 h. It was found that in this initial run, the reaction did not go to completion (43% conversion) and yielded several products. However, the enyne products could be isolated in 26% yield as a mixture of **180** and **181** in excellent ratio as seen by ^1H NMR analysis (Scheme 81). While this initial result was very encouraging, we found that the reaction was not reproducible, and in later runs, we obtained enynes with various **180/181** ratios.

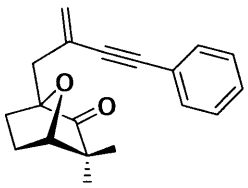
Scheme 81



182 **180** **181**

180:**181** = 97:3

Along with enynes **180** and **181**, we also observed enyne **218** as a byproduct from the reaction in 10-15% yield. The trimethylsilyl (TMS) group in the product (**180**) appeared to have exchanged with a phenyl group, presumably derived from Ph_3P. A similar type of exchange reaction between aryl group bound to the palladium center and aryl group bound to the phosphine ligand was first reported in 1991.[78]



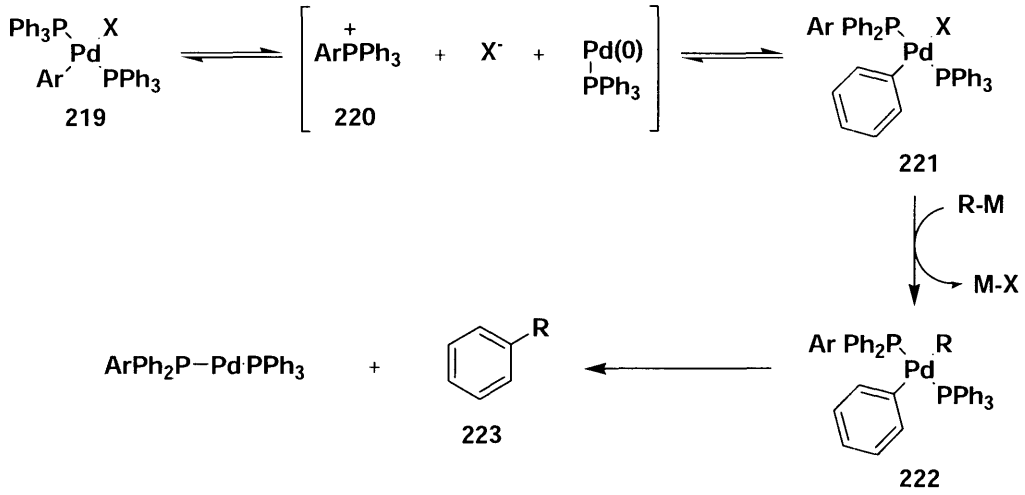
218

Studies on such exchange reaction have also been published.[79] Chenard and coworkers have suggested the presence of the intermediate of type **220** in cross-coupling reactions

[78] Kong, K.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313.
[79] (a) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441. (b) Grushin, V. V. *Organometallics* **2000**, *19*, 1888.

involving palladium and phosphine ligand.[80] As outlined in Scheme 82, an oxidative addition of Ar-X to palladium would generate palladium species **219**. This intermediate could reductively eliminate to give phosphonium salt intermediate **220**. This phosphonium salt can re-enter the catalytic cycle through another oxidative addition with Pd(0) by insertion of the Pd(0) into P-Ph bond. In the presence of organometallic compound (R-M) as a coupling partner, transmetallation of **221** with R-M ensues to generate intermediate **222**. Reductive elimination of **222** would then furnish cross-coupled product **223** with the phenyl group from Ph_3P incorporated.

Scheme 82

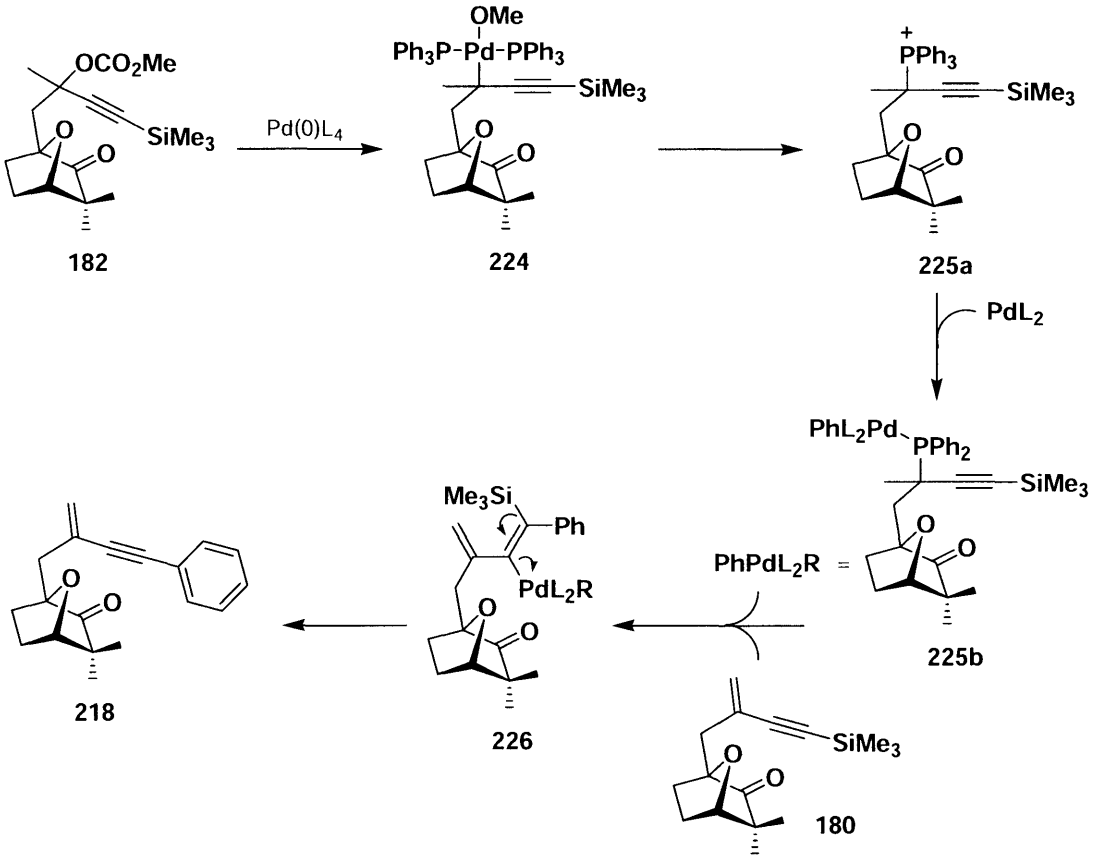


We speculated that the intermediate of type **220** may have been responsible for the formation of byproduct **218** in our reaction even though the mode of reaction may be somewhat different from that presented in Scheme 82. In our proposed mechanism, Pd(0) would add to methyl carbonate **182** in an S_N2' fashion to generate an allenylpalladium species, which should be in equilibrium with propargylpalladium species **224**. Reductive elimination of **224** would then lead to phosphonium salt **225**. The phosphonium salt **225a** could oxidatively add to a Pd(0) to give palladium intermediate **225b**. This intermediate could potentially undergo a

[80] Segelstein, B. E.; Butler, T. W.; Chenard, B. L. *J. Org. Chem.* **1995**, *60*, 12.

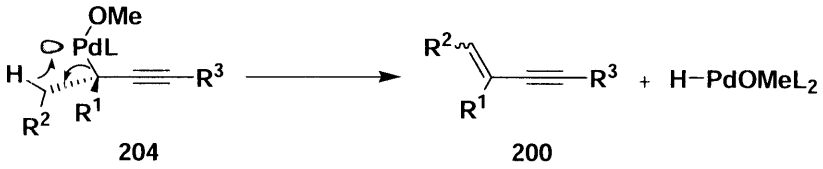
carbopalladation with enyne **180** to form intermediate **226**, which upon β-elimination would furnish enyne **218** as a byproduct.

Scheme 83



We attempted to optimize the reaction by applying combinations of different parameters. In many runs the reaction would not go to completion and more of both palladium catalyst and phosphine ligand were used to push the reaction further. In several runs, enyne **218** still formed as a byproduct. In most runs, when the catalyst combination of $Pd(OAc)_2$ and Ph_3P was utilized, the desired enyne **180** was always favored over the more substituted regioisomer, enyne **181**.

Scheme 84

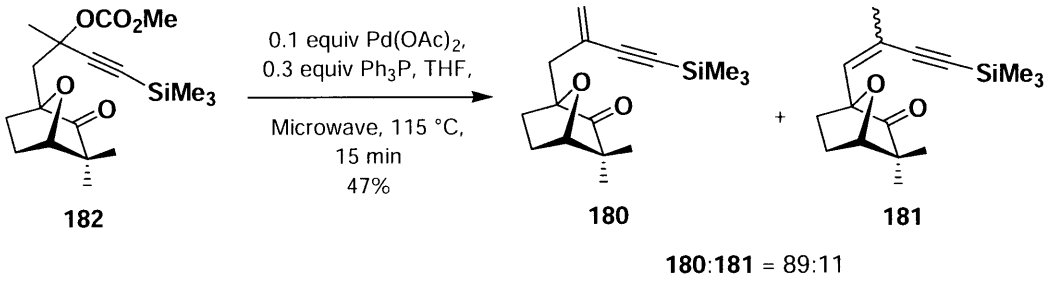


As mentioned earlier, one of the possible modes of β-elimination of propargylpalladium to form an enyne is as shown in Scheme 84. In order for **204** to undergo β-H elimination, the palladium center would have to possess an available coordinating orbital. For this reason, we also investigated the relative amount of palladium catalyst and phosphine ligand. The original Tsuji procedure calls for a 1:3 ratio of $Pd(OAc)_2/Ph_3P$, which we thought there could be too much phosphine ligand present, hence, hindering the coordinating orbital from facilitating the β-H elimination process. By using less phosphine ligand, there would be less competition for the coordinating site on palladium from the phosphine species, and therefore, β-H elimination could happen more easily. However, we found that overall the reaction was more efficient when a 1:3 mixture of $Pd(OAc)_2/Ph_3P$ was maintained.

We decided to examine the stabilizing effect of Et_3N as both an additive and solvent in our experiments. In all of our previous attempts, the contents in the reaction vessel often turned dark brown or black, which was a sign that palladium catalyst in the reaction may have decomposed. When we subjected carbonate **182** to 1.0 equiv of $Pd(OAc)_2$ and 3.0 equiv of Ph_3P in refluxing Et_3N for 45 min, we found that the reaction did not go to completion, but afforded a 25% yield of only the desired enyne **180** along with recovered starting material. In another run, we employed Et_3N as an additive, thus, we subjected carbonate **182** to 0.4 equiv of $Pd(OAc)_2$, 0.8 equiv of Ph_3P, and 4.8 equiv of Et_3N in THF and the resulting mixture was refluxed for 16 h. In this run, we were able to obtain the enynes **180** and **181** in 14% yield as an 80:20 mixture. Enyne **218** was also produced in 10% yield.

Microwave irradiation[81] was also investigated for the synthesis of enyne **182**. In the initial run, we found that the reaction proceeded to completion very rapidly within 30 min. The reaction was generally very clean and afforded a mixture of enynes **182**, **183** and **218**. The optimal result was obtained when carbonate **184** was subjected to microwave irradiation at 115 °C for 15 min (150 W, atmospheric pressure) in the instant cooling mode. Under these conditions, we were able to isolate enynes **182** and **183** in 47% yield as an 89:11 mixture with very little of enyne **218**.

Scheme 85



The best yield of enyne **180** under microwave conditions was modest, which leaves a lot of room for improvement for this reaction. In addition, in order to optimize this reaction further, there are a large number of factors that could be varied to achieve better results.

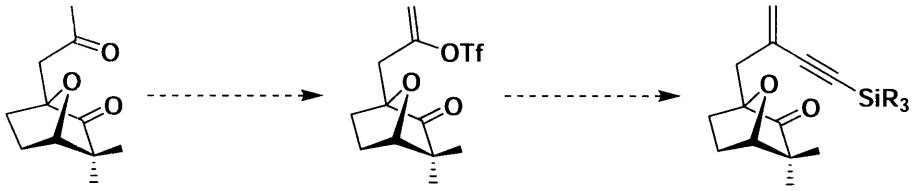
Synthesis of Enyne 95 via Vinyl Triflate Formation

After failed attempts to synthesize enyne **95** efficiently via elimination of the propargyl alcohol **179**, we turned our attention to the preparation of compound **95** by a different strategy. We planned to install the alkyne moiety in enyne **95** employing a Sonogashira cross-coupling

[81] For reviews, see: (a) Loupy, A., Ed. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002. (b) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250. (c) de la Hoz, A.; Díaz-Ortiz, Á.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164.

reaction. This required access to vinyl triflate **177** which we envisioned generating by trapping the lithium enolate of ketone **128** with a triflating agent.

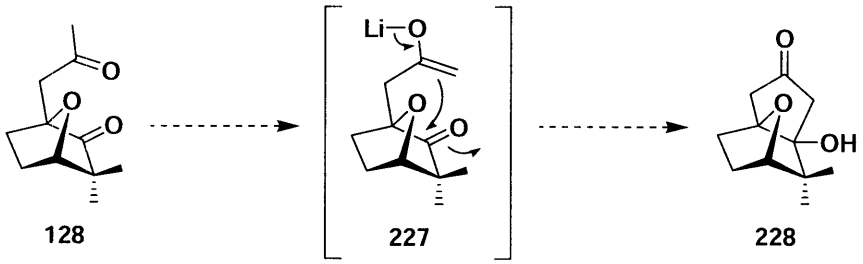
Scheme 86



128 **177** **178**

A former group member, Jason Diffendal, previously attempted to prepare vinyl triflate **177** by subjecting dione **128** to 1.1 equiv of LDA at −78 °C in THF and treating the lithium enolate intermediate with Tf_2NPh (McMurry's reagent[82]). He found that he could not isolate any of the desired vinyl triflate. He speculated that the lithium enolate intermediate generated may have reacted intramolecularly with the ketone carbonyl on the six-membered ring to give tricyclic compound **228** shown. However, this tricyclic compound was never isolated.

Scheme 87



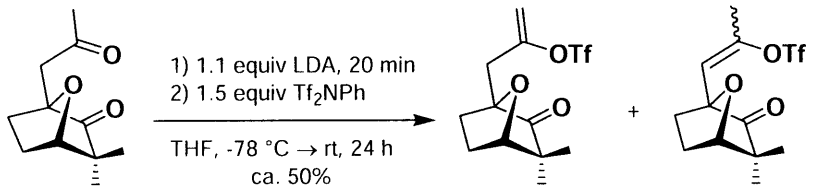
128 **227** **228**

We decided to reinvestigate this reaction since it could allow access to enyne **95** in only three steps from dione **128**. We subjected dione **128** to 1.1 equiv of LDA at −78 °C in THF for 20 min before it was treated with Tf_2NPh and the reaction was allowed to warm to room temperature overnight. In contrast to what Jason Diffendal had found, ^1H NMR analysis of the crude product indicated it contained a mixture of **177** and **229** in 65:35 ratio (Scheme 88). The

[82] McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

combined yield of the desired vinyl triflate was modest (ca. 50%) in the initial run, suffering from incomplete conversion, with ca. 18% of the starting material recovered, and formation of other unidentifiable byproducts.

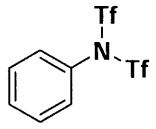
Scheme 88



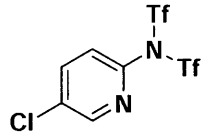
128 **177** **229**

177:**229** = 65:35

We therefore investigated this reaction further. From the initial trial, we found that the products were difficult to separate from *N*-phenyltriflimide byproduct and the reaction was also incomplete, indicating that McMurry's reagent may not be reactive enough. We proceeded to explore a more reactive triflating agent, the Comins' reagent (**231**)[83] and that it afforded a mixture of vinyl triflates in higher yield. However, the regioselectivity of vinyl triflates was the reverse of that first obtained when we used McMurry's reagent. Comins' reagent was subsequently used in all of our enolate trapping reactions, which are summarized in Table 3.



230
(Mcmurry's Reagent)



231
(Comins' Reagent)

[83] Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

Table 3 Investigation of the Vinyl Triflate Formation Reaction: **128** → **177** + **229**

Entry	Amide Base	Temperature (°C)	**177/229**	Yield (%)
1	LDA	−78	30:70	70
2	LDA	−118	33:67	78
3	LiHMDS	−78	7:93	65
4	LiTMP	−78	54:46	67
5	LiTMP	−98	60:40	58
6	LiTMP	−118	75:25-80:20	65-73
7	LiTMP/DMPU	−78	54:46	64
8	LiTMP/LiCl	−78	28:72	72
9	LiTMP/LiCl	−98	53:47	69
10	LiTMP/TMEDA	−118	67:33	78
11	LiTMP/HMPA	−118	59:41	43
12	LICA	−78	28:72	67
13	LICA	−118	20:80	75
14	LOBA	−78	35:65 (crude)	N/A
15	KHMDS	−78	7:93	70
16	KDA	−78	15:85	38

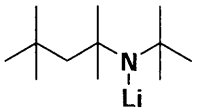
LiHMDS = Lithium hexamethyldisilazide, LiTMP = Lithium tetramethylpiperidide, LICA = Lithium isopropylcyclohexylamide, LOBA = Lithium *t*-octyl-*t*-butylamide, DMPU = *N,N'*-Dimethylpropyleneurea, TMEDA = *N,N,N',N'*-Tetramethylethylene-diamine, HMPA = *N,N,N,N',N',N'*-Hexamethylphosphotriamide, KHMDS = Potassium hexamethyldisilazide

As seen in Table 3, our studies of vinyl triflate formation were performed with a variety of bases. Temperatures seemed to have effect on selectivity. When the reaction was conducted at lower temperature, the regioselectivity in the product seemed to improve, especially with LiTMP (entries 4-6). We then tried to use different additives, hoping that changing the aggregates of organolithium may help to improve the ratio of products and yield further, but we found no improvement (entries 7-11). Other hindered lithium and potassium amide bases resulted in worse selectivity than LiTMP.

We also tried to use a bulkier base than LiTMP, such as lithium *t*-octyl-*t*-butylamide (LOBA) as introduced by Corey.[84] Initially, we had problems preparing the parent amine.

[84] (a) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 491. (b) *Organic Syntheses*; Wiley & Sons: New York, 1993; Collect. Vol. VIII, 93.

However, we were finally able to obtain a small amount of it from various runs to use in our experiments with lithium enolate. When dione **130** was treated with LOBA at −78 °C followed by treatment with Comins' reagent and allowed to warm to room temperature over 16 h, the reaction was found to be incomplete. The crude ^{1}H NMR showed ca. 60% conversion and **177/229** ratio of 35:65 (entry 14). This material was not purified for yield.



LOBA

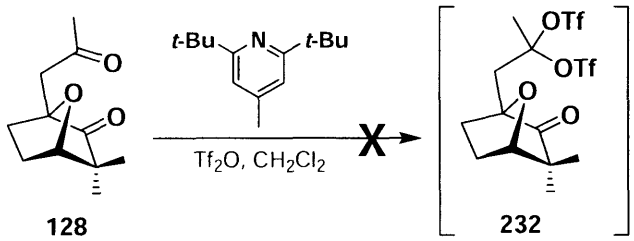
In addition to "external quenching," we also attempted "internal quenching," a concept also introduced by Corey.[85] This concept involves addition of lithium amide base to the substrate in the presence of a trapping agent, in the case reported by Corey, TMSCl. In our case, we attempted the internal quenching using Comins' reagent and LiTMP. Thus, LiTMP solution was added to a −78 °C solution of dione **128** and Comins' reagent. The resulting solution was then allowed to warm to room temperature over 24 h. It was found that the reaction did not go to completion (ca. 70% conversion) and the ratio of **177/229** was disappointing (39:61). We speculated that perhaps the reaction of lithium enolate with Comins' reagent was not rapid. Therefore, the lithium enolate was allowed to equilibrate. This situation may also be true in all of the previous cases using Comins' reagent.

In addition to attempts to trap metal enolates with Comins' reagent, we also attempted to synthesize vinyl triflate **177** by soft enolization method. Thus, dione **128** was reacted with triflic anhydride (Tf_2O) in the presence of 2,6-di-*t*-butyl-4-methylpyridine[86] or Et_3N in CH_2Cl_2, but no

[85] Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.
[86] (a) Stang, P. J.; Fisk, T. E. *Synthesis* **1979**, 438. (b) Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283.

reaction was observed and starting material was recovered. We speculated that this is probably due to the inability of dione **128** to form bis-triflate ester **232**.

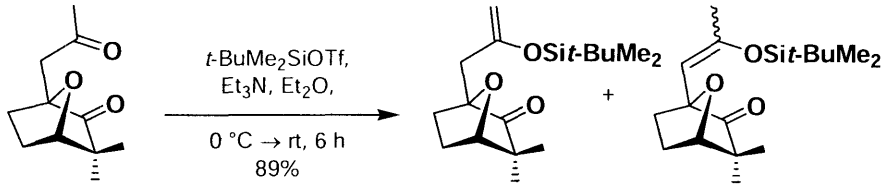
Scheme 89



128 **232**

As we could not successfully prepare vinyl triflate **177** regioselectively directly from dione **128**, an alternative method was considered, namely, the preparation of a silyl enol ether derivative as a precursor to vinyl triflate. A method, reported by Corey, presents a useful route for us to access vinyl triflate from *t*-butyldimethylsilyl (TBDMS) enol ether.[87] This method involved in situ generation of gaseous trifluoromethanesulfonyl fluoride (CF_3SO_2F = TfF) from CsF and Tf_2NPh in dry DME in a well-sealed flask containing substrate. We planned to access the silyl enol ether derivative from dione **128** employing the method reported by Cazeau and coworkers.[88] Thus dione **128** was subjected to TBDMSOTf in Et_2O/Et_3N and TBDMS enol ethers **233** and **234** were obtained in good yield as a 66:34 mixture (Scheme 90).

Scheme 90



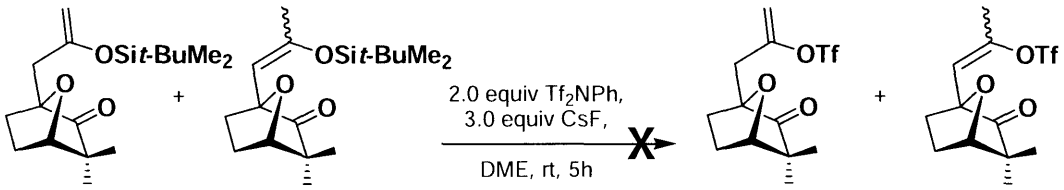
128 **233** **234**

233:**234** = 66:34

[87] Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290.
[88] Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075.

Unfortunately, when we treated the mixture of **233** and **234** with Tf_2NPh and CsF, we did not observe any product but only observed a trace amount of dione **128**. Both starting materials largely remained in the reaction (Scheme 91). After having experienced only failure in the preparation of vinyl triflate **177** from dione **128**, we decided to abandon this strategy and moved on to the next alternative discussed earlier in this chapter.

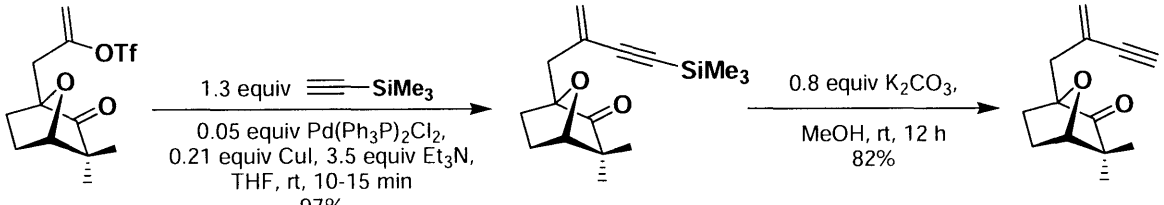
Scheme 91



233 **234** **177** **229**

Even though we could not successfully prepare **177** efficiently, we had accumulated a good quantity of both **177** and **229**. Although the separation of the two isomeric vinyl triflates was not trivial, at the end we could still obtain the desired vinyl triflate **177** in good purity. Next, we proceeded to attempt Sonogashira coupling of vinyl triflate **177** with trimethylsilyl acetylene. The reaction proceeded quickly and efficiently to generate enyne **180** in almost quantitative yield. Subsequent desilylation proceeded uneventfully to afford enyne **95** in excellent yield (Scheme 92).

Scheme 92

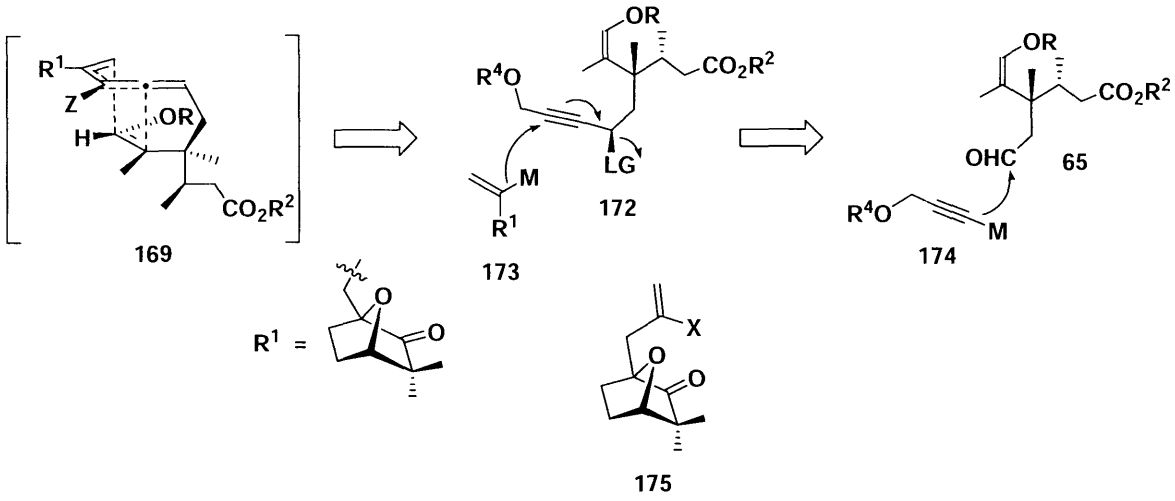


177 **180** **95**

Synthetic Elaboration of Dione 128 to Vinyl Halide 175

Even though the Sonogashira reaction, and subsequently desilylation, of vinyl triflate **177** proceeded very efficiently, we could not rely on the synthesis of vinyl triflate in providing us with sufficient amount of enyne **95**. Thus, we turned our attention to an alternative strategy discussed earlier in the chapter. As mentioned before, we considered two different strategies for accessing the vinylallene intermediate **169**. One of these strategies is outlined here again in Scheme 93.

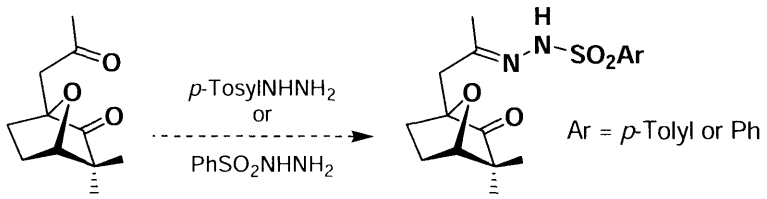
Scheme 93



We identified vinyl halide **175** as the target from dione **128**, which we envisioned to access via Shapiro fragmentation. Shapiro fragmentation is a mechanistically interesting reaction, concerning which a number of reviews are available.[89] The starting material required in a Shapiro reaction is an arenesulfonylhydrazone derivative of a carbonyl compound. In a traditional sense, this material is prepared from a carbonyl group and benzene- or toluenesulfonylhydrazine in a condensation reaction. An example is illustrated below with dione **128**.

[89] (a) Shapiro, R. H. *Org. React.* **1977**, *23*, 405. (b) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55. (c) Chamberlin, A. R.; Bloom, S. H. *Org. React.* **1990**, *39*, 1.

Scheme 94

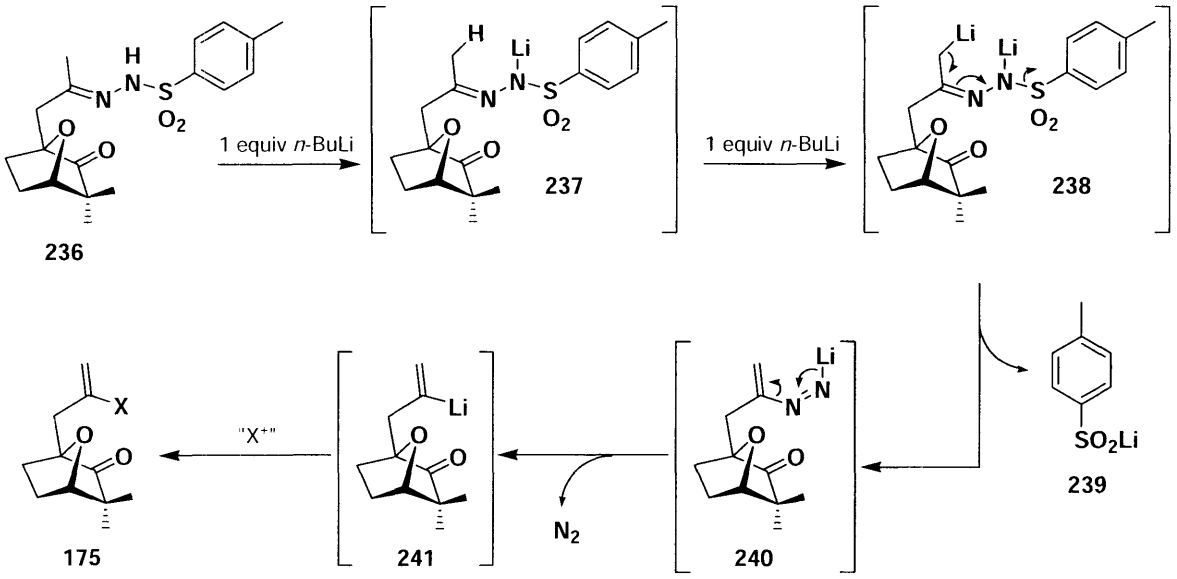


128 **235**

In the fragmentation process (Scheme 95), the hydrazone (e.g., **236**) is treated with alkyllithium reagent at low temperature (usually −78 °C) in TMEDA, hexane, or hexane-TMEDA mixture. After deprotonation is complete, the reaction mixture is warmed to ca. 0 °C to induce the fragmentation. If an alkene is the desired product (e.g., **175**; X = H), at least 2.0 equiv of base is required (to induce the fragmentation) as it has been shown that the vinyllithium intermediate (e.g., **241**) can deprotonate toluene- or benzenesulfenyl anion (e.g., **239**) in an *o*-metalation process to give the alkene.

However, when a product other than the alkene (e.g., **175**; X = H) is desired, at least 3.0 equiv of base is required to prevent *o*-metalation of **239** by vinyllithium **241**. In addition, polar aprotic solvents, such as THF, cannot be employed in a Shapiro reaction because when the reaction is warmed, vinyllithium **241** could also deprotonate the solvent. This could be troublesome because many of these hydrazone derivatives are not soluble in non-polar solvents. Having to use a large excess of alkyllithium base is an inconvenient, potentially dangerous and wasteful practice, especially when the synthesis is conducted on a large scale. In addition, more electrophile is required to quench both intermediate vinyllithium **241** and excess alkyllithium reagent.

Scheme 95



The Bond modification[90] of the Shapiro reaction introduced a more efficient and synthetically useful hydrazone derivative, which does not require more than 2.0 equiv of alkyllithium reagent in the deprotonation step. This derivative is prepared by the condensation of ketone with 2,4,6-triisopropylphenylsulfonylhydrazine (trisylhydrazine). Because both *o*-positions of the phenyl nucleus are blocked by isopropyl groups, excess base is not required. In addition, the trisylhydrazone derivative decomposes faster (5-10 min at 0 °C) than the tosyl- or phenyl-counterpart, probably due to its steric hindrance. This means that the reaction can be conducted in THF, where prolonged warming is not required and therefore side reactions of intermediate vinyllithium with solvent are minimized.

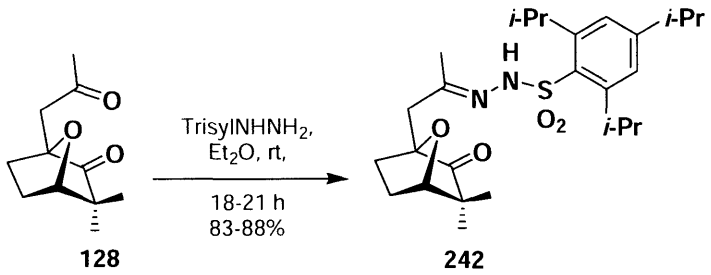
It is worth noting the selectivity of the reaction with respect to the formation of the (*E*)- and (*Z*)-hydrazones. The "syn-dianion" effect, first noticed by Dauben and coworkers,[91] controls the location of lithium cation on the nitrogen atom (**237**, Scheme 95), which is dictated by the

[90] Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.
[91] Dauben, W. G.; Rivers, G. T.; Zimmerman, W. T. *J. Am. Chem. Soc.* **1977**, *99*, 3414.

geometry of the hydrazone, and thus determines the site of the second deprotonation. Therefore, for the application of Shapiro reaction in our synthesis of **175** to be successful and to solve the regiochemical problem we have had in other strategies (vide supra), it was necessary to exclusively generate the (*E*)-hydrazone.

We started our studies on the application of the Shapiro fragmentation in the synthesis of vinyl halide **175** by preparing hydrazone **242** from dione **128** in Et_2O at room temperature. The condensation proceeded smoothly to afford the trisylhydrazone in excellent yield. Gratifyingly, we obtained the (*E*)-hydrazone as the major product (usually containing less than 5% of the (*Z*)-isomer). Based on our observations, we believed that the desired (*E*)-isomer is less soluble in ether than its (*Z*)-counterpart. By allowing the reaction to stir at room temperature overnight (while ether is evaporated slowly), most of the (*E*)-hydrazone slowly crystallizes while leaving the (*Z*)-hydrazone in the solution.

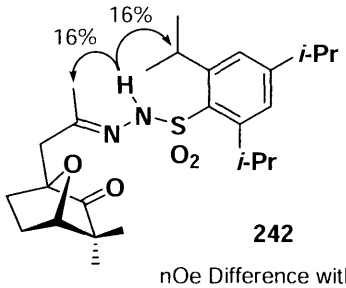
Scheme 96



128 **242**

Hydrazone product **242** was collected by filtration of the reaction mixture through a fritted funnel and cold pentane was used to wash the crystals of the product. The (*E*)-hydrazone obtained can readily isomerize to the (*Z*)-isomer over time in solution. Therefore, this material is best stored as a dry solid at −18 °C under argon. Confirmation of the geometry of the compound was carried out by an nOe difference NMR experiment and by comparing the ^1H NMR spectra of

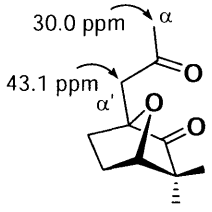
the pure (*E*)- and (*Z*)-isomer which are easily separable by column chromatography using Et_2O-CH_2Cl_2 solvent system as eluent.



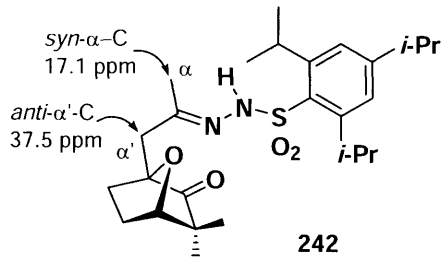
242

nOe Difference with the proton on N irradiated

Further confirmation was obtained by examining the ^{13}C NMR spectrum of hydrazone **242** as suggested by Fuchs.[92] The chemical shifts of both α-C and α′-C are shifted upfield in the spectrum of the hydrazone (see below). In general, the difference of the chemical shifts of *syn*-α-C in the hydrazone and α-C in the ketone (12-15 ppm) is larger than the difference of the shifts between *anti*-α′-C in the hydrazone and α′-C in the ketone (3-6 ppm). Accordingly, chemical shift of α-C of trisylhydrazone **242** is shifted upfield by ca. 13 ppm as compared to α-C of **128**, and α′-C of **242** is shifted upfield by ca. 6 ppm as compared to α′-C of **128**.



128



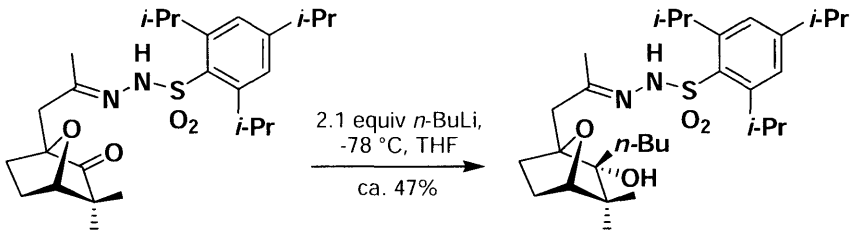
242

Having the correct hydrazone in hand, we next investigated the Shapiro fragmentation of **242**. The solution of hydrazone **242** in THF at −78 °C was treated with 2.0 equiv of *n*-BuLi; however, the desired Shapiro fragmentation product was not obtained. Instead, *n*-BuLi unexpectedly added to the carbonyl group on the ring to give tertiary alcohol **243** while the

[92] Bunnell, C. A.; Fuchs, P. L. *J. Org. Chem.* **1977**, *42*, 2614.

hydrazone unit was left intact. Only one diastereomer of the alcohol was obtained. Based on the examination of molecular models, the carbonyl group on the six-membered ring of hydrazone **242** should be more accessible to a nucleophilic attack from the same face as the bridging oxygen than the opposite face. Therefore, the stereochemistry of the carbinol carbon is tentatively assigned as shown (Scheme 97).

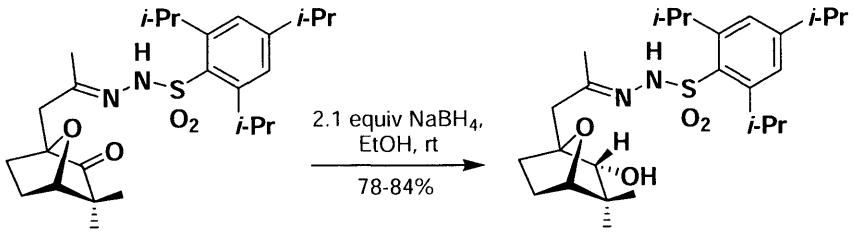
Scheme 97



242 **243**

From the result of this experiment, we decided to reduce the ketone on the six-membered ring to a secondary alcohol before submitting the compound to the Shapiro reaction conditions. The reduction of hydrazone **242** was carried out by reaction with sodium borohydride in ethanol at room temperature for 1 h. The reduction proceeded smoothly to give the corresponding alcohol **244** as a white solid. No reduction of the (*E*)-hydrazone or isomerization to the (*Z*)-hydrazone was detected. Again, only one diastereomer was obtained and it is tentatively assigned for the same reason (vide supra) as shown.

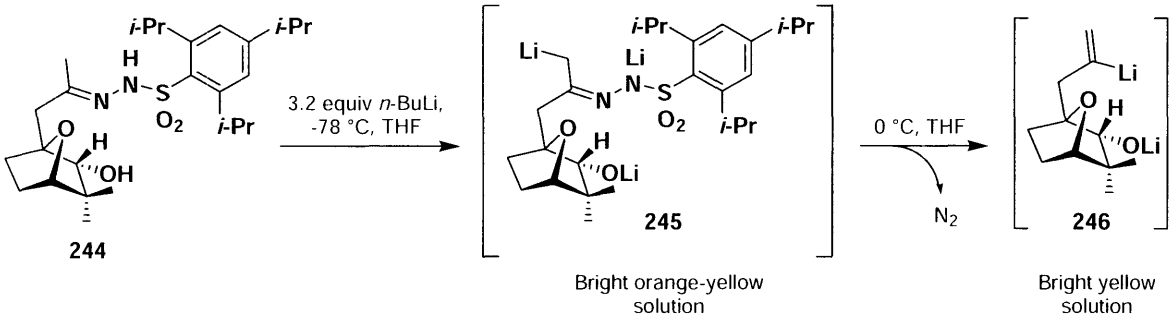
Scheme 98



242 **244**

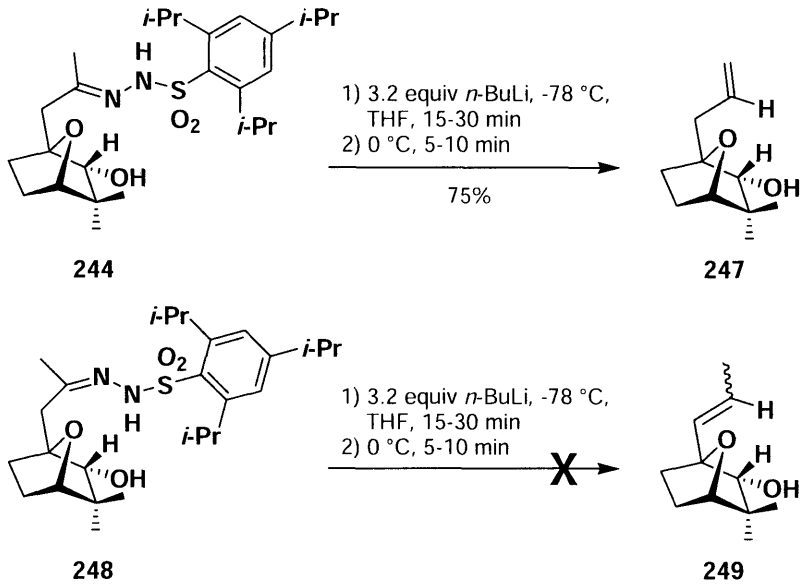
We then began our studies of the Shapiro reaction using alcohol **244** as our substrate. Thus the −78 °C solution of alcohol **244** in THF was treated with 3.2 equiv of *n*-BuLi. Upon mixing, the reaction mixture turned from colorless to a bright orange-yellow solution, indicating that trianion **245** is formed. After 15-30 min, this mixture was warmed to 0 °C, causing the discharge of the orange-yellow color to give a bright yellow solution together with the evolution of nitrogen gas. After ca. 5-10 min at 0 °C, the fragmentation was found to be complete by TLC.

Scheme 99



In our initial experiment, we decided to quench vinyllithium **246** with water to test the efficiency of the reaction (Scheme 100). Upon aqueous workup, alkene **247** was obtained in 85-90% yield as measured by ^{1}H NMR analysis of the crude product and was isolated in 75% yield by column chromatography. We were glad to see that the reaction proceeded as expected and that only the desired regioisomer of alkene was generated from the (*E*)-hydrazone as shown.

Scheme 100



As an interesting experimental note, we also attempted to subject the pure (*Z*)-hydrazone to the identical Shapiro reaction condition. We found that no reaction occurred and most of the (*Z*)-hydrazone starting material was recovered. We speculated that this result may have been influenced by the hindered neopentyl-like center and, therefore, not approachable by *n*-BuLi.[93] The results described here ensured us that vinyllithium **246** could be successfully and quite efficiently generated and we were ready for trapping experiments.

We planned to trap vinyllithium **246** as a vinyl halide; namely a vinyl bromide, which should be less sensitive than the iodide analog. From surveying the literature, the ideal source of

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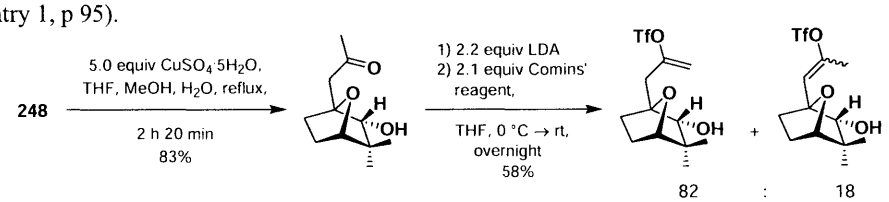
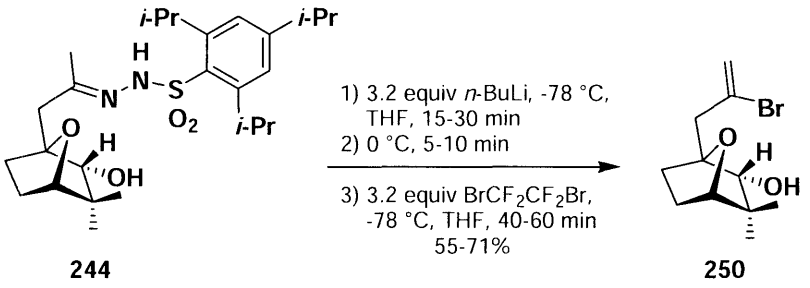
[93] For the purpose of recovering the corresponding ketone, the (*Z*)-hydrazone was subjected to the conditions reported by Attanasi (Attanasi, O.; Gasperoni, S.; Carletti, C. *J. Prakt. Chem.* **1980**, *322*, 1063.) The vinyl triflate was synthesized from this ketone using LDA and Comins' reagent at −78 °C in THF. We found that the ratio of vinyl triflates obtained was significantly better than when dione **128** was used as the starting material (compare Table 3, entry 1, p 95).



"Br^+" is 1,2-dibromo-1,1,2,2-tetrafluoroethane ($BrCF_2CF_2Br$) because it is more reactive than its hydrogen analog ($BrCH_2CH_2Br$, bp 131 °C/760 mmHg) and thus should react readily with vinyllithium **246**. The volatility of $BrCF_2CF_2Br$ (bp 46-47 °C/760 mmHg) should facilitate the purification of the desired product. The success of the reaction depends on trapping vinyllithium **246** without pre-mature quenching to give the alkene, thus extra care should be taken in drying the starting materials. The electrophile was added at −78 °C as a solution in THF to a solution of the vinyllithium at the same temperature. Fortunately, the trapping went smoothly to furnish the desired vinyl bromide **250** in good yield (Scheme 101).[94]

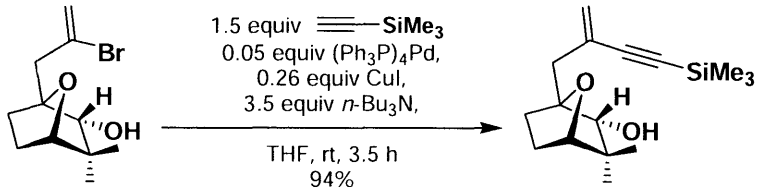
Scheme 101



244 **250**

Besides being a precursor for the synthesis of vinylallene **169**, vinyl bromide **250** could serve as a coupling partner with trimethylsilylacetylene. Sonohashira coupling of bromide **250** proceeded efficiently to give enyne **251** in excellent yield after a couple of optimization experiments (Scheme 102).

Scheme 102



250 **251**

[94] Vinyl bromide **247** was obtained in 55 and 56% yields in reactions run on 60 and 96 mg of **244**, respectively. When the reaction was run on 378 mg of **244**, vinyl bromide **247** was obtained in 71% yield.

We have successfully prepared the key vinyl bromide **250** for our vinylallene synthesis. Although there was a slight variation in the synthesis which involved the reduction of ketone **242** to an alcohol (compare **175**, where X = Br, and **250**), this is still an efficient synthetic route, considering that we have overcome the regioselectivity problem in the alkene formation present in other routes (vide supra).

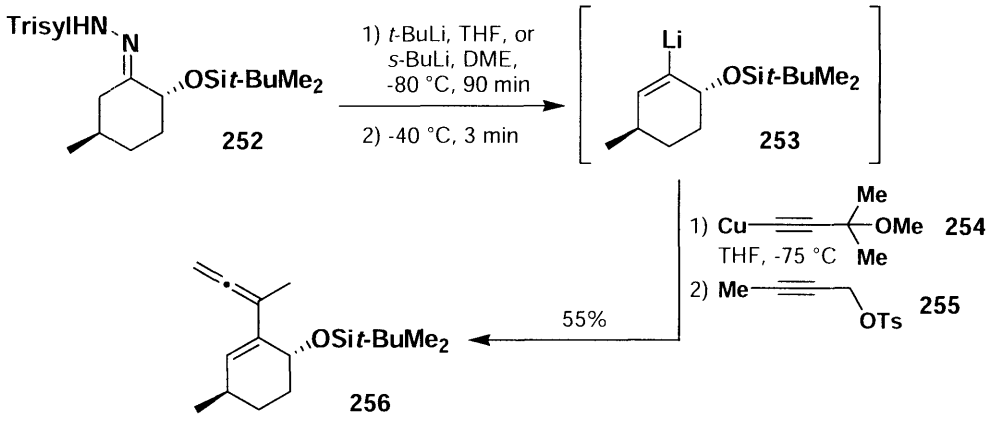
Synthesis of a Key Vinylallene[24c,95] Intermediate from Vinyl Bromide 250: A Model Study

We decided to study the synthesis of a model vinylallene intermediate from vinyl bromide **250** prepared by the route described in the previous section. In these studies, we planned to prepare a vinyl cuprate from vinyl bromide **250** or a related compound and use it to prepare a model vinylallene. As a result, we have to convert **250** to a derivative which would be more suitable for copper chemistry. Furthermore, we also have to choose a reaction partner to react with the vinyl cuprate as a model for the synthesis of the vinylallene intermediate.

To the best of our knowledge, there is only one example in the literature of the synthesis of a vinylallene derivative achieved by a Shapiro reaction sequence.[96] As shown in Scheme 103, vinyllithium **253** generated from Shapiro fragmentation of trisylhydrazone **252** was converted in situ to mixed higher-order vinyl cuprate by treatment with alkynylcopper **254**, followed by addition to propargyl tosylate **255** to furnish vinylallene **256** in good yield.

[95] *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1-2.
[96] Baudouy, R.; Sartoretti, J. *Tetrahedron* **1983**, *39*, 3293.

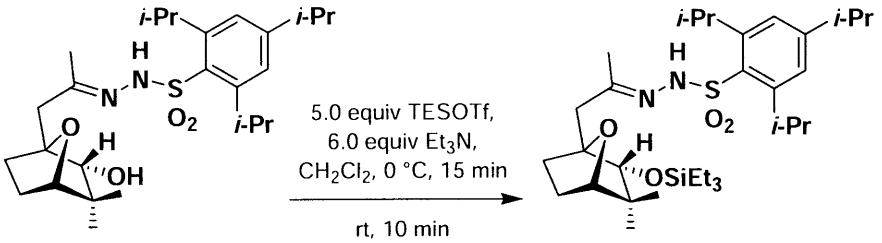
Scheme 103



Initially, we intended to employ a one-pot Shapiro fragmentation in our vinylallene synthesis. However, as described above, in order for the Shapiro reaction to be performed successfully, the ketone on the bicyclic ring would have to be reduced to the corresponding alcohol **244** and Shapiro fragmentation of this material would generate vinyllithium **246** (Scheme 99, p 105) with free alkoxide anion. We were concerned that this free alkoxide anion might have a negative effect on the formation of the mixed vinyl cuprate. Therefore, we sought a way to protect this alcohol before performing the Shapiro reaction.

We chose to protect the hydroxyl group of **244** as triethylsilyl (TES) ether by subjecting hydrazone alcohol **244** to TESOTf and Et_3N in CH_2Cl_2 at 0 °C. During the protection step, partial silylation of one of the hydrazone nitrogens was observed. Nonetheless, the desired TES-protected alcohol was obtained in ca. 72% yield.

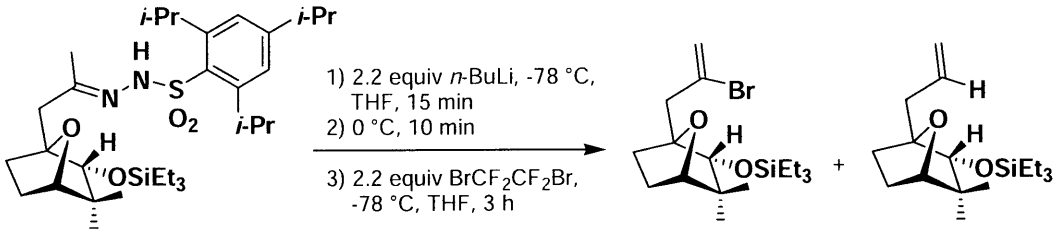
Scheme 104



244 **257**

We proceeded to test the Shapiro reaction by subjecting hydrazone **257** to conditions identical to those employed for the preparation of vinyl bromide **250** from hydrazone **244** (Scheme 101, p 107). Disappointingly, the reaction proceeded poorly to provide both vinyl bromide **258** and alkene **259** in approximately 49% and 11%, respectively (Scheme 105). We hypothesized that the presence of a bulky TES group in the molecule may have hindered the reaction between vinyllithium intermediate and $BrCF_2CF_2Br$.

Scheme 105

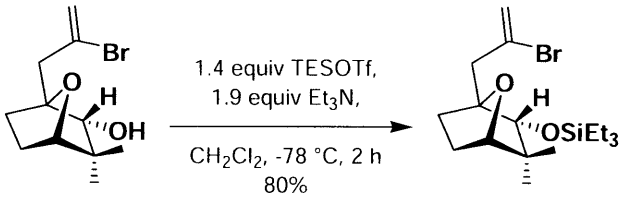


257 **258** **259**

49% 11%

As the Shapiro fragmentation of TES-protected hydrazone **257** did not produce the corresponding vinyllithium as efficiently as the non-protected derivative (**244**, Scheme 101, p 107), we decided to abandon the idea of conducting the vinylallene synthesis in one pot. Instead, we decided to perform the synthesis of vinyl bromide **250** as usual and install the TES protecting group later. This step of the synthesis could be carried out employing similar conditions analogous to those employed previously (Scheme 106).

Scheme 106



250 **258**

In our proposed model studies for the synthesis of our key vinylallene intermediate, we intended to use similar conditions as reported by Baudouy.[96] Treatment of bromide **258** with 2.0 equiv of *t*-BuLi should provide the corresponding vinyllithium. As for the copper reagent, we planned to use the copper acetylide derivative prepared from copper(I) iodide and the lithiated derivative of 3-methyl-3-methoxy-1-butyne.[97] Mixing the vinyllithium with the copper acetylide derivative would provide the required mixed vinyl cuprate.[98] For the propargyl partner, we planned to use a tosylate derivative in our reaction.

Assuming that we have access to a generalized enantiomerically enriched propargyl alcohol, which we use to prepare tosylate derivative **261**, and that we are employing the correct enantiomer of vinyl bromide **258** in our model studies, the S_N2' *anti*-addition[77] with complete stereoselectivity is anticipated to furnish the product shown (**262**) in Scheme 107 as the only product.

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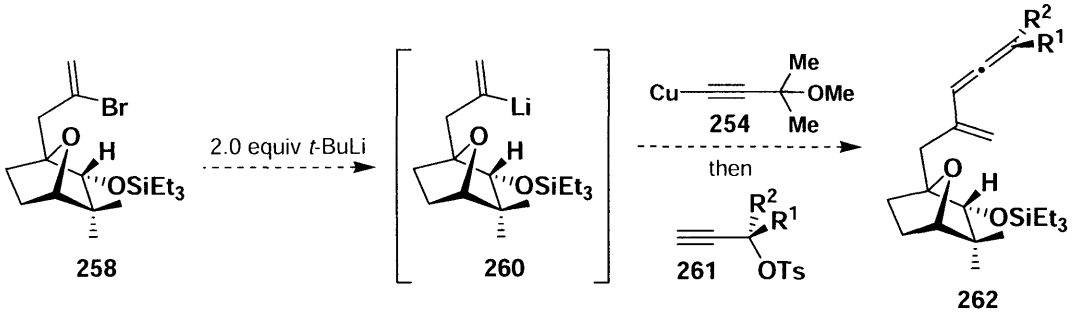
[97] Used as the non-transferable ligand in higher-order mixed cuprates, see: Corey, E. J.; Floyd, D. M.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418.

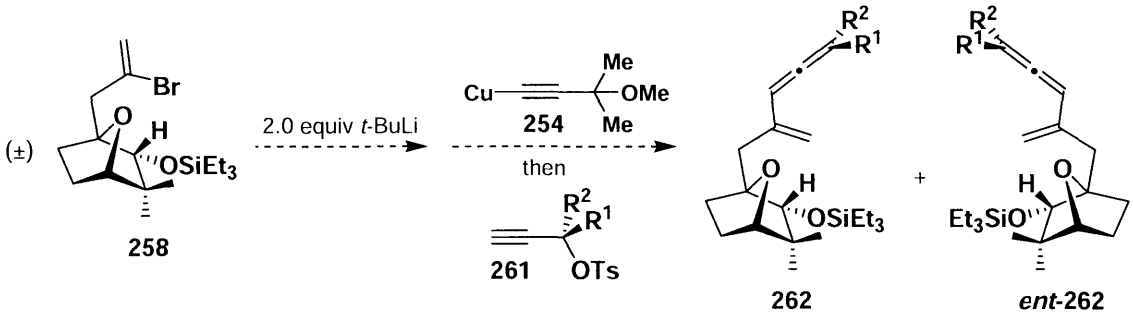
[98] A number of books and reviews are available on copper chemistry. For a general review, see: *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002. For excellent accounts of organocopper chemistry and the practical aspects of it, see: (a) *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; The Practical Approach in Chemistry Series; Oxford University Press: New York, 1994. (b) Lipshutz, B. H. Organocopper Chemistry. In *Organometallics in Synthesis: A Manual*, 2nd ed.; Schlosser, M., Ed.; John Wiley & Sons, Ltd.: Chichester, England, 2002; p 665.

Scheme 107



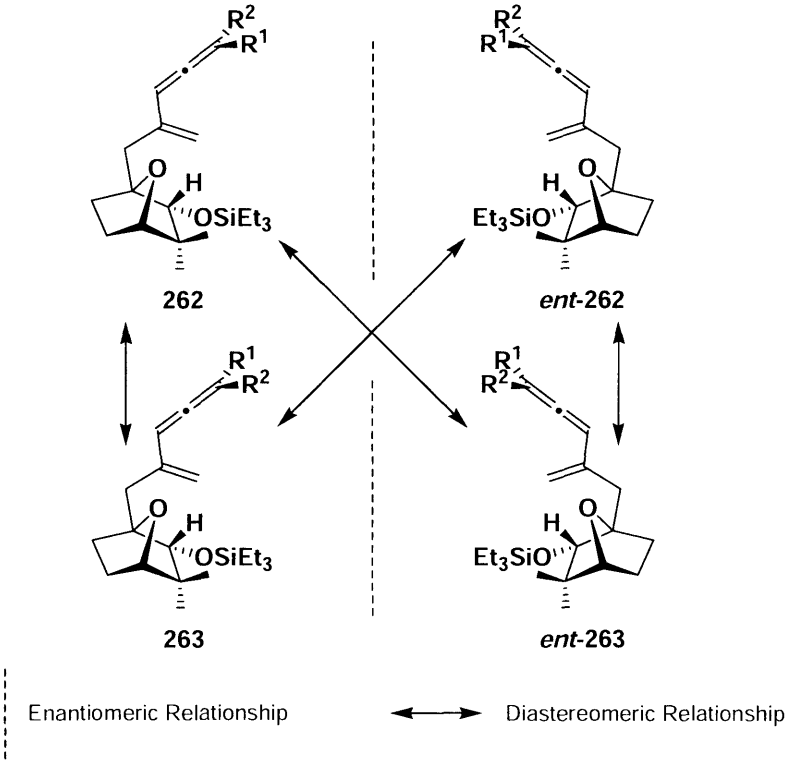
So far in our studies the material we have used for the synthesis of A-ring vinyl bromide **258** is racemic. If we assume that we still have access to enantiomerically enriched **261** and that the *anti*-addition remains completely stereoselective, the successful reaction should afford products illustrated in Scheme 108.

Scheme 108



The synthesis of **261** may not be trivial and, as a result, the more easily accessible racemic mixture would most likely be employed in our actual model studies. With the assumption that *highly* stereoselective S_N2' *anti*-addition would still operate, we would obtain four different stereoisomeric products. These four stereoisomeric products can be grouped into either two enantiomeric pairs [(**262**, ***ent*-262**) and (**263**, ***ent*-263**)] or four diastereomeric pairs [(**262**, **263**), (**262**, ***ent*-263**), (***ent*-262, 263**), and (***ent*-262**, ***ent*-263**)] as shown in Scheme 109. In theory, all four stereoisomeric products should be obtained in equal amounts.

Scheme 109

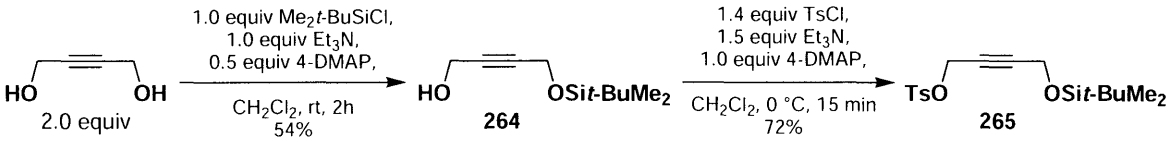


However, we cannot assume that complete *anti*-selectivity is always operating (i.e., anti/syn = 100:0). As a result, the amount of each product will most likely not be evenly distributed, or it will not be observed as a 50:50 diastereomeric mixture in ^{1}H NMR spectrum. In this situation, the analysis of data could be difficult. For instance, the uneven distribution of products could be a result of unequal reaction rates between the two enantiomers of **258** with an enantiomer of **261** or vice versa (Scheme 108). It could also be because the anti-stereoselectivity in the addition step is not completely 100:0. For all of these likely unfortunate shortcomings, we decided against any of the secondary propargyl tosylate derivatives as the reaction partner.

We were left with the choice between primary (**261**, $R^1 = R^2 = H$) and tertiary (**261**, $R^1 = R^2 \neq H$) propargyl derivatives. Because we have decided to use tosylate as the leaving group, we chose to use a primary propargyl tosylate in our model studies because it is more easily prepared

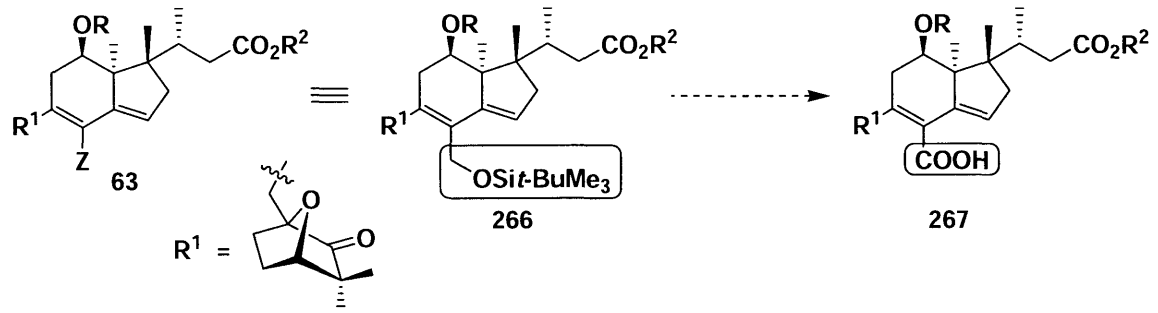
and handled than the tertiary derivative. We chose to prepare primary propargyl tosylate **265** shown in Scheme 110. Tosylate derivative **265** was easily prepared in two steps from 2-butyne-1,4-diol. To alleviate the problem of bis-silylation of the alcohol, the diol was used in excess. However, we obtained alcohol **264** in only 54% yield together with 36% of the bis-silylated product. Tosylation was conducted in standard conditions and delivered tosylate **265** in good yield.

Scheme 110



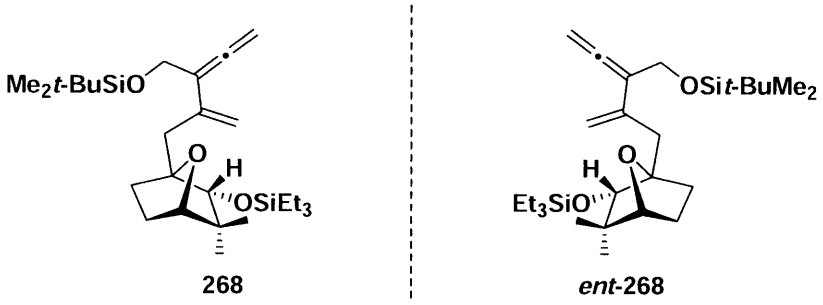
In addition to serving as a primary tosylate derivative, **265** also bears a silyloxymethylene group. This model substrate will allow us to test addition of a vinyl cuprate in the presence of this side-chain, which in the actual reaction substrate could be elaborated to the carboxylic acid moiety present in the natural product (Scheme 111).

Scheme 111



Since we had both of the required starting materials in hand, we were ready to perform our model experiments. The expected product upon reaction of racemic **258** and **265** should still be a racemic mixture (**268** and ***ent*-268**), which would be observed as a single product in the ^{1}H NMR spectrum.

Scheme 112



268 ***ent*-268**

Thus, a −78 °C solution of carefully dried vinyl bromide **258** in a 5:1 mixture of *n*-pentane/Et_2O[99] was treated with 2.0 equiv of *t*-BuLi. In initial experiments, a room temperature *t*-BuLi solution was added directly to the reaction mixture. This practice resulted in major decomposition of the bromide, presumably reacting in the formation of an alkyne via β-elimination.[100] A much cleaner reaction was observed when a pre-cooled (−78 °C) solution of *t*-BuLi in pentane was added to the −78 °C solution of the vinyl bromide down the side wall of the cooled reaction flask. Addition of this solution to the copper acetylide derivative solution (prepared as described previously) resulted in a bright yellow and slightly cloudy mixture. This mixture was warmed to ca. −50 °C for 15 min and then cooled back to −78 °C for the addition of **265**.

A pre-cooled (−78 °C) solution of tosylate **265** in THF was added to the mixed vinyl cuprate solution. The resulting mixture was warmed to room temperature over 4.5 h, followed

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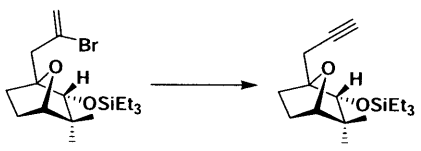
[99] Generation of vinyllithium from vinyl bromide via lithium-bromide exchange with *t*-BuLi is not trivial. Temperature or solvent composition or both have to be considered to achieve optimal results. See: (a) Köbrich, G.; Trapp, H. *Chem. Ber.* **1974**, *107*, 847. (b) Neumann, H.; Seebach, D. *Tetrahedron Lett.* **1976**, *17*, 4839. (c) Bailey, W. F.; Wachter-Jurcsak, N. M.; Pineau, M. R.; Ovaska, T. V.; Warren, R. R.; Lewis, C. E. *J. Org. Chem.* **1996**, *61*, 8216.

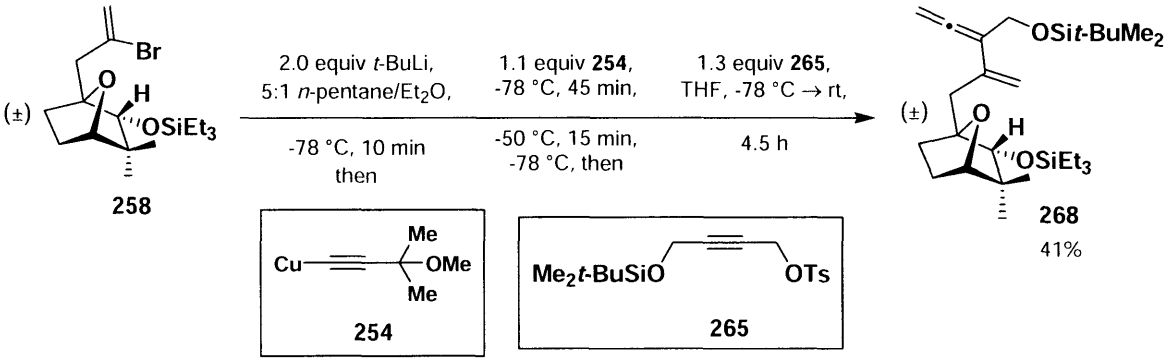
[100] A very common problem in vinyllithium generation from vinyl bromide and *t*-BuLi:



258

by aqueous workup. Following a few purification attempts both by conventional column chromatography and preparative TLC, the desired vinylallene was successfully obtained in 41% from vinyl bromide **258** (Scheme 113). This material was fully characterized by ^{1}H and ^{13}C NMR, IR and high resolution MS.

Scheme 113



Summary

In this chapter we have demonstrated several approaches to achieve an efficient synthesis of the A-ring intermediate required for the total synthesis of glycinoeclepin A. We unsuccessfully pursued the first strategy which relies on the stereoselective addition of an enynyl metal species to the aldehyde of the C,D-ring precursor. This strategy was later abandoned and we continued to pursue an alternative strategy which relies on the generation of a vinylallene intermediate via vinyl metal S_N2' *anti*-addition to a propargyl alcohol derivative. Our studies on this strategy resulted in a successful generation of a model vinylallene. We hope that with the further development and optimization of this reaction in the near future, the total synthesis of glycinoeclepin A will soon be successfully completed.

Part III

Experimental Procedures

General Procedures. All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin layer chromatography was performed on EMD (Merck) precoated glass-backed silica gel 60 F-254 0.25 mm plates. Preparative-scale thin layer chromatography was performed on Analtech precoated glass-backed silica gel GF 2000 μm plates. Column chromatography was performed on Silicycle silica gel 60 (230-400 mesh) or Sorbent Technologies silica gel 60 (230-450 mesh).

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane and diethyl ether were purified by pressure filtration through activated alumnia. Tetrahydrofuran was distilled under argon from sodium benzophenone ketyl or dianion or purified by pressure filtration through activated alumina. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Benzene, diisopropylamine, *n*-butylamine, triethylamine, triethylsilyl trifluoromethanesulfonate, and were distilled under argon from calcium hydride. Copper(I) iodide was either extracted with THF for 24 h in a Soxhlet extractor or re-crystallized from saturated aqueous potassium iodide solution and then dried under vacuum (0.1 mmHg). Palladium(II) chloride (bis)triphenylphosphine was recrystallized from boiling chloroform. *n*-BuLi was titrated

according to the Watson-Eastham method using BHT in THF or toluene at 0 °C with 1,10-phenanthroline as an indicator.[101]

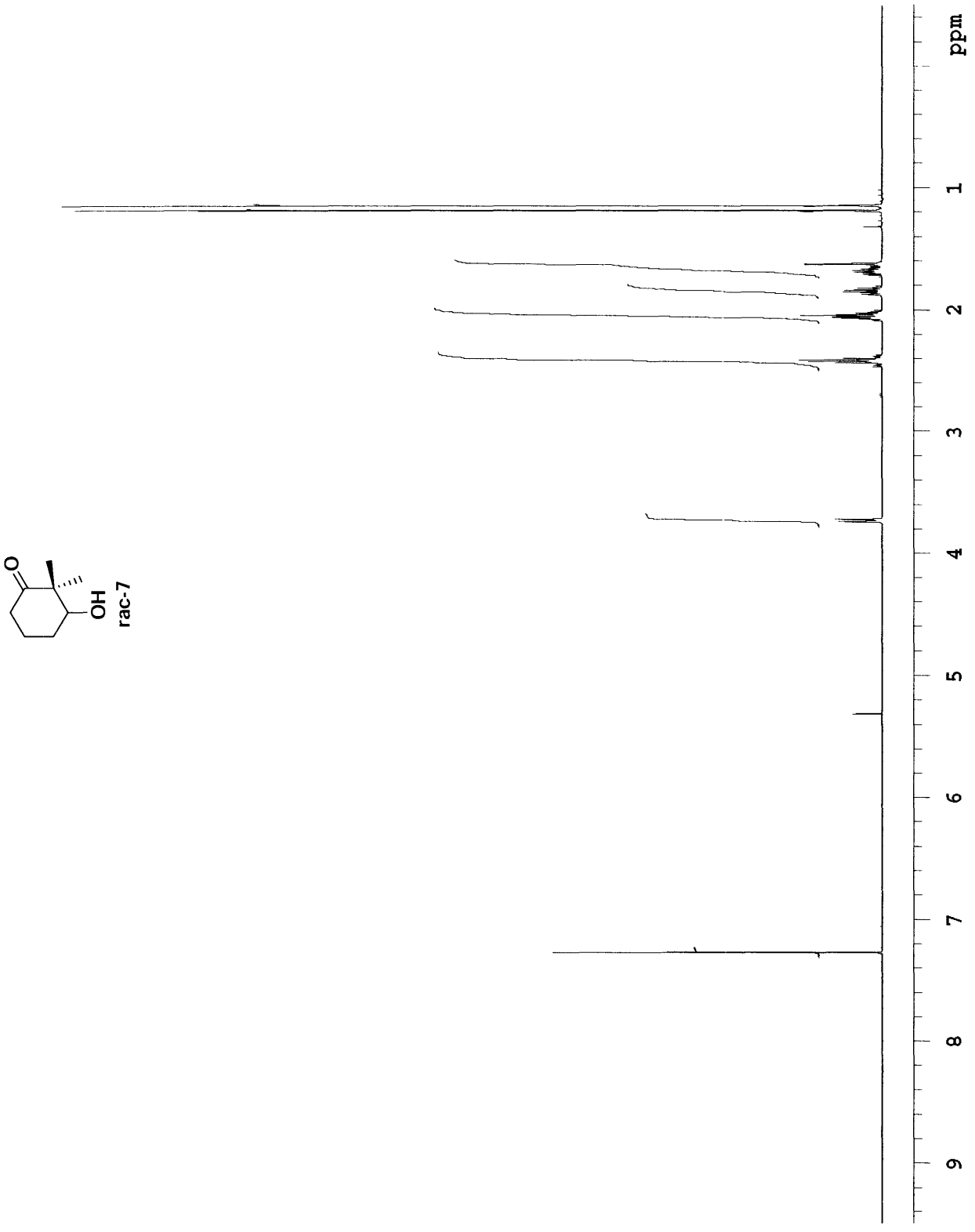
Instrumentation. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on Varian XL-300 (300 MHz), Varian Unity 300 (300 MHz), and Varian Inova 500 (500 MHz) spectrometers. ^{13}C NMR spectra were recorded on Varian XL-300 (75 MHz) and Varian Inova 500 (125 MHz) spectrometers. ^{1}H NMR chemical shifts and ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane. High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 telsa Fourier transform mass spectrometer. Low-resolution Mass Spectra (LRMS) were measured on a Hewlett Packard 5890 Series II Gas Chromatograph with Hewlett Packard 5971 series mass selective detection. Elemental analyses were performed by E&R Microanalytical Laboratory, Inc. of Parsippany, NJ.

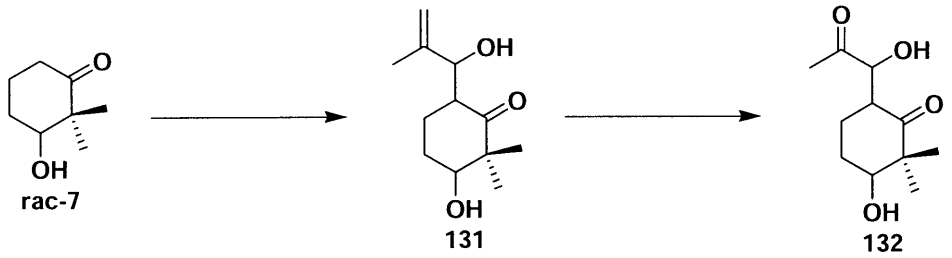
[101] (a) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165. (b) Ellison, R. A.; Griffin, R.; Kotsonis, F. N. *J. Organomet. Chem.* **1972**, *36*, 209.

3-Hydroxy-2,2-dimethylcyclohexanone (rac-7)

A 250-mL, one-necked, round-bottomed flask fitted with a rubber septum and an argon inlet needle was charged with 180 mL of THF and 2,2-dimethylcyclohexane-1,3-dione (**5**) (12.0 g, 85.6 mmol). A solution of sodium borohydride (0.810 g, 21.4 mmol) in 10 mL of water was then added via pipette over 5 min, and the resulting mixture was stirred at rt for 20 min. The reaction mixture was transferred to a 500-mL separatory funnel containing 100 mL of saturated NaCl solution and the aqueous layer was separated and extracted with three 100-mL portions of Et_2O. The combined organic phases were washed with 100 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 12.2 g of a colorless oil. Column chromatography on 400 g of silica gel (elution with 20% EtOAc-hexane) provided 9.129 g (75%) of hydroxy ketone **rac-7** as a colorless oil. Compound **rac-7** exhibits spectroscopic properties identical to values reported elsewhere.[102]

[102] See reference 20(a).


O
OH
rac-7
ppm
1
2
3
4
5
6
7
8
9

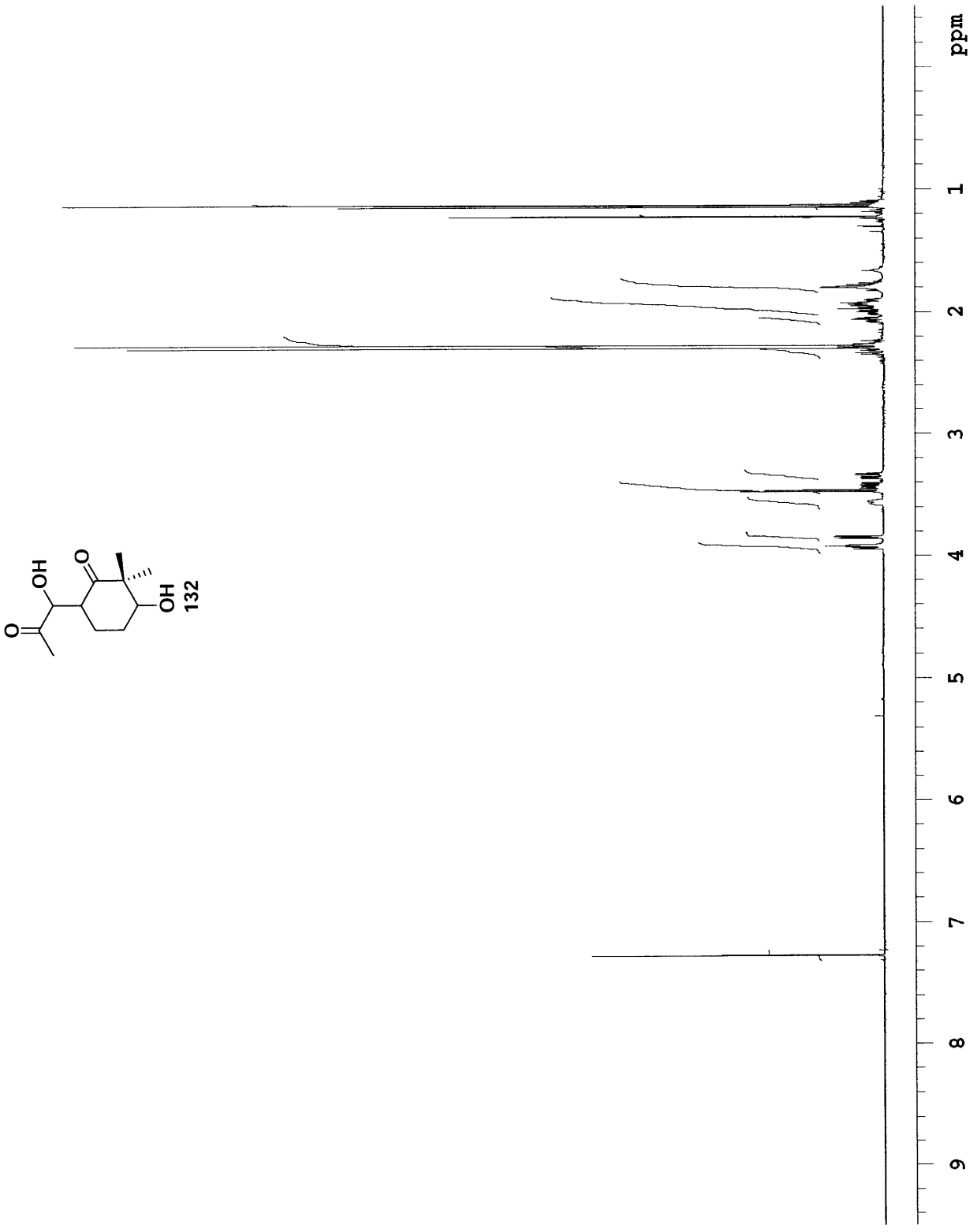


A 500-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, a rubber septum, and a ground-glass stopper was charged with a 3-cm football-shaped magnetic stir bar, diisopropylamine (8.2 mL, 5.9 g, 59 mmol) and 160 mL of THF and then cooled at 0 °C while 24.8 mL of *n*-BuLi solution (2.22 M in hexanes, 55 mmol) was added dropwise over 8 min. The resulting yellow solution was stirred at 0 °C for 20 min and then cooled to –78 °C.

A solution of ketone **rac-7** (dried by azeotropic distillation of benzene) (2.53 g, 17.8 mmol) in 7 mL of THF (pre-cooled at −78 °C) was then added dropwise over 10 min (with 3 mL THF rinse), and the resulting yellow solution was stirred at −78 °C for 40 min. A solution of methacrolein (3.00 mL, 2.54 g, 35.6 mmol) in 7 mL of THF (pre-cooled at −78 °C) was then added dropwise over 7 min (with 3 mL THF rinse), and the resulting thick yellow mixture was stirred at −78 °C for 3 h. Half-saturated aq NH_4Cl solution (50 mL) pre-cooled at 0 °C was then added dropwise over 5 min. The resulting mixture was immediately transferred to a 500-mL separatory funnel with the aid of 50 mL of EtOAc and 30 mL of water and the aqueous layer was separated and extracted with three 100-mL portions of EtOAc. The combined organic phases were washed with 100 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 4.29 g of **131** as a yellow oil which was used in the next step without purification.

A 500-mL, one-necked, round-bottomed flask was charged with 160 mL of CH_2Cl_2, 20 mL of MeOH, and the alkene **131** prepared as described above. The resulting solution was

cooled to –78 °C and a stream of ozone was bubbled through the reaction mixture via pipette (ca. 30 min) until the solution turned purple-blue. The resulting solution was degassed with a stream of argon for 10 min at –78 °C, and then Me_2S (6.5 mL 5.5 g, 89 mmol) was added via pipette over 2 min. The pale yellow solution was allowed to warm to rt over 2 h, and then concentrated to afford 5.86 g of a yellow oil. Column chromatography on 95 g of silica gel (gradient elution with 70-100% MTBE-hexane) gave 3.029 g of impure products. This impure material was further purified on 75 g of silica gel (gradient elution with 70-100% MTBE-hexane) to give 2.127 g (56%) of diol **132** (55:45 mixture of diastereomers) as a pale yellow oil. For *both* diastereomers: IR (film) 3423, 2972, 2938, 1702, 1252, 1134, 1066 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) for *major* diastereomer: 3.85 (dd, J = 3.0, 8.5 Hz, 1H), 3.56-3.58 (m, 1H), 3.47 (d, J = 8.0 Hz, 1H), 3.35 (ddd, J = 3.0, 6.0, 13.5 Hz, 1H), 2.28 (s, 3H), 1.92-2.09 (m, 3H), 1.73-1.83 (m, 2H), 1.14 (s, 3H), 1.13 (s, 3H); for *minor* diastereomer: 3.92-3.95 (m, 2H), 3.47 (d, J = 8.0 Hz, 1H), 3.43 (ddd, J = 3.5, 6.5, 13.5 Hz, 1H), 2.30 (s, 3H), 2.23-2.36 (m, 2H), 1.90-1.96 (m, 2H), 1.80 (br s, 1H), 1.22 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) for *major* diastereomers: 214.7, 210.1, 77.9, 76.6, 52.0, 49.6, 29.5, 25.9, 23.7, 21.0, 18.8; for *minor* diastereomer: 216.2, 210.9, 78.8, 78.1, 50.8, 48.8, 27.9, 26.3, 25.0, 24.2, 20.7. HRMS-ESI Calcd for $C_{11}H_{18}O_4$: 237.1097 $[M+Na]^+$. Found: 237.1094.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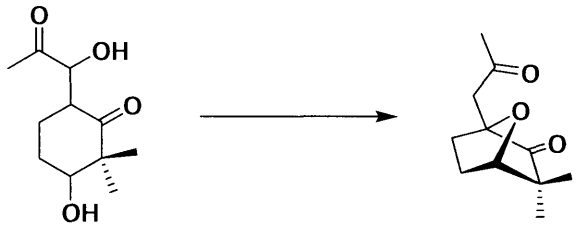
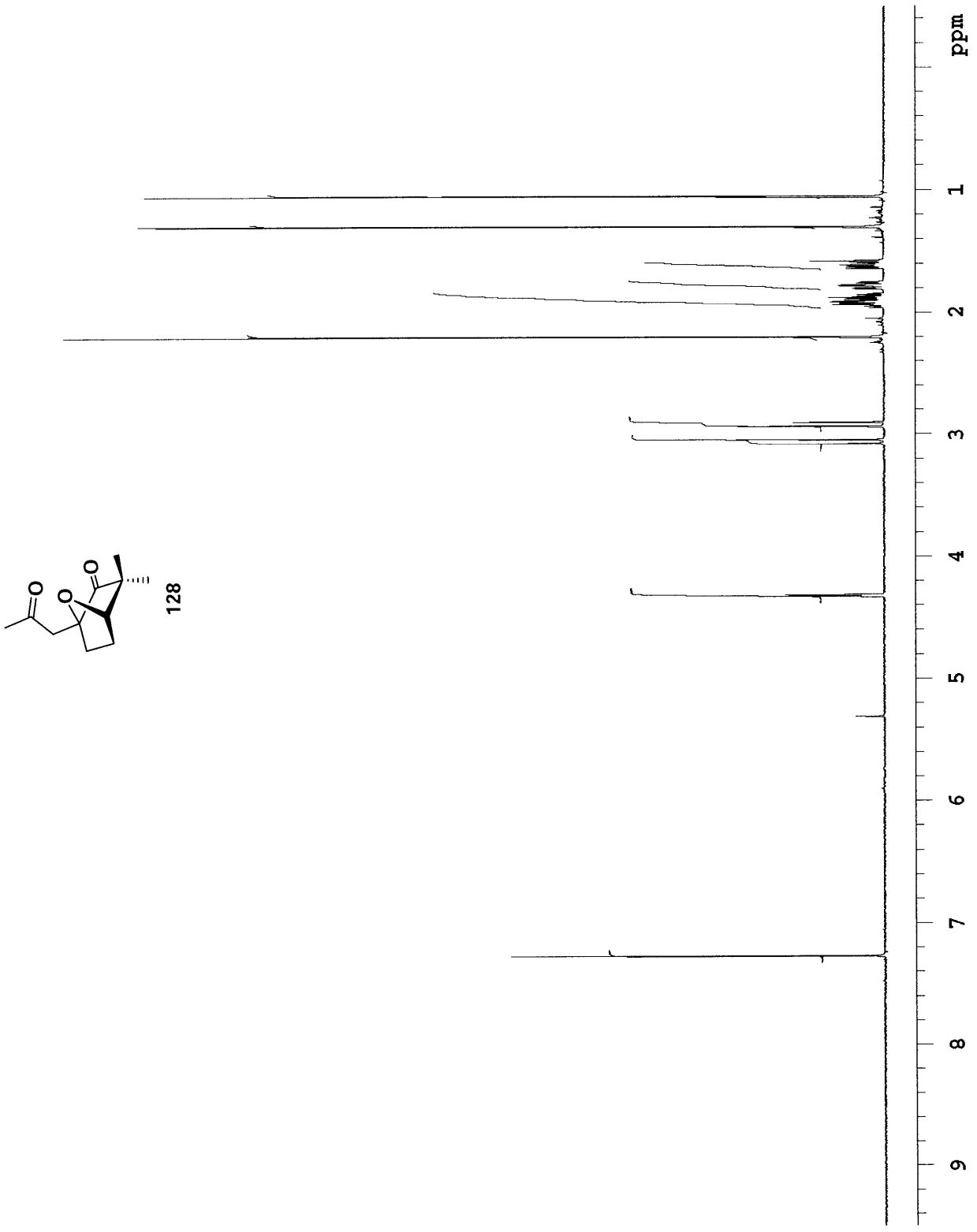


132 128

3,3-Dimethyl-1-(2-oxopropyl)-7-oxabicyclo[2.2.1]heptan-2-one (128)

A 500-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with quinolinium camphorsulfonate (2.504 g, 6.93 mmol) and 200 mL of benzene. The mixture was heated at reflux until the solid dissolved (ca. 15 min), and then allowed to cool to rt. A solution of diketone **132** (1.489 g, 6.93 mmol) in 30 mL of benzene was added in one portion, and the reaction mixture was heated at 40-50°C for 40 h. The dark brown solution was transferred to a 1-L separatory funnel aided by 30 mL of EtOAc. The dark brown solution was extracted with two 50-mL portions of saturated $NaHCO_3$ solution, two 50-mL portions of 10% aq HCl solution, and two 50-mL portions of sat. aq. NaCl solution. The combined aqueous phases were back-extracted with four 50-mL portions of EtOAc and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated to give 1.434 g of a brown oil. Column chromatography on 70 g of silica gel (elution with 20% EtOAc-hexane) provided 0.572 g (42%) of **128** as a pale yellow oil: IR (CH_2Cl_2) 2986, 1733, 1267, 1046 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 4.30 (d, J = 4.9 Hz, 1H), 3.04 (d, J = 16.8 Hz, 1H), 2.90 (d, J = 16.5 Hz, 1H), 2.18 (s, 3H), 1.82-1.94 (m, 2H), 1.72-1.78 (m, 1H), 1.56-1.61 (m, 1H), 1.27 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 217.0, 204.1, 85.7, 84.4, 49.4, 43.1, 31.1, 30.0, 25.0, 23.3, 20.2. HRMS-ESI Calcd for $C_{11}H_{16}O_3$: 219.0997 $[M+Na]^+$. Found: 219.0997.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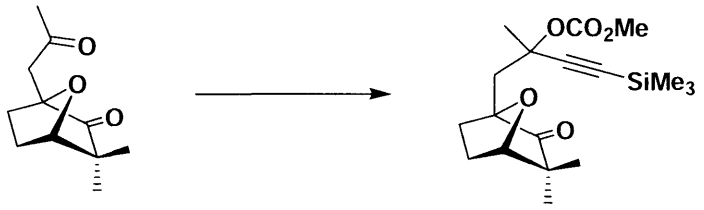
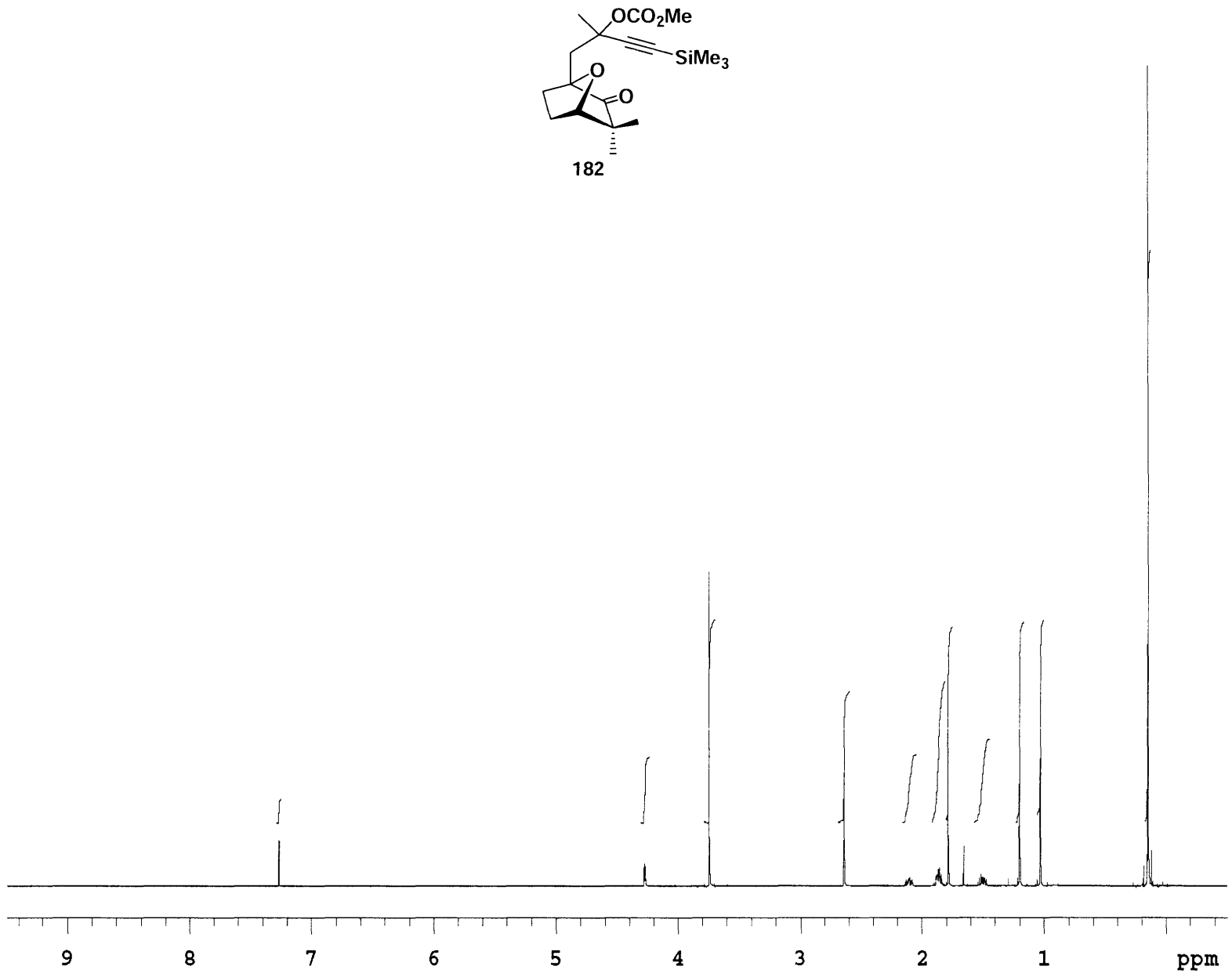


128 182

Carbonic acid 1-(3,3-dimethyl-2-oxo-7-oxa-bicyclo[2.2.1]hept-1-ylmethyl)-1-methyl-3-trimethylsilyl-prop-2-ynyl ester methyl ester (182)

A 10-mL, one-necked, pear-shaped flask fitted with a rubber septum and an argon inlet needle was charged with 2 mL of THF and trimethylsilylacetylene (0.097 g, 0.14 mL, 0.98 mmol) and cooled to −118 °C (external temperature) in ethanol-liquid nitrogen slush bath. To this solution was added a solution of *n*-BuLi (2.45 M in hexanes, 0.36 mL, 0.90 mmol) via syringe over 1 min, and the resulting solution was stirred for 20 min at −118 °C. A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter and rubber septum was charged with the dione **128** (0.161 g, 0.820 mmol) and 5 mL of THF, and cooled at −118 °C. The lithium acetylide solution was then transferred via cannula into the reaction mixture (1 mL of THF used to rinse) over 3 min. The reaction mixture was stirred for 20 min at −118 °C and rapidly treated with methyl chloroformate (0.23 g, 0.19 mL, 2.46 mmol). The resulting mixture was allowed to warm to rt over 3 h and it was added with 10 mL of sat. aq. $NaHCO_3$ solution. The aqueous layer was separated and extracted with three 10-mL portions of EtOAc. The combined organic phases were washed with 30 mL of sat. aq. NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a 0.257 g of a crude yellow oil. Column chromatography on 25 g of silica gel (gradient elution with 0-40% EtOAc-hexane) afforded 0.185 g (64%) of the desired carbonate **182** as a pale yellow oil: IR (film) 2976, 2872, 2176, 1759, 1441, 1255, 845 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 4.28 (d, J = 4.0 Hz, 1H), 3.75 (s, 3H), 2.64 (s, 2H), 2.08-2.14 (m, 1H), 1.83-1.90 (m, 2H), 1.79 (s, 3H), 1.47-1.54 (m, 1H), 1.20 (s, 3H), 1.03 (s, 3H), 0.15 (s,

9H); ^{13}C NMR (125 MHz, $CDCl_3$): 217.2, 153.3, 105.1, 90.8, 87.1, 83.8, 76.0, 54.5, 48.9, 39.1, 30.0, 27.8, 25.0, 23.3, 20.2, -0.1. HRMS-EI Calcd for $C_{18}H_{28}O_5Si$: 375.1598 $[M+Na]^+$. Found: 375.1597.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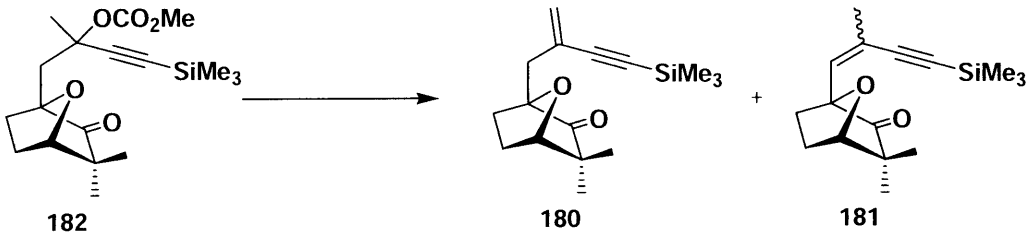
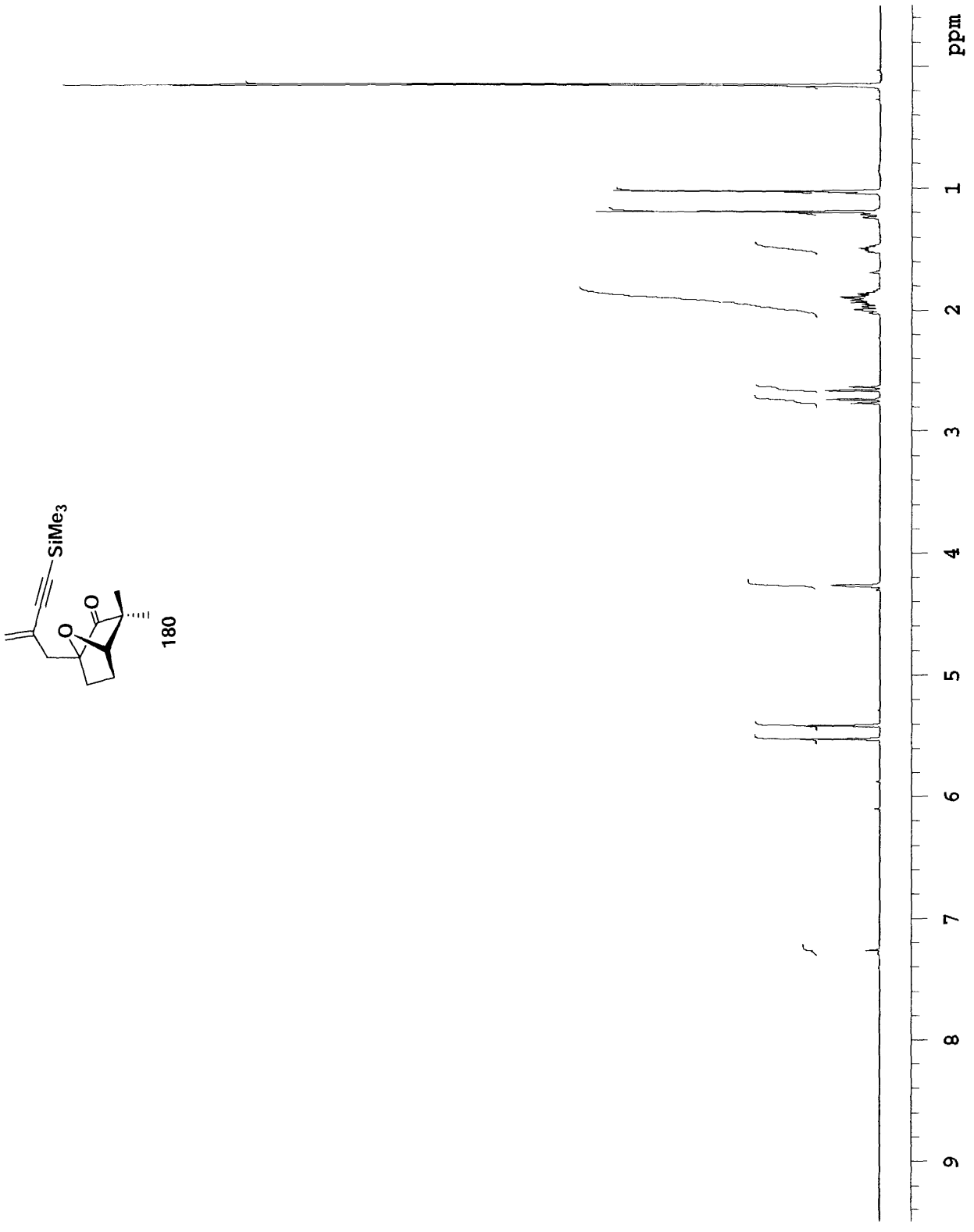


182 180 181

3,3-Dimethyl-1-(2-methylene-4-trimethylsilylbut-3-ynyl)-7-oxa-bicyclo[2.2.1]heptan-2-one (180 and 181)

A 10-mL, thick-walled glass tube fitted with a rubber septum was charged with $Pd(OAc)_2$ (0.010 g, 0.045 mmol), Ph_3P (0.035 g, 0.14 mmol), 0.5 mL of THF, and a solution of the propargylic carbonate **182** (0.159 g, 0.45 mmol) in 1.3 mL of THF. The reaction vessel was sealed with a matching cap and then heated in a CEM "Discover" microwave apparatus at 115 °C for 15 min (150 W, atmospheric pressure). The resulting brown mixture obtained was filtered through a short plug of 5 g of florisil with the aid of 80 mL of Et_2O and then concentrated to afford 0.106 g of a brown oil. Column chromatography on 13 g of silica gel (gradient elution with 0-15% EtOAc-hexane) provided 0.059 g (47%) of the bicyclic enynes **180** and **181** (89:11 by ^1H NMR analysis) as a pale yellow oil. For **180**: IR (film): 2966, 2870, 2147, 1761, 1250, 844 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.54 (d, J = 1.5 Hz, 1H), 5.43 (app s, 1H), 4.28 (d, J = 5.0 Hz, 1H), 2.77 (d, J = 15.0 Hz, 1H), 2.66 (d, J = 15.0 Hz, 1H), 1.84-2.04 (m, 3H), 1.48-1.53 (m, 1H), 1.21 (s, 3H), 1.04 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 217.1, 126.4, 126.2, 106.0, 94.8, 87.8, 83.9, 49.4, 36.0, 29.1, 25.4, 23.1, 20.2, 0.0. HRMS-EI Calcd for $C_{18}H_{28}O_5Si$: 299.1438 $[M+Na]^+$. Found: 299.1443.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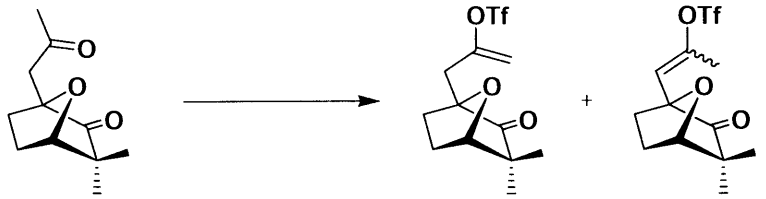
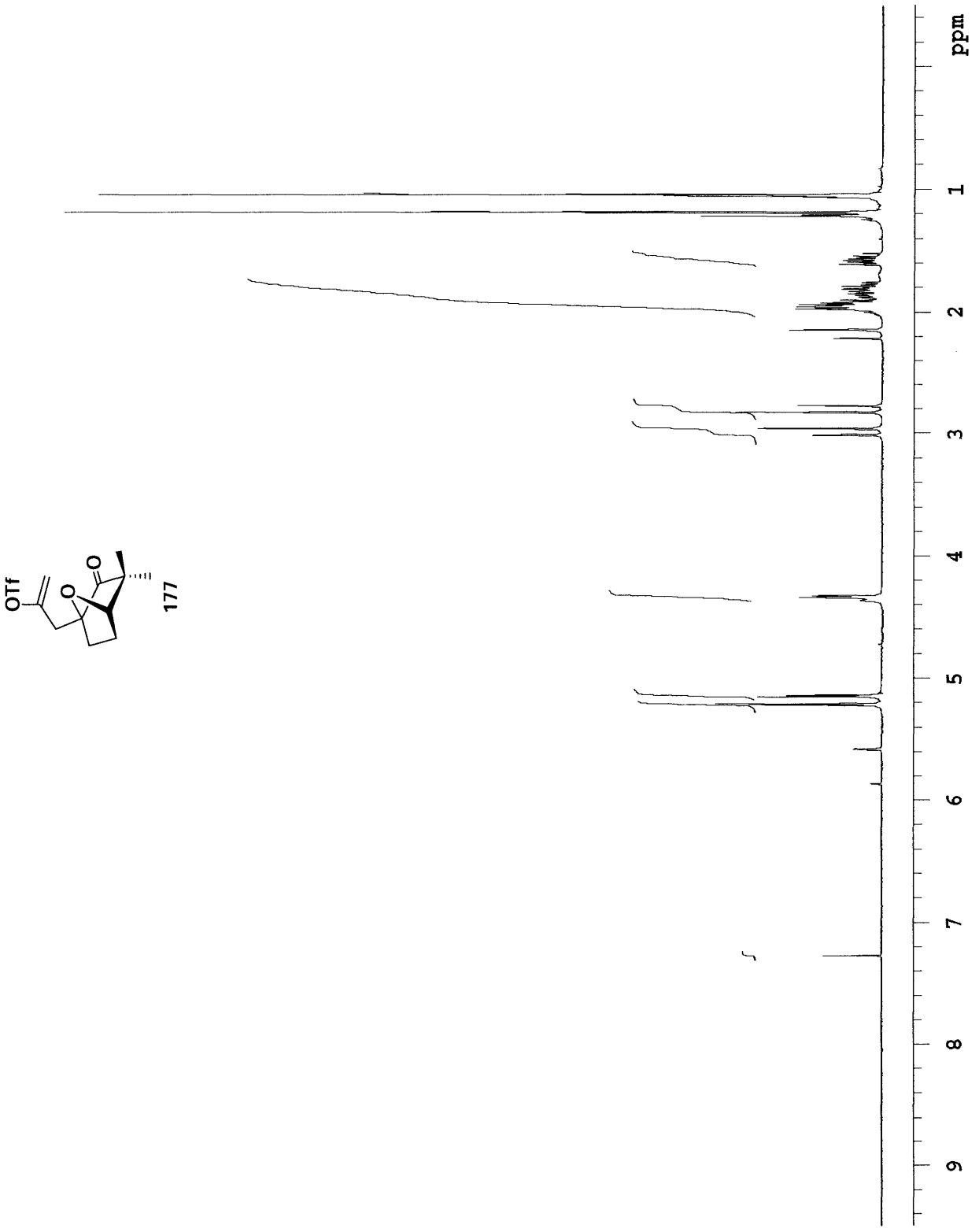


128 177 229

Trifluoromethanesulfonic acid 1-(3,3-dimethyl-2-oxo-7-oxa-bicyclo[2.2.1]hept-1-ylmethyl)-vinyl ester (177 and 229)

A 25-mL, one-necked, round-bottomed flask fitted with a rubber septum and an argon inlet needle was charged with 6.5 mL of THF and 2,2,6,6-tetramethylpiperidine (0.11 mL, 0.092 g, 0.65 mmol). The resulting solution was cooled at 0 °C and 0.23 mL of *n*-BuLi (2.45 M in hexanes, 0.56 mmol) was added dropwise over 1 min. The resulting pale yellow solution was stirred at 0 °C for 15 min and then cooled at −118 °C (external temperature) in an ethanol-liquid nitrogen slush bath. A solution of the dione **128** (0.091 g, 0.46 mmol) in 3 mL of THF in a 10-mL, pear-shaped flask was cooled at −118 °C and then transferred via a 25-cm cannula over 5 min into the solution of LiTMP. The resulting yellow-orange solution was stirred for 40 min and *N*-(5-chloro-2-pyridyl)trifimide (Comins' reagent) (0.366 g, 0.93 mmol) was added in one portion. The reaction mixture was allowed to gradually warm to rt over 22 h and then treated with 10 mL of water and 5 mL of 10% aq NaOH solution. The resulting mixture was diluted with 10 mL of Et_2O and 5 mL of water and the aqueous layer was separated and extracted with three 10-mL portions of Et_2O. The combined organic phases were washed with 10 mL of 10% aq NaOH solution, dried over K_2CO_3, filtered, and concentrated to yield 0.318 g of a red oil. Column chromatography on 16 g of silica gel (gradient elution with 0-20% EtOAc-hexane) afforded 0.110 g (73%) of the vinyl triflates **177** and **229** (80:20 mixture by ^1H NMR analysis) as a pale yellow oil. For **177**: IR (film) 2976, 2874, 1764, 1670, 1420, 1212, 1142 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.23 (d, J = 3.5 Hz, 1H), 5.15 (d, J = 3.5 Hz, 1H), 4.35 (d, J = 4.5 Hz, 1H),

3.00 (d, J = 16.0 Hz, 1H), 2.82 (d, J = 16.0 Hz, 1H), 1.90-2.01 (m, 2H), 1.79-1.87 (m, 1H), 1.55-1.61 (m, 1H), 1.20 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 216.2, 152.0, 114.9, 108.1, 86.5, 84.3, 49.3, 33.9, 29.4, 25.3, 22.8, 20.1. HRMS-EI Calcd for $C_{12}H_{15}F_3O_5S$: 351.0484 $[M+Na]^+$. Found: 351.0490.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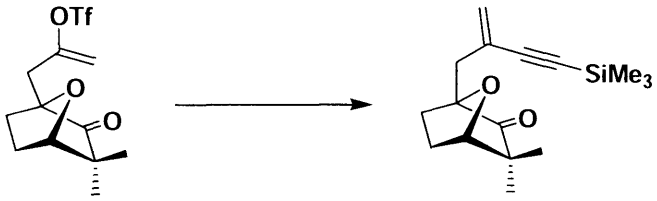
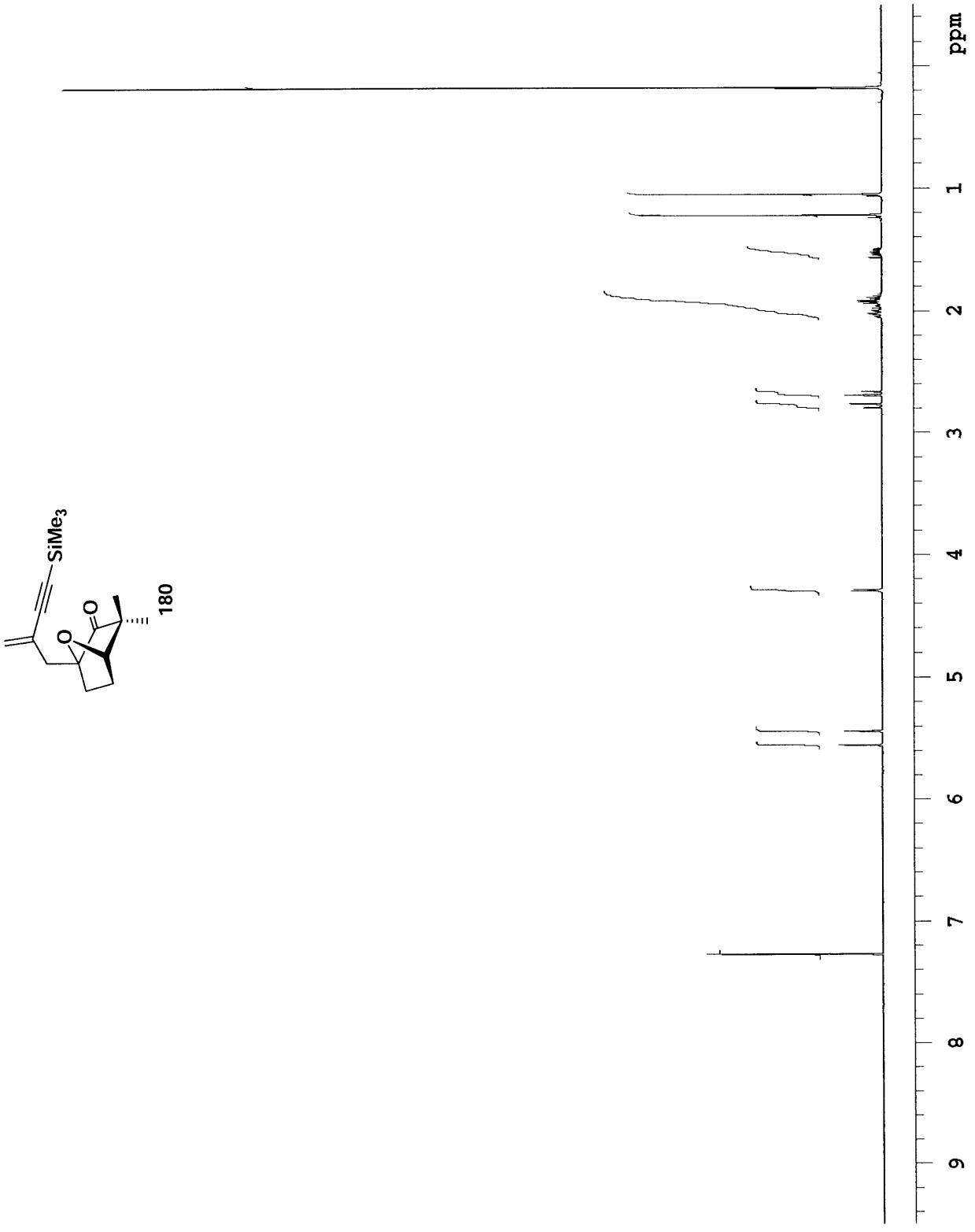


177 180

3,3-Dimethyl-1-(2-methylene-4-trimethylsilylbut-3-ynyl)-7-oxa-bicyclo[2.2.1]heptan-2-one (180)

A 10-mL, two-necked, round-bottomed flask fitted with a rubber septum and an argon inlet adapter was charged with $Pd(PPh_3)_2Cl_2$ (0.010 g, 0.014 mmol), CuI (0.008 g, 0.04 mmol), and 1 mL of THF, and trimethylsilylacetylene (0.048 mL, 0.033 g, 0.34 mmol) was added via syringe in one portion. A solution of the vinyl triflates **177** (0.033 g, 0.34 mmol) in 1.8 mL of THF was added dropwise via cannula over 1 min. Triethylamine (0.13 mL, 0.092 g, 0.91 mmol) was added to the reaction mixture via syringe in one portion and the resulting dark brown reaction mixture was stirred for 20 min and then 5 mL of saturated aq NH_4Cl solution was added in one portion. The resulting mixture was diluted with 20 mL of Et_2O and 10 mL of water, and the aqueous layer was separated and extracted with three 10-mL portions of Et_2O. The combined organic phases were washed with 20 mL of saturated aq NaCl, dried over $MgSO_4$, filtered, and concentrated to afford 0.090 g of a yellow oil. Column chromatography on 9 g of silica gel (gradient elution with 0-5% EtOAc-hexane) afforded 0.067 g (97%) of the enynes **180** as a colorless oil: IR (film) 2966, 2870, 2147, 1761, 1250, 844 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.54 (d, J = 1.5 Hz, 1H), 5.43 (app s, 1H), 4.28 (d, J = 5.0 Hz, 1H), 2.77 (d, J = 15.0 Hz, 1H), 2.66 (d, J = 15.0 Hz, 1H), 1.84-2.04 (m, 3H), 1.48-1.53 (m, 1H), 1.21 (s, 3H), 1.04 (s, 3H), 0.17 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 217.1, 126.4, 126.2, 106.0, 94.8, 87.8, 83.9, 49.4, 36.0, 29.1, 25.4, 23.1, 20.2, 0.0. HRMS-EI Calcd for $C_{16}H_{24}O_2Si$: 299.1438 $[M+Na]^+$. Found: 299.1443.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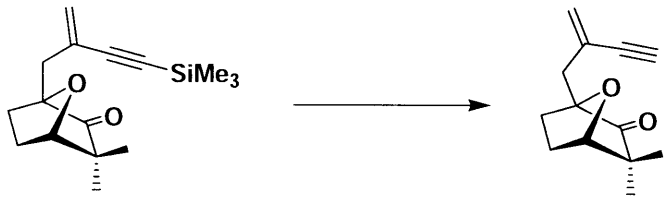
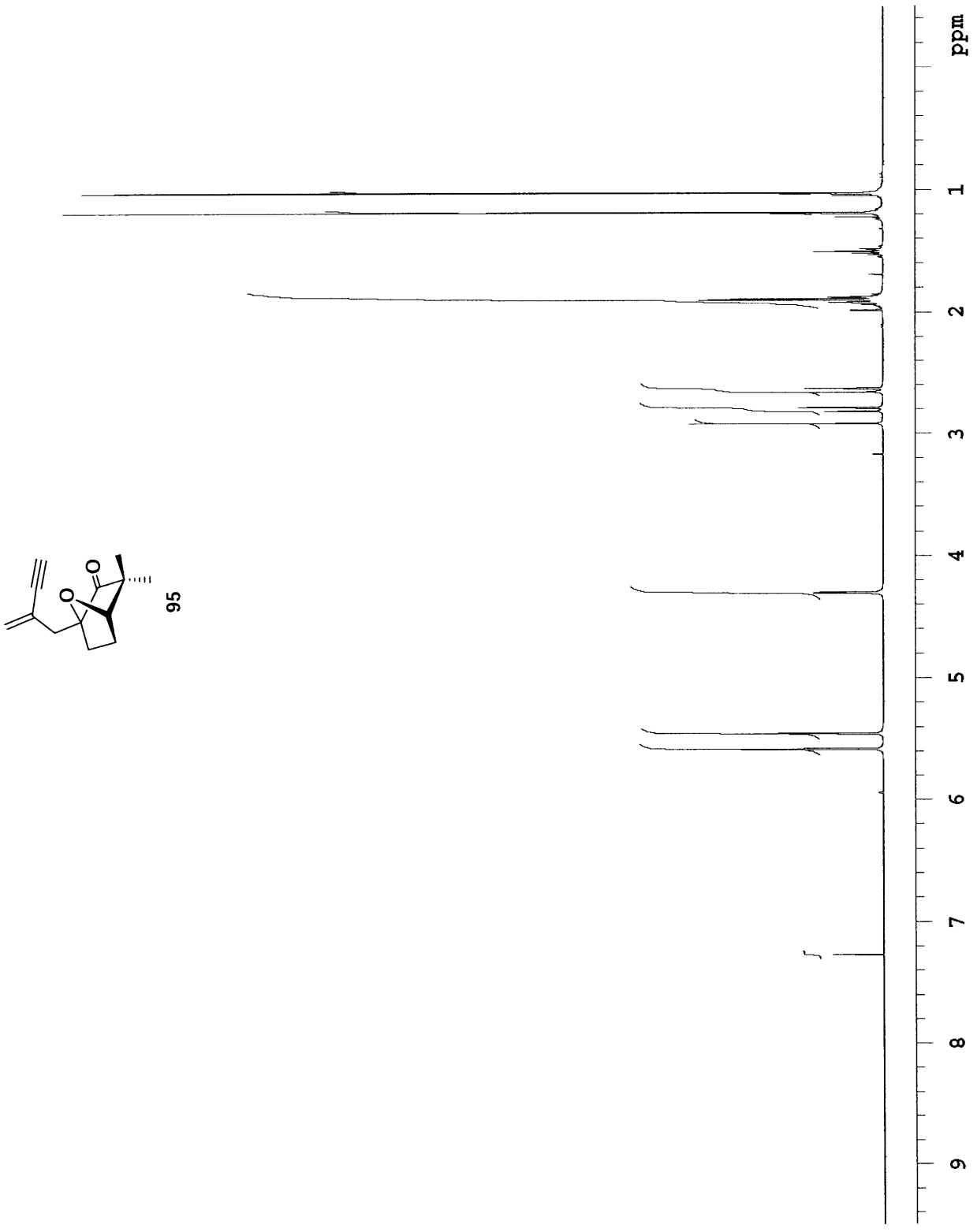


180 95

3,3-Dimethyl-1-(2-methylene-but-3-ynyl)-7-oxa-bicyclo[2.2.1]heptan-2-one (95)

A 50-mL, one-necked, recovery flask fitted with a rubber septum and an argon inlet needle was charged with the enynes **180** (0.284 g, 1.03 mmol), 20 mL of MeOH, and K_2CO_3 (0.107 g, 0.77 mmol). The reaction mixture was stirred at rt under argon for 100 min and then filtered and concentrated to afford 0.303 g of a crude yellow oil. Column chromatography on 21 g of silica gel (elution with 5% EtOAc-hexane) afforded 0.175 g (83%) of the enynes **95** as a colorless oil: IR (film) 3273, 2973, 2870, 2099, 1760, 1610 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.58 (s, 1H), 5.46 (s, 1H), 4.30 (d, J = 3.5 Hz, 1H), 2.92 (s, 1H), 2.80 (d, J = 15.0 Hz, 1H), 2.64 (d, J = 15.0 Hz, 1H), 1.88-1.94 (m, 3H), 1.48-1.53 (m, 1H), 1.19 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 217.2, 127.4, 125.3, 88.1, 84.7, 84.0, 77.6, 49.4, 35.9, 29.4, 25.3, 22.9, 20.1. HRMS-EI Calcd for $C_{13}H_{16}O_2$: 227.1043 $[M+Na]^+$. Found: 227.1045.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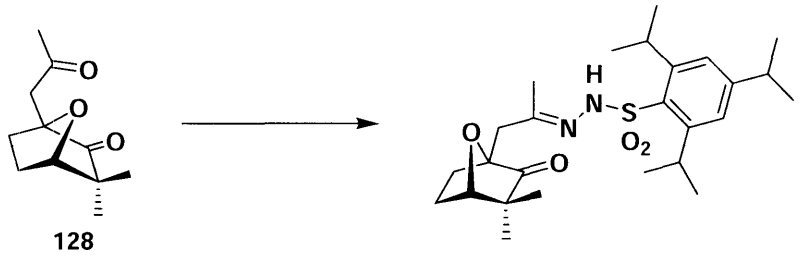
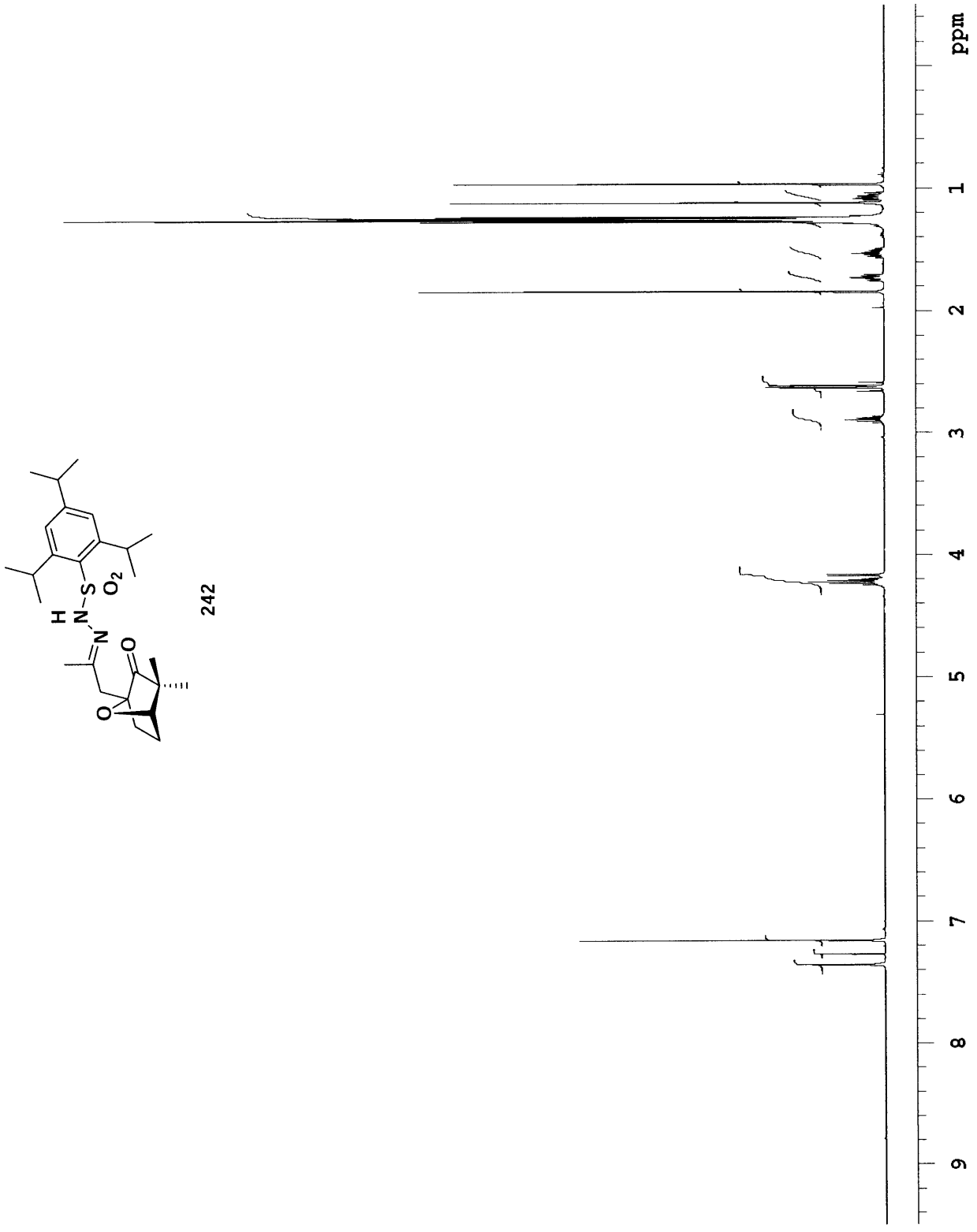


128 242

3,3-Dimethyl-1-[2-(2,4,6-triisopropylphenylsulfonylhydrazoyl)-propyl]-7-oxa-bicyclo[2.2.1]-heptan-2-one (242)

A 25-mL recovery flask fitted with argon inlet adapter was charged with 11 mL of Et_2O and the diketone **128** (0.219 g, 1.11 mmol). 2,4,6-Triisopropylsulfonylhydrazine (0.367 g, 1.23 mmol) was added in one portion, and the resulting heterogeneous mixture was stirred at rt for 21 h. The resulting mixture was concentrated to a volume of ca. 2-3 mL. The pale yellow cloudy mixture was triturated with 10 mL of *n*-pentane and filtered through a fritted-glass funnel washing solid on the funnel was washed with ca. 20 mL of ice-cold *n*-pentane. The solid on the funnel was treated with 20 mL of CH_2Cl_2 which dissolved the solid. The solution was drawn through the funnel into a tared 50-mL recovery flask and concentrated to afford a pale yellow solid. Traces of solvents were removed at 0.05 mmHg to afford 0.466 g (88%) of pure (*E*)-trisylhydrazone **242** as a pale yellow powder: mp 161-163 °C (dec); IR (film) 3237, 2956, 2926, 2868, 1763, 1600, 1461 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.36 (br s, 1H), 7.16 (s, 2H), 4.23 (sept, J = 7.0 Hz, 2H), 4.17 (d, J = 5.0 Hz, 1H), 2.89 (sept, J = 7.0 Hz, 1H), 2.62 (app dd, J = 14.0, 22.0 Hz, 2H), 1.85 (s, 3H), 1.70-1.76 (m, 1H), 1.49-1.56 (m, 1H), 1.24-1.27 (m, 19H), 1.12 (s, 3H), 1.03-1.09 (m, 1H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 216.8, 153.4, 152.5, 151.4, 131.3, 123.9, 87.2, 84.1, 49.0, 37.5, 30.0, 27.2, 25.3, 25.0, 24.9, 23.8, 23.2, 20.2, 17.1. HRMS-ESI Calcd for $C_{26}H_{40}N_2SO_4$: 499.2601 $[M+Na]^+$. Found: 499.2588.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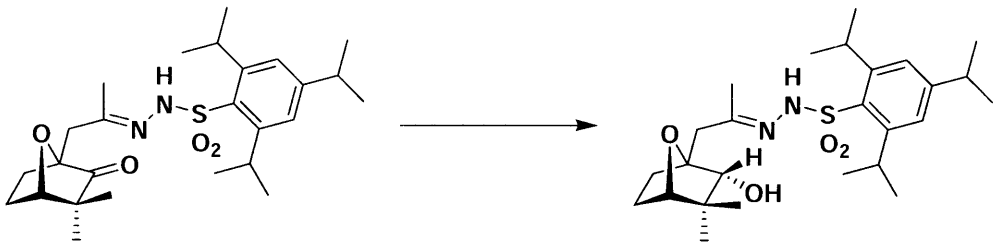
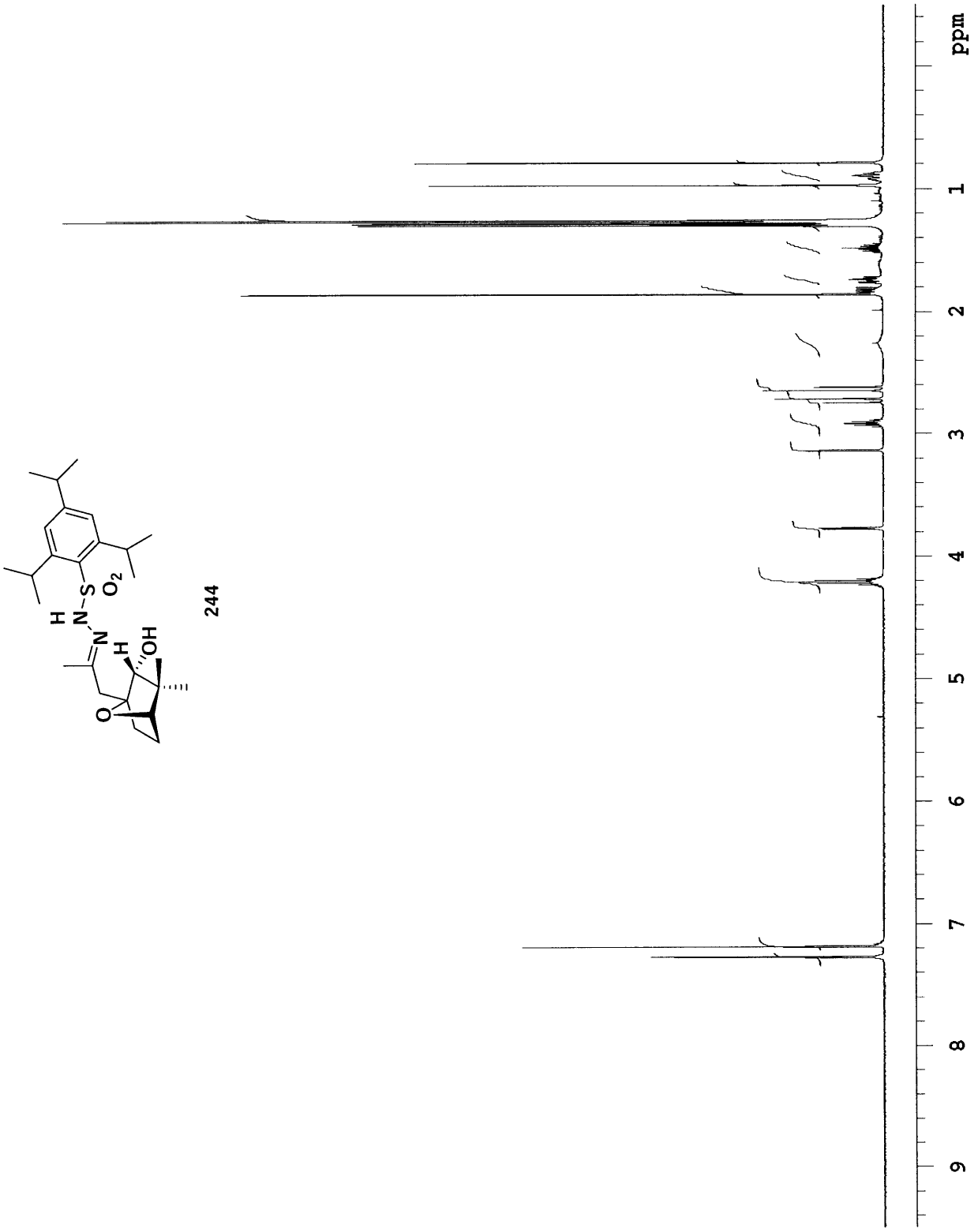


242 244

3,3-Dimethyl-1-(2-(2,4,6-triisopropylphenylsulfonylhydrazoyl)-propyl)-7-oxa-bicyclo[2.2.1]-heptan-2-ol (244)

A 100-mL recovery flask fitted with argon inlet adapter was charged with 30 mL of ethanol and trisylhydrazone **242** (0.450 g, 0.94 mmol). $NaBH_4$ (0.076 g, 2.0 mmol) was added in one portion and the reaction mixture was stirred at rt for 75 min and then diluted with 10 mL of saturated aq NaCl solution. The milky white mixture was diluted with 20 mL of Et_2O and 10 mL of water. The aqueous phase was separated and extracted with three 20-mL portions of Et_2O, and the combined organic phases were washed with 20 mL of saturated aq NaCl, dried over $MgSO_4$, filtered, and concentrated to give 0.468 g of a pale yellow solid. Column chromatography on 23 g of silica gel (gradient elution with 0-10% Et_2O-CH_2Cl_2) furnished 0.375 g (83%) of **244** as a white solid: mp 136-138 °C; IR (film) 3513, 3195, 2961, 2930, 2870, 1600 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.28 (br s, 1H), 7.19 (s, 2H), 4.21 (sept, J = 6.5 Hz, 2H), 3.77 (d, J = 5.0 Hz, 1H), 3.14 (d, J = 1.0 Hz, 1H), 2.92 (sept, J = 7.0 Hz, 1H), 2.73 (d, J = 15.0 Hz, 1H), 2.63 (d, J = 15.0 Hz, 1H), 2.26 (br s, 1H), 1.86 (s, 3H), 1.80-1.85 (m, 1H), 1.72-1.77 (m, 1H), 1.44-1.51 (m, 1H), 1.29 (d, J = 7.0 Hz, 6H), 1.27 (d, J = 7.0 Hz, 6H), 1.26 (d, J = 7.0 Hz, 6H), 0.97 (s, 3H), 0.87-0.93 (m, 1H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 154.8, 153.7, 151.4, 131.1, 123.9, 87.8, 86.1, 81.8, 44.3, 42.6, 34.4, 30.0, 26.3, 25.7, 25.1, 24.9, 23.80, 18.9, 17.2. HRMS-ESI Calcd for $C_{26}H_{42}N_2SO_4$: 479.2938 $[M+H]^+$. Found: 479.2938. Anal. Cald for $C_{26}H_{42}N_2SO_4$: C, 65.24; H, 8.84; N, 5.85. Found: C, 65.49; H, 8.97; N, 5.90.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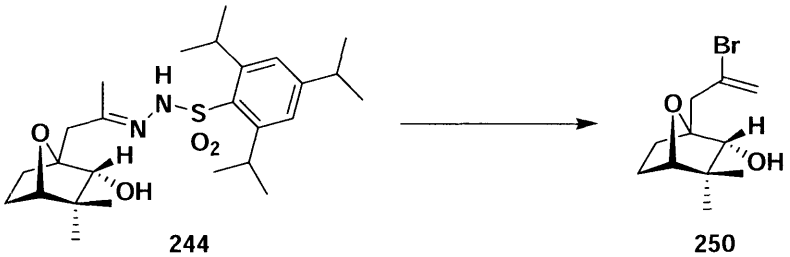
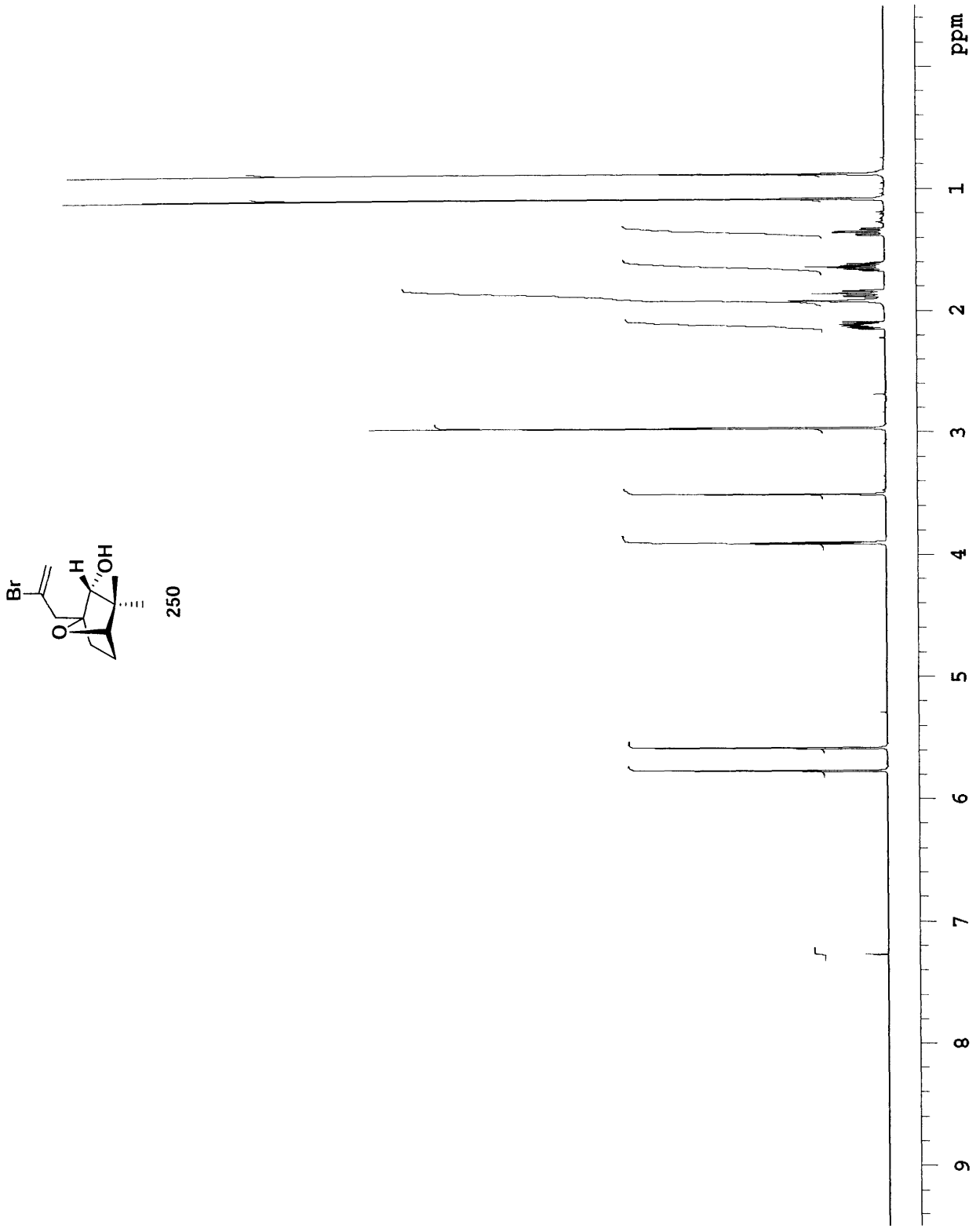


244 250

1-(2-Bromoallyl)-3,3-dimethyl-7-oxa-bicyclo[2.2.1]heptan-2-ol (250)

A 50-mL recovery flask fitted with a rubber septum and an argon inlet needle was charged with trisylhydrazone **244** (dried by azeotropic distillation of benzene) (0.378 g, 0.79 mmol) and 13 mL of THF. The colorless solution was cooled to −78 °C and 1.15 mL of *n*-BuLi (2.20 M in hexanes, 2.50 mmol) was added dropwise over 1 min. The resulting bright orange solution was stirred at −78 °C for 15 min and then warmed at 0 °C for 10 min before re-cooling to −78 °C. A solution of 1,2-dibromotetrafluoroethane (0.30 mL, 0.65 g, 2.5 mmol) in 1 mL of THF (pre-cooled at −78 °C) was added dropwise via cannula over 3 min (with 1 mL THF rinse), and the resulting light yellow solution was stirred at −78 °C for 40 min. The reaction mixture was diluted with 10 mL of water, the cooling bath was removed, and the reaction mixture was allowed to warm to rt over 15 min. The resulting mixture was transferred to a separatory funnel with the aid of 10 mL of water and 15 mL of Et_2O. The aqueous layer was separated and extracted with three 10-mL portions of ether. The combined organic phases were washed with 20 mL of saturated aq NaCl, dried over $MgSO_4$, filtered, and concentrated to give 0.326 g of yellow oil. Column chromatography on 10 g of silica gel (gradient elution with 0-5% Et_2O-CH_2Cl_2) afforded 0.147 g (71%) of **250** as a pale yellow oil: IR (film) 3442, 2962, 1627 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.77 (s, 1H), 5.58 (d, J = 1.5 Hz, 1H), 3.90 (d, J = 5.0 Hz, 1H), 3.51 (d, J = 0.5 Hz, 1H), 2.96 (s, 2H), 2.11-2.17 (m, 1H), 1.92 (br s, 1H), 1.83-1.88 (m, 1H), 1.60-1.67 (m, 1H), 1.32-1.38 (m, 1H), 1.08 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 128.2, 120.9,

88.1, 86.3, 81.3, 45.7, 42.1, 29.8, 26.2, 25.5, 18.9. HRMS-ESI Calcd for $C_{11}H_{17}BrO_4$: 283.0304 $[M+Na]^+$. Found: 283.0303.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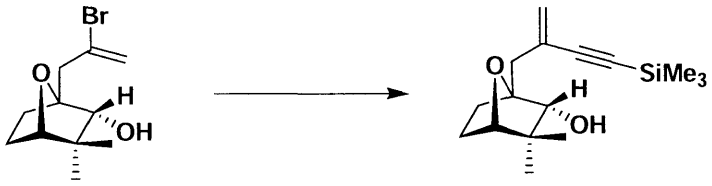
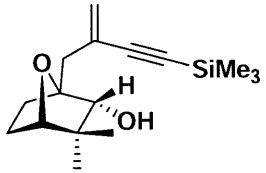


250 251

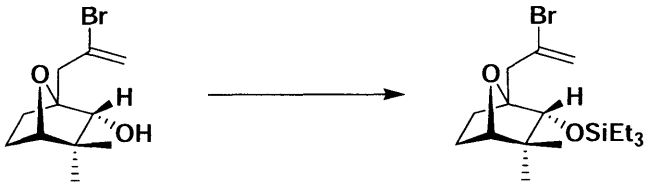
3,3-Dimethyl-1-(2-methylene-4-trimethylsilylbut-3-ynyl)-7-oxa-bicyclo[2.2.1]heptan-2-ol (251)

A 25-mL, one-necked, round-bottomed flask fitted with a rubber septum and an argon inlet needle and wrapped in aluminum foil was charged with $(PPh_3)_4Pd$ (0.011 g, 0.0095 mmol), CuI (0.010 g, 0.053 mmol), and 1 mL of THF. A solution of the vinyl bromide **250** (0.051 g, 0.20 mmol) in 1 mL of THF was added via cannula over 1 min (1 mL of THF rinse), and trimethylsilylacetylene (0.042 mL, 0.029 g, 0.30 mmol) was then added dropwise over 10 sec to give a dark yellow mixture. The reaction mixture was stirred at rt for 5 min and *n*-$BuNH_2$ (0.068 mL, 0.050 g, 0.69 mmol) was then added dropwise over 10 sec. The resulting clear light yellow solution was allowed to stir for 3.5 h. The reaction mixture was diluted with 10 mL of saturated aq NH_4Cl solution, 10 mL of Et_2O, and 15 mL of water. The aqueous phase was separated and extracted with three 10-mL portions of Et_2O, and the combined organic phases were washed with 20 mL of saturated aq NaCl, dried over $MgSO_4$, filtered, and concentrated to afford 0.082 g of yellow oil. Column chromatography on 6 g of silica gel (elution with CH_2Cl_2) furnished 0.051 g (94%) of the enyne **251** as a colorless oil: IR (film) 3460, 2961, 2145, 1605, 1465, 1251, 843 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.52 (d, J = 2.0 Hz, 1H), 5.44 (d, J = 1.0 Hz, 1H), 3.85 (d, J = 5.5 Hz, 1H), 3.55 (s, 1H), 2.67 (d, J = 13.0 Hz, 1H), 2.62 (d, J = 13.5 Hz, 1H), 2.19 (d, J = 3.0 Hz, 1H), 2.12-2.17 (m, 1H), 1.85-1.90 (m, 1H), 1.60-1.67 (m, 1H), 1.25-1.31 (m, 1H), 1.10 (s, 3H), 0.88 (s, 3H), 0.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 126.9, 126.6, 106.5, 95.2, 88.6,

86.0, 82.1, 43.0, 42.7, 30.0, 26.4, 25.6, 18.9, -0.03. HRMS-ESI Calcd for $C_{16}H_{26}O_2Si$: 301.1594 $[M+Na]^+$. Found: 301.1590.



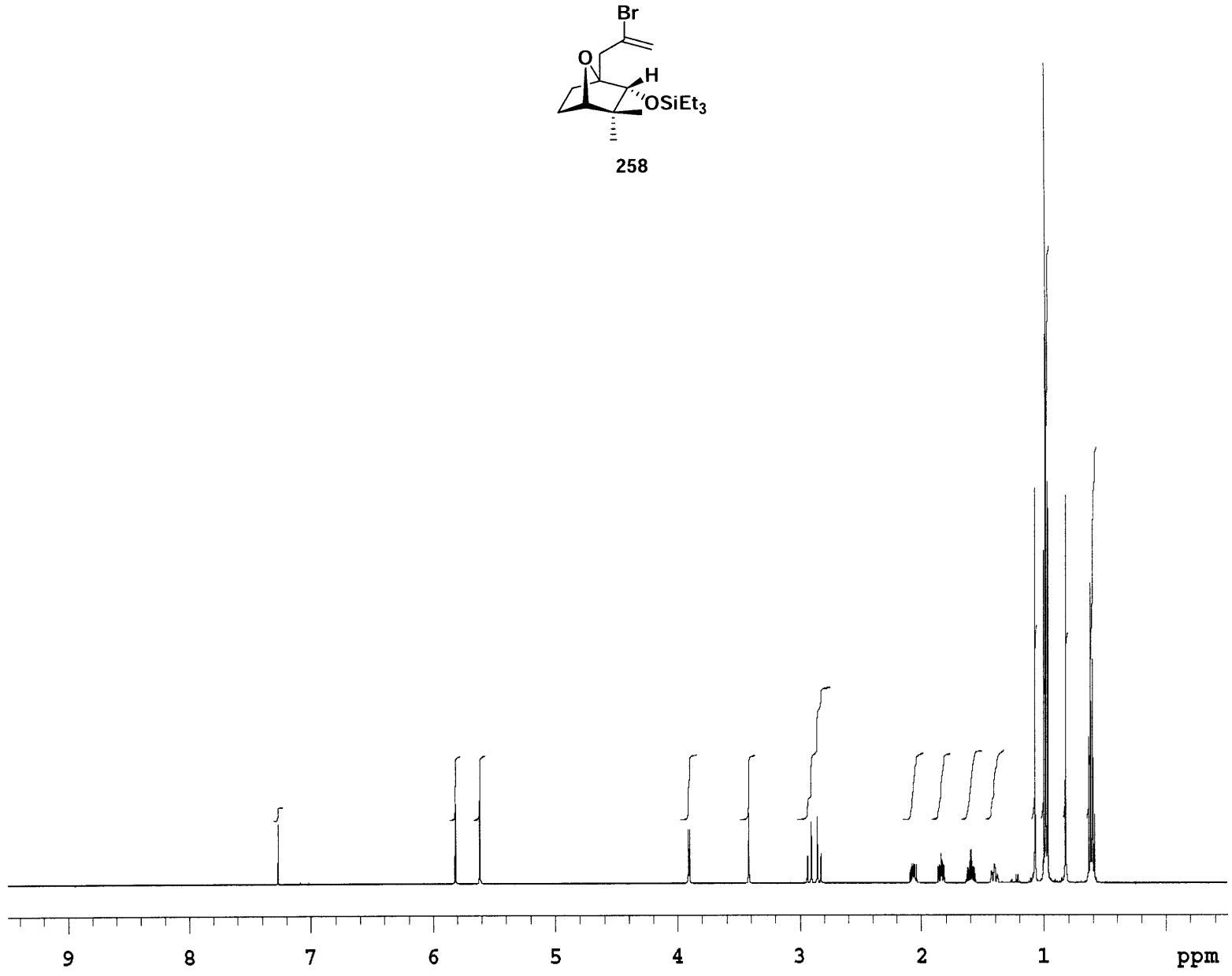
251



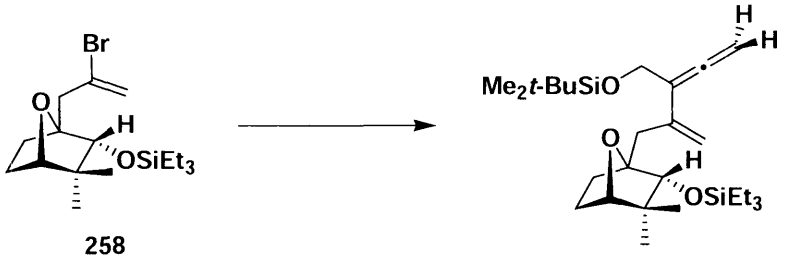
250 258

1-(2-Bromoallyl)-3,3-dimethyl-7-oxa-bicyclo[2.2.1]-2-triethylsilyloxyheptane (258)

A 50-mL recovery flask fitted with a rubber septum and an argon inlet needle was charged with the vinyl bromide **250** (dried by azeotropic distillation of benzene) (0.147 g, 0.56 mmol), 11 mL of CH_2Cl_2, and Et_3N (0.15 mL, 0.11 g, 1.1 mmol). The solution was cooled to −78 °C and Et_3SiOTf (0.18 mL, 0.21 g, 0.79 mmol) was added dropwise over 30 sec. The resulting pale yellow solution was allowed to stir at −78 °C for 110 min and then diluted with 10 mL of half-saturated aq $NaHCO_3$ solution. The cooling bath was removed and the reaction mixture was allowed to warm to rt over 15 min and then diluted with 15 mL of Et_2O and 10 mL of water. The aqueous phase was separated and extracted with three 10-mL portions of Et_2O, and the combined organic phases were washed with 20 mL of saturated aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.232 g of a pale yellow oil. Column chromatography on 21 g of silica gel (gradient elution with 30-50% CH_2Cl_2-hexanes) afforded 0.169 g (80%) of vinyl bromide **258** as a pale yellow oil: IR (film) 2958, 2912, 2877, 1627, 1463, 1122 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.82 (s, 1H), 5.61 (s, 1H), 3.91 (d, J = 5.0 Hz, 1H), 3.42 (s, 1H), 2.92 (d, J = 16.0 Hz, 1H), 2.84 (d, J = 16.0 Hz, 1H), 2.04-2.09 (m, 1H), 1.81-1.86 (m, 1H), 1.56-1.63 (m, 1H), 1.38-1.43 (m, 1H), 1.07 (s, 3H), 0.98 (t, J = 8.0 Hz, 9H), 0.82 (s, 3H), 0.61 (q, J = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): 128.3, 120.4, 88.8, 86.9, 82.8, 44.4, 42.0, 29.6, 26.3, 24.3, 19.7, 7.2, 5.4. HRMS-ESI Calcd for $C_{17}H_{31}BrO_2Si$: 397.1174 $[M+Na]^+$. Found: 397.1183.



258



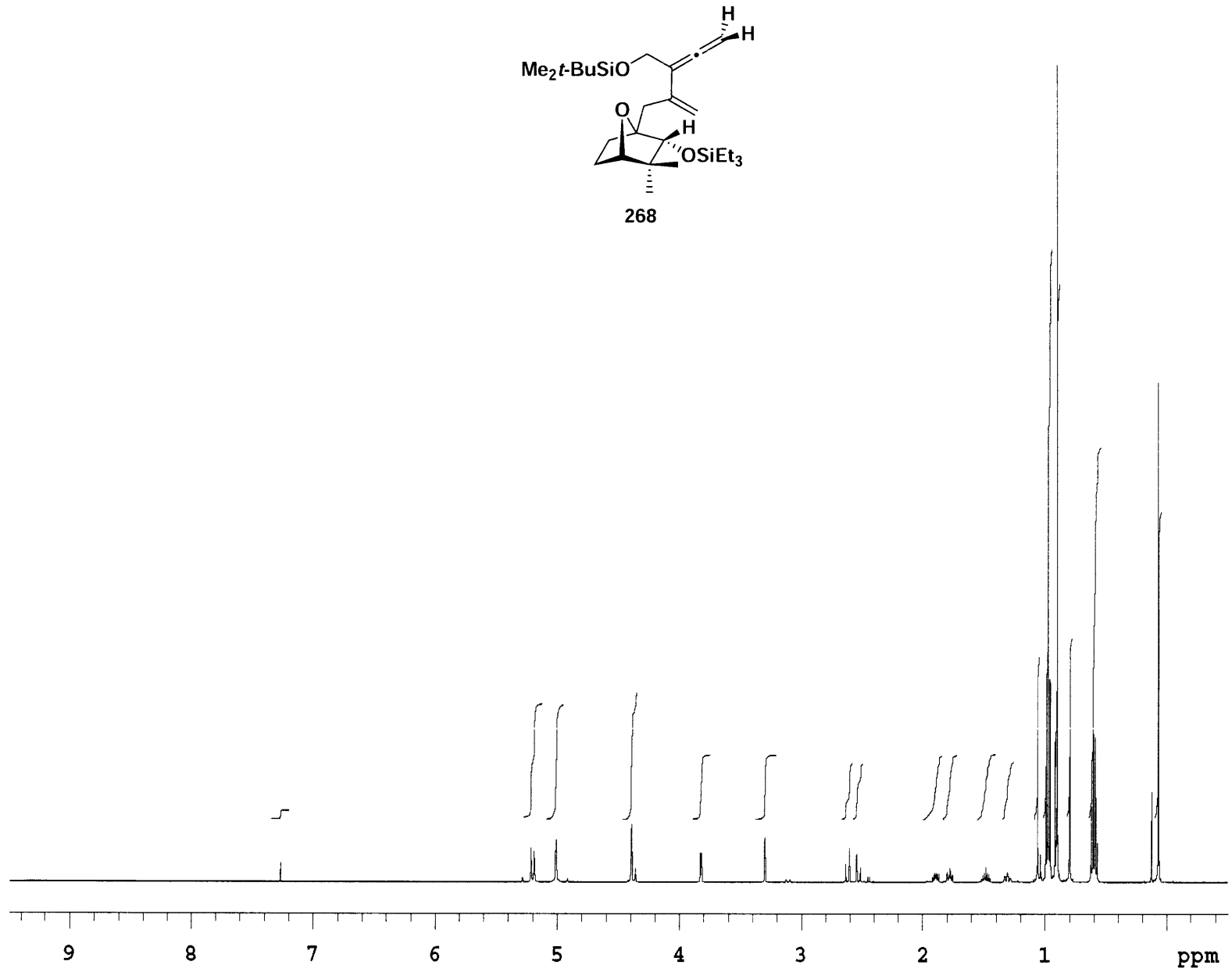
258 268

1-[3-(*tert*-Butyl-dimethyl-silyloxymethyl)-2-methylene-penta-3,4-dienyl]-3,3-dimethyl-2-triethylsilyloxy-7-oxa-bicyclo[2.2.1]heptane (268)

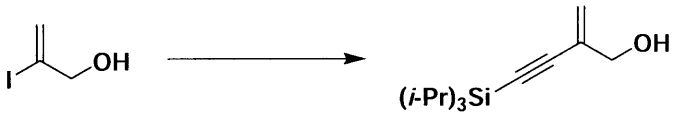
A 10-mL, pear-shaped flask fitted with a rubber septum and an argon inlet needle was charged with 0.5 mL of THF and 3-methoxy-3-methyl-1-butyne (0.034 g, 0.35 mmol). The resulting colorless solution was cooled at 0 °C and 0.15 mL of *n*-BuLi (2.20 M in hexanes, 0.33 mmol) was added dropwise over 15 sec. A separate 10-mL, pear-shaped flask equipped with a rubber septum pierced with an argon inlet needle was charged with CuI (0.064 g, 0.34 mmol) and 0.5 mL of THF to give a suspension, which was cooled at 0 °C. After 10 min, the lithium acetylide solution, prepared as described above, was added via cannula to the CuI suspension (0.5 mL THF rinse) over 1 min to give a bright orange solution, which was allowed to stir at 0 °C for 35 min and then cooled at −78 °C.

A 25-mL, two-necked, pear-shaped flask equipped with an argon inlet adapter and a rubber septum was charged with vinyl bromide **258** (0.113 g, 0.30 mmol), 1.5 mL of *n*-pentane, and 0.3 mL of Et_2O, and the flask was immersed in the dry ice-acetone bath up to its neck. A 10-mL, pear-shaped flask equipped with a rubber septum pierced with an argon inlet needle was charged with 0.5 mL of *n*-pentane, and *t*-BuLi (1.47 M in pentane, 0.41 mL, 0.60 mmol), and was cooled at −78 °C. The resulting *t*-BuLi solution was added by cannula down the sides of the reaction flask (0.5-mL *n*-pentane rinse) over 2 min. The resulting vinyllithium solution was allowed to stir at −78 °C for 10 min, and the copper(I) acetylide prepared as described above was

then added via cannula (0.5-mL THF rinse) over 2 min. The resulting slightly heterogeneous bright yellow mixture was stirred at −78 °C for 45 min, warmed to −50 °C for 15 min, and then cooled back to −78 °C. A solution of *p*-toluenesulfonyl-4-*t*-butyldimethylsilyloxy-2-butyne (0.140 g, 0.39 mmol) in 0.5 mL of THF was cooled at −78 °C and then added to the vinyl cuprate solution via cannula (0.5-mL THF rinse) over 1 min. The resulting yellow heterogeneous mixture was allowed to stir at −78 °C for 15 min and warmed to rt over 4.5 h. The reaction mixture was diluted with 10 mL of a 9:1 solution of saturated aq NH_4Cl/NH_4OH, 10 mL of Et_2O, and 15 mL of water. The deep blue aqueous phase was separated and extracted with three 10-mL portions of Et_2O. The combined organic phases were washed with 25 mL of saturated aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.190 g of a yellow oil. Column chromatography on 15 g of silica gel (gradient elution with 20-100% CH_2Cl_2-hexanes) afforded 0.088 g of **268**. This material was purified by column chromatography on 9 g of silica gel (gradient elution with 50-60% CH_2Cl_2-hexanes) to furnish 0.073 g of **268**. This impure material was further purified by preparative TLC (two elutions with 2% EtOAc-hexanes) to give 0.0593 g (41%) of allene **268** as a colorless oil: IR (film) 2957, 2879, 1938, 1615, 1463, 1119, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.20 (app d, J = 12.5 Hz, 2H), 5.01 (app d, J = 1.5 Hz, 2H), 4.39-4.40 (m, 2H), 3.82 (d, J = 5.5 Hz, 1H), 3.30 (d, J = 0.5 Hz, 1H), 2.62 (d, J = 15.0 Hz, 1H), 2.53 (d, J = 14.5 Hz, 1H), 1.87-1.92 (m, 1H), 1.75-1.80 (m, 1H), 1.45-1.52 (m, 1H), 1.28-1.33 (m, 1H), 1.06 (s, 3H), 0.97 (t, J = 8.0 Hz, 9H), 0.90 (s, 9H), 0.80 (s, 3H), 0.60 (q, J = 8.0 Hz, 6H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): 209.6, 137.4, 114.2, 108.7, 89.4, 86.3, 84.4, 79.4, 62.2, 42.0, 37.4, 29.7, 26.5, 26.1, 22.9, 19.7, 18.6, 7.2, 5.4, -5.0. HRMS-ESI Calcd for $C_{27}H_{50}O_3Si_2$: 501.3196 $[M+Na]^+$. Found: 501.3195.



268

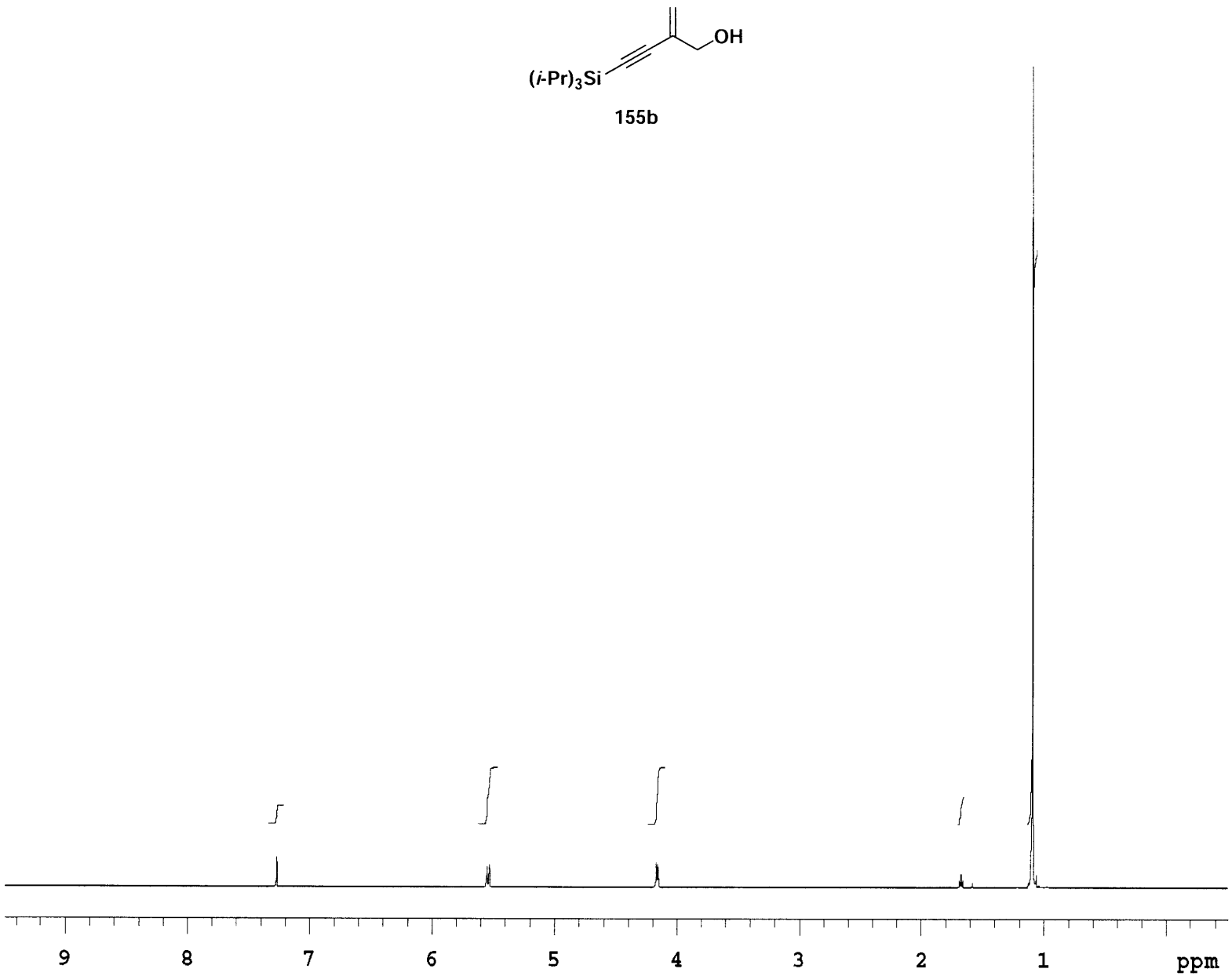


153 155b

General Procedure for the Preparation of Enyne Alcohols.

2-Methylene-4-(triisopropylsilyl)but-3-yn-1-ol (155b).

A 50-mL, one-necked, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with $(Ph_3P)_4Pd$ (0.089 g, 0.077 mmol), CuI (0.042 g, 0.22 mmol) and 10 mL of THF. A solution of the vinyl iodide **153** (0.464 g, 2.52 mmol) in 3 mL of THF was added via cannula over 2 min (the flask was rinsed with 2 mL of THF) and triethylamine (0.46 mL, 0.33 g, 3.28 mmol) was then added via syringe over 30 s. The resulting yellow mixture was stirred at rt for 3 min, and then triisopropylsilylacetylene (0.74 mL, 0.60 g, 3.28 mmol) was added via syringe over 2 min. The reaction mixture was stirred at rt for 11.5 h and then heated at reflux for 9 h. The reaction mixture was allowed to cool to rt and then filtered through 10 g of silica gel with the aid of three 15-mL portions of Et_2O. Concentration of the filtrate afforded 0.689 g of a brown oil. Column chromatography on 35 g of silica gel (gradient elution with 0-10% EtOAc-hexane) provided 0.336 g (56%) of enyne **155b** as a yellow oil: IR (film) 3356, 2942, 2865, 2145, 1617 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.54 (dd, J = 1.5, 10.5 Hz, 2H), 4.12 (td, J = 1.5, 7.0 Hz, 2H), 1.68 (dt, J = 1.5, 7.0 Hz, 1H), 1.09 (app s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$): 131.7, 120.8, 104.7, 93.0, 65.5, 18.8, 11.4. HRMS-EI Calcd for $C_{14}H_{26}OSi$: 238.1747 $[M]^+$. Found: 238.1741.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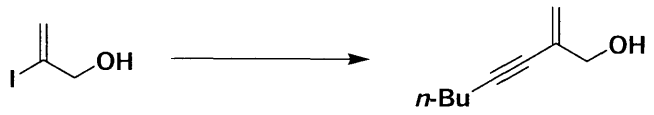
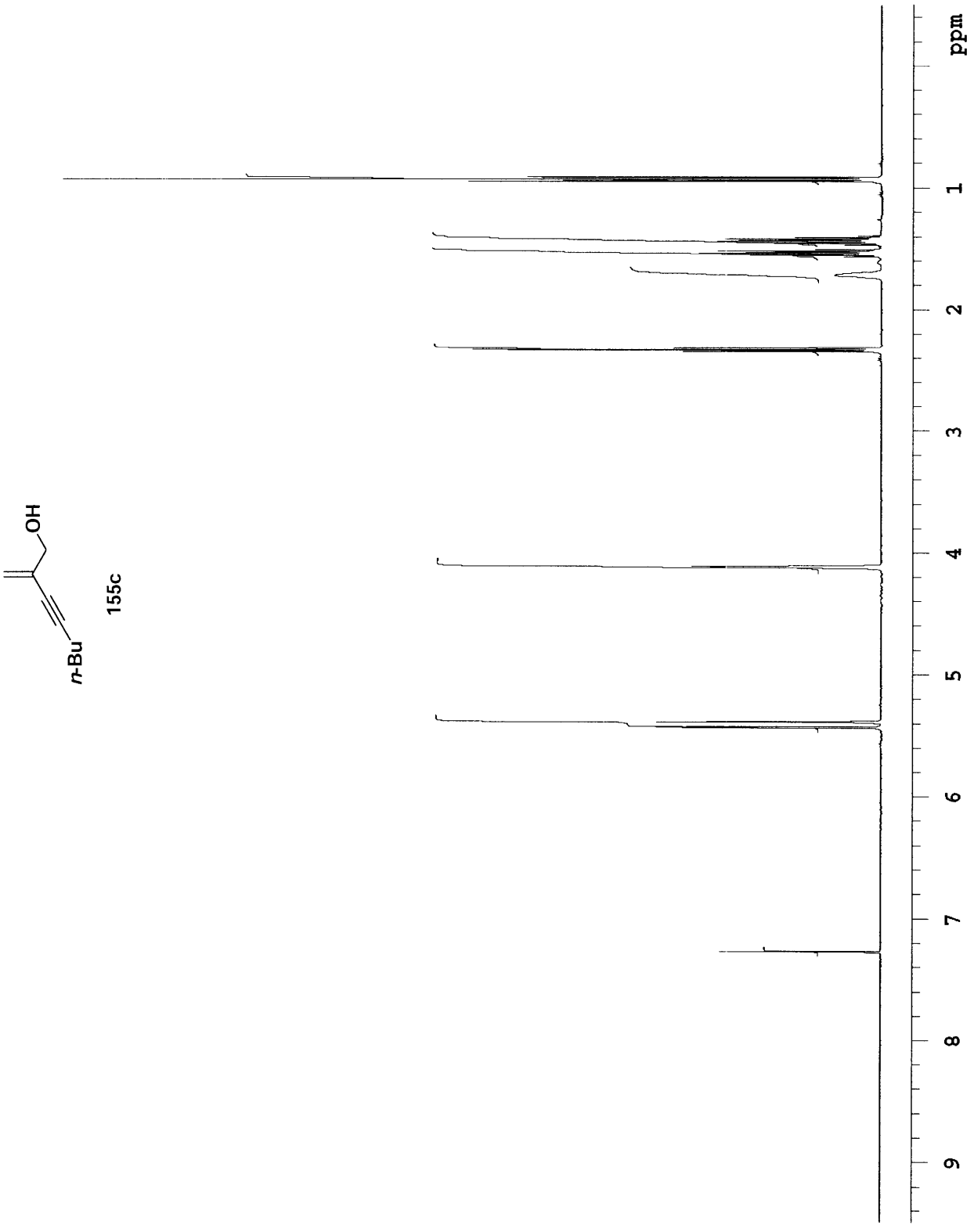


153 155c

2-Methylene-4-*n*-butylbut-3-yn-1-ol (155c).

Reaction of vinyl iodide **153** (0.799 g, 4.34 mmol), 1-hexyne (2.50 mL, 1.78 g, 21.7 mmol), $(Ph_3P)_4Pd$ (0.225 g, 0.19 mmol), CuI (0.098 g, 0.52 mmol), and triethylamine (6.00 mL, 4.39 g, 43.4 mmol) in 75 mL of THF at rt for 26 h according to the general procedure afforded 0.984 g of a dark brown oil. This material was purified by column chromatography on 100 g of silica gel (elution with CH_2Cl_2) to provide 0.477 g (79%) of enyne **155c** as a yellow oil: IR (film) 3343, 2958, 2873, 2223, 1618 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.43 (d, J = 1.5 Hz, 1H), 5.39 (app s, 1H), 4.12 (d, J = 5.0 Hz, 2H), 2.33 (t, J = 7.0 Hz, 2H), 1.72 (br s, 1H), 1.51-1.56 (m, 2H), 1.39-1.46 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 131.8, 119.1, 92.6, 78.4, 65.9, 30.9, 22.2, 19.2, 13.8. HRMS-EI Calcd for $C_9H_{14}O$: 138.1039 $[M]^+$. Found: 138.1037.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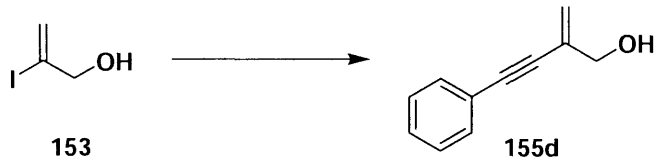
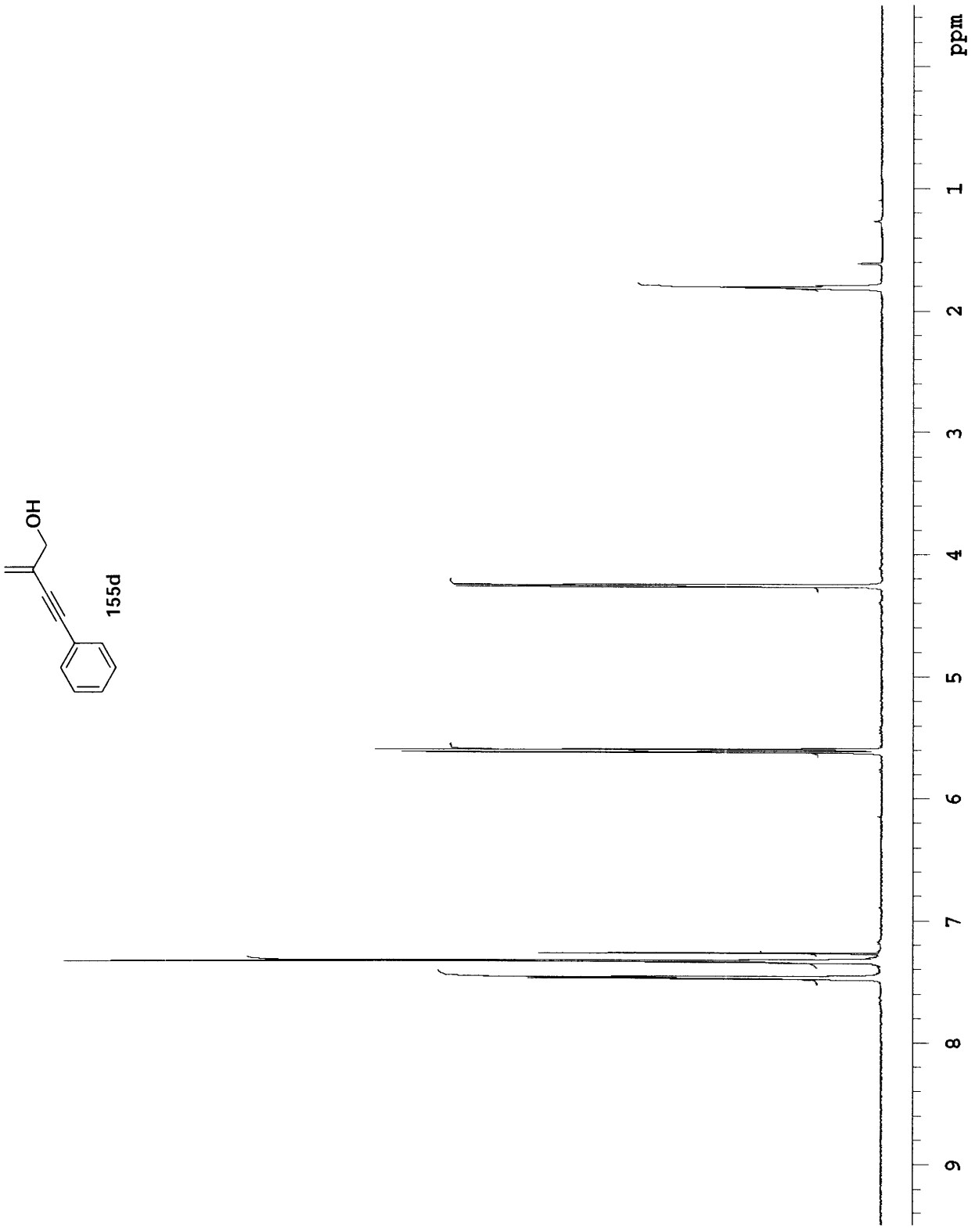


153 155d

2-Methylene-4-phenylbut-3-yn-1-ol (155d).

Reaction of vinyl iodide **153** (1.113 g, 6.05 mmol), phenylacetylene (0.86 mL, 0.80 g, 7.86 mmol), $(Ph_3P)_4Pd$ (0.203 g, 0.18 mmol), CuI (0.063 g, 0.33 mmol), and triethylamine (1.10 mL, 0.799 g, 7.89 mmol) in 15 mL of THF at rt for 2 h according to the general procedure afforded 1.298 g of a brown oil. This material was purified by column chromatography on 24 g of silica gel (gradient elution with 0-20% EtOAc-hexane) to provide 0.890 g of a yellow oil. This material was further purified on 22 g of silica gel (gradient elution with 0-20% EtOAc-hexane) to afford 0.674 g (70%) of enyne **155d** as a pale yellow oil: IR (film) 3334, 3060, 2925, 2866, 2208, 1614 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.45-7.48 (m, 2H), 7.32-7.35 (m, 3H), 5.61 (dd, J = 1.5, 12.0 Hz, 2H), 4.26 (d, J = 6.5 Hz, 2H), 1.80 (app t, J = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 131.9, 131.4, 128.7, 128.5, 122.9, 120.7, 91.1, 87.1, 65.6. HRMS-EI Calcd for $C_{11}H_{10}O$: 158.0726 $[M]^+$. Found: 158.0731.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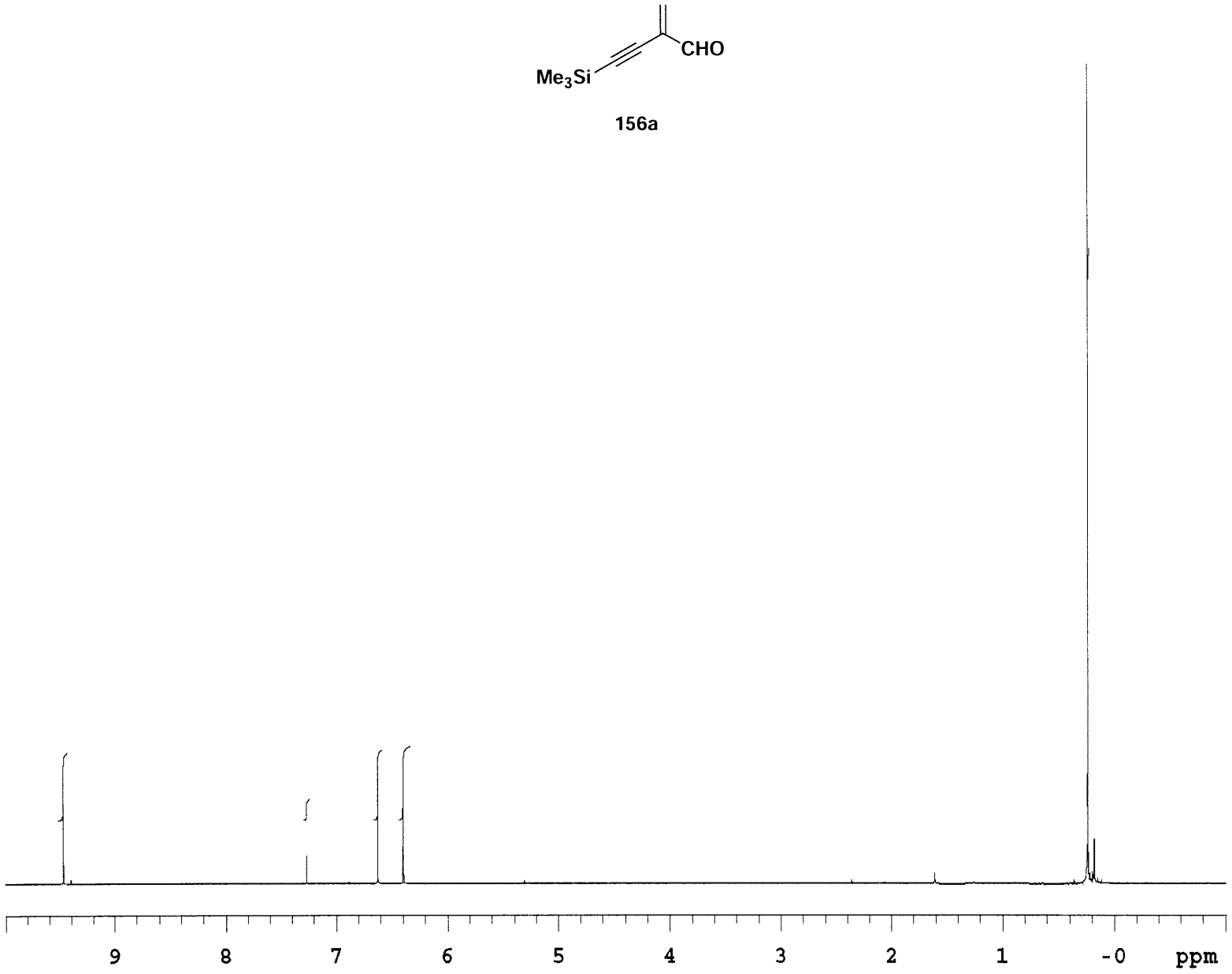
155a 156a

General Procedure for the Oxidation of Allylic Alcohols to Enynyl Aldehydes.

2-Methylene-4-(trimethylsilyl)but-3-ynal (156a).

A 50-mL, two-necked, pear-shaped flask fitted with an argon inlet adapter and a rubber septum was charged with a solution of the allylic alcohol (**155a**) (0.942 g, 6.11 mmol) in 30 mL of dichloromethane and cooled at 0 °C while Dess-Martin periodinane (2.856 g, 6.73 mmol) was added in one portion. The heterogeneous reaction mixture was stirred at 0 °C for 5 min and then allowed to warm to rt. After 20 min, the reaction mixture was cooled to –78 °C, diluted with 30 mL of pentane, poly(4-vinylpyridine) (3.227 g, 30.69 mmol) was added in one portion, and the resulting mixture was stirred at –78 °C for 25 min. A 2.5-cm diameter jacketed column fitted with a rubber septum at the top and a short needle at the bottom was charged with a 6-cm plug of silica gel which was cooled at –78 °C by filling the jacket with dry ice-acetone. The reaction mixture was transferred into the column by cannula and filtered through the silica gel under a positive pressure of argon into a 200-mL recovery flask fitted with a rubber septum with a short needle as vent. The reaction flask and the column were rinsed with four 15-mL portions of 4:1 pentane-ether. The filtrate was concentrated by rotary evaporation at 25 °C (20 mmHg) to a volume of ca. 3 mL and this solution was then cooled to –78 °C and diluted with 5 mL of toluene. The resulting solution was concentrated by rotary evaporation at 25 °C to a volume of ca. 3 mL and the resulting pale yellow solution was cooled to –78 °C and further concentrated at 0.05 mmHg (ca. 15 min) to furnish aldehyde **156a** as a yellow oil. For spectroscopic analysis, this material was dissolved in ca. 1 mL of $CDCl_3$ and 4-isopropylbenzaldehyde (0.92 mL, 0.90 g,

6.1 mmol) was added as an internal standard. The resulting solution was transferred to an NMR tube via cannula under a positive pressure of argon. The yield of aldehyde **156a** was determined by ^{1}H NMR analysis to be 52%: IR (film) 2960, 2928, 2144, 1749, 1624 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 9.48 (s, 1H), 6.63 (d, J = 1.5 Hz, 1H), 6.40 (d, J = 1.5 Hz, 1H), 0.25 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 190.0, 139.6, 133.1, 101.8, 97.5, -0.1.

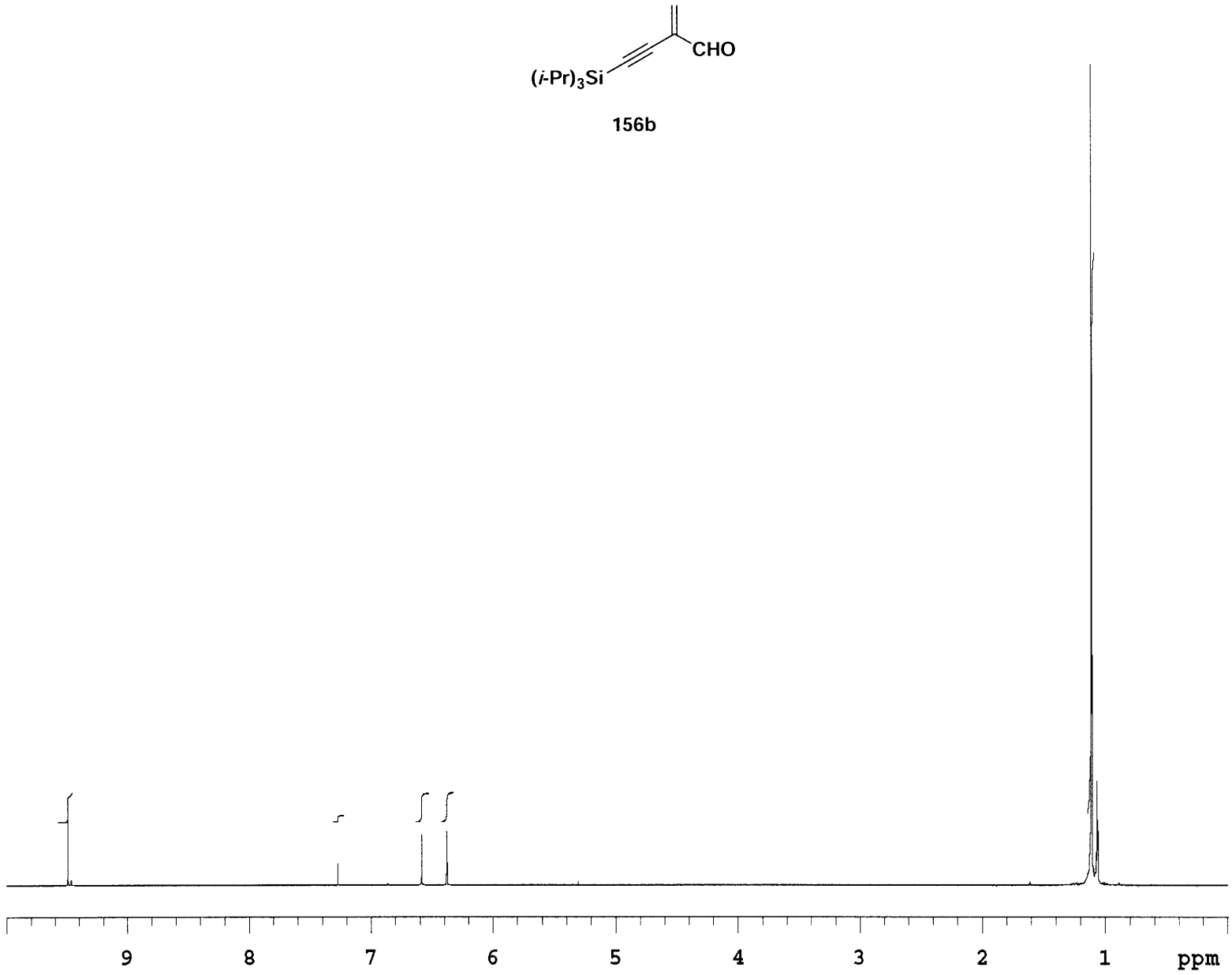


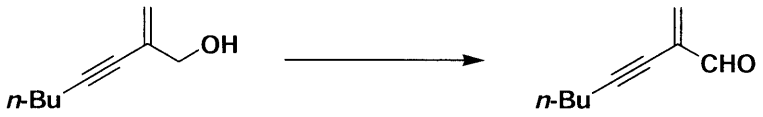
156a

155b **156b**

2-Methylene-4-(triisopropylsilyl)but-3-ynal (156b).

Reaction of a solution of the allylic alcohol (**155b**) (0.040 g, 0.17 mmol) in 3 mL of dichloromethane with Dess-Martin periodinane (0.089 g, 0.19 mmol) and then poly(4-vinylpyridine) (0.092 g, 0.85 mmol) according to the general procedure gave aldehyde **156b** as a yellow oil in 78% yield as determined by ^{1}H NMR analysis: IR (film) 2944, 2867, 2143, 1718, 1624 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 9.49 (s, 1H), 6.59 (d, J = 0.6 Hz, 1H), 6.38 (d, J = 0.9 Hz, 1H), 1.14 (apparent s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$): 190.0, 138.6, 133.3, 99.7, 98.5, 18.8, 11.3.

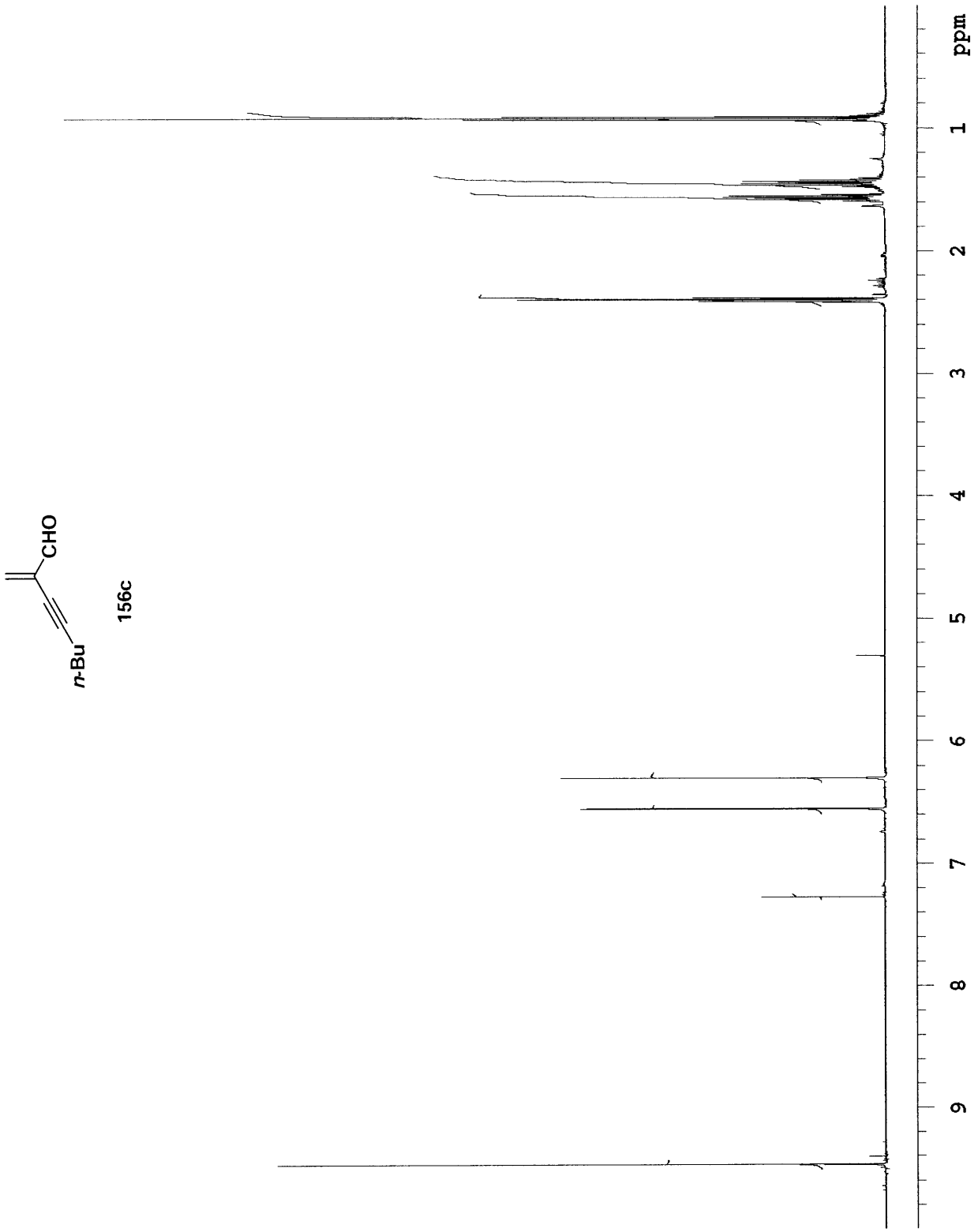

CHO
(i-Pr)3Si
156b
9
8
7
6
5
4
3
2
1
ppm



155c **156c**

2-Methylene-4-(*n*-butyl)but-3-ynal (156c).

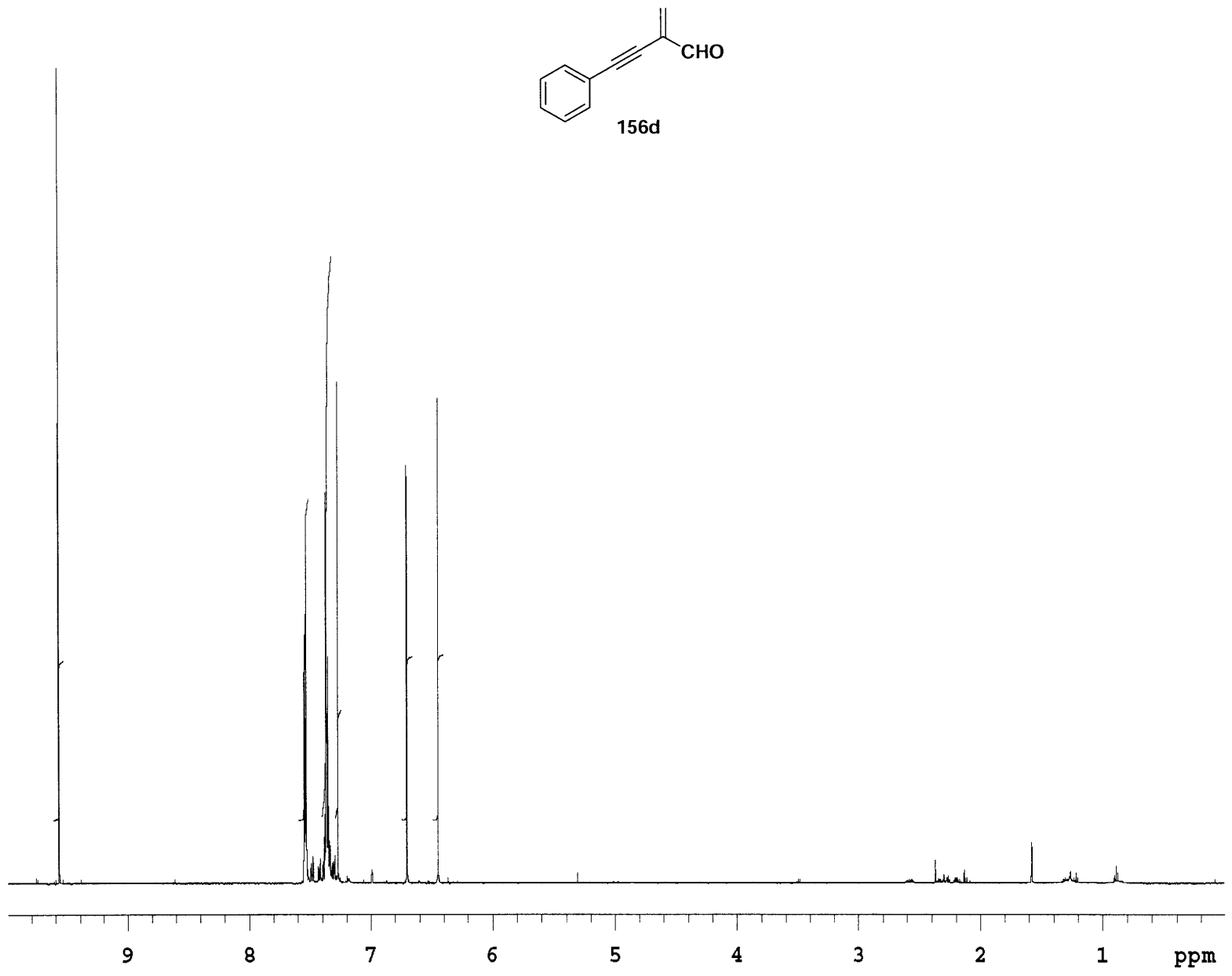
Reaction of a solution of the allylic alcohol **155c** (0.105 g, 0.76 mmol) in 2 mL of dichloromethane with Dess-Martin periodinane (0.358 g, 0.84 mmol) and then poly(4-vinylpyridine) (0.399 g, 3.80 mmol) according to the general procedure gave aldehyde **156c** as a yellow oil in 59% yield as determined by ^{1}H NMR analysis: IR (film) 2958, 2932, 2234, 1706, 1635 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 9.47 (s, 1H), 6.55 (d, J = 0.5 Hz, 1H), 6.30 (app s, 1H), 2.40 (t, J = 7.0 Hz, 2H), 1.54-1.60 (m, 2H), 1.41-1.48 (m, 2H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 190.9, 138.5, 133.8, 97.7, 73.6, 30.6, 22.2, 19.3, 13.8.

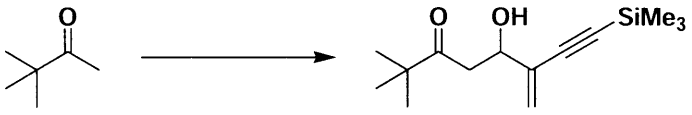

CHO
n-Bu
156c
ppm
1
2
3
4
5
6
7
8
9

155d 156d

2-Methylene-4-(phenyl)but-3-ynal (156d).

Reaction of a solution of the allylic alcohol **155d** (0.093 g, 0.59 mmol) in 3 mL of dichloromethane with Dess-Martin periodinane (0.358 g, 0.84 mmol) and then poly(4-vinylpyridine) (0.312 g, 2.94 mmol) according to the general procedure gave aldehyde **156d** as a yellow oil in 41% yield as determined by ^{1}H NMR analysis: IR (film) 3057, 2925, 2851, 2213, 1701, 1628 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 9.57 (s, 1H), 7.53-7.55 (m, 2H), 7.35-7.37 (m, 3H), 6.70 (d, J = 1.0 Hz, 1H), 6.45 (d, J = 0.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 190.2, 138.9, 133.3, 132.1, 129.3, 128.6, 122.3, 95.7, 82.3.


CHO
156d
9
8
7
6
5
4
3
2
1
ppm



158a

General Procedure for the Aldol Reaction of Enyne Aldehydes.

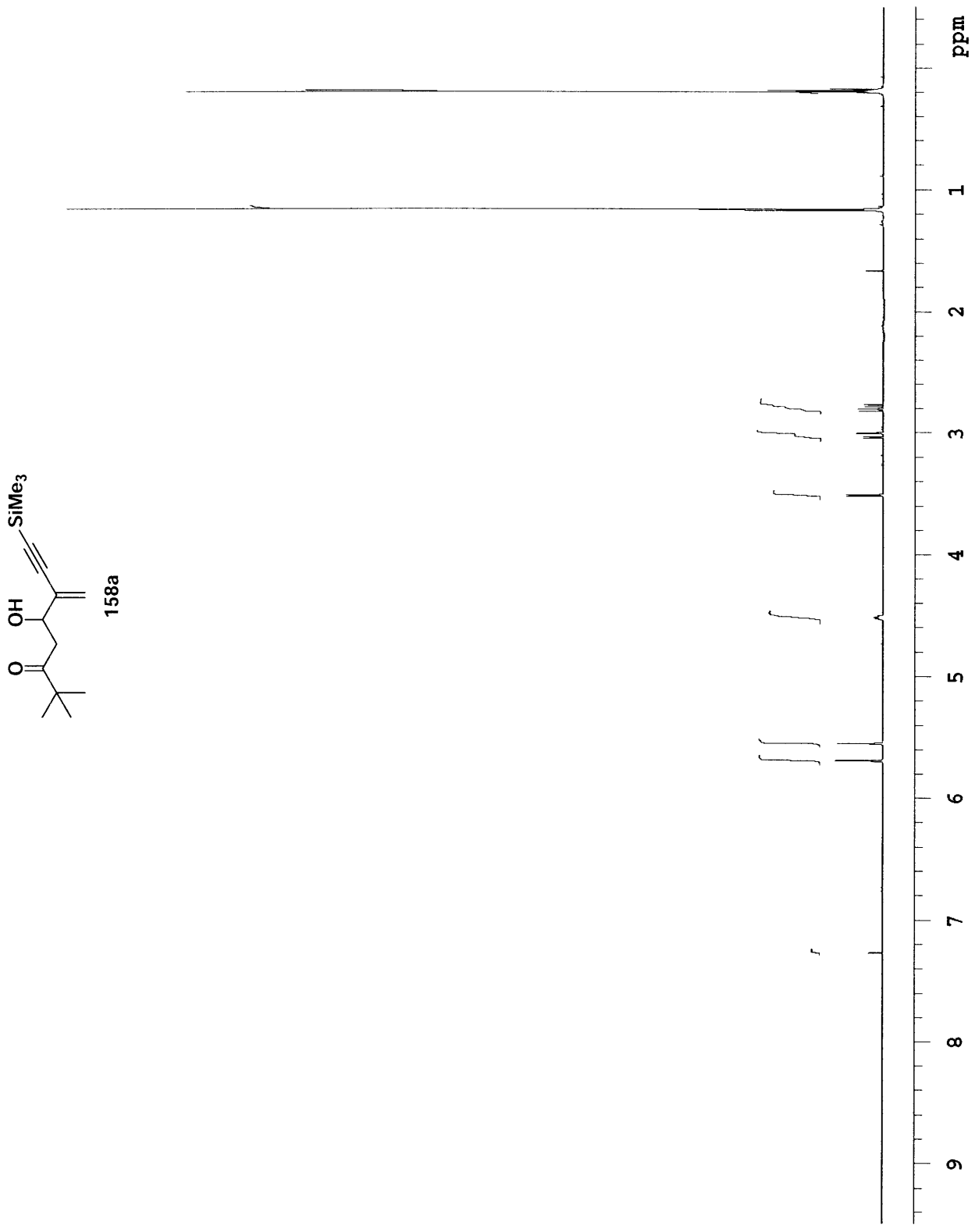
5-Hydroxy-2,2-dimethyl-6-methylene-8-(trimethylsilyl)oct-7-yn-3-one (158a).

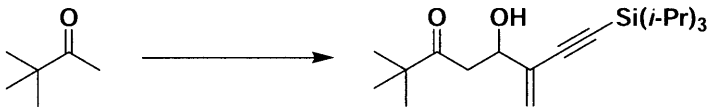
A 25-mL, two-necked, round-bottomed flask fitted with an argon inlet adapter and a rubber septum was charged with 12 mL of THF and diisopropylamine (0.19 mL, 0.13 g, 1.3 mmol) and cooled at 0 °C while 0.50 mL of *n*-BuLi solution (2.41 M in hexanes, 1.2 mmol) was added dropwise via syringe over 30 s. The resulting yellow solution was stirred at 0 °C for 15 min and then cooled to –78 °C.

A 10-mL, one-necked, pear-shaped flask was charged with 1.5 mL of THF and pinacolone (0.12 mL, 0.10 g, 1.0 mmol) and cooled to –78 °C. The resulting solution was transferred to the solution of LDA via cannula over 3 min (the flask was rinsed with 0.5 mL of THF) and the resulting cloudy pale-yellow mixture was stirred at –78 °C for 2 h.

Oxidation of allylic alcohol **155a** (0.423 g, 2.74 mmol) with Dess-Martin periodinane (1.284 g, 3.027 mmol) in 27 mL of CH_2Cl_2 was carried out according to the General Procedure to furnish aldehyde **156a** (estimated yield of 1.5 mmol based on previous experiments). This material (not allowed to warm above –78 °C once solvent was removed) was dissolved in 3 mL of THF, and then transferred via cannula over 2 min into the solution of lithium enolate prepared as described above. The resulting clear, yellow solution was stirred at –78 °C for 2 h and then treated dropwise with 1 mL of half-saturated aq NH_4Cl solution (pre-cooled at 0 °C). The resulting mixture was diluted with 15 mL of Et_2O and 10 mL of water, and the aqueous phase was separated and extracted with three 7-mL portions of Et_2O. The combined organic phases

were washed with 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.406 g of a yellow oil. Column chromatography on 20 g of silica gel (gradient elution with 0-10% EtOAc-hexane) afforded 0.242 g (94%) of **158a** as a pale yellow oil: IR (film) 3473, 2964, 2906, 2873, 2143, 1705, 1625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.69 (t, J = 1.5 Hz, 1H), 5.55 (t, J = 1.5 Hz, 1H), 4.50-4.52 (m, 1H), 3.51 (d, J = 5.0 Hz, 1H), 3.02 (dd, J = 3.0, 17.5 Hz, 1H), 2.79 (dd, J = 8.5, 17.5 Hz, 1H), 1.16 (s, 9H), 0.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 217.3, 132.8, 122.1, 103.0, 96.9, 70.0, 44.7, 41.9, 26.3, 0.1. HRMS-ESI Calcd for $C_{14}H_{24}O_2Si$: 253.1618 $[M+H]^+$. Found: 253.1625.

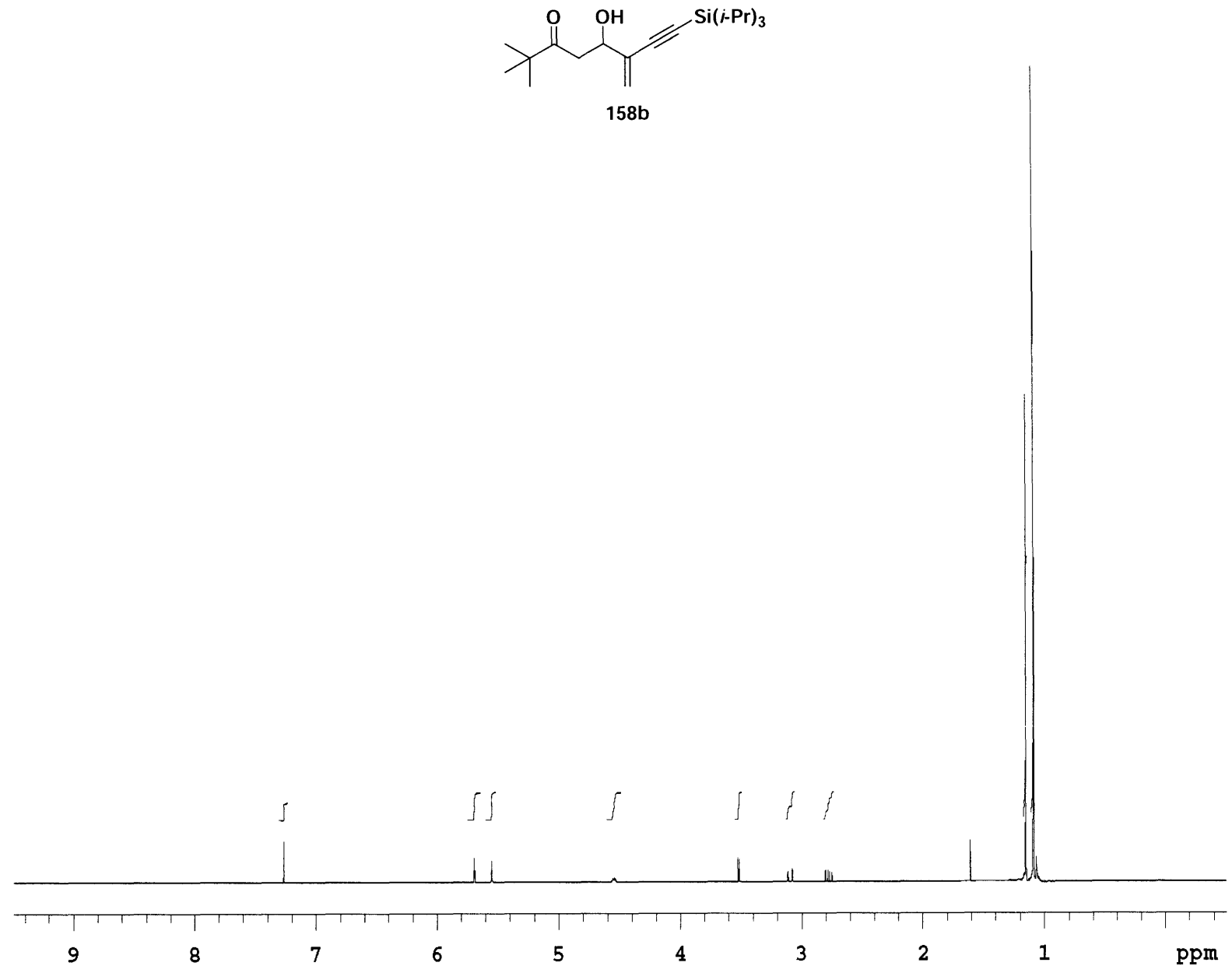

SiMe3
OH
O
158a
ppm
1
2
3
4
5
6
7
8
9

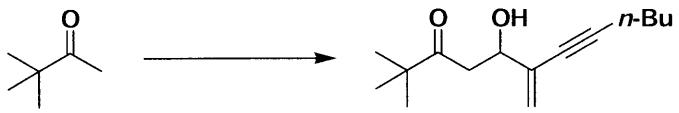


158b

5-Hydroxy-2,2-dimethyl-6-methylene-8-(triisopropylsilyl)oct-7-yn-3-one (158b).

A solution of lithium enolate derivative of pinacolone was generated as described in the General Procedure from the reaction of diisopropylamine (0.024 mL, 0.017 g, 0.17 mmol) and 0.67 mL of *n*-BuLi solution (2.41 M in hexanes, 0.16 mmol) in 3 mL of THF followed by addition of pinacolone (0.017 mL, 0.013 g, 0.13 mmol) in 2 mL of THF. A solution of aldehyde **156b** (ca. 0.2 mmol) in 3 mL of THF was prepared as described in the General Procedure from oxidation of allylic alcohol **155b** (0.061 g, 0.26 mmol) with Dess-Martin periodinane (0.120 g, 0.28 mmol) in 5 mL of CH_2Cl_2. Reaction of **156b** with the ketone enolate then afforded 0.070 g of a yellow oil, which was purified by column chromatography on 10 g of silica gel (gradient elution with 0-10% EtOAc-hexane) to provide 0.031 g (70%) of aldol **158b** as a pale yellow oil: IR (film) 3482, 2944, 2866, 2142, 1700, 1616 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.69 (t, J = 1.5 Hz, 1H), 5.55 (t, J = 1.5 Hz, 1H), 4.53-4.56 (m, 1H), 3.52 (d, J = 4.0 Hz, 1H), 3.10 (dd, J = 3.0, 18.0 Hz, 1H), 2.78 (dd, J = 8.5, 18.0 Hz, 1H), 1.15 (s, 9H), 1.09 (s, 21H); ^{13}C NMR (125 MHz, $CDCl_3$): 217.3, 132.9, 121.6, 105.0, 93.1, 70.1, 44.6, 42.2, 26.3, 18.8, 11.4. HRMS-ESI Calcd for $C_{20}H_{36}O_2Si$: 359.2377 $[M+Na]^+$. Found: 359.2376.

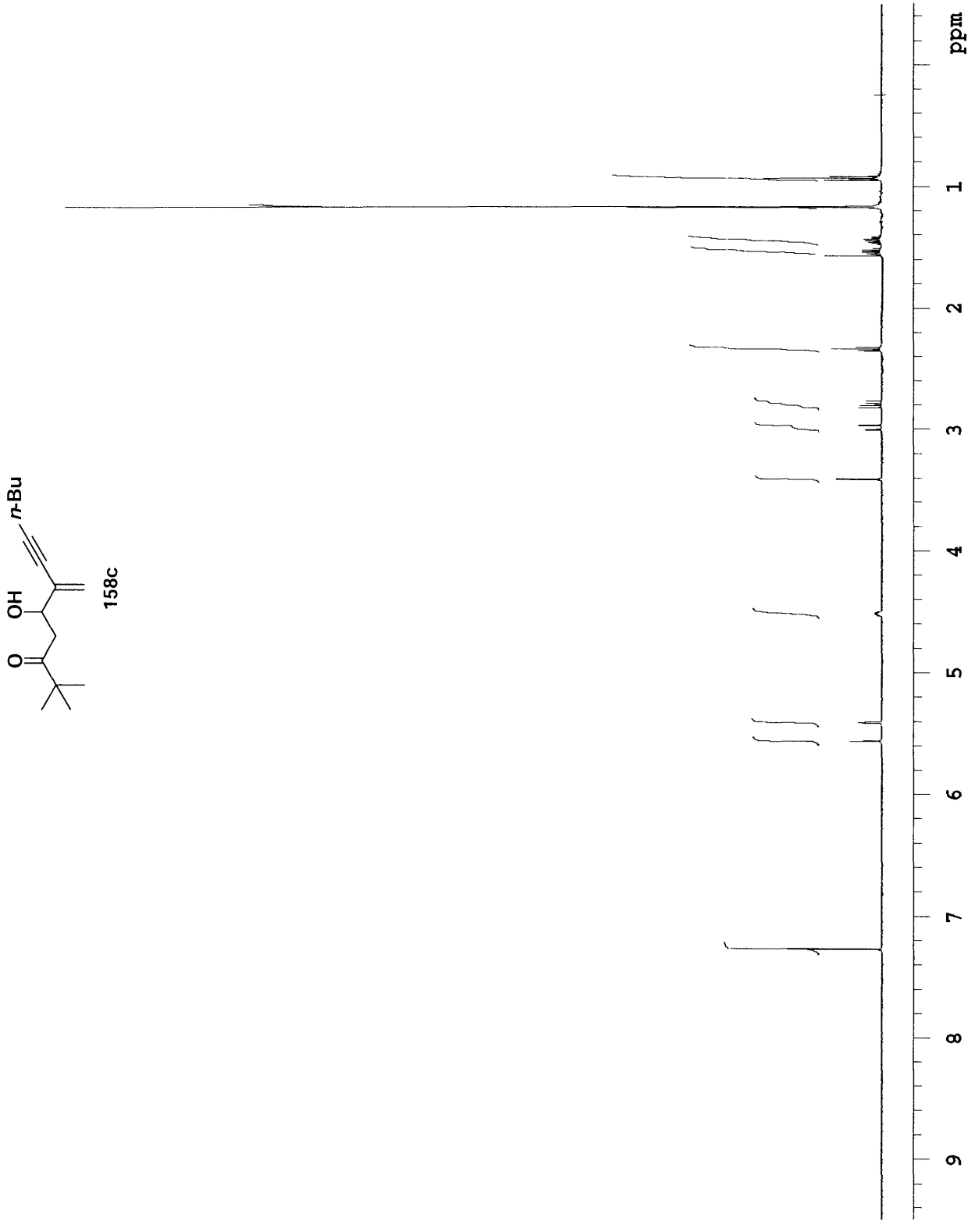

O
OH
Si(i-Pr)3
158b
9
8
7
6
5
4
3
2
1
ppm



158c

5-Hydroxy-2,2-dimethyl-6-methylene-8-(*n*-butyl)oct-7-yn-3-one (158c).

A solution of the lithium enolate derivative of pinacolone was generated as described in the General Procedure from the reaction of diisopropylamine (0.17 mL, 0.12 g, 1.2 mmol) and 0.43 mL of *n*-BuLi solution (2.35 M in hexanes, 1.0 mmol) in 10 mL of THF followed by addition of pinacolone (0.105 mL, 0.085 g, 0.84 mmol) in 3 mL of THF. A solution of aldehyde **156c** (ca. 0.9 mmol) in 3 mL of THF was prepared as described in the General Procedure from oxidation of allylic alcohol **155c** (0.218 g, 1.57 mmol) with Dess-Martin periodinane (0.742 g, 1.57 mmol) in 5 mL of CH_2Cl_2. Reaction of the aldehyde with the ketone enolate then afforded 0.235 g of a yellow oil, which was purified by column chromatography on 12 g of silica gel (gradient elution with 0-10% EtOAc-hexane) to provide 0.185 g of impure **158c** as a yellow oil. This material was further purified on 18 g of silica gel (gradient elution with 0-10% EtOAc-hexane) to afford 0.140 g (70%) of **158c** as a pale yellow oil: IR (film) 3481, 2961, 2222, 1700, 1616 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.56 (t, J = 1.5 Hz, 1H), 5.41 (s, 1H), 4.50-4.53 (m, 1H), 3.41 (d, J = 4.0 Hz, 1H), 2.99 (dd, J = 3.0, 17.5 Hz, 1H), 2.79 (dd, J = 8.5, 18.0 Hz, 1H), 2.34 (t, J = 7.0 Hz, 2H), 1.51-1.55 (m, 2H), 1.40-1.47 (m, 2H), 1.16 (s, 9H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 197.5, 133.2, 119.9, 92.8, 78.4, 70.5, 44.7, 42.3, 30.9, 26.4, 22.2, 19.2, 13.8. HRMS-ESI Calcd for $C_{15}H_{24}O_2$: 259.1669 $[M+Na]^+$. Found: 259.1674.


n-Bu
OH
O
158c
ppm
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6
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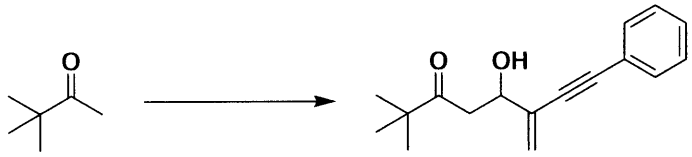
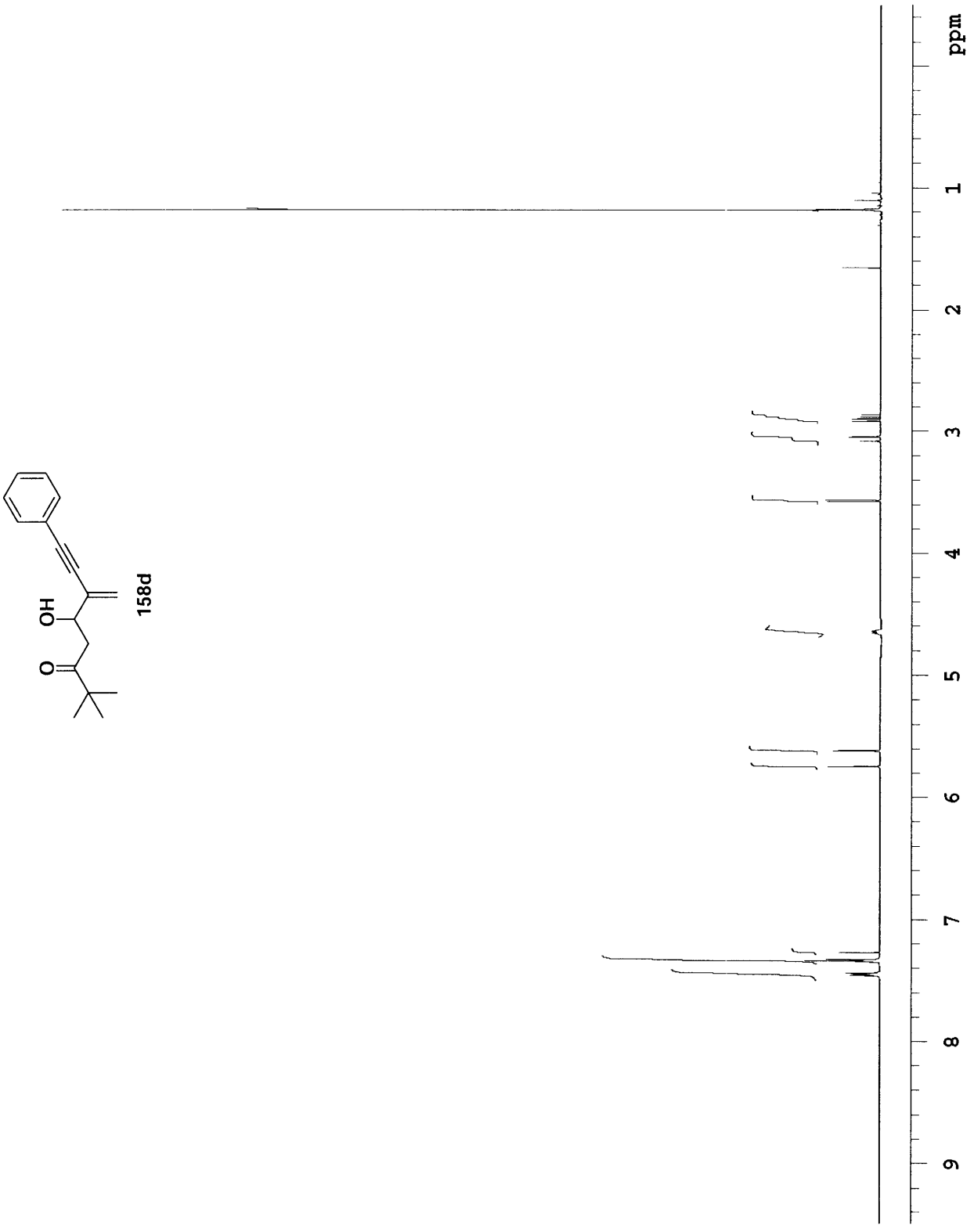
9



158d

5-Hydroxy-2,2-dimethyl-6-methylene-8-(phenyl)-oct-7-yn-3-one (158d).

A solution of the lithium enolate derivative of pinacolone was generated as described in the General Procedure from the reaction of diisopropylamine (0.054 mL, 0.039 g, 0.39 mmol) and 0.16 mL of *n*-BuLi solution (2.30 M in hexanes, 0.36 mmol) in 4 mL of THF followed by addition of pinacolone (0.037 mL, 0.030 g, 0.30 mmol) in 2 mL of THF. A solution of aldehyde **156d** (ca. 0.3 mmol) in 2 mL of THF was prepared as described in the General Procedure from oxidation of allylic alcohol **155d** (0.130 g, 0.82 mmol) with Dess-Martin periodinane (0.388 g, 0.90 mmol) in 4 mL of CH_2Cl_2. Reaction of **156d** with the ketone enolate then afforded 0.097 g of a yellow oil, which was purified by column chromatography on 5 g of silica gel (gradient elution with 0-20% EtOAc-hexane) to provide 0.054 g (71%) of **158d** as a pale yellow oil: IR (film) 3462, 3057, 2970, 2201, 1701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.43-7.46 (m, 2H), 7.32-7.35 (m, 3H), 5.75 (t, J = 1.5 Hz, 1H), 5.61 (t, J = 1.5 Hz, 1H), 4.64-4.65 (m, 1H), 3.57 (d, J = 4.5 Hz, 1H), 3.06 (dd, J = 3.0, 18.0, 1H), 2.89 (dd, J = 8.5, 17.5 Hz, 1H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 217.2, 132.8, 131.8, 128.7, 128.6, 123.0, 121.5, 91.5, 87.2, 70.3, 44.7, 42.2, 26.4. HRMS-ESI Calcd for $C_{17}H_{20}O_2$: 279.1356 $[M+Na]^+$. Found: 279.1362.


OH
O
158d
ppm
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3
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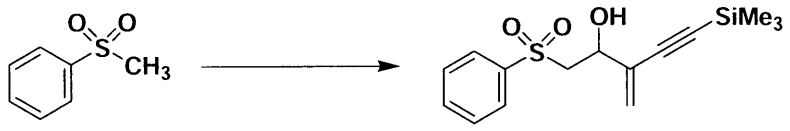
5
6
7
8
9



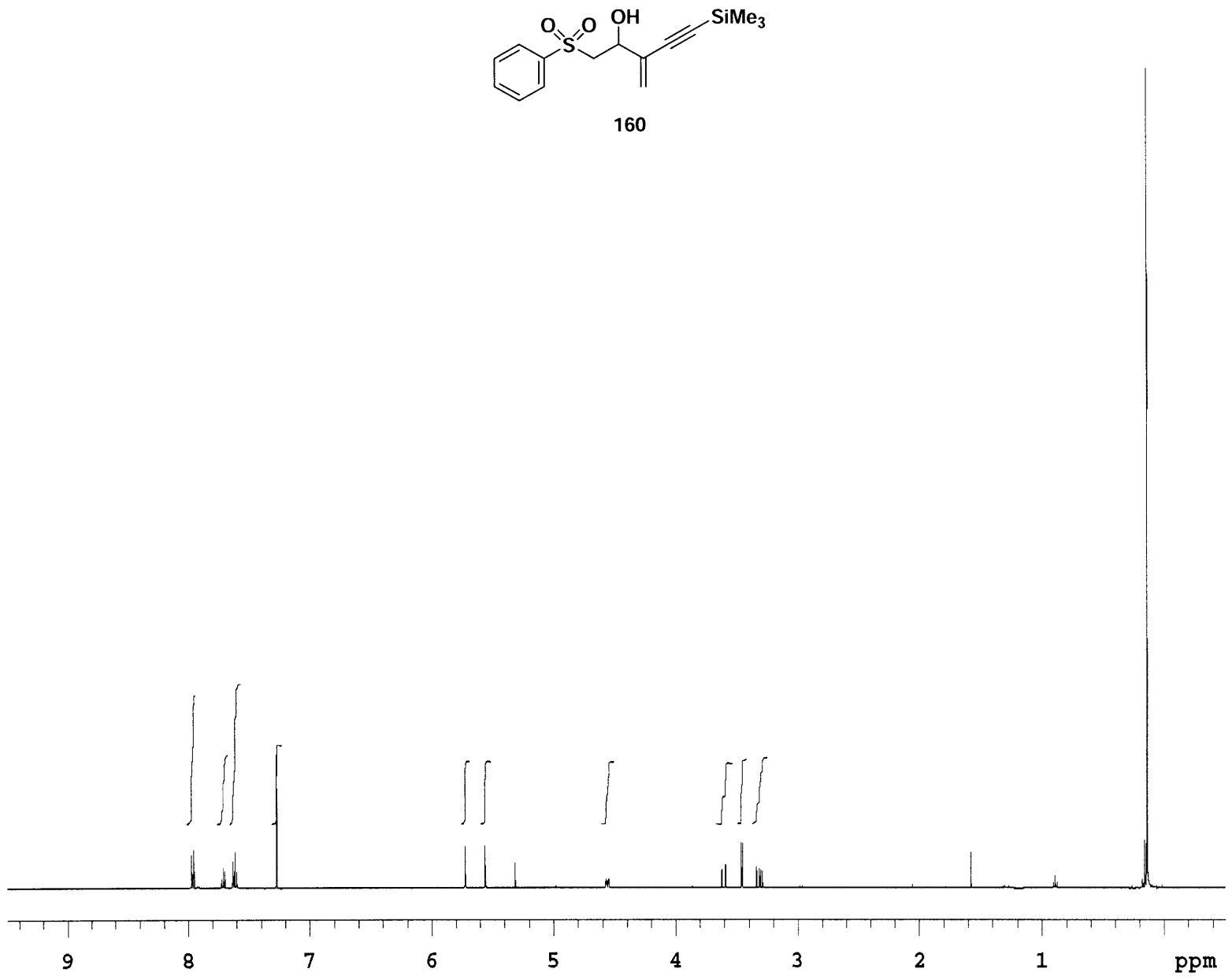
159 160

1-Phenylsulfonyl-2-hydroxy-3-methylene-5-(trimethylsilyl)-4-pentyne (160).

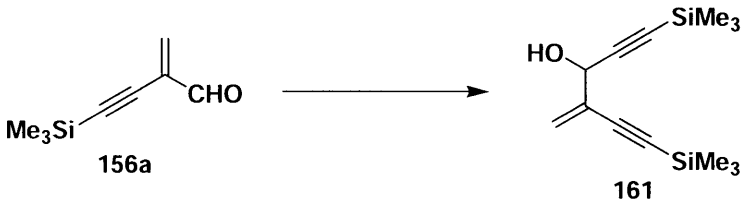
A 25-mL, two-necked, round-bottomed flask fitted with an argon inlet adapter and a rubber septum was charged with phenyl methyl sulfone (0.095 g, 0.60 mmol) and 5 mL of THF and cooled at –78 °C while 0.28 mL of *n*-BuLi solution (2.40 M in hexanes, 0.67 mmol) was added dropwise via syringe over 30 s. The resulting yellow solution was stirred at –78 °C for 1 h.

Oxidation of allylic alcohol **155a** (0.198 g, 1.28 mmol) with Dess-Martin periodinane (0.659 g, 1.54 mmol) in 5 mL of CH_2Cl_2 was carried out according to the General Procedure to furnish aldehyde **156a** (estimated yield of 0.7 mmol based on previous experiments). This material (not allowed to warm above –78 °C once solvent was removed) was dissolved in 3 mL of THF, and then transferred via cannula over 5 min into the solution of lithiated sulfone prepared as described above. The resulting clear yellow solution was allowed to stir at –78 °C for 1.7 h and then treated dropwise with 10 mL of half-saturated aq NH_4Cl solution (pre-cooled at 0 °C). The resulting mixture was allowed to warm to rt over 15 min and diluted then with 15 mL of Et_2O and 10 mL of water. The aqueous phase was separated and extracted with four 10-mL portions of Et_2O, and the combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.248 g of an orange-yellow oil. Column chromatography on 13 g of silica gel (gradient elution with 10-40% EtOAc-hexane) afforded 0.114 g (61%) of alcohol **160** as a white solid: mp 122-123 °C; IR (film) 3492, 3067, 2960, 2147, 1307 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.95-7.98 (m, 2H), 7.71 (tt, J = 1.5,

8.0 Hz, 1H), 7.60-7.63 (m, 2H), 5.72 (t, J = 1.5 Hz, 1H), 5.56 (t, J = 1.0 Hz, 1H), 4.54-4.58 (m, 1H), 3.61 (dd, J = 2.0, 14.5 Hz, 1H), 3.46 (d, J = 3.0 Hz, 1H), 3.31 (dd, J = 9.5, 15.0 Hz, 1H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 139.1, 134.3, 130.5, 129.6, 128.2, 123.2, 101.4, 97.9, 68.4, 61.2, -0.07. HRMS-ESI Calcd for $C_{15}H_{20}O_3SSi$: 331.0795 $[M+Na]^+$. Found: 331.0801.



160

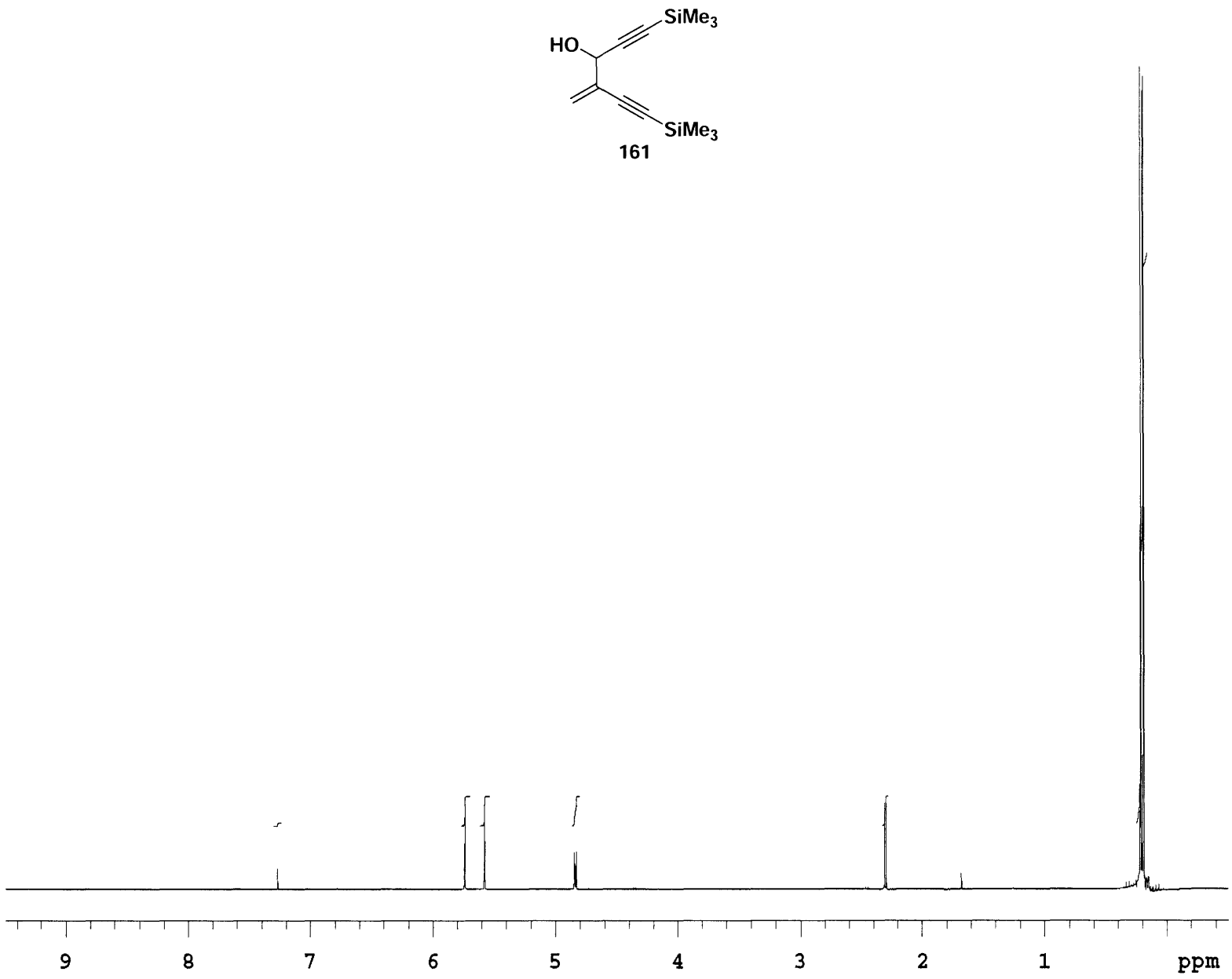


1,6-Bis(trimethylsilyl)-3-hydroxy-4-methylenehexa-1,5-diyne (161).

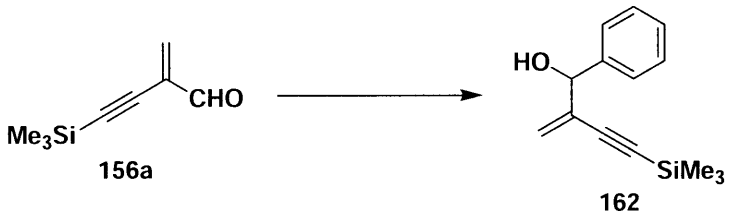
A 50-mL, two-necked, round-bottomed flask fitted with an argon inlet adapter and rubber septum was charged with 12 mL of THF and trimethylsilylacetylene (0.26 mL, 0.182 g, 1.85 mmol) and cooled at –78 °C while 0.67 mL of *n*-BuLi solution (2.50 M in hexanes, 1.68 mmol) was added dropwise via syringe over 30 s. The resulting pale yellow solution was stirred at –78 °C for 1 h.

Oxidation of allylic alcohol **155a** (0.129 g, 0.84 mmol) with Dess-Martin periodinane (0.394 g, 0.92 mmol) in 4 mL of CH_2Cl_2 was carried out according to the General Procedure to furnish aldehyde **156a** (estimated yield of 0.44 mmol based on previous experiments). This material (not allowed to warm above –78 °C once solvent was removed) was dissolved in 3 mL of THF, and then transferred via cannula over 3 min into the solution of lithium trimethylsilylacetylide prepared as described above. The resulting clear yellow solution was allowed to stir at –78 °C for 15 min and then treated with 5 mL of saturated aq NH_4Cl solution. The resulting mixture was diluted with 10 mL of Et_2O and 5 mL of water, and the aqueous phase was separated and extracted with three 10-mL portions of Et_2O. The combined organic phases were washed with 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.118 g of yellow oil. Column chromatography on 15 g of silica gel (gradient elution with 0-5% EtOAc-hexane) afforded 0.081 g (38% overall from **155a**) of alcohol **161** as a pale yellow oil: IR (film) 3356, 2961, 2178, 2149, 1616 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 5.74 (t, J = 1.5 Hz, 1H), 5.59 (t, J = 1.5 Hz, 1H), 4.84 (dt, J = 1.0, 7.5 Hz, 1H), 2.23 (d,

J = 2.0 Hz, 1H), 0.22 (s, 9H), 0.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 131.4, 123.1, 103.1, 101.6, 97.7, 91.9, 65.3, 0.05, -0.04. HRMS-ESI Calcd for $C_{13}H_{22}OSi_2$: 273.1101 $[M+Na]^+$. Found: 273.1107.



161



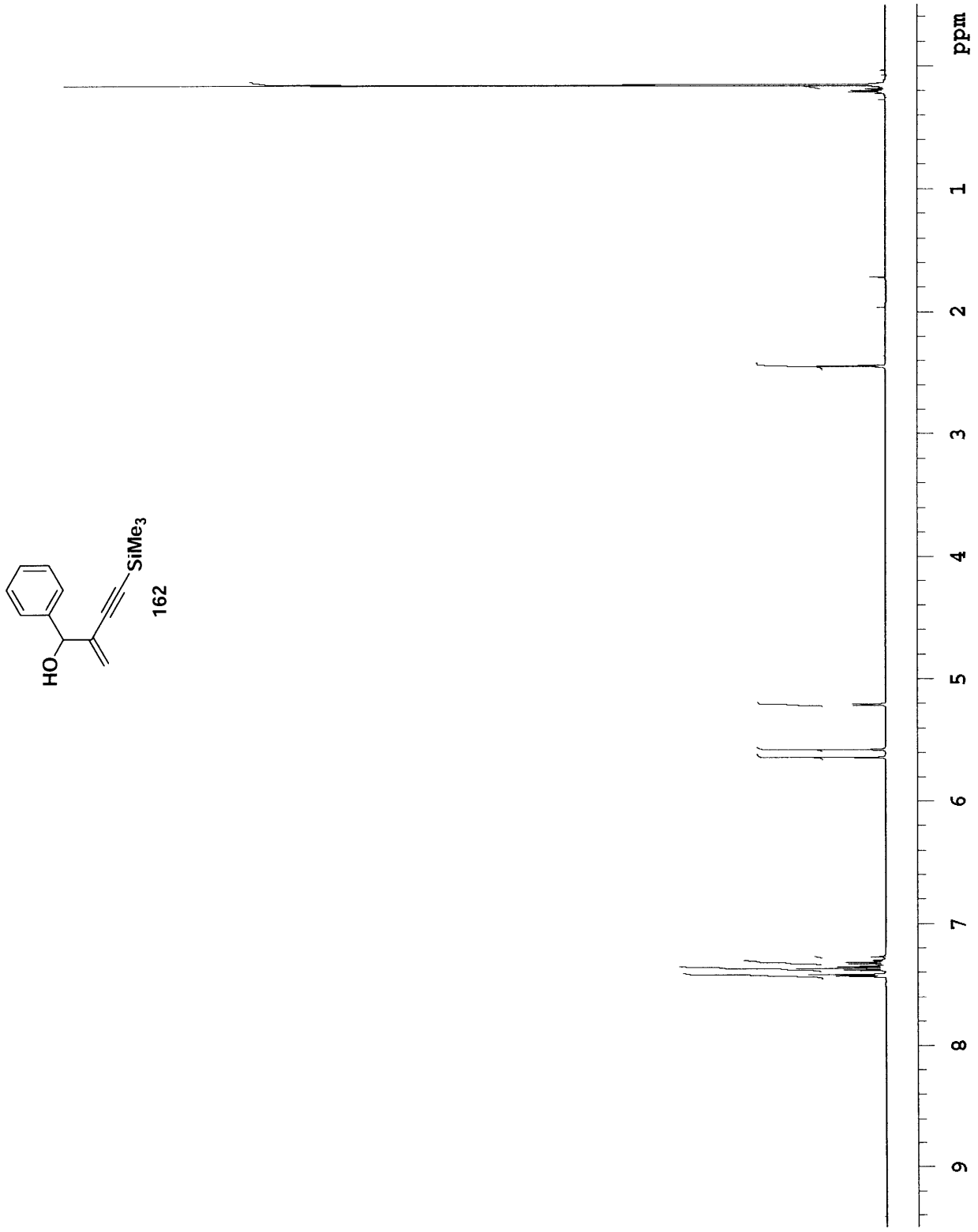
156a 162

1-Phenyl-1-hydroxy-2-methylene-4-(trimethylsilyl)-3-butyne (162).

A 50-mL, two-necked, round-bottomed flask fitted with an argon inlet adapter and a rubber septum was charged with 30 mL of THF and 1.24 mL of PhLi solution (1.80 M in hexanes, 2.23 mmol) and cooled at –78 °C.

Oxidation of allylic alcohol **155a** (0.149 g, 0.97 mmol) with Dess-Martin periodinane (0.459 g, 1.07 mmol) in 5 mL of CH_2Cl_2 was carried out according to the General Procedure to furnish aldehyde **156a** (estimated yield of 1.0 mmol based on previous experiments). This material (not allowed to warm above –78 °C once solvent was removed) was dissolved in 3 mL of THF, and then transferred via cannula over 3 min into the solution of PhLi described above. The resulting clear yellow solution was allowed to stir at –78 °C for 1 h and then treated dropwise with 5 mL of saturated aq NH_4Cl solution. The resulting mixture was diluted with 10 mL of Et_2O and 5 mL of water, and the aqueous phase was separated and extracted with three 10-mL portions of Et_2O. The combined organic phases were washed with 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.249 g of yellow oil. Column chromatography on 25 g of silica gel (gradient elution with 0-5% EtOAc-hexane) afforded 0.089 g (40% overall from **155a**) of alcohol **162** as a pale yellow oil: IR (film) 3385, 3088, 3065, 3031, 2146 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 7.41-7.43 (m, 2H), 7.34-7.38 (m, 2H), 7.31 (tt, J = 2.5, 7.0 Hz, 1H), 5.63 (t, J = 1.5 Hz, 1H), 5.57 (dd, J = 1.0, 1.5 Hz, 1H), 5.22 (d, J = 5.0 Hz, 1H), 2.29 (d, J = 5.0 Hz, 1H), 0.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): 141.4, 134.4, 128.5, 128.1, 126.8, 121.9,

102.6, 98.0, 76.4, -0.04. HRMS-ESI Calcd for $C_{14}H_{18}OSi$: 253.1019 $[M+Na]^+$. Found: 253.1024.


HO
SiMe3
162
ppm
1
2
3
4
5
6
7
8
9

CHARNSAK THONGSORNKLEEB

EDUCATION

Massachusetts Institute of Technology — Cambridge, MA
Ph.D. Organic Chemistry — *February 2006*
Advisor: Professor Rick L. Danheiser
Thesis Title: "Studies Toward the Total Synthesis of Glycinoeclepin A."

University of Connecticut — Storrs, CT
B.S., Chemistry with a minor in Mathematics, *magna cum laude* — *May 2000*
Advisor: Professor William F. Bailey

RESEARCH EXPERIENCE

Massachusetts Institute of Technology — Cambridge, MA
Graduate Research Assistant — *January 2001-December 2005*

- Developed an efficient generation of the A-ring portion of Glycinoeclepin A, a natural compound potentially useful as an environmentally-benign pest control agent in soybeans and related crops.
- Developed a novel synthetic method for the generation of 2-alkynyl acroleins from alcohol precursors, which are useful as synthetic building blocks containing valuable functional groups in organic synthesis.

University of Connecticut — Storrs, CT
Undergraduate Research Assistant — *May 1998-May 2000*

- Synthesized a number of allyl ether substrates from alcohol precursors.
- Studied the utilization of *t*-BuLi as a reagent for the deprotection of alcohols from allyl ethers.

TEACHING EXPERIENCE

Massachusetts Institute of Technology — Cambridge, MA
Teaching Assistant: Asymmetric Synthesis — *January 2003-May 2003*

- Assisted the course instructor by preparing class handouts, updating class website and coordinating with the departmental Administrative Assistants.
- Provided assistance to graduate students by conducting office hours and question/answer sessions.

Massachusetts Institute of Technology — Cambridge, MA
Teaching Assistant: General Chemistry and Organic Chemistry — *September 2000-May 2001*

- Led biweekly recitation sections and provided assistance to students by conducting office hours and review sessions.

- Graded homework and exams.

University of Connecticut Storrs, CT
Chemistry Tutor for University Athletes *August 1999-December 1999*
- Provided academic support in general chemistry to student athletes throughout semester as requested.

VOLUNTEER EXPERIENCE

Massachusetts Institute of Technology Cambridge, MA
Chemistry Outreach Volunteer *January 2001-June 2005*
- Presented educational and exciting chemistry demonstrations to local high school students.
- Promoted sciences, specifically chemistry, as a possible exciting and challenging career.

31st International Chemistry Olympiad Bangkok, Thailand
Program Volunteer *July 1999*
- Coordinated with mentors from participating countries and organizers in various events throughout the program.
- Assisted mentors in everyday needs during the entire 1-week program.

PUBLICATIONS

- Thongsornkleeb, C.; Danheiser, R. L. A Practical Method for the Synthesis of 2-Alkynylpropenals. *J. Org. Chem.* **2005**, *70*, 2364-2367.
- Bailey, W. F.; England, M. D.; Mealy, M. J.; Thongsornkleeb, C.; Teng, L. Facile O-Deallylation of Allyl Ethers via S_N2' Reaction with *tert*-Butyllithium. *Org. Lett.* **2000**, *2*, 489-491.

HONORS AND AWARDS

- Golden Key International Honor Society Member, 2000-present
- The Catherine DeStefano Rossi Memorial Scholar, University of Connecticut, 1999-2000
- Honors Program Scholar, University of Connecticut, Spring 1999-Fall 1999
- New England Scholar, University of Connecticut, 1999
- Dean's List Scholar, College of Liberal Arts and Sciences, University of Connecticut, Spring 1998-Fall 1999
- Pfizer Research Experience for Undergraduate (REU) Program Intern, University of Connecticut, 1998
- The Development and Promotion of Sciences and Technology Scholar, Thailand, 1996-present

AFFILIATIONS

American Chemical Society, Organic Division