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Chandra Potter Date

Progress Toward the Total Synthesis of PM-toxin A

And

Future Development of Mild Lewis Acid Activated Alkynylation of Epoxides

By

Chandra Potter
Master of Science

Chemistry

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Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

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Date

Progress Toward the Total Synthesis of PM-toxin A

And

Future Development of Mild Lewis Acid Activated Alkynylation of Epoxides

By

Chandra Potter
B.S., College of Charleston, 2009

Advisor: Frank E. McDonald, Ph.D.

An abstract of
a thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
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in Chemistry
2011

Abstract

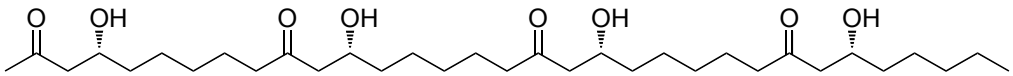
Progress Toward the Total Synthesis of PM-toxin A

And

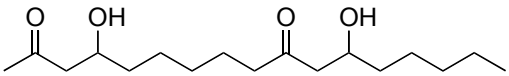
Future Development of Mild Lewis Acid Activated Alkynylation of Epoxides

By Chandra Potter

The natural product, PM-toxin A (**1**), is a pathogen that causes leaf blight and sterility to the male maize. In preparation for the synthesis of (**1**) we have synthesized racemic model compound (**2**). The development of a synthetic pathway for (**2**), described herein, demonstrates the viability of each technical step in the asymmetric synthesis of PM-toxin A. A key step in the synthesis is the nucleophilic opening of an epoxide via an acetylide ion to afford the homopropargylic alcohol. Current methodology for the alkynylation of epoxides uses *n*-butyllithium, for the deprotonation of the terminal alkyne, and boron trifluoride-diethyl etherate or boron trifluoride-tetrahydrofuran, to activate the epoxide, at low temperatures (e.g., -78 °C). Future work will include development of mild reaction conditions for successful Lewis acid activated alkynylation of epoxides using a tertiary amine for the deprotonation of the terminal alkyne.



PM-toxin A (**1**)



model substrate of PM-toxin A (**2**)

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are the people behind the scenes and I owe them a huge debt of gratitude. The McDonald laboratory has become a wonderful place to work with diverse individuals like Kristen Stoltz, Adam Stockhausen, Emily Wein, Victoria Jiang, Dr. Kento Ishida.

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Table of Contents

List of Schemes

List of Figures

Abbreviations

Ac	acetate
APCI	atmospheric pressure chemical ionization
app d	apparent doublet
app sxt	apparent sextet
app t	apparent triplet
Aq	aqueous
Bn	benzyl
bp	boiling point
Bz	benzoyl
$CDCl_3$	deuterated chloroform
$CHCl_3$	chloroform
cod	1,5-cyclooctadiene
d	doublet
DCM	dichloromethane
DI	deionized
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DVDS	1,1,3,3-tetramethyl-1,3-divinyldisiloxane
ESI	electrospray ionization
EtBr	ethyl bromide
Et_2O	diethyl ether
EtOAc	ethyl acetate
FT-IR	Fourier transform infrared spectroscopy
h	hour
HRMS	high resolution mass spectromotry
Hz	hertz
K_2CO_3	potassium carbonate
KF	potassium fluoride
$KHCO_3$	potassium bicarbonate
M	molar concentration
m	multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
MeOH	methanol
mg	milligram
$MgSO_4$	magnesium sulfate
min	minute
mL	milliliter
mmol	millimole
MS	molecular sieves
μL	microliter
$NaHCO_3$	sodium bicarbonate
Na_2SO_4	sodium sulfate
n-BuLi	*n*-butyllithium

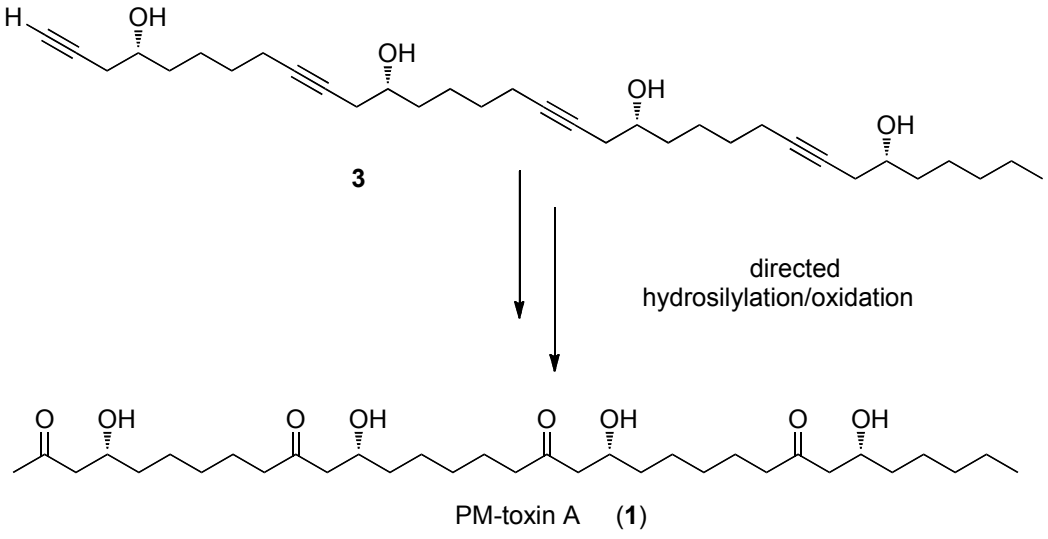
NH_4Cl	ammonium chloride
NMR	nuclear magnetic resonance
Ph	phenyl
p-TSA	*para*-toluenesulfonic acid
PMB	*para*-methoxybenzyl
Py	pyridine
q	quartet
RBF	round bottom flask
RT	room temperature
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilane
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMDS	bis(dimethylsilyl)amine

Versatility of the Alkynylation of Epoxides

Introduction

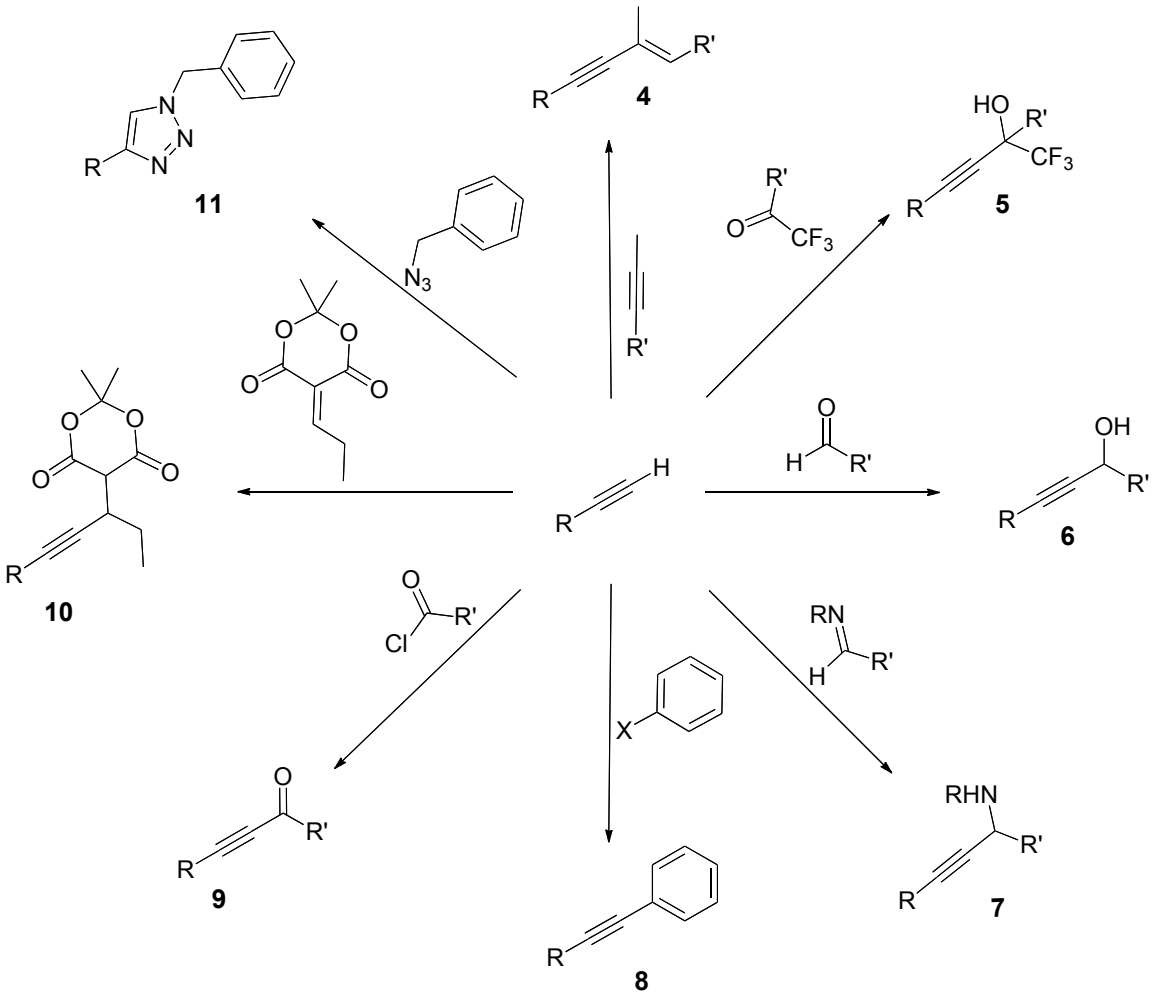
The focus of much research in the chemical community is the development of new methodologies for the concise synthesis of chiral non-racemic molecules. The discovery of simple, scalable, and inexpensive methods for constructing compounds ranging from enantiopure building blocks to structurally complex natural products is a large part of that research. The alkynylation of carbonyl and epoxide electrophiles can accomplish the creation of a chiral non-racemic alkynyl alcohol, which is an extremely versatile synthon (Scheme 1). As in other directed functionalization reactions, a chiral homopropargylic or propargylic alcohol can, with careful planning, influence the stereoselectivity of future steps of a synthesis.

Scheme 1. Proposed example of homopropargylic alcohol facilitating functionalization.



Alkynylation reactions with electrophiles such as aldehydes, acid chlorides, ketones, and imines as well as carbon-carbon and carbon-nitrogen double bonds can quickly synthesize a wide variety of functionalize compounds (Figure 1).[1-6] The application of chiral additives or catalysts can render these reactions enantioselective.

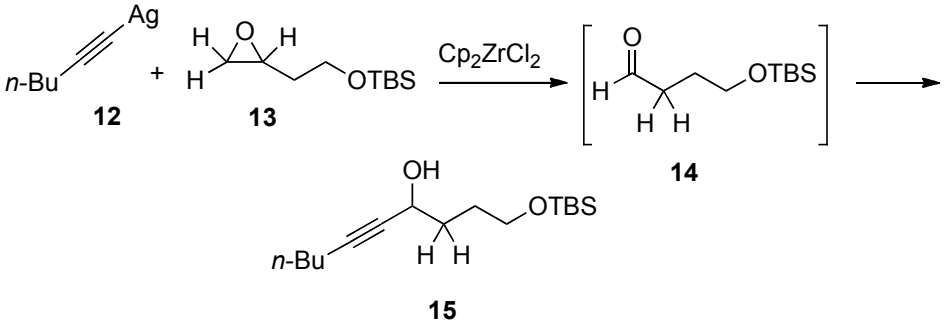
Figure 1. Examples of widely used alkynylations.



The only general methodology used for epoxide alkynylation to form homopropargylic alcohols is the classical method that employs *n*-butyllithium (*n*-BuLi) as the base and boron trifluoride-diethyl etherate (BF_3•Et_2O) or boron

trifluoride-tetrahydrofuran (BF_3•THF) as the Lewis acid. In addition to using an aldehyde, propargylic alcohols have been produced by employing zinc halides and other additives or ligands to induce rearrangement of the epoxide through an aldehyde intermediate (Scheme 2).[2,7-13]

Scheme 2. Rearrangement of epoxide through aldehyde intermediate.



The use of enantiopure epoxides as viable coupling substrates in enantioselective syntheses is a very attractive approach for preparing chiral non-racemic alcohols. Investigations into a scalable, high throughput manufacturing system for the production of enantiopure epoxides have been underway over the past decade.[14] Such systems allow for the hydrolytic kinetic resolution (HKR) of epoxides, followed by recovery of the active catalyst and release of the enantio-enriched epoxide and corresponding diol without the need for manual separation of the catalyst followed by reactivation.

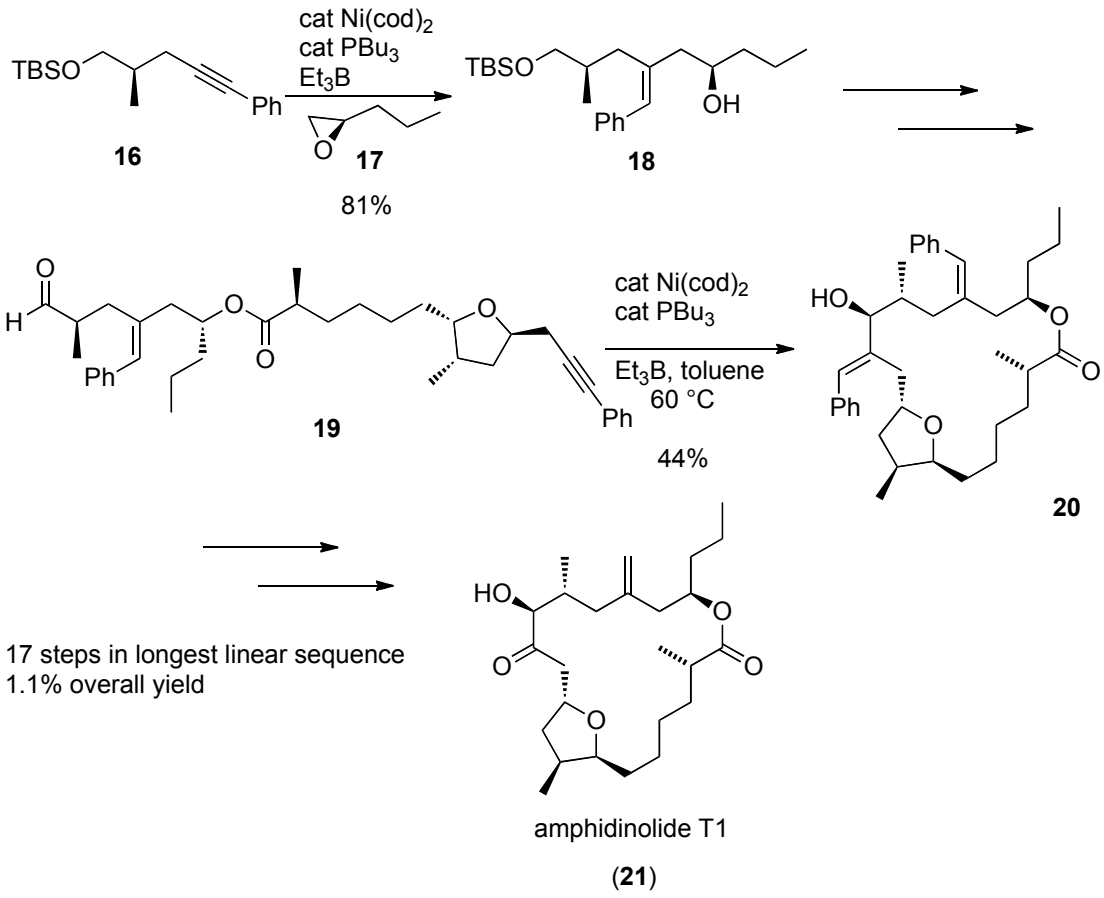
Alkyne-epoxide cross-coupling reactions can benefit from these investigations. The expansion of this clever reaction will allow: natural products and structurally complex target molecules to be assembled more concisely, convergent syntheses creating large synthons to conserve time, materials and a flexible route for analog synthesis, enantiopure epoxides to utilize concise

enantioselective synthesis. These advances may allow for the synthesis of once unattainable compounds and is a direct manifestation of the need for shorter synthetic routes for target molecules.

Examples

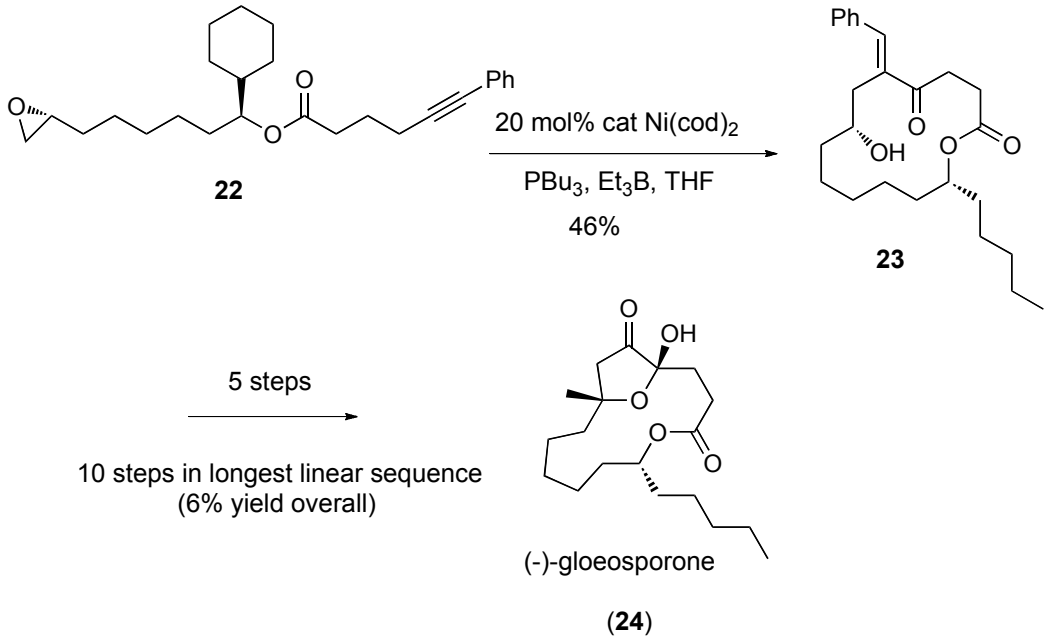
Several natural products are candidates for alkyne-epoxide cross coupling reactions. The Jamison group has synthesized amphidinolide T1 (**21**) (Scheme 3) utilizing the nickel-catalyzed reductive coupling first with alkyne **16** and epoxide **17**, followed by a second alkyne-aldehyde coupling of **19** to close the macrocycle **20**.[15-17] Other amphidinolides are accessible through many of the same intermediates, allowing for easier access to these potential anti-cancer molecules.[16]

Scheme 3. Amphidinolide T1, the reductive coupling of the synthesis.



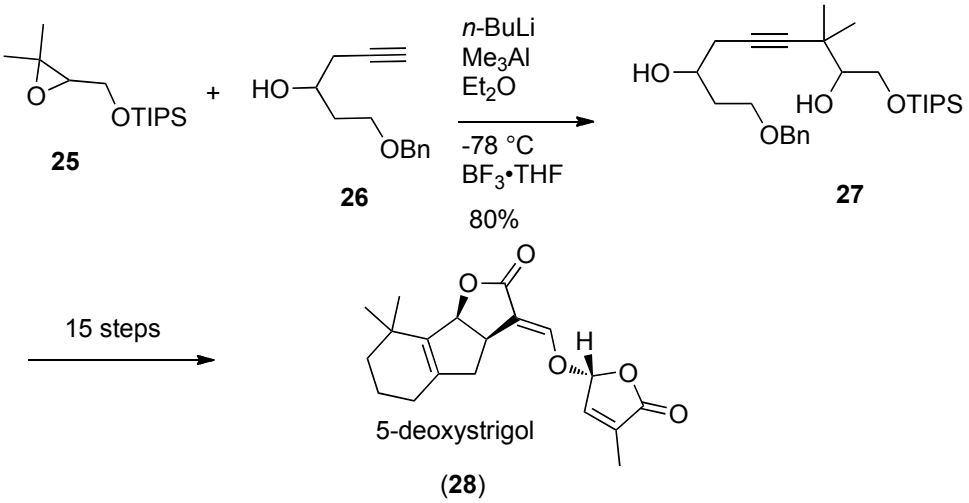
Nickel was also used in the total synthesis of (-)-gloeosporone (**24**) (Scheme 4) by a late-stage macrocyclization **23** to give the final product.[18]

Scheme 4. Key synthetic steps of (-)-gloeosporone.



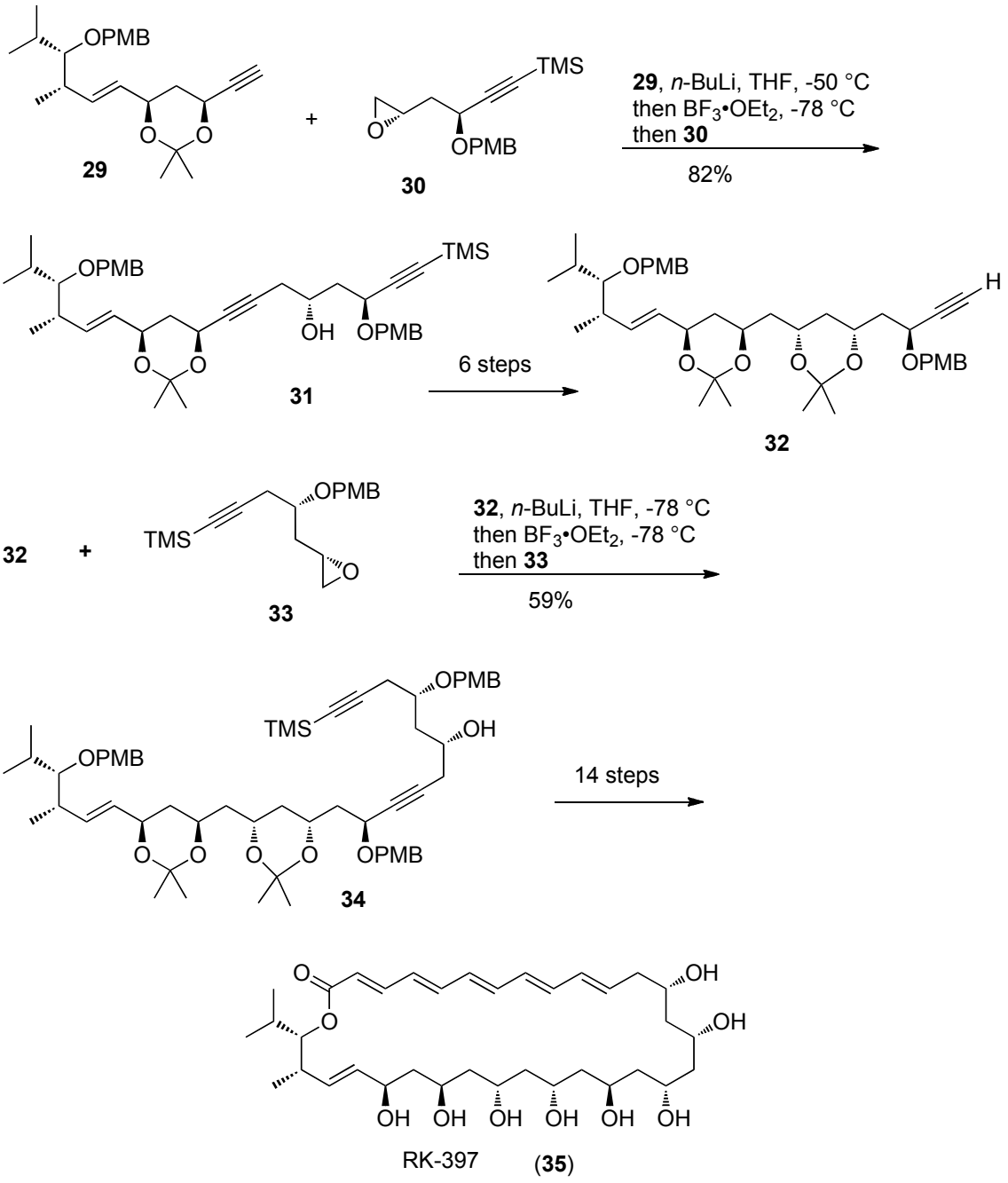
Conversely, trimethylaluminum was used in a variation on traditional methods to couple the epoxide **25** with the alkyne **26** at an early stage in the total synthesis of (±)-5-deoxystrigol (**28**) (Scheme 5).[19] These syntheses all made use of chiral non-racemic starting materials that retained their stereochemistry throughout the reaction or, if necessary, worked with racemic mixtures that were later subjected to kinetic resolution. The alkynylations of epoxides were used to good effect early in the synthesis, but failed to take advantage of the functionalization possible through that reaction as our group has done. The use of a convergent synthesis could be employed to decrease the amount of steps required while increasing the overall yield.

Scheme 5. Key synthetic steps of (±)-5-deoxystrigol.



Our group has shown that alternating polyol chains like those found in RK-397 (**35**) (Scheme 6) can be constructed using traditional alkyne and epoxide coupling methods while also demonstrating the ease with which multiple isomers can be created to give access to multiple synthetic targets.[20,21] Several other groups have completed the total synthesis of RK-397 after our group first reported it, primarily using traditional aldol methodology for stereoselective synthesis.[22,23] Each synthesis has used a different process but all have attempted to couple large synthons to keep the total number of steps to a minimum.[24-27]

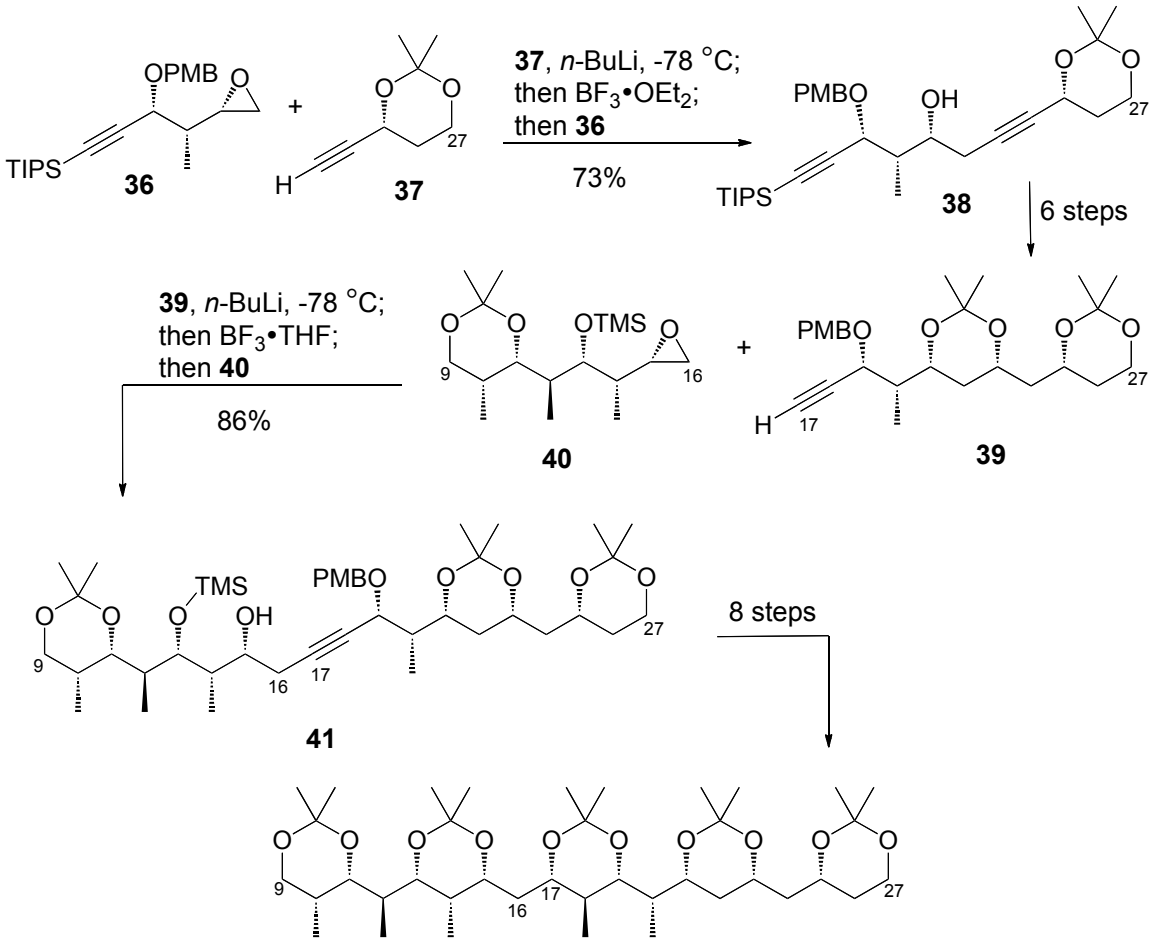
Scheme 6. Key methodology steps of first synthesis of RK-397.



The central substructure, C9-C27, of aflastatin A (**42**) (Scheme 7) was also synthesized in this manner by our group.[28] Aflastatin A[29] was observed to inhibit the biosynthesis of aflatoxin in *Aspergillus parasiticus* without inhibiting the

growth of the organism itself. The Evans group also synthesized the central substructure but by a different method.[30,31]

Scheme 7. Key steps of the central substructure of aflastatin A synthesis.



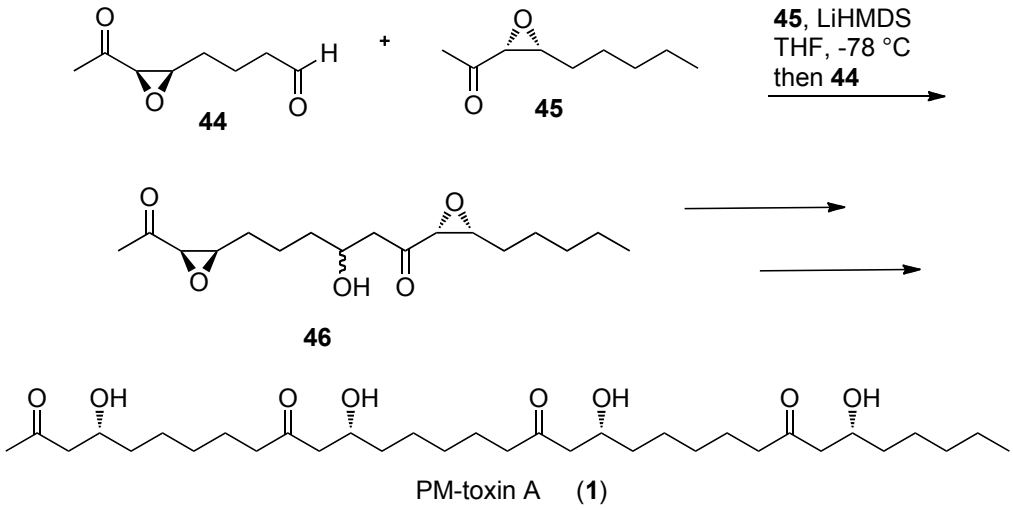
Toward the Total Synthesis of PM-toxin A

Introduction and Background

A model system was used to develop our methodology toward the synthesis of PM-toxin A (**1**), produced by corn pathogen *Phyllosticta maydis.*[32] The development of a more concise synthesis of this natural product (**1**) would allow researchers to test compounds for bioactivity.

Our model system demonstrates the versatility of our target reaction, epoxide alkynylation, and provides a platform for improved methodology to be developed in the future. Miyashita, utilizing three cross-aldol reactions for the coupling of substrates, has previously reported the synthesis of PM-toxin A (**1**) in 2000 (Scheme 8). [33] Epoxide **44** was used as an important synthon in multiple couplings.

Scheme 8. Key step of PM-toxin A synthesis by Miyashita group.



Miyashita's synthesis had 23 total steps due to the need to remove functional groups as well as separate oxidation and reduction steps between each coupling reaction. Our proposed total synthesis may be completed in half

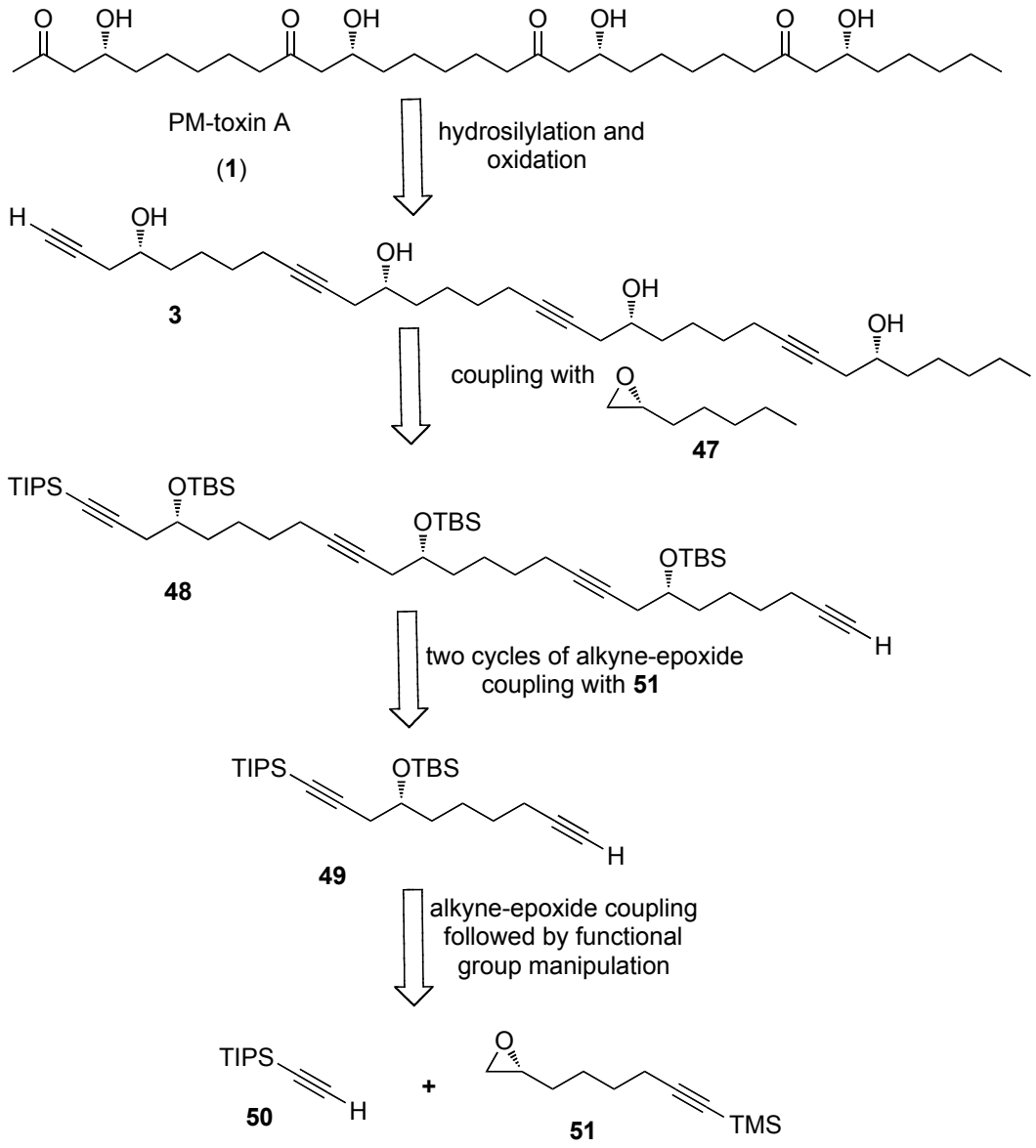
as many steps by accomplishing multiple directed hydrosilylations and oxidations in one pot. We will also take advantage of varying protective group strength and therefore can selectively deprotect only the desired functional group, thus reducing the need to deprotect and reprotect. Miyashita was also forced to selectively remove extraneous functional groups that will be unnecessary in our more concise synthesis.

To further establish the validity of epoxide alkynylations as a suitable synthetic tool, we have targeted PM-toxin A (**1**) to demonstrate the efficacy and efficiency of this system. Miyashita's synthesis involved 3 crossed-aldol reactions and culminated in the use of 16 equivalents of an organoselenium reagent to affect the last step for stereo- and regiospecific epoxide opening. Although (**1**) was obtained pure in a 46% yield, several steps were required for the individual functionalization of each component.[34]

By coupling already functionalized pieces, we propose the following retro-synthetic process (Scheme 9), which may provide (**1**) in half as many steps as those reported by Miyashita. Commercially available alkenes and alkynes can be quickly assembled to produce the desired natural product (**1**). Epoxidation of suitable alkenes using 3-chloroperoxybenzoic acid or peroxyacetic acid followed by hydrolytic kinetic resolution will produce bi-functional synthons that can be assembled in a straightforward manner using the traditional epoxide alkynylation methodology while retaining chirality.[35-37] These enantiopure homopropargylic alcohols will then direct the hydrosilylation of the adjacent acetylene, which will be subsequently oxidized to the *tetrakis*-β-hydroxy ketone, PM-toxin A (**1**).[38-41]

This allows the total number of steps required in the synthesis to be significantly diminished from that previously reported.

Scheme 9. Proposed retro-synthesis of PM-toxin A using traditional methodology.

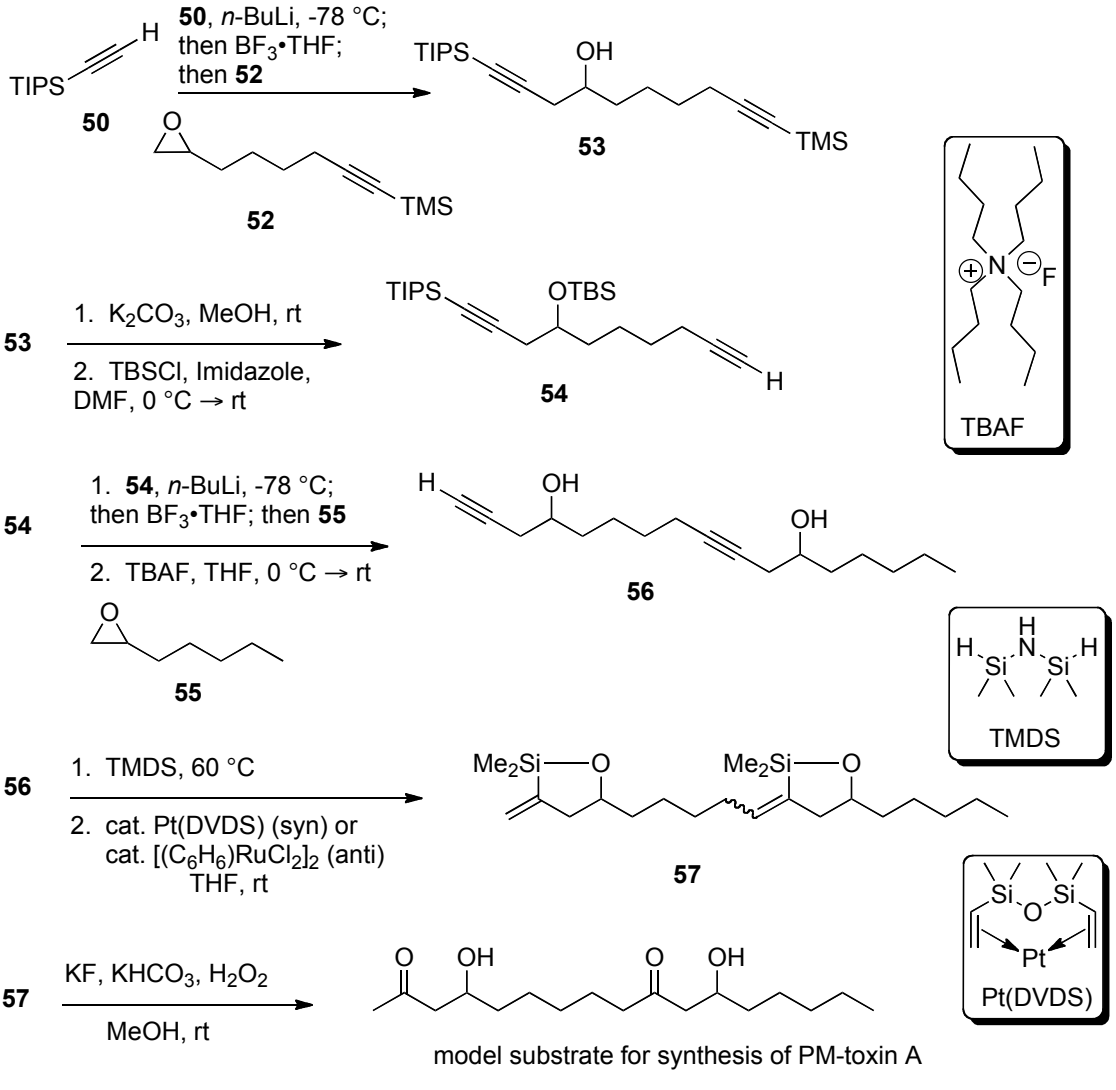


Results and Discussion

Model System

A short test of the methodology behind the proposed synthesis of PM-toxin A is detailed below (Scheme 10). The use of racemic epoxides and only two iterations of the key couplings have allowed for quick affirmation of the feasibility of all steps proposed in the synthetic plan.

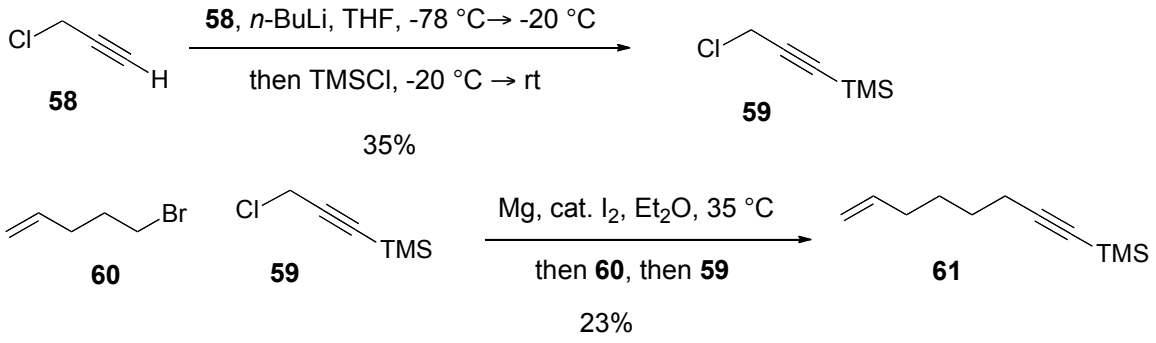
Scheme 10. Proposed model system to test conditions.



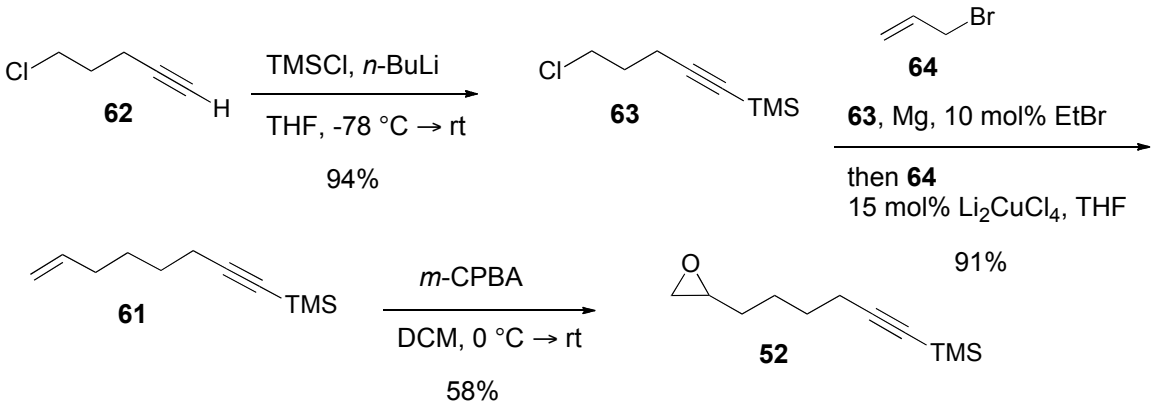
(**2**)

Key steps involved in the system were the synthesis of starting materials **52** and **55**, the alkyne-epoxide coupling, and the double hydrosilylation. The original attempt to synthesize compound **61** from **59** and **60** resulted in low yields[37,42] (Scheme 11) and led to the use of slightly different conditions to improve the synthesis. Therefore, epoxide **52** was synthesized in three steps from commercially available 5-chloro-1-pentyne **62** through alkyne protection[43] followed by a Grignard coupling[44] and completed with an epoxidation (Scheme 12).

Scheme 11. Original method used to synthesize **61**.

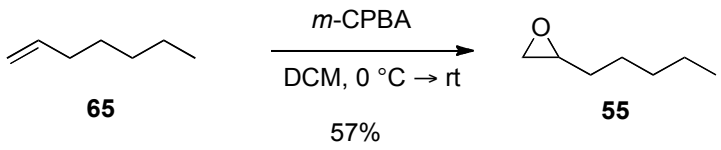


Scheme 12. Improved synthesis of epoxide synthon **52**.



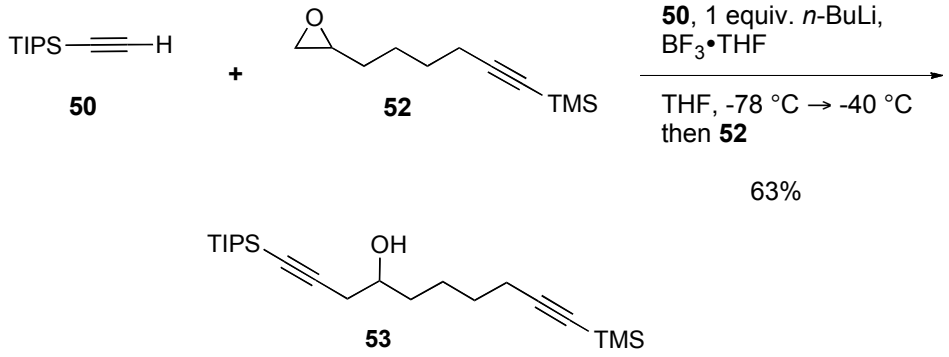
Compound **55** was synthesized from commercially available 1-heptene in one step (Scheme 13).

Scheme 13. Synthesis of 1,2-epoxyheptane.

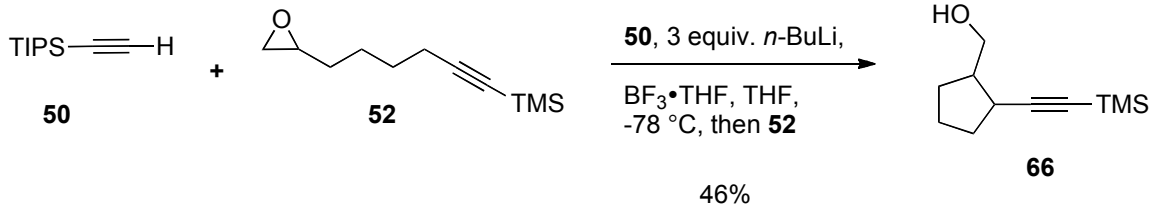


Two separate carbon-carbon bond-forming steps were accomplished *via* alkyne-epoxide coupling, the first of which joined **50** with **52** (Scheme 14). The careful use of 1 equivalent of *n*-BuLi was necessary to prevent cyclization of compound **52** (Scheme 15). Improved deprotonation was observed at -40 °C versus -78 °C.

Scheme 14. The first key carbon-carbon bond-forming step of model system.



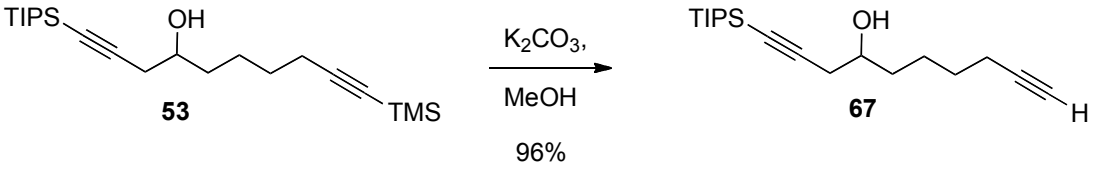
Scheme 15. Intramolecular cyclization of epoxide **52**.



The innate selectivity of different silyl protecting groups was taken advantage of to selectively deprotect the trimethylsilyl (TMS) alkynyl protecting group *via* basic methanolysis without removing the triisopropylsilyl (TIPS) alkynyl protecting group (Scheme 16). This later allows for the regioselective coupling

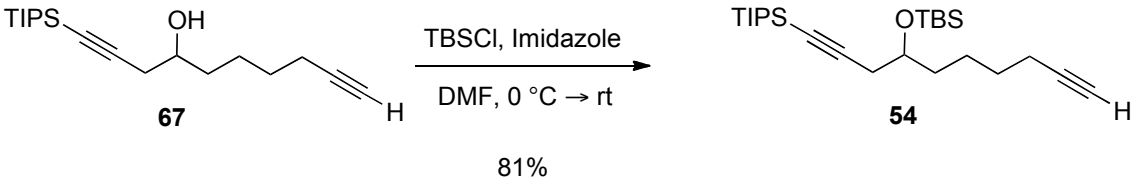
with 1,2-epoxyheptane at the desired alkynyl position rather than the protected alkynyl position.

Scheme 16. Selective deprotection of alkynyl TMS group.



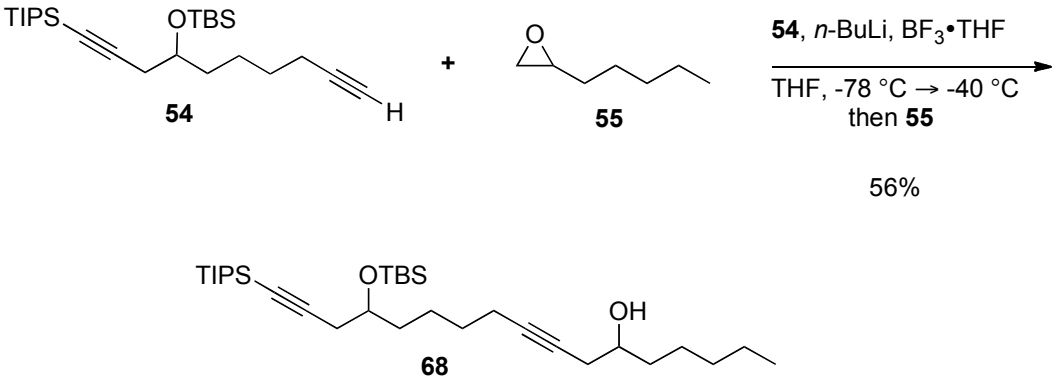
Mild conditions allow for the selective protection of the secondary alcohol with *tert*-butyldimethylsilyl chloride (TBSCl) without affecting the alkyne (Scheme 17).

Scheme 17. Selective protection of the secondary alcohol with TBSCl.



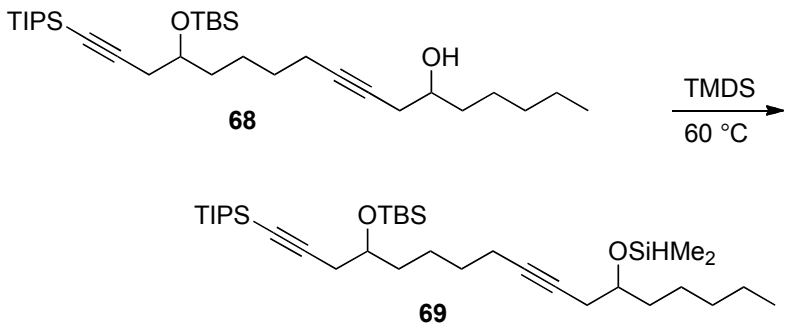
The second alkyne-epoxide coupling between **54** and **55** was accomplished in the same manner as the first carbon-carbon bond-forming step (Scheme 18).

Scheme 18. The second key carbon-carbon bond-forming step of model system.



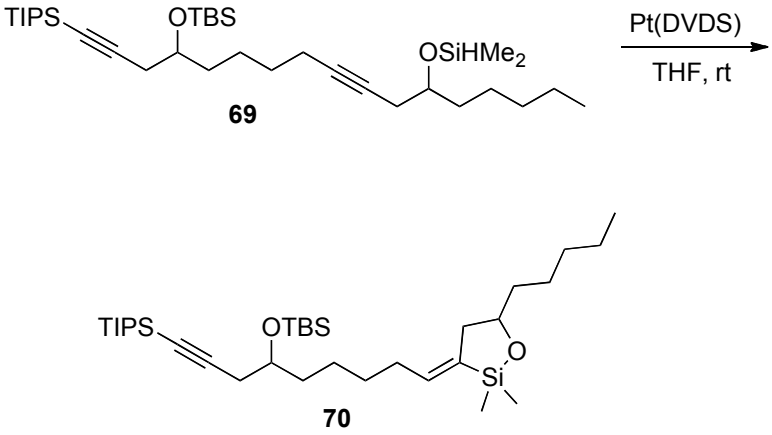
The hydroxyl directed hydrosilylation was first attempted at a single homopropargylic alcoholic position, after the coupling of **54** and **55** (Scheme 19) and before the global deprotection that results in the formation of **56**. This allowed us to test the steps at a single site before attempting the subsequent reaction at two sites. The use of 0.75 equivalents of neat bis(dimethylsilyl)amine (TMDS) produced dimethylsilyl ether **69**. Previous work with similar substrates has reported sensitivity to air, moisture, and silica gel.[21] Therefore, **69** was used without further purification. However, an aliquot was taken to obtain ^{1}H NMR spectra to monitor the reaction and to verify production of **69**, as only decomposition was observed *via* TLC.

Scheme 19. Formation of dimethylsilyl ether **69**.



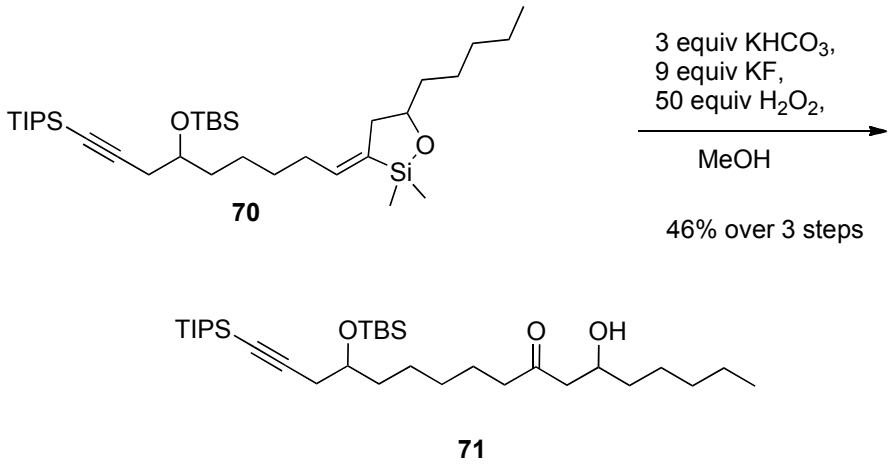
A solution of platinum salt 1,1,3,3-tetramethyl-1,3-divinyldisiloxane in xylenes [Pt(DVDS)] was used to form the cyclized siloxane **70** (Scheme 20). The *syn* delivery of a hydride from the silane to the adjacent alkyne resulted in the observed structure.[39,45,46] In a similar fashion to the previous reaction, **70** was used without further purification. However, an aliquot was taken to obtain ^{1}H NMR spectra to monitor the reaction and to verify production of **70,** as TLC data was not conclusive.

Scheme 20. Hydroxyl directed hydrosilylation-cyclization to form siloxane **70**.



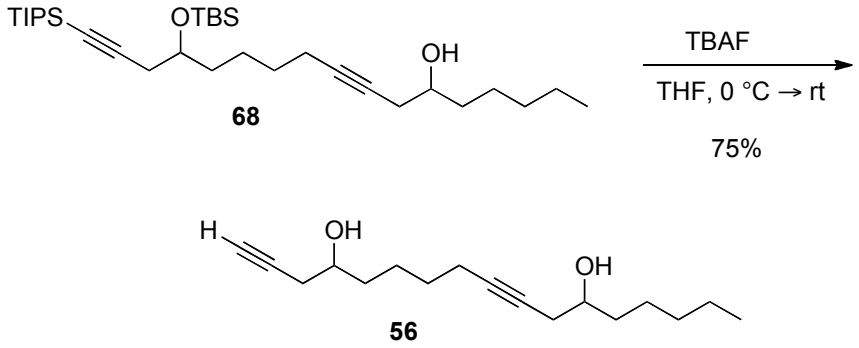
Extra equivalents of potassium fluoride were necessary to promote the oxidation of siloxane **70** to complete the third step in the directed hydrosilylation/oxidation to form β-hydroxy ketone **71** (Scheme 21).

Scheme 21. Oxidation to form β-hydroxy ketone **71**.



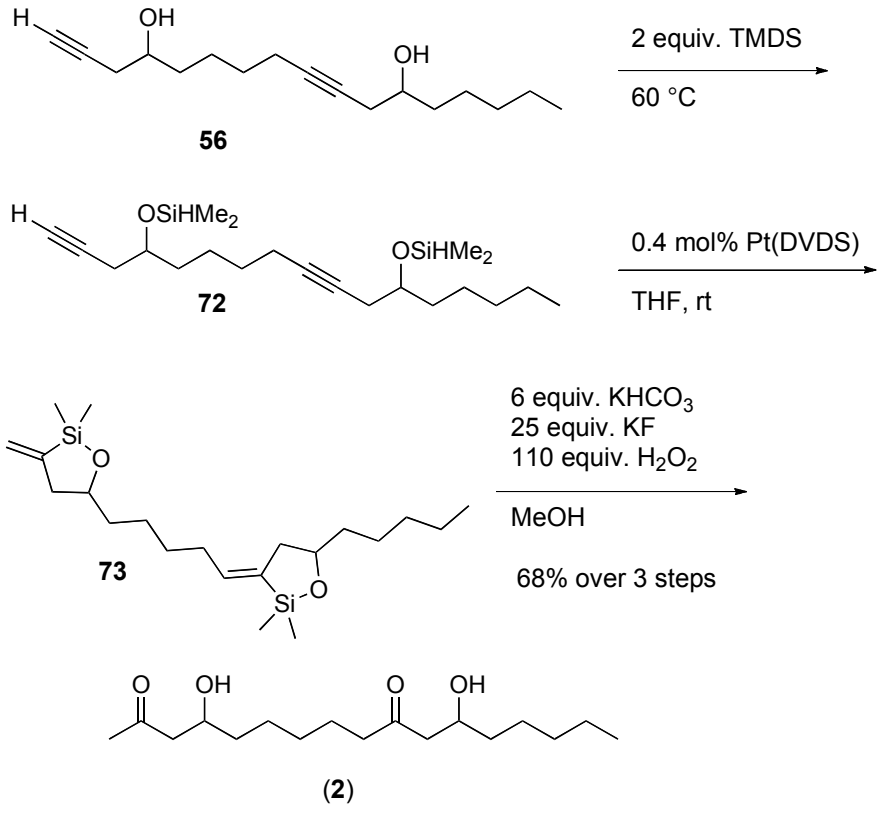
Universal deprotection using tetrabutylammonium fluoride (TBAF) afforded **56** (Scheme 22) to allow for the subsequent double hydroxyl directed hydrosilylation/oxidation to complete the synthesis of the model system.

Scheme 22. Universal deprotection of compound **68**.



After the single hydroxyl directed hydrosilylation/oxidation was accomplished, the double hydroxyl directed hydrosilylation/oxidation to produce (**2**) was achieved through an increase in equivalents of reagents (Scheme 23).

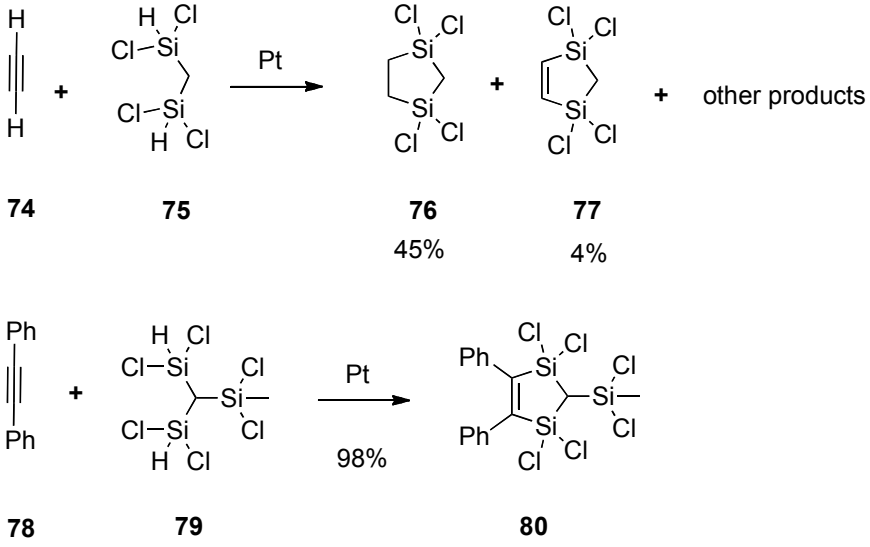
Scheme 23. Double directed hydrosilylation followed by oxidation to produce bis-β-hydroxy ketone (**2**).



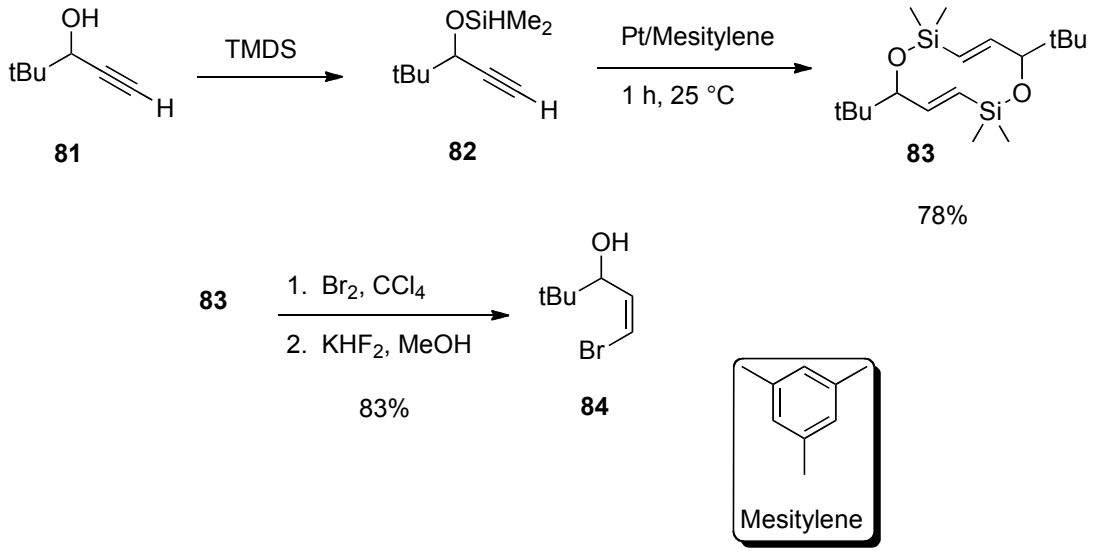
It was only necessary to repeat this series of reactions once. Aliquots were taken during the first set of reactions to confirm production of the desired product in each step *via* ^{1}H NMR spectra. However, upon repeating the steps no aliquots were removed allowing for a more accurate assessment of yield.

To the best of our knowledge this is the first multiple hydrosilylation at two separate alkynyl alcohol positions. However, there is a report of double hydrosilylations on the same alkyne bond using a different silylating agent[47] (Scheme 24) and an instance of intermolecular dimerization of two equivalents of terminal propargylic hydrosilyl ethers (Scheme 25).[48]

Scheme 24. Yoo's platinum catalyzed double hydrosilylation of acetylene and diphenylacetylene.



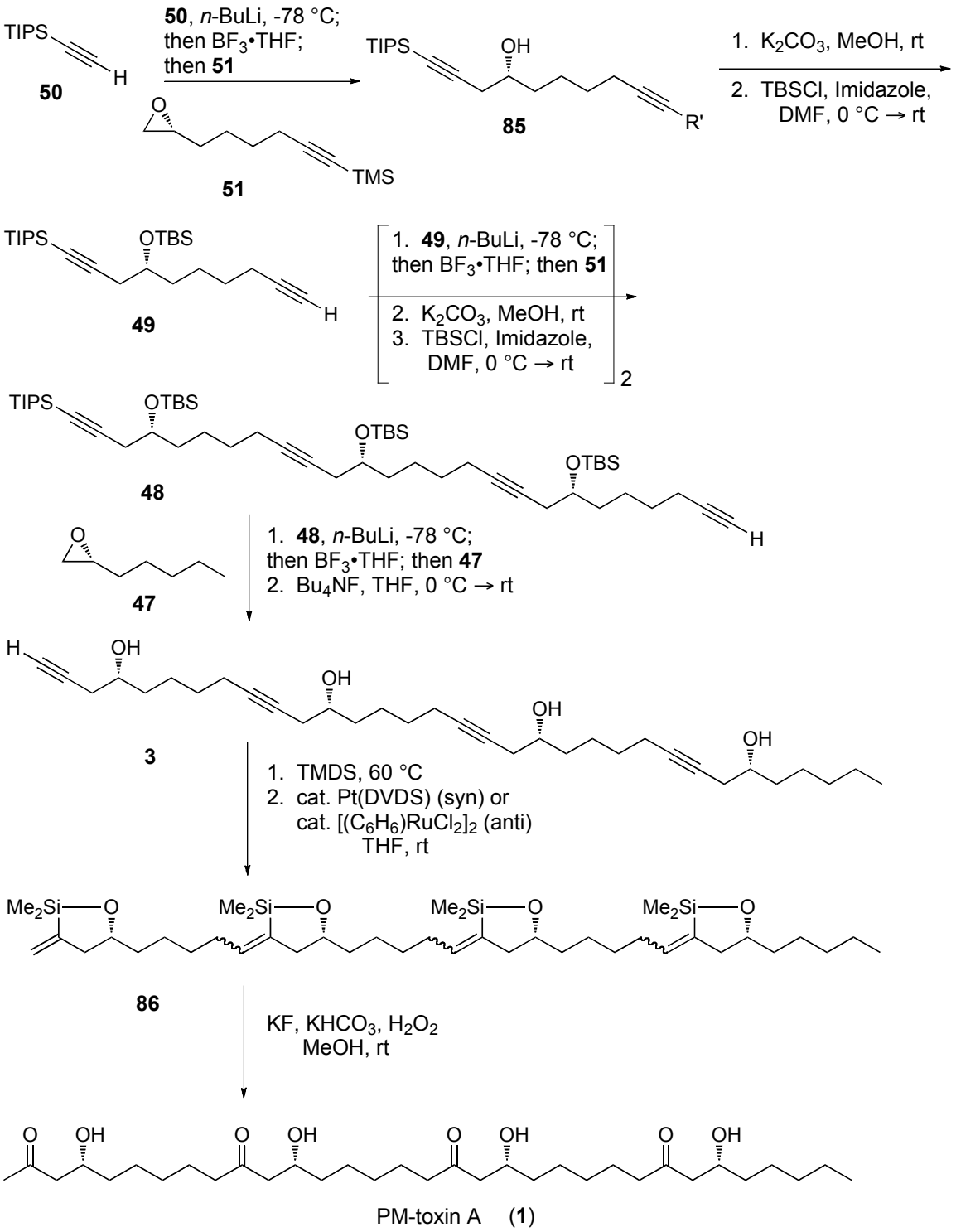
Scheme 25. Caporusso's intermolecular dimerization.



Progress Toward the Total Synthesis of PM-toxin A

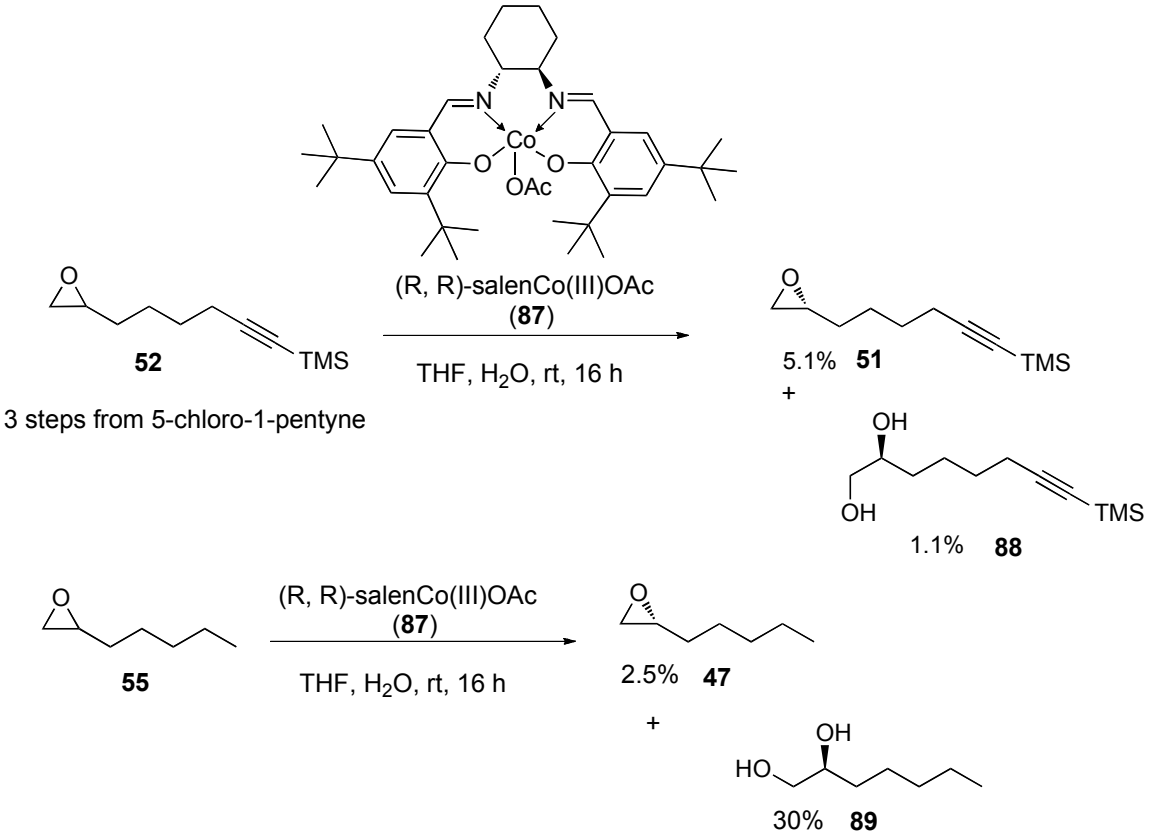
After completion of the model system, all steps of the synthesis have been accomplished with racemic substrates. The HKR of the epoxide synthons is the only step not included in the model system that must be accomplished in the total synthesis of (**1**). A proposed total synthesis of PM-toxin A (Scheme 26) follows closely with that of the model system.

Scheme 26. Proposed Total Synthesis of PM-toxin A.



In preparation of the total synthesis, the HKR of both epoxide synthons is currently in progress (Scheme 27).

Scheme 27. Current progress in total synthesis of PM-toxin A.



Conclusions and Future Directions

Completion of Total Synthesis of PM-toxin A

The completion of the model system (**2**) demonstrates the viability of the proposed synthesis. This confirmation allows us to move forward with the first enantioselective synthesis of PM-toxin A (**1**) without the need to develop different conditions for any of the proposed steps. The experience of performing each individual step has provided insights into the optimization necessary for completion of this particular project. After optimization of the HKR of both epoxide synthons, optimization of all carbon-carbon bond-forming steps will

follow. This will be accomplished in the course of the total synthesis of PM-toxin A as presented previously (Scheme 24).

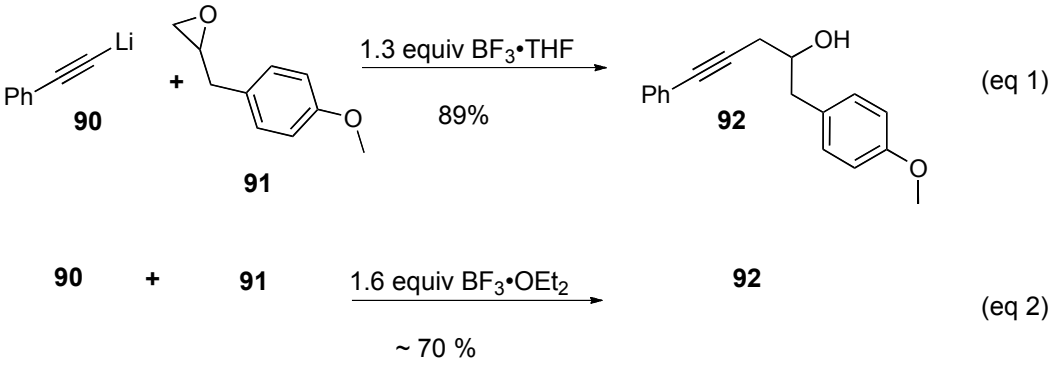
Development of Mild Lewis Acid Activated Epoxide Alkynylation

Exploring another method to construct carbon-carbon bonds that does not require the use of cryogenic conditions is applicable in the development of new methodologies for the total synthesis of larger compounds of interest and natural products. The coupling of alkynes and electrophiles (e.g., aldehydes and imines), without the use of alkyllithiums or Grignard reagents, using a mild alkynylphilic Lewis acid or a copper and amine combination is not novel, but the use of epoxides as the electrophile has yet to be exploited. The current literature suggests extensive screening of reagents, solvents, temperatures, and catalysts will be necessary to determine the exact nature of the coupling of alkynes and epoxides as reaction conditions vary wildly from one instance to the next.

The use of mild Lewis acids with tertiary amines to accomplish the alkylation of epoxides has the possible benefit of greater substrate tolerance. Alcohol functional groups may not need to be protected to prevent side reactions from occurring. This theory will be explored during experimentation.

Traditional methodology involves deprotonation of the alkyne before addition to the electrophile. However, this requires reagents that are stringently air and moisture sensitive strong bases such as *n*-BuLi and reactive Lewis acidic BF_3-etherate complexes.[49-51] A simple change from the use of BF_3•Et_2O to BF_3•THF resulted in a ca. 20% increase in yield of homopropargylic alcohols from ca. 70% to ca. 90% (Scheme 28).[51,52]

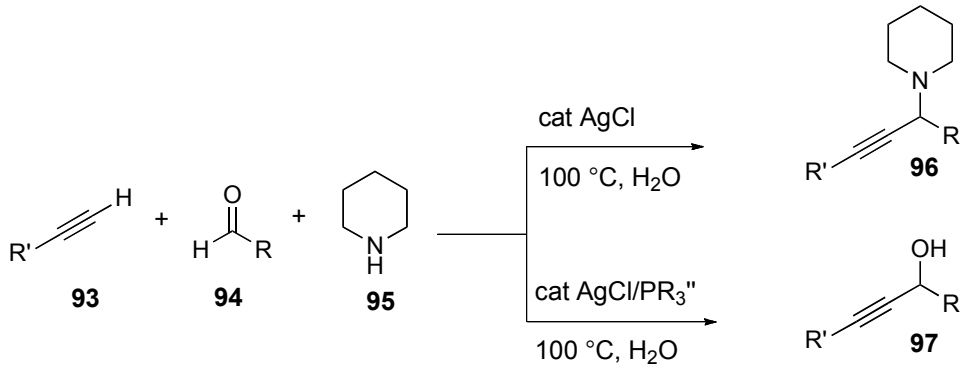
Scheme 28. Findings of Knight group in 2001.



This indicates that the selection of Lewis acid has a significant effect on the reaction's outcome. Knight thought that the more stable BF_3•THF complex did not allow for the epoxide to polymerize as he observed with the BF_3•Et_2O.[52] Furthermore, the use of zinc halides has been shown to cause a rearrangement of the epoxide to the aldehyde through a hydride shift producing propargylic alcohols when coupled with alkynes rather than the desired homopropargylic alcohol (Scheme 2). Therefore, identification of conditions for this reaction will result in dramatic improvement in reaction simplicity and yield.

In general, as the reactivity of the electrophile increases the selectivity decreases. For that reason a balance is needed for the successful development of high yielding reactions for stereo- and regioselective synthesis. Consequently, many parameters can be varied depending on the desired outcome, including solvent, catalyst, substituent, equivalencies, and temperature. The push for milder conditions and "green chemistry" investigations has caused several laboratories to explore aqueous solvent systems.[53-56] This has required a change in other conditions as well. These changes include new catalysts with ligands that are more effective in water, such as Cy_3PAgCl (Scheme 29).[4]

Scheme 29. Demonstration of catalyst and Lewis acid selectivity



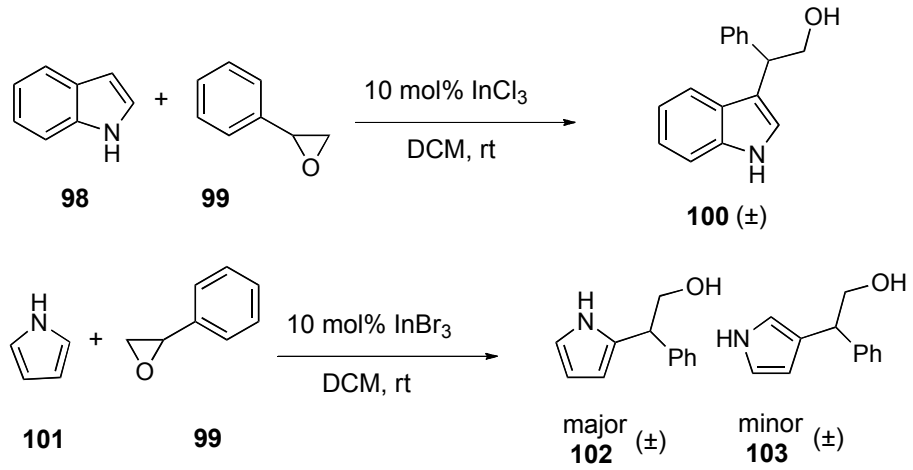
Addition of the phosphine ligand converted the coupling from producing propargylic amine **96**, to producing exclusively propargylic alcohol **97**. Other ideas include using tandem catalysis like ruthenium and indium to achieve dual activation of both alkyne and epoxide.[13] Other catalysts of interest have been copper, rhodium, gold, nickel, zirconium, and palladium amongst others.[1,13,15,18,19,53,57-61] A drawback of the use of these catalysts is a possible increase in time and higher temperature for these reactions, both of which increase as electrophilicity of the substrate and strength of the Lewis acid decrease.

The previously described milder conditions have been published for use with alkynes plus carbonyl and imines but not epoxides, or for use with epoxides plus nucleophiles other than alkynes.

The Yadav group has investigated the Lewis acid catalyzed alkylation of indoles with epoxides as well as the regioselective ring opening of epoxides with pyrrole.[62,63] Of particular interest is the use of indium Lewis acids, specifically $InBr_3$ and $InCl_3$ (Scheme 30). He found the use of pyrrole and indole as substrates negated the need for base to facilitate deprotonation, however a non-

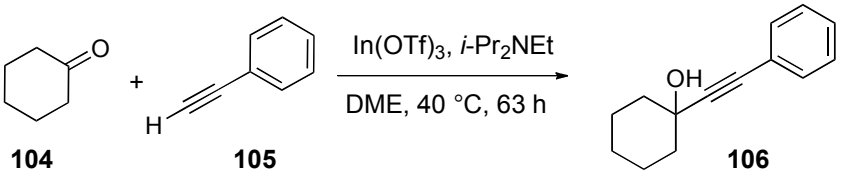
nucleophilic base will be required for the conditions envisioned by our group. A potential benefit to this procedure is the use of catalytic amounts of the Lewis acid rather than stoichiometric amounts.

Scheme 30. Yadav conditions for addition of indole or pyrrole to epoxide.



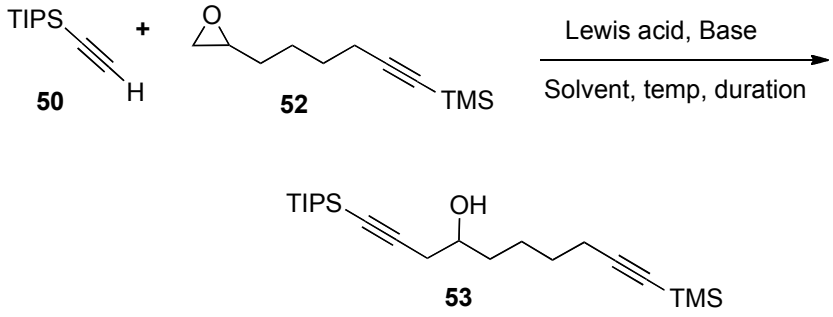
Based on the work of both Yadav (Scheme 30) and Shibasaki (Scheme 31), we envision indium triflate as a possible Lewis acid, with a tertiary base to mediate the alkynylation of an epoxide. Shibasaki's procedure requires stringent drying of the indium triflate prior to use[64,65], whereas Yadav's method does not require precautions against air and moisture.

Scheme 31. Shibasaki's Lewis Acid Catalyzed Alkynylation of Cyclohexanone.



Simple synthons can be designed for use in the testing of Lewis acid, solvent, base, temperature and duration in the coupling of epoxides and terminal alkynes. The substrates envisioned in this screening are those from the PM-toxin A synthesis (Scheme 32).

Scheme 32. Model system for testing reaction conditions



Control experiments using the traditional methodology have previously been performed to allow for a simple reference to be used for TLC and ^{1}H NMR determination of reaction results. This success will show a direct correlation to current synthesis projects and demonstrate the utility of this methodology.

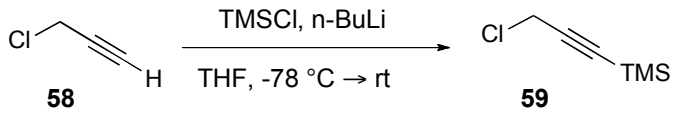
Examples of changes we can make include: the excessive drying of catalysts,[64] co- or pre-activation of the substrates with Lewis acid,[42,57,62,63] monitoring of reactions via React IR allowing for the assessment of alkyne deprotonation, and leading to better choices of tertiary base, changes in solvents allowing an increase in temperature of the reaction or improved solubility,[5,66,67] addition of electron withdrawing or donating groups on the substrates could to overcome possible reactivity challenges,[68] and increasing equivalents to push the reaction to completion.

Experimental Details

All reactions were carried out under an inert atmosphere of argon in oven-dried glassware. All solvents, other than those used during workup, were anhydrous unless otherwise stated. Anhydrous solvents were dried using 3Å molecular sieves (MS), 10-12 mesh purchased from Sigma-Aldrich. All reagents were purchased from Sigma-Aldrich and used as received unless otherwise stated. Solvents and other materials used in workup, extraction and column chromatography were used as received from commercial suppliers without prior purification. Analytical thin layer chromatography (TLC) was performed on precoated glass or aluminum backed EMD 0.25 mm silica gel 60 plates. This was used to track reaction progress unless otherwise stated. Visualization was accomplished with UV light, *p*-anisaldehyde, or iodine. Flash column chromatography was carried out using SiliCycle® Silia*Flash*® silica gel P60 (40-63μm, 60Å). ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively on a VNMR 400 or Varian Inova 400 spectrometer at room temperature in $CDCl_3$ with internal $CHCl_3$ as the reference (7.24 ppm for ^{1}H and 77.23 ppm for ^{13}C) unless otherwise stated. Chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (*J* values) in Hertz (Hz). Multiplicity was indicated using the following abbreviations: s = singlet, d = doublet, app d = apparent doublet, t = triplet, app t = apparent triplet, q = quartet, qn = quintet, sep = septet, m = multiplet, b = broad signal. IR spectra were collected on a Mattson Genesis II FT-IR spectrometer as neat films on sodium chloride discs. Mass spectra (high resolution ESI and APCI) were

recorded on a Finnigan LTQ FTMS Mass spectrometer (Mass Spectrometry Facility, Emory University).

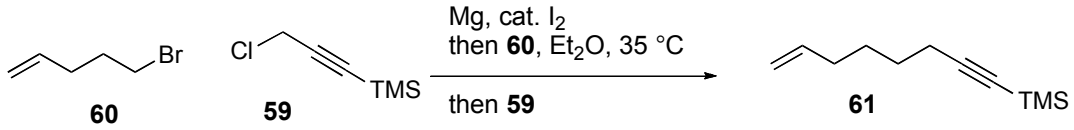
Method A:



(3-Chloroprop-1-yn-1-yl)trimethylsilane **59**.

To propargyl chloride **58** (2.39 mL, 33.4 mmol) in dry THF (7.00 mL) at -78 °C was added a 2.5 M solution of *n*-BuLi in hexane (13.5 mL, 33.8 mmol) dropwise over 30 min. The solution was stirred for 2.5 h before TMSCl (4.55 ml, 36.0 mmol) was added dropwise after which the solution was allowed to warm to rt and continued to be stirred for an additional 2 h. The reaction was quenched with H_2O before being extracted with Et_2O, washed with brine and then the combined organic extracts were dried over $MgSO_4$. Concentration *in vacuo,* followed by purification *via* distillation afforded **59** as a colorless oil (1.73 g, 35%), bp 45 °C (15 mmHg).[59] Spectra matched that of the known compound.[69,70]

^{1}H NMR (400 MHz; $CDCl_3$): δ 4.12 (s, 2 H), 0.17 (s, 9 H).



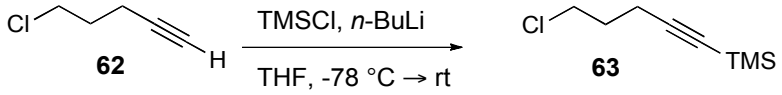
1-(trimethylsilyl)-oct-7-ene-1-yne **61**.[37] (Method A continued)

A mixture of magnesium turnings (0.143 g, 5.89 mmol) and one crystal of Iodine in dry Et_2O (2.75 mL) was heated at reflux until the yellow color lessoned (ca 45 min). To the mixture was added dropwise a solution of 5-bromo-1-pentene **60** (0.611 mL, 5.17 mmol) in dry Et_2O (1.35 mL), while maintaining a

steady rate of reflux. After stirring the mixture for 1 h, a solution of **59** (0.569 g, 3.88 mmol) in dry Et_2O (1.00 mL) was added dropwise, again maintaining a steady rate of reflux. The mixture was stirred 19 h, diluted with H_2O, and extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of ether by distillation **61** (0.130 g, 23%) was collected and used without further purification. Spectra matched that of the known compound.[37]

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.88 (m,1 H), 4.99 (m, 2 H), 2.03 (m, 2 H), 1.48 (m, 2 H), 1.35 (m, 4 H), 0.13 (s, 9H).

Method B:

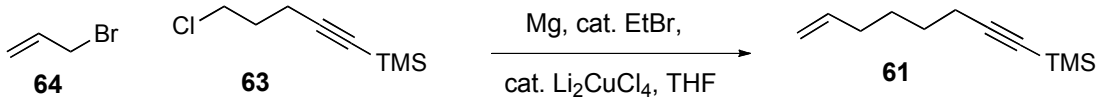


1-(trimethylsilyl)-5-chloro-1-pentyne **63**.

To a stirring solution of alkyne **62** (10.34 g, 98.81 mmol) in dry THF (77.0 mL) at -78 °C under an argon atmosphere was added a 2.42 M solution of *n*-BuLi in hexane (39.50 mL, 95.55 mmol) in a dropwise manner over 10 min and then allowed to warm slowly to -40 °C over 2 h. After cooling to -78 °C, TMSCl (13.87 g, 127.6 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature over 1 h. After completion, the solution was poured into saturated aqueous NH_4Cl and extracted with dichloromethane (DCM). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure followed by

distillation afforded **63** as a colorless oil (15.66 g, 94%), bp 65-75 °C (3 mmHg). Spectra matched that of the known compound.[43]

^{1}H NMR (400 MHz; $CDCl_3$): δ 3.62 (t, 2 H, *J* = 6.4 Hz), 2.39 (t, 2 H, *J* = 7.2 Hz), 1.94 (qn, 2 H, *J* = 6.4, 6.8 Hz), 0.12 (s, 9H)

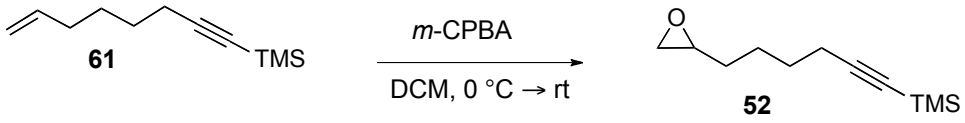


64 **63** **61**

1-(trimethylsilyl)-oct-7-ene-1-yne **61**. (Method B continued)

To a 100 mL two neck pear flask equipped with a reflux condenser, argon valve, and magnetic stirrer was added Mg (2.58 g, 106 mmol), anhydrous THF (36.0 mL), alkyne **63** (14.7 g, 84.0 mmol), and EtBr (0.62 mL, 8.2 mmol). The mixture was heated at 35 °C for 3 h to produce 5-trimethylsilyl-4-pentynylmagnesium chloride. The solution was transferred *via* cannula under argon pressure to a cooled, -78 °C, stirring mixture of anhydrous THF (60.0 mL), allyl bromide **64** (13.32 g, 106.8 mmol) and Li_2CuCl_4 (0.10 M in THF, 12.50 mL, 1.250 mmol, 1.5 mol%). The mixture was allowed to warm to rt. Once the reaction was determined to be complete the solution was cooled to 0 °C before quenching with saturated aqueous NH_4Cl and extracting with pentane. The combined extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford **61** as a yellow oil (13.85 g, 91%). Spectra matched that of the known compound.[44]

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.76 (m, 1 H), 5.01-4.96 (app dt, 1 H, *J* = 2.0, 17.2 Hz), 4.94-4.91 (app dd, 1 H, *J* = 2.0, 10.0 Hz), 2.20 (app t, 2 H, *J* = 6.8 Hz), 2.05 (app q, 2 H, *J* = 6.4, 7.6, 14.0 Hz), 1.52-1.43 (m, 4 H), 0.11 (s, 9 H).

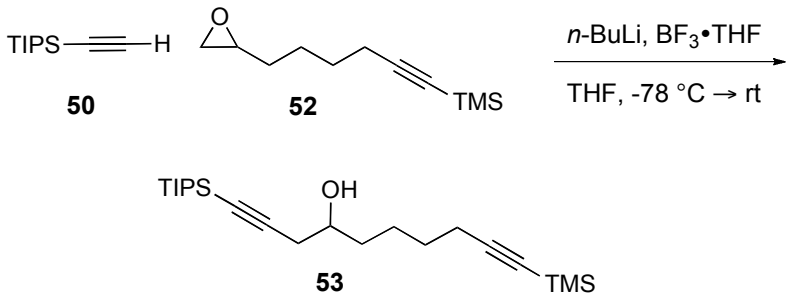


1-(trimethylsilyl)-oct-7,8-epoxy-1-yne **52**.

A solution of alkene **61** (6.26 g, 34.7 mmol) cooled to 0 °C in stirring dry DCM (20.0 mL) under argon atmosphere. A solution of *m*-CPBA (9.06 g, 36.7 mmol) in dry DCM (20.0 mL) was added and the solution was stirred for 4 h warming slowly to rt. Once complete, the reaction was quenched with saturated aqueous $NaHCO_3$, followed by extraction with ether, and washing with brine. The combined extracts were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure before flash column chromatography (pent/Et_2O, 95:5) afforded **52** as a yellow oil (1.71 g, 25%; **61** recovered, 1.49 g, 24%). On 15.31 g, 85 mmol scale reaction was allowed to proceed for 4 h with yield of 8.70 g, 52%, **61** recovered, 1.45 g, 5%.

^{1}H NMR (400 MHz; $CDCl_3$): δ 2.87 (q, 1 H, *J* = 0.8, 2.8 Hz), 2.71 (dd, 1 H, *J* = 0.8, 4.0 Hz), 2.43 (dd, 1 H, *J* = 2.4, 2.8 Hz), 2.21 (t, 2 H, *J* = 6.4 Hz), 1.52 (bm, 6 H), 0.10 (s, 9 H) ; **^{13}C NMR** (100 MHz; $CDCl_3$): δ 106.8, 84.3, 51.7, 46.5, 31.8, 28.1, 25.0, 19.5, 0.03; **HRMS (APCI):** *m/z* calcd. for $C_{11}H_{21}OSi$ ($M+H^+$) 197.1356, found 197.1354; **FT-IR**: 2939, 2175, 1249, 844 cm^{-1};

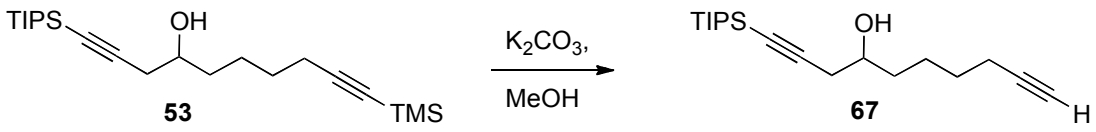
HMQC (400 MHz; $CDCl_3$):		
	Carbon ppm δ	**Proton ppm δ**
1	51.7	2.87 (q, *J* = 0.8, 2.8 Hz)
2	46.5	2.71 (dd, *J* = 0.8, 4.0 Hz)
3	46.5	2.43 (dd, *J* = 2.6 Hz)
4	19.5	2.21 (t, *J* = 6.4 Hz)
5	31.8, 28.1, 25.0	1.52 (bm)
6	0.03	0.104 (s)



50 **52** **53**

1-(Triisopropylsilyl)-10-(trimethylsilyl)deca-1,9-diyn-4-ol **53**.

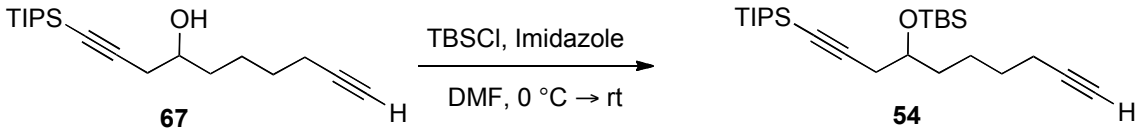
To a stirring solution of alkyne **50** (5.21 mg, 2.86 mmol) in dry THF (2.10 mL) under argon atmosphere at -78 °C was added a 2.5 M solution of *n*-BuLi in hexane (1.10 mL, 2.75 mmol). The reaction was allowed to warm to 0 °C over 2 h where it was maintained for 2 h before cooling to -78 °C. BF_3•THF (4.94 g, 3.53 mmol) was added and stirring continued for 30 min before epoxide **52** (455 mg, 2.49 mmol), dissolved in dry THF (9.00 mL), was added and stirred for 4 h while slowly warming to rt. When reaction was determined complete by TLC it was quenched with brine and extracted with ether. Combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure before flash column chromatography (Hex/EtOAc, 98:2) to afford **53** as a colorless oil (519 mg, 50%). On 5.2 g, 27 mmol scale reaction was allowed to proceed for 3 h at -40 °C before the addition of BF_3•THF with yield of 5.7 g, 63%. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 3.72 (app sxt, 1 H, *J* = 5.6 Hz), 2.47 (dd, 1 H, *J* = 4.8, 16.8 Hz), 2.35 (dd, 1 H, *J* = 6.4, 16.8 Hz), 2.20 (t, 2 H, *J* = 6.4 Hz), 1.96 (d, OH, *J* = 5.6 Hz), 1.51 (bm, 5 H), 1.42, (m, 1 H), 1.03 (m, 21 H), 0.11 (s, 9 H); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 107.5, 104.8, 84.7, 83.8, 70.0, 35.8, 29.0, 28.7, 25.0, 19.9, 18.8, 11.3, 0.3; **HRMS (APCI)** *m/z* calcd. for $C_{22}H_{43}OSi_2$ ($M+H^+$) 379.2847, found 397.2844; **FT-IR**: 3388, 2941, 2865, 2173, 1463, 1249 cm^{-1}.



1-(Triisopropylsilyl)deca-1,9-diyn-4-ol **67**.[71]

To a solution of alkyne **53** (274 mg, 0.722 mmol) in MeOH (3.43 mL) was added K_2CO_3 (127 mg, 0.909 mmol) at rt. After stirring at rt overnight, the mixture was concentrated under reduced pressure. The residue was diluted with H_2O and extracted with ether. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* affording **67** as a yellow oil (213 mg, 96%) that was collected and used without further purification.

^{1}H NMR (400 MHz; $CDCl_3$): δ 3.72 (t, 1 H, *J* = 5.6 Hz), 2.47 (dd, 1 H, *J* = 4.8, 17.2 Hz), 2.38 (dd, 1 H, *J* = 5.2, 22.0 Hz), 2.17 (m, 2 H), 1.98 (b, OH), 1.91 (t, 1 H, *J* = 2.8 Hz), 1.49 (m, 5 H), 1.43 (m, 1 H), 1.03 (m, 21 H); **^{13}C NMR** (100 MHz; $CDCl_3$,): δ 104.7, 84.5, 83.8, 70.0, 68.5, 35.7, 29.1, 28.5, 24.9, 18.8, 18.5, 11.3; **HRMS (APCI)** *m/z* calcd. for $C_{19}H_{35}OSi$ ($M+H^+$) 307.2452, found 307.2452; **FT-IR**: 3403, 3312, 2941, 2865, 2172, 1462, 1086, 1009, 883 cm^{-1}.

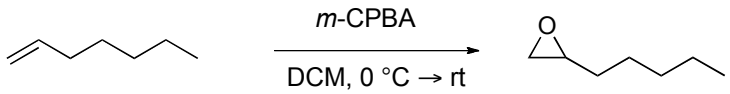


1-(Triisopropylsilyl)deca-1,9-diyn-4-*tert*-butyldimethylsilylether **54**.

To a stirring solution of alcohol **67**, combined yields, (2.68 g, 8.73 mmol) in dry DMF (13.0 mL) at 0 °C under argon atmosphere was added TBSCl (1.42 g, 9.15 mmol) and imidazole (1.68 g, 24.5 mmol). The reaction was allowed to warm to rt overnight. After the reaction was determined to be complete by TLC it was quenched with deionized (DI) H_2O, extracted with ether, and washed with

DI H_2O (5 x). Combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure before purification by flash column chromatography (hex/EtOAc, 98:2) afforded **54** as a yellow viscous oil (2.99 g, 81%).

^{1}H NMR (400 MHz; $CDCl_3$): δ 3.76 (m, 1 H), 2.39 (app dd, A-B pattern, 1 H, *J* = 5.2, 16.0 Hz), 2.36 (app dd, A-B pattern, 1 H, *J* = 6.8, 16.8 Hz), 2.17 (m, 2 H), 1.91 (t, 1 H, *J* = 2.4), 1.66 (m, 1 H), 1.51 (m, 4 H), 1.39 (m, 1 H), 1.03 (m, 21 H), 0.85 (s, 9 H), 0.04 (d, 6 H, *J* = 4.0 Hz); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 105.7, 84.6, 82.3, 71.1, 68.4, 35.9, 29.0, 28.8, 26.0, 24.4, 18.8, 18.5, 18.2, 11.4, -4.2, -4.5; **HRMS (APCI)** *m/z* calcd. for $C_{25}H_{49}OSi_2$ ($M+H^+$) 421.3322, found 421.3315; **FT-IR**: 3313, 2939, 2865, 2175, 1465, 1361, 1253, 1099 cm^{-1}.



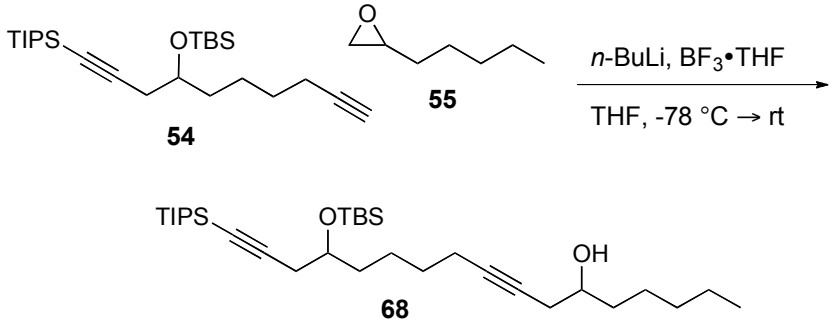
65 **55**

1,2-epoxyheptane **55**.

To a stirring solution of 1-heptene **65** (5.21 g, 51.4 mmol) in dry DCM (120.0 mL) under argon atmosphere at 0 °C was added *m*-CPBA (13.29 g, 59.29 mmol) in one portion and the solution stirred for 3 h warming to rt. Once complete, the reaction was quenched with saturated aqueous $NaHCO_3$, followed by extraction with ether, and washing with brine. The combined extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure before flash column chromatography (hex/EtOAc, 98:2) afforded **55** as a yellow oil (3.34 g, 57%). Spectra matched that of the known compound.[72]

^{1}H NMR (400 MHz; $CDCl_3$): δ 2.88 (app qn, 1 H, *J* = 2.8, 4.0 Hz), 2.72 (t, 1 H,

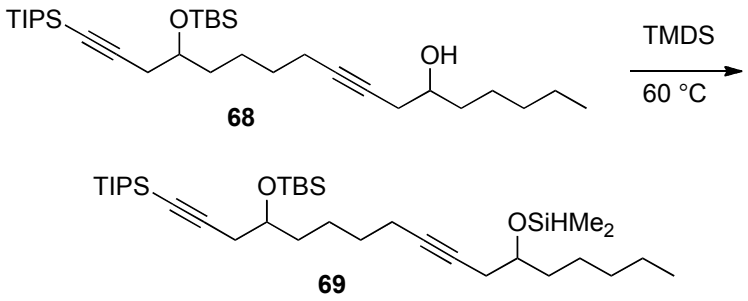
J = 4.0 Hz), 2.44 (dd, 1H, *J* = 2.8, 5.2 Hz), 1.50-1.39 (m, 4 H), 1.31-1.28 (m, 4 H), 0.86 (t, 3H, *J* = 7.2 Hz).



4-((*Tert*-butyldimethylsilyl)ether)-1-(triisopropylsilyl)heptadeca-1,9-diyn-11-ol **68**. To a stirring solution of alkyne **54** (2.50 g, 5.94 mmol) in dry THF (7.50 mL) at -78 °C under argon atmosphere was added a 2.50 M solution of in *n*-BuLi hexanes (2.73 mL, 6.83 mmol) at a dropwise rate. The reaction was allowed to warm to -40 °C where it was maintained for 2 h, then cooled to -78 °C to add BF_3•THF (731 μL, 6.63 mmol). After 30 min epoxide **55** (748 mg, 6.48 mmol) was added and the mixture was allowed to warm to rt over 3 h. The reaction was quenched with brine and extracted with ether. The combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure before flash column chromatography (hex/EtOAc, 95:5) afforded **68** as a yellow oil (1.59 g, 50%). On 922 mg, 2.19 mmol scale reaction was allowed to proceed for 5 h before the addition of BF_3•THF with yield of 338 mg, 29%, **54** recovered, 451 mg, 49%.

^{1}H NMR (400 MHz; $CDCl_3$): δ 3.75 (m, 1 H), 3.65 (m, 1 H), 2.38 (m, 3 H), 2.24 (m, 1 H), 2.15 (m, 2 H), 1.89 (dd, OH, *J* = 0.8, 5.2 Hz), 1.63 (m, 1 H), 1.47 (m, 5 H), 1.41 (m, 2 H), 1.28 (m, 6 H), 1.03 (m, 21 H), 0.85 (s, 12 H),

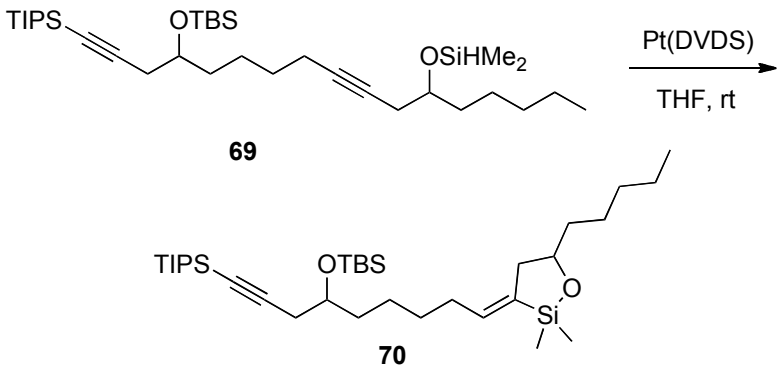
0.03 (d, 6 H, *J* = 4.4 Hz); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 105.6, 82.9, 82.1, 76.3, 71.0, 70.3, 36.3, 35.9, 31.9, 29.2, 28.9, 27.9, 25.9, 25.5, 24.5, 22.7, 18.8, 18.7, 18.1, 14.1, 11.4, -4.3, -4.5; **HRMS (APCI)** *m/z* calcd. for $C_{32}H_{63}O_2Si_2$ ($M+H^+$) 535.4361, found 535.4372; **FT-IR**: 3386, 2927, 2861, 2171, 1465, 1361, 1253, 1095 cm^{-1}.



4-((*Tert*-butyldimethylsilyl)ether)-1-(triisopropylsilyl)heptadeca-1,9-diyn-11-(dimethylhydrosilyl)ether **69**.[39]

Under argon atmosphere was stirred alcohol **68** (269 mg, 0.504 mmol) and TMDS (70 μL, 0.39 mmol) at rt. The reaction mixture was warmed to 60 °C for 24 h, and then cooled to rt. Concentration *in vacuo* afforded **69** which was used in the next step without further purification. An aliquot was taken for confirmation of reaction *via* ^{1}H NMR spectroscopy.

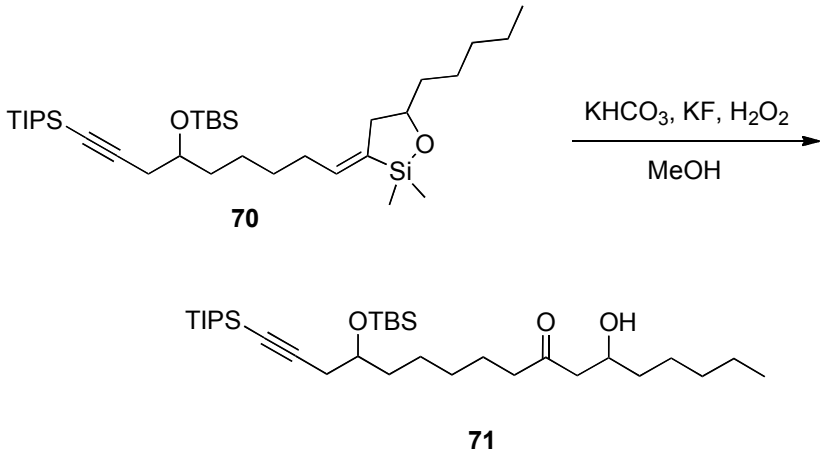
^{1}H NMR (400 MHz; $CDCl_3$): δ 4.65 (qn, 1 H, *J* = 2.4, 3.2, 5.6 Hz), 3.75 (m, 1 H), 3.70 (m, 1 H), 2.36 (m, 2 H), 2.25 (m, 2 H), 2.12 (app t, 2 H, *J* = 6.4 Hz), 1.72 – 1.34 (m, 14 H), 1.03 (m, 21 H), 0.85 (m, 12 H), 0.20 (dd, 6 H, *J* = 1.6, 4.4 Hz), 0.04 (d, 6 H, *J* = 4.4 Hz); **HRMS (APCI)** *m/z* calcd. for $C_{34}H_{69}O_2Si_3$ ($M+H^+$) 593.4605, found 593.4599.



(E)-3-(6-((*tert*-butyldimethylsilyl)ether)-9-(triisopropylsilyl)non-8-yn-1-ylidene)-2,2-dimethyl-5-pentyl-1,2-siloxane **70**.[73]

To a stirred solution of crude dimethylhydrosilyl ether **69** from **68** in dry THF (5.0 mL) was added a 2% wt/vol solution of Pt(DVDS) in xylenes (20 μL, 1.1 μmol) at rt. The reaction was stirred for 24 h. Concentration under reduced pressure afforded siloxane **70** which used in the next step without purification. An aliquot was taken for confirmation of reaction *via* ^{1}H NMR spectroscopy.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.75 (m, 1 H), 3.96 (qn, 1 H, *J* = 5.6, 6.8 Hz), 3.75 (m, 1 H), 2.36 (m, 3 H), 2.07 (b, 3 H), 1.66 (m, 1 H), 1.55 (m, 3 H), 1.39 (m, 6 H), 1.28 (m, 4 H), 1.03 (m, 21 H), 086 (s, 12 H), 0.18 (d, 6 H, *J* = 9.2 Hz), 0.04 (d, 6 H, *J* = 5.6 Hz); **HRMS (APCI)** *m/z* calcd. for $C_{34}H_{69}O_2Si_3$ ($M+H^+$) 593.4600, found 593.4603; **FT-IR**: 2927, 2861, 2175, 1465, 1253, 1076 cm^{-1}.

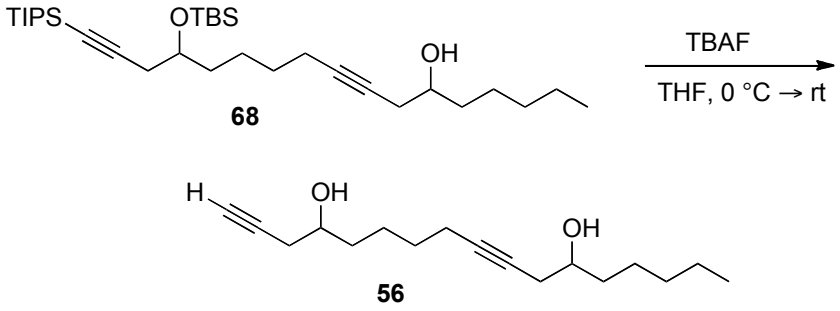


14-((*Tert*-butyldimethylsilyl)ether)-6-hydroxy-17-(triisopropylsilyl)heptadec-16-yn-8-one **71**.[21]

To a stirred solution of crude siloxane **70** from **68** in MeOH (3.30 mL) under argon atmosphere was added $KHCO_3$ (203 mg, 20.3 mmol) and KF (266 mg, 4.57 mmol) was followed by the slow addition of 30% H_2O_2 in H_2O (2.80 mL, 27.4 mmol). The reaction was stirred at rt for 24 h, and was then quenched by pouring into a cooled saturated aqueous Na_2SO_3 and stirring for 3 h. This solution was extracted with ether and the combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure before purification by flash column chromatography (hex/EtOAc, 98:2) afforded **71** as a viscous yellow oil (128 mg, 46% over 3 steps from **68**, recovery of starting material **70**, 77 mg, 29%).

^{1}H NMR (400 MHz; $CDCl_3$): δ 3.98 (m, 1 H), 3.73 (m, 1 H), 3.04 (d, OH, *J* = 3.6 Hz), 2.60-2.42 (m, 2 H), 2.37 (m, 4 H), 1.57 (m, 2 H), 1.37 (m, 4 H), 1.27 (b, 10 H) 1.03 (m, 21 H), 0.85 (s, 12 H), 0.04 (d, 6 H, *J* = 6.8 Hz); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 212.6,105.8, 82.2, 71.1, 67.8, 49.1, 43.7, 36.5, 36.2, 31.9, 29.4, 28.9, 25.9, 25.3, 24.9, 23.7, 22.7, 18.8, 18.2, 14.2, 11.4, -4.3, -4.5;

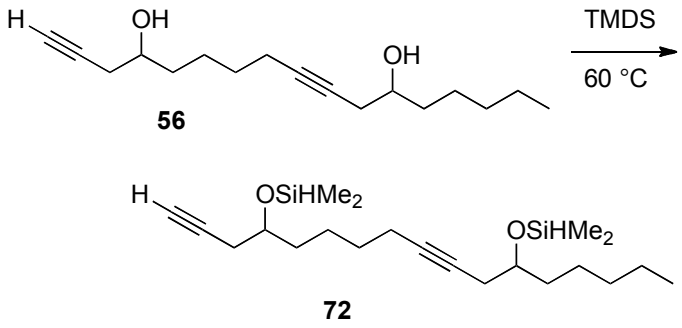
HRMS (ESI) *m/z* calcd. for $C_{32}H_{64}O_3NaSi_2$ ($M+Na^+$) 575.4286, found 575.4284; **FT-IR**: 3444, 2931, 2861, 2171, 1708, 1465 cm^{-1}.



Heptadeca-1,9-diyne-4,12-diol **56**.[74]

To a stirring solution of protected diyne diol **68** (526 mg, 0.983 mmol) in dry THF (9.50 mL) under argon atmosphere was added a 1.0 M solution of TBAF in THF (1.22 mL, 1.22 mmol) at 0 °C. The reaction was allowed to warm to rt over 24 h, and was then quenched with saturated aqueous $NaHCO_3$, poured into DI H_2O, and extracted with ether. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure before purification *via* flash column chromatography (hex/EtOAc, 20:5) afforded **56** as a white wax (196 mg, 75%).

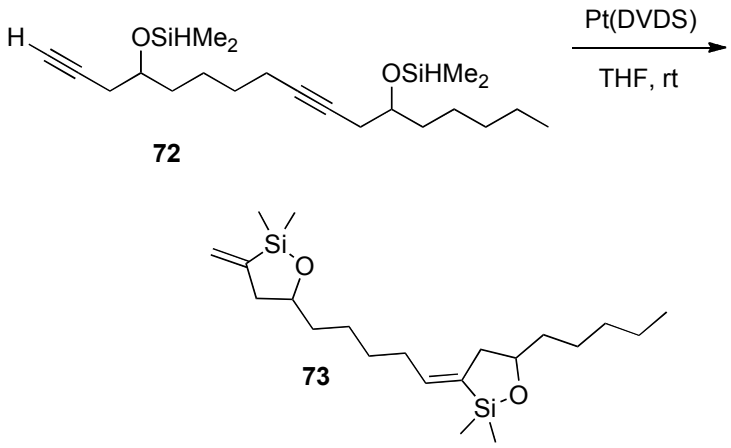
^{1}H NMR (400 MHz; $CDCl_3$): δ 3.73 (qn, 1 H, *J* = 5.6, 6.4), 3.65 (qn, 1 H, *J* = 5.6, 6.8 Hz), 2.42-2.20 (m, 4 H), 2.16 (b, 2 H), 2.03 (t, 1 H, *J* = 2.4, 2.8 Hz), 1.95 (d, OH, *J* = 4.4 Hz), 1.92 (d, OH, *J* = 4.8 Hz), 1.53-1.36 (m, 8 H), 1.30-1.25 (m, 6 H), 0.855 (t, 3 H, *J* = 6.4 Hz); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 89.7, 87.8, 84.3, 84.0, 83.7, 83.5, 43.2, 42.5, 38.7, 36.7, 35.6, 34.7, 34.4, 32.3, 31.7, 29.6, 25.6, 21.0; **HRMS (APCI)** *m/z* calcd. for $C_{17}H_{29}O_2$ ($M+H^+$) 265.2162, found 265.2161; **FT-IR**: 3297, 2927, 2858, 2117, 1450 cm^{-1}.



2,14-Dimethyl-4-pentyl-12-(prop-2-yn-1-yl)-3,13-dioxa-2,14-disilapentadec-6-yne **72**.[39]

Under argon atmosphere was stirred diyne **56** (109 mg, 0.393 mmol) and TMDS (150 μL, 0.84 mmol) at rt. Reaction was warmed to 60 °C for 24 h, and then cooled to rt. Concentration *in vacuo* afforded **72** which was used in the next step without further purification. An aliquot was taken during a previous repetition of this experiment for confirmation of reaction *via* ^{1}H NMR spectroscopy.

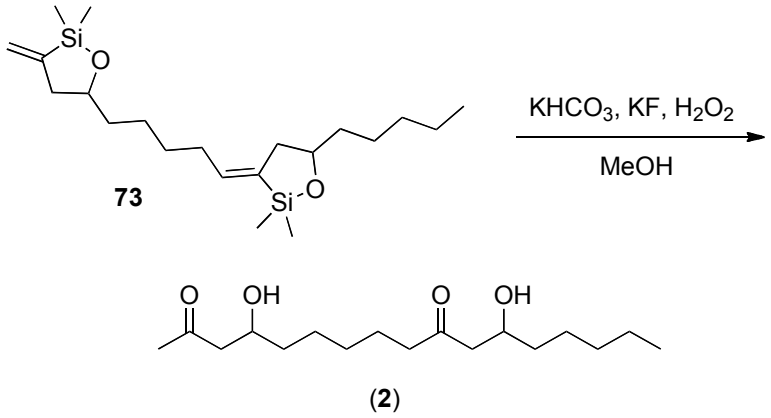
^{1}H NMR (400 MHz; $CDCl_3$): δ 4.65 (m, 1 H), 3.76 (m, 1 H), 3.71 (m, 1 H), 2.38-2.21 (m, 4 H), 2.14 (b, 2 H), 1.97 (t, 1 H, *J* = 2.8 Hz), 1.65-1.54 (m, 2 H), 1.50-1.44 (m, 4 H), 1.42-1.34 (m, 2 H), 1.32-1.23 (m, 6 H), 0.87 (t, 3 H, *J* = 7.2 Hz), 0.21 (m, 12 H); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 81.8, 81.6, 77.4, 73.5, 72.6, 70.2, 36.7, 36.2, 31.9, 29.1, 27.9, 27.5, 25.4, 25.0, 22.8, 19.0, 14.3, -0.59, -0.63, -0.69, -0.72.



(E)-3-(5-(2,2-dimethyl-3-methylene-1,2-oxasilolan-5-yl)pentylidene)-2,2-dimethyl-5-pentyl-1,2-oxasilolane **73**.[73]

To the stirring crude mixture of **72** from **56** in THF (2.00 mL) was added a 2% wt/vol solution of Pt(DVDS) in xylenes (30.0 μL, 1.57 μmol) at rt. The mixture was stirred overnight, and then concentrated under reduced pressure. Siloxane **73** was used in the next step without further purification. An aliquot was taken during a previous repetition of this experiment for confirmation of reaction *via* ^{1}H NMR spectroscopy.

^{1}H NMR (400 MHz; $CDCl_3$): δ 5.75 (m, 2 H), 5.71 (app d, 1 H, *J* = 1.6 Hz), 5.37 (app d, 1 H, *J* = 2.0 Hz), 3.96 (m, 2 H), 2.29-2.19 (m, 2 H), 2.08-2.02 (m, 4 H), 1.56 (b, 4 H), 1.41 (b, 6 H), 1.28 (b, 4 H), 0.87 (t, 3 H, *J* = 6.4 Hz).

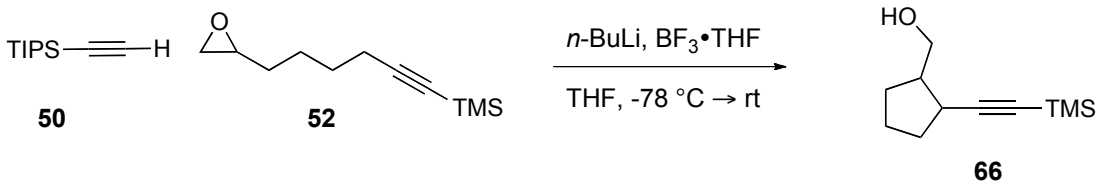


(**2**)

4,12-Dihydroxyheptadecane-2,10-dione (**2**).[21]

To a stirred crude solution of siloxane **73** from **56** in MeOH (2.75 mL) was added $KHCO_3$ (254 mg, 2.49 mmol) and KF (587 mg, 10.0 mmol) followed by the slow addition of 30% H_2O_2 in H_2O (4.60 mL, 43.1 mmol). The mixture was stirred at rt for 36 h, and was then quenched by pouring into cooled, saturated aqueous Na_2SO_3 and stirring for 3 h. The solution was extracted with ether and the combined extracts were dried over anhydrous Na_2SO_4 and concentrated before purifying by flash column chromatography (hex/EtOAc, 1:1) afforded (**2**) as a white wax (80.6 mg, 68% over 3 steps from **56**).

^{1}H NMR (400 MHz; $CDCl_3$): δ 3.99 (b, 2 H), 3.02 (app d, 2OH, *J* = 8.8 Hz), 2.62-2.36 (m, 2H), 2.50 (m, 2H), 2.41 (t, 2H, *J* = 7.2 Hz), 2.16 (s, 3H), 1.62-1.23 (m, 16H), 0.86 (t, 3H, *J* = 6.8 Hz); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 212.7 (s), 210.3 (s), 67.9 (d), 67.5 (d), 50.1 (t), 49.2 (t), 43.7 (t), 36.6 (t), 36.2 (t), 31.9 (t), 30.9 (q), 29.9 (t), 29.2 (t), 25.4 (t), 23.6 (t), 22.8 (t), 14.3 (q); **HRMS (APCI)** *m/z* calcd. for $C_{17}H_{32}O_4Na$ ($M+Na^+$) 323.2193, found 323.2190; **FT-IR**: 3306, 2951, 2854, 1713, 1695, 1463 cm^{-1}.

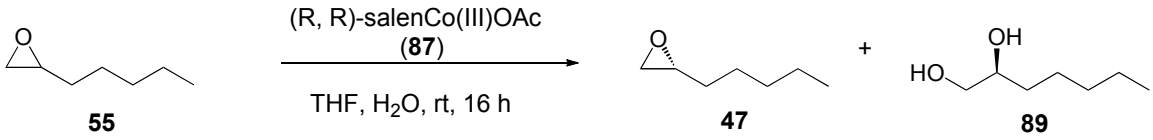


50 **52** **66**

(2-((Trimethylsilyl)ethynyl)cyclopentyl)methanol **66**.

To a stirring solution of alkyne **50** (616 mg, 3.38 mmol) in dry THF (2.00 mL) under argon atmosphere at -78 °C was added a solution of 2.4 M *n*-BuLi in hexanes (3.80 ml, 9.12 mmol) in a dropwise manner over 15 min. After 1 h at -78 °C BF_3•THF (1.10 mL, 9.97 mmol) was added and stirring continued for 30 min at -78 °C, epoxide **52** (1.79 g, 9.13 mmol) was added dissolved in dry THF (2.00 mL) and stirred for 3 h at -78 °C. When reaction was determined complete by TLC, it was quenched with brine, extracted with ether, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure before flash column chromatography (hex/EtOAc, 98:2) afforded **66** as a yellow oil (824 mg, 46%).

^{1}H NMR (400 MHz; $CDCl_3$): δ 3.77 (b, OH), 3.60 (dd, 1 H, *J* =3.2, 10.8 Hz), 3.44 (dd, 1 H, *J* = 6.8, 11.2 Hz), 2.21 (m, 2 H), 1.52 (b, 4 H), 0.11 (s, 9 H); **^{13}C NMR** (100 MHz; $CDCl_3$): δ 107.2, 84.9, 71.4, 50.6, 33.8, 28.5, 24.9, 19.9, 0.33; **HRMS (APCI)** *m/z* calcd. for $C_{11}H_{20}O_1Si_1$ ($M+H^+$) 197.1356, found 197.1361; **FT-IR**: 3398, 2947, 2865, 2175, 1431 cm^{-1}.



(R)-1,2-epoxyheptane **47** and (S)-1,2-heptanediol **89**.[21]

To a stirring solution of epoxide **55** (1.03 g, 8.97 mmol) in THF (3.7 mL) was added HKR catalyst **87**[75-77] (59.7 mg, 77.0 μmol) and stirred for 5 min before adding DI H_2O (0.80 mL, 44.4 μmol). Reaction was monitored by TLC and determined complete at 16 h after which it was extracted with ether. The combined extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and flash column chromatography (hex/EtOAc 98:2) afforded **47** (25.1 mg, 2.5%). Continued chromatography (hex/EtOAc 2:3) afforded **89** (363 mg, 30%).

Epoxide **47**.

^{1}H NMR (400 MHz; $CDCl_3$): δ 2.89 (m, 1 H), 2.73 (dd, 1 H, *J* = 4.0 Hz), 2.45 (dd, 1 H, *J* = 4.0 Hz), 1.41 – 1.24 (m, 8 H), 0.83 (t, 3 H, *J* = 4.0 Hz);

HRMS (APCI) *m/z* calcd. for $C_7H_{15}O_1$ ($M+H^+$) 115.1117, found 115.1116.

Diol **89**.

^{1}H NMR (400 MHz; $CDCl_3$): δ 3.68 (m, 2 H), 3.42 (dd, 1 H, *J* = 7.6, 10.8 Hz), 2.08 (bd, 2 OH), 1.41 (m, 3 H), 1.29 (m, 5 H), 0.87 (t, 3 H, *J* = 6.8 Hz).

(R)-1-(trimethylsilyl)-oct-7,8-epoxy-1-yne **51** and (S)-8-(trimethylsilyl)-oct-7-yne-1,2-diol **88**.[21]

To a stirring solution of epoxide **52** (2.12 g, 10.8 mmol) in THF (4.5 mL) was added HKR catalyst **87**[75-77] (25.2 mg, 381 μmol) and stirred for 5 min before adding DI H_2O (0.80 mL, 44.4 μmol). Reaction was monitored by TLC and determined complete at 16 h after which it was extracted with ether. The combined extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and flash column chromatography (hex/EtOAc 98:2) afforded **51** (53.8 mg, 2.5%). Continued chromatography (hex/EtOAc 2:3) afforded **88** (51.5 mg, 2.2%).

Epoxide **51**.

^{1}H NMR (400 MHz; $CDCl_3$): δ 2.88 (m, 1 H), 2.72 (dd, 1 H, *J* = 3.6, 5.2 Hz), 2.44 (dd, 1 H, *J* = 2.8, 4.4 Hz), 2.21 (app t, 2 H, *J* = 6.4 Hz), 1.53 (b, 6 H), 0.113 (s, 9 H); **HRMS (APCI)** *m/z* calcd. for $C_{11}H_{21}O_1Si$ ($M+H^+$) 197.1354, found 197.1362.

Diol **88**.

^{1}H NMR (400 MHz; $CDCl_3$): δ 3.80 (m, 1 H), 3.61 (dd, 1 H, *J* = 3.2, 11.2 Hz), 3.46 (dd, 1 H, *J* = 7.2, 10.8 Hz), 2.22 (app t, 2 H, *J* = 7.2 Hz), 2.12 (d, 1 OH, *J* = 4.4 Hz), 1.54 (b, 6 H), 0.123 (s, 9 H); **HRMS (APCI)** *m/z* calcd. for $C_7H_{15}O_1$ ($M+H_2O+2H^+$) 235.1730, found 234.1850.

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