## Title

Trimethylaluminum-Triflimide Complexes for the Catalysis of Highly Hindered Diels-Alder Reactions and Their Use Towards the Enantiospecific Total Synthesis of Rhodexin A



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## Publication Date

2012

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

# Trimethylaluminum-Triflimide Complexes for the Catalysis of Highly Hindered Diels-Alder Reactions and Their Use Towards the Enantiospecific Total Synthesis of Rhodexin A

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

Mikhail A. Guzaev

2012

ABSTRACT OF THE DISSERTATION

Trimethylaluminum-Triflimide Complexes for the Catalysis of Highly Hindered Diels-Alder Reactions and Their Use Towards the Enantiospecific Total Synthesis of Rhodexin A

by

Mikhail A. Guzaev

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2012

Professor Michael Jung, Chair

Rhodexin A is a cardiac glycoside first isolated from the leaves and roots of *Rhodea Japonica* in 1951, which shown potent activity against leukemia K562 cells (IC50 19 nM). A previous synthesis of rhodexin A has been accomplished by the Jung group. A novel synthetic approach, utilizing a convergent Diels-Alder reaction with two optically active fragments deriving from Wieland–Miescher ketone and carvone, is reported. Additionally a novel Lewis acid system was developed and utilized during the synthesis and its further applications are described in Chapter 2.

The dissertation of Mikhail A. Guzaev is approved.

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2012

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ACKNOWLEDGEMENTS

My deepest gratitude towards my professor and mentor, Dr. Michael E. Jung, cannot be overstated. Dr. Jung has always provided stimulating ideas and direction in our research together that have always motivated and inspired me. Dr. Jung's understanding of complex molecule synthesis, NMR techniques, and reaction mechanisms have been a singular source of knowledge and wisdom. I am tremendously grateful for the opportunity to have worked under his tutelage. I am also very grateful to Professor Neil K. Garg for his input and advice during my graduate career, as well as his outstanding and deeply challenging synthesis course, which has given me a foundation in organic synthesis that serves me well to this day. I would also like to thank my dissertation and oral exam committee, Professor Steven G. Clarke and Professor Yi Tang, for their patience and attention.

I would also like to thank present and past members of the Jung research group, who created and intellectual environment that I have come to treasure. My deep thanks as well to members of my graduating year and also to my friends and colleagues in the department.

My work and studies have all been made possible only with the love and support of my family, for which I will be eternally grateful.

Chapter 2 is a version of Jung, M. E.; Guzaev, M. *Org. Lett*. **2012**, *14*, 5169.

Funding has been provided by UCLA Graduate Division Dissertation Year Fellowship.

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PUBLICATIONS AND PRESENTATIONS

Michael E. Jung and **Mikhail A. Guzaev**, "Progress Towards the Total Synthesis of Rhodexin A," *241st ACS National Meeting & Exposition*, Anaheim, CA, United States, March 27-31, 2011 (Poster Presentation).

Michael E. Jung and **Mikhail A. Guzaev**, "Trimethylaluminum-Triflimide Complexes for the Catalysis of Highly Hindered Diels-Alder Reactions," *Org. Lett*. **2012**, *14*, 5169.

# Chapter 1

# Progress Towards Enantiospecific Total Synthesis of Rhodexin A

## Introduction

The effect of cardiac glycosides on tumor cells has been reported to be linked to their ability to induce increased levels of $Ca^{2+}$ ions in the cell.[1] Rhodexin A **1** is a glycoside first isolated from the leaves and roots of *Rhodea Japonica* in 1951, and has been shown to have similar cardiotonic activity to that of other cardiac glycosides (**Figure 1**).[2] Rhodexin A is structurally similar to Ouabain **2**, an endogenous hormone, which has previously been used in the treatment of heart arrhythmia and is currently being used for *in vitro* studies to block the $Na^+/K^+$ ATPase pump. It is suspected that rhodexin A functions through a similar pathway, resulting in inhibition of mitosis and promotion of apoptosis. Rhodexin A is similar in structure and function to Ouabain, but was found to display a greater degree of cytotoxic action. Rhodexin A has also shown potent activity against leukemia K562 cells (IC50 19 nM), which has generated interest in synthetic exploration of the structure as well as producing sample for further biological testing.[3]

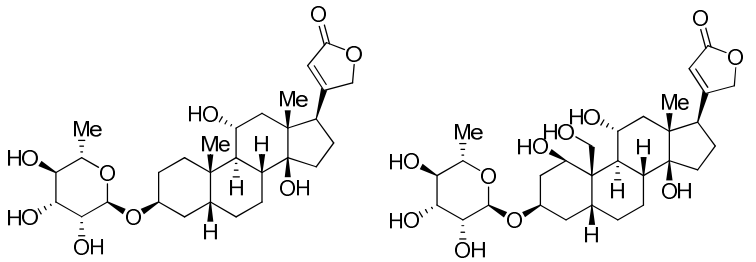


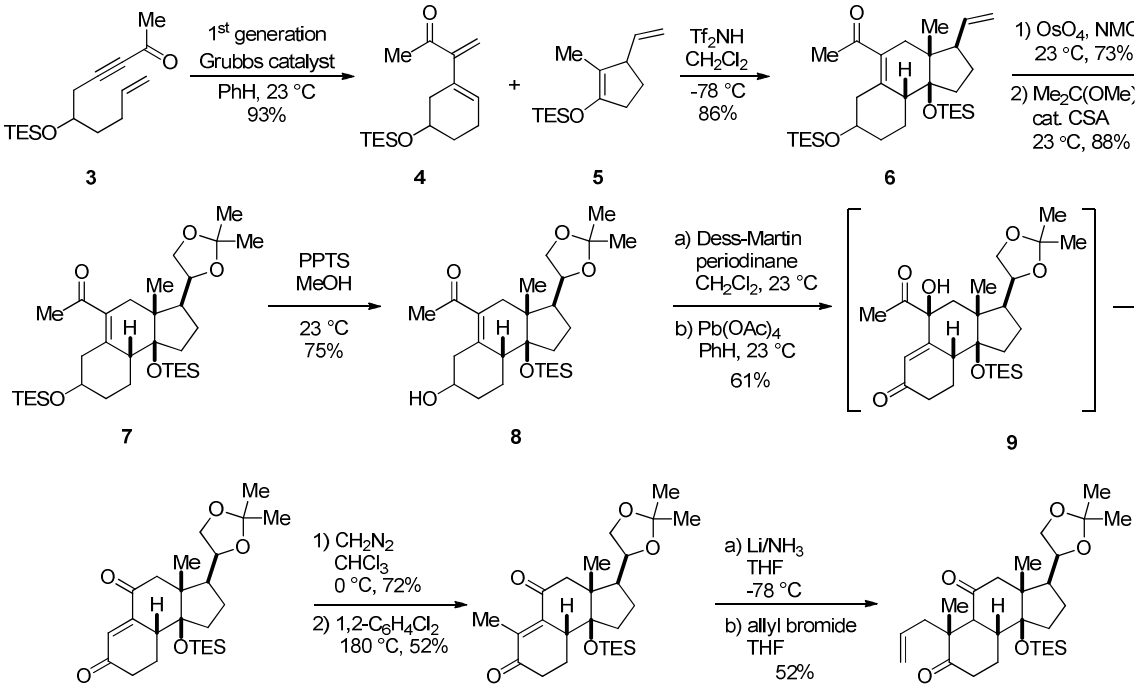

**Figure 1.** Rhodexin A and Ouabain

## Background

Previous synthetic efforts towards rhodexin A have been accomplished by the Jung group.[4] The previous synthesis started with the enynone **3**, achieved via the known enynol in two steps, which under enyne metathesis conditions was transformed to diene **4** (**Scheme 1**).[6a] Diene **4** and dienophile **5**[5] could be joined using a number of catalytic methods; initially 5:1 $AlMe_3/AlBr_3$ was employed.[6] However, the best results were achieved with 10 mol% triflimide ($Tf_2NH$) catalysis, yielding the tricyclic adduct **6** in 86% yield as a 2:1 mixture of two diastereomers at the secondary silyl ether group. The diastereomeric mixture was considered trivial due to the forthcoming oxidation of that stereocenter.

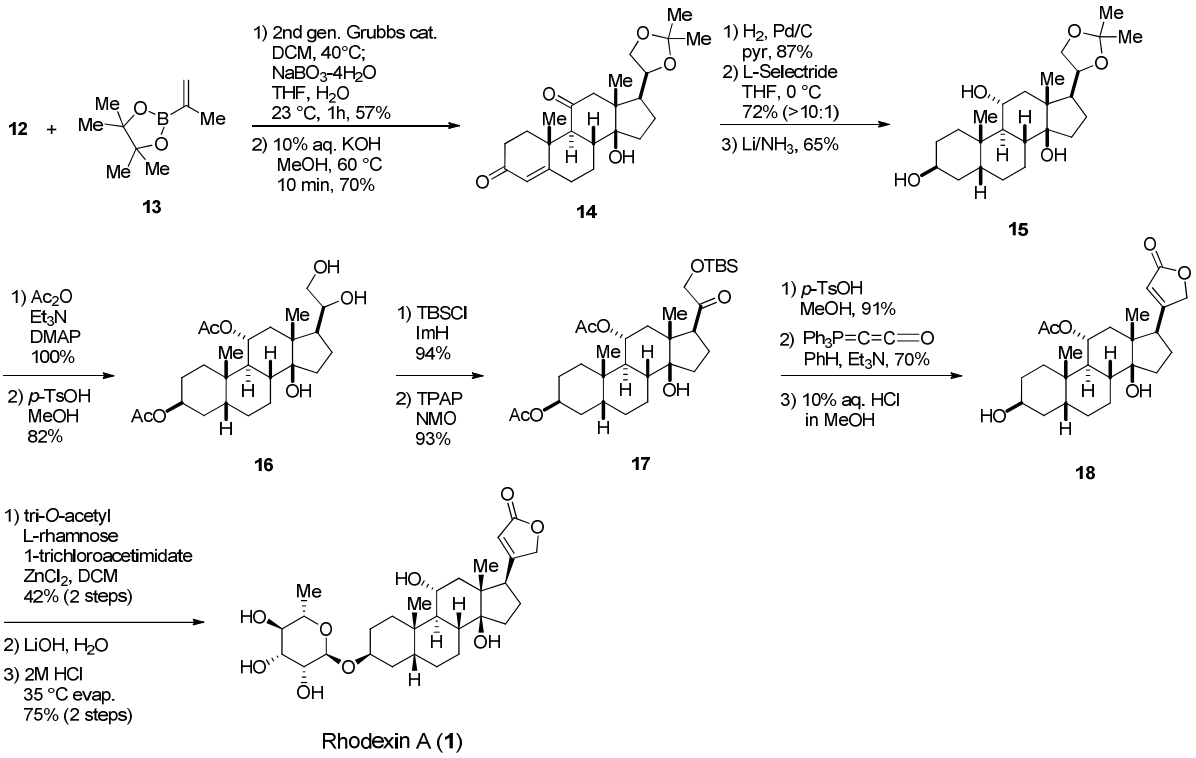
Dihydroxylation of the vinyl side chain and the protection of the diol as the acetonide was accomplished to give **7**. Selective hydrolysis of the secondary silyl ether yielded alcohol **8**, which underwent an unusual triple oxidation with Dess-Martin periodinane (DMP). The oxidation is thought to occur via the hydroxyenedione intermediate **9**, to give the enedione **10**. Although the oxidation could be accomplished with excess DMP, the authors preferred the use of lead tetraacetate ($Pb(OAc)_4$) for the final cleavage.

The compound was methylated via a two-step sequence of 1,3-diploar cycloaddition of diazomethane to **10** to give the pyrazoline, followed by extrusion of nitrogen to afford the methyl enedione **11** in 37% overall yield. Dissolving metal reduction of **11** and trapping with allyl bromide gave the allylated compound **12**.




**Scheme 1.** Previous Progress Towards Rhodexin A

Cross-metathesis of the alkene of **12** and the isopropenyl (pinacolato)boronate **13**, using the Grubbs second generation catalyst, afforded the alkenyl boronate, which was oxidized with sodium perborate to give the diketone **14** in 57% overall yield (**Scheme 2**). Base catalyzed aldol condensation furnished the desired enone **14**. An X-ray crystal structure confirmed the stereochemistry of the compound. Catalytic hydrogenation with palladium on carbon in the presence of pyridine gave the desired *cis* AB ring junction in 87% yield. Regioselective reduction with L-Selectride provided the desired axial alcohol, and dissolving metal reduction of the more hindered C-11 ketone afforded the equatorial alcohol **15**. Protection of the diol as the diacetate followed by acidic cleavage of the acetonide and silyl ether moities liberated the triol **16**.




**Scheme 2.** Completion of the Synthesis of Rhodexin A

Selective protection of the primary alcohol as the silyl ether and oxidation gave the ketone **17** in excellent yield. Hydrolysis of the TBS ether, followed by reaction with the Bestmann reagent[7] (triphenylphosphoranylideneketene) provided the butenolide in 70% yield. Selective removal of the less hindered acetate in the presence of the butenolide was carried out with HCl in methanol to give the diol **18**. Reaction of the tri-*O*-acetyl L-rhamnose 1−trichloroacetimidate with the less hindered secondary alcohol using $ZnCl_2$, followed by global removal of the acetates with base, and recyclization of the butenolide moiety, that was found to be unstable to deprotection conditions, mediated by 2 M HCl afforded rhodexin A (**1**).

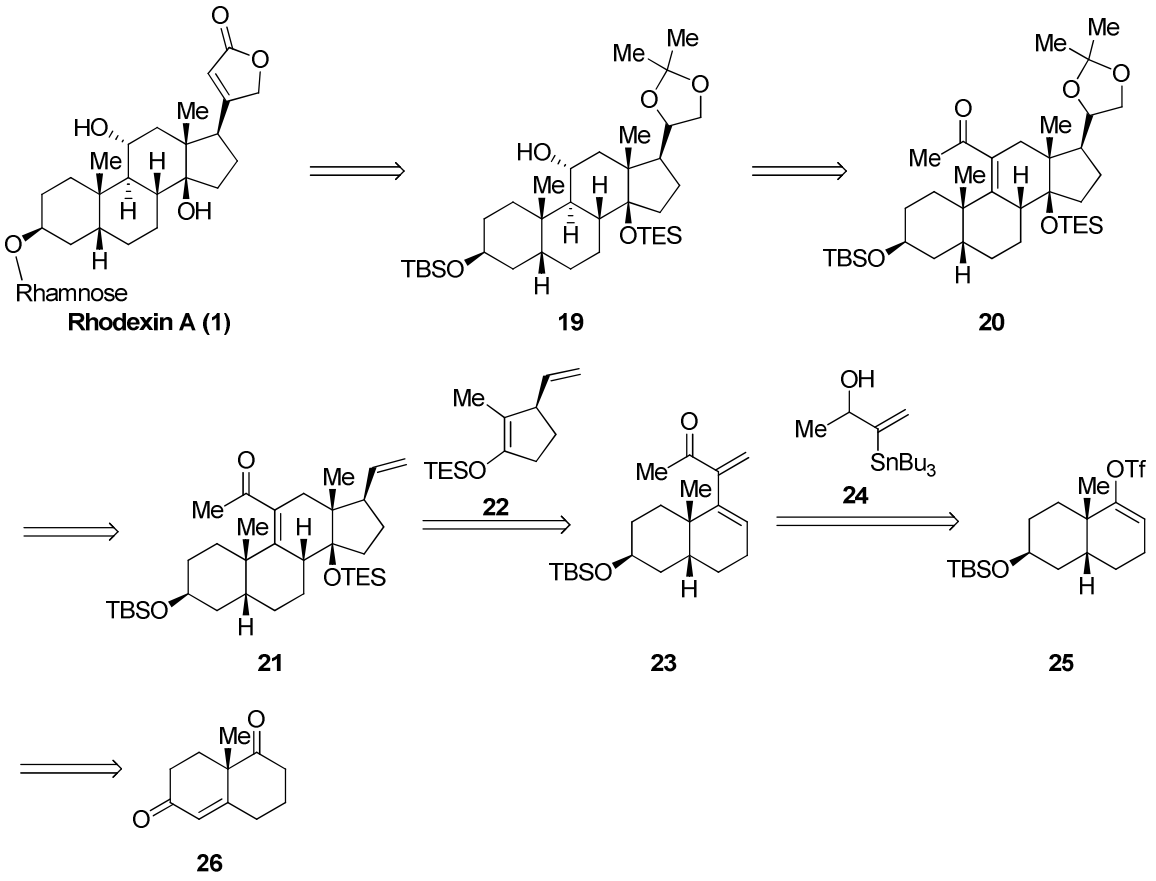
This demonstrated the first total synthesis of rhodexin A, employing a hindered inverse electron demand Diels-Alder reaction to generate four contiguous stereocenters of the BCD ring

system in a single step in excellent yield. Also employed was a novel annulation method for the formation of the A ring.

## Results and Discussion

Due to some degree of difficulty being encountered in the previous synthesis of rhodexin A in the construction of the A ring, and our continuing interest in developing hindered Diels-Alder reactions for their use in organic synthesis, we embarked on a novel route towards the total synthesis of the cardiac glycoside.

The new approach would involve construction of the butenolide of rhodexin A **1** in the final stages of the synthesis, utilizing the ketal **19** (**Scheme 3**). Ketal **19** would be formed via oxidative deacylation of enone **20**, followed by reduction to establish the hydroxyl stereocenter. Enone **20** was seen as arising from the tetracycle **21** via dihydroxylation and ketalization. Tetracycle **21** would be a product of a Diels–Alder reaction between the optically active silyl enol ether **22** and the diene **23**. The diene **23** would arise from a Stille coupling between the vinyl stannane **24** and the vinyl triflate **25**, which would evolve from functionalization of the Wieland–Miescher ketone **26**.

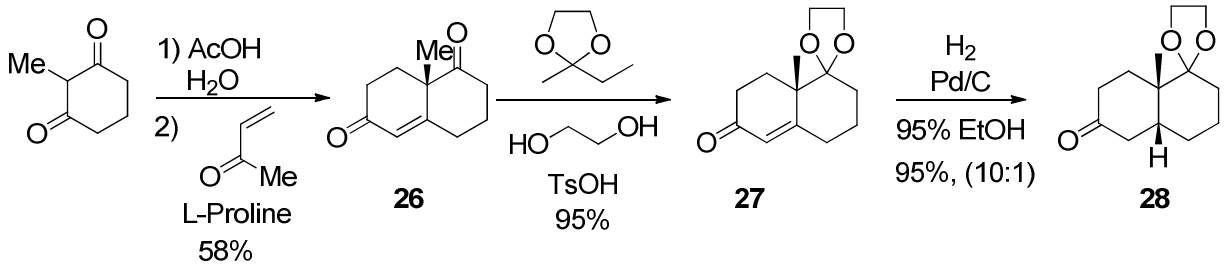



**Scheme 3.** Retrosynthesis

This new synthetic pathway was conceived as a more convergent means of accomplishing the hindered Diels-Alder reaction seen in the previous effort by establishing the A ring of the cardiac glycoside early in the synthesis. The novel strategy would rely on the angular methyl at the AB ring juncture to impart the desired facial selectivity in the key cycloaddition. The Wieland–Miescher ketone **26** was seen as a convenient source of chirality in this enantiospecific approach.

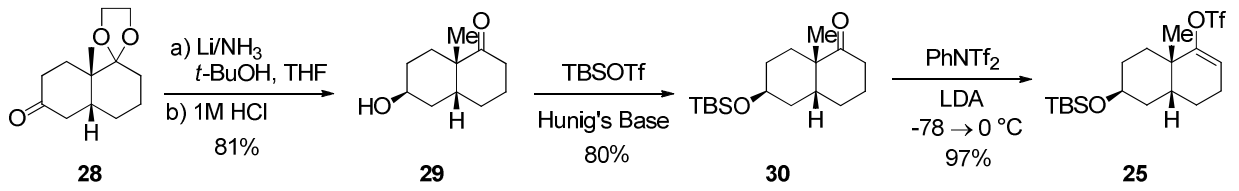
Our efforts began with the synthesis and functionalization of the AB ring system (**Scheme 4**). Synthesis of Wieland–Miescher ketone **26** using established methods gave reasonable yields and 98% enantiopurity.[8] A highly selective trans-ketalization procedure was

employed in order to protect solely the unconjugated ketone, using 2-methyl-2-ethyl-l,3-dioxolane and ethylene glycol, catalyzed by *p*-toluenesulfonic acid (TsOH), giving the ketal **27** in excellent yield and selectivity.[9] Catalytic hydrogenation with palladium on carbon gave mainly the *cis*–decalin **28** in 95% yield as a 10:1 ratio of chromatographically separable isomers.




**Scheme 4.** Initial synthesis

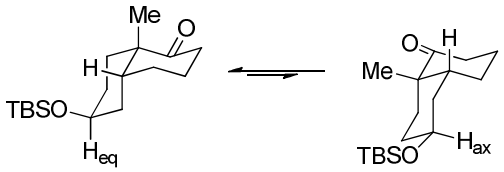
Diastereoselective reduction of **28** was subsequently undertaken. Sodium borohydride reduction ($NaBH_4$) was known to give the undesired isomer. Therefore, initially it was assumed that a bulky reducing agent would be required in order to impart the desired selectivity.[10] However, alternative reducing procedures using L-Selectride or sodium triethylborohydride failed to give the desired product, failing to react in the former case and imparting the undesired selectivity in the latter. Fortunately, dissolving metal reduction with lithium in ammonia of compound **28**, followed by cleavage of the ketal during acidic workup, afforded the alcohol **29** in 81% yield (**Scheme 5**).




**Scheme 5.** Formation of the Vinyl Triflate

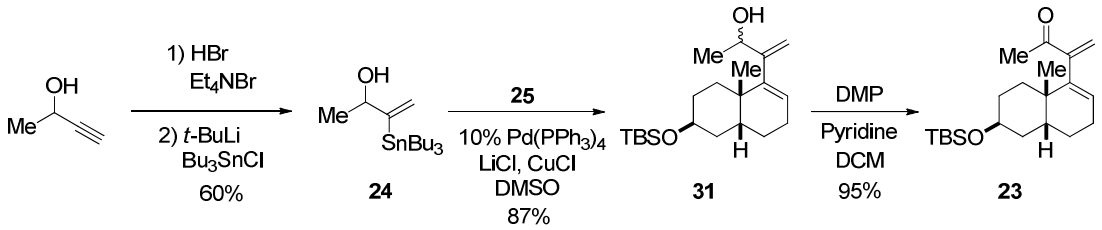
Protection of the newly formed alcohol **29** as the silyl ether using *tert*-butyl dimethyl silyl triflate (TBSOTf) yielded the TBS ether **30**. Formation of the enolate with lithium diisopropylamide (LDA) and trapping with phenyl triflimide ($PhNTf_2$), afforded the vinyl triflate **25**.

Conformational analysis of the silyl ether **30** via $^1H$ NMR studies revealed that conformational isomer **30A** is likely to be dominant (**Scheme 6**). The signal for the equatorial $H_{eq}$ in conformer **30A** would be expected to appear as a indistinct multiplet due to being a dddd of four small couplings. Conformer **30B**, with an axial conformation of $H_{ax}$, would be expected to be a dddd of two large anti-periplanar axial couplings and two small equatorial couplings, giving rise to a more distinctly coupled approximate triplet of triplets. Since an indistinct multiplet is observed in the $^1H$ NMR spectrum, conformer **30A** is considered to be dominant. MM2 calculations confirmed this conclusion, with conformer **30A** being more stable than conformer **30B** by 4.6 kcal/mol. The preferred conformation of this *cis*-decalin would be expected to play an important role in imparting facial selectivity in the key Diels-Alder reaction, as it was hoped that the angular methyl group would block the top face of the molecule.




**Scheme 6.** Conformational Analysis of Silyl Ether **30**

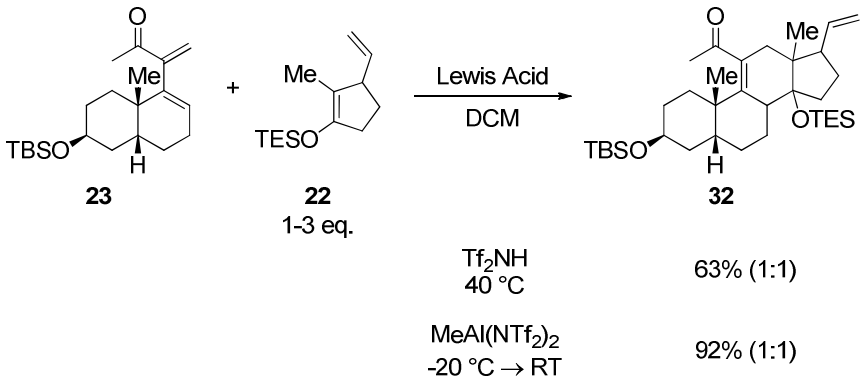
With the planned vinyl triflate **25** coupling partner in hand, synthesis of the organostannane **24** via a hydrobromination, metal-halogen exchange, and trapping sequence was undertaken following procedures of Corey, *et. al* (**Scheme 7**).[11] Stille coupling of the organostannane and the vinyl triflate afforded the allylic alcohol **31** in 87% yield.[11] Oxidation with Dess-Martin periodinane in the presence of pyridine yielded the diene **23** in excellent yield.[12] Other oxidations were attempted; however, yields were considerably lower with pyridinium chlorochromate and manganese dioxide proved prohibitively slow.[13,14] The Swern oxidation, which often provided comparable results, proved to be unreliable yields on larger scales.[15]




**Scheme 7.** Formation of the Diene

Having formed the desired diene **23**, investigation of the key Diels–Alder reaction with the silyl enol ether **22** ensued.[5] A number of conventional Lewis acid systems, including $SnCl_4$, $TiCl_4$, $BF_3{\cdot}OEt_2$ and $EtAlCl_2$, failed to catalyze the cycloaddition. The mixed Lewis acid system $AlMe_3/AlBr_3$ enjoyed some success, but giving the cycloadduct in fairly low yields. Triflimide

($Tf_2NH$) catalysis, however, proved successful at higher temperatures (**Scheme 8**). Use of $MeAl(NTf_2)_2$ [16] was found to be preferential affording a 92% yield of the cycloaddition product **32**, as a 1:1 mixture of two diastereomers. The reaction proceeded well with 1.3 equivalents of silyl enol ether **22**. Conditions were attempted with an excess of the enol to in order to influence the diastereomeric ratio, however, no affect on the diastereoselectivity was observed. To the best of our knowledge this is the first successful use of aluminum triflimide salts to affect a Diels–Alder reaction. Further details of this catalyst system are discussed further in Chapter 2.




**Scheme 8.** Diels-Alder cycloaddition

Although the Diels-Alder cycloadduct was successfully obtained, the diastereomeric mixture was cause for concern. A chiral mismatch of substrates offered a reasonable explanation for a 1:1 ratio of products, arising from both enantiomers of the silyl enol ether **22** reacting with a single enantiomer of the diene **23**, giving rise to an undesired mixture of products (**Figure 2**). As discussed in **Scheme 6**, the top face of the molecule is expected to be inaccessible due to steric hindrance caused by the angular methyl group. Despite this setback, efforts were made to further advance the synthesis, both to confirm the feasibility of the further chemistry and as a way of elucidating the structure of one of the isomers by intercepting an intermediate from the previous total synthesis.

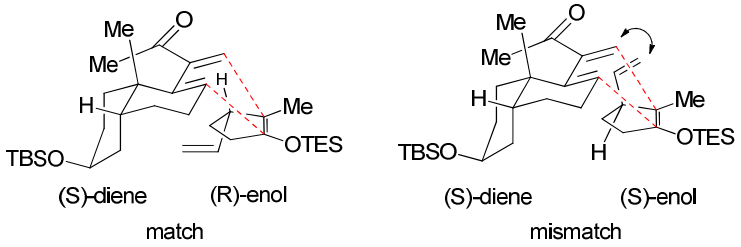
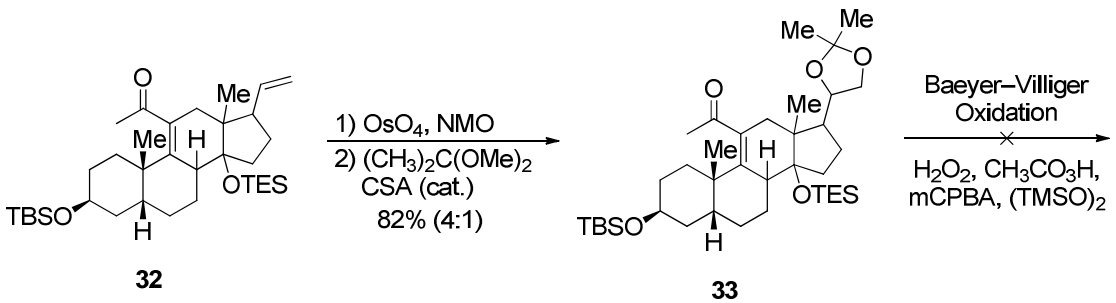



**Figure 2.** Chiral Mismatch

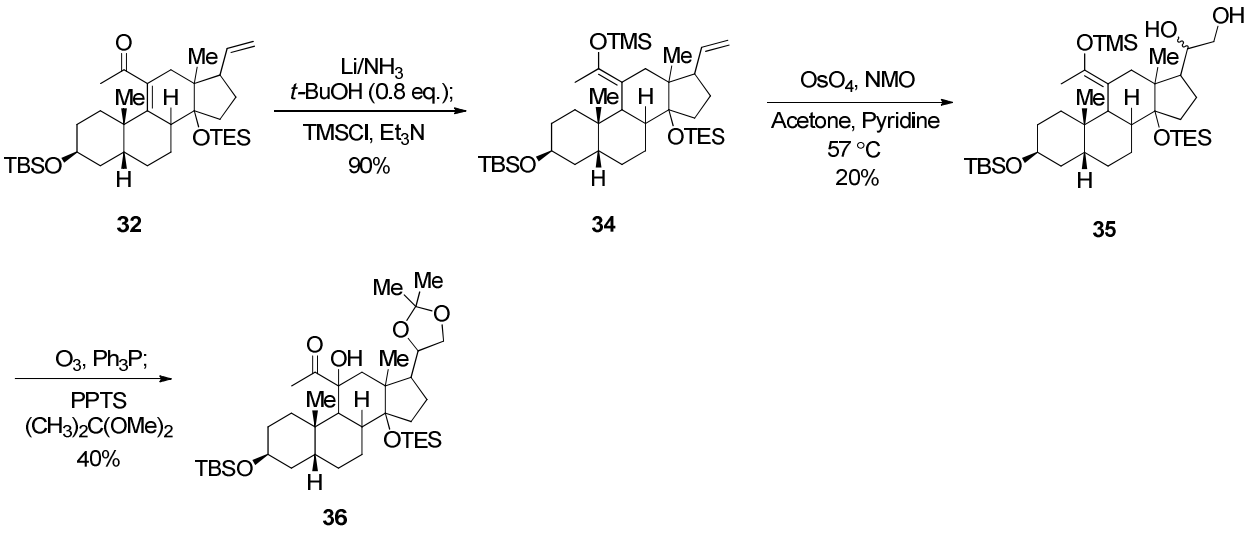
Both isomers of the cycloadduct **32** were separately subjected to catalytic dihydroxylation with osmium tetroxide ($OsO_4$). Subsequently, each diol was protected with dimethoxypropane to give the acetonide **33** in 82% yield, as a 4:1 mixture of diastereomers at the new secondary alkoxy center (**Scheme 9**). Baeyer-Villiger oxidation of the enone of **33** was then attempted under a variety of conditions, including: hydrogen peroxide ($H_2O_2$) mediated by base, peracetic acid, mCPBA, and tin tetrachloride ($SnCl_4$) assisted bis(trimethylsilyl) peroxide ($(TMSO)_2$).[17] However, no oxidation product was ever obtained. An alternative strategy was needed.




**Scheme 9.** Attempted Baeyer-Villiger Oxidation

A stepwise oxidative approach was therefore considered. The enone was reduced with lithium and ammonia in the presence of *tert*-butanol (*t*-BuOH) as a proton source and the resulting lithium enolate was trapped with trimethylchlorosilane, that was pretreated with triethylamine ($Et_3N$), to give the silyl enol ether **34** (**Scheme 10**).[18] It is important to note that

only one of the diastereomers of **32** obtained from the Diels-Alder reaction would undergo this trapping, the other isomer yielding only the saturated ketone. Upon successful trapping it was assumed that the subsequent oxidation of the silyl enol ether double bond would be significantly easier than previous attempts at oxidation. However, upon attempted dihydroxylation with $OsO_4$, it became apparent that the alkene is more susceptible to oxidation then the silyl enol ether, which not only failed to oxidize, but was also prone to hydrolysis, yielding the diol **35** in 20% yield in addition to the ketone produced by hydrolysis of the silyl enol ether.



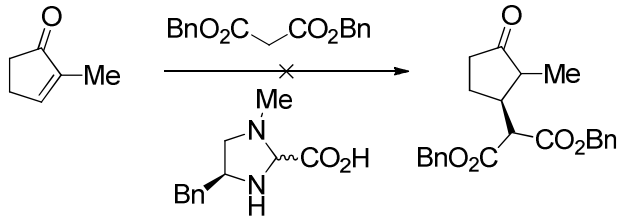

**Scheme 10.** Dissolving Metal Reduction and Trapping

Rubottom oxidation of **35** with mCPBA was attempted, but the silyl enol ether failed to react.[19] The compound was subjected to ozonolysis with the hopes of obtaining the ketone directly, however, only the hydroxy ketone **36** was obtained in 40% yield, after protection as the acetonide.[20]

Due to low yields in the latter parts of the synthesis, particularly, during the formation of diol **35**, as well as the inability to take one of the diastereomers of **32** through further chemistry for structure confirmation, it became apparent that an enantiospecific synthesis of the dienophile

fragment should be under undertaken. It was hoped that an enantiopure dienophile substrate would simplify the latter part of the synthesis, first, by presumably yielding a single diastereomer in the key Diels-Alder reaction, as well as potentially offering greater orthogonality for oxidation of the enone moiety.

Our first attempt at the synthesis of an enantiopure dienophile fragment began with phenylalanine derived organocatalysis (**Scheme 11**). Although the addition of dibenzyl malonate was described on cyclohexenone, the reaction failed to proceed when applied to 2-methyl-2-cyclopenten-1-one.[21] The methyl substituent probably prevents productive catalysis from proceeding. Although it seems probable that the addition would proceed in the cyclopentenone case, the difficulty of selectively installing a methyl group with the desired regioselectivity halted efforts in this area.

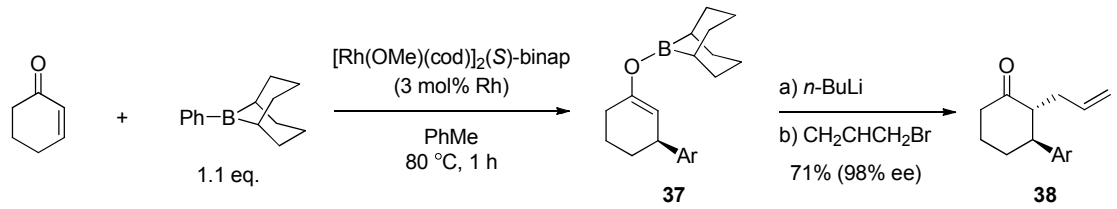



**Scheme 11.** Organocatalytic Addition of Dibenzylmalonate

We then turned to rhodium-catalyzed conjugate addition as a possible solution. Due to the tendency of unsubstituted vinylboronic acids to polymerize, the choice of starting substrates proved to be limited.[22] Potassium vinyltrifluoroboronate was an accessible substrate to use, since the addition of fluoroboronates has been demonstrated to be highly effective in the presence of a chiral ligand.[23] Although the model case of the unsubstituted cyclopentenone was highly successful, the reaction on 2-methyl-2-cyclopenten-1-one failed to proceed (**Scheme 12**). Again, it seemed likely that the steric bulk of the methyl group impeded the reaction.

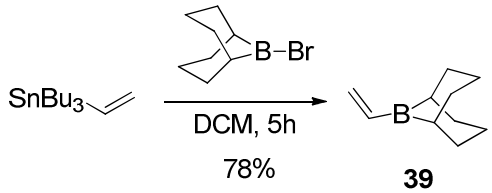

**Scheme 12.** Rhodium Catalyzed Potassium Vinyl Trifluoroboronate Addition

An alternative rhodium catalyzed approach was considered. Recently the asymmetric addition of 9-aryl-9-borabicyclo[3.3.1]nonanes (9-BBN) to enones has been demonstrated. Interestingly, the anhydrous conditions, unusual for rhodium catalyzed conjugate additions, resulted in the formation of a boron enolate **37** which allowed a transmetallation event with *n*–butyllithium and subsequent alkylation of the α-position of the ketone in a regioselective manner to form compound **38** in excellent yields and enantioselectivity (**Scheme 13**).[24]



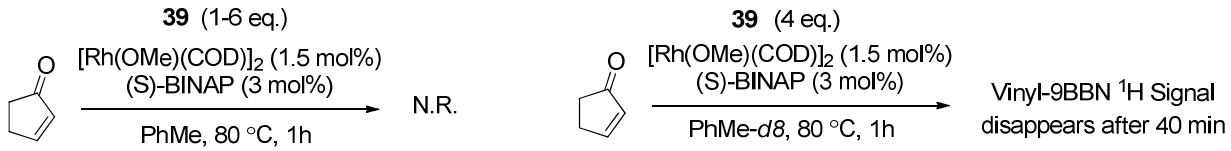

**Scheme 13.** Literature Conjugate Addition of Ar(9-BBN) to Enones with Trapping

This strategy appeared to be an ideal solution for the problems encountered with other forms of enantioselective conjugate addition, if it could be applied to a vinyl 9-BBN substrate rather than aromatic substrates as demonstrated. Vinyl 9-BBN **39** has been described in the literature and it was synthesized via transmetallation of vinyltributyltin with bromo 9-BBN (**Scheme 14**).[25]




**Scheme 14.** Synthesis of Vinyl 9-BBN

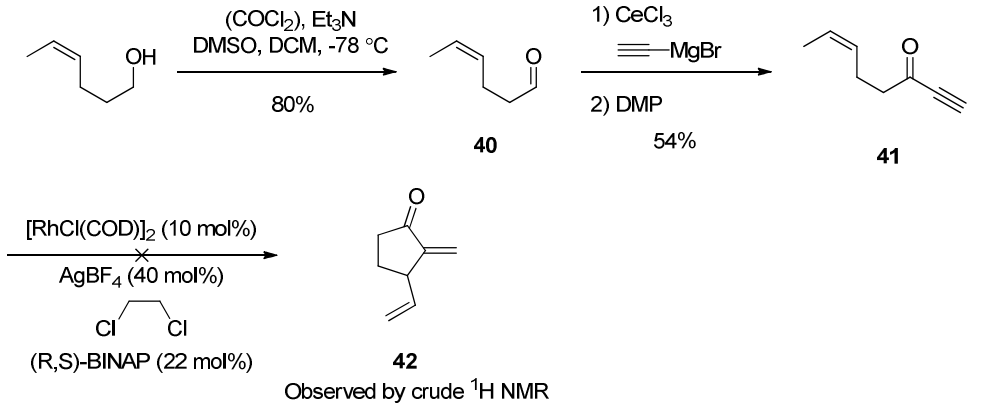
Unfortunately, when the rhodium catalyzed conjugate addition of the vinyl 9-BBN **39** was attempted, no product formation was detected by crude NMR (**Scheme 15**). An NMR experiment was conducted in $d_8$-toluene and although the proton signal of **39** disappeared rapidly, even when used in large excess, the cyclopentenone appeared unaffected. This led to the conclusion that the vinyl 9-BBN is an unsuitable substrate for this transformation, likely due to its pronounced tendency towards polymerization.




**Scheme 15**. Attempted Conjugate Addition of Vinyl 9-BBN

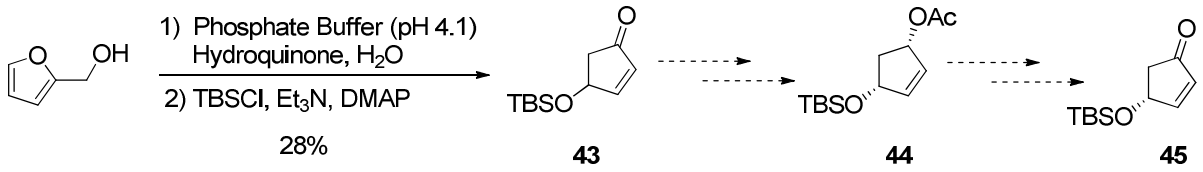
After failure of various conjugate addition methodologies to give the desired results, we considered an alternative strategy of forming the cyclopentanone unit *de novo*. Rhodium cycloisomerization of enynes is well established to yield chiral cyclopentyl units and we pursued an analogous route.[26] Swern oxidation of 4-hexen-1-ol afforded aldehyde **40** in good yield (**Scheme 16**). Aldehyde **40** was reacted with ethynylmagnesium bromide in the presence of cerium trichloride ($CeCl_3$) and oxidized to give the enynone **41** in 54% yield over 2 steps.[27] The enynone **41** was exposed to rhodium catalysis, with a racemic catalyst in this case, to test the feasibility of the reaction. Although the results were initially promising, with what was believed to be product being observed by crude $^1$H NMR experiments, the target compound **42** proved to

be poorly tolerant to column chromatography. Direct distillation of the product from the crude reaction mixture was attempted, but the enone **42** eluded isolation.




**Scheme 16.** Enyne Cycloisomerization Approach

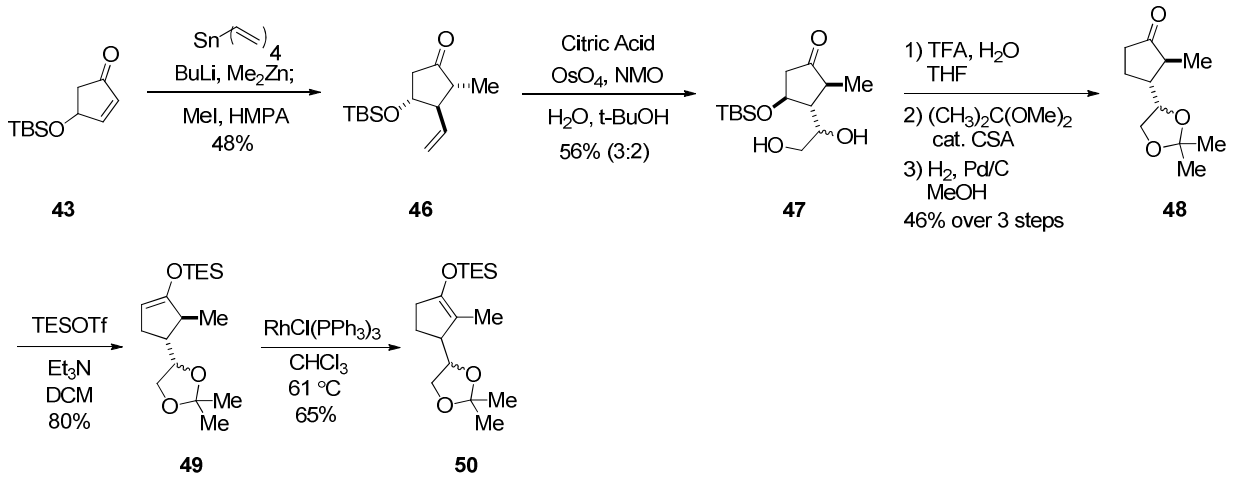
Having had poor success with catalytic enantioselective methodologies, an enzymatic resolution approach was therefore considered. The route was based on the established synthesis of the TBS ether **43**, formed via hydrolysis and protection of furfuryl alcohol, followed by reduction and resolution with the pancreatin enzyme in the presence of vinyl acetate to form the resolved compound **44** (**Scheme 17**).[28] Hydrolysis of the acetate and oxidation would yield the enone **45**, which could be further elaborated via steric induction.




**Scheme 17**. Planned Enzymatic Resolution Route

Since the enzymatic resolution was well established and had been previously reproduced within the group, initial efforts focused on establishing the feasibility of further elaboration. Having obtained the racemic starting compound **43**, conjugate addition of a vinyl zincate and

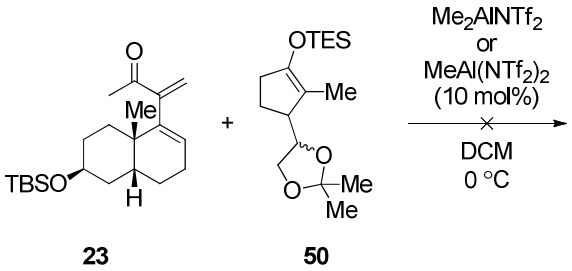
trapping with methyl iodide (MeI) gave the olefin **46** (**Scheme 18**).[29] Catalytic dihydroxylation of the alkene with osmium tetroxide in the presence of citric acid yielded the diol **47** as a 3:2 mixture of inseparable diastereomers.[30] Acid-catalyzed cleavage of the TBS group and elimination to the enone, followed by protection of the diol with dimethoxypropane, and finally palladium on carbon catalyzed hydrogenation afforded the acetonide **48** in 46% over three steps, without purification of any of the intermediates. Thermodynamic formation of the silyl enol ether was attempted, unfortunately, the kinetic product **49** was formed almost exclusively. Enolization at elevated temperatures with sodium iodide and triethylsilyl chloride (TESCl) in acetonitrile yielded a greater proportion of the more substituted product. This result, was still unsatisfactory, however. Heating **49** with Wilkinson's catalyst in chloroform ($CHCl_3$), fortunately, allowed for the migration of the silyl enol ether to form the desired, more substituted, silyl enol ether **50** in 65% yield.[31]




**Scheme 18.** Synthesis of Acetonide Silyl Enol Ether

The Diels-Alder reaction between the diene **23** and the dienophile **50** was attempted under $Me_2AlNTf_2$ and $MeAl(NTf_2)_2$ catalysis, but proved unsuccessful (**Scheme 19**). Although both substrates were stable to the reaction conditions, no product was observed even using

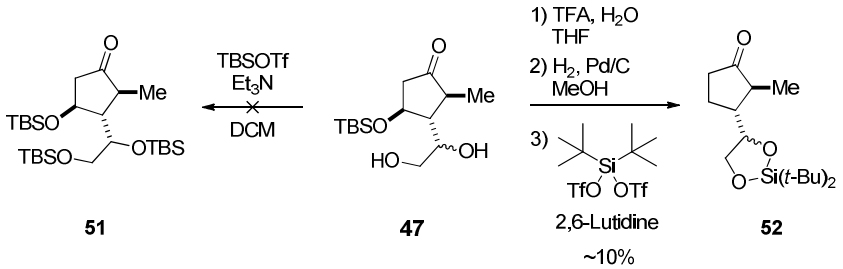
extented reaction times. We suspect that the acetonide competitively chelates the Lewis acid, impeding the reaction.[32] Modifications of the dienophile **50** were therefore considered.




**23** **50**

**Scheme 19.** Diels-Alder Reaction with Acetonide Silyl Enol Ether

Installation of protecting groups that would not compete for the chelation of the Lewis acid used during the Diels-Alder was undertaken. Protection of diol **47** as the bis-TBS ether failed to proceed. Although the primary alcohol could be successfully protected, the secondary alcohol proved unreactive, failing to form the desired compound **51** (**Scheme 20**). Protection with the di(*tert*-butyl)silylditriflate to form the cyclic bis-silyl ether **52** was attempted, but the overall yield proved prohibitively low.[33] Furthermore, the final compound proved unstable to purification on silica gel and a pure analytical sample could not be isolated. This synthetic approach was subsequently abandoned in favor of a new route.

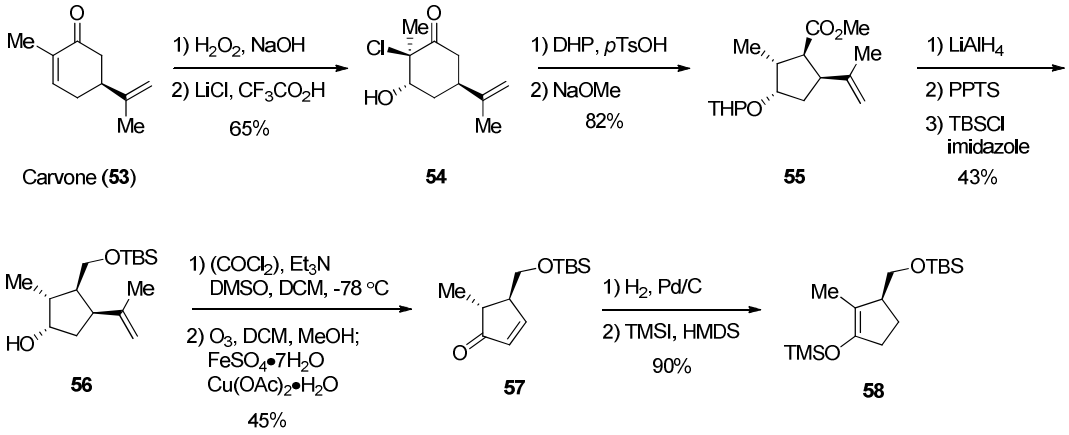



**51** **47** **52**

**Scheme 20.** Attempts at Alternative Protection of the Diol

Having had poor success with a more elaborate side chain installed on the dienophile partner of Diels-Alder reaction, a less complex target was desired. The technical and scale

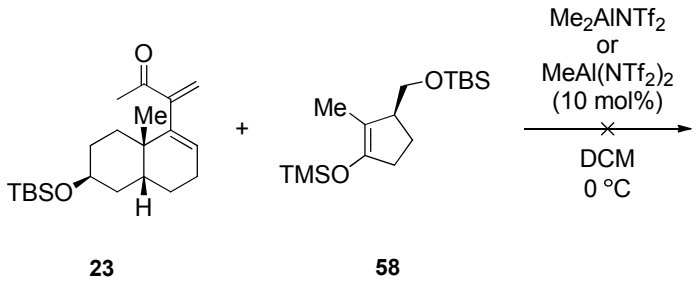
limitations of chiral resolution and enantioselective methodologies encouraged us to draw on an available chiral pool. Fortunately, upon consideration of possible targets, an existing synthetic route was encountered that drew on carvone **53** as the source of chirality to synthesize a chiral silyl enol very similar to the target desired in our synthesis (**Scheme 21**).[34] The synthesis began with epoxidation of carvone **53** with hydrogen peroxide in base and regioselective opening of the epoxide with lithium chloride (LiCl) in combination with trifluoroacetic acid to give the alcohol **54** in 65% yield. Protection of the alcohol gave the tetrahydropyranyl (THP) ether as an expected mixture of diastereomers, which then underwent the Favorskii rearrangement with sodium methoxide to give the methyl ester **55**.[35] Although the THP group does cause the inconvenience of forming diastereomers, in this case, the coordinating ability of this group proved important for the selectivity of the Favorskii rearrangement.[34] Reduction of the ester of **55** with hydride, followed by cleavage of the THP afforded the free diol. Selective protection of the primary alcohol afforded the alcohol **56**. It is worth noting that the TBS protection procedure as described results in a mixture of the mono and di-protected products. Although the di-protected product could be recycled after deprotection, we found it more convenient to use a sub-stochiometric (0.8 eq.) amount of TBSCl, yielding a ~3:2 mixture of product and starting material.




**Scheme 21**. Literature Route to a Chiral Silyl Enol Ether

Although the free alcohol **56** could be oxidized with PCC to the ketone, our preference was to use a Swern oxidation.[15] Ozonolysis of the double bond followed by the Criegee rearrangement with the use of ferrous sulfate ($FeSO_4$) and cuprous sulfate ($CuSO_4$) gave the enone **57** in satisfactory yield.[36] Catalytic hydrogenation of the double bond with palladium on carbon to give the ketone, followed an interesting thermodynamic enolization with the Jung reagent, trimethylsilyl iodide (TMSI), in the presence of hexamethyldisilizane (HMDS) gave the silyl enol ether **58** in 90% yield over 2 steps.[37]

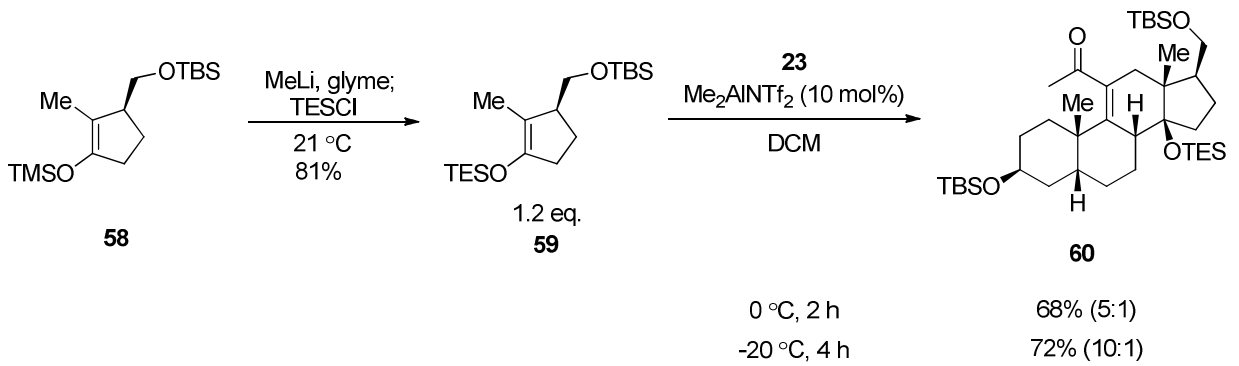
The silyl enol ether **58** was applied directly in reaction with the diene **23**. However, the results were disappointing (**Scheme 22**). Crude $^{13}C$ NMR studies indicated a significant presence of a diketone byproduct, indicating that this substrate was likely too sensitive to the reaction conditions and that hydrolysis was taking at the Mukaiyama-Michael adduct with little net cycloaddition taking place.




**23** **58**

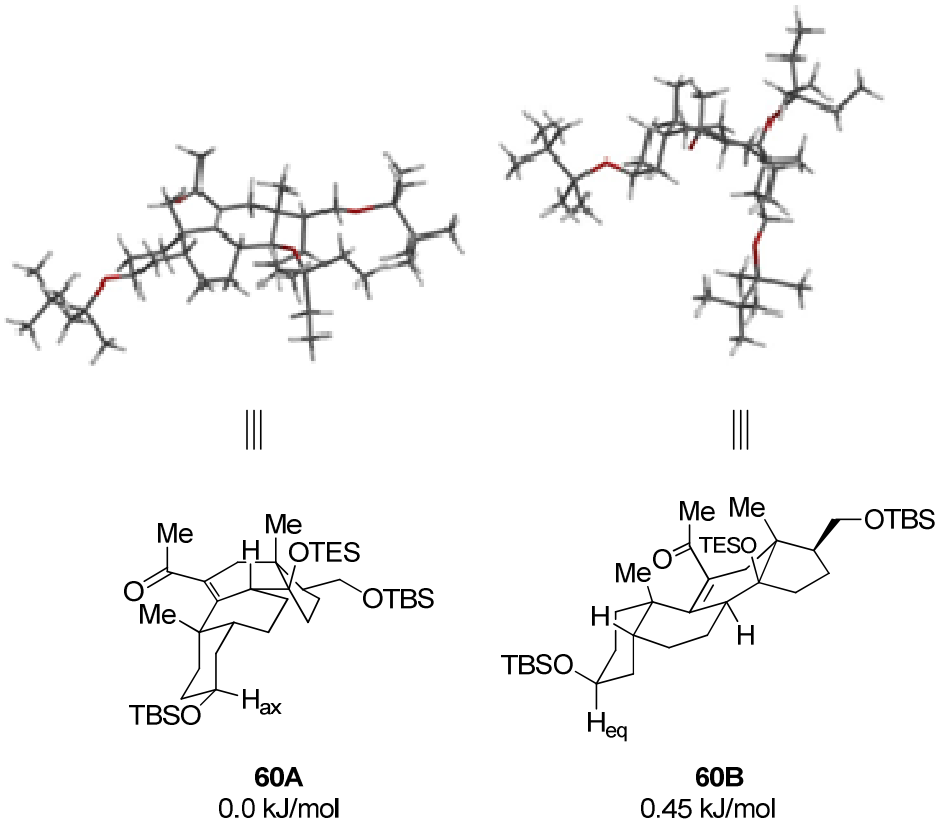
**Scheme 22.** Diels-Alder Reaction with Silyl Enol Ether **58**

Synthesis of a more stable version of the dienophile **58** was undertaken. Direct enolization with TES triflate, surprisingly, yielded almost exclusively the less substituted silyl enol ether. Attempts to migrate the double bond with Wilkinson's catalyst met with some success, but in low yields. Fortunately, treatment of the silyl enol ether **58** with methyllithium (MeLi) in 1,2-dimethoxyethane generated the lithium enolate regioselectively and trapping with TESCl yielded the more substituted silyl enol ether **59** (**Scheme 23**).[38] Interestingly, compound **58** was found to be completely unreactive towards methyllithium in both THF and diethyl ether, even at reflux temperatures and upon addition of lithium iodide. Finally, reaction of the diene **23** and dienophile **59** catalyzed with 10 mol% $Me_2AlNTf_2$ at -20 °C for 4 hours yielded the cycloadduct **60** as a single diastereomer in 72% yield as a 10:1 mixture of diasteromers. The absolute structural configuration of tetracycle **60** remains undetermined and the major product is drawn as would be expected based on mechanistic rationale.




**Scheme 23.** Diels-Alder Reaction with Silyl Enol Ether **59**

Interestingly, the diastereomers of **60** showed distinct characteristic splitting patters at the proton of the secondary hydroxyl group, similar to those discussed in **Scheme 6**. The major diastereomer **60A** showed a finely defined splitting, leading us to believe that it undertakes a conformation with $H_{ax}$ in the axial position; while the minor diastereomer **60B** appeared as a undefined multiplet, indicating an equatorial conformation of $H_{eq}$ (**Scheme 24**). The endo/exo and facial selectivity approach of the minor diastereomer was based on the least sterically encumbered approach derived from models. Computational analysis of the two structures confirmed diasteromer **60A** as being more energetically favorable.



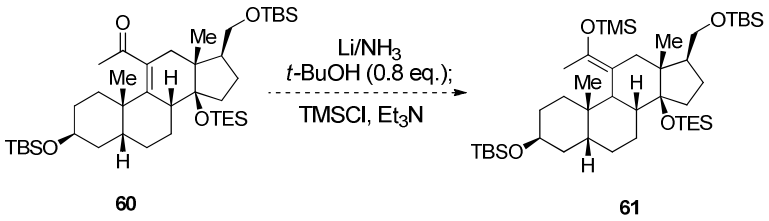

**60A**
0.0 kJ/mol

**60B**
0.45 kJ/mol

**Scheme 24.** Computational Analysis of Diastereomers of **60** B3LYP/6-31G(d) gas phase calculations.

## Future Work

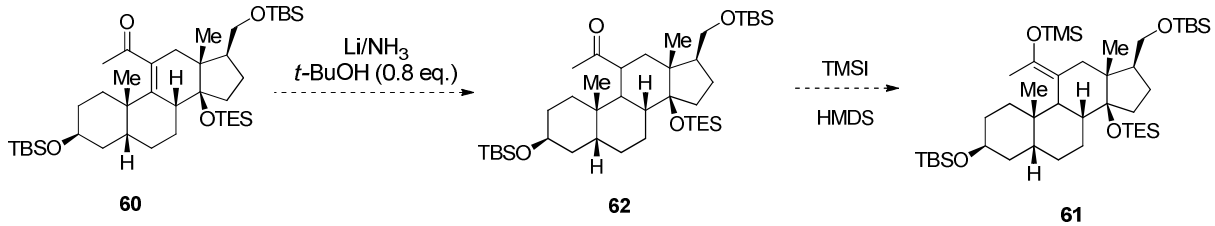
With the diene **23** and silyl enol ether **59** both accessed by enantiospecific routes and successfully combined into tetracycle **60**, it remains to be seen whether the core can be elaborated with dissolving metal reduction and trapping with TMSCl (**Scheme 25**). As previously discovered, depending on the particular configuration of the core, it may not be well suited to that line of chemistry and trapping with a silyl group may prove challenging.




**60** **61**

**Scheme 25.** Proposed Elaboration of Tetracycle **60**

In alternative approach, a stepwise method could be attempted, with tetracycle **60** undergoing reduction to the ketone **62** and the thermodynamic silyl enol ether **61** formation via the unusual, but, highly effective enolization with the Jung reagent and hexamethyldisilizane (**Scheme 26**).




**60** **62** **61**

**Scheme 26.** Proposed Stepwise Elaboration

If successfully obtained, silyl enol ether **61** could be oxidized via the sequence of ozonolysis and lead tetraacetate oxidation. Further remaining challanges would revolve around

transforming the primary silyl ether to the butenolide moiety and cleavage of the remaining silyl groups.

## Conclusion

The desired enantiopure fragments of the tetracyclic core of rhodexin A have been synthesized. The diene arising from Wieland–Miescher ketone via organoctalysis, and the dienophile exploiting carvone as the chiral source. The fragments successfully underwent the key Diels-Alder reaction, catalyzed by $Me_2AlNTf_2$, in good yield. The absolute structure configuration of the achieved intermediate remains unconfirmed.

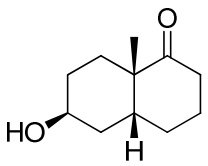
## Experimental

**General:** All reactions were carried out under an argon atmosphere unless otherwise specified. Tetrahydrofuran (THF), diethyl ether, toluene, and benzene were distilled from benzoquinone ketyl radical under an argon atmosphere. Dichloromethane (DCM), triethylamine (TEA), and diisopropylethylamine (DIPEA) were distilled from calcium hydride under an argon atmosphere. Triflimide ($Tf_2NH$) was purchased from Acros Organics in 98% purity, weighed out in a nitrogen-filled glovebox, and used as a 0.1 M solution in DCM. All other solvents or reagents were purified according to literature procedures. $^1H$ NMR spectra were recorded on Bruker spectrometers (at 400 & 500 MHz) and are reported relative to deuterated solvent signals. Data for $^1H$ NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. $^{13}C$ NMR spectra were recorded on Bruker Spectrometers (at 100 & 125 MHz). Data for $^{13}C$ NMR spectra are reported in terms of chemical shift. The chemical shifts are reported in parts per million (ppm, δ). All Fourier Transform Infrared (FTIR) samples were prepared as thin films on NaCl plates and spectra were recorded on a Perkin Elmer RX1 FTIR spectrometer and are reported in terms of frequency of absorption ($cm^{-1}$). Thin-layer chromatography (TLC) was carried out using pre-coated silica gel sheets (Merck 60 $F_{254}$). Visual detection was performed using ceric ammonium nitrate or *p*-anisaldehyde stains. Flash chromatography was performed using SilicaFlash™ P60 (60 A, 40-63 μm) silica gel from SiliCycle Inc. with compressed air.

**(4a*R*,6*S*,8a*S*) 6-hydroxy-8a-methyloctahydronaphthalen-1(2*H*)-one (29):** The ketal **28** (4.98 g, 22.2 mmol) was dissolved in THF (50 mL) and *t*-butanol (50 mL) and the resulting solution

was cooled to -78 °C using a Dry Ice and acetone bath. A Dry Ice filled condenser was added to the flask and anhydrous ammonia (100 mL) was condensed into the reaction vessel. The external cooling bath was removed and lithium wire was gradually added to the reaction until the blue color persisted for at least 30 min. To the reaction was added 1M HCl (100 mL) followed by concentrated HCl until the solution became acidic. The reaction was allowed to warm to 21 °C and stirred for 2 h. The resulting mixture was saturated with solid NaCl and extracted with ethyl acetate (3 X 50 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (1:1 hexanes/ethyl acetate) to yield the alcohol **29** (3.65 g, 90%) as a clear oil.

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




4.00 (m, 1H)

2.47-2.36 (m, 1H)

2.29-2.22 (m, 1H)

2.20-1.14 (m, 1H)

2.09-2.05 (m, 1H)

2.03-1.96 (m, 1H)

2.04-1.82 (m, 2H)

1.78-1.65 (m, 2H)

1.55-1.45 (m, 4H)

1.32-1.24 (m, 1H)

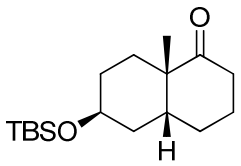
1.18 (s, 3H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 216.0, 66.2, 48.7, 40.0, 39.9, 37.7, 35.4, 30.0, 28.5, 26.3, 23.2.

$[\alpha]_D^{21}$ -0.6° (c 1.0, $CHCl_3$).

**(4a*R*,6*S*,8a*S*)-6-((1,1-Dimethylethyl)dimethylsilyloxy)-8a-methyloctahydronaphthalen-1(2H)-one (30):** The alcohol **29** (3.65 g, 20 mmol) was dissolved in anhydrous DMF (40 mL). To the solution were added imidazole (2.99 g, 44 mmol) and *t*-butyldimethylsilyl chloride (TBSCl, 4.50 g, 30 mmol). The reaction was allowed to stir for 2 h and quenched with saturated $NaHCO_3$ (100 mL) and diluted with diethyl ether (50 mL). The organics were collected and the aqueous layer was extracted with diethyl ether (2 X 50 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (10:1 hexanes/ethyl acetate) to yield ketone **30** (4.62 g, 78%) as a white glass.

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




3.91 (m, 1H)

2.38 (ddd, *J* = 14.9, 11.0, 6.8 Hz, 1H)

2.13 (ddd, *J* = 15.1, 5.3, 5.3 Hz, 3H)

1.85-1.68 (m, 3H)

1.53-1.45 (m, 1H)

1.41-1.31 (m, 4H)

1.25 (ddd, *J* = 13.3, 11.1, 4.0 Hz, 1H)

1.11 (s, 3H)

0.78 (s, 9H)

0.0 (s, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 215.9, 66.9, 48.9, 39.6, 37.8, 36.3, 20.5, 28.5, 26.3, 25.7, 25.6, 23.1, 18.0, -4.95, -4.98.

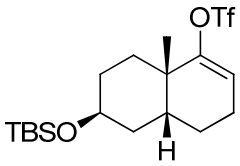
HRMS (ESI, m/z): 297.2260, calcd for $C_{17}H_{33}O_2Si$ $(M+H)^+$ 297.2250.

$[\alpha]_D^{21}$ -6.4° (c 1.0, $CHCl_3$).

**(4a*R*,6*S*,8a*S*)-6-((1,1-Dimethylethyl)dimethylsilyloxy)-8a-methyl-3,4,4a,5,6,7,8,8a-octa-hydro-naphthalen-1-yl trifluoromethanesulfonate (25):** To a solution of dry diisopropylamine (5.45 mL, 39.0 mmol) in anhydrous THF (40 mL) stirred at -78 °C under argon was added *n*-butyllithium (22.5 mL of a 1.6 M solution in hexanes, 36.0 mmol) dropwise and the resulting solution was allowed to stir for 30 min. The ketone **30** was added (8.90 g, 30.1 mmol) as a solution in THF (30 mL) over 30 min and the solution was allowed to stir for an additional 30 min. The reaction was warmed to 0 °C and stirred for 1 h. A solution of N-phenyl triflimide

($PhNTf_2$, 11.80 g, 33.0 mmol) in THF (30 mL) was added over 15 min and the reaction was stirred for 1 h at the same temperature. The reaction was quenched with saturated $NaHCO_3$ (100 mL) and diluted with diethyl ether (100 mL). The organics were collected and the aqueous layer was extracted with diethyl ether (2 X 100 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (20:1 hexanes/diethyl ether) to yield the vinyl triflate **25** (12.40 g, 96%) as a white oil.

$^1H$ NMR ($CDCl_3$, 500 MHz) δ:




5.65 (dd, *J* = 8.0, 8.0 Hz, 1H)

3.92 (m, 1H)

2.22-2.16 (m, 2H)

1.97-1.91 (m, 1H)

1.82-1.76 (m, 1H)

1.70-166 (m, 2H)

1.59-1.44 (m, 5H)

1.22 (s, 3H)

0.89 (s, 9H)

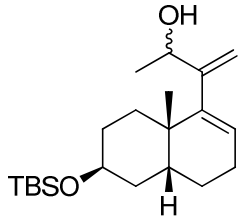
0.04 (s, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 154.9, 118.3 (q, $J$ = 312.5 Hz), 115.9, 66.7, 38.3, 37.9, 35.6, 30.4, 28.9, 25.7, 23.5, 22.5, 18.0, -4.86, -4.90, (1 upfield carbon not observed).

$[\alpha]_D^{21}$ +0.1° (c 1.0, $CHCl_3$).

**3-((4a*R*,6*S*,8a*S*)-6-((1,1-Dimethylethyl)dimethylsilyloxy)-8a-methyl-3,4,4a,5,6,7,8,8a-octa-hydronaphthalen-1-yl)but-3-en-2-ol (31):** The compound was prepared by a modification of the procedure of Han X.; Stoltz B. M.; Corey, E. J. *J. Am. Chem. Soc*. **1999**, *121*, 7600-7605. A Schlenk flask was charged with LiCl (4.75 g, 112.20 mmol) and flame dried under high vacuum. After the flask was cool $Pd(PPh_3)_4$ (2.16 g, 1.87 mmol) and CuCl (9.26 g, 93.50 mmol) were added, and the mixture was degassed (4X) under high vacuum with an Ar purge. A solution of the vinyl triflate **25** (8.0 g, 18.70 mmol) in DMSO (150 mL) was added via cannula and the resulting mixture was rigorously degassed (4X) by the freeze-thaw process (-78 to 25 °C, Ar). The reaction mixture was stirred at 21 °C for 1 h, and then heated to 60 °C for 48 h. After completion as monitored by TLC (10:1 hexanes/ethyl acetate), the reaction was cooled to 21 °C, diluted with diethyl ether (1.0 L) and washed with a mixture of brine (200 mL) and 5% aqueous $NH_4OH$ (40 mL). The aqeous layer was extracted with diethyl ether (2 X 300 mL) and the combined organic layers were washed with water (2 X 200 mL) and brine (2 X 200 mL) and then dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (10:1 hexanes/ethyl acetate) to yield the allylic alcohol **31** (5.82 g, 87%) as a 4:5 mixture of inseparable diastereomers (determined by $^1$H NMR analysis).

$^{1}$H NMR ($CDCl_3$, 500 MHz) δ:




5.48-5.46 (dd, *J* = 3.9, 3.6 Hz, 0.44H)

5.46-5.45 (dd, *J* = 3.8, 3.7 Hz, 0.56H)

5.17-5.16 (m, 0.56H)

5.14-5.13 (m, 0.44 H)

4.85-4.83 (m, 0.44H)

4.82-4.80 (m, 0.56H)

4.46 (q, *J* = 6.5 Hz, 0.56H)

4.39 (q, *J* = 6.8 Hz, 0.44H)

3.96-3.90 (m, 1H)

2.07-1.99 (m, 2H)

1.89-1.74 (m, 2H)

1.66-1.60 (m, 1H)

1.57-1.36 (m, 6H)

1.31 (d, *J* = 6.7 Hz, 1.30H)

1.26 (d, *J* = 6.4 Hz, 1.70H)

1.18 (s, 1.3 H)

1.15 (s, 1.7H)

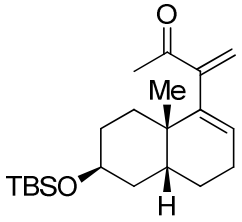
0.88 (s, 9H)

0.04-0.00 (m, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 155.1, 129.4, 127.1, 127.0, 126.6, 123.5, 111.8, 110.5, 69.1, 68.6, 67.1, 36.5, 36.4, 31.2, 31.0, 30.96, 25.8, 25.8, 24.0, 23.8, 22.6, 21.3, 18.08, 18.06, -4.9.

**3-((4a*R*,6*S*,8a*S*)-6-((1,1-Dimethylethyl)dimethylsilyloxy)-8a-methyl-3,4,4a,5,6,7,8,8a-octa-hydronaphthalen-1-yl)but-3-en-2-one (23):** The allylic alcohol **31** (11.7 g, 33.3 mmol) was dissolved in DCM (330 mL) and pyridine (26.8 mL, 332.5 mmol) was added. The resulting solution was cooled to 0 °C and Dess Martin periodinane (21.2 g, 49.9 mmol) was added gradually over 5 min. The mixture was allowed to stir for 2 h. After completion as monitored by TLC (10:1 hexanes/ethyl acetate), the reaction was diluted with diethyl ether (400 mL) and filtered through a pad of Celite. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (20:1 hexanes/ethyl acetate with 1% TEA) to yield the dienone **23** (10.84 g, 94%) as a clear oil.

$^{1}$H NMR ($CDCl_3$, 500 MHz) δ:




5.85 (bs, 1H)

5.46 (d, *J* = 1.3 Hz, 1H)

5.40 (dd, *J* = 3.8, 3.8 Hz, 1H)

3.88-3.83 (m, 1H)

2.30 (s, 3H)

` 2.08-2.04 (m, 2H)

1.78-1.69 (m, 2H)

1.61-1.54 (m, 3H)

1.47-1.34 (m, 4H)

1.00 (s, 3H)

0.86 (s, 9H)

0.009 (s, 3H)

0.003 (s, 3H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 200.8, 151.7, 142.3, 127.7, 124.6, 67.3, 38.1, 36.7, 31.4, 30.9, 26.9, 25.84, 25.77, 24.5, 24.1, 18.1, -4.9, (1 upfield carbon not observed).

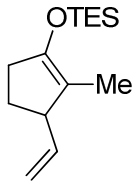
FTIR (DCM): 3052, 2982, 2680, 2402, 2302, 1676, 1598, 1536, 1420, 1264, 894, 730 $cm^{-1}$.

HRMS (ESI, m/z): 349.2560, calcd for $C_{21}H_{37}O_2Si$ $(M+H)^+$ 349.2563.

$[\alpha]_D^{21}$ -12.5° (c 1.0, $CHCl_3$).

**Triethyl((2-methyl-3-ethenylcyclopent-1-en-1-yl)oxy)silane (22):** The compound was prepared by a modification of the procedure of Funk, R. L., Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5253. A suspension of CuI (9.5 g, 49.9 mmol) in 100 mL THF was cooled to -20 ºC under an atmosphere of argon and vinylmagnesium bromide was added (100 mL of 1.0 M solution in THF, 100 mmol). The resulting black mixture was allowed to stir for 0.5 h and subsequently cooled to -40 ºC. To this solution was added 2-methyl-2-cyclopenten-1-one (4.0g, 41.6 mmol) via cannula as a solution in 10 mL THF and the reaction was allowed to stir for 1 h. The reaction was cooled to -78 ºC and HMPA (75 mL, 416 mmol) followed by TESCl (21 mL, 125 mmol) were added and the reaction was allowed to warm to 21 ºC overnight. The reaction was quenched with a minimal amount of saturated $NaHCO_3$ until no further bubbling was apparent. The crude reaction mixture was filtered over Celite, and the filter cake was washed with hexanes. The filtrates were washed with saturated $NaHCO_3$ (100 mL). The organics were collected and the aqueous layer was extracted with hexanes (2 X 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), and then dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was distilled under reduced pressure (49 °C, 0.5 mmHg) to yield the pure silyl enol ether (6.44 g, 65%).

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




5.62 (ddd, *J* = 21.3, 12.2, 10.6 Hz, 1H)

4.98 (dd, *J* = 21.3, 2.5 Hz, 1H)

4.91 (dd, *J* = 12.5, 2.5 Hz, 1H)

3.03-2.94 (m, 1H)

2.36-2.24 (m, 2H)

2.11-2.01 (m, 1H)

1.61-1.53 (m, 1H)

1.47 (s, 3H)

0.99 (t, $J$ = 10 Hz, 9H)

0.65 (q, $J$ = 10 Hz, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 147.8, 142.9, 114.6, 113.3, 40.1, 32.7, 27.5, 10.3, 6.6, 5.4.

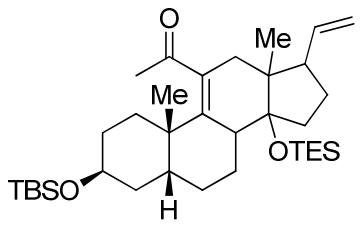
FTIR (DCM): 2991, 1685, 1630, 1245, 1211, 1093, 989, 839 $cm^{-1}$.

**1-((3*S*,5*R*,10*S*)-3-((1,1-Dimethylethyl)dimethylsilyloxy)-10,13-dimethyl-14-(triethylsilyloxy)-17-vinyl-2,3,4,5,6,7,8,10,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-11-yl)ethanone (32):** The catalyst $MeAl(NTf_2)_2$ was prepared by addition of $Tf_2NH$ (0.5 mL of 0.1 M solution in DCM, 0.05 mmol) to trimethylaluminum ($Me_3Al$, 0.3 mL of 0.1 M solution in toluene, 0.03 mmol) in 4 mL of DCM at 21 °C, and the solution was allowed to stir for 15 min. The reaction was cooled to 0 ºC and the dienone **23** (0.5 mmol) and the silyl enol ether **22** (0.65 mmol) were added in 1 mL of DCM. The reaction was warmed to 21 ºC and allowed to stir for 2 h. The reaction was quenched with addition of TEA (0.5 mL) and filtered through a plug of silica gel. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (2:1 hexanes/benzene to benzene) to yield the tetracycles as a separable 1:1 mixture of diastereomers.

**32A:** 128.5 mg, 45%.

$^1$H NMR ($CDCl_3$, 500 MHz) δ:

5.72 (ddd, $J$ = 16.4, 9.2, 9.2 Hz, 1H)



4.99 (d, $J$ = 10 Hz, 1H)

4.92 (d, $J$ = 17.3 Hz, 1H)

3.96 (m, 1H)

2.31 (s, 3H)

2.30-2.24 (m, 1H)

2.17-2.11 (m, 1H)

2.01 (dd, $J$ = 16.5, 3.7 Hz, 1H)

1.93-1.76 (m, 4H)

1.71-1.53 (m, 8H)

1.41 (bd, $J$ = 12.9 Hz, 1H)

1.38-1.32 (m, 1H)

1.30-1.22 (m, 2H)

1.18 (s, 3H)

0.94 (t, $J$ = 8 Hz, 9H)

0.86 (s, 9H)

0.78 (s, 3H)

0.62 (q, $J$ = 8 Hz, 6H)

0.00 (s, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 208.5, 140.4, 132.0, 128.4, 115.7, 83.9, 67.4, 46.2, 41.1, 38.1, 36.5, 34.3, 32.2, 31.6, 30.9, 30.2, 28.9, 27.1, 25.9, 25.8, 22.7, 21.9, 18.5, 18.1, 14.2, 7.4, 6.9, −4.80, -4.81.

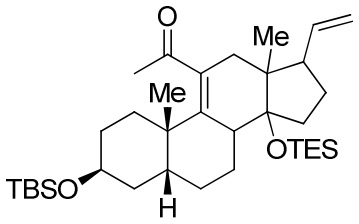
FTIR (DCM): 3052, 2984, 2952, 2926, 2874, 2306, 1686, 1420, 1264, 1138, 1080, 1056 $cm^{-1}$.

HRMS (ESI, m/z): 587.4337, calcd for $C_{35}H_{62}O_3Si_2$ $(M+H)^+$ 587.4316.

$[\alpha]_D^{21}$ +4.9° (c 1.0, $CHCl_3$).

**32B:** 134.2 mg, 47%.

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




5.66 (ddd, *J* = 16.8, 9.2, 8.3 Hz, 1H)

4.97 (d, *J* = 10 Hz, 1H)

4.91 (d, *J* = 17 Hz, 1H)

3.82-3.75 (m, 1H)

2.29 (s, 3H)

2.29-2.24 (m, 1H)

2.0 (m, 2H)

1.85-1.75 (m, 4H)

1.73-1.55 (m, 7H)

1.52-1.43 (m, 3H)

1.31-1.18 (m, 5H)

0.95 (t, *J* = 7.9 Hz, 9H)

0.88 (s, 9H)

0.75 (s, 3H)

0.62 (q, *J* = 7.9 Hz, 6H)

0.04 (s, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 210.5, 139.9, 137.2, 132.2, 116.0, 83.8, 67.5, 46.0, 45.7, 43.0, 42.7, 40.0, 38.4, 34.9, 34.4, 32.6, 32.0, 30.5, 29.9, 27.4, 26.0, 25.9, 25.6, 18.4, 18.3, 7.4, 7.0, -4.59, -4.63.

FTIR (DCM): 3054, 2978, 2950, 2922, 2880, 2301, 1690, 1411, 1265, 1138, 1072, 1056 $cm^{-1}$.

HRMS (ESI, m/z): 587.4307, calcd for $C_{35}H_{62}O_3Si_2$ $(M+H)^+$ 587.4316.

$[\alpha]_D^{21}$ +12.5° (c 1.0, $CHCl_3$).

**1-((3*S*,5*R*,10*S*)-3-((1,1-Dimethylethyl)dimethylsilyloxy)-17-(1,2-dihydroxyethyl)-10,13-dimethyl-14-(triethylsilyloxy)-2,3,4,5,6,7,8,10,12,13,14,15,16,17-tetradecahydro-1*H*-cyclo-**

**penta[*a*]phenanthren-11-yl)ethanone (33X):** The cycloadduct **32A** (0.50 g, 0.85 mmol) was dissolved in *t*-BuOH/THF/$H_2O$ (10:2:1, 10 mL) and *N*-methylmorpholine-*N*-oxide (NMO, 0.13 g, 1.12 mmol) was added. To the solution was added osmium tetroxide ($OsO_4$, 0.085 mL of 0.1 M solution in $H_2O$, 0.0085 mmol) and the reaction was allowed to stir for 14 h. The reaction was diluted with ethyl acetate (20 mL) and water (40 mL). The organic layer was collected and the aqeous layer was extracted with ethyl acetate (2 X 20 mL), the combined organic layers were washed with water (10 mL), brine (20 mL), and dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (2:1 hexanes/ethyl acetate) to yield the diol (0.79 g, 93%) as a 4:1 (determined by $^1$H NMR analysis) mixture of separable diastereomers **33XAA** & **33XAB** (structures unassigned).

**33XAA:**

$^1$H NMR ($CDCl_3$, 500 MHz) δ:

4.01-3.97 (m, 1H)

3.67-3.60 (m, 3H)

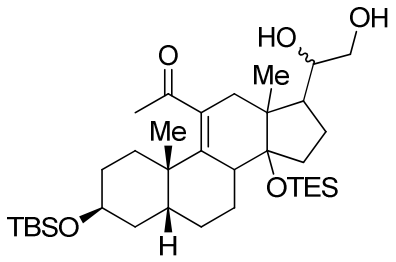
3.31 (m, 1H)

2.36 (s, 3H)

2.16-2.13 (m, 2H)

2.06 (bdd, *J* = 7.8, 7.8 Hz, 1H)

1.94-1.87 (m, 1H)



1.83-1.73 (m, 4H)

1.67-1.56 (m, 5H)

1.55-1.53 (m, 2H)

1.45-1.41 (m, 1H)

1.36-1.30 (m, 1H)

1.29-1.26 (m, 4H)

1.17 (s, 3H)

0.94 (t, $J$ = 8.0 Hz, 9H)

0.91 (s, 3H)

0.86 (s, 9H)

0.61 (q, $J$ = 8.0 Hz, 6H)

0.000 (s, 3H)

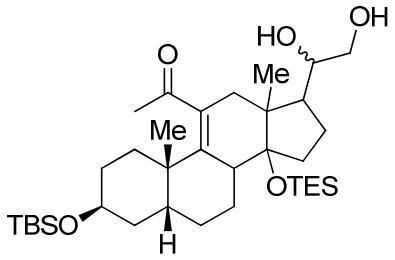
-0.004 (s, 3H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 209.8, 132.5, 83.7, 74.8, 67.3, 66.3, 45.4, 41.8, 41.2, 40.4, 37.9, 36.4, 34.7, 33.1, 32.0, 30.9, 30.2, 29.2, 27.3, 25.9, 22.6, 21.5, 18.1, 17.9, 7.4, 7.0, -4.8, (1 olefin carbon not observed).

HRMS (ESI, m/z): 643.4207, calcd for $C_{35}H_{64}O_5Si_2$ $(M+Na)^+$ 643.4190.

$[\alpha]_D^{21}$ -6.1° (c 1.0, $CHCl_3$).

**33XAB:**




$^1$H NMR ($CDCl_3$, 500 MHz) δ:

3.84-3.76 (m, 1H)

3.71-3.66 (m, 1H)

3.53-3.45 (m, 2H)

3.37-2.32 (m, 1H)

2.30 (s, 3H)

2.16 (bd, *J* = 17.5 Hz, 1H)

1.88-1.50 (m, 14H)

1.48-1.40 (m, 2H)

1.35-1.30 (m, 1H)

1.29-1.21 (m, 2H)

1.16 (s, 3H)

1.02-0.95 (m, 12H)

0.86 (s, 9H)

0.71 (q, $J$ = 6.5 Hz, 6H)

0.02 (s, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 210.1, 131.5, 125.5, 85.1, 71.4, 67.3, 65.7, 58.5, 45.5, 40.4, 39.9, 38.9, 37.1, 31.6, 31.4, 30.3, 30.1, 29.7, 26.6, 25.9, 23.5, 22.7, 20.8, 18.2, 14.2, 7.4, 6.8, -4.71, –4.74.

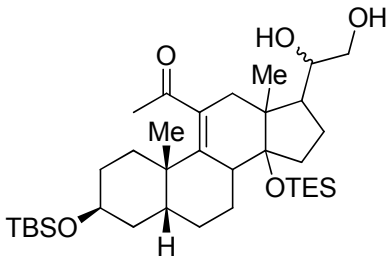
HRMS (ESI, m/z): 643.4211, calcd for $C_{35}H_{64}O_5Si_2$ $(M+Na)^+$ 643.4190

$[\alpha]_D^{21}$ -16.6° (c 1.0, $CHCl_3$).

**1-((3*S*,5*R*,10*S*)-3-((1,1-Dimethylethyl)dimethylsilyloxy)-17-(1,2-dihydroxyethyl)-10,13-dimethyl-14-(triethylsilyloxy)-2,3,4,5,6,7,8,10,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-11-yl)ethanone (33XB):** The Cycloadduct **32B** (0.50 g, 0.85 mmol) was dissolved in *t*-BuOH/THF/$H_2O$ (10:2:1, 10 mL) and *N*-methylmorpholine-*N*-oxide (NMO, 0.13 g, 1.12 mmol) was added. To the solution was added osmium tetroxide ($OsO_4$, 0.085 mL of 0.1 M solution in $H_2O$, 0.0085 mmol) and the reaction was allowed to stir for 14 h. The reaction was diluted with ethyl acetate (20 mL) and water (40 mL). The organic layer was collected and the aqueous layer was extracted with ethyl acetate (2 X 20 mL), the combined organic layers were washed with water (10 mL), brine (20 mL), and dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (2:1 hexanes/ethyl acetate) to yield the diol **33XB** (0.79 g, 93%) as

a 4:1 mixture (determined by $^1$H NMR analysis) of inseparable diastereomers (structures unassigned).

**33XB:**




$^1$H NMR ($CDCl_3$, 500 MHz) δ:

3.81-3.73 (m, 1H)

3.62-3.58 (m, 0.25H)

3.57-3.45 (m, 2.50H)

3.36-3.30 (m, 0.25H)

2.96-2.90 (m, 0.75H)

2.79-2.71 (m, 1H)

2.61-2.57 (m, 0.25H)

2.33 (s, 2.25H)

2.31 (s, 0.75H)

2.12-2.03 (m, 2H)

1.95-1.74 (m, 7H)

1.71-1.56 (m, 5H)

1.55-1.40 (m, 3.3H)

1.37-1.32 (m, 0.7H)

1.27-1.21 (m, 4H)

0.99-0.92 (m, 9H)

0.88-0.84 (m, 12H)

0.69-0.57 (m, 6H)

0.04 (s, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 212.9(A), 212.8(B), 138.7(A), 137.4(B), 132.4(B), 130.9(A), 84.5(A), 83.6(B), 74.8(B), 72.9(A), 67.40(B), 67.38(A), 66.1(B), 64.8(A), 44.9(B), 44.7(A), 43.3, 43.3, 43.0, 42.7, 42.1, 40.3, 40.2, 39.9, 38.2, 37.9, 35.4, 34.0, 33.3, 32.5, 32.4, 32.1, 31.8, 30.9, 30.7, 30.3, 30.1, 29.7, 28.0, 27.3, 26.0, 25.6, 25.4, 22.61, 22.55, 18.3, 18.1, 17.8, 7.4, 7.3, 7.0, 6.9, -4.59, -4.63.

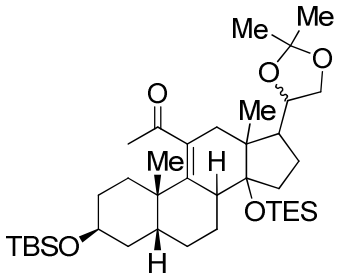
HRMS (ESI, m/z): 643.4216, calcd for $C_{35}H_{64}O_5Si_2$ $(M+Na)^+$ 643.4190.

**1-((3*S*,5*R*,10*S*)-3-((1,1-Dimethylethyl)dimethylsilyloxy)-17-(2,2-dimethyl-1,3-dioxolan-4-yl)-10,13-dimethyl-14-((triethylsilyl)oxy)-2,3,4,5,6,7,8,10,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-11-yl)ethanone (33):** In a typical procedure, one of the isomers of diol **33X** was dissolved in dimethoxypropane (5 ml/mmol) and camphorsulfonic acid (CSA, 2 mol%) was added. The reaction was allowed to stir for 2 h, quenched with saturated $NaHCO_3$ (10 mL/mmol) and diluted with diethyl ether (10 mL/mmol). The organic layer was collected and the aqueous layer was extracted with diethyl ether (2 X 10 mL/mmol). The combined

organic layers were washed with brine (20 mL/mmol), and then dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (10:1 hexanes/ethyl acetate) to give acetonide **33** (85-95%) as a clear oil.

**33AA:**

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




4.01-3.98 (m, 2H)

3.98-3.94 (m, 1H)

3.45 (dd, *J* = 8.0, 8.0 Hz, 1H)

2.38 (s, 3H)

2.12-2.02 (m, 3H)

1.95-1.88 (m, 1H)

1.84-1.75 (m, 3H)

1.69-1.50 (m, 7H)

1.44-1.40 (m, 1H)

1.34 (s, 3H)

1.33-1.32 (m, 1H)

1.31 (s, 3H)

1.28-1.20 (m, 3H)

1.18 (s, 3H)

9.94 (t, *J* = 8.0 Hz, 9H)

0.91 (s, 3H)

0.86 (s, 9H)

0.60 (q, *J* = 8.0 Hz, 6H)

-0.006 (s, 3H)

-0.009 (s, 3H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 208.5, 132.4, 128.8, 109.1, 83.7, 76.8, 69.6, 67.4, 45.2, 42.5, 41.2, 41.1, 37.8, 36.3, 34.3, 33.2, 32.4, 30.7, 30.5, 29.3, 27.2, 27.0, 25.9, 25.8, 21.9, 21.6, 18.3, 18.1, 7.4, 7.0, -4.8, -4.9.

HRMS (ESI, m/z): 683.4534, calcd for $C_{38}H_{68}O_5Si_2$ $(M+Na)^+$ 683.4503.

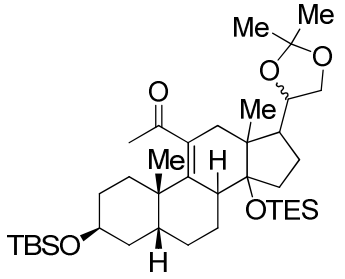
$[\alpha]_D^{21}$ -4.4° (c 1.0, $CHCl_3$).

**33AB:**

$^1$H NMR ($CDCl_3$, 500 MHz) δ:

4.05-3.99 (m, 1H)

3.97-3.94 (m, 1H)



3.93-3.89 (m, 1H)

3.38 (bdd, $J$ = 8.7, 6.5 Hz, 1H)

2.28 (s, 3H)

2.19-2.10 (m, 2H)

1.85-1.76 (m, 7H)

1.67-1.56 (m, 6H)

1.51-1.44 (m, 2H)

1.35 (s, 3H)

1.33 (s, 3H)

1.30-1.25 (m, 2H)

1.16 (s, 3H)

0.94 (t, $J$ = 7.9 Hz, 9H)

0.86 (s, 9H)

0.85 (s, 3H)

0.62 (q, $J$ = 7.9 Hz, 6H)

0.00 (s, 6H).

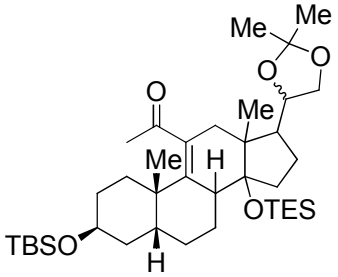
$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 208.4, 131.6, 107.7, 104.6, 84.2, 77.6, 68.9, 67.3, 44.7, 41.0, 40.8, 38.2, 36.7, 36.2, 33.9, 31.7, 31.1, 30.1, 28.6, 26.9, 26.7, 26.1, 25.9, 22.7, 22.1, 20.7, 19.1, 18.1, 7.4, 6.9, -4.80, -4.81.

HRMS (ESI, m/z): 683.4537, calcd for $C_{38}H_{68}O_5Si_2$ $(M+Na)^+$ 683.4503.

$[\alpha]_D^{21}$ -11.7° (c 1.0, $CHCl_3$).

**33BA:**

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




4.01-3.92 (m, 2H)

3.81-3.75 (m, 1H)

3.40 (bdd, *J* = 7.5, 6.7 Hz, 1H)

2.30 (s, 3H)

2.15 (d, *J* = 17.0 Hz, 1H)

2.02 (dd, *J* = 17.0, 3.1 Hz, 1H)

1.94 (bd, *J* = 12.2 Hz, 1H)

1.81-1.71 (m, 5H)

1.69-1.54 (m, 6H)

1.49-141 (m, 3H)

1.33 (s, 3H)

1.30 (s, 3H)

1.29-1.24 (m, 2H)

1.21 (s, 3H)

0.93 (t, *J* = 7.6 Hz, 9H)

0.90 (s, 3H)

0.87 (s, 9H)

0.60 (q, *J* = 7.6 Hz, 6H)

0.03 (s, 6H).

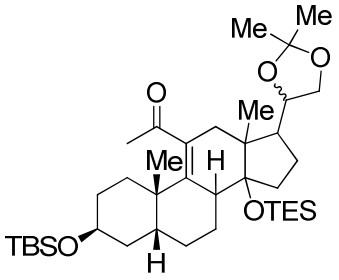
$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 209.8, 136.1, 132.8, 109.2, 83.7, 78.0, 69.3, 67.4, 44.9, 43.0, 42.7, 42.4, 40.0, 38.4, 35.0, 33.6, 32.6, 32.0, 30.4, 29.8, 27.2, 26.9, 26.2, 26.0, 25.9, 22.0, 18.31, 18.30, 7.3, 7.0, -4.61, -4.63.

HRMS (ESI, m/z): 684.4485, calcd for $C_{38}H_{68}O_5Si_2$ $(M+Na)^+$ 683.4503.

$[\alpha]_D^{21}$ +9.7° (c 1.0, $CHCl_3$).

**33BB:**

$^{1}$H NMR ($CDCl_3$, 500 MHz) δ:




3.97-3.90 (m, 2H)

3.80-3.73 (m, 1H)

3.39-3.34 (m, 1H)

2.28 (s, 3H)

2.12 (dd, *J* = 17.1, 3.1 Hz, 1H)

1.98 (bd, *J* = 12.0 Hz, 1H)

1.86-1.76 (m, 6H)

1.75-1.71 (m, 1H)

1.69-1.57 (m, 4H)

1.54-1.42 (m, 5H)

1.34 (s, 3H)

1.33 (s, 3H)

1.27-1.19 (m, 1H)

1.22 (s, 3H)

0.94 (t, *J* = 7.8 Hz, 9H)

0.87 (s, 9H)

0.82 (s, 3H)

0.62 (q, $J$ = 7.8 Hz, 6H)

0.04 (s, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 210.5, 137.9, 131.6, 107.6, 83.9, 77.8, 68.7, 67.4, 44.4, 43.1, 43.0, 42.9, 40.0, 38.3, 35.9, 33.7, 32.7, 32.0, 30.7, 30.0, 27.5, 26.6, 26.1, 26.0, 25.5, 23.0, 18.9, 18.3, 7.3, 7.0, -4.59, -4.63.

HRMS (ESI, m/z): 683.4513, calcd for $C_{38}H_{68}O_5Si_2$ $(M+Na)^+$ 683.4503.

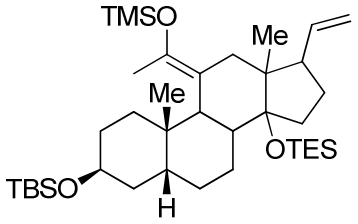
$[\alpha]_D^{21}$ +13.6° (c 1.0, $CHCl_3$).

**((1,1-Dimethylethyl)dimethylsilyloxy)-(((3*S*,5*R*,10*S*,*E*)-10,13,14-((triethylsilyl)oxy)-11-(1-((trimethylsilyl)oxy)ethylidene)-17-vinylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)dimethylsilane (34):** Anhydrous ammonia ($NH_3$, 10 mL) was condensed via a coldfinger filled with a mixture of dry ice and acetone unto strips of lithium (Li, 0.0265 g, 3.8 mmol) and allowed to reflux for 1 h and subsequently cooled to -78 °C. A solution of the tetracycle **32A** (0.741 g, 1.26 mmol) and *tert*-butanol (*t*-BuOH, 0.074 g, 1.08 mmol) in THF (10 mL) was added via cannula. The reaction was allowed to stir for 30 min and any unreacted lithium was quenched with freshly distilled isoprene until the blue color dispersed completely. The ammonia was removed under a flow of argon and with gradual warming to room temperature. The remaining solvent was removed under vacuum (0.1 mmHg) for 30 min. The white residue was dissolved in THF (10 mL) and cooled to 0 °C. To the reaction was added a mixture of

trimethylchlorosilane (TMSCl, 0.959 mL, 7.56 mmol) and triethylamine (1.05 mL, 7.56 mmol) after removing any precipitate via centrifuge and the reaction was allowed to stir for 1 h. The reaction was quenched with saturated $NaHCO_3$ (10 mL) and diluted with hexanes (20 mL). The organic layer was collected and the aqueous layer was extracted with hexanes (2 X 20 mL). The combined organic layers were washed with water (50 ml) and brine (50 mL), and then dried over anhydrous $Na_2SO_4$. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (50:1 hexanes/diethyl ether & 3% TEA) to yield the silyl enol ether **34** (0.750 g, 90%) as a clear oil.

$^1$H NMR ($CDCl_3$, 500 MHz) δ:

5.66 (ddd, *J* = 17.3, 10.4, 7.1 Hz, 1H)




5.00-4.94 (m, 2H)

3.88-3.82 (m, 1H)

2.45-2.36 (m, 3H)

2.21 (bd, *J* = 7.1 Hz, 1H)

2.01-1.81 (m, 3H)

1.81-1.78 (m, 1H)

1.80 (s, 3H)

1.72-1.64 (m, 2H)

1.63-1.56 (m, 4H)

1.52-1.47 (m, 1H)

1.44-1.33 (m, 3H)

1.25 (s, 3H)

1.20-1.16 (m, 1H)

1.10-1.06 (m, 1H)

0.99 (t, $J$ = 8.0 Hz, 9H)

0.98 (s, 3H)

0.88 (s, 9H)

0.78-0.64 (m, 6H)

0.14 (s, 9H)

0.06 (s, 3H)

0.05 (s, 3H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 142.9, 140.4, 115.6, 115.0, 86.8, 68.2, 50.1, 49.0, 45.0, 44.7, 40.0, 38.6, 38.4, 35.7, 32.1, 31.3, 29.7, 27.9, 27.4, 26.9, 26.0, 25.6, 24.5, 19.9, 18.5, 7.6, 7.2, 0.8, -4.6, -4.8.

$[\alpha]_{\mathrm{D}}^{21}$ +8.68° (c 1.0, PhH).

**1-((3*S*,5*R*,10*S*,*E*)-3-((1,1-Dimethylethyl)dimethylsilyloxy)-10,13-dimethyl-14-((triethylsilyl)-oxy)-11-(1-((trimethylsilyl)oxy)ethylidene)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)ethane-1,2-diol (35):** The silyl enol ether **34** (0.10 g, 0.15 mmol) and *N*-methylmorpholine-*N*-oxide (NMO, 0.023 g, 0.20 mmol) were dissolved in acetone (5 mL). To the solution was added osmium tetroxide ($OsO_4$, 0.015 mL of 0.1 M solution in $H_2O$, 0.0015 mmol) and pyridine (0.012 mL, 0.15 mmol). The reaction was heated to 60 °C for 14 h. The reaction was diluted with ethyl acetate (20 mL) and water (40 mL). The organic layer was collected and the aqueous layer was extracted with ethyl acetate (2 X 20 mL), the combined organic layers were washed with water (10 mL), brine (20 mL), and dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (2:1 hexanes/ethyl acetate & 3% TEA) to yield the diol **35** (0.021 g, 20%) as a clear oil.

$^1$H NMR ($CDCl_3$, 500 MHz) δ:

3,88-3.79 (m, 1H)

3.63 (dd, *J* = 10.8, 2.4 Hz, 1H)

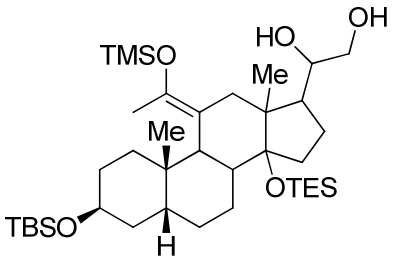
3.59-3.54 (m, 1H)

3.25 (dd, *J* = 10.8, 7.2 Hz, 1H)

2.65 (bd, *J* = 7.3 Hz, 1H)

2.37-2.30 (m, 2H)

2.07-2.04 (m, 1H)



1.96-1.88 (m, 4H)

1.86-1.81 (m, 1H)

1.84 (s, 3H)

1.67-1.59 (m, 3H)

1.46-1.37 (m, 5H)

1.26-1.23 (m, 1H)

1.15-1.09 (m, 4H)

1.00 (s, 3H)

0.99 (s, 3H)

0.97 (t, $J$ = 9.0 Hz, 9H)

0.88 (s, 9H)

0.78-0.66 (m, 6H)

0.75 (q, $J$ = 9.0 Hz, 3H)

0.66 (q, $J$ = 9.0 Hz, 3H)

0.16 (s, 9H)

0.06 (s, 3H)

0.04 (s, 3H).

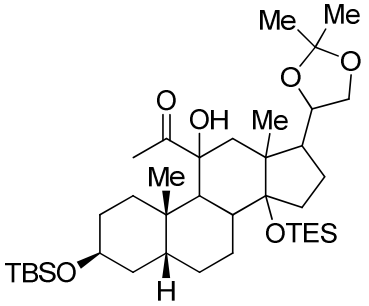
$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 142.3, 115.3, 86.8, 75.1, 68.4, 66.3, 48.8, 45.9, 45.0, 40.3, 38.6, 38.5, 38.1, 35.3, 34.4, 32.0, 27.8, 27.4, 27.0, 26.1, 26.0, 25.8, 22.8, 19.6, 18.9, 18.5, 7.6, 7.2, –4.6, -4.8.

**1-((3*S*,5*R*,10*S*)-3-((1,1-Dimethylethyl)dimethylsilyloxy)-17-(2,2-dimethyl-1,3-dioxolan-4-yl)-11-hydroxy-10,13-dimethyl-14-((triethylsilyl)oxy)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-11-yl)ethanone (36):** The diol **35** (0.346 g, 0.47 mmol) was dissolved in DCM (5 mL). The solution was cooled to -78 °C and ozone was bubbled through the solution until a light blue color appeared. Triphenylphosphine ($Ph_3P$, 0247 g, 0.94 mmol) was added and the solution was allowed to warm to room temperature and stirred for 1 h. To the reaction were added dimethoxypropane (5 ml) and camphorsulfonic acid (CSA, 0.002 g, 0.01 mmol). The reaction was allowed to stir for 2 h. The reaction was quenched with saturated $NaHCO_3$ (10 mL) and diluted with diethyl ether (10 mL). The organic layer was collected and the aqueous layer was extracted with diethyl ether (2 X 10 mL). The combined organic layers were washed with brine (50 mL) and then dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (10:1 hexanes/ethyl acetate) to yield the acetonide **36** (0.128 g, 40%) as a clear oil.

$^1$H NMR ($CDCl_3$, 500 MHz) δ:

4.01-3.91 (m, 2H)

3.85-3.77 (m, 1H)



3.58 (bs, 1H)

3.41 (dd, $J$ = 8.6, 8.3 Hz, 1H)

3.02-2.94 (m, 1H)

2.31 (s, 3H)

2.26-2.19 (m, 2H)

2.13-2.07 (m, 2H)

2.01-1.92 (m, 2H)

1.88-1.82 (m, 2H)

1.79-1.72 (m, 1H)

1.68 (bd, $J$ = 15.7 Hz, 1H)

1.54-1.37 (m, 6H)

1.34 (s, 3H)

1.32 (s, 3H)

1.27-1.19 (m, 3H)

1.04-0.96 (m, 9H)

0.99 (s, 3H)

0.88 (s, 3H)

0.87 (s, 9H)

0.75 (q, $J$ = 8.0 Hz, 3H)

0.68 (q, $J$ = 8.0 Hz, 3H)

0.04 (s, 3H)

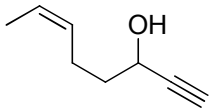
0.03 (s, 3H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 217.2, 109.3, 85.9, 82.5, 76.6, 69.4, 68.0, 57.9, 47.5, 45.8, 45.4, 38.6, 38.0, 37.4, 36.8, 35.3, 31.7, 28.9, 27.55, 27.46, 26.69, 26.67, 26.1, 26.0, 23.8, 22.5, 19.3, 18.4, 7.6, 7.2, -4.6, -4.8.

**(*Z*)-Oct-6-en-1-yn-3-ol (41X):** A solution of dimethyl sulfoxide (DMSO, 6.24 mL, 80 mmol) in DCM (200 mL) was cooled to -78 °C under the atmosphere of argon. Oxalyl chloride ($(COCl)_2$, 3.50 mL, 40 mmol) was added gradually, followed by *cis*-4-hexen-1-ol (2.0 g, 20.0 mmol). Triethylamine (14 mL, 200 mmol) was added dropwise to the turbid mixture. The reaction was allowed to stir for 1 h at -78 °C, warmed to 21 °C and allowed to stir for an additional 1 h. The reaction was quenched with saturated $NH_4Cl$ (100 mL). The organic layer was collected and the aqueous layer was extracted with diethyl ether (2 X 50 mL). The combined organic layers were washed with brine (20 mL), and then dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was filtered through a plug of silica gel eluting with dry diethyl ether to give the crude aldehyde as a clear oil, which was used without further purification in the next reaction.

The crude aldehyde was dissolved in dry THF (40 mL) and anhydrous cerium trichloride ($CeCl_3$, 0.492 g, 2 mmol) was added. The resulting suspension was cooled to 0 °C and ethynyl magnesium bromide (52 mL of 0.5 M solution, 26 mmol) was added gradually. The reaction was allowed to warm to 21 °C, stirred for 1 h, and quenched with saturated $NaHCO_3$ (20 mL) and diluted with diethyl ether (20 mL). The organic layer was collected and the aqueous layer was extracted with diethyl ether (2 X 20 mL). The combined organic layers were washed with brine (20 mL), and then dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (10:1 hexanes/ethyl acetate) to give the alcohol **41X** (1.13 g, 46%) as a clear oil.

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




4.22-5.44 (m, 1H)

5.41-5.32 (m, 1H)

4.40-4.33 (m, 1H)

2.47 (d, *J* = 2.1 Hz, 1H)

2.41 (bd, *J* = 5.6 Hz, 1H)

2.25-2.17 (m, 2H)

1.79-1.72 (m, 2H)

1.61 (d, *J* = 6.2 Hz, 3H).

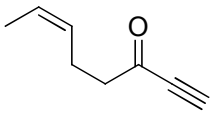
$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 129.0, 125.0, 84.8, 72.9, 61.7, 37.1, 22.4, 12.6.

**(*Z*)-Oct-6-en-1-yn-3-one (41):** The alcohol **41X** (11.7 g, 9.1 mmol) was dissolved in DCM (40 mL). The resulting solution was cooled to 0 °C and Dess Martin periodinane (5.8 g, 13.7 mmol) was added gradually over 5 min. The mixture was allowed to warm to 21 °C and stirred for 2 h. After completion of the reaction as monitored by TLC (10:1 hexanes/ethyl acetate), the reaction was diluted with diethyl ether (40 mL) and filtered through a pad of Celite. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (20:1 hexanes/ethyl acetate) to yield the octynone **41** (1.05 g, 93%) as a clear oil.

$^1$H NMR ($CDCl_3$, 500 MHz) δ:

5.54-5.46 (m, 1H)

5.36-5.28 (m, 1H)




3.22 (s, 1H)

2.64 (t, *J* = 7.4 Hz, 2H)

2.41 (dt, *J* = 7.4, 7.3 Hz, 2H)

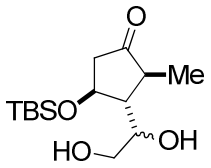
1.62 (d, *J* = 7.5 Hz, 3H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 186.7, 127.5, 125.6, 81.2, 78.4, 45.1, 21.2, 12.6.

**4-((1,1-Dimethylethyl)dimethylsilyloxy)-3-(1,2-dihydroxyethyl)-2-methyl-cyclopentanone (47):** The TBS ether **46**, *N*-methylmorpholine-*N*-oxide (NMO, 0.43 g, 3.7 mmol), and citric acid

monohydrate (0.446 g, 2.12 mmol) were dissolved in a mixture of 1:1 *t*-BuOH/$H_2O$ (3 mL). Osmium tetroxide ($OsO_4$, 0.283 mL of 0.1 M solution in $H_2O$, 0.0283 mmol) was added and the solution was allowed to stir for 14 h. The reaction was diluted with ethyl acetate (10 mL) and water (10 mL). The organic layer was collected and the aqueous layer was extracted with ethyl acetate (2 X 10 mL), the combined organic layers were washed with water (5 mL), brine (10 mL), and dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (1:1 hexanes/ethyl acetate) to yield the diol **47** (0.46 g, 56%) as a 3:2 mixture (determined by $^1$H NMR analysis) of inseparable diastereomers (structures unassigned).

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




4.70 (ddd, *J* = 8.0, 7.7, 7.7 Hz, 1H)

4.31 (ddd, *J* = 8.0, 8.0, 7.2 Hz, 0.66H)

3.98-3.93 (m, 0.66H)

3.88-3.84 (m, 1H)

3.76-3.62 (m, 3.3H)

3.16 (bm, 1H)

2.98-2.90 (bm, 0.66H)

2.81-2.57 (m, 3.3H)

2.27-2.15 (m, 3.3H)

1.89-1.81 (m, 1.66H)

1.17 (d, $J$ = 7.2 Hz, 2H))

1.13 (d, $J$ = 7.5 Hz, 3H)

0.88 (s, 9H)

0.12 (s, 3H)

0.9 (s, 2H)

0.07 (s, 3H)

0.6 (s, 2H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 217.1, 216.1, 71.8, 71.4, 70.1, 68.7, 65.6, 65.4, 54.8, 54.3, 47.2, 47.2, 45.5, 43.9, 25.6, 25.6, 17.7, 17.6, 15.4, 13.1, -4.0, -4.5, -4.9, -5.0.

**3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-methylcyclopentanone (48):** The diol **47** (0.46 g, 1.6 mmol) was dissolved in a 1:1:1 mixture of THF/trifluoroacetic acid/$H_2O$ (6 mL) and allowed to stir for 2 h. The crude reaction mixture was concentrated *in vacuo* at 60 °C and subsequently azeotroped with benzene (3 X 5 mL). The crude product was redissolved in dimethoxypropane (5 mL) and camphorsulfonic acid (CSA, 7.4 mg, 0.032 mmol) was added. The solution was allowed to stir for 2 h, quenched with saturated $NaHCO_3$ (10 mL) and diluted with ethyl acetate (10 mL). The organic layer was collected and the aqueous layer was extracted with ethyl acetate (2 X 10 mL). The combined organic layers were washed with brine (10 mL), and then dried over

anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was dissolved in methanol (5 mL), and palladium on carbon (10 wt. %, 46 mg) was added, the reaction was equipped with a balloon of hydrogen gas, and stirred vigorously for 3 h. The reaction vessel was subsequently purged with argon gas, filtered over Celite, and the filter cake was further washed with ethyl acetate. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (10:1 hexanes/ethyl acetate) to yield the acetonide **48** (0.146 g, 46%) as a 5:4 mixture (determined by $^1$H NMR analysis) of inseparable diastereomers (structures unassigned).

$^1$H NMR ($CDCl_3$, 400 MHz) δ:

4.19-4.13 (m, 1H)

4.10-4.02 (m, 2H)

3.71-3.64 (m, 1.6H)

3.22-3.14 (m, 0.8H)

2.44-2.30 (m, 2H)

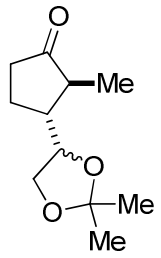
2.19-2.06 (m, 3H)

2.03-1.71 (m, 5H)

1.57-1.47 (m, 0.8H)

1.41 (s, 3H)

1.39 (s, 2.4H)



1.26 (s, 3H)

1.34 (s, 2.4H)

1.18 (d, $J$ = 7.0 Hz, 2.4H)

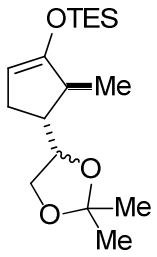
1.08 (d, $J$ = 7.0 Hz, 3H).

$^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 220.4, 220.0, 109.2, 108.8, 79.8, 76.8, 67.7, 67.4, 48.0, 47.5, 46.9, 46.5, 36.84, 36.79, 26.6, 26.4, 25.5, 25.4, 23.4, 22.1, 14.5, 13.0.

**((4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-5-methylcyclopent-1-en-1-yl)oxy)triethylsilane (49):** A solution of the acetonide **48** (0.05 g, 0.25 mmol) in DCM (5 mL) was cooled to -78 °C under argon. To the solution was added DIPEA (0.065 mL, 0.375 mmol), followed by TESOTf (0.099 mL, 0.375 mmol). The solution was allowed to stir for 0.5 h at -78 °C, then warmed to 21 °C and stirred for an additional 2 h. The reaction was quenched with saturated $NaHCO_3$ (10 mL) and diluted with hexanes (10 mL), the organic layer was collected, and the aqueous layer was extracted with hexanes (2 X 10 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (40:1 hexanes/ethyl acetate & 3% TEA) to yield the silyl enol ether **49** (0.070 g, 90%) as a 10:9 mixture (determined by $^1$H NMR analysis) of inseparable diastereomers (structures unassigned).

$^1$H NMR ($CDCl_3$, 500 MHz) δ:

4.50-4.47 (m, 1H)




4.47-4.45 (m, 0.9H)

4.12-4.06 (m, 1.8H)

4.04-3.96 (m, 2H)

3.62-3.56 (m, 1.9H)

2.45-2.36 (m, 1.8H)

2.32-2.24 (m, 2H)

2.14-2.09 (m, 1H)

2.00-1.92 (m, 1.9H)

1.88-1.82 (m, 0.9H)

1.42 (bs, 5.4H)

1.35 (bs, 6H)

1.12 (d, $J$ = 7.1 Hz, 2.7H)

1.06 (d, $J$ = 6.9 Hz, 3H)

0.97 (t, $J$ = 7.9 Hz, 17.1H)

0.67 (q, $J$ = 7.9 Hz, 11.4H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 157.3, 156.7, 108.6, 108.4, 98.6, 98.4, 79.7, 78.8, 67.6, 67.6, 46.7, 46.5, 43.1, 41.7, 29.7, 29.1, 26.8, 26.6, 25.42, 25.40, 18.8, 18.3, 6.7, 6.5, 4.62, 4.61.

**((3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-methylcyclopent-1-en-1-yl)oxy)triethylsilane (50):** The silyl enol ether **49** (0.070 g, 0.23 mmol) was dissolved in chloroform (5 mL) and Wilkinson's catalyst ($RhCl(Ph_3P)_3$, 11 mg, 0.012 mmol) was added. The solution was heated to 61 °C and allowed to stir for 14 h. The reaction was allowed to cool and filtered through a pad of silica gel previously deactivated with TEA. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (40:1 hexanes/ethyl acetate & 1% TEA) to yield the silyl enol ether **50** (0.050 g, 72%) as a ~1:1 mixture (determined by $^1$H NMR analysis) of inseparable diastereomers (structures unassigned).

$^1$H NMR ($CDCl_3$, 400 MHz) δ:

4.21 (ddd, *J* = 7.3, 7.2, 6.3, 0.95H)

4.05-3.98 (m, 2H)

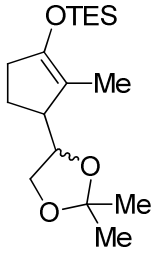
3.90 (dd, *J* = 7.6, 6.4 Hz, 0.95H)

3.59 (dd, *J* = 6.8, 6.8 Hz, 1H)

3.55 (dd, *J* = 7.5, 7.5 Hz, 0.95H)

2.83-2.76 (m, 0.95H)

2.62-2.56 (m, 1H)



2.37-2.17 (m, 3.9H)

2.00-1.83 (m, 1.95H)

1.79-1.71 (m, 0.95H)

1.63-1.57 (m, 1H)

1.57 (bs, 2.85H)

1.54 (bs, 3H)

1.43 (s, 3H)

1.40 (s, 3H)

1.34 (s, 5.7H)

0.98 (t, $J$ = 7.3 Hz, 17.6H)

0.65 (q, $J$ = 7.3 Hz, 6H)

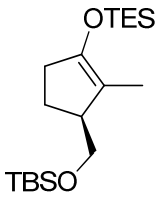
0.64 (q, $J$ = 7.3 Hz, 5.7H).

$^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 157.7, 154.9, 129.0, 126.5, 108.1, 95.9, 78.6, 78.4, 67.7, 66.5, 47.7, 47.0, 32.8, 32.6, 32.5, 26.4, 25.6, 25.1, 24.2, 23.1, 21.0, 11.1, 10.9, 6.6, 5.41, 5.38.

**(*S*)-((1,1-Dimethylethyl)dimethylsilyloxy)-(2-methyl-3-triethylsilyloxy-cyclopent-2-en-1-yl)methoxysilane (59):** The silyl enol ether **58** (5.37 g, 17.1 mmol), used crude from the previous step, was dissolved in dimethoxyethane (170 mL) that was freshly distilled from

sodium/benzophenone. To the solution was added methyllithium (MeLi, 20.5 mL of 1.0 M solution in diethyl ether, 20.5 mmol) at 21 °C and the reaction was allowed to stir for 1 h. To the reaction was added a mixture of TESCl (3.72 mL, 22.2 mmol) and triethylamine (2.08 mL, 22.2 mmol) after removing any precipitate via centrifuge. The resulting solution was allowed to stir for an additional 30 min and quenched with saturated $NaHCO_3$ (200 mL) and diluted with hexanes (200 mL). The organic layer was collected and the aqueous layer was extracted with hexanes (2 X 100 mL). The combined organic layers were washed with water (50 ml) and brine (50 mL), and then dried over anhydrous $Na_2SO_4$. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (50:1 hexanes/diethyl ether & 3% TEA) to yield the silyl enol ether **59** (4.92 g, 81%) as a clear oil.

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




3.62 (dd, *J* = 9.7, 4.9 Hz, 1H)

3.40 (dd, *J* = 9.7, 7.2 Hz, 1H)

2.58-2.51 (m, 1H)

2.33-2.25 (m, 1H)

2.23-2.16 (m, 1H)

1.94-1.86 (m 1H)

1.65-1.57 (m, 1H)

1.53 (s, 3H)

0.98 (t, *J* = 7.9 Hz, 9H)

0.89 (s, 9H)

0.64 (q, *J* = 7.9 Hz, 6H)

0.04 (s, 6H).

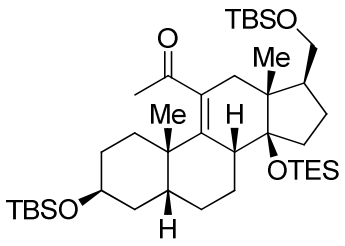
$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 148.0, 113.6, 66.2, 47.7, 32.4, 26.0, 23.8, 18.3, 10.6, 6.7, 5.4, -5.3, -5.4.

$[\alpha]_D^{21}$ -7.7° (c 1.0, $CHCl_3$).

**1-((3*S*,5*R*,8*R*,10*S*,13*R*,14*S*,17*S*)-3-((1,1-Dimethylethyl)dimethylsilyloxy)-17-(((1,1-dimethyl-ethyl)dimethylsilyloxy)methyl)-10,13-dimethyl-14-((triethylsilyl)oxy)-2,3,4,5,6,7,8,10,12,13-14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-11-yl)ethanone (60):** The catalyst $Me_2AlNTf_2$ was prepared by addition of $Tf_2NH$ (0.25 mL of 0.1 M solution in DCM, 0.025 mmol) to trimethylaluminum ($Me_3Al$, 0.3 mL of 0.1 M solution in toluene, 0.03 mmol) in 4 mL of DCM at 21°C, and the solution was allowed to stir for 15 min. The reaction was cooled to -20 ºC and the diene **23** (0.174 g, 0.5 mmol) and the silyl enol ether **59** (0.178 g, 0.65 mmol) were added in 1 mL of DCM and allowed to stir for 4 h. The reaction was quenched with addition of TEA (0.5 mL) and filtered through a plug of silica gel. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (20:1 hexanes/ethyl acetate) to yield the tetracycle **60** (254 mg, 72%) as a 10:1 mixture (determined by $^1$H NMR analysis) of separable diastereomers.

**60A:**

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




3.81-3.76 (m, 1H)

3.58 (dd, *J* = 9.9, 7.9 Hz, 1H)

3.49 (dd, *J* = 9.9, 7.0 Hz, 1H)

2.28 (s, 3H)

2.05-1.99 (m, 2H)

1.96-1.90 (m, 2H)

1.83-1.65 (m, 6H)

1.64-1.44 (m, 5H)

1.33-1.24 (m, 4H)

1.12 (s, 3H)

0.94 (t, *J* = 8.0 Hz, 9H)

0.88 (s, 9H)

0.86 (s, 9H)

0.83 (s, 3H)

0.61 (q, *J* = 8.0 Hz, 6H)

0.07 (s, 6H)

0.04 (s, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 210.2, 137.0, 132.5, 84.3, 67.5, 65.2, 44.2, 42.71, 42.66, 42.2, 40.0, 38.4, 36.1, 34.0, 32.6, 32.1, 30.5, 30.3, 29.9, 29.7, 27.4, 25.99, 25.97, 23.3, 18.3, 18.0, 7.4, 7.0, -4.59, -4.61, -5.3, -5.4.

HRMS (ESI, m/z): 727.4953, calcd for $C_{40}H_{76}O_4Si3$ $(M+Na)^+$ 727.4949.

$[\alpha]_D^{21}$ +9.6° (c 1.0, $CHCl_3$).

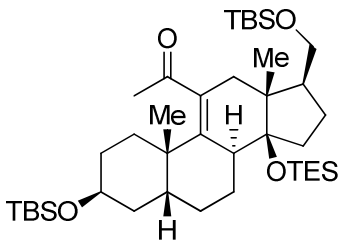
**60B:**

$^1$H NMR ($CDCl_3$, 500 MHz) δ:

3.97-3.92 (m, 1H)

3.62 (dd, *J* = 9.9, 8.5 Hz, 1H)

3.53 (dd, *J* = 10.3, 6.6, 1H)




2.33 (s, 3H)

2.31-2.27 (m, 1H)

2.20-2.13 (m, 1H)

2.09-2.03 (m, 1H)

2.02-1.84 (m, 4H)

1.83-1.51 (m, 8H)

1.46-1.39 (m, 2H)

1.37-1.31 (m, 2H)

1.25 (s, 3H)

1.19 (s, 3H)

0.94 (t, $J$ = 7.7 Hz, 9H)

0.88 (s, 9H)

0.87 (s, 9H)

0.61 (q, $J$ = 7.7 Hz, 6H)

0.03 (s, 6H)

0.00 (s, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 208.6, 132.3, 127.8, 84.4, 67.4, 65.6, 44.5, 41.1, 40.8, 38.1, 36.5, 33.8, 32.2, 30.9, 30.3, 29.7, 27.1, 26.0, 25.95, 25.88, 25.7, 23.1, 21.9, 18.5, 18.1, 18.0, 7.4, 7.0, -4.80, -4.82, -5.3, -5.4.

HRMS (ESI, m/z): 727.4940, calcd for $C_{40}H_{76}O_4Si3$ $(M+Na)^+$ 727.4949.

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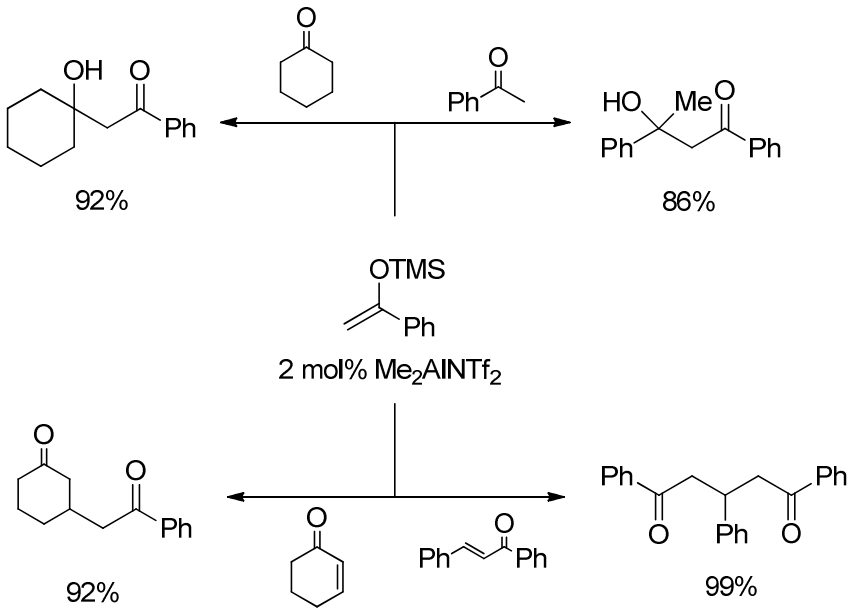
# Chapter 2

# Trimethylaluminum-Triflimide Complexes for the Catalysis of Highly Hindered Diels-Alder Reactions

## Introduction

The Diels-Alder reaction is ubiquitous in organic synthesis.[1] In particular substituted silyloxydienes have proven very useful in this reaction, due to their ease of formation, stability, and versatility.[2] Previous research found that two catalyst systems - a 5:1 mixture aluminum tribromide ($AlBr_3$) and trimethylaluminum ($AlMe_3$) and *tert*-butyldimethylsilyl triflimide ($TBSNTf_2$), prepared via reaction of a silyl enol ether and triflimide ($Tf_2NH$) - were valuable and potent catalysts for more challenging transformation of this kind.[3] However, during our studies of a novel approach towards rhodexin A, both methods failed to provide satisfactory results.[4]

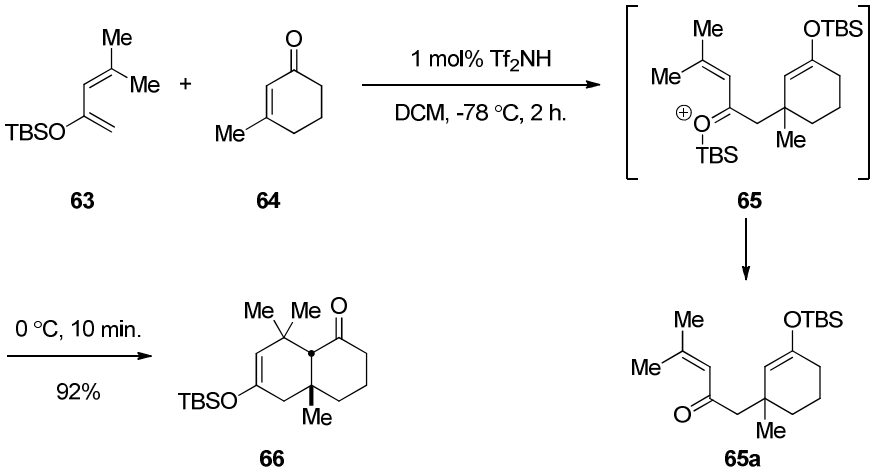



**Scheme 27. Aluminum Bis(trifluoromethylsulfonyl) Amide Catalysis by Yamamoto et. al.**

Yamamoto and co-workers recently reported the generation of highly active Lewis acid species through the formation of triflimide complexes with trimethylaluminum.[5] A variety of Mukaiyama aldol and Mukaiyama-Michael additions were performed using this catalyst system resulting in the products in very good yields (**Scheme 27**). However, to the best of our

knowledge these species have never been applied to the Diels-Alder reaction. Therefore, exploring their viability was of great synthetic interest to us.

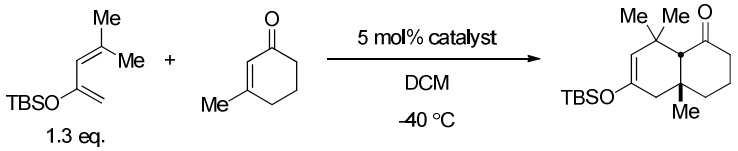
Recently, a triflimide-promoted stepwise Mukaiyama-Michael vinylogous aldol addition of the hindered silyloxy dienes **63** to the hindered enones **64** to give formal Diels-Alder cycloadducts has been reported in our group (**Scheme 28**). This method allows easy synthetic access to highly hindered systems that are difficult to obtain via alternative Lewis acid catalysis or by any other synthetic route. Although good yields could be obtained in many systems, transformations were complicated by considerably prolonged reactions times under $AlBr_3$-$AlMe_3$ catalysis and the tendency of triflimide catalysis to stop at the Mukaiyama-Michael intermediates, such as the enone derived by desilylation of **65**, namely **65a**, without proceeding to the cyclized product **66**. In an attempt to improve upon these conditions, we explored the use of the potentially more highly active Lewis acid systems described by Yamamoto and co-workers.




**Scheme 28.** Triflimide-Catalyzed Diels-Alder Reaction.

## Results and Discussion

Initial research on these catalyst systems focused on discerning the reactivity difference between conventional triflimide catalysis and the aluminum based complexes. The reaction of the silyl enol ether **63** with 3-methyl-2-cyclohexen-1-one **64** has previously been shown to yield the desired cycloadduct **66** in 92% yield under $Tf_2NTBS$ catalysis (prepared in situ from reaction of **1** with triflimide) (**Table 1, entry 1**).[3] It was observed that $Me_2AlNTf_2$ (prepared by mixing $AlMe_3$ with equimolar amounts of $Tf_2NH$) resulted in a marked rate acceleration of this reaction, while affording comparable yields of the cycloadduct **66**, 96% in 1.5 h (**Table 1, entry 2**). Use of an additional equivalent of triflimide (to generate $MeAl(NTf_2)_2$) provided further rate acceleration with a similar yield, 94%, in only 0.5 h (**Table 1, entry 3**). Interestingly, the tris(triflimido)aluminum species, $Al(NTf_2)_3$, did not result in constructive catalysis, creating instead a complex mixture of products (**Table 1, entry 4**).[6]




**63** **64** **66**

| entry | catalyst | time (h) | yield %[a] |
|---|---|---|---|
| 1 | $Tf_2NH$ | 4 | 92 |
| 2 | $Me_2AlNTf_2$ | 1.5 | 96 |
| 3 | $MeAl(NTf_2)_2$ | 0.5 | 94 |
| 4 | $Al(NTf_2)_3$ | 0.1 | N/A |

[a] Isolated yield based on 3-methyl-2-cyclohexen-1-one.

**Table 1.** Aluminum-Triflimide Catalysts

Based on these findings, $Me_2AlNTf_2$ and $MeAl(NTf_2)_2$ were identified as potentially useful catalysts for highly hindered Diels-Alder cycloadditions. $Me_2AlNTf_2$ catalyst loading of

3-10% gave excellent and uniform yields. Alternative solvents were explored for this reaction, but it was found that the catalyst system was poorly soluble in toluene and benzene, the yields decreased dramatically in diethyl ether, and THF was highly prone to polymerization under the reaction conditions.

Based on these results, $Me_2AlNTf_2$ was screened as a catalyst in a series of Diels-Alder cycloadditions with hindered dienes and/or dienophiles (**Table 2**). Initially, the focus of the work was on improving the extensive reaction times and/or difficult conditions of substrates that have been reacted with the mixed Lewis acid catalyst ($AlBr_3$-$AlMe_3$) or $Tf_2NTBS$. Using $Me_2AlNTf_2$ as the catalyst, the silyl enol ether **63** with was reacted with the enone **64** to produce the desired cycloadduct **66** in excellent yield (96%) under mild conditions (0 °C, 0.5 h) (**Table 2, entry 1**). Similarly, reaction of **63** with the enone **67** afforded the previously obtained product **68** in 71% yield, with the reaction time drastically reduced from the reported 48 h.[3] As had been observed earlier, the double bond of the product silyl enol ether migrated easily and yielded exclusively the migrated product (**Table 2, entry 2**). Likewise, the reaction of **63** with the hindered enone **69** rapidly gave the desired cycloadduct **70** in good yield (**Table 2, entry 3**). The hindered cyclpentenyl diene system **71** also reacted well with the dienophiles **64**, **67**, and **69** under $Me_2AlNTf_2$ catalysis to afford the cycloadducts **72, 73,** and **74** in fair to excellent yields (41-99%). In the first two cases, a mixture of diastereomers was obtained, 5:2 for **72nx** and 1:1 for **73nx**, while in the last case a single diastereomer was obtained and was assumed to be the endo isomer (**Table 2, entry 4-6**). In order to investigate the formation of bridged polycyclic compounds, the cyclic diene, 2-trialkylsilyloxy-3-methyl-1,3-cyclohexadiene **75**, was obtained and reacted with the same series of dienophiles. With the dienophile **64**, we obtained an approximate 5:4 inseparable mixture of the endo and exo adducts **76nx** in 48% yield (**Table 2,**

**entry 7**). Dienophile **67** yielded a 3:2 mixture of endo and exo diastereomers **77** and **78** in 92% yield (**Table 2, entry 8**). Finally the very hindered dienophile **69** afforded only the endo adduct **79** in fair yield (**Table 2, entry 9**). All of the cycloadditions shown in **Table 2** occurred under very mild conditions, despite considerable steric encumbrance of the products, demonstrating the efficacy of this new catalyst system.

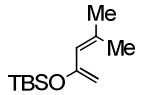
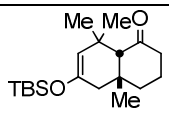
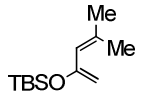
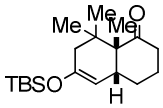
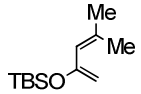
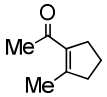
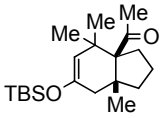
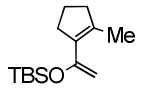
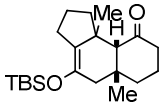
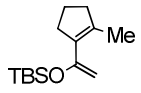
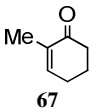
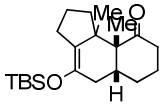
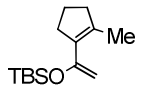
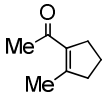
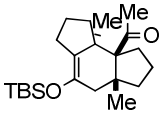
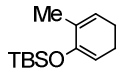
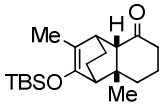
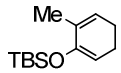
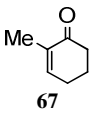
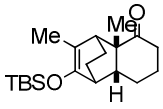
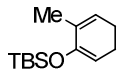
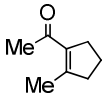
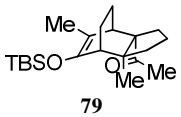
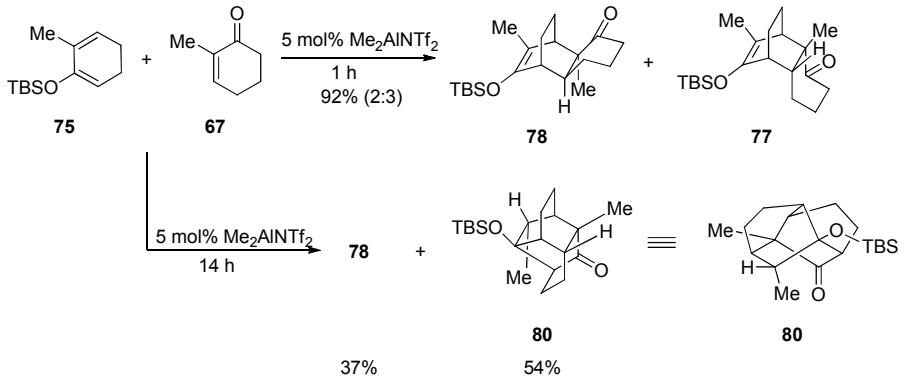
| entry | diene | dienophile | temp (°C); time (h) | product | yield % (endo:exo) |
|---|---|---|---|---|---|
| 1 |  **63** |  **64** | 0, 0.5 |  **66** | 96 |
| 2 |  **63** |  **67** | 0, 1 |  **68** | 71 |
| 3 |  **63** |  **69** | 0; 1 |  **70** | 68 |
| 4 |  **71** |  **64** | 0; 2 |  **72nx** | 99 (5:2) |
| 5 |  **71** |  **67** | 0; 3 |  **73nx** | 41 (1:1) |
| 6 |  **71** |  **69** | 0; 2 |  **74** | 56 |
| 7 |  **75** |  **64** | 0; 3 |  **76nx** | 48 (~5:4) |
| 8 |  **75** |  **67** | 0; 1 |  **77** & **78** | 92 (3:2) |
| 9 |  **75** |  **69** | 0; 1 |  **79** | 45 |

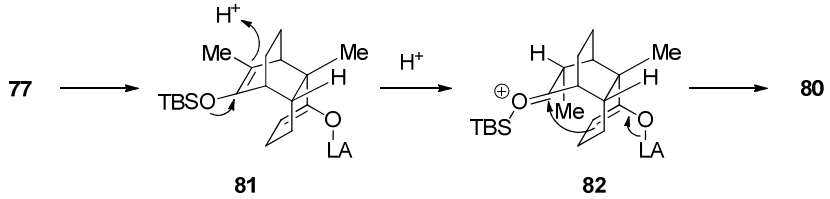
**Table 2.** $Me_2AlNTf_2$ Catalyzed Cycloadditions

Interestingly, when silyloxycyclohexadiene **75** and the enone **67** were left under the same reaction conditions for a prolonged duration of 14 h, in addition to the expected exo adduct **78**, the novel twistanone **80** was isolated (**Scheme 29**).




**Scheme 29.** Formation of Twistanone Compound **80**

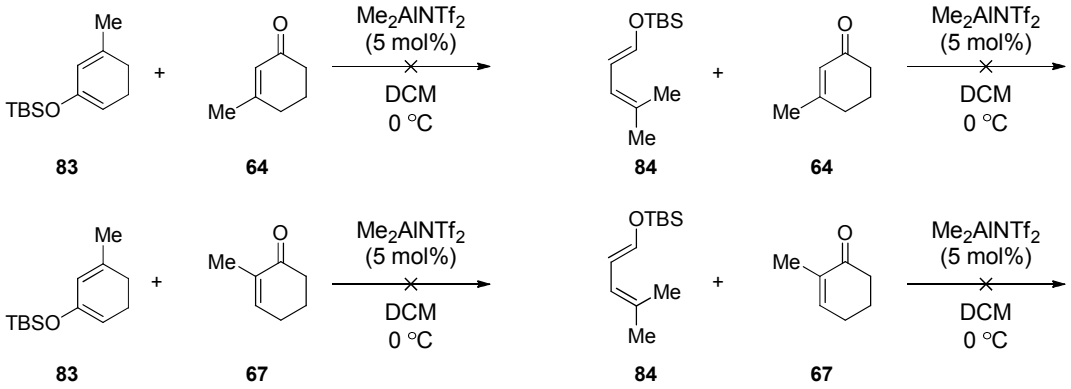
It is likely that this compound is formed via enolization of the cycloadduct **77** to give an enol derivative **81** followed by protonation of the silyl enol ether from the less hindered exo face to give the stabilized carbocation **82** and final C-C bond formation via an aldol-like reaction (**Scheme 30**). This finding proved helpful in elucidating the diastereoselectivity of the reaction, as this structure is geometrically accessible only via the endo Diels-Alder product **77**.




**Scheme 30.** Possible Mechanism for the Formation of Twistanone **80**

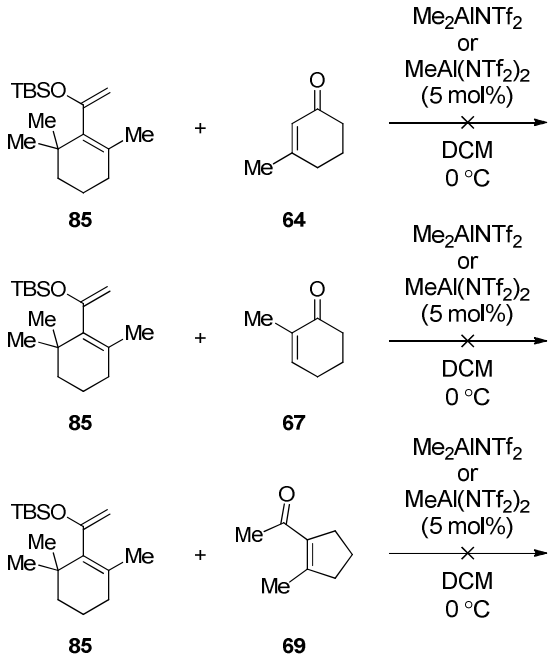
Finally, the dienes **83** and **84** were synthesized, the first via treatment of 3-methyl-2-cyclohexen-1-one with LDA and TBSCl and the second as described in the literature and used under the standard conditions described earlier.[7,8] However, both dienes failed to form appreciable amounts of the expected cycloadducts with the dienophiles **64** and **67** (**Scheme 31**). Use of diene **83** resulted in a complex mixture of products and it is possible that due to its particular structure and geometry it is prone to cationic rearrangements. Use of diene **84** also

proved unsuccessful and it seems likely that it may be more nucleophilic at the C-2 position rather than the C-4 position.




**Scheme 31.** Use of Dienes **83** and **84** the Diels-Alder Reaction

Diene **85** was also synthesized using a literature procedure and screened against dienophiles **64**, **67,** and **69** (**Scheme 32**).[9] In all cases the reaction failed to proceed, under both $Me_2AlNTf_2$ and $MeAl(NTf_2)_2$ catalysis. Although both the diene and the dienophiles were found to be stable for multi-hour intervals under the reaction conditions, no product formation was observed, the diene eventually succumbing to hydrolysis.




**Scheme 32.** Use of Diene **85** the Diels-Alder Reaction

## Conclusions

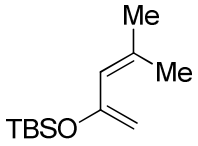
In summary, the efficacy of the complexes of $AlMe_3$ in combination with $Tf_2NH$ in catalyzing very hindered Diels-Alder reactions was demonstrated. The reactivity of $Me_2AlNTf_2$ has permitted isolation of products that are either difficult to obtain or completely inaccessible through conventional $Tf_2NH$ catalysis, including a number of compounds containing two or three contiguous quaternary centers. In addition, $MeAl(NTf_2)_2$ shows promise as an even more powerful Lewis acid with even greater rate acceleration.

## Experimental

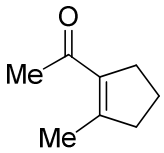
**General:** All reactions were carried out under an argon atmosphere unless otherwise specified. Tetrahydrofuran (THF), diethyl ether, toluene, and benzene were distilled from benzoquinone ketyl radical under an argon atmosphere. Dichloromethane (DCM), triethylamine (TEA), and diisopropylethylamine (DIPEA) were distilled from calcium hydride under an argon atmosphere. Triflimide ($Tf_2NH$) was purchased from Acros Organics in 98% purity, weighed out in a nitrogen-filled glovebox, and used as a 0.1 M solution in DCM. All other solvents or reagents were purified according to literature procedures. $^1H$ NMR spectra were recorded on Bruker Avance 500 spectrometer at 500 MHz and are reported relative to deuterated solvent signals. Data for $^1H$ NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. $^{13}C$ NMR spectra were recorded on a Bruker Avance 500 spectrometer at 125 MHz. Data for $^{13}C$ NMR spectra are reported in terms of chemical shift. The chemical shifts are reported in parts per million (ppm, δ). DEPT 135 signals are given as: + for primary and tertiary C-atom (positive DEPT 135 signal); - for secondary C-atom (negative DEPT 135 signal); $C_q$ for quaternary C-atom (DEPT 135 signal intensity zero). All Fourier Transform Infrared (FTIR) samples were prepared as thin films on NaCl plates and spectra were recorded on a Perkin Elmer RX1 FTIR spectrometer and are reported in terms of frequency of absorption ($cm^{-1}$). Thin-layer chromatography (TLC) was carried out using pre-coated silica gel sheets (Merck 60 $F_{254}$). Visual detection was performed using ceric ammonium nitrate or *p*-anisaldehyde stains. Flash chromatography was performed using SilicaFlash™ P60 (60 A, 40-63 μm) silica gel from SiliCycle Inc. with compressed air.

**General Procedure for Lewis Acid Catalyzed Cycloaddition.** $Me_2AlNTf_2$ was prepared by addition of $Tf_2NH$ (0.25 mL of 0.1 M solution in DCM, 0.025 mmol) to trimethylaluminum ($Me_3Al$, 0.3 mL of 0.1 M solution in toluene, 0.03 mmol) in 4 mL of DCM at 21 ºC, and the solution was allowed to stir for 15 min. The reaction was cooled to 0 ºC and the enone (0.5 mmol) and the silyl enol ether (0.65 mmol) were added in 1 mL of DCM. The reaction was allowed to stir for 1-3 h. The reaction was quenched by addition of TEA (0.5 mL) and filtered through a plug of silica gel. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (20:1 hexanes/diethyl ether with 1% TEA).

**((1,1-Dimethylethyl)dimethylsilyloxy)-4-methyl-1,3-pentadiene (63):** This compound was prepared following the literature procedure of Jung, M. E., Ho, D. *Org. Lett.* **2007**, *9*, 375-78.



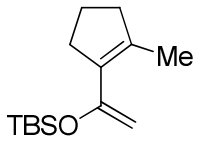

**1-(2-Methylcyclopent-1-en-1-yl)ethanone (69):** This compound was prepared following the literature procedure of Gilbert, J. C., Wiechman, B. *J. Org. Chem.* **1984**, *49*, 2049-50.




**1-[1-((1,1-Dimethylethyl)dimethylsilyloxy)]ethenyl-2-methylcyclopentene (71):** A solution of 1-acetyl-2-methylcyclopentene (1.0 g, 8.1 mmol) in DCM (50 mL) was cooled to -78 °C under argon. To the solution was added DIPEA (1.83 mL, 10.5 mmol), followed by TBSOTf (2.4 mL, 10.5 mmol). The solution was allowed to stir for 0.5 h at -78 °C, then warmed to 21 °C and

stirred for an additional 2 h. The reaction was quenched with saturated $NaHCO_3$ (100 mL), the organic layer was collected, and the aqueous layer was extracted with diethyl ether (2 X 25 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was distilled under reduced pressure (70-73 °C, 0.5 mmHg) to yield the pure silyloxydiene **71** (1.64 g, 85%).

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




4.29 (s, 1H)

4.21 (s, 1H)

2.52-2.46 (m, 2H)

2.41-2.37 (m, 2H)

1.92 (s, 3H)

1.81-1.74 (m, 2H)

0.96 (s, 9H)

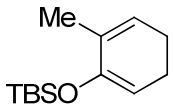
0.19 (s, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 155.4, 137.9, 131.9, 93.0, 40.3, 35.4, 25.8, 21.4, 18.3, 16.0, -4.5.

FTIR (DCM): 3050, 2990, 2980, 2948, 2665, 2303, 1681, 1420, 1270, 896, 844, 750 $cm^{-1}$.

**2-((1,1-Dimethylethyl)dimethylsilyloxy)-3-methylcyclohexa-1,3-diene (75):** To a solution of dry diisopropylamine (3.3 mL, 23.6 mmol) in anhydrous THF (25 mL) stirred at -78 °C under argon was added *n*-butyllithium (8.72 mL of a 2.5 M solution in hexanes, 21.8 mmol) dropwise and the resulting solution was allowed to stir for 30 min. Distilled 2-methyl-2-cyclohexen-1-one was added (2 g, 18.2 mmol) as a solution in THF (25 mL) over 15 min. The reaction was allowed to stir for 1 h. TBSCl (4.1 g, 27.2 mmol) was dissolved in THF (25 mL) and added to the reaction over 5 min. The reaction was allowed to warm to 21 °C overnight, then quenched with saturated $NaHCO_3$ (100 mL) and diluted with diethyl ether (50 mL). The organic layer was collected and the aqueous layer was extracted with diethyl ether (2 X 50 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent *in vacuo*, the residue was distilled under reduced pressure (68-70 °C, 0.5 mmHg) to yield the pure silyloxydiene (3.06 g, 75%).

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




5.61 (m, 1H)

4.86 (t, *J* = 4.5 Hz, 1H)

2.14-2.06 (m, 2H)

2.05-1.96 (m, 2H)

1.73 (d, *J* = 1.8 Hz, 3H)

0.94 (s, 9H)

0.16 (s, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 149.9, 132.7, 124.0, 101.5, 25.8, 23.1, 22.4, 18.2, 17.9, -4.5.

FTIR (DCM): 3056, 2988, 2978, 2952, 2688, 2306, 1678, 1420, 1268, 896, 844, 756 $cm^{-1}$.

**(4a*R*,8a*S*)-6-((1,1-Dimethylethyl)dimethylsilyloxy)-)-4a,8,8-trimethyl-3,4,4a,5,8,8a-hexahydronaphthalen-1(2*H*)-one (66):** 155 mg, 96%. Physical data obtained were in agreement with literature values: Jung, M. E.; Ho, D. *Org. Lett*. **2007**, *9*, 375-78.

**(4a*R*,8a*R*)-6-((1,1-Dimethylethyl)dimethylsilyloxy)-8,8,8a-trimethyl-2,3,4,4a,8,8a-hexahydronaphthalen-1(7*H*)-one (68):** 115 mg, 71%. Physical data obtained were in agreement with literature values: Jung, M. E.; Ho, D. *Org. Lett*. **2007**, *9*, 375-78.

**1-((3a*S*,7a*R*)-6-((1,1-Dimethylethyl)dimethylsilyloxy)-4,4,7a-trimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-3a-yl)ethanone (70):** 161 mg, 96%.

$^1$H NMR ($CDCl_3$, 500 MHz) δ:

4.63 (s, 1H)

2.33-2.25 (m, 1H)

2.17 (s, 3H)

2.11-1.96 (m, 2H)

1.86-1.74 (m, 2H)

1.73-1.63 (m, 1H)

1.59-1.47 (m, 2H)

1.10 (s, 3H)

0.99 (s, 3H)

0.92 (s, 9H)

0.87 (s, 3H)

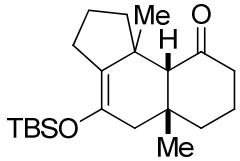
0.15 (s, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 212.1, 146.7, 114.1, 64.7, 44.4, 40.2, 40.1, 36.8, 31.0, 30.6, 29.0, 28.0, 26.1, 25.8, 19.6, 18.0, -4.20, -4.23.

FTIR (thin film): 3058, 2990, 2305, 1703, 1430, 1270, 896, 760 $cm^{-1}$.

**(5a*R*,9a*S*)-4-((1,1-Dimethylethyl)dimethylsilyloxy)-5a,9b-dimethyl-2,3,5a,6,7,8,9a,9b-octa-hydro-1*H*-cyclopenta[*a*]naphthalen-9(5*H*)-one (72nx):** 171 mg, 99%, 5:2 mixture of inseparable diastereomers (determined by $^1$H NMR analysis).

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




2.50-2.30 (m, 3H)

2.30-2.05 (m, 3H)

2.00-1.90 (m, 2H)

1.90-1.70 (m, 2H)

1.70-1.48 (m, 5H)

1.03 (s, 0.85H)

0.992 (s, 2.14H)

0.987 (s, 2.14H)

0.92 (s, 0.85H)

0.91 (s, 9H)

0.10-0.02 (m, 6H).

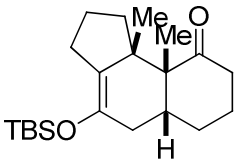
$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 214.4, 214.3, 139.3, 138.8, 125.3, 122.2, 66.2, 64.2, 46.0, 44.6, 44.4, 44.0, 42.4, 41.2, 39.0, 38.2, 38.0, 37.6, 36.6, 31.7, 30.0, 28.5, 27.9, 26.2, 25.62, 25.57, 23.9, 22.1, 22.0, 21.0, 19.9, 17.99, 17.96, -4.06, -4.09, -4.13, -4.22, (several upfield carbons not observed).

FTIR (DCM): 3145, 2922, 2850, 2240, 1786, 1682, 1452, 1370, 1255, 1132, 1090, 910, 720 $cm^{-1}$.

**(5a*R*,9ab*RS*)-4-((1,1-Dimethylethyl)dimethylsilyloxy)-9a,9b-dimethyl-2,3,5a,6,7,8,9a,9b-octahydro-1*H*-cyclopenta[a]naphthalen-9(5*H*)-one (73n):** 35.6 mg, 20.4%.

$^{1}$H NMR ($CDCl_3$, 500 MHz) δ:

2.56 (ddd, *J* = 16.3, 5.9, 5.9 Hz, 1H)



2.44-2.31 (m, 3H)

2.30-2.21 (m, 1H)

2.19-2.12 (m, 1H)

1.98-1.76 (m, 6H)

1.70-1.54 (m, 2H)

1.40-1.33 (m, 1H)

1.08 (s, 3H)

1.03 (s, 3H)

0.94 (s, 9H)

0.12 (s, 3H)

0.11 (s, 3H).

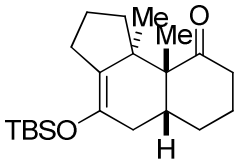
$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 216.9, 138.3, 123.7, 52.8, 48.0, 43.3, 41.0, 37.2, 34.2, 31.3, 26.5, 25.8, 25.3, 24.4, 22.0, 21.9, 18.2, -3.8, -4.0.

FTIR (DCM): 3150, 2926, 2852, 2252, 1784, 1700, 1462, 1376, 1349, 1298, 1250, 1196, 1090, 1036, 902, 722 $cm^{-1}$.

**73x:** 36.6 mg, 21%.

$^{1}$H NMR ($CDCl_3$, 500 MHz) δ:

2.76-2.69 (m, 1H)




2.61-2.56 (m, 1H)

2.50-2.44 (m, 1H)

2.38-2.29 (m, 2H)

2.18-2.03 (m, 3H)

1.96-1.93 (m, 1H)

1.90-1.84 (m, 2H)

1.74-1.68 (m, 1H)

1.58 (bs, 1H)

1.56 (d, $J$ = 13.5 Hz, 1H)

1.34 (s, 3H)

1.26-1.21 (m, 1H)

0.94 (s, 3H)

0.91 (s, 9H)

0.07 (s, 3H)

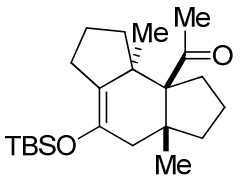
0.06 (s, 3H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 214.0, 136.3, 127.4, 53.6, 47.3, 40.8, 39.2, 35.6, 32.2, 27.8, 25.8, 24.9, 24.8, 23.3, 23.2, 20.2, 18.1, -3.8, -4.0.

FTIR (DCM): 3150, 2924, 2852, 2252, 1786, 1680, 1460, 1370, 1248, 1128, 1090, 900, 722 $cm^{-1}$.

**1-((5a*R*,8a*S*,8b*R*)-4-((1,1-Dimethylethyl)dimethylsilyloxy)-5a,8b-dimethyl-1,2,3,5,5a,6,7-8,8a,8b-decahydro-indacen-8a-yl)ethanone (74):** 102 mg, 56%.

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




2.50-2.43 (m, 1H)

2.23-2.16 (m, 1H)

2.19 (s, 3H)

2.04 (d, *J* = 18.0 Hz, 1H)

1.99 (dd, *J* = 14.0, 8.6 Hz, 1H)

1.90-1.65 (m, 8H)

1.47 (s, 3H)

1.45-1.32 (m, 2H)

0.99 (s, 3H)

0.93 (s, 9H)

0.12 (s, 3H)

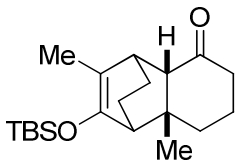
0.10 (s, 3H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 212.8, 138.4, 122.8, 65.8, 46.1, 45.4, 45.1, 39.0, 38.2, 31.7, 29.2, 25.8, 24.5, 24.1, 22.3, 21.0, 18.7, 18.2, -3.8, -4.0.

FTIR (DCM): 3056, 2988, 2308, 1708, 1424, 1268, 896, 756 $cm^{-1}$.

**(4a*S*,8a*R*)-2-((1,1-Dimethylethyl)dimethylsilyloxy)-3,8a-dimethyl-4,4a,6,7,8,8a-hexahydro-1,4-ethanonaphthalen-5(1*H*)-one (76nx):** 80 mg, 48%, 5:4 mixture of inseparable diastereomers (determined by $^1$H NMR analysis).

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




2.76 (m, 1H)

2.43 (ddd, *J* = 18.0, 7.2, 3.3 Hz, 0.55H)

2.34 (ddd, *J* = 16.8, 4.7, 4.7 Hz, 0.42H)

2.14 (ddd, *J* = 17.0, 8.8, 8.8 Hz, 0.6H)

2.0-1.93 (m, 1H)

1.90-1.81 (m, 3.4H)

1.82-1.73 (m, 1H)

1.68-1.65 (m, 1H)

1.63 (s, 1.7H)

1.56 (s, 1.3H)

1.50-1.46 (m, 0.4H)

1.40-1.23 (m, 3.6H)

1.18 (s, 1.7H)

1.07 (s, 1.3H)

0.97-0.92 (m, 9H)

0.14-0.08 (m, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 215.8, 215.0, 150.3, 149.3, 112.2, 111.7, 59.9, 57.1, 48.5, 47.6, 42.0, 41.3, 39.32, 39.25, 39.19, 38.8, 35.3, 33.2, 30.2, 27.8, 25.61, 25.60, 21.3, 21.2, 19.8, 19.0, 18.5, 18.0, 13.9, 12.9, -3.80, -3.84, -4.27, -4.29, (two upfield carbons not observed).

FTIR (DCM): 2948, 2928, 2854, 2252, 1680, 1470, 1378, 1336, 1254, 1164, 1088, 904, 834, 724 $cm^{-1}$.

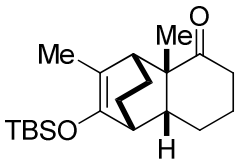
**(1*R*,4*R*,4a*R*,8a*R*)-2-((1,1-Dimethylethyl)dimethylsilyloxy)-3,4a-dimethyl-4,4a,6,7,8,8a-hexahydro-1,4-ethanonaphthalen-5(1*H*)-one (77):** 92 mg, 55%.

$^{1}$H NMR ($CDCl_3$, 500 MHz) δ:

2.57 (dd, *J* = 2.9, 2.9 Hz, 1H)

2.42 (dm, *J* = 19.1 Hz, 1H)

2.11-1.02 (m, 2H)




1.85-1.77 (m, 2H)

1.77-1.68 (m, 3H)

1.58 (s, 3H)

1.52-1.41 (m, 2H)

1.22-1.15 (m, 2H)

1.13 (s, 3H)

0.92 (s, 9H)

0.081 (s, 3H)

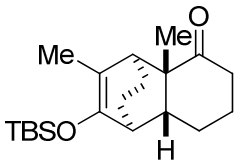
0.076 (s, 3H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 216.4, 147.8, 116.3, 53.0, 51.4, 43.4, 42.8, 37.7, 30.0, 27.1, 26.4, 25.7, 20.6, 19.8, 18.1, 14.0, -3.8, -4.1.

FTIR (DCM): 3056, 2982, 2958, 2862, 2310, 1698, 1464, 1424, 1384, 1268, 1198, 926, 898, 838, 756 $cm^{-1}$.

**(1*S*,4*S*,4a*R*,8a*R*)-2-((1,1-Dimethylethyl)dimethylsilyloxy)-3,4a-dimethyl-4,4a,6,7,8,8a-hexahydro-1,4-ethanonaphthalen-5(1*H*)-one (78):** 62 mg, 37%.

$^{1}$H NMR ($CDCl_3$, 500 MHz) δ:




2.59-2.53 (m, 2H)

2.18-2.08 (m, 2H)

1.95-1.88 (m, 1H)

1.83-1.72 (m, 3H)

1.66 (s, 3H)

1.61-1.52 (m, 2H)

1.47-1.40 (m, 1H)

1.25-1.16 (m, 2H)

1.03 (s, 3H)

0.96 (s, 9H)

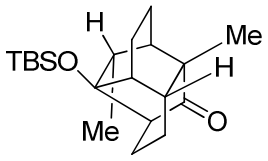
0.13 (s, 6H).

$^{13}$C NMR ($CDCl_3$, 75 MHz) δ: 217.6, 148.8, 113.2, 51.9, 46.2, 43.5, 41.2, 38.4, 29.6, 27.8, 25.8, 21.8, 21.1, 19.4, 18.1, 15.3, -3.91, -3.93.

FTIR (DCM): 3056, 2988, 2956, 2860, 2690, 2308, 1700, 1698, 1424, 1268, 1194, 898, 834, 754 $cm^{-1}$.

**5-((1,1-Dimethylethyl)dimethylsilyloxy)-1,10-dimethyldecahydro-1,6:2,5-dimethanonaphthalen-9-one (80):** $Me_2AlNTf_2$ was prepared by addition of $Tf_2NH$ (0.25 mL of 0.1 M solution in DCM, 0.025 mmol) to trimethylaluminum ($AlMe_3$, 0.3 mL of 0.1 M solution in toluene, 0.03 mmol) in 4 mL of DCM at 21 °C, and the solution was allowed to stir for 15 min. The reaction was cooled to 0 ºC and the enone **67** (0.5 mmol) and the silyl enol ether **75** (0.65 mmol) were added in 1 mL of DCM. The reaction was allowed to stir for 14 h. The reaction was quenched with addition of TEA (0.5 mL) and filtered through a plug of silica gel. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography on silica gel (20:1 hexanes/diethyl ether with 1% TEA) to yield the enone **78** (62 mg, 37%) and the twistanone **80** (90 mg, 54%) as a clear oil.

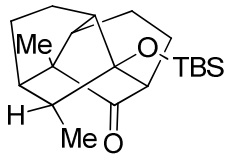
$^1H$ NMR ($CDCl_3$, 500 MHz) δ:




2.21 (d, *J* = 4.5 Hz, 1H)

2.07-1.96 (m, 2H)

1.81-1.64 (m, 4H)




1.58-1.46 (m, 3H)

1.42-1.34 (m, 3H)

1.08 (d, *J* = 7.1 Hz, 3H)

0.97 (s, 3H)

0.89 (s, 9H)

0.11 (s, 3H)

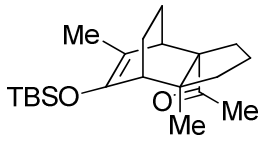
0.09 (s, 3H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 220.7, 76.7($C_q$), 59.2(+), 52.1($C_q$), 43.0(+), 42.6(+), 40.3(+), 40.0(+), 25.9(+), 22.8(-), 21.6(-), 21.5(-), 18.5($C_q$), 16.0(-), 13.9(+), 13.4(+), -2.0, -2.3.

FTIR (DCM): 3056, 2960, 2948, 2882, 2310, 1724, 1472, 1424, 1268, 1172, 1138, 1062, 922, 838, 754 $cm^{-1}$.

**1-((3a*S*,4*R*,7*R*,7a*S*)-6-((1,1-Dimethylethyl)dimethylsilyloxy)-5,7a-dimethyl-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-ethanoinden-3a-yl)ethanone (79):** 78 mg, 45%.

$^1$H NMR ($CDCl_3$, 500 MHz) δ:




2.38-2.34 (m, 1H)

2.15-2.04 (m, 1H)

2.09 (s, 3H)

1.91-1.80 (m, 4H)

1.75 (s, 3H)

1.73-1.62 (m, 4H)

1.31-1.23 (m, 1H)

1.20-1.12 (m, 1H)

1.04 (s, 3H)

0.92 (s, 9H)

0.09 (s, 6H).

$^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 212.3, 149.7, 114.7, 66.5, 52.9, 50.7, 44.3, 40.5, 35.2, 30.3, 28.0, 26.8, 25.7, 22.3, 21.5, 18.1, 14.0, -3.6, -4.1.

FTIR (DCM): 3054, 2960, 2860, 2308, 1686, 1472, 1424, 1342, 1270, 1238, 1188, 1120, 930, 840, 756 $cm^{-1}$.

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