

MIT Open Access Articles

Ladder Polyether Synthesis via Epoxide-Opening Cascades Directed by a Disappearing Trimethylsilyl Group

The MIT Faculty has made this article openly available. **Please share** how this access benefits you. Your story matters.

Citation: Heffron, Timothy P., Graham L. Simpson, Estibaliz Merino, and Timothy F. Jamison. "Ladder Polyether Synthesis via Epoxide-Opening Cascades Directed by a Disappearing Trimethylsilyl Group." *The Journal of Organic Chemistry* 75, no. 8 (April 16, 2010): 2681-2701.

As Published: <http://dx.doi.org/10.1021/jo1002455>

Publisher: American Chemical Society (ACS)

Persistent URL: <http://hdl.handle.net/1721.1/82123>

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

Terms of Use: Article is made available in accordance with the publisher's policy and may be subject to US copyright law. Please refer to the publisher's site for terms of use.





Published in final edited form as:

J Org Chem. 2010 April 16; 75(8): 2681–2701. doi:10.1021/jo1002455.

Ladder Polyether Synthesis via Epoxide-Opening Cascades Directed by a Disappearing Trimethylsilyl Group

Timothy P. Heffron¹, Graham L. Simpson, Estibaliz Merino, and Timothy F. Jamison^{*}
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts
02139

Abstract

Epoxide-opening cascades offer the potential to construct complex polyether natural products expeditiously and in a manner that emulates the biogenesis proposed for these compounds. Herein we provide a full account of our development of a strategy that addresses several important challenges of such cascades. The centerpiece of the method is a trimethylsilyl (SiMe₃) group that serves several purposes and leaves no trace of itself by the time the cascade has come to an end. The main function of the SiMe₃ group is to dictate the regioselectivity of epoxide opening. This strategy is the only general method of effecting *endo*-selective cascades under basic conditions.

Introduction

The ladder polyether natural products (Figure 1) are a fascinating family of molecules that possess very complex structures, display extremely potent and dramatic biological effects, and are the toxic constituents of marine phenomena known collectively as the Red Tide. Consequently these natural products have inspired intensive investigations by scientists with diverse areas of expertise. For example, several laboratories have investigated methods for synthesizing these compounds, devising ingenious and effective strategies specifically tailored for the challenges presented.²

How Nature assembles such complex structures also has captured the imagination of generations of chemists and biologists. One of the two structural features that characterizes the ladder polyethers is the repeating oxygen-carbon-carbon pattern that is present in the entire range of the polyether network, regardless of the size of the intervening rings and independent of any functional groups present on the rings. The other pattern, stereochemical in nature, is that all of the junctions between the fused rings are *trans*, and consecutive ring junctions are *syn* to one another. It is this *trans-syn* arrangement of the rings that is responsible for the “ladder” topography of these molecules. The ring junctions in all of the ladder polyethers isolated to date are *trans* (with one exception), and the *trans-syn* relationship is seen in all cases where relevant (again with one exception). In maitotoxin there is a *cis*-fused junction between two tetrahydropyran rings, and elsewhere in the same natural product, a *trans-anti-trans* arrangement of three tetrahydropyrans is found.³

Over twenty years ago Nakanishi put forth an intriguing hypothesis that accounts for these structural and stereochemical features, the transformation of a polyepoxide into a ladder

tfj@mit.edu.

¹Current address: Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080

Supporting Information Available. Experimental procedures and data for all new compounds (PDF). This information is available free of charge via the internet at <http://pubs.acs.org>.

polyether via an extraordinary series or “cascade” of epoxide-opening events.⁴ The oxygen and two carbon atoms of each epoxide account for the repeating C–C–O pattern found in the backbone, and with the proviso that all of the ring openings proceed with inversion of configuration, the *trans-syn* stereochemical feature is thereby also explained. The intellectual appeal of Nakanishi’s proposal is that these two aspects provide a simple explanation for the structural complexity found in the ladder polyethers. However, this two-decade-old hypothesis remains unconfirmed, and it remains unknown whether such a cascade of epoxide-opening reactions is a component of the construction process.

In spite of this uncertainty, a significant amount of effort has been directed toward emulating Nakanishi’s proposed cascades. A fundamental problem in these endeavors is highlighted in studies that predate the first elucidation of the structure of a ladder polyether natural product. Coxon found that the opening of a *trans*-disubstituted epoxide by an oxygen-centered nucleophile separated by three CH₂ groups favors the smaller, five-membered heterocycle, not the larger tetrahydropyran.⁵ Though exceptions have been observed, such “*exo*” regioselectivity tends to dominate such processes, including those leading to larger rings.

This *exo* tendency raises an important question about the Nakanishi hypothesis: If Nature uses epoxide-opening cascades, how is this bias toward the smaller ring overcome? While “enzyme control” is a logical response to this question, it is incomplete because it does not answer the fundamental mechanistic question of “how?” Moreover, as noted above, there is as yet no evidence for such enzymatic process.

A contrasting approach to reversing the regioselectivity that has been investigated by several groups is largely based on substrate control. For example, the pioneering work of Nicolaou in this area utilizes an alkenyl group to direct the regioselectivity of epoxide opening electronically, i.e., by providing greater stabilization of the developing positive charge at the adjacent epoxide carbon atom, rather than that distal to the alkene “directing group”.⁶

In the context of cascades (more than one epoxide) alternative yet conceptually related directing group approaches have been explored by several research groups. Murai reported the first of these, in which a methoxymethyl group in conjunction with a Lewis acid directs a series of epoxide openings in the desired *endo* fashion. The design principle and proposed basis of the regioselectivity is chelation of a lanthanide salt by the oxygen of the methoxymethyl group and that of the epoxide (Figure 2).⁷

McDonald has reported several examples of cascades leading to both *trans*-fused polyoxepanes and polytetrahydropyrans where a methyl group at each ring junction provides what is thought to be an electronic bias in the same vein as Nicolaou’s alkene-directed epoxide ring-openings (Figure 3).⁸

The regioselectivity control elements (MeOCH₂ or Me groups) utilized in each of these cases, however, are either not present at all (methoxymethyl groups) or not present at every ring junction in the natural products (Me groups). In fact, the ratio of the frequency of H atoms to Me groups at ring junction carbons in ladder polyether natural products is approximately 4:1. Finally, since these groups are not easily removed or modified after the cyclization, their utility in target-oriented synthesis is also somewhat limited. It should be noted that in the preparation of a polyoxepane by way of epoxide-opening cascades, McDonald and coworkers disclosed an impressive example in which the central two rings formed did not require direction by a methyl group (Figure 4).^{8e}

Inspired by the proposed biosynthesis of ladder polyethers, we sought to develop related cascades, in particular those leading to four consecutive tetrahydropyran (THP) rings, since this tetrad of THP rings is found in the majority of the known ladder polyether natural

products. One significant difference between our approach and those of Murai and McDonald was that we required that any directing group employed be easily removed after the cascade in order to reveal the substitution pattern that appears at well over half of ring junctions in the natural products – two hydrogen atoms.⁹

Trimethylsilyl emerged as our directing group of choice primarily because of its demonstrated control of regioselectivity in the opening of epoxysilanes by a wide range of nucleophiles (intermolecular).¹⁰ The most compelling precedent was the regioselective opening of epoxysilanes with oxygen-centered nucleophiles, promoted by Brønsted or Lewis acids,¹¹ the means by which we initially envisioned affecting the cascade.^{12,13}

Despite the precedented regioselectivity in the opening of epoxysilanes, the effect of the SiMe₃ group on cyclization was still an issue. In order to achieve the desired relative stereochemistry at the ring junction in a synthesis of *trans*-fused ladder polyether subunits, the SiMe₃ would be axial in the predicted transition state (Figure 5).

No such cyclization with an axial SiMe₃ group had been reported and, in fact, Schaumann had reported that epoxy-alcohol cyclizations with SiMe₃ in an *equatorial* position led to unspecified ratios of 5-*exo* and 6-*endo* products (Figure 6). It is possible that the diastereomeric mixture of epoxides used as starting material was the source of low regioselectivity (eq 1, Figure 6). Nonetheless, when a single diastereomer was used, the formation of 6-*endo* products could be ascribed to a significant conformational predisposition, such as avoidance of forming a strained *trans*-5,5 system (eq 2, Figure 6).¹⁴

Herein we provide a detailed account of the development of a general strategy for stereoselective synthesis of polyepoxysilanes and of our studies of Lewis and Brønsted acid-promoted, epoxide-opening cascades of these compounds. As discussed below, these traditional methods of effecting cascades of these compounds overwhelmed the directing ability of Me₃Si groups that we had previously established and thus did not lead to the desired *trans-syn*-polyether framework. To our surprise and delight, a less common means of promoting epoxide-opening transformations (Brønsted bases) not only afforded ladder polyether subunits by way of a series of *endo* epoxide openings, but also removed the Me₃Si group during the course of the cascades.

Results and Discussion

We began our program directed toward the rapid assembly of *trans*-fused polyether natural products by way of epoxide-opening cascades using methods that we had previously developed for a related stepwise, or iterative, synthesis of polytetrahydropyrans.¹⁵ This strategy had four basic design elements: 1. Synthesis of a trisubstituted alkenylsilane; 2. enantioselective, reagent-controlled epoxidation of the alkenylsilanes; 3. Lewis acid-promoted cyclization by way of an epoxide-opening reaction; 4. removal of the Me₃Si directing group (Scheme 1).

A. Iterative Synthesis of Oligo(alkenylsilanes)

The first task we thus faced was assembly of a variety of oligo(alkenylsilanes) for polyepoxidation. Toward this end, a three-carbon homologation that we had previously developed was used to prepare enyne **18**, which was then subjected to Shi asymmetric epoxidation (Scheme 2).^{15a} The epoxide product was not easily separated from the ketone catalyst, and thus preliminary studies were performed on the mixture. The low yield of this two-step process is attributed to the loss of material to C-H oxidation of the primary alcohol. Further in the synthesis, dienyl iodide intermediate **23** proved to be unstable, decomposing rapidly after isolation and thus resulting in reduced yields. These properties also necessitated

the immediate conversion to the corresponding diene and diepoxide **24**. Nevertheless, this example demonstrates that despite low yields, suitable quantities of the diene were made available using this iterative sequence to enable evaluation of the asymmetric epoxidation.

Using the same iterative methods, triene **27** was produced. However, because of the lengthy synthesis and low yields resulting from instability of the intermediate iodides **23** and **26** (Scheme 3), an alternative, convergent approach was thus developed.

B. Convergent Synthesis of Poly(alkenylsilane) Precursors

It was envisioned that the coupling of an alkenyl metal species (e.g. aluminum, boron, copper, zirconium, zinc) with an allylic electrophile would provide the desired product (Figure 7).¹⁶ We found that alkenyl-aluminum, alkenyl-zirconium and some alkenyl-copper species proved most suitable for preservation of Z-olefin geometry. Hydroalumination of alkyne **20** with DIBAL followed by treatment with 100 mol% methyl lithium gave the corresponding aluminate. *In situ* transmetallation to the more nucleophilic higher-order cuprates (using CuCl•2LiCl or CuI•P(OEt)₃)¹⁷ allowed coupling with a range of electrophiles. Solvent also played a crucial role, with Et₂O proving to be superior in the regio- and stereoselective hydrometallation, and THF providing higher reactivity in the subsequent alkylation.

For example, coupling with methyl iodide afforded the alkene **29** in 69% yield in a one-pot procedure (Scheme 4). This sequence compares favorably with the yield from the two-step iterative route of 56%.

Accordingly, the same strategy provided a direct route to prepare diene **31** (Scheme 5). One-pot coupling of the alkenyl cuprate reagent derived from hydrozirconation/transmetallation of pyran **20** with allylic bromide **30**¹⁸ gave diene **31** in 32% overall yield.

Similarly, triene **27** was available using the direct coupling of an alkenyl cuprate derived from hydroalumination/transmetallation of alkyne **20**,^{16c} with dienylyl mesylate **34**^{15b} (Scheme 6).

C. Asymmetric Epoxidations of Alkenylsilanes Using Shi's Fructose-Derived Ketone

Epoxidation of olefins **29**, **31**, and **27** using Shi epoxidation conditions afforded epoxides **35**, **24**, and **28**, respectively, in moderate to excellent yields and with good to high diastereoselectivities (Scheme 7). In these epoxidations the Shi ketone generally exerts a high degree of reagent control. Due to the lower reactivity of the alkenylsilanes to electrophilic reagents, several adjustments to the reaction conditions were typically necessary.

Unfortunately, separation of the epoxide products from the excess Shi ketone (**19**) using standard chromatography was difficult in all cases. However, the use of a Baeyer-Villiger oxidation effected conversion of the Shi ketone to a lactone.¹⁹ Treatment of the partially purified reaction mixture with *m*-CPBA/NaHCO₃ in CH₂Cl₂, followed by 1 M NaOH to saponify the lactone and extract the corresponding carboxylate, proved to be an efficient means to remove excess Shi ketone and allowed for a straightforward, subsequent purification by silica gel chromatography.

D. Epoxide-Opening Cascades of Polyepoxysilanes Promoted by Lewis and Brønsted Acids

Building upon our results from the regioselective cyclization of monoepoxysilanes, we turned our attention toward cascades (more than one epoxide per substrate) under similar

conditions.^{15a} Simply put, the incorporation of even just one additional epoxide complicated significantly the outcome under similar reaction conditions. Our initial studies of cascades employed diepoxide **36**²⁰, which contains a primary alcohol as the internal, trapping nucleophile (Scheme 8). With either Brønsted acids or BF₃·Et₂O, similar results were obtained. Although there was a significant amount of acid-promoted decomposition, a common bicyclic compound was generated in each of these attempts. Acetylation and ¹H NMR analysis confirmed that the product contained a secondary alcohol. In order to distinguish between isomeric bicyclic compounds **37** and **38**, 2D NMR experiments were undertaken, and HMBC analysis of the acetylated product revealed the undesired isomer **37** was the major product (Figure 8).

A diepoxide containing a *tert*-butyl carbonate (**39**) as an internal nucleophile was also studied (Scheme 9). Under identical conditions as those used for **36**, above, the outcome of the reaction was similar: An undesired compound containing two linked five-membered rings (**40**) was the only product isolated.

The fact that the cascades behave so differently from systems containing the one-epoxide model systems may be due to several factors. Were the cascade to proceed by a nucleophile (OH in **36** or mixed carbonate in **39**) attacking proximal epoxide, followed by opening of the distal epoxide, then the one-epoxide cases would likely have been good models of systems with more than one epoxide. Our hypothesis that an additional epoxide should have little effect was quite clearly incorrect. One possible explanation is summarized in Figure 9. Even in the event that the first cyclization had gone as planned, a conformational aspect of the resulting intermediate might disfavor subsequent cyclizations. All of the twenty-six low energy conformations (within 10.0 kcal) of **35** predicted by Molecular Mechanics computations (Spartan '08, MMFF94, gas phase) indicated a chair conformation for the tetrahydropyran. Of these, nearly half (12) displayed the SiMe₃ group in an equatorial position, e.g., as in **35b**. Such conformations are unlikely to be able continue in the cascade (i.e., form a second THP ring) and may readily decompose.

In order to explore this hypothesis, we made two structural modifications, form the first THP *prior* to the cascade, and attach no SiMe₃ groups to the THP. The embodiment of this idea was diepoxide **41**,²¹ and the pre-formed THP should have three major advantages. For one, the absence of the SiMe₃ should give a strong preference for a diequatorial chair conformation of the THP, thus enhancing the population of productive conformers. For a similar reason, the reduction of conformational mobility of the chain between the nucleophile and the proximal epoxide engendered by the THP ring should also facilitate cyclization. Finally, after the first cyclization, the rigid *trans*-dioxadecalin framework would then be locked in a conformation in which the alcohol could access the *next* epoxide.

However, as shown in Scheme 10, another undesired and very rapid reaction ensued upon treating diepoxide **41** with BF₃·Et₂O at -78 °C, conditions identical to those we had used in previous cyclizations. The majority of the material was lost to decomposition, and only one new compound that retained the pyran ring could be isolated. One of the two trimethylsilyl groups in the starting material had been lost; the major product of the reaction contained only one and was determined to be spiroketal **42** (Scheme 10).²²

In each of the attempted cascades described above, unexpected products were isolated as the major compounds produced. Mechanistic insight into how these products could be produced proved instrumental in our understanding of the behavior of epoxysilanes. In the case of diepoxide **36**, a bisfuran (**37**) was formed, a puzzling result in light of the *6-endo* regioselectivity observed in the acid-mediated cyclizations of monoepoxysilanes.^{15a} In order to arrive at a bistetrahydrofuran, the two epoxysilanes must be opened, regioselectively, in

the contrary 5-*exo* fashion (Figure 10, **A**). With an internal nucleophile present (an alcohol in **36**), the first epoxide must be opened selectively at the β position relative to SiMe_3 , contrary to earlier studies showing exceptionally high α selectivity. In the second cyclization, though, the epoxide must be opened selectively at the α position relative to SiMe_3 . An analogous mechanism could be invoked for compound **39**, where the internal nucleophile was a *t*-butyl carbonate.

Alternatively, the observed formation of bisfuran **37** can be rationalized by proceeding through a mechanism whereby the first epoxide opened is distal to the internal nucleophile (Figure 10, **B**). If the distal epoxide is activated by the acid, the neighboring *epoxide* may serve as a nucleophile upon that activated epoxide.^{8, 23, 24} After formation of a furan, the intended nucleophile could then undergo cyclization to form the bisfuran.

In the case of the cascade cyclization of diepoxide **41**, the spiroketal product **42** can also be rationalized by a mechanism in which the distal epoxide is activated first (Figure 11). In this case the neighboring epoxide again would behave as a nucleophile. Next, the silyl group would eliminate and an acid catalyzed rearrangement may lead to the spiroketal product.

Based on the suggested mechanisms for the outcomes in the attempted cascades of polyepoxysilanes under acid promotion, it appeared that initiation of the cascade was by reaction of the distal epoxide (relative to the internal nucleophile) *with the other epoxide* in the substrate, rather than by our internal nucleophile. This phenomenon would be consistent with the electron-rich nature of the epoxysilane, i.e., not only more basic (toward the acidic promoter), but also more nucleophilic (toward another acid-activated epoxysilane). The addition of one additional epoxide having such a profound impact on the success of the cascade cyclization necessitated a significant reworking of the overall cascade strategy. The crux of problem appeared to lie in the fact that the cascade was not starting at the desired location, i.e., at the nucleophile. Accordingly, in order to enhance the nucleophilicity of the internal nucleophile in epoxy-alcohol cyclizations, we initiated a study of these reactions under basic conditions.²⁵

E. Cyclizations of Epoxysilanes Under Basic Conditions

Before beginning cascade attempts, however, the cyclization of monoepoxysilane **43** under basic conditions was first studied.²⁶ With bases that would readily deprotonate the alcohol (hydride, *t*-butoxide, and hydroxide bases), the starting material primarily decomposed and only trace amounts of cyclized products could be detected (Scheme 11).

However, weaker bases exhibited profoundly different behavior. In a screen of conditions for the intramolecular cyclization of epoxysilane **43** it was discovered that K_2CO_3 in MeOH at elevated temperature provided the desired product (Table 1, entry 3)^{25b} The results of an expanded study of basic conditions are shown in Table 1.

This survey of conditions demonstrated that while the use of carbonate bases generally led to less than complete conversion of the starting material, little if any decomposition took place (entries 1–11). It was found that the counterion of the carbonate base affected the reactivity, with Li_2CO_3 providing the lowest conversion of starting material in MeOH (entry 1) and Cs_2CO_3 leading to near complete conversion (entry 4). This trend in reactivity may be the result of the greater solubility of the carbonate bases that lead to more complete conversion of the starting material. The added reactivity of Cs_2CO_3 relative to other carbonate bases has been described in other cases.²⁷

After initially studying MeOH as solvent, it was found that the use of either EtOH or *i*-PrOH as the solvent reduced reaction rate (entries 5 and 6). In water, the reactivity was again

sluggish but showed the opposite reactivity trend when the counterion of the carbonate base is considered (entries 7–9). Interestingly, the regioselectivity observed when the reaction was carried out in water was significantly higher. It may be that, because of the low solubility of the substrate in water, any reaction that takes place does so on the surface and a limited amount of deprotonation actually occurs. If this is the case, more of the product may result from promotion of the cyclization by the carbonate counterion (a Lewis acid promoted cyclization) leading to the higher regioselectivity obtained. Again, the lower solubility of Li_2CO_3 relative to Cs_2CO_3 may contribute to this observed reactivity trend.

Although the regioselectivity in the cyclization of disubstituted epoxide **46** under acidic conditions was reported by Coxon to favor the tetrahydrofuran, the corresponding cyclization under basic conditions had not been reported.⁵ In order to demonstrate that the SiMe_3 group was still necessary to achieve even the modest 6-*endo* selectivity observed in the cyclizations discussed above, we performed the base promoted cyclization of epoxide **46** under conditions we found for the corresponding epoxysilane **43** (Scheme 12). Not surprisingly, in this reaction furan **47** was produced as the major regioisomer.

The above studies demonstrated that it is possible to perform epoxy-alcohol cyclizations under basic conditions. Moreover, the SiMe_3 group was critical for the production of the pyran as the major regioisomer. Having demonstrated that the base-promoted cyclization of a monoepoxysilane was possible, we moved on to study polyepoxides and cascade cyclizations under basic conditions.

F. Cascade Cyclizations of Polyepoxysilanes Under Basic Conditions

To begin studying cascade cyclizations of polyepoxysilanes under basic conditions we returned to diepoxide **36** (Scheme 13). The initially attempted cascade cyclization of diepoxide **36**, under conditions that had been successfully applied to the monoepoxide (700 mol% Cs_2CO_3 in MeOH at 50 °C for 20 h), achieved less than 10% conversion of the starting material.²⁸ Among the factors that may contribute to the decrease in reactivity observed for bisepoxysilane **36**, relative to the monoepoxysilane (**43**), are the added steric encumbrance at the proximal epoxide and/or a conformational preference that is unfavorable for cyclization. Only by extending the reaction time was useful consumption of the starting material observed. Upon longer reaction time (2–7 days), the conversion of starting material remained sluggish and many products were produced as a complex mixture. Among those identified were monopyran **35** in which only one epoxide had been opened and enone **50**.²⁹ Another, tentatively identified, compound was the corresponding furan regioisomer (**49**) in which the first epoxide had been opened but the other epoxide remained intact.

The isolation of monopyran **35**, although a predicted intermediate in a base promoted cascade that would lead to a bispyran, was the source of some concern. It was conceivable that the developing diaxial interactions that would need to be faced in the formation of the second ring posed too great an energetic barrier to overcome when a SiMe_3 group was placed at the ring junction. Under acidic conditions this intermediate could not be forced to the bispyran. Indeed, under any conditions, the formation of a fused pyran system in which a SiMe_3 group is forced into the axial position at a ring junction has not been achieved.

When monopyran **35** was resubjected to the basic conditions being used in this study, however, a lone product was isolated (Scheme 14). With every indication suggesting that this product was a bispyran, it was immediately apparent that this compound had only one SiMe_3 group remaining. In order to confirm that the silyl group that was removed was that at the ring junction, an iterative synthesis of a bispyran was performed using our previously developed iterative synthesis of poly-THPs.^{15a} The bispyran produced using this method was identical in all respects to that obtained from the reaction of monopyran **51** with

Cs₂CO₃ in MeOH. Most significantly, this established that an intermediate isolated from the attempted cascade cyclization of diepoxide **36** was directly converted to a bispyran (**51**) under the same reaction conditions. During this cascade cyclization, after 2–4 days at 50 °C less than 30% of the starting material (**36**) had been consumed, and the distribution of products was not consistent, prompting a careful screen of the reaction parameters. During the search for conditions that led to a consistent and more rapid consumption of starting material, the presence of enone **50** proved to be constant.

Simply by increasing the amount of Cs₂CO₃ (from 700 mol% to 3000 mol%) the production of enone **50** was suppressed. Alternatively, the addition of an equivalent amount of CsF allowed for a reduction in the amount of Cs₂CO₃ (2000 mol%) used. It is possible that the rearrangement of the epoxysilanes to the enone is a competitive thermal process and the introduction of more base makes the cyclization faster relative to the rearrangement process. Of greatest interest in these studies was the production of cascade product bispyran **51** (Scheme 15).

It is interesting to note that in the base-promoted cyclization of **35** to **51** only a single regioisomer was isolated (Scheme 14). This was especially encouraging because in the cyclization of monoepoxysilane **43** using Cs₂CO₃/MeOH a 1.7:1 mixture of regioisomers was isolated (Table 1, entry 4). Moreover, a mixture of regioisomers appeared to be formed when the same conditions were applied to the incomplete conversion of bisepoxysilane **36** (Scheme 13). In the case where high regioselectivity was observed, a pyran scaffold had been already in place. Recognizing a potential template effect on the regioselectivity in base-promoted cyclizations, monoepoxide **52**, diepoxide **55** and triepoxide **57** were targeted for further study.

G. Epoxide-Opening Cascades Leading to *trans-syn*-Fused Ladder Polyethers

Heating epoxide **52** with Cs₂CO₃ in methanol (3000 mol%, 55 °C) gave a good yield of the monocyclization but with slow final protidesilylation to provide Me₃Si-diad **51** after 3 days (Scheme 16). In an attempt to increase the rate of protidesilylation, several additives and alternative conditions were examined.³⁰ It was found that addition of cesium fluoride to the reaction mixture and prolonged heating allowed for the removal of all of the Me₃Si groups to give all-proton diad **53**. These optimized conditions (2000 mol% (1.92 M in MeOH) Cs₂CO₃ and CsF) were applied to the remaining polyepoxides **24** and **28**.

Heating diepoxide **24** to 65 °C for 3 days with Cs₂CO₃ and CsF provided the product of the cascade cyclization of both epoxides in the substrate, triad **54** (Scheme 17). Moreover, all SiMe₃ directing groups had been protidesilylated; leaving a tristetrahydropyran in which *no directing groups remained*.

In the cascade reaction of diepoxide **24**, all three SiMe₃ groups are replaced with protons and two new pyrans are formed. Remarkably, in this one reaction *five* operations take place. Also, despite the possibility of 5-*exo* cyclization in two different epoxide openings, only one product, triad **54**, is isolated. Most impressively, cyclization of the triepoxide **28** allowed isolation of the corresponding tetrad with all-proton ring junctions in an average yield of 76% per operation with 7 operations in one-pot (Scheme 18). Isolation of the tetrad was facilitated by conversion to the corresponding acetate **55**.

This constitutes the first report of an epoxide-opening cascade cyclization leading to the ubiquitous poltetrahydropyran motif found in the majority of the marine polyether natural products. The cascade takes place under carefully engineered basic and hydroxylic conditions to provide the polyether products *with no directing groups remaining* – the Me₃Si group disappears during the course of the reaction.

H. Cascade of Polyepoxides with H in place of SiMe₃ on first Tetrahydropyran Ring

In order to investigate the effect of the axial Me₃Si-group on cyclization, selective protidesilylation using TBAF in THF afforded vinylsilanes **56**, **57**, and **58** in good yields. Finally, Shi epoxidation afforded the corresponding epoxides (Scheme 19).

Evaluation of epoxides **52**, **41**, and **59** in cascade cyclizations provided the all-proton diad **53**, triad **60**, and tetrad **55** in slightly improved yields relative to **35**, **24**, and **28** (Scheme 20).

I. Proposed Mechanism of Epoxide-Opening Cascades

We propose that the polyepoxide cascade cyclizations proceed *via* a repeating protidesilylation/cyclization sequence (Figure 12). Following initial cyclization, hydroxyl-assisted stereospecific protidesilylation of the tetrahydropyranyl-SiMe₃ under basic conditions is followed by *endo*-selective epoxide cyclization. A second protidesilylation of the new tetrahydropyran ring continues the cascade. The reaction sequence is terminated with a final stereospecific protidesilylation of the α -trimethylsilyl group.

As no SiMe₃ group remains at the ring junction of the product, we suggest that the silyl group is removed before cyclization upon the second epoxide. The protidesilylation likely proceeds through a homo-Brook rearrangement that, because of the protic solvent in which the reaction takes place, is trapped stereospecifically by a proton.³¹

Further support for the suggestion that the SiMe₃ group is protidesilylated prior to cyclization was obtained in the attempted desilylation of **61**. When the β -hydroxyl group had been previously protected as the benzyl ether, no conversion of the starting material could be detected under the reaction conditions (Scheme 21).

Conclusion

This account describes the first report of an epoxide-opening cascade cyclization leading to the ubiquitous polytetrahydropyran motif of the marine polyether natural products. Specifically, the combination of a Me₃Si group, a Brønsted base, a fluoride source, and a hydroxylic solvent enables the first construction of the THP tetrad found in the majority of the ladder polyether toxins.

Over the past two years, we have been developing methods of epoxide-opening cascades in which no directing group attached to the epoxide is required for high *endo* selectivity.^{2h-i, 9, 32} For example, in 2007, we reported that water, either deionized or buffered near neutral pH, was the optimum promoter for cascades involving *trans*-disubstituted epoxides and for which a “templating” ring was also present.⁹ As such, this strategy provided high yields of triad **54** and tetrad **55** without the need for the trimethylsilyl group.

It must be emphasized, however, that these results do *not* demonstrate that the SiMe₃ group is unnecessary in all cases. Rather, the SiMe₃ group remains the superior director of regioselectivity under basic conditions. Without the SiMe₃ group, such cascades are notoriously difficult to direct in the *endo* fashion, and only a limited number of successful examples have been reported.^{32c} Thus, in cases where acid-sensitive functional groups are present elsewhere in the substrate or in cascades where acidic or neutral promoters are ineffective or low-yielding, the trimethylsilyl-directed cascades may prove to be essential. Areas for further investigation include mechanistic investigations into the precise role of the SiMe₃-group in the cascade, further improvement in the efficiency of the synthesis of poly(epoxysilanes), differentiation of the trialkylsilyl groups for a means of converting selected ones to Me groups after the cascade, cascades in which larger rings (7 or 8) are

targeted, and application of the cascades to preparation of larger fragments of the marine ladder polyethers.

Experimental Section

General Information

Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran (THF) and Et₂O were distilled from a blue solution of benzophenone ketyl. Analytical thin layer chromatography (TLC) was performed using silica gel 60 F₂₅₄ plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid (PMA) or aqueous potassium permanganate (KMnO₄). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on silica gel (230–400 mesh). ³³H and ¹³C NMR spectra were recorded in CDCl₃, unless otherwise noted, on a 500 MHz spectrometer. Chemical shifts in ¹H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, and br = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ¹³C NMR spectra are reported in ppm from the central peak of CDCl₃ (77.2 ppm), C₆D₆ (128.4 ppm), or CD₂Cl₂ (54.0 ppm) on the δ scale. High Resolution mass spectra (HR-MS) were obtained on a 3 Tesla Fourier Transform Mass Spectrometer. Optical rotations were measured on a polarimeter at 589 nm.

(Z)-5,8-Bis-trimethylsilyl-oct-4-en-7-yn-1-ol (18)

To a solution of 1-trimethylsilyl-1-propyne (1.0 mL, 6.5 mmol) in THF (4.3 mL) at -78 °C was added a 2.5 M solution of *n*-BuLi in hexane (2.7 mL) and TMEDA (1.0 mL, 6.7 mmol). The solution was warmed to 0 °C and stirred 45 min. The solution was then transferred *via* cannula to a slurry of CuI (1.4 g, 7.2 mmol) and Bu₃P (1.6 mL, 6.5 mmol) in THF (5.7 mL) at -78 °C. The solution was warmed to -20 °C and the alkenyl iodide (1.4 mmol) was added. The reaction mixture was allowed to warm to room temperature gradually and stirred overnight. The reaction was quenched with 1 M HCl and the organic layer was separated. The aqueous layer was extracted with Et₂O (3 × 20 mL). The combined organic layers were washed with water, brine, dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography (isolated yield = 67%). R_f = 0.41 (20% EtOAc in hexane); IR (thin film, NaCl) 3314, 2956, 2898, 2173, 1618, 1420, 1249, 1053, 841, 759 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.24 (t, *J* = 7.6 Hz, 1H), 3.68 (t, *J* = 6.4 Hz, 2H), 2.99 (s, 2H), 2.24 (dt, *J* = 7.6, 7.3 Hz, 2H), 1.68 (m, 2H), 0.19 (s, 9H), 0.16 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 143.6, 134.5, 106.5, 88.3, 63.3, 33.5, 29.4, 28.9, 0.8, 0.7; HR-MS (ESI) Calcd for C₁₄H₂₈NaOSi₂ (M + Na)⁺ 291.1571, found 291.1577.

(2R,3R)-2-Trimethylsilyl-2-(3-trimethylsilyl-prop-2-ynyl)-tetrahydro-pyran-3-ol (20)

To olefin **18** (6.4 g, 24 mmol) was added CH₃CN/DMM (760 mL, 1:2 v:v), a 0.05 M solution of Na₂B₄O₇·10 H₂O in 4.0 × 10⁻⁴ M Na₂-(EDTA) (500 mL), *n*-Bu₄NHSO₄ (1.6 g, 4.8 mmol), and chiral ketone **19** (12 g, 48 mmol). To this solution was added, simultaneously over 20 min *via* pressure equalizing addition funnels, a solution of Oxone[®] (59 g, 96 mmol) in 4.0 × 10⁻⁴ M Na₂-(EDTA) (400 mL) and a 0.89 M solution of K₂CO₃ (400 mL). After the Oxone[®] and K₂CO₃ solutions had been added, the resulting mixture stirred 10 min then diluted with water (800 mL) and extracted with hexane (3 × 400 mL). The combined organic layers were dried over MgSO₄, and concentrated *in vacuo*. The epoxide product could not be separated from the ketone catalyst by column chromatography and was carried on to the next step as a mixture.

To a solution of the crude epoxide in CH₂Cl₂ (150 mL) at 0 °C was added BF₃·Et₂O (0.3 mL, 1.2 mmol) and the reaction mixture stirred 20 min. The reaction was quenched with saturated NaHCO₃. The aqueous layer was separated and extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography (10–20% EtOAc in hexane) to afford **20** (0.9 g, 19% over two steps): R_f = 0.53 (20%, EtOAc in hexane); [α]²⁵_D = -20.0 (*c* = 2.0, in CHCl₃); IR (thin film, NaCl) 3470, 2957, 2175, 1249, 1089, 1003, 842, 759 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.96 (m, 1H), 3.68 (ddd, *J* = 12.2, 9.5, 3.4 Hz, 1H), 3.54 (app dt, *J* = 11.9, 4.6 Hz, 1H), 2.88 (d, *J* = 16.8 Hz, 1H), 2.45 (d, *J* = 17.1 Hz, 1H), 2.29 (d, *J* = 4.6 Hz, 1H), 2.02–1.95 (m, 1H), 1.89–1.80 (m, 1H), 1.74–1.68 (m, 1H), 1.52–1.45 (m, 1H), 0.20 (s, 9H), 0.15 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 104.4, 88.9, 75.2, 70.7, 61.6, 28.7, 25.7, 22.1, 0.6, -0.2; HR-MS (ESI) Calcd for C₁₄H₂₈NaO₂Si₂ (M + Na)⁺ 307.1520, found 307.1517.

(2*R*,3*R*)-2-[(*E*)-3-Iodo-3-trimethylsilylanyl-allyl]-2-trimethylsilylanyl-tetrahydro-pyran-3-ol (**21**)

To a solution of **20** (3.5 g, 12 mmol) in Et₂O (35 mL) was added a 1 M solution of DIBAL in hexane (30 mL). The resulting solution was heated 24 h at reflux then cooled to -78 °C and diluted with Et₂O (10 mL). A solution of I₂ (13 g, 49 mmol) in Et₂O (20 mL) was added. After stirring 2 h at -78 °C the reaction was warmed to 0 °C and stirred 1 h. The mixture was quenched by pouring into 1 M HCl (50 mL) and ice (15 g). The organic layer was separated, and the aqueous layer was extracted with Et₂O (3 × 100 mL). The combined organic layers were washed with saturated Na₂S₂O₃, brine, dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography (10–20% EtOAc in hexane) to yield alkenyl iodide **21** (3.2 g, 62%, >95% *E*): R_f = 0.50 (20%, EtOAc in hexane); [α]²⁵_D = -10.5 (*c* = 15.8, in CHCl₃); IR (thin film, NaCl) 3476, 2955, 2866, 1394, 1251, 1070, 837 757 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.27 (dd, *J* = 7.9, 6.1 Hz, 1H), 3.71–3.62 (m, 2H), 3.49 (ddd, *J* = 11.9, 8.5, 3.4 Hz, 1H), 2.55 (15.9, 7.9 Hz, 1H), 2.44 (dd, *J* = 15.9, 6.1 Hz, 1H), 1.94–1.88 (m, 1H), 1.78–1.66 (m, 2H), 1.59–1.52 (m, 1H), 0.28 (s, 9H), 0.16 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 152.8, 109.4, 75.9, 71.6, 63.3, 39.8, 29.2, 24.1, 1.8, 0.6; HR-MS (ESI) Calcd for C₁₄H₂₉INaO₂Si₂ (M + Na)⁺ 435.0643, found 435.0636.

(2*R*,3*R*)-2-[(*Z*)-3,6-Bis-trimethylsilylanyl-hex-2-en-5-ynyl]-2-trimethylsilylanyl-tetrahydro-pyran-3-ol (**22**)

To a solution of 1-trimethylsilyl-1-propyne (0.9 mL, 6.2 mmol) in THF (10.5 mL) at -78 °C was added a 2.5 M solution of *n*-BuLi in hexane (2.6 mL) and TMEDA (1.0 mL, 6.5 mmol). The solution was warmed to 0 °C and stirred 45 min. The solution was then transferred to a slurry of CuI (1.3 g, 7.0 mmol) and DMAP (760 mg, 6.3 mmol) in THF (8.5 mL) at -78 °C. The solution was warmed to -20 °C, alkenyl iodide **21** (570 mg, 1.4 mmol) was added, and the reaction mixture was allowed to warm to room temperature gradually and stirred overnight. The reaction was quenched with 1 M HCl and the organic layer was separated. The aqueous layer was extracted with Et₂O (3 × 25 mL). The combined organic layers were washed with water, brine, dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield **22** (220 mg, 42%): R_f = 0.49 (20% EtOAc in hexane); [α]²⁵_D = -9.3 (*c* = 8.6, in CHCl₃); IR (thin film, NaCl) 3463, 2955, 2898, 2173, 1610, 1408, 1249, 1091, 839, 759 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.49 (t, *J* = 6.4 Hz, 1H), 3.78–3.65 (m, 2H), 3.57–3.48 (m, 1H), 3.04 (s, 2H), 2.61 (t, *J* = 6.4 Hz, 2H), 2.01–1.91 (m, 1H), 1.85 (d, *J* = 7.0 Hz, 1H), 1.87–1.77 (m, 1H), 1.76–1.65 (m, 1H), 1.60–1.49 (m, 1H), 0.21 (s, 9H), 0.16 (s, 9H), 0.15 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 139.2, 134.8, 106.0, 88.2, 76.0, 70.9, 62.2, 35.6, 29.0, 27.9, 23.1, 0.5, 0.3, 0.1; HR-MS (ESI) Calcd for C₂₀H₄₀NaO₂Si₃ (M + Na)⁺ 419.2234, found 419.2241.

(2*R*,3*R*)-2-((2*Z*,5*E*)-6-Iodo-3,6-bis-trimethylsilylanyl-hexa-2,5-dienyl)-2-trimethylsilylanyl-tetrahydro-pyran-3-ol (23)

To a solution of enyne **22** (0.5 g, 1.2 mmol) in Et₂O (5.0 mL) was added a 1 M solution of DIBAL in hexane (2.9 mL). The resulting solution was heated 24 h at reflux then cooled to -78 °C and diluted with Et₂O (0.5 mL). A solution of I₂ (1.2 g, 4.8 mmol) in Et₂O (1.0 mL) was added. After stirring 2 h at -78 °C the reaction was warmed to 0 °C and stirred 1 h. The reaction was quenched by pouring into 1 M HCl (5 mL) and ice (2 g). The organic layer was separated, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic layers were washed with saturated Na₂S₂O₃, brine, dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography (10% EtOAc in hexane) to yield alkenyl iodide **23** (0.3 g, 51%, >95% *E*): R_f = 0.33 (10% EtOAc in hexane); [α]_D²⁵ = -2.3 (*c* = 21.3, in CHCl₃); IR (thin film, NaCl) 3463, 2953, 2898, 2855, 1725, 1407, 1249, 1092, 839, 758 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.07 (t, *J* = 7.9 Hz, 1H), 6.13 (t, *J* = 6.4 Hz, 1H), 3.72-3.63 (m, 2H), 3.50 (ddd, *J* = 11.0, 6.7, 3.7 Hz, 1H), 2.83 (d, *J* = 7.6 Hz, 2H), 2.62-2.50 (m, 2H), 1.95-1.88 (m, 2H), 1.82-1.74 (m, 1H), 1.72-1.64 (m, 1H), 1.54-1.46 (m, 1H), 0.25 (s, 9H), 0.16 (s, 9H), 0.15 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 155.6, 139.4, 138.1, 107.1, 75.8, 70.6, 62.2, 42.4, 35.6, 27.9, 22.9, 1.3, 0.3, 0.0; HR-MS (ESI) Calcd for C₂₀H₄₁INaO₂Si₃ (M + Na)⁺ 547.1351, found 547.1349.

(2*R*,3*R*)-2-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-Methyl-3-trimethylsilylanyl-oxiranylmethyl)-3-trimethylsilylanyl-oxiranylmethyl]-2-trimethylsilylanyl-tetrahydro-pyran-3-ol (24)

To a slurry of CuCN (0.12 g, 1.4 mmol) in Et₂O (3.0 mL) at 0 °C was added a 1.6 M solution of MeLi in Et₂O (1.7 mL). After 15 min a solution of alkenyl iodide **23** (0.32 g, 0.6 mmol) in Et₂O (1.0 mL) was slowly added. The solution was maintained at 0 °C for 20 h at which time the reaction was carefully quenched with saturated NH₄Cl. The aqueous layer was separated and extracted with Et₂O (3 × 5 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude product was partially purified by column chromatography (10% EtOAc in hexane) to yield diene **38** (details below).

To a solution of crude diene **38** (40 mg, 97 μmol) was added CH₃CN/DMM (3.1 mL, 1:2 v:v), a 0.05 M solution of Na₂B₄O₇·10 H₂O in 4.0 × 10⁻⁴ M Na₂-(EDTA) (2.1 mL), *n*-BuNH₂SO₄ (7 mg, 21 μmol), and chiral ketone **19** (50 mg, 2.0 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone[®] (0.20 g, 0.33 mmol) in 4.0 × 10⁻⁴ M Na₂-(EDTA) (1.4 mL) and a 0.89 M solution of K₂CO₃ (1.4 mL). After the Oxone[®] and K₂CO₃ solutions had been added, the resulting mixture was diluted with water and extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The epoxide product could not be separated from the ketone catalyst and so was dissolved in CH₂Cl₂ (350 μL) and to this was added NaHCO₃ (29 mg, 340 μmol), and *m*-CPBA (12 mg, 68 μmol) and the reaction stirred 5 min. The reaction was quenched with 1 M NaOH and extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc in hexane) to afford bisepoxide epoxide **24** (8 mg, 23% over 2 steps, dr 8:1): R_f = 0.55 (30% EtOAc in hexane); [α]_D²⁵ = +17.4 (*c* = 2.3, in CHCl₃); IR (thin film, NaCl) 3442, 2955, 2853, 2360, 1250, 1091, 838, 755 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.08-4.02 (m, 1H); 3.66 (dt, *J* = 11.4, 3.5 Hz, 1H), 3.42 (td, *J* = 11.4, 2.8 Hz, 1H), 3.17 (dd, *J* = 8.7, 1.3 Hz, 1H), 2.66 (d, *J* = 7.1 Hz, 1H), 2.65 (d, *J* = 7.1 Hz, 1H), 2.18-2.06 (m, 2H), 1.98-1.90 (m, 2H), 1.79-1.69 (m, 2H), 1.68-1.60 (m, 2H), 1.11 (s, 3H), 0.10 (s, 9H), 0.08 (s, 9H), 0.00 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 76.8, 72.0, 64.4, 62.8, 60.6, 55.5, 38.5, 36.5, 29.6, 25.6, 23.3, 0.9, -0.4, -1.1; HR-MS (ESI) Calcd for C₂₁H₄₄NaO₄Si₃ (M + Na)⁺ 467.2445, found 467.2443.

(2R,3R)-2-Trimethylsilyl-2-((Z)-3-trimethylsilyl-but-2-enyl)-tetrahydro-pyran-3-ol (29)

To a solution of alkyne **20** (100 mg, 0.35 mmol) in Et₂O (1 ml) at 0 °C was added dropwise DIBALH (neat, 187 μl, 1.05 mmol). After gas evolution had ceased the solution was heated to reflux for 18h. The solution was cooled to 0 °C and treated with MeLi (1.6 M in Et₂O, 0.57 ml, 0.91 mmol). After stirring at room temperature for 1h the solution was cooled to -78 °C. CuCN (32 mg, 0.35 mmol) and LiCl (30 mg, 0.7 mmol) were weighed into a flask in a glove box under Ar. THF (1ml) was added and the solution stirred at room temperature for 5 min before cooling to -78 °C. The solution of CuCN•2LiCl was added by cannula to the vinyl alanate solution at -78 °C before addition of a solution of methyl iodide (88 μl, 1.4 mmol) in THF (500 ml). The solution was warmed to room temperature over 2 h then heated to 40 °C for 2 h. The reaction mixture was poured on to 1N HCl (5 ml) and ice. The organic layer was separated, and the aqueous layer was extracted with Et₂O (4 × 5 ml). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography (5% EtOAc in hexane) to yield olefin **29** (73 mg, 69%): R_f = 0.64 (20% EtOAc in hexane); [α]_D²⁵ = -17.0 (c = 1.2, in CHCl₃); IR (thin film, NaCl) 3486, 2953, 2932, 2869, 1249, 1086, 1069, 1016, 835, 756 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) δ 6.09 (app tq, J = 6.9, 1.9 Hz, 1H), 3.75-3.66 (m, 2H), 3.51 (ddd, J = 10.7, 6.3, 3.6 Hz, 1H), 2.56-2.51 (m, 2H), 1.99-1.88 (m, 1H), 1.85-1.62 (m, 3H) 1.77 (d, J = 1.7 Hz, 3H), 1.56-1.44 (m, 1H), 0.15 (s, 9H), 0.14 (s, 9H); ¹³C NMR δ (125 MHz, CDCl₃) δ 137.8, 137.1, 76.4, 71.0, 62.5, 35.7, 28.1, 25.6, 23.3, 0.4, 0.3; HR-MS (ESI) Calcd for C₁₅H₃₂NaO₂Si₂ (M + Na)⁺ 323.1833, found 323.1831.

(2R,3R)-2-((2Z,5Z)-3,6-bistrimethylsilylhepta-2,5-dienyl)-2-trimethylsilyl-tetrahydropyran-3-ol (31)

To a stirred solution of (Z)-3-trimethylsilyl-2-buten-1-ol³⁴ (500 mg, 3.47 mmol) in Et₂O (12 mL) at 0 °C under argon was added PBr₃ (166 μL, 1.74 mmol) and stirred for 2 h. The reaction was quenched by addition of a saturated solution of NaHCO₃ (2 ml). The aqueous layer was separated and extracted with Et₂O (3 × 5 ml). The combined organic layers were washed with water (3 × 5 ml), brine, dried over MgSO₄, filtered through a pad of silica and concentrated *in vacuo*. The crude bromide **30** was used without further purification. Using a modified procedure based on the work of Lipshutz,³⁵ a solution of alkyne **20** (50 mg, 0.18 mmol) in THF (350 μL) was added to Cp₂ZrHCl (136 mg, 0.53 mmol) under Ar. The resulting slurry was heated at 50°C for 3 h then cooled to -78°C and treated with MeLi (1.6 M in Et₂O, 120 μL, 0.19 mmol). The mixture was allowed to warm to room temperature over 1 h and then recooled to -78 °C. A solution of Me₂CuCNLi₂ was added dropwise (prepared by addition of MeLi (1.6M in Et₂O, 240 μL, 0.89 mmol) to a slurry of CuCN (17 mg, 0.19 mmol) in Et₂O (200 μL) at 0°C under Ar and stirring for 10 min). After 15 min a solution of the crude (Z)-4-bromobut-2-en-2-yl-trimethylsilane (146 mg, 0.70 mmol) in THF (700 μL) was added. The reaction was heated at 50°C for 15 h. The reaction was quenched by addition of aqueous NH₄OH/NH₄Cl (10% v/v) in saturated (2 mL). The product was extracted with Et₂O (4 × 20 mL) and dried over MgSO₄. The solution was filtered through a pad of celite and the solvent removed *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield the diene **31** (23 mg, 32%, >95% Z): R_f = 0.38 (10% EtOAc in hexane); [α]_D²⁵ = -3.76 (c = 2.6, in CHCl₃); IR (thin film, NaCl) 3447, 2952, 2854, 2360, 2341, 1247, 1091, 836, 755 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.07 (tt, J = 6.4, 1.6 Hz, 1H), 5.91 (tq, J = 7.2, 1.8 Hz, 1H), 3.75-3.66 (m, 2H), 3.52 (ddd, J = 11.4, 5.9, 3.9 Hz, 1H), 2.88-2.84 (m, 2H), 2.70 (ddt, J = 16.3, 6.4, 1.6 Hz, 1H), 2.51 (ddt, J = 16.0, 6.6, 1.6 Hz, 1H), 1.97-1.87 (m, 2H), 1.75-1.85 (m, 1H), 1.77 (q, J = 1.4 Hz, 3H), 1.64-1.72 (m, 1H), 1.44-1.52 (m, 1H), 0.17 (s, 9H), 0.14 (s, 9H), 0.11 (s, 9H); ¹³C NMR (100MHz, CDCl₃) δ 141.5, 140.2, 137.7, 135.7, 75.9, 70.3, 61.6, 39.2, 35.3, 27.1, 24.9, 22.4, 0.3, 0.1, -0.3; HR-MS (ESI) Calcd for C₂₁H₄₄NaO₂Si₃ (M+Na)⁺ 435.2541, found 435.2545.

(2Z,5E)-6-Iodo-3,6-bis-trimethylsilyl-hexa-2,5-dien-1-ol (32)

To a solution of (*Z*)-6-(*tert*-Butyl-dimethyl-silyloxy)-1,4-bis-trimethylsilyl-hex-4-en-1-yne^{15b} (9.6 g, 25 mmol) in Et₂O (60 mL) was added a 1 M solution of DIBAL in hexane (60 mL). The resulting solution was heated 24 h at reflux. This solution was then cooled to -78 °C, diluted with Et₂O (50 mL), and a solution of I₂ (25 g, 98 mmol) in Et₂O (150 mL) was added. After stirring 2 h at -78 °C, the reaction mixture was warmed to 0 °C and stirred 1 h, then warmed to room temperature and stirred 40 min before the reaction was quenched by pouring into 1 M HCl (200 mL) and ice (70 g). The organic layer was separated and the aqueous layer was extracted with Et₂O (3 × 250 mL). The combined organic layers were washed with saturated Na₂S₂O₃, brine, dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield alkenyl iodide **32** (5.6 g, 55%, >95% *E*): R_f = 0.28 (20% EtOAc in hexane); IR (thin film, NaCl) 3324, 2954, 1250, 839 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.10 (t, *J* = 7.6 Hz, 1H), 6.14 (tt, *J* = 7.0, 1.5 Hz, 1H), 4.23 (dd, *J* = 6.7, 5.8 Hz, 2H), 2.87 (dd, *J* = 7.6, 1.5 Hz, 2H), 0.27 (s, 9H), 0.17 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 154.4, 141.5, 141.4, 108.0, 62.3, 41.9, 1.2, 0.3; HR-MS (ESI) Calcd for C₁₂H₂₉INaOSi₂ (M + Na)⁺ 391.0381, found 391.0394.

(2Z,5Z)-3,6-Bis-trimethylsilyl-hepta-2,5-dien-1-ol (33)

To a slurry of CuCN (1.28 g, 14.29 mmol) in Et₂O (36 mL) at 0 °C was added a 1.6 M solution of MeLi in Et₂O (17.9 mL). After 15 min a solution of **32** (3.15 g, 6.35 mmol) in Et₂O (5.0 mL) was slowly added. The solution was maintained at 0 °C for 20 h at which time the reaction was carefully quenched with saturated NH₄Cl. The aqueous layer was separated and extracted with Et₂O (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography (10% EtOAc in hexane) to yield the dienol **33** (1.69 g, 4.4 mmol, 69%): R_f = 0.45 (10% EtOAc in hexane); IR (thin film, NaCl) 3315, 2954, 2898, 1616, 1444, 1406, 1249, 1035, 996, 837 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.12 (t, *J* = 7.0 Hz, 1H), 5.96-5.89 (m, 1H), 4.21 (t, *J* = 5.5 Hz, 2H), 3.48-3.55 (m, 1H), 2.84 (d, *J* = 7.0 Hz, 2H), 1.79 (s, 3H), 1.47-1.44 (m, 1H), 0.17 (s, 9H), 0.12 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 143.8, 141.0, 140.9, 137.0, 62.9, 39.4, 25.4, 0.9, 0.5; HR-MS (ESI) Calcd for C₁₃H₂₈NaOSi₂ (M + Na)⁺ 279.1576, found 279.1576.

(2R,3R)-2-(Trimethyl-silyl)-2-((2Z,5Z,8Z)-3,6,9-tris-trimethylsilyl-deca-2,5,8-trienyl)-tetrahydropyran-3-ol (27)

To a stirred solution of dienol **33** (890 mg, 2.32 mmol) in CH₂Cl₂ (4.6 ml) maintained at 0 °C under argon was added NEt₃ (647 μl, 4.6 mmol) and methanesulfonyl chloride (198 μl, 2.55 mmol) and stirred for 15 min. The reaction mixture was diluted with water (5 ml) and citric acid was added until pH 3-4. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (4 × 5 ml). The combined organic layers were washed with water (3 × 5 ml), brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude dienyl mesylate product **34** was used without further purification. Using a modified procedure based on the work of Ziegler:³⁶ To a stirred solution of **20** (570 mg, 2.0 mmol) in Et₂O (4 ml) maintained at 0 °C under argon, was added DIBALH (neat, 1.07 ml, 6.0 mmol). After gas evolution had ceased the solution was heated to reflux for 20 h. The solution was cooled to 0 °C and treated with MeLi (1.6M in Et₂O, 1.4 ml, 2.24 mmol). The mixture was allowed to warm to room temperature over 1.5 h and then re-cooled to -78 °C. To the reaction mixture was added a solution of CuI•P(OEt)₃ (713 mg, 2.0 mmol) in THF (7.0 ml). To the resulting light brown mixture was added a cooled solution of crude dienyl mesylate **34** in THF (1.0 ml) at -78 °C. The reaction mixture was allowed to warm slowly to room temperature over 18 h. The reaction mixture was poured on to 1N HCl (50 ml) and ice. The organic layer was separated, and the aqueous layer was extracted with Et₂O (4 × 50 ml). The

combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried over MgSO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (5% EtOAc in hexane) to give the desired triene **27** (321 mg, 31%, >95% Z); $R_f = 0.39$ (20% EtOAc in hexane); $[\alpha]_D^{25} = -6.0$ ($c = 1.67$ in CHCl_3); IR (thin film, NaCl) 3461, 2953, 2897, 1613, 1444, 1247, 1092, 836, 756 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.08 (t, $J = 6.4$ Hz, 1H), 5.96-5.87 (m, 2H), 3.75-3.65 (m, 2H), 3.48-3.55 (m, 1H), 2.89 (d, $J = 7.0$ Hz, 2H), 2.86 (d, $J = 7.0$ Hz, 2H), 2.65 (AB dd, $J = 15.8, 5.8$ Hz, 1H) and 2.54 (AB dd, $J = 16.2, 6.7$ Hz, 1H), 2.01-1.98 (m, 1H), 1.85 (d, $J = 7.6$, 1H), 1.87-1.77 (m, 1H), 1.78 (s, 3H), 1.76-1.65 (m, 1H), 1.54-1.46 (m, 1H), 0.21 (s, 9H), 0.18 (s, 9H), 0.17 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.0, 141.8, 140.1, 138.8, 137.8, 135.2, 75.8, 70.4, 61.8, 39.8, 39.2, 35.3, 27.3, 24.8, 22.6, 0.4, 0.3, 0.1, -0.2; HR-MS (ESI) Calcd for $\text{C}_{27}\text{H}_{56}\text{NaO}_2\text{Si}_4$ ($\text{M} + \text{Na}$) $^+$ 547.3250, found 547.3267.

(2S,3R)-2-((2R,3S)-3-Methyl-3-trimethylsilylanyl-oxiranylmethyl)-2-trimethylsilylanyl-tetrahydro-pyran-3-ol (35)

To olefin **29** (140 mg, 0.46 mmol) was added $\text{CH}_3\text{CN}/\text{DMM}$ (16 mL, 1:2 v:v), a 0.05 M solution of $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10 \text{H}_2\text{O}$ in 4.0×10^{-4} M Na_2 -(EDTA) (10.2 mL), *n*- Bu_4NHSO_4 (0.03 g, 0.09 mmol), and chiral ketone **19** (220 mg, 0.87 mmol). To this solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone[®] (0.22 g, 0.87 mmol) in 4.0×10^{-4} M Na_2 -(EDTA) (7.5 mL) and a 0.89 M solution of K_2CO_3 (7.5 mL). After the Oxone[®] and K_2CO_3 solutions had been added, the resulting mixture stirred 10 min then diluted with water (50 mL) and extracted with hexane (3×50 mL). The combined organic layers were dried over MgSO_4 , and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc in hexane) to yield epoxide **35** (90 mg, 62%, dr >95:5); $R_f = 0.49$ (20% EtOAc in hexane); $[\alpha]_D^{25} = +18.3$ ($c = 6.0$, in CHCl_3); IR (thin film, NaCl) 3436, 2955, 2854, 1440, 1408, 1370, 1250, 1091, 1025, 837, 755 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.06 (app dt, $J = 9.8, 4.6$ Hz, 1H), 3.79-3.74 (m, 1H), 3.55 (app dt, $J = 10.4, 3.0$ Hz, 1H), 3.09 (dd, $J = 8.5, 1.2$ Hz, 1H), 2.10 (d, $J = 5.5$ Hz, 1H), 2.06 (dd, $J = 15.0, 1.2$ Hz, 1H), 1.97-1.93 (m, 1H), 1.78-1.70 (m, 4H), 1.24 (s, 3H), 0.18 (s, 9H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 77.1, 72.0, 64.6, 61.9, 54.2, 36.3, 29.4, 25.6, 23.3, 0.9, -1.1; HR-MS (ESI) Calcd for $\text{C}_{15}\text{H}_{32}\text{NaO}_3\text{Si}_2$ ($\text{M} + \text{Na}$) $^+$ 339.1782, found 339.1772.

(2R,3R)-2methylsilylanyl-oxiranylmethyl]-3-trimethylsilylanyl-oxiranylmethyl]-3-trimethylsilylanyl-oxiranylmethyl]-2-trimethylsilylanyl-tetrahydro-pyran-3-ol (28)

To a solution of the triene **27** (89 mg, 0.17 mmol) was added $\text{CH}_3\text{CN}/\text{DMM}$ (5.3 mL, 1:2 v:v), a 0.05 M solution of $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10 \text{H}_2\text{O}$ in 4.0×10^{-4} M Na_2 -(EDTA) (3.5 mL), *n*- BuNHSO_4 (17.5 mg, 52 μmol), and chiral ketone **19** (130 mg, 0.5 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone[®] (626 mg, 1.02 mmol) in 4.0×10^{-4} M Na_2 -(EDTA) (4.5 mL) and a 0.89 M solution of K_2CO_3 (4.5 mL). After the Oxone[®] and K_2CO_3 solutions had been added, the resulting mixture was diluted with water and extracted with CH_2Cl_2 (4×15 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The epoxide product could not be separated from the ketone catalyst and so was dissolved in CH_2Cl_2 (2 mL) and to this was added NaHCO_3 (180 mg, 2.15 μmol), and *m*-CPBA (148 mg, 0.86 mmol) and the reaction stirred 30 min. The reaction was quenched with 1 M NaOH and extracted with CH_2Cl_2 (4×5 mL). The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by column chromatography (5–20% EtOAc in hexane) to afford triepoxide **28** (29 mg, 30%, dr 92:8); $R_f = 0.52$ (30% EtOAc in hexane); $[\alpha]_D^{25} = +24.5$ ($c = 3.67$ in CHCl_3); IR (thin film, NaCl) 3444 (br), 2955, 2899, 2853, 2360, 1250, 1091, 839, 755 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.02-4.08 (m, 1H), 3.67 (dt, $J = 11.6, 4.0$ Hz, 1H), 3.42 (td, $J = 11.1, 2.7$ Hz, 1H), 3.21 (d, $J = 8.2, 1.2$ Hz, 1H), 2.92 (dd, $J = 8.5, 3.0$ Hz, 1H), 2.71 (dd, $J = 7.9, 3.7$ Hz, 1H),

2.06-2.22 (m, 3H), 1.90-1.98 (m, 1H), 1.68-1.80 (m, 3H), 1.58-1.68 (m, 1H), 1.35-1.47 (m, 2H), 1.11 (s, 3H), 0.10 (s, 9H), 0.08 (s, 9H), -0.02 (s, 9H), -0.09 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 76.4, 71.4, 63.6, 62.2, 60.3, 60.0, 55.9, 55.0, 54.9, 38.6, 38.4, 36.0, 28.9, 24.8, 22.9, 0.4, -0.9, -0.9, -1.5; HR-MS (ESI) Calcd for $\text{C}_{27}\text{H}_{56}\text{NaO}_5\text{Si}_4$ (M + Na) $^+$ 595.3097, found 595.3107.

3-[(2R,3S)-3-((2R,3S)-3-Methyl-3-silanyl-oxiranylmethyl)-3-silanyl-oxiranyl]-propan-1-ol (36)

To a solution of acetate **65** (1.3 g, 3.7 mmol) in THF (8.0 mL) and MeOH (8.0 mL) at 0 °C was added a 1.0 M solution of LiOH (8.0 mL) and the mixture stirred 20 min. The mixture was diluted with water and extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo* to afford bisepoxide **36** (1.0 g, 84%): $R_f = 0.47$ (50% EtOAc in hexane); $[\alpha]_D^{25} = +4.4$ ($c = 18.3$, CHCl_3); IR (thin film, NaCl) 3445, 2957, 2360, 2341, 1441, 1418, 1371, 1250, 1062, 840, 756 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.68 (dt, $J = 5.5, 4.0$ Hz, 2H), 2.88 (dd, $J = 7.9, 4.0$ Hz, 1H), 2.71 (dd, 8.2, 3.7 Hz, 1H), 2.16 (dd, $J = 14.3, 3.4$ Hz, 1H), 1.85-1.71 (m, 4H), 1.55-1.28 (m, 2H), 1.19 (s, 3H), 0.17 (s, 9H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 63.7, 62.7, 62.4, 56.7, 55.1, 38.4, 30.5, 27.6, 22.9, -0.9, -1.5; HR-MS (ESI) Calcd for $\text{C}_{15}\text{H}_{32}\text{O}_3\text{Si}_2$ (M + H) $^+$ 317.1968 found, 317.1958.

(2S,4R,5R,2'S)-5-Methyl-2,5-bis-trimethylsilanyl-octahydro-[2,2']bifuranyl-4-ol (62)

To a solution of bisepoxide **36** (10 mg, 32 μmol) in CH_2Cl_2 (0.3 mL) at -78 °C was added $\text{Et}_2\text{O} \cdot \text{BF}_3$ (7 mg, 32 μmol) and the mixture stirred 2 h. The reaction was quenched with saturated NaHCO_3 and extracted with CH_2Cl_2 (3×2 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford bisfuran **62** (5.0 mg, 50%): IR (thin film, NaCl) 3375, 2953, 1739, 1451, 1246, 1052, 1063, 839 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.80 (d, $J = 11.6$ Hz, 1H), 3.99-3.94 (m, 2H), 3.88-3.83 (m, 1H), 3.79-3.74 (m, 1H), 2.26 (dd, $J = 14.0, 5.8$ Hz, 1H), 1.95-1.91 (m, 3H), 1.82 (d, $J = 14$ Hz, 1H), 1.33-1.28 (m, 1H), 0.94 (s, 3H), 0.09 (s, 9H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 85.1, 83.3, 82.1, 81.1, 67.0, 35.7, 29.6, 26.1, 25.4, -1.5, -1.8; HR-MS (ESI) Calcd for $\text{C}_{15}\text{H}_{33}\text{O}_3\text{Si}_2$ (M + H) $^+$ 317.1963, found 317.1967.

Acetic acid (2S,4R,5R,2'S)-5-methyl-2,5-bis-trimethylsilanyl-octahydro-[2,2']bifuranyl-4-yl ester (37)

To a solution of bisfuran **62** (6 mg, 19 μmol) in CH_2Cl_2 (0.4 mL) was added *i*-Pr $_2$ EtN (80 mg, 0.6 mmol), Ac_2O (60 mg, 0.6 mmol), and DMAP (2 mg, 16 μmol). The mixture stirred overnight and was quenched with saturated NH_4Cl and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3×3 mL). The combined organic layers were washed with water, brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude material was purified by column chromatography (20% EtOAc in hexane) to afford acetate **37** (5.0 mg, 87%): $R_f = 0.47$ (20% EtOAc in hexane); $[\alpha]_D^{25} = -50.0$ ($c = 1.0$, CHCl_3); IR (thin film, NaCl) 2959, 1743, 1450, 1368, 1246, 1109, 1072, 1045, 838, 754 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.16 (d, $J = 5.6$ Hz, 1H), 3.95-3.91 (m, 1H), 3.88-3.83 (m, 1H), 3.63-3.59 (m, 1H), 2.42 (dd, $J = 14.6, 5.8$ Hz, 1H), 2.20 (d, $J = 14.6$ Hz, 1H), 2.02 (s, 3H), 1.96-1.82 (m, 4H), 1.03 (s, 3H), 0.07 (s, 18H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.3, 85.3, 84.8, 82.0, 80.0, 68.0, 39.6, 28.4, 26.0, 25.0, 21.7, -0.6, -1.8; HR-MS (ESI) Calcd for $\text{C}_{17}\text{H}_{34}\text{NaO}_4\text{Si}_2$ (M + Na) $^+$ 381.1888, 381.1893.

(4Z,7E)-8-Iodo-5,8-bis-trimethylsilanyl-octa-4,7-dien-1-ol (63)

To a solution of alkyne **18** (18.7 g, 69.8 mmol) in Et_2O (170 mL) at 0 °C was added a 1 M solution of DIBAL in hexane (170 mL). The resulting solution was heated 24 h at reflux.

The solution was then cooled to $-78\text{ }^{\circ}\text{C}$, diluted with Et_2O (50 mL), and a solution of I_2 (71.0 g, 279.1 mmol) in Et_2O (150 mL) was added. After stirring 2 h at $-78\text{ }^{\circ}\text{C}$ the reaction was quenched by pouring into 1 M HCl (200 mL) and ice (40 g). The organic layer was separated and the aqueous layer was extracted with Et_2O ($3 \times 200\text{ mL}$). The combined organic layers were washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$, brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield alkenyl iodide **63** (22.9 g, 83%, >95% *E*): $R_f = 0.39$ (20% EtOAc in hexane); IR (thin film, NaCl) 3324, 2953, 2896, 1614, 1407, 1249, 1057, 839, 756 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.07 (t, $J = 7.6\text{ Hz}$, 1H), 5.93 (t, $J = 7.6\text{ Hz}$, 1H), 3.65 (t, $J = 6.4\text{ Hz}$, 2H), 2.81 (d, $J = 7.6\text{ Hz}$, 2H), 2.21 (q, $J = 14.9, 7.3\text{ Hz}$, 2H), 1.64 (t, $J = 7.3\text{ Hz}$, 2H), 1.42 (s, 1H-OH), 0.25 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.6, 143.3, 137.3, 107.2, 62.7, 42.3, 33.2, 28.6, 1.3, 0.4; HR-MS (ESI) Calcd for $\text{C}_{14}\text{H}_{29}\text{NaIOSi}_2$ ($\text{M} + \text{Na}$) $^+$ 419.0694, found 419.0674.

(4Z,7Z)-5,8-Bis-trimethylsilanyl-nona-4,7-dien-1-ol (**64**)

To a slurry of CuCN (2.5 g, 28.4 mmol) in Et_2O (34.0 mL) at $0\text{ }^{\circ}\text{C}$ was added a 1.4 M solution of MeLi in Et_2O (35.5 mL) and the mixture stirred 15 min. A solution of alkenyl iodide **63** (5.0 g, 12.6 mmol) in Et_2O (12.8 mL) was slowly added. The reaction was stirred for 20 h at $0\text{ }^{\circ}\text{C}$ then was carefully quenched with saturated NH_4Cl and extracted with Et_2O ($3 \times 40\text{ mL}$). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford diene **64** (3.1 g, 86%): $R_f = 0.39$ (20% EtOAc in hexane); IR (thin film, NaCl) 3322, 2953, 1615, 1248, 1058, 836, 755 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.95-5.89 (m, 2H), 3.66 (t, $J = 6.4\text{ Hz}$, 2H), 2.85-2.82 (m, 2H), 2.21 (app q, $J = 7.0\text{ Hz}$, 2H), 1.78 (d, $J = 2.7\text{ Hz}$, 3H), 1.67-1.62 (m, 2H), 0.15 (s, 9H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 142.1, 141.5, 139.2, 135.6, 62.9, 39.3, 33.3, 28.7, 24.9, 0.5, 0.0; HR-MS (ESI) Calcd for $\text{C}_{15}\text{H}_{32}\text{NaOSi}_2$ ($\text{M} + \text{Na}$) $^+$ 307.1884, found 307.1889.

Acetic acid 3-[(2R,3S)-3-((2R,3S)-3-methyl-3-silanyl-oxiranylmethyl)-3-silanyl-oxiranyl]-propyl ester (**65**)

To a solution of alcohol **64** (2.5 g, 8.7 mmol) in CH_2Cl_2 (87 mL) at $0\text{ }^{\circ}\text{C}$ was added pyridine (0.8 g, 10.4 mmol), Ac_2O (1.1 g, 10.4 mmol), and DMAP (0.11 g, 0.9 mmol). The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl and concentrated *in vacuo*. The remaining contents were extracted with Et_2O ($3 \times 50\text{ mL}$). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude product was partially purified by column chromatography (20% EtOAc in hexane) and carried to the next step.

To a solution of the acetate (2.0 g, 6.2 mmol) in $\text{CH}_3\text{CN}/\text{DMM}$ (192 mL, 1:2 v:v) was added a 0.05 M solution of $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{ H}_2\text{O}$ in $4.0 \times 10^{-4}\text{ M}$ Na_2 -(EDTA) (129 mL), *n*-BuNH SO_4 (0.4 g, 1.2 mmol), and chiral ketone **19** (3.2 g, 12.3 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone $^{\text{®}}$ (12.5 g, 20.0 mmol) in $4.0 \times 10^{-4}\text{ M}$ Na_2 -(EDTA) (86.0 mL) and a 0.89 M solution of K_2CO_3 (86.0 mL). After the Oxone $^{\text{®}}$ and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (200 mL) and extracted with EtOAc ($4 \times 400\text{ mL}$). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The epoxide product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) to afford bisepoxide **65** (1.3 g, 42% over 2 steps, dr >95:5): $R_f = 0.47$ (20% EtOAc in hexane); $[\alpha]_D^{25} = +3.7$ ($c = 2.7$, CHCl_3); IR (thin film, NaCl) 2958, 1742, 1367, 1250, 1045, 840, 756 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.18-4.09 (m, 2H), 2.87 (dd, $J = 7.9, 4.9\text{ Hz}$, 1H), 2.73 (dd, $J = 8.2, 3.7\text{ Hz}$, 1H), 2.18 (dd, $J = 14.7, 3.9\text{ Hz}$, 1H), 2.05 (s, 3H), 1.92-1.72 (m, 3H), 1.58-1.50 (m, 1H), 1.34 (dd, $J = 14.6, 8.5\text{ Hz}$, 1H), 1.22 (s, 3H), 0.19 (s,

9H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.8, 64.7, 63.7, 62.8, 56.6, 55.5, 38.9, 28.0, 27.0, 23.4, 21.7, -0.5, -1.1; HR-MS (ESI) Calcd for $\text{C}_{17}\text{H}_{34}\text{O}_4\text{Si}_2$ ($\text{M} + \text{Na}$) $^+$ 381.1888 found, 381.1997.

Carbonic acid *tert*-butyl ester (2*R*,3*S*)-3-((2*R*,3*S*)-3-methyl-3-trimethylsilylanyl-oxiranylmethyl)-3-trimethylsilylanyl-oxiranylmethyl ester (39)

To a solution of the dienyl alcohol **33** (0.7 g, 2.8 mmol) in CH_2Cl_2 (28 mL) was added Et_3N (0.8 mL, 5.6 mmol), BOC_2O (1.2 g, 5.6 mmol), and DMAP (30 mg, 0.3 mmol). The mixture stirred at room temperature overnight then was quenched with saturated NH_4Cl and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3×20 mL). The combined organic layers were washed with water, brine, dried over MgSO_4 , and concentrated *in vacuo*. The unpurified product mixture was carried on to the next step.

To a solution of the crude carbonate (1.0 g, 1.0 mmol) in $\text{CH}_3\text{CN}/\text{DMM}$ (94 mL, 1:2 v:v) was added a 0.05 M solution of $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10 \text{H}_2\text{O}$ in 4.0×10^{-4} M Na_2 -(EDTA) (63 mL), *n*- Bu_4NHSO_4 (0.2 g, 0.6 mmol), and chiral ketone **19** (1.6 g, 6.0 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone[®] (6.1 g, 9.9 mmol) in 4.0×10^{-4} M Na_2 -(EDTA) (42 mL) and a 0.89 M solution of K_2CO_3 (42 mL). After the Oxone[®] and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (150 mL) and extracted with EtOAc (4×200 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The asymmetric epoxidation procedure was repeated two times. The epoxide product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) to afford **39** (0.5 g, 39% over 3 steps, dr 6:1): $R_f = 0.62$ (20% EtOAc in hexane); $[\alpha]_D^{25} = +6.4$ ($c = 4.7$, CHCl_3); IR (thin film, NaCl) 2958, 1744, 1456, 1370, 1280, 1253, 1164, 1095, 842, 757 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.37 (dd, $J = 11.9, 2.4$ Hz, 1H), 4.03 (dd, $J = 11.9, 8.5$ Hz, 1H), 3.23 (dd, $J = 7.9, 3.1$ Hz, 1H), 2.74 (dd, $J = 7.6, 4.3$ Hz, 1H), 2.07 (dd, $J = 14.6, 3.7$ Hz, 1H), 1.59 (dd, $J = 14.6, 7.6$ Hz, 1H), 1.51 (s, 9H), 1.22 (s, 3H), 0.21 (s, 9H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 153.9, 83.2, 67.5, 62.4, 60.9, 55.8, 55.6, 38.1, 28.4, 23.3, -0.7, -1.1; HR-MS (ESI) Calcd for $\text{C}_{13}\text{H}_{36}\text{NaO}_5\text{Si}$ ($\text{M} + \text{Na}$) $^+$ 411.1993, found 411.2007.

(*S*)-4-((2*S*,4*R*,5*R*)-4-Hydroxy-5-methyl-2,5-bis-trimethylsilylanyl-tetrahydro-furan-2-yl)-[1,3]dioxolan-2-one (40)

To a solution of **39** (42 mg, 0.11 mmol) in CH_2Cl_2 (1.5 mL) at -78 °C was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (24 μL , 0.11 mmol). After 2 min the reaction was quenched with saturated NaHCO_3 and extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield **40** (13 mg, 36%): $R_f = 0.31$ (20% EtOAc in hexane); $[\alpha]_D^{25} = -20.0$ ($c = 1.0$, CHCl_3); IR (thin film, NaCl) 3496, 2955, 1786, 1250, 1180, 1074, 838, 754 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.35 (dd, $J = 8.9, 6.6$ Hz, 1H), 4.52 (dd, $J = 9.0, 6.6$ Hz, 1H), 4.45 (app t, $J = 9.0$ Hz, 1H), 4.32 (app t, $J = 4.6$ Hz, 1H), 2.35 (dd, $J = 14.3, 5.0$ Hz, 1H), 2.13 (d, $J = 14.3$ Hz, 1H), 1.80 (d, $J = 3.8$ Hz, 1H-OH), 0.99 (s, 3H), 0.14 (s, 9H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.1, 84.3, 82.6, 80.8, 80.7, 68.2, 41.7, 25.4, -1.1, -1.3; HR-MS (ESI) Calcd for $\text{C}_{14}\text{H}_{28}\text{NaO}_5\text{Si}$ ($\text{M} + \text{Na}$) $^+$ 355.1367, found 355.1375.

(2*S*,3*R*)-2-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-Methyl-3-silylanyl-oxiranylmethyl)-3-silylanyl-oxiranylmethyl]-tetrahydro-pyran-3-ol (41)

To a solution of the diene **57** (preparation below) (0.1 g, 0.4 mmol) in $\text{CH}_3\text{CN}/\text{DMM}$ (12.0 mL, 1:2 v:v) was added a 0.05 M solution of $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10 \text{H}_2\text{O}$ in 4.0×10^{-4} M Na_2 -(EDTA) (8.0 mL), *n*- Bu_4NHSO_4 (30 mg, 80 μmol), and chiral ketone **19** (0.2 g, 0.8 mmol). To this

rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone[®] (0.8 g, 1.3 mmol) in 4.0×10^{-4} M Na₂-(EDTA) (5.3 mL) and a 0.89 M solution of K₂CO₃ (5.3 mL). After the Oxone[®] and K₂CO₃ solutions had been added, the resulting mixture was diluted with water (20 mL) and extracted with EtOAc (4×10 mL). The combined organic layers were washed with brine, dried over MgSO₄, concentrated *in vacuo*. The asymmetric epoxidation procedure was repeated. The epoxide product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) to yield bisepoxide **41** (66 mg, 27% over 2 steps, dr 5:1): $R_f = 0.53$ (50% EtOAc in hexane); $[\alpha]_D^{25} = -2.62$ ($c = 26.7$, CHCl₃); IR (NaCl) 3444, 2955, 2854, 2361, 1750, 1440, 1412, 1373, 1251, 1096, 1048, 840, 756 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.93-3.88 (m, 1H), 3.60-3.54 (m, 1H), 3.34 (td, $J = 11.3, 4.0$ Hz, 1H), 3.22 (ddd, $J = 9.0, 5.6, 3.2$ Hz, 1H), 3.16 (dd, $J = 8.7, 3.1$ Hz, 1H), 2.74 (dd, $J = 7.5, 4.3$ Hz, 1H), 2.33 (br s, 1H-OH), 2.16 (dt, $J = 14.8, 3.2$ Hz, 1H), 2.11-2.07 (m, 1H), 2.01 (dd, $J = 14.6, 4.1$ Hz, 1H), 1.76 (ddd, $J = 14.8, 8.9, 6.0$ Hz, 1H), 1.73-1.63 (m, 2H), 1.56 (dd, $J = 14.8, 7.5$ Hz, 1H), 1.48-1.37 (m, 1H), 1.19 (s, 3H), 0.18 (s, 9H), 0.09 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 81.7, 70.3, 68.6, 62.7, 61.1, 56.5, 55.6, 38.4, 34.0, 33.0, 26.5, 23.3, -0.5, -1.1; HR-MS (ESI) Calcd for C₁₈H₃₆NaO₄Si₂ (M + Na)⁺ 395.2044, found 395.2040.

Spiroketal (42)

To a solution of bisepoxide **41** (10 mg, 27 μ mol) in CH₂Cl₂ (0.3 mL) at -78 °C was added BF₃·Et₂O (5 μ L, 40 μ mol) and the mixture stirred 2 min. The reaction was quenched with saturated NaHCO₃ and extracted with CH₂Cl₂ (3×2 mL). The combined organic layers were washed with water, brine, dried over MgSO₄, and concentrated *in vacuo*.

To a solution of the crude mixture in CH₂Cl₂ (0.5 mL) was added Et₃N (6 μ L, 40 μ mol), Ac₂O (3 μ L, 30 μ mol), and DMAP (1 mg, 8 μ mol). The mixture stirred overnight then was quenched with saturated NH₄Cl and concentrated *in vacuo*. The remaining contents were extracted with Et₂O (3×2 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography to yield what has been tentatively assigned the structure of spiroketal **42** (1 mg, 11% over 2 steps): IR (thin film, NaCl) 3584, 2939, 2862, 1743, 1247, 1096, 1048, 1025, 842 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.30 (dd, $J = 5.5, 1.0$ Hz, 1H), 3.94-3.89 (m, 1H), 3.62 (ddd, $J = 13.6, 9.2, 4.4$ Hz, 1H), 3.40 (app dt, $J = 11.9, 2.8$ Hz, 1H), 3.00-2.95 (m, 1H), 2.63-2.53 (m, 2H), 2.04 (s, 3H), 1.89-1.68 (m, 7 H), 1.43-1.35 (m, 1H), 1.33 (s, 3H), 0.08 (s, 9H); HR-MS (ESI) Calcd for C₁₇H₃₀NaO₅Si (M + Na)⁺ 365.1760, found 365.1758.

3-(3-Methyl-3-trimethylsilanyl-oxiranyl)-propan-1-ol (43)

To a solution of acetate **64** (0.8 g, 3.4 mmol) in THF (10 mL) and MeOH (10 mL) at 0 °C was added a 1.0 M solution of LiOH (10.2 mL) and the mixture stirred 20 min. The reaction was diluted with water and extracted with Et₂O (3×20 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo* to afford epoxide **43** (0.6 g, 91%): $R_f = 0.37$ (50% EtOAc in hexane); IR (thin film, NaCl) 3419, 1957, 1446, 1251, 1062, 841 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.61 (t, $J = 6.1$ Hz, 2H), 2.68 (dd, $J = 8.2, 3.7$ Hz, 1H), 1.77-1.65 (m, 3H), 1.42 (dt, $J = 13.7, 7.9$ Hz, 1H), 1.17 (s, 3H), 0.06 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 66.0, 62.3, 55.8, 30.3, 27.4, 22.9, -1.6; HR-MS (ESI) Calcd for C₉H₂₀O₂Si (M + Na)⁺ 211.1125, found 211.1119.

Acetic acid 3-(3-methyl-3-trimethylsilanyl-oxiranyl)-propyl ester (66)

To a solution of **67** (1.0 g, 4.7 mmol) in CH₂Cl₂ (15 mL) at 0 °C was added *m*-CPBA (0.8 g, 5.1 mmol). The resulting solution was warmed to room temperature and stirred 3.5 h. The reaction was quenched with a solution of 5% NaOH and extracted with CH₂Cl₂ (3×10 mL). The combined organic layers were washed with water, brine, dried over MgSO₄ and

concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford epoxide **66** (0.8 g, 74%): $R_f = 0.39$ (20% EtOAc in hexane); IR (thin film, NaCl) 2958, 1742, 1448, 1368, 1251, 1039, 841 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.11 (m, 2H), 2.70 (dd, $J = 7.6, 4.7$ Hz, 1H), 2.04 (s, 3H), 1.87-1.66 (overlapping m, 3H), 1.54-1.45 (m, 1H), 1.21 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.8, 65.8, 64.7, 55.6, 28.0, 27.0, 23.4, 21.7, -1.2; HR-MS (ESI) Calcd for $\text{C}_{11}\text{H}_{22}\text{NaO}_3\text{Si}$ ($\text{M}^+ + \text{Na}$) $^+$ 253.1230, found 253.1223.

(Z)-Acetic acid 5-trimethylsilylanyl-hex-4-enyl ester (67)

To a solution of alcohol **68** (2.8 g, 14 mmol) in CH_2Cl_2 (130 mL) at 0 °C was added Et_3N (1.8 g, 18 mmol), Ac_2O (1.8 g, 18 mmol), and DMAP (0.2 g, 1.4 mmol). The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3 \times 30 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford acetate **67** (2.8 g, 94%): $R_f = 0.65$ (20% EtOAc in hexane); IR (thin film, NaCl) 2954, 1744, 1620, 1441, 1366, 1248, 1042, 838 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.92 (tq, $J = 12.5, 5.4, 2.7$ Hz, 1H), 4.96 (t, $J = 10.9$ Hz, 2H), 2.19-2.11 (m, 2H), 2.04 (s, 3H), 1.74 (s, 3H), 1.72-1.63 (m, 2H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.3, 141.0, 136.1, 64.3, 29.4, 28.6, 25.1, 21.4, 0.2; HR-MR (ESI) Calcd for $\text{C}_{11}\text{H}_{22}\text{NaO}_2\text{Si}$ ($\text{M} + \text{Na}$) $^+$ 237.1281, found 237.1271.

(Z)-5-Trimethylsilylanyl-hex-4-en-1-ol (68)

To a slurry of CuCN (3.2 g, 35 mmol) in Et_2O (45 mL) at 0 °C was added a 1.4 M solution of MeLi in Et_2O (50 mL) and the mixture stirred 15 min. A solution of (E)-5-iodo-5-(trimethylsilyl)pent-4-en-1-ol¹⁵ (5.1 g, 18 mmol) in Et_2O (14 mL) was slowly added. The solution stirred 20 h at 0 °C then was carefully quenched with saturated NH_4Cl and extracted with Et_2O (3 \times 40 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford olefin **68** (3.1 g, 99%): $R_f = 0.31$ (20% EtOAc in hexane); IR (thin film, NaCl) 3332, 2951, 1619, 1442, 1248, 1054, 838, 755 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.97 (dt, $J = 7.6, 1.2$ Hz, 1H), 3.65 (t, $J = 6.7$ Hz, 2H), 2.16 (q, $J = 14.9, 7.6$ Hz, 2H), 1.75 (d, $J = 1.2$ Hz, 3H), 1.63 (m, 2H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.8, 135.6, 62.9, 33.3, 28.5, 24.9, 0.1; HR-MS (ESI) Calcd for $\text{C}_9\text{H}_{20}\text{NaSiO}$ ($\text{M} + \text{Na}$) $^+$ 195.1176, found 195.1188.

Representative Procedure for the Base-Promoted Cyclization of 43

To a solution of epoxide **43** (30 mg, 0.1 mmol) in MeOH (1.5 mL) was added Cs_2CO_3 (33 mg, 1.0 mmol). The reaction mixture was heated to 50 °C for 20 h. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O . The combined organic layers were dried over MgSO_4 and concentrated *in vacuo* to afford a mixture of pyran **44** and furan **45** (29 mg, 97%, 1.7:1 **44**:**45**).

2-Methyl-2-trimethylsilylanyl-tetrahydro-pyran-3-ol (44)

$R_f = 0.33$ (20% EtOAc in hexane); IR (thin film, NaCl) 3444, 2952, 2866, 1246, 1076, 1033, 838 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.74 (td, $J = 11.6, 3.1$ Hz, 1H), 3.59-3.49 (m, 2H), 2.10 (d, $J = 9$ Hz, 1H), 2.03-1.96 (m, 1H), 1.92-1.83 (m, 1H), 1.68-1.62 (m, 1H), 1.47-1.41 (m, 1H), 1.24 (s, 3H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 72.9, 71.8, 60.1, 25.9, 21.5, 18.7, -2.2; HR-MS (ESI) Calcd for $\text{C}_9\text{H}_{20}\text{NaO}_2\text{Si}$ ($\text{M} + \text{Na}$) $^+$ 211.1125, found 211.1136.

1-(Tetrahydro-furan-2-yl)-1-trimethylsilanyl ethanol (45)

R_f = 0.45 (20% EtOAc in hexane); IR (NaCl) 3469, 2957, 2863, 1461, 1290, 1247, 1060, 839, 752, 623 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.85 (m, 2H), 3.74 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 1.90-1.70 (m, 4H), 1.09 (s, 3H), 0.07 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 85.3, 68.9, 67.6, 26.7, 25.2, 20.1, -2.6; HR-MS (ESI) Calcd for $\text{C}_9\text{H}_{20}\text{NaO}_2\text{Si}$ ($M + \text{Na}$) $^+$ 211.1125, found 211.1120.

3-(3-Methyl-oxiranyl)-propan-1-ol (46)

Synthesized according to a reported procedure.³⁷

Representative Procedure for the Base-Promoted Cyclization of 46

To a solution of **46** (10 mg, 0.1 mmol) in MeOH (0.5 mL) was added Cs_2CO_3 (20 mg, 0.6 mmol). The resulting solution was heated to 50 °C and stirred 20 h. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O . The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. ^1H NMR of the unpurified reaction mixture showed a mixture of furan **47** and pyran **48** (6 mg, 60%, 5:1 **47:48**).

1-(Tetrahydro-furan-2-yl)-ethanol (47)

Spectral data were identical to that reported.^{5, 38}

2-Methyl-tetrahydro-pyran-3-ol (48)

Spectral data were identical to that reported.^{5, 39}

Representative Procedure for the Base-Promoted Cyclization of 36

To bisepoxide **36** (20 mg, 0.1 mmol) was added a 1.92 M solution of Cs_2CO_3 in MeOH (1.0 mL). The resulting solution was heated to 55–60 °C for 5 days. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (3 \times 5 mL). The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by column chromatography (**35**: 2 mg, 14%).

2-(3-Hydroxy-propyl)-3-methyl-cyclopent-2-enone (50)

R_f = 0.16 (80% EtOAc in hexane); IR (thin film, NaCl) 3421, 2920, 1694, 1639, 1441, 1386, 1176, 1061 cm^{-1} ; ^1H NMR (500 MHz) δ 3.51 (t, J = 6.1 Hz, 2H), 2.56-2.53 (m, 2H), 2.44-2.41 (m, 2H), 2.33 (t, J = 7.0 Hz, 2H), 2.09 (s, 3H), 1.66-1.60 (m, 2H); ^{13}C NMR (125 MHz) δ 196.3, 172.9, 140.7, 61.5, 34.9, 32.5, 31.9, 18.9, 17.9; HR-MS (ESI) Calcd for $\text{C}_9\text{H}_{14}\text{NaO}_2$ ($M + \text{Na}$) $^+$ 177.0886, found 177.0885.

(2R,3R,4aS,8aR)-2-Methyl-2-trimethylsilanyl-octahydro-pyrano[3,2-b]pyran-3-ol (51)

R_f = 0.48 (50%, EtOAc in hexane); $[\alpha]_D^{25}$ = +20.9 (c = 4.3, in CHCl_3); IR (thin film, NaCl) 3444, 2953, 2865, 1453, 1347, 1248, 1100, 1069, 1039, 839 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.93-3.89 (m, 1H), 3.58 (dd, J = 11.6, 5.2 Hz, 1H), 3.41-3.35 (m, 1H), 3.12 (ddd, J = 13.1, 8.9, 4.3 Hz, 1H), 2.98 (ddd, J = 13.4, 9.2, 4.6 Hz, 1H), 2.19 (app dt, J = 11.6, 4.9 Hz, 1H), 2.03-1.97 (m, 1H), 1.80-1.69 (m, 3H), 1.40-1.31 (m, 1H), 1.28 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 7.6, 77.0, 75.5, 74.3, 68.0, 37.3, 29.9, 25.9, 25.2, 0.3; HR-MS (ESI) Calcd for $\text{C}_{12}\text{H}_{24}\text{NaO}_3\text{Si}$ ($M + \text{Na}$) $^+$ 267.1387, found 267.1385.

General Procedure for Base-Promoted Cyclization of Epoxides 24, 28, 41, 52, 59 (Schemes 16, 17, 18 and 20)

Cs_2CO_3 and CsF were weighed into a flame-dried Schlenk tube in a glove box under Ar. To the tube was added a solution of the epoxide in MeOH. The tube was sealed and the

resulting slurry heated to 65 °C for 3–5 days. The MeOH was removed *in vacuo* and the reaction mixture partitioned between saturated NH₄Cl (10 ml) and EtOAc (10 ml). The layers were separated and the aqueous layer extracted with EtOAc (4 × 10ml). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by column chromatography (EtOAc/hexane) to give the pure product.

(2S,3R,4aS,8aR)-2-methyl-octahydropyrano[3,2-b]pyran-3-ol (53)

Following the general procedure, epoxide **52** (4 mg, 12.1 μmol) was heated at 65°C with Cs₂CO₃ (103 mg, 0.32 mmol) and CsF (48 mg, 0.32 mmol) in MeOH (165 μl) for 4 days. After standard workup, purification by column chromatography (50–75% EtOAc in hexane) afforded the diad **53** (1.2 mg, 55%); R_f = 0.34 (60 % EtOAc in hexane); [α]²⁵_D = -11.2 (c = 0.26 in CHCl₃); IR (thin film, NaCl) 3413, 2926, 2852, 1114, 1096, 1051, 1026 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.94-3.87 (m, 1H), 3.43-3.32 (m, 2H), 3.23 (ddd, *J* = 9.0, 6.1, 6.0 Hz, 1H), 3.06-2.96 (m, 2H), 2.34 (dt, *J* = 11.6, 4.3 Hz, 1H), 2.10-2.02 (m, 1H), 1.77-1.68 (m, 3H), 1.52-1.36 (m, 1H), 1.30 (d, *J* = 6.1, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 78.5, 77.8, 77.1, 71.8, 68.0, 39.2, 29.5, 25.7, 18.1; HR-MS (ESI) submitted.

(2S,3R,4aS,8aR)-2-Methyl-octahydropyrano[3,2-b]pyran-3-ol (53)

Following the general procedure, epoxide **52** (8 mg, 32.7 μmol) was heated at 65°C with Cs₂CO₃ (267 mg, 0.82 mmol) and CsF (125 mg, 0.82 mmol) in MeOH (427 μl) for 3 days to afford the diad **53** (3.5 mg, 62%).

(2S,3R,4aS,8aS,9aR,10aR)-2-Methyl-decahydro-1,8,10-trioxa-anthracen-3-ol (54)

Following the general procedure, bisepoxide **24** (8 mg, 18 μmol) was heated at 65°C with Cs₂CO₃ (147 mg, 0.45 mmol) and CsF (68 mg, 0.45 mmol) in MeOH (234 μl) for 5 days. After standard workup, purification by column chromatography (50–75% EtOAc in hexane) afforded the triad **54** (1.6 mg, 39%). Spectral data were identical to the previously prepared material.^{15a}

2aS,3aR,4aS,8aS,9aR,10aR)-2-Methyl-decahydro-1,8,10-trioxa-anthracen-3-yl acetate (60)

Following the general procedure, bisepoxide **41** (17 mg, 46 μmol) was heated at 65 °C with Cs₂CO₃ (300 mg, 0.91 mmol) and CsF (140 mg, 0.91 mmol) in MeOH (480 μl) for 3 days. After standard workup, partial purification by column chromatography (50–75% EtOAc in hexane) afforded the crude triad that was taken up in CH₂Cl₂ (810 μL). DMAP (14 mg, 0.11 mmol), pyridine (16 μL, 0.11 mmol) and acetic anhydride (11 μL, 0.11 mmol) were added and the mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous NH₄Cl. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (4 × 5 mL). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography (50% EtOAc in hexane) to afford **60** (4.3 mg, 35% over 2 steps) R_f = 0.60 (50% EtOAc in hexane); [α]²⁵_D = -4.3 (c = 0.46, CHCl₃); IR (thin film, NaCl) 2960, 2866, 2361, 1734, 1653, 1559, 1384, 1259, 1093, 1022, 841, 800 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.56 (ddd, *J* = 11.4, 9.6, 4.8 Hz, 1H), 3.96-3.90 (m, 1H), 3.47-3.35 (m, 2H), 3.19-3.01 (m, 4H), 2.47-2.42 (m, 1H), 2.36-2.30 (m, 1H), 2.12-2.06 (m, 2H), 2.07 (s, 3H), 1.78-1.71 (m, 2H), 1.53-1.42 (m, 2H), 1.20 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.2, 78.4, 76.4, 75.9, 72.4, 68.2, 35.8, 35.3, 29.4, 25.7, 21.3, 18.0; HR-MS (ESI) Calcd for C₁₄H₂₂NaO₅ (M+Na)⁺ 293.1365, found 293.1362.

(2R,3S,4aR,5aS,6aR,10aS,11aR,12aS)-2-Methyl-tetradecahydro-1,5,7,11-tetraoxa-naphthacen-3-yl acetate (55)

Following the general procedure, triepoxide **28** (25 mg, 43 μmol) was heated at 65 °C with Cs_2CO_3 (235 mg, 0.72 mmol) and CsF (109 mg, 0.72 mmol) in MeOH (460 μL) for 5 days. After standard workup, partial purification by column chromatography (50–75% EtOAc in hexane) afforded the crude tetrad that was taken up in CH_2Cl_2 (800 μL). DMAP (12 mg, 0.1 μmol), pyridine (15 μL , 0.1 μmol) and acetic anhydride (10 μL , 0.1 μmol) were added and the mixture was stirred at room temperature for 14 h. The reaction was quenched with saturated aqueous NH_4Cl . The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 \times 5 mL). The combined organic layers were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (50% EtOAc in hexane) to afford the acetylated tetrad **57** (2.1 mg, 15%); $R_f = 0.55$ (EtOAc); $[\alpha]_D^{25} = -7.6$ ($c = 0.13$ in CHCl_3); IR (thin film, NaCl) 2927, 2861, 1384, 1250, 1097, 1042 cm^{-1} ; ^1H NMR (400 MHz, CD_2Cl_2) δ 4.52 (ddd, $J = 11.4, 9.6, 4.8$ Hz, 1H), 3.91–3.85 (m, 1H), 3.47–3.32 (m, 2H), 3.18–3.08 (m, 4H), 3.08–2.97 (m, 2H), 2.40 (dt, $J = 11.1, 4.2$ Hz, 1H), 2.32–2.22 (m, 2H), 2.06–2.00 (m, 1H), 2.05 (s, 3H), 1.76–1.67 (m, 2H), 1.52–1.37 (m, 4H), 1.17 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 170.0, 78.9, 77.7, 77.6, 77.4, 77.1, 76.8, 76.7, 76.2, 72.6, 68.4, 36.1, 35.7, 35.5, 29.8, 26.1, 21.4, 18.1.

(2R,3S,4aR,5aS,6aR,10aS,11aR,12aS)-2-Methyl-tetradecahydro-1,5,7,11-tetraoxa-naphthacen-3-yl acetate (55)

Following the general procedure, triepoxide **28** (18 mg, 35.9 μmol) was heated at 65°C with Cs_2CO_3 (300 mg, 0.92 mmol) and CsF (140 mg, 0.92 mmol) in MeOH (480 μL) for 5 days. After standard workup, partial purification by column chromatography (50–75% EtOAc in hexane) afforded the crude tetrad that was taken up in CH_2Cl_2 (800 μL). DMAP (14 mg, 0.1 μmol), pyridine (16 μL , 0.1 mmol) and acetic anhydride (10 μL , 0.1 μmol) were added and the mixture was stirred at room temperature for 14 h. The reaction was quenched with saturated aqueous NH_4Cl . The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 \times 5 mL). The combined organic layers were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (50% EtOAc in hexane) to afford the acetylated tetrad **55** (2.1 mg, 20%).

(2S,3R)-2-((Z)-3-Trimethylsilyanyl-but-2-enyl)-tetrahydro-pyran-3-ol (56)

To a solution of olefin **29** (0.20 g, 0.67 mmol) in THF (6.5 mL) was added a 1 M solution of TBAF in THF (2.0 mL). The reaction mixture stirred at room temperature overnight then was quenched with water (10 mL). The aqueous layer was separated and extracted with EtOAc (3 \times 10 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (20% EtOAc in hexane) to afford monodesilylated olefin **56** (0.14 g, 95%): $R_f = 0.27$ (20% EtOAc in hexane); $[\alpha]_D^{25} = -23.9$ ($c = 9.2$, in CHCl_3); IR (thin film, NaCl) 3422, 2945, 2853, 1618, 1442, 1248, 1097, 1035, 838, 756 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.13 (app tq, $J = 6.3, 1.7$ Hz, 1H), 3.91–3.87 (m, 1H), 3.37 (ddd, $J = 13.6, 8.8, 4.7$ Hz, 1H), 3.31 (dt, $J = 11.1, 3.5$ Hz, 1H) 3.06 (ddd, $J = 11.7, 7.2, 4.6$ Hz, 1H), 2.66–1.60 (m, 1H), 2.34–2.27 (m, 1H), 2.11–2.05 (m, 2H), 1.78 (d, $J = 1.5$ Hz, 3H), 1.70–1.63 (m, 1H), 1.43–1.34 (m, 1H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.8, 138.0, 83.0, 78.0, 71.6, 68.4, 35.8, 33.4, 26.2, 25.6, 0.5; HR-MS (ESI) Calcd for $\text{C}_{12}\text{H}_{24}\text{NaO}_2\text{Si}$ ($M + \text{Na}$)⁺ 251.1438, found 251.1433.

(2S,3R)-2-((2R,3S)-3-Methyl-3-trimethylsilyanyl-oxiranylmethyl)-tetrahydro-pyran-3-ol (52)

To olefin **56** (96 mg, 0.42 mmol) was added $\text{CH}_3\text{CN}/\text{DMM}$ (12.8 mL, 1:2 v:v), a 0.05 M solution of $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10 \text{H}_2\text{O}$ in 4.0×10^{-4} M $\text{Na}_2\text{-(EDTA)}$ (8 mL), *n*- Bu_4NHSO_4 (26 mg,

0.8 mmol), and chiral ketone **19** (0.192 g, 0.74 mmol). To this solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone[®] (930 g, 1.51 mmol) in 4.0×10^{-4} M Na₂-(EDTA) (6.4 mL) and a 0.89 M solution of K₂CO₃ (6.4 mL). After the Oxone[®] and K₂CO₃ solutions had been added, the resulting mixture stirred 20 min then diluted with water (10 mL) and extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were dried over MgSO₄, and concentrated *in vacuo*. The crude material was purified by column chromatography (10–20% EtOAc in hexane) to yield epoxide **52** (87 mg, 85%, dr >95:5); R_f = 0.46 (20% EtOAc in hexane); [α]_D²⁵ = +8.6 (*c* = 4.7, in CHCl₃); IR (thin film, NaCl) 3438, 2956, 2853, 1440, 1251, 1097, 1039, 841, 756 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.92 (m, 1H), 3.64 (ddd, *J* = 15.4, 9.2, 4.4 Hz, 1H), 3.36 (app dt, *J* = 11.3, 3.7 Hz, 1H), 3.22 (ddd, *J* = 8.9, 5.3, 2.9 Hz, 1H), 3.01 (dd, *J* = 9.5, 2.4 Hz, 1H), 2.37 (d, *J* = 4.7 Hz, 1H), 2.16–2.09 (m, 2H), 1.77–1.66 (m, 2H), 1.47–1.38 (m, 1H), 1.24 (s, 3H), 0.13 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 81.9, 70.1, 68.8, 62.7, 55.3, 33.8, 32.7, 26.6, 23.3, -1.1; HR-MS (ESI) Calcd for C₁₂H₂₄NaO₃Si (M + Na)⁺ 267.1387, found 267.1385.

(2R,3R)-2-((2Z,5Z)-3,6-bistrimethylsilylhepta-2,5-dienyl)-tetrahydropyran-3-ol (57)

To a solution of diene **31** (86 mg, 0.2 mmol) in THF (2.1 mL) was added a 1 M solution of TBAF in THF (2.1 mL). The reaction mixture was stirred at 40 °C for 4 h. The reaction was quenched with water and extracted with Et₂O (4 × 20 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (20% EtOAc in hexane) to afford monodesilylated diene **57** (60 mg, 85%); R_f = 0.30 (20% EtOAc in hexane); [α]_D²⁵ = -6.6 (*c* = 9.1, in CHCl₃); IR (thin film, NaCl) 3405, 2951, 2852, 2360, 1616, 1442, 1248, 1097, 836 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.12 (ddt, *J* = 8.0, 6.2, 1.5 Hz, 1H), 5.90 (tq, *J* = 7.0, 1.6 Hz, 1H), 3.90 (ddt, *J* = 11.4, 3.9, 1.7 Hz, 1H), 3.29–3.43 (m, 2H), 3.09 (ddd, *J* = 8.8, 7.0, 4.9 Hz, 1H), 2.87–2.89 (m, 2H), 2.67 (ddd, *J* = 14.6, 8.2, 4.9 Hz, 1H), 2.32–2.39 (m, 1H), 2.06–2.13 (m, 1H), 1.78 (dd, *J* = 2.8, 1.4 Hz, 3H), 1.65–1.72 (m, 2H), 1.36–1.46 (m, 1H), 0.18 (s, 9H), 0.12 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 141.3, 141.0, 138.8, 135.7, 82.5, 71.3, 67.8, 39.6, 35.7, 32.8, 25.7, 24.9, 0.4, 0.0; HR-MS (ESI) Calcd for C₁₈H₃₆NaO₂Si₂ (M + Na)⁺ 363.2146, found 363.2151.

(2S,3R)-2-[(2R,3S)-3-((2R,3S)-3-Methyl-3-silanyl-oxiranylmethyl)-3-silanyl-oxiranylmethyl]-tetrahydro-pyran-3-ol (41)

To a solution of the diene **57** (0.1 g, 0.4 mmol) in CH₃CN/DMM (12.0 mL, 1:2 v:v) was added a 0.05 M solution of Na₂B₄O₇·10 H₂O in 4.0×10^{-4} M Na₂-(EDTA) (8.0 mL), *n*-Bu₄NHSO₄ (30 mg, 80 μmol), and chiral ketone **19** (0.2 g, 0.8 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone[®] (0.8 g, 1.3 mmol) in 4.0×10^{-4} M Na₂-(EDTA) (5.3 mL) and a 0.89 M solution of K₂CO₃ (5.3 mL). After the Oxone[®] and K₂CO₃ solutions had been added, the resulting mixture was diluted with water (20 mL) and extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine, dried over MgSO₄, concentrated *in vacuo*. The asymmetric epoxidation procedure was repeated. The epoxide product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) to yield bisepoxide **41** (27 mg, 29%, dr 92:8); R_f = 0.53 (50% EtOAc in hexane); [α]_D²⁵ = -2.62 (*c* = 26.7, CHCl₃); IR (thin film, NaCl) 3444, 2955, 2854, 2361, 1750, 1440, 1412, 1373, 1251, 1096, 1048, 840, 756 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.93–3.88 (m, 1H), 3.60–3.54 (m, 1H), 3.34 (td, *J* = 11.3, 4.0 Hz, 1H), 3.22 (ddd, *J* = 9.0, 5.6, 3.2 Hz, 1H), 3.16 (dd, *J* = 8.7, 3.1 Hz, 1H), 2.74 (dd, *J* = 7.5, 4.3 Hz, 1H), 2.33 (br s, 1H-OH), 2.16 (dt, *J* = 14.8, 3.2 Hz, 1H), 2.11–2.07 (m, 1H), 2.01 (dd, *J* = 14.6, 4.1 Hz, 1H), 1.76 (ddd, *J* = 14.8, 8.9, 6.0 Hz, 1H), 1.73–1.63 (m, 2H), 1.56 (dd, *J* = 14.8, 7.5 Hz, 1H), 1.48–1.37 (m, 1H), 1.19 (s, 3H), 0.18 (s, 9H), 0.09 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 81.7, 70.3, 68.6, 62.7, 61.1, 56.5,

55.6, 38.4, 34.0, 33.0, 26.5, 23.3, -0.5, -1.1; HR-MS (ESI) Calcd for $C_{18}H_{36}NaO_4Si_2$ ($M + Na$)⁺ 395.2044, found 395.2040.

(2S,3R)-2-((2Z,5Z,8Z)-3,6,9-tris-trimethylsilyl-deca-2,5,8-trienyl) tetrahydropyran-3-ol (58)

To a solution of triene **27** (150 mg, 0.33 mmol) in THF (3.3 mL) was added a 1 M solution of TBAF in THF (1.0 mL). The reaction mixture was stirred at 30 °C overnight. The reaction was quenched with water and extracted with Et₂O (4 × 20 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (10% EtOAc in hexane) to afford monodesilylated product **58** (83 mg, 56%): $R_f = 0.30$ (20% EtOAc in hexane); $[\alpha]_D^{25} = -12.7$ ($c = 2.36$ in CHCl₃); IR (thin film, NaCl) 3405 (br), 2952, 2896, 2852, 1614, 1441, 1406, 1247, 1098, 836, 755 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.10 (t, $J = 6.5$ Hz, 1H), 5.87-5.95 (m, 2H), 3.90 (br d, $J = 10.5$ Hz, 1H), 3.33-3.42 (m, 1H), 3.34-3.27 (m, 1H), 3.03-3.10 (m, 1H), 2.92 (d, $J = 7.0$ Hz, 2H), 2.86 (d, $J = 7.0$ Hz, 2H), 2.72-2.64 (m, 1H), 2.39-2.30 (m, 1H), 2.12-2.05 (m, 1H), 1.78 (s, 3H), 1.72-1.63 (m, 3H), 1.45-1.33 (m, 1H), 0.17 (s, 9H), 0.13 (s, 9H), 0.12 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 141.8, 141.7, 140.7, 139.0, 138.8, 135.2, 82.5, 71.0, 67.8, 39.9, 39.1, 35.4, 32.9, 25.7, 24.8, 0.4, 0.3, 0.1; HRMS calculated for $C_{24}H_{48}NaO_2Si_3$ 475.2854, found 475.2861.

(2S,3R)-2-[(2R,3S)-3-((2R,3S)-3-((2R,3S)-3-Methyl-3-trimethylsilyl-oxiranylmethyl)-3-trimethylsilyl-oxiranylmethyl)-3-trimethylsilyl-oxiranylmethyl]-tetrahydro-pyran-3-ol (59)

To a solution of the triene **58** (77 mg, 0.17 mmol) was added CH₃CN/DMM (5.3 mL, 1:2 v:v), a 0.05 M solution of Na₂B₄O₇·10 H₂O in 4.0×10^{-4} M Na₂-(EDTA) (3.5 mL), *n*-BuNH₄SO₄ (17.5 mg, 52 μmol), and chiral ketone **19** (132 mg, 0.5 mmol). To this rapidly stirring solution was added, simultaneously over 20 min *via* syringe pump, a solution of Oxone[®] (626 mg, 1.02 mmol) in 4.0×10^{-4} M Na₂-(EDTA) (4.5 mL) and a 0.89 M solution of K₂CO₃ (4.5 mL). After the Oxone[®] and K₂CO₃ solutions had been added, the resulting mixture was diluted with water and extracted with CH₂Cl₂ (4 × 20 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The epoxide product could not be separated from the ketone catalyst and so was dissolved in CH₂Cl₂ (1.1 mL) and to this was added NaHCO₃ (47 mg, 0.56 μmol), and *m*-CPBA (20 mg, 0.11 mmol) and the reaction stirred 30 min. The reaction was quenched with 1 M NaOH and extracted with CH₂Cl₂ (4 × 5 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude material was purified by column chromatography (10–20% EtOAc in hexane) to afford triepoxide **59** (43 mg, 50%, dr 90:10): $R_f = 0.52$ (50% EtOAc in hexane); $[\alpha]_D^{25} = +2.72$ ($c = 3.67$ in CHCl₃); IR (thin film, NaCl) 3455, 2956, 2852, 1440, 1412, 1251, 1096, 840, 756 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.88-3.97 (m, 1H), 3.53-3.63 (m, 1H), 3.32-3.41 (m, 1H), 3.22-3.30 (m, 2H), 2.92 (dd, $J = 8.0, 4.5$ Hz, 1H), 2.71 (dd, $J = 8.7, 4.0$ Hz, 1H), 2.15-2.24 (m, 2H), 2.08-2.15 (m, 1H), 1.85-1.74 (m, 3H), 1.53 (dd, $J = 14.5, 7.8$ Hz, 1H), 1.37-1.48 (m, 1H), 1.25-1.34 (m, 2H), 1.23 (s, 3H), 0.11 (s, 9H), 0.08 (s, 9H), -0.01 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 81.3, 70.1, 68.1, 62.2, 60.4, 60.1, 56.0, 55.8, 55.3, 38.6, 37.6, 38.8, 32.7, 26.0, 22.8, -0.9, -1.1, -1.6; HR-MS (ESI) Calcd for $C_{24}H_{48}NaO_5Si_3$ ($M + Na$)⁺ 523.2702, found 523.2696.

(3-Benzyloxy-2-methyl-tetrahydro-pyran-2-yl)-trimethyl-silane (61)

To a solution of pyran **44** (0.1 g, 0.5 mmol) in THF (1.5 mL) at 0 °C was added NaH (50 mg, 2.1 mmol), benzyl bromide (0.1 g, 0.8 mmol) and TBAI (2 mg, 50 μmol). The solution was warmed to room temperature and stirred overnight. The reaction was quenched with water and extracted with Et₂O (3 × 5 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography (5–10% EtOAc in hexane) to yield **61** (0.1 g, 68%): $R_f = 0.51$ (10% EtOAc

in hexane); IR (thin film, NaCl) 2952, 2854, 1454, 1244, 1092, 1077, 1026, 837, 744, 697 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.37-7.27 (m, 5H), 4.63 (d, $J = 11.6$ Hz, 1H), 4.38 (d, $J = 11.6$ Hz, 1H), 3.74 (ddd, $J = 11.3, 7.6, 3.4$ Hz, 1H), 3.56 (ddd, $J = 10.4, 6.4, 3.7$ Hz, 1H), 3.25 (dd, $J = 6.4, 3.7$ Hz, 1H), 1.99-1.79 (m, 3H), 1.49-1.42 (m, 1H), 1.25 (s, 3H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 139.6, 128.9, 128.4, 128.0, 81.5, 73.3, 71.3, 62.4, 23.5, 23.4, 21.7, -0.8; HR-MS (ESI) Calcd for $\text{C}_{16}\text{H}_{26}\text{NaO}_2\text{Si}$ ($\text{M} + \text{Na}$) $^+$ 301.1594, found 301.1601.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

For fellowship support T.P.H. thanks Johnson & Johnson and Boehringer-Ingelheim. G.L.S. thanks the UK/US Fulbright Commission and the Royal Commission for the Exhibition of 1851, and E.M. thanks the Spanish Ministry of Science and Education. We are grateful to Karen C. O'Brien and Aaron R. Van Dyke for preparing intermediates, Dr. Jeff Simpson for aid in the acquisition and interpretation of NMR spectra, and to Dr. Li Li (MIT) for obtaining mass spectrometric data.

References

- For reviews on ladder ether synthesis: (a) Sasaki M, Fuwa H. *Nat. Prod. Rep* 2008;25:401–426. [PubMed: 18389143] (b) Nakata T. *Chem Rev* 2005;105:4314–4347. [PubMed: 16351046] (c) Alvarez E, Candenias M-L, Pérez R, Ravelo JL, Martín JD. *Chem. Rev* 1995;95:1953–1980. (d) Hoberg JO. *Tetrahedron* 1998;54:12631–12670. (e) Marmsäter FP, West FG. *Chem. Eur. J* 2002;8:4347–4353. (f) Hirama, M.; Rainier, JD., editors. *Tetrahedron Symposium-in-Print* 90. Vol. 58. 2002. p. 1779-2040. (g) Evans PA, Delouvie B. *Curr. Opin. Drug Discovery Dev* 2002;5:986–999. (h) Vilotijevic, I.; Jamison, TF., editors. *Angew. Chem. Int. Ed. Vol. 48.* 2009. p. 5250-5281. (i) Morten CJ, Byers JA, Van Dyke AR, Vilotijevic I, Jamison TF. *Chem. Soc. Rev* 2009;38:3175–3192. [PubMed: 19847350]
- (a) Gallimore AR, Spencer JB. *Angew. Chem., Int. Ed* 2006;45:4406–4413. (b) Nicolaou KC, Frederick MO. *Angew. Chem., Int. Ed* 2007;46:5278–5282. (c) Nicolaou KC, Frederick MO, Burtoloso ACB, Denton RM, Rivas F, Cole KP, Aversa RJ, Gibe R, Umezawa T, Suzuki T. *J. Am. Chem. Soc* 2008;130:7466–7476. [PubMed: 18481856]
- (a) Nakanishi K. *Toxicon* 1985;23:473–479. [PubMed: 3895583] (b) Lee MS, Repeta DJ, Nakanishi K, Zagorski MG. *J. Am. Chem. Soc* 1986;108:7855–7856. See also: (c) Chou H-N, Shimizu Y. *J. Am. Chem. Soc* 1987;109:2184–2185.
- Coxon JM, Hartshorn MP, Swallow WH. *Aust. J. Chem* 1973;26:2521–2526.
- (a) Nicolaou KC, Duggan ME, Hwang C-K, Somers PK. *J. Chem. Soc., Chem. Commun* 1985:1359–1362. (b) Nicolaou KC, Prasad CVC, Somers PK, Hwang C-K. *J. Am. Chem. Soc* 1989;111:5330–5334.
- Tokiwano T, Fujiwara K, Murai A. *Synlett* 2000:335–338.
- (a) McDonald FE, Wang X, Do B, Hardcastle KI. *Org. Lett* 2000;2:2917–2919. [PubMed: 10964398] (b) McDonald FE, Bravo F, Wang X, Wei X, Toganoh M, Rodríguez JR, Do B, Neiwert WA, Hardcastle KI. *J. Org. Chem* 2002;67:2515–2523. [PubMed: 11950296] (c) Bravo F, McDonald FE, Neiwert WA, Do B, Hardcastle KI. *Org. Lett* 2003;5:2123–2126. [PubMed: 12790544] (d) Bravo F, McDonald FE, Neiwert WA, Hardcastle KI. *Org. Lett* 2004;6:4487–4489. [PubMed: 15548057] (e) Valentine JC, McDonald FE, Neiwert WA, Hardcastle KI. *J. Am. Chem. Soc* 2005;127:4586–4587. [PubMed: 15796519]
- Our laboratory has also reported another approach to this problem, one in which no directing groups are attached to the epoxides and in which the cascades were conducted in aqueous environments: Vilotijevic I, Jamison TF. *Science* 2007;317:1189–1192. [PubMed: 17761875] This work and other recent related investigations are described at the end of the Results and Discussion section of this manuscript

10. For examples of the regioselective opening of epoxysilanes: (a) Fristad WE, Bailey TR, Paquette LA. *J. Org. Chem* 1980;45:3028–3037. (b) Ehlinger E, Magnus P. *J. Am. Chem. Soc* 1980;102:5004–5011. (c) Davis AP, Hughes GJ, Lowndes PR, Robbins CM, Thomas EJ, Whitman GH. *J. Chem. Soc., Perkin Trans 1* 1981:1934–1941. (d) Tamao K, Nakajo E, Ito Y. *J. Org. Chem* 1987;52:4412–4414. (e) Shimizu M, Yoshioka H. *Tetrahedron Lett* 1989;30:967–970. (f) Yoshida J-I, Maekawa T, Morita Y, Isoe S. *J. Org. Chem* 1992;57:1321–1322. (g) Jankowski P, Raubo P, Wicha J. *Synlett* 1994:985–992. (h) Raubo P, Wicha J. *Tetrahedron: Asymmetry* 1996;7:763–770. (i) Hodgson DM, Comina PJ. *J. Chem. Soc., Chem. Commun* 1996:755–756. For a review: (j) Hudrlik, PF.; Hudrlik, AM. α , β -Epoxysilanes. In: Larson, GL., editor. *Advances in Silicon Chemistry*. Vol. 2. Greenwich, CT: JAI Press; 1993. p. 1-89.
11. (a) Robbins CM, Whitham GH. *J. Chem. Soc., Chem. Commun* 1976:697–698. (b) Hudrlik PF, Hudrlik AM, Rona RJ, Misra RN, Withers GP. *J. Am. Chem. Soc* 1977;99:1993–1996.
12. The directing ability demonstrated by SiMe₃ in regioselective epoxide openings has been the subject of much speculation and study: (a) Hudrlik PF, Ma D, Bhamidipati RS, Hudrlik AM. *J. Org. Chem* 1996;61:8655–8658. (b) Berti G, Canedoli S, Crotti P, Macchia F. *J. Chem. Soc., Perkin Trans. 1* 1984:1183–1188. (c) Hudrlik PF, Wan C-H, Withers GP. *Tetrahedron Lett* 1976;19:1453–1456. (d) Eisch JJ, Trainor JT. *J. Org. Chem* 1963;28:2870–2876. For crystallographic evidence of a lengthened C-O bond in epoxysilanes and discussion: (e) Hodgson DM, Comina PJ, Drew MGB. *J. Chem. Soc., Perkin Trans. 1* 1997:2279–2289. (f) Kabat MM. *J. Org. Chem* 1995;60:1823–1827. (g) Molander GA, Mautner K. *J. Org. Chem* 1989;54:4042–4050. (i) Illa O, Gornitzka H, Baceiredo A, Bertrand G, Branchadell V, Ortuño RM. *J. Org. Chem* 2003;68:7707–7710. [PubMed: 14510546] (j) Siriwardane U, Chu SSC, Buynak JD. *Acta Crystallogr. Sect. C* 1989;45:531–533. (k) Yamamoto K, Kawanami Y, Miyazawa M. *J. Chem. Soc., Chem. Commun* 1993:436–437. (l) Kawai T, Isobe M, Peters SC. *Aust. J. Chem* 1995;48:115–131. (m) Fristad WF, Bailey TR, Paquette LA. *J. Am. Chem. Soc* 1979;101:4420–4423. (n) Hine, J. *Structural Effects on Equilibria in Organic Chemistry*. New York: Wiley; 1975.
13. We have reported a preliminary account of some of the investigations described herein: Simpson GL, Heffron TP, Merino E, Jamison TF. *J. Am. Chem. Soc* 2006;128:1056–1057. [PubMed: 16433504]
14. Aidwidjaja G, Flörke H, Kirschning A, Schaumann E. *Tetrahedron Lett* 1995;36:8771–8774.
15. (a) Heffron TP, Jamison TF. *Org. Lett* 2003;5:2339–2442. [PubMed: 12816443] (b) Heffron TP, Trenkle JD, Jamison TF. *Tetrahedron* 2003;59:8913–8917.
16. For examples of hydrometallation/transmetallation/coupling of trimethylsilylalkynes with Z-geometry: Aluminum: (a) Uchida K, Utimoto K, Nozaki H. *J. Org. Chem* 1976;41:2215. (b) Eisch JJ, Damasevitz GA. *J. Org. Chem* 1976;41:2214. Aluminum→Copper: (c) Ziegler FE, Mikami K. *Tetrahedron Lett* 1984;25:131. Copper: (d) Obayashi M, Utimoto K, Nozaki H. *J. Organomet. Chem* 1979;177:145. Boron→Copper: (e) Uchida K, Utimoto K, Nozaki H. *J. Org. Chem* 1976;41:2941. (f) Uchida K, Utimoto K, Nozaki H. *Tetrahedron* 1977;33:2987. (g) Obayashi M, Utimoto K, Nozaki H. *Tetrahedron Lett* 1977:1805.
17. A range of other copper salts (CuCl, CuI/DMAP, CuBr•SMe₂, (2-thiophene)Cu(CN)Li) proved either unreactive or served to scramble the *E/Z* geometry of the alkenyl product.
18. Han S, Kass SR. *Tetrahedron Lett* 1997;38:7503–7505.
19. Wang Z-X, Miller SM, Anderson OP, Shi Y. *J. Org. Chem* 2001;66:521. [PubMed: 11429824]
20. See Supplementary Information for details for details of the preparation of **36**.
21. This compound was produced in analogous fashion to polyepoxides **35**, **24**, **28**. For details see Supplementary Information.
22. The structure of spiroketal **42** was assigned on the basis of ¹H NMR, HR-MS, and HMBC analysis that shows a ¹³C signal at 106 ppm.
23. For examples of epoxides as nucleophiles: (a) Crisóstomo FRP, Martín T, Martín VS. *Org. Lett* 2004;6:565–568. [PubMed: 14961624] (b) Alvarez E, Díaz MT, Pérez R, Ravelo JL, Regueiro A, Vera JA, Zurita D, Martín JD. *J. Org. Chem* 1994;59:2848–2876. (c) David F. *J. Org. Chem* 1981;46:3512–3519. (d) Tokumasu M, Sasaoka A, Takagi R, Hiraga Y, Ohkata K. *J. Chem. Soc., Chem. Commun* 1997:875–876.

24. (a) Hayashi N, Fujiwara K, Murai A. *Tetrahedron Lett* 1996;37:6173–6176. (b) Hayashi N, Fujiwara K, Murai A. *Tetrahedron* 1997;53:12425–12468. (c) Fujiwara K, Hayashi N, Tokiwano T, Murai A. *Heterocycles* 1999;50:561–593.
25. For examples of hydroxy-epoxide cyclizations under basic conditions: (a) Boons G-J, Brown DS, Clase JA, Lennon IC, Ley SV. *Tetrahedron Lett* 1994;35:319–322. (b) Emery F, Vogel P. *J. Org. Chem* 1995;60:5843–5854. (c) Masamune T, Ono M, Sato S, Murai A. *Tetrahedron Lett* 1978;4:371–374. (d) Murai A, Ono M, Masamune T. *J. Chem. Soc., Chem. Commun* 1976:864–865.
26. See Supplementary Information for the details of the preparation of **43**.
27. Matsubara, S. Rubidium and Cesium in Organic Synthesis. In: Yamamoto, H.; Oshima, K., editors. *Main Group Metals in Organic Synthesis*. Vol. 1. New York: Wiley; 2003. p. 35-50.
28. The use of 700 mol% Li_2CO_3 in H_2O led to no conversion of starting material (**36**) after 3 days at 50 °C.
29. For related examples: (a) Stork G, Colvin E. *J. Am. Chem. Soc* 1971;93:2080–2081. (b) Stork G, Jung ME. *J. Am. Chem. Soc* 1974;96:3682–3684. (c) Flörke H, Schaumann E. *Synthesis* 1996:647–651. (d) Gröbel B-T, Seebach D. *Angew. Chem. Int. Ed* 1974;13:83–84. (e) Boeckman RK, Bruza KJ. *Tetrahedron Lett* 1974;16:3365–3368. (f) Hudrlik PF, Hudrlik AM, Misra RN, Peterson D, Withers GP, Kulkarni AK. *J. Org. Chem* 1980;45:4444–4448.
30. Treatment under several conditions known to effect protiodesilylation of β -hydroxy silanes (TBAF/THF, $\text{KO}^t\text{Bu}/\text{DMSO}$, $\text{KO}^t\text{Bu}/\text{DMF}$, CsF, CsOH in THF, DMF and MeOH) gave no desired product with decomposition and elimination predominating.
31. (a) Peterson DJ. *J. Org. Chem* 1968;33:780–784. (b) Magnus P, Roy G. *J. Chem. Soc., Chem. Commun* 1979:822–823. (c) Hudrlik PF, Hudrlik AM, Kulkarni AK. *J. Am. Chem. Soc* 1982;104:6809–6811. (d) Hudrlik PF, Holmes PE, Hudrlik AM. *Tetrahedron Lett* 1988;29:6395–6398.
32. (a) Van Dyke AR, Jamison TF. *Angew. Chem. Int. Ed* 2009;48:4430–4432. (b) Byers JA, Jamison TF. *J. Am. Chem. Soc* 2009;131:6383–6385. [PubMed: 19385615] (c) Morten CJ, Jamison TF. *J. Am. Chem. Soc* 2009;131:6678–6679. [PubMed: 19402635] (d) Morten CJ, Jamison TF. *Tetrahedron* 2009;65:6648–6655. [PubMed: 20161178] (e) Tanuwidjaja J, Ng S-S, Jamison TF. *J. Am. Chem. Soc* 2009;131:12084–12085. [PubMed: 19663441]
33. Still WC, Kahn M, Mitra A. *J. Org. Chem* 1978;43:2923–2925.
34. Han S, Kass SR. *Tetrahedron Lett* 1997;38:7503.
35. Lipshutz BH, Ellsworth EL. *J. Am. Chem. Soc* 1990;112:7440.
36. Ziegler FE, Mikami K. *Tetrahedron Lett* 1984;25:131.
37. Hansen, K. Ph.D. Thesis. Cambridge, MA: Harvard University; 1998.
38. Taillez B, Bertrand MP, Surzur J-M. *J. Chem. Soc., Perkin Trans. 2* 1983:547–554.
39. Bartner P, Boxler DL, Brambilla R, Mallams AK, Morton JB, Reichert P, Sancilio FD, Surprenant H, Tomalesky G. *J. Chem. Soc., Perkin Trans. 1* 1979:1600–1624.

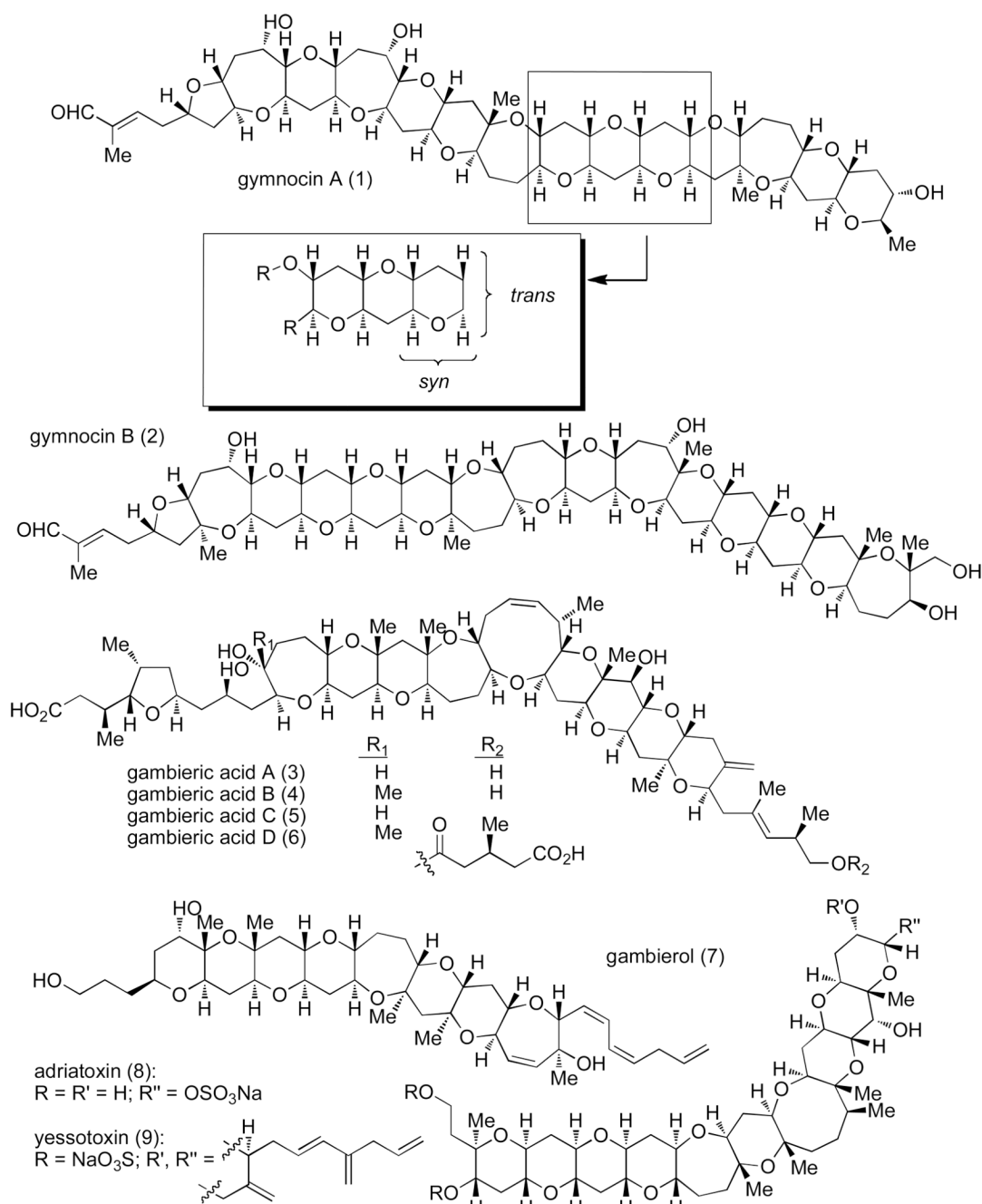


Figure 1.
Representative examples of polyethers containing the characteristic *trans-syn* topography.

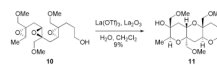


Figure 2.
Chelation-directed cascades (Murai).

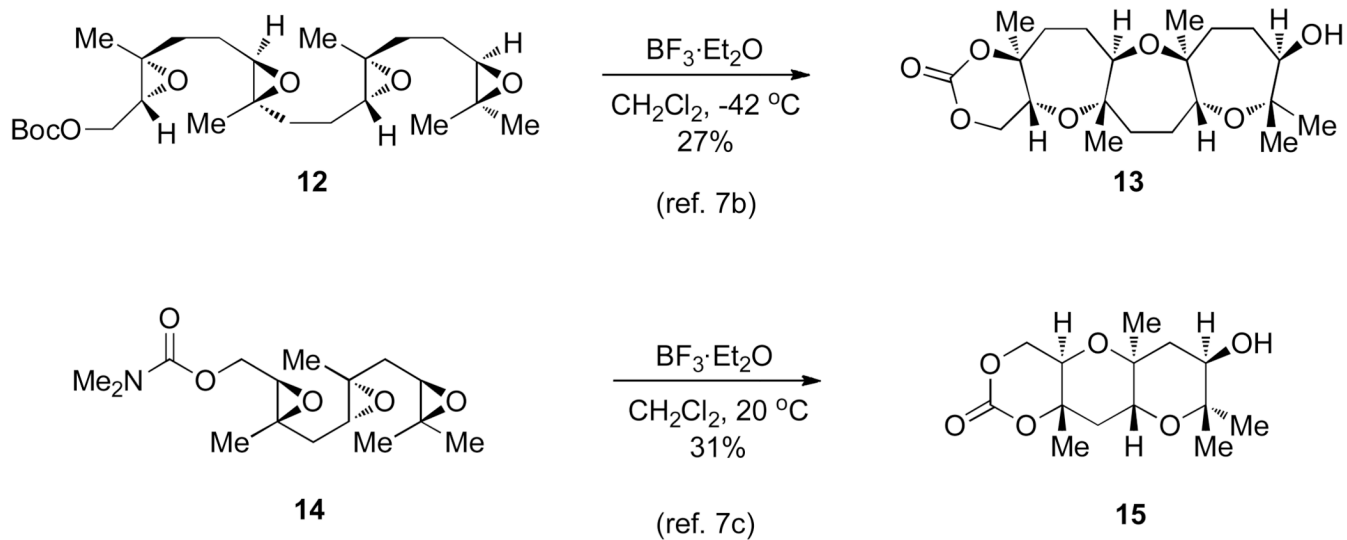


Figure 3.
Cascades directed by methyl groups at each nascent ring junction (McDonald).



Figure 4. McDonald's cascade synthesis of a polyoxepane that contains two ring junctions without directing groups.

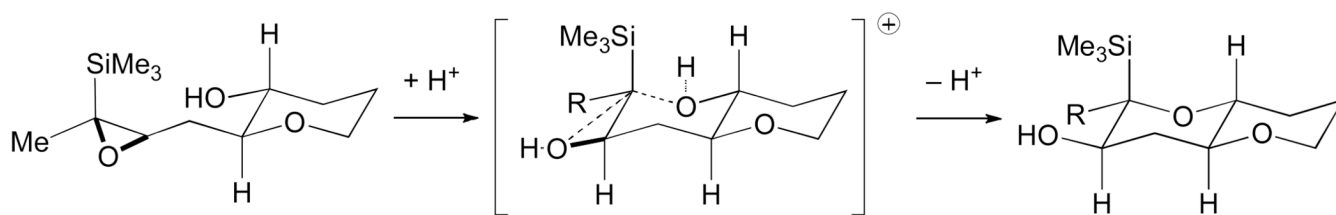


Figure 5.
The SiMe_3 group resides in a pseudo-axial position in the transition state in the cyclization of an epoxysilane.

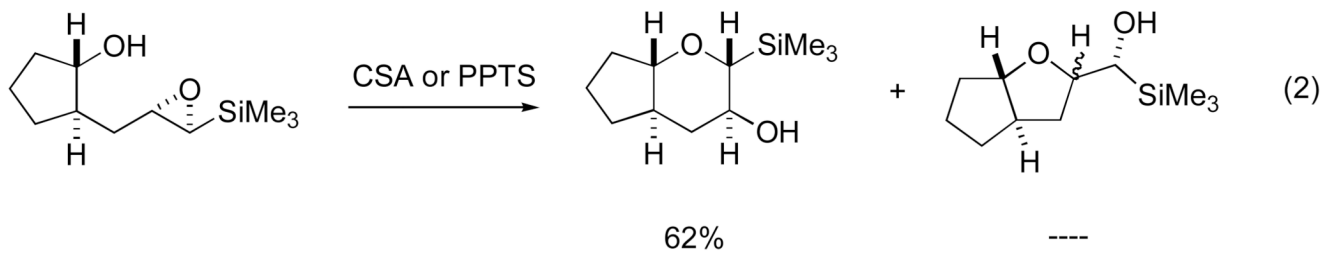
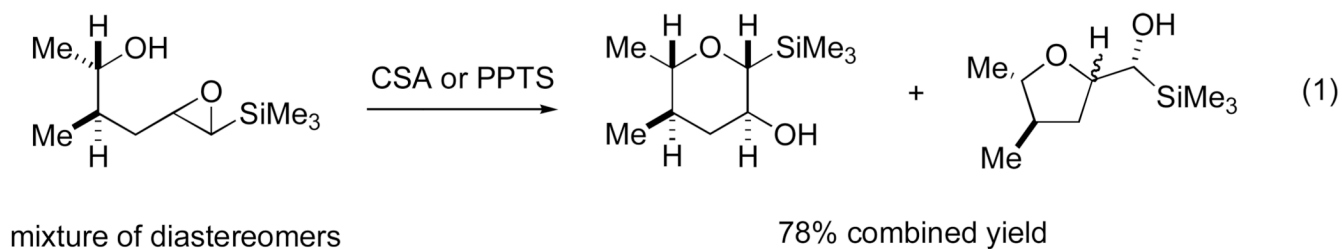


Figure 6. Cyclizations of epoxysilanes in which SiMe₃ would occupy a pseudo-equatorial position in the proposed transition state (Schaumann and coworkers).

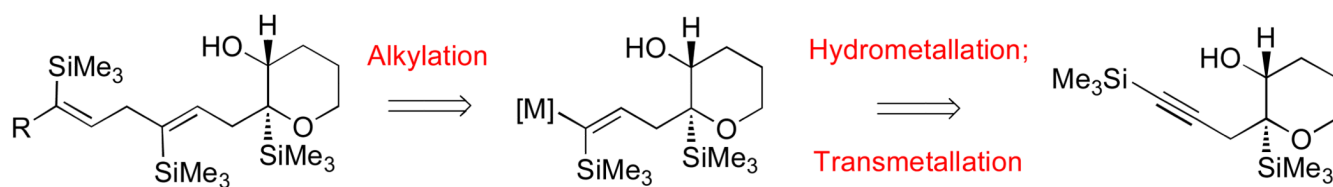


Figure 7.
Convergent strategy of polyene synthesis utilizing a four-stage, one-pot reaction.

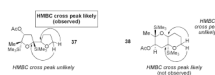


Figure 8.
HMBC analysis used to distinguish between two potential products of cascade.

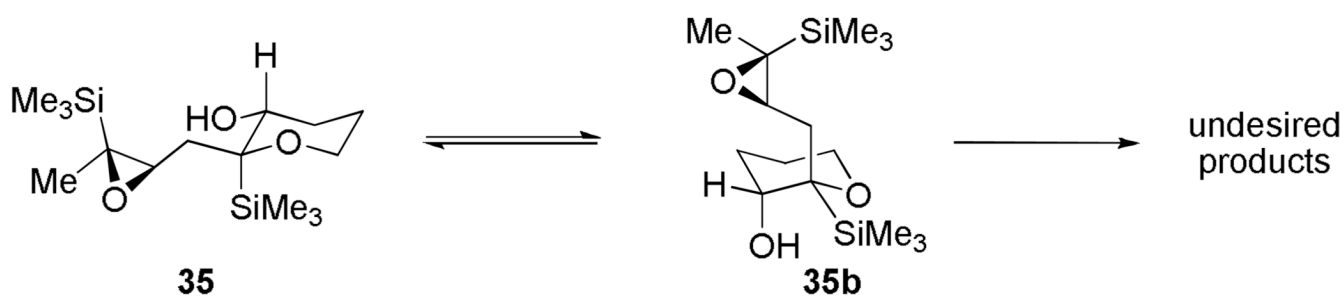


Figure 9.
One conformation of **35** cannot lead to the desired cyclization product.

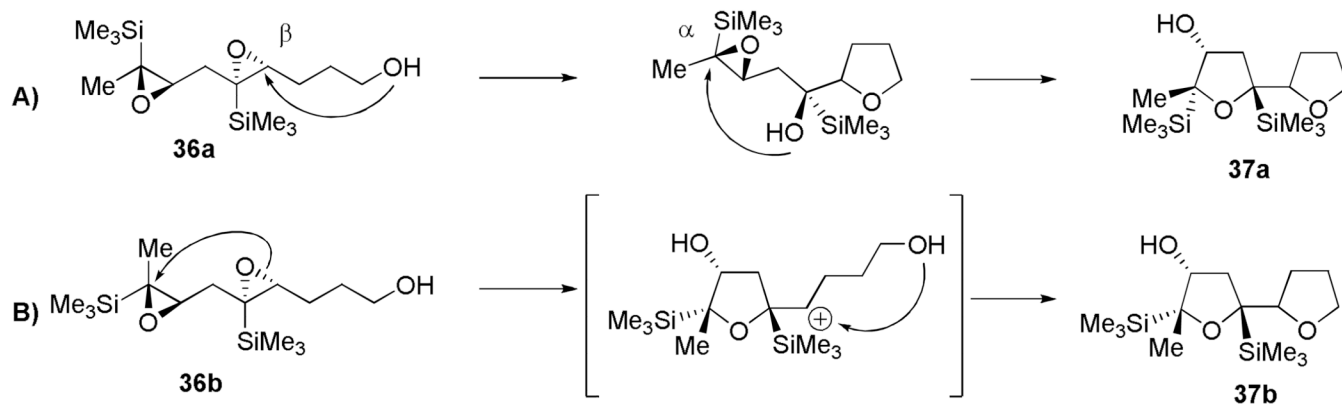


Figure 10.
Possible sequences of steps in cascades leading to the formation of bisfuran **37**.

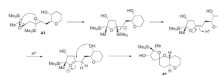


Figure 11.
Proposed mechanism for the formation. of spiroketal **42**

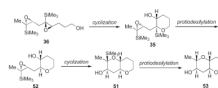
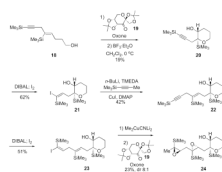
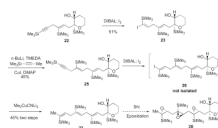


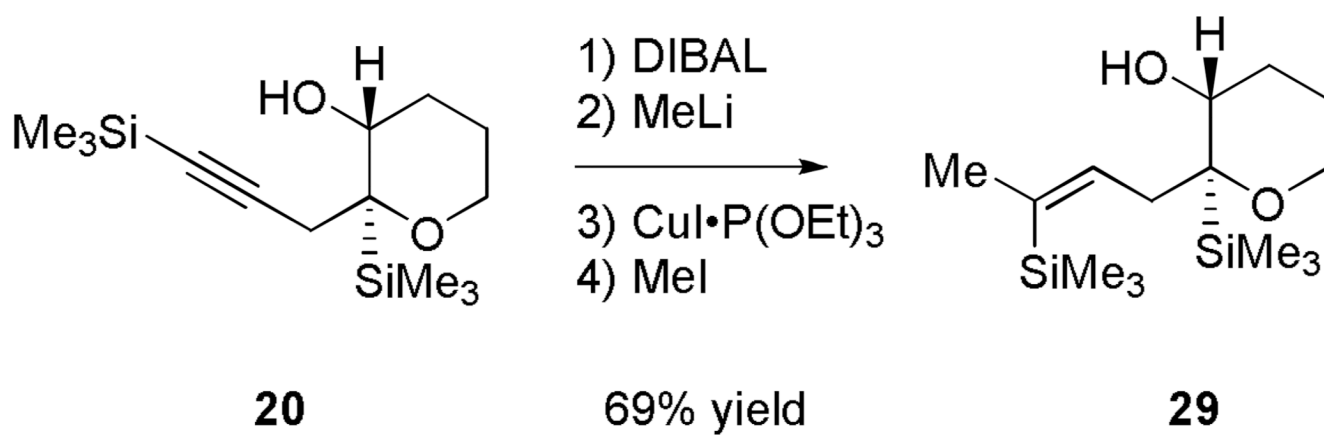
Figure 12.
Suggested mechanism for the cascade formation of bispyran **53**.

**Scheme 1.**

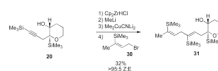


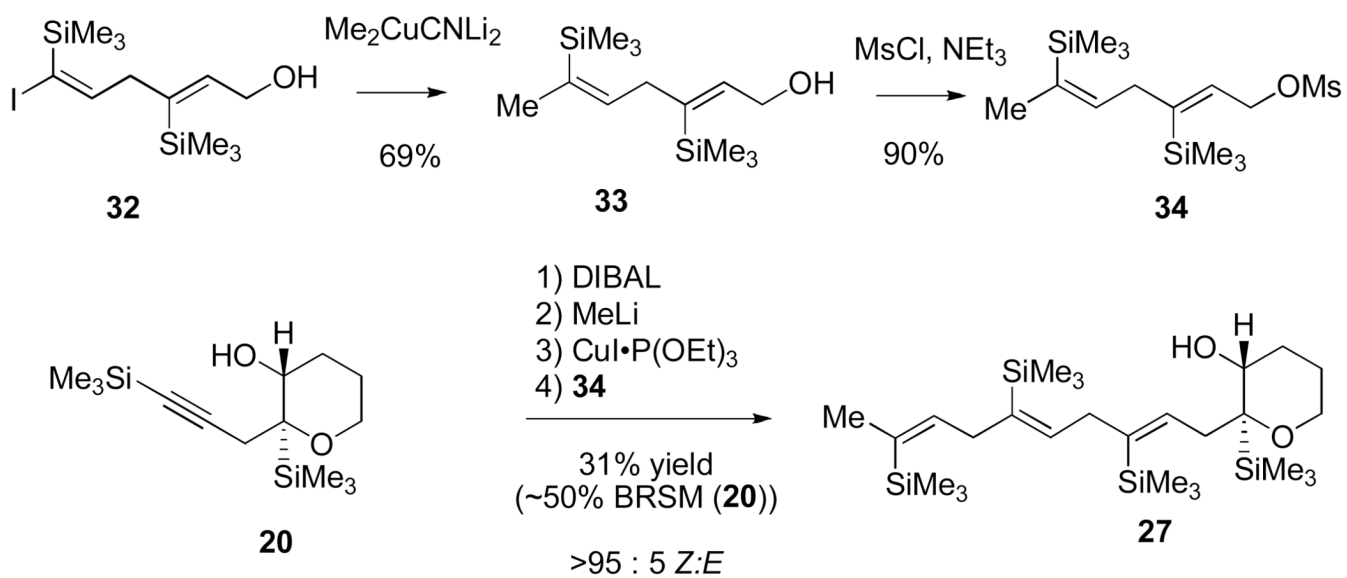
Scheme 2.

**Scheme 3.**

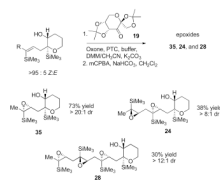


Scheme 4.

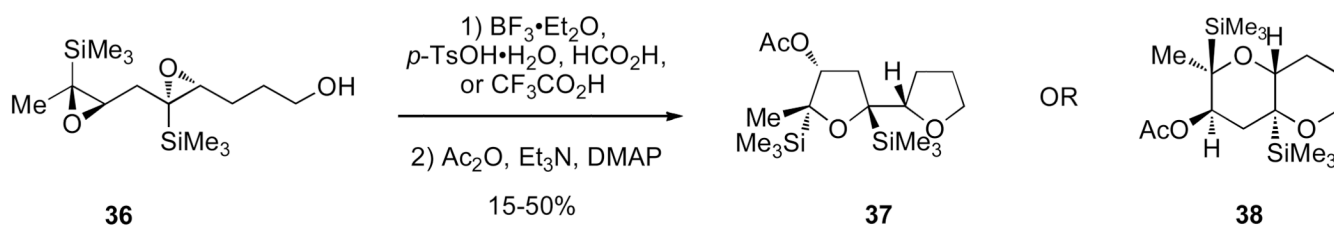
**Scheme 5.**



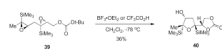
Scheme 6.

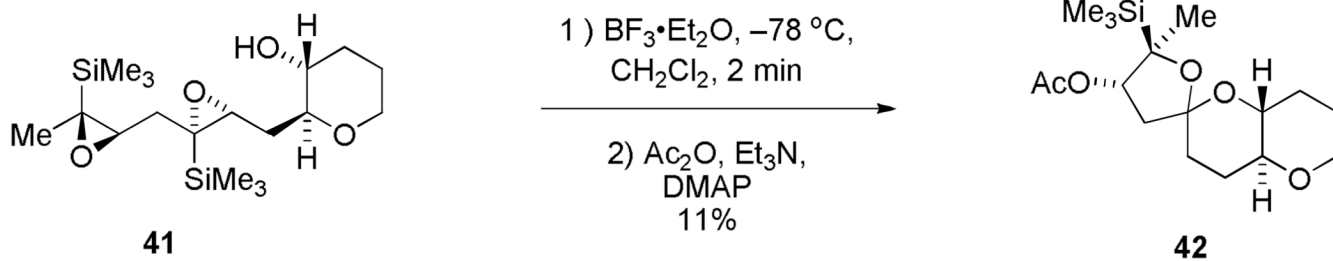


Scheme 7.

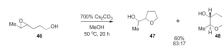


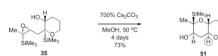
Scheme 8.

**Scheme 9.**



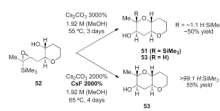
Scheme 10.

**Scheme 12.**

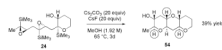
**Scheme 14.**



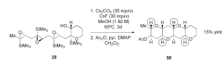
Scheme 15.

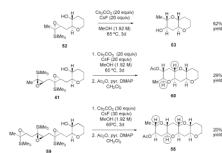


Scheme 16.



Scheme 17.

**Scheme 18.**



Scheme 20.

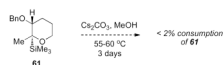
**Scheme 21.**

Table 1

Cyclization of epoxysilane **43** under basic conditions (50 °C, 20 h reaction time in each case).



Entry	Base ^a	Solvent	Conversion ^b	44 : 45 ^b
1	Li ₂ CO ₃	MeOH	20%	5 : 1
2	Na ₂ CO ₃	MeOH	25%	2 : 1
3	K ₂ CO ₃	MeOH	85%	2 : 1
4	Cs ₂ CO ₃	MeOH	97%	1.7 : 1
5	Cs ₂ CO ₃	EtOH	70%	1.7 : 1
6	Cs ₂ CO ₃	<i>i</i> -PrOH	25%	2.5 : 1
7	Li ₂ CO ₃	H ₂ O	45%	8.5 : 1
8	Na ₂ CO ₃	H ₂ O	<10%	>19 : 1
9	K ₂ CO ₃	H ₂ O	trace	n.d.
10	Li ₂ CO ₃	MeOH/H ₂ O (1:9)	30%	8.5 : 1
11	Li ₂ CO ₃	MeOH/H ₂ O (1:1)	20%	5 : 1
12	KHCO ₃	MeOH	trace	n.d.

^a700 mol% used in each case.

^bDetermined by ¹H NMR analysis of the unpurified product mixture. In each case **43**, **44** and **45** were the only compounds observed.

^cAll yields reported are for the combined yield of **44** and **45** and are based on conversion of starting material (as determined by ¹H NMR of the unpurified product mixture).