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

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

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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.

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 mahtotoxin 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.

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

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polyether via an extraordinary series or “cascade” of epoxide-opening events. 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. 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”.

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).

McDonald has reported several examples of cascades leading to both trans-fused
polyoxyepanes 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).

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 polyoxypane 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).

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

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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 diasteromeric 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 epoxide-opening reactions 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 polymer 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

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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). 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% methyllithium 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 3018 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 dienyl mesylate 3415b (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 subjections 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.\textsuperscript{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 \textit{36},\textsuperscript{20} which contains a primary alcohol as the internal, trapping nucleophile (Scheme 8). With either Brønsted acids or BF$_3$·Et$_2$O, 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 $^1$H NMR analysis confirmed that the product contained a secondary alcohol. In order to distinguish between isomeric bicyclic compounds \textit{37} and \textit{38}, 2D NMR experiments were undertaken, and HMBC analysis of the acetylated product revealed the undesired isomer \textit{37} was the major product (Figure 8).

A diepoxide containing a \textit{tert}-butyl carbonate (\textit{39}) as an internal nucleophile was also studied (Scheme 9). Under identical conditions as those used for \textit{36}, above, the outcome of the reaction was similar: An undesired compound containing two linked five-membered rings (\textit{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 \textit{36} or mixed carbonate in \textit{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 \textit{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 SiMe$_3$ group in an equatorial position, e.g., as in \textit{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 SiMe$_3$ groups to the THP. The embodiment of this idea was diepoxide \textit{41},\textsuperscript{21} and the pre-formed THP should have three major advantages. For one, the absence of the SiMe$_3$ 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 \textit{41} with BF$_3$·Et$_2$O 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 \textit{42} (Scheme 10).\textsuperscript{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 \textit{36}, a bisfuran (\textit{37}) was formed, a puzzling result in light of the 6-\textit{endo} regioselectivity observed in the acid-mediated cyclizations of monoepoxysilanes.\textsuperscript{15a} In order to arrive at a bistetrahydrofuran, the two epoxysilanes must be opened, regioselectively, in

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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 SiMe₃, 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 SiMe₃. 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. 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 polyeoxysilanes 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.

E. Cyclizations of Epoxysilanes Under Basic Conditions

Before beginning cascade attempts, however, the cyclization of monoeoxysilane 43 under basic conditions was first studied. 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 K₂CO₃ in MeOH at elevated temperature provided the desired product (Table 1, entry 3). 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 Li₂CO₃ providing the lowest conversion of starting material in MeOH (entry 1) and Cs₂CO₃ 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 Cs₂CO₃ relative to other carbonate bases has been described in other cases.

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$_2$CO$_3$ relative to Cs$_2$CO$_3$ 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$_2$CO$_3$ 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 monoeoxysilane (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 protodesilylation to provide Me₃Si-diad 51 after 3 days (Scheme 16). In an attempt to increase the rate of protodesilylation, 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 protodesilylated; 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 SiMe$_3$ on first Tetrahydropyran Ring

In order to investigate the effect of the axial Me$_3$Si-group on cyclization, selective protiodesilylation 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 protiodesilylation/cyclization sequence (Figure 12). Following initial cyclization, hydroxyl-assisted stereospecific protiodesilylation of the tetrahydropyranyl-SiMe$_3$ under basic conditions is followed by endo-selective epoxide cyclization. A second protiodesilylation of the new tetrahydropyran ring continues the cascade. The reaction sequence is terminated with a final stereospecific protiodesilylation of the $\alpha$-trimethylsilyl group.

As no SiMe$_3$ group remains at the ring junction of the product, we suggest that the silyl group is removed before cyclization upon the second epoxide. The protiodesilylation 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 SiMe$_3$ group is protiodesilylated prior to cyclization was obtained in the attempted desilylation of 61. When the $\beta$-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 Me$_3$Si 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 SiMe$_3$ group is unnecessary in all cases. Rather, the SiMe$_3$ group remains the superior director of regioselectivity under basic conditions. Without the SiMe$_3$ 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 SiMe$_3$-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 Et$_2$O were distilled from a blue solution of benzophenone ketyl. Analytical thin layer chromatography (TLC) was performed using silica gel 60 F$_{254}$ plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid (PMA) or aqueous potassium permanganate (KMnO$_4$). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on silica gel (230–400 mesh).

$^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$, unless otherwise noted, on a 500 MHz spectrometer. Chemical shifts in $^1$H NMR spectra are reported in parts per million (ppm) on the $\delta$ 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 $^{13}$C NMR spectra are reported in ppm from the central peak of CDCl$_3$ (77.2 ppm), C$_6$D$_6$ (128.4 ppm), or CD$_2$Cl$_2$ (54.0 ppm) on the $\delta$ 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-trimethylsilanyl-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 $-78^\circ$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 Bu$_3$P (1.6 mL, 6.5 mmol) in THF (5.7 mL) at $-78^\circ$C. 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 Et$_2$O (3 × 20 mL). The combined organic layers were washed with water, brine, dried over MgSO$_4$, and concentrated in vacuo. The crude product was purified by column chromatography (isolated yield = 67%).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 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 C$_{14}$H$_{28}$NaOSi$_2$ (M + Na)$^+$ 291.1571, found 291.1577.

(2$R$,3$R$)-2-Trimethylsilylanyl-2-(3-trimethylsilanyl-prop-2-ynyl)-tetrahydro-pyran-3-ol (20)

To olefin 18 (6.4 g, 24 mmol) was added CH$_3$CN/DMM (760 mL, 1:2 v:v), a $0.05$ M solution of Na$_2$B$_4$O$_7$·10 H$_2$O in 4.0 $\times$ 10$^{-4}$ M Na$_2$-(EDTA) (500 mL), $n$-Bu$_4$NSO$_4$ (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$^\circledR$ (59 g, 96 mmol) in 4.0 $\times$ 10$^{-4}$ M Na$_2$-(EDTA) (400 mL) and a $0.89$ M solution of K$_2$CO$_3$ (400 mL). After the Oxone$^\circledR$ and K$_2$CO$_3$ 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 MgSO$_4$, 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 CH$_2$Cl$_2$ (150 mL) at 0 °C was added BF$_3$·Et$_2$O (0.3 mL, 1.2 mmol) and the reaction mixture stirred 20 min. The reaction was quenched with saturated NaHCO$_3$. The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (3 × 100 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 (10–20% EtOAc in hexane); $\delta^1$H NMR (500 MHz, CDCl$_3$) δ 3.96 (s, 1H), 3.68 (dd, J = 12.2, 9.5, 3.4 Hz, 1H), 3.54 (app dt, J = 11.9, 4.6 Hz, 1H), 2.88 (d, J = 6.8 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), 0.16 (s, 9H); IR (thin film, NaCl) 3476, 2955, 2866, 1394, 1251, 1070, 837 757 cm$^{-1}$; $1^3$C NMR (150 MHz, CDCl$_3$) δ 104.4, 88.9, 75.2, 70.7, 61.6, 28.7, 25.7, 22.1, 0.6, 0.3, 0.1; HR-MS (ESI) Calcd for C$_{14}$H$_{28}$NaO$_2$Si$_2$ (M + Na)$^+$ 307.1520, found 307.1517.

(2R,3R)-2-[(E)-3-iodo-3-trimethylsilylallyl]-2-trimethylsilyl-tetrahydro-pyran-3-ol (21)

To a solution of 20 (3.5 g, 12 mmol) in Et$_2$O (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 Et$_2$O (10 mL). A solution of I$_2$ (13 g, 49 mmol) in Et$_2$O (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 Et$_2$O (3 × 100 mL). The combined organic layers were washed with saturated Na$_2$S$_2$O$_3$, brine, dried over MgSO$_4$, 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): $\delta^1$H NMR (500 MHz, CDCl$_3$) δ 7.27 (dd, J = 7.9, 3.4 Hz, 1H), 7.11-7.06 (m, 2H), 6.86 (d, J = 11.9, 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); $1^3$C NMR (125 MHz, CDCl$_3$) 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 C$_{14}$H$_{29}$InaO$_2$Si$_2$ (M + Na)$^+$ 435.0643, found 435.0636.

(2R,3R)-2-[(Z)-3,6-Bis-trimethylsilyl-hex-2-en-5-ynyl]-2-trimethylsilyl-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 Cul (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 Et$_2$O (3 × 25 mL). The combined organic layers were washed with water, brine, dried over MgSO$_4$, and concentrated in vacuo. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield 22 (220 mg, 42%): $\delta^1$H NMR (500 MHz, CDCl$_3$) δ 6.48 (s, 1H), 2.99-2.90 (m, 1H), 1.85 (d, J = 7.0 Hz, 1H), 1.75-1.69 (m, 1H), 1.69-1.59 (m, 1H), 0.27 (s, 9H), 0.16 (s, 9H), 0.15 (s, 9H); $1^3$C NMR (125 MHz, CDCl$_3$) 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 C$_{29}$H$_{40}$NaO$_2$Si$_3$ (M + Na)$^+$ 419.2234, found 419.2241.

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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 aqeous layer was extracted with Et2O (3 × 10 mL). The combined organic layers were washed with saturated Na2SO4, 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): Rf = 0.33 (10% EtOAc in hexane); [α]25D = −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 (dd, 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 C28H40InN2O3Si3 (M + Na)+ 547.1351, found 547.1349.

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 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-BuNHSO4 (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): Rf = 0.55 (30% EtOAc in hexane); [α]25D = +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, 3H), 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 C21H38NaO4Si3 (M + Na)+ 467.2445, found 467.2443.

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(2R,3R)-2-Trimethylsilanyl-2-((Z)-3-trimethylsilanyl-but-2-enyl)-tetrahydro-pyran-3-ol (29)

To a solution of alkyne 20 (100 mg, 0.35 mmol) in Et$_2$O (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 18 h. The solution was cooled to 0 °C and treated with MeLi (1.6 M in Et$_2$O, 0.57 ml, 0.91 mmol). After stirring at room temperature for 1 h 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 (1 ml) 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 Et$_2$O (4 × 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 (5% EtOAc in hexane) to yield olefin 29 (73 mg, 69%): R$_f$ = 0.64 (20% EtOAc in hexane); [α]$^2$$_D$ = −17.0 (c = 1.2, in CHCl$_3$); IR (thin film, NaCl) 3486, 2953, 2932, 2869, 1249, 1086, 1016, 835, 756 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 6.09 (app tq, $J$ = 6.9, 1.9 Hz, 1H), 3.75-3.66 (m, 2H), 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); $^{13}$C NMR δ (125 MHz, CDCl$_3$) 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 C$_{21}$H$_{32}$Na$_2$O$_2$Si$_2$ (M + Na)$^+$ 323.1833, found 323.1831.

(2R,3R)-2-((2Z,5Z)-3,6-bistrimethylsilanylhepta-2,5-dienyl)-2-trimethylsilanyl-tetrahydropyran-3-ol (31)

To a stirred solution of (Z)-3-trimethylsilyl-2-buten-1-ol$^{34}$ (500 mg, 3.47 mmol) in Et$_2$O (12 ml) at 0 °C under argon was added PBr$_3$ (166 µL, 1.74 mmol) and stirred for 2 h. The reaction was quenched by addition of a saturated solution of NaHCO$_3$ (2 ml). The aqueous layer was separated and extracted with Et$_2$O (3 × 5 ml). The combined organic layers were washed with water (3 × 5 ml), brine, dried over MgSO$_4$, 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 alkynol 20 (50 mg, 0.18 mmol) in THF (350 µL) was added to Cp$_2$ZrCl (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 Et$_2$O, 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 Me$_2$CuCNLi$_2$ was added dropwise (prepared by addition of MeLi (1.6 M in Et$_2$O, 240 µL, 0.89 mmol) to a slurry of CuCN (17 mg, 0.19 mmol) in Et$_2$O (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 NH$_4$OH/NH$_4$Cl (10% v/v) in saturated (2 mL). The product was extracted with Et$_2$O (4 × 20 ml) and dried over MgSO$_4$. 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]$^2$$_D$ = −3.76 (c = 2.6, in CHCl$_3$); IR (thin film, NaCl) 3447, 2952, 2854, 2360, 2341, 1247, 1091, 836, 755 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.07 (tt, $J$ = 6.4, 1.6 Hz, 1H), 5.91 (td, $J$ = 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); 1.71-1.87 (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); $^{13}$C NMR (100MHz, CDCl$_3$) 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 C$_{21}$H$_{44}$Na$_2$O$_2$Si$_3$ (M+Na)$^+$ 435.2541, found 435.2545.
(2Z,5E)-6-ido-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\(^{15}\) (9.6 g, 25 mmol) in Et\(_2\)O (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 Et\(_2\)O (50 mL), and a solution of I\(_2\) (25 g, 98 mmol) in Et\(_2\)O (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 Et\(_2\)O (3 × 250 mL). The combined organic layers were washed with saturated Na\(_2\)SO\(_4\) 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 32 (5.6 g, 55%, >95% \(E\)): \(R_f = 0.28\) (20% EtOAc in hexane); IR (thin film, NaCl) 3315, 2954, 2898, 1789, 1616, 1444, 1406, 1249, 1035, 996, 837 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.10\) (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); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 154.4, 141.5, 141.4, 108.0, 62.3, 41.9, 1.2, 0.3\); HR-MS (ESI) Calcd for C\(_{13}\)H\(_{29}\)NaOSi\(_2\) (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 Et\(_2\)O (17.9 mL). After 15 min a solution of 32 (3.15 g, 6.35 mmol) in Et\(_2\)O (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 NH\(_4\)Cl. The aqueous layer was separated and extracted with Et\(_2\)O (3 × 50 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 (10% EtOAc in hexane) to yield 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\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.06\) (m, 1H), 4.21 (t, \(J = 7.0\) Hz, 1H), 5.96-5.89 (m, 1H), 1.79 (s, 3H), 1.47-1.44 (m, 1H), 0.17 (s, 9H), 0.12 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 154.4, 141.5, 141.4, 108.0, 62.3, 41.9, 1.2, 0.3\); HR-MS (ESI) Calcd for C\(_{13}\)H\(_{29}\)NaOSi\(_2\) (M + Na\(^{+}\)) 391.0381, found 391.0394.

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

To a stirred solution of dienol 33 (890 mg, 2.32 mmol) in CH\(_2\)Cl\(_2\) (4.6 ml) maintained at 0 °C under argon was added NEt\(_3\) (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 CH\(_2\)Cl\(_2\) (3 × 50 mL). The combined organic layers were washed with sat. Na\(_2\)SO\(_4\) 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 Et\(_2\)O (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 Et\(_2\)O, 1.4 ml, 2.24 mmol). The mixture was allowed to warm to room temperature over 1.5 h and then recooled 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 1 N HCl (50 ml) and ice. The organic layer was separated, and the aqueous layer was extracted with Et\(_2\)O (4 × 50 ml). The


combined organic layers were washed with saturated aqueous NH₄Cl and brine, dried over MgSO₄ 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): Rf = 0.39 (20% EtOAc in hexane); [α]D²⁵ = −6.0 (c = 1.67 in CHCl₃); IR (thin film, NaCl) 3461, 2953, 2897, 1613, 1444, 1247, 1092, 836, 756 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 142.0, 141.8, 140.1, 138.7, 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 C₂₇H₅₆NaO₂Si₄ (M + Na)⁺ 547.3250, found 547.3267.

(2S,3R)-2-((2R,3S)-3-Methyl-3-trimethylsilanyloxiranylmethyl)-2-trimethylsilanyltetrahydro-pyran-3-ol (35)

To olefin 29 (140 mg, 0.46 mmol) was added CH₂CN/DMM (16 mL, 1:2 v:v), a 0.05 M solution of Na₂B₄O₇·10 H₂O in 4.0 × 10⁻⁴ M Na₂-(EDTA) (10.2 mL), n-Bu₄NHSO₄ (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 Na₂-(EDTA) (7.5 mL) and a 0.89 M solution of K₂CO₃ (7.5 mL). After the Oxone® and K₂CO₃ 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 MgSO₄ 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): Rf = 0.49 (20% EtOAc in hexane); [α]D²⁵ = +18.3 (c = 6.0, in CHCl₃); IR (thin film, NaCl) 3436, 2955, 2854, 1440, 1408, 1370, 1250, 1091, 1025, 837, 755 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₃H₂₆NaO₂Si₄ (M + Na)⁺ 339.1782, found 339.1772.

(2R,3R)-2-methyl-3-trimethylsilanyloxiranylmethyl)-3-trimethylsilanyloxiranylmethyl)-3-trimethylsilanyloxiranylmethyl)-2-trimethylsilanyltetrahydro-pyran-3-ol (28)

To a solution of the triene 27 (89 mg, 0.17 mmol) was added CH₂CN/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-Bu₄NHSO₄ (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 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 × 15 mL). The combined organic layers where 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 (2 mL) and to this was added NaHCO₃ (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 CH₂Cl₂ (4 × 5 mL). The combined organic layers were dried over MgSO₄ 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): Rf = 0.52 (30% EtOAc in hexane); [α]D²⁵ = +24.5 (c = 3.67 in CHCl₃); IR (thin film, NaCl) 3444 (br), 2955, 2899, 2853, 2360, 1250, 1091, 839, 755 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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),

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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); 13C NMR (125 MHz, CDCl3) 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 C27H56NaO5Si4 (M + Na)+ 595.3097, found 595.3107.

3-[(2R,3S)-3-[(2R,3S)-3-Methyl-3-silyl-oxiranylmethyl]-3-silyl-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 Et2O (3 × 20 mL). The combined organic layers were washed with brine, dried over MgSO4, and concentrated in vacuo to afford bisepoxide 36 (1.0 g, 84%): Rf = 0.47 (50% EtOAc in hexane); [α]25D = +4.4 (c = 18.3, CHCl3); IR (thin film, NaCl) 3445, 2957, 2360, 2341, 1441, 1418, 1371, 1250, 1062, 840, 756 cm−1; 1H NMR (500 MHz, CDCl3) δ 3.68 (dt, J = 5.5, 4.0 Hz, 2H), 2.88 (dd, J = 7.9, 4.0 Hz, 1H), 2.71 (dd, J = 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); 13C NMR (125 MHz, CDCl3) 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 C15H32O3Si2 (M + H)+ 317.1968 found 317.1958.

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

To a solution of bisfuran 36 (10 mg, 32 µmol) in CH2Cl2 (0.3 mL) at −78 °C was added Et2O•BF3 (7 mg, 32 µmol) and the mixture stirred 2 h. The reaction was quenched with saturated NaHCO3 and extracted with CH2Cl2 (3 × 2 mL). The combined organic layers were washed with brine, dried over MgSO4, 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, 2957, 2360, 2341, 1441, 1418, 1371, 1250, 1062, 840, 756 cm−1; 1H NMR (500 MHz, CDCl3) δ 7.9; HR-MS (ESI) Calcd for C15H32O3Si2 (M + Na)+ 317.1963, found 317.1967.

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

To a solution of bisfuran 62 (6 mg, 19 µmol) in CH2Cl2 (0.4 mL) was added i-Pr2EtN (80 mg, 0.6 mmol), Ac2O (60 mg, 0.6 mmol), and DMAP (2 mg, 16 µmol). The mixture stirred overnight and was quenched with saturated NH4Cl and concentrated in vacuo. The remaining contents were extracted with Et2O (3 × 3 mL). The combined organic layers were washed with water, brine, dried over MgSO4, and concentrated in vacuo. The crude material was purified by column chromatography (20% EtOAc in hexane) to afford acetate 37 (5.0 mg, 87%): Rf = 0.47 (20% EtOAc in hexane); [α]25D = −50.0 (c = 1.0, CHCl3); IR (thin film, NaCl) 2959, 1743, 1450, 1368, 1246, 1109, 1072, 1045, 838, 754 cm−1; 1H NMR (500 MHz, CDCl3) δ 5.16 (d, J = 11.6 Hz, 1H), 3.99-3.91 (m, 1H), 3.88-3.83 (m, 1H), 3.63-3.59 (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); 13C NMR (125 MHz, CDCl3) 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 C15H34NaO4Si2 (M + Na)+ 381.1888, 381.1893.

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

To a solution of alkyne 18 (18.7 g, 69.8 mmol) in Et2O (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.

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The solution was then cooled to −78 °C, diluted with Et₂O (50 mL), and a solution of I₂ (71.0 g, 279.1 mmol) in Et₂O (150 mL) was added. After stirring 2 h at −78 °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 Et₂O (3 × 200 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 63 (22.9 g, 83%, >95% E): R₁ = 0.39 (20% EtOAc in hexane); IR (thin film, NaCl) 3322, 2953, 1615, 1248, 1058, 836, 755 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.95-5.89 (m, 2H), 3.66 (t, J = 6.4 Hz, 2H), 2.85-2.82 (m, 2H), 2.21 (app q, J = 7.0 Hz, 2H), 1.78 (d, J = 2.7 Hz, 3H), 1.67-1.62 (m, 2H), 1.05 (s, 9H), 0.25 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 155.6, 143.3, 137.3, 107.2, 62.9, 39.3, 33.3, 28.6, 13.3, 4.9 Hz, 1H), 2.73 (dd, J = 8.2, 3.7 Hz, 1H), 2.18 (dd, J = 14.7, 3.9 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 Hz, 1H), 1.22 (s, 3H), 0.19 (s,

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

To a slurry of CuCN (2.5 g, 28.4 mmol) in Et₂O (34.0 mL) at 0 °C was added a 1.4 M solution of MeLi in Et₂O (35.5 mL) and the mixture stirred 15 min. A solution of alkenyl iodide 63 (5.0 g, 12.6 mmol) in Et₂O (12.8 mL) was slowly added. The reaction was stirred for 20 h at 0 °C then was carefully quenched with saturated NH₄Cl and extracted with Et₂O (3 × 40 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford bisepoxide product 65 (22.9 g, 83%, >95% E): R₁ = 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, CDCl₃) δ 5.95-5.89 (m, 2H), 3.66 (t, J = 6.4 Hz, 2H), 2.81 (d, J = 7.6 Hz, 2H), 2.21 (q, J = 14.9, 7.3 Hz, 2H), 1.64 (t, J = 7.3 Hz, 2H), 1.42 (s, 1H-OH), 0.25 (s, 9H), 0.15 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 155.6, 143.3, 137.3, 107.2, 62.9, 39.3, 33.3, 28.6, 13.3, 4.9 Hz, 1H), 2.18 (dd, J = 14.7, 3.9 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 Hz, 1H), 1.22 (s, 3H), 0.19 (s,

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 CH₂Cl₂ (87 mL) at 0 °C was added pyridine (0.8 g, 10.4 mmol), Ac₂O (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 NH₄Cl and extracted with Et₂O (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated in vacuo. The remaining contents were 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 partially purified by column chromatography (20% EtOAc in hexane) and carried to the next step.

To a solution of the acacetate (2.0 g, 6.2 mmol) in CH₃CN/DMM (192 mL, 1:2 v:v) was added a 0.05 M solution of Na₂B₄O₇·10 H₂O in 4.0 × 10⁻⁴ M Na₂-(EDTA) (129 mL), n-BuNH₂SO₄ (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® (12.5 g, 20.0 mmol) in 4.0 × 10⁻⁴ M Na₂-(EDTA) (86.0 mL) and a 0.89 M solution of K₂CO₃ (86.0 mL). After the Oxone® and K₂CO₃ solutions had been added, the resulting mixture was diluted with water (200 mL) and extracted with EtOAc (4 × 400 mL). The combined organic layers where washed with brine, dried over MgSO₄, 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): R₁ = 0.47 (20% EtOAc in hexane); [α]D²⁵ = +3.7 (c = 2.7, CHCl₃); IR (thin film, NaCl) 2958, 1742, 1367, 1250, 1045, 840, 756 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.18-4.09 (m, 2H), 2.87 (dd, J = 7.9, 4.9 Hz, 1H), 2.73 (dd, J = 8.2, 3.7 Hz, 1H), 2.18 (dd, J = 14.7, 3.9 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 Hz, 1H), 1.22 (s, 3H), 0.19 (s,

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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 C$_{17}$H$_{34}$O$_4$Si$_2$ (M + Na)$^+$ 381.1888 found, 381.1997.

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

To a solution of the dienyl alcohol 33 (0.7 g, 2.8 mmol) in CH$_2$Cl$_2$ (28 mL) was added Et$_3$N (0.8 mL, 5.6 mmol), BOC$_2$O (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$_4$Cl and concentrated in vacuo. The remaining contents were extracted with Et$_2$O (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 CH$_2$Cl$_2$ (9.0 mL, 1:2 v:v) was added a 0.05 M solution of Na$_2$B$_4$O$_7$·10 H$_2$O in 4.0 × 10$^{-4}$ M Na$_2$-(EDTA) (63 mL), n-Bu$_4$NHSO$_4$ (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$_2$CO$_3$ (42 mL). After the Oxone® and K$_2$CO$_3$ 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$^{-1}$; $^1$H 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); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 131.8, 126.4, 71.4, 54.0, 38.1, 28.4, 23.3, −0.7, −1.1; HR-MS (ESI) Calcd for C$_{13}$H$_{36}$NaO$_5$Si (M + Na)$^+$ 411.1993, found 411.2007.

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

To a solution of 39 (42 mg, 0.1 mmol) in CH$_2$Cl$_2$ (1.5 mL) at −78 °C was added BF$_3$·Et$_2$O (24 µL, 0.11 mmol). After 2 min the reaction was quenched with saturated NaHCO$_3$, and extracted with CH$_2$Cl$_2$ (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); [α]$_{D}^{25}$ = −20.0 (c = 1.0, CHCl$_3$); IR (thin film, NaCl) 3496, 2955, 1786, 1250, 1180, 1074, 838, 754 cm$^{-1}$; $^1$H 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 (dd, $J$ = 14.3 Hz, 1H), 1.30 (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 C$_{14}$H$_{26}$NaO$_5$Si (M + Na)$^+$ 553.1367, found 553.1355.

**((2S,3R)-2-((2R,3S)-3-((2R,3S)-Methyl-3-silyl-oxiranylmethyl)-3-silyl-oxiranylmethyl)-tetrahydro-pyran-3-ol (41)**

To a solution of the diene 57 (preparation below) (0.1 g, 0.4 mmol) in CH$_3$CN/DMM (12.0 mL, 1:2 v:v) was added a 0.05 M solution of Na$_2$B$_4$O$_7$·10 H$_2$O in 4.0 × 10$^{-4}$ M Na$_2$-(EDTA) (8.0 mL), n-Bu$_4$NHSO$_4$ (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, and 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): Rf = 0.53 (50% EtOAc in hexane); [α]D²⁵ = −2.62 (c = 267, CHCl₃); IR (NaCl) 3444, 2955, 2854, 2361, 1750, 1440, 1412, 1373, 1251, 1096, 1048, 756 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.93-3.88 (m, 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 (dd, 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 C₁₇H₃₆NaO₄Si₂ (M + Na)⁺ 395.2044, found 395.2040.

Spiroketal (42)

To a solution of bisepoxide 41 (10 mg, 27 µmol) in CH₂Cl₂ (0.3 mL) at −78 °C was added BF₃•Et₂O (5 µL, 40 µmol) 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 µL, 40 µmol), Ac₂O (3 µL, 30 µmol), and DMAP (1 mg, 8 µmol). 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 C₁₇H₃₆NaO₄Si₂ (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%): Rf = 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 C₉H₁₉O₂Si (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

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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\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 171.8, 65.8, 64.7, 55.6, 28.0, 27.0, 23.4, 21.7, -1.2; HR-MS (ESI) Calcd for \( \text{C}_{11}\text{H}_{22}\text{NaO}_3\text{Si} \) (M\(^+\) + Na\(^+\)) 253.1230, found 253.1223.

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

To a solution of alcohol 68 (2.8 g, 14 mmol) in CH\(_2\)Cl\(_2\) (130 mL) at 0 °C was added Et\(_3\)N (1.8 g, 18 mmol), Ac\(_2\)O (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\(_4\)Cl and concentrated in vacuo. The remaining contents were extracted with Et\(_2\)O (3 x 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); IR (thin film, NaCl) 2947, 1744, 1620, 1441, 1366, 1248, 1042, 838 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 3.74 (td, \( J = 11.6, 3.1 \) Hz, 1H), 3.59-3.49 (m, 2H), 3.10 (m, 2H), 1.75 (d, \( J = 1.2 \) Hz, 3H), 1.63 (m, 2H), 0.13 (s, 9H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 141.8, 135.6, 130.8, 62.9, 33.3, 28.5, 24.9, 0.1; HR-MS (ESI) Calcd for \( \text{C}_{11}\text{H}_{22}\text{NaO}_3\text{Si} \) (M + Na\(^+\)) 237.1281, found 237.1271.

(\(Z\))-5-Trimethylsilyl-hex-4-en-1-ol (68)

To a slurry of CuCN (3.2 g, 35 mmol) in Et\(_2\)O (45 mL) at 0 °C was added a 1.4 M solution of MeLi in Et\(_2\)O (50 mL) and the mixture stirred 15 min. A solution of (E)-5-iodo-5-(trimethylsilyl)pent-4-en-1-ol\(^{15}\) (5.1 g, 18 mmol) in Et\(_2\)O (14 mL) was slowly added. The solution stirred 20 h at 0 °C then was carefully quenched with saturated NH\(_4\)Cl and extracted with Et\(_2\)O (3 x 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, 2952, 2866, 1248, 1054, 838, 755 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 141.8, 135.6, 62.9, 33.3, 28.5, 24.9, 0.1; HR-MS (ESI) Calcd for \( \text{C}_{9}\text{H}_{20}\text{NaSiO} \) (M + Na\(^+\)) 195.1176, found 195.1188.

Representative Procedure for the Base-Promoted Cyclization of 43

To a solution of epoxide 43 (30 mg, 0.11 mmol) in MeOH (1.5 mL) was added Cs\(_2\)CO\(_3\) (33 mg, 1.0 mmol). The reaction mixture was heated to 50 °C for 20 h. The reaction was quenched with saturated NH\(_4\)Cl and extracted with Et\(_2\)O. 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-trimethylsilyl-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\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 72.9, 71.8, 60.1, 25.9, 21.5, 18.7, -2.2; HR-MS (ESI) Calcd for \( \text{C}_{9}\text{H}_{20}\text{NaO}_2\text{Si} \) (M + Na\(^+\)) 211.1125, found 211.1136.

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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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 85.3, 68.9, 67.6, 26.7, 25.2, 20.1, −2.6; HR-MS (ESI) Calcd for C₉H₂₀NaO₂Si (M + 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 Cs₂CO₃ (20 mg, 0.6 mmol). The resulting solution was heated to 50 °C and stirred 20 h. The reaction was quenched with saturated NH₄Cl and extracted with Et₂O. The combined organic layers were dried over MgSO₄ 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 Cs₂CO₃ in MeOH (1.0 mL). The resulting solution was heated to 55–60 °C for 5 days. The reaction was quenched with saturated NH₄Cl and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over MgSO₄ 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); ¹³C 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 C₉H₁₄NaO₂ (M + 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); [α]D²⁵ = +20.9 (c = 4.3, in CHCl₃); IR (thin film, NaCl) 3444, 2953, 2865, 1453, 1347, 1248, 1100, 1069, 1039, 839 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₂H₂₄NaO₃Si (M + 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)

Cs₂CO₃ 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 × 10 ml). 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%); Rᵣ = 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 Hz, 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); Rᵣ = 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-tetraoxanaphthacen-3-yl acetate (55)

Following the general procedure, triepoxide 28 (25 mg, 43 µmol) was heated at 65 °C with Cs$_2$CO$_3$ (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$_2$Cl$_2$ (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$_4$Cl. The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (4 × 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); [α]$^\text{D}_{25}$ = −7.6 (c = 0.13 in CHCl$_3$); IR (thin film, NaCl) 2927, 2961, 1384, 1250, 1097, 1042 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 4.52 (dd, $J$ = 11.4, 9.6, 4.8 Hz, 1H), 3.91-3.87 (m, 1H), 3.37 (ddd, $J$ = 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$_2$Cl$_2$) 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-tetraoxanaphthacen-3-yl acetate (55)

Following the general procedure, triepoxide 28 (18 mg, 35.9 µmol) was heated at 65°C with Cs$_2$CO$_3$ (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$_2$Cl$_2$ (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$_4$Cl. The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (4 × 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-Trimethylsilylanybut-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 × 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); [α]$^\text{D}_{25}$ = −23.9 (c = 9.2, in CHCl$_3$); IR (thin film, NaCl) 3422, 2945, 2853, 1618, 1442, 1248, 1097, 1035, 838, 756 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 6.13 (app t, $J$ = 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, 3H); $^{13}$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 C$_{12}$H$_{24}$NaO$_2$Si (M + Na)$^+$ 251.1438, found 251.1433.

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

To olefin 56 (96 mg, 0.42 mmol) was added CH$_3$CN/DMM (12.8 mL, 1:2 v:v), a 0.05 M solution of Na$_2$B$_4$O$_7$·10 H$_2$O in 4.0 × 10$^{-4}$ M Na$_2$-EDTA (8 mL), n-Bu$_4$NSO$_4$ (26 mg,
tetrahydro-pyran-3-ol (41)

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); Rf = 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 (dd, J = 15.4, 9.2, 4.4 Hz, 1H), 3.36 (app dt, J = 11.3, 3.7 Hz, 1H), 3.22 (dd, 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 C₁₂H₂₄Na₂O₅Si (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 the 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%); Rf = 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 (dd, J = 8.8, 7.0, 4.9 Hz, 1H), 2.87-2.89 (m, 2H), 2.67 (dd, J = 14.6, 8.2, 4.9 Hz, 1H), 2.32-2.39 (m, 2H), 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 C₁₈H₃₆NaO₅Si₂ (M + Na)⁺ 363.2146, found 363.2151.

(2S,3R)-2-[(2R,3S)-3-[(2R,3S)-3-Methyl-3-silyl-oxiranyl(methyl)-3-silyl-oxiranyl(methyl)]-tetrahydro-pyran-3-ol (41)

To a solution of the diene 57 (0.1 g, 0.44 mmol) in CH₃CN/DMM (12.0 mL, 1:2 v:v) was added a 0.05 M solution of Na₂Bu₄O⁻/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, and 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); Rf = 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 (dd, 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 (dd, 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, 31.8, 28.4, 24.9, 24.2, 19.9, 18.8, 15.6, 13.4, 13.0, 10.6, 10.0, 8.2, 7.8, 6.9, 6.4, 5.8, 5.5, 4.0, 3.6, 3.3, 2.9, 2.4, 2.0, 1.7, 1.6, 1.4, 1.3, 1.2, 1.1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, 0.0, -0.1; HR-MS (ESI) Calcd for C₄₁H₆₄NO₁₅Si₄ (M + Na)⁺ 727.3801, found 727.3800.

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(2S,3R)-2-[(2Z,5Z,8Z)-3,6,9-tris-trimethylsilylanyl-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%): [a]²⁵D = −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 C₄₂H₇₈NaO₄Si₃ 745.2854, found 745.2861.

(2S,3R)-2-[(2R,3S)-3-(2R,3S)-3-Methyl-3-trimethylsilylanyl-oxiranymethyl]-3-trimethylsilylanyl-oxiranymethyl]-3-trimethylsilylanyl-oxiranymethyl]-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 Na₂B₄O₇·10H₂O in 4.0 × 10⁻⁴ M Na₂-(EDTA) (3.5 mL), n-BuNHSO₄ (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 washed 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): [α]²⁵D = +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 83.6, 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; HRMS (ESI) Calcd for C₄₂H₇₈NaO₄Si₃ (M + Na)+ 523.2702, found 523.2696.

(3-Benzzyloxy-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 washed 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%): [α]²⁵D = 0.51 (10% EtOAc

J Org Chem. Author manuscript; available in PMC 2011 January 11.
in hexane); IR (thin film, NaCl) 2952, 2854, 1454, 1244, 1092, 1077, 1026, 837, 744, 697 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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 C\(_{16}\)H\(_{26}\)NaO\(_2\)Si (M + Na)\(^+\) 301.1594, found 301.1601.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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**References**


9. 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.


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]


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.


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.


26. See Supplementary Information for the details of the preparation of 43.


28. The use of 700 mol% Li$_2$CO$_3$ in H$_2$O led to no conversion of starting material (36) after 3 days at 50 °C.


30. Treatment under several conditions known to effect protodesilylation of β-hydroxy silanes (TBAF/THF, KO$_t$Bu/DMSO, KO$_t$Bu/DMF, CsF, CsOH in THF, DMF and MeOH) gave no desired product with decomposition and elimination predominating.


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 SiMe$_3$ 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.

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{OH} \\
\text{H} & \quad \text{SiMe}_3 \\
\text{SiMe}_3 & \\
\text{1) DIBAL} & \quad \text{2) MeLi} \\
\text{3) CuI} & \quad \text{4) Me} \\
\text{Me} & \quad \text{SiMe}_3 \\
\text{H} & \quad \text{SiMe}_3 \\
\text{69\% yield} & \\
\text{20} & \quad \text{29}
\end{align*}
\]
Scheme 5.
Scheme 6.

![Chemical structures and reactions](image_url)

1) DIBAL
2) MeLi
3) CuI•P(OEt)$_3$
4) 34

31% yield (~50% BRSM (20))

>95 : 5 Z:E
Scheme 7.
Scheme 8.

1) $\text{BF}_3\cdot\text{Et}_2\text{O}$, 
$\rho\text{-TsOH}\cdot\text{H}_2\text{O}, \text{HCO}_2\text{H}$, 
or $\text{CF}_3\text{CO}_2\text{H}$

2) $\text{Ac}_2\text{O}, \text{Et}_3\text{N}, \text{DMAP}$

15-50%
Scheme 9.
Scheme 10.

1) BF$_3$•Et$_2$O, –78 °C, CH$_2$Cl$_2$, 2 min
2) Ac$_2$O, Et$_3$N, DMAP
11%

41 42
Scheme 11.
Scheme 12.
Scheme 13.
Scheme 14.
Scheme 15.
Scheme 16.
Scheme 17.
Scheme 18.
Scheme 19.
Scheme 20.
Scheme 21.
Table 1

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (^a)</th>
<th>Solvent</th>
<th>Conversion (^b)</th>
<th>44 : 45 (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Li(_2)CO(_3)</td>
<td>MeOH</td>
<td>20%</td>
<td>5 : 1</td>
</tr>
<tr>
<td>2</td>
<td>Na(_2)CO(_3)</td>
<td>MeOH</td>
<td>25%</td>
<td>2 : 1</td>
</tr>
<tr>
<td>3</td>
<td>K(_2)CO(_3)</td>
<td>MeOH</td>
<td>85%</td>
<td>2 : 1</td>
</tr>
<tr>
<td>4</td>
<td>Cs(_2)CO(_3)</td>
<td>MeOH</td>
<td>97%</td>
<td>1.7 : 1</td>
</tr>
<tr>
<td>5</td>
<td>Cs(_2)CO(_3)</td>
<td>EtOH</td>
<td>70%</td>
<td>1.7 : 1</td>
</tr>
<tr>
<td>6</td>
<td>Cs(_2)CO(_3)</td>
<td>(i)-PrOH</td>
<td>25%</td>
<td>2.5 : 1</td>
</tr>
<tr>
<td>7</td>
<td>Li(_2)CO(_3)</td>
<td>H(_2)O</td>
<td>45%</td>
<td>8.5 : 1</td>
</tr>
<tr>
<td>8</td>
<td>Na(_2)CO(_3)</td>
<td>H(_2)O</td>
<td>&lt;10%</td>
<td>&gt;19 : 1</td>
</tr>
<tr>
<td>9</td>
<td>K(_2)CO(_3)</td>
<td>H(_2)O</td>
<td>trace</td>
<td>n.d.</td>
</tr>
<tr>
<td>10</td>
<td>Li(_2)CO(_3)</td>
<td>MeOH/H(_2)O (1:9)</td>
<td>30%</td>
<td>8.5 : 1</td>
</tr>
<tr>
<td>11</td>
<td>Li(_2)CO(_3)</td>
<td>MeOH/H(_2)O (1:1)</td>
<td>20%</td>
<td>5 : 1</td>
</tr>
<tr>
<td>12</td>
<td>KHCO(_3)</td>
<td>MeOH</td>
<td>trace</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

\(^a\) 700 mol% used in each case.

\(^b\) Determined by \(^1\)H NMR analysis of the unpurified product mixture. In each case 43, 44 and 45 were the only compounds observed.

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