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

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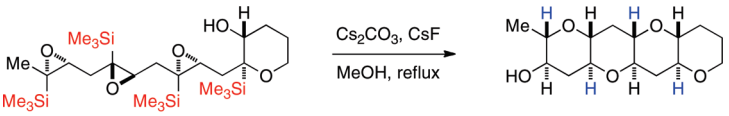

Epoxide-opening cascades offer the potential to construct complex polyether natural products expeditiously and in a manner that emulates the biogenesis proposed for these compounds. Herein we provide a full account of our development of a strategy that addresses several important challenges of such cascades. The centerpiece of the method is a trimethylsilyl ($SiMe_3$) 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 $SiMe_3$ 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.[1]

How Nature assembles such complex structures also has captured the imagination of generations of chemists and biologists. One of the two structural features that characterizes the ladder polyethers is the repeating oxygen−carbon−carbon pattern that is present in the entire range of the polyether network, regardless of the size of the intervening rings and independent of any functional groups present on the rings. The other pattern, stereochemical in nature, is that all of the junctions between the fused rings are *trans*, and consecutive ring junctions are *syn* to one another. It is this *trans-syn* arrangement of the rings that is responsible for the "ladder" topography of these molecules. The ring junctions in all of the ladder polyethers isolated to date are *trans* (with one exception), and the *trans-syn* relationship is seen in all cases where relevant (again with one exception). In maitotoxin there is a *cis*-fused junction between two tetrahydropyran rings, and elsewhere in the same natural product, a *trans-anti-trans* arrangement of three tetrahydropyrans is found.[2]

More than 20 years ago Nakanishi put forth an intriguing hypothesis that accounts for these structural and stereochemical features, the transformation of a polyepoxide into a ladder polyether via an extraordinary series or "cascade" of epoxide-opening events.[3] 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

(1) For reviews on ladder ether synthesis, see: (a) Sasaki, M.; Fuwa, H. *Nat. Prod. Rep.* **2008**, *25*, 401–426. (b) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314–4347. (c) Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953–1980. (d) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631–12670. (e) Marmsäter, F. P.; West, F. G. *Chem.—Eur. J.* **2002**, *8*, 4347–4353. (f) Hirama, M.; Rainier, J. D., Eds. *Tetrahedron* **2002**, *58*, 1779−2040. (Tetrahedron Symposium-in-Print 90) . (g) Evans, P. A.; Delouvrie, B. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 986–999. (h) Vilotijevic, I.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5250–5281. (i) Morten, C. J.; Byers, J. A.; Van Dyke, A. R.; Vilotijevic, I.; Jamison, T. F. *Chem. Soc. Rev.* **2009**, *38*, 3175–3192.

(2) (a) Gallimore, A. R.; Spencer, J. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4406–4413. (b) Nicolaou, K. C.; Frederick, M. O. *Angew. Chem., Int. Ed.* **2007**, *46*, 5278–5282. (c) Nicolaou, K. C.; Frederick, M. O.; Burtoloso, A. C. B.; Denton, R. M.; Rivas, F.; Cole, K. P.; Aversa, R. J.; Gibe, R.; Umezawa, T.; Suzuki, T. *J. Am. Chem. Soc.* **2008**, *130*, 7466–7476.

(3) (a) Nakanishi, K. *Toxicon* **1985**, *23*, 473–479. (b) Lee, M. S.; Repeta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855–7856. (c) See also: Chou, H.-N.; Shimizu, Y. *J. Am. Chem. Soc.* **1987**, *109*, 2184–2185.

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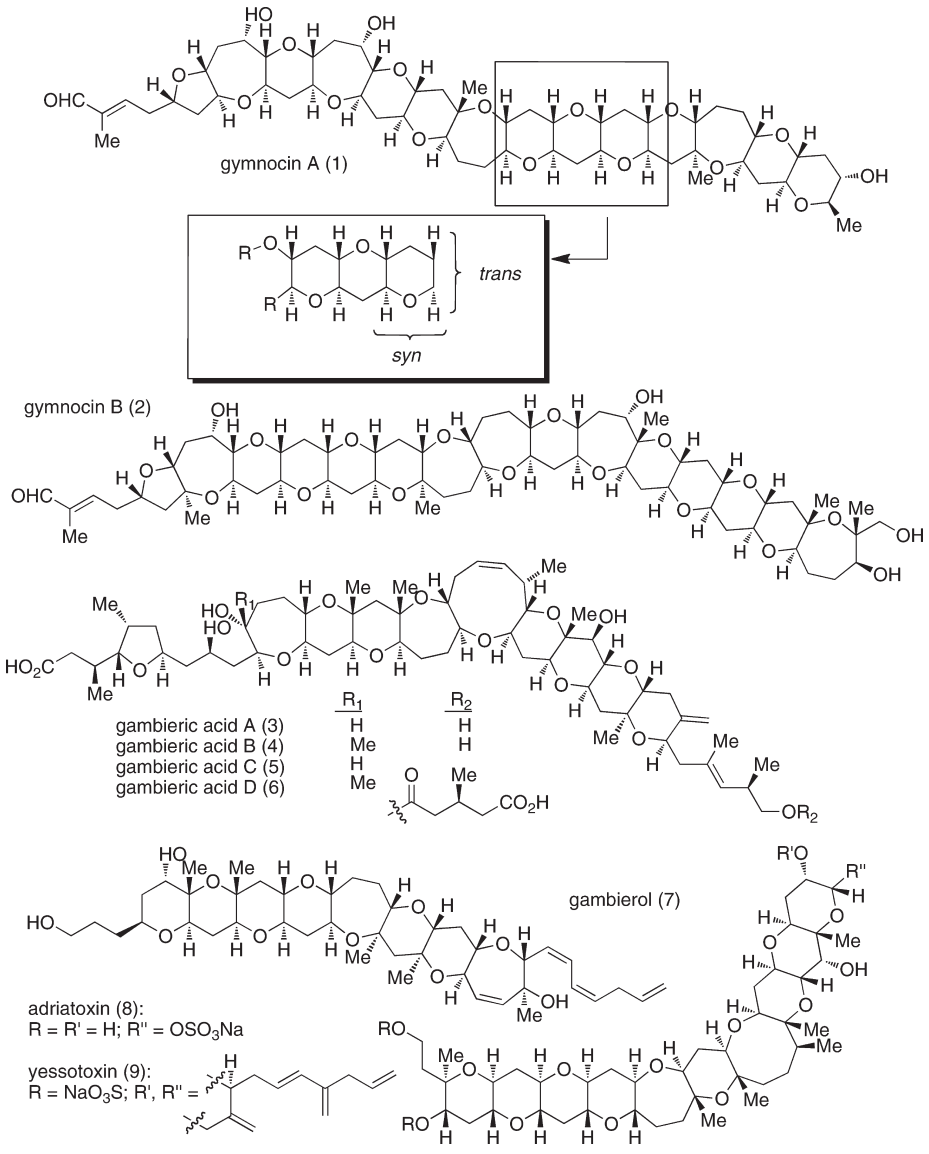


FIGURE 1. Representative examples of polyethers containing the characteristic *trans-syn* topography.

complexity found in the ladder polyethers. However, this 2-decade-old hypothesis remains unconfirmed, and it remains unknown whether such a cascade of epoxide-opening reactions is a component of the construction process.

Despite 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 CH_2 groups favors the smaller, five-membered heterocycle, not the larger tetrahydropyran.[4] 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?

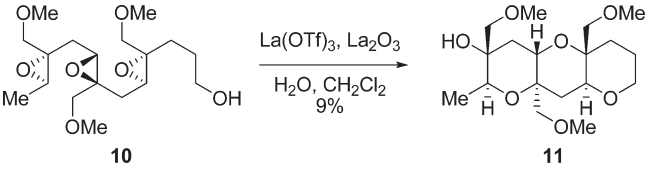


FIGURE 2. Chelation-directed cascades (Murai).

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".[5]

(4) Coxon, J. M.; Hartshorn, M. P.; Swallow, W. H. *Aust. J. Chem.* **1973**, *26*, 2521–2526.

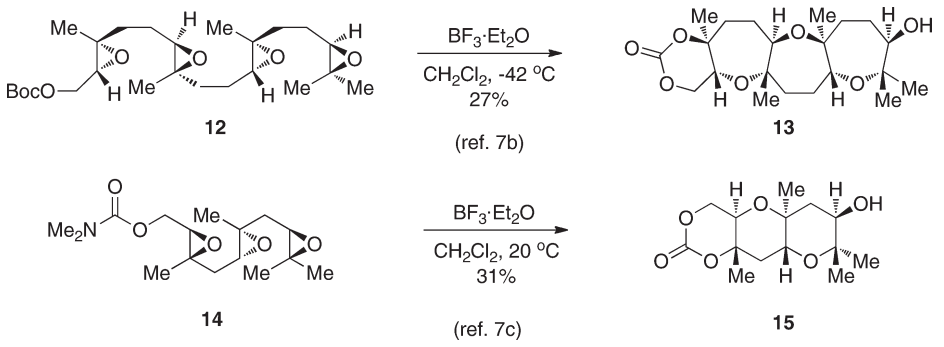


FIGURE 3. Cascades directed by methyl groups at each nascent ring junction (McDonald).

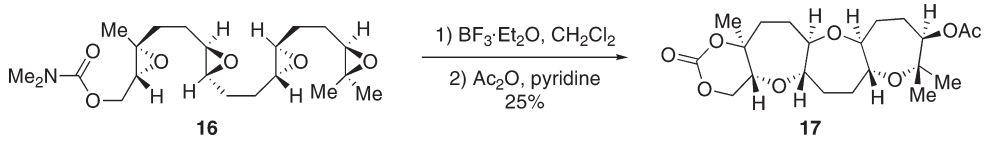


FIGURE 4. McDonald's cascade synthesis of a polyoxepane that contains two ring junctions without directing groups.

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).[6]

McDonald has reported several examples of cascades leading to both *trans*-fused polyoxepanes and polytetrahydropyrans where a methyl group at each ring junction provides what is thought to be an electronic bias in the same vein as Nicolaou's alkene-directed epoxide ring openings (Figure 3).[7]

The regioselectivity control elements ($MeOCH_2$ or Me groups) utilized in each of these cases, however, are either not present at all (methoxymethyl groups) or not present at every ring junction in the natural products (Me groups). In fact, the ratio of the frequency of H atoms to Me groups at ring junction carbons in ladder polyether natural products is approximately 4:1. Finally, since these groups are not easily removed or modified after the cyclization, their utility in target-oriented synthesis is also somewhat limited. It should be noted that in the preparation of a polyoxepane by way of epoxide-opening cascades, McDonald and co-workers disclosed an impressive example in which the central two rings formed did not require direction by a methyl group (Figure 4).[7e]

Inspired by the proposed biosynthesis of ladder polyethers, we sought to develop related cascades, in particular those leading to four consecutive tetrahydropyran (THP) rings, since this tetrad of THP rings is found in the majority of the known ladder polyether natural products. One significant difference between our approach and those of Murai and McDonald was that we required that any directing group employed be easily removed after the cascade in order to reveal the substitution pattern that appears at well over half of the ring junctions in the natural products: two hydrogen atoms.[8]

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).[9] The most compelling precedent was the regioselective opening of epoxysilanes with oxygen-centered nucleophiles, promoted by Brønsted or Lewis acids,[10] the means by which we initially envisioned affecting the cascade.[11,12]

Despite the precedented regioselectivity in the opening of epoxysilanes, the effect of the $SiMe_3$ group on cyclization was still an issue. To achieve the desired relative stereochemistry at the ring junction in a synthesis of *trans*-fused ladder polyether subunits, the $SiMe_3$ would be axial in the predicted transition state (Figure 5).

(5) (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359–1362. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330–5334.

(6) Tokiwano, T.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 335–338.

(7) (a) McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917–2919. (b) McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodríguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515–2523. (c) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2003**, *5*, 2123–2126. (d) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *Org. Lett.* **2004**, *6*, 4487–4489. (e) Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586–4587.

(8) 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, T. F. *Science* **2007**, *317*, 1189–1192. This work and other recent related investigations are described at the end of the Results and Discussion section of this manuscript.

(9) For examples of the regioselective opening of epoxysilanes, see: (a) Fristad, W. E.; Bailey, T. R.; Paquette, L. A. *J. Org. Chem.* **1980**, *45*, 3028–3037. (b) Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 5004–5011. (c) Davis, A. P.; Hughes, G. J.; Lowndes, P. R.; Robbins, C. M.; Thomas, E. J.; Whitman, G. H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1934–1941. (d) Tamao, K.; Nakajo, E.; Ito, Y. *J. Org. Chem.* **1987**, *52*, 4412–4414. (e) Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1989**, *30*, 967–970. (f) Yoshida, J.-I.; Maekawa, T.; Morita, Y.; Isoe, S. *J. Org. Chem.* **1992**, *57*, 1321–1322. (g) Jankowski, P.; Raubo, P.; Wicha, J. *Synlett* **1994**, 985–992. (h) Raubo, P.; Wicha, J. *Tetrahedron: Asymmetry* **1996**, *7*, 763–770. (i) Hodgson, D. M.; Comina, P. J. *J. Chem. Soc., Chem. Commun.* **1996**, 755–756. For a review, see: (j) Hudrlik, P. F.; Hudrlik, A. M. α,β-Epoxysilanes. In *Advances in Silicon Chemistry*; Larson, G. L., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 1−89.

(10) (a) Robbins, C. M.; Whitham, G. H. *J. Chem. Soc., Chem. Commun.* **1976**, 697–698. (b) Hudrlik, P. F.; Hudrlik, A. M.; Rona, R. J.; Misra, R. N.; Withers, G. P. *J. Am. Chem. Soc.* **1977**, *99*, 1993–1996.

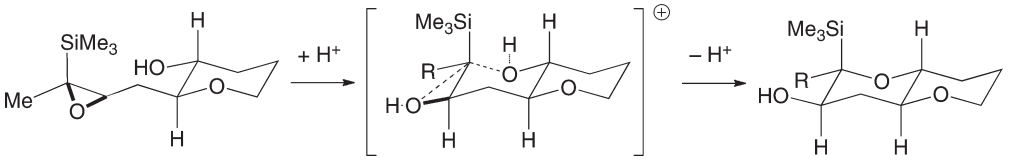


FIGURE 5. The $SiMe_3$ group resides in a pseudoaxial position in the transition state in the cyclization of an epoxysilane.

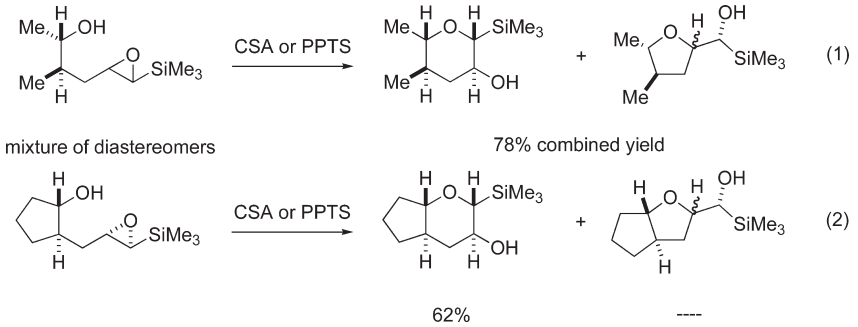


FIGURE 6. Cyclizations of epoxysilanes in which $SiMe_3$ would occupy a pseudoequatorial position in the proposed transition state (Schaumann and co-workers).

No such cyclization with an axial $SiMe_3$ group had been reported, and in fact, Schaumann had reported that epoxy-alcohol cyclizations with $SiMe_3$ 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).[13]

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 Me_3Si groups that we had previously established and thus did not lead to the desired *trans-syn* polyether framework. To our surprise and delight, a less common means of promoting epoxide-opening transformations (Brønsted bases) not only afforded ladder polyether subunits by way of a series of *endo* epoxide openings but also removed the Me_3Si 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.[14] This strategy had four basic design elements: (i) synthesis of a trisubstituted alkenylsilane; (ii) enantioselective, reagent-controlled epoxidation of the alkenylsilanes; (iii) Lewis acid promoted cyclization by way of an epoxide-opening reaction; and (iv) removal of the Me_3Si directing group (Scheme 1).

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).[14a] The epoxide product was not easily separated from the ketone catalyst, and thus preliminary studies were performed on the mixture. The low yield of this two-step process is attributed to the loss of material to C−H oxidation of the primary alcohol. Further in the synthesis, dienyl iodide intermediate **23** proved to be unstable, decomposing rapidly after isolation and thus resulting in reduced yields. These properties also necessitated the immediate conversion to the corresponding diene and diepoxide **24**. Nevertheless, this example demonstrates that despite low yields, suitable quantities of the diene were made available using this iterative sequence to enable evaluation of the asymmetric epoxidation.

Using the same iterative methods, triene **27** was produced. However, because of the lengthy synthesis and low yields

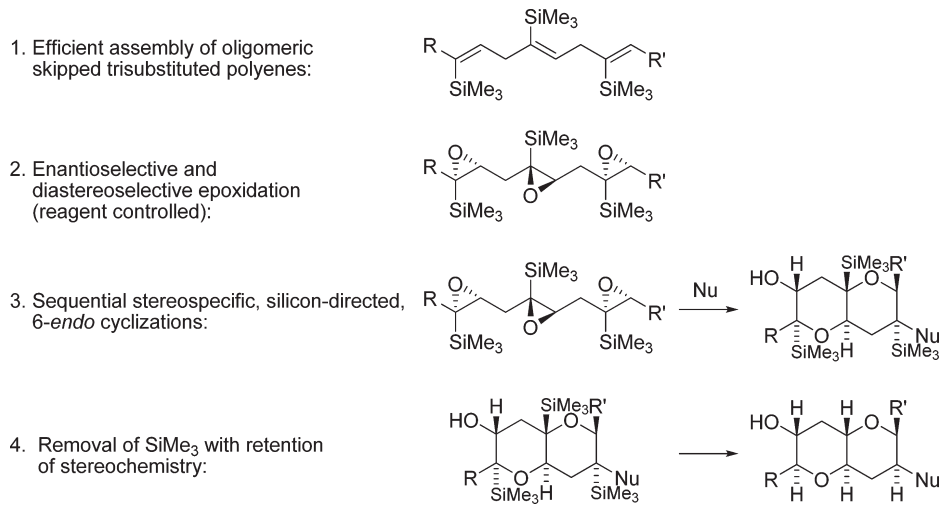
(11) The directing ability demonstrated by $SiMe_3$ in regioselective epoxide openings has been the subject of much speculation and study: (a) Hudrlik, P. F.; Ma, D.; Bhamidipati, R. S.; Hudrlik, A. M. *J. Org. Chem.* **1996**, *61*, 8655–8658. (b) Berti, G.; Canedoli, S.; Crotti, P.; Macchia, F. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1183–1188. (c) Hudrlik, P. F.; Wan, C.-H.; Withers, G. P. *Tetrahedron Lett.* **1976**, *19*, 1453–1456. (d) Eisch, J. J.; Trainor, J. T. *J. Org. Chem.* **1963**, *28*, 2870–2876. For crystallographic evidence of a lengthened C-O bond in epoxysilanes and discussion, see: (e) Hodgson, D. M.; Comina, P. J.; Drew, M. G. B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2279–2289. (f) Kabat, M. M. *J. Org. Chem.* **1995**, *60*, 1823–1827. (g) Molander, G. A.; Mautner, K. *J. Org. Chem.* **1989**, *54*, 4042–4050. (h) Illa, O.; Gornitzka, H.; Baceiredo, A.; Bertrand, G.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2003**, *68*, 7707–7710. (i) Siriwardane, U.; Chu, S. S. C.; Buynak, J. D. *Acta Crystallogr., Sect. C* **1989**, *45*, 531–533. (j) Yamamoto, K.; Kawanami, Y.; Miyazawa, M. *J. Chem. Soc., Chem. Commun.* **1993**, 436–437. (k) Kawai, T.; Isobe, M.; Peters, S. C. *Aust. J. Chem.* **1995**, *48*, 115–131. (l) Fristad, W. F.; Bailey, T. R.; Paquette, L. A. *J. Am. Chem. Soc.* **1979**, *101*, 4420–4423. (m) Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley: New York, 1975.

(12) We have reported a preliminary account of some of the investigations described herein: Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056–1057.

(13) Aidwidjaja, G.; Flörke, H.; Kirschning, A.; Schaumann, E. *Tetrahedron Lett.* **1995**, *36*, 8771–8774.

(14) (a) Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339–2442. (b) Heffron, T. P.; Trenkle, J. D.; Jamison, T. F. *Tetrahedron* **2003**, *59*, 8913–8917.

SCHEME 1



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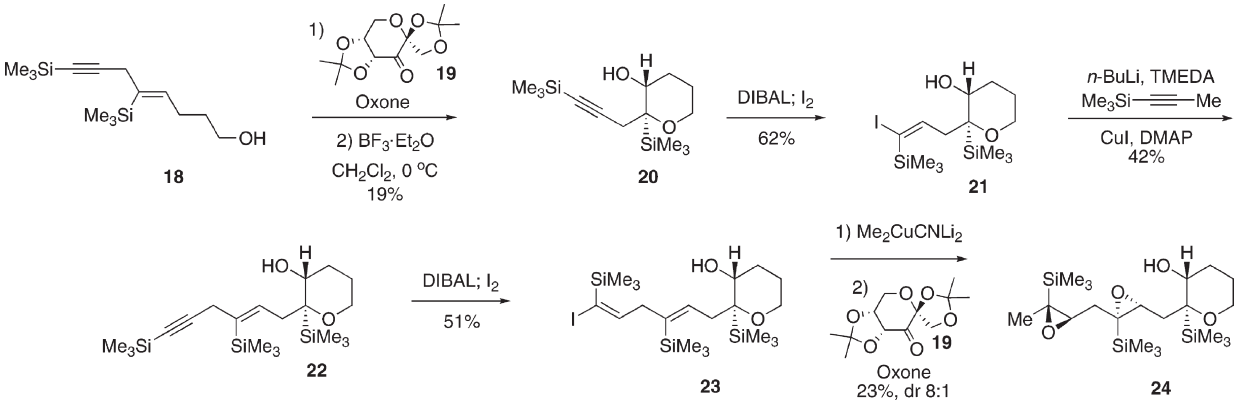

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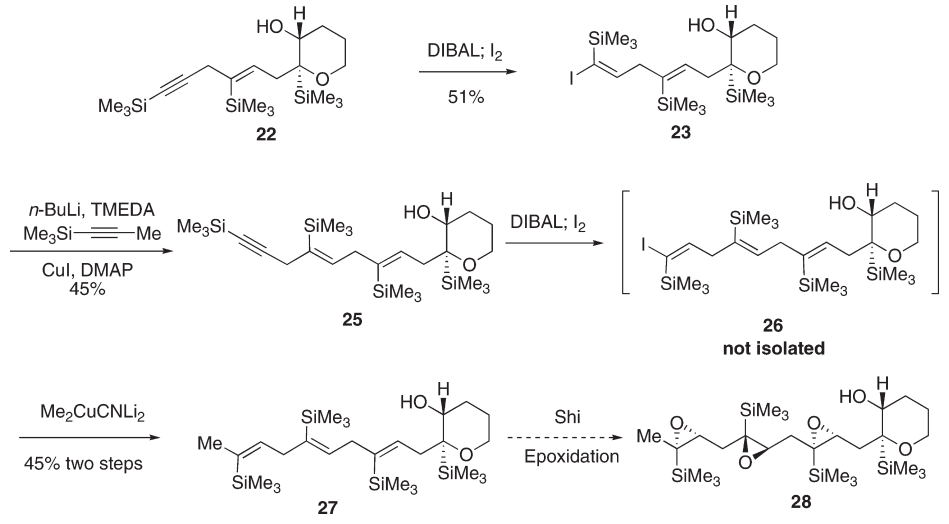


resulting from instability of the intermediate iodides **23** and **26** (Scheme 3), an alternative, convergent approach was thus developed.

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).[15] 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* transmetalation to the more nucleophilic higher-order cuprates (using CuCl·2LiCl or CuI·P(OEt)$_3$)[16] allowed coupling with a range of electrophiles. Solvent also played a crucial role, with Et_2O proving to be superior in the regio- and stereoselective hydrometalation and THF providing higher reactivity in the subsequent alkylation.

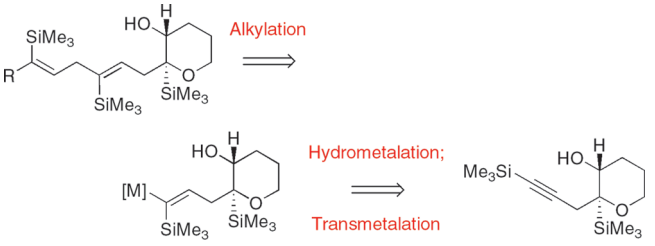
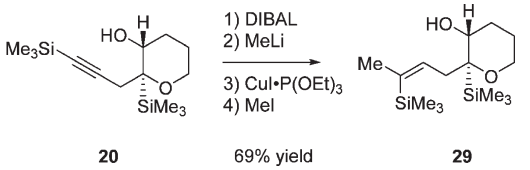


FIGURE 7. Convergent strategy of polyene synthesis utilizing a four-stage, one-pot reaction.

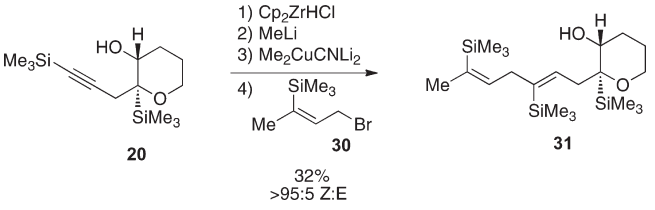
For example, coupling with methyl iodide afforded the alkene **29** in 69% yield in a one-pot procedure (Scheme 4). This sequence compares favorably with the yield from the two-step iterative route of 56%.

SCHEME 4



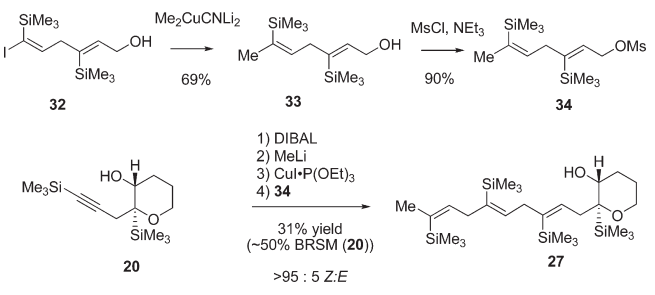
Accordingly, the same strategy provided a direct route to prepare diene **31** (Scheme 5). One-pot coupling of the alkenyl cuprate reagent derived from hydrozirconation/transmetalation of pyran **20** with allylic bromide **30**[17] gave diene **31** in 32% overall yield.

SCHEME 5



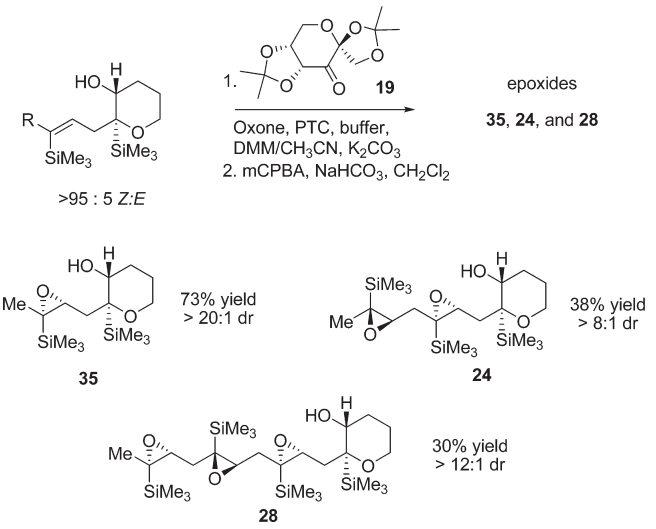
Similarly, triene **27** was available using the direct coupling of an alkenyl cuprate derived from hydroalumination/transmetalation of alkyne **20**,[15c] with dienyl mesylate **34**[14b] (Scheme 6).

SCHEME 6



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.

SCHEME 7



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.[18] Treatment of the partially purified reaction mixture with *m*-CPBA/$NaHCO_3$ in CH_2Cl_2, 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.

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.[14a] Simply put, the incorporation of even just one additional epoxide complicated significantly the outcome under similar reaction conditions. Our initial studies of cascades employed diepoxide **36**,[19]

(15) For examples of hydrometalation/transmetalation/coupling of trimethylsilylalkynes with *Z*-geometry, see the following. Aluminum: (a) Uchida, K.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1976**, *41*, 2215. (b) Eisch, J. J.; Damasevitz, G. A. *J. Org. Chem.* **1976**, *41*, 2214. Aluminum → copper: (c) Ziegler, F. E.; Mikami, K. *Tetrahedron Lett.* **1984**, *25*, 131. Copper: (d) Obayashi, M.; Utimoto, K.; Nozaki, H. *J. Organomet. Chem.* **1979**, *177*, 145. Boron → copper: (e) Uchida, K.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1976**, *41*, 2941. (f) Uchida, K.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1977**, *33*, 2987. (g) Obayashi, M.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1977**, 1805.

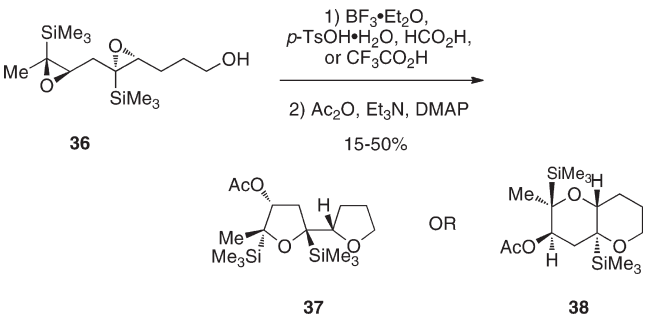
(16) A range of other copper salts (CuCl, CuI/DMAP, CuBr·SMe_2, (2-thiophene)Cu(CN)Li) proved either unreactive or served to scramble the *E*/*Z* geometry of the alkenyl product.

(17) Han, S.; Kass, S. R. *Tetrahedron Lett.* **1997**, *38*, 7503–7505.

(18) Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 521.

(19) See Supporting Information for details for details of the preparation of **36**.

SCHEME 8



which contains a primary alcohol as the internal, trapping nucleophile (Scheme 8). With either Brønsted acids or $BF_3 \cdot Et_2O$, similar results were obtained. Although there was a significant amount of acid-promoted decomposition, a common bicyclic compound was generated in each of these attempts. Acetylation and ^1H NMR analysis confirmed that the product contained a secondary alcohol. To distinguish between isomeric bicyclic compounds **37** and **38**, 2D NMR experiments were undertaken, and HMBC analysis of the acetylated product revealed the undesired isomer **37** was the major product (Figure 8).

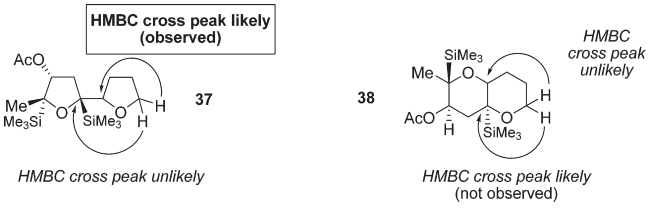
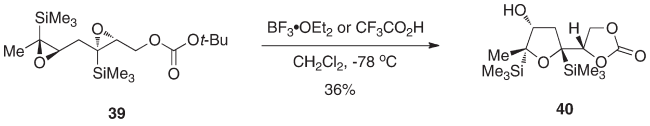


FIGURE 8. HMBC analysis used to distinguish between two potential products of cascade.

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

SCHEME 9



The fact that the cascades behave so differently from systems containing the one-epoxide model systems may be due to several factors. Were the cascade to proceed by a nucleophile (OH in **36** or mixed carbonate in **39**) attacking the 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 26 low energy conformations (within 10.0 kcal) of **35** predicted by Molecular Mechanics computations (Spartan '08, MMFF94, gas phase) indicated a chair conformation for the tetrahydropyran. Of these, nearly half (12) displayed the $SiMe_3$ group in an equatorial position, e.g., as in **35b**. Such conformations are unlikely to be able continue in the cascade (i.e., form a second THP ring) and may readily decompose.

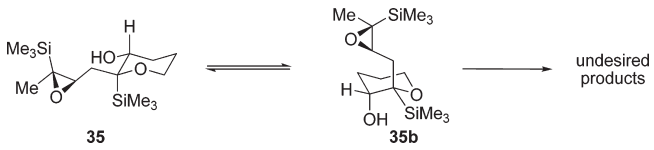
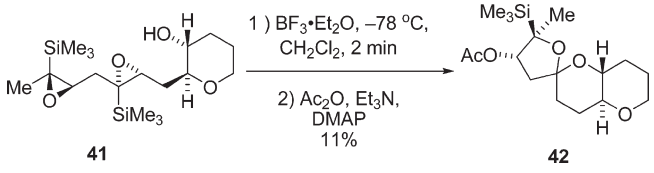


FIGURE 9. One conformation of **35** cannot lead to the desired cyclization product.

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 **41**,[20] and the preformed 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 **41** with $BF_3 \cdot Et_2O$ at -78 °C, conditions identical to those we had used in previous cyclizations. The majority of the material was lost to decomposition, and only one new compound that retained the pyran ring could be isolated. One of the two trimethylsilyl groups in the starting material had been lost; the major product of the reaction contained only one and was determined to be spiroketal **42** (Scheme 10).[21]

SCHEME 10



In each of the attempted cascades described above, unexpected products were isolated as the major compounds produced. Mechanistic insight into how these products could be produced proved instrumental in our understanding of the behavior of epoxysilanes. In the case of diepoxide **36**, a bisfuran (**37**) was formed, a puzzling result in light of the 6-*endo* regioselectivity observed in the acid-mediated cyclizations of monoepoxysilanes.[14a] To arrive at a bistetrahydrofuran, the two epoxysilanes must be opened, regioselectively,

(20) This compound was produced in analogous fashion as polyepoxides **35**, **24**, **28**. For details see Supporting Information.

(21) The structure of spiroketal **42** was assigned on the basis of ^1H NMR, HR-MS, and HMBC analysis that shows a ^{13}C signal at 106 ppm.

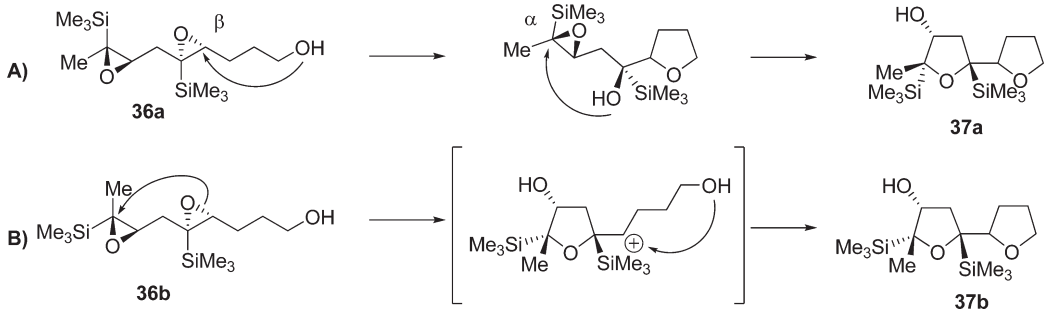


FIGURE 10. Possible sequences of steps in cascades leading to the formation of bisfuran **37**.

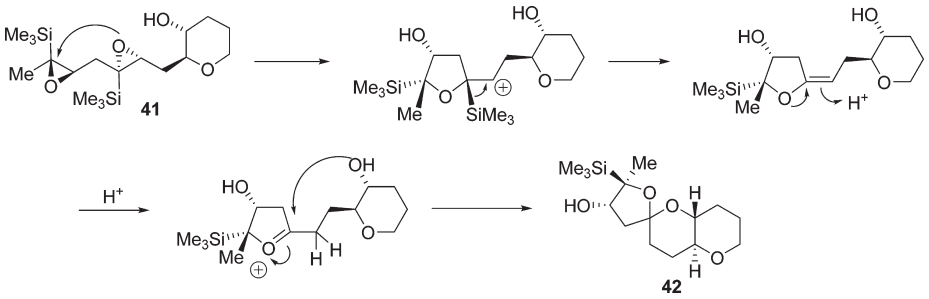


FIGURE 11. Proposed mechanism for the formation. of spiroketal **42**.

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

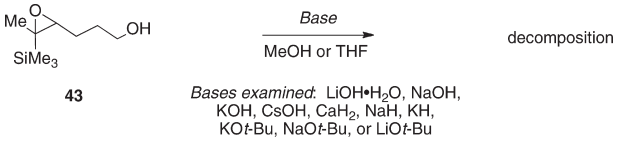
Alternatively, the observed formation of bisfuran **37** can be rationalized by proceeding through a mechanism whereby the first epoxide opened is distal to the internal nucleophile (Figure 10B). If the distal epoxide is activated by the acid, the neighboring *epoxide* may serve as a nucleophile upon that activated epoxide.[7,22,23] 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.

On the basis of the suggested mechanisms for the outcomes in the attempted cascades of polyepoxysilanes under acid promotion, it appeared that initiation of the cascade was by reaction of the distal epoxide (relative to the internal nucleophile) *with the other epoxide* in the substrate, rather than by our internal nucleophile. This phenomenon would be consistent with the electron-rich nature of the epoxysilane, i.e., not only more basic (toward the acidic promoter) but also more nucleophilic (toward another acid-activated epoxysilane). The addition of one additional epoxide having such a profound impact on the success of the cascade cyclization necessitated a significant reworking of the overall cascade strategy. The crux of the 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.[24]

Cyclizations of Epoxysilanes under Basic Conditions. Before beginning cascade attempts, however, the cyclization of monoepoxysilane **43** under basic conditions was first studied.[25] With bases that would readily deprotonate the alcohol (hydride, *tert*-butoxide, and hydroxide bases), the starting material primarily decomposed and only trace amounts of cyclized products could be detected (Scheme 11).

SCHEME 11



However, weaker bases exhibited profoundly different behavior. In a screen of conditions for the intramolecular

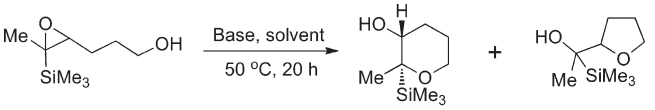
(22) For examples of epoxides as nucleophiles, see: (a) Crisóstomo, F. R. P.; Martín, T.; Martín, V. S. *Org. Lett.* **2004**, *6*, 565–568. (b) Alvarez, E.; Díaz, M. T.; Pérez, R.; Ravelo, J. L.; Regueiro, A.; Vera, J. A.; Zurita, D.; Martín, J. D. *J. Org. Chem.* **1994**, *59*, 2848–2876. (c) David, F. *J. Org. Chem.* **1981**, *46*, 3512–3519. (d) Tokumasu, M.; Sasaoka, A.; Takagi, R.; Hiraga, Y.; Ohkata, K. *J. Chem. Soc., Chem. Commun.* **1997**, 875–876.

(23) (a) Hayashi, N.; Fujiwara, K.; Murai, A. *Tetrahedron Lett.* **1996**, *37*, 6173–6176. (b) Hayashi, N.; Fujiwara, K.; Murai, A. *Tetrahedron* **1997**, *53*, 12425–12468. (c) Fujiwara, K.; Hayashi, N.; Tokiwano, T.; Murai, A. *Heterocycles* **1999**, *50*, 561–593.

(24) For examples of hydroxy-epoxide cyclizations under basic conditions, see: (a) Boons, G.-J.; Brown, D. S.; Clase, J. A.; Lennon, I. C.; Ley, S. V. *Tetrahedron Lett.* **1994**, *35*, 319–322. (b) Emery, F.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 5843–5854. (c) Masamune, T.; Ono, M.; Sato, S.; Murai, A. *Tetrahedron Lett.* **1978**, *4*, 371–374. (d) Murai, A.; Ono, M.; Masamune, T. *J. Chem. Soc., Chem. Commun.* **1976**, 864–865.

(25) See Supporting Information for the details of the preparation of **43**.

TABLE 1. Cyclization of Epoxysilane 43 under Basic Conditions (50 °C, 20 h Reaction Time in Each Case)



43 44 45

entry	base[a]	solvent	conversion (%)[b]	44:45[c]
1	Li_2CO_3	MeOH	20	5:1
2	Na_2CO_3	MeOH	25	2:1
3	K_2CO_3	MeOH	85	2:1
4	Cs_2CO_3	MeOH	97	1.7:1
5	Cs_2CO_3	EtOH	70	1.7:1
6	Cs_2CO_3	*i*-PrOH	25	2.5:1
7	Li_2CO_3	H_2O	45	8.5:1
8	Na_2CO_3	H_2O	>10	< 19:1
9	K_2CO_3	H_2O	tr	nd
10	Li_2CO_3	MeOH/H_2O (1:9)	30	8.5:1
11	Li_2CO_3	MeOH/H_2O (1:1)	20	5:1
12	$KHCO_3$	MeOH	tr	nd

[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. tr = trace. nd = not determined. [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).

cyclization of epoxysilane **43**, it was discovered that K_2CO_3 in MeOH at elevated temperature provided the desired product (Table 1, entry 3)[24b] The results of an expanded study of basic conditions are shown in Table 1.

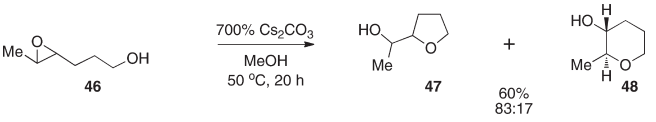
This survey of conditions demonstrated that while the use of carbonate bases generally led to less than complete conversion of the starting material, little if any decomposition took place (entries 1−11). It was found that the counterion of the carbonate base affected the reactivity, with Li_2CO_3 providing the lowest conversion of starting material in MeOH (entry 1) and Cs_2CO_3 leading to near complete conversion (entry 4). This trend in reactivity may be the result of the greater solubility of the carbonate bases that lead to more complete conversion of the starting material. The added reactivity of Cs_2CO_3 relative to other carbonate bases has been described in other cases.[26]

After initially studying MeOH as solvent, it was found that the use of either EtOH or *i*-PrOH as the solvent reduced the reaction rate (entries 5 and 6). In water, the reactivity was again sluggish but showed the opposite reactivity trend when the counterion of the carbonate base is considered (entries 7−9). Interestingly, the regioselectivity observed when the reaction was carried out in water was significantly higher. It may be that, because of the low solubility of the substrate in water, any reaction that takes place does so on the surface and a limited amount of deprotonation actually occurs. If this is the case, more of the product may result from promotion of the cyclization by the carbonate counterion (a Lewis acid promoted cyclization) leading to the higher regioselectivity obtained. Again, the lower solubility of Li_2CO_3 relative to Cs_2CO_3 may contribute to this observed reactivity trend.

Although the regioselectivity in the cyclization of disubstituted epoxide **46** under acidic conditions was reported by

(26) Matsubara, S. Rubidium and cesium in organic synthesis. In *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley: New York, 2003; Vol. 1, pp 35−50.

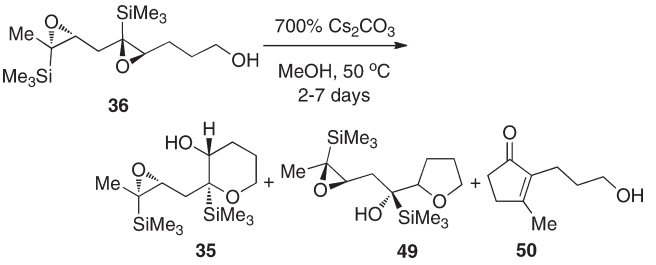
SCHEME 12



Coxon to favor the tetrahydrofuran, the corresponding cyclization under basic conditions had not been reported.[4] 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.

SCHEME 13

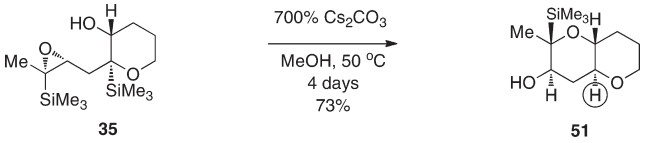


Cascade Cyclizations of Polyepoxysilanes under Basic Conditions. To begin studying cascade cyclizations of polyepoxysilanes under basic conditions, we returned to diepoxide **36** (Scheme 13). The initially attempted cascade cyclization of diepoxide **36**, under conditions that had been successfully applied to the monoepoxide (700 mol % Cs_2CO_3 in MeOH at 50 °C for 20 h), achieved less than 10% conversion of the starting material.[27] Among the factors that may contribute to the decrease in reactivity observed for bisepoxysilane **36**, relative to the monoepoxysilane (**43**), are the added steric encumbrance at the proximal epoxide and/or a conformational preference that is unfavorable for cyclization. Only by extending the reaction time was useful consumption of the starting material observed. Upon longer reaction time (2−7 days), the conversion of starting material remained sluggish and many products were produced as a complex mixture. Among those identified were monopyran **35** in which only one epoxide had been opened and enone **50**.[28] Another, tentatively identified compound was the

(27) The use of 700 mol % Li_2CO_3 in H_2O led to no conversion of starting material (**36**) after 3 days at 50 °C.

(28) For related examples, see: (a) Stork, G.; Colvin, E. *J. Am. Chem. Soc.* **1971**, *93*, 2080–2081. (b) Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682–3684. (c) Flörke, H.; Schaumann, E. *Synthesis* **1996**, 647–651. (d) Gröbel, B.-T.; Seebach, D. *Angew. Chem., Int. Ed.* **1974**, *13*, 83–84. (e) Boeckman, R. K.; Bruza, K. J. *Tetrahedron Lett.* **1974**, *16*, 3365–3368. (f) Hudrlik, P. F.; Hudrlik, A. M.; Misra, R. N.; Peterson, D.; Withers, G. P.; Kulkarni, A. K. *J. Org. Chem.* **1980**, *45*, 4444–4448.

SCHEME 14



35 **51**

corresponding furan regioisomer (**49**) in which the first epoxide had been opened but the other epoxide remained intact.

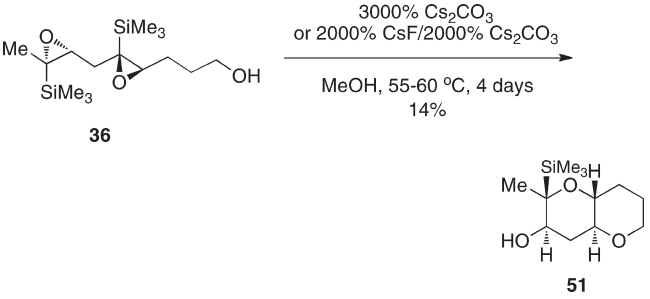
The isolation of monopyran **35**, although a predicted intermediate in a base-promoted cascade that would lead to a bispyran, was the source of some concern. It was conceivable that the developing diaxial interactions that would need to be faced in the formation of the second ring posed too great an 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. 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.[14a] The bispyran produced using this method was identical in all respects to that obtained from the reaction of monopyran **51** with Cs_2CO_3 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 Cs_2CO_3 (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 Cs_2CO_3 (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).

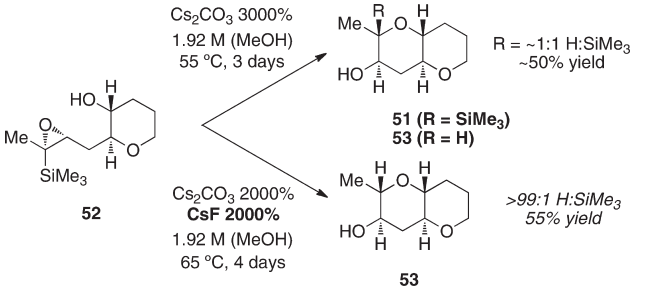
It is interesting to note that in the base-promoted cyclization of **35** to **51** only a single regioisomer was isolated (Scheme 14). This was especially encouraging because in the cyclization of monoepoxysilane **43** using Cs_2CO_3/MeOH a 1.7:1 mixture of regioisomers was isolated (Table 1, entry 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

SCHEME 15



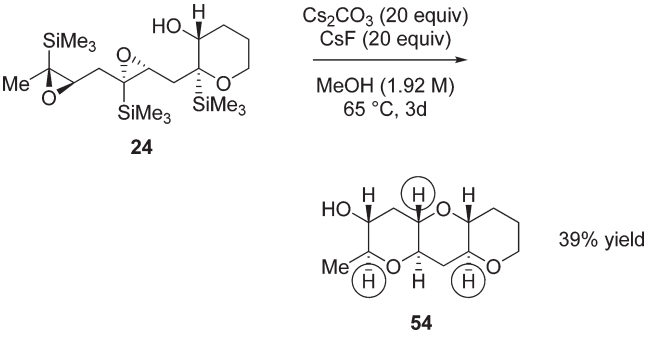
36 **51**

SCHEME 16



52 **53**

SCHEME 17



24 **54**

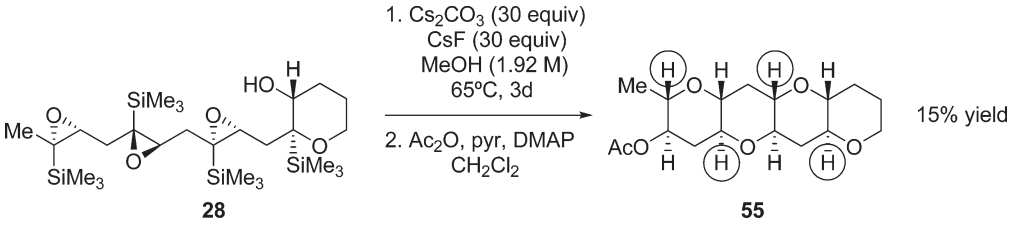
potential template effect on the regioselectivity in base-promoted cyclizations, monoepoxide **52**, diepoxide **55** and triepoxide **57** were targeted for further study.

Epoxide-Opening Cascades Leading to *trans-syn*-Fused Ladder Polyethers. Heating epoxide **52** with Cs_2CO_3 in methanol (3000 mol %, 55 °C) gave a good yield of the monocyclization but with slow final protiodesilylation to provide Me_3Si-diad **51** after 3 days (Scheme 16). In an attempt to increase the rate of protiodesilylation, several additives and alternative conditions were examined.[29] It was found that addition of cesium fluoride to the reaction mixture and prolonged heating allowed for the removal of all of the Me_3Si groups to give all-proton diad **53**. These optimized conditions (2000 mol % (1.92 M in MeOH) Cs_2CO_3 and CsF) were applied to the remaining polyepoxides **24** and **28**.

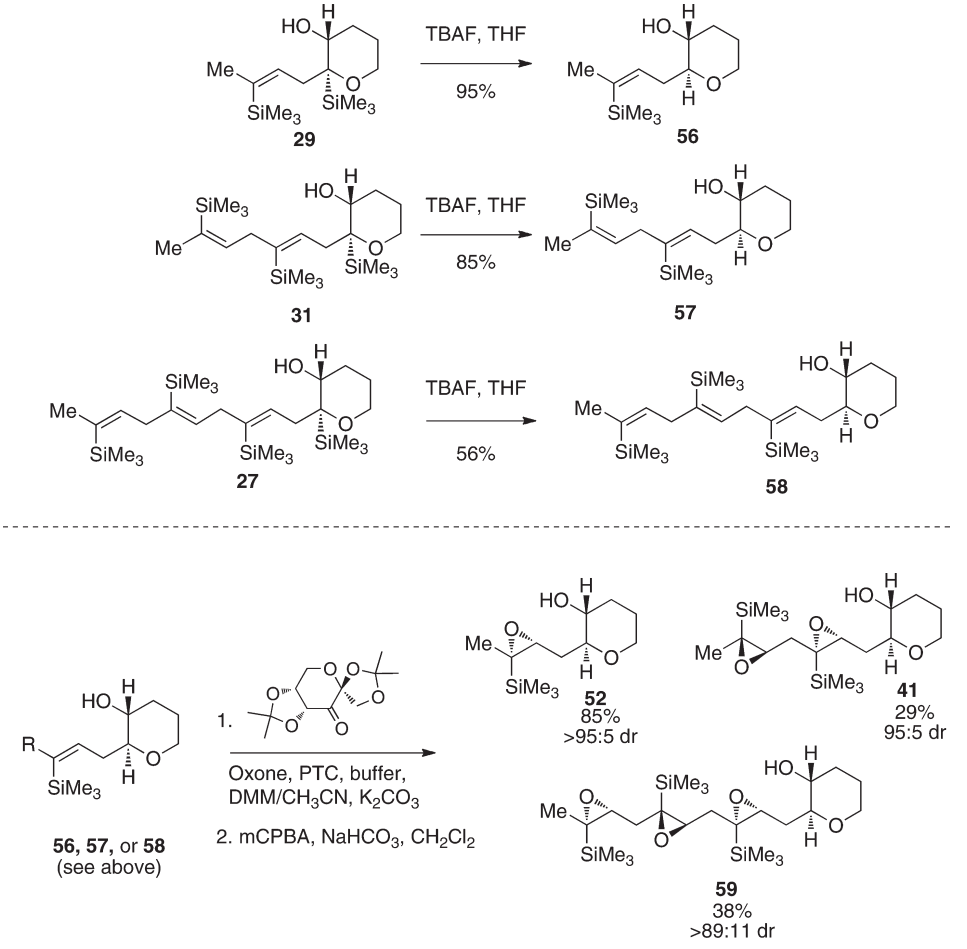
Heating diepoxide **24** to 65 °C for 3 days with Cs_2CO_3 and CsF provided the product of the cascade cyclization of both epoxides in the substrate, triad **54** (Scheme 17). Moreover, all

(29) Treatment under several conditions known to effect protiodesilylation 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.

SCHEME 18



SCHEME 19



$SiMe_3$ directing groups had been protiodesilylated; leaving a tristetrahydropyran in which *no directing groups remained*.

In the cascade reaction of diepoxide **24**, all three $SiMe_3$ 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**.

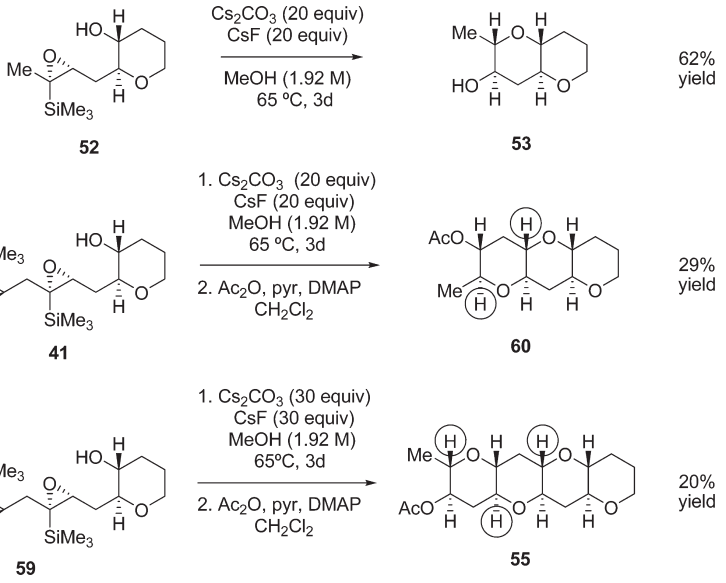
This constitutes the first report of an epoxide-opening cascade cyclization leading to the ubiquitous poltetrahydropyran motif found in the majority of the marine polyether natural products. The cascade takes place under carefully engineered basic and hydroxylic conditions to provide the polyether products *with no directing groups remaining*; the Me_3Si group disappears during the course of the reaction.

Cascade of Polyepoxides with H in Place of $SiMe_3$ on the First Tetrahydropyran Ring. To investigate the effect of the axial Me_3Si-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).

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

SCHEME 20



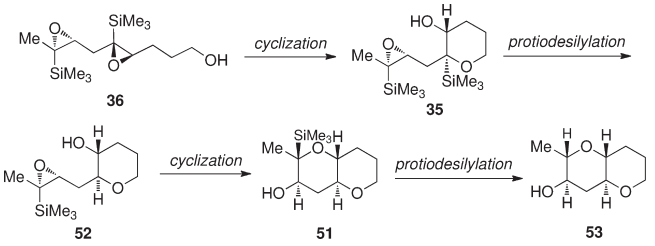


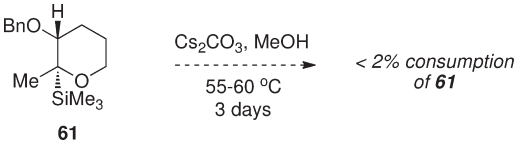
FIGURE 12. Suggested mechanism for the cascade formation of bispyran **53**.

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 α-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.[30]

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 β-hydroxyl group had been previously protected as the benzyl ether, no conversion of the starting material could be detected under the reaction conditions (Scheme 21).

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_3Si 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 2 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.[1h,i,8,31] 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.[8] 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.[31c] 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

(30) (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780–784. (b) Magnus, P.; Roy, G. *J. Chem. Soc., Chem. Commun.* **1979**, 822–823. (c) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6809–6811. (d) Hudrlik, P. F.; Holmes, P. E.; Hudrlik, A. M. *Tetrahedron Lett.* **1988**, *29*, 6395–6398.

(31) (a) Van Dyke, A. R.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 4430–4432. (b) Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6383–6385. (c) Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6678–6679. (d) Morten, C. J.; Jamison, T. F. *Tetrahedron* **2009**, *65*, 6648–6655. (e) Tanuwidjaja, J.; Ng., S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 12084–12085.

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 nonaqueous 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_2O 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).[32] ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on a 500 MHz spectrometer. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, and br = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.2 ppm), C_6D_6 (128.4 ppm), or CD_2Cl_2 (54.0 ppm) on the δ scale. High resolution mass spectra (HR-MS) were obtained on a 3 T 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 °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_3P (1.6 mL, 6.5 mmol) in THF (5.7 mL) at −78 °C. The solution was warmed to −20 °C, and the alkenyl iodide (1.4 mmol) was added. The reaction mixture was allowed to warm to room temperature gradually and stirred overnight. The reaction was quenched with 1 M HCl, and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (isolated yield = 67%). R_f = 0.41 (20% EtOAc in hexane); IR (thin film, NaCl) 3314, 2956, 2898, 2173, 1618, 1420, 1249, 1053, 841, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.24 (t, J = 7.6 Hz, 1H), 3.68 (t, J = 6.4 Hz, 2H), 2.99 (s, 2H), 2.24 (dt, J = 7.6, 7.3 Hz, 2H), 1.68 (m, 2H), 0.19 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 134.5, 106.5, 88.3, 63.3, 33.5, 29.4, 28.9, 0.8, 0.7; HR-MS (ESI) calcd for $C_{14}H_{28}NaOSi_2$ $(M + Na)^+$ 291.1571, found 291.1577.

(2*R*,3*R*)-2-Trimethylsilanyl-2-(3-trimethylsilanyl-prop-2-ynyl)-tetrahydro-pyran-3-ol (20). To olefin **18** (6.4 g, 24 mmol) were added CH_3CN/DMM (760 mL, 1:2 v/v), a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4.0×10^{-4} M Na_2-(EDTA) (500 mL), *n*-Bu_4NHSO_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 (59 g, 96 mmol) in 4.0×10^{-4} M Na_2-(EDTA) (400 mL) and a 0.89 M solution of K_2CO_3 (400 mL). After the Oxone and K_2CO_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_2Cl_2 (150 mL) at 0 °C was added $BF_3 \cdot Et_2O$ (0.3 mL, 1.2 mmol), and the reaction mixture was stirred 20 min. The reaction was quenched with saturated $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_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) to afford **20** (0.9 g, 19% over two steps): R_f = 0.53 (20%, EtOAc in hexane); $[\alpha]^{25}_D$ = −20.0 (c = 2.0, in $CHCl_3$); IR (thin film, NaCl) 3470, 2957, 2175, 1249, 1089, 1003, 842, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.96 (m, 1H), 3.68 (ddd, J = 12.2, 9.5, 3.4 Hz, 1H), 3.54 (app dt, J = 11.9, 4.6 Hz, 1H), 2.88 (d, J = 16.8 Hz, 1H), 2.45 (d, J = 17.1 Hz, 1H), 2.29 (d, J = 4.6 Hz, 1H), 2.02−1.95 (m, 1H), 1.89−1.80 (m, 1H), 1.74−1.68 (m, 1H), 1.52−1.45 (m, 1H), 0.20 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 104.4, 88.9, 75.2, 70.7, 61.6, 28.7, 25.7, 22.1, 0.6, −0.2; HR-MS (ESI) calcd for $C_{14}H_{28}NaO_2Si_2$ $(M + Na)^+$ 307.1520, found 307.1517.

(2*R*,3*R*)-2-[(*E*)-3-Iodo-3-trimethylsilanyl-allyl]-2-trimethylsilanyl-tetrahydro-pyran-3-ol (21). To a solution of **20** (3.5 g, 12 mmol) in Et_2O (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_2O (10 mL). A solution of I_2 (13 g, 49 mmol) in Et_2O (20 mL) was added. After stirring for 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_2O (3 × 100 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$ and 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*): R_f = 0.50 (20%, EtOAc in hexane); $[\alpha]^{25}_D$ = −10.5 (c = 15.8, in $CHCl_3$); IR (thin film, NaCl) 3476, 2955, 2866, 1394, 1251, 1070, 837 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, J = 7.9, 6.1 Hz, 1H), 3.71−3.62 (m, 2H), 3.49 (ddd, J = 11.9, 8.5, 3.4 Hz, 1H), 2.55 (15.9, 7.9 Hz, 1H), 2.44 (dd, J = 15.9, 6.1 Hz, 1H), 1.94−1.88 (m, 1H), 1.78−1.66 (m, 2H), 1.59−1.52 (m, 1H), 0.28 (s, 9H), 0.16 (s, 9H); ^{13}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 $C_{14}H_{29}INaO_2Si_2$ $(M + Na)^+$ 435.0643, found 435.0636.

(2*R*,3*R*)-2-((*Z*)-3,6-Bis-trimethylsilanyl-hex-2-en-5-ynyl)-2-trimethylsilanyl-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 were added a 2.5 M solution of *n*-BuLi in hexane (2.6 mL) and TMEDA (1.0 mL, 6.5 mmol). The solution was warmed to 0 °C and stirred 45 min. The solution was then transferred to a slurry of CuI (1.3 g, 7.0 mmol) and DMAP (760 mg, 6.3 mmol) in THF (8.5 mL) at −78 °C. The solution was warmed to −20 °C, alkenyl iodide **21** (570 mg, 1.4 mmol) was added, and the reaction mixture was allowed to warm to room temperature gradually and stirred overnight. The reaction was quenched with 1 M HCl, and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with water and 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%): R_f = 0.49 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = −9.3 (c = 8.6, in $CHCl_3$); IR (thin film, NaCl) 3463, 2955, 2898, 2173, 1610, 1408, 1249, 1091, 839, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.49 (t, J = 6.4 Hz, 1H), 3.78−3.65 (m, 2H), 3.57−3.48 (m, 1H), 3.04 (s, 2H), 2.61 (t, J = 6.4 Hz, 2H), 2.01−1.91 (m, 1H), 1.85 (d, J = 7.0 Hz, 1H), 1.87−1.77 (m,

(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

1H), 1.76−1.65 (m, 1H), 1.60−1.49 (m, 1H), 0.21 (s, 9H), 0.16 (s, 9H), 0.15 (s, 9H); ^{13}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 $C_{20}H_{40}NaO_2Si_3$ $(M + Na)^+$ 419.2234, found 419.2241.

(2*R*,3*R*)-2-((2*Z*,5*E*)-6-Iodo-3,6-bis-trimethylsilanyl-hexa-2,5-dienyl)-2-trimethylsilanyl-tetrahydro-pyran-3-ol (23). To a solution of enyne **22** (0.5 g, 1.2 mmol) in Et_2O (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 Et_2O (0.5 mL). A solution of I_2 (1.2 g, 4.8 mmol) in Et_2O (1.0 mL) was added. After stirring for 2 h at −78 °C, the reaction was warmed to 0 °C and stirred 1 h. The reaction was quenched by pouring into 1 M HCl (5 mL) and ice (2 g). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (10% EtOAc in hexane) to yield alkenyl iodide **23** (0.3 g, 51%, >95% *E*): R_f = 0.33 (10% EtOAc in hexane); $[\alpha]^{25}_D$ = −2.3 (*c* = 21.3, in $CHCl_3$); IR (thin film, NaCl) 3463, 2953, 2898, 2855, 1725, 1407, 1249, 1092, 839, 758 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (t, *J* = 7.9 Hz, 1H), 6.13 (t, *J* = 6.4 Hz, 1H), 3.72−3.63 (m, 2H), 3.50 (ddd, *J* = 11.0, 6.7, 3.7 Hz, 1H), 2.83 (d, *J* = 7.6 Hz, 2H), 2.62−2.50 (m, 2H), 1.95−1.88 (m, 2H), 1.82−1.74 (m, 1H), 1.72−1.64 (m, 1H), 1.54−1.46 (m, 1H), 0.25 (s, 9H), 0.16 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{20}H_{41}INaO_2Si_3$ $(M + Na)^+$ 547.1351, found 547.1349.

(2*R*,3*R*)-2-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-Methyl-3-trimethylsilanyl-oxiranylmethyl)-3-trimethylsilanyl-oxiranylmethyl]-2-trimethylsilanyl-tetrahydro-pyran-3-ol (24). To a slurry of CuCN (0.12 g, 1.4 mmol) in Et_2O (3.0 mL) at 0 °C was added a 1.6 M solution of MeLi in Et_2O (1.7 mL). After 15 min a solution of alkenyl iodide **23** (0.32 g, 0.6 mmol) in Et_2O (1.0 mL) was slowly added. The solution was maintained at 0 °C for 20 h at which time the reaction was carefully quenched with saturated NH_4Cl. The aqueous layer was separated and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was partially purified by column chromatography (10% EtOAc in hexane) to yield diene **38** (details below).

To a solution of crude diene **38** (40 mg, 97 μmol) were added CH_3CN/DMM (3.1 mL, 1:2 v/v), a 0.05 M solution of $Na_2B_4O_7\cdot 10H_20$ in 4.0 × 10^{-4} M Na_2-(EDTA) (2.1 mL), *n*-$BuNHSO_4$ (7 mg, 21 μmol), and chiral ketone **19** (50 mg, 2.0 mmol). To this rapidly stirring solution were added, simultaneously over 20 min *via* syringe pump, a solution of Oxone (0.20 g, 0.33 mmol) in 4.0 × 10^{-4} M Na_2-(EDTA) (1.4 mL) and a 0.89 M solution of K_2CO_3 (1.4 mL). After the Oxone and K_2CO_3 solutions had been added, the resulting mixture was diluted with water and extracted with EtOAc (4 × 10 mL). The combined organic layers where washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The epoxide product could not be separated from the ketone catalyst and so was dissolved in CH_2Cl_2 (350 μL). To this was added $NaHCO_3$ (29 mg, 340 μmol) and *m*-CPBA (12 mg, 68 μmol), and the reaction was stirred 5 min. The reaction was quenched with 1 M NaOH and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc in hexane) to afford bisepoxide epoxide **24** (8 mg, 23% over 2 steps, dr 8:1): R_f = 0.55 (30% EtOAc in hexane); $[\alpha]^{25}_D$ = +17.4 (*c* = 2.3, in $CHCl_3$); IR (thin film, NaCl) 3442, 2955, 2853, 2360, 1250, 1091, 838, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.08−4.02 (m, 1H); 3.66 (dt, *J* = 11.4, 3.5 Hz, 1H), 3.42 (td, *J* = 11.4, 2.8 Hz, 1H), 3.17 (dd, *J* = 8.7, 1.3 Hz, 1H), 2.66 (d, *J* = 7.1 Hz, 1H), 2.65 (d, *J* = 7.1 Hz, 1H), 2.18−2.06 (m, 2H), 1.98−1.90 (m, 2H), 1.79−1.69 (m, 2H), 1.68−1.60 (m, 2H), 1.11 (s, 3H), 0.10 (s, 9H), 0.08 (s, 9H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{21}H_{44}NaO_4Si_3$ $(M + Na)^+$ 467.2445, found 467.2443.

(2*R*,3*R*)-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_2O (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_2O, 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 glovebox under Ar. THF (1 mL) was added, and the solution was 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 and then heated to 40 °C for 2 h. The reaction mixture was poured onto 1 N HCl (5 mL) and ice. The organic layer was separated, and the aqueous layer was extracted with Et_2O (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); $[\alpha]^{25}_D$ = −17.0 (*c* = 1.2, in $CHCl_3$); IR (thin film, NaCl) 3486, 2953, 2932, 2869, 1249, 1086, 1069, 1016, 835, 756 cm^{-1}; ^{1}H NMR δ (500 MHz, $CDCl_3$) δ 6.09 (app tq, *J* = 6.9, 1.9 Hz, 1H), 3.75−3.66 (m, 2H), 3.51 (ddd, *J* = 10.7, 6.3, 3.6 Hz, 1H), 2.56−2.51 (m, 2H), 1.99−1.88 (m, 1H), 1.85−1.62 (m, 3H) 1.77 (d, *J* = 1.7 Hz, 3H), 1.56−1.44 (m, 1H), 0.15 (s, 9H), 0.14 (s, 9H); ^{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 $C_{15}H_{32}NaO_2Si_2$ $(M + Na)^+$ 323.1833, found 323.1831.

(2*R*,3*R*)-2-((2*Z*,5*Z*)-3,6-bistrimethylsilanylhepta-2,5-dienyl)-2-trimethylsilanyl-tetrahydropyran-3-ol (31). To a stirred solution of (*Z*)-3-trimethylsilyl-2-buten-1-ol[33] (500 mg, 3.47 mmol) in Et_2O (12 mL) at 0 °C under argon was added PBr_3 (166 μL, 1.74 mmol), and the solutions was 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_2O (3 × 5 mL). The combined organic layers were washed with water (3 × 5 mL) and 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,[34] a solution of alkyne **20** (50 mg, 0.18 mmol) in THF (350 μL) was added to Cp_2ZrHCl (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_2O, 120 μL, 0.19 mmoL). The mixture was allowed 2w A solution of $Me_2CuCNLi_2$ was added dropwise (prepared by addition of MeLi (1.6 M in Et_2O, 240 μL, 0.89 mmol) to a slurry of CuCN (17 mg, 0.19 mmol) in Et_2O (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_4OH/NH_4Cl (10% v/v) in saturated (2 mL). The product was extracted with Et_2O (4 × 20 mL) and dried over $MgSO_4$. The solution was filtered through a pad of Celite, and the solvent was 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%

(33) Han, S.; Kass, S. R. *Tetrahedron Lett*. **1997**, *38*, 7503.
(34) Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc*. **1990**, *112*, 7440.

EtOAc in hexane); $[\alpha]^{25}_D = -3.76$ ($c = 2.6$, in $CHCl_3$); IR (thin film, NaCl) 3447, 2952, 2854, 2360, 2341, 1247, 1091, 836, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.07 (tt, $J = 6.4$, 1.6 Hz, 1H), 5.91 (tq, $J = 7.2$, 1.8 Hz, 1H), 3.75−3.66 (m, 2H), 3.52 (ddd, $J = 11.4$, 5.9, 3.9 Hz, 1H), 2.88−2.84 (m, 2H), 2.70 (ddt, $J = 16.3$, 6.4, 1.6 Hz, 1H), 2.51 (ddt, $J = 16.0$, 6.6, 1.6 Hz, 1H), 1.97−1.87 (m, 2H), 1.75−1.85 (m, 1H), 1.77 (q, $J = 1.4$ Hz, 3H), 1.64−1.72 (m, 1H), 1.44−1.52 (m, 1H), 0.17 (s, 9H), 0.14 (s, 9H), 0.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{21}H_{44}NaO_2Si_3$ $(M+Na)^+$ 435.2541, found 435.2545.

(2*Z*,5*E*)-6-Iodo-3,6-bis-trimethylsilanyl-hexa-2,5-dien-1-ol (32). To a solution of (*Z*)-6-(*tert*-butyl-dimethyl-silanyloxy)-1,4-bis-trimethylsilanyl-hex-4-en-1-yne[14b] (9.6 g, 25 mmol) in Et_2O (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 and diluted with Et_2O (50 mL), and a solution of I_2 (25 g, 98 mmol) in Et_2O (150 mL) was added. After stirring for 2 h at −78 °C, the reaction mixture was warmed to 0 °C, 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_2O (3 × 250 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$ and 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) 3324, 2954, 1250, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (t, $J = 7.6$ Hz, 1H), 6.14 (tt, $J = 7.0$, 1.5 Hz, 1H), 4.23 (dd, $J = 6.7$, 5.8 Hz, 2H), 2.87 (dd, $J = 7.6$, 1.5 Hz, 2H), 0.27 (s, 9H), 0.17 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 141.5, 141.4, 108.0, 62.3, 41.9, 1.2, 0.3; HR-MS (ESI) calcd for $C_{12}H_{29}INaOSi_2$ $(M + Na)^+$ 391.0381, found 391.0394.

(2*Z*,5*Z*)-3,6-Bis-trimethylsilanyl-hepta-2,5-dien-1-ol (33). To a slurry of CuCN (1.28 g, 14.29 mmol) in Et_2O (36 mL) at 0 °C was added a 1.6 M solution of MeLi in Et_2O (17.9 mL). After 15 min a solution of **32** (3.15 g, 6.35 mmol) in Et_2O (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_4Cl. The aqueous layer was separated and extracted with Et_2O (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 the dienol **33** (1.69 g, 4.4 mmol, 69%): $R_f = 0.45$ (10% EtOAc in hexane); IR (thin film, NaCl) 3315, 2954, 2898, 1616, 1444, 1406, 1249, 1035, 996, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.12 (t, $J = 7.0$ Hz, 1H), 5.96−5.89 (m, 1H), 4.21 (t, $J = 5.5$ Hz, 2H), 3.48−3.55 (m, 1H), 2.84 (d, $J = 7.0$ Hz, 2H), 1.79 (s, 3H), 1.47−1.44 (m, 1H), 0.17 (s, 9H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 141.0, 140.9, 137.0, 62.9, 39.4, 25.4, 0.9, 0.5; HR-MS (ESI) calcd for $C_{13}H_{28}NaOSi_2$ $(M + Na)^+$ 279.1576, found 279.1576.

(2*R*,3*R*)-2-(Trimethyl-silanyl)-2-((2*Z*,5*Z*,8*Z*)-3,6,9-tris-trimethylsilanyl-deca-2,5,8-trienyl)-tetrahydropyran-3-ol (27). To a stirred solution of dienol **33** (890 mg, 2.32 mmol) in CH_2Cl_2 (4.6 mL) maintained at 0 °C under argon were added NEt_3 (647 μL, 4.6 mmol) and methanesulfonyl chloride (198 μL, 2.55 mmol), and the solution was tirred 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_2Cl_2 (4 × 5 mL). The combined organic layers were washed with water (3 × 5 mL) and brine, dried over Na_2SO_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,[35] to a stirred solution of **20** (570 mg, 2.0 mmol) in Et_2O (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 (1.6 M in Et_2O, 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 $CuI \cdot P(OEt)_3$ (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 onto 1 N HCl (50 mL) and ice. The organic layer was separated, and the aqueous layer was extracted with Et_2O (4 × 50 mL). The combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (5% EtOAc in hexane) to give the desired triene **27** (321 mg, 31%, >95% *Z*): $R_f = 0.39$ (20% EtOAc in hexane); $[\alpha]^{25}_D = -6.0$ ($c = 1.67$ in $CHCl_3$); IR (thin film, NaCl) 3461, 2953, 2897, 1613, 1444, 1247, 1092, 836, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (t, $J = 6.4$ Hz, 1H), 5.96−5.87 (m, 2H), 3.75−3.65 (m, 2H), 3.48−3.55 (m, 1H), 2.89 (d, $J = 7.0$ Hz, 2H), 2.86 (d, $J = 7.0$ Hz, 2H), 2.65 (AB dd, $J = 15.8$, 5.8 Hz, 1H) and 2.54 (AB dd, $J = 16.2$, 6.7 Hz, 1H), 2.01−1.98 (m, 1H), 1.85 (d, $J = 7.6$, 1H), 1.87−1.77 (m, 1H), 1.78 (s, 3H), 1.76−1.65 (m, 1H), 1.54−1.46 (m, 1H), 0.21 (s, 9H), 0.18 (s, 9H), 0.17 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 141.8, 140.1, 138.8, 137.8, 135.2, 75.8, 70.4, 61.8, 39.8, 39.2, 35.3, 27.3, 24.8, 22.6, 0.4, 0.3, 0.1, −0.2 ; HR-MS (ESI) calcd for $C_{27}H_{56}NaO_2Si_4$ $(M + Na)^+$ 547.3250, found 547.3267.

(2*S*,3*R*)-2-((2*R*,3*S*)-3-Methyl-3-trimethylsilanyl-oxiranylmethyl)-2-trimethylsilanyl-tetrahydro-pyran-3-ol (35). To olefin **29** (140 mg, 0.46 mmol) were added CH_3CN/DMM (16 mL, 1:2 v/v), a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4.0×10^{-4} M Na_2-(EDTA) (10.2 mL), *n*-Bu_4NHSO_4 (0.03 g, 0.09 mmol), and chiral ketone **19** (220 mg, 0.87 mmol). To this solution were added, simultaneously over 20 min *via* syringe pump, a solution of Oxone (0.22 g, 0.87 mmol) in 4.0×10^{-4} M Na_2-(EDTA) (7.5 mL) and a 0.89 M solution of K_2CO_3 (7.5 mL). After the Oxone and K_2CO_3 solutions had been added, the resulting mixture was stirred 10 min, then diluted with water (50 mL), and extracted with hexane (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc in hexane) to yield epoxide **35** (90 mg, 62%, dr >95:5): $R_f = 0.49$ (20% EtOAc in hexane); $[\alpha]^{25}_D = +18.3$ ($c = 6.0$, in $CHCl_3$); IR (thin film, NaCl) 3436, 2955, 2854, 1440, 1408, 1370, 1250, 1091, 1025, 837, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.06 (app dt, $J = 9.8$, 4.6 Hz, 1H), 3.79−3.74 (m, 1H), 3.55 (app dt, $J = 10.4$, 3.0 Hz, 1H), 3.09 (dd, $J = 8.5$, 1.2 Hz, 1H), 2.10 (d, $J = 5.5$ Hz, 1H), 2.06 (dd, $J = 15.0$, 1.2 Hz, 1H), 1.97−1.93 (m, 1H), 1.78−1.70 (m, 4H), 1.24 (s, 3H), 0.18 (s, 9H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.1, 72.0, 64.6, 61.9, 54.2, 36.3, 29.4, 25.6, 23.3, 0.9, −1.1; HR-MS (ESI) calcd for $C_{15}H_{32}NaO_3Si_2$ $(M + Na)^+$ 339.1782, found 339.1772.

(2*R*,3*R*)-2methylsilanyl-oxiranylmethyl)-3-trimethylsilanyl-oxiranylmethyl)-3-trimethylsilanyl-oxiranylmethyl]-2-trimethylsilanyl-tetrahydro-pyran-3-ol (28). To a solution of the triene **27** (89 mg, 0.17 mmol) were added CH_3CN/DMM (5.3 mL, 1:2 v/v), a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_20$ in 4.0×10^{-4} M Na_2-(EDTA) (3.5 mL), *n*-$BuNHSO_4$ (17.5 mg, 52 μmol), and chiral ketone **19** (130 mg, 0.5 mmol). To this rapidly stirring solution were added, simultaneously over 20 min *via* syringe pump, a solution of Oxone (626 mg, 1.02 mmol) in 4.0×10^{-4} M Na_2-(EDTA) (4.5 mL) and a 0.89 M solution of K_2CO_3 (4.5 mL). After the Oxone and K_2CO_3 solutions had been added, the resulting mixture was diluted with water and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers where

(35) Ziegler, F. E.; Mikami, K. *Tetrahedron Lett.* **1984**, *25*, 131.

washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The epoxide product could not be separated from the ketone catalyst and so was dissolved in CH_2Cl_2 (2 mL). To this were added $NaHCO_3$ (180 mg, 2.15 μmol) and *m*-CPBA (148 mg, 0.86 mmol), and the reaction was stirred 30 min. The reaction was quenched with 1 M NaOH and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (5−20% EtOAc in hexane) to afford triepoxide **28** (29 mg, 30%, dr 92:8): R_f = 0.52 (30% EtOAc in hexane); $[\alpha]^{25}_D$ = +24.5 (*c* = 3.67 in $CHCl_3$); IR (thin film, NaCl) 3444 (br), 2955, 2899, 2853, 2360, 1250, 1091, 839, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.02−4.08 (m, 1H), 3.67 (dt, *J* = 11.6, 4.0 Hz, 1H), 3.42 (td, *J* = 11.1, 2.7 Hz, 1H), 3.21 (d, *J* = 8.2, 1.2 Hz, 1H), 2.92 (dd, *J* = 8.5, 3.0 Hz, 1H), 2.71 (dd, *J* = 7.9, 3.7 Hz, 1H), 2.06−2.22 (m, 3H), 1.90−1.98 (m, 1H), 1.68−1.80 (m, 3H), 1.58−1.68 (m, 1H), 1.35−1.47 (m, 2H), 1.11 (s, 3H), 0.10 (s, 9H), 0.08 (s, 9H), −0.02 (s, 9H), −0.09 (s, 9H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 76.4, 71.4, 63.6, 62.2, 60.3, 60.0, 55.9, 55.0, 54.9, 38.6, 38.4, 36.0, 28.9, 24.8, 22.9, 0.4, −0.9, −0.9, −1.5 ; HR-MS (ESI) calcd for $C_{27}H_{56}NaO_5Si_4$ $(M + Na)^+$ 595.3097, found 595.3107.

3-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-Methyl-3-silanyl-oxiranylmethyl)-3-silanyl-oxiranyl]-propan-1-ol (36). To a solution of acetate **65** (1.3 g, 3.7 mmol) in THF (8.0 mL) and MeOH (8.0 mL) at 0 °C was added a 1.0 M solution of LiOH (8.0 mL), and the mixture was stirred for 20 min. The mixture was diluted with water and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford bisepoxide **36** (1.0 g, 84%): R_f = 0.47 (50% EtOAc in hexane); $[\alpha]^{25}_D$ = +4.4 (*c* = 18.3, $CHCl_3$); IR (thin film, NaCl) 3445, 2957, 2360, 2341, 1441, 1418, 1371, 1250, 1062, 840, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.68 (dt, *J* = 5.5, 4.0 Hz, 2H), 2.88 (dd, *J* = 7.9, 4.0 Hz, 1H), 2.71 (dd, 8.2, 3.7 Hz, 1H), 2.16 (dd, *J* = 14.3, 3.4 Hz, 1H), 1.85−1.71 (m, 4H), 1.55−1.28 (m, 2H), 1.19 (s, 3H), 0.17 (s, 9H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.7, 62.7, 62.4, 56.7, 55.1, 38.4, 30.5, 27.6, 22.9, −0.9, −1.5; HR-MS (ESI) calcd for $C_{15}H_{32}O_3Si_2$ $(M + H)^+$ 317.1968, found 317.1958.

(2*S*,4*R*,5*R*,2′*S*)-5-Methyl-2,5-bis-trimethylsilanyl-octahydro-[2,2′]bifuranyl-4-ol (62). To a solution of bisepoxide **36** (10 mg, 32 μmol) in CH_2Cl_2 (0.3 mL) at −78 °C was added $Et_2O \cdot BF_3$ (7 mg, 32 μmol), and the mixture was stirred for 2 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford bisfuran **62** (5.0 mg, 50%): IR (thin film, NaCl) 3375, 2953, 1739, 1451, 1246, 1052, 1063, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (d, *J* = 11.6 Hz, 1H), 3.99−3.94 (m, 2H), 3.88−3.83 (m, 1H), 3.79−3.74 (m, 1H), 2.26 (dd, *J* = 14.0, 5.8 Hz, 1H), 1.95−1.91 (m, 3H), 1.82 (d, *J* = 14 Hz, 1H), 1.33−1.28 (m, 1H), 0.94 (s, 3H), 0.09 (s, 9H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.1, 83.3, 82.1, 81.1, 67.0, 35.7, 29.6, 26.1, 25.4, −1.5, −1.8; HR-MS (ESI) calcd for $C_{15}H_{33}O_3Si_2$ $(M + H)^+$ 317.1963, found 317.1967.

Acetic Acid (2*S*,4*R*,5*R*,2′*S*)-5-Methyl-2,5-bis-trimethylsilanyl-octahydro-[2,2′]bifuranyl-4-yl Ester (37). To a solution of bisfuran **62** (6 mg, 19 μmol) in CH_2Cl_2 (0.4 mL) were added *i*-Pr_2EtN (80 mg, 0.6 mmol), Ac_2O (60 mg, 0.6 mmol), and DMAP (2 mg, 16 μmol). The mixture was stirred overnight, quenched with saturated NH_4Cl, and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3 × 3 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (20% EtOAc in hexane) to afford acetate **37** (5.0 mg, 87%): R_f = 0.47 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = −50.0 (*c* = 1.0, $CHCl_3$); IR (thin film, NaCl) 2959, 1743, 1450, 1368, 1246, 1109, 1072, 1045, 838, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.16 (d, *J* = 5.6 Hz, 1H), 3.95−3.91 (m, 1H), 3.88−3.83 (m, 1H), 3.63−3.59 (m, 1H), 2.42 (dd, *J* = 14.6, 5.8 Hz, 1H), 2.20 (d, *J* = 14.6 Hz, 1H), 2.02 (s, 3H), 1.96−1.82 (m, 4H), 1.03 (s, 3H), 0.07 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 85.3, 84.8, 82.0, 80.0, 68.0, 39.6, 28.4, 26.0, 25.0, 21.7, −0.6, −1.8; HR-MS (ESI) calcd for $C_{17}H_{34}NaO_4Si_2$ $(M + Na)^+$ 381.1888, 381.1893.

(4*Z*,7*E*)-8-Iodo-5,8-bis-trimethylsilanyl-octa-4,7-dien-1-ol (63). To a solution of alkyne **18** (18.7 g, 69.8 mmol) in Et_2O (170 mL) at 0 °C was added a 1 M solution of DIBAL in hexane (170 mL). The resulting solution was heated 24 h at reflux. The solution was then cooled to −78 °C and diluted with Et_2O (50 mL), and a solution of I_2 (71.0 g, 279.1 mmol) in Et_2O (150 mL) was added. After stirring for 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 Et_2O (3 × 200 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield alkenyl iodide 63 (22.9 g, 83%, >95% *E*): R_f = 0.39 (20% EtOAc in hexane); IR (thin film, NaCl) 3324, 2953, 2896, 1614, 1407, 1249, 1057, 839, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (t, *J* = 7.6 Hz, 1H), 5.93 (t, *J* = 7.6 Hz, 1H), 3.65 (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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 143.3, 137.3, 107.2, 62.7, 42.3, 33.2, 28.6, 1.3, 0.4; HR-MS (ESI) calcd for $C_{14}H_{29}NaIOSi_2$ $(M + Na)^+$ 419.0694, found 419.0674.

(4*Z*,7*Z*)-5,8-Bis-trimethylsilanyl-nona-4,7-dien-1-ol (64). To a slurry of CuCN (2.5 g, 28.4 mmol) in Et_2O (34.0 mL) at 0 °C was added a 1.4 M solution of MeLi in Et_2O (35.5 mL), and the mixture was stirred for 15 min. A solution of alkenyl iodide 63 (5.0 g, 12.6 mmol) in Et_2O (12.8 mL) was slowly added. The reaction was stirred for 20 h at 0 °C, then was carefully quenched with saturated NH_4Cl, and extracted with Et_2O (3 × 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 diene 64 (3.1 g, 86%): R_f = 0.39 (20% EtOAc in hexane); IR (thin film, NaCl) 3322, 2953, 1615, 1248, 1058, 836, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.95−5.89 (m, 2H), 3.66 (t, *J* = 6.4 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), 0.15 (s, 9H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 141.5, 139.2, 135.6, 62.9, 39.3, 33.3, 28.7, 24.9, 0.5, 0.0; HR-MS (ESI) calcd for $C_{15}H_{32}NaOSi_2$ $(M + Na)^+$ 307.1884, found 307.1889.

Acetic Acid 3-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-Methyl-3-silanyl-oxiranylmethyl)-3-silanyl-oxiranyl]-propyl Ester (65). To a solution of alcohol **64** (2.5 g, 8.7 mmol) in CH_2Cl_2 (87 mL) at 0 °C were added pyridine (0.8 g, 10.4 mmol), Ac_2O (1.1 g, 10.4 mmol), and DMAP (0.11 g, 0.9 mmol). The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was partially purified by column chromatography (20% EtOAc in hexane) and carried to the next step.

To a solution of the acetate (2.0 g, 6.2 mmol) in CH_3CN/DMM (192 mL, 1:2 v/v) were added a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_20$ in 4.0 × 10^{-4} M Na_2-(EDTA) (129 mL), *n*-$BuNHSO_4$ (0.4 g, 1.2 mmol), and chiral ketone **19** (3.2 g, 12.3 mmol). To this rapidly stirring solution were added, simultaneously over 20 min *via* syringe pump, a solution of Oxone (12.5 g, 20.0 mmol) in 4.0 × 10^{-4} M Na_2-(EDTA) (86.0 mL) and a 0.89 M solution of K_2CO_3

(86.0 mL). After the Oxone and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (200 mL) and extracted with EtOAc (4 × 400 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The epoxide product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) to afford bisepoxide **65** (1.3 g, 42% over 2 steps, dr >95:5): R_f = 0.47 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = +3.7 (c = 2.7, $CHCl_3$); IR (thin film, NaCl) 2958, 1742, 1367, 1250, 1045, 840, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.18−4.09 (m, 2H), 2.87 (dd, J = 7.9, 4.9 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, 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 $C_{17}H_{34}O_4Si_2$ $(M + Na)^+$ 381.1888 found, 381.1997.

Carbonic Acid *tert*-Butyl Ester (2*R*,3*S*)-3-((2*R*,3*S*)-3-Methyl-3-trimethylsilanyl-oxiranylmethyl)-3-trimethylsilanyl-oxiranylmethyl Ester (39). To a solution of the dienyl alcohol **33** (0.7 g, 2.8 mmol) in CH_2Cl_2 (28 mL) were added Et_3N (0.8 mL, 5.6 mmol), BOC_2O (1.2 g, 5.6 mmol), and DMAP (30 mg, 0.3 mmol). The mixture stirred at room temperature overnight, then was quenched with saturated NH_4Cl, and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with water and 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_3CN/DMM (94 mL, 1:2 v/v) were added a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_20$ in 4.0 × 10^{-4} M Na_2-(EDTA) (63 mL), n-Bu_4NHSO_4 (0.2 g, 0.6 mmol), and chiral ketone **19** (1.6 g, 6.0 mmol). To this rapidly stirring solution were added, simultaneously over 20 min *via* syringe pump, a solution of Oxone (6.1 g, 9.9 mmol) in 4.0 × 10^{-4} M Na_2-(EDTA) (42 mL) and a 0.89 M solution of K_2CO_3 (42 mL). After the Oxone and K_2CO_3 solutions had been added, the resulting mixture was diluted with water (150 mL) and extracted with EtOAc (4 × 200 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The asymmetric epoxidation procedure was repeated two times. The epoxide product was separated from the ketone catalyst by column chromatography (20% EtOAc in hexane) to afford **39** (0.5 g, 39% over 3 steps, dr 6:1): R_f = 0.62 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = +6.4 (c = 4.7, $CHCl_3$); IR (thin film, NaCl) 2958, 1744, 1456, 1370, 1280, 1253, 1164, 1095, 842, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.37 (dd, J = 11.9, 2.4 Hz, 1H), 4.03 (dd, J = 11.9, 8.5 Hz, 1H), 3.23 (dd, J = 7.9, 3.1 Hz, 1H), 2.74 (dd, J = 7.6, 4.3 Hz, 1H), 2.07 (dd, J = 14.6, 3.7 Hz, 1H), 1.59 (dd, J = 14.6, 7.6 Hz, 1H), 1.51 (s, 9H), 1.22 (s, 3H), 0.21 (s, 9H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 83.2, 67.5, 62.4, 60.9, 55.8, 55.6, 38.1, 28.4, 23.3, −0.7, −1.1; HR-MS (ESI) calcd for $C_{13}H_{36}NaO_5Si$ $(M + Na)^+$ 411.1993, found 411.2007.

(*S*)-4-((2*S*,4*R*,5*R*)-4-Hydroxy-5-methyl-2,5-bis-trimethylsilanyl-tetrahydro-furan-2-yl)-[1,3]dioxolan-2-one (40). To a solution of **39** (42 mg, 0.11 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C was added $BF_3 \cdot Et_2O$ (24 μL, 0.11 mmol). After 2 min the reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to yield **40** (13 mg, 36%): R_f = 0.31 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = −20.0 (c = 1.0, $CHCl_3$); IR (thin film, NaCl) 3496, 2955, 1786, 1250, 1180, 1074, 838, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.35 (dd, J = 8.9, 6.6 Hz, 1H), 4.52 (dd, J = 9.0, 6.6 Hz, 1H), 4.45 (app t, J = 9.0 Hz, 1H), 4.32 (app t, J = 4.6 Hz, 1H), 2.35 (dd, J = 14.3, 5.0 Hz, 1H), 2.13 (d, J = 14.3 Hz, 1H), 1.80 (d, J = 3.8 Hz, 1H−OH), 0.99 (s, 3H), 0.14 (s, 9H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 84.3, 82.6, 80.8, 80.7, 68.2, 41.7, 25.4, −1.1, −1.3; HR-MS (ESI) calcd for $C_{14}H_{28}NaO_5Si$ $(M + Na)^+$ 355.1367, found 355.1375.

(2*S*,3*R*)-2-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-Methyl-3-silanyl-oxiranylmethyl)-3-silanyl-oxiranylmethyl]-tetrahydro-pyran-3-ol (41). To a solution of the diene **57** (preparation below) (0.1 g, 0.4 mmol) in CH_3CN/DMM (12.0 mL, 1:2 v/v) were added a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_20$ in 4.0 × 10^{-4} M Na_2-(EDTA) (8.0 mL), n-Bu_4NHSO_4 (30 mg, 80 μmol), and chiral ketone **19** (0.2 g, 0.8 mmol). To this rapidly stirring solution were added, simultaneously over 20 min *via* syringe pump, a solution of Oxone (0.8 g, 1.3 mmol) in 4.0 × 10^{-4} M Na_2-(EDTA) (5.3 mL) and a 0.89 M solution of K_2CO_3 (5.3 mL). After the Oxone and K_2CO_3 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 $MgSO_4$, 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): R_f = 0.53 (50% EtOAc in hexane); $[\alpha]^{25}_D$ = −2.62 (c = 26.7, $CHCl_3$); IR (NaCl) 3444, 2955, 2854, 2361, 1750, 1440, 1412, 1373, 1251, 1096, 1048, 840, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.93−3.88 (m, 1H), 3.60−3.54 (m, 1H), 3.34 (td, J = 11.3, 4.0 Hz, 1H), 3.22 (ddd, J = 9.0, 5.6, 3.2 Hz, 1H), 3.16 (dd, J = 8.7, 3.1 Hz, 1H), 2.74 (dd, J = 7.5, 4.3 Hz, 1H), 2.33 (br s, 1H−OH), 2.16 (dt, J = 14.8, 3.2 Hz, 1H), 2.11−2.07 (m, 1H), 2.01 (dd, J = 14.6, 4.1 Hz, 1H), 1.76 (ddd, J = 14.8, 8.9, 6.0 Hz, 1H), 1.73−1.63 (m, 2H), 1.56 (dd, J = 14.8, 7.5 Hz, 1H), 1.48−1.37 (m, 1H), 1.19 (s, 3H), 0.18 (s, 9H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.7, 70.3, 68.6, 62.7, 61.1, 56.5, 55.6, 38.4, 34.0, 33.0, 26.5, 23.3, −0.5, −1.1; HR-MS (ESI) calcd for $C_{18}H_{36}NaO_4Si_2$ $(M + Na)^+$ 395.2044, found 395.2040.

Spiroketal (42). To a solution of bisepoxide **41** (10 mg, 27 μmol) in CH_2Cl_2 (0.3 mL) at −78 °C was added $BF_3 \cdot Et_2O$ (5 μL, 40 μmol), and the mixture was stirred for 2 min. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*.

To a solution of the crude mixture in CH_2Cl_2 (0.5 mL) were added Et_3N (6 μL, 40 μmol), Ac_2O (3 μL, 30 μmol), and DMAP (1 mg, 8 μmol). The mixture was stirred overnight, then quenched with saturated NH_4Cl, and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3 × 2 mL), dried over $MgSO_4$, 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, $CDCl_3$) 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 $C_{17}H_{30}NaO_5Si$ $(M + Na)^+$ 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 was stirred for 20 min. The reaction was diluted with water and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford epoxide **43** (0.6 g, 91%): R_f = 0.37 (50% EtOAc in hexane); IR (thin film, NaCl) 3419, 1957, 1446, 1251, 1062, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 66.0, 62.3, 55.8, 30.3, 27.4, 22.9, −1.6; HR-MS (ESI) calcd for $C_9H_{20}O_2Si$ $(M + Na)^+$ 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 CH_2Cl_2

(15 mL) at 0 °C was added *m*-CPBA (0.8 g, 5.1 mmol). The resulting solution was warmed to room temperature and was stirred for 3.5 h. The reaction was quenched with a solution of 5% NaOH and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford epoxide **66** (0.8 g, 74%): R_f = 0.39 (20% EtOAc in hexane); IR (thin film, NaCl) 2958, 1742, 1448, 1368, 1251, 1039, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.11 (m, 2H), 2.70 (dd, J = 7.6, 4.7 Hz, 1H), 2.04 (s, 3H), 1.87−1.66 (overlapping m, 3H), 1.54−1.45 (m, 1H), 1.21 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 65.8, 64.7, 55.6, 28.0, 27.0, 23.4, 21.7, −1.2; HR-MS (ESI) calcd for $C_{11}H_{22}NaO_3Si$ $(M^+ + Na)^+$ 253.1230, found 253.1223.

(*Z*)-Acetic Acid 5-Trimethylsilanyl-hex-4-enyl Ester (67). To a solution of alcohol **68** (2.8 g, 14 mmol) in CH_2Cl_2 (130 mL) at 0 °C were added Et_3N (1.8 g, 18 mmol), Ac_2O (1.8 g, 18 mmol), and DMAP (0.2 g, 1.4 mmol). The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated NH_4Cl and concentrated *in vacuo*. The remaining contents were extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford acetate **67** (2.8 g, 94%): R_f = 0.65 (20% EtOAc in hexane); IR (thin film, NaCl) 2954, 1744, 1620, 1441, 1366, 1248, 1042, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (tq, J = 12.5, 5.4, 2.7 Hz, 1H), 4.96 (t, J = 10.9 Hz, 2H), 2.19−2.11 (m, 2H), 2.04 (s, 3H), 1.74 (s, 3H), 1.72−1.63 (m, 2H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 141.0, 136.1, 64.3, 29.4, 28.6, 25.1, 21.4, 0.2; HR-MR (ESI) calcd for $C_{11}H_{22}NaO_2Si$ $(M + Na)^+$ 237.1281, found 237.1271.

(*Z*)-5-Trimethylsilanyl-hex-4-en-1-ol (68). To a slurry of CuCN (3.2 g, 35 mmol) in Et_2O (45 mL) at 0 °C was added a 1.4 M solution of MeLi in Et_2O (50 mL) and the mixture was stirred for 15 min. A solution of (*E*)-5-iodo-5-(trimethylsilyl)-pent-4-en-1-ol (5.1 g, 18 mmol) in Et_2O (14 mL) was slowly added. The solution was stirred for 20 h at 0 °C, then carefully quenched with saturated NH_4Cl, and extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (20% EtOAc in hexane) to afford olefin **68** (3.1 g, 99%): R_f = 0.31 (20% EtOAc in hexane); IR (thin film, NaCl) 3332, 2951, 1619, 1442, 1248, 1054, 838, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.97 (dt, J = 7.6, 1.2 Hz, 1H), 3.65 (t, J = 6.7 Hz, 2H), 2.16 (q, J = 14.9, 7.6 Hz, 2H), 1.75 (d, J = 1.2 Hz, 3H), 1.63 (m, 2H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 135.6, 62.9, 33.3, 28.5, 24.9, 0.1; HR-MS (ESI) calcd for $C_9H_{20}NaSiO$ $(M + Na)^+$ 195.1176, found 195.1188.

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

2-Methyl-2-trimethylsilanyl-tetrahydro-pyran-3-ol (44). R_f = 0.33 (20% EtOAc in hexane); IR (thin film, NaCl) 3444, 2952, 2866, 1246, 1076, 1033, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.74 (td, J = 11.6, 3.1 Hz, 1H), 3.59−3.49 (m, 2H), 2.10 (d, J = 9 Hz, 1H), 2.03−1.96 (m, 1H), 1.92−1.83 (m, 1H), 1.68−1.62 (m, 1H), 1.47−1.41 (m, 1H), 1.24 (s, 3H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.9, 71.8, 60.1, 25.9, 21.5, 18.7, −2.2; HR-MS (ESI) calcd for $C_9H_{20}NaO_2Si$ $(M + Na)^+$ 211.1125, found 211.1136.

1-(Tetrahydro-furan-2-yl)-1-trimethylsilanyl Ethanol (45). R_f = 0.45 (20% EtOAc in hexane); IR (NaCl) 3469, 2957, 2863, 1461, 1290, 1247, 1060, 839, 752, 623 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.85 (m, 2H), 3.74 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 1.90−1.70 (m, 4H), 1.09 (s, 3H), 0.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.3, 68.9, 67.6, 26.7, 25.2, 20.1, −2.6; HR-MS (ESI) calcd for $C_9H_{20}NaO_2Si$ $(M + Na)^+$ 211.1125, found 211.1120.

3-(3-Methyl-oxiranyl)-propan-1-ol (46). Synthesized according to a reported procedure.[36]

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

1-(Tetrahydro-furan-2-yl)-ethanol (47). Spectral data were identical to those reported.[4,37]

2-Methyl-tetrahydro-pyran-3-ol (48). Spectral data were identical to those reported.[4,38]

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

2-(3-Hydroxy-propyl)-3-methyl-cyclopent-2-enone (50). R_f = 0.16 (80% EtOAc in hexane); IR (thin film, NaCl) 3421, 2920, 1694, 1639, 1441, 1386, 1176, 1061 cm^{-1}; ^1H NMR (500 MHz) δ 3.51 (t, J = 6.1 Hz, 2H), 2.56−2.53 (m, 2H), 2.44−2.41 (m, 2H), 2.33 (t, J = 7.0 Hz, 2H), 2.09 (s, 3H), 1.66−1.60 (m, 2H); ^{13}C NMR (125 MHz) δ 196.3, 172.9, 140.7, 61.5, 34.9, 32.5, 31.9, 18.9, 17.9; HR-MS (ESI) calcd for $C_9H_{14}NaO_2$ $(M + Na)^+$ 177.0886, found 177.0885.

(2*R*,3*R*,4a*S*,8a*R*)-2-Methyl-2-trimethylsilanyl-octahydro-pyrano[3,2-*b*]pyran-3-ol (51). R_f = 0.48 (50%, EtOAc in hexane); $[\alpha]^{25}_D$ = +20.9 (c = 4.3, in $CHCl_3$); IR (thin film, NaCl) 3444, 2953, 2865, 1453, 1347, 1248, 1100, 1069, 1039, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.93−3.89 (m, 1H), 3.58 (dd, J = 11.6, 5.2 Hz, 1H), 3.41−3.35 (m, 1H), 3.12 (ddd, J = 13.1, 8.9, 4.3 Hz, 1H), 2.98 (ddd, J = 13.4, 9.2, 4.6 Hz, 1H), 2.19 (app dt, J = 11.6, 4.9 Hz, 1H), 2.03−1.97 (m, 1H), 1.80−1.69 (m, 3H), 1.40−1.31 (m, 1H), 1.28 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 77.6, 77.0, 75.5, 74.3, 68.0, 37.3, 29.9, 25.9, 25.2, 0.3; HR-MS (ESI) calcd for $C_{12}H_{24}NaO_3Si$ $(M + Na)^+$ 267.1387, found 267.1385.

General Procedure for Base-Promoted Cyclization of Epoxides 24, 28, 41, 52, and 59 (Schemes 16, 17, 18, and 20). Cs_2CO_3 and CsF were weighed into a flame-dried Schlenk tube in a glovebox under Ar. To the tube was added a solution of the epoxide in MeOH. The tube was sealed, and the resulting slurry was heated to 65 °C for 3−5 days. The MeOH was removed *in vacuo*, and the reaction mixture partitioned between saturated NH_4Cl (10 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (EtOAc/hexane) to give the pure product.

(36) Hansen, K. B. Ph.D. Thesis, Harvard University, Cambridge, MA, 1998.

(37) Taillez, B.; Bertrand, M. P.; Surzur, J.-M. *J. Chem. Soc., Perkin Trans. 2* **1983**, 547–554.

(38) Bartner, P.; Boxler, D. L.; Brambilla, R.; Mallams, A. K.; Morton, J. B.; Reichert, P.; Sancilio, F. D.; Surprenant, H.; Tomalesky, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1600–1624.

(2*S*,3*R*,4a*S*,8a*R*)-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 Cs_2CO_3 (103 mg, 0.32 mmol) and CsF (48 mg, 0.32 mmol) in MeOH (165 μL) for 4 days. After standard workup, purification by column chromatography (50−75% EtOAc in hexane) afforded the diad **53** (1.2 mg, 55%): R_f = 0.34 (60% EtOAc in hexane); $[\alpha]^{25}_D$ = −11.2 (*c* = 0.26 in $CHCl_3$); IR (thin film, NaCl) 3413, 2926, 2852, 1114, 1096, 1051, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.94−3.87 (m, 1H), 3.43−3.32 (m, 2H), 3.23 (ddd, *J* = 9.0, 6.1, 6.0 Hz, 1H), 3.06−2.96 (m, 2H), 2.34 (dt, *J* = 11.6, 4.3 Hz, 1H), 2.10−2.02 (m, 1H), 1.77−1.68 (m, 3H), 1.52−1.36 (m, 1H), 1.30 (d, *J* = 6.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.5, 77.8, 77.1, 71.8, 68.0, 39.2, 29.5, 25.7, 18.1; HR-MS (ESI) submitted.

(2*S*,3*R*,4a*S*,8a*R*)-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 Cs_2CO_3 (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%).

(2*S*,3*R*,4a*S*,8a*S*,9a*R*,10a*R*)-2-Methyl-decahydro-1,8,10-trioxaanthracen-3-ol (54). Following the general procedure, bisepoxide **24** (8 mg, 18 μmol) was heated at 65 °C with Cs_2CO_3 (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.[14a]

2a*S*,3a*R*,4a*S*,8a*S*,9a*R*,10a*R*)-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 Cs_2CO_3 (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, which was taken up in CH_2Cl_2 (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 NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_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 **60** (4.3 mg, 35% over 2 steps): R_f = 0.60 (50% EtOAc in hexane); $[\alpha]^{25}_D$ = −4.3 (*c* = 0.46, $CHCl_3$); IR (thin film, NaCl) 2960, 2866, 2361, 1734, 1653, 1559, 1384, 1259, 1093, 1022, 841, 800 cm-1; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{14}H_{22}NaO_5$ $(M + Na)^+$ 293.1365, found 293.1362.

(2*R*,3*S*,4a*R*,5a*S*,6a*R*,10a*S*,11a*R*,12a*S*)-2-Methyl-tetradecahydro-1,5,7,11-tetraoxa-naphthacen-3-yl Acetate (55). Following the general procedure, triepoxide **28** (25 mg, 43 μmol) was heated at 65 °C with Cs_2CO_3 (235 mg, 0.72 mmol) and CsF (109 mg, 0.72 mmol) in MeOH (460 μL) for 5 days. After standard workup, partial purification by column chromatography (50−75% EtOAc in hexane) afforded the crude tetrad, which was taken up in CH_2Cl_2 (800 μL). DMAP (12 mg, 0.1 μmol), pyridine (15 μL, 0.1 μmol), and acetic anhydride (10 μL, 0.1 μmol) were added, and the mixture was stirred at room temperature for 14 h. The reaction was quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (50% EtOAc in hexane) to afford the acetylated tetrad **57** (2.1 mg, 15%); R_f = 0.55 (EtOAc); $[\alpha]^{25}_D$ = −7.6 (*c* = 0.13 in $CHCl_3$); IR (thin film, NaCl) 2927, 2861, 1384, 1250, 1097, 1042 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 4.52 (ddd, *J* = 11.4, 9.6, 4.8 Hz, 1H), 3.91−3.85 (m, 1H), 3.47−3.32 (m, 2H), 3.18−3.08 (m, 4H), 3.08−2.97 (m, 2H), 2.40 (dt, *J* = 11.1, 4.2 Hz, 1H), 2.32−2.22 (m, 2H), 2.06−2.00 (m, 1H), 2.05 (s, 3H), 1.76−167 (m, 2H), 1.52−1.37 (m, 4H), 1.17 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 170.0, 78.9, 77.7, 77.6, 77.4, 77.1, 76.8, 76.7, 76.2, 72.6, 68.4, 36.1, 35.7, 35.5, 29.8, 26.1, 21.4, 18.1.

(2*R*,3*S*,4a*R*,5a*S*,6a*R*,10a*S*,11a*R*,12a*S*)-2-Methyl-tetradecahydro-1,5,7,11-tetraoxa-naphthacen-3-yl Acetate (55). Following the general procedure, triepoxide **28** (18 mg, 35.9 μmol) was heated at 65 °C with Cs_2CO_3 (300 mg, 0.92 mmol) and CsF (140 mg, 0.92 mmol) in MeOH (480 μL) for 5 days. After standard workup, partial purification by column chromatography (50−75% EtOAc in hexane) afforded the crude tetrad, which was taken up in CH_2Cl_2 (800 μL). DMAP (14 mg, 0.1 μmol), pyridine (16 μL, 0.1 mmol), and acetic anhydride (10 μL, 0.1 μmol) were added, and the mixture was stirred at room temperature for 14 h. The reaction was quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 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%).

(2*S*,3*R*)-2-((*Z*)-3-Trimethylsilyanyl-but-2-enyl)-tetrahydropyran-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 and 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); $[\alpha]^{25}_D$ = −23.9 (*c* = 9.2, in $CHCl_3$); IR (thin film, NaCl) 3422, 2945, 2853, 1618, 1442, 1248, 1097, 1035, 838, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.13 (app tq, *J* = 6.3, 1.7 Hz, 1H), 3.91−3.87 (m, 1H), 3.37 (ddd, *J* = 13.6, 8.8, 4.7 Hz, 1H), 3.31 (dt, *J* = 11.1, 3.5 Hz, 1H) 3.06 (ddd, *J* = 11.7, 7.2, 4.6 Hz, 1H), 2.66−1.60 (m, 1H), 2.34−2.27 (m, 1H), 2.11−2.05 (m, 2H), 1.78 (d, *J* = 1.5 Hz, 3H), 1.70−1.63 (m, 1H), 1.43−1.34 (m, 1H), 0.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.0, 83.0, 78.0, 71.6, 68.4, 35.8, 33.4, 26.2, 25.6, 0.5; HR-MS (ESI) calcd for $C_{12}H_{24}NaO_2Si$ $(M + Na)^+$ 251.1438, found 251.1433.

(2*S*,3*R*)-2-((2*R*,3*S*)-3-Methyl-3-trimethylsilanyl-oxiranylmethyl)-tetrahydro-pyran-3-ol (52). To olefin **56** (96 mg, 0.42 mmol) were added CH_3CN/DMM (12.8 mL, 1:2 v/v), a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4.0 × 10^{-4} M Na_2-(EDTA) (8 mL), *n*-Bu_4NHSO_4 (26 mg, 0.8 mmol), and chiral ketone **19** (0.192 g, 0.74 mmol). To this solution were added, simultaneously over 20 min *via* syringe pump, a solution of Oxone (930 g, 1.51 mmol) in 4.0 × 10^{-4} M Na_2-(EDTA) (6.4 mL) and a 0.89 M solution of K_2CO_3 (6.4 mL). After the Oxone and K_2CO_3 solutions had been added, the resulting mixture was stirred for 20 min, then diluted with water (10 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (10−20% EtOAc in hexane) to yield epoxide **52** (87 mg, 85%, dr >95:5): R_f = 0.46 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = +8.6 (*c* = 4.7, in $CHCl_3$); IR (thin film, NaCl) 3438, 2956, 2853, 1440, 1251, 1097, 1039, 841, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.92 (m, 1H), 3.64 (ddd, *J* = 15.4, 9.2, 4.4 Hz, 1H), 3.36 (app dt, *J* = 11.3, 3.7 Hz, 1H), 3.22 (ddd,

J = 8.9, 5.3, 2.9 Hz, 1H), 3.01 (dd, J = 9.5, 2.4 Hz, 1H), 2.37 (d, J = 4.7 Hz, 1H), 2.16−2.09 (m, 2H), 1.77−1.66 (m, 2H), 1.47−1.38 (m, 1H), 1.24 (s, 3H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{12}H_{24}NaO_3Si$ $(M + Na)^+$ 267.1387, found 267.1385.

(2*R*,3*R*)-2-((2*Z*,5*Z*)-3,6-bistrimethylsilanylhepta-2,5-dienyl)-tetrahydropyran-3-ol (57). To a solution of diene **31** (86 mg, 0.2 mmol) in THF (2.1 mL) was added a 1 M solution of TBAF in THF (2.1 mL). The reaction mixture was stirred at 40 °C for 4 h. The reaction was quenched with water and extracted with Et_2O (4 × 20 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 diene **57** (60 mg, 85%): R_f = 0.30 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = −6.6 (c = 9.1, in $CHCl_3$); IR (thin film, NaCl) 3405, 2951, 2852, 2360, 1616, 1442, 1248, 1097, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (ddt, J = 8.0, 6.2, 1.5 Hz, 1H), 5.90 (tq, J = 7.0, 1.6 Hz, 1H), 3.90 (ddt, J = 11.4, 3.9, 1.7 Hz, 1H), 3.29−3.43 (m, 2H), 3.09 (ddd, J = 8.8, 7.0, 4.9 Hz, 1H), 2.87−2.89 (m, 2H), 2.67 (ddd, J = 14.6, 8.2, 4.9 Hz, 1H), 2.32−2.39 (m, 1H), 2.06−2.13 (m, 1H), 1.78 (dd, J = 2.8, 1.4 Hz, 3H), 1.65−1.72 (m, 2H), 1.36−1.46 (m, 1H), 0.18 (s, 9H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{18}H_{36}NaO_2Si_2$ $(M + Na)^+$ 363.2146, found 363.2151.

(2*S*,3*R*)-2-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-Methyl-3-silanyl-oxiranylmethyl)-3-silanyl-oxiranylmethyl]-tetrahydro-pyran-3-ol (41). To a solution of the diene **57** (0.1 g, 0.4 mmol) in CH_3CN/DMM (12.0 mL, 1:2 v/v) were added a 0.05 M solution of $Na_2B_4O_7\cdot 10H_20$ in 4.0 × 10^{-4} M Na_2-(EDTA) (8.0 mL), n-Bu_4NHSO_4 (30 mg, 80 μmol), and chiral ketone **19** (0.2 g, 0.8 mmol). To this rapidly stirring solution were added, simultaneously over 20 min *via* syringe pump, a solution of Oxone (0.8 g, 1.3 mmol) in 4.0 × 10^{-4} M Na_2-(EDTA) (5.3 mL) and a 0.89 M solution of K_2CO_3 (5.3 mL). After the Oxone and K_2CO_3 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 $MgSO_4$, 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): R_f = 0.53 (50% EtOAc in hexane); $[\alpha]^{25}_D$ = −2.62 (c = 26.7, $CHCl_3$); IR (thin film, NaCl) 3444, 2955, 2854, 2361, 1750, 1440, 1412, 1373, 1251, 1096, 1048, 840, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93−3.88 (m, 1H), 3.60−3.54 (m, 1H), 3.34 (td, J = 11.3, 4.0 Hz, 1H), 3.22 (ddd, J = 9.0, 5.6, 3.2 Hz, 1H), 3.16 (dd, J = 8.7, 3.1 Hz, 1H), 2.74 (dd, J = 7.5, 4.3 Hz, 1H), 2.33 (br s, 1H−OH), 2.16 (dt, J = 14.8, 3.2 Hz, 1H), 2.11−2.07 (m, 1H), 2.01 (dd, J = 14.6, 4.1 Hz, 1H), 1.76 (ddd, J = 14.8, 8.9, 6.0 Hz, 1H), 1.73−1.63 (m, 2H), 1.56 (dd, J = 14.8, 7.5 Hz, 1H), 1.48−1.37 (m, 1H), 1.19 (s, 3H), 0.18 (s, 9H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.7, 70.3, 68.6, 62.7, 61.1, 56.5, 55.6, 38.4, 34.0, 33.0, 26.5, 23.3, −0.5, −1.1; HR-MS (ESI) calcd for $C_{18}H_{36}NaO_4Si_2$ $(M + Na)^+$ 395.2044, found 395.2040.

(2*S*,3*R*)-2-((2*Z*,5*Z*,8*Z*)-3,6,9-tris-trimethylsilanyl-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 Et_2O (4 × 20 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 (10% EtOAc in hexane) to afford monodesilylated product **58** (83 mg, 56%): R_f = 0.30 (20% EtOAc in hexane); $[\alpha]^{25}_D$ = −12.7 (c = 2.36 in $CHCl_3$); IR (thin film, NaCl) 3405 (br), 2952, 2896, 2852, 1614, 1441, 1406, 1247, 1098, 836, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 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) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 141.7, 140.7, 139.0, 138.8, 135.2, 82.5, 71.0, 67.8, 39.9, 39.1, 35.4, 32.9, 25.7, 24.8, 0.4, 0.3, 0.1; HRMS calculated for $C_{24}H_{48}NaO_2Si_3$ 475.2854, found 475.2861.

(2*S*,3*R*)-2-[(2*R*,3*S*)-3-((2*R*,3*S*)-3-((2*R*,3*S*)-3-Methyl-3-trimethylsilanyl-oxiranylmethyl)-3-trimethylsilanyl-oxiranylmethyl)-3-trimethylsilanyl-oxiranylmethyl]-tetrahydro-pyran-3-ol (59). To a solution of the triene **58** (77 mg, 0.17 mmol) were added CH_3CN/DMM (5.3 mL, 1:2 v/v), a 0.05 M solution of $Na_2B_4O_7\cdot 10H_20$ in 4.0 × 10^{-4} M Na_2-(EDTA) (3.5 mL), n-$BuNHSO_4$ (17.5 mg, 52 μmol), and chiral ketone **19** (132 mg, 0.5 mmol). To this rapidly stirring solution were added, simultaneously over 20 min *via* syringe pump, a solution of Oxone (626 mg, 1.02 mmol) in 4.0 × 10^{-4} M Na_2-(EDTA) (4.5 mL) and a 0.89 M solution of K_2CO_3 (4.5 mL). After the Oxone and K_2CO_3 solutions had been added, the resulting mixture was diluted with water and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers where washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The epoxide product could not be separated from the ketone catalyst and so was dissolved in CH_2Cl_2 (1.1 mL). To this were added $NaHCO_3$ (47 mg, 0.56 μmol) and *m*-CPBA (20 mg, 0.11 mmol), and the reaction was stirred for 30 min. The reaction was quenched with 1 M NaOH and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (10−20% EtOAc in hexane) to afford triepoxide **59** (43 mg, 50%, dr 90:10): R_f = 0.52 (50% EtOAc in hexane); $[\alpha]^{25}_D$ = +2.72 (c = 3.67 in $CHCl_3$); IR (thin film, NaCl) 3455, 2956, 2852, 1440, 1412, 1251, 1096, 840, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 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) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.3, 70.1, 68.1, 62.2, 60.4, 60.1, 56.0, 55.8, 55.3, 38.6, 37.6, 38.8, 32.7, 26.0, 22.8, −0.9, −1.1, −1.6 ; HR-MS (ESI) calcd for $C_{24}H_{48}NaO_5Si_3$ $(M + Na)^+$ 523.2702, found 523.2696.

(3-Benzyloxy-2-methyl-tetrahydro-pyran-2-yl)-trimethyl-silane (61). To a solution of pyran **44** (0.1 g, 0.5 mmol) in THF (1.5 mL) at 0 °C were 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 Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (5−10% EtOAc in hexane) to yield **61** (0.1 g, 68%): R_f = 0.51 (10% EtOAc in hexane); IR (thin film, NaCl) 2952, 2854, 1454, 1244, 1092, 1077, 1026, 837, 744, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 4.63 (d, J = 11.6 Hz, 1H), 4.38 (d, J = 11.6 Hz, 1H), 3.74 (ddd, J = 11.3, 7.6, 3.4 Hz, 1H), 3.56 (ddd, J = 10.4, 6.4, 3.7 Hz, 1H), 3.25 (dd, J = 6.4, 3.7 Hz, 1H), 1.99−1.79 (m, 3H), 1.49−1.42 (m, 1H), 1.25 (s, 3H), 0.08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 128.9, 128.4, 128.0, 81.5, 73.3, 71.3, 62.4, 23.5, 23.4, 21.7, −0.8; HR-MS (ESI) calcd for $C_{16}H_{26}NaO_2Si$ $(M + Na)^+$ 301.1594, found 301.1601.

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Supporting Information Available: Experimental procedures and data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.