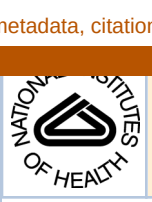

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A Dioxane Template for Highly Selective Epoxy Alcohol Cyclizations

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Abstract

Ladder polyether natural products are a class of natural products denoted by their high functional group density and large number of well-defined stereocenters. They comprise the toxic component of harmful algal blooms (HABs), having significant negative economic and environmental ramifications. However, their mode of action, namely blocking various cellular ion channels, also denotes their promise as potential anticancer agents. Understanding their potential mode of biosynthesis will not only help with developing ways to limit the damage of HABs, but would also facilitate the synthesis of a range of analogues with interesting biological activity. 1,3-Dioxan-5-ol substrates display remarkable 'enhanced template effects' in water-promoted epoxide cyclization processes en route to the synthesis of these ladder polyether natural products. In many cases they provide near complete *endo* to *exo* selectivity in the cyclization of epoxy alcohols, thereby strongly favouring the formation of tetrahydropyran (THP) over tetrahydrofuran (THF) rings. The effects of various Brønsted and Lewis acidic and basic conditions are explored to demonstrate the superior selectivity of the template over the previously reported THP-based epoxy alcohols. In addition, the consideration of other synthetic routes are also considered with the goal of gaining rapid access to a plethora of potential starting materials applicable towards the synthesis of ladder polyethers. Finally, cascade sequences with polyepoxides are investigated, further demonstrating the versatility of this new reaction template.

Keywords

cyclization; template; epoxide; polyether; selectivity

Introduction

Developing new means to effect 6-*endo* cyclization processes remains a relevant synthetic challenge due to an inherent preference of the Baldwin-rules predicted 5-*exo* adduct. Such transformations are particularly pertinent in the construction of marine ladder polyethers. These products continue to garner much interest due to their innate structural complexity, their potential as anti-cancer and anti-bacterial agents (Figure 1),[1] as well as their undesirable environmental and economic consequences, such as harmful algal blooms.[2] It has been proposed by Nakanishi,[2b,3] Shimizu,[4] and Nicolaou[5] that Nature may construct these elaborate structures *via* a ring-opening/ring-closing sequence of a polyepoxide precursor. Laboratory emulation of these proposed cascades has been hindered by the fact that the 5-*exo* product (tetrahydrofuran, THF) is generally favored over the desired 6-*endo* product (tetrahydropyran, THP), as demonstrated by Coxon in the 1970s (Scheme 1 **A**).[6,7,8]

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In prior investigations we observed highly *endo*-selective epoxide-opening cyclizations templated by a pre-formed tetrahydropyran (THP) ring and promoted by neutral water (Scheme 1 **B**).[9,10] The presence of the oxygen in the heterocyclic ring was vital for the desired selectivity. It has also been suggested that enzymes may catalyze the formation of an initial THP ring, and that this THP then "templates" the cascade favoring an all *endo* ring closure sequence.[9,11] Given the lack of selectivity when no endocyclic oxygen is present in the template (Scheme 1 **C**), we have undertaken a systematic study of the structure-selectivity relationships of these and related cascade templates. Toward this end, we first explored a 1,3-dioxane ring in the context of the synthesis of the HIJK rings of gymnocin A.[12] However, the sensitivity to hydrolysis of this benzylidene acetal under Lewis acidic and aqueous conditions precluded a comparison with our previous system. We herein report methylene acetal (**1**) is robust towards epoxy alcohol cyclization processes. Uniquely, this new template demonstrates a striking selectivity profile (Scheme 1 **D**). In contrast to the original THP template, where high (>10:1) selectivity was observed in a narrow pH range, the methylene acetal-based 1,3-dioxane affords the desired *endo* cyclization product for electronically unbiased, *trans*-disubstituted epoxides independent of promoter used (acid, base, and water)—well over 100:1 under certain conditions. We believe that these observations have important implications on the mechanism of *endo*-selective epoxide-opening cyclizations, and the stability of this template makes it well suited for use in target-directed synthesis.

Results and Discussion

Employing a chiron-based approach[13] the synthesis of **1** began with a Wittig olefination of 2-deoxy-D-ribose **2** followed by selective 1,3-protection to form PMP acetal **3** (Scheme 2).[14] The free secondary alcohol was masked as its TBDPS ether and the PMP group removed to afford diol **4**. Installation of the methylene acetal (**5**) and ozonolysis of the corresponding enoate revealed aldehyde **6**. Subjection of the aldehyde to a Takai olefination with 1,1-diiodoethane,[15] followed by Shi epoxidation (**7**) and removal of the TBDPS group in presence of TBAF gave the desired epoxyalcohol **1**.

We compared the selectivity of cyclization in H_2O relative to the previously disclosed THP template. A 14.1:1 ratio favoring the formation of the *endo* product when cyclizations were performed in deionized water (DI H_2O) under ambient conditions (Table 1, entry 1). While this is an improvement on the 10:1 selectivity previously observed with the THP ring,[9] the rate of reaction was significantly decreased, requiring over a month to reach completion. Presumably this is due to the additional inductively withdrawing oxygen atom decreasing the nucleophilicity of the hydroxyl group. However, an increased reaction temperature not only accelerated the reaction (entries 2–6), but also afforded a modest improvement in site selectivity for the *endo* product (20:1) at 100 °C (entry 5) and 35:1 at 125 °C (entry 6). This phenomenon is unique to this template as such effects were not observed with the previous generation THP systems. Both cyclization products from the dioxane are stable to elevated temperatures, suggesting that it is unlikely that degradation of the minor *exo* product accounts for the increase in selectivity under these conditions. Other ramifications of the increased reaction temperature include the lowering of the pH of the (unbuffered) water,[16] and an increase in ionic strength of the medium. Either one of which could modulate selectivity by facilitating proton transfer during cyclization, in addition to stabilizing charged transition state intermediates. This combination may be more relevant with this system. Lastly, reactions performed in polypropylene tubes at 70 °C (not shown) furnished 24.1:1 preference of **8** demonstrating that SiO_2 in the glass of the reaction vessels was not responsible in promoting the high *endo* selectivity.

Accordingly we next explored the effect of pH on the selectivity of cyclization (Figure 2).[9] In buffered solutions (0.1 M KP*i*) near neutral pH, the selectivity increased by nearly an order of magnitude relative to corresponding results with the THP template and by two orders of magnitude relative to the cyclohexanol-based template (Scheme 1 **C**, Figure 2). A maximum 126:1 ratio of **8:9** was noted at pH 6.8, reprising a trend of optimum site selectivity near neutral pH. Also remarkably even low and high pH (3.0 and 12.2) provided an *endo*/*exo* selectivity of 7.0:1 and 4.3:1 respectively. This preference for *endo* cyclization processes under such conditions is unprecedented; several other templates we have examined were deemed nonselective (~1:1).[9]

In order to gain insight to this unique and near-perfect *endo* regioselectivity, we prepared trisubstituted epoxy alcohols from aldehyde **6** (Scheme 3). Epoxy alcohol **15a** was prepared from olefination of **6** using a stabilized Wittig reagent, followed by complete reduction of the ester (compounds **11–13**). It should be noted that Wittig olefination with isopropyltriphenylphosphonium iodide to furnish **13** directly from **6** furnished the product in poor yield and was not amenable to scale up. Shi epoxidation and removal of the TBDPS group furnished **15a**. In parallel, methyl ketone **16** was subjected to Wittig conditions to provide alkene **17** in >9:1 *E:Z* ratio. Again, this was followed by epoxidation (**18**) and protecting group removal to reveal **15b**.

Alcohols **15a** and **15b** were subjected to various neutral, acidic, and basic conditions (Table 2). As noted above, alcohol **1** furnished a near 20:1 preference for the *endo* product in neutral water. Cyclization of **1** in the presence of Cs_2CO_3 and CSA afforded **8** and **9** in ratios of 4.6:1 (70% yield) and 4.2:1 (87% yield) respectively, while BF_3•OEt_2 yielded *only* ether **8** (82% yield). These three results are in stark contrast to the selectivity of the THP template as *water was not required* to obtain good to complete *endo* selectivity. Previously approximately a 1:1 ratio of the two cyclic ethers were observed, modestly favoring the *exo* adduct in cases employing Cs_2CO_3 and CSA.[10b] Likely due to enhanced stabilization of developing positive charge in the transition state, *gem*-dimethyl substituted **15a** favored the formation of the *endo* product **19a** in presence of DI H_2O (64% yield), CSA (94% yield), and BF_3•OEt_2 (88% yield); CSA offered significant improvement relative to the THP template (>20:1 vs 5.8:1 *endo:exo*).[17,10b] Though *exo* product **20a** was favored in presence of Cs_2CO_3, likely due to steric effects, the magnitude of selectivity was decreased, suggesting a directing counter effect of the dioxane ring. The THP variant of epoxy alcohol **15b** provided *endo* product in water and in presence of Cs_2CO_3;[10b] however, in the case of the dioxane template no such product was observed. Instead, recovered starting material was observed in both cases. Under acidic conditions **20b** was isolated in 80% yield both in presence of BF_3•OEt_2 and CSA. Terminal epoxides **23** and **26** were also prepared under a similar processes from aldehyde **6** and ketone **16** (Scheme 4). These alcohols gave exclusive formation of the corresponding 5-*exo* products under all conditions when hydrolysis or methanolysis of the epoxide was not observed.

Having confirmed the stability of methylene acetal group under the cyclization condition, in addition to the understanding of the selectivity criteria, we next investigated the feasibility of this template in a cascade process. Sulfone **32** was prepared in three steps from available 3-pentenoic acid and subjected to Julia/Barbier conditions with aldehyde **6** (Scheme 5). Shi epoxidation (**34**) proved sluggish as the rate of epoxidation of the alkene closest to the template proving to be slow. Gratifyingly, under prolonged reaction times exhaustive epoxidation was possible, and removal of the TBDPS group with TBAF furnished diepoxide **35**.

Subjecting diepoxy alchohol **35** to cyclization at 70 °C in deionized water led to the isolation of the 6,6,6 adduct **36** in 51% yield with no 6,6,5 adduct **37** isolated (Table 3, entry

1).[17] The balance of the material was the result of hydrolysis of the epoxides. This yield could be improved to 54% when using water buffered to pH 7.0 with less hydrolysis by products being observed (entry 2). This result confirms that the 1,3-dioxane-5-ol template initiates the first cyclization with near complete *endo* selectivity. Furthermore, in this case the second cyclization proved equally selective as predicted by our previous results with fused THP rings (Scheme 6).[10c] Curious to see if these trends persisted under other conditions, we subjected the epoxide to basic conditions and noted a 1.4:1 ratio of **32** to **33** (Table 3, entry 3). No 6,5,5 ring products were observed, indicating that the first cyclization remains under high *endo* controlled governed by the dioxane ring. Again, the poor *endo:exo* selectivity for the second ring closure may be predicted should this be determined by the THP ring (Table 2).[10b] A similar trend was noted when preformed in presence of CSA with a 2.5:1 ratio of **32:33** observed (Table 3, entry 4). In both cases a higher isolated yield of the products were observed due to increased rates of reaction mitigating destruction of the epoxide rings.

We propose that the origin of the selectivity is the consequence of several cooperative factors, with the two most important generally being the conformation of the template ring and the stabilization of developing positive charge in the transition state. It has been documented that the preferred conformation of 1,3-dioxane-5-ol orients the hydroxyl moiety axially; forming two hydrogen bonds with the endocyclic oxygen atoms (Scheme 7).[18] This diaxial conformation places the reactive sites too far apart to interact in a productive manner, explaining the enhanced stability of the epoxy alcohol starting material. We previously reasoned that the regioselectivity of the THP ring originated by way of a reactive twist conformation,[10a] which aligns the attacking hydroxyl group at the optimal 100° trajectory to the distal carbon of the epoxide.[19] A plausible explanation for the enhanced selectivity, therefore, is the tendency for 1,3-dioxane rings to even more readily adopt such a twist conformation.[20] As reported by Eliel over 40 years ago, 1,3-dioxanes often adopt more puckered conformations due to the presence of shortened endocyclic C–O bond lengths that in turn distort the ring bond angles.[18c,d] This was further corroborated by Rychnovski in 1993, who demonstrated through various means that substitution at the 4- or 6-positions orients the ring into the twist conformation to minimize steric interaction with C2 substituents that are augmented by the short C–O bond distances.[20a] These observations are absent with the THP system as the ring is only slightly distorted by the single endocyclic oxygen atom. Of note, particularly with unbiased alcohol **1**, is the increased selectivity under acidic conditions (Figure 2, Table 2, Scheme 4), possibly due to the development of positive charge at the distal site, resulting in a concerted conformational/electronic effect reinforcing reactivity at the *endo* position. This phenomenon is further highlighted by alcohol **15a** (Table 2), where in presence of CSA the selectivity was very high with the dioxane ring, yet only 6:1 with the THP template.[10b] The presence of a proximal methyl group (**15b** and **23**) serves to stabilize developing positive charge in the transition state, leading to cyclization at this position. Moreover, that **19b** is not observed (see Table 2) may be a consequence of the decreased nucleophilicity of the hydroxyl group resulting from the presence of an additional endocyclic oxygen atom and a sterically congested transition state.

Conclusion

In summary we have demonstrated the application of a powerful new 1,3-dioxane template that provides very high *endo* selectivity in epoxy alcohol cyclization reactions, selectivity that is opposite to that very commonly observed and predicted by the Baldwin rules for ring closure. It is now clearly evident that the number of oxygen atoms in the template ring plays a critical role in epoxide-opening regioselectivity. This high level of selectivity also extends to cascade processes under a variety of reaction conditions. Not only is this template highly selective, it offers the possibility of subsequent removal of the methylene acetal, revealing

two chemically different hydroxyl groups.[21] Thus we anticipate that this new scaffold will enable the synthesis of ladder polyether natural products. Such investigations of this motif are underway in our laboratories and will be reported in due course.

Experimental Section

General Considerations

All reactions were run under aerobic conditions (air) with flame-dried glassware using standard techniques for manipulating air-sensitive compounds unless otherwise stated. Anhydrous solvents were obtained by filtration through drying columns or by distillation over sodium and calcium hydride. Flash column chromatography was performed using 230–400 mesh silica with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm), aqueous potassium permanganate, vanillin, and/or *p*-anisaldehyde. Preparative High Performance Liquid Chromatography was performed using normal phase elution on a system equipped with simultaneous diode array UV detection. Data are reported as follows: (column type, eluent, flow rate: retention time (t_r)). Automated flash chromatography was performed using Biotage Isolera One Instruments. Nuclear magnetic resonance spectra were recorded either on 300, 400, 500, or 600 MHz Bruker or Varian spectrometers. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ = 7.27 ppm or benzene, δ = 7.15 m = multiplet and br = broad), coupling constant in Hz and integration. Chemical shifts for ^{13}C NMR spectra were recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (77.36 ppm), or C_6D_6 (128 ppm) as the internal standard. Optical rotations were measured on a Jasco Model 1010 polarimeter at 589 nm. High-resolution mass spectra (HRMS) were obtained on a Bruker Daltronics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. Infrared spectra were recorded using an Agilent Cary 630 FTIR. Gas chromatography (GC) data was collected on a Varian CP-3800 GC using an Agilent CHIRALDEX -TA column (30m x 0.25 mm).

(4*S*,5*R*)-4-(((2*R*,3*R*)-3-methyloxiran-2-yl)methyl)-1,3-dioxan-5-ol (1)—To a solution of silyl ether **7** (0.102 g, 0.248 mmol) in THF (0.400 μL) was added a 1M solution of TBAF in THF (0.497 μL, 0.497 mmol). The reaction solution was stirred at rt for 20 min, then applied directly to a column of SiO_2 (eluted with a gradient 30% to 100% EtOAc in hexanes) to yield **1** as a colorless oil (0.038 g, 89%). Chiraldex™ G-TA 30 m x 0.25 mm x 0.12 μm film thickness, 125 °C 10 min, 2 °C/min to 150 °C, 10 °C/min to 180 °C, hold 10 min, T_R = 20.09 min. R_f = 0.70 (100% EtOAc). $[\alpha]_D^{22}$ = +2.1 (*c* = 1.00, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6) δ 4.90 (d, *J* = 6.0 Hz, 1H), 4.25 (d, *J* = 6.0 Hz, 1H), 4.05 (dd, *J* = 10.6, 5.1 Hz, 1H), 3.61 (app td, *J* = 9.5, 5.2 Hz, 1H), 3.24 (ddd, *J* = 9.3, 5.6, 4.0 Hz, 1H), 3.15 (app t, *J* = 10.3 Hz, 1H), 2.82 (ddd, *J* = 6.5, 3.8, 2.3 Hz, 1H), 2.48 (qd, *J* = 5.2, 2.2 Hz, 1H), 2.43 (br s, 1H), 1.93 (app dt, *J* = 14.9, 3.9 Hz, 1H), 1.71 (ddd, *J* = 14.9, 6.7, 5.8 Hz, 1H), 0.98 (d, *J* = 5.2 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ 93.6, 80.2, 71.6, 65.9, 56.5, 54.3, 34.8, 17.8. FTIR (thin film, NaCl) 3423, 2964, 2923, 2853, 2774, 1653, 1457, 1438, 1381, 1257, 1225, 1175, 1150, 1073, 1028 cm^{-1}. HRMS (DART) Calcd for $C_8H_{14}O_4$ $[M+H]^+$: 175.0965, found 175.0973.

***E*)-ethyl 4-((2*R*,4*S*,5*R*)-5-hydroxy-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)but-2-enoate (3)—**To a slurry of 2-deoxyribose **2** (17.6 g, 131 mmol) in THF (300 mL) was added (carbethoxymethylene) triphenylphosphorane ($Ph_3P{=}CHCO_2Et$, 50 g, 143 mmol). Upon heating at 75 °C for 3 h the solution became a homogenous golden yellow. The

reaction was then cooled to rt and concentrated under reduced pressure to afford the crude enoate as a heavy, orange-brown oil, which was carried on into PMP acetal protection without further purification. The crude diol was dissolved in CH_2Cl_2 (250 mL), to which was added first *p*-anisaldehyde dimethyl acetal (50 mL, 299 mmol) and then (+/-)-camphorsulfonic acid (6.0 g, 25 mmol). Upon addition of CSA, the reaction solution immediately turned paler, becoming a light orange-brown. After stirring 16 h at rt, the reaction was quenched with sat. $NH_4Cl_{(aq.)}$ (~200 mL), extracted with CH_2Cl_2 (3 × 200 mL), dried with Na_2SO_4 and concentrated under reduced pressure. This was purified by column chromatography (gradient 20% to 30% to 50% EtOAc in hexanes) to afford PMP acetal **3** as a yellow oil (36.1 g, 86%) R_f = 0.46 (1:1 EtOAc, hexanes). $[\alpha]_D^{22}$ = −26.1 (*c* = 1.23, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.08 (dt, *J* = 15.7, 7.2 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.96 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.44 (s, 1H), 4.24 (dd, *J* = 10.2, 4.2 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.72−3.53 (m, 3H), 2.80 (dddd, *J* = 15.1, 6.9, 3.2, 1.6 Hz, 1H), 2.56 (app dtd, *J* = 15.1, 7.5, 1.4 Hz, 1H), 2.19 (d, *J* = 5.2 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 160.2, 144.8, 130.2, 127.6, 123.9, 113.8, 101.1, 80.5, 71.4, 65.5, 60.6, 55.5, 34.8, 14.4. FTIR (thin film) 3462, 2979, 2935, 1716, 1655, 1615, 1251, 1174, 1080, 1034 cm^{-1}. HRMS (ESI) Calcd for $C_{17}H_{22}O_6$ $[M+H]^+$: 323.1489, found 323.1482.

(5*S*,6*R*,*E*)-ethyl 6-((*tert*-butyldiphenylsilyl)oxy)-5,7-dihydroxyhept-2-enoate (4)—To a solution of alcohol **3** (17.6 g, 53 mmol) in DMF (25 mL) was added first imidazole (5.4 g, 80 mmol) and then TBDPSCl (16.3 mL, 17.5 g, 64 mmol). The resulting viscous solution was stirred at rt for 16 h, then quenched by addition of sat. $NH_4Cl_{(aq)}$ (~50 mL). The aqueous layer was separated and extracted with EtOAc (3x~150 mL) and the combined organic layers were washed with brine (~50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude silyl ether as a pale yellow oil (R_f = 0.52, 1:4 EtOAc, hexanes). This crude material was carried forward into acetal hydrolysis without further purification. To a solution of one half of this crude material in a 12:3:1 v:v:v mixture of MeOH:THF:H_2O (212 mL) was added *p*-toluenesulfonic acid monohydrate (1.0 g, 5.3 mmol). The solution was heated to 70 °C for 2 h. The solution was cooled in an ice bath, quenched with Et_3N (1.1 mL, 810 mg, 8.0 mmol), and concentrated under reduced pressure to a clear, golden yellow oil, which was purified by column chromatography (gradient 20% to 30% to 50% EtOAc in hexanes) to provide **4** as a heavy yellow oil (10.1 g, 86% over 2 steps). R_f = 0.67 (1:1 EtOAc, hexanes). $[\alpha]_D^{22}$ = +21.6 (*c* = 4.9, $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.66 (m, 4H), 7.49-7.44 (m, 2H), 7.44-7.38 (m, 4H), 6.88 (app dt, *J* = 15.6, 7.3 Hz, 1H), 5.82 (app dt, *J* = 15.7, 1.5 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.85 (app dq, *J* = 8.8, 4.4 Hz, 1H), 3.73 (ddd, *J* = 11.1, 6.4, 3.7 Hz, 1H), 3.68-3.59 (m, 2H), 2.58 (d, *J* = 4.5 Hz, 1H), 2.44 (dddd, *J* = 14.8, 7.1, 3.8, 1.5 Hz, 1H), 2.28 (dddd, *J* = 14.8, 8.9, 7.4, 1.4 Hz, 1H), 2.08 (app t, *J* = 6.0 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.10 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 145.2, 136.0, 135.9, 133.6, 133.0, 130.4, 130.3, 128.1, 128.1, 124.0, 75.7, 73.0, 63.9, 60.5, 36.1, 27.2, 19.6, 14.5. FTIR (thin film) 3448, 3072, 2932, 2858, 1718, 1654, 1473, 1428, 1271, 1166, 1112, 1045 cm^{-1}. HRMS (ESI) Calcd for $C_{25}H_{34}O_5Si$ $[M+Na]^+$: 465.2068, found 465.2049.

(*E*)-ethyl 4-((4*S*,5*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-1,3-dioxan-4-yl)but-2-enoate (5)—To a solution of diol **4** (5.5 g, 12.0 mmol) in CH_2Cl_2 (50 mL) was added first dimethoxymethane (1.6 mL, 18.0 mmol) and then BF_3•OEt_2 (2.2 mL, 18.0 mmol). The solution, which turned yellow upon addition of BF_3•OEt_2, was stirred 1.25 h. at rt, then quenched with sat. $NaHCO_{3(aq)}$ (~50 mL). The aqueous layer was separated, diluted with brine (~50 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with brine (~50 mL), dried over $MgSO_4$, filtered, and concentrated Under reduced pressure to afford crude **5** as a colorless oil, which was purified by automated

chromatography (Biotage® SNAP HP-Sil, gradient 0% to 30% EtOAc in hexanes) to afford **5** as a colorless oil (5.05 g, 90%). R_f = 0.55 (1:4 EtOAc, hexanes). $[\alpha]_D^{22}$ = +14.2 (*c* = 2.6, $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68−7.61 (m, 4H), 7.49−7.44 (m, 2H), 7.44−7.38 (m, 4H), 6.91 (ddd, *J* = 15.7, 7.5, 6.7 Hz, 1H), 5.81 (app dt, *J* = 15.7, 1.5 Hz, 1H), 4.89 (d, *J* = 6.1 Hz, 1H), 4.53 (d, *J* = 6.1 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.90−3.85 (m, 1H), 3.57−3.49 (m, 2H), 3.35 (dd, *J* = 10.7, 9.5 Hz, 1H), 2.73 (app ddt, *J* = 15.1, 6.7, 1.9 Hz, 1H), 2.18 (dddd, *J* = 15.3, 8.6, 7.6, 1.4 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 144.8, 136.0, 135.9, 133.5, 132.9, 130.4, 130.3, 128.1, 128.0, 123.9, 93.4, 81.0, 71.6, 67.3, 60.4, 34.5, 27.1, 19.4, 14.5. FTIR (thin film, NaCl) 3072, 2932, 2858, 1720, 1657, 1473, 1428, 1267, 1184, 1111, 1033 cm^{-1}. HRMS (ESI) Calcd for $C_{26}H_{34}O_5Si$ $[M+Na]^+$: 477.2068, found 477.2080.

2-((4*S*,5*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-1,3-dioxan-4-yl)acetaldehyde (6)— Enoate **5** (1.00 g, 2.20 mmol) was dissolved in CH_2Cl_2 (22 mL), and the resulting solution cooled to −78 °C. A stream of ozone was bubbled through until a pale blue color evolved, about 2.5 h. Conversion of **5** may also be monitored by TLC (R_f of **5** = 0.55; R_f of ozonide = 0.50 (1:4 EtOAc, hexanes)). Argon was bubbled through the solution to remove residual ozone, and then PPh_3 (664 mg, 2.53 mmol) was added, at which point the cold bath was removed and the reaction was allowed to warm to rt over 1.5 h. The solution was then concentrated under reduced pressure and purified by column chromatography (gradient 5% to 10% to 20% EtOAc in hexanes) to provide **6** as a colorless oil (788 mg, 93%). R_f = 0.44 (1:4 EtOAc, hexanes). $[\alpha]_D^{22}$ = −6.5 (*c* = 1.26, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (dd, *J* = 2.6, 1.4 Hz,1H), 7.68−7.61 (m, 4H), 7.51−7.38 (m, 6H), 4.87 (d, *J* = 6.2 Hz, 1H), 4.58 (d, *J* = 6.2 Hz, 1H), 4.00 (app td, *J* = 9.0, 2.8 Hz, 1H), 3.90 (dd, *J* = 10.7, 4.9 Hz, 1H), 3.57 (app td, *J* = 9.4, 5.0 Hz, 1H), 3.40 (app t, *J* = 10.3 Hz, 1H), 2.80 (ddd, *J* = 16.6, 2.8, 1.4 Hz, 1H), 2.41 (ddd, *J* = 16.6, 9.1, 2.7 Hz, 1H), 1.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 135.9, 135.9, 133.3, 132.7, 130.5, 130.4, 128.2, 128.0, 93.3, 77.5, 71.6, 67.1, 45.8, 27.1, 19.4. FTIR (thin film) 3072, 2932, 2858, 1729, 1473, 1217, 1171, 1066, 1035 cm^{-1}. HRMS (ESI) Calcd for $C_{22}H_{28}O_4Si$ $[M+Na]^+$: 407.1649, found 406.1660.[22]

***tert*-butyl(((4*S*,5*R*)-4-(((2*R*,3*R*)-3-methyloxiran-2-yl)methyl)-1,3-dioxan-5-yl)oxy)diphenylsilane (7)—** A dry round bottom flask was charged with $CrCl_2$ (1.92 g, 15.6 mmol), to which was added dry THF (20 mL) to afford a pale green slurry. Meanwhile, **6** (0.500 g, 1.30 mmol) was added to a dry round bottom flask, and the flask was evacuated on high vac and backfilled with argon. This procedure was repeated, and then **6** was diluted in dry THF (3 mL). 1,1-Diiodoethane **S1** (1.1 g, 3.9 mmol) was added, and this mixture of was added dropwise to the $CrCl_2$ slurry. The flask contained **6** and $MeCHI_2$ was washed out with a further portion of dry THF (3 mL). The mixture was stirred at rt for 3.5 h, over which time the color changed from pale green to chocolate brown. The reaction was then quenched by pouring onto brine (~50 mL). The aqueous layer was separated and extracted with Et_2O (4 × 100 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude alkene as an orange-brown oil. ^{1}H NMR analysis revealed this material to be of ~91:9 *E:Z* stereopurity, and contained some unreacted 1,1-diiodoethane, which does not adversely affect the next step. This crude material was carried forward into Shi epoxidation without further purification. R_f of alkene = 0.64 (1:9 EtOAc, hexanes).

To a solution of this crude alkene in 2:1 v/v DMM:MeCN (48 mL) was added a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in 4×10^{-4} Na_2EDTA (24 mL), nBu_4HSO_4 (0.098 g, 0.066 mmol), and Shi ketone (0.455 g, 1.76 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 40 min via syringe pump, a solution of Oxone (4.32 g, 7.02 mmol) in 4×10^{-4} Na_2EDTA (15.8 mL) and a 0.89 M solution of K_2CO_3 (15.8 mL, 14.0 mmol). After the K_2CO_3 and Oxone solutions had been added, the

resulting mixture was stirred an additional 60 min, at which point it was diluted with water (~100 mL). The aqueous layer was separated and extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced. ^{1}H NMR analysis at this point indicated incomplete conversion, so the crude material was subjected again to identical epoxidation conditions and worked up as before. The crude epoxide **7** was purified by column chromatography (gradient 3% to 25% EtOAc in hexanes) to provide **7**, a colorless oil, as an inseparable mixture of diastereomers (0.408 g of a <10:1 mixture of diastereomers, 76% over 2 steps). Epoxide **7** could be purified slightly further via preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5 μm particle size, 25 cm length; 0.4% *i*PrOH in hexanes, 20 mL/min.; t_R of major and minor diastereomers = 7.3 min; collect only the first ¼ of the peak to obtain material in high dr) to afford **7** in 10:1–15:1 dr. Better purification was achieved by via a Biotage high performance silica gel column (Biotage® SNAP HP-Sil, gradient 0% to 20% Et_2O in benzene). The two diastereomers co-spot by TLC, but early fractions are enriched in the minor diastereomer and late fractions are high purity **7** (>20:1 dr by ^{1}H NMR). R_f = 0.56 (1:4 EtOAc, hexanes). $[\alpha]_D^{22}$ = −6.6 (*c* = 0.81, $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68−7.61 (m, 4H), 7.48−7.43 (m, 2H), 7.43−7.37 (m, 4H), 4.90 (d, *J* = 6.1 Hz, 1H), 4.55 (d, *J* = 6.1 Hz, 1H), 3.84 (dd, *J* = 10.7, 3.6 Hz, 1H), 3.58−3.51 (m, 2H), 3.37−3.30 (m, 1H), 2.77−2.70 (m, 2H), 1.96 (ddd, *J* = 14.5, 5.8, 1.8 Hz, 1H), 1.72 (ddd, *J* = 13.8, 8.3, 5.0 Hz, 1H), 1.28 (d, *J* = 5.1 Hz, 3H), 1.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 135.9, 133.7, 132.9, 130.3, 130.2, 128.1, 127.9, 93.3, 80.3, 71.6, 67.4, 56.8, 54.2, 34.1, 27.1, 19.5, 17.8. FTIR (thin film) 3072, 2931, 2857, 1473, 1428, 1176, 1112, cm^{-1}. HRMS (ESI) Calcd for $C_{24}H_{32}O_4Si$ $[M+Na]^+$: 435.1962, found 435.1975.

(*E*)-ethyl 4-((4*S*,5*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-1,3-dioxan-4-yl)-2-methylbut-2-enoate (10)—To a dry flask with stir bar was added (carbethoxyethylidene)tri-phenylphosphorane (0.941g, 2.6 mmol) and CH_2Cl_2 (5 mL). Aldehyde **6** was diluted in CH_2Cl_2 (1 mL) and added via syringe. The resulting solution was stirred for 16 h, concentrated under reduced pressure, and purified by automated chromatography (Biotage® SNAP KP-Sil, gradient 5% to 40% EtOAc in hexanes) to furnish **10** as a colorless oil (0.957g, 89%). R_f = 0.51 (1:4 EtOAc, hexanes). $[\alpha]_D^{22}$ = +10.7 (*c* = 4.95, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71−7.65 (m, 4H), 7.48−7.39 (m, 6H), 6.82 (td, *J* = 6.9, 1.4 Hz, 1H), 4.90 (d, *J* = 6.1 Hz, 1H), 4.54 (d, *J* = 6.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.92 (dd, *J* = 10.7, 4.9 Hz, 1H), 3.63−3.53 (m, 2H), 3.38 (t, *J* = 10.2 Hz, 1H), 2.74−2.69 (m, 1H), 2.17 (dd, *J* = 16.1, 7.7 Hz, 1H), 1.77 (app d, *J* = 1.2 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.08 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 137.3, 135.63, 135.59, 133.2, 132.6, 129.96, 129.91, 129.5, 127.72, 127.60, 93.1, 81.0, 71.2, 67.2, 60.3, 30.9, 26.8, 19.1, 14.2, 12.5. FTIR (thin film) 2959, 2932, 2857, 1710, 1428, 1219, 1111, 948, 821 cm^{-1}. HRMS (ESI) Calcd for $C_{27}H_{36}O_5Si$ $[M+Na]^+$: 491.2224, found 491.2220.

(*E*)-4-((4*S*,5*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-1,3-dioxan-4-yl)-2-methylbut-2-en-1-ol (11)—Ester **10** (0.783 g, 1.67 mmol) was diluted in toluene (10 mL) and cooled to −78 °C. A solution of DIBAL-H in toluene (1M, 3.8 mL, 3.8 mmol) was added via syringe and the reaction mixture was stirred for 30 min, and then warmed to rt for 1 h. After this time the solution was cooled to 0 °C, methanol was added (20 mL), followed by a saturated solution of Rochelle's salt. After extraction with EtOAc (3 × 100 mL), drying with Na_2SO_4, and concentration under reduced pressure, **10** was purified by automated chromatography (Biotage® SNAP HP-Sil, gradient 25% to 100% EtOAc in hexanes) to give a colorless oil. (0.510 g, 72%). R_f = 0.11 (1:4 EtOAc, hexanes). $[\alpha]_D^{22}$ = −1.4 (*c* = 9.36, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72−7.66 (m, 4H), 7.48−7.40 (m, 6H), 5.46 (t, *J* = 6.8 Hz, 1H), 4.90 (d, *J* = 6.0 Hz, 1H), 4.53 (d, *J* = 6.10 Hz, 1H), 3.97 (s, 2H), 3.90 (app dd, *J* = 10.7, 5.0 Hz, 1H), 3.62−3.58 (m, 1H), 3.48 (app td, *J* = 8.8, 1.8 Hz, 1H), 3.37 (t, *J* = 10.3 Hz, 1H),

2.65 (dd, *J* = 15.3, 6.9 Hz, 1H), 2.07−2.01 (m, 2H), 1.61 (s, 3H), 1.10 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.8, 135.73, 135.64, 133.4, 132.7, 129.93, 129.88, 127.70, 127.58, 120.9, 93.1, 82.0, 71.2, 68.4, 67.2, 29.7, 26.8, 19.1, 13.7. FTIR (thin film) 3430, 2931, 2856, 1427, 1103, 1033 cm^{-1}. HRMS (ESI) Calcd for $C_{25}H_{34}O_4Si$ $[M+Na]^+$: 449.2119, found 449.2190.

(*E*)-4-((4*S*,5*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-1,3-dioxan-4-yl)-2-methylbut-2-en-1-yl methanesulfonate (12)—Alcohol **11** (0.460 g, 1.1 mmol) was added to a round-bottomed flask with stir bar. To this was added toluene (1.1 mL), Et_3N (0.307 mL, 2.2 mmol), and trimethylamine hydrochloride salt (0.011 g, 0.11 mmol). The resulting mixture was cooled to 0 °C after which MsCl (0.124 mL, 1.6 mmol) in toluene (1.6 mL) was added dropwise. After stirring at this temperature for 1 h *N,N*-dimethylethylenediamine (0.150 mL) was added and the solution stirred for an additional 20 min. The reaction was diluted with water (20 mL), extracted with CH_2Cl_2 (3 × 50 mL), washed with brine (20 mL), and dried with Na_2SO_4. Purification by column chromatography (20% EtOAc in hexanes) furnished **12** as a pale yellow oil (0.431 g, 78%). R_f = 0.23 (1:4 EtOAc, hexanes). $[\alpha]_D^{22}$ = +1.1 (*c* = 0.46, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.63 (m, 4H), 7.48−7.40 (m, 6H), 5.61 (d, *J* = 1.0 Hz, 1H), 4.87 (d, *J* = 6.1 Hz, 1H), 4.58 (s, 2H), 4.52 (d, *J* = 6.1 Hz, 1H), 3.89 (app dd, *J* = 10.7, 5.0 Hz, 1H), 3.56−3.53 (m, 1H), 3.47 (t, *J* = 4.4 Hz, 1H), 3.35 (t, *J* = 10.2 Hz, 1H), 2.98 (s, 3H), 2.06 (s, 1H), 1.65 (s, 3H), 1.07 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.75, 135.69, 133.3, 132.7, 130.4, 130.06, 130.01, 128.5, 127.81, 127.69, 93.1, 81.5, 76.1, 71.3, 67.1, 37.9, 30.0, 26.9, 19.2, 13.9. FTIR (thin film) 3073, 2934, 2858, 1356, 1174, 1100, 924 cm^{-1}. HRMS (ESI) Calcd for $C_{26}H_{36}O_6SSi$ $[M+Na]^+$: 527.1894, found 527.1903.

***tert*-butyl(((4*S*,5*R*)-4-(3-methylbut-2-en-1-yl)-1,3-dioxan-5-yl)oxy)diphenylsilane (13)—**To a dried flask equipped with a stir bar was added LAH (0.012 g, 0.32 mmol) and Et_2O (8 mL). The mixture was cooled to 0 °C, after which was added **12** (0.400 g, 0.79 mmol) in 4 mL Et_2O. The resulting solution was allowed to warm to rt over 16 h and was then diluted with water (30 mL). The resulting product was extracted with Et_2O (3 × 50 mL) and the combined extracts were dried with $MgSO_4$. Purification by automated chromatography (Biotage® SNAP HP-Sil, gradient 2% to 20% EtOAc in hexanes) gave **13** as a colorless oil (0.158 g, 49%). R_f = 0.55 (1:9 EtOAc, hexanes). $[\alpha]_D^{22}$ = −3.5 (*c* = 0.36, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72−7.60 (m, 4H), 7.49−7.40 (m, 6H), 5.19 (app dt, *J* = 6.8, 1.3 Hz 1H), 4.93 (d, *J* = 6.0 Hz, 1H), 4.55 (d, *J* = 6.1 Hz, 1H), 3.86 (app dd, *J* = 10.7, 5.1 Hz, 1H), 3.59−3.56 (m, 1H), 3.45 (app dt, *J* = 8.8, 4.4 Hz, 1H), 3.35 (t, *J* = 10.3 Hz, 1H), 2.62 (dd, *J* = 15.3, 6.8 Hz, 1H), 2.01 (app dt, *J* = 15.3, 6.7 Hz, 1H), 1.72 (s, 3H), 1.58 (s, 3H), 1.09 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.84, 135.74, 133.66, 133.60, 132.8, 129.96, 129.90, 127.75, 127.63, 119.7, 93.3, 82.4, 71.4, 67.3, 30.2, 26.9, 25.8, 19.2, 17.9. FTIR (thin film) 2930, 2856, 1472, 1428, 1109, 1039 cm^{-1}. Calcd for $C_{25}H_{34}O_3Si$ $[M+Na]^+$: 433.2169, found 433.2175.

***tert*-butyl(((4*S*,5*R*)-4-(((*R*)-3,3-dimethyloxiran-2-yl)methyl)-1,3-dioxan-5-yl)oxy)diphenylsilane (14)—**To a solution of **13** (0.170 g. 0.410 mmol) in 2:1 v/v DMM:MeCN (15 mL) was added a 0.05 M solution of $Na_2B_4O_7{\bullet}10H_2O$ in 4×10^{-4} Na_2EDTA (7.7 mL), *n*-Bu_4HSO_4 (0.029 g, 0.010 mmol), and Shi ketone (0.170 g, 0.656 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 40 min via syringe pump, a solution of Oxone (1.45 g, 4.72 mmol) in 4×10^{-4} Na_2EDTA (5.5 mL) and a 0.89 M solution of K_2CO_3 (5.5 mL, 5.4 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 60 min, at which point it was diluted with water (~100 mL). The aqueous layer was separated and extracted with EtOAc (3 × 100 mL), and the combined organic layers were

washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced. The crude epoxide **14** was purified by automated chromatography (Biotage® SNAP HP-Sil, gradient 0% to 40% EtOAc in hexanes) to provide **14**, a colorless oil, as an inseparable mixture of diastereomers (0.151 g of a ~6:1 mixture of diastereomers, 86%). Epoxide **14** could be purified further via a Biotage high performance silica gel column using benzene as the mobile phase (Biotage® SNAP HP-Sil, gradient 0% to 20% Et_2O in benzene). The two diastereomers co-spot by TLC, but early fractions are enriched in the minor diastereomer and late fractions are high purity **14** (>20:1 dr by ^1H NMR). R_f = 0.57 (1:4 EtOAc, hexanes). $[\alpha]_D^{22}$ = −10.6 (*c* = 1.47, CH_2Cl_2). ^1H NMR (600 MHz, $CDCl_3$) δ 7.68−7.61 (m, 4H), 7.47−7.38 (m, 6H), 4.93 (d, *J* = 6.0 Hz, 1H), 4.56 (d, *J* = 6.1 Hz, 1H), 3.86 (app dd, *J* = 10.8, 4.8 Hz, 1H), 3.62−3.54 (m, 2H), 3.34 (t, *J* = 10.2 Hz, 1H), 2.86 (t, *J* = 6.1 Hz, 1H), 2.03 (ddd, *J* = 14.5, 6.3, 2.6 Hz, 1H), 1.64 (ddd, *J* = 14.6, 8.7, 5.9 Hz, 1H), 1.31 (s, 3H), 1.25 (s, 3H), 1.07 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.76, 135.67, 133.4, 132.5, 130.08, 129.96, 127.82, 127.66, 93.1, 80.8, 71.3, 67.4, 61.1, 57.4, 31.3, 26.9, 24.7, 19.2, 18.8. FTIR (thin film, NaCl) 2928, 2856, 1462, 1399, 2856, 1172, 1109 cm^{-1}. HRMS (ESI) Calcd for $C_{25}H_{34}O_4Si$ $[M+Na]^+$: 449.2119, found 449.2123.

(4*S*,5*R*)-4-(((*R*)-3,3-dimethyloxiran-2-yl)methyl)-1,3-dioxan-5-ol (15a)—To a solution of silyl ether **14** (0.129 g, 0.302 mmol) in THF (0.500 μL) was added a 1 M solution of TBAF in THF (0.5 μL, 0.500 mmol). The reaction solution was stirred at rt for 20 min, then applied directly to a column of SiO_2 (eluted with a gradient 30% to 100% EtOAc in hexanes) to yield **15a** as a colorless oil (0.033 g, 58%). R_f = 0.18 (40% EtOAc, hexanes). $[\alpha]_D^{22}$ = −6.6 (*c* = 0.59, CH_2Cl_2). ^1H NMR (300 MHz, C_6D_6) δ 4.93 (d, *J* = 6.1 Hz, 1H), 4.31 (d, *J* = 6.1 Hz, 1H), 4.10 (dd, *J* = 10.8, 5.4 Hz, 1H), 3.71 (app td, *J* = 9.2, 5.1 Hz, 1H), 3.36 (m, 1H), 3.22 (t, *J* = 10.3 Hz, 2H), 3.08 (dd, *J* = 7.3, 4.5 Hz, 1H), 1.95−1.86 (m, 2H), 1.07 (s, 6H).^{13}C NMR (125 MHz, C_6D_6) δ 93.4, 80.5, 71.2, 60.3, 57.5, 31.4, 24.7, 18.7. FTIR (thin film) 3423, 2964, 2923, 2853, 2774, 1653, 1457, 1438, 1381, 1257, 1225, 1175, 1150, 1073, 1028 cm^{-1}. HRMS (ESI) Calcd for $C_9H_{16}O_4$ $[M+Na]^+$: 211.0941, found 211.0955.

1-((4*S*,5*R*)-5-((*tert*-butyldiphenylsilyl)oxy)-1,3-dioxan-4-yl)propan-2-one (16)—To a dry flask equipped with a stir bar was added aldehyde **6** (1.004 g, 2.6 mmol) and Et_2O (13 mL). The resulting solution was cooled to 0 °C after which was added MeMgBr (3 M, 1.6 mL, 3.9 mmol). After stirring for 45 min at this temperature the reaction was quenched with sat. NH_4Cl_{aq}, extracted with Et_2O (3 × 50 mL), and dried with $MgSO_4$ to furnish the intermediate alcohol as a yellow oil (0.844 g, 2.1 mmol) that was carried forward to the oxidation.

To this oil was added CH_2Cl_2 (15 mL), MS 4Å (3.5 g), 4-methylmorpholine *N*-oxide (0.370 g, 3.2 mmol), tetrapropylammonium perruthenate (0.037 g, 0.1 mmol) and the resulting mixture was stirred for 3 h. The mixture was filtered on Celite® and purified by automated chromatography (Biotage® SNAP HP-Sil, gradient 10% to 50% EtOAc in hexanes) to give **16** as a colorless oil (0.602 g, 60% over 2 steps). R_f = 0.48 (3:7 EtOAc, hexanes). $[\alpha]_D^{22}$ = −8.3 (*c* = 0.61, CH_2Cl_2). ^1H NMR (600 MHz, $CDCl_3$) δ 7.67−7.63 (m, 4H), 7.49−7.40 (m, 6H), 4.85 (d, *J* = 6.1 Hz, 1H), 4.57 (d, *J* = 6.2 Hz, 1H), 3.97 (td, *J* = 9.4, 1.9 Hz, 1H), 3.90 (dd, *J* = 10.7, 5.0 Hz, 1H), 3.52 (td, *J* = 9.5, 4.9 Hz, 1H), 3.40 (t, *J* = 10.4 Hz, 1H), 2.77 (dd, *J* = 16.1, 2.1 Hz, 1H), 2.37 (m, 1H), 2.12 (s, 3H), 1.04 (s, 9H).^{13}C NMR (150 MHz, $CDCl_3$) δ 206.4, 135.68, 135.65, 133.1, 132.7, 130.09, 130.05, 127.83, 127.73, 93.0, 78.2, 71.3, 66.9, 45.6, 30.9, 26.8, 19.2. FTIR (thin film) 2933, 2858, 1721, 1428, 1108, 1034 cm^{-1}. HRMS (ESI) Calcd for $C_{23}H_{30}O_4Si$ $[M+Na]^+$: 421.1806, found 421.1808.

***tert*-butyl(((4*S*,5*R*)-4-((*E*)-2-methylbut-2-en-1-yl)-1,3-dioxan-5-yl)oxy)diphenylsilane (17)—**To a dry flask equipped with a stir bar was added ethyltriphenylphosphonium bromide (0.459 g, 1.24 mmol) and THF (17 mL). The resuling slurry was cooled to 0 °C followed by the addition of *n*BuLi (2.65 M, 0.396 mL, 1.05 mmol). After stirring at this temperature for 40 min the orange/red solution was cooled to −78 °C. Ketone **16** (0.379 g, 0.952 mmol) in THF (1.5 mL) was added dropwise via syringe. The ketone was azeotroped with toluene prior to use. The reaction mixture was allowed to warm to rt over 16 h after which it was quenched with sat. NH_4Cl_{aq} (~50 mL), extracted with EtOAc (3 × 50 mL), and dried over $MgSO_4$. Purification by automated chromatography (Biotage® SNAP HP-Sil, gradient 1% to 40% EtOAc in hexanes) gave **17** as a colorless oil (0.273 g, 71%,). The alkene was isolated as an inseparable 2.7:1 mixture of *E:Z* isomers, and used without further purification. R_f = 0.79 (1:4 EtOAc, hexanes). $[\alpha]_D^{22}$ = −9.3 (*c* = 0.40, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72−7.65 (m, 6H), 7.49−7.40 (m, 9H), 5.41−5.39 (m, 1H), 4.92 (m, 1H), 4.53 (m, 1H), 3.88 (dd, *J* = 10.5, 4.1 Hz, 1H), 3.58−3.54 (m, 3H), 3.38−3.35 (m, 1H), 2.56 (d, *J* = 14.0 Hz, 1H), 2.10−2.06 (m, 1H), 1.78 (s, 3H), 1.58 (d, *J* = 6.7 Hz 3H), 1.08 (m, 14H).^{13}C NMR (150 MHz, $CDCl_3$) δ 136.13, 136.04, 133.8, 133.12, 132.93, 130.28, 130.23, 128.05, 127.94, 121.8, 93.5, 81.5, 77.5, 77.3, 77.1, 71.6, 68.4, 34.1, 27.2, 24.2, 19.5, 13.7. FTIR (thin film) 2930, 2857, 1471, 1428, 1107, 1035, 946 cm^{-1}. HRMS (ESI) Calcd for $C_{25}H_{34}O_3Si$ $[M+Na]^+$: 433.2169, found 433.2183.

***tert*-butyl(((4*S*,5*R*)-4-(((2*R*,3*R*)-2,3-dimethyloxiran-2-yl)methyl)-1,3-dioxan-5-yl)oxy)diphenylsilane (18)—**To a solution of **17** (0.270 g, 0.659 mmol) in 2:1 v/v DMM:MeCN (25 mL) was added a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in 4 × 10^{-4} Na_2EDTA (12 mL), nBu_4HSO_4 (0.029 g, 0.010 mmol), and Shi ketone (0.272 g, 1.05 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 40 min via syringe pump, a solution of Oxone (2.32 g, 7.57 mmol) in 4 × 10^{-4} Na_2EDTA (8.5 mL) and a 0.89 M solution of K_2CO_3 (8.5 mL, 7.57 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 60 min, at which point it was diluted with water (~100 mL). The aqueous layer was separated and extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced. The crude epoxide **18** was purified by automated chromatography (Biotage® SNAP HP-Sil, gradient 0% to 40% EtOAc in hexanes) to provide **18**, a colorless oil, as an inseparable mixture of diastereomers (0.255 g of a ~3:1 mixture of diastereomers, 91%). Epoxide **18** could be purified further via a Biotage high performance silica gel column using benzene as the mobile phase (Biotage® SNAP HP-Sil, gradient 0% to 20% Et_2O in benzene). The two diastereomers co-spot by TLC, but early fractions are enriched in the minor diastereomer and late fractions are higher purity **18** (>9:1 dr by ^{1}H NMR). R_f = 0.58 (1:4 EtOAc, hexanes). $[\alpha]_D^{22}$ = −14.3 (*c* = 1.69, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71−7.66 (m, 4H), 7.50−7.42 (m, 6H), 4.91 (d, *J* = 6.0 Hz, 1H), 4.58 (d, *J* = 6.1 Hz, 1H), 3.87 (dd, *J* = 10.7, 5.0 Hz, 1H), 3.64−3.62 (m, 1H), 3.51 (td, *J* = 9.4, 5.0 Hz, 1H), 3.38 (t, *J* = 10.3 Hz, 1H), 2.87 (t, *J* = 5.5 Hz, 1H), 2.28 (dd, *J* = 14.2, 1.8 Hz, 1H), 1.40 (s, 3H), 1.38−1.34 (m, 1H), 1.24 (d, *J* = 5.6 Hz, 3H), 1.09 (s 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.77, 135.69, 132.6, 130.06, 129.95, 128.3, 127.82, 127.66, 93.0, 79.9, 71.4, 67.7, 61.0, 59.0, 34.2, 26.9, 23.0, 19.2, 14.6. FTIR (thin film, NaCl) 2931, 2857, 1471, 1427, 1170, 1103, 1035 cm^{-1}. HRMS (ESI) Calcd for $C_{25}H_{34}O_4Si$ $[M+Na]^+$: 449.2119, found 449.2113.

(4*S*,5*R*)-4-(((2*R*,3*R*)-2,3-dimethyloxiran-2-yl)methyl)-1,3-dioxan-5-ol (15b)—To a solution of silyl ether **18** (0.199 g, 0.467 mmol) in THF (0.500 μL) was added a 1 M solution of TBAF in THF (0.7 μL, 0.700 mmol). The reaction solution was stirred at rt for 20 min, then applied directly to a column of SiO_2 (eluted with a gradient 30% to 100% EtOAc in hexanes) to yield **15b** as a colorless oil (0.079 g, 90%). R_f = 0.28 (40% EtOAc, hexanes).

$[\alpha]_D^{22}$ = −18.4 (*c* = 2.47, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6) δ 4.86 (d, *J* = 6.1 Hz, 1H), 4.25 (d, *J* = 6.0 Hz, 1H), 4.10 (app dd, *J* = 10.7, 5.0 Hz, 1H), 3.42 (app td, *J* = 8.1, 5.2 Hz, 1H), 3.36−3.32 (m, 1H), 3.21 (t, *J* = 10.4 Hz, 1H), 2.96 (t, *J* = 3.6 Hz, 1H), 2.58 (q, *J* = 5.6 Hz, 1H), 1.94 (dd, *J* = 14.4, 5.1 Hz, 1H), 1.72 (dd, *J* = 14.4, 7.3 Hz, 1H), 1.20 (s, 3H), 1.04 (d, *J* = 5.6 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6) δ 93.2, 79.5, 71.1, 67.1, 61.8, 59.1, 35.9, 22.9, 14.3. FTIR (thin film) 3405, 2968, 2856, 1455, 1379, 1168, 1059, 1025, 938 cm^{-1}. HRMS (ESI) Calcd for $C_8H_{14}O_4$ $[M+Na]^+$: 211.0941, found 211.0957.

***tert*-butyl(((4*S*,5*R*)-4-(2-methylallyl)-1,3-dioxan-5-yl)oxy)diphenylsilane (21)—** To a dry flask equipped with a stir bar was added methyltriphenylphosphonium bromide (0.260 g, 0.728 mmol) and THF (8.5 mL). The resuling slurry was cooled to 0 °C followed by the addition of *n*BuLi (2.32M, 0.241 mL, 0.56 mmol). After stirring at this temperature for 40 min the orange/red solution was cooled to −78 °C. Ketone **16** (0.225 g, 0.560 mmol) in THF (1.0 mL) was added dropwise via syringe. The ketone was azeotroped with toluene prior to use. The reaction mixture was allowed to warm to rt over 16 h after which it was quenched with sat. NH_4Cl_{aq} (~50 mL), extracted with EtOAc (3 × 50 mL), and dried over $MgSO_4$. Purification by automated chromatography (Biotage® SNAP HP-Sil, gradient 0% to 20% EtOAc in hexanes) gave **21** as a colorless oil (0.209 g, 94%,). R_f = 0.59 (1:9 EtOAc, hexanes). $[\alpha]_D^{22}$ = −16.3 (*c* = 0.93, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4H), 7.48−7.40 (m, 6H), 4.93 (d, *J* = 6.1 Hz, 1H), 4.85 (s, 1H), 4.77 (s, 1H), 4.56 (d, *J* = 6.1 Hz, 1H), 3.90 (app dd, *J* = 10.7, 5.0 Hz, 1H), 3.60 (d, *J* = 8.5 Hz, 1H), 3.52 (d, *J* = 5.0 Hz, 1H), 3.39 (t, *J* = 10.3 Hz, 1H), 2.66 (d, *J* = 14.5 Hz, 1H), 1.95 (app dd, *J* = 14.5, 10.2 Hz, 1H), 1.79 (s, 3H), 1.10 (s, 9H).^{13}C NMR (150 MHz, $CDCl_3$) δ 142.6, 136.10, 136.03, 133.7, 133.1, 130.30, 130.26, 128.06, 127.98, 112.9, 93.5, 80.8, 71.7, 67.9, 40.3, 27.2, 22.8, 19.5. FTIR (thin film) 2931, 2852, 1471, 1428, 1107, 1036, 948 cm^{-1}. HRMS (ESI) Calcd for $C_{24}H_{32}O_3Si$ $[M+Na]^+$: 419.2013, found 419.2012.

***tert*-butyl(((4*S*,5*R*)-4-(((*R*)-2-methyloxiran-2-yl)methyl)-1,3-dioxan-5-yl)oxy)diphenylsilane (22)—** To a solution of **21** (0.208 g, 0.524 mmol) in 2:1 v/v DMM:MeCN (20 mL) was added a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in 4×10^{-4} Na_2EDTA (10 mL), nBu_4HSO_4 (0.029 g, 0.010 mmol), and Shi ketone (0.240 g, 0.839 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 40 min via syringe pump, a solution of Oxone (1.85 g, 6.026 mmol) in 4×10^{-4} Na_2EDTA (6.9 mL) and a 0.89 M solution of K_2CO_3 (6.9 mL, 6.14 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 60 min, at which point it was diluted with water (~100 mL). The aqueous layer was separated and extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced. The crude epoxide **22** was purified by automated chromatography (Biotage® SNAP HP-Sil, gradient 1% to 30% EtOAc in hexanes) to provide **22**, a colorless oil, as an inseparable mixture of diastereomers (0.196 g of a ~6:1 mixture of diastereomers, 89%). Epoxide **22** could be purified further via a Biotage high performance silica gel column using benzene as the mobile phase (Biotage® SNAP HP-Sil, gradient 0% to 20% Et_2O in benzene). The two diastereomers co-spot by TLC, but early fractions are enriched in the minor diastereomer and late fractions are higher purity **22** (>14:1 dr by ^{1}H NMR). R_f = 0.48 (1:4 EtOAc, hexanes). $[\alpha]_D^{22}$ = −14.3 (*c* = 1.69, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.48−7.39 (m, 6H), 4.90 (d, *J* = 6.1 Hz, 1H), 4.57 (d, *J* = 6.1 Hz, 1H), 3.87 (app dd, *J* = 10.5, 4.8 Hz, 1H), 3.62 (app dt, *J* = 8.7, 1.6 Hz, 1H), 3.44−3.43 (m, 1H), 3.37 (t, *J* = 10.2 Hz, 1H), 2.61 (app dd, *J* = 13.9, 4.9 Hz, 2H), 2.30 (d, *J* = 14.0 Hz, 1H), 1.38 (s, 3H), 1.26 (dd, *J* = 14.0, 10.5 Hz, 1H), 1.06 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.04, 135.98, 133.5, 132.9, 130.32, 130.26, 128.07, 127.98, 93.2, 80.1, 71.7, 67.6, 55.3, 39.4, 27.2, 22.0, 21.4,

19.5. FTIR (thin film, NaCl) 2931, 2857, 1471, 1427, 1170, 1103, 1035 cm^{-1}. HRMS (ESI) Calcd for $C_{24}H_{32}O_4Si$ $[M+Na]^+$: 435.1962, found 435.1961.

(4*S*,5*R*)-4-(((*R*)-2-methyloxiran-2-yl)methyl)-1,3-dioxan-5-ol (23)—To a solution of silyl ether **22** (0.155 g, 0.376 mmol) in THF (0.564 μL) was added a 1M solution of TBAF in THF (0.564 μL, 0.564 mmol) at 0 °C. The reaction solution was stirred at 0 °C for 20 min, then applied directly to a column of SiO_2 pretreated with 5% Et_3N in EtOAc (eluted with a gradient 20% to 100% EtOAc in hexanes) to yield **23** as a colorless oil (0.065 g, 95%). R_f = 0.68 (100% EtOAc). $[\alpha]_D^{22}$ = −27.5 (*c* = 0.70, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6) δ 4.85 (d, *J* = 6.1, 1H), 4.24 (d, *J* = 6.1 Hz, 1H), 4.06 (dd, *J* = 10.4, 4.5 Hz, 1H), 3.41−3.27 (m, 2H), 3.20 (q, *J* = 11.0 Hz, 1H), 2.78 (br s, 1H), 2.37 (d, *J* = 4.9 Hz, 1H), 2.25 (d, *J* = 4.9 Hz, 1H), 1.86−1.67 (m, 2H), 1.17 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6) δ 92.9, 79.3, 70.9, 66.6, 55.5, 55.0, 40.5, 20.8. FTIR (thin film) 3425, 2924, 2860, 1393, 1165, 1061, 1027, 941 cm^{-1}. HRMS (ESI) Calcd for $C_8H_{14}O_4$ $[M+Na]^+$: 197.0784, found 197.0790.

(((4*S*,5*R*)-4-allyl-1,3-dioxan-5-yl)oxy)(*tert*-butyl)diphenylsilane (24)—To a dry flask equipped with a stir bar was added methyltriphenylphosphonium bromide (0.260 g, 0.728 mmol) and THF (8.5 mL). The resuling slurry was cooled to 0 °C followed by the addition of *n*-BuLi (2.32 M, 0.241 mL, 0.56 mmol). After stirring at this temperature for 40 min the orange/red solution was cooled to −78 °C. Aldehyde **6** (0.220 g, 0.560 mmol) in THF (1.0 mL) was added dropwise via syringe. The aldehyde was azeotroped with toluene prior to use. The reaction mixture was allowed to warm to rt over 16 h after which it was quenched with sat. NH_4Cl_{aq} (~50 mL), extracted with EtOAc (3 × 50 mL), and dried over $MgSO_4$. Purification by automated chromatography (Biotage® SNAP HP-Sil, gradient 0% to 20% EtOAc in hexanes) gave **24** as a colorless oil (0.187 g, 87%,). R_f = 0.59 (1:9 EtOAc, hexanes). $[\alpha]_D^{22}$ = −8.4 (*c* = 2.77, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69−7.64 (m, 4H), 7.48−7.39 (m, 6H), 5.85−5.78 (m, 1H), 5.07−5.04 (m, 2H), 4.92 (d, *J* = 6.0 Hz, 1H), 4.54 (d, *J* = 6.1 Hz, 1H), 3.84 (app dd, *J* = 10.7, 4.9 Hz, 1H), 3.54−3.49 (m, 2H), 3.34 (t, *J* = 10.2 Hz, 1H), 2.68−2.64 (m, 1H), 2.13−2.10 (m, 1H), 1.08 (s, 9H).^{13}C NMR (150 MHz, $CDCl_3$) δ 136.07, 135.98, 134.6, 133.7, 133.0, 130.28, 130.21, 128.04, 127.93, 117.4, 93.5, 82.0, 71.6, 67.3, 36.2, 27.2, 19.5. FTIR (thin film) 3072, 2932, 2856, 1472, 1428, 1107, 1038, 703 cm^{-1}. HRMS (ESI) Calcd for $C_{23}H_{30}O_3Si$ $[M+Na]^+$: 405.1856, found 435.1869.

***tert*-butyl(((4*S*,5*R*)-4-((*R*)-oxiran-2-ylmethyl)-1,3-dioxan-5-yl)oxy)diphenylsilane (25)—**To a solution of **24** (0.236 g, 0.612 mmol) in 2:1 v/v DMM:MeCN (22 mL) was added a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in 4×10^{-4} Na_2EDTA (11.5 mL), nBu_4HSO_4 (0.029 g, 0.010 mmol), and Shi ketone (0.279 g, 0.979 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 40 min via syringe pump, a solution of Oxone (2.16 g, 7.04 mmol) in 4×10^{-4} Na_2EDTA (8.0 mL) and a 0.89 M solution of K_2CO_3 (8.0 mL, 7.12 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 60 min, at which point it was diluted with water (~100 mL). The aqueous layer was separated and extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced. The crude epoxide **25** was purified by automated chromatography (Biotage® SNAP HP-Sil, gradient 0% to 40% EtOAc in hexanes) to provide **25**, a colorless oil, as an inseparable mixture of diastereomers (0.2135 g of a ~2:1 mixture of diastereomers, 87%). Epoxide **25** could be purified further via a Biotage high performance silica gel column using benzene as the mobile phase (Biotage® SNAP HP-Sil, gradient 1% to 20% Et_2O in benzene). The two diastereomers co-spot by TLC, but early fractions are enriched in the minor diastereomer and late fractions are higher purity **25** (>14:1 dr by ^{1}H NMR). R_f = 0.46 (1:4 EtOAc, hexanes). $[\alpha]_D^{22}$ = −22.5 (*c* = 1.72, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.48−7.38 (m, 6H), 4.91 (d, *J* = 6.1

Hz, 1H), 4.58 (d, *J* = 6.1 Hz, 1H), 3.87 (dd, *J* = 10.7, 5.0 Hz, 1H), 3.66 (app dt, *J* = 9.4, 1.8 Hz, 1H), 3.48 (m, 1H), 3.38 (t, *J* = 10.4 Hz, 1H), 3.04 (m, 1H), 2.77 (app dd, *J* = 5.1, 4.0 Hz, 1H), 2.41 (app dd, *J* = 5.1, 2.8 Hz, 1H), 1.91 (app ddd, *J* = 14.3, 7.4, 2.3 HZ, 1H), 1.52 (m, 1H), 1.04 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.06, 135.98, 133.6, 133.0, 130.30, 130.27, 128.06, 127.97, 93.4, 79.9, 71.6, 67.7, 49.2, 48.0, 35.3, 27.1, 19.5. FTIR (thin film) 3049, 2931, 2857, 1472, 1428, 1107, 1035, 947 cm^{-1}. HRMS (ESI) Calcd for $C_{23}H_{30}O_4Si$ $[M+Na]^+$: 421.1806, found 421.1811.

(*E*)-Pent-3-en-1-ol (31)—To a flamed dired flask with stir bar was added CH_2Cl_2 (60 mL) and 3-pentenoic acid (1.50 mL, 14.8 mmol). The resulting solution was cooled to −78 °C after which DIBAL-H (60 mL, 1.0 M in CH_2Cl_2). After stirring at −78 °C for 30 min the reaction mixture was warmed to rt for 1 h afterwhich a saturated solution of Rochelle's salt was added and stirred for 12 h. The organic layer was separated and the aqueous phase extracted with 3×50 mL of CH_2Cl_2, dried with Na_2SO_4 and concentrated under reduced pressure. The crude alcohol **31** was purified by automated chromatography (Biotage® SNAP HP-Sil, gradient 30% to 100% EtOAc in hexanes) to provide **31**, a colorless oil (0.816 g, 65%). R_f = 0.44 (1:1 EtOAc, hexanes). ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.61−5.55 (m, 1H), 5.44−5.38 (m, 1H), 3.65−3.62 (t, *J* = 6.3 Hz, 2H), 2.29−2.24 (q, *J* = 6.4 Hz, 2H), 1.70 (app dquintet, *J* = 6.4, 1.3 Hz, 3H). Spectrum matches commercial standard.

(*E*)-5-(pent-3-en-1-ylsulfonyl)-1-phenyl-1*H*-tetrazole (32)—Alcohol **31** (0.50 g, 5.8 mmol), 1-phenyltetrazole-5-thiol (2.1 g, 11.6 mmol), PPh_3 (2.28 g, 8.7 mmol) were added to a flame dried flask with THF (50 mL). The resulting solution was cooled to 0 °C under an argon after which DIAD (2 mL, 10.4 mmol) was added over 5 min via syringe pump. The solution was stirred at 0 °C for 5 min, then at rt for 3 h and then quenched with sat. $NaCl_{aq}$ (~100 mL). After extraction with Et_2O (3×100 mL), drying with Na_2SO_4, and concentrating under reduced pressure, the crude sulfide was purified by automated chromatography (Biotage® SNAP HP-Sil, gradient 7% to 60% EtOAc in hexanes) to provide the sulfide, a colorless oil (1.4 g, 98%). R_f = 0.54 (3:7 EtOAc, hexanes). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.60−7.54 (m, 5H), 5.59−5.53 (m, 1H), 5.48−5.42 (m, 1H), 3.43 (t, *J* = 7.2 Hz, 2H), 2.54−2.49 (q, *J* = 7.2 Hz, 2H), 1.67 (app dq, *J* = 6.2, 1.3 Hz, 3H).

This sulfide was diluted in EtOH (80 mL) and cooled to 0 °C after which H_2O_2 (2.6 g of 30% wt H_2O, 24.0 mmol) and $(NH_4)_6Mo_7O_{24}$ (0.71g, 0.58 mmol) were added. The reaction mixture was allowed to reach rt over 16 h quenched with sat. $NaCl_{aq}$ (~100 mL). After extraction with Et_2O (3×100 mL), drying with Na_2SO_4, and concentrating under reduced pressure, crude **32** was purified by automated chromatography (Biotage® SNAP HP-Sil, gradient 5% to 60% EtOAc in hexanes) to provide sulfone **32**, a colorless oil (1.47 g, 93%). R_f = 0.48 (3:7 EtOAc, hexanes). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.72 (m, 2H), 7.68−7.60 (m, 3H), 5.66−5.63 (m, 1H), 5.46−5.42 (m, 1H), 3.81−3.79 (m, 2H), 2.67 (q, *J* = 7.6 Hz, 2H), 1.69 (dd, *J* = 6.4, 0.6 Hz, 3H). Spectrum was consistent with reported values.[23]

***tert*-Butyl(((4*S*,5*R*)-4-((2*E*,5*E*)-hepta-2,5-dien-1-yl)-1,3-dioxan-5-yl)oxy)diphenylsilane (33)—**To a dry round bottomed flask with stir bar was added **32** (0.500 g, 1.83 mmol). To this was added THF (9 mL) and the resulting solution was cooled to −78 °C. To this solution was added a freshly prepared solution of KHMDS in THF over 5 min via syringe pump (2.10 mL, 1 M, 2.10 mmol) and then stirred at this temperature for 1 h. Aldehyde **6** (0.806 g, 2.10 mmol) dried via azeotroping with toluene was diluted in THF (5 mL) and added over 5 min via syringe pump. The reaction was left to warm to room temperature over 16 h, quenched with sat. $NaCl_{aq}$ (~100 mL). After extraction with Et_2O (3×100 mL), drying with $MgSO_4$, and concentrating under reduced pressure, crude **33** was purified by automated chromatography (Biotage® SNAP HP-Sil, gradient 5% to 60%

EtOAc in hexanes) to provide **33**, a colorless oil (0.487 g, 61%). R_f = 0.81 (3:7 EtOAc, hexanes). $[\alpha]_D^{22}$ = +3.2 (*c* = 0.67, CH_2Cl_2). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.68−7.63 (m, 4H), 7.47−7.44 (m, 2H), 7.41−7.38 (m, 4H), 5.45−5.39 (m, 4H), 4.91 (d, *J* = 6.0 Hz, 1H), 4.53 (d, *J* = 6.1 Hz, 1H), 3.82 (app dd, *J* = 10.7, 5.0 Hz, 1H), 3.52 (app dt, *J* = 9.3, 4.7 Hz, 1H), 3.45 (app td, *J* = 8.5, 2.5 Hz, 1H), 3.32 (t, *J* = 10.3 Hz, 1H), 2.67 (d, *J* = 4.5 Hz, 2H), 2.61−2.58 (m, 1H), 2.09 (app dd, *J* = 9.8, 3.8 Hz, 1H), 1.68−1.67 (m, 3H), 1.06 (d, *J* = 5.4 Hz, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.08, 135.98, 133.8, 133.1, 131.7, 130.23, 130.17, 129.7, 128.0, 127.9, 126.2, 125.8, 93.5, 82.3, 71.6, 67.2, 35.9, 34.8, 27.2, 19.5, 18.2. FTIR (thin film) 2930, 2854, 1427, 1167, 1102, 960 cm^{-1}. HRMS (ESI) Calcd for $C_{27}H_{36}O_3Si$ $[M+NH_4]^+$: 454.2772, found 454.2778.

***tert*-Butyl(((4*S*,5*R*)-4-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-methyloxiran-2-yl)methyl)oxiran-2-yl)methyl)-1,3-dioxan-5-yl)oxy)diphenylsilane (34)—**To a solution of **33** (0.450 g, 1.03 mmol) in 2:1 v/v DMM:MeCN (38 mL) was added a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in 4 × 10^{-4} Na_2EDTA (20 mL), *n*Bu_4HSO_4 (0.062 g, 0.021 mmol), and Shi ketone (0.387 g, 1.50 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 60 min via syringe pump, a solution of Oxone (3.81 g, 12.40 mmol) in 4 × 10^{-4} Na_2EDTA (14.0 mL) and a 0.89 M solution of K_2CO_3 (14.0 mL, 12.40 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 4 h, at which point it was diluted with water (~200 mL). The aqueous layer was separated and extracted with EtOAc (3 × 200 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced. Analysis of the crude mixture determined that the epoxidation was incomplete and the crude epoxy alkene was resubjected to the identical reaction conditions. Following the second work up the crude epoxide **34** was purified by automated chromatography (Biotage® SNAP HP-Sil, gradient 1% to 30% EtOAc in hexanes) to provide **34**, a colorless oil, as an inseparable mixture of diastereomers (0.424 g of a ~6:1 mixture of diastereomers, 88%). Epoxide **34** could be purified further via a Biotage high performance silica gel column using benzene as the mobile phase (Biotage® SNAP HP-Sil, gradient 0% to 20% Et_2O in benzene). The two diastereomers co-spot by TLC, but early fractions are enriched in the minor diastereomer and late fractions are higher purity **34** (>10:1 dr by ^{1}H NMR). R_f = 0.44 (1:4 EtOAc, hexanes). $[\alpha]_D^{22}$ = 6.5 (*c* = 1.35, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.46−7.37 (m, 6H), 4.89 (d, *J* = 6.0 Hz, 1H), 4.54 (d, *J* = 6.1 Hz, 1H), 3.84 (app dd, *J* = 10.7, 3.5 Hz, 1H), 3.54 (app dd, *J* = 5.7, 3.8 Hz, 2H), 3.33 (d, *J* = 10.5 Hz, 1H), 2.83−2.76 (m, 4H), 1.95 (app dd, *J* = 5.9, 1.9 Hz, 1H), 1.74 (app dt, *J* = 6.0, 4.4 Hz, 2H), 1.67 (app dd, *J* = 7.0, 4.7 Hz, 1H), 1.32 (d, *J* = 5.0 Hz, 3H), 1.04 (s, 9H).. ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.05, 135.95, 133.6, 132.8, 130.37, 130.25, 128.10, 127.95, 93.3, 80.2, 71.6, 67.3, 56.8, 55.8, 55.0, 54.7, 35.3, 33.9, 27.2, 19.5, 17.8 FTIR (thin film) 2927, 2855, 1470, 1174, 1104, 1033, 945 cm^{-1}. HRMS (ESI) Calcd for $C_{27}H_{36}O_5Si$ $[M+NH_4]^+$: 486.2670, found 486.2684.

(4*S*,5*R*)-4-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-methyloxiran-2-yl)methyl)oxiran-2-yl)methyl)-1,3-dioxan-5-ol (35)—To a solution of silyl ether **34** (0.270 g, 0.620 mmol) in THF (1.00 μL) was added a 1 M solution of TBAF in THF (1.00 μL, 1.00 mmol) at 0 °C. The reaction solution was stirred at 0 °C for 30 min, then applied directly to a column of SiO_2 pretreated with 5% Et_3N in EtOAc (eluted with a gradient 20% to 100% EtOAc in hexanes) to yield **35** as a colorless oil (0.112 g, 78%). R_f = 0.65 (100% EtOAc). $[\alpha]_D^{22}$ = +23.2 (*c* = 0.75, CH_2Cl_2). ^{1}H NMR (500 MHz, C_6D_6) δ 4.99 (d, *J* = 6.1 Hz, 1H), 4.57 (d, *J* = 6.2 Hz, 1H), 4.15 (app dd, *J* = 10.8, 5.1 Hz, 1H), 3.68 (m, 1H), 3.45 (m, 1H), 3.32 (t, *J* = 10.4 Hz, 1H), 3.00 (m, 1H), 2.93−2.87 (m, 2H), 2.84−2.80 (m, 2H), 2.12 (dt, *J* = 15.0, 4.0 Hz, 1H), 1.30 (d, *J* = 9.0Hz, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 93.4, 79.8, 71.1, 65.4, 56.8,

55.65, 55.52, 55.0, 35.1, 34.4, 17.7. FTIR (thin film) 3413, 2923, 2855, 1437, 1174, 1073, 1027, 940 cm^{-1}. HRMS (ESI) Calcd for $C_{11}H_{18}O_5$ $[M+H]^+$: 231.1227, found 231.1232.

General Cyclization Protocols[24]

Representative procedure for reaction in water or buffered water—A sample of epoxy alcohol (5–10 mg, 0.03–0.06 μmol, >15:1 dr) was dissolved in deionized water to 0.02 M in a glass vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was stirred at the desired temperature and time. In the case of buffered reactions 0.1M phosphate buffer was used to control the pH of the reaction. Upon completion the solution was then washed out of the reaction vial with a large volume of MeOH (typically 6–8 washes of ~2 mL each) and concentrated under reduced pressure (2 torr, 40 °C). The combined yield was found and ratio of *endo:exo* products was determined by ^{1}H NMR or GC-FID following isolation of both products together after column chromatography (30% EtOAc in hexanes to 50% EtOAc in hexanes). Then the product mixture was again chromatographed to separate the *endo* product, 6,6-fused from the *exo* product, 6,5-fused product. In cases of difficult separation, acetylation of the free alcohol facilitated purification of the product mixtures.

Representative procedure for reaction promoted by Cs_2CO_3: A sample of epoxy alcohol (5–10 mg, 0.03–0.06 μmol, >15:1 dr) was dissolved in a solution of Cs_2CO_3 (30 equiv) in anhydrous MeOH to 0.02 M in a glass vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was stirred under air at rt for 1–2 d. The solution was then diluted with Et_2O, quenched with sat. NH_4Cl, and the aqueous layer was extracted with Et_2O. The combined organics were dried with $MgSO_4$ and concentrated under reduced pressure. The combined yield was found and ratio of *endo:exo* products was determined by ^{1}H NMR or GC-FID following isolation of both products together after column chromatography (30% EtOAc in hexanes to 50% EtOAc in hexanes). Then the product mixture was again chromatographed to separate the *endo* product, 6,6-fused from the *exo* product, 6,5-fused product. In cases of difficult separation, acetylation of the free alcohol facilitated purification of the product mixtures.

Representative procedure for reaction promoted by CSA—A sample of epoxy alcohol (5–10 mg, 0.03–0.06 μmol, >15:1 dr) was dissolved in CH_2Cl_2 to 0.02 M in an oven-dried round-bottom flask. To this was added (+/-)-CSA (1 equiv), and the solution was stirred under argon at rt for 4–15 h. The solution was then quenched with sat. $NaHCO_3$, and the aqueous layer was extracted with Et_2O and dried with $MgSO_4$. The combined organics were concentrated under reduced pressure. The combined yield was found and ratio of *endo:exo* products was determined by ^{1}H NMR or GC-FID following isolation of both products together after column chromatography (30% EtOAc in hexanes to 50% EtOAc in hexanes). Then the product mixture was again chromatographed to separate the *endo* product, 6,6-fused from the *exo* product, 6,5-fused product. In cases of difficult separation, acetylation of the free alcohol facilitated purification of the product mixtures.

Representative procedure for reaction promoted by BF_3•OEt_2: A sample of epoxy alcohol (5–10 mg, 0.03–0.06 μmol, >15:1 dr) was dissolved in CH_2Cl_2 to 0.02 M in an oven-dried round-bottom flask and cooled to −78 °C. To this was added, dropwise, a 0.1 M solution of BF_3•OEt_2 in CH_2Cl_2 (0.25 equiv), and the solution was stirred at −78 °C under argon for 30 min. The solution was then allowed to warm gradually to rt over 5 min. and quenched with sat. $NaHCO_3$. The aqueous layer was extracted with Et_2O and dried with $MgSO_4$. The combined organics were concentrated under reduced pressure. The combined yield was found and ratio of *endo:exo* products was determined by ^{1}H NMR or GC-FID following isolation of both products together after column chromatography (30% EtOAc in

hexanes to 50% EtOAc in hexanes). Then the product mixture was again chromatographed to separate the *endo* product, 6,6-fused from the *exo* product, 6,5-fused product. In cases of difficult separation, acetylation of the free alcohol facilitated purification of the product mixtures.

(4a*R*,6*S*,7*R*,8a*S*)-6-methylhexahydropyrano[3,2-*d*][1,3]dioxin-7-ol (8): Chiraldex™ G-TA 30 m x 0.25 mm x 0.12 μm film thickness, 125 °C 10 min, 2 °C/min to 150 °C, 10 °C/min to 180 °C, hold 10 min, T_R = 17.59 min. R_f = 0.65 (100% EtOAc). $[\alpha]_D^{22}$ = −8.8 (*c* = 0.15, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 (d, *J* = 6.2 Hz, 1H), 4.62 (d, *J* = 6.2 Hz, 1H), 4.18 (dd, *J* = 10.4, 4.2 Hz, 1H), 3.44−3.36 (m, 2H), 3.34−3.23 (m, 3H), 2.43 (app dt, *J* = 11.4, 4.3 Hz, 1H), 1.61 (app q, *J* = 11.2 Hz, 1H), 1.56 (s, 1H), 1.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 93.9, 78.8, 76.8, 73.5, 71.6, 69.4, 38.3, 18.0. FTIR (thin film, NaCl) 3365, 2963, 2923, 2862, 1463, 1401, 1349, 1279, 1211, 1161, 1118, 1075, 1059, 1024 cm^{-1}. HRMS (DART) Calcd for $C_8H_{14}O_4$ $(M+H)^+$: 175.0965, found 175.0967.

(*R*)-1-((4a*R*,6*S*,7a*S*)-tetrahydro-4*H*-furo[3,2-*d*][1,3]dioxin-6-yl)ethanol (9): Chiraldex™ G-TA 30 m x 0.25 mm x 0.12 μm film thickness, 125 °C 10 min, 2 °C/min to 150 °C, 10 °C/min to 180 °C, hold 10 min, T_R = 18.86 min. R_f = 0.53 (100% EtOAc). $[\alpha]_D^{22}$ = −17.9 (*c* = 0.045, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (d, *J* = 6.2 Hz, 1H), 4.63 (d, *J* = 6.2 Hz, 1H), 4.40 (dd, *J* = 9.7, 3.7 Hz, 1H), 4.07−4.00 (m, 2H), 3.58 (app t, *J* = 9.6 Hz, 1H), 3.48−3.40 (m, 2H), 2.23 (app dt, *J* = 11.1, 5.8 Hz, 1H), 2.09 (app dt, *J* = 11.1, 9.2 Hz, 1H), 1.86 (d, *J* = 3.8 Hz, 1H), 1.18 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 94.2, 81.8, 80.7, 73.8, 72.0, 69.1, 29.3, 18.2. FTIR (thin film, NaCl) 3450, 2921, 2851, 1463, 1256, 1155, 1126, 1053 cm^{-1}. HRMS (DART) Calcd for $C_8H_{14}O_4$ $(M+Na)^+$: 197.0784, found 197.0794.

4a*R*,7*R*,8a*S*)-6,6-dimethylhexahydropyrano[3,2-*d*][1,3]dioxin-7-ol (19a): R_f = 0.67 (100% EtOAc). $[\alpha]_D^{22}$ = 18.6 (*c* = 0.85, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.01 (d, *J* = 6.2 Hz, 1H), 4.62 (d, *J* = 6.2 Hz, 1H), 4.10 (app dd, *J* = 10.0, 4.5 Hz, 1H), 3.56 (app dt, *J* = 11.5, 5.2 Hz, 1H), 3.44 (app td, *J* = 9.5, 4.6 Hz, 1H), 3.38 (t, *J* = 10.0 Hz, 1H), 3.24 (app ddd, *J* = 11.8, 9.0, 4.3 Hz, 1H), 2.20 (app dt, *J* = 11.6, 4.5 Hz, 1H), 1.73 (m, 2H), 1.26 (d, *J* = 20.5 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 94.0, 77.7, 76.7, 73.3, 70.1, 66.9, 34.3, 27.7, 16.9. FTIR (thin film) 3481, 2980, 2943, 2862, 1461, 1369, 1166, 1101, 1074, 1022, 941 cm^{-1}. HRMS (ESI) Calcd for $C_9H_{16}O_4$ $(M+Na)^+$: 211.0941, found 211.0947.

2-((4a*R*,6*S*,7a*S*)-tetrahydro-4*H*-furo[3,2-*d*][1,3]dioxin-6-yl)propan-2-ol (20a): R_f = 0.59 (100% EtOAc). $[\alpha]_D^{22}$ = −13.1 (*c* = 0.21, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.10 (d, *J* = 6.2 Hz, 1H), 4.62 (d, *J* = 6.3 Hz, 1H), 4.41 (app dd, *J* = 9.7, 3.7 Hz, 1H), 3.93 (app dd, *J* = 9.8, 6.2 Hz, 1H), 3.3.59 (t, *J* = 9.6 Hz, 1H), 3.46−3.41 (m, 2H), 2.26−2.22 (m, 1H), 2.05−2.00 (m, 1H), 1.91 (s, 1H), 1.25 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 94.2, 83.9, 80.6, 73.9, 72.4, 72.1, 30.6, 26.6, 24.2. FTIR (thin film) 3479, 2976, 2924, 2872, 1376, 1157, 1128, 1063, 981 cm^{-1}. HRMS (ESI) Calcd for $C_9H_{16}O_4$ $(M+Na)^+$: 211.0941, found 211.0953.[25]

(*R*)-1-((4a*R*,6*S*,7a*S*)-6-methyltetrahydro-4*H*-furo[3,2-*d*][1,3]dioxin-6-yl)ethanol (20b): R_f = 0.55 (100% EtOAc). $[\alpha]_D^{22}$ = −17.9 (*c* = 0.42, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.08 (d, *J* = 6.2 Hz, 1H), 4.61 (d, *J* = 6.2 Hz, 1H), 4.41 (app dd, *J* = 9.6, 4.2 Hz, 1H), 3.63−3.59 (m, 2H), 3.50 (app tdd, *J* = 9.5, 4.3, 1.0 Hz, 1H), 3.36 (app td, *J* = 9.5, 7.9 Hz, 1H), 2.26 (app ddd, *J* = 11.7, 7.6, 0.8 Hz, 1H), 2.16 (br s, 1H), 1.74 (t, *J* = 10.9 Hz,1H), 1.31 (s, 3H), 1.18−1.16 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 94.2, 85.1, 80.7, 73.3, 72.4, 71.8, 38.6, 22.0, 17.7. FTIR (thin film) 3473, 2978, 2874, 1452, 1374, 1270,

1129, 1061, 1000, 904 cm^{-1}. HRMS (ESI) Calcd for $C_9H_{16}O_4$ $(M+Na)^+$: 209.0784, found 209.0791.

((4a*R*,6*S*,7a*S*)-6-methyltetrahydro-4*H*-furo[3,2-*d*][1,3]dioxin-6-yl)methanol (28): R_f = 0.56 (100% EtOAc). $[\alpha]_D^{22}$ = −33.0 (*c* = 0.36, CH_2Cl_2). ^1H NMR (600 MHz, $CDCl_3$) δ 5.09 (d, *J* = 6.3 Hz, 1H), 4.62 (d, *J* = 6.3 Hz, 1H), 4.40 (dd, *J* = 9.6, 4.2 Hz, 1H), 3.62 (t, *J* = 9.8 Hz, 1H), 3.53−3.49 (m, 2H), 3.46−3.41 (m, 2H), 2.34 (dd, *J* = 11.5, 7.5 Hz, 1H), 1.89 (dd, *J* = 7.8, 5.4 Hz, 1H), 1.80 (t, *J* = 11.1 Hz 1H), 1.34 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 94.3, 83.1, 80.9, 72.7, 71.7, 69.6, 38.2, 24.4. FTIR (thin film) 3388, 2972, 2871, 1453, 1373, 1277, 1151, 1129, 1050 cm^{-1}. HRMS (DART) Calcd for $C_8H_{14}O_4$ $(M+Na)^+$: 197.0784, found 197.0786.

((4a*R*,6*S*,7a*S*)-tetrahydro-4*H*-furo[3,2-*d*][1,3]dioxin-6-yl)methanol (30): R_f = 0.53 (100% EtOAc). $[\alpha]_D^{22}$ = −40.8 (*c* = 0.36, CH_2Cl_2). ^1H NMR (600 MHz, $CDCl_3$) δ 5.10 (d, *J* = 6.3 Hz, 1H), 4.63 (d, *J* = 6.3 Hz, 1H), 4.43 (app dd, *J* = 9.7, 4.0 Hz, 1H), 4.30 (app ddt, *J* = 9.6, 4.9, 3.2 Hz, 1H), 3.77 (app ddd, *J* = 11.9, 5.6, 3.1 Hz, 1H), 3.65−3.62 (m, 1H), 3.57 (app ddd, *J* = 12.0, 7.0, 5.0 Hz, 1H), 3.42−3.35 (m, 2H), 2.16−2.07 (m, 2H), 1.81 (app dd, *J* = 6.9, 5.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 94.3, 80.2, 77.8, 74.3, 71.7, 65.3, 30.8. FTIR (thin film) 3435, 2871, 1259, 1158, 1126, 1044, 932, 901 cm^{-1}. HRMS (ESI) Calcd for $C_7H_{12}O_4$ $(M+Na)^+$: 183.0628, found 183.0638.

(4a*R*,5a*S*,7*R*,8*S*,9a*R*,10a*S*)-8-methyloctahydro-4*H*-pyrano[2',3':5,6]pyrano[3,2-*d*][1,3]dioxin-7-ol (36): As per the general procedure in buffered or unbuffered water except that the mixture was left to stir for five days at 70 °C to ensure complete cyclization. Cyclizations performed on 15 mg of alcohol starting material. R_f = 0.48 (100% EtOAc). $[\alpha]_D^{22}$ = −6.1 (*c* = 0.30, CH_2Cl_2). ^1H NMR (600 MHz, $CDCl_3$) δ 5.02 (d, *J* = 6.2 Hz, 1H), 4.63 (d, *J* = 6.2 Hz, 1H), 4.18 (app dd, *J* = 10.4, 4.3 Hz, 1H), 3.43 (t, *J* = 10.0 Hz, 1H), 3.40−3.11 (m, 6H), 2.39 (app ddt, *J* = 11.8, 8.4, 3.9 Hz, 2H), 1.63 (dd, *J* = 22.1, 11.0 Hz, 2H), 1.31 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 94.0, 78.7, 77.19, 77.07, 76.5, 73.9, 71.6, 69.2, 38.5, 35.0, 18.0. FTIR (thin film) 3379, 2928, 2872, 1452, 1164, 1116, 1079, 1031 cm^{-1}. HRMS (ESI) Calcd for $C_{11}H_{18}O_5$ $(M+H)^+$: 231.1227, found 231.1234. Chemical shifts for the dioxane methylene protons, as well at the terminal CH_3 indicates an all 6,6,6 system.

(*R*)-1-((4a*R*,5a*S*,7*S*,8a*R*,9a*S*)-octahydrofuro[2',3':5,6]pyrano[3,2-*d*][1,3]dioxin-7-yl)ethanol (37): R_f = 0.40 (100% EtOAc). $[\alpha]_D^{22}$ = −7.0 (*c* = 0.30, CH_2Cl_2). ^1H NMR (600 MHz, $CDCl_3$) δ 5.04 (d, *J* = 6.2 Hz, 1H), 4.61 (d, *J* = 8.1 Hz, 1H), 4.23 (app dd, *J* = 10.2, 4.3 Hz, 1H), 4.12−4.09 (m, 1H), 4.02 (td, *J* = 6.2, 3.1 Hz, 1H), 3.51−3.42 (m, 3H), 3.34−3.30 (m, 1H), 2.55 (dt, *J* = 10.6, 3.9 Hz, 1H), 2.12 (dt, *J* = 11.5, 5.9 Hz, 1H), 2.00 (t, *J* = 10.4 Hz, 1H), 1.92 (d, *J* = 3.2 Hz, 1H), 1.70 (q, *J* = 11.1 Hz, 1H), 1.15 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 94.2, 82.1, 81.5, 77.7, 75.0, 73.7, 69.37, 69.21, 35.2, 28.7, 18.1 FTIR (thin film) 3436, 2927, 2876, 1449, 1163, 1108, 1076, 1020 cm^{-1}. HRMS (ESI) Calcd for $C_{11}H_{18}O_5$ $(M+H)^+$: 231.1227, found 231.1231. Chemical shifts for the dioxane methylene protons, as well at the terminal CH_3 indicates an all 6,6,5 system.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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24. Acetylation of alcohol and COSY analysis performed when needed to confirm the cyclization adduct. See supporting information for details.

25. An attempt to oxidize **20a** with TPAP (5 mol %) and NMO (1.5 equiv) led to recovered starting material, confirming the presence of the tertiary alcohol.

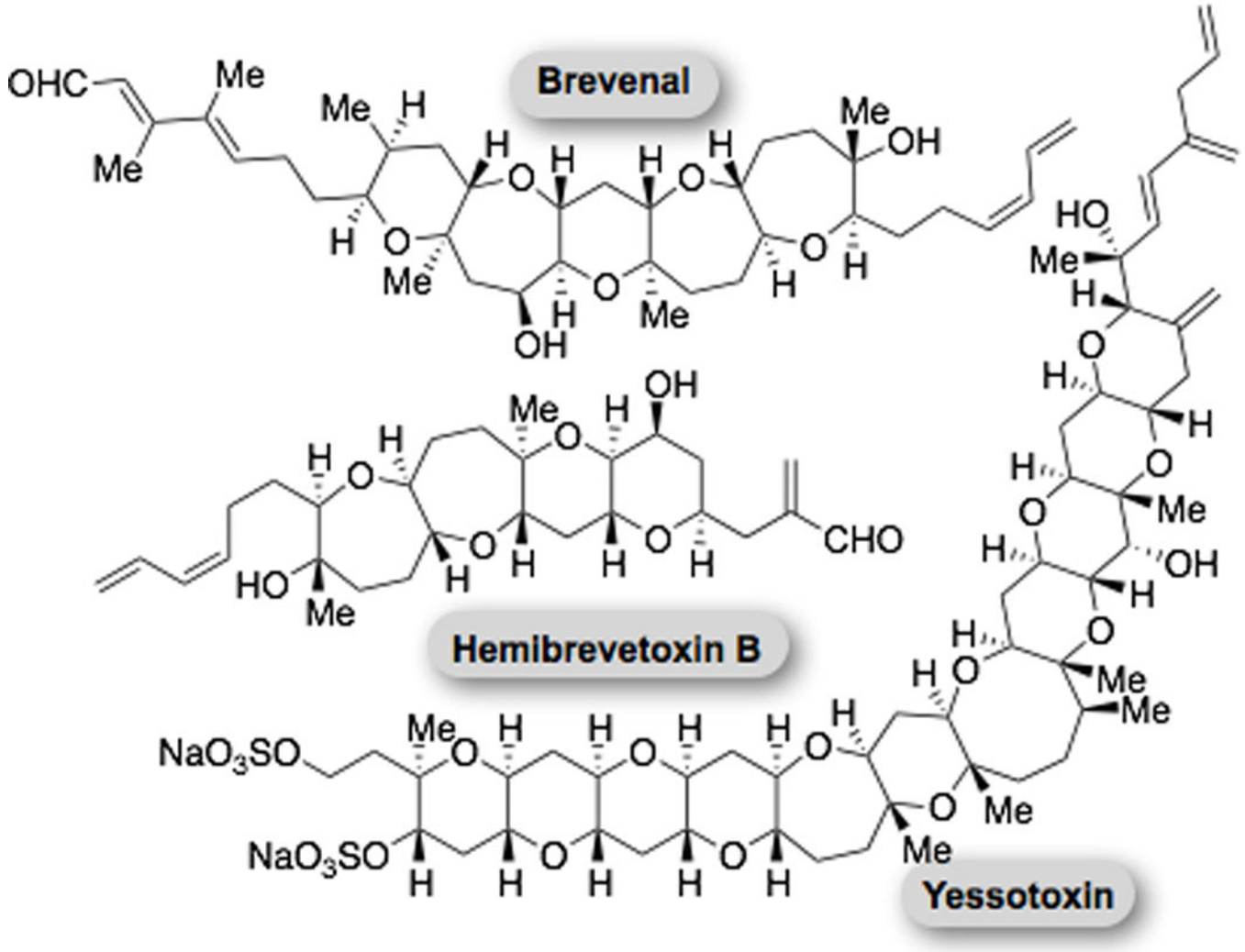


Figure 1.
Selected examples of ladder polyether containing marine natural products.

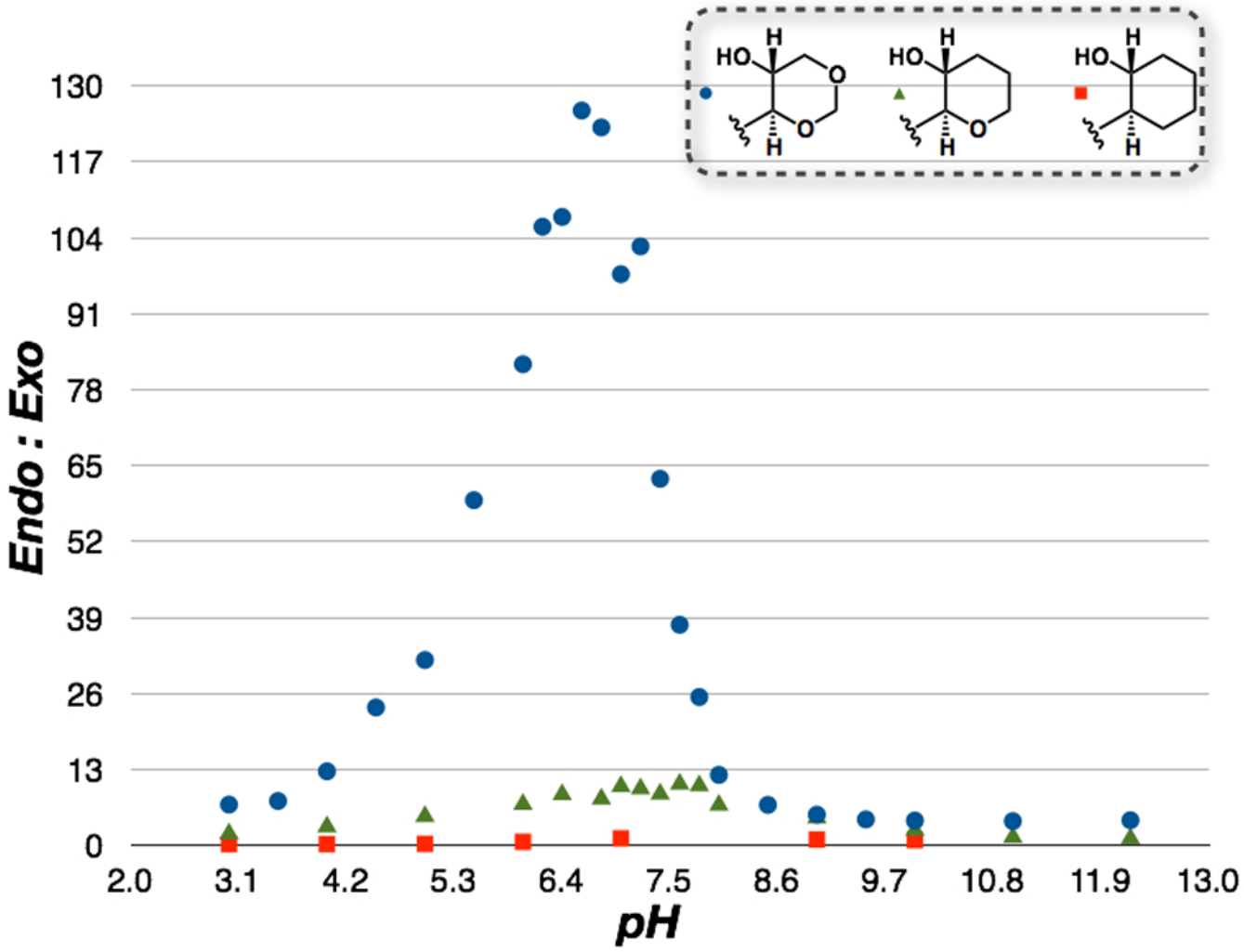
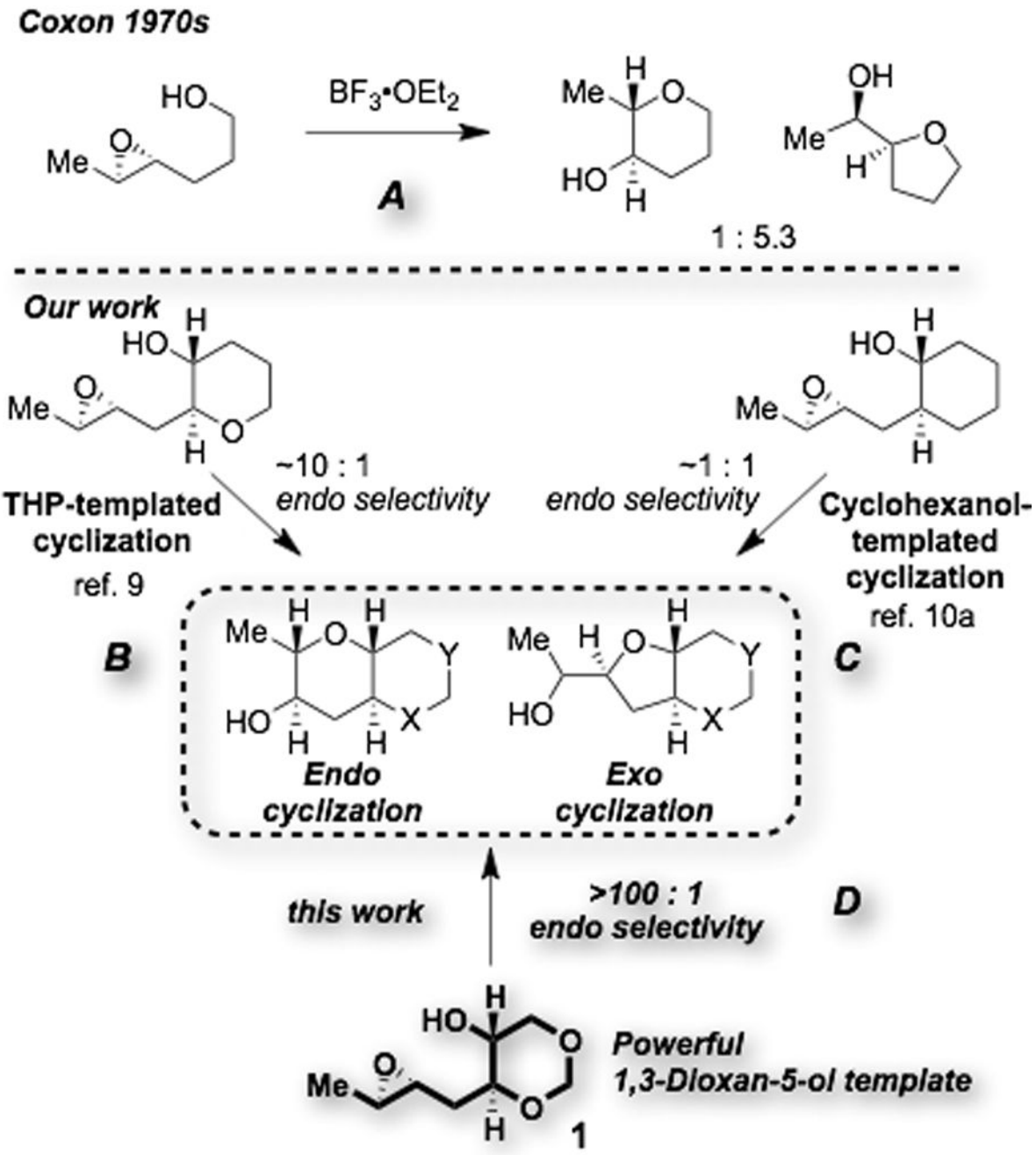
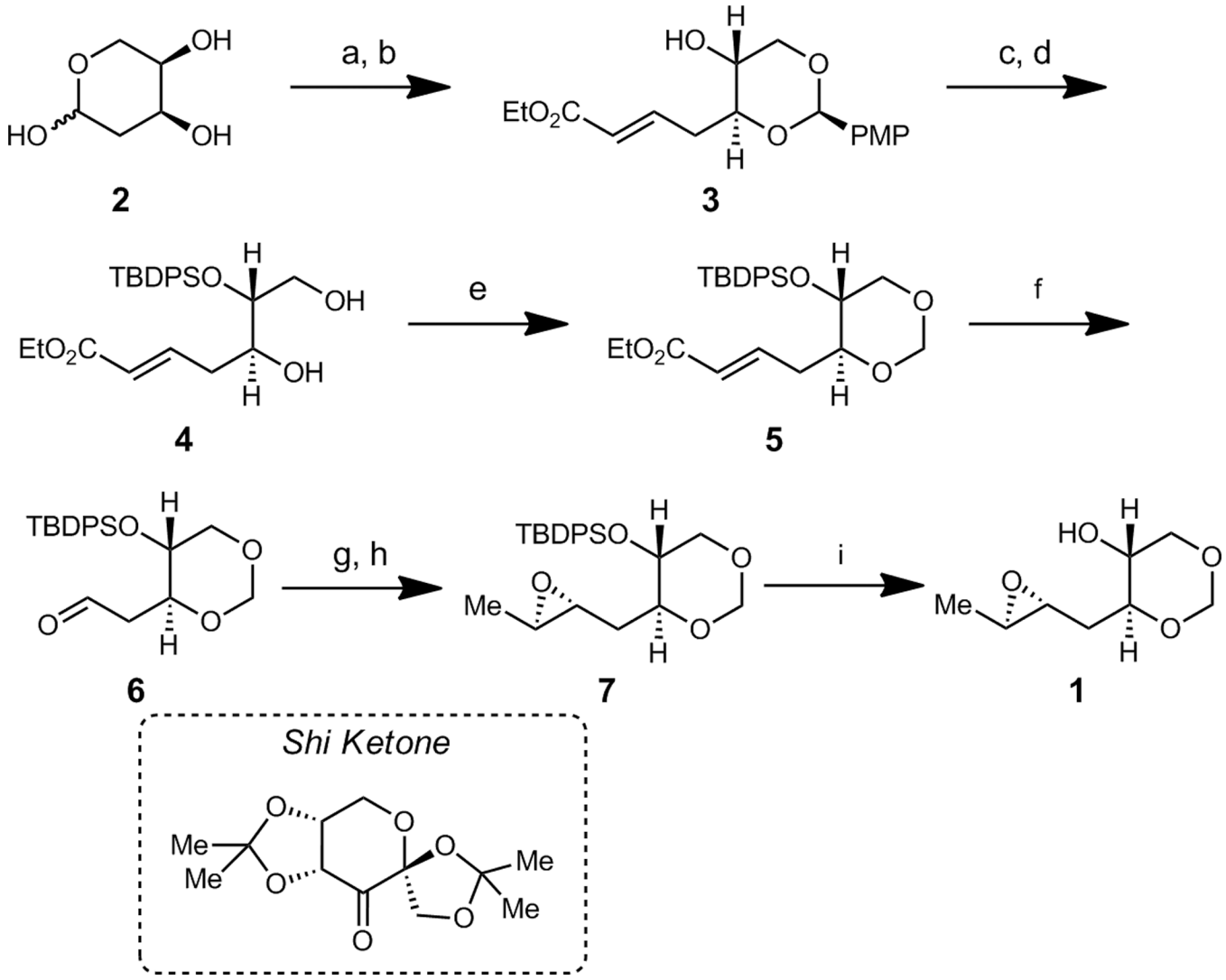


Figure 2.
Dependence of regioselectivity upon pH.

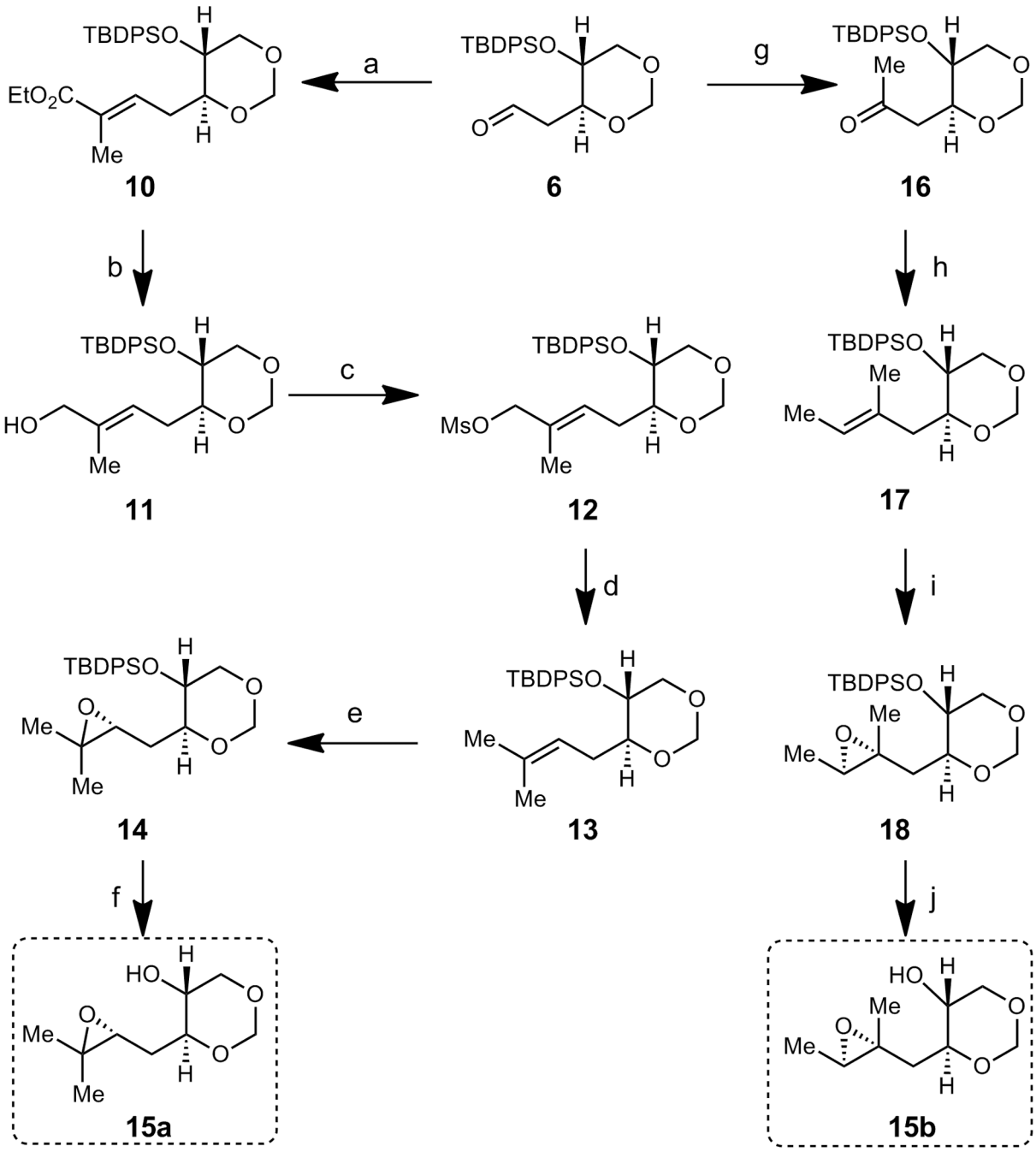


Scheme 1.
Templated cyclizations of epoxy alcohols.



Scheme 2.

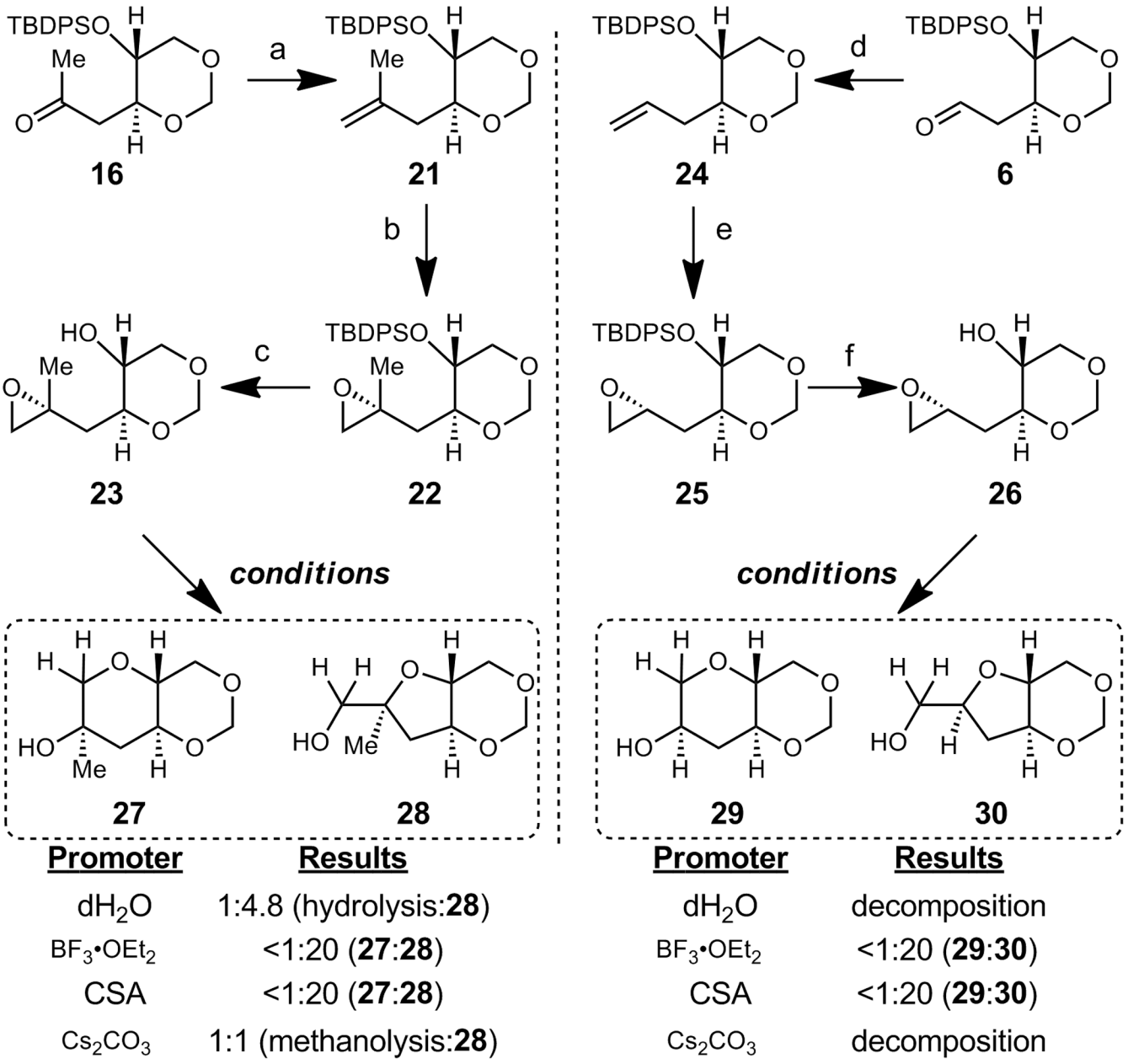
Synthesis of epoxy alcohol **1**. Reagents and conditions: a) $Ph_3P{=}CHCO_2Et$, THF, 70 °C; b) *p*-anisaldehyde dimethyl acetal, CSA, CH_2Cl_2, rt, 70% over 2 steps; c) TBDPSCl, imid., DMF, rt; d) *p*TSA, CH_2Cl_2, 70 °C, 86% over 2 steps; e) DMM, $BF_3{\bullet}OEt_2$, CH_2Cl_2, rt, 78%; f) O_3, CH_2Cl_2, −78 °C, 93%; g) CH_3CHI_2, $CrCl_2$, THF, rt, 80%; h) Shi ketone, Oxone®, K_2CO_3, *n*Bu_4NHSO_4, $Na_2B_4O_7{\bullet}10H_2O$, Na_2EDTA, 2:1 DMM:CH_3CN, −5 °C → 0 °C, 72%; i) TBAF, THF, rt, 89%. CSA=camphorsulfonic acid, TBDPS=*tert*-butyldiphenylsilyl, *p*TSA= *para*-toluenesulfonic acid, DMM=dimethoxymethane, TBAF= tetrabutylammonium fluoride, EDTA = ethylenediaminetetraacetic acid.



Scheme 3.

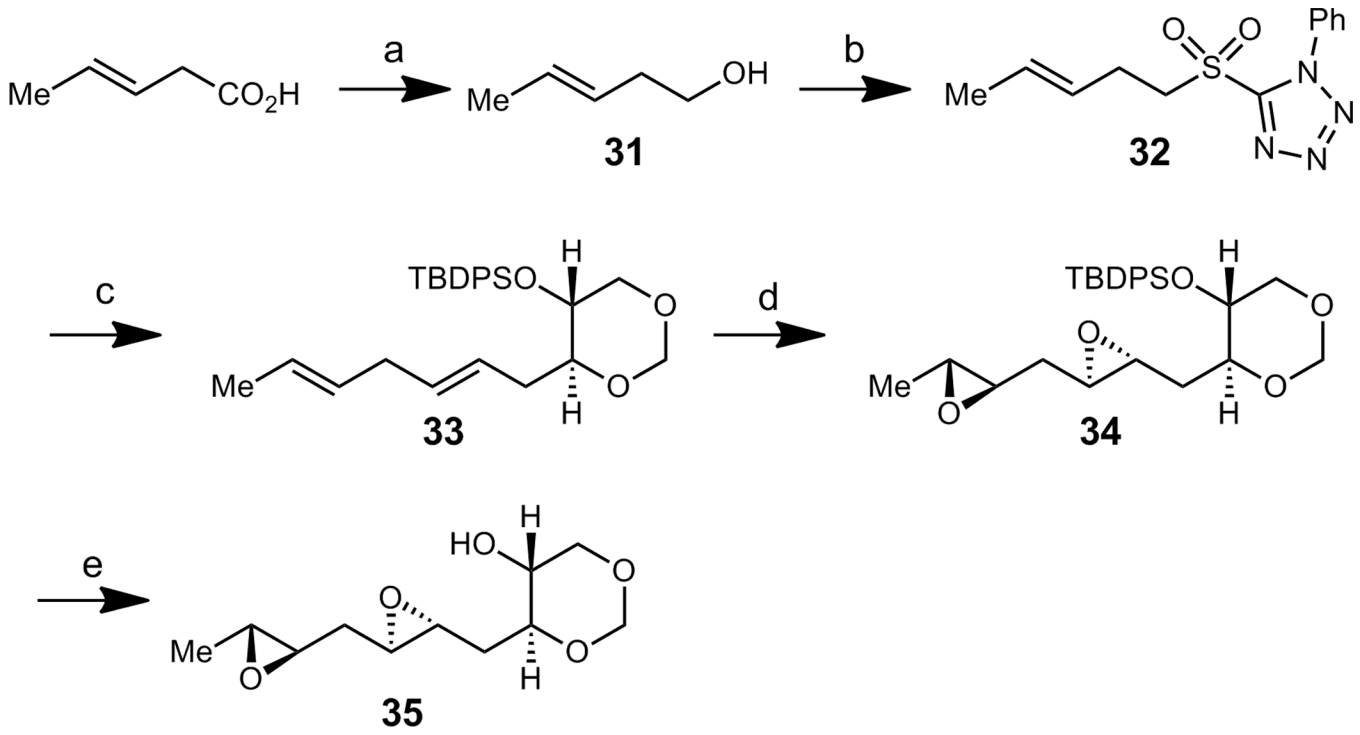
Synthesis of trisubstituted epoxides. Reagents and conditions: a) $Ph_3P{=}CMeCO_2Et$, CH_2Cl_2, rt, 89%; b) DIBAL-H, PhMe, −78 °C → rt, 72%; c) MsCl, Et_3N, $Me_3N{\bullet}HCl$, toluene, 0 °C, 78%; d) LAH, Et_2O, 0 °C, 49%; e) Shi ketone, Oxone®, K_2CO_3, *n*Bu_4NHSO_4, $Na_2B_4O_7{\bullet}10H_2O$, Na_2EDTA, 2:1 DMM:CH_3CN, −5 °C → 0 °C, 86%; f) TBAF, THF, rt, 58%; g) MeMgBr, Et_2O, 0 °C then TPAP, NMO, CH_2Cl_2, rt, 60% over 2 steps; h) $Ph_3PEt^+Br^-$ *n*BuLi, THF, −78 °C → rt, 71%; i) Shi ketone, Oxone®, K_2CO_3, *n*Bu_4NHSO_4, $Na_2B_4O_7{\bullet}10H_2O$, Na_2EDTA, 2:1 DMM:CH_3CN, −5 °C → 0 °C, 91%; j) TBAF, THF, rt, 90%. DIBAL=diisobutyl aluminum, NMO=*N*-methylmorpholine *N*-oxide, TPAP=

tetrapropylammonium perruthenate, LAH=lithium aluminum hydride, MsCl=methanesulfonyl chloride.



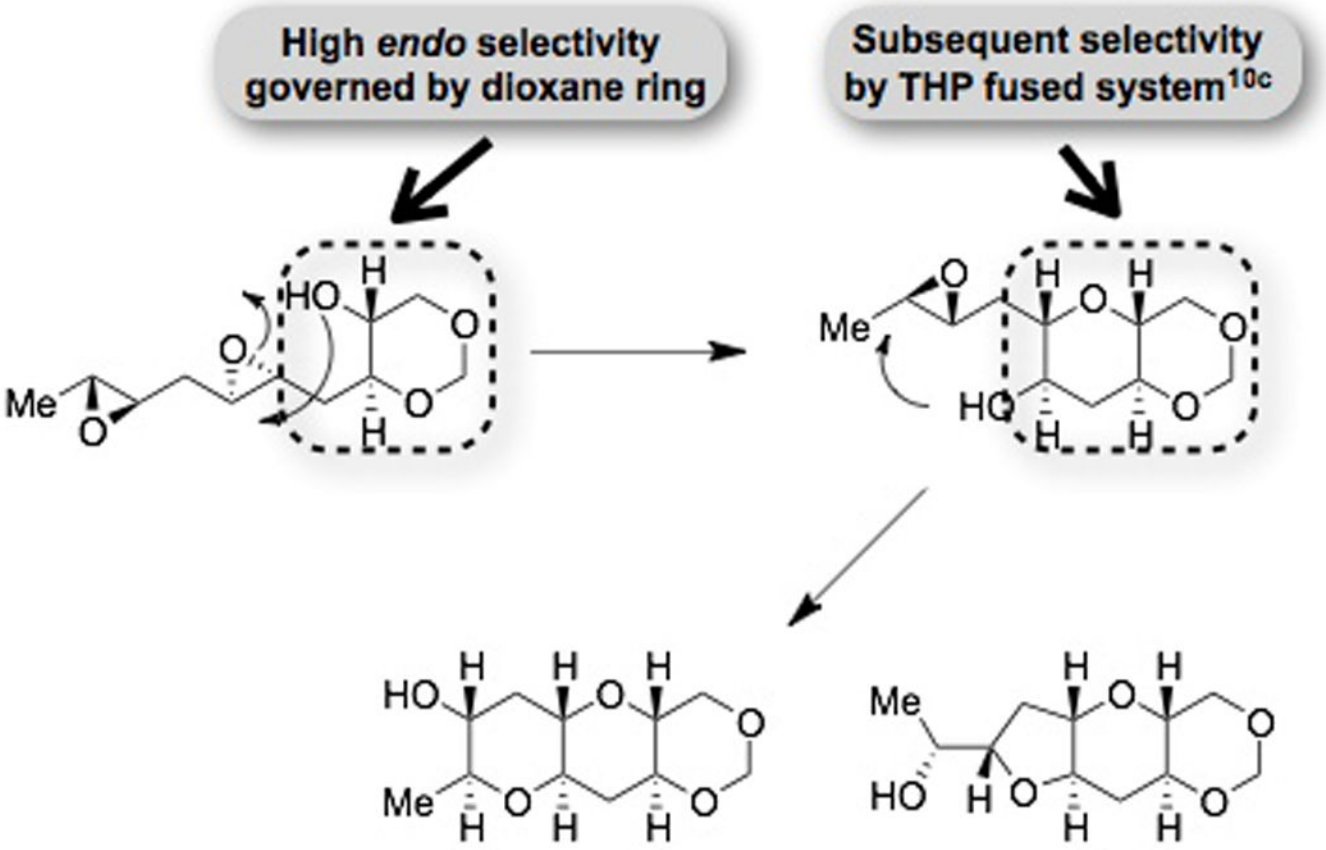
Scheme 4.

Synthesis and cyclization of terminal epoxides. Reagents and conditions: a) $Ph_3PMe^+Br^-$, *n*-BuLi, THF, −78 °C → rt, 94%; b) Shi ketone, Oxone®, K_2CO_3, nBu_4NHSO_4, $Na_2B_4O_7•10H_2O$, Na_2EDTA, 2:1 DMM:CH_3CN, −5 °C → 0 °C, 89%; c) TBAF, THF, rt, 95%; d) $Ph_3PMe^+Br^-$, *n*BuLi, THF, −78 °C → rt, 87%; e) Shi ketone, Oxone®, K_2CO_3, nBu_4NHSO_4, $Na_2B_4O_7•10H_2O$, Na_2EDTA, 2:1 DMM:CH_3CN, −5 °C → 0 °C, 87%; f) TBAF, THF, rt, 69%.

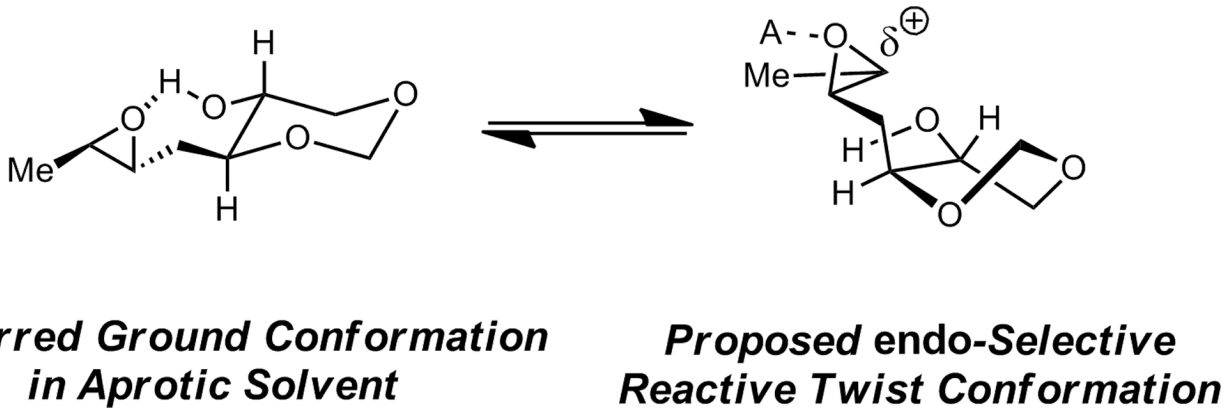


Scheme 5.

Synthesis of diepoxide **35**. Reagents and conditions: a) DIBAL-H, CH_2Cl_2, −78 °C, 65%; b) 1-phenyltetrazole-5-thiol, DIAD, PPh_3, THF, rt, then H_2O_2, $(NH_4)_6Mo_7O_{24}$, CH_3CH_2OH, rt, 93%; c) **6**, KHMDS, DMPU, THF, −78 °C → rt, 61% (85% brsm); d) Shi ketone, Oxone®, K_2CO_3, *n*Bu_4NHSO_4, $Na_2B_4O_7$•$10H_2O$, Na_2EDTA, 2:1 DMM:CH_3CN, −5 °C → 0 °C, 88%; e) TBAF, THF, rt, 78%. DIBAL=diisobutylaluminium, DIAD=diisopropyl azodicarboxylate, HMDS=hexamethyldisilazide, DMPU=*N,N*'-dimethylpropylene urea.



Scheme 6.
Proposed order of selectivity for cascade cyclizations.

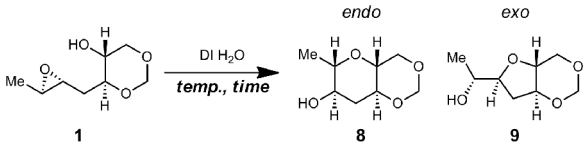


Preferred Ground Conformation in Aprotic Solvent ***Proposed* endo-*Selective Reactive Twist Conformation***

Scheme 7.
Proposed selectivity model of epoxy alcohol **1**.

Table 1

Cyclization of 1,3-dioxane alchohol **1**.



Entry[a]	Temp. (°C)	Time	Ratio 8 : 9[b]	Yield (%)[c]
1	22	35 d	14.1 : 1	62
2	40	4 d	14.6 : 1	49
3	55	2 d	19.9 : 1	54
4	70	16 h	19.4 : 1	57
5	100	12 h	19.8 : 1	62
6	125	4 h	34.8 : 1	66

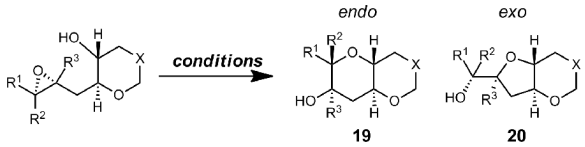
[a] All reactions were performed at 0.02 M and carried to >98% conversion.

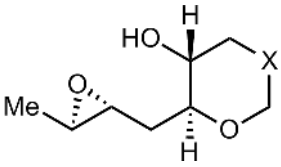
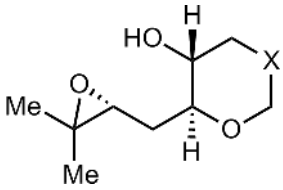
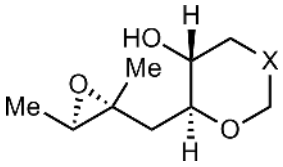
[b] Ratios were determined by GC using dodecane as an external standard.

[c] Isolated yield of combined products.

Table 2

Effects of epoxide substitution on *endo* selectivity.



Conditions				
		X=O, 1	**X=O, 15a**	**X=O, 15b**
dH_2O[a]	X=O	**19.4:1**[e]	>**20:1**[f]	---[g]
	X=CH_2[11b]	10.0:1[f]	>20:1[f]	4.9:1[f]
BF_3[b]	X=O	>**200:1**[e]	>**20:1**[f]	<**1:20**[f]
	X=CH_2[11b]	1.4:1[f]	>20:1[f]	1:11.0[f]
CSA[c]	X=O	**4.2:1**[e]	>**20:1**[f]	<**1:20**[f]
	X=CH_2[11b]	1:1.2[f]	5.8:1[f]	1:5.2[f]
Cs_2CO_3[d]	X=O	**4.6:1**[e]	**1:2.9**[f]	---[h]
	X=CH_2[11b]	1:2.7[f]	1:17.0[f]	3.0:1[f]

[a] Performed at 0.02 M, 70 °C, 16 h.

[b] 0.25 equiv BF_3•OEt_2, DCM, 0.02 M, −78 °C, 0.5 h.

[c] 1.0 equiv CSA, DCM, 0.02 M, rt, 4 h

[d] 30 equiv Cs_2CO_3, MeOH, 0.02 M, rt, 16 h.

[e] Ratios were determined by GC using dodecane as an external standard.

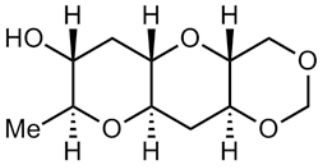
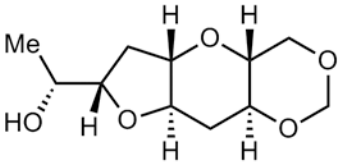
[f] Ratios determined by ^1H NMR.

[g] A 7.8:1 mixture of **15b:20b** was obtained. *Endo* product (**19b**) not observed.

[h] A 2.7:1 mixture of **15b:20b** was obtained. *Endo* product (**19b**) not observed.

Table 3

Cyclization ratios for diepoxide **35**.

Entry	Promoter	 **36**	 **37**	Yield (%)[a]
1	DI H_2O[b]	1	n/a	50
2	pH 7.0 buffer[c]	1	n/a	54
3	Cs_2CO_3[d]	1.4	1	75
4	CSA[e]	2.5	1	85

[a]Yield of isolated product.

[b]Reaction performed in DI H_2O [0.02 M] at 70 °C for 5 d.

[c]Reaction performed in KP*i* buffer pH 7.0 [0.02 M] at 70 °C for 5 d.

[d]Reaction performed in MeOH at rt for 3 d.

[e]Reaction performed in CH_2Cl_2 at rt for 3 d.