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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 analogs 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 favoring 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 · epoxides · polyethers · regioselectivity · template synthesis

## Introduction

Developing new means to effect 6-*endo* cyclization processes remains a relevant synthetic challenge owing to an inherent preference for the 5-*exo* adduct, as predicted by Baldwin's rules. Such transformations are particularly pertinent in the construction of marine ladder polyethers. These products continue to garner much interest owing to their innate structural complexity, their potential as anti-cancer and antibacterial agents (Figure 1),[1] as well as their undesirable environmental and economic consequences, such as harmful algal blooms.[2] It has been proposed by the research groups of Nakanishi,[2b,3] Shimizu,[4] and Nicolaou[5] that Nature may construct these elaborate structures through 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 the research group of Coxon in the 1970 s (Scheme 1, **A**).[6–8]

In prior investigations, we observed highly *endo*-selective epoxide-opening cyclizations templated by a preformed tetrahydropyran (THP) ring and promoted by neutral water (Scheme 1, **B**).[9,10] The presence of the oxygen atom 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] Howev-

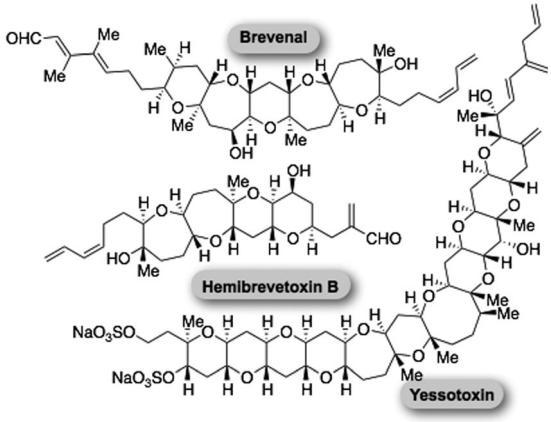


Figure 1. Selected examples of ladder-polyether-containing marine natural products.

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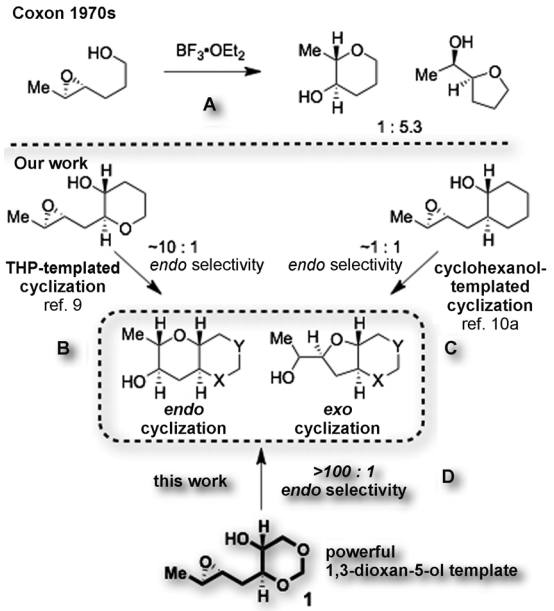


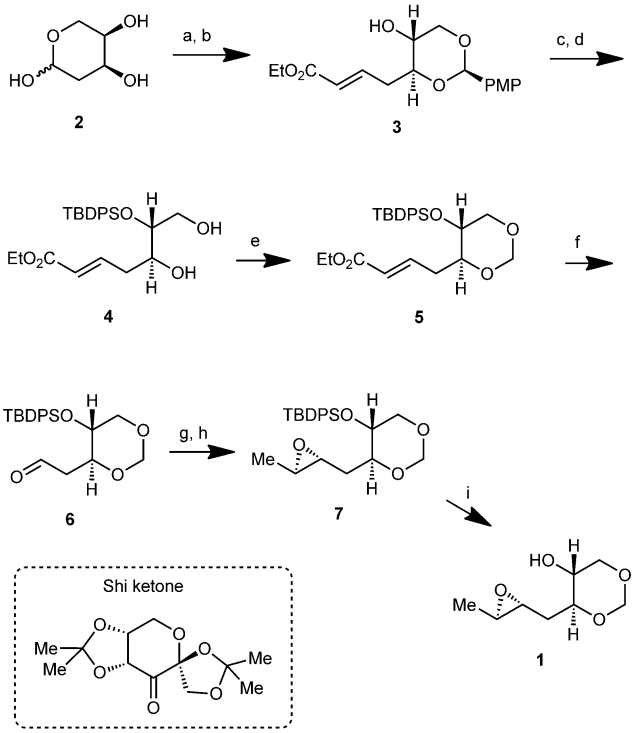

Scheme 1. Templated cyclizations of epoxy alcohols.

er, the sensitivity to hydrolysis of this benzylidene acetal under Lewis acidic and aqueous conditions precluded a comparison with our previous system. We herein report that 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 reaction conditions. We believe that these observations have important implications for the mechanism of *endo*-selective epoxide-opening cyclizations and that the stability of this template makes it well suited for use in target-directed synthesis.

## Results and Discussion

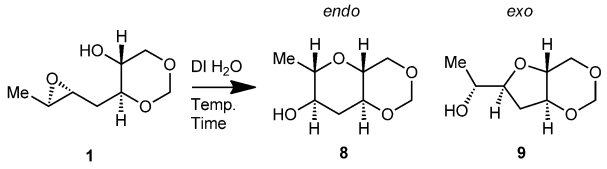
Employing a chiron-based approach,[13] the synthesis of **1** began with a Wittig olefination of 2-deoxy-D-ribose (**2**) followed by selective 1,3 protection to form PMP acetal **3** (Scheme 2).[14] The free secondary alcohol was masked as its TBDPS ether and the PMP group removed to afford diol **4**.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

We compared the selectivity of cyclization in $H_2O$ relative to that previously disclosed for the THP template. When cyclizations were performed in deionized water (DI $H_2O$) under ambient conditions, the endo/exo products were formed in the ratio, 14:1 (Table 1, entry 1). Although this is an improvement on the 10:1 selectivity previously found with the THP ring,[9] the rate of reaction was significantly




Scheme 2. Synthesis of epoxy alcohol **1**. Reagents and reaction 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, imidazole, DMF, RT; d) *p*TSA, $CH_2Cl_2$, 70 °C, 86% over 2 steps; e) DMM, $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, RT, 78%; f) $O_3$, $CH_2Cl_2$, −78 °C, 93%; g) $CH_3CHI_2$, $CrCl_2$, THF, RT, 80%; h) Shi ketone, Oxone, $K_2CO_3$, $n Bu_4NHSO_4$, $Na_2B_4O_7{\cdot}10H_2O$, $Na_2EDTA$, 2:1 DMM/$CH_3CN$, −5 °C to 0 °C, 72%; i) TBAF, THF, RT, 89%. CSA = camphorsulfonic acid, DMF = *N*,*N*-dimethylformamide, DMM = dimethoxymethane, EDTA = ethylenediaminetetraacetic acid, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, *p*TSA = *para*-toluenesulfonic acid.

Table 1. Cyclization of 1,3-dioxane alcohol **1**.




| Entry[a] | Temp. [°C] | Time | **8**/**9**[b] | Yield [%][c] |
|---|---|---|---|---|
| 1 | 22 | 35 days | 14.1:1 | 62 |
| 2 | 40 | 4 days | 14.6:1 | 49 |
| 3 | 55 | 2 days | 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 greater than 98% conversion. [b] Ratios were determined by GC using dodecane as an external standard. [c] Yield of combined isolated products.

lower, requiring over a month to reach completion. Presumably this is due to the presence of an additional inductively withdrawing oxygen atom, thus decreasing the nucleophilicity of the hydroxyl group. However, conducting the reaction at a higher reaction temperatures not only led to a faster reaction (Table 1, entries 2–6), but also afforded modest improvements in site selectivity for the *endo* product, the ratios being 20:1 and 35:1 for the reactions conducted at 100 °C and 125 °C, respectively (Table 1, entry 5 and 6). This phenomenon is unique to this template as such effects were not observed with the previously investigated THP systems. Both cyclization products derived 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 reaction conditions. Other ramifications of the higher reaction temperature include a lower pH value of the (unbuffered) water[16] and a higher ionic strength of the medium. Either of these ramifications could modulate selectivity by facilitating proton transfer during cyclization, in addition to stabilizing charged transition-state intermediates. This combination may be more relevant for this system. Lastly, reactions performed in polypropylene tubes at 70 °C (not shown) furnished a 24.1:1 preference of **8** thus demonstrating that $SiO_2$ in the glass of the reaction vessels was not responsible for promoting the high *endo* selectivity.

Accordingly, we next explored the effect of the pH value on the selectivity of cyclization (Figure 2).[9] In potassium-phosphate-based buffered solutions (0.1 M) with a near neutral pH value, the selectivity increased by nearly an order of magnitude relative to that of the THP template and by two orders of magnitude relative to that of the cyclohexanol-based template (Scheme 1, **C**; Figure 2). The ratio, **8**/**9**, reached a maximum of 126:1 at pH 6.8, thus reprising a trend of optimum site selectivity near neutral pH values. Remarkably, even at low and high pH values (3.0 and 12.2), the *endo*/*exo* levels of selectivity were 7.0:1 and 4.3:1, respectively. This preference for *endo* cyclization processes under such reaction conditions is unprecedented; several other templates we have examined were deemed nonselective (ca. 1:1).[9]

To gain insight into this unique and near-perfect *endo* regioselectivity, we prepared trisubstituted epoxy alcohols from aldehyde **6** (Scheme 3). Epoxy alcohol **15a** was prepared through olefination of **6** by using a stabilized Wittig reagent, followed by complete reduction of the ester (compounds **11**–**13**). Notably, Wittig olefination with isopropyltriphenylphosphonium iodide to furnish **13** directly from **6** led to the product being isolated in poor yield and was thus not amenable to scale up. Shi epoxidation of **13** and removal of the TBDPS group furnished **15a**. In parallel, methyl ketone

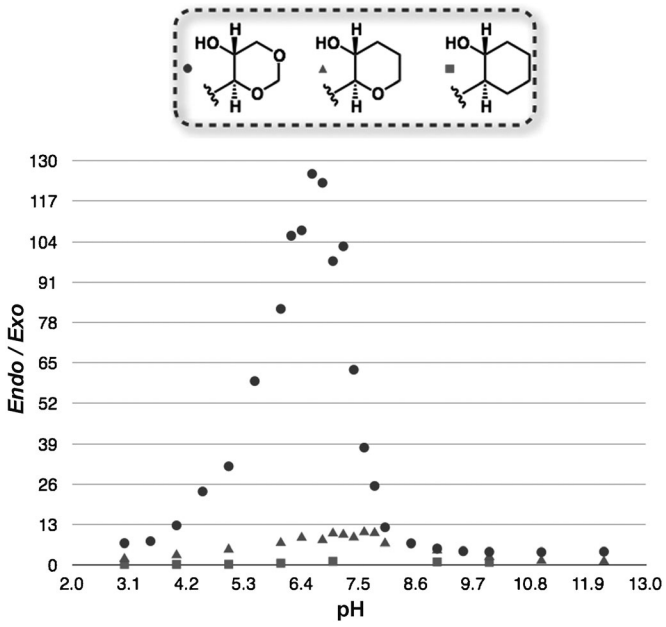
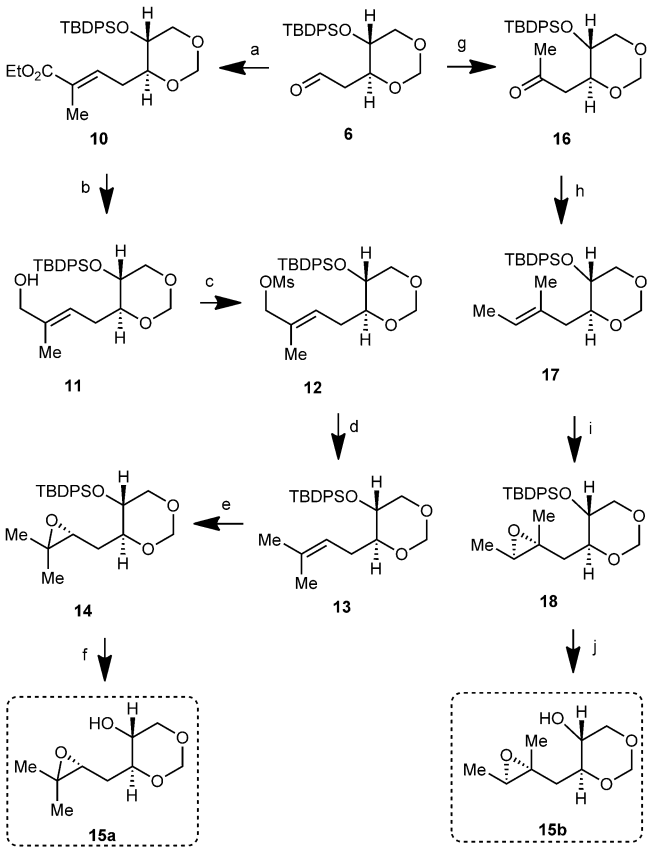



Figure 2. Dependence of regioselectivity upon pH value.



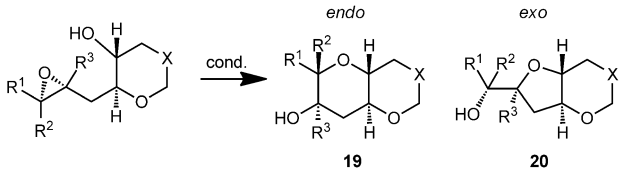

Scheme 3. Synthesis of trisubstituted epoxides. Reagents and reaction conditions: a) $Ph_3P{=}CMeCO_2Et$, $CH_2Cl_2$, RT, 89%; b) DIBAL-H, PhMe, −78 °C to RT, 72%; c) MsCl, $Et_3N$, $Me_3N{\cdot}HCl$, toluene, 0 °C, 78%; d) LAH, $Et_2O$, 0 °C, 49%; e) Shi ketone, Oxone, $K_2CO_3$, $nBu_4NHSO_4$, $Na_2B_4O_7{\cdot}10H_2O$, $Na_2EDTA$, 2:1 DMM/$CH_3CN$, −5 °C to 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 to RT, 71%; i) Shi ketone, Oxone, $K_2CO_3$, $nBu_4NHSO_4$, $Na_2B_4O_7{\cdot}10H_2O$, $Na_2EDTA$, 2:1 DMM/$CH_3CN$, −5 °C to 0 °C, 91%; j) TBAF, THF, ET, 90%. DIBAL = diisobutyl aluminum, LAH = lithium aluminum hydride, MsCl = methanesulfonyl chloride, NMO = *N*-methylmorpholine *N*-oxide, TPAP = tetrapropylammonium perruthenate.

**16** was subjected to Wittig conditions to provide alkene **17** in greater than 9:1 *E*/*Z* ratio. Again, this was followed by epoxidation (giving **18**) and protecting-group removal, thus revealing epoxy alcohol **15b**.

Alcohols **15a** and **15b** were subjected to various neutral, acidic, and basic reaction conditions (Table 2). As noted above, cyclization of alcohol **1** in neutral water led to a 20:1 preference for the *endo* product. 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; however, cyclization in the presence of $BF_3{\cdot}OEt_2$ yielded only ether **8** (82% yield). These three results are in stark contrast to the selectivity of the cyclization of the THP template because water was not required to obtain good-to-complete *endo* selectivity. Previously, the ratio of the two cyclic ethers was found to be approximately 1:1, modestly favoring the *exo* adduct in cases employing $Cs_2CO_3$ and CSA.[10b] Presumably, owing 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 $BF_3{\cdot}OEt_2$ (88% yield); CSA offered significant improvement relative to the THP template (>20:1 versus 5.8:1 *endo*/*exo*).[10b,17] Although, *exo* product **20a** was favored when the reaction was conducted in the presence of $Cs_2CO_3$, presumably owing 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 the presence of $Cs_2CO_3$;[10b] however, in the case of the dioxane template, no such product was observed. Instead, starting material was recovered in both cases. Under acidic conditions, **20b** was isolated in 80% yield both in the presence of $BF_3{\cdot}OEt_2$ and CSA. Terminal epoxides **23** and **26** were also prepared by using a similar process involving aldehyde **6** and ketone **16** (Scheme 4). The use of these alcohols led to exclusive formation of the corresponding 5-*exo* products under all reaction conditions; neither hydrolysis nor methanolysis of the epoxide was 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

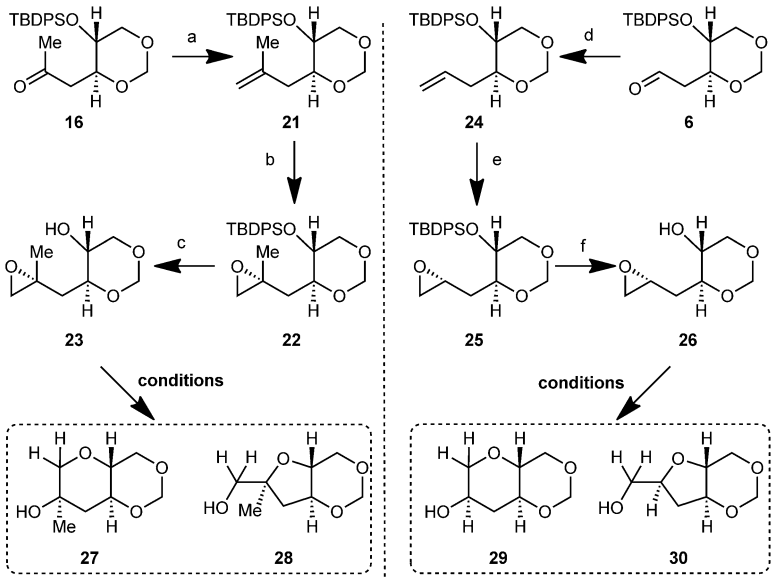
Table 2. Effects of epoxide substitution on *endo* selectivity.




**1**: $R^1$ = Me; $R^2$,$R^3$ = H, X = O
**15a**: $R^1$,$R^2$ = Me; $R^3$ = H, X = O
**15b**: $R^1$,$R^3$ = Me; $R^2$ = H, X = O

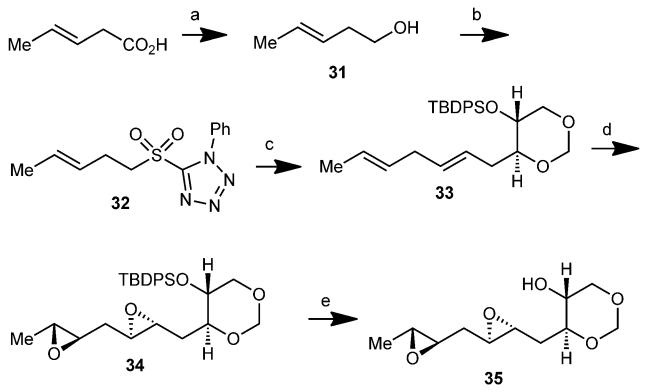
| Reaction conditions | | 1 | 15a | 15b |
|---|---|---|---|---|
| DI $H_2O$[a] | X = O | 19.4:1[e] | >20:1[f] | –[g] |
| | X = $CH_2$[i] | 10.0:1[f] | >20:1[f] | 4.9:1[f] |
| $BF_3$[b] | X = O | >200:1[e] | >20:1[f] | <1:20[f] |
| | X = $CH_2$[i] | 1.4:1[f] | >20:1[f] | 1:11.0[f] |
| CSA[c] | X = O | 4.2:1[e] | >20:1[f] | <1:20[f] |
| | X = $CH_2$[i] | 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 = $CH_2$[i] | 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 $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, 0.02 M, −78 °C, 0.5 h. [c] 1.0 equiv CSA, $CH_2Cl_2$, 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 $^1$H NMR spectroscopy. [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. [i] See ref. [11b].




| Promoter | Results | Promoter | Results |
|---|---|---|---|
| DI $H_2O$ | 1:4.8 (hydrolysis:**28**) | DI $H_2O$ | decomposition |
| $BF_3{\cdot}OEt_2$ | <1:20 (**27**/**28**) | $BF_3{\cdot}OEt_2$ | <1:20 (**29**/**30**) |
| CSA | <1:20 (**27**/**28**) | CSA | <1:20 (**29**/**30**) |
| $Cs_2CO_3$ | 1:1 (methanolysis:**28**) | $Cs_2CO_3$ | decomposition |

Scheme 4. Synthesis and cyclization of terminal epoxides. Reagents and reaction conditions: a) $Ph_3PMe^+Br^-$, *n*BuLi, THF, −78 °C to RT, 94%; b) Shi ketone, Oxone, $K_2CO_3$, $nBu_4NHSO_4$, $Na_2B_4O_7{\cdot}10H_2O$, $Na_2EDTA$, 2:1 DMM/$CH_3CN$, −5 °C to 0 °C, 89%; c) TBAF, THF, RT, 95%; d) $Ph_3PMe^+Br^-$, *n*BuLi, THF, −78 °C to RT, 87%; e) Shi ketone, Oxone, $K_2CO_3$, $nBu_4NHSO_4$, $Na_2B_4O_7{\cdot}10H_2O$, $Na_2EDTA$, 2:1 DMM/$CH_3CN$, −5 °C to 0 °C, 87%; f) TBAF, THF, RT, 69%.

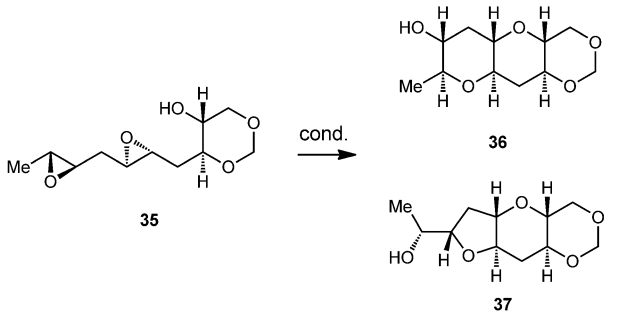



Scheme 5. Synthesis of diepoxide **35**. Reagents and reaction conditions: a) DIBAL-H, $CH_2Cl_2$, −78 °C, 65 %; b) 1-phenyltetrazole-5-thiol, DIAD, $PPh_3$, THF, RT, then $H_2O_2$, $(NH_4)_6Mo_7O_{24}$, $CH_3CH_2OH$, RT, 93 %; c) **6**, KHMDS, DMPU, THF, −78 °C to RT, 61 % (85 % brsm); d) Shi ketone, Oxone, $K_2CO_3$, $n$Bu$_4$NHSO$_4$, $Na_2B_4O_7{\cdot}10H_2O$, $Na_2$EDTA, 2:1 DMM/$CH_3CN$, −5 °C to 0 °C, 88 %; e) TBAF, THF, RT, 78 %. DIAD = diisopropyl azodicarboxylate, DIBAL = diisobutylaluminium, DMPU = *N*,*N*′-dimethylpropylene urea, HMDS = hexamethyldisilazide.

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 of **33** (to give diepoxide **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**.

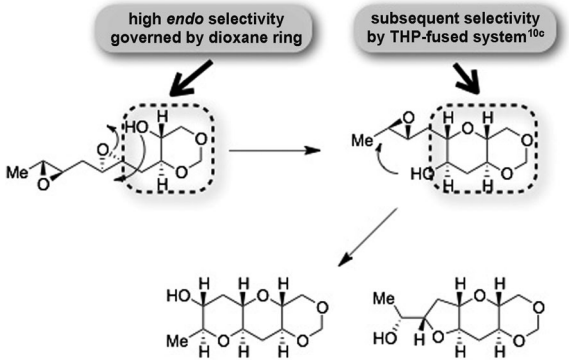
Subjecting diepoxy alcohol **35** to cyclization at 70 °C in deionized water led to the isolation of the 6,6,6 adduct **36** in 51 % yield with no 6,6,5 adduct **37** isolated (Table 3, entry 1).[17] The balance of the material was the result of hydrolysis of the epoxides. This yield could be improved to 54 % when using water buffered to pH 7.0 with less hydrolysis byproducts being observed (Table 3, 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 reaction conditions, we subjected the epoxide to

Table 3. Cyclization ratios for diepoxide **35**.




| Entry | Promoter | **36** | **37** | Yield [%][a] |
|---|---|---|---|---|
| 1 | DI $H_2O$[b] | 1 | 0 | 50 |
| 2 | pH 7.0 buffer[c] | 1 | 0 | 54 |
| 3 | $Cs_2CO_3$[d] | 1.4 | 1 | 75 |
| 4 | CSA[e] | 2.5 | 1 | 85 |

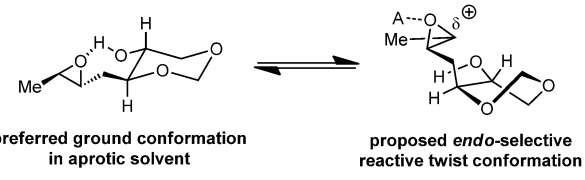
[a] Yield of isolated product. [b] Reaction performed in DI $H_2O$ (0.02 M) at 70 °C for 5 days. [c] Reaction performed in potassium phosphate based buffer at pH 7.0 (0.02 M) at 70 °C for 5 days. [d] Reaction performed in MeOH at RT for 3 days. [e] Reaction performed in $CH_2Cl_2$ at RT for 3 days.




Scheme 6. Proposed order of selectivity for cascade cyclizations.

basic conditions and noted a 1.4:1 ratio of **32**/**33** (Table 3, entry 3). No 6,5,5 ring products were observed, indicating that the first cyclization is highly *endo* controlled, as 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 the reaction was performed in the presence of CSA, a 2.5:1 ratio of **32**/**33** being observed (Table 3, entry 4). In both cases, a higher yield of the isolated products were observed owing to increased rates of reaction mitigating destruction of the epoxide rings.

We propose that the selectivity is determined by several cooperative factors, the two most important being, generally, 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 is characterized by an axially orientated hydroxy moiety that forms 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, thus explaining the enhanced stability of the




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

epoxy alcohol starting material. We previously reasoned that the regioselectivity of the cyclization of the THP-templated substrate could be explained by the involvement of a reactive twist conformation,[10a] which aligns the attacking hydroxy group at the optimal 100° trajectory to the distal carbon atom 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 and Sister over 40 years ago, 1,3-dioxanes often adopt more puckered conformations owing to the presence of shortened endocyclic C–O bonds that in turn distort the ring bond angles.[18c,d] This result was further corroborated by Rychnovski et al., who in 1993 demonstrated, through various means, that substitution at either the 4- or 6-positions orients the ring into the twist conformation to minimize steric interaction with C2 substituents, interactions that are augmented by the short C–O bonds.[20a] These effects are absent in the THP system because the ring is only slightly distorted by the single endocyclic oxygen atom. Notably, particularly with unbiased alcohol **1**, there is increased selectivity under acidic conditions (Figure 2, Table 2, Scheme 4), possibly owing 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 for the dioxane-templated substrate, yet only 6:1 for the THP-templated substrate.[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 the hindered 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 clear 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, thus 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 either 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 precoated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by using either UV absorbance (254 nm), aqueous potassium permanganate, vanillin, *p*-anisaldehyde, or a combination of these. Preparative high-performance liquid chromatography (HPLC) 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, $\delta = 7.27$ ppm or benzene, $\delta = 7.15$; app = apparent, m = multiplet and br = broad). 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 were collected on a Varian CP-3800 GC using an Agilent CHIRALDEX Y-TA column (30 m × 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 1 M 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 $SiO_2$ (gradient: 30–100% EtOAc in hexanes) to yield **1** as a colorless oil (0.038 g, 89%). Chiraldex G-TA: 30 m × 0.25 mm × 0.12 μm film thickness, 125 °C 10 min, then 2 °C min$^{-1}$ to 150 °C, then 10 °C min$^{-1}$ to 180 °C, then hold 10 min, $t_R = 20.09$ min. $R_f = 0.70$ (EtOAc); $[\alpha]_D^{20} = +2.1$ ($c = 1.00$ in $CH_2Cl_2$); $^1$H NMR (500 MHz, $C_6D_6$): $\delta = 4.90$ (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 ppm (d, $J = 5.2$ Hz, 3H); $^{13}$C NMR (125 MHz, $C_6D_6$): $\delta = 93.6$, 80.2, 71.6, 65.9, 56.5, 54.3, 34.8, 17.8 ppm; IR (thin film, NaCl): $\tilde{\nu} = 3423$, 2964, 2923, 2853, 2774, 1653, 1457, 1438, 1381, 1257, 1225, 1175, 1150, 1073, 1028 cm$^{-1}$; HRMS (DART): *m*/*z* calcd for $C_8H_{14}O_4$: 175.0965 $[M+H]^+$; 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 used in the subsequent PMP acetal protection step 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 (CSA; 6.0 g, 25 mmol). Upon addition of CSA, the reaction solution immediately turned paler, becoming a light orange brown. After stirring the mixture for 16 h at RT, the reaction was quenched with sat. aq. $NH_4Cl$ (ca. 200 mL) and the resulting reaction mixture was extracted with $CH_2Cl_2$ (3 × 200 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (gradient: 20–50% EtOAc in hexanes) to afford PMP acetal **3** as a yellow oil (36.1 g, 86%). $R_f = 0.46$ (1:1 EtOAc/hexanes); $[\alpha]_D^{22} = -26.1$

($c=1.23$ in $CDCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta=7.40$ (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 ppm (t, $J=7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=$ 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 ppm; IR (thin film): $\tilde{\nu}=3462$, 2979, 2935, 1716, 1655, 1615, 1251, 1174, 1080, 1034 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{17}H_{22}O_6$: 323.1489 $[M+H]^+$; 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. aq. $NH_4Cl$ (ca. 50 mL). The aqueous layer was separated and extracted with EtOAc ($3\times150$ mL) and the combined organic layers were washed with brine (ca. 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: 20–50% 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); $[\alpha]_D^{22}=+21.6$ ($c=4.9$ in $CDCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta=7.71$–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 ppm (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=166.4$, 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 ppm; IR (thin film): $\tilde{\nu}=3448$, 3072, 2932, 2858, 1718, 1654, 1473, 1428, 1271, 1166, 1112, 1045 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{25}H_{34}O_5Si$: 465.2068 $[M+Na]^+$; 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 $BF_3{\cdot}OEt_2$ (2.2 mL, 18.0 mmol). The solution, which turned yellow upon addition of $BF_3{\cdot}OEt_2$, was stirred 1.25 h. at RT, then quenched with sat. aq. $NaHCO_3$ (ca. 50 mL). The aqueous layer was separated, diluted with brine (ca. 50 mL), and extracted with $CH_2Cl_2$ ($3\times50$ mL). The combined organic layers were washed with brine (ca. 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: 0–30% EtOAc in hexanes) to afford **5** as a colorless oil (5.05 g, 90%). $R_f=0.55$ (1:4 EtOAc/hexanes); $[\alpha]_D^{22}=+14.2$ ($c=2.6$ in $CDCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta=7.68$–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 ppm (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=166.5$, 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 ppm; IR (thin film, NaCl): $\tilde{\nu}=3072$, 2932, 2858, 1720, 1657, 1473, 1428, 1267, 1184, 1111, 1033 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{26}H_{34}O_5Si$: 477.2068 $[M+Na]^+$; 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: 5–20% EtOAc in hexanes) to provide **6** as a colorless oil (788 mg, 93%). $R_f=0.44$ (1:4 EtOAc/hexanes); $[\alpha]_D^{22}=-6.5$ ($c=1.26$ in $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta=9.71$ (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 ppm (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=200.7$, 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 ppm; IR (thin film): $\tilde{\nu}=$ 3072, 2932, 2858, 1729, 1473, 1217, 1171, 1066, 1035 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{22}H_{28}O_4Si$: 407.1649 $[M+Na]^+$; 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 using high vacuum 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 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 the mixture into brine (ca. 50 mL). The aqueous layer was separated and extracted with $Et_2O$ ($4\times$ 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 ca. 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 is 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 $Na_2B_4O_7{\cdot}10H_2O$ in $4\times10^{-4}$ M $Na_2EDTA$ (24 mL), $n$Bu$_4$HSO$_4$ (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 through a syringe pump, a solution of Oxone (4.32 g, 7.02 mmol) in $4\times10^{-4}$ M $Na_2EDTA$ (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 (ca. 100 mL). The aqueous layer was separated and extracted with EtOAc ($3\times100$ 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: 3–25% EtOAc in hexanes) to provide **7**, a colorless oil, as an inseparable mixture of diastereomers (0.408 g of a less than 10:1 mixture of diastereomers, 76% over 2 steps). Epoxide **7** could be purified slightly further by using 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$^{-1}$; $t_R$ of major and minor diastereomers is 7.3 min; collect only the first quarter of the peak to obtain material in high d.r.) to afford **7** in 10:1–15:1 d.r. The compound was obtained in higher purity by using Biotage high-performance silica-gel column (Biotage SNAP HP-Sil, gradient: 0–20% $Et_2O$ in benzene). The two diastereomers appear as one spot by TLC, but early fractions are enriched in the minor diastereomer and late fractions contain **7** in high purity (>20:1 d.r., as determined using $^1$H NMR analysis). $R_f=0.56$ (1:4 EtOAc/hexanes); $[\alpha]_D^{22}=-6.6$ ($c=0.81$ in $CDCl_3$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta=$ 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 ppm (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta=136.0$,

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 ppm; IR (thin film): $\tilde{\nu}$ = 3072, 2931, 2857, 1473, 1428, 1176, 1112 $cm^{-1}$; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{32}O_4Si$: 435.1962 $[M+Na]^+$; 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 (0.941 g, 2.6 mmol) and $CH_2Cl_2$ (5 mL). Aldehyde **6** was diluted in $CH_2Cl_2$ (1 mL) and added by syringe. The resulting solution was stirred for 16 h, concentrated under reduced pressure, and purified by automated chromatography (Biotage SNAP KP-Sil, gradient: 5–40% EtOAc in hexanes) to furnish **10** as a colorless oil (0.957 g, 89%). $R_f$ = 0.51 (1:4 EtOAc/hexanes); $[\alpha]_D^{22}$ = +10.7 (*c* = 4.95 in $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 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 ppm (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 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 ppm; IR (thin film): $\tilde{\nu}$ = 2959, 2932, 2857, 1710, 1428, 1219, 1111, 948, 821 $cm^{-1}$; HRMS (ESI): *m*/*z* calcd for $C_{27}H_{36}O_5Si$: 491.2224 $[M+Na]^+$; 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 (1 M, 3.8 mL, 3.8 mmol) was added by 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: 25–100% 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 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 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 ppm (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 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 ppm; IR (thin film): $\tilde{\nu}$ = 3430, 2931, 2856, 1427, 1103, 1033 $cm^{-1}$; HRMS (ESI): *m*/*z* calcd for $C_{25}H_{34}O_4Si$: 449.2119 $[M+Na]^+$; 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 in $CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 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 ppm (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 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 ppm; IR (thin film): $\tilde{\nu}$ = 3073, 2934, 2858, 1356, 1174, 1100, 924 $cm^{-1}$; HRMS (ESI): *m*/*z* calcd for $C_{26}H_{36}O_6SSi$: 527.1894 $[M+Na]^+$; 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: 2–20% 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 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 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 ppm (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 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 ppm; IR (thin film): $\tilde{\nu}$ = 2930, 2856, 1472, 1428, 1109, 1039 $cm^{-1}$. HRMS (ESI): *m*/*z* calcd for $C_{25}H_{34}O_3Si$: 433.2169 $[M+Na]^+$; 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 $Na_2B_4O_7{\cdot}10H_2O$ in $4\times10^{-4}$ M $Na_2EDTA$ (7.7 mL), $nBu_4HSO_4$ (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 by syringe pump, a solution of Oxone (1.45 g, 4.72 mmol) in $4\times10^{-4}$ M $Na_2EDTA$ (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 (ca. 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 pressure. The crude epoxide **14** was purified by automated chromatography (Biotage SNAP HP-Sil, gradient: 0–40% EtOAc in hexanes) to provide **14**, a colorless oil, as an inseparable mixture of diastereomers (0.151 g of an approximate 6:1 mixture of diastereomers, 86%). Epoxide **14** could be purified further by using a Biotage high-performance silica-gel column using benzene as the mobile phase (Biotage SNAP HP-Sil, gradient: 0–20% $Et_2O$ in benzene). The two diastereomers appeared as one spot by TLC, but early fractions are enriched in the minor diastereomer and late fractions contain **14** in high purity (>20:1 d.r. by $^1$H NMR analysis). $R_f$ = 0.57 (1:4 EtOAc/hexanes); $[\alpha]_D^{22}$ = −10.6 (*c* = 1.47 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 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 ppm (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 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 ppm; IR (thin film, NaCl): $\tilde{\nu}$ = 2928, 2856, 1462, 1399, 2856, 1172, 1109 $cm^{-1}$; HRMS (ESI): *m*/*z* calcd for $C_{25}H_{34}O_4Si$: 449.2119 $[M+Na]^+$; 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 30–100% 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 in $CH_2Cl_2$); $^1$H NMR (300 MHz, $C_6D_6$): $\delta$ = 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 ppm (s, 6H); $^{13}$C NMR (125 MHz, $C_6D_6$): $\delta$ = 93.4, 80.5, 71.2, 60.3, 57.5, 31.4, 24.7, 18.7 ppm; IR (thin film): $\tilde{\nu}$ = 3423, 2964, 2923, 2853, 2774, 1653, 1457, 1438, 1381, 1257, 1225, 1175, 1150, 1073, 1028 $cm^{-1}$; HRMS (ESI): *m*/*z* calcd for $C_9H_{16}O_4$: 211.0941 $[M+Na]^+$; 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. aq. $NH_4Cl$, 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 4 Å (3.5 g), 4-methylmorpholine *N*-oxide (0.370 g, 3.2 mmol), tetrapropylammonium perruthenate (0.037 g, 0.1 mmol); the resulting mixture was stirred for 3 h. The mixture was filtered on Celite and purified by automated chromatography (Biotage SNAP HP-Sil, gradient: 10–50% 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 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=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 ppm (s, 9H);$^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$=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 ppm; IR (thin film): $\tilde{\nu}$=2933, 2858, 1721, 1428, 1108, 1034 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{23}H_{30}O_4Si$: 421.1806 $[M+Na]^+$; 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 by 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. aq. $NH_4Cl$ (ca. 50 mL), extracted with EtOAc (3×50 mL), and dried over $MgSO_4$. Purification by automated chromatography (Biotage SNAP HP-Sil, gradient: 1–40% 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 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=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 ppm (m, 14H);$^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$=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 ppm; IR (thin film): $\tilde{\nu}$=2930, 2857, 1471, 1428, 1107, 1035, 946 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{25}H_{34}O_3Si$: 433.2169 $[M+Na]^+$; 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 $Na_2B_4O_7{\cdot}10H_2O$ in $4\times10^{-4}$ M $Na_2EDTA$ (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 by syringe pump, a solution of Oxone (2.32 g, 7.57 mmol) in $4\times10^{-4}$ M $Na_2EDTA$ (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 (ca. 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: 0–40% EtOAc in hexanes) to provide **18**, a colorless oil, as an inseparable mixture of diastereomers (0.255 g of an approximate 3:1 mixture of diastereomers, 91%). Epoxide **18** could be purified further by a Biotage high-performance silica-gel column using benzene as the mobile phase (Biotage SNAP HP-Sil, gradient: 0–20% $Et_2O$ in benzene). The two diastereomers appear as a single spot by TLC, but early fractions are enriched in the minor diastereomer and late fractions contain **18** in high purity (>9:1 d.r. by $^1$H NMR analysis). $R_f$=0.58 (1:4 EtOAc/hexanes); $[\alpha]_D^{22}=-14.3$ ($c$=1.69 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=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 ppm (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$=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 ppm; IR (thin film, NaCl): $\tilde{\nu}$=2931, 2857, 1471, 1427, 1170, 1103, 1035 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{25}H_{34}O_4Si$: 449.2119 $[M+Na]^+$; 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 30–100% 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 in $CH_2Cl_2$); $^1$H NMR (300 MHz, $C_6D_6$): $\delta$=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 ppm (d, $J$=5.6 Hz, 3H); $^{13}$C NMR (125 MHz, $C_6D_6$): $\delta$=93.2, 79.5, 71.1, 67.1, 61.8, 59.1, 35.9, 22.9, 14.3 ppm; IR (thin film): $\tilde{\nu}$=3405, 2968, 2856, 1455, 1379, 1168, 1059, 1025, 938 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_8H_{14}O_4$: 211.0941 $[M+Na]^+$; 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 resulting 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. Ketone **16** (0.225 g, 0.560 mmol) in THF (1.0 mL) was added dropwise by 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. aq. $NH_4Cl$ (ca. 50 mL), extracted with EtOAc (3×50 mL), and dried over $MgSO_4$. Purification by automated chromatography (Biotage SNAP HP-Sil, gradient: 0–20% 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 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=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 ppm (s, 9H);$^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$=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 ppm; IR (thin film): $\tilde{\nu}$=2931, 2852, 1471, 1428, 1107, 1036, 948 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{24}H_{32}O_3Si$: 419.2013 $[M+Na]^+$; 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 $Na_2B_4O_7{\cdot}10H_2O$ in $4\times10^{-4}$ M $Na_2EDTA$ (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 by syringe pump, a solution of Oxone (1.85 g, 6.026 mmol) in $4\times10^{-4}$ M $Na_2EDTA$ (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 (ca. 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 pressure. The crude epoxide **22** was purified by automated chromatography (Biotage SNAP HP-Sil, gradient: 1–30% EtOAc in hexanes) to provide **22**, a colorless oil, as an inseparable mixture of diastereomers (0.196 g of an approximate 6:1 mixture of diastereomers, 89%). Epoxide **22** could be purified further by using a Biotage high-performance silica-gel column using benzene as the mobile phase (Biotage SNAP HP-Sil, gradient: 0–20% $Et_2O$ in benzene). The two diastereomers appear as one spot by TLC, but early fractions are enriched in the minor diastereomer and late fractions contain **22** in high purity (>14:1 d.r. by

$^1$H NMR analysis). $R_f$=0.48 (1:4 EtOAc/hexanes); $[\alpha]_D^{22}=-14.3$ ($c$=1.69 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=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 ppm (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$ 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 ppm; IR (thin film, NaCl): $\tilde{\nu}$=2931, 2857, 1471, 1427, 1170, 1103, 1035 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{24}H_{32}O_4Si$: 435.1962 $[M+Na]^+$; 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 1 M 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 20–100% 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 in $CH_2Cl_2$); $^1$H NMR (300 MHz, $C_6D_6$): $\delta$=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 ppm (d, $J$=6.7 Hz, 3H); $^{13}$C NMR (100 MHz, $C_6D_6$): $\delta$=92.9, 79.3, 70.9, 66.6, 55.5, 55.0, 40.5, 20.8 ppm; IR (thin film): $\tilde{\nu}$=3425, 2924, 2860, 1393, 1165, 1061, 1027, 941 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_8H_{14}O_4$: 197.0784 $[M+Na]^+$; 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 by 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. aq. $NH_4Cl$ (ca. 50 mL), extracted with EtOAc (3×50 mL), and dried over $MgSO_4$. Purification by automated chromatography (Biotage SNAP HP-Sil, gradient: 0–20% 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 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=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 ppm (s, 9H);$^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$=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 ppm; IR (thin film): $\tilde{\nu}$=3072, 2932, 2856, 1472, 1428, 1107, 1038, 703 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{23}H_{30}O_3Si$: 405.1856 $[M+Na]^+$; 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 $Na_2B_4O_7{\cdot}10H_2O$ in $4\times10^{-4}$ M $Na_2EDTA$ (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 by syringe pump, a solution of Oxone (2.16 g, 7.04 mmol) in $4\times10^{-4}$ M $Na_2EDTA$ (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 (ca. 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: 0–40% EtOAc in hexanes) to provide **25**, a colorless oil, as an inseparable mixture of diastereomers (0.2135 g of an approximate 2:1 mixture of diastereomers, 87%). Epoxide **25** could be purified further by using a Biotage high-performance silica-gel column using benzene as the mobile phase (Biotage SNAP HP-Sil, gradient: 1–20% $Et_2O$ in benzene). The two diastereomers appear as one spot by TLC, but early fractions are enriched in the minor diastereomer and late fractions contain **25** in high purity (>14:1 d.r. by $^1$H NMR analysis). $R_f$=0.46 (1:4 EtOAc/hexanes); $[\alpha]_D^{22}=-22.5$ ($c$=1.72 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$=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 ppm (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$=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 ppm; IR (thin film): $\tilde{\nu}$=3049, 2931, 2857, 1472, 1428, 1107, 1035, 947 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{23}H_{30}O_4Si$: 421.1806 $[M+Na]^+$; found: 421.1811.

**(*E*)-Pent-3-en-1-ol (31)**: To a flame-dried 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 after which 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: 30–100% 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; $CDCl_3$): $\delta$=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 ppm (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 by syringe pump. The solution was stirred at 0 °C for 5 min, then at RT for 3 h and then quenched with sat. aq. NaCl (ca. 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: 7–60% 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; $CDCl_3$): $\delta$=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 ppm (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 $(NH_4)_6Mo_7O_{24}$ (0.71 g, 0.58 mmol) were added. The reaction mixture was allowed to reach RT over 16 h quenched with sat. aq. NaCl (ca. 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: 5–60% 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; $CDCl_3$): $\delta$=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 ppm (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 by 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 by azeotroping with toluene was diluted in THF (5 mL) and added over 5 min by syringe pump. The reaction was left to warm to room temperature over 16 h, quenched with sat. aq. NaCl (ca. 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: 5–60% 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 in $CH_2Cl_2$); $^1$H NMR (400 MHz; $CDCl_3$): $\delta$=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 ppm (d, $J=5.4$ Hz, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta=136.08$, 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 ppm; IR (thin film): $\tilde{\nu}=2930$, 2854, 1427, 1167, 1102, 960 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{27}H_{36}O_3Si$: 454.2772 $[M+NH_4]^+$; 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 $Na_2B_4O_7{\cdot}10H_2O$ in $4\times10^{-4}$ M $Na_2EDTA$ (20 mL), $n$Bu$_4$HSO$_4$ (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 by syringe pump, a solution of Oxone (3.81 g, 12.40 mmol) in $4\times10^{-4}$ M $Na_2EDTA$ (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 (ca. 200 mL). The aqueous layer was separated and extracted with EtOAc ($3\times200$ 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: 1–30% EtOAc in hexanes) to provide **34**, a colorless oil, as an inseparable mixture of diastereomers (0.424 g of an approximate 6:1 mixture of diastereomers, 88%). Epoxide **34** could be purified further by using a Biotage high-performance silica-gel column using benzene as the mobile phase (Biotage SNAP HP-Sil, gradient: 0–20% $Et_2O$ in benzene). The two diastereomers appear as one spot by TLC, but early fractions are enriched in the minor diastereomer and late fractions contain **34** in high purity (>10:1 d.r. by $^1$H NMR analysis). $R_f=0.44$ (1:4 EtOAc/hexanes); $[\alpha]_D^{22}=6.5$ ($c=1.35$ in $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta=7.64$ (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 ppm (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta=136.05$, 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 ppm; IR (thin film): $\tilde{\nu}=2927$, 2855, 1470, 1174, 1104, 1033, 945 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{27}H_{36}O_5Si$: 486.2670 $[M+NH_4]^+$; 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 mL) was added a 1 M solution of TBAF in THF (1.00 mL, 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 20–100% EtOAc in hexanes) to yield **35** as a colorless oil (0.112 g, 78%). $R_f=0.65$ (100% EtOAc); $[\alpha]_D^{22}=+23.2$ ($c=0.75$ in $CH_2Cl_2$); $^1$H NMR (500 MHz, $C_6D_6$): $\delta=4.99$ (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 ppm (d, $J=9.0$ Hz, 3H); $^{13}$C NMR (126 MHz, $C_6D_6$): $\delta=93.4$, 79.8, 71.1, 65.4, 56.8, 55.65, 55.52, 55.0, 35.1, 34.4, 17.7 ppm; IR (thin film): $\tilde{\nu}=$ 3413, 2923, 2855, 1437, 1174, 1073, 1027, 940 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{11}H_{18}O_5$: 231.1227 $[M+H]^+$; 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 mmol, >15:1 d.r.) 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, 0.1 M phosphate buffer was used to control the pH value of the reaction mixture. Upon completion, the solution was then washed out of the reaction vial with a large volume of MeOH (typically 6–8 washes of ca. 2 mL each) and concentrated under reduced pressure (2 torr, 40 °C). The combined yield was found the *endo*/*exo* ratio of products was determined by either $^1$H NMR analysis or GC-FID following isolation of both products together after column chromatography (30–50% EtOAc in hexanes). Then the product mixture was again chromatographed to separate the *endo* product, the 6,6-fused product, from the *exo* product, the 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 mmol, >15:1 d.r.) 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 days. The solution was then diluted with $Et_2O$, quenched with sat. aq. $NH_4Cl$, 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 the *endo*/*exo* ratio of products was determined by either $^1$H NMR analysis or GC-FID following isolation of both products together after column chromatography (30–50% EtOAc in hexanes). Then the product mixture was again chromatographed to separate the *endo* product, the 6,6-fused product, from the *exo* product, the 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 mmol, >15:1 d.r.) 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. aq. $NaHCO_3$, 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 the *endo*/*exo* ratio of products was determined by either $^1$H NMR or GC-FID following isolation of both products together after column chromatography (30–50% EtOAc in hexanes). Then the product mixture was again chromatographed to separate the *endo* product, the 6,6-fused product, from the *exo* product, the 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 $BF_3{\cdot}OEt_2$*: A sample of epoxy alcohol (5–10 mg, 0.03–0.06 mmol, >15:1 d.r.) 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 $BF_3{\cdot}OEt_2$ 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. aq. $NaHCO_3$. 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 the *endo*/*exo* ratio of products was determined by either $^1$H NMR analysis or GC-FID following isolation of both products together after column chromatography (30–50% EtOAc in hexanes). Then the product mixture was again chromatographed to separate the *endo* product, the 6,6-fused product, from the *exo* product, the 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 × 0.25 mm × 0.12 μm film thickness, 125 °C for 10 min, then 2 °C min$^{-1}$ to 150 °C, then 10 °C min$^{-1}$ to 180 °C, then hold 10 min, $t_R=17.59$ min; $R_f=0.65$ (100% EtOAc); $[\alpha]_D^{22}=-8.8$ ($c=0.15$ in $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta=5.02$ (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 ppm (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta=93.9$, 78.8, 76.8, 73.5, 71.6, 69.4, 38.3, 18.0 ppm; IR (thin film, NaCl): $\tilde{\nu}=3365$, 2963, 2923, 2862, 1463, 1401, 1349, 1279, 1211, 1161, 1118, 1075, 1059, 1024 cm$^{-1}$; HRMS (DART): $m/z$ calcd for $C_8H_{14}O_4$: 175.0965 $[M+H]^+$; 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 × 0.25 mm × 0.12 μm film thickness, 125 °C for 10 min, then 2 °C min$^{-1}$ to 150 °C, then 10 °C min$^{-1}$ to 180 °C, then hold 10 min, $t_R$ = 18.86 min; $R_f$ = 0.53 (100 % EtOAc); $[\alpha]_D^{22} = -17.9$ ($c$ = 0.045 in $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 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 ppm (d, $J$ = 6.2 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 94.2, 81.8, 80.7, 73.8, 72.0, 69.1, 29.3, 18.2 ppm; IR (thin film, NaCl): $\tilde{\nu}$ = 3450, 2921, 2851, 1463, 1256, 1155, 1126, 1053 cm$^{-1}$; HRMS (DART): $m/z$ calcd for $C_8H_{14}O_4$: 197.0784 $[M+Na]^+$; 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 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 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 ppm (d, $J$ = 20.5 Hz, 6H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 94.0, 77.7, 76.7, 73.3, 70.1, 66.9, 34.3, 27.7, 16.9 ppm; IR (thin film): $\tilde{\nu}$ = 3481, 2980, 2943, 2862, 1461, 1369, 1166, 1101, 1074, 1022, 941 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_9H_{16}O_4$: 211.0941 $[M+Na]^+$; 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 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 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), 3.59 (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 ppm (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 94.2, 83.9, 80.6, 73.9, 72.4, 72.1, 30.6, 26.6, 24.2 ppm; IR (thin film): $\tilde{\nu}$ = 3479, 2976, 2924, 2872, 1376, 1157, 1128, 1063, 981 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_9H_{16}O_4$: 211.0941 $[M+Na]^+$; 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 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 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 ppm (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 94.2, 85.1, 80.7, 73.3, 72.4, 71.8, 38.6, 22.0, 17.7; IR (thin film): $\tilde{\nu}$ = 3473, 2978, 2874, 1452, 1374, 1270, 1129, 1061, 1000, 904 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_9H_{16}O_4$: 209.0784 $[M+Na]^+$; 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 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 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 ppm (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 94.3, 83.1, 80.9, 72.7, 71.7, 69.6, 38.2, 24.4 ppm; IR (thin film): $\tilde{\nu}$ = 3388, 2972, 2871, 1453, 1373, 1277, 1151, 1129, 1050 cm$^{-1}$; HRMS (DART): $m/z$ calcd for $C_8H_{14}O_4$: 197.0784 $[M+Na]^+$; 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 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 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 ppm (app dd, $J$ = 6.9, 5.8 Hz, 1H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 94.3, 80.2, 77.8, 74.3, 71.7, 65.3, 30.8 ppm; IR (thin film): $\tilde{\nu}$ = 3435, 2871, 1259, 1158, 1126, 1044, 932, 901 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_7H_{12}O_4$: 183.0628 $[M+Na]^+$; 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 either 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, $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 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 ppm (d, $J$ = 6.1 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 94.0, 78.7, 77.19, 77.07, 76.5, 73.9, 71.6, 69.2, 38.5, 35.0, 18.0 ppm; IR (thin film): $\tilde{\nu}$ = 3379, 2928, 2872, 1452, 1164, 1116, 1079, 1031 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{11}H_{18}O_5$: 231.1227 $[M+H]^+$; found: 231.1234; chemical shifts for the dioxane methylene protons, as well at the presence of a terminal $CH_3$ group 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 in $CH_2Cl_2$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 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 ppm (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 94.2, 82.1, 81.5, 77.7, 75.0, 73.7, 69.37, 69.21, 35.2, 28.7, 18.1 ppm; IR (thin film): $\tilde{\nu}$ = 3436, 2927, 2876, 1449, 1163, 1108, 1076, 1020 cm$^{-1}$; HRMS (ESI): $m/z$ calcd for $C_{11}H_{18}O_5$: 231.1227 $[M+H]^+$; found: 231.1231; chemical shifts for the dioxane methylene protons, as well at the presence of a terminal $CH_3$ group indicates an all-6,6,5 system.

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[1] a) K. G. Sellner, G. J. Doucette, G. J. Kirkpatrick, *J. Ind. Microbiol. Biotechnol.* **2003**, *30*, 383; b) G. Ronzitti, F. Callegani, C. Malaguti, G. P. Rossini, *Br. J. Cancer* **2004**, *90*, 1100.

[2] a) M. Schrope, *Nature* **2008**, *452*, 24; b) K. Nakanishi, *Toxicon* **1985**, *23*, 473.

[3] M. S. Lee, G. Qin, K. Nakanishi, M. G. Zagorski, *J. Am. Chem. Soc.* **1989**, *111*, 6234.

[4] H. N. Chou, Y. Shimizu, *J. Am. Chem. Soc.* **1987**, *109*, 2184.

[5] a) K. C. Nicolaou, C. V. C. Prasad, P. K. Somers, C. K. Hwang, *J. Am. Chem. Soc.* **1989**, *111*, 5330; b) K. C. Nicolaou, M. O. Frederick, R. J. Aversa, *Angew. Chem.* **2008**, *120*, 7292; *Angew. Chem. Int. Ed.* **2008**, *47*, 7182.

[6] J. E. Baldwin, *J. Chem. Soc. Chem. Commun.* **1976**, 734.

[7] J. M. Coxon, M. P. Hartshorn, W. H. Swallow, *Aust. J. Chem.* **1973**, *26*, 2521.

[8] For selected reviews on ladder polyether synthesis, see: a) A. R. Gallimore, *Nat. Prod. Rep.* **2009**, *26*, 266; b) C. J. Morten, J. A. Byers, A. R. Van Dyke, I. Vilotijevic, T. F. Jamison, *Chem. Soc. Rev.* **2009**, *38*, 3175; c) I. Vilotijevic, T. F. Jamison, *Angew. Chem.* **2009**, *121*, 5352; *Angew. Chem. Int. Ed.* **2009**, *48*, 5250; d) I. Vilotijevic, T. F. Jamison, *Mar. Drugs* **2010**, *8*, 763; e) E. A. Anderson, *Org. Biomol. Chem.* **2011**, *9*, 3997.

[9] I. Vilotijevic, T. F. Jamison, *Science* **2007**, *317*, 1189.

[10] a) J. A. Byers, T. F. Jamison, *J. Am. Chem. Soc.* **2009**, *131*, 6383; b) C. J. Morten, T. F. Jamison, *J. Am. Chem. Soc.* **2009**, *131*, 6678; c) C. J. Morten, J. A. Byers, T. F. Jamison, *J. Am. Chem. Soc.* **2011**, *133*, 1902.

[11] K. Hotta, X. Chen, R. S. Paton, A. Minami, H. Li, K. Swaminathan, I. I. Mathews, K. Watanabe, H. Oikawa, K. N. Houk, C.-Y. Kim, *Nature* **2012**, *483*, 355.

[12] A. R. Van Dyke, T. F. Jamison, *Angew. Chem.* **2009**, *121*, 4494; *Angew. Chem. Int. Ed.* **2009**, *48*, 4430.

  

[13] S. Hanessian, *Total Synthesis of Natural Products: The "Chiron" Approach*, Pergamon Press, New York, **1983**.
[14] For similar approaches, see: a) K. C. Nicolaou, D. A. Nugiel, C. Couladouros, C. K. Hwang, *Tetrahedron* **1990**, *46*, 4517; b) H. Fuwa, M. Sakaki, K. Tachibana, *Tetrahedron* **2001**, *57*, 3019; c) M. Inoue, J. Wang, G.-X. Wang, Y. Ogasawara, M. Hirama, *Tetrahedron* **2003**, *59*, 5645.
[15] J. J. Mousseau, J. A. Bull, A. B. Charette, *Angew. Chem.* **2010**, *122*, 1133; *Angew. Chem. Int. Ed.* **2010**, *49*, 1115.
[16] *CRC Handbook of Chemistry and Physics*, 92nd ed. (Ed.: W. M. Haynes), CRC Press, **2011**.
[17] All yields reported are based on isolated material.
[18] a) N. Baggett, J. S. Brimacombe, A. B. Foster, M. Stacey, D. H. Whiffen, *J. Chem. Soc.* **1960**, 2574; b) N. Baggett, M. A. Bukhari, A. B. Foster, J. Lehmann, J. M. Webber, *J. Chem. Soc.* **1963**, 4157; c) E. L. Eliel, M. C. K. Sister, *J. Am. Chem. Soc.* **1968**, *90*, 3444; d) E. L. Eliel, *Acc. Chem. Res.* **1970**, *3*, 1.
[19] a) G. Stork, J. F. Cohen, *J. Am. Chem. Soc.* **1974**, *96*, 5270; b) J. Na, K. N. Houk, C. G. Shevlin, K. D. Janda, R. A. Lerner, *J. Am. Chem. Soc.* **1993**, *115*, 8453; c) J. M. Coxon, A. J. Thorpe, *J. Org. Chem.* **1999**, *64*, 5530; d) S. Wan, H. Gunaydin, K. N. Houk, P. E. Floreancig, *J. Am. Chem. Soc.* **2007**, *129*, 7915.
[20] a) S. D. Rychnovsky, G. Yang, J. P. Powers, *J. Org. Chem.* **1993**, *58*, 5251; b) E. Juaristi, G. A. Rosquete-Pina, A. J. Mota, *Pure Appl. Chem.* **2003**, *75*, 589.
[21] For facile hydrolysis of the methylene acetal, see: W. F. Bailey, L. M. J. Zarcone, A. D. Rivera, *J. Org. Chem.* **1995**, *60*, 2532.
[22] For a similar method employing a dihydroxylation/oxidative cleavage route, see the Supporting Information.
[23] Y. Zhang, L. Deng, G. Zhao, *Org. Biomol. Chem.* **2011**, *9*, 4518.
[24] Acetylation of the alcohol and COSY analysis were performed when needed to confirm the structure of the cyclization adduct; see the Supporting Information for details.
[25] An attempt to oxidize **20a** with TPAP (5 mol%) and NMO (1.5 equiv) led to recovered starting material.

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