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Studies on the Stereoselective Synthesis of the Marine Antitumor Agent Eleutherobin

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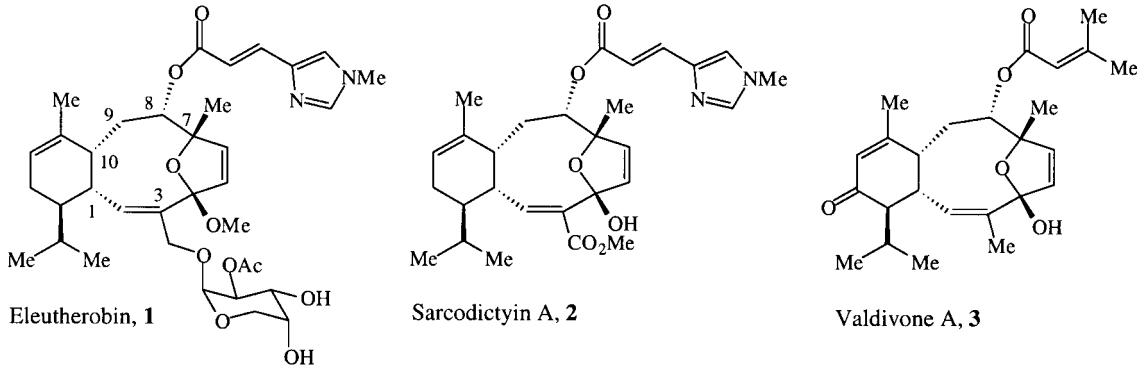
Abstract—(+)-Carvone has been converted into the sulfone **14** which comprises the left-hand side of the cytotoxic sesquiterpene, eleutherobin **1**. Julia coupling of **14** to the aldehyde **21**, followed by oxidation, dissolving metal reduction and stereoselective reduction of the C8 carbonyl group resulted in **29**, which has the correct stereochemistry at C8 and C9. Further conversion of **29** into **37**, and attempted intramolecular cyclization resulted in fragmentation to the furan **39** and **38**. Asymmetric epoxidation of the allylic alcohols **42** and **48** resulted in neighboring group participation from the adjacent dimethoxy acetal and formation of the rearranged oxepane derivatives **44**, **45** and **49**, respectively.

Introduction

Eleutherobin **1** was isolated from the fermentation broth of the soft, red-colored coral *Eleutherobia cf. albiflora*, found in the Indian Ocean.[1] It is a member of the eunicellans, a class of marine diterpenes possessing the core carbon skeleton shown in the diterpene **1**,[2] and is closely related to sarcodictyin A **2**,[3] as well as valdivone A **3** (Scheme 1).[4] There are over thirty known members of this family of diterpenes,[5] and apart from the recent synthetic efforts on **1** and **2** (see below), there has been relatively little work on their synthesis with the notable exception of Overmans synthesis of eunicellin.[6]

Eleutherobin **1** has been shown to possess cytotoxic activity with a IC_{50} of 10.7 nM against the HCT116 human colon carcinoma cell line and a IC_{50} of 13.7 nM against the A2780 human ovarian carcinoma cell line. Because of the interest in the comparison of biological activity of **1** with taxol, there has been considerable effort devoted to the total synthesis of **1**. To-date there have been two reported total syntheses of **1** from the Nicolaou and Danishefsky groups, respectively,[7,8]



Scheme 1.

Keywords: carvone; eleutherobin; cytotoxic.
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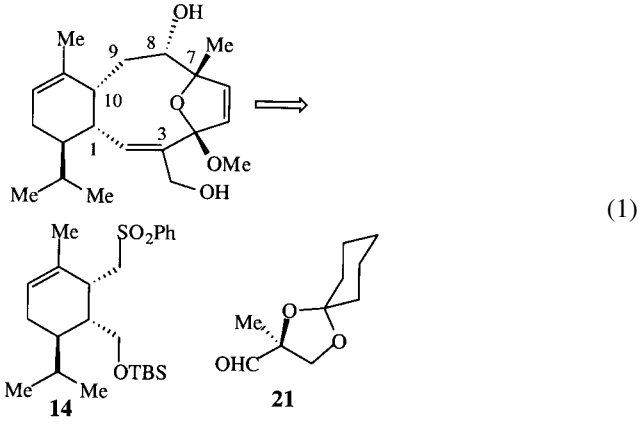
and also two approaches to the syntheses of **1** and **2** have been published.[9,10]



(1)

The strategy we have pursued involves the conversion of carvone **4** into a *cis*-disubstituted derivative **14** (Scheme 2) that allows the construction of the *sec*- and *tert*-alcohols C8/C7 via a Julia coupling to the left-hand fragment **21** (Scheme 3), Eq. (1).

Synthesis of Sulfone 14

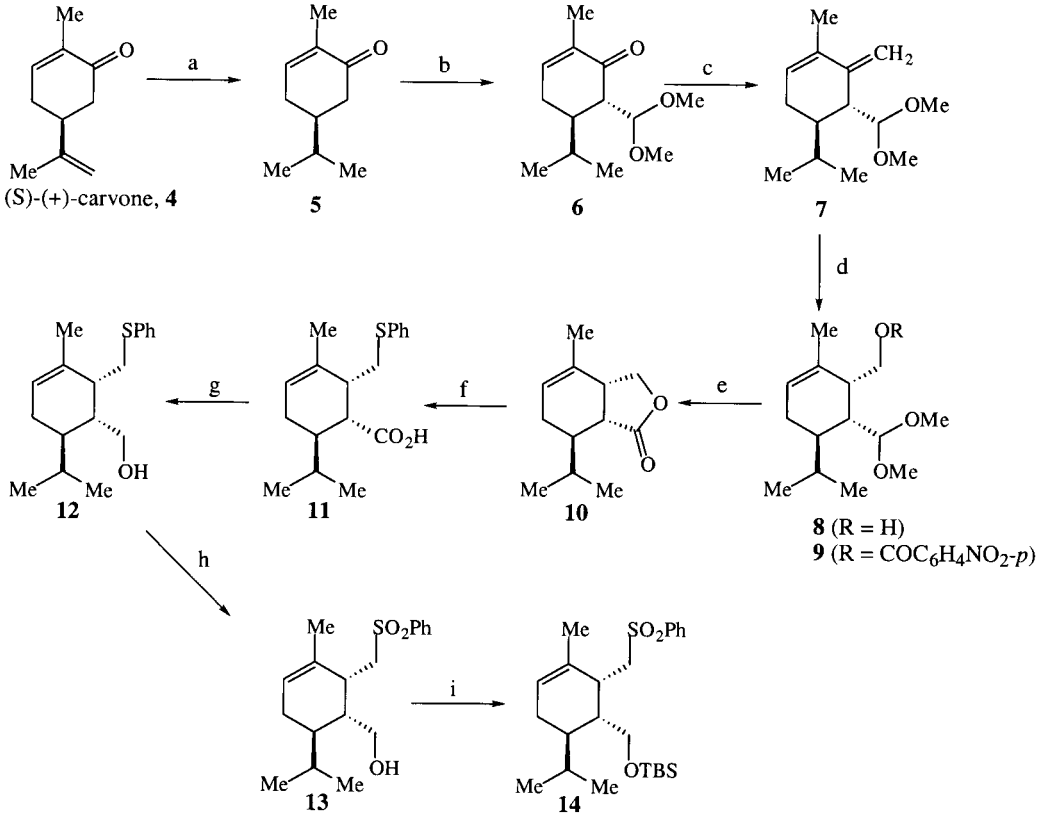
Hydrogenation of (+)-carvone **4**,[11] gave **5,** which was subsequently treated $TiCl_4$/*i*-Pr_2NEt at −78°C followed by trimethylorthoformate to provide the acetal **6** as a single diastereomer in 61% yield, together with 37% of recovered starting material, Scheme 2.[12] While **6** proved to be resistant to a wide variety of methenylating reagents such as triphenylphosphonium methylide,[13] Lombardo's reagent (Zn/CH_2Br_2/$TiCl_4$),[14] Zn/Cp_2ZrCl_2/CH_2Br_2,[15] as well as $TMSCH_2MgBr$ and $TMSCH_2Li$,[16] treatment of the enone **6** with Cp_2TiMe_2[17] in THF gave the diene **7** in 71% yield.

Hydroboration of the diene **7** using 9-BBN[18] in THF (0.5 M, 1.1 equiv.) gave, after oxidative work-up, the alcohol **8** (61%) as a single diastereomer. The stereochemistry of the alcohol **8** was confirmed by X-ray analysis of the corresponding *p*-nitrobenzoate ester **9**.

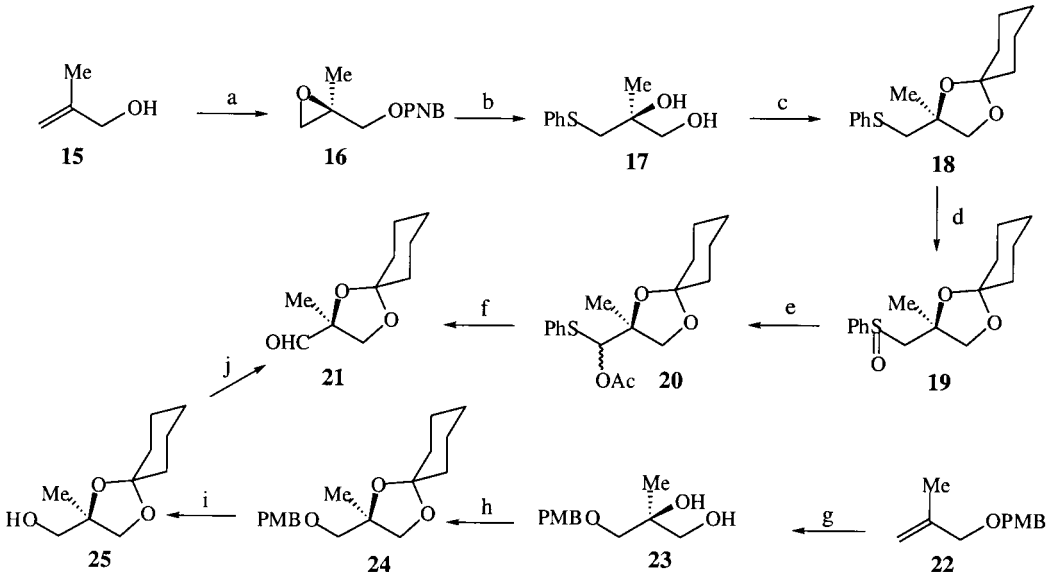
Jones oxidation[19] of **8** gave cleanly the lactone **10**. Subsequent *O*-alkyl cleavage of the lactone **10** with lithium phenylthiolate in DMF gave **11,** which was esterified and reduced to give the alcohol **12**. Several oxidants were examined for the oxidation of sulfide to sulfone, and hydrogen peroxide/sodium tungstate dihydrate[20] converted **12** into **13** (89%). Finally, silylation of **13** yielded the desired sulfone **14** in excellent yield.

Synthesis of Aldehyde 21

The requisite aldehyde **21** was synthesized in six steps in an overall 45% yield as shown in Scheme 3.[21] Sharpless asymmetric epoxidation of 2-methyl-2-propene-1-ol 15 followed



Scheme 2. (a) $(Ph_3P)_3RhCl/H_2$/PhH, **5** (93%). (b) $TiCl_4/CH_2Cl_2$, then *i*-Pr_2NEt followed by $CH(OMe)_3$, −78°C to 0°C, **6** (61%) and **5** (37%). (c) Cp_2TiMe_2/THF/reflux, **7** (71%). (d) 9-BBN (1.1 equiv.)/THF, 60–65°C, followed by $NaOH/H_2O_2$, **8** (61%) and **7** (22%). Conversion of **8** into **9**, 4-nitrobenzoyl chloride/imidazole/DMAP/CH_2Cl_2, **9** (82%). (e) Jones reagent/acetone, **10** (73%). (f) LiH/PhSH/DMF/110°C, **11** (89%). (g) MeI/K_2CO_3/acetone, then DIBAL-H/CH_2Cl_2/−78 to 0°C, **12** (86%). (h) $Na_2WO_4.2H_2O$/Aliquat® 336/H_2O_2/CH_2Cl_2, reflux, **13** (89%). (i) TBSCl/imidazole/DMF, **14** (96%).



Scheme 3. (a) (+)-DIPT/Ti(O*i*-Pr)$_4$/cumene hydroperoxide/4 Å molecular sieves/CH_2Cl_2/−20°C, then P(OMe)$_3$/4-nitrobenzoyl chloride/imidazole, **16** (52%, >98% e.e. after recrystallization). (b) PhSH/NaOH/dioxane/H_2O, **17** (96%). (c) *p*-TsOH/1-methoxycyclohexene/DMF, **18** (97%). (d) *m*-Chloroperoxybenzoic acid/CH_2Cl_2/−20°C, **19** (99%). (e) Ac_2O/NaOAc/reflux, **20** (94%). (f) MeOH/K_2CO_3/reflux, **21** (99%). (g) *t*-BuOH/H_2O (1:1)/AD-mix-β/0°C, **23** (88%, 97% ee). (h) *p*-TsOH/cyclohexanone/3 Å molecular sieves/150°C, **24** (90%). (i) LiOH·H_2O/THF/H_2O (1:1)/reflux, **25** (92%). (j) Dess–Martin triacetoxyperiodinane/CH_2Cl_2, **21** (83%).

by in situ protection gave the known epoxide **16** in 90% e.e. The e.e. could be improved to >98% by recrystallization from diisopropyl ether, as determined using the chiral NMR shift reagent[22] Eu(hfc)$_3$ in benzene-d_6. The epoxide **16** was converted into the diol **17**[23] and protected as its cyclohexyl ketal **18**. After oxidation to the sulfoxide **19**,[24] Pummerer rearrangement[25] gave **20** as a 1:1.6 mixture of diastereomers, which could be converted into the aldehyde **21** by hydrolysis with potassium carbonate in methanol.

An alternative route using the more recently developed asymmetric dihydroxylation technology was also used to synthesize the aldehyde **21**. Using the literature method **22** was converted into **23**.[26] The diol **23** was ketalized to give **24**, which on treatment with LiOH/THF/water gave **25**. Oxidation of **25** with the Dess–Martin periodinane reagent[27] gave **21**. This route is five steps and proceeds in an overall yield of 50%.

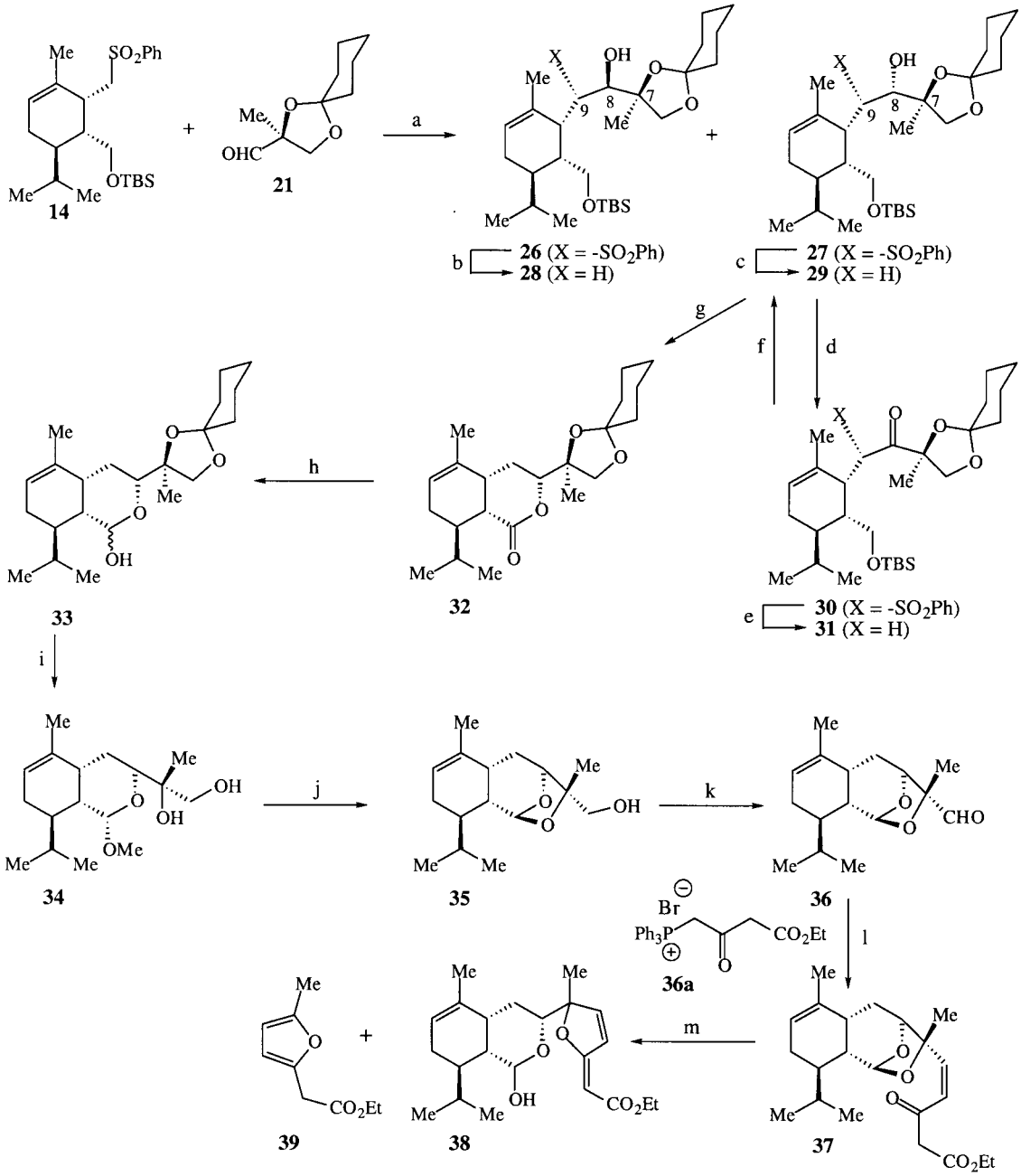
Julia Coupling of 14 and 21

Treatment of the sulfone **14** with *n*-BuLi (1.03 equiv.) followed by the addition of the aldehyde **21** gave the coupled products **26** and **27** as a 50:1 mixture at the newly formed C-8 stereogenic center in 66% yield, Scheme 4.[28] The major component **26** possessed the incorrect stereochemistry at C-8 as shown by X-ray crystallographic analysis. The same transformation could also be accomplished using EtMgBr[29] (1.13 equiv.) in benzene to give the sulfones **26** and **27** as a 10:1 mixture (**26**:**27**) at C-8 in 64% yield. The latter method was preferred because it was found to be more reproducible.

The stereochemistry of sulfone **27** was established by a series of correlation experiments. Sodium in liquid ammonia reduction of the separated sulfones **26** and **27** gave the alcohols **28** and **29**, respectively, which conclusively established the C-8 stereochemistry in the sulfone. It is believed that the C-9 stereochemistry of the sulfone **27** is as drawn because oxidation of the mixture of sulfones **26** and **27** gave a single ketosulfone **30**. Subsequent reduction of the sulfone **30** using sodium in liquid ammonia[30] gave the ketone **31** in good yield. It was found that DIBAL-H reduced the ketone **31** to preferentially give the alcohol **28** possessing the incorrect stereochemistry at C-8, while the Selectride® reagents favored the desired C-8 stereochemistry with K-Selectride® yielding the best results (15:1, **29**:**28**, 82% overall yield).

Deprotection of the silyl ether **29** followed by oxidation using tetrapropylammonium perruthenate (TPAP)[31] gave the lactone **32**. Subsequent reduction of **32** with DIBAL-H provided the lactol **33** as a single diastereomer. Treatment of **33** with *p*-TsOH in methanol gave the acetal **35** in 67% yield, together with the methoxy acetal **34** in 23% yield. The methoxy acetal **34** appeared to possess the α-stereochemistry at C-2 (H-1,2 coupling constant of 8.7 Hz) presumably due to the anomeric effect. The diol **34** could be separated and re-equilibrated to provide a further quantity of the acetal **35**.

Oxidation of the alcohol **35** using the Dess–Martin periodinane gave the crystalline aldehyde **36**. Treatment of the aldehyde **36** with the ylide derived from phosphonium salt **36a**[32] gave the β-keto ester **37** (*Z*:*E*, 14:1). Although the yields using the literature conditions[33] were low and irreproducible, this problem was overcome by the use of DMPU as a co-solvent. Treatment of **37** with BF_3·Et_2O/CH_2Cl_2 produced complex reaction mixture from which we could isolate **38** and the furan **39**. It appeared that cleavage of the C-7,8 bond was the reaction pathway under several of the Lewis acidic conditions.

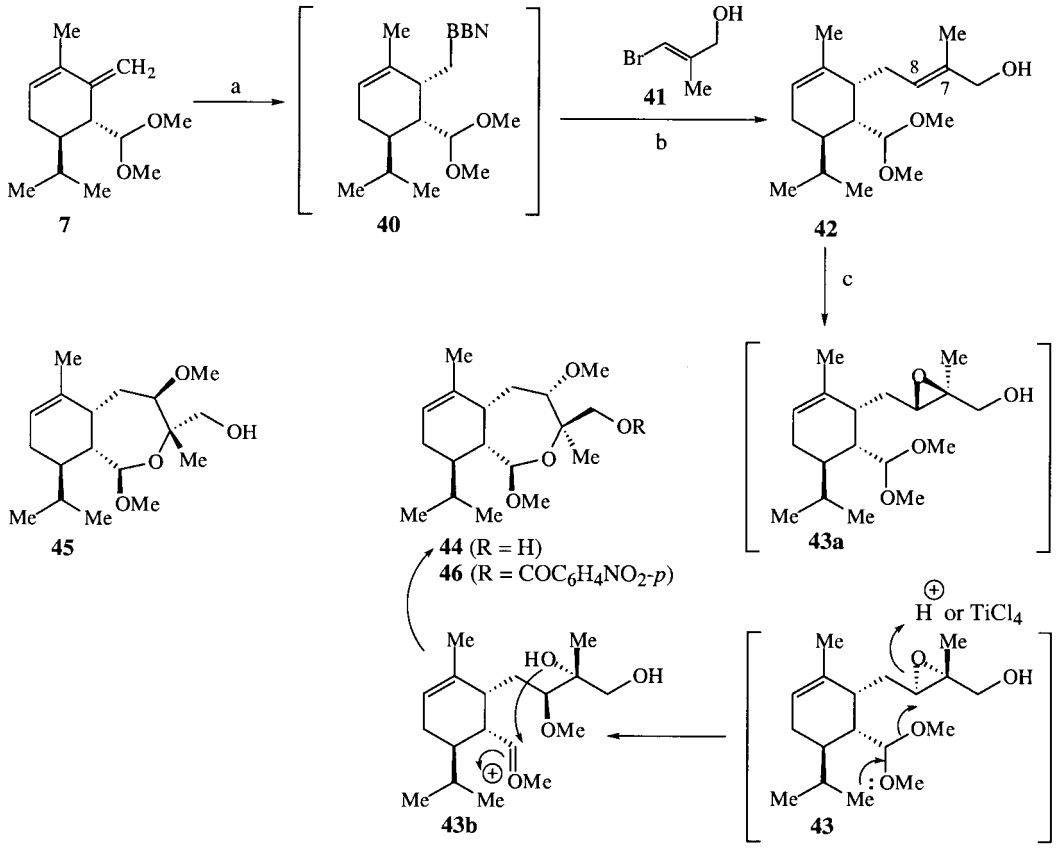


Scheme 4. (a) *n*-BuLi (1.03 equiv.)/THF/−78 to 0°C, then add **21**, −78 to 25°C, **26/27** (50:1) (66%), or EtMgBr (1.13 equiv.), PhH, reflux, then add **21** 25°C, **26/27** (10:1) (64%). (b) $Na/NH_3/THF/-78°C$, **28** (53%). (c) $Na/NH_3/THF/-78°C$, **29** (21%). (d) Dess–Martin triacetoxyperiodinane/CH_2Cl_2, **30** (94%). (e) $Na/NH_3/THF/-78°C$, **31** (92%). (f) K-Selectride®/THF/0°C, **29** (77%). (g) (i) TBAF/THF/25°C, 99%; (ii) TPAP/NMO/4 Å molecular sieves/CH_2Cl_2/25°C, **32** (87%). (h) DIBAL-H/CH_2Cl_2/−78°C. (i) *p*-TsOH/MeOH/25°C, **35** (67% over two steps), **34** (23% over two steps). (j) *p*-TsOH/MeOH/25°C, **35** (70%), **34** (21%). (k) Dess–Martin triacetoxyperiodinane/CH_2Cl_2, **30** (89%). (l) NaH/DMPU/**36a**/25 to 40°C, **37** (84%) + *E*-isomer (6%). (m) $BF_3{\cdot}Et_2O/CH_2Cl_2$, **38** (56%), **39** (18%).

Asymmetric Epoxidation of the C7–C8 Double Bond

Suzuki and co-workers first reported the coupling of alkyl 9-BBN adducts with vinyl or aryl halides using palladium catalysis in 1986.[34] Hydroboration of the diene **7** with 9-BBN gave the alkyl-9-BBN adduct **40**, Scheme 5. Treatment of the 9-BBN adduct **40** with the vinyl bromide **41** under standard Suzuki conditions [$PdCl_2(dppf)_2/K_2CO_3$/DMF/THF] gave no coupling, however, the use of one of Suzuki's alternative conditions[35] [$Pd(PPh_3)_4$ (3 mol%)/NaOH (3 M in H_2O)/THF/65°C/6 h] yielded the coupled adduct **42** in 44% yield over the two steps. Treatment of allylic alcohol **42** with AD mix α[36] gave a slow reaction, and the ^1H NMR of the crude reaction mixture indicated preferential dihydroxylation at the internal C-11,12 olefin as shown in by the disappearance of the H-12 signal. Classical dihydroxylation conditions[37] (OsO_4/NMO/acetone/H_2O) gave a complex mixture.

Corey and co-workers have shown that the use of an aromatic protecting group α to the olefin often improves the enantioselectivity of the dihydroxylation via aryl–aryl



Scheme 5. (a) 9-BBN. (b) $Pd(PPh_3)_4$/**41**/THF/3M NaOH/65°C, **42** (44%), **7** (33%). (c) (+)-DIPT/Ti(O*i*-Pr)$_4$/TBHP/3 Å molecular sieves/CH_2Cl_2/−40°C, **45** (84%), **43** (10%). Whereas (−)-DIPT/Ti(O*i*-Pr)$_4$/TBHP/3 Å molecular sieves/CH_2Cl_2/−25°C gave **44** (36%), **43** (64%).

or π-stacking interactions in the binding pocket of the catalyst.[26] It was hoped that this interaction may also be used to improve the regioselectivity of the dihydroxylation. Unfortunately, after protection of the primary hydroxyl functionality as its 4-methoxybenzoyl ester, treatment with AD mix α gave a complex mixture with substantial over-hydroxylation as well as preferential dihydroxylation of the internal C-11,12 olefin as judged by ^{1}H NMR analysis of the crude reaction mixture.

An alternative method for oxygenation of the allylic alcohol **42** was the use of Sharpless' asymmetric allylic epoxidation chemistry.[38] Epoxidation of the C-7,8 olefin using the (+)-DIPT/Ti(O*i*-Pr)$_4$/TBHP system would be expected to yield the epoxide **43** with the correct absolute stereochemistry at C-7 and C-8. Unfortunately, in order to convert the epoxide **43** into the acetal **34**, the epoxide functionality must be opened in an S_N2 process, causing an inversion of the C-8 stereochemistry. An alternative approach would involve the use of the *Z*-olefin geometry at the C-7,8 position which, upon opening of the epoxide at C-8 with an oxygen nucleophile, would yield the correct C-7 and C-8 stereochemistry.

In the event, treatment of allylic alcohol **42** with (+)-DIPT/Ti(O*i*-Pr)$_4$/TBHP at −40°C yielded **43** (10%) and the rearranged adduct **45** (84%). The allylic alcohol **42** was allowed to react with (−)-DIPT/Ti(O*i*-Pr)$_4$/TBHP and gave **44** (36%) along with **43b** (64%). Protection of the primary hydroxyl function as its *p*-nitrobenzoate ester yielded the crystalline **46**, whose structure was confirmed by X-ray crystallography (Fig. 1). Although the C-8 stereochemistry is correct for the synthesis of eleutherobin, the crucial C-7 stereochemistry is incorrect.

It is believed that the epoxide **43** is initially formed, but it is rapidly opened in an intramolecular manner to give the intermediate **43b** which rearranges to give the *O*-methyl ether **44**. Recently, Gennari[9] has reported the formation of these same epoxides from **42**, and under his milder reaction conditions they can be isolated, although further transformation into the acetals is promoted by acids.[39]

The most direct method to obtain the correct C-7 and C-8 stereochemistry for eleutherobin was to use the opposite *Z*-olefin geometry. Construction of the appropriate *Z*-vinyl halide **47** was possible using a known one step procedure.[40] Suzuki coupling between **40** and **47** under the conditions

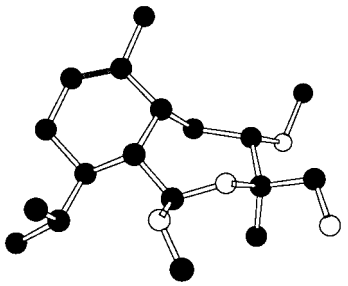
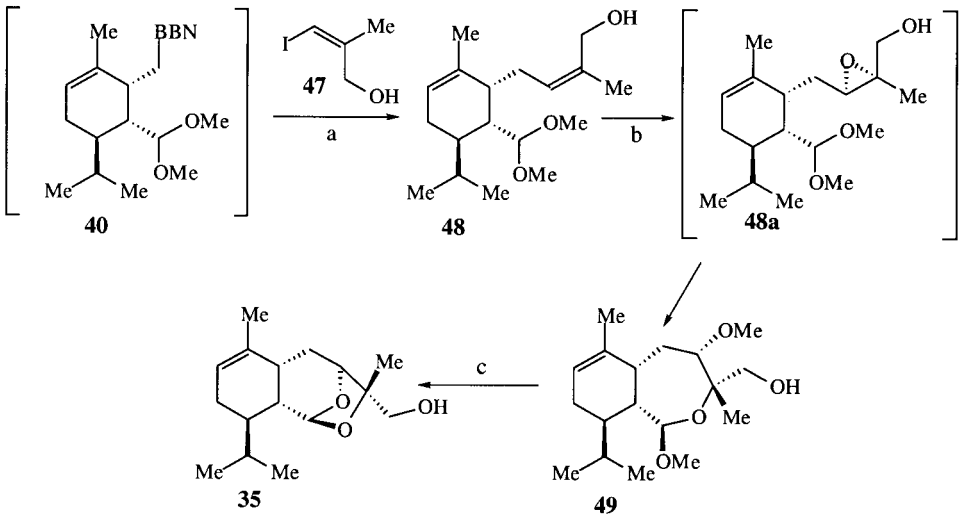


Figure 1. Chem 3D representation of **46** (–$COC_6H_4NO_2$) from X-ray coordinates.



Scheme 6. (a) $Pd(PPh_3)_4$/**47**/THF/3M NaOH/65°C, **48** (35%). (b) (+)-DET/Ti(O*i*-Pr)$_4$/TBHP/3 Å molecular sieves/CH_2Cl_2/−20°C, **49** (63%). (c) MeCN/Me_3SiCl/NaI at 0°C, **35** (15%).

used previously [$Pd(PPh_3)_4$ (3 mol%)/NaOH (3 M in H_2O)/THF/65°C, 6 h] gave trace amounts of the desired coupled product **48**, Scheme 6. The yield of this reaction could be improved to 35% yield over two steps by increasing the amount of $Pd(PPh_3)_4$ to 15 mol%, the amount of **47** was increased from 1 to 2.7 equiv., and the reaction time was extended from 6 to 48 h. Treatment of the allylic alcohol **48** with [(+)-DIPT (50 mol%)/Ti(O*i*-Pr)$_4$ (40 mol%)/TBHP/−10°C)] gave largely the starting alcohol **48**, and a small amount of what appeared to be the epoxide **48a**. Treatment of the allylic alcohol **48** under modified Sharpless conditions [(+)-DIPT (3 equiv.)/Ti(O*i*-Pr)$_4$ (2.5 equiv.)/TBHP/−10°C)] gave the expected *O*-methyl ether **49** as a single diastereomer in 50% yield. Furthermore, the use of (+)-DET instead of (+)-DIPT and the presence of equimolar reagents [(+)-DET (1.3 equiv.)/Ti(O*i*-Pr)$_4$ (1.0 equiv.)/TBHP/−8°C] gave the optimum results with a yield of 63% and was shown to be a single diastereomer by ^{1}H and ^{13}C NMR analysis.

In order to verify the C-7 and C-8 stereochemistry, conversion of *O*-methyl ether **49** into the previously prepared acetal **35** was necessary. Treatment of **49** with trimethylsilyl iodide, generated in situ from trimethylsilyl chloride and sodium iodide, in propene-saturated acetonitrile[41] gave the acetal **35** as the major demethylated product, but in a poor yield. Several other methods were tried in order to improve the deprotection of the *O*-methyl ether **49**, including TMSSMe/ZnI_2/Bu_4NI,[42] EtSH/BF_3·Et_2O,[43] and BBr_3,[44] but all attempts led to extensive decomposition.

The sulfone route in Scheme 4, although lengthy, provides good stereocontrol at the crucial tertiary and secondary (C7–C8) stereogenic centers.

During the course of this research the Nicolaou group reported their successful syntheses of **1** and **2** that starts with carvone and proceeds through some very similar intermediates to ones described above,[7] and consequently, we have not continued this approach.

Experimental

Melting points were taken on a Thomas–Hoover capillary tube apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrophotometer neat unless otherwise indicated. ^{1}H NMR spectra were recorded on a General Electric QE-300 spectrometer at 300 MHz in the indicated solvent and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded on a General Electric QE-300 spectrometer at 75 MHz in the solvent indicated and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. Mass spectra were obtained on a VG ZAB2E or a Finnigan TSQ70. Optical rotations were recorded on a Perkin–Elmer 241 MC polarimeter using a sodium lamp at 589 nm in $CHCl_3$ with 1% ethanol.

Routine monitoring of reactions was performed using Merck 60 F_{254} silica gel, aluminum-backed TLC plates. PLC was performed using Merck 60 F_{254} silica gel, glass supported plates. Flash column chromatography was performed with the indicated eluents on Merck 60H F_{254} silica gel.

Solvents and commercial reagents were purified in accord with Perrin and Armarego[45] or used without further purifcation.

1-Methyl-(4*S*)-isopropyl-(5*R*)-dimethyl acetal-1-cyclohexen-6-one 6. To a stirred solution of **5** (86.7 g, 0.57 mol) in CH_2Cl_2 (1.6 L) was added $TiCl_4$ (110.7 g, 64.0 mL, 0.58 mol) at −78°C over a 5 min period. After an additional 15 min, *i*-Pr_2NEt (74.2 g, 100.0 mL, 0.57 mol) was added to the orange solution over 5 min. The dark red solution was stirred an additional 1.5 h at −78°C, and $CH(OMe)_3$ (121.2 g, 125.0 mL, 1.1 mol) was added over 7 min. After 4 h at −78°C, the mixture was warmed to 0°C over 25 min. The dark solution was poured into saturated aqueous NH_4Cl (1.5 L) and extracted with

CH_2Cl_2 (3×800 mL). The dried ($MgSO_4$) extract was concentrated in vacuo to give a yellow liquid. This reaction was repeated on 87.3 g scale of the enone under identical conditions. The combined crude liquids were passed quickly through a short plug of silica gel, eluting with 20% Et_2O/petroleum ether. The filtrate was concentrated in vacuo and purified in 50 mL batches of the crude liquid by chromatography over silica gel, eluting with 12–15% Et_2O/petroleum ether, to give starting enone **5** (38.2 g, 0.25 mol, 37%) followed by the acetal **6** (158.6 g, 0.70 mol, 61% yield) as a pale yellow liquid. $[\alpha]_D^{23}=+19$ (c=2.50, $CHCl_3$). IR (film) 2958, 2833, 1678 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.55–6.65 (1H, m), 4.64 (1H, d, J=7.2 Hz), 3.32 (3H, s), 3.30 (3H, s), 2.80 (1H, dd, J=3.0, 7.2 Hz), 2.1–2.3 (1H, m), 1.90–2.05 (1H, m), 1.75 (3H, d, J=1.5 Hz), 1.6–1.8 (2H, m), 0.87 (3H, d, J=5.4 Hz), 0.85 (3H, d, J=5.4 Hz). ^{13}C NMR ($CDCl_3$) δ 198.8, 143.1, 135.2, 103.6, 53.9, 53.1, 52.3, 40.8, 29.4, 25.9, 20.5, 15.9. HRMS (CI) calcd for $C_{13}H_{23}O_3$ 227.1672. Found 227.1643.

1-Methyl-(4*R*)-isopropyl-(5*S*)-dimethyl acetal-6-yl-1-cyclohexene 7. To a stirred solution of titanocene dichloride (136 g, 0.55 mol) in Et_2O (1.8 L) was added MeLi (800 mL, 1.12 mol, 1.4 M in Et_2O) via cannula over 1.25 h at 0°C in the dark. The orange–brown solution was allowed to warm to ambient temperature. After 2 h cold H_2O (750 mL) was added slowly to the mixture, and the resulting suspension extracted Et_2O (3×700 mL). The dried ($MgSO_4$) extract was concentrated in vacuo in the dark and the orange solid was immediately dissolved in THF (100 mL). The dimethyl titanocene solution was added to a stirred solution of **6** (45.0 g, 0.20 mol) in THF (200 mL) via cannula in the dark. An additional amount of THF (2×25 mL) was used to rinse the dimethyl titanocene flask. After heating the dark red solution at reflux in the dark for 20 h, the mixture was concentrated in vacuo. The crude slurry was dissolved in Et_2O (500 mL), and silica gel (500 mL) was added slowly. The solid was filtered and rinsed with Et_2O (1.5 L). The filtrate was concentrated in vacuo and the silica gel cycle repeated twice. The dark liquid was distilled at 112–115°C/2.5 mmHg to give **7** (31.5 g, 0.14 mol, 71% yield) as a colorless liquid. $[\alpha]_D^{23}=-117$ (c=1.27, $CHCl_3$). IR (film) 2942, 1608 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.47 (1H, br s), 5.05 (1H, s), 4.88 (1H, s), 4.23 (1H, d, J=8.4 Hz), 3.30 (3H, s), 3.28 (3H, s), 2.66 (1H, dd, J=2.1, 8.4 Hz), 2.1–2.3 (2H, m), 1.78 (3H, d, J=1.2 Hz), 1.45–1.55 (1H, m), 1.30–1.45 (1H, m), 0.86 (3H, d, J=3.3 Hz), 0.84 (3H, d, J=3.3 Hz). ^{13}C NMR ($CDCl_3$) δ 145.2, 135.5, 128.7, 115.9, 108.1, 58.2, 55.9, 50.3, 43.2, 31.3, 28.9, 24.9, 23.6, 22.9. HRMS (CI) calcd for $C_{14}H_{24}O_2$ 225.1895. Found 225.1892.

1-Methyl-(4*R*)-isopropyl-(5*R*)-dimethyl acetal-(6*S*)-hydroxymethyl-1-cyclohexene 8. A solution of 9-BBN (515 mL, 0.26 mol, 0.5 M in THF) was added to **7** (52.32 g, 0.23 mol). After heating the stirred solution at 60–65°C for 18 h, the mixture was cooled to 0°C and NaOH (150 mL, 4 M in H_2O) was added followed by the dropwise addition of H_2O_2 (150 mL, 30% in H_2O). After 30 min at 0°C and 45 min at ambient temperature, the THF was evaporated in vacuo and the aqueous layer was extracted with Et_2O (4×300 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over Florisil®, eluting with 5–50% Et_2O/petroleum ether followed by chromatography over silica gel eluting with 30–50% Et_2O/petroleum ether, to give the starting diene **7** (10.40 g, 0.05 mol, 22%) followed by the alcohol **8** (33.33 g, 0.14 mol, 61% yield) as a colorless oil. $[\alpha]_D^{23}=+66$ (c=0.89, $CHCl_3$). IR (film) 3453, 2957 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.38 (1H, br s), 4.40 (1H, d, J=5.0 Hz), 3.6–3.7 (3H, m), 3.47 (3H, s), 3.39 (3H, s), 2.4–2.45 (1H, m), 1.95–2.05 (2H, m), 1.7–1.85 (2H, m), 1.69 (3H, s), 1.15–1.3 (1H, m), 0.90 (3H, d, J=6.3 Hz), 0.82 (3H, d, J=6.3 Hz). ^{13}C NMR (C_6D_6) δ 133.6, 122.7, 106.5, 62.2, 55.1, 54.1, 42.0, 39.8, 36.6, 27.1, 24.7, 22.1, 21.2, 17.4. HRMS (CI) calcd for $C_{14}H_{27}O_3$ 243.1960. Found 243.1951.

1-Methyl-(4*R*)-isopropyl-(5*R*)-dimethyl acetal-(6*S*)-[4′-nitrobenzoyloxymethyl]-1-cyclohexene 9. To a stirred solution of **8** (121 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) at room temperature under an argon atmosphere was added imidazole (38 mg, 0.55 mmol), 4-nitrobenzoyl chloride (102 mg, 0.55 mmol) and 4-dimethylaminopyridine (DMAP) (3 mg). After 24 h. the mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (10 mL), brine (10 mL), dried ($MgSO_4$), and evaporated to give a residue which was purified by flash chromatography over silica gel, eluting with 15% ether/petroleum ether, to give **9** (160 mg, 82%) as a white crystalline solid. A small sample was recrystallized by vapor defusion from ether/petroleum ether. IR (Nujol) 2923, 2854, 1728 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.15–8.3 (4H, m), 5.46 (1H, br s), 4.67 (1H, dd, J=5.1, 11.3 Hz), 4.47 (1H, dd, J=5.3, 11.3 Hz), 4.36 (1H, d, J=5.1 Hz), 3.36 (3H, s), 3.31 (3H, s), 2.6–2.65 (1H, m), 1.3–2.1 (8H, m), 0.89 (3H, d, J=6.6 Hz), 0.82 (3H, d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 164.6, 150.3, 136.3, 133.0, 130.6, 130.6, 123.6, 123.5, 106.6, 66.8, 55.6, 55.1, 52.8, 40.4, 38.0, 36.2, 27.0, 24.4, 22.4, 21.2, 16.5. HRMS (CI) calcd for $C_{21}H_{30}NO_6$ 392.2073. Found 392.2069.

(1*S*,5*R*,6*R*) 2-Methyl-isopropyl-8-oxabicyclo[4.3.0]non-2-en-7-one 10. To a stirred solution of **8** (28.33 g, 0.12 mol) in acetone (600 mL) was slowly added Jones reagent (250 mL) over 25 min. After 11 h, the mixture was transferred to an Erlenmeyer flask, diluted with H_2O (200 mL), and quenched with *i*-PrOH (25 mL). Solid $NaHCO_3$ was added portion-wise until the effervescence ceased. The slurry was filtered through Celite® and rinsed with acetone (4 L). The acetone was removed in vacuo and the aqueous layer was extracted with Et_2O (4×300 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30% Et_2O/petroleum ether to give **10** (16.67 g, 0.086 mol, 73% yield) as a colorless oil. IR (film) 2961, 1771 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.5–5.6 (1H, m), 4.36 (1H, dd, J=7.2, 8.9 Hz), 4.15 (1H, dd, J=4.4, 8.9 Hz), 2.85–2.9 (1H, m), 2.75–2.8 (1H, m), 1.9–2.15 (2H, m), 1.75–1.85 (2H, m), 1.6–1.8 (3H, m), 0.95 (3H, d, J=6.4 Hz), 0.92 (3H, d, J=6.4 Hz). ^{13}C NMR ($CDCl_3$) δ 178.5, 130.0, 124.1, 70.6, 43.5, 41.3, 39.1, 36.8, 27.6, 23.6, 21.0, 19.2. HRMS (CI) calcd for $C_{12}H_{19}O_2$ 195.1385. Found 195.1379.

1-Methyl-(4*R*)-isopropyl-(5*R*),(6*S*)-7-thiophenyl-8-oic-1-cyclohexene 11. To a stirred solution of PhSH (13.1 g,

12.2 mL, 0.12 mol) in DMF (40 mL) was added LiH (945 mg, 0.12 mol) portion-wise. After 45 min, a solution of **10** (16.67 g, 0.086 mol) in DMF (40 mL) was added via cannula to the lithium thiolate solution. An additional amount of DMF (3 mL) was used to rinse the lactone flask. After heating the yellow solution at 110°C for 4 h, the solution was cooled to 0°C, poured into a HCl solution (200 mL, 2 M in H_2O) and Et_2O (300 mL), and extracted with Et_2O (4×300 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5–50% Et_2O/petroleum ether, to give **11** (23.25 g, 0.076 mol, 89% yield) as an off-white solid. mp 69–70°C. $[\alpha]_D^{23}=+47$ ($c=0.90$, $CHCl_3$). IR (film) 3500–2500, 2960, 1703 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35–7.4 (2H, m), 7.15–7.3 (3H, m), 5.40 (1H, br s), 3.22 (1H, dd, $J=7.6$, 13.4 Hz), 3.04 (1H, dd, $J=4.1$, 13.4 Hz), 2.7–2.8 (1H, m), 2.45–2.55 (1H, m), 1.9–2.1 (3H, m), 1.85–1.9 (1H, m), 1.63 (3H, br s), 0.87 (3H, d, $J=6.5$ Hz), 0.77 (3H, d, $J=6.5$ Hz). ^{13}C NMR ($CDCl_3$) δ 180.7, 136.3, 133.9, 130.6, 128.8, 126.3, 122.3, 46.1, 40.2, 35.9, 34.9, 27.6, 23.5, 21.9, 20.8, 16.3. HRMS (CI) calcd for $C_{18}H_{24}O_2S$ 304.1497. Found 304.1488.

1-Methyl-(4*R*)-isopropyl-(5*R*)-hydroxymethyl-(6*S*)-7-thiophenylmethyl-1-cyclohexene 12. To a stirred solution of **11** (23.25 g, 0.076 mol) in acetone (575 mL) was added solid K_2CO_3 (53.0 g, 0.38 mol). After 10 min, MeI (104.9 g, 46 mL, 0.74 mol, filtered through a small plug of basic alumina prior to use) was added. After 1.5 h, H_2O (10 mL) was added, filtered and concentrated in vacuo. The oil was dissolved in Et_2O (300 mL) and saturated aqueous NaCl (300 mL) and extracted with Et_2O (4×300 mL). The dried ($MgSO_4$) extract was concentrated in vacuo to give the methyl ester derivative of **11** (24.16 g, 0.076 mol) as off-white solid which was used directly. $[\alpha]_D^{23}=+40$ ($c=1.19$, $CHCl_3$). IR (film) 2958, 1730 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.15–7.4 (5H, m), 5.39 (1H, br s), 3.70 (3H, s), 3.15 (1H, dd, $J=7.4$, 12.4 Hz), 2.96 (1H, dd, $J=3.7$, 12.4 Hz), 2.69 (1H, dd, $J=4.7$, 9.9 Hz), 2.4–2.45 (1H, m), 1.9–2.0 (3H, m), 1.75–1.85 (1H, m), 1.62 (3H, br s), 0.88 (3H, d, $J=6.5$ Hz), 0.73 (3H, d, $J=6.5$ Hz). ^{13}C NMR ($CDCl_3$) δ 174.3, 136.5, 134.2, 130.6, 128.8, 126.4, 122.2, 51.5, 46.1, 41.0, 35.4, 34.8, 27.5, 23.5, 22.0, 20.8, 15.9. HRMS (CI) calcd for $C_{19}H_{26}O_2S$ 318.1654. Found 318.1651.

To a stirred solution of crude ester (24.16 g, 0.076 mol) in CH_2Cl_2 (1 L) was added DIBAL-H (170 mL, 0.17 mol, 1.0 M in CH_2Cl_2) over 1.25 h via a dropping funnel at −78°C. After an additional 30 min, the mixture was warmed to 0°C for 20 min and recooled to −78°C. The mixture was quenched by the dropwise addition of MeOH (30 mL) followed by the addition of a sodium tartrate solution (700 mL, 10% in H_2O). The mixture was allowed to warm to ambient temperature and stirred for 2 h followed by extraction with CH_2Cl_2 (4×400 mL). The dried ($MgSO_4$) extracted was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30% Et_2O/petroleum ether to give **12** (19.15 g, 0.066 mol, 86% over steps steps) as a colorless oil. IR (film) 3418, 2959 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.20–7.45 (5H, m), 5.39 (1H, br s), 3.83 (1H, dd, $J=4.9$, 11.8 Hz), 2.96 (1H, dd, $J=9.6$, 11.8 Hz), 2.9–3.1 (2H, m), 2.4–2.5 (1H, m), 1.7–2.0 (4H, m), 1.6–1.65 (2H, m), 0.88 (3H, d, $J=6.8$ Hz), 0.81 (3H, d, $J=6.8$ Hz). ^{13}C NMR ($CDCl_3$) δ 136.1, 134.6, 130.1, 129.0, 126.6, 122.7, 61.6, 41.0, 39.3, 36.0, 34.2, 26.7, 24.2, 21.9, 21.0, 15.9. HRMS (CI) calcd for $C_{18}H_{26}OS$ 290.1704. Found 290.1704.

1-Methyl-(4*R*)-isopropyl-(5*R*)-hydroxymethyl-(6*S*)-7-sulfonylphenylmethyl-1-cyclohexene 13. To a stirred solution of **12** (18.34 g, 0.063 mol) in CH_2Cl_2 (200 mL) and H_2O (7.5 mL) was added $Na_2WO_4{\cdot}H_2O$ (1.63 g, 4.9 mmol) and Aliquat® 336 (15 mL) followed by the dropwise addition of H_2O_2 (30 mL, 30% in H_2O). The yellow solution was heated to reflux, and an additional amount of H_2O_2 (70 mL, 30% in H_2O) was added portion-wise periodically during the course of the reaction. After 40 h the mixture was cooled to ambient temperature, solid $NaHSO_3$ was added portion-wise until effervescence ceased followed by extraction with CH_2Cl_2 (3×200 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 50% EtOAc/petroleum ether, to give **13** (18.00 g, 0.054 mol, 89%) as an off-white solid. mp 103–104°C. $[\alpha]_D^{23}=+136$ ($c=1.23$, $CHCl_3$). IR (film) 3525, 2959 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.9–8.0 (2H, m), 7.55–7.7 (3H, m), 5.34 (1H, br s), 3.88 (1H, dd, $J=3.9$, 12.3 Hz), 3.62 (1H, dd, $J=10.2$, 12.3 Hz), 3.45 (1H, dd, $J=5.7$, 15.9 Hz), 2.85–3.0 (2H, m), 1.75–2.0 (4H, m), 1.45–1.5 (3H, m), 1.25–1.4 (2H, m), 0.86 (3H, d, $J=6.8$ Hz), 0.81 (3H, d, $J=6.8$ Hz). ^{13}C NMR ($CDCl_3$) δ 139.1, 134.7, 134.0, 129.4, 128.0, 123.0, 60.9, 57.4, 42.0, 35.6, 33.6, 26.5, 24.2, 21.3, 21.0, 15.2. HRMS (CI) calcd for $C_{18}H_{27}O_3S$ 323.1681. Found 323.1673.

1-Methyl-(4*R*)-isopropyl-(5*R*)-*tert*-butyldimethylsilyl-(oxy)methyl-(6*S*)-7-sulfonylphenylmethyl-1-cyclohexene 14. To a stirred solution of **13** (3.00 g, 9.32 mmol) in DMF (6 mL) was added imidazole (1.50 g, 22.0 mmol) and *tert*-butyldimethylsilylchloride (1.45 g, 9.62 mmol). After 4 h, the mixture was quenched with saturated aqueous NaCl (50 mL) and extracted with Et_2O (3×100 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% Et_2O/petroleum ether, to give **14** (3.915 g, 9.00 mmol, 96%) as a colorless oil. $[\alpha]_D^{23}=+52$ ($c=1.09$, $CHCl_3$). IR (film) 2956, 2929, 2891, 2857 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.9–8.0 (2H, m), 7.5–7.65 (3H, m), 5.38 (1H, br s), 3.84 (1H, dd, $J=4.4$, 14.5 Hz), 3.75 (1H, dd, $J=4.3$, 10.6 Hz), 3.70 (1H, dd, $J=6.2$, 10.6 Hz), 3.07 (1H, dd, $J=5.8$, 14.5 Hz), 2.84 (1H, m), 1.75–2.0 (3H, m), 1.64 (3H, br s), 1.45 (2H, m), 0.86 (3H, d, $J=6.6$ Hz), 0.85 (9H, s), 0.79 (3H, d, $J=6.6$ Hz), 0.06 (3H, s), 0.04 (3H, s). ^{13}C NMR ($CDCl_3$) δ 140.7, 134.5, 133.3, 129.1, 127.8, 123.2, 63.2, 57.2, 40.9, 36.9, 35.8, 27.0, 25.9, 23.9, 22.1, 20.9, 18.1, 16.9, −5.4, −5.8. HRMS (CI) calcd for $C_{24}H_{41}O_3SSi$ 437.2546. Found 437.2540.

(2*R*)-Methyl, 3-[4-nitrobenzoyl(oxy)]-1,2-epoxy-propane 16. To a solution of powdered 3 Å molecular sieves (approximately 3.5 g) in CH_2Cl_2 (150 mL) at −20°C was added (+)-DIPT (1.40 g, 6.0 mmol) in CH_2Cl_2 (10 mL) via cannula followed sequentially by $Ti(OPr^i)_4$ (1.42 g, 1.5 mL, 5.0 mmol) and cumene hydroperoxide (1.31 g, 36 mL, 0.20 mol). After 1 h, a solution of 2-methallyl alcohol **15** (7.20 g, 8.40 mL, 0.100 mol) in CH_2Cl_2 (15 mL) was added

dropwise via cannula. After 16 h, the mixture was treated dropwise with $P(OMe)_3$ (18.62 g, 17.70 mL, 150 mmol), taking care that the temperature did not rise above −20°C. On warming to 0°C, Et_3N (17.0 mL, 0.122 mmol) was added followed by a suspension of 4-nitrobenzoyl chloride (18.60 g, 0.10 mmol) in CH_2Cl_2 (100 mL) via cannula. After 1 h, the mixture was filtered through a pad of Celite®, the filtrate was washed with sequentially with a tartaric acid solution (100 mL, 10% in H_2O), saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl (100 mL). The dried (Na_2SO_4) extract was filtered through a small pad of silica gel and concentrated under in vacuo (60°C, 0.2 mmHg). The oil, which solidified on standing, was recrystallized (twice from Et_2O, then *i*-Pr_2O) to give **16** (12.25 g, 0.053 mol, 52%, >98% e.e.) as an off-white solid. The enantiomeric excess was determined by chiral shift analysis of the methyl signal at 1.2 ppm using $Eu(hfc)_3$ (7 mg of **16**, 4.5 mg of $Eu(hfc)_3$, 0.5 mL of C_6D_6). $[\alpha]_D^{23}=-6$ (c=2.98, $CHCl_3$). mp 85–86°C.

1-Thiophenyl-(2*S*),3-propandiol 17. To a solution of **16** (9.46 g, 39.90 mmol) in dioxane (37 mL) was added PhSH (4.30 mL, 41.85 mmol) and then NaOH (21.0 mL, 42.0 mmol, 2 M in H_2O) dropwise. After 2 h at ambient temperature, solid $NaHCO_3$ (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (4×100 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 70% EtOAc/petroleum ether, to give **17** (7.56 g, 38.2 mmol, 96%) as a colorless oil. IR (film) 3406, 2929 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35–7.45 (2H, m), 7.2–7.3 (2H, m), 7.1–7.2 (1H, m), 3.55 (1H, dd, J=5.7, 11.2 Hz), 3.46 (1H, dd, J=5.0, 11.2 Hz), 3.05–3.25 (4H, m), 1.22 (3H, s). ^{13}C NMR ($CDCl_3$) δ 136.6, 129.3, 128.9, 126.1, 73.1, 68.4, 42.9, 23.3. HRMS (CI) calcd for $C_{10}H_{14}O_2S$ 198.0715. Found 198.0707.

1-Thiophenyl-(2*S*),3-propandiol cyclohexyl ketal 18. To a stirred solution of **17** (7.84 g, 39.60 mmol) in DMF (10 mL) was added 1-methoxycyclohexene (6.00 g, 53.6 mmol) followed by *p*-toluene sulfonic acid (0.30 g, 1.50 mmol). After 40 h at ambient temperature, the mixture was diluted with saturated aqueous brine (250 mL), extracted with EtOAc (3×300 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% EtOAc/petroleum ether, to give **18** (10.68 g, 38.4 mmol, 97%) as a colorless oil. IR (film) 2932 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35–7.4 (2H, m), 7.25–7.35 (2H, m), 7.1–7.2 (1H, m), 3.99 (1H, d, J=8.6 Hz), 3.71 (1H, d, J=8.6 Hz), 3.15 (2H, s), 1.50–1.65 (8H, m), 1.39 (3H, s), 1.3–1.5 (2H, m). ^{13}C NMR ($CDCl_3$) δ 137.0, 129.2, 128.8, 126.0, 110.4, 80.7, 72.6, 43.5, 36.7, 36.3, 25.0, 24.7, 23.9, 23.80. HRMS (CI) calcd for $C_{16}H_{22}O_2S$ 278.1341. Found 278.1335.

1-Phenylsulfinyl-(2*S*),3-propandiol cyclohexyl ketal 19. To a stirred solution of **18** (10.54 g, 37.90 mmol) in CH_2Cl_2 (200 mL) at −20°C was added a solution of *m*-chloroperoxybenzoic acid (7.90 g, 41.20 mmol, approximately 90%) in CH_2Cl_2 (100 mL) via cannula. After 30 min, the mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL) and extracted with Et_2O (4×100 mL), followed by washing of the combined extracts with saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl (100 mL). The dried (Na_2SO_4) extract was concentrated in vacuo to give **63** (11.14 g, 37.90 mmol, 99%) as a colorless oil. IR (film) 2935, 1042 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.4–7.65 (5H, m), 4.37 (1H, d, J=8.9 Hz), 4.06 (1H, d, J=8.9 Hz), 3.77 (2H, m), 2.8–3.0 (2H, m), 1.3–1.8 (10H, m). ^{13}C NMR ($CDCl_3$) δ 144.8, 144.6, 130.8, 129.2, 123.8, 123.7, 110.8, 110.2, 78.5, 73.7, 71.8, 68.3, 68.0, 36.8, 36.4, 36.1, 35.9, 26.7, 24.94, 24.90, 24.4, 23.8, 23.6. HRMS (CI) calcd for $C_{16}H_{22}O_3S$ 295.1368. Found 295.1363.

1-Thiophenyl-1-acetoxy-(2*S*),3-propandiol cyclohexyl ketal 20. To a stirred solution of **19** (10.87 g, 37.0 mmol) in Ac_2O (100 mL) was added NaOAc (20.0 g, 244 mmol) and the mixture heated at reflux. After 16 h, the mixture was cooled to ambient temperature, NaOH (100 mL, 1 M in H_2O) was added and the mixture stirred for 1 h at ambient temperature, followed by extraction with CH_2Cl_2 (3×200 mL). The combined extracts were washed with saturated aqueous NaCl (300 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% EtOAc/petroleum ether, to give the diastereoisomeric acetates **20** (1.7:1), (11.69 g, 34.8 mmol, 94%) as a colorless oil. IR (film) 2933, 1749 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.45–7.55 (6H, m), 7.25–7.35 (4H, m), 6.26 (1H, s, major), 6.19 (1H, s, minor), 4.23 (1H, d, J=9.3 Hz, major), 4.02 (1H, d, J=8.8 Hz, minor), 3.79 (1H, d, J=9.3 Hz, major), 3.72 (1H, d, J=8.8 Hz, minor), 2.05 (3H, s, major), 2.01 (3H, s, minor), 1.25–1.75 (20H, m), 1.45 (3H, s), 1.44 (3H, s). ^{13}C NMR ($CDCl_3$) δ 169.5, 169.2, 133.6, 132.6, 132.5, 132.3, 129.0, 128.9, 128.2, 128.0, 111.4, 111.1, 85.2, 84.8, 82.0, 81.9, 71.9, 71.0, 36.5, 36.1, 36.0, 35.8, 25.0, 23.8, 22.7, 20.9. HRMS (CI) calcd for $C_{18}H_{24}O_4S$ 336.1395. Found 336.1388.

1-Propanal-(2*S*),3-diol cyclohexyl ketal 21. To a stirred solution of **20** (3.50 g, 10.42 mmol) in MeOH (20 mL) was added solid K_2CO_3 (0.950 g, 6.88 mmol) and the mixture heated at reflux. After 5 h, the mixture was cooled to ambient temperature, concentrated in vacuo and Et_2O (100 mL) was added, precipitating a white solid. After filtration through Celite® (Et_2O rinse), the organic phase was concentrated in vacuo followed by purification by Kügelrohr distillation (oven temperature 100°C, 1 mmHg) to give **21** (1.91 g, 10.3 mmol, 99%) as a colorless oil. IR (film) 2939, 2863, 1737 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.66 (1H, s), 4.23 (1H, d, J=8.9 Hz), 3.73 (1H, d, J=8.9 Hz), 1.35–1.7 (10H, m), 1.35 (3H, s). ^{13}C NMR ($CDCl_3$) δ 202.3, 111.8, 84.1, 70.4, 36.3, 35.9, 24.9, 23.8, 19.4. HRMS (CI) calcd for $C_{10}H_{17}O_3$ 185.1178. Found 185.1171.

(*S*)-3-4-Methoxybenzoyl(oxy)-2-methyl-1,2-propanediol 23. To a stirred solution of 1:1 *t*-BuOH/H_2O (48 mL) was added AD-mix-β (6.79 g) and the biphasic mixture was cooled to 0°C. The benzoate **22** (1.00 g, 4.85 mmol) was added and the heterogeneous slurry was stirred vigorously at 0°C for 3.5 h and left to warm to room temperature overnight. Sodium sulfite (7.30 g) was added and stirring continued for a further 30 min. The aqueous layer was extracted with EtOAc (3×50 mL) and the combined extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography over silica

gel, eluting with EtOAc gave **23** (1.02 g, 88%, 97% ee) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.94 (2H, m), 6.87 (2H, m), 4.30 (1H, d, J=11.2 Hz), 4.17 (1H, d, J=11.2 Hz), 3.81 (3H, s), 3.56 (1H, d, J=11.6 Hz), 3.46 (1H, d, J=11.6 Hz), 3.36 (2H, br s), 1.23 (3H, s).

(*S*)-3-4-Methoxybenzoyl(oxy)-2-methyl-1,2-propanediol cyclohexyl ketal 24. To a stirred solution of **23** (2.46 g, 10.29 mmol) in cyclohexanone (30 mL) was added *p*-toluenesulfonic acid (192 mg, 1.02 mmol) and 3 Å molecular sieves (0.5 g). The mixture was heated at 150°C overnight and then cooled to room temperature. Filtration, concentration in vacuo, and flash chromatography over silica gel, eluting with EtOAc gave **24** (2.96 g, 90%) as a colorless oil. IR (film) 2935, 2862, 1718 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.98 (2H, m), 6.91 (2H, m), 4.20 (2H, q, J=10.9 Hz), 4.04 (1H, d, J=8.6 Hz), 3.84 (3H, s), 3.75 (1H, d, J=8.6 Hz), 1.72–1.51 (10H, m), 1.37 (3H, s). ^{13}C NMR ($CDCl_3$) δ 212.1, 131.6, 113.6, 110.5, 71.3, 68.1, 55.4, 41.9, 36.4, 36.2, 27.0, 25.02, 24.96, 23.8, 23.0. HRMS (CI) calcd for $C_{18}H_{25}O_5$ (MH^+) 321.1702. Found 321.1694.

1-Propanol-(2*S*),3-diol cyclohexyl ketal 25. To a stirred solution of **24** (914 mg, 2.98 mmol) in 1:1 THF/H_2O (10 mL) was added lithium hydroxide monohydrate (625 mg, 14.90 mmol) and the resulting solution was stirred at reflux overnight. The solution was poured into brine (10 mL) and extracted with Et_2O (2×10 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography over silica gel, eluting with EtOAc gave **25** (510 mg, 92%) as a colorless oil. IR (film) 3460 (br), 2976, 2950, 2876 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.94 (1H, m), 3.70 (1H, m), 3.47 (2H, m), 1.91 (1H, br t), 1.71–1.50 (10H, m), 1.27 (3H, s). HRMS (CI) calcd for $C_{10}H_{19}O_3$ (MH^+) 187.1334. Found 187.1331.

1-Propanal-(2*S*),3-diol cyclohexyl ketal 21. To a solution of **25** (21.1 mg, 113.4 μmol) in CH_2Cl_2 (3.73 mL) was added Dess–Martin triacetoxyperiodinane (69.0 mg, 161.5 μmol). After 30 min the mixture was diluted with Et_2O (3 mL), quenched with saturated aqueous $NaHCO_3$ (2 mL), and $Na_2S_2O_3$ (35 mg). After 10 min stirring the solution became clear, and the layers were separated and the aqueous layer extracted with Et_2O (3×3 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography over silica gel, eluting with 50% EtOAc/hexane, gave **21** (17.3 mg, 83%) as a colorless oil.

1-Methyl-(4*R*)-isopropyl-(5*R*)-*tert*-butyldimethylsiloxymethyl-(6*S*)-[(7*S*)-phenylsulfonyl-(9*S*)-methyl-(8*S*),9,10-butanetriol 9,10-cyclohexyl ketal]-1-cyclohexene 26 and 1-methyl-(4*R*)-isopropyl-(5*R*)-*tert*-butyldimethylsiloxy-(6*S*)-[(7*S*)-phenylsulfonyl-(9*S*)-methyl-(8*R*),9,10-butantriol 9,10-cyclohexyl ketal]-methyl-1-cyclohexene 27. *Procedure 1:* To a stirred solution of **14** (3.91 g, 8.97 mmol) in benzene (18 mL) was added EtMgBr (3.75 mL, 10.13 mmol, 2.7 M in Et_2O) and the mixture was heated at reflux. After 16 h, the solution was allowed to cool to ambient temperature and a solution of **21** (4.95 g, 9.11 mmol) in benzene (8 mL) was added via cannula. After 2 h, the mixture was quenched with saturated aqueous NH_4Cl (100 mL), extracted with EtOAc (3×100 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10–30% Et_2O/petroleum ether, to give a mixture of **26** and **27** (3.56 g, 5.74 mmol, 64%) as an off-white solid. The diastereomers **26** and **27** could be separated by PLC of the mixture, eluting with 15% Et_2O/petroleum ether.

Procedure 2: To a stirred solution of **14** (1.17 g, 2.68 mmol) in THF (9 mL) at −78°C was added *n*-BuLi (1.20 mL, 2.76 mmol, 2.3 M in hexanes). The mixture was immediately warmed to 0°C. After 15 min, the mixture was recooled to −78°C and a solution of **21** (0.495 g, 2.69 mmol) in THF (6 mL) was added via cannula. After 1 h, the mixture was warmed to 0°C for an additional 1 h, quenched with saturated aqueous NH_4Cl (100 mL), and extracted with EtOAc (3×100 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10–30% Et_2O/petroleum ether, to give **26** and **27** (1.10 g, 1.77 mmol, 66%) as an off-white solid. Crystals of **26** suitable for X-ray crystallography were obtained by recrystallization from hexanes. Data for **26**. mp 139–140°C. $[\alpha]_D^{23}$=+75 (c=0.44, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.05–8.1 (2H, m), 7.45−7.6 (3H, m), 5.48 (1H, br s), 4.72 (1H, br s), 4.29 (1H, d, J=9.4 Hz), 4.12 (1H, dd, J=2.2, 10.9 Hz), 4.05 (1H, d, J=5.9 Hz), 3.91 (1H, d, J=9.4 Hz), 3.83 (1H, dd, J=5.9, 10.9 Hz), 3.11 (1H, d, J=4.1 Hz), 3.05 (OH, m), 1.40–2.15 (16H, m), 1.35 (3H, s), 1.24 (3H, s), 0.93 (9H, s), 0.87 (3H, d, J=6.9 Hz), 0.74 (3H, d, J=6.9 Hz), 0.14 (3H, s), 0.11 (3H, s). ^{13}C NMR ($CDCl_3$) δ 141.0, 134.2, 133.2, 130.4, 129.1, 128.2, 125.6, 108.7, 84.6, 75.9, 71.2, 65.7, 63.6, 42.9, 42.8, 37.4, 35.9, 35.6, 33.3, 26.5, 26.0, 25.0, 24.9, 23.9, 23.6, 23.4, 21.0, 18.7, 14.4, −5.1, −5.6. HRMS (CI) calcd for $C_{34}H_{57}O_6SSi$ 621.3586. Found 621.3601. Data for **27**. ^{1}H NMR ($CDCl_3$) δ 7.85–7.95 (2H, m), 7.55–7.6 (1H, m), 7.45–7.5 (2H, m), 5.50 (1H, br s), 4.25 (1H, br d, J=11.1 Hz), 4.11 (1H, d, J=8.0 Hz), 4.06 (1H, d, J=10.3 Hz), 3.90 (1H, dd, J=5.5, 11.1 Hz), 3.65–3.8 (2H, m), 3.54 (1H, d, J=8.0 Hz), 3.12 (OH, br s), 1.5–2.0 (12H, m), 1.35–1.5 (2H, m), 0.9–1.0 (12H, m), 0.80 (3H, d, J=6.6 Hz), 0.06 (3H, s), 0.05 (3H, s).

1-Methyl-(4*R*)-isopropyl-(5*R*)-*tert*-butyldimethylsiloxymethyl-(6*S*)-[7-(9*S*)-methyl-(8*R*),9,10-butantriol 9,10-cyclohexyl ketal]-1-cyclohexene 28. To a solution of **26** (90 mg, 0.15 mmol) in THF (1 mL) and NH_3 (5 mL, distilled over Na) at −78°C was added Na (30 mg, 1.30 mmol). After 10 min, the blue solution was quenched at −78°C with solid NH_4Cl. After warming to ambient temperature, the mixture was diluted with CH_2Cl_2 and filtered through Celite® (CH_2Cl_2 rinse). The extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% Et_2O/petroleum ether, to give **28** (38 mg, 0.08 mmol, 53%) as a colorless oil. $[\alpha]_D^{23}$=+127 (c=1.24, $CHCl_3$). IR (film) 3430, 2923 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.26 (1H, br s), 4.24 (1H, d, J=1.7 Hz), 4.14 (1H, d, J=8.7 Hz), 3.85 (1H, dd, J=5.0, 11.1 Hz), 3.72 (1H, d, J=8.7 Hz), 3.6–3.65 (2H, m), 2.2–2.25 (1H, m), 1.3–1.9 (20H, m), 1.23 (3H, s), 0.90 (9H, s), 0.88 (3H, d, J=6.8 Hz), 0.80 (3H, d, J=6.8 Hz), 0.10 (3H, s), 0.09 (3H, s). ^{13}C NMR ($CDCl_3$) δ 138.9, 119.3, 109.7, 82.4, 76.6, 73.3, 62.8, 41.8, 37.2, 36.7, 36.5, 36.2, 32.1, 26.6, 25.9,

25.2, 24.3, 23.9, 23.9, 22.9, 21.1, 19.3, 18.3, 15.3, −5.0, −5.4. HRMS (CI) calcd for $C_{28}H_{52}O_4Si$ 480.3635. Found 480.3606.

1-Methyl-(4*R*)-isopropyl-(5*R*)-*tert*-butyldimethylsiloxymethyl-(6*S*)-[7-(9*S*)-methyl-(8*S*),9,10-butantriol 9,10-cyclohexyl ketal]-1-cyclohexene 29. To a solution of **27** (38 mg, 0.06 mmol) in THF (1 mL) and NH_3 (2 mL, distilled over Na) at −78°C was added Na (0.020 g, 0.87 mmol). After 15 min, the blue solution was quenched at −78°C with solid NH_4Cl. After warming to ambient temperature, the mixture was diluted with CH_2Cl_2 and filtered through Celite® (CH_2Cl_2 rinse). The extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% Et_2O/petroleum ether, to give **29** (6.0 mg, 0.013 mmol, 21%) as a colorless oil. $[\alpha]_D^{23}=+54°$ (c=0.90, $CHCl_3$). IR (film) 3566, 2934 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.32 (1H, br s), 3.90 (1H, d, J=8.4 Hz), 3.75 (2H, m), 3.68 (1H, d, J=8.4 Hz), 3.52 (1H, apparent t), 2.50 (1H, m), 2.44 (1H, d, J=3.7 Hz), 1.3–2.0 (20H, m), 1.26 (3H, s), 0.9–1.0 (12H, m), 0.83 (3H, d, J=6.7 Hz), 0.05 (6H, s). ^{13}C NMR ($CDCl_3$) δ 137.1, 120.9, 110.1, 83.5, 73.7, 71.2, 62.4, 40.5, 36.6, 36.4, 34.6, 31.5, 27.0, 26.0, 25.1, 24.2, 23.9, 22.3, 20.9, 20.5, 18.2, 17.2, −5.3, −5.4. HRMS (CI) calcd for $C_{28}H_{52}O_4Si$ 480.3635. Found 480.3609.

1-Methyl-(4*R*)-isopropyl-(5*R*)-*tert*-butyldimethylsiloxymethyl-(6*S*)-[(7S)-phenylsulfonyl-(9*S*)-methyl-9,10-butandiol-8-one 9,10-cyclohexyl ketal]-1-cyclohexene 30. To a solution of **26/27** (1.35 g, 2.18 mmol) in CH_2Cl_2 (20 mL) was added Dess–Martin periodinane (1.15 g, 2.71 mmol). After 2 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL), and $NaHSO_3$ (15 mL, 1 M in H_2O), diluted with Et_2O (15 mL) and stirred until the solution became clear. The layers were allowed to separate, and the aqueous layer was extracted with Et_2O (3×50 mL). The combined extracts were washed with saturated aqueous NaCl (100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by chromatography over silica gel, eluting with 20% Et_2O/petroleum ether, to give **30** (1.26 g, 2.04 mmol, 94%) as a colorless oil. $[\alpha]_D^{23}=-0.5$ (c=0.99, $CHCl_3$). IR (film) 2938, 1719 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.5–8.0 (2H, m), 7.5–7.65 (3H, m), 5.69 (1H, d, J=1.5 Hz), 5.32 (1H, br s), 3.75–3.9 (2H, m), 3.78 (1H, d, J=9.0 Hz), 3.61 (1H, dd, J=3.3, 10.8 Hz), 3.25 (1H, br s), 1.35–1.95 (21H, m), 0.93 (9H, s), 0.84 (3H, d, J=6.7 Hz), 0.76 (3H, d, J=6.7 Hz), 0.11 (3H, s), 0.10 (3H, s). ^{13}C NMR ($CDCl_3$) δ 204.4, 140.0, 135.6, 133.7, 129.7, 128.6, 123.4, 112.3, 112.3, 86.6, 73.7, 68.3, 63.2, 43.6, 42.0, 36.4, 36.0, 35.7, 27.0, 26.03, 25.96, 24.9, 24.3, 24.0, 23.6, 23.5, 20.4, 18.6, 15.2, −5.1, −5.4. HRMS (CI) calcd for $C_{34}H_{55}O_6SiS$ 619.3489. Found 619.3478.

1-Methyl-(4*R*)-isopropyl-(5*R*)-*tert*-butyldimethylsiloxymethyl-(6*S*)-[7-(9*S*)-methyl-9,10-butandiol-8-one 9,10-cyclohexyl ketal]-1-cyclohexene 31. To NH_3 (250 mL, distilled over Na) at −78°C was added Na (1.30 g, 54.20 mmol). After 30 min, a solution of **30** (3.39 g, 5.49 mmol) in THF (50 mL) was added via cannula and stirred for a further 30 min. The mixture was quenched at −78°C by the sequential addition of isoprene (4 mL) followed by solid NH_4Cl. After warming to ambient temperature, the mixture was diluted with H_2O (100 mL) and extracted with EtOAc (4×100 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10% Et_2O/petroleum ether, to give **31** (2.42 g, 5.06 mmol, 92%) as a colorless oil. $[\alpha]_D^{23}=+66$ (c=1.10). IR (film) 2956, 1716 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.30 (1H, br s), 4.24 (1H, d, J=8.8 Hz), 3.76 (1H, d, J=8.8 Hz), 3.64 (1H, dd, J=5.8, 10.6 Hz), 3.51 (1H, dd, J=8.0, 10.6 Hz), 2.9–3.0 (2H, m), 2.65 (1H, dd, J=8.0, 10.4 Hz), 1.4–2.0 (16H, m), 1.39 (3H, s), 0.91 (3H, d, J=5.9 Hz), 0.86 (9H, s), 0.81 (3H, d, J=5.9 Hz), 0.00 (3H, s), −0.01 (3H, s). ^{13}C NMR ($CDCl_3$) δ 212.6, 136.9, 121.2, 111.5, 86.0, 72.0, 63.0, 40.7, 37.8, 37.5, 36.1, 35.7, 33.1, 27.0, 25.9, 25.0, 24.2, 23.8, 23.7, 22.4, 21.1, 18.2, 17.0, −5.4, −5.5. HRMS (CI) calcd for $C_{28}H_{47}O_4Si$ 479.3557. Found 479.3537.

1-Methyl-(4*R*)-isopropyl-(5*R*)-*tert*-butyldimethylsiloxymethyl-(6*S*)-[7-(9*S*)-methyl-(8*R*),9,10-butantriol 9,10-cyclohexyl ketal]-1-cyclohexene 28 and 1-methyl-(4*R*)-isopropyl-(5*R*)-*tert*-butyldimethylsiloxymethyl-(6*S*)-[7-(9*S*)-methyl-(8*S*),9,10-butantriol 9,10-cyclohexyl ketal]-1-cyclohexene 29. To a solution of **31** (221 mg, 0.462 mmol) in THF (1.5 mL) was added K-Selectride® (2.1 mL, 2.1 mmol, 1 M in THF) was added dropwise over 5 min via syringe pump at 0°C. After 1 h, the mixture was allowed to warm to ambient temperature, and an additional amount of K-Selectride® (1 mL, 1.0 mmol, 1 M in THF) was added. After 7 h total reaction time, the solution was cooled to 0°C and quenched with aqueous ethanol solution (3 mL, 50% in H_2O), followed by NaOH (3 mL, 3 M in H_2O) and H_2O_2 (3 mL, 30% in H_2O). After 15 min at 0°C, the solution was diluted with H_2O (30 mL) and extracted with Et_2O (5×30 mL). The dried ($MgSO_4$) extract was concentrated in vacuo, filtered through a small plug of silica gel (30% Et_2O/petroleum ether rinse) and purified by MPLC, eluting with 7% Et_2O/petroleum ether, to give the undesired alcohol **28** (11 mg, 0.0229 mmol, 5%) as a colorless oil followed by the desired alcohol **29** (171 mg, 0.356 mmol, 77%) as a colorless oil.

1-Methyl-(4*R*)-isopropyl-(5*R*)-keto-(6*S*)-[7-(8*S*)-(9*S*)-methyl-9,10-butanediol 9,10-cyclohexyl ketal]-8,11-oxido-1-cyclohexene 32. To a stirred solution of **29** (1.84 g, 3.83 mmol) in THF (27 mL) was added *n*-Bu_4NF (TBAF) (16 mL, 16 mmol, 1 M in THF) at ambient temperature. After 10 min, saturated aqueous $NaHCO_3$ (200 mL) was added and the THF evaporated in vacuo. The aqueous layer was extracted with Et_2O (4×200 mL), dried ($MgSO_4$), concentrated in vacuo and purified by chromatography over silica gel, eluting with 50% Et_2O/petroleum ether, to give the diol (1.40 g, 3.83 mmol, 99%) as a viscous, colorless oil. IR (film) 3441, 2937, 1447 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.35 (1H, br s), 3.94 (1H, d, J=8.6 Hz), 3.6–3.8 (4H, m), 2.5–2.55 (1H, m), 1.0–2.1 (20H, m), 1.28 (3H, s), 0.92 (3H, d, J=6.7 Hz), 0.83 (3H, d, J=6.7 Hz). HRMS (CI) calcd for $C_{22}H_{38}O_4$ 266.2770. Found 366.2753. Used directly in the next step.

To a stirred solution of the diol (1.40 g, 3.83 mmol) in CH_2Cl_2 (47 mL) with powdered 4 Å molecular sieves (approx 5 g) was added *N*-methylmorpholine *N*-oxide (NMO) (1.76 g, 15.0 mmol) and *n*-Pr_4NRuO_4 (TPAP)

(50 mg, 0.14 mmol) at ambient temperature. An additional amount of TPAP (29 mg, 0.08 mmol) was added during the course of the reaction. After 27 h, the mixture was diluted with Et_2O (100 mL), filtered through silica gel (500 mL Et_2O rinse) and concentrated in vacuo. The residue was purified by chromatography over silica gel, eluting with 50% Et_2O/petroleum ether to give **32** (1.21 g, 3.34 mmol, 87%) as a colorless oil. $[\alpha]_D^{23}=-40$ (c=0.78, $CHCl_3$). IR (film) 2935, 2863, 1729 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.51 (1H, br s), 4.10 (1H, d, J=9.0 Hz), 3.97 (1H, dd, J=2.6, 11.7 Hz), 3.67 (1H, d, J=9.0 Hz), 2.7–2.8 (1H, m), 2.5–2.6 (1H, br s), 2.26 (1H, dt, J=3.6, 14.4 Hz), 1.9–2.1 (2H, m), 1.4–1.9 (19H, m), 0.91 (6H, d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$) δ 173.7, 131.8, 125.0, 110.7, 80.6, 79.2, 69.8, 43.0, 40.3, 36.2, 35.6, 31.3, 26.6, 25.7, 25.1, 24.6, 24.1, 23.84, 23.78, 21.1, 20.7, 20.3. HRMS (CI) calcd for $C_{22}H_{34}O_4$ 262.2457. Found 362.2445.

1-Methyl-(4*R*)-isopropyl-(5*R*)-(6*S*)-[7-(8*S*)-(9*S*)-methyl-9,10-butandiol 9,10-cyclohexyl ketal]-(11*S*)-hydroxyl-8,11-oxido-1-cyclohexene 33. A stirred solution of **32** (1.21 g, 3.34 mmol) in CH_2Cl_2 (43 mL) was cooled to −78°C and DIBAL-H (3.4 mL, 3.4 mmol, 1.0 M in CH_2Cl_2) was added via syringe pump over 10 min. An additional amount of DIBAL-H (0.4 mL, 0.4 mmol, 1 M in CH_2Cl_2) was added during the course of the reaction. After 70 min, the mixture was quenched with MeOH (0.5 mL) followed by HCl (50 mL, 2 M in H_2O), warmed to ambient temperature and stirred for 15 min. The aqueous layer was extracted with CH_2Cl_2 (4×50 mL), dried ($MgSO_4$) and concentrated in vacuo to give **33** as a colorless oil which was >95% pure by ^1H NMR and used without further purification. IR (film) 3429, 2983, 2859 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.42 (1H, br s), 4.76 (1H, dd, J=5.7, 8.6 Hz), 4.01 (1H, d, J=8.7 Hz), 3.65 (1H, d, J=8.7 Hz), 3.24 (1H, d, J=11.2 Hz), 2.74 (1H, d, J=5.6 Hz), 2.5 (1H, br s), 2.1 (1H, br s), 1.96 (1H, d, J=13.7 Hz), 1.3–1.8 (21H, m), 0.90 (3H, d, J=6.3 Hz), 0.87 (3H, d, J=6.3 Hz). HRMS (CI) calcd for $C_{22}H_{36}O_4$ 364.2614. Found 364.2606.

1-Methyl-(4*R*)-isopropyl-(5*R*)-(6*S*)-[7-(8*S*)-(9*S*)-methyl-10-butanol]-8,9,(11*R*)-bis-oxido-1-cyclohexene 35 and 1-methyl-(4*R*)-isopropyl-(5*R*)-(6*S*)-[7-(8*S*)-(9*S*)-methyl-9,10-butandiol]-(11*S*)-methoxy-8,11-oxido-1-cyclohexene 34. To a stirred solution of crude **33** (1.22 g, 3.34 mmol) in MeOH (173 mL) was added *p*-toluenesulfonic acid (2.13 g, 11.2 mmol) at ambient temperature. After 14 h, solid $NaHCO_3$ was added followed by saturated aqueous $NaHCO_3$, and the mixture filtered and rinsed with H_2O and Et_2O. The filtrate was concentrated in vacuo to remove the MeOH, extracted with EtOAc (6×200 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography over silica gel, eluting with 50% Et_2O/petroleum ether, to give **35** (590 mg, 2.21 mmol, 67%) as a colorless oil. Further elution with EtOAc gave the diol **34** (225 mg, 0.76 mmol, 23%) as a colorless oil. Data for **35**. $[\alpha]_D^{23}=-11$ (c=1.09). IR (film) 3448, 2926 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.61 (1H, s), 5.39 (1H, m), 4.05 (1H, d, J=3.4 Hz), 3.49 (1H, d, J=10.5 Hz), 3.42 (1H, d, J=10.5 Hz), 2.55–2.7 (1H, m), 2.0–2.15 (2H, m), 1.8–2.0 (2H, m), 1.5–1.8 (6H, m), 1.45 (3H, s), 0.87 (3H, d, J=7.0 Hz), 0.76 (3H, d, J=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 135.5, 121.7, 102.7, 81.6, 68.8, 40.7, 36.0, 33.0, 28.3, 26.0, 24.1, 21.2, 15.9, 14.7. HRMS (CI) calcd for $C_{16}H_{27}O_3$ 267.1960. Found 267.1967. Data for **34**. IR (film) 3445, 2961 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.41 (1H, br s), 4.40 (1H, d, J=8.7 Hz), 3.64 (1H, dd, J=3.5, 11.1 Hz), 3.4–3.6 (4H, m), 3.46 (1H, dd, J=1.3, 12.0 Hz), 2.7 (OH, s), 2.4–2.6 (2H, m), 1.9–2.1 (3H, m), 1.75–1.85 (1H, m), 1.4–1.7 (8H, m), 0.90 (3H, d, J=6.3 Hz), 0.87 (3H, d, J=6.3 Hz). HRMS (CI) calcd for $C_{17}H_{30}O_4$ 298.2144. Found 298.2139.

To a solution of **34** (339 mg, 1.14 mmol) in MeOH (5 mL) was added *p*-toluene sulfonic acid (304 mg, 1.60 mmol) at ambient temperature. After 16 h, the mixture was quenched with solid $NaHCO_3$, diluted with H_2O (25 mL) and extracted with EtOAc (4×50 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 50% Et_2O/petroleum ether, to give **35** (213 mg, 0.801 mmol, 70%) as a colorless oil and. Further elution with EtOAc gave starting material **34** (71 mg, 0.238 mmol, 21%).

1-Methyl-(4*R*)-(5*R*)-isopropyl(6*S*)-[7-(8*S*)-(9*R*)-methyl-10-butanal]-8,9,(11*R*)-bis-oxido-1-cyclohexene 36. To a solution of **34** (52.0 mg, 0.195 mmol) in CH_2Cl_2 (2.5 mL) was added Dess–Martin periodinane (120 mg, 0.283 mmol) at ambient temperature. After 2 h the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and $NaHSO_3$ (5 mL, 1 M in H_2O), diluted with Et_2O (5 mL), and stirred until the solution was clear. The layers were allowed to separate and the aqueous layer was extracted with Et_2O (3×20 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30% Et_2O/petroleum ether, to give **36** (46.0 mg, 0.174 mmol, 89%) as an off-white solid. $[\alpha]_D^{23}=+44$ (c=0.99, $CHCl_3$). IR (film) 2959, 1732 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.65 (1H, s), 5.80 (1H, s), 5.4–5.45 (1H, m), 4.42 (1H, d, J=5.0 Hz), 2.5–2.6 (1H, m), 2.0–2.1 (1H, m), 1.8–2.0 (2H, m), 1.5–1.8 (7H, m), 1.40 (3H, s), 0.91 (3H, d, J=6.9 Hz), 0.79 (3H, d, J=6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 204.2, 135.0, 122.0, 103.9, 85.4, 77.2, 40.5, 36.0, 32.8, 28.0, 26.0, 24.1, 21.1, 14.7, 13.6. HRMS (CI) calcd for $C_{16}H_{25}O_3$ 265.1804. Found 265.1795.

1-Methyl-(4*R*)-isopropyl-(5*R*)-(6*S*)-[7-(8*S*)-(9*S*)-methyl-10-*Z*-octen-12-on-14-oate ethyl ester]-8,9,(15*R*)-bis-oxido-1-cyclohexene 37. To a solution of the phosphonium salt (307 mg, 0.651 mmol) in THF (2 mL) and *N,N′*-dimethylpropyleneurea (DMPU) (2 mL) was added NaH (55 mg, 1.38 mmol, 60% in mineral oil) at ambient temperature. After 20 min, a solution of **36** (101 mg, 0.383 mmol) in THF (1 mL) was added via cannula. An additional amount of THF (2×0.5 mL) was added to rinse the aldehyde flask. After 50 min at ambient temperature, the solution was heated to 40°C. After 1.5 h, the mixture was allowed to cool to ambient temperature and quenched with saturated aqueous NH_4Cl (10 mL), extracted with Et_2O (3×20 mL), washed with saturated aqueous NaCl (50 mL), and extracted with Et_2O (3×50 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 15–30% Et_2O/petroleum ether, to give the desired *cis* isomer **37** (121 mg, 0.322 mmol, 84%) as a colorless oil followed by the undesired *trans* isomer (8.0 mg, 0.213 mmol, 6%) as a

colorless oil. Data for **37**. IR (film) 2958, 1741, 1695, 1649 cm^{-1}. ^1H NMR (C_6D_6) δ 6.30 (1H, d, J=13.1 Hz, enol), 6.04 (1H, d, J=12.5 Hz, ketone), 5.84 (1H, s, enol), 5.76 (1H, s, ketone), 5.61 (1H, d, J=12.5 Hz, ketone), 5.3–5.4 (1H, m), 5.21 (1H, dd, J=1.9, 13.1 Hz, enol), 5.01 (1H, s, enol), 4.87 (1H, d, J=3.5 Hz, enol), 4.45 (1H, d, J=3.4 Hz, ketone), 3.91 (2H, q, J=7.2 Hz), 3.18 (2H, s, ketone), 2.5–2.7 (1H, m), 2.0–2.2 (1H, m), 1.7–2.0 (4H, m), 1.5–1.7 (9H, m), 0.91 (3H, t, J=7.3 Hz), 0.82 (3H, apparent t), 0.6–0.7 (3H, m). ^{13}C NMR (C_6D_6) δ 193.7, 173.5, 169.8, 166.8, 154.6, 153.3, 136.0, 135.8, 124.5, 121.9, 120.4, 102.5, 102.1, 94.0, 83.6, 83.3, 80.7, 79.6, 61.0, 60.3, 50.8, 41.0, 40.8, 36.4, 33.4, 30.2, 28.7, 28.6, 26.2, 24.6, 24.5, 21.4, 21.3, 19.7, 18.2, 14.9, 14.1, 14.0. HRMS (CI) calcd for $C_{22}H_{33}O_5$ 377.2328. Found 377.2321. Data for *trans*-**37**. ^1H NMR (C_6D_6) δ 6.78 (1H, apparent t, ketone/enol), 6.52 (1H, d, J=15.5 Hz, ketone), 6.26 (1H, d, J=15.5 Hz, enol), 5.75 (1H, s, enol), 5.72 (1H, s, ketone), 5.37 (1H, br s), 5.17 (1H, s, enol), 3.9–4.0 (2H, m), 3.60 (1H, d, J=2.7 Hz, enol), 3.56 (1H, d, J=2.7 Hz, ketone), 3.26 (2H, s, ketone), 2.45–2.65 (1H, m), 2.0–2.1 (1H, m), 1.7–1.9 (2H, m), 1.1–1.7 (10H, m), 0.8–1.0 (3H, m), 0.82 (3H, d, J=6.8 Hz), 0.6–0.7 (3H, m). HRMS (CI) calcd for $C_{22}H_{33}O_5$ 377.2328. Found 377.2324.

1-Methyl-(4*R*)-isopropyl-(5*R*)-(6*S*)-[7-(8*S*)-(9*S*)-methyl-10-*Z*-octen-12-en-14-oate ethyl ester]-8,15-oxido-9,12-oxido-1-cyclohexene 38. To a stirred solution of **37** (24.5 mg, 0.0652 mmol) in CH_2Cl_2 (1 mL) was added $BF_3{\cdot}Et_2O$ (3.5 mg, 3.0 μL, 0.024 mmol) at −78°C. After 1 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL) and extracted with CH_2Cl_2 (4×2 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by PLC, eluting with 30% Et_2O/petroleum ether, to give **38** (14 mg, 0.037 mmol, 56%) as a colorless oil. Data for **38**. IR (film) 3424, 2969, 2927, 1696, 1635 cm^{-1}. ^1H NMR (C_6D_6) δ 7.69 (1H, d, J=5.9 Hz), 6.33 (1H, dd, J=1.2, 5.9 Hz), 5.73 (1H, d, J=1.2 Hz), 5.27 (1H, br s), 4.48 (1H, d, J=8.3 Hz), 4.0–4.2 (2H, m), 3.30 (1H, d, J=11.4 Hz), 2.32 (1H, br s), 2.16 (1H, br s), 1.9–2.1 (2H, m), 1.55–1.75 (3H), 1.48 (3H, s), 1.2–1.45 (4H, m), 1.02 (3H, t, J=7.1 Hz), 0.85 (3H, d, J=6.6 Hz), 0.78 (3H, d, J=6.6 Hz). HRMS (CI) calcd for $C_{22}H_{33}O_5$ 377.2328. Found 377.2319.

5-Methyl-1-furyl-ethyl acetate 39. To a stirred solution of **38** (22 mg, 0.059 mmol) in CH_2Cl_2 (1 mL) was added $BF_3{\cdot}Et_2O$ (1.5 mg, 1.3 μL, 0.011 mmol) at −35°C. After 30 min, the mixture was allowed to warm to −20°C over 1 h followed by warming to 0°C. After 1 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (4×15 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by PLC, eluting with 30% Et_2O/petroleum ether, to give sequentially **39** (trace), **38** (2.6 mg, 6.9 μmol, 12%) as a colorless oil.

To a stirred solution of **37** (18.5 mg, 0.0492 mmol) in CH_2Cl_2 (1 mL) was added $BF_3{\cdot}Et_2O$ (31.2 mg, 27.0 μL, 0.220 mmol) at −78°C. After 20 min, the mixture was warmed to −5°C. After 1.25 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (4×15 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by PLC, eluting with 30% Et_2O/petroleum ether to give **39** (1.5 mg, 0.089 mmol, 18%) as a colorless liquid. IR (film) 2926, 1730 cm^{-1}. ^1H NMR (C_6D_6) δ 6.02 (1H, d, J=2.9 Hz), 7.73 (1H, d, J=2.9 Hz), 3.84 (2H, q, J=7.4 Hz), 3.40 (2H, s), 1.96 (3H, s), 0.86 (3H, t, J=7.4 Hz). HRMS (CI) calcd for $C_9H_{13}O_3$ 169.0865. Found 169.0867.

1-Methyl-(4*R*)-isopropyl-(5*R*)-dimethyl acetal-(6*R*)-[7-9-methyl-9-*E*-butene-10-ol]-1-cyclohexene 42. A solution of 9-BBN (0.5 M in THF, 10.5 mL, 5.25 mmol) was added dropwise to **7** (1.12 g, 5.0 mmol). After 20 h at 45°C, the mixture was allowed to cool to ambient temperature. To a stirred solution of freshly prepared $Pd(PPh_3)_4$ (175 mg, 0.15 mmol) and the vinyl bromide **41** (755 mg, 5.0 mmol) in THF (3 mL) was added the borane adduct prepared above followed by NaOH (5.0 mL, 3 M in H_2O) in the dark. The resulting mixture was heated at 65°C for 6 h, cooled to 0°C and treated with H_2O_2 (1.5 mL, 30% in H_2O). After stirring at ambient temperature for 1 h, H_2O (25 mL) was added and the mixture was extracted with Et_2O (5×50 mL). The combined extracts were washed with saturated aqueous NaCl (2×50 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 25% Et_2O/petroleum ether, to give starting diene **7** (367 mg, 1.64 mmol, 33%) followed by **42** (651 mg, 2.20 mmol, 44%) as a yellow oil. IR (film) 3378, 2955 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.50 (1H, m), 5.29 (1H, br s), 4.28 (1H, d, J=5.8 Hz), 3.95 (2H, s), 3.31 (6H, s), 2.2–2.25 (3H, m), 1.5–1.9 (8H, m), 1.64 (3H, s), 0.85 (3H, d, J=7.0 Hz), 0.77 (3H, d, J=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 137.2, 133.7, 127.5, 121.1, 107.1, 69.3, 54.5, 54.3, 40.9, 39.2, 36.4, 28.8, 27.4, 24.5, 23.0, 21.3, 16.8, 13.8. HRMS (CI) calcd for $C_{18}H_{33}O_3$ 297.2417. Found 297.2429.

1-Methyl-(4*R*)-isopropyl-(5*R*)-(6*R*)-[7-(8*R*)-methoxy-(9*S*)-methyl-10-butanol]-(11*R*)-methoxy-9,11-oxido-1-cyclohexene 45 and 1-methyl-(4*R*)-isopropyl-(5*R*)-dimethyl acetal-(6*R*)-[7-(9*R*)-methyl-(8*R*),9-epoxy-10-butanol]-1-cyclohexene 43. To a stirred solution of (+)-diisopropyltartrate (56 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) at −40°C was added powdered 3 Å molecular sieves (60 mg) followed by $Ti(OPr^i)_4$ (56 mg, 0.20 mmol) and *tert*-butylhydroperoxide (0.66 mL, 2.0 mmol, 3 M in isooctane). After 45 min, a solution of **42** (296 mg, 1.0 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After 24 h, the mixture was allowed to warm to 0°C and poured into a stirred solution of ferrous sulfate heptahydrate (1.6 g), tartaric acid (0.5 g) and H_2O (5 mL) at 0°C. After 10 min, the two phases were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined extracts were poured into a stirred, precooled solution of (0°C, 1.0 mL) prepared from NaCl (5 g) and NaOH (30 g) in H_2O (90 mL). The mixture was stirred at 0°C for 1 h, diluted with H_2O (5 mL) and the two phases separated. The aqueous layer was extracted with Et_2O (2×10 mL), the combined extracts washed with saturated aqueous NaCl (20 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 40% Et_2O/petroleum ether, to give the acetal **45** (262 mg, 0.840 mmol, 84%) as a colorless oil followed by the epoxide **43** (31 mg, 0.0993 mmol, 10%) as a colorless oil. Data for **45**. IR (film) 3433, 2928 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.42 (1H, br s), 5.05 (1H, s), 4.51 (1H, d, J=7.9 Hz), 3.65–3.75 (2H, m), 3.37 (3H, s), 3.34 (3H, s), 3.19 (1H, dd, J=8.7, 3.7 Hz), 2.44 (OH, br s), 1.8–1.95 (5H,

m), 1.73 (3H, s), 1.45–1.55 (2H, m), 1.18 (3H, s), 0.86 (3H, d, J=6.2 Hz), 0.83 (3H, d, J=6.2 Hz). ^{13}C NMR ($CDCl_3$) δ 133.9, 123.6, 99.7, 79.2, 67.6, 57.9, 55.1, 45.7, 39.2, 34.1, 29.5, 27.1, 24.0, 21.6, 20.8, 20.3, 17.7. HRMS (CI) calcd for $C_{18}H_{33}O_4$ 313.2379. Found 313.2373. Data for 43. IR (film) 3446, 2958 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.34 (1H, br s), 4.31 (1H, d, J=5.4 Hz), 3.5–3.65 (2H, m), 3.36 (3H, s), 3.34 (3H, s), 3.24 (1H, dd, J=4.5, 7.5 Hz), 2.4–2.5 (1H, m), 1.6–2.15 (6H, m), 1.68 (3H, d, J=1.5 Hz), 1.45–1.6 (1H, m), 1.26 (3H, s), 0.87 (3H, d, J=6.8 Hz), 0.78 (3H, d, J=6.8 Hz). ^{13}C NMR ($CDCl_3$) δ 136.5, 121.9, 107.2, 66.1, 61.5, 60.3, 55.0, 54.8, 41.5, 36.6, 35.6, 29.0, 27.2, 24.2, 22.9, 21.3, 16.3, 14.5. HRMS (CI) calcd for $C_{18}H_{33}O_4$ 313.2379. Found 313.2372.

1-Methyl-(4*R*)-isopropyl-(5*R*)-(6*R*)-[7-(8*S*)-methoxy-(9*R*)-methyl-10-butanol]-(11*R*)-methoxy-9,11-oxido-1-cyclohexene 44 and 1-methyl-(4*R*)-isopropyl-(5*R*)-dimethyl acetal-(6*R*)-[7-(9*R*)-methyl-(8*R*),9-epoxy-10-butanol]-1-cyclohexene 43. *Procedure 1:* To a stirred solution of (−)-diisopropyltartrate (28 mg, 0.12 mmol) and powdered 3 Å molecular sieves (approx. 500 mg) in CH_2Cl_2 (4 mL) was added sequentially Ti(OPr^i)$_4$ (28 mg, 0.10 mmol) and *tert*-butylhydroperoxide (0.66 mL, 2.0 mmol, 3 M in isooctane) at −25°C. After 45 min, a solution of **42** (296 mg, 1.00 mmol) in CH_2Cl_2 (1 mL) was added via syringe. After 24 h, the mixture was allowed to warm to 0°C and poured into a stirred solution of ferrous sulfate heptahydrate (3.2 g), tartaric acid (1.0 g) and H_2O (10 mL) at 0°C. After 10 min, the two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined extracts were poured into a stirred, precooled solution of (0°C, 5 mL) prepared from NaCl (5 g) and NaOH (30 g) in H_2O (90 mL). The mixture was stirred at 0°C for 1 h, diluted with H_2O (5 mL) and the two phases separated. The aqueous layer was extracted with Et_2O (2×10 mL), and the combined extracts washed with saturated aqueous NaCl (20 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 40% Et_2O/petroleum ether, to give the acetal **44** (220 mg, 0.705 mmol, 71%, d.s. >20:1) as a colorless oil.

Procedure 2: To a stirred solution of (−)-diisopropyltartrate (14 mg, 0.060 mmol) and two scoops of powdered 4 Å molecular sieves (approximately 1 g) in CH_2Cl_2 (2 mL) were added sequentially Ti(OPr^i)$_4$ (12 mg, 12 μL, 0.041 mmol) and *tert*-butylhydroperoxide (230 μL,1.2 mmol, 5 M in isooctane) at −20°C. After 30 min, a precooled solution of **42** (100 mg, 0.338 mmol) in CH_2Cl_2 (0.5 mL) was added via cannula. An additional amount CH_2Cl_2 (0.5 mL) was added to rinse the alcohol flask. After 1.75 h at −20°C the mixture was allowed to warm to 0°C, and poured into a stirred solution of ferrous sulfate heptahydrate (1.6 g), tartaric acid (0.5 g) and H_2O (5 mL) at 0°C. After 10 min, the two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined extracts were poured into a stirred, precooled solution of (0°C, 10 mL) prepared from NaCl (5 g) and NaOH (30 g) in H_2O (90 mL). The mixture was stirred at 0°C for 1 h, diluted with H_2O (5 mL) and the two phases separated. The aqueous layer was extracted with Et_2O (2×10 mL), the combined extracts washed with saturated aqueous NaCl (20 mL). The dried (Na_2SO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 40% Et_2O/petroleum ether, to give the acetal **44** (38 mg, 0.12 mmol, 36%, d.s. >20:1) as a colorless oil. Further elution gave the epoxide **43** (67 mg, 0.21 mmol, 64%, d.s. >20:1) as a colorless oil. Data for **44**. IR (film) 3465, 2932 cm^{-1}. ^{1}H NMR (C_6D_6) δ 5.35 (1H, br s), 4.45 (1H, d, J=7.1 Hz), 3.6–3.8 (2H, m), 3.51 (1H, dd, J=3.0, 11.6 Hz), 3.09 (3H, s), 3.07 (3H, s), 2.41 (OH, br s), 2.21 (1H, t, J=7.7 Hz), 2.0–2.1 (1H, m), 1.2–2.0 (8H, m), 1.08 (3H, s), 0.95–1.05 (1H, m), 0.96 (3H, d, J=6.6 Hz), 0.94 (3H, d, J=6.6 Hz). HRMS (CI) calcd for $C_{18}H_{33}O_4$ 313.2379. Found 313.2388.

1-Methyl-(4*R*)-isopropyl-(5*R*)-(6*R*)-[7-(8*S*)-methoxy-(9*R*)-methyl-10-[4′-nitrobenzoyloxy]-butane]-(11*R*)-methoxy-9,11-oxido-1-cyclohexene 46. To a stirred solution of **44** (62 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (25 mg, 35 μL, 0.25 mmol) followed by *p*-nitrobenzoyl chloride (37 mg, 0.20 mmol). After 24 h at ambient temperature, the mixture directly subjected to PLC, eluting with 20% Et_2O/petroleum ether, to give **46** (78 mg, 0.17 mmol, 89%) as an off-white solid. Crystals suitable for X-ray crystallography were obtained by recrystallization from Et_2O. IR (film) 2924, 2853, 1722 cm^{-1}. ^{1}H NMR (C_6D_6) δ 7.85 (2H, m), 7.63 (2H, m), 5.36 (1H, br s), 4.4–4.65 (3H, m), 3.20 (3H, s), 3.15–3.25 (1H, m), 3.02 (3H, s), 2.25 (1H, t, J=7.7 Hz), 1.4–2.1 (11H, m), 1.24 (3H, s), 0.96 (3H, d, J=6.8 Hz), 0.91 (3H, d, J=6.8 Hz). HRMS (CI) calcd for $C_{25}H_{36}NO_7$ 462.2492. Found 462.2478.

2-Methyl-3-*Z*-iodo-propenol 47. To a stirred solution of CuI (2.3 g, 0.012 mol) in Et_2O (120 mL) was added MeMgBr (100 mL, 0.30 mol, 3.0 M in Et_2O) at −15°C. After 20 min propargyl alcohol (6.7 g, 7.0 mL, 0.12 mol) was added via a syringe pump over 30 min at −15°C. The mixture was allowed to warm to ambient temperature over 2 h. After 16 h at ambient temperature, the mixture was recooled to 0°C, and I_2 (39 g, 0.15 mol) added. After 15 min, the mixture was warmed to ambient temperature for 50 min, carefully quenched with HCl (300 mL, 10% in H_2O), and extracted with Et_2O (4×300 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 50% Et_2O/petroleum ether, to give **47** (12.2 g, 0.062 mmol, 52%) as a yellow oil. IR (film) 3334, 2913 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 5.96 (1H, s), 4.23 (2H, s), 1.96 (3H, s), 1.59 (OH, br s). HRMS (CI) calcd for C_4H_7IO 197.9542. Found 197.9538.

1-Methyl-(4*R*)-isopropyl-(5*R*)-dimethylacetal-(6*R*)-[9-methyl-9-*Z*-butene-10-ol]-1-cyclohexene 48. To **7** (227 mg, 1.01 mmol) was added 9-BBN (2.4 mL, 1.2 mmol, 0.5 M in THF) and the mixture heated in a sealed tube to 50°C. After 18 h, the mixture was allowed to cool to ambient temperature, and NaOH (1.0 mL, 3 mmol, 3 M in H_2O) was added followed by a solution of the iodide **222** (410 mg, 2.7 mmol) in THF (800 μL) via cannula. Freshly prepared $Pd(PPh_3)_4$ (170 mg, 0.147 mmol) was added to the mixture, and it was heated at 65°C in a sealed tube in the dark for two days. The mixture was allowed to cool to ambient temperature, diluted with saturated aqueous NaCl (20 mL), and extracted with Et_2O (4×25 mL). The dried

($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel eluting with 30% Et_2O/petroleum ether, to give **48** (105 mg, 0.355 mmol, 35%) as a yellow oil. IR (film) 3418, 2957 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.3–5.4 (2H, m), 4.15 (1H, d, J=5.6 Hz), 4.06 (1H, d, J=12.0 Hz), 3.95 (1H, d, J=12.0 Hz), 3.37 (3H, s), 3.34 (3H, s), 2.4–2.5 (1H, m), 2.1–2.3 (2H, m), 1.5–2.1 (5H, m), 0.86 (3H, d, J=6.6 Hz), 0.77 (3H, d, J=6.6 Hz). HRMS (CI) calcd for $C_{18}H_{31}O_3$ 295.2273. Found 295.2267.

1-Methyl-(4*R*)-isopropyl-(5*R*)-(6*R*)-[7-(8*S*)-methoxy-(9*S*)-methyl-10-butanol]-(11*R*)-methoxy-9,11-oxido-1-cyclohexene 49. To a stirred solution of (+)-diethyltartrate (67 mg, 0.325 mmol) in CH_2Cl_2 (1.2 mL) with one scoop of powdered 4 Å molecular sieves (approx 500 mg) at −20°C was added $Ti(OPr^i)_4$ (72.2 mg, 75 μL, 0.254 mmol) and *tert*-butylhydroperoxide (360 μL, 1.8 mmol, 5 M in isooctane). After 30 min, a solution of **48** (74 mg, 0.25 mmol) in CH_2Cl_2 (160 μL) was added dropwise via cannula. An additional amount of CH_2Cl_2 (2×80 μL) was added to rinse the allylic alcohol flask. The mixture was then allowed to warm to −8°C. After 19 h, the mixture was warmed to 0°C poured into a stirred solution of ferrous sulfate heptahydrate (3.2 g), tartaric acid (1.0 g) and H_2O (10 mL) at 0°C. After 20 min, the two phases were separated and the aqueous layer was extracted with Et_2O (4×20 mL). The combined extracts were poured into a stirred, precooled solution (0°C) of NaCl (5 g) and NaOH (30 g) in H_2O (100 mL), and stirred at 0°C for 1.5 h. The two phases were separated and the aqueous layer was extracted with Et_2O (4×50 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 40% Et_2O/petroleum ether (2–4% Et_3N) to give the acetal **49** (49 mg, 0.16 mmol, 63%) as a colorless oil. $[\alpha]_D^{23}$=+31 (c=0.97, $CHCl_3$). IR (film) 3450, 2928 cm^{-1}. ^1H NMR (C_6D_6) δ 5.33 (1H, br s), 4.82 (1H, d, J=5.7 Hz), 3.91 (1H, d, J=11.6 Hz), 3.76 (1H, d, J=11.6 Hz), 3.3–3.4 (1H, m), 3.22 (3H, s), 2.93 (3H, s), 2.3–2.4 (2H, m), 1.7–2.0 (5H, m), 1.63 (3H, s), 1.49 (3H, s), 1.25–1.35 (1H, m), 0.91 (3H, d, J=6.8 Hz), 0.84 (3H, d, J=6.8 Hz). ^{13}C NMR (C_6D_6) δ 136.8, 121.5, 103.2, 88.6, 78.5, 66.8, 57.3, 56.0, 45.2, 37.2, 36.6, 31.0, 29.9, 27.0, 25.2, 24.6, 21.9, 15.9. HRMS (CI) calcd for $C_{18}H_{32}O_4$ 313.2379. Found 313.2376.

A solution of MeCN (0.5 mL) at 0°C containing Me_3SiCl (65 μL, 0.513 mmol) and NaI (96 mg, 0.641 mmol) was stirred for 30 min, and propene was bubbled through the solution for 5 min. To the mixture was added a solution of **49** (32 mg, 0.103 mmol) in MeCN (200 μL) and the resulting solution heated at 60°C for 16 h. The solution was cooled to room temperature and washed with saturated aqueous $NaHCO_3$ (1 mL), saturated aqueous $Na_2S_2O_3$ (1 mL), dried (Na_2SO_4) and evaporated in vacuo to give a residue that contained approximately 15% of **35**, as judged by the ^1H NMR of the crude product.

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