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Methylation-Ring Opening of 3,3-Disubstituted 2,3-Epoxy Alcohols. Synthesis of Chiral Quaternary Fragments for Assembly of Briaran Diterpenes.

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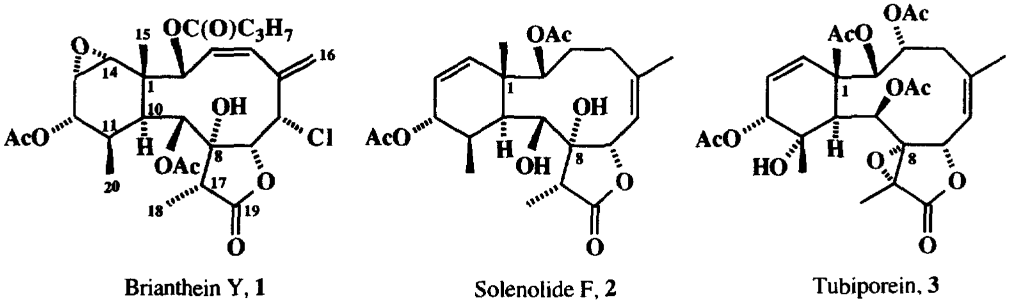
Abstract: Two chiral quaternary carbon-containing fragments suitable for elaboration to the briaran diterpenes were obtained by regioselective methylation of functionalized 3,3-disubstituted 2,3-epoxy-1-ols. The factors which favor methylation at the more hindered position of a trisubstituted 2,3-epoxy alcohol were determined. © 1997 Elsevier Science Ltd.

INTRODUCTION

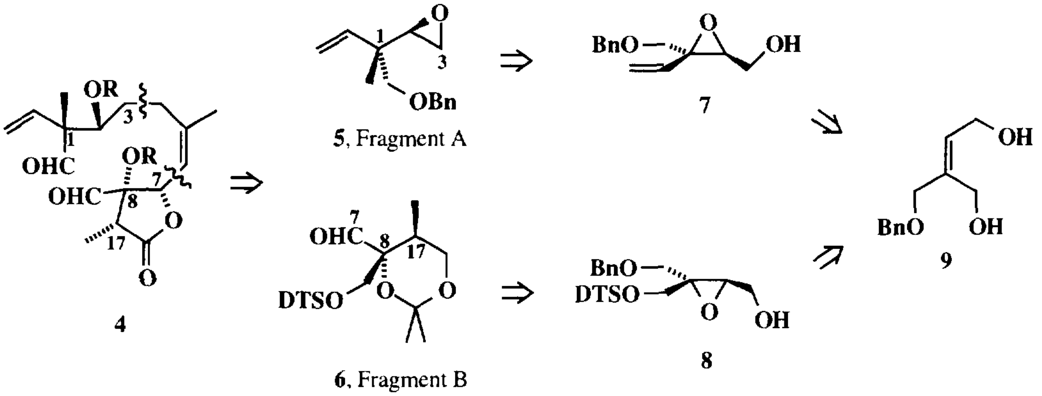
The briaran diterpenes (e.g. **1**, Scheme 1) are biologically active natural products isolated from various marine organisms.[1] A principal structural component of these diterpenes is a fused 6,10,5-tricyclic ring system that is highly oxygenated. For example, diterpene **1**[2] and the related diterpenes **2**[3] and **3**[4] all have an impressive array of oxygen functionality and stereochemical complexity associated with the ten-membered ring. The elaborate briaran architecture, containing in some cases as many as eleven contiguous chiral centers, and the antiinflammatory and antiviral activities reported for these compounds have stimulated studies toward preparation of a briaran 6,10 fused ring system.[5] We have also examined a synthetic route to the briaran diterpenes by investigating the regioselective methylation of appropriately functionalized 3,3-disubstituted-2,3-epoxy alcohols to access the chiral quaternary carbon centers, C(1) and C(8), of the briaran ten-membered ring. We report herein our studies on the addition of a methyl group to the more hindered carbon of a trisubstituted epoxide. The application of this reaction in the synthesis of a fragment for convergent assembly of the briaran ring system is described.



Brianthein Y, **1**　　Solenolide F, **2**　　Tubiporein, **3**

Scheme 1

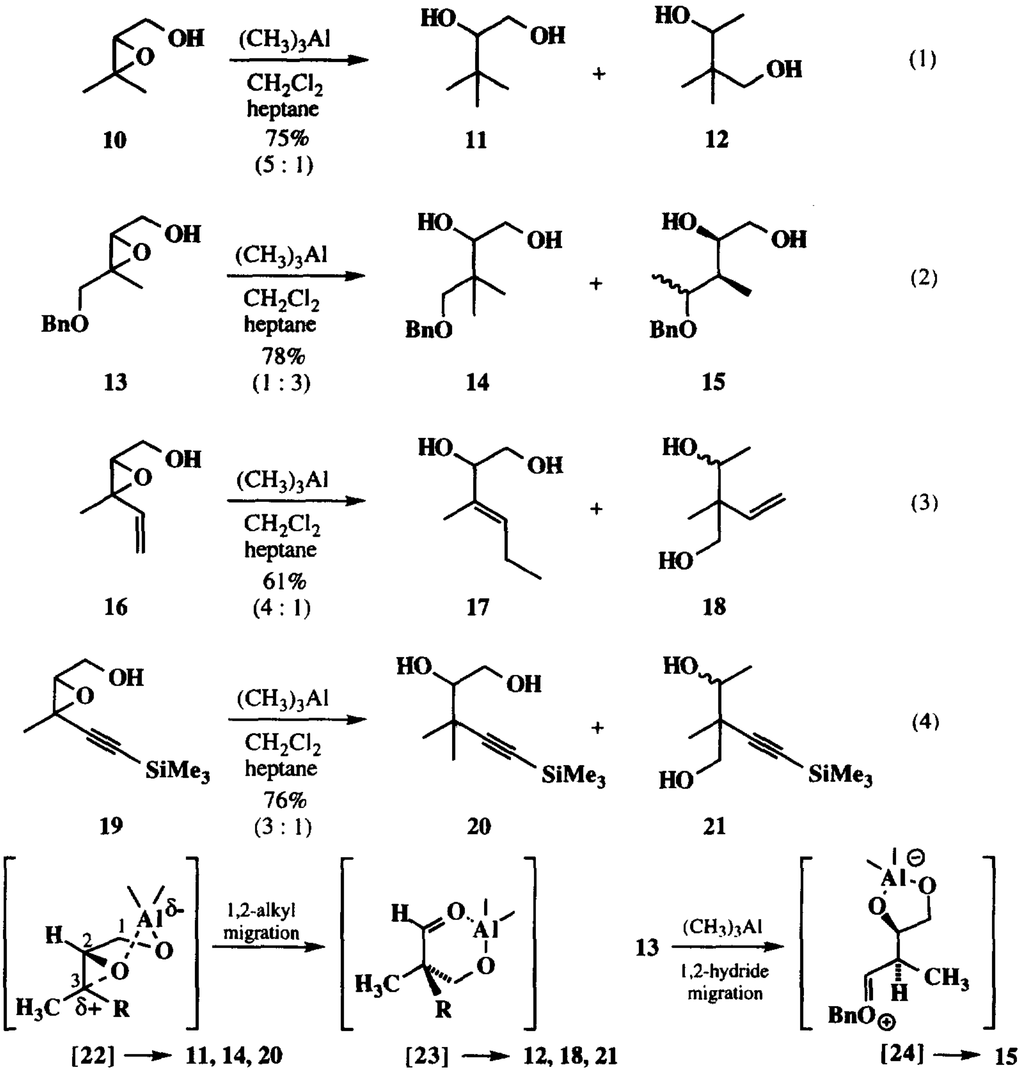
Scheme 2 illustrates a retrosynthetic analysis of a ten-membered ring analog of Solenolide F (**2**) from a proximal McMurry coupling[6] target, dialdehyde **4**. The synthetic strategy entails separation of the quaternary centers C(1) and C(8) to give Fragments A and B. It was envisioned that the ultimate coupling of Fragments A and B may be accomplished using a briaran C(4)-C(6) unit capable of nucleophilic reaction at either terminus (e.g. propyne equivalent). The stereogenic methyl groups adjacent to the oxygen-bearing stereocenters at C(2) and C(8) strongly suggested the use of a strategy involving the regioselective methylation of suitably substituted epoxides. This epoxide-cleavage disconnection led retrosynthetically to a common intermediate, diol **9**. The synthetic plan thus entailed a divergent strategy from diol **9**, a substrate that is well suited for conversion to the epoxy alcohols **7** and **8** using Sharpless methodology. Subsequent regioselective epoxide ring openings of **7** and **8** were planned to establish the quaternary centers of Fragments A and B. Whereas an abundance of literature precedent exists for the nucleophilic methylation-ring opening of epoxides at their less substituted position, a key step in the **8** → **6** sequence, there are no reports of methylation-ring opening at the more substituted position. Consequently, the **7** → **5** transformation presented an interesting synthetic challenge.



Scheme 2. Retrosynthetic Analysis (DTS = dimethylthexylsilyl)

SYNTHESIS

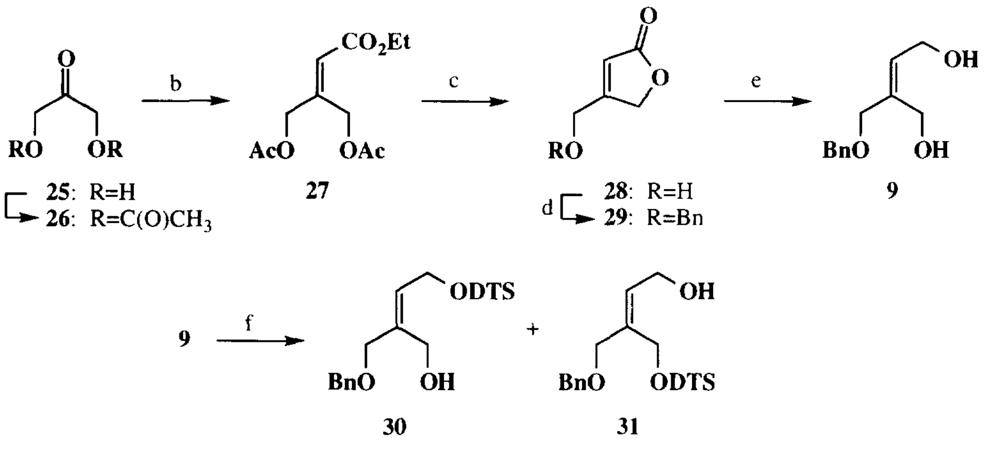
The reactions of 2,3-epoxy-1-ols with trimethylaluminum have been shown by Nozaki[7] and Roush[8] to result in predominant C(3)-methylation and thereby afford 1,2-diols as the major products. However, the application of this reaction to substrates having a fully substituted C(3) center has not been reported previously.[9,10] We examined the key step of the **7** → **5** transformation by reaction of the model epoxides **10**, **13**, **16** and **19** with trimethylaluminum using the Roush conditions (eqs 1-4). Treatment of these epoxides in CH_2Cl_2 with three equivalents of $(CH_3)_3Al$ (2.0M in heptane) at 0 °C followed by warming to room temperature gave a mixture of products in each case. HPLC or GC analysis of the crude reaction mixtures determined the ratios of products, and determination of product diol structure was assisted by $NaIO_4$ cleavage to effect conversion of the 1,2-diol products to their corresponding aldehydes.[8] The reaction of epoxide **10** with



$(CH_3)_3Al$ gave a 5:1 ratio of diols **11**:**12** in a combined 75% yield. The addition of methyl to C(3) of the postulated chelate species **[22]** to afford diol **11** as the major product was an encouraging result for the synthetic plan. Likewise, the methylation-ring opening at C(3) was predominant with epoxide **19** to give diol **20**. Diols **12** and **21**, the minor products in these reactions (eqs 1,4), are formed as a consequence of hydroxymethyl migration[11] from C(2) to C(3) of chelate **[22]** prior to methylation of the chelate species. The 1,2-migration is believed to form transient aldehyde **[23]**[12] and afford the 1,3-diol on subsequent reaction with the methylating[7] agent. The formation of complex **[23]** is analogous to the Lewis acid-induced 1,2-alkyl migration of tertiary allylic epoxides reported by Jung.[13] Interestingly, the reaction of epoxide **13** with

$(CH_3)_3Al$ did not yield a product derived from hydroxymethyl group migration. Rather, the major product is derived from methylation of the oxocarbenium species [**24**], an intermediate formed as a consequence of 1,2-hydride migration on aluminum chelation.[14] A C(3) alkoxymethyl group thus appears to promote neighboring group migration with accompanying epoxide ring cleavage. Roush has noted previously in studies on 2,3-disubstituted epoxy-1-ols that C(3) alkoxymethyl substituents decrease the selectivity of methylation at C(3) due to inductive destabilization of the incipient C(3) carbocation.[8] The reaction of vinyl epoxide **16** with $(CH_3)_3Al$ did not yield a product derived from C(3) methylation. In this reaction (eq 3), the principal mode of reactivity, S_N2' methylation, results in formation of a single diastereomer, assigned as (*E*)-1,2-diol **17** based on spectral analysis of the corresponding $NaIO_4$-derived aldehyde.[15] The minor product **18** arises as the result of 1,2-alkyl migration as previously noted. The tendency for S_N2' reaction on propargylic epoxide **19** is effectively blocked by the silyl group, thus enabling the methylation-ring opening to occur at C(3). Of interest to our synthetic plan, the transformation of the acetylenic silane in **20** to a vinyl group may offer a solution to the ineffective C(3) methylation observed with epoxide **16**. We were encouraged by our model study success in establishing the quaternary C(3) centers of **11** and **20**, and, consequently, we began the synthesis of Fragment A.

Synthesis of Diol 9. The synthesis of the common precursor to Fragments A and B, and the point of divergence in the synthetic plan are shown in Scheme 3. Commercially available 1,3-dihydroxyacetone (**25**) was converted to the corresponding bisacetate **26** using the literature procedure.[16] A subsequent Horner-Wadsworth-Emmons olefination using triethylphosphonoacetate gave vinyl ester **27** in 62% overall yield. Prolonged treatment of **27** with a catalytic amount of *p*-toluenesulfonic acid in 90% ethanol at reflux resulted in

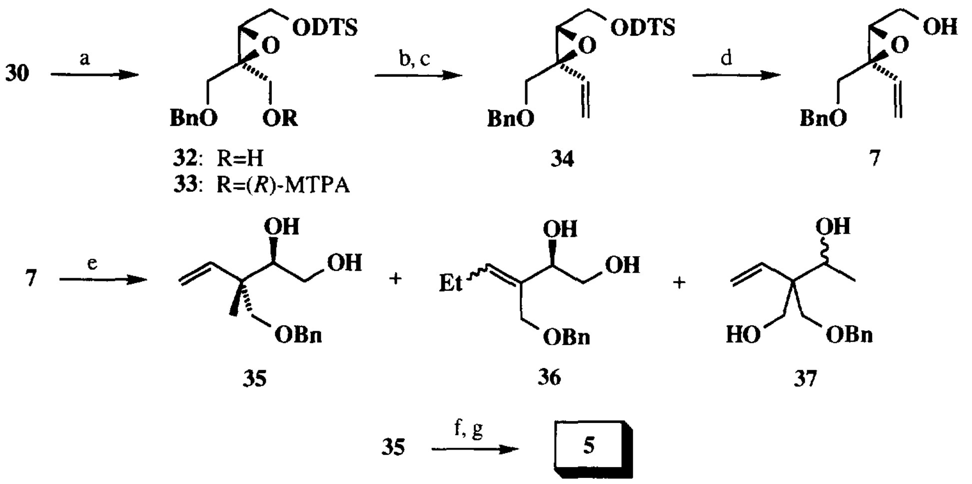


Scheme 3

Reagents and conditions: (a) Ac_2O, pyridine, rt; (b) NaH, $(Et_2O)_2P(O)CH_2CO_2Et$, DMF, 0 °C; (c) 90% EtOH, TsOH (cat), reflux; (d) $Cl_3CC(=NH)OBn$ (1.2 eq), CF_3SO_3H (cat), Hexane:CH_2Cl_2 (2:1), rt; (e) DIBAL (2.5 eq), Et_2O, -78 °C to rt; (f) i. *n*-BuLi (1.0 eq), -78 °C, THF, ii. DTS-Cl (0.9 eq), rt.

gradual acetate cleavage. Lactone formation ensued under these conditions and gave butenolide **28** in 88% yield. The use of base-mediated methods for the hydroxyl protection of **28** as a benzyl ether proved to be problematic, presumably a consequence of alkoxide-mediated lactone ring openings. However, an acid catalyzed benzylation was accomplished according to the method of Bundle *et al.*[17] by treatment of **28** with benzyl 2,2,2-trichloroacetimidate and catalytic triflic acid. The benzyl protected lactone **29** was obtained in 78% yield. Lactone reduction was accomplished by reaction of **29** with an excess of diisobutylaluminum hydride in Et_2O to give diol **9** in 95% yield. During the course of this reduction we noted that a reaction quench below 0 °C resulted in predominant formation of 3-(benzyloxymethyl)furan, a consequence of partial reduction to the hemiacetal followed by facile dehydration on work-up. Diol **9**, prepared in 5 steps in 40% overall yield, was now available for divergent synthesis of Fragments A and B. A mono-protection step was examined with the intent of generating roughly equivalent amounts of precursors for Fragments A and B. Our initial selection of *p*-methoxybenzyl as the protection group proved unsuitable due to the formation of substantial amounts of bis-protected material on attempted mono-protection of **9**. However, we were gratified to find that treatment of **9** with one equivalent of *n*-BuLi followed by reaction with dimethylthexylsilyl chloride resulted in an 83% conversion of **9** to a 1:1 mixture of the monosilylated alcohols **30** and **31**. The separation of **30** and **31** was achieved by silica chromatography and the structural assignments were confirmed by inspection of the ^1H NMR spectra of their respective acetate derivatives.[18]

Fragment A. The transformation of allylic alcohol **30** to Fragment A is shown in Scheme 4. Sharpless epoxidation[19] of **30** at -20 °C gave epoxy alcohol **32** in 92% yield. Esterification using (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride and DMAP gave the Mosher ester **33**. ^1H NMR and HPLC[20] analysis of **33** indicated a diastereomeric purity of 90%.[21] At this stage, we felt it was prudent to examine the methylation-ring opening reaction of the corresponding and readily accessible C(3)-vinyl derivative. Swern oxidation[22] of **32** followed by immediate Wittig olefination[23,24] on the crude epoxy aldehyde afforded vinyl epoxide **34**. Removal of the dimethylthexylsilyl protection group was readily accomplished using tetra(*n*-butyl)ammonium fluoride, and silica gel chromatography gave alcohol **7** in 44% overall yield from **32**. At this stage, we required the addition of methyl to the disubstituted epoxide carbon of **7** (eventual briaran C(1)). Treatment of **7** with three equivalents of $(CH_3)_3Al$ (2.0M in heptane) gave the desired product **35** with two minor products, **36** and **37**, in a combined 75% yield. HPLC analysis of the crude reaction mixture established the **35**: **36**: **37** ratio as 1.0: 0.3: 0.2. For characterization, the crude products were converted to their corresponding acetonide derivatives (2,2-dimethoxypropane, catalytic pyridinium *p*-toluenesulfonic acid) and carefully separated by column chromatography. The acetonide corresponding to diol **35** was hydrolized (THF, 2N HCl) to afford **35** as a single diastereomer, and the stereochemistry tentatively was assigned on the basis of previous *anti*-opening results.[9,25] It should be noted, however, that examples of *syn*-opening have been reported,[7,26] and the stereochemistry in **35** therefore remains undefined. We speculate that the emergence of direct epoxide cleavage as the major process, as opposed to S_N2' opening, in the reaction of epoxide **7** is due to the inability of the C(3)-vinyl substituent to achieve complete coplanarity with the developing C(3)-carbocation. Indeed, the larger steric requirement of the C(3)-benzyloxymethyl group of **7**, in comparison to the C(3)-methyl group of **16**, apparently



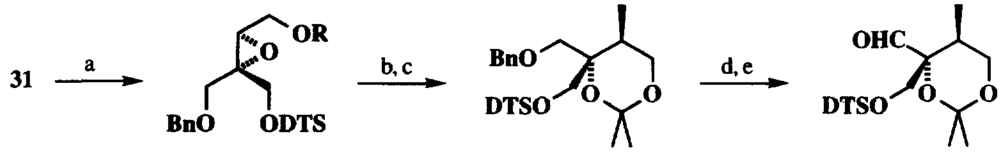
Scheme 4

Reagents and conditions: (a) D-(-)-DET, Ti(OiPr)$_4$, *t*-BuOOH, 4 Å mol sieves, CH_2Cl_2, -20 °C; (b) i. $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, ii. Et_3N, 0 °C; (c) $Ph_3P^+CH_3Br^-$, *n*-BuLi, THF, -20 °C; (d) (*n*-Bu)$_4$NF, THF, 0 °C; (e) $(CH_3)_3Al$ (3.0 eq), CH_2Cl_2, 0 °C - 25 °C; (f) CH_3SO_2Cl, Et_3N, CH_2Cl_2, -78 °C - 0 °C; (g) KOH (s), CH_2Cl_2.

is sufficient to discourage S_N2' addition. Diol **36**[27] is the apparent product of an S_N2' addition by the methylating agent to the initial chelate species. Competitive migration of the C(2) hydroxymethyl group to C(3) is again responsible for the formation of the minor isomer, diol **37**. Given that direct C(3)-methylation of **7** is also enhanced relative to the reactivity exhibited by epoxide **13** (eq 2), an adjacent pi-system appears to restrain neighboring group migration so that greater reaction may proceed at the allylic epoxide carbon, a feature that previously has been shown by Nicolaou to enhance contra-kinetic epoxide opening.[28]

The $(CH_3)_3Al$ stoichiometry in the reaction of **7** was examined and found to be optimal at three equivalents. The use of less than three equivalents of $(CH_3)_3Al$ resulted in a sluggish rate of reaction whereas the use of five or more equivalents of $(CH_3)_3Al$ resulted in decreased C(3) selectivity. The use of alternative aluminum-based methylation reagents ($Li(CH_3)_4Al$[29], $(CH_3)_2AlOAl(CH_3)_2$[30]) did not result in any appreciable addition of methyl to the more substituted epoxide position. Thus, in practice, the crude diol mixture obtained using the Roush methylation conditions was reacted directly with methanesulfonyl chloride and triethylamine. Subsequent treatment with KOH (s) in CH_2Cl_2 afforded epoxide **5**, Fragment A, in 25% yield from **7**. This example illustrates that the epoxide ring opening reaction of $(CH_3)_3Al$ has potential in the synthesis of quaternary centers; however, further studies will be necessary on trisubstituted epoxy alcohols to determine the factors that would promote even greater C(3) selectivity.[31]

Fragment B. The synthesis of Fragment B from alcohol **31** is shown in Scheme 5. Sharpless asymmetric epoxidation[19] of **31** was accomplished at -20 °C to afford epoxide **8** in 86% yield. HPLC and ^1H NMR analyses on the corresponding Mosher ester **38** indicated a 92% diastereomeric excess.[20,21] At this stage, to effect the addition of methyl to the less substituted epoxide carbon, **8** was treated with an excess of lithium dimethylcuprate in Et$_2$O according to the Kishi protocol.[32] The resultant crude 1,3-diol was dissolved in 2,2-dimethoxypropane and treated with a catalytic amount of pyridinium *p*-toluenesulfonic acid to give acetonide **39** in 54% overall yield. This three step sequence from the point of divergence in the synthetic scheme established the C(8) quaternary center of the briaran 10-membered ring. To prepare this fragment for eventual coupling at C(7), **39** was treated with Li in NH$_3$ to effect debenzylation,[33] and followed by Swern oxidation on the crude alcohol to give aldehyde **6**, Fragment B, in 64% yield.



8: R=H
38: R=(*R*)-MTPA

39

6

Scheme 5

Reagents and conditions: (a) D-(-)-DET, Ti(OiPr)$_4$, *t*-BuOOH, 4 Å mol sieves, CH$_2$Cl$_2$, -20 °C; (b) Me$_2$CuLi (8 eq), Et$_2$O, -20 °C; (c) (CH$_3$O)$_2$C(CH$_3$)$_2$, PPTS (0.1 eq), rt; (d) Li (5 eq), NH$_3$; (e) i. (COCl)$_2$, DMSO, CH$_2$Cl$_2$, -78 °C, ii. Et$_3$N, 0 °C.

SUMMARY

We have described the syntheses of two fragments, constituting C(1)-C(3),C(10) [Fragment A] and C(7)-C(9) [Fragment B] of the briaran ring system, for convergent assembly of the briaran ten-membered ring. Key features in the syntheses of Fragments A and B are the methylation-ring openings of trisubstituted 2,3-epoxy-1-ols, and the syntheses of both epoxy alcohols from a common intermediate, diol **9**. The synthesis of Fragment A features the first example of methyl addition to the more substituted position of a trisubstituted epoxy alcohol.

EXPERIMENTAL

General procedures. All reactions were conducted in flame-dried glassware under an inert atmosphere of argon. Anhydrous solvents were obtained by distillation from Na/K benzophenone ketyl (diethyl ether and tetrahydrofuran), Na (toluene and benzene), or calcium hydride (dichloromethane, dimethylformamide, dimethylsulfoxide, and pyridine). After reaction work-up, solvents were removed by rotary evaporation unless otherwise indicated. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 F$_{254}$ plates, and column chromatography was performed using EM Science silica gel 60, 230-400 ASTM mesh. Analytical high-performance liquid chromatography (HPLC) was performed with a Waters 600E system chromatograph equipped with a Waters 745B data integrator. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a General Electric QE 300 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual undeuterated solvent (δ7.26 for CHCl$_3$). Infrared spectra were determined with a Mattson Galaxy Series FTIR 3000 spectrometer. Optical rotations were determined using a Jasco DIP-370 digital polarimeter. Melting points were determined on an Electrothermal digital melting-point apparatus. Combustion microanalyses were performed by Midwest Microlab of Indianapolis, IN. High-resolution mass spectra were recorded by the Facility for Advanced Instrumentation at the University of California, Davis.

Ethyl 3-(acetoxymethyl)-4-acetoxy-2-butenoate (**27**). To a suspension of sodium hydride (0.72 g, 30.1 mmol) in THF (150 mL) at 0 °C was added dropwise triethylphosphonoacetate (5.70 mL, 28.7 mmol). The reaction solution was allowed to stir 1h at 0 °C and then slowly warmed to room temperature. The resulting homogeneous yellow solution was recooled to 0 °C and 1,3-dihydroxypropan-2-one 1,3-diacetate[16] (5.00 g, 28.7 mmol) was added in one portion. After stirring 12h at room temperature, the reaction was quenched by addition of saturated aqueous NH_4Cl and diluted with Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic extract was washed with saturated brine, dried ($MgSO_4$), and concentrated. The resulting oil was purified by chromatography (2:3, hexane:ethyl acetate) to give 6.07 g (86%) of **27** as a colorless liquid. Purification by fractional distillation, bp 127 °C (0.80 mm Hg), afforded the product in lower yield (40%); IR ($CHCl_3$) 1724, 1662, 1036 cm^{-1}; TLC R_f 0.23 (4:1, hexane:ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 5.99 (t, J = 1.5 Hz, 1H), 5.25 (s, 2H), 4.72 (d, J = 1.1 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 2.72 (s, 3H), 2.08 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.3, 169.0, 164.3, 148.9, 117.6, 62.8, 60.2, 59.7, 19.7, 19.6, 13.4; Anal. Calcd. for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 53.85; H, 6.31.

4-(Hydroxymethyl)-2(5H)-furanone (**28**). To a solution of triester **27** (11.0 g, 45.0 mmol) in 90% ethanol (225 mL) was added *p*-toluenesulfonic acid monohydrate (0.86 g, 4.50 mmol). The resulting solution was heated to reflux for 7 days after which the solvent was removed by rotary evaporation. The residue was purified by chromatography (ethyl acetate) to give 4.56 g (88%) of **28** as a white solid; mp 47-49 °C; IR ($CDCl_3$) 3366, 1720, 1610 cm^{-1}; TLC R_f 0.29 (ethyl acetate); ^{1}H NMR ($CHCl_3$) δ 5.78 (t, J = 1.6 Hz, 1H), 4.67-4.68 (m, 1H), 4.67 (d, J = 1.2 Hz, 2H), 4.33 (d, J = 1.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 174.4, 171.6, 113.1, 71.1, 57.8; Anal. Calcd. for $C_5H_6O_3$: C, 52.63; H, 5.30. Found: C, 52.35; H, 5.25.

4-(Benzyloxymethyl)-2(5H)-furanone (**29**). To a solution of butenolide **28** (7.00 g, 61.4 mmol) in a 2:1 mixture of hexane and dichloromethane (300 mL) were added successively benzyl 2,2,2-trichloroacetimidate (13.7 mL, 73.7 mmol) and trifluoromethanesulfonic acid (0.81 mL, 9.21 mmol). The reaction mixture was gently heated until all the solids had dissolved. After 25 min., the reaction mixture was filtered and the filtered solids were rinsed with hexane. The combined organic solution was washed with saturated aqueous $NaHCO_3$, saturated brine, and dried over $MgSO_4$. The solvents were removed to give a yellow oil which was purified by silica gel chromatography (2:1, hexane:ethyl acetate) to afford 9.77g (78%) of **29** as an oil; IR 1720, 1610, 1100 cm^{-1}; TLC R_f 0.19 (2:1, hexane:ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.29-7.36 (m, 5H), 5.93 (s, 1H), 4.71 (s, 2H), 4.51 (s, 2H), 4.30 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 173.0, 166.9, 136.9, 128.1, 127.6, 127.3, 114.9, 72.7, 70.9, 65.1; Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.77; H, 5.90.

(E)-2-(Benzyloxymethyl)-2-butene-1,4-diol (**9**). To a solution of butenolide **29** (11.2 g, 55.0 mmol) in Et_2O (275 mL) at -78 °C was added dropwise via addition funnel diisobutylaluminum hydride (138 mL of a 1.00 M solution in hexanes, 138 mmol). The resulting homogeneous solution was stirred 25 min at -78 °C and followed by stirring 2 h at 0 °C, and then 2h at 25 °C. The mixture was recooled to -78 °C and quenched by slow addition

of MeOH (40 mL). The reaction mixture was slowly poured into a 2 L Erlenmyer flask containing a mixture of saturated aqueous Rochelle's salt (400 mL) and ether (300 mL). The resultant mixture was stirred vigorously at room temperature for 5h whereupon the layers were separated and the aqueous phase was extracted with Et_2O. The combined organic extract was washed with saturated brine, dried over Na_2SO_4, and concentrated to give 11.0 g (95%) of **9** as a yellow oil; IR ($CHCl_3$) 3366, 1602, 1009 cm^{-1}; TLC R_f 0.26 (ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.29-7.34 (m, 5H), 5.81 (t, J = 6.7 Hz, 1H), 4.51 (s, 2H), 4.17 (m, 4H), 4.07 (s, 2H), 3.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 137.9, 137.7, 129.6, 128.3, 127.6, 127.6, 72.9, 72.2, 58.4, 57.7.

(E)-2-(Benzyloxymethyl)-4-(dimethylthexylsilyloxy)-2-butene-1-ol (**30**) and *(Z)-3-(Benzyloxymethyl)-4-(dimethylthexylsilyloxy)-2-butene-1-ol* (**31**). To a solution of diol **9** (11.0 g, 53.0 mmol) in THF (250 mL) cooled to -78 °C was added dropwise *n*-butyllithium (33.0 mL of a 1.6 M solution in hexane, 53 mmol). The reaction mixture was slowly warmed to room temperature over 1 h and then recooled to -78 °C whereupon dimethylthexylsilyl chloride (9.40 mL, 47.6 mmol) was added dropwise. The resulting homogeneous solution was warmed to room temperature over 5 h and then quenched by addition of saturated aqueous NH_4Cl and diluted with ether. The layers were separated and the aqueous layer was extracted with ether. The combined organic extract was washed with saturated brine, dried ($MgSO_4$) and concentrated. Purification of the resulting yellow oil by chromatography (7.5:2.5, hexane:ethyl acetate) gave 5.94 g of alcohol **30**, 2.96 g of alcohol **31**, and 6.00 g of a mixed fraction. The mixed fraction was recolumned using the same eluent mixture to afford and additional 1.50 g of **30** and 4.50 g of **31**. The combined yield for silylation was 83%; **30**, IR ($CHCl_3$) 3431, 1603, 1059 cm^{-1}; TLC R_f0.33 (3:1, hexane:ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.31-7.34 (m, 5H), 5.67 (t, J = 5.7 Hz, 1H), 4.52 (s, 2H), 4.28 (d, J = 5.9 Hz, 2H), 4.21 (d, J = 5.9 Hz, 2H), 4.08 (s, 2H), 2.63 (t, J = 5.9 Hz, 1H), 1.58-1.67 (m, 1H), 0.88 (d, J = 6.8 Hz, 6H), 0.85 (s, 6H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 138.0, 137.6, 128.9, 128.1, 127.3, 127.5, 71.9, 58.7, 58.2, 33.9, 24.9, 20.1, 18.3, -3.21; HRMS calcd for $C_{20}H_{34}O_3Si$ (M^++H) 351.2355, found 351.2349; **31**, IR: ($CHCl_3$) 3395, 1603, 1028 cm^{-1}; TLC R_f0.27 (3:1, hexane-ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.30-7.34 (s, 5H), 5.78 (t, J = 6.4 Hz, 1H), 4.48 (s, 2H), 4.18-4.24 (m, 2H), 4.23 (s, 2H), 4.08 (s, 2H), 3.02-3.12 (m, 1H), 1.58-1.67 (m, 1H), 0.87 (d, J = 6.8 Hz, 6H), 0.85 (s, 6H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 138.0, 137.6, 128.9, 128.1, 127.5, 127.3, 72.1, 58.7, 58.2, 33.9, 24.9, 20.1, 18.3, -3.21; HRMS calcd for $C_{20}H_{34}O_3Si$ (M^++H) 351.2355, found 351.2339.

(2S,3S)-2-(Benzyloxymethyl)-4-(dimethylthexylsilyloxy)-2,3-butenoxide-1-ol (**32**). A 250 mL flask was charged with 0.75 g of 4 Å powdered molecular sieves and dichloromethane (115 mL). The suspension was cooled to -20 °C and D-(-)-diethyl tartrate (1.26 g, 6.11 mmol) and Ti(O-*i*-Pr)$_4$ (1.40 mL, 4.90 mmol) were added. The reaction mixture was stirred 10 min at -20 °C before the addition of TBHP (20.0 mL of a 3.00 M solution in isooctane, 61.1 mmol). The resulting solution was stirred 1h at -20 °C at which time a solution of alcohol **30** (8.56 g, 24.5 mmol) in CH_2Cl_2 (5.00 mL) was added via cannula. The resulting mixture was stirred 4h at -20 °C before quenching by slowly pouring the reaction solution into a solution of $FeSO_4 \cdot 7H_2O$ (9.40 g, 34.0 mmol) and tartaric acid (2.60 g, 17 mmol) in H_2O (29 mL) at 0 °C. The resulting two-phase mixture was allowed to stir for 10 min and the layers were separated. The aqueous phase was extracted with Et_2O and the combined organic extract was treated with 30% NaOH (w/v) in saturated brine (3.00 mL) and vigorously stirred 1h at 0 °C. The solution was diluted with H_2O (20 mL) and the layers were separated. The aqueous phase was

extracted with Et_2O and the combined organic extract was dried over $MgSO_4$ and concentrated to give 8.24g (92%) of **32** as a pale yellow oil, $[\alpha]_D^{24}$ +1.5° (c 1.7, $CHCl_3$); IR ($CHCl_3$) 3439, 2957, 1253, 1121, 1066 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (s, 5H), 4.58 (s, 2H), 3.70-3.97 (m, 5H), 3.61 (d, J = 11.1 Hz, 1H), 3.16 (t, J = 5.8 Hz, 1H), 2.36-2.42 (m, 1H), 1.57-1.64 (m, 1H), 0.88 (d, J = 7.0 Hz, 6H), 0.85 (s, 6H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 137.7, 128.4, 127.8, 127.7, 73.4, 71.5, 61.9, 61.5, 61.4, 60.0, 34.1, 25.2, 20.3, 20.2, 18.5, -3.48, -3.20; HRMS calcd for $C_{20}H_{34}O_4Si$ (M^++H) 367.2304, found 367.2320.

(3S,4S)-3-(Benzyloxymethyl)-5-(dimethylthexylsilyloxy)-2,3-pentadiene-3,4-oxide (**34**). To a flask charged with dichloromethane (109 mL) at -78 °C was added sequentially oxalyl chloride (5.70 mL, 65.5 mmol) and DMSO (7.75 mL, 109 mmol). The reaction mixture was stirred for 15 min at -78 °C before addition of a solution of epoxy alcohol **32** (8.00 g, 21.8 mmol) in dichloromethane (5.00 mL). The resulting mixture was stirred 1h at -78 °C. Triethylamine (1.25 mL, 109 mmol) was then added and the mixture was slowly warmed to 0 °C over 30 min and quenched by addition of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted with a 1:1 mixture of hexane:ethyl acetate. The combined organic extract was washed with saturated brine and dried (Na_2SO_4). Removal of the solvents gave 5.50 g of the epoxy aldehyde as a yellow oil that was used in the next step without further purification; IR ($CHCl_3$) 2957, 2870, 1725, 1254, cm^{-1}; TLC R_f 0.32 (7:3, hexane:ethyl acetate); ^1H NMR ($CDCl_3$) δ 9.52 (s, 1H), 7.32 (s, 5H), 4.56 (s, 2H), 4.06 (d J = 11.7 Hz, 1H), 3.90-3.92 (m, 2H), 3.71 (d, J = 11.7 Hz, 1H), 3.47 (t, J = 3.7 Hz, 1H), 1.57-1.62 (m, 1H), 0.87 (d, J = 7.0 Hz, 6H), 0.83 (s, 6H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 198.0, 137.5, 128.4, 127.8, 127.7, 73.6, 67.8, 65.3, 62.6, 59.6, 34.1, 25.2, 20.2, 20.2, 18.4, -3.5.

To a suspension of methyltriphenylphosphonium bromide (8.70 g, 24.3 mmol) in THF (65.0 mL) at -20 °C was added dropwise *n*-butyllithium (8.40 mL of a 2.50 M solution in hexanes, 21.0 mmol). The resulting mixture was stirred 20 min at -20 °C and then warmed to 0 °C over 10 min. A solution of the crude (2*S*, 3*S*)-2-(benzyloxymethyl)-4-(dimethylthexylsilyloxy)-2,3-butenoxide-1-al (5.50 g, 15.1 mmol) in THF (10 mL) was added via cannula and the resultant mixture was stirred at 0 °C for an additional 1.5 h. The reaction was quenched by addition of MeOH (10 drops) and the mixture was concentrated to half volume to give a slurry which was then diluted with petroleum ether (25 mL) and filtered (celite). The solids were washed with petroleum ether (25 mL) and the combined filtrate was concentrated to give 5.00g (63%) of **34** as an orange oil. A small quantity of **34** was purified by chromatography (10:1, hexane:ethyl acetate): IR ($CHCl_3$) 3030, 2956, 1641, 1252, 1129, 1087 cm^{-1}; TLC R_f 0.58 (7:3, hexane:ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.33 (s, 5H), 5.93 (dd, J = 17.7, 10.8 Hz, 1H), 5.35-5.40 (m, 2H), 4.57 (ABq, J = 11.9 Hz, 2H), 3.75 (d, J = 11.4 Hz, 1H), 3.67 (t, J = 5.4 Hz, 1H), 3.60 (d, J = 11.4 Hz, 1H), 3.21 (t, J = 5.3 Hz, 1H), 1.57-1.67 (m, 1H), 0.88 (d, J = 7.0 Hz, 6H), 0.83 (s, 6H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.2, 131.7, 118.9, 128.4, 127.7, 127.6, 73.0, 72.5, 62.4, 61.8, 60.8, 34.2, 25.2, 20.3, 18.5, -3.2, -3.4.

(2S,3S)-3-(Benzyloxymethyl)-2,4-pentadiene-2,3-oxide-1-ol (**7**). To a solution of vinyl epoxide **34** (5.00g, 13.8 mmol) in THF (70 mL) at 0 °C was added tetra(*n*-butylammonium)fluoride (20.0 mL of a 1.00 M solution in THF, 20.0 mmol). The resulting solution was stirred 0.5 h at 0 °C. The reaction mixture was quenched by addition of H_2O, diluted with ethyl acetate, and the layers were separated. The aqueous layer was extracted with ethyl acetate (5x10 mL) and the combined organic extract was washed with saturated brine, dried over Na_2SO_4,

and concentrated. The resulting oil was purified by chromatography (1:1, hexane:ethyl acetate) to afford 2.10 g (70%) of **7** as an oil, $[\alpha]_D^{24}$ -38.2° (c 0.004, $CHCl_3$); IR ($CHCl_3$) 3432, 3039, 2922, 1641, 1116, 1102, 1029 cm^{-1}; TLC *Rf* 0.46 (1:1, hexane:ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.33 (s, 5H), 5.89 (dd, J = 17.5, 11.0 Hz, 1 H), 5.36-5.45 (m, 2H), 4.56 (ABq, J = 11.9 Hz, 2H), 3.70 (d, J = 11.2 Hz, 2H), 3.64-3.75 (m, 2H), 3.30 (dd, J = 6.4, 2.4 Hz, 1H), 2.02 -2.10 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 138.2, 132.0, 128.3, 128.2, 127.7, 73.4, 72.4, 62.7, 61.7, 60.6; HRMS calcd for $C_{13}H_{16}O_3$ (M^++H) 221.1177, found 221.1165.

(3R,4S)-3-(Benzyloxymethyl)-3-methyl-1,4-pentadiene-4,5-oxide (**5**). To a solution of epoxy alcohol **7** (2.10 g, 9.53 mmol) in dichloromethane (21.0 mL) at 0 °C was added dropwise trimethylaluminum (14.3 mL of a 2.00 M solution in heptane, 28.6 mmol). The resulting homogeneous solution was slowly warmed to room temperature and stirred 16h. The reaction mixture was recooled to 0 °C and carefully quenched by the addition of a saturated aqueous solution of Rochelle's salt (35 mL). The mixture was diluted with ethyl acetate (50 mL) and stirred vigourously for 1h. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic extract was washed with saturated brine, and dried over Na_2SO_4. The solvents were removed to give 1.96 g of a mixture of products. The crude reaction mixture was dissolved in dichloromethane (40.0 mL), cooled to -78 °C, and treated successively with Et_3N (1.73 mL) and methanesulfonyl chloride (0.83 mL, 10.7 mmol). After stirring 1h at -78 °C, the reaction was warmed over 1h to -20 °C and followed by addition of 10% aqueous HCl. The layers were separated and the aqueous phase was extracted with dichloromethane. The combined organic extract was washed with saturated aqueous $NaHCO_3$, saturated brine, and dried over Na_2SO_4. The solvent was removed to afford 2.0 g of a yellow oil that was dissolved in dichloromethane (35 mL) and treated with solid potassium hydroxide (*ca.* 20 pellets). After stirring 10 h at 25 °C, the reaction mixture was decanted from the KOH pellets and the flask was rinsed with dichloromethane. The combined organic extracts were washed sequentially with H_2O, saturated brine, and dried over Na_2SO_4. Removal of the solvents and purification of the residue by chromatography (3:2, hexane:ethyl acetate) afforded 0.40 g (25 %) of **5** as a colorless oil; $[\alpha]_D^{24}$ +13.8° (c 1.02, $CHCl_3$); IR ($CHCl_3$) 1641, 1116, 1102 cm^{-1}; TLC *Rf* 0.46 (95:5, hexane:ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.33 (s, 5H), 5.84 (dd, J = 18.2, 10.6 Hz, 1 H), 5.10-5.16 (m, 2H), 4.54 (s, 2H), 3.39 (s, 2H), 3.06 (dd, J = 4.1, 2.9 Hz, 1H), 2..65-2.71 (m, 2H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.2, 132.0, 128.3, 128.2, 127.7, 73.4, 72.4, 62.7, 61.7, 60.6; HRMS calcd for $C_{14}H_{18}O_2$ (M^+-H) 217.1228, found 217.1219.

Isolation of (2S ,3R)-3-(benzyloxymethyl)-3-methyl-4-penten-1,2-diol (**35**). The crude diol mixture (207 mg) that was obtained on trimethylaluminum reaction of **7** was dissolved in 2,2-dimethoxypropane (4.0 mL). To this solution was added a catalytic amount of pyridinium *p*-toluenesulfonic acid (*ca.* 10 mg). The resulting heterogeneous mixture was stirred 15 min at room temperature and then diluted with CH_2Cl_2 and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extract was washed with saturated brine and dried over Na_2SO_4. Concentration by rotary evaporation gave a yellow oil which was purified by silica gel chromatography (9.5:0.5, hexane:ethyl acetate) to give 93 mg of the *O*-isopropylidene of **35** as a colorless oil: TLC *Rf* 0.25 (9.5:0.5, hexane:ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.32 (m, 5H), 5.90 (dd, J = 17.1, 11.1 Hz, 1H), 5.06-5.15 (m, 2H), 4.52 (s, 2H), 4.19 (t, J = 6.7 Hz, 1H), 3.88 (dd, J = 8.36, 6.7 Hz, 1H), 3.72 (dd, J = 8.41, 7.2 Hz, 1H), 3.44 (d, *J* = 8.9 Hz, 1H), 3.34 (d, *J* = 8.9 Hz, 1H), 1.40 (s, 3H), 1.35 (s, 3H), 1.01 (s, 3H). The isopropylidene derivative was dissolved in THF (1 mL) and to this solution was added aqueous HCl (2.0N, 0.50 mL). The resulting solution was heated at 35 °C for 1.5h. The reaction mixture was then cooled, diluted with Et_2O, and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O and the combined organic extract was washed with saturated brine and dried over Na_2SO_4. Concentration by rotary evaporation gave a yellow oil that was chromatographed (3:2, hexane:ethyl acetate) to give 46 mg of **35** as a colorless oil; TLC *Rf* 0.22 (3:2, hexane:ethyl acetate); IR (neat) 3396, 1635, 1092 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29-7.38 (m, 5H), 5.81 (dd, *J* = 17.4, 11.1 Hz, 1H), 5.12 (d, *J* = 10.9 Hz, 1H), 5.10 (d, *J* = 18.2 Hz, 1H), 4.52 (br. s, 2H), 3.75 (dd, *J* = 7.8, 3.3 Hz, 1H), 3.47-3.65 (m, 3H), 3.35 (1/2 ABq, *J* = 9.0 Hz, 1H), 2.58 (br. s, 1H), 1.98 (br. s, 1H) 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 140.8, 137.5, 128.5, 127.9, 127.6, 114.7, 77.3, 76.8, 73.7, 63.2, 43.9, 16.3; MS, m/z (relative intensity) EI: 237 (M^++1, 25), 181 (16), 91 (100).

Also obtained during chromatography of the initial isopropylidene mixture were fractions containing the *O*'isopropylidene of **36** (mixture of diastereomers): TLC *Rf* 0.19 (9.5:0.5, hexane:ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.31-7.35 (m, 5H), 5.84 (t, *J* = 7.2 Hz, 1H), 4.58-4.48 (m, 3H), 4.16-4.02 (m, 2H), 3.74 (apparent t, *J* = 7.1 Hz, 2H), 2.09-2.20 (m, 2H), 1.64 (s, 3H), 1.62 (s, 3H), 1.01 (t, *J* = 7.2 Hz, 3H); and the *O*'isopropylidene of **37** (a ~2:1 mixture of diastereomers, minor isomer signals in [] when differentiated): TLC *Rf* 0.22 (9.5:0.5, hexane:ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.25-7.42 (m, 8H), 6.12 (dd, *J* = 17.3, 11.1 Hz, 1H), [5.71 (dd, *J* = 17.0, 10.9 Hz, 1H)], 5.18-5.22 (m, 4H), 4.61-4.41 (m, 4H), 3.64-4.21 (m, 5H), 1.50 (s, 3H), [1.48 (s, 3H)], 1.43 (s, 3H), [1.41 (s, 3H)], [1.12 (d, *J* = 7.1 Hz, 3H)], 1.02 (d, *J* = 7.3 Hz, 3H).

General Experimental Procedure for Methylation of 2,3-Epoxy-1-ols. To a solution of 3,3-dimethyl-2,3-epoxy-1-ol (**10**) (300 mg, 2.90 mmol) in dichloromethane (7 mL) at 0 °C was added dropwise trimethylaluminum (4.40 mL of a 2.0 M solution in heptane, 8.80 mmol). The resulting homogeneous solution was warmed to room temperature and stirred 16 h. The reaction mixture was recooled to 0 °C and quenched by the addition of aqueous 2N HCl (10 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic extract was washed with saturated brine and dried (Na_2SO_4). The solvents were removed and the crude product mixture was filtered through a short column of silica (1:1, hexane:ethyl acetate) to give 260 mg (75%) of diols **11** and **12**. HPLC analysis indicated a 5:1 ratio of **11**:**12**. The diol mixture was treated with $NaIO_4$ (0.70 g, 3.30 mmole) in a 1:1 mixture of THF:H_2O (10 mL). The reaction was stirred at room temperature for 2h and then filtered (celite). The filtrate was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$. The layers were separated and the organic phase was dried (Na_2SO_4). Removal of the solvents and purification of the residue by chromatography (9:1, hexane:ethyl acetate) gave 80 mg of pivaldehyde and 35 mg of 1,3-diol **12**[34]; ^1H NMR ($CDCl_3$) δ 3.75 (m, 1H), 3.57 (d, *J* = 10.7 Hz, 1H), 3.48 (d, *J* = 10.7 Hz, 1H), 2.38-2.61 (br. s, 2H), 1.16 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 3H), 0.86 (s, 3H).

Methylation of Epoxy Alcohol 13. Using the general experimental procedure outlined above, treatment of **13** (440 mg) with $(CH_3)_3Al$ gave 370 mg (78%) of a mixture of diols **14** and **15**. HPLC analysis on the mixture determined a 1:3 ratio of **14**:**15**. Subsequent $NaIO_4$ cleavage afforded 31 mg of the corresponding aldehyde of **14**, IR ($CHCl_3$) 2710, 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.57 (s, 1H), 7.35-7.28 (m, 5H), 4.51 (s, 2H), 3.45 (s, 2H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 205, 138, 128, 127, 75.0, 73.3, 47.9, 19; and 223 mg of the corresponding aldehyde of **15** as a 3:1 mixture of diastereomers; IR ($CHCl_3$) 2718, 1723 cm^{-1}; ^1H NMR, major diastereomer ($CDCl_3$) δ 9.74 (d, *J* = 3.0 Hz, 1H), 7.37-7.29 (m, 5H), 4.63 (1/2ABq, *J* = 15.1 Hz, 1H), 4.45 (1/2ABq, *J* = 14.8 Hz, 1H), 3.83 (m, 1H), 2.58 (m, 1H), 1.25 (d, *J* = 6.1 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR, major diastereomer ($CDCl_3$) δ 204.0, 138.1, 128.7, 128.4, 127.6, 75.3, 70.7, 51.7, 16.8, 10.1.

*Methylation of Epoxy Alcohol **16***. Treatment of **16** (97 mg) with $(CH_3)_3Al$ gave 67 mg (61%) of a mixture of diols **17** and **18**. GC analysis on the mixture determined a 4:1 ratio of **17**:**18**. Subsequent $NaIO_4$ cleavage afforded 8 mg of the corresponding volatile aldehyde[15] of **17**, IR (neat) 1684, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.40 (s, 1H), 6.48 (dt, *J* = 7.3, 1.3 Hz, 1H), 2.37 (overlapping dq, 2H), 1.74 (s, 3H), 1.11 (t, *J* = 7.6 Hz, 3H); and 12 mg of **18** as a ~1.5:1 mixture of diastereomers, IR (neat) 3373 (br), 3083, 2975, 1639 cm^{-1}; ^1H NMR, major diastereomer ($CDCl_3$) δ 5.72 (dd, *J* = 17.5, 11.1 Hz, 1 H), 5.15 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.13 (dd, *J* = 11.0, 1.2 Hz, 1H), 3.90 (q, *J* = 6.4 Hz, 1H), 3.61 (m, 2H), 2.64 (br. s, 2H), 1.12 (d, *J* = 6.5 Hz, 3H), 1.01 (s, 3H); ^{13}C NMR, major diastereomer ($CDCl_3$) δ 141.6, 115.0, 73.5, 70.2, 22.3, 18.3, 14.5.

*Methylation of Epoxy Alcohol **19***. Treatment of **19** (62 mg) with $(CH_3)_3Al$ gave 52 mg (76%) of a mixture of diols **20** and **21**. GC analysis on the mixture determined a 3:1 ratio of **20**:**21**. Subsequent $NaIO_4$ cleavage afforded 24 mg of the corresponding aldehyde of **20**, IR (neat) 2962, 2167, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.46 (s, 1H), 1.30 (s, 6H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 198.1, 106.1, 89.4, 41.0, 22.9, -0.02; and 11 mg of **21** isolated as a ~1.5:1 mixture of diastereomers, IR (neat) 3328 (br), 2987, 2900, 2166 cm^{-1}; ^1H NMR, major diastereomer ($CDCl_3$) δ 3.64 (m, 3H), 2.45 (br. m, 2H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.11 (s, 3H), 0.16 (s, 9H); ^{13}C NMR, major diastereomer ($CDCl_3$) δ 107.1, 89.3, 72.4, 69.3, 44.2, 20.5, 17.4, 0.16.

(2R,3S)-3-(Benzyloxymethyl)-4-(dimethylthexylsilyloxy)-2,3-butenoxide-1-ol (**8**). A 100 mL flask was charged with 0.33 g of 4 Å powdered molecular sieves, and dichloromethane (55 mL). The suspension was cooled to -20 °C and freshly distilled D-(-)-diethyl tartrate (0.55g, 2.68 mmol) and Ti(O-*i*-Pr)$_4$ (0.65 mL, 2.16 mmol) were added sequentially. The reaction mixture was stirred 10 min at -20 °C before the addition of TBHP (8.90 mL of a 3.00 M solution in isooctane, 26.8 mmol). The resulting solution was stirred 1h at -20 °C at which time was added a solution of alcohol **31** (2.50 g, 7.14 mmol) in CH_2Cl_2 (3.00 mL). The resulting mixture was stirred 4h at -20 °C before quenching by pouring into a solution of $FeSO_4 \cdot 7H_2O$ (14.2 g, 51.2 mmol) amd tartaric acid (3.92g, 25.6mmol) in H_2O (44.0 mL) at 0 °C. The resulting two-phase mixture was allowed to stir for 10 min and the layers were separated. The aqueous phase was extracted with ether and the combined organic extract was treated with 30% NaOH (w/v) in saturated brine (4.50 mL) and vigorously stirred 1h at 0 °C. The solution was diluted with H_2O (20 mL) and the layers were separated. The aqueous phase was extracted with ether (3x) and the combined organic extract was dried ($MgSO_4$) and concentrated to give 3.40g (86%) of **8** as a pale yellow oil; $[\alpha]_D^{24}$ +6.8° (c 1.75, $CHCl_3$); IR ($CHCl_3$) 3439, 2957, 1253, 1121, 1066 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (s, 5H), 4.56 (ABq, *J* = 17.2, 11.7 Hz, 2H), 4.12 (d, *J* = 10.9 Hz, 1H), 3.68-3.90 (m, 2H), 3.87 (d, *J* = 11.2 Hz, 1H), 3.58 (d, *J* = 10.9 Hz, 1H), 3.41 (d, *J* = 11.2 Hz, 1H), 3.21 (t, *J* = 6.2 Hz, 1H), 2.23-2.27 (m, 1H), 1.56-1.65 (m, 1H), 0.86 (d, *J* = 6.8 Hz, 6H), 0.84 (s, 6H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 137.8, 128.4, 127.7, 127.6, 73.4, 70.5, 62.5, 61.4, 61.0, 58.7, 34.1, 25.1, 20.3, 20.1, 18.5, -3.6; HRMS calcd for $C_{20}H_{34}O_4Si$ (M^++H) 367.2304, found 367.2320.

Preparation of (R)-Mosher Esters from Alcohols. (N,N-Dimethylamino)pyridine (0.15 mmol) and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.15 mmol) were added to a solution of the epoxy alcohol (**32** or **8**, 0.05 mmol) in CH_2Cl_2 at 0 °C. After warming to room temperature and stirring for 1h, the reaction was quenched by addition of water and then diluted with ethyl acetate. The organic layer was separated and washed with saturated aqueous $NaHCO_3$, saturated brine, and dried ($MgSO_4$). The solvents were removed and the residue was analyzed by HPLC. Filtration of the residue through a short column of silica provided a sample of Mosher ester for ^1H NMR analysis.

(2S,3S) - 1 - (Dimethylthexylsilyloxy) - 2 - (benzyloxymethyl) - 2,4 - (O -isopropylidene)-3-methylbutane (**39**). To a suspension of copper iodide (14.1 g, 74.2 mmol) in ether (40 mL) at -20 °C was added dropwise methyllithium (100 mL of a 1.40 M solution in Et_2O, 148 mmol). The resultant homogeneous solution was stirred 35 min at -20 °C and then cooled to -40 °C. A solution of epoxy alcohol **8** (3.40 g, 0.30 mmol) in ether (5.00 mL) was added dropwise via cannula. The reaction mixture was stirred 1 h at -40 °C and then warmed to -20 °C over 1 h whereupon the reaction was quenched by addition of saturated aqueous NH_4Cl. The quenched reaction solution was poured into an ice-cooled 1:1 mixture of saturated aqueous NH_4Cl : 2% NH_3 (50 mL) and vigorously stirred. The resulting heterogeneous mixture was filtered and the layers were separated. The aqueous phase was extracted with Et_2O and the combined organic extract was washed with saturated aqueous NH_4Cl until the aqueous phase remained colorless. The organic layer was washed with saturated brine, dried over $MgSO_4$, and concentrated to give a pale green oil which was purified by chromatography (1:1, hexane:ethyl acetate) to give 2.75 g (77%) of the corresponding 1,3-diol as a pale yellow oil; IR ($CHCl_3$) 3423, 1249, 1153 cm^{-1}; TLC R_f0.51 (1:1, hexane:ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.27-7.35 (m, 5H), 4.55 (s, 2H), 3.48-3.72 (m, 6H), 3.12-3.18 (b, 1H), 2.80-2.86 (b, 1H), 1.93-1.56 (m, 1H), 1.58-1.64 (m, 1H), 1.03 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 6H), 0.86 (s, 6H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 137.6, 128.4, 127.8, 127.7, 76.0, 73.7, 71.4, 64.8, 63.9, 38.8, 34.1, 25.1, 20.3, 18.5, 11.6, -3.6.

To a solution of (2*S*,3*S*)-2-methyl-3-(benzyloxymethy)-4-(dimethylthexylsilyloxy)butan-1,3-diol (2.75 g, 7.19 mmol) in 2,2-dimethoxypropane (36.0 mL) was added pyridinium *p*-toluenesulfonic acid (180 mg, 0.72 mmol). The resulting heterogeneous mixture was stirred 23 h at room temperature. The reaction mixture was then diluted with Et_2O and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ and the layers were separated. The aqueous layer was extracted with ether and the combined organic extract was washed with saturated brine and dried over Na_2SO_4. Removal of the solvents gave a yellow oil that was purified by deactivated silica gel chromatography (9.5:0.5, hexane:ethyl acetate, Note: silica gel was deactivated by prior storing over acetone for 12 h) to give 2.12 g (70%) of acetonide **39** as a colorless oil, $[\alpha]^{26}_{D}$ +11.7° (c 0.75, $CHCl_3$); IR ($CHCl_3$) 1245, 1185 cm^{-1}; TLC R_f 0.36 (9.5:0.5, hexane:ethyl acetate); ^1H NMR ($CDCl_3$) δ 7.27-7.34 (m, 5H), 4.62 (d, *J* = 12.1 Hz, 1H), 4.50 (d, *J* = 12.1 Hz, 1H), 3.96 (dd, *J* = 11.8, 4.11 Hz, 1H), 3.53-3.71 (m, 4H), 3.46 (d, *J* = 9.9 Hz, 1H), 1.71-1.75 (m, 1H), 1.58-1.63 (m, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 6H), 0.82 (s, 6H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.4, 128.2, 127.9, 127.5, 98.1, 76.9, 73.7, 71.9, 63.6, 62.9, 34.2, 30.5, 28.8, 26.8, 25.0, 20.3, 20.2, 18.6, 18.5, 12.7, -3.6; HRMS calcd for $C_{23}H_{39}O_4Si$ (M^+-CH_3) 407.2617, found 407.2631

(2S,3S)-2-(Dimethylthexylsilyloxymethyl)-2,4-(O-isopropylidene)-3-methylbutanal (**6**). Ammonia was condensed (10 mL) into a 3-necked flask fitted with a dry ice-acetone condensor and cooled to -78 °C. Li wire (0.09 g, 13.0 mmol) was added portionwise to the ammonia, and the reaction mixture was stirred until all the Li had dissolved To the resulting deep blue solution was added dropwise via cannula a solution of acetonide **39** (1.00 g, 2.37 mmol) in THF (2 mL). After stirring 10 min at -78 °C, the cooling bath was removed and the reaction was allowed to warm to the reflux temperature. The reaction was quenched by addition of MeOH, diluted with ether, and stirred 2 h at 25 °C. The layers were separated and the aqueous layer was extracted with ether. The combined organic extract was washed saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to give 0.60 g of the corresponding alcohol as a colorless oil, TLC R_f 0.58 (3:1, hexane:ethyl acetate); IR ($CHCl_3$) 3451, 1239, 1171 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (dd, J= 11.8, 4.7 Hz, 1H), 3.72 (d, J= 10.2 Hz, 1H), 3.54-3.63 (m, 4H), 2.58-2.62 (m, 1H), 2.02-2.05 (m, 1H), 1.58-1.63 (m, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 6.9 Hz, 6H), 0.82 (s, 6H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 101.0, 73.1, 66.7, 65.7, 63.4, 38.5, 34.2, 25.1, 24.9, 24.4, 20.2, 18.4, 10.2, -3.6.

To a flask charged with dichloromethane (9.0 mL) at -78 °C was added oxalyl chloride (0.47 mL, 5.41 mmol) and DMSO (0.64 mL, 9.02 mmol). The mixture was stirred for 15 min at -78 °C before addition of a solution of the crude (2*S*,3*S*)-2-(dimethylsilylthexylsilyloxymethyl)-2,4-(*O*-isopropylidene)-3-methylbutan-1-ol (0.60 g, 1.80 mmol) in dichloromethane (0.50 mL). The mixture was stirred 1h at -78 °C. Triethylamine (1.25 mL, 9.0 mmol) was added and the mixture was warmed to 0 °C over 30 min and quenched by addition of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with a 1:1 mixture of hexane:ethyl acetate. The combined organic extract was washed with saturated brine and dried (Na_2SO_4). Removal of the solvents and purification of the residue by chromatography (9:1, hexane:ethyl acetate) gave 0.50 g (64%) of **6** as an oil; $[\alpha]_D^{24}$ +44.5° (c 0.75, $CHCl_3$); IR ($CHCl_3$) 2959, 2787, 1734, 1252, 1197, 1113 cm^{-1}; TLC R_f 0.26 (9:1, hexane:ethyl acetate); ^1H NMR ($CDCl_3$) δ 9.76 (s, 1H), 3.68 (dd, J = 11.9, 3.1 Hz, 1H), 3.58 (ABq, J = 10.3 Hz, 2H), 3.46 (dd, J = 12.1, 2.1 Hz, 1H), 2.20-2.23 (m, 1H), 1.52-1.55 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H), 1.14 (d, J = 7.1 Hz, 3H), 0.83 (d, J = 6.8 Hz, 6H), 0.78 (s, 6H), 0.054 (s, 3H), 0.036 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 204, 99.0, 81.1, 63.7, 63.2, 34.1, 29.7, 25.9, 25.0, 23.8, 20.2. 20.1, 18.5, 18.4, 12.3, -3.9, -3.8; HRMS calcd for $C_{17}H_{33}O_4Si$ (M^+ - H) 329.2147, found 329.2156.

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