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Stereospecific and biomimetic synthesis of C_S and C_2 symmetric 2,5-disubstituted tetrahydrofuran rings as central building blocks of biogenetically intriguing oxasqualenoids

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Abstract—The enantioselective synthesis of optically active (+)-tetraol **12**, corresponding to the C9–C16 subunit of biogenetically and biologically intriguing oxasqualenoids **2**–**4**, has been accomplished by the biomimetic and stereospecific cyclization of diepoxide **22**. The experimental details for the preparation of the known *meso* tetraol **11**, corresponding to the C9–C16 subunit of teurilene **1**, are also described.

1. Introduction

There are numerous examples of biologically active polycyclic natural products that are biosynthesized by sequential cascade cyclizations of acyclic precursors. Polycarbocyclic triterpenes such as steroids are derived from squalene precursors[1] and polyethers such as antibiotics,[2] marine toxins,[3] and acetogenins[4] are derived from polyepoxides. Recently, biologically active and structurally unique triterpene polyethers with some tetrahydrofuran (THF) rings, which are thought to be biogenetically squalene-derived natural products (oxasqualenoids), have been isolated from both marine and terrestrial plants. It is of great interest to consider the biogenesis[5] of the highly symmetric squalene-derived triterpene polyethers, teurilene **1**, longilene peroxide **2**, and glabrescol **3**, among others (Scheme 1). The polyethers teurilene **1** and longilene peroxide **2** were isolated from the red alga *Laurencia obtusa* by Kurosawa et al.[6] and from the wood of *Eurycoma longifolia* by Itokawa et al.,[7] respectively, and their stereostructures were elucidated by X-ray crystallographic analysis. Both compounds **1** and **2** exhibit prominent cytotoxic activities on KB cells (**1**: $IC_{50}=7.0$ μg/mL; **2**: $IC_{50}=5.3$ μg/mL).[8] On the other hand, glabrescol **3**[9] and an epoxy tri-THF diol **4**[10] were extracted from the endemic Jamaican plant *Spathelia glabrescens* (Rutaceae) by Jacobs et al., and the correct structures were finally determined by their total synthesis.[11–13] Although there is no report on the biological activities of both compounds, these polyethers containing five or three THF rings may be expected to exhibit ionophoric functions[14,15] as well as cytotoxicities,[8] because of the recent active research studies on remarkable interactions (membrane transport and ion channel) of neutral oligotetrahydrofuranyl derivatives with metal cations in natural products[16] and artificial systems.[17,18] However, because these compounds are available only in restricted amounts from natural sources, the development of an efficient synthesis was desired.

Considering the familiar examples of biogenesis discussed above,[1–4] the C_S symmetric (*meso*) polyether **1** might be derived from the C_2 symmetric (*d*,*l*) tetraepoxide **5** by sequential cascade cyclizations. On the other hand, C_2 symmetric polyethers **2** and **3** could be obtained from C_S symmetric tetraepoxide **6** and hexaepoxide **7** in the same manner, respectively, except for the discriminating enantiotopic terminal epoxides. In this case, it may be invaluable to realize the complementary conservation of molecular symmetry between the biogenetic precursors and natural products (C_S versus C_2). Although there is no symmetric element in compound **4**, it could easily be imagined that **4** is biogenetically produced by similar sequential cascade cyclizations of pentaepoxide **8**. Thus, the structurally symmetric arrays and the biogenetically unique features coupled with their biological activities and ionophoric functions have prompted a significant synthetic effort for these polyethers.[12,19–21] In this context, we have also

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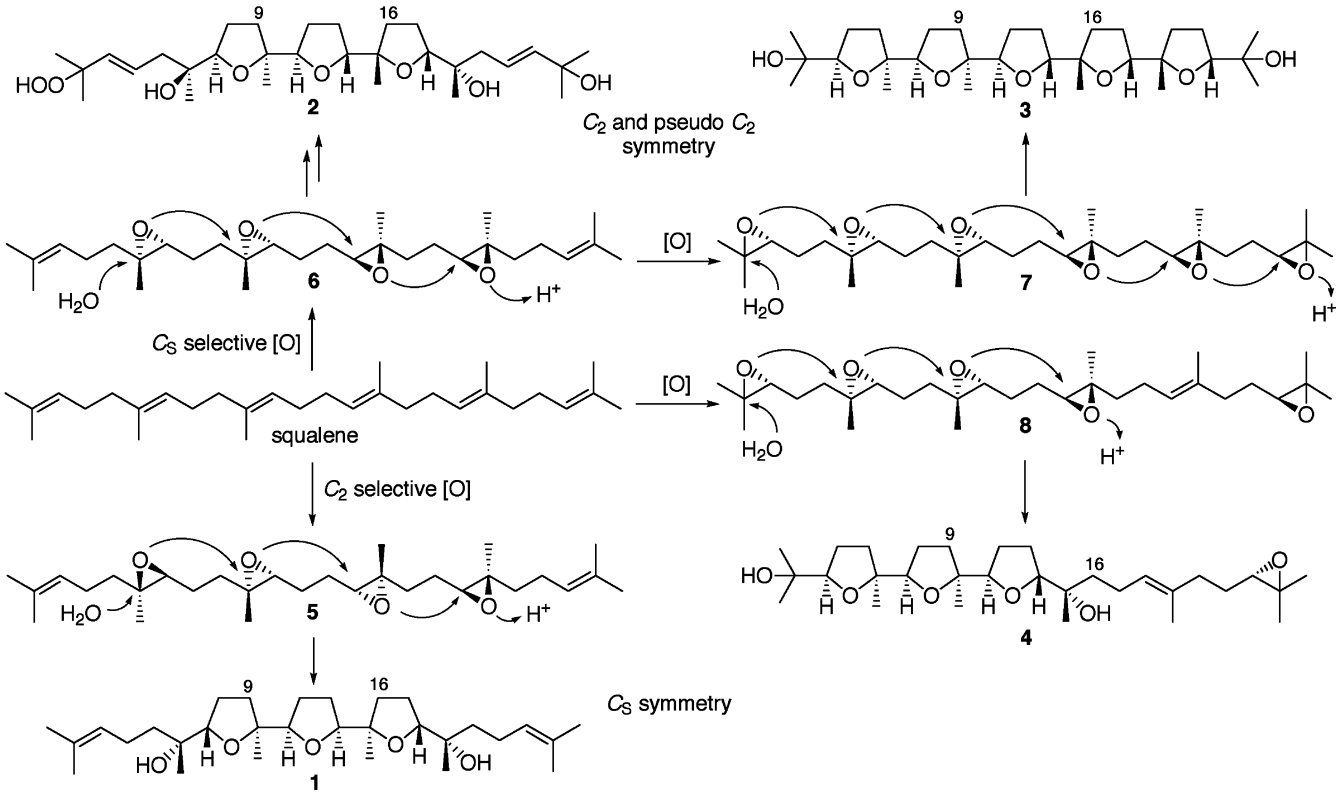


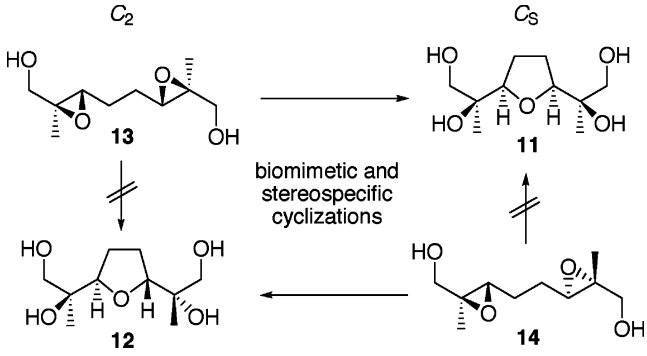
Scheme 1. Complementary conservation of molecular symmetry (C_S versus C_2) in the hypothetical biogenesis of oxasqualenoids **1**–**3**.

accomplished the total synthesis of teurilene **1**,[22,23] (–)-longilene peroxide **2**,[24] (–)-glabrescol **3**,[11,23] an epoxy tri-THF diol (–)-**4**,[13] and relevant polyethers[25,26] based on the concept of two-directional synthesis utilizing their intrinsic molecular symmetry as the fundamental strategy. In our syntheses of **1**–**4**, C_S and C_2 symmetric diepoxides **9** and **10**, respectively, have been employed as the central C9–C16 subunit. Herein, we report in detail a biomimetic and stereospecific preparation method of the C_{10} building blocks **9** and **10**.

2. Results and discussion

Hoye and Jenkins have already reported the biomimetic and stereospecific cyclizations of bisglycidic alcohols C_2 **13** and C_S **14** to the C9–C16 fragments C_S **11** and C_2 **12**, respectively (Scheme 2).[27] However, isolation and characterization of the polar *meso* tetraol **11** itself were not described in the paper, and the preparation of the tetraol **12** was as a racemate. Therefore, to carry out the asymmetric synthesis of **2**–**4**, the optically active tetraol **12** was required.

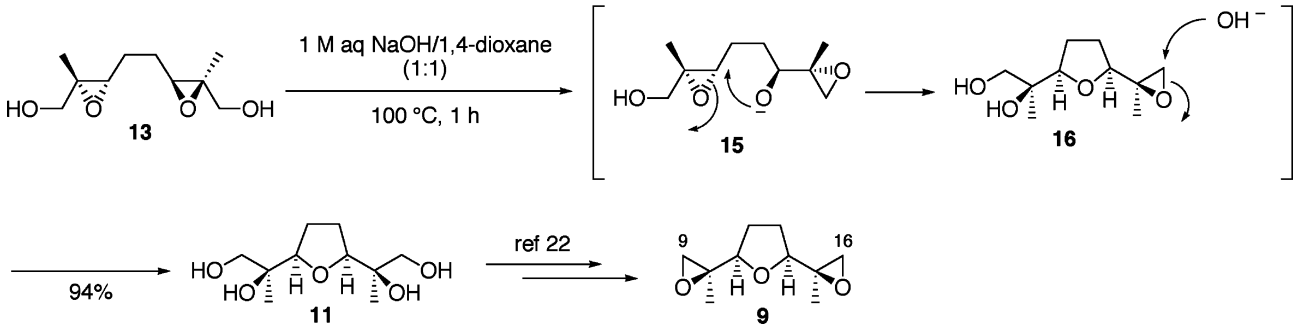
Firstly, according to Hoye's procedure[27] the known bisglycidic alcohol **13**[28] was heated at 100°C in 1 M aqueous sodium hydroxide/1,4-dioxane (1:1) for 1 h to produce the *meso* tetraol **11** (Scheme 3), which was isolated in 94% yield after column chromatography on silica gel and fully characterized. As the reaction mechanism was demonstrated by Hoye and Jenkins, the



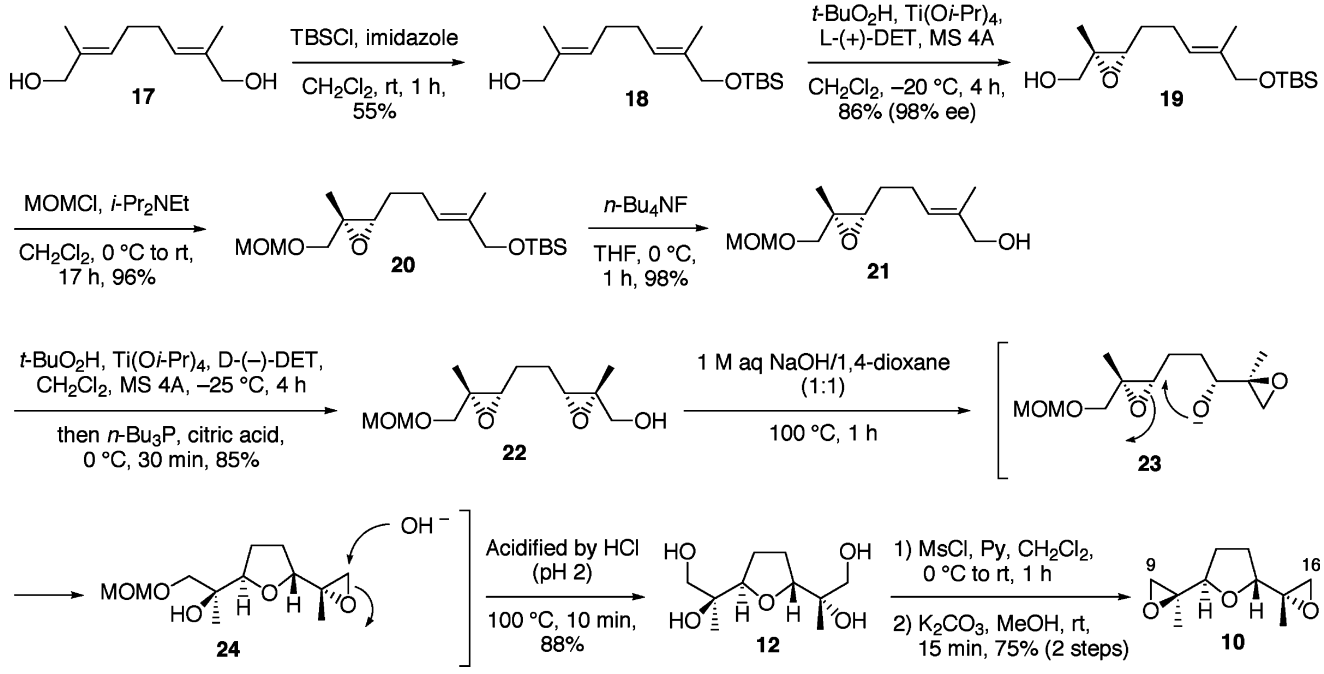
Scheme 2. Biomimetic and stereospecific cyclizations of bisglycidic alcohols C_2 **13** and C_S **14** to C_S **11** and C_2 **12**, respectively, reported by Hoye and Jenkins.

bisglycidic alcohol **13** was transformed into the diepoxide **9** by way of a stereospecific reaction pathway involving base-catalyzed Payne rearrangement (**13**→**15**), intramolecular epoxide-opening (**15**→**16**), and bimolecular epoxide-opening by hydroxide ion (**16**→**11**).

Next, the same stereospecific procedure was applied to the preparation of the optically active C_2 diepoxide **10**, which began with monoprotection of the known diol **17**[28] as a *tert*-butyldimethylsilyl (TBS) ether (Scheme 4). Sharpless asymmetric epoxidation[29] of the allylic alcohol **18** using (–)-diethyl L-tartrate [L-(–)-DET] afforded the epoxy alcohol **19** in 86% yield. The enantiomeric



Scheme 3. Stereospecific preparation of the *meso* diepoxide **9**.



Scheme 4. Asymmetric synthesis of the C_2 symmetric diepoxide **10**.

excess of **19** was determined to be 98% ee by derivatization of **19** to a Mosher ester with (*S*)-α-methyl-α-(trifluoromethyl)phenylacetyl chloride [(*S*)-MTPACl] and integration of the signals in the ^{1}H NMR spectrum.[30] Methoxymethyl (MOM) protection, desilylation, and the second epoxidation using D-(–)-DET afforded the diepoxide **22**. The THF ring formation from **22** according to Hoye's procedure[27] still proceeded stereospecifically via intermediates **23** and **24** to afford tetraol **12** in high yield after in situ acid treatment. The mesylation of both primary hydroxy groups in the tetraol **12** and subsequent basic treatment of the dimesylate finally provided the desired C_2 symmetric diepoxide **10** as an optically active form in 75% yield in two steps.

3. Conclusion

We have achieved the enantioselective preparation of optically active tetraol **12**, corresponding to the C9–C16 subunit of oxasqualenoids **2**–**4**, by the biomimetic and stereospecific cyclization of diepoxide **22**, wherein the two enantiotopic glycidic alcohol functional groups were enantiodifferentiated. We have also described the experimental details for the reproducible preparation of the known C_S symmetric tetraol **11**, corresponding to the C9–C16 subunit of *meso* teurilene **1**, by the biomimetic and stereospecific cyclization[27] of bisglycidic alcohol **13**.[28] In particular, the tetraol **12** will be useful as a C_{10} chiral building block for synthesizing optically active de novo functional molecules[17,18] including THF rings as well as analogs of natural polyethers **2**–**4**. Application of the chiral synthon **12** to the total synthesis of other oxasqualenoids is under investigation in our laboratory.

4. Experimental

4.1. General methods

^{1}H NMR spectra were recorded in deuteriochloroform on JEOL model JNM-LA 300 (300 MHz) and 400 (400 MHz) spectrometers. ^{13}C NMR spectra were measured

in deuteriochloroform on JEOL model JNM-LA 300 (75 MHz) and 400 (100 MHz) spectrometers. Infrared (IR) spectra were recorded on JASCO A-102 and Shimadzu FTIR-8600 spectrophotometers. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. Low- and high- (EI, CI, and FAB) resolution mass spectra were determined on JEOL model JMX-AX 500, SX-102, and JMS-700 T spectrometers. Analytical thin-layer chromatography was carried out by precoated silica gel (Merck TLC plates silica gel 60 F_{254}). The silica gel used for column chromatographies was Merck Silica gel 60 (70–230 mesh). All reactions were performed in oven-dried glassware. Tetrahydrofuran (THF) was distilled over sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2) and pyridine (Py) were distilled over calcium hydride. Methanol (MeOH) was distilled over magnesium. Activation of powdered 4 Å molecular sieves (MS 4 Å) involved heating in a vacuum oven at 160°C and 0.05 mmHg pressure for at least 3 h.

4.2. *meso* Tetraol 11

A solution of the known bisglycidic alcohol **13**[28] (4.06 g, 20.1 mmol) in 60 mL of 1,4-dioxane and 60 mL of a 1 M aqueous solution of sodium hydroxide was stirred at 100°C for 1 h. The mixture was cooled to room temperature and neutralized with conc. hydrochloric acid. The organic and aqueous layers were evaporated under reduced pressure, and ethanol was added to the residue to precipitate sodium chloride. After filtration through a pad of Celite under reduced pressure to remove the precipitated sodium chloride, the filtrate was concentrated in vacuo. The residue was purified by column chromatography (chloroform/methanol = 85:15) on 150 g of silica gel to provide *meso* tetraol **11** (4.14 g, 93.6% yield) as a colorless oil: $R_f = 0.36$ (chloroform/methanol = 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (2H, br s), 3.87 (2H, br t, $J = 5.0$ Hz), 3.67 (2H, d, $J = 11.4$ Hz), 3.41 (2H, d, $J = 11.4$ Hz), 1.98–1.76 (4H, m), 1.17 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.2, 73.6, 66.6, 26.3, 21.7; IR (neat) 3350, 2980, 2930, 2870, 1455, 1370, 1127, 1040, 883, 742 cm^{-1}; CI-MS m/z (relative intensity) 221 [(M+H)$^+$, 18], 203 (14), 189 (11), 185 (15), 171 (17), 167 (21), 153 (26), 145 (36), 127 (100), 75 (30); CI-HRMS calcd for $C_{10}H_{21}O_5$ [(M+H)$^+$] 221.1389, found 221.1376.

4.3. (2*E*,6*E*)-8-*tert*-Butyldimethylsilyloxy-2,7-dimethyl-2,6-octadien-1-ol 18

To a solution of the known diol **17**[28] (5.90 g, 34.7 mmol) and 5.90 g (86.7 mmol) of imidazole in 50 mL of dichloromethane was added dropwise a solution of 5.23 g (34.7 mmol) of *tert*-butylchlorodimethylsilane dissolved in 20 mL of dichloromethane at room temperature under a nitrogen atmosphere, and the resulting mixture was stirred at the same temperature for 1 h. Brine (50 mL) was added to the solution, and the dichloromethane layer was separated. The aqueous layer was extracted with dichloromethane (4×30 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate = 95:5→70:30→20:80) on 120 g of silica gel to give the disilyl ether (2.71 g, 19.6% yield), TBS ether **18** (5.42 g, 54.9% yield), and the starting diol **17** (1.49 g, 25.2% yield), respectively, as each colorless oil.

4.3.1. Disilyl ether. $R_f = 0.90$ (hexane/ethyl acetate = 80:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43–5.36 (2H, m), 4.00 (4H, s), 2.11–2.06 (4H, m), 1.60 (6H, s), 0.91 (18H, s), 0.06 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 124.3, 68.7, 27.5, 26.0, 18.4, 13.5, −5.26; FAB-MS m/z (relative intensity) 397 [(M−H)$^+$, 11], 199 (16), 147 (27), 73 (100); FAB-HRMS calcd for $C_{22}H_{45}O_2Si_2$ [(M−H)$^+$] 397.2959, found 397.2957.

4.3.2. TBS ether 18. $R_f = 0.36$ (hexane/ethyl acetate = 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47–5.35 (2H, m), 4.01 (2H, br s), 4.00 (2H, br s), 2.16–2.04 (4H, m), 1.67–1.50 (1H, br s), 1.67 (3H, s), 1.60 (3H, s), 0.91 (9H, s), 0.06 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.0, 134.8, 126.0, 124.0, 69.0, 68.6, 27.6, 27.4, 25.9, 18.4, 13.7, 13.5, −5.27; IR (neat) 3342, 2957, 2928, 2856, 1472, 1464, 1389, 1362, 1252, 1111, 1067, 1005, 939, 837, 814, 775, 667 cm^{-1}; FAB-MS m/z (relative intensity) 284 (M$^+$, 0.9), 283 [(M−H)$^+$, 3.5], 185 (91), 93 (100), 75 (28), 73 (21); FAB-HRMS calcd for $C_{16}H_{31}O_2Si$ [(M−H)$^+$] 283.2093, found 283.2102.

4.3.3. Diol 17. $R_f = 0.20$ (hexane/ethyl acetate = 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46–5.37 (2H, m), 3.99 (4H, s), 2.16–2.06 (4H, m), 1.96 (2H, br s), 1.66 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 125.5, 68.7, 27.4, 13.7; IR (neat) 3310, 2900, 2845, 1437, 1380, 1355, 1307, 1218, 1058, 1002, 846 cm^{-1}; EI-MS m/z (relative intensity) 152 [(M−H_2O)$^+$, 3.0], 84 (57), 69 (20), 68 (100), 67 (39), 55 (25); EI-HRMS calcd for $C_{10}H_{16}O$ [(M−H_2O)$^+$] 152.1202, found 152.1198.

4.4. (2*S*,3*S*,6*E*)-8-*tert*-Butyldimethylsilyloxy-2,7-dimethyl-2,3-epoxyoct-6-en-1-ol 19

To a suspension of 4 Å molecular sieves (1.5 g) in 150 mL of dichloromethane were sequentially added freshly distilled titanium tetraisopropoxide (0.63 mL, 2.16 mmol) and (+)-diethyl L-tartrate (0.52 mL, 3.02 mmol) at −20°C under a nitrogen atmosphere with stirring. The reaction mixture was stirred at −20°C as *tert*-butyl hydroperoxide (12.8 mL, 51.8 mmol, 4.06 M in dichloromethane) was added dropwise over ca. 5 min. The resulting mixture was stirred at −20°C for 30 min. A solution of allylic alcohol **18** (12.3 g, 43.2 mmol) dissolved in 40 mL of dichloromethane was then added dropwise over a period of 25 min, and the mixture was stirred for an additional 4 h at −20°C. The catalyst was quenched with 15 mL of water and the mixture was stirred at 0°C for 30 min. Hydrolysis of the tartrate was effected by adding 10 mL of a 30% aqueous solution of sodium hydroxide saturated with sodium chloride and stirring vigorously at 0°C for 30 min. The lower organic phase was removed and combined with four 40 mL dichloromethane extractions of the aqueous phase. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo.

The residue was purified by column chromatography (hexane/ethyl acetate = 70:30) on 350 g of silica gel to provide epoxy alcohol **19** (11.2 g, 86.3% yield, 98% ee by NMR analysis of the Mosher ester) as a colorless oil: $R_f = 0.36$ (hexane/ethyl acetate = 70:30); $[\alpha]_D^{24}$ −9.80 (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.47–5.37 (1H, m), 4.01 (2H, s), 3.67 (1H, d, $J = 12.3$ Hz), 3.56 (1H, dd, $J = 12.3$, 5.9 Hz), 3.04 (1H, t, $J = 6.3$ Hz), 2.28–2.13 (2H, m), 1.80–1.53 (3H, m), 1.62 (3H, s), 1.28 (3H, s), 0.91 (9H, s), 0.07 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 123.0, 68.4, 65.4, 60.9, 59.9, 28.1, 25.9, 24.4, 18.4, 14.3, 13.4, −5.30; IR (neat) 3435, 2955, 2928, 2856, 1464, 1389, 1362, 1252, 1111, 1067, 1007, 939, 837, 814, 775, 667 cm^{-1}; FAB-MS *m*/*z* (relative intensity) 301 [$(M+H)^+$, 13], 300 (M^+, 4.0), 169 (45), 111 (39), 93 (26), 75 (55), 73 (100); FAB-HRMS calcd for $C_{16}H_{33}O_3Si$ [$(M+H)^+$] 301.2199, found 301.2217.

4.4.1. (*R*)-MTPA ester of 19. To a solution of epoxy alcohol **19** (9.2 mg, 30.6 μmol), 4-*N*,*N*-dimethylaminopyridine (11.2 mg, 91.8 μmol), and triethylamine (13 μL, 91.8 μmol) in 1 mL of dichloromethane was added (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (11 μL, 61.2 μmol) at room temperature under a nitrogen atmosphere, and the mixture was then stirred at the same temperature for 1 h. The mixture was concentrated under reduced pressure until half volume. The residue was directly subjected to column chromatography (hexane/ethyl acetate = 90:10) on 3 g of silica gel to provide (*R*)-MTPA ester of **19** (14.9 mg, 94.2% yield) as a colorless oil: $R_f = 0.13$ (hexane/ethyl acetate = 50:50); $[\alpha]_D^{25}$ +22.3 (*c* 0.73, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.51 (2H, m), 7.44–7.38 (3H, m), 5.39 (1H, tq, $J = 7.3$, 1.4 Hz), 4.41 (1H, d, $J = 11.7$ Hz), 4.13 (1H, d, $J = 11.5$ Hz), 4.00 (2H, s), 3.56 (3H, d, $J = 0.98$ Hz), 2.86 (1H, t, $J = 6.3$ Hz), 2.25–2.08 (2H, m), 1.69–1.51 (2H, m), 1.59 (3H, s), 1.26 (3H, s), 0.91 (9H, s), 0.06 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 135.6, 132.0, 129.7, 128.4, 127.4, 123.3 (q, $J = 288$ Hz), 122.7, 84.7 (q, $J = 28.1$ Hz), 70.3, 68.3, 61.1, 58.1, 55.5, 28.1, 25.9, 24.2, 18.4, 14.2, 13.4, −5.31; IR (neat) 2955, 2930, 2856, 1755, 1471, 1464, 1391, 1252, 1186, 1170, 1120, 1082, 1024, 837, 777 cm^{-1}; FAB-MS *m*/*z* (relative intensity) 517 [$(M+H)^+$, 4.7], 515 [$(M-H)^+$, 4.6], 385 (4.9); FAB-HRMS calcd for $C_{26}H_{38}O_5F_3Si$ [$(M-H)^+$] 515.2441, found 515.2433.

4.5. (2*E*,6*S*,7*S*)-1-*tert*-Butyldimethylsilyloxy-8-methoxymethoxy-2,7-dimethyl-6,7-epoxyoct-2-ene 20

To a solution of epoxy alcohol **19** (8.19 g, 27.2 mmol) and *N*-ethyldiisopropylamine (7.0 mL, 40.9 mmol) in 130 mL of dichloromethane was added dropwise chloromethyl methyl ether (2.7 mL, 35.4 mmol) at 0°C under a nitrogen atmosphere, and the mixture was then stirred at room temperature for 17 h. The organic layer was washed with water (100 mL×2), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate = 90:10) on 190 g of silica gel to afford the MOM ether **20** (8.97 g, 95.5% yield) as a colorless oil: $R_f = 0.63$ (hexane/ethyl acetate = 80:20); $[\alpha]_D^{25}$ −5.25 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.42 (1H, tq, $J = 7.3$, 1.4 Hz), 4.63 (2H, s), 4.01 (2H, s), 3.54 (1H, d, $J = 11.0$ Hz), 3.49 (1H, d, $J = 11.0$ Hz), 3.37 (3H, s), 2.90 (1H, t, $J = 6.3$ Hz), 2.29–2.13 (2H, m), 1.72–1.55 (2H, m), 1.61 (3H, s), 1.32 (3H, s), 0.91 (9H, s), 0.06 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 123.0, 96.5, 72.0, 68.4, 60.7, 59.6, 55.3, 28.3, 25.9, 24.4, 18.4, 14.5, 13.4, −5.30; IR (neat) 2955, 2930, 2856, 1464, 1361, 1252, 1153, 1111, 1051, 837, 775 cm^{-1}; FAB-MS *m*/*z* (relative intensity) 343 [$(M-H)^+$, 0.2], 313 (0.6), 75 (20); FAB-HRMS calcd for $C_{18}H_{35}O_4Si$ [$(M-H)^+$] 343.2304, found 343.2302.

4.6. (2*E*,6*S*,7*S*)-8-Methoxymethoxy-2,7-dimethyl-6,7-epoxyoct-2-en-1-ol 21

To a solution of MOM ether **20** (8.80 g, 25.6 mmol) in 50 mL of tetrahydrofuran was added dropwise tetrabutylammonium fluoride (38 mL, 38.0 mmol, 1 M in tetrahydrofuran) at 0°C under a nitrogen atmosphere, and the mixture was stirred at the same temperature for 1 h. Water (60 mL) was added to the solution, and the aqueous layer was extracted with ethyl acetate (4×60 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate = 40:60) on 150 g of silica gel to furnish the allylic alcohol **21** (5.77 g, 98.1% yield) as a colorless oil: $R_f = 0.33$ (hexane/ethyl acetate = 50:50); $[\alpha]_D^{24}$ −3.85 (*c* 0.73, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.45 (1H, tq, $J = 7.2$, 1.2 Hz), 4.63 (2H, s), 4.01 (2H, s), 3.54 (1H, d, $J = 10.8$ Hz), 3.48 (1H, d, $J = 10.8$ Hz), 3.37 (3H, s), 2.90 (1H, t, $J = 6.2$ Hz), 2.23 (2H, br q, $J = 7.5$ Hz), 1.75–1.58 (2H, m), 1.69 (3H, s), 1.32 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 124.6, 96.5, 72.1, 68.7, 60.9, 59.5, 55.3, 28.1, 24.5, 14.6, 13.7; IR (neat) 3443, 2934, 2864, 1456, 1387, 1213, 1151, 1109, 1047, 920, 710 cm^{-1}; FAB-MS *m*/*z* (relative intensity) 231 [$(M+H)^+$, 3.6], 199 (16), 169 (60), 75 (21); FAB-HRMS calcd for $C_{12}H_{23}O_4$ [$(M+H)^+$] 231.1596, found 231.1585.

4.7. (2*R*,3*R*,6*S*,7*S*)-8-Methoxymethoxy-2,7-dimethyl-2,3-epoxy-6,7-epoxyoctan-1-ol 22

To a suspension of 4 Å molecular sieves (1.2 g) in 150 mL of dichloromethane were sequentially added freshly distilled titanium tetraisopropoxide (0.36 mL, 1.22 mmol) and (−)-diethyl D-tartrate (0.30 mL, 1.71 mmol) at −25°C under a nitrogen atmosphere with stirring. The reaction mixture was stirred at −25°C as *tert*-butyl hydroperoxide (7.3 mL, 29.4 mmol, 4.06 M in dichloromethane) was added dropwise over ca. 5 min. The resulting mixture was stirred at −25°C for 30 min. A solution of the allylic alcohol **21** (5.63 g, 24.5 mmol) dissolved in 50 mL of dichloromethane was then added dropwise over a period of 30 min, and the mixture was stirred for an additional 4 h at −25°C. To the solution were consecutively added tributylphosphine (1.2 mL, 4.89 mmol) and 257 mg (1.22 mmol) of citric acid monohydrate dissolved in 60 mL of 10% acetone in diethyl ether, and the mixture was stirred at 0°C for 30 min. After filtration through a pad of Celite under reduced pressure, the filtrate was concentrated in

vacuo. The residue was purified by column chromatography (hexane/ethyl acetate = 20:80) on 180 g of silica gel to yield epoxy alcohol **22** (5.09 g, 84.5% yield) as a colorless oil: $R_f = 0.13$ (hexane/ethyl acetate = 50:50); $[\alpha]_D^{25}$ −2.66 (*c* 1.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (2H, s), 3.62 (2H, br s), 3.54 (2H, s), 3.37 (3H, s), 2.07 (1H, br s), 1.91–1.60 (4H, m), 1.35 (3H, s), 1.32 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.5, 71.7, 65.7, 61.0, 60.6, 60.0, 59.7, 55.3, 25.5, 25.4, 14.5, 14.2; IR (neat) 3449, 2932, 2889, 2826, 1458, 1387, 1213, 1151, 1109, 1045, 959, 918, 885, 829, 704, 689 cm^{-1}; FAB-MS *m*/*z* (relative intensity) 247 [$(M+H)^+$, 3.6], 185 (100), 93 (100), 75 (23); FAB-HRMS calcd for $C_{12}H_{23}O_5$ [$(M+H)^+$] 247.1546, found 247.1560.

4.8. (2*R*,5*R*)-2,5-Bis[(1*S*)-1,2-dihydroxy-1-methylethyl]-tetrahydrofuran 12

A solution of epoxy alcohol **22** (3.55 g, 14.4 mmol) in 45 mL of 1,4-dioxane and 45 mL of a 1 M aqueous solution of sodium hydroxide was stirred at 100°C for 1 h. The mixture was cooled to room temperature, adjusted to pH 2 with conc. hydrochloric acid, and stirred at 100°C for an additional 10 min. The mixture was cooled to room temperature and neutralized with a 1 M aqueous solution of sodium hydroxide. The organic and aqueous layers were evaporated under reduced pressure, and ethanol was added to the residue to precipitate sodium chloride. After filtration through a pad of Celite under reduced pressure to remove the precipitated sodium chloride, the filtrate was concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/methanol = 80:20) on 100 g of silica gel to provide the C_2 symmetric tetraol **12** (2.80 g, 87.9% yield) as a colorless oil: $R_f = 0.17$ (ethyl acetate/methanol = 90:10); $[\alpha]_D^{25}$ +6.27 (*c* 1.13, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 3.99–3.92 (2H, m), 3.68 (2H, d, $J = 11.2$ Hz), 3.42 (2H, d, $J = 11.2$ Hz), 2.10–1.79 (4H, m), 1.61 (4H, br s), 1.16 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.7, 73.5, 67.1, 27.2, 21.0; IR (neat) 3358, 2976, 2939, 2880, 1456, 1375, 1215, 1047, 950, 889, 756 cm^{-1}; FAB-MS *m*/*z* (relative intensity) 221 [$(M+H)^+$, 4.9], 203 (1.6), 75 (21); FAB-HRMS calcd for $C_{10}H_{21}O_5$ [$(M+H)^+$] 221.1389, found 221.1381.

4.9. (2*R*,5*R*)-2,5-Bis[(1*S*)-1-methyl-1,2-epoxyethyl]-tetrahydrofuran 10

To a solution of tetraol **12** (1.58 g, 7.18 mmol) and pyridine (3 mL, 36.8 mmol) in 3 mL of dichloromethane was added dropwise methanesulfonyl chloride (1.67 mL, 21.6 mmol) at 0°C under a nitrogen atmosphere, and the mixture was stirred at room temperature for 1 h. A saturated aqueous solution of sodium bicarbonate (10 mL) was added to the solution, and the aqueous layer was extracted with dichloromethane (4×10 mL). The organic layer was washed with 2 M aqueous hydrochloric acid saturated with sodium chloride, and the aqueous layer was extracted with dichloromethane (3× 15 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford the dimesylate which was taken to the next step without further purification.

To a solution of the above dimesylate in 30 mL of methanol was added potassium carbonate (3.97 g, 28.7 mmol), and the mixture was stirred under a nitrogen atmosphere at room temperature for 15 min. Water (60 mL) was added to the reaction mixture, and the aqueous layer was extracted with dichloromethane (3× 40 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane/ethyl acetate = 70:30) on 60 g of silica gel to furnish diepoxide **10** (985 mg, 74.5% yield from the tetraol **12**) as a colorless oil: $R_f = 0.30$ (hexane/ethyl acetate = 70:30); $[\alpha]_D^{25}$ +9.75 (*c* 0.843, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.95–3.87 (2H, m), 2.71 (2H, d, $J = 4.8$ Hz), 2.60 (2H, d, $J = 4.8$ Hz), 2.09–1.93 (2H, m), 1.86–1.69 (2H, m), 1.34 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.5, 57.4, 52.3, 27.6, 17.2; IR (neat) 3047, 2976, 2876, 1447, 1379, 1356, 1286, 1177, 1063, 1005, 951, 912, 856, 814, 727 cm^{-1}; EI-MS *m*/*z* (relative intensity) 184 (M^+, 0.5), 127 (32), 97 (66), 95 (48), 84 (43), 83 (42), 81 (88), 71 (100), 69 (69), 67 (36), 57 (40), 55 (51); EI-HRMS calcd for $C_{10}H_{16}O_3$ (M^+) 184.1100, found 184.1121.

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