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Asymmetric total synthesis of (+)-curcutetraol and (+)-sydonol

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ABSTRACT

The asymmetric total syntheses of (+)-curcutetraol and (+)-sydonol, phenolic bisabolane-type sesquiterpenoids having chiral tertiary alcohol moiety in the *o*-position of a phenol, were achieved in high enantiomeric excesses (99% ee). The chiral tertiary benzylic alcohol moiety of these compounds was constructed by an asymmetric synthesis using an easily available chiral aminal, (−)-(2*R*,5*S*)-2-methoxycarbonyl-3-phenyl-1,3-diazabicyclo[3.3.0]octane. The absolute configurations of both (+)-curcutetraol and (+)-sydonol have been assumed to be *S*-configuration based on the stereochemical course of the well established asymmetric synthesis used in the syntheses.

1. Introduction

Many phenolic sesquiterpenoids of the bisabolane family, possessing one or two stereogenic centers, have been isolated from both terrestrial and marine organisms. They often display characteristic biological activities[1–9] in contrast with non-phenolic sesquiterpenoids. For example, (+)-curcuphenol, isolated from sponges (the subgenus *Mycale (Arenochalina)* and the genera *Didiscus*, *Epipolasis*, and *Myrmekioderma*),[1] strongly inhibits the activity of gastric H, K-ATPase.[1b] On the other hand, (−)-curcuphenol, isolated from the gorgonian coal (*Pseudopterogorgia rigida*) and the terrestrial plant (*Lasianthaea podocephata*),[2] exhibits antibacterial activities against *Staphylococcus aureus* and *Vibrio anguillarum*.[2a] Thus, a number of studies have been carried out to date on syntheses of both racemic and chiral curcuphenol.[10] Meanwhile, there has been few reports on biological activities of curcutetraol (**1**),[5] sydonol (**2**),[6] sydonic acid,[7] waraterpol,[8] ligustiphenol,[9] and curcutriolamide,[5] which contain a tertiary benzylic alcohol moiety in the *o*-position of a phenol (Fig. 1), and there was no report on their asymmetric synthesis to the best of our knowledge.

(+)-Curcutetraol (**1**) was isolated from the marine bacterium CNH-741 and fungus CNC-979 by Lindel and co-workers in 2005. It is the first bisabolane sesquiterpenoid with a tertiary benzylic alcohol moiety as a single stereogenic center in the *o*-position of a phenol isolated from the marine environment. The structure of (+)-**1** was determined on the basis of an extensive NMR spectroscopic analysis and confirmed by synthesis of the racemic compound.[5] The absolute configuration of its tertiary benzylic alcohol moiety was proposed to be *S* by the comparison of its experimental CD spectrum with the calculated one.[5] The *S*-configuration of (+)-**1** was also assumed by an asymmetric synthesis of (+)-**1** as shown in our preliminary communication.[11]

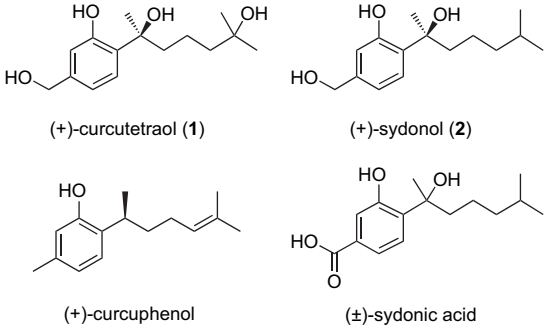

Figure 1. Phenolic bisabolane sesquiterpenoids.

5′-Deoxygenated curcutetraol is known as sydonol (**2**). (+)-Sydonol (**2**) was isolated from a strain of *Aspergillus* sp. by Nukina and co-workers in 1981 and exhibited antifungal activity against *Cochliobolus lunata* (IFO 6299). The structure of (+)-**2** was characterized by comparison of the spectral properties and chromatographic behavior of natural **2** with a compound synthesized from (±)-sydonic acid.[6] The absolute stereochemistry of natural **2** has not been determined yet although natural **2** was isolated in optically active form. Thus, we undertook an asymmetric synthesis of (+)-sydonol (**2**) by employing similar reaction sequences used in the synthesis of (+)-**1**. Herein, we report the asymmetric total

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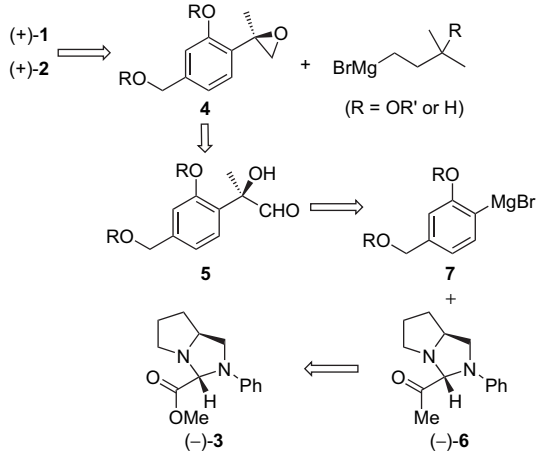
syntheses of (+)-**1** and (+)-**2** by applying an asymmetric synthesis of an α-hydroxy aldehyde using a chiral aminal, (−)-(2*R*,5*S*)-2-methoxycarbonyl-3-phenyl-1,3-diazabicyclo[3.3.0]octane (**3**).[12]

2. Results and discussion

Our synthetic plan for the synthesis of (+)-curcutetraol (**1**) and (+)-sydonol (**2**) is shown in Scheme 1. The bisabolane skeleton of (+)-**1** and (+)-**2** would be synthesized by the regioselective ring-opening reaction of (*R*)-epoxide **4**. Required (*R*)-**4** could be obtained from (*R*)-α-hydroxy aldehyde **5**, a key intermediate of this synthetic plan. (*R*)-Configuration of **5** should be constructed by the reaction of acetyl aminal **6** and aryl Grignard reagent **7** based on the stereochemical course of the reaction reported previously.[12]



Scheme 1. Retrosynthetic analysis of (+)-curcutetraol (**1**) and (+)-sydonol (**2**).

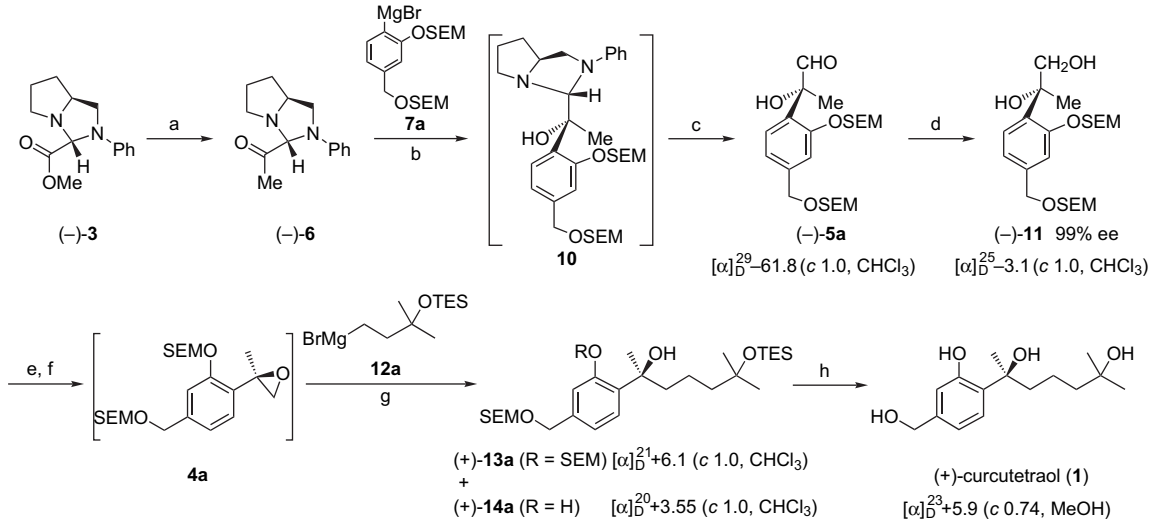
The synthetic route of (+)-**1** is summarized in Scheme 2. Acetyl aminal (−)-**6**[12] was obtained in 88% yield by the reaction of methoxycarbonyl aminal (−)-**3** and MeMgBr in the presence of $MgCl_2$ in THF at −78 °C for 15 min.

Since the tertiary benzylic alcohol moiety at *o*-position of a phenol is labile under acidic conditions,[13] silyl ethers (triethylsilyl (TES), *tert*-butyldimethylsilyl (TBDMS), or triisopropylsilyl (TIPS) ether), which could be easily cleaved under mild conditions by fluoride ion, were chosen as protective groups of the hydroxy groups of aryl Grignard reagent **7**. Protected aryl bromides were prepared from 2-bromo-5-hydroxymethylphenol (**8**)[14] and TESCl, TBDMSCl, or TIPSCl in the presence of imidazole in DMF, respectively. Unfortunately, the corresponding Grignard reagents were not prepared from those protected aryl bromides by treating with activated magnesium turnings in the presence of iodine or 1,2-dibromoethane in Et_2O or THF. Then, 2-(trimethylsilyl)ethoxymethyl (SEM) ether, which also could be cleaved by fluoride ion, was examined as an alternative protective group. Bromide **9** was prepared from **8** and SEMCl in the presence of NaH in THF in 78% yield (Scheme 3). The corresponding Grignard reagent **7a** was successfully prepared from **9** by using activated magnesium turnings in the presence of 1,2-dibromoethane in refluxing THF. A THF solution of acetyl aminal (−)-**6** was added dropwise to Grignard reagent **7a** at −78 °C and the mixture was stirred at the same temperature for 1 h. The resulting crude hydroxy aminal **10** was treated with 2% aqueous HCl in Et_2O at 0 °C for 15 h to afford α-hydroxy aldehyde (−)-**5a** ($[\alpha]_D^{29}$ −61.8 (*c* 1.0, $CHCl_3$)), a key intermediate for a synthesis of (+)-**1** and (+)-**2**, in 82% yield.

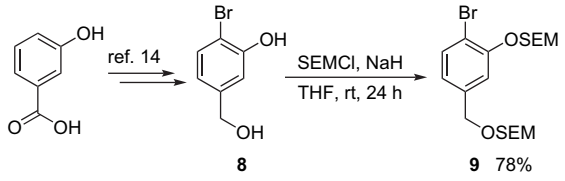
Reduction of (−)-**5a** with sodium borohydride in ethanol at room temperature for 30 min gave diol (−)-**11** ($[\alpha]_D^{25}$ −3.1 (*c* 1.0, $CHCl_3$)) in 83% yield. The enantiomeric excess of (−)-**11** was 99% by chiral HPLC analysis (Daicel Chiralcel OD-H). When the corresponding lithium reagent **7b**, prepared from bromide **9** and butyllithium in Et_2O at −78 °C, was used in place of Grignard reagent **7a**, (−)-**5a** ($[\alpha]_D^{22}$ −49.2 (*c* 1.0, $CHCl_3$)) was obtained in 74% yield with 82% ee.

Primary hydroxy group of diol (−)-**11** (99% ee) was tosylated by TsCl in pyridine at room temperature for 4.5 h. The resulting crude mono-tosylate was treated with NaH in THF at 0 °C for 12 h afforded almost pure epoxide **4a**, which was used in the next step without purification. When epoxide **4a** was treated with 3-methyl-3-triethylsiloxybutylmagnesium bromide (**12a**)[15] in the presence of CuI in THF at −10 °C for 1 h, a mixture of bis-SEM ether **13a** and mono-SEM ether **14a** was obtained. The mixture was separated by column chromatography to give (+)-**13a** and (+)-**14a** in 52% and 47% yields from (−)-**11**, respectively.

Removal of the SEM group and triethylsilyl (TES) group of each (+)-**13a** and (+)-**14a** with an excess amount of



Scheme 2. Reagents and conditions: (a) $MgCl_2$, THF, reflux, 1 h, then MeMgBr, THF, −78 °C, 88%; (b) **7a**, THF, −78 °C, 1 h; (c) 2% aq HCl, Et_2O, 0 °C, 15 h, 82% (from (−)-**6**); (d) $NaBH_4$, EtOH, rt, 30 min, 83%; (e) TsCl, pyridine, rt, 4.5 h; (f) NaH, THF, 0 °C, 12 h; (g) **12a**, CuI, THF, −10 °C, 1 h, 99% (from (−)-**11**; (+)-**13a**, 52% and (+)-**14a**, 47%); (h) TBAF, MS 4 Å, THF, reflux, 4–5 h, 80% from (+)-**13a** and 87% from (+)-**14a**.



Scheme 3. Preparation of bromide **9**.

tetrabutylammonium fluoride (TBAF) in the presence of MS 4 Å (crushed, activated) in refluxing THF for 4–5 h gave (+)-**1** in 80% and 87% yields, respectively. Addition of 4 Å molecular sieves was effective to reduce the formation of the corresponding ethoxymethyl ether.[16] The spectroscopic data (^{1}H and ^{13}C NMR, IR) of synthetic (+)-**1** ($[\alpha]_D^{23}$+5.9 (*c* 0.74, MeOH)) were in good accordance with those reported for the natural (+)-**1** ($[\alpha]_D^{20}$ +5.24 (*c* 0.74, MeOH)[5]).

According to the similar procedure used in the reaction of epoxide **4a** and **12a**, bis-SEM ether (+)-**13b** and mono-SEM ether (+)-**14b** were obtained in 28% and 49% yields from (−)-**11** (99% ee), respectively, using 3-methylbutylmagnesium bromide (**12b**) in place of **12a** (Scheme 4). Removal of the SEM group of (+)-**14b** with an excess amount of TBAF (DMPU, 80 °C, 1.5 h) gave (+)-**2** in 47% yield. In this case, the addition of 4 Å molecular sieves in THF or the reaction in DMPU was not effective to reduce the formation of the corresponding ethoxymethyl ether (ca. 40%).[16] The spectroscopic data (^{1}H and ^{13}C NMR, IR) of synthetic (+)-**2** were in good accordance with those reported for the natural (+)-**2**,[6] although the specific rotation of the synthetic (+)-**2** ($[\alpha]_D^{24}$+9.0 (*c* 1.0, MeOH)) was slightly larger than that of natural (+)-**2** ($[\alpha]_D^{20}$ +7.2 (*c* 1.0, MeOH)[6]). The enantiomeric excess of (+)-**2** was confirmed to be 99% by chiral HPLC analysis (Daicel Chiralcel OD-H) of (+)-**15**, derived from (+)-**2** with TBDMSCl in the presence of imidazole in DMF (54% yield). The enantiomeric excess of (+)-**15**, derived from (−)-**5a** ($[\alpha]_D^{22}$ −49.2 (*c* 1.0, $CHCl_3$), 82% ee), was 82% by chiral HPLC analysis (Daicel Chiralcel OD-H). These results showed that no racemization at the chiral tertiary benzylic alcohol moiety occurred in this synthetic route.

3. Conclusion

In conclusion, the asymmetric total syntheses of (+)-curcutetraol (**1**) and (+)-sydonol (**2**), phenolic bisabolane-type sesquiterpenoids, were accomplished with high enantiomeric excesses (99% ee). The chiral tertiary benzylic alcohol moiety of α-hydroxy aldehyde (−)-**5a**, a key intermediate of the synthesis of (+)-**1** and (+)-**2**, was constructed by a stereoselective Grignard reaction of acetyl aminal (−)-**6**, derived from easily available chiral methoxycarbonyl aminal (−)-**3**. Although the absolute configuration of (−)-**5a** has not been determined directly, it is reasonable to assume that the absolute configurations of both (+)-**1** and (+)-**2** are *S* by analogy to results reported previously.[12]

4. Experimental

4.1. General

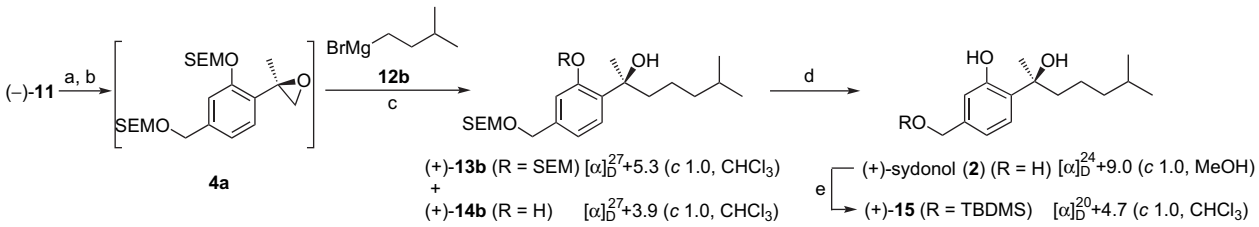
All air-sensitive experiments were carried out under an atmosphere of argon. IR spectra were recorded on an HORIBA FT-730 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-EX-270 spectrometer using tetramethylsilane as an internal standard. Optical rotations were measured on a JASCO P-1000 automatic polarimeter. HPLC analyses were carried out on JASCO instruments (pump, PU-2080 plus; detector, UV-2075). Elemental analyses were carried out on a Vario EL III Elemental analyzer. TLC analyses were done on silica-gel 60 F_{254}-precoated aluminum backed sheets (E. Merck). Preparative TLC was performed on silica-gel-coated plates (Wakogel B-5F, 20 cm×20 cm). Wakogel C-200 and Silica gel 60N (spherical, neutral, 63–210 μm) were used for column chromatography.

4.2. 1-Bromo-2-(2-trimethylsilylethoxymethoxy)-4-(2-trimethylsilylethoxymethoxymethyl)benzene (9)

To a stirred suspension of sodium hydride (60% mineral oil dispersion, 0.720 g, 18.0 mmol), washed with hexane prior to use, in THF (5.0 mL), 2-bromo-5-hydroxymethylphenol (**8**)[14] (1.22 g, 6.0 mmol) in THF (8.0 mL) was added through a syringe at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. A solution of 2-trimethylsilylethoxymethyl chloride (2.50 g, 16.5 mmol) in THF (7.0 mL) was added dropwise through a syringe to the solution. After the reaction mixture was stirred at room temperature for 24 h, water was added to the reaction mixture at 0 °C. The organic layer was separated and the aqueous layer was extracted with Et_2O three times. The combined organic layer was washed with brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, crude product was purified by silica-gel column chromatography (hexane/CH_2Cl_2=1:1) to give bromide **9** (2.17 g, 78%) as a colorless oil. IR (neat): ν_{max} 2953, 2895, 1582, 1484, 1397, 1250 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) 7.50 (d, *J*=7.9 Hz, 1H), 7.16 (d, *J*=1.8 Hz, 1H), 6.88 (dd, *J*=1.8, 7.9 Hz, 1H), 5.30 (s, 2H), 4.75 (s, 2H), 4.54 (s, 2H), 3.78–3.84 (m, 2H), 3.63–3.69 (m, 2H), 0.92–0.99 (m, 4H), 0.02 (s, 9H), 0.00 (s, 9H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ (ppm) 153.7, 138.8, 133.0, 122.0, 115.3, 111.7, 94.2, 93.4, 68.6, 66.7, 65.3, 18.2, 18.0, −1.28. Anal. Calcd for $C_{19}H_{35}BrO_4Si_2$: C, 49.23; H, 7.61. Found: C, 49.17; H, 7.76.

4.3. (2*R*,5*S*)-2-Acetyl-3-phenyl-1,3-diazabicyclo-[3.3.0]octane (6)

A solution of methoxycarbonyl aminal (−)-**3** (0.246 g, 1.0 mmol) in THF (10 mL) was added to anhydrous magnesium chloride (0.105 g, 1.1 mmol, dried prior to use at 100 °C for 1 h under vacuum) through a syringe and the mixture was refluxed for 1 h. Then, the reaction mixture was cooled to −78 °C, and an Et_2O solution (1.4 M) of methylmagnesium bromide (1.4 mL, 2.0 mmol) was



Scheme 4. Reagents and conditions: (a) TsCl, pyridine, rt, 4.5 h; (b) NaH, THF, 0 °C, 12 h; (c) **12b**, CuI, THF, −10 °C, 30 min, 77% (from (−)-**11**; (+)-**13b**, 28% and (+)-**14b**, 49%); (d) TBAF, DMPU, 80 °C, 1.5 h, 47% (from (+)-**14b**); (e) TBDMSCl, imidazole, DMF, rt, 30 min, 54%.

added dropwise through a syringe. The reaction was monitored carefully by TLC and saturated aqueous NH_4Cl was added to the reaction mixture quickly after the disappearance of (−)-**3** by TLC (about 15 min after the end of the addition of the Grignard reagent). The reaction mixture was then warmed to room temperature. After the organic layer was separated, the aqueous layer was extracted with Et_2O three times. The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by silica-gel (spherical, neutral) column chromatography (hexane/Et_2O=1:10) to give acetyl aminal (−)-**6** (0.203 g, 88%) as a pale yellow oil. $[\alpha]_D^{25}$ −46.9 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 2965, 2872, 1713, 1599, 1505, 1351, 1157 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ (ppm) 7.21 (dd, *J*=7.9, 7.6 Hz, 2H), 6.75 (t, *J*=7.6 Hz, 1H), 6.48 (d, *J*=7.9 Hz, 2H), 4.37 (s, 1H), 3.93 (ddd, *J*=13.8, 7.3, 4.6 Hz, 1H), 3.75–3.82 (m, 1H), 3.17–3.25 (m, 1H), 3.13 (dd, *J*=8.6, 6.6 Hz, 1H), 2.81–2.86 (m, 1H), 2.12 (s, 3H), 2.10–2.14 (m, 1H), 1.67–1.97 (m, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ (ppm) 207.8, 145.5, 129.3, 117.5, 112.4, 86.5, 62.9, 55.0, 53.2, 30.5, 25.1, 24.33. Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 73.29; H, 8.07; N, 12.06.

4.4. (−)-2-Hydroxy-2-[2-(2-trimethylsilylethoxymethoxy)-4-(2-trimethylsilylethoxymethoxymethyl)phenyl]propanal (5a)

To a stirred THF solution of 2-(2-trimethylsilylethoxymethoxy)-4-(2-trimethylsilylethoxymethoxymethyl)phenylmagnesium bromide (**7a**) prepared from bromide **9** (0.545 g, 1.2 mmol) and Mg turnings (37.4 mg, 1.5 mmol) in refluxing THF (2.4 mL) for 30 min in the presence of a small amount of 1,2-dibromoethane (ca. 0.3 mmol), acetyl aminal (−)-**6** (0.136 g, 0.6 mmol) in THF (1.5 mL) was added dropwise through a syringe at −78 °C. The reaction mixture was stirred at −78 °C for 2 h. Saturated aqueous NH_4Cl and water were added to the reaction mixture. The aqueous layer was extracted with Et_2O three times. The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, crude hydroxy aminal **10** was obtained as a yellow oil. Dilute hydrochloric acid (2%, 6.0 mL) was added to a stirred solution of the resulting crude hydroxy aminal **10** in Et_2O (6.0 mL), and stirring was continued at 0 °C for 15 h. The organic layer was separated and the aqueous layer was extracted with Et_2O three times. The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography (hexane/Et_2O=2:1) to afford α-hydroxy aldehyde (−)-**5a** (0.220 g) in 82% overall yield from (−)-**6** as a colorless oil. $[\alpha]_D^{29}$ −61.8 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3450, 2952, 2896, 1739 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ (ppm) 9.76 (s, 1H), 7.47 (d, *J*=7.9 Hz, 1H), 7.13 (d, *J*=1.6 Hz, 1H), 7.03 (dd, *J*=7.9, 1.6 Hz, 1H), 5.25 (d, *J*=6.9 Hz, 1H), 5.23 (d, *J*=6.9 Hz, 1H), 4.74 (s, 2H), 4.57 (s, 2H), 4.06 (s, 1H), 3.63–3.74 (m, 4H), 1.65 (s, 3H), 0.91–0.98 (m, 4H), 0.01 (s, 9H), −0.01 (s, 9H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ (ppm) 200.7, 154.1, 140.2, 128.5, 127.2, 121.1, 113.4, 94.2, 92.8, 78.0, 68.7, 66.8, 65.3, 21.7, 18.2, 18.0, −1.31, −1.36. Anal. Calcd for $C_{22}H_{40}O_6Si_2$: C, 57.85; H, 8.83. Found: C, 57.99; H, 9.09.

4.5. (−)-2-[2-(2-Trimethylsilylethoxymethoxy)-4-(2-trimethylsilylethoxymethoxymethyl)phenyl]-propane-1,2-diol (11)

Sodium borohydride (10.1 mg, 0.28 mmol) was added to a stirred solution of α-hydroxy aldehyde (−)-**5a** (0.114 g, 0.25 mmol) in ethanol (0.75 mL) at room temperature. The reaction mixture was stirred at the same temperature for 15 min. Water was added to quench the reaction. The mixture was diluted with Et_2O and dilute hydrochloric acid (about 0.7%) was added until pH of the aqueous layer became <7. The organic layer was separated and the aqueous layer was extracted with Et_2O three times. The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by preparative TLC (hexane/Et_2O=1:2) to afford diol (−)-**11** (94.8 mg, 83%) as a colorless oil. $[\alpha]_D^{25}$ −3.1 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3435, 2952, 2896, 1615, 1577, 1409, 1401, 1377, 1249 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ (ppm) 7.42 (d, *J*=7.9 Hz, 1H), 7.15 (d, *J*=1.5 Hz, 1H), 7.01 (dd, *J*=7.9, 1.5 Hz, 1H), 5.32 (d, *J*=6.9 Hz, 1H), 5.30 (d, *J*=6.9 Hz, 1H), 4.75 (s, 2H), 4.56 (s, 2H), 3.97 (dd, *J*=10.9, 5.3 Hz, 1H), 3.96 (s, 1H), 3.73–3.79 (m, 2H), 3.63–3.70 (m, 3H), 2.03 (dd, *J*=6.9, 5.3 Hz, 1H), 1.56 (s, 3H), 0.93–1.00 (m, 4H), 0.02 (s, 9H), 0.00 (s, 9H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ (ppm) 154.4, 138.7, 131.6, 127.4, 121.0, 113.7, 94.1, 92.7, 75.1, 69.1, 68.8, 66.8, 65.2, 24.3, 18.1, 18.0, −1.31, −1.36. Anal. Calcd for $C_{22}H_{42}O_6Si_2$: C, 57.60; H, 9.23. Found: C, 57.24; H, 9.27.

The enantiomeric excess of (−)-**11** ($[\alpha]_D^{25}$ −3.1 (*c* 1.0, $CHCl_3$)) was 99% by HPLC analysis using a chiral column (Daicel Chiralcel OD-H (25 cm×0.46 cm i.d.); 254 nm UV detector; eluent hexane/*i*-PrOH=97:3; flow rate 0.5 mL/min; t_{major} 29.8 min, t_{minor} 35.9 min).

4.6. (+)-6-Triethylsilyloxy-6-methyl-2-[2-(2-trimethylsilylethoxymethoxy)-4-(2-trimethylsilylethoxymethoxymethyl)phenyl]heptan-2-ol (13a) and (+)-2-(1-hydroxy-5-triethylsilyloxy-1,5-dimethylhexyl)-5-(2-trimethylsilylethoxymethoxymethyl)phenol (14a)

p-Toluenesulfonyl chloride (0.203 g, 1.06 mmol) was added to a stirred solution of diol (−)-**11** (0.244 g, 0.53 mmol) in pyridine (1.1 mL). The reaction mixture was stirred at room temperature for 4.5 h. Water and saturated aqueous $CuSO_4$ were added to the reaction mixture. The mixture was extracted with Et_2O three times. The combined organic layer was washed with water (twice) and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude mono-tosylate was obtained as a colorless oil (0.349 g) and used next step without further purification.

To a stirred suspension of sodium hydride (60% mineral oil dispersion, 64.2 mg, 1.6 mmol), washed with hexane prior to use, in THF (1.0 mL), the crude mono-tosylate (0.349 g) in THF (4.5 mL) was added through a syringe at 0 °C. The reaction mixture was stirred at 0 °C for 12 h. Water was added to the reaction mixture, and the organic layer was separated. The aqueous layer was extracted with Et_2O three times. The combined organic layer was washed with brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, almost pure epoxide **4a** (0.235 g) was obtained as a yellow oil and used next step without further purification.

To a stirred suspension of copper iodide (0.101 g, 0.53 mmol) in THF (1.0 mL), an Et_2O solution of 3-methyl-3-triethylsiloxybutylmagnesium bromide (**12a**), prepared from (3-bromo-1,1-dimethylpropoxy)triethylsilane (1.49 g, 5.3 mmol) and Mg turnings (0.154 g, 6.4 mmol) in Et_2O (5.5 mL, containing a catalytic amount of iodine) for 2 h,[15] was added dropwise through a syringe at −10 °C. After the mixture was stirred at −10 °C for 30 min, epoxide **4a** (0.235 g) in THF (3.2 mL) was added dropwise through a syringe. The reaction mixture was stirred at −10 °C for 1 h. Saturated aqueous NH_4Cl and water were added to the reaction mixture. After separation of the organic layer, the aqueous layer was extracted with Et_2O three times. The combined organic layer was washed with brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by silica-gel column chromatography (hexane/Et_2O=from 5:1 to 1:1) to afford bis-SEM ether (+)-**13a** (0.176 g) in 52% overall yield from diol (−)-**11** as a colorless oil and mono-SEM ether (+)-**14a** (0.128 g) in 47% overall yield from diol (−)-**11** as a colorless oil. Compound

(+)-**13a**: $[\alpha]_D^{21}$ +6.1 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3469, 2953, 2911, 2875, 1614, 1577, 1502, 1460, 1380, 1250 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ (ppm) 7.27 (d, *J*=7.9 Hz, 1H), 7.13 (d, *J*=1.6 Hz, 1H), 6.95 (dd, *J*=7.9, 1.6 Hz, 1H), 5.32 (d, *J*=7.1 Hz, 1H), 5.29 (d, *J*=7.1 Hz, 1H), 4.75 (s, 2H), 4.55 (s, 2H), 3.91 (s, 1H), 3.74–3.81 (m, 2H), 3.63–3.70 (m, 2H), 1.80–1.90 (m, 2H), 1.57 (s, 3H), 1.22–1.34 (m, 4H), 1.13 (s, 3H), 1.12 (s, 3H), 0.93–1.01 (m, 4H), 0.88 (t, *J*=7.9 Hz, 9H), 0.50 (q, *J*=7.9 Hz, 6H), 0.03 (s, 9H), 0.00 (s, 9H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ (ppm) 154.6, 137.9, 134.4, 126.7, 120.8, 113.6, 94.1, 92.8, 75.1, 73.3, 68.9, 66.8, 65.2, 45.4, 42.9, 29.9, 29.8, 27.4, 19.4, 18.2, 18.0, 7.21, 6.80, −1.28. Anal. Calcd for $C_{33}H_{66}O_6Si_3$: C, 61.63; H, 10.34. Found: C, 61.85; H, 10.73. Compound (+)-**14a**: $[\alpha]_D^{20}$ +3.55 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3271, 2953, 2912, 2876, 1629, 1577, 1512, 1458, 1381, 1250 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ (ppm) 9.31 (s, 1H), 6.95 (d, *J*=7.9 Hz, 1H), 6.82 (d, *J*=1.6 Hz, 1H), 6.77 (dd, *J*=7.9, 1.6 Hz, 1H), 4.73 (s, 2H), 4.50 (s, 2H), 3.63–3.69 (m, 2H), 3.03 (s, 1H), 1.75–1.95 (m, 2H), 1.61 (s, 3H), 1.30–1.48 (m, 4H), 1.16 (s, 3H), 1.15 (s, 3H), 0.86–0.99 (m, 11H), 0.52 (q, *J*=7.8 Hz, 6H), 0.02 (s, 9H); ^{13}C NMR (67.8 MHz) 155.9, 138.5, 128.9, 126.1, 118.6, 116.8, 94.0, 78.7, 73.4, 68.7, 65.2, 44.8, 42.8, 30.0, 29.8, 29.0, 18.9, 18.2, 7.18, 6.77, −1.29. Anal. Calcd for $C_{27}H_{52}O_5Si_2$: C, 63.23; H, 10.22. Found: C, 63.23; H, 10.60.

4.7. (+)-Curcutetraol (1)

Tetrabutylammonium fluoride hydrate (0.524 g) in benzene (2 mL) was evaporated under reduced pressure five times to remove water azeotropically and dried under vacuum. A crushed 4 Å MS (ca. 60 mg), activated at 120 °C under vacuum for 5 h, and THF (0.5 mL) were added. A solution of bis-SEM ether (+)-**13a** (0.129 g, 0.20 mmol) in THF (1.5 mL) was added to the mixture at room temperature and the mixture was refluxed for 5 h. After water and Et_2O were added to the reaction mixture and the organic layer was separated, the aqueous layer was extracted with Et_2O four times. The combined organic layer was washed with brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, crude product was purified by silica-gel (spherical, neutral) column chromatography (Et_2O to Et_2O/MeOH=5:1) to afford (+)-curcutetraol (**1**) (42.7 mg, 80%) as a brownish oil. When mono-SEM ether (+)-**14a** (51.5 mg, 0.10 mmol) was treated with tetrabutylammonium fluoride hydrate (0.264 g, water was removed in the same manner as described above) for 4 h in the same way, (+)-**1** (23.4 mg, 87%) was obtained as a brownish oil. (+)-Curcutetraol (**1**): $[\alpha]_D^{23}$ +5.9 (*c* 0.74, MeOH); IR (neat): ν_{max} 3337, 2971, 1625, 1577, 1513, 1376, 1297, 1266, 1167, 1021 cm^{-1}; ^1H NMR (270 MHz, CD_3OD): δ (ppm) 7.10 (d, *J*=7.7 Hz, 1H), 6.78 (d, *J*=1.6 Hz, 1H), 6.75 (br s, 1H), 4.50 (s, 2H), 1.70–1.98 (m, 2H), 1.57 (s, 3H), 1.20–1.48 (m, 4H), 1.10 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (67.8 MHz, CD_3OD): δ (ppm) 156.7, 142.6, 131.1, 127.4, 118.6, 116.0, 77.9, 71.4, 64.8, 45.1, 44.4, 29.1, 20.1.

4.8. (+)-6-Methyl-2-[2-(2-trimethylsilylethoxymethoxy)-4-(2-trimethylsilylethoxymethoxymethyl)phenyl]heptan-2-ol (13b) and (+)-2-(1-hydroxy-1,5-dimethylhexyl)-5-(2-trimethylsilylethoxymethoxymethyl)phenol (14b)

3-Methylbutylmagnesium bromide (**12b**) was prepared from 1-bromo-3-methylbutane (1.51 g, 10 mmol) and Mg turnings (0.268 g, 11 mmol) in Et_2O (10 mL) for 3 h in the presence of a small amount of iodine.

According to the similar procedure used for the preparation of (+)-**13a** and (+)-**14a**, almost pure epoxide **4a** (0.159 g) prepared from diol (−)-**11** (0.176 g, 0.38 mmol) was treated with 3-methylbutylmagnesium bromide (**12b**) (0.78 mL). The crude product was purified by preparative TLC (hexane/Et_2O=2:1) to afford bis-SEM ether (+)-**13b** (55.9 mg) in 28% overall yield from diol (−)-**11** as a colorless oil and mono-SEM ether (+)-**14b** (72.2 mg) in 49% overall yield from diol (−)-**11** as a colorless oil. Compound (+)-**13b**: $[\alpha]_D^{27}$ +5.3 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3503, 2953, 2898, 1250 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ (ppm) 7.28 (d, *J*=7.9 Hz, 1H), 7.13 (d, *J*=1.6 Hz, 1H), 6.96 (dd, *J*=7.9, 1.6 Hz, 1H), 5.32 (d, *J*=7.1 Hz, 1H), 5.29 (d, *J*=7.1 Hz, 1H), 4.75 (s, 2H), 4.56 (s, 2H), 3.82 (s, 1H), 3.74–3.80 (m, 2H), 3.63–3.71 (m, 2H), 1.73–1.99 (m, 2H), 1.56 (s, 3H), 1.42–1.53 (m, 1H), 1.08–1.27 (m, 4H), 0.93–1.01 (m, 4H), 0.81 (d, *J*=6.6 Hz, 6H), 0.03 (s, 9H), 0.00 (s, 9H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ (ppm) 154.6, 138.0, 134.5, 126.8, 120.8, 113.7, 94.2, 92.8, 75.1, 69.0, 66.8, 65.3, 42.6, 39.5, 27.9, 27.7, 22.7, 22.3, 18.2, 18.1, −1.26, −1.29. Anal. Calcd for $C_{27}H_{52}O_5Si_2$: C, 63.23; H, 10.22. Found: C, 63.31; H, 10.34. Compound (+)-**14b**: $[\alpha]_D^{27}$ +3.9 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3273, 2952, 1577, 1374, 1250, 1158, 1104 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ (ppm) 9.21 (s, 1H), 6.96 (d, *J*=7.9 Hz, 1H), 6.83 (d, *J*=1.6 Hz, 1H), 6.79 (dd, *J*=7.9, 1.6 Hz, 1H), 4.73 (s, 2H), 4.51 (s, 2H), 3.64–3.70 (m, 2H), 2.72 (s, 1H), 1.71–1.89 (m, 2H), 1.61 (s, 3H), 1.46–1.51 (m, 1H), 1.09–1.35 (m, 4H), 0.93–0.99 (m, 2H), 0.83 (d, *J*=6.6 Hz, 6H), 0.03 (s, 9H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ (ppm) 155.9, 138.6, 128.9, 126.1, 118.6, 116.8, 94.0, 78.6, 68.8, 65.3, 42.9, 39.1, 29.1, 27.8, 22.7, 22.6, 21.8, 18.2, −1.28. Anal. Calcd for $C_{21}H_{38}O_4Si$: C, 65.92; H, 10.01. Found: C, 65.73; H, 10.35.

4.9. (+)-Sydonol (2)

Tetrabutylammonium fluoride hydrate (0.799 g) in benzene (2 mL) was evaporated under reduced pressure three times to remove water azeotropically and dried under vacuum. A solution of mono-SEM ether (+)-**14b** (72.2 mg, 0.19 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (1.9 mL) was added through a syringe to tetrabutylammonium fluoride. The reaction mixture was stirred at 80 °C for 1.5 h. Water and Et_2O were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with Et_2O three times. The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, crude product was purified by silica-gel column chromatography (hexane/Et_2O=1:3) to afford (+)-sydonol (**2**) (47.6 mg, 47%) as a colorless oil. $[\alpha]_D^{24}$ +9.0 (*c* 1.0, MeOH); IR (neat): ν_{max} 3305, 2952, 1628, 1577, 1512 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ (ppm) 6.97 (d, *J*=7.6 Hz, 1H), 6.73–6.83 (m, 2H), 4.56 (s, 2H), 1.73–1.97 (m, 2H), 1.62 (s, 3H), 1.36–1.58 (m, 1H), 1.09–1.36 (m, 4H), 0.83 (d, *J*=6.6 Hz, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ (ppm) 155.8, 141.4, 129.1, 126.3, 117.9, 115.9, 78.5, 64.8, 42.9, 39.1, 28.9, 27.9, 22.6, 21.8. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.48; H, 9.89.

4.10. (+)-2-(1-Hydroxy-1,5-dimethylhexyl)-5-*tert*-butyldimethylsiloxymethylphenol (15)

To a solution of (+)-**2** (27.2 mg, 0.11 mmol) in DMF (1.1 mL), imidazole (23.3 mg, 0.32 mmol) was added at 0 °C and the mixture was stirred at room temperature for 10 min. Then a solution of *tert*-butyldimethylsilyl chloride (TBDMSCl) (51.1 mg, 0.34 mmol) in DMF (0.6 mL) was added to the mixture. The reaction mixture was stirred at room temperature for 30 min. Water and Et_2O were added to the reaction mixture, and the organic layer was separated. The aqueous layer was extracted with Et_2O three times. The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, crude product was purified by silica-gel column chromatography (hexane/Et_2O=3:1) to afford (+)-**15** (21.5 mg, 54%) as a colorless oil. $[\alpha]_D^{20}$ +4.7 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3300, 2953, 2858, 1629, 1578, 1512, 1462 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ (ppm) 9.08 (s, 1H), 6.95 (d, *J*=7.9 Hz, 1H), 6.83 (d, *J*=2.0 Hz, 1H), 6.78 (dd, *J*=7.9, 2.0 Hz, 1H), 4.67 (s, 2H), 2.24 (s, 1H), 1.73–1.94 (m, 2H), 1.64 (s, 3H), 1.43–1.55 (m, 1H), 1.10–1.37 (m, 4H), 0.94 (s, 9H),

0.83 (d, J=6.6 Hz, 6H), 0.10 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ (ppm) 155.8, 142.2, 127.9, 125.9, 116.8, 115.0, 78.8, 64.5, 42.9, 39.1, 29.1, 27.9, 26.1, 22.7, 22.6, 21.8, 18.6, −5.1. Anal. Calcd for $C_{21}H_{38}O_3Si$: C, 68.80; H, 10.45. Found: C, 68.74; H, 10.54.

The enantiomeric excess of (+)-**15** was determined to be 99% by chiral HPLC analysis (Daicel Chiralcel OD-H (25 cm×0.46 cm i.d.); 254 nm UV detector; eluent hexane/*i*-PrOH=98.5:1.5; flow rate 0.5 mL/min; t_{major} 18.7 min, t_{minor} 24.3 min).

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