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First asymmetric total synthesis of (+)-curcutetraol

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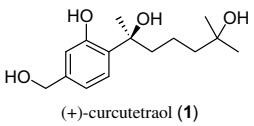
Abstract

The first asymmetric total synthesis of (+)-curcutetraol, a marine phenolic bisabolane-type sesquiterpene, was achieved in eight steps in ca. 50% overall yield. The chiral tertiary benzylic alcohol moiety in the *o*-position of a phenol was constructed in high optical yield (99% ee) by an asymmetric synthesis using a chiral aminal, (2*R*,5*S*)-2-methoxycarbonyl-3-phenyl-1,3-diazabicyclo[3.3.0]octane.

Keywords: Curcutetraol; Sesquiterpene; Asymmetric total synthesis; Tertiary benzylic alcohol

Many phenolic sesquiterpenoids of the bisabolane family have been isolated from both terrestrial and marine organisms.[1] In spite of their rather simple structures, they often display characteristic biological activities.[1,2]

(+)-Curcutetraol (**1**), isolated from the bacterium CNH-741 and the fungus CNC-979 by Lindel and co-workers in 2005, is a phenolic bisabolane-type sesquiterpene with a tertiary benzylic alcohol moiety as a single stereogenic center (Fig. 1).[3] The structure of (+)-**1** was determined on the basis of an extensive NMR spectroscopic analysis, and its absolute configuration was proposed to be *S* by the comparison of its experimental CD spectrum with the calculated one. To date, it is the most polar member of the phenolic bisabolane sesquiterpenoids with its four hydroxy groups and it is the first bisabolane sesquiterpenoid with a tertiary benzylic alcohol moiety in the *o*-position of a phenol isolated from the marine environment. Although Lindel and co-workers have reported a total synthesis of racemic curcutetraol at the same time in seven steps in a low overall yield, there is no report on the asymmetric synthesis of (+)-**1** to the best of our knowledge. Herein, we report the first asymmetric total synthesis of (+)-**1**, 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 (**2**).[4]



(+)-curcutetraol (**1**)

Fig. 1. Structure of (+)-curcutetraol (**1**).

Our synthetic plan for the synthesis of (+)-**1** is shown in Scheme 1. We envisaged that (*R*)-α-hydroxy aldehyde **4** could be converted to the target compound (+)-**1** via epoxide **3**. (*R*)-Configuration of **4** should be constructed by the stereoselective reaction of an acetyl aminal, (2*R*,5*S*)-2-acetyl-3-phenyl-1,3-diazabicyclo[3.3.0]octane (**6**), and aryl Grignard reagent **5** based on the stereochemical course of the reaction.[4]

The synthetic route of (+)-curcutetraol (**1**) is summarized in Scheme 2. Acetyl aminal **6** was obtained in 88% yield by the reaction of methoxycarbonyl aminal **2** and MeMgBr in the presence of $MgCl_2$ after examinations of the reaction conditions in detail (THF, −78 °C, 15 min).[4]

Considering the lability of tertiary benzylic alcohol moiety at *o*-position of phenol under acidic conditions,[5] silyl ethers (triethylsilyl (TES), *t*-butyldimethylsilyl (TBDMS),

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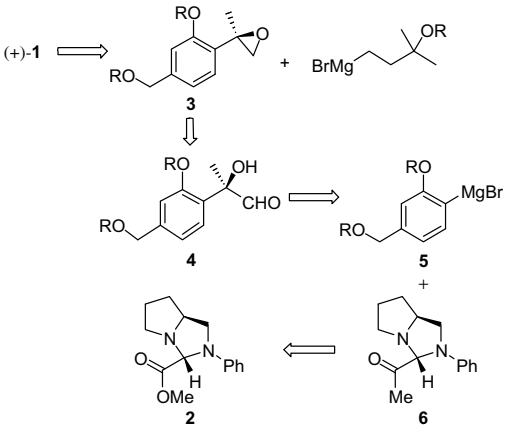
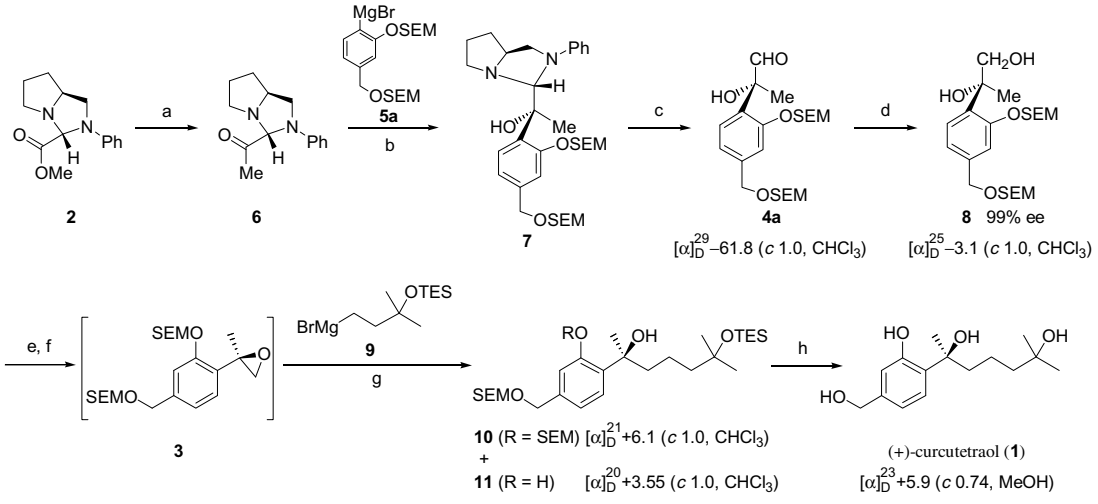


Scheme 1. Retrosynthetic analysis of (+)-curcutetraol (**1**).

or triisopropylsilyl (TIPS) ether) or trimethylsilylethoxymethyl (SEM) ether, which could be easily cleaved under mild conditions by fluoride ion, were chosen as protective groups of the hydroxy groups of Grignard reagent **5**. Among those protected 2-bromo-5-hydroxymethylphenol,[6] the corresponding Grignard reagent was successfully prepared only from bis-SEM ether by using activated magnesium turnings in the presence of 1,2-dibromoethane. (−)-2-Hydroxy-2-[2-(2-trimethylsilylethoxymethoxy)-4-(2-trimethylsilylethoxymethoxymethyl)phenyl]propanal (**4a**) ($[\alpha]_D^{29}$ −61.8 (*c* 1.0, $CHCl_3$)), a key intermediate for a synthesis of (+)-**1**, was obtained in 82% yield by the reaction of acetyl aminal **6** and Grignard reagent **5a** (THF, −78 °C, 1 h) followed by the hydrolysis of the resulting hydroxy aminal **7** under mild acidic conditions (2% aq HCl, Et_2O, 0 °C, overnight). Reduction of **4a** with sodium borohydride (EtOH, rt, 30 min) gave (−)-2-[2-(2-trimethylsilylethoxymethoxy)-4-(2-trimethylsilylethoxymethoxymethyl)phenyl]-propane-1,2-diol (**8**) ($[\alpha]_D^{25}$ −3.1 (*c* 1.0, $CHCl_3$)) in 83% yield. The enantiomeric excess of **8** was 99% by chiral HPLC analysis (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_R, 29.8 min, t_S, 35.9 min)).[7]

Then, monotosylation of diol **8** (TsCl, pyridine, rt, 4.5 h) and treatment of the monotosylate with NaH (THF, 0 °C, overnight) afforded almost pure epoxide **3**, which was used in the next step without purification. Epoxide **3** was treated with 3-methyl-3-triethylsiloxybutylmagnesium bromide (**9**)[8] in the presence of CuI (THF, −10 °C, 1 h) to afford a mixture of bis-SEM ether **10** and mono-SEM ether **11**, which was separated by column chromatography (Silica gel 60 N, spherical, neutral, 63–210 μm) to give **10** ($[\alpha]_D^{21}$ +6.1 (*c* 1.0, $CHCl_3$)) and **11** ($[\alpha]_D^{20}$ +3.55 (*c* 1.0, $CHCl_3$)) in 52% and 47% yield from **8**, respectively. Removal of the SEM group and TES group of each **10** and **11** with an excess amount of tetrabutylammonium fluoride (TBAF) (MS 4 Å, THF, reflux, 4–5 h) gave (+)-**1** in 80% and 87% yield, respectively. Addition of 4 Å molecular sieves (crushed, activated) was effective to reduce the formation of the corresponding ethoxymethyl ether.[9] The spectroscopic data (^1H and ^{13}C NMR, IR) of synthetic (+)-**1** were in good accordance with those reported for the natural product,[3] although the specific rotation of the synthetic (+)-**1** ($[\alpha]_D^{23}$ +5.9 (*c* 0.74, MeOH)) was slightly larger than that of natural (+)-**1** ($[\alpha]_D^{20}$ +5.24 (*c* 0.74, MeOH)).[10]

In conclusion, the first asymmetric total synthesis of (+)-curcutetraol (**1**) was accomplished in eight steps with ca. 50% overall yield. The chiral tertiary benzylic alcohol moiety in the *o*-position of a phenol was constructed in high optical yield (99% ee) by an asymmetric synthesis of α-hydroxy aldehyde **4a**, having a chiral quaternary center, starting from easily available chiral methoxycarbonyl aminal **2**. Although the absolute configurations of **4a** and (+)-**1** have not been determined directly, it is reasonable to assume that the absolute configuration of (+)-**1** is *S* by



Scheme 2. Reagents and conditions: (a) $MgCl_2$, THF, reflux, 1 h, then MeMgBr, THF, −78 °C, 88%; (b) **5a**, THF, −78 °C, 1 h; (c) 2% aq HCl, Et_2O, 0 °C, ovn, 82% (from **6**); (d) $NaBH_4$, EtOH, rt, 30 min, 83%; (e) TsCl, pyridine, rt, 4.5 h; (f) NaH, THF, 0 °C, ovn; (g) **9**, CuI, THF, −10 °C, 1 h, 99% (from **8**; **10**, 52% and **11**, 47%); (h) TBAF, MS 4 Å, THF, reflux, 4–5 h, 80% from **10** and 87% from **11**.

analogy to results reported previously.[4] The synthetic route developed here can be applied to the synthesis of the analogs and other related natural products. Further synthetic studies are now in progress.

Acknowledgment

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7. When aryl lithium reagent **5b**, prepared from bis-SEM ether of 2-bromo-5-hydroxymethylphenol and butyllithium, was used in place of Grignard reagent **5a**, **4a** ($[\alpha]_D^{22}$ −49.2 (*c* 1.0, $CHCl_3$)) was obtained in 74% yield with 82% ee.

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10. *Selected data*: (−)-2-Hydroxy-2-[2-(2-trimethylsilylethoxymethoxy)-4-(2-trimethylsilylethoxymethoxymethyl)phenyl]propanal (**4a**): 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.
(−)-2-[2-(2-Trimethylsilylethoxymethoxy)-4-(2-trimethylsilylethoxymethoxymethyl)phenyl]propane-1,2-diol (**8**): Colorless oil; $[\alpha]_D^{25}$ −3.1 (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3435, 2952, 2896, 1615, 1577, 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.
(+)-Curcutetraol (**1**): Brownish oil; $[\alpha]_D^{23}$ +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.