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TETRAHEDRON: *ASYMMETRY*

A practical enantioselective synthesis of (*S*)-3-hydroxytetradecanoic acid

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Abstract

(*S*)-3-Hydroxytetradecanoic acid **1** has been synthesized in an overall yield of 27% from (*S*)-epichlorohydrin **2** as follows: (1) regio and chemoselective epoxide opening of **2** with a Grignard reagent under the catalysis by Cu(I) followed by consecutive epoxide formation; (2) regioselective epoxide opening of (*S*)-1,2-epoxytridecane **4** with cyanide anion under pH controlled conditions followed by consecutive nitrile hydrolysis with alkaline H_2O_2 gave crude **1**; (3) its purification via the *N*,*N*-dicyclohexylammonium salt **6**. The method thus devised is practical and scalable for the industrial production of **1**.

1. Introduction

Being a natural component of lipid A, the endotoxic principle of lipopolysaccharide (LPS) embedded in the cell surface of Gram-negative bacteria, (*R*)-3-hydroxytetradecanoic acid has attracted much attention from the community of synthetic chemists as well as glycobiochemists.[1,2] Being incorporated into therapeutic agents featuring the structural motif of lipid A,[2] its antipode **1** is reported to be able to enhance the immunoadjuvant activity inherent in lipid A (Fig. 1).

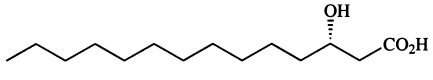

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Figure 1.

Therefore, we devised a practical, scalable approach to both enantiomers of 3-hydroxytetradecanoic acid. In the present communication, it is illustrated with emphasis on the industrial viability as applied to the synthesis of **1**, the pharmaceutically more intriguing enantiomer.[2]

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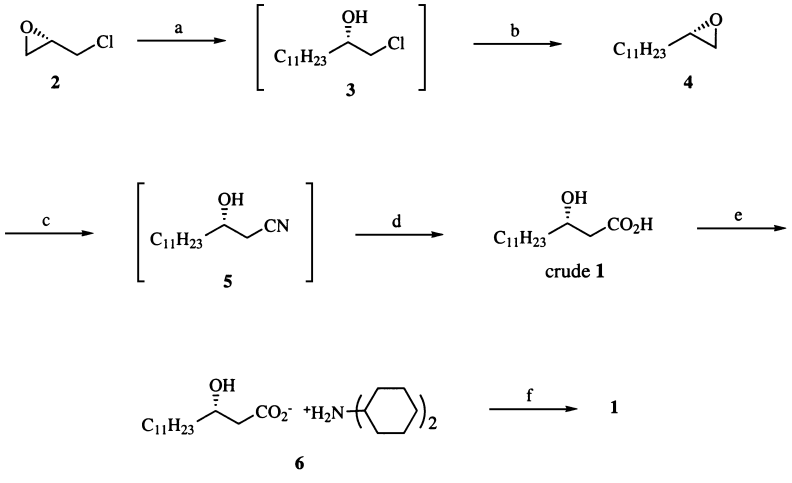
2. Results and discussion

The starting point of our synthesis was optically active epichlorohydrin (Scheme 1), both enantiomers of which were commercially available with high enantiomeric excesses (>99.9% ee) from industrial sources such as Chirex (US) and Daiso (Japan). It was subjected to the Cu(I)-catalyzed[3] chemoselective nucleophilic displacement by a Grignard reagent. When *n*-decylmagnesium bromide was prepared in a mixed solvent system of toluene:THF (10:9), its concentration could be increased to as high as 1.8 M,[4] and more beneficially, in the presence of a catalytic amount of CuI, the less hindered epoxide terminus of (*S*)-epichlorohydrin **2** could be opened expeditiously at a temperature as high as 5–8°C, the range being industrially viable and easily controllable as well. It was shown by capillary GLC (Shimadzu CBP1) that an unidentified by-product formed incipiently eventually turned into 12-tricosanol in five hours. Being less volatile, the latter turned out to be easily separated by distillation from the recyclized product, (*S*)-1,2-epoxytridecane **4**, after the base treatment as described below.

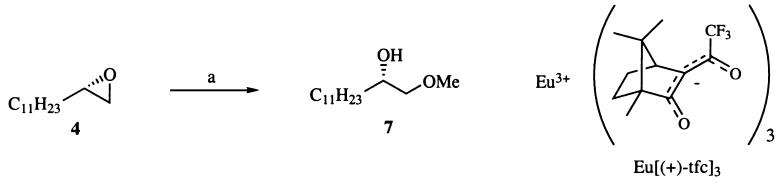


Scheme 1. Reagents and conditions: (a) 1.1 equiv. *n*-$C_{10}H_{21}MgBr$, 0.9 mol% CuI, toluene:THF (29:18), 3–15°C, 5 h; (b) 48% NaOH aq., MeOH:toluene (19:39), rt, 4.5 h, 55% from **2**; (c) 1.2 equiv. NaCN aq., MeOH, H_2SO_4, pH 10.8–12.2, 47–52°C, 1.8 h; (d) (i) H_2O_2 aq., NaOH aq., MeOH, reflux, 7.5 h; (ii) HCl aq., 74% from **4**; (e) (*c*-$C_6H_{11})_2NH$, MeCN:MeOH (6:1), 0°C, 68%; (f) (i) 0.36N H_2SO_4 aq., rt, 0.5 h; (ii) 0.50×10^{-4}N H_2SO_4 aq., rt, 0.5 h, overall 98%

After quenching the Grignard reaction, the resulting toluene solution was diluted with MeOH and treated with an aqueous solution of NaOH to convert (*S*)-1-chloro-2-tridecanol **3** completely into (*S*)-1,2-epoxytridecane **4**. Essentially pure **4** was then obtained by distillation in vacuo in an overall yield of 55% from **2**.

Before moving on to the next step, the enantiomeric excess of **4** was determined as follows. Its enantiomeric excess being too difficult to assess in a direct manner, **4** was converted into (*S*)-1-methoxy-2-tridecanol **7** with NaOMe in MeOH according to the method reported by Ohta and Tetsukawa (Scheme 2).[5] The 1-methoxy-2-ol **7** was then analyzed by ^{1}H NMR spectroscopy in the presence of Eu[(+)-tfc]$_3$. No splitting was observed with the signal due to the C*H*$_3$O group of **7** under conditions where the racemate, prepared separately from racemic epichlorohydrin, showed the significant chemical shift difference ($\Delta\Delta\delta$). Taking into account the error of measurement inherent in ^{1}H NMR spectroscopy, it was concluded that the enantiomeric excess of **4** was not less than 97% ee.

Having confirmed that the stereochemical integrity did not deteriorate during the Grignard reaction, we then attempted the C_1 homologation with cyanide anion. When the epoxide **4** was treated with NaCN in aqueous alcohol under the usual conditions,[6] a complex mixture resulted, probably due to the basicity increasing with the progress of the reaction. Thus, in the course of the reaction, the pH was kept strictly

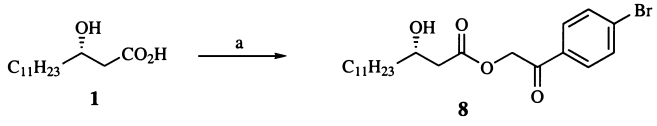


Scheme 2. Reagents and conditions: (a) NaOMe, MeOH, reflux, 2 h, 43%

adjusted between 10.8 and 12.2 with concd H_2SO_4,[7] which eventually allowed β-hydroxynitrile **5** to be secured pure enough to be employed directly in the next step.

Hydrolysis of the penultimate intermediate **5** proceeded successfully, only when effected through the action of alkaline H_2O_2[8] in aqueous MeOH. Since **5** was delivered as a methanolic solution after the epoxide opening with cyanide anion, it should be natural to assume that the hydrolysis step in question could be telescoped into the preceeding step. Indeed, these two reactions could be conducted successfully in a seamless way to give crude **1** in an overall yield of 74% from **4**.

Before entering into purification of **1** thus obtained, its enantiomeric excess was assessed to see if **1** could survive the relatively harsh conditions applied without significant racemization. According to the method of Keegan et al.,[9] crude **1** was converted into *p*-bromophenacyl ester **8**, and the latter analyzed by HPLC on Chiralpak® AS (Scheme 3). By comparing the chromatograms between **8** and its racemate prepared from racemic **4**, the enantiomeric excess of **8** was determined reliably as 96.6%. This implied that the telescoped conversion of **4** into **1** only led to a nominal racemization from >97% ee to 96.6% ee.



Scheme 3. Reagents and conditions: (a) 2,4′-dibromoacetophenone, Et_3N, EtOAc, rt, 19.5 h, quant.

Finally, crude **1** was purified by way of its crystalline salt with *N*,*N*-dicyclohexylamine **6** according to the literature precedent.[10] A single crystallization of **6** from MeCN:MeOH (6:1) succeeded in significantly upgrading both chemical and enantiomeric purity. The salt **6** thus purified in a yield of 68% was treated with H_2SO_4 to liberate the free acid **1**. As a result, (*S*)-3-hydroxytetradecanoic acid **1** was obtained as crystals in 99.5% ee and 98% yield from **6**, and its overall yield from (*S*)-epichlorohydrin **2** amounted to 27%.

3. Conclusion

We have devised a scalable, industrially viable approach to (*S*)-3-hydroxytetradecanoic acid **1**, which dispenses with both tedious chromatographic purification and expensive asymmetric catalyst. Our methodology has enabled an expeditious synthesis of **1** starting from commercially available (*S*)-epichlorohydrin **2** to give **1** with 99.5% ee in an overall yield of 27%.

4. Experimental

4.1. General

^1H NMR spectra were recorded on a Varian UNITY-400 spectrometer at 400 MHz by using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. FT-IR spectra were recorded on a Perkin–Elmer

1600 spectrometer. Mass spectral analyses were performed with a Hewlett Packard 5890 series II (GC) and an HP5971A (MS). High-resolution mass spectra were recorded on a Jeol JMS-DX-303 spectrometer. Elemental analyses were performed with a Perkin–Elmer 240 C analyzer. Optical rotations were measured with a Horiba SEPA-200. Melting points were measured with an Electrothermal 1A8104. Melting points (mps) and boiling points (bps) were uncorrected.

*4.2. (S)-1,2-Epoxytridecane **4***

Under an atmosphere of N_2, 1,2-dibromoethane (0.040 ml, 0.46 mmol) was added to a suspension of Mg turnings (2.5 g, 0.10 mol) in dry THF (18 ml). To the water-cooled mixture was added a solution of 1-bromodecane (22 g, 98 mmol) in dry toluene (20 ml) dropwise at a gentle reflux over a period of 20 min. The mixture was then stirred at ambient temperature for an additional 30 min. Under an atmosphere of N_2, the Grignard reagent solution thus prepared (ca. 55 ml) was added dropwise to an ice-cooled mixture of CuI (0.15 g, 0.79 mmol), (*S*)-epichlorohydrin **2** [Chirex Inc.; >99.9% ee assured by chiral GLC (Supelco γ-DEX™ 225; 30 m×0.25 mm ∅; carrier gas: He, 93 ml/min; oven temperature: 70°C; detection: FID); 8.3 g, 90 mmol], and dry toluene (5.0 ml) at about 3°C over a period of 3 h. After the addition was complete, the dropping funnel used was rinsed with dry toluene (4.0 ml). The reaction mixture was stirred at a temperature between 5°C and 8°C for 5 h, during which the progress of the reaction was monitored by GLC [Shimadzu CBP1; 25 m×0.25 mm ∅; carrier gas: He, 111 ml/min; oven temperature: 40–250°C (10°C/min) +250°C (19 min); detection: FID]. After 12N HCl aqueous solution (10 ml) was added, the mixture was concentrated in vacuo to remove THF.

To the residue was added water (20 ml), and layers were separated. The aqueous layer was extracted with toluene (5.0 ml×2). To the combined organic layer and toluene extracts were added MeOH (19 ml) and 48% NaOH aqueous solution (8.0 ml). The mixture was stirred at ambient temperature for 4.5 h, and the completion of the reaction was confirmed by running the GLC analysis under the same conditions as mentioned above. After evaporating MeOH in vacuo, layers were separated, and the aqueous layer was extracted with toluene (5.0 ml×2). The combined organic layer and toluene extracts were washed with water (5.0 ml), dried over $MgSO_4$ (3.0 g), and concentrated in vacuo. The residue was distilled in vacuo to give **4** (9.7 g) in 55% yield from **2** as a colorless oil: bp 104–107°C/4–5 mmHg (lit.[11] 123–125°C/13 mmHg); $[\alpha]_D^{21}$ −10.7 (*c* 1.17, Et_2O) {lit.[11] $[\alpha]_D^{21}$ −11.0 (*c* 1.20, Et_2O)}; ^{1}H NMR δ 0.88 (3H, t, *J*=6.8 Hz), 1.20–1.30 (16H, m), 1.40–1.50 (2H, m), 1.50–1.60 (2H, m), 2.46 (1H, dd, J_1=5.1 Hz, J_2=2.8 Hz), 2.75 (1H, dd, J_1=5.1 Hz, J_2=3.9 Hz), 2.91 (1H, ddt, J_1=5.5 Hz, J_2=3.9 Hz, J_3=2.8 Hz); IR ν (film) 3042 (w), 2925 (s), 2854 (s), 1466 (m), 1410 (w), 1378 (w), 1260 (w), 1129 (w), 917 (w), 836 (m), 722 (w) cm^{-1}; MS (70 eV) m/z 198 (M^+).

*4.3. Determination of the enantiomeric excess of **4***

To a solution of **4** (0.08 g, 0.40 mmol) in dry MeOH (1.0 ml) was added 28% NaOMe in MeOH (0.1 ml), and the homogeneous mixture was stirred and heated at reflux for 2 h. 1.0N HCl aqueous solution (1.0 ml) was added, and then MeOH was evaporated in vacuo. The residue was extracted with Et_2O (1.0 ml×2). The combined Et_2O extracts were dried over $MgSO_4$ (0.1 g) and concentrated in vacuo to give **7** (0.04 g, 43%): ^{1}H NMR δ 0.88 (3H, t, *J*=7.0 Hz), 1.20–1.40 (18H, m), 1.40–1.50 (2H, m), 3.23 (1H, dd, J_1=9.6 Hz, J_2=8.0 Hz), 3.39 (3H, s), 3.42 (1H, dd, J_1=9.6 Hz, J_2=6.4 Hz), 3.70–3.80 (1H, m).

(±)-1-Methoxy-2-tridecanol *rac*-**7** was prepared from (±)-epichlorohydrin via (±)-1,2-epoxytridecane in the same manner as described above.

When ^{1}H NMR spectroscopy was observed with *rac*-**7** in the presence of 0.3 molar equiv. of tris[(+)-3-(trifluoromethylhydroxymethylene)camphorato]europium(III), the singlet due to its OCH_3 group split

into two singlets: 4.66 ppm for **4**; and 4.53 ppm for its antipode. However, no such splitting was detected with **7** under the same ^{1}H NMR conditions as above. Thus, taking into account the intrinsic error of ^{1}H NMR spectroscopy, the enantiomeric excess of **7** was determined to be not less than 97% ee.

4.4. N,N-*Dicyclohexylammonium (S)-3-hydroxytetradecanoate* ***6***

To a solution of **4** (>97% ee; 1.9 g, 9.7 mmol) in MeOH (8.0 ml) was added 29% (w/w) aqueous solution of NaCN (1.97 g, 11.6 mmol). The reaction mixture was stirred at a temperature between 48°C and 52°C for 1.8 h during which time its pH was maintained strictly between 10.8 and 12.4 by adding 97% H_2SO_4 (0.40 g, 4.0 mmol). The completion of the reaction was confirmed by GLC under the same conditions as applied in the preparation of **4**.

White inorganic precipitates were filtered off, and washed with MeOH (18 ml). To the combined filtrate and washing were added 30% aqueous solution of H_2O_2 (2.0 ml) and 48% aqueous solution of NaOH (2.0 ml). The mixture was stirred and heated at reflux for 10 h, during which time the progress of the reaction was monitored by TLC [Merck Kieselgel 60; *n*-hexane:AcOEt:AcOH (20:10:1)]. The mixture was allowed to cool to ambient temperature, and 2.0N HCl aqueous solution (20 ml) was added. After the mixture was ice-cooled with stirring, solids precipitated were collected by filtration, washed with water (5.0 ml), and dried at an oven temperature of 40°C to give crude **1** (1.8 g) as a pale yellow solid.

This was dissolved in MeOH (1.8 ml). To the solution was added a solution of *N*,*N*-dicyclohexylamine (1.3 g, 7.1 mmol) in MeCN (10 ml). After the mixture was ice-cooled with stirring, solids precipitated were collected by filtration, washed with ice-chilled MeCN (6.0 ml), dried at an oven temperature of 40°C to give **6** (2.1 g, 51% from **4**) as white crystals: mp 97.5–98.5°C [lit.[12]: mp 94–95°C for the (*R*) isomer]; $[\alpha]_D^{20}$ +4.97 (*c* 1.99, MeOH) {lit.[12]: $[\alpha]_D^{20}$ −4.4 (*c* 2.0, MeOH) for the (*R*) isomer}.

4.5. Determination of the enantiomeric excess of ***6***

1.0N HCl aqueous solution (2.0 ml) was added to **6** (0.05 g, 0.10 mmol) at an ambient temperature. The suspension was stirred, and extracted with Et_2O (5.0 ml). The Et_2O extract was concentrated in vacuo to give free acid **1** as white crystals. This was dissolved in AcOEt (3.0 ml). To the solution were added 2,4′-dibromoacetophenone (0.05 g, 0.2 mmol) and Et_3N (0.03 ml, 0.2 mmol). The resulting solution was then stirred at ambient temperature for 19.5 h. The inorganic precipitates were filtered off, and washed with hot AcOEt (2.0 ml). The combined filtrate and washing were concentrated in vacuo to give **8** (0.07 g, quant.) as white crystals: ^{1}H NMR δ 0.88 (3H, t, *J*=6.8 Hz), 1.20–1.40 (20H, br. s), 2.57 (1H, dd, J_1=15.4 Hz, J_2=9.2 Hz), 2.69 (1H, dd, J_1=15.4 Hz, J_2=3.2 Hz), 3.30 (1H, br. s), 4.10–4.20 (1H, m), 5.32 (1H, d, *J*=16.4 Hz), 5.43 (1H, d, *J*=16.4 Hz), 7.65 (2H, d, *J*=8.4 Hz), 7.79 (2H, d, *J*=8.4 Hz).

Racemic **8** was also prepared in the same manner as described above, and its structural identity was confirmed by ^{1}H NMR.

HPLC on Chiralpak® AS [elution: *n*-hexane:2-propanol (97:3) at a flow rate of 1.0 ml/min; temperature: 35°C; detection: UV at 254 nm)] gave a complete separation between the enantiomers of *rac*-**8**: t_R 23.0 min for **8**; 26.2 min for its antipode. HPLC analysis of **8** under the same conditions as described above showed its enantiomeric excess to be 99.4% ee.

4.6. (S)-3-Hydroxytetradecanoic acid ***1***

After **6** (4.4 g, 99.5% ee) was suspended in 0.36N H_2SO_4 (35 ml), the mixture was stirred at ambient temperature for 30 min. Solids precipitated were collected by filtration and washed with water (30 ml) to give crude **1** as white crystals. This was suspended again in 5.0×10^{-4}N H_2SO_4 (20 ml) and stirred

at ambient temperature for 30 min. The solids were collected by filtration, washed with water (15 ml), and dried at an oven temperature of 40°C to give **1** (2.5 g) in 98% yield from **6**: mp 72.8–73.1°C (lit.[10]: mp 71.8°C); $[\alpha]_D^{25}$ +16.0 (*c* 1.03, $CHCl_3$) {lit.[10]: $[\alpha]_D^{25}$ +16.1 (*c* 1, $CHCl_3$)}; ^{1}H NMR δ 0.88 (3H, t, *J*=7.2 Hz), 1.20–1.40 (18H, m), 1.40–1.60 (2H, m), 2.47 (1H, dd, J_1=16.5 Hz, J_2=9.0 Hz), 2.58 (1H, dd, J_1=16.5 Hz, J_2=3.2 Hz), 4.00–4.10 (1H, m); IR ν (KBr) 3554 (s), 2919 (s), 2846 (s), 1676 (s), 1469 (s), 1433 (m), 1394 (m), 1361 (w), 1294 (s), 1258 (m), 1225 (s), 1068 (m), 939 (m), 874 (m), 720 (w), 524 (m) cm^{-1}; HRMS (200 eV; CI) 245.2135, calcd for $C_{14}H_{28}O_3$ $[(M+H)^+]$ 245.2118. Anal. calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55; found: C, 68.80; H, 11.61. The enantiomeric excess of **1** thus obtained was determined to be 99.5% ee after analyzing **8** [2.66 g; prepared from **1** (1.44 g, 5.87 mmol) quantitatively] by chiral HPLC under the same conditions as described above.

Acknowledgements

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