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Synthesis of Chiral Long-chain α -Hydroxy Acids from L-Ascorbic Acid. Useful Components for the Synthesis of Cerebrosides ¹

Kazuyuki Yamagata, Yoshiro Yamagiwa and Tadao Kamikawa*

Department of Chemistry, Faculty of Science and Technology, Kinki University, Kowakae, Higashi-Osaka 577, Japan

Nucleophilic ring opening of chiral epoxy diols, derived from L-ascorbic acid, with 2-lithio-1,3-dithianes allowed preparation of long-chain (R)- and (S)- α -hydroxy acids of high optical purity.

Long-chain α -hydroxy acids are constituents of cerebrosides 1 and 2, isolated from the sponge Halichondria japonica² and





 $Piv = Me_3CCO$, $Ns = m - NO_2C_6H_4SO_2$

Scheme 1. Reagents and conditions: i, PivCl/py/-15 °C/2 h (yield 83%); ii, NsCl/py/40 °C/3 days (86%); iii, KOH/MeOH/0 °C-r.t./2 h (66%); iv, $(NCO_2Et)_2/PPh_3/C_6H_6/r.t. (77%)$

Nucleophilic ring opening of 6 with the lithio derivative of 1,3dithiane 8a gave 3*R*-alcohol 9a. Desulphurization with Raney Ni gave 10a, which, after benzoylation, was hydrolysed with dil. hydrochloric acid to the diol 11a. Cleavage of 11a with sodium periodate followed by permanganate oxidation gave the chiral α benzoyloxy acid 12a in 56% overall yield from 6 (Scheme 2). The optical purity (>98%) was confirmed by ¹H NMR spectrum (500 MHz) using the chiral shift reagent (+)- tris[2,6-bis(hepta-

from the starfish Acanthaster planci,³ respectively. To confirm the 'alleged' absolute configuration of 1,[†] we tried to synthesize chiral long-chain α -hydroxy acids. Although many methods have been reported,⁴ a simple general method for the preparation of chiral long-chain analogues is still lacking because long-chain intermediates crystallize extremely easily under the low temperature reaction conditions which are necessary for the preparation of chiral substances.

We report herein a general synthetic method of (R)- and (S)- α -hydroxy acids from L-ascorbic acid. In our synthesis, the C-2 chirality was introduced *via* regioselective ring opening of chiral epoxy diols **6** and **7**.

L-Ascorbic acid was transformed into the isopropylidene glycol 4 by a known method.⁵ The primary hydroxy group was protected with pivaloyl chloride and the secondary alcoholic group was converted into *m*-nitrobenzenesulphonate to give 5. Treatment of 5 with methanolic potassium hydroxide gave 3R-epoxide 6 in 47% overall yield from 4. The 3S-epoxide 7 was obtained by the Mitsunobu reaction ⁶ in 77% yield (Scheme 1). The optical purities of 6 and 7 were confirmed by comparison with the reported optical rotation values ⁷ (Table 1) and ¹H NMR spectra.

[†] Structure 1 was inferred from spectroscopic data and the absolute configuration was assigned by analogy of many cerebrosides isolated from marine organisms.

and a man and a man and a man a m	Table 1. Physical cons	stants of chiral epoxic	des and <i>a</i> -hydroxy	acid derivatives
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Compd	B.p. (°C/Torr) <i>"</i> or m.p. [°C]	$[\alpha]_D^{\circ}$ (conc., solvent)	$[\Phi]$ nm (conc. in CHCl ₃)
6	(65.5/12)	-11.5 (c, 2.10, EtOH) -9.6 (c, 0.93, EtOH) ^b	
7	(72.5/15)	+1.10 (c, 2.00, EtOH) + 0.8 (c, 0.76, EtOH) ^b	
12a	[72–73]	$-1.58(c, 1.14, CHCl_{2})$	-409(300)(c, 1.04)
12b	71-72	$+1.39(c, 1.15, CHCl_{3})$	+455(300)(c, 1.02)
12c	[75–76]	-0.84 (c, 1.05, CHCl ₃)	-374(300)(c, 1.05)
12d	[64-65]	-3.25 (c, 0.92, CHCl ₃)	-150(300)(c, 0.20) -140(300)(c, 0.20) ^c

" 1 Torr \approx 1 mmHg. " Ref. 7. " Ref. 3.



d; $R = C_{20}H_{41}$, $R^1 = H$, $R^2 = Me$, 2R

Scheme 2. Reagents and conditions: i, BuLi/THF/HMPA/-30-20 °C; 6 or 7 (a; yield 99%), (b; 99%), (c; 77%); ii, Raney Ni/EtOH (a; 92%), (b; 100%), (c; 96%); iii, BzCl/py/40 °C; iv, 0.5 mol dm⁻³ HCl/THF/70 °C (a; 91%), (b; 92%), (c; 94%); v, NaIO₄/THF/r.t.; vi, KMnO₄/KHPO₄/-Bu'OH/r.t. (a; 67%), (b; 66%), (c; 71%); vii, CH₂N₂; viii, MeONa/MeOH/r.t. (12d; 72%)

fluoropropoxy)-1,1,1,2,6,7,7,7-octafluoroheptane-3,5-dionato]europium(III).

The enantiomer 12b was also prepared from 7 in 60% overall yield. The ORD curves of 12a and 12b were almost perfect mirror images of each other. This method was successfully applied to the longer hydroxy acid 12c in 49% overall yield. The synthetic hydroxy methyl ester 12d was identical with that derived from the natural cerebroside 2 in all respects.

Experimental

A typical procedure is exemplified by the following reaction sequence: to a cooled $(-40 \,^{\circ}\text{C})$ solution of 2-lithio-2-octadecyl-1,3-dithiane (prepared from **8a**, 1.6 g, 4.3 mmol) in tetrahydrofuran (THF) (15 cm³)-hexamethylphosphoramide HMPA (2.5 cm³) was added the epoxide **6** (0.5 g, 3.47 mmol) in THF (8 cm³). The mixture was stirred overnight at room temperature. Work-up and purification of the crude product [SiO₂, C₆H₆-AcOEt (95:5)] gave **9a** (1.78 g, 99%) as an oil.

The mixture of **9a** (1.74 g, 3.37 mmol) and Raney Ni (W-2, 20 g) in ethanol was heated under reflux for 40 min. Removal of the solvent gave **10a** (1.28 g) as a colourless solid.

Benzoylation of 10a followed by acid hydrolysis gave 11a as a colourless solid.

A solution of NaIO₄ (0.21 g, 0.84 mmol) in a small amount of water was added at room temperature to the solution of **11a** (0.38 g, 0.80 mmol) in THF (3 cm³). The mixture was stirred for 3 h at 50 °C and finally poured into water and extracted with ether. After evaporation of the solvent, the residue was suspended in t-butyl alcohol (5 cm³) and KH₂PO₄ (1.25 mol dm⁻³; 3.2 cm³) and 1 mol dm⁻³ KMnO₄ solution (5.0 cm³) was added. After the solution had been stirred for 15 min, the excess of reagent was destroyed by addition of aqueous Na₂SO₃, and the mixture was acidified with 1 mol dm⁻³ HCl and extracted with ether. The organic phase was evaporated and the residue was recrystallized from hexane-acetone to give **12a** (0.303 g, 83%), m.p. 72.0–73.0 °C.

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