Perkin Communications

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

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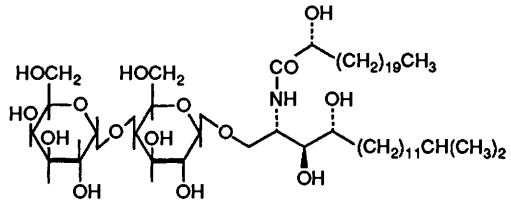
Nucleophilic ring opening of chiral epoxy diols, derived from L-ascorbic acid, with 2-lithio-1,3-dithianes allowed preparation of long-chain (*R*)- and (*S*)-α-hydroxy acids of high optical purity.

Long-chain α-hydroxy acids are constituents of cerebrosides **1** and **2**, isolated from the sponge *Halichondria japonica*[2] and



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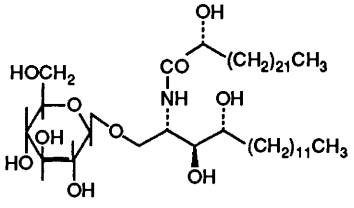

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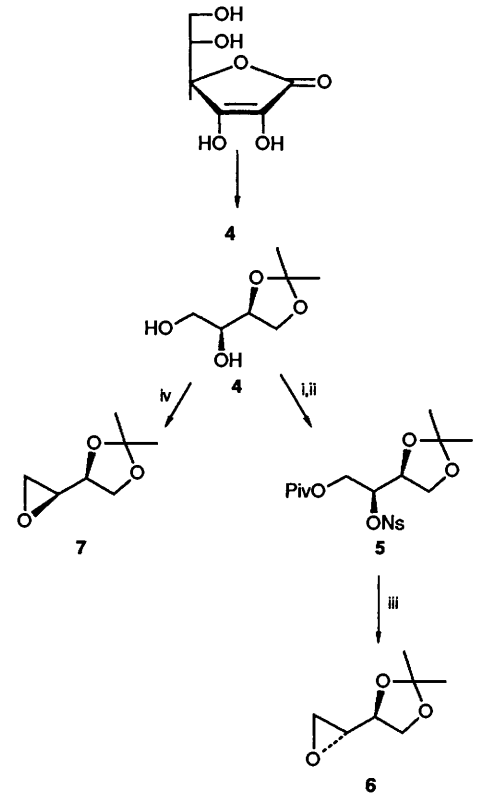
from the starfish *Acanthaster planci*,[3] respectively. To confirm the 'alleged' absolute configuration of **1**,† we tried to synthesize chiral long-chain α-hydroxy acids. Although many methods have been reported,[4] a simple general method for the preparation of chiral long-chain analogues is still 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 3*R*-epoxide **6** in 47% overall yield from **4**. The 3*S*-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 ^{1}H NMR spectra.



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%)

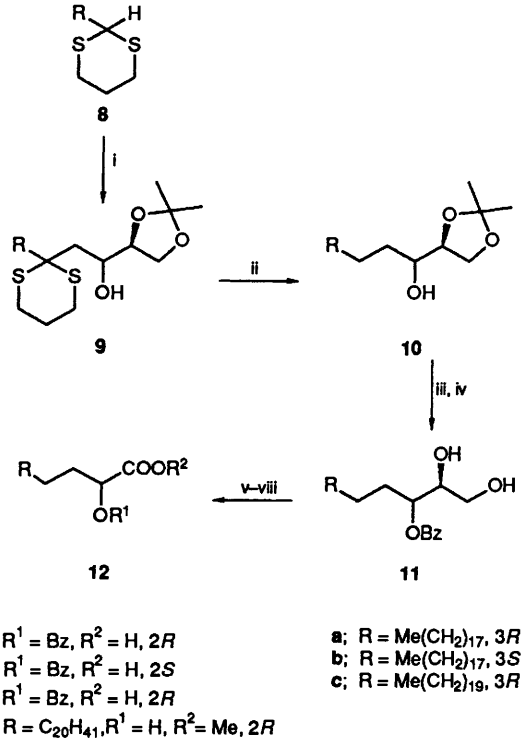
Nucleophilic ring opening of **6** with the lithio derivative of 1,3-dithiane **8a** gave 3*R*-alcohol **9a**. Desulphurization with Raney Ni gave **10a**, which, after benzoylation, was hydrolysed with dil. hydrochloric acid to the diol **11a**. Cleavage of **11a** with sodium periodate followed by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

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

Table 1. Physical constants of chiral epoxides and α-hydroxy acid derivatives

Compd.	B.p. (°C/Torr)[a] or m.p. [°C]	$[\alpha]_D$/° (conc., solvent)	[Φ] 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, $CHCl_3$)	−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]

[a] 1 Torr ≈ 1 mmHg. [b] Ref. 7. [c] Ref. 3.



a; R^1 = Bz, R^2 = H, 2*R*
b; R^1 = Bz, R^2 = H, 2*S*
c; R^1 = Bz, R^2 = H, 2*R*
d; R = $C_{20}H_{41}$, R^1 = H, R^2 = Me, 2*R*

a; R = $Me(CH_2)_{17}$, 3*R*
b; R = $Me(CH_2)_{17}$, 3*S*
c; R = $Me(CH_2)_{19}$, 3*R*

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, $NaIO_4$/THF/r.t.; vi, $KMnO_4$/$KHPO_4$/-Bu^{t}OH/r.t. (**a**; 67%), (**b**; 66%), (**c**; 71%); vii, CH_2N_2; 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 °C) solution of 2-lithio-2-octadecyl-1,3-dithiane (prepared from **8a**, 1.6 g, 4.3 mmol) in tetrahydrofuran (THF) (15 cm^3)–hexamethylphosphoramide HMPA (2.5 cm^3) was added the epoxide **6** (0.5 g, 3.47 mmol) in THF (8 cm^3). The mixture was stirred overnight at room temperature. Work-up and purification of the crude product [SiO_2, C_6H_6–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 $NaIO_4$ (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 cm^3). 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 cm^3) and KH_2PO_4 (1.25 mol dm^{-3}; 3.2 cm^3) and 1 mol dm^{-3} $KMnO_4$ solution (5.0 cm^3) was added. After the solution had been stirred for 15 min, the excess of reagent was destroyed by addition of aqueous Na_2SO_3, 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.

Acknowledgements

The authors thank Professor T. Komori of Kyushu University for providing the spectral data of the natural hydroxy methyl ester. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.

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Paper 0/03856C
Received 5*th July* 1990
Accepted 30*th August* 1990