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## Synthesis of (-)-6-Hydroxyshikimic Acid from ((5*S*,6*R*)-5,6-Dihydroxy-1,3-cyclohexadienyl)methanenitrile.

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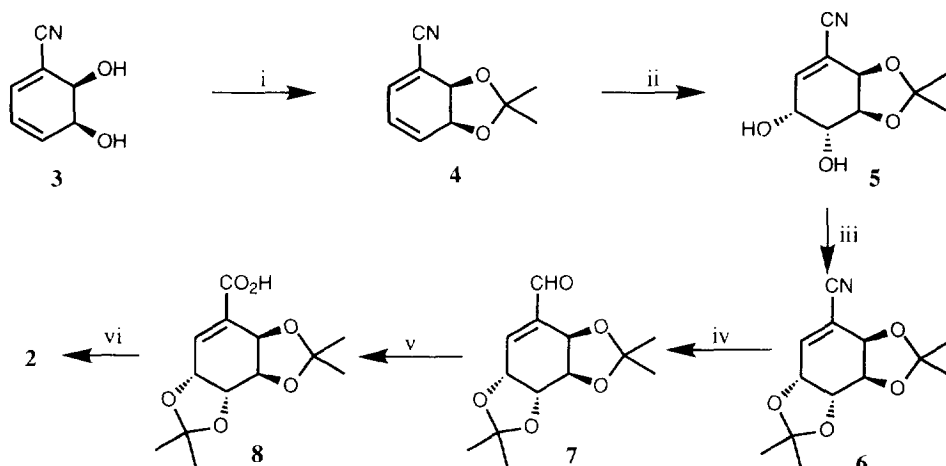
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**Abstract:** A six step synthesis of (-)-6-hydroxyshikimic acid **2** has been developed starting from ((5*S*, 6*R*)-5,6-dihydroxy-1,3-cyclohexadienyl)methanenitrile **3**, produced by biotransformation of cyanobenzene by the enzyme toluene dioxygenase. Copyright © 1996 Elsevier Science Ltd

(-)-Shikimic acid **1** is a key intermediate in the shikimate pathway which plays a central role in the biosynthesis of aromatic amino acids and a wide range of natural products such as gallic acid, isoprenoid quinones and lignin.<sup>1</sup> Owing to its biochemical significance, the synthesis of shikimic acid and its derivatives continue to attract the interest of chemists.<sup>2</sup>

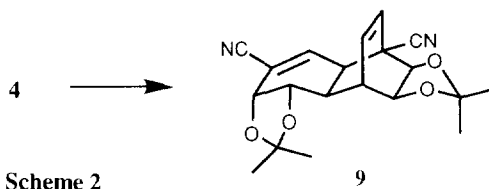


We wish to report a short synthesis of the hydroxyshikimic acid **2** starting from ((5*S*, 6*R*)-5,6-dihydroxy-1,3-cyclohexadienyl)methanenitrile **3** (Scheme 1).



**Scheme 1.** Reagents: i, 2,2-Dimethoxypropane/ $H^+$ ; ii, cat.  $OsO_4$ /4-methylmorphine-N-oxide; iii, 2,2-dimethoxypropane/ $H^+$ ; iv, DIBAL; v,  $NaClO_2/H_2O_2$ ; vi,  $H_2O/H^+$

The diol **3** is obtained by biotransformation of cyanobenzene in very high yield using a recombinant toluene dioxygenase expressed in *Escherichia coli* JM109(pDTG601). Its absolute configuration has been firmly established.<sup>3</sup> Reaction of the diol **3** with 2,2-dimethoxypropane in the presence of acid gave the protected cyano compound **4** in 94 % yield. Interestingly, dimerisation occurred when a saturated solution of nitrile **4** in dichloromethane was allowed to stand at room temperature for 6 days (Scheme 2). The dimer **9** and the unreacted monomer **4** were isolated in 46 % and 50 % yields respectively. The structure of the dimer **4** was unambiguously confirmed by X-ray crystallography (Fig. 1). Analogous dimers have been obtained from similar dihydroxycyclohexa-1,3-dienes.<sup>4</sup>



Hydroxylation of **4** with osmium tetroxide and *N*-methylmorpholine-*N*-oxide<sup>5</sup> as co-oxidant afforded the diol **5** in 72 % yield. In turn, the diol **5** was converted into the di-isopropylidene derivative **6** in 94 % yield. The structure of **6** was confirmed by X-ray crystallography (Fig. 2). Base catalysed hydrolysis of **6** to **8** proved to be troublesome: no carboxylic acid **8** was obtained after repeated attempts under a variety of conditions. Accordingly, it was decided to reduce the nitrile **6** to aldehyde **7**, then oxidise the aldehyde to the carboxylic acid **8**. Reduction of the nitrile **6** with DIBAL<sup>6</sup> gave the aldehyde **7** in 38 % yield. This was oxidised by sodium chlorite in the presence of hydrogen peroxide<sup>7</sup> to the carboxylic acid **8** in 71 % yield. Deprotection of **8** gave the hydroxy shikimic acid **2** in 100 % yield.

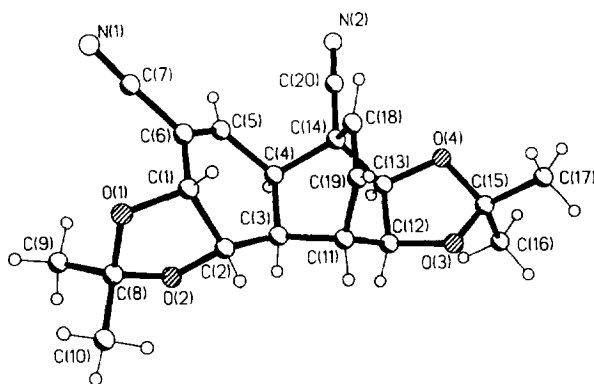


Figure 1. X-ray crystal structure of dimer **9**.

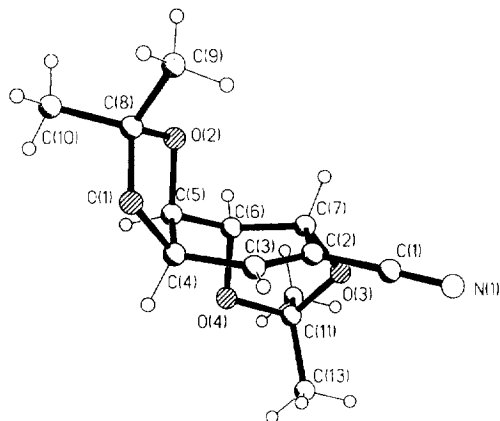


Figure 2. X-ray crystal structure of diol **5**.

### Experimental

General.—<sup>1</sup>H NMR spectra were recorded on Bruker AC-400 or 250 MHz spectrometers. <sup>13</sup>C NMR spectra were determined at 100.62 MHz on the Bruker AC-400 spectrometer. Optical rotations were determined using an AA-1000 polarimeter (Optical Activity Ltd), with a 2 dm cell. Optical rotations are given in units of 10<sup>-1</sup> deg cm<sup>2</sup> g<sup>-1</sup>. MS spectra were recorded with a Kratos MS80 spectrometer. Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected.

**((5*S*, 6*R*)-5,6-Dihydroxy-1,3-cyclohexadienyl)methanenitrile **3**.** Diol **3** was prepared by bio-oxidation using recombinant toluene dioxygenase from *Pseudomonas putida* F1, expressed in *Escherichia coli* JM109(pDTG601).<sup>8</sup> The preculture medium was prepared in a 2,800 ml Fernbach flask containing in 500 ml deionised water: glucose, 5 g; yeast extract, 2.5 g; tryptone, 5 g; KPO<sub>4</sub>, 100 mM pH 7.0; and ampicillin, 50 mg. The preculture was inoculated with 0.5 ml of a previously frozen culture containing the same medium plus 25% glycerol. The preculture was incubated, with shaking, at 35 °C for 12 to 14 h, at which time the O.D.<sub>660 nm</sub> was about 10. A 20 L fermentor was prepared containing 10 L of growth medium consisting of (in g L<sup>-1</sup>): glucose, 5.0; (NH<sub>4</sub>)<sub>2</sub>HPO<sub>4</sub>, 4.62; (NH<sub>4</sub>)H<sub>2</sub>PO<sub>4</sub>, 2.81; MgSO<sub>4</sub>·7H<sub>2</sub>O, 2.0; KCl, 4.0; citric acid, 2.0; (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, 5.0; ferric ammonium citrate, 0.324; thiamine, 0.034; ampicillin, 0.1; trace metals, 2.0 ml L<sup>-1</sup>. Trace metals containing (in g L<sup>-1</sup> 0.1 M HCl): Na<sub>2</sub>SO<sub>4</sub>, 10.0; ZnCl<sub>2</sub>, 2.0; MnSO<sub>4</sub>·H<sub>2</sub>O, 2.0; CoCl<sub>2</sub>·6H<sub>2</sub>O, 2.0; CuSO<sub>4</sub>·5H<sub>2</sub>O, 0.3. The fermentor was inoculated with the grown preculture and the culture was grown controlling the dissolved oxygen at about 30% of saturation, the pH at 7.0 (with NH<sub>3</sub>OH) and the temperature at 37 °C. When the initial glucose was consumed, a feed of additional glucose solution was fed continuously at a rate which would not allow for the accumulation of excess glucose in the culture medium. The toluene dioxygenase was induced during growth with isopropyl β-D-thiogalactopyranoside.

After the culture was grown, the benzonitrile was added drop-wise to the air inlet of the fermentor at a rate which did not allow the accumulation of the substrate. The total volume of the fermentor broth, after feeding and biotransformation, was 12.5 L to which had been added 137 g (1.33 mol) of benzonitrile. The broth contained 171 g of diol **3** (1.25 mol), 94% conversion. The remainder was starting material or lost to volatilisation due to sparging of the culture. After bio-oxidation, the broth was adjusted to pH 6 and whole

cells were removed by centrifugation. The clarified broth was concentrated 10-20 fold by evaporation under reduced pressure at 40 °C and the precipitate was removed. The concentrated broth was continuously extracted with ethyl acetate and the crude diol **3** was recovered after evaporation of the solvent and drying under reduced pressure. Further purification was carried out by charcoal treatment of the crude material in ethyl acetate followed by recrystallisation to give the diol **3** m.p. 84-85.5 °C. Found  $M^+$ : 137.0473.  $C_7H_7NO_2$  requires 137.0475;  $[\alpha]_D^{18.5} = +183.8$  (c 0.6, MeOH);  $\delta_H$  (250 MHz,  $D_2O$ ) 4.32 (2 H, m, H-1, H-6), 6.10 (1 H, dd,  $J$  5.38, 9.23 Hz, H-4), 6.23 (1 H, dd,  $J$  3.34, 9.23 Hz, H-5), 6.86 (1 H, d,  $J$  5.38 Hz, H-3);  $\delta_C$  (62.9 MHz,  $D_2O$ ) 66.84, (CH-O), 67.10 (CH-O), 112.37 (C-2), 119.62 (CN), 124.25 (C-4), 136.44 (C-5), 140.97 (C-4);  $m/z$  (relative abundance) (EI) 137 (M)<sup>+</sup>, 42 (%), 119 (89), 108 (77), 103 (73), 91 (100), 85 (48), 80 (91), 76 (31), 69 (71), 64 (44), 56 (45), 53 (52).

**(1R, 6S)-2-Cyano-8,8-dimethyl-7,9-dioxabicyclo[4.3.0]nona-2,4-diene 4.** 2,2-Dimethoxypropane (30 ml) and toluene-4-sulfonic acid (0.05 g) were added to the nitrile **3** (4 g, 29 mmol) in DMF (20 ml). The mixture was allowed to stand at room temperature for 20 h, and diluted with ethyl acetate (150 ml). The solution was washed with 5 %  $NaHCO_3$  (15 ml), water (4 x 20 ml), brine (20 ml), dried ( $MgSO_4$ ) and evaporated under reduced pressure to give derivative **4** as needles (4.85 g, 94 %); mp 72-73.5 °C (from dichloromethane/n-hexane). Found  $[M + H]^+$ : 178.0868.  $C_{10}H_{12}NO_2$  requires 178.0867;  $[\alpha]_D^{27.1} = +171.5$  (c 0.44,  $CHCl_3$ );  $\nu_{max}/cm^{-1}$  ( $CHCl_3$ ) 2216 (CN), 1530 (C=C);  $\delta_H$  (250 MHz;  $CDCl_3$ ) 1.42 (6 H, s, 2 Me), 4.68-4.76 (2 H, m, H-1, H-6), 6.13 (1 H, dd,  $J$  5.53, 9.59 Hz, H-4), 6.25-6.26 (1 H, m, H-5), 6.71 (1 H, d,  $J$  5.53 Hz, H-3);  $\delta_C$  (62.9 MHz;  $CDCl_3$ ) 24.61 (Me), 26.46 (Me), 69.63 (CH-O), 69.68 (CH-O), 106.49 (O-C-O), 110.64, 117.77, 122.32, 130.68, 136.54 (C=, CN);  $m/z$  (relative abundance) (CI) 178 ( $[M + H]^+$ , 26 %), 162 (26), 120 (100), 91 (12), 64 (15), 59 (74).

**(1S, 2R, 5R, 6S, 7S, 8S, 9S, 10R)-1,4-Dicyano-5,6,9,10-bis(isopropylidenedioxy)-tricyclo[6.2.2.0]dodeca-3,11-diene 9.** A saturated solution of nitrile **4** (0.5 g) in dichloromethane was allowed to stand at room temperature for 6 days. It was then subjected to flash chromatography (dichloromethane) to give unreacted nitrile **4** (first fraction, 0.23 g, 46 %) and dimer **9** (second fraction, 0.25 g, 50 %) as a crystalline solid; m.p. 211 °C (EtOAc/petroleum ether 40-60 °C). (Found C, 67.85; H, 6.34; N, 7.85.  $C_{20}H_{22}N_2O_4$  requires C, 67.77; H, 6.26; N, 7.91 %);  $[\alpha]_D^{27.1} = +110.9$  (c 0.432,  $CHCl_3$ );  $\nu_{max}/cm^{-1}$  3056 (=C-H), 2307 (CN), 2224 (CN), 1384 (C=C);  $\delta_H$  (400 MHz;  $CDCl_3$ ) 1.30 (3 H, s, Me), 1.33 (3 H, s, Me), 1.35 (3H, s, Me), 1.39 (3 H, s, Me), 2.41 (1 H, d,  $J$  8.89 Hz, H-7), 2.84 (1 H, ddd,  $J$  1.16, 4.25, 8.89 Hz, H-2), 3.03 (1 H, brd,  $J$  6.5 Hz, H-8), 4.16-4.19 (1 H, m, H-6), 4.23 (1 H, dd,  $J$  1.17, 4.65, H-5), 4.43 (2 H, apps, H-9, H-10), 6.00 (1 H, d,  $J$  8.20 Hz, H-11), 6.14 (1 H, dd,  $J$  6.5, 8.2 Hz, H-12), 6.72 (1 H, dd,  $J$  1.17, 4.25 Hz, H-3);  $\delta_C$  (62.9 MHz;  $CDCl_3$ ) 24.98 (Me), 25.14 (Me), 26.30 (Me), 27.79 (Me), 32.76, 37.53, 39.18, 43.77, 68.90, 76.34, 77.56, 79.42, 109.52 (O-C-O), 110.85 (O-C-O), 116.44, 117.25, 119.63, 128.83, 130.49, 140.84 (C=, CN);  $m/z$  (relative abundance) (CI) 372 ( $[M + NH_4]^+$ , 100 %), 339 (10 %), 281 (10 %), 100 (20 %).

**(1R, 4R, 5R, 6R)-2-Cyano-4,5-dihydroxy-8,8-dimethyl-7,9-dioxabicyclo[4.3.0]non-2-ene 5.** 4-Methylmorphine-N-oxide (0.7 g, 5.98 mmol) was added to a solution of nitrile **4** (1.0 g, 5.65 mmol) in tert-BuOH/THF/ $H_2O$  (10 : 3 : 1, v/v, 60 ml). The resulting solution was cooled to 0 °C, a catalytic amount of  $OsO_4$  (2.5 w %, in 2-methyl-2-propanol, 0.3 g) was added and the mixture was allowed to stand at 0 °C for 5

days. Aqueous sodium sulphite (5 %, 15 ml) was added, the mixture was stirred at room temperature for one hour. It was filtered through a pad of Celite. The filtrate was diluted with water (25 ml) and extracted with diethyl ether (3 x 50 ml). The organic phase was dried (MgSO<sub>4</sub>), evaporated under reduced pressure to give a brown oily liquid which was subjected to flash chromatography (diethyl ether) to give the diol **5** as a white solid (0.86 g, 72 %). Recrystallisation from ethyl acetate/petroleum ether 40-60 °C gave a colourless crystalline solid (0.7 g, 58.7 %) m.p. 113.5-114 °C (Found [M + H]<sup>+</sup> : 212.0923. C<sub>10</sub>H<sub>14</sub>NO<sub>4</sub> requires 212.0922); Found: C, 56.68; H, 6.14; N, 6.50. C<sub>10</sub>H<sub>13</sub>NO<sub>4</sub> requires C, 56.85; H, 6.21; N, 6.63 %; [α]<sub>D</sub><sup>27.1</sup> = -29.5 (c 0.44, CHCl<sub>3</sub>); ν<sub>max</sub>/cm<sup>-1</sup> (CHCl<sub>3</sub>) 3406 (br, OH), 2230 (CN), 1640 (C=C); δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 1.39 (6 H, s, 2 Me), 2.78 (1 H, d, *J* 3.36 Hz, OH), 2.82 (1 H, d, *J* 7.83 Hz, OH), 4.37 (1 H, brs, H-5), 4.46, (1 H, brs, H-4), 4.48 (1 H, dd, *J* 4.99, 4.99 Hz, H-6), 4.64 (1 H, d, *J* 4.99 Hz, H-1), 6.52 (1 H, brs, H-3); δ<sub>C</sub> (62.9 MHz; CDCl<sub>3</sub>) 25.94 (Me), 27.49 (Me), 65.04 (CH-O), 68.99 (CH-O), 70.63 (CH-O), 75.02 (CH-O), 110.75 (O-C-O), 114.30, 116.90, 144.42 (C=, CN); m/z (relative abundance) (CI) 212 ([M + H]<sup>+</sup>, 38), 196 (15), 136 (22), 59 (100).

**(1R, 4R, 8R, 9R)-2-Cyano-6,6,11,11-tetramethyl-5,7,10,12-tetraoxabicyclo[7,3,0,0<sup>9</sup>,1]dodec-2-ene 6.** Diol **5** (3.0 g, 14 mmol) was dissolved in DMF (40 ml). To the solution was added 2,2-dimethoxypropane (50 ml) and toluene-4-sulfonic acid (0.05 g). The resulting mixture was allowed to stand at room temperature for 20 h and diluted with ethyl acetate (180 ml). The solution was washed with 5 % NaHCO<sub>3</sub> (20 ml), water (4 x 20 ml), brine (20 ml) and dried (MgSO<sub>4</sub>). Crystalline nitrile **6** (3.33 g, 94 %) was obtained after evaporation of the solvent under reduced pressure: m.p. 90-90.5 °C (methanol/water) (Found [M + H]<sup>+</sup>: 252.1236. C<sub>13</sub>H<sub>18</sub>NO<sub>4</sub> requires 252.1236); [α]<sub>D</sub><sup>24.8</sup>; = +62.8 (c 0.23, CHCl<sub>3</sub>); ν<sub>max</sub>/cm<sup>-1</sup> (CHCl<sub>3</sub>) 2228 (CN); δ<sub>H</sub> (250 MHz; CDCl<sub>3</sub>) 1.33 (3 H, s, Me), 1.37 (3 H, s, Me), 1.39 (6 H, s, 2 Me), 4.57 (1 H, m, H-8), 4.58-4.63 (2 H, m, H-1, H-4), 4.66 (1 H, dd, *J* 2.61, 5.07 Hz, H-9), 6.44 (1 H, m, H-3); δ<sub>C</sub> (62.9 MHz; CDCl<sub>3</sub>) 26.05 (Me), 27.51 (Me), 27.68 (Me), 69.30 (CH-O), 69.41 (CH-O), 72.00 (CH-O), 72.42 (CH-O), 113.89 (O-C-O), 116.74 (O-C-O), 128.82 (C=C), 130.49 (C=C), 141.10 (CN); m/z (relative abundance) (CI) 252 ([M + H]<sup>+</sup>, 32 %), 236 (100), 194 (28), 178 (15), 150 (10), 136 (25), 101 (10), 59 (62), 41 (58).

**(1R, 4R, 8R, 9R)-2-Formyl-6,6,11,11-tetramethyl-5,7,10,12-tetraoxabicyclo[7,3,0,0<sup>9</sup>,1]dodec-2-ene 7.** To the nitrile **5** (1.0 g, 3.98 mmol) in dry THF (25 ml) under an atmosphere of nitrogen at 0 °C was added DIBAL (9 ml of 1 M hexane solution, 9 mmol). The mixture was stirred at 0 °C for 2 h. The mixture was allowed to warm to room temperature and was stirred at room temperature for another 2 h. It was cooled to 0 °C and methanol (10 ml) and 1N HCl (20 ml) were added. The resulting mixture was stirred at 0 °C for 1 h and was extracted with diethyl ether (4 x 50 ml). The organic phase was washed with saturated NaHCO<sub>3</sub> (15 ml), brine (10 ml). The organic phase was evaporated under reduced pressure and the product was isolated by flash chromatography (petroleum ether 40-60 °C/diethyl ether, 8 : 3, v/v) to give the aldehyde **7** as clear liquid (R<sub>f</sub> 0.28, 0.39 g, 38.7 %); (Found [M + H]<sup>+</sup> : 255.1232. C<sub>13</sub>H<sub>19</sub>O<sub>5</sub> requires 255.1233); [α]<sub>D</sub><sup>24.8</sup> = -7.9 (c 0.12, CHCl<sub>3</sub>); ν<sub>max</sub>/cm<sup>-1</sup> 1698 (C=O); δ<sub>H</sub> (250 MHz; CDCl<sub>3</sub>) 1.297 (3 H, s, Me), 1.3006 (3 H, s, Me), 1.387 (3 H, s, Me), 1.398 (3 H, s, Me), 4.63 (1 H, ddd, *J* 4.95, 2.62, 1.16 Hz, H-8), 4.69 (1 H, dd, *J* 2.62, 5.96 Hz, H-9), 4.78 (1 H, dd, *J* 2.33, 4.95 Hz, H-4), 4.94 (1 H, d, *J* 5.96 Hz, H-1), 6.58 (1 H, apps, H-3), 9.59 (1 H, s, CHO); δ<sub>C</sub> (62.9 MHz; CDCl<sub>3</sub>) 25.43 (Me), 26.06 (Me), 27.30 (Me), 66.88 (C-O), 70.37 (C-O), 71.88 (C-O), 73.89 (C-

O), 109.35 (O-C-O), 109.77 (O-C-O), 137.10 (C=C), 145.33 (C=C), 192.60 (C=C); *m/z* (relative abundance) (CI) 272 ([M + NH<sub>4</sub>]<sup>+</sup>, 40 %), 255 (100), 239 (30), 139 (15).

**(1R, 4R, 8R, 9R)-6,6,11,11-Tetramethyl-5,7,10,12-tetraoxabicyclo[7,3,0,0<sup>9,1</sup>]dodec-2-ene-2-carboxylic acid 8.** A solution of NaClO<sub>2</sub> (80 % purity, 0.34 g, 3.0 mmol) in water (5 ml) was added dropwise to a mixture of the aldehyde 7 (0.58 g, 2.28 mmol) in acetonitrile (15 ml), NaH<sub>2</sub>PO<sub>4</sub> (0.2 M, 7 ml) and H<sub>2</sub>O<sub>2</sub> (35 %, 0.66 g, 6.79 mmol). The resulting mixture was stirred at room temperature for 1h. Aqueous Na<sub>2</sub>SO<sub>3</sub> (10 %, 10 ml) was added to destroy unreacted H<sub>2</sub>O<sub>2</sub> and NaClO<sub>2</sub>. The mixture was acidified (conc. HCl) and extracted with diethyl ether (3 x 40 ml). The ethereal phase was separated, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give a yellow liquid. The residue was purified by flash chromatography (diethyl ether) to give the carboxylic acid 8 as a syrup (0.44 g, 72 %). Found [M + H]<sup>+</sup> : 271.1182. C<sub>13</sub>H<sub>19</sub>O<sub>6</sub> requires 271.1182; [α]<sub>D</sub><sup>28.5</sup> = +50.9 (c 0.122, CHCl<sub>3</sub>); *v*<sub>max</sub>/cm<sup>-1</sup> 3216 (br, OH), 1703 (C=O); δ<sub>H</sub> (250 MHz; CDCl<sub>3</sub>) 1.31 (3 H, s, CH<sub>3</sub>), 1.34 (3 H, s, CH<sub>3</sub>), 1.38 (3 H, s, CH<sub>3</sub>), 1.40 (3 H, s, CH<sub>3</sub>), 4.58-4.62 (1 H, m, H-4), 4.69 (1 H, m, H-8), 4.70 (1 H, m, H-9), 4.95 (1 H, d, *J* 6.11 Hz, H-1), 6.85 (1 H, apparent s, H-3); δ<sub>C</sub> (62.9 MHz; CDCl<sub>3</sub>) 25.80 (CH<sub>3</sub>), 26.19 (CH<sub>3</sub>), 27.49 (CH<sub>3</sub>), 27.76 (CH<sub>3</sub>), 68.74 (C-O), 70.43 (C-O), 72.17 (C-O), 73.24 (C-O), 109.36 (O-C-O), 109.77 (O-C-O), 128.28 (C=C), 138.74 (C=C), 170.74 (C=O); *m/z* (relative abundance) (CI) 212 ([M + H]<sup>+</sup>, 38), 196 (15), .

**(3R, 4R, 5R, 6R)-3,4,5,6-Tetrahydrocyclohex-1-ene-1-carboxylic acid 9.** The acid 8 (0.27 g, 1 mmol) was dissolved in methanol (5 ml) and water (7 ml), then concentrated HCl (3 drops) was added. The resulting mixture was allowed to stand at room temperature for 3 days and was lyophilised to give (3R, 4R, 5R, 6R)-3,4,5,6-tetrahydrocyclohex-1-ene-1-carboxylic acid 9. as a hygroscopic solid (0.19 g, 100 %), pure by NMR: (Found *m/z* [M + NH<sub>4</sub>]<sup>+</sup> 208.0821. C<sub>7</sub>H<sub>14</sub>NO<sub>6</sub> requires (M+NH<sub>4</sub>) 208.0821); [α]<sub>D</sub><sup>27.1</sup> = -169 (c 0.23, MeOH); *v*<sub>max</sub>/cm<sup>-1</sup> 3367 (br, OH), 1695 (C=O); δ<sub>H</sub> (250 MHz; D<sub>2</sub>O) 3.78 (1 H, dd, *J* 3.49, 10.46 Hz, H-5), 3.85 (1 H, dd, *J* 4.07, 10.46 Hz, H-4), 4.37 (1 H, dd, *J* 4.94, 4.07 Hz, H-3), 4.56 (1 H, d, *J* 3.49 Hz, H-6), 6.88 (1 H, d, *J* 4.94 Hz, H-2); δ<sub>C</sub> (62.9 MHz; D<sub>2</sub>O) 66.28 (CH-O), 66.34 (CH-O), 69.53 (CH-O), 69.04 (CH-O), 132.89 (C=C), 140.54 (C=C), 169.81 (C=O); *m/z* (relative abundance) (FAB, NBA) 191 ([M+H]<sup>+</sup>, 10%), 171 (10), 154 (100), 136 (78), 120 (12), 107 (28), 89 (30).

*X-Ray Crystallography.*- All measurements were made using a Siemens P3R3 four-circle diffractometer equipped with an Oxford Cryosystems Cryostream Cooler (version 2.4). Graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) was used to collect the intensity data in the ω-2θ mode. Unit cell parameters and orientation matrices were obtained by least-squares refinement of the setting angles of 2θ high angle reflections.

The crystallographic program system was SHELXTL PLUS<sup>9</sup> and SHELXL-93<sup>10</sup>; the refinement program uses atomic scattering factors taken from International Tables for Crystallography.<sup>11</sup> The structures were solved by direct methods and refined using full-matrix least-squares on F<sup>2</sup>. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were inserted using a riding model and given isotropic thermal parameters equal to 1.2 (or 1.5 for methyl groups) times the equivalent isotropic displacement parameter of the atom to which they are attached. The weighting scheme was of the form w<sup>-1</sup> = [σ<sup>2</sup>(F<sub>o</sub>)<sup>2</sup> + (aP)<sup>2</sup> + bP] where P = [max.(F<sub>o</sub><sup>2</sup>, 0) + 2F<sub>c</sub><sup>2</sup>]/3. The R factors are defined as R(F) = Σ||F<sub>o</sub>| - |F<sub>c</sub>||/Σ|F<sub>o</sub>| and wR(F<sup>2</sup>) = [Σ[w(F<sub>o</sub><sup>2</sup> -

$F_o^2)/\Sigma[w(F_o^2)^2]^{1/2}$ . A summary of the crystal data and refinement details is given in the Table. Additional material available from the Cambridge Crystallographic Data Centre includes full listings of bond lengths and angles, and thermal parameters.

**Table.** Crystal data and structure refinement details for diol **5** and dimer **9**.

Formula	$C_{13}H_{17}NO_4$	$C_{20}H_{22}N_2$
M	251.28	354.40
Crystal system	Orthorhombic	Orthorhombic
a/Å	6.304(3)	8.37(2)
b/Å	10.567(6)	8.649(5)
c/Å	21.800(10)	25.31(4)
U/Å <sup>3</sup>	1452.2(13)	1832(4)
Temperature/K	220(2)	230(2)
Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
Z	4	4
D <sub>x</sub> /g cm <sup>-3</sup>	1.149	1.285
Crystal size/mm	0.30x0.20x0.13	0.30x0.21x0.11
μ/mm <sup>-1</sup>	0.085	0.090
F(000)	536	752
θ <sub>min</sub> , θ <sub>max</sub> /°	1.87, 24.08	2.49, 22.55
Index ranges	0/7, 0/12, -1/25	0/9, -1/9, -1/27
Number of data collected	1433	1701
Independent reflections	1415	1633
	[R(int)=0.018]	[R(int)=0.034]
Weighting parameters:		
a	0.0557	0.0837
b	0.000	2.2659
R(F) [I>2σ(I)]	0.0427	0.0572
wR(F <sup>2</sup> ) (all data)	0.1147	0.1790
Goodness of fit on F <sup>2</sup>	1.028	1.053
Largest diff. peak & hole/e Å <sup>-3</sup>	±0.2	±0.2
Data, restraints, parameters	1413, 0, 168	1631, 0, 236
Extinction coefficient	0.017(2)	0.017(3)

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