



## Short and Efficient Synthesis of Enantiomerically Pure Building Blocks for the Preparation of Carbocyclic Nucleosides and Prostaglandins via Diastereoselective Dihydroxylation of 5-Menthyloxy-2[5H]-furanone

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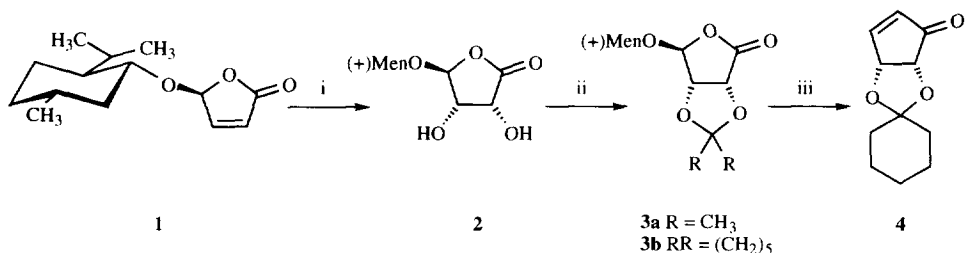
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**Abstract** : A short and efficient synthesis of both enantiomerically pure 2,3-(Cyclohexylidenedioxy)-4-cyclopentenones **4** and *ent*-**4** from the readily available 5-menthyloxy-2[5H]-furanones **1** and *ent*-**1** is presented. The key step is the substrate controlled diastereoselective dihydroxylation of **1** and *ent*-**1**. Copyright © 1996 Elsevier Science Ltd

The photochemistry of the well-known 5-menthyloxy-2[5H]-furanones **1** and *ent*-**1** has been a subject of our research in the past.<sup>1</sup> Recently we studied the preparation of their precursor 5-hydroxy-2[5H]-furanone by photooxygenation of furfural<sup>2</sup> on a multimolar scale (> 20 mol/d) using concentrated sunlight.<sup>3</sup> Now we can report that 5-menthyloxy-2[5H]-furanones **1** and *ent*-**1**, which are easily available from 5-hydroxy-2[5H]-furanone in enantiomerically pure form,<sup>4</sup> can be used for the preparation of enantiomerically pure dihydroxycyclopentenone derivatives **4** and *ent*-**4**.

Acetals of enantiomerically pure *cis*-2,3-dihydroxy-4-cyclopentenone are frequently used intermediates<sup>5</sup> for the preparation of important natural products and their analogues, for example Prostaglandin E<sub>2</sub><sup>6</sup>, neplanocin A<sup>7</sup> and aristeromycin<sup>8</sup>. They have been prepared from cyclopentadiene<sup>6a,9</sup>, D-ribonolactone<sup>7c,10</sup>, D-ribose and D-lyxose<sup>11</sup>, D-mannose<sup>7c</sup>, L-tartaric acid<sup>8c,12</sup>, toluene and chloro- and bromobenzene<sup>13</sup>.

We will now describe a simple three step procedure for the preparation of enantiomerically pure **4** and *ent*-**4** in good yield starting from (+)-(5*S*)-5-(+)-menthyl)oxy-2[5H]-furanone **1** and (-)-(5*R*)-5-(-)-menthyl)oxy-2[5H]-furanone *ent*-**1** respectively (Scheme 1): Furanone **1** is dihydroxylated diastereoselectively with a slight excess of KMnO<sub>4</sub> to give 62 % of (+)- $\alpha$ -L-(+)-menthyl)erythruronofuranoside **2** as the sole product (500 MHz <sup>1</sup>H NMR, de  $\geq$  98 %). The methyl glucoside of *ent*-**2** has been used for the preparation of the hydroxyamino acid moiety of AI-77-B<sup>14</sup>. Borontrifluoride mediated acetalization<sup>15</sup> of **2** gives acetals (+)-**3a** and (+)-**3b** in 89 % and 84 % yield respectively. <sup>1</sup>H NMR-Spectra of **2**, **3a** and **3b** show a sharp singlet for the acetal proton H1, indicating a dihedral angle of 90° between H1 and H2 and thus proving a *trans* relationship. Obviously the (+)-menthyl substituent shields the ul-side of **1** effectively. Dihydroxylation can occur on the lk-side only.



i) KMnO<sub>4</sub>, 62 %; ii) R<sub>2</sub>CO, BF<sub>3</sub>·OEt<sub>2</sub>, 89 % (3a), 84 % (3b); iii) (H<sub>3</sub>CO)<sub>2</sub>POCH<sub>2</sub>Li, 87 % (45 % from 1)

### Scheme 1

The cyclohexylidene-acetal **3b** is reacted with lithium dimethyl methylphosphonate<sup>7c,16</sup> to give (-)-2,3-(cyclohexylidenedioxy)-4-cyclopentenone **4** in 87 % yield. Analytical data of **4** are in accordance with the literature, except for the melting point which is found to be 87 °C instead of 65 °C as reported by Borchering et al.<sup>7c</sup>. Consequently the enantiomeric purity of **4** was checked by chiral capillary GC. No trace of **ent-4** was found indicating an ee > 99 %.

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## Experimental Section

**(+)-α-L-((+)-Menthyl)erythruronofuranoside 2.** (+)-(5*S*)-5-((+)-Menthyl)oxy-2[5H]-furanone **1** (239 g, 1.00 mol) was dissolved in a mixture of acetone (3 l) and water (300 ml) in a 5 l beaker with a large magnetic stirring bar. The solution was cooled to -5 °C and KMnO<sub>4</sub> (158 g, 1.00 mol) was added with stirring, maintaining the temperature below 0 °C. The mixture was stirred for 2 h before another portion of KMnO<sub>4</sub> (16 g, 0.10 mol) was added. Stirring was continued for 30 min and conversion of **1** was checked by TLC since an additional portion of KMnO<sub>4</sub> may be necessary for complete conversion. The mixture was heated to 50 °C for 10 min without stirring and filtered with suction. The clear and colourless filtrate (excess KMnO<sub>4</sub> can be destroyed with MeOH and the mixture filtered again) was concentrated at room temperature to give a white solid which was dried in vacuum. The crude product was pulverized and spread out on a glass plate until the smell of menthol had disappeared (1 - 2 d. Caution is necessary as the product is very sensitive towards vapours of bases and strong acids). The material obtained (169 g, 0.62 mol, 62 %) was analytically pure. R<sub>f</sub> = 0.30 (CHCl<sub>3</sub>/MeOH 9:1), [α]<sub>D</sub><sup>20</sup> = +180 (c = 1.00, MeOH), mp = 175 °C. IR (KBr, cm<sup>-1</sup>) 3365, 2960, 2930, 2870, 1775, 1365, 1305, 1180, 1155, 1120, 1035, 915, 775, 755. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500 MHz) δ 5.88 (d, J = 7.6, 1H, OH), 5.77 (d, J = 3.8, 1H, OH), 5.40 (s, 1H), 4.33 (dd, J<sub>1</sub> = 4.6, J<sub>2</sub> = 7.7 Hz, 1H), 3.96 (t, J = 4.3 Hz, 1H), 3.41 (dt, J<sub>1</sub> = 4.3, J<sub>2</sub> = 10.7 Hz, 1H), 2.15 (br d, J = 11 Hz, 1H), 1.92 (dsep, J<sub>1</sub> = 2.4, J<sub>2</sub> = 6.8 Hz, 1H), 1.60 (m, 2H), 1.37 (m, 1H), 1.17 (m, 1H), 0.96 (m, 1H), 0.80 (d, J = 6.8 Hz, 3H), 0.80 - 0.68 (m, 2H), 0.73 (d, J = 6.8 Hz, 3H), 0.68 (d, J = 6.8 Hz, 3H). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 125 MHz) δ 175.6 (C), 101.9 (CH), 76.3 (CH), 71.6 (CH), 68.1 (CH), 46.8 (CH), 39.2 (CH<sub>2</sub>), 33.7 (CH<sub>2</sub>), 30.6 (CH), 25.1 (CH), 22.5 (CH<sub>2</sub>), 21.9 (CH<sub>3</sub>), 20.5 (CH<sub>3</sub>), 15.3 (CH<sub>3</sub>). MS *m/z* (rel. int.) 244 (M<sup>+</sup> - CO, 2), 129 (5), 106

(18), 95 (16), 83 (100), 81 (35), 71 (14), 69 (28), 57 (37), 55 (40). Anal. Calcd for  $C_{14}H_{24}O_5$ : C, 61.73; H, 8.88; found: C, 61.38; H, 8.93.

**(+)-2,3-O-Isopropylidene- $\alpha$ -L-(+)-menthylerythronofuranoside 3a.** Diol **2** (30 g, 110 mmol) was suspended in ethylacetate (150 ml) and acetone (7.68 g, 132 mmol) and cooled in an ice bath.  $BF_3 \cdot OEt_2$  (15.6 g, 110 mmol) was added dropwise to the stirred suspension and stirring was continued until **2** had dissolved (4 - 6 h). The ice bath was removed and the slightly yellow solution was stirred for 2 h at room temperature before being poured into a stirred suspension of  $NaHCO_3$  (30 g) in ethylacetate (150 ml). After being stirred for at least 2 h (or overnight) the suspension was filtered, the filtrate dried over  $MgSO_4$  and concentrated to a yellow oil which was purified by flash chromatography with hexanes/ether 10:1 to give a colourless syrup (30.6 g, 98.0 mmol, 89 %) which solidifies upon standing.  $R_f = 0.72$  ( $CHCl_3/MeOH$  9:1),  $[\alpha]_D^{20} = +112$  ( $c = 0.99$ ,  $CHCl_3$ ),  $mp = 67$  °C. IR (KBr,  $cm^{-1}$ ) 2955, 2930, 2870, 1810, 1795, 1455, 1390, 1380, 1230, 1155, 1105, 970, 920, 900, 840.  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  5.62 (s, 1H), 4.61 (d,  $J = 5.4$  Hz, 1H), 4.54 (d,  $J = 5.4$  Hz, 1H), 3.57 (dt,  $J_1 = 4.2$ ,  $J_2 = 10.7$  Hz, 1H), 2.13 (br d,  $J = 11$  Hz, 1H), 1.94 (dsep,  $J_1 = 2.7$ ,  $J_2 = 7.0$  Hz, 1H), 1.66 (m, 2H), 1.46 (s, 3H), 1.38 (s, 3H), 1.22 (m, 2H), 1.00 (m, 1H), 0.94 (d,  $J = 6.5$  Hz, 3H), 0.86 (d,  $J = 7.1$  Hz, 3H), 0.85 (m, 1H), 0.75 (d,  $J = 6.8$  Hz, 3H).  $^{13}C$  NMR ( $CDCl_3$ , 75 MHz)  $\delta$  173.7 (C), 114.3 (C), 100.5 (CH), 79.7 (CH), 77.5 (CH), 74.6 (CH), 47.5 (CH), 39.5 ( $CH_2$ ), 34.2 ( $CH_2$ ), 31.3 (CH), 26.7 (CH), 25.7 ( $CH_3$ ), 25.5 ( $CH_3$ ), 23.1 ( $CH_2$ ), 22.2 ( $CH_3$ ), 20.8 ( $CH_3$ ), 15.6 ( $CH_3$ ). MS  $m/z$  (rel. int.) 313 ( $M^+ + 1$ , 0.1), 139 (20), 129 (6), 100 (100), 85 (18), 83 (46), 81 (12), 69 (12). Anal. Calcd for  $C_{17}H_{28}O_5$ : C, 65.36; H, 9.03; found: C, 65.55; H, 9.08.

**(+)-2,3-O-Cyclohexylidene- $\alpha$ -L-(+)-menthylerythronofuranoside 3b.** The acetalization of **2** with cyclohexanone was carried out as described for **3a** giving **3b** as a white solid (84 %).  $R_f = 0.74$  ( $CHCl_3/MeOH$  9:1),  $[\alpha]_D^{20} = +96$  ( $c = 1.16$ ,  $CHCl_3$ ),  $mp = 55$  °C. IR (KBr,  $cm^{-1}$ ) 2935, 2865, 1800, 1450, 1370, 1165, 1115, 1075, 1040, 925.  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  5.63 (s, 1H), 4.80 (d,  $J = 5.4$  Hz, 1H), 4.51 (d,  $J = 5.4$  Hz, 1H), 3.57 (dt,  $J_1 = 4.4$ ,  $J_2 = 10.7$  Hz, 1H), 2.14 (br d,  $J = 11$  Hz, 1H), 1.94 (dsep,  $J_1 = 2.5$ ,  $J_2 = 7.1$  Hz, 1H), 1.71 - 1.55 (m, 10H), 1.42 - 1.36 (m, 2H), 1.26 (m, 2H), 1.22 (m, 1H), 0.96 - 0.83 (m 2H), 0.94 (d,  $J = 6.4$  Hz, 3H), 0.86 (d,  $J = 7.1$  Hz, 3H), 0.74 (d,  $J = 7.0$  Hz, 3H).  $^{13}C$  NMR ( $CDCl_3$ , 75 MHz)  $\delta$  173.9 (C), 115.0 (C), 100.7 (CH), 79.3 (CH), 77.5 (CH), 74.3 (CH), 47.6 (CH), 39.6 ( $CH_2$ ), 36.4 ( $CH_2$ ), 35.2 ( $CH_2$ ), 34.2 ( $CH_2$ ), 31.4 (CH), 25.5 (CH), 24.8 ( $CH_2$ ), 23.8 ( $CH_2$ ), 23.7 ( $CH_2$ ), 23.1 ( $CH_2$ ), 22.2 ( $CH_3$ ), 20.8 ( $CH_3$ ), 15.6 ( $CH_3$ ). MS  $m/z$  (rel. int.) 353 ( $M^+$ , 4), 312 (22), 309 (21), 215 (43), 211 (34), 185 (14), 182 (18), 171 (51), 169 (54), 141 (34), 140 (82), 139 (85), 138 (67), 123 (30), 111 (14), 99 (99), 97 (75), 83 (100), 81 (75), 73 (10), 69 (63). Anal. Calcd for  $C_{20}H_{32}O_5$ : C, 68.15; H, 9.15; found: C, 68.00; H, 9.03.

**(-)-2,3-(Cyclohexylidenedioxy)-4-cyclopentenone 4<sup>7c</sup>.** A 1 l three-necked flask fitted with a septum and a 100 ml addition funnel with a glass jacket allowing the addition funnel to be cooled was flame dried. The flask was charged with dimethyl methylphosphonate (7.45 g, 60.0 mmol) in dry THF (400 ml) and cooled to -78 °C. **3b** (21.0 g, 60.0 mmol) was dissolved in THF (50 ml) and poured into the addition funnel which was cooled to -78 °C, too. *n*-Butyllithium (15 % in hexane (1.6 M), 25.6 g, 60.0 mmol) was added dropwise from a syringe to the stirred phosphonate solution (15 - 20 min) and stirring was continued for 30 min. The cooled

solution of **3b** was added in one portion in a few seconds. After stirring for additional 2 h the reaction mixture was allowed to warm to room temperature (45 - 60 min). The solution was poured into a stirred mixture of ether (500 ml) and water (100ml) and the layers were separated quickly. The aqueous layer was extracted with ether (50 ml) and the combined organic phase was washed with brine, dried over MgSO<sub>4</sub> and concentrated at room temperature. The residue was purified by flash chromatography with hexanes/ether 5:1 to give **4** as a colourless syrup (10.1 g, 52.0 mmol, 87 %) which solidifies in the freezer. Nonetheless **4** is a remarkably volatile solid with a strong, gasoline-like odour and should not be subjected to vacuum for a prolonged time.  $R_f$  = 0.68 (CHCl<sub>3</sub>/MeOH 9:1),  $[\alpha]_D^{20}$  = -73 (c = 1.00, CHCl<sub>3</sub>), mp = 87 °C. IR (KBr, cm<sup>-1</sup>) 2945, 2930, 2870, 1800, 1450, 1370, 1360, 1165, 1120, 925. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.61 (dd,  $J_1$  = 2.3,  $J_2$  = 5.7 Hz, 1H), 6.20 (d,  $J$  = 5.7 Hz, 1H), 5.26 (ddd,  $J_1$  = 0.7,  $J_2$  = 2.3,  $J_3$  = 5.4 Hz, 1H), 4.46 (d,  $J$  = 5.4 Hz, 1H), 1.59 (m, 8H), 1.38 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)  $\delta$  203.3 (C), 159.9 (CH), 134.3 (CH), 116.4 (C), 78.3 (CH), 76.2 (CH), 37.3 (CH<sub>2</sub>), 35.7 (CH<sub>2</sub>), 24.9 (CH<sub>2</sub>), 23.8 (CH<sub>2</sub>), 23.6 (CH<sub>2</sub>). MS  $m/z$  (rel. int.) 194 (M<sup>+</sup>, 42), 165 (22), 151 (100), 98 (15), 97 (25), 96 (23), 80 (9), 69 (19), 68 (73), 55 (99). Anal. Calcd for C<sub>11</sub>H<sub>14</sub>O<sub>3</sub>: C, 68.02; H, 7.26; found: C, 67.91; H, 7.21. Chiral GC: 25 m CS  $\beta$ -IP capillary column ( $\emptyset$  0.1 mm) on a HP 5890 Series II gas chromatograph, 1.0 bar H<sub>2</sub>, 130 °C; RT: **4**, 40.0 min; **ent-4**, 42.5 min.

## References and Notes

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