

Conversion of (±)-4-Hydroxy-2-oxabicyclo[3.3.0]oct-7-en-3-one into the anti-HIV Agent Carbovir

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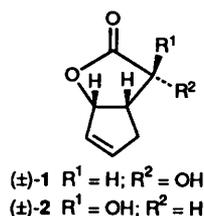
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The lactone (±)-1 was resolved using *Pseudomonas fluorescens* lipase and vinyl acetate; the ester (–)-3 obtained by this process was subsequently converted into the anti-HIV agent carbovir (–)-9.

The bicyclic hydroxy lactones **1**, **2** are attractive synthons¹ since they are produced from two readily available starting materials namely cyclopentadiene and glyoxylic acid.²

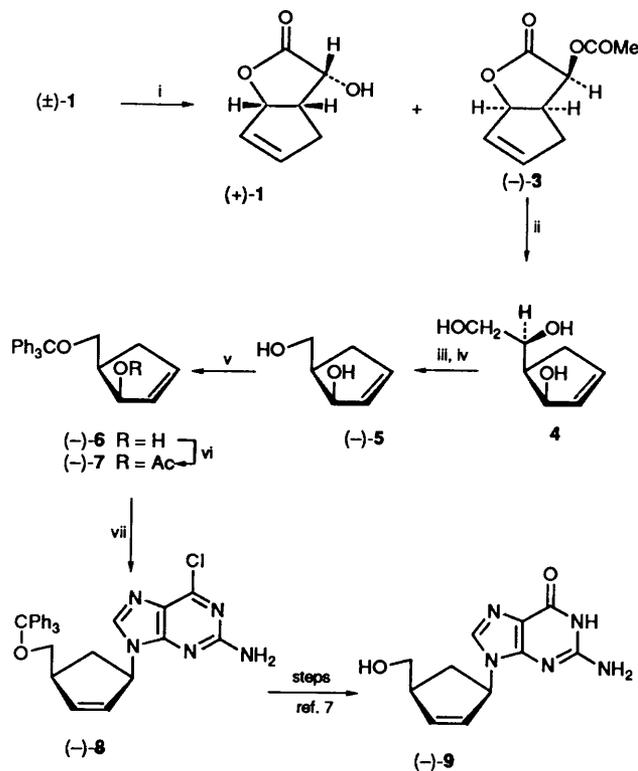
Using the reaction conditions and work up procedure described in the Experimental section the hydroxy lactones **1** and **2** are produced in the ratio 4:1 on a large scale (10–250 g) (crude yield ca. 65%). The compounds were separated by chromatography over silica and the disposition of 4-OH in the epimers was elucidated by NMR spectroscopy.² The epimer **1** crystallizes from the crude product. The minor component **2** can then be removed by trituration whereupon **1** can be obtained in greater than 95% purity in 31% yield. Recrystallization from diethyl ether gave pure **1**. Confirmation of the proposed structure for the lactone **1** was obtained by X-ray crystallography.³



The hydroxy lactone **1** was resolved by an enzyme-catalysed process. Thus the lactone (±)-**1** was partially acetylated using *Pseudomonas fluorescens* lipase (pfl) in vinyl acetate. At 40% conversion the acetate (–)-**3** was obtained in a state of high optical purity (>95% ee: monitored by GC over a Lipodex D column) while at 60% conversion the optically pure alcohol (+)-**1** could be isolated (>95% ee).

The acetate (–)-**3** was converted, in three steps, into the diol (–)-**5** via the triol **4** (overall yield 50%). The three operations can be conducted without purification of the intermediates. Tritylation of the primary hydroxy group in the diol (–)-**5** gave the ester (–)-**6** and acetylation of the secondary hydroxy group gave the ester (–)-**7** [$[\alpha]_D^{25} - 85$ (*c* 1.0, CHCl₃)]. Note that the compound (–)-**7** can be obtained from (±)-**5** (a minor product obtained from a modified Prins reaction on cyclopentadiene followed by hydrolysis of the formate esters⁴) by tritylation to give (±)-**6** and enantioselective acetylation using pfl and vinyl acetate.⁵ Compounds of type **7** are excellent precursors of 2',3'-dideoxydihydrocarbocyclic nucleosides through the use of Trost-style organopalladium chemistry.^{4,6,7} Thus, reaction of the allylic acetate (–)-**7** with 2-amino-6-chloropurine and sodium hydride in the presence of tetrakis(triphenylphosphine)palladium(0) gave the cyclopentene derivative (–)-**8** [$[\alpha]_D^{25} - 75$ (*c* 1.0, CHCl₃)] a known precursor⁷ of the anti-HIV agent carbovir (–)-**9**. Interest in this anti-viral substance remains at a high level.⁸

The synthetic potential of the lactones **1** and **2** can be further

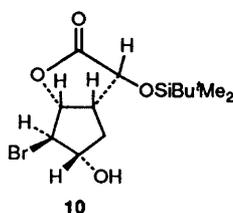


Scheme 1 Reagents and conditions: i, Pfl, vinyl acetate; ii, LiAlH₄, THF; iii, NaIO₄, Et₂O–H₂O; iv, NaBH₄, MeOH; v, Ph₃CCl, Et₃N, Me₂NC₅H₄N, CH₂Cl₂; vi, Ac₂O, pyridine; vii, 2-amino-6-chloropurine, NaH, DMF, (Ph₃P)₄Pd, THF

demonstrated by the fact that, after silylation of the hydroxy group, the lactone **1** reacted with *N*-bromoacetamide in aqueous acetone with exquisite selectivity to afford the highly functionalised lactone **10**. At present we are investigating other aspects of the chemistries of the lactones **1**, **2** and **10**.

Experimental

Cyclopentadiene (240 cm³, 2.87 mol), aq. glyoxylic acid (225 cm³, 50% w.v. solution, 2.01 mol) and water (800 cm³) were vigorously stirred at 0 °C to room temp. for 4 d. The solution was extracted with heptane (4 × 250 cm³) (to remove unchanged cyclopentadiene), saturated with sodium chloride and further extracted with ethyl acetate (12 × 500 cm³). The combined organic layers were concentrated to 1.5 dm³, cooled to 0 °C and washed with cold saturated aqueous sodium hydrogen carbonate (2 × 200 cm³) (to remove unchanged



glyoxylic acid). The aqueous solution was extracted with ethyl acetate ($3 \times 500 \text{ cm}^3$). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to give the lactones (\pm)-1 and (\pm)-2 as a yellow mobile oil which crystallised on storage (ca. 65% yield). NMR spectroscopy showed the ratio 1:2 was 4:1. The crude product was triturated with methyl *tert*-butyl ether to remove the oily lactone (\pm)-2 and the lactone (\pm)-1 (88 g, 628 mmol) was isolated as a sand coloured crystalline solid (greater than 95% pure by NMR spectroscopy) which could be used in the next step. Recrystallisation from diethyl ether gave pure (\pm)-4-hydroxy-2-oxabicyclo[3.3.0]oct-7-en-3-one 1.

Alternatively chromatography of the crude product over silica using hexane in ethyl acetate (ratio 2:3) as eluent to give, in the first fractions, the lactone (\pm)-2; $\nu_{\text{max}}/\text{cm}^{-1}$ 3427, 1764, 1615, 1184, 1116 and 986; $\delta_{\text{H}}(\text{CDCl}_3)$ 6.1 (1 H, m, 7-H or 8-H), 5.9 (1 H, m, 8-H or 7-H), 5.55 (1 H, m, 1-H), 4.15 (1 H, d, *J* 7, 4-H), 3.5 (1 H, br s, OH) and 3.05–2.55 (3 H, m, 5-H and $2 \times$ 6-H); $\delta_{\text{C}}(\text{CDCl}_3)$ 178.2, 136.9, 129.2, 87.5, 74.3, 44.3 and 36.6. Later fractions contained the lactone (\pm)-1 m.p. 68–69 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ 3443, 3023, 1765, 1615 and 1134; $\delta_{\text{H}}(\text{CDCl}_3)$ 6.33 (1 H, m, 7-H or 8-H), 5.93 (1 H, m, 8-H or 7-H), 5.33 (1 H, dt, *J* 6, 2, 1-H), 4.72 (1 H, d, *J* 9, 4-H), 3.5 (1 H, br s, OH) and 3.21–2.45 (3 H, m, 5-H and $2 \times$ 6-H); $\delta_{\text{C}}(\text{CDCl}_3)$ 177.6, 140.9, 127.4, 86.4,

67.0, 40.4 and 30.7 (Found: C, 59.9; H, 5.7. $\text{C}_7\text{H}_8\text{O}_3$ requires C, 60.0; H, 5.75%).

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