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

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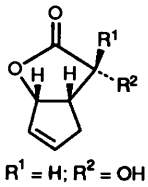
The lactone (±)-**1** was resolved using *Pseudomonas fluorescens* lipase and vinyl acetate; the ester (−)-**3** obtained by this process was subsequently converted into the anti-HIV agent carbovir (−)-**9**.

The bicyclic hydroxy lactones **1**, **2** are attractive synthons[1] 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]

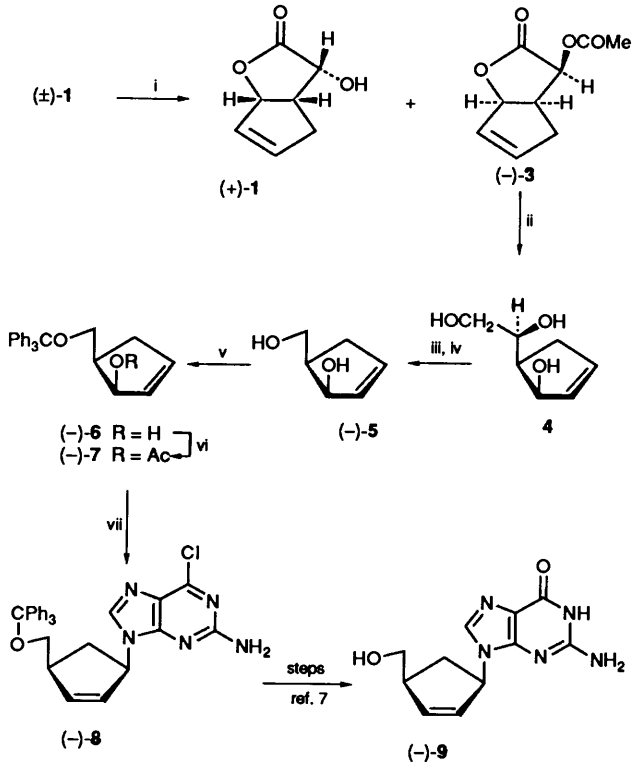


(±)-**1** R^1 = H; R^2 = OH
(±)-**2** R^1 = OH; R^2 = H

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 (−)-**6** and acetylation of the secondary hydroxy group gave the ester (−)-**7** $[\alpha]_D^{25}$ −85 (*c* 1.0, $CHCl_3$). 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 esters[4]) by tritylation to give (±)-**6** and enantioselective acetylation using pfl and vinyl acetate.[5] Compounds of type **7** are excellent precursors of 2′,3′-dideoxydidehydrocarbocyclic 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, $CHCl_3$) a known precursor[7] 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

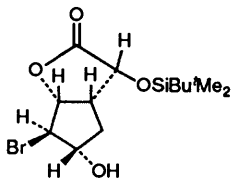


Scheme 1 *Reagents and conditions*: i, Pfl, vinyl acetate; ii, $LiAlH_4$, THF; iii, $NaIO_4$, Et_2O–H_2O; iv, $NaBH_4$, MeOH; v, Ph_3CCl, Et_3N, $Me_2NC_5H_4N$, CH_2Cl_2; vi, Ac_2O, pyridine; vii, 2-amino-6-chloropurine, NaH, DMF, $(Ph_3P)_4Pd$, THF

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 cm^3, 2.87 mol), aq. glyoxylic acid (225 cm^3, 50% w.v. solution, 2.01 mol) and water (800 cm^3) were vigorously stirred at 0 °C to room temp. for 4 d. The solution was extracted with heptane (4 × 250 cm^3) (to remove unchanged cyclopentadiene), saturated with sodium chloride and further extracted with ethyl acetate (12 × 500 cm^3). The combined organic layers were concentrated to 1.5 dm^3, cooled to 0 °C and washed with cold saturated aqueous sodium hydrogen carbonate (2 × 200 cm^3) (to remove unchanged



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glyoxylic acid). The aqueous solution was extracted with ethyl acetate (3 × 500 cm^3). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to give the lactones (±)-**1** and (±)-**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 (±)-**2** and the lactone (±)-**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 (±)-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 (±)-**2**; ν_{max}/cm^{-1} 3427, 1764, 1615, 1184, 1116 and 986; $\delta_H(CDCl_3)$ 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 × 6-H); $\delta_C(CDCl_3)$ 178.2, 136.9, 129.2, 87.5, 74.3, 44.3 and 36.6. Later fractions contained the lactone (±)-**1** m.p. 68–69 °C; ν_{max}/cm^{-1} 3443, 3023, 1765, 1615 and 1134; $\delta_H(CDCl_3)$ 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 × 6-H); $\delta_C(CDCl_3)$ 177.6, 140.9, 127.4, 86.4, 67.0, 40.4 and 30.7 (Found: C, 59.9; H, 5.7. $C_7H_8O_3$ requires C, 60.0; H, 5.75%).

Acknowledgements

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