Regio- and Stereo-specific Synthesis of *cis*-(±)-1-Acetoxy-4-(acetoxymethyl)cyclopent-2-ene: a Key Intermediate in the Synthesis of Carbocyclic Nucleosides and *pseudo*-Ribofuranoses

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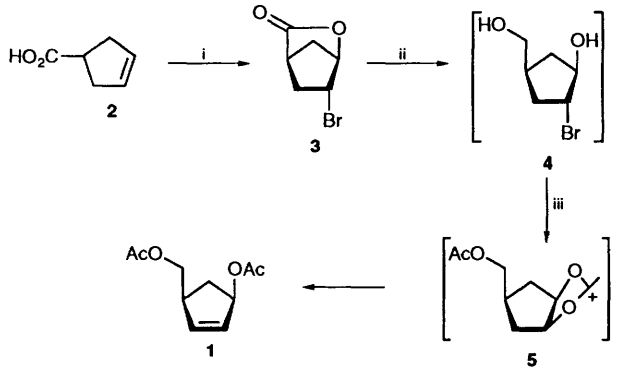
The synthesis of *cis*-(±)-1-acetoxy-4-(acetoxymethyl)cyclopent-2-ene **1** from cyclopent-3-ene-1-carboxylic acid **2** by way of bromolactonisation, reductive ring opening and diacylation with *in situ* elimination of HBr is described.

The *cis*-diacetate **1** is a key intermediate in the convergent synthesis of carbocyclic nucleosides by way of palladium-catalysed coupling with purines or pyrimidines.[1] Compounds derived from the *cis*-diacetate **1** have been enzymatically resolved and used in the enantioselective synthesis of the anti-HIV agent carbovir[2] and *pseudo*-ribofuranoses.[3] The *cis*-diacetate **1** is currently prepared by a Prins reaction between cyclopentadiene and formaldehyde in acetic acid. This reaction proceeds in low yield to give an inseparable mixture of the *cis*-diacetate **1**, the corresponding *trans*-diacetate and their respective allylic regioisomers. Hydrolysis of this mixture followed by careful chromatographic separation of the diols and diacylation then provides the *cis*-diacetate **1**.[1] We now communicate a regio- and stereo-specific synthesis of the *cis*-diacetate **1** from the acid **2**.

The acid **2** is directly prepared (70%) on a multigramme scale from dimethyl malonate and *cis*-1,4-dichlorobut-2-ene.[4] Bromolactonisation of the acid **2** gave the bromolactone **3**[5] (b.p. 150–160 °C at 0.1 mmHg, 70–95%) which was reduced using sodium bis(2-methoxyethoxy)aluminium hydride to give the crude bromo diol **4**; use of lithium aluminium hydride under various conditions always resulted in a mixture of the bromo diol **4** and 3-hydroxymethylcyclopentanone. The crude bromo diol **4** was diacylated using acetic anhydride and triethylamine or pyridine. Subsequent addition of silver acetate lead to *in situ* elimination of HBr and gave the *cis*-diacetate **1**. On the basis that this last step may be proceeding *via* the *meso*-acetoxonium ion **5** we repeated the reaction using (−)-sparteine as the base. Although the *cis*-diacetate **1** again formed as the racemate this procedure reproducibly gave the highest yields (78% from the bromo lactone **3**).

In summary, we have developed a regio- and stereo-specific route to *cis*-(±)-1-acetoxy-4-(acetoxymethyl)cyclopent-2-ene **1** (55% overall yield from dimethyl malonate).



Scheme 1 *Reagents and conditions:* i, TMSBr, DMSO, Pr^i_2EtN, $CHCl_3$, reflux, 12 h; ii, $[(MeOCH_2CH_2O)_2AlH_2]Na$, THF, −25 °C, 2 min; iii, Ac_2O, sparteine, cat. DMAP, DMF, 25 °C, 12 h, then AgOAc added, reflux, 6 h.

Experimental

cis-(±)-1-*Acetoxy*-4-(*acetoxymethyl*)*cyclopent*-2-*ene* **1**.—Sodium bis(2-methoxyethoxy)aluminium hydride (3.46 mol dm^{-3} in toluene; 2.7 cm^3, 9.3 mmol) was added dropwise over a period of 15 s to a mechanically stirred solution of the bromo lactone **3**[5] (1.74 g, 9.11 mmol) in dry THF (20 cm^3) at −25 °C (CCl_4/CO_2 bath) under argon. After a further 120 s water (0.34 cm^3) was added to the mixture followed by aqueous sodium hydroxide (15% w/v; 0.34 cm^3) and further water (1.0 cm^3). The reaction mixture was filtered, the filtrate diluted with EtOAc (10 cm^3) and saturated aqueous ammonium chloride (10 cm^3) and extracted with EtOAc (2 × 15 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude bromo diol **4** as a colourless oil (1.67 g).

A solution of the crude bromo diol **4** (378 mg), acetic anhydride (0.38 cm^3, 4.0 mmol), 4-*N*,*N*-dimethylaminopyridine (20 mg, 0.16 mmol) and (−)-sparteine (2.72 g, 11.6 mmol) in dry DMF (5 cm^3) was stirred at 25 °C under argon. After 12 h the flask was covered in tin foil to exclude light and silver acetate (356 mg, 2.13 mmol) was added to the reaction mixture which was then refluxed for 6 h. After cooling to room temperature, the reaction mixture was diluted with ether (20 cm^3) and filtered through Celite 545 (Fluka). The Celite was washed with saturated aqueous sodium hydrogen carbonate (10 cm^3), water (10 cm^3) and ether (10 cm^3) and the combined filtrates were extracted with ether (2 × 10 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography [35% ether–light petroleum (b.p. 40–60 °C)] gave a colourless oil, the cis-*diacetate* **1** (317 mg, 78%); ν_{max}(neat)/cm^{-1} 2948m, 1742s, 1439m, 1337s and 1253s; δ_H(400 MHz; $CDCl_3$; $SiMe_4$; *J*/Hz) 6.00 (1 H, ddd, *J* 5.5, 2.5 and 1, =CH), 5.92 (1 H, ddd, *J* 5.5, 2 and 2, CH=), 5.67–5.62 (1 H, m, OCH), 4.05 (2 H, d, *J* 6.5, OCH_2), 2.99–2.91 (1 H, m, CH), 2.49 (1 H, ddd, *J* 14.5, 8 and 8, H of CH_2), 2.07 (3 H, s, Me), 2.04 (3 H, s, Me) and 1.56 (1 H, ddd, *J* 14.5, 4 and 4, H of CH_2); δ_C(100 MHz; $CDCl_3$) 170.9 (C=O), 170.7 (C=O), 136.9 (=C), 131.3 (C=), 79.1 (OCH), 67.4 (OCH_2), 43.7 (CH), 33.4 (CH_2), 21.3 (Me) and 20.9 (Me).

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