A General Route to Optically Pure Prostaglandins from a D-Glucose Derivative

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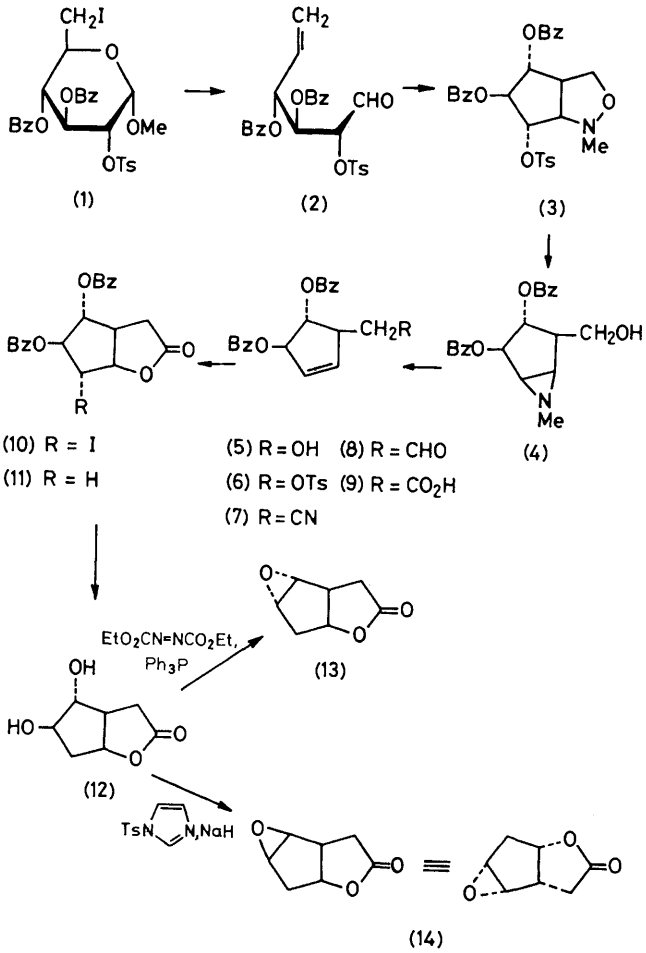
Summary The epoxy-lactone (**14**), which is a key intermediate in one synthetic route to prostaglandins, has been prepared from a readily available D-glucose derivative.

WHEREAS reactions for converting monosaccharide derivatives into functionalised cyclohexanes are well developed,[1] parallel procedures for obtaining cyclopentane analogues are less well known. Several reports of such methods have, however, recently appeared,[2,3] but few of them are simple

and efficient. A notable exception is the method reported by Bernet and Vasella[3] which results in the bonding of C-1 to C-5 of *aldehydo*-5,6-dideoxyhex-5-enose derivatives and the production of bicyclic compounds containing fused cyclopentane–isoxazolidine ring systems. Our interest in functionalised cyclopentanes obtainable from carbohydrates[1] relates to their potential value as precursors of non-carbohydrate natural products (notably prostaglandins) and we here outline the synthesis of the epoxylactone (**14**) from a readily accessible glucose derivative. Prostaglandin $F_2\alpha$ is obtainable from this compound (the synthesis having been effected with the racemic form;[4] the required enantiomer is known[5]), and the approach represents a carbohydrate-into-prostaglandin conversion of general applicability. Stork's synthesis of prostaglandin $F_2\alpha$ from glucose[6] is a major synthetic achievement and a powerful illustration of the transfer of carbohydrate functionality and stereochemistry; however, it is specific. Our objective has been to prepare an optically pure compound which can serve as a precursor of a range of members of the series and their analogues.



SCHEME

Bz = PhCO–, Ts = *p*-$MeC_6H_4SO_2$–.

The cyclopentane ring formation was achieved by use of a modification of the method of Bernet and Vasella.[3] Treatment of the methyl 6-deoxy-6-iodo-α-D-glucopyranoside (**1**)[1] with zinc in refluxing ethanol followed by reaction of the resulting aldehyde (**2**), without purification, with *N*-methylhydroxylamine hydrochloride in ethanol–pyridine (5:2, 45 °C), gave the isoxazolidine (**3**) (73%, m.p. 129—131 °C, $[\alpha]_D$ −53° in $CHCl_3$) which was readily isolated. Not only, therefore, can these procedures be applied with 6-bromohexoside derivatives containing base-stable protecting groups,[3] but they can be used with iodo-analogues containing benzoyl and toluene-*p*-sulphonyl ester functions.

Reduction of the product (**3**) with hydrogen over Raney nickel at atmospheric pressure caused not just the expected reductive opening of the heterocyclic ring[3] but also intramolecular displacement of the sulphonyloxy-group,[7] and the product was the aziridine (**4**) (74%, m.p. 116—118 °C, $[\alpha]_D$ −117° in $CHCl_3$). Conversion of this into the syrupy alkene (**5**) (83% after chromatography, $[\alpha]_D$ −185° in $CHCl_3$) was effected by treatment with *m*-chloroperbenzoic acid in dichloromethane at room temperature,[8] and the side chain was then elaborated to an acetic acid substituent. Standard esterification gave the toluene-*p*-sulphonate (**6**) (94%, m.p. 99—100 °C, $[\alpha]_D$ −115° in $CHCl_3$); treatment with sodium cyanide in dimethyl sulphoxide produced the nitrile (**7**) (80% after chromatography, $[\alpha]_D$ −110° in $CHCl_3$). The aldehyde (**8**) (78%, $[\alpha]_D$ −180° in $CHCl_3$) was obtained by way of its 1,2-di-(*N*-phenylamino)ethane derivative by reduction of the nitrile with Raney nickel and sodium hypophosphite in the presence of the diamine;[9] mild acid hydrolysis and its oxidation with pyridinium dichromate in *NN*-dimethylformamide[10] gave the acid (**9**) (85%).

Iodolactonisation[11] of the unpurified acid (**9**) afforded the bicyclic compound (**10**) (84%, m.p. 162—164 °C, $[\alpha]_D$ + 11° in $CHCl_3$), the structure and absolute configuration of which were confirmed by single crystal *X*-ray diffraction analysis. Reduction with tributyltin hydride in benzene[12] afforded the deiodinated diester (**11**) (88%, m.p. 108—110 °C, $[\alpha]_D$ −98° in $CHCl_3$) from which the diol (**12**) (84%, m.p. 110—111 °C, $[\alpha]_D$ −14° in MeOH) was obtained by use of potassium carbonate in methanol.

Diethyl azodicarboxylate–triphenylphosphine (which together preferentially activate sterically accessible hydroxy-groups)[13] were applied to the diol (**12**) in the hope that the required *endo*-epoxide (**14**) would be obtained. Instead, they gave the isomeric product (**13**) (m.p. 68—70 °C, $[\alpha]_D$ +69° in $CHCl_3$) exclusively, conceivably because the triphenylphosphonium intermediate formed from the *endo*-hydroxy-group was stabilised by co-ordination with the lactone ring oxygen atoms. Treated with toluene-*p*-sulphonylimidazole and sodium hydride in *NN*-dimethylformamide[14] at 0 °C, the diol (**12**) gave the required epoxide (**14**), also exclusively. Its ^1H n.m.r. spectrum (80 MHz) was identical to that of an authentic sample, and its melting point was not depressed on admixture (m.p. 76—77 °C, $[\alpha]_D$ −108° in $CHCl_3$; lit.[5] m.p. 76—77 °C, $[\alpha]_D$ −115° in $CHCl_3$).

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