Stereospecific Introduction of an Asymmetric Centre at C-6 in a Glycoside

Deborah Nicoll-Griffith and Larry Weiler*

Department of Chemistry, University of British Columbia, Vancouver, B.C., Canada V6T 1Y6

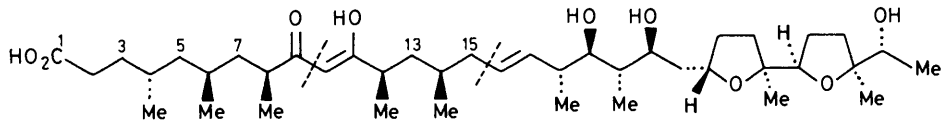
Stereospecific addition of $Me_2Cu(CN)Li_2$ to a bicyclic conjugated lactone, derived from D-glucose *via* an intramolecular Wadsworth–Emmons reaction, affords a rational route to introduce a chiral centre at C-6 on the glucose skeleton.

For the past decade or so carbohydrates have been used extensively as chiral precursors in the synthesis of a variety of natural products.[1] In an effort directed at the synthesis of the antibiotic ionomycin (**1**)[2] we considered a route to the left-hand side of the molecule using glucose as the starting material. We have reported a synthesis of the dimethyl derivative (**2**) from D-glucose,[3] and it was felt that (**2**) would serve as a useful precursor for C-1 to C-15 of ionomycin, providing there was an effective method to control the chirality at C-4 in the ionomycin precursor. This corresponds to controlling the stereochemistry in the introduction of an asymmetric centre at C-6 on the glucose skeleton.

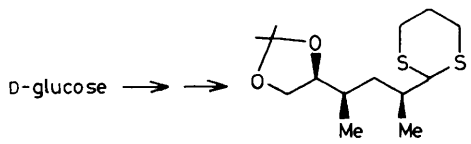
Attempts to use the asymmetric centres in the ring to induce chirality in a side-chain exocyclic to the pyranose are rare[4] and unpredictable,[5] however C-6 can be incorporated into a second ring and the rigidity of the bicyclic system can be used to introduce a new asymmetric centre at this carbon.[6†]

We chose to form a lactone bridge between C-6 and the C-4 hydroxy group in a glucose derivative. The model compound for these studies was the alcohol (**3**) which was prepared by tritylation of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside.[7] The free alcohol was acylated with bromoacetyl bromide to give the C-4 bromoacetate which was heated with triethyl phosphite to yield the phosphonoacetate (**4**). The trityl (Tr) ether was cleaved by catalytic hydrogenolysis, and the C-6

† An elegant route to give the opposite stereochemistry to that desired in ionomycin has been developed in a synthesis of maytansinol: M. Isobe, M. Kitamura, and T. Goto, *J. Am. Chem. Soc.*, 1982, **104**, 4997.



(1)



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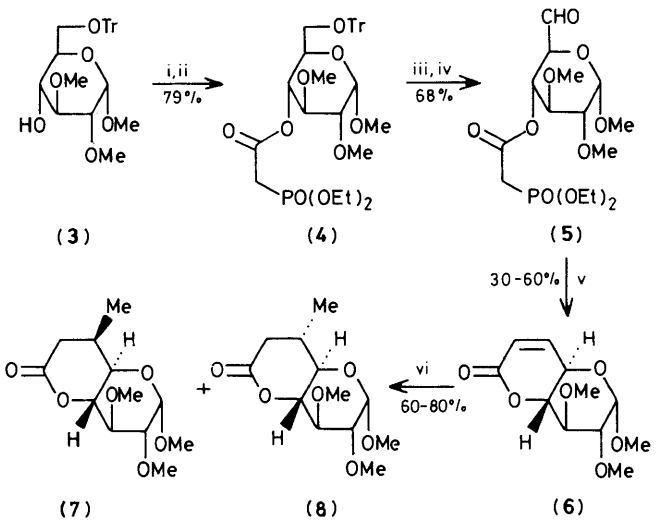
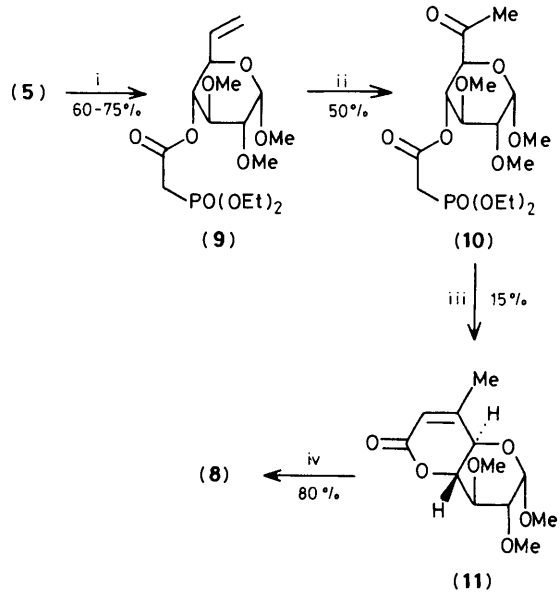


Scheme 1. i, $BrCH_2COBr$, 4-*N*,*N*-dimethylaminopyridine, pyridine, tetrahydrofuran (THF); ii, $(EtO)_3P$, heat; iii, H_2, Pd–C, MeOH; iv, Me_2SO, dicyclohexylcarbodi-imide, $CHCl_2CO_2H$; v, NaH, THF, heat; vi, $Me_2Cu(CN)Li_2$, Et_2O, −78 to −40 °C.



Scheme 2. i, $TiCl_4$, CH_2Br_2, Zn; ii, $Hg(OAc)_2$, Me_2CO–H_2O then H_2CrO_4; iii, NaH, THF, heat; iv, H_2, PtO_2, MeOH.

alcohol was oxidized using the Moffat conditions to give the aldehyde (**5**). Cyclization with base afforded the α,β-unsaturated lactone (**6**) which could be obtained in *ca.* 40% yield from (**4**) after removal of the salts by a Sephadex filtration. This is one of the first syntheses of a bicyclic unsaturated uronolactone.[8] At low temperature the mixed cyanocuprate, $Me_2Cu(CN)Li_2$[9] added to (**6**) to give the conjugate addition product in 60—80% yield (Scheme 1). The ratio of the axial product (**7**) to equatorial product (**8**) was 13 : 1 under the best conditions. The structure of the major isomer (**7**) was proven by n.m.r. spectroscopy, in particular by a difference nuclear Overhauser experiment.‡ Irradiation of the C-4 methine [δ 4.05 (dd, *J* 9, 10 Hz)] produced significant enhancements only in the signals of the C-2 methine (δ 3.20) and the C-6 methyl group (δ 1.07). Thus the C-6 methyl must be *cisoid* to the protons at C-4 and C-2.

‡ We are very grateful to M. Bernstein and L. D. Hall for this experiment.

We were not able to obtain sufficient quantities of the C-6 epimer (**8**) produced in the above reaction to be able to identify it. However, this compound can be prepared in the following manner. Treatment of the aldehyde (**5**) with the titanium methylene complex[10] gave the alkene (**9**) in reasonable yield (Scheme 2). The alkene was oxymercurated and oxidized to the ketone (**10**) which was cyclized to the β-methyl lactone (**11**). Catalytic reduction of the double bond in (**11**) was stereoselective and gave the equatorial isomer (**8**) which was easily differentiated from the axial compound (**7**) by n.m.r. spectroscopy and by capillary g.c.

This model study demonstrates that organocuprate addition to the conjugated lactone (**6**), yields the major axial product (**7**), with precisely the stereochemistry we require for an ionomycin precursor. Furthermore, these reactions constitute a method to introduce an asymmetric centre stereospecifically at C-6 on a glucose derivative in a rational and predictable manner.

We are grateful to the Natural Sciences and Engineering

Research Council for financial support and for the award of a postgraduate scholarship to D. N.-G.

Received, 27th February 1984; Com. 254

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