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# 1,6-ANHYDROGLUCOSE IN ORGANIC SYNTHESIS; PREPARATION OF FRAGMENTS SUITABLE FOR NATURAL PRODUCT SYNTHESIS

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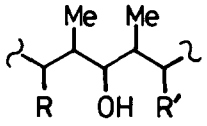
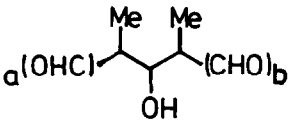
*SUMMARY: 1,6-Anhydroglucose has been used for the stereocontrolled preparation of optically active units which should be suitable for the synthesis of propionate-derived natural products.*

The convergent total synthesis of optically active compounds possessing a number of chiral centres requires fragments with the correct relative and absolute configuration, together with functionality which allows them to be incorporated into the synthetic schemes. Ideally such fragments should be readily available from an enantiomerically pure starting material by a stereocontrolled route which allows for the unambiguous determination of their relative and absolute configuration.

The sequence (1) can be identified in the structures of several biologically active natural products including tirandamycin,[1] monensin,[2] rifamycins[3] and erythromycin A.[4]




(1)




(2)

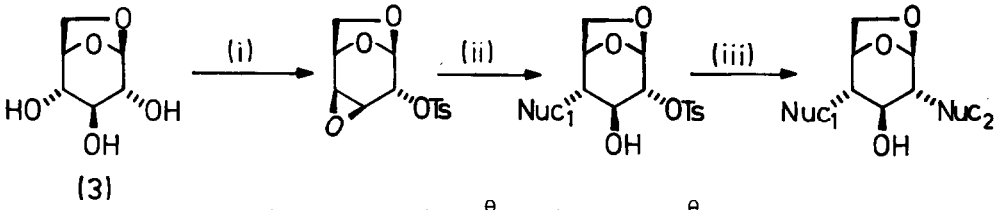
$_a$(OHC) and (CHO)$_b$ = differentiated "masked aldehyde" groups.

Consequently the preparation of fragments equivalent to (2), with defined relative and absolute configuration is of considerable synthetic interest,[5] and this letter outlines the preparation of two such synthetic equivalents.

Our approach which is outlined below starts from 1,6-anhydroglucose (3) which is readily available either by pyrolysis of starch or by the hydrolysis of β-phenylglucoside.[6]

1,6-Anhydroglucose has found widespread use in carbohydrate synthesis,[7] and has been used recently in a number of target orientated total syntheses.[8] The synthetic potential of 1,6-anhydroglucose derives largely from the facile differentiation of the three axial hydroxyl groups, via the formation of the 3,4-epoxy-tosylate (4).[9] The epoxide group of (4) is opened trans-diaxially by a range of nucleophiles[7] including organometallic reagents.[8] Subsequent formation of the 2,3-epoxide followed by a second trans-diaxial opening allows the stereo-controlled introduction of two groups in a straightforward manner, as outlined in Scheme 1.

Scheme 1

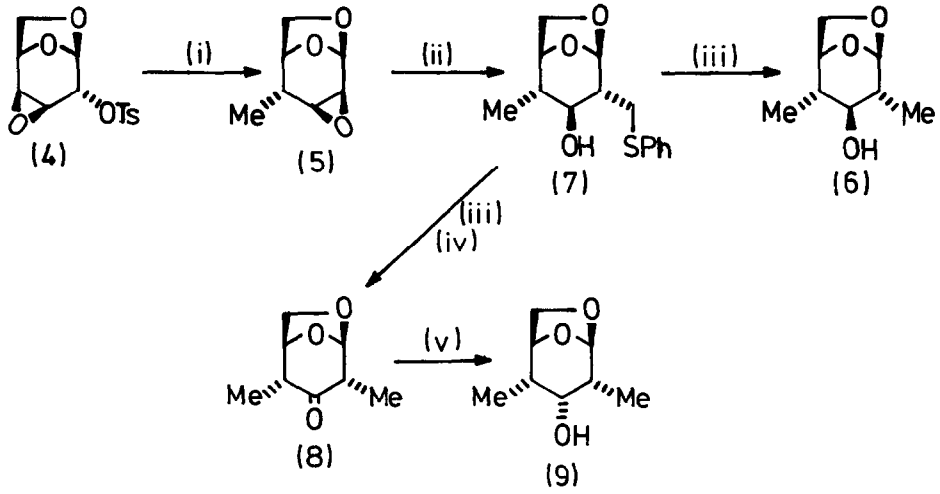



i) Ref. 9: ii) $Nuc_1^{\ominus}$: iii) Base; $Nuc_2^{\ominus}$.

The preparation of fragments corresponding to (2) according to Scheme 1 requires the introduction of two methyl groups. In principle this could be achieved in one pot, given that the intermediate alkoxide from the first opening would close to the epoxide (5), and that this epoxide would open under the prevailing reaction conditions. We were unable to achieve this one-pot conversion of (4) into (6) in acceptable yield, the best conditions which we encountered (MeMgCl, THF, CuBr (cat.), RT → reflux) gave only 7% of the desired dimethyl-alcohol (6) after extensive chromatography. The reason for this probably lies in the reluctance of the epoxide (5) to open cleanly with carbon nucleophiles, as discussed below.

The initial opening of the epoxy-tosylate (4) and closure to the methyl-epoxide (5) was straightforward, using a modification of Ley's conditions.[8b] However, opening the resulting methyl-epoxide (5) with organometallic reagents proved to be much more difficult. The only reagent which we found to open (5) reproducibly in good yield was the lithium anion of thioanisole[10] as shown in Scheme 2. The reduction of the thiomethyl group in (7) was best carried out with sodium in liquid ammonia, and gave a good yield of the desired dimethyl-alcohol (6). Inversion of stereochemistry at C-3 could be achieved cleanly by conversion to

Scheme 2




(i) MeMgCl, CuBr (cat.), 74%; NaOMe, 78%: (ii) $PhSCH_2Li$, 74%: (iii) $Na/NH_3$, 95%: (iv) PDC, 76%: (v) $NaBH_4$, $Pr^iOH$, THF, 77%.

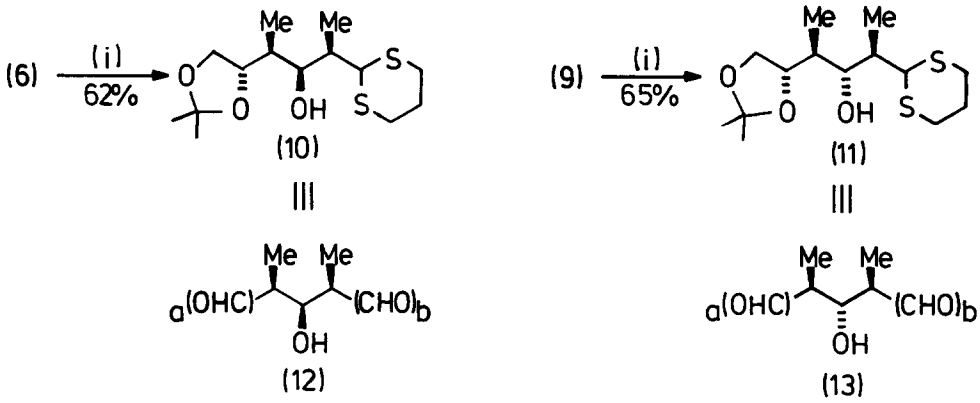
the corresponding ketone (8) followed by borohydride reduction in THF/isopropanol, to give the isomeric dimethyl-alcohol (9) with high stereoselectivity ( >9:1), after reduction of the thiomethyl group.

The isomeric dimethyl-alcohols (6) and (9) were converted into their acyclic equivalents (10) and (11) by treatment with propane-1,3-dithiol/$BF_3$, followed by formation of the 5,6-acetonides as shown below. The fragments (10) and (11) represent synthetic equivalents for the stereoisomers (12) and (13) of the generalised fragment (2). Fragment (10) represents the C-3 to C-7 sequence of monensin, and fragment (11) represents the C-21 to C-25 sequence of rifamycin A, the C-7 to C-11 sequence of triandamycin and the C-1 to C-5 sequence of erythronolide A.

In conclusion, we have developed a direct, stereocontrolled, enantiospecific preparation of synthetic equivalents of the fragments (16) and (17), from a common precursor which are suitable for incorporation into a number of synthetic schemes, and we are currently investigating the total synthesis of certain natural products using methodology outlined here.

We thank Professor S.V. Ley and Dr. A.H. Davidson for useful discussions and the S.E.R.C. for a postgraduate research assistantship (to P.J.H.).

Scheme 3




(i) $HS(CH_2)_3SH$, $BF_3.OEt_2$; $(MeO)_2CMe_2$, TsOH

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