A Simple, Stereocontrolled Synthesis of a Thromboxane B_2 Synthon

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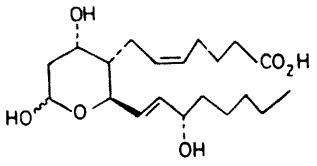
Summary A short stereocontrolled synthesis of a key intermediate in thromboxane B_2 synthesis has been accomplished starting from the carbohydrate laevoglucosan

IN recent years an impressive number of natural products have been synthesised from carbohydrate precursors [1] We report a simple, carbohydrate-based synthesis of the key intermediate (**11**) which has been used previously in thromboxane B_2 syntheses [2,3]

The starting material, laevoglucosan (1,6-anhydro-β-D-glucopyranose) (**2**), is readily available from a wide variety of carbohydrate sources, for example, by controlled pyrolysis of starch [4] This compound has several advantages including cost, absolute configuration, and chemical reactivity arising from its rigid bicyclic framework and the three axial hydroxy groups In the first step, laevoglucosan was converted into the known epoxy-tosylate (**3**)[5] which, on treatment with allylmagnesium chloride in the presence of a catalytic amount of cuprous iodide[6] [inverse addition, 6 equiv CH_2=$CHCH_2MgCl$, 0 1 equiv CuI, dry tetrahydrofuran (THF), 0 °C, 20 h], gave the allyl derivative (**4**),† m p. 65—67 °C, $[\alpha]_D^{25} = -58°$ (*c*, 0·9, $CHCl_3$), in 88% yield There is ample literature precedent for the stereo- and regiospecific opening of this epoxide [4] Treatment of (**4**) with lithium triethylborohydride[7] (3 equiv $LiEt_3BH$, dry THF,

† All new compounds had satisfactory spectral and analytical data

room temperature, 8 h) followed by tosylation of the resultant alcohol {oil, b p *ca* 85 °C/0·4 mmHg, $[\alpha]_D^{25}$ = −88° (*c*, 0·7, $CHCl_3$)} produced (**5**),† m p 100—100·5 °C, $[\alpha]_D^{25}$ = −70·0° (*c*, 1·0, CH_2Cl_2), in 51% yield



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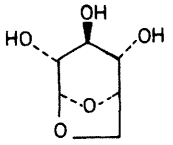

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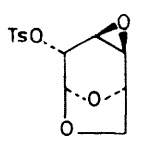

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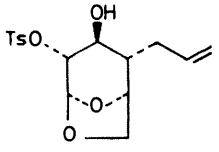

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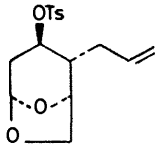

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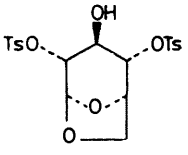

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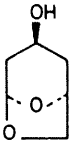

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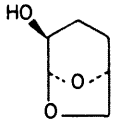

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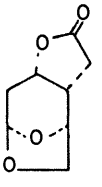

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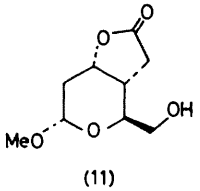

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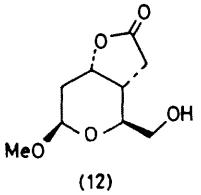

(12)

Ts = *p*-$MeC_6H_4SO_2^-$

Previously we had demonstrated[8] that lithium triethylborohydride reduction of the di-tosylate (**6**) gives a high yield of the two alcohols (**7**) and (**8**) in the ratio of 5·25 : 1 The mechanism of this reaction does not involve direct displacement of the two tosylate groups but proceeds by way of intermediate formation of (**3**) followed by hydride attack at C-4 to produce (**9**) and subsequent hydride attack at C-2 to give predominantly (**7**) In the case of (**4**) the 4α-allyl group serves to make the reduction completely regiospecific such that only the 3β-alcohol is obtained with no trace of the isomeric 2β-alcohol

Oxidation of (**5**) with ruthenium dioxide–excess of sodium metaperiodate in aqueous acetone[9] (room temperature, 2·5 h) gave directly the highly crystalline tricyclic lactone (**10**)† in 80% yield, m p 151—151·5 °C, $[\alpha]_D^{25}$ = −6·4° (*c*, 0·3, CH_2Cl_2) Amberlyst 15 acid resin in methanol proved to be the method of choice for cleavage of the 1,6-anhydro bridge to produce the two known bicyclic lactones (**11**) and (**12**) in 81% yield, in the ratio of 1·55 : 1 The α-(**11**) and β-isomers (**12**) could be readily separated by flash column chromatography on silica gel[10] (Et_2O–MeOH, 9 : 1) to give pure samples of each. Although pure, the α-isomer (**11**) was obtained as an oil‡ $[\alpha]_D^{25}$ = + 92·7° (*c*, 1·53, $CHCl_3$) (lit +86·6°,[2b] +100°,[2c] +85°[2d]) and this proved to be identical to an authentic sample, by i r and n m r spectroscopy as well as t l c mobility In addition, this isomer was converted quantitatively into the *p*-phenylbenzoate derivative, m p 154—155 °C, $[\alpha]_D^{25}$ = +50·3° (*c*, 0·6, $CHCl_3$) (lit ,[2c] m p 149—150 °C, $[\alpha]_D^{20}$ = +48·6°) The β-isomer is a crystalline compound, m p 125—126 °C, $[\alpha]_D^{25}$ = −99° (*c*, 0·42,$CHCl_3$) and has identical i r and n m r spectra to those reported [3a,b] The α-isomer (**11**)[3a,b] and its t-butyldiphenylsilyl derivative[2a] have been converted by standard 'prostaglandin' methodology into thromboxane B_2 and its C-15 epimer Apart from its simplicity, this synthesis offers the additional potential advantage of permitting the stereospecific introduction of other C-4 side chains by organometallic-induced opening of the epoxide (**3**) with subsequent inversion of the C-3 configuration [*e g* , by superoxide displacement of the tosylate group in a derivative of (**5**)]

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‡ Two references (ref 2c, 3b) state that this compound is an oil, while two other references (ref 2b, 2d) give a m p of 101—101·5 and 102—103 °C, respectively

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