The Synthesis of Optically Active Tetrahydropyrans by the Addition of a Stabilised Wittig Reagent to Pyranose Sugars

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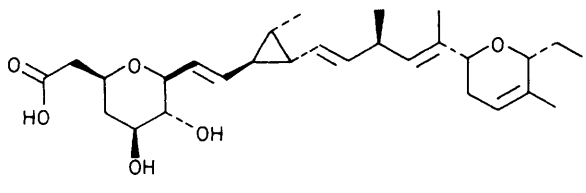
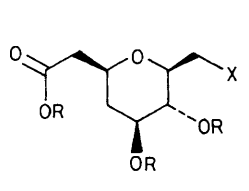
The addition of the phosphonate–sulphone (**8**) to the carbohydrates (**9**) and (**10**) gave the tetrahydropyrans (**11**) and (**12**) as mixtures of α- and β-isomers; treatment of the mixture with sodium hydride gave the pure β-isomers.

Carbohydrates are an extremely valuable source of chiral starting materials for natural product synthesis, especially for compounds containing tetrahydropyran units.[1] One of the main problems to be overcome in the conversion of the pyranose sugars into tetrahydropyrans is the stereoselective introduction of a suitably functionalised carbon atom at C-1. In this communication we describe a high yielding method for carrying out this transformation and one which can lead to either the α- or β-isomer with a good degree of stereoselectivity.

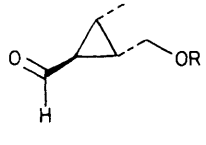
For our work on ambruticin[2] (**1**) we required a method for the conversion of D-glucose into a fragment (**2**) having a group X which could be used to carry out a Wittig type reaction with the cyclopropane (**3**).[3] Since it was known that 4-deoxy derivatives such as (**4**) were readily available from glucose[4] the main problem was the stereoselective introduction of the CH_2X unit at C-1 of the sugar. Although there are several published methods[1,5] for the formation of *C*-glycopyrans from



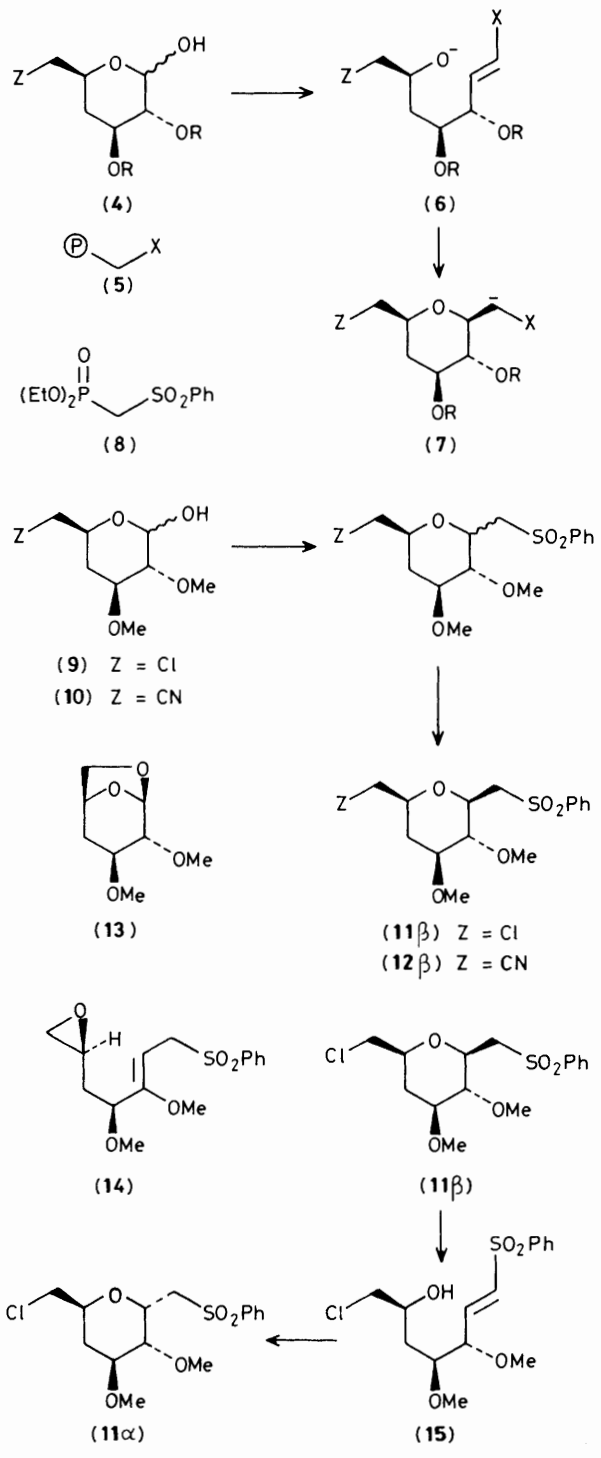
(**1**)

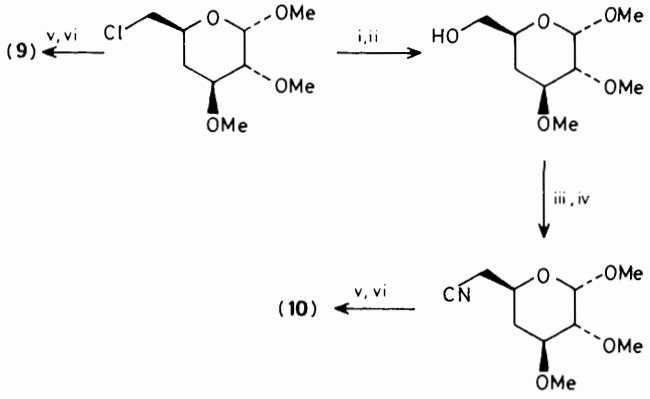


(**2**)



(**3**)





Scheme 1. *Reagents:* i, NaOAc, dimethylformamide (DMF), 130 °C, 48 h, 84%; ii, KOH, MeOH, 20 °C, 3 h, 90%; iii, $MeSO_2Cl$, pyridine, 20 °C, 90%; iv, NaCN, NaI, DMF, 80 °C, 24 h, 80%; v, Ac_2O, H_2SO_4 (catalytic), 20 °C, 2 h, 95%; vi, aqueous CF_3CO_2H, 70 °C, 25 min, 75%.

sugars none of them seemed particularly well suited to our requirements. One possible approach involved the addition of a Wittig reagent (**5**) to generate the intermediate (**6**) which should ring-close to give the anion (**7**) which could be used in the coupling reaction. Hence the functional group X would not only be used to introduce the new carbon atom but also to carry out the coupling reaction.

After several attempts using different Wittig reagents we found that the best results were obtained using the sodium anion of the phosphonate–sulphone (**8**).[6] The anion (1 equiv.) added to the lactols (**9**) and (**10**) to give the tetrahydropyrans† (**11**) and (**12**), as mixtures of α- and β-isomers‡ (ratio α:β 3:2), in good yield [60% for (**11α,β**), 76% for (**12α,β**)]. Use of excess of phosphonate–sulphone (**8**) led to a decrease in yield and in the case of the chloro-compound (**9**) increased amounts of the anhydro-sugar (**13**). The stereochemical assignments were made on the basis of the n.m.r. signal for the proton at C-2. In the β-isomers it appears as a triplet at δ 2.9, *J* 9 Hz, which indicates that the two protons at C-2 and C-1 are in the axial position. These assignments were confirmed when it was shown that the mixture of isomers could be converted into the β-isomer (β:α > 10:1) by treatment with sodium hydride (0.4 equiv.) in tetrahydrofuran (THF) overnight [76% for (**11β**), 72% for (**12β**)]. In the case of the chloro-compound (**11**) a small amount (~10%) of the epoxide (**14**) was obtained under the epimerisation conditions.

We have also shown that for compound (**11β**) the α-isomer could be obtained *via* the following sequence of reactions: (i) treatment with n-butyl-lithium at −78 °C followed by quenching with acetic acid to give the ring-opened material (**15**); (ii) treatment of (**15**) with sodium hydride (1 equiv.) at 0 °C for 10 min, which gave mainly the α-isomer [α:β, 4:1; yield from (**11β**), 75%].

The lactols (**9**) and (**10**) were made from the readily available[4] methyl 6-chloro-4,6-dideoxy-α-D-galacto-pyranoside (Scheme 1). We have also converted the cyanide (**12**) into the ester (**16**) and acid (**17**) as required for the left-hand tetrahydropyran ring of ambruticin.

† All new compounds gave satisfactory elemental analysis. Yields refer to pure isolated material homogeneous by t.l.c. and 360 MHz ^1H n.m.r. spectroscopy.

‡ The α- and β-isomers (**11**) and (**12**) were easily separable by flash column chromatography.

In conclusion we have outlined a method by which a functionalised carbon atom can be introduced stereoselectively into a pyranose sugar. The reactions of the sulphones (**11**), (**12**), and (**16**) and the application of these reactions to the synthesis of ambruticin will be reported elsewhere.

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