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INTRAMOLECULAR 1,3–DIPOLAR ADDITIONS IN 4–O–ALLYL PYRANOSIDE 6–NITRONES: AN APPROACH TO CHIRAL PYRANO–PYRANS AND PYRANO–OXEPANS

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ABSTRACT

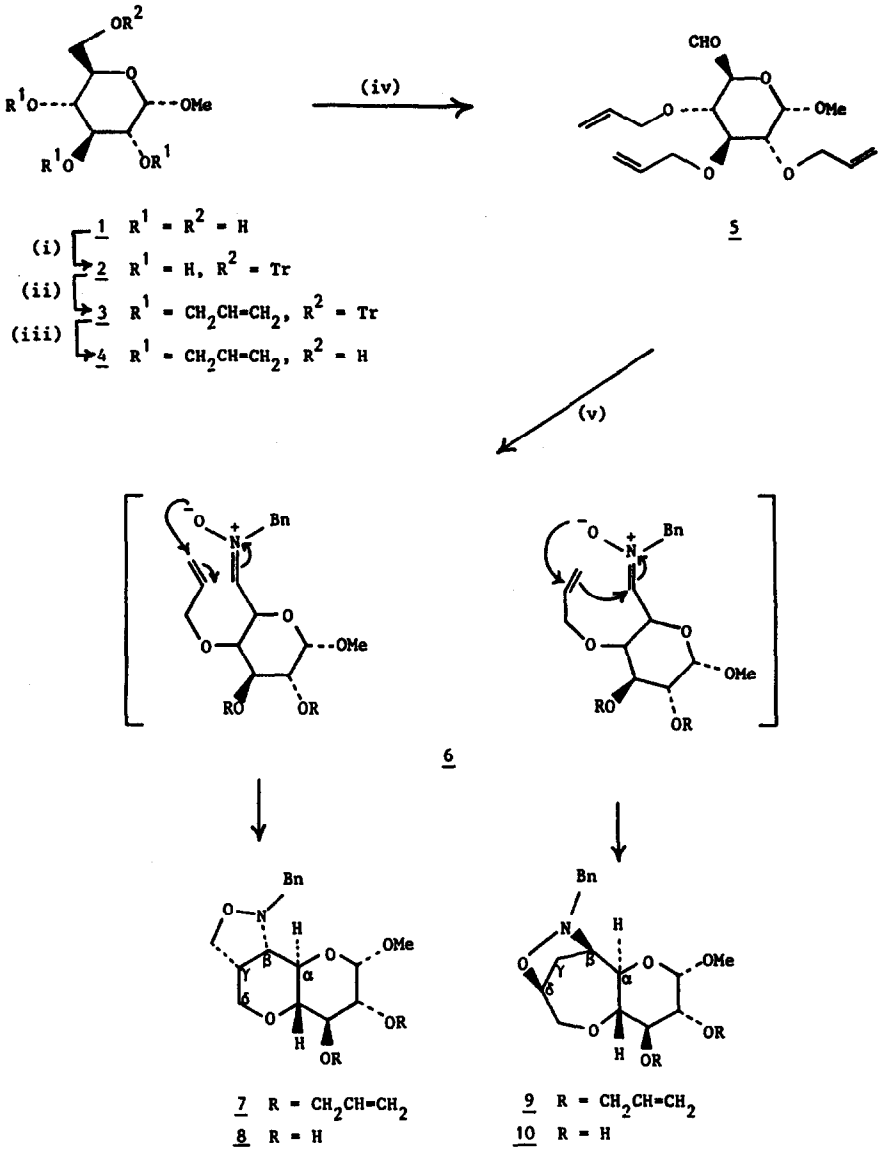
Treatment of the easily prepared 6–aldehydo–glucopyranoside allyl ether (5) with N–benzylhydroxylamine gave nitrone (6), which underwent a 1,3–dipolar addition to the 4–O–allyl group giving after deprotection and hydrogenolysis the chiral pyrano–pyran (11) and the pyrano–oxepan (13).

Pyrano–pyrans and pyrano–oxepans are important targets for chemical synthesis because they are constituents of the marine toxin brevetoxin B[1]. Particularly significant in this area of chemical synthesis is the work of Nicolaou[2] and others[3,4] who have produced derivatives of the fused O–heterocycles which may be readily adapted for further fusion of more ether rings.

In this letter we disclose a new route to such compounds from simple sugar derivatives using 1,3–dipolar intramolecular nitrone additions. Intermolecular versions of this reaction were first applied to sugars by Tronchet[5] to produce furanose isoxazolidines. Vasella[6] and subsequently others[7] developed intramolecular additions with eneose nitrones, to form highly substituted homochiral carbocycles, the chiral centres occurring at "on template" sites[8,9]. Herein we extend the intramolecular reactions with sugar derivatives to create chirality in an erstwhile symmetric "off template"[9] allyl protecting group.

The chemistry envisaged is most readily achieved by inducing a nitrone group situated at the 6–position in an aldehydo–glycopyranoside to add to an allyl ether group at its 4–position [see (7)←(6)→(9) in the Scheme]. 2,3,4–Triallylated pyranoside 6–nitrones are the easiest compounds to obtain which possess the required structural elements, since their preparation requires a minimum number of protection–deprotection steps, as illustrated in the Scheme by the synthesis of the glucose derivative (6).

Thus when the pyranoside aldehyde (5) was treated in ethanol at 20° with *N*–benzylhydroxylamine hydrochloride (1.01 mol equiv) in the presence of triethylamine (1.1 mol equiv) for 15 h. the nitrone (6) which formed, subsequently added to the adjacent allyl group to give a quantitative yield of a material comprising two non–polar compounds (7 and 9) in a ratio of 2:1 respectively (^{1}H–nmr). Deallylation of the mixture during 1h. in boiling aqueous ethanol in the presence of tris(triphenylphosphine) rhodium (1) chloride (0.13 mol equiv) and tosic acid (1.1 mol equiv) gave the fused isoxazolidine diol (8) in crystalline form, m.p. 185–6°, $[\alpha]_D$ + 43.2°(MeOH) in 50% yield. Column chromatography of the mother liquor gave the bridged isoxazolidine diol (10) $[\alpha]_D$ + 129.5° (MeOH), in 26% yield.



1 $R^1 = R^2 = H$

2 $R^1 = H$, $R^2 = Tr$

3 $R^1 = CH_2CH{=}CH_2$, $R^2 = Tr$

4 $R^1 = CH_2CH{=}CH_2$, $R^2 = H$

5

6

7 $R = CH_2CH{=}CH_2$

8 $R = H$

9 $R = CH_2CH{=}CH_2$

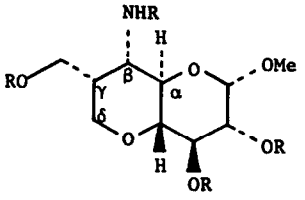
10 $R = H$

Reagents: (i) TrCl, DMAP, NEt_3, DMF; (ii) NaH, DMF, $CH_2{=}CHCH_2Br$; (iii) AcOH, H_2O; (iv) $(COCl)_2$, DMSO, -50°; (v) BnNHOH

SCHEME

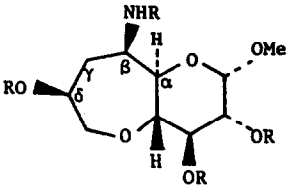
The structures of these compounds were derived from their ^1H– and ^{13}C– nmr spectra. All the proton–proton couplings were determined using ^1H Cosy, 2–D J–resolved spectroscopy, and a variety of proton–proton decoupling experiments. The salient features which distinguished between the two regioisomers (8 and 10) was

the presence, in the spectrum of the major compound, of a high field one proton multiplet at δ_H 3.02 coupled to five other protons and a methine carbon signal at δ_C 42.12 (DEPT), which would be expected for the C–γ methine in the fused structure (8).



11 R = H

12 R = Ac



13 R = H

14 R = Ac

The minor component on the other hand exhibited two high field geminally coupled (12.5 Hz) proton signals at δ_H 2.42 (dt) and 2.18 (d) and a methylene carbon signal at δ_C 30.66 (DEPT), which would be expected for the C–γ methylene in the bridged structure (10).

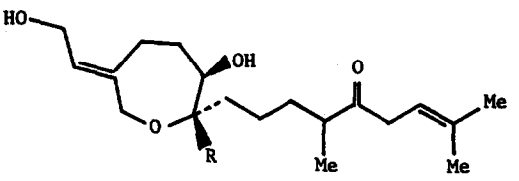
The stereochemistry at the junction of the isoxazolidine and the oxepan rings in the compound (10) was ascertained from vicinal proton couplings and nOe experiments. For compound (8) the stereochemistry at the isoxazolidine and oxane ring junctions was most reliably determined from the relevant vicinal couplings observed for the acetylated reduced compound (12).

Removal of the *N*–benzyl protecting groups and cleavage of the N–O bonds in compounds (8 and 10) was accomplished by palladium catalysed hydrogen transfer from cyclohexene in refluxing ethanol. The amino–alcohols (11 and 13) so obtained were characterized as their tetra–acetyl derivatives (12 and 14). The vicinal couplings of 12.0, 4.0, 2.0 and 1.0 Hz respectively for $J_{\alpha\beta}$, $J_{\beta\gamma}$, $J_{\gamma\delta a}$ and $J_{\gamma\delta e}$ clearly define the stereochemistry in (12) and consequently in (7).

Contrary to expectations based on mechanistic predictions[10] a solvent effect on the isomer distribution in the cycloaddition was observed when the ethanol solvent was replaced by 2,2,2–trifluoroethanol. Under these conditions the fused and bridged isoxazolidenes (7 and 9) were formed in almost equal amounts.

Thus this intramolecular nitrone cycloaddition offers a route to oxygen heterocycles of common occurrence in nature. The highly functionalized chiral pyranopyran (11) and pyrano–oxepan (13) may both be converted by subsequent deamination and partial deoxygenation into compounds that are quite closely related to rings in brevetoxin B. Furthermore functional group manipulations are conceivable that will enable fusion of additional pyran rings to be carried out[4].

The pyranoside rings in (11) and (13) may be readily opened and their carbon chain easily degraded. Consequently they are useful chiral synthons[8] for natural products that possess only one oxygen heterocycle. For example, the synthesis , from (13), of 2–*nor*–zoapatanol (16), which is related to the fertility regulator (15)[11] is feasible because the stereochemistry in (13) is compatible with the chiral centres 2 and 3, in the target molecule (16).



15 R = H

16 R = Me

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†. All new compounds had the correct elemental composition, as determined by ms and/or combustion analysis, and gave clean, interpretable ^{13}C– and ^{1}H– nmr spectra.

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