Intramolecular 1,3-Dipolar Cycloaddition of a Nitrone Derived from 3-*O*-Allyl-D-(+)-glucose: an Expedient Synthesis of a Chiral Oxepane Derivative

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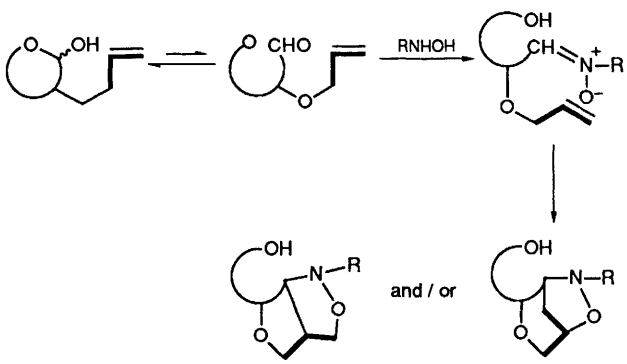
The intramolecular 1,3-dipolar cycloaddition of the *N*-benzylnitrone of 3-*O*-allyl-D-(+)-glucose yielded a chiral oxepane derivative **2**, potentially useful for the synthesis of other chiral systems.

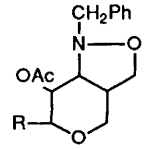
The intramolecular 1,3-dipolar cycloaddition involving unsaturated nitrones has shown its potential as a powerful synthetic method.[1] This facile reaction is all the more useful in view of its operational simplicity. The application of such a reaction to a carbohydrate derivative is expected to provide an easy access to useful chiral systems. This cycloaddition reaction has indeed been applied to degraded sugar derivatives for the synthesis of chiral carbocycles.[2,3] We envisaged that a nitrone formed from a sugar might undergo an intramolecular 1,3-dipolar cycloaddition to the alkenic bond of an *O*-allyl residue in the sugar molecule thus providing a novel strategy for the synthesis of chiral oxygen heterocycles (Scheme 1).

Thus, heating a solution of 3-*O*-allyl-D-(+)-glucose **1**† in ethanol with *N*-benzylhydroxylamine followed by acetylation of the crude product gave rise to a compound (55–60% yield) (in addition to the tetraacetate of **1**), which appeared to be a cyclised derivative (Scheme 2) from spectral studies (mass, IR, ^{1}H NMR and ^{13}C NMR).‡ However, it was not possible from the spectral data alone to distinguish rigorously between the two alternative regioisomeric structures, *viz.* isoxazolidines **2** and **3**, or to establish the stereochemistry at the chiral centres, although the occurrence of a triplet at δ 27.7 in the ^{13}C



Scheme 1

1 **2**



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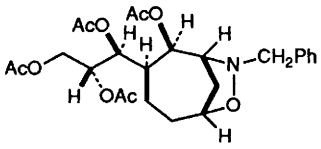
R = –CH(OAc)–CH(OAc)–CH$_2$OAc

Scheme 2 *Reagents*: PhCH$_2$NHOH, then Ac$_2$O–pyridine

† The sugar **1** was synthesized by treatment of 1,2:5,6-di-*O*-cyclohexylidene-α-D-(+)-glucofuranose with allyl bromide and sodium hydride, followed by hydrolysis with 0.125 mol dm^{-3} sulphuric acid.

‡ For **4**: m.p. 165–166 °C; $[\alpha]_D^{25}$ +108° (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.04 (s, 3H), 2.08 (s, 3H), 2.12 (s, 3H), 2.18 (s, 3H), 2.22 (m, 1H), 2.60 (d, *J* 12 Hz, 1H), 3.58 (d, *J* 12 Hz, 1H), 3.64–3.82 (m, 2H), 3.88 (d, *J* 13 Hz, 1H), 4.02 (d, *J* 13 Hz, 1H), 4.12 (d, *J* 8 Hz, 1H), 4.22 (dd, *J* 12, 6 Hz, 1H), 4.36 (dd, *J* 12, 4 Hz, 1H), 4.58–4.68 (m, 1H), 5.02–5.16 (m, 2H), 5.36–5.44 (m, 1H) and 7.38 (br. s, 5H); ^{13}C NMR ($CDCl_3$): δ 20.6 (q), 20.9 (q), 27.7 (t), 61.0 (t), 62.7 (t), 63.1 (d), 69.5 (d), 71.8 (d), 72.4 (d), 73.1 (t), 74.8 (d), 78.8 (d), 127.5 (d), 128.3 (d), 128.8 (d), 136.7 (s), 169.6 (s), 169.8 (s), 170.3 (s) and 170.5 (s).



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NMR spectrum and a pair of signals at δ 2.22 and 2.60 in the ^{1}H NMR spectrum indicated the presence of a –C–CH_2–C– moiety as in **2**. An X-ray crystallographic analysis of this derivative established the complete structure and stereochemistry to be as represented by **4**.§

Whether the isoxazolidine **4** was the exclusive product of the reaction could not be settled since a minor compound present in the reaction mixture is yet to be characterised. However, the preponderant formation of the bridged isoxazolidine **4** is rather striking, because intramolecular nitrone cycloadditions involving *O*-allyl residues generally lead to fused isoxazolidines as the major isomers.[1] The factors responsible for this reversal of regioselectivity in this case cannot be ascertained at present. The possible role of the hydroxy group adjacent to the nitrone functionality in controlling the regioselectivity is under investigation.

The result of this simple reaction is of special practical significance. The chiral isoxazolidine **4** is basically a 3,5-disubstituted oxepane derivative. Because of the known[4] facile cleavage of the N–O bond and the presence of modifiable functionalities, **4** represents a potential starting material for a number of oxepane derivatives including the oxepane diterpenoids zoapatanol[5] and montanol.[5] The ready availability of different *O*-allyl sugars and simplicity of the reaction makes this novel study a starting point for the synthesis of useful oxygen heterocycles. The generality and utility of the reaction are currently under investigation.

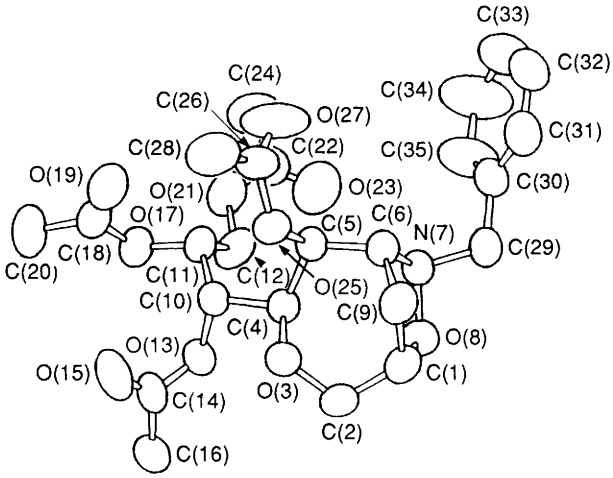

Fig. 1 ORTEP diagram showing the structure and solid-state conformation of compound **4**; hydrogen atoms have been omitted for clarity

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§ *Crystal data*: $C_{24}H_{31}NO_{10}$, M = 493.52, monoclinic, space group $P2_1$, a = 12.571(1), b = 9.025(1), c = 11.390(1) Å, β = 90.14° (from 25 orientation reflections, 41° < θ < 48°, U = 1292.2(4) Å^3, Z = 2, D_c = 1.268 g cm^{-3}, μ(Cu-Kα radiation, λ = 1.5418 Å) = 8.0 cm^{-1}; crystal size: 0.20 × 0.30 × 0.50 mm. Intensity data (+h, +k, +l, θ_{max} = 75°, 2967 reflections) were recorded on an Enraf–Nonius CAD-4 diffractometer (Cu-Kα radiation, graphite monochromator, ω–2θ scans). The structure was solved by direct methods (MULTAN11/82). Full-matrix least-squares refinement [$\Sigma w\Delta^2$ minimized; $w = 1/\sigma^2(|F_o|)$, $\Delta = (|F_o| - |F_c|)$] of atomic parameters (anisotropic C, O; fixed H contributions) converged at R = 0.048 (R_w = 0.071) over 2201 reflections with $I > 3.0\ \sigma(I)$. Crystallographic calculations were performed on PDP11/44 and MicroVAX computers by use of the Enraf–Nonius Structure Determination Package. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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