Stereoselectivity of Intramolecular Cyclisations of Nitrones Derived from 3-Oxahept-6-enals

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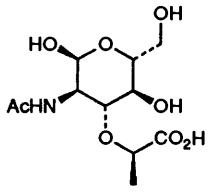
Intramolecular cycloadditions of the nitrones **9** and **14** show moderate to good stereoselections in favour of the *cis*-fused diastereoisomers **10** or **16**, respectively.

Amino sugars occupy a central position in Nature as ubiquitous components of glycoproteins. Of special interest is their association with both immune responses and infection mechanisms; especially prominent in this class are *N*-acetylmuramic acid **1**, a key component of the 'muramyl dipeptide', the minimum structural component of various bacterial cell walls[1] and neuraminic acid **2**, the parent member of the sialic acids,[2] which is often found at the termini of glycoproteins. As a preliminary to synthetic studies towards these classes of amino sugars, we became interested in the prospects of employing intramolecular [1.3]-dipolar cycloadditions[3,4] of nitrones **3**, derived from 3-oxahept-6-enals, to access the bicyclo[4.3.0]nonanes **4**. This approach was especially suited to our initial aim which was the elaboration of relatives of amino sugars which lacked an anomeric hydroxyl function but possessed many of the other key structural and stereochemical features of the natural compounds. Such compounds might be expected to be recognized as amino sugars but then to interfere with processes such as cell-wall assembly, for which the presence of the anomeric hydroxyl group should not be important, in similar fashion to the biological effects displayed by, for example, azasugars such as castanospermine[5] or *C*-nucleosides.[6]



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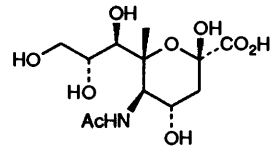

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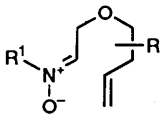

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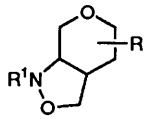

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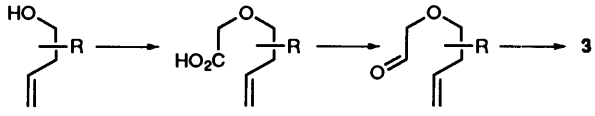
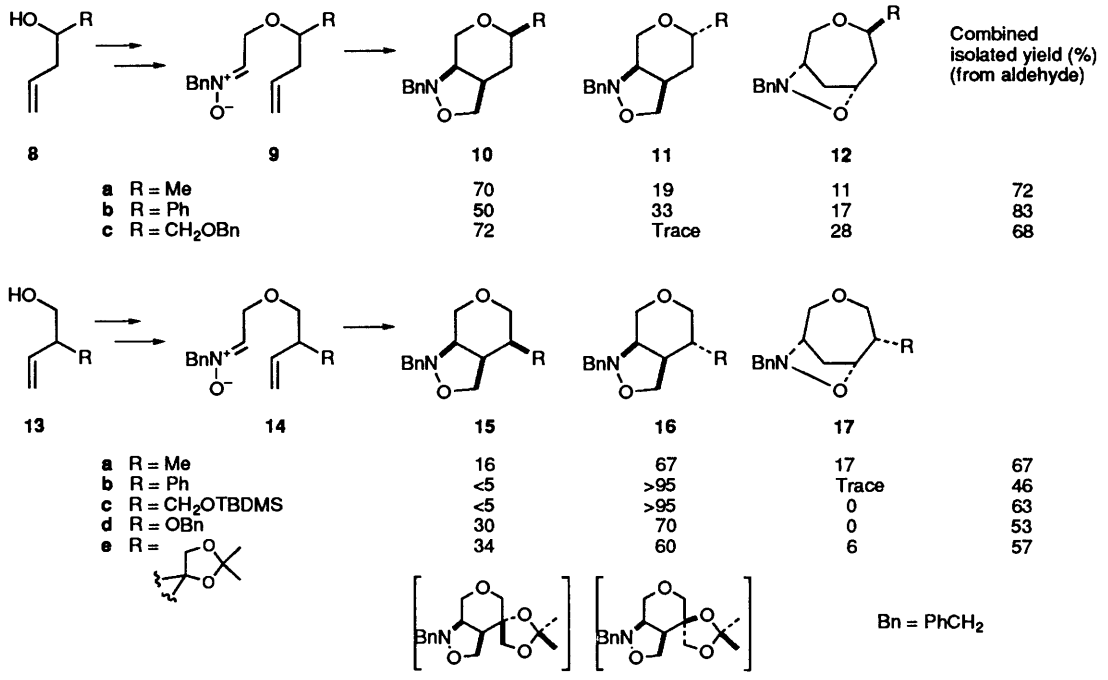
For our studies, we required a series of representative homoallylic alcohols **5**. These were then converted into the required nitrones **3** by *O*-alkylation to give the 3-oxa carboxylic acids **6**. This was best achieved by deprotonation (NaH or BuLi in THF) followed by reflux for 2 h with sodium iodoacetate; isolated yields were generally ~ 90%. The corresponding bromo acid or esters usually gave inferior yields. Conversion into the corresponding methyl esters was then followed by reduction to the aldehydes **7** using Dibal-H (hexane, −78 °C, ~ 2 h). As an alternative, reduction to the corresponding alcohols ($LiAlH_4$, ether, 20 °C) followed by oxidation (Swern[7] or TPAP[8]) also gave acceptable yields of the required aldehydes. However prepared, these were immediately transformed into the nitrones **9** and **14** which were then heated in toluene (60–80 °C; 10–21 h) until TLC indicated complete consumption of the starting material. The homoallylic alcohols **8a** and **8b** were obtained from the appropriate aldehyde and allylmagnesium chloride while the alcohol **8c** was prepared from glycidyl tosylate by sequential reactions with sodium benzyl oxide (THF, 65 °C, 1 h) and vinylmagnesium bromide–CuI.[9] The alcohol **13a** is commercially available; the phenyl analogue **13b** was obtained in one step from styrene oxide and vinylmagnesium bromide. The silyloxymethyl derivative **13c** was prepared from (*Z*)-butene-1,4-diol by monosilylation and alkylation of the remaining free hydroxyl with iodomethyltributylstannane; subsequent tin-lithium exchange and [2.3]-sigmatropic rearrangement[10] gave the alkoxide of the alcohol **13c** which was alkylated directly using sodium iodoacetate to give the required acid (*cf.* **6**). The benzyloxy derivative **13d** was prepared from but-3-ene-1,2-diol[11] by silylation of the primary hydroxyl, benzylation of the secondary hydroxyl and removal of the silicon group. Finally, the dioxolane derivative **13e** was obtained from 1,3-dioxolane-4-carboxylic acid.[12] Esterification (Me_2SO_4, K_2CO_3, Me_2CO, 65 °C, 4 h), enolisation (LDA, −78 °C, THF), condensation with phenylselenoacetaldehyde and elimination[13] then gave the desired 4-vinyl derivative which was reduced ($LiAlH_4$, Et_2O) to the alcohol **13e**.



5 **6** **7**

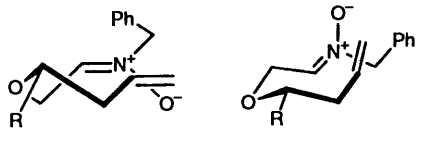
The results of the [1.3]-dipolar cyclisations of the nitrones **9** and **14** are presented in Table 1. The structures of the separated diastereoisomers were determined largely from NMR data. The bicyclo[4.2.1]nonanes **12** and **17**, if formed, were easily identified by ^{13}C NMR spectra. The 4-substituted isomers **12** showed two characteristic lowfield methylene resonances at ~ 32 and 42 ppm together with a highfield methine (> 80 ppm) due to the 6-CH(O) group. A similarly highfield methine and a single lowfield methylene distinguished the corresponding 5-substituted products **17** as neither feature would be expected in such spectra of the related isomers **15** and **16**. Similar chemical-shift arguments in the ^1H NMR spectra confirmed these assignments while the stereochemistry is based tentatively upon NOE data. The structures of the major isomers (**10** and **11**; **15** and **16**) were assigned partly on the evidence of ^{13}C NMR data but mainly on the basis of ^1H NMR coupling constant data, after COSY spectra had been

Table 1 Products from intramolecular cycloadditions of the nitrones **9** and **14**



used to assign fully the richly detailed proton resonances. These data were consistent with an approximate chair conformation for the pyran ring; this enabled the assignment of axial or equatorial positions to all the substituent protons or groups and hence allowed the stereochemistries to be deduced (see Experimental section). NOE data was used to confirm these as well as an X-ray crystallographic determination of the minor isomer **11b**.*

The predominant formation of the 'all-*cis*' diastereoisomers **10** from the 4-substituted 3-oxa nitrones **9** suggests conformation **18** is preferred during the cyclisations. ^{1}H NMR data of the nitrones **9** and **14** indicated that these were all single geometric isomers, presumably having a *Z* configuration.[3] The stereoselectivities of the cyclisations are, therefore, largely controlled by an 'equatorial' positioning of the substituent together with a preference for a less eclipsed orientation of the reacting centres (**18**) relative to the alternative, more boat-like conformation **19**. In the 5-substituted examples **14**, the preference for an equatorial positioning of the substituent now on the β-face in a transition state related to **18** leads to a preponderance of the diastereoisomers **16** at the expense of the 'all-*cis*' isomers **15**. Overall, these predictive models appear largely to depend upon the size of the substituents although some of the results suggest that factors other than simple steric features may be involved.



18 **19**

Experimental

(1RS,4RS,6RS)- *and* (1RS,4SR,6RS)-9-*Benzyl*-4-*phenyl*-3,8-*dioxa*-9-*azabicyclo*[4.3.0]*nonane* **10b** *and* **11b** *and* (1RS,4SR,6SR)-8-*Benzyl*-4-*phenyl*-3,7-*dioxa*-8-*azabicyclo*[4.2.1]*nonane* **12b**.—*O*-Benzylhydroxylamine (0.37 g, 3 mmol) was added to an ice-cold, stirred solution of (±)-4-phenyl-3-oxahept-6-enal (0.57 g, 3 mmol) in dry ether (50 cm^3) containing anhydrous magnesium sulfate (1 g). After 1 h, the cooling bath was removed and the mixture stirred for a further 1 h before it was filtered and evaporated to give the crude *nitrone* **9b** (0.87 g, 98%) as a colourless oil, ν_{max}/cm^{-1}(film) 1641 and 1604; δ_H(80 MHz; $CDCl_3$) 2.40 (2 H, m, CH_2CH=), 3.65 (1 H, m, CHPh), 4.25 (2 H, d, *J* 4.3,† CH_2O), 4.78 (2 H, s, CH_2Ph), 4.92 (1 H, d, *J* 10, CH_cH_t=CH), 4.97 (1 H, d, *J* 17, CH_cCH_t=CH), 5.88 (1 H, ddt, *J* 17, 10 and 7, CH=CH_2), 6.73 (1 H, t, *J* 4.3, CH=N) and 7.20–7.40 (10 H, m, 2 × Ph); *m/z* 295 (M^+, 8%), 161 (18), 107 (10), 105 (13), 91 (100) and 77 (7) (Found: M^+, 295.1573. $C_{19}H_{21}NO_2$ requires *M*, 295.1572).

The nitrone **9b** (0.87 g) was heated in toluene at 60 °C for 10 h and the residue after evaporation separated by column chromatography [60 mesh flash silica; light petroleum (b.p. 60–80 °C)–ethyl acetate–triethylamine (6:1:0.1)] to give: (i), the (1RS,4RS,6RS)-*azabicyclo*[4.3.0]*nonane* **10b** (0.33 g, 38%) as a colourless oil, R_f 0.23, ν_{max}/cm^{-1} 914; δ_H(400 MHz; $CDCl_3$), 1.88 (1 H, ddd, *J* 13.3, 6.4 and 2.0, 5-H_{eq}), 2.04 (1 H, br q, *J* ~ 11.7, 5-H_{ax}), 2.86 (1 H, br dq, *J* 11.7 and 6.4, 6-H), 2.87–2.96 (1 H, m, $\omega_{1/2}$ 22 Hz, 1-H), 3.65 (1 H, br d, *J* 7.8, 7-H_A), 3.84 (1 H, dd, *J* 12.9 and 2.3, 2-H_{eq}), 4.02 (1 H, d, *J* 13.3, PhCH_ACH_B), 4.06 (1 H, d, *J* 13.3, PhCH_ACH_B), 4.04–4.14 (2 H, m), 4.33 (1 H, dd, *J* 11.6 and 2.0, 4-H_{ax}) and 7.07–7.46 (10 H, m, 2 × Ph); δ_C(100 MHz) 34.74 (5-CH_2), 41.91 (6-CH), 62.24 (2-CH_2), 62.63 (1-CH), 66.58 (PhCH_2), 71.25 (7-CH_2), 78.27 (4-CH), 126.17, 127.65, 127.75, 128.53, 128.58, 129.63 (all PhCH), 137.00 and 142.55 (both PhC); *m/z* 295 (M^+, 19%), 161 (44), 105 (16), 91 (100) and 77 (17) (Found: M^+, 295.1571); (ii), the (1RS,4SR,6RS)-*azabicyclo*[4.3.0]*nonane* **11b** (0.25 g, 29%) as colourless crystals, m.p. 107–109 °C [Found: C, 77.5; H, 7.3; N, 4.7. $C_{19}H_{21}NO_2$ requires C, 77.29; H, 7.17; N, 4.74%], R_f 0.38, ν_{max}/cm^{-1} 914; δ_H(400 MHz; $CDCl_3$) 1.94–2.04 (2 H, m, 5-CH_2), 3.18–3.27 (1 H, m, $\omega_{1/2}$ 20 Hz, 6-H), 3.37 (1 H, dt, *J* 10.7 and 6.6, 1-H), 3.52 (1 H, dd, *J* 11.8 and 10.7, 2-H_{ax}), 3.81 (1 H, d, *J* 12.7,

* We thank Dr. M. J. Begley (Nottingham University) for these measurements, details of which will be published elsewhere.

† *J* Values in Hz.

PhCH_ACH$_B$), 3.96 (1 H, br t, J ~8.3, 7-H$_A$), 4.02 (1 H, dd, J 11.8 and 6.6, 2-H$_{eq}$), 4.11 (1 H, d, J 12.7, PhCH$_A$CH_B), 4.39 (1 H, dd, J 9.3 and 7.9, 7-H$_B$), 4.51 (1 H, dd, J 9.6 and 4.6, 4-H$_{ax}$) and 7.16–7.38 (10 H, m, 2 × Ph); δ_C(100 MHz) 31.83 (5-CH$_2$), 37.19 (6-CH), 58.97 (2-CH$_2$), 60.65 (1-CH), 67.48 (PhCH$_2$), 69.51 (7-CH$_2$), 74.68 (4-CH), 125.70, 127.59, 128.44, 128.53, 129.05, (all PhCH), 137.00 and 141.98 (both PhC); m/z 295 (M$^+$, 21%), 161 (53), 105 (12) and 91 (100); and (iii), the (1RS,4SR,6SR)-8-*azabicyclo*[4.2.1]*nonane* **12b** (0.138 g, 16%) as a colourless oil, R_f 0.50, ν_{max}/cm^{-1} 917; δ_H(400 MHz; CDCl$_3$), 1.62 (1 H, dd, J 13.9 and 11.8, 5-H$_A$), 2.01 (1 H, dd, J 13.9 and 4.1, 5-H$_B$), 2.36 (1 H, dd, J 11.7 and 7.7, 9-H$_A$), 2.42 (1 H, d, J 7.7, 9-H$_B$), 3.46 (1 H, dt, J 11.7 and 6.5, 1-H), 3.72 (1 H, d, J 12.7, 2-H$_A$), 3.81 (1 H, d, J 12.9, PhCH_ACH$_B$), 3.90 (1 H, dd, J 12.7 and 5.7, 2-H$_B$), 4.18 (1 H, d, J 12.9, PhCH$_A$CH_B), 4.72 (1 H, m, 4-H), 4.97 (1 H, m, 6-H) and 7.10–7.41 (10 H, m, 2 × Ph); δ_C(100 MHz) 32.27 (5-CH$_2$), 42.97 (9-CH$_2$), 63.98 (1-CH), 64.25 (PhCH$_2$), 74.90 (2-CH$_2$), 76.55 (4-CH), 77.70 (6-CH), 127.07, 127.45, 128.26, 128.33, 128.45, 129.21 (all PhCH), 137.39 and 143.35 (both PhC); m/z 295 (M$^+$, 4%), 160 (26), 105 (81), 91 (100), 77 (31) and 70 (29) (Found: M$^+$, 295.1562).

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