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A Rapid Entry to Carbocycles from Carbohydrates *via* Intramolecular Nitrone Cycloaddition

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Cyclopentane (1) and cyclohexane (2) have been synthesised from D-ribose and D-mannose respectively involving a stereoselective intramolecular nitrone cycloaddition as a key step.

In connection with a programme on the synthesis of polyhydroxylated cyclopentanoid and cyclohexanoid natural products from sugars, *e.g.* aristeromycin¹ and crotepoxide,² we sought to devise a general synthesis of highly oxygenated carbocyclic synthons suitable for further elaboration into a variety of target molecules. Encouraged by a previous report that hex-5-enoses cyclised to form pentano-isoxazolidines on treatment with N-alkylhydroxylamines,³ we now describe a short and flexible method of preparing five- and six-membered carbocycles, cyclopentane (1) and cyclohexane (2), *via* an intramolecular nitrone cycloaddition (IMNC).

The route to the functionalised cyclopentane (1) is shown in



Reagents: i, Ac₂O, pyridine; ii, OsO₄, NaIO₄, aq. dioxan; iii, NaBH₄, aq. EtOH; iv, 1 M HCl, THF.



Scheme 1. The acetonide (3),⁴ readily available from D-ribose, reacted with an excess of vinylmagnesium bromide in tetrahydrofuran (THF), presumably via a chelation controlled transition model shown in Figure 1, to give triol (4)[†] in ca. 9:1 diastereoselectivity, m.p. 74 °C; $[\alpha]_D - 31^\circ$ (c 1.8, CHCl₃). The stereochemistry of the newly formed alcohol in (4) was assigned by analogy⁵ and was confirmed by degradation studies.‡ Glycol cleavage oxidation of the vicinal diol moiety in (4) afforded the lactol (5), which on heating with N-methyl hydroxylamine underwent an IMNC⁶ reaction to give the isoxazolidine (6) as a single diastereoisomer in 94% yield, m.p. 79–80°C; $[\alpha]_D$ -59° (c 0.6, CHCl₃). The stereochemistry of the ring junction in (6) was confirmed by nuclear Overhauser enhancement (n.O.e.) experiments. It is noteworthy that the cycloaddition could proceed with a lactol function and with an unprotected hydroxy group. Acetylation of (6) followed by catalytic hydrogenolysis of the N-O bond then provided the differentially protected cyclopentane (1), $[\alpha]_{\rm D} - 84^{\circ} (c \ 0.9, \text{CHCl}_3).$

On the other hand, the synthesis of the functionalised cyclohexane (2) is illustrated in Scheme 2. Thus chelation controlled addition of vinylmagnesium bromide to the acetonide (7)⁷ derived from D-mannose gave the diol (8) in *ca*. 5:1 diastereoselectivity and in 93% yield, m.p. 54–55 °C; $[\alpha]_D$ +42° (*c* 1.1, CHCl₃). The stereochemistry of the new chiral centre in (8) was confirmed by degradation studies.[‡] The diol



Scheme 1. Reagents: i, CH₂CHMgBr, THF, (72%); ii, NaIO₄, aq. MeOH, (90%); iii, Me(H)NOH·HCl, NaHCO₃, aq. EtOH, reflux, (94%); iv, Ac₂O, pyridine (85%); v, Pd(OH)₂, H₂, EtOH/AcOH, (75%). Ac = CH₃CO.



Scheme 2. Reagents: i, $CH_2CHMgBr$, THF, (93%); ii, $PhCH_2Br$, NaH, THF, (79%); iii, aq. AcOH, (64%); iv, NaIO₄, aq. MeOH; v, Me(H)NOH·HCl, NaHCO₃, aq. ethanol, reflux, [65% from (9)]; vi, Pd(OH)₂, H₂, EtOH/AcOH, (60%).

[†] All new compounds gave satisfactory analytical and spectral data.

[‡] The triol (4) was converted into compound (11) which possesses a plane of symmetry, thereby confirming the stereochemistry of the newly formed alcohol [equation (1)]. Transformation of (8) into the known volemitol hepta-acetate⁸ (12) confirmed its stereochemistry [equation (2)].

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(8) was protected as the corresponding benzyl ether which was then selectively hydrolysed to form the vicinal diol (9), $[\alpha]_D$ -120° (c 1.0, CHCl₃). Glycol cleavage oxidation of (9), followed by immediate reaction with *N*-methyl hydroxylamine, afforded the isoxazolidine (10) as the major adduct in ca. 6:1 stereoselectivity, m.p. 103–104 °C; $[\alpha]_D + 11^\circ$ (c 1.1, CHCl₃). The stereochemistry of (10) was assigned tentatively by ¹H n.m.r. spectroscopic studies which indicated that the compound existed in a boat conformation in solution. Selective hydrogenolysis of the N–O bond in (10) then yielded the functionalised cyclohexane (2) as an oil, $[\alpha]_D -7^\circ$ (c 1.0, CHCl₃).

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