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

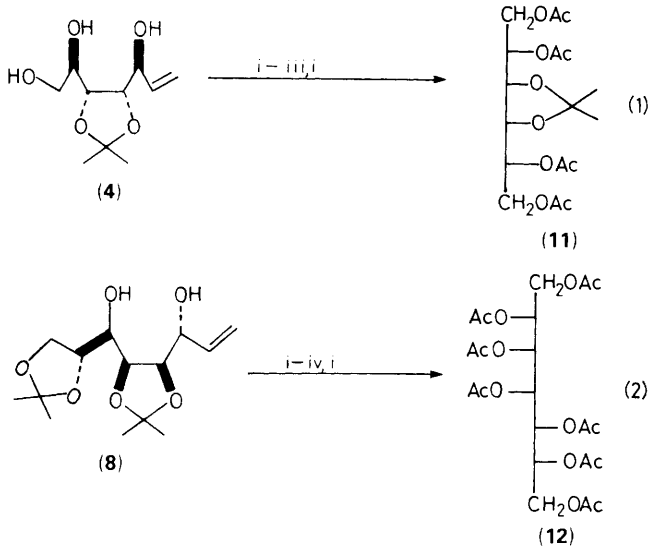
**Tony K. M. Shing,* David A. Elsley, and John G. Gillhouley**

*Department of Chemistry, The Victoria University of Manchester, Manchester M13 9PL, U.K.*

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.* aristeromycin[1] 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, $Ac_2O$, pyridine; ii, $OsO_4$, $NaIO_4$, aq. dioxan; iii, $NaBH_4$, aq. EtOH; iv, 1 M HCl, THF.

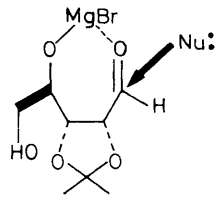


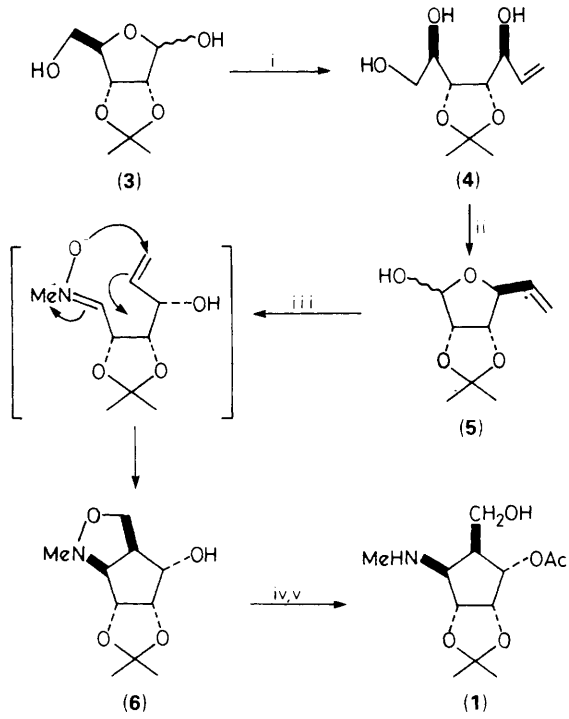

**Figure 1**

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° (*c* 1.8, $CHCl_3$). The stereochemistry of the newly formed alcohol in (**4**) was assigned by analogy[5] 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 IMNC[6] reaction to give the isoxazolidine (**6**) as a single diastereoisomer in 94% yield, m.p. 79—80 °C; $[\alpha]_D$ −59° (*c* 0.6, $CHCl_3$). 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**), $[\alpha]_D$ −84° (*c* 0.9, $CHCl_3$).

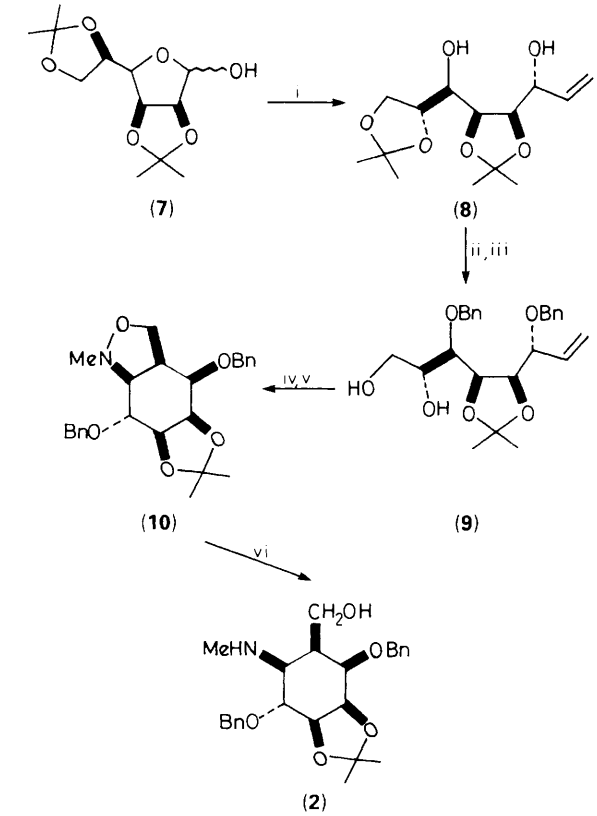
On the other hand, the synthesis of the functionalised cyclohexane (**2**) is illustrated in Scheme 2. Thus chelation controlled addition of vinylmagnesium bromide to the acetonide (**7**)[7] derived from D-mannose gave the diol (**8**) in *ca.* 5 : 1 diastereoselectivity and in 93% yield, m.p. 54—55 °C; $[\alpha]_D$ +42° (*c* 1.1, $CHCl_3$). The stereochemistry of the new chiral centre in (**8**) was confirmed by degradation studies.‡ The diol

† 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-acetate[8] (**12**) confirmed its stereochemistry [equation (2)].




**Scheme 1.** *Reagents*: i, $CH_2CHMgBr$, THF, (72%); ii, $NaIO_4$, aq. MeOH, (90%); iii, Me(H)NOH·HCl, $NaHCO_3$, aq. EtOH, reflux, (94%); iv, $Ac_2O$, pyridine (85%); v, $Pd(OH)_2$, $H_2$, EtOH/AcOH, (75%). Ac = $CH_3CO$.




**Scheme 2.** *Reagents*: i, $CH_2CHMgBr$, THF, (93%); ii, $PhCH_2Br$, NaH, THF, (79%); iii, aq. AcOH, (64%); iv, $NaIO_4$, aq. MeOH; v, Me(H)NOH·HCl, $NaHCO_3$, aq. ethanol, reflux, [65% from (**9**)]; vi, $Pd(OH)_2$, $H_2$, EtOH/AcOH, (60%).

(**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, $CHCl_3$). 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° (*c* 1.1, $CHCl_3$). 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° (*c* 1.0, $CHCl_3$).

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