Chiral Cyclohexanes From Carbohydrates: Successful Carbocyclisation of a D-Arabino-Hex-5-enopyranoside Derivative

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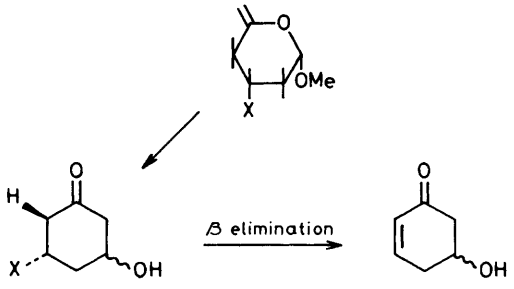
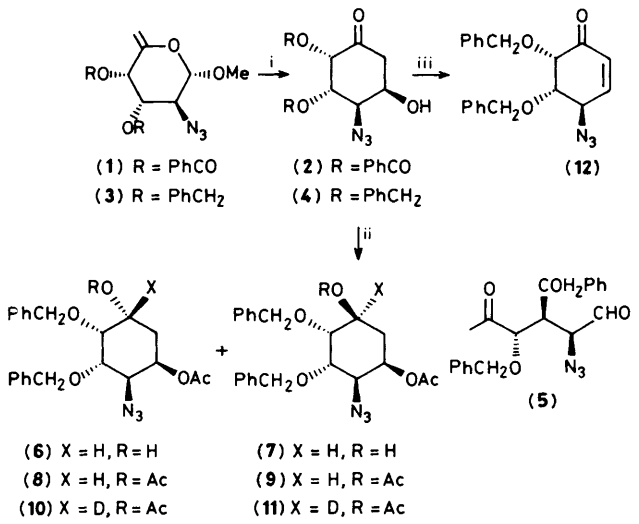
Carbocyclisation of a hex-5-enopyranoside of D-*arabino* configuration under modified Ferrier's conditions gave chiral substituted cyclohexanes, which are precursors of aminocyclitols and useful synthetic intermediates, in good yield and without side reactions.

New routes to cyclitols have been recently developed using Ferrier's carbocyclic ring closure of 5,6 unsaturated sugars.[1] This method has been applied to neutral monosaccharides[2] and disaccharides[3] of D-*xylo* configuration. More recently one example of carbocyclization of a 3-azido-5,6-unsaturated sugar has been reported.[4] With certain stereochemical arrangements of starting sugar, the authors observed the undesired formation of cyclohexenone through β elimination of hydrazoic acid from the expected cyclohexanone (Scheme 1). This indicates the limitations involved in extending Ferrier's route to the carbocyclization of 5,6-unsaturated sugars, particularly in the D-*arabino* series. Nevertheless this approach was pursued for the synthesis of some chiral functionalised cyclohexenones that we require for the synthesis of chiral alkaloids, starting from 5,6-unsaturated D-*arabino* sugars. We report here the successful cyclization without side reaction.

Initially compound (**1**) was treated with mercury(II)



Scheme 1



Scheme 2. *Reagents:* i, $(CF_3CO_2)_2Hg$, Me_2CO–H_2O; ii, $(CF_3SO_2)_2O$, pyridine; iii, $NaBX_4$, H_2O–THF.

chloride in hot aqueous acetone according to the method of Ferrier.[1] The expected cyclohexanone (**2**) was present in the reaction mixture but purification was impossible; the compound probably underwent β elimination of benzoic acid.

The use of benzyl ethers as protecting groups in (**3**)† under the same conditions gave better results, although several unidentified by-products were formed. When reaction was performed at room temperature, the cyclohexanone (**4**) was isolated as a single isomer in 55% yield {m.p. 75 °C, $[\alpha]_D$ −40.4° (*c* 0.6, $CHCl_3$)}. Its purification was difficult because of the presence of the mercury(II) salt. To overcome this problem, other acidic conditions were examined. Treatment of (**3**) with an equimolecular amount of toluene-*p*-sulphonic acid or sulphuric acid in dry acetone gave a mixture of (**4**) and another product tentatively identified as the very unstable derivative (**5**) on the basis of its ^1H n.m.r. spectrum. Addition of water to the reaction mixture almost completely transformed (**4**) into (**5**). All attempts to isolate pure (**5**) failed. These results strongly support the need to use mercury(II) ions‡ as previously reported by Ferrier.[1] Reaction of (**3**) (2.5 g, 6.6 mmol) with mercury(II) trifluoroacetate in aqueous acetone at room temperature overnight cleanly afforded (**4**) (1.8 g, 75%), readily purified by column chromatography.

It was thought that reduction of the carbonyl group of (**4**) would give the azido cyclitol derivatives. Reaction of (**4**) with sodium borohydride in aqueous tetrahydrofuran (THF) yielded a 1.3:1 mixture of epimeric alcohols (**6**) {44%, $[\alpha]_D^{20}$ −27° ($CHCl_3$)} and (**7**) {33%, $[\alpha]_D^{20}$ −7.5° ($CHCl_3$)}.

After chromatographic separation, (**6**) and (**7**) were acetylated (acetic anhydride, pyridine, 4-*N*,*N*-dimethylaminopyridine as a catalyst) to give (**8**) {$[\alpha]_D^{20}$ +7.3° ($CHCl_3$)} and (**9**) {$[\alpha]_D^{20}$ +8.4° ($CHCl_3$)} respectively. The deuteriated analogues (**10**) {$[\alpha]_D^{20}$ +8.2° ($CHCl_3$)} and (**11**) {$[\alpha]_D^{20}$ +6.8° ($CHCl_3$)} were prepared by the same sequence using sodium borodeuteride. Examination of the ^1H n.m.r. spectra of (**8**), (**10**), (**9**), and (**11**) established the stereochemistry of these compounds without ambiguity, and consequently confirmed that of (**4**). Lithium tri-s-butylborohydride, as well as di-isobutylaluminium hydride in dry THF, reduced (**4**) into a 9:1 mixture of (**6**) and (**7**) in 95% yield.

Finally the dehydration of (**4**) into (**12**) {$[\alpha]_D^{20}$ −230° ($CHCl_3$)}§ was cleanly effected by treatment with trifluoromethanesulphonic anhydride (1 equiv.) in pyridine at −15 °C in 75% yield after chromatography.

This generalization of Ferrier's reaction to a D-*arabino* hex-5-enopyranoside opens up a route to various substituted aminocyclitols, which can be regarded as derivatives of actinamine,[6] and to a chiral intermediate in our planned synthesis of alkaloids.

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† This compound {$[\alpha]_D$ +68.4° ($CHCl_3$)} was prepared from methyl α-D-glucopyranoside by conventional methods, F. Chretien, to be published.

‡ It seems that both acetone and mercury(II) ions are required for this reaction. Acetone could effect the glycosidic bond cleavage by transacetalation. Mercury(II) ions play a role in the aldol cyclisation,[1] thus explaining the high asymmetric stereocontrol. A stabilizing effect of mercury(II) ions by chelation of the aldol product is also probable.[5]

§ *Spectral data.* ^1H n.m.r. (400 MHz, $CDCl_3$): (**4**) δ 2.16 [d, 1H, OH *J*(OH,5-H) 3.5 Hz], 2.54 [1H, 6-H, *J*(6,6′) 14, *J*(5,6) 6.5, *J*(6,2) 1 Hz], 2.88 [dd, 1H, 6-H, *J*(5,6′) 4.5 Hz], 3.97 [dd, 1H, 3-H, *J*(3,4) 7.5, *J*(2,3) 3 Hz], 4.09 [dd, 1H, 2-H, *J*(2,3) 3, *J*(2,6) 1 Hz], 4.16 [dd, 1H, 4-H, *J*(4,5) 3 Hz], 4.33 (m, 1H, 5-H), 4.42, 4.55, 4.66, and 4.72 (CH_2Ph, *J* 12 Hz), and 7.32 (m, 10H, aromatic). (**12**) δ 3.92 [dd, 1H, 3-H, *J*(2,3) 2.5, *J*(3,4) 7 Hz], 4.05 [dd, 1H, 2-H, *J*(2,6) 1 Hz], 4.49 and 4.57 (m, 3H, CH_2Ph), 4.66 [dt, 1H, 4-H, *J*(4,5) 2.5, *J*(4,6) 2 Hz], 4.72 (d, 1H, CH_2Ph), 6.03 [m, 1H, H-6, *J*(5,6) 11 Hz], 6.68 (dd, 1H, 5-H), and 7.36 (m, 10H, aromatic).