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Preliminary communication

Expedient syntheses of inososes from carbohydrates: conformational and stereoelectronic aspects of the Ferrier reaction

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The conversion of 6-deoxyhex-5-enopyranosides (e.g., **1**, Table I and Scheme 1) into cyclohexanones [inosose derivatives, e.g., **2**, Table I and Scheme 1] by reaction with $HgCl_2$ (1.1 equiv) in aqueous dioxane or aqueous acetone was first disclosed by Ferrier[1]. Although the importance of this reaction has been recognised[2–4], its scope has not been examined fully. Machado et al.[5] recognised the relationship between the conformation of the starting carbohydrate and the stereochemistry of the Ferrier product, and we now report a more detailed mechanistic study.

TABLE I

Ferrier reactions

Olefin	Product	Conditions [a]	Ref.	Yield (%)
1	**2**	1.1 equiv $HgCl_2$–A	1	83
3	**4**	1 equiv $HgCl_2$–A [b]	2, 12	84
5	**6**	catalytic $Hg(SO_4)$–B	5	80
7	**8**	$Hg(CF_3CO_2)_2$–A	8	75
9	**10**	catalytic $HgSO_4$–B [c]		85
11	**12**	catalytic $HgSO_4$–B	9	quantitative

[a] A, 1:2 H_2O–dioxane or 1:2 H_2O–acetone; B, 1:2 H_2O (0.5 mmol H_2SO_4)–dioxane. [b] With 1.1 equiv of $HgCl_2$, **4** and its epimer were isolated in the ratio 2:1[12]. [c] With 1.1 equiv of $HgCl_2$, elimination of the azido group occurs[9].

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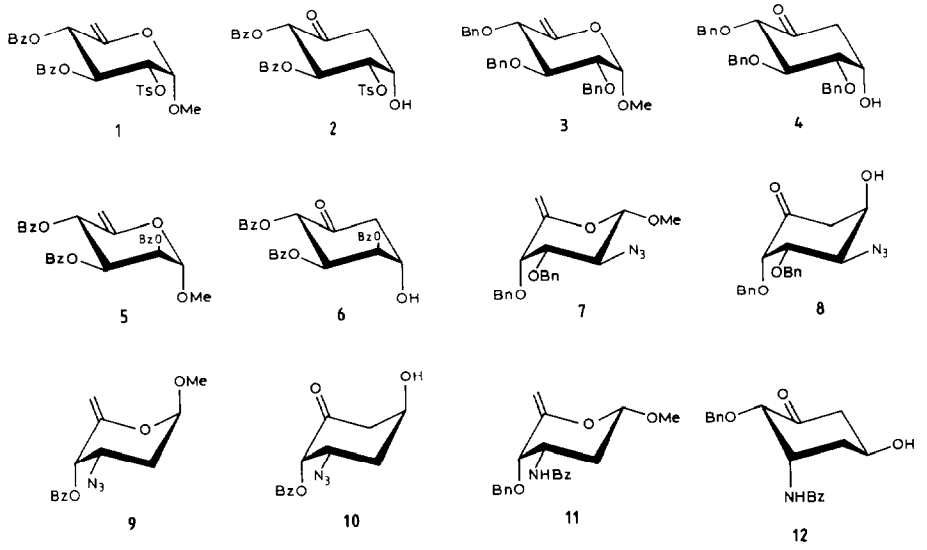
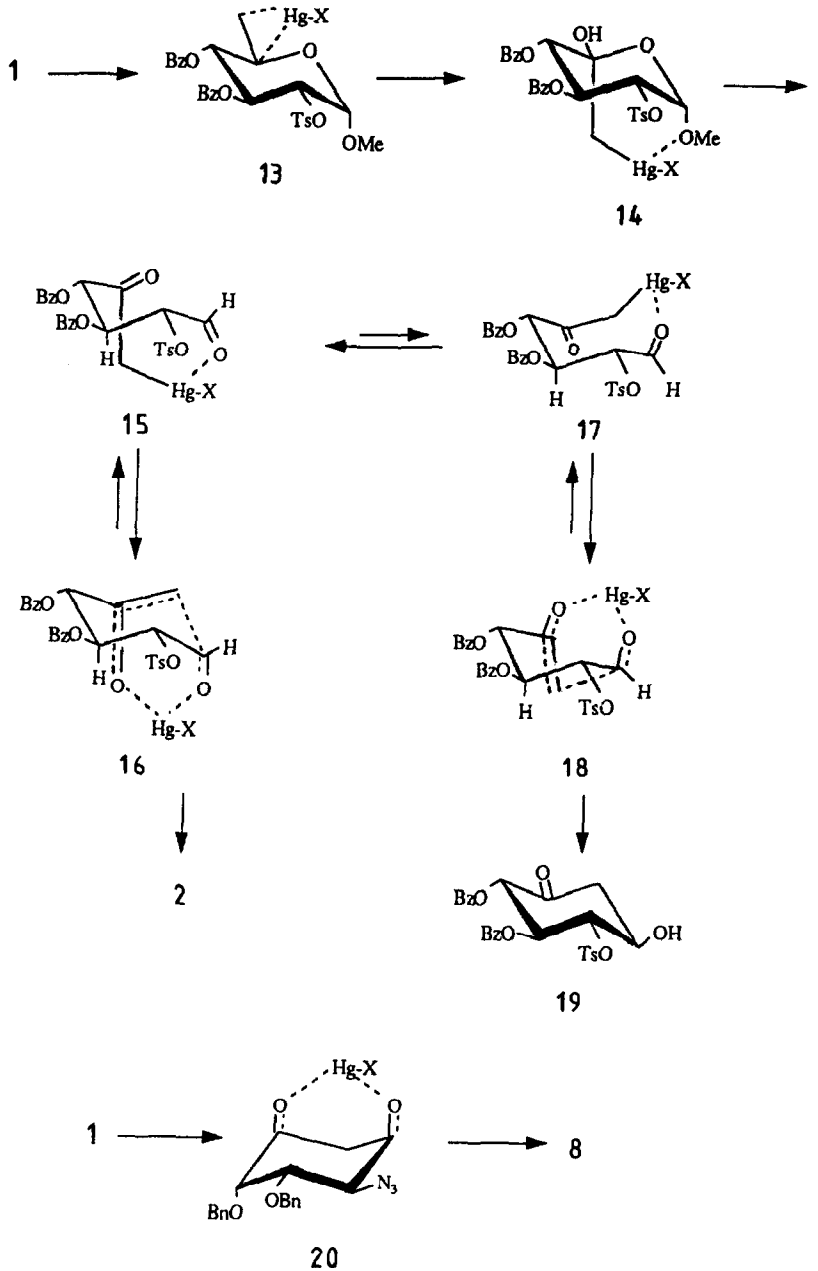


Scheme 1.

The hex-5-enopyranosides (**1, 3, 5, 7, 9,** and **11**; Table I and Scheme 1) studied were prepared by well established procedures[6–10]. Each hexenopyranoside was dissolved in methanol and the conformation (in the absence of $HgCl_2$) was determined by 300-^{1}H NMR spectroscopy. With the exception of **7** and **9**, the data agreed with those in the literature and the conformations are shown in Scheme 1. The structures and conformations of the products (**2, 4, 6, 8, 10,** and **12**, respectively; Scheme 1) were also determined by ^{1}H NMR spectroscopy.

Laszlo et al.[6], in a study of the mercury salt-mediated ring-transformation of methyl hex-5-enopyranoside derivatives, noted that, in the cyclohexanone products, the newly generated HO-5 and the 3-substituent were *trans* (C-1 in the hex-5-enopyranoside becomes C-5 in the cyclohexanone). The same outcome was found for the transformations shown in Table I. The high stereoselectivity associated with this reaction has been attributed[6] to a highly strained, boat transition state in which C-6 is connected to the 3-substituent via the mercury cation. An alternative, more precise explanation involves the sequence **1** → **13** → **14** → **15** → **16** → **2** (Scheme 2) and a six-membered chair transition state **16** which accounts for the stereochemistry at C-5 of the major product, and the sequence **15** → **17** → **18** → **19** which accounts for the stereochemistry of the minor isomer.

The results in Table I indicate that the methyl hex-5-enopyranoside derivatives **1, 3,** and **5**, in the $^4C_1$ conformation with MeO-1 axial, each gave a hydroxycyclohexanone derivative (**2, 4,** and **6**, respectively) with HO-5 directed downward. By contrast, **7, 9,** and **11**, each in the $^1C_4$ conformation, gave a hydroxycyclohexanone derivative with HO-5 directed upward. The stereoelectronic explanation involves the addition of mercury to the olefinic bond of, for example, **1** to give **13** which is



Scheme 2.

trapped by water to give **14**. Indeed, stable isolable products analogous to **14**, obtained by trapping of the carbonium ion (or the mercurinium ion precursor) with dry methanol, have been reported by Ferrier and Prasit[11]. The formation of **14** is followed by opening of the pyranoside ring with concomitant loss of MeO-1 to

yield the ketoaldehyde intermediates **15** and **17**. The transition state **16** derived from **15** has a chair conformation and is favoured over the twist form **18**. The equilibrium between **15** and **17** would be expected to be well to the left, resulting in the preponderant formation of **2** with only a minor proportion of the C-5 epimer **19**.

The mechanism noted above for the reaction of **1** (and also **3** and **5**) in the $^4C_1$ conformation also applies to **7**, **9**, and **11**, which are in the $^1C_4$ conformation. The reason for the predominance of the stereochemistry of the main product from, for example, **7** is due to the transition state **20** which yields **8**.

The presence of an axial substituent at C-3 should destabilise **16** by a 1,3-diaxial interaction, shift the equilibrium towards **15** and **17**, and result in an increase in the proportion of the minor isomer. A more detailed account of these mechanistic interpretations will be published elsewhere.

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