A New Ferrier System: 2-*C*-Acetoxymethylglycals.[1] A Convenient Entry to 2-*C*-Methylene Glycosides

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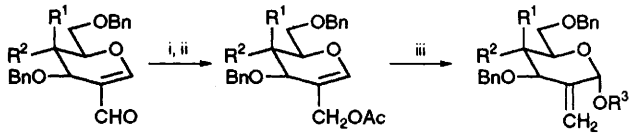
Synthesis of tri-*O*-benzyl-2-*C*-acetoxymethylglycals and subsequent Ferrier rearrangement to give 2-*C*-methylene glycosides is described.

2-*C*-Substituted glycals are an important class of branched-chain deoxy sugars[2] and unsaturated nucleosides.[3,4] However, only a few methods for the preparation of 2-*C*-substituted glycals have been reported,[5] mostly involving several steps. We now report the synthesis and chemistry of 2-*C*-acetoxymethylglycals **3** and **4** which are of interest as novel substrates for the Ferrier rearrangement. This well studied rearrangement[6] is extensively employed for the synthesis of 2,3-unsaturated glycosides starting usually from acetylated glycals. There is also a precedent for the Ferrier rearrangement in the simple tri-*O*-benzyl glucal.[7]

Although our substrates **3** and **4** apparently present a competitive Ferrier system, we envisaged that reaction of **3** and **4** might provide a convenient access for the synthesis of unsaturated glycosides with regioselective formation of an exocyclic methylene group at C-2. This would constitute a new variant of the Ferrier rearrangement. The C-2 methylene group is a key structural feature of molecules involved in the



1 **3** **5**
2 **4** **6**

Bn = $PhCH_2$

1, 3, 5 | $R^1 = OBn, R^2 = H$
2, 4, 6 | $R^1 = H, R^2 = OBn$

5a, 6a; $R^3 = Me$
5b, 6b; $R^3 = Et$
5c, 6c; $R^3 = Bu^t$
5d, 6d; $R^3 = Bn$

Scheme 1 *Reagents and conditions*: i, $NaBH_4$, MeOH, 1 h, room temp.; ii, Ac_2O, pyridine, DMAP (cat.), CH_2Cl_2, 2 h, room temp.; iii, 1.2 equiv. R^3OH, 0.3 equiv. $BF_3{\cdot}Et_2O$, 0 °C, CH_2Cl_2, 2 h

mechanism-based inactivation of ribonucleotide diphosphate reductase,[8] and can also be further elaborated to provide 2-*C*-substituted carbohydrate derivatives.

Reduction of 2-*C*-formylglycals[9] **1** and **2** with sodium borohydride in methanol afforded the corresponding 2-*C*-hydroxymethylglycals (70% yield). Acetylation of the hydroxy group with acetic anhydride, pyridine and a catalytic amount 4-*N*,*N*-dimethylaminopyridine (DMAP) yielded the corresponding 2-*C*-acetoxymethylglycals **3** and **4** in 80–85% yield (Scheme 1). The acetates **3** and **4** were purified by column chromatography (SiO_2) and analysed by spectral techniques.

When the exocyclic 2-*C*-acetoxymethylglycal **4** was exposed to $BF_3{\cdot}Et_2O$ in the presence of methanol for 2 h at 0 °C the exomethylene glycoside was obtained (72%) as a mixture of anomers in the ratio of 85 : 15 from which the α-isomer **6a** was isolated in pure form as the major product. The analytical and spectral data were in accordance with the assigned structure.†

The utility and generality of the reaction were established by extension to other alcohols‡ (Scheme 1), with yields ranging from 55 to 75%. This rearrangement takes place readily in the glucal as well as in the galactal series. In all the cases, the α-glycoside[6,10] was the major product. The anomeric configuration was assigned from ^1H NMR NOE experiments, which showed no enhancement for the C-1 and C-5 methine signals for representative products **5a** and **6a** in the galactal and glucal series.

We are currently extending this concise approach to 2′-*C*-methylene sugars in the furanose series with a view to synthesise 2′-*C*-methylene nucleosides[3,8] of biological importance.

† For **6a**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.1–7.4 (m, 15H, OCH_2Ph), 5.3 (s, 1H, $=CH_2$), 5.15 (s, 1H, $=CH_2$), 5.05 (s, 1H, 1-H), 4.45–4.90 (m, 6H, $-OCH_2Ph$), 4.40 (d, 1H, 3-H, $J_{3,4}$ 9.0 Hz), 3.9 (m, 1H, 5-H), 3.75 (dd, 1H, 6-H, $J_{5,6}$ 4.5 Hz, $J_{6,6'}$ 10.5 Hz), 3.70 (dd, 1H, 6′-H, $J_{5,6'}$ 1.5 Hz, $J_{6,6'}$ 10.5 Hz), 3.6 (t, 1H, 4-H, $J_{3,4} = J_{4,5} = 9.0$ Hz) and 3.36 (s, 3H, OMe); ^{13}C NMR 142.33 (s), 138.32 (s), 138.26 (s), 138.09 (s), 128.41 (d), 128.30 (d), 127.83 (d), 127.73 (d), 127.67 (d), 127.59 (d), 111.70 (t), 102.41 (d), 81.17 (d), 79.93 (d), 74.90 (t), 73.43 (t), 71.47 (d), 68.79 (t) and 54.47 (q).

‡ All specific rotations were taken in dichloromethane with *c ca.* 1: $[\alpha]_D^{25}$: **5a**, 34.88; **5b**, 31.63; **5c**, 45.41; **5d**, 49.93; **6a**, 31.64; **6b**, 34.67; **6c**, 40.54; **6d**, 44.20.

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