Acetyl Perchlorate Mediated Rearrangement of Tri-*O*-benzyl-D-glucal. Evidence for a 1,6-Hydride Shift

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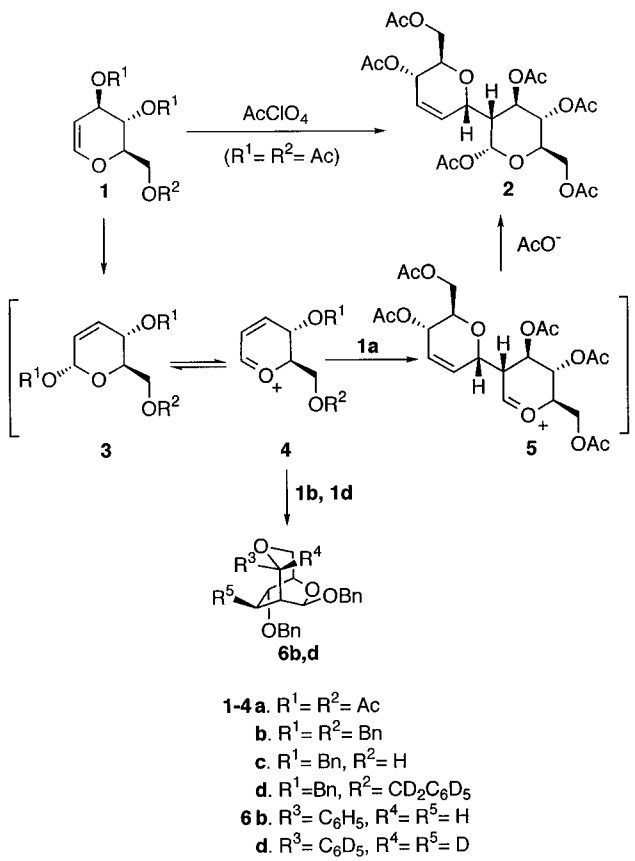
The Lewis acid mediated reaction of glycals with nucleophiles, the Ferrier reaction[3] (Scheme 1, **1** to **3**), has seen widespread use in the synthesis of glycosidic bonds.[4] In the absence of an external nucleophile the glycal, itself, can function as the nucleophile albeit, normally, with only moderate efficacy.[5] We have recently reported that, on treatment with acetyl perchlorate, 3-*O*-acyl glycals undergo an efficient dimerization leading to C-disaccharides.[6] Here we report that attempts to use the more nucleophilic tri-*O*-benzyl-D-glucal **1b** in this process results in an unprecedented rearrangement via a 1,6 hydride shift.

The dimerization proceeds via loss of the 3-*O*-acyl group to generate allylic oxacarbenium ion **4** which then combines with a second equivalent of the starting glycal to produce a new oxacarbenium ion **5**, Scheme 1. The process is then terminated by capture of this species by an acetate anion. In an attempt to inhibit this trapping process and generate oligomers we explored the use of the corresponding tri-*O*-benzyl-D-glucal **1b**. However, on treatment with 0.5 equivalents of acetyl perchlorate at −78 °C, this substrate afforded a complex mixture of products from which the desired C-disaccharide could not be isolated. Instead the major component of the product mixture, isolated in yields ranging from 20 to 40%, was the bicyclic acetal **6b**. This structure was fully established by a variety of NMR experiments (^{1}H, ^{13}C, COSY, HETCOR, FLOCK, NOE) and single-crystal X-ray diffraction.[7]

We rationalize the formation of this product via the initial generation of the conjugated oxacarbenium ion **4b**, Scheme 2. An intramolecular 1,6-hydride shift then regenerates the glycal producing a benzylic oxacarbenium ion (**7**). Cyclization through attack of the vinyl ether affords, after trapping of oxacarbenium ion **8** with (the initially formed) benzyl alcohol, the observed acetal **6b**.

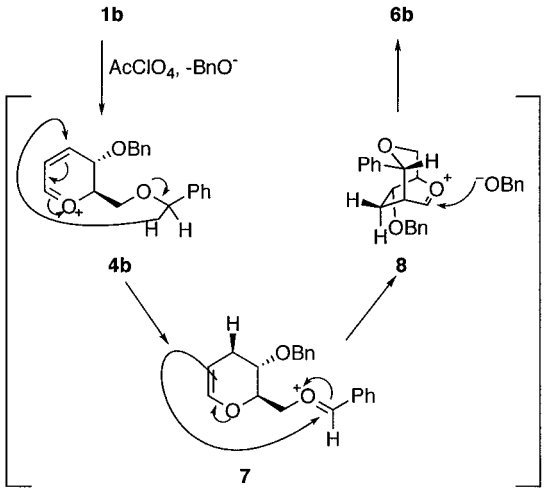
To the best of our knowledge such 1,6-hydride sifts are unprecedented in "Ferrier" type chemistry of glycals. To verify that this is a plausible pathway we have prepared and studied the rearrangement of the corresponding 6-*O*-heptadeuteriobenzyl ether **1d**. Following established procedures tri-*O*-acetyl-D-glucal **1a** was successively hydrolyzed to the triol,[8] selectively protected at the primary alcohol with TBDMSCl, dibenzylated, and then treated with tetrabutylammonium fluoride to afford the known

Scheme 1



1-4a. $R^1 = R^2$ = Ac
b. $R^1 = R^2$ = Bn
c. R^1 = Bn, R^2 = H
d. R^1 = Bn, R^2 = $CD_2C_6D_5$
6b. $R^3 = C_6H_5$, $R^4 = R^5$ = H
d. $R^3 = C_6D_5$, $R^4 = R^5$ = D

Scheme 2



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(7) X-ray experimental details and structure data for **6** are available from the Cambridge Crystallographic Data Centre. The experimental details, atomic coordinates and bond lengths and angles can be obtained, on request, from the director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
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3,4-di-*O*-benzyl-D-glucal **1c**.[9] Treatment of this compound with dimsylsodium and d_7-benzyl chloride smoothly afforded the desired labeled glucal **1d**. Identical treatment of this substrate with acetyl perchlorate, as before, afforded the corresponding bicyclic acetal **6d**. Examination of the NMR spectra indicated that the deuterium labels were located exclusively at C(5) {replacing proton at $\delta = 5.47$} and C(9) {replacing proton at $\delta = 2.38$}. This, particularly the β-stereochemistry of the deuterium at C(9), is consistent with the proposed intramolecular 1,6 hydride shift. The lower yield (11%) of the rearranged product **11** obtained in this experiment probably reflects a kinetic isotope effect for the deuteride shift in which a slower process permits greater deviation from the desired pathway. Attempts to enhance this pathway through the use of a 6-*O*-(*p*-methoxybenzyl) analogue gave an even more complex mixture of products. We presume that the increased stability of the *p*-methoxybenzylic oxacarbenium ion inhibits reaction with the vinyl ether.

Experimental Section

General. Acetyl perchlorate was prepared according to standard procedures.[10] All other reagents were commercially available and used as received. Dichloromethane and DMSO were distilled from CaH_2. Unless otherwise stated, NMR spectra were recorded in $CDCl_3$; ^1H at 400 MHz, ^2H at 76.8 MHz, and ^{13}C at 100 MHz. Melting points are uncorrected.

(1*S*,3*R*,4*R*,5*R*,8*S*)-3,8-Di-*O*-benzyl-5-phenyl-2,6-dioxabicyclo[3.2.2]nonane (6b). A precooled (−78 °C) solution of acetyl perchlorate (12.5 mL of a 0.1 M solution in CH_2Cl_2, 1.25 mmol) was added dropwise to a stirred solution of tri-*O*-benzyl-D-glycal **1b** (1.04 g, 2.5 mmol) in a rotaflow tube in CH_2Cl_2 at −78 °C under a stream of nitrogen. The tube was sealed and the reaction stirred at −78 °C for 20 h. The reaction was quenched by the addition of methanolic sodium bicarbonate solution and extracted with CH_2Cl_2. The organic phase was washed with water, and the aqueous layers were extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash column chromatography (ethyl acetate:petroleum ether 1:9) afforded the title acetal **6b** as an amorphous white solid (416 mg, 40%). A small sample was recrystallized from ether/petroleum ether. Mp 73.6−74.3 °C. $[\alpha]^{20}_D = -36.8$ (*c* 2.0, $CHCl_3$). ^1H 7.5−7.2 (15H, m), 5.47 (1H, s), 5.18 (1H, d $J = 4.5$ Hz), 5.10 (1H, d $J = 12.2$ Hz), 4.70 (1H, d $J = 12.2$ Hz), 4.59 (2H, s), 4.35 (1H, d $J = 5.0$ Hz), 4.17 (1H, dd $J = 9.2$, 4.0 Hz), 4.10 (1H, dd $J = 13.1$, 5.2 Hz), 4.00 (1H, d $J = 7.1$ Hz), 2.38 (1H, m), 2.35 (1H, m), 1.44 (1H, m). ^{13}C 142.6, 138.4, 138.1, 128.4, 128.3, 128.0, 127.7, 127.6, 127.4, 126.9, 125.9, 98.4, 77.4, 76.0, 73.0, 71.4, 70.4, 69.0, 44.8, 25.6. ν_{max} 1603, 1495, 1453, 1134, 1046, 736, 699 cm^{-1}. *m/z* (CI/NH_3) 434 (0.87%, M + NH_4^+), 265(62), 155(58), 108(100). Anal. Calcd for $C_{27}H_{28}O_4$: C, 77.86; H, 6.78. Found: C, 77.53; H,6.75.

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[6-*O*-$^2H_7$-Benzyl]-3,4,6-tri-*O*-benzyl-D-glucal (1d). A solution of 3,4-Di-*O*-benzyl-D-glucal (**1c**) (322 mg, 0.99 mmol) in DMSO (5 mL) was added to a solution of dimsylsodium (36.7 mg of an 80% oil dispersion of NaH in 3 mL of DMSO). After 2.5 h at room-temperature d_7-benzyl chloride (264 mg, 1.97 mmol) was added. After a further 2 h, TLC indicated complete reaction, and the mixture was diluted with ether and poured into aqueous NaCl solution. The organic layer was washed with aqueous NaCl solution, and the aqueous extracts were back extracted with ether. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated to afford a pale brown solid. Recrystallization from ether/hexane afforded the title glucal **1d** (359 mg, 70%). Mp 54.5−55.5 °C. $[\alpha]^{20}_D = +0.4$ (*c* = 4.8, $CHCl_3$). ^1H 7.3−7.1 (10H, m), 6.35 (1H, dd $J = 6.0$, 1.2 Hz), 4.80 (1H, dd $J = 6.0$, 2.8 Hz), 4.76 (1H, d $J = 11.2$ Hz), 4.57 (1H, d $J = 12.0$ Hz), 4.48 (1H, d $J = 11.6$ Hz), 4.13 (1H, m), 3.98 (1H, m), 3.78 (1H, dd $J = 6.0$, 8.4 Hz), 3.73 (1H, dd $J = 10.8$, 5.2 Hz), 3.68 (1H, dd $J = 10.8$, 2.8 Hz). ^2H (CH_2Cl_2) 7.37 (5D, m), 4.52 (2D, m). ^{13}C 144.7, 138.3, 138.1, 128.37, 128.36, 127.9, 127.7, 127.6, 99.9, 76.7, 75.7, 74.3, 73.7, 72.1 (quint, $J = 23$ Hz), 70.4, 68.4. ν_{max} 1650, 1453, 1105, 1051, 730, 697 cm^{-1}. *m/z* (DCI/NH_3) 441 (0.7%, M + NH_4^+), 423 (0.03%, M^+), 108(100). HRMS (M + NH_4^+) calcd for $C_{27}H_{25}D_7NO_4$ 441.2771, found 441.2771. Anal. Calcd for $C_{27}H_{21}D_7O_4$: C, 76.58; H, 6.65. Found: C, 76.26; H,6.71.

(1*S*,3*R*,4*R*,5*R*,8*S*,9*R*)-[5-^{2}H,5-{$^2H_5$-phenyl},9-^{2}H]-3,8-Di-*O*-benzyl-5-phenyl-2,6-dioxabicyclo[3.2.2]nonane (6d). Treatment of d_7-glucal **1d** (287 mg, 0.68 mmol) in an identical fashion to that described above afforded, after chromatography, the title acetal **6d** as an amorphous white solid (32 mg, 11%). $[\alpha]^{20}_D = -37$ (*c* 0.8, $CHCl_3$). ^1H 7.38−7.16 (10H, m), 5.07 (1H, d $J = 4.4$ Hz), 4.99 (1H, d $J = 12.0$ Hz), 4.59 (1H, d $J = 12.0$ Hz), 4.48 (2H, s), 4.23 (1H, d $J = 5.2$ Hz), 4.06 (1H, d $J = 4.0$ Hz), 3.99 (1H, dd $J = 13.2$, 5.2 Hz), 3.88 (1H, d $J = 13.2$ Hz), 2.22 (1H, t $J = 4.8$ Hz), 1.31 (1H, bt $J = 4.4$ Hz). ^2H ($CHCl_3$) 7.27 (5D, bs), 5.33 (1D, bs), 2.25 (1D, bs). ^{13}C 142.4, 138.4, 138.1, 128.4, 128.3, 127.7, 127.6, 127.5, 126.4 (t, $J = 23$ Hz), 125.2 (t, $J = 24$ Hz), 98.4, 77.5, 75.6 (t, $J = 22$ Hz), 73.0, 71.4, 70.4, 69.0, 44.7, 25.3 (t, $J = 21$ Hz). ν_{max} 1606, 1493, 1454, 1354, 1195, 1128, 1045, 737, 699 cm^{-1}. *m/z* (CI/NH_3) 441 (0.1%, M + NH_4^+), 91(100). HRMS (M + NH_4^+) calcd for $C_{27}H_{25}D_7NO_4$ 441.2771, found 441.2771.

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Supporting Information Available: ^1H NMR spectra and a table of ^1H, ^{13}H, and ^2H NMR assignments for **6b** and **6d**. ORTEP representations of the X-ray structure of compound **6b** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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