Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 379–383

TETRAHEDRON: *ASYMMETRY*

Intervention of catalytic amounts of water in the allylic rearrangements of glycal derivatives

Regine Blattner,* Robert J. Ferrier and Richard H. Furneaux

Industrial Research Ltd, PO Box 31-310, Lower Hutt, New Zealand

Received 29 October 1999; accepted 10 November 1999

Abstract

It is confirmed that tri-*O*-acetyl-D-glucal with thiophenol in the presence of $BF_3 \cdot OEt_2$ as catalyst gives the allylically rearranged *S*-phenyl 4,6-di-*O*-acetyl-2,3-dideoxy-1-thio-α- and β-D-*erythro*-hex-2-enopyranosides as the main products, and now demonstrated that the presence of catalytic proportions of water diverts the reaction in favour of the isomeric *S*-phenyl 4,6-di-*O*-acetyl-2-deoxy-3-phenylthio-1-thio-D-*arabino*- and -D-*ribo*-hexopyranosides. It is proposed that these products are formed from an intermediate enal.

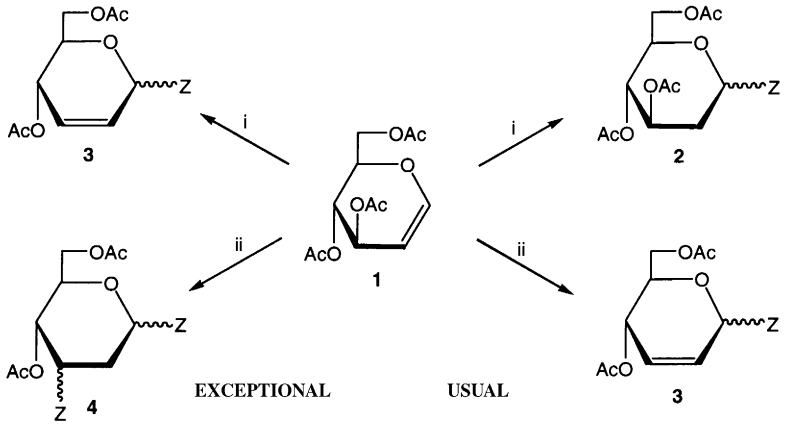
O-Acylated glycals, such as tri-*O*-acetyl-D-glucal **1**, as vinyl ethers, readily undergo direct addition reactions with nucleophilic species (Z) in the presence of protonic acids to give 2-deoxyglycosyl compounds **2**, whereas Lewis acids (BF_3 being most commonly used) usually promote substitution at the anomeric centre with allylic rearrangement to afford 2,3-unsaturated glycosyl derivatives **3**[1,2] (Scheme 1), both types of process having usefulness for the synthesis of glycosidic products of various kinds.

There are, however, exceptions to both these generalisations. For example, several instances have been recorded of 2,3-unsaturated nucleoside analogues (**3**, Z=heterocyclic base) having been formed from glycal esters and purine and pyrimidine bases under the influence of strong protonic acids,[3] and 2,3-unsaturated glycosyl fluorides have been made by the use of hydrogen fluoride.[4] On the other hand, there are cases in which saturated 2-deoxy-adducts are the main products of reactions catalysed by Lewis acids (as indicated in Scheme 1). We here call attention to several examples of such adducts **4** that have the nucleophilic species as substituents at C-3 as well as C-1, and present evidence pertinent to their mode of formation:

– While reactions of 3,4-di-*O*-benzoyl-D-arabinal and -D-xylal in dichloromethane with 3–4 mol equiv. of methanol and in the presence of $BF_3 \cdot Et_2O$ give, initially, the 2,3-unsaturated methyl glycosides, these products are finally replaced by methyl 4-*O*-benzoyl-2-deoxy-3-*O*-methyl-α- and β-D-*erythro*- and *threo*-pentopyranosides.[5]

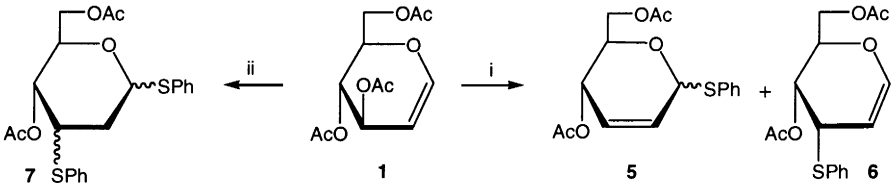
* Corresponding author. E-mail: r.blattner@irl.cri.nz

0957-4166/00/$ - see front matter
PII: S0957-4166(99)00499-1



Scheme 1. Reagents: (i) H^+, :Z; (ii) Lewis acid, :Z

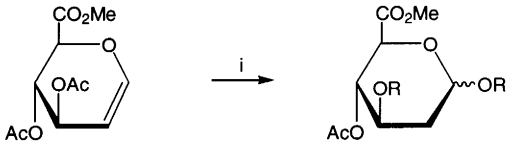
– Although the reaction of tri-*O*-acetyl-D-glucal **1** in benzene with thiophenol and added $BF_3 \cdot Et_2O$ has been shown unequivocally to give a mixture of the 2,3-unsaturated *S*-phenyl 1-thioglycosides **5** with minor amounts of the 3-phenylthio-D-allal isomer **6** (Scheme 2),[6] one report suggested that *S*-phenyl 2-deoxy-3-phenylthio-1-thio-glycosides **7** are the products of this reaction.[7]



α–*ribo* 3
β–*ribo* 5
α-*arabino* 5
β-*arabino* 1

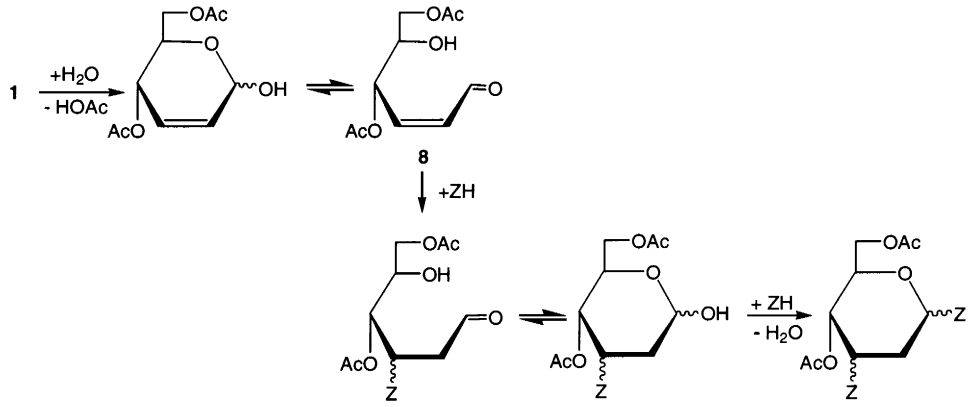
Scheme 2. Reagents: (i) PhSH, $BF_3 \cdot Et_2O$; (ii) PhSH, $BF_3 \cdot Et_2O$, H_2O (catalytic)

– Di-*O*-acetyl-L-rhamnal with benzyl alcohol in benzene, again with $BF_3 \cdot Et_2O$, shows mixed products, the major being the rearranged 2,3-unsaturated glycosides (88% after saponification), but 11% (after saponification) of 1,3-di-*O*-benzyl-2-deoxy adducts are also formed.[8]
– The 3,4-di-*O*-acetate of the glycal derived from methyl glucuronate in reactions separately with ethyl glycolate, methyl lactate and ethyl 3-hydroxybutanoate in CH_2Cl_2, also with $BF_3 \cdot Et_2O$ as catalyst, affords the saturated products shown in Scheme 3 in 75, 50 and 30% yields, respectively.[9]



Scheme 3. Reagents: (i) $BF_3 \cdot Et_2O$, ROH. R=EtO_2CCH_2-, $MeO_2CCH(CH_3)$-, $EtO_2CCH_2CH(CH_3)$-

While some authors[5,8] have suggested that the 1,3-disubstituted adducts arise by additions to first-formed 2,3-unsaturated compounds we are impressed by the consistent 1,3-pattern of disubstitution and favour an alternative pathway which involves 2,3-unsaturated aldehydes, e.g. **8**, as exemplified in Scheme 4. That is, the presence of water is deemed to lead to the anomalous addition processes, and importantly, as indicated in Scheme 4, the water can function catalytically.



Scheme 4.

To test this hypothesis and to examine the inconsistencies reported for the reaction of tri-*O*-acetyl-D-glucal **1** and thiophenol (Scheme 2[6,7]), the former (0.80 mmol) and the latter (1.75 mmol) in benzene (2.5 mL) containing $BF_3 \cdot Et_2O$ (0.40 mmol) were kept in the dark at room temperature for 15 min. A sample was withdrawn and the catalyst was neutralised. Examination by ^1H and ^{13}C NMR spectroscopy showed complete conversion to the 2,3-unsaturated thioglycosides **5** and a small proportion of the 3-*S*-phenylthio-D-allal isomer **6**, as expected.[6] No further change occurred to the bulk solution on standing at room temperature in the dark for 72 h (NMR data). In a parallel experiment, identical except that water (0.28 mmol, 0.35 mol equiv.) was added after 5 min, none of the unsaturated first products remained after 72 h; rather, *S*-phenyl 4,6-di-*O*-acetyl-2-deoxy-3-phenylthio-1-thio-α- and β-D-*ribo*-, and α- and β-D-*arabino*-hexopyranosides **7** were present as the only products in the approximate ratios 3:5:5:1.

From a preparative experiment (tri-*O*-acetyl-D-glucal, 6.4 mmol) conducted with 4 mol% of water and at reflux temperature for 10 min under bright light [used with the intention of generating the (*E*)-isomer of enal **8**[10] and thereby favouring Michael-like addition, but discovered not to be necessary] the α- and β-*ribo*- and the α-*arabino*-products were isolated pure, and the β-*arabino*-isomer as the main component of a mixed fraction (Tables 1 and 2).[11] The total isolated yield was 83%.

Table 1
^1H NMR parameters for the ring protons of the *S*-phenyl 4,6-di-*O*-acetyl-2-deoxy-3-phenylthio-1-thio-D-hexopyranosides **7**

	^1H Chemical shifts (δ)						$^3J_{H,H}$ Coupling constants (Hz)						
Isomer	H-1	H-2	H-2′	H-3	H-4	H-5	$J_{1,2}$	$J_{1,2'}$	$J_{2,2'}$	$J_{2,3}$	$J_{2',3}$	$J_{3,4}$	$J_{4,5}$
α-*arabino*	5.59	2.41	2.14	3.59	4.97	4.47	0	5.4	10.0	4.2	13.1	10.1	10.1
β-*arabino*	4.69	2.30	2.11	3.17	4.82	3.54	1.8	11.4	13.5	4.5	12.6	10.5	10.5
α-*ribo*	5.49	2.63	2.34	3.92	5.04	4.68	6.1	4.1	14.7	4.9	6.0	4.3	8.0
β-*ribo*	5.24	- 2.18 -		3.96	4.91	4.2	4.1	9.5	-	-	-	4.3	9.2

Table 2
^{13}C NMR chemical shifts (δ) for the *S*-phenyl 4,6-di-*O*-acetyl-2-deoxy-3-phenylthio-1-thio-D-hexopyranosides **7**

Isomer	C-1	C-2	C-3	C-4	C-5	C-6	CH_3CO
α-*arabino*	84.4	37.6	45.7	70.9	70.2	63.2	21.1, 21.0
β-*arabino*	82.8	36.8	48.2	76.9	68.8	62.1	19.8, 19.6
α-*ribo*	83.5	35.0	46.2	69.6	68.4	63.2	21.1, 20.9
β-*ribo*	79.4	35.3	46.4	68.4	72.1	62.3	19.8, 19.3

Of relevance to these observations are the findings that the formally prepared enal **8** readily adds thioacetic acid to give the 3-acetylthio-2-deoxy free sugar,[12] that 1,3-dibromo-2-deoxy compounds have been identified as reaction products of tri-*O*-acetyl-D-glucal and HBr,[13] and that the relevant enal has been invoked as intermediate in the reaction of 4,6-*O*-benzylidene-2,3-dideoxy-D-*erythro*-hex-2-enose with methoxide ion, which affords 4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-D-*arabino*- and D-*ribo*-hexopyranoses.[14]

It is concluded that adventitious water may be held responsible for at least some of the anomalous addition reactions referred to above, but in the case of the reactions of the uronic acid-based glycal with methyl lactate and ethyl 3-hydroxybutanoate, which gave 50 and 30% of 1,3-disubstituted 2-deoxy adducts (Scheme 3), water is likely to have been generated by elimination from the alcohol substrates.[9] This type of explanation is, however, unlikely to account for the 75% of corresponding adducts obtained with ethyl glycolate (Scheme 3), or for the production of the 2,3-unsaturated glycosides from this glycal (92%) and from tri-*O*-acetyl-D-glucal (84%) with dimethyl malate,[9] which would also be expected to dehydrate under the reaction conditions.

References

1. (a) Collins, P. M.; Ferrier, R. J. *Monosaccharides. Their Chemistry and Their Roles in Natural Products*; Wiley; Chichester, 1995. (b) Ferrier, R. J. *Adv. Carbohydr. Chem.* **1965**, *20*, 67; **1969**, *24*, 199–266.
2. Ferrier, R. J.; Zubkov, O. A. *Org. React.*, in press.
3. (a) Fuertes, M.; Garcia-Munoz, G.; Madronero, R.; Stud, M.; Rico, M. *Tetrahedron* **1970**, *26*, 4823–4837. (b) Leutzinger, E. E.; Meguro, T.; Townsend, L. B.; Shuman, D. A.; Schweizer, M. P.; Stewart, C. M.; Robins, R. K. *J. Org. Chem.* **1972**, *37*, 3695–3703.
4. (a) Lundt, I.; Pedersen, C. *Acta Chem. Scand.* **1971**, *25*, 2320–2326. (b) Bock, K.; Pedersen, C. *Acta Chem. Scand.* **1971**, *25*, 2757–2764.
5. Bock, K.; Christiansen, J. K.; Pedersen, C. *Carbohydr. Res.* **1971**, *20*, 73–81.
6. (a) Valverde, S.; Garcia-Ochoa, S.; Martin-Lomas, M. *J. Chem. Soc., Chem. Commun.* **1987**, 383–384. (b) Whittman, M. D.; Halcomb, R. L.; Danishefsky, S. J.; Golik, J.; Vyas, D. *J. Org. Chem.* **1990**, *55*, 1979–1981. (c) De Raadt, A.; Ferrier, R. J. *Carbohydr. Res.* **1991**, *216*, 93–107.
7. Dunkerton, L. V.; Adair, N.K.; Euske, J. M.; Brady, K. T.; Robinson, P. D. *J. Org. Chem.* **1988**, *53*, 845–850.
8. Kirschning, A.; Hary, U.; Ries, M. *Tetrahedron* **1995**, *51*, 2297–2304.
9. Wieczorek, E.; Thiem, J. *Synlett* **1998**, 467–468.
10. Fraser-Reid, B.; Radatus, B. *J. Am. Chem. Soc.* **1970**, *92*, 5288–5290. (b) Tam, S. Y.-K.; Fraser-Reid, B. *Carbohydr. Res.* **1975**, *45*, 29–43. (c) Madaj, J.; Rak, J.; Sokolowski, T.; Wisniewski, A. *J. Org. Chem.* **1996**, *61*, 2988–2994.

11. A stirred solution of tri-*O*-acetyl-D-glucal (1.74 g) and thiophenol (1.54 g, 2.2 mol equiv.) in benzene (20 mL) containing water (50 μL, 0.044 mol equiv.) was heated under reflux (heat lamp). After 2 min $BF_3 \cdot Et_2O$ (50 μL, 0.06 mol equiv.) was added and the heating was continued for 10 min. The catalyst was neutralised ($NaHCO_3$) and the products were fractionated by flash column chromatography on silica gel (light petroleum:CH_2Cl_2:EtOAc, 12:1:1). Data for the *S*-phenyl 4,6-di-*O*-acetyl-2-deoxy-3-phenylthio-1-thio-D-hexopyranosides **7** in order of elution: α-D-*arabino*- m.p. 110.5–111°C (from EtOH); $[\alpha]_D$ + 223 (*c* 1.3, CH_2Cl_2); anal. calcd for $C_{22}H_{24}O_5S_2$: C, 61.1; H, 5.6; S, 14.8; found: C, 61.1; H, 5.9; S, 14.7; β-D-*ribo*- m.p. 77–78°C (from aq. EtOH); $[\alpha]_D$ + 76 (*c* 0.9, CH_2Cl_2); anal. found: C, 61.3; H, 5.7; S, 14.6; β-D-*arabino*- (in 3:1 mixture with β-D-*ribo*) $[\alpha]_D$ –33 (*c* 3.1, CH_2Cl_2); α-D-*ribo*- m.p. 110–110.5°C (from EtOH); $[\alpha]_D$ + 217 (*c* 1.5, CH_2Cl_2); anal. found: C, 60.9; H, 5.9; S, 14.8%. See Tables 1 and 2 for NMR data; other resonances were present as required by the assigned structures.
12. Priebe, W.; Grynkiewicz, G.; Neamati, N.; Perez-Soler, R. *Tetrahedron Lett.* **1991**, *32*, 3313–3316.
13. (a) Maki, T.; Tejima, S. *Chem. Pharm. Bull.* **1968**, *16*, 2242–2247. (b) Bock, K.; Lundt, I.; Pedersen, C. *Acta Chem. Scand.* **1969**, *23*, 2083–2094.
14. Guthrie, R. D.; Irvine, R. W.; Davison, B. E.; Henrick, K.; Trotter, J. *J. Chem. Soc., Perkin Trans. 2* **1981**, 468–472.