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Branched-chain functionalised carbohydrates via β-functionalised organolithium compounds

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Abstract

The reaction of the epoxysugar **1** with an excess of lithium powder and a catalytic amount of DTBB (5 mol%) in THF at −78°C leads to the formation of the corresponding β-oxido functionalised organolithium intermediates **2**, which by treatment with different electrophiles [H_2O, D_2O, Me_3SiCl, PhCHO, Me_2CO, $(CH_2)_5CO$] at −78°C to room temperature afford, after hydrolysis with water, the expected enantiomerically pure compounds **3**. Starting from the epimeric epoxide **4** and following the same procedure, using water as electrophile, the compound **6** was isolated, the correponding intermediate **5** having been involved in the process.

From a biological point of view, carbohydrates play a vital role in molecular recognition, cell signalling, biomolecular transport, the immune system and, in fact, in virtually every essential biological process.[1] From a chemical point of view, carbohydrates have long been utilised as useful starting materials in the synthesis of chiral natural products, D-glucose being probably the starting material most extensively used;[2] this is an example of the so called EPC-synthesis, which allows the preparation of enantiomerically pure compounds using the pool of easily available chiral natural compounds.[3] One important family of sugar derivatives are the corresponding branched-chain functionalised carbohydrates,[4] which are glycosidic components of antibiotics. In nature, most of the branched-chain sugars contain a polar substituent at the branching carbon atom, the alcohol functionality being the most commonly found.[4] On the other hand, in the last few years we have applied an arene-catalysed lithiation[5] to the preparation of functionalised organolithium compounds[6] starting from different materials, such as chlorinated compounds,[7] ethers[8] or thioethers,[9] sulfones[10] and heterocycles.[11,12] Concerning this last type of compound, the reductive opening of epoxides using lithium and a stoichiometric[13] or catalytic[14]

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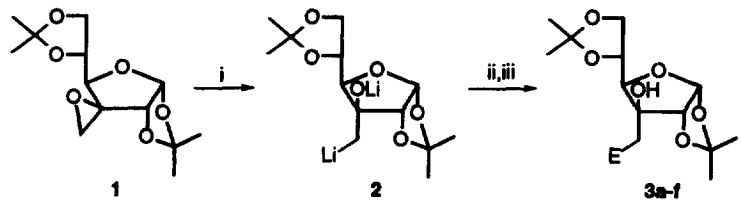
amount of an arene is a useful methodology, which allows the generation of β-oxido functionalised organolithium intermediates. In this paper we apply the aforementioned arene-catalysed lithiation to the ring opening of epoxides derived from D-glucose in order to prepare branched-chain functionalised carbohydrate derivatives.[4]

The reaction of the protected epoxy D-glucose **1**[15] with an excess of lithium powder (1:14 molar ratio) and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB; 1:0.1 molar ratio, 5 mol%) in THF at −78°C for 2 h followed by treatment with different electrophiles [E^+=H_2O, D_2O, Me_3SiCl, PhCHO, Me_2CO, $(CH_2)_5CO$] at temperatures ranging between −78°C and room temperature led, after hydrolysis with water, to the expected products **3a–f**, the corresponding intermediate **2** being probably involved in the process (Scheme 1 and Table 1).



Scheme 1. *Reagents and conditions*: i, Li, DTBB (5%), THF, −78°C, 2 h; ii, E^+=H_2O, D_2O, Me_3SiCl, PhCHO, Me_2CO, $(CH_2)_5CO$, −78 to 20°C; iii, H_2O

In the case of prochiral carbonyl compounds, such as benzaldehyde, a 2:3 diastereoisomeric mixture was obtained (Table 1, entry 4), which was separated by column chromatography (silica gel, hexane/ethyl acetate) giving the corresponding pure diastereoisomers, one of them (the most polar one) was recrys-

Table 1
Preparation of compounds **3** from the epoxide **1**

Entry	Electrophile E^+	Product[a] No.	E	Yield (%)[b]	R_f[c]	$[\alpha]_D^{RT}$ (c)[d]
1	H_2O	**3a**	H	95	0.31	21.1 (0.72)
2	D_2O	**3b**	D	95[e]	0.31	22.9 (1.25)
3	Me_3SiCl	**3c**	Me_3Si	50 (70)	0.27	27.8 (1.18)
4	PhCHO	**3d**	PhCHOH	50[f] (65)	0.29	33.3 (1.11)
					0.24[g]	19.5 (1.12)
5	Me_2CO	**3e**	Me_2COH	20 (55)	0.27	27.8 (1.50)
6	$(CH_2)_5CO$	**3f**	$(CH_2)_5COH$	60	0.34[h]	30.1 (1.79)

[a] All products **3** were pure (>95% from GLC and 300 MHz ^1H NMR) and were fully characterised by spectroscopic means (IR, ^1H and ^{13}C NMR and MS). [b] Isolated yield after column chromatography (neutral silica gel, hexane/ethyl acetate) based on the starting material **1**; in parenthesis GLC yield. [c] Silica gel, hexane/ethyl acetate: 4/1. [d] In CH_2Cl_2; in parenthesis concentration given in g/100 ml. [e] 75% Deuterium incorporation (from MS). [f] 2/3 Diastereoisomeric mixture (75 MHz ^{13}C NMR). [g] Mp 94-5°C (CH_2Cl_2/pentane); the stereochemistry of this compound was confirmed by X-ray analysis (see text). [h] Mp 108-9°C (CH_2Cl_2/pentane).

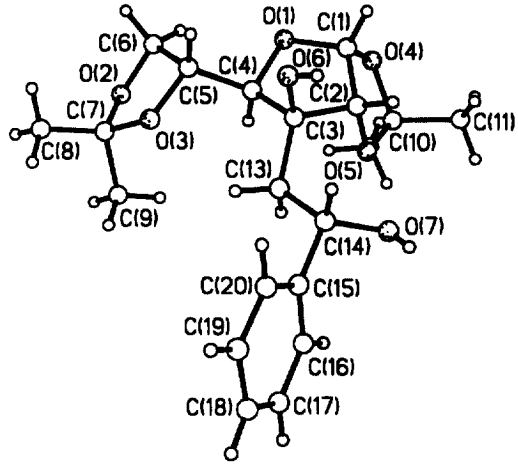
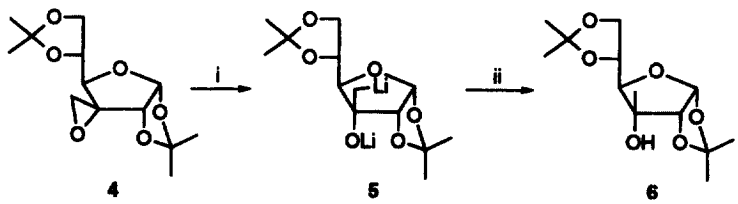


Figure 1.

tallised and analysed by X-ray difraction, confirming the stereochemistry at both formed stereocentres (Fig. 1).[16]

When the epimeric epoxide **4**[17] was submitted to the same procedure as shown in Scheme 1, and using water as electrophile, the expected 'reduced' product **6**[18] was obtained, consistent with the intermediate **5** being involved in the process (Scheme 2).



Scheme 2. *Reagents and conditions*: i, ii as in Scheme 1 with $E^+=H_2O$

Just to confirm the stereochemistry of the new stereocentre in **6** we performed the addition of methyllithium to the ketone **II**[15] in THF at temperatures ranging between −78°C and room temperature, thus generating the same compound **6**.[19,20]

From the results reported here we conclude that the epoxysugars **1** and **4** are convenient precursors for the generation of enantio- and regiochemically pure β-functionalised organolithium compounds, which are versatile intermediates for the preparation of branched-chain functionalised sugars. We are now studying the synthetic scope of this reaction using different sugar derivatives. Note that the use of oxosugars, such as compound **II**[15] as an electrophilic component, opens the door for obtaining dimeric structures having two monosaccharide units (disaccharide type molecules).

Acknowledgements

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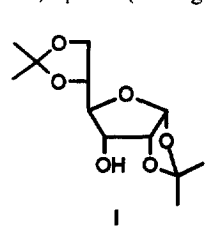
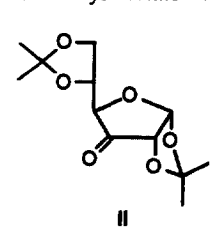
15. Compound **I** was prepared from 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-ulosa (**II**) [prepared by oxidation of the corresponding commercially available alcohol **I** with PCC in a mixture of acetic anhydride and CH_2Cl_2 at room temperature for 30 min: 73%; R_f 0.31 (silica gel, hexane/ethyl acetate: 4/1); $[\alpha]_D^{RT}$ 131.5 (CH_2Cl_2; *c* 1.27)] by treatment with equimolecular amounts of potassium *tert*-butoxide and trimethylsulfoxonium iodide in *tert*-butanol at 50°C for 2.5 h, followed by hydrolysis with water: 82%; R_f 0.48 (silica gel, hexane/ethyl acetate: 4/1); $[\alpha]_D^{RT}$ 55.4 (CH_2Cl_2; *c* 1.08).



I



II

16. (a) *Crystal data* (to be deposited at the Cambridge Crystallographic Data Centre): $C_{20}H_{28}O_7$, M=380.42; monoclinic, a=14.5447(13), b=6.6448(10), c=21.591(3) Å, β=91.129(9); U=2086.3(5) Å; space group $P2_1$; Z=4; D_c=1.211 Mg m^{-3}; λ=0.71073 Å; μ=0.091 mm^{-1}; F(000)=816; T=24–25±1°C. Intensity data were measured on a CAD-4 diffractometer. The data were reduced by routine methods.[16b] The structure was solved by direct methods[16c] and refined to all 3037 unique F_o^2 by full matrix least squares.[16d] Most of the hydrogen atoms were seen in difference Fourier maps, but for the final refinement all H atoms were placed at idealised positions and refined as rigid atoms, with the exception of

the OH and the methyl group hydrogens, which were located in Fourier calculations; these groups were refined as rigid rotators. Final w$R2$=0.1440 for all data and 499 parameters; $R1$=0.0547 for 2366 $F_o>4\alpha(F_o)$. The enantiomorph was fixed according to the known stereochemistry of four of the chiral centres in the molecule. (b) Data were processed on an AlphaStation 200 4/166 (OpenVMS Alpha V6.2), using the program XCAD4B (K. Harms, University of Marburg) and the commercial package SHELXTL-PLUS Release 5.05/V. © 1996 Siemens Analytical X-Ray Instruments, Inc., Madison, WI. (c) SHELXS-97: Fortran program for crystal structure solution. © 1997 G. M. Sheldrick. (d) SHELXL-97: Fortran program for crystal structure solution. © 1997 G. M. Sheldrick.

17. Compound **4** was prepared from ketone **II**[15] by reaction with chloroiodomethane (1:2 molar ratio) and lithium bromide in THF at −78°C for 10 min, followed by treatment with *n*-butyllithium at −78°C to room temperature: ca. 30% overall yield; R_f 0.15 (silica gel, hexane/ethyl acetate: 4/1); $[\alpha]_D^{RT}$ 85.6 (CH_2Cl_2; *c* 1.2).
18. >95%; R_f 0.13 (silica gel, hexane/ethyl acetate: 4/1); $[\alpha]_D^{RT}$ 23.7 (CH_2Cl_2; *c* 1.26).
19. 48%; R_f 0.11 (silica gel, hexane/ethyl acetate: 4/1); $[\alpha]_D^{RT}$ 25.8 (CH_2Cl_2; *c* 1.10).
20. In the literature has been reported that nucleophilic addition to the C-3 carbonyl group of **II**[15] takes place to the convex β-position by the preferential control due to the rigid bicyclic structure. See, for instance: (a) Peterson, M. A.; Mitchell, J. R. *J. Org. Chem.* **1997**, *62*, 8237. (b) Yamauchi, N.; Kishida, M.; Sawada, K.; Ohashi, Y.; Eguchi, T.; Kakinura, K. *Chem. Lett.* **1998**, 475. (c) See also Ref. 4.