COMMUNICATION

Synthesis of symmetric difucopyranose dianhydrides

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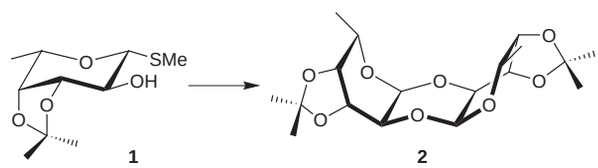
By activation of methyl 3,4-*O*-isopropylidene-1-methyl thio-β-L-fucopyranoside (1) with copper bromide–tetrabutylammonium bromide, bis(3,4-*O*-isopropylidene-α-L-fucopyranose)-1,2′ : 1′,2-dianhydride (2) with almost C_2-symmetry was obtained. Starting with the monosaccharide precursors 3 and 4 a corresponding activation led to the disaccharide derivative 5 which in turn was converted into the mixed D,L-dianhydride 7 employing an intramolecular imidate glycosylation.

The formation of ketose dianhydrides by treatment of the monomers with mineral acids,[1–3] anhydrous hydrogen fluoride or pyridinium poly(hydrogen fluoride) as solvents[4–7] has been studied previously. Under such severe conditions often a variety of products were formed containing pyranoses and furanoses, interlinked *via* 1,2- and 2,3-bonds. Similarly, a mixed ketose–aldose system was obtained in this way,[8] however, aldoses gave the corresponding fluoride and did not undergo self-condensation. The first dialdose dianhydride derivative was isolated from the hydrolysate of a tree bark extract[9] and subsequently synthesized by Fujywara *et al.*[10] Recently, the formation of some other examples of dialdose dianhydrides has been reported.[11–14]

En route to the synthesis of a fucose hexasaccharide,[15] an attempt at controlled oligomerisation of compound **1** led to the dianhydride **2**. Therefore, fucose was acetylated, thiomethylated with TMSSMe under TMSOTf catalysis, deacetylated and positions 3 and 4 isopropylidenated. Under copper bromide–tetrabutylammonium bromide catalysis compound **2** † could be isolated in 22% yield from a complex mixture of oligosaccharides (Scheme 1). The ^{1}H NMR shows a symmetric compound



Scheme 1 *Reagents*: Bu_4NBr, $CuBr_2$

with $J_{1,2}$ = 4.6 and $J_{2,3}$ = 3.1 Hz. The $J_{1,2}$ coupling is about 1 Hz smaller than that expected for a chair conformation. This observation strongly suggests a boat conformation in solution. In fact, an X-ray structure analysis of the crystalline material shows three helically twisted boats for the two sugar rings and the connecting dioxane ring (Fig. 1). The two sugar rings adopt an uncommon $^3T^O$-*L*-conformation ‡ and the system exhibits almost C_2-symmetry.

Subsequently the synthesis of a corresponding compound with a D- and an L-fucose was investigated. This molecule should prefer chair conformations throughout, have a centre of inversion instead of a C_2-axis, and should be achiral.

D-Fucose, obtained from 1 : 2; 3 : 4-di-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranose by reduction with lithium aluminium hydride and de-isopropylidenation, was thiomethylated as described above, isopropylidenated at positions 3 and 4 and *p*-methoxybenzylated at position 2 to give the donor **4**. As acceptor molecule benzyl 3,4-*O*-isopropylidene-α-L-fucose (**3**) was prepared from L-fucose by a Fischer glycosylation with subsequent isopropylidenation. Using copper bromide–tetrabutylammonium bromide activation, these two compounds gave the corresponding α-linked disaccharide **5** in 84% yield. For elimination of traces of the β-linked isomer and due to problems with catalytic hydrogenation directly after the thioglycoside mediated glycosylation, the removal of the two benzyl groups was carried out in two steps. First, the 2′-position was deblocked with DDQ and then the 1-position was

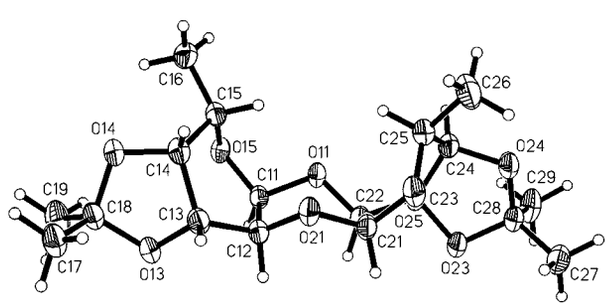


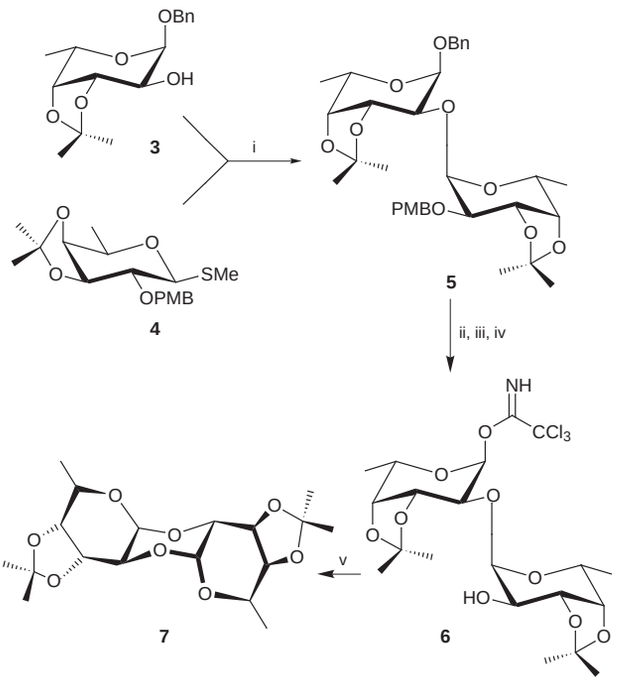
Fig. 1 X-Ray structure of **2**.[16,17] For orientation compare Scheme 1.

† Mp: 195 °C; $[\alpha]_D^{20}$ 159.8 (*c* 1.0, $CHCl_3$); δ_H(400 MHz, $CDCl_3$) 5.11 (d, 1H, $J_{1,2}$ 4.6 Hz, H-1), 4.57 (dd, 1H, $J_{2,3}$ 3.1, $J_{3,4}$ 7.6 Hz, H-3), 4.15 (dd, 1H, $J_{3,4}$ 7.6, $J_{4,5}$ 2.0 Hz, H-4), 4.13 (dq, 1H, $J_{4,5}$ 2.0, $J_{5,6}$ 6.6 Hz, H-5), 3.83 (dd, 1H, $J_{1,2}$ 4.6, $J_{2,3}$ 3.1 Hz, H-2), 1.47 (s, 3H, Pr^i), 1.35 (s, 3H, Pr^i), 1.27 (d, 3H, $J_{5,6}$ 6.6 Hz, H-6); δ_C(63 MHz, $CDCl_3$) 109.2 (Pr^i), 93.5 (C-1), 73.5 (C-4), 72.5 (C-3), 65.8 (C-5), 64.1 (C-2), 25.7 (Pr^i), 24.5 (Pr^i), 15.4 (C-6) ppm; *m*/*z* (EI) (372.18), 357 (M − 15) [Calc. for $C_{18}H_{28}O_8$ (372.42): C, 58.05; H, 7.58. Found: C, 58.02; H, 7.46%]. *Crystal data*. For **2**: $C_{18}H_{28}O_8$, M = 372.4, λ 1.541 78 Å, monoclinic, *C*2, a = 24.52(2), b = 6.231(5), c = 24.98(2) Å, β = 95.84(7)°, U = 3797(5) Å^3, Z = 8, D_c = 1.303 Mg m^{-3}, μ = 0.0857 mm^{-1}, F(000) = 1600, T = −100 °C, reflections collected 6977, independent reflections 6358 [R(int) = 0.0193] refined on F^2 to R = 0.0385, wR_2 = 0.1021 for data with $I > 2\sigma(I)$. For **7**: $C_{18}H_{28}O_8$, M = 372.4, λ 1.541 78 Å, triclinic, $P\bar{1}$, a = 6.199(2), b = 8.083(2), c = 9.716(3) Å, α = 86.12(2), β = 88.78(3), γ = 67.09(2)°, U = 447.4(2) Å^3, Z = 1, D_c = 1.382 Mg m^{-3}, μ = 0.0909 mm^{-1}, F(000) = 200, T = −100 °C, reflections collected 2073, independent reflections 1643 [R(int) = 0.0132] refined on F^2 to R = 0.0403, wR_2 = 0.1198 for data with $I > 2\sigma(I)$.

Data for both crystals were collected on an Enraf-Nonius CAD4 diffractometer using Cu-Kα radiation. Data analysis was carried out with the program CADSHEL.[16] Both structures were solved using direct methods with the SHELX86 program.[17] In both structures the non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were included in geometric positions. In structure **2** there are two molecules in the asymmetric unit. Both structures were refined using SHELXL93.[18] Atomic coordinates, bond lengths and angles and the thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc*., *Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/217.

‡ Cremer–Pople parameters[19] for the four sugar rings (two molecules in the asymmetric unit): Q = 0.682(2) Å, θ = 96.9(2)°, φ = 142.9(2)°. Values for ideal $^3B^O$ conformation: θ = 90°, φ = 120° and for ideal $^3T^O$ conformation: θ = 90°, φ = 150°.[20]

deprotected by catalytic hydrogenation. The disaccharide could be activated with potassium carbonate and trichloroacetonitrile. Under such weakly basic conditions no formation of a 2′-imidate occurred but the quantitative transfer to the disaccharide α-imidate **6** was observed. By activation with TMSOTf, the compound cyclised easily, and in 50% yield the expected product **7** was obtained. Alternatively, the last two steps could be carried out in a one-pot synthesis to yield the material **7**§ in 30%, roughly similar to the overall yield of the two single steps (Scheme 2). The ^{1}H NMR spectrum shows a



Scheme 2 *Reagents*: i, Bu_4NBr, $CuBr_2$; ii, DDQ; iii, H_2, Pd/C; iv, CCl_3CN, K_2CO_3; v, TMSOTf

symmetric compound with $J_{1,2} = 1.5$ and $J_{3,4} = 2.5$ Hz. Both, the $J_{1,2}$ and the $J_{3,4}$ couplings are 2 Hz smaller than expected for compounds with a normal α-linkage. All the other couplings are in an expected range for typical chair conformations. As anticipated the achiral compound does not show any optical rotation. Surprisingly, the X-ray structure analysis (Fig. 2) indicates two boat conformations for the sugar rings and the expected chair conformation for the central 1,4-dioxane ring. The sugar rings adopt $^2B^5$ conformations¶ and the system has an inversion centre.

Experimental

Glycosylation with thioglycosides

Compounds **4** (502 mg, 1.41 mmol) and **3** (415 mg, 1.41 mmol) were evaporated three times with toluene and dissolved in DCM–DMF (1 : 1) under argon. The solution was stirred with freshly activated molecular sieves (1.5 g) for 1 h, tetrabutylammonium bromide (1.24 g, 3.84 mmol) was added and the solution again stirred for 1 h followed by addition of copper(II) bromide (890 mg, 4.05 mmol). After 1 d the suspension was filtered through Celite, diluted with ethyl acetate and washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and evaporated. Following flash chromatography (toluene–ethyl acetate 5 : 1) the syrupy product **5** containing traces of the β-glycoside (717 mg, 1.19 mmol, 84%) was obtained.

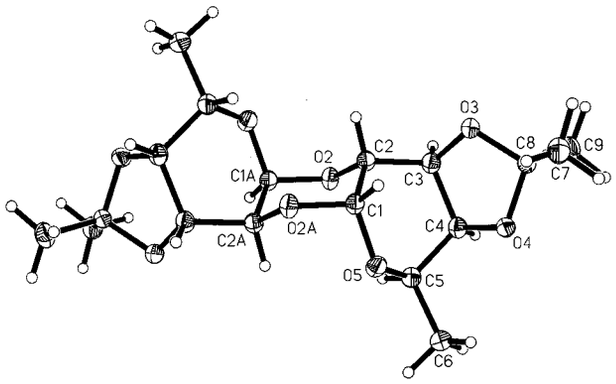


Fig. 2 X-Ray structure of **7**. For orientation compare Scheme 2.

Glycosylation with glycosyl trichloroacetimidates

Under an argon atmosphere at −15 °C, a solution of **6** (65 mg, 0.12 mmol) in anhydrous diethyl ether (5 ml) was treated with trimethylsilyl triflate (0.02 ml, 0.11 mmol), dissolved in diethyl ether (0.5 ml). The combined solutions were allowed to warm to room temperature and stirred for 1 d. Subsequently, sodium hydrogen carbonate was added and after filtration, column chromatography [light petroleum (bp 50–70 °C)–ethyl acetate 3 : 1] gave the colourless crystalline product **7** (23 mg, 0.061 mmol, 51%).

Acknowledgements

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§ Mp: 218 °C (decomp.); δ_H(400 MHz, $CDCl_3$) 5.08 (d, 1H, $J_{1,2}$ 1.5 Hz, H-1), 4.47 (dq, 1H, $J_{4,5}$ 1.5, $J_{5,6}$ 6.6 Hz, H-5), 4.36 (dd, 1H, $J_{2,3}$ 7.6, $J_{3,4}$ 2.5 Hz, H-3), 4.20 (t ≈ dd, 1H, $J_{3,4}$ 2.5, $J_{4,5}$ 1.5 Hz, H-4), 4.10 (dd, 1H, $J_{1,2}$ 1.5, $J_{2,3}$ 7.6 Hz, H-2), 1.46 (s, 3H, Pr^i), 1.34 (s, 3H, Pr^i), 1.32 (d, 3H, $J_{5,6}$ 6.6 Hz, H-6) ppm; δ_C(100 MHz, $CDCl_3$) 109.2 (Pr^i), 89.6 (C-1), 74.2 (C-2), 73.2 (C-3), 69.8 (C-5), 63.4 (C-4), 26.3 (Pr^i), 24.0 (Pr^i), 17.3 (C-6) [Calc. for $C_{18}H_{28}O_8$ (372.42): C, 58.05; H, 7.58. Found: C, 57.79; H, 7.48%].

¶ Cremer–Pople parameters[19] for the sugar ring: $Q = 0.640(1)$ Å, $\theta = 90.2(1)°$, $\varphi = 290.4(1)°$. Values for ideal $^2B^5$ conformation: $\theta = 90°$, $\varphi = 300°$ and for ideal $^2T^5$ conformation: $\theta = 90°$, $\varphi = 270°$.[20]