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Note

β-Anomeric selectivity in the glycosidation of D-mannofuranurono-6,3-lactone catalyzed by boron trifluoride diethyl etherate

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Abstract

The BF_3-promoted glycosylation of D-mannofuranurono-6,3-lactone with dodecanol or methanol afforded *n*-alkyl β-D-mannofuranosidurono-6,3-lactone. Reduction of *n*-dodecyl β-D-mannofuranosidurono-6,3-lactone with sodium borohydride yielded the corresponding alkyl β-D-mannofuranoside. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

D-Mannofuranurono-6,3-lactone **1** is obtained by acid hydrolysis of alginic acid[1] and its crystalline form is the β-anomer.[2] Contrary to D-glucofuranurono-6,3-lactone,[3] D-mannofuranurono-6,3-lactone has been scarcely used in glycosylation reactions; the few examples concerned the acid-catalyzed glycosidation with methanol to yield the corresponding methyl D-mannofuranosidurono-6,3-lactone in which the thermodynamically favoured α-D anomer predominates.[4,5] Isbell and Salam, in 1982, reported the preparation of methyl α-D-mannofuranosidurono-6,3-lactone **2** in 74% yield, by refluxing lactone **1** in methanol for 6 h in the presence of Dowex 50W-X4 resin (Scheme 1, a). The reaction was stereoselective and the α-configuration was evidenced by a positive optical rotation of $+49.6°$ (*c* 1.0, H_2O).[4]

The aim of the present work was to investigate the reactivity of D-mannofuranurono-6,3-lactone in heterogeneous media using $BF_3{\cdot}Et_2O$ as a promoter and to compare the stereoselectivity of the glycosylation with that obtained by Isbell and Salam.

2. Results and discussion

Under our conditions, the reaction of D-mannofuranurono-6,3-lactone **1** with dodecanol in refluxing tetrahydrofuran for 2 h in the presence of boron trifluoride diethyl etherate afforded almost exclusively dodecyl β-D-mannofuranosidurono-6,3-lactone **3** (68% yield, α/β 1:9). Purification of the crude product by column chromatography led to the pure β-anomer (57% yield) in addition to a mixture of the two anomers (9% yield, α/β 3:1) (Scheme 1, b). The structure of the pure anomer was determined by its specific rotation, $[\alpha]_D^{20}$ $-27.5°$ (*c* 1.0, $CHCl_3$), in accordance with Hudson's rules.[6] This unexpected stereoselectivity was confirmed by NMR spectroscopy, especially by running COSY, HETCOR and *t*-ROESY experiments on the anomeric mixture (Table 1).

The $^3J_{H1-H2}$ coupling constants of 2.0 and 4.6 Hz were assigned respectively to α and β-anomers, since a

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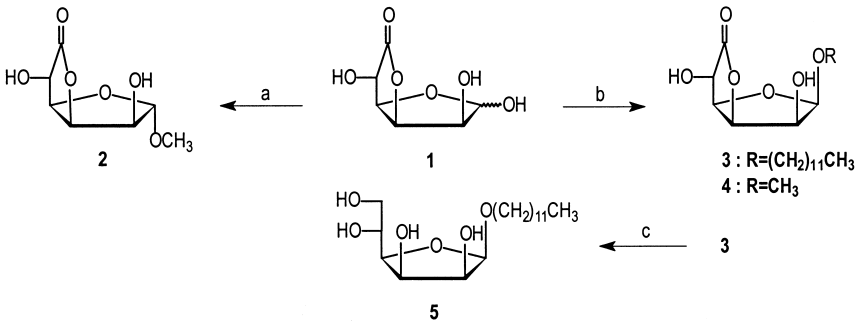

Scheme 1. Reagents: (a) CH_3OH, Dowex 50W-X4 resin; (b) n-$C_{12}H_{25}OH$ (2 equiv) or CH_3OH (6 equiv), $BF_3{\cdot}Et_2O$ (2–3 equiv), THF; (c) $NaBH_4$ (4 equiv), THF.

$J_{1,2}$ value smaller than 4 Hz in a furanoside is indicative of trans coupled protons.[7] The t-ROESY[8] experiment was used to confirm the anomeric configuration of the major compound **3** since the selectivity of the reaction was unexpected. We measured that the relative cross-peaks volumes between H-1 and H-3 were higher than those found between H-2 and H-4 (42.1 and 27.9, respectively).

This result implies that the distance between H-1 and H-3 is shorter than between H-2 and H-4 and that all these protons are in a syn relationship. In the case of the α-anomer, the distance between H-1 and H-3 would have been larger than between H-2 and H-4, with a trans relationship. This t-ROESY experiment was therefore an additional evidence of the β-configuration of the major product **3**.

The stereoselectivity of the reaction was unexpected since the formation of the 1,2-*cis* mannofuranoside should be inhibited by steric hindrance. Considering the low flexibility of this bicyclic structure, the existence of a conformational intermediate in solution which could allow the highly selective formation of this 1,2-cis isomer is unlikely. This result could rather be explained by preferential coordination between boron trifluoride and the α-anomer of the mannuronolactone **1** for steric reasons:[9] indeed the presence of the hydroxyl groups and the lactone unit on the β-face of the starting mannofuranuronolactone may inhibit interactions between the β-anomer and BF_3. This could kinetically promote the formation of the β-glycoside.

When D-mannurono-6,3-lactone **1** was treated with methanol under the same conditions, the reaction was stereospecific in favor of methyl β-D-mannofuranosidurono-6,3-lactone **4** characterized by a negative optical rotation of $-11.5°$ (c 1.0, CH_3OH): no α-anomer was isolated after column chromatography. The low yield of the reaction (30%) resulted probably from the work-up procedure used to neutralize BF_3 (addition of triethylamine), as well as from the purification step (removal of salts) which required the absence of water given the instability of the methyl glycoside in aqueous media.[4]

Our attention was subsequently directed towards the preparation of the n-dodecyl β-D-mannofuranoside **5**. Treatment of a solution of lactone **3** in THF with two equivalents of sodium borohydride yielded **5** in 60% yield.

The result reported here is of interest as this is one of the very few examples where a β-D-mannofuranoside derivative has been synthesized without using the tethering strategy.[10] Further research on the usefulness of this novel route for the synthesis of disaccharides containing a β-D-mannofuranoside moiety at a non reducing position is in progress.

3. Experimental

3.1. General methods

All reagents were commercially available from Sigma or Acros and used without further purification. Tetrahydrofuran was dried over sodium/benzophenone and distilled. TLC were conducted on precoated non activated plates (E. Merck 60 F_{254}) and compounds were visualized using a 5% soln of H_2SO_4 in EtOH followed by heating. For column chromatography, E. Merck 60H (5–40 μm) Silica Gel was used. IR spectrum was recorded on a IRFT Nicolet 205 spectrometer. Optical rotation was measured on a Perkin–Elmer 341 polarimeter at 20 °C using a 1-dm cell. ^1H and ^{13}C NMR spectra were recorded on Bruker ARX 400 spectrometer (400 and 100 MHz for ^1H and ^{13}C, respectively) and on a Bruker DRX500 (500 and 125 MHz for ^1H and ^{13}C, respectively) in $CDCl_3$ at 298K. Chemical shifts are given in δ-units measured downfield from Me_4Si at 0 ppm using the residual solvent signal as secondary reference.

3.2. n-Dodecyl β-D-mannofuranosidurono-6,3-lactone (3)

To a suspension of D-mannofuranurono-6,3-lactone (**1**, 100 mg, 0.57 mmol) in dry THF (2 mL) were added 1-dodecanol (254 μL, 1.14 mmol) and $BF_3{\cdot}Et_2O$ (140

Table 1
^{1}H NMR chemical shifts (δ values) [a] and coupling constants (Hz) measured at 400 MHz and ^{13}C NMR chemical shifts (δ values) measured at 100 MHz and recorded in $CDCl_3$ for compound **3** and the anomeric mixture of **3**

Compound	H-1	H-2	H-3	H-4	H-5	OCH_{α}	OCH_{β}	OCH_2CH_2	CH_2	CH_3
3	4.96d ($^{3}J_{1,2}$ 4.6)	4.20dt ($^{3}J_{2,3}$ 4.9)	4.85t ($^{3}J_{3,4}$ 4.9)	4.74dd ($^{3}J_{4,5}$ 6.8)	4.35d	3.40dt (^{3}J6.8 9.4)	3.72dt (^{3}J 7.0)	1.48–1.52m	1.12–1.25m	0.81t (^{3}J 6.6)
α anomer of **3**	5.06d ($^{3}J_{1,2}$ 2.0)	4.34dd ($^{3}J_{2,3}$ 4.6)	5.00t ($^{3}J_{3,4}$ 4.6)	4.78dd ($^{3}J_{4,5}$ 6.1)	4.46d	3.46dt (^{3}J6.6 9.7)	3.72dt (^{3}J 6.6)	1.53–1.61m	1.21–1.35m	0.88t (^{3}J 6.6)
Compound	C-1	C-2	C-3	C-4	C-5	C-6	OCH_2	CH_2	CH_2CH_3	CH_3
3	101.5	73.4	77.4	74.9	69.6	174.0	70.4	25.8–31.9	22.7	14.1
α anomer of **3**	109.1	76.6	79.1	75.3	69.4	174.2	69.1	26.1–32.0	22.8	14.2

[a] Signal multiplicities: d, doublet; t, triplet.

μL, 1.14 mmol). The reaction medium was refluxed until homogeneous. After solvent removal, the residue was dissolved in EtOAc (10 mL). The organic layer was successively washed with 5% aq HCl (3 × 2 mL), H_2O (6 × 3 mL), dried ($MgSO_4$) and concentrated. The crude oil was purified by chromatography (1:1 light petroleum–Et_2O, then Et_2O and finally 95:5 Et_2O:MeOH) affording **3** (111 mg, 57%) in addition to a mixture of α, β anomers (17 mg, 9% α/β 3:1). **3**: mp 94–102 °C (Et_2O); $[\alpha]_D^{20}$ −27° (*c* 1, $CHCl_3$); TLC (9:1 CH_2Cl_2–MeOH): R_f 0.49; IR (HCB); ν 1777 (C=O) and 3350 cm^{-1} (OH). Anal. Calcd for $C_{18}H_{32}O_6$: C, 62.77; H, 9.36. Found: C, 62.71; H, 9.44.

3.3. Methyl β-D-mannofuranosidurono-6,3-lactone (4)

To a suspension of D-mannofuranurono-6,3-lactone (**1**, 50 mg, 0.28 mmol) in dry THF (2 mL) were added MeOH (69 μL, 1.70 mmol) and $BF_3{\cdot}Et_2O$ (104 μL, 0.85 mmol). The reaction medium was refluxed overnight. After solvent removal, the residue was dissolved in 7:3 EtOAc:BuOH (10 mL) and triethylamine (50 μL) was added for neutralization. The mixture was filtrated on Celite® 521, concentrated and the residue was purified on silica gel (9:1 CH_2Cl_2:MeOH). A second purification on Sephadex LH-20 using MeOH as eluent afforded **4** (16 mg, 30%): $[\alpha]_D^{20}$ −11° (*c* 1, MeOH); TLC (4:1 CH_2Cl_2–MeOH): R_f 0.29; IR (HCB); ν 1776 (C=O) and 3300 cm^{-1} (OH). ^1H NMR (CD_3OD): δ 4.85–4.91 (m, 2H, H-1 H-3), 4.74 (dd, 1H, $J_{3,4}$ 4.6, $J_{4,5}$ 6.6 Hz, H-4), 4.49 (d, 1H, H-5), 4.20 (t, 1H, $J_{1,2}$ 4.6, $J_{2,3}$ 4.6 Hz, H-2), 3.40 (s, 3H, OCH_3); ^{13}C NMR (CD_3OD): δ 177.3 (C=O), 104.0 (C-1), 79.7 (C-3), 77.0 (C-4), 74.7 (C-2), 70.8 (C-5), 56.3 (OCH_3). Anal. Calcd for $C_7H_{10}O_6$: C, 44.22; H, 5.30. Found: C, 44.29; H, 5.39.

3.4. *n*-Dodecyl β-D-mannofuranoside (5)

To a solution of *n*-dodecyl β-D-mannofuranosidurono-6,3-lactone (**3**, 25 mg, 0.073 mmol) in dry THF (2 mL) at 0 °C was added $NaBH_4$ (11 mg, 0.290 mmol). After stirring at room temperature overnight, 7:3 EtOAc–BuOH (10 mL) was added and the soln was successively washed with 5% aq HCl (2 × 1 mL) and 5% aq $NaHCO_3$ (0.5 mL). The organic layer was concentrated and purification by chromatography (95:5 EtOAc–MeOH) afforded **5** (15 mg, 60%): mp 52–54 °C (Et_2O); $[\alpha]_D^{20}$ −55° (*c* 1, MeOH); TLC (9:1 EtOAc–MeOH): R_f 0.33. ^1H NMR (CD_3OD): δ 4.86 (d, 1H, $J_{1,2}$ 4.7 Hz, H-1), 4.13–4.18 (m, 1H, H-3), 4.06 (t, 1H, $J_{2,3}$ 4.7 Hz, H-2), 3.87–3.93 (m, 2H, H-4 H-5), 3.79 (dd, 1H, $J_{5,6a}$ 2.0, $J_{6a,6b}$ 12.3 Hz, H-6a), 3.71 (dt, 1H, $J_{H'\text{-}1a,H'\text{-}2}$ 6.6, $J_{H'\text{-}1a,H'\text{-}1b}$ 9.6 Hz, OCH′-1a), 3.63 (dd, 1H, $J_{5,6b}$ 4.8 Hz, H-6b), 3.43 (dt, 1H, $J_{H'\text{-}1b,H'\text{-}2'}$6.4 Hz, OCH′-1b), 1.53–1.64 (m, 2H, OCH_2CH_2), 1.29 (s, 18H, CH_2), 0.90 (t, 3H, *J* 6.4 Hz, CH_3); ^{13}C NMR (CD_3OD): δ 103.0 (C-1), 81.4 (C-4), 73.9 (C-2), 71.9 (C-3 C-5), 69.7 (OCH_2), 64.7 (C-6), 33.1 30.8–30.5 27.3 (CH_2), 23.7 (CH_2CH_3), 14.5 (CH_3). Anal. Calcd for $C_{18}H_{36}O_6$: C, 62.04; H, 10.41. Found: C, 61.79; H, 10.49.

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