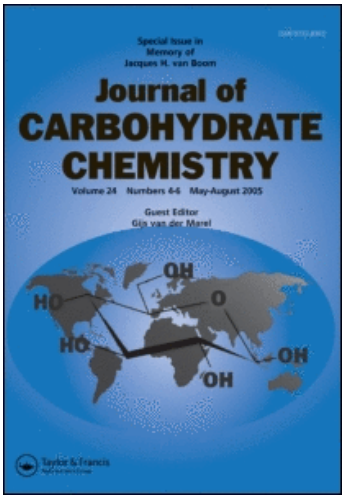

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SYNTHESIS OF METHYL α-D-ALLOPYRANOSIDE AND METHYL α-D-*Ribo*-HEXOPYRANOSIDE: A CONVENIENT CHEMOENZYMATIC APPROACH

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ABSTRACT

An efficient chemoenzymatic synthesis of methyl α-D-allopyranoside and methyl 3-deoxy-α-D-*ribo*-hexopyranoside starting from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside is described.

INTRODUCTION

In recent years we have been involved in a project concerning the study of the lipase mediated acylation of the secondary hydroxyl groups of methyl glycosides.[1-5] We have used as substrates for such reactions a number of monosaccharides of both the D- and L-series. Whereas some of the monosaccharide substrates were available from commercial products, others had to be synthesized before the enzymic experiment could be performed.

In the most recent aspect of the project, which involved studying the influence of the 3-hydroxyl group of the sugar on the regioselectivity of the enzymic reaction,[5] the substrates under investigation were methyl 6-*O*-butyryl-α-D- and L-allopyranosides **1a** and **2a** (FIG. 1) and the corresponding 3-deoxy derivatives, methyl 6-*O*-butyryl-3-deoxy-α-D- and L-*ribo*-hexopyranosides **3a** and **4a**. Whereas the 6-acylated products can be easily obtained by enzymic butyrylation[5,6] of the methyl α-D and L-glycosides **1b-4b**, the syntheses of these four last compounds are not trivial.

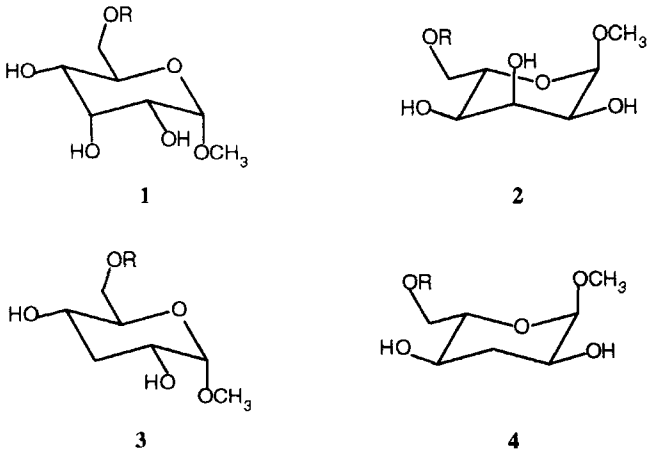


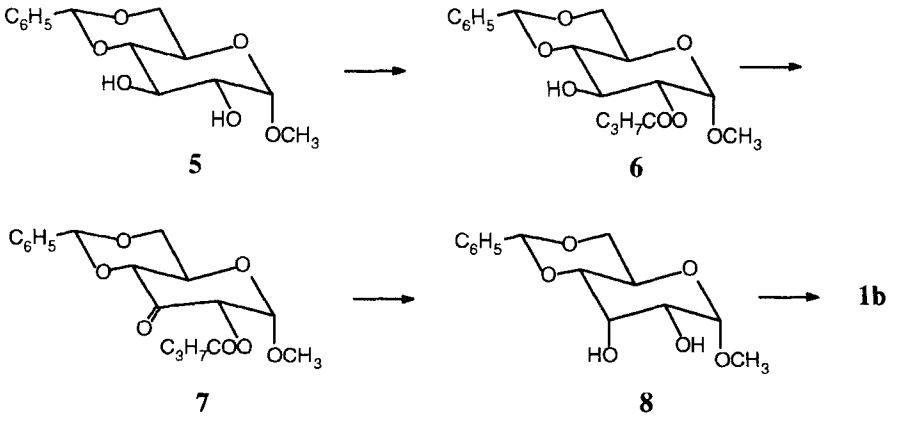
FIG. 1. **a**: R=COC_3H_7; **b**: R=H

We planned to start from methyl α-D- or L-glucopyranoside, elaborating the 3-equatorial hydroxyl by inversion to get the allosides **1b** and **2b**, or by removing the hydroxy group to get the 3-deoxysugars **3b** and **4b**. The choice of a methyl glycoside as starting material instead of the reducing sugar, was preferred since synthesis of the free allose followed by its methanolic glycosidation gives low product yields.[7]

RESULTS AND DISCUSSION

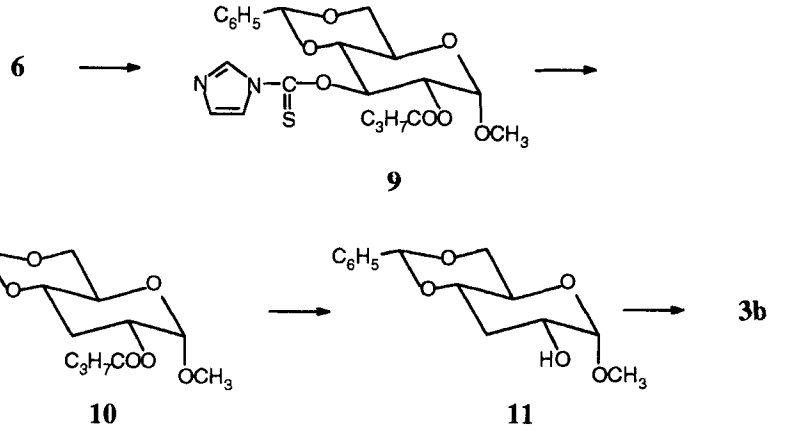
Some syntheses of **1b** and **3b** starting from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside are described[8-12] in the literature, but in overall yields of 35-45%. We have devised a new chemoenzymatic procedure which remarkably improves the yields (about 60-65%), starting from the same compound used in the chemical synthesis. Enzymic acylation[13a,b] of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**5**) with lipase PS adsorbed on celite, using 2,2,2-trifluoroethyl butyrate (TFEB) as acylating agent, afforded in high yield methyl 4,6-*O*-benzylidene-2-*O*-butyryl-α-D-glucopyranoside (**6**, Scheme 1). Compound **6** was oxidized[8] to the 3-keto derivative **7** which, in turn, yielded directly and efficiently known methyl 4,6-*O*-benzylidene-α-D-allopyranoside (**8**)[9] by sodium borohydride reduction. The 2-ester group of **7** was also removed during the reduction step. Hydrolytic deprotection of the 4,6-*O*-benzylidene function yielded the desired methyl α-D-allopyranoside (**1b**).[9]

From the same enzymatically prepared precursor **6**, used for the synthesis of the allopyranoside **1b**, methyl 3-deoxy-α-D-*ribo*-hexopyranoside (**3b**) was also obtained (Scheme 2). Following the procedure of Rasmussen *et al.*[10] compound **6** was converted in



SCHEME 1

high yield to the imidazolylthiocarbonyl derivative **9**, which, when submitted to tri-*n*-butylstannane reduction,[10] afforded the 3-deoxy derivative **10**. Finally, **10** was easily converted to **3b**,[12,14] *via* methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*ribo*-hexopyranoside[15] (**11**) by treatment with methanolic sodium methoxide and hydrolytic removal of the 4,6-*O*-benzylidene group with Dowex-50 (H^+).



SCHEME 2

Our attempts to apply the chemoenzymatic procedure to the synthesis of the sugars of the L-series, **2b** and **4b**, failed. When methyl 4,6-*O*-benzylidene-α-L-glucopyranoside was submitted to the enzymatic reaction described above, only very low yields of the 2-*O*-butyryl compound were obtained, confirming the lack of reactivity of the 2-position in the L-gluco series.[4] Compounds **2b** and **4b** were synthesized[5] according to the procedures published for the D-enantiomers.[8-10]

EXPERIMENTAL

General procedures. ^{1}H NMR spectra were recorded with Bruker AC-200 or AM-500 spectrometers in deuteriochloroform solutions, using Me_4Si as an internal standard, unless otherwise stated. Optical rotations were measured with a Perkin Elmer 241 polarimeter at 25 °C, as chloroform solutions, unless otherwise stated. Analytical thin layer chromatography (TLC) was carried out on Merck 60 F_{254} silica gel plates (0.25 mm thickness) and the spots were detected by spraying with 50% aqueous H_2SO_4 and heating at 110 °C. Flash chromatography was performed with Merck 60 silica gel (230-400 mesh). Methyl 4,6-*O*-benzylidene-α-D- and L-glucopyranoside were prepared according to Evans.[16] *Pseudomonas cepacia* lipase (lipase PS) (LPS) (specific activity 30.5 units/mg solid), a generous gift from Amano Pharmaceutical Co., was supported on celite according to Bovara *et al.*[17] Tetrahydrofuran and toluene were distilled just prior to use from sodium, dimethyl sulfoxide from calcium hydride, and methanol from magnesium. Methylene chloride and 1,2-dichloroethane were dried over 3Å molecular sieves. Evaporation of solvents under reduced pressure was always effected with the bath temperature kept below 40 °C.

Methyl 4,6-*O*-Benzylidene-2-*O*-butyryl-α-D-glucopyranoside (6). To a solution of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**5**) (20 g, 71.0 mmol) in a toluene-THF 4:1 mixture (350 mL) 2,2,2-trifluoroethyl butyrate (TFEB, 80 mL) and *Pseudomonas cepacia lipase* (LPS) supported on celite (100 g) were added. After stirring at 45 °C for 7 h, the enzyme was filtered off and the solvent evaporated under reduced pressure. The crude product was submitted to flash chromatography (hexane-ethyl acetate 3:2 as eluant) affording 24.4 g (98%) of methyl 4,6-*O*-benzylidene-2-*O*-butyryl-α-D-glucopyranoside (**6**), mp 117-118 °C (from methylene chloride); $[\alpha]_D$ +94.3° (*c* 1.0); ^{1}H NMR δ 1.00 (t, 3H, J = 7.5 Hz, CH_3), 1.72 (m, 2H, CH_2), 2.42 (t, 2H, J = 7.5 Hz, CH_2CO), 3.42 (s, 3H, MeO), 3.58 (dd, 1H, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 10.0 Hz, H-4), 3.78 (dd, 1H, $J_{5,6b}$ = 10.5 Hz, $J_{6a,6b}$ = 10.0 Hz, H-6b), 3.87 (ddd, 1H, $J_{5,6a}$ = 5.0 Hz, H-5), 4.20 (dd, 1H, $J_{2,3}$ = 10.0 Hz, H-3), 4.32 (dd, 1H, H-6a), 4.82 (dd, 1H, $J_{1,2}$ = 3.5 Hz, H-2), 4.98 (d, 1H, H-1), 5.57 (s, 1H, CHPh), 7.35-7.55 (m, 5H, Ph).

Anal. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86. Found: C, 61.29; H, 6.80.

Methyl 4,6-*O*-Benzylidene-2-*O*-butyryl-α-D-*ribo*-hexopyranosid-3-ulose (7). To a solution of **6** (10 g, 28.4 mmol) in 400 mL of dimethyl sulfoxide containing 24 g (116.3 mmol) of dicyclohexylcarbodiimide was added orthophosphoric acid (1.6 g, 16.3 mmol). The reaction mixture was stirred overnight at room temperature. After work-up as described by Baker and Buss,[8] the crude product was purified by flash chromatography (methylene chloride-acetone 20:1 as eluant) yielding 8.97 g (90%) of **7**, mp 154-155 °C

(from ethyl acetate); $[\alpha]_D$ +57.1° (*c* 1.0); ^{1}H NMR δ 1.01 (t, 3H, J = 7.5 Hz, CH_3), 1.74 (m, 2H, CH_2), 2.45 (dt, 1H, J = 7.5 Hz, J = 15.0 Hz, CH_aCO), 2.55 (dt, 1H, CH_bCO), 3.48 (s, 3H, MeO), 3.96 (dd, 1H, $J_{5,6b}$ = 9.5 Hz, $J_{6a,6b}$ = 10.0 Hz, H-6b), 4.14 (ddd, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6a}$ = 4.5 Hz, H-5), 4.38 (dd, 1H, $J_{2,4}$ = 1.5 Hz, H-4), 4.44 (dd, 1H, H-6a), 5.24 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 5.43 (dd, 1H, $J_{1,2}$ = 4.0 Hz, H-2), 5.60 (s, 1H, CHPh), 7.32-7.58 (m, 5H, Ph).

Anal. Calcd for $C_{18}H_{22}O_7$: C, 61.71; H, 6.33. Found: C, 61.66; H, 6.40.

Methyl 4,6-*O*-Benzylidene-α-D-allopyranoside (8). To a solution of **7** (8.97 g, 25.6 mmol) in 18 mL of distilled *N,N*-dimethylformamide and 850 mL of dry methanol, sodium borohydride (17 g, 423.0 mmol) was added in portions. After the reaction mixture was stirred at room temperature for 1 h, the crude product was recovered according to Baker and Buss[8] and purified by flash chromatography (methylene chloride-acetone 4:1 as eluant) affording 6.17 g (85%) of known **8**.[8,9]

Methyl α-D-Allopyranoside (1b). A mixture of **8** (6.17 g, 21.9 mmol) and Dowex-50x8 (H^+) (15 g) in water (70 mL) was heated at 60 °C for 1 h. The resin was filtered off and the solvent evaporated under reduced pressure to give 3.81 g (89%) of methyl α-D-allopyranoside[9] (**1b**), amorphous solid; $[\alpha]_D$ +151.0° (*c* 1.0, water); ^{1}H NMR, (D_2O, reference to HDO at 4.55 ppm), δ 3.23 (s, 3H, MeO), 3.43 (dd, 1H, $J_{3,4}$ = 3.0 Hz, $J_{4,5}$ = 10.0 Hz, H-4), 3.57 (dd, 1H, $J_{1,2}$ = 4.0 Hz, $J_{2,3}$ = 3.5 Hz, H-2), 3.60 (dd, 1H, $J_{5,6b}$ = 6.0 Hz, $J_{6a,6b}$ = 10.0 Hz, H-6b), 3.62 (ddd, 1H, $J_{5,6a}$ = 1.0 Hz, H-5), 3.72 (d, 1H, H-6a), 3.91 (dd, 1H, H-3), 4.61 (d, 1H, H-1).

Anal. Calcd for $C_7H_{14}O_6$: C, 43.30; H, 7.27. Found: C, 44.0; H, 7.15.

Methyl 4,6-*O*-Benzylidene-2-butyryl-3-*O*-(imidazolylthiocarbonyl)-α-D-gluco-pyranoside (9). To a solution of **6** (10 g, 28.4 mmol) in 1,2-dichloroethane (140 mL) 1,1'-thiocarbonyldiimidazole (11.5 g, 64.6 mmol) was added and the reaction mixture was refluxed for 2 h under an argon atmosphere. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (ethyl acetate-hexane 1:1 as eluant) to yield 12.9 g (98%) of pure **9**, oil; $[\alpha]_D$ +35.2° (*c* 1.0); ^{1}H NMR, δ 0.81 (t, 3H, J = 7.5 Hz, CH_3), 1.55 (m, 2H, CH_2), 2.29 (t, 2H, J = 7.5 Hz, CH_2CO), 3.49 (s, 3H, MeO), 3.86 (dd, 1H, $J_{5,6b}$ = 9.5 Hz, $J_{6a,6b}$ = 10.0 Hz, H-6b), 3.92 (dd, 1H, $J_{3,4}$ = 10.0 Hz, $J_{4,5}$ = 10.0 Hz, H-4), 4.07 (ddd, 1H, $J_{5,6a}$ = 4.5 Hz, H-5), 4.38 (dd, 1H, H-6a), 5.01 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 5.23 (dd, 1H, $J_{2,3}$ = 10.0 Hz, H-2), 5.55 (s, 1H, CHPh), 6.45 (dd, 1H, H-3), 7.04 (dd, 1H, J = 1.5 Hz, J = 1.0 Hz, Im), 7.30-7.50 (m, 5H, Ph), 7.61 (dd, 1H, J = 1.5 Hz, J = 1.0 Hz, Im), 8.32 (dd, 1H, J = 1.0 Hz, J = 1.0 Hz, Im).

Anal. Calcd for $C_{22}H_{26}O_7N_2S$: C, 57.14; H, 5.63. Found: C, 57.02; H, 5.74.

Methyl 4,6-*O*-Benzylidene-2-*O*-butyryl-3-deoxy-α-D-*ribo*-hexopyranoside (10). A solution of **9** (12.9 g, 27.9 mmol) in dry toluene (110 mL) was added dropwise under

argon to a refluxing solution of tri-*n*-butylstannane (15.5 mL, 55.9 mmol) in toluene (650 mL). After 1 h the reaction mixture was submitted to work-up as described by Rasmussen *et al.*,[10] followed by flash chromatography (toluene-acetone 100:1 as eluant) to afford 7.79 g (83%) of pure **10**, mp 107-108 °C (from toluene); $[\alpha]_D$ +78.3° (*c* 1.0); ^{1}H NMR, δ 0.97 (t, 3H, J = 7.5 Hz, CH_3), 1.69 (m, 2H, CH_2), 2.36 (t, 2H, J = 7.5 Hz, CH_2CO), 2.14 (ddd, 1H, $J_{2,3ax}$ = 12.0 Hz, $J_{3eq,3ax}$ = 11.0 Hz, $J_{3ax,4}$ = 12.0 Hz, H-3ax), 2.24 (ddd, 1H, $J_{2,3eq}$ = 5.0 Hz, $J_{3eq,4}$ = 4.0 Hz, H-3eq), 3.46 (s, 3H, MeO), 3.66 (ddd, 1H, $J_{4,5}$ = 9.0 Hz, H-4), 3.75 (dd, 1H, $J_{5,6b}$ = 10.0 Hz, $J_{6a,6b}$ = 10.0 Hz, H-6b), 3.82 (ddd, 1H, $J_{5,6a}$ = 4.5 Hz, H-5), 4.30 (dd, 1H, H-6a), 4.84 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.95 (ddd, 1H, H-2), 5.55 (s, 1H, CHPh), 7.31-7.55 (m, 5H, Ph).

Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.28; H, 7.14. Found: C, 64.11; H, 7.29.

Methyl 4,6-*O*-Benzylidene-3-deoxy-α-D-*ribo*-hexopyranoside (11). 7.79 g (23.2 mmol) of **10** were dissolved in methanolic sodium methoxide (0.07 M, 220 mL). After 1 h at room temperature the reaction mixture was neutralized with Dowex-50x8 (H^+), filtered and the solvent evaporated under reduced pressure to yield a crude product which was purified by flash chromatography (ethyl acetate-hexane 1:1 as eluant) to give 5.55 g (90%) of the known methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*ribo*-hexopyranoside **11**.[15]

Methyl 3-Deoxy-α-D-*ribo*-hexopyranoside (3b). A mixture of **11** (5.55 g, 20.9 mmol) and Dowex-50x8 (H^+) (14.0 g) was heated in water (100 mL) at 60 °C for 1 h. The resin was filtered-off and the solvent evaporated under reduced pressure to give 3.31 g (89%) of **3b**,[12,14] oil; $[\alpha]_D$ +157.8° (*c* 1.0, MeOH); ^{1}H NMR, (D_2O), δ 1.51 (ddd, 1H, $J_{2,3ax}$ = 12.0 Hz, $J_{3eq,3ax}$ = 11.0 Hz, $J_{3ax,4}$ = 11.0 Hz, H-3ax), 1.96 (ddd, 1H, $J_{2,3eq}$ = 5.0 Hz, $J_{3eq,4}$ = 5.0 Hz, H-3eq), 3.24 (s, 3H, MeO), 3.32 (ddd, 1H, $J_{4,5}$ = 11.0 Hz, $J_{5,6a}$ = 2.5 Hz, $J_{5,6b}$ = 6.0 Hz, H-5), 3.42 (ddd, 1H, H-4), 3.51 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, H-6b), 3.61 (ddd, 1H, $J_{1,2}$ = 3.5 Hz, H-2), 3.65 (dd, 1H, H-6a), 4.50 (d, 1H, H-1).

Anal. Calcd for $C_7H_{14}O_5$: C, 47.19; H, 7.92. Found: C, 47.32; H, 7.81.

Enzymic acylation of methyl 4,6-*O*-benzylidene-α-L-glucopyranoside. 60 mg (0.21 mmol) of methyl 4,6-*O*-benzylidene-α-L-glucopyranoside were submitted to enzymic acylation with TFEB and LPS supported on celite in the conditions described for **5**. The reaction was monitored by TLC (hexane-ethyl acetate 3:2 as eluant) and, after 4 days, the crude product after recovering was submitted to flash chromatography (hexane-ethyl acetate 3:2) affording 8 mg of 2-butyrate (by ^{1}H NMR analysis).

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