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ENZYMIC ACYLATION OF SUGARS. RATIONALE OF THE REGIOSELECTIVE BUTYRYLATION OF SECONDARY HYDROXY GROUPS OF D- AND L-GALACTO AND MANNOPYRANOSIDES.

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Abstract - Methyl 6-O-butyryl-α-D- and -L-galactopyranoside and methyl 6-O-butyryl-α-D- and -L-mannopyranoside, which present three contiguous secondary hydroxy groups in different orientations, have been acylated using three hydrolytic enzymes, Porcine pancreatic, *Candida cylindracea*, and *Pseudomonas fluorescens* lipases in organic solvents. Some generalization of the obtained results is discussed.

INTRODUCTION

The use of hydrolytic enzymes in unnatural nonaqueous media has opened a new entry into regioselective protection of polyhydroxylated moieties. Simple monosaccharides furnish readily available substrates to test the scope of this transesterification procedure which utilizes enzymes such as lipases and proteases to move an acyl group from a proper carrier to an acceptor polyalcohol.[1-11] Most of the sugars however carry one primary alcoholic function whose reactivity, higher than that of the secondary functions, has usually prevented from focusing the attention on the study of the relative reactivity of secondary hydroxyl groups.

Some results on the double acylation of D-glucose, galactose and mannose have been reported;[2] they indicate, after formation of the 6-butyrate, a preferred butyrylation at the 2 and/or 3 over the 4 position, analogously to the results obtainable by chemical acylation.

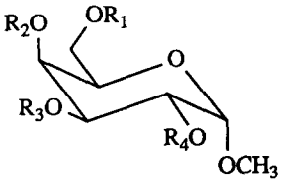
In an attempt to discover the reasons of the complete absence of reactivity at C-4 we have first studied[3,10] four substrates in which the primary alcohol is absent, namely methyl α-L- and α-D-rhamnopyranoside and methyl α-L- and α-D-fucopyranoside, and found that direct enzymic butyrylation at C-4 was possible for the two sugars belonging to the L series. A proper sequence of three hydroxyl groups seems necessary to give good yields and regioselection;[10] moreover, is this sequence which determines the butyrylation site, whereas other structural features have only minor importance.

In order to extend and generalize the preceeding results and to determine the possible influence of the ester function at C-6 on the regiochemical outcome of the reaction we decided to submit the methyl α-glycopyranosides of 6-O-butyryl-D-galactose and mannose and of their L enantiomers to enzymic butyrylation through the lipase/trifluoroethyl butyrate system.

RESULTS

Substrate synthesis. 6-O-Butyryl derivatives of methyl α-D- and α-L-galacto and mannopyranosides

1b-4b have been prepared according to Therisod and Klibanov[1] by enzymic butyrylation of the four methyl α-glycopyranosides **1a-4a** performed in pyridine and using porcine pancreatic lipase/trifluoroethyl butyrate (PPL/TFEB) as acylating agent. Reactions were fast and good yields in the monobutyryl derivatives were obtained before formation of significant amounts of dibutyrates.



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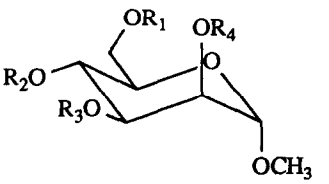

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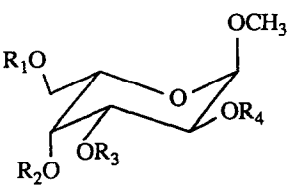

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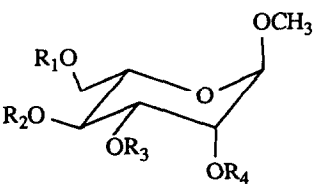


4

a: $R_1 = R_2 = R_3 = R_4 = H$
b: R_1 = COPr; $R_2 = R_3 = R_4 = H$
c: $R_1 = R_4$ = COPr; $R_2 = R_3 = H$
d: $R_1 = R_3$ = COPr; $R_2 = R_4 = H$
e: $R_1 = R_2$ = COPr; $R_3 = R_4 = H$
f: $R_1 = R_2 = H$; $R_3 = R_4$ = Bn
g: $R_1 = R_2$ = COPr; $R_3 = R_4$ = Bn
h: $R_1 = R_2$ = COPr; R_3, $R_4 = C(CH_3)_2$

Enzymic butyrylation. The four substrates **1b-4b** have been submitted to enzymic butyrylation according to the procedures already employed on the corresponding 6-deoxy sugars fucose and rhamnose.[3] Three commercial crude lipase preparations have been used, namely porcine pancreatic (PPL), *Pseudomonas fluorescens* (PFL), and *Candida cylindracea* (CCL) lipases (see Experimental).

In all the cases examined TFEB was used as acyl donor for the transesterification reactions performed at 45 °C. Conversions were continued until the almost complete disappearance of starting material (monitored by t.l.c. analysis); this result was obtained after 2 days in the best case (entry 2, Table 1) or was not obtained even after 12 days, when reactions were in any case stopped. The dibutyrate fraction was separated by column chromatography and the relative ratios of the diesters were obtained by ^{1}H-NMR spectroscopy through careful integration of the signals previously assigned on the spectrum of each dibutyrate obtained pure through the procedure described in the following section.

Table 1 summarizes the obtained yields and the product distribution.

Table 1. Enzymatic butyrylation of compounds **1b-4b.**

entry	substr.	enzyme	time (days)	yield (%)	%diesters		
					c (C-2)	**d** (C-3)	**e** (C-4)
1	**1b**	PPL	4	89	95	0	5
2	**1b**	PFL	2	88	92	0	8
3	**1b**	CCL	7	89	90	5	5
4	**2b**	PPL	12	8	25	23	52
5	**2b**	PFL	12	8	53	25	22
6	**2b**	CCL	12	50	42	55	3
7	**3b**	PPL	12	10	17	36	47
8	**3b**	PFL	12	25	54	16	30
9	**3b**	CCL[a]	12	57	7	66	18
10	**4b**	PPL	12	72	5	5	90
11	**4b**	PFL	12	75	4	6	90
12	**4b**	CCL	12	64	27	54	19

[a] in this case, in the dibutyrate fraction 9% of the 3,4-dibutyrate was detected by ^{1}H-NMR analysis.

Product characterization. Owing to the high cost of L-galactose and L-mannose, large amounts of starting material are available only for the commercial D-enantiomers; so each D-dibutyrate could be obtained pure and fully characterized, whereas for the L-series products only the ^{1}H-NMR analysis of the enzymic diester fraction was performed.

Two in the three dibutyrates of D-galactoside, namely **1c** and **1d**, were obtained pure by silica gel column chromatography, the former from the PPL reaction mixture, the latter from the mixture of the dibutyrates obtained by chemical butyrylation of 6-O-bytyryl derivative **1b**. The 4,6-di-O-butyryl derivative **1e** was present in small and trace amounts in, respectively, the enzymic and the chemical mixture, so a synthesis starting from the known[12] methyl 2,3-di-O-benzyl-α-D-galactopyranoside **1f** was performed. Compound **1f** was butyrylated to **1g** which on hydrogenolysis on Pd/C in ethyl acetate gave pure **1e**.[13]

Only one in the dibutyrates of D-mannoside can be obtained pure by column chromatography of the chemical butyrylation mixture (see Experimental), the 3,6-dibutyrate **2d**, as all attempts to separate **2c** from **2e**, which eluted together in several chromatographic conditions, failed in our hands. They were separated utilizing the "graded hydrolysis isopropylidenation" procedure[14] which, when applied to the mixture of **2c** and **2e**, converted only **2e** into the 2,3-di-O-isopropylidene derivative **2h** and left **2c** unchanged. After column chromatography of this mixture, which gave pure **2c**, on hydrolysis of **2h** pure **2e** was obtained.

Table 2. ^{1}H-NMR data of compounds **1b-e** and **2b-e**.

	chemical shifts, δ							
	H-1	H-2	H-3	H-4	H-5	H-6_a	H-6_b	MeO
1b	4.67	3.74	3.68	3.82	3.92	4.18	4.24	3.36
1c	4.92	5.02	4.01	3.97	3.97	4.23	4.44	3.39
1d	4.82	4.00	5.04	4.00	4.00	4.21	4.30	3.41
1e	4.84	3.78	3.96	5.34	4.10	4.10	4.10	3.42
2b	4.72	3.94	3.86	3.63	3.74	4.35	4.43	3.38
2c	4.71	5.11	4.00	3.60	3.73	4.29	4.55	3.38
2d	4.73	4.02	5.10	3.84	3.80	4.35	4.49	3.40
2e	4.77	3.93	3.89	5.02	3.88	4.16	4.25	3.38

	coupling constants, Hz						
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
1b	3.5	10.0	3.0	≤ 1	4.5	7.5	11.5
1c	3.5	10.5	3.5	≤ 1	7.0	6.0	11.5
1d	4.0	10.5	3.0	≤ 1	7.0	6.0	11.5
1e	4.0	10.5	3.5	≤ 1	a	a	a
2b	1.0	3.0	9.5	9.5	2.0	5.5	12.0
2c	1.5	3.5	9.5	10.0	2.0	4.5	12.0
2d	2.0	3.5	9.5	a	2.0	4.5	12.0
2e	1.5	3.0	9.5	10.0	2.0	5.5	12.0

[a] not measurable

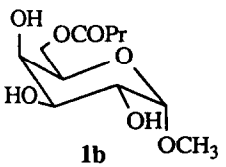
DISCUSSION

Methyl 6-O-butyryl α-D-galactopyranoside **1b** was found the best substrate for all the three lipases (Table 1, entries 1-3). A yield approaching 90% was always obtained in a reaction time ranging from two to seven days with a regioselectivity over 90% in favor of the 2,6-dibutyrate **1c**. Interesting to note, its 6-deoxy analog, D-fucoside, is converted with the same efficiency and regioselectivity.[10] In this case the presence of the acyloxy substitution on C-6 does not play any significant role in the reaction.

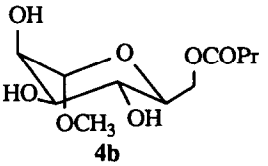
Though requiring longer reaction times and furnishing slightly lower yields L-mannoside **4b** (entries 10-11) evidenced a highly regioselective behavior of PPL and PFL favoring the butyrylation of the 4-OH hydroxyl group. It is worthy of note that L-mannoside, as its 6-deoxy analog, is butyrylated at C-4. CCL worked very poorly on **4b** (entry 12) yielding a random distribution of products.

According to 6-deoxy analogs, the other two sugars **2b** and **3b** were poor substrates; in some cases they gave less than 10% yield after 12 days and very often random distributions of product were obtained.

The present results confirm in large extent the conclusions drawn in the study of the 6-deoxy analogs of **1-4**. In that case we could come to the conclusion that a proper sequence of hydroxyl groups determines the orientation of the substrates at the active site of the enzyme. D-Galactoside **1b** (entries 1-3) and L-mannoside **4b** (entries 10-11) have the proper axial-equatorial-equatorial (AEE) sequence[10] and are regioselectively transformed at the equatorial terminus.



1b



4b

The groups at C-1 and at C-6 can, however, largely influence the extent of conversion (entries 10,11 vs 1,2) without affecting the regiochemistry. The EEA sequence, present in **2b** and **3b**, is worse than the AEE sequence and gives always poorly selective reactions, though in some case (entry 6) a yield of 50% is approached.

When comparing the behavior of the three lipases, it can be concluded that in general CCL (entries 3,6,9) furnishes better yields than PPL and PFL but with lower selectivity. The last two enzymes usually behave similarly, especially in the case of good substrates.

Moreover, is noteworthy that the enzymatic approach gives high yields of the D-galactoside 2,6-diester **1c**, which, when obtained by chemical butyrylation, requires tedious separation procedures in order to be purified from the 3-regioisomer **1d** (see Experimental).[15]

EXPERIMENTAL

General methods - ^{1}H-NMR spectra were recorded with a Bruker AC-200 spectrometer in deuteriochloroform solutions. Optical rotations were measured with a Perkin Elmer 241 polarimeter at 25 °C. Analytical thin layer chromatography (t.l.c.) was carried out on Merk 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[16] was performed with Merk 60 silica gel (230-400 mesh). Methyl α-D-mannopyranoside and methyl α-D-galactopyranoside were purchased from Fluka, methyl α-L-mannopyranoside and methyl α-L-galactopyranoside were prepared through a Fisher reaction.[17,18] Porcine pancreatic lipase (type II) (PPL) (specific activity 11.8 units/mg solid) and *Candida cylindracea* lipase (type VII) (CCL) (specific activity 665 units/mg solid) were purchased from Sigma; *Pseudomonas fluorescens* lipase (lipase P) (PFL) (specific activity 30.5 units/mg solid) was a generous gift from Amano Pharmaceutical Co., Frankfurt. CCL was used as received; PPL and PFL were kept under vacuum prior to use in order to lower the water content to 0.5%. Tetrahydrofuran and pyridine were distilled just prior use from, respectively, sodium/benzophenone and calcium hydride. Methylene chloride and acetone were dried over 3Å molecular sieves. Evaporation under reduced pressure was always effected with the bath temperature kept below 40 °C.

Methyl 6-O-butyryl-α-D-galactopyranoside (1b)

2,2,2-trifluoroethyl butyrate (TFEB, 2.5 ml) and porcine pancreatic lipase (3 g) were added to a solution of methyl α-D-galactopyranoside (**1a**) (1 g, 5.15 mmol) in anhydrous pyridine (12 ml) and the suspension was stirred overnight at 45 °C. The enzyme was then removed by filtration and washed with hot acetone (15 ml).

The solvent was evaporated under reduced pressure to give a residue (1.6 g) which was purified by flash chromatography (methylene chloride-methanol 9:1). The obtained product (1.07 g, 4.05 mmol) was identified as methyl 6-O-butyryl-α-D-galactopyranoside (**1b**), m.p. 153-154 °C (from ethyl acetate), $[\alpha]_D$ +130° (c 1.0, methanol). Anal. Calcd for $C_{11}H_{20}O_7$: C, 50.00; H, 7.57. Found: C, 49.82; H, 7.46. For ^{1}H-NMR data see table 2.

Methyl 6-O-butyryl-α-L-galactopyranoside (3b)

Analogously, methyl α-L-galactopyranoside (**3a**) (1 g, 5.15 mmol) afforded methyl 6-O-butyryl-α-L-galactopyranoside (**3b**) (1.05 g, 3.97 mmol) m.p. 152-153 °C (from ethyl acetate), $[\alpha]_D$ -129.7° (c 1.0, methanol). Anal. Calcd for $C_{11}H_{20}O_7$: C, 50.00; H, 7.57. Found: C, 50.07; H, 7.55. The ^{1}H-NMR spectrum was identical to the spectrum of **1b**.

Methyl 6-O-butyryl-α-D-mannopyranoside (2b)

The same enzymatic procedure was repeated on **2a** (1 g, 5.15 mmol) to yield 1.8 g of crude product, which by flash chromatography (ethyl acetate) afforded methyl 6-O-butyryl-α-D-mannopyranoside (**2b**) (1.10 g, 4.16 mmol), oil, $[\alpha]_D$ +40.6° (c 1.1, chloroform). Anal. Calcd for $C_{11}H_{20}O_7$: C, 50.00; H, 7.57. Found: C, 49.60; H, 7.59. For ^{1}H-NMR data see table 2.

Methyl 6-O-butyryl-α-L-mannopyranoside (4b)

Analogously, methyl α-L-mannopyranoside (**4a**) (1 g, 5.15 mmol) afforded methyl 6-O-butyryl-α-L-mannopyranoside (**4b**) (1.28 g, 4.85 mmol), oil, $[\alpha]_D$ -40.4° (c 1.3, chloroform). Anal. Calcd for $C_{11}H_{20}O_7$: C, 50.0; H, 7.57. Found: C, 49.60; H, 7.47. The ^{1}H-NMR spectrum was identical to the spectrum of **2b**.

General procedure for PPL and PFL catalyzed transesterification of compounds 1b-4b.

The sugar substrate (0.1 g) was dissolved into the solvent (2 ml), THF for **2b**, **4b**, THF-pyrydine 4:1 for **1b**, **3b**; TFEB (0.5 ml) and PPL or PFL (0.5 g) were added, the suspension was vigorously stirred at 45 °C and the reaction mixture was monitored by t.l.c. for the conversion. At the end of the reaction, the enzyme was filtered off, washed with hot acetone and the solvent was removed by evaporation under reduced pressure. The dibutyrate fraction was separated by flash chromatography (ethyl acetate-hexane 3:2) and analyzed by ^{1}H-NMR for the determination of the product ratios (see table 2).

General procedure for CCL catalyzed transesterification of compounds 1b-4b.

All conditions but the solvent, in this case methylene chloride-acetone 4:1, were the same as in the above procedure.

Methyl 2,6-di-O-butyryl-α-D-galactopyranoside (1c)

PPL catalyzed transesterification of compound **1b** (0.3 g, 1.14 mmol), followed by flash cromatography (ethyl acetate-hexane 1:1) of the reaction mixture yielded methyl 2,6-di-O-butyryl-α-D-galactopyranoside (**1c**) (0.32 g, 0.96 mmol), amorphous solid, $[\alpha]_D$ +115.6° (c 0.8, chloroform). Anal. Calcd for $C_{15}H_{26}O_8$: C, 53.89; H, 7.78. Found: C, 53.56; H, 7.47. For ^{1}H-NMR data see table 2.

Methyl 3,6-di-O-butyryl-α-D-galactopyranoside (1d)

To a solution of methyl 6-O-butyryl-α-D-galactopyranoside (**1b**) (2 g, 7.56 mmol) in pyridine (20 ml) butyryl chloride (1 ml, 9.54 mmol) was added at 0 °C and the mixture was stirred overnight at room temperature. Evaporation with toluene under vacuum afforded a residue, which yielded, after three recycles by flash chromatography (methylene chloride-methanol 30:1) a tributyrate fraction (1.2 g), pure methyl 3,6-di-O-butyryl-α-D-galactopyranoside (**1d**) (0.36 g, 1.08 mmol) toghether with a mixture of **1c** and **1d** (0.40 g), followed by the slower-moving product **1c** (0.58 g, 1.74 mmol). Only 0.023 g (0.07 mmol) of **1e** (most polar compound) could be obtained.

1d, m.p. 47-48 °C (from chloroform), $[\alpha]_D$ +147° (c 1.1, chloroform). Anal. Calcd for $C_{15}H_{26}O_8$: C, 53.89; H, 7.78. Found: C, 53.52; H, 7.66. For ^{1}H-NMR data see table 2.

Methyl 4,6-di-O-butyryl-α-D-galactopyranoside (1e)

Methyl 2,3-di-O-benzyl-α-D-galactopyranoside (**1f**) (1 g, 2.67 mmol), prepared according to ref. 12, was dissolved in pyridine (10 ml), butyryl chloride (0.6 ml, 5.74 mmol) was added at 0 °C and the solution was stirred overnight at room temperature. After evaporation with toluene under vacuum and extraction with methylene chloride, the crude product (1.3 g) was purified by flash chromatography eluting with hexane-ethyl acetate 80:20 to give methyl 4,6-di-O-butyryl-2,3-di-O-benzyl-α-D-galactopyranoside (**1g**) (0.7 g, 1.36 mmol), oil, $[\alpha]_D$ +48.1° (c 1.0, chloroform). Anal. Calcd for $C_{29}H_{38}O_8$: C, 67.70; H, 7.39. Found: C, 67.32; H, 7.65. ^{1}H-NMR, δ: 3.40 (3H, s, MeO), 3.78 (1H, dd, $J_{1,2}$ 3.5 and $J_{2,3}$ 10.0 Hz, H-2), 3.98 (1H, dd, $J_{3,4}$ 3.5 Hz, H-3), 4.10 (3H, bs, H-5, H-6_a and H-6_b), 4.58-4.85 (4H, 2 ABq, C$\underline{H_2}$Ph), 4.71 (1H, d, H-1), 5.57 (1H, dd, $J_{4,5}$ 1 Hz, H-4) and 7.10-7.40 (10H, m, 2 Ph).

Compound **1g** (0.7 g, 1.36 mmol) was dissolved in ethyl acetate (70 ml), treated with Pd-C (10%, 0.07 g) and shaken overnight at room temperature under hydrogen atmosphere. The catalyst was removed by filtration and the solvent evaporated under reduced pressure. The obtained residue (0.48 g) was purified by flash chromatography (ethyl acetate-hexane 7:3) to give pure methyl 4,6-di-O-butyryl-α-D-galactopyranoside (**1e**) (0.42 g, 1.25 mmol), oil, $[\alpha]_D$ +103°(c 1.5, chloroform). Anal. Calcd for $C_{15}H_{26}O_8$: C, 53.89; H, 7.78. Found: C, 53.50; H, 7.74. For ^{1}H-NMR data see table 2.

Methyl 3,6-di-O-butyryl-α-D-mannopyranoside (2d)

To a solution of methyl 6-O-butyryl-α-D-mannopyranoside (**2b**) (3 g, 11.34 mmol) in pyridine (30 ml) butyryl chloride (1.5 ml, 14.31 mmol) was added at 0 °C and the mixture was stirred overnight at room temperature. Evaporation with toluene under vacuum afforded a crude mixture (4.1 g) which was purified by flash chromatography eluting with ethyl acetate-hexane 3:2 to give, after the tributyrate fraction (1.05 g, 2.61 mmol), pure **2d** (2.05 g, 6.15 mmol) and a more polar fraction (0.54 g, 1.62 mmol) consisting in a 4:1 mixture (by ^{1}H-NMR analysis) of methyl 2,6-di-O-butyryl-α-D-mannopyranoside (**2c**) and methyl 4,6-di-O-butyryl-α-D-mannopyranoside (**2e**).

2d, oil, $[\alpha]_D$ +47.9° (c 1.3, chloroform). Anal. Calcd for $C_{15}H_{26}O_8$: C, 53.89.; H, 7.78. Found: C, 53.64; H, 7.42. For ^{1}H-NMR data see table 2.

Methyl 2,6-di-O-butyryl-α-D-mannopyranoside (2c)

The mixture of **2c** and **2e** (0.54 g, 1.62 mmol) was dissolved in acetone (4 ml), 2,2-Dimethoxypropane (4 ml) and *p*-toluenesulfonic acid (0.063 g, 0.33 mmol) were added and the solution was stirred for 15 minutes at room temperature. Water (6 ml) was added and the stirring was continued for 4 hours. Then the solution was concentrated under vacuum and, after addition of 0.1 M sodium hydrogen carbonate (3.3 ml), extracted with ethyl acetate. The solvent was dried over Na_2SO_4, evaporated under vacuum and the obtained residue (0.59 g) purified by flash chromatography eluting with ethyl acetate-hexane 1:1 to give methyl 4,6-di-O-butyryl-2,3-O-isopropylidene-α-D-mannopyranoside (**2h**) which eluted first (0.12 g, 0.32 mmol), and unchanged methyl 2,6-O-dibutyryl-α-D-mannopyranoside (**2c**) (0.37 g, 1.10 mmol) which eluted second.

2h, oil,$[\alpha]_D$ +8.3° (c 1.0, chloroform). Anal. Calcd for: $C_{18}H_{30}O_8$: C, 57.75; H, 8.02. Found: C, 57.54; H, 7.82. ^{1}H-NMR, δ: 1.35 and 1.57 (6H, 2 s, Me), 3.41 (3H, s, OMe), 3.82 (1H, ddd, $J_{4,5}$ 10.5, $J_{5,6a}$ 2.5 and $J_{5,6b}$ 5.5 Hz, H-5), 4.13 (1H, dd, $J_{6a,6b}$ 12 Hz, H-6a), 4.14 (1H, d, $J_{2,3}$ 5.0 Hz, H-2), 4.20 (1H, dd, $J_{3,4}$ 7.5 Hz, H-3), 4.20 (1H, dd, H-6b), 4.97 (1H, bs, H-1) and 5.06 (1H, dd, H-4).

2c, oil, $[\alpha]_D$ +7.5°(c 1.3, chloroform). Anal. Calcd for $C_{15}H_{26}O_8$: C, 53.89.; H, 7.78. Found: C, 53.90; H, 7.88. For ^{1}H-NMR data see table 2.

Methyl 4,6-di-O-butyryl-α-D-mannopyranoside (2e)

Methyl 4,6-di-O-butyryl-2,3-O-isopropylidene-α-D-mannopyranoside (**2h**) (0.12 g, 0.32 mmol) was treated with 60% acetic acid (50 ml) and the mixture was stirred at 60 °C for 6 hours. After evaporation under reduced pressure the crude product (0.11 g) was purified by flash chromatography eluting with hexane-ethyl acetate 3:2 to give methyl 4,6-di-O-butyryl-α-D-mannopyranoside (**2e**) (0.09 g,0.27 mmol), m.p. 82-83 °C (from ethyl acetate), $[\alpha]_D$ +60.5° (c 1.0, chloroform). Anal. Calcd for $C_{15}H_{26}O_8$: C, 53.89; H, 7.78. Found: C, 53.51; H, 7.39. For ^{1}H -NMR data see table 2.

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