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Regioselective Alkylation of Benzyl β-D-Lactoside and its Derivatives by Stannylation

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The preparation of benzyl 2,3,6,2',6'-penta-*O*-benzyl-β-D-lactoside, which is a key intermediate for chemical synthesis of oligosaccharide components of glycosphingolipids, was achieved by an improved method. The 3'-*O*-*p*-methoxybenzyl and 3'-*O*-methyl derivatives were prepared from benzyl 2,3,6,2',6'-penta-*O*-benzyl-β-D-lactoside through stannylation. By using benzyl β-D-lactoside as starting material, benzyl 3'-*O*-methyl-, 3'-*O*-benzyl- and 3'-*O*-*p*-methoxybenzyl-β-D-lactoside were regioselectively synthesized using the same procedure.

Almost all oligosaccharide components of glycosphingolipids isolated from mammalian cell membranes have a lactose unit with elongation of the chain at position 3' or 4' [1]. Therefore, chemical synthesis of glycosphingolipids requires suitably protected lactose intermediates with a free hydroxyl group at position 3' or 4' for the attachment of a further sugar residue. For this purpose benzyl 2,3,6,2',6'-penta-*O*-benzyl-β-D-lactoside (**1**) has been used by several laboratories [2-4]. We now report the improved preparation of **1** and several 3'-substituted derivatives thereof through stannylation [5], and also the regioselective alkylation at the 3'-OH group of benzyl β-D-lactoside (**2**) by the same procedure. These 3'-*O*-substituted lactose derivatives are useful not only for the synthesis of oligosaccharides containing 3'- or 4'-substituted lactose moieties, but also for studying galactose-specific receptors [6] as, for example, the galactose-binding lectin from rat peritoneal macrophages. Investigation of this lectin with partially methylated lactose derivatives revealed that the hydroxyl functions at C-3' and C-4' are the most important ones for recognition of the galactose residue by this receptor [7-10].

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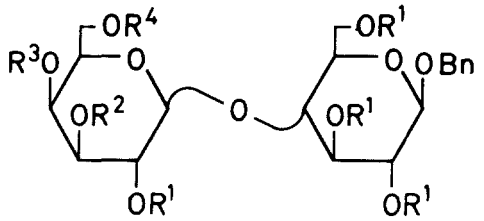


Compound	R^1	R^2	R^3	R^4
1	Bn	H	H	Bn
2	H	H	H	H
3	H	isopropylidene		H
4	H	H	isopropylidene	
5	Bn	H	Ac	Bn
6	Bn	Ac	Ac	Bn
7	Bn	Bn-O-CH_3	H	Bn
8	Bn	Bn-O-CH_3	Ac	Bn
9	Bn	Me	H	Bn
10	Bn	Me	Ac	Bn
11	H	Me	H	H
12	H	Bn	H	H
13	H	Bn-O-CH_3	H	H
14	H	Bn	H	Bn

Results and Discussion

Isopropylidenation of D-lactose or **2**, which was used for the preparation of **1**, was shown to produce a mixture of 3′, 4′ and 4′,6′-*O*-ketals [11, 12], and the product ratio changed depending on the reaction conditions applied. When **2** was treated with a large amount of acetone for 3 h under reflux in the presence of *p*-toluenesulfonic acid and anhydrous $CuSO_4$, the 3′, 4′ (**3**) and 4′,6′-ketals (**4**) were obtained in 62% and 20% yield, respectively. On the other hand, treatment of **2** with excess amounts of 2,2-dimethoxypropane at 67°C for 1.5 h gave the 3′,4′-ketal (**3**) in 74% yield together with a minor portion of an unidentified by-product that migrates faster than **3** on TLC and could therefore readily be separated by column chromatography. This is similar to the formation of the 3,4-ketal of benzyl β-D-galactopyranoside carried out in 2,2-dimethoxypropane without addition of solvents, in 97% yield [13]. The 3′,4′-ketal was then converted into **1** by conventional benzylation [14] and hydrolysis. Compound **1** has been used for chain extension at the 3′-position [2] as well as at the 4′-position (T. Yoshino and T. Iwamoto, unpublished results). However, it would be more desirable if **1** can be converted into the 4′-protected derivative for a glycosylation at the 3′-position. Therefore, the 4′-*O*-acetyl derivative (**5**) was prepared through 3′,4′-methoxyethylidenation with trimethyl orthoacetate in the presence of *p*-toluenesulfonic acid, followed by treatment with 90% acetic acid.

Table 1. 300 MHz ^{1}H-NMR data of the benzyl β-D-lactoside derivatives (pyranose ring protons).

Compound	Chemical shifts (ppm)							Coupling constants (Hz)						
	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
1	4.42	3.36	3.59	4.03	3.42	3.84	3.77	6.9	9.6	9.1	10.2	3.3	1.8	10.5
2[a]	4.41	3.31	3.57	3.72	3.50	3.95	3.77	7.5	7.8	9.9	9.9	4.8	1.5	12.1
5	4.47	3.35	3.57	4.03	3.43	3.82	3.75	7.5	7.8	8.6	9.3	4.5	2.4	11.1
6	4.46	3.34	3.56	4.02	~3.5	3.80	3.72	7.8	7.5	10.1	9.0	4.2	3.0	10.7
8	4.48	3.41	3.58	4.03	3.50	~3.8		7.8	9.5	9.3	9.3	8.9	8.4	c
10	4.47	3.41	3.56	3.97	3.43	3.81	3.75	7.5	9.6	8.9	8.9	4.0	10	10.7
Ac of **2**	4.46	4.95	5.14	3.80	3.55	4.40	4.11	7.2	9.2	9.2	9.2	6.9	6.3	11.4
Ac of **11**	4.39	4.93	5.15	3.79	3.59	4.50	4.16	7.8	9.3	9.3	10.0	5.1	1.7	12.0
Ac of **12**	4.36	4.92	5.14	3.76	~3.5	4.10	4.10	7.8	9.3	9.3	9.3	6.5	2.8	11.6
Ac of **13**	4.49	4.97	5.16	3.8	3.58	~4.1		8.1	9.6	9.3	c	6.5	c	11.4
Ac of **14**	4.44	4.92	5.14	3.69	3.51	4.10	4.10	6.9	9.3	9.3	9.3	c	c	11.7

Compound	Chemical shifts (ppm)							Coupling constants (Hz)						
	H-1′	H-2′	H-3′	H-4′	H-5′	H-6′a	H-6′b	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',6'a}$	$J_{5',6'b}$	$J_{6'a,6'b}$
1	4.50	3.51	3.51	3.95	3.38	3.62	3.44	7.8	8.1	3.5	<0.5	7.2	1.2	9.6
2	4.52	3.63	3.70	3.88	3.31	3.58	3.58	7.8	8.1	3.0	<0.5	7.8	-	b
5	4.50	3.50	3.64	5.35	3.39	3.76	3.34	7.8	9.9	3.7	<0.5	c	c	c
6	4.51	3.49	4.86	5.38	3.40	3.50	3.30	7.8	9.6	3.6	1.8	9.8	3.0	10.4
8	4.50	3.52	3.76	5.35	3.37	~3.8	3.37	7.6	8.5	3.0	<0.5	c	c	c
10	4.50	3.48	3.17	5.48	3.37	3.69	3.32	7.5	9.2	2.4	<0.5	<0.5	4.2	10.4
Ac of **2**	4.49	5.08	4.93	5.32	3.84	4.09	4.09	7.0	10.1	3.9	<0.5	5.5	-	b
Ac of **11**	4.52	4.97	3.27	5.39	3.41	4.10	4.10	7.8	9.8	3.9	<0.5	7.2	-	b
Ac of **12**	4.50	4.98	3.48	5.48	3.91	4.10	4.10	7.2	8.0	4.0	2.0	6.3	-	b
Ac of **13**	4.52	5.11	3.79	5.39	3.87	4.10	4.10	7.8	10.4	3.0	<0.5	5.7	-	b
Ac of **14**	4.50	5.02	3.54	5.47	c	4.20	4.01	7.2	8.4	3.5	<0.5	7.0	4.2	11.7

[a] measured in ^2H_2O.
[b] H-6a and H-6b are equivalent.
[c] unresolved due to overlapping resonances.

For glycosylation at the 4′position, 3′*O*-alkylation of **1** was investigated by using dibutyltin oxide (stannylation procedure). According to Slife's procedure [5], **1** was heated in anhydrous methanol with an equimolar amount of dibutyltin oxide for 1 h under reflux, and after removal of methanol, dried under vacuum. The residue was treated with *p*-methoxybenzyl chloride at 90°C in acetonitrile, affording the 3′*O*-*p*-methoxybenzyl derivative (**7**) in 55% yield. The substitution position was determined by ^{1}H-NMR spectroscopy of its *O*-acetate (**8**) which showed a characteristic downfield shift for the resonance of H-4′ in the galactose moiety (5.349 ppm; $J_{3',4'}$ 3.0 Hz), that is comto the data of **5** and 3′,4′di-*O*-acetate (**6**) (see Table 1).

Methylation of **1** was also attempted by the same procedure at 95°C in a sealed tube and the 3′*O*-methylated derivative (**9**) was obtained in 36% yield along with the recovery of 32% of **1**. The substitution position was determined in the same way as described above,

Table 2. Reaction conditions and results of alkylation of benzyl β-D-lactoside (**2**).

Alkyl halide	Temperature (°C)	Time (d)	Solvent	Yield (%)	Compound
CH_3I	100	4	dioxane	71	**11**
$PhCH_2Br$[a]	100	2	dioxane	36	**12**
$PhCH_2Br$[a,b]	82	3	acetonitrile	56	**12**
$p\text{-}CH_3OPhCH_2Cl$	82	4	acetonitrile	77	**13**

[a] No reaction with benzyl chloride under the same conditions.
[b] 3′, 6′-Di-*O*-benzyllactoside (**14**) was also produced in 16% yield.

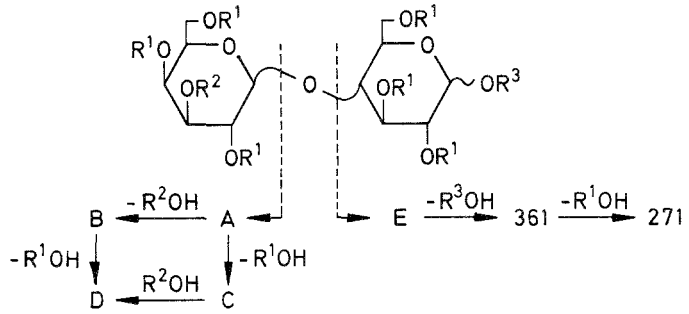
based on the signals at 5.482 ppm ($J_{3',4'}$ 2.4 Hz) for H-4′ of **10**. The benzyl groups of **9** were removed by catalytic hydrogenation with Pd/C and 3′-*O*-methyl-D-lactose was obtained in 90% yield. Partial benzoylation and benzylation of methyl β-D-lactoside had been studied and revealed that the 3-OH group of the glucose moiety in **3** is the least reactive group for both substitutions, which led to substituted lactosides with free 3-OH groups within a complex mixture [15-17]. On the other hand, regioselective benzylation at the 3-OH group in methyl β-D-galactoside by using dibutyltin oxide has been reported [18]. The application of the same procedure for **2** was studied to obtain benzyl 3′-*O*-methyl- (**11**), 3′-*O*-benzyl- (**12**) and 3′-*O*-*p*-methoxybenzyl-β-D-lactosides (**13**). This method has also been used earlier to introduce a benzyl or allyl group into the 3-position of benzyl β-D-galactopyranoside [19] or to synthesize the 3′-*O*-allyl derivative of β-methyl lactoside [20]. The results obtained in this study are summarized in Table 2, showing that the main product in each reaction was the corresponding 3′-substituted derivative; methylation and *p*-methoxybenzylation of **2** took place regioselectively at position 3′. Benzylation with benzyl bromide in dioxane gave the 3′-*O*-benzylether (**12**) in 36% yield and multibenzylated by-products. The yield of **12** was improved to 56% by conducting the reaction in acetonitrile, however, giving also the 3′,6′-di-*O*-benzylether in 16% yield. When benzyl chloride was used instead of benzyl bromide, no reaction took place under the same conditions.

The position of alkylation in each reaction was determined on the basis of the characteristic downfield shifts of the H-4′ proton after acetylation of each product (see Table 1). Benzyl 3′-*O*-methyl-β-D-lactoside (**11**) was converted by catalytic hydrogenation into 3′-*O*-methyl-D-lactose, which was compared with **11** and **12** by electron impact mass spectrometry as the trimethylsilyl derivatives, showing the charactistic fragment ions of a mono-*O*-methyl hexose residue together with fragments due to an unsubstituted hexose residue [7] (Fig. 1).

Experimental

General Methods

TLC was conducted on plastic sheets coated with 0.2 mm silica gel 60 (Merck, Darmstadt, W. Germany); the compounds were located by spraying with 0.2% orcinol in 1.5 M sulfuric acid and heating. Solvent systems used for TLC were toluene/ethyl acetate, 1/1 by vol (solvent A); and chloroform/methanol/water, 60/35/8 by vol (solvent B). Silica gel



R^1	R^2	R^3	A	B	C	D	E
$SiMe_3$	Me	$SiMe_3$	393	361	303	271	451
$SiMe_3$	Me	Bn	393	361	303	271	469
$SiMe_3$	Bn	Bn	469	361	379	271	469

Figure 1. Mass chromatographic fragmentation pattern (70 eV, electron impact) of 3′-substituted lactoses.

used for column chromatography was Wako-gel C-300 (300 mesh). Column chromatography was done under slightly increased pressure using an air-compressor. IR spectra were taken with a Hitachi 260-50 spectrophotometer. NMR spectra were recorded at 25°C with a Hitachi-Perkin-Elmer R-20 instrument at 60 MHz and a Varian XL-300 instrument at 300 MHz with [^{2}H]chloroform as solvent and tetramethylsilane as internal standard. Signal assignments for the major compounds were made by 2D-COSY experiments. If not stated otherwise, spectra were recorded at 300 MHz. Electron impact mass spectra were recorded at 70 eV by direct inlet of the trimethylsilylated compounds with an ion source temperature of 200°C.

*Benzyl 3′,4′-O-Isopropylidene-β-D-lactoside (**3**)*

A suspension of benzyl β-D-lactoside (**2**) (14.15 g, 32.8 mmol) in 2,2-dimethoxypropane (210 ml) containing *p*-toluenesulfonic acid (1.2 g) was heated at 67°C with magnetic stirring. After 1.5 h the mixture was neutralized with triethylamine and concentrated to dryness under reduced pressure. The resulting syrup was dissolved in methanol (100 ml), refluxed for 0.5 h, and concentrated to dryness. This syrup was chromatographed on silica gel using a gradient solvent system of chloroform/methanol (18/1 to 4/1), giving **3** (11.5 g, 74% yield) as main product. TLC (solvent B), R_F 0.61; NMR of the acetate of **3** (60 MHz), δ 7.20 (m, 5H, Ph), 2.08, 2.06, 2.01, 1.96 (s, 5 × 3H, CH_3CO), 1.49, 1.28 [s, 2 × 3H, $(CH_3)_2C$].

*Benzyl 2,3,6,2′,6′-Penta-O-benzyl-β-D-lactoside (**1**)*

Compound **3** was converted to **1** by conventional benzylation and release of the isopropylidene group by heating in 90% acetic acid for 1 h at 100°C.

*Benzyl 4′,6′-O-Isopropylidene-β-D-lactoside (**4**)*

When the isopropylidenation of **2** (1.71 g, 4 mmol) was conducted according to a conventional method by refluxing in acetone (1.3 l) containing *p*-toluenesulfonic acid (0.25 g) and anhydrous $CuSO_4$ (0.1 g) for 3 h, the ketals **3** (1.21 g, 62% yield) and **4** (0.4 g, 20% yield) were isolated after silica gel column chromatography (chloroform/methanol, 9/1 by vol). TLC of **4** (solvent B), R_F 0.57; NMR of the acetate of **4** (60 MHz); δ ± 7.3 (m, 5H, Ph), 2.10, 2.02, 1.98 (s, 5 × 3H, CH_3CO), 1.39, 1.34 [s, 2 × 3H, $(CH_3)_2C$].

*Benzyl 2,3,6,2′,6′-Penta-O-benzyl-4′-O-acetyl-β-D-lactoside (**5**)*

A solution of **1** (400 mg, 0.45 mmol) and trimethyl orthoacetate (2.84 ml, 28.3 mmol) in dry benzene in the presence of *p*-toluenesulfonic acid (32 mg) was stirred at room temperature for 1.5 h. The mixture was then diluted with chloroform (200 ml) and neutralized with cold saturated aqueous $NaHCO_3$. After having successively washed with water and dried over $MgSO_4$, the chloroform solution was concentrated to dryness, giving the 3′,4′-methoxyethylidene lactoside (416 mg, 98% yield). The product ratio of exo/endo was 1/1 as estimated by NMR integration. NMR, δ 1.52, 1.51 (s, C-CH_3), 3.75, 3.27 (s, O-CH_3); TLC (solvent A), R_F 0.68.

A solution of the 3′,4′-methoxyethylidene lactoside (400 mg in 8 ml 90% acetic acid) that was obtained as described for **3**, followed by benzylation was stirred at room temperature for 1 h. The mixture was evaporated to dryness, giving **5** as a syrup (70 mg, 97% yield), which was homogeneous on TLC (solvent A), R_F 0.53; i.r., 3475 (OH) and 1745, 1240 and 1050 cm^{-1} (AcO); NMR (see Table 1 for ring protons), δ 7.40-7.20 (m, Ph); 4.97, 4.92, 4.80, 4.75, 4.73, 4.67, 4.63, 4.49, 4.47, 4.44, 4,24 ($PhCH_2$), 2.04 (s, 3H, CH_3CO).

*Benzyl 2,3,6,2′,6′-Penta-O-benzyl-3′,4′-di-O-acetyl-β-D-lactoside (**6**)*

Conventional acetylation (acetic anhydride/pyridine) of **1** (10 mg) gave **6** (11 mg), which was identical with the acetylation product of **5** on TLC and in the NMR spectra. TLC (solvent A), R_F, 0.70; NMR (see Table 1 for ring protons), δ 7.40-7.20 (m, Ph), 4.96, 4.92, 4.74, 4.71, 4.66, 4.61, 4.59, 4.51, 4.47, 4.46, 4.42, 4.20 ($PhCH_2$), 1.98, 1.94 (s, 2 × 3H, CH_3CO).

*Benzyl 2,3,6,2′,6′-Penta-O-benzyl-3′-O-p-methoxybenzyl-β-D-lactoside (**7**)*

A suspension of **1** (88 mg, 0.1 mmol) and *n*-dibutyltin oxide (26 mg, 0.11 mmol) in methanol (5 ml) was refluxed for about 1 h. The resulting clear solution was concentrated to dryness and dried. The white residue was dissolved in acetonitrile and reacted with *p*-methoxybenzyl chloride (0.1 ml) at 90°C for three days. The reaction mixture was concentrated to dryness and chromatographed on silica gel with a gradient solvent system of toluene/ethyl acetate (9/1 to 7/3), giving **7** (53 mg, 55%). TLC (solvent A), R_F 0.63.

Conventional acetylation of **7** gave **8**. NMR (see Table 1 for ring protons), δ 7.40-7.27 (m, Ph), 5.01-4.23 ($PhCH_2$), 3.82 (s, 3H, OCH_3), 2.04 (s, 3H, CH_3CO).

*Benzyl 2,3,6,2′,6′-Penta-O-benzyl-3′-O-methyl-β-D-lactoside (**9**)*

Methylation of **1** (44 mg, 50 μmol) was carried out essentially in the same way as described for **7** except for using dioxane as solvent and a sealed tube as reaction vessel to yield 32 mg (36%); 14 mg of **1** (32%) were recovered. TLC (solvent A), R_F 0.5. Conventional acetylation of **9** gave **10**. NMR (see Table 1 for ring protons), δ 7.37-7.27 (m, Ph), 5.0-4.4 ($PhCH_2$), 3.43 (s, 3H, CH_3), 2.05 (s, 3H, CH_3CO).

3′-O-Methyl-D-lactose

Compound **9** (100 mg) was subjected to catalytic hydrogenation with 10% Pd/C (100 mg) with vigorous stirring overnight, giving 3′-O-methyl-D-lactose as a white solid substance (33 mg, 90% yield). TLC (solvent B), R_F 0.13; for the mass spectrum, see Fig. 1.

*General Procedure for 3′-O-Alkylation of **2***

Stannylation of **2** was carried out essentially in the same way as described for the synthesis of **7**. The stannylated compound was suspended in a solvent (dioxane or acetonitrile) with sonication and reacted with alkyl halide (about 1.5 molar excess as compared to **2**, except of a 10-fold excess in the case of methyl iodide) at 95-100°C for several days. The reaction mixture was concentrated to dryness under reduced pressure and the products were separated by silica-gel column chromatography using a gradient of chloroform/methanol from 8/2 to 7/3. In the case of benzylation with benzyl bromide in acetonitrile, also the 3′,6′-di-O-benzylated derivative **14** was obtained.

The reaction conditions for each alkylation (methylation, benzylation and *p*-methoxybenzylation) and the NMR data of ring protons for the acetates of each product are shown in Tables 1 and 2; the mass spectrometric fragmentation pattern for the 3′-O-methyl and -benzyl compounds is given in Fig. 1. Acetylation of each of the 3′-O-alkylated products was conducted with acetic anhydride/pyridine.

Benzyl 2,3,6,2′,4′,6′-hexa-O-acetyl-3′-O-methyl-β-D-lactoside. NMR, δ 7.33-7.27 (m, Ph), 4.87, 4.60 (d, J = 12.3 Hz, $PhCH_2$), 2.2-2.0 (s, 6 × 3H, CH_3CO).

Benzyl 2,3,6,2′,4′,6′-hexa-O-acetyl-3′-O-benzyl-β-D-lactoside. NMR, δ 7.35-7.20 (m, Ph), 4.86 and 4.66 (d, J = 12.3 Hz, $PhCH_2$), 4.85, 4.60 (d, J = 12.0 Hz, $PhCH_2$), 2.15-2.00 (s 6 × 3H, CH_3CO).

Benzyl 2,3,6,2′,4′-penta-O-acetyl-3′,6′-di-O-benzyl-β-D-lactoside. NMR, δ 7.35-7.20 (m, Ph), 4.9-4.3 ($PhCH_2$) 2.15-2.0 (s, CH_3CO).

Benzyl 2,3,6,2′,4′,6′-hexa-O-acetyl-3′-O-methoxybenzyl-β-D-lactoside. NMR, δ 7.27, 6.85 and 7.22 (m, 5H, Ph), 4.89, 4.60 (d, J = 12.3 Hz, $PhCH_2$), 3.80 (s, 3H, OCH_3), 2.10-1.98 (s, 6 × 3H, CH_3CO).

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