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Improved preparation of 2,3:5,6:3′,4′-tri-*O*-isopropylidenelactose dimethyl acetal and its 6′-*O*-(1-methoxy-1-methylethyl) derivative [1]

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Abstract

Efficient preparations both of 2,3:5,6:3′,4′-tri-*O*-isopropylidenelactose dimethyl acetal (**5**, 95% yield) and its 6′-*O*-(1-methoxy-1-methylethyl) derivative (65% yield), useful intermediates for the conversion of lactose into biologically relevant oligosaccharides, by 'one-pot' acetonation procedures with 2,2-dimethoxypropane are reported. The acetonation of **5** with 2-methoxypropene in the presence of pyridinium tosylate and 4 Å molecular sieves unexpectedly revealed the formation, in a first kinetic reaction phase, of similar amounts of the 2′-*O*- and 6′-*O*-(1-methoxy-1-methylethyl) acetals. The structures of all new products were fully characterized by NMR analyses, which also allowed some deductions on the conformation of the galactopyranosyl rings.

Keywords: Lactose; 2,3:5,6:3′,4′-Tri-*O*-isopropylidenelactose dimethyl acetal; 2,3:5,6:3′,4′-Tri-*O*-isopropylidene-6′-*O*-(1-methoxy-1-methylethyl)lactose dimethyl acetal; Methoxyisopropylation

1. Introduction

Lactose (**1**) is, after sucrose, the second most abundant natural disaccharide, easily and cheaply available in large amounts from whey, a waste product of the cheese industry. The exploitation of lactose as a starting material for synthetic elaboration requires efficient methodologies for the selective protection of some or all of its seven alcoholic functions, as well as of its reducing end.

The introduction of 2,2-dimethoxypropane (DMP) [1] and 2-methoxypropene (2-MP) [2,3] as acetonating agents opened the way to the preparation of isopropylidene derivatives of di- and oligo-saccharides without breaking interglycosidic bonds. A peculiar characteristic of these reactions is the formation of various acetonation products from the same sugar by an appropriate choice of the reagent and by varying the reaction conditions. In the case of lactose

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[1] Dedicated to the memory of Professor Giuseppe Bellucci.

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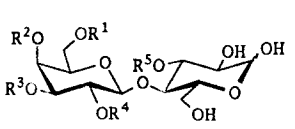
up to five different isopropylidene derivatives are known.

Baer and Abbas [4], subjecting lactose (**1**) to 2,2-dimethoxypropane at room temperature under acid catalysis, obtained in 76% isolated yield the kinetic product of the galactose moiety, that is, 4′,6′-*O*-isopropylidenelactose (**2**), while at 85 °C [5] the major acetonation product was the thermodynamic 3′,4′-*O*-isopropylidene derivative **3** in mixture with **2**, isolated respectively in 45 and 21% yields.

The di-*O*-isopropylidene derivative (**4**) of lactose, having, apart from substitution of the 4′,6′-diol function, a rather unusual 1,3,6-trioxacyclooctane acetal ring engaging two hydroxyl groups located on the two monosaccharide units (OH-3 and OH-2′), was obtained [6] in the reaction of **1** with 2-methoxypropene.

On treating **1** with neat DMP under reflux, Hough et al. [7] obtained the interesting triacetonide **5** in moderate yields (45%), the reducing glucose moiety in its acyclic form completely protected. Later, Yoshino et al. [8] found that in Hough's procedure the tetraacetonide **6**, arising from methoxyisopropylation of the 6′-OH group of **5**, was also formed and could be isolated in 29% yield.



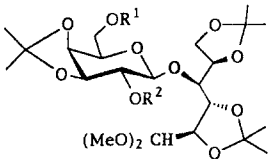
1 $R^1=R^2=R^3=R^4=R^5=H$

2 $R^3=R^4=R^5=H$; $R^1,R^2=Me_2C$

3 $R^1=R^4=R^5=H$; $R^2,R^3=Me_2C$

4 $R^3=H$; $R^1, R^2= R^4,R^5=Me_2C$

MIP = -C(OMe)Me_2



5 $R^1=R^2=H$

6 R^1=MIP; $R^2=H$

7 $R^1=H$; R^2=MIP

8 $R^1=R^2$=MIP

9 $R^1=R^2$=Ac

10 $R^1=R^2$=Bn

11 R^1=MIP; R^2=Ac

12 R^1=Ac; R^2=MIP

13 R^1=Tr; $R^2=H$

14 $R^1=R^2$=Tr

The acetonides **5** and **6** are useful starting materials for the preparation of selectively modified lactose derivatives through functionalization at positions 2′ or 6′, or both, followed by acid hydrolysis. Following these lines, a straightforward preparation of the biologically relevant 2′-fucosyllactose [9] and of some 2′-*O*-alkyl- and 2′,6′-di-*O*-alkyl-lactose derivatives [8] was reported, the sole drawback of these synthetic procedures being the low yields in the preparation of the starting acetonides.

We report here some useful improvements in the formation of both **5** and **6** by 'one-pot' treatment of the crude acetonation product prepared according to Yoshino et al. [8], and some unexpected results in the methoxyisopropylation of **5** with 2-methoxypropene.

2. Results and discussion

When lactose (**1**) was subjected to the DMP reaction under the conditions of Yoshino et al. [8], a flash-chromatographic purification of the crude product gave compounds **5** and **6** in yields (respectively, 57 and 32%) close to the reported ones.

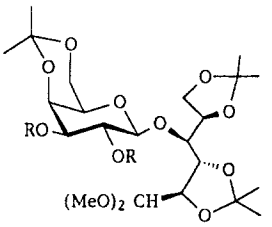
As previously found [10] for the high-yield preparation of alkyl 3,4-*O*-isopropylidene-D-galactopyranosides, when the crude acetonation mixture of **5** and **6**, neutralized with triethylamine, was dissolved in 10:1 MeOH–H_2O, and the solution warmed to 80 °C for 1.5 h, the Et_3NH^+ formed 'in situ' was sufficiently acidic for the removal of the 6′-*O*-(1-methoxy-1-methylethyl) group of **6** and its consequent complete transformation into **5**.

The crude reaction product obtained with this 'one-pot' acetonation–demethoxyisopropylation procedure was shown, by TLC and NMR spectroscopy, to contain besides the tosylate salt only the triacetonide **5** and a very small amount of the unreported 2,3:5,6:4′,6′-tri-*O*-isopropylidenelactose dimethyl acetal (**15**) (~ 3% isolated yield), probably also present in the crude acetonation product.

Pure samples of **5** can thus be obtained on a decagram scale by flash chromatography (95% yield) or by crystallization from ethyl acetate/hexane (60% yield). Crude **5** obtained by this method can also be utilized without purification for the high-yield preparation of 2′,6′-disubstituted derivatives of **5** with minimal purification steps. This possibility was exemplified by preparing the hitherto unknown dibenzyl ether **10** (75% yield from **1**).

In view of the preparation in higher amounts of the mixed acetonide **6**, the crude reaction product prepared according to Yoshino et al. [8] was treated again with neat DMP and TsOH at room temperature, under the conditions in which benzyl β-D-galactopyranoside, as well as other analogues, was transformed in high yield into the 6-*O*-(1-methoxy-1-methylethyl)-3,4-*O*-isopropylidene derivatives [11]. TLC analysis of the reaction mixture showed that after 4 h the relative amounts of **5** and **6** were inverted with concomitant formation of small amounts of two new products. The composition of the reaction

mixture remained the same for reaction times as long as 3 days; a closely analogous result was also obtained starting from pure **5**. Chromatographic separation allowed isolation of pure samples of **6** and **5**, respectively, in 65 and 18% yield. The two minor components, both isolated in 5% yield, were identified through NMR spectroscopy as the previously unreported 2′-*O*-MIP derivative **7** and 2′,6′-di-*O*-MIP derivative **8**.



15 R = H
16 R = Ac

The acetylation of **7** with acetic anhydride and pyridine gave the expected acetate **12** (45% isolated yield), but some of the diacetate **9** (25% yield) was also formed as a result of a partial removal of the mixed-acetal group under the acetylation conditions.

In the quest for a more selective method for the 6′-*O*-methoxyisopropylation of **5** with DMP, we turned our attention to the use of 2-methoxypropene, which revealed no particular advantage from the preparative point of view, but allowed some interesting observations, giving, in the presence of pyridinium tosylate and activated powdered 4 Å molecular sieves in dichloromethane, mixtures of acetonides in ratios dependent on the reaction conditions. For short times (15 min) at 0 °C, quite similar amounts of the 6′-*O*-MIP (**6**, 32%) and 2′-*O*-MIP derivative (**7**, 21%) were isolated after flash chromatography, together with unreacted **5** (31%) and the di-*O*-MIP derivative **8** (13%). Longer reaction at room temperature (12 h) gave a product distribution close to that obtained by double acetonation with DMP, and allowed the isolation of **6** in 67% yield.

These results point to the occurrence of a first kinetic phase, followed by a slow equilibration at room temperature, involving the acyclic acetal groups, but leaving the isopropylidene acetal groups untouched. This disagrees with the accepted hypothesis [3] that the addition of 2-alkoxypropenes to carbohydrates gives products of 'strictly kinetic control', involving specifically primary alcoholic groups.

In particular, the fact that in the initial stages of the reaction similar amounts of the two mono-*O*-methoxyisopropyl derivatives **6** and **7** were formed shows that the primary alcoholic function (OH-6′) and the secondary one (OH-2′) have a very similar reactivity toward 2-methoxypropene. This fact could be explained by the operation of an intramolecular hydrogen bond between OH-6′ and one of the only apparently distant methoxyl groups at C-1 with consequent lowering of the reactivity of OH-6′. Such a situation, revealed by a simple inspection of a molecular model of **5**, could also facilitate access of the reagent to OH-2′ by keeping the bulk of the anomeric substituent away from this position. An interaction of this type in the solid state in some analogues of **5** was deduced by Kogelberg and Meyer [12] from the use of computational methods.

Further evidence in favor of a particular conformational situation for **5** is given by the significant difference between its specific rotations in aprotic ($[\alpha]_D$ +36° in $CHCl_3$) and in protic solvents ($[\alpha]_D$ +19° in MeOH), which would be expected to hinder intramolecular H-bonding. Furthermore, NMR evidence points to a restricted rotation around the C-5′–C-6′ bond ($J_{5',6'a}$ and $J_{5',6'b}$ 1.74 and 8.97 Hz, respectively) in **5**, which is absent in its 6′-*O*-protected derivatives (Table 1). We intend to check this hypothesis by an X-ray diffraction study.

Finally, we reexamined the preparation of the 6′-*O*-trityl derivative **13**, for which Yoshino et al. [8] reported an unusually low yield (40%) without characterization of the side products [2]. Treatment of **5** with excess of trityl chloride in pyridine in the presence of 4-dimethylaminopyridine gave after 4 h at 60 °C a result close to those reported by Yoshino et al. [8], that is, the isolation, after workup and chromatography, of **13** in 45% yield, the sole side-product being the previously unreported 2′,6′-di-*O*-trityl derivative **14** (8% isolated yield), and unreacted **5** being recovered in 46% yield.

NMR data of products **5–16**, previously unreported, or, in some cases, incompletely and/or incorrectly reported, are collected in Tables 1–3. We note that only the 2′,6′-di-*O*-trityl derivative **14** shows coupling constants greatly different from those expected for a $^4C_1$ conformation of the galactopyranosyl moiety (Table 1) and close to those found by Kogelberg and Meyer [12] for the 2′,6′-disulfate analogue existing in a $^{3,O}B$ conformation.

Further studies into the use of **5** and **6** for the

[2] Mention of the preparation of **13** was also made by Kogelberg and Meyer [12] as an unpublished result.

Table 1
^{1}H NMR parameters (chemical shift, δ; J in Hz; CD_3CN) of the galactopyranosyl portion of lactose derivatives **5–16**

	H-1′	H-2′	H-3′	H-4′	H-5′	H-6′a	H-6′b	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',6'a}$	$J_{5',6'b}$	$J_{6'a,6'b}$
5 [a]	4.42	3.52	4.09	4.06	3.82	3.94	3.66	8.26	6.75	n.d. [b]	n.d.	8.97	1.74	11.28
6	4.39	3.33	3.95	4.14	3.85	3.58	3.51	8.15	7.33	5.43	2.08	6.24	6.52	9.50
7	4.41	3.55	4.05	4.08	3.74	3.69	3.62	8.08	5.61	n.d.	n.d.	n.d.	n.d.	n.d.
8	4.48	3.57	4.08	4.17	3.79	3.59	3.53	7.70	6.20	5.61	1.99	6.65	6.26	9.25
9 [c]	4.86	5.42	3.92	3.68	3.52	4.48	4.44	8.43	7.82	5.28	2.18	6.50	5.70	11.43
10	4.72	3.34	4.15	4.18	3.94	3.71	3.68	8.04	5.65	n.d.	n.d.	n.d.	n.d.	n.d.
11 [a]	4.78	5.02	4.10	4.20	3.84	3.72	3.58	8.38	7.60	5.20	1.94	7.03	5.70	9.09
12 [c]	4.58	3.80	3.94	3.81	3.58	4.33	4.30	7.27	5.80	5.87	2.13	6.53	5.72	n.d.
13	4.37	3.37	4.04	4.39	3.87	3.33	3.23	8.22	5.69	5.43	2.05	4.69	5.68	8.61
14	5.04	3.62	4.08	4.15	3.83	3.33	3.30	2.97	3.38	n.d.	2.04	6.15	6.40	n.d.
15	4.38	[d]	[d]	[e]	3.30	[e]	3.72	7.54	n.d.	n.d.	n.d.	n.d.	1.68	12.70
16	4.86	5.12	4.91	4.31	3.44	4.04	3.76	7.84	10.47	3.60	1.01	2.08	1.34	12.75

[a] In $CDCl_3$.
[b] n.d., Not determined.
[c] In C_6D_6.
[d] δ 3.40–3.46 (m, 2 H).
[e] δ 3.95–4.07 (m, 2 H, overlapped with H-3 and H-6b, see Table 2).

Table 2
^{1}H NMR parameters (chemical shift, δ; J in Hz; CD_3CN) of the glucose portion of lactose derivatives **5–16**

	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
5 [a]	4.37	4.60	3.92	4.02	4.34	4.21	4.03	6.71	7.95	1.49	2.70	5.05	7.03	8.78
6	4.39	4.07	3.82	4.40	4.23	3.99	4.03	6.98	5.83	1.40	n.d. [b]	n.d.	n.d.	n.d.
7	4.37	4.46	4.03	3.75	4.21	4.08	4.00	6.86	7.65	n.d.	n.d.	6.90	6.30	8.58
8	4.37	4.10	3.73	4.36	4.18	4.01	4.06	6.49	6.87	1.26	n.d.	6.29	n.d.	8.53
9 [c]	4.34	4.76	4.11	4.24	4.21	4.07	4.26	5.54	7.22	1.17	n.d.	n.d.	n.d.	n.d.
10	4.37	4.48	4.16	4.31	3.97	4.00	4.16	6.04	7.08	n.d.	n.d.	n.d.	n.d.	n.d.
11 [a]	4.36	4.46	3.97	4.08	4.31	3.97	3.97	6.07	7.07	1.69	2.77	n.d.	n.d.	n.d.
12 [c]	4.28	4.61	4.19	4.06	4.27	4.05	4.26	6.04	7.66	1.24	n.d.	n.d.	n.d.	n.d.
13	4.25	4.23	3.79	4.26	4.02	3.97	4.09	n.d.	n.d.	5.22	1.50	n.d.	n.d.	n.d.
14	4.21	3.74	4.21	3.93	4.08	3.92	3.96	3.49	7.55	n.d.	n.d.	n.d.	n.d.	n.d.
15	4.35	4.55	[d]	3.79	4.22	4.11	[d]	6.44	7.63	1.43	5.30	5.63	6.28	n.d.
16	4.35	4.53	3.98	3.90	4.24	3.89	3.89	6.43	7.26	1.34	n.d.	n.d.	n.d.	n.d.

[a] In $CDCl_3$.
[b] n.d., Not determined.
[c] In C_6D_6.
[d] δ 3.95–4.07 (m, 2 H, overlapped with H-4′ and H-6′a, see Table 1).

Table 3
Selected ^{13}C NMR signals (chemical shift, δ; CD_3CN) of lactose derivatives **5–16**

	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	C-1	C-2	C-3	C-4	C-5	C-6
5 [a]	103.31	73.98	79.34	73.43	74.56	62.27	107.01	75.21	78.05	75.68	77.42	64.38
6	104.46	74.83	80.04	74.45	73.02	60.60	106.23	77.76	78.50	76.13	77.98	66.07
7	103.53	74.20	81.05	74.83	75.33	62.55	108.08	76.14	78.39	76.50	77.33	66.46
8	103.45	73.88	80.39	74.62	72.70	60.30	106.63	78.25	76.94	76.22	77.38	66.68
9 [b]	100.81	72.90	77.64	74.02	71.16	63.31	105.67	76.03	78.28	74.62	78.72	65.06
10	103.29	81.34	79.81	74.56	72.50	69.76	106.22	76.40	78.45	77.92	76.23	66.37
11 [a]	100.27	72.90	77.28	73.68	72.02	59.60	105.00	74.99	78.03	73.68	78.12	64.67
12 [b]	103.04	73.94	79.94	72.84	71.13	63.43	106.02	75.81	77.96	75.55	77.79	66.02
13	104.12	74.66	80.01	74.47	72.65	63.07	105.94	77.65	77.30	75.79	78.50	66.25
14	103.84	73.69	78.49	72.85	72.53	63.62	106.47	75.77	76.15	74.89	77.18	67.25
15	104.55	72.60	73.28	69.10	67.25	63.21	106.21	75.53	78.67	77.72	77.72	66.29
16	100.97	69.82	72.50	67.45	66.69	62.91	105.94	75.48	78.81	75.54	78.19	65.58

[a] In $CDCl_3$.
[b] In C_6D_6.

preparation of oligosaccharides of immunological relevance are planned.

3. Experimental

General methods and products.—Melting points were determined with a Köfler apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at 20 ± 2 °C. NMR spectra were recorded with a Bruker 200 AC instrument in the stated solvent (Me_4Si was used as the internal standard, unless stated otherwise). Analytical TLC was carried out on silica gel plates (Macherey-Nagel Alugram^R sil G/UV_{254}) with detection by charring with ethanolic 10% H_2SO_4 or ethanolic 10% phosphomolybdic acid. Silica Gel 60 (Macherey-Nagel, 70–230 and 230–400 mesh, respectively) was used without pretreatment for column and flash chromatography. 2-Methoxypropene (Aldrich) was distilled just before use; lactose (Sigma) was dried at 50 °C and 0.1 Torr for 8 h; powdered 4 Å molecular sieves (Aldrich) were activated by heating for at least 24 h at 400 °C. All reactions were conducted under Ar. $MgSO_4$ was used as the drying agent for solutions.

The following standard procedure was used for acetylations: a solution of the compound in a 2:1 (v/v) mixture (15 mL/mmol) of pyridine and Ac_2O was left at room temperature for 24 h, then repeatedly co-evaporated in vacuo with toluene, and the residue was purified by chromatography on silica.

'Solid foam' refers to amorphous compounds recovered pure by chromatography for which all attempts at crystallization failed.

Acetonation of lactose (**1**).—This procedure was performed in close accordance with the method described by Yoshino et al. [8] on 9.45 g (27.6 mmol) of anhydrous **1** in DMP (80 mL) and TsOH (384 mg). The crude reaction product (16.87 g), obtained after neutralization with an excess of triethylamine (1.0 mL), evaporation, and three co-evaporations with toluene (3 × 50 mL), was subjected to flash chromatography on silica gel (4:6 hexane–EtOAc + 0.1% Et_3N), yielding **6** (5.12 g, 32%) and then **5** (8.00 g, 57%).

2,3:5,6:3′,4′-Tri-*O*-isopropylidene-6′-*O*-(1-methoxy-1-methylethyl)lactose dimethyl acetal (**6**); syrup; R_f 0.47 (4:6 hexane–EtOAc); $[\alpha]_D$ +22.7° (*c* 1.3, $CHCl_3$). ^{1}H NMR (CD_3CN): see Table 2; further signals, δ 1.28 (s, 12 H, dioxolane CMe_2, and MIP CMe_2); 1.31, 1.32, 1.39, and 1.43 (4 s, each 3 H, 2 × dioxolane CMe_2); 3.14 (s, 3 H, MIP OMe); 3.37 and 3.38 (2 s, each 3 H, 2 × OMe-1). ^{13}C NMR (CD_3CN): see Table 3; further signals, δ 24.61, 24.70, 25.23, 26.97, 27.53, and 28.45 (3 × dioxolane C*Me*$_2$); 26.49 (MIP C*Me*$_2$); 48.82 (MIP OMe); 54.04 and 56.33 (2 × OMe-1); 100.74 (MIP *C*Me$_2$); 109.03, 110.06, and 110.50 (3 × dioxolane *C*Me$_2$).

Routine acetylation of **6** (829 mg, 1.5 mmol) yielded, after flash chromatography of the crude product on silica gel (6:4 hexane–EtOAc + 0.1% Et_3N), the 2′-*O*-acetyl derivative (**11**) (780 mg, 83%) as a solid foam; R_f 0.36 (6:4 hexane–EtOAc); mp 49–51 °C; $[\alpha]_D$ +38.5° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): see Table 2; further signals, δ 1.32 (s, 6 H, MIP CMe_2); 1.34 (s, 6 H), 1.37 (s, 6 H), 1.48 and 1.56 (2 s, each 3 H), 3 × dioxolane CMe_2; 2.13 (s, 3 H, MeCO); 3.21 (s, 3 H, MIP OMe); 3.41 and 3.42 (2 s, each 3 H, 2 × OMe-1). ^{13}C NMR ($CDCl_3$): see Table 3; further signals, δ 20.94 (*Me*CO); 24.23, 24.38, 24.64, 26.30, 27.47, and 27.76 (3 × dioxolane C*Me*$_2$); 26.19 (MIP C*Me*$_2$); 48.55 (MIP OMe); 53.25 and 55.59 (2 × OMe-1); 100.09 (MIP *C*Me$_2$); 107.94, 110.27, and 110.71 (3 × dioxolane *C*Me$_2$); 169.60 (Me*CO*).

2,3:5,6:3′,4′-Tri-*O*-isopropylidenelactose dimethyl acetal (**5**); crystalline solid; R_f 0.25 (4:6 hexane–EtOAc); mp 127–129 °C (EtOAc–hexane); $[\alpha]_D$ +36.3° (*c* 1.0, $CHCl_3$) and $[\alpha]_D$ +19.2° (*c* 1.0, MeOH); lit. [8] mp 129–130 °C, $[\alpha]_D$ +39.1°. ^{1}H NMR ($CDCl_3$): see Table 2; further signals, δ 1.32 (s, 3 H), 1.33 (s, 3 H), 1.39 (s, 6 H), and 1.50 (s, 6 H), 3 × CMe_2; 3.49 and 3.50 (2 s, each 3 H, 2 × OMe). ^{13}C NMR (CD_3CN): see Table 3; further signals, δ 23.83, 25.54, 26.12, 26.12, 26.93, and 28.00 (3 × C*Me*$_2$); 54.22 and 57.40 (2 × OMe); 108.20, 109.74, and 110.30 (3 × *C*Me$_2$).

The acetylation of **5** (240 mg, 0.47 mmol), as described above, gave, after flash chromatography on silica gel (1:1 hexane–EtOAc), the 2′,6′-di-*O*-acetyl derivative (**9**) (264 mg, 95%) as a solid foam; R_f 0.47 (1:1 hexane–EtOAc); mp 110–114 °C; $[\alpha]_D$ +23.7° (*c* 1.1, $CHCl_3$); lit. [7] mp 113–115 °C, $[\alpha]_D$ +25.2°. ^{1}H NMR (C_6D_6): see Table 2; further signals, δ 1.15, 1.26, 1.39, 1.49, 1.57, and 1.59 (6 s, each 3 H, 3 × CMe_2); 1.77 and 1.99 (2 s, each 3 H, 2 × MeCO); 3.23 and 3.29 (2 s, each 3 H, 2 × OMe). ^{13}C NMR (C_6D_6): see Table 3; further signals, δ 20.40 and 20.69 (2 × *Me*CO); 24.72, 26.37, 26.49, 26.76, 27.80, and 27.87 (3 × C*Me*$_2$); 53.20 and 55.78 (2 × OMe); 107.95, 110.58, and 110.86 (3 × *C*Me$_2$); 169.14 and 169.91 (2 × Me*CO*).

Acetonation–demethoxyisopropylation.—The crude acetonation product (16.72 g) containing **5** and **6,** obtained from **1** (10.0 g, 29.2 mmol) according to Yoshino et al. [8], was dissolved, after rigorous elimination of excess of Et_3N (12 h at 0.1 Torr and room temperature), in 10:1 MeOH–water (330 mL) and the solution was heated at 80 °C. After 1.5 h, TLC analysis (4:6 hexane–EtOAc) revealed the complete transformation of **6** (R_f 0.47) into **5** (R_f 0.25). The solution was allowed to reach room temperature, evaporated in vacuo, and coevaporated three times with toluene (3 × 50 mL). Flash chromatography of the crude mixture (16.0 g) on silica gel (1:1 hexane–EtOAc + 0.1% Et_3N) yielded **5** (14.1 g, 95%) and **15** (508 mg, 3%).

Pure samples of **5** were also obtained in 60% yield by crystallization (EtOAc–hexane) of the crude product obtained as above.

2,3:5,6:4′,6′-Tri-*O*-isopropylidenelactose dimethyl acetal (**15**); solid foam; R_f 0.26 (EtOAc); mp 48–51 °C; $[\alpha]_D$ +14.9° (*c* 1.2, $CHCl_3$). ^1H NMR (CD_3CN): δ 1.29, 1.31, 1.33, 1.37, 1.39, and 1.40 (6 s, each 3 H, 3 × CMe_2); 3.34 and 3.36 (2 s, each 3 H, 2 × OMe). ^{13}C NMR (CD_3CN): δ 18.96 and 29.64 (dioxane C*Me*$_2$); 25.27, 26.63, 26.81, and 27.51 (2 × dioxolane C*Me*$_2$); 53.34 and 55.95 (2 × OMe); 99.17 (dioxane *C*Me$_2$); 109.14 and 110.37 (2 × dioxolane *C*Me$_2$). Anal. Calcd for $C_{23}H_{40}O_{12}$: C, 54.3; H, 7.9. Found: C, 54.0; H, 8.1.

The acetylation of **15** (92.6 mg, 0.19 mmol) gave, after flash chromatography on silica gel (1:1 hexane–EtOAc + 0.1% Et_3N), the 2′,3′-di-*O*-acetyl derivative (**16**) (89.5 mg, 80%) as a crystalline solid; R_f 0.30 (1:1 hexane–EtOAc); mp 69–71 °C (from hexane); $[\alpha]_D$ +31.2° (*c* 1.1, $CHCl_3$). ^1H NMR (CD_3CN): δ 1.27, 1.31, 1.33, 1.33, 1.36, and 1.42 (6 s, each 3 H, 3 × CMe_2); 1.99 and 2.03 (2 s, each 3 H, 2 × *Me*CO). ^{13}C NMR (CD_3CN): δ 18.94 and 29.59 (dioxane C*Me*$_2$); 20.91 and 21.02 (2 × *Me*CO); 24.87, 26.64, 26.64, and 27.72 (2 × dioxolane C*Me*$_2$); 52.99 and 55.79 (2 × OMe); 99.35 (dioxane *C*Me$_2$); 108.89 and 110.79 (2 × dioxolane *C*Me$_2$); 170.46 and 170.93 (2 × Me*CO*). Anal. Calcd for $C_{27}H_{44}O_{14}$: C, 54.7; H, 7.5. Found: C, 54.4; H, 7.6.

Double acetonation with 2,2-dimethoxypropane.—The crude acetonation mixture (1.4 g) of **5** and **6** obtained from **1** (780 mg, 2.3 mmol) was treated, after rigorous elimination of excess of Et_3N (12 h at 0.1 Torr and room temperature), with neat 2,2-dimethoxypropane (30 mL) and *p*-toluenesulfonic acid (37 mg, 0.2 mmol) and stirred at room temperature. TLC analysis (3:7 hexane–EtOAc) revealed a rapid change; after stirring for 4 h a stationary situation was reached in which the relative amounts of **5** (R_f 0.31) and **6** (R_f 0.62) were inverted and small amounts of products **8** (R_f 0.82) and **7** (R_f 0.54) had formed. Triethylamine (1.0 mL) was added, the solution was evaporated in vacuo, and the residue (1.46 g) was subjected to flash chromatography (1:1 hexane–EtOAc + 0.1% Et_3N) to yield **8** (74 mg, 5%), **6** (847 mg, 64%), **7** (66 mg, 5%), and **5** (267 mg, 23%).

2,3:5,6:3′,4′-Tri-*O*-isopropylidene-2′,6′-di-*O*-(1-methoxy-1-methylethyl)lactose dimethyl acetal (**8**); syrup; R_f 0.82 (3:7 hexane–EtOAc); $[\alpha]_D$ +8.7° (*c* 1.3, $CHCl_3$). ^1H NMR (CD_3CN): see Table 2; further signals, δ 1.28, 1.29, 1.29, and 1.30 (4 s, each 3 H, 2 × MIP CMe_2); 1.31, 1.33, 1.35, 1.37, 1.38, and 1.45 (6 s, each 3 H, 3 × dioxolane CMe_2); 3.15 and 3.20 (2 s, each 3 H, 2 × MIP OMe); 3.37 and 3.38 (2 s, each 3 H, 2 × OMe-1). ^{13}C NMR (CD_3CN): see Table 3; further signals, δ 24.58, 24.73, 25.68, 25.98, 27.47, and 28.00 (3 × dioxolane C*Me*$_2$); 26.36 and 26.44 (MIP-6′ C*Me*$_2$); 27.12 and 27.21 (MIP-2′ C*Me*$_2$); 48.83 (MIP-6′ OMe); 49.78 (MIP-2′ OMe); 54.27 and 56.41 (2 × OMe-1); 100.80 (MIP-6′ *C*Me$_2$); 102.05 (MIP-2′ *C*Me$_2$); 109.34, 109.68, and 110.34 (3 × dioxolane *C*Me$_2$).

2,3:5,6:3′,4′-Tri-*O*-isopropylidene-2′-*O*-(1-methoxy-1-methylethyl)lactose dimethyl acetal (**7**); syrup; R_f 0.54 (3:7 hexane–EtOAc); $[\alpha]_D$ +31.1° (*c* 1.1, $CHCl_3$). ^1H NMR (CD_3CN): see Table 2; further signals, δ 1.26 and 1.29 (2 s, each 3 H, MIP CMe_2); 1.30, 1.33, 1.33, 1.35, 1.38, and 1.44 (6 s, each 3 H, 3 × dioxolane CMe_2); 3.20 (s, 3 H, MIP OMe); 3.41 and 3.42 (2 s, each 3 H, 2 × OMe-1). ^{13}C NMR (CD_3CN): see Table 3; further signals, δ 25.65, 26.08, 26.38, 26.49, 27.30, and 28.01 (3 × dioxolane C*Me*$_2$); 27.11 (MIP C*Me*$_2$); 49.79 (MIP OMe); 54.93 and 57.69 (2 × OMe-1); 102.05 (MIP *C*Me$_2$); 109.40, 110.06, and 110.06 (3 × dioxolane *C*Me$_2$).

Compound **7** (224 mg, 0.38 mmol) was acetylated and gave, after flash chromatography of the crude product on silica gel (6:4 hexane–EtOAc + 0.1% Et_3N), **9** (57 mg, 25%) and 6′-*O*-acetyl-2,3:5,6:3′,4′-tri-*O*-isopropylidene-2′-*O*-(1-methoxy-1-methylethyl)lactose dimethyl acetal (**12**) (104 mg, 45%) as a solid foam; R_f 0.47 (6:4 hexane–EtOAc); mp 79–83 °C; $[\alpha]_D$ +21.5° (*c* 1.3, $CHCl_3$). ^1H NMR (C_6D_6): see Table 2; further signals, δ 1.13, 1.24, 1.29, 1.37, 1.40, and 1.43 (6 s, each 3 H, 3 × dioxolane CMe_2); 1.34 (s, 6 H, MIP CMe_2); 1.75 (s, 3 H, *Me*CO); 3.19 (s, 3 H, MIP OMe); 3.20 and 3.24 (2 s, each 3 H, 2 × OMe-1). ^{13}C NMR (C_6D_6): see Table 3; further

signals, δ 20.45 (*Me*CO); 25.64, 25.64, 26.21, 26.25, 27.40, and 27.61 (3 × dioxolane C*Me*$_2$); 26.99 and 27.04 (MIP C*Me*$_2$); 49.51 (MIP OMe); 53.37 and 55.77 (2 × OMe-1); 101.60 (MIP *C*Me$_2$); 108.64, 109.52, and 109.88 (3 × dioxolane *C*Me$_2$); 170.14 (Me*CO*).

2′,6′-Di-O-benzyl-2,3:5,6:3′,4′-tri-O-isopropylidenelactose dimethyl acetal (**10**).—Sodium hydride (57 mmol), obtained from 1.72 g of an 80% dispersion in mineral oil after washing with hexane (3 × 30 mL), suspended in dry DMF (50 mL) was treated at 0 °C with a solution of crude product **5** (2.3 g) obtained from **1** (1.53 g, 4.47 mmol) by the acetonation–demethoxyisopropylation method. The mixture was stirred for 15 min at 0 °C and 30 min at room temperature, cooled at 0 °C, treated with benzyl bromide (2.5 mL, 21 mmol), and further stirred for 15 min at 0 °C and 3 h at room temperature. Excess of NaH was destroyed with MeOH under stirring for 30 min, first at 0 °C, then at room temperature. The solvents were evaporated under reduced pressure, the residue was taken up in ice and water (40 mL), and the solution was extracted with CH_2Cl_2 (4 × 50 mL). The product obtained after evaporation of the dried organic phase was subjected to flash chromatography on silica gel (8:2 hexane–EtOAc) to yield pure **10** as a syrup (2.31 g, 75%); R_f 0.27 (8:2 hexane–EtOAc); $[\alpha]_D$ +14.4° (*c* 0.7, $CHCl_3$). ^{1}H NMR (CD_3CN): see Table 2; further signals, δ 1.34 (s, 6 H), 1.36 (s, 3 H), 1.40 (s, 3 H), 1.43 (s, 6 H), 3 × CMe$_2$; 3.35 (s, 6 H, 2 × OMe); 4.56 and 4.60 (AB system, 2 H, $J_{A,B}$ 12.10 Hz, benzylic CH_2); 4.77 and 4.88 (AB system, 2 H, $J_{A,B}$ 12.00 Hz, benzylic CH_2); 7.36–7.42 (m, 10 H, aromatic H). ^{13}C NMR (CD_3CN): see Table 3; further signals, δ 25.71, 26.67, 27.02, 27.34, 27.78, and 28.28 (3 × C*Me*$_2$); 54.20 and 56.10 (2 × OMe); 73.76 and 74.09 (2 × benzylic CH_2); 109.06, 110.15, and 110.64 (3 × *C*Me$_2$); 128.28, 128.43, 128.55, 128.83, 129.00, and 129.20 (aromatic CH); 139.43 and 139.58 (aromatic C). Anal. Calcd for $C_{37}H_{52}O_{12}$: C, 64.5; H, 7.6. Found: C, 65.1; H, 7.5.

Methoxyisopropylation of **5** *with 2-methoxypropene.*—To a mixture of 2,3:5,6:3′,4′-tri-*O*-isopropylidenelactose dimethyl acetal (**5**) (1.00 g, 1.97 mmol), pyridinium *p*-toluenesulfonate (80 mg), and activated powdered 4 Å molecular sieves (300 mg) in dry CH_2Cl_2 (40 mL), cooled at 0 °C under Ar, was slowly added, after 15 min stirring, a solution of 2-methoxypropene in dry CH_2Cl_2 (1:10, 3 mL, 3.15 mmol) with careful control of the internal temperature (±2 °C). TLC analysis (3:7 hexane–EtOAc) revealed a rapid reaction: after 15 min at 0 °C, four spots were present, which corresponded to the products **8** (R_f 0.82), **6** (R_f 0.62), **7** (R_f 0.54), and unreacted **5** (R_f 0.31). The reaction was quenched by addition of solid Na_2CO_3 (50 mg) followed by stirring for 30 min, filtered, and evaporated under reduced pressure, and subjected to flash chromatography (elution first with 1:1 hexane–EtOAc + 0.1% Et_3N, then with EtOAc). The following products were obtained in the order: **8** (0.167 g, 13%), **6** (0.766 g, 67%), and unreacted **5** (0.310 g).

When an identical mixture was maintained for 4 h at 0 °C, then warmed slowly at room temperature and allowed to react for 12 h, a similar treatment led, after flash chromatography, to the following products: **8** (0.128 g, 10%), **6** (0.366 g, 32%), **7** (0.240 g, 21%), and unreacted **5** (0.150 g).

Tritylation of 2,3:5,6:3′,4′-tri-O-isopropylidenelactose dimethyl acetal (**5**).—A solution of **5** (5.55 g, 10.85 mmol), trityl chloride (6.00 g, 21.53 mmol), and 4-dimethylaminopyridine (308 mg, 2.51 mmol) in dry pyridine was stirred at 60 °C for 4 h. After evaporation and co-evaporation with toluene (3 × 50 mL), the residue (11.04 g) was taken up in water (20 mL), the products were extracted with EtOAc (3 × 30 mL), the organic phase was dried ($MgSO_4$), and the solvent evaporated in vacuo. Flash chromatography of the residue (7.11 g) on silica gel (8:2 hexane–EtOAc, then 4:6 hexane–EtOAc) yielded **14** (831 mg, 8%), **13** (3.69 g, 45%), and unreacted **5** (2.61 g, 46%).

2,3:5,6:3′,4′-Tri-*O*-isopropylidene-2′,6′-di-*O*-trityllactose dimethyl acetal (**14**); R_f 0.42 (7:3 hexane–EtOAc); mp 95–97 °C (from MeOH–H_2O); $[\alpha]_D$ −41.5° (*c* 1.12, $CHCl_3$). ^{1}H NMR (CD_3CN): see Table 2; further signals, δ 1.00, 1.10, 1.13, 1.27, 1.30, and 1.35 (6 s, each 3 H, 3 × CMe$_2$); 3.19 and 3.23 (2 s, each 3 H, 2 × OMe); 7.27–7.54 (m, 30 H, aromatic H). ^{13}C NMR (CD_3CN): see Table 3; further signals, δ 25.13, 25.32, 26.77, 27.14, 27.14, and 27.47 (3 × C*Me*$_2$); 54.27 and 56.37 (2 × OMe); 87.57 (*C*Ph$_3$-6′); 89.24 (*C*Ph$_3$-2′); 108.85, 109.59, and 110.30 (3 × *C*Me$_2$); 128.04, 128.26, 128.80, 128.80, 129.52, and 129.97 (aromatic CH); 145.15 and 145.42 (aromatic C). Anal. Calcd for $C_{61}H_{68}O_{12}$: C, 73.7; H, 6.9. Found: C, 73.8; H, 7.1.

2,3:5,6:3′,4′-Tri-*O*-isopropylidene-6′-*O*-tritylactose dimethyl acetal (**13**); R_f 0.60 (1:1 hexane–EtOAc); mp 119–120 °C (from petroleum ether); $[\alpha]_D$ +17.7° (*c* 1.37, $CHCl_3$). ^{1}H NMR (CD_3CN): see Table 2; further signals, δ 1.29 (s, 3 H), 1.30 (s, 6 H), 1.37, 1.40, and 1.42 (3 s, each 3 H), 3 × CMe$_2$; 3.08 and 3.17 (2 s, each 3 H, 2 × OMe); 7.25–7.48

(m, 15 H, aromatic H). ^{13}C NMR (CD_3CN): see Table 3; further signals, δ 25.34, 26.58, 26.66, 26.99, 27.51, and 28.47 ($3 \times CMe_2$); 53.60 and 56.21 ($2 \times$ OMe); 87.65 (CPh_3); 109.31, 110.26, and 110.69 ($3 \times CMe_2$); 128.16, 128.85, and 129.51 (aromatic CH); 144.95 (aromatic C). Anal. Calcd for $C_{42}H_{54}O_{12}$: C, 67.2; H, 7.25. Found: C, 67.0; H, 7.4.

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