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THE ACETONATION OF LACTOSE AND BENZYL β-LACTOSIDE WITH 2-METHOXYPROPENE

Manuel ALONSO-LOPEZ[a], Joëlle BARBAT[b], Elizabeth FANTON[b], Alfonso FERNANDEZ-MAYORALAS[a], Jacques GELAS[b], Derek HORTON[c], Manuel MARTIN-LOMAS[a*], and Soledad PENADES[a]

[a] *Instituto de Química Orgánica, C.S.I.C., Juan de la Cierva 3, 28006 Madrid (Spain)*

[b] *Ecole Nationale Supérieure de Chimie de Clermont-Ferrand, BP 45, 63170 Aubière (France)*

[c] *Department of Chemistry, The Ohio State University, 140 W 18th Avenue, Columbus, Ohio 43210 (USA)*

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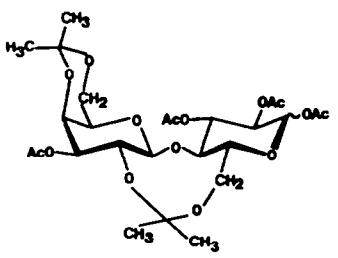
Abstract - *The acetonation of lactose with 2-methoxypropene afforded 4,6-O-isopropylidene lactose (2) and a diacetal which, after acetylation, gave an α,β-anomeric mixture of 1,2,6,3'-tetra-O-acetyl-3,2':4',6'-di-O-isopropylidene lactose (4). Acetonation of benzyl β-lactoside afforded the mixed acetals benzyl 6,6'-di-O-(methoxydimethyl)methyl (6), 6'-O-(methoxydimethyl)methyl- (7) and 6-O-(methoxydimethyl)methyl-β-lactoside (8), the cyclic acetal benzyl 4',6'-O-isopropylidene-β-lactoside (9) and a diacetal which, after acetylation gave benzyl 2,6,3'-tri-O-acetyl-3,2':4',6'-di-O-isopropylidene-β-lactoside (11). The favoured formation of eight-membered 3,2'-cyclic acetals in lactose derivatives has been further demonstrated by acetonation of benzyl 2,3',6'-tri-O-benzyl-β-lactoside (13) and benzyl 2,6,3',6'-tetra-O-benzyl-β-lactoside (12). As an example of the synthetic utility of this acetonation reaction, the chiral macrocyclic polyhydroxyether 25 has been synthesized from benzyl 3',4'-O-isopropylidene-β-lactoside.*

Acid catalyzed acetonation of oligosaccharides under standard thermodynamic conditions may affect glycosidic cleavage. The mild conditions of the kinetic acetonation procedure with 2-methoxypropene[1] are compatible with retention of the interglycosidic linkage and may afford new acetals of potential synthetic utility. We now report the behaviour of this reagent in reaction with lactose and with benzyl β-lactoside whose selectively protected derivatives are of interest in the synthesis of oligosaccharides[2,3].

Several isopropylidene acetals of lactose and methyl and benzyl β-lactosides have been described[2,4,5-7]. The kinetic acetonation of lactose with 2-methoxypropene has been previously reported by some of us in a preliminary communication[4], and structure 1 was tentatively assigned to the product isolated after acetylation of the reaction mixture on the basis of ^{1}H-n.m.r. spectroscopy. We now have re-investigated this reaction and have performed a careful study of the reaction of benzyl β-lactoside with 2-metoxy-propene. Since it is known[1] that acetonation reactions under kinetic conditions give products in which the anomeric center remains un-substituted, the behaviour of benzyl β-lactoside must closely parallel that of lactose and difficulties in product characterization due to the presence of anomeric mixtures, are avoided. The course of the acetonation reaction have been further investigated using partially protected benzyl β-lactoside derivatives and its synthetic



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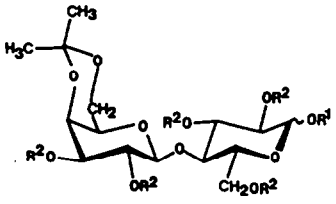
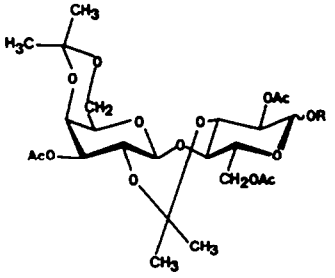
potentiality has been shown by the one-pot synthesis of the chiral macrocyclic polyhydroxyether **25**.

RESULTS AND DISCUSSION

Attempted acetonation of lactose with 2-methoxypropene, at 0ºC in the presence of toluene-*p*-sulfonic acid, resulted in a large amount of unreacted starting material. The reaction was then conducted at 25ºC with an excess (4.5 equivalents) of the reagent to bring about complete conversion of the initial lactose. Column chromatography of the reaction mixture afforded 4',6'-O-isopropylidene lactose (**2**, 54%)[7] and a faster moving diacetal (21%) having the anomeric position free (doublets at δ 6.65 and 6.45, in the ^{1}H-n.m.r. spectrum). Conventional acetylation of **2** gave **3**[7]. Acetylation of the diacetal gave a 2:3 α,β anomeric mixture (n.m.r.) of tetraacetates which proved inseparable by chromatography. Comparison of the 200 MHz ^{1}H-n.m.r. spectra of this mixture with that of **3** showed a weak upfield shift of the H-3' signal, leaving only the signals attributed to the anomeric and H-2 protons at lowfield; on the other hand, the signals assigned to H-2 and H-3 in the spectrum of **3** were absent in the low field region of the spectrum of the diacetal tetraacetates. These observations were incompatible with structure **1** and indicated that the structure of the diacetal tetraacetates must be 1,2,6,3'-tetra-O-acetyl-3,2':4',6'-di-O-isopropylidene lactose (**4**).



2, $R^1 = R^2 = H$
3, $R^1 = R^2 = Ac$
9, $R^1 = \beta Bzl$, $R^2 = H$
10, $R^1 = \beta Bzl$, $R^2 = Ac$



4, R = Ac
11, R = βBzl

The acetonation under kinetic conditions of benzyl β-lactoside was then investigated using pyridinium toluene-*p*-sulfonate as catalyst and very carefully controlled experimental conditions. Pyridinium toluene-*p*-sulfonate has been reported[16,17] to be a mild and efficient catalyst in the protection and deprotection of alcohols possessing acid sensitive groups. Treatment of benzyl β-lactoside with 2-methoxypropene (2 equiv.) at 0ºC under argon, in the presence of pyridinium toluene-*p*-sulfonate gave (t.l.c.) a mixture whose composition rapidly changed. After 90 min the main reaction product (45% after chromatography) was benzyl 6,6'-di-O-(methoxydimethyl) methyl-β-lactoside (**5**). The ^{13}C-n.m.r. spectra of **5** showed signals for methyl (24.5 and 24.7 p.p.m.), methoxy (48.4 and 48.5 p.p.m.) and acetal (100.4 and 100.2 p.p.m.) carbon atoms respectively. Conventional acetylation of **5** gave a penta-acetate (**6**). A shorter reaction time (20 min) allowed the isolation of **5** (10%), benzyl 6'-O-(methoxydimethyl) methyl-β-lactoside (**7**, 15%), and 6-O-methoxydimethyl) methyl-β-lactoside (**8**, 8%). The ^{13}C-n.m.r. spectra of these compounds showed signals for the methoxy (48.4 and 48.5 p.p.m., respectively), and methyl (24.4 and 24.7, and 24.8 p.p.m. respectively) groups. After a longer reaction time (20 h), benzyl 4',6'-O-isopropylidene-β-lactoside[2] (**9**, 50 %) and two by-products (13% and 11%) were isolated. The ^{13}C-n.m.r. spectra of these latter compounds showed signals for methoxy (50.2 and 48.7 p.p.m., respectively) and methyl (29.2, 28.6, 24.5, and 18.6 and 29.1, 24.5, 24.3, and 18.7 p.p.m., respectively) groups. Acetylation of **9** gave **10**[2]. Acetylation of the major by-product afforded a triacetate the ^{13}C-n.m.r. spectrum of which showed signals for methyl carbon atoms (29.3, 27.8, 24.1, and 18.3 p.p.m.) and no signal assignable to methoxyl group. The ^{1}H-n.m.r. spectrum of this compound showed signals for acetoxyl (δ 2.15, 2.05, and 2.04) and isopropylidene methyl acetal (δ 1.43, 1.42, 1.34, and 1.33) groups and was analised by homonuclear 2D-correlation (COSY) spectroscopy (*Table 1*). On these basis structure **11** was unequivocally assigned.

When the acetonation reaction was carried out in the presence of Drierite, the same reaction pattern (t.l.c.) was observed although longer reaction time was required. With toluene *p*-sulfonic acid as catalyst in the conditions previously reported for the acetonation of lactose[4] shorter reaction time was needed but the same products were formed (t.l.c.). Compound **5** in N,N-dimethylformamide, in the presence

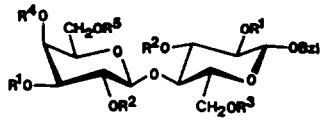
of a catalytic amount of pyridinium toluene-*p*-sulfonate gave first **7**,**8**, and benzyl β-lactoside, and then **9** as the major product.

TABLE 1

^{1}H-n.m.r. data (δ scale, J, in Hz) for compound **11**, *as obtained by two-dimensional spectroscopy*

H-1	4.47	$J_{1,2}$	8.2
H-2	5.02	$J_{2,3}$	9.4
H-3	3.81	$J_{3,4}$	8.0
H-4	4.11	$J_{4,5}$	9.6
H-5	3.47	$J_{5,6a}$	3.2
H-6a	4.55	$J_{5,6b}$	2.1
H-6b	4.14	$J_{6a,6b}$	12.0
H-1'	4.40	$J_{2',3'}$	9.6
H-2'		$J_{3',4'}$	3.6
H-3'	4.65	$J_{4',5'}$	1.0
H-4'	4.29	$J_{5',6'a}$	2.2
H-5'	3.30	$J_{5',6'b}$	1.5
H-6'a	3.95	$J_{6'a,6'b}$	12.8
H-6'b	3.80		

The formation of cyclic acetals in acetal-exchange reactions is believed to proceed[8,9] *via* mixed-acetal intermediates. These compounds have been isolated in the acetalation reaction of methyl-α-D-gluco-pyranoside with benzophenone dimethyl acetal[10] and of several D-gluco- and D-



5, $R^1 = R^2 = R^4 = H$, $R^3 = R^5 = C(CH_3)_2OCH_3$

6, $R^1 = R^2 = R^4 = Ac$, $R^3 = R^5 = C(CH_3)_2OCH_3$

7, $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = C(CH_3)_2OCH_3$

8, $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = C(CH_3)_2OCH_3$

12, $R^1 = R^3 = R^5 = Bzl$, $R^2 = R^4 = H$

13, $R^1 = R^5 = Bzl$, $R^2 = R^3 = R^4 = H$

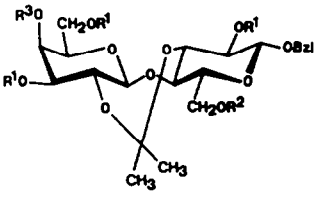
14, $R^1 = R^3 = R^5 = Bzl$, $R^2 = R^4 = Ac$

15, $R^1 = R^5 = Bzl$, $R^2 = R^3 = R^4 = Ac$

galacto-pyranosides with 2,2-dimethoxypropane and acetophenone dimethyl acetal[11] and can be synthesised by the reaction of alcohols with α-haloethers[12] or enol ethers[13,14]. The acetonation reaction with 2-alkoxy propenes could be envisaged[1] as proceeding by initial attack at the most accesible hydroxyl group to give a mixed-acetal intermediate, with subsequent ring closure at the hydroxyl group, then the most sterically available. However, mixed-acetal derivatives have not been frequently isolated in the reaction of 2-alkoxy-propene with sugars although some examples have been reported[18]. As postulated[1], these mixed-acetals seem to equilibrate before ring-closure to give the kinetically controlled cyclic acetals. The isolation, after acetylation of the acetonation products, of the diacetal derivatives **4** and **11**, bearing a 4',6'-acetal substituent and a second acetal grouping spanning O-2' in a eight-membered ring that engages O-3 instead of O-6 as previously reported[4], parallels previous results in the reaction of maltose with 2,2-dimethoxy-propane[15] and possess some interesting questions. The isolation of **11** after acetylation of an acetonation product whose ^{13}C-n.m.r. spectra clearly showed the presence of a methoxyl group seems to indicate that, in some cases, ring-closure may take place in the acetylation conditions and that the structure of the acetonation products cannot always be inferred from the structure of the isolated acetylation compounds. We have also observed that acetylation of either **7** or **8** gives complex mixtures even when the reaction was performed at low temperature. The formation of **4** and **11** could be interpreted by attack of the reagent to the relatively reactive HO-2' and subsequent ring-closure with participation of HO-3. We have not been able to characterize the intermediate 2'-O-(methoxydimethyl) methyl derivative although the major by-product whose acetylation afforded **11** could possible have such structure. The presence of **6** and **8** in the reaction mixture and our failure to isolate products in which HO-6 is involved in a cyclic acetal may also indicate that the formation of the eight-membered 3,2'-cyclic acetal instead of the nine-membered 6,2'-cyclic acetal may be somehow favoured in our acetonation/acetylation conditions.

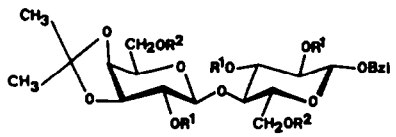
In order to obtain new data which may be of interest in the study of this reaction we have synthesised benzyl 2,6,3',6'-tetra-O-benzyl-β-lactoside (**12**) and benzyl 2,3',6'-tri-O-benzyl-β-lactoside (**13**)

and have studied the reaction of these compounds with 2-methoxypropene. Treatment of benzyl β-lactoside with bis-tributyltin oxide and subsequently with benzyl bromide in the presence of N-methylimidazole[3] gave **12** (47%) after 28 h. Conventional acetylation of **12** afforded a triacetate (**14**) whose ^{1}H-n.m.r. spectrum showed low-field signals for H-4', H-3, and H-2'. When the benzylation reaction was stopped after 7 h, the tri-O-benzyl derivative **13** was obtained in 50% yield. This compound gave, after acetylation, a tetra-O-acetate (**15**) the ^{1}H-n.m.r. spectrum of which showed low-field signals for H-4', H-3, H-2' and H-6. Reaction of **12** with 3 equiv. of 2-methoxypropene at 0ºC for 24 h gave benzyl 2,6,3',6'-tetra-O-benzyl-3,2'-O-isopropylidene-β-lactoside (**16**, 61%) and unreacted **12**. Conventional acetylation of **16** gave a monoacetate (**19**) the ^{1}H-n.n.r. spectrum of which showed a low-field signal for H-4' at δ 5.56. Treatment of **13** with 2 equiv. of 2-methoxypropene at 0ºC for 19 h gave benzyl 2,3',6'-tri-O-benzyl-6-O-(methoxydimethyl) methyl-3,2'-O-isopropylidene-β-lactoside (**17**, 36%), benzyl 2,3,6'-tri-O-benzyl-3,2'-O-isopropylidene-β-lactoside (**18**, 17%) and a compound which spontaneously transformed into **13** (20%). The ^{1}H-n.m.r. spectrum of **17** showed a signal at δ 3.19 assigned to the methoxyl group protons and four signals at δ 1.42, 1.36, 1.31, and 1.30 for the isopropylidene group methyl protons. This compound gave, after conventional acetylation and subsequent mild acid hydrolysis, a monoacetate (**20**) whose ^{1}H-n.m.r. spectrum showed a low-field signal at δ 5.54 assigned to H-4'. Acetylation of either **20** or **18** afforded diacetate **21**.

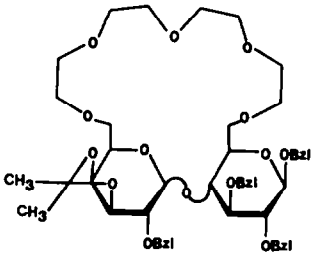


16, $R^1 = R^2 = Bzl$, $R^3 = H$
17 $R^1 = Bzl$, $R^2 = C(CH_3)_2OCH_3$, $R^3 = H$
18 $R^1 = Bzl$, $R^2 = R^3 = H$
19 $R^1 = R^2 = Bzl$, $R^3 = Ac$
20 $R^1 = Bzl$, $R^2 = H$, $R^3 = Ac$
21 $R^1 = Bzl$, $R^2 = R^3 = Ac$

It could be concluded from the above acetonation experiments that in our reaction conditions the eight-membered 3,2'-cyclic acetal ring is easily formed and that cyclic acetal formation involving HO-6 seems to be somehow precluded in these lactose derivatives. These experiments also shows how kinetic acetonation can be used to prepare a series of lactose derivatives with high synthetic potentiality. As an example, 6,6'-dihydroxy derivatives can be easily synthesized in one-pot reaction with reasonable yield. Thus, the chiral macrocyclic poly-hydroxyether benzyl 2,3,2'-tri-O-benzyl-3',4'-O-isopropylidene-6,6'-O-(3,6,9-trioxaundecane,1,11-diyl)-β-lactoside (**25**) has been easily prepared from benzyl 3',4'-O-isopropylidene-β-lactoside (**22**). Reaction of **22** with 2-methoxypropene in the usual conditions for three hours, subsequent treatment with benzyl bromide and sodium hydride overnight, and final mild acid hydrolysis afforded benzyl 2,3,4-tri-O-benzyl-3',4'-O-isopropyldiene-β-lactoside (**23**) in 42% yield in one-pot. Acetylation of **23** afforded a diacetate (**24**) the ^{1}H-n.m.r. spectrum of which showed low-field signals for H-6



22, $R^1 = R^2 = H$
23, $R^1 = Bzl$, $R^2 = H$
24, $R^1 = Bzl$, $R^2 = Ac$



25

and H-6' between δ 4.5 and 4.1. Condensation of **23** with tetraethylene glycol ditosylate in the presence of sodium hydroxyde gave **25** in 43% yield. The f.a.b. mass spectrum of **25** gave a peak (90%) at m/z 923 corresponding to $|M + Na^+|$ and the microanalytical and ^{1}H- and ^{13}C-n.m.r. data were in agreement with this structure.

EXPERIMENTAL

General.- Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. T.l.c. was performed on silica gel GF_{254} (Merck) with detection by charring with sulfuric acid. Column chromatography was performed on Merck silica gel (70-230). ^{1}H-N.m.r. spectra (300 MHz) were recorded using a Varian XL-300 spectrometer, and ^{13}C-n.m.r. spectra on a Bruker VP-80 (20 MHz) or a Varian XL-300 (75 MHz) spectrometer. The COSY spectrum was recorded with a Varian XL-300 spectrometer. The two-dimensional map was composed of 256-512 data-point spectra, each incremented by 1.7 ms. A delay of 4s was allowed between each pulse sequence. The data were acquired with quadrature phase detection in both dimensions, and the final data were symmetrised. Optical rotations were determined with a Perkin-Elmer 141 polarimeter.

Acetonation of lactose.- A solution of lactose monohydrate (3.6 g) in anhydrous N,N-dimethylformamide (40 mL) containing a catalytic amount of toluene-*p*-sulfonic acid (20 mg) was shaken at room temperature. 2-Methoxypropene (4.5 equivalents) was slowly added during 3 h. The reaction mixture was neutralized with solid Na_2CO_3 and evaporated *in vacuo* . The residue was fractionated on a silica gel column. Elution with 8:1 chloroform-methanol gave first a compound (21% yield) having m.p. 95-125ºC, $|\alpha|_D^{21}$ + 21.9º (24 h, water). Acetylation of this compound (1 g) with boiling acetic anhydride (10 mL) and anhydrous sodium acetate (0.85 g) gave the α,β-anomeric mixture which was purified by column chromatography (1:1 hexane-ethyl acetate). M.p. 105-107ºC, $|\alpha|^{21}$ +33.5º (chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 6.27 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1_α), 5.67 (d, 1H, $J_{1,2}$ 8.6 Hz, H-1_β), 5.07 (dd, 1H, H-2_β), 5.04 (dd, 1H, H-2_α), 4.68 (dd, 1H, H-$3'_\alpha$), 4.66 (dd, 1H, H-$3'_\beta$), 4.59 (d, 1H, $J_{1',2'}$ 8.7 Hz, H-$1'_\alpha$), 4.58 (dd, 1H, H-$6a_\alpha$), 4.56 (dd, 1H, H-$6a_\beta$), 4.53 (d, 1H, H-$1'_\beta$), 4.42 (dd, 1H, H-$6b_\alpha$), 4.38 (dd, 1H, H-$6b_\beta$), 4.30 (d, 1H, H-4'), 2.05-2.15 (3s, 12H, OAc), 1.35-1.55 (m, CMe).

Eluted second was the α,β-anomeric mixture **2** (54%), m.p. 120-180ºC, $|\alpha|_D^{21}$ +26.2º (36 h, water; lit[7], m.p. 120-160ºC, $|\alpha|_D^{25}$+25º (12 h, water. Acetylation as above gave **3**, m.p. 185-187ºC, $|\alpha|_D^{21}$ + 32.6º (chloroform); lit[7], m.p. 172-174ºC, $|\alpha|_D$ - 30.9º (chloroform).

Acetonation of benzyl β-lactoside

a) Treatment of benzyl β-lactoside (1 g) in dry N,N-dimethylformamide (10 mL) with 2-methoxypropene (0.8 mL, 3.7 equiv.) in the presence of pyridinium toluene-*p*-sulfonate (21 mg) at 0ºC, under argon, for 90 min. gave, after neutralization with Na_2CO_3 and evaporation, a residue which was chromatographed on a column of silica gel. Elution with 7:1 chloroform-methanol gave **5** (600 mg) as a syrup, $|\alpha|_D^{20}$ -14.6º (c 1.02, pyridine). ^{13}C-N.m.r. data: 105.6, 103.2, 100.4, 100.2, 48.4, 48.5, 24.5 and 24.7.

Acetylation of **5** (0.12 g) in pyridine (1.2 mL) with acetic anhydride (0.12 mL) at 4ºC for 3 days gave, after chromatography (1:2 ethyl acetate-hexane), pure **6** (0.08 g) as a syrup. ^{13}C-N.m.r. data (d_5-pyridine): 170.2, 170.1, 169.9, 169.7, 168.8, 100.6, 100.2, 100.0, 99.0, 48.7, 48.6, 24.8, 24.3, 24.2, 24.1, 20.9, 20.7 (2C), 20.6. ^{1}H-N.m.r. data: δ 7.30-7.40 (m, 5H, aromatic), 3.16 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3), 1.28 and 1.40 (s, 6H, CH_3).

b) Benzyl β-lactoside (1 g) was treated as above for 20 min. After column chromatography (7:1 chloroform-methanol) pure **5** (0.13 g), **7** (0.18 g) and **8** (0.09 g) were obtained as syrups.

Compound **7** had $|\alpha|_D$ -20.9º (c 1.01, pyridine). ^{13}C-N.m.r. data (d_5-pyridine): 105.7, 103.6, 100.4, 48.5, 24.5 (2C).

Compound **8** had $|\alpha|_D$ -23.3º (c 0.92, pyridine). ^{13}C-N.m.r. data (d_5-pyridine): 105.6, 103.3, 100.3, 48.4, 24.8 and 24.7.

c) Benzyl β-lactoside (2 g) was treated as above for 24 h. After column chromatography (10:1 chloroform-methanol) two by-products (0.30 g and 0.28 g respectively) were first obtained and then pure **9** (1.1 g).

^{13}C-N.m.r. data for the fastest-moving by-product ($CDCl_3$): 102.4, 101.6, 99.5, 99.2, 50.2, 29.2, 28.6, 24.5, and 18.6.

^{13}C-N.m.r. data for the slowest-moving by-product ($CDCl_3$): 103.8, 101.5, 100.6, 99.2, 48.7, 29.1,

24.5, 24.3, and 18.7.

Acetylation of the fastest-moving by-product (0.13 g) conventionally with acetic anhydride (0.39 mL) in pyridine (1.30 mL) gave **11** (0.09 g) after 3 days. ^{13}C-N.m.r. data ($CDCl_3$): 101.9, 99.3, 99.2, 98.4, 29.3, 27.8, 24.1, and 18.3. For ^{1}H-n.m.r. data, *see Table 1*.

Compound **9** was identical in all respects to benzyl 4',6'-O-isopropylidene-β-lactoside[2] and gave, after acetylation, compound **10** identical in all respects to benzyl 2,3,6,2',3'-penta-O-acetyl-4',6'-O-isopropylidene-β-lactoside (**10**)[2].

Benzyl 2,6,3',6'-tetra-O-benzyl-β-lactoside (**12**).- Benzyl β-lactoside (1 g, 2.3 mmol) in toluene (75 mL) was treated with 3Å molecular sieves (5.5 g) and bis-tri-n-butyltinoxide (4.75 mL , 9.3 mmol) overnight, with stirring at 120ºC and under argon. The mixture was cooled at 95ºC and benzyl bromide (10 mL) and N-methylimidazole (0.55 mL, 6.7 mmol) were added and stirring continued at the same temperature for 28 h. The mixture was filtered, washed with hot chloroform-methanol, and evaporated. The residue was treated with hexane (200 mL) and kept overnight at -10ºC. After decantation, the sirupy residue was introduced in a silica gel column. Elution with 2:1 chloroform-ethyl acetate gave **12** (0.85 g, 47%) as a sirup. $|\alpha|_D^{20}$ -11.4º (c 0.5, chloroform). ^{13}C-N.m.r. data (75 MHz, $CDCl_3$): δ 138.9, 137.8, 137.6, 128.6, 128.4, 127.9, 127.4, 126.9, 104.2, 102.3, 83.3, 81.4, 80.5, 74.8, 73.8, 73.6, 73.3, 72.3, 71.2, 71.0, 69.9, 69.2, and 66.7. (Found: C, 70.83; H, 6.54. Calcd. for $C_{47}H_{52}O_{11}$: C, 71.19; H, 6.61).

Benzyl 3,2',4'-tri-O-acetyl-2,6,3',6'-tetra-O-benzyl-β-lactoside (**14**).- Acetylation of **12** conventionally with acetic anhydride in pyridine gave **14** as a syrup. $|\alpha|_D^{20}$ +23.8º (c, 0.4, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.20-7.40 (m, 25H, aromatic), 5.51 (d, 1H, $J_{3',4'}$ 3.1 Hz, H-4'), 5.08 (t, 1H, $J_{2,3} \simeq J_{3,4}$ 9.5 Hz, H-3), 4.90 (dd, 1H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 9.8 Hz, H-2'), 3.80 (t, 1H, $J_{3,4} \simeq J_{4,5}$ 9.5 Hz, H-4), 3.27 (dd, 1H, $J_{2',3'}$ 9.8, $J_{3',4'}$ 3.1 Hz, H-3'), 2.10, 1.96, 1.90 (3s, 3H each, 3 Ac). (Found: C, 68.98; H, 6.19. Calcd. for $C_{53}H_{58}O_{14}$: C, 69.26; H, 6.36).

Benzyl 2,3',6'-tri-O-benzyl-β-lactoside (**13**).- Benzyl β-lactoside (1.5 g, 3.47 mmol) in toluene (100 mL) was treated with 3Å molecular sieves (6 g) bis-tri-n-butyltin oxide (7.13 mL, 14.0 mmol) overnight at 120ºC with stirring, under argon. The mixture was cooled at 95ºC and benzyl bromide (10 mL) and N-methylimidazole (0.28 mL, 3.47 mmol) were added and stirring continued at 95ºC for 7 h. The mixture was then treated as described for **12**. Compound **13** (1.21 g, 50%) was obtained as a solid, m.p. 109-111ºC, $|\alpha|_D^{20}$ -4.1º (c, 0.7, chloroform). ^{13}C-N.m.r. data (75 MHz, $CDCl_3$): δ 138.8, 137.7, 137.4, 128.5, 128.1, 127.9, 127.4, 126.9, 103.9, 102.3, 82.1, 81.4, 80.8, 75.3, 74.7, 74.1, 73.6, 72.0, 71.3, 70.2, 69.3, 66.4, 64.8, and 62.3. (Found: C, 68.05; H, 6.52. Calcd. for $C_{40}H_{46}O_{11}$: C, 68.36; H, 6.60).

Benzyl 3,6,2',4'-tetra-O-acetyl-2,3',6'-tri-O-benzyl-β-lactoside (**15**).- Acetylation of **13** conventionally with acetic anhydride-pyridine afforded **15** as a syrup, $|\alpha|_D^{20}$ +31.9º (c, 0.9, chloroform). ^{1}H-N.m.r. ($CDCl_3$): δ 7.10-7.30 (m, 20H, aromatic), 5.55 (d, 1H, $J_{3',4'}$ 3.6 Hz, H-4'), 5.13 (t, 1H, $J_{2,3} \simeq J_{3,4}$ 9.1 Hz, H-3), 4.98 (dd, 1H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 10.0 Hz, H-2'), 4.53 (d, 1H, $J_{1,2}$ 7.6 Hz, H-1), 4.41 (dd, 1H, $J_{5,6a}$ 1.8, $J_{6a,6b}$ 11.7 Hz, H-6a), 4.33 (d, 1H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.09 (dd, 1H, $J_{5,6b}$ 5.2, $J_{6a,6b}$ 11.7 Hz, H-6b), 3.65 (dd, 1H, $J_{3,4}$ 9.1, $J_{4,5}$ 9.5 Hz, H-4), 3.57 (m, 1H, H-5), 3.42 (dd, 1H, $J_{2',3'}$ 10.0, $J_{3',4'}$ 3.6 Hz, H-3'), 3.36 (dd, 1H, $J_{1,2}$ 7.6, $J_{2,3}$ 9.1 Hz, H-2), 2.07, 2.06, 2.00, 1.86 (4s, 3H each, 4 Ac). (Found: C, 66.59; H, 6.28. Calcd. for $C_{48}H_{54}O_{11}$: C, 66.19; H, 6.25).

Acetonation of benzyl 2,6,3',6'-tetra-O-benzyl-β-lactoside (**12**).- Compound **12** (0.3 g, 0.38 mmol), in N,N-dimethylformamide (3 mL) was treated with 2-methoxypropene (0.11 mL, 1.18 mmol) and pyridinium toluene-*p*-sulfonate (3 mg) at 0ºC under argon and with stirring for 24 h. The mixture was neutralized with sodium carbonate, filtered, and concentrated and the residue was chromatographed on a column of silica gel. Elution with 7:2 hexane-ethyl acetate gave benzyl 2,6,3',6'-tetra-O-benzyl-3,2'-O-isopropylidene-β-lactoside (**16**, 0.19 g, 61%) and unreacted **12** (0.04 g). Compound **16** had m.p. 131-133ºC (7:2 hexane-ethyl acetate), $|\alpha|_D^{20}$ -28.6º (c 0.5, benzene). ^{1}H-N.m.r. data (d_6-acetone): δ 7.4 (m, 25H, aromatic) 4.55 (d, 1H, $J_{1,2}$ 7.8 Hz, H-1), 4.47 (d, 1H, $J_{1,2}$ 8.6 Hz, H-1'), 4.30 (dd, $J_{2',3'}$ 9.7 Hz, H-2'),

4.16 (m, 1H, H-4'), 4.06 (m, 1H, H-5'), 4.00 (dd, 1H, H-6a), 3.82 (m, 2H, H-3, H-4), 3.75 (m, 2H, H-6'b, H-6'a), 3.62 (m, 1H, H-6b), 3.54 (m, 1H, H-5), 3.48 (dd, 1H, $J_{3',4'}$, 2.1 Hz, H-3'), 3.22 (m, 1H, H-2), 2.10 (s, 3H, Me) and 1.04 (s, 3H, Me). ^{13}C-N.m.r. data (d_6-acetone): 146.4-144.5 (aromatic), 137-134.4 (aromatic), 109.1 (anomeric), 109.0 (acetalic), 107.3 (anomeric), 35.2 (Me), 31.3 (Me). (Found: C, 72.35; H, 6.48. Calcd. for $C_{50}H_{56}O_{11}$: C, 72.09; H, 6.78).

Benzyl 4'-O-acetyl-2,6,3',6'-tetra-O-benzyl-3,2'-O-isopropylidene-β-lactoside (**19**).- Acetylation of **16** conventionally with acetic anhydride-pyridine gave **19**, $[\alpha]_D^{20}$ -27.4º (c 0.5, benzene). ^{1}H-n.m.r. data ($CDCl_3$): δ 5.56 (d, 1H, $J_{3',4'}$ 2.6 Hz, H-4'), 2.10 (s, 3H, 1 Ac), 1.41 and 1.32 (2s, 3H each, 2 Me). (Found: C, 71.56; H, 6.79. Calcd. for $C_{52}H_{58}O_{12}$: C, 71.38; H, 6.68).

Acetonation of benzyl 2,3',6'-tri-O-benzyl-β-lactoside (**13**).- Compound **13** (0.22 g, 0.31 mmol) in N,N-dimethylformamide (1.6 mL) was treated with 2-methoxypropene (0.06 mL, 0.64 mmol) and pyridinium toluene-*p*-sulfonate (3 mg) at 0ºC, under argon for 19 h. The mixture was neutralized with sodium carbonate and concentrated to give a residue which was chromatographed on a column of silica gel. Elution with 5:1 hexane-ethyl acetate gave first benzyl 2,3',6'-tri-O-benzyl-3,2'-O-isopropylidene-6-O-(methoxydimethyl) methyl-β-lactoside (**17**, 0.09 g, 36%) as an unstable syrup. ^{1}H-N.m.r. data (C_6D_6): δ 3.19 (s, 3H, OMe), 1.42, 1.36, 1.31, and 1.30 (4s, 3H each, 4 Me). Compound **17** (0.19 g) was conventionally acetylated with acetic anhydride-pyridine overnight. Evaporation of the mixture gave a residue which was treated with acetone (7 mL) and pyridinium toluene-*p*-sulfonate (3.5 mg) at room temperature for 2 h. The mixture was neutralized with sodium carbonate, filtered and evaporated to give a residue which was introduced in a column of silica gel. Elution with 7:3 hexane-ethyl acetate gave pure benzyl 4-O-acetyl-2,3',6'-tri-O-benzyl-3,2'-O-isopropylidene-β-lactoside (**20**, 0.14 g, 78%) as a syrup, $[\alpha]_D^{20}$ -12.2º (c, 0.4, chloroform). ^{1}H-N.m.r data ($CDCl_3$): δ 7.20-7.40 (m, 20H, aromatic), 5.57 (d, 1H, $J_{3',4'}$ 3.2 Hz, H-4'), 2.11 (s, 3H, 1 Ac), 1.44 and 1.33 (2s, 3H each, 2 Me). (Found: C, 68.55; H, 6.70. Calcd. for $C_{45}H_{52}O_{12}$: C, 68.86; H, 6.68).

Elution with 2:1 hexane-ethyl acetate gave benzyl 2,3',6'-tri-O-benzyl-3,2'-O-isopropylidene-β-lactoside (**18**, 0.041 g, 17%) which was conventionally acetylated with acetic anhydride-pyridine to give benzyl 6,4'-di-O-acetyl-2,3',6'-tri-O-benzyl-3,2'-O-isopropylidene-β-lactoside (**21**) as a sirup, $[\alpha]_D^{20}$ -30.6º (c, 0.5, chloroform). ^{1}H-N.m.r. data (C_6D_6): δ 7.10-7.30 (m, 20H, aromatic), 5.50 (d, 1H, $J_{3',4'}$ 3.4 Hz, H-4'), 1.63 and 1.54 (2s, 3H each, 2Ac), 1.42 and 1.39 (2s, 3H each, 2 Me). ^{13}C-N.m.r. data ($CDCl_3$, 75 MHz): δ 170.4, 169.7 (CO), 102.4, 102.1, 100.2 (CMe_2, C-1, and C-1'), 80.3, 78.2, 77.2, 73.7, 73.4, 72.8, 71.9, 71.1, 67.7, 67.4, 63.5, 28.3, 24.4, and 20.8. (Found: C, 68.10; H, 6.70. Calcd. for $C_{47}H_{54}O_{13}$: C, 68.26; H, 6.58). This compound was also obtained by conventional acetylation of **20**.

Finally, a compound was eluted (0.055 g) which was spontaneously transformed into **13**.

Benzyl 2,3,2'-tri-O-benzyl-3',4'-O-isopropylidene-β-lactoside (**23**).- Benzyl 3',4'-O-isopropylidene-β-lactoside (**22**, 1.5 g, 3.18 mmol) in N,N-dimethylformamide (15 mL) was treated with 2-methoxypropene (0.9 mL, 9.5 mmol) and pyridinium toluene-*p*-sulfonate (5 mg) for 3 h at 0ºC under argon. Sodium hydride (1.1 g) and benzyl bromide (2 mL, 16.8 mmol) were then added and the mixture was kept overnight at room temperature with stirring. Methanol (3 mL) and water (3 mL) were successively added and then toluene-*p*-sulfonic acid until the mixture was slightly acidic (pH 3-4) and the mixture stirred for 10 min. Aqueous sodium hydrogen carbonate was then added and the mixture extracted with dichloromethane, and the extracts were dried (Na_2SO_4) and evaporated to give a syrup which was chromatographed on a silica gel column. Elution with 2:3 hexane-ethyl acetate gave pure **23** (1 g, 42%) as a syrup, $[\alpha]_D^{20}$ +21.9 (c, 0.5, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.28-7.35 (m, 20H, aromatic), 4.54, 4.47 (2d, 1H each H-1, H-1'), 4.20 (t, 1H, $J_{2',3'} \simeq J_{3',4'}$ 6.3 Hz, H-3'), 4.04 (dd, 1H, $J_{4',5'}$ 2.0 Hz, H-4'), 3.87 (t, 1H, $J_{3,4} \simeq J_{4,5}$ 9.1 Hz, H-4), 3.83 (m, 2H, H-6a, H-6b), 3.73 (m, 1H, H-5'), 3.58 (m, 3H, H-3, H-6'a, H-6'b), 3.43-3.39 (dd each, 1H each, H-2, H-2'), 3.28 (m, 1H, H-5), 1.40 and 1.33 (2s, 3H each, Me). ^{13}C-N.m.r. data ($CDCl_3$, 75 MHz): δ 138.5-137.3 (C-*ipso*), 128.2-127.6 (aromatic), 110.1, 102.7, 101.9, 82.9, 81.9, 80.5, 79.8, 76.3, 75.7, 75.5, 75.0, 74.0, 73.2, 71.3, 62.0, 60.9, 27.9, and 26.3. (Found: C, 69.41; H, 6.69. Calcd. for $C_{43}H_{50}O_{11}$: C, 69.52; H, 6.78).

Benzyl 6,6-di-O-acetyl-2,3,2'-tri-O-benzyl-3',4'-O-isopropylidene-β-lactoside (**24**).- Acetylation of **23** conventionally with acetic anhydride-pyridine gave **24** $|\alpha|_D^{20}$ +16.3º (c, 1.1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.37-7.26 (m, 20H, aromatic), 4.52 (dd, 1H, $J_{5,6a}$ 1.7, $J_{6a,6b}$ 11.6 Hz, H-6a), 4.49 (d, 1H, $J_{1,2}$ 7.7 Hz, H-1), 4.44 (d, 1H, $J_{1',2'}$ 7.7 Hz, H-1'), 4.27-4.14 (m, 4H, H-6b, H-3', H-6'a, H-6'b), 4.08 (dd, 1H, $J_{4',5'}$ 2.0, $J_{3',4'}$ 5.5, H-4'), 3.84 (t, 1H, $J_{3,4} \simeq J_{4,5}$ 9.2 Hz, H-4), 3.78 (m, 1H, H-5'), 3.62 (t, 1H, $J_{2,3}$ 8.8 Hz, H-3), 3.48 (m, 2H, H-2, H-5), 3.38 (dd, 1H, H-2'), 2.10, 1.96 (2s, 3H each, Ac), 1.38, 1.32 (2s, 3H each, Me). ^{13}C-N.m.r. data ($CDCl_3$, 75 MHz): δ 170.5, 138.8, 138.4, 138.2, 137.2, 128.4, 127.4, 110.1, 102.2, 101.7, 82.4, 81.9, 80.2, 79.2, 77.0, 75.0, 74.9, 73.4, 73.2, 71.0, 63.3, 63.1, 27.7, 26.2, 20.8, 20.7. (Found: C, 68.49; H, 6.94. Calcd. for $C_{47}H_{54}O_{13}$: C, 68.27; H, 6.58).

Benzyl 2,3,2'-tri-O-benzyl-3',4'-O-isopropylidene-6,6'-O-(3,6,9-trioxaundecane-1,11-diyl)-β-lactoside (**25**).- Compound **23** (0.87 g, 1.17 mmol) in dry tetrahydrofuran (25 mL) was treated with sodium hydroxide (1.02 g, 25.5 mmol) at 45ºC with stirring for 15 min. The mixture was then heated at 65ºC and tetraethyleneglycol ditosilate (1.5 g, 3 mmol) in dry tetrahydrofuran (30 mL) was added dropwise during 4 h. Stirring was continued for 24 h and the mixture was then cooled, centrifuged, and concentrated. The residue was dissolved in water, the solution extracted with dichloromethane, the extract dried (Na_2SO_4) and concentrated. The residue was introduced in a column of silica gel and eluted with 1:2 hexane-ethyl acetate to give pure **25** (0.45 g, 43%) as a syrup, $|\alpha|_D^{20}$ +10º (c, 0.5, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.45-7.23 (m, 20H, aromatic), 4.59 (d, 1H, $J_{1',2'}$ 8.2 Hz, H-1'), 4.47 (d, 1H, $J_{1,2}$ 7.6 Hz, H-1), 4.22 (dd, 1H, $J_{4',5'}$ 1.6, $J_{3',4'}$ 5.5 Hz, H-4'), 4.15 (t, 1H, $J_{2',3'}$ 5.5 Hz, H-3'), 4.13 (t, 1H, $J_{2,3} \simeq J_{3,4}$ 9.1 Hz, H-3), 4.00 (dd, 1H, $J_{6a,6b}$ 11.4, $J_{5,6a}$ 2.2 Hz, H-6a), 3.96 (m, 1H, H-6'a), 3.80-3.49 (m, 20H, H-4, H-6b, H-5', H-6'b, $|OCH_2CH_2O|_4$), 3.45 (dd, 1H, H-2), 3.37 (dd, 1H, H-2'), 3.25 (m, 1H, H-5), 1.39, and 1.36 (2s, 3H each, Me). ^{13}C-N.m.r. data ($CDCl_3$, 75 MHz): δ 139.2, 138.8, 138.7, 137.7, 128.6, 127.3, 109.7, 102.9, 101.6, 83.0, 80.8, 79.7, 75.4, 75.3, 75.0, 74.1, 73.5, 72.5, 71.3, 71.0, 70.8, 70.7, 70.5, 70.2, 69.6, 68.5, 28.0, and 26.5. F.a.b. mass spectrum: m/z 923 $|M + Na^+|$ (90%). (Found: C, 67.79; H, 7.29. Calcd. for $C_{51}H_{64}O_{14}$: C, 68.00, H, 7.11.

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REFERENCES

1. J. Gelas and D. Horton, *Heterocycles* , **16**, 1587 (1981), and references therein.
2. A. Fernández-Mayoralas, M. Martín-Lomas, and D. Villanueva, *Carbohydr. Res.*, **140**, 81 (1985).
3. A. Fernández-Mayoralas and M. Martín-Lomas, *Carbohydr. Res.*, **154**, 93 (1986).
4. E. Fanton, J. Gelas, and D. Horton, *J. Chem. Soc. Chem. Commun.*, 21 (1980).
5. L.A.W. Thelwall in "*Developments in Food Carbohydrates*", C.K.Lee, Ed. Applied Science Publishers, 275 (1980).
6. L. Hough, A.C. Richardson, and L.A.W. Thelwall, *Carbohydr. Res.*, **75**, C11 (1979).
7. H.H. Baer, and S.A. Abbas, *Carbohydr. Res.*, **77**, 117 (1979); *ibid* , **84**, 53 (1980).
8. R. Cortés-García, L. Hough, and A.C. Richardson, *J. Chem. Soc. Perkin Trans. I*, 3176 (1981).
9. F.A.J. Meskens, *Synthesis* , 501 (1981).
10. M.E. Evans, F.W. Parrish, and L. Long, Jr., *Carbohydr. Res.*, **3**, 453 (1967).
11. A. Lipták, P. Fügedi, J. Kerékgyártó, and P. Nánási, *Carbohydr. Res.*, **113**, 225 (1983).
12. S. David, A. Thieffry, and A. Veyrieres, *J. Chem. Soc. Perkin Trans. I*, 1796 (1981).
13. M.L. Wolfrom, A. Beattie, and S.S. Bhattacharjee, *J. Org. Chem.*, **33**, 1067 (1968).
14. T. Mukaiyama, M. Oshima, and M. Murakami, *Chem. Lett.*, 265 (1984).
15. Y. Ueno, K. Hori, R. Yamauchi, M. Kiso, A. Hasegawa, and K. Kato, *Carbohydr. Res.*, **89**, 271 (1981).
16. R. Sterzycki, *Synthesis*, 725 (1979).
17. M. Miyashita, A. Yoshikoshi, and P. Grieco, *J. Org. Chem.*, **42**, 3772 (1977).
18. J. Gelas, and D. Horton, *Carbohydr. Res.*, **45**, 181 (1975).