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Syntheses of all the possible monomethyl ethers and several deoxyhalo analogues of methyl β-lactoside as ligands for the *Ricinus communis* lectins

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ABSTRACT

The synthesis of all the possible monomethyl ethers of methyl β-lactoside (1) has been performed from 1 in a straightforward way, making use of the different reactivity of the hydroxyl groups in alkylation and stannylation reactions. In addition, the deoxyfluoro derivatives of 1 at positions, 6, 3′, 4′, epi-4′, and 6′ have been prepared by reaction of the appropriate substrates with diethylaminosulfur trifluoride or tetrabutylammonium fluoride. Finally, the 6-deoxyiodo and 6′-bromodeoxy analogues of 1 have also been prepared.

INTRODUCTION

As a part of a project on the molecular recognition between lactose analogues and galactose-binding proteins, we have reported on the binding of methyl β-lactoside[1] (1) and all its monodeoxy derivatives by the β-D-galactoside-specific lectins ricin (RCA 60) and agglutinin (RCA 120), isolated from *Ricinus communis* seeds[1,2]. On the basis of the dissociation constants observed, we have suggested that the glucose moiety having the $^4C_1$ chair conformation is involved in the recognition, mainly through a hydrophobic interaction between the lectins and the C-3 region of the disaccharide, while HO-3′, HO-4′, and HO-6′ are involved in hydrogen bonding to the protein. Besides, a smaller polar interaction between HO-2′ and the receptors seems to be operative.

It is accepted that the total hydrogen-bonding donor and acceptor capacity of a hydroxyl group to interact with a protein group may be assessed by using a deoxy analogue[3]. However, the separation of the energetic contributions of the donor and acceptor components is a more difficult task and has been proved usually

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through the use of deoxyfluoro[4] or, in general, deoxyhalo compounds, and *O*-methyl derivatives[5]. The use of the former compounds has been recently challenged[6], since a variation of the local three-dimensional structure of the complex may occur because of the higher electronegativity of the fluorine atom with respect to oxygen. The use of *O*-methyl derivatives has been recently recommended[7], since they not only measure the accepting capacity of a given hydroxyl group, but also may predict the position of the recognition site on the periphery or in the interior of the protein. On this basis, we now report the synthesis of all the possible monomethyl ethers of methyl β-lactoside and several deoxyfluoro, deoxyiodo, and bromodeoxy analogues of methyl β-lactoside (**1**). These compounds have been used as ligands for ricin and agglutinin[8] in order to determine the role of the different hydroxyl groups as hydrogen bond donors or acceptors, and the involvement of the remote glucose residue in the binding, assuming that the conformational changes between the free and bound states will be minor, as reported for the binding of methyl β-lactoside to ricin B-chain[9]. On the other hand, the synthesis of partially modified methyl β-lactoside derivatives has become a topic of interest[10] since the discovery that methyl β-lactoside causes the suppression of metastatic lung colonies in mice injected with mouse B16 melanoma cells[11].

RESULTS AND DISCUSSION

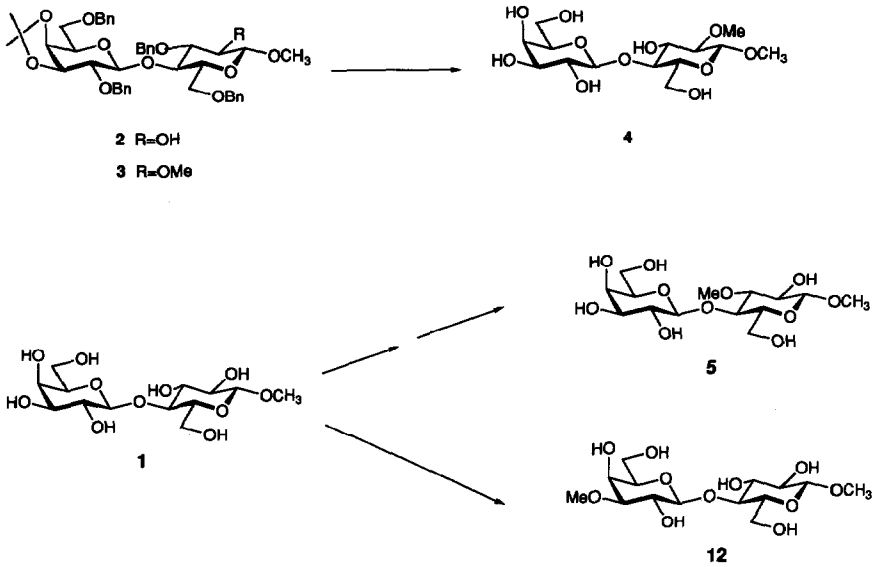
The syntheses of the following compounds have not been optimised with respect to chemical yields since the main target of this research has been the molecular recognition studies by ricin and agglutinin, two different galactose-binding proteins. Nevertheless, all the final derivatives and the key intermediates have been completely analysed with respect to their NMR parameters in order to support their unambiguous structural characterisation and purity.

The strategy for the synthesis of the target derivatives was to achieve a regioselectivity as good as possible in order to decrease the number of steps of protection and deprotection. Thus, in the case of monomethyl ethers, several intermediates were obtained which made use of the different reactivity of the hydroxyl groups, and increased selectively their nucleophilicity, employing tributyltin ethers or dibutylstannylene derivatives[12].

Methyl 2-*O*-methyl-β-lactoside (**4**) (Scheme 1) was obtained by conventional *O*-methylation of methyl 3,6,2′,6′-tetra-*O*-benzyl-3′,4′-*O*-isopropylidene-β-lactoside (**2**), previously prepared in our laboratory[2], to give **3** (98%), followed by hydrogenolysis and acid hydrolysis (95%).

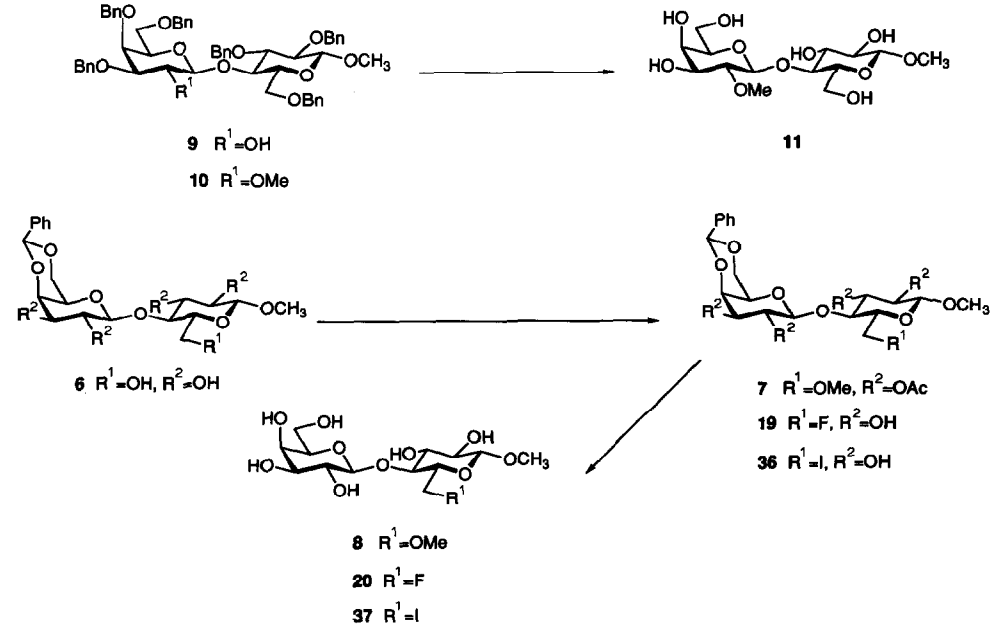
The synthesis of methyl 3-*O*-methyl-β-lactoside (**5**) has been reported previously[2]. Alternative routes to this compound have appeared recently[13].

Methyl 6-*O*-methyl-β-lactoside (**8**) (Scheme 2) was prepared by selective *O*-methylation of methyl 4′,6′-O-benzylidene-β-lactoside (**6**) via the corresponding 6-tributyltin ether, using *N*-methylimidazole as catalyst[14]. The tin salts were carefully removed, and the compound was first characterised after acetylation as

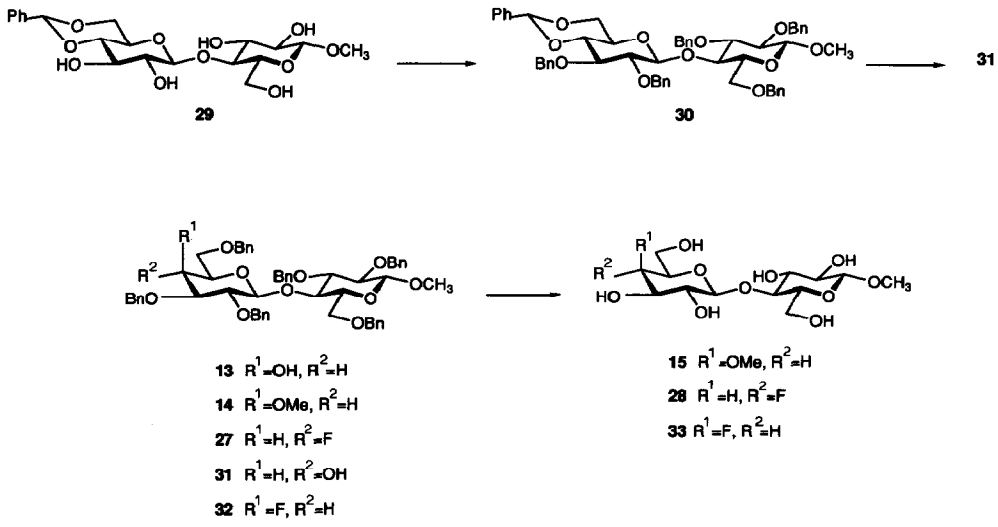


Scheme 1.

methyl 2,3,2′,3′-tetra-*O*-acetyl-4′,6′-*O*-benzylidene-6-*O*-methyl-β-lactoside (7, 19%). Acid hydrolysis of the acetal group and subsequent Zemplén deacylation gave **8** (95%).



Scheme 2.



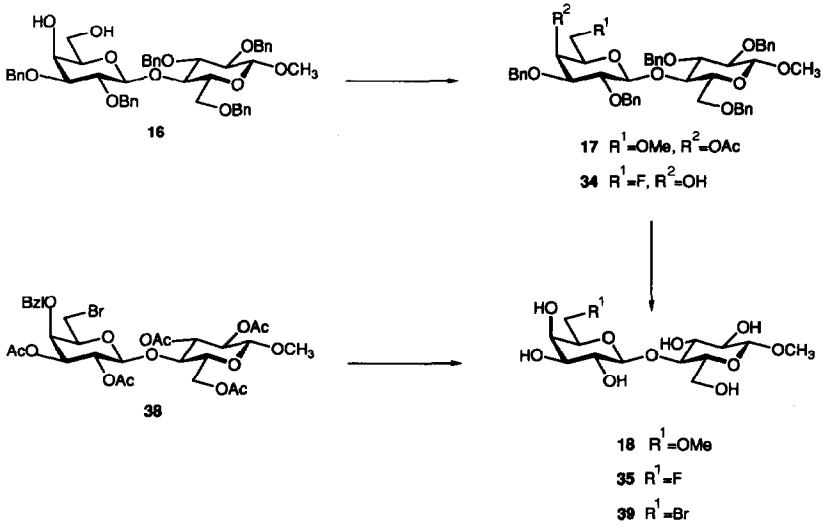
Scheme 3.

Methyl 2′-*O*-methyl-β-lactoside (**11**) (Scheme 2) was prepared from methyl 2,3,6,3′,4′,6′-hexa-*O*-benzyl-β-lactoside (**9**) obtained, among other products, in the partial benzylation under phase-transfer conditions[15] of methyl β-lactoside with 11% yield. Conventional *O*-methylation of **9** gave **10** (82%) and hydrogenolysis yielded **11** (95%). This compound has been synthesised previously through a long protection and deprotection scheme[16].

Methylation at O-3′ (Scheme 1) of lactose derivatives (benzyl β-lactoside) has already been achieved using a long route from the partially protected 3,4-diol[17,18]. We found direct *O*-methylation to be a simpler alternative. Thus, methyl 3′-*O*-methyl-β-lactoside (**12**) was easily prepared from methyl β-lactoside (**1**) via the corresponding 3′,4′-*O*-dibutylstannylene derivative[19], and characterised as methyl 2,3,6,2′,4′,6′-hexa-*O*-acetyl-3′-*O*-methyl-β-lactoside (54%) after treatment with acetic anhydride and pyridine. Simple Zemplén deacylation yielded **12** (90%).

Methyl 4′-*O*-methyl-β-lactoside (**15**) (Scheme 3) was obtained from methyl 2,3,6,2′,3′,6′-hexa-*O*-benzyl-β-lactoside[2] (**13**), obtained by regioselective opening of a 4′,6′-*O*-benzylidene ring under reducing conditions. Methylation of **13** with NaH and MeI afforded methyl 2,3,6,2′,3′,6′-hexa-*O*-benzyl-4′-*O*-methyl-β-lactoside (**14**, 65%). Benzyl groups were removed by hydrogenolysis to give **15** (88%). Other alternatives to differentiate this position in lactose derivatives have been reported recently[18].

Methyl 6′-*O*-methyl-β-lactoside (**18**) (Scheme 4) was prepared by stannylation of methyl 2,3,6,2′,3′-penta-*O*-benzyl-β-lactoside[20] (**16**), obtained by benzylation of methyl 4′,6′-*O*-benzylidene-β-lactoside (**6**), followed by removal of the acetal group with aqueous acetic acid. Thus, treatment of **16** with bis(tributyltin) oxide and methyl iodide gave methyl 2,3,6,2′,3′-penta-*O*-benzyl-6′-*O*-methyl-β-lactoside,



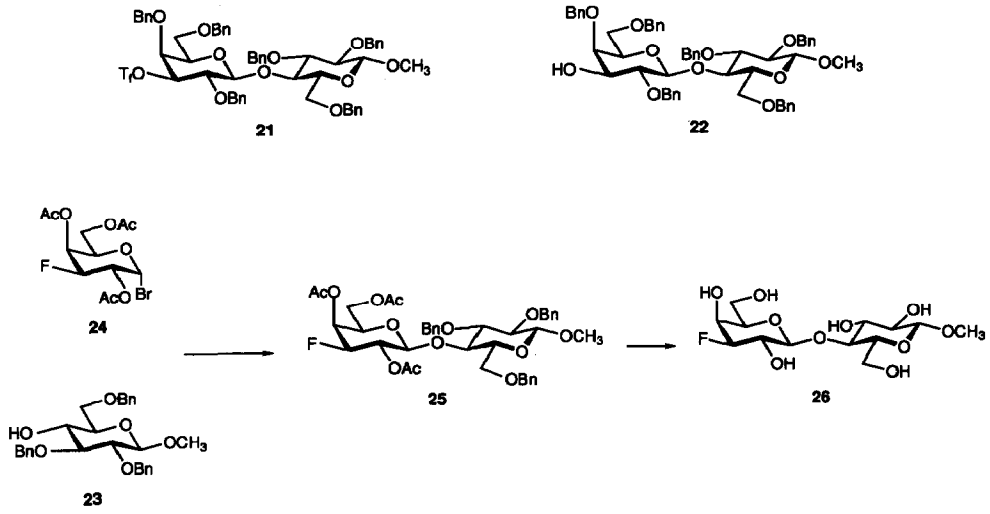
Scheme 4.

which was characterised as its 4′-acetyl derivative **17** (46%). Deacylation and hydrogenolysis yielded **18** (77%).

The synthesis of the deoxyfluoro derivatives was rather more cumbersome, since the orientation of several hydroxyl groups had to be inverted prior to the reaction with the fluorinating reagent. The use of fluorinated carbohydrates is a topic of interest[21], due to the importance of these derivatives as modified ligands in different processes[21,22] and to the challenging problems which represent their synthesis[23].

The regioselectivity of diethylaminosulfur trifluoride[24] (DAST) was used for the synthesis of methyl 6-deoxy-6-fluoro-β-lactoside (**20**) (Scheme 2). Thus, direct treatment of methyl 4′,6′-*O*-benzylidene-β-lactoside (**6**) with 2 equivalents of diethylaminosulfur trifluoride in CH_2Cl_2 for 1 h afforded as main product methyl 4′,6′-*O*-benzylidene-6-deoxy-6-fluoro-β-lactoside (**19**, 31%), a compound in which only one out of five hydroxyl groups was modified. Deprotection of the acetal ring with aqueous acetic acid gave **20** (67%). This compound has been recently prepared from **1** by a route which involves, as key step, a protease-catalysed regioselective esterification[10].

Methyl 3′-deoxy-3′-fluoro-β-lactoside (**26**) (Scheme 5) required more effort. Treatment of methyl 2,3,6,2′,4′,6′-hexa-*O*-benzyl-3′-*O*-triflyl-β-lactoside (**21**) with sodium benzoate, in order to invert the stereochemistry at C-3′, resulted in cleavage and elimination reactions. In addition, the reaction of methyl 2,3,6,2′,4′,6′-hexa-*O*-benzyl-β-lactoside (**22**) with DAST gave a complex mixture of polyfluorinated compounds (from ^{19}F NMR), and the tandem triflate formation/NBu_4F displacement only provided elimination products. In view of these results, we proceeded via glycosylation of methyl 2,3,6-tri-*O*-benzyl-β-D-glucopyranoside[25]



Scheme 5.

(**23**) with 2,4,6-tri-*O*-acetyl-3-deoxy-3-fluoro-α-D-galactopyranosyl bromide[26] (**24**), in the presence of mercuric cyanide and mercuric bromide, to obtain **25** (44%). Hydrogenolysis of the benzyl groups and Zemplén deacylation gave the desired methyl 3′-deoxy-3′-fluoro-β-lactoside **26** (96%).

Methyl 4′-deoxy-4′-fluoro-β-cellobioside (methyl 4′-deoxy-4′-epi-fluoro-β-lactoside) (**28**) (Scheme 3) was prepared by treatment of methyl 2,3,6,2′,3′,6′-hexa-*O*-benzyl-β-lactoside[2] (**13**) with DAST to give **27** (60%), followed by hydrogenolysis of the benzyl groups (→ **28**, 91%).

Methyl 4′-deoxy-4′-fluoro-β-lactoside (**33**) (Scheme 3) was prepared from methyl 2,3,6,2′,3′,6′-hexa-*O*-benzyl-β-cellobioside (**31**), which was obtained from methyl 4′,6′-*O*-benzylidene-β-cellobioside[27] (**29**) via benzylation (**30**, 90%) and regioselective opening (**31**, 53%), since the Mitsunobu inversion[28] at C-4′ of **13** failed. In addition, the reaction of **31** with DAST surprisingly gave retention of the configuration at C-4′, producing **27**. When the reaction was repeated with an *O*-trityl group at the 6′ position[29], the corresponding retention product was again obtained (from NMR). Finally, nucleophilic displacement of the corresponding triflate of **31** with tetrabutylammonium fluoride in benzene yielded the desired methyl 2,3,6,2′,3′,6′-hexa-*O*-benzyl-4′-deoxy-4′-fluoro-β-lactoside (**32**, 66%). Conventional hydrogenolysis gave **33** (94%).

Methyl 6′-deoxy-6′-fluoro-β-lactoside (**35**) (Scheme 4) was synthesised from methyl 2,3,6,2′,3′-penta-*O*-benzyl-β-lactoside[20] (**16**) by reaction with DAST, to give methyl 2,3,6,2′,3′-penta-*O*-benzyl-6′-deoxy-6′-fluoro-β-lactoside (**34**; 47%), and hydrogenolysis (→ **35**, 91%). The protease-catalysed approach has been recently used to obtain this product[10].

Methyl 6-deoxy-6-iodo-β-lactoside (**37**; 60%) (Scheme 2) was obtained by acid hydrolysis of methyl 4′,6′-*O*-benzylidene-6-deoxy-6-iodo-β-lactoside (**36**). Bock and co-workers[30] have reported a longer route to this compound.

Methyl 6′-bromo-6′-deoxy-β-lactoside (**39**; 75%) (Scheme 4) was prepared by deacylation of methyl 2,3,6,2′,3′-penta-*O*-acetyl-4′-*O*-benzoyl-6′-bromo-6′-deoxy-β-lactoside[16] (**38**) with catalytic sodium methoxide solution.

EXPERIMENTAL

General methods.—Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. TLC was performed on Silica Gel GF_{254} (Merck) with detection by charring with H_2SO_4. Column chromatography was performed on silica gel (70—230 mesh, Merck). Spectra were recorded with a Varian XL-300, Varian Unity (500 MHz), or Bruker AM-200 spectrometer. The ^{19}F NMR chemical shifts were referenced to external CF_3CO_2H. Optical rotations were measured with a Perkin–Elmer 241 MC polarimeter.

Methyl 2-O-methyl-β-lactoside (**4**).—A solution of methyl 3,6,2′,6′-tetra-*O*-benzyl-3′,4′-*O*-isopropylidene-β-lactoside (**2**; 0.1 g, 0.13 mmol) in THF (5 mL) was treated with NaH (2 equiv, 6 mg) and, 30 min later, with MeI (20 equiv, 0.17 mL). After stirring under Ar for 1 h at room temperature, an additional amount (0.4 mL) of MeI was added to complete the reaction. The mixture was quenched with MeOH, concentrated, and chromatographed (4:1 hexane–EtOAc) to give methyl 3,6,2′,6′-tetra-*O*-benzyl-3′,4′-*O*-isopropylidene-2-*O*-methyl-β-lactoside (**3**; 0.1 g, 98%) as an oil, $[\alpha]_D^{20}$ −15° (*c* 0.5, $CHCl_3$). NMR data ($CDCl_3$): ^1H (300 MHz), δ 7.36–7.16 (m, 20 H, 4 Ph), 4.85 and 4.65 (ABq, 2 H, *J* 10.5 Hz, CH_2Ph), 4.72 and 4.58 (ABq, 2 H, *J* 11.7 Hz, CH_2Ph), 4.49 and 4.33 (ABq, 2 H, *J* 12.1 Hz, CH_2Ph), 4.43 and 4.24 (ABq, 2 H, *J* 12.0 Hz, CH_2Ph), 4.33 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1′), 4.12 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.03 (dd, 1 H, $J_{3',4'}$ 5.6 $J_{4',5'}$ 1.4 Hz, H-4′), 3.95 (t, 1 H, $J_{3',4'}$ 6.1 Hz, H-3′), 3.84 (t, 1 H, $J_{3,4} = J_{4,5} = 9.4$ Hz, H-4), 3.72 (dd, 1 H, $J_{5,6a}$ 4.1, $J_{6a,6b}$ 9.8 Hz, H-6a), 3.66 (dd, 1 H, $J_{5,6b}$ 1.5 Hz, H-6b), 3.62–3.56 (m, 3 H, H-5,6′a,6′b), 3.50 (s, 3 H, OCH_3), 3.46 (s, 3 H, OCH_3), 3.40 (t, 1 H, $J_{2,3} = J_{3,4} = 9.0$ Hz, H-3), 3.33 (m, 1 H, H-5), 3.27 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 6.8 Hz, H-2′), 3.01 (dd, 1 H, $J_{1,2}$ 7.8, $J_{2,3}$ 9.05 Hz, H-2), 1.34 and 1.28 (2 s, each 3 H, CMe_2); ^{13}C (50 MHz), δ 139.0, 138.5, 138.4, 138.3 (4 C-ipso, Ph), 128.2–127.2 (Ph), 109.7 (CMe_2), 104.3, 101.8 (C-1,1′), 83.4, 83.1, 80.6, 79.3, 76.3, 75.0, 73.6, 71.9, (C-2/5 and C2′/5′), 73.3, 73.2, 73.1 (4 CH_2Ph), 68.9, 68.2 (C-6,6′), 60.6, 56.8 (2 OCH_3), 27.9, 26.3 (Me_2C). Anal. Calcd for $C_{56}H_{62}O_{11}$: C, 70.11; H, 7.06. Found: C, 69.51; H, 7.07.

A solution of **3** (90 mg, 0.12 mmol) in 1:1 CH_2Cl_2–EtOH (10 mL) was hydrogenated in the presence of 10% Pd–C for 15 h at atmospheric pressure. The catalyst was removed by filtration through Celite, and the solvents were evaporated. The residue was then treated with aq 50% AcOH (10 mL) at 65°C for 1 h. The mixture was cooled and concentrated, and the residual AcOH eliminated by codistillation with toluene. Column chromatography (4:1 $CHCl_3$–MeOH) gave **4**

(27 mg, 95%); mp 234–235°C; $[\alpha]_D^{20}$ −7° (*c* 0.8, H_2O). NMR data (D_2O): ^1H (300 MHz, δ 4.45 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.43 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 3.98 (dd, 1 H, $J_{5,6a}$ 2.2, $J_{6a,6b}$ 12.2 Hz, H-6a), 3.92 (bd, 1 H, $J_{3',4'}$ 3.4 Hz, H-4'), 3.78 (dd, 1 H, $J_{5,6b}$ 5.1, $J_{6a,6b}$ 12.2 Hz, H-6b), 3.77 (dd, 1 H, $J_{5',6'a}$ 2.1, $J_{6'a,6'b}$ 8.5 Hz, H-6'a), 3.74 (m, 1 H, H-6'b), 3.71 (m, 1 H, H-5'), 3.67 (m, 1 H, H-3), 3.66 (t, 1 H, $J_{3,4}$ 9.0 Hz, H-4), 3.64 (dd, 1 H, $J_{2',3'}$ 9.5, $J_{3',4'}$ 3.0 Hz, H-3'), 3.58 (s, 3 H, OCH_3 n), 3.57 (m, 1 H, H-5), 3.57 (s, 3 H, OCH_3 1), 3.53 (dd, 1 H, $J_{1',2'}$ 7.7, $J_{2',3'}$ 9.9 Hz, H-2'), 3.06 (dd, 1 H, $J_{1,2}$ 8.1, $J_{2,3}$ 8.8 Hz, H-2); ^{13}C (125 MHz), δ 104.2 (C-1'), 104.1 (C-1), 83.5 (C-2), 79.5 (C-4), 76.6 (C-5') 75.9 (C-5), 75.1 (C-3), 73.8 (C-3'), 72.2 (C-2'), 69.8 (C-4'), 62.3 (C-6'), 61.3 (C-6), 61.2 (OCH_3 n), 58.4 (OCH_3 1). Anal. Calcd for $C_{14}H_{26}O_{11} \cdot H_2O$: C, 43.30; H, 7.27. Found: C, 43.59; H, 7.31.

Methyl 6-O-methyl-β-lactoside (**8**).—A mixture of methyl 4',6'-*O*-benzylidene-β-lactoside (**6**; 0.466 g, 1.1 mmol), bis(tributyltin) oxide (3 equiv, 1.6 mL), 3A molecular sieves (1.5 g), and MeCN (15 mL) was boiled under Ar overnight. The mixture was cooled to 60–65°C, and *N*-methylimidazole (1 equiv, 83 μL) and MeI (20 equiv, 1.3 mL) were added. The reaction was left for 5 days, periodically adding more MeI and molecular sieves. The mixture was filtered while hot through Celite. The cake was washed with hot $CHCl_3$–MeOH, and the filtrate and washings evaporated to give a yellow syrup, which was stirred with hexane for 5 h and left overnight at −10°C in order to remove tin salts. The solution was decanted and the residue conventionally acetylated with Ac_2O and pyridine. Column chromatography (2:1 hexane–EtOAc) gave methyl 2,3,2',3'-tetra-*O*-acetyl-4',6'-*O*-benzylidene-6-*O*-methyl-β-lactoside (**7**; 0.121 g, 19%), isolated as a syrup, $[\alpha]_D^{20}$ +26° (*c* 0.9, $CHCl_3$). NMR data ($CDCl_3$): ^1H (300 MHz), δ 7.49–7.26 (m, 5 H, Ph), 5.47 (s, 1 H, C*H*Ph), 5.25 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 10.3 Hz, H-2'), 5.19 (t, 1 H, $J_{2,3} = J_{3,4} = 9.5$ Hz, H-3), 4.92 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.8 Hz, H-2), 4.91 (dd, 1 H, $J_{2',3'}$ 10.2, $J_{3',4'}$ 3.7 Hz, H-3'), 4.55 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'). 4.37 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 4.32 (dd, 1 H, $J_{3',4'}$ 3.6, $J_{4',5'}$ 0.5 Hz, H-4'), 4.3 (dd, 1 H, $J_{5',6'a}$ 1.5, H-6'a), 4.04 (dd, 1 H, $J_{5',6'b}$ 1.7, $J_{6'a,6'b}$ 12.5 Hz, H-6'b), 3.92 (t, 1 H, $J_{3,4} = J_{4,5} = 9.6$ Hz, H-4), 3.7 (dd, 1 H, $J_{5,6a}$ 3.4, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.64 (dd, 1 H, $J_{5,6b}$ 2.0, $J_{6a,6b}$ 11.0 Hz, H-6b), 3.49 (s, 3 H, OCH_3), 3.54–3.42 (m, 2 H, H-5,5'), 3.49 (s, 3 H, OCH_3), 3.44 (s, 3 H, OCH_3); ^{13}C (50 MHz), δ 170.8, 170.4, 169.7, 168.6 (4 C=O), 137.5 (C-ipso, Ph), 129.1, 128.2, 126.5 (Ph), 101.8, 101.3, 100.5 (C-1,1' and *C*HPh), 74.9, 74.8, 73.3, 72.5, 72.2, 71.6, 69.2, 66.3 (C-2/5 and C-2'/5'), 69.8, 68.5 (C-6,6'), 59.4, 56.9 (2 OCH_3), 20.8, 20.7, 20.6 (4 Ac). Anal. Calcd for $C_{29}H_{38}O_{15}$: C, 55.59; H, 6.11. Found: C, 55.88; H, 6.10.

A solution of **7** (89 mg, 0.14 mmol) in AcOH (4 mL) was heated at 100°C, then water (2 mL) was added in small portions within 5 min. After 1 h, the solvents were evaporated, and the last traces of volatile compounds removed by codistillation with dry toluene. The crude product was then deacetylated under Zemplén conditions. After evaporation of solvent, the residue was purified by column chromatography (4:1 $CHCl_3$–MeOH) to provide **8** (50 mg, 95%); mp 95–97°C; $[\alpha]_D^{20}$ +1° (*c* 1.1, H_2O). NMR data (D_2O): ^1H (300 MHz), δ 4.38 (d, 1 H, $J_{1',2'}$ 8.0

Hz, H-1'), 4.37 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 3.92 (d, 1 H, $J_{3',4'}$ 3.5 Hz, H-4'), 3.81 (dd, 1 H, $J_{5,6a}$ 1.5 Hz, H-6a), 3.78 (dd, 1 H, $J_{5',6'a}$ 3.0, $J_{6'a,6'b}$ 11.1 Hz, H-6'a), 3.74 (m, 1 H, H-6'b), 3.72 (m, 1 H, H-6b), 3.70 (m, 1 H, H-5'), 3.67 (m, 1 H, H-5), 3.66 (dd, 1 H, $J_{2',3'}$ 10.2, $J_{3',4'}$ 3.1 Hz, H-3'), 3.63 (m, 2 H, H-3,4), 3.56 (s, 3 H, OCH_3 1), 3.53 (dd, $J_{1',2'}$ 7.5, $J_{2',3'}$ 10.0 Hz, H-2'), 3.39 (s, 3 H, OCH_3 n), 3.29 (t, 1 H, H-2); ^{13}C (125 MHz), δ 104.4 (C-6'), 104.3 (C-6), 79.5 (C-4), 76.6 (C-5'), 75.6 (C-3), 74.7 (C-5), 74.0 (C-2), 73.8 (C-3'), 72.2 (C-2'), 71.5 (C-6), 69.8 (C-4'), 62.3 (C-6'), 61.9 (OCH_3 n), 58.5 (OCH_3 1). Anal. Calcd for $C_{14}H_{26}O_{11} \cdot H_2O$: C, 43.40; H 7.27. Found: C, 43.76; H, 7.45.

Methyl 2'-O-methyl-β-lactoside (**11**)—Methyl β-lactoside (**1**; 1 g, 2.8 mmol) was stirred with powdered KOH (1.5 g) and benzyl chloride (6 mL) at 100°C for 45 min. The mixture was cooled to room temperature. Chloroform (60 mL) was added, and the solution was washed with water, 0.5 M H_2SO_4, and water, dried (Na_2SO_4), and concentrated. Column chromatography (6:1 hexane–EtOAc) of the residue gave methyl 2,3,6,3',4',6'-hexa-*O*-benzyl-β-lactoside (**9**; 0.270 g, 11%), isolated as a syrup; $[\alpha]_D^{20}$ + 13° (*c* 0.9, $CHCl_3$). NMR data ($CDCl_3$): ^1H (300 MHz), δ 7.29–7.10 (m, 30 H, Ph), 4.87 and 4.76 (ABq, 2 H, *J* 11.2 Hz, CH_2Ph), 4.79 and 4.46 (ABq, 2 H, *J* 11.2 Hz, CH_2Ph), 4.78 and 4.59 (ABq, 2 H, *J* 11.0 Hz, CH_2Ph), 4.61 and 4.50 (ABq, 2 H, *J* 11.6 Hz, CH_2Ph), 4.57 (d, 2 H, CH_2Ph), 4.48 (d, 1 H, $J_{1',2'}$ 7.6 Hz, H-1'), 4.20 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 4.19 and 4.12 (ABq, 2 H, *J* 11.7 Hz, CH_2Ph), 3.91 (t, 1 H, $J_{6'a,6'b}$ 9.6 Hz, H-6'a), 3.88 (dd, 1 H, $J_{5,6a}$ 4.0, $J_{6a,6b}$ 11.6 Hz, H-6a), 3.83–3.77 (m, 1 H, H-6'b), 3.78 (bd, 1 H, $J_{3',4'}$ 3.0 Hz, H-4'), 3.72 (dd, 1 H, $J_{5,6b}$ 1.9, $J_{6a,6b}$ 11.4 Hz, H-6b), 3.54 (t, *J* 9.0 Hz, H-3 or 4), 3.48 (s, 3 H, OCH_3), 3.46 (t, *J* 8.4 Hz, H-3 or 4), 3.38 (ddd, 1 H, $J_{4,5}$ 9.9, $J_{5,6a}$ 3.7, $J_{5,6b}$ 1.9 Hz, H-5), 3.31 (dd, 1 H, $J_{1,2}$ 7.8, $J_{2,3}$ 9.0 Hz, H-2), 3.25–3.21 (m, 1 H, H-2'), 3.22 (dd, 1 H, $J_{2',3'}$ 9.6, $J_{3',4'}$ 2.9 Hz, H-3'), 3.14 (m, 1 H, H-5'), 3.09 (d, 1 H, OH); ^{13}C (50 MHz), δ 139.2, 138.9, 138.5, 138.4, 138.0, 137.9 (6 C-ipso, Ph), 128.4–127.0 (Ph), 104.8, 103.7 (C-1,1'), 83.4, 82.2, 81.9, 77.0, 74.5, 73.4, 72.8, 72.3 (C-2/5 and C-2'/5'), 75.0, 74.8, 74.6, 73.5, 72.3 (6 CH_2Ph), 68.6, 68.0 (C-6,6'), 57.0 (OCH_3). Anal. Calcd for $C_{55}H_{60}O_{11}$: C, 73.64; H, 6.74. Found: C, 73.86, H, 6.52.

A solution of **9** (0.237 g, 0.26 mmol) in THF (5 mL) was treated with NaH (2 equiv, 13 mg) at room temperature under Ar. After 30 min, MeI (20 equiv, 0.33 mL) was added. The mixture was quenched 3 h later with MeOH and concentrated. Column chromatography (5 : 1 hexane–EtOAc) yielded methyl 2,3,6,3',4',6'-hexa-*O*-benzyl-2'-*O*-methyl-β-lactoside (**10**; 0.198 g, 82%) isolated as a syrup; $[\alpha]_D^{20}$ +4° (*c* 1.5, $CHCl_3$). NMR data ($CDCl_3$): ^1H (300 MHz), δ 7.33–7.06 (m, 30 H, 6 Ph), 4.94 and 4.66 (ABq, 2 H, *J* 10.8 Hz, CH_2Ph), 4.86 and 4.64 (ABq, 2 H, *J* 11.2 Hz, CH_2Ph), 4.79 and 4.45 (ABq, 2 H, *J* 11.3 Hz, CH_2Ph), 4.61 (s, 2 H, CH_2Ph), 4.58 and 4.48 (ABq, 2 H, *J* 12 Hz, CH_2Ph), 4.31 (d, 1 H, $J_{1',2'}$ 7.6 Hz, H-1'), 4.23 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.21 and 4.12 (ABq, 2 H, *J* 11.8 Hz, CH_2Ph), 3.86–3.78 (m, 4 H, H-4',6'a,6'b), 3.53–4.47 (m, 5 H, H-6'a,6'b), 3.49 (s, 3 H, OCH_3), 3.47 (s, 3 H, OCH_3), 3.24–3.19 (m, 3 H, H-2,2'); ^{13}C (50 MHz), δ 128.2–126.7 (Ph), 104.5, 103.0 (C-1,1'), 82.9, 82.4, 81.7, 81.6, 77.1, 75.1, 73.6, 72.8

(C-2/5 and C-2′/5′), 75.1, 74.7, 74.5, 73.2, 73.1, 72.4 (6 CH_2Ph), 69.5, 67.9 (C-6,6′), 60.8, 56.9 (2 OCH_3). Anal. Calcd for $C_{56}H_{62}O_{11}$: C, 73.82; H, 6.86. Found: C, 73.94; H, 6.96.

Hydrogenation of **10** (0.198 g, 0.2 mmol) with 10% Pd–C in 1:1 CH_2Cl_2–EtOH (14 mL), as described for **3**, afforded **11** (60 mg, 75%); mp 165–166°C; $[\alpha]_D^{20}$ +17° (*c* 0.7, H_2O); lit.[16] mp 172–173° (from EtOH); $[\alpha]_D^{25}$ +7.7° (*c* 0.9, H_2O). NMR data (D_2O): ^1H (300 MHz), δ 4.47 (d, 1 H, $J_{1',2'}$ 7.9 Hz, H-1′), 4.39 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 3.97 (dd, 1 H, $J_{5,6a}$ 0.7, $J_{6a,6b}$ 12.0 Hz, H-6a), 3.91 (bd, 1 H, $J_{3',4'}$ 3.4, $J_{4',5'}$ 0.5 Hz, H-4′), 3.79 (m, 1 H, H-6′a), 3.77 (m, 1 H, H-6b), 3.75 (m, 1 H, H-5), 3.74 (m, 1 H, H-6′b), 3.66 (m, 1 H, H-3′), 3.64 (m, 1 H, H-4), 3.63 (m, 1 H, H-3), 3.58 (s, 3 H, OCH_3 1), 3.56 (s, 3 H, OCH_3 n), 3.29 (m, 1 H, H-2), 3.25 (dd, 1 H, $J_{1',2'}$ 7.8, $J_{2',3'}$ 10.0 Hz, H-2′); ^{13}C (125 MHz), δ 104.3 (C-1), 104.0 (C-1′), 82.2 (C-2′), 79.7 (C-4), 76.5 (C-5′), 76.2 (C-5), 75.6 (C-3), 74.1 (C-2), 73.6 (C-3′), 69.9 (C-4′), 62.3 (C-6′), 61.9 (OCH_3 n), 61.4 (C-6), 58.5 (OCH_3 1). Anal. Calcd for $C_{14}H_{26}O_{11}$: C, 45.40; H, 7.08. Found: C, 45.38; H, 7.21.

Methyl 3′-O-methyl-β-lactoside (**12**).—A mixture of methyl β-lactoside (**1**; 0.3 g, 0.842 mmol), powdered 3A molecular sieves (1.2 g), and dibutyltin oxide (1.2 equiv, 0.252 g) in MeCN (20 mL) was stirred overnight at 90°C under Ar. The mixture was cooled to 40–50°C, and tetrabutylammonium bromide (0.272 g, 0.843 mmol) and MeI (10 equiv, 0.53 mL) were added. The mixture was left for 3 days, adding more MeI each day. When the reaction did not progress further, water was added and the mixture filtered through Celite. After concentration, column chromatography (9:1 $CHCl_3$–MeOH) of the residue provided 0.264 g of a syrup, which was acetylated with Ac_2O and pyridine. Conventional workup of the crude product gave methyl 2,3,6,2′,4′,6′-hexa-*O*-acetyl-3′-*O*-methyl-β-lactoside (0.286 g, 54.4%) as a syrup; $[\alpha]_D^{20}$ −2° (*c* 0.7, $CHCl_3$). NMR data ($CDCl_3$): ^1H (300 MHz), δ 5.43 (dd, 1 H, $J_{3',4'}$ 3.3, $J_{4',5'}$ 0.8 Hz, H-4′), 5.18 (t, 1 H, $J_{2,3} = J_{3,4} = 9.2$ Hz, H-3), 4.97 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 10.0 Hz, H-2′), 4.88 (dd, 1 H, $J_{1,2}$ 7.8, $J_{2,3}$ 9.5 Hz, H-2), 4.47 (dd, 1 H, $J_{5,6a}$ 2.1, $J_{6a,6b}$ 11.9 Hz, H-6a), 4.39 (d, 1 H, $J_{1',2'}$ 8.1 Hz, H-1′), 4.39 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.16 (dd, 1 H, $J_{5,6b}$ 5.1, $J_{6a,6b}$ 11.8 Hz, H-6b), 4.09 (d, 2 H, H-6′a,6′b), 3.77 (m, 1 H, H-5′), 3.77 (t, 1 H, $J_{3,4} = J_{4,5} = 9.4$ Hz, H-4), 3.61 (ddd, 1 H, $J_{4,5}$ 9.9, $J_{5,6a}$ 2.2, $J_{5,6b}$ 5.1 Hz, H-5), 3.48 (s, 3 H, OCH_3), 3.33 (s, 3 H, OCH_3), 3.27 (dd, 1 H, $J_{2',3'}$ 10.1, $J_{3',4'}$ 3.4 Hz, H-3′), 2.13, 2.12, 2.08, 2.07, 2.04, 2.03 (6 s, each 3 H, 6 Ac); ^{13}C (50 MHz), δ 170.3 170.0, 169.6, 169.1 (6 C=O), 101.2, 101.1 (C-1,1′), 79.7, 76.1, 72.8, 72.6, 71.6, 70.8, 70.6, 64.8 (C-2/5 and C2′/5′), 62.1, 61.3 (C-6,6′), 57.9, 56.8 (2 OCH_3). Anal. Calcd for $C_{26}H_{38}O_{17}$: C, 50.16; H, 6.15. Found: C, 50.30; H, 6.42.

Zemplén deacylation of methyl 2,3,6,2′,4′,6′-hexa-*O*-acetyl-3′-*O*-methyl-β-lactoside with methanolic NaOMe (0.286 g, 0.46 mmol) followed by column chromatography (4:1 $CHCl_3$–MeOH) gave **12** (0.153 g, 90%); mp 114–115°C; $[\alpha]_D^{20}$ +13° (*c* 0.9, H_2O). NMR data (D_2O): ^1H (300 MHz), δ 4.47 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1′), 4.41 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 4.17 (d, 1 H, $J_{3',4'}$ 3.2 Hz, H-4′), 4.00 (dd, 1 H, $J_{5,6a}$ 1.8, $J_{6a,6b}$ 12.3 Hz, H-6a), 3.82 (dd, 1 H, $J_{5,6b}$ 4.3, $J_{6a,6b}$ 12.0 Hz, H-6b), 3.80

(m, 1 H, H-6'a), 3.79 (m, 1 H, H-6'b), 3.72 (m, 1 H, H-5'), 3.66 (m, 1 H, H-4), 3.65 (m, 1 H, H-5), 3.63 (m, 1 H, H-3), 3.57 (dd, 1 H, $J_{1',2'}$ 7.8, $J_{2',3'}$ 10.0 Hz, H-2'), 3.56 (s, 3 H, OCH_3 1), 3.51 (s, 3 H, OCH_3 n), 3.37 (dd, 1 H, $J_{2',3'}$ 9.9, $J_{3',4'}$ 3.2 Hz, H-3'), 3.31 (dd, 1 H, $J_{1,2}$ 8.0 Hz, H-2); ^{13}C (125 MHz), δ 104.3 (C-1), 104.1 (C-1'), 82.9 (C-3'), 79.5 (C-4), 76.5 (C-5'), 76.0 (C-5), 75.6 (C-3), 74.0 (C-2), 71.2 (C-2'), 62.3 (C-6'), 61.2 (C-6), 58.4 (OCH_3 1), 57.5 (OCH_3 n). Anal. Calcd for $C_{14}H_{26}O_{11}$: C, 45.40; H, 7.08. Found: C, 45.18; H, 7.42.

Methyl 4'-O-methyl-β-lactoside (**15**).—A solution of methyl 2,3,6,2',3',6'-hexa-*O*-benzyl-β-lactoside (**13**; 0.522 g, 0.62 mmol) in THF (11 mL) was treated with NaH (30 mg, 1.23 mmol) under Ar. When gas emission was complete (ca. 30 min), MeI (5 equiv, 0.192 mL) was added. The mixture was stirred for 2.3 h, and then quenched with MeOH. Concentration and column chromatography (5:1 hexane–EtOAc) of the mixture afforded methyl 2,3,6,2',3',6'-hexa-*O*-benzyl-4'-*O*-methyl-β-lactoside (**14**; 0.394 g, 65%); mp 98–99°C; $[\alpha]_D^{20}$ +17° (*c* 1.1, $CHCl_3$). NMR data ($CDCl_3$): ^1H (300 MHz), δ 7.40–7.22 (m, 30 H, 6 Ph), 4.98 and 4.71 (ABq, 2 H, *J* 10.8 Hz, CH_2Ph), 4.86 and 4.74 (ABq, 2 H, *J* 11.1 Hz, CH_2Ph), 4.80 and 4.67 (ABq, 2 H, *J* 11.5 Hz, CH_2Ph), 4.73 (d, 2 H, *J* 11.6 Hz, CH_2Ph), 4.53 and 4.39 (ABq, 2 H, *J* 12.1 Hz, CH_2Ph), 4.42 and 4.33 (ABq, 2 H, *J* 11.7 Hz, CH_2Ph), 4.41 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 4.28 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 3.93 (dd, 1 H, $J_{2,3}$ 9.6, $J_{3,4}$ 9.0 Hz, H-3), 3.78 (dd, 1 H, $J_{5,6a}$ 4.3, $J_{6a,6b}$ 10.9 Hz, H-6a), 3.72 (dd, 1 H, $J_{5,6b}$ 2.0, $J_{6a,6b}$ 10.9 Hz, H-6b), 3.65 (dd, 1 H, $J_{5',6'a}$ 7.7, $J_{6'a,6'b}$ 9.8 Hz, H-6'a), 3.62 (bd, 1 H, $J_{3',4'}$ 2.6 Hz, H-4'), 3.59–3.52 (m, 2 H, H-4,2'), 3.40–3.27 (m, 5 H, H-2,5,3',5',6'b); ^{13}C (50 MHz), δ 139.2, 138.9, 138.8, 138.4, 138.1 (C-ipso, Ph), 128.4–127.2 (Ph), 104.7, 102.6 (C-1,1'), 82.9, 82.2, 81.9, 80.1, 76.6, 75.4, 75.2, 72.8 (C-2/5 and C-2'/5'), 75.4, 75.3, 74.8, 73.4, 73.1, 72.5 (6 CH_2Ph), 68.4, 67.9 (C-6,6'), 61.3, 57.0 (2 OCH_3). Anal. Calcd for $C_{56}H_{62}O_{11}$: C, 73.82; H, 6.86. Found: C, 74.10; H, 6.58.

Overnight hydrogenation and workup of **14** (0.364 g, 0.4 mmol), as described above, afforded **15** (0.130 g, 88%); mp 213–214°C (from EtOH); $[\alpha]_D^{20}$ −19° (*c* 0.9, MeOH). NMR data (D_2O): ^1H (300 MHz), δ 4.41 (d, 1 H, $J_{1',2'}$ 7.76 Hz, H-1'), 4.39 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 3.99 (dd, 1 H, $J_{5,6a}$ 1.8, $J_{6a,6b}$ 12.2 Hz, H-6a), 3.81 (m, 2 H, H-6b,6'a), 3.73 (m, 1 H, H-5'), 3.72 (dd, 1 H, $J_{2',3'}$ 9.9, $J_{3',4'}$ 3.6 Hz, H-3'), 3.64 (m, 2 H, H-3,6'b), 3.63 (bd, 1 H, $J_{3',4'}$ 3.0 Hz, H-4'), 3.61 (m, 2 H, H-4,5), 3.56 (s, 3 H, OCH_3 1), 3.39 (s, 3 H, OCH_3 n), 3.49 (dd, 1 H, $J_{1',2'}$ 7.5, $J_{2',3'}$ 10.0 Hz, H-2'), 3.31 (t, 1 H, $J_{1,2} = J_{2,3} = 8.5$ Hz, H-2); ^{13}C (125 MHz), δ 104.4 (C-1), 104.2 (C-1'), 80.3 (C-4'), 79.8 (C-4), 76.9 (C-5'), 76.1 (C-5), 75.8 (C-3), 74.3 (C-3'), 74.1 (C-2), 72.6 (C-2'), 62.8 (OCH_3 n), 61.9 (C-6'), 61.5 (C-6), 58.6 (OCH_3 1). Anal. Calcd for $C_{14}H_{26}O_{11}$: C, 45.40; H, 7.08. Found: C, 45.28; H, 7.20.

Methyl 6'-O-methyl-β-lactoside (**18**).—A stirred mixture of methyl 2,3,6,2',3'-penta-*O*-benzyl-β-lactoside (**16**; 0.320 g, 0.4 mmol), powdered 3A molecular sieves (0.629 g), and bis(tributyltin) oxide (1.2 equiv, 0.24 mL) in MeCN (10 mL) was heated overnight at 90°C under Ar. The mixture was cooled to 40–50°C, and then *N*-methylimidazole (1.7 equiv, 0.250 mL) and MeI (20 equiv, 0.5 mL) were added.

The mixture was kept stirring for one week, periodically adding more MeI. The reaction was quenched with MeOH, filtered through Celite, and concentrated. Column chromatography (10:1 → 4:1 hexane–EtOAc) gave 0.254 g (78%) of a pure compound as a yellow oil. Conventional acetylation and workup yielded methyl 4′-*O*-acetyl-2,3,6,2′-3′-penta-*O*-benzyl-6′-*O*-methyl-β-lactoside (**17**; 0.156 g, 46%); $[\alpha]_D^{20}$ +26° (*c* 1.0, $CHCl_3$). NMR data ($CDCl_3$): ^1H (300 MHz), δ 7.45–7.24 (m, 25 H, 5 Ph), 5.49 (bd, 1 H, $J_{3',4'}$ 3.3 Hz, H-4′), 5.04 and 4.80 (ABq, 2 H, *J* 10.6 Hz, CH_2Ph), 4.89 and 4.74 (ABq, 2 H, *J* 11.1 Hz, CH_2Ph), 4.82 and 4.76 (ABq, 2 H, *J* 11.2 Hz, CH_2Ph), 4.74 and 4.49 (ABq, 2 H, *J* 11.4 Hz, CH_2Ph), 4.48 (d, 1 H, $J_{1',2'}$ 7.6 Hz, H-1′), 4.32 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 3.40 (t, $J_{2,3} = J_{3,4} = 9.3$ Hz, H-3), 3.83 (dd, 1 H, $J_{5,6a}$ 4.2, $J_{6a,6b}$ 10.9 Hz, H-6a), 3.73 (dd, 1 H, $J_{5,6b}$ 1.7, $J_{6a,6b}$ 10.9 Hz, H-6b), 3.59 (t, 1 H, $J_{3,4} = J_{4,5} = 9.0$ Hz, H-4), 3.56 (s, 3 H, OCH_3), 3.52 (dd, 1 H, $J_{1',2'}$ 7.6, $J_{2',3'}$ 9.5 Hz, H-2′), 3.46–3.37 (m, 4 H, H-2,5,3′,5′), 3.28 (dd, 1 H, $J_{5',6'a}$ 5.2, $J_{6'a,6'b}$ 9.7 Hz, H-6′a), 3.22 (dd, 1 H, $J_{5',6'b}$ 6.6, $J_{6'a,6'b}$ 9.7 Hz, H-6′b), 3.22 (s, 3 H, OCH_3); ^{13}C (50 MHz), δ 170.1 (C=O), 139.3, 138.7, 138.6, 138.2, 137.9 (C-ipso, Ph), 128.2–127.1 (Ph), 104.6, 102.3 (C-1,1′), 82.7, 81.7, 79.6, 79.4, 76.5, 75.0, 71.6, 66.6 (C-2/5 and C-2′/5′), 75.2, 74.9, 74.8, 73.1, 71.7 (5 CH_2Ph), 70.1, 68.2, (C-6,6′), 59.1, 56.9 (2 OCH_3), 20.8 (Ac). Anal. Calcd for $C_{51}H_{58}O_{12}$: C, 70.98; H, 6.77. Found: C, 71.00; H, 6.60.

Compound **17** (0.138 g, 0.16 mmol) was deacetylated with NaOMe in MeOH. The solution was neutralised with Amberlite IR-120 (H^+) and concentrated. Column chromatography of the crude product gave a syrup which was subsequently hydrogenated in the presence of 10% Pd–C in 1:1 CH_2Cl_2–EtOH (12 mL), to provide **18** (47 mg, 77%) as a white solid; mp 98–100°C; $[\alpha]_D^{20}$ +2° (*c* 1.1, H_2O). NMR data (D_2O): ^1H (300 MHz), δ 4.4 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1′), 4.39 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 3.98 (dd, 1 H, $J_{5,6a}$ 1.4, $J_{6a,6b}$ 12.3 Hz, H-6a), 3.91 (bd, 1 H, $J_{3',4'}$ 3.4 Hz, H-4′), 3.87 (m, 1 H, H-5′), 3.86 (m, 1 H, H-6′a), 3.80 (m, 1 H, H-6b), 3.67 (dd, 1 H, $J_{3',4'}$ 3.2 Hz, H-3′), 3.65 (m, 2 H, H-3,6′b), 3.64 (m, 1 H, H-4), 3.60 (m, 1 H, H-5), 3.56 (s, 3 H, OCH_3 1), 3.54 (dd, 1 H, $J_{1',2'}$ 7.9, $J_{2',3'}$ 9.9 Hz, H-2′), 3.39 (s, 3 H, OCH_3 n), 3.30 (dd, 1 H, H-2); ^{13}C (125 MHz), δ 104.3 (C-6,6′), 80.4 (C-4), 76.0 (C-3), 75.8 (C-5), 74.4 (C-5′), 74.1 (C-2), 73.8 (C-3′), 72.7 (C-4′), 72.1 (C-2′), 70.0 (C-6′), 61.5 (C-6), 59.7 (OCH_3 n), 58.5 (OCH_3 1). Anal. Calcd for $C_{14}H_{26}O_{11} \cdot H_2O$: C, 43.30; H, 7.27. Found: C, 43.78; H, 7.23.

Methyl 6-deoxy-6-fluoro-β-lactoside (**20**).—A stirred solution of methyl 4′,6′-*O*-benzylidene-β-lactoside (**6**; 0.29 g, 0.45 mmol) in dry CH_2Cl_2 (5 mL) under Ar was cooled to −40°C, and then diethylaminosulfur trifluoride (DAST; 2 equiv, 120 μL) was added dropwise. After stirring for 3 min at this temperature, the cooling bath was removed, and the mixture was allowed to reach room temperature. After 1 h, the mixture was cooled to −20°C, MeOH was slowly added to the yellow solution, and then the solvents were evaporated. The residue was chromatographed (4:1 $CHCl_3$–MeOH), giving methyl 4′,6′-*O*-benzylidene-6-deoxy-6-fluoro-β-lactoside (**19**; 62 mg, 31%) as a white solid; mp 125–128°C; $[\alpha]_D^{20}$ −33° (*c* 0.38, H_2O). NMR data (D_2O): ^{19}F (282 MHz), δ −158.4 (ddd, $J_{F,H-5}$ 31.5, $J_{F,H-6a}$ 46.1, $J_{F,H-6b}$ 48.0

Hz); ^{1}H (300 MHz), δ 7.58–7.46 (m, 5 H, Ph), 5.75 (s, 1 H, C*H*Ph), 4.89 (ddd, 1 H, $J_{5,6a}$ 2.4, $J_{6a,6b}$ 10.8, $J_{F,H-6a}$ 46.3 Hz, H-6a), 4.78 (ddd, 1 H, $J_{5,6b}$ 1.3, $J_{6a,6b}$ 10.9, $J_{F,H-6b}$ 47.0 Hz, H-6b), 4.53 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 4.45 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 4.37 (bd, 1 H, $J_{3',4'}$ 3.6, $J_{4',5'}$ 0.7 Hz, H-4'), 4.26 (d, 2 H, H-6'a,6'b), 3.83 (dd, 1 H, $J_{2',3'}$ 10.0, $J_{3',4'}$ 3.6 Hz, H-3'), 3.79 (m, 1 H, H-5'), 3.78–3.68 (m, 4 H, H-3,4,5,2'), 3.57 (s, 3 H, OCH_3), 3.32 (dd, 1 H, $J_{1,2}$ 8.1, $J_{2,3}$ 9.2 Hz, H-2). Anal. Calcd for $C_{20}H_{27}FO_{10}$: C, 53.81; H 6.10. Found: C, 53.65; H, 5.98.

A solution of **19** (87 mg, 0.2 mmol) in AcOH (4 mL) was heated at 100°C, and water (1 mL) was added in small portions. After heating for 1 h, the solvents were evaporated by co-distillation with toluene and the residue was chromatographed (4:1 $CHCl_3$–MeOH) to give **20** (47 mg, 67%) as a white solid; mp 163–164°C; $[\alpha]_D^{20}$ −1° (*c* 1.2, H_2O). lit.[10]: $[\alpha]_D^{20}$ −0.1° (*c* 1, H_2O). NMR data (D_2O): ^{19}F (282 MHz), δ −155.5 (ddd, $J_{F,H-5}$ 24.9, $J_{F,H-6a}$ 47.0, $J_{F,H-6b}$ 48.2 Hz); ^{1}H (300 MHz), δ 4.85 (ddd, 1 H, $J_{5,6a}$ 2.7, $J_{6a,6b}$ 10.8, $J_{F,H-6a}$ 46.7 Hz, H-6a), 4.79 (ddd, 1 H, $J_{5,6b}$ 1.3, $J_{6a,6b}$ 10.8, $J_{F,H-6b}$ 48.3 Hz, H-6b), 4.44 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 4.44 (d, 1 H, $J_{1',2'}$ 7.6 Hz, H-1'), 3.92 (d, 1 H, $J_{3',4'}$ 3.2 Hz, H-4'), 3.80–3.65 (m, 6 H, H-3,4,5,5',6'a,6'b), 3.66 (dd, 1 H, $J_{2',3'}$ 10.0, $J_{3',4'}$ 3.3 Hz, H-3'), 3.57 (s, 3 H, OCH_3), 3.54 (dd, 1 H, H-2'), 3.32 (dd, 1 H, $J_{1,2}$ 8.1, $J_{2,3}$ 8.9 Hz, H-2); ^{13}C (125 MHz), δ 104.5 (C-1), 104.2 (C-1'), 82.5 (d, $J_{F,C-6}$ 167.0 Hz, C-6), 79.5 (d, $J_{F,C-4}$ 5.3 Hz, C-4), 76.6 (C-5'), 75.9 (d, $J_{F,C-5}$ 18.3 Hz, C-5), 75.5 (C-3), 74.0 (C-2), 73.8 (C-3'), 72.2 (C-2'), 69.8 (C-4'), 62.2 (C-6'), 58.6 (OCH_3). Anal. Calcd for $C_{13}H_{23}FO_{10}$: C, 43.58; H, 6.47. Found: C, 43.46; H, 6.76.

Methyl 3'-deoxy-3'-fluoro-β-lactoside (**26**).—A solution of HBr in AcOH (1 mL) was added to a solution of 1,2,4,6-tetra-*O*-acetyl-3-deoxy-3-fluoro-α,β-D-galactopyranose (0.196 g, 0.56 mmol) in dry CH_2Cl_2 (1 mL), and stirred for 1 h at room temperature. The mixture was concentrated, the acids were removed by co-distillation with toluene, and a solution of the residue, 2,4,6-tri-*O*-acetyl-3-deoxy-3-fluoro-α-D-galactopyranosyl bromide (**24**), in 1 mL of CH_2Cl_2 was added dropwise to a mixture of **23** (1.2 equiv, 0.31 mmol), $Hg(CN)_2$ (1 equiv, 0.150 g), $HgBr_2$ (1 equiv, 0.242 g), and powdered 3A molecular sieves (1.5 g) in CH_2Cl_2 (14 mL) that had been already stirred for 1 h at room temperature under Ar. After 20 h, TLC (3:1 hexane–EtOAc) showed that all the glycosyl bromide had reacted. The mixture was filtered through Celite, diluted with CH_2Cl_2, and subsequently washed with aq KI and water, dried, and concentrated. The residue was chromatographed (7:1 → 3:1 hexane–EtOAc) to give methyl 2',4',6'-tri-*O*-acetyl-2,3,6-tri-*O*-benzyl-3'-deoxy-3'-fluoro-β-lactoside (**25**) as a syrup (0.15 g, 44% from **24**); $[\alpha]_D^{20}$ +11° (*c* 1.8, $CHCl_3$). NMR data ($CDCl_3$): ^{19}F (282 MHz), δ −124.31 (ddd, $J_{F,H-4'}$ 5.2, $J_{F,H-2'}$ 11.7, $J_{F,H-3'}$ 47.7 Hz); ^{1}H (300 MHz), δ 7.31–7.19 (m, 15 H, 3 Ph), 5.35 (dt, 1 H, $J_{F,H-4'}$ 4.5 Hz, H-4'), 5.12 (ddd, $J_{1',2'}$ 8.0, $J_{2',3'}$ 9.7, $J_{F,H-2'}$ 11.9 Hz, H-2'), 4.85 and 4.74 (ABq, 2 H, *J* 10.9 Hz, CH_2Ph), 4.80 and 4.63 (ABq, 2 H, *J* 11.2 Hz, CH_2Ph), 4.71 and 4.42 (ABq, 2 H, *J* 12.1 Hz, CH_2Ph), 4.49 (d, 1 H, $J_{1',2'}$ 8.1 Hz, H-1'), 4.23 (ddd, 1 H, $J_{2',3'}$ 9.8, $J_{3',4'}$ 3.9, $J_{F,H-3'}$ 47.5 Hz, H-3'), 4.22 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 3.94 (dd, $J_{5',6'a}$ 7.8, $J_{6'a,6'b}$ 11.2 Hz, H-6'a), 3.88 (t, 1 H, $J_{3,4} = J_{4,5} = 9.3$

Hz, H-4), 3.78 (ddd, 1 H, $J_{5,6'b}$ 6.0, $J_{6'a,6'b}$ 11.2, $J_{F,H-6'b}$ 1.3 Hz, H-6'b), 3.71–3.69 (m, 2 H, H-6a,6b), 3.51 (t, 1 H, $J_{2,3} = J_{3,4} = 8.9$ Hz, H-3), 3.50 (s, 3 H, OCH_3), 3.39–3.29 (m, 2 H, H-5,5'), 3.34 (dd, 1 H, $J_{1,2}$ 7.7, $J_{2,3}$ 9.1 Hz, H-2); ^{13}C (50 MHz), δ 170.1, 169.8 169.0 (3 C=O), 139.0, 138.5, 138.1 (C-ipso, Ph), 128.5–127.3 (Ph), 104.7 (C-1), 99.6 (d, $J_{F,C-1'}$ 10.9 Hz, C-1'), 89.0 (d, $J_{F,C-3'}$ 193.0 Hz, C-3'), 82.4, 81.8, 76.7, 74.6, 70.6 (d, $J_{F,C-2'}$ 19.2, C-2'), 69.6 (d, $J_{F,C-5'}$ 6.0 Hz, C-5'), 66.6 (d, $J_{F,C-4'}$ 16.4, C-4'), 75.0, 74.7, 73.6 (CH_2Ph), 67.8 (C-6), 60.6 (d, $J_{F,C-6'}$ 2.7 Hz, C-6'), 57.0 (OCH_3), 20.8, 20.6 (Ac). Anal. Calcd for $C_{40}H_{47}FO_{13}$: C, 63.65; H, 6.28. Found: C, 63.61, H, 6.64.

A solution of **25** (0.123 g, 0.16 mmol) in 20 mL of 1:1 CH_2Cl_2–EtOH was hydrogenated overnight, employing 10% Pd–C as catalyst, then filtered through Celite, and concentrated. The crude product was treated with methanolic NaOMe for 30 min. The mixture was neutralised with Amberlite IR-120 (H^+), filtered, and concentrated to yield, after column chromatography (4:1 $CHCl_3$–MeOH), **26** (56 mg, 96%) as a white solid; mp 121–122°C; $[\alpha]_D^{20}$ −5° (c 0.9, H_2O). NMR data (D_2O): ^{19}F (282 MHz), δ −123.29 (ddd, $J_{F,H-4'}$ 6.7, $J_{F,H-2'}$ 14.2, $J_{F,H-3'}$ 51.4 Hz); ^1H (300 MHz), δ 4.59 (ddd, 1 H, $J_{2',3'}$ 9.6, $J_{3',4'}$ 3.5, $J_{F,H-3'}$ 48.0 Hz, H-3'), 4.49 (d, 1 H, $J_{1'2'}$ 7.8 Hz, H-1'), 4.39 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 4.21 (dd, 1 H, $J_{3',4'}$ 3.5, $J_{F,H-4'}$ 6.5 Hz, H-4'), 3.98 (dd, 1 H, $J_{5,6a}$ 2.1, $J_{6a,6b}$ 12.3 Hz, H-6a), 3.83 (ddd, 1 H, $J_{1',2'}$ 7.8, $J_{2',3'}$ 9.6, $J_{F,H-2'}$ 15.2 Hz, H-2'), 3.80 (dd, 1 H, $J_{5,6b}$ 5.4, $J_{6a,6b}$ 12.6 Hz, H-6b), 3.78 (d, 1 H, H-6'a), 3.75–3.69 (m, 2 H, H-5',6'b), 3.66 (t, 1 H, H-4), 3.64 (t, 1 H, H-3), 3.61 (m, 1 H, H-5), 3.57 (s, 3 H, OCH_3), 3.30 (dd, 1 H, $J_{1,2}$ 7.7, $J_{2,3}$ 9.5 Hz, H-2); ^{13}C (125 MHz), δ 104.4 (C-1), 103.4 (d, $J_{F,C-1'}$ 12.2 Hz, C-1'), 93.1 (d, $J_{F,C-3'}$ 182.5 Hz, C-3'), 79.5 (C-4), 75.7 (C-5), 75.3 (d, $J_{F,C-5'}$ 7.1 Hz, C-5'), 74.7 (C-3), 74.2 (C-2), 71.0 (d, $J_{F,C-2'}$ 18.8 Hz, C-2'), 68.0 (d, $J_{F,C-4'}$ 16.6 Hz, C-4'), 62.0 (d, $J_{F,C-6'}$ 3.3 Hz, C-6'), 61.3 (C-6), 58.5 (OCH_3). Anal. Calcd for $C_{13}H_{23}FO_{10}$: C, 43.58; H, 6.47. Found: C, 43.29; H, 6.68.

Methyl 4'-deoxy-4'-fluoro-β-cellobioside (**28**).—DAST (2 equiv, 60 μL) was added to a solution of methyl 2,3,6,2',3',6'-hexa-*O*-benzyl-β-lactoside (**13**; 0.2 g, 0.22 mmol) in dry CH_2Cl_2 (20 mL) at −40°C under Ar. The yellow solution was stirred for 45 min, and then left for 2 h at room temperature. The mixture was quenched with MeOH at −20°C, and concentrated. Column chromatography of the residue (5:1 hexane–EtOAc) gave methyl 2,3,6,2',3',6'-hexa-*O*-benzyl-4'-deoxy-4'-fluoro-β-cellobioside (**27**; 0.12 g, 60%) as an oil; $[\alpha]_D^{20}$ +13° (*c* 1.1, $CHCl_3$). NMR data ($CDCl_3$): ^{19}F (282 MHz), δ −198.73 (dd, $J_{F,H-4'}$ 50.6, $J_{F,H-3'}$ 16.1 Hz); ^1H (300 MHz), δ 7.33–7.18 (m, 30 H, Ph), 4.97 and 4.73 (ABq, 2 H, *J* 11.3 Hz, CH_2Ph), 4.84 and 4.68 (ABq, 2 H, *J* 11.1 Hz, CH_2Ph), 4.83 and 4.72 (ABq, 2 H, *J* 11.6 Hz, CH_2Ph), 4.74 (s, 2 H, CH_2Ph), 4.61 and 4.39 (ABq, 2 H, *J* 12.0 Hz, CH_2Ph), 4.48 (ddd, 1 H, $J_{3',4'}$ 8.4, $J_{4',5'}$ 9.7, $J_{F,H-4'}$ 50.8 Hz, H-4'), 4.47 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.46 and 4.37 (ABq, 2 H, *J* 11.7 Hz, CH_2Ph), 4.27 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 3.98 (t, 1 H, $J_{2,3} = J_{3,4} = 9.3$ Hz, H-4), 3.82 (dd, 1 H, $J_{5,6a}$ 3.9, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.68 (m, 2 H, H-6b,6'a), 3.55 (t, 1 H, $J_{2,3} = J_{3,4} = 9.0$ Hz, H-3), 3.48 (dd, 1 H, $J_{3',4'}$ 8.5 Hz, H-3'), 3.45 (ddd, 1 H, $J_{5',6'b}$ 5.1, $J_{6'a,6'b}$ 11.4, $J_{F,H-6'b}$ 2.0 Hz, H-6'b) 3.38

(dd, $J_{1,2}$ 7.7, $J_{2,3}$ 9.1 Hz, H-2), 3.36–3.27 (m, 3 H, H-5,2′,5′); ^{13}C (200 MHz), δ 139.2, 138.7, 138.3, 138.1, 138.0 (6 C-ipso, Ph), 128.3–126.6 (Ph), 104.7, 102.1 (C-1,1′), 90.3 (d, $J_{F,C-4'}$ 182.5 Hz, C-4′), 82.4 (d, $J_{F,C-5'}$ 17.3 Hz, C-5′), 81.6 (d, $J_{F,C-3'}$ 11.6 Hz, C-3′), 73.4 (d, $J_{F,C-2'}$ 8.1 Hz, C-2′), 82.7–73.0 (C-2/5 and 6 CH_2Ph), 68.8, 68.1 (C-6,6′), 57.0 (OCH_3). Anal. Calcd for $C_{55}H_{59}FO_{10}$: C, 73.47; H, 6.61. Found: C, 73.18; H, 6.76.

Hydrogenolysis of **27** (81 mg, 0.09 mmol) in 10 mL of 1:1 CH_2Cl_2–EtOH and workup as described above afforded **28** (26 mg, 81%) as a white solid; mp 90–93°C; $[\alpha]_D^{20}$ −24° (*c* 1.2, H_2O). NMR data (D_2O): ^{19}F (282 MHz), δ −202.93 (dd, $J_{F,H-4'}$ 51.0, $J_{F,H-3'}$ 16.1 Hz); ^{1}H 300 MHz), δ 4.56 (d, 1 H, $J_{1',2'}$ 7.9 Hz, H-1′), 4.40 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 4.35 (dt, 1 H, $J_{3',4'} = J_{4',5'} = 9.2$, $J_{F,H-4'}$ 50.7 Hz, H-4′), 3.99 (dd, 1 H, $J_{5,6a}$ 2.0, $J_{6a,6b}$ 12.3 Hz, H-6a), 3.91 (dt, 1 H, $J_{5',6'a}$ 2.0, $J_{6'a,6'b}$ 12.3 Hz, H-6′a), 3.86 (dt, 1 H, H-3′), 3.81 (dd, 1 H, $J_{5,6b}$ 4.7, $J_{6a,6b}$ 12.2 Hz, H-6b), 3.71 (ddd, 1 H, $J_{5',6'a}$ 2.2, $J_{5',6'b}$ 4.8 Hz, H-5′), 3.66–3.56 (m, 4 H, H-3,4,5,6′b), 3.55 (s, 3 H, OCH_3), 3.37 (dd, 1 H, $J_{1',2'}$ 7.8, $J_{2',3'}$ 9.8 Hz, H-2′), 3.30 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.3 Hz, H-2); ^{13}C (125 MHz), δ 104.5 (C-1), 103.8 (C-1′), 90.4 (d, $J_{F,C-4'}$ 179.0 Hz, C-4′), 79.5 (C-4), 76.0 (C-5), 75.6 (C-3), 74.8 (d, $J_{F,C-3'}$ 7.8 Hz, C-3′), 74.5 (d, $J_{F,C-5'}$ 14.4 Hz, C-5′), 74.3 (C-2), 74.2 (d, $J_{F,C-2'}$ 10.5 Hz, C-2′), 61.3 (C-6′), 61.2 (C-6), 58.6 (OCH_3). Anal. Calcd for $C_{13}H_{23}FO_{10}$: C, 43.58; H, 6.47. Found: C, 43.27; H, 6.60.

Methyl 4′-deoxy-4′-fluoro-β-lactoside (**33**).—Powdered NaH (2 equiv per OH, 10 mmol, 0.240 g) was added gradually to a solution of methyl 4′,6′-*O*-benzylidene-β-cellobioside (**29**; 0.42 g, 0.94 mmol) in 17 mL of *N*,*N*-dimethylformamide. The suspensión was swirled for 30 min at room temperature under Ar, and then benzyl bromide (21 equiv, 2.36 mL) was added dropwise. The mixture became solid and was stirred overnight until a clear solution was formed. Then MeOH was added cautiously to destroy the excess of reagent, and the solution was concentrated to dryness. Chromatography of the crude product, first with hexane and then with 4:1 hexane–EtOAc, gave methyl 2,3,6,2′,3′-penta-*O*-benzyl-4′,6′-*O*-benzylidene-β-cellobioside (**30**; 0.76 g, 90%) as a white solid; mp 143–145°C; $[\alpha]_D^{20}$ +4° (*c* 2.1, $CHCl_3$). NMR data ($CDCl_3$): ^{1}H (300 MHz), δ 7.42–7.15 (m, 30 H, 6 Ph), 5.41 (s, 1 H, C*H*Ph), 4.83 and 4.79 (ABq, 2 H, *J* 10.7 Hz, CH_2Ph), 4.83 and 4.63 (ABq, 2 H, *J* 11.1 Hz, CH_2Ph), 4.74 and 4.68 (ABq, 2 H, *J* 11.3 Hz, CH_2Ph), 4.68 (d, 2 H, CH_2Ph), 4.51 and 4.30 (ABq, 2 H, *J* 12.1 Hz, CH_2Ph), 4.45 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1′), 4.21 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 4.11 (dd, 1 H, $J_{5',6'a}$ 5.0, $J_{6'a,6'b}$ 10.5 Hz, H-6′a), 3.91 (t, 1 H, $J_{3,4} = J_{4,5} = 9.4$ Hz, H-4), 3.77 (dd, 1 H, $J_{5,6a}$ 3.9, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.60 (dd, 1 H, $J_{6a,6b}$ 10.8 Hz, H-6b), 3.53–3.23 (m, 5 H, H-3,2′,3′,4′,6′b), 3.34 (dd, 1 H, $J_{1,2}$ 7.7, $J_{2,3}$ 9.1 Hz, H-2), 3.26 (m, 1 H, H-5), 3.06 (m, 1 H, H-5′); ^{13}C (50 MHz), δ 139.1, 138.7, 138.6, 138.4, 138.2, 137.4 (C-ipso, Ph), 128.9–126.0 (Ph), 104.7, 102.8, 101.1 (C-1,1′ and *C*HPh), 82.8, 82.5, 81.8, 81.7, 81.1, 76.8, 75.0, 65.8 (C-2/5 and C-2′/5′), 75.4, 75.3, 74.9, 74.8, 73.2 (5 CH_2Ph), 68.8, 67.9 (C-6,6′), 57.0 (OCH_3). Anal. Calcd for $C_{54}H_{58}O_{11}$: C, 73.45; H, 6.62. Found: C, 73.51; H, 6.50.

To a solution of **30** (0.73 g, 0.90 mmol) and $NaBH_3CN$ (0.73 g, 11.62 mmol) in dry THF (50 mL) containing powdered 3A molecular sieves (0.75 g) was added dropwise a saturated solution of HCl in diethyl ether until the solution was acidic (pH paper, gas evolution). After 3 h, the mixture was filtered and concentrated to dryness. The crude product was dissolved in CH_2Cl_2. The extract was washed with water and satd aq $NaHCO_3$, dried over sodium sulfate, filtered, and evaporated. The crude product was purified by chromatography (5:1 hexane–EtOAc) to give methyl 2,3,6,2′,3′,6′-hexa-*O*-benzyl-β-cellobioside (**31**; 0.428 g, 53%) as a syrup; $[\alpha]_D^{20}$ +7° (*c* 1.5, $CHCl_3$). NMR data ($CDCl_3$): ^1H (300 MHz), δ 7.33–7.11 (m, 30 H, 6 Ph), 4.87 and 4.66 (ABq, 2 H, *J* 11.1 Hz, CH_2Ph), 4.79 and 4.73 (ABq, 2 H, *J* 11.4 Hz, CH_2Ph), 4.78 and 4.62 (ABq, 2 H, *J* 11.1 Hz, CH_2Ph), 4.69 (d, 2 H, CH_2Ph), 4.53 and 4.35 (ABq, 2 H, *J* 12.1 Hz, CH_2Ph), 4.41 (d, 1 H, $J_{1',2'}$ 7.3 Hz, H-1′), 4.37 and 4.31 (ABq, 2 H, *J* 12.1 Hz, CH_2Ph), 4.20 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 3.90 (t, 1 H, $J_{3,4} = J_{4,5} = 9.3$ Hz, H-4), 3.75 (dd, 1 H, $J_{5,6a}$ 4.0, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.63 (dd, 1 H, $J_{5,6b}$ 1.8, $J_{6a,6b}$ 11.0 Hz, H-6b), 3.57–3.41 (m, 4 H, H-3′,4′,6′a,6′b), 3.47 (s, 3 H, OCH_3), 3.34–3.23 (m, 3 H, H-5,2′,3′), 3.31 (dd, 1 H, $J_{1,2}$ 7.7, $J_{2,3}$ 9.1 Hz, H-2), 3.17 (m, 1 H, H-5′), 2.78, (d, 1 H, *J* 1.9 Hz, 4′-OH); ^{13}C (50 MHz), δ 139.2, 138.8, 138.7, 138.5, 138.2, 137.8 (C-ipso, Ph), 128.4–127.2 (Ph), 104.7, 102.3 (C-1,1′), 84.4, 82.7, 82.0, 81.7, 76.6, 75.0, 73.4, 73.1 (C-2/5 and C-2′/5′), 75.2, 75.0, 74.9, 74.8, 73.6, 73.2 (6 *C*H_2Ph), 71.2, 68.2 (C-6,6′), 57.0 (OCH_3). Anal. Calcd for $C_{55}H_{60}O_{11}$: C, 73.64; H, 6.74. Found: C, 73.35; H, 6.90.

Trifluoromethanesulfonic anhydride (2.5 equiv, 0.18 mL) was added to a cold (ice–water bath) solution of methyl 2,3,6,2′,3′,6′-hexa-*O*-benzyl-β-cellobioside (**31**; 0.39 g, 0.43 mmol) in CH_2Cl_2 (6 mL) and pyridine (5 equiv, 0.18 mL) under Ar, and stirred for 1.5 h at room temperature. The mixture was diluted with CH_2Cl_2 and washed sequentially with cold satd aq $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated. A solution of the residue in benzene (9 mL) under Ar was treated with 3 equiv of tetrabutylammonium fluoride at 80°C for 10 min. The solvent was removed and the residue dissolved in CH_2Cl_2. The mixture was poured into cold aq 1% $NaHCO_3$ and shaken vigorously in a separatory funnel. The organic phase was removed and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with aq 5% $NaHSO_3$ and satd aq $NaHCO_3$, and dried over anhyd sodium sulfate. The solvents were evaporated and the residue chromatographed (5:1 hexane–EtOAc), affording methyl 2,3,6,2′,3′,6′-hexa-*O*-benzyl-4′-deoxy-4′-fluoro-β-lactoside (**32**; 0.260 g, 66%) as an oil; $[\alpha]_D^{20}$ +17° (*c* 1.1, $CHCl_3$). NMR data ($CDCl_3$): ^{19}F (282 MHz), δ −142.10 (dd, $J_{F,H-4'}$ 50.0, $J_{F,H-3'}$ 27.7 Hz); ^1H (300 MHz), δ 7.29–7.13 (m, 30 H, 6 Ph), 4.88–4.27 (ABq, 12 H, CH_2Ph), 4.74 (ddd, 1 H, $J_{3',4'}$ 2.8, $J_{F,H-4'}$ 49.0 Hz, H-4′), 4.32 (d, 1 H, $J_{1',2'}$ 7.7 Hz, H-1′), 4.21 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 3.89 (t, 1 H, $J_{3,4} = J_{4,5} = 9.3$ Hz, H-4), 3.75 (dd, 1 H, $J_{5,6a}$ 4.0, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.63 (dd, 1 H, $J_{5,6b}$ 1.6, $J_{6a,6b}$ 11.1 Hz, H-6b), 3.58 (t, 1 H, H-3), 3.50–3.43 (m, 2 H, H-6′a,6′b), 3.48 (s, 3 H, OCH_3), 3.31 (dd, 1 H, $J_{1,2}$ 7.0, $J_{2,3}$ 9.5 Hz, H-2), 3.35–3.15 (m, 4 H, H-5,2′,3′,5′); ^{13}C (50 MHz), δ 139.0, 138.7, 138.5, 138.3, 138.0, 137.9 (C-ipso, Ph), 128.4–127.3 (Ph), 104.7, 102.2

(C-1,1'), 85.3 (d, $J_{F,C-4'}$ 182.2 Hz, C-4'), 82.8, 81.8, 79.4, 75.1 (C-2/5), 79.3 (d, $J_{F,C-5'}$ 17.3 Hz, C-5'), 76.7 (d, $J_{F,C-2'}$ 7.3 Hz, C-2'), 71.7 (d, $J_{F,C-3'}$ 17.7 Hz, C-3'), 75.5, 75.4, 74.9, 73.5, 73.1, 72.1 (6 CH_2Ph), 68.1 (C-6), 67.1 (d, $J_{F,C-6'}$ 5.2 Hz, C-6'), 56.9 (OCH_3). Anal. Calcd for $C_{55}H_{59}FO_{10}$: C, 73.47; H, 6.61. Found: C, 73.57; H, 6.90.

Hydrogenolysis and workup of **32** (0.150 g, 0.17 mmol) was performed as described above, to give **33** (56 mg, 94%) as a white solid; mp 219–221°C; $[\alpha]_D^{20}$ −7° (*c* 0.9, H_2O). NMR data (D_2O): ^{19}F (282 MHz), δ −141.22 (dt, $J_{F,H-3'} = J_{F,H-5'} = 30.2$, $J_{F,H-4'}$ 50.2 Hz); ^1H (300 MHz), δ 4.84 (dd, 1 H, $J_{3',4'}$ 2.7, $J_{F,H-4'}$ 50.3 Hz, H-4'), 4.53 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 4.39 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 3.99 (dd, 1 H, $J_{5,6a}$ 1.8, $J_{6a,6b}$ 12.3 Hz, H-6a), 3.91–3.78 (m, 4 H, H-6b,5',6'a,6'b), 3.73 (dd, 1 H, $J_{2',3'}$ 10.1, $J_{3',4'}$ 2.7 Hz, H-3'), 3.63 (t, 1 H, $J_{2,3} = J_{3,4} = 9.4$ Hz, H-3), 3.62 (t, 1 H, H-4), 3.59 (m, 1 H, H-5), 3.58 (m, 1 H, H-2'), 3.56 (s, 3 H, OCH_3), 3.29 (dd, 1 H, $J_{1,2}$ 7.9, $J_{2,3}$ 9.2 Hz, H-2); ^{13}C (125 MHz), δ 104.4 (C-1'), 104.2 (C-1), 90.8 (d, $J_{F,C-4'}$ 176.6 Hz, C-4'), 79.7 (C-4), 76.2 (C-5), 75.7 (C-3), 75.2 (d, $J_{F,C-5'}$ 17.4 Hz, H-5'), 74.3 (C-2), 72.7 (d, $J_{F,C-3'}$ 18.0 Hz, C-3'), 72.3 (C-2'), 61.4 (C-6), 61.4 (d, $J_{F,C-6'}$ 8.7 Hz, C-6'), 58.6 (OCH_3). Anal Calcd. for $C_{13}H_{23}FO_{10}$: C, 43.58; H, 6.47. Found: C, 43.70; H, 6.44.

Methyl 6'-deoxy-6'-fluoro-β-lactoside (**35**).—To a solution of **16** (0.31 g, 0.384 mmol) in dry CH_2Cl_2 (10 mL) at −40°C under Ar was added dropwise DAST (2 equiv, 0.1 mL). After 15 min, the cooling bath was removed and, 20 min later, TLC indicated complete reaction. The mixture was cooled to −20°C and MeOH was added. Evaporation of the solvents yielded a residue which was chromatographed (3:1 hexane–EtOAc) to give methyl 2,3,6,2',3'-penta-*O*-benzyl-6'-deoxy-6'-fluoro-β-lactoside (**34**; 0.146 g, 47%) as a syrup; $[\alpha]_D^{20}$ +23° (*c* 1.8, $CHCl_3$). NMR data ($CDCl_3$): ^{19}F (282 MHz), δ −233.33 (dt, $J_{F,H-6'a} = J_{F,H-6'b} = 46.6$, $J_{F,H-5'}$ 11.0 Hz); ^1H (300 MHz), δ 7.34–7.15 (m, 25 H, 5 Ph), 4.87 and 4.68 (ABq, 2 H, *J* 10.7 Hz, CH_2Ph), 4.78 and 4.63 (ABq, 2 H, *J* 11.1 Hz, CH_2Ph), 4.69 (s, 2 H, CH_2Ph), 4.61 (s, 2 H, CH_2Ph), 4.53 and 4.31 (ABq, 2 H, *J* 12.1 Hz, CH_2Ph), 4.40 (ddd, 1 H, $J_{5',6'a}$ 6.6, $J_{6'a,6'b}$ 9.2, $J_{F,H-6'a}$ 46.5 Hz, H-6'a), 4.36 (d, 1 H, $J_{1',2'}$ 7.9 Hz, H-1'), 4.28 (ddd, 1 H, $J_{5',6'b}$ 5.7, $J_{6'a,6'b}$ 9.4, $J_{F,H-6'b}$ 46.4 Hz, H-6'b), 4.22 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 3.94 (t, 1 H, $J_{3,4} = J_{4,5} = 9.3$ Hz, H-4), 3.84 (bs, 1 H, H-4'), 3.77 (dd, $J_{5,6a}$ 4.0, $J_{6a,6b}$ 10.9 Hz, H-6a), 3.64 (dd, 1 H, $J_{5,6b}$ 1.7, $J_{6a,6b}$ 11.0 Hz, H-6b), 3.49 (t, 1 H, $J_{2,3} = J_{3,4} = 9.0$ Hz, H-3), 3.48 (s, 3 H, OCH_3), 3.47 (m, 1 H, H-5), 3.34 (dd, 1 H, $J_{1,2}$ 7.7, $J_{2,3}$ 9.1 Hz, H-2), 3.27 (dd, 1 H, $J_{2',3'}$ 9.3, $J_{3',4'}$ 3.5 Hz, H-3'), 3.31–3.22 (m, 2 H, H-5,5'), 2.22 (bs, 1 H, OH); ^{13}C (50 MHz), δ 139.0, 138.7, 138.5, 138.3, 137.7 (C-ipso, Ph), 128.5–127.3 (Ph), 104.7, 102.3 (C-1,1'), 82.7, 81.7, 80.6, 79.2, 76.5, 75.1 (C-2/5 and 2',3'), 81.0 (d, $J_{F,C-6'}$ 166.5 Hz, C-6'), 75.2, 74.8, 73.1, 72.2 (5 CH_2Ph), 71.9 (d, $J_{F,C-5'}$ 24.1 Hz, C-5'), 68.2 (C-6), 65.7 (d, $J_{F,C-4'}$ 3.7 Hz, C-4'), 57.0 (OCH_3). Anal. Calcd for $C_{48}H_{53}FO_{10}$: C, 71.27; H 6.60. Found: C, 71.15; H 6.70.

Hydrogenolysis and workup of **34** (0.112g, 0.14 mmol) was performed as described above, to yield **35** (45 mg, 91%) as a white solid; mp 228–230°C; $[\alpha]_D^{20}$ −1° (*c* 0.8, H_2O); lit.[10] $[\alpha]_D^{20}$ −12° (*c* 1.0, MeOH). NMR data (D_2O): ^{19}F (282 MHz), δ

−154.60 (dt, $J_{F,H\text{-}6'a} = J_{F,H\text{-}6'b} = 46.7$, $J_{F,H\text{-}5'}$ 14.7 Hz); ^{1}H (300 MHz), δ 4.68 (ddd, 1 H, $J_{5',6'a}$ 4.2, $J_{6'a,6'b}$ 9.9, $J_{F,H\text{-}6'a}$ 45.7 Hz, H-6'a), 4.63 (ddd, 1 H, $J_{5',6'b}$ 7.3, $J_{F,H\text{-}6'b}$ 47.2 Hz, H-6'b), 4.47 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 4.40 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 4.01 (ddd, 1 H, $J_{5',6'a}$ 4.2, $J_{5',6'b}$ 7.0, $J_{F,H\text{-}5'}$ 15.0 Hz, H-5'), 3.98 (m, 1 H, $J_{6a,6b}$ 11.5 Hz, H-6a), 3.82 (m, 1 H, H-6b), 3.78 (dd, 1 H, $J_{3',4'}$ 3.6, $J_{4',5'}$ 1.1 Hz, H-4'), 3.68 (dd, 1 H, $J_{2',3'}$ 10.1, $J_{3',4'}$ 3.5 Hz, H-3'), 3.65–3.59 (m, 3 H, H-3,4,5), 3.54 (s, 3 H, OCH_3), 3.54 (dd, 1 H, $J_{1',2'}$ 7.6, $J_{2',3'}$ 9.9 Hz, H-2'), 3.28 (dd, 1 H, $J_{1,2}$ 7.8, $J_{2,3}$ 8.8 Hz, H-2); ^{13}C (125 MHz), δ 104.5 (C-1,1'), 84.3 (d, $J_{F,C\text{-}6'}$ 164.3 Hz, C-6'), 79.8 (C-4), 76.1 (C-5), 76.0 (C-3), 74.9 (d, $J_{F,C\text{-}5'}$ 19.7, C-5'), 74.2 (C-2), 73.7 (C-3'), 72.1 (C-2'), 69.4 (d, $J_{F,C\text{-}4'}$ 7.3 Hz, C-4'), 61.5 (C-6), 58.6 (OCH_3). Anal. Calcd for $C_{13}H_{23}FO_{10}$: C, 43.58; H, 6.47. Found: C, 43.33; H, 6.72.

Methyl 6-deoxy-6-iodo-β-lactoside (**37**).—Methyl 4',6'-*O*-benzylidene-6-deoxy-6-iodo-β-lactoside[2] (**36**; 0.282 g, 0.51 mmol) was heated with AcOH (12 mL) and water (6 mL) to give, after chromatography (4:1 $CHCl_3$–MeOH), **37** (0.142 mg, 60%) as a solid; mp 117–118°C; $[\alpha]_D^{20}$ +11° (*c* 1.0, H_2O); lit.[30] mp 126–128°C; $[\alpha]_D^{20}$ −10.6° (*c* 0.5, H_2O). NMR data (D_2O): ^{1}H, δ 4.55 (d, 1 H, $J_{1',2'}$ 7.7 Hz, H-1'), 4.47 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 3.93 (d, 1 H, $J_{3',4'}$ 3.3 Hz, H-4'), 3.78 (dd, 1 H, $J_{5',6'}$ 3.3, $J_{6'a,6'b}$ 11.8 Hz, H-6'a), 3.75 (dd, 1 H, H-6'b), 3.73 (m, 2 H, H-6a,5'), 3.68 (t, 1 H, $J_{2,3} = J_{3,4} = 9.0$ Hz, H-3), 3.67 (dd, 1 H, $J_{2',3'}$ 9.8, $J_{3',4'}$ 3.8 Hz, H-3'), 3.59 (t, 1 H, H-4), 3.59 (s, 3 H, OCH_3), 3.54 (dd, 1 H, $J_{1',2'}$ 8.3, $J_{2',3'}$ 9.8 Hz, H-2'), 3.49 (dd, 1 H, $J_{5,6b}$ 6.0, $J_{6a,6b}$ 11.0 Hz, H-6b), 3.41 (ddd, 1 H, $J_{4,5}$ 9.0, $J_{5,6a}$ 2.9, $J_{5,6b}$ 6.0 Hz, H-5), 3.32 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.0 Hz, H-2); ^{13}C (125 MHz), δ 104.3 (C-1,1'), 76.7 (C-4,5'), 76.4 (C-5), 75.2 (C-3), 74.1 (C-2), 73.8 (C-3'), 72.2 (C-2'), 69.8 (C-4'), 62.3 (C-6'), 58.7 (OCH_3), 7.2 (C-6). Anal. Calcd for $C_{13}H_{23}IO_{10}$: C, 33.49; H, 4.97. Found: C, 33.29, H, 4.95.

Methyl 6'-bromo-6'-deoxy-β-lactoside (**39**).—Methyl 2,3,6,2',3'-penta-*O*-acetyl-4'-*O*-benzoyl-6'-bromo-6'-deoxy-β-lactoside[16] (**38**; 0.230 g, 0.31 mmol) was deacylated with a catalytic amount of 1 M NaOMe (0.06 equiv per *O*-acetyl group) at room temperature for 3 h. Neutralisation with Amberlite IR-120 (H^+), evaporation, and column chromatography (4:1 $CHCl_3$–MeOH) afforded **39** (180 g, 75%) as a white solid; mp decomp; $[\alpha]_D^{20}$ +30° (*c* 1.1, H_2O). NMR data (D_2O): ^{1}H (300 MHz), δ 4.49 (d, 1 H, $J_{1',2'}$ 8.3 Hz, H-1'), 4.40 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 4.04 (d, 1 H, $J_{3',4'}$ 3.3 Hz, H-4'), 4.00 (dd, 1 H, $J_{5,6a}$ 1.4, $J_{6a,6b}$ 12.0 Hz, H-6a), 3.94 (m, 1 H, H-5'), 3.80 (m, 1 H, H-6b), 3.72–3.57 (m, 6 H, H-3,4,3',5',6'a,6'b), 3.57 (s, 3 H, OCH_3), 3.54 (dd, 1 H, $J_{1',2'}$ 7.7, $J_{2',3'}$ 9.9 Hz, H-2'), 3.33 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.0 Hz, H-2); ^{13}C (125 MHz), δ 104.4 (C-1,1'), 80.6 (C-4), 76.4 (C-5'), 76.1 (C-5), 75.6 (C-3), 74.1 (C-2), 73.7 (C-3'), 72.0 (C-2'), 70.4 (C-4'), 61.6 (C-6), 58.6 (OCH_3), 31.5 (C-6'). Anal. Calcd. for $C_{13}H_{23}BrO_{10}$: C, 37.25; H, 5.53. Found: C, 37.20; H, 5.63.

REFERENCES

1 A. Rivera-Sagredo, D. Solis, T.Diaz-Mauriño, J. Jiménez-Barbero, and M. Martín-Lomas, *Eur. J. Biochem.*, 197 (1991) 217–228.

2 A. Rivera-Sagredo, D. Solis, T. Diaz-Mauriño, J. Jiménez-Barbero, and M. Martín-Lomas, *Carbohydr. Res.*, 232 (1992) 207–226.
3 R.U. Lemieux, L.T.J. Delbaere, H. Beierbeck, and U. Spohr, *Ciba Foundation Symposium No. 158. Host Guest Molecular Interactions: From Chemistry to Biology*, Wiley, New York, 1990.
4 C.P.J. Glaudemans, *Chem. Rev.*, 91 (1991) 25–33.
5 K. Adelhorst, K. Bock, H. Pedersen, and S. Refn, *Acta Chem. Scand., Ser. B*, 42 (1988) 196–201; J. Kihlberg, S.J. Hultgren, S. Normark, and G. Magnusson, *J. Am. Chem. Soc.*, 111 (1989) 6364–6368.
6 P.S. Vermesch, J.J.G. Tesmer, and F.A. Quiocho, *J. Mol. Biol.*, 226 (1992) 923–929.
7 P.V. Nikrad, H. Beierbeck, and R.U. Lemieux, *Can. J. Chem.*, 70 (1992) 241–253.
8 D. Solis, P. Fernandez, T. Diaz-Mauriño, J. Jiménez-Barbero, and M. Martín-Lomas, *Eur. J. Biochem.*, in press.
9 V.L. Bevilacqua, D.S. Thomson, and J.H. Prestegard, *Biochemistry*, 29 (1990) 5529–5537.
10 C. Shaopei, S. Hakomori, and T. Toyokuni, *J. Org. Chem.*, 57 (1992) 3431–3437.
11 H. Oguchi, T. Toyokuni, B. Dean, H. Ito, E. Otsuji, V.L. Jones, K.K. Sadozai, and S. Hakomori, *Cancer Commun.*, 2 (1990) 311–314.
12 S. David and S. Hanessian, *Tetrahedron*, 41 (1985) 643–663.
13 Y. Nishida and J. Thiem, *Abstracts of Papers*, XVIth International Carbohydrate Symposium, Paris, 1992, A220.
14 C.W. Holzapfel, J.M. Koekemoer, and C.F. Marais, *S. Afr. J. Chem.*, 37 (1984) 19–26; A. Fernández-Mayoralas and M. Martín-Lomas, *Carbohydr. Res.*, 154 (1986) 93–101.
15 A. Fernández-Mayoralas, M. Martín-Lomas, and D. Villanueva, *Carbohydr. Res.*, 140 (1985) 81–91.
16 K Bock and K Adelhorst, *Carbohydr. Res.*, 202 (1990) 131–149.
17 V. Pozsgay, J.R. Brisson, and H.J. Jennings, *J. Org. Chem.*, 56 (1991) 3377–3385.
18 R.H. Youssef, B.A. Silwanis, A. Riel-Sokkay, A.S. Nematallo, and M.A. Nashed, *Carbohydr. Res.*, 240 (1993) 287–293.
19 S. David, A. Thieffry, and A. Veyrières, *J. Chem. Soc., Perkin Trans. 1*, (1981) 1796–1801.
20 H.P. Wessel, T. Iversen, and D. Bundle, *Carbohydr. Res.*, 130 (1984) 5–21.
21 N.F. Taylor, *ACS Symp. Ser.*, 374 (1988).
22 J.T. Welch, *Tetrahedron*, 43 (1987) 3123–3197.
23 S. Tsuchiya, *Adv. Carbohydr. Chem. Biochem.*, 48 (1990) 91–277; J. Mann, *Chem. Soc. Rev.*, 16 (1987) 381–436; R.E. Banks and J.C. Tatlow, *J. Fluorine Chem.*, 33 (1986) 227–346.
24 P.J. Card, *J. Carbohydr. Chem.*, 4 (1985) 451–487; P.J. Card and G.S. Reddy, *J. Org. Chem.*, 48 (1983) 4734–4743.
25 P.J. Garegg and S. Oscarson, *Carbohydr. Res.*, 108 (1982) 97.
26 P. Kovac and C.P.J. Glaudemans, *Carbohydr. Res.*, 123 (1983) 326–331.
27 K. Takeo, T. Fukatsu, and T. Yasato, *Carbohydr. Res.*, 107 (1982) 71–90.
28 O. Mitsunobu, *Synthesis*, (1981) 1–28.
29 P. Kovac and C.P.J. Glaudemans, *J. Carbohydr. Chem.*, 2 (1983) 313–327; C.W. Somawardhana and E.G. Brunngraber, *Carbohydr. Res.*, 121 (1983) 51–60.
30 K. Adelhorst and K. Bock, *Acta Chem. Scand.*, 46 (1992) 1114–1121.