Carbohydrate Research, 176 (1988) 271–286
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

SYNTHETIC RECEPTOR ANALOGUES: PREPARATION AND CALCULATED CONFORMATIONS OF THE 2-DEOXY, 6-*O*-METHYL, 6-DEOXY, AND 6-DEOXY-6-FLUORO DERIVATIVES OF METHYL 4-*O*-α-D-GALACTOPYRANOSYL-β-D-GALACTOPYRANOSIDE (METHYL β-D-GALABIOSIDE)*

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(Received August 28th, 1987; accepted for publication, October 31st, 1987)

ABSTRACT

The 2-deoxy (**7**), 6-*O*-methyl (**15**), 6-deoxy (**22**), and 6-deoxy-6-fluoro (**31**) derivatives of methyl β-D-galabioside (**1**) have been synthesised. Thus, **7** was prepared by xanthate reduction using tributyltin hydride, whereas **22** was obtained by catalytic hydrogenation of a 6-deoxy-6-iodogalabioside. Regioselective monofluorination of methyl 2,3-di-*O*-benzoyl-β-D-galactopyranoside with Et_2NSF_3 and subsequent α-D-galactosylation provided **31**. Molecular mechanics calculations yielded similar conformations for **1**, **7**, **15**, **22**, and **31** with differences in ϕ_H and ψ_H of <5°. No indications of intramolecular hydrogen bonds, as displayed by **1** in the crystal, were found for **7**, **15**, **22**, or **31**.

INTRODUCTION

We have reported the synthesis[1] and conformational analysis[2a] of the 3-*O*-methyl, 3-*C*-methyl, and 3-deoxy derivatives of methyl 4-*O*-α-D-galactopyranosyl-β-D-galactopyranoside (methyl β-D-galabioside, **1**) which are of interest in investigation of the binding epitope[2] of the tetrasaccharide globoside (and derivatives) in the adhesion of micro-organisms, toxins, and antibodies. We now report the synthesis and conformation (by molecular mechanics calculations) of the 2-deoxy (**7**), 6-*O*-methyl (**15**), 6-deoxy (**22**), and 6-deoxy-6-fluoro (**31**) derivatives of methyl β-D-galabioside.

RESULTS AND DISCUSSION

Methyl 2-deoxy-4-*O*-α-D-galactopyranosyl-β-D-*lyxo*-hexopyranoside (**7**) was

*Part 3. For Part 2, see ref. 2a.
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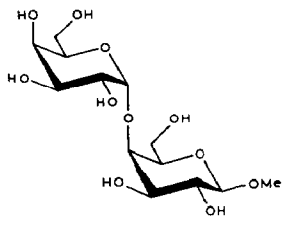
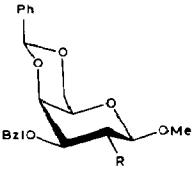
0008-6215/88/$ 03.50

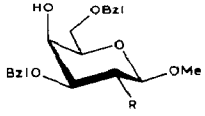
prepared from methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside[1] (**2**). Treatment of **2** with sodium hydride and imidazole in tetrahydrofuran followed by addition of carbon disulfide and methyl iodide[3] gave the *S*-methyl dithiocarbonate **3** (98%). In order to avoid anticipated acid-catalysed decomposition of a labile 2-deoxygalactoside, the 4,6-*O*-benzylidene group in **3** was cleaved with sodium cyanoborohydride and hydrogen chloride in ether[4] prior to reduction of the (methylthio)thiocarbonyl group, which then gave the alcohol **4** (82%). Reduction of the (methylthio)thiocarbonyl group of **4** with tributyltin hydride gave **5** (96%) as the only product. This result is in contrast to that obtained with compounds containing vicinal hydroxyl and (methylthio)thiocarbonyl groups since the hydroxyl group then has to be protected[1]. Treatment of **5** with 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl chloride, using silver trifluoromethanesulfonate as promoter[5], gave the disaccharide derivative **6** (73%). Hydrogenolysis of the benzyl groups in **6** then gave methyl 2-deoxy-4-*O*-α-D-galactopyranosyl-β-D-*lyxo*-hexopyranoside (**7**, 74%).



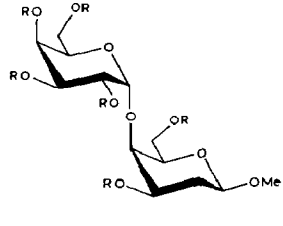
1



2 R = OH
3 R = OCSSMe

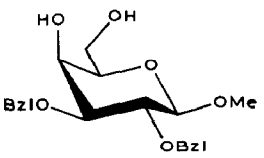


4 R = OCSSMe
5 R = H



6 R = Bzl
7 R = H

Routes to the 6-*O*-methyl (**15**), 6-deoxy (**22**), and 6-deoxy-6-fluoro (**31**) derivatives of **1** were then investigated. Selective modification[7] of HO-6 in the diol **8**[6] by treatment with tris(dimethylamino)phosphine and carbon tetrachloride followed by attempted reduction with lithium triethylborohydride gave the 4,6-anhydro derivative **9** (55%) and not the desired methyl 2,3-di-*O*-benzyl-β-D-fucopyranoside. Preparations of 4,6-anhydrogalactose derivatives by treatment of 2,3-di-*O*-alkyl-6-*O*-toluene-*p*-sulfonylgalactopyranosides with methanolic sodium methoxide have been reported[8]. Attempted substitution of HO-6 in **8** by iodine, using triphenylphosphine, imidazole, and iodine[9], gave several products. In view of these results, the desired modifications were performed on disaccharide derivatives.



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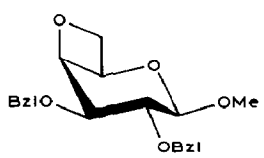

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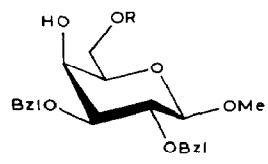
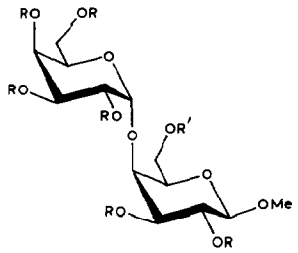
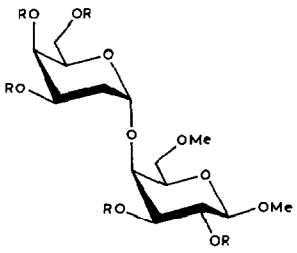


10 R = Ts
11 R = Adamantoyl

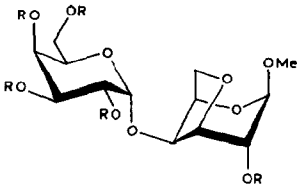
Reaction of **8** with tosyl chloride and adamantoyl chloride gave **10** (55%) and **11** (74%), respectively. The ^{1}H-n.m.r. spectra of the respective 4-acetates revealed that HO-4 was unprotected. Reaction of **10** and **11** with 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl chloride, using silver trifluoromethanesulfonate as promoter[5], gave the disaccharide derivative **12** (66%) and methyl 6-*O*-adamantoyl-2,3-di-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-β-D-galactopyranoside. The latter compound could not be purified, but was converted into pure **13** (51% from **8**) by treatment with boiling methanolic sodium methoxide–dichloromethane. Methylation[10] of **13** with sodium methylsulfinylmethanide and methyl iodide gave the 6-methyl ether **14** (86%) and hydrogenolysis then gave methyl 4-*O*-α-D-galactopyranosyl-6-*O*-methyl-β-D-galactopyranoside (**15**, 96%).



12 R = Bzl, R' = Ts
13 R = Bzl, R' = H



14 R = Bzl
15 R = H

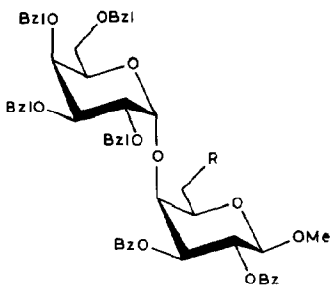


16 R = Bzl

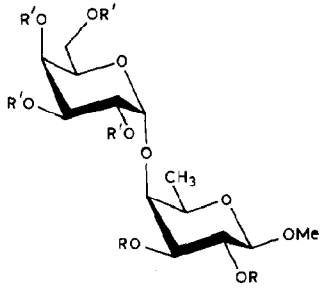
Synthesis of the 6-deoxygalabioside **22** was attempted by reduction of the 6-*O*-tosyl group of **12** with lithium triethylborohydride[11] in boiling tetrahydrofuran or, alternatively, *via* substitution of the tosyl group with sodium iodide in boiling *N,N*-dimethylformamide. In each reaction, only the 3,6-anhydro derivative **16**[12] was formed (59 and 67%, respectively). The conversion **12**→**16** was effected with boiling *N,N*-dimethylformamide in the absence of other reagents but not with boiling tetrahydrofuran. Likewise, **16** was formed[12] (59%) on attempted substitution of the hydroxyl group of **13** by iodine[9] and attempted fluorination of **13** using diethylaminosulfur trifluoride[13] (DAST).

Partial debenzoylation of **17**[5] with methanolic sodium methoxide gave the 2,3-dibenzoate **18** (49%) with HO-6 unprotected. Treatment of **18** with trifluoromethanesulfonic anhydride followed by tris(dimethylamino)sulfonium difluorotrimethylsilicate[14] (TASF) gave mainly elimination[12], whereas a 1,6-methoxyl group migration[12] occurred on reaction of **18** with DAST[13]. Therefore, a practical preparation of **31** *via* **18** was unsuccessful.

The primary hydroxyl group of **18** was replaced by iodine on treatment with iodine, triphenylphosphine, and imidazole[9]. The resulting 6-deoxy-6-iodo compound **19** (91%) was hydrogenated in the presence of triethylamine to give the D-fucoside derivative **20** (96%). Debenzoylation of **20** with methanolic sodium methoxide gave **21** (85%), which was then hydrogenated to give methyl 4-*O*-α-D-galactopyranosyl-β-D-fucopyranoside[5] (**22**, 83%).



17 R = OBz
18 R = OH
19 R = I



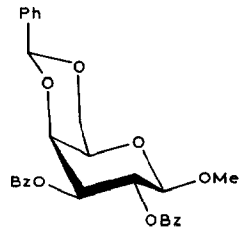
20 R = Bz, R' = Bzl
21 R = H, R' = Bzl
22 R = R' = H

Removal of the 4,6-*O*-benzylidene group from **23**[15], using boiling methanolic 1% iodine[16], gave the diol **24**[15] (99%). *O*-Debenzylidenation by hydrolysis with trifluoroacetic acid[17] or hydrogenolysis (Pd/C) in acetic acid gave substantially lower yields of **24** (74 and 27%, respectively). Addition of 1.05 equiv. of DAST[13] to a solution of **24** in dichloromethane gave the 6-deoxy-6-fluorogalactoside **25** (54%) and the 4,6-dideoxy-4,6-difluoroglucoside **26** (12%). Other routes to 6-deoxy-6-fluoro-D-galactopyranosides either give a low (15%) yield, as in the treatment[18] of methyl β-D-galactopyranoside with DAST, or require multistep sequences starting from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[14] or from derivatives of D-glucose[19]. The chemical shift (230 p.p.m.) of the ^{19}F resonance of **25** and the $J_{F\text{-}6,H\text{-}5}$ and $J_{F\text{-}6,H\text{-}6}$ values (12.2 and 45.8 Hz, respectively) are consistent[20] with fluorine substitution at C-6, but not at C-4. The chemical shift (δ 4.72) of H-6,6′ and the downfield shift (1.3 p.p.m.) for H-4 on acetylation of HO-4 corroborated the position of the fluorine atom in **25**.

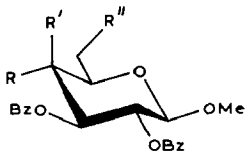
The ^{19}F resonances (234 p.p.m., $J_{F\text{-}6,H\text{-}5}$ 25.0, $J_{F\text{-}6,H\text{-}6}$ 45.3 Hz; 199 p.p.m., $J_{F\text{-}4,H\text{-}4}$ 50.5, $J_{F\text{-}4,H\text{-}3}$ 13.2 Hz) of **26** indicated[20] the presence of fluorine substituents at positions 6 and 4, respectively. The ^{19}F chemical shifts were within 1.5 p.p.m. of those reported for methyl 4,6-dideoxy-4,6-difluoro-α-D-glucopyranoside[21] (**27**). The small $J_{F\text{-}4,H\text{-}3}$ value and the lack of coupling between F-4 and H-5, as reported for 1,2,3,6-tetra-*O*-acetyl-4-deoxy-4-fluoro-β-D-glucopyranose[22], showed that F-4 was equatorial. This inference was supported also by the large $J_{H\text{-}3,H\text{-}4}$ and $J_{F\text{-}4,C\text{-}2}$[23] values (9.3 and 8.2 Hz, respectively). Comparison of ^{13}C-n.m.r. data for **26** with data for **27**[21], **28**[23], and **29**[23] (*cf.* Table I) confirmed the structure determined for **26**.

Treatment of **25** with 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl chloride, using silver trifluoromethanesulfonate as promoter[5], gave the methyl 6-deoxy-6-fluoro-β-D-galabioside derivative **30** (87%). Debenzoylation of **30** with methanolic sodium methoxide–dichloromethane followed by hydrogenolysis gave methyl 6-deoxy-6-fluoro-4-*O*-α-D-galactopyranosyl-β-D-galactopyranoside (**31**, 73%).

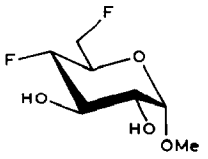
The conformations of the synthetic receptor analogues **7**, **15**, **22**, and **31** were calculated using the interactive program SUGAR[24] combined with Allinger's MM2-



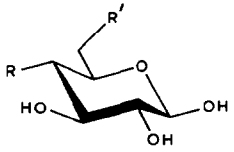
23



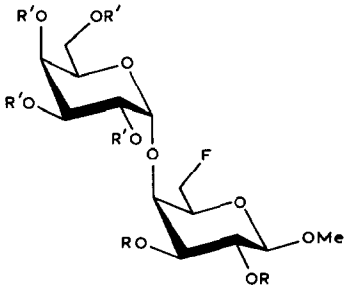
24 R = H, R' = R'' = OH
25 R = H, R' = OH, R'' = F
26 R = R'' = F, R' = H



27



28 R = F, R' = OH
29 R = OH, R' = F



30 R = Bz, R' = Bzl
31 R = R' = H

82 program[25]. SUGAR calculates molecular coordinates, by the HSEA approach[26], which can then be used (*via* the MIMIC[27] program) as input data for the MM2-82 program. The latter program performs a complete energy-minimisation of the oligosaccharide (including bending, stretching, and twisting of the monosaccharide units), in contrast to the often-used HSEA-type programs. This facility can be important for the calculation of the conformations of oligosaccharide analogues where the structure of the monosaccharide units might have departed from those in the crystals of the parent compounds used as input in HSEA-type programs. SUGAR in combination with MM2-82 gave[24a] an energy-minimised conformation for the blood-group A tetrasaccharide that was in good agreement with the n.O.e. data[24b]. This was not the case with other programs[24b].

The calculated conformations, as described by the torsional angles of the glycosidic linkage (ϕ_H and ψ_H) and the C-5–C-6 bond (ω_1), were similar for **1, 7, 15, 22**, and **31** (*cf.* Table II). Thus, the dihedral angles ϕ_H and ψ_H varied by only 4° and 3° between the minimum energy conformations. This finding is in good agreement with the results of a conformational investigation of methyl β-D-galabioside (**1**) and its 3-*O*-methyl, 3-deoxy, 3-*C*-methyl, 3-*C*-ethyl, and 6-deoxy (**22**) derivatives[2a]. The influence on ϕ_H and ψ_H of the three possible orientations of the hydroxymethyl group was small for the compounds investigated. The *gauche–trans* conformation (*i.e.*, the orientation of the C-6–O-6 bond to the C-5–O-5 and C-4–C-5 bonds) for

TABLE I

^{13}C-CHEMICAL SHIFTS AND ^{13}C–^{19}F COUPLING CONSTANTS FOR **26–29**

Atom	*Chemical shifts (δ, p.p.m.)*			
	26[a]	**27**[b]	**28**[c]	**29**[c]
C-1	101.7	100.0	97.1	97.3
C-2	71.0	71.9	74.9	75.3
C-3	72.7	72.0	75.0	76.8
C-4	85.9	88.8	90.3	69.7
C-5	72.4	68.2	72.3	75.6
C-6	80.5	81.7	61.4	83.5
Atoms	*Coupling constants (J, Hz)*			
	26[a]	**27**[b]	**28**[c]	**29**[c]
F-4,C-1			1.4	
F-4,C-2	8.2		8.8	
F-4,C-3	19.6	15	18.0	
F-4,C-4	187.8	181	180.0	
F-4,C-5	23.8	19	24.5	
F-6,C-4	7.4	7.3		6.9
F-6,C-5	18.4	17		18.7
F-6,C-6	175.8	171		167.6

[a]$CDCl_3$ (internal Me_4Si). [b]Data from ref. 21; $CDCl_3$ (internal Me_4Si). [c]Data from ref. 23; D_2O (external Me_4Si).

TABLE II

CALCULATED MINIMUM-ENERGY CONFORMATIONS FOR METHYL β-D-GALABIOSIDE (**1**) AND THE ANALOGUES **7, 15, 22**, AND **31**[a,b]

Compound	*C-5–C-6*[c] *conformation*	ϕ_H[d]/ψ_H[e] (°)	ω_1[f,g] (°)	ω_2[h] (°)	*Calculated energy (kcal/mole)*
1	GT	−40/−16	63	63	25.92
	GG	−45/−13	−58	63	26.20
	TG	−43/−16	171	63	26.39
7	GT	−40/−16	63	63	26.19
	GG	−45/−13	−56	63	26.45
	TG	−44/−15	171	63	26.62
15	GT	−41/−16	64	63	27.18
	TG	−43/−17	179	63	27.39
	GG	−46/−13	−54	63	30.40
22		−41/−16		63	25.43
31	TG	−44/−13	178	59	23.96
	GT	−41/−14	66	63	24.25
	GG	−47/− 9	−59	61	24.34

[a]Calculated using the program SUGAR[24a] together with the MM2-82 program[25]. [b]The conformations for each compound are arranged according to increasing energy. [c]The 5′-hydroxymethyl group was kept in the *gauche–trans* conformation. [d]ϕ_H = H-1′–C-1′–O-1′–C-4. [e]ψ_H = H-4–C-4–O-1′–C-1′. [f]ω_1 = O-5–C-5–C-6–O-6. [g]ω_1 = O-5–C-5–C-6–F-6 for **31**. [h]ω_2 = O-5′–C-5′–C-6′–O-6′.

TABLE III

SELECTED INTER-ATOMIC DISTANCES IN THE CALCULATED MINIMUM-ENERGY CONFORMATIONS OF METHYL β-D-GALABIOSIDE (1) AND THE ANALOGUES **7, 15, 22,** AND **31**

Compound	*C-5–C-6 conformation*	*Distances (Å)*				
		O-3/O-5'	*O-6/O-2'*[a]	*H-4/H-1'*	*O-3/H-5'*	*O-3/H-1'*
1	GT	3.42	4.61	2.28	2.49	4.26
	GG	3.37	2.77	2.31	2.41	4.28
	TG	3.42	4.62	2.33	2.45	4.30
7	GT	3.42	4.61	2.29	2.50	4.27
	GG	3.38	2.77	2.32	2.41	4.29
	TG	3.43	4.62	2.33	2.45	4.30
15	GT	3.44	4.68	2.30	2.48	4.28
	TG	3.45	4.44	2.33	2.45	4.31
	GG	3.38	2.84	2.33	2.40	4.29
22		3.42		2.29	2.48	4.27
31	TG	3.38	4.34	2.30	2.41	4.28
	GT	3.39	4.63	2.28	2.48	4.25
	GG	3.29	2.83	2.29	2.38	4.25

[a]F-6/O-2' for **31**.

the hydroxymethyl group was the most stable for **1, 7,** and **15,** whereas the *trans–gauche* conformation was most stable for **31,** but the energy differences were generally small (*cf.* Table II).

Determination of the crystal structure of galabiose revealed[28] an intramolecular hydrogen bond between HO-3 and O-5'. For the compounds investigated here, the calculated O-3–O-5' distances (*cf.* Table III) were >3 Å, which is too long to permit a hydrogen bond. In solutions in $(CD_3)_2SO$, an intramolecular hydrogen bond was detected between HO-6 and HO-2' of **1** and a *trans–gauche* orientation was determined for the C-5 hydroxymethyl group[2a]. In the present computational investigation, only the *gauche–gauche* orientation about the C-5–C-6 bond was compatible with an HO-6···HO-2' or F-6···HO-2' hydrogen bond (atom–atom distances, 2.77–2.84 Å). Table III shows the calculated proton–proton and proton–oxygen interatomic distances that can be correlated[2a] with n.m.r. data.

A comparison of the minimum energy conformations calculated for **1** and **22,** using the HSEA approach[2a] with the conformations calculated here (SUGAR + MM2), show only minor differences in dihedral angles (differences in ϕ_H and ψ_H of <1° and <2°, respectively) and in the selected interatomic distances (differences <0.1 Å).

Thus, each of the analogues **7, 15, 22,** and **31** had a calculated conformation similar to that of methyl β-D-galabioside (**1**). As concluded earlier from both n.m.r. and calculational studies[2a], modification of a single hydroxyl group in **1** seems to have little consequence with respect to the preferred conformation. Therefore, an n.m.r. study of the conformations of **7, 15, 22,** and **31** was not performed.

EXPERIMENTAL

General methods. — ^{1}H- and ^{13}C-n.m.r. spectra {$CDCl_3$ [internal Me_4Si] or D_2O [internal sodium 3-(trimethylsilyl)propanesulfonate]} were recorded with a Varian XL-300 spectrometer. ^{19}F-N.m.r. spectra were obtained for solutions in $CDCl_3$ and D_2O (external trifluoroacetic acid) and the chemical shifts (Φ) are expressed in p.p.m. upfield from the signal for $CFCl_3$. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. Recrystallisations were from ethyl acetate–heptane unless otherwise stated, and melting points were determined with a Reichert melting-point microscope. T.l.c. was performed on Kieselgel 60 F_{254} (Merck) with detection by u.v. light or charring with sulfuric acid. Column chromatography was performed on Kieselgel 60 (Merck, 230–400 mesh). Organic solutions were dried over Na_2SO_4. Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-galactopyranoside[1] (**2**), methyl 2,3-di-*O*-benzyl-β-D-galactopyranoside[6] (**8**), methyl 2,3,6-tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-β-D-galactopyranoside[5] (**17**), and methyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside[15] (**23**) were prepared as described, and had melting points and optical rotations in agreement with literature data. 2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl chloride (1.85 mmol) was prepared[29] by treatment of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose[30] (1.00 g, 1.86 mmol) in dry dichloromethane (5 mL) with *N,N*-dimethylformamide (1 mL) and oxalyl chloride (1 mL) at room temperature. The reaction was monitored by t.l.c. (ethyl acetate–heptane, 1:1). The mixture was diluted with ice-cold toluene (30 mL), then quickly washed with ice-cold water (10 mL) and ice-cold saturated aqueous sodium hydrogencarbonate (10 mL), dried, and concentrated. Satisfactory elemental analyses could not be obtained for the amorphous compounds **7**, **15**, **22**, and **31**. However, these were pure according to t.l.c. analysis and ^{1}H-n.m.r. spectroscopy. The conformational calculations were made on a VAX 11/780 computer, using the programs SUGAR[24a] and MM2-82[25]. Coordinates for the α- and β-D-galactopyranoside residues were taken from a library of energy-minimized (MM2-82) monosaccharide crystal structures. The conformation of the C-5′ hydroxymethyl group in the disaccharides was kept in the *gauche–trans* conformation during calculations; methyl α-D-galactopyranoside (specifically deuterated at C-6) showed a slight preference for the *gauche–trans* conformer (47%) over the *trans–gauche* conformer (39%) in D_2O[31].

Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-[(methylthio)thiocarbonyl]-β-D-galactopyranoside (**3**). — To a solution of **2**[1] (3.50 g, 9.41 mmol) in dry tetrahydrofuran (25 mL) were added imidazole (15 mg) and sodium hydride (50% in oil; 900 mg, 18.8 mmol), and the mixture was stirred for 1 h at room temperature[3]. Carbon disulfide (4.47 mL) was added and stirring was continued for 1 h. Iodomethane (1.18 mL) was added and the reaction mixture was diluted with dichloromethane (150 mL) after 15 min. The mixture was washed with water (30 mL), 0.2M hydrochloric acid (30 mL), saturated aqueous sodium hydrogencarbonate (30 mL), and water (30 mL), dried, and concentrated. Column chromatography (ethyl acetate–

heptane, 1:3) of the residue gave **3** (4.26 g, 98%), m.p. 137–138°, $[\alpha]_D^{25}$ +43° (*c* 0.8, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 6.35 (dd, 1 H, *J* 9.8 and 8.1 Hz, H-2), 5.51 (s, 1 H, PhC*H*), 4.67 (s, 2 H, PhCH_2), 4.48 (d, 1 H, *J* 7.8 Hz, H-1), 4.33 (dd, 1 H, *J* 12.2 and 1.2 Hz, H-6), 4.19 (dd, 1 H, *J* 3.7 and 1.0 Hz, H-4), 4.05 (dd, 1 H, *J* 12.3 and 1.8 Hz, H-6), 3.71 (dd, 1 H, *J* 9.9 and 3.5 Hz, H-3), 3.51 (s, 3 H, MeO), 3.39 (bs, 1 H, H-5), 2.60 (s, 3 H, MeS).

Anal. Calc. for $C_{23}H_{26}O_6S_2$: C, 59.7; H, 5.7. Found: C, 59.3; H, 5.7.

*Methyl 3,6-di-*O*-benzyl-2-*O*-[(methylthio)thiocarbonyl]-β-*D*-galactopyranoside* (**4**). — Saturated ethereal hydrogen chloride was added at room temperature to a solution of **3** (1.00 g, 2.16 mmol) and sodium cyanoborohydride (1.38 g, 21.6 mmol) in dry tetrahydrofuran (15 mL) containing powdered molecular sieves (3 Å, 1.8 g) until the solution became acidic (pH paper)[4]. The reaction was monitored by t.l.c. and, when complete, solid sodium hydrogencarbonate was added, followed by dichloromethane (60 mL) and saturated aqueous sodium hydrogencarbonate (10 mL). The mixture was filtered, and the organic phase was dried and then stirred with silica gel, sodium hydrogencarbonate, and sodium sulphate for 24 h. Filtration of the mixture, concentration of the organic phase, and column chromatography (ethyl acetate–heptane, 2:3) of the residue gave **4** (818 mg, 82%), as a syrup, $[\alpha]_D^{25}$ −4° (*c* 0.6, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 6.20 (dd, 1 H, *J* 9.5 and 8.3 Hz, H-2), 4.67 and 4.59 (ABq, 2 H, *J* 12.2 Hz, PhCH_2), 4.60 (s, 2 H, PhCH_2), 4.40 (d, 1 H, *J* 8.1 Hz, H-1), 4.09 (bs, 1 H, H-4, shifted to δ 5.62 on acetylation), 3.83 (dd, AB-type, 1 H, *J* 10.0 and 6.4 Hz, H-6), 3.76 (dd, AB-type, 1 H, *J* 9.5 and 6.1 Hz, H-6), 3.63 (bt, 1 H, *J* 6.5 Hz, H-5), 3.63 (dd, 1 H, *J* 9.5 and 3.4 Hz, H-3), 3.48 (s, 3 H, MeO), 2.59 (s, 3 H, MeS).

Anal. Calc. for $C_{23}H_{28}O_6S_2$: C, 59.5; H, 6.1. Found: C, 59.5; H, 6.0.

*Methyl 3,6-di-*O*-benzyl-2-deoxy-β-*D*-*lyxo*-hexopyranoside* (**5**). — A solution of **4** (773 mg, 1.67 mmol) in dry toluene (13 mL) was added, under argon, to a refluxing solution of tributyltin hydride (617 μL, 2.33 mmol) in toluene (10 mL) during 1 h[3]. 2,2′-Azobisisobutyronitrile (20 mg) was added, and the solution was boiled for 30 min under reflux and then concentrated. Column chromatography (ethyl acetate–heptane, 1:2) of the residue gave **5** (574 mg, 96%), as a syrup, $[\alpha]_D^{25}$ −9.5° (*c* 0.65, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 4.64 and 4.58 (ABq, 2 H, *J* 12.0 Hz, PhCH_2), 4.60 (s, 2 H, PhCH_2), 4.33 (dd, 1 H, *J* 9.8 and 2.2 Hz, H-1), 3.98 (bs, 1 H, H-4), 3.84 (dd, AB-type, 1 H, *J* 9.7 and 5.9 Hz, H-6), 3.75 (dd, AB-type, 1 H, *J* 9.7 and 6.0 Hz, H-6), 3.54 (ddd, 1 H, *J* 11.8, 5.0, and 3.2 Hz, H-3), 3.50 (s, 3 H, MeO), 3.48 (m, 1 H, H-5), 2.03 (ddd, 1 H, *J* 12.8, 5.1, and 2.2 Hz, H-2*e*), 1.84 (dt, 1 H, *J* 9.8 and 12.1 Hz, H-2*a*).

Anal. Calc. for $C_{21}H_{26}O_5$: C, 70.4; H, 7.3. Found: C, 70.6; H, 7.4.

*Methyl 3,6-di-*O*-benzyl-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-galactopyranosyl)-β-*D*-lyxo-hexopyranoside* (**6**). — A solution of freshly prepared 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl chloride (625 mg, 1.12 mmol) in dry toluene (2 mL) was added, with exclusion of light and under nitrogen, to a stirred solution of **5** (200 mg, 0.559 mmol), silver trifluoromethanesulfonate (258 mg, 1.01 mmol), 2,4,6-tri-

methylpyridine (148 μL, 1.12 mmol), and molecular sieves (4Å, 0.4 g) in dry toluene (5 mL) at −40°[5]. The mixture was allowed to attain room temperature, then filtered, and concentrated. Column chromatography (ethyl acetate–heptane, 1:4) of the residue gave **6** (360 mg, 73%), as a syrup, $[\alpha]_D^{25}$ +31° (*c* 0.9, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 4.18 (bd, 1 H, *J* 1.7 Hz, H-4 or H-4′), 3.73 (dd, 1 H, *J* 10.0 and 6.4 Hz, H-6 or H-6′), 3.50 (s, 3 H, MeO), 2.04 (m, 2 H, H-2).

Anal. Calc. for $C_{55}H_{60}O_{10}$: C, 75.0; H, 6.9. Found: C, 74.6; H, 6.8.

*Methyl 2-deoxy-4-*O*-α-*D*-galactopyranosyl-β-*D*-lyxo-hexopyranoside* (**7**). — Pd/C (10%, 140 mg) was added to a solution of **6** (350 mg, 0.398 mmol) in acetic acid (10 mL). The mixture was hydrogenated for 30 min at atmospheric pressure, then filtered through Celite, and concentrated. Column chromatography (methanol–dichloromethane, 1:4) of the residue gave, after freeze-drying, amorphous **7** (100 mg, 74%), $[\alpha]_D^{25}$ +77° (*c* 0.8, water). ^{1}H-N.m.r. data (D_2O): δ 4.96 (d, 1 H, *J* 4.2 Hz, H-1′), 4.61 (dd, 1 H, *J* 9.8 and 2.2 Hz, H-1), 4.30 (bt, 1 H, *J* 6.4 Hz, H-5′), 4.01 (dd, 1 H, *J* 3.2 and 1.0 Hz, H-4′), 3.52 (s, 3 H, MeO), 2.00 (ddd, 1 H, *J* 10.8, 4.0, and 2.0 Hz, H-2*e*), 1.68 (dt, 1 H, *J* 9.7 and 11.9 Hz, H-2*a*).

*Methyl 4,6-anhydro-2,3-di-*O*-benzyl-β-*D*-galactopyranoside* (**9**). — Tris(dimethylamino)phosphine (133 μL, 0.73 mmol) was added to a solution of **8**[6] (210 mg, 0.561 mmol) and tetrachloromethane (109 μL, 1.12 mmol) in dry tetrahydrofuran (3 mL) at −45°[7]. After 45 min, M lithium triethylborohydride in tetrahydrofuran (2.25 mL, 2.25 mmol) was added and the solution was boiled under reflux for 5 h under dry nitrogen. Water (0.1 mL) was added, the solution was concentrated, and the residue was dissolved in ethyl ether (20 mL). The solution was washed with saturated aqueous sodium chloride (10 mL), M hydrochloric acid (10 mL), and saturated aqueous sodium hydrogencarbonate (10 mL), dried, and concentrated. Column chromatography (ethyl acetate–heptane, 2:3) of the residue gave **9** (110 mg, 55%), m.p. 64–65°, $[\alpha]_D^{25}$ −23.5° (*c* 0.5, chloroform). N.m.r. data ($CDCl_3$): ^{1}H, δ 5.10 (dd, 1 H, *J* 5.5 and 3.4 Hz, H-4), 4.73 (d, 1 H, *J* 5.6 Hz, H-1), 4.31 (dd, 1 H, *J* 10.0 and 5.6 Hz, H-2, shifted to δ 5.82 on debenzylation and acetylation), 3.61 (dd, 1 H, *J* 10.0 and 3.4 Hz, H-3, shifted to δ 5.05 on debenzylation and acetylation), 3.46 (s, 3 H, MeO); ^{13}C, δ 106.0 (C-1), 81.4, 80.0, 77.3, 76.8, 74.6, 72.4, 70.1, 55.7 (OCH_3).

Anal. Calc. for $C_{21}H_{24}O_5$: C, 70.8; H, 6.8. Found: C, 71.0; H, 6.6.

*Methyl 2,3-di-*O*-benzyl-6-*O*-toluene-*p*-sulfonyl-β-*D*-galactopyranoside* (**10**). — Toluene-*p*-sulfonyl chloride (458 mg, 2.41 mmol) was added to a solution of **8**[6] (500 mg, 1.34 mmol) in dry pyridine (6 mL) at −20°. The solution was kept for 16 h at room temperature, and then for 30 min at 60°. The solution was then diluted with dichloromethane (30 mL), washed with saturated aqueous sodium hydrogencarbonate (15 mL) and water (10 mL), dried, and concentrated. Column chromatography (ethyl acetate–heptane, 2:3; then ethyl acetate) of the residue gave **10** as a syrup (388 mg, 55%), and **8** (93 mg, 19%). Compound **10** had $[\alpha]_D^{25}$ +10° (*c* 0.6, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 4.86 and 4.68 (ABq, 2 H, *J* 11.2 Hz, PhCH_2), 4.71 and 4.68 (ABq, 2 H, *J* 11.5 Hz, PhCH_2), 4.26 (dd, AB-type,

1 H, *J* 10.2 and 5.5 Hz, H-6), 4.23 (d, 1 H, *J* 7.3 Hz, H-1), 4.19 (dd, AB-type, 1 H, *J* 10.2 and 7.1 Hz, H-6), 3.92 (bs, 1 H, H-4, shifted to δ 5.46 on acetylation), 3.66 (bt, 1 H, *J* 6.3 Hz, H-5), 3.55 (dd, AB-type, 1 H, *J* 9.3 and 7.3 Hz, H-2), 3.51 (s, 3 H, MeO), 3.48 (dd, AB-type, 1 H, *J* 9.3 and 3.2 Hz, H-3), 2.45 (s, 3 H, PhCH_3).

Anal. Calc. for $C_{28}H_{32}O_8S$: C, 63.6; H, 6.1. Found: C, 63.4; H, 5.8.

Methyl 6-O-adamantoyl-2,3-di-O-benzyl-β-D-galactopyranoside (**11**). — Adamantoyl chloride (549 mg, 2.76 mmol) was added to a solution of **8**[6] (600 mg, 1.60 mmol) and 4-dimethylaminopyridine (20 mg, 0.16 mmol) in dry pyridine (10 mL) at 0°. After 16 h at room temperature and 3 h at 60°, the solution was diluted with dichloromethane (50 mL), washed with saturated aqueous sodium hydrogencarbonate (20 mL) and water (20 mL), dried, and concentrated. Column chromatography (ethyl acetate–heptane, 1:4) of the residue gave **11** (631 mg, 74%), m.p. 88–90°, $[\alpha]_D^{25}$ −1° (*c* 1.5, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 4.89 and 4.72 (ABq, 2 H, *J* 11.1 Hz, PhCH_2), 4.76 and 4.69 (ABq, 2 H, *J* 11.6 Hz, PhCH_2), 4.31 (d, 2 H, *J* 6.1 Hz, H-6), 4.24 (d, 1 H, *J* 7.3 Hz, H-1), 3.84 (dd, 1 H, *J* 3.7 and 1.2 Hz, H-4, shifted to δ 5.45 on acetylation), 3.62 (dd, AB-type, 1 H, *J* 9.5 and 7.8 Hz, H-2), 3.56 (bt, 1 H, *J* 6.6 Hz, H-5), 3.55 (s, 3 H, MeO), 3.48 (dd, AB-type, 1 H, *J* 9.5 and 3.8 Hz, H-3), 2.03–1.65 (m, 15 H, the adamantoyl residue).

Anal. Calc. for $C_{32}H_{40}O_7$: C, 71.6; H, 7.5. Found: C, 71.9; H, 7.4.

Methyl 2,3-di-O-benzyl-4-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-6-O-toluene-p-sulfonyl-β-D-galactopyranoside (**12**). — Treatment of **10** (200 mg, 0.379 mmol) with 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl chloride (~0.758 mmol), as described for **6**, gave, after column chromatography (ethyl acetate–heptane, 1:4), **12** (262 mg, 66%), as a syrup, $[\alpha]_D^{25}$ +38° (*c* 0.6, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 4.89 (d, 1 H, *J* 3.4 Hz, H-1′), 4.22 (d, 1 H, *J* 7.1 Hz, H-1), 3.51 (s, 3 H, MeO), 3.37 (dd, 1 H, *J* 10.0 and 2.9 Hz, H-3 or H-3′), 3.21 (dd, 1 H, *J* 8.5 and 4.9 Hz, H-5 or H-5′), 2.37 (s, 3 H, PhCH_3).

Anal. Calc. for $C_{62}H_{66}O_{13}S$: C, 70.8; H, 6.3. Found: C, 71.6; H, 6.5.

Methyl 2,3-di-O-benzyl-4-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-β-D-galactopyranoside (**13**). — Treatment of **11** (658 mg, 1.23 mmol) with 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl chloride (~2.46 mmol), as described for **6**, gave, after column chromatography (ethyl acetate–heptane, 1:6), impure methyl 6-*O*-adamantoyl-2,3-di-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-β-D-galactopyranoside (875 mg), which was dissolved in dichloromethane–methanolic 0.2M sodium methoxide (1:1, 18 mL). The solution was boiled under reflux for 21 h, neutralised with acetic acid (108 μL), and concentrated. Column chromatography (ethyl acetate–heptane, 2:3) of the residue gave **13** (562 mg, 51%), as a syrup, $[\alpha]_D^{25}$ +36° (*c* 0.7, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.04 (d, 1 H, *J* 2.9 Hz, H-1′), 4.29 (bt, 1 H, *J* 6.6 Hz, H-5′), 4.23 (d, 1 H, *J* 7.6 Hz, H-1), 3.62 (dd, 1 H, *J* 9.7 and 7.6 Hz, H-2), 3.54 (s, 3 H, MeO).

Anal. Calc. for $C_{55}H_{60}O_{11}$: C, 73.6; H, 6.7. Found: C, 74.1; H, 6.6.

Methyl 2,3-di-O-benzyl-6-O-methyl-4-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-β-D-galactopyranoside (**14**). — Sodium hydride (50% in oil; 224 mg,

4.74 mmol) was dissolved (sonication, 18 h) in methyl sulfoxide (8 mL) under nitrogen at room temperature[10]. Compound **13** (156 mg, 0.174 mmol) was then added and, after stirring for 3 h, iodomethane (592 μL, 9.48 mmol). After 3 h at room temperature, the solution was diluted with ethyl ether (30 mL), washed with water (3 × 10 mL), dried, and concentrated. Column chromatography (ethyl acetate–heptane, 1:3) of the residue gave **14** (136 mg, 86%), as a syrup, $[\alpha]_D^{25}$ +61° (*c* 0.8, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 4.98 (d, 1 H, *J* 2.7 Hz, H-1′), 4.42 (dd, 1 H, *J* 9.2 and 5.5 Hz, H-6 or H-6′), 4.25 (d, 1 H, *J* 7.5 Hz, H-1), 3.99 (d, 1 H, *J* 2.7 Hz, H-4 or H-4′), 3.66 (dd, 1 H, *J* 9.8 and 7.5 Hz, H-2), 3.58 (s, 3 H, 1-OMe), 3.55 (bt, 1 H, *J* 8.5 Hz, H-5 or H-5′), 3.25 (dd, 1 H, *J* 8.7 and 5.0 Hz, H-6 or H-6′), 3.12 (s, 3 H, 6-OMe).

Anal. Calc. for $C_{56}H_{62}O_{11}$: C, 73.8; H, 6.9. Found: C, 73.5; H, 6.6.

*Methyl 4-*O*-α-*D*-galactopyranosyl-6-*O*-methyl-β-*D*-galactopyranoside* (**15**). — Debenzylation of **14** (129 mg, 0.142 mmol), as described for **7**, and freeze-drying gave amorphous **15** (50 mg, 96%), $[\alpha]_D^{25}$ +90° (*c* 0.8, water). ^{1}H-N.m.r. data (D_2O): δ 4.90 (d, 1 H, *J* 3.4 Hz, H-1′), 4.35 (d, 1 H, *J* 7.8 Hz, H-1), 4.34 (bt, 1 H, *J* 6.8 Hz, H-5′), 4.01 (bd, 1 H, *J* 2.4 Hz, H-4′), 3.98 (d, 1 H, *J* 3.2 Hz, H-4), 3.55 (s, 3 H, 1-OMe), 3.51 (dd, 1 H, *J* 10.4 and 7.9 Hz, H-2), 3.40 (s, 3 H, 6-OMe).

*Methyl 3,6-anhydro-2-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-galactopyranosyl)-β-*D*-galactopyranoside*[12] (**16**). — (*a*) A solution of **12** (50 mg, 48 μmol) in M lithium triethylborohydride[11] in tetrahydrofuran (1.25 mL) was boiled under reflux for 20 h, then diluted with dichloromethane (10 mL), washed with saturated aqueous sodium hydrogencarbonate (5 mL) and water (5 mL), dried, and concentrated. Column chromatography (ethyl acetate–heptane, 1:4) of the residue gave **16**[12] (22 mg, 59%).

(*b*) A solution of **12** (50 mg, 48 μmol) and sodium iodide (126 mg, 0.90 mmol) in *N,N*-dimethylformamide (1 mL) was boiled under reflux for 20 h, then diluted with ethyl ether (10 mL), washed with water (5 mL), aqueous sodium thiosulfate (5 mL), and water (5 mL), dried, and concentrated. Column chromatography of the residue, as above, gave **16**[12] (25 mg, 67%).

(*c*) A mixture of **13** (50 mg, 56 μmol), triphenylphosphine (44 mg, 170 μmol), imidazole (11 mg, 170 μmol), iodine (28 mg, 110 μmol), and toluene (2 mL) was heated for 2 h at 80° (ref. 9). The mixture was diluted with toluene (8 mL), washed with saturated aqueous sodium hydrogencarbonate (5 mL) and water (5 mL), dried, and concentrated. Column chromatography of the residue, as above, gave **16**[12] (26 mg, 59%).

*Methyl 2,3-di-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-galactopyranosyl)-β-*D*-galactopyranoside* (**18**). — Methanolic M sodium methoxide (2.8 mL) was added to a solution of methyl 2,3,6-tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-β-D-galactopyranoside[5] (**17**; 2.83 g, 2.75 mmol) in dichloromethane–methanol (1:3, 56 mL) at 0°. The reaction was monitored by t.l.c. and was terminated after 3 h by addition of acetic acid (170 μL, 2.8 mmol). The solution was concentrated and the residue was subjected to column chromatography (ethyl

acetate–heptane, 1:2) to give **18** (936 mg, 37%), as a syrup. Starting material **17** (909 mg, 32%) was recovered and debenzoylated, as above, to give more **18** (303 mg, 12%), thus raising the total yield of **18** to 1.24 g (49%). Compound **18** had $[\alpha]_D^{25}$ +87° (*c* 0.7, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.63 (dd, 1 H, *J* 10.3 and 7.8 Hz, H-2), 5.31 (dd, 1 H, *J* 10.3 and 2.6 Hz, H-3), 4.74 (d, 1 H, *J* 3.2 Hz, H-1′), 4.58 (d, 1 H, *J* 7.8 Hz, H-1), 4.35 (bd, 1 H, *J* 2.4 Hz, H-4), 4.09 (dd, AB-type, *J* 9.8 and 2.7 Hz, H-3′), 4.01 (dd, AB-type, *J* 9.8 and 3.2 Hz, H-2′), 3.50 (s, 3 H, MeO).

Anal. Calc. for $C_{55}H_{56}O_{13}$: C, 71.4; H, 6.1. Found: C, 71.8; H, 6.2.

*Methyl 2,3-di-*O*-benzoyl-6-deoxy-6-iodo-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-galactopyranosyl)-β-*D*-galactopyranoside* (**19**). — Triphenylphosphine (333 mg, 1.27 mmol), imidazole (121 mg, 1.78 mmol), and iodine (322 mg, 1.27 mmol) were added to a solution of **18** (470 mg, 0.508 mmol) in toluene (15 mL) at 80°. After 1 h, the mixture was diluted with toluene (25 mL) and the solid residue was dissolved in acetone (5 mL). The combined organic phases were washed with saturated aqueous sodium hydrogencarbonate (10 mL) and water (10 mL), dried, and concentrated. Column chromatography (ethyl acetate–heptane, 1:4) of the residue gave **19** (480 mg, 91%), m.p. 143–145°, $[\alpha]_D^{25}$ +86° (*c* 0.7, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.68 (dd, 1 H, *J* 10.6 and 7.8 Hz, H-2), 5.15 (dd, 1 H, *J* 10.6 and 3.1 Hz, H-3), 4.92 (d, 1 H, *J* 3.4 Hz, H-1′), 4.59 (d, 1 H, *J* 7.8 Hz, H-1), 4.30 (bdd, 1 H, *J* 9.4 and 5.3 Hz, H-6′), 3.85 (bt, 1 H, *J* 7.0 Hz, H-5), 3.60 (dd, 1 H, *J* 10.3 and 6.4 Hz, H-6), 3.56 (s, 3 H, MeO), 3.44 (dd, 1 H, *J* 10.3 and 7.0 Hz, H-6), 3.38 (dd, 1 H, *J* 9.4 and 8.2 Hz, H-6′), 2.90 (dd, 1 H, *J* 8.2 and 5.3 Hz, H-5′).

Anal. Calc. for $C_{55}H_{55}IO_{12}$: C, 63.8; H, 5.4. Found: C, 63.8; H, 5.4.

*Methyl 2,3-di-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-galactopyranosyl)-β-*D*-fucopyranoside* (**20**). — Pd/C (10%, 100 mg) and triethylamine (70 μL, 0.50 mmol) were added to a solution of **19** (417 mg, 0.402 mmol) in ethyl acetate–ethanol (1:5, 12 mL). The mixture was hydrogenated for 30 min at atmospheric pressure, then filtered through Celite, and concentrated. A solution of the residue in dichloromethane (30 mL) was washed with water (10 mL), dried, and concentrated. Column chromatography (ethyl acetate–heptane, 1:4) of the residue gave **20** (352 mg, 96%), as a syrup, $[\alpha]_D^{25}$ +96° (*c* 0.9, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.72 (dd, 1 H, *J* 10.9 and 7.8 Hz, H-2), 5.22 (dd, 1 H, *J* 10.9 and 3.1 Hz, H-3), 4.91 (d, 1 H, *J* 3.4 Hz, H-1′), 4.59 (d, 1 H, *J* 7.8 Hz, H-1), 4.35 (bdd, 1 H, *J* 9.4 and 5.0 Hz, H-6′), 4.18 (dd, AB-type, 1 H, *J* 10.2 and 2.7 Hz, H-3′), 4.04 (dd, AB-type, 1 H, *J* 10.2 and 3.4 Hz, H-2′), 3.84 (q, 1 H, *J* 6.3 Hz, H-5), 3.53 (s, 3 H, MeO), 3.40 (t, 1 H, *J* 8.9 Hz, H-6′), 3.06 (dd, 1 H, *J* 8.6 and 5.1 Hz, H-5′), 1.42 (d, 3 H, *J* 6.3 Hz, H-6).

Anal. Calc. for $C_{55}H_{56}O_{12}$: C, 72.7; H, 6.2. Found: C, 72.8; H, 6.4.

*Methyl 4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-galactopyranosyl)-β-*D*-fucopyranoside* (**21**). — A solution of **20** (290 mg, 0.320 mmol) in dichloromethane–methanolic 0.1M sodium methoxide (1:1, 8 mL) was stirred for 12 h at room temperature, then neutralised with acetic acid (25 μL), and concentrated. Column chromatography

(ethyl acetate–heptane, 7:3) of the residue gave **21** (191 mg, 85%), as a syrup, $[\alpha]_D^{25}$ +29.5° (*c* 0.3, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 4.94 (d, 1 H, *J* 3.4 Hz, H-1′), 4.11 (d, 1 H, *J* 7.3 Hz, H-1), 3.86 (bs, 1 H, H-4 or H-4′), 3.64 (bq, 1 H, *J* 6.2 Hz, H-5), 3.54 (s, 3 H, MeO), 3.43 (dd, AB-type, 1 H, *J* 10.0 and 7.3 Hz, H-2), 3.34 (dd, AB-type, 1 H, *J* 10.0 and 2.6 Hz, H-3), 3.27 (dd, 1 H, *J* 10.0 and 3.4 Hz, H-2′), 1.36 (d, 3 H, *J* 6.2 Hz, H-6).

Anal. Calc. for $C_{41}H_{48}O_{10}$: C, 70.3; H, 6.9. Found: C, 69.9; H, 7.0.

*Methyl 4-*O*-α-*D*-galactopyranosyl-β-*D*-fucopyranoside* (**22**). — Debenzylation of **21** (141 mg, 0.201 mmol), as described for **7**, and column chromatography (dichloromethane–methanol, 5:1) of the residue gave, after freeze-drying, amorphous **22**[5] (57 mg, 83%), $[\alpha]_D^{25}$ +109° (*c* 0.7, water); lit.[5] $[\alpha]_D$ +105° (*c* 1, water). ^{1}H-N.m.r. data (D_2O): δ 5.01 (d, 1 H, *J* 3.9 Hz, H-1′), 4.40 (bt, 1 H, *J* 6.2 Hz, H-5′), 4.32 (d, 1 H, *J* 7.6 Hz, H-1), 4.02 (bd, 1 H, *J* 3.3 Hz, H-4′), 3.92 (dd, AB-type, 1 H, *J* 10.5 and 3.3 Hz, H-3′), 3.53 (s, 3 H, MeO), 3.47 (dd, 1 H, *J* 10.2 and 7.6 Hz, H-2), 1.34 (d, 3 H, *J* 6.6 Hz, H-6).

*Methyl 2,3-di-*O*-benzoyl-β-*D*-galactopyranoside*[15] (**24**). — Compound **23**[15] (1.00 g, 2.04 mmol) was added to a 1% (w/v) solution of iodine in methanol (20 mL) and the mixture was boiled under reflux for 6 h. Sodium thiosulfate (125 mg) was then added to the resulting clear solution[16], the mixture was concentrated, the residue was dissolved in ethyl acetate (50 mL), and the solution was washed with water (25 mL). The aqueous phase was extracted with ethyl acetate (50 mL), and the combined organic phases were dried and concentrated. Column chromatography (ethyl acetate–heptane, 1:1) of the residue gave **24** (815 mg, 99%), m.p. 81–82° (from $CHCl_3$), $[\alpha]_D^{25}$ +80° (*c* 0.6, chloroform); lit.[15] m.p. 80° (from $CHCl_3$), $[\alpha]_D$ +80.6°. ^{1}H-N.m.r. data ($CDCl_3$): δ 5.76 (dd, 1 H, *J* 10.2 and 8.0 Hz, H-2), 5.31 (dd, 1 H, *J* 10.2 and 3.2 Hz, H-3), 4.65 (d, 1 H, *J* 8.0 Hz, H-1), 4.41 (bd, 1 H, *J* 3.2 Hz, H-4), 4.05 (dd, AB-type, 1 H, *J* 11.5 and 5.4 Hz, H-6), 3.98 (dd, AB-type, 1 H, *J* 11.5 and 4.8 Hz, H-6), 3.79 (bt, 1 H, *J* 5.1 Hz, H-5), 3.55 (s, 3 H, MeO).

*Methyl 2,3-di-*O*-benzoyl-6-deoxy-6-fluoro-β-*D*-galactopyranoside* (**25**) *and methyl 2,3-di-*O*-benzoyl-4,6-dideoxy-4,6-difluoro-β-*D*-glucopyranoside* (**26**). — Diethylaminosulfur trifluoride[13] (DAST; 96 μL, 0.78 mmol) in dichloromethane (1 mL) was added to a solution of **24** (300 mg, 0.746 mmol) in dichloromethane (20 mL) at −75° under dry nitrogen. The solution was kept for 48 h at room temperature and then boiled under reflux for 5 h. Methanol (200 μL) was added at room temperature and, after 18 h, the solution was concentrated. Column chromatography (ethyl acetate–heptane, 1:3) of the residue gave **25** (162 mg, 54%) and **26** (37 mg, 12%). Compound **25** had m.p. 133–136° and $[\alpha]_D^{25}$ +101° (*c* 0.6, chloroform). N.m.r. data ($CDCl_3$): ^{1}H, δ 5.73 (dd, 1 H, *J* 10.4 and 7.9 Hz, H-2), 5.34 (dd, 1 H, *J* 10.4 and 3.4 Hz, H-3), 4.72 (dd, 2 H, *J* 46.6 and 5.9 Hz, H-6), 4.65 (d, 1 H, *J* 7.9 Hz, H-1), 4.36 (d, 1 H, *J* 3.4 Hz, H-4, shifted to δ 5.69 on acetylation), 4.04 (dtd, 1 H, *J* 12.4, 5.9, and 1.1 Hz, H-5), 3.56 (s, 3 H, MeO); ^{19}F, Φ 230 (td, *J* 45.8 and 12.2 Hz, F-6).

Anal. Calc. for $C_{21}H_{21}FO_7$: C, 62.4; H, 5.2. Found: C, 62.4; H, 5.4.

Compound **26** had m.p. 138–140°, $[\alpha]_D^{25}$ +72.5° (*c* 0.8, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 5.81 (dt, 1 H, *J* 14.3 and 9.3 Hz, H-3), 5.40 (ddd, 1 H, *J* 9.8, 7.8, and 0.6 Hz, H-2), 4.69 (d, 1 H, *J* 7.8 Hz, H-1), 3.88 (m, 1 H, H-5), 3.54 (s, 3 H, MeO); ^{13}C, δ 101.7 (s, C-1), 85.9 (dd, *J* 187.8 and 7.4 Hz, C-4), 80.5 (d, *J* 175.8 Hz, C-6), 72.7 (d, *J* 19.6 Hz, C-3), 72.4 (dd, *J* 23.8 and 18.4 Hz, C-5), 71.0 (d, *J* 8.2 Hz, C-2), 57.2 (s, OMe); ^{19}F, Φ 199.4 (dd, *J* 50.5 and 13.2 Hz, F-4), 234.1 (td, *J* 45.3 and 25.0 Hz, F-6).

Anal. Calc. for $C_{21}H_{20}F_2O_6$: C, 62.1; H, 5.0. Found: C, 62.0; H, 5.0.

Methyl 2,3-di-O-benzoyl-6-deoxy-6-fluoro-4-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-β-D-galactopyranoside (**30**). — Treatment of **25** (325 mg, 0.804 mmol) with 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl chloride (~1.69 mmol), as described for **6**, gave, after column chromatography (ethyl acetate–heptane, 1:4) of the crude product, **30** (647 mg, 87%), as a syrup, $[\alpha]_D^{25}$ +93° (*c* 1, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 5.72 (dd, 1 H, *J* 10.5 and 7.5 Hz, H-2), 5.21 (dd, 1 H, *J* 10.5 and 2.8 Hz, H-3), 4.83 (ddd, 1 H, *J* 45.3, 9.7, and 6.1 Hz, H-6), 4.63 (d, 1 H, *J* 7.5 Hz, H-1), 4.58 (ddd, 1 H, *J* 47.5, 9.6, and 6.6 Hz, H-6), 4.36 (bd, 1 H, *J* 2.8 Hz, H-4), 4.31 (bdd, 1 H, *J* 9.0 and 4.9 Hz, H-6′), 3.54 (s, 3 H, MeO), 3.41 (t, 1 H, *J* 9.0 Hz, H-6′), 3.01 (dd, 1 H, *J* 8.4 and 4.9 Hz, H-5′); ^{19}F, Φ 228.5 (td, *J* 45.5 and 14.0 Hz, F-6).

Anal. Calc. for $C_{55}H_{55}FO_{12}$: C, 71.3; H, 6.0. Found: C, 71.4; H, 6.4.

Methyl 6-deoxy-6-fluoro-4-O-α-D-galactopyranosyl-β-D-galactopyranoside (**31**). — A solution of **30** (619 mg, 0.668 mmol) in dichloromethane–methanolic 0.1M sodium methoxide (1:1, 10 mL) was stirred for 3.5 h at room temperature, then neutralised with Duolite (H^+) resin, filtered, and concentrated. The residue was dissolved in acetic acid (10 mL), Pd/C (10%, 450 mg) was added, and the mixture was hydrogenated for 5 h at atmospheric pressure, then filtered, and concentrated. A solution of the syrupy residue in water (20 mL) was washed with ethyl ether (20 mL) and freeze-dried to give crude **31** which was subjected to column chromatography (ethanol–dichloromethane, 1:3) to give, after freeze-drying, amorphous **31** (174 mg, 73%), $[\alpha]_D^{25}$ +112° (*c* 2, water). N.m.r. data (D_2O): ^1H, δ 4.89 (d, 1 H, *J* 3.6 Hz, H-1′), 4.40 (d, 1 H, *J* 7.8 Hz, H-1), 4.32 (bt, 1 H, *J* 6.5 Hz, H-5′), 4.05 (bd, 1 H, *J* 3.3 Hz, H-4), 4.01 (bd, 1 H, *J* 3.1 Hz, H-4′), 3.89 (dd, AB-type, 1 H, *J* 10.5 and 3.1 Hz, H-3′), 3.81 (dd, AB-type, *J* 10.5 and 3.6 Hz, H-2′), 3.56 (s, 3 H, MeO), 3.53 (dd, 1 H, *J* 10.0 and 7.8 Hz, H-2); ^{19}F, Φ 228 (td, *J* 45.7 and 11.3 Hz, F-6).

ACKNOWLEDGMENTS

We thank M. Levin for technical assistance. This work was supported by The Swedish Natural Science Research Council and The National Swedish Board for Technical Development.

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