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Synthesis of specifically monofluorinated ligands related to the O-polysaccharide of *Shigella dysenteriae* type 1 †

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Abstract

The synthesis is reported of galactopyranose nucleophiles monofluorinated at positions 3, 4, or 6 and protected by 4,6-*O*-benzylidene, 3,6-di-*O*-benzyl, or 3,4-*O*-isopropylidene groups, respectively. The condensation of these nucleophiles with 2,3,4-tri-*O*-benzoyl-α-L-rhamnosyl bromide gave, after deprotection, the disaccharide analogues of methyl *O*-α-L-rhamnopyranosyl-(1 → 2)-α-D-galactopyranoside, monofluorinated at position 3, 4, or 6 of the galactoside residue.

1. Introduction

Shigella dysenteriae type 1 is the most virulent of the bacteria referred to as Shigella [2]. It causes dysentery in humans with a high incidence of mortality, particularly in the developing countries [3–6]. It has been suggested that serum antibodies to the bacterium's O-specific polysaccharide (O-SP) might be protective against Shigellosis [7]. An understanding of the interaction of the antigenic determinant of the O-SP and its homologous antibodies is expected to provide the structural criteria for the design of a synthetic vaccine.

The repeating unit of the O-SP is the heterotetrasaccharide **I** [8,9]. Recently this laboratory identified fragment **II** as the immunodeterminant for a monoclonal IgM

† Part 8 of the series Synthesis of ligands related to the O-specific antigen of *Shigella dysenteriae* type 1. For part 7 see ref. 1.

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[10]. Among the monosaccharide units, the galactopyranosyl residue had the highest affinity for the antibody.

3)-α-D-Glc*p*NAc-(1 → 3)-α-L-Rha*p*-(1 → 3)-α-L-Rha*p*-(1 → 2)-α-D-Gal*p*-(1 →
(I)

3)-α-L-Rha*p*-(1 → 2)-α-D-Gal*p*-(1 →
(II)

It is generally accepted that hydrogen bonding plays an important role in the recognition of carbohydrates by proteins in general and by immunoglobulins in particular [11,12]. To determine the possible involvement of the individual hydroxyl groups of the galactopyranosyl residue in the binding of **II**, specifically deoxygenated and fluorinated fragments of that ligand are required as probes. The evaluation of the different contributions to the binding energy might then suggest further modifications needed for the design of a better hapten. We have previously reported the synthesis of some monodeoxygenated methyl α-glycosides of **II** [13]. Here, we describe the preparation of analogues of methyl *O*-α-L-rhamnopyranosyl-(1 → 2)-α-D-galactopyranoside, deoxyfluorinated at position 3, 4, or 6 of the D-galactose moiety, namely compounds **24**, **27** and **30**, respectively.

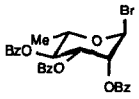
2. Results and discussion

The synthesis of the disaccharides **22**, **25**, and **28** was achieved by coupling the nucleophiles **9**, **18**, and **21** with the known [14] 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (**1**) using silver trifluoromethanesulfonate–*sym*-collidine as the promoter [15].

Initially, we focused on the introduction of a fluorine at C-3 of an appropriately protected methyl α-D-hexopyranoside precursor. Thus, the gulopyranosides **4** and **7**, bearing electron withdrawing and electron donating protecting groups, respectively, were prepared from the known galactopyranoside intermediates [13] **2** and **5**, via the keto derivatives **3** and **6**. In both cases, a mixture of 2 products (1:9, *galacto–gulo*) was obtained, from which the major compounds **4** and **7** were isolated (ca. 70%). However, the reaction of both **4** and **7** with diethylaminosulfur trifluoride [16] (DAST) resulted in complex mixtures *. An attempted two-step nucleophilic displacement with tris(dimethylamino)sulfur (trimethylsilyl)difluoride [17] (TAS-F) at C-3 of **4**, activated via a trifluoromethanesulfonate moiety, was still unsatisfactory *. Therefore, this approach was discontinued.

Preparation of methyl 3-deoxy-3-fluoro-α-D-galactopyranoside (**8**) from the glucofuranose precursor **10** was reported before [18] but the pure substance was not isolated. It was obtained, in admixture with the β anomer, upon treatment of 3-deoxy-3-fluoro-α-D-galactopyranose (**11**) with methanolic HCl. With the aim of improving the known preparation [18] of **8**, we made the intermediate **11**, as

* Unpublished results.



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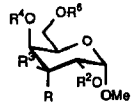
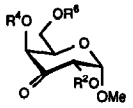
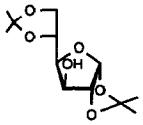


	R	R^2	R^3	R^4	R^6
2	H	Bz	OH	Bz	Bz
4	OH	Bz	H	Bz	Bz
5	H	Bn	OH	Bn	Bn
7	OH	Bn	H	Bn	Bn
8	H	H	F	H	H
9	H	H	F	- CHPh -	



	R^2	R^4	R^6
3	Bz	Bz	Bz
6	Bn	Bn	Bn



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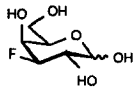
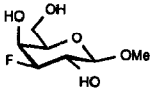


11



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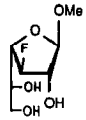
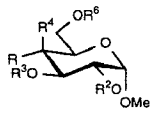


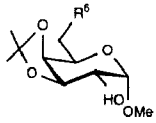
13

described [18,19], from the glucofuranose **10**. Methyl glycosidation of **11** afforded a mixture of four compounds (TLC), from which pure methyl 3-deoxy-3-fluoro-α-D-galactopyranoside (**8**) crystallized readily (62%). Chromatography of the mother liquor gave more **8**, as well as the hitherto unknown crystalline methyl 3-deoxy-3-fluoro-β-D-galactofuranoside (**13**), and the known [19] β-galactopyranoside **12**. The assignment of the β configuration to **13** was based on a comparison of the ^{13}C NMR data for the isolated compound with those [20] of methyl β-D-galactofuranoside and methyl α-D-galactofuranoside. Benzylidenation of **8** gave the nucleophile-acceptor [18] **9**, bearing a free hydroxyl group at C-2.

Previous studies [21,22] have shown that selective fluorination at position 4 of methyl α-D-glucopyranoside using DAST requires protection of the primary hydroxyl group. We have attempted to develop an efficient synthesis of the intermediate **18** from the alcohol [13] **15**. Despite a previous description [23] of fluorination at C-4 of glucopyranose with DAST, treatment * of a different substance (**15**)

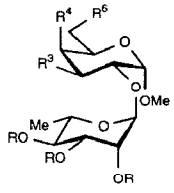


	R^2	R^3	R^4	R^6	R
14	H	H	H	- CHPhO -	
15	Bz	Bn	H	Bn	OH
16	Bz	Bn	H	Bn	OTf
17	Bz	Bn	F	Bn	H
18	H	Bn	F	Bn	H
19	H	H	F	H	H



	R^6
20	OH
21	F

Tf = triflyl (trifluoromethylsulfonyl)



	R	R^3	R^4	R^6
22	Bz	F	- OCH(Ph)O -	
23	Bz	F	OH	OH
24	H	F	OH	OH
25	Bz	OBn	F	OBn
26	Bz	OH	F	OH
27	H	OH	F	OH
28	Bz	- $OC(Me_2)O$ -		F
29	Bz	OH	OH	F
30	H	OH	OH	F

with this reagent gave complex mixtures. Therefore, as described for several preparations [17,24–26] of galactopyranosides fluorinated at C-4, a two-step process was chosen. Trifluoromethanesulfonate **16**, prepared from **15**, was treated in benzene with Amberlyst A-26 (F^- form) as the fluoride ion source [26–28] to give **17** (75% from **15**), together with partially deprotected **18** (9% from **15**). When **16** was treated [7] with TAS-F, the reaction proceeded slowly at room temperature but afforded **17** in high yield (88% from **15**). Thus, fluorination was found satisfactory with both reagents, but TAS-F is preferred to Amberlyst for the preparation of **17**, since no debenzoylation (**15**, **17** → **18**) occurs, and the use of benzene is obviated. Zemplén debenzoylation of **17** then gave the target nucleophile **18**. Lastly, hydrogenolysis of **18** afforded the deprotected monosaccharide [21,24,29] **19**.

The difficulty [30–32] of introducing a fluorine atom at position 6 of methyl α-D-galactopyranoside is known. However, we recently reported [1] an acceptable preparation of compound **21** in three steps from methyl α-D-galactopyranoside via the 3,4-*O*-isopropylidene precursor [33] **20** (45% overall yield).

Preparation of the 3-deoxy-3-fluoro, 4-deoxy-4-fluoro, and 6-deoxy-6-fluoro disaccharides (**24**, **27** *and* **30**).—Compounds **22**, **25**, and **28** were obtained following the protocol used for the preparation of the corresponding monodeoxygenated disac-

charides [13]. Thus, each of the nucleophiles **9**, **18**, and **21** was condensed with the acylated glycosyl donor **1** under base-deficient conditions [15] using silver trifluoromethanesulfonate as the promoter and *sym*-collidine as the acid scavenger. The reactions were somewhat slower than those involving the deoxygenated counterparts and a higher ratio of donor-to-acceptor, as well as longer reaction times, were necessary to achieve 85–90% yields of the coupling products. Deprotection of the fully protected disaccharides **22**, **25**, and **28** was performed by deacetalation of the galactopyranosyl residue via acid hydrolysis (**28** → **29**) or by hydrogenolysis (**22** → **23** and **25** → **26**), followed by Zemplén debenzoylation (**23** → **24**, **26** → **27**, and **29** → **30**). All three oligosaccharides, **24**, **27**, and **30**, were obtained crystalline, and their NMR spectra were consistent with their predicted structures.

3. Experimental

General methods.—Melting points were determined on a Kofler hot stage. Optical rotations were measured at 25° C with a Perkin–Elmer automatic polarimeter, Model 241 MC. TLC on precoated slides of Silica Gel G F254 (Analtech) was performed with solvent mixtures of appropriately adjusted polarity consisting of *A*, chloroform–methanol; *B*, hexane–EtOAc; *C*, hexane–acetone; *D*, toluene–acetone; *E*, toluene–EtOAc. Detection was effected by charring with 5% H_2SO_4 in EtOH and, when applicable, with UV light. Preparative chromatography was performed by elution from columns of Silica Gel 60 (particle size 0.04–0.063 mm). Unless stated otherwise, the NMR spectra were recorded at 25° C, for solutions in $CDCl_3$ on a Varian Gemini-300 spectrometer (300 MHz for ^1H, 75 MHz for ^{13}C) and on a Varian XL-300 spectrometer (282.2 MHz for ^{19}F). Internal references: for solutions in $CDCl_3$, C_6F_6 (0.00 ppm for ^{19}F), $CDCl_3$ (77.00 ppm for ^{13}C), and Me_4Si (0.00 ppm for ^1H); for solutions in D_2O or CD_3OD, CD_3OD (49.00 ppm for ^{13}C) and HOD (4.78 ppm for ^1H). Proton signal assignments were made by first-order analysis of the spectra, and were supported by homonuclear decoupling experiments. Of the two magnetically nonequivalent geminal protons at C-6, the one resonating at lower field is denoted H-6a and the one at higher field is denoted H-6b. The ^{13}C NMR assignments were made by two-dimensional ^{13}C–^1H correlation spectroscopy (HETCOR) and, when necessary, by comparison with the spectra of related substances. Interchangeable assignments are marked with an asterisk. Low resolution chemical ionization mass spectra (CIMS) were obtained using NH_3 as the ionizing gas. Reactions requiring anhydrous conditions were performed under nitrogen or argon. Before use, AgOTf was dried at 133 Pa/50° C for 1 h, CH_2Cl_2 was dried over Drierite. Solutions in organic solvents were dried with anhydrous sodium sulfate, and concentrated at 2 kPa/40° C. TAS-F purchased from Aldrich was used as supplied.

Methyl 2,4,6-tri-O-benzoyl-α-D-gulopyranoside (**4**).—Acetic acid was added slowly, at 0° C, to a stirred suspension of the known [13] methyl 2,4,6-tri-*O*-benzoyl-α-D-galactopyranoside (**2**, 775 mg, 1.5 mmol), pyridinium dichromate (864 mg, 2.3

mmol), and powdered 4A molecular sieves (1.2 g) in CH_2Cl_2 (15 mL). Stirring was continued at room temperature for 4.5 h, when TLC (solvent *D*, 9:1) showed complete disappearance of the starting material. EtOAc (50 mL) was added, the suspension was filtered through Celite, and the filtrate washed with EtOAc. The crude material was passed over Florisil to afford methyl 2,4,6-tri-*O*-benzoyl-α-D-*xylo*-hexopyranosid-3-ulose (**3**); ^{1}H NMR: δ 8.13–7.27 (m, 15 H, Ph), 6.05 (d, 1 H, $J_{1,2}$ 4.1 Hz, H-2), 5.66 (d, 1 H, $J_{4,5}$ 1.3 Hz, H-4), 5.44 (d, 1 H, H-1), 4.73 (dd, overlapped, 1 H, $J_{5,6a}$ 6.6, $J_{6a,6b}$ 10.3 Hz, H-6a), 4.67 (m, overlapped, 1 H, H-5), 4.56 (dd, 1 H, $J_{5,6b}$ 5.1 Hz, H-6b), and 3.52 (s, 3 H, OMe); ^{13}C NMR: δ 192.79 (C-3), 165.75, 164.96, 164.68 (3 C=O), 133.81–128.28 (Ph), 100.61 (C-1), 76.19 (C-4), 74.37 (C-2), 69.83 (C-5), 61.96 (C-6), and 55.89 (OMe); CIMS: *m/z* 522 $[M + NH_4]^+$.

To a solution of the foregoing product **3** in MeOH (25 mL) was added portionwise sodium borohydride (434 mg, 11.42 mmol), and acetic acid (300 μL) to maintain the pH of the solution at 7–8. After 20 min, TLC (solvent *E*, 19:1) showed that no starting material remained and that two products were formed (1:9 *galacto–gulo*, ^{1}H NMR). The suspension was concentrated and the residue was taken up in EtOAc. Washing with water, 5% aq HCl, and satd aq NaCl, followed by chromatography (solvent *E*, 19:1) of the residue, afforded amorphous **4** (565 mg, 72.5%); $[\alpha]_D$ +63° (*c* 1.2, $CHCl_3$); ^{1}H NMR: δ 8.17–7.41 (m, 15 H, Ph), 5.53 (d, 1 H, $J_{3,4}$ 3.7 Hz, H-4), 5.38 (dd, 1 H, $J_{2,3}$ 3.7, $J_{1,2}$ 3.4 Hz, H-2), 5.24 (d, 1 H, H-1), 4.75 (bt, 1 H, H-5), 4.63 (dd, 1 H, $J_{5,6a}$ 7.3, $J_{6a,6b}$ 11.4 Hz, H-6a), 4.46 (dd, 1 H, $J_{5,6b}$ 5.3 Hz, H-6b), 4.36 (m, 1 H, H-3), 3.95 (d, 1 H, $J_{3,OH}$ 8.5 Hz, OH-3), and 3.54 (s, 3 H, OMe); ^{13}C NMR: δ 165.96, 165.56, 165.09 (3 C=O), 133.54–128.29 (Ph), 98.59 (C-1), 71.62 (C-4), 67.97 (C-2,3), 63.43 (C-5), 63.02 (C-6), and 56.23 (OMe); CIMS: *m/z* 524 $[M + NH_4]^+$. Anal. Calcd for $C_{28}H_{26}O_9$: C, 66.40; H, 5.17. Found C, 66.38; H, 5.22.

*Methyl 2,4,6-tri-*O*-benzyl-α-D-gulopyranoside* (**7**).—Compound **5** [13] (661 mg, 1.42 mmol) was treated with pyridinium dichromate (803 mg, 2.13 mmol), powdered 4A molecular sieves (1.13 g), and acetic acid (140 μL) in CH_2Cl_2 (12 mL). When TLC (solvent *D*, 9:1) showed complete disappearance of the starting material, conventional processing, as described for the preparation of **3**, gave crude methyl 2,4,6-tri-*O*-benzyl-α-D-*xylo*-hexopyranosid-3-ulose (**6**), ^{1}H NMR: δ 7.34–7.16 (m, 15 H, Ph), 5.01 (d, 1 H, $J_{1,2}$ 4.1 Hz, H-1), 4.80 (d, 1 H, *J* 12.8 Hz, CH_2Ph), 4.64 (d, 1 H, H-2), 4.55 (d, overlapped, 1 H, *J* 12.0 Hz, CH_2Ph), 4.51 (d, overlapped, 1 H, CH_2Ph), 4.45 (d, overlapped, 1 H, CH_2Ph), 4.41 (d, 1 H, *J* 12.2 Hz, CH_2Ph), 4.30 (d, 1 H, CH_2Ph), 4.15 (dt, 1 H, $J_{4,5}$ 1.6, $J_{5,6}$ 6.3 Hz, H-5), 3.87 (d, 1 H, H-4), 3.69 (d, 2 H, H-6a,6b), and 3.38 (s, 3 H, OMe); CIMS: *m/z* 480 $[M + NH_4]^+$.

Compound **6** was treated with sodium borohydride (410 mg, 10.79 mmol) and acetic acid (300 μL), as described for the preparation of **4**, to afford a mixture of two products (1:9 *galacto–gulo*, ^{1}H NMR). The suspension was concentrated and the residue was taken up in EtOAc. Workup, as described above, followed by chromatography (solvent *D*, 12:1), afforded **7** (430 mg, 65%) as a colorless oil; $[\alpha]_D$ +4.5° (*c* 1, $CHCl_3$); ^{1}H NMR: δ 7.38–7.18 (m, 15 H, Ph), 4.80 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1), 4.69 (d, 1 H, *J* 12.2 Hz, CH_2Ph), 4.57 (d, overlapped, 1 H, *J* 12.0 Hz,

CH_2Ph), 4.56 (d, 1 H, CH_2Ph), 4.51 (d, 1 H, J 11.9 Hz, CH_2Ph), 4.45 (d, 1 H, CH_2Ph overlapped), 4.44 (d, 1 H, CH_2Ph overlapped), 4.23 (m, 1 H, H-5), 4.12 (m, 1 H, H-3), 3.79 (bt, 1 H, $J_{2,3}$ 3.5 Hz, H-2), 3.65–3.49 (m, 4 H, H-4,6a,6b, OH-3), and 3.43 (s, 3 H, OMe); ^{13}C NMR: δ 138.00–127.32 (Ph), 99.40 (C-1), 77.33 (C-4), 73.37, 72.99, 70.72 (3 CH_2Ph), 71.54 (C-2), 69.16 (C-6), 66.46 (C-3), 65.08 (C-5), and 55.83 (OMe); CIMS: m/z 482 $[M + NH_4]^+$. Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found C, 72.19; H, 7.02.

*Methyl 3-deoxy-3-fluoro-α-*D*-galactopyranoside* (**8**) *and methyl 3-deoxy-3-fluoro-β-*D*-galactofuranoside* (**13**).—Acetyl chloride (590 μL) was added dropwise with stirring to cold (0° C) MeOH (84 mL). After 5 min, compound **11** [18,19] (4.39 g, 24.1 mmol) was added, and the solution was refluxed for 24 h. After cooling to room temperature the mixture was neutralized with Dowex-3 resin (OH^- form) and filtered. Concentration of the filtrate afforded a solid, which was washed with a little MeOH. The MeOH washings were saved (see below) and the residue was crystallized from EtOH to give pure **8** (2.93 g, 62%); mp 185–186° C; $[\alpha]_D$ +184° (*c* 1, H_2O); $[\alpha]_D$ +174° (*c* 1, MeOH) {lit. [18] mp 160–170° C (from EtOAc), $[\alpha]_D$ +150° (*c* 1, MeOH)}; ^1H NMR (D_2O): δ 4.86 (bt, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 4.68 (ddd, 1 H, $J_{3,F}$ 40.9, $J_{2,3}$ 9.5, $J_{3,4}$ 4.8 Hz, H-3), 4.21 (m, 1 H, H-4), 4.07 (ddd, 1 H, $J_{2,F}$ 11.6 Hz, H-2), 3.87 (bt, 1 H, $J_{5,6}$ 5.8 Hz, H-5), 3.73 (d, 2 H, H-6a,6b), and 3.38 (s, 3 H, OMe); ^{13}C NMR (D_2O): δ 100.52 (d, $J_{C,F}$ 10.5 Hz, C-1), 92.06 (d, $J_{C,F}$ 182.0 Hz, C-3), 71.07 (d, $J_{C,F}$ 6.3 Hz, C-5), 68.45 (d, $J_{C,F}$ 17.1 Hz, C-4), 67.82 (d, $J_{C,F}$ 18.4 Hz, C-2), 61.89 (d, $J_{C,F}$ 3.1 Hz, C-6), and 56.04 (OMe); ^{19}F NMR (D_2O): δ −40.48 (dddd, $J_{F,3}$ 49.3, $J_{F,2}$ 11.2, $J_{F,4}$ 5.7, $J_{F,1}$ 5.5 Hz, F-3); CIMS: m/z 214 $[M + NH_4]^+$. Anal. Calcd for $C_7H_{13}FO_5$: C, 42.86; H, 6.68; F, 9.68. Found C, 42.91; H, 6.84; F, 9.34.

The MeOH washings (*vide supra*) combined with the mother liquor were concentrated and chromatographed (solvent *D* 1.8:1), to afford first **13** (282 mg, 6%); mp 108–109° C (from EtOH); $[\alpha]_D$ −84.5° (*c* 1.2, H_2O); ^1H NMR (D_2O): δ 4.48 (s, 1 H, H-1), 4.42 (ddd, 1 H, $J_{3,F}$ 54.8, $J_{2,3}$ 1.9, $J_{3,4}$ 4.0 Hz, H-3), 3.80 (bd, overlapped, 1 H, $J_{2,F}$ 16.6 Hz, H-2), 3.78 (dt, overlapped, 1 H, $J_{4,F}$ 24.5, $J_{4,5}$ 4.6 Hz, H-4), 3.39 (dt, 1 H, $J_{5,6a}$ 6.8, $J_{5,6b}$ 4.2 Hz, H-5), 3.22 (d, 1 H, $J_{6a,6b}$ 11.8 Hz, H-6a), 3.14 (dd, 1 H, $J_{5,6b}$ 6.8 Hz, H-6b), 2.91 (s, 3 H, OMe); ^{13}C NMR (D_2O): δ 109.31 (d, $J_{C,F}$ 4.3 Hz, C-1), 98.33 (d, $J_{C,F}$ 182.4 Hz, C-3), 83.68 (d, $J_{C,F}$ 27.4 Hz, C-2), 79.09 (d, $J_{C,F}$ 25.3 Hz, C-4), 71.78 (d, $J_{C,F}$ 6.4 Hz, C-5), 63.36 (d, C-6), and 55.76 (OMe); ^{19}F NMR (D_2O): δ −25.99 (ddd, $J_{F,3}$ 53.0, $J_{F,4}$ 24.9, $J_{F,2}$ 16.5 Hz, F-3); CIMS: m/z 214 $[M + NH_4]^+$. Anal. Calcd for $C_7H_{13}FO_5$: C, 42.86; H, 6.68; F, 9.68. Found C, 42.81; H, 6.87; F, 9.42.

Eluted next was a mixture of products followed by an additional amount of **8** (380 mg, 8%, total yield of **8** 70%). The slowest moving product (90 mg, 2%) was identified as **12** by comparison of its ^{13}C NMR data with those reported [19], ^{19}F NMR (D_2O): δ −37.52 (ddd, $J_{F,3}$ 48.1, $J_{F,2}$ 13.1, $J_{F,4}$ 6.1 Hz, F-3).

*Methyl 4,6-*O*-benzylidene-3-deoxy-3-fluoro-α-*D*-galactopyranoside* (**9**).—*p*-Toluenesulfonic acid monohydrate (50 mg) was added to a solution of **8** (2.76 g, 14 mmol) in benzaldehyde dimethyl acetal (21 mL), and the mixture was stirred at room temperature for 3.5 h. Triethylamine (3.5 mL) and sodium carbonate were

added and stirring was continued for 30 min. The mixture was concentrated, the residue was taken up in CH_2Cl_2, and the solution was extracted with water, then shaken with ice-cold 5% aq CF_3CO_2H, to hydrolyze selectively the mixed acetal formed concurrently with **9**, until only one product was present (TLC, solvent *A*, 19:1). The organic phase was washed with water, dried and concentrated leaving a white solid which was chromatographed (solvent *D*, 5.2:1) to give **9** (3.71 g, 934%); mp 171–172° C (from EtOH); $[\alpha]_D$ +142° (*c* 1.1, $CHCl_3$) {lit. [18] mp 160–161° C (from EtOH–petroleum ether); $[\alpha]_D$ +144° (*c* 0.5, $CHCl_3$)}; ^{1}H NMR: δ 7.51–7.32 (m, 5 H, Ph), 5.56 (s, 1 H, C*H*Ph), 4.96 (t, 1 H, $J_{1,2}$ 4.1, $J_{1,F}$ 4.1 Hz, H-1), 4.70 (dd, 1 H, $J_{2,3}$ 9.8, $J_{3,4}$ 3.7, $J_{3,F}$ 48.7 Hz, H-3), 4.44 (dd, 1 H, $J_{4,F}$ 5.5 Hz, H-4), 4.33–4.22 (m, 2 H H-2,6a), 4.06 (d, 1 H, $J_{6a,6b}$ 13.4 Hz, H-6b), 3.67 (bs, 1 H, H-5), and 3.45 (s, 3 H, OMe); ^{13}C NMR: δ 137.44–126.26 (Ph), 100.88 (*C*HPh), 100.47 (d, $J_{C,F}$ 9.4 Hz, C-1), 89.63 (d, $J_{C,F}$ 189.7Hz, C-3), 74.59 (d, $J_{C,F}$ 15.9 Hz, C-4), 69.06 (C-6), 67.35 (d, $J_{C,F}$ 18.7 Hz, C-2), 62.35 (d, $J_{C,F}$ 5.8 Hz, C-5), and 55.80 (OMe); ^{19}F NMR: δ −46.63 (m, $J_{F,3}$ 48.6, $J_{F,4}$ 5.5 Hz, F-3); CIMS: *m/z* 302 $[M + NH_4]^+$, 285 $[M + H]^+$. Anal. Calcd for $C_{14}H_{17}FO_5$: C, 59.14; H, 6.03; F, 6.68. Found C, 59.13; H, 6.21; F, 6.62.

*Methyl 2-O-benzoyl-3,6-di-O-benzyl-4-deoxy-4-fluoro-α-*D*-galactopyranoside* (**17**). —(*a*) Trifluoromethanesulfonic anhydride (4.47 mL, 26.5 mmol) was added dropwise, at −25° C, to a stirred solution of methyl 2-*O*-benzoyl-3,6-di-*O*-benzyl-α-D-glucopyranoside [13] (**15**, 3.15 g, 6.6 mmol) and pyridine (7 mL, 86.5 mmol) in CH_2Cl_2 (33 mL). The cooling bath was removed, and the mixture was stirred for 1 h at room temperature. The solution was successively washed with cold water and satd aq NaCl, dried, and concentrated to give triflate **16**, ^{1}H NMR: δ 8.04–7.14 (m, 15 H, Ph), 5.17–5.08 (m, 3 H, H-1,2,4), 4.85 (d, 1 H, *J* 10.3 Hz, OC*H*$_2$Ph), 4.77 (d, 1 H, OC*H*$_2$Ph), 4.63 (d, 1 H, *J* 11.8 Hz, OC*H*$_2$Ph), 4.55 (d, 1 H, OC*H*$_2$Ph), 4.32 (t, 1 H, $J_{2,3}$ 9.3, $J_{3,4}$ 9.3 Hz, H-3), 4.08 (bdt, 1 H, $J_{4,5}$ ~ 10.0 Hz, H-5), 3.78 (dd, 1 H, $J_{5,6a}$ 2.2, $J_{6a,6b}$ 11.2 Hz, H-6a), 3.72 (dd, 1 H, $J_{5,6b}$ 3.6 Hz, H-6b), and 3.40 (s, 3 H, OMe); ^{13}C NMR: δ 165.26 (C=O), 137.36–127.54 (Ph), 96.87 (C-1), 81.31 (C-4), 76.79 (C-3), 75.31 (*C*H$_2$OPh), 74.01 (C-2), 73.69 (*C*H$_2$OPh), 67.97 (C-5), 67.55 (C-6), and 55.78 (OMe); CIMS: *m/z* 628 $[M + NH_4]^+$.

A solution of the crude **16** in benzene (10 mL) was added to a suspension of Amberlyst A-26 resin (F^- form, 50 g) in benzene (500 mL), the resin and solvent having been dried overnight in a Soxhlet extractor containing activated 3A molecular sieves. The mixture was stirred at 80° C for 1.5 h, then allowed to come back to room temperature and filtered. The washings were combined with the filtrates and concentrated. Chromatography of the residue (solvent *B*, 5.6:1 → 3:1) gave first **17** (2.35 g, 75%); $[\alpha]_D$ +108° (*c* 1.1, $CHCl_3$); ^{1}H NMR: δ 8.09–7.28 (m, 15 H, Ph), 5.44 (dd, 1 H, $J_{1,2}$ 3.1, $J_{2,3}$ 10.4 Hz, H-2), 5.13 (d, 1 H, H-1), 4.98 (bd, 1 H, $J_{4,F}$ 50.1 Hz, H-4), 4.77 (d, 1 H, *J* 12.1 Hz, OC*H*$_2$Ph), 4.70 (d, 1 H, OC*H*$_2$Ph), 4.63 (d, 1 H, *J* 12.1 Hz, OC*H*$_2$Ph), 4.59 (d, 1 H, OC*H*$_2$Ph), 4.06 (ddd, 1 H, $J_{3,4}$ 2.2 Hz, H-3), 4.00 (bdt, 1 H, H-5), 3.78 (dd, 1 H, $J_{5,6a}$ 7.3, $J_{6a,6b}$ 9.3 Hz, H-6a), 3.71 (dd, 1 H, $J_{5,6b}$ 6.3 Hz, H-6b), and 3.38 (s, 3 H, OMe); ^{13}C NMR: δ 165.70 (C=O), 137.63–127.51 (Ph), 97.35 (C-1), 86.72 (d, $J_{C,F}$ 184.3 Hz, C-4), 73.69 (OCH_2Ph), 73.48 (d, $J_{C,F}$ 18.2 Hz, C-3), 72.03 (OCH_2Ph), 70.67 (C-2), 68.00 (d, $J_{C,F}$ 10.6 Hz, C-5), 67.85

(C-6), and 55.58 (OMe); ^{19}F NMR: δ −57.57 (dt, $J_{F,4}$ 50.1, $J_{F,3}$ 28.3, $J_{F,5}$ 28.3 Hz, F-4); CIMS: m/z 498 $[M + NH_4]^+$. Anal. Calcd for $C_{28}H_{29}FO_6$: C, 69.98; H, 6.08; F, 3.95. Found: C, 69.82; H, 6.08; F, 3.61.

Eluted next was **18** (231 mg, 9.4%) identical with the material described below.

(*b*) To a solution of crude **16**, prepared from **15** (1 g, 2.1 mmol) as described above, in CH_2Cl_2 (15 mL) stirred at −20° C, was added portionwise TAS-F (1 g, 3.6 mmol). Cooling was removed when the temperature of the bath reached 10° C, and stirring was continued for 24 h. Since some starting material still remained, more TAS-F (600 mg, 2.2 mmol) was added. The solution was kept at room temperature for another 16 h. TLC (solvent *B*) showed the presence of one major and one minor product. Concentration and chromatography (solvent *B*, 5.6:1) gave **17** (887 mg, 88%), identical with that prepared by method *a*.

Methyl 3,6-di-O-benzyl-4-deoxy-4-fluoro-α-D-galactopyranoside (**18**).—(*a*) Zemplén debenzoylation of **17** (2.15 g, 5.76 mmol) gave **18** in a virtually theoretical yield.

(*b*) Compound **15** (1 g, 2.1 mmol) was treated with trifluoromethanesulfonic anhydride as described for the preparation of **16**. After conventional processing, the residue was dissolved in benzene and treated with Amberlyst A-26 resin (F^- form, 10 g), as described for the preparation of **17**. When no starting material remained the suspension was filtered and the filtrate was concentrated. The residue was taken up in MeOH (10 mL), and the solution was made strongly alkaline by the addition of M sodium methoxide. When the reaction was complete (TLC, solvent *B*), the solution was worked up as usual. The residue was chromatographed to give **18** (654 mg, 87%); mp 98–99° C (from acetone–diisopropyl ether); $[\alpha]_D$ +102° (*c* 1.1, $CHCl_3$); ^{1}H NMR: δ 7.42–7.26 (m, 10 H, Ph), 4.89 (dd, overlapped, 1 H, $J_{4,F}$ 50.0, $J_{3,4}$ 2.4 Hz, H-4), 4.87 (d, overlapped, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.79 (d, overlapped, 1 H, J 11.7 Hz, OCH_2Ph), 4.69 (d, 1 H, OCH_2Ph), 4.60 (d, 1 H, J 11.9 Hz, OCH_2Ph), 4.55 (d, 1 H, OCH_2Ph), 4.07 (ddd, 1 H, $J_{2,3}$ 10.1 Hz, H-2), 3.90 (bdt, 1 H, $J_{5,F}$ 29.3, $J_{5,6}$ 6.6 Hz, H-5), 3.74–3.61 (m, 3 H, H-3,6a,6b), 3.44 (s, 3 H, OMe), and 2.19 (d, 1 H, $J_{OH,2}$ 6.8 Hz, OH-2); ^{13}C NMR: δ 137.67–127.63 (Ph), 99.37 (C-1), 85.67 (d, $J_{C,F}$ 183.2 Hz, C-4), 76.43 (d, $J_{C,F}$ 20.2 Hz, C-3), 73.63 (OCH_2Ph), 71.76 (OCH_2Ph), 68.44 (C-2), 68.29 (d, $J_{C,F}$ 22.4 Hz, C-5), 67.96 (d, $J_{C,F}$ 5.5 Hz, C-6), and 55.60 (OMe); ^{19}F NMR: δ −58.00 (dt, $J_{F,4}$ 50.2, $J_{F,3} = J_{F,5}$ = 28.8 Hz, F-4); CIMS: m/z 376 $[M + NH_4]^+$. Anal. Calcd for $C_{21}H_{25}FO_5$: C, 67.00; H, 6.69; F, 5.05. Found: C, 66.91; H, 6.74; F, 5.00.

Methyl 4-deoxy-4-fluoro-α-D-galactopyranoside (**19**).—A mixture of **18** (435 mg, 1.2 mmol) and 10% Pd–C catalyst (200 mg) in 1:8 acetone–EtOH (15 mL) was stirred overnight under hydrogen at atmospheric pressure. Conventional processing afforded **19** (228 mg, 96%); mp 103–104° C (from acetone); $[\alpha]_D$ +162° (*c* 0.9, H_2O); $[\alpha]_D$ +143° (*c* 0.8, MeOH) {lit. [21] mp 120–122.5° C (from EtOAc), $[\alpha]_D$ +144.5° (*c* 1.7, MeOH); lit. [29] mp 99–101° C (from MeOH–EtOAc), $[\alpha]_D$ +148° (*c* 1, MeOH)}.

Methyl O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-(1 → 2)-4,6-O-benzylidene-3-deoxy-3-fluoro-α-D-galactopyranoside (**22**).—A solution of **9** (852 mg, 3.0 mmol), **1** (Ref. 14, 2.26 g, 4.2 mmol), and *sym*-collidine (498 μL, 3.7 mmol) in CH_2Cl_2 (20

mL) was added with stirring at −20° C to a suspension of AgOTf (1.23 g, 4.8 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at −20° C for 10 min, at which time it was slightly acidic. After stirring at room temperature for 1 h, the suspension was cooled to −20° C, more **1** (600 mg, 1.1 mmol) and AgOTf (240 mg, 0.8 mmol) were added, stirring was continued for 1 h, and then for 30 min at room temperature. TLC (solvent *C*) showed that little starting material remained, and that one major product was formed. *sym*-Collidine (500 μL, 3.7 mmol) was added, the mixture was filtered through Celite, and the filtrate was washed with a mixture of aq 5% $NaHCO_3$ and 5% $Na_2S_2O_3$, then with water. Evaporation of water from the residue was followed by azeotroping with toluene to remove the excess of *sym*-collidine and water, respectively. Chromatography (solvent *C*, 3.5:1) gave amorphous **22** (2 g, 90%); $[\alpha]_D$ +158° (*c* 1.1, $CHCl_3$); ^{1}H NMR: δ 8.08–7.20 (m, 20 H, Ph), 5.89 (dd, 1 H, $J_{2',3'}$ 3.0, $J_{3',4'}$ 10.0 Hz, H-3'), 5.75 (bd, 1 H, H-2'), 5.64 (t, 1 H, $J_{4',5'}$ 10.1 Hz, H-4'), 5.56 (s, 1 H, C*H*Ph), 5.22 (d, 1 H, $J_{1',2'}$ 1.9 Hz, H-1'), 5.07 (m, overlapped, 1 H, H-1), 5.01 (ddd, overlapped, 1 H, $J_{2,3}$ 9.8, $J_{3,4}$ 3.8, $J_{3,F}$ 48.5 Hz, H-3), 4.50 (bt, 1 H, $J_{4,F}$ 4.7 Hz, H-4), 4.37 (ddd, overlapped, 1 H, $J_{1,2}$ 3.5, $J_{2,F}$ 10.2 Hz, H-2), 4.31 (d, overlapped, 1 H, $J_{6a,6b}$ 12.5 Hz, H-6a), 4.29 (m, overlapped, 1 H, H-5'), 4.12 (dd, 1 H, $J_{5,6b}$ 1.5 Hz, H-6b), 3.72 (bs, 1 H, H-5), 3.48 (s, 3 H, OMe), 1.34 (d, 3 H, $J_{5',6'}$ 6.4 Hz, H-6'); ^{13}C NMR: δ 165.91, 165.59, 165.44 (3 C=O), 137.37–126.23 (Ph), 100.80 (*C*HPh), 100.07 (d, $J_{C,F}$ 9.6 Hz, C-1), 100.00 (C-1'), 87.42 (d, $J_{C,F}$ 191.7 Hz, C-3), 75.18 (d, $J_{C,F}$ 17.2 Hz, C-2), 74.77 (d, $J_{C,F}$ 16.0 Hz, C-4), 71.90 (C-4'), 70.59 (C-2'), 69.70 (C-3'), 69.05 (C-5'), 67.17 (d, $J_{C,F}$ 2.9 Hz, C-6), 61.99 (d, $J_{C,F}$ 5.6 Hz, C-5), 55.59 (OMe), and 17.69 (C-6'); ^{19}F NMR: δ −45.88 (m, $J_{F,3}$ 48.4 Hz, F-3); CIMS: *m/z* 760 $[M + NH_4]^+$. Anal. Calcd for $C_{41}H_{39}FO_{12}$: C, 66.30; H, 5.29; F, 2.56. Found C, 66.56; H, 5.44; F, 2.36.

Methyl O-*(2,3,4-tri-*O*-benzoyl-α-*L*-rhamnopyranosyl)-(1 → 2)-3-deoxy-3-fluoro-α-*D*-galactopyranoside* (**23**).—A mixture of amorphous **22** (2.1 g, 2.89 mmol) and 10% Pd–C (400 mg) in 1:5 acetone–EtOH (50 mL) was stirred overnight in a hydrogen atmosphere at atmospheric pressure. Conventional workup followed by chromatography (solvent *C*, 2.1:1) afforded **23** (1.70 g, 92%); $[\alpha]_D$ +166° (*c* 1, $CHCl_3$); ^{1}H NMR: δ 8.10–7.21 (m, 15 H, Ph), 5.89 (dd, 1 H, $J_{2',3'}$ 3.4, $J_{3',4'}$ 10.2 Hz, H-3'), 5.75 (dd, 1 H, $J_{1',2'}$ 1.8 Hz, H-2'), 5.66 (t, 1 H, $J_{4',5'}$ 10.0 Hz, H-4'), 5.21 (d, 1 H, H-1'), 5.07 (d, overlapped, 1 H, $J_{1,2}$ 4.2 Hz, H-1), 4.91 (ddd, overlapped, 1 H, $J_{2,3}$ 8.6, $J_{3,4}$ 3.5, $J_{3,F}$ 49.4 Hz, H-3), 4.37–4.23 (m, 3 H, H-2, 4, 5'), 4.01–3.85 (m, 3 H, H-6a,6b,5), 3.45 (s, 3 H, OMe), 3.01 (s, 1 H, OH-4), 2.50 (dd, 1 H, $J_{OH,6a}$ 4.3, $J_{OH,6b}$ 7.4 Hz, OH-6), and 1.35 (d, 3 H, $J_{5',6'}$ 6.1 Hz, H-6'); ^{13}C NMR: δ 165.93, 165.62 (3 C=O), 133.56–128.32 (Ph), 99.48 (C-1'), 99.47 (d, $J_{C,F}$ 9.5 Hz, C-1), 87.42 (d, $J_{C,F}$ 184.5 Hz, C-3), 75.55 (d, $J_{C,F}$ 17.2 Hz, C-2), 71.80 (C-4'), 70.68 (C-2'), 69.70 (C-3'), 74.77 (d, $J_{C,F}$ 17.0 Hz, C-4), 68.53 (d, $J_{C,F}$ 5.4 Hz, C-5), 67.21 (C-5'), 62.68 (bs, C-6), 55.34 (OMe), and 17.66 (C-6'); ^{19}F NMR: δ −41.00 (m, $J_{F,3}$ 49.3, *J* 5.5 Hz, F-3); CIMS: *m/z* 672 $[M + NH_4]^+$. Anal. Calcd for $C_{34}H_{35}FO_{12}$: C, 62.38; H, 5.40; F, 2.90. Found C, 62.43; H, 5.46; F, 2.72.

Methyl O-*α-*L*-rhamnopyranosyl-(1 → 2)-3-deoxy-3-fluoro-α-*D*-galactopyranoside* (**24**).—Conventional debenzoylation (Zemplén) of **23** (1.24 g, 1.9 mmol) gave, after chromatography (solvent *A*, 4.5:1), disaccharide **24** (640 mg, 98%); mp 188–189° C

(from MeOH–EtOH); $[\alpha]_D$ +63° (*c* 1, H_2O); ^1H NMR (D_2O): δ 4.93 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 4.90 (bs, 1 H, H-1'), 4.75 (ddd, 1 H, $J_{3,4}$ 3.2, $J_{2,3}$ 9.5, $J_{3,F}$ 48.3 Hz, H-3, 4.66 (dd, 1 H, $J_{4,F}$ 7.4 Hz, H-4), 4.07 (d, 1 H, $J_{2,F}$ 10.9 Hz, H-2), 3.96 (dd, 1 H, $J_{2',3'}$ 3.3, $J_{1',2'}$ 1.5 Hz, H-2'), 3.84 (bt, 1 H, $J_{5,6}$ 5.9 Hz, H-5), 3.78–3.62 (m, 4 H, H-3',5',6a,6b), 3.40 (t, overlapped, 1 H, $J_{3',4'}$ 10.0, $J_{4',5'}$ 10.0 Hz, H-4'), 3.38 (s, overlapped, 3 H, OMe), and 1.27 (d, 3 H, $J_{5',6'}$ 6.2 Hz, H-6'); ^{13}C NMR (D_2O): δ 103.15 (C-1'), 99.98 (d, $J_{C,F}$ 10.3 Hz, C-1), 91.28 (d, $J_{C,F}$ 183.6 Hz, C-3), 75.39 (d, $J_{C,F}$ 17.5 Hz, C-2), 72.91 (C-4'), 71.09 (C-2'*), 71.04 (C-3'*), 70.99 (d, $J_{C,F}$ 8.1 Hz, C-5), 70.29 (C-5'), 68.58 (d, $J_{C,F}$ 16.7 Hz, C-4), 61.86 (d, $J_{C,F}$ 2.8 Hz, C-6), 55.90 (OMe), and 17.67 (C-6'); ^{19}F NMR (D_2O): δ −39.92 (m, $J_{F,3}$ 49.0, $J_{F,2}$ 11.4, $J_{F,4}$ 5.1 Hz, F-3); CIMS: *m/z* 360 $[M + NH_4]^+$. Anal. Calcd for $C_{13}H_{23}FO_9$: C, 45.61; H, 6.77; F, 5.55. Found C, 45.55; H, 6.70; F, 5.25.

Methyl O-*(2,3,4-tri-*O*-benzoyl-α-*L*-rhamnopyranosyl)-(1 → 2)-3,6-di-*O*-benzyl-4-deoxy-4-fluoro-α-*D*-galactopyranoside* (**25**).—A mixture of **18** (935 mg, 2.5 mmol), **1** (2.38 g, 4.41 mmol), and *sym*-collidine (520 μL, 3.95 mmol) in CH_2Cl_2 (25 mL) was treated with AgOTf (1.29 g, 5.0 mmol) in CH_2Cl_2 (10 mL) as described for the preparation of **22**. Further additions of **1** and AgOTf were also found necessary in order to drive the reaction to completion. After conventional workup, chromatography (solvent *B*, 4:1) gave **25** (2.56 g, 91.5%); mp 165–166° C (from EtOAc–hexane); $[\alpha]_D$ +121° (*c* 1.2, $CHCl_3$); ^1H NMR: δ 8.08–7.20 (m, 25 H, Ph), 5.89 (dd, 1 H, $J_{2',3'}$ 3.4, $J_{3',4'}$ 10.1 Hz, H-3'), 5.78 (dd, 1 H, $J_{1',2'}$ 1.8 Hz, H-2'), 5.65 (t, 1 H, $J_{4',5'}$ 10.0 Hz, H-4'), 5.26 (d, 1 H, H-1'), 4.94 (d, overlapped, 1 H, H-1), 4.87 (d, 1 H, *J* 12 Hz, CH_2OPh), 4.86 (dd, overlapped, 1 H, $J_{3,4}$ 2.7, $J_{4,F}$ 51.5 Hz, H-4), 4.76 (d, 1 H, CH_2OPh), 4.59 (d, 1 H, *J* 11.9 Hz, CH_2OPh), 4.54 (d, overlapped, 1 H, CH_2OPh), 4.30 (dq, 1 H, $J_{5',6'}$ 6.3 Hz, H-5'), 4.11 (dd, 1 H, $J_{2,3}$ 9.8, $J_{1,2}$ 3.6 Hz, H-2), 3.99–3.85 (m, 2 H, H-3,5), 3.69 (dd, 1 H, $J_{5,6a}$ 6.9, $J_{6a,6b}$ 9.6 Hz, H-6a), 3.45 (ddd, 1 H, $J_{5,6b}$ 6.6, $J_{6b,F}$ 1.0 Hz, H-6b), 3.45 (s, 3 H, OMe), 1.34 (d, 3 H, H-6'); ^{13}C NMR: δ 165.93, 165.62 (3 C=O), 138.00–127.80 (Ph), 100.02 (C-1'), 99.27 (C-1), 87.52 (d, $J_{C,F}$ 183.4 Hz, C-4), 77.16 (C-2), 74.75 (d, $J_{C,F}$ 17.8 Hz, C-3), 73.67 (CH_2OPh), 72.97 (CH_2OPh), 71.84 (C-4'), 70.60 (C-2'), 69.87 (C-3'), 68.06 (C-6*), 67.90 (d, $J_{C,F}$ 12.2 Hz, C-5), 67.22 (C-5'*), 55.39 (OMe), and 17.70 (C-6'); ^{19}F NMR: δ −58.00 (dt, $J_{F,4}$ 50.1, $J_{F,3}$ 28.8, $J_{F,5}$ 28.8 Hz, F-4); CIMS: *m/z* 852 $[M + NH_4]^+$. Anal. Calcd for $C_{48}H_{47}FO_{12}$: C, 69.05; H, 5.68; F, 2.26. Found C, 68.92; H, 5.65; F, 2.18.

Methyl O-*(2,3,4-tri-*O*-benzoyl-α-*L*-rhamnopyranosyl)-(1 → 2)-4-deoxy-4-fluoro-α-*D*-galactopyranoside* (**26**).—Conventional debenzylation of **25** (2.44 g, 2.92 mmol) using 10% Pd–C (600 mg) in 1:5 acetone–EtOH (50 mL) as described for the preparation of **19** gave, after workup and chromatography (solvent *B*, 1.5:1), compound **26** (1.76 g, 92%); $[\alpha]_D$ +166° (*c* 1, $CHCl_3$); ^1H NMR: δ 8.08–7.24 (m, 15 H, Ph), 5.87 (dd, 1 H, $J_{2',3'}$ 3.4, $J_{3',4'}$ 10.1 Hz, H-3'), 5.78 (bs, 1 H, H-2'), 5.68 (t, 1 H, $J_{4',5'}$ 9.9 Hz, H-4'), 5.26 (bs, 1 H, H-1'), 5.04 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.92 (dd, 1 H, $J_{3,4}$ 2.6, $J_{4,F}$ 50.6 Hz, H-4), 4.39 (dq, 1 H, $J_{5',6'}$ 6.3 Hz, H-5'), 4.21 (bdd, 1 H, $J_{5,F}$ 28.0 Hz, H-5), 3.99 (m, overlapped, 1 H, *J* 10.5 Hz, H-2), 3.89–3.76 (m, overlapped, 3 H, H-3,6a,6b), 3.47 (s, 3 H, OMe), 3.39 (d, 1 H, $J_{3,OH}$ 4.4 Hz, OH-3), 2.23 (m, 1 H, OH-6), and 1.37 (d, 3 H, H-6'); ^{13}C NMR: δ 165.90, 165.69 (3 C=O),

133.61–128.37 (Ph), 99.95 (C-1'), 99.09 (C-1), 89.67 (d, $J_{C,F}$ 181.6 Hz, C-4), 78.92 (C-2), 71.64 (C-4'), 70.58 (C-2'), 69.98 (C-3'), 69.38 (d, $J_{C,F}$ 18.0 Hz, C-3), 67.41 (d, $J_{C,F}$ 16.4 Hz, C-5), 67.30 (C-5'), 61.28 (d, $J_{C,F}$ 5.5 Hz, C-6), 55.30 (OMe), and 17.74 (C-6'); ^{19}F NMR: δ −57.91 (dt, $J_{F,4}$ 50.7, $J_{F,3}$ 29.2, $J_{F,5}$ 30.1 Hz, F-4); CIMS: *m/z* 672 $[M + NH_4]^+$. Anal. Calcd for $C_{34}H_{35}FO_{12}$: C, 62.38; H, 5.40; F, 2.90. Found C, 62.30; H, 5.60; F, 2.51.

Methyl O-α-L-*rhamnopyranosyl-(1 → 2)-4-deoxy-4-fluoro-α-*D-*galactopyranoside* (**27**).—Conventional debenzoylation (Zemplén) of **26** (1.56 g, 2.38 mmol) afforded, after chromatography (solvent *A*, 4.5:1), compound **27** (749 mg, 92%); mp 202–203° C (from EtOH); $[\alpha]_D$ +56° (*c* 0.9, water); ^{1}H NMR (D_2O): δ 4.94 (m, overlapped, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.90 (d, 1 H, $J_{1',2'}$ 1.5 Hz, H-1'), 4.87 (m, overlapped, 1 H, $J_{4,F}$ 56.4 Hz, H-4), 3.99 (dd, overlapped, 1 H, $J_{2',3'}$ 3.4 Hz, H-2'), 4.02–3.30 (m, 2 H, H-3,5), 3.76–3.20 (m, 4 H, H-2,6a,6b,3'), 3.67 (m, overlapped, 1 H, H-5'), 3.41 (s, overlapped, 3 H, OMe), 3.41 (m, overlapped, 1 H, H-4'), and 1.38 (d, 3 H, $J_{5',6'}$ 6.3 Hz, H-6'); ^{13}C NMR (D_2O): δ 103.89 (C-1'), 99.91 (C-1), 91.40 (d, $J_{C,F}$ 178.3 Hz, C-4), 77.92 (C-2), 72.93 (C-4'), 71.14 (C-3'), 71.04 (C-2'), 70.37 (d, $J_{C,F}$ 17.9 Hz, C-3), 70.26 (C-5'), 68.29 (d, $J_{C,F}$ 18.1 Hz, C-5), 61.02 (d, $J_{C,F}$ 5.6 Hz, C-6), 56.06 (OMe), and 17.70 (C-6'); ^{19}F NMR (D_2O): δ −57.91 (dt, $J_{F,4}$ 49.7, $J_{F,3}$ 28.8, $J_{F,5}$ 28.8 Hz, F-4); CIMS: *m/z* 360 $[M + NH_4]^+$. Anal. Calcd for $C_{13}H_{23}FO_9 \cdot H_2O$: C, 43.33, H, 6.98; F, 5.41. Found C, 43.36; H, 7.00; F, 5.00.

Methyl O-*(2,3,4-tri-*O-*benzoyl-α-*L-*rhamnopyranosyl)-(1 → 2)-6-deoxy-6-fluoro-3,4-*O-*isopropylidene-α-*D-*galactopyranoside* (**28**).—A mixture of **21** (Ref. 1, 708 mg, 3 mmol), **1** (2.5 g, 4.63 mmol), and *sym*-collidine (550 μL, 4.17 mmol) in CH_2Cl_2 (30 mL) was treated with AgOTf (1.36 g, 5.29 mmol) in CH_2Cl_2 (10 mL) as described for the preparation of **22** (the subsequent additions of **1** and AgOTf were not found necessary in this case). When little starting material remained, conventional workup followed by chromatography (solvent *B*, 5.6:1) gave amorphous **28** (1.77 g, 85%); $[\alpha]_D$ +161° (*c* 1.1, $CHCl_3$); ^{1}H NMR: δ 8.13–7.21 (m, 15 H, Ph), 5.90 (dd, 1 H, $J_{2',3'}$ 3.2, $J_{3',4'}$ 10.0 Hz, H-3'), 5.79 (bd, 1 H, $J_{1',2'}$ 1.3 Hz, H-2'), 5.65 (t, 1 H, $J_{4',5'}$ 10.1 Hz, H-4'), 5.31 (bs, 1 H, H-1'), 4.91 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.76–4.58 (m, 2 H, H-6a,6b), 4.44 (dd, 1 H, $J_{2,3}$ 7.9, $J_{3,4}$ 5.4 Hz, H-3), 4.31–4.22 (m, 3 H, H-4,5,5'), 3.83 (dd, 1 H, H-2), 3.50 (s, 3 H, OMe), 1.52, 1.34 (2 s, 6 H, CMe_2), and 1.36 (d, 3 H, $J_{5',6'}$ 6.2 Hz, H-6'); ^{13}C NMR: δ 165.52–121.22 (Ph), 109.85 (CMe_2), 98.87 (C-1), 98.55 (C-1'), 82.50 (d, $J_{C,F}$ 169 Hz, C-6), 77.20 (C-2), 75.11 (C-3), 73.03 (d, $J_{C,F}$ 7.5 Hz, C-4), 71.92 (C-4'), 70.78 (C-2), 69.66 (C-3'), 67.06 (C-5'), 66.30 (d, $J_{C,F}$ 21.5 Hz, C-5), 55.57 (OMe), 28.12, 26.26 (CMe_2) and 31.69 (C-6'); ^{19}F NMR: δ −66.07 (dt, $J_{F,6}$ 47.2, $J_{F,5}$ 15.3 Hz, F-6); CIMS: *m/z* 712 $[M + NH_4]^+$. Anal. Calcd for $C_{37}H_{39}FO_{12}$: C, 63.97; H, 5.66; F, 2.73. Found C, 63.70; H, 5.66; F, 2.85.

Methyl O-*(2,3,4-tri-*O-*benzoyl-α-*L-*rhamnopyranosyl)-(1 → 2)-6-deoxy-6-fluoro-α-*D-*galactopyranoside* (**29**).—Compound **28** (1.3 g, 1.82 mmol) was dissolved in acetic acid (6 mL), water (600 μL) was added, and the solution was heated at 70° C for 4 h. Concentration of the mixture and azeotroping with toluene afforded after chromatography (solvent *C*, 1.5:1) amorphous **29** (1.09 g, 92%); $[\alpha]_D$ +170° (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ 8.04–7.21 (m, 15 H, Ph), 5.91 (dd, overlapped, 1 H, $J_{2',3'}$

3.2 Hz, H-3'), 5.89 (bd, overlapped, 1 H, H-2'), 5.69 (t, 1 H, $J_{4',5'}$ 9.8, $J_{3',4'}$ 9.8 Hz, H-4'), 5.29 (bs, 1 H, H-1'), 5.03 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 4.65 (m, 2 H, H-6a,6b), 4.42 (m, 1 H, H-5'), 4.21–4.13 (m, 3 H, H-3,4,5), 4.06 (dd, 1 H, $J_{2,3}$ 9.5 Hz, H-2), 3.83 (d, 1 H, J 3.7 Hz, OH), 3.45 (s, 3 H, OMe), 3.14 (s, 1 H, OH), and 1.37 (d, 3 H, $J_{5',6'}$ 6.3 Hz, H-6'); ^{13}C NMR: δ 166.15–128.38 (Ph), 99.88 (C-1'), 99.09 (C-1), 83.00 (d, $J_{C,F}$ 168.6 Hz, C-6), 78.81 (C-2), 71.61 (C-4'), 70.68 (C-2'), 70.21 (C-3'), 69.30 (d, $J_{C,F}$ 7.6 Hz, C-4), 69.66 (d, $J_{C,F}$ 22.0 Hz, C-5), 68.26 (C-3), 67.20 (C-5'), 55.10 (OMe), and 17.74 (C-6'); ^{19}F NMR: δ −67.38 (dt, $J_{F,6}$ 47.3, $J_{F,5}$ 15.7 Hz, F-6); CIMS: m/z 672 $[M + NH_4]^+$. Anal. Calcd for $C_{34}H_{35}FO_{12}$: C, 62.38; H, 5.39; F, 2.90. Found C, 62.18; H, 5.50; F, 2.51.

Methyl O-α-L-*rhamnopyranosyl-(1 → 2)-6-deoxy-6-fluoro-α-*D-*galactopyranoside* (**30**).—Conventional debenzoylation (Zemplén) of **29** (800 mg, 1.22 mmol) afforded, after usual workup and chromatography (solvent *A*, 4.5 : 1), compound **30** (377 mg, 90%); mp 170–171° C (from MeOH–EtOAc); $[\alpha]_D$ +70° (*c* 1, H_2O); ^{1}H NMR (D_2O): δ 4.95 (d, 1 H, H-1 overlapped), 4.95 (bs, overlapped, 1 H, H-1'), 4.67 (ddd, overlapped, 1 H, $J_{5,6a}$ 3.9, $J_{6a,6b}$ 10.1, $J_{6a,F}$ 45.6 Hz, H-6a), 4.66 (ddd, overlapped, 1 H, $J_{5,6b}$ 7.0, $J_{6b,F}$ 48.0 Hz, H-6b), 4.19 (ddd, 1 H, $J_{5,F}$ 16.4 Hz, H-5), 4.06 (m, 2 H, H-2',4), 3.91 (dd, 1 H, $J_{2,3}$ 10.1, $J_{3,4}$ 3.4 Hz, H-3), 3.82 (dd, 1 H, $J_{1,2}$ 3.6 Hz, H-2), 3.78 (dd, overlapped, 1 H, $J_{2',3'}$ 3.6, $J_{3',4'}$ 9.9 Hz, H-3'), 3.72 (m, overlapped, 1 H, H-5'), 3.46 (t, 1 H, $J_{4',5'}$ 9.7 Hz, H-4'), 3.44 (s, 3 H, OMe), and 1.32 (d, 3 H, $J_{5',6'}$ 6.1 Hz, H-6'); ^{13}C NMR (D_2O): δ 99.88 (C-1'*), 99.09 (C-1*), 83.50 (d, $J_{C,F}$ 165.8 Hz, C-6), 77.30 (C-2), 72.11 (C-4'), 70.32 (C-3'), 70.23 (C-2'), 69.41 (C-5'), 69.26 (d, $J_{C,F}$ 23.0 Hz, C-5), 69.66 (d, $J_{C,F}$ 5.6 Hz, C-4), 68.39 (C-3), 55.12 (OMe), and 16.88 (C-6'); ^{19}F NMR (D_2O): δ −68.23 (dt, $J_{F,6}$ 47.0, $J_{F,5}$ 16.5 Hz, F-6); CIMS: m/z 360 $[M + NH_4]^+$. Anal. Calcd for $C_{13}H_{23}FO_9 \cdot 0.5H_2O$: C, 44.44; H, 6.88; F, 5.41. Found C, 44.23; H, 6.65; F, 5.35.

References

[1] L.A. Mulard, P. Kováč, and C.P.J. Glaudemans, *Carbohydr. Res.*, 259 (1994) 117–129.
[2] K. Shiga, *Zentralbl. Bacteriol.*, 24 (1898) 817–824.
[3] A.A. Ries, *Interscience Conference of Antimicrobial Agents and Chemotherapy*, Chicago IL, 29 Sept.–29 Oct. 1991, American Society for Microbiology, Washington, D.C., *Abstr.* 186.
[4] D.N. Taylor, A.C. Trofa, J. Sadoff, C.Y. Chu, D. Bryla, J. Shiloach, D. Cohen, S. Ashkenazi, Y. Lerman, W. Egan, R. Scheerson, and J.B. Robbins, *Infect. Immun.*, 61 (1993) 3678–3687.
[5] C.Y. Chu, B. Liu, D. Watson, S. Szu, D. Bryla, J. Shiloach, R. Schneerson, and J.B. Robbins, *Infect. Immun.*, 59 (1991) 4450–4458.
[6] M.L. Cohen, *Science*, 257 (1992) 1050–1055.
[7] J.B. Robbins, C.Y. Chu, and R. Schneerson, *Clin. Infect. Dis.*, 15 (1992) 346–361.
[8] B.A. Dmitriev, Yu.A. Knirel, and N.K. Kochetkov, *Eur. J. Biochem.*, 66 (1976) 559–566.
[9] S. Sturm, B. Jann, P. Fortnagel, and K.N. Timmis, *Microbial Pathogenesis*, 1 (1986) 307–324.
[10] V. Pavliak, E.M. Nashed, V. Pozsgay, P. Kováč, A. Karpas, C. Chu, R. Schneerson, J.B. Robbins, and C.P.J. Glaudemans, *J. Biol. Chem.*, 268 (1993) 25797–25802.
[11] F.A. Quiocho and N.K. Vyas, *Nature*, 310 (1984) 381–386.
[12] C.P.J. Glaudemans, *Chem. Rev.*, 91 (1991) 25–33.
[13] L.A. Mulard, P. Kováč, and C.P.J. Glaudemans, *Carbohydr. Res.*, 251 (1994) 213–232.
[14] R.K. Ness, H.G. Fletcher, Jr., and C.S. Hudson, *J. Am. Chem. Soc.*, 73 (1951) 296–300.

[15] P.J. Garegg and T. Norberg, *Acta Chem. Scand., Ser. B*, 33 (1979) 116–118.
[16] W.J. Middleton, *J. Org. Chem.*, 40 (1975) 574–578.
[17] B. Doboszewski, G.W. Hay, and W.A. Szarek, *Can. J. Chem.*, 65 (1987) 412–419.
[18] J.S. Brimacombe, A.B. Foster, J.H. Westwood, and L.D. Hall, *Can. J. Chem.*, 48 (1970) 3946–3952.
[19] P. Kováč and C.P.J. Glaudemans, *Carbohydr. Res.*, 123 (1983) 326–331.
[20] K. Bock and C. Pedersen, *Adv. Carbohydr. Chem. Biochem.*, 41 (1983) 27–66.
[21] P.J. Card and G.S. Reddy, *J. Org. Chem.*, 48 (1983) 4734–4743.
[22] C.W. Somawardhana and E.G. Brunngraber, *Carbohydr. Res.*, 121 (1983) 51–60.
[23] K. Koch and R.J. Chambers, *Carbohydr. Res.*, 241 (1993) 295–299.
[24] J.E.N. Shin, A. Maradufu, J. Marion, and A.S. Perlin, *Carbohydr. Res.*, 84 (1980) 328–335.
[25] A. Maradufu and A.S. Perlin, *Carbohydr. Res.*, 32 (1974) 261–277.
[26] G.J.D. Daves, P. Kováč, and C.P.J. Glaudemans, *J. Carbohydr. Chem.*, 9 (1990) 101–112.
[27] S. Colonna, A. Re, G. Gelbard, and E. Cesarotti, *J. Chem. Soc., Perkin Trans. 1*, (1979) 2248–2252.
[28] P. Kováč and C.P.J. Glaudemans, *J. Carbohydr. Chem.*, 2 (1983) 313–327.
[29] D.M. Marcus and J.H. Westwood, *Carbohydr. Res.*, 17 (1971) 269–274.
[30] A.C. Richardson, *Carbohydr. Res.*, 10 (1969) 395–402.
[31] N.F. Taylor and P.W. Kent, *J. Chem. Soc.*, (1958) 872–875.
[32] M. Sharma, G.G. Potti, O.D. Simmons, and W. Korytnyk, *Carbohydr. Res.*, 162 (1987) 41–51.
[33] G. Catelani, F. Colonna, and A. Marra, *Carbohydr. Res.*, 182 (1988) 297–300.