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Synthesis of Glycyrrhizin Analogues Containing Fluorinated β(1→2)-linked Disaccharides

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Abstract—For studies on the recognition mechanisms for Glycyrrhizin-induced biological activities, seven Glycyrrhizin analogues with 3′-, 4′-, 6′-, 3-, and 4-fluorinated 2-*O*-β-D-glucopyranosyl-β-D-glucopyranoses (**1**–**5**) and 3- and 4-fluorinated 2-*O*-β-D-glucopyranuronosyl-β-D-glucopyranoses (**6** and **7**) were synthesized through a stepwise glycosylation procedure. 1,2-Di-*O*-acetyl-4,6-di-*O*-benzyl-3-deoxy-3-fluoro- (**13**) and 1,2-di-*O*-acetyl-3,6-di-*O*-benzyl-4-deoxy-4-fluoro-D-glucopyranose (**14**) were employed for the first β-glycosylation of methyl glycyrrhetate, promoted with trimethylsilyl trifluoromethanesulfonate. Copyright © 1996 Elsevier Science Ltd

Introduction

Glycyrrhizin (GL), which was isolated from aqueous extracts of licorice (*Glycyrrhiza glabra*), is a triterpenoid saponin consisting of a glycyrrhetic acid (GA) and a β(1→2)-linked disaccharide of glucuronic acids. It is known that GL has a variety of biological activities such as anti-inflammatory,[1] hypolipidemic,[2] and antiviral effects,[3] and interferon-inducing activity.[4] The inhibitory effects of GL on the activities of some protein kinases were also reported.[5] However, the biochemical mechanisms including the structural recognition involved in these biological activities of GL have not been well elucidated. Especially, the roles of the sugar moiety of GL, which are presumed to be important for the binding with protein, have scarcely been investigated.

Recently, Saito et al. proposed a binding mechanism between the GL analogues and active sites on the cell for their cytoprotective effects on carbon tetrachloride-induced hepatic injury.[6] They have mentioned that the terminal glucuronic acid is more important for the binding than the inner one, because the analogues having 2-*O*-β-D-glucopyranuronosyl-β-D-glucopyranose and 2-*O*-β-D-glucopyranuronosyl-β-D-galactopyranose were more effective than GL, and those without glucuronic acid as a terminal sugar were less effective. From their results, it is presumed that the carboxyl group of the inner sugar is not involved in the binding reaction , and its 3- and 4-positions may act as a hydrophobic region. Presumably, the carboxyl group and some of the hydroxyl groups of the terminal sugar are the key polar functional groups to bind with protein.

The structural recognition resembling that inferred for the above-mentioned case should be the major role of the sugar moiety of GL for inducing any other biological activities of GL. Accordingly, we now report the preparation of some GL analogues containing the fluorine atom in the sugar moiety, because the replacement of a hydroxyl group by a fluorine atom may enhance either the hydrogen bonding with protein, or that with an adjacent hydroxyl group to form a hydrophobic surface of the molecule.

Key words: Glycyrrhizin, Fluorinated disaccharide, Glycosylation.

Results and Discussion

We have already synthesized the Glycyrrhizin analogues which have sophorose and 6,6′-dideoxysophorose as the sugar moiety through the stepwise glycosylation.[7] Saito et al. have also prepared some analogues by slightly modified procedures.[6]

For the first glycosylation[8] to prepare the sophorose analogue, 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-D-glucopyranose (**8**), was coupled with methyl glycyrrhetate (GmOH) to give **9** using a reagent system of trimethylsilyl bromide (TMSBr), cobalt bromide ($CoBr_2$), and molecular sieves 4 Å (MS4A). This is a successfully modified procedure from that developed for the α-glycosylation with these reagents and tetrabutylammonium bromide.[9]

Compound **8** was readily prepared from 3,4,6-tri-*O*-benzyl-1,2-*O*-(1-ethoxyethylidene)-α-D-glucopyranose by acid hydrolysis with 80% aq acetic acid.[8] In the present work, this procedure was applied to the preparation of the fluorinated 2-*O*-acetyl-1-hydroxyl compounds analogous to **8**.

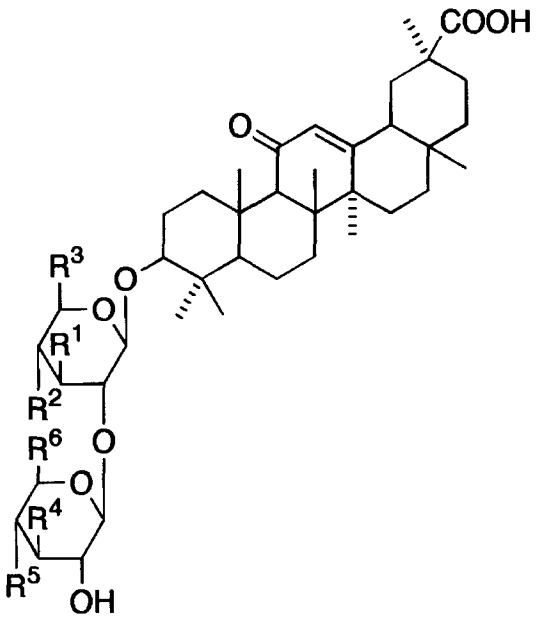
However, the hydrolysis of the fluorinated 1,2-orthoacetate **11** and **12**, whose structure was confirmed by ^{1}H NMR spectroscopy, gave the ca 1:1 mixture of the 1-*O*- and 2-*O*-acetyl derivatives. As mentioned in a recent report, regioselectivity in the ring-opening reaction of 1,2-orthoacetate derivatives depends on the configuration at C-4.[10] In our case, the influence of the electron-withdrawing effect of the fluorine atom at C-3

or C-4 is a dominant reason why the 1-*O*-acetyl derivative was formed in almost equal amount to the 2-*O*-acetyl isomer.

As practically observed, **11** and **12** were stable during a silica-gel column chromatography, whereas 3,4,6-tri-*O*-benzyl-1,2-*O*-(1-ethoxyethylidene)-α-D-glucopyranose was hydrolysed on a silica gel column unless triethylamine (0.1%) was added to the solvent used for elution. This indicates that the protonation at the oxygen atoms is diminished by the influence of the fluorine atom. Probably, almost no difference in the protonating ability exists between O-1 and O-2 of the orthoacid intermediates[11] derived from **11** and **12**.

Therefore, **11** and **12** were hydrolysed with aq sulfuric acid to give the 1,2-dihydroxyl compounds, which were then acetylated with acetic anhydride in pyridine. Thus, the 1,2-diacetate **13** and **14** were to be used for the first step of the glycosylation.

The glycosylation of GmOH with **13** using TMSBr, $CoBr_2$, and MS4A in dichloromethane gave the desired



	R^1	R^2	R^3	R^4	R^5	R^6
GL	OH	OH	COOH	OH	OH	COOH
1	OH	OH	CH_2OH	F	OH	CH_2OH
2	OH	OH	CH_2OH	OH	F	CH_2OH
3	OH	OH	CH_2OH	OH	OH	CH_2F
4	F	OH	CH_2OH	OH	OH	CH_2OH
5	OH	F	CH_2OH	OH	OH	CH_2OH
6	F	OH	CH_2OH	OH	OH	COOH
7	OH	F	CH_2OH	OH	OH	COOH

Graphic 1.

β-glycoside in low yields (Table 1). The yield of the glycoside was improved by the use of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a promoter[12,13] for the glycosylation. The reaction of an equimolar mixture of GmOH and **13** was conducted in dichloromethane at room temperature. The yields of the β-glycoside **15** in the presence of 1, 2, 3, and 5 equiv. of TMSOTf were 5, 26, 48, and 55%, respectively. The glycosylation of GmOH with **14** in the presence of 5 equiv. of TMSOTf gave **17** in 39% yield.

The yields of **15** and **17** were low even though the glycosyl donors (**13** and **14**) were almost completely consumed within the reaction period at a large proportion of TMSOTf. This is mostly due to the formation of the acetyl ester of GmOH, observed in every reaction using TMSOTf, through transesterification.[14,15]

Deacetylation of **15** and **17** with methanolic sodium methoxide gave **16** and **18**, respectively.

The second glycosylation was performed through a Koenigs–Knorr type reaction with silver trifluoromethanesulfonate (AgOTf) and tetramethylurea (TMU). The glycosylation of **10**,[7] which was derived from **9**, with the glycosyl bromides prepared from the tetra-*O*-acetyl derivatives of 3-deoxy-3-fluoro- (**19**),[16] 4-deoxy-4-fluoro- (**20**),[17] and 6-deoxy-6-fluoro-D-glucopyranose (**21**)[18] with hydrogen bromide in acetic acid proceeded smoothly to afford **24**, **25**, and **26** in 92, 73, and 82% yields, respectively.

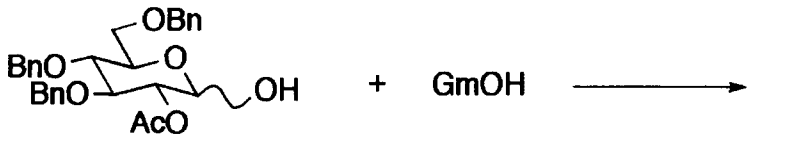
Compounds **16** and **18** were glycosylated with 2 molar equiv. of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**22**) by using AgOTf and TMU to form **27** and **28** in 90 and 93% yields, respectively. Similarly, **16** and **18** were glycosylated with 6 mol of the freshly prepared bromide of methyl glucuronate **23**[19] to give **29** and **30**, respectively.

The completely protected glycosides obtained through the stepwise glycosylation were deacetylated with methanolic sodium methoxide, hydrogenated in the presence of palladium hydroxide on carbon in ethanol to remove benzyl groups, and then saponificated in a 1:1 mixture of ethanol and water to furnish the desired compounds **1**–**7**. The degradation by β-elimination[20] of the acetylated glucuronic acid moiety of **29** and **30** might have occurred during deacetylation, and accordingly lowered the yields of **6** and **7**. The structures of all compounds were confirmed by NMR spectroscopy.

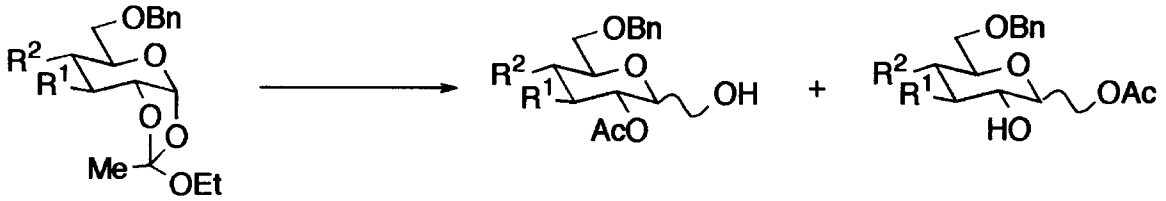
Experimental

General methods

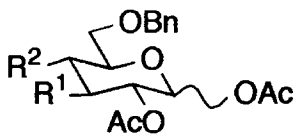
The melting points were determined with a Yanagimoto MP-500D melting-point apparatus and are uncorrected. The optical rotations were measured with a Horiba SEPA-200 polarimeter at 20 °C. The NMR spectra were recorded with a Varian VXR-300 spectrometer at 300 MHz for ^1H NMR and at 75.4 MHz for ^{13}C NMR. Assignment of all proton and carbon signals



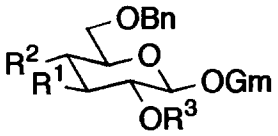
8 + GmOH → **9** R = Ac; **10** R = H



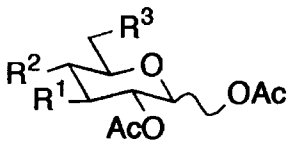
	R^1	R^2
11	F	OBn
12	OBn	F



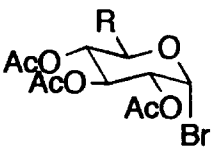
	R^1	R^2
13	F	OBn
14	OBn	F



	R^1	R^2	R^3
15	F	OBn	Ac
16	F	OBn	H
17	OBn	F	Ac
18	OBn	F	H

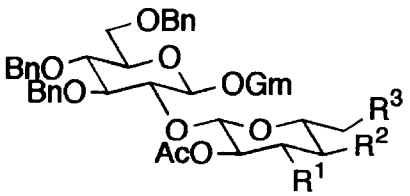


	R^1	R^2	R^3
19	F	OAc	OAc
20	OAc	F	OAc
21	OAc	OAc	F

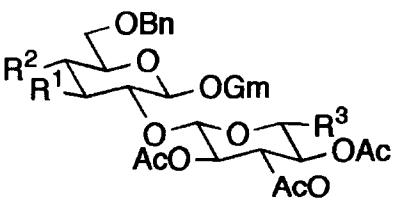


22 $R = CH_2OAc$

23 R = COOMe



	R^1	R^2	R^3
24	F	OAc	OAc
25	OAc	F	OAc
26	OAc	OAc	F



	R^1	R^2	R^3
27	F	OBn	CH_2OAc
28	OBn	F	CH_2OAc
29	F	OBn	COOMe
30	OBn	F	COOMe

Graphic 2.

Table 1. Glycosylation of GmOH with **13** in dichloromethane in the presence of molecular sieves 4 Å

TMSBr (equiv.)	MX_2 (equiv.)	Reaction time (h) for bromination	Reaction time (h) for glycosylation	Yield of **15** (%)
1.1	1.1 $CoBr_2$	1.5	6	11
2.0	1.0 $CoBr_2$	1.5	16	26
2.0	3.0 $CoBr_2$	1.5	16	32
2.0	3.0 $CoCl_2$	2.0	16	26

was performed based on H—H and C—H COSY measurements. The chemical shifts of the protons were calculated from that of the satellite peak of $CDCl_3$ at $\delta = 7.26$ and that of the peak of C_5D_5N at $\delta = 8.73$, and those of the carbons are relative to the central peak of $CDCl_3$ at $\delta = 77.0$ and to the peak of C_5D_5N at $\delta = 150.0$. The ^1H NMR data are shown in the experimental section and the ^{13}C NMR data are summarized in Table 2. The notations for the protons and carbons of the aglycon, the inner sugar, and the terminal sugar are as nonprimed, primed, and double-primed, respectively. Column chromatography was performed on silica gel (Wakogel C-300). TLC was performed on Silica Gel G 60 (Merck, No. 5721).

4,6-Di-*O*-benzyl-3-deoxy-1,2-*O*-(1-ethoxyethylidene)-3-fluoro-α-D-glucopyranose (11). A solution of 1,2,4,6-tetra-*O*-acetyl-3-deoxy-3-fluoro-D-glucopyranose (**19**, 2.71 g, 7.74 mmol) in 1,2-dichloroethane (10.8 mL) and 25% hydrogen bromide solution in acetic acid (13.5 mL) was kept at room temperature for 3 h with an exclusion of moisture. The solution was evaporated to give a pale orange syrup, which was dissolved in nitromethane (6.3 mL). To the solution, 2,4,6-trimethylpyridine (6.2 mL, 46.4 mmol), tetrabutylammonium bromide (0.63 g, 1.94 mmol), and ethanol (0.46 mL, 7.74 mmol) were added successively, and kept at 40 °C for 20 h. The mixture was poured into ice and extracted with chloroform. The organic layer was washed with 5% aq hydrogen chloride, 5% aq sodium hydrogencarbonate, and water, succesively, and dried over anhyd sodium sulfate. The solution was concentrated to a syrupy residue, which was dissolved in 0.15 N methanolic sodium methoxide (27.5 mL). After being kept at room temperature for 2 h, the solution was concentrated and chromatographed using a mixed solvent of chloroform:methanol (20:1) to give a crystalline residue (1,63 g, 84%). The residue was dissolved in *N,N*-dimethylformamide (16 mL), and benzyl bromide (2.31 mL, 19.4 mmol) and sodium hydride (60% dispersion in oil, 0.62 g, 15.5 mmol) were added at 0 °C under stirring. Stirring was continued at 0 °C for 2 h. Neutralization with acetic acid, followed by evaporation, left a syrup, which was dissolved in chloroform and washed with water. The organic layer was dried over anhyd sodium sulfate and evaporated to give a syrupy product. A small quantity of the syrup was purified through a short column of silica gel with a mixed solvent of toluene–ethyl acetate to provide a sample of **11** for the NMR measurements. ^1H NMR ($CDCl_3$): δ 1.20 (3H, t, $\underline{CH_3}CH_2$), 1.68 (3H, s, CH_3), 3.55 (2H, q, $CH_3\underline{CH_2}$), 3.64 (1H, dd, $J_{5,6a} = 3.5$ Hz, $J_{6a,6b} = 10.5$ Hz, H-6a), 3.69 (1H, dd, $J_{5,6b} = 2.0$ Hz, H-6b), 3.76 (1H, ddd, $J_{4,5} = 9.6$ Hz, H-5), 3.85 (1H, ddd, $J_{3,4} = 3.7$ Hz, $J_{4,F} = 20.3$ Hz, H-4), 4.48 (1H, ddd, $J_{1,2} = 5.3$ Hz, $J_{2,3} = 2.9$ Hz, $J_{2,F} = 12.1$ Hz, H-2), 4.48–4.60 (2H, AB, $\delta_A = 4.50$, $\delta_B = 4.58$, $J_{A,B} = 12.5$ Hz, Ph*CH2*), 4.48–4.76 (2H, AB, $\delta_A = 4.50$, $\delta_B = 4.74$, $J_{A,B} = 11.4$ Hz, Ph*CH2*), 4.91 (1H, ddd, $J_{3,F} = 46.4$ Hz, H-3), 5.79 (1H, d, H-1), 7.25–7.35 (10H, m, 2 × Ph).

3,6-Di-*O*-benzyl-4-deoxy-1,2-*O*-(1-ethoxyethylidene)-4-fluoro-α-D-glucopyranose (12). 1,2,3,6-Tetra-*O*-acetyl-4-deoxy-4-fluoro-D-glucopyranose (**20**, 2.24 g, 6.40 mmol) was processed in the same manner as described for the preparation of **11** to give syrupy **12**. ^1H NMR ($CDCl_3$): δ 1.19 (3H, t, $\underline{CH_3}CH_2$), 1.66 (3H, s, CH_3), 3.54 (2H, q, $CH_3\underline{CH_2}$), 3.70 (1H, ddd, $J_{5,6a} = 4.4$ Hz, $J_{6a,6b} = 11.0$ Hz, $J_{6a,F} = 1.3$ Hz, H-6a), 3.75 (1H, ddd, $J_{5,6b} = 2.6$ Hz, $J_{6b,F} = 1.3$ Hz, H-6b), 3.89 (1H, dddd, $J_{4,5} = 9.0$ Hz, $J_{5,F} = 9.5$ Hz, H-5), 3.95 (1H, ddd, $J_{2,3} = 3.0$ Hz, $J_{3,4} = 3.6$ Hz, $J_{3,F} = 22.8$ Hz, H-3), 4.43 (1H, dd, $J_{1,2} = 5.3$ Hz, H-2), 4.58–4.68 (2H, AB, $\delta_A = 4.60$, $\delta_B = 4.66$, $J_{A,B} = 12.2$ Hz, Ph*CH2*), 4.65–4.76 (2H, AB, $\delta_A = 4.67$, $\delta_B = 4.74$, $J_{A,B} = 12.0$ Hz, Ph$\underline{CH_2}$), 4.73 (1H, ddd, $J_{4,F} = 49.0$ Hz, H-4), 5.74 (1H, d, H-1), 7.26–7.35 (10H, m, 2 × Ph).

Hydrolysis of 11 and 12 with aqueous acetic acid. A mixture of **11** (194 mg) and 80% aq acetic acid was stirred at 80 °C for 1.5 h. The mixture was evaporated and chromatographed using a mixed solvent of toluene:ethyl acetate (4:1) to give a syrup (121 mg), whose ^1H NMR spectrum in $CDCl_3$ showed two signals of H-1; at δ 5.42 for the 2-*O*-acetyl compound (α-form) and at δ 6.26 for the 1-*O*-acetyl isomer (α-form) with the ratio of 4:3.

Similarly, the hydrolysis of **12** (93 mg) gave a syrup (23 mg), whose ^1H NMR spectrum also showed two signals of H-1; at δ 5.43 and 6.23 with the ratio of 1:1.

Preparation of 1,2-di-*O*-acetyl-4.6-di-*O*-benzyl-3-deoxy-3-fluoro- (13) and 1,2-di-*O*-acetyl-3,6-di-*O*-benzyl-4-deoxy-4-fluoro-D-glucopyranose (14). The most part of the syrupy **11** was heated in a mixture of acetic acid (24 mL) and 1 N sulfuric acid (12 mL) at 80 °C for 2 h. After cooling, the mixture was extracted with chloroform, and the organic layer was washed with water and 5% aq sodium hydrogencarbonate, successively. Evaporation gave a residue, which was dissolved in pyridine (24 mL) and acetic anhydride (18 mL), and the solution was kept at room temperature for 2 h. Evaporation and a column chromatography using a mixed solvent of toluene:ethyl acetate (6:1) to afford a syrup of **13** (2.02 g, 59% yield from **19**) as an anomeric mixture (α:β = 6:1). ^1H NMR for the α-anomer ($CDCl_3$): δ 2.08 (3H, s, Ac), 2.10 (3H, s, Ac), 3.67 (1H, ddd, $J_{5,6a} = 2.2$ Hz, $J_{6a,6b} = 11.4$ Hz, $J_{6a,F} = 1.8$ Hz, H-6a), 3.76 (1H, dd, $J_{5,6b} = 3.0$ Hz, H-6b), 3.89 (1H, ddd, $J_{4,5} = 9.7$ Hz, H-5), 3.93 (1H, ddd, $J_{3,4} = 8.0$ Hz, $J_{4,F} = 17.5$ Hz, H-4), 4.48–4.64 (2H, AB, $\delta_A = 4.50$, $\delta_B = 4.62$, $J_{A,B} = 12.2$ Hz, Ph$\underline{CH_2}$), 4.52–4.84 (2H, AB, $\delta_A = 4.54$, $\delta_B = 4.82$, $J_{A,B} = 10.9$ Hz, Ph$\underline{CH_2}$), 4.92 (1H,

Table 2. ^{13}C NMR spectral data (δ/ppm with $J_{C,H}$/Hz in parentheses) for **9**, **15**, **17**, **24–30** in $CDCl_3$ and **1–7** in C_5D_5N

	9	**15**	**17**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
C-3	89.5	89.8	89.8	90.3	90.1	90.3	90.1	90.4	90.1	90.4	88.9	88.9	89.1	89.7	89.3	89.8	89.5
C-5	55.2	55.2	55.3	55.4	55.3	55.4	55.3	55.3	55.4	55.4	55.6	55.6	55.6	55.6	55.6	55.6	55.6
C-9	61.8	61.8	61.8	61.9	61.8	61.9	61.8	61.8	61.8	61.8	62.3	62.3	62.3	62.3	62.3	62.3	62.3
C-11	200.1	200.0	200.0	200.0	200.0	200.1	200.0	200.1	200.2	200.2	199.8	199.8	199.8	199.8	199.8	199.7	199.7
C-12	128.5	128.5	128.4	128.4	128.4	128.5	128.5	128.5	128.5	128.5	128.8	128.8	128.8	128.8	128.8	128.8	128.8
C-13	169.3	169.2	169.0	169.1	169.1	169.1	169.2	169.1	169.2	169.1	169.9	169.9	169.8	169.9	169.9	169.9	169.9
C-18	48.4	48.4	48.4	48.2	48.4	48.4	48.4	48.4	48.4	48.2	48.9	48.9	48.9	48.94	8.9	48.9	48.9
C-30	176.9	176.9	176.9	176.9	176.9	176.9	176.9	176.9	176.9	176.9	179.4	179.4	179.3	179.4	179.4	179.4	179.4
C-1′	103.2	102.2 (11.4)	103.0	103.7	103.7	103.7	102.7 (11.9)	103.6	102.6 (11.9)	103.5	105.1	105.1	105.0	104.1 (12.6)	104.8	104.2 (11.3)	104.6
C-2′	73.6	72.2 (18.1)	72.4 (9.8)	77.8	77.9	77.9	79.0 (16.7)	77.2 (4.7)	79.4 (16.5)	77.7 (9.0)	83.3	83.5	84.4	77.4 (16.2)	82.9 (8.7)	78.6 (15.5)	84.3 (2.3)
C-3′	83.1	95.9 (187.1)	79.8 (17.9)	85.9	85.8	85.8	98.9 (184.0)	83.6 (17.2)	98.7 (183.9)	83.4 (17.1)	78.4	78.5	78.7	100.7 (182.1)	75.8 (17.8)	100.5 (182.3)	75.8 (16.5)
C-4′	78.2	76.0 (16.5)	90.5 (184.0)	78.6	78.6	78.6	75.8 (16.6)	90.7 (184.8)	75.7 (16.5)	90.7 (184.0)	71.7	71.7	71.6	76.0 (31.8)	90.8 (180.8)	76.0 (30.0)	90.6 (181.5)
C-5′	75.0	73.6 (9.1)	73.2 (23.6)	74.7	74.7	74.7	73.1 (9.7)	72.8 (23.0)	73.1 (9.5)	72.7 (23.3)	78.2	78.2	78.2	76.9 (8.4)	75.1 (23.8)	77.0 (9.0)	75.1 (22.2)
C-6′	68.9	68.6	68.7	68.8	68.8	68.9	68.5	68.7	68.5	68.6	62.9	62.9	62.9	63.1	62.9	62.7	62.6
C-1″				99.3 (11.1)	99.6	99.7	100.8	99.9	101.0	100.1	105.3	105.8	106.4	103.6	106.0	104.3	106.8
C-2″				71.9 (17.7)	71.9 (7.6)	71.9	71.9	72.0	71.6	71.7	75.4 (16.5)	77.0 (9.3)	77.0	76.3	77.1	76.0	76.8
C-3″				92.1 (191.2)	72.9 (19.4)	73.1	72.9	73.1	72.3	72.5	99.2(182.3)	75.4 (25.0)	78.2	78.6	78.2	77.7	77.4
C-4″				68.3 (18.4)	86.8 (188.0)	68.6 (6.6)	68.2	68.2	69.5	69.4	69.3 (17.7)	90.5 (179.3)	70.1 (6.5)	72.5	71.9	74.0	73.5
C-5″				70.8 (7.5)	71.0 (23.6)	72.3 (20.2)	71.7	71.7	72.9	72.7	77.3 (8.1)	75.8 (17.4)	76.8 (18.3)	78.4	78.5	77.5	77.8
C-6″				61.8	62.2	81.1 (176.4)	61.9	61.9	166.7	166.7	61.9	61.3	83.3 (171.7)	62.1	61.5	172.7	172.3

ddd, $J_{2,3}=9.6$ Hz, $J_{3,F}=53.2$ Hz, H-3), 5.15 (1H, ddd, $J_{1,2}=3.8$ Hz, $J_{2,F}=12.6$ Hz, H-2), 6.32 (1H, dd, $J_{1,F}=3.5$ Hz, H-1), 7.21–7.40 (10H, m, 2 × Ph). The signals for the β-anomer were not assigned. Anal.: calcd for $C_{24}H_{27}FO_7$: C, 64.56; H, 6.10; found: C, 63.94; H, 6.00.

The most part of **12** was similarly hydrolysed to give a syrup of **14** (1.56 g, 55% yield from **20**) as an anomeric mixture (α:β=3:1). ^{1}H NMR for the α-anomer ($CDCl_3$): δ 2.00 (3H, s, Ac), 2.14 (3H, s, Ac), 4.01 (1H, ddd, $J_{2,3}=10.2$ Hz, $J_{3,4}=8.6$ Hz, $J_{3,F}=14.5$ Hz, H-3), 4.02 (1H, dddd, $J_{4,5}=10.0$ Hz, $J_{5,6a}=3.4$ Hz, $J_{5,6b}=5.8$ Hz, $J_{5,F}=6.3$ Hz, H-5), 4.55–4.64 (2H, AB, $\delta_A=4.57$, $\delta_B=4.62$, $J_{A,B}=12.5$ Hz, PhC<u>H</u>$_2$), 4.67–4.89 (2H, AB, $\delta_A=4.69$, $\delta_B=4.87$, $J_{A,B}=11.5$ Hz, PhC<u>H</u>$_2$), 4.69 (1H, ddd, $J_{4,F}=49.6$ Hz, H-4), 5.01 (1H, ddd, $J_{1,2}=3.8$ Hz, $J_{2,F}=1.0$ Hz, H-2), 6.30 (1H, dd, $J_{1,F}=3.0$ Hz, H-1), 7.26–7.38 (10H, m, 2 × Ph). The β-anomer: δ 1.98 (3H, s, Ac), 2.08 (3H, s, Ac), 3.70 (1H, dddd, $J_{4,5}=9.2$ Hz, $J_{5,6a}=2.2$ Hz, $J_{5,6b}=3.7$ Hz, $J_{5,F}=8.6$ Hz, H-5), 3.77 (1H, ddd, $J_{2,3}=9.5$ Hz, $J_{3,4}=8.5$ Hz, $J_{3,F}=15.8$ Hz, H-3), 4.54–4.65 (2H, AB, $\delta_A=4.56$, $\delta_B=4.63$, $J_{A,B}=12.0$ Hz, PhC<u>H</u>$_2$), 4.68–4.88 (2H, AB, $\delta_A=4.70$, $\delta_B=4.86$, $J_{A,B}=11.6$ Hz, PhC<u>H</u>$_2$), 4.71 (1H, ddd, $J_{4,F}=50.0$ Hz, H-4), 5.09 (1H, ddd, $J_{1,2}=8.3$ Hz, $J_{2,F}=0.6$ Hz, H-2), 5.63 (1H, d, H-1), 7.26–7.36 (10H, m, 2 × Ph). Anal.: calcd for $C_{24}H_{27}FO_7$: C, 64.56; H, 6.10; found: C, 63.86; H, 6.06%.

Glycosylation of methyl glycyrrhetate (GmOH) with 13 using trimethylsilyl bromide (TMSBr) and cobalt bromide ($CoBr_2$). To a mixture of **13** (82.1 mg, 0.184 mmol), $CoBr_2$ (120.7 mg, 0.552 mmol), molecular sieves 4 Å (MS4A, 82.1 mg), and dichloromethane (1.64 mL), TMSBr (49 μL, 0.368 mmol) was added, and the mixture was stirred at room temperature for 1.5 h. A solution of GmOH (89.2 mg, 0.184 mmol) in dichloromethane (0.82 mL) was added to the reaction mixture, and the stirring was continued for 16 h. The mixture was filtered through Celite and made up to a chloroform solution (30 mL), which was washed with 5% aq sodium hydrogencarbonate and water. After drying over anhyd sodium sulfate, the solution was evaporated and chromatographed using a gradient mixed-solvent system of toluene:ethyl acetate (30:1→3:1) to give **15** (57.4 mg, 32%). ^{1}H NMR ($CDCl_3$): δ 0.78, 0.81, 0.93, 1.12, 1.14, 1.14, and 1.34 (each singlet corresponds to CH_3), 2.11 (3H, s, Ac), 3.44 (1H, ddd, $J_{4',5'}=9.6$ Hz, $J_{5',6a'}=5.0$ Hz, $J_{5',6b'}=2.2$ Hz, $J_{5',F}=2.5$ Hz, H-5′), 3.65 (1H, dd, $J_{6a',6b'}=10.8$ Hz, H-6a′), 3.69 (3H, s, CH_3O), 3.72 (1H, ddd, $J_{3',4'}=8.4$ Hz, $J_{4',F}=13.0$ Hz, H-4′), 3.74 (1H, dd, H-6b′), 4.41 (1H, d, $J_{1',2'}=8.0$ Hz, H-1′), 4.53–4.63 (2H, AB, $\delta_A=4.55$, $\delta_B=4.61$, $J_{A,B}=12.3$ Hz, PhC<u>H</u>$_2$), 4.54–4.83 (2H, AB, $\delta_A=4.56$, $\delta_B=4.81$, $J_{A,B}=11.0$ Hz, PhC<u>H</u>$_2$), 4.60 (1H, ddd, $J_{2',3'}=9.1$ Hz, $J_{3',F}=52.5$ Hz, H-3′), 5.12 (1H, ddd, $J_{2',F}=13.7$ Hz, H-2′), 5.67 (1H, s, H-12), 7.25–7.35 (10H, m, 2 × Ph). The results of the reactions with the different amount of $CoBr_2$, and that with cobalt chloride were summarized in Table 1.

Glycosylation of GmOH with 13 using trimethylsilyl trifluoromethanesulfonate (TMSOTf). To a mixture of **13** (555 mg, 1.24 mmol), GmOH (603 mg, 1.24 mmol), MS4A (1.67 g), and dichloromethane (16.7 mL), TMSOTf (1.20 mL, 6.22 mmol) was added, and the mixture was stirred at room temperature for 4.5 h. The mixture was diluted with dichloromethane, filtered through Celite, and washed with 5% aq sodium hydrogencarbonate and water, successively. After drying over anhyd sodium sulfate, the solution was evaporated to give a syrup, which was chromatographed using a gradient mixed-solvent system of toluene:ethyl acetate (30:1→3:1) to provide **15** (593 mg, 55%). The reactions of about 100 mg of **13** with 1, 2, and 3 equiv. of TMSOTf gave **15** in 5, 26, and 48% yields, respectively.

Glycosylation of GmOH with 14 using TMSOTf. To a mixture of **14** (777 mg, 1.74 mmol), GmOH (845 mg, 1.74 mmol), MS4A (2.3 g), and dichloromethane (23 mL), TMSOTf (1.68 mL, 8.70 mmol) was added, and the mixture was stirred at room temperature for 3 h. The work up including chromatographic separation according to that described for the reaction of **13** afforded **17** (584 mg, 39%). ^{1}H NMR ($CDCl_3$): δ 0.76, 0.80, 0.90, 1.11, 1.13, 1.14, and 1.34 (each singlet corresponds to CH_3), 1.99 (3H, s, Ac), 3.60 (1H, dddd, $J_{4',5'}=9.2$ Hz, $J_{5',6a'}=5.0$ Hz, $J_{5',6b'}=2.2$ Hz, $J_{5',F}=10.5$ Hz, H-5′), 3.67 (1H, ddd, $J_{6a',6b'}=11.0$ Hz, $J_{6a',F}=2.0$ Hz, H-6a′), 3.68 (1H, ddd, $J_{2',3'}=9.6$ Hz, $J_{3',4'}=8.4$ Hz, $J_{3',F}=14.8$ Hz, H-3′), 3.69 (3H, s, CH_3O), 3.79 (1H, dd, $J_{6b',F}=2.4$ Hz, H-6b′), 4.42 (1H, d, $J_{1',2'}=8.0$ Hz, H-1′), 4.51 (1H, ddd, $J_{4',F}=50.3$ Hz, H-4′), 4.56–4.65 (2H, AB, $\delta_A=4.58$, $\delta_B=4.63$, $J_{A,B}=12.4$ Hz, PhC<u>H</u>$_2$), 4.59–4.85 (2H, AB, $\delta_A=4.61$, $\delta_B=4.83$, $J_{A,B}=12.0$ Hz, PhC<u>H</u>$_2$), 5.00 (1H, dd, H-2′), 5.67 (1H, s, H-12), 7.25–7.37 (10H, m, 2 × Ph).

Methyl (3β)-3-(4,6-di-*O*-benzyl-3-deoxy-3-fluoro-β-D-glucopyranosyloxy)-11-oxoolean-12-en-30-oate (16). To a solution of **15** (344 mg, 0.395 mmol) in dichloromethane (2.5 mL) and methanol (3.0 mL), 1.5 N methanolic sodium methoxide (0.8 mL) was added, and the resulting solution was kept at room temperature for 5 h. Neutralization with acetic acid, followed by evaporation left a syrup, which was chromatographed using a mixed solvent of toluene:ethyl acetate (8:1) to give **16** (285 mg, 87%); mp 99.0–100.2 °C, $[\alpha]_D$ +77.7° (*c* 2, chloroform). Anal.: calcd for $C_{51}H_{69}FO_8$: C, 73.88; H, 8.39; found: C, 73.35; H, 8.42%.

Methyl (3β)-3-(3,6-di-*O*-benzyl-4-deoxy-4-fluoro-β-D-glucopyranosyloxy)-11-oxoolean-12-en-30-oate (18). A solution of **17** (483 mg, 0.555 mmol) in dichloromethane (3.0 mL) and methanol (4.5 mL) was trated with 1.5 N methanolic sodium methoxide (0.7 mL) at room temperature for 16 h. The mixture was worked up in the same manner as described for the isolation of **16** to provide **18** (440 mg, 96%); mp 100.0–101.0 °C, $[\alpha]_D$ +82.2° (*c* 1, chloroform). Anal.: calcd for $C_{51}H_{69}FO_8$: C, 73.88; H, 8.39; found: C, 73.08; H, 8.36%.

Glycosylation of methyl (3β)-3-(3,4,6-tri-*O*-benzyl-β-D-glucopyranosyloxy)-11-oxoolean-12-en-30-oate (10) with the glycosyl bromides derived from 1,2,4,6-tetra-*O*-acetyl-3-deoxy-3-fluoro- (19), 1,2,3,6-tetra-*O*-acetyl-4-deoxy-4-fluoro-(20),and1,2,3,4-tetra-*O*-acetyl-6-deoxy-6-fluoro-α-D-glucopyranose (21). A solution of **19** (67.2 mg, 0.192 mmol) and 25% hydrogen bromide in acetic acid (0.5 mL) in 1,2-dichloroethane (0.3 mL) was kept at room temperature for 2 h. Evaporation and coevaporation with toluene gave a syrup, which was then made up to a dichloromethane solution (1.9 mL). To the solution, **10** (135.4 mg, 0.148 mmol), silver trifluoromethanesulfonate (AgOTf; 76.1 mg, 0.296 mmol), and tetramethylurea (TMU; 53 μL, 0.444 mmol) were successively added at 0 °C, at which temperature the resulting mixture was stirred for 3 h under shading. The mixture was filtered through Celite, and washed with water. The organic layer was dried over anhyd sodium sulfate, evaporated, and chromatographed using a gradient mixed-solvent system of toluene:ethyl acetate (30:1→3:1) to give methyl (3β)-3-[2-*O*-(2,4,6-tri-*O*-acetyl-3-deoxy-3-fluoro-β-D-glucopyranosyl)-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyloxy]-11-oxoolean-12-en-30-oate (**24**, 164 mg, 92%); mp 106.3–108.5 °C, $[\alpha]_D$ +41.8° (c 1, chloroform). ^{1}H NMR ($CDCl_3$): δ 0.81, 0.85, 1.09, 1.13, 1.15, 1.15, and 1.35 (each singlet corresponds to CH_3), 2.06, 2.08, and 2.11 (each singlet corresponds to Ac), 3.42 (1H, ddd, $J_{4',5'}$=9.0 Hz, $J_{5',6a'}$=4.5 Hz, $J_{5',6b'}$=2.0 Hz, H-5′), 3.46 (1H, dddd, $J_{4'',5''}$=10.2 Hz, $J_{5'',6a''}$=2.0 Hz, $J_{5'',6b''}$=4.3 Hz, $J_{5'',F}$=1.8 Hz, H-5″), 3.56 (1H, dd, $J_{3',4'}$=8.4 Hz, H-4′), 3.61 (1H, dd, $J_{2',3'}$=8.8 Hz, H-3′), 3.62 (1H, dd, $J_{6a',6b'}$=10.8 Hz, H-6a′), 3.68 (1H, dd, H-6b′), 3.69 (3H, s, CH_3O), 3.78 (1H, dd, $J_{1',2'}$=7.7 Hz, H-2′), 4.05 (1H, ddd, $J_{6a'',6b''}$=12.3 Hz, $J_{6a'',F}$=1.5 Hz, H-6a″), 4.22 (1H, dd, H-6b″), 4.34 (1H, d, H-1′), 4.39 (1H, ddd, $J_{2'',3''}$=9.0 Hz, $J_{3'',4''}$=8.8 Hz, $J_{3'',F}$=52.2 Hz, H-3″), 4.52–4.62 (2H, AB, δ_A=4.54, δ_B=4.60, $J_{A,B}$=12.0 Hz, PhC<u>H</u>$_2$), 4.57–4.78 (2H, AB, δ_A=4.59, δ_B=4.76, $J_{A,B}$=11.0 Hz, PhC<u>H</u>$_2$), 4.73–4.92 (2H, AB, δ_A=4.75, δ_B=4.90, $J_{A,B}$=10.5 Hz, PhC<u>H</u>$_2$), 4.97 (1H, d, $J_{1'',2''}$=8.0 Hz, H-1″), 5.10 (1H, ddd, $J_{2'',F}$=12.0 Hz, H-2″), 5.20 (1H, ddd, $J_{4'',F}$=12.5 Hz, H-4″), 5.67 (1H, s, H-12), 7.16–7.37 (15H, m, 3×Ph). Anal.: calcd for $C_{70}H_{91}FO_{16}\cdot H_2O$: C, 68.61; H, 7.64; found: C, 68.59; H, 7.63%.

The reaction of **20** with **10** was performed in the same manner and in the same scale as that of **19** to afford the 4″-fluoro isomer **25** (131 mg, 73%); mp 107.2–108.7 °C, $[\alpha]_D$ +46.9° (*c* 1, chloroform).^{1}H NMR ($CDCl_3$): δ 0.81, 0.83, 1.05, 1.12, 1.14, 1.15, and 1.35 (each singlet corresponds to CH_3), 2.06, 2.07, and 2.09 (each singlet corresponds to Ac), 3.41 (1H, ddd, $J_{4',5'}$=9.0 Hz, $J_{5',6a'}$=4.7 Hz, $J_{5',6b'}$=1.8 Hz, H-5′), 3.54 (1H, dd, $J_{3',4'}$=9.0 Hz, H-4′), 3.60 (1H, dd, $J_{2',3'}$=9.0 Hz, H-3′), 3.61 (1H, dd, $J_{6a',6b'}$=10.0 Hz, H-6a′), 3.64 (1H, dddd, $J_{4'',5''}$=9.5 Hz, $J_{5'',6a''}$=4.9 Hz, $J_{5'',6b''}$=2.0 Hz, $J_{5'',F}$=21.8 Hz, H-5″), 3.67 (1H, dd, H-6b′), 3.69 (3H, s, CH_3O), 3.78 (1H, dd, $J_{1',2'}$=7.5 Hz, H-2′), 4.19 (1H, ddd, $J_{6a'',6b''}$=12.0 Hz, $J_{6a'',F}$=1.2 Hz, H-6a″), 4.30 (1H, dd, $J_{6b'',F}$=2.0 Hz, H-6b″), 4.32 (1H, d, H-1′), 4.47 (1H, ddd, $J_{3'',4''}$=8.9 Hz, $J_{4'',F}$=50.3 Hz, H-4″), 4.51–4.61 (2H, AB, δ_A=4.53, δ_B=4.59, $J_{A,B}$=12.0 Hz, PhC<u>H</u>$_2$), 4.58–4.80 (2H, AB, δ_A=4.60, δ_B=4.78, $J_{A,B}$=11.0 Hz, PhC<u>H</u>$_2$), 4.72—4.89 (2H, AB, δ_A=4.74, δ_B=4.87, $J_{A,B}$=10.2 Hz, PhC<u>H</u>$_2$), 4.91 (1H, ddd, $J_{1'',2''}$=8.0 Hz, $J_{2'',3''}$=9.7 Hz, H-2″), 5.11 (1H, d, H-1″), 5.25 (1H, ddd, $J_{3'',F}$=18.6 Hz, H-3″), 5.67 (1H, s, H-12), 7.16–7.37 (15H, m, 3×Ph). Anal.: calcd for $C_{70}H_{91}FO_{16}\cdot H_2O$: C, 68.61; H, 7.64; found: C, 68.44; H, 7.60%.

The reaction of **21** with **10** was performed in the same manner and in the same scale as that of **19** to afford the 6″-fluoro isomer **26** (146 mg, 82%); mp 241.2–242.8 °C, $[\alpha]_D$ +51.6° (c 1, chloroform). ^{1}H NMR ($CDCl_3$): δ 0.81, 0.86, 1.08, 1.13, 1.15, 1.15, and 1.35 (each singlet corresponds to CH_3), 2.01, 2.03, and 2.04 (each singlet corresponds to Ac), 3.42 (1H, ddd, $J_{4',5'}$=9.0 Hz, $J_{5',6a'}$=4.5 Hz, $J_{5',6b'}$=1.8 Hz, H-5′), 3.54 (1H, dd, $J_{3',4'}$=8.4 Hz, H-4′), 3.58 (1H, dd, $J_{2',3'}$=8.6 Hz, H-3′), 3.58 (1H, dddd, $J_{4'',5''}$=10.0 Hz, $J_{5'',6a''}$=4.0 Hz, $J_{5'',6b''}$=3.0 Hz, $J_{5'',F}$=17.2 Hz, H-5″), 3.61 (1H, dd, $J_{6a',6b'}$=10.5 Hz, H-6a′), 3.68 (1H, dd, H-6b′), 3.69 (3H, s, CH_3O), 3.79 (1H, dd, $J_{1',2'}$=7.5 Hz, H-2′), 4.34 (1H, d, H-1′), 4.38 (1H, ddd, $J_{6a'',6b''}$=10.2 Hz, $J_{6a'',F}$=47.0 Hz, H-6a″), 4.43 (1H, ddd, $J_{6b'',F}$=47.0 Hz, H-6b″), 4.51–4.62 (2H, AB, δ_A=4.53, δ_B=4.60, $J_{A,B}$=12.2 Hz, PhC<u>H</u>$_2$), 4.57–4.80 (2H, AB, δ_A=4.59, δ_B=4.78, $J_{A,B}$=10.5 Hz, PhC<u>H</u>$_2$), 4.73–4.89 (2H, AB, δ_A=4.75, δ_B=4.87, $J_{A,B}$=10.0 Hz, PhC<u>H</u>$_2$), 4.98 (1H, dd, $J_{1'',2''}$=7.8 Hz, $J_{2'',3''}$=9.2 Hz, H-2″), 5.06 (1H, dd, $J_{3'',4''}$=9.2 Hz, H-4″), 5.07 (1H, d, H-1″), 5.15 (1H, dd, H-3″), 5.67 (1H, s, H-12), 7.15–7.40 (15H, m, 3×Ph). Anal.: calcd for $C_{70}H_{91}FO_{16}$: C, 69.63; H, 7.60; found: C, 69.00; H, 7.55%.

Glycosylation of 16 with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (22). A mixture of **16** (104 mg, 0.126 mmol), **22** (104 mg, 0.252 mmol), AgOTf (81.3 mg, 0.315 mmol), TMU (46μL, 0.380 mmol), and dichloromethane (2.0 mL) was stirred at 0 °C for 3.5 h. The reaction mixture was filtered through Celite, and washed with water. After drying over anhyd sodium sulfate, the solution was evaporated and chromatographed using a mixed solvent of toluene:ethyl acetate (6:1) to give methyl (3β)-3-[2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4,6-di-*O*-benzyl-3-deoxy-3-fluoro-β-D-glucopyranosyloxy]-11-oxo-olean-12-en-30-oate (**27**, 132 mg, 90%); mp 187.8–189.4 °C, $[\alpha]_D$ +54.2° (*c* 1, chloroform).^{1}H NMR ($CDCl_3$): δ 0.81, 0.83, 1.04, 1.12, 1.15, 1.15, and 1.34 (each singlet corresponds to CH_3), 2.00, 2.02, 2.05, and 2.06 (each singlet corresponds to Ac), 3.37 (1H, dddd, $J_{4',5'}$=9.7 Hz, $J_{5',6a'}$=4.7 Hz, $J_{5',6b'}$=2.2 Hz, $J_{5',F}$=2.5 Hz, H-5′), 3.62 (1H, dd, $J_{6a',6b'}$=10.6 Hz, H-6a′), 3.65 (1H, ddd, $J_{4'',5''}$=9.5 Hz, $J_{5'',6a''}$=2.2 Hz, $J_{5'',6b''}$=4.3 Hz, H-5″), 3.67 (1H, dd, H-6b′), 3.69 (1H, ddd, $J_{3',4'}$=8.4 Hz, $J_{4',F}$=14.8 Hz, H-4′), 3.69 (3H, s, CH_3O), 3.82 (1H, ddd, $J_{1',2'}$=7.6 Hz, $J_{2',3'}$=8.9 Hz, $J_{2',F}$=14.5 Hz, H-2′), 4.07 (1H, dd, $J_{6a'',6b''}$=12.2 Hz, H-6a″), 4.24 (1H, dd, H-6b″), 4.33 (1H, d, H-1′), 4,51 (1H, ddd, $J_{3',F}$=52.3 Hz, H-3′), 4.51–4.61 (2H, AB, δ_A=4.53, δ_B=4.59, $J_{A,B}$=12.2 Hz, PhC<u>H</u>$_2$), 4.54–4.79 (2H, AB, δ_A=4.56, δ_B=4.77, $J_{A,B}$=11.0 Hz, PhC<u>H</u>$_2$), 4.82 (1H, d, $J_{1'',2''}$=7.9 Hz, H-1″), 4.97 (1H, dd, $J_{2'',3''}$=9.5 Hz, H-2″), 5.09 (1H, ddd, $J_{3'',4''}$=9.5 Hz, H-4″), 5.20 (1H, dd, H-3″), 5.67 (1H,

s, H-12), 7.16–7.33 (10H, m, 2 × Ph). Anal.: calcd for $C_{65}H_{87}FO_{17}$: C, 67.34; H, 7.56; found: C, 67.34; H, 7.65%.

Glycosylation of 18 with 22. A mixture of **18** (110 mg, 0.133 mmol), **22** (110 mg, 0.266 mmol), AgOTf (85.3 mg, 0.332 mmol), TMU (48 μL, 0.399 mmol), and dichloromethane (2.0 mL) was stirred at 0 °C for 2.5 h. The mixture was worked up as described for the preparation of **27** to afford the 4′-fluoro isomer **28** (143 mg, 93%); mp 219.8–221.0 °C, $[\alpha]_D$ +57.8° (*c* 1, chloroform). ^{1}H NMR ($CDCl_3$): δ 0.81, 0.83, 1.07, 1.13, 1.14, 1.15, and 1.35 (each singlet corresponds to CH_3), 2.01, 2.01, 2.04, and 2.05 (each singlet corresponds to Ac), 3.57 (1H, dd, $J_{5',6a'}$ = 4.6 Hz, $J_{6a',6b'}$ = 10.6 Hz, H-6a′), 3.59 (1H, dddd, $J_{4',5'}$ = 9.0 Hz, $J_{5',6b'}$ = 2.2 Hz, $J_{5',F}$ = 10.5 Hz, H-5′), 3.65 (1H, ddd, $J_{2',3'}$ = 9.0 Hz, $J_{3',4'}$ = 8.5 Hz, $J_{3',F}$ = 15.2 Hz, H-3′), 3.69 (3H, s, CH_3O), 3.72 (1H, dd, H-6b′), 3.76 (1H, dd, $J_{1',2'}$ = 7.5 Hz, H-2′), 3.76 (1H, ddd, $J_{4'',5''}$ = 9.0 Hz, $J_{5'',6a''}$ = 2.3 Hz, $J_{5'',6b''}$ = 4.3 Hz, H-5″), 4.01 (1H, dd, $J_{6a'',6b''}$ = 12.2 Hz, H-6a″), 4.21 (1H, dd, H-6b″), 4.39 (1H, d, H-1′), 4.43 (1H, ddd, $J_{4',F}$ = 51.0 Hz, H-4′), 4.60 (2H, s, PhC<u>H</u>$_2$), 4.63–4.83 (2H, AB, δ_A = 4.65, δ_B = 4.81, $J_{A,B}$ = 10.5 Hz, PhC<u>H</u>$_2$), 4.98 (1H, dd, $J_{1'',2''}$ = 8.0 Hz, $J_{2'',3''}$ = 9.2 Hz, H-2″), 5.06 (1H, d, H-1″), 5.08 (1H, dd, $J_{3'',4''}$ = 9.2 Hz, H-4″), 5.14 (1H, dd, H-3″), 5.67 (1H, s, H-12), 7.13–7.43 (15H, m, 3 × Ph). Anal.: calcd for $C_{65}H_{87}FO_{17}$: C, 67.34; H, 7.56; found: C, 67.30; H, 7.58%.

Glycosylation of 16 with methyl 2,3,4-tri-*O*-acetyl-α-D-glucoronatopyranosyl bromide (23). A mixture of **16** (119 mg, 0.144 mmol), **23** (343 mg, 0.864 mmol), AgOTf (222 mg, 0.864 mmol), TMU (138 μL, 1.15 mmol), and dichloromethane (2.4 mL) was stirred at 0 °C for 4 h. The work up according to that for the reaction with **22** gave **29** (126 mg, 77%); mp 164.4—165.4 °C, $[\alpha]_D$ +45.3° (c 0.5, chloroform). ^{1}H NMR ($CDCl_3$): δ 0.80 0.82, 1.02, 1.12, 1.15, 1.15, and 1.34 (each singlet corresponds to CH_3), 2.01, 2.01, and 2.04 (each singlet corresponds to Ac), 3.37 (1H, dddd, $J_{4',5'}$ = 9.3 Hz, $J_{5',6a'}$ = 4.2 Hz, $J_{5',6b'}$ = 1.8 Hz, $J_{5',F}$ = 1.5 Hz, H-5′), 3.61 (1H, dd, $J_{6a',6b'}$ = 10.3 Hz, H-6a′), 3.66 (1H, ddd, $J_{3',4'}$ = 8.4 Hz, $J_{4',F}$ = 12.4 Hz, H-4′), 3.68 (1H, dd, H-6b′), 3.69 (3H, s, CH_3O), 3.71 (3H, s, CH_3O), 3.80 (1H, ddd, $J_{1',2'}$ = 7.5 Hz, $J_{2',3'}$ = 8.8 Hz, $J_{2',F}$ = 14.5 Hz, H-2′), 3.99 (1H, d, $J_{4'',5''}$ = 9.7 Hz, H-5″), 4.33 (1H, d, H-1′), 4,51 (1H, ddd, $J_{3',F}$ = 51.6 Hz, H-3′), 4.51–4.61 (2H, AB, δ_A = 4.53, δ_B = 4.59, $J_{A,B}$ = 12.0 Hz, PhC<u>H</u>$_2$), 4.53–4.79 (2H, AB, δ_A = 4.55, δ_B = 4.77, $J_{A,B}$ = 11.0 Hz, PhC<u>H</u>$_2$), 4.84 (1H, d, $J_{1'',2''}$ = 7.8 Hz, H-1″), 4.98 (1H, dd, $J_{2'',3''}$ = 9.6 Hz, H-2″), 5.22 (1H, dd, $J_{3'',4''}$ = 9.5 Hz, H-3″), 5.23 (1H, ddd, H-4″), 5.66 (1H, s, H-12), 7.15–7.35 (10H, m, 2 × Ph). Anal.: calcd for $C_{65}H_{87}FO_{17}$: C, 67.11; H, 7.48; found: C, 66.73; H, 7.41%.

Glycosylation of 18 with 23. A mixture of **18** (130 mg, 0.157 mmol), **23** (373 mg, 0.942 mmol), AgOTf (242 mg, 0.942 mmol), TMU (151 μL, 1.26 mmol), and dichloromethane (2.7 mL) was stirred at 0 °C for 3 h. The work up according to that for the reaction with **22** gave **30** (140 mg, 78%); mp 221.6–222.3 °C, $[\alpha]_D$ +51.8° (c 0.5, chloroform). ^{1}H NMR ($CDCl_3$): δ 0.81 0.84, 1.05, 1.12, 1.15, 1.15, and 1.35 (each singlet corresponds to CH_3), 2.00, 2.02, and 2.04 (each singlet corresponds to Ac), 3.57 (1H, dddd, $J_{4',5'}$ = 9.0 Hz, $J_{5',6a'}$ = 4.4 Hz, $J_{5',6b'}$ = 2.5 Hz, $J_{5',F}$ = 10.0 Hz, H-5′), 3.57 (1H, dd, $J_{6a',6b'}$ = 10.0 Hz, H-6a′), 3.64 (1H, ddd, $J_{2',3'}$ = 9.0 Hz, $J_{3',4'}$ = 8.8 Hz, $J_{3',F}$ = 14.8 Hz, H-3′), 3.68 (3H, s, CH_3O), 3.70 (3H, s, CH_3O), 3.75 (1H, dd, $J_{1',2'}$ = 7.5 Hz, H-2′), 3.76 (1H, dd, H-6b′), 3.89 (1H, ddd, $J_{4'',5''}$ = 9.6 Hz, H-5″), 4.39 (1H, d, H-1′), 4.44 (1H, ddd, $J_{4',F}$ = 50.6 Hz, H-4′), 4.59 (2H, s, PhC<u>H</u>$_2$), 4.62–4.83 (2H, AB, δ_A = 4.64, δ_B = 4.81, $J_{A,B}$ = 10.3 Hz, PhC<u>H</u>$_2$), 4.99 (1H, dd, $J_{1'',2''}$ = 8.0 Hz, $J_{2'',3''}$ = 8.7 Hz, H-2″), 5.07 (1H, d, H-1″), 5.15 (1H, dd, $J_{3'',4''}$ = 9.2 Hz, H-3″), 5.22 (1H, dd, H-4″), 5.67 (1H, s, H-12), 7.14–7.43 (10H, m, 2 × Ph). Anal.: calcd for $C_{64}H_{85}FO_{17}$: C, 67.11; H, 7.48; found: C, 66.82; H, 7.50%.

Removal of the protecting groups of 24–30. A solution of the totally protected glycoside (130 mg) in chloroform (1.3 mL) and methanol (3.9 mL) was mixed with 1.5 N methanolic sodium methoxide (0.4 mL), and kept at room temperature for 3 h. The solution was neutralized with acetic acid, evaporated, and chromatographed using a mixed solvent of chloroform:methanol (20:1) to give a syrupy compound. The compound was dissolved in ethanol (amount depended on the solubility of the compound), and hydrogenated in the presence of 20% palladium hydroxide on carbon (25 mg) at 1.5 atm of hydrogen for 16 h. Filtration of the reaction mixture and subsequent evaporation gave a glassy residue, which was heated with 5% sodium hydroxide in ethanol:water (1:1; 2.5 mL) at 80 °C for 4 h. After cooling, the solution was neutralized with Dowex 50W (H^+), evaporated, and chromatographed using a mixed solvent of chloroform–methanol to afford a glassy product, which was crystallized from ethanol. Through this procedure, the compounds **24–30** were deprotected to the following glycosides in yields of 30–40%.

(3β)-3-[2-*O*-(3-deoxy-3-fluoro-β-D-glucopyranosyl)-β-D-glucopyranosyloxy]-11-oxoolean-12-en-30-oic acid (1). Mp 224.5–225.1 °C. $[\alpha]_D$ +86.0° (*c* 0.5, pyridine). ^{1}H NMR ($CDCl_3$): δ 0.81, 1.10, 1.14, 1.26, 1.32, 1.37, and 1.44 (each singlet corresponds to CH_3), 3.88–3.95 (2H, m, H-5′ and H-5″), 4.17 (1H, dd, $J_{3',4'}$ = 9.2 Hz, $J_{4',5'}$ = 9.8 Hz, H-4′), 4.26 (1H, ddd, $J_{1'',2''}$ = 7.6 Hz, $J_{2'',3''}$ = 8.8 Hz, $J_{2'',F}$ = 14.2 Hz, H-2″), 4.27 (1H, dd, $J_{1',2'}$ = 7.3 Hz, $J_{2',3'}$ = 8.9 Hz, H-2′), 4.33 (1H, dd, H-3′), 4.36 (1H, dd, $J_{5'',6a''}$ = 5.0 Hz, $J_{6a'',6b''}$ = 12.0 Hz, H-6a″), 4.49–4,57 (3H, H-6a′, H-6b′, and H-6b″), 4.58 (1H, ddd, $J_{3'',4''}$ = 9.3 Hz, $J_{4'',5''}$ = 9.0 Hz, $J_{4'',F}$ = 14.7 Hz, H-4″), 4.92 (1H, d, H-1′), 5.13 (1H, ddd, $J_{3'',F}$ = 52.5 Hz, H-3″), 5.44 (1H, d, H-1″), 6.00 (1H, s, H-12). Anal. calcd for $C_{43}H_{65}FO_{13}ßH_2O$: C, 62.45; H, 8.17; found: C, 61.69; H, 8.14%.

(3β)-3-[2-*O*-(4-deoxy-4-fluoro-β-D-glucopyranosyl)-β-D-glucopyranosyloxy]-11-oxoolean-12-en-30-oic acid (2). Mp 225.0–226.1 °C. $[\alpha]_D$ +82.5° (*c* 0.5, pyridine). ^{1}H

NMR ($CDCl_3$): δ 0.81, 1.10, 1.16, 1.27, 1.31, 1.37, and 1.44 (each singlet corresponds to CH_3), 3.89–3.97 (2H, m, H-5′ and H-5″), 4.13 (1H, dd, $J_{1'',2''}=7.5$ Hz, $J_{2'',3''}=9.1$ Hz, H-2″), 4.18 (1H, dd, $J_{3',4'}=9.2$ Hz, $J_{4',5'}=9.5$ Hz, H-4′), 4.26 (1H, dd, $J_{1',2'}=7.4$ Hz, $J_{2',3'}=9.0$ Hz, H-2′), 4.34 (1H, dd, H-3′), 4.30–4,39 (3H, H-6a′, H-6a″, and H-6b″), 4.43 (1H, ddd, $J_{3'',4''}=9.3$ Hz, $J_{3'',F}=17.2$ Hz, H-3″), 4.54 (1H, br. d, H-6b′), 4.92 (1H, d, H-1′), 5.23 (1H, ddd, $J_{4'',5''}=9.0$ Hz, $J_{4'',F}=50.5$ Hz, H-4″), 5.42 (1H, d, H-1″), 6.01 (1H, s, H-12). Anal.: calcd for $C_{43}H_{65}FO_{13}ß2H_2O$: C, 61.12; H, 8.23; found: C, 61.53; H, 8.27%.

(3β)-3-[2-*O*-(6-deoxy-6-fluoro-β-D-glucopyranosyl)-β-D-glucopyranosyloxy]-11-oxoolean-12-en-30-oic acid (3). Mp 227.0–229.0 °C. $[\alpha]_D$ +86.4° (*c* 0.5, pyridine).^{1}H NMR ($CDCl_3$): δ 0.81, 1.11, 1.22, 1.30, 1.37, 1.39, and 1.44 (each singlet corresponds to CH_3), 3.92 (1H, m, H-5′), 3.95 (1H, br. dd, $J_{5'',F}=22.0$ Hz, H-5″), 4.14 (1H, dd, $J_{1'',2''}=7.5$ Hz, $J_{2'',3''}=8.7$ Hz, H-2″), 4.17 (1H, dd, $J_{1',2'}=7.4$ Hz, $J_{2',3'}=8.6$ Hz, H-2′), 4.19 (1H, dd, $J_{3',4'}=8.5$ Hz, $J_{4',5'}=9.0$ Hz, H-4′), 4.20 (1H, dd, $J_{3'',4''}=8.8$ Hz, $J_{4'',5''}=9.0$ Hz, H-4″), 4.25 (1H, dd, H-3″), 4.34 (1H, dd, H-3′), 4.37 (1H, dd, $J_{5',6a'}=5.3$ Hz, $J_{6a',6b'}=11.7$ Hz, H-6a′), 4.54 (1H, dd, $J_{5',6b'}=2.0$ Hz, H-6b′), 4.93 (1H, d, H-1′), 5.14 (1H, ddd, $J_{5'',6a''}=1.8$ Hz, $J_{6a'',6b''}=10.0$ Hz, $J_{6a'',F}=48.5$ Hz, H-6a″), 5.17 (1H, ddd, $J_{5'',6b''}=3.3$ Hz, $J_{6b'',F}=47.2$ Hz, H-6b″), 5.37 (1H, d, H-1″), 6.01 (1H, s, H-12). Anal.: calcd for $C_{43}H_{65}FO_{13}$: C, 63.84; H, 8.10; found: C, 63.43; H, 8.17%.

(3β)-3-(3-deoxy-3-fluoro-2-*O*-β-D-glucopyranosyl-β-D-glucopyranosyloxy)-11-oxoolean-12-en-30-oic acid (4). Mp 232.0–233.7 °C. $[\alpha]_D$ +81.2° (*c* 0.5, pyridine).^{1}H NMR ($CDCl_3$): δ 0.81, 1.10, 1.13, 1.25, 1.32, 1.38, and 1.43 (each singlet corresponds to CH_3), 3.81(1H, m, H-5′), 3.98 (1H, ddd, $J_{4'',5''}=9.0$ Hz, $J_{5'',6a''}=1.5$ Hz, $J_{5'',6b''}=4.0$ Hz, H-5″), 4.11 (1H, dd, $J_{5',6a'}=3.0$ Hz, $J_{6a',6b'}=11.2$ Hz, H-6a′), 4.13 (1H, dd, $J_{1'',2''}=7.5$ Hz, $J_{2'',3''}=8.6$ Hz, H-2″), 4.16 (1H, dd, $J_{5',6b'}=6.5$ Hz, H-6b′), 4.21 (1H, dd, $J_{3'',4''}=8.3$ Hz, H-4″), 4.29 (1H, dd, H-3″), 4.32 (1H, dd, $J_{3',4'}=8.8$ Hz, $J_{4',5'}=9.2$ Hz, $J_{4',F}=27.0$ Hz, H-4′), 4.44 (1H, dd, $J_{6a'',6b''}=11.5$ Hz, H-6a″), 4,58 (1H, H-6b″), 4.59 (1H, ddd, $J_{1',2'}=7.7$ Hz, $J_{2',3'}=9.0$ Hz, $J_{2',F}=13.0$ Hz, H-2′), 4.84 (1H, d, H-1′), 5.15 (1H, ddd, $J_{3',F}=52.8$ Hz, H-3′), 5.46 (1H, d, H-1″), 6.00 (1H, s, H-12). Anal.: calcd for $C_{43}H_{65}FO_{13}\cdot H_2O$: C, 62.45; H, 8.17; found: C, 62.36; H, 8.15%.

(3β)-3-(4-deoxy-4-fluoro-2-*O*-β-D-glucopyranosyl-β-D-glucopyranosyloxy)-11-oxoolean-12-en-30-oic acid (5). Mp 224.5–226.0 °C. $[\alpha]_D$ +85.1° (*c* 0.5, pyridine). ^{1}H NMR ($CDCl_3$): δ 0.81, 1.11, 1.16, 1.27, 1.34, 1.38, and 1.43 (each singlet corresponds to CH_3), 3.88–3.98 (2H, m, H-5′ and H-5″), 4.14 (1H, dd, $J_{1'',2''}=7.5$ Hz, $J_{2'',3''}=9.0$ Hz, H-2″), 4.19–4.29 (2H, H-6a′ and H-6b′), 4.25 (1H, dd, $J_{1',2'}=7.6$ Hz, $J_{2',3'}=9.1$ Hz, H-2′), 4.31 (1H, dd, $J_{3'',4''}=9.2$ Hz, H-3″), 4.34 (1H, dd, $J_{4'',5''}=9.5$ Hz, H-4″), 4.45–4.56 (2H, H-6a″and H-6b″), 4.47 (1H, ddd, $J_{3',4'}=9.0$ Hz, $J_{3',F}=16.3$ Hz, H-3′), 4.91 (1H, d, H-1′), 5.02 (1H, ddd, $J_{4',5'}=9.2$ Hz, $J_{4',F}=50.8$ Hz, H-4′), 5.40 (1H, d, H-1″), 6.00 (1H, s, H-12). Anal.: calcd for $C_{43}H_{65}FO_{13}\cdot H_2O$: C, 62.45; H, 8.17; found: C, 62.16; H, 8.20%.

(3β)-3-(3-deoxy-3-fluoro-2-*O*-β-D-glucopyranosyl-β-D-glucopyranuronosyloxy)-11-oxoolean-12-en-30-oic acid (6). Mp 227.5–229.0 °C. $[\alpha]_D$ +90.5° (*c* 0.5, pyridine).^{1}H NMR ($CDCl_3$): δ 0.81, 1.11, 1.14, 1.26, 1.34, 1.38, and 1.44 (each singlet corresponds to CH_3), 3.79 (1H, m, H-5′), 4.10–4.20 (2H, H-6a′ and H-6b′), 4.15 (1H, dd, $J_{1'',2''}=7.5$ Hz, $J_{2'',3''}=8.7$ Hz, H-2″), 4.30 (1H, dd, $J_{3'',4''}=8.5$ Hz, H-3″), 4.30 (1H, dd, $J_{3',4'}=8.8$ Hz, $J_{4',F}=25.5$ Hz, H-4′), 4.30 (1H, d, $J_{4'',5''}=9.2$ Hz, H-5″), 4.36 (1H, dd, H-4″), 4.58 (1H, ddd, $J_{1',2'}=7.6$ Hz, $J_{2',3'}=9.0$ Hz, $J_{2',F}=13.0$ Hz, H-2′), 4.85 (1H, d, H-1′), 5.15 (1H, ddd, $J_{3',F}=52.0$ Hz, H-3′), 5.47 (1H, d, H-1″), 5.99 (1H, s, H-12). Anal.: calcd for $C_{42}H_{63}FO_{14}$: C, 62.21; H, 7.83; found: C, 61.77; H, 7.86%.

(3β)-3-(4-deoxy-4-fluoro-2-*O*-β-D-glucopyranosyl-β-D-glucopyranuronosyloxy)-11-oxoolean-12-en-30-oic acid (7). Mp 252.2–253.7 °C. $[\alpha]_D$ +96.7° (*c* 1, pyridine).^{1}H NMR ($CDCl_3$): δ 0.81, 1.11, 1.14, 1.26, 1.34, 1.38, and 1.44 (each singlet corresponds to CH_3), 3.79 (1H, m, H-5′), 4.18 (1H, dd, $J_{1'',2''}=7.5$ Hz, $J_{2'',3''}=9.0$ Hz, H-2″), 4.20 (1H, d, $J_{4'',5''}=9.2$ Hz, H-5″), 4.20–4.29 (2H, H-6a′ and H-6b′), 4.24 (1H, dd, $J_{1',2'}=7.6$ Hz, $J_{2',3'}=9.2$ Hz, H-2′), 4.32 (1H, dd, $J_{3'',4''}=8.8$ Hz, H-3″), 4.50 (1H, dd, H-4″), 4.47 (1H, ddd, $J_{3',4'}=9.0$ Hz, $J_{3',F}=13.0$ Hz, H-3′), 4.93 (1H, d, H-1′), 5.03 (1H, ddd, $J_{4',5'}=9.5$ Hz, $J_{4',F}=51.0$ Hz, H-4′), 5.42 (1H, d, H-1″), 5.99 (1H, s, H-12). Anal.: calcd for $C_{42}H_{63}FO_{14}$: C, 62.21; H, 7.83; found: C, 62.15; H, 7.90%.

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