Syntheses of Glycyrrhetic Acid α-Diglycosides and Enol α-Glycosides

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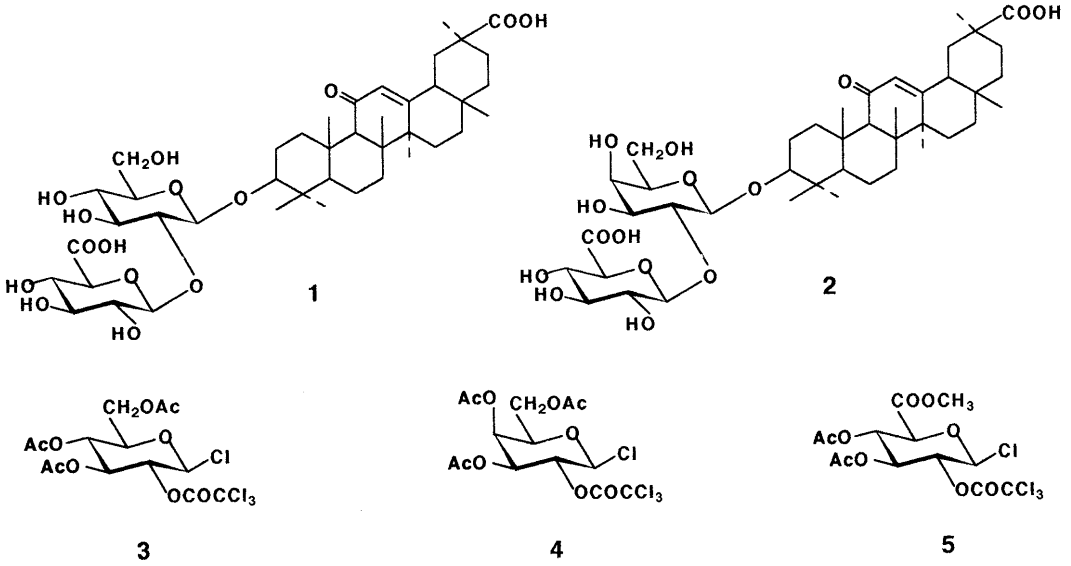
Glycyrrhetinate α-monoglycoside derivatives 8, 10 and 12, all having a trichloroacetyl group at the C-2 position of the pyranose ring, were treated with NH_3-saturated ether at 0 °C to give the corresponding alcohols 13, 15 and 17, accompanied by 2′-chloroderivatives, 14, 16 and 18, respectively. Glycosylations of the alcohols 13, 15 and 17 with methyl 2,3,4-tri-*O*-acetyl-α-D-glucuronatopyranosyl bromide 19 in the presence of AgOTf in dry CH_2Cl_2 gave the corresponding α-diglycosides 20, 22 and 24 together with the enol α-glycosides 21, 23 and 25, respectively. Glycosylations of the diglycoside derivatives 20, 22 and 35 having no reactive OH group in the molecules with 19 for longer reaction times gave quantitatively the enol α-glycoside derivatives 21, 23 and 36, respectively. Glycosylation of the monoglycoside derivative 37, which has a poorly reactive OH group at the C-4 position on the pyranose ring, with 19 gave an enol α-glycoside 38. The mechanism of the formation of enol α-glycosides was investigated. Removal of the protecting groups of 20, 22 and 24 by successive treatment with 1.5 N NaOMe in MeOH and 5% KOH in EtOH–H_2O (1 : 1) gave the free α-diglycosides 26—28, and removal of those of 31, 21, 23, 25 and 36 by treatment with 5% KOH in EtOH–H_2O (1 : 1) under reflux gave the free enol α-glycosides 41—45, respectively.

Keywords glycyrrhetic acid; α-monoglycoside; glycosylation; α-diglycoside; enol-α-glycoside; α,β-unsaturated ketone

In previous papers,[1,2] we reported the syntheses and cytoprotective effects against carbon tetrachloride-induced hepatic injury *in vivo* and *in vitro* of glycyrrhetic acid β-diglycosides in which various β(1→2)-linked disaccharides, consisting of combinations of two of glucopyanose, galactopyranose and glucuronopyranose, were β-linked to the *O*-3 position of the aglycone. In this paper, we describe the synthesis of glycyrrhetic acid α-diglycosides having disaccharides such as 2-*O*-(β-D-glucuronopyranosyl)-α-D-glucopyranose, -α-D-galactopyranose and -α-D-glucuronopyranose at the *O*-3 position of the aglycon for comparison of their cytoprotective effects against CCl_4-induced hepatic injury with those of the β-diglycosides. During the synthetic study of the α-diglycosides, we found that the α,β-unsaturated ketone group on the C-ring of the aglycon reacted with acetylated sugar bromides in the Koenigs–Knorr reactions[3,4] to form enol α-glycosides, and reported it in a short communication.[5] Further details of the formation of enol α-glycoside derivatives are also given here.

As we have already reported, glycyrrhetic acid β-diglycosides such as **1** and **2** having 2-*O*-(β-D-glucuronopyranosyl)-β-D-glucopyranose and -β-D-galactopyranose as sugar components at the *O*-3 position of the aglycon were synthesized in stepwise glycosylations.[2] In the first glycosylation, 2-*O*-trichloroacetyl-β-D-glycopyranosyl chlorides **3**—**5**,[6-8] which were prepared in one step by the reaction of corresponding β-pyranose



Ac = $COCH_3$

Fig. 1

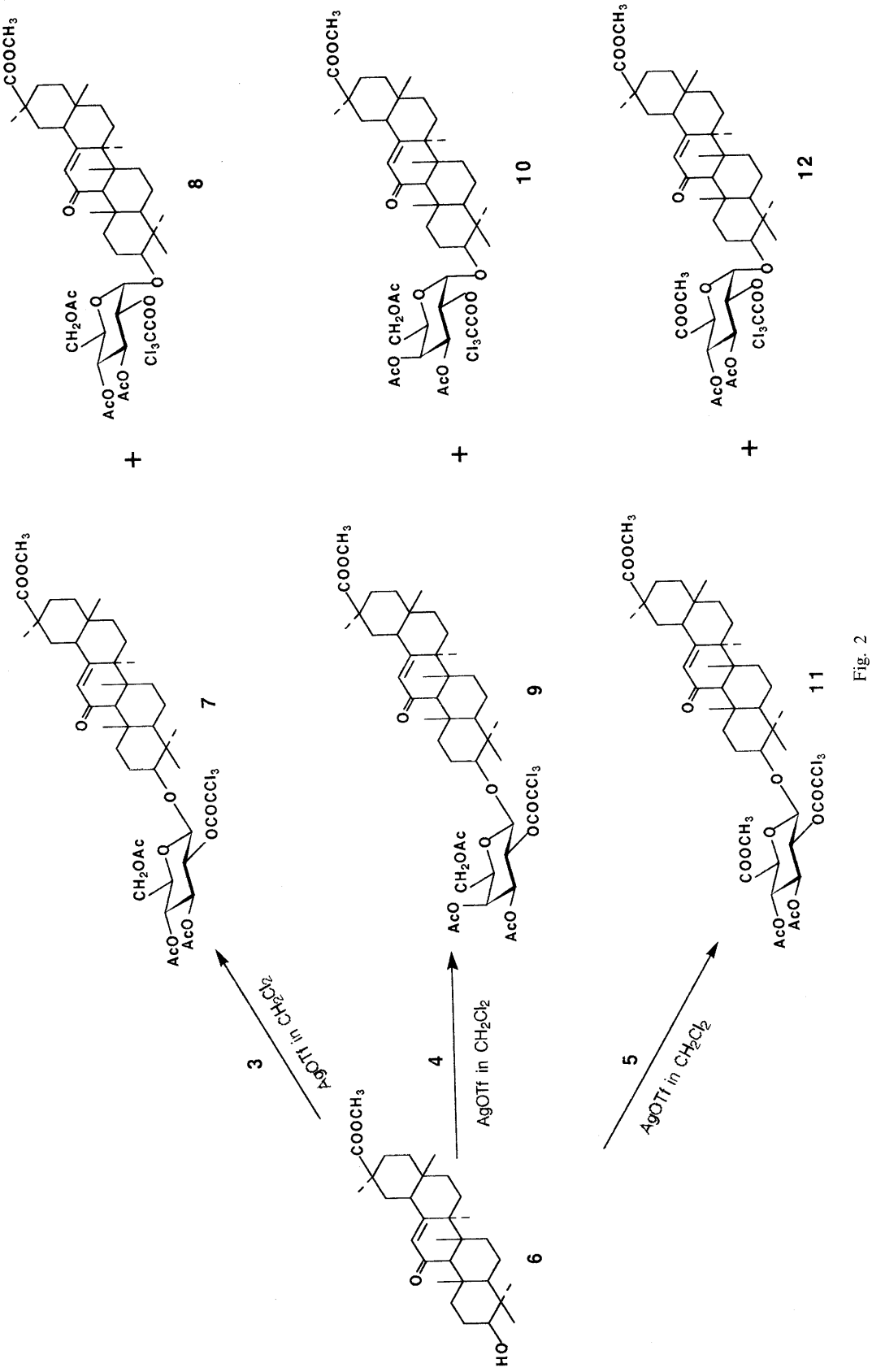


Fig. 2

peracetates with PCl_5, were reacted with methyl glycyrrhetinate **6**[9] to give pairs of β- and α-monoglycosides (**7** and **8**, **9** and **10**, and **11** and **12**, respectively). Detrichloroacetylation of the β-monoglycosides **7**, **9** and **11** by treatment with NH_3-saturated ether at 0 °C gave quantitatively the corresponding alcohols, which had only one free OH group at the C-2 position on the pyranose, and were further glycosylated with acetylated glycopyranosyl bromides to obtain the desired β-diglycoside derivatives.

For the synthesis of the glycyrrhetic acid α-diglycosides, the α-monoglycosides **8**, **10** and **12** were utilized as the starting materials in this study. Treatment of **8**, **10** and **12** with NH_3-saturated ether at 0 °C gave the corresponding alcohols **13** (74.1%), **15** (63.8%) and **17** (66.7%) together with compounds **14** (14.5%), **16** (<3.5%) and **18** (16.3%), respectively, in contrast to the results with the β-monoglycosides **7**, **9** and **11**. Fast atom bombardment mass spectra (FAB-MS) of **13**, **15** and **17** showed quasimolecular ion peaks at *m/z* 795, 795 and 781 $[M+Na]^+$, respectively. In the ^{1}H-NMR spectra of **13**, **15** and **17**, the signals of the H-2 protons on the pyranoses were shifted to higher fields of δ 3.65, 3.95 and 3.69 together with anomeric protons at δ 5.08 (d, J=4.0 Hz), 5.13 (d, J=4.0 Hz) and 5.18 (d, J=4.0 Hz), respectively. FAB-MS of **14** and **16** showed the same quasimolecular ion peak at *m/z* 813 $[M+Na]^+$, and that of **18** showed a quasimolecular ion peak at *m/z* 799 $[M+Na]^+$. The ^{1}H-NMR spectra of **14** and **18** exhibited signals of anomeric and H-2 protons on the pyranose ring at δ 5.14 (d, J=1.1 Hz) and 4.34 (dd, J=3.0, 1.1 Hz), 5.24 (d, J=3.0 Hz) and 4.30 (dd, J=3.0, 3.0 Hz), respectively, which indicated, together with the elemental analyses and FAB-MS of **14** and **18**, that a chlorine atom was substituted at the C-2 position on the pyranose ring. Furthermore, the coupling constants ($J_{2,3}$) of the H-2 protons of **14** and **18** indicated that the chlorine atom is axial. Compound **16** was not completely purified so that the ^{1}H-NMR spectrum was not sufficiently

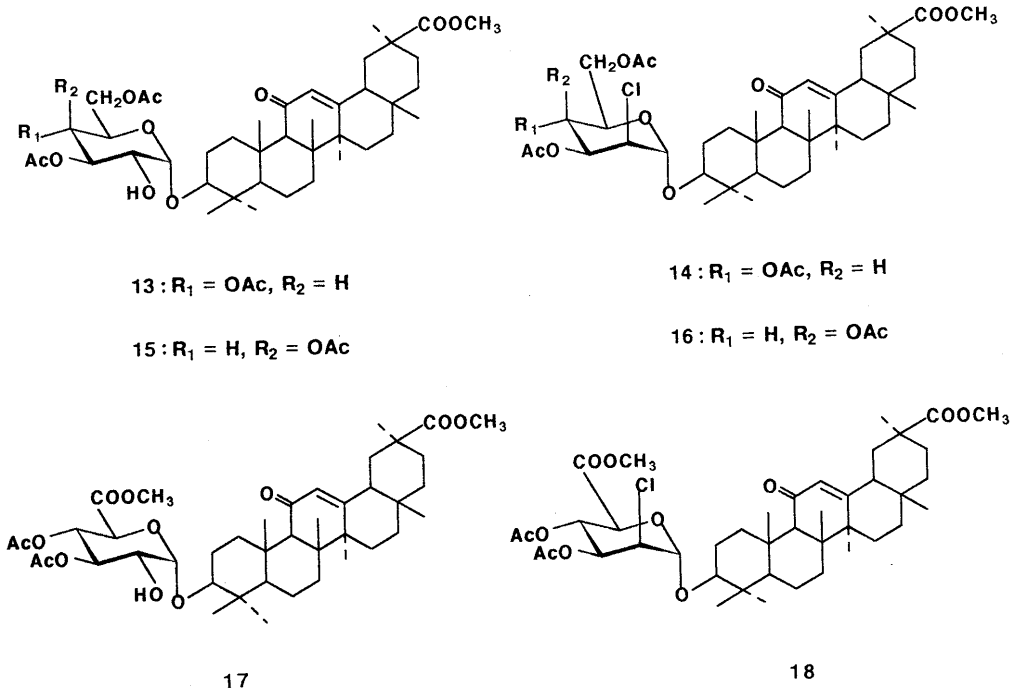


Fig. 3

TABLE I. Glycosylations of Glycyrrhetic Acid Derivatives with **19** or **30**

Entry	Substrate	Bromide	Catalyst	Reaction time (h)	Product (yield %)
1	**13**	**19**	AgOTf	2.5	**20** (35.2), **21** (18.5)
2	**15**	**19**	AgOTf	3.5	**22** (44.6), **23** (28.2)
3	**15**	**19**	AgOTf	12	**23** (90.5)
4	**15**	**19**	$Hg(CN)_2/HgBr_2$	20	**23** (92.8)
5	**17**	**19**	AgOTf	4	**24** (31.3), **25** (20.3)
6	**29**	**19**	AgOTf	15	**31** (91.2)
7	**29**	**19**	$Hg(CN)_2/HgBr_2$	20	**31** (89.7)
8	**29**	**30**	$Hg(CN)_2/HgBr_2$	20	**32** (90.2)
9	**34**	**19**	AgOTf	1.5	**35** (67.9), **36** (4.5)
10	**22**	**19**	AgOTf	15	**23** (90.5)
11	**22**	**19**	$Hg(CN)_2/HgBr_2$	23	**23** (79.5)
12	**35**	**19**	AgOTf	10	**36** (91.5)
13	**35**	**19**	$Hg(CN)_2/HgBr_2$	20	**36** (89.6)
14	**37**	**19**	AgOTf	20	**38** (65.3)

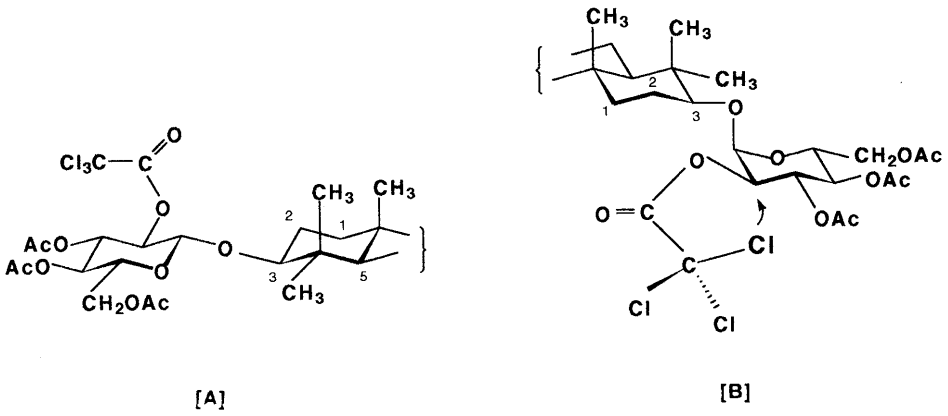


Fig. 4

informative. However, scince it gave the same quasimolecular ion peak as that of **14**, **16** was similarly presumed to be a chlorinated product at the C-2 position on the pyranose. Although the mechanism of formation of the chlorinated products **14**, **16** and **18** have not been fully elucidated yet, it may be as follows: in the most stable conformers, [A] for β-monoglycoside **7** and [B] for α-monoglycoside **8** (Fig. 4), the trichloracetyl group in [A] may be easily hydrolyzed because of the lesser steric hindrance from the backbone of the aglycon. On the other hand, the reaction in [B] is hindered by the steric bulky aglycon so that the hydrolysis of the trichloroacetyl group of **8** is retarded and one of the three chlorine atoms of the group lies close to the β-site of the C-2 position of the pyranose. Consequently, **8** gave the alcohol **13** in smaller yield than the β-monoglycoside **7**, accompanied by the formation of the chlorinated product **14**.

Glycosylations of the alcoholic monoglycosides **13**, **15**, and **17** with methyl 2,3,4-tri-*O*-acetyl-α-D-glucuronatopyranosyl bromide (**19**)[10] in the presence of silver triflate (AgOTf)[11,12] in dry CH_2Cl_2 under stirring for 2.5—4.0 h at room temperature gave pairs of compounds **20** (35.2%) and **21** (18.5%), **22** (44.6%) and **23** (28.2%), and **24** (31.3%) and **25** (20.3%), respectively (entries 1, 2 and 5 in Table I). FAB-MS of **20** and **22** showed the same quasimolecular ion peak at *m/z* 1111 $[M+Na]^+$, and that of **24**, a quasimolecular ion peak at *m/z* 1097 $[M+Na]^+$, which suggests that **20**, **22** and **24** are the corresponding methyl glycyrrhetinate diglycosides. The ^{1}H-NMR spectra of **20**, **22** or **24** each exhibited a pair of doublets due to anomeric protons at δ 5.15 (J=3.8 Hz) and 4.68 (J=7.6 Hz), 5.20 (J=4.0 Hz) and 4.75 (J=7.7 Hz) or 5.25 (J=3.8 Hz) and 4.67 (J=7.9 Hz). As the first of each pair of doublets was due to the anomeric protons of α-D-gluco- and α-D-galactopyranose and methyl α-D-glucuronatopyranose rings, which are linked directly to the *O*-3 position of the aglycon, the latters were assignable to anomeric protons of methyl glucuronatopyranose rings newly introduced at the *O*-2 positions of the pyranose rings. From the coupling constants of the latter doublets, all the newly introduced methyl glucuronatopyranose rings were indicated to be β. Removal of the protecting groups of **20**, **22** and **24** by successive treatment with 1.5 N NaOMe in MeOH and 5% KOH in EtOH–H_2O (1 : 1) gave compounds **26**—**28** in the yields of 66.0, 67.2 and 61.3%, respectively. Products **26**—**28** showed quasimolecular ion peaks at *m/z* 831, 831 and 845 $[M+Na]^+$, respectively in the FAB-MS, and pairs of anomeric carbon signals at δ 97.4 and 106.8, 97.9 and 106.8, and 97.9 and 106.8, respectively, in the ^{13}C-NMR spectra (Table IV).

Product **21** showed a quasimolecular ion peak at *m/z* 1427 $[M+Na]^+$ in the FAB-MS, indicating that **21** was a triglycoside derivative having one acetylated glucopyranose and two acetylated methyl glucuronatopyranoses in the molecule. In the ^{1}H-NMR spectrum of **21**, three doublets due to the anomeric protons were observed at δ 5.14, 4.70 and 5.65 with coupling constants of 3.3, 7.6 and 3.3 Hz, respectively. Two of the doublets at δ 5.14 and 4.70 were similar to those of **20** in both chemical shifts and coupling constants so that those doublets could be assignable to the anomeric protons of α-D-glucopyranose and one of the two methyl β-D-glucuronatopyranose rings of the disaccharide linked to the *O*-3 position on the aglycon. Therefore, it was presumed that the third doublet at δ 5.65 was due to the anomeric proton of the other methyl α-D-glucuronatopyranose ring, and was assumed that the pyranose was attached to the *O*-11 position on the C-ring of the aglycon, forming an enol α-D-glycoside. The structures of **23** and **25** were also presumed to be triglycosides in which an enol α-D-glucuronatopyranoside linkage was formed on the C-ring as in **21** on the basis of spectral analyses; **23** and **25** showed quasimolecular ion peaks at *m/z* 1427 and 1413 $[M+Na]^+$, respectively, in the FAB-MS. In the ^{1}H-NMR spectra, **23** exhibited three anomeric protons at δ 5.22 (d, J=3.7 Hz), 4.76 (d, J=7.7 Hz) and 5.65 (d, J=3.7 Hz), and **25** exhibited three at δ 5.25 (d, J=3.3 Hz), 4.68 (d, J=7.3 Hz) and 5.65 (d, J=3.3 Hz).

The formation and structure of the enol α-D-glycosides were further confirmed by the reactions of methyl 3-*O*-acetylglycyrrhetinate **29** with **19** and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **30**.[13] Generally, alkylation of α,β-unsaturated ketones with alkyl halides occurs at the γ-carbon *via* enolate intermediates to give *C*-alkylated compounds.[14—16] However, the reaction of **29** with **19** in the presence of AgOTf in CH_2Cl_2 for 15 h or in the presence of a mixed catalyst, $Hg(CN)_2$ and

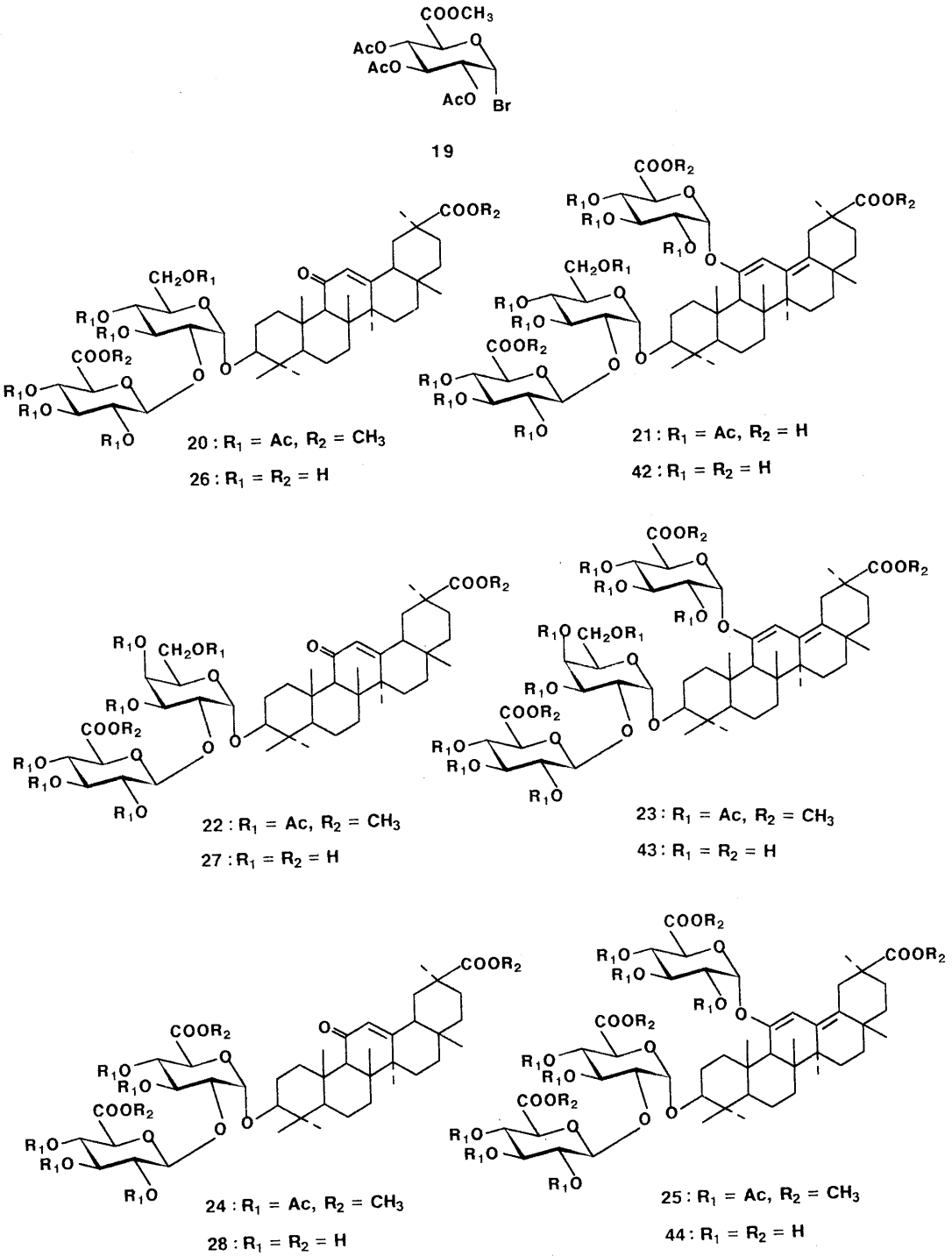


Fig. 5

$HgBr_2$,[17] in CH_2Cl_2 for 20 h at room temperature gave an enol α-glycoside **31** in the yield of 91.2% or 89.7% (entries 6 and 7 in Table I). Compound **31** showed a quasimolecular ion peak at *m/z* 865 $[M+Na]^+$, and a doublet due to an anomeric proton at δ 5.68 with the coupling constant of 3.5 Hz, together with the signals of two methoxy and four acetyl groups in the ^{1}H-NMR spectrum. Furthermore, the reaction of **29** with **30** in the presence of the mixed catalyst in CH_2Cl_2 at room temperature for 20 h also gave an enol α-glycoside (**32**) in 90.2% yield (entry 8). Compound **32** showed a quasimolecular ion peak at *m/z* 879 $[M+Na]^+$ in the FAB-MS, and an anomeric proton signal at δ 5.64 (d, $J=3.7$ Hz) together with signals of one methoxy and five acetyl groups in the ^{1}H-NMR spectrum. From the chemical shifts of the anomeric protons, it was clear that **31** and **32** were *O*-glycosides, not *C*-glycosides. The stereochemistry of the enol α-glycosidic linkages of the products may be explained by the fact that, in oxonium cation intermediates such as [C] and [D] (Fig. 7) derived from **19** and **30**, respectively, the quasi axial substituent ($COOCH_3$ in [C] and CH_2OAc in [D]) at C-5 hinders

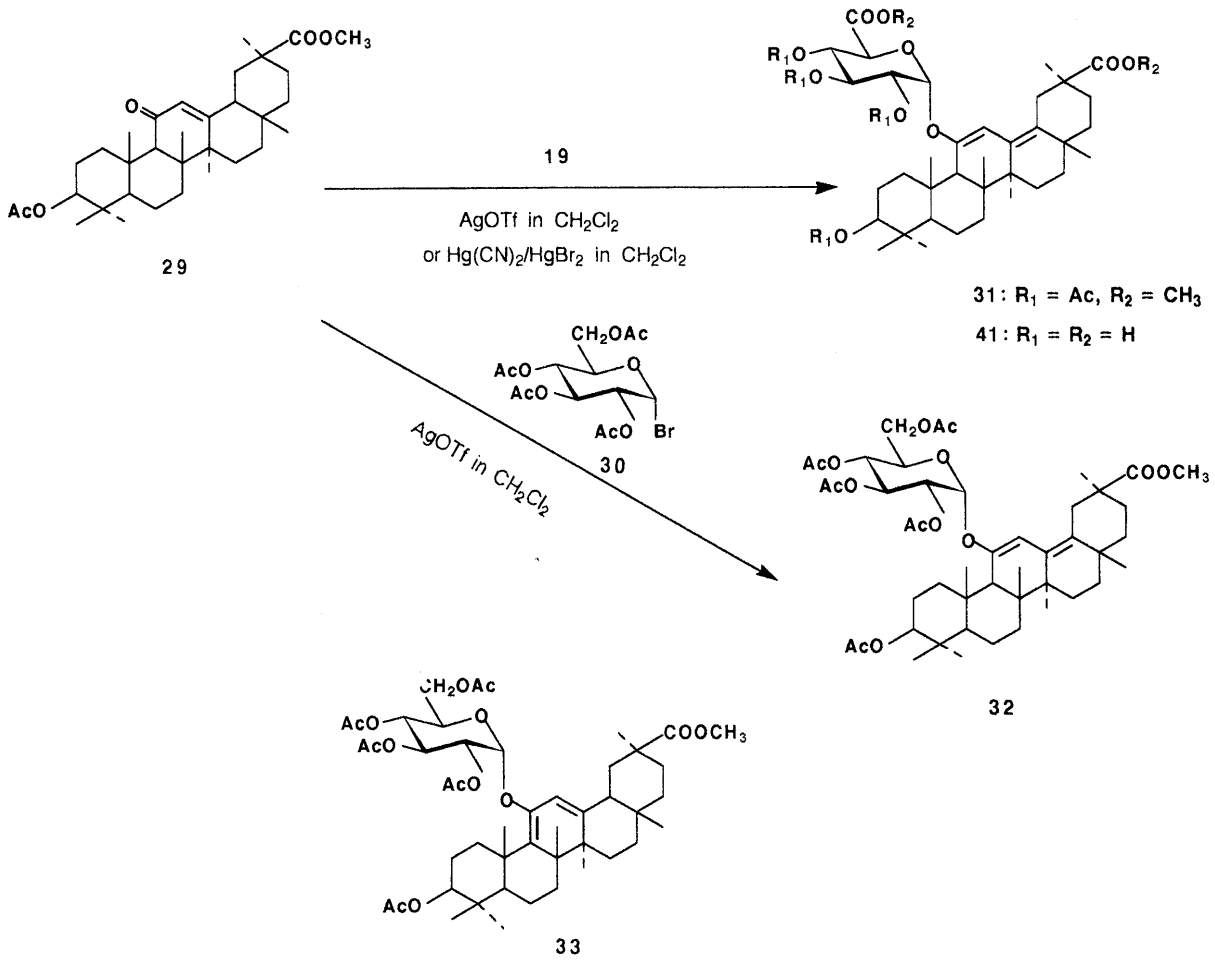


Fig. 6

TABLE II. ^{13}C-NMR Chemical Shifts for Carbons on Aglycons of **29** and **32**[a)]

	29	32
C-3	80.4	80.2
C-11	199.5	154.8
C-12	128.7	103.1
C-13	168.9	132.4 or 133.8
C-18	48.6	132.4 or 133.8
C-19	41.3	33.1
C-30	176.7	178.4

a) Spectra were obtained in d_5-pyridine. Only the relevant carbons that were compared are listed. Assignments were based on ^{1}H–^{13}C COSY methods.

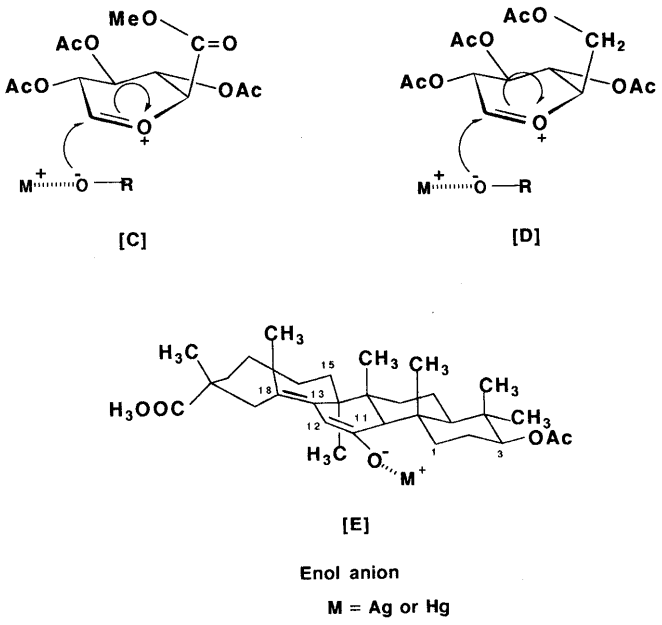


Fig. 7

the β-site of the anomeric carbon of each intermediate. Consequently, a bulky enolate anion such as [E] derived from **29** attacks the anomeric carbons of [C] and [D] from the α-site to give the enol α-glycosides. Enol structures of the products were elucidated by comparing the ^{13}C-NMR and ^{1}H-NMR spectra of **32** with those of **29**. The ^{13}C-NMR spectrum of **29** exhibited signals of a carbonyl carbon at C-11 at δ 199.5 and two olefin carbons at C-12 and C-13 at δ 128.7 and 168.9, respectively (Table II). On the other hand, in the ^{13}C-NMR spectrum of **32**, the signal due to the carbonyl carbon was missing, and four signals due to olefinic carbons were observed at δ 103.1, 132.4, 133.8 and 154.8, which suggested that the structure of the enol glycoside was either **32** or **33** (Fig. 6). However, in the ^{1}H-NMR spectrum of the enol

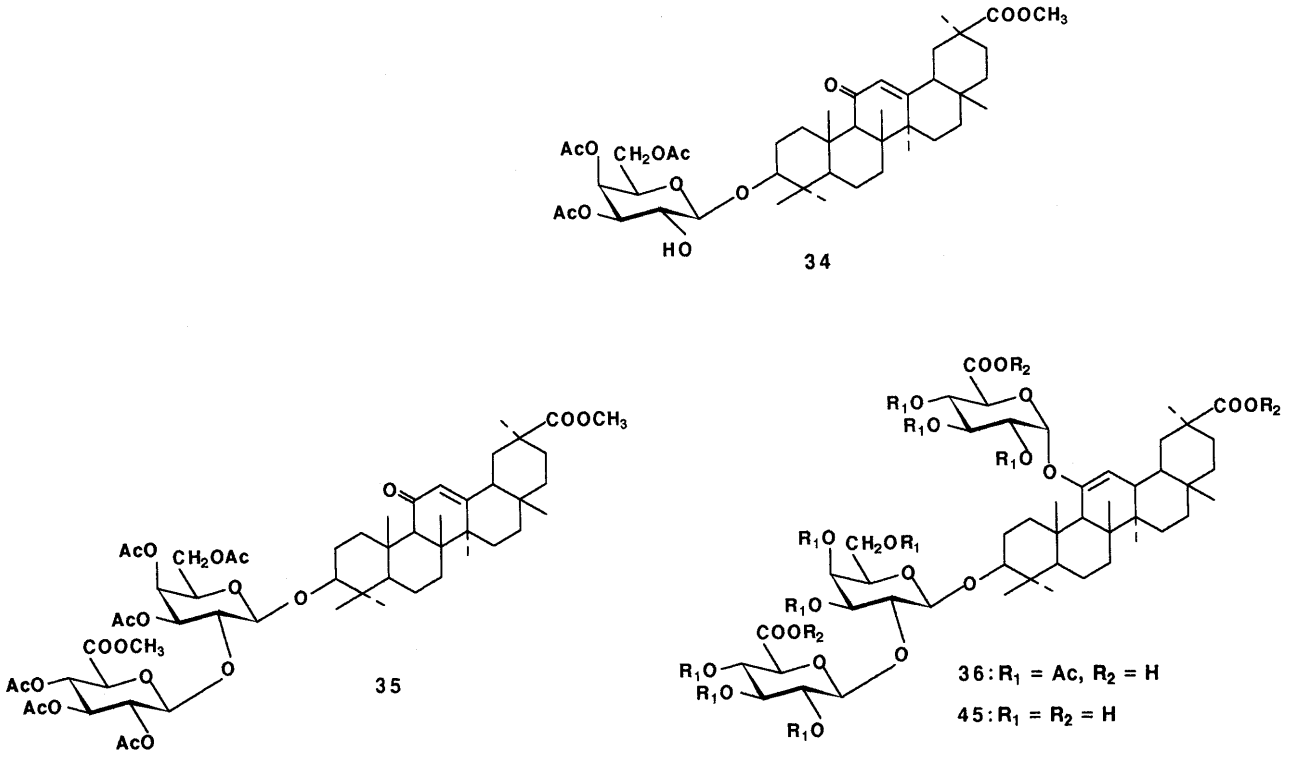


Fig. 8

glycoside, a proton signal due to H-18 on the aglycon had disappeared and that due to H-9 was intact, indicating that the structure of the enol glycoside was **32**.

When the glycosylation of **15** with **19** was carried out for a longer period (12 h) (entry 3), **23** was quantitatively obtained. On the contrary, when glycosylation of **34** with **19** was carried out for a shorter period (1.5 h) (entry 9), the enol α-glycoside **36** was obtained in 4.5% yield together with the β-diglycoside **35** in 67.9% yield. Glycosylations of **22** and **35** with **19** in the presence of AgOTf for longer reaction times (entries 10 and 12) gave the corresponding enol α-glycosides **23** and **36** in the yields of 90.5 and 91.5%, respectively. Thus, in the glycosylation of glycyrrhetic acid derivatives such as **15** and **34** having a reactive OH group with **19** in the presence of AgOTf as a catalyst, normal glycosylation first occurred at the *O*-2 position of the pyranoses linked to the *O*-3 position on the aglycons to give the diglycosides **22** and **35**, respectively, followed by enol glycosylation to afford the triglycosides **23** and **36**, respectively. In the case of the glycosylation of **29** having no reactive OH group, enol glycosylation directly occurred at the α,β-unsaturated ketone group on the C-ring of the aglycon. When the mixed catalyst of $Hg(CN)_2$ and $HgBr_2$ instead of AgOTf was used in these glycosylations, the enol α-glycosides were similarly obtained in good yields (entries 4, 7, 8, 11 and 13).

The glycosylation of methyl 3-*O*-(2′,3′,6′-tri-*O*-acetyl-β-D-glucopyranosyl)glycyrrhetinate (**37**) was investigated. In general, the order of reactivity in forming glycosidic linkages for all-equatorial hydroxyl groups attached to C-2, 3, 4 and 6 on a pyranose ring is 6-OH≫3-OH>2-OH>4-OH.[18,19] The poor reactivity of the 4-OH group was confirmed by the reaction of **37** with **19** in the presence of AgOTf in CH_2Cl_2 to give a diglycoside derivative (**38**) in the yield of 65.3% (entry 14). This product showed a quasimolecular ion peak at *m/z* 1111 $[M+Na]^+$ like those of **20**, **22** and **35** in the FAB-MS, and exhibited two anomeric proton signals at δ 4.57 (d, J=7.7 Hz) and 5.67 (d, J=3.3 Hz) in the ^{1}H-NMR spectrum, the latter of which was assignable to the anomeric proton of the newly introduced pyranose ring. These spectral data indicated that the structure of the diglycoside was either **38** or **39**. The structural assignment of the diglycoside was carried out by comparing the chemical shifts of the H-12 proton on the aglycon with those of glycosides synthesized in this study (Table III). When the ^{1}H-NMR spectra of

Table III. ^{1}H-NMR Chemical Shifts and Coupling Constants for Vinyl (H-12) and Anomeric Protons of Glycosides **20**—**23** and **35**—**38** and **40**

	Vinyl protons	Anomeric protons		
		3-*O*-Inner pyranose	3-*O*-Outer pyranose	11-*O*-Pyranose
20	5.67 (s)	5.15 (d, 3.8)	4.68 (d, 7.6)	—
21	6.01 (s)	5.14 (d, 3.3)	4.70 (d, 7.6)	5.65 (d, 3.3)
22	5.67 (s)	5.21 (d, 4.0)	4.75 (d, 7.7)	—
23	6.02 (s)	5.22 (d, 3.7)	4.76 (d, 7.7)	5.65 (d, 3.7)
35	5.66 (s)	4.33 (d, 7.7)	4.75 (d, 8.1)	—
36	5.98 (s)	4.49 (d, 7.7)	4.77 (d, 7.7)	5.67 (d, 3.7)
37	5.68 (s)	4.55 (d, 7.7)	—	—
38	6.00 (s)	4.57 (d, 7.7)	—	5.67 (d, 3.3)
40	5.98 (s)	4.59 (d, 7.7)	—	5.67 (d, 3.3)

Multiplicities (s=singlet, d=doublet) and coupling constants (J in hertz) are shown in parentheses.

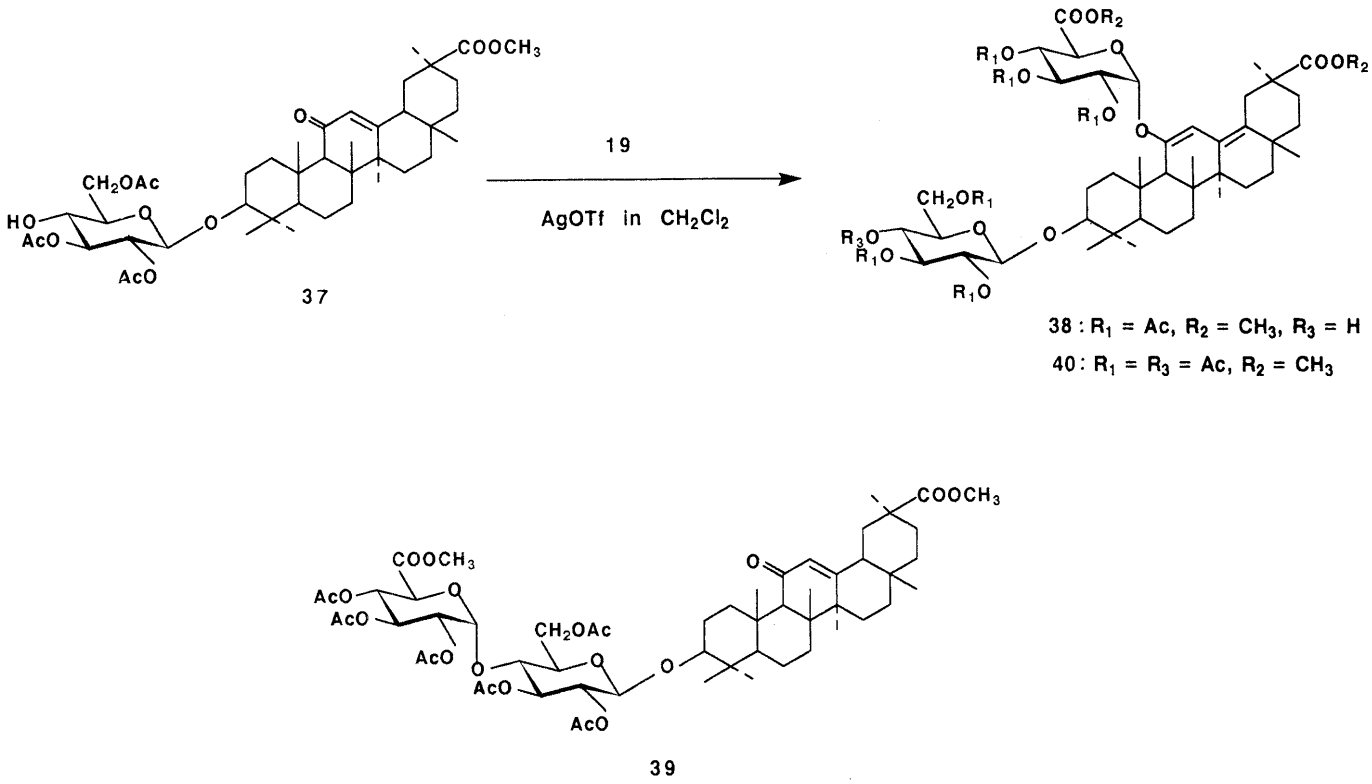


Fig. 9

TABLE IV. ^{13}C-NMR Chemical Shifts for Synthetic Glycosides **26**—**28** in C_5D_5N[a]

	26	27	28		26	27	28
Aglycon				Aglycon			
C-1	39.1	39.1	39.0	C-23	28.7[c]	28.7[c]	28.8[c]
C-2	26.6[b]	26.6[b]	26.6[b]	C-24	16.5	16.6	16.7
C-3	85.2	85.3	85.8	C-25	17.2	16.8	16.7
C-4	39.3	39.3	40.6	C-26	18.8	18.8	18.6
C-5	55.4	55.5	55.4	C-27	23.5	23.5	21.1
C-6	17.7	17.7	17.8	C-28	28.7[c]	28.7[c]	27.0
C-7	32.9	32.9	33.9	C-29	28.9[c]	28.9[c]	28.6[c]
C-8	44.0	44.0	43.9	C-30	179.1	179.1	180.8
C-9	62.0	62.2	60.8	Inner sugar			
C-10	37.3	37.3	37.1	C-1	97.4	97.9	97.9
C-11	199.4	199.5	199.0	C-2	83.2	80.7	82.7
C-12	128.6	128.6	124.0	C-3	74.2	70.2[d]	73.6
C-13	169.5	169.5	165.7	C-4	71.8	70.5[d]	77.6
C-14	45.5	45.5	45.1	C-5	77.7[d]	72.5	73.3[d]
C-15	26.7[b]	26.9[b]	26.9[b]	C-6	62.7	62.0	173.2
C-16	26.7[b]	26.7[b]	26.7[b]	Outer sugar			
C-17	32.1	32.1	32.5	C-1	106.8	106.8	106.8
C-18	48.7	48.7	48.7	C-2	73.7	77.6	73.9
C-19	41.7	41.7	42.7	C-3	77.5[d]	77.6	77.5
C-20	43.4	43.4	43.4	C-4	73.1	73.1	73.1[d]
C-21	31.5	31.5	32.0	C-5	75.3	75.2	75.2
C-22	38.4	38.3	37.7	C-6	172.3	172.3	172.3

a) Spectral assignments were based on the reported spectral data.[1,2,22] *b*—*d*) These values may be interchangeable in each column.

glycosides **20**, **22** and **35** were compared with those of the corresponding enol α-diglycosides **21**, **23** and **36**, the chemical shifts of the vinyl protons (H-12) on the aglycons changed from δ 5.66—5.67 to δ 5.98—6.02. A similar change of the chemical shift of H-12 from δ 5.68 for **37**[5] to δ 6.00 for **38** was observed, which suggests that the product obtained by the glycosylation of **37** with **19** is **38**, not **39**. The structure of **38** was further confirmed by acetylation to give the corresponding heptaacetate **40**.

Removal of the protecting groups of enol α-glycoside derivatives **31**, **21**, **23**, **25** and **36** by treatment with 5% KOH in EtOH–H_2O (1 : 1) under reflux gave compounds **41**—**45** in the yields of 67.0, 71.6, 65.3, 73.4 and 59.4%, respectively.

TABLE V. ^{13}C-NMR Chemical Shifts for Enol Glycosides **41**—**45** in C_5D_5N[a]

		41	42	43	44	45
Carbons on aglycons		181.2 (C-30), 156.2 (C-11), 134.4 and 131.4 (C-13 and 18), 103.2 (C-12), 88.5, 56.2, 56.2 (C-9), 44.4, 42.7, 41.7, 40.7, 40.1, 40.1, 39.5, 38.5, 36.3, 35.0, 33.3, 31.1, 28.8, 28.6, 25.2, 21.4, 20.5, 20.2, 18.6, 18.4, 18.0, 16.1	180.1 (C-30), 155.7 (C-11), 134.3 and 131.4 (C-13 and 18), 102.8 (C-12), 83.5, 56.1, 55.6 (C-9), 44.3, 42.6, 41.5, 40.1, 39.4, 39.1, 38.3, 36.2, 36.2, 34.9, 33.1, 31.0, 31.0, 29.2, 25.3, 25.1, 25.1, 22.6, 18.2, 18.0, 17.8, 16.8	181.0 (C-3), 155.7 (C-11), 134.3 and 131.5 (C-13 and 18), 102.9 (C-12), 82.1, 56.2, 55.6 (C-9), 44.4, 42.7, 41.6, 40.0, 39.4, 39.1, 39.1, 38.4, 36.3, 35.0, 33.1, 30.7, 30.5, 29.5, 28.8, 25.1, 24.1, 21.3, 18.2, 18.1, 17.8, 16.9	181.0 (C-30), 155.7 (C-11), 134.3 and 131.4 (C-13 and 18), 102.9 (C-12), 82.8, 56.1, 55.6 (C-9), 44.4, 42.7, 41.6, 41.0, 39.0, 38.9, 38.4, 36.3, 35.0, 33.1, 31.0, 30.6, 29.5, 28.9, 25.1, 23.3, 20.4, 20.2, 18.3, 18.1, 17.8, 16.8	180.0 (C-30), 156.3 (C-11), 134.4 and 131.4 (C-13 and 18), 103.2 (C-12), 88.5, 56.2, 55.7 (C-9), 44.4, 42.7, 41.6, 40.3, 38.9, 38.4, 36.3, 34.9, 33.3, 31.1, 29.9, 28.4, 27.3, 25.1, 23.3, 23.3, 20.4, 20.2, 18.3, 18.1, 17.8, 16.5
3-*O*-Inner sugar	C-1		97.0	97.2	97.2	105.2
	C-2		82.7	80.9	82.8	83.7
	C-3		74.0	70.3	73.6[b]	78.2
	C-4		71.7	70.7	77.7	69.3
	C-5		77.6	72.7	73.4[b]	77.6
	C-6		62.6	62.5	172.7	61.7
3-*O*-Outer sugar	C-1		106.7	106.8	106.8	106.8
	C-2		73.4[b]	73.3[b]	73.0[c]	73.4
	C-3		77.2	77.5	77.6	76.2
	C-4		73.0	73.1[b]	73.1[c]	72.9[b]
	C-5		75.0	75.1	75.2	75.2
	C-6		172.7	172.7[c]	172.7	172.8[c]
11-*O*-Sugar	C-1	97.6	95.1	96.2	96.4	97.7
	C-2	72.9	72.8	73.0	73.0[c]	73.1[b]
	C-3	73.6[b]	73.5[b]	73.5[b]	73.8	73.8
	C-4	77.7	77.6[b]	77.7	77.9	76.6
	C-5	73.4[b]	73.3	73.0	73.5[b]	73.4
	C-6	173.1	173.2	172.8[c]	173.4	172.9[c]

a) Spectral assignments were based on the reported spectral data.[1,2,22] *b*, *c*) These values may be interchangeable in each column.

Experimental

Materials Dry dichloromethane (CH_2Cl_2) was obtained by refluxing with NaH followed by distillation. Other chemicals and solvents were of reagent grade, and were obtained from commercial sources.

Measurements The thin-layer chromatography (TLC) was run on Kieselgel HF_{254} (Merck), and spots were detected by spraying the plates with $Ce(SO_4)_2$–10%H_2SO_4 (1:9) reagent, followed by heating at 100 °C for 10 min. Column chromatography was carried out on Wakogel C-200. An SSC-6300/SSC-3000 apparatus (Senshu Scientific Co., Ltd.) was employed for analytical HPLC using an ODS-1251-D column (4.6 mm × 250 mm), with an SSC autoinjector 6310, and an SSC fraction collector 6320 was used for preparative HPLC with an ODS-4251-D column (10 mm × 250 mm). ^{1}H- and ^{13}C-NMR spectra were obtained with a JEOL JNM-GX NMR spectrometer at 270 and 67.8 MHz, respectively, and chemical shifts are given in δ with tetramethylsilane as an internal standard. Only assignable signals protons on aglycons in ^{1}H-NMR spectra are listed in the experimental section. FAB-MS were recorded on a JEOL JMS-DX 300 mass spectrometer. Optical rotations were measured at 20 °C with a JASCO J-20A spectropolarimeter.

Treatment of 8 with NH_3-Saturated Ether Compound **8** (2.66 g) was added to NH_3-saturated ether (100 ml) at 0 °C. The mixture was vigorously shaken for 10 min at the same temperature, subjected to suction until the solution had no remaining odor of ammonia, and evaporated to give a residue. The residue was subjected to column chromatography (a gradient of 0—3.0% acetone in benzene), followed by application of preparative HPLC (solvent system, 15% H_2O in acetone), to give compounds **13** (1.66 g, 74.1%) and **14** (334 mg, 14.5%). FAB-MS of **13** *m/z*: 795 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.81, 0.90, 1.05, 1.14, 1.15, 1.16 and 1.36 (each 3H, s, CH_3), 2.04, 2.08 and 2.08 (each 3H, s, $COCH_3$), 2.33 (1H, s, H-9), 2.86 (1H, br d, J=13.6 Hz, H-18), 3.29 (1H, dd, J=11.7, 4.4 Hz, H-3), 3.69 (3H, s, OCH_3), 5.67 (1H, s, H-12), 5.08 (1H, d, J=4.0 Hz, H-1′), 3.65 (1H, overlapped with OCH_3, H-2′), 5.16 (1H, dd, J=9.7, 9.7 Hz, H-3′), 5.10 (1H, dd, J=9.7, 9.7 Hz, H-4′), 4.10 (1H, m, H-5′), 4.12 (1H, dd, J=11.8, 1.8 Hz, H-6a′), 4.25 (1H, dd, J=11.8, 4.2 Hz, H-6b′). *Anal.* Calcd for $C_{43}H_{64}O_{12}$: C, 66.82; H, 8.35. Found: C, 66.84; H, 8.22. FAB-MS of **14** *m/z*: 813 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.81, 0.87, 1.03, 1.13, 1.15, 1.15 and 1.37 (each 3H, s, CH_3), 2.06, 2.09 and 2.09 (each 3H, s, $COCH_3$), 2.33 (1H, s, H-9), 2.85 (1H, br d, J=13.9 Hz, H-18), 3.27 (1H, dd, J=11.4, 4.4 Hz, H-3), 3.69 (3H, s, OCH_3), 5.67 (1H, s, H-12), 5.14 (1H, d, J= 1.1 Hz, H-1′), 4.34 (1H, dd, J=3.0, 1.1 Hz, H-2′), 5.36 (1H, dd, J=9.5, 3.0 Hz, H-3′), 5.41 (1H, dd, J=9.5, 9.5 Hz, H-4′), 4.12 (1H, ddd, J=9.5, 5.1, 2.2 Hz, H-5′), 4.15 (1H, dd, J=12.5, 2.2 Hz, H-6a′), 4.22 (1H, dd, J= 12.5, 5.1 Hz, H-6b′). *Anal.* Calcd for $C_{43}H_{63}O_{11}Cl$: C, 65.26; H, 8.02. Found: C, 65.04; H, 8.13.

Treatment of 10 with NH_3-Saturated Ether The same reaction of compound **10** (4 g) as described for **8** gave, after purification by column chromatography and preparative HPLC, compound **15** (2.15 g, 63.8%) and a crude product, **16** (120 mg, <3.5%). The product **16** could not be purified by preparative HPLC. FAB-MS of **15** *m/z*: 795 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.81, 0.87, 1.04. 1.13, 1.15, 1.16 and 1.36 (each 3H, s, CH_3), 2.04, 2.06 and 2.14 (each 3H, s, $COCH_3$), 2.33 (1H, s, H-9), 2.87 (1H, br d, J=13.6 Hz, H-18), 3.30 (1H, dd, J=11.7, 4.4 Hz, H-3), 3.69 (3H, s, OCH_3), 5.67 (1H, s, H-12), 5.13 (1H, d, J=4.0 Hz, H-1′), 3.95 (1H, dd, J=11.0, 4.0 Hz, H-2′), 5.04 (1H, dd, J=11.0, 3.0 Hz, H-3′), 5.42 (1H, d, J=3.0 Hz, H-4′), 4.31 (1H, dd, J=6.2, 4.0 Hz, H-5′), 4.08 (1H, dd, J=11.4, 4.0 Hz, H-6a′), 4.10 (1H, dd, J=11.4, 6.2 Hz, H-6b′). *Anal.* Calcd for $C_{43}H_{64}O_{12}$: C, 66.82; H, 8.35. Found: C, 66.99;

H, 8.39. FAB-MS of **16** *m/z*: 813 $[M+Na]^+$.

Treatment of 12 with NH_3-Saturated Ether The same reaction of compound **12** (2 g) as described for **8** gave, after purification by column chromatography and preparative HPLC, compounds **17** (1.12 g, 66.7%) and **18** (240 mg, 16.3%). FAB-MS of **17** *m/z*: 781 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.81, 0.90, 1.07, 1.13, 1.15, 1.15 and 1.35 (each 3H, s, CH_3), 2.04 and 2.10 (each 3H, s, $COCH_3$), 2.32 (1H, s, H-9), 2.86 (1H, br d, $J=13.9$ Hz, H-18), 3.34 (1H, dd, $J=13.9$, 4.0 Hz, H-3), 3.69 and 3.76 (each 3H, s, OCH_3), 5.66 (1H, s, H-12), 5.18 (1H, d, $J=4.0$ Hz, H-1′), 3.69 (1H, overlapped with OCH_3, H-2′), 5.23 (1H, dd, $J=9.9$, 9.9 Hz, H-3′), 5.10 (1H, dd, $J=9.9$, 9.9 Hz, H-4′), 4.40 (1H, d, $J=9.9$ Hz, H-5′). *Anal.* Calcd for $C_{42}H_{62}O_{12}$: C, 66.47; H, 8.23. Found: C, 66.40; H, 8.09. FAB-MS of **18** *m/z*: 799 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.81, 0.86, 1.05, 1.13, 1.15, 1.15 and 1.33 (each 3H, s, CH_3), 2.08, and 2.10 (each 3H, s, $COCH_3$), 2.33 (1H, s, H-9), 2.85 (1H, br d, $J=13.6$ Hz, H-18), 3.34 (1H, dd, $J=11.7$, 4.4 Hz, H-3), 3.69 and 3.77 (each 3H, s, OCH_3), 5.66 (1H, s, H-12), 5.24 (1H, d, $J=3.0$ Hz, H-1′), 4.30 (1H, dd, $J=3.0$, 3.0 Hz, H-2′), 5.39 (1H, dd, $J=8.8$, 3.0 Hz, H-3′), 5.41 (1H, dd, $J=8.8$, 8.8 Hz, H-4′), 4.12 (1H, d, $J=8.8$ Hz, H-5′). *Anal.* Calcd for $C_{43}H_{63}ClO_{11}$: C, 64.89; H, 7.91. Found: C, 64.65; H, 8.03.

Glycosylation of 13 with 19 AgOTf (200 mg) and 1,1,3,3-tetramethylurea (TMU) (110 μl) were added to a mixture of **13** (400 mg), **19** (618 mg) and Drierite (200 mg) in dry CH_2Cl_2 (10 ml) at 0 °C, then the mixture was stirred under shielding from light for 2.5 h at room temperature. The reaction mixture was filtered, and the filtrate was poured into ice-water (50 ml) and extracted with CH_2Cl_2 (50 ml × 3). The combined organic extracts were successively washed with $NaHCO_3$-saturated water and water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a residue that was subjected to column chromatography (a gradient of 0—5% acetone in benzene) to give compounds **20** (119 mg, 35.2%) and **21** (135 mg, 18.5%). FAB-MS of **20** *m/z*: 1111 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.81, 0.87, 1.01, 1.14, 1.15, 1.19 and 1.36 (each 3H, s, CH_3), 1.99, 2.02, 2.03, 2.04, 2.05 and 2.07 (each 3H, s, $COCH_3$), 2.33 (1H, s, H-9), 2.85 (1H, br d, $J=14.1$ Hz, H-18), 3.20 (1H, dd, $J=11.4$, 4.4 Hz, H-3), 3.69 and 3.74 (each 3H, s, OCH_3), 5.67 (1H, s, H-12), 5.15 (1H, d, $J=3.8$ Hz, H-1′), 3.74 (1H, overlapped with OCH_3, H-2′), 5.34 (1H, dd, $J=9.7$, 9.7 Hz, H-3′), 4.96 (1H, dd, $J=9.7$, 9.7 Hz, H-4′), 4.15 (1H, m, H-5′), 4.04 (1H, dd, $J=12.1$, 2.1 Hz, H-6a′), 4.26 (1H, dd, 12.1, 4.4 Hz, H-6b′), 4.68 (1H, d, $J=7.6$ Hz, H-1″),[a] 4.92 (1H, H-2″),[a] 5.16—5.25 (2H, H-3″ and 4″),[a] 4.04 (1H, H-5″)[a] (these protons with *a*) showed virtual long-range spin-spin coupling of a linear five-spin system).[20,21] *Anal.* Calcd for $C_{56}H_{80}O_{21}$: C, 61.75; H, 7.40. Found: C, 61.47; H, 7.53. FAB-MS of **21** *m/z*: 1427 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.78, 0.86, 0.96, 0.98, 1.01, 1.01 and 1.07 (each 3H, s, CH_3), 1.95, 1.96, 1.98, 2.03, 2.04, 2.07, 2.08, 2.09 and 2.11 (each 3H, s, $COCH_3$), 2.29 (1H, s, H-9), 3.20 (1H, dd, $J=11.7$, 4.8 Hz, H-3), 3.70, 3.70 and 3.76 (each 3H, s, OCH_3), 6.01 (1H, s, H-12), 5.14 (1H, d, $J=3.3$ Hz, H-1′), 3.80 (1H, dd, $J=9.9$, 3.3 Hz, H-2′), 5.38 (1H, dd, $J=9.9$, 9.9 Hz, H-3′), 4.97 (1H, dd, $J=9.9$, 9.9 Hz, H-4′), 4.18 (1H, m, H-5′), 4.06 (1H, dd, $J=12.1$, 1.8 Hz, H-6a′), 4.26 (1H, dd, $J=12.1$, 4.4 Hz, H-6b′), 4.70 (1H, d, $J=7.6$ Hz, H-1″), 5.08—5.15 (1H, H-2″), 5.16 (1H, dd, $J=9.5$, 9.5 Hz, H-3″), 5.37 (1H, dd, $J=9.5$, 9.5 Hz, H-4″), 4.00 (1H, d, $J=9.5$ Hz, H-5″), 5.65 (1H, d, $J=3.3$ Hz, H-1‴), 5.01 (1H, dd, $J=9.7$, 3.3 Hz, H-2‴), 5.61 (1H, dd, $J=9.7$, 9.7 Hz, H-3‴), 5.22 (1H, dd, $J=9.7$, 9.7 Hz, H-4‴), 4.15 (1H, d, $J=9.7$ Hz, H-5‴). *Anal.* Calcd for $C_{69}H_{96}O_{30}$: C, 58.97; H, 6.88. Found: C, 58.93; H, 6.77.

Glycosylation of 15 with 19 a) AgOTf (350 mg) and TMU (200 μl) were added to a mixture of **15** (700 mg), **19** (1.1 g) and Drierite (400 mg) in dry CH_2Cl_2 (10 ml) at 0 °C, then the mixture was stirred under shielding from light for 3.5 h at room temperature, and worked up as described for **13** to give a residue. The residue was subjected to column chromatography (a gradient of 0—6.2% acetone in benzene) to give compounds **22** (438 mg, 44.6%) and **23** (456 mg, 28.2%). FAB-MS of **22** *m/z*: 1111 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.81, 0.86, 1.06, 1.12, 1.15, 1.19 and 1.36 (each 3H, s, CH_3), 1.98, 2.02, 2.02, 2.03, 2.03 and 2.15 (each 3H, s, $COCH_3$), 2.33 (1H, s, H-9), 2.86 (1H, br d, $J=13.6$ Hz, H-18), 3.21 (1H, dd, $J=11.3$, 4.4 Hz, H-3), 3.69 and 3.75 (each 3H, s, OCH_3), 5.67 (1H, s, H-12), 5.21 (1H, d, $J=4.0$ Hz, H-1′), 3.97 (1H, dd, $J=10.6$, 4.0 Hz, H-2′), 5.23 (1H, dd, $J=10.6$, 3.3 Hz, H-3′), 5.41 (1H, d, $J=3.3$ Hz, H-4′), 4.35 (1H, dd, $J=6.0$, 6.0 Hz, H-5′), 4.02—4.12 (2H, H-6a′ and 6b′), 4.75 (1H, d, $J=7.7$ Hz, H-1″),[a] 4.93 (1H, H-2″),[a] 5.18—5.28 (2H, H-3″ and 4″)[a], 4.04 (1H, H-5″)[a] (these protons with *a*) showed virtual long-range spin-spin coupling of a linear five-spin system). *Anal.* Calcd for $C_{56}H_{80}O_{21}$: C, 61.75; H, 7.40. Found: C, 61.24; H, 7.66. FAB-MS of **23** *m/z*: 1427 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.78, 0.84, 0.96, 0.98, 1.01, 1.02 and 1.07 (each 3H, s, CH_3), 1.94, 1.96, 1.98, 2.04, 2.04, 2.04, 2.07, 2.11 and 2.17 (each 3H, s, $COCH_3$), 2.29 (1H, s, H-9), 3.20 (1H, dd, $J=11.4$, 4.0 Hz, H-3), 3.70, 3.70 and 3.77 (each 3H, s, OCH_3), 6.02 (1H, s, H-12), 5.22 (1H, d, $J=3.7$ Hz, H-1′), 3.99 (1H, dd, $J=10.6$, 3.7 Hz, H-2′), 5.27 (1H, dd, $J=10.6$, 3.3 Hz, H-3′), 5.42 (1H, d, $J=3.3$ Hz, H-4′), 4.38 (1H, dd, $J=6.2$, 6.2 Hz, H-5′), 4.03—4.13 (2H, H-6a′ and 6b′), 4.76 (1H, d, $J=7.7$ Hz, H-1″), 5.11 (1H, dd, $J=9.9$, 7.7 Hz, H-2″), 5.19 (1H, dd, $J=9.9$, 9.9 Hz, H-3″), 5.38 (1H, dd, $J=9.9$, 9.9 Hz, H-4″), 4.05 (1H, d, $J=9.9$ Hz, H-5″), 5.65 (1H, d, $J=3.7$ Hz, H-1‴), 5.01 (1H, dd, $J=9.9$, 3.7 Hz, H-2‴), 5.61 (1H, dd, $J=9.9$, 9.9 Hz, H-3‴), 5.23 (1H, dd, $J=9.9$, 9.9 Hz, H-4‴), 4.16 (1H, d, $J=9.9$ Hz, H-5‴). *Anal.* Calcd for $C_{69}H_{96}O_{30}$: C, 58.97; H, 6.88. Found: C, 58.72; H, 6.81.

b) AgOTf (350 mg) and TMU (200 μl) were added to a mixture of **15** (500 mg), **19** (800 mg) and Drierite (400 mg) in dry CH_2Cl_2 (10 ml) at 0 °C, then the mixture was stirred under shielding from light for 12 h at room temperature, and worked up as described for **13** to give a residue. The residue was subjected to column chromatography (a gradient of 0—5% acetone in benzene) to give compound **23** (828 mg, 90.5%).

c) $Hg(CN)_2$ (200 mg) and $HgBr_2$ (200 mg) were added to a mixture of **15** (250 mg), **19** (400 mg) and Drierite (200 mg) in dry CH_2Cl_2 (10 ml) at 0 °C, then the mixture was stirred under shielding from light for 20 h at room temperature, and worked up as described for **13** to give a residue. The residue was subjected to column chromatography (a gradient of 0—5% acetone in benzene) to give compound **23** (425 mg, 92.8%).

Glycosylation of 17 with 19 AgOTf (240 mg) and TMU (130 μl) were added to a mixture of **17** (473 mg), **19** (500 g) and Drierite (250 mg) in dry CH_2Cl_2 (10 ml) at 0 °C, then the mixture was stirred under shielding from light for 4 h at room temperature. It was worked up as described for **13** to give a residue. The residue was subjected to column chromatography (a gradient of 0—5% acetone in benzene) to give compounds **24** (210 mg, 31.3%) and **25** (175 mg, 20.3%). FAB-MS of **24** *m/z*: 1097 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.89, 1.03, 1.15, 1.22, 1.24, 1.25 and 1.34 (each 3H, s, CH_3), 2.00, 2.02, 2.02, 2.05 and 2.06 (each 3H, s, $COCH_3$), 2.24 (1H, s, H-9), 2.75 (1H, br d, $J=13.8$ Hz, H-18), 3.21 (1H, dd, $J=12.3$, 6.4 Hz, H-3), 3.69, 3.73 and 3.74 (each 3H, s, OCH_3), 5.67 (1H, s, H-12), 5.25 (1H, d, $J=3.8$ Hz, H-1′), 3.78 (1H, dd, $J=9.9$, 3.8 Hz, H-2′), 5.41 (1H, dd, $J=9.9$, 9.9 Hz, H-3′), 5.07 (1H, dd, $J=9.9$, 9.9 Hz, H-4′), 4.49 (1H, d, $J=9.9$ Hz, H-5′), 4.67 (1H, d, $J=7.9$ Hz, H-1″),[a] 4.93 (1H, H-2″),[a] 5.19—5.24 (2H, H-3′ and 4″),[a] 4.00 (1H, H-5″)[a] (these protons with *a*) showed virtual long-range spin-spin coupling in a linear five-spin system). *Anal.* Calcd for $C_{55}H_{78}O_{21}$: C, 61.44; H, 7.31. Found: C, 61.25; H, 7.27. FAB-MS of **25** *m/z*: 1413 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.78, 0.87, 0.96, 0.98, 1.01, 1.02 and 1.07 (each 3H, s, CH_3), 1.95, 1.97, 1.98, 2.03, 2.04, 2.08, 2.08 and 2.11 (each 3H, s, $COCH_3$), 2.29 (1H, s, H-9), 3.25 (1H, dd, $J=11.7$, 4.0 Hz, H-3), 3.70, 3.70, 3.75 and 3.76 (each 3H, s, OCH_3), 6.00 (1H, s, H-12), 5.25 (1H, d, $J=3.3$ Hz, H-1′), 3.82 (1H, dd, $J=9.9$, 3.3 Hz, H-2′), 5.44 (1H, dd, $J=9.9$, 9.9 Hz, H-3′), 5.10 (1H, dd, $J=9.9$, 9.9 Hz, H-4′), 4.48 (1H, d, $J=9.9$ Hz, H-5′), 4.68 (1H, d, $J=7.3$ Hz, H-1″), 5.10—5.17 (1H, H-2″), 5.17 (1H, dd, $J=9.5$, 9.5 Hz, H-3″), 5.37 (1H, dd, $J=9.5$, 9.5 Hz, H-4″), 4.01 (1H, d, $J=9.5$ Hz, H-5″), 5.65 (1H, d, $J=3.3$ Hz, H-1‴), 5.01 (1H, dd, $J=9.9$, 3.7 Hz, H-2‴), 5.60 (1H, dd, $J=9.9$, 9.9 Hz, H-3‴), 5.22 (1H, dd, $J=9.9$, 9.9 Hz, H-4‴), 4.15 (1H, d, $J=9.9$ Hz, H-5‴). *Anal.* Calcd for $C_{68}H_{94}O_{30}$: C, 58.70; H, 6.81. Found: C, 58.43; H, 6.87

3-*O*-[2′-*O*-(β-D-Glucuronopyranosyl)-α-D-glucopyranosyl]glycyrrhetic Acid (26) A solution of **20** (180 mg) in MeOH (7.0 ml) was treated with 1.5 N NaOH–MeOH (2.0 ml), then the mixture was allowed to stand overnight at room temperature. It was neutralized with acetic acid, then evaporated to give a residue that was subjected to column chromatography (MeOH–CH_2Cl_2, 1 : 9) to obtain a residue. This residue was dissolved in 5% KOH in EtOH–H_2O (1 : 1) (3.0 ml) and refluxed for 2 h. After cooling, the mixture was passed through Amberlite IR-120B (H^+ form), and eluted with distilled water. The eluate was mixed with pyridine (5 ml) and evaporated to give a residue. The residue was subjected to column chromatography ($CHCl_3$–MeOH–H_2O, 65 : 35 : 10, lower layer) to give compound **26** (92 mg, 66.0%). FAB-MS *m/z*: 831 $[M+Na]^+$. $[\alpha]_D = +104.5°$ ($c=1.0$, pyridine). ^{13}C-NMR: see Table IV. *Anal.* Calcd for $C_{42}H_{64}O_{15}\cdot 2H_2O$: C, 59.70; H, 8.11. Found: C, 59.79; H, 7.87.

3-*O*-[2′-*O*-(β-D-Glucuronopyranosyl)-α-D-galactopyranosyl]glycyrrhetic Acid (27) Removal of the protecting groups of compound **22**

(300 mg) was performed as described for **20** to give compound **27** (151 mg, 67.2%). FAB-MS *m/z*: 831 $[M+Na]^+$. $[\alpha]_D = +100.1°$ ($c=1.0$, pyridine). ^{13}C-NMR: see Table IV. *Anal.* Calcd for $C_{42}H_{64}O_{15}\cdot 1/3H_2O$: C, 61.90; H, 8.00. Found: C, 61.86; H, 7.71.

3-*O*-[2′-*O*-(β-D-Glucuronopyranosyl)-α-D-glucuronopyranosyl]glycyrrhetic Acid (28) Removal of the protecting groups of compound **24** (250 mg) was performed as described for **20** to give compound **28** (123 mg, 61.3%). FAB-MS *m/z*: 845 $[M+Na]^+$. $[\alpha]_D = +61.7°$ ($c=1.0$, pyridine). ^{13}C-NMR: see Table IV. *Anal.* Calcd for $C_{42}H_{64}O_{15}\cdot 2H_2O$: C, 58.73; H, 7.74. Found: C, 58.69; H, 7.59.

Methyl 3-*O*-Acetyl-glycyrrhetinate (29) A solution of **6** (3.0 g) in dry pyridine (60 ml) and acetic anhydride (60 ml) was allowed to stand overnight at room temperature. The reaction mixture was coevaporated with toluene (100 ml × 4) to give compound **29** (2.84 g, 87.2%). FAB-MS *m/z*: 507 $[M+Na]^+$. *Anal.* Calcd for $C_{33}H_{50}O_5$: C, 75.27; H, 9.59. Found: C, 74.95; H, 9.54.

Reaction of 29 with 19 a) A suspension of **29** (100 mg) and Drierite (100 mg) in dry CH_2Cl_2 (5 ml) was stirred under shielding from light for 1 h at room temperature, then **19** (150 mg), AgOTf (73 mg) and TMU (40 μl) were added. The mixture was further stirred for 15 h at room temperature, then filtered. The filtrate was poured into ice-water (50 ml) and extracted with CH_2Cl_2 (50 ml × 3). The combined organic extracts were successively washed with $NaHCO_3$-saturated water and water, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a residue. The residue was subjected to column chromatography (a gradient of 0—1.6% acetone in benzene) to afford compound **31** (146 mg, 91.2%). FAB-MS *m/z*: 865 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.78, 0.78, 0.89, 0.97, 0.98, 1.01 and 1.07 (each 3H, s, CH_3), 2.02, 2.02, 2.04 and 2.06 (each 3H, s, $COCH_3$), 2.33 (1H, s, H-9), 3.69 and 3.70 (each 3H, s, OCH_3), 4.59 (1H, dd, $J=11.4$, 4.7 Hz, H-3), 5.96 (1H, s, H-12), 5.68 (1H, d, $J=3.5$ Hz, H-1′), 4.99 (1H, dd, $J=9.7$, 3.5 Hz, H-2′), 5.57 (1H, dd, $J=9.7$, 9.7 Hz, H-3′), 5.22 (1H, dd, $J=9.7$, 9.7 Hz, H-4′), 4.12 (1H, d, $J=9.7$ Hz, H-5′). *Anal.* Calcd for $C_{41}H_{66}O_{14}$: C, 65.07; H, 7.85. Found: C, 65.08; H, 7.87.

b) A suspension of **29** (800 mg), Drierite (500 mg), $Hg(CN)_2$ (756 mg) and $HgBr_2$ (1.1 g) in dry CH_2Cl_2 (20 ml) was stirred under shielding from light for 1 h at room temperature, then **19** (2.4 g) was added. The mixture was further stirred for 20 h at room temperature, then filtered. The filtrate was treated according to the preparative method just described above to give a residue, which was subjected to column chromatography (a gradient of 0—1.6% acetone in benzene) to afford compound **31** (1.15 g, 89.7%).

Reaction of 29 with 30 A suspension of **29** (800 mg) and Drierite (520 mg) in dry CH_2Cl_2 (20 ml) was stirred under shielding from light for 1 h at room temperature, then **30** (2.4 g), $Hg(CN)_2$ (760 mg) and $HgBr_2$ (1.1 g) were added. The mixture was further stirred for 20 h at room temperature, then worked up as described for the reaction of **29** with **19** to give compound **32** (1.17 g, 90.2%). FAB-MS *m/z*: 879 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.78, 0.88, 0.89, 0.97, 1.03, 1.03 and 1.07 (each 3H, s, CH_3), 2.01, 2.02, 2.04, 2.04 and 2.06 (each 3H, s, $COCH_3$), 2.31 (1H, s, H-9), 3.70 (3H, s, OCH_3), 4.59 (1H, dd, $J=11.6$, 5.1 Hz, H-3), 5.89 (1H, s, H-12), 5.64 (1H, d, $J=3.7$ Hz, H-1′), 4.97 (1H, dd, $J=9.9$, 3.7 Hz, H-2′), 5.53 (1H, dd, $J=9.9$, 9.9 Hz, H-3′), 5.09 (1H, dd, $J=9.9$, 9.9 Hz, H-4′), 3.80 (1H, ddd, $J=9.9$, 4.8, 2.2 Hz, H-5′), 3.98 (1H, dd, $J=12.5$, 2.2 Hz, H-6a′), 4.19 (1H, dd, $J=12.5$, 4.8 Hz, H-6b′). *Anal.* Calcd for $C_{47}H_{68}O_{14}$: C, 65.87; H, 8.00. Found: C, 65.68; H, 8.07.

Glycosylation of 34 with 19 A suspension of **34** (1.0 g), Drierite (500 mg), AgOTf (400 mg) and TMU (220 μl) in dry CH_2Cl_2 (20 ml) was stirred under shielding from light for 1 h at room temperature, then **19** (1.5 g) was added. The mixture was further stirred for 1.5 h at the same temperature, then worked up as described for the reaction of **29** with **19** to give compounds **35** (769 mg, 67.9%) and **36** (65.8 mg, 4.5%). Compound **35** was identified by direct comparison with an authentic sample[2] (FAB-MS and ^{1}H-NMR spectrum). FAB-MS of **36** *m/z*: 1427 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.77, 0.85, 0.97, 0.97, 0.97, 1.06 and 1.07 (each 3H, s, CH_3), 1.99, 1.99, 2.00, 2.00, 2.01, 2.01, 2.02, 2.08 and 2.14 (each 3H, s, $COCH_3$), 2.28 (1H, s, H-9), 3.17 (1H, dd, $J=11.7$, 4.0 Hz, H-3), 3.70, 3.70 and 3.76 (each 3H, s, OCH_3), 5.98 (1H, s, H-12), 4.49 (1H, d, $J=7.7$ Hz, H-1′), 3.95 (1H, dd, $J=9.9$, 7.7 Hz, H-2′), 4.99 (1H, dd, $J=9.9$, 3.7 Hz, H-3′), 5.22 (1H, d, $J=3.7$ Hz, H-4′), 3.90 (1H, dd, $J=7.0$, 7.0 Hz, H-5′), 4.06 (1H, dd, $J=7.0$, 1.8 Hz, H-6a′) and 4.29 (1H, dd, $J=7.0$, 4.4 Hz, H-6b′), 4.77 (1H, d, $J=7.7$ Hz, H-1″), 5.08—5.15 (1H, H-2″), 5.16 (1H, dd, $J=9.5$, 9.5 Hz, H-3″), 5.37 (1H, dd, $J=9.5$, 9.5 Hz, H-4″), 4.00 (1H, d, $J=9.5$ Hz, H-5″), 5.67 (1H, d, $J=3.7$ Hz, H-1‴), 5.01 (1H, dd, $J=9.7$, 3.7 Hz, H-2‴), 5.61 (1H, dd, $J=9.7$, 9.7 Hz, H-3‴), 5.22 (1H, dd, $J=9.7$, 9.7 Hz, H-4‴), 4.15 (1H, d, $J=9.7$ Hz, H-5‴). *Anal.* Calcd for $C_{55}H_{78}O_{21}$: C, 61.44; H, 7.31. Found: C, 61.22; H, 7.18.

Glycosylation of 22 with 19 a) A suspension of **22** (100 mg) and Drierite (100 mg) in dry CH_2Cl_2 (5 ml) was stirred under shielding from light for 1 h at room temperature, then **19** (150 mg), AgOTf (35 mg) and TMU (20 μl) were added. The mixture was further stirred for 15 h at the same temperature, then filtered. The filtrate was worked up as described for the reaction of **29** with **19** to give compound **23** (117.5 mg, 90.5%).

b) A suspension of **22** (200 mg), Drierite (100 mg), $Hg(CN)_2$ (95 mg) and $HgBr_2$ (130 mg) in dry CH_2Cl_2 (10 ml) was stirred under shielding from light for 1 h at room temperature, then **19** (290 mg) was added. The mixture was further stirred for 23 h at the same temperature, then filtered. The filtrate was worked up as described for the reaction of **29** with **19** to give compound **23** (206 mg, 79.5%).

Glycosylation of 35 with 19 a) A suspension of **35** (100 mg) and Drierite (100 mg) in dry CH_2Cl_2 (5 ml) was stirred under shielding from light for 1 h at room temperature, then **19** (150 mg), AgOTf (35 mg) and TMU (20 μl) were added. The mixture was further stirred for 10 h at the same temperature, and worked up as described for the reaction of **29** with **19** to obtain compound **36** (118 mg, 91.5%).

b) A suspension of **35** (700 mg) and Drierite (300 mg), $Hg(CN)_2$ (320 mg) and $HgBr_2$ (460 mg) in dry CH_2Cl_2 (10 ml) was stirred under shielding from light for 1 h at room temperature, then **19** (1.62 g) was added. The mixture was further stirred for 20 h at the same temperature to give, on work-up as described for **29**, compound **36** (810 mg, 89.6%).

Glycosylation of 37 with 19 A suspension of **37** (200 mg) and Drierite (200 mg) in dry CH_2Cl_2 (5 ml) was stirred under shielding from light for 1 h at room temperature, then **19** (430 mg), AgOTf (205 mg) and TMU (56 μl) were added . The mixture was further stirred for 20 h at the same temperature, then worked up as described for the reaction of **29** with **19** to give compound **38** (184 mg, 65.3%). FAB-MS *m/z*: 1111 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.76, 0.76, 0.94, 0.95, 0.97, 1.06 and 1.25 (each 3H, s, CH_3), 1.98, 2.02, 2.03, 2.05, 2.10 and 2.12 (each 3H, s, $COCH_3$), 2.27 (1H, s, H-9), 3.06 (1H, exchangeable with D_2O, OH), 3.17 (1H, dd, $J=11.7$, 4.4 Hz, H-3), 3.69 (6H, s, $OCH_3 \times 2$), 6.00 (1H, s, H-12), 4.57 (1H, d, $J=7.7$ Hz, H-1′), 5.00 (1H, dd, $J=9.9$, 9.9 Hz, H-2′), 5.07 (1H, dd, $J=9.9$, 9.9 Hz, H-3′), 3.63 (1H, dd, $J=9.9$, 9.9 Hz, H-4′), 3.55 (1H, ddd, $J=9.9$, 3.7, 1.8 Hz, H-5′), 4.37 (1H, dd, $J=12.1$, 1.8 Hz, H-6a′) and 4.55 (1H, dd, $J=12.1$, 3.7 Hz, H-6b′), 5.67 (1H, d, $J=3.3$ Hz, H-1″), 4.97 (1H, dd, $J=9.9$, 3.3 Hz, H-2″), 5.62 (1H, dd, $J=9.9$, 9.9 Hz, H-3″), 5.19 (1H, dd, $J=9.9$, 9.9 Hz, H-4″), 4.14 (1H, d, $J=9.9$ Hz, H-5″). *Anal.* Calcd for $C_{56}H_{80}O_{21}$: C, 61.75; H, 7.40. Found: C, 61.61; H, 7.48

Acetylation of 38 Compound **38** (100 mg) was dissolved in pyridine (10 ml) and acetic anhydride (10 ml), and the mixture was allowed to stand overnight at room temperature. It was co-evaporated with toluene (30 ml × 5) to give a residue, which was subjected to column chromatography (a gradient of 0—5% AcOEt in benzene) to give compound **39** (81 mg, 78.0%). FAB-MS *m/z*: 1153 $[M+Na]^+$. ^{1}H-NMR ($CDCl_3$) δ: 0.76, 0.76, 0.94, 0.95, 0.96, 1.06 and 1.25 (each 1H, s, CH_3), 1.97, 1.98, 2.02, 2.02, 2.02, 2.04 and 2.07 (each 3H, s, $COCH_3$), 2.27 (1H, s, H-9), 3.17 (1H, dd, $J=11.7$, 4.8 Hz, H-3), 3.69 (6H, s, $OCH_3 \times 2$), 5.98 (1H, s, H-12), 4.59 (1H, d, $J=7.7$ Hz, H-1′), 5.05 (1H, dd, $J=9.5$, 7.7 Hz, H-2′), 5.23 (1H, dd, $J=9.5$, 9.5 Hz, H-3′), 5.13 (1H, dd, $J=9.5$, 9.5 Hz, H-4′), 3.66 (1H, overlapped with OCH_3, H-5′), 4.21 (1H, dd, $J=12.1$, 2.2 Hz, H-6a′), 4.33 (1H, dd, $J=12.1$, 4.0 Hz, H-6b′), 5.67 (1H, d, $J=3.3$ Hz, H-1″), 4.97 (1H, dd, $J=9.9$, 3.3 Hz, H-2″), 5.61 (1H, dd, $J=9.9$, 9.9 Hz, H-3″), 5.18 (1H, dd, $J=9.9$, 9.9 Hz, H-4″), 4.13 (1H, d, $J=9.9$ Hz, H-5″). *Anal.* Calcd for $C_{58}H_{82}O_{22}$: C, 61.58; H, 7.31. Found: C, 61.33; H, 7.38.

Removal of the Protecting Groups of 31 A solution of **31** (618 mg) in 5% KOH in EtOH–H_2O (1 : 1) (25 ml) was allowed to stand for 12 h at room temperature, then refluxed for 2 h. After cooling, the reaction mixture was passed through Amberlite IR-120B (H^+ form) and eluted with distilled water. The eluent was evaporated to give a residue that was subjected to column chromatography ($CHCl_3$–MeOH–H_2O, 65 : 35 : 10, lower layer) to obtain compound **41** (335 mg, 67.0%). FAB-MS *m/z*: 669 $[M+Na]^+$. $[\alpha]_D = +40.8°$ ($c=1.1$, pyridine). *Anal.* Calcd for $C_{36}H_{54}O_{10}\cdot 2H_2O$: C, 63.32; H, 8.56. Found: C, 63.03; H, 8.33.

Removal of the Protecting Groups of 21, 23, 25 and 36 Compounds **21** (300 mg), **23** (350 mg), **25** (170 mg) and **36** (650 mg) were similarly

deprotected to give compounds **42**, **43**, **44**, and **45**, respectively. **42**: (153 mg, 71.6%) (FAB-MS *m/z*: 1007 $[M+Na]^+$, $[\alpha]_D = +74.5°$ ($c = 1.06$, pyridine), *Anal.* Calcd for $C_{48}H_{72}O_{21} \cdot H_2O$: C, 57.47; H, 7.44. Found: C, 57.23; H, 7.22). **43**: (163 mg, 65.3%) (FAB-MS *m/z*: 1007 $[M+Na]^+$, $[\alpha]_D = +53.3°$ ($c = 1.4$, pyridine), *Anal.* Calcd for $C_{48}H_{72}O_{21} \cdot H_2O$: C, 57.47; H, 7.44. Found: C, 57.31; H, 7.61). **44**: (91 mg, 73.3%) (FAB-MS *m/z*: 1021 $[M+Na]^+$, $[\alpha]_D = +7.3°$ ($c = 1.8$, pyridine), *Anal.* Calcd for $C_{48}H_{70}O_{22} \cdot H_2O$: C, 56.68; H, 7.14. Found: C, 56.39; H, 7.49). **45**: (280 mg, 59.4%) (FAB-MS *m/z*: 1007 $[M+Na]^+$, $[\alpha]_D = +2.2°$ ($c = 1.0$, pyridine), *Anal.* Calcd for $C_{48}H_{72}O_{21} \cdot 2H_2O$: C, 56.46; H, 7.50. Found: C, 56.17; H, 7.31).

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