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Indonesian Medicinal Plants. IV.[1] On the Constituents of the Bark of *Fagara rhetza* (Rutaceae). (2). Lignan Glycosides and Two Apioglucosides

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Two new lignan glycosides, named hazaleanin A (1) and hazaleanin B (2), and two new apioglucosides, named isopropyl apioglucoside (3) and 4-hydroxyguaiacol apioglucoside (4), were isolated from the bark of *Fagara rhetza* (Rutaceae), an Indonesian medicinal plant from Flores Island, Indonesia. The chemical structures of 1, 2, 3, and 4 have been elucidated on the basis of chemical and physicochemical evidence, including a chiral synthesis of an aglycone derivative of 1.

Keywords Indonesian medicinal plant; *Fagara rhetza*; Rutaceae; lignan glycoside; hazaleanin; apioglucoside; lignan chiral synthesis

As a part of our chemical studies of Indonesian medicinal plants,[2] we reported in the previous paper[1] the chemical characterization of the alkaloidal, phenylpropanoidal, and acid amide constituents isolated from the ethyl acetate-soluble portion of the bark of *Fagara rhetza* (Rutaceae), a medicinal plant called "hazalea" from Flores Island, Indonesia.[3] In a parallel study, we have been investigating the chemical constituents of the *n*-butanol- and water-soluble portions of the bark (Chart 1). We have isolated two new lignan glycosides, designated hazaleanin A (**1**) and hazaleanin B (**2**) from the former portion, and two new apioglucosides, designated isopropyl apioglucoside (**3**) and 4-hydroxyguaiacol apioglucoside (**4**) from the latter portion. In this paper, we describe in detail the structure elucidation of those glycosidic constituents (**1**—**4**).

The aqueous phase, which was obtained by partition with ethyl acetate and water of the methanol extract of the bark, gave a residue amounting to 8.0% of the bark upon evaporation. The aqueous solution was further partitioned into an *n*-butanol–water mixture. The *n*-butanol-soluble portion (1.5% from the bark) was then subjected to silica gel column chromatography and high-performance liquid chromatography (HPLC) with a reversed-phase adsorbent to afford two new lignan glycosides, hazaleanin A (**1**, 0.007%) and hazaleanin B (**2**, 0.014%). On the other hand, separation of the water-soluble portion (6.5%) by successive chromatography on a Cosmosil (a reverse-phased adsorbent) column and a silica gel column followed by reversed-phase HPLC, furnished two new apioglucosides, isopropyl apioglucoside (**3**, 0.03%) and 4-hydroxyguaiacol apioglucoside (**4**, 0.01%).

Hazaleanin B (2) Hazaleanin B (**2**) was obtained as a white amorphous solid which colored purple with ferric chloride ($FeCl_3$) reagent on a thin-layer chromatogram (TLC). In the fast atom bombardment (FAB)-mass spectrum (MS), **2** gave a molecular ion peak (M^+) at m/z 788, which corresponded to $C_{39}H_{48}O_{17}$, together with two

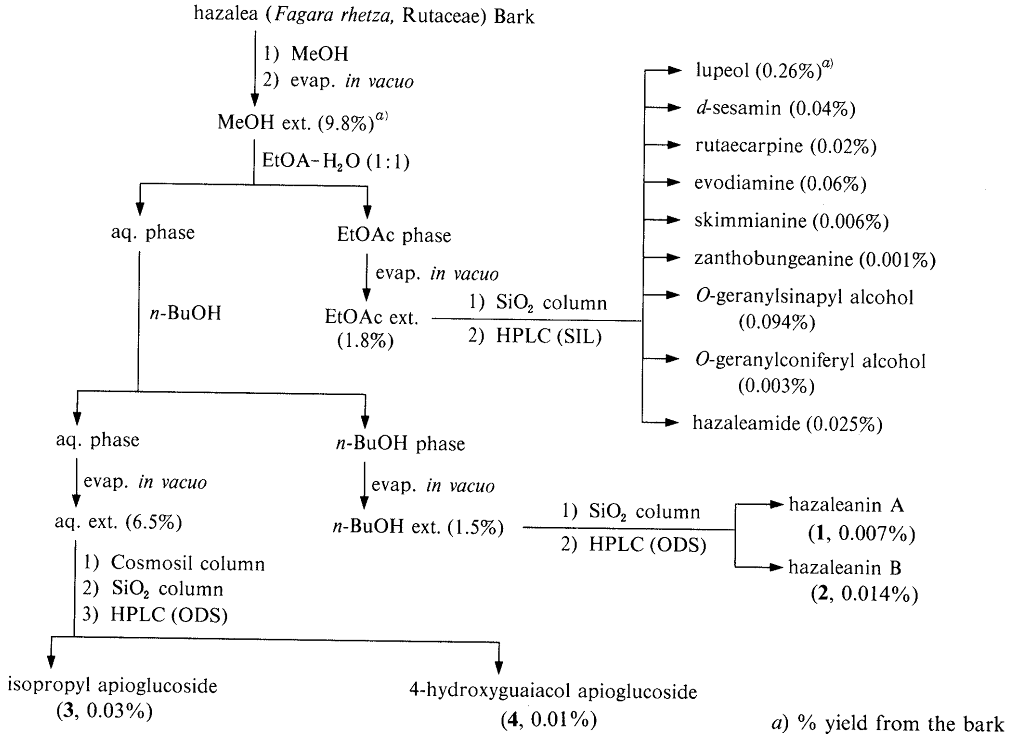


Chart 1

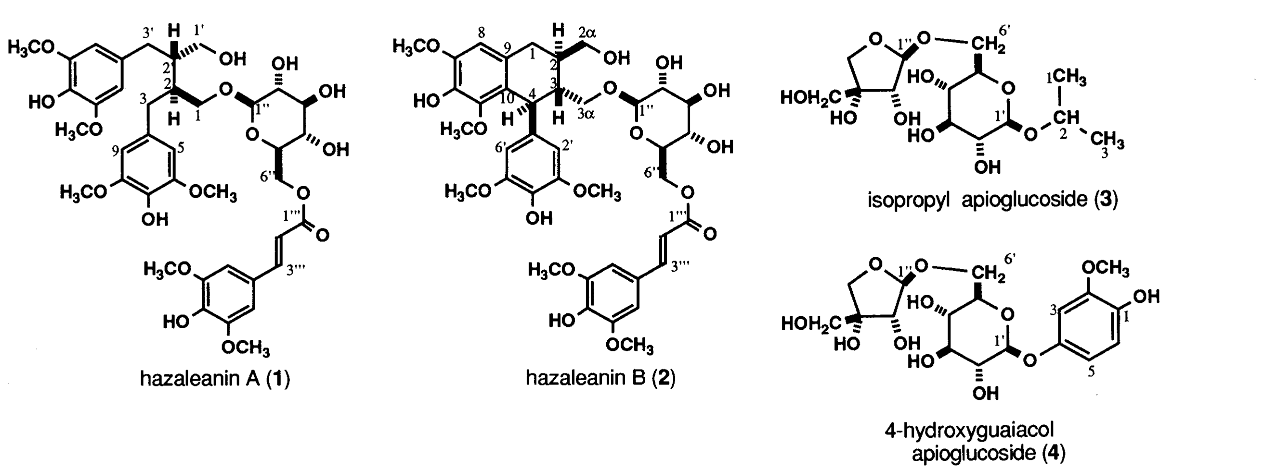


Fig. 1

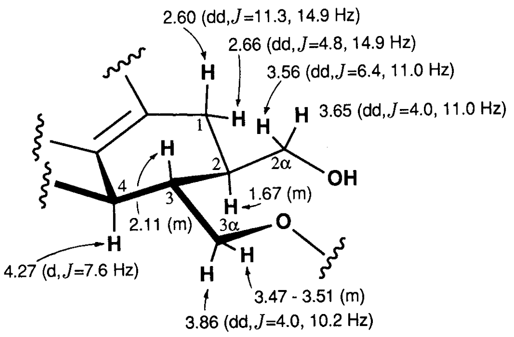


Fig. 2

ion peaks at m/z 789 $(M+H)^+$ and at m/z 827 $(M+K)^+$. The infrared (IR) spectrum of **2** showed significant absorption bands due to hydroxyl groups ($3420\,cm^{-1}$) and an α,β-unsaturated ester group (1696, $1629\,cm^{-1}$).

The proton nuclear magnetic resonance (^1H-NMR) spectrum of hazaleanin B (**2**) showed signals ascribable to six methoxyl groups, one methylene group, three methylene groups adjacent to oxygen functions, two E-olefin protons (δ 6.38, d, $J=15.8$ Hz; δ 7.59, d, $J=15.8$ Hz), five aromatic protons, seven methine protons, and one anomeric proton (δ 4.34, d, $J=8.1$ Hz), suggesting that **2** is a monosaccharide. The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **2** (Table I) showed carbon signals due to a hexose moiety, six methoxyl groups, three aromatic rings (totally 18C), one double bond, and one ester carbonyl group. Furthermore, ^1H–^1H correlation spectroscopy (COSY) revealed the connectivities of protons at C-1, -2, -3, -4, -2α, and -3α (Fig. 2), so that hazaleanin B (**2**) was presumed to be a lignan glycoside ester.

On alkaline treatment with sodium methoxide in methanol, hazaleanin B (**2**) gave a lignan glucoside (**5**) and methyl sinapate. In the ^{13}C-NMR spectrum of **5** (Table I), the singal of 5″-C (δ_C 78.7) was observed at lower field (+2.6 ppm), while the signal of 6″-C (δ_C 63.6) was at higher field (−1.9 ppm) than those of **2**, thus indicating that the sinapic acid moiety is attached to the hydroxyl group at C-6″ in the sugar moiety of **5**.[4)]

Enzymatic hydrolysis of the lignan glucoside (**5**) with cellulase liberated D-glucose ($[\alpha]_D$ +47.4° in H_2O) and an aglycone (**6**), the physical data of which, including the optical rotation, were identical with those for (2R,3R)-(+)-lyoniresinol isolated from *Lyonia ovalifolia* var. *elliptica* (Rhodoraceae).[5)]

TABLE I. ^{13}C-NMR Data for Hazaleanin B (**2**), **5**, and **6** (in CD_3OD, δ in ppm)

	2	5	6		2	5
Aglycone moiety				Sugar moiety		
C-1	34.6	34.6	33.6	C-1″	105.6	105.6
C-2	41.7	41.4	40.9	C-2″	75.8	76.0
C-3	47.3	47.5	49.8	C-3″	78.8	79.0
C-4	43.8	43.6	42.3	C-4″	72.5	72.4
C-5	148.3	148.7	147.7	C-5″	76.1	78.7
C-6	140.1	140.1	139.3	C-6″	65.5	63.6
C-7	149.3	149.4	148.6	Acyl moiety		
C-8	108.5	108.6	107.8	C-1‴	169.8	
C-9	130.1	131.0	130.2	C-2‴	116.4	
C-10	127.3	127.2	126.2	C-3‴	148.6	
C-1′	135.3	135.2	134.5	C-4‴	140.4	
C-2′,6′	107.7	107.7	106.8	C-5‴,9‴	107.8	
C-3′,5′	149.7	149.8	149.0	C-6‴,8‴	150.2	
C-4′	139.6	139.7	138.9	C-7‴	127.3	
C-2α	66.9	67.0	66.8	6‴,8‴-OCH_3	57.7	
C-3α	72.8	72.2	64.1			
3′,5′-OCH_3	57.3	57.4	56.7			
7-OCH_3	57.6	57.6	56.6			
5-OCH_3	60.7	60.9	60.1			

As for the location of the glucosidic linkage in **5**, the glycosylation shifts[6)] observed in the ^{13}C-NMR of **5** (as compared with **6**) for the signals assignable to 3α-C (+8.1 ppm) and 3-C (−2.3 ppm) were consistent with the above conclusion (Table I). Furthermore, the coupling constant ($J=8.0$ Hz) observed for the anomeric proton (1″-H) in the ^1H-NMR spectrum of **5** ($J=8.0$ Hz) indicated the β-glucoside linkage for the D-glucose moiety. Consequently, the structure of hazaleanin B has been determined to be **2**, as shown.

Hazaleanin A (1) Hazaleanin A (**1**), a white amorphous solid, colored purple with $FeCl_3$ reagent on TLC. Its high-resolution FAB-MS revealed the molecular composition of $C_{39}H_{50}O_{17}$, 2 mass units (2H) larger than that of hazaleanin B (**2**). The IR and ultraviolet (UV) spectra of **1** showed similar absorption patterns to those of **2**. Furthermore, the ^1H-NMR spectrum of **1** was also similar to that of **2** except for signals due to protons related to

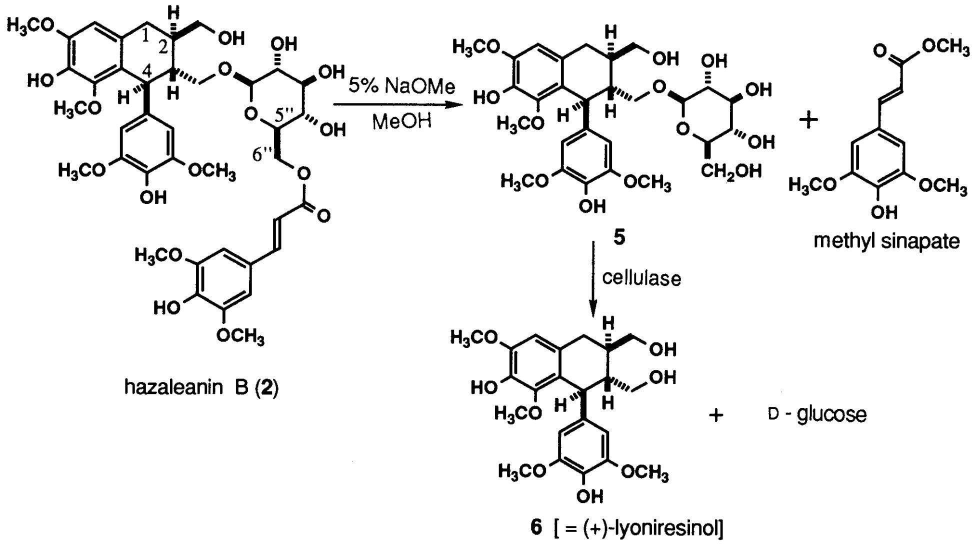


Fig. 3

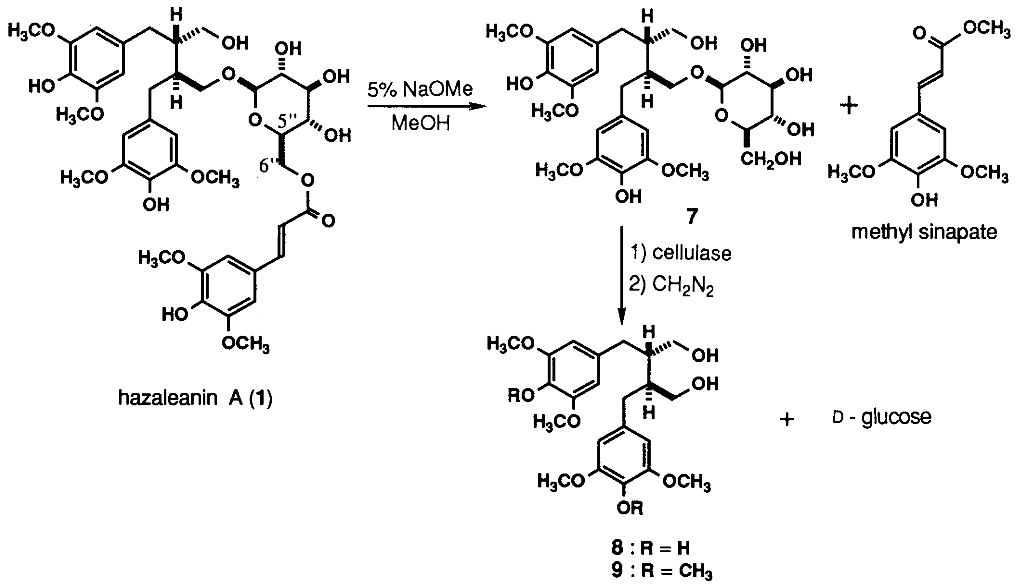


Fig. 4

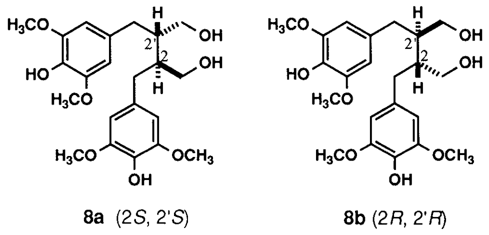

8a (2*S*, 2′*S*) 8b (2*R*, 2′*R*)

Fig. 5

aromatic rings [δ 3.70 (6H, s), 3.72 (6H, s), 3.83 (6H, s), 6.27 (2H, s), 6.31 (2H, s), 6.83 (2H, s)]. From the above evidence, it has been presumed that hazaleanin A (**1**) is a seco-type derivative of hazaleanin B (**2**).

On treatment with sodium methoxide in methanol, hazaleanin A (**1**) gave a lignan glucoside (**7**) and methyl sinapate. In the ^{13}C-NMR spectrum of **1**, esterification shifts[4] were observed for the signals due to 5″-C (−2.9 ppm) and 6″-C (+1.8 ppm) as compared with those of **7**, thus indicating that the sinapic acid moiety in **1** is attached

Table II. ^{13}C-NMR Data for Hazaleanin A (**1**), **7**, and **8** (in CD_3OD, δ in ppm)

	1	**7**	**8**		**1**	**7**
Aglycone moiety				Sugar moiety		
C-1	70.9	71.1	61.7	C-1″	104.4	104.7
C-2	41.1	41.2	43.5	C-2″	75.0	75.3
C-3	36.4	36.7	36.2	C-3″	77.9	78.2
C-4	134.1	134.2[a]	132.6	C-4″	71.8	71.7
C-5,9	107.1	107.2	106.6	C-5″	75.1	78.0
C-6,8	148.7	148.9	148.5	C-6″	64.6	62.8
C-7	132.8[a]	133.0[b]	133.9	Acyl moiety		
C-1′	62.5	62.7	61.7	C-1‴	168.9	
C-2′	43.7	43.7	43.5	C-2‴	115.4	
C-3′	36.4	36.3	36.2	C-3‴	147.2	
C-4′	134.1	134.3[a]	132.6	C-4‴	139.5	
C-5′,9′	107.0	107.2	106.6	C-5‴,9‴	106.7	
C-6′,8′	148.7	148.9	148.5	C-6‴,8‴	149.2	
C-7′	133.0[a]	133.2[b]	133.9	C-7‴	126.2	
6,8-OCH_3	56.5	56.6	56.0	6‴,8‴-OCH_3	56.7	
6′,8′-OCH_3	56.6	56.6	56.0			

a, *b*) The assignments in each column may be interchangeable.

to the hydroxyl group at C-6″ of the sugar moiety (Table II). Furthermore, enzymatic hydrolysis of compound **7** with cellulase afforded an optically active aglycone **8** ($[\alpha]_D$ +30.6° in $CHCl_3$) and D-glucose ($[\alpha]_D$ +47.5° in H_2O). The ^1H- and ^{13}C-NMR spectra of **8** showed only half the expected number of proton and carbon signals, which suggested that **8** has a symmetrical structure. From these findings, the structure of the aglycone **8** was considered to be **8a** (2*S*,2′*S*) or **8b** (2*R*,2′*R*).

In order to determine the absolute configuration of the aglycone (**8**), we next tried to synthesize an optically active hexamethyl ether (**9**), which was obtained by methylation of **8** with diazomethane.

The γ-lactone alcohol (**10**), which was prepared from L-glutamic acid by employing Yamada's procedure,[7] was chosen as the starting compound for the synthesis of **9**. The ^1H-NMR analysis of the (+)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA)[8] of **10** indicated the enantiomeric excess (ee) to be 88%.

The synthesis of **9** from **10** was accomplished by referring to Koga's procedure.[9] Thus, **10** was converted to the benzyl ether (**11**) by treatment with sodium hydride and benzyl bromide. Condensation of the γ-lactone benzyl ether (**11**) with 3,4,5-trimethoxybenzaldehyde under aldol reaction conditions and subsequent dehydration provided in 75% yield a $\Delta^{2',3'}$ adduct (**12**), which was a mixture of *E* and *Z* isomers. On catalytic hydrogenation over palladium charcoal–palladium chloride, **12** gave a (2′*S*)-γ-lactone alcohol (**13**), which was then converted into a (2′*S*)-triol (**14**) by reduction with lithium aluminum hydride ($LiAlH_4$) in 65% yield from **12**. It was presumed that the catalytic hydrogenation of the $\Delta^{2',3'}$ bond in **12** occurred from the β-side due to the presence of the bulky 1α-benzyloxymethyl group, thus resulting in the 2′*S* configuration of **14**.

The triol (**14**) was subjected to sodium periodate oxidation to afford a (2′*S*)-lactol (**15**), which was oxidized with Collins' reagent[10] into a β-substituted (2′*S*)-γ-lactone (**16**) in a moderate yield from **14**. The γ-lactone **16** was then successively treated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) and hexamethylphosphoramide (HMPA) and the resulting lithium anion was quenched with 3,4,5-trimethylbenzyl bromide to give a (2*S*,2′*S*)-2,2′-disubstituted γ-lactone (**17**) in 82% yield. Finally, $LiAlH_4$ reduction of **17** afforded a (2*S*,2′*S*)-lignan (**18**), whose physical data were found to be identical with those of **9**, including the sign of the optical rotation (**9**, $[\alpha]_D$ +23.6° and **18**, $[\alpha]_D$ +20.0°, both in $CHCl_3$). The enantiomeric excess of **18** was calculated to be 84%, based on the ^1H-NMR analysis of its di-(+)-MTPA ester.[8] As a result of the chiral synthesis of **9**, the absolute configurations at C-2 and C-2′ of the aglycone (**8**) have both been determined to be *S*.

As for the location of the glucose moiety in **7**, the ^{13}C-NMR analysis of the aglycone (**8**) provided supporting

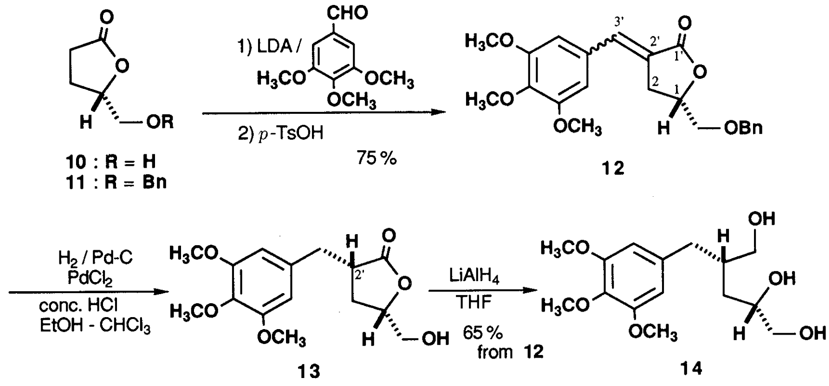
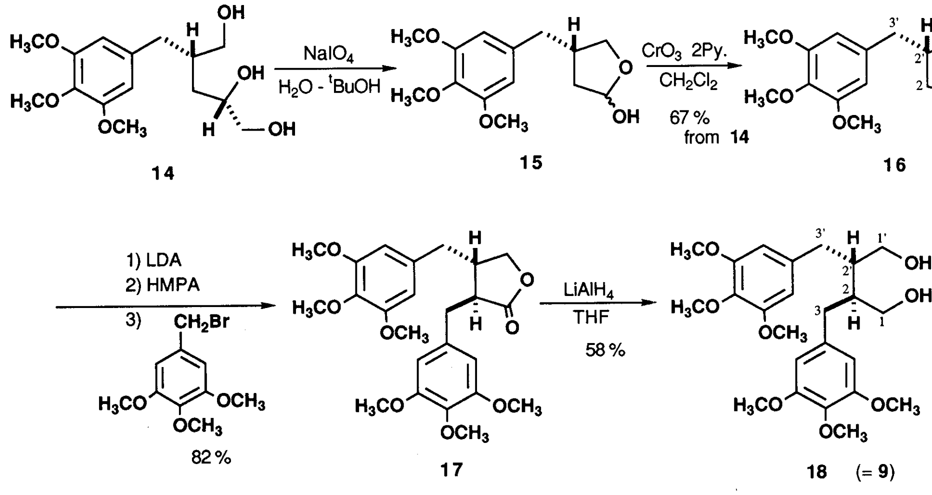


Chart 2



ᵗBu = *tert*-Bu

Chart 3

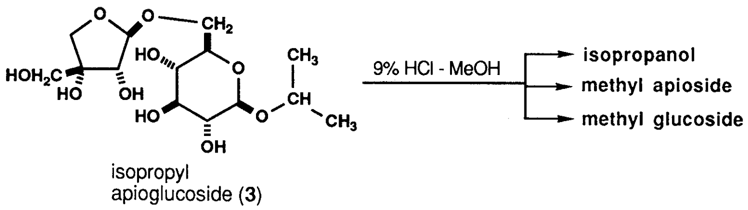


Fig. 6

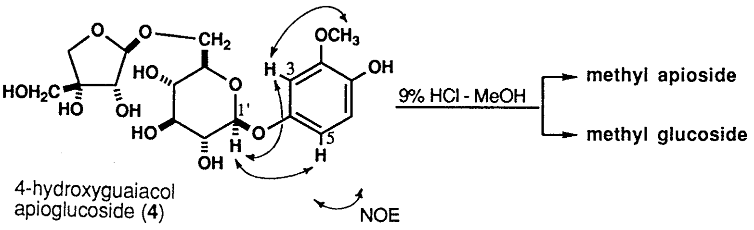


Fig. 7

Table III. ^{13}C-NMR Data for Sugar Moieties of **3** and **4** (in C_5D_5N, δ in ppm)

	3	4
C-1′	102.4	103.6
C-2′	74.8	74.9
C-3′	77.5	77.7
C-4′	71.5	71.6
C-5′	76.7	77.2
C-6′	68.7	68.9
C-1″	110.8	111.0
C-2″	78.2	78.5
C-3″	80.2	80.3
C-4″	74.7	74.9
C-5″	65.3	65.4

evidence. Thus, glycosylation shifts⁶⁾ were observed for the signals of 1-C (+9.4 ppm) and 2-C (−2.3 ppm) as compared with those of the aglycone (**8**) (Table II), so it has been shown that D-glucose is attached to the C-1 hydroxyl group of **8**. Furthermore, the coupling constant (J=8.0 Hz) of the anomeric proton of hazaleanin A (**1**) indicated the presence of a β-glucosidic linkage. Based on the above-mentioned findings, the structure of hazaleanin A has been elucidated as **1**.

Isopropyl Apioglucoside (3) Isopropyl apioglucoside (**3**) gave a pseudo-molecular ion peak at m/z 355, which corresponded to $C_{14}H_{27}O_{10}$ $(M+H)^+$, in the high-resolution secondary ion mass spectrum (SIMS). The IR spectrum of **3** showed absorption bands due to hydroxyl groups (3380 cm^{-1}), while the ^{1}H-NMR spectrum showed signals due to an isopropoxyl group and two anomeric protons (δ 4.31, d, J=7.8 Hz; δ 4.99, d, J=2.2 Hz), which indicated that **3** is a disaccharide. Furthermore, the ^{13}C-NMR spectrum of **3** also showed the presence of two anomeric carbons (δ_C 102.4, 110.8) (Table III).

On methanolysis, isopropyl apioglucoside (**3**) gave 2-propanol and two methyl glycosides, *i.e.*, methyl apioside and methyl glucoside, which were respectively hydrolyzed with 5% aqueous sulfuric acid to afford D-apiose and D-glucose. Detailed NMR analysis of **3**, *e.g.* the glycosylation shift⁶⁾ observed for the signal assignable to 6′-C of D-glucose in the ^{13}C-NMR, the coupling constant (J=7.8 Hz) of the anomeric proton of D-glucose, and the chemical shift (δ_C 110.8) of the anomeric carbon of D-apiose,¹¹⁾ has led to the formulation of the structure of **3** as isopropyl β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside.

4-Hydroxyguaiacol Apioglucoside (4) The molecular formula of 4-hydroxyguaiacol apioglucoside (**4**) was determined as $C_{18}H_{26}O_{12}$ on the basis of the high-resolution FAB-MS. The IR spectrum of **4** showed absorption bands due to hydroxyl groups (3400 cm^{-1}) and an aromatic ring (1615, 1511 cm^{-1}), while the UV spectrum suggested the presence of an aromatic ring (285 nm). Methanolysis of **4** provided methyl apioside and methyl glucoside, which were further hydrolyzed to afford D-apiose and D-glucose, respectively.

The ^{1}H-NMR spectrum of 4-hydroxyguaiacol apioglucoside (**4**) showed the signals attributable to two anomeric protons (δ 4.70, d, J=7.3 Hz; δ 4.98, d, J=2.2 Hz), suggesting both glycosidic linkages to be β, one methoxyl group, and three aromatic protons (δ 6.58, dd, J=2.6, 8.5 Hz; δ 6.70, d, J=8.5 Hz; δ 6.75, d, J=2.6 Hz), suggesting the presence of a 1,2,4-trisubstituted phenyl ring, and sugar moiety protons which were similar to those in the case of isopropyl apioglucoside (**3**). The nuclear Overhauser enhance and exchange spectroscopy (NOESY) experiments on **4** showed the presence of NOEs between the anomeric proton (δ 4.70) of glucose and two aromatic protons (δ 6.58, 6.75) and between methoxyl protons (δ 3.83) and one aromatic proton (δ 6.75) (Fig. 7). These findings indicated that the sugar moiety is attached to the C-4 hydroxyl group of 4-hydroxyguaiacol.

Since the signal assignable to 6′-C of D-glucose was observed at lower field (δ_C 68.9 ppm) in the ^{13}C-NMR spectrum⁶⁾ of **4** (Table III), the sugar sequence in **4** was found to be apiosyl(1→6)-glucose. Furthermore, the coupling constant (J=7.3 Hz) of the anomeric proton of D-glucose and the chemical shift (δ_C 111.0) of the anomeric carbon of D-apiose¹¹⁾ indicated both glycoside linkages in **4** to have β-orientation. Consequently, the structure of **4** has been elucidated to be 4-hydroxyguaiacol 4-*O*-β-D-apiofuranosyl(1→6)-β-D-glucopyranoside.

In conclusion, following the characterization of four alkaloids, two phenylpropanoids, *O*-geranylsinapyl alcohol, O-geranylconiferyl alcohol, and one acid amide, named hazaleamide as reported in our previous paper,1) we have isolated two new lignan glycosides, hazaleanins A (**1**) and B (**2**), and two new apioglucosides, isopropyl apioglucoside (**3**) and 4-hydroxyguaiacol apioglucoside (**4**), from the bark of *Fagara rhetza*, which is a rutaceous Indonesian medicinal plant collected on Flores Island.

Experimental

The instruments used to obtain physical data and the experimental conditions for chromatography were the same as in our previous paper.1)

Isolation of Hazaleanin A (1), Hazaleanin B (2), Isopropyl Apioglucoside (3), and 4-Hydroxyguaiacol Apioglucoside (4) The *n*-butanol-soluble portion (60 g), which was obtained by repeated solvent partitions of the methanol extract of the bark of *Fagara rhetza* (Rutaceae) (Chart 1), was subjected to column chromatography (SiO_2, 1.5 kg, $CHCl_3 \rightarrow CHCl_3$: MeOH : $H_2O \rightarrow$ MeOH) and subsequently to HPLC on reversed-phase Cosmosil $5C_{18}$ (MeOH : $H_2O = 1:1$) to afford hazaleanin A (**1**, 180 mg, 0.007% from the bark) and hazaleanin B (**2**, 380 mg, 0.014%). On the other hand, the water-soluble portion (17 g) (Chart 1) was purified by successive chromatographies, *i.e.*, 1) reversed-phase column chromatography (Cosmosil, H_2O : MeOH), 2) ordinary phase column chromatography (SiO_2, 300 g, $CHCl_3$: MeOH : $H_2O = 7:3:1$ lower phase $\rightarrow 6:4:1 \rightarrow 5:5:1$), and 3) reversed-phase HPLC (Cosmosil $5C_{18}$, MeOH : $H_2O = 1:4$), to afford isopropyl apioglucoside (**3**, 78 mg, 0.03%) and 4-hydroxyguaiacol apioglucoside (**4**, 26 mg, 0.01%).

Hazaleanin A (**1**): A white amorphous solid, $[\alpha]_D$ $-3.6°$ ($c=0.92$, MeOH at 26 °C). IR (KBr) cm^{-1}: 3400, 1695, 1627, 1605, 1515. UV λ_{max}^{MeOH} nm (ε): 325 (11500), 280 (5500), 236 (sh, 17800). ^{1}H-NMR (CD_3OD) δ: 1.89 (1H, m, 2′-H), 2.07 (1H, m, 2-H), 2.53 (1H, dd, J=7.0, 14.0 Hz, 3-H_a), 2.57 (2H, d, J=6.7 Hz, 3′-H_2), 2.69 (1H, dd, J=7.0, 14.0 Hz, 3-H_b), 3.25 (1H, dd, J=8.0, 8.8 Hz, 2″-H), 3.35—3.42 (2H, m, 3″-H, 4″-H), 3.47—3.52 (3H, m, 1-H_a, 1′-H_a, 5″-H), 3.65 (1H, dd, J=5.5, 11.0 Hz, 1′-H_b), 3.70 (6H, s, 6-OCH_3, 8-OCH_3), 3.72 (6H, s, 6′-OCH_3, 8′-OCH_3), 3.83 (6H, s, 6‴-OCH_3, 8‴-OCH_3), 4.03 (1H, dd, J=5.6, 9.6 Hz, 1-H_b), 4.27 (1H, d, J=8.0 Hz, 1″-H), 4.39 (1H, dd, J=6.4, 11.9 Hz, 6″-H_a), 4.49 (1H, dd, J=2.2, 11.9 Hz, 6″-H_b), 6.27 (2H, s, 5′-H, 9′-H), 6.31 (2H, s, 5-H, 9-H), 6.39 (1H, d, J=15.8 Hz, 2‴-H), 6.83 (2H, s, 5‴-H, 9‴-H), 7.59 (1H, d, J=15.8 Hz, 3‴-H). ^{13}C-NMR: as given in Table I. FAB-MS m/z: 797 $(M+Li)^+$, 791 $(M+H)^+$, 790 (M^+). High-resolution FAB-MS m/z: Calcd for $C_{39}H_{50}O_{17}$: 790.3048. Found: 790.3052 (M^+).

Hazaleanin B (**2**): A white amorphous solid, $[\alpha]_D$ $+7.5°$ ($c=1.10$, MeOH at 26 °C). IR (KBr) cm^{-1}: 3420, 1696, 1629, 1605, 1514. UV λ_{max}^{MeOH} nm (ε): 320 (11500), 272 (6300), 240 (sh, 15700). ^{1}H-NMR (CD_3OD) δ: 1.67 (1H, m, 2-H), 2.11 (1H, m, 3-H), 2.60 (1H, dd, J=11.3, 14.9 Hz, 1-H_a), 2.66 (1H, dd, J=4.8, 14.9 Hz, 1-H_b), 3.27 (1H, dd, J=8.1, 8.2 Hz, 2″-H), 3.32 (3H, s, 5-OCH_3), 3.38 (2H, m, 3″-H, 4″-H), 3.47—3.51 (2H, m, 3α-H_a, 5″-H), 3.56 (1H, dd, J=6.4, 11.0 Hz, 2α-H_a), 3.65 (1H, dd, J=4.0, 11.0 Hz, 2α-H_b), 3.72 (6H, s, 3′-OCH_3, 5′-OCH_3), 3.79 (3H, s, 7-OCH_3), 3.83 (6H, s, 6‴-OCH_3, 8‴-OCH_3), 3.86 (1H, dd, J=4.0, 10.2 Hz, 3α-H_b), 4.27 (1H, d, J=7.6 Hz, 4-H), 4.32 (1H, dd, J=6.0, 11.8 Hz, 6″-H_a), 4.34 (1H, d, J=8.1 Hz, 1″-H), 4.46 (1H, dd, J=1.8, 11.8 Hz, 6″-H), 6.38 (1H, d, J=15.8 Hz, 2‴-H), 6.42 (2H, s, 2′-H, 6′-H), 6.49 (1H, s, 8-H), 6.85 (2H, s, 5‴-H, 9‴-H), 7.59 (1H, d, J=15.8 Hz, 3‴-H). ^{13}C-NMR: as given in Table II. FAB-MS m/z: 827 $(M+K)^+$, 789 $(M+H)^+$, 788 (M^+). High-resolution FAB-MS m/z: Calcd for $C_{39}H_{48}O_{17}$: 788.2895. Found: 788.2935 (M^+).

Isopropyl Apioglucoside (**3**): A white amorphous solid, $[\alpha]_D$ $-84.4°$ ($c=0.67$, MeOH at 25 °C). IR (KBr) cm^{-1}: 3380, 1047. ^{1}H-NMR (CD_3OD) δ: 1.19 (3H, d, J=6.2 Hz, 1-H_3), 1.23 (3H, d, J=6.2 Hz, 3-H_3), 3.13 (1H, dd, J=7.8, 8.0 Hz, 2′-H), 3.25 (1H, dd, J=8.0, 8.0 Hz, 4′-H), 3.31—3.39 (2H, m, 3′-H, 5′-H), 3.57—3.60 (3H, m, 6′-H_a, 5″-H_2), 3.75 (1H, d, J=9.8 Hz, 4″-H_a), 3.88 (1H, d, J=2.2 Hz, 2″-H), 3.95—3.97 (2H, m, 6′-H_b, 4″-H_b), 4.00 (1H, septet, J=6.2 Hz, 2-H), 4.31 (1H, d, J=7.8 Hz, 1′-H), 4.99 (1H, d, J=2.2 Hz, 1″-H). ^{13}C-NMR (C_5D_5N) δ_C: 21.8 (1-C), 23.7 (3-C), 65.3 (5″-C), 68.7 (6′-C), 70.9 (2-C), 71.5 (4′-C), 74.7 (4″-C), 74.8 (2′-C), 76.7 (5′-C), 77.5 (3′-C), 78.2 (2″-C), 80.2 (3″-C), 102.4 (1′-C), 110.8 (1″-C). SIMS m/z: 355 $(M+H)^+$. High-resolution SIMS m/z: Calcd for $C_{14}H_{26}O_{10}+H$: 355.1603. Found: 355.1608 $(M+H)^+$.

4-Hydroxyguaiacol Apioglucoside (**4**): A white amorphous solid, $[\alpha]_D$ $-91.4°$ ($c=0.50$, MeOH at 25 °C). IR (KBr) cm^{-1}: 3400, 1615, 1511, 1062. UV λ_{max}^{MeOH} nm (ε): 285 (2000). ^{1}H-NMR (CD_3OD) δ: 3.30—3.33 (1H, m, 2′-H), 3.38—3.43 (2H, m, 3′-H, 4′-H), 3.52—3.54 (1H, m, 5′-H), 3.57 (2H, s, 5″-H_2), 3.61 (1H, dd, J=6.4, 10.8 Hz, 6′-H_a), 3.74 (1H, d, J=9.8 Hz, 4″-H_a), 3.83 (3H, s, OCH_3), 3.89 (1H, d, J=2.2 Hz, 2″-H), 3.95 (1H, d, J=9.8 Hz, 4″-H_b), 4.01 (1H, dd, J=2.0, 10.8 Hz, 6′-H_b), 4.70 (1H, d, J=7.3 Hz, 1′-H), 4.98 (1H, d, J=2.2 Hz, 1″-H), 6.58 (1H, dd, J=2.6, 8.5 Hz, 5-H), 6.70 (1H, d, J=8.5 Hz, 6-H), 6.75 (1H, d, J=2.6 Hz, 3-H). ^{13}C-NMR (C_5D_5N) δ_C: 55.8 (OCH_3), 65.4 (5″-C), 68.9 (6′-C), 71.6 (4′-C) 74.9 (2′-C), 74.9 (4″-C), 77.2 (5′-C), 77.7 (3′-C), 78.5 (2″-C), 80.3 (3″-C), 103.6 (1′-C), 104.0 (3-C), 109.8 (5-C), 111.0 (1″-C), 116.4 (6-C), 143.4 (1-C), 148.9 (2-C), 152.1 (4-C). FAB-MS m/z: 457 $(M+Na)^+$, 434 $(M+H)^+$. High-resolution FAB-MS m/z: Calcd for $C_{18}H_{26}O_{12}+Na$: 457.1323. Found: 457.1349 $(M+Na)^+$.

Alkaline Hydrolysis of Hazaleanin B (2) Giving 5 A solution of hazaleanin B (**2**, 380 mg) in dry MeOH (6.0 ml) was treated with 28% NaOMe–MeOH (1.2 ml) at room temperature for 3 h. The reaction mixture was neutralized with Dowex 50W × 8 (H^+ form) and the resin was removed by filtration. The solvent was evaporated under reduced pressure from the filtrate to give a product. Purification of the product by column chromatography (SiO_2 15 g, $CHCl_3$: MeOH : $H_2O = 15:3:1$ lower phase) afforded a lignan glucoside (**5**, 211 mg, 75%) and methyl sinapate (83 mg, 73%), which was identical with an authentic sample by TLC (benzene : acetone = 5 : 1, *Rf* 0.46; *n*-hexane : acetone = 1 : 1, *Rf* 0.53; $CHCl_3$: acetone = 9 : 1, *Rf* 0.40) and gas liquid chromatography (GLC) [1) column, OV-17; column temperature, 170 °C; injection temperature, 190 °C; carrier gas, N_2; flow rate, 60 ml/min; detector, hydrogen flame ionization detector (FID); t_R, 15.80 min, 2) column, OV-101; column temperature, 170 °C; injection temperature, 190 °C; carrier gas, N_2; flow rate, 60 ml/min; detector, FID; t_R, 23.10 min].

5: A white amorphous solid, $[\alpha]_D$ $+35.8°$ ($c=0.58$, MeOH at 25 °C). IR (KBr) cm^{-1}: 3400, 1600, 1505. UV λ_{max}^{MeOH} nm (ε): 280 (3800). ^{1}H-NMR (CD_3OD) δ: 1.70 (1H, m, 2-H), 2.08 (1H, m, 3-H), 2.61 (1H, dd, J=11.6, 15.2Hz, 1-H_a), 2.71 (1H, dd, J=4.6, 15.2 Hz, 1-H_b), 3.21—3.39 (4H, m, 2″-H, 3″-H, 4″-H, 5″-H), 3.34 (3H, s, 5-OCH_3), 3.45 (1H, dd, J=4.1, 10.0 Hz, 3α-H_a), 3.55 (1H, dd, J=6.7, 11.1 Hz, 2α-H_b), 3.64 (2H, dd, J=4.9, 11.1 Hz, 2α-H_a, 6″-H_b), 3.74 (6H, s, 3′-OCH_3, 5′-OCH_3), 3.83 (1H, dd, J=2.1, 10.2 Hz, 6″-H_a), 3.85 (3H, s, 7-OCH_3), 3.89 (1H, dd, J=5.3, 9.8 Hz, 3α-H_b), 4.28 (1H, d, J=8.0 Hz, 1″-H), 4.41 (1H, d, J=6.2 Hz, 4-H), 6.42 (2H, s, 2′-H, 6′-H), 6.57 (1H, s, 8-H). ^{13}C-NMR: as given in Table I. FAB-MS m/z: 583 $(M+H)^+$, 582 (M^+). High-resolution FAB-MS m/z: Calcd for $C_{28}H_{38}O_{13}$: 582.2312. Found: 582.2310 (M^+).

Enzymatic Hydrolysis of 5 with Cellulase Giving 6 A solution of **5** (200 mg) in H_2O (10 ml) was treated with cellulase (Sigma, *ca.* 100 mg) at 37 °C for 12 h. The reaction mixture was extracted with EtOAc, and the EtOAc extract was evaporated under reduced pressure to afford an aglycone (**6**, 144 mg, quantitatively). The aqueous phase was passed through a silica gel column (SiO_2 5 g, $CHCl_3$: MeOH : $H_2O = 7:3:1$ lower phase) to afford D-glucose ($[\alpha]_D$ $+47.4°$, $c=0.10$, 24 h after dissolution in H_2O).

6: A white amorphous solid, $[\alpha]_D$ $+54.5°$ ($c=0.28$, MeOH at 25 °C). IR ($CHCl_3$) cm^{-1}: 3440, 1612, 1492, 1456. ^{1}H-NMR ($CDCl_3$) δ: 1.73 (1H, m, 2-H), 1.89 (1H, m, 3-H), 2.54—2.70 (2H, m, 1-H_2), 3.28 (3H, s, 5-OCH_3), 3.51—3.76 (4H, m, 2α-H_2, 3α-H_2), 3.78 (6H, s, 3′-OCH_3, 5′-OCH_3), 3.87 (3H, s, 7-OCH_3), 3.99 (1H, d, J=7.6 Hz, 4-H), 5.45 (2H, br s, OH × 2), 6.34 (2H, s, 2′-H, 6′-H), 6.44 (1H, s, 8-H). ^{13}C-NMR: as given in Table I. EI-MS m/z (%): 420 (M^+, 3.4), 57 (100). High-resolution EI-MS m/z: Calcd for $C_{22}H_{28}O_8$: 420.1784. Found: 420.1794 (M^+). These physical data for **6** were identical with those reported for (+)-lyoniresinol.5)

Methanolysis of 5 A solution of **5** (1 mg) in 9% HCl–MeOH (0.2 ml) was heated under reflux for 20 h. After cooling, the reaction mixture was neutralized with Ag_2CO_3 powder. The precipitates were removed by filtration and the solvent was evaporated under reduced pressure from the filtrate. The residue was dissolved in pyridine (0.1 ml) and *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) (0.2 ml), and the whole was left standing at room temperature for 30 min. The reaction mixture was subjected to GLC to identify methyl glucoside. GLC conditions: 1) column, 3% SE-30; column temperature, 140 °C; injection temperature, 160 °C; carrier gas, N_2; flow rate, 40 ml/min; detector, FID; t_R, 9.44, 12.40 min. 2) column, 2% OV-17; column temperature, 170 °C; injection temperature, 190 °C; carrier gas, N_2; flow rate, 40 ml/min; detector, FID; t_R, 11.55, 13.22 min.

Alkaline Hydrolysis of Hazaleanin A (1) Giving 7 A lignan glucoside (**7**, 87 mg, 88%) and methyl sinapate (36 mg, 88%) were obtained from hazaleanin A (**1**, 135 mg) through a procedure similar to that described above for obtaining **5** from hazaleanin B (**2**).

7: A white amorphous solid, $[\alpha]_D$ $+8.9°$ ($c=1.12$, MeOH at 24 °C). IR (KBr) cm^{-1}: 3400, 1614, 1516. UV λ_{max}^{MeOH} nm (ε): 274 (3200). ^{1}H-NMR ($CDCl_3$) δ: 1.90 (1H, m, 2′-H), 2.07 (1H, m, 2-H), 2.55 (1H, dd, $J=11.3$, 13.7, 3-H_a), 2.58 (1H, dd, $J=11.6$, 13.7 Hz, 3′-H_a), 2.65 (1H, dd, $J=6.4$, 13.7 Hz, 3′-H_b), 2.73 (1H, dd, $J=6.4$, 13.7 Hz, 3-H_b), 3.21 (1H, dd, $J=7.9$, 8.0 Hz, 2″-H), 3.24—3.34 (2H, m, 3″-H, 4″-H), 3.45 (1H, dd, $J=6.4$, 9.8 Hz, 1-H_a), 3.55 (1H, dd, $J=6.7$, 11.0 Hz, 1′-H_a), 3.65—3.72 (2H, m, 1′-H_b, 6″-H_a), 3.74 (12H, s, $OCH_3 \times 4$), 3.82—3.86 (2H, m, 5″-H, 6″-H), 4.10 (1H, dd, $J=5.8$, 9.8 Hz, 1-H_b), 4.24 (1H, d, $J=7.9$ Hz, 1″-H), 6.31 (2H, s, 5′-H, 9′-H), 6.33 (2H, s, 5-H, 9-H). ^{13}C-NMR: as given in Table II. FAB-MS *m/z*: 585 $(M+H)^+$, 584 (M^+). High-resolution FAB-MS *m/z*: Calcd for $C_{28}H_{40}O_{13}$: 584.2469. Found: 584.2440 (M^+).

Enzymatic Hydrolysis of 7 Giving 8 The aglycone (**8**, 42 mg, quantitatively) and D-glucose (22 mg, quantitatively, $[\alpha]_D$ $+46.3°$, $c=0.10$, 24 h after dissolving in H_2O) were obtained from **7** (63 mg) by enzymatic hydrolysis as described above for the hydrolysis of **5**, liberating **6**.

8: A white amorphous solid, $[\alpha]_D$ $+30.6°$ ($c=0.82$, $CHCl_3$ at 23 °C). IR (KBr) cm^{-1}: 3400, 1616, 1516. UV λ_{max}^{MeOH} nm (ε): 274 (3000). ^{1}H-NMR ($CDCl_3$) δ: 1.87 (2H, br s, 2-H, 2′-H), 2.65, 2.75 (4H, d of ABq, $J=7.0$, 13.5 Hz, 3-H_2, 3′-H_2), 3.58 (2H, dd, $J=3.5$, 11.5 Hz, 1-H_a, 1′-H_a), 3.83 (12H, s, $OCH_3 \times 4$), 3.86 (2H, dd, $J=3.5$, 11.5 Hz, 1-H_b, 1′-H_b), 5.45 (2H, br s, $OH \times 2$), 6.46 (4H, s, 5-H, 9-H, 5′-H, 9′-H). ^{13}C-NMR: as given in Table II. FAB-MS *m/z*: 423 $(M+H),^+$ 422 (M^+). High-resolution FAB-MS *m/z*: Calcd for $C_{22}H_{30}O_8$: 422.1941. Found: 422.1913 (M^+).

Methanolysis of 7 A solution of **7** (2 mg) in 9% HCl–MeOH (0.2 ml) was heated under reflux for 20 h. After cooling, the reaction mixture was neutralized with an Ag_2CO_3 powder. The precipitates were removed by filtration and the solvent was evaporated under reduced pressure from the filtrate. The residue was dissolved in pyridine (0.1 ml) and BSTFA (0.2 ml) and the whole was left standing at room temperaure for 30 min. The reaction mixture was subjected to GLC to identify methyl glucoside. The GLC conditions were the same as for the analysis of the product obtained above by methanolysis of **5**.

Methylation of 8 Giving 9 A solution of **8** (20 mg) in MeOH (5 ml) was treated with a diazomethane–ether solution in an ice-water bath for 12 h. Thre reaction mixture was evaporated under reduced pressure to give a product, which was purified by HPLC (YMC AL-312, $CHCl_3$: MeOH : $H_2O=1:3:1$) to afford **9** (18 mg, 85%).

9: A white amorphous solid, $[\alpha]_D$ $+23.6°$ ($c=0.11$, $CHCl_3$ at 23 °C). IR ($CHCl_3$) cm^{-1}: 3400, 1588, 1456. ^{1}H-NMR ($CDCl_3$) δ: 1.89 (2H, m, 2-H, 2′-H), 2.69—2.76 (4H, m, 3-H_2, 3′-H_2), 3.54 (2H, br d, 1-H_a, 1′-H_a), 3.79 (12H, s, 6-OCH_3, 8-OCH_3, 6′-OCH_3, 8′-OCH_3), 3.81 (6H, s, 7-OCH_3, 7′-OCH_3), 3.83 (2H, br d, 1-H_b, 1′-H_b), 6.35 (4H, s, 5-H, 9-H, 5′-H, 9′-H). ^{13}C-NMR ($CDCl_3$) δ_C: 36.7 (2-C, 2′-C), 43.7 (3-C, 3′-C), 56.1 ($O\underline{C}H_3 \times 4$), 60.3 (1-C, 1′-C), 60.8 ($O\underline{C}H_3 \times 2$), 106.0 (5-C, 9-C, 5′-C, 9′-C), 136.2 (4-C, 4′-C), 136.5 (7-C, 7′-C), 153.1 (6-C, 8-C, 6′-C, 8′-C). EI-MS *m/z* (%): 450 (M^+, 19), 182 (100). High-resolution EI-MS *m/z*: Calcd for $C_{24}H_{34}O_8$: 450.2254. Found: 450.2260 (M^+).

The γ-Lactone (10) The γ-lactone (**10**) was synthesized from L-glutamic acid by Yamada's procedure.$^{7)}$

10: A colorless oil, $[\alpha]_D$ $+32.2°$ ($c=1.53$, EtOH at 25 °C). IR ($CHCl_3$) cm^{-1}: 3420, 1771. ^{1}H-NMR ($CDCl_3$) δ: 2.08—2.35 (2H, m), 2.47—2.70 (2H, m), 3.66 (1H, dd, $J=4.3$, 12.5 Hz), 3.90 (1H, dd, $J=2.6$, 12.5 Hz), 4.61—4.69 (1H, m). EI-MS *m/z* (%): 116 (M^+, 9), 85 (100). High-resolution EI-MS *m/z*: Calcd for $C_5H_8O_3$: 116.0474. Found: 116.0475 (M^+). The enantiomeric excess (ee) was calculated to be 88% by ^{1}H-NMR analysis of the MTPA of **10**.

Benzylation of 10 Giving 11 A solution of **10** (11.98 g, 0.10 mol) in dimethylformamide (DMF) (10 ml) was added to a mixture of NaH (60% in oil, 5.36 g, 0.134 mol, 1.3 eq) in DMF (20 ml), and the mixture was stirred at room temperature for 1 h. Then the reaction mixture was treated with benzyl bromide (13.5 ml, 0.133 mol, 1.1 eq) in an icecooling bath and the whole was stirred at room temperature for 2 h. After addition of benzene (300 ml), the reaction mixture was washed with 10% aqueous HCl, water, aqueous saturated $NaHCO_3$, and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (16 g), which was purified by column chromatography (SiO_2 800 g, *n*-hexane : EtOAc $=1:1$) to afford **11** (11.89 g, 57.7 mmol, 56%).

11: A white amorphous solid, $[\alpha]_D$ $+19.3°$ ($c=2.19$, EtOH at 22°C). IR ($CHCl_3$) cm^{-1}: 1779, 1598. ^{1}H-NMR ($CDCl_3$) δ: 2.06—2.33 (2H, m), 2.39—2.66 (2H, m), 3.56 (1H, dd, $J=4.3$, 10.8 Hz), 3.67 (1H, dd, $J=3.3$, 10.8 Hz), 4.56 (2H, s), 4.65 (1H, m), 7.32 (5H, br s). EI-MS *m/z* (%): 206 (M^+, 100). High-resolution EI-MS *m/z*: Calcd for $C_{12}H_{14}O_3$: 206.0941. Found: 206.0941 (M^+).

Preparation of 12 from 11 A solution of **11** (5.5 g, 28.1 mmol) in THF (2.0 ml) was treated with LDA reagent [prepared from diisopropylamine (15.8 ml, 112.5 mmol, 4 eq), *n*-BuLi (15% in *n*-hexane, 23.4 ml, 36.6 mmol, 1.3 eq), and THF (8 ml)] under stirring at -78 °C for 10 min. Then a solution of 3,4,5-trimethoxybenzaldehyde (5.5 g, 28.1 mmol, 1.0 eq) in THF (12 ml) was added at once to the reaction mixture, and the whole was further stirred at -78 °C for 2.5 h. The mixture was treated with concentrated aqueous HCl (10 ml) and extracted with EtOAc. The combined organic phase was washed with aqueous saturated $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (11.9 g). A solution of the product in *m*-xylene (210 ml) was treated with *p*-toluenesulfonic acid monohydrate (187 mg) and the whole was refluxed for 2 h, then cooled, washed with aqueous saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (9.66 g), which was purified by column chromatography (SiO_2 500 g, *n*-hexane : $CHCl_3=1:3$) to afford **12** (8.11 g, 21.1 mmol, 75%).

12: A white amorphous solid, $[\alpha]_D$ $+67.8°$ ($c=0.93$, $CHCl_3$ at 20 °C). IR ($CHCl_3$) cm^{-1}: 1743, 1651, 1582, 1463. ^{1}H-NMR ($CDCl_3$) δ: 3.05—3.24 (2H, m), 3.50 (2H, m), 3.89 (6H, s), 3.90 (3H, s), 4.58 (2H, s), 4.78 (1H, m), 6.72 (2H, s), 7.30 (5H, s), 7.47 (1H, br s). EI-MS *m/z* (%): 384 (M^+, 5.7), 85 (100). High-resolution EI-MS *m/z*: Calcd for $C_{22}H_{24}O_6$: 384.1570. Found: 384.1569 (M^+).

Preparation of 14 from 12 *via* 13 A solution of **12** (4.9 g, 12.8 mmol) in EtOH (50 ml) and $CHCl_3$ (50 ml) containing 10% Pd–C (1.2 g) and concentrated aqueous HCl (2 drops) was hydrogenated at room temperature for 2 h. The catalyst was removed by filtration, and the solvent was evaporated from the filtrate under reduced pressure to give a product (**13**, 4.8 g). The product in THF (100 ml) was added to a suspension of $LiAlH_4$ (416 mg, 11.0 mmol) in THF (15 ml), and the mixture was stirred at room temperature for 1 h. After addition of aqueous saturated Et_2O to the reaction mixture, the whole was passed through a Celite column. The solvent was evaporated from the eluate under reduced pressure to give a product (3.0 g). Purification of the product by column chromatography (SiO_2 120 g, $CHCl_3$: MeOH $=10:1$) afforded a triol (**14**, 2.7 g, 8.9 mmol, 65% from **12**).

14: A white amorphous solid, $[\alpha]_D$ $-11.8°$ ($c=0.39$, EtOH at 22 °C). IR ($CHCl_3$) cm^{-1}: 3350, 1589, 1458. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (2H, m), 1.89 (1H, m), 2.41 (2H, d, $J=6.9$ Hz), 3.31 (2H, m), 3.45 (1H, m), 3.59 (2H, d, $J=11.2$ Hz), 3.73 (6H, s), 3.75 (3H, s), 6.30 (2H, s). EI-MS *m/z*: (%): 300 (M^+, 42), 181 (100). High-resolution EI-MS *m/z*: Calcd for $C_{15}H_{24}O_6$: 300.1573. Found: 300.1586 (M^+).

Preparation of 16 from 14 *via* 15 A solution of the triol (**14**, 2.7 g, 89.2 mmol) in *tert*-BuOH (30 ml) was added to a solution of $NaIO_4$ (3.8 g, 17.8 mmol, 2 eq) in H_2O (30 ml) and *tert*-BuOH (30 ml), and the whole was stirred at room temperature for 20 min. The reaction mixture was extracted with EtOAc, and the EtOAc extract was washed with 5% aqueous Na_2CO_3, aqueous saturated $NaHCO_3$, and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (**15**, 2.2 g). The product was dissolved in CH_2Cl_2 (25 ml), the solution was added to Collins' reagent (16.8 g, 64.9 mmol) in CH_2Cl_2 (150 ml), and the whole was stirred at room temperature for 1 h. After addition of a mixture of *n*-hexane and Et_2O (1 : 1, 100 ml), the whole was further stirred for 10 min, then passed through a Celite column. The cluate was evaporated under reduced pressure to give a product (1.9 g). Purification of the product by column chromatography (SiO_2 100 g, $CHCl_3$: $CH_2Cl_2=10:1$) afforded **16** (1.6 g, 6.0 mmol, 67% from **14**).

16: A pale yellow oil, $[\alpha]_D$ $-4.7°$ ($c=0.69$, $CHCl_3$ at 22 °C). IR ($CHCl_3$) cm^{-1}: 1771, 1591, 1458. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (1H, dd, $J=6.8$, 17.3 Hz, 2.54 (1H, dd, $J=7.9$, 17.3 Hz), 2.63 (2H, m), 2.77 (1H, m), 3.76 (3H, s), 3.78 (6H, s), 3.98 (1H, dd, $J=5.9$, 9.1 Hz), 4.28 (1H, dd, $J=6.9$, 9.1 Hz), 6.29 (2H, s). EI-MS *m/z* (%): 266 (M^+, 42), 181 (100). High-resolution EI-MS *m/z*: Calcd for $C_{14}H_{18}O_5$: 266.1151. Found: 266.1151 (M^+).

Preparation of 17 from 16 A solution of **16** (116 mg, 0.44 mmol) in THF (1.5 ml) was added to LDA reagent [prepared from diisopropylamine (0.25 ml, 1.8 mmol, 4 eq) and *n*-BuLi (15% in *n*-hexane, 0.37 ml, 0.57 mmol, 1.3 eq) in THF (2.0 ml)], and the mixture was stirred at -78 °C for 15 min. The reaction mixture was then treated with HMPA (0.10 ml, 0.57 mmol, 1.3 eq) and a solution of 3,4,5-trimethoxybenzyl bromide (149 mg, 0.57 mmol, 1.3 eq) in THF (2.0 ml), and the whole was stirred at -78 °C for a further 4 h. After warming of the reaction mixture to room temperature, aqueous saturated NH_4Cl was added and the whole was extracted with EtOAc. The EtOAc extract was washed with 10% aqueous HCl, water, aqueous saturated $NaHCO_3$, and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (230 mg), which was purified by column chromatography (SiO_2 7 g, *n*-hexane : EtOAc = 1 : 1) to afford **17** (160 mg, 0.36 mmol, 82%).

17: A pale yellow oil. $[\alpha]_D$ +20.1° (c=0.14, $CHCl_3$ at 22 °C). IR $CHCl_3$) cm^{-1}: 1760, 1601, 1458. ^{1}H-NMR ($CDCl_3$) δ: 2.50—2.69 (4H, m), 2.97 (2H, d, J=5.9 Hz), 3.81 (12H, s), 3.82 (6H, s), 3.85 (1H, m), 4.12 (1H, m), 6.21 (2H, s), 6.39 (2H, s). EI-MS m/z (%): 446 (M^+, 5.3), 181 (100). High-resolution EI-MS m/z: Calcd for $C_{24}H_{30}O_8$: 446.1941. Found: 446.1942 (M^+).

Preparation of 18 from 17 A solution of **17** (155 mg, 0.35 mmol) in THF (1 ml) was added to a suspension of $LiAlH_4$ (10.6 mg, 0.28 mmol, 1.6 eq) in THF (3 ml) in an ice-cooling bath, and the mixture was stirred at room temperature for 1 h. After quenching of the reaction by adding aqueous saturated Et_2O, the whole was passed through a Celite column. The solvent was evaporated from the eluate under reduced pressure to yield a product (161 mg). Purification of the product by column chromatography (SiO_2 8 g, *n*-hexane : EtOAc = 1 : 6) and HPLC (Cosmosil $5C_{18}$-AR, MeOH : H_2O = 10 : 1) afforded **18** (90.3 mg, 0.20 mmol, 58%).

18: A white amorphous solid, $[\alpha]_D$ +20.0° (c=1.58, $CHCl_3$ at 22 °C). High-resolution EI-MS m/z: Calcd for $C_{24}H_{34}O_8$: 450.2254. Found: 450.2261 (M^+). IR, ^{1}H-NMR, ^{13}C-NMR, and EI-MS data for **18** were identical with those for **9**. The enantiomeric excess (ee) of **18** was calculated to be 84% by ^{1}H-NMR analysis of the corresponding (+)-MTPA diester.

Methanolysis of Isopropyl Apioglucoside (3) Isopropyl apioglucoside (**3**, 20 mg) was dissolved in 9% HCl–MeOH (4 ml) and the mixture was heated under reflux for 12 h, then cooled. The reaction mixture was neutralized with Ag_2CO_3 powder, and the precipitates were removed by filtration. The solvent was evaporated under reduced pressure from the filtrate to give a product (14 mg). 2-Propanol was detected in the product by GLC analysis [conditions: column, OV-101; column temperature, 40 °C; injection temperature, 50 °C; carrier gas, N_2; flow rate, 20 ml/min; detector, FID; t_R, 2.85 min]. The product in pyridine was treated with BSTFA at room temperature for 30 min, and the product was analyzed by GLC to determine methyl apioside and methyl glucoside. [conditions: 1) column, 3% SE-30; column temperature, 120 °C; injection temperature, 140 °C; carrier gas, N_2; flow rate, 40 ml/min; detector, FID; t_R, 12.10, 13.20, 14.20 min (methyl apioside) and 2) column, 2% OV-17; column temperature, 170 °C; injection temperature, 190 °C; carrier gas, N_2 flow rate, 40 ml/min; detector, FID; t_R, 5.40 min (methyl apioside), 32.20, 36.50 min (methyl glucoside)]. The methanolyzed product was purified by column chromatography (SiO_2 2 g, $CHCl_3$: MeOH = 10 : 1) to afford methyl apioside (4 mg) and methyl glucoside (6 mg). Methyl apioside (4 mg) thus obtained was treated with 5% aqueous HCl (0.5 ml) at room temperature for 1 h. The reaction mixture was neutralized with Ag_2CO_3 powder and the precipitate was removed by filtration. The solvent was evaporated off under reduced pressure from the filtrate to afford D-apiose [1.8 mg, $[\alpha]_D$ +9.0° (c=0.15, 24 h after dissolution in H_2O, at 25 °C)]. D-Glucose [2.2 mg, $[\alpha]_D$ +48.2° (c=0.18, 24 h after dissolving in H_2O, at 25 °C] was obtained from methyl glucoside (5 mg) through the same procedure as described above for D-apiose from methyl apioside.

Methanolysis of 4-Hydroxyguaiacol Apioglucoside (4) The methanolyzed product (11 mg) was obtained from 4-hydroxyguaiacol apioglucoside (**4**, 20 mg) by a reaction similar to that described above for methanolysis of isopropyl apioglucoside (**3**). The product was treated with pyridine and BSTFA to obtain a sample for GLC analysis to determine methyl apioside and methyl glucoside. Furthermore, the methanolyzed product was separated by column chromatography (SiO_2 2 g, $CHCl_3$: MeOH = 10 : 1) to afford methyl apioside (5 mg) and methyl glucoside (5 mg). Methyl apioside (5 mg) and methyl glucoside (5 mg) were each hydrolyzed with 5% aqueous HCl at room temperature for 1 h to afford D-apiose [$[\alpha]_D$ +9.4° (c=0.12, 24 h after dissolution in H_2O)] and D-glucose [$[\alpha]_D$ +51° (c=0.13, 24 h after dissolution in H_2O)].

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