Stereoselective Reactions. XVIII.[1] Synthesis and Cytotoxicity of the Demethyl Derivatives of Steganes

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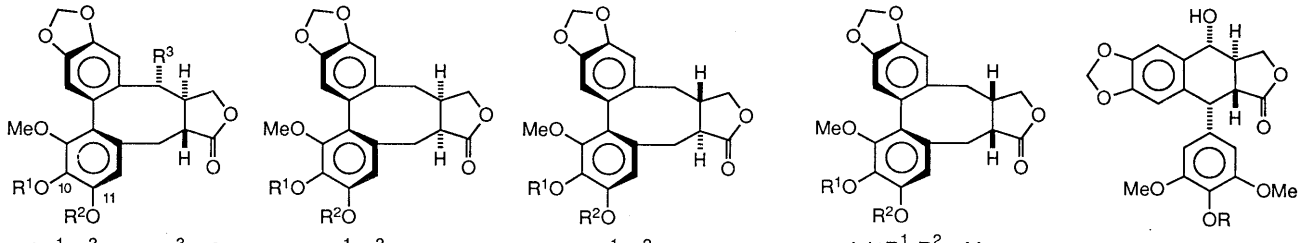
Demethyl derivatives of steganes and deoxypodorhizon, 3, 4, 6, 7, 9, 10, 12, 13, 18, 23, were prepared by the selective demethylation of the methoxy group of steganes and deoxypodorhizon, 2, 5, 8, 11, 22. The cytotoxicity of these derivatives was evaluated against KB cell and was found not to exceed that of the parent steganes. 4-Demethyldeoxypodorhizon (18) was found to show more potent cytotoxicity than deoxypodorhizon (22).

Keywords stegane; cytotoxicity, selectivity; synthesis; demethylation; lignan

We have been involved in these years in the asymmetric total synthesis of steganin lignans (for example steganacin (**1**)) and have found that isopicrostegane (**11**), one of the four stegane stereoisomers, **2, 5, 8, 11**, shows a promising cytotoxicity against KB cell.[2,3] The mechanism of action was found to involve inhibition of microtubule assembly, as has been reported in the case of podophyllotoxin (**14**).[4,5] On the other hand, demethylpodophyllotoxin (**15**) has been reported to show higher cytotoxicity than its parent compound and to inhibit deoxyribonucleic acid (DNA) replication.[5] Its derivative has been used clinically in cancer chemotherapy. We report herein the synthesis and cytotoxicity of 10- and 11-demethyl derivatives of steganes (**3, 4, 6, 7, 9, 10, 12, 13**) and 3- and 4-demethyldeoxypodorhizon (**18, 23**).[6]

Oxidative Coupling of 19 To synthesize demethyl derivatives of steganes our study began with the synthesis and nonphenolic oxidative coupling of **19**. Conjugate addition reaction of the lithiated piperonal diphenylthioacetal (**16**) with butenolide and trapping of the resulting enolate with 4-benzyloxy-3,5-dimethoxybenzyl bromide provided **17**.[6] Reductive desulfurization of **17** and benzylation of **18** afforded **19**. Oxidative coupling of **19** with the use of VOF_3 in methylene chloride–trifluoroacetic acid provided a mixture of **20** and **21** in a ratio of 5:1 in a low yield of 7%. Debenzylation by hydrogenolysis and subsequent



1: R^1, R^2 = Me, R^3 = OAc
2: R^1, R^2 = Me, R^3 = H
3: R^1, R^3 = H, R^2 = Me
4: R^1 = Me, R^2, R^3 = H

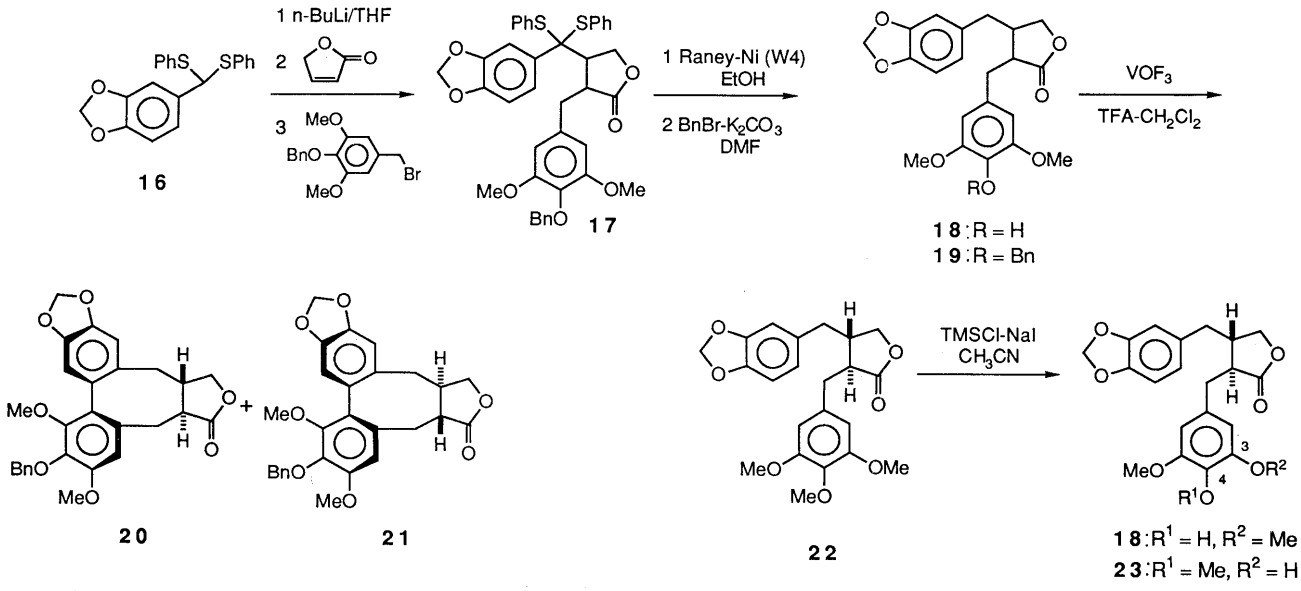
5: R^1, R^2 = Me
6: R^1 = H, R^2 = Me
7: R^1 = Me, R^2 = H

8: R^1, R^2 = Me
9: R^1 = H, R^2 = Me
10: R^1 = Me, R^2 = H

11: R^1, R^2 = Me
12: R^1 = H, R^2 = Me
13: R^1 = Me, R^2 = H

14: R = Me
15: R = H

Chart 1



16

17

18: R = H
19: R = Bn

20

21

22

18: R^1 = H, R^2 = Me
23: R^1 = Me, R^2 = H

Chart 2

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methylation provided isostegane (**8**) and stegane (**2**), respectively.[7] It is quite interesting to note that in contrast to the oxidation of **22** stereoselectively providing **8** in an excellent yield,[8] oxidation of **19** gave rise to a mixture of stereoisomers in a quite low yield.

Direct Demethylation of 22 and Steganes Since the conversion of **19** to **20** was not efficient, we turned our attention to the synthesis of demethylsteganes by direct demethylation of steganes. Treatment of **22** with chlorotrimethylsilane (TMSCl) and sodium iodide in acetonitrile[7] was found to produce **18** in 42% yield along with **23** in 3% yield. The structure of the major product was confirmed by direct comparison with **18** obtained by reduction of **17**. Application of these conditions to demethylation of steganes provided the desired demethylsteganes. The results of the reaction are summarized in Table I.

In the demethylation reaction of steganes, two isomers were, however, obtained in comparable yields. The position of demethylation was assigned based on the direct comparison with **9** and **3** obtained from **20** and **21**, and Hückel molecular orbital calculations.

As shown in Fig. 1, the linear combination of atomic orbital (LCAO) coefficients of highest occupied molecular orbital (HOMO) of A indicate that oxygen of the 4-methoxy group in **22** is more reactive than that at the 3- or 5-position. This is in good agreement with the result

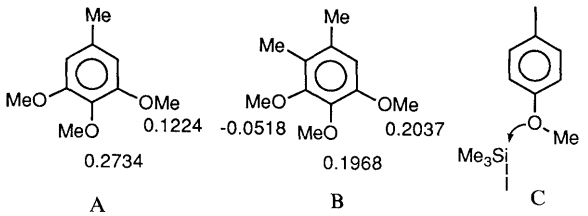

Fig. 1. LCAO Coefficients of HOMO

TABLE I. Demethylation of Steganes and Deoxypodorhizon

Steganes	10-Demethyl-(%)[a]	11-Demethyl-(%)[a]	Recovery (%)
2	**3** 13(19)	**4** 13(19)	30
5	**6** 32(41)	**7** 26(33)	22
8	**9** 18(24)	**10** 18(25)	27
11	**12** 16(42)	**13** 14(40)	64
22	**18** 42(66)	**23** 3(5)	36

a) Numbers in parentheses are corrected yields based on the consumed starting material.

TABLE II. Cytotoxicity of 10- and 11-Demethylsteganes and 3- and 4-Demethyldeoxypodorhizon against KB Cell[a]

Compound	ED_{50} (μg/ml)	Compound	ED_{50} (μg/ml)
1	<0.3	**11**	<0.3
2	0.94	**12**	4.10
3	39.0	**13**	1.48
4	73.0	**22**	16.8
5	28.0	**18**	3.00
6	34.9	**23**	59.0
7	97.0		
8	1.33		
9	39.5		
10	48.5		

a) All compounds are racemic.

of demethylation of **22**. On the other hand, B, which reflects steganes (**2, 5, 8, 11**),[10] indicates that the methoxy groups of the two positions have similar reactivity, affording two demethylated products in equal amounts, and thus supporting the structures of the isomers obtained from steganes. Since demethylation would take place by the initial attack of oxygen of the methoxy group on the silicon atom (C), the LCAO coefficients well reflect the differences in reactivity.

Isomerization and Correlation of Demethylsteganes The structures of 10- and 11-demethylsteganes were determined by applying a combination of selective thermal atropisomerization and base-induced epimerization at the α-position to the lactone carbonyl.[7] Since the structures of 10-demethylisostegane (**9**) and 10-demethylstegane (**3**) were confirmed by conversion of **20** and **21**, respectively, other demethylisomers were correlated with **9** and **3**. Thus thermal atropisomerization of **9** at 215 °C for 2 h produced a 1 : 1 mixture of **9** and **3**. Upon treatment of **3** with 10% aqueous NaOH in benzene for 15 min at room temperature and subsequent acidification with 10% aqueous HCl for relactonization, epimerization at the α-position to the lactone carbonyl group took place to afford a mixture of **3** and 10-demethylpicrostegane (**6**). Thermal atropisomerization of **6** produced a mixture of **6** and 10-demethylisopicrostegane (**12**).

That the structures of 10-demethylsteganes were determined as above supports the assigned structures of 11-demethylsteganes, because the 11-demethyl series were derived from the corresponding steganes.

Cytotoxicity of Demethylsteganes and Demethyldeoxypodorhizon The cytotoxicity of these compounds was evaluated against KB cell. The results are summarized in Table II. Demethylsteganes show weaker cytotoxicity than their parent steganes (**2, 5, 8, 11**), and the isopicrostegane derivatives (**12, 13**) were the most active, as in the case of the parent stegane (**11**). It is quite interesting that 4-demethyldeoxypodorhizon (**18**) shows more potent activity than deoxypodorhizon (**22**).

Further studies aimed at the development of potent antitumor compounds are in progress in our laboratory.[13]

Experimental

Melting points were measured using a Büchi 510 melting point apparatus and are not corrected. Infrared (IR) spectra were taken with a Jasco infrared spectrometer, model DS-402G. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken in $CDCl_3$ unless otherwise noted with a JNM-PS100 spectrometer, or with a JEOL FX100 spectrometer at 100 MHz, or with a Hitachi R-24 spectrometer at 60 MHz. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet: t, triplet; m, multiplet. Mass spectra (MS) were taken with a JEOL01, SG-2 mass spectrometer or a JEOL DX-300 mass spectrometer.

4-Benzyloxy-3,5-dimethoxybenzyl Bromide Phosphorus tribromide (1.9 ml) was added dropwise to a solution of 4-benzyloxy-3,5-dimethoxybenzyl alcohol[11] (13.3 g, 48.4 mmol) in ether (1 l) under ice-water bath cooling. The mixture was stirred at room temperature for 12 h. The whole was washed with satd. $NaHCO_3$ and brine. Concentration afforded colorless needles which were recrystallized from benzene–hexane to afford the corresponding bromide (14.3 g) as colorless needles of mp 58—59 °C. NMR δ: 3.78 (6H, s, CH_3O), 4.40 (2H, s, CH_2Br), 4.97 (2H, s, CH_2Ph), 6.52 (2H, s, Ar-H), 7.13—7.65 (5H, m, Ph-H). MS *m/z*: 338 ($M^+ + 2$), 336 (M^+). *Anal.* Calcd for $C_{16}H_{17}BrO_3$: C, 56.99, H, 5.08. Found: C, 56.84; H, 5.01.

(±)-*trans*-3-(1,1-Diphenylthiopiperonyl)-2-[(4-benzyloxy-3,5-dimethoxy)benzyl]-4-butanolide (17) A hexane solution of BuLi (11.7 ml,

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16.5 mmol) was added to a cooled (−78 °C) solution of **16** (6.34 g, 18.0 mmol) in tetrahydrofuran (THF, 75 ml) and the mixture was stirred for 30 min. A solution of γ-butenolide (1.26 g, 15.0 mmol) in THF (30 ml) was added to the above solution and the whole was stirred for 1 h. After the addition of hexamethylphosphoramide (HMPA) (6.45 g, 36.0 mmol) and 4-benzyloxy-3,5-dimethoxybenzyl bromide[11] (5.06 g, 15.0 mmol) in THF (45 ml), the whole was stirred for 2 h, then quenched with satd. aq. NH_4Cl (100 ml) and extracted with three portions of 100 ml of ethyl acetate. The extracts were successively washed with satd. $NaHCO_3$ (50 ml), and satd. NaCl (100 ml) and then dried over $MgSO_4$. Concentration (13.6 g) and silica gel column chromatography (CH_2Cl_2 : ether = 99 : 1) afforded a yellow glass (2.03 g, 67%). NMR δ: 2.60—3.48 (5H, m, C<u>H</u>$_2$ × 2, C<u>H</u>), 3.66 (6H, s, C<u>H</u>$_3$). 4.40 (1H, dd, J = 2, 11 Hz, C<u>H</u>$_2$), 4.96 (2H, s, PhC<u>H</u>$_2$O), 5.90 (2H, s, OC<u>H</u>$_2$O), 6.08 (2H, s, Ar-<u>H</u>), 6.61 (2H, d, J = 9 Hz, Ar-<u>H</u>), 6.96—7.48 (16H, m, Ar-<u>H</u>). IR ($CHCl_3$): 1765 cm^{-1}. *Anal.* Calcd for $C_{40}H_{36}O_7S_2$: C, 69.34; H, 5.24. Found: C, 69.07; H, 5.20.

(±)-*trans*-2-(4-Hydroxy-3,5-dimethoxybenzyl)-3-piperonyl-4-butanolide (18) A mixture of **17** (4.15 g, 5.99 mmol) and Raney-Ni (W4) (80 ml) in ethyl acetate (80 ml) was stirred at room temperature for 30 min. Filtration (washed with ethyl alcohol) and concentration afforded a yellow oil (1.45 g). Purification by silica gel column chromatography (benzene : acetone = 98 : 2) afforded a colorless glass (1.21 g, 52%). NMR δ: 2.52 (4H, s, C<u>H</u>, C<u>H</u>$_2$), 2.86 (2H, d, J = 5 Hz, C<u>H</u>, C<u>H</u>$_2$), 3.82 (6H, s, C<u>H</u>$_3$O × 2), 4.02—4.24 (2H, m, C<u>H</u>$_2$), 5.38 (1H, s, O<u>H</u>), 5.86 (2H, s, OC<u>H</u>$_2$O), 6.24—6.74 (5H, m, Ar-<u>H</u>). IR ($CHCl_3$): 3500, 1765 cm^{-1}. MS *m/z*: 386 (M^+). *Anal.* Calcd for $C_{21}H_{22}O_7$: C, 65.28; H, 5.74. Found: C, 65.04; H, 5.63.

(±)-*trans*-2-(4-Benzyloxy-3,5-dimethoxybenzyl)-3-piperonyl-4-butanolide (19) A mixture of **18** (0.27 g, 0.70 mmol), benzyl bromide (0.36 g, 2.10 mmol) and potassium carbonate (0.29 g, 2.10 mmol) in *N*,*N*-dimethylformamide (DMF, 3.0 ml) was stirred at 55 °C for 6 h and then diluted with water (5.0 ml). The mixture was extracted with ethyl acetate (30 ml) and benzene (20 ml). The combined extracts were washed with water, satd. $NaHCO_3$, and brine, and then dried over $MgSO_4$. Concentration afforded a yellow oil (0.45 g). Purification by silica gel column chromatography (benzene : acetone = 98 : 2) afforded a colorless glass (0.28 g, 84%). NMR δ: 2.48 (4H, d, J = 3 Hz, C<u>H</u>$_2$), 2.80—2.96 (2H, m, C<u>H</u>, C<u>H</u>$_2$), 3.76 (6H, s, C<u>H</u>$_3$O), 5.87 (2H, s, OC<u>H</u>$_2$O), 6.29—6.80 (5H, m, Ar-<u>H</u>), 7.07—7.56 (5H, m, Ar-<u>H</u>). IR ($CHCl_3$): 1765 cm^{-1}. MS *m/z*: 476 (M^+). *Anal.* Calcd for $C_{28}H_{28}O_7$: C, 70.57; H, 5.92. Found: C, 70.63; H, 5.88.

(±)-10-Benzyloxyisostegane (20) and (±)-10-Benzyloxystegane (21) A mixture of **19** (0.18 g, 0.38 mmol) and VOF_3 (0.14 g, 1.14 mmol) in a mixture of trifluoroacetic acid (2.4 ml) and methylene chloride (4.6 ml) was stirred at −45 °C for 9 h and then quenched with satd. $NaHCO_3$. The mixture was extracted with ethyl acetate. The extract was washed with water, satd. NaCl and then dried over $MgSO_4$. Concentration afforded a yellow oil (2.0 g). Purification by silica gel column chromatography (methylene chloride) afforded a mixture of **20** and **21** as a glass (13 mg, 7.1%) and **19** (12 mg, 6.6% recovery). Purification of the mixture of **20** and **21** by silica gel thin layer chromatography (ethyl acetate–hexane = 1 : 4) afforded **20** and **21** separately.

20: Colorless fine needles (benzene–hexane) of mp 217—218.5 °C. NMR δ: 1.90—2.76 (2H, m, C<u>H</u>, C<u>H</u>$_2$), 3.56 (3H, s, C<u>H</u>$_3$O), 3.60—3.85 (2H, m, C<u>H</u>, C<u>H</u>$_2$), 3.88 (3H, s, C<u>H</u>$_3$O), 4.26—4.48 (1H, m, C<u>H</u>$_2$), 5.04 (2H, s, PhC<u>H</u>$_2$O), 5.98 (2H, s, OC<u>H</u>$_2$O), 6.60 (2H, d, J = 2 Hz, Ar-<u>H</u>), 6.68 (1H, s, Ar-<u>H</u>), 7.32—7.60 (5H, m, Ph-<u>H</u>). IR ($CHCl_3$): 1775, 1595 cm^{-1}. MS *m/z*: 474 (M^+), Calcd for $C_{28}H_{26}O_7$: 474.1679. Found: 474.1694.

21: A colorless glass. NMR δ: 2.28—2.70 (2H, m, C<u>H</u>, C<u>H</u>$_2$), 2.94—3.19 (1H, m, C<u>H</u>), 3.21 (3H, s, C<u>H</u>$_3$O), 3.55—3.80 (1H, m, C<u>H</u>$_2$), 3.84 (3H, s, C<u>H</u>$_3$O), 3.92—4.44 (4H, m, C<u>H</u>, C<u>H</u>$_2$), 4.89 (2H, s, PhC<u>H</u>$_2$O), 5.92 (2H, s, OC<u>H</u>$_2$O), 6.52 (2H, d, J = 1 Hz, Ar-<u>H</u>), 6.59 (1H, d, J = 2 Hz, Ar-<u>H</u>), 7.34 (5H, d, J = 4 Hz, Ph-<u>H</u>). IR ($CHCl_3$): 1775, 1598 cm^{-1}. MS *m/z*: 474 (M^+).

(±)-10-Demethylisostegane (9) A solution of **20** (3.5 mg) in ethanol (5 ml) was stirred in the presence of 5% Pd on carbon (5 mg) under a hydrogen atmosphere. Short-path column chromatography afforded **9** as colorless prisms (methanol) of mp 216—217 °C. NMR (C_6D_6) δ: 0.76—2.30 (6H, m, C<u>H</u>), 2.86—3.70 (2H, m, C<u>H</u>), 3.26 (3H, s, C<u>H</u>$_3$O), 3.35 (3H, s, C<u>H</u>$_3$O), 5.37 and 5.40 (each 1H, d, J = 2 Hz, OC<u>H</u>$_2$O), 6.19, 6.35, and 6.68 (each 1H, s, Ar-<u>H</u>). IR (KBr): 3440, 1764, 1604 cm^{-1}. MS *m/z*: 384 (M^+), Calcd for $C_{21}H_{20}O_7$: 384.1208. Found: 384.1205.

(±)-10-Demethylstegane (3) A solution of **21** (3.5 mg) in ethanol (5 ml) was stirred in the presence of 5% Pd on carbon (5 mg) under hydrogen atmosphere. Short-path column chromatography afforded **3** as colorless prisms (methanol) of mp 193—195 °C. NMR (C_6D_6) δ: 0.8—3.06 (7H, m, C<u>H</u>), 3.20 and 3.44 (each 3H, s, C<u>H</u>$_3$O), 3.50—3.60 (1H, m, C<u>H</u>), 5.31 (1H, s, O<u>H</u>), 5.36 and 5.40 (each 1H, d, J = 2 Hz, OC<u>H</u>$_2$O). IR (KBr): 3420, 1764, 1605 cm^{-1}. MS *m/z*: 384 (M^+), Calcd for $C_{21}H_{20}O_7$: 384.1208. Found: 384.1206.

General Procedure for Demethylation Exemplified by the Synthesis of (±)-*trans*-4-Demethyldeoxypodorhizon (18) and (±)-*trans*-3-Demethyldeoxypodorhizon (23) To a solution of **22** (200 mg, 0.50 mmol) in acetonitrile (1 ml) was added sodium iodide (150 mg, 1 mmol) and TMSCl (109 mg, 1 mmol). The mixture was stirred at room temperature for 5 h and then water (10 ml) was added. The mixture was extracted with benzene. The extract was washed with 10% $NaHSO_3$ and brine, and was then dried over $MgSO_4$. Concentration afforded a glass (200 mg). Purification by silica gel column chromatography (benzene : acetone = 98 : 2) afforded **22** (72 mg, 36% recovery), **18** (82 mg, 42%), and **23** (5 mg, 3%).

23: A pale yellow glass. NMR δ: 2.23—2.59 (5H, m, C<u>H</u>, C<u>H</u>$_2$), 2.71—2.96 (2H, m, C<u>H</u>, C<u>H</u>$_2$), 3.79 and 3.85 (each 3H, s, C<u>H</u>$_3$O), 3.95—4.23 (1H, m, C<u>H</u>), 5.90 (2H, s, OC<u>H</u>$_2$O), 6.24—6.72 (5H, m, Ar-<u>H</u>). IR (KBr): 3520, 1765, 1593 cm^{-1}. MS *m/z*: 386 (M^+), Calcd for $C_{21}H_{22}O_7$: 386.1364. Found: 386.1357.

(±)-10-Demethylstegane (3) and (±)-11-Demethylstegane (4) Prepared from stegane (**2**) according to the general procedure. Yields are given in Table I.

4: Colorless prisms ((methanol) of mp 215—216 °C. NMR ($(CD_3)_2CO$) δ: 3.80 and 3.86 (each 3H, s, C<u>H</u>$_3$O), 4.19—4.46 (1H, m, C<u>H</u>), 6.01 (2H, s, OC<u>H</u>$_2$O), 6.37, 6.64, and 6.77 (each 1H, s, Ar-<u>H</u>). IR (KBr): 3440, 1764, 1610 cm^{-1}. MS *m/z*: 384 (M^+), Calcd for $C_{21}H_{20}O_7$: 384.1208. Found: 384.1215.

(±)-10-Demethylpicrostegane (6) and (±)-11-Demethylpicrostegane (7) Prepared from picrostegane (**5**) according to the general procedure. Yields are given in Table I.

6: Colorless prisms (methanol) of mp 211—212 °C. NMR (C_6D_6) δ: 0.8—3.06 (7H, m, C<u>H</u>), 3.20 and 3.34 (each 3H, s, C<u>H</u>$_3$O), 3.45—3.81 (2H, m, C<u>H</u>), 5.31 (1H, s, O<u>H</u>), 5.74 and 5.79 (each 1H, d, J = 2 Hz, OC<u>H</u>$_2$O). IR (KBr): 3450, 1765, 1608 cm^{-1}. MS *m/z*: 384 (M^+), Calcd for $C_{21}H_{20}O_7$: 384.1208. Found: 384.1216.

7: Colorless prisms (methanol) of mp 267—268 °C. NMR ($(CD_3)_2CO$) δ: 3.81 and 3.94 (each 3H, s, C<u>H</u>$_3$O), 4.00—4.20 (1H, m, C<u>H</u>), 4.40—4.68 (2H, m, C<u>H</u>), 6.02 (2H, s, OC<u>H</u>$_2$O), 6.67, 6.75, and 6.79 (each 1H, s, Ar-<u>H</u>). IR (KBr): 3350, 1740, 1606 cm^{-1}. MS *m/z*: 384 (M^+), Calcd for $C_{21}H_{20}O_7$: 384.1208. Found: 384.1223.

(±)-10-Demethylisostegane (9) and (±)-11-Demethylisostegane (10) Prepared from isostegane (**8**) according to the general procedure. Yields are given in Table I.

9: Colorless prisms of mp 216—217 °C. Identical with **9** obtained by hydrogenolysis of **20**.

10: Colorless prisms (methanol) of mp 278 °C. NMR ($(CD_3)_2CO$) δ: 3.80 and 3.90 (each 3H, s, C<u>H</u>$_3$O), 4.28—4.49 (1H, m, C<u>H</u>), 5.99 and 6.00 (each 1H, d, J = 1 Hz, OC<u>H</u>$_2$O), 6.51, 6.63, and 6.84 (each 1H, s, Ar-<u>H</u>). IR (KBr): 3340, 1768, 1608 cm^{-1}. MS *m/z*: 384 (M^+), Calcd for $C_{21}H_{20}O_7$: 384.1208. Found: 384.1217.

(±)-10-Demethylisopicrostegane (12) and (±)-11-Demethylisopicrostegane (13) Prepared from isopicrostegane (**11**) according to the general procedure. Yields are given in Table I.

12: Colorless prisms (methanol) of mp 205—208 °C. NMR (C_6D_6) δ: 3.42 and 3.46 (each 3H, s, C<u>H</u>$_3$O), 4.29 (1H, s, O<u>H</u>), 5.56 and 5.59 (each 1H, d, J = 2 Hz, OC<u>H</u>$_2$O). IR (KBr): 3380, 1758, 1607 cm^{-1}. MS *m/z*: 384 (M^+), Calcd for $C_{21}H_{20}O_7$: 384.1208. Found: 384.1211.

13: Colorless prisms (methanol) of mp 212—214 °C. NMR ($(CD_3)_2CO$) δ: 3.79 and 3.86 (each 3H, s, C<u>H</u>$_3$O), 3.88—4.12 (1H, m, C<u>H</u>), 4.28—4.58 (1H, m, C<u>H</u>), 5.98 (2H, s, OC<u>H</u>$_2$O), 6.75, 6.83, and 6.91 (each 1H, s, Ar-<u>H</u>). IR (KBr): 3400, 1777, 1608 ccm^{-1}. MS *m/z*: 384 (M^+), Calcd for $C_{21}H_{20}O_7$: 384.1208. Found: 384.1186.

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