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Stereoselective Reactions. VIII.[1] Stereochemical Requirement for the Benzylic Oxidation of Lignan Lactone. A Highly Selective Synthesis of the Antitumor Lignan Lactone Steganacin by the Oxidation of Stegane

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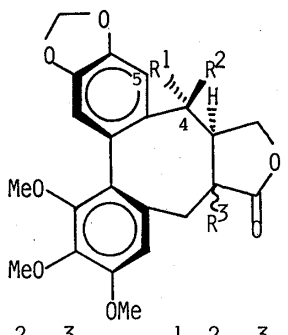
A highly efficient synthesis of the antitumor steganin lignan steganacin (**1**) was accomplished. Bromination of stegane (**7**) with *N*-bromosuccinimide followed by treatment with aqueous tetrahydrofuran afforded steganol (**3**) in 85% yield. Acetylation of **3** gave **1** in 72% yield. Stegane (**7**) was also oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in AcOH to give **1** directly in 10% yield. Stereochemical requirements for the benzylic oxidation of dibenzocyclooctadiene lignan lactones are discussed.

Keywords——steganacin; stegane; benzylic oxidation; isomer selectivity; regioselectivity; stereoselectivity; stereoelectronic control; podophyllotoxin; antitumor lignan lactone

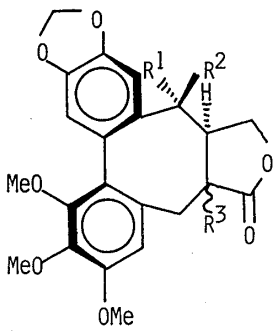
Considerable efforts have been devoted to total syntheses of the antitumor lignan lactones steganacin (**1**)[2-10] and podophyllotoxin (**12**).[11-15] As a consequence of our studies directed toward the asymmetric total syntheses of these lignan lactones we have already reported highly efficient syntheses of optically pure stegane (**7**), picrostegane (**8**), isostegane (**9**), and isopicrostegane (**10**) bearing the steganacin (**1**) carbon framework and isodeoxypodophyllotoxin (**13**) bearing the podophyllotoxin (**12**) framework.[1,10] The final crucial step in the accomplishment of these syntheses was considered to be the selective introduction of oxygen functionality at the requisite benzylic position. However, in the synthesis of steganacin (**1**), the initially attempted oxidation of isostegane (**9**), the most readily accessible intermediate in our synthetic scheme,[10] with a variety of reagents unexpectedly failed to afford the desired benzylic oxidation products. To overcome this difficulty, exhaustive experiments using racemic compounds were undertaken. Finally we found that the benzylic oxidation was highly dependent on the stereochemical features of the dibenzocyclooctadiene lignan lactone. In the present paper we describe the highly efficient synthesis of racemic steganacin (**1**) by means of the highly regio- and stereo-selective benzylic oxidation of stegane (**7**) with *N*-bromosuccinimide (NBS).

Benzylic Oxidation of 3-Piperonyl-4-butanolide (15)

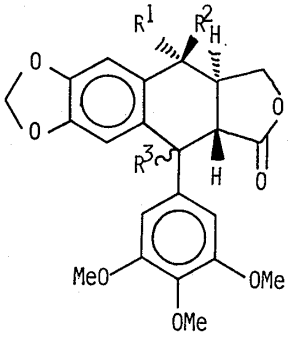
As a model study, the benzylic oxidation of **15**[16] bearing a partial structure of **7**—**10** and **13** was examined using a variety of reagents.[17] Some of the results are shown in Table I. Oxidation of **15** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in AcOH afforded **16**[18] bearing an acetyloxy group in 66% yield. Oxidation of **15** with DDQ in MeOH afforded **19**. Bromination of **15** with NBS in the presence of benzoyl peroxide (BPO) in refluxing CCl_4 also proceeded smoothly to give **17**,[18] which was easily converted to a mixture of **18**[18] and **21**[18] in 80% yield simply by silica gel column chromatography of **17**. The structures of the oxidized products (**16**, **18**) were confirmed by converting them to the known ketone (**20**),[19]



	R^1	R^2	R^3		R^1	R^2	R^3
1:	OAc	H	β-H	5:	Br	H	β-H
2:	H	OAc	β-H	6:	O		β-H
3:	OH	H	β-H	7:	H	H	β-H
4:	H	OH	β-H	8:	H	H	α-H



9: $R^1=R^2=H$, $R^3=\beta$-H
10: $R^1=R^2=H$, $R^3=\alpha$-H
11: $R^1=R^2=O$, $R^3=\beta$-H



12: $R^1=OH$, $R^2=H$, $R^3=\beta$-H
13: $R^1=R^2=H$, $R^3=\alpha$-H

Fig. 1

prepared from **14**.[20] Thus, we confirmed that the benzylic oxidation of **15** proceeded without any difficulty.

Oxidation of Isodeoxypodophyllotoxin (13) with DDQ

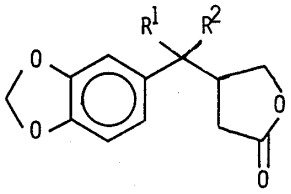
Based on the model study the oxidation of **13**[21] was examined. Thus, **13** was oxidized with DDQ in refluxing AcOH. The product, however, was dehydroanhydropicropodophyllin (**22**),[22] instead of the compound bearing an acetyloxy group. Due to the extremely low solubility of **13** in CCl_4, **13** failed to react with NBS.

Synthesis of Steganacin (1) by the Oxidation of Stegane (7)

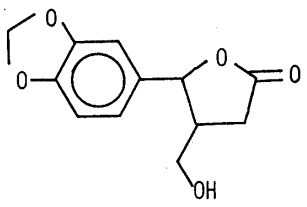
Oxidation of dibenzocyclooctadiene lignan lactones (**7**—**10**) was examined.[23] Some of the results are summarized in Table II. Oxidation of isostegane (**9**)[20b] with DDQ in AcOH or with NBS–BPO in CCl_4 led to the recovery of **9**. Release of the conformational rigidity by opening the lactone ring of **9** did not affect the reactivity; reactions of **24** and **26** (prepared from **9**) with NBS–BPO afforded a mixture of intractable materials.[24] Similar results were obtained in the oxidation of picrostegane (**8**) and isopicrostegane (**10**). Treatment of **8** or **10** with DDQ in AcOH led to the formation of a mixture of **8** and **10** by epimerization at the α-position of the lactone carbonyl, and no products oxidized at the benzylic position were obtained.[24,25]

In contrast to the disappointing results described above, oxidation of stegane (**7**), having exactly the same relative configuration as naturally occurring steganacin (**1**), afforded the desired products. Stegane (**7**) was oxidized with DDQ in AcOH at 60—80 °C to give steganacin (**1**) and episteganacin (**2**) in 10 and 4% yields, respectively, and no other product oxidized at the other benzylic position was isolated.[24] Since a separate experiment showed that steganacin (**1**) isomerized into episteganacin (**2**) in AcOH,[26] the initial product in the oxidation of **7** with DDQ in AcOH seems to be **1**.

Then we turned our efforts to find out the more effective oxidizing agent than DDQ, which requires the formation of a sterically demanding charge transfer complex. Finally we found that the bromination of **7** with NBS proceeded excellently. Oxidation of **7** with NBS in the presence of a catalytic amount of BPO in refluxing CCl_4 afforded highly pure 4-bromostegane (**5**) in nearly quantitative yield. The structure of **5** was elucidated based on nuclear Overhauser effect (NOE) measurements. An increase of 13% in the intensity at C_5-H (δ 6.82) was observed when C_4-H (δ 5.10) was irradiated. An increase of 11% in the intensity at C_4-H was also observed when C_5-H was irradiated. These data clearly support the indicated relative configuration of **5**. It is also interesting to note that the isomer-selective benzylic



14: $R^1=R^2=SCH_3$
15: $R^1=R^2=H$
16: R^1, $R^2=H$, OAc
17: R^1, $R^2=H$, Br
18: R^1, $R^2=H$, OH
19: R^1, $R^2=H$, OCH_3
20: $R^1=R^2=O$



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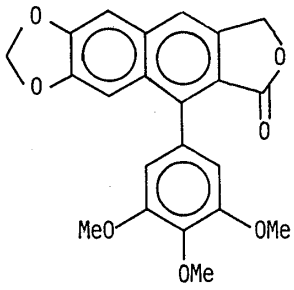

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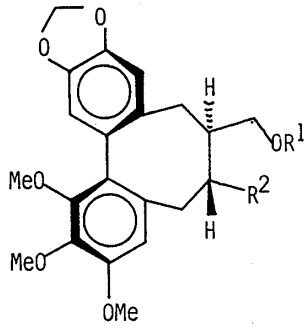
Fig. 2



23: $R^1=H$, $R^2=CON(CH_2)_4$
24: $R^1=COPh$, $R^2=CON(CH_2)_4$
25: $R^1=H$, $R^2=CH_2OH$
26: $R^1=Ac$, $R^2=CH_2OAc$

Fig. 3

TABLE I. Benzylic Oxidation of **15**

Entry	Reagent	Solvent	Product	Yield (%)[a]
1	DDQ	AcOH	**16**	66
2	DDQ	Dioxane–H_2O	**20**	9
3	DDQ	MeOH	**19**	59
4	CrO_3	AcOH	**20**	2
5	NBS–BPO	CCl_4	**18**	59[b]
			21	22[b]

a) Isolated yields.
b) Yield after column chromatography of the crude product (**17**) on silica gel.

TABLE II. Oxidation of Stegane (**7**) and Other Isomers (**8**—**10**)[a]

Entry	Substrate	Reagent	Product (%)	Recovery (%)
1	**7**	NBS–BPO	**3** (85)[b]	e)
			4 (0.6)[b]	
2	**7**	DDQ–AcOH	**1** (10)	14
			2 (4)	
3	**7**	$Pb(OAc)_4$–AcOH	**1** (4)	32
4	**8**	DDQ–AcOH	**10** (2)[c]	34
5	**9**	DDQ–AcOH	d)	93
6	**10**	DDQ–AcOH	**8** (4)[c]	41

a) Isolated yield after chromatography purification.
b) Yield after treatment with aq. THF.
c) Isomerization product.
d) No product was isolated.
e) **7** was completely consumed.

oxidation of stegane (**7**) using a mixture of **7** and isostegane (**9**) (*ca.* 4:6) obtained by the thermal atropisomerization of **9**[1] gave **5**, with full recovery of **9**.[27]

According to the procedure for the model compound (**18**), silica gel column chromatog-

raphy of **5** directly afforded steganol (**3**) in 57% yield. It was also found that **5** was convertible into **3** and episteganol (**4**) in 85 and 0.6% yields, respectively, by treating **5** with aqueous tetrahydrofuran (THF) at room temperature.[28] Steganol (**3**) was acetylated to afford **1** in 72% yield.

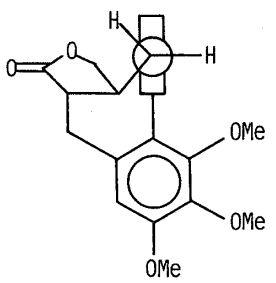
Stereochemical Requirement for the Benzylic Oxidation

The above results mean that among four possible stereoisomers (**7**—**10**) only stegane (**7**) was oxidized at the benzylic position and oxidation took place at the desired benzylic position of the two and, furthermore, the desired C–H bond of the two was selectively oxidized. In other words, the introduction of an acetyloxy or bromine function into the dibenzocyclooctadiene lignan lactones (**7**—**10**) was achieved by isomer-, regio-, and stereo-selective benzylic oxidation.

These selectivities may be rationalized as follows. Inspection of molecular models of the four stereoisomers (**7**—**10**) showed that only the requisite hydrogen atom of **7** could be situated in a nearly orthogonal position to the plane of the adjacent aromatic ring, as shown in Fig. 4. Furthermore, the reported infrared (IR) carbonyl absorptions of steganone (**6**) (1665, 1667 cm^{-1})[2,4,5] and isosteganone (**11**) (1707, 1710 cm^{-1})[4,5] prove that the sp^2-hybridized carbon generated at the corresponding benzylic position of stegane (**7**) can conjugate with the aromatic ring, while that of **9** cannot. These are clearly consistent with the mechanistic consideration for DDQ oxidation that the C–H, during abstraction as a hydride, must remain in constant overlap with the π-system and the developing sp^2-hybridized benzylic center must attain planarity with the adjacent π-system.[29] The constant overlap of the C–H with the π-system and the stabilization of the resulting sp^2-hybridized radical species by conjugation with the π-system are also essential for bromination by NBS–BPO.

The stereoselective introduction of an acetyloxy or bromine function onto an sp^2-hybridized carbon species such as a benzylic carbonium ion or a benzylic radical generated by the abstraction of a hydride or a hydrogen radical, respectively, may be controlled through the stereoelectronic effect originating from the conformational rigidity of stegane (**7**) as shown in Fig. 4.

Recent publications by Robin[30] and Sneden[31] on the isolation and structural determination of neoisostegane (**27**) from *Steganotaenia araliacea* Hochst are worthy of comment. Unlike the homologous steganin lignans, neoisostegane (**27**) bears no functionality at C-4 and has the same relative configuration as isostegane (**9**). The stereochemical requirements for the benzylic oxidation (C-4) of dibenzocyclooctadiene lignans clarified above leads to the conclusion that only compounds having the same relative configuration as stegane (**7**) can be oxidized, but other isomers cannot. Since this should be the case in chemical oxidation as



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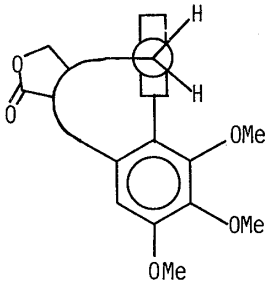
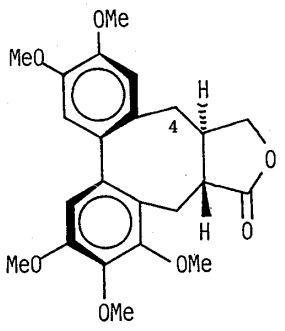


8—**10**

Fig. 4



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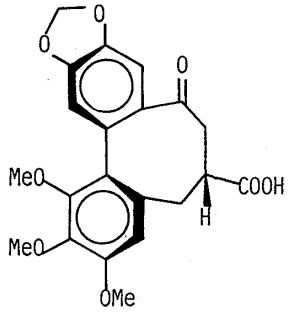

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Fig. 5

well as in enzymatic oxidation, isolation of neoisostegane, the first naturally occurring dibenzocyclooctadiene lignan lactone bearing no oxygen functionality at C-4, is considered to be quite implicative.

Thus, based on the highly isomer-, regio-, and stereo-selective benzylic oxidation, an efficient synthesis of steganacin (**1**) was achieved. Since successful syntheses of steganacin (**1**) reported to date all include hydroxymethylation of the keto acid (**28**) as a key step,[4-9] the present oxidation procedure provides a new and highly efficient synthetic route to racemic **1**. Successful application of the method to the synthesis of optically pure steganin lignan has been achieved in our laboratory.[3b]

Experimental[32]

Piperonal Dimethyldithioacetal——MeSH (6.4 ml, 119 mmol) was added to a solution of piperonal (8.1 g, 54 mmol) in $CHCl_3$ (100 ml) at −15 °C. The mixture was stirred at −15 °C for 1 h, then conc. HCl (1.5 ml) was added and the whole was stirred at 5 °C for 3 h. The reaction mixture was washed successively with water (50 ml), 10% aq. NaOH (30 ml × 3), water (30 ml × 3) and satd. aq. NaCl (30 ml), then dried over $MgSO_4$. Concentration *in vacuo* afforded a pale yellow oil. Distillation gave the dithioacetal (9.60 g, 80%) as a pale yellow oil of bp 164—166 °C (6 mmHg). IR ν_{max}^{film} cm^{-1}: 928, 840, 765. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (6H, s, $SCH_3 \times 2$), 4.68 (1H, s, CH), 5.92 (2H, s, OCH_2O), 6.59—7.05 (3H, m, aromatic H). MS *m/z*: 228 (M^+). *Anal.* Calcd for $C_{10}H_{12}O_2S_2$: C, 52.60; H, 5.30. Found: C, 52.44; H, 5.21.

3-(1-(3,4-Methylenedioxyphenyl)-1,1-di(methylthio)methyl)-4-butanolide (14)[20]——A solution of *n*-BuLi (2 mmol) in *n*-hexane (1.35 ml) was added to a cooled (−78 °C) solution of the dithioacetal (456 mg, 2 mmol) in THF (4 ml) under argon and the whole was stirred for 25 min. A solution of crotonolactone (168 mg, 2 mmol) in THF (2 ml) was added and the whole was stirred at −78 °C for 3 h. The reaction mixture was quenched with 5% aq. citric acid (5 ml) and extracted with ether (30 ml × 3). The combined extracts were washed with satd. aq. $NaHCO_3$ (20 ml) and satd. aq. NaCl (20 ml × 2), then dried over $MgSO_4$. Concentration *in vacuo* afforded a yellow oil (567 mg). Purification by silica gel column chromatography (ether–*n*-hexane, 2 : 1) gave **14** (494 mg, 79%) as colorless prisms of mp 87—88 °C (from MeOH). IR ν_{max}^{KBr} cm^{-1}: 1778 (γ-lactone), 1602 (aromatic). ^{1}H-NMR ($CDCl_3$) δ: 1.99 (3H, s, SCH_3), 2.05 (3H, s, SCH_3), 2.40—2.70 (2H, m, CH_2O), 2.85—3.45 (1H, m, CH), 4.00—4.48 (2H, m, CH_2O), 5.94 (2H, s, OCH_2), 6.65—7.32 (3H, m, aromatic H). MS *m/z*: 312 (M^+). *Anal.* Calcd for $C_{14}H_{16}O_4S_2$: C, 53.82; H, 5.16. Found: C, 53.99; H, 5.16.

3-Piperonyl-4-butanolide (15)——A mixture of **14** (3.29 g, 10.5 mmol) and Raney nickel (W-4, 19 g) in EtOH (130 ml) was stirred at room temperature for 1 h and filtered through celite. The filtrate was concentrated *in vacuo* to afford a colorless oil. Purification by silica gel column chromatography ($CHCl_3$–ether, 10 : 1) gave **15** (1.49 g, 64%) as a colorless oil. IR ν_{max}^{film} cm^{-1}: 1775 (γ-lactone). ^{1}H-NMR ($CDCl_3$) δ: 1.9—2.8 (5H, m, $ArCH_2CHCH_2CO$), 3.8—4.4 (2H, m, CH_2O), 5.90 (2H, s, OCH_2O), 6.4—6.8 (3H, m, aromatic H). MS *m/z*: 220 (M^+). Spectral data were identical with those reported earlier[10a,c]

3-(1-(Acetoxy)-1-(3,4-methylenedioxyphenyl)methyl)-4-butanolide (16)——A green colored solution of **15** (168 mg, 0.76 mmol) and DDQ (346 mg, 1.5 mmol) in AcOH (1.5 ml) was stirred at room temperature for 40 h and diluted with AcOEt (100 ml). The whole was washed with satd. aq. $NaHCO_3$ (20 ml), 10% aq. NaOH (10 ml) and satd. aq. NaCl (50 ml), and dried over $MgSO_4$. Concentration *in vacuo* afforded a yellow oil (166 mg). Purification by silica gel column chromatography (ether–*n*-hexane, 1 : 1) gave **15** (29% recovery) and **16** (99 mg, 66% based on the consumed **15**) as a colorless oil. IR ν_{max}^{film} cm^{-1}: 1770 (γ-lactone), 1730 (OAc). ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s, $COCH_3$), 2.2—3.4 (3H, m, $CHCH_2CO$), 3.9—4.5 (2H, m, CH_2O), 5.6—6.5 (1H, m, CHOAc), 5.96 (2H, s, OCH_2O), 6.78 (3H, s, aromatic H). MS *m/z*: 278 (M^+).

3-(1-(Hydroxy)-1-(3,4-methylenedioxyphenyl)methyl)-4-butanolide (18)——i) A mixture of **15** (110 mg, 0.5 mmol), NBS (98 mg, 0.55 mmol), and BPO (2.4 mg, 0.01 mmol) in CCl_4 (20 ml) was heated to reflux for 1.5 h, then diluted with AcOEt (80 ml). The whole was washed with 15% aq. NaOH (5 ml), satd. aq. $NaHCO_3$ (10 ml), and satd. aq. NaCl (20 ml), and dried over $MgSO_4$. Concentration *in vacuo* afforded the nearly pure bromide (**17**)[18] (150 mg, quant.). MS *m/z*: 300 (M^+), 298 (M^+). ^{1}H-NMR ($CDCl_3$) δ : 4.86 (1H, d, J = 10 Hz, CHBr). Purification by silica gel preparative thin layer chromatography (PTLC) (ether–*n*-hexane, 1 : 9) gave **18**[18] (69 mg, 59%) of mp 122—125 °C; IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH), 1760 (γ-lactone); ^{1}H-NMR ($CDCl_3$) δ: 2.0—3.1 (4H, m, $CHCH_2O$, OH), 4.0—4.8 (3H, m, CHOH, CH_2O), 5.97 (2H, s, OCH_2O), 6.76 (3H, s, aromatic H); MS *m/z*: 236 (M^+), and **21**[18] (26 mg, 22%) as a colorless oil; IR ν_{max}^{film} cm^{-1}: 3400 (OH), 1770 (γ-lactone); ^{1}H-NMR ($CDCl_3$) δ: 1.8—1.5 (1H, br s, OH), 2.5—2.9 (3H, m, $CHCH_2CO$), 3.2—3.9 (2H, br d, $CHCH_2OH$), 5.2—5.6 (1H, m, CHOH), 5.94 (2H, s, OCH_2O), 6.77 (3H, s, aromatic H); MS *m/z*: 236 (M^+).

ii) A mixture of **16** (72 mg, 0.26 mmol) and K_2CO_3 (10 mg, 0.07 mmol) in MeOH (5 ml) was stirred at room temperature for 2 h. The whole was diluted with AcOEt (100 ml) and washed with 10% aq. HCl (2 ml), and aq. NaCl

(20 ml). After being dried over $MgSO_4$, the AcOEt layer was concentrated *in vacuo* to give a yellow oil (57 mg). Purification by silica gel column chromatography (ehter–*n*-hexane, 2 : 1) gave **18**[18] (34 mg, 55%) and **21**[18] (17 mg, 28%).

3-(1-(Methoxy)-1-(3,4-methylenedioxyphenyl)methyl)-4-butanolide (19)—A mixture of DDQ (367 mg, 1.62 mmol) and **15** (178 mg, 0.81 mmol) in MeOH (93 ml) was heated to reflux for 2 h. The whole was concentrated *in vacuo*. The residue was dissolved in AcOEt (50 ml) and washed with 10% aq. NaOH (5 ml), 5% aq. citric acid (10 ml), and satd. aq. NaCl (20 ml). After being dried over $MgSO_4$ the AcOEt solution was concentrated *in vacuo* to give a brown oil (183 mg). Purification by silica gel column chromatography (CH_2Cl_2) afforded **15** (37% recovery) and **19**[18] (71 mg, 59% based on the consumed **15**) as a pale yellow oil. IR ν_{max}^{film} cm^{-1}: 1760 (γ-lactone). ^{1}H-NMR ($CDCl_3$) δ: 2.0—3.1 (3H, m, CHCH$_2$CO), 3.20 (3H, s, OCH$_3$), 3.9—4.4 (3H, m, CH(OCH$_3$)CHCH$_2$O), 5.98 (2H, s, OCH$_2$O), 6.75 (3H, s, aromatic H). MS *m/z*: 250 (M^+).

3-(3,4-Methylenedioxybenzoyl)-4-butanolide (20)——i) A mixture of **14** (211 mg, 0.68 mmol), HgO (30 mg, 1.36 mmol), and $BF_3 \cdot OEt_2$ (0.71 ml, 1.4 mmol) in THF (4 ml) and water (0.5 ml) was stirred at room temperature for 2 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in AcOEt (50 ml). The AcOEt layer was washed with satd. aq. $NaHCO_3$ (10 ml) and satd. aq. NaCl (10 ml), then dried over $MgSO_4$. Concentration *in vacuo* afforded a pale yellow solid (121 mg). Recrystallization from ether–*n*-pentane (1 : 1, 10 ml) gave **20** (72 mg, 41%) as colorless needles of mp 115—117 °C (reported[19] mp 118—119 °C). IR ν_{max}^{Nujol} cm^{-1}: 1762 (γ-lactone), 1664 (ArCO). ^{1}H-NMR ($CDCl_3$) δ: 2.4—3.3 (2H, m, CH$_2$CO), 4.0—4.7 (3H, m, CHCH$_2$O), 6.08 (2H, s, OCH$_2$O), 6.8—7.7 (3H, m, aromatic H). Melting point and spectral data were identical with those reported.[19]

ii) A solution of **18** (18 mg, 0.076 mmol) in CH_2Cl_2 (2 ml) was added to Collins reagent (0.84 mmol), prepared from CrO_3 (85 mg, 0.84 mmol) and pyridine (134 mg, 1.67 mmol), in CH_2Cl_2 (8 ml). The whole was stirred at room temperature for 1 h. A mixture of ether (15 ml) and *n*-hexane (15 ml) was added and the whole was stirred for 1 h. Filtration through celite followed by concentration *in vacuo* afforded a brown oil (17 mg). Crystallization from a mixture of $CHCl_3$ (1 ml), ether (2 ml), and pentane (3 ml) gave **20** (9 mg, 51%) as colorless needles of mp 116—117.5 °C. Spectral data were identical with those described above.

Dehydroanhydropicropodophyllin (22)——A mixture of isodeoxypodophyllotoxin (**13**)[21] (106 mg, 0.27 mmol) and DDQ (242 mg, 1.06 mmol) in AcOH (15 ml) was heated to reflux for 1.5 h. The mixture was diluted with AcOEt (100 ml) and $CHCl_3$ (100 ml) and washed with satd. aq. NaCl (100 ml × 2), 10% aq. NaOH (30 ml), and satd. aq. NaCl (30 ml). The organic layer was dried over $MgSO_4$. Concentration *in vacuo* afforded a brown solid (93 mg). Purification by silica gel thin layer chromatography (TLC) ($CHCl_3$–ether, 40 : 1) gave **13** (30 mg, 28% recovery) and **22** (33 mg, 43% based on the consumed **13**) as colorless fine needles of mp 259—263 °C (from $CHCl_3$–MeOH) (reported mp 267—268 °C,[22a] 266.5—267.5 °C[22b]). IR ν_{max}^{Nujol} cm^{-1}: 1765 (γ-lactone), 1585 (aromatic). ^{1}H-NMR ($CDCl_3$) δ: 3.84 (6H, s, OCH$_3$ × 2), 3.97 (3H, s, OCH$_3$), 5.37 (2H, s, OCH$_2$), 6.07 (2H, s, OCH$_2$O), 6.56 (2H, s, aromatic H), 7.14 (1H, s, aromatic H), 7.21 (1H, s, aromatic H), 7.70 (1H, br s, aromatic H). MS *m/z*: 394 (M^+). Spectral data were identical with those reported.[22]

(1*S,2*S**,7a*R**,7b*R**)-1-Pyrrolidinocarbonyl-2-benzoyloxymethyl-5,6-methylenedioxy-8,9,10-trimethoxy-1,2,3,12-tetrahydrodibenzo[4.5 : 6.7]cyclooctene (24)**——A solution of isostegane (**9**)[1,10b,20b] (500 mg, 1.26 mmol) and pyrrolidine (1.2 ml, 13.9 mmol) in THF (7 ml) was stirred at room temperature for 48 h. Concentration *in vacuo* followed by the addition of a small amount of benzene gave **23** (686 mg) as colorless prisms of mp 203—208 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1610 (amide); ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.9 (7H, m, OH, N(CH$_2$CH$_2$)$_2$, CHCO), 2.50 (4H, br s, ArCH$_2$ × 2), 3.1—3.8 (6H, m, CH$_2$OH, N(CH$_2$CH$_2$)$_2$), 3.55 (3H, s, OCH$_3$), 3.89 (6H, s, OCH$_3$ × 2), 5.90 (2H, br s, OCH$_2$O), 6.55 (1H, s, aromatic H), 6.70 (1H, s, aromatic H), 6.80 (1H, s, aromatic H). A mixture of **23** (686 mg) obtained above, NEt_3 (0.35 ml, 2.5 mmol), and benzoyl chloride (0.17 ml, 1.5 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature for 20 h, then diluted with CH_2Cl_2 (50 ml). The mixture was washed with 10% aq. HCl (20 ml), satd. aq. NaCl (20 ml), satd. aq. $NaHCO_3$ (20 ml), and satd. aq. NaCl (20 ml), and dried over $MgSO_4$. Concentration *in vacuo* gave a pale brown solid (675 mg). Purification by silica gel column chromatography (CH_2Cl_2–AcOEt, 10 : 1) gave **24** (568 mg, 79%) as pale brown needles of mp 229.5—231 °C (from ether–$CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1712 (ester), 1632 (amide). ^{1}H-NMR ($CDCl_3$) δ: 1.5—2.3 (4H, m, N(CH$_2$CH$_2$)$_2$), 2.3—3.0 (5H, m, ArCH$_2$ × 2, CH), 3.1—3.8 (4H, m, N(CH$_2$CH$_2$)$_2$), 3.56 (3H, s, OCH$_3$), 3.89 (6H, s, OCH$_3$ × 2), 4.0—4.3 (2H, m, CH$_2$O), 5.9—6.1 (2H, br s, OCH$_2$O), 6.56 (1H, s, aromatic H), 6.72 (1H, s, aromatic H), 6.82 (1H, s, aromatic H), 7.2—8.2 (5H, m, C_6H_5CO). *Anal.* Calcd for $C_{33}H_{35}NO_8$: C, 69.09; H, 6.15. Found: C, 68.79; H, 6.12.

(1*S,2*S**,7a*R**,7b*R**)-1,2-Bis(hydroxymethyl)-5,6-methylenedioxy-8,9,10-trimethoxy-1,2,3,12-tetrahydrodibenzo[4.5 : 6.7]cyclooctene (25)**——A solution of isostegane (**9**)[1,10b,20b] (370 mg, 0.93 mmol) in THF (15 ml) was added to a cooled (−78 °C) suspension of $LiAlH_4$ (70.7 mg, 1.86 mmol) in THF (15 ml). The whole was stirred at −78 °C for 3 h and then at room temperature for 3 h and quenched by the successive addition of water (0.07 ml), 15% aq. NaOH (0.07 ml), and water (0.21 ml). The mixture was filtered and the filtrate was concentrated *in vacuo* to give a colorless solid (350 mg) of mp 176.5—180.5 °C. Recrystallization of the solid (320 mg) from AcOEt–*n*-hexane (1 : 1, 16 ml) gave **25** (270 mg, 79%) as colorless needles of mp 185—186 °C. IR ν_{max}^{KBr} cm^{-1}: 3500—3200 (OH), 1596 (aromatic). ^{1}H-NMR ($CDCl_3$) δ: 1.4—2.3 (4H, m, CHCH$_2$ × 2), 2.5—2.7 (2H, m), 3.60 (3H, s, OCH$_3$), 3.89 (3H, s, OCH$_3$), 3.90 (3H, s, OCH$_3$), 3.4—3.9 (6H, m), 5.9—6.0 (2H, m, OCH$_2$O), 6.60 (1H, s, aromatic H), 6.78 (2H, s,

aromatic H). MS *m/z*: 402 (M^+). *Anal.* Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.73; H, 6.55.

(1*S,2*S**,7a*R**,7b*R**)-1,2-Bis(acetoxymethyl)-5,6-methylenedioxy-8,9,10-trimethoxy-1,2,3,4-tetrahydrodibenzo[4.5:6.7]cyclooctene (26)**——A mixture of the diol (**25**) (228 mg, 0.567 mmol) and acetyl chloride (0.16 ml, 2.27 mmol) in pyridine (5 ml) was stirred at room temperature for 13 h. The reaction mixture was treated with satd. aq. NaCl (20 ml) and extracted with AcOEt (200 ml). The extract was washed successively with satd. aq. $CuSO_4$ (20 ml × 4), water (20 ml), satd. aq. $NaHCO_3$ (20 ml), water (20 ml × 3), and satd. aq. NaCl (20 ml), then dried over $MgSO_4$. Concentration *in vacuo* afforded a red viscous oil (361 mg). Purification by silica gel column chromatography (ether–*n*-hexane, 1 : 1) gave **26** (243 mg, 88%) as colorless pillars of mp 145—146 °C (from ether). IR ν_{max}^{KBr} cm^{-1}: 1740 (ester), 1595 (aromatic). ^{1}H-NMR ($CDCl_3$) δ: 1.6—1.9 (2H, m), 2.07 (6H, s, $OCOCH_3$ × 2), 2.1—2.3 (2H, m), 2.5—2.7 (2H, m), 3.59 (3H, s, OCH_3), 3.89 (6H, s, OCH_3 × 2), 3.8—4.1 (2H, m), 4.1—4.3 (2H, m), 5.96 (2H, s, OCH_2O), 6.53 (1H, s, aromatic H), 6.7—6.8 (2H, m, aromatic H). MS *m/z*: 486 (M^+). *Anal.* Calcd for $C_{26}H_{30}O_9$: C, 64.18; H, 6.22. Found: C, 63.97; H, 6.16.

Attempted Oxidation of Picrostegane (8)——A mixture of picrostegane (**8**) (20 mg, 0.05 mmol) and DDQ (45 mg, 0.18 mmol) in AcOH (2 ml) was stirred at 70—80 °C for 72 h. The whole was diluted with AcOEt (80 ml) and washed with 15% aq. NaOH (10 ml × 10), water (20 ml), and satd. aq. NaCl (20 ml × 3). The AcOEt layer was dried over $MgSO_4$. Concentration *in vacuo* afforded a brown glass (11 mg). Purification by silica gel TLC (benzene–ether, 9 : 1) gave picrostegane (**8**) (6.7 mg, 34% recovery) and isopicrostegane (**10**) (0.3 mg, 2%). Spectral data were identical with those reported.[1,10b]

Attempted Oxidation of Isopicrostegane (10)——A mixture of isopicrostegane (**10**) (20 mg, 0.05 mmol) and DDQ (45 mg, 0.18 mmol) in AcOH (4 ml) was stirred at 70—80 °C for 72 h. The whole was diluted with AcOEt (80 ml) and washed with 15% aq. NaOH (10 ml × 10), water (20 ml), and satd. aq. NaCl (20 ml × 3). The AcOEt layer was dried over $MgSO_4$. Concentration *in vacuo* afforded a brown glass (13 mg). Purification by silica gel TLC (benzene–ether, 9 : 1) gave isopicrostegane (**10**) (8.1 mg, 41% recovery) and picrostegane (**8**) (0.8 mg, 4%). Spectral data were identical with those reported.[1,10b]

(±)-Steganacin (1) and (±)-Episteganacin (2)——i) DDQ (227 mg, 0.9 mmol) was added to a solution of stegane (**7**)[1,10b] (100 mg, 0.25 mmol) in AcOH (3 ml). The mixture was allowed to warm to 60 °C over a period of 1.5 h and stirred for 18 h and at 80 °C for 45 h. The whole was diluted with AcOEt (150 ml). The AcOEt layer was washed with 10% aq. NaOH (30 ml × 6), water (30 ml), and satd. aq. NaCl (30 ml × 3), and dried over $MgSO_4$. Concentration *in vacuo* afforded a dark brown oil (48 mg). Purification by silica gel TLC ($CHCl_3$–ether, 10 : 1) gave **7** (14 mg, 14% recovery) and a colorless solid. Purification of the above colorless solid by silica gel TLC (benzene–ether, 9 : 1) gave (±)-steganacin (**1**) (10 mg, 10% based on the consumed **7**) as a colorless solid of mp 215—216 °C (from $CHCl_3$–EtOH) (reported mp 214—217 °C[5a,6c]); mixed mp 211—216 °C (using authentic sample kindly provided by Professor R. A. Raphael);[5a] IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1775 (γ-lactone), 1735 (OAc), 1600 (aromatic); ^{1}H-NMR ($CDCl_3$) δ: 1.90 (3H, s, $OCOCH_3$), 2.3—2.8 (2H, m), 2.9—3.2 (1H, m), 3.73 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.9—4.1 (2H, m), 4.2—4.4 (1H, m), 5.82 (1H, d, J = 10 Hz, CHOAc), 6.03 (2H, s, OCH_2O), 6.44 (1H, s, aromatic H), 6.60 (1H, s, aromatic H), 6.90 (1H, s, aromatic H); MS *m/z*: 456 (M^+), 441, 413, 396, 366; high resolution MS Calcd for $C_{24}H_{24}O_9$: 456.1418; Found: 456.1377, and (±)-episteganacin (**2**) (4 mg, 4% based on the consumed **7**) as a colorless viscous oil which was identical with (±)-**2** prepared by the acetylation (acetyl chloride in pyridine) of (±)-**4**; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1777 (γ-lactone), 1747 (OAc), 1596 (aromatic); ^{1}H-NMR ($CDCl_3$) δ: 2.12 (3H, s, $OCOCH_3$), 2.2—3.4 (4H, m), 3.56 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.0—4.4 (2H, m), 5.88 (1H, d, J = 8 Hz, CHOAc), 6.04 (1H, d of ABq, J_{AB} = 1 Hz, OCH_2O), 6.06 (1H, d of ABq, J_{AB} = 1 Hz, OCH_2O), 6.51 (1H, s, aromatic H), 6.76 (1H, s, aromatic H), 6.79 (1H, s, aromatic H); MS *m/z*: 456 (M^+), 441, 413, 396, 381, 366. Spectral data, TLC behavior, and melting point of **1** were identical with those of authentic samples kindly provided by Professors R. A. Raphael,[5] A. S. Kende,[4] and F. E. Ziegler.[6]

ii) A solution of (±)-stegane (**7**)[1,10b] (20 mg, 0.05 mmol) and $Pb(OAc)_4$ (24 mg, 0.055 mmol) in AcOH (2 ml) was stirred at 75 °C for 48 h. The reaction mixture was poured into ice water (50 ml) and extracted with AcOEt (50, 20 ml). The combined AcOEt layers were washed with satd. aq. $NaHCO_3$ (20 ml × 4), water (20 ml × 3) and satd. aq. NaCl (20 ml), then dried over $MgSO_4$. Concentration *in vacuo* afforded a yellow glass (23 mg). Purification by silica gel TLC (benzene–ether, 9 : 1) gave **7** (6.3 mg, 32% recovery) and **1** (0.6 mg, 4% based on the consumed **7**). Spectral data were identical with those described above.

iii) (±)-Steganol (**3**), prepared below, was acetylated according to the reported procedure[4-6] to give **1** in 72% yield.

(±)-Steganol (3)——i) A mixture of (±)-stegane (**7**)[1,10b] (20 mg, 0.05 mmol), NBS (9.8 mg, 0.055 mmol) and BPO (0.25 mg, 0.001 mmol) in CCl_4 (7 ml) was stirred under reflux for 2 h. The whole was diluted with AcOEt (50 ml) and washed with 15% aq. NaOH (15 ml × 2), water (15 ml), 10% aq. $Na_2S_2O_3$ (15 ml × 3), water (15 ml × 3), and satd. aq. NaCl (15 ml). The organic layer was dried over $MgSO_4$. Concentration *in vacuo* gave the unstable (±)-4-bromostegane (**5**) (25.8 mg, quant.) as a pale yellow glass, MS *m/z*: 478, 476 (M^+), 396 ($M^+ - HBr$). Purification by silica gel TLC (benzene–AcOEt, 3 : 1) gave (±)-steganol (**3**) (11.8 mg, 57%) as colorless pillars of mp 148—150 °C. IR ν_{max}^{KBr} cm^{-1}: 3330 (OH), 1752 (γ-lactone). ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.7 (4H, m), 2.8—3.2 (1H, m), 3.8—4.0 (1H, m), 3.72 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.3—4.6 (2H, m), 6.02 (2H, br s, OCH_2O), 6.44 (1H, s,

aromatic H), 6.56 (1H, s, aromatic H), 6.76 (1H, s, aromatic H). MS *m/z*: 414 (M^+), 396, 330. *Anal.* Calcd for $C_{22}H_{22}O_8 \cdot 1/2H_2O$: C, 62.41; H, 5.48. Found: C, 62.68; H, 5.40.

ii) A solution of **5** (208 mg), obtained from (±)-**7** (160 mg, 0.4 mmol) as above, in 5 ml of aq. THF (water–THF, 1:9) was stirred at room temperature for 48 h. Usual work-up and purification by silica gel column chromatography (benzene–AcOEt, 3:1) gave **3** (141 mg, 85%) and **4** (1.0 mg, 0.6%) as a yellow glass; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590 (OH), 1782 (γ-lactone), 1591 (aromatic); ^{1}H-NMR ($CDCl_3$) δ: 1.92 (1H, d, *J*=4 Hz, OH), 2.1—3.4 (4H, m, $ArCH_2CHCH$), 3.62 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.08 (1H, dd, *J*=9 and 11 Hz, $COOCH_2CH$), 4.34 (1H, dd, *J*=8 and 9 Hz, $COOCH_2CH$), 4.99 (1H, dd, *J*=4 and 8 Hz, OCH_2), 6.02 (1H, d, *J*=1.5 Hz, OCH_2O), 6.07 (1H, d, *J*=1.5 Hz, OCH_2O), 6.50 (1H, s, aromatic H), 6.70 (1H, s, aromatic H), 7.08 (1H, s, aromatic H); MS *m/z*: 414 (M^+). Spectral data for **3** and **4** were identical with those reported.[4,5b]

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Only a trace amount of the oxidized product having an acetyloxy function was obtained, and the structure could not be determined.

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