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ASYMMETRIC TOTAL SYNTHESIS OF NATURAL (−)- AND UNNATURAL (+)-STEGANACIN

DETERMINATION OF THE ABSOLUTE CONFIGURATION OF NATURAL ANTITUMOR STEGANACIN[1,2]

KIYOSHI TOMIOKA, TSUNBO ISHIGURO, YŌICHI IITAKA and KENJI KOGA*
Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

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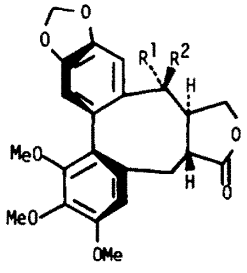
Abstract—A virtually complete asymmetric control in the synthesis of 2,3-disubstituted butan-4-olide (**10**) was demonstrated by employing the butenolide (**12**) as the chiral acceptor for the conjugate 1,4-addition. Highly efficient asymmetric total synthesis of natural (−)- and unnatural (+)-steganacin was accomplished. The absolute stereostructure of natural antitumor steganacin was determined to be **1**.

In 1973 Kupchan reported the isolation and structural elucidation of the new steganin lignans.[3,4] Steganacin (**1**), a representative of these novel dibenzocyclooctadiene lignan lactones, was found to show significant antitumor activity *in vivo* against KB cell. The structure of steganacin was originally proposed to be **7** with the absolute configuration indicated by the direct X-ray crystallographic analysis of episteganol (**2**).[5]

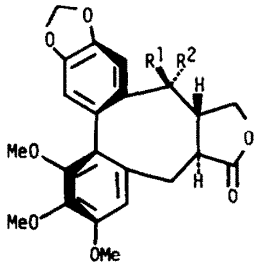
Since then considerable efforts have been devoted to the total syntheses of steganacin (**1**) and related lignans.[6-11] As a consequence of our studies directed toward the asymmetric total syntheses of steganacin and related lignans, we have exploited the asymmetric synthesis of both enantiomers of 2,3-disubstituted 2-butan-4-olide (**9**, **10**), the promising intermediate for steganin lignans, with a predictable absolute configuration. As is shown in Chart 1, this synthesis was designed based on the novel applications of (*S*)-4-hydroxymethyl-butan-4-olide (**11**, R = H), readily available from L-glutamic acid, as a chiral source in the asymmetric induction and as a carbon framework of the target molecule.[12]

In previous papers, we have reported the synthesis of highly optically pure (−)- and (+)-deoxypodorhizon (**9** and **10**) employing the technique of 1,3-asymmetric induction,[1] as is shown in Chart 2.

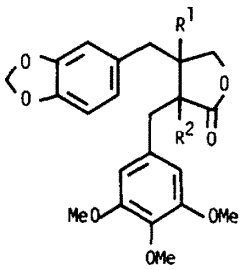
In the present paper we wish to report the highly efficient asymmetric synthesis of optically pure (+)-deoxypodorhizon (**10**) by the method of



1 R^1=OAc R^2=H
2 R^1=H R^2=OH
3 R^1=OH R^2=H
4 R^1=Br R^2=H
5 R^1, R^2=O
6 R^1=R^2=H



7 R^1=OAc R^2=H
8 R^1=R^2=H



9 R^1=α-H R^2=β-H
10 R^1=β-H R^2=α-H

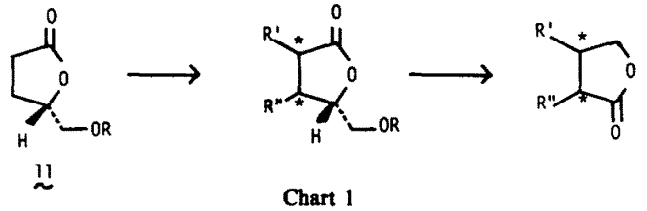


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Chart 1

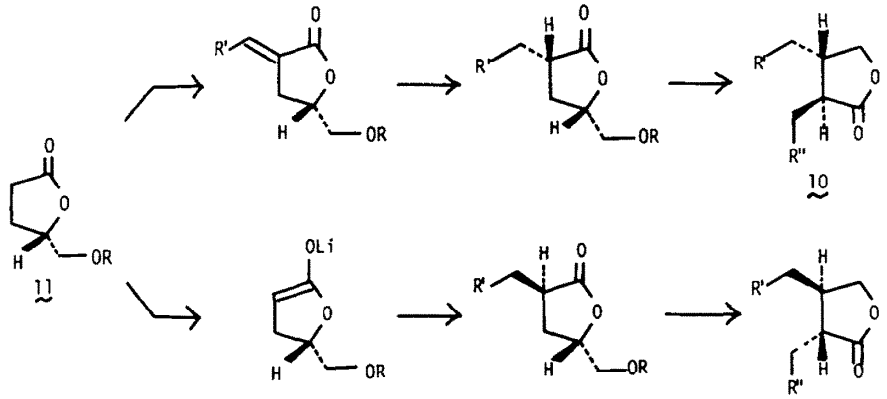


Chart 2

1,2-asymmetric induction and the establishment of the total synthesis of optically pure natural (−)- and unnatural (+)-steganacin with a definite absolute configuration.

Design of the asymmetric synthesis by the method of 1,2-asymmetric induction

The 1,4-addition reactions of a variety of nucleophiles with crotonolactone, followed by the trapping of the resulting lactone enolate anion with electrophiles, have been reported by several authors to proceed in a satisfactory manner.[13-16] The method of C–C bond formation at the β-position of lactone CO of **11** via 1,2-asymmetric induction is shown in Chart 3.

Thus, the reaction of the chiral butenolide derivative **12**, available from **11**, with a nucleophile can be expected to give the enolate anion of the 2-substituted butan-4-olide (**13**). The subsequent reaction of **13** with an electrophile can also be expected to give the 2,3-disubstituted butan-4-olide (**14**). It is highly probable that the reaction of **12** with a nucleophile will take place from the less hindered β-side opposite to the $ROCH_2$ group to give **13** predominantly, furthermore, the reaction of **13** with an electrophile will take place from the α-side opposite to the nucleophile first introduced giving **14**. Therefore, after the lactone carbonyl transposition procedure involving the reduction of **14** to the triol, the oxidative cleavage of the glycol function, resulting in the formation of the lactol, and then Collins oxidation to the lactone, 2,3-disubstituted butan-4-olide (**15**) can be obtained in a highly optically pure form without any additional procedure for enantioenrichment.[12]

Synthesis of the chiral butenolide (**12**)

One of the critical steps in the present synthesis was the preparation of the optically pure butenolide (**12**) from **11**. The results are summarized in Table 1. The phenylselenation of **11** was carried out to give **16** (59% for **16** (X = Se, R = CH_2Ph), 94% for **16** (X = Se, R = CPh_3)).[17] Thiophenyl derivatives **16** (X = SPh) were also prepared by the standard procedure.[18]

The thermal elimination procedure[18] for **16** (X = SO), prepared by the oxidation of **16** (X = S) with $NaIO_4$, resulted in the formation of **12** with a low optical purity, as is shown in Table 1 (Entries 3, 5), probably because of the racemization under the conditions used. The susceptibility of **12** to racemization was also observed when a solution of crude **12** (R = CH_2Ph) was washed with 10% aq. NaOH on the occasion of an extractive work-up (Entry 2).

Without washing with an alkaline solution, the optically pure butenolide **12** (R = CH_2Ph) could be synthesized from **11** (R = CH_2Ph) in 50% overall yield via **16** (X = Se) (Entry 1). Optically pure **12** (R = CPh_3) could also be synthesized in 82% overall yield by the reaction of **16** (X = Se, R = CPh_3) with $NaIO_4$ in water–AcOEt[20] at 50° (Entry 4).

The optical purity of **12** was determined by converting it into **11** (R = H), as described in the Experimental.

Asymmetric 1,4-addition with the chiral butenolide (**12**)

The utility of **12** by the method of 1,2-asymmetric induction was proved by the synthesis of an optically and diastereomerically pure key intermediate (**17**), as is shown in Chart 4. The chiral butenolide (**12** (R = CH_2Ph)) was reacted with the S-stabilized anion (**18**) at −78° in THF for 3 hr. Then the resulting enolate anion was reacted with piperonyl bromide to afford **19**, containing a small amount of an impurity, in 96% yield. The reductive desulfurization of the **19** obtained above with Raney nickel resulted in the concomitant removal of the benzyl protecting group to afford, after careful separation by column chro-

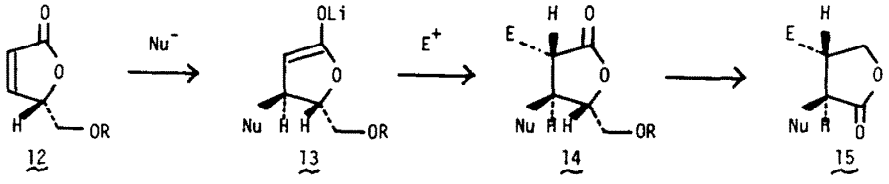
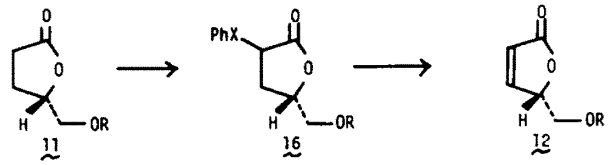


Chart 3

Table 1. Synthesis of the chiral butenolide (12)



Entry	R	X	Yield(%)[a]	$[\alpha]_D^{20}$(EtOH)	Optical Purity(%)[d]
1	CH_2Ph	Se	50[b]	-107°	100
2	CH_2Ph	Se	c	-33.6°	31
3	CH_2Ph	S	28	-79.4°	74
4	CPh_3	Se	82	-97.8°	100
5	CPh_3	S	31	-59.1°	60

a) Isolated overall yield from 11. b) Yield was corrected for the consumed starting material. c) After the oxidative elimination the extracts were washed with 10% aq. NaOH. Yield was comparable with that obtained in Entry 1. d) Optical purity was determined by converting 12 into 11(R=H).

matography, the products **17** and **20**, which consisted predominantly of one diastereomer (**19**, 57%) with a preference of 98:2. The optical purity and structure of **17** were confirmed by converting it into the optically pure (+)-deoxypodorhizon (**10**).[1,21] The minor isomer obtained in 1% yield from **12** (R = CH_2Ph) was determined to be **20** by the following spectral data and experimental result. Mass spectrum of **20** showed the molecular ion at 430, consistent with that of **20**. ^{13}C NMR spectrum also supported the carbon framework of **20**. The experimental result that **20** retained its structure unchanged in the attempted isomerization by a base also supported the structural assignment of **20**.[22]

The experimental results clearly show that the 1,4-addition of the nucleophile to the chiral butenolide **12** (R = CH_2Ph) took place predominantly from the less hindered β-side of **12** and that the subsequent alkylation of the resulting enolate anion took place from the α-side opposite to the nucleophile introduced. The complete stereoselection in the 1,4-addition reaction was achieved by employing trityl ether **12** (R = CPh_3) as the acceptor for the 1,4-addition.

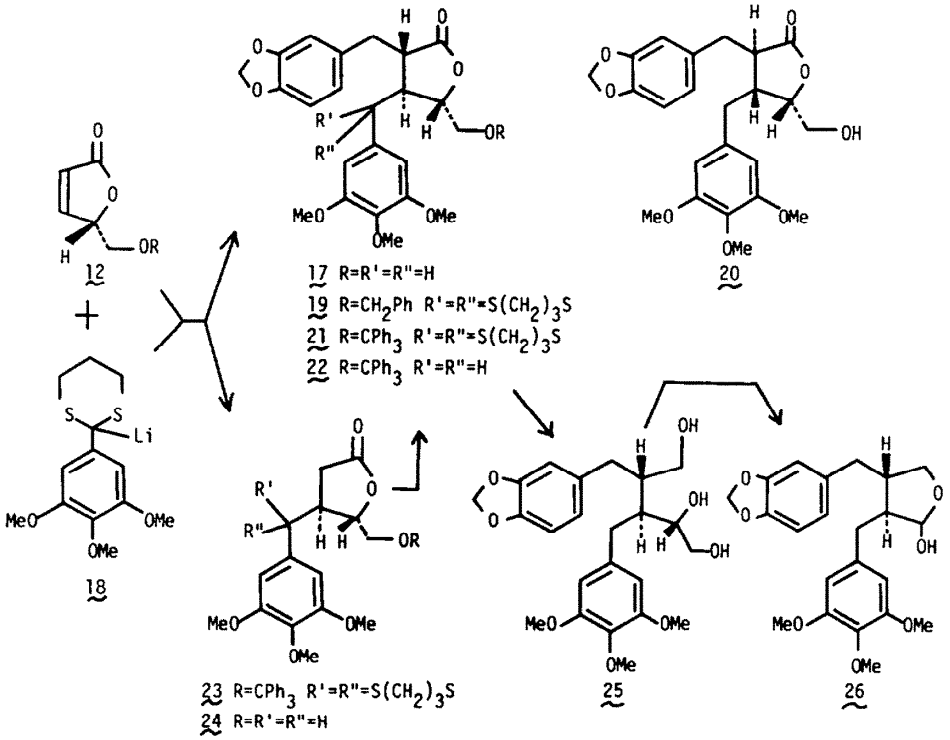


Chart 4

Table 2. Stereoselective 1,4-addition with **12**

Entry	R	Yield of 17(%)[a]	Stereoselectivity (17:20)[b]
1	CH_2Ph	56	98:2
2	CPh_3	36	100:0

a) Isolated overall yield of 17 from 12. b) The ratio was determined by the isolation of 17 and 20.

The 1,4-addition and subsequent alkylation were carried out using **12** ($R=CPh_3$) bearing the bulky trityl group. The crude product was directly reduced with Raney Ni to afford, after column chromatography, **17** (28%) and **22** (9%). **22** was detritylated to give **17** in 93% yield. Though the overall yield was somewhat lower, the absence of **20** means that a complete stereoselection was realized.[23] An effort was made to improve the chemical yield and finally the practical synthetic route shown in Chart 4 was established. The chiral butenolide **12** ($R=CPh_3$) was caused to react with **18**. Desulfurization of the crude **23**[24] and the subsequent detritylation gave, after short column chromatography on silica gel, **24** as a crystalline compound in 65% overall yield from **12** ($R=CPh_3$). Piperonylation of the dianion of **24** with two equivalents of piperonyl bromide[25] gave **17** in 62% yield.

Synthesis of optically pure (+)*-deoxypodorhizon* (**10**)

The lactone carbonyl transposition procedure worked very well, giving (+)-deoxypodorhizon (**10**) in 78% overall yield from **17**. Thus the reduction of **17** with $LiAlH_4$ gave **25** in 97% yield. The oxidative glycol cleavage of **25** with $NaIO_4$ gave the lactol **26** in 85% yield. Collins oxidation of **26** afforded optically pure (+)-deoxypodorhizon (**10**) in 95% yield.[26] The optical rotation and spectral data were completely identical with those reported earlier.[1]

Synthesis of (+)*-steganacin* (**7**) *and correction of the absolute configuration of natural* (−)*-steganacin to* **1**

(+)-Deoxypodorhizon (**10**) prepared above was subjected to nonphenolic oxidative coupling, according to the Schlessinger procedure for the racemic modification,[13] to afford (−)-isostegane (**27**) in 61% yield. The attempted benzylic oxidation of **27** using a variety of reagents under a variety of conditions failed unexpectedly to give the desired product oxidized at the benzylic position. Then we turned our attention to the oxidation of stegane (**8**), the parent skeleton of steganacin. The thermal atropisomerization[12] of **27** at 200° gave (+)-stegane (**8**) selectively. DDQ oxidation of **8** in AcOH at 75° gave (+)-steganacin (**7**) of $[\alpha]_D^{23}+135°$ ($CHCl_3$) in 11% yield.

Spectral data (^1H NMR, IR, MS) and tlc behavior were completely identical with those of natural (−)-steganacin (**1**)[3] kindly provided by Prof. A. T. Sneden and with those of the synthetic racemic modification provided by Kende,[6] Raphael[7] and Ziegler.[8]

It is important to attract attention here that, to our surprise, the optically pure (+)-steganacin (**7**), whose absolute configuration is unequivocal based on the asymmetric synthetic pathway[1,12] and consistent with that proposed by Kupchan,[3] showed a sign of the optical rotation value opposite to that of natural (−)-steganacin ($[\alpha]_D^{23}-114°(CHCl_3)$).[27] It was concluded from this fact that the absolute configuration of natural steganacin should be corrected to **1**, the opposite of that originally proposed (**7**) by Kupchan.

Efficient synthesis of (−)*-steganacin* (**1**) *and related lignans*

The advantage of our asymmetric synthesis is that both enantiomers with the predictable absolute configuration can be obtained from the chiral lactone (**11**).[1,12] (−)-Steganacin (**1**) with a natural absolute configuration was synthesized as follows. (+)-Isostegane (**28**) was prepared from (−)-deoxyprodorhizon (**9**)[1,12] according to the procedure described above. Bromination of (−)-stegane (**6**), prepared by the thermal atropisomerization of (+)-isostegane (**28**),[12] with NBS–BPO in CCl_4 afforded 4-bromostegane (**4**) in a quantitative yield.[28] (−)-Steganol (**3**) ($[\alpha]_D^{23}-190°(CHCl_3)$, reported $[\alpha]_D^{23}-163°(CHCl_3)$[3]) was obtained in 85% overall yield simply by treating **4** with aqueous THF.[28] (−)-Steganacin (**1**) ($[\alpha]_D^{23}-127°(CHCl_3)$) was obtained in 72% yield by the acetylation of **3**. Optical rotation, spectral data (^1H NMR, IR, MS), and tlc behavior of the present synthetic (−)-steganacin (**1**) were identical with those of natural (−)-steganacin.

(−)-Steganone (**5**) ($[\alpha]_D^{23}-191°(CHCl_3)$, reported $[\alpha]_D^{23}-202°(CHCl_3)$[3], $[\alpha]_D^{23}-140°(CHCl_3)$[4a], $[\alpha]_D^{23}-197°(CHCl_3)$[7c]) was synthesized in 81% yield by the oxidation of (−)-steganol (**3**). Reduction of **5** with L-Selectride[8c] afforded (−)-episteganol (**2**) ($[\alpha]_D^{23}-107°$ (pyridine), reported $[\alpha]_D^{23}-126°$ (pyridine)[3]) in 69% yield.

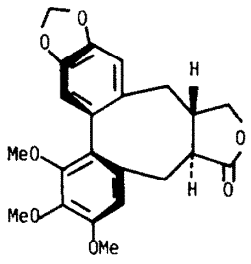
It was, thus, concluded that (−)-steganacin (**1**) and related lignans prepared above were identical with natural steganin lignans.

Confirmation of the absolute configuration

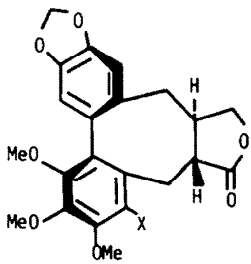
X-ray crystallographic analysis with heavy atom was undertaken to make doubly sure of the absolute configuration. Since it is hard to imagine any possibility of isomerization at the β-position of the lactone ring in (+)-isostegane (**28**) during the above conversion to (−)-steganacin (**1**) and related lignans (**2**, **3**, **5**), the confirmation of the absolute configuration of naturally occurring (−)-steganacin was carried out using (+)-isostegane (**28**).

Bromination of (+)-**28** with $PyHBr_3$[29] afforded (+)-12-bromoisostegane (**29**) (m.p. 157–158° (from MeOH), $[\alpha]_D^{23}+122°(CHCl_3)$) as colorless plates in 94% yield.

The crystal of (+)-**29** contains four molecules in a monoclinic cell with a space group of $P2_1$ and with cell dimension of $a=12.218(6)$, $b=23.107(12)$,



27



28 X=H
29 X=Br

$c = 7.353(5)$ Å and $\beta = 90.60(4)°$. The structure was solved by the heavy atom method to an R value of 0.056 without including hydrogen atoms, on the basis of 2530 observed reflections.

The absolute configuration was determined by the use of the anomalous dispersion effect of Br atoms for CuKα radiation. Among the 67 pairs of reflections for which both the ratios, $|Fo(hkl)|/|Fo(h\bar{k}\bar{l})|$ and $|Fc(hkl)|/|Fc(h\bar{k}\bar{l})|$, differ more than 5% from unity, 61 pairs clearly showed the absolute configuration given in Fig. 1. The R values for the correct and inverted structures were calculated to be 0.056 and 0.063 respectively when the anomalous dispersion corrections were applied for the Br atoms.

It is now confirmed that the absolute configuration of natural (−)-steganacin is **1**.

The highly efficient asymmetric total syntheses of optically pure steganin lignans (17% overall yield for (−)-steganacin (**1**) from the chiral synthon, (*S*)-4-trityloxymethyl-butan-4-olide (**11**, R = CPh_3), readily available in quantity from the commercially available L-glutamic acid),[1,12] holds great promise for the asymmetric total syntheses of other pharmacollogically potent natural and unnatural lignans.

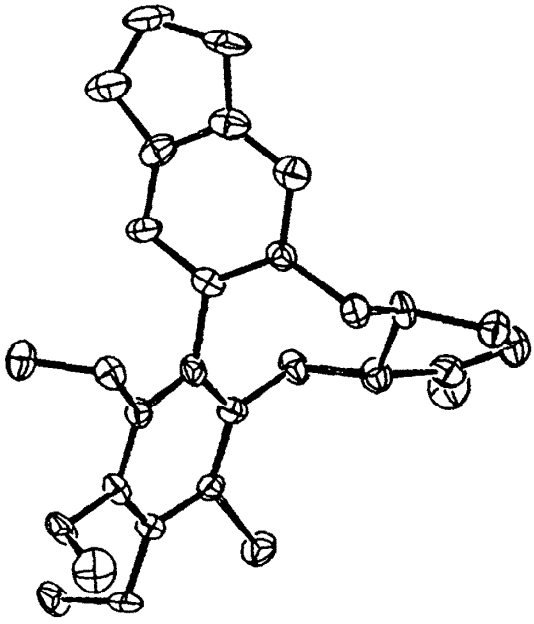


Fig. 1. Computer drawing of (+)-**29** showing the absolute structure of A molecule, one of the two independent molecules contained in an asymmetric unit.

EXPERIMENTAL[30]

(4S)-(+)-2-Phenylseleno-4-benzyloxymethyl-butan-4-olide (**16**, X = Se, R = CH_2Ph)

A soln of **11** (R = CH_2Ph)[1,12] (1.18 g, 5.73 mmol) in THF (1 ml) and HMPA (2.2 ml, 12.5 mmol) was added to a cooled (−78°) soln of LDA (12.5 mmol) in THF (25 ml), prepared as usual, and the whole was stirred at −78° for 0.5 hr. Diphenyl diselenide (1.95 g, 6.25 mmol)[31] was added and the mixture was stirred at −78° for 1 hr, at −20° for 4 hr, and then at room temp for 19 hr. The mixture was treated by the addition of sat NH_4Claq (10 ml) and extracted with AcOEt (100 ml × 2). The combined organic layers were washed successively with water, 10% NaOHaq, water, and sat NaClaq, and then dried over $MgSO_4$. Concentration *in vacuo*, followed by purification using column chromatography on silica gel (ether-n-hexane/1:1), afforded **16a** (X = Se, R = CH_2Ph) (680 mg, 39% based on **11** consumed) as a pale yellow oil of $[\alpha]_D^{20} + 23.9°$ ($c = 0.970$, EtOH), IR ($CHCl_3$) cm^{-1}: 1767, ^1H NMR ($CDCl_3$)δ: 2.1–2.7 (2H, m, $CH_2CHSePh$), 3.3–3.7 (2H, m, $CHCH_2O$), 3.95 (1H, dd of ABX, $J_{AX} = 5$ Hz, $J_{BX} = 8$ Hz, $CH_2CHSePh$), 4.2–4.6 (1H, m, CHO), 4.47 (2H, S, CH_2Ph), 7.0–7.4 (8H, m, aromatic H), 7.4–7.6 (2H, m, aromatic H); MS: 362 (M^+), 360 (M^+), and **16b** (X = Se, R = CH_2Ph) (360 mg, 20% based on **11** consumed) as a pale yellow oil of $[\alpha]_D^{23} + 49.3°$ ($c = 1.10$, EtOH), IR($CHCl_3$) cm^{-1}: 1762; ^1H NMR ($CDCl_3$)δ: 2.0–2.9 (2H, m, $CH_2CHSePh$), 3.2–3.7 (2H, m, CH CH_2O), 3.90 (1H, t of ABX, $J_{AX} = J_{BX} = 10$ Hz, $CH_2CHSePh$), 4.4–4.6 (1H, m, CHO), 4.43 (2H, s, OCH_2Ph), 7.0–7.3 (8H, m, aromatic H), 7.4–7.6 (2H, m, aromatic H), MS: 362 (M^+), and **11** (R = CH_2Ph) (180 mg, 15% recovery). For the oxidative elimination a mixture of the two diastereomers (**16a** and **16b** (X = Se, R = CH_2Ph)) obtained above was used.

(4S)-(−)-4-Benzyloxymethyl-2-buten-4-olide (**12** (R = CH_2Ph))

A soln of $NaIO_4$ (6.06 g, 28.3 mmol) in MeOH–water (1:1, 100 ml) was added to the soln of **16** (X = Se, R = CH_2Ph) (3.40 g, 9.42 mmol) obtained above.[32] The whole was stirred at room temp for 0.5 hr and extracted with AcOEt (200 ml × 4). The combined organic layers were washed successively with 10% $NaHSO_3$aq, water, and sat NaClaq, and then dried over $MgSO_4$. Concentration *in vacuo* gave a dark brown oil. Purification by silica gel column chromatography (ether–n-hexane/1:1) gave **12** (R = CH_2Ph) (1.63 g, 85%) as a pale yellow oil of $[\alpha]_D^{20} - 107°$ ($c = 1.09$, EtOH). IR (film) cm^{-1}: 1755. ^1H NMR ($CDCl_3$)δ: 3.70 (2H, d, J = 6 Hz, CH_2OCH_2Ph), 4.55 (2H, s, CH_2Ph), 5.0–5.2 (1H, m, OCH), 6.11 (1H, dd, J = 2 and 6 Hz, CH = CH), 7.24 (5H, s, aromatic H), 7.40 (1H, dd, J = 2 and 6 Hz, CH = CH). MS: 204 (M^+).

(4S)-(+)-2-Phenylseleno-4-trityloxymethyl-butan-4-olide (**16** (X = Se, R = CPh_3))

A soln of **11** (R = CPh_3)[1,12] (1.00 g, 2.79 mmol) in THF (10 ml) was added to a soln of LDA (6.14 mmol) in THF (20 ml) at −78°. After stirring for 35 min, a soln of phenylselenyl bromide, prepared from diphenyl diselenide (477 mg, 1.53 mmol) and Br_2 (0.039 ml, 1.53 mmol), in THF (10 ml) was added and the whole was stirred at −78° for 1.5 hr. The mixture was added by sat. NH_4Claq (10 ml) and sat NaClaq (10 ml) and extracted with AcOEt (100 ml × 2, 50 ml). The combined AcOEt layers were washed successively with 10% HClaq, water, sat NaClaq, 10% $NaHSO_3$aq, water, and sat NaClaq, and then dried over $MgSO_4$. Concentration *in vacuo* afforded a faint yellow solid (1.53 g). Purification of the solid (400 mg) by silica gel column chromatography ($CHCl_3$–benzene/1:2) afforded two separable diastereoisomers, **16a** (X = Se, R = CPh_3) (188 mg, 50%) as a colorless solid with a higher R_f value and **16b** (X = Se, R = CPh_3) as colorless solid with a lower R_f value (163 mg, 44%). Recrystallization from benzene–n-hexane gave the analytical sample of **16a** as colorless needles of m.p. 90–91°. $[\alpha]_D^{20} + 29.6°$ ($c = 0.162$, $CHCl_3$). IR (KBr) cm^{-1}: 1765. ^1H

NMR ($CDCl_3$)δ: 2.0–2.6 (2H, m $CH_2CHSePh$), 3.05 (1H, dd of ABX, J_{AB} = 11 Hz, J_{AX} = 4 Hz, CH_2O), 3.37 (1H, dd of ABX, J_{AB} = 11 Hz, J_{BX} = 3 Hz, CH_2O), 4.08 (1H, dd of A'B'X', $J_{A'X'}$ = 5 Hz, $J_{B'X'}$ = 9 Hz, $CHSePh$), 4.3–4.5 (1H, m, CHO), 7.1–7.5 (18H, m, aromatic H). MS: 514 (M^+), 512 (M^+). Anal. ($C_{30}H_{26}O_3Se$) C, H.

Recrystallization from benzene gave an analytical sample of **16b** as colorless needles of m.p. 182–183°. $[\alpha]_D^{23}$ + 43.1° (c = 0.320, $CHCl_3$). IR (KBr) cm^{-1}: 1768, 1757. ^1H NMR ($CDCl_3$)δ: 2.07 (1H, ddd of ABMX, J_{AB} = 14 Hz, J_{AM} = 9 Hz, J_{AX} = 8 Hz, $CHCH_2CHSePh$), 2.62 (1H, ddd of ABMX, J_{AB} = 14 Hz, J_{BM} = 10 Hz, J_{BX} = 7 Hz, $CHCH_2CHSePh$), 3.07 (1H, dd of A'B'X', $J_{A'B'}$ = 11 Hz, $J_{A'X'}$ = 5 Hz, $CHCH_2O$), 3.18 (1H, dd of A'B'X', $J_{A'B'}$ = 11 Hz, $J_{B'X'}$ = 6 Hz, $CHCH_2O$), 4.00 (1H, dd of ABM, J_{AM} = 9 Hz, J_{BM} = 10 Hz, $CH_2CHSePh$), 4.3–4.7 (1H, m, CHO), 7.1–7.5 (18H, m, aromatic H), 7.5–7.7 (2H, m, aromatic H). MS: 514 (M^+), 512 (M^+). Anal. ($C_{30}H_{26}O_3Se$) C, H.

(4S) - (−) - *Trityloxymethyl* - 2 - *buten* - 4 - *olide* (**12** (R = CPh_3))

A soln of **16** (X = Se, R = CPh_3)[32] (3.60 g, 7.02 mmol) in AcOEt (200 ml) was added to a soln of $NaIO_4$ (6.01 g, 28.1 mmol) and 18-crown-6 (67 mg, 0.28 mmol) in water (60 ml).[20] The mixture was heated at 50° for 14 hr and AcOEt layer was separated. The aqueous layer was extracted with AcOEt (150 ml). The combined AcOEt layers were washed successively with 10% $NaHSO_3$aq, water, sat $NaHCO_3$aq, water, sat NaClaq, and then dried over $MgSO_4$. Concentration *in vacuo* afforded a yellow solid (2.89 g). Purification by silica gel column chromatography (benzene–ether/100:1) gave **12** (R = CPh_3) (2.18 g, 87%) as colorless needles of m.p. 152.5–154° (from benzene–n-hexane). $[\alpha]_D^{20}$ − 97.8° (c = 1.10, $CHCl_3$). IR (KBr) cm^{-1}: 1765, 1600. ^1H NMR ($CDCl_3$)δ: 3.39 (2H, d, J = 5 Hz, CH_2), 4.9–5.1 (1H, m, CH), 6.16 (1H, dd, J = 2 and 6 Hz, CH = CHCO), 7.1–7.5 (16H, m, aromatic H and CH = CHCO). MS: 356 (M^+). Anal. ($C_{24}H_{20}O_3$) C, H.

(4S) - (+) - 4 - *Hydroxymethyl butan* - 4 - *olide* (**11** (R = H))

(i) Catalytic hydrogenation of **12** (R = CH_2Ph) (1.00 g, 4.90 mmol) of $[\alpha]_D^{20}$ − 107° (C = 1.09, EtOH) was carried out with 5% Pd–C (100 mg) and $PdCl_2$ (10 mg) in EtOH (50 ml) under an atmospheric pressure of H_2. The mixture was filtered, and the filtrate was concentrated *in vacuo* to afford a pale yellow oil (576 mg). Purification by silica gel column chromatography (ether–$CHCl_3$/5:1) gave **11** (R = H) as a pale yellow oil of $[\alpha]_D^{26}$ + 32.7° (c = 2.92, EtOH) (reported[34] $[\alpha]_D^{26}$ + 31.3° (c = 2.92, EtOH)).

(ii) Catalytic hydrogenation of **12** (R = CPh_3) (620 mg, 1.74 mmol) of $[\alpha]_D^{20}$ − 97.8° (c = 1.10, $CHCl_3$) was carried out with 5% Pd–C (50 mg) and $PdCl_2$ (100 mg) in AcOEt–EtOH (5:6, 22 ml) under an atmospheric pressure of H_2. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give a pale yellow oil (619 mg). Purification by silica gel column chromatography (ether–$CHCl_3$/5:1) gave **11** (R = H) (168 mg, 92%) as a colorless oil of $[\alpha]_D^{26}$ + 32.2° (c = 3.24, EtOH).

2 - (3,4,5 - *Trimethoxyphenyl*) - 1,3 - *dithiane*

1,3-Propanedithiol (10 ml, 100 mmole) was added to a soln of 3,4,5-trimethoxybenzaldehyde (17.8 g, 89 mmole) in $CHCl_3$ (200 ml). After stirring for 2 hr at room temp conc HCl (3 ml) was added and the whole was stirred for 2 hr at room temp. The mixture was washed successively with water and sat NaClaq, and then dried over K_2CO_3. Concentration *in vacuo* afforded a colorless solid, which was then recrystallized from AcOEt to give the desired dithiane (22.0 g, 86%) as colorless needles of m.p. 85–87.5°. IR (KBr) cm^{-1}: 1590. ^1H NMR ($CDCl_3$)δ: 1.7–2.3 (2H, m, $CH_2CH_2CH_2$), 2.7–3.2 (4H, m, $CH_2CH_2CH_2$), 3.80 (3H, s, OCH_3), 3.85 (6H, s, OCH_3 × 2), 5.06 (1H, s, ArCH), 6.65 (2H, s, aromatic H). MS: 286 (M^+), 212. Analytical sample was prepared by recrystallizing the above needles from AcOEt–n-hexane to give colorless needles of m.p. 88.5–89.0°. Anal. ($C_{13}H_{18}O_3S_2$) C, H.

(+) - (2S, 3S, 4S) - 2 - *Piperonyl* - 3 - (2 - (3,4,5 - *trimethoxylphenyl*) - 1,3 - *dithiane* - 2 - *yl*) - 4 - *benzyloxymethyl* - *butan* - 4 - *olide* (**19**)

A soln of 2-(3,4,5-trimethoxyphenyl)-1,3-dithiane (2.89 g, 10.1 mmole) in THF (20 ml) was added to a cooled (−78°) soln of n-BuLi (10.1 mmole) in THF (30 ml) under argon. After stirring for 0.5 hr, a soln of (−)-**12** (R = CH_2Ph) (1.58 g, 7.75 mmole) of $[\alpha]_D^{20}$ − 107° (EtOH) in THF (10 ml) was added over a period of 3 min, and the mixture was stirred at −78° for 3 hr. A soln of piperonyl bromide (2.34 g, 10.9 mmol) in THF (15 ml) was added, after which the whole was stirred at −78° for 0.5 hr and then allowed to warm up to room temp for 15 hr. After the addition of sat NH_4Claq (40 ml), the mixture was extracted with AcOEt (300, 200, 100 ml). The combined extracts were washed successively with 10% HClaq, water, sat. $NaHCO_3$aq, water, and sat. NaClaq, and then dried over $MgSO_4$. Concentration *in vacuo* afforded a dark brown viscous oil (1.89 g), which was purified by silica gel column chromatography (CH_2Cl_2–ether = 40:1 and then 20:1) to give (+)-**19** (5.03 g, 96%) as a pale yellow glass of $[\alpha]_D^{20}$ + 1.78° (c = 2.14, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1767, 1585. ^1H NMR ($CDCl_3$)δ: 1.6–2.1 (2H, m, CH_2), 2.3–3.5 (10H, m, CH_2 × 4, CH × 2), 3.81 (6H, s, OCH_3 × 2), 3.84 (3H, s, OCH_3), 4.41 (2H, s, $PhCH_2$), 4.9-5.1 (1H, m, OCH), 5.7–5.9 (2H, m, OCH_2O), 6.2–6.3 (2H, m, aromatic H), 6.4–6.6 (1H, m, aromatic H), 7.07 (2H, s, aromatic H). MS: 624 (M^+). HRMS (Found: 624.1895. Calc for $C_{33}H_{36}O_8S_2$: 624.1849).

(3S, 4S) - (+) - 3 - (2 - (3,4,5 - *Trimethoxyphenyl*) - 1,3 - *dithian* - 2 - *yl*) - 4 - *trityloxymethyl* - *butan* - 4 - *olide* (**23**)

A soln of n-BuLi (5.47 mmol) in n-hexane (3.1 ml) was added to a cooled (−78°) soln of 2-(3,4,5-trimethoxyphenyl)-1,3-dithian (1.5 g, 5.47 mmol) in THF (20 ml) under argon. After stirring for 30 min, a soln of **12** (R = CPh_3) (1.5 g, 4.21 mmol) in THF (25 ml) was added and the whole was stirred at −78° for 2 hr. The mixture was quenched by sat NH_4Claq (10 ml) and extracted with AcOEt (150 ml, 100 ml × 2). The combined extracts were washed successively with 10% HClaq, water, sat $NaHCO_3$aq, water, and sat. NaClaq, and then dried over $MgSO_4$. Concentration *in vacuo* afforded a faint yellow solid (2.94 g). Recrystallization from AcOEt gave (+)-**23** (1.60 g, 59%) as colorless prisms of m.p. 189.5-190.5°. $[\alpha]_D^{20}$ + 15.2° (c = 2.01, $CHCl_3$). IR (KBr) cm^{-1}: 1780. NMR ($CDCl_3$)δ: 1.6–2.1 (2H, m, $CH_2CH_2CH_2$), 2.5–3.5 (9H, m, $CH_2CH_2CH_2$, $COCH_2CH$, OCH_2), 3.77 (6H, s, OCH_3 × 2), 3.79 (3H, s, OCH_3), 4.7–4.9 (1H, m, OCH), 7.0–7.4 (17H, m, aromatic H). MS: 642 (M^+). Anal. ($C_{37}H_{38}O_6S_2$) C, H.

(3S, 4S) - (+) - 3 - (3,4,5, - *Trimethoxybenzyl*) - 4 - *hydroxymethyl* - *butan* - 4 - *olide* (**24**)

(i) A mixture of (+)-**23** (9.28 g, 14.5 mmol) and Raney Ni (W-4, 72 g) in EtOH (1.4 l) was heated to reflux for 5 hr and then filtered. The filtrate was concentrated *in vacuo* to give a colorless solid. After the addition of AcOEt (350 ml), the mixture was washed successively with sat NaClaq, sat $NaHCO_3$aq, water, and sat. NaClaq, and then dried over $MgSO_4$. Concentration *in vacuo* gave a colorless solid (7.27 g). Purification of the above solid (7.00 g) by silica gel column chromatography (benzene–AcOEt/1:3) gave (+)-**24** (2.50 g, 65%) as colorless needles of m.p. 119–120° (from benzene). $[\alpha]_D^{20}$ + 26.7° (c = 0.998, $CHCl_3$). IR (KBr) cm^{-1}: 3460, 1780. ^1H NMR ($CDCl_3$)δ: 2.1–2.9 (6H, m, $ArCH_2CHCH_2$, OH), 3.4–3.7 (2H, m, CH_2OH), 3.80 (3H, s, OCH_3), 3.82 (6H, s, OCH_3 × 2), 4.2–4.4 (1H, m, CH), 6.34 (2H, s, aromatic H). MS: 296 (M^+). Anal. ($C_{15}H_{20}O_6$) C, H.

(ii) (−)-**12** (R = CPh_3) (790 mg, 2.22 mmol) was treated in the same way as has been described above to give a crude

1,4-addition product (**23**) (1.60 g). Desulfurization with Raney Ni (W-4,15 g) in EtOH (60 ml) gave a colorless glass (1.28 g). Purification by silica gel column chromatography (benzene–AcOEt/1:2) afforded (+)-**24** (430 mg) from (−)-**12** (R = CPh_3) in 65% overall yield.

(2S, 3S, 4S) - (+) - 2 - *Piperonyl* - 3 - (3,4,5 - *trimethoxybenzyl*) - 4 - *hydroxymethyl* - *butan* - 4 - *olide* (**17**)

(i) A mixture of (+)-**19** (2.98 g, 4.78 mmol) and Raney Ni (W-4, 13.2 g) in EtOH (140 ml) was heated to reflux for 6 hr and then filtered through a pad of celite. The filtrates were concentrated *in vacuo* to afford a viscous oil (3.32 g), which was subsequently purified by silica gel column chromatography (ether) to give (+)-**17** (1.18 g, 57%) as a colorless glass of $[\alpha]_D^{20} + 63.5°$ ($c = 1.53$, EtOH); IR ($CHCl_3$) cm^{-1}: 3700–3300, 1770; NMR ($CDCl_3$)δ: 1.6–3.7 (9H, m, $ArCH_2CH \times 2$, CH_2OH), 3.81 (9H, s, $OCH_3 \times 3$), 4.1–4.3 (1H, m, OCH), 5.90 (2H, s, OCH_2O), 6.18 (2H, s, aromatic H), 6.5–6.7 (3H, m, aromatic H); MS 430 (M^+); Anal. ($C_{23}H_{26}O_8$) C, H; and (−)-**20** (24.1 mg, 1.2%) as a colorless glass of $[\alpha]_D^{20} - 12.2°$ ($c = 0.54$, EtOH); IR (film) cm^{-1}: 3500, 1760; NMR ($CDCl_3$)δ: 1.9–3.1 (9H, m, $ArCH_2CH \times 2$, CH_2OH), 3.82 (3H, s, OCH_3), 3.83 (6H, s, $OCH_3 \times 2$), 4.2–4.4 (1H, m, OCH), 5.91 (2H, s, OCH_2O), 6.31 (2H, s, aromatic H), 6.3–6.7 (3H, m, aromatic H); MS: 430 (M^+); Anal. ($C_{23}H_{26}O_8 + \frac{1}{3}H_2O$) C, H.

(ii) A soln of n-BuLi (5.84 mmol) in n-hexane (3.7 ml) was added to a cooled (−78°) soln of 2-(3,4,5-trimethoxyphenyl)-1,3-dithiane (1.6 g, 5.84 mmol) in THF (20 ml) under argon, and the whole was stirred at −78° for 0.5 hr. A soln of **12** (R = CPh_3) (1.60 g, 4.49 mmol) in THF (10 ml) was then added, and the whole was stirred at −78° for 2.5 hr. A soln of piperonyl bromide (1.35 g, 6.29 mmol) in THF (8 ml) was added, and the whole was stirred at −78° for 1.5 hr and then at room temp for 9.5 hr. After the addition of sat. NH_4Claq (10 ml) and sat NaClaq (20 ml), the mixture was extracted with AcOEt (100 ml × 3). The combined extracts were washed successively with 10% HClaq, water, sat $NaHCO_3$aq, water, and sat NaClaq, and then dried over $MgSO_4$. Concentration *in vacuo* afforded a yellow glass (4.25 g). The crude product (**21**) (3.6 g) obtained above was reduced with Raney Ni (W-4, 43 g) in refluxing EtOH (160 ml) for 12 hr. After filtration through celite, the filtrate was concentrated *in vacuo* to give a colorless oil (2.39 g). Purification by silica gel column chromatography (benzene–ether/10:1 and then benzene–AcOEt/2:1) afforded (+)-**22** (238 mg, 9%) as a pale yellow oil of $[\alpha]_D^{20} + 44.0°$ ($c = 0.382$, $CHCl_3$); IR ($CHCl_3$) cm^{-1}: 1769; NMR ($CDCl_3$)δ: 2.2–3.3 (8H, m, $ArCH_2CH \times 2$, OCH_2), 3.63 (6H, s, $OCH_3 \times 2$), 3.74 (3H, s, OCH_3), 4.1–4.3 (1H, m, OCH), 5.8–5.9 (2H, m, OCH_2O), 6.00 (2H, s, aromatic H), 6.3–6.7 (3H, m, aromatic H), 7.1–7.4 (15H, m, aromatic H); MS: 672 (M^+); and (+)-**17** (453 mg, 28%) as a colorless glass of $[\alpha]_D^{20} + 60.4°$ ($c = 1.57$, EtOH).

(+)-**22** was converted to (+)-**17** of $[\alpha]_D^{20} + 59.3°$ ($c = 0.536$, EtOH) in 93% yield by treating it in conc HCl–MeOH (3:97).

(iii) A soln of (+)-**24** (200 mg, 0.676 mmol) of $[\alpha]_D^{20} + 26.7°$ ($c = 0.998$, EtOH) in THF (3 ml) was added to a cooled (−78°) soln of LDA (1.49 mmol) and HMPA (0.26 ml, 1.49 mmol) in THF (4 ml) under argon, after which the whole was stirred at −78° for 1 hr. A soln of piperonyl bromide (320 mg, 1.49 mmol)[25] in THF (2.5 ml) was then added, and the whole was stirred at −78° for 4 hr and then at room temp for 18 hr. The mixture was quenched with 10% HClaq (5 ml) and extracted with AcOEt (80 ml × 2, 60 ml). The combined extracts were successively washed with 10% HClaq, water, sat $NaHCO_3$aq, water, and sat NaClaq, and then dried over $MgSO_4$. Concentration *in vacuo* afforded a pale yellow viscous oil (526 mg). Purification by silica gel column chromatography (benzene–ether/2:1) gave the recovered (+)-**24** (18.7 mg, 9% recovery) and (+)-**17** (164 mg, 62% based on **24** consumed) as a pale yellow viscous oil of $[\alpha]_D^{20} + 62.6°$ ($c = 1.45$, EtOH). Spectral data and tlc behavior of this sample were identical with those prepared in (i).

(2S, 3S, 4S) - (+) - 3 - (3',4',5' - *Trimethoxybenzyl*) - 4 - *piperonyl* - 1,2,5 - *pentanetriol* (**25**)

A solution of (+)-**17** (1.18 g, 2.74 mmol) in THF (10 ml) was added to a stirred suspension of $LiAlH_4$ (417 mg, 11.0 mmol) in THF (50 ml) at −78°, after which the whole was stirred at room temp for 1 hr. The mixture was quenched by the successive addition of water (0.4 ml), 15% NaOHaq (0.4 ml), and water (1.2 ml), and then filtered. The filtrates were concentrated *in vacuo* to afford a colorless glass (1.17 g), which was purified by silica gel column chromatography (AcOEt–EtOH/40:1) to give (+)-**25** (1.16 g, 97%) as a colorless glass of $[\alpha]_D^{20} + 9.17°$ ($c = 0.916$, EtOH). IR ($CHCl_3$) cm^{-1}: 3400. NMR ($CDCl_3$)δ: 1.7–2.2 (2H, m, $ArCH_2CH \times 2$), 2.3–2.8 (4H, m, $ArCH_2 \times 2$), 3.1–4.4 (8H, m, $CH_2OH \times 2$, CHOH), 3.74 (6H, s, $OCH_3 \times 2$), 3.78 (3H, s, OCH_3), 5.83 (2H, s, OCH_2O), 6.24 (2H, s, aromatic H), 6.3–6.7 (3H, m, aromatic H). MS: 434 (M^+). Anal. ($C_{23}H_{30}O_8 + \frac{1}{2}H_2O$) C, H.

(3S, 4S) - (+) - 2 - *Hydroxy* - 3 - (3',4',5' - *trimethoxybenzyl*) - 4 - *piperonyl* - *tetrahydrofurane* (**26**)

A soln of the above **25** (1.10 g, 2.53 mmol) in t-BuOH (30 ml) was added to a soln of $NaIO_4$ (1.08 g, 5.07 mmol) in 50% t-BuOHaq (60 ml)[33], and the whole was stirred at room temp for 50 min. After the addition of sat NaClaq (10 ml), the mixture was extracted with AcOEt (200 ml × 3). The combined extracts were successively washed with 10% $NaHSO_3$aq, sat $NaHCO_3$aq, and sat NaClaq, and then dried over $MgSO_4$. Concentration *in vacuo* afforded a pale yellow viscous oil (967 mg). Purification by silica gel column chromatography ($CHCl_3$–ether/5:1) gave **26** (865 mg, 85%) as a colorless glass of $[\alpha]_D^{20} + 48.1°$ ($c = 1.03$, EtOH). IR ($CHCl_3$) cm^{-1}: 3400. NMR ($CDCl_3$)δ: 1.77 (1H, s, OH), 1.9–2.9 (6H, m, $ArCH_2CH \times 2$), 3.78 (6H, s, $OCH_3 \times 2$), 3.81 (3H, s, OCH_3), 3.8–4.1 (2H, m, CH_2O), 5.1–5.3 (1H, m, CHOH), 5.88 (2H, s, OCHHO), 6.2–6.7 (5H, m, aromatic H). MS: 402 (M^+). Anal. ($C_{22}H_{26}O_7$) C, H.

(+)-*Deoxypodorhizon* (**10**)

A soln of **26** (753 mg, 1.87 mmol) in CH_2Cl_2 (100 ml) was added to a suspension of the Collins reagent, prepared from CrO_3 (1.87 g, 18.7 mmol) and pyridine (3.02 ml, 37.4 mmol), in CH_2Cl_2 (400 ml). After it had been stirred at room temp for 80 min, the mixture was diluted with ether-n-hexane (1:1) (800 ml) and the whole was stirred additional 20 min. The mixture was filtered through celite and the filtrates were concentrated *in vacuo* to give a dark brown oil (750 mg). Purification by silica gel column chromatography ($CHCl_3$–ether/98:2) afforded (+)-**10** (712 mg, 95%) as a pale yellow glass of $[\alpha]_D^{25} + 25.3°$ ($c = 0.400$, $CHCl_3$)) (reported $[\alpha]_D^{25} - 21.6°$ ($c = 0.4$, $CHCl_3$))[1,21] IR ($CHCl_3$) cm^{-1}: 1770. NMR ($CDCl_3$)δ: 2.3–2.7 (4H, m), 2.8–2.9 (2H, m), 3.80 (9H, s, $OCH_3 \times 3$), 3.9–4.3 (2H, m, OCH_2), 5.89 (2H, s, OCH_2O), 6.31 (2H, s, aromatic H), 6.3–6.7 (3H, m, aromatic H). MS: 400 (M^+). Anal. ($C_{22}H_{24}O_7$) C, H.

(+)-*Isostegane* (**28**)

(+)-Isostegane was prepared by a modification of the Schlessinger procedure for racemic modification.[13]

A soln of (−)-**9**[1,12] (200 mg, 5 mmol) of $[\alpha]_D^{25} - 25.2°$ ($c = 0.410$, $CHCl_3$) in CH_2Cl_2 (200 ml) was added dropwise over a period of 40 min to a green soln of VOF_3 (1.86 g, 15 mmol) and CF_3COOH (32 ml) in CH_2Cl_2 (60 ml) at −40° under argon. The whole was stirred at −40° for 5 hr and then neutralized with sat $NaHCO_3$aq. The mixture was extracted with AcOEt (700 ml × 3). The combined extracts were washed successively with water and sat NaClaq, and then dried over $MgSO_4$. Concentration *in vacuo* afforded brown foam (1.99 g). Purification by silica gel column chromatography (benzene–ether/10:1) gave (+)-**28** (1.27 g, 64%) as colorless pillars of m.p. 206–207° (from MeOH).[35]

$[\alpha]_D^{23}$ + 154° (c = 0.700, $CHCl_3$). IR (KBr) cm^{-1}: 1781; ($CHCl_3$): 1780. NMR (C_6D_6)δ: 1.3–2.2 (5H, m), 2.8–3.9 (3H, m), 3.38 (3H, s, OCH_3) 3.47 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 5.39 (1H, d of AB, J_{AB} = 1 Hz, OCHHO), 5.45 (1H, d of AB, J_{AB} = 1 Hz, OCHHO), 6.3–6.7 (3H, m, aromatic H). MS: 398 (M^+), 383 (M^+–CH_3), 367 (M^+–OCH_3). Anal. ($C_{22}H_{22}O_7$) C, H.

(−)-*Isostegane* (**27**)

(−)-Isostegane was synthesized by the procedure described above, starting from (+)-**10** of $[\alpha]_D^{25}$ + 25.3 (c = 0.400, $CHCl_3$). Colorless prisms of m.p. 169–170° (from MeOH).[35] $[\alpha]_D^{23}$ − 161° (c = 0.668, $CHCl_3$). Anal. ($C_{22}H_{22}O_7$) C, H. Spectral data and TLC behavior were identical with those of (+)-**28**.

(−)-*Stegane* (**6**)

(+)-Isostegane **28** (7.43 g, 18.7 mmol) of $[\alpha]_D^{23}$ + 154° (c = 0.700, $CHCl_3$) was heated until it melted at 215°, then continued to heat it at 195° for 3.5 hr under argon. After it had cooled to room temp, a small amount of benzene–$CHCl_3$ was added to dissolve the solid. Purification by HPLC (Waters LC 500, Prep PAK 500 silica, benzene–AcOEt/16:1, 100 ml/min) gave (+)-**28** (5.04 g, 61% recovery) and (−)-**6** (2.93 g, 39%) as colorless pillars of m.p. 179–179.5° (from MeOH). $[\alpha]_D^{23}$ − 196° (c = 0.500, $CHCl_3$). IR (KBr) cm^{-1}: 1767; ($CHCl_3$): 1771. NMR (C_6D_6)δ: 1.5–1.8 (1H, m), 1.8–2.3 (2H, m), 2.4–2.6 (1H, m), 2.8–3.2 (3H, m), 3.37 (3H, s, OCH_3), 3.50 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.4–3.7 (1H, m), 5.41 (1H, d of AB, J_{AB} = 1 Hz, OCHHO), 5.46 (1H, d of AB, J_{AB} = 1 Hz, OCHHO), 6.39 (2H, s, aromatic H), 6.67 (1H, s, aromatic H). MS: 398 (M^+), 383 (M^+–CH_3), 367 (M^+–OCH_3) Anal. ($C_{22}H_{22}O_7$) C, H.

(+)-*Stegane* (**8**)

(+)-Stegane was synthesized by the procedure described above starting from (−)-**27** of $[\alpha]_D^{23}$ − 161° (c = 0.668, $CHCl_3$). Colorless pillars of m.p. 178–179° (from MeOH). $[\alpha]_D^{23}$ + 196° (c = 0.520, $CHCl_3$). Anal. ($C_{22}H_{22}O_7$) C, H.

(+)-*Steganacin* (**7**)

A mixture of (+)-**8** (130 mg, 0.327 mmol) of $[\alpha]_D^{23}$ + 195° (c = 0.500, $CHCl_3$), prepared from (−)-**27**, and DDQ (297 mg, 1.18 mmol) in AcOH (3 ml) was stirred at 75° for 50 hr. The whole was then diluted with AcOEt (150 ml). The AcOEt soln was washed successively with 15% NaOHaq, water, and sat. NaClaq, and then dried over $MgSO_4$. Concentration *in vacuo* afforded brown foam (57.6 mg). Purification by silica gel TLC (benzene–ether/9:1) gave (+)-**8** (21.8 mg, 17% recovery), (+)-**7** (13.6 mg, 11% based on **8** consumed) as colorless foam of $[\alpha]_D^{23}$ + 135° (c = 0.700, $CHCl_3$) (reported $[\alpha]_D^{23}$ − 114° (c = 0.74, $CHCl_3$))[3,27]; IR ($CHCl_3$) cm^{-1}: 1774, 1743; 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), 3.87 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.8–4.1 (2H, m), 4.2–4.4 (1H, m), 5.82 (1H, d, J = 10 Hz, CHOAc), 6.03 (2H, s, OCH_2O), 6.45 (1H, s, aromatic H), 6.60 (1H, s, aromatic H), 6.91 (1H, s, aromatic H); MS: 456 (M^+), 396, 366; HRMS Calc for $C_{24}H_{24}O_9$: 456.1421. Found: 456.1429, and (+)-episteganacin (0.8 mg, 0.7%) as a colorless glass; NMR ($CDCl_3$)δ: 2.12 (3H, s, $OCOCH_3$), 2.2–3.4 (4H, m), 3.55 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.0–4.4 (2H, m), 5.88 (1H, d, J = 8 Hz, CHOAc), 6.03 (1H, d of AB, J = 1 Hz, OCHHO), 6.06 (1H, d of AB, J = 1 Hz, OCHHO), 6.51 (1H, s, aromatic H), 6.76 (1H, s, aromatic H), 6.78 (1H, s, aromatic H); MS: 456 (M^+).

(4R)-4-*Bromostegane* (**4**)

A mixture of (−)-**6** (100 mg, 0.25 mmol) of $[\alpha]_D^{23}$ − 196° (c = 0.500, $CHCl_3$), prepared from (+)-**28**, NBS (49.1 mg, 0.28 mmol), and BPO (1.2 mg, 0.005 mmol) in CCl_4 (36 ml) was stirred under reflux for 2 hr. The whole was then diluted with AcOEt (200 ml). The AcOEt soln was washed successively with 15% NaOHaq, 10% $Na_2S_2O_3$aq, and sat NaClaq, and then dried over $MgSO_4$. Concentration *in vacuo* afforded **4** (116 mg, 97%) as a pale yellow glass. IR ($CHCl_3$) cm^{-1}: 1778. NMR ($CDCl_3$)δ: 2.4–3.2 (3H, m), 3.5–3.7 (1H, m), 3.7–3.9 (1H, m, CHCHHO), 3.80 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.49 (1H, dd, J = 7, 9 Hz, CHCHHO), 5.10 (1H, d, J = 11 Hz, CHBr), 6.02 (1H, s, aromatic H), 6.55 (1H, s, aromatic H), 6.82 (1H, s, C5-H). NOE measurements: A 13% increase at C5-H was observed when C4-H (δ5.10) was irradiated. MS: 478, 476 (M^+), 396, 366, 300.

(−)-*Steganol* (**3**)

The crude **4** (2.08 g), prepared as above, was added to water–THF (1:9, 30 ml) under ice-bath cooling. The whole was then stirred at 0° for 24 hr. Subsequently the mixture was diluted with benzene–THF (10:1, 220 ml) and dried over $MgSO_4$. Concentration *in vacuo* gave a faint yellow glass (1.16 g). Purification by silica gel column chromatography (n-hexane–ether/1:2) gave (−)-**3** (799 mg, 85% overall yield from **6**) as a colorless glass of $[\alpha]_D^{23}$ − 190° (c = 0.870, $CHCl_3$) (reported $[\alpha]_D^{23}$ − 163° (c = 0.87, $CHCl_3$))[3]; IR ($CHCl_3$) cm^{-1}: 3600–3400, 1772; NMR ($CDCl_3$)δ: 2.1–2.7 (4H, m), 2.8–3.2 (1H, m), 3.8–4.0 (1H, m), 3.68 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.3–4.6 (2H, m, OCH_2), 5.99 (2H, brs, OCH_2O), 6.44 (1H, s, aromatic H), 6.54 (1H, s, aromatic H), 6.75 (1H, d, aromatic H); MS: 414 (M^+), 396, 330, 315; Anal. ($C_{22}H_{22}O_8 + \frac{1}{2}H_2O$) C, H; and (−)-**2** (5.8 mg, 0.6%).

(−)-*Steganacin* (**1**)

Acetyl chloride (0.02 ml, 0.3 mmol) was added to a cooled (0°) soln of (−)-**3** (50 mg, 0.121 mmol) of $[\alpha]_D^{23}$ − 190° (c = 0.870, $CHCl_3$) in pyridiene (2 ml); the whole was then stirred at room temp for 2 hr. After the additon of sat NaClaq (20 ml), the mixture was diluted with AcOEt (150 ml) and washed successively with 10% HClaq, water, sat. $NaHCO_3$aq, water, and sat NaClaq. The AcOEt layer was dried over $MgSO_4$. Concentration *in vacuo* afforded a red glass (82.7 mg). Purification by silica gel column chromatography (benzene–ether/10:1) gave (−)-**1** (39.6 mg, 72%) as a colorless glass of $[\alpha]_D^{23}$ − 127° (c = 0.740, $CHCl_3$) (reported $[\alpha]_D^{23}$ − 114° (c = 0.74, $CHCl_3$)).[3,27] IR ($CHCl_3$) cm^{-1}: 1775, 1736. NMR ($CDCl_3$)δ: 1.90 (3H, s, OCH_3), 2.3–2.8 (2H, m), 2.9–3.2 (1H, m), 3.73 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.8–4.1 (2H, m), 4.2–4.4 (1H, m), 5.83 (1H, d, J = 9 Hz, CHOAc), 6.02 (2H, s, OCH_2O), 6.45 (1H, s, aromatic H), 6.60 (1H, s, aromatic H), 6.91 (1H, s, aromatic H). MS: 456 (M^+), 396, 366, 300. Anal. ($C_{24}H_{24}O_9$) C, H.

(−)-*Steganone* (**5**)

A soln of (−)-**3** (50 mg, 0.121 mmol) of $[\alpha]_D^{23}$ − 190° (c = 0.870, $CHCl_3$) in CH_2Cl_2 (5 ml) was added to a suspension of PCC (52.3 mg, 0.237 mmol) and AcONa (4.1 mg, 0.05 mmol) in CH_2Cl_2 (10 ml) at room temp. The whole was then stirrred for 3 hr and diluted with ether–n-hexane (1:1/10 ml). The mixture was stirred for 20 min and filtered through celite. The filtrate was concentrated *in vacuo* to give a colorless solid (50.6 mg). Purification by silica gel column chromatography (n-hexane–ether/1:1) gave (−)-**5** (40.2 mg, 81%) as colorless pillars of m.p. 157–158° (from MeOH) (reported 155–156°,[3] 155.5–157°[7c]). $[\alpha]_D^{23}$ − 191° (c = 0.760, $CHCl_3$) (reported $[\alpha]_D^{23}$ − 202° (c = 0.76, $CHCl_3$),[3] − 140° (c = 1.16, $CHCl_3$),[4a] − 197° (c = 0.77, $CHCl_3$)[7c]). IR (KBr) cm^{-1}: 1769, 1672. NMR ($CDCl_3$)δ: 2.5–3.3 (4H, m $ArCH_2CH$), 3.61 (3H, s, OCH_3), 3.89 (6H, s, OCH_3 × 2), 4.2–4.6 (2H, m, OCH_2), 6.11 (1H, brs, OCH_2O), 6.54 (1H, s, aromatic H), 6.64 (1H, s, aromatic H), 7.53 (1H, s, aromatic H). MS: 412 (M^+). Anal. ($C_{22}H_{20}O_8$) C, H.

(−)-*Episteganol* (**2**)

Reduction of steganone was carried out according to the

procedure used for the racemic modification reported by Ziegler.[8c]

A soln of L-Selectride (0.1 mmol) in THF (0.1 ml) was added to a cooled (−78°) soln of (−)-**5** (35 mg, 0.085 mmol) in THF (3 ml). The whole was then stirred at −78° for 40 min and quenched with acetone (0.4 ml). After dilution with AcOEt (100 ml), the mixture was washed with sat K_2CO_3aq and dried over $MgSO_4$. Concentration *in vacuo* afforded a colorless solid (57 mg). Recrystallization from CH_2Cl_2–n-hexane gave (−)-**2** (24.5 mg, 69%) as colorless needles of m.p. 244.5–245.5°. $[\alpha]_D^{23}$ − 107° (*c* = 0.67, pyridine) (reported $[\alpha]_D^{23}$ − 126° (*c* = 0.68, pyridine)).[3] IR (KBr) cm^{-1}: 3590, 1782. 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), 4.08 (1H, dd of ABX, J_{AB} = 9 Hz, J_{BX} = 8 Hz, $OCHCH$), 4.99 (1H, dd of A'B'X, $J_{A'B'}$ = 4 Hz, $J_{A'X}$ = 8 Hz, $HOCHCH$), 6.02 (1H, d, J = 1.5 Hz, $OCHHO$), 6.07 (1H, d, J = 1.5 Hz, $OCHHO$), 6.50 (1H, s, aromatic H), 6.70 (1H, s, aromatic H), 7.08 (1H, s, aromatic H). MS: 414 (M^+). Anal. ($C_{22}H_{22}O_8 + \frac{1}{3}H_2O$) C, H.

(+)-12-*Bromoisostegane* (**29**)

This compound was prepared according to the procedure for the racemic modification reported by Schlessinger.[13]

A mixture of (+)-**28** (50 mg, 0.126 mmol) and pyridinium bromide perbromide (48 mg, 0.152 mmol) in $CHCl_3$ (10 ml) was stirred at room temp for 24 hr. After dilution with AcOEt (90 ml), the whole was washed successively with 10% HClaq, water, 10% $Na_2S_2O_3$aq, water, sat $NaHCO_3$aq, water, and sat. NaClaq, and then dried over $MgSO_4$. Concentration *in vacuo* afforded a colorless solid (67 mg) of m.p. 156–158°. $[\alpha]_D^{23}$ + 122° (*c* = 1.04, $CHCl_3$). IR (KBr) cm^{-1}: 1780. NMR ($CDCl_3$)δ: 1.9–2.5 (4H, m), 2.5–2.7 (1H, m), 3.55 (3H, s, OCH_3), 3.6–3.9 (2H, m), 3.94 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.2–4.4 (1H, m), 5.99 (1H, d, J = 1 Hz, $OCHHO$), 6.02 (1H, d, J = 1 Hz, $OCHHO$), 6.63 (1H, s, aromatic H), 6.72 (1H, s, aromatic H). MS: 478, 476 (M^+). Anal. ($C_{22}H_{21}O_7Br$) C, H.

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[19]A facile proton abstraction from butenolide system by a base has been reported: G. A. Krau and B. Roth, *Tetrahedron Letters* 3129 (1977).

[20]Because of the unstability of trityl ether (**11**, **12**, **16**) in such solvents as THF–water and MeOH–water, the two-phase system described in the text was employed. The addition of the crown ether was found to accelerate the reaction rate to a certain extent.

[21]The optical antipode of **10** is the natural lignan lactone. [a]P. B. Macdoniel and J. R. Cole, *J. Pharm. Sci.* **62**, 1992 (1972); [b]S. Nishibe, S. Hisada and I. Inagaki, *Yakugaku Zassh* **94**, 522 (1974).

[22]It is reasonable to assume that epimerization at the α-position of lactone CO would lead to the thermodynamically stable *trans* isomer **17**.

[23]No trace of **20** could be detected by the usual analytical method (TLC, NMR).

[24]Direct recrystallization of the crude **23** gave the pure **23** in 59% yield, as has been described in the Experimental.

[25]Two equivalents of piperonyl bromide were necessary to obtain **17**, probably due to the destruction of piperonyl bromide by the base, such as lithium alkoxide, of the dianion.

[26]Jones oxidation gave also **10** in a comparable yield.

[27]The optical rotation of the natural steganacin kindly provided by Prof. A. T. Sneden was $[\alpha]_D^{23}$ − 155° (*c* = 0.24, $CHCl_3$). Although this value is not very accurate because of the small amount of the material, the sign of the optical rotation was definitely negative.

[28]Detail of the benzylic oxidation of stegane by NBS–BPO will be reported in due course.

[29]Bromination of the racemic isostegane has been reported by Schlessinger; see Ref. 13.

[30]Melting points were measured using Büchi 510 m.p. apparatus and are not corrected. Optical rotations were taken with a JASCO DIP-181 automatic polarimeter. IR were taken with a JASCO Infrared Spectrometer Model-DS-402G. NMR were taken with a JNM–PS 100 Spectrometer and with a JEOL FX-100 Spectrometer. Chemical shift values are expressed in ppm relative to internal TMS. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Mass spectra (MS) were taken with a JEOL-01 SG-2 Mass Spectrometer.

[31]Phenylselenyl bromide could be used in place of diphenyl diselenide.

[32]A mixture of two diastereomers was used; the difference in the reactivity between the two diastereomers was negligible.

[33]This reaction could be conveniently carried out in an AcOEt–water two-phase system in place of the solvent described.

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[35]The melting points of **27** and **28** were different, probably because of the dimorphous state. The other data, except for the sign of the optical rotation, were completely identical with each other.