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Stereoselective Reactions. VII.¹⁾ Synthesis of Racemic and Optically Pure Stegane, Isostegane, Picrostegane, and Isopicrostegane via Highly Selective Isomerization²⁾

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Novel isomerizations of isostegane (**6**) into the three other possible isomers, namely, isopicrostegane (**7**), picrostegane (**8**), and stegane (**9**) are described. All the possible enantiomers were synthesized.

Keywords— isomerization; dibenzocyclooctadiene; antitumor lignan lactone; atropisomerization; enantiomer; asymmetric synthesis; steganacin; ¹³C-NMR

The dibenzo[4,5:6,7]cycloocta[1,2-*c*]furanone system is found in the carbon skeleton of a novel type of lignan lactones including steganacin (**1**), steganangin (**2**), steganol (**3**), and steganone (**4**).^{3,4)} Steganacin and steganangin are known to be endowed with remarkable antitumor activity.³⁾ Since the initial report by Kupchan on the isolation of **1**—**4**, considerable efforts have been expended on the total syntheses of these antitumor lignan lactones.^{1,4-9)} Schlessinger *et al.* have reported that oxidation of (±)-deoxypodorhizon ((±)-**5**) resulted in the stereoselective formation of (±)-isostegane ((±)-**6**), whose structure was established by X-ray analysis.¹⁰⁾ Brown and Robin have also reported the syntheses of (±)-isostegane ((±)-**6**), (±)-isopicrostegane ((±)-**7**), and (±)-picrostegane ((±)-**8**).¹¹⁾ Although three among the four possible isomers of the steganacin type lignan skeleton have been synthesized in racemic forms as described above, stegane ((±)-**9**), the parent skeleton of steganacin (**1**), has remained unknown. During our studies aimed at the asymmetric total synthesis of the antitumor lignan lactone steganacin (**1**),¹⁾ we found a novel isomerization reaction of (±)-isostegane ((±)-**6**) into (±)-stegane ((±)-**9**), (±)-picrostegane ((±)-**8**), and (±)-isopicrostegane ((±)-**7**). In this paper we describe the novel and highly selective isomerization of these stegane isomers and, further, their application to the synthesis of all of the possible enantiomers.

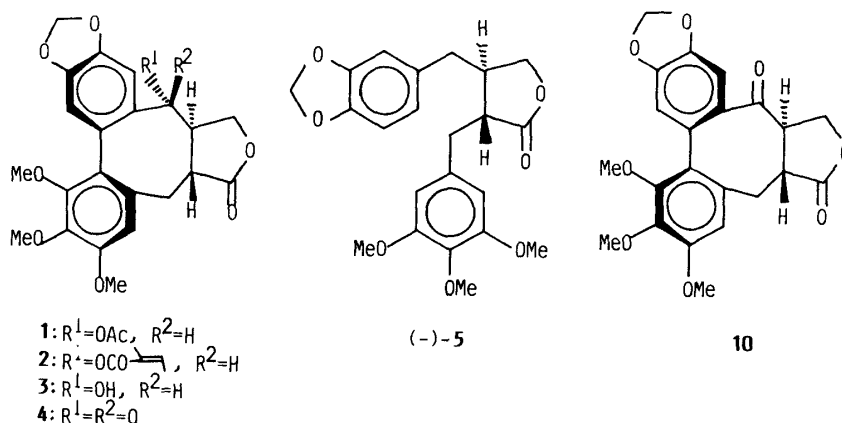


Fig. 1

Isomerization of ($\pm$)-Isostegane (($\pm$)-6). First Synthesis of ($\pm$)-Stegane (($\pm$)-9)

The four possible isomers bearing the steganacin skeleton are related as follows. Rotational isomerization of a bond joining two aromatic rings of isostegane (6) leads to stegane (9). In the same way, isopicrostegane (7) is correlated to picrostegane (8). On the other hand, isomerization at the α -position of lactone carbonyl of isostegane (6) leads to isopicrostegane (7), and that in the case of stegane (9) leads to picrostegane (8). These relations are shown in Chart 1.¹²⁾

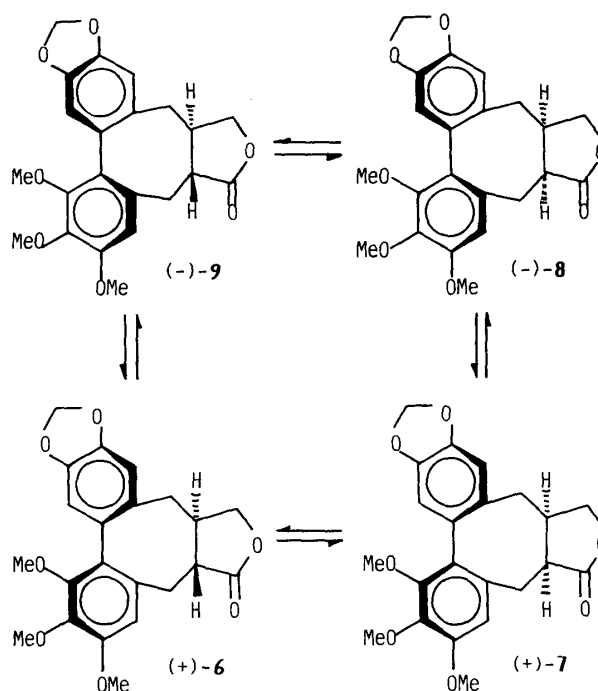


Chart 1

Isomerization of ($\pm$)-isostegane (($\pm$)-6), prepared from ($\pm$)-5 according to the Schlessinger procedure,¹⁰⁾ was first attempted using the similar condition (KOH, EtOH, reflux) to that described by Kende *et al.* for the isomerization of ($\pm$)-isosteganone (($\pm$)-10) to ($\pm$)-steganone (($\pm$)-4).^{5b)} However, ($\pm$)-6 was recovered unchanged. Then ($\pm$)-6 was treated with AcOK (10 eq) in AcOH at reflux for 22 h.¹³⁾ Careful purification of the crude products by medium pressure liquid chromatography on silica gel afforded all four possible isomers, ($\pm$)-6 (14% recovery), ($\pm$)-7 (38%), ($\pm$)-8 (19%), and ($\pm$)-9 (1%), as shown in Table I (entry 1). Proton nuclear magnetic resonance ($^1\text{H-NMR}$) and infrared (IR) spectra and melting points of ($\pm$)-6, ($\pm$)-7, and ($\pm$)-8 agreed well with those reported.^{10,11)} The fourth compound was assigned as ($\pm$)-stegane (($\pm$)-9) based on the spectral data and isomerization studies. $^{13}\text{C-NMR}$ (Table II) and mass spectra (MS) of ($\pm$)-9 confirmed that this compound was an isomer bearing the same carbon framework. The results of isomerization studies with the racemic and optically active forms are summarized in Table I.¹⁴⁾

Isomerization of ($-$)-stegane (($-$)-9) with NaOH in aq. EtOH afforded, after acidification with aq. HCl for relactonization, ($-$)-9 and ($-$)-8 in 50 and 45% isolated yields, respectively (entry 2). However, ($\pm$)-8 was recovered unchanged from the attempted isomerization of ($\pm$)-8 under the same condition as described above (entry 4). This seems to imply that isomerization at the α -position of the lactone carbonyl and opening of the lactone ring are the competitive processes, and picrostegane (8) is the more stable product in the isomerization. This was confirmed by the isomerization with *tert*-BuOK in *tert*-BuOH, under the condition such that hydrolysis of the lactone ring is minimized. In fact ($-$)-9 was

TABLE I. Isomerizations of 6, 7, 8, and 9^{a)}

Entry	Conditions	Isostegane (6) (%)	Isopicrostegane (7) (%)	Picrostegane (8) (%)	Stegane (9) (%)
1	AcOK–AcOH 120 °C, 22 h	14 ^{d)}	38	19	1
2 ^{b, c)}	NaOH–aq. EtOH r.t., 24 h	0	0	45	50 ^{d)}
3 ^{c)}	<i>tert</i> -BuOK– <i>tert</i> -BuOH 70 °C, 24 h	0	0	51	5 ^{d)}
4 ^{b)}	NaOH–aq. EtOH r.t., 24 h	0	0	99 ^{d)}	0
5 ^{c)}	<i>tert</i> -BuOK– <i>tert</i> -BuOH 70 °C, 48 h	0	0	81 ^{d)}	6
6 ^{b)}	NaOH–aq. EtOH r.t., 24 h	99 ^{d)}	0	0	0
7	<i>tert</i> -BuOK– <i>tert</i> -BuOH 70 °C, 24 h	99 ^{d)}	0	0	0
8	Neat, 195 °C 3.5 h	61 ^{d)}	0	0	39
9	Neat, 195 °C 2 h	59	0	0	41 ^{d)}
10 ^{c)}	Neat, 190 °C 10 min	0	60	40 ^{d)}	0

a) Isolated yields. b) Aqueous HCl was added to relactonize the products.
c) In optically active form. d) Starting material.

converted to a mixture of (–)-8 and (–)-9, consisting mainly of (–)-8 with the preference of 10:1 (entry 3). Picrostegane (–)-8 was also isomerized to the mixture of (–)-8 and (–)-9, consisting mainly of (–)-8 with preference of 14:1 (entry 5).

Isomerization of (±)-isostegane ((±)-6) into (±)-isopicrostegane ((±)-7) was not observed under the basic conditions described above (entry 6 and 7), though (±)-7 is known to isomerize into (±)-6.¹¹⁾

Thermal isomerization by rotation of the pivot bond was also examined.¹⁵⁾ On being heated without solvent at 195 °C for 3.5 h, (±)-6 gave a mixture of (±)-6 (61%) and (±)-stegane ((±)-9) (39%) as described in the synthesis of (–)-9 from (+)-6¹⁾ (entry 8). A mixture of (±)-9 (41%) and (±)-6 (59%) was obtained from (±)-9 (entry 9). (–)-Picrostegane ((–)-8) was converted to a mixture of (–)-8 (40%) and (+)-7 (60%) (entry 10).¹¹⁾

These findings supported the structure of newly found stegane (9) in racemic and optically active forms. The isomerization of (±)-6 into a mixture of all four possible isomers with AcOK in refluxing AcOH may be attributed to the sum of the rotational isomerization and isomerization at the α-position of the lactone carbonyl.

As a result of these highly selective isomerizations, all four possible isomers in racemic modifications are now available. ¹³C-NMR data for these four isomers are presented in Table II.

Synthesis of Optically Pure Isostegane (6), Isopicrostegane (7), Picrostegane (8), and Stegane (9)

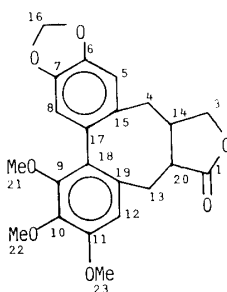
In previous papers,^{1,4b,c,16)} we have presented highly efficient asymmetric syntheses of optically pure (–)- and (+)-deoxypodorhizon ((–)-5 and (+)-5). Syntheses of optically pure stegane isomers were carried out starting from (–)-5 and (+)-5.

Nonphenolic oxidative coupling of (–)-5 gave (+)-isostegane ((+)-6) of $[\alpha]_D^{23} +154^\circ$

TABLE II. ^{13}C -NMR of **6**, **7**, **8**, and **9**^{a)}

Carbon ^{b)}	Isostegane (6)	Isopicrostegane (7)	Picrostegane (8)	Stegane (9)
C-13	32.1 t	29.3 t	30.1 t	32.3 t
C-4	33.8 t	35.7 t	30.6 t	33.6 t
{ C-20	46.7 d	40.3 d	37.1 d	39.8 d
{ C-14	49.8 d	42.4 d	44.7 d	43.0 d
C-23	55.8 q	55.9 q	56.1 q	55.8 q
{ C-22	60.4 q	60.7 q	60.7 q	60.5 q
{ C-21	60.6 q	60.9 q	61.0 q	60.7 q
C-3	69.7 t	72.9 t	69.3 t	70.8 t
C-16	100.9 t	101.0 t	101.2 t	101.0 t
C-12	107.4 d	108.4 d	107.6 d	108.9 d
{ C-8	108.5 d	110.0 d	110.2 d	110.1 d
{ C-5	111.5 d	111.9 d	110.9 d	111.4 d
C-19	126.2 s	126.9 s	126.9 s	127.5 s
{ C-18	128.1 s	129.4 s	128.9 s	129.8 s
{ C-17	132.3 s	131.7 s	130.0 s	130.6 s
C-15	135.8 s	132.2 s	133.7 s	133.4 s
C-10	140.6 s	141.1 s	141.0 s	140.8 s
{ C-7	145.6 s	145.7 s	146.2 s	146.1 s
{ C-6	147.4 s	147.4 s	147.4 s	146.9 s
C-9	151.6 s	150.3 s	150.8 s	151.3 s
C-11	153.1 s	152.1 s	153.4 s	152.5 s
C-1	176.2 s	177.1 s	179.1 s	178.3 s

- a) Taken in CDCl_3 using TMS as an internal standard. The figures after numbers are the multiplicities in the case of off-resonance. s, singlet; d, doublet; t, triplet; q, quartet.
 b) Assignment in parentheses may be interchanged.



(CHCl_3). Thermal isomerization of (+)-**6** gave (–)-stegane ((–)-**9**) of $[\alpha]_{\text{D}}^{23} - 196^\circ$ (CHCl_3). Isomerization of (–)-**9** with NaOH in aq. EtOH gave (–)-picrostegane ((–)-**8**) of $[\alpha]_{\text{D}}^{23} - 57.2^\circ$ (CHCl_3). (–)-**8** was converted to (+)-isopicrostegane ((+)-**7**) of $[\alpha]_{\text{D}}^{23} + 155^\circ$ (CHCl_3). The absolute stereochemistries of these isomers are shown in Chart 1. The optical antipodes of these isomers were also synthesized from (+)-**5**.

The usefulness of the present isomerization reactions, especially the synthesis of (–)-stegane ((–)-**9**), was demonstrated in the successful asymmetric total synthesis of the natural antitumor lignan lactone steganacin (**1**).^{1,4b)}

Experimental¹⁷⁾

(–)-Isostegane ((–)-**6**)—(–)-Isostegane was synthesized by the same procedure as used for the synthesis of (+)-**6**¹⁾ starting from (+)-deoxypodorhizon ((+)-**5**)^{1,4b,16)} of $[\alpha]_{\text{D}}^{25} + 25.3^\circ$ ($c = 0.400$, CHCl_3) in 41% yield. Colorless prisms of mp 169–170°C¹⁸⁾ (from MeOH). $[\alpha]_{\text{D}}^{23} - 161^\circ$ ($c = 0.668$, CHCl_3). Anal. Calcd for $\text{C}_{22}\text{H}_{22}\text{O}_7$: C, 66.32; H, 5.57. Found: C, 66.04; H, 5.56. Spectral data (^1H -NMR, IR (CHCl_3)) and thin layer chromatography (TLC) behavior were identical with those of (+)-isostegane ((+)-**6**).¹⁾ The present crystalline (–)-isostegane was considered

to be dimorphous with respect to (+)-6,¹¹ showing different mp and IR spectrum (KBr).

(±)-Isostegane ((±)-6)—(±)-Isostegane of mp 172—174.5 °C (from ether) was synthesized from (±)-5 by the same procedure. Spectral data and melting point were identical with those reported.^{10,11}

(+)-Stegane ((+)-9)—(+)-Stegane was synthesized by the thermal atropisomerization of (−)-isostegane ((−)-6) according to the procedure described for the synthesis of (−)-9.¹¹ Mp 179 °C (from MeOH). $[\alpha]_D^{23} + 196^\circ$ ($c = 0.520$, CHCl₃). Anal. Calcd for C₂₂H₂₂O₇: C, 66.32; H, 5.57. Found: C, 66.06; H, 5.61. Spectral and TLC behavior were identical with those of (−)-9.¹¹

(±)-Stegane ((±)-9) (Entry 8)—(±)-Stegane was synthesized by the same procedure starting from (±)-isostegane ((±)-6). Colorless prisms of mp 130.5—133 °C (from MeOH). IR $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$: 1767 (lactone). Anal. Calcd for C₂₂H₂₂O₇: C, 66.32; H, 5.57. Found: C, 66.06; H, 5.64.

(−)-Picrostegane ((−)-8) (Entry 2)—A solution of 2 N aq. NaOH (1.5 ml, 3 mmol) was added to a solution of (−)-stegane ((−)-9)¹¹ (150 mg, 0.376 mmol) of $[\alpha]_D^{23} - 196^\circ$ ($c = 0.500$, CHCl₃) in EtOH (10 ml) and the whole was stirred at room temperature for 24 h. A solution of 10% aq. HCl (6 ml) was added and the whole was stirred for an additional 24 h. The mixture was made alkaline with satd. aq. NaHCO₃ and extracted with AcOEt (100 ml × 3). The combined extracts were washed with satd. aq. NaCl and dried over MgSO₄. Concentration *in vacuo* afforded a colorless foam (160 mg). Purification by silica gel TLC (benzene–AcOEt (10:1)) gave (−)-stegane ((−)-9) (74.4 mg, 50% recovery) and (−)-picrostegane ((−)-8) (66.9 mg, 45%) as colorless pillars of mp 181—181.5 °C (from MeOH). $[\alpha]_D^{23} - 57.2^\circ$ ($c = 0.690$, CHCl₃). IR $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$: 1782 (lactone), 1598 (aromatic). ¹H-NMR (C₆D₆) δ : 1.8—2.5 (5H, m), 2.6—2.8 (1H, m), 3.32 (3H, s, OCH₃), 3.44 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 3.6—3.8 (2H, m), 5.35 (1H, d of ABq, $J_{AB} = 1 \text{ Hz}$, OCH₂O), 5.43 (1H, d of ABq, $J_{AB} = 1 \text{ Hz}$, OCH₂O), 6.18 (1H, s, aromatic H), 6.41 (1H, s, aromatic H), 6.82 (1H, s, aromatic H). MS m/z : 398 (M⁺), 367, 353, 329. Anal. Calcd for C₂₂H₂₂O₇: C, 66.32; H, 5.57. Found: C, 66.04; H, 5.51.

(+)-Picrostegane ((+)-8)—(+)-Picrostegane was synthesized by the same procedure as used for (−)-8 starting from (+)-stegane ((+)-9)¹¹ of $[\alpha]_D^{23} + 196^\circ$ ($c = 0.520$, CHCl₃). Colorless pillars of mp 180—182 °C (from MeOH). $[\alpha]_D^{23} + 59.5^\circ$ ($c = 0.672$, CHCl₃). Anal. Calcd for C₂₂H₂₂O₇: C, 66.32; H, 5.57. Found: C, 66.40; H, 5.62. Spectral data were identical with those of (−)-8.

(±)-Picrostegane ((±)-8)—(±)-Picrostegane was synthesized by the same procedure as used for (−)-8 starting from (±)-stegane ((±)-9). Colorless needles of mp 182—184 °C (from CHCl₃–ether). IR $\nu_{\max}^{\text{Nujol}} \text{cm}^{-1}$: 1760 (lactone). Spectral data (¹H-NMR, MS) and TLC behavior were identical with those of (+)- and (−)-picrostegane.

(+)-Isopicrostegane ((+)-7) (Entry 10)—(−)-Picrostegane ((−)-8) (22.4 mg, 0.056 mmol) of $[\alpha]_D^{23} - 57.2^\circ$ ($c = 0.690$, CHCl₃) was heated to melt at 190 °C for 10 min under argon. Purification by silica gel TLC (benzene–AcOEt (7:1)) gave (−)-picrostegane ((−)-8) (8.9 mg, 40% recovery) and (+)-isopicrostegane ((+)-7) (13.5 mg, 60%) as colorless plates of mp 194—195 °C (from MeOH). $[\alpha]_D^{23} + 155^\circ$ ($c = 0.220$, CHCl₃). IR $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$: 1760 (lactone), 1594 (aromatic). ¹H-NMR (C₆D₆) δ : 1.6—2.0 (2H, m), 2.1—2.5 (3H, m), 2.9—3.1 (1H, m), 3.2—3.4 (1H, m), 3.5—3.7 (1H, m), 3.48 (3H, s, OCH₃), 3.63 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 5.40 (1H, d of ABq, $J_{AB} = 1 \text{ Hz}$, OCH₂O), 5.44 (1H, d of ABq, $J_{AB} = 1 \text{ Hz}$, OCH₂O), 6.44 (1H, s, aromatic H), 6.92 (1H, s, aromatic H), 7.31 (1H, s, aromatic H). MS m/z : 398 (M⁺), 383, 368, 353. Anal. Calcd for C₂₂H₂₂O₇: C, 66.32; H, 5.57. Found: C, 66.04; H, 5.48.

(−)-Isopicrostegane ((−)-7)—(−)-Isopicrostegane was synthesized by the same procedure as described above for (+)-isopicrostegane ((+)-7) starting from (+)-picrostegane ((+)-8) of $[\alpha]_D^{23} + 59.5^\circ$ ($c = 0.672$, CHCl₃). Colorless pillars of $[\alpha]_D^{23} - 158^\circ$ ($c = 0.662$, CHCl₃). Anal. Calcd for C₂₂H₂₂O₇: C, 66.32; H, 5.57. Found: C, 66.20; H, 5.63. Spectral data and TLC behavior were identical with those of (+)-isopicrostegane ((+)-7).

(±)-Isopicrostegane ((±)-7)—(±)-Isopicrostegane was synthesized by the same procedure as described above starting from (±)-picrostegane ((±)-8). Colorless prisms of mp 179—181 °C (from CHCl₃–ether). IR $\nu_{\max}^{\text{Nujol}} \text{cm}^{-1}$: 1780 (lactone). Spectral data and TLC behavior were identical with those of (+)- and (−)-isopicrostegane and those reported.¹¹

Theraml Isomerization of (±)-Stegane ((±)-9) to (±)-Isostegane ((±)-6) (Entry 9)—(±)-Stegane ((±)-9) (100 mg, 0.25 mmol) was heated to melt at 195 °C for 2 h. Purification by silica gel column chromatography (benzene–AcOEt (10:1)) gave (±)-stegane ((±)-9) (41 mg, 41% recovery) and (±)-isostegane ((±)-6) (59 mg, 59%).

Isomerization of (−)-Picrostegane ((−)-8) to (−)-Stegane ((−)-9) (Entry 5)—A solution of (−)-picrostegane ((−)-8) (25 mg, 0.063 mmol) and *tert*-BuOK (1 mg, 0.01 mmol) in *tert*-BuOH (2 ml) was heated at 70 °C for 48 h, then diluted with AcOEt (100 ml). The whole was washed successively with 10% aq. HCl (10 ml), water (10 ml), satd. aq. NaHCO₃ (10 ml), water (10 ml × 3), and satd. aq. NaCl (10 ml), then dried over MgSO₄. Concentration *in vacuo* afforded colorless needles (22 mg). Purification by silica gel TLC (benzene–AcOEt (10:1)) gave (−)-picrostegane ((−)-8) (20.2 mg, 81% recovery) and (−)-stegane ((−)-9) (1.5 mg, 6%).

Isomerization of (±)-Isostegane ((±)-6) to the Other Three Isomers ((±)-7, ((±)-8, and ((±)-9) (Entry 1)—A solution of (±)-isostegane ((±)-6) (1.0 g, 3.5 mmol) and AcOK (2.5 g, 25 mmol) in AcOH (30 ml) was heated to reflux for 22 h. The mixture was concentrated *in vacuo*. The residue was diluted with CHCl₃ (100 ml) and washed with satd. aq. NaHCO₃ (30 ml) and satd. aq. NaCl (30 ml). After being dried over MgSO₄, the whole was concentrated *in vacuo* afforded a colorless oil. Purification by silica gel column chromatography (CH₂Cl₂–ether (10:1)) gave a solid (150 mg) from the first fraction and a solid (700 mg) from the second fraction.

The solid obtained from the first fraction was purified by silica gel column chromatography (benzene-ether (10:1)) to give ($\pm$)-stegane (($\pm$)-**9**) (6 mg, 0.6%) and ($\pm$)-isostegane (($\pm$)-**6**) (143 mg, 14% recovery).

The solid obtained from the second fraction was purified by silica gel column chromatography (benzene-ether (10:1)) to give ($\pm$)-picrostegane (($\pm$)-**8**) (190 mg, 19%) and ($\pm$)-isopicrostegane (($\pm$)-**7**) (379 mg, 38%).

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- 12) For simplicity, the structures of (+)-isostegane ((+)-**6**), (+)-isopicrostegane ((+)-**7**), (–)-picrostegane ((–)-**8**), and (–)-stegane ((–)-**9**) are drawn. These compounds are stereochemically related with each other.
- 13) We fortuitously found the present conditions during an oxidation study of **6** with DDQ-AcOK in AcOH.
- 14) In the communication²⁾ we reported that isomerization of **6** could be achieved in refluxing AcOH distilled from KMnO_4 . However the isomerization of **6** could not be reproduced when we used AcOH obtained by the simple distillation. The reason for this is unclear.
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- 17) Melting points were measured using a Büchi 510 melting point apparatus and are not corrected. Optical rotations were taken with a JASCO DIP-181 automatic polarimeter. IR spectra were taken with a JASCO Infrared Spectrometer Model DS-402 G and a JASCO IRA-1 Grating Infrared Spectrometer. ^1H -NMR spectra were taken with a JNM-PS 100 Spectrometer, with a JEOL-FX 100 Spectrometer at 100 MHz, or with a Hitachi R-24 Spectrometer at 60 MHz. ^{13}C -NMR spectra were taken with a JEOL FX-100 Spectrometer at 25 MHz. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. MS spectra were taken with a JEOL-01, SG-2 Mass Spectrometer.