[Chem. Pharm. Bull. 34(4)1501—1504(1986)]

Stereoselective Reactions. XII.[1] Synthesis of Antitumor-Active Steganacin Analogs, Picrosteganol and Epipicrosteganol, by Selective Isomerization

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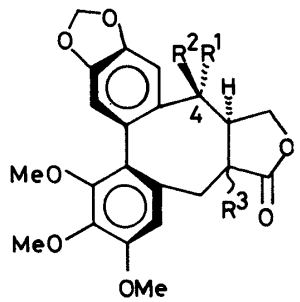
(Received September 2, 1985)

New steganacin analogs with definite absolute configurations, (−)-picro- and (−)-epipicrosteganol, were synthesized by isomerization of (−)-steganol and (−)-episteganol, respectively, at the α-position to the lactone carbonyl. The structure of (−)-epipicrosteganol was confirmed by X-ray crystallographic analysis. Selective epimerization at the C-4 benzylic position was observed upon acidic treatment of (−)-steganacin, giving (−)-episteganacin.

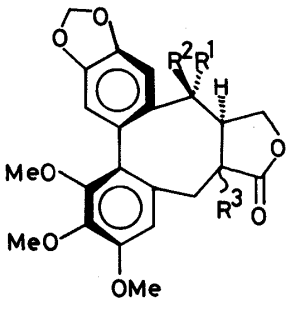
Keywords——antitumor lignan; steganacin; analog; isomerization; X-ray analysis

In 1973 Kupchan reported the isolation and structural elucidation of the new steganin lignans, among which steganacin (**1**) showed significant antitumor activity.[2] The absolute structure of steganacin was originally proposed to be the antipode of **1** by Kupchan and later corrected to **1** by us[3] and Brown *et al.*[4] on the basis of independent asymmetric total syntheses of **1** and related lignans.

Because of the significant antitumor activity exhibited by steganacin (**1**) and related natural lignans, several steganacin analogs were synthesized and evaluated for antitumor activity.[5−7] These analogs can be classified into two groups, the first group of compounds which lack an oxygen function at the C-4 benzylic position, such as stegane (**6**), picrostegane (**9**), isostegane (**13**), and isopicrostegane (**15**), and the second group of compounds which bear an oxygen function at the C-4 benzylic position, such as steganol (**2**), picrosteganol (**7**), epiisosteganol (**11**), and isopicrosteganol (**14**). As regards the first group, all possible stereoisomers including enantiomers were synthesized through novel isomerization of the stegane skeleton.[8] Of the second group, which can be considered as oxidized modifications of the first group, compounds having the stegane and isostegane skeletons (**3**, **4**, **10**—**12**) have been synthesized so far, but the compounds having picro- and isopicrostegane skeletons (**7**, **8**, **14**) remain to be synthesized.[5−7,9] In the present paper, we describe the first successful



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



	R^1	R^2	R^3
10	H	OAc	β-H
11	H	OH	β-H
12	O		β-H
13	H	H	β-H
14	OH	H	α-H
15	H	H	α-H

Fig. 1

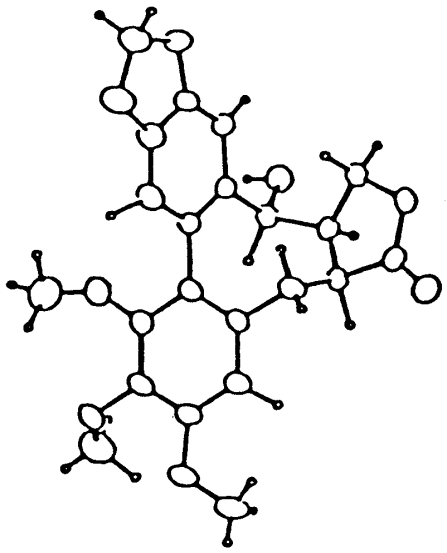


Fig. 2. Computer Drawing of **8**

syntheses of the new picro-type analogs (**7**, **8**) with definite absolute configuration by the selective isomerization of steganol (**2**) and episteganol (**4**).[3)]

The stereoisomerism in the second group of compounds can arise (i) from restricted rotation around the biaryl bond (natural series (**1**—**5**) *vs.* iso-series (**10**—**12**)), and/or (ii) from *trans* (**1**—**5**) *vs. cis* (picro-series: **7**, **8**, **14**) γ-lactone ring junctions, and/or (iii) from α (**1**, **2**, **7**, **14**) *vs.* β (epi-series: **3**, **4**, **8**, **10**, **11**) oriented oxygen function at the C-4 benzylic position. Attempted thermal atropisomerization[8)] of steganacin (**1**),[3c)] steganol (**2**),[3c)] and episteganol (**4**)[3c)] into iso-type compounds was found to be fruitless, giving a mixture of intractable materials. Then, we turned our attention to the isomerization at the α-position to the lactone carbonyl. Based on our earlier observations[8)] that stegane (**6**) was isomerized to picrostegane (**9**) under anhydrous basic conditions, such as *tert*-BuOK in *tert*-BuOH, we attempted to isomerize steganol (**2**) and episteganol (**4**). However, no detectable amount of isomerized products was formed, the starting materials being recovered. After many unsuccessful trials it was found that isomerization at the α-position to the lactone carbonyl could be achieved by treating episteganol (**4**) with 2 N NaOH in DMSO–EtOH at 20 °C, then with acid for re-closure of the lactone ring, to afford the new analog, epipicrosteganol (**8**), as a crystalline compound in 42% yield. The structure of **8** was confirmed by X-ray crystallographic analysis as follows.

Crystals of (−)-**8** were grown in MeOH as colorless plates. The diffraction data were collected on a Philips PW1100 diffractometer for a crystal with approximate dimensions of $0.3 \times 0.2 \times 0.15$ mm using CuK_α radiation monochromated by means of a graphite plate.

The crystal data were: (−)-**8**, $C_{22}H_{22}O_8$, $M_r = 414.4$. Orthorhombic, space group $P22_12_1$, $Z = 4$. Lattice constants, $a = 11.864$ (1), $b = 21.002$ (2), $c = 8.0916$ (9) Å, $V = 2016$ Å^3, $D_{calc} = 1.365$ gcm^{-3}, μ for Cu$K_\alpha = 4.08$ cm^{-1}.

A total of 1582 reflections were measured as above the 2σ(I) level, out of 2004 theoretically possible reflections in the 2θ range of 6—130°. The crystal structure was determined by the direct method and atomic parameters were refined by least-squares calculations with block-diagonal matrix approximations.

The final R value was 0.059 for 1582 reflections including all 22 hydrogen atoms, for which isotropic thermal parameters were assigned.[10)] The molecular structure of (−)-**8** is illustrated in Fig. 2.

Under the same conditions as described for **8**, steganol (**2**) was also subjected to isomerization, giving picrosteganol (**7**) in 10% yield.

Epimerization at the C-4 benzylic position of steganacin (**1**) occurred on heating **1** at

90 °C in AcOH to give episteganacin (**3**) in 36% yield. The structure of **3** was confirmed by comparison with an authentic specimen prepared from episteganol (**4**).

In conclusion, it was shown that selective isomerization at the α-position to the lactone carbonyl can occur upon treatment of steganol (**2**) and episteganol (**4**) under basic conditions, giving new picro-type analogs (**7**, **8**), and epimerization at the C-4 benzylic position of steganacin (**1**) can take place under acidic conditions, giving the epi-type analog (**3**). The isopicro-type analog (**14**) still remains to be synthesized. Evaluation of the antitumor activity of these new steganacin analogs is in progress.

Experimental[11]

(−)-Epipicrosteganol (8)——A 2 N solution of NaOH (0.35 ml) was added to a solution of (−)-episteganol (**4**) ($[\alpha]_D^{23}$ −107° (*c*=0.67, pyridine))[3c] (25.3 mg, 0.061 mmol) in a 4:5 mixture of DMSO and EtOH (0.9 ml). The whole was stirred at room temperature for 24 h. After addition of 10% aq. HCl (0.4 ml, 1.1 mmol), the whole was stirred for 24 h and diluted with 100 ml of AcOEt. The solution was washed with satd. aq. K_2CO_3, then dried over $MgSO_4$. Concentration *in vacuo* and silica gel thin layer chromatography (TLC) (ether–*n*-hexane, 4:1) gave (−)-episteganol (**4**) (8.0 mg, 32% recovery) and (−)-epipicrosteganol (**8**) (10.5 mg, 42%) as colorless plates of mp 227—228 °C (from MeOH); $[\alpha]_D^{23}$ −57.5° (*c*=0.24, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—3300 (OH), 1768 (γ-lactone), 1598 (aromatic); ^{1}H-NMR ($CDCl_3$) δ: 1.9—2.2 (1H, br s, OH), 2.2—3.3 (4H, m), 3.70 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3),4.1—4.3 (1H, m), 4.5—4.9 (2H, m), 6.02 (1H, d of AB, *J*=1 Hz, OCH_2O), 6.04 (1H, d of AB, *J*=1 Hz, OCH_2O), 6.69 (1H, s, aromatic H), 6.71 (1H, s, aromatic H), 7.02 (1H, s, aromatic H); ^{13}C-NMR ($CDCl_3$) δ: 30.5 (t), 68.2 (d), 43.9 (d), 44.2 (d), 56.1 (q), 60.9 (q), 67.8 (t), 101.4 (t), 106.2 (d), 107.4 (d), 110.3 (d), 125.3 (s), 128.0 (s), 132.9 (s), 134.1 (s), 141.1 (s), 146.7 (s), 147.5 (s), 150.5 (s), 153.8 (s), 178.6 (s); MS *m/z*: 414 (M^+), 396 ($M^+ - H_2O$), 331, 330, 315, 313, 299; *Anal.* Calcd for $C_{22}H_{22}O_7$: C, 63.76; H, 5.35. Found C, 63.52; H, 5.34. The structure of **8** was confirmed by X-ray crystallographic analysis as described in the text.

(−)-Picrosteganol (7)——A 2 N solution of NaOH (0.3 ml) was added to a solution of (−)-steganol (**2**) ($[\alpha]_D^{23}$ −190° (*c*=0.870, $CHCl_3$))[3c] (130 mg, 0.31 mmol) in a 5:7 mixture of DMSO–EtOH (1.2 ml) and the whole was stirred at room temperature for 48 h. After addition of 10% aq. HCl (0.4 ml, 1.1 mmol), the whole was stirred for 24 h and diluted with 100 ml of AcOEt. The solution was washed with satd. aq. K_2CO_3, then dried over $MgSO_4$. Concentration *in vacuo* and silica gel column chromatography (ether–*n*-hexane, 3:1) gave (−)-steganol (**2**) (96.1 mg, 74% recovery) and (−)-picrosteganol (**7**) (13.1 mg, 10%) as colorless needles of mp 178—179 °C (from CH_2Cl_2–*n*-hexane); $[\alpha]_D^{23}$ −56.5° (*c*=0.52, $CHCl_3$); IR ν_{max}^{KBr} cm^{-1}: 3480 (OH), 1754 (γ-lactone), 1595 (aromatic); ^{1}H-NMR ($CDCl_3$) δ: 1.77 (1H, d, *J*=9 Hz, OH), 2.4—4.0 (5H, m), 3.69 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.46 (1H, t of ABX, $J_{AB}=J_{AX}$=8 Hz, OCH_2CH), 4.84 (1H, dd, *J*=9 and 5 Hz, CHOH), 6.02 (1H, d of AB, *J*=1 Hz, OCH_2O), 6.05 (1H, d of AB, *J*=1 Hz, OCH_2O), 6.46 (1H, s, aromatic H), 6.74 (2H, s, aromatic H); ^{13}C-NMR ($CDCl_3$) δ: 30.5 (t), 74.9 (d), 44.7 (d), 44.9 (d), 56.1 (q), 60.7 (q), 61.0 (q), 68.5 (t), 101.6 (t), 107.9 (d), 108.9 (d), 112.3 (d), 126.1 (s), 127.6 (s), 131.4 (s), 133.4 (s), 141.4 (s), 146.9 (s), 150.6 (s), 154.1 (s), 178.4 (s). MS *m/z*: 414 (M^+), 330. *Anal.* Calcd for $C_{22}H_{22}O_7$: C, 63.76; H,5.35. Found C, 63.70; H, 5.40.

(−)-Episteganacin (3)——i) Acetyl chloride (0.01 ml, 0.14 mmol) was added to an ice-cooled pyridine (1 ml) solution of (−)-episteganol (**4**) ($[\alpha]_D^{23}$ −107° (*c*=0.67, pyridine)) (17.0 mg, 0.041 mmol), prepared by the stereoselective reduction of (−)-steganone (**5**)[3a,12] according to the reported procedure for the racemic modification,[3a,12] and the mixture was stirred at room temperature for 2 h. The whole was diluted with 150 ml of AcOEt and washed successively with 10% aq. HCl, satd. aq. $NaHCO_3$, and satd. aq. NaCl, then dried over $MgSO_4$. Concentration *in vacuo* and silica gel column chromatography (benzene–ether, 20:1) gave (−)-episteganacin (**4**) (3.4 mg, 18%) as a colorless caramel; $[\alpha]_D^{23}$ −89.8° (*c*=0.41, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1775 (γ-lactone), 1748 (OAc), 1596 (aromatic); ^{1}H-NMR ($CDCl_3$) δ: 2.12 (3H, s, $OCOCH_3$), 2.2—3.4 (4H, m, $ArCH_2CH$), 3.56 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.0—4.4 (2H, m, OCH_2), 5.88 (1H, d, *J*=8 Hz, AcOCH), 6.0—6.1 (2H, m, OCH_2O), 6.50 (1H, s, aromatic H), 6.76 (1H, s, aromatic H), 6.78 (1H, s, aromatic H); MS *m/z*: 456 (M^+), 414, 396, 366, 330. Spectroscopic data and TLC behavior were identical with those of authentic sample.[12]

ii) A solution of (−)-steganacin (**1**) ($[\alpha]_D^{23}$ −127° (*c*=0.740, $CHCl_3$)) (11 mg, 0.0241 mmol) in 0.5 ml of AcOH was stirred at 90 °C for 48 h then diluted with 50 ml of AcOEt. The whole was washed successively with aq. $NaHCO_3$, water, and aq. NaCl, then dried over $MgSO_4$. Concentration *in vacuo* and purification by silica gel TLC (benzene–AcOEt, 6:1) gave (−)-steganacin (**1**) (7.0 mg, 64% recovery) and (−)-episteganacin (**3**) (4.0 mg, 36%) as a pale yellow caramel.

References and Notes

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10) The final atomic parameters will be deposited with the Cambridge Crystallographic Data Center and the F_o and F_c table may be obtained from one of the authors (Y.I.) upon request.
11) 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. Infrared (IR) spectra were taken with a JASCO Infrared Spectrometer Model DS-402 G and a JASCO IRA-I Grating Infrared Spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken with a JNM-PS 100 Spectrometer and a JEOL FX-100 Spectrometer. ^{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; q, quartet; m, multiplet; br, broad. Mass spectra (MS) were taken with a JEOL-01, SG-2 Mass Spectrometer.
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