

[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 (–)-episteganol.

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 us³⁾ 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

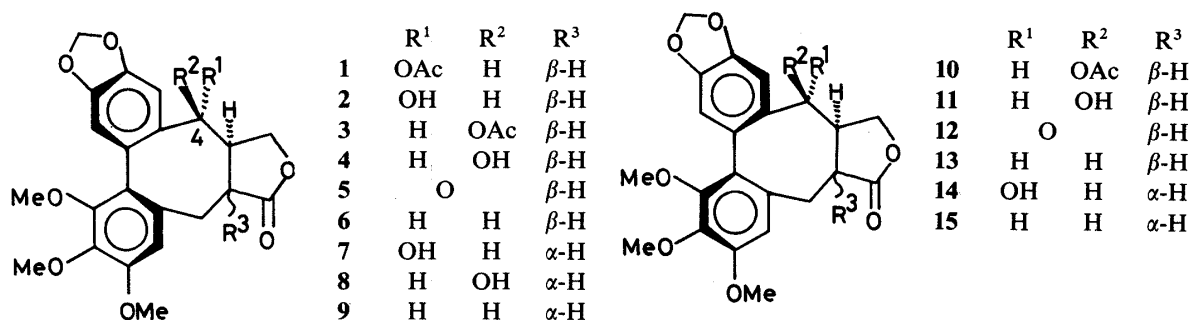


Fig. 1

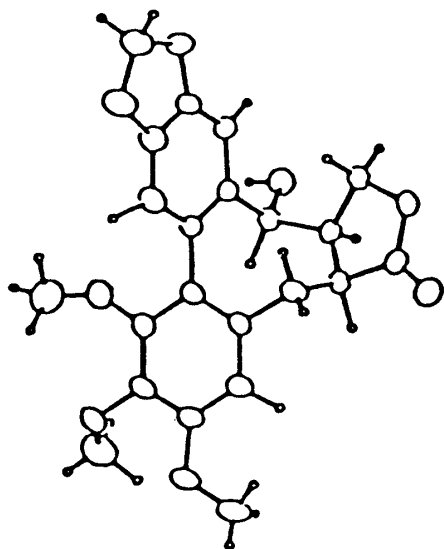


Fig. 2. Computer Drawing of 8

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 atropisomerization⁸⁾ 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 observations⁸⁾ 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 × 0.2 × 0.15 mm using CuK_α radiation monochromated by means of a graphite plate.

The crystal data were: (–)-8, $\text{C}_{22}\text{H}_{22}\text{O}_8$, $M_r = 414.4$. Orthorhombic, space group $P2_12_12_1$, $Z = 4$. Lattice constants, $a = 11.864$ (1), $b = 21.002$ (2), $c = 8.0916$ (9) Å, $V = 2016$ Å³, $D_{\text{calc}} = 1.365$ gcm^{–3}, μ for $\text{CuK}_\alpha = 4.08$ cm^{–1}.

A total of 1582 reflections were measured as above the $2\sigma(I)$ 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.

Experimental¹¹⁾

(–)-**Epipicrosteganol (8)**—A 2N solution of NaOH (0.35 ml) was added to a solution of (–)-episteganol (**4**) ($[\alpha]_D^{23} - 107^\circ$ ($c=0.67$, 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. K₂CO₃, then dried over MgSO₄. 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); $[\alpha]_D^{23} - 57.5^\circ$ ($c=0.24$, CHCl₃); IR $\nu_{\max}^{\text{CHCl}_3} \text{ cm}^{-1}$: 3600–3300 (OH), 1768 (γ -lactone), 1598 (aromatic); ¹H-NMR (CDCl₃) δ : 1.9–2.2 (1H, br s, OH), 2.2–3.3 (4H, m), 3.70 (3H, s, OCH₃), 3.88 (3H, s, OCH₃), 3.90 (3H, s, OCH₃), 4.1–4.3 (1H, m), 4.5–4.9 (2H, m), 6.02 (1H, d of AB, $J=1$ Hz, OCH₂O), 6.04 (1H, d of AB, $J=1$ Hz, OCH₂O), 6.69 (1H, s, aromatic H), 6.71 (1H, s, aromatic H), 7.02 (1H, s, aromatic H); ¹³C-NMR (CDCl₃) 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 ($M^+ - \text{H}_2\text{O}$), 331, 330, 315, 313, 299; Anal. Calcd for C₂₂H₂₂O₇: 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 2N solution of NaOH (0.3 ml) was added to a solution of (–)-steganol (**2**) ($[\alpha]_D^{23} - 190^\circ$ ($c=0.870$, CHCl₃))^{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. K₂CO₃, then dried over MgSO₄. 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 CH₂Cl₂–*n*-hexane); $[\alpha]_D^{23} - 56.5^\circ$ ($c=0.52$, CHCl₃); IR $\nu_{\max}^{\text{KBr}} \text{ cm}^{-1}$: 3480 (OH), 1754 (γ -lactone), 1595 (aromatic); ¹H-NMR (CDCl₃) δ : 1.77 (1H, d, $J=9$ Hz, OH), 2.4–4.0 (5H, m), 3.69 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 3.91 (3H, s, OCH₃), 4.46 (1H, t of ABX, $J_{AB}=J_{AX}=8$ Hz, OCH₂CH), 4.84 (1H, dd, $J=9$ and 5 Hz, CHOH), 6.02 (1H, d of AB, $J=1$ Hz, OCH₂O), 6.05 (1H, d of AB, $J=1$ Hz, OCH₂O), 6.46 (1H, s, aromatic H), 6.74 (2H, s, aromatic H); ¹³C-NMR (CDCl₃) 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 C₂₂H₂₂O₇: 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**) ($[\alpha]_D^{23} - 107^\circ$ ($c=0.67$, 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. NaHCO₃, and satd. aq. NaCl, then dried over MgSO₄. Concentration *in vacuo* and silica gel column chromatography (benzene–ether, 20:1) gave (–)-episteganacin (**4**) (3.4 mg, 18%) as a colorless caramel; $[\alpha]_D^{23} - 89.8^\circ$ ($c=0.41$, CHCl₃); IR $\nu_{\max}^{\text{CHCl}_3} \text{ cm}^{-1}$: 1775 (γ -lactone), 1748 (OAc), 1596 (aromatic); ¹H-NMR (CDCl₃) δ : 2.12 (3H, s, OCOCH₃), 2.2–3.4 (4H, m, ArCH₂CH), 3.56 (3H, s, OCH₃), 3.88 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 4.0–4.4 (2H, m, OCH₂), 5.88 (1H, d, $J=8$ Hz, AcOCH), 6.0–6.1 (2H, m, OCH₂O), 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**) ($[\alpha]_D^{23} - 127^\circ$ ($c=0.740$, CHCl₃)) (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. NaHCO₃, water, and aq. NaCl, then dried over MgSO₄. 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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- 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 (^1H -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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