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NOVEL ISOMERIZATION OF DIBENZOCYCLOOCTADIENE LIGNAN LACTONE
——FIRST SYNTHESIS OF (±)-STEGANE——

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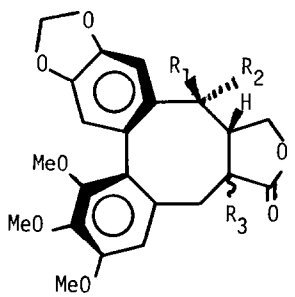
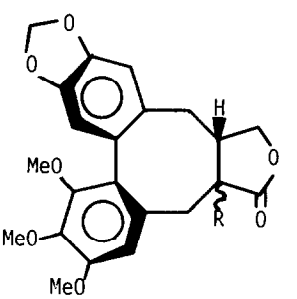
Summary: (±)-Isostegane isomerized into (±)-isopicrostegane, (±)-picrostegane, and (±)-stegane, the parent compound of steganacin-type dibenzocyclooctadiene lignan lactones.

Since the initial report by Kupchan on the isolation of steganacin(1) and steganangin(2)[1], considerable effort has been expended on the total syntheses of these antileukemic dibenzocyclooctadiene lignan lactones[2]. Although the syntheses of three among four possible isomers of steganacin-type lignan skeleton, i.e., (±)-isostegane(3)[2c,3], (±)-isopicrostegane(4)[2c], and (±)-picrostegane(5)[2c], have been reported, (±)-stegane(6) itself, the parent compound of steganacin-type lignan lactones, has remained unknown. During our studies towards the asymmetric total synthesis of antileukemic lignan lactones[4], we found a new isomerization of 3 into 4, 5, and 6 as summarized in Table.



1 R_1=OAc, R_2=H, R_3=α-H
2 R_1=OCO-  , R_2=H, R_3=α-H
5 R_1=R_2=H, R_3=β-H
6 R_1=R_2=H, R_3=α-H



3 R=α-H
4 R=β-H

Although the isomerization of (±)-isostegane(3)[5](mp.172-174.5°C(from Et_2O), m/e 398) in the similar way to that described in steganone(7)[6](KOH, EtOH, reflux) (to open the lactone ring and make easier to isomerize) was first attempted, 3 was recovered unchanged. Next, 3 was treated with AcOK(10eq.) in AcOH at reflux for 22 hr to give, after careful purification using medium pressure liquid chromatography(Lobar column, Merck Art.10402, CH_2Cl_2:Et_2O(10:1) then benzene:Et_2O(10:1)), four possible isomers, i.e., 3 (14%)(mp.172-174.5°C(from Et_2O)), 4 (38%) (mp.179-181°C(from Et_2O), IR($CHCl_3$) 1771cm^{-1}, NMR(C_6D_6) δ 7.39, 6.96, 6.48(each 1H,s), 5.56-5.36(2H), 3.83, 3.65, 3.51(each 3H,s), m/e 398), 5 (19%)(mp.182-185°C(from Et_2O), IR($CHCl_3$) 1770cm^{-1}, NMR(C_6D_6) δ 6.78, 6.46, 6.23(each 1H,s), 5.50-5.35(2H), 3.78, 3.42, 3.37(each 3H,s), m/e 398), and 6 (1%)(mp.130.5-133.0°C(from MeOH), IR($CHCl_3$) 1767cm^{-1}, NMR(C_6D_6) δ 6.63(1H,s), 6.37(2H,s), 5.60-5.40(2H), 3.81, 3.51, 3.42(each 3H,s), m/e 398)[7]. Simple treatment of 3 in AcOH in the absence of AcOK(reflux 92 hr) gave also the mixture of four possible isomers as

shown in Table. The compounds 4 and 5 were identified as (±)-isopicrostegane(4) and (±)-picrostegane(5) respectively by comparison with data(mp, IR, NMR) of 4 and 5 reported by Brown[2c]. The structure of (±)-stegane(6) was confirmed by the interconversion of 6 into 3 as described below.

Assuming that the rotation of single bond joining the two aromatic rings would occur without epimerization at α-position of lactone moiety under the same condition as that described in the isomerization of 5 to 4[2c], the thermal isomerization of 3 into 6 was thought to be possible. In fact, by heating without solvent at 195°C for 2 hr under argon, 3 gave a mixture of 3 (67%) and 6 (28%), while picro-type compounds(4 and 5) being absent. To confirm this novel isomerization of 3 into 6, the reverse isomerization of 6 into 3 was undertaken(195°C, 2 hr) to give a mixture of 6 (41%) and 3 (59%)[8].

These findings, as well as the thermal isomerization of 5 into 4 and alkaline isomerization of 4 into 3[2c], support the structure of newly found (±)-stegane(6).

By this new isomerization described herein, all of four possible isomers are now available. Further studies directed towards the asymmetric total synthesis of antileukemic lignan lactones are in progress in our laboratory.

Table: Isomerization of (±)-isostegane(3)

	AcOH/AcOK [a] reflux 22 hr(%)	AcOH [a] reflux 92 hr (%)	Neat [a] 195°C 2 hr (%)	Neat [a,b] 195°C 2 hr (%)
3	14	8	67	59
4	38	42	0	0
5	19	25	0	0
6	1	3	28	41

a) Isolated yields.
b) 6 was used as a starting material.

References and Notes

1) S. M. Kupchan, R. W. Britton, M. F. Ziegler, C. J. Gilmore, R. J. Restivo, and R. F. Bryan, J. Am. Chem. Soc., 95, 1335(1973)
2) a) G. R. Krow, K. M. Damodaran, E. Michener, R. Wolf, and J. Guare, J. Org. Chem., 43 3950 (1978) and references cited therein. b) F. E. Ziegler, K. W. Fowler, and N. D. Sinha, Tetrahedron Letters, 1978, 2767 c) E. Brown and J-P. Robin, Tetrahedron Letters, 1978, 3613
3) R. E. Damon, R. H. Schlessinger, and J. F. Blount, J. Org. Chem., 41, 3772(1976)
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5) 3 was prepared according to the reported procedure. See reference 3.
6) A. S. Kende, L. S. Liebeskind, C. Kubiak, and R. Eisenberg, J. Am. Chem. Soc., 98, 6389(1976)
7) Satisfactory spectral and analytical data were obtained for all compounds.
8) Interestingly isosteganacin does not isomerize thermally to steganacin. See reference 6.

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