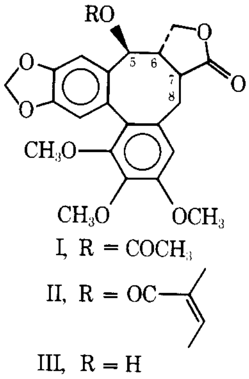
Total Synthesis of (±)-Steganacin

Sir:

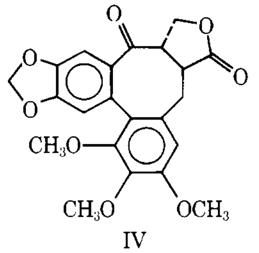
The isolation and structure determination of a novel class of dibenzocyclooctadiene lignan lactones represented by the antileukemic esters steganacin (I) and steganangin (II) have been described recently by Kupchan and his collaborators.[1] We wish to report the first total synthesis of (±)-steganacin and the companion lignans steganol (III) and steganone (IV) by a short and efficient route suitable for large scale preparation of these rare natural lactones. Our synthesis rests upon three strategic principles: (a) utilization of diethyl malonate as a lynch-pin upon which both aromatic residues are elaborated, (b) formation of the 8-membered ring by nonphenolic oxidative coupling, and (c) late introduction[2] of functionality at C-5 and subsequent generation of the trans-fused lactone ring.



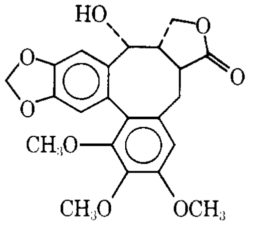
I, R = COCH$_3$

II, R = OC—

III, R = H



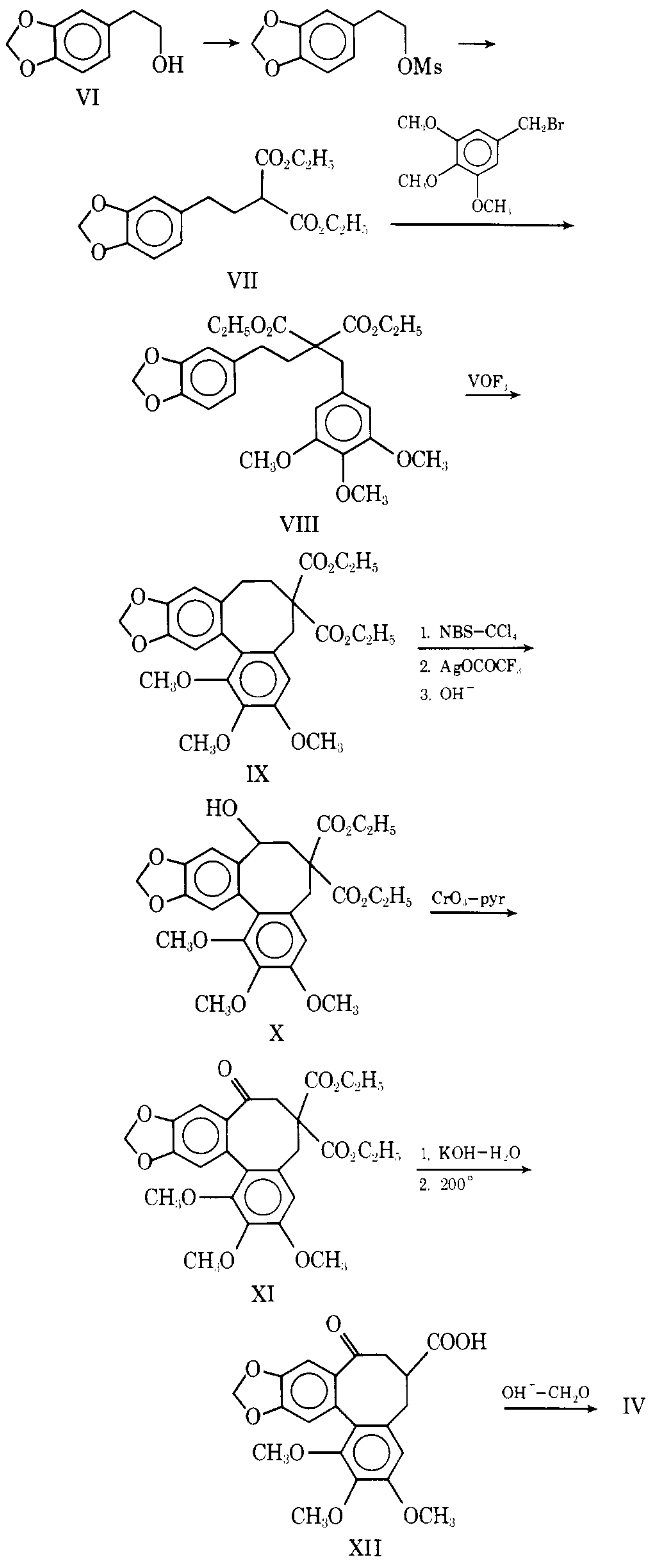
IV



V

Homopiperonyl alcohol (VI), prepared from piperonal in 78% overall yield by modifications of known procedures (Scheme I),[3] was converted (CH_3SO_2Cl-Et_3N, CH_2Cl_2, 0°, 20 min) to the oily mesylate which was treated with 2.2 equiv of sodiodiethyl malonate (benzene, reflux, 18 hr). Work-up and removal of excess diethyl malonate in vacuo produced crude diester (VII), which was alkylated with 3,4,5-trimethoxybenzyl bromide[5] (NaH, DMF, 0°, 30 min) to yield the crystalline dialkylation product VIII,[6] mp 79.5-81.0°, in 52% overall yield from alcohol VI. Dropwise addition of a 0.02 *M* solution of diester VIII in methylene chloride containing 5% trifluoroacetic anhydride to 3.5 molar equiv of VOF_3 (25°, 1 hr)[7] followed by bicarbonate work-up and Florisil filtration gave an oil which on trituration with methanol gave 45% of nearly colorless crystals, mp 110-111°, assigned the dibenzocyclooctadiene structure IX.[6] This substance exhibited, inter alia: NMR (100 MHz, $CDCl_3$, δ) 6.68, 6.64, 6.56 (three singlets, aromatic protons) and 3.88, 3.84, 3.52 (three singlets, OCH_3); uv$_{max}$ (EtOH) 289, 253, 210; mass spectrum *m/e* 486(M$^+$), 471, 441, 422, ir($CHCl_3$) 1725 cm^{-1}. In the NMR, the methoxyl signal at distinctly higher field (δ 3.52) than the other two is characteristic of similarly substituted biaryls[8] and is attributed to the anisotropic shielding of protons situated above the plane of the aromatic ring.

Scheme I



To introduce an oxygen function at C-5 of this dibenzocyclooctadiene system the following three-stage operation was performed without purification of intermediates. Treatment of diester IX with freshly recrystallized *N*-bromosuccinimide (CCl_4, reflux, 2 hr) with benzoyl peroxide as initiator yields a single monobromo-substitution product[9] which with silver trifluoroacetate (DMSO, 25°, 1 hr) followed by work-up with aqueous triethylamine gives the hydroxydiester X, ir ($CHCl_3$) 3400, 1725 cm^{-1}. Direct oxidation of this alcohol with dipyridine-chromium trioxide in methylene chloride[10] yields on work-up and trituration with ether the colorless crystalline ketodiester XI, mp 127-129° in 60%

overall yield from the cyclization product IX. Selective functionalization of IX at C-5 rather than C-8 was designed into the synthesis by providing the bulky *gem*-dicarbethoxy substituents on C-7.

Saponification (2.7 *M* KOH, 50% EtOH, reflux, 6 hr) and decarboxylation (neat, 200°) converted ketodiester XI into the ketoacid XII in 95% yield. Treatment of this ketoacid with 37% aqueous formaldehyde (0.4 *M* KOH, H_2O, 25°, 1 hr)[11] gave in 77% yield a single crystalline lactone, mp 229–230°, identical by mass spectrum, uv, 100-MHz NMR,[12] and careful chromatographic comparison by HPLC and TLC in eight solvent systems with an authentic sample of natural steganone IV.[13]

Further proof of identity of our synthetic ketone was available from its reduction with $NaBH_4$ (CH_2Cl_2–methanol, 25°, 2 min) to give two major products, (±)-steganol (III), mp 155–158° (loss of methanol of crystallization) and (±)-episteganol (V), mp 215.5–217.5°, in the ratio 45:55, respectively, separable by silica gel chromatography (20% cyclohexane in ether). Finally, acetylation of steganol (Ac_2O, pyridine, 50°, 2 hr) gave (±)-steganacin, mp 212.5–214.5°, ir ($CHCl_3$) 1767, 1729 cm^{-1}, identical by uv, NMR, MS, and both TLC and HPLC chromatography with natural steganacin.[13]

The new availability of these unusual dibenzocyclooctadiene lactones in 10% overall yield from homopiperonyl alcohol permits for the first time a complete stereochemical correlation in this series and examination of the relative stabilities of the cis- and trans-fused 8-5 lactone systems. These and related studies will be reported in a separate communication.

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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) Attempted oxidative closures of C-5 oxygenated systems (ketone, ketal, alcohol, protected alcohol) give no 8-membered ring products.

(3) Cf. R. G. Niak and R. S. Wheeler, *J. Chem. Soc.*, 1780 (1938). Modifications: (a) $NaBH_4$ reduction of piperonal, (b) HBr gas on a chloroform solution of piperonyl alcohol, (c) phase-transfer catalyzed reaction of the resulting benzyl bromide with NaCN,[4] (d) hydrolysis (6 *M* NaOH, 40% EtOH, reflux, 18 hr) of the nitrile, and (e) $LiAlH_4$ reduction of the resulting 3,4-methylenedioxyphenylacetic acid.

(4) C. M. Starks, *J. Am. Chem. Soc.*, **93,** 195 (1971).

(5) Prepared in >95% yield by $NaBH_4$ reduction of 3,4,5-trimethoxybenzaldehyde followed by bubbling HBr gas through a chloroform solution of the resulting alcohol.

(6) All new compounds gave satisfactory mass spectra, analytical, and spectroscopic data.

(7) S. M. Kupchan, A. J. Liepa, V. Kameswaran, and R. F. Bryan, *J. Am. Chem. Soc.*, **95,** 6861 (1973).

(8) A. Brossi, J. O'Brien, and S. Teitel, *Helv. Chim. Acta*, **52,** 678 (1969).

(9) The monobromo compound shows NMR (100 MHz, $CDCl_3$) δ 5.15 doublet of doublets, $J = 11$ Hz, $J < 1$ Hz, indicative of benzylic bromination at C-5; ir ($CHCl_3$) 1725 cm^{-1}; mass spectrum *m/e* 565 (M^+).

(10) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35,** 4000 (1970).

(11) Cf. D. Becker, L. R. Hughes, and R. A. Raphael, *J. Chem. Soc., Chem. Commun.*, 431 (1974). Our yield was obtained by quenching the reaction after 1 hr (10% H_2SO_4), partitioning between neutrals (steganone) and unreacted starting material, and resubjecting the recovered starting material to the reaction conditions. After three successive cycles the reported yield was obtained. Reaction times of longer than 1 hr led to substantial amounts of ketone reduction by a cross-Cannizzaro reaction.

(12) NMR (JEOL PFT 100 MHz and JEOL CW 100 MHz, $CDCl_3$,δ) 7.53, 6.63, 6.53 (all singlet, all 1 H); 6.10 (s, 2 H); ~4.35 (mult, 2 H); 3.89 (s, 6 H); 3.60 (s, 3 H). These values are reproducibly 0.04–0.08 ppm higher than those previously reported for steganone[1] but they are identical with those obtained from an authentic sample[13] measured on our instruments.

(13) We thank Professor Kupchan for supplying authentic samples of steganacin and steganone. Chromatographic comparison of authentic and synthetic compounds were performed on silica gel using the following solvent systems: chloroform; benzene; 20% ethyl acetate, chloroform; 20% ethyl acetate, benzene; 20% ether, benzene; 40% acetone, hexane; 20% cyclohexane, ether; 50% cyclohexane, ether. HPLC comparison was made on 3 × 2 ft × ⅛ in. Corasil columns with chloroform as solvent at 0.6 ml/min.

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Formation of Radical Anion from Tetracyanoethylene in Dimethyl Sulfoxide

Sir:

Tetracyanoethylene (TCNE) is one of the strongest electron acceptors and has been used in the studies of electron donor-acceptor (EDA) complexes.[1,2] It has been disclosed that, when TCNE is dissolved in a polar solvent of electron donating nature, a radical anion of TCNE is readily formed through ionic dissociation of the EDA complex between a TCNE molecule and a solvent one either spontaneously or upon photoillumination. Photoinduced formation of the TCNE radical anion in tetrahydrofuran was first reported by Ward,[3] and later studied in detail by Ilten and Calvin.[4] Stewart et al. found that the radical anion was formed spontaneously upon mixing TCNE into either dimethyl sulfoxide (DMSO) or *N,N*-dimethylacetamide.[5,6] They observed that the formation of the radical anion was so prompt that its concentration reached a maximum before starting the measurements of the radical anion by the electron spin resonance (ESR) method. This enabled them to observe only the decay process but not the formation process of the radical anion. The prompt formation was attributed to the efficient formation of the ground state EDA complex between a TCNE molecule and a solvent molecule and to the high enthalpy of complex formation, which caused the ionic dissociation through the appreciably populated triplet state of the complex. However, we recently found that the spontaneous formation of the TCNE radical anion in DMSO solution showed kinetic features much different from those reported by Stewart et al.[5,6] The difference is that the formation process was slow enough to be measured by a conventional ESR method, and that the radical anion is so stable that its decay was not observed in the present investigation.

DMSO was distilled under a reduced pressure, degassed by the freeze–pump–thaw method and stored under vacuum over molecular sieves which were baked beforehand. TCNE was recrystallized from dichloromethane and sublimed twice. It was mixed into DMSO under vacuum by breaking a break seal immediately before starting quantitative measurements of the radical anion from the intensity of its well-known ESR spectrum.[7] The samples were treated in complete darkness to avoid the effect of light on the formation of the radical anion.

The observed concentration of the TCNE radical anion is shown in Figure 1 as a function of time after the mixing. It increases gradually and then reaches a plateau value, which agrees with the concentration of TCNE fed. The formation of the radical anion is evidently much slower than that reported previously.[5,6] The formation was found to be enhanced by light from an incandescent lamp (100 W) as shown by a dashed curve in Figure 1. Even the room light was found to increase the rate of formation. The prompt formation of the radical anion observed previously seems to have resulted from this effect of light. Also the present re-