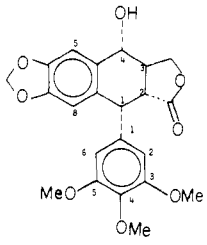
(14) E. Schroeter, *Justus Liebigs Ann. Chem.*, **426**, 83 (1922).
(15) B. M. Trost, T. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976), and earlier references cited therein; D. Seebach and M. Teschner, *Chem. Ber.*, **109**, 1601 (1976).

Barry M. Trost,* George Lunn
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706
Received May 16, 1977

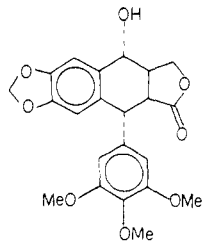
Oxidative Aryl–Benzyl Coupling. A Biomimetic Entry to Podophyllin Lignan Lactones

Sir:

The elegant studies of Gensler and his school have provided synthetic access to the biologically active Podophyllum lignan lactones represented by the antineoplastic substance podophyllotoxin (I) and its cis-lactone isomer picropodophyllin (II).[1,2]

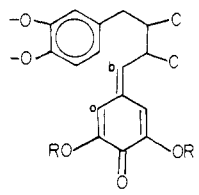


I

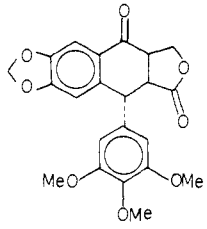


II

During the planning of our recent steganacin synthesis,[3] it became apparent that ionic or radical cyclization of a hypothetical quinone methide (III) at sites a and b could provide a biogenetic model leading respectively to the stegane and podophyllin ring systems. We now report a new and efficient total synthesis of (±)-picropodophyllone (IV) based on these considerations.

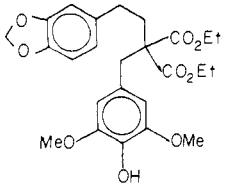


III

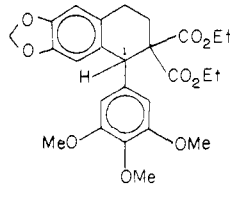


IV

Our key synthetic intermediate was the phenol V,[4] mp 80–81 °C, prepared in three steps (63% overall) from homopiperonyl alcohol by conventional procedures.[5] This phenol is the demethyl derivative of our earlier steganacin precursor.[3] Oxidation of phenol V with thallium(III) trifluoroacetate[6] (1.3–1.5



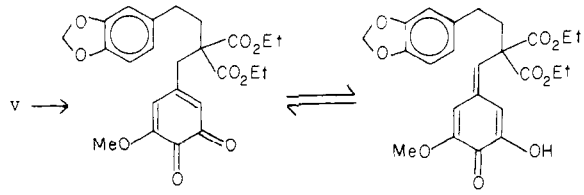
V



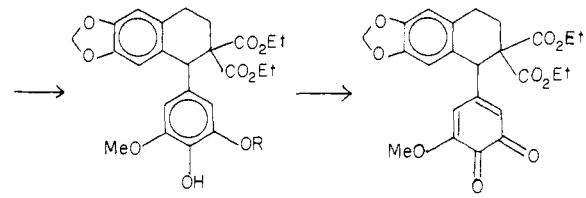
VI

equiv, $ClCH_2CH_2Cl$, 84 °C, 30 min) produced a deep red solution which on bisulfite reduction followed by extraction with ethyl acetate and methylation (Me_2SO_4, K_2CO_3 in acetone, reflux 12 h) gave in 55% yield a colorless crystalline diester, mp 149–152 °C. Combustion analysis, UV, MS, and NMR of this product were uniquely consistent with structure VI, which was specifically supported by the NMR singlet at δ 4.76 corresponding to the tertiary benzylic proton at C-1 (cf. δ 4.58, d, for 4-deoxypodophyllotoxin).[7]

Formation of the aryltetralin system from phenol V is in striking contrast to the isolation of the dibenzocyclooctadiene system from VOF_3 oxidation of the corresponding methyl ether.[8] We propose that in the present instance phenol V undergoes oxidative demethylation, at least in part, to the uncyclized *o*-quinone VII which can undergo prototropic equilibration with the quinone methide VIII.[9] Acid-catalyzed cyclization of the latter would in turn yield catechol IXa, partially oxidized to red tricyclic *o*-quinone X under the reaction conditions.

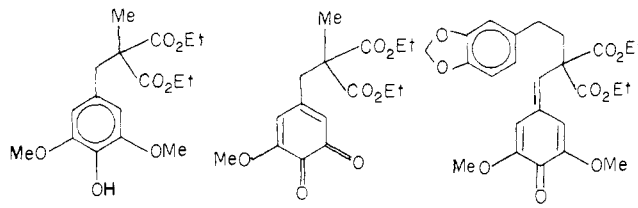


VII VIII



IX a R = H
IX b R = CH_3 X

The following observations are in accord with the above scheme. First, preparative TLC (SiO_2, ether–hexane) of the reduced cyclization products gave in 52% yield a ca. 5:1 mixture of the catechol IXa [mp 137–138 °C, NMR δ 3.79 (s, 3′-OCH_3), 4.78 (s, 1 H at C-1)] and the phenol IXb (M^+· 472). Second, thallium(III) trifluoroacetate oxidation of the model phenol XI yields, among other products, the red *o*-



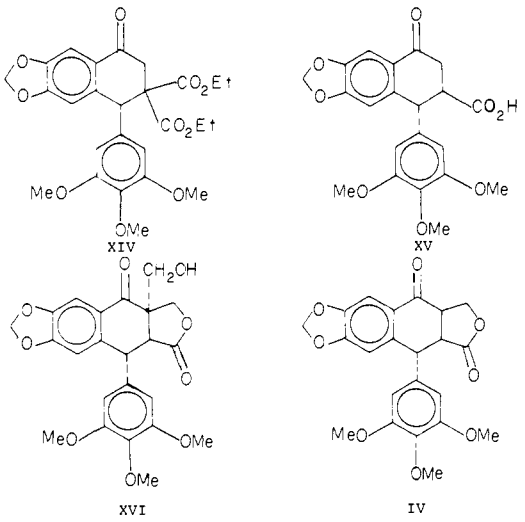
XI XII XIII

quinone XII. Third, sodium metaperiodate (1.5 equiv, aq EtOH, room temp, 2 h)[10] converts phenol V cleanly to the deep red *o*-quinone VII ($\lambda_{max}^{CHCl_3}$ 470 nm, $\nu_{max}^{CHCl_3}$ 1724 and 1667 cm^{-1}, M^+·466) which in refluxing 1,2-dichloroethane containing a drop of trifluoroacetic acid rapidly cyclizes to catechol IXa, presumably by the prototropic shift depicted above. Our product analysis indicates, however, that part of the cyclization of V must proceed through an analogous quinone methide, XIII.[11]

Introduction of C-4 oxygen in diester VI was achieved in one operation (4 equiv of NBS, 1 equiv of H_2O, dioxane, room temp, 20-min irradiation with GE sun lamp) to yield the keto diester XIV, mp 152–153 °C, in 90% yield. Saponification (1 M NaOH, aq MeOH, reflux, 4 h) and decarboxylation at 110 °C gave 67% of the keto acid XV, mp 221–223 °C (MeOH), identical by IR, NMR, and mixture melting point with a sample kindly provided by Professor Gensler.

Treatment of keto acid XV with excess 37% formaldehyde (5% NaOH, room temp, 24 h) produced the hydroxylactone

XVI, mp 107–109 °C, in 59% yield.[12] Oxidation with Jones reagent followed by an acidic workup gave 71% of crystalline (±)-picropodophyllone IV after SiO_2 chromatography. Alternatively, hydroxylactone XVI underwent thermal (190 °C, xylene) retroaldol loss of formaldehyde to yield (±)-picropodophyllone IV in 70% yield.



Synthetic picropodophyllone, (±)-IV, mp 198–199.5 °C, gave a proton NMR spectrum (100 MHz Fourier, in $CDCl_3$), IR, MS, UV, and TLC data in six solvent systems indistinguishable from data obtained on authentic (−)-IV, mp 153–154 °C, prepared from natural podophyllotoxin (I) by equilibration[13] to picropodophyllin (II) followed by MnO_2[14] or Jones oxidation. Since IV can be reduced to II with zinc borohydride and the latter converted to podophyllotoxin (I) by the Gensler enolate quenching procedure,[2] our work provides formal access to the latter natural antitumor agent. The novel aryl–benzyl oxidative coupling reported here achieves the conversion of phenol V to (±)-picropodophyllone IV in 13% yield over six steps; the scope of this coupling is under investigation.[15]

References and Notes

(1) W. J. Gensler, C. Samour, S. J. Wang, and F. Johnson, *J. Am. Chem. Soc.*, **82**, 1714 (1960).
(2) W. J. Gensler and C. Gatsonis, *J. Org. Chem.*, **31**, 4004 (1966).
(3) A. S. Kende and L. S. Liebeskind, *J. Am. Chem. Soc.*, **98**, 267 (1976).
(4) All new compounds were characterized by IR, UV, proton NMR, and MS or combustion analyses.
(5) Diethyl malonate was monoalkylated (NaH, C_6H_6, 80 °C, 14 h) with homopiperonyl mesylate and the resulting product further alkylated with 4-benzoyloxy-3,5-dimethoxybenzyl bromide (4 NaH, 1 H_2O, C_6H_6/DMF, 70 °C, 12 h). The bromide was made in 70% yield from 3,4,5-trimethoxybenzaldehyde by selective demethylation (LiI, pyridine, reflux, 3 h), benzoylation (PhCOCl, Et_3N, C_6H_6, room temp, 4 h), reduction ($NaBH_4$, EtOH, room temp, 1 h), and treatment with HBr gas in $CHCl_3$ (room temp, 30 min).
(6) M. A. Schwartz, B. F. Rose, and B. Vishnuvajjala, *J. Am. Chem. Soc.*, **95**, 612 (1973); A. McKillop, B. P. Swann, and E. C. Taylor, *Tetrahedron*, **26**, 4031 (1970).
(7) D. C. Ayers, J. A. Harris, P. N. Jenkins, and L. Phillips, *J. Chem. Soc., Perkin Trans. 1*, 1343 (1972).
(8) Direct oxidative cyclization of the methyl ether of V to the dibenzocyclooctadiene skeleton has been achieved [$Tl(OCOCF_3)_3$, BF_3·Et_2O, CCl_4, 12 h, room temp] in 60% yield following the procedure of A. McKillop, A. G. Turrell and E. C. Taylor, *J. Org. Chem.*, **42**, 765 (1977); P. S. Rutledge, unpublished observations.
(9) For another example of tautomerism in an *o*-quinone, see S. Mazza, S. Danishefsky, and P. McCurry, *J. Org. Chem.*, **39**, 3610 (1974).
(10) D. C. Ayers and J. A. Harris, *J. Chem. Soc., Perkin Trans. 1*, 2059 (1973).
(11) R. Ahmed, F. G. Schreiber, R. Stevenson, J. R. Williams, and H. M. Yeo, *Tetrahedron*, **32**, 1339 (1976) A. F. A. Wallis, *Aust. J. Chem.*, **26**, 1571 (1973).
(12) Cf. A. P. Wagh and A. B. Kulkarni, *Indian J. Chem.*, **13**, 882 (1975); K. N. Campbell, J. A. Cella, and B. Campbell, *J. Am. Chem. Soc.*, **75**, 4681 (1953).
(13) W. J. Gensler and C. D. Gatsonis, *J. Org. Chem.*, **31**, 3224 (1966).
(14) W. J. Gensler, F. A. Johnson, and A. D. B. Sloan, *J. Am. Chem. Soc.*, **82**, 6074 (1960).

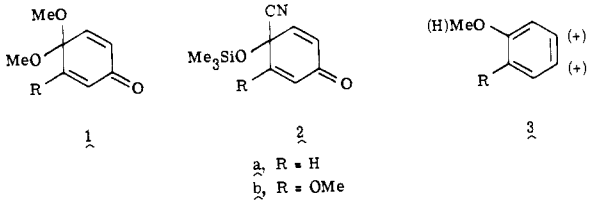
(15) We are grateful to the National Cancer Institute, USPHS (Grant CA 18846) and to the Hoffmann-La Roche Co. for financial support of this research.

Andrew S. Kende*, Lanny S. Liebeskind, John E. Mills
P. Stewart Rutledge, Dennis P. Curran
Department of Chemistry, University of Rochester
Rochester, New York 14627
Received April 1, 1977

A General Approach to the Synthesis of Phenanthrenoid Compounds. An Alternative to Oxidative Phenolic Coupling

Sir:

Oxidative phenolic coupling has long been recognized as a pivotal step in the biosynthesis of many natural products containing biaryl subunits.[1] In spite of the fact that nature accomplishes these coupling processes with remarkable efficiency, attempts to duplicate these reactions in the laboratory have met with mixed success.[2] The purpose of this communication is to outline our preliminary efforts which have been directed toward the construction of polycyclic biaryl compounds. In this context we have found that *p*-quinone monoketals **1** and silyl cyanohydrin derivatives **2** can be viewed



1 2 3

a, R = H
b, R = OMe

as hypothetical aryl cation equivalents **3** (vide infra) in annelation reactions with binucleophilic agents (Scheme I).

The present study has been directed toward an examination of the dihydrophenanthrene synthesis illustrated in Scheme I. The protected quinones **1a**, **2a**, and **2b** used in the study were prepared accordingly to literature procedures.[3,4] Quinone ketal **1b** was prepared by the thallium(III) oxidation of 3,4-di-

Scheme I