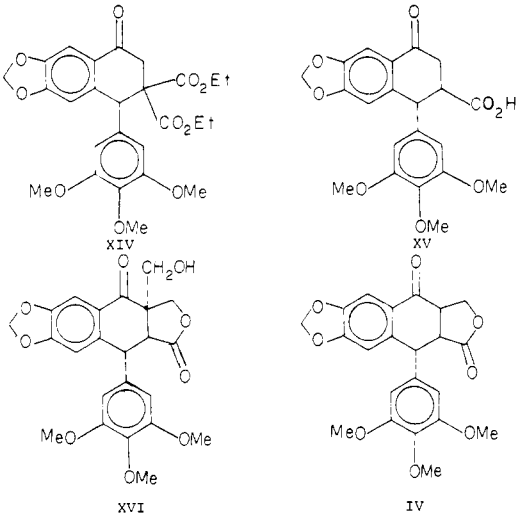
XVI, mp 107–109 °C, in 59% yield.[12] Oxidation with Jones reagent followed by an acidic workup gave 71% of crystalline (±)-picropodophyllone IV after SiO_2 chromatography. Alternatively, hydroxylactone XVI underwent thermal (190 °C, xylene) retroaldol loss of formaldehyde to yield (±)-picropodophyllone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

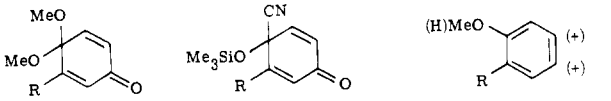
(15) We are grateful to the National Cancer Institute, USPHS (Grant CA 18846) and to the Hoffmann-La Roche Co. for financial support of this research.

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

2 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

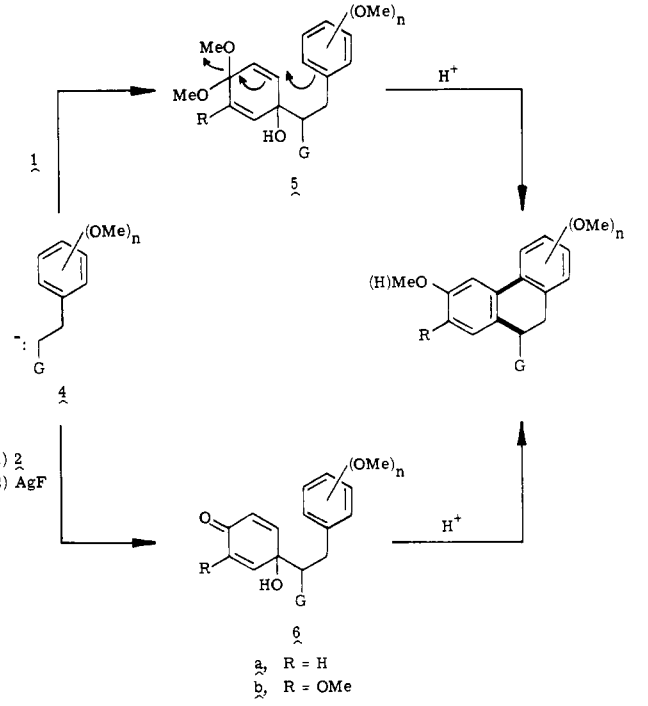
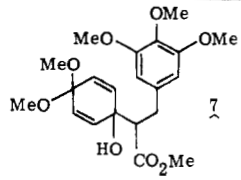
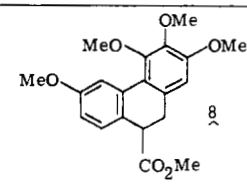
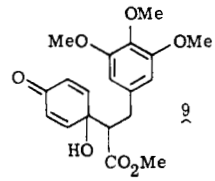
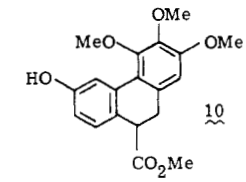
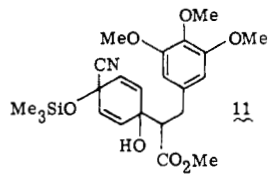
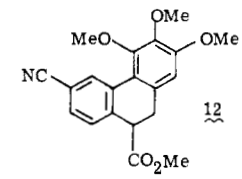
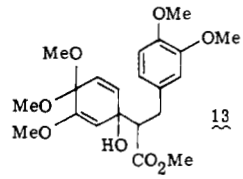
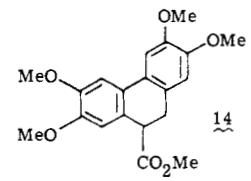
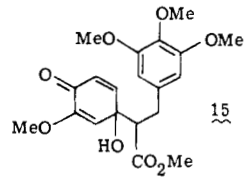
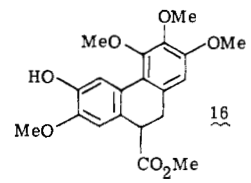
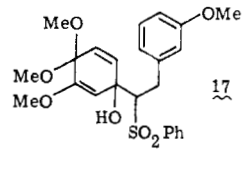
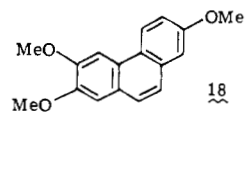
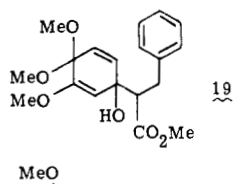
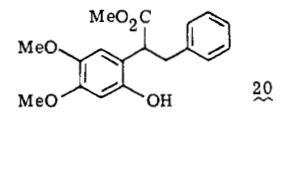
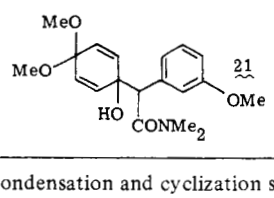
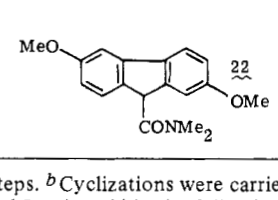


Table I. Acid-Catalyzed Cyclization of *p*-Quinol Derivatives (Scheme I)[a]

Entry	Quinol Derivative	Product	Mp, °C	Yield, %[a]	Lewis Acid[b]
1	 7	 8	95.5-97	77	P_2O_5-$MeSO_3H$[c] CH_2Cl_2
2	 9	 10	147-149	78	P_2O_5-$MeSO_3H$ CH_2Cl_2
3	 11	 12	77.5-79	61	$SnCl_4$ $MeNO_2$
4	 13	 14	172.5-173.5	74	$SnCl_4$ CH_2Cl_2
5	 15	 16	175-176	47	$SnCl_4$ CH_2Cl_2
6	 17	 18	104-106[d]	62	$BF_3 \cdot Et_2O$ $MeNO_2$
7	 19	 20	—	64	$BF_3 \cdot Et_2O$ $MeNO_2$
8	 21	 22	142-143	61	$BF_3 \cdot Et_2O$ $MeNO_2$

[a] Yield based upon condensation and cyclization steps. [b] Cyclizations were carried out at 25°C for 10–20 min. A 0.1 M solution of alcohol in the indicated solvent was treated with the indicated Lewis Acid in the following molar ratios: $SnCl_4$ (4 equiv); $BF_3 \cdot Et_2O$ (2 equiv); P_2O_5-$MeSO_4$ (1 ml per mmol ROH). [c] P. E. Eaton, G. R. Carlson, and J. T. Lee, *J. Org. Chem.*, 4071 (1973). [d] See ref. 9.

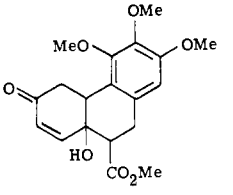
methoxyphenol[5] (70%, mp 63.5–64.5 °C) according to the procedure of McKillop and Taylor.[3] The functionalized phenethyl carbanions **4** (G = CO_2Me, SO_2Ph) were prepared via deprotonation with lithium diisopropylamide (LDA)[6] or *n*-butyllithium, respectively. A general procedure for the synthesis of *p*-quinol derivatives **5** and **6** (G = CO_2Me) follows.

To a 1 M solution of the enolate of methyl 3-(3,4,5-trimethoxyphenyl)propionate[7] generated from 1.0 equiv of ester and 1.1 equiv of LDA[6] at −78 °C is added a THF solution of either **1a** or **1b**. After stirring for 20 min (−78 °C) the reaction is quenched with 1.2 equiv of 1 M aqueous ammonium chloride solution. The desired quinol ketals **5** are then isolated by ether

extraction in 75–95% yield. Representative ketal **7** (Table I) was conveniently chromatographed on neutral alumina (Activity III) and recrystallized, mp 77–78 °C (87%). The *p*-quinols of general structure **6** are prepared in an analogous fashion employing the quinone silyl cyanohydrins **2a** and **2b**.[4,6] Alternatively, we have found that ketals **5** can be hydrolyzed to the *p*-quinols **6** in good yield with oxalic acid (4 mg/mmol) in THF–water (5:1, 25 °C, 1 h). In the preparation of the sulfone ketals (cf. **17**, Table I), the requisite sulfone **4** (G = SO_2Ph) was metalated with *n*-butyllithium (−78 °C, 10 min; −10 °C, 1 h).

The results of the acid-catalyzed cyclization reactions of a series of *p*-quinols and *p*-quinol ketals are summarized in Table I.[8] In general we have found it unnecessary to purify the quinol derivatives prior to acid-catalyzed cyclization. Accordingly, the yields reported in Table I represent the combined yields for the condensation and cyclization steps (Scheme I). The structural assignments for the substitution patterns of the 9,10-dihydrophenanthrenes listed in Table I rest upon ^1H and ^{13}C NMR analysis and, in selected cases, correlation with known structures. The physical properties of phenanthrene **18** are identical with those reported.[9] The dihydrophenanthrene **14** (entry 4) was correlated with the corresponding phenanthrene via DDQ oxidation,[10] mp 202–205 °C (lit.[11] 202–204 °C). The ring substitution patterns in dihydrophenanthrenes **8, 10, 12,** and **16** may be conveniently analyzed by ^1H NMR spectroscopy. It is well documented that 9,10-dihydrophenanthrenes bearing oxygen substituents at C_4 exhibit a characteristic deshielded C_5 aromatic proton.[12] Analysis of the spin multiplicity of this signal facilitates the assignment of the substitution pattern of the mono- or disubstituted aromatic rings in the above-mentioned derivatives.

It was observed that the choice of Lewis acid catalyst in certain instances was critical to the success of the cyclization process (entries 1, 2, Table I). As an example, treatment of **7** and **9** with either $SnCl_4$, CF_3CO_2H, or $BF_3{\cdot}Et_2O$ in solvents such as CH_2Cl_2, C_6H_6, or CH_3NO_2 afforded, in addition to the expected adducts **8** and **10,** respectively, the tricyclic enone **23**[13] in nearly equal amounts. Since **23** was stable to the above



23

cyclization conditions, and since **10** is not a contaminant in the cyclization of **7, 23** is neither a penultimate intermediate in the cyclization of quinol **9** nor is **7** converted to **9** under these conditions.

Efforts to carry out related cyclizations on substrates lacking methoxy-activated aromatic rings have failed to date (entry 7). The products derived from these reactions result from dienone–phenol rearrangements rather than ring closure. The scope of these and related annelation reactions will be reported in due course.

Acknowledgements. Support from the National Institutes of Health is gratefully acknowledged.

References and Notes

(1) A. R. Battersby in "Oxidative Coupling of Phenols", W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N.Y., 1967; A. I. Scott, *Q. Rev. Chem. Soc.*, **19,** 1 (1965); D. H. R. Barton, *Chem. Br.*, **3,** 330 (1967); K. L. Stuart, *Chem. Rev.*, **71,** 47 (1971).
(2) (a) For an excellent discussion of recent methods, see M. A. Schwartz, B. F. Rose, R. A. Holton, S. W. Scott, and B. Vishnuvjjala, *J. Am. Chem. Soc.*, **99,** 2571 (1977); (b) for reviews, see T. Kametani, *Synthesis*, 657 (1972); T. Kametani, *Bioorg. Chem.*, **3,** 430 (1974); S. Tobinaga, *ibid.*, **4,** 110 (1975).
(3) A. McKillop, D. H. Perry, M. edwards, S. Antus, L. Farkas, M. Nógrádi, and E. C. Taylor, *J. Org. Chem.*, **41,** 282 (1976).
(4) D. A. Evans, J. M. Hoffman, and L. K. Truesdale, *J. Am. Chem. Soc.*, **95,** 5822 (1973).
(5) J. M. Godfry, M. U. Sargent, and J. A. Elix, *J. Chem. Soc., Perkin Trans. 1,* 1353 (1974).
(6) D. A. Evans and R. Y. Wong, *J. Org. Chem.*, **42,** 350 (1977).
(7) R. H. F. Manske and H. L. Holmes, *J. Am. Chem. Soc.*, **67,** 95 (1945); H. Rapoport and J. C. Campion, *ibid.*, **73,** 2239 (1951).
(8) Satisfactory analytical data on all cyclization products have been obtained.
(9) A. Ronlán, O. Hammerich, and V. D. Parker, *J. Am. Chem. Soc.*, **95,** 7132 (1973).
(10) E. A. Braude, A. G. Brook, and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954).
(11) R. B. Herbert and C. J. Moody, *J. Chem. Soc., Chem. Commun.*, 121 (1970).
(12) R. M. Letcher and L. R. M. Nhamo, *J. Chem. Soc., Perkin Trans. 1,* 2941 (1972); R. M. Letcher and L. R. M. Nhamo, *ibid.*, 1179 (1973).
(13) Compound **23** may be aromatized [CH_3COBr, $(CH_3CO)_2O$, CH_2Cl_2] to the **10** *O*-acetate, mp 122–123 °C, in 87% yield.

David A. Evans,* Paul A. Cain, Rayman Y. Wong
Contribution No. 5605, Laboratories of Chemistry
California Institute of Technology,
Pasadena, California 91125
Received, June 13, 1977

A Stereospecific Total Synthesis of (±)-Methylenomycin A. A Novel Antibiotic Possessing an α-Methylene Ketone Functionality

Sir:

We wish to report here the first total synthesis of methylenomycin A, an antibiotic recently isolated from a strain of *Streptomyces violaceoruber,*[1] and shown by x-ray crystallographic analysis[2] to possess structure **1.**[3] Our interest in this synthetic target was prompted both by its demonstrated in vitro activity[1] against gram-positive and gram-negative bacteria as