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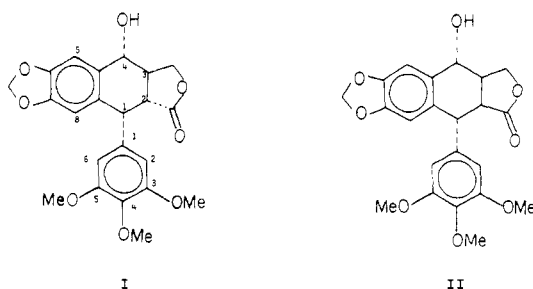
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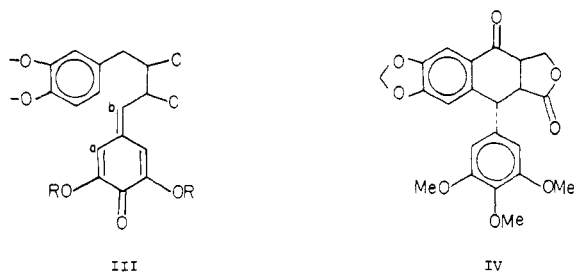
## Oxidative Aryl-Benzyl Coupling. A Biomimetic Entry to Podophyllin Lignan Lactones

Sir:

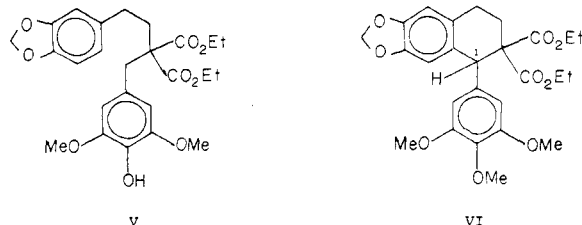
The elegant studies of Gensler and his school have provided synthetic access to the biologically active Podophyllin lignan lactones represented by the antineoplastic substance podophyllotoxin (I) and its cis-lactone isomer picropodophyllin (II).<sup>1,2</sup>



During the planning of our recent steganacin synthesis,<sup>3</sup> 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.



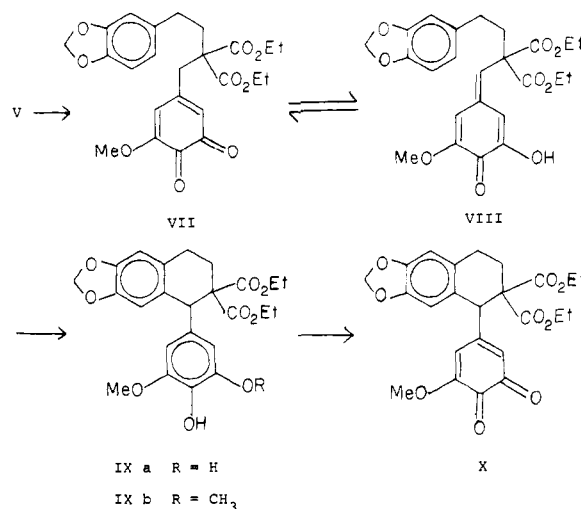
Our key synthetic intermediate was the phenol V,<sup>4</sup> mp 80–81 °C, prepared in three steps (63% overall) from homopiperonyl alcohol by conventional procedures.<sup>5</sup> This phenol is the demethyl derivative of our earlier steganacin precursor.<sup>3</sup> Oxidation of phenol V with thallium(III)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



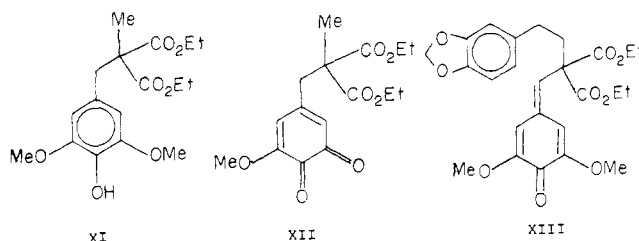
equiv,  $\text{ClCH}_2\text{CH}_2\text{Cl}$ , 84 °C, 30 min) produced a deep red solution which on bisulfite reduction followed by extraction with ethyl acetate and methylation ( $\text{Me}_2\text{SO}_4$ ,  $\text{K}_2\text{CO}_3$  in acetone, reflux 12 h) gave in 55% yield a colorless crystalline diester, 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  $\delta$  4.76 corresponding to the tertiary benzylic proton at C-1 (cf.  $\delta$  4.58, d, for 4-deoxypodophyllotoxin).<sup>7</sup>

Formation of the aryltetralin system from phenol V is in striking contrast to the isolation of the dibenzocyclooctadiene system from  $\text{VOF}_3$  oxidation of the corresponding methyl ether.<sup>8</sup> 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.<sup>9</sup> Acid-catalyzed cyclization of the latter would in turn yield catechol IXa, partially oxidized to red tricyclic *o*-quinone X under the reaction conditions.



The following observations are in accord with the above scheme. First, preparative TLC ( $\text{SiO}_2$ , 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  $\delta$  3.79 (s, 3'-OCH<sub>3</sub>), 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*-

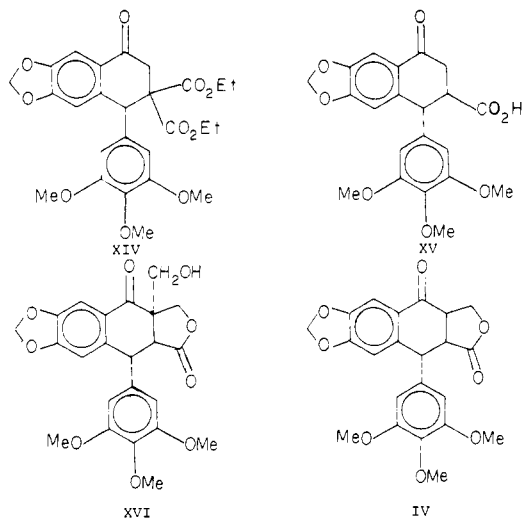


quinone XII. Third, sodium metaperiodate (1.5 equiv, aq EtOH, room temp, 2 h)<sup>10</sup> converts phenol V cleanly to the deep red *o*-quinone VII ( $\lambda_{\text{max}}^{\text{CHCl}_3}$  470 nm,  $\nu_{\text{max}}^{\text{CHCl}_3}$  1724 and 1667  $\text{cm}^{-1}$ ,  $M^+$  466) which in refluxing 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.<sup>11</sup>

Introduction of C-4 oxygen in diester VI was achieved in one operation (4 equiv of NBS, 1 equiv of  $\text{H}_2\text{O}$ , 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.<sup>12</sup> Oxidation with Jones reagent followed by an acidic workup gave 71% of crystalline (±)-picropodophyllone IV after SiO<sub>2</sub> 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<sub>3</sub>), 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<sup>13</sup> to picropodophyllin (II) followed by MnO<sub>2</sub><sup>14</sup> 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,<sup>2</sup> 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.<sup>15</sup>

## References and Notes

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- (2) W. J. Gensler and C. Gatsonis, *J. Org. Chem.*, **31**, 4004 (1966).
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- (4) All new compounds were characterized by IR, UV, proton NMR, and MS or combustion analyses.
- (5) Diethyl malonate was monoalkylated (NaH, C<sub>6</sub>H<sub>6</sub>, 80 °C, 14 h) with homopiperonyl mesylate and the resulting product further alkylated with 4-benzoyloxy-3,5-dimethoxybenzyl bromide (4 NaH, 1 H<sub>2</sub>O, C<sub>6</sub>H<sub>6</sub>/DMF, 70 °C, 12 h). The bromide was made in 70% yield from 3,4,5-trimethoxybenzaldehyde by selective demethylation (LiAlH<sub>4</sub>, pyridine, reflux, 3 h), benzoylation (PhCOCl, Et<sub>3</sub>N, C<sub>6</sub>H<sub>6</sub>, room temp, 4 h), reduction (NaBH<sub>4</sub>, EtOH, room temp, 1 h), and treatment with HBr gas in CHCl<sub>3</sub> (room temp, 30 min).
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- (8) Direct oxidative cyclization of the methyl ether of V to the dibenzocyclooctadiene skeleton has been achieved [Ti(OCOCF<sub>3</sub>)<sub>3</sub>, BF<sub>3</sub>·Et<sub>2</sub>O, CCl<sub>4</sub>, 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.
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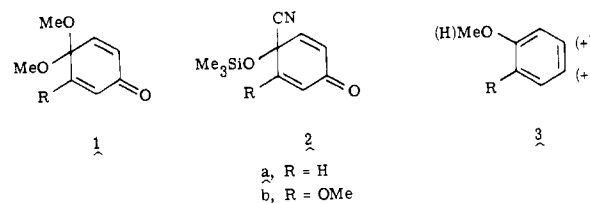
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## A General Approach to the Synthesis of Phenanthrenoid Compounds. An Alternative to Oxidative Phenolic Coupling

Sir:

Oxidative phenolic coupling has long been recognized as a pivotal step in the biosynthesis of many natural products containing biaryl subunits.<sup>1</sup> 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.<sup>2</sup> 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



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.<sup>3,4</sup> Quinone ketal **1b** was prepared by the thallium(III) oxidation of 3,4-di-

Scheme I

