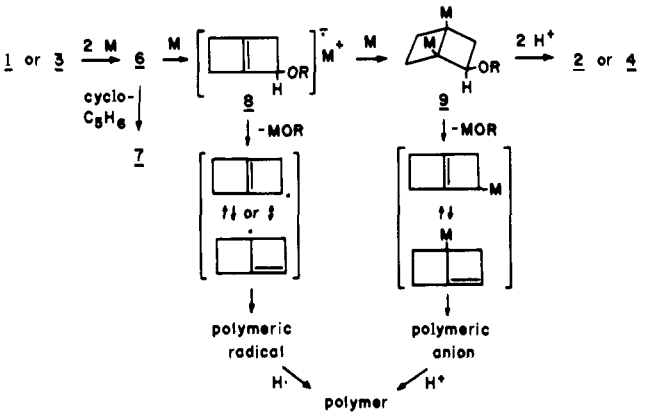
Scheme I



from Diels–Alder reaction of olefin **6** with 1,3-cyclopentadiene, we have no explanation for the apparent specificity in forming only one of the isomers of **7**, and we are unable to establish which isomer (**7a** or **7b**) we have. We also wish to point out that no dimeric products were observed in our Na/NH_3 reactions, unlike the analogous reductions of 1-Br-4-Cl[2.2.0].[8d,10]

From the facts that sodium was weighed to ±0.1 g and the expected errors in determining the percentages of the components from the limited reductions of **1** and **3** in Table I, it is difficult to precisely express the number of electrons used in producing each product. Assuming that two electrons are involved in forming olefin **6** which yields adduct **7**, and four electrons effect the **1** → **2** and **3** → **4** conversions, two or three electrons may be used to form the polymer. That this insoluble polymer is not the simple result of olefin polymerization of **6** is evidenced by the *absence* of $-OCH_3$ in its infrared spectrum (KBr pellet).

Reaction of **1** with lithium (~4 equiv consumed) in THF under reflux for 3 h gave a deep blue solution. Filtration (to remove excess Li) through glass wool with N_2 or Ar pressure and quenching with *t*-BuOH led to rapid loss of the blue color and precipitation of a light yellow polymer; no **2** could be found. Some "low molecular weight" material (containing a small amount of **1**) was removed from the polymer by heating it in CCl_4. The (^1H and ^{13}C) NMR and IR spectra of this CCl_4 soluble material (**1** removed) showed the *absence* of $-OCH_3$, $>C-OR$, $>CH-CH_3$, and $>C-CH_3$ groups, but did indicate some vinyl absorptions.

The ESR spectrum of the filtered blue solution in THF showed only a weak broad signal. Addition of oxygen immediately produced a yellow solution exhibiting an ESR signal attributed to $O_2^{-}\cdot$.[12] The ^{13}C NMR spectrum of the blue solution (THF) showed only a small amount of unreacted starting material **1**. These spectral data indicate that the species in the blue solution is polymeric and the reaction with O_2 ($\rightarrow O_2^{-}\cdot$) show it to be carbanionic in character although the presence of some paramagnetic sites cannot be discounted.

A mechanistic scheme which accommodates the above results is given in Scheme I. This suggests that three electrons are used to produce the polymer in the reductions of Table I by eliminating MOR from the olefin anion radical **8**. The stereospecificity in yielding **9** with exo C_2OR is attributed to the expected thermodynamic preference of exo vs. endo,[13] and the probable M · · OR through-space bonding. Since excellent yields of **2** and **4** are produced with no polymer formation in both media with excess alkali metal, the reduction of **8** → **9** must be considerably faster than the intramolecular elimination of MOR from radical anion **8**. This also accounts for the relatively large amounts of **2** and **4** formed in the experiments listed in Table I.

Acknowledgment. We wish to thank the National Science Foundation (CHE-76-01410) for support of this research.

References and Notes

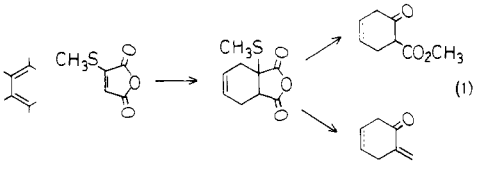
(1) For paper 16, see R. N. McDonald and R. R. Reitz, *J. Am. Chem. Soc.*, **98**, 8144 (1976).
(2) R. N. McDonald and C. A. Curi, *Tetrahedron Lett.*, 1423 (1976).
(3) 1 was converted to **2** in 66% isolated yield in Na/NH_3, but considerable **2** was lost during workup. No other products were observed, and the true yield of **2** from this reduction was probably >90%.
(4) R. N. McDonald and C. E. Reineke, *J. Org. Chem.*, **32**, 1878 (1967).
(5) (a) R. N. McDonald and C. E. Reineke, *J. Org. Chem.*, **32**, 1888 (1967); (b) R. N. McDonald and G. E. Davis, *J. Am. Chem. Soc.*, **94**, 5078 (1972).
(6) The deuterium analysis was accomplished by measuring peak areas relative to that of the OCH_3 methyl in the proton decoupled ^{13}C NMR spectra of **2** and **2**-*1,4-d*$_2$. No other absorptions interferred in this analysis; however, this appears to be about the lower limit of proton which can be reasonably observed at these bridgehead positions by this method. The mass spectrometric[7] and NMR analyses of **2** and **2**-*1,4-d*$_2$ show good agreement and will be discussed in the full paper of this research.
(7) We thank Professor R. G. Cooks for the mass spectral analyses of these compounds.
(8) (a) K. B. Wiberg, G. J. Burgmaier, and P. Warner, *J. Am. Chem. Soc.*, **93**, 246 (1971); (b) M. E. Jason, J. A. McGinnety, and K. B. Wiberg, *ibid.*, **96**, 6531 (1974); (c) C. J. Casanova and H. R. Rogers, *J. Org. Chem.*, **39**, 3803 (1974); (d) K. B. Wiberg, W. F. Bailey, and M. E. Jason, *bid.*, **39**, 3803 (1974).
(9) A quantitative yield of **2** from 1 is obtained in this solvent using either *t*-BuOH or pinacol as the proton source.
(10) We gratefully acknowledge Professor Wiberg's suggestion of this method of olefin **6** trapping and details of these experiments applied to olefin **5** from the Ph.D. thesis of M. Jason where a 30-s time delay of cyclopentadiene addition was used.
(11) The ^{13}C NMR spectrum of adduct 7 will be given in the full paper describing a new synthesis of bicyclo[2.2.0]hexan-*exo*-2-ol.[4]
(12) We thank Professor W. C. Danen for this spectral determination.
(13) H. L. Goering and C. B. Schewene, *J. Am. Chem. Soc.*, **87**, 3516 (1965), report ΔH = 1.2 kcal/mol for the *exo*- and *endo*-2-norbornyl acetates from equilibration studies.

Richard N. McDonald,* Cesin A. Curi
Department of Chemistry, Kansas State University
Manhattan, Kansas 66506
Received January 25, 1977

New Synthetic Reagents. Methylthiomaleic Anhydride: A Synthon for Protected Carbomethoxyketene

Sir:

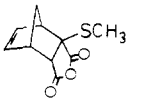
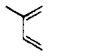
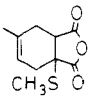
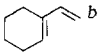
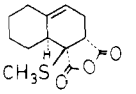
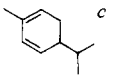
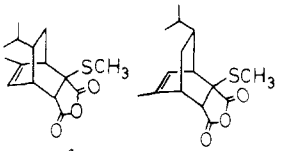
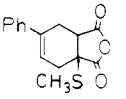
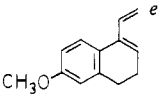
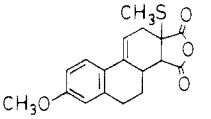
β-Keto esters are among the most important synthetic intermediates for elaboration of complex molecules. Normally they are prepared by carboxylations of ketones;[1] more recently, alkylations of dianions of simple β-keto esters make more complex ones available.[2] α-Methylene ketones are also valuable intermediates. Most noteworthy is the recent development of a new annulation procedure based upon these compounds.[3] We wish to report an annulative approach to these intermediates employing a new reagent, 2-methylthiomaleic anhydride (**1**), as represented by eq 1. This study also illustrates the utility of sulfur in controlling regiochemistry of dienophiles.[4]



(1)

The reagent is prepared by addition of excess methanethiol to acetylenedicarboxylic acid (ethanol, 25 °C),[5] which gives a 6:1 ratio of 2-methylthiofumaric and maleic acids, followed by dissolving in thionyl chloride (*caution:* vigorous evolution of gas) and stirring at room temperature for 1 h and 60 °C for 7 h.[6] Removal of excess thionyl chloride by heating at 120 °C at aspirator pressure (drying tower) and distillation of the residue at 123–125° (0.5 mm) gives the crystalline anhydride,[7a-c] mp 36–37 °C (ether), in 68–77% yields: IR 1845, 1745, 1565 cm^{-1}; ^1H NMR δ 6.28 and 2.56; ^{13}C NMR 162.43,

Table I. Diels–Alder Reactions of 1

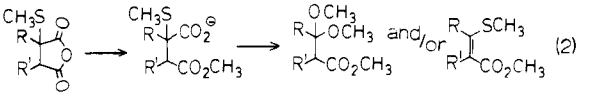
Entry	Diene	Temp, °C	Time, h	Adduct[a]	Mp, °C	Yield, %
1		0	95	 **2**	65–6	90
2		85	21	 **3**		80
3	 *b*	70	24	 **4**	84–5	81
4	 *c*	90	24*g*	 **6***f* **5***f*		51
5	 *d*	90	24*g*	 **7**	106–7	91
6	 *e*	84	2*g*	 **8**	140–6	82

[a] The IR spectra typically had carbonyl bands at 1780 ± 10 and 1851 ± 9 cm^{-1}. The NMR spectra showed the S–CH_3 signals at 2.24 ± 0.05. Also see ref 7a–c. [b] K. Suga, S. Watanabe, and K. Kamma, *Can. J. Chem.*, **45**, 933 (1967). [c] Y. W. G. Dauben, M. E. Lorber, N. D. Vietmeyer, R. H. Shapiro, J. H. Duncan, and K. Tomer, *J. Am. Chem. Soc.*, 90, 4762 (1968). [d] A. Z. Shikhmamedbekova and S. I. Sadykh-Zade, *Azerb. Khim. Zh.*, 73 (1962); *Chem. Abstr.*, 58, 4444f (1963). [e] P. A. Robins and J. Walker, *J. Chem. Soc.*, 3249 (1956); Z. G. Hajos, D. R. Parrish, and M. W. Goldberg, *J. Org. Chem.*, 30, 1213 (1965). [f] Approximately 2:1 mixture of **5**:**6**. [g] In this case, halfway through the reaction, an additional equivalent of diene was added.

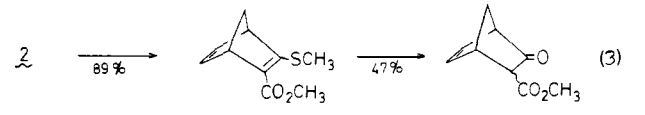
162.09, 155.52, 118.48, and 15.15.

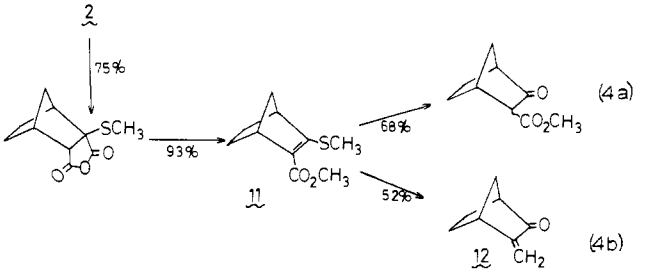
The Diels–Alder reactions, summarized in Table I, are usually carried out by mixing the diene with **1** neat at 0 to 80 °C in the presence of BHT[8] or hydroquinone as stabilizer. The adducts can be purified by crystallization or by a base extraction–reacidification procedure followed by treatment with thionyl chloride/pyridine to re-form the anhydride. The crude anhydride may be taken directly onto the subsequent reactions without any purification. Endo selectivity is seen since **2** shows a clean doublet (δ 3.22, J = 5 Hz) for the proton α to the carbonyl group. High regioselectivity is seen (Table I, entries 2, 3, 5, and 6) where in each case only a single regioisomer is detected. For example, in the 270-MHz spectrum (acetone-d_6) of adduct **7** irradiation of the vinyl proton reveals an AB pattern (J = 19.7 Hz) at δ 2.06 and 2.95 for the adjacent allylic methylene group indicative of its being next to the quaternized carbon bearing sulfur. The regio- and stereochemistry of adduct **4** was clearly indicated by its NMR spectrum which showed the methine α to the carbonyl group as a dd (J = 8.1 and 2.5 Hz) at δ 3.24 indicative of a pseudo-axial hydrogen adjacent to a methylene group. The depicted stereochemistry represents that anticipated for "endo" addition. The observation of a single adduct with **1** and 1-vinyl-6-methoxy-3,4-dihydronaphthalene contrasts with methylmaleic anhydride[9] and indicates the regiocontrol exercised by sulfur in the dienophile. Indeed, it appears that sulfur may be a general control element in cycloadditions. In the case of α-phellandrene, sulfur controlled the regiochemistry to the extent of 2:1.

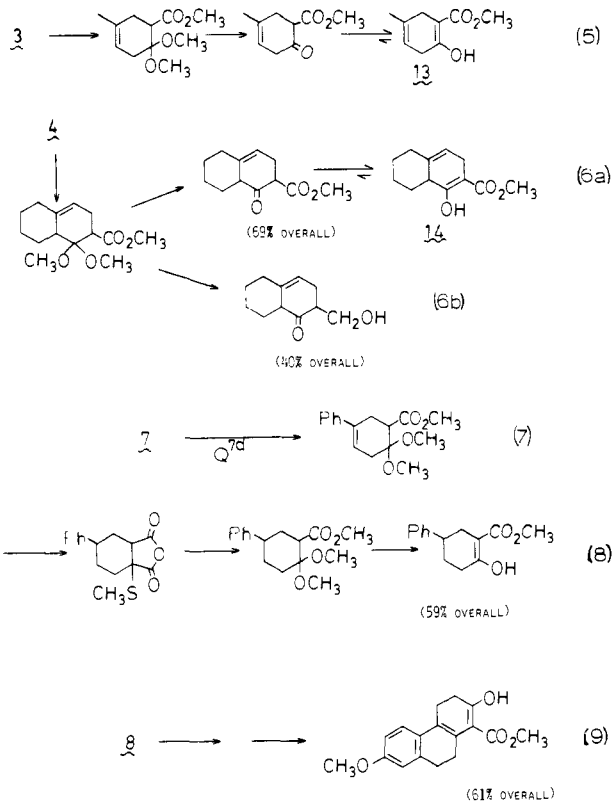
The potential of these versatile adducts is realized in part by their subjection to oxidative decarboxylation[10] which gives a protected form of the β-keto ester (see eq 2). Methanolysis


(2)

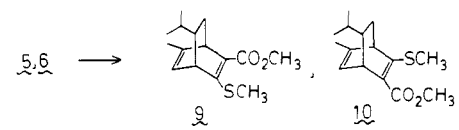
in the presence of sodium bicarbonate at room temperature followed by in situ treatment with NCS at 0 °C leads to either the ketal or enol thioether as summarized in eq 3–9.[7] Except for the norbornyl (eq 3 and 4) and bicyclo[2.2.2]octyl (vide


(3)

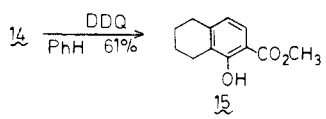

(4a) (4b)



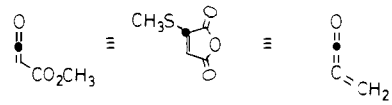
infra) systems, the ketal ester is the major if not exclusive product. Determination of the regioisomerism of **5** and **6** was effected after their oxidative decarboxylation to **9** and **10**. Eu^{3+}-induced shifts for **9** show that the bridgehead proton (δ 3.87 b) proximal to the ester does not couple to the vinyl proton, whereas in **10** this coupling (proton at δ 4.04, dd, J = 7, 2 Hz) is evident and verified by spin decoupling. Equations 4 and 8 illustrate the ability to reduce the double bond without desulfurizing [H_2, $Pd(OH)_2/C$,[11] H_2O, Na_2CO_3 then $SOCl_2$, pyridine, ether].



The ketal esters can be hydrolyzed to the keto esters with dilute aqueous hydrochloric acid, and the vinyl sulfides can be hydrolyzed by mercuric chloride in aqueous acetonitrile at reflux. The double bond does not necessarily migrate under the conditions of the hydrolysis. Thus, **14** appears to be regio- and stereoisomerically pure as determined by the presence of the typical vinyl proton at δ 5.37 and a single methyl ester at δ 3.86. Most of the β-keto esters exist mainly in their enolized forms (IR and NMR).[12] Most interesting is the ability to modify the ester before unmasking the carbonyl group. For example, reduction of **11** followed by hydrolysis leads directly to the α-methylene ketone **12**[13] (IR 1650 and 1730 cm^{-1}; NMR δ 5.76, 5.18, 3.16, and 2.76). This approach to β-keto esters also becomes an approach to salicylic esters. Dehydrogenation of **14** produces **15**,[14] mp 49–50 °C.



The versatility of α-alkylthiocarbonyl compounds in synthesis increases the potential applications of this approach.[15] We have clearly demonstrated its potential as an annulative approach to β-keto esters, α-methylene ketones, and salicylic



esters. The ready availability of the reagent from very inexpensive starting materials and the facility of its reactions provide a stimulus for additional exploration of its chemistry and the chemistry of its cycloadducts.

A typical experimental procedure follows. Methylthiomaleic anhydride (1.02 g, 7.1 mmol), 1-vinylcyclohexene (1.66 g, 15.4 mmol) and BHT (7.2 mg) were heated at 78 °C for 24 h. After cooling, the mixture was diluted with ether and cooled to −78 °C to give 1.45 g (81%) of crystalline adduct **4** (recrystallized from ether). To a slurry of 603.5 mg (7.18 mmol) of sodium bicarbonate in 15 mL of methanol at room temperature was added 306.6 mg (1.22 mmol) of anhydride **4**. After 1 h, the mixture was cooled to 0 °C and 351 mg (2.63 mmol) of NCS added. Reaction proceeded for 8 h at 0 °C and was then quenched by addition of aqueous sodium sulfite solution. After extraction with ether, drying, and evaporation in vacuo, 260.1 mg (84% yield) of ketal ester was obtained as a colorless semisolid. The ketal ester was dissolved in 20 mL of ether and 20 mL of 10% aqueous hydrochloric acid added. After 1 h at room temperature, the ether layer was separated and the water layer extracted with additional ether. After drying and evaporation, 184.4 mg (73% yield) of keto ester **13** was obtained as a colorless oil which gave 173.6 mg (69% overall yield from **4**) of **13** as a colorless solid upon distillation at 95–105 °C (0.3 mm).

Acknowledgment. We wish to thank the National Science Foundation and the National Institutes of Health, General Medical Sciences Grant GM-13598, for their generous support of our programs. G.L. thanks the Science Research Council for a postdoctoral fellowship. We express our sincerest appreciation to Dr. Kjell Undheim for his participation in the program during a sabbatical stay in our laboratories.

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(1) For a review see H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 11. For a few recent developments see O. A. Plantesna, H. deKoning, and H. O. Huisman, *Tetrahedron Lett.*, 2945 (1975); M. R. Czarny, K. K. Maheshwari, J. A. Nelson, and T. A. Spencer, *J. Org. Chem.*, **40**, 2079 (1975); R. G. Salomon and M. F. Salomon, *ibid.*, **40**, 1488 (1975); Y. Ito and Y. Takami, *Chem. Lett.*, 1035 (1974); E. J. Corey and R. H. K. Chen, *J. Org. Chem.*, **38**, 4086 (1973).
(2) S. N. Huckin and L. Weiler, *J. Am. Chem. Soc.*, **96**, 1082 (1974).
(3) Cf. Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, **38**, 3244 (1973); G. Stork and J. d'Angelo, *J. Am. Chem. Soc.*, **96**, 7114 (1974).
(4) Cf. B. M. Trost and A. J. Bridges, *J. Am. Chem. Soc.*, **98**, 5017 (1976); T. Cohen, A. J. Mura, Jr., D. W. Shull, E. R. Fogel, R. J. Ruffner, and J. R. Fabek, *J. Org. Chem.*, **41**, 3218 (1976). Also see D. A. Evans, C. A. Bryan, and C. L. Sims, *J. Am. Chem. Soc.*, **94**, 2891 (1972).
(5) Cf. B. Weibull, *Ark. Kemi*, **3**, 225 (1951); W. E. Truce and R. B. Kruse, *J. Am. Chem. Soc.*, **81**, 5372 (1959).
(6) The cyclization of the diacids to the anhydride with thionyl chloride was developed by Dr. K. Undheim.
(7) (a) This compound was fully characterized by spectral analysis. (b) This compound had a satisfactory elemental analysis (±0.3%) and/or elemental composition by high resolution mass spectroscopy. (c) Yields are for isolated pure compounds unless otherwise noted. (d) This represents the yield for unpurified product.
(8) BHT = 2,6-di-*tert*-butyl-4-methylphenol.
(9) W. E. Bachman and J. M. Chemerda, *J. Am. Chem. Soc.*, **70**, 1468 (1948).
(10) B. M. Trost and Y. Tamaru, *J. Am. Chem. Soc.*, **99**, 3101 (1977); *Tetrahedron Lett.*, 3797 (1975); *J. Am. Chem. Soc.*, **97** 3528 (1975).
(11) M. Pearlman, *Tetrahedron Lett.*, 1663 (1967).
(12) **13:** IR 3100–3400, 1660, 1620 cm^{-1}; ^1H NMR δ 5.45 and 5.34 (two broad abs, 1 H), 3.80 (s, 3 H), 2.70–3.0 (m, 4 H), 1.74 (bs, 3 H). **14:** IR 3100–3400, 1655, 1617 cm^{-1}; ^1H NMR δ 5.37 (1 H, b), 3.86 (3 H, s), 2.6–3.0 (3 H, m), 1.0–2.6 (9 H, m); ^{13}C NMR δ 172.7, 171.3, 136.2, 115.2, 94.5, 51.4, 41.4, 35.0, 32.1, 27.7, 26.5, 25.1. For ^{13}C comparisons see "Carbon-13 NMR", Sadtler Research Laboratories, Inc., Spectrum No. 1611C. Also see G. Höfle, *Tetrahedron*, **32**, 1431 (1976). For keto–enol tautomerism in β-keto esters see S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkit, *Tetrahedron*, **19**, 1625 (1963).
(13) H. Krieger, K. Manninen, and J. Paasivirta, *Suom. Kemistil. B*, **39**, 8 (1966); *Chem. Abstr.*, **64**, 17441c (1966), and earlier references; W. F. Erman, *J. Org. Chem.*, **32**, 765 (1967).

(14) E. Schroeter, *Justus Liebigs Ann. Chem.*, **426**, 83 (1922).
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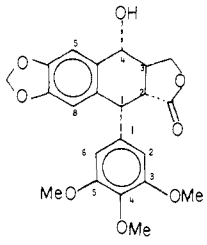
Barry M. Trost,* George Lunn
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706
Received May 16, 1977

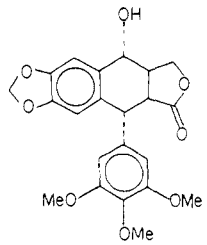
Oxidative Aryl–Benzyl Coupling. A Biomimetic Entry to Podophyllin Lignan Lactones

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]

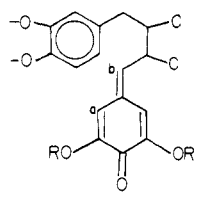


I

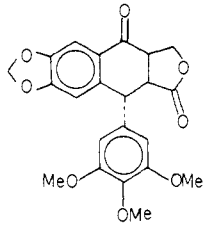


II

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.

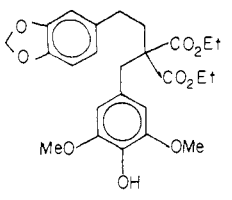


III

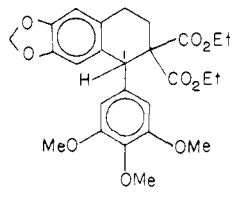


IV

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 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]

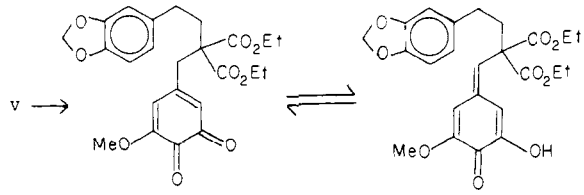


V

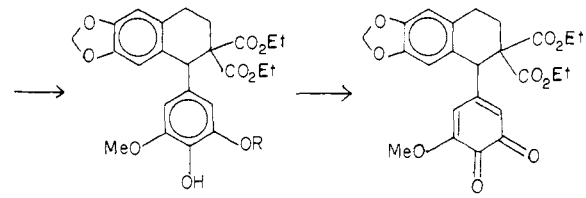


VI

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.

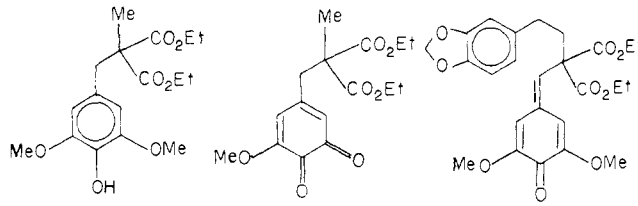


VII VIII



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*-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]



XI XII XIII

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