(1947).
(4) (a) A. I. Titov and A. N. Baryshnikova, *J. Gen. Chem. USSR*, **17**, 829 (1947); (b) A. I. Titov and N. G. Laptev, *ibid.*, **19**, 267 (1949).
(5) T. L. Davis, D. E. Worrall, N. L. Drake, R. W. Helmkamp, and A. M. Young, *J. Am. Chem. Soc.*, **43**, 594 (1921).
(6) S. Tsutsumi and E. Iwata, *J. Chem. Soc. Jpn., Pure Chem. Sect.*, **72**, 141 (1951); *Chem. Abstr.*, **46**, 6604a (1952).
(7) T. Osawa, T. Yoshida, and K. Namba, *Kogyo Kayaku Kyokaishi*, **27**, 162 (1966).
(8) The oxides of Ag, Cu, Pb, Pt, and W and the nitrates of Ag, Al, Ba, Bi, Ca, Cd, Co, Cr, Cu, Fe, K, Mg, Mn, Na, Ni, Pb, Sn, Sr, U, and Zn were examined.[6,7]
(9) R. O. C. Norman, W. J. E. Parr, and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 369 (1974). These workers have achieved limited success using palladium salts and nitrogen dioxide in chloroacetic acid.
(10) H. Komoto, F. Hayano, T. Takami, and S. Yamato, *J. Polym. Sci., Part A-1*, **9**, 2983 (1971).
(11) A summary of the relative rates and isomer distributions for mercuration under several different conditions is found in L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, **1**, 35 (1963).
(12) F. C. Whitemore, "Organic Compounds of Mercury", Chemical Catalog Co., New York, N.Y., 1921, p 34.
(13) H. C. Brown and C. W. McGary, *J. Am. Chem. Soc.*, **77**, 2300 (1955).
(14) H. C. Brown and C. W. McGary, *J. Am. Chem. Soc.*, **77**, 2306 (1955).
(15) Perchloric acid catalyzes the isomerization of the arylmercuric acetates in acetic acid: ref 14.
(16) (a) H. Zollinger, *Adv. Phys. Org. Chem.*, **2**, 168 (1964); (b) W. Kitching, *Organomet. Chem. Rev., Sect. A*, **3**, 35 (1968).
(17) D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 655 (1975).
(18) (a) D. Cook, S. J. Kuhn, and G. A. Olah, *J. Chem. Phys.*, **33**, 1669 (1960). (b) R. W. Sprague, A. B. Garrett, and H. H. Sisler, *J. Am. Chem. Soc.*, **82**, 1059 (1960).
(19) F. Challenger and E. Rothstein, *J. Chem. Soc.*, 1258 (1934).
(20) (a) E. C. Taylor, R. H. Danforth, and A. McKillop, *J. Org. Chem.*, **38**, 2088 (1973); (b) B. Davies and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 65 (1975); (c) E. C. Taylor, H. W. Altland, and A. McKillop, *J. Org. Chem.*, **40**, 3441 (1975).
(21) C. Eaborn, Z. S. Salih, and D. R. M. Walton, *J. Chem. Soc., Perkin Trans. 2*, 172 (1972).
(22) G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, **86**, 1067 (1964).
(23) The nitrode-*tert*-butylation of 4-*tert*-butyltoluene in acetic anhydride gives no more than 1.0% 4-nitrotoluene: M. Bishop, unpublished results.
(24) The steric requirements of nitration reagents are always greater than the steric requirements of comparable nitrosation reagents, e.g., the nitronium ion compared to the nitrosonium ion or acetyl nitrate compared to acetyl nitrite.
(25) Y. Ogata and H. Tezuka, *J. Am. Chem. Soc.*, **89**, 5428 (1967).
(26) J. Turkevich, H. A. McKenzie, L. Friedman, and R. Spurr, *J. Am. Chem. Soc.*, **71**, 4045 (1949).
(27) E. Dreher and R. Otto, *Justus Liebigs Ann. Chem.*, **154**, 174 (1870).
(28) E. Wroblevsky, *Justus Liebigs Ann. Chem.*, **168**, 176 (1873).
(29) G. A. Olah and S. J. Kuhn, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 480.
(30) J. P. Freeman and I. G. Shepard, *Org. Synth.*, **43**, 84 (1963).

Stereoselective Total Synthesis of Diterpene Resin Acids

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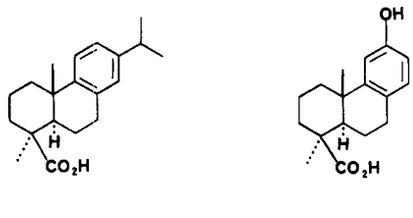
Stereoselective total syntheses of diterpene resin acids (±)-callitrisic acid (1) and (±)-podocarpic acid (2) are described. The synthetic approach to both natural products utilizes a highly stereoselective reductive elimination–alkylation reaction for establishing the axial stereochemistry of the carbomethoxyl functional group at position 1 in esters **12A** and **12B**. Thus treatment of vinyl esters **11A** or **11B** with lithium metal in liquid ammonia/DME followed by methyl iodide effects comcomitant reduction, deoxygenation, and stereoselective alkylation in a single step, therefore providing a general synthetic procedure for the construction of podocarpane type natural products.

The diterpene class of naturally occurring substances forms an enormous group of plant and fungal products derived, biogenetically, from four isoprene units via geranylgeranyl pyrophosphate.[1] Notable features of the diterpene natural products are the fascinating variation encountered in their structures and the wide range of their biological activities. Two diterpene molecules, which have common structure features in rings A and B, are resin acids callitrisic acid (1) and podocarpic acid (2). Callitrisic acid (1) was isolated from the Australian white cypress pine *Callitris columelaris* in 1967.[2] Several syntheses of callitrisic acid (1) have been reported.[3] Interestingly enough Haworth and Baker's synthesis,[3a] the first total synthesis of a diterpenoid natural product, occurred 28 years before callitrisic acid (1) was isolated. Podocarpic acid (2) was first isolated in 1873 from *Podocarpus cupressium*.[4] The structure and stereochemistry of podocarpic acid (2), however, were not characterized until 1940.[5] A number of syntheses of podocarpic acid (2) and deoxypodocarpic acid have been published.[6] The latter acid has been successfully converted to podocarpic acid (2); therefore, synthesis of it also constitutes a total synthesis of podocarpic acid (2). Both callitrisic acid (1) and podocarpic acid (2) have common structural features in rings A and B; namely, they both have a trans A,B ring fusion, an axially oriented carboxylic acid functional group at position 1, an axial methyl group at position 4a, and an equatorial methyl group at position 1. During the course of our investigations aimed at a total synthesis of the antifungal antibiotic LL-Z1271α we developed a new and highly stereoselective method for the construction of ring A of podocarpane type natural products. This new method has general applicability in the synthesis of podocarpane type naturally occurring substances as exemplified by our previously reported syntheses.[3g,6g,7] We wish to report, herein, the full details of our total syntheses of diterpene resin acids (±)-callitrisic acid (1) and (±)-podocarpic acid (2).

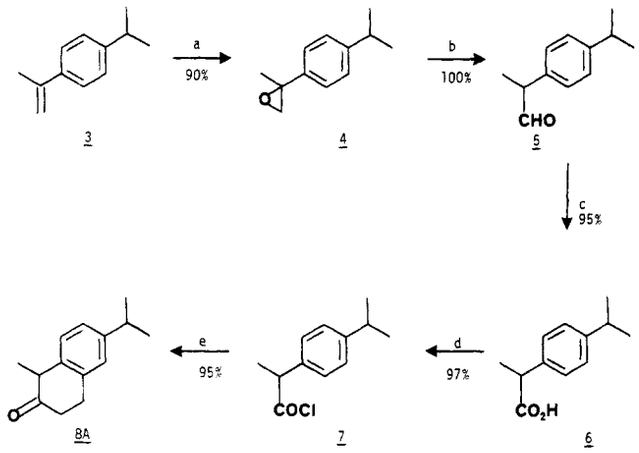
Chart I



1 2

Synthesis of (±)-Callitrisic Acid (1). The starting material chosen for our synthesis of (±)-callitrisic acid (1) is 6-isopropyl-1-methyl-2-tetralone (**8A**, Scheme I), which was previously prepared by Stork and Schulenberg[8] from cumene as well as 2-acetonaphthone by lengthy multistep sequences. We have developed a short and efficient alternate route to tetralone **8A** beginning with 4-isopropenylisopropylbenzene (3).[9] Epoxidation of alkene **3** with *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of disodium hydrogen phosphate

Scheme I

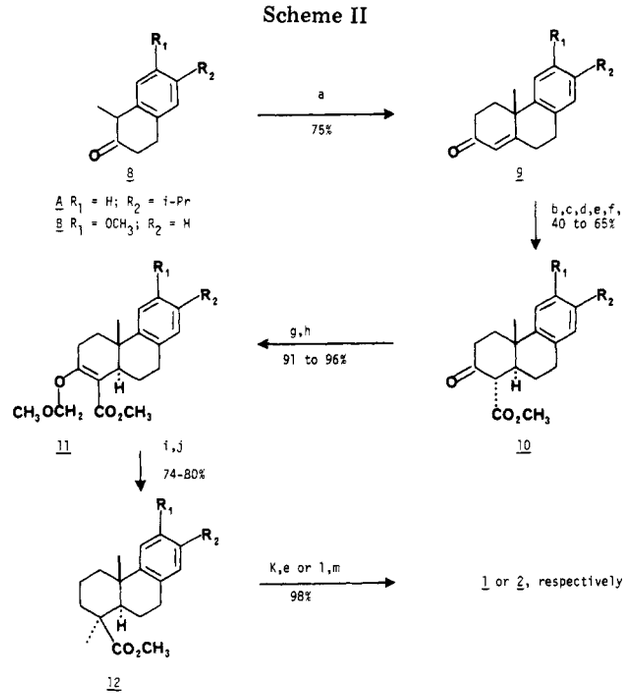


a) m-CPBA, Et_2O, Na_2HPO_4; b) $BF_3{\cdot}OEt_2$, Et_2O; c) CrO_3, H_2SO_4, H_2O, acetone; d) $SOCl_2$, C_6H_6; e) anhydrous $AlCl_3$, CH_2Cl_2, -20±2°, $CH_2{=}CH_2$.

in ether gives oxirane **4** in 90% yield.[10] Treatment of epoxide **4** with 1.2 equiv of boron trifluoride etherate in ether for 40 min at 0–25 °C followed by an aqueous workup affords aldehyde **5** in quantitative yield.[11] Oxidation of aldehyde **5** with Jones reagent at 0–25 °C for 30 min produces crystalline carboxylic acid **6** (mp 68–69 °C) in 95% yield.[12] Treatment of carboxylic acid **6** with 1.5 equiv of thionyl chloride at room temperature for 24 h followed by removal of excess thionyl chloride via codistillation with benzene gives acid chloride **7** in 97% yield.[13] Finally, tetralone **8A** was prepared from acid chloride **7** utilizing Sims and co-workers' modification of the Friedel–Crafts reaction.[14] Acid chloride **7** was added dropwise to a stirred suspension of 1.03 equiv of anhydrous aluminum chloride in dry dichloromethane at −20 ± 2 °C. As soon as a homogeneous, light green solution of acid chloride–aluminum chloride complex formed (about 5 min after the addition) then a gentle stream of ethylene was allowed to bubble into the stirred reaction mixture over a period of 20 min. The resulting green-brown solution was stirred for an additional 10 min at −20 ± 2 °C, and then allowed to stir for 3 h at room temperature. After aqueous workup at 0 °C, tetralone **8A** was obtained in 95% yield (83% overall yield from alkene **3**). This reaction can be monitored by GLC, but it can also be conveniently monitored, simply and reproducibly, by the color change of the reaction mixture.

Robinson annelation of tetralone **8A** with 1.3 equiv of methyl vinyl ketone in the presence of a catalytic amount of sodium ethoxide in absolute ethanol affords tricyclic enone **9A** (Scheme II, R_1 = H; R_2 = *i*-Pr) in 75% yield.[15] Simultaneous reduction of enone **9A** to a trans A,B ring fusion and introduction of the carbomethoxyl group at position 1 were accomplished using Stork and co-workers' reductive carbomethoxylation procedure.[16] Sequential treatment of enone **9A** with 3 equiv of lithium metal in anhydrous liquid ammonia–ether, quickly removing the ammonia, adding excess anhydrous dry ice (freshly sublimed twice), quenching with water, extracting with ether to remove neutral side products, acidifying with 10% hydrochloric acid solution at 0 °C, and esterification with ethereal diazomethane produces crystalline β-keto ester **10A** in 64% yield. Keto ester **10A** was found to exist exclusively in the keto form. Compounds with 2-keto-1-carbomethoxyl functional groups in *trans*-decalin rings are reported to exist in the keto form as opposed to the enol form.[17] Wenkert and Jackson rationalize this observation by

Scheme II



a) MVK, EtOH, NaOEt; b) Li, NH_3, Et_2O; c) $-NH_3$; d) CO_2; e) H_3O^+, 0°; f) CH_2N_2, Et_2O; g) NaH, HMPA; h) CH_3OCH_2Cl; i) Li, NH_3, DME; j) CH_3I; k) KO*t*-Bu, DMSO; l) n-PrSLi, HMPA m) HI, HOAc.

a combination of two facts: first, $\Delta^{1,2}$-alkenes in trans-fused decalin rings are energetically unfavorable configurations; second, there is a strong steric repulsion between the carbomethoxyl group at position 1 and the equatorial hydrogen at position 10 (the peri effect).[17,18]

Alkylation of β-keto ester **10A** using 1.2 equiv of sodium hydride in hexamethylphosphoric triamide (HMPA) followed by addition of 1.2 equiv of chloromethyl methyl ether gives vinyl ether ester **11A** in 96% yield.[19,20] Finally, reductive elimination–alkylation of vinyl ether ester **11A** using 7 equiv of lithium metal in anhydrous liquid ammonia/1,2-dimethoxyethane (DME), followed by quenching with excess methyl iodide, affords (±)-methyl callitrisate (**12A**) in 74% yield as the only isomer observed (NMR, GLC) or isolated (LC). Methyl ester **12A** was cleaved to (±)-callitrisic acid (**1**) in 98% yield using potassium *tert*-butoxide in anhydrous dimethyl sulfoxide (Me_2SO) at 100 °C for 6 h followed by acidification.[2] Both synthetic callitrisic acid and methyl callitrisate were identical with authentic samples[21] with respect to IR, NMR, TLC, GLC, and LC.

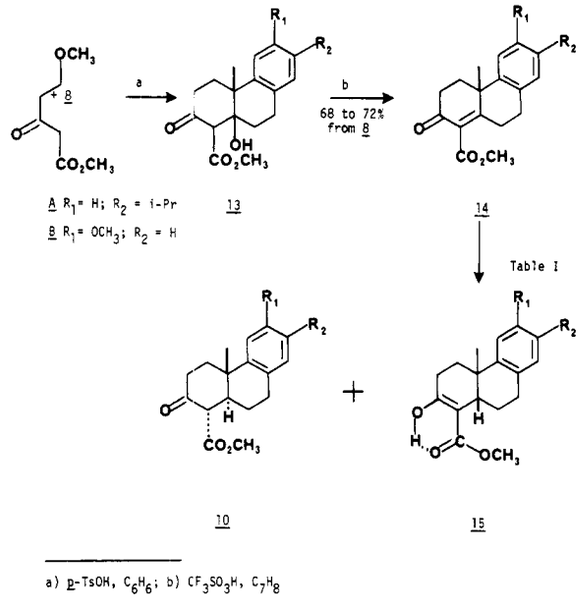
Synthesis of (±)-Podocarpic Acid (2). The starting material chosen for our synthesis of podocarpic acid (**2**) is tricyclic enone **9B** (Scheme II, R_1 = OCH_3; R_2 = H) previously prepared by Kuehne from 2,7-dimethoxynaphthalene via 7-methoxy-1-methyl-2-tetralone (**8B**).[22,23] Reductive carbomethoxylation[16] of enone **9B** affords crystalline β-keto ester **10B** in 40% yield. Alkylation of β-keto ester **10B** using sodium hydride in HMPA followed by chloromethyl methyl ether gives vinyl ether ester **11B** in 91% yield.[19,20] Reductive elimination–alkylation of vinyl ether ester **11B** using 6.1 equiv of lithium metal in DME followed by the addition of excess methyl iodide produces (±)-methyl *O*-methylpodocarpate (**12B**) in 80% yield as the only isomer observed (NMR, GLC) or isolated (LC). Synthetic ether ester **12B** was identical with an authentic sample[24] prepared from (+)-podocarpic acid (**2**) with respect to IR, NMR, TLC, and GLC. Ester **12B** can be selectively and quantitatively cleaved to *O*-methylpodocarpic acid using lithium *n*-propylmercaptide in HMPA.[25] The latter ether has been converted to (±)-podocarpic acid (**2**) with hy-

driodic acid in refluxing glacial acetic acid; therefore, our synthesis of (±)-methyl *O*-methylpodocarpate (**12B**) constitutes a total synthesis of (±)-podocarpic acid (**2**).

This new reductive elimination–alkylation reaction which is utilized in converting vinyl ether esters **11A,B** to equatorially methylated esters **12A,B**, respectively, are highly stereoselective. This high degree of stereoselectivity results from two reinforcing principles of stereoelectronic control: first, it is well known that exocyclic enolate anions (such as the ester enolate anion generated by reduction of vinyl ether esters **11A,B**, with lithium in liquid ammonia/DME) in cyclohexane rings have a decided preference for alkylation in which the alkylating agent approaches from the less hindered equational direction;[26a] second, the exocyclic enolate anions, generated in the reaction (**11A,B**, → **12A,B**, respectively), are also seriously hindered on the β side (axial direction) by a 1,3-axial methyl interaction of the methyl group at position 4a.[26b] This sequence of events from vinyl ether ester **11A,B**, to esters **12A,B**, respectively, represents a new type of reductive elimination–alkylation reaction. This reaction sequence is unique because it effects reduction, deoxygenation, and concomitant stereoselective methylation is a single step, thus providing an efficient and general pathway for the construction of podocarpane type natural products.

An Alternate Synthetic Route to β-Keto Esters 10A,B. An alternate synthetic route to β-keto esters **11A,B** (Scheme III) was investigated in the hope of circumventing the often-

Scheme III



times troublesome reductive carbomethoxylation reaction (**9A,B** → **10A,B**, respectively). Although this alternate route produces keto esters **10A,B**, in good overall yield (44–52%), the stereoeselectivity in the reduction step (**14A,B** → **10A,B** + **15A,B**, respectively) is considerably less efficient (Table I). Acid-catalyzed Robinson annelation of 1.6 equiv of methyl 5-methoxy-3-oxopentanoate with 6-isopropyl-1-methyl-2-tetralone (**8A**) in refluxing benzene for 60 h in the presence of a catalytic amount of *p*-toluenesulfonic acid[28] gives a mixture of tricyclic alcohol **13A** (15%) and keto ester **14A** (38%). When the same annelation is performed in refluxing toluene for 48 h a mixture of keto ester **14A** (39%) and enone **9A** (25%) was obtained. Utilizing trifluoromethanesulfonic acid in refluxing toluene for 70 h to effect the annelation reaction also affords a mixture of keto ester **14A** (20%) and enone **9A** (24%). Optimum conditions for the conversion of tetralone **9A** to tricyclic enone ester **14A** were determined to be as follows. A solution of 1.6 equiv of methyl 5-methoxy-3-oxopentanoate, 6-isopropyl-1-methyl-2-tetralone (**9A**), and a catalytic amount of *p*-toluenesulfonic acid in toluene was allowed to stir at reflux for 8 h using a Dean-Stark water separator to afford a mixture of ketol **13A** and enone **14A** in a 3:2 ratio, respectively. This crude mixture was then heated at reflux for 1 h in toluene in the presence of a catalytic amount of trifluoromethanesulfonic acid using a Dean-Stark water separator to give enone **14A** in 68% overall yield from tetralone **8A**. The best method found for the acid-catalyzed Robinson annelation of methyl 5-methoxy-2-oxopentanoate with 7-methoxy-1-methyl-2-tetralone was to heat this mixture in refluxing benzene in the presence of *p*-toluenesulfonic acid for 72 h using a Dean-Stark water separator followed by treatment with a catalytic amount of trifluoromethanesulfonic acid in refluxing toluene for 1 h again using a Dean-Stark water separator to give tricyclic enone ester **14B** in 72% overall yield from tetralone **8B**.

Table I

Compd	Reagents and conditions	Product ratio 10:15	Yield, %
14A	5% Pd–$BaSO_4$/EtOH/50 min/1 atm/RT	63.2:36.8	95[a]
		68.6:31.4	94[b]
	5% Pd/C/EtOH/1 h/1 atm/RT	52:48	90[a]
	5% Pd–$SrCO_3$/MeOH/17 h/1 atm/RT	46:54	85[a]
	PtO_2/HOAc/18 h/1 atm/RT	Trace Trace	*c*
	Li/NH_3/*t*-BuOH/THF	68.5:31.5	90[a]
	Zn/HOAc/Et_2O/6 h/RT	69:31	60[a]
	$NaBH_4$/pyridine/50 min/RT	58:42	90[a]
	$LiAlH(Ot\text{-}Bu)_3$/Et_2O/20 h/RT	Trace Trace	*d*
	$NaAlH_2(CH_3OCH_2CH_2O)_2$/CuBr/THF	No reaction	
14B	5% Pd–$BaSO_4$/EtOH/3 h/1 atm/RT	69.5:30.5	95[a]
		73.5:26.5	98[b]

[a] Estimated by GLC. [b] Isolated yield. [c] Complex mixture. [d] Allylic alcohol in 85% yield.

A number of methods for reduction of enones **14A,B** to β-keto esters **10A,B**, respectively, were explored (Table I). The best conditions for catalytic hydrogenation of enones **14A,B** were with 5% palladium on barium sulfate in absolute ethanol, which affords a mixture of trans β-keto esters **10A,B** and cis β-keto esters **15A,B** in 73.5–68.6 and 26.5–31.4% yield, respectively.[17,30] Compounds **15A,B** were each homogeneous on TLC; however, each showed two peaks in a ratio of 81–80:19–20, respectively, on GLC analysis. Spectral analysis (IR, NMR) showed that each compound **15A,B** exists as a mixture of enol–keto tautomers in a ratio of 70–75:30–25, respectively.

The use of dissolving metal reagents for the reduction of α,β-unsaturated ketones to saturated ketones with the more stable configuration at the β-carbon atom has been widely utilized in stereoselective syntheses.[31] Interestingly enough, when enone **14A** is reduced with 2.2 equiv of lithium metal in liquid ammonia/tetrahydrofuran (THF)/*tert*-butyl alcohol (1.25 equiv) both trans β-keto ester **10A** and cis β-keto ester **15A** were produced in 90% yield as a 68.5:31.5 ratio, respectively. Reduction of enone **14A** with zinc powder in glacial acetic acid—ether[32] for 6 h at room temperature also gives a mixture of trans β-keto ester **10A** and cis β-keto ester **15A** in 60% yield as a 69:31 ratio, respectively.

Enone esters **14A,B** should be good electrophiles in a Michael reaction and therefore compounds **14A,B** may readily undergo 1,4-reduction with appropriate hydride reducing agents. Reduction of enone esters **14A,B** in this fashion is

expected to be a facile process because these reactions should produce very stable enolate anions of either β-keto esters **10A,B** or **15A,B.** Adank and co-workers reported the use of sodium borohydride in pyridine to effect 1,4-reduction of some enones.[33] Reduction of enone **14A** with 1.23 equiv of sodium borohydride in dry pyridine at room temperature for 50 min produces a mixture of trans β-keto ester **10A** and cis β-keto ester **15A** in 90% yield as a 58:42 ratio, respectively. Dilling and Plepys recently reported that the reduction of certain α,β-unsaturated ketones could be effected by lithium tri-*tert*-butoxyaluminum hydride in ether to give primarily saturated ketones.[34] However, when enone **14A** was treated with 2.56 equiv of lithium tri-*tert*-butoxyaluminum hydride in ether for 20 h at room temperature only reduction to the corresponding allylic alcohol was observed. This was confirmed spectroscopically (IR 3400 cm^{-1}, OH; 1725 cm^{-1}, conjugated ester) and by oxidation of this alcohol back to enone **14A** with Jones reagent.[12] Recently, Semmelhack and Stauffer reported that complex hydridometallic species generated from sodium bis(2-methoxyethoxy)aluminum hydride and copper(I) bromide in THF at 0 °C selectively reduces some α,β-unsaturated esters and ketones.[35] But, when enone ester **14A** was allowed to react with this complex, generated in situ, only unchanged starting material was recovered quantitatively.

Conclusion

Both (±)-callitrisic acid (**1**) and (±)-podocarpic acid (**2**) have been successfully synthesized in a limited number of specific and highly stereoselective steps. The best method for the preparation of trans β-keto esters **10A,B** is via Stork and co-workers' reductive carbomethoxylation procedure, although reduction of enone esters **14A,B** provides a good, but less stereoselective, alternative pathway. Reductive elimination–alkylation of vinyl ether esters **11A,B** has been shown to be a very efficient and stereoselective method with general applicability for the construction of ring A of podocarpane type natural products.

Experimental Section

General Procedure. Melting points were determined on a Fisher-Johns, a Thomas-Hoover, or a Büchi melting point apparatus. All melting points and boiling points are uncorrected. Evaporative distillation refers to bulb to bulb short-path distillation in which the bulb was heated in an Aldrich Kugelrohr apparatus.[36] The temperatures cited for these distillations refer to the maximum temperature attained by the air chamber during the distillation. Microanalyses were preformed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Analytical gas phase chromatography (GLC) was performed on a Varian Aerograph Model 1400, equipped with a flame ionization detector with helium as the carrier gas, using the following types of columns and flow rates: (a) 5-ft, stainless steel, 0.125-in. column, packed with 3% SE-30 on Varaport-30, 100/120 mesh (Varian); (b) 6-ft, stainless steel, 0.125-in. column, packed with 5% OV-17 on Varaport-30, 80/100 mesh (Varian); (c) 6-ft, stainless steel, 0.125-in. column, packed with 5% FFAP on Varaport-30, 80/100 mesh (Varian); flow rates of 15 mL/min at ambient temperature for all columns. Silica gel PF 254 + 336 (E. Merck No. 7748) and silica gel 60 (E. Merck No. 7734, 70–230 mesh, available from Brinkmann Instruments) were used for thin layer and column chromatography, respectively. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 700, or a Perkin-Elmer grating infrared spectrophotometer, Model 237B. Samples were taken as 10% solutions in spectroquality carbon tetrachloride or chloroform using balanced 0.1-mm sodium chloride cells or were taken as thin films between sodium chloride plates. Nuclear magnetic resonance (NMR) spectra were measured on a Varian Associates Model T-60 spectrometer in the solvent indicated. Mass spectra (MS) were obtained on a Hitachi Perkin-Elmer Model RMU-6H single-focusing mass spectrometer.

Finally, for all reactions performed under an atmosphere of dry nitrogen, the equipment was dried in an oven at 120 °C for several hours, then allowed to cool in an atmosphere of dry nitrogen using an apparatus designed by Johnson and Schneider.[37] All liquid transfers were made with nitrogen-filled syringes. The term "petroleum ether" refers to Baker "Analyzed Reagent", bp 30–60 °C. The general workup procedure was to extract the aqueous layer with ether (three times); the combined ethereal extracts were washed with water (three times) and saturated sodium chloride solution (once), and then dried (Na_2SO_4), filtered (through Na_2SO_4 or $MgSO_4$), and concentrated in vacuo.

2-Methyl-2-(4-isopropyl)phenyloxirane (4).[10] *m*-Chloroperbenzoic acid (*m*-CPBA, 40.2 g of 81.3% assay,[38] 189.4 mmol, Aldrich), disodium hydrogen phosphate (Na_2HPO_4, 30.7 g, 216.2 mmol), and anhydrous ether (300 mL, freshly distilled from lithium aluminum hydride) were placed in a 1-L three-necked round-bottomed flask, equipped with a mechanical stirrer, a thermometer, and a pressure-equalizing addition funnel. The stirred suspension was cooled in an ice bath and 4-isopropenylisopropylbenzene[9] (16.03 g, 100.0 mmol) dissolved in dry ether (100 mL) was added under nitrogen as a slow stream over a period of 30 min. The rate of addition was adjusted so that the temperature of the reaction did not rise above 5 °C. After stirring for 1 h the ice bath was removed and the mixture was further allowed to stir at room temperature with monitoring by GLC (column a). After stirring for 4 h at room temperature, the reaction was complete and the resulting white suspension was transferred to a separatory funnel using ether and enough water to dissolve all the solid material. The organic layer was separated and the aqueous layer was extracted with ether (three times). The combined ethereal extracts were washed with cold 5% sodium hydroxide solution (3 × 100 mL), then worked up in the usual way. Evaporative distillation (50 °C at 0.2 mm) gave 15.88 g (90.1%) of pure oxirane **4**: IR (film), 3060 (C–H, epoxy), 3030 (C–H, aromatic), 2980, 2960, and 2890 (C–H, aliphatic), 1895, 1795, and 1720 (1,4-disubstituted aromatic overtone), 1604, 1510, 1450, and 1418 (aromatic skeletal), 1455 (–CH_3, bending), 1380 and 1365 (isopropyl), 910, 865, 790, and 750 (epoxy ring), and 835 cm^{-1} (C–H bending, aromatic); NMR (CCl_4) δ 1.25 (d, 6, J = 7 Hz, –CH**Me**$_2$), 1.56 (s, 3, –CH_3), 2.38–3.12 (two overlapped m, 3, epoxy methylene and –C**H**Me$_2$), and 6.96–7.29 ppm (m, 4, aromatic).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.71; H, 9.26.

2-(4-Isopropyl)phenylpropanal (5).[11] Boron trifluoride etherate (3.0 mL, 24.4 mmol, distilled from calcium hydride) was added at 0 °C (ice bath) to a stirred solution of oxirane **4** (3.55 g, 20.1 mmol) dissolved in anhydrous ether (50 mL, freshly distilled from lithium aluminum hydride) under nitrogen. After stirring for 10 min, the ice bath was removed and the reaction mixture was allowed to stir for 30 min at room temperature. The reaction mixture was then diluted with ether (100 mL), washed with saturated sodium bicarbonate solution (4 × 40 mL), then worked up in the usual way to give 3.55 g (100%) of aldehyde **5** as a colorless liquid. The crude product was used immediately for the next reaction without further purification. The analytical sample was prepared by evaporative distillation (35 °C at 0.02 mm) of a small sample: IR (CCl_4) 2960 and 2875 (C–H, aliphatic), 2800 and 2700 (–CHO and overtone), 1725 (CO), 1506, 1455, and 1420 (aromatic skeletal), 1380 and 1365 (isopropyl), 1280, 1055, 1015, and 825 cm^{-1} (C–H bending, aromatic); NMR (CCl_4) δ 1.25 (d, 6, J = 7 Hz, –CH**Me**$_2$), 1.40 (d, 3, J = 8 Hz, COCHC**H**$_3$), 2.88 (m, 1, J = 7 Hz, –C**H**Me$_2$), 3.52 (quartet of doublets, 1, CH_3C**H**CHO), 6.90–7.30 (m, 4, aromatic), and 9.60 ppm (d, 1, J = 2 Hz, –HCC**H**O).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.63; H, 9.01.

2-(4-Isopropyl)phenylpropanoic Acid (6).[12] To a vigorously stirred solution of aldehyde **5** (30.0 g, 170.0 mmol) in reagent grade acetone (800 mL) at 5 °C (ice bath) was added Jones reagent (70 mL of 2.67 M solution, 187 mmol) at such a rate that the reaction temperature was maintained at 5 °C (over a period of 1 h). After stirring for 10 min, the ice bath was removed and the resulting orange mixture was further stirred for 30 min at room temperature. The excess oxidizing reagent was then quenched by dropwise addition of 2-propanol until the orange color disappeared in the upper layer of the two-phase mixture. The reaction mixture was diluted with ether (600 mL) and water (400 mL), then the organic layer was separated, and the aqueous layer was extracted with ether (4 × 150 mL). The combined organic extracts were washed with water (once), then extracted with saturated sodium bicarbonate solution (5 × 300 mL). The total basic extracts were acidified at 0 °C (ice bath) with stirring, with 10% hydrochloric acid solution. This acidified solution was then worked up in the usual way to afford 31.1 g (95.1%) of crystalline carboxylic acid **6.** The analytical sample was prepared by recrystallization (three times) from methanol and water, followed by sublimation (40 °C at 0.02 mm): mp 68–69 °C; IR (CCl_4) 3300–2500 (–CO_2H, dimeric), 1710 (CO), 1510, 1460, and 1410 (aromatic skeletal), 1420 (–OH bending), 1290 (C–O), 1230 (–CO_2–), and 925 cm^{-1} (–OH bending, dimeric); NMR (CCl_4) δ 1.26 (d, 6, J = 7 Hz, –CH**Me**$_2$), 1.48 (d, 3, J = 8 Hz, –CH_3), 2.86 (m, 1, J = 7 Hz, –C**H**Me$_2$), 3.63 (q, 1, J = 8 Hz, –C**H**CO_2H), 6.95–7.32 (m, 4, aromatic), and 12.01 ppm (s, 1, –CO_2H).

Anal. Calcd for $C_{12}H_{16}C_2$: C, 74.97; H, 8.39. Found: C, 74.95; H, 8.28.

2-(4-Isopropyl)phenylpropanoic Acid Chloride (7).[13] Carboxylic acid **6** (14.65 g, 76.3 mmol, dried over phosphorus pentoxide for 24 h at room temperature under reduced pressure), thionyl chloride (8.2 mL, 115.0 mmol), and a few boiling stones (silicon carbide) were introduced in a flask attached with an efficient condenser carrying a calcium chloride drying tube. The mixture was allowed to react for 24 h at room temperature followed by 30 min at 50 °C (bath temperature). The resulting yellowish-green liquid was then transferred to a round-bottomed flask with anhydrous benzene (10 mL, freshly distilled from calcium hydride) and the excess thionyl chloride was removed azeotropically with benzene on a Büchi rotoevaporator. After about an equal volume of dry benzene (20 mL) was added to the concentrate, the azeotropic distillation was repeated. Evaporative distillation (45 °C at 0.02 mm) of the crude product afforded 15.63 g (97.3%) of pure acid chloride **7** as a colorless liquid: IR (CCl_4) 3030 (C–H, aromatic), 2960 and 2870 (C–H, aliphatic), 1785 and 1840 (CO), 1510, 1450, and 1420 (aromatic skeletal), 1375 and 1365 (isopropyl), 920 (C–CO–Cl), and 710 cm^{-1} (C–Cl); NMR (CCl_4) δ 1.28 (d, 6, J = 7 Hz, –CH**Me**$_2$), 1.56 (d, 3, J = 7 Hz, COCHC**H**$_3$), 2.88 (m, 1, J = 7 Hz, –C**H**Me$_2$), 4.02 (q, 1, J = 8 Hz, –COC**H**CH$_3$), and 7.23 ppm (s, 4, aromatic).

Anal. Calcd for $C_{12}H_{15}OCl$: C, 68.41; H, 7.18. Found: C, 68.38; H, 7.22.

1-Methyl-6-isopropyl-2-tetralone (8A).[14] Anhydrous aluminum chloride (6.80 g, 51.0 mmol, J. T. Baker) and dry dichloromethane (500 mL, freshly distilled from phosphorus pentoxide) were placed under nitrogen in a 1-L three-necked flask equipped with a magnetic stirrer, a condenser, a gas inlet tube, and a pressure-equalizing dropping funnel. Acid chloride **7** (10.40 g, 49.4 mmol) dissolved in anhydrous dichloromethane (120 mL) was added to the stirred suspension at −20 ± 2 °C (external, temperature dry ice/acetone) slowly over a period of 15 min. As soon as a homogeneous light green solution of acid chloride–aluminum chloride complex started to form (5 min after the addition of **7** started), a gentle stream of ethylene was bubbled into the vigorously stirred mixture at −20 ± 2 °C (external temperature) over a period of 20 min. After stirring for 10 min the cooling bath was removed. The resulting brown solution was allowed to stir for 3 h at room temperature, then cooled in an ice bath and the red-brown reaction was carefully quenched with ice–water (150 mL). The resulting mixture was then stirred until all of the solid material was dissolved to give a colorless two-phase system (30 min). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were washed with 5% hydrochloric acid solution (once), water (once), and saturated sodium bicarbonate solution (twice), then worked up in the usual way to give a slightly yellow oil of crude ketone **8A.** Evaporative distillation (55 °C at 0.02 mm) of the crude product 9.44 g (94.5%) of pure ketone **8A** as a colorless liquid. 2,4-Dinitrophenylhydrazone derivative, recrystallized (three times) from ethanol and water, mp 143–144 °C (lit.[8] 142.5–144 °C). Semicarbazone, recrystallized (three times) from methanol: mp 166–167 °C (lit.[8] 166–166.5 °C); IR (CCl_4) 3030 (C–H, aromatic), 2960 and 2870 (C–H, aliphatic), 1890 and 1762 (1,2,4-substituted aromatic overtone), 1715 (CO), 1495, 1452, and 1425 (aromatic skeletal), 1385 and 1360 (isopropyl), 1165, 1050, and 1015 (1,2,4-substituted aromatic ring, bending), and 985, 880, and 820 cm^{-1} (C–H bending, aromatic); NMR (CCl_4) δ 1.28 (d, 6, J = 7 Hz, CH**Me**$_2$), 1.42 (d, 3, J = 7 Hz, –COCHC**H**$_3$), 2.3–3.1 (m, 5, ring methylenes, –C**H**Me$_2$), 3.39 (q, 1, J = 7 Hz, benzylic methine), and 7.06 ppm (unresolved s, 3, aromatic); GLC analysis on column a (column temperature 150 °C, retention time 11.4 min) and column b (column temperature 180 °C, retention time 14.0 min) shows the product to be greater than 99.9% of a single substance.

2,3,4,4a,9,10-Hexahydro-7-isopropyl-4a-methyl-2-oxophenanthrene (9A)[15] To a stirred solution of ketone **8A** (0.744 g, 3.67 mmol) in absolute ethanol (2 mL) at −30 °C (bath temperature, dry ice/acetone) under nitrogen atmosphere was added sodium ethoxide (6.8 mg, 0.1 mmol). After stirring for 10 min at −30 °C, the pale yellow solution was cooled to −65 °C (bath temperature, dry ice/acetone) and methyl vinyl ketone (0.40 mL, 4.93 mmol, freshly distilled, bp 81 °C) was added dropwise to it. After the temperature of the cooling bath was allowed slowly to rise to 0 °C (30 min), the reaction mixture was stirred for 1.5 h at 0 °C (ice bath), then for 24 h at room temperature, followed by 3 h at reflux. After the red-brown reaction mixture was cooled to room temperature, it was poured into a separatory funnel containing water (29 mL), ether (20 mL), and 5% hydrochloric acid solution (5 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined ethereal extracts were washed with saturated sodium bicarbonate solution (1 × 20 mL), then worked up in the usual way to give 1.102 g (118%) of a red oil. Chromatography on silica gel (100 g, 70–230 mesh, E. Merck) in a 1.5-cm diameter column using a 20:80 mixture of ether and petroleum ether to elute 50-mL sized fractions gave 0.70 g (75.0%) of pure enone **9A** in fractions 24–31. The analytical sample was prepared by evaporative distillation (72 °C at 0.02 mm) of a small sample of chromatographed product: IR (CCl_4) 3050 (=CH), 3030 (C–H, aromatic), 2960, 2930, and 2870 (C–H, aliphatic), 1675 (CO), 1625 (C=C), 1495, 1450, and 1410 (aromatic skeletal), and 950, 880, and 820 cm^{-1} (C–H bending aromatic); NMR (CCl_4) δ 1.22 (d, 6, J = 7 Hz, –CH**Me**$_2$), 1.55 (s, 3, –CH$_3$), 1.82–3.03 (m, 9, methylenes), 5.75 (s, 1, –C=CH), and 6.80–7.22 ppm (m, 3, aromatic); GLC analysis on column a (column temperature 200 °C, retention time 15.6 min) and column b (column temperature 240 °C, retention time 12.8 min) indicates the product to be greater than 99.5% of a single product. Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.90; H, 8.61.

Methyl 1,2,3,4,4a,9,10,10aα-Octahydro-7-isopropyl-4aβ-methyl-2-oxo-1α-phenanthrenecarboxylate (10A).[16] Anhydrous liquid ammonia (100 mL, distilled through two potassium hydroxide towers) was collected in a 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer and a dry ice condenser carrying a soda-lime drying tube. Lithium wire (5 cm, 29.0 mg-atom) was cut, washed in hexane to remove mineral oil, quickly dried with Kimwipe, and then added to the vigorously stirred ammonia in four small pieces. After the resulting dark blue mixture was stirred at reflux (−33 °C) for 10 min, a solution of enone **9A** (2.460 g, 9.67 mmol) dissolved in anhydrous ether (40 + 10 + 10 mL, freshly distilled from lithium aluminum hydride) was added rapidly (5 min) to it (after the addition, the reaction mixture remained blue). As soon as the addition was complete, dry ice and acetone in the condenser were replaced with ice–water and the remaining ammonia was evaporated in a warm water bath as quickly as possible (15 min). After the soda-lime drying tube was replaced by two Drierite towers, 40 mL of dry ether was added and the resulting suspension was heated (hot water bath) at reflux for 15 min to drive off any residual ammonia. The reaction contents were then cooled to −78 °C (dry ice/acetone) and excess anhydrous, powdered dry ice (ca. 2.5 g, doubly sublimed and condensed with liquid nitrogen) was added to the white slurry. The cooling bath was then removed and the resulting slurry was allowed to stir for 30 min at room temperature, followed by quenching at −78 °C with a large excess of powdered dry ice (50 g) and cold water (50 mL). After the cooling bath was removed and the slightly yellow reaction mixture thawed, it was transferred, with a small amount of cold water, to a precooled separatory funnel. The ether layer was then separated and set aside; it was subsequently washed with saturated sodium chloride solution, then dried (Na_2SO_4) and concentrated in vacuo to give 0.758 g (30.6%) of a red oil, which was found largely to be the trans reduction product of enone **9A.** Very cold ether (200 mL) was then added to the aqueous layer and the resulting two-phase system was carefully acidified (pH ~2) at 0 °C with stirring by dropwise addition of cold 10% hydrochloric acid solution. The aqueous layer turned cloudy and then became clear as the freed carboxylic acid dissolved in the ether layer. After the layers were separated, the aqueous layer was extracted with very cold ether (4 × 50 mL). The very cold ethereal extracts were combined and washed with cold saturated sodium chloride solution (2 × 200 mL), then allowed to filter (glass wool) into a stirred excess ethereal diazomethane solution at 0 °C (ice bath). After the mixture was stirred for 30 min at room temperature, the excess diazomethane was titrated with glacial acetic acid until only faintly yellow diazomethane color remained. The resulting solution was then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 1.982 g (65.2%) of a slightly yellow, crystalline keto ester **10A.** Trituration of the crude product in ether gave 1.940 g (63.7%) of pure keto ester **10A:** mp 106.5–107 °C; IR ($CHCl_3$) 3030 (C–H, aromatic), 2955 and 2870 (C–H, aliphatic), 1740 (CO, ester), 1710 (CO), 1495, 1455, and 1428 (aromatic skeletal), 1380 and 1355 (isopropyl), 1270 and 1150 (C–O–C), and 820 cm^{-1} (C–H bending, aromatic); NMR ($CDCl_3$) δ 1.22 (d, 6, J = 7 Hz, CH**Me**$_2$), 1.35 (s, 3, –CH$_3$), 1.5–3.1 (m, 10, methylenes and methine), 3.40 (d, 1, J = 12 Hz, –COCHCO–), 3.80 (s, 3, COOCH$_3$), and 6.90–7.33 ppm (m, 3, aromatic); GLC analysis on column a (column temperatures 222 °C, retention time 9.84 min) and column b (column temperature 225 °C, retention time 9.13 min) shows β-keto ester **10A** to be a single product.

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found: C, 76.27; H, 8.30.

Methyl 1,2,3,4,4a,9,10,10aα-Octahydro-6-methoxy-4aβ-methyl-2-oxo-1α-phenanthrenecarboxylate (10B).[16] To a stirred solution of lithium (0.047 g, 6.77 mg-atoms) in anhydrous liquid ammonia (50 mL) was added rapidly enone **9B** (0.482 g, 1.99 mmol, dried over phosphorus pentoxide under reduced pressure) dissolved in anhydrous ether (10 + 2 + 2 mL, freshly distilled from lithium alu-

minum hydride). Then the ammonia was quickly evaporated with a hot water bath (5 min). The soda-lime drying tube of the dry ice condenser was replaced by a Drierite tower and 10 mL of dry ether was then added to the reaction mixture, followed by refluxing for 15 min to drive off any residual ammonia. The reaction was then cooled to −78 °C (dry ice/acetone) and excess anhydrous dry ice powder (ca. 2 g, sublimed through two Drierite towers, condensed by liquid nitrogen, resublimed, and recondensed) was added. After the cooling bath was removed, the reaction mixture was stirred for 30 min at room temperature followed by 30 min in a water bath at room temperature. Then, the reaction was cooled to −78 °C and excess powdered dry ice (10 g) was added followed by 10 mL of water. When the solid reaction mixture melted, it was transferred, with cold water (three times) and ether (three times), to a separatory funnel containing ice–water. The ether layer was separated and set aside; subsequent evaporation of the solvent gave 0.210 g (43%) of a yellow solid, the major component of which was identified to be the trans reduction product of enone **9B**. After 25 mL of ether was added, the aqueous layer was acidified with hydrochloric acid solution (1:1 mixture of concentrated HCl and ice). The layers were separated and the aqueous layer was extracted with cold ether (2 × 50 mL). The combined cold ethereal extracts were washed with cold saturated soidum chloride solution (2 × 25 mL) and then allowed to filter (glass wool plug) into excess ethereal diazomethane solution at 0 °C (ice bath). After the mixture was stirred for 30 min at 0 °C and 30 min at room temperature, the excess diazomethane was titrated with glacial acetic acid. The resulting solution was then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.332 g (55.2%) of crude keto ester **10B**. Chromatography of the crude product on silica gel (75 g, 75–325 mesh, E. Merck) using a 50:50 mixture of ether and petroleum ether to elute 35-mL fractions, gave 0.238 g (39.6%) of pure keto ester **10B** in fractions 8–12. The analytical sample was prepared by recrystallization (three times) from ether and chloroform: colorless, cubic crystals, mp 146–147 °C; IR ($CHCl_3$) 2945 and 2835 (C–H), 1740 (CO, ester), 1710 (CO), 1605, 1500, and 1430 (aromatic skeletal), 1290 and 1145 (C–O–C), and 1045 cm^{-1} (Ph–O–C); NMR ($CDCl_3$) δ 1.35 (s, 3, $-CH_3$), 1.4–3.0 (m, 9, methylenes and methine), 3.40 (d, 1, J = 12 Hz, –COCHCO–), 3.78 (s, 6, $PhOCH_3$ and $-COOCH_3$), and 6.6–7.2 ppm (m, 3, aromatic).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.38; H, 7.26.

Methyl 3,4,4a,9,10,10aα-Hexahydro-7-isopropyl-2-(methoxymethoxy)-4aβ-methyl-1-phenanthrenecarboxylate (11A).[19,20] Sodium hydride (0.0994 g of 50% dispersion in mineral oil, 4.14 mmol, Ventrol) was worked up with anhydrous ether (2 × 3 mL, freshly distilled from lithium aluminum hydride) under dry nitrogen. The residual ether was thoroughly evaporated with warming (infrared heat lamp) and nitrogen purging. Keto ester **10A** (1.0832 g, 3.44 mmol) dissolved in anhydrous hexamethylphosphoric triamide (HMPA, 25 + 10 + 5 mL, freshly distilled from calcium hydride and collected over moleculear sieves 13X) was slowly added to the sodium hydride. After stirring for 3 h at room temperature, the pink-brown mixture was cooled to 0 °C (ice bath) and chloromethyl methyl ether (9.32 mL, 4.2 mmol) was added. The cooling bath was then removed and the reaction mixture was allowed to stir for 2 h at room temperature. The resulting white slurry was poured into ice–water (200 mL) and saturated sodium bicarbonate solution (100 mL), and worked up in the usual way to give 1.4062 g (113.7%) of a light green oil. The crude oil was chromatographed on silica gel (100 g, 70–230 mesh, E. Merck) in a 1.5-cm diameter column using 20:80 mixture of ether and petroleum to elute 25-mL fractions. Fractions 19–26 gave 1.194 g (96.4%) of pure vinyl ether ester **11A** as a colorless liquid. The analytical sample was prepared by evaporative distillation (102 °C at 0.02 mm) of small sample: IR (CCl_4) 2960 and 2900 (C–H, aliphatic), 1725 (CO, ester), 1670 (C=C), 1498, 1460, and 1428 (aromatic, skeletal), 1375 and 1365 (isopropyl), 1290 and 1150 (CO–C), 1250 (=C–O–C), 1190, 1165, 1070, and 1038 (–C–O–C–O–C–), and 985, 880, and 820 cm^{-1} (C–H bending aromatic); NMR (CCl_4) δ 1.10 (s, 3, $-CH_3$), 1.26 (d, 6, J = 7 Hz, $-CHMe_2$), 1.4–2.6 (m, 9, methylenes and methine), 2.86 (q, 1, J = 7 Hz, $-CHMe_2$), 3.45 (s, 3, $-OCH_2CH_3$), 3.75 (s, 3, $-COOCH_3$), 4.85 (AB, 2, J = 7 and 4 Hz, $-OCH_2O-$), and 6.85–7.10 ppm (m, 3, aromatic).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.69; H, 8.50.

Methyl 3,4,4a,9,10,10aα-Hexahydro-6-methoxy-2-(methoxymethoxy)-4aβ-methyl-1-phenanthrenecarboxylate (11B).[19,20] Sodium hydride (0.573 g of 57% dispersion in oil, 13.6 mmol, Ventron) was washed with anhydrous ether (3 × 5 mL, freshly distilled from lithium aluminum hydride) under dry nitrogen atomosphere. After the ether was removed as above, anhydrous hexamethylphosphoric triamide (HMPA, 10 mL, freshly distilled from calcium hydride and stored over molecular sieves 13X) was added, followed by keto ester **10B** (3.024 g, 10.0 mmol) dissolved in dry HMPA (20 + 5 + 5 mL). After stirring for 3 h at room temperature, the resulting brown reaction mixture was quenched with chloromethyl methyl ether (2.0 mL, 26.3 mmol) and the mixture was allowed to stir for an additional 2 h at room temperature. The resulting yellow mixture was then poured into a separatory funnel containing ice–water (100 mL), saturated sodium bicarbonate solution (50 mL), and ether (50 mL). After the layers were separated, the aqueous layer was extracted with ether (5 × 40 mL). The combined ethereal extracts were washed with water (5 × 100 mL) and saturated sodium bicarbonate solution (2 × 100 mL), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 3.60 g (104%) of yellow oil. The crude product was recrystallized from ether and hexane to give 3.140 g (90.6%) of pure crystalline **11B**, mp 87–88 °C. An analytical sample was prepared by recrystallization from ether: mp 88–89 °C; IR (CCl_4) 2960 and 2870 (C–H, alipahtic), 2850 ($PhOCH_3$), 1720 (CO, ester), 1670 (C=C), 1604, 1500, 1450, and 1425 (aromatic skeletal), 1360, 1290 (C–O–C), 1250 (=C–O–C), 1195, 1170, 1070, and 1040 (–C–O–C–O–C–), and 985 cm^{-1} (C–H bending, aromatic); NMR (CCl_4) δ 1.09 (s, 3, $-CH_3$), 1.4–3.0 (m, 9, methylenes and methine), 3.40 (s, 3, $-OCH_2OCH_3$), 3.66 (s, 3, $-COOCH_3$), 3.70 (s, 3, $PhOCH_3$), 4.80 (AB, 2, J = 6 Hz, $-OCH_2O-$), and 6.6–7.2 ppm (m, 3, aromatic).

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.30; H, 7.53.

Methyl 1,2,3,4,4a,9,10,10aα-Octahydro-7-isopropyl-4aβ-methyl-1α-methyl-1β-phenanthrenecarboxylate (Methyl Callitrisate) (12A). Lithium wire (3.4 cm, 19.6 mg-atoms) was cut, then added to anhydrous liquid ammonia (100 mL, distilled through two potassium hydroxide towers, then from sodium metal). After the dark blue mixture was refluxed (−33 °C) for 20 min with stirring, was added to it vinyl ether ester **11A** (1.005 g, 2.80 mmol) dissolved in anhydrous 1,2-dimethoxyethane (DME, 30 + 15 + 15 mL, freshly distilled from lithium aluminum hydride and collected over activated molecular sieves 3A), followed by stirring at reflux (−33 °C) for 10 min. The blue reaction mixture was then rapidly quenched with excess methyl iodide (2 mL, 32.2 mmol) and the resulting white slurry was allowed to stir at reflux (−33 °C) for 1 h. The reaction flask was warmed (hot water bath) with stirring for 1 h, allowing ammonia to evaporate. After the mixture was cooled to room temperature, it was poured into ice–water (100 mL) and acidified to pH ~2 with 10% hydrochloric acid solution. After the layers were separated, the aqueous layer was extracted with ether (5 × 50 mL). The combined ethereal extracts were washed with saturated sodium sulfite solution (3 × 100 mL), then worked up in the usual way to give 0.926 g (105%) of a light yellow oil. The crude product was chromatographed on silica gel (100 g, 70–230 mesh, E. Merck) in a column of 1.5 cm diameter using a 5:95 mixture of ether and petroleum to elute 25-mL size fractions. Fractions 24–31 gave 0.655 g (74.4%) of pure crystalline (±)-methyl callitrisite (**12A**), mp 94–95 °C. Recrystallization (three times) of a small sample from ether gave analytically pure ester **12A** as elongated prisms: mp 94–94.5 °C (lit. 91–92,[3a] 98–99 °C[3b]); IR (CCl_4) 3030 (C–H, aromatic), 2960, 2875, and 2850 (CH, aliphatic), 1728 (CO, ester), 1610, 1495, 1455, and 1415 (aromatic skeletal), 1378 and 1360 (isopropyl), 1265 and 1150 (C–O–C), 985, 880, and 820 (C–H bending, aromatic), and 1180, 1230, and 1130 cm^{-1}; NMR (CCl_4) δ 0.95 (s, 3, C_{4a} CH_3), 1.20 (d, 6, J = 7 Hz, $-CHMe_2$), 1.24 (s, 3, C_1 CH_3), 1.42–2.95 (m, 11, methylenes and methines), 3.58 (s, 3, $-OCH_3$), 6.75 (s, 1, C_8 H, aromatic), and 6.98 (AB, 2, C_5H and C_6 H, aromatic).

Synthetic (±)-methyl callitrisate was found to have identical physicochemical properties with the authentic sample;[21] IR and NMR spectra of both samples were superimposable; both samples had identical R_f values on TLC and retention time on GLC both in separate and coinjected samples using columns a and b. GLC data on separate and coinjected samples of (±)-methyl callitrisate are listed below.

Column	Column temp, °C	Retention time, min
a	220	10.31
b	240	13.00

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.30; H, 9.61.

Methyl 1,2,3,4,4a,9,10,10aα-Octahydro-6-methoxy-4aβ-methyl-1α-methyl-1β-phenanthrenecarboxylate (Methyl *O*-Methyl Podocarpate) (12B). To a stirred solution of lithium (0.122 g, 17.6 mg-atoms) in anhydrous liquid ammonia (100 mL) was added vinyl ether ester **11B** (1.005 g, 2.90 mmol) dissolved in anhydrous 1,2-dimethoxyethane (DME, 20 + 5 + 5 mL, distilled from lithium aluminum hydride and stored over molecular sieves 3A). After the blue reaction mixture was stirred at reflux (−33 °C) for 10 minutes, it was rapidly quenched with methyl iodide (1.0 mL, 16.1 mmol). The resulting slightly yellow slurry was allowed to stir at reflux (−33 °C) for 1 h, then the ammonia

was removed by distillation in a hot water bath for over a period of 1 h. The reaction mixture was then poured into ice–water (50 mL) and acidified (pH ~2) with 10% hydrochloric acid solution, and the aqueous mixture was extracted with ether (5 × 50 mL). The combined ethereal extracts were washed with 10% sodium sulfite solution (50 mL), water (4 × 50 mL), and saturated sodium chloride solution (50 ml), then worked up in the usual way to give 0.863 g (98.4%) of crude product. Recrystallization of crude product from chloroform and hexane afforded 0.699 g (79.7%) of pure crystalline (±)-methyl *O*-methyl podocarpate (**12B**), mp 129–134 °C. The analytical sample (mp 136–137 °C, lit. 128–129,[6b] 128–130 °C[6c]) was prepared by column chromatography on silica gel followed by recrystallization (twice) from chloroform and hexane: IR ($CHCl_3$) 3030 (C–H, aromatic), 2985 and 2860 (C–H, aliphatic), 1720 (CO, ester), 1610, 1578, 1500, and 1455 (aromatic skeletal), 1465 and 1380 (CH_2, bending), 1250 and 1050 (C–O–C), and 980, 880, 810 cm^{-1} (C–H, bending, aromatic); NMR ($CDCl_3$) δ 1.05 (s, 3, $C_{4a}CH_3$), 1.28 (s, 3, C_1CH_3), 1.35–2.90 (m, 11, methylenes and methine), 3.66 (s, 3, $-COOCH_3$), 3.76 (s, 3, $PhOCH_3$), and 6.7–7.3 ppm (m, 3, aromatic).

Synthetic (±)-methyl *O*-methyl podocarpate was identical with an authentic sample[24] prepared for (+)-podocarpic acid with respect to IR, NMR, TLC, and GLC. GLC data both on separate and coinjected samples using columns a, b, and c are listed below.

Column	Column temp, °C	Retention time, min
a	220	13.1
b	250	13.8
c	240	24.9

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.33; H, 8.59.

1,2,3,4,4a,9,10,10aα-Octahydro-7-isopropyl-4aβ-methyl-1α-methyl-1β-phenanthrenecarboxylic Acid (Callitrisic Acid or 4-*epi*-Dehydroabietic Acid) (1).[2] A mixture of methyl callitrisate (**12A**, 0.080 g, 0.25 mmol) and potassium *tert*-butoxide (0.100 g, 0.89 mmol) in anhydrous dimethyl sulfoxide (Me_2SO, 6 mL, freshly distilled from calcium hydride and stored over activated molecular sieves 4A) was stirred at 100 °C (bath temperature) for 6 h. After the reaction mixture was cooled to room temperature, it was poured into ice–water (20 mL). The aqueous mixture was then extracted with ethyl acetate (2 × 10 mL) to remove neutral impurities, followed by acidification at 0 °C, with stirring, with 10% hydrochloric acid solution. The freed carboxylic acid was extracted with ethyl acetate (5 × 10 mL). The combined ethyl acetate extracts were worked up in the usual way to give 0.078 g (101.4%) of light yellow crystals. The crude product was chromatographed on silica gel (16 g, 70230 mesh, E. Merck) in a 1-cm diameter column using a 20:80 mixture of ether and petroleum ether to elute 5-mL fractions. Fractions 15–20 yielded 0.0745 g (97.5%) of pure (±)-callitrisic acid (1). Recrystallization from ethyl acetate gave (±)-callitrisic acid (1) as colorless prisms: mp 200–201 °C (lit. 202–203,[3a] 202 °C[3b]); IR ($CHCl_3$, saturated solution) 3300–2500 (OH, dimeric carboxylic acid), 2960 and 2875 (C–H, aliphatic), 1725 (shoulder) and 1695 (CO, acid), 1609, 1495, 1470, and 1410 (aromatic skeletal), 1455 ($-CH_2$, bending), 1378 and 1365 (isopropyl), 1265 (C–O), and 987, 885, and 825 cm^{-1} (C–H, bending, aromatic); NMR ($CDCl_3$, saturated solution) δ 1.09 (s, 3, $C_{4a}CH_3$), 1.22 (d, 6, J = 7 Hz, $-CHMe_2$), 1.35 (s, 3, C_1CH_3), 1.4–3.0 (m, 12, methylenes and methine), 6.90 (s, 1, C_8H, aromatic), 7.10 ppm (AB, 2, C_5H and C_6H, aromatic), and 11.0 ppm (bs, 1, $-CO_2H$).

Methyl 2,3,4,4a,9,10-Hexahydro-7-isopropyl-4aβ-methyl-2-oxo-1-phenanthrenecarboxylate (14A)[28] Isopropyl ketone **8A** (3.480 g, 17.2 mmol), methyl 5-methoxy-3-oxopentanoate[27] (4.135 g, 25.8 mmol), toluene (80 mL), and *p*-toluenesulfonic acid (0.150 g) were placed, under nitrogen, in a 100-mL two-necked flask fitted with a Dean-Stark water separator. After refluxing for 8 h, the resulting red-brown mixture was diluted with ether (100 mL), then poured into water (100 mL) and saturated sodium bicarbonate solution (100 mL). After the layers were separated, the aqueous layer was extracted with ether (three times). The combined ethereal extracts were washed with saturated sodium bicarbonate solution (once), then worked up in the usual way to give 6.507 g of a red oil. The IR and NMR spectra of this crude product showed that it was a mixture of enone ester **14A** and keto ester alcohol **13A** in about 3:2 ratio. This crude product dissolved in toluene (80 mL) was refluxed with a catalytic amount of trifluoromethanesulfonic acid (2 drops) for 1 h under nitrogen atomosphere. The water formed during the reaction was removed by a Dean-Stark water separator. The resulting dark red reaction mixture, after a similar workup as described above, gave 5.440 g of crude enone ester **14A**. The crude product was chromatographed on silica gel (544 g, 70–230 mesh, E. Merck) in a 3-cm diameter column using a mixture of 25:75 ether and petroleum to elute 250-mL fractions. Fractions 35–45 gave 3.6709 g (68.3%) of pure crystalline enone ester **14A**. The analytical sample was prepared by recrystallization (four times) from ether: mp 139.5–140 °C; IR ($CHCl_3$) 3030 (C–H, aromatic), 2985, 2950, and 2840 (C–H, aliphatic), 1725 (CO, ester), 1665 (CO), 1623 (C=C), 1495, 1450, and 1430 (aromatic skeletal), and 1245 and 1030 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 1.26 (d, 6, J = 7 Hz, $-CHMe_2$), 1.63 (s, 3, $-CH_3$), 2.0–3.1 (m, 9, methylenes and methine), 3.86 (s, 3, $-OCH_3$), and 6.8–7.3 ppm (m, 3, aromatic); MS *m/e* 312 (P^+), 297, 280, 265, 252, 238, and 223.

Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.80; H, 7.74. Found: C, 76.82; H, 7.73.

Methyl 2,3,4,4a,9,10-Hexahydro-6-methoxy-4aβ-methyl-2-oxo-1-phenanthrenecarboxylate (14B).[28] A mixture of ketone **8B** (2.44 g, 12.8 mmol), methyl 5-methoxy-2-oxopentanoate[27] (2.097 g, 13.09 mmol), and *p*-toluenesulfonic acid (0.10 g) in anhydrous benzene (50 mL, freshly distilled from calcium hydride) was refluxed, with a Dean-Stark water separator, for 72 h under nitrogen. The resulting greenish-brown mixture was diluted with ether (100 mL), then poured into saturated sodium bicarbonate solution (200 mL). After the layers were separated, the aqueous layer was extracted with ether (3 × 100 mL). The combined organic extracts were then washed with saturated sodium bicarbonate solution (once), then worked up in the usual way to give a greenish-yellow oil. This crude product dissolved in toluene (40 mL) was allowed to reflux for 1 h in the presence of a catalytic amount of trifluoromethanesulfonic acid (2 drops). The water formed from the reaction was removed by a water separator. The resulting dark red reaction mixture, after a similar workup as described above, afforded 3.925 g of crude enone ester **14B** as a red oil. The crude product was chromatographed on silica gel (600 g, 70–230 mesh, E. Merck) in a 4-cm diameter column. The column was eluted with 8 L of 25:75, 6 L of 30:70, 5 L of 35:65, and 5 L of 40:60 ether and petroleum ether solutions, respectively, taking 250-mL fractions. Fractions 59–75 yielded 2.786 g (72.3%) of pure enone ester **14B** as yellow crystals. A small sample was recrystallized from ether (four times) to give analytically pure **14B**: mp 98:0 °C; IR ($CHCl_3$) 3030 (C–H, aromatic), 2990 and 2935 (C–H, aliphatic), 1728 (CO, ester), 1665 (CO), 1620 (C=C), 1610, 1575, 1500, 1450, and 1430 (aromatic skeletal), and 1290, 1245, and 1040 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 1.62 (s, 3, $-CH_3$), 1.95–3.05 (m, 9, methylenes and methine), 3.80 (s, 3, $PhOCH_3$), 3.86 (s, 3, $-COOCH_3$), and 7.33–6.66 (m, 3, aromatic); MS *m/e* 300 (P^+), 268, 253, 240, 225, 198, 197, 83, 74, and 31.

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.97; H, 6.63.

Catalytic Hydrogenation of Isopropyl Enone Ester (14A).[29,30] Catalytic hydrogenation was performed on a Sloping-Manifold hydrogenator,[29] at room temperature and essentially under atmospheric pressure of hydrogen. Enone ester **14A** (0.0814 g, 0.26 mmol) was added to a magnetically stirred suspension of 5% palladium on barium sulfate (0.0273 g, MCB) in 4 mL of absolute ethanol. After 30 min, the theoretical amount of hydrogen had been consumed and with an additional 20 min, there was no more change in hydrogen uptake. The reaction mixture was then filtered through Celite on a sintered glass filter and the solvent was removed in vacuo to give 0.0957 g of a light yellow oil. The crude product on TLC (microscope glass coated with silica gel, eluted by a mixture of 40:60 ether and petroleum ether) showed two spots of R_f values 0.44 and 0.91. On the other hand, GLC analysis of the crude product on column a (column temperature 210 °C) showed essentially three peaks of retention times 6.6, 8.1, and 12.0 min in a ratio of 30.0:63.2:6.8, respectively.

The crude product was chromatographed on silica gel (11 g, 70–230 mesh, E. Merck) in a 1-cm diameter column. The column was eluted with a mixture of 20:80 ether and petroleum ether taking 5-mL sized fraction per every 15 min. Fractions 4–9 gave 0.02412 g (31.4% of total

yield) of A/B cis-fused keto ester **15A** as a colorless liquid and fractions 15–21 gave 0.05272 g (68.6%) of crystalline A/B trans-fused keto ester **10A** (mp 105–107 °C) in 94% total yield.

Keto ester **10A** prepared by catalytic hydrogenation was found to have identical properties on TLC and GLC, and superimposable NMR and IR spectra with the one prepared via the reductive carbomethoxylation procedure.

On the other hand, in GLC analysis using column a (column temperature 210 °C), cis-fused keto ester **15A,** homogeneous on TLC, showed two peaks of retention times 6.0 and 12.6 min in a ratio of 81:10, respectively. Evaporative distillation (140 °C at 0.5 mm) provided analytically pure keto ester **15A:** IR ($CHCl_3$) 3030 (C–H, aromatic), 3000, 2960, and 2875 (C–H, aliphatic), 1745, 1715 (small shoulder, CO, ester and ketone), 1650 (CO, conjugated ester), 1618 (C=C), 1496, 1455, 1445, and 1420 (aromatic skeletal), 1380 and 1360 (isopropyl), 1285 and 1240 (C–O–C), 1190 (=C–O), 1055, 1010, and 825 cm^{-1} (C–H bending, aromatic); NMR ($CDCl_3$) δ 1.25 (distorted d, 9, $-CHMe_2$ and $-CH_3$), 1.5–3.1 (m, 10, methylenes and methine), 3.80–3.84 (fused s, 3, $-OCH_3$), 6.85–7.45 (m, 3, aromatic), and 12.40 ppm (s, 0.7, =COH).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found: C, 76.45; H, 8.35.

Catalytic Hydrogenation of Methoxy Enone Ester 14B.[29,30] A solution of enone ester **14B** (9.3778 g, 1.26 mmol) in dry ethanol (10 mL) was hydrogenated in the presence of 5% palladium on barium sulfate (0.1265 g, MCB). After stirring for 2 h, 1 equiv of hydrogen was consumed and the reaction mixture was further stirred for 1 h without additional hydrogen uptake. After filtration followed by concentration of the filtrate in vacuo, 0.3785 g of a viscous liquid was obtained, which was crystallized on standing. The crude product on TLC (microscope glass coated with silica gel, eluted with 30:70 ether and petroleum ether solution) showed two spots of R_f values 0.18 and 0.63, respectively. GLC analysis of the crude product on column a showed (column temperature 220 °C) three peaks of retention times 5.02, 6.0, and 8.63 min in a ratio of 17.8:69.5:12.7, respectively.

The crude product was chromatographed on silica gel (38 g, 70–230 mesh, E. Merck) using a 1.5-cm diameter column eluting with a solution of 30:70 ether and petroleum ether, taking 15-mL size fractions. Fractions 4–7 gave 0.0989 g (26.5% of total yield) of crystalline cis-fused keto ester **15B** (mp 120–120.5 °C) and fractions 16–20 afforded 0.2750 g (73.5%) of crystalline trans-fused keto ester **10B** (mp 144–145.5 °C) in 98% total yield.

The trans-fused keto ester **10B** produced by catalytic hydrogenation was found to have superimposable IR and NMR spectra with those of the one synthesized via the reductive carbomethoxylation procedure. TLC and GLC analysis of the two samples revealed that they were identical. On the other hand, A/B cis-fused keto ester **15B,** homogeneous on TLC, in GLC analysis using column a (column temperature 220 °C) produced two peaks of retention times 5.02 and 8.63 min in a ratio of 80:20, respectively. An analytical sample of keto ester **15B** was prepared by recrystallization (three times) from ether: mp 120–120.5 °C; IR (CCl_4) 3030 (C–H, aromatic), 3000, 2950, and 2925 (C–H, aliphatic), 2850 ($PhOCH_3$), 1745–1725 (CO, ester and ketone), 1654 (CO, ester, enolic), 1610 (C=C), 1500, 1445, and 1425 (aromatic skeletal), 1280 (=C–O), and 1230 and 1045 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 1.32 (s, 3, $-CH_3$), 1.5–2.9 (m, 9, methylenes and methine), 3.73 (s, 3 $PhOCH_3$), 3.79 (s, 3, $-COOCH_3$) 6.45–6.98 (m, 3, aromatic), and 12.26 ppm (s, 0.75, =COH).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.57; H, 7.32.

Dissolving Metal Reductions of Isopropyl Enone Ester 14A.[31,32] To a stirred solution of lithium (4 mg, 0.58 mg/atom) in anhydrous liquid ammonia (10 mL) was added enone ester **14A** (0.040 g, 0.128 mmol) dissolved in a mixture of anhydrous tetrahydrofuran (THF) and dry *tert*-butyl alcohol (3.0 mL, 0.16 mmol); the solution was made by mixing 19.8 mL of THF (freshly distilled from lithium aluminum hydride) to 0.2 mL of *tert*-butyl alcohol (freshly distilled from calcium hydride). After addition of enone **14A,** the blue color persisted for 2 min, then the reaction was quenched with solid ammonium chloride. After the ammonia was evaporated, the reaction mixture was extracted with ether (5 × 100 mL). The combined ethereal extracts were washed with saturated sodium chloride solution (3 × 100 mL), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to yield 0.0405 g of a light yellow oil. GLC analysis of the crude product on column a (column temperature 210 °C, retention times 6.94, 8.40, and 12.0 min) indicated that trans-fused keto ester **10A** and cis-fused keto ester **15A** were produced in a ratio of 68.5:31.5 in 90% total yield.

Metal Hydride Reduction of Isopropyl Enone Ester 14A.[33,34] A mixture of enone ester **14A** (0.020 g, 0.064 mmol) and sodium borohydride (3 mg, 0.079 mmol) in anhydrous pyridine (1.5 mL, freshly distilled from calcium hydride) was stirred for 50 min at room temperature. Then, the mixture was poured into water (100 mL) and 10% hydrochloric acid solution (10 mL), followed by extraction with ether (5 × 50 mL). The combined ethereal extracts were washed with saturated sodium bicarbonate solution (100 mL), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to afford 0.0228 g of an oil. The crude product of GLC analysis using column a (column temperature 210 °C, retention times 7.12, 8.63, and 12.81 min) showed that trans-fused keto ester **10A** and cis-fused keto ester **15A** were produced in 58:42 ratio in 90% total yield.

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Registry No.—**1,** 21699-54-7; **4,** 58812-64-9; **5,** 58812-65-0; **6,** 58812-67-2; **7,** 58840-14-5; **8A,** 58812-66-1; **8B,** 58209-23-7; **9A,** 58846-74-5; **9B,** 41437-73-4; **10A,** 58812-68-3; **10B,** 41437-69-8; **11A,** 58812-69-4; **11B,** 41437-70-1; **12A,** 21699-55-8; **12B,** 41437-72-3; **13A,** 62462-00-4; **14A,** 62462-01-5; **14B,** 62462-02-6; **15A,** 62462-03-7; **15B,** 62462-04-8; 4-isopropenylisopropylbenzene, 2388-14-9; methyl vinyl ketone, 107-25-5; chloromethyl methyl ether, 107-30-2; methyl 5-methoxy-3-oxopentanoate, 62462-05-9.

References and Notes

(1) (a) J. A. Barltrop and N. A. J. Rogers, *Q. Rev., Chem Soc.*, **16,** 117 (1962); (b) J. R. Hanson in "Chemistry of Terpenes and Terpenoids", A. A. Newman, Ed., Academic Press, New York, N.Y., 1972, pp 186–191; (c) T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compounds", Vol. 2, Academic Press, New York, N.Y., pp 185–274; (d) K. Nakanishi in "Natural Products Chemistry", Vol. 1, K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nozoe, Ed., Academic Press, New York, N.Y., 1974, pp 185–312.
(2) (a) R. M. Carmen and H. C. Deeth, *Aust. J. Chem.*, **20,** 2789 (1967); (b) L. J. Gough, *Tetrahedron Lett.*, 295 (1968).
(3) (a) R. D. Haworth and R. L. Baker, *J. Chem. Soc.*, 1299 (1939); (b) M. Sharma, U. R. Ghatau, and P. C. Dutta, *Tetrahedron,* **19,** 985 (1963); (c) R. M. Carmen, H. C. Deeth, R. A. Marty, K. Mori, and M. Matsui, *Tetrahedron Lett.*, 3359 (1968); (d) K. Mori and M. Matsui, *Tetrahedron,* **24,** 6573 (1968); (e) J. W. Huffman, *J. Org. Chem.*, **35,** 3154 (1970); (f) S. W. Pelletier and D. L. Herald, Jr., *Chem. Commun.*, 10 (1971); (g) S. C. Welch and J. H. Kim, *Synth. Commun.*, **6,** 27 (1976).
(4) A. C. Oudemans, *Ber.*, **6,** 1122 (1873).
(5) (a) I. R. Sherwood and W. F. Short, *J. Chem. Soc.*, 1006 (1938); (b) W. P. Campbell and D. Todd, *J. Am. Chem. Soc.*, **62,** 1287 (1940); **64,** 928 (1942).
(6) (a) B. K. Bhattacharyya, *J. Indian Chem. Soc.*, **22,** 165 (1945); (b) R. D. Haworth and B. P. Moore, *J. Chem. Soc.*, 633 (1946); (c) W. E. Parham, E. L. Wheeler, and R. M. Dodson, *J. Am. Chem. Soc.*, **77,** 1166 (1955); (d) F. E. King, T. J. King, and J. G. Topliss, *Chem. Ind. (London)*, 113 (1956); (e) E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **80,** 211, 217 (1958); (f) E. Wenkert and A. Tahara, *ibid.*, **82,** 3229 (1960); (g) U. R. Ghatak, D. K. Datta, and S. C. Ray, *ibid.*, **82,** 1728 (1960); (h) S. N. Mahapatra and R. M. Dodson, *Chem. Ind. (London)*, 253 (1963); (i) E. Wenkert, A. Afonso, J. B-son Bredenberg, C. Kaneko, and A. Tahara, *J. Am. Chem. Soc.*, **86,** 2038 (1964); (j) W. L. Meyer and K. K. Maheshwari, *Tetrahedron Lett.*, 2175 (1964); (k) K. Mori and M. Matsui, *ibid.*, 175 (1966); (l) F. Giarrusso and R. E. Ireland, *J. Org. Chem.*, **33,** 3560 (1968); (m) T. A. Spencer, R. J. Friary, W. W. Schmiegel, J. F. Simeone, and D. S. Watt, *ibid.*, **33,** 719 (1968); (n) S. W. Pelletier, R. L. Chappell, and S. Prabhakar, *J. Am. Chem. Soc.*, **90,** 2889 (1968); (o) V. Mancini, F. Frigvelli, and A. Taticchi, *Gazz. Chim. Ital.*, **99,** 953 (1969); (p) M. E. Kuehne and J. A. Nelson, *J. Org. Chem.*, **35,** 161 (1970); (q) S. C. Welch and C. P. Hagan, *Synth. Commun.*, **3,** 29 (1973); (r) B. M. Trost and M. Precel, *J. Am. Chem. Soc.*, **95,** 7862 (1973); (s) T. Sone, S. Terashima, and S. K. Yamada, *Chem. Pharm. Bull.*, **24,** 1288 (1976).
(7) S. C. Welch and C. P. Hagan, *Synth. Commun.*, **2,** 221 (1972); S. C. Welch, C. P. Hagan, D. H. White, W. P. Fleming, and J. W. Trotter, *J. Am. Chem. Soc.*, **99,** 549 (1977).
(8) G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **84,** 284 (1962).
(9) Available from Aldrich Chemical Co., Milwaukee, Wis. (Catalog No. I-1,965-9).
(10) H. Hibbert and P. Burt, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1964, p 494.
(11) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596 (1957); E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87,** 1353 (1965).
(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21,** 1547 (1956).
(13) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 1159.
(14) J. J. Sims, L. H. Selman, and M. Cadogan, *Org. Synth.* **51,** 109 (1972); J. J. Sims, M. Cadogan, and L. H. Selman, *Tetrahedron Lett.*, 951 (1971).
(15) J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29,** 2501 (1964).
(16) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87,** 275 (1965); T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J.

Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968).
(17) (a) E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **81**, 5601 (1959); (b) T. A. Spencer, T. D. Weaver, M. A. Schwartz, W. J. Greco, Jr., and J. L. Smith, *Chem. Ind. (London)*, 577 (1964).
(18) L. Velluz, J. Valls, and G. Nomine, *Angew. Chem., Int. Ed. Engl.*, **4**, 181 (1965).
(19) R. M. Coates and J. E. Shaw, *J. Org. Chem.*, **35**, 2597 (1970).
(20) This reaction must be conducted in a well-ventilated hood; the chemist should wear rubber gloves during the workup because both hexamethylphosphoric triamide and chloromethyl methyl ether are carcinogens.
(21) We are grateful to Professor R. M. Carman for providing an authentic sample of (±)-methyl callitrisate.
(22) M. E. Kuehne, *J. Am. Chem. Soc.*, **83**, 1493 (1961).
(23) We are grateful to Professor S. R. Wilson, Indiana University, for providing generous samples of 7-methoxy-2-tetralone and tricyclic enone **9B**.
(24) L. H. Briggs, R. C. Cambie, and J. L. Hoare, *Tetrahedron*, **7**, 262 (1959). *O*-Methyl methyl podocarpate was prepared from (+)-podocarpic acid (Aldrich 11,979-2) by esterification with ethereal diazomethane followed by alkylation using methyl iodide and anhydrous potassium carbonate in refluxing acetone for 18 h.
(25) P. A. Bartlett and W. S. Johnson, *Tetrahedron Lett.*, 4459 (1970).
(26) (a) For examples of alkylation of unhindered exocyclic enolate anions see H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968); R. E. Ireland and L. N. Mander, *ibid.*, **32**, 689 (1967); **34**, 142 (1969); (b) For an example of alkylation of a hindered exocyclic enolate anion see F. E. Ziegler and J. A. Kloek, *Tetrahedron Lett.*, 315 (1974).
(27) Prepared by Mr. P. S. Chu in our laboratory from methyl hydrogen malonate, isopropylmagnesium chloride, and 3-methoxypropanoyl chloride in 70% yield according to the procedure of R. E. Ireland and J. A. Marshall, *J. Am. Chem. Soc.*, **81**, 2907 (1959).
(28) C. H. Heathcock and J. E. Ellis, *Chem. Commun.*, 1474 (1971); J. E. Ellis, J. S. Dutcher, and C. H. Heathcock, *Synth. Commun.*, **4**, 71 (1974); I. N. Nazarov and S. I. Zavyalov, *Zh. Obshch. Khim.*, **23**, 1703 (1953); *J. Gen. Chem. USSR (Engl. Transl.)*, **23**, 1793 (1953).
(29) R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, New York, N.Y., 1965, pp 11–14.
(30) Z. G. Hajos, R. A. Micheli, D. R. Parrish, and E. P. Oliveto, *J. Org. Chem.*, **32**, 3008 (1967); Z. G. Hajos and D. R. Parrish, *ibid.*, **38**, 3239 (1973).
(31) D. Caine, *Org. React.*, **23**, 1–258 (1976); G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **86**, 1761 (1964).
(32) L. F. Fieser and J. E. Herz, *J. Am. Chem. Soc.*, **75**, 121 (1953); S. K. Pradham, G. Subrahmanyam, and H. J. Ringlod, *J. Org. Chem.*, **32**, 3004 (1967).
(33) K. Adank, H. A. Pfenninger, W. G. Stoll, and M. Viscontini, *Helv. Chim. Acta*, **46**, 1030 (1963); S. B. Kadin, *J. Org. Chem.*, **31**, 620 (1966).
(34) W. L. Dilling and R. A. Plepys, *J. Org. Chem.*, **35**, 2971 (1970).
(35) M. F. Semmelhack and R. D. Stauffer, *J. Org. Chem.*, **40**, 3619 (1975).
(36) Aldrich Chemical Co., Milwaukee, Wis., Catalog No. Z10,046-3.
(37) W. S. Johnson and W. P. Schneider, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 132.
(38) R. L. Augustine, "Oxidation", Vol. 1, Marcel Dekker, New York, N.Y., 1969, p 222.

Rearrangements of Penicillin Sulfoxides. 1

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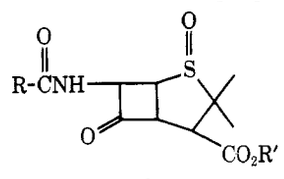
Penicillin sulfoxides are converted to 3-halo-3-methylcepham-4-carboxylic acid esters or the corresponding cephem derivatives by heating the penicillin sulfoxide precursor in the polyhaloalkane solvent in the presence of an equimolar amount of a neutral or basic catalyst, respectively. Basic catalysts such as pyridine or 4-picoline afford cephem derivatives, whereas the quaternary ammonium salts bring about the formation of 3-halocepham derivatives.

Several recent articles have reported the conversion of penicillins into cephalosporins by treatment of penicillin sulfoxides with reagents such as anhydrides,[2] acids,[3] diazo compounds–amine hydrochlorides,[4] 2-mercaptobenzothiazole followed by halogenation and dimethylformamide treatment,[5] thionyl chloride–triethylamine,[6] and trimethylchlorosilane–α-picoline.[7]

The present paper describes a novel, convenient process for the conversion of penicillin sulfoxides to a variety of cephalosporin derivatives. Most of the reported reactions, whereby the expansion of penicillin sulfoxides to ceph systems have been carried out, have involved acidic reagents. It was speculated that the reaction should also proceed under basic conditions. For this purpose, sulfoxide **1** was treated with a number of basic reagents in a variety of solvents. The desired deacetoxycephem **2** was indeed obtained in certain instances; however, in most cases the major or only product was the known[2,8] isothiazole **3** (Table I).



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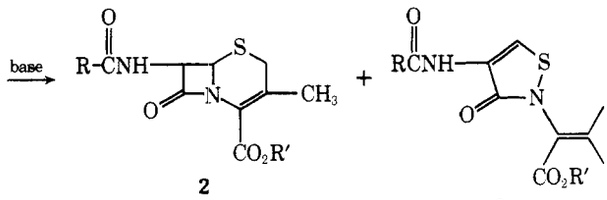
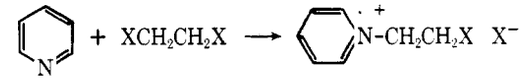


2 **3**

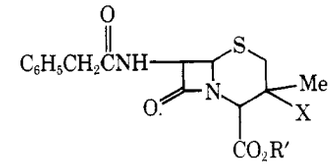
R = $C_6H_5CH_2$-, R′ = *p*-$NO_2C_6H_4CH_2$-

The best yields of cephem **2** were obtained in the presence of pyridine in 1,2-dichloroethane. The reaction was then repeated with various molar ratios of pyridine:sulfoxide **1**, ranging from trace amounts to very large molar excesses of base. The best results were obtained when 2 mol of pyridine/mol of sulfoxide **1** was used. In the presence of a large excess of pyridine, the quaternary salt **4a** precipitated out of solution



4a, X = Cl
b, X = Br

in crystalline form and it was found that this salt was a better catalyst for the rearrangement than pyridine itself. In 1,2-dichloroethane in the presence of 1 to 2 mol of salt **4a**/mol of sulfoxide **1**, the only detectable product obtained was a novel cephalosporin, which was subsequently shown to be cepham **5a**.[10]



5a, X = Cl
b, X = Br