mL of dry Et_2O and converted to 17.9 g of crude **9** by the procedure described for **7**. Column chromatography of this material on silica gel with 1% EtOAc–hexane afforded 3.1 g of diarylamine, 1.3 g of biphenyl, and a 20% yield of pure **9**: mp 130–132 °C; ^1H NMR ($CDCl_3$) δ 2.22 (s, 3, Ar CH_3), 2.50 (s, 3, Ar CH_3), 6.2–7.8 (m, 11, Ar H); mass spectrum, *m/e* (relative intensity) 304 (10), 303 (45), 227 (15), 226 (100), 225 (5), 209 (5), 151 (4), 77 (3). Anal. Calcd for $C_{20}H_{18}NP$: C, 79.19; H, 5.98; N, 4.62. Found: C, 79.42; H, 5.84; N, 4.82.

Compound **9** (0.303 g, 0.001 mol) was dissolved in 5 mL of acetone. To this solution was added 0.2 g of 30% H_2O_2. The oxide of **9** precipitated immediately. After the mixture was stirred for 2 min, the white solid was collected by filtration to give 0.31 g (97%) of analytically pure material: mp >310 °C; ^1H NMR (TFA) δ 1.88 (s, 3, Ar CH_3), 2.04 (s, 3, Ar CH_3), 6.4–7.6 (m, 12, Ar H); IR (Nujol) 3260 and 3160 (NH), 1175 cm^{-1} (P=O); mass spectrum, *m/e* (relative intensity) 320 (18), 319 (93), 318 (100), 304 (8), 243 (6), 242 (42), 226 (9), 195 (6), 194 (17), 180 (11), 160 (6), 152 (7), 151 (6), 91 (6), 77 (6). Anal. Calcd for $C_{20}H_{18}NOP$: C, 75.22; H, 5.68; N, 4.39. Found: C, 75.16; H, 5.64; N, 4.34.

Registry No. **3**, 79735-27-6; **5**, 79735-28-7; **6**, 79722-68-2; **7**, 79722-69-3; **7** phosphine oxide, 73785-73-6; **8**, 79735-29-8; **8** phosphine oxide, 79735-30-1; **9**, 79735-31-2; **9** phosphine oxide, 79735-32-3; 2′-methylacetanilide, 120-66-1; bromobenzene, 108-86-1; 2-methyldiphenylamine, 1205-39-6; 3′,5′-dimethylacetanilide, 2050-45-5; 3,5-dimethyldiphenylamine, 51786-49-3; phosphorus trichloride, 7719-12-2; diphenylamine, 122-39-4.

In Vitro Reactions of Alkaloids. 2. Selective Decarbalkoxylation of Geminal Diesters, β-Keto Esters, and δ-Keto-β,γ-unsaturated Esters

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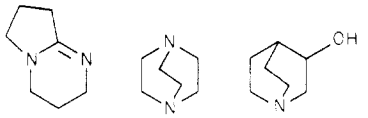
Received June 9, 1981

The reactivity of brucine, tropine, nicotine, reserpine, yohimbine hydrochloride, and quinidine has been demonstrated by the decarbalkoxylation of diethyl bis(3,4-dichlorobenzyl)malonate, ethyl β-(1-adamantyl)-β-oxopropionate, and 4-carbethoxy-3-methyl-2-cyclohexen-1-one. All reactions were conducted in dry *o*-xylene at 144–146 °C for 24 h with equivalent ratios (8:1) of base to substrate. These conditions were chosen for the purpose of establishing maximum selectivity. Brucine, nicotine, and yohimbine hydrochloride were shown to be selective toward the β-keto ester system, whereas tropine, reserpine, and quinidine were more selective catalysts toward decarbalkoxylation of δ-keto-β,γ-unsaturated esters. Brucine gave higher yields with all esters decarbalkoxylated and thus is the most reactive. The ability of these alkaloids to decarbalkoxylate esters, with some selectivity, suggests that one of the roles of alkaloids in plants may be to catalyze certain decarboxylation reactions.

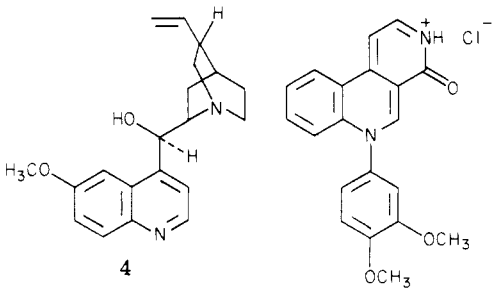
We have reported[1-6] the carbalkoxylation of geminal diesters, β-keto esters, and δ-keto-β,γ-unsaturated esters with the tertiary amine bases 1,5-diazabicyclo[4.3.0]non-5-ene (**1**), 1,4-diazabicyclo[2.2.2]octane (**2**), and 3-quinuclidinol (**3**), in nonaqueous solvents in good yields.



1 2 3

The similarity of the bicyclic moiety of these bases with that found in alkaloids such as quinine and the fact that the substrates (β-keto esters, geminal diesters, and δ-keto-β,γ-unsaturated esters) used are similar to those found in biological systems led us to postulate that one of the roles of alkaloids in plants could be to catalyze metabolic decarboxylation and decarbalkoxylation reactions. Some scientists have speculated[7] that alkaloids are by-products of plant metabolism, while others have proposed that they might serve as protective materials, reservoirs for protein, plant stimulants, plant regulators, and detoxifying agents. However alkaloids are still referred to as secondary metabolites, implying that they have no confirmed role in plant metabolic processes.

We have previously tested[8] our postulation by investigating the in vitro reactivity of quinine (**4**) and perloline hydrochloride (**5**) toward the three types of esters mentioned above. The results showed that decarbalkoxylation of the esters occurred in good yields. However a general statement concerning selectivity could not be made since the reactions were not performed under identical conditions. The conditions chosen were those that would result in the maximization of yields. Therefore an investigation was warranted into whether a broad spectrum of alkaloids would be reactive. Furthermore the question of selectivity needed to be answered in order to allow the postulation of a catalytic role for alkaloids in plants.



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This paper describes an investigation of the relative selectivity of the alkaloids brucine (**6**), tropine (**7**), nicotine (**8**), reserpine (**9**), yohimbine hydrochloride (**10**), and

(1) D. H. Miles and E. J. Parish, *Tetrahedron Lett.*, 3987 (1972).
(2) E. J. Parish, B. S. Huang, and D. H. Miles, *Synth. Commun.*, *5*, 341 (1975).
(3) E. J. Parish and D. H. Miles, *J. Org. Chem.* **38**, 1223 (1973).
(4) B. S. Huang, E. J. Parish, and D. H. Miles, *J. Org. Chem.*, **39**, 2647 (1974).
(5) E. J. Parish, N. V. Mody, P. A. Hedin, and D. H. Miles, *J. Org. Chem.*, **39**, 1592 (1974).
(6) D. H. Miles and B. S. Huang, *J. Org. Chem.*, **41**, 208 (1976).
(7) S. W. Pelletier, Ed., "Chemistry of the Alkaloids", Van Nostrand-Reinhold Co., New York, 1970, pp 1–9.
(8) D. H. Miles and B. S. Huang, *Synth. Commun.* **6**, 533 (1976).

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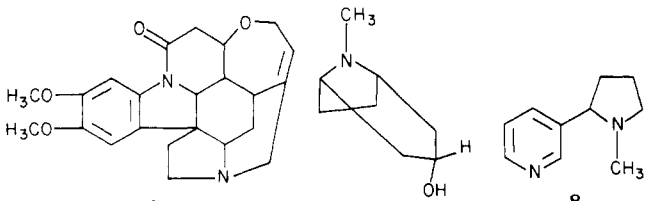
Chart I



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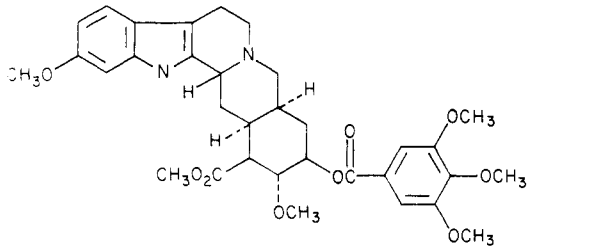
7

8



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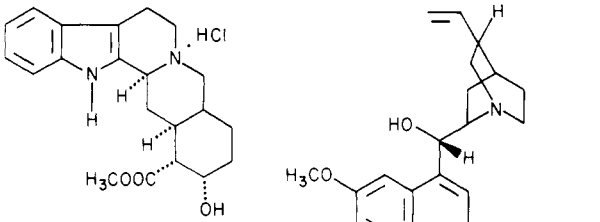

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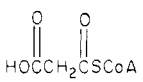
11

quinidine (11) toward three ester types (Chart I). These alkaloids were chosen because of their availability and biological activity toward mammals. The esters utilized in this study were selected for several reasons. First, one ester from each of the geminal diester, β-keto ester, and δ-keto-β,γ-unsaturated types was chosen. These are diethyl bis(3,4-dichlorobenzyl)malonate (12), ethyl β-(1-adamantyl)-β-oxopropionate (14), and 4-carbethoxy-3-methyl-2-cyclohexen-1-one (16). Second, the three esters chosen had given high yields of the monoester (13), ketone (15), and α,β-unsaturated ketone (17) product molecules. Furthermore the products are crystalline solids which can be easily characterized. Third, these esters are analogous to esters and acids found in biological systems which are important to the various metabolic functions in plants and animals. The geminal diester system can be associated with the malonyl-CoA (18) pathway in the biosynthesis of fatty acids[9] and other natural products such as orsellenic acid.[10] Acetoacetyl-CoA (19) is an example[11] of a naturally



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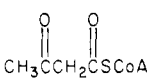

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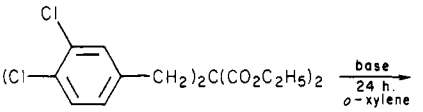
occurring β-keto ester system which is important to the biogenesis of steroids and plant phenolics. It is a precursor along with acetyl-CoA to a variety of polyketo CoA ester chains which can cyclize to a variety of compounds. The majority of these compounds contain an even number of carbon atoms. However compounds like eleutherinol (20) contain an odd number of carbon atoms which presumably

(9) S. J. Wakil, Ed., "Lipid Metabolism", Academic Press, New York, 1970.
(10) P. Bernfeld, "Biogenesis of Natural Products", 2nd ed., Pergamon Press, New York, 1967, 1033–1034.
(11) J. B. Hendrickson, "The Molecules of Nature", W. A. Benjamin, Reading, MA, 1965, p 22.

Table I. Decarbethoxylation of Diethyl Bis(3,4-dichlorobenzyl)malonate (12) Using Various Bases



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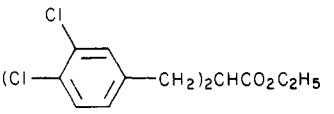

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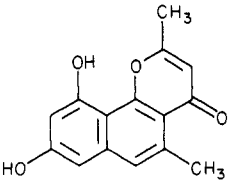
base	% yield of monoester 13	% recov of diester 12
brucine (6)	17.3	76.3
tropine (7)	5.6	94.1
nicotine (8)	2.0	88.0
reserpine (9)	0.2	68.5
yohimbine hydrochloride (10)	0.2	92.7
quinidine (11)	4.2	80.5

result from decarboxylation of a β-keto acid or CoA ester system.



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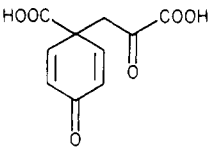
A precursor of tyrosine and *p*-coumaric acid in plant metabolism is compound 21,[11] which can be associated with the δ-keto-β,γ-unsaturated ester system.



21

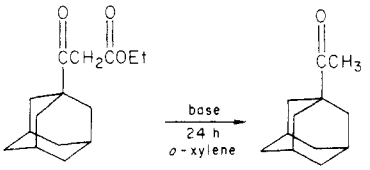
Since these studies were performed for the purpose of determining the selectivity of various structural types, in a manner that would parallel enzyme selectivity, the reaction conditions were held constant. Reaction mixtures were refluxed for 24 h in dry *o*-xylene with an 8:1 equivalent ratio of alkaloid to substrate.

Previous work[6] indicated that diethyl bis(3,4-dichlorobenzyl)malonate (12) is a more reactive geminal diester than less sterically hindered geminal diesters when treated with various bases. The reactivity of the selected alkaloids with substrate 12 is presented in Table I. The yield of monoester produced by brucine (6) is significant in that it is 3–85 times higher than for the other alkaloids.

The reactivity of the selected alkaloids toward the β-keto ester substrate ethyl β-(1-adamantyl)-β-oxopropionate (14) is presented in Table II. Nicotine (8) and yohimbine hydrochloride (10) have the highest reactivity; brucine (6) has a moderate reactivity and the remaining three alkaloids show relatively low reactivity.

The reactivity of the selected alkaloids toward the δ-keto-β,γ-unsaturated ester substrate 4-carbethoxy-3-methyl-2-cyclohexen-1-one (16) is presented in Table III. Quinidine shows the highest reactivity, while the reactivity of the other alkaloids is around 30% or less.

Table II. Decarbethoxylation of Ethyl β-(1-Adamantyl)-β-oxopropionate (14) Using Various Bases

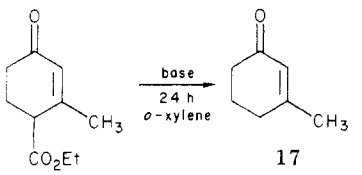


14 15

base	% yield of ketone 15[a]
brucine (6)	49.0
tropine (7)	2.1
nicotine (8)	81.0
reserpine (9)	7.5
yohimbine hydrochloride (10)	89.7
quinidine (11)	12.5

[a] The percentage recovery of starting keto ester 14 is equal to 100% yield of ketone. This percentage is based upon isolated keto ester 14.

Table III. Decarbethoxylation of 4-Carbethoxy-3-methyl-2-cyclohexen-1-one (16) Using Various Bases



16 17

base	% yield of α,β-unsatd ketone 17	% recov of ester 16
brucine (6)	27.6	68.5
tropine (7)	24.7	70.8
nicotine (8)	25.0	74.0
reserpine (9)	34.5	24.8
yohimbine hydrochloride (10)	14.3	72.5
quinidine (11)	56.9	

Table IV. Bases Which Are More Selective toward β-Keto Ester 14

	% yield (GLC)		
base	monoester 13	ketone 15	α,β-unsatd ketone 17
brucine (6)	17.3	49.0	27.6
nicotine (8)	2.0	81.0	25.0
yohimbine hydrochloride (10)	0.2	89.7	14.3

These studies show that a broad spectrum of alkaloids is reactive toward β-keto esters, geminal diesters and δ-keto-β,γ-unsaturated esters with a high degree of selectivity. The selectivity of the alkaloids is indicated in Table IV and V. Brucine (6), nicotine (8), and yohimbine hydrochloride (10) are selective toward the decarbalkoxylation of the β-keto ester 13, while reserpine (9), tropine (7), and quinidine (11) are selective toward decarbalkoxylation of the δ-keto-β,γ-unsaturated ester 16. Brucine (6) seems to be the most reactive alkaloid since higher yields were obtained for all esters decarbalkoxylated with this reagent. Higher yields of all products can be obtained by using more severe reaction conditions.

Table V. Bases Which Are More Selective toward δ-Keto-β,γ-unsaturated Ester 16

	% yield (GLC)		
base	monoester 13	ketone 15	α,β-unsatd ketone 17
tropine (7)	5.6	2.1	24.7
reserpine (9)	0.2	7.5	34.5
quinidine (11)	4.2	12.5	56.9

Reactions involving base-catalyzed carboxylation and decarbalkoxylation of various acids and esters have been extensively studied.[12-15] Many of the earlier studies showed that primary amines are effective catalysts. This is exemplified by the naturally occurring decarboxylation of acetoacetate by the enzyme acetoacetate decarboxylase through a Schiff base intermediate. Secondary amines were generally considered to be much less effective, while tertiary amines were considered to be completely ineffective. This study demonstrates that tertiary alkaloids which contain a tertiary amine moiety can be effective catalysts of decarbalkoxylation reactions under relatively nonpolar reaction conditions such as one might expect to encounter in the lipid portions of living organisms. This fact in combination with the known ability of tertiary amines to undergo protonation and alkylation in a manner that is easily reversible leads us to postulate that alkaloids can catalyze important metabolic reactions in plants. The selectivity of alkaloids for particular types of substrates as demonstrated in this study is in line with this proposed rule.

In short, the evidence presented in this study demonstrates that a variety of alkaloids are reactive in vitro with some degree of selectivity toward substrates which are analogous to those that occur in plants. In vivo studies will be performed to test the postulation of a catalytic role for alkaloids.

Experimental Section

General Procedures. Nuclear magnetic resonance spectra were obtained with a JEOLCO Minimar spectrometer equipped with a spin decoupler. Tetramethylsilane was used as the internal standard and chloroform-*d* (99.8%, $CDCl_3$) and acetone-d_6 (99+%, CD_3COCD_3) were used as solvents. Mass spectral data (MS, GC–MS) were obtained with a Hewlett-Packard Model 5930 or a Perkin-Elmer 270 mass spectrometer. Infrared spectra were obtained with a Perkin-Elmer Model 137B infracord, a Beckman-IR5A spectrophotometer, or a Perkin-Elmer Model 521 grating infrared spectrophotometer. The spectra of liquids were taken on films formed between two sodium chloride plates; potassium bromide was used in preparing pellets of solid samples for infrared spectra. The 1603-cm band of a polystyrene film (0.05 mm) was used as a reference peak. Column chromatography was performed in glass columns (wet or dry packed) with sintered glass, using Woelm adsorption silica gel (activity 1) of M Woelm Eschwege Germany (distributed by ICN Pharmaceuticals) as the solid support. Thin-layer chromatography (TLC) was performed with E. Merck (Darmstardt) silica gel G coated glass plates (Applied Science Laboratories, Inc.). Chromatoplates (20 × 20 cm and 5 × 20 cm) were prepared by using a Desaga spreader with a thickness of 0.25 mm for qualitative TLC and 0.50 mm for preparative TLC. The plates were activated at 110 °C for 1 h. Potassium dichromate in sulfuric acid was used as the detecting agent. Gas–liquid chromatography (GLC) was performed with a Hewlett-Packard Model 402 gas chromatograph

(12) K. J. Pederson, *J. Am. Chem. Soc.*, **60**, 595 (1938).
(13) F. H. Westheimer and W. A. Jones, *J. Am. Chem. Soc.*, **63**, 3282 (1941).
(14) K. J. Pederson, *Acta Chem. Scand.*, **8**, 710 (1954).
(15) R. W. Hay, *Aust. J. Chem.*, **18**, 337 (1965).

with a hydrogen flame detector. Glass columns (6 ft × 3.0 mm i.d. and 12 ft × 3.0 mm i.d.) bent in a U shape were used. The column substrates and solid supports used in the GLC analyses were obtained from Applied Science Laboratories or from Hewlett-Packard Analytical Instruments. Melting points were obtained on a Fisher-Jones apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tn.

General Procedure for Treatment of Diethyl Bis(3,4-dichlorobenzyl)malonate (12), Ethyl β-(1-Adamantyl)-β-oxopropionate (14), and 4-Carbethoxy-3-methyl-2-cyclohexen-1-one (16) with Brucine (6), Tropine (7), Nicotine (8), Reserpine (9), Yohimbine Hydrochloride (10), and Quinidine (11). A mixture of 0.5 mmol of the appropriate ester and 4.0 mmol of the appropriate alkaloid in 169 mmol of *o*-xylene was heated at reflux (144–146 °C) for 24 h. The reaction mixture was acidified with dilute hydrochloric acid and extracted with ethyl ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate and analyzed by GLC. A glass column (6 ft, 5% SE-30 on 80/100 mesh Chromosorb W column, nitrogen flow rate 10 mL/min, column temperature 138 °C) was utilized. The appropriate products were identified by comparison of GLC retention times with those of authentic samples. Structural determinations of isolated samples were performed by MS, IR, NMR, and GLC analyses.

Acknowledgment. Support for this research was provided by the Biological and Physical Sciences Institute and the Office of Graduate Studies at Mississippi State University. We are indebted to Professor Lyell Behr and Ms. Shirley Randle for their assistance during the preparation of this paper.

Registry No. 6, 357-57-3; **7**, 120-29-6; **8**, 54-11-5; **9**, 50-55-5; **10**, 65-19-0; **11**, 56-54-2; **12**, 79665-12-6; **13**, 28751-26-0; **14**, 19386-06-2; **15**, 1660-04-4; **16**, 487-51-4; **17**, 1193-18-6.

Stereospecific 1,4-Additions of Methyl Cyanocuprate to Enol Phosphates of α,β-Epoxycyclohexanones: Application to the Total Synthesis of (±)-α-Multistriatin[1]

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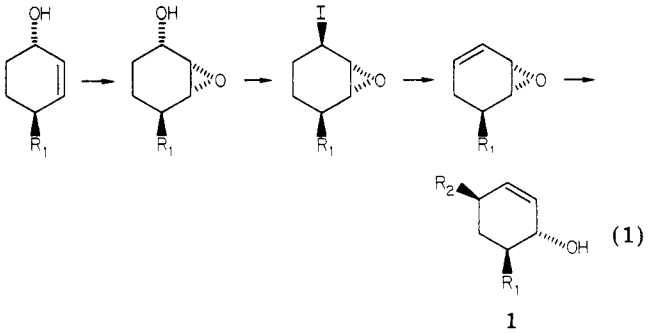
Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109

Received July 31, 1981

A highly stereospecific synthesis of (±)-α-multistriatin, one of the three components of the aggregation pheromone of the European elm bark beetle, is described. The synthesis involves a new route to substituted cyclohex-2-en-1-ols via trans 1,4-additions to enol phosphates of α,β-epoxycyclohexanones and subsequent reductive cleavage of a β-hydroxy enol phosphate.

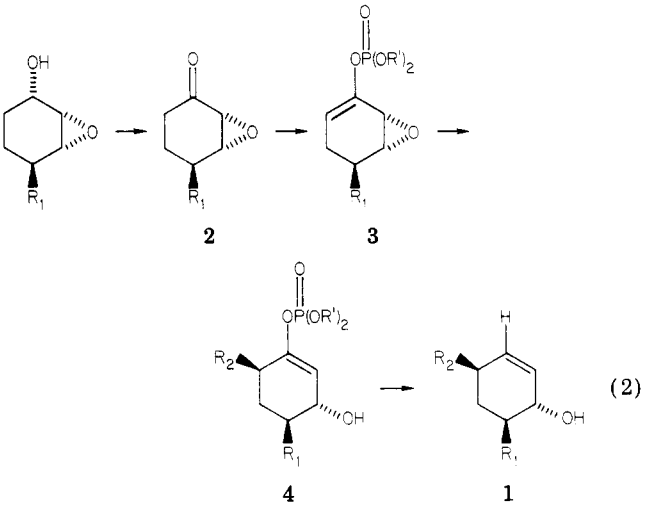
In a preliminary paper,[2] we reported the stereospecific synthesis of cis 4,6-disubstituted cyclohex-2-en-1-ols 1 via sequential trans 1,4-additions of alkyl cyanocuprates to vinyl epoxides. This synthetic sequence required the inversion of a hydroxyl group in order to effect a trans elimination (sequence 1).



(1)

1

As an alternative route to compounds such as 1, we sought to circumvent the dehydration of the hydroxy epoxide intermediate and utilize the keto epoxide system 2. We previously had shown that the double bond of an enol silyl ether is compatible with the trans 1,4-addition of cyanocuprates.[2] Since it is well-known that enol phosphates and phosphoramidates can be reductively cleaved to alkenes,[3] we investigated the use of such ketone derivatives in an effort to produce 1 from 2 (sequence 2). In



2 3

4 1

(2)

this report we present the successful utilization of enol phosphates of α,β-epoxycyclohexanones in the conversion of ketones such as 2 into cis 4,6-disubstituted cyclohex-2-en-1-ols 1. We also describe herein a highly stereospecific

(1) A preliminary report on this synthetic strategy to α-multistriatin was made at the 3rd IUPAC Meeting on Organic Synthesis, Madison, WI, June 15–20, 1980.

(2) Marino, J. P.; Hatanaka, N. *J. Org. Chem.* **1979**, *44*, 4467.

(3) Fetizon, M.; Jurion, M.; Anh, N. T. *Chem. Commun.* **1969**, 112; Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.

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