(16) Doering, W. von E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67. *Angew. Chem.* **1963**, *75*, 27.
(17) Hansen, H.-J.; Schmid, H. *Tetrahedron* **1974**, *30*, 1959. Vittorelli, P.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1975**, *58*, 1293. Jolidon, S.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 2436. Lythgoe, B.; Metcalfe, D. A. *Tetrahedron Lett.* **1975**, 2447.
(18) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435. (b) Trost, B. M.; Taber, D. F.; Alper, J. B. *Tetrahedron Lett.* **1976**, 3857. (c) Ficini, J.; d'Angelo, J.; Noire, J. *J. Am. Chem. Soc.* **1974**, *96*, 1213.
(19) Bowers, W. S.; Fales, H. M.; Thompson, M. J.; Uebel, E. C. *Science* **1966**, *154*, 1020.
(20) Nakazaki, M.; Isoe, S. *Bull. Chem. Soc., Jpn.* **1961**, *34*, 741; **1963**, *36*, 1198.
(21) Pawson, B. A.; Cheung, H.-C.; Gurbaxani, S.; Saucy, G. *J. Chem. Soc., Chem. Commun.* **1968**, 1057. Blount, J. F.; Pawson, B. A.; Saucy, G. *Ibid.* **1969**, 715. Pawson, B. A.; Cheung, H.-C.; Gurbaxani, S.; Saucy, G. *J. Am. Chem. Soc.* **1970**, *92*, 336.
(22) Cerny, V.; Dolejs, L.; Labler, L.; Sorm, F.; Slama, K. *Tetrahedron Lett.* **1967**, 1053. *Collect. Czech. Chem. Commun.* **1967**, *32*, 3926.
(23) Rogers, I. H.; Manville, J. F.; Sahota, T. *Can. J. Chem.* **1974**, *52*, 1192. Manville, J. F. *Ibid.* **1975**, *53*, 1579. *Ibid.* **1976**, *54*, 2365.
(24) Sakai, T.; Hirose, Y. *Chem. Lett.* **1973**, 491.
(25) Mori, K.; Matsui, M. *Tetrahedron* **1968**, *24*, 3127. Ayyar, K. S.; Rao, G. S. K. *Can. J. Chem.* **1968**, *46*, 1467. Birch, A. J.; Macdonald, P. L.; Powell, V. H. *J. Chem. Soc. C* **1970**, 1469. Drabkina, A. A.; Tsizin, Y. S. *J. Gen. Chem. USSR (Engl. Transl.)* **1973**, *44*, 422, 691. Trost, B. M.; Tamaru, Y. *Tetrahedron Lett.* **1975**, 3797. Negishi, E.; Sabanski, M.; Katz, J.-J.; Brown, H. C. *Tetrahedron* **1976**, *32*, 925.
(26) Bunnel, C. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1977**, *99*, 5184.
(27) Felix, D.; Müller, R. K.; Horn, U.; Joos, R.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 1276.
(28) Biller, S. A.; Evans, D. A. Unpublished results.
(29) Müller, R. K.; Joos, R.; Felix, D.; Schreiber, J.; Wintner, C.; Eschenmoser, A. *Org. Synth.* **1976**, *55*, 114.
(30) Cason, J.; Prout, F. S. *J. Am. Chem. Soc.* **1944**, *66*, 46.
(31) Manville, J. F.; Bock, K. *Org. Magn. Reson.* **1977**, *9*, 596.
(32) Purchased from Ventron/Alfa Inorganics.
(33) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

Total Synthesis of *dl*-Bisnorvernolepin

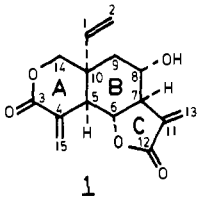
G. R. Kieczykowski, Martha L. Quesada, and R. H. Schlessinger*

Contribution from the Department of Chemistry, University of Rochester, Rochester, New York 14627. *Received June 4, 1979*

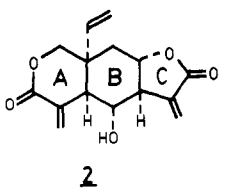
Abstract: A 19-step total synthesis of the racemic form of bisnorvernolepin, **4**, has been achieved starting from ethyl crotonate. The synthesis is both regiospecific and stereospecific in that it leads to the exclusive formulation of bisnorvernolepin without concomitant formulation of bisnorvernomenin. The synthesis begins with the preparation of compound **5**, a harbinger of the vernolepin B ring and conjoiner of rings A and C. Compound **5** is then converted into the *cis*-2-oxydecalin **20** which is stereoselectively converted into the α-methoxymethyloxy epoxide **28**. Regiospecific ring opening of **28**, facilitated by the chiral center in ring A, followed by successive establishment of the C and A ring lactones yields bisnorvernolepin.

Background

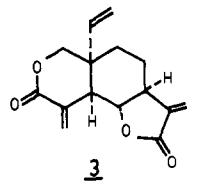
Since their isolation and characterization by Kupchan,[1] the elemanolide dilactones vernolepin (**1**) and vernomenin (**2**) have elicited a flurry of synthetic activity,[2] culminating in four total syntheses.[3] Quite apart from the pronounced cytotoxic activity of vernolepin, and to a lesser extent vernomenin, interest in the synthesis of these sesquiterpenes derives from the impressive functional and stereochemical array that resides in ring B of these natural products. Grieco's synthesis of desoxyvernolepin (**3**)[4] suggested that bis-α-methylenation of compound **4**, bis-



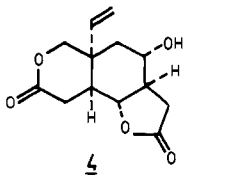
1



2



3

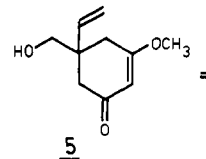


4

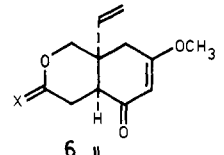
norvernolepin would be feasible, and thus, **4** became our penultimate synthetic target. Indeed, compound **4** became our ultimate objective, because, prior to completion of our work, both Grieco and Danishefsky succeeded in converting **4** into racemic vernolepin.[3]

Having selected our target, we embarked on a series of retrosynthetic considerations which led to definition of the monocyclic system **5**—a substance whose appeal arises from the chemical flexibility intrinsic to its vinylogous ester residue. Inherent within **5** was the possibility of conjoining another ring to it by attaching, to the hydroxymethyl group of **5**, a two-carbon unit having a terminal electrophilic center. Cyclization via a nucleophilic center developed adjacent to the carbonyl residue was anticipated to yield the *cis*-2-oxydecalin **6**.

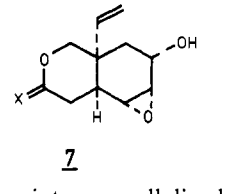
Of several avenues now open to fashion the natural product from **6**, one of particular simplicity emerged. Vinylogous esters are known to be reductively convertible into enones,[5] Thus, conversion of **6** into its corresponding enone followed by ste-



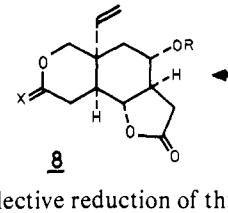
5



6



7



8

reoselective reduction of this enone into an α-allylic alcohol[6] and subsequent Henbest epoxidation of the latter would afford the *cis*-α-hydroxy epoxide **7**.[7] Providing the hydroxyl group of **7** were protected in some form, regiospecific and stereospecific epoxide ring opening[8] with a two carbon nucleophile ought to exclusively yield the lactone **8**. Although tenuously defined, this course of action, in principle, would mobilize the

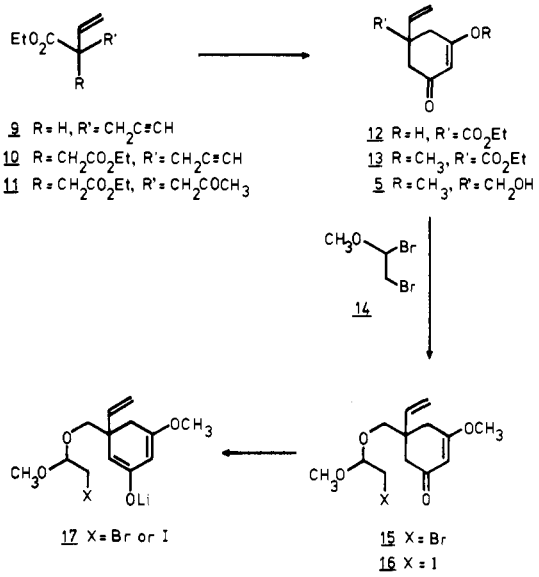
0002-7863/80/1502-0782$01.00/0

remaining chiral centers required for completion of the synthetic exercise.

Results

(i) Synthesis of the Vinylogous Ester 5. The approach chosen to prepare **5** utilizes successive alkylation of ethyl crotonate, a Claisen condensation, and, finally, selective ester reduction. Treatment of ethyl crotonate with a 1:1.2 mixture of lithium diisopropylamide/hexamethylphosphoramide in THF followed by alkylation with propargyl bromide gave the acetylenic ester **9**.[9] An interesting operational question posed itself at this junction because the next synthetic step required selective deprotonation of **9** at the methine hydrogen adjacent to the ester residue. Complicating this intended deprotonation reaction was the acidity of the acetylenic proton of **9**. No conclusive literature precedence was available to suggest which of the two acidic sites in **9** would suffer proton abstraction, and, therefore, recourse to experiment was sought. Fortunately, deprotonation of **9** in the kinetic manner resulted in exclusive generation of the desired ester enolate, and its subsequent alkylation with ethyl bromoacetate uneventfully provided **10**.[10] Mercuric sulfate catalyzed hydration of **10** afforded the methyl ketone **11** which, on Claisen cyclization mediated by potassium *tert*-butoxide in *tert*-butyl alcohol, gave the diketone ester **12**. By this process, a 73% overall yield of **12** was consistently obtained from ethyl crotonate.[11]

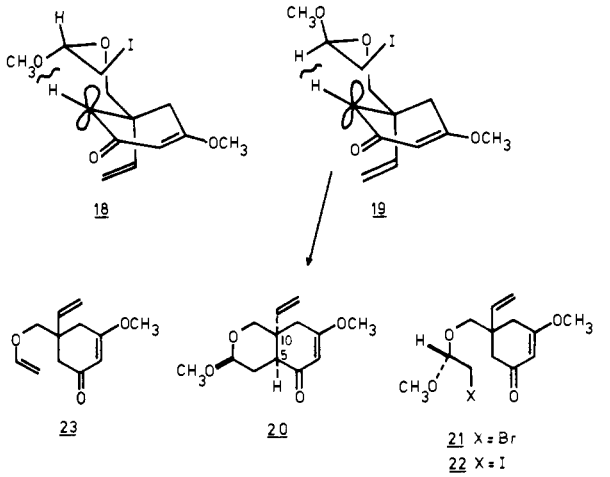
Again an operational problem of selectivity arose, for we required exclusive reduction of the ester residue of **12** into its corresponding alcohol. It occurred to us that this might be accomplished by preparing the vinylogous ester analogue of **12**, protecting the vinylogous ester carbonyl group at its corresponding enolate, and then reducing the ester portion of the molecule using a hydride reagent. We are gratified to find that Barton had successfully carried out reductions of this type in the presence of enones protected as their corresponding enolates.[12] Thus, the transformation **12** → **5** was initiated by conversion of the former into the vinylogous ester **13** using methanol and trimethyl orthoformate under acidic conditions. Reduction of **13** into the vinylogous ester alcohol **5** was then carried out in excellent yield by kinetic formation of the vinylogous ester enolate[5] followed by treatment of it with lithium aluminum hydride. Inverse quenching of the reaction was necessary to ensure destruction of excess hydride commensurate with enolate protonation.



(ii) Preparation of the Bicyclic Vinylogous Ester 20. Several possible two-carbon residues together with means of attaching them to the alcohol portion of compound **5** were considered. It was found that dibromide **14**,[13] on the reaction with **5** in the presence of *N*,*N*-dimethylaniline gave the bromide **15**.[14] The bromide **15** also could be converted into the corresponding iodide **16** using sodium iodide in refluxing acetone.

An examination of molecular models representing cyclization (via intramolecular alkylation) of the anion **17**, obtained by deprotonation of either **15** or **16**, shows the anion to have two equally populated epimeric forms, **18** and **19**.[15] It was readily determined from these models that, during bond formation, a serious interaction occurs between the acetal methoxy group and the hydrogen atom carried by the enolate **18**, while an interaction of this type does not occur in **19**. Thus, a clear difference in the ease of cyclization for these epimers was anticipated.

Both the bromide and the iodide were examined with respect to cyclization. Bromide **15**, when kinetically deprotonated with lithium bis(trimethyl)silylamide, undergoes cyclization at 0 °C to give a 1:1 mixture of the β-methoxy-*cis*-2-oxydecalin **20** and the unreacted bromide having the side chain configuration depicted in **21**. The same behavior was exhibited by the iodide **16** at −40 °C to afford a 1:1 mixture of **20** and **22**. Several attempts to force the complete cyclization of **15** into bicyclic material led only to complicated reaction mixtures. The iodide **16** proved only marginally better affording a mixture of **22** and three bicyclic substances consisting, by NMR analysis, of compound **20**, its α-methoxy analogue, and a *trans*-2-oxydecalin system. The foregoing mixture proved extraordinarily difficult to resolve chromatographically.

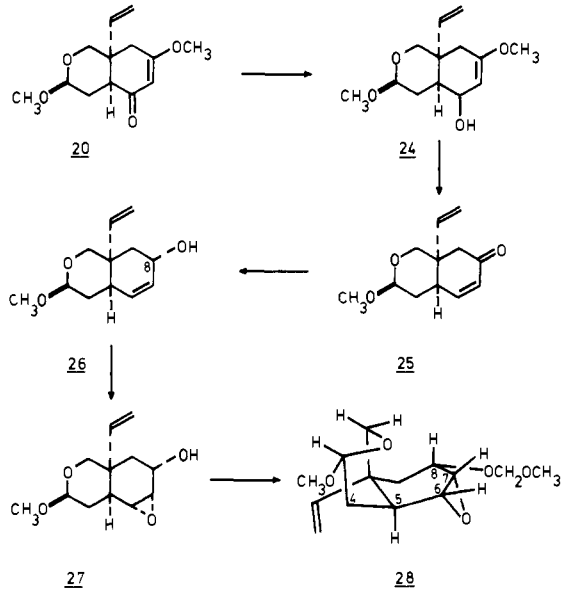


Since a yield no greater than 50% for **20** appeared realizable, and since the cyclization mixtures of either **20** and **21** or **20** and **22** could not be readily separated by chromatography, it became necessary to seek a means of reconstituting either **21** or **22** as the alcohol **5** without prior separation of **20**. The bromide **21** resisted all attempts at hydrolysis without causing significant destruction of the vinylogous ester. Eventually, we found that treatment of a mixture of **20** and **22** with a concoction of activated zinc metal containing 5% copper metal suspended in methanolic dimethyl sulfoxide resulted in formation of a 1:1:2 mixture of alcohol **5**, vinyl ether **23**, and **20**.[16] Acid workup of the reaction rapidly hydrolyzes **23** into **5**, thus affording a 1:1 mixture of alcohol **5** and vinylogous ester **20** which proved trivial to separate by chromatography. The overall yield of **20** from **16** based on recovered and reused **5** was 83%. The exclusive formation of **20** held a very considerable technical advantage for us with respect to simplifying the NMR spectra of this substance as well as subsequent intermediates derived therefrom.

Provisional assignment of stereochemistry for the compound **20** follows from its ^{1}H NMR spectra. Compound **20** exhibits vicinal coupling constants for the angular methine proton that indicate ring B is equatorial to ring A at C_5 and axial to ring A at C_{10}. Assigning a configuration to the acetal residue

present in **20** proved somewhat difficult since only limited literature data are available regarding vicinal coupling constants of cyclic ethers. However, the interdependence of vicinal coupling constants with the electronegativity of a heteroatom substituent in or on a chair-configured six-membered ring has been investigated in simple cases by Booth.[17] An increase in the electronegativity of a substituent causes a decrease in the vicinal coupling constants where the maximum electronegativity effect on $J_{H1,H2}$ appears to coincide with trans coplanarity for the system $X\text{-}C_1\text{-}C_2\text{-}H_2$. This geometric situation exists in **20** when ring A is in the chair configuration with the methoxy group equatorial to this ring. Reasonable agreement was obtained in this case between the observed coupling constants derived from the methine acetal proton and those values calculated from the Booth relationship.

(iii) Preparation of the *cis*-α-Epoxy Ether 28. Reduction of the vinylogous ester **20** with LAH in THF at 22 °C followed by neutral workup afforded the acetal enol ether alcohol **24** in essentially quantitative yield.[18] Compound **24,** when subjected



to a variety of acid hydrolysis conditions, gave the enone **25** in moderate yield with concurrent formation of the corresponding β-hydroxy ketone. The conversion of **24** into **25** in 96% yield was realized by using 5% by weight of iodine in anhydrous THF.[19] ^{1}H NMR data suggested that enone **25** exists in a conformational form similar to that described for compound **20**.

We felt the axial vinyl group 1,3-disposed to the carbonyl group would cause reduction of **25** to occur from the β face of the molecule by axial hydride attack—a result which should yield the corresponding equatorial α-allylic alcohol.[6] Somewhat to our surprise, reduction of **25** with DIBAL-H in 1:1 hexane-toluene at 0 °C gave a 97% yield of a 3:2 mixture of allylic alcohols.[20] These alcohols were readily separable by simple chromatography, and their ^{1}H NMR spectra were very similar. However, the proton α to the alcohol at C_8 would be expected to be slightly downfield in the β-allylic alcohol when compared with the α-allylic alcohol. The actual values for the C_8-methine proton of the major compound was at δ 4.14, while that of the minor compound was at δ 4.26. This suggests (but does not prove) that the major product, **26,** is the α alcohol and that the minor product is the β isomer. These assignments proved correct based on subsequent chemical transformations carried out on compound **26**.

The 3:2 ratio of α and β alcohols was somewhat disappointing but redeemable, since the undesired β alcohol could be cleanly recycled into enone **25** by oxidation with pyridinium chlorochromate.[21] Hence, an overall yield of 95% could be obtained for the α-allylic alcohol **26** from the enone **25**.

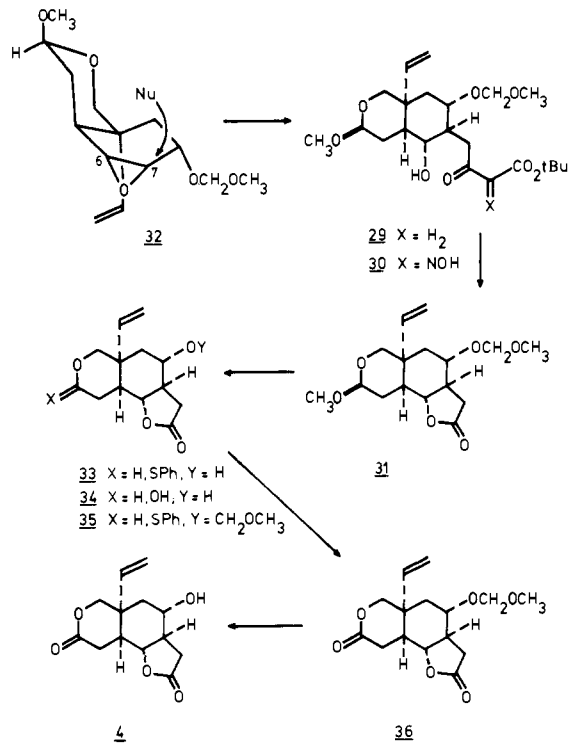
Stereoselective epoxidation of **26** was carried out as described by Henbest.[7] Thus, *m*-chloroperoxybenzoic acid in ethyl acetate at −20 °C for 20 h[22] gave the *cis*-epoxy alcohol **27**. The lengthy reaction times utilized result from the lower temperature needed to minimize subsequent epoxidation of the angular vinyl group.[23] The problem of protecting the alcohol portion of the epoxy alcohol remains before attempting nucleophilic ring opening of the epoxide. Our selection of the methoxy methyloxy protecting group was based upon its ease of formation, its ease of removal, its relatively small steric bulk, and its simple proton pattern. Reaction of the epoxy alcohol **27** with sodium hydride and chloromethyl methyl ether in THF at 22 °C afforded the corresponding epoxy ether **28** in essentially quantitative yield.

Molecular models suggest that **28** would prefer not to exist in a conformation that positions the angular vinyl group axial to ring B, since this would result in a strong interaction between the vinyl group and the α-epoxy residue. The corresponding ring flip conformation of **28** in which the vinyl group is axial to ring A shows good correlation between calculated and observed couplings. This conformation of **28** shows equal $C_{4\alpha}\text{-}C_{5\alpha}$ and $C_{4\beta}\text{-}C_{5\alpha}$ dihedral angles of 60° predicting equivalent couplings of between 1 and 7 Hz (usually 2-3 Hz) compatible with the observed 4- and 4-Hz values. A modified Karplus equation applicable to epoxides[24] was used for the angular C_5 hydrogen and C_6 epoxy hydrogen of **28** which have a measured dihedral angle of 110°. A coupling constant of zero was calculated in this instance and was found in agreement with the observed value (ca. 0). The C_7 epoxy hydrogen coupled with the C_8 methine of the alcohol provides a calculated value of 2.5 Hz (45°) close to the observed coupling of 2.0 Hz.

Placing ring A of **28** in a chair conformation results in significant interaction between the methoxy group which is now axial to ring A and the epoxide hydrogen at C_6. However, a boat conformation for ring A alleviates this problem by placing the methoxy group pseudoequatorial. By using the Booth heteroatom effect for vicinal coupling constants,[17] values calculated for the acetal methine proton of **28** gave good agreement with the observed values: 8, 4, and 6, 5 Hz, respectively.

(iv) Preparation of Bisnorvernolepin 4. With the obtention of compound **28,** we were ready to examine the epoxide ring-opening reaction. Our spirits were considerably dampened when at this point Danishefsky reported that attempted ring opening of a similar epoxide with dilithioacetate had been unsuccessful even under drastic reaction conditions.[3] We nevertheless felt that success might be achieved with a more energetic nucleophile in combination with the epoxide **28**. Experience gained in these laboratories over the past few years suggested to us that *tert*-butyl dilithioacetoacetate might possess sufficient reactivity to bring about this transformation.[25] The viability of epoxide ring opening with this nucleophile was first examined by using simple model systems.[26] We then applied this methodology to the epoxide **28**. Thus, treatment of **28** with an excess of *tert*-butyl dilithioacetoacetate in glyme at 40 °C for 11.5 h afforded the corresponding β-keto ester **29**. Addition of potassium *tert*-butoxide in *tert*-butyl alcohol to a solution of **29**, isoamyl nitrite, and THF gave the oxime **30** which, without isolation, was treated with acetic anhydride and acetic acid to afford the lactone **31** in 65% overall yield from the alcohol **27**.[27]

The above results also confirm that, even though the epoxide conformation **28** is energetically preferred, ring opening at C_7 occurred via the ring flip form **32**. This follows from the fact that only the desired ring-opened product was obtained from the epoxide. We conclude from this result that nucleophilic attack at C_6 in conformation **28** must have been energetically



more costly than the energy required to ring flip the system, which, in turn, suffered displacement at C_7. Clearly, the acetal residue is far enough removed from the site of reaction in the epoxide so that steric effects associated with this moiety would be minimal.

The concluding and most tedious phase of our preparation of bisnorvernolepin was the transformation of the ring A acetal into its corresponding lactone. We had anticipated that conversion of the acetal into the lactone along with removal of the methoxy methyloxy protecting group could be accomplished to give **4** in one step; however, a lengthy investigation proved this plan to be experimentally untenable. Eventually, the following two schemes were developed. Treatment of **31** with thiophenol and boron trifluoride etherate in methylene chloride gave the corresponding thioacetal, **33,** as a mixture of epimers about the acetal carbon. Two-step oxidation of this material first with ceric ammonium nitrate (CAN) followed by treatment of the intermediate hemiacetal, **34,** with Jones reagent gave **4** in 35% purified yield.[28] The latter substance was found identical in all respects with racemic **4** kindly given to us by Professor Danishefsky,[29] Alternatively, the thioacetal was treated with bromomethyl methyl ether to give the ring B protected alcohol, **35,** which was oxidized, first with CAN and then with pyridinium chlorochromate affording the methoxy methyloxy analogue of **4,** compound **36,** in 83% overall yield from **31**. Compound **36** is an excellent potential intermediate for conversion into vernolepin since Grieco has used the corresponding THP derivative of **4** for the bismethylenation sequence that leads to the natural product. Finally, hydrolysis of the methoxy methyloxy protecting group of **36** was achieved in 60% yield using HCl gas in acetonitrile.[30] The latter reaction completed our work on this problem, an effort which required 19 steps starting from ethyl crotonate and which proceeds in 16% overall yield.

Experimental Section[31]

Alkylation of Ethyl Crotonate with Propargyl Bromide; Ester 9. To a solution of diisopropylamine (11.2 mL, 80 mM) in THF (160 mL, 0.5 M) at 0 °C was added *n*-butyllithium (80 mM, 36.4 mL, 2.2 M in hexane) over a period of 10 min. The resulting pale yellow solution was stirred for 15 min at 0 °C, cooled to −78 °C, and HMPA (16.8 mL, 96.6 mM) then was added. The HMPA was not soluble initially at −78 °C and formed a suspension which became homogenous and yellow green in color after 40 min. Ethyl crotonate (9.93 mL, 80 mM) was added over a period of 5 min and the resulting solution stirred for 10 min at which time propargyl bromide (9.40 mL, 125 mM) was added as quickly as possible. The yellow green color dissipated almost immediately; however, the reaction was allowed to continue for 30 min at −78 °C, whereupon it was quenched at −78 °C with saturated NH_4Cl (100 mL) and H_2O (400 mL). The solution was diluted by one-half of its original volume with hexanes (3 × 150 mL). The combined organic solutions were filtered through anhydrous $MgSO_4$ and concentrated by heating in a flask fitted with a 45-cm Vigreaux column. Subsequent distillation of the residue afforded 10.35 g (85%) of ester **9**, bp 72–73 °C (10 mm), as a colorless liquid: R_f (100° 6′) 0.8 min; R_f (silica, 2% $CH_3OH/CHCl_3$) 0.77, (1:1 ether/hexanes) 0.72; ν_{max} 3310 (m, C≡C—H), 1730 (s, C=O), 1640 (w, C=O); δ 1.28 (t, J = 7, 3 H), 2.02 (t, J = 2.5, 1 H), 2.54 (ABX_2, J_{AB} = 16.5, $\Delta\nu_{AB}$ 14.6, 2 H, was further split by two protons $J_{AX_1} = J_{BX_1} = 7$, $J_{AX_2} = J_{BX_2} = 2.5$), 3.25 (d of t, J_d = 8, J_t = 7, 1 H), 4.21 (q, J = 7, 2 H), 5.24 (d of d, J_{d_1} = 10, J_{d_2} = 1, 1 H), 5.26 (d of d, J_{d_1} = 18.5, J_{d_2} = 1, 1 H), 5.95 (d of d, J_{d_1} = 18.5, J_{d_2} = 10, 1 H) ppm; *m/e* 152 (0.5), 124 (6), 113 (28), 107 (11), 93 (12), 85 (14), 80 (20), 79 (100), 78 (25), 77 (83).

Alkylation of Ester 9 with Ethyl Bromoacetate; Preparation of Diester 10. To a solution of diisopropylamine (4.2 mL, 30 mM) in THF (60 mL, 0.5 M) at 0 °C was added *n*-butyllithium (30 mM, 12 mL, 2.5 M in hexane) over 5 min. The resulting pale yellow solution was stirred 15 min at 0 °C, cooled to −78 °C, whereupon HMPA (10.8 mL, 62 mM) was added. The HMPA was not initially soluble at −78 °C and formed a suspension which became homogeneous and yellow green in color after 30 min. Ester **9** (4.53 g, 30 mM) was added and the resulting solution stirred at 15 min at −78 °C at which time ethyl bromoacetate (3.66 mL, 33 mM) was rapidly added. The reaction turned yellow within a few minutes, but was maintained at −78 °C for 1.75 h before quenching with saturated NH_4Cl (50 mL) and H_2O (100 mL). The resulting biphase mixture was extracted with hexanes (200 and 100 mL). The combined organic extracts were washed with 10% $NaHSO_3$ (25 mL) and 3% $NaHCO_3$ (25 mL). Filtration through anhydrous $MgSO_4$ and evaporation of the volatiles at reduced pressure afforded 7.08 g (102%) of a yellow liquid. Distillation gave the diester **10** as a colorless liquid: 5.17 g (73%); bp 83–85 °C (0.27 mm). The crude sample (90–95% by GC) was normally used for the subsequent reaction without purification by distillation. For example, this procedure was repeated on an 80-mm scale and the sample so obtained (20.8 g, 109%) was used directly for the next reaction. Physical data for diester **10** are: R_f (200°, 6′) 2 min; R_f (silica-2% $CH_3OH/CHCl_3$) 0.56, (silica-1:1 ether/hexanes) 0.57; ν_{max} 3310 (m, C≡C—H), 1730 (s, C=O), and 1640 (w, C=C); δ 1.24 (t, J = 7, 6 H), 2.01 (t, J = 2.5, 1 H), 2.85 (ABX, J_{AB} = 18, $\Delta\nu_{AB}$ = 18.5, $J_{AX} = J_{BX}$ = 2.5, 2 H), 2.94 (s, 2 H), 4.12 (q, J = 7, 2 H), 4.18 (q, J = 7, 2 H), 5.21 (d, J = 18, 1 H), 5.23 (d, J = 11, 1 H), 6.00 (d of d, J_{d_1} = 8, J_{d_2} = 11, 1 H); *m/e* 238 (0.9), 199 (10), 193 (17), 164 (16), 137 (10), 125 (13), 91 (100).

Hydration of Diester 10; Preparation of Keto Diester 11. To a suspension of distilled diester **10** (3.405 g, 14.3 mM) and mercuric sulfate (92.4 mg, 0.022 equiv) in ethanol/water (10.2 mL/4.35 mL, 1 M) at 0 °C was added sulfuric acid (1 mL) over 30 s. The reaction was then warmed to room temperature and became a cloudy solution after 20 min. After stirring for an additional 40 min, the reaction was diluted to twice its original volume with water and extracted with methylene chloride (4 × 25 mL). The combined organic extracts were filtered through $MgSO_4$ and evaporated to give 3.557 g (97%) of keto diester **11** as a colorless liquid (bp 58–89 °C at 1 × 10^{-6} mm). Hydration of crude diester **10** (20.8 g, 80 mM) gave the keto diester **11** (20.9 g, 102%) which was used without purification for the next reaction. Physical data for the keto diester **11** are as follows: R_f (200°, 6′) 1.53 min; R_f (silica-2% $CH_3OH/CHCl_3$) 0.32, (silica-1:1 ether/hexanes) 0.29; ν_{max} 1730 (s, b, C=O) and 1640 (w, C=C); δ 1.24 (t, J = 7, 6 H), 2.16 (s, 3 H), 3.00 (s, 2 H), 3.21 (ABq, J_{AB} = 17, $\Delta\nu_{AB}$ = 10.5, 2 H), 4.09 (q, J = 7, 2 H), 4.17 (q, J = 7, 2 H), 5.13 (d, J = 18, 1 H), 5.16 (d, J = 11, 1 H), 6.01 (d of d, J_{d_1} = 18, J_{d_2} = 11, 1 H), the inner two lines of the 4-line pattern are further split into doublets by 1.5 Hz; *m/e* 256 (3), 213 (62), 201 (27), 185 (71), 170 (38), 168 (41), 141 (100), 139 (39), 138 (62), 137 (98), 113 (55), 110 (48), 95 (72).

Cyclization of the Keto Diester 11; Preparation of Ester 12. To neat keto diester **11** (1.791 g, 7.0 mM) at 0 °C was added potassium *tert*-

butoxide in *tert*-butyl alcohol (1 M, 7.7 mL, 7.7 mM) over a 2-min period. The reaction turned bright yellow then orange with a small amount of solid forming around the edges of the reaction vessel. After 5 min at 0 °C most of the reaction had solidified; whereupon, it was warmed to room temperature and stirred for 10 min by which time the reaction had become clear orange. Ice and water (20 mL) were added along with sufficient 10% HCl to bring the pH of the reaction mixture to 8. The solution was extracted with ether (20 mL) and the ether washed with 2% KOH (2 × 5 mL). The combined aqueous extracts were again extracted with ether (30 mL) and the ether extract washed with 2% KOH (2 × 5 mL). The combined aqueous extracts were then acidified with 10% HCl (10 mL) and extracted with $CHCl_3$ (4 × 30 mL) and then extracted with ethyl acetate (2 × 25 mL). The ethereal, chloroform, and ethyl acetate extracts were dried separately by filtration through $MgSO_4$. Evaporation of the ether extract gave 42 mg (2.9%) of a yellow oil which contained ca. 40% of the desired ketone **12** by ^1H NMR analysis. The chloroform solution on evaporation, followed by reevaporation from benzene (100 mL), gave 1.348 g of a yellow viscous oil which slowly solidified to afford 1.275 g (87%) of the diketone **12** as a waxy solid, essentially pure by ^1H NMR. The ethyl acetate extracts on evaporation gave 73 mg (5.7%) of the diketo acid.

Cyclization of the crude keto diester **11** (20.9 g, 80 mm) afforded 14.1 g (84%) of the diketone **12**; R_t (170°, 2′) 1.65 min; R_f (silica-5% $CH_3OH/CHCl_3$) 0.14, (silica-ethyl acetate) 0.28; ν_{max} 3600–2400 (b, OH), 1730 (s, C=O), and 1610 (s, b, enol); δ 1.23 (t, J = 7, 3 H), 2.80 (AB_q, J_{AB} = 17, $\Delta\nu_{AB}$ = 41.7, 4 H), 3.37 (b, s, 0.22 H), 4.16 (q, J = 7, 2 H), 5.22 (d, J = 18, 1 H), 5.25 (d, J = 11, 1 H), 5.51 (s, 0.87 H), 5.93 (d of d, J_{d_1} = 18, J_{d_2} = 11, 1 H), 10.51 (sharp s, 0.92 H); *m/e* 210 (0.8), 182 (4), 164 (4), 138 (5), 137 (7), 123 (3), 110 (6), 109 (3), 96 (3), 95 (17), 81 (3), 67 (24), 43 (100).

Preparation of the Vinylogous Ester 13. A mixture of the diketone **12** (10.01 g, 47.7 mM), *p*-TSA (0.2 g), and methanol (200 mL) was heated at 60 °C for 3 h. Trimethyl orthoformate (5.2 mL, 47.5 mM) was added and heating at 60 °C was continued for an additional 30 min. The methanol was removed under vacuum and the residue taken up in ether (100 mL) and washed with 3% $NaHCO_3$ (20 mL). The aqueous phase was then extracted with ether (100 mL and 50 mL), and the ether extracts were then combined. Sodium sulfate and charcoal were added to the extracts, and the resulting suspension was warmed on a steam bath for a few minutes. Filtration of this mixture through $MgSO_4$ followed by evaporation afforded essentially pure vinylogous ester **13**, 10.05 g (94%), as a yellow oil which was used without purification for the next reaction. R_t (170°, 2′) 2.2 min; R_f (silica-3% $CH_3OH/CHCl_3$) 0.57, (silica-ether) 0.53; ν_{max} 1730 (s, C=O), 1650 (s, C=O), and 1610 (s, C=C); δ 1.22 (t, J = 7, 3 H), 2.70 (ABX, J_{AB} = 17, $\Delta\nu_{AB}$ = 38.4, 2 H split further by J_{AX} = 1.5), 2.80 (ABX, J_{AB} = 17, $\Delta\nu_{AB}$ = 39.5, 2 H split further by J_{AX} = 1.5), 3.72 (s, 3 H), 4.13 (q, J = 7, 2 H), 5.16 (d, J = 18, 1 H), 5.19 (d, J = 10.5, 1 H), 5.33 (d, J = 1.5, 1 H), 5.87 (d of d, J_{d_1} = 18, J_{d_2} = 11, 1 H); *m/e* 224 (4), 196 (3), 179 (8), 150 (100), 137 (4), 123 (12), 109 (14), 98 (16), 91 (13), 69 (20), 68 (22).

Preparation of the Vinylogous Ester Alcohol 5. To a solution of diisopropylamine (6.7 mL, 47.8 mM) in THF (43 mL) at 0 °C was added *n*-butyllithium (47.8 mM, 19.9 mL, 2.4 M in hexane) over a period of ca. 8 min. The resulting pale yellow solution was stirred for 15 min at 0 °C and then cooled to −78 °C at which time the vinylogous ester **13** (9.73 g, 43.4 mM) in THF (20 mL) was added to the dark red reaction and the mixture then warmed to 0 °C and stirred 10 min during which time it lightened to a bright orange-red color. Solid LAH (1.65 g, 43.5 mM) was carefully added to the reaction over several minutes and the resulting suspension stirred for 10 min at 0 °C (green-brown suspension). The reaction was cooled to −78 °C and then added to a vigorously stirred solution of saturated NH_4Cl (185 mL) at 0 °C. Dilute HCl (125 mL, 10%) was added to the mixture and the solution extracted with $CHCl_3$ (2 × 200 mL and 2 × 300 mL). The extracts were predried over anhydrous Na_2SO_4 and then filtered through $MgSO_4$. Concentration of the chloroform solution gave a viscous yellow oil (9.15 g, theoretical 7.91 g) which was used without purification: R_t (170°, 2′) 1.9 min; R_f (silica-3% $CH_3OH/CHCl_3$) 0.28, (silica-ether) 0.19; ν_{max} 3700–3200 (w, b, OH), 3620 (sharp, w, OH), 1650 (s, C=O), and 1610 (s, C=C); δ 2.45 (ABq, J_{AB} = 17, $\Delta\nu_{AB}$ = 12.3, 2 H), 2.56 (ABX, J_{AB} = 18, $\Delta\nu_{AB}$ = 35.7, 2 H, further split by J_{AX} = 1.5), 2.92 (t, J = 4, 1 H), 3.48 (d, J = 4, 2 H), 3.72 (s, 3 H), 5.10 (d of d, J_{d_1} = 18, J_{d_2} = 1.5, 1 H), 5.19 (d of d, J_{d_1} = 11, J_{d_2} = 1.5, 1 H), 5.36 (d, J = 1.5, 1 H), 5.74 (d of d, J_{d_1} = 18, J_{d_2} = 11, 1 H, two extra small peaks present which when combined with the inner two lines of the four-line pattern look like an ABq with J_{AB} = 5 and $\Delta\nu_{AB}$ = 10.9); *m/e* 182 (14), 164 (15), 154 (17), 152 (38), 151 (70), 123 (44), 109 (88), 99 (34), 98 (50), 91 (44), 79 (20), 77 (22), 69 (70), and 68 (100).

Preparation of Bromo Acetal 15. To a solution of **5** (2.71 g, theory 2.34 g, 12.87 mM), *N,N*-dimethylaniline (2.63 mL, 20.8 mM), and methylene chloride (23.5 mL) at room temperature was added 1,2-dibromo-1-methoxyethane (**14**) (4.1 g, 18.8 mM) over a 2-min period. The reaction slowly turned a clear green from yellow-orange in color. After stirring 30 min, *N,N*-dimethylaniline (0.4 mL, 3.2 mM) and dibromide **14** (0.59 g, 2.7 mM) were added, followed by 15 min of additional stirring. Ether (100 mL) was then added and the mixture washed with 2% H_2SO_4 (2 × 25 mL), 15% $NaHSO_3$ (10 mL), and 3% $NaHCO_3$ (10 mL). The ether solution was filtered through $MgSO_4$ and evaporated to an oil which was chromatographed on 62 g of silica eluted with 1:2 ether/hexanes, 1:1 ether/hexanes, and ether, successively. Evaporation of these eluents gave 3.64 g of bromide **15** as an oil (89%): R_t (200°, 2′, 32° 1′ to 250°, 2′) 2.8 min; R_f (silica-3% $CH_3OH/CHCl_3$) 0.56, (silica-ether) 0.52; ν_{max} 1650 (s, C=O) and 1610 (s, C=C); δ 2.50 (ABX, J_{AB} = 16, $\Delta\nu_{AB}$ = 23, 2 H, split further by J_{AX} = 1.5) 2.61 (ABq, J_{AB} = 17.5, $\Delta\nu_{AB}$ = 44.7, 2 H), 3.37 (d, J = 6, 2 H), 3.41 (s, 3 H), 3.42 (ABq, J_{AB} = 9, $\Delta\nu_{AB}$ = 15.6, 2 H), 3.71 (s, 3 H), 4.63 (t, J = 6, 1 H), 5.12 (d, J = 8, 1 H), 5.16 (d, J = 10, 1 H), 5.37 (d, J = 1.5, 1 H), and 5.79 (d of d, J_{d_1} = 18, J_{d_2} = 10, 1 H, center two lines of the four-line pattern split further by J = 2); *m/e* 320 (0.5), 318 (0.5), 289 (3), 287 (3), 237 (3), 235 (3), 207 (7), 181 (19), 165 (41), 151 (100), 139 (61), 137 (64), 123 (21).

Preparation of Iodide 16. A suspension of NaI (7.74 g, 51.6 mM), bromide **15** (3.63 g, 11.39 mM) and acetone (13 mL) was refluxed with stirring and the exclusion of light for 59 h. The solvent was removed under vacuum and then ether (25 mL) was added, and the volatiles were again removed at the water pump. Ether (100 mL) and water (10 mL) were added to the orange-green paste; the organic phase was then separated and successively washed with 10% $NaHSO_3$ (10 mL) and then 3% $NaHCO_3$ (10 mL). The organic phase was dried over Na_2SO_4, warmed on the steam bath over charcoal, filtered through $MgSO_4$, and then concentrated to dryness. Chromatography of the residue using 60 g of silica and elution with 1:1 ether/hexanes followed by ether afforded 3.84 g (92%) of iodide **16** as an oil. The overall yield of this iodide from the vinylogous ester **13** was 77%: R_t (200°, 2′, 32°, 1′ to 250°, 2′) 3.2 min; R_f (silica-3% $CH_3OH/CHCl_3$) 0.56, (silica-ether) 0.52; ν_{max} 1650 (s, C=O), and 1610 (s, C=C); δ 2.50 (ABX, J_{AB} = 16, $\Delta\nu_{AB}$ = 23.0, 2 H, split further by J_{AX} = 2), 2.61 (ABq, J_{AB} = 17.5, $\Delta\nu_{AB}$ = 45.8, 2 H), 3.22 (d, J = 6, 2 H), 3.37 (s, 3 H), 3.42 (ABq, J_{AB} = 9, $\Delta\nu_{AB}$ = 15.6, 2 H), 3.71 (s, 3 H), 4.54 (t, J = 6, 1 H), 5.10 (d, J = 18, 1 H), 5.14 (d, J = 10, 1 H), 5.35 (d, J = 2, 1 H), 5.77 (d of d, J_{d_1} = 18, J_{d_2} = 10, 1 H center two of four-line pattern split further by J = 2 Hz); *m/e* 366 (2), 336 (10), 308 (9), 207 (10), 185 (100), 181 (28), 165 (31), 152 (92), 151 (72), 147 (10), 123 (19), 109 (18), 91 (16).

Cyclization of the Iodide 16; Preparation of Bicyclic Acetal 20. To a solution of hexamethyldisilizane (2.67 mL, 12 mM), in THF (12 mL) at 0 °C was added *n*-butyllithium (12 mM, 5 mL of 2.4 M in hexane) over several minutes. The pale yellow solution was stirred at 0 °C for 15 min, whereupon an aliquot (7.8 mL) of this solution was added (over 5 min) to a solution of the iodide **16** (1.64 g, 4.48 mM) in THF (30 mL) at −78 °C. The resulting yellow solution was stirred 40 min at −78 °C and then warmed to −40 °C and stirred at that temperature for 3 h. The reaction was quenched at −40 °C with saturated NH_4Cl (5 mL), diluted with H_2O (20 mL), and extracted with ether (3 × 50 mL). The combined organic extracts were predried with Na_2SO_4, then filtered through $MgSO_4$, and concentrated under vacuum. The oil so obtained (1.56 g) was determined by ^1H NMR analysis to be a 1:1 mixture of the bicyclic compound **20** and the iodide **22**. This mixture was taken up in dry Me_2SO (4.5 mL), and activated zinc (1.20 g, 18.4 mM) and copper (57.4 mg, 0.9 mM) were added followed by methanol (0.75 mL). The resulting mixture was then stirred vigorously for 1 h, whereupon water (9 mL) and sulfuric acid (9 mL of 10%) were added and the resulting suspension stirred 10 min then filtered through cotton. The filtrate was extracted with $CHCl_3$ (4 × 25 mL) and the combined organic extracts then washed with 3% $NaHCO_3$ (5 mL), filtered through $MgSO_4$, and evaporated to dryness. The oil thus obtained (now a mixture of bicyclic compound **20** and the alcohol **5**) was chromatographed using 20 g of silica. Elution with 1:1 ether/hexanes afforded 488 mg (46%) of **20** (mp 63–66 °C)

and elution with ether gave 365 mg (45%) of alcohol **5**, The yield of **20** based on recovered and reused alcohol **5** was 83%. The bicyclic compound **20** was normally used without further purification; however, recrystallization of 91.4 mg (ether/hexanes) afforded 85.4 mg of **20** (mp 65.5-66.5 °C): R_f (200°, 2′) 1.6 min; R_f (silica-3% $CH_3OH/CHCl_3$) 0.49, (silica-ether) 0.52; ν_{max} 1640 (s, C=O) and 1610 (s, C=C); δ 1.77 (ABX_2, J_{AB} = 14, $\Delta\nu_{AB}$ = 12, 8, 2 H, further split by J_{BX_1} = 12 and J_{BX_2} = 3 and by J_{AX_1} = 6 and J_{AX_2} = 2), [this ABX_2 system has the appearance of 2 AB quartets with δ 1.73 (ABX, J_{AB} = 14, $\Delta\nu_{AB}$ = 17.6 split by J_{BX} = 3 and J_{AX} = 2) and δ 1.82 (ABX, J_{AB} = 14, $\Delta\nu_{AB}$ = 7.7 split by J_{BX} = 3 and J_{AX} = 2)], 2.61 (ABX, J_{AB} = 18.5, $\Delta\nu_{AB}$ = 96.2, 2 H, further split by J_{AX} = 2), 2.73 (d of d, J_{d_1} = 12, J_{d_2} = 6, 1 H), 3.33 (s, 3 H), 3.34 (ABq, J_{AB} = 11.5, $\Delta\nu_{AB}$ = 42.5, 2 H), 3.67 (s, 3 H), 4.68 (d of d, J_{d_1} = 3, J_{d_2} = 2, 1 H), 5.03 (d of d, J_{d_1} = 18, J_{d_2} = 1.5, 1 H), 5.07 (d of d, J_{d_1} = 11, J_{d_2} = 1.5, 1 H), 5.23 (d, J = 2, 1 H), 5.58 (d of d, J_{d_1} = 18, J_{d_2} = 11, 1 H, the inner two lines of the four-line pattern are split further by J = 2); *m/e* 238 (39), 208 (80), 207 (55), 197 (21), 175 (26), 165 (71), 151 (90), 150 (43), 137 (24), 122 (100), 107 (30), 98 (52), 69 (53), 68 (52), 58 (52). The zinc used in this experiment was activated in the following manner: Zinc (60-200) mesh was stirred for ca. 2 min with 5% HCl, then washed successively with distilled H_2O, methanol, ether, and dried under vacuum.

Preparation of Enone 25. To a suspension of LAH (69.6 mg, 1.83 mM) in ether (7.2 mL, 0.25 M) at 0 °C was added neat, compound **20** (429 mg, 1.8 mM) over a 2-min period. After stirring the mixture for 30 min at 0 °C, the reaction was diluted to ca. 20 mL with ether and the excess LAH destroyed at 0 °C by drop wise addition of saturated Na_2SO_4. The resulting suspension was warmed to room temperature and addition of saturated Na_2SO_4 continued (30 min) until a pure white suspension formed. The suspension was then filtered through $MgSO_4$ and the filter cake washed with 2 × 15 mL portions of ether. The filtrate was evaporated under vacuum leaving a colorless oil [R_f (silica-3% $CH_3OH/CHCl_3$) 0.29]. The flask containing this oil was flushed with nitrogen, whereupon THF (10.5 mL) and iodine (23.3 mg, 0.09 mM, ca. 5% by weight) were added. The resulting orange solution was stirred for 20 min at room temperature, at which time 10% $NaHSO_3$ (2 mL) was added followed by H_2O (8 mL). Extraction of this mixture with ether (3 × 15 mL) followed by filtration through $MgSO_4$ and evaporation of the organic solvents afforded 387 mg of a colorless liquid. Chromatography of this substance on silica (15.5 g) using 1:2 ether/hexanes afforded 362 mg (97%) of enone **25** as a white solid (mp 49-52 °C). The material, thus obtained, was used without further purification for subsequent reactions. Crystallization of 75 mg of the enone **25** from ether/hexanes gave 59 mg (mp 51-52.5 °C) which has the following physical properties: R_f (180°, 2′) 1.0 min; R_f (silica-3% $CH_3OH/CHCl_3$) 0.7, (silica-2:1 ether/hexanes) 0.48; ν_{max} 1675 (s, C=O), 1640 (w, C=C), and 1620 (w, C=C); δ 1.79 (ABX_2, J_{AB} = 14, $\Delta\nu_{AB}$ = 33.2, 2 H, the AB system was further split by J_{BX_1} = 12, J_{BX_2} = 3.5, J_{AX_1} = 5, and J_{AX_2} = 1.5), 2.75 (d of d, J_{d_1} = 12, J_{d_2} = 6, 1 H), 2.76 (ABq, J_{AB} = 17, $\Delta\nu_{AB}$ = 60.1, 2 H), 3.38 (ABq, J_{AB} = 12, $\Delta\nu_{AB}$ = 58.3, 2 H), 3.42 (s, 3 H), 4.77 (d of d, J_{d_1} = 3.5, J_{d_2} = 1.5, 1 H), 5.08 (d of d, J_{d_1} = 18, J_{d_2} = 1.5, 1 H), 5.15 (d of d, J_{d_1} = 10, J_{d_2} = 1.5, 1 H), 5.60 (d of d, J_{d_1} = 18, J_{d_2} = 10, 1 H, the inner two lines split further to look like an ABq at 5.60, J = 4, and $\Delta\nu$ = 9.2), 5.97 (d, J = 10, 1 H), 6.81 (d of d, J_{d_1} = 10, J_{d_2} = 6, 1 H); *m/e* 208 (14), 178 (14), 146 (22), 133 (5), 121 (10), 120 (88), 118 (9), 105 (9), 92 (100), and 91 (55).

Preparation of the Allylic Alcohol 26. To a solution of enone **25** (362 mg, 1.74 mM in 1:1 hexane/toluene 7 mL, 0.25 M) at 0 °C was added DIBAL-H (1.4 mL, 1.9 mM, 0.35 M in hexane) over a period of 3 min. The clear reaction mixture turned pale yellow during the addition of the hydride reagent and then turned colorless when 1.2 mL of the reagent had been added. After stirring 40 min, the excess DIBAL-H was quenched with a few drops of saturated NH_4Cl solution, and the solution diluted with 20 mL of ether. Solid NH_4Cl (100 mg) and Celite (3 g) were added and the slurry was stirred at room temperature for 30 min. The slurry was filtered through $MgSO_4$ and the cake washed three times with 20-mL portions of ether. Evaporation of the ether left an oil (374 mg) which was chromatographed on 18.7 g of silica. Elution with 1:1 ether/hexanes afforded 216 mg (59%) of the desired α alcohol **26** as a white solid (mp 55.5-56.5 °C) and elution with ether afforded 139 mg (38%) of the β alcohol (mp 59-61 °C, contaminated with a small amount of the α alcohol). Physical data for the α alcohol **26** are given as follows: R_f (180°, 2′) 1.0 min; R_f (silica-3% $CH_3OH/CHCl_3$) 0.53 (silica-2:1 ether/hexanes) 0.33; ν_{max} 3650-3250 (b, OH) and 3570 (sharp, m-w, OH), 1635 (w, C=C), and 1600 (w, C=C); δ 1.63 (ABX_2, J_{AB} = 14, $\Delta\nu_{AB}$ = 36.9, 2 H, quartet split by J_{BX_1} = 10, J_{BX_2} = 3.5, J_{AX_1} = 5, and J_{AX_2} = 3.5), 2.01 (ABX, J_{AB} = 14.5, $\Delta\nu_{AB}$ = 60.3, 2 H, split further by J_{AX} = 6 and J_{BX} = 4), 2.21 (d, J = 7, 1 H), 2.54 (m, J_{d_1} = 10, J_{d_2} = 5, J_{d_3} = 3, 1 H), 3.35 (s, 3 H), 3.42 (ABq, J_{AB} = 11.5, $\Delta\nu_{AB}$ = 26.6, 2 H), 4.14 (m, J_{d_1} = 6, J_{d_2} = 4, J_{d_3} = 7, 1 H), 4.53 (t, J_{d_1} = J_{d_2} = 3.5, 1 H), 5.12 (d of d, J_{d_1} = 18, J_{d_2} = 1.5, 1 H), 5.15 (d of d, J_{d_1} = 11, J_{d_2} = 1.5, 1 H), 5.77 (d, J = 3, 2 H), 5.89 (d of d, J_{d_1} = 18, J_{d_2} = 11, 1 H); *m/e* 210 (0.1), 192 (0.5), 179 (7), 178 (4), 161 (2), 148 (7), 130 (28), 122 (100), 121 (30), 107 (42), 104 (28), 91 (33), 79 (32). Physical data for the β alcohol are given as follows: R_f (180°, 2′) 1.0 min; R_f (silica-3% $CH_3OH/CHCl_3$) 0.37, (silica-2:1 ether/hexanes) 0.23; ν_{max} 3650-3250 (b, OH), 3590 (sharp, m-w, OH), 1635 (w, C=C), 1600 (w, C=C); δ 1.70 (ABX_2, J_{AB} = 14, $\Delta\nu_{AB}$ = 23.7, 2 H, split further by J_{BX_1} = 12, J_{BX_2} = 4, J_{AX_1} = 5, and J_{AX_2} = 2), 1.91 (ABX, J_{AB} = 13, $\Delta\nu_{AB}$ = 16.5, 2 H, split by J_{BX} = 9, and J_{AX} = 8), 2.35 (broad, s, 1 H, OH), 2.40 (m, J_{d_1} = 12, J_{d_2} = J_{d_3} = 5, OH), 3.34 (s, 3 H), 3.37 (ABq, J_{AB} = 12, $\Delta\nu_{AB}$ = 37.1, 2 H), 4.26 (d of d, J_{d_1} = 9, J_{d_2} = 8, 1 H), 4.67 (d of d, J_{d_1} = 4, J_{d_2} = 2, 1 H), 5.09 (d of d, J_{d_1} = 18, J_{d_2} = 1.5, 1 H), 5.10 (d of d, J_{d_1} = 11, J_{d_2} = 1.5, 1 H), 5.66 (d of d, J_{d_1} = 18, J_{d_2} = 11, 1 H), 5.67 (m, J_d = 5, 2 H); *m/e* 210 (0.5), 192 (1), 179 (4), 178 (8), 161 (10), 148 (13), 130 (8), 122 (100), 121 (21), 107 (42), 104 (13), 91 (22), 79 (24).

Oxidation of β Alcohol into Enone 25. Pyridinium chlorochromate (170 mg, 0.79 mM) was added to a solution of the β alcohol (109 mg, 0.52 mM) in CH_3Cl (2.1 mL). A black oily residue quickly deposited on the sides of the flask. The reaction was stirred for 1 h and an additional 17 mg of 0.08 mM pyridinium chlorochromate was added. After an additional hour of stirring, the reaction was diluted with ether (8 mL). The black residue was washed twice more with ether (10 mL) and the combined ethereal solution filtered through a short Florisil pad followed by filtration through $MgSO_4$. Evaporation of the solvent gave a solid (108 mg, 100%) identical with authentic enone **25**.

Preparation of the Epoxy Alcohol 27. To a solution of α alcohol **26** (315 mg, 1.5 mM) in ethyl acetate (4.65 mL) at −50 °C was added *m*-CPBA (85%, 1.223 g 6.0 mM), whereupon the white suspension was warmed to −20 °C and stirred at that temperature for 22 h. Sodium hydroxide (5% solution, 22 mL) was added and the mixture extracted with $CHCl_3$ (4 × 15 mL). Filtration through $MgSO_4$ and evaporation of the solvent left an oil (416 mg) which on chromatography (31 g silica, elution with 2:1 ether/hexanes followed by ether) afforded 300 mg of an oil which on trituration with 2:1 ether/hexanes afforded the epoxy alcohol **27** as a white solid (289 mg, 85%, mp 105-106 °C): R_f (180°, 2′) 1.6 min; R_f (silica-3% $CH_3OH/CHCl_3$) 0.40, (silica-ether) 0.35; ν_{max} 3650-3300 (b, OH), 3570 (w, sharp OH), and 1640 (w, C=C); δ 1.53-1.96 (m, J_{d_1} = J_{d_2} = J_{d_3} = 6, J_{d_4} = 4, 2 H), 1.72 (ABX, J_{AB} = 14, $\Delta\nu_{AB}$ = 21.9, 2 H, split further by J_{AX} = J_{BX} = 6), 2.43 (d of d, J_{d_1} = J_{d_2} = 6, 1 H), 2.65 (d, J = 9.5, 1 H), 3.39 (s, 3 H), 3.14-3.40 (m, contains one-half of ABq, J_{AB} = 12, J = 3, 3 H), 3.48 (one-half ABq, J_{AB} = 12, $\Delta\nu$ = ?, 1 H), 4.16 (m, J_{d_1} = 9.5, J_{d_2} = J_{d_3} = 6, J_{d_4} = 3, 1 H), 4.51 (d of d, J_{d_1} = 6, J_{d_2} = 4, 1 H), 5.06 (d of d, J_{d_1} = 11, J_{d_2} = 1.5, 1 H), 5.09 (d of d, J_{d_1} = 18, J_{d_2} = 1.5, 1H), 5.87 (d of d, J_{d_1} = 18, J_{d_2} = 11, 1 H); *m/e* 226 (0.5), 196 (6), 195 (5), 165 (4), 164 (9), 146 (20), 138 (24), 135 (21), 122 (25), 120 (32), 118 (26), 109 (44), 107 (23), 95 (39), 94 (100), 92 (70), 91 (65), 81 (33), 79 (41), 77 (23).

Preparation of the Methoxy Methyloxy Ether 28. Sodium hydride (50% oil dispersion, 120.3 mg, 2.51 mM) was washed under N_2 with three portions of dry hexanes and then dried by gentle warming under N_2. THF (2.7 mL) was added to the hydride, the suspension cooled to 0 °C, and the epoxy alcohol **27** (279 mg, 1.23 mM) added so as to avoid a vigorous reaction. After 5 min, the sides of the flask were rinsed down with THF (1 mL) and the grey suspension was warmed to room temperature for 5 min, whereupon chloromethyl methyl ether (188 μL, 2.48 mM) was added. The reaction slowly turned to an almost white suspension and after 5.5 h was quenched with 3% $NaHCO_3$ (5 mL). Extraction with CH_2Cl_2 (3 × 10 mL), filtration through $MgSO_4$, and evaporation of the volatiles under vacuum gave 347 mg (104%) of **28** as a colorless oil, homogeneous on TLC. NMR analysis of this material, which could be used without further purification, showed it to be **28** contaminated with a small amount of mineral oil and a residue from the chloromethyl methyl ether. Compound **28** could be obtained pure (oil) by chromatography (silica-1:1 ether/hexanes): R_f (silica-3% $CH_3OH/CHCl_3$) 0.60, (silica-ether) 0.68; ν_{max} 1640 (w, C=C), δ 1.62 (d, J = 8, 2 H), 1.83 (m, J_{d_1} = 6, J_{d_2} =

5, $J_{d_3} = J_{d_4} = 4$, 2 H), 2.22 (t, $J = 4$, 1 H), 3.13 (d, $J = 4$, 1 H), 3.43 (s, 7 H), 3.53 (ABq, $J_{AB} = 12$, $\Delta\nu_{AB} = 27.5$, 2 H), 4.14 (d of t, $J_t = 8$, $J_d = 2$, 1 H), 4.46 (d of d, $J_{d_1} = 6$, $J_{d_2} = 5$, 1 H), 4.76 (s, 2 H), 5.08 (d of d, $J_{d_1} = 11$, $J_{d_2} = 1.5$, 1 H), 5.09 (d of d, $J_{d_1} = 18$, $J_{d_2} = 1.5$, 1 H), 5.91 (d of d, $J_{d_1} = 18$, $J_{d_2} = 11$, 1 H); *m/e* 270 (0.1), 240 (2), 239 (1), 208 (2), 195 (3), 178 (14), 164 (3), 146 (12), 137 (11), 122 (9), 121 (10), 120 (15), 109 (8), 107 (6), 94 (12), 92 (14), 91 (14), 79 (12), 45 (100).

Preparation of Keto Ester 29. To a solution of diisopropylamine (25.5 mM, 2.58 mL) in dimethoxyethane (12 mL, 0.5 M) at 0 °C was added *n*-butyllithium (25.2 mM, 10.5 mL, 2.4 M in hexane) over a period of 5 min. The resulting pale yellow solution was stirred for 15 min at 0 °C, whereupon *tert*-butyl acetoacetate (1.93 mL, 11.6 mM) was added over a 5-min period. The resulting yellow solution was stirred for 30 min at 0 °C, by which time it had turned slightly cloudy. The solution was then warmed to room temperature and a solution of epoxide **28** (308 mg, 1.14 mM) in DME (2.50 mL) was added. The temperature of the reaction was then raised to 40 °C and stirring with heating continued for 11.5 h. The now bright red reaction mixture was cooled to 0 °C and then quenched with 10% HCl (16 mL) and water (5 mL). The aqueous phase was extracted with ether (3 × 50 mL) and the ethereal solution filtered through $MgSO_4$. Concentration of the solution under vacuum afforded a yellow liquid (1.618 g) which was chromatographed (75 g of silica elution was 2:1 ether/hexanes followed by ether) to remove the *tert*-butyl acetoacetate and most of its self-condensation products. The desired product (446 mg, 92% pure by NMR analysis) thus obtained was used in the subsequent transformation without further purification. Physical data for the keto ester **29** are reported on material 92% pure: R_f (3% $CH_3OH/CHCl_3$) 0.25; ν_{max} 3600–3250 (b, OH), 1720 (s, C=O), 1705 (s, C=O), and 1640 (w, C=C); δ 1.50 (s, 9 H), 1.1–2.5 (m, ca. 17.2 H), 2.5–3.1 (m, ca. 2.7 H), the region between 1.1 to 3.1 excluding the singlet at 1.5 should represent 10 H not the reported 10.9 H, 3.36 (s, 3 H), 3.47 (s, 3 H), 3.67 (broad singlet, 3.1–4.2, ca. 10.6 H, expected 11 H), 4.43–4.79 (m, 3 H), 5.22 (d, $J = 18$, 1 H), 5.28 (d, $J = 11$, 1 H), 6.01 (d of d, $J_{d_1} = 18$, $J_{d_2} = 11$); *m/e* 427 (0.2), 411 (0.6), 383 (0.8), 379 (1), 366 (1), 355 (0.9), 342 (2), 323 (3), 310 (11), 283 (7), 262 (9), 261 (7), 248 (15), 230 (21), 204 (10), 203 (9), 170 (16), 143 (17), 121 (14), 120 (14), 91 (13), 59 (66), 45 (100), parent not observed at *m/e* 428.

Preparation of Lactone 31. To a solution of keto ester **29** (446 mg, 1.04 mM) in THF (4.1 mL) at room temperature was added isoamyl nitrite (0.41 mL, 3.05 mM) followed by potassium *tert*-butoxide in *tert*-butyl alcohol (1.04 mM, 1.04 mL, of a 1 M solution). This mixture was stirred for 12 h at room temperature during which time it changed from yellow to orange to brown in color. Acetic anhydride (1.45 mL) was added, and the reaction heated at 60 °C for 9.5 h at which time acetic acid (0.5 mL) and acetic anhydride (0.4 mL) were added. After a total of 40 h of heating, the reaction was cooled, water (10 mL) added, and the mixture extracted with $CHCl_3$ (3 × 15 mL) and then dried through $MgSO_4$ and the solvent removed under vacuum to give 468 mg of an oil. This material was chromatographed on silica (47 g) and eluted with 1:1 ether/hexanes followed by ether affording 227 mg (64% overall yield from the epoxy alcohol **27**) of the lactone **31** (mp 150–155 °C) as a pale yellow solid. Although this material was used without purification for the next reaction, one recrystallization from $CHCl_3$–ether afforded material melting at 158–160 °C: R_f (silica 3% $CH_3OH/CHCl_3$) 0.31; ν_{max} 1780 (s, C=O) and 1640 (w, C=C); δ 1.60–2.30 (m, 4 H), 1.64 (ABX, $J_{AB} = 14$, $\Delta\nu_{AB} = 35.3$, 2 H, split further by $J_{BX} = 11$ and $J_{AX} = 4$), 2.61 (ABX, $J_{AB} = 16$, $\Delta\nu_{AB} = 28.9$, 2 H, split further by $J_{BX} = 12$ and $J_{AX} = 7$), 3.35 (s, 3 H), 3.48 (s, 3 H), 3.61 (d of d of d, $J_{d_1} = J_{d_2} = 11$, $J_{d_3} = 4$, 1 H), 3.71 (s, 2 H), 4.26 (d of d, $J_{d_1} = J_{d_2} = 11$, 1 H), 4.62 (ABq, $J_{AB} = 7$, $\Delta\nu_{AB} = 7.1$, 3 H), 5.22 (d, $J = 11$, 1 H), 5.27 (d, $J = 18$, 1 H), 6.00 (d of d, $J_{d_1} = 18$, $J_{d_2} = 11$, 1 H); *m/e* 312 (trace), 280 (4), 235 (10), 220 (6), 188 (13), 161 (4), 151 (4), 108 (8), 107 (7), 105 (8), 93 (5), 91 (7), 79 (9), 45 (100).

Preparation of Hemithioacetal 33. To a stirred mixture of lactone **31** (11.8 mg, 0.355 mM) and thiophenol (0.180 mL, 1.75 mM) in methylene chloride (3.5 mL) at room temperature was added boron trifluoride etherate (0.130 mL, 1.06 mM). After 1 h, the pale yellow solution was cooled to 0 °C for 5 min before extracting with $CHCl_3$ (4 × 10 mL). The combined extracts were filtered through $MgSO_4$, evaporated under vacuum, and the resulting oil chromatographed on silica (4.6 g). Elution with 1:1 ether/hexanes (to remove PhSH and $PhSCH_2SPh$) then ether afforded 121.3 mg (99%) of a lactone mixture epimeric at the thioacetal carbon atom. These two materials were easily separable (silica ether). The β thiophenyl isomer (mp 148–149.5 °C) exhibits the following physical data: R_f (silica-5% $CH_3OH/CHCl_3$) 0.42, (silica-ether) 0.35; ν_{max} 3650–3250 (w, b, OH), 3600 (w, sharp, OH), 1780 (s, C=O), 1640 (w, C=C), and 1585 (w, C=C); δ 1.63 (ABX, $J_{AB} = 14$, $\Delta\nu_{AB} = 28.8$, 2 H, further split by $J_{BX} = 10.5$, $J_{AX} = 5$), 1.75–2.80 (m, 5), 2.67 (ABX, $J_{AB} = 16$, $\Delta\nu_{AB} = 20.5$, 2 H, split further by $J_{BX} = 12$ and $J_{AX} = 7$) 3.80 (d of d of d, $J_{d_1} = J_{d_2} = 10.5$, $J_{d_3} = 5$, 1 H), 3.83 (ABq, $J_{AB} = 12$, $\Delta\nu_{AB} = 75.0$, 2 H), 4.78 (d of d, $J_{d_1} = J_{d_2} = 11$, 1 H), 5.22 (d, $J = 11$, 1 H), 5.27 (d, $J = 18$, 1 H), 5.56 (d, $J = 6$, 1 H), 5.91 (d of d, $J_{d_1} = 18$, $J_{d_2} = 11$, 1 H), 7.12–7.55 (m, 5 H); *m/e* 346 (2), 237 (95), 236 (15), 219 (25), 201 (15), 191 (20), 173 (35), 155 (20), 145 (24), 131 (45), 129 (26), 119 (18), 110 (100), 109 (60), 108 (45), 91 (40). The α-thiophenyl isomer (brittle foam) gave the following physical data: R_f (silica-5% $CH_3OH/CHCl_3$) 0.37, (silica-ether) 0.13; ν_{max} 3650–3250 (w, b, OH) 3600 (w, sharp, OH), 1780 (s, C=O), 1640 (w, C=C), and 1585 (w, C=C); δ 1.55 (ABX, $J_{AB} = 14$, $\Delta\nu_{AB} = 27.7$, 2 H, further split by $J_{BX} = 11$, $J_{AX} = 5$); 1.82–2.44 (m, 5 H), 2.54 (ABX, $J_{AB} = 16$, $\Delta\nu_{AB} = 28.9$, 2 H, further split by $J_{BX} = 12$ and $J_{AX} = 7$), 3.64 (d of d of d, $J_{d_1} = J_{d_2} = 11$, $J_{d_3} = 5$, 1 H), 3.69 (s, 2 H), 4.26 (d of d, $J_{d_1} = J_{d_2} = 11$, 1 H), 4.93 (m, $J_{d_1} = 9$, $J_{d_2} = 5$, 1 H), 5.18 (d, $J = 11$, 1 H), 5.23 (d, $J = 18$, 1 H), 5.89 (d of d, $J_{d_1} = 18$, $J_{d_2} = 11$, 1 H), 7.13–7.60 (m, 5 H); *m/e* 346 (trace), 344 (trace), 237 (9), 236 (14), 219 (3), 201 (2), 191 (2), 179 (3), 177 (5), 173 (4), 151 (5), 147 (5), 145 (4), 131 (6), 129 (5), 123 (5), 119 (4), 110 (100), 109 (34), 108 (50), 91 (16).

Preparation of Hemithioacetal 35. To a stirred solution consisting of **33** (both thioacetal isomers) (88 mg, 0.254 mM) in methylene chloride (3 mL) at room temperature was added *N,N*-dimethylaniline (100 μL, 0.789 mM) followed by bromomethyl methyl ether (60 μL, 0.735 mM) added over a period of 3 min. After an additional 20 min of stirring, *N,N*-dimethylaniline (50 μL, 0.394 mM) and bromomethyl methyl ether (30 μL, 0.368 mM) were added and the resulting green solution stirred for 25 min. Ether (30 mL) was added and the resulting solution washed with 3% H_2SO_4 (3 × 3 mL), 3% $NaHCO_3$ (3 mL), filtered through $MgSO_4$, and evaporated to dryness under vacuum to yield **35** as a mixture of thioacetal epimers (95 mg, 95.8%, oil). This mixture was not purified for use in the subsequent reaction; however, for spectroscopic characterization, the mixture was easily separated into its component parts using silica (7 g). Elution with 1:1 ether/hexanes afforded 27 mg of the β-thiophenyl isomer (glass) and elution with 2:1 ether/hexanes gave 60 mg of the α-thiophenyl isomer (mp 99–100 °C). The combined recovery from the column was 88%. Physical data for the β-thiophenyl isomer are given as follows: R_f (silica-5% $CH_3OH/CHCl_3$) 0.80, (silica-ether) 0.85; ν_{max} 1785 (s, C=O), 1640 (w, C=C), and 1590 (w, C=C); δ 1.65 (ABX, $J_{AB} = 14$, $\Delta\nu_{AB} = 35.3$, 2 H, further split by $J_{BX} = 11$ and $J_{AX} = 5$), 1.80–2.60 (m, 4 H), 2.64 (ABX, $J_{AB} = 16$, $\Delta\nu_{AB} = 21.1$, 2 H, further split by $J_{BX} = 12$ and $J_{AX} = 7$), 3.36 (s, 3 H), 3.68 (d of d of d, $J_{d_1} = J_{d_2} = 11$, $J_{d_3} = 5$, 1 H), 3.84 (ABq, $J_{AB} = 12$, $\Delta\nu_{AB} = 76.1$, 2 H), 4.60 (ABq, $J_{AB} = 7$, $\Delta\nu_{AB} = 7.1$, 2 H), 4.78 (d of d, $J_{d_1} = J_{d_2} = 11$, 1 H), 5.20 (d, $J = 11$, 1 H), 5.26 (d, $J = 18$, 1 H), 5.56 (d, $J = 6$, 1 H), 5.91 (d of d, $J_{d_1} = 18$, $J_{d_2} = 11$, 1 H), 7.14–7.55 (m, 5 H); *m/e* 390 (0.1), 281 (9), 235 (21), 219 (2), 217 (2), 207 (2), 189 (3), 161 (3), 151 (4), 147 (3), 133 (4), 121 (4), 110 (46), 109 (16), 108 (16), 107 (11), 45 (100). Physical data for the α-thiophenyl isomer are as follows: R_f (silica-5% $CH_3OH/CHCl_3$) 0.73, (silica-ether) 0.70; ν_{max} 1785 (s, C=O), 1640 (w, C=C), and 1590 (w, C=C); δ 1.60 (ABX, $J_{AB} = 14$, $\Delta\nu_{AB} = 34.2$, 2 H, further split by $J_{BX} = 11$ and $J_{AX} = 5$), 1.8–2.2 (m, 4 H), 2.56 (ABX, $J_{AB} = 16$, $\Delta\nu_{AB} = 30.0$, 2 H further split by $J_{BX} = 12$ and $J_{AX} = 7$), 3.31 (s, 3 H), 3.54 (d of d of d, $J_{d_1} = J_{d_2} = 11$, $J_{d_3} = 5$, 1 H), 3.68 (ABq, $J_{AB} = 12$, $\Delta\nu \simeq 0$, 2 H), 4.29 (d of d, $J_{d_1} = J_{d_2} = 11$, 1 H), 4.53 (ABq, $J_{AB} = 7$, $\Delta\nu_{AB} = 7.1$, 2 H), 4.94 (m, $J_{d_1} = 9$, $J_{d_2} = 5$, 1 H), 5.18 (d, $J = 11$, 1 H), 5.22 (d, $J = 18$, 1 H), 5.89 (d of d, $J_{d_1} = 18$, $J_{d_2} = 11$, 1 H), 7.12–7.56 (m, 5 H); *m/e* 390 (trace), 281 (3), 280 (11), 235 (25), 219 (2), 217 (3), 207 (2), 189 (3), 161 (3), 151 (5), 147 (3), 133 (5), 121 (5), 110 (53), 109 (17), 108 (15), 107 (12), 45 (100).

Preparation of Dilactone 36. To a solution of **35** (76.8 mg, 0.197 mM) in acetonitrile (2.2 mL) at room temperature was added aqueous ceric ammonium nitrate (ca. 1.11 mM, 2.2 mL of a solution of CAN, 685 mg dissolved in 2.5 mL of water). The initial yellow-orange solution lightened to yellow upon stirring for 30 min. The solution was diluted with water (5 mL) and extracted with $CHCl_3$ (4 × 10 mL), the combined extracts washed with 3% $NaHCO_3$ (2 mL), filtered through $MgSO_4$, and evaporated to dryness under vacuum. The re-

sulting yellow oil was dissolved in methylene chloride (2.2 mL) and pyridinium chlorochromate (481 mg, 2.23 mM) was added to the mixture. The reaction turned orange-green then red-brown within a few minutes. A short time later, a black insoluble residue formed with a supernatant orange-brown solution. The reaction was allowed to stir for 9.5 h, whereupon, water (5 mL) was added and the solution extracted with $CHCl_3$ (4 × 10 mL). The combined extracts were filtered through $MgSO_4$ and concentrated to dryness under vacuum. The yellow oil thus obtained (75 mg, 129%) chromatographed on silica (4 g). Elution with 1:1 ether/hexanes followed by ether afforded 51 mg (88%) of the bislactone **36** (mp 109-110.5 °C). This material was combined with 45 mg of material to comparable purity and recrystallized from CH_2Cl_2/ether to give 88 mg (mp 132.5-134°C, 92% for the recrystallization, 18% overall yield from ethyl crotonate) of the lactone **36**; R_f (silica-5% $CH_3OH/CHCl_3$) 0.46, (silica-ether) 0.07, (silica-ethyl acetate) 0.63; ν_{max} 1790 (s, C=O), 1740 (s, C=O), and 1640 (w, C=C); δ 1.80 (ABX, J_{AB} = 14.5, $\Delta\nu_{AB}$ = 38.9, 2 H, further split by J_{BX} = 9.5 and J_{AX} = 5, 2.04-2.40 (m, ca. 2 H), 2.64 (ABX, J_{AB} = 16, $\Delta\nu_{AB}$ = 24.8, 2 H, further split by J_{BX} = 2 and J_{AX} = 7), 2.78 (d, J = 4, ca. 2 H), 3.36 (s, 3 H), 3.77 (d of d of d, $J_{d_1} = J_{d_2}$ = 9.5, J_{d_3} = 5, 1 H), 4.06 (d of d, $J_{d_1} = J_{d_2}$ = 11, 1 H), 4.31 (s, 2 H), 4.61 (ABq, J_{AB} = 7, $\Delta\nu_{AB}$ = 4.8, 2 H), 5.33 (d, J = 18, 1 H), 5.33 (d, J = 10, 1 H), 5.83 (d of d, J_{d_1} = 18, J_{d_2} = 10, 1 H); *m/e* 296 (0.1), 266 (2), 251 (1), 238 (3), 236 (8), 204 (7), 158 (6), 145 (6), 121 (5), 113 (7), 105 (4), 91 (6), 79 (8), 45 (100).

Preparation of Bisnorvernolepin (4). Method I. To a solution of **33** (17.8 mg, 0.051 mL) in acetonitrile (1 mL) and water (0.2 mL) at room temperature was added ceric ammonium nitrate (109.6 mg, 0.20 mM). The resulting yellow-orange solution was stirred for 30 min at which time an additional 0.2 mL of water was added. After 15 min, Jones reagent (0.51 mM, 0.19 mL of ca. 2.67 M solution) was added to the reaction mixture. An orange precipitate formed immediately and the solution then became green. After 10 min, acetone (1 mL) was added and the reaction stirred an additional 15 min before destroying the excess Jones reagent with isopropyl alcohol (50 μL). The now green-black suspension was stirred an additional 5 min, whereupon Celite and solid $NaHCO_3$ were added until the pH of the mixture reached neutrality. The solvent was removed under vacuum and the resulting green-black solid deposited on silica. Elution first with $CHCl_3$ and then with ethyl acetate afforded bisnorvernolepin **4** (6 mg, 46%) as an oil identical with respect to its NMR spectrum (excepting a small amount of upfield impurities) with a spectrum obtained from authentic bisnorverolepin supplied to us by Professor S. Danishefsky, University of Pittsburgh. Trituration of this oil with 4:1 ether/CH_2Cl_2 afforded 4.5 mg (35%) of crystalline bisnorvernolepin, mp 173-174.5 °C (corrected, 179-180.5 °C, lit. 179-180 °C).

Method II. A slow stream of HCl gas was bubbled through a solution of bislactone **36** (16.9 mg, 0.057 mM) in acetonitrile (1.5 mL) at 0 °C for 20 s. The solution was stirred at 0 °C for 5 min and then further stirred at this temperature another 5 min with a slow stream of N_2 bubbled through the solution. The solvent was removed under vacuum and the residue was chromatographed on silica (3 g). Elution first with $CHCl_3$ afforded a fraction (2.4 mg) rich in **4**, but containing some starting material and a weak spot in the TLC intermediate between the starting material and the desired product. Elution with ethyl acetate afforded 12 mg of an oil which then dissolved in 4:1 ether/CH_2Cl_2 slowly crystallized to give **4** (8.5 mg, 59%, mp 179-180.5 °C) identical in all respects with an authentic sample of bisnorvernolepin. The ether/CH_2Cl_2 soluble portion plus the first chromatographic fraction, when allowed to slowly crystallize from 4:1 ether/CH_2Cl_2, afforded another 3.7 mg (26%) of essentially pure bisnorvernolepin (mp 168-175 °C). Physical data for the sample of **4** prepared by the method outlined above are given as follows: R_f (silica-5% $CH_3OH/CHCl_3$) 0.19, (silica-ethyl acetate) 0.28; ν_{max} 3600-3150 (w, b, OH), 3580 (w, sharp OH), 1790 (s, C=O), 1740 (s, C=O), and 1640 (w, C=C); δ ($CDCl_3$-PFT-100), 1.76 (ABX, J_{AB} = 14, $\Delta\nu_{AB}$ = 32.1, split further by J_{BX} = 10.8 and J_{AX} = 4.9), 1.82 (OH), 2.08- 2.40 (m), 2.68 (ABq, J_{AB} = 16, $\Delta\nu_{AB}$ = 35.5, split further by J_{BX} = 12.2 and J_{AX} = ca. 7), 2.79 (d, J = 5.8), 3.73-4.03 (m), 4.03 (d of d, $J_{d_1} = J_{d_2}$ = 10.8), 4.46 (s), 5.38 (d, J = 17.9), 5.39 (d, J = 9.8), 5.84 (d of d, J_{d_1} = 17.9, J_{d_2} = 9.8); δ (acetone-d_6-MH-100), 1.75 (ABX, J_{AB} = 14.5, $\Delta\nu_{AB}$ = 34.4, split further by J_{BX} = 10 and J_{AX} = 5), 2.0-2.95 (m), 1.4-2.95 (ca. 8 H), 3.99 (m, $J_{d_1} = J_{d_2}$ = 10, $J_{d_3} = J_{d_4}$ = 5, 1 H), 4.23 (d, J = 5, 1 H), 4.29 (d of d, $J_{d_1} = J_{d_2}$ = 11, 1 H), 4.45 (ABq, J_{AB} = 12, $\Delta\nu_{AB}$ = 17.2, 2 H), 5.31 (d, J = 11, 1 H), 5.39 (d, J = 18, 1 H), 5.98 (d of d, J_{d_1} = 18, J_{d_2} = 11, 1 H); *m/e* 252 (0.6), 234 (0.6), 224 (16), 204 (44), 180 (8), (32), 176 (32), 163 (28), 162 (94), 158 (20), 145 (86), 134 (24), 121 (26), 120 (52), 117 (42), 109 (40), 107 (26), 106 (24), 93 (80), 92 (100), 91 (34), 79 (48), 67 (28), 57 (48), 55 (62).

Acknowledgments. This research was supported by Public Health Service Grant CA-18485002. Support from the Hoffmann-La Roche Foundation is gratefully acknowledged. G.R.K. thanks the Uniroyal, Hooker, and Sherman-Clarke Funds for fellowships.

References and Notes

(1) (a) S. M. Kupchan, R. J. Hemingway, D. Werner, A. Karim, A. T. McPhail, and G. A. Sim, *J. Am. Chem. Soc.*, **90**, 3596 (1968); (b) S. M. Kupchan, R. J. Hemingway, D. Werner, and A. Karim, *J. Org. Chem.*, **34**, 3903 (1969); (c) A. T. McPhail and G. A. Sim, *J. Chem. Soc. B*, 198 (1971); (d) S. M. Kupchan, *Trans. N.Y. Acad. Sci.*, **32**, 85 (1970); (e) L. Sequeira, R. J. Hemingway, and S. M. Kupchan, *Science*, **161**, 789 (1968); (f) S. M. Kupchan, *Pure Appl. Chem.*, **21**, 277 (1970); (g) J. L. Hartwell and B. J. Abbott, *Adv. Pharmacol. Chemother.*, 7, 117 (1969); (h) S. M. Kupchan, D. C. Fessler, M. A. Eakin, and T. J. Giacobbe, *Science*, **168**, 376 (1970); (i) S. M. Kupchan, T. J. Giacobbe, I. S. Krull, A. M. Thomas, M. A. Eakin, and D. C. Fessler, *J. Org. Chem.*, **35**, 3539 (1970); (j) S. M. Kupchan, R. L. Hanson, and H. A. Hardy, *Science*, **168**, 378 (1970); (k) C. H. Smith, J. Larner, A. M. Thomas, and S. M. Kupchan, *Biochim. Biophys. Acta*, **276**, 94 (1972); (l) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971); (m) S. M. Kupchan, T. J. Giacobbe, and I. S. Krull, *Tetrahedron Lett.*, 2859 (1970).

(2) (a) P. A. Grieco and K. Hiroi, *Tetrahedron Lett.*, 1831 (1973); (b) A. Tanake, T. Nakata, and K. Tamashita, *Agric. Biol. Chem.*, **37**, 3465 (1973); (c) R. D. Clark and C. H. Heathcock, *Tetrahedron Lett.*, 1713 (1974); (d) F. E. Ziegler, A. F. Marino, O. A. C. Petroff, and W. L. Stadt, *ibid.*, 2035 (1974); (e) J. A. Marshall and D. E. Seitz, *Syn. Commun.*, **4**, 395 (1974); (f) J. V. Frosch, I. T. Harrison, B. Lythgoe, and A. K. Saksena, *J. Chem. Soc., Perkin Trans. 1*, 2005 (1974); (g) H. Marshall, F. Vogel, and P. Weyerstahl, *Chem. Ber.*, **107**, 2852 (1974); (h) J. A. Marshall and D. E. Seitz, *J. Org. Chem.*, **40**, 534 (1975); (i) S. Danishefsky and T. Kithara, *ibid.*, **40**, 538 (1975); (j) P. A. Grieco, K. Hiroi, J. J. Reap, and J. A. Noguez, *ibid.*, **40**, 1150 (1975); (k) C. G. Chavdarian and C. H. Heathcock, *ibid.*, **40**, 2970 (1975); (l) P. A. Grieco, J. J. Reap, and J. A. Noguez, *Syn. Commun.*, **5**, 155 (1975); (m) B. M. Trost and C. H. Miller, *J. Am. Chem. Soc.*, **97**, 7182 (1975); (n) R. Scheffold, L. Revesz, J. Aeversold, and A. Schaltegger, *Chimia*, **30**, 57 (1976); (o) S. Danishefsky, P. Schuda, and K. Kato, *J. Org. Chem.*, **41**, 1081 (1976); (p) R. D. Clark and C. H. Heathcock, *ibid.*, **41**, 1396 (1976); (q) P. M. Wege, R. D. Clark, and C. H. Heathcock, *ibid.*, **41**, 3144 (1976); (r) C. G. Chavdarian, S. L. Woo, R. D. Clark, and C. H. Heathcock, *Tetrahedron Lett.*, 1769 (1976); (s) P. A. Grieco, J. A. Noguez, Y. Masaki, K. Hiroi, and M. Nishizawa, *J. Med. Chem.* **20**, 71 (1977); (t) P. A. Grieco, J. A. Noguez, and Y. Masaki, *J. Org. Chem.*, **42**, 495 (1977); (u) M. Isobe, H. Iio, T. Kawai, and T. Goto, *Tetrahedron*, **35**, 941 (1979); (v) F. Zutterman, P. DeClercq, and M. Vandewalle, *ibid.*, 3191 (1977).

(3) (a) P. A. Grieco, M. Nishizawa, S. D. Burke, and N. Marinovic, *J. Am. Chem. Soc.*, **98**, 1612 (1976); (b) S. Danishefsky, T. Kitahara, P. F. Schuda, and S. J. Etheredge, *ibid.*, **98**, 3038 (1976); (c) P. A. Grieco, M. Nishizawa, T. Oguri, S. D. Burke, and N. Marinovic, *ibid.*, **99**, 5773 (1977); (d) S. Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheredge, *ibid.*, **99**, 6066 (1977); (e) G. R. Kieczykowski and R. H. Schlessinger, *ibid.*, **100**, 1938 (1978); (f) M. Isobe, H. Iio, T. Kwai, and T. Goto, *ibid.*, **100**, 1940 (1978).

(4) P. A. Grieco, J. A. Noguez, and Y. Masaki, *Tetrahedron Lett.*, 4213 (1975).

(5) G. Stork and R. L. Danheiser, *J. Org. Chem.*, **38**, 1775 (1973).

(6) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 738 (1976).

(7) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).

(8) See E. Eliel, "The Stereochemistry of Carbon Compounds", McGraw-Hill, New York, 1962.

(9) Generation of this anion was carried out by using the method described by J. L. Herrmann, G. R. Kieczykowski, and R.H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973).

(10) This sequence of reactions was initially developed by Dr. J. L. Herrmann. Compound **10** may also be obtained by first alkylating ethyl crotonate with ethyl bromoacetate, and subsequently alkylating this product with propargyl bromide. The latter method, however, gives somewhat lower overall yields.

(11) R. Scheffold et al. describe a completely different approach to this β-dicarbonyl intermediate (reference 2n).

(12) D. H. R. Barton, R. H. Hesse, M. M. Pechet, and C. Wiltshire, *J. Chem. Soc., Chem. Commun.*, 1017 (1972).

(13) D. C. Rowlands, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Org. Chem.*, **17**, 807 (1952).

(14) The use of other acid scavengers such as pyridine and triethylamine resulted in product formation but lower yields with equivalent amounts of the dibromide were realized. For an example of dehydrohalogenation of α,β-dibromo ethers, see J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **74**, 271 (1955).

(15) Structures **18** and **19** were incorrectly represented in our initial communication describing this synthesis (reference 3e).

(16) Inspiration for this work arose from similar work carried out by E. J. Corey and R. A. Ruden, *J. Org. Chem.*, **38**, 834 (1973). Interestingly, the reaction requires a protic medium but fails in the presence of water or *tert*-butyl alcohol. If methanol is used as the exclusive solvent, a substantial reduction of the iodide occurs with the mixed acetal moiety remaining intact.

(17) H. Booth, *Tetrahedron Lett.*, 411 (1965), and references cited therein.
(18) The alcohol was reasonably stable when kept under basic or neutral conditions. Slightly acidic solvents such as $CDCl_3$ were sufficient to cause extensive decomposition of the compound.
(19) This reaction is sensitive to the amount of iodine used, giving lower yields of enone when larger amounts were used. The use of iodine for this reaction originated from a seminar given by Professor K. Nakanishi at the University of Rochester.
(20) Several different hydride reagents were examined for the reduction of enone **25.** Most were found to give significant amount of 1,4 reduction together with varying ratios of the alcohols. Vitride, for example, gave the highest ratio of **26**, 85:15, with 20% 1,4 reduction. DIBAL-H, ultimately used in this reduction, gave only trace amounts of 1,4-reduction.
(21) The preparation and use of pyridinium chlorochromate in the oxidation of alcohols is described by E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(22) Epoxidations of allylic alcohols although generally stereospecific frequently contain some *trans*-epoxide alcohol. It has been reported that the use of $VO(acac)_2$ and $Mo(CO)_6$ with peroxides increases the stereoselectivity of epoxidations. Attempted use of these reagents on alcohol **26** resulted in significant oxidation of the allylic alcohol back into the enone **25.** For examples of the use of $VO(acac)_2$ and $Mo(CO)_6$, see T. Itoch, K. Kaneda, and S. Teranishi, *J. Chem. Soc., Chem. Commun.*, 421 (1976), and S. Tanaka, H. Yamamoto, H. Nozak, K. B. Sharpless, R. C. Michaelson, and J. D. Cutting, *J. Am. Chem. Soc.*, **96**, 5254 (1974), and references cited therein.
(23) Although a rigorous structure proof of the proposed diepoxide was not completed, isolation of a material from epoxidations carried out at 0 °C provided a ^1H NMR spectrum devoid of vinyl protons and a mass spectrum 16 units higher than the desired monoepoxide.
(24) K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, **29**, 1136 (1964).
(25) This dianion was generated with 2 equiv of lithium diisopropylamide. The procedure used follows that described by S. N. Huckin and L. Wieler, *J. Am. Chem. Soc.*, **96**, 1082 (1974). The dianion derived from methyl acetoacetate has previously been reported to ring open epoxides by T. A. Bryson, *J. Org. Chem.*, **38**, 3428 (1973).
(26) For a more detailed account of the reaction of these epoxides with *tert*-butyl dilithioacetoacetate, see G. R. Kieczykowski, M. R. Roberts, and R. H. Schlessinger, *J. Org. Chem.*, **43**, 788 (1978); (b) for a description of epoxide opening with dilithioacetate, see S. Danishefsky, M. Tsai, and T. Kitahara, *ibid.*, **42**, 394 (1977).
(27) Oximination α to ketones has ample literature precedence. For an example in which *tert*-butyl acetoacetate was oximinated and degraded to acetic acid, see K. Schank, *Ber.*, **100**, 1245 (1967). Significant quantities of the lactone **31** are formed in this reaction; however, to effectuate complete conversion of the oxime **30** into the lactone **31**, acetic anhydride was used. Interestingly, when only 1 equiv of isoamyl nitrite was used, the major product of the reaction was the oxime.
(28) Oxidation of sulfides to sulfoxides with ceric ammonium nitrate has been reported by T. L. Ho and C. M. Wong, *Synthesis*, 561 (1972). The conversion of **33** into **34** probably occurs by ready sulfoxide rearrangement, facilitated by the adjacent ether oxygen atom, into the corresponding sulfinic ester followed by hydrolysis of this ester into the hemiacetal.
(29) The authors wish to thank Professor S. Danishefsky for a generous sample of bisnorvernolepin which was employed for direct NMR, mass spec, IR, TLC, and melting point comparison with the material made by the route described herein.
(30) Another 25% of bisnorvernolepin was obtained from this reaction with a melting point slightly lower than the pure sample. However, the NMR, IR, and mass spectra along with the TLC showed essentially no differences between this material and completely pure material.
(31) Nuclear magnetic resonance spectra were recorded at 100 Hz on a Jeolco Model JNM-PS-100 high-resolution spectrometer or on a Jeolco Model JNP-PS-100 high-resolution Fourier transform spectrometer. Samples were examined in deuteriochloroform containing 1% by volume of tetramethylsilane unless otherwise noted. Infrared spectra were recorded on a Perkin-Elmer Model 467 grating spectrophotometer. Mass spectra were obtained on a Du Pont Model 21-490 B mass spectrometer. Melting points were determined on a Fisher-Johns melting point block and reported uncorrected.

Gas chromatography was performed on a Hewlett-Packard series 5700 A gas chromatograph with a series 5702 A temperature programmer and 5705 A thermal conductivity detector. Columns were either 6 ft × 0.125 in. or 2 ft × 0.125 in. aluminum tubing packed with 15% S. E. 30 on acid-washed Chromosorb W, 80–100 mesh, and were cured at 270 °C. The carrier gas was dry helium and a flowrate of 20 ± 2 mL/min was maintained. Thin-layer chromatography utilized precoated Analtech medium hard Silica Gel GHLF glass plates of 0.25-mm thickness. Elution of the plate was carried out at approximately a 60° angle and visualization was made by means of an ultraviolet light, and or an iodine chamber, and or by charring with 10% sulfuric acid containing 2% cobaltous chloride. Preparative chromatography was performed as follows: the silica, no. 7731 silica gel G type 60 for TLC, was placed in a sintered glass funnel packed dry. Solvent was flushed through the silica gel under water aspirator vacuum and the silica repressed to avoid channeling between the glass and the silica. The compound to be purified was deposited with a minimal amount of solvent and then eluted with solvent by using a water aspirator as the vacuum source.

Reactions requiring heating were immersed in thermostated silicon oil baths. Reactions requiring −78 °C temperatures were performed in CO_2 acetone baths and those requiring 0 °C utilized ice baths. Temperatures between 0 and −78 °C were maintained by using a Flexi-Cool in conjunction with a heater override system manufactured by FTS Systems Inc. (temperature accuracy ±0.5 °C).

High vacuum distillations utilized a CVC 4 in. oil diffusion pump with a 165-L/min Alcatel rough pump.

All reactions were run in flamed vessels under an atmosphere of nitrogen except those in which water was present. All additions, wherever possible, were made via syringe through a septum, and all reactions were stirred using magnetic stirrers. All solutions were concentrated on a rotary evaporator at 20–30 °C and at pressures of 15–20 mmHg except where otherwise noted. Tetrahydrofuran (THF), diethyl ether, and 1,2-dimethoxyethane (DME) were distilled from lithium aluminum hydride (LAH) immediately before use. When these solvents were used in amide base reactions, nitrogen was bubbled through the solvent for 15 min before use. All lithium amide bases were generated in situ immediately before use. Potassium *tert*-butoxide in *tert*-butyl alcohol was prepared from potassium metal and *tert*-butyl alcohol and stored in the dark under nitrogen at −20 °C.

Methylene chloride was distilled from calcium chloride, *tert*-butyl alcohol from calcium hydride, and methanol from magnesium turnings immediately before use. The following solvents were distilled under nitrogen and stored under an atmosphere of nitrogen over sieves, where appropriate, in bottles fitted with septums: dimethyl sulfoxide (Me_2SO) from calcium hydride; toluene and hexane from lithium aluminum hydride; acetonitrile from phosphorus pentoxide; acetic acid from acetic anhydride.

Diisobutylaluminum hydride (DIBAL-H) in hexane was obtained from Texas Alkyls and used without titration. Sodium hydride (NaH), calcium hydride, and lithium aluminum hydride were purchased from Alfa. Solutions of *n*-butyllithium (BuLi) in hexane were obtained from Alfa and titrated in benzene with *tert*-butyl alcohol/benzene using 1,10-phenanthroline as the indicator.

The Ambient Temperature Ullmann Reaction and Its Application to the Total Synthesis of (±)-Steganacin[1]

Frederick E. Ziegler,*[2] Irene Chliwner, Kerry W. Fowler,[3] Sheldon J. Kanfer, Stephen J. Kuo, and Nanda D. Sinha

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06520. *Received June 25, 1979*

Abstract: The details of a new method for preparing unsymmetrical biphenyls at room temperature by a modification of the classical Ullmann reaction are discussed. An intramolecularly coordinated organocopper reagent is treated with an aryl iodide bearing a potential coordinating ligand to form the biphenyl. Nitrogen and sulfur have been utilized as ligands and as protecting groups for carbonyls. The application of this methodology to the synthesis of the antileukemic steganacin is detailed.

Introduction

The two antileukemic lactones, steganacin (**31b**) and steganangin (**31c**), which co-occur in nature with steganone (**31a**) and steganol (**31d**) were isolated from *Steganotaenia araliacea* by Kupchan in 1973.[4] These substances[5,6] are representative of a growing class of lignans bearing the dibenzo[*a*,*c*]cyclooctene ring system.[7]

0002-7863/80/1502-0790$01.00/0