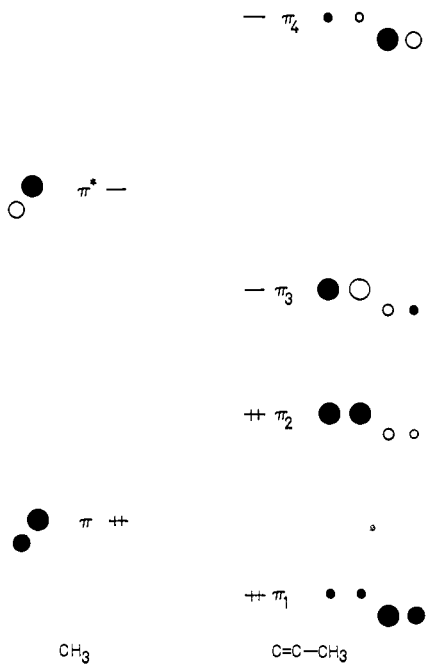

Figure 3. Interaction diagram for the PMO analysis of the ee conformations of the butenes by method B.

analyses. As seen in this table, both method A and method B predict *trans*-2-butene to be less stable than *cis*-2-butene when idealized geometries are employed. However, when the analyses are based upon *optimized* or *experimental* geometries, both fragmentation modes lead to the correct result. In the case of method A, this is found to be due mainly to a difference in the π levels of the two isomers, leading to a larger $\pi_+ - \pi$ destabilizing interaction in the cis isomer; such a result could not have been anticipated by qualitative arguments.

Regardless of the geometry employed, the analysis based on method A predicts isobutene to be less stable than either 2-butene. This is the wrong result.

The three isomers are ordered correctly by method B. This finding demonstrates that the PMO analysis is not independent of the fragmentation mode, and it appears to be general for 1,1- and 1,2-disubstituted alkenes.[6] The reason for the failure in the case of method A can be seen upon inspection of Figures 1 and 2. In isobutene, the appropriate $CH_3 \cdots CH_3$ orbital for interaction with π^* is π_+ but, in the 2-butenes, the orbital which interacts with π^* is π_-. For the PMO analysis to be applicable to a series of compounds, e.g., positional isomers, the fragmentation method employed should lead not only to the same set of fragment orbitals, but also to the same *interactions* in every case. Both method A and method B are appropriate for the examination of *cis*- and *trans*-2-butene since these criteria are met, but only method B is suitable when isobutene is included.

We conclude that the PMO method is applicable to isomeric olefins, without the necessity of introducing steric effects in an ad hoc manner, provided that (1) the different geometries of the different molecules are taken into account and (2) the analysis is based upon a one-bond fragmentation.[7]

References and Notes

(1) Molecular Orbitals from Group Orbitals. 5. For part 4, see M.-H. Whangbo and S. Wolfe, *Can. J. Chem.*, **55**, 2778 (1977).
(2) For leading references, see W. L. Jorgensen and L. Salem, "The Organic Chemist's Book of Orbitals", Academic Press, New York, N.Y., 1973.
(3) M.-H. Whangbo, H. B. Schlegel, and S. Wolfe, *J. Am. Chem. Soc.*, **99**, 1296 (1977).
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(5) For a vigorous reaction to this kind of thinking, see J. Burdon and I. W. Parsons, *J. Am. Chem. Soc.*, **99**, 7445 (1977).
(6) M.-H. Whangbo, D. J. Mitchell, and S. Wolfe, *J. Am. Chem. Soc.*, in press.
(7) This research was supported by the National Research Council of Canada.
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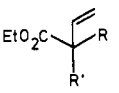
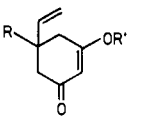
Total Synthesis of (±)-Vernolepin

Sir:

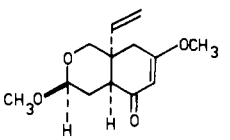
Vernolepin (**29**) and vernomenin (**30**)[1] have been the subject of intense synthetic investigation,[2] recently culminating in the description of two total syntheses leading to the attendant formation of both naturally occurring products.[3] Herein, we describe our own work in this area which results in the exclusive formulation of vernolepin. Our synthesis begins with the preparation of compound **5**, a harbinger of the vernolepin B ring and conjoiner of rings A and C. Elaboration of **5** into the *cis*-2-oxydecalin **10** constitutes the next phase of the synthesis.



1 R = I-; R' = H
2 R = $CH_2C{\equiv}CH$; R' = H
3 R = $CH_2C{\equiv}CH$; R' = CH_2CO_2Et
4 R = CH_2COCH_3; R' = CH_2CO_2Et



5 R = CO_2Et; R' = H
6 R = CO_2Et; R' = CH_3
7 R = CH_2OH; R' = CH_3
8 R = $CH_2OCHIOCH_3$; ICH_2Br; R' = CH_3
9 R = $CH_2OCHIOCH_3$; ICH_2I; R' = CH_3



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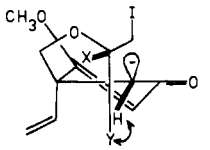

11 X = H; Y = OCH_3
12 X = OCH_3; Y = H

The presence of a remote chiral center, not present in the natural product, imparts sufficient conformational rigidity to **10** to permit its stereospecific conversion into the expoxide **20.** Regiospecific ring opening of the aforementioned epoxide followed by successive establishment of the C and A lactone rings yields the molecule prevernolepin, **25.**[4]

Preparation of **5** was initiated by kinetic deprotonation of ethyl crotonate, using a mixture of lithium diisopropylamide and hexamethylphosphoramide (LDA/HMPA), to generate the anion **1** which was caused to react with propargyl bromide affording the acetylene **2** (bp 78 °C at 10 mm).[5] Further alkylation of **2,** adjacent to the ester residue, was realized via kinetic deprotonation (LDA/HMPA) followed by treatment with ethyl bromoacetate. The resulting acetylene diester **3** (bp 84–85 °C at 0.29 mm),[6] by mercuric sulfate mediated hydration, gave rise to the methyl ketone **4** (bp 94 °C at 1×10^{-3} mm) which, on reaction with potassium *tert*-butoxide in *tert*-butyl alcohol, was converted into the dione ester **5**[6] (waxy solid, 75% yield from **1**).

Having now established the elements of ring B of vernolepin, we then turned our attention to the manipulation of this material into a suitable precursor of the *cis*-2-oxydecalin **10.**

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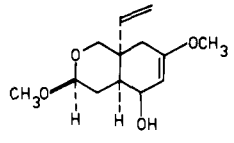
Admixture of **5** with methanol, trimethyl orthoformate, and *p*-toluenesulfonic acid, followed by heating, gave the vinylogous ester **6** (oil).[6] Selective reduction of the ethyl ester residue of **6,** in the presence of the vinylogous ester moiety, was accomplished utilizing methodology already established by Barton and coworkers[7] and by Stork and Danheiser.[8] Thus, **6** was kinetically deprotonated with LDA at the methylene carbon adjacent to the vinylogous ester carbonyl group,[8] and then treated with lithium aluminum hydride[7] to give the alcohol vinylogous ester **7** (oil).[6] The remaining two carbon element needed to begin formation of the A ring of vernolepin was then added by reaction of **7** with 1,2-dibromo-2-methoxyethane[9] in the presence of *N,N*-dimethylaniline which gave rise to the bromo acetal **8** (oil).[6] The bromide **8** was then converted into its corresponding iodide **9** (oil, 77% yield from **5**)[6] using sodium iodide in refluxing acetone.

It was anticipated that the kinetic enolate derived from **9** would cyclize to **10** since this enolate must be a mixture of isomers with respect to the carbon atom bearing the methoxy and iodomethyl groups. The orientation of these groups as depicted in **11** results in serious interaction of the methoxy group with the hydrogen atom carried by the enolate carbon, whereas this interaction is not present in the structure **12,** leading therefore, to the conclusion that **12** would cyclize in preference to **11,** and, thus, give rise exclusively to compound **10.** Consistent with this surmise was the observation that compound **9,** when kinetically deprotonated with lithium hexamethyldisilizane, undergoes cyclization at −40 °C to give a 1:1 mixture of **10** and the iodo acetal **9.**[10] This mixture could not be readily resolved by chromatographic means, and, thus, it was treated with zinc metal containing 5% by weight of copper metal suspended in methanolic dimethyl sulfoxide.[11] By this procedure, a readily separable mixture of **10** and the alcohol **7** were obtained. Based on recovered and reused alcohol, compound **10** (mp 65.5–66.5 °C) could be prepared in 82% yield.

Conversion of **10** into a compound suitable for introduction of the C ring of vernolepin was commenced by reduction of **10** with lithium aluminum hydride to give the alcohol **13** which



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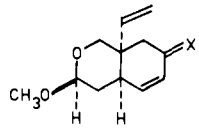
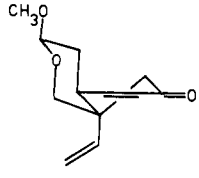


14 X = O
15 X = α OH; β H
18 X = α H; β OH



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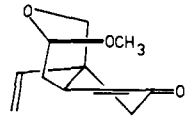

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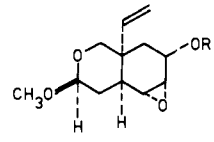
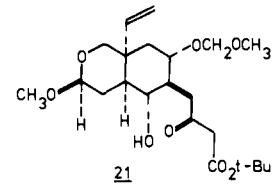
on treatment with 5% by weight of iodine in anhydrous THF gave the enone **14** (mp 51–52.5 °C) in 96% yield from **10.** At this juncture, the A ring methoxy group becomes significant in the subsequent transformation which involves stereospecific reduction of the enone into its corresponding α-allylic alcohol, **15.** The enone **14** can exist in two conformations, **16** and **17,** and molecular models suggest that **16** should be the favored conformation owing to the equatorial preference of the A ring methoxy group as opposed to the axial orientation of this group in **17.** Based on Baldwin's predictions concerning the reduction of enones, **16** should reduce to the desired alcohol **15** while **17** should reduce to the undesired β-allylic alcohol **18.**[12]

Several different hydride reagents were examined for the reduction of **14** and most were found to give significant amounts of 1,4 reduction together with varying ratios of the alcohols **15** and **18.**[13] Diisobutylaluminum hydride, however, gave only trace amounts of 1,4 reduction with a 6:4 ratio of **15** to **18,** respectively. Fortuitously, this mixture proved trivial to separate, and thus, compound **15** (mp 55.5–56.5 °C) could be obtained in 60% yield uncontaminated with **18** (mp 59–61 °C). The latter alcohol was oxidized back into the enone **14** using pyridinium chlorochromate,[14] thereby giving a 95% yield for the conversion of **14** into **15** based on recovered and reused **14.**

Regiospecific and stereospecific introduction of the C ring of vernolepin was then carried out starting with epoxidation of **15** at −20 °C with *m*-chloroperbenzoic acid to give the *cis*-α-hydroxy epoxide **19** (mp 105–106 °C).[15] Reaction of **19** with sodium hydride and chloromethyl methyl ether gave the α-methoxymethyloxy epoxide **20** (oil)[6] which on reaction with a 10-fold excess of *tert*-butyl dilithioacetoacetate[16] gave the adduct **21.**[17] The four-carbon fragment introduced by this



19 R = H
20 R = CH_2OCH_3



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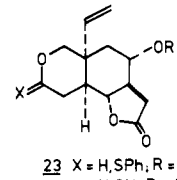
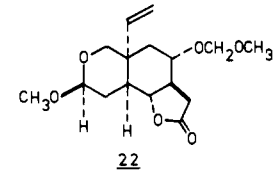


23 X = H,SPh; R = H
24 X = H,OH; R = H
25 X = O; R = H
26 X = H; SPh; R = CH_2OCH_3
27 X = H,OH; R = CH_2OCH_3
28 X = O; R = CH_2OCH_3



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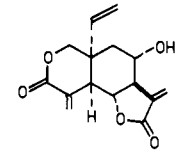

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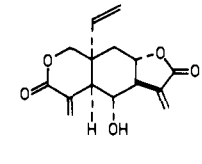

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reaction was degraded into the lactone **22** in two steps: first by treatment with sodium nitrite in acetic acid/THF at 25 °C for 1.5 h, and second by the addition of acetic anhydride followed by heating at 60 °C for 1.5 h. This combination of events affords the lactone **22** (mp 158–160.5 °C) in 55% yield from **15.**[18]

Establishment of the A-ring lactone was accomplished by treatment of **22** with thiophenol and boron trifluoride etherate to give the sulfide alcohol **23** (mp 70–78 °C, 98% yield) as a mixture of epimers about the thioacetal carbon. Oxidation of **23** using ceric ammonium nitrate gave the corresponding hemiacetal **24,**[19] which, without isolation, was further oxidized with Jones reagent into prevernolepin **25** (mp 179–180 °C, lit.[3] 179–180 °C) in 36% yield.[20] Alternatively, **23** was reacted with bromomethyl methyl ether to give the sulfide **26** (oil) in 96% yield. Oxidation of this material with ceric ammonium nitrate gave the hemiacetal **27** which on further oxidation with pyridinium chlorochromate afforded the dilactone **28** (132.5–134 °C) in 75% yield from **26.**[21] Since prevernolepin has been converted into vernolepin,[3] our preparation of this substance constitutes a total synthesis of the racemic natural product.[22]

Acknowledgments. This research was supported by P.H.S. Grant CA-18485-02. Support from the Hoffmann-La Roche Foundation is gratefully acknowledged.

References and Notes

(1) S. M. Kupchan, R. Hemmingway, D. Werner, and A. Karim, *J. Am. Chem. Soc.*, **90**, 2596 (1968); S. M. Kupchan, R. Hemingway, D. Werner, A. Karim, A. McPhail, and G. A. Sim., *J. Org. Chem.*, **34**, 3913 (1969); and S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971). Of these two molecules, vernolepin is cytotoxic, whereas vernomenin is biologically much less active.

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(4) For an excellent discussion of the various strategies that have been employed in efforts to prepare vernolepin by total synthesis, see S. Danishefsky, P. F. Schuda, and K. Kato, *J. Org. Chem.*, **41**, 1081 (1976). The strategy leading to vernolepin that is described here differs considerably from previous routes in that a conformationally mobile *cis*-2-oxydecalin system is present throughout the critical stages that build the stereochemistry associated with this natural product.

(5) Generation of this anion was carried out using the method described by J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973). A referee has objected to the phrase "kinetic deprotonation" when applied to a crotonate ester because only one type of enolate may be formed from such systems. To our minds, "kinetic deprotonation" is an experimental act involving the addition of an organic acid to a slight excess of base sufficiently powerful to inhibit meaningful and subsequent acid–base equilibrium. Therefore, care must be exercised with respect to confusing the term "kinetic deprotonation" (manner) with the term "kinetic enolate" (type).

(6) This compound, while fully characterized, was utilized in unpurified form for the subsequent reaction described.

(7) Protection of carbonyl groups toward hydride reduction by prior enolate formation has been described by D. H. R. Barton, R. H. Hesse, M. M. Phechet, and C. Wiltshire, *J. Chem. Soc.*, 1017 (1972).

(8) For previous examples of kinetic deprotonation of vinylogous esters, see G. Stork and R. L. Danheiser, *J. Org. Chem.*, **38**, 1775 (1973).

(9) Prepared by the method described by D. C. Rowlands, K. W. Greenlee, and J. M. Derfer, *J. Org. Chem.*, **17**, 907 (1952).

(10) This reaction, when carried out at 0 °C, will yield the α-methoxy isomer of **10** in addition to **10** itself. The α-methoxy compound has been isolated pure and found to exhibit an NMR spectrum different from that of **10**.

(11) Inspiration for this reaction arose from similar work carried out by E. J. Corey and R. A. Ruden, *J. Org. Chem.*, **38**, 834 (1973). Workup of this reaction under neutral conditions gives a mixture of **10**, **7**, and the vinyl ether analogue of **7**. The latter material is rapidly converted into **7** using an acidic workup for the reaction. Interestingly, the corresponding bromide **8** does not undergo this reaction.

(12) For a definitive discussion of hydride reduction of unsaturated ketones, see J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 738 (1976).

(13) Vitride, for example, gave an 85:15 ratio of the alcohols **15** and **18**, respectively, together with 20% 1,4 reduction. As anticipated from molecular models, the corresponding α-methoxy isomer of **14** gives different alcohol ratios on reduction. We do not attribute the low stereospecificity exhibited by **14** on hydride reduction to a failure of the Baldwin rules,[12] but, rather, we would suggest that the acetal portion of **14**, by prior complexation with the hydride reagent, is the culpable agent of these results.

(14) For a description of this reagent and its use in the oxidation of alcohols, see E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).

(15) The relative stereochemistry of this epoxide alcohol follows from the outstanding work of H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).

(16) The procedure used for generation of this dianion follows that described by S. N. Huckin and L. Wieler, *J. Am. Chem. Soc.*, **96**, 1082 (1974). The dianion derived from methyl acetoactate has been reported to ring open epoxides by T. A. Bryson, *J. Org. Chem.*, **38**, 3428 (1973).

(17) S. Danishefsky, M. Y. Tsai, and T. Kitahara, *J. Org. Chem.*, **42**, 394 (1977), have reported that *cis*-α-trimethylsilyloxy epoxides ring open with dilithioacetate to give products formally derived from 1,2-diols. In this instance, our results stand in marked contrast to this work. We have in addition, examined a simple *cis*-α-methoxymethyloxy epoxide bearing a geminal dimethyl group in the α' position. This epoxide, on reaction with *tert*-butyl dilithioacetoacetate also opens in the same manner observed for the epoxide **20**. We thus conclude that both aforementioned epoxides must have a steric buttressing effect on the entering nucleophile which defines the regiospecificity of this reaction and which completely overwhelms the counter directive effect anticipated on the basis of Danishefsky's results.

(18) The degradation of **21** into **22** is essentially a second-order Beckmann rearrangement and is reminiscent of the conversion of strychnine into Wieland–Gumlich aldehyde. For a recent and extensive discussion of the latter transformation, see J. R. Hymon, H. Schmid, P. Karrer, A. Boller, H. Els, P. Fahrni, and A. Furst, *Helv. Chim. Acta*, **52**, 1564 (1969). We thank Professor David Cane of Brown University for bringing this reference to our attention.

(19) 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 **23** into **24** 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. The hemiacetal is extremely water soluble and was, therefore, not normally characterized when prepared.

(20) The formation of prevernomenin was not detected in this reaction sequence. The authors thank Professor S. Danishefsky for a generous sample of prevernolepin which was employed for direct NMR, mass spectrum, IR, and melting point comparison with the material made by the route described herein.

(21) Acidic removal of the methoxymethyloxy group of **28** readily affords prevernolepin in high yield. Compound **28** is an excellent material for potential conversion into vernolepin since both Grieco and Danishefsky[3] have used the corresponding THP derivative of prevernolepin for elaboration into vernolepin.

(22) This synthesis was first discussed in its entirety at the Gordon Conference on Natural Products, Aug 1977. The authors extend special thanks to Ms. Martha Quesada whose help with large-scale reactions and whose expertise with chromatography was critical to the completion of this work.

(23) Holder of Uniroyal, Hooker, and Sherman–Clarke fellowships.

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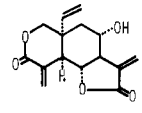
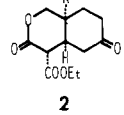
Synthesis of Sesquiterpene Antitumor Lactones. 2. A New Stereocontrolled Total Synthesis of (±)-Vernolepin

Sir:

Vernolepin (**1**), a novel sesquiterpene from *Vernonia hymenolepis* has been shown to have significant in vitro cytotoxicity (KB) and in vivo tumor inhibitory activity against Walker intramuscular carcinosarcoma in rats.[1] Extensive studies have recently culminated in the total syntheses by Grieco[2] and by Danishefsky.[3] We would like to report a new stereospecific total synthesis of **1**.[4]



1



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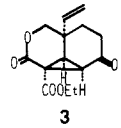
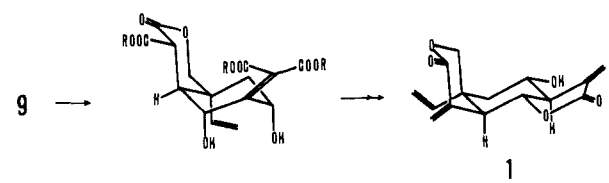


3

Previous work in our laboratory,[5] which established the facile construction of a cis-fused δ-valerolactone system (**2**) by intramolecular Michael addition[6] and the subsequent conversion to the cyclopropane derivative (**3**), demonstrated the feasibility of the total synthesis of **1** via **3** as a key intermediate. Our stereochemical strategy toward this elemanoid could further be developed along the lines of Scheme I, which

Scheme I



1

0002-7863/78/1500-1940$01.00/0