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

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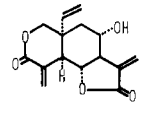
Synthesis of Sesquiterpene Antitumor Lactones. 2. A New Stereocontrolled Total Synthesis of (±)-Vernolepin

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]



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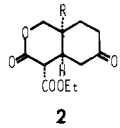

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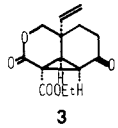
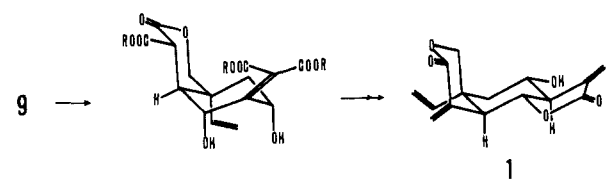


3

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



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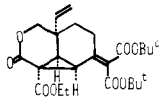
firstly involved elaboration of a system having two *axial* hydroxyl groups and an exo double bond in the B ring which is held in the unnatural conformation owing to interference of the bulky substituents.[7] Secondly, induction of the asymmetric center at the C-7 position could be ensured by hydride reduction with assistance of the axial hydroxyl groups, and thus the reduction eventuated in conformation inversion to natural form.



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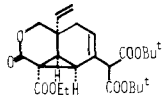

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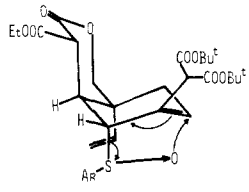

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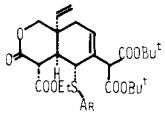
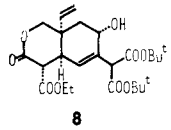


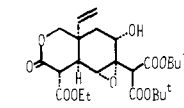
6

Condensation of **3** with *tert*-butyl malonate in the presence of $TiCl_4$-Py in THF[8] (affording **4**) and subsequent treatment with DBU (THF, room temperature, 2 h) gave in 58% overall yield the thermodynamically more stable deconjugated product **5:** mp 86–87 °C; δ (ppm) 5.97 (br d, J = 6 Hz), 3.94 (s), 4.05 (2 H, AB q, J = 11 Hz), 2.84 (d, J = 9.5 Hz), 2.55 (br d, J = 18 Hz), 2.40 (d, J = 9.5 Hz), 2.20 (dd, J = 18, 6 Hz[9]). Opening of the cyclopropane ring in **5** at C-6 position was achieved efficiently by sodium *p*-methoxythiophenolate[4b,10] in THF to afford **6** (88%) (δ 5.96 (br t, J = 4 Hz), 4.35 (s), 4.19 (2 H, AB q, J = 9 Hz), 3.58 (d, J = 10 Hz), 3.25 (br s, >CHS), 3.04 (dd, J = 10, 3 Hz, junction H), 2.32 (2 H, d, AB q, J = 4, 18 Hz)), in which the arylthio group is axially oriented. After oxidation of **6** at −78 °C (CH_2Cl_2, mCPBA), the resulting diastereoisomeric sulfoxides **7** (84%) were heated in EtOH at 60 °C for 10 h in the presence of trimethyl phosphite affording the allyl alcohol (**8**) in 87% yield by [2,3]-sigmatropic rearrangement.[10]



8

Epoxidation of **8** with mCPBA in wet CH_2Cl_2 (room temperature, 20 h) occurred selectively and gave in 81% yield the epoxy alcohol (**9**): δ 5.8–5.1 (3 H, ABX, J = 17, 11 Hz), 4.18 (2 H, AB q, J , 11 Hz), 4.11 (s), 3.56 (d, J = 9.5 Hz), 3.20 (br s, H oxirane), 3.06 (d, J = 9.5 Hz). Reduction of **9** with $NaBH_3CN$ in wet THF afforded the 7-epi isomer of **11** which would be produced by intermolecular hydride attack on the intermediate **10.** The epoxide, however, could be successfully converted to the diol **10** by treatment with $NaBH_3CN$ in dry HMPA[11] (room temperature, 2 h). Interestingly, no double-bond reduction took place under these conditions. The two hydroxyl groups of the product (**10**) were proven to be both axial (δ 4.68 (dd, J = 8, 7 Hz, H-8), 4.52 (d, J = 4.5 Hz, H-6)), and a reasonable intermediate in this reaction could, therefore, be a cyclic cyanoborohydride, such as **10a** in which X is CN. So without isolating **10,** the reaction mixture was treated with 5 to 6 equiv of BH_3-THF at −45 °C for 6 h to complete the exchange of CN to H. This reaction proceeded as was expected



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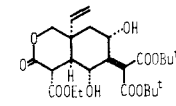

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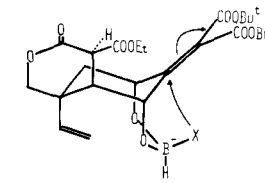
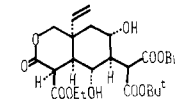


10a



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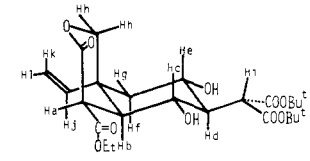

11a

to afford **11** (70% yield), an intramolecular conjugate reduction product: mp 128–129 °C; δ 3.74 (d, J = 4 Hz, H_a), 2.60 (dd, J = 11, 4 Hz, H_b), 3.60 (dd, J = 11, 10 Hz, H_c), 2.08 (td, J = 10, 2.5 Hz, H_d), 3.84 (br ddd, J = 10, 9, 5 Hz, H_e), 1.60 (dd, J = 14, 9 Hz, H_f), 1.85 (dd, J = 14, 5 Hz, H_g), 4.17 (s, H_h), 3.95 (d, J = 2.5 Hz, H_i).[12]

The total synthesis of **1** was completed from **11** by the following procedure. **11** was hydrolyzed (Amberlite IRA400, MeOH, room temperature, 30 min); the resulting carboxylic acid was eluted from the resin with aqueous TFA; the eluate after standing for 30 min at room temperature was evaporated to dryness; and the residue was successively treated with Et_2NH-formalin (15 min at room temperature and then 30 min at 100 °C[13a]) and with NaOAc-AcOH (30 min at 100 °C).[13] The crude product was extracted with CH_2Cl_2 and then chromatographed[14] on silicagel to afford **1** in 22% yield. Crystallization from $CHCl_3$ gave colorless prisms, mp 206 °C (uncorrected), whose physical properties (NMR, IR, mass spectrum) were identical with those reported already.[2,3]

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(1) S. M. Kupchan, R. J. Hemingway, D. Werner, A. Karim, A. T. McPhail, and G. A. Sim, *J. Am. Chem. Soc.*, **90,** 3596 (1968).

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(3) S. Danishefsky, T. Kitahara, P. F. Schuda, and S. J. Etheredge, *J. Am. Chem. Soc.*, **98,** 3028 (1976); S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *ibid.*, **98,** 6715 (1976); S. Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheredge, *ibid.*, **99,** 6066 (1977).

(4) Results of this work presented to (a) *Int. Cong. Pure Appl. Chem., Tokyo, 26th* (Sept. 1977); (b) *20th Symp. Chem. Nat. Prod., Sendai, 20th* (Oct 1976).

(5) M. Isobe, H. Iio, T. Kawai, and T. Goto, *Tetrahedron Lett.*, 703 (1977).

(6) For a similar intramolecular cyclization see (a) D. F. Taber, Ph.D. dissertation at Columbia University, 1975; (b) S. Torii, T. Okamoto, and S. Kadono, *Chem. Lett.*, 495 (1977); (c) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Wiley, New York, N.Y., 1965, Chapter 5.6.

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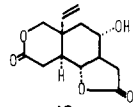
(9) All of the NMR spectra were measured in $CDCl_3$ or pyridine-d_5 with JEOL MH-100 or FX-100.

(10) *p*-Methoxyphenyl sulfoxide worked better than phenyl sulfoxide to prevent syn-elimination; see also ref 4a. For general reactivity see (a) S. Danishefsky and G. Rovnyak, *J. Chem. Soc., Chem. Commun.*, 820, 821 (1972); (b) D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7,** 147 (1974); (c) K. Kondo, T. Umemoto, Y. Takahatake, and D. Tunemoto, *Tetrahedron Lett.*, 113 (1977); (d) D. F. Taber, *J. Am. Chem. Soc.*, **99,** 3513 (1977).

(11) (a) R. O. Hutchins, B. E. Maryanoff, and C. A. Milewski, *Chem. Commun.*, 1097 (1971); (b) R. O. Hutchins and D. Kandasamy, *J. Org. Chem.*, **40,** 2530 (1975).

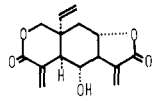
(12) In order to confirm the stereochemistry of **11**, it was transformed by successive treatments with basic alumina and aqueous TFA and then heating at 160 °C into **12**, which proved to be identical with the bisnorvernolepin[2,3] (**12**) derived from an authentic sample furnished by Professor Danishefsky, whom the authors thank for providing the sample and many NMR spectra.



12

(13) (a) Decarboxylation occurred partially which was completed by the subsequent heating with methylenation. (b) J. Martin, P. C. Watts, and F. Johnson, *Chem. Commun.*, 27 (1970); (c) P. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 500 (1973).

(14) Vernomenin (**13**) a congener of **1**, is largely absent (probably below 10%) owing to selective lactonization.



13

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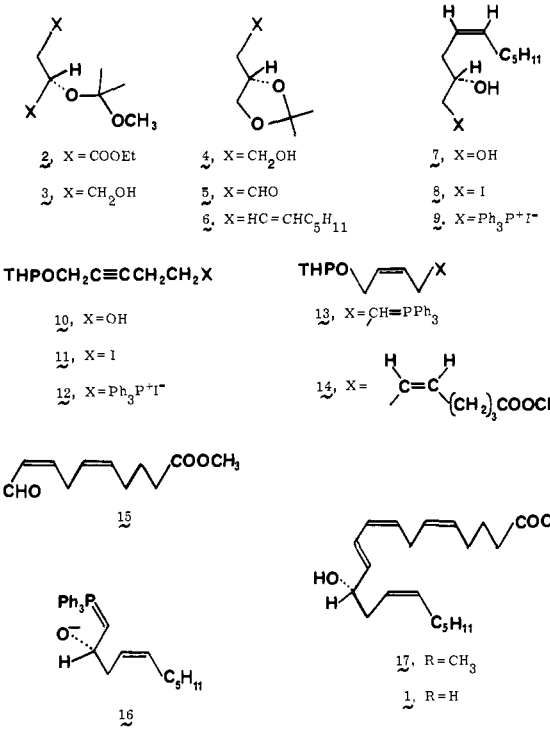
Received November 14, 1977

Total Synthesis of (*S*)-12-Hydroxy-5,8,14-*cis*,-10-*trans*-eicosatetraenoic Acid (Samuelsson's HETE)

Sir:

The title substance (**1**), commonly referred to by the discoverers' abbreviation HETE,[1,2] is a biologically significant human metabolite of arachidonic acid. Although very little is known at present concerning the biological role(s) of HETE in cell function there can be little doubt that crucial findings will emerge from future studies of this compound and its immediate precursor, the corresponding hydroperoxide. Since the biosynthesis of these substances from arachidonic acid is not inhibited by aspirin or indomethacin,[1] in contrast to the prostaglandin endoperoxides PGG_2 and PGH_2, the formation of HETE is expected to be especially interesting in the case of human subjects receiving such medication. It is also noteworthy that very high levels of HETE have been observed in epidermal tissue of humans affected by the serious skin disease psoriasis.[3] For these reasons and also because of the difficulty of obtaining material from natural sources in greater than submilligram quantities, we have developed the chemical synthesis of HETE described herein. The synthesis leads directly to the natural antipode without the need for resolution.

Reaction of the diethyl ester of (*S*-(−)-malic acid (natural form) with 2-methoxypropene[4] under catalysis by a trace of phosphorous oxychloride[5] at 23 °C for 1 h afforded the protected ester **2**[6] (100%) which underwent reduction to **3** ($LiAlH_4$ in THF, reflux, 5 h, 79%) and cyclization (BF_3·Et_2O in ether at 23 °C for 2 h) to give the 1,2-acetonide of 1,2,4-butanetriol **4**[7] (86%), $[\alpha]^{25}_D$ −1.86° (*c* 1.6, CH_3OH). Collins oxidation[7] of **4** produced the aldehyde **5** which was transformed into the cis olefin **6** $[\alpha]^{20}_D$ +23.8° (*c* 1.8, $CHCl_3$), by reaction with 1-hexylidenetriphenylphosphorane in THF (30 min at −78 °C, 30 min at 0 °C, and 3 h at 25 °C)[7] (68% overall yield from **4**). The diol **7** (from **6** and 1 N hydrochloric acid in THF at 47 °C for 3 h) was converted to the primary mesitylenesulfonate (1 equiv of sulfonyl chloride in ether–pyridine at −20 °C for 1 h and 0 °C for 32 h), and thence to the iodo alcohol **8** (96%) with sodium iodide in acetone in darkness at 25 °C for 70 h, and finally to the phosphonium iodide **9** (triphenylphosphine in benzene at 40 °C for 5 days in darkness, 86%).



A second component for the convergent synthesis of **1**, the aldehyde **15**, was prepared as follows. 5-Tetrahydropyranyloxy-3-pentyn-1-ol (**10**)[8] was converted via sequential reaction with *p*-toluenesulfonyl chloride–pyridine and sodium iodide in acetone to the iodide **11** (90%) and thence with 3 equiv of triphenylphosphine in acetonitrile at 25 °C for 96 h (in the presence of precipitated calcium carbonate) into the acetylenic phosphonium salt **12** (70%). Hydrogenation of **12** over palladium/calcium carbonate afforded the corresponding cis ethylenic phosphonium salt (97%) which upon reaction with 1 equiv of *n*-butyllithium in THF (to generate ylide **13**) and further treatment with methyl 4-formylbutyrate[9] produced the cis,cis diene **14** (72%). Cleavage of the tetrahydropyranyl group in **14** (methanol containing *p*-toluenesulfonic acid, 1 h at 25 °C, 94%) and oxidation of the resulting alcohol with excess activated manganese dioxide[10] in ether led cleanly to the easily isomerizable cis,cis aldehyde **15** which was used *immediately* in the final coupling step because of its lability.[11]

The coupling of the aldehyde **15** and the phosphonium reagent **9** was effected via the β-oxido ylide derived from the latter.[7,12] Reaction of **9** (rigorously dried by repeated azeotropic distillation of solvent from a toluene–THF solution) with 2 equiv of methyllithium in THF solution at −78 °C for 5 min and −25 °C for 30 min afforded the deep red oxido ylide **16.** The solution was diluted with 10 vol of toluene, cooled to −78 °C and treated with the aldehyde **15** at that temperature for 5 min and at −30 °C for 1 min. Hexamethylphosphoric amide (4 equiv) was added to accelerate elimination of triphenylphosphine oxide and the reaction mixture was allowed to warm over 2 h from −30 to −10 °C. Extractive isolation and chromatography on silica gel (petroleum ether–ether for development) afforded as the major reaction products the methyl ester **17** and triphenylphosphine oxide. The structure of **17** was completely corroborated by spectral data, especially important being the ^1H NMR spin-decoupled spectra which showed a single trans double bond between carbons 10 and 11, and the UV spectrum[1] (found, λ_{max} 237 nm (ϵ 32 800)). The ^1H NMR spectra of synthetic **17** and the methyl ester (CH_2N_2) of naturally derived HETE were identical, as were the mass spectra[13]

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