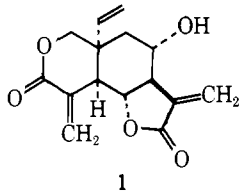
Total Synthesis of (±)-Vernolepin and (±)-Vernomenin

Sir:

Vernolepin (**1**)[1] and vernomenin (**2**),[1] highly functionalized elemanolide dilactones, are the major constituents of *Vernonia hymenolepis*. Vernolepin, the major active principle, exhibits inhibitory activity against the Walker intramuscular carcinosarcoma 256 in rats at 12 mg/kg. We wish to record in this communication the total synthesis of (±)-vernolepin (**1**) and (±)-vernomenin (**2**).



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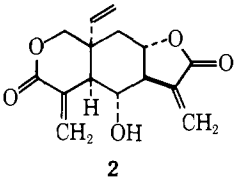

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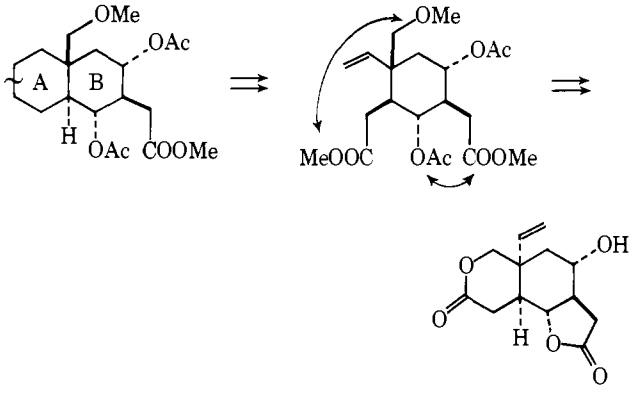
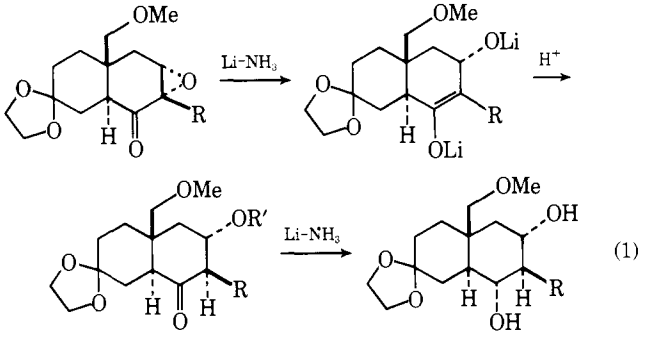
Previous work[2] in our laboratory, which established the feasibility of bis-α-methylenation of dilactone systems, suggested the approach outlined in Scheme I which requires

Scheme I



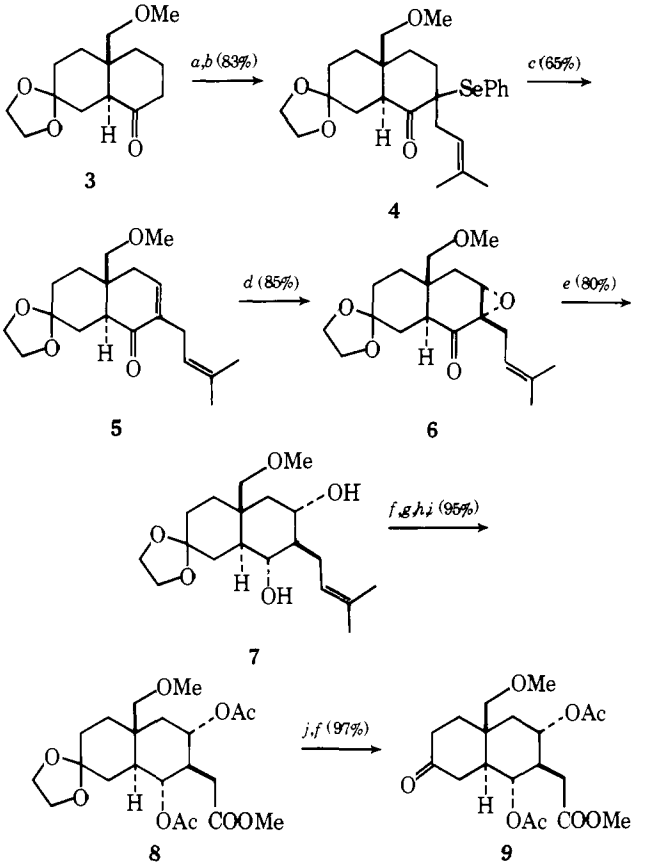
construction of an AB-*trans*-decalin derivative with all five chiral centers intact, cleavage of ring A, and bislactonization. In order to realize the synthetic scheme, we set out to prepare the key intermediate decalone, **9** (Chart I). Our approach called for the reduction (lithium–liquid ammonia) of an appropriately substituted epoxy ketone (eq 1) in the presence of a proton source (ammonium chloride).[3] Of prime importance to the success of such a reaction is *α-protonation* of the regiospecifically generated enolate followed by reduction (lithium–ammonia) of the resultant keto function before elimination of the intermediate aldol. We now detail the synthesis of vernolepin and vernomenin.



(1)

Kinetic enolate formation of the *trans*-decalone, **3**[4,5] (mp 59°), followed by trapping with phenylselenenyl chloride[6] provided a keto selenide which was treated with base and alkylated with prenyl bromide, affording an 83% yield of crystalline selenide **4,** mp 157–158°. Selenoxide formation

Chart I. The Synthesis of *trans*-Decalone **9**

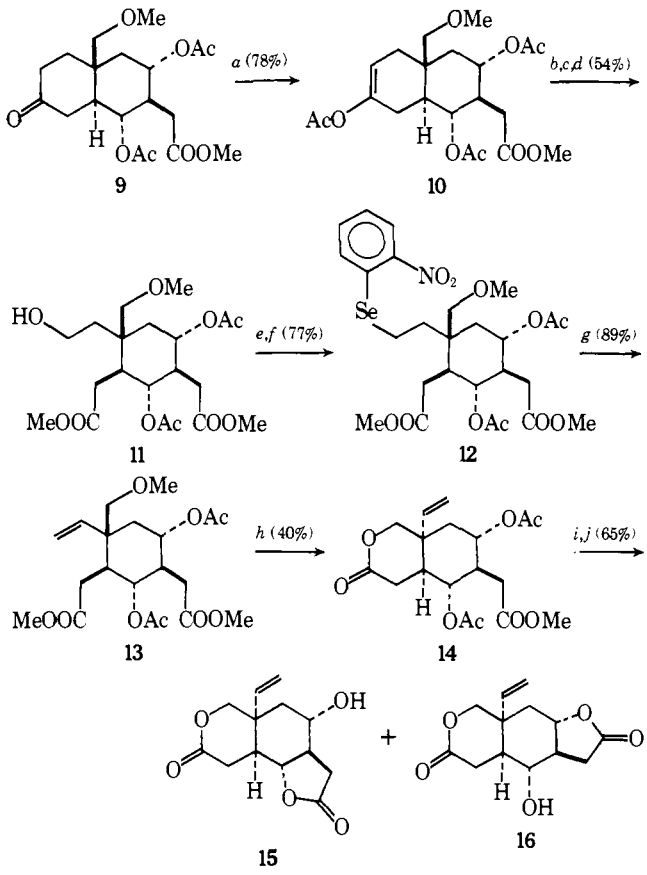


[a] LDA, THF (−78°); PhSeCl–THF (−78°)/1 h. [b] LDA, THF–HMPA (9:1), 0°; prenyl bromide, room temp, 20 h. [c] 30% H_2O_2, THF, 0° (30 min) → room temp (1 h). [d] *t*-BuOOH (10 equiv), triton B (2.4 equiv, 40% in MeOH), THF, room temp, 20 h. [e] Li, NH_4Cl, NH_3–THF, −33°, 20 min. [f] Ac_2O, Py, room temp. [g] O_3, CH_2Cl_2 (−78°). [h] Jones reagent. [i] CH_2N_2, Et_2O. [j] 5% HCl–THF (1:2), room temp, 24 h.

accompanied by facile elimination of phenylselenenic acid gave a 65% isolated, chromatographically pure yield of endocyclic enone **5,** mp 90.5–91.0°. It should be noted that <20% of the exocyclic dienone was produced. Epoxidation of enone **5** was smoothly carried out with *tert*-butyl hydroperoxide in tetrahydrofuran containing triton B. None of the β-epoxide could be detected. Attempts to prepare **6** by the more conventional method (basic hydrogen peroxide) led to none of the desired α-epoxide. Treatment of epoxy ketone **6** with a large excess of lithium–ammonium chloride (ca. 1:1) in liquid ammonia–tetrahydrofuran (ca. 1:1) at −33° for 20 min[7] afforded the dihydroxy decalin **7** (80%) which was directly converted to its diacetate. Straightforward cleavage of the prenyl double bond and hydrolysis of the ketal provided the key intermediate **9** (mp 127–128°) in 91% overall yield from **7**.

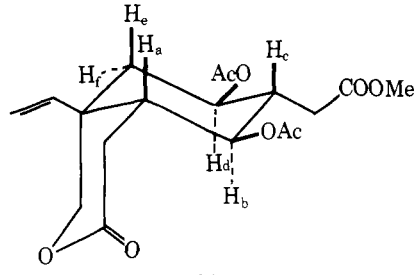
Having assembled all the asymmetric carbon atoms, we focused our attention on the next stage of the synthetic scheme which requires the selective cleavage of the C-2, C-3 bond of ring A with formation of the angular vinyl substituent and the carboxylic acid function at C-3. Enolacetylation of **9** afforded exclusively (78%) the crystalline Δ^2-enol acetate **10,** mp 133–134°. Ozonolysis of compound **10** followed by treatment with sodium borohydride and ethereal diazomethane provided the hydroxyethyl compound **11** which was smoothly converted into the desired olefinic cyclohexane derivative **13** via the alkyl *o*-nitrophenylselenide **12**[8] (Chart II). Cleavage of the methyl ether, accomplished with boron tribromide in methylene chloride at −12°, was

Chart II. Synthesis of Bisnorvernolepin and Bisnorvernomenin



[a] Isopropenyl acetate, TsOH, reflux, 9 h. [b] O_3, CH_2Cl_2–MeOH (1:1), −78°. [c] $NaBH_4$, −78°. [d] CH_2N_2, Et_2O. [e] MsCl, Py, 5°, 15 h. [f] o-$O_2NC_6H_4SeCN$, BH_4^-, DMF, room temp, 20 h. [g] 50% H_2O_2, THF, 24 h, room temp. [h] BBr_3, CH_2Cl_2, −78° (30 min) → −12° (4 h). [i] K_2CO_3, MeOH, 3 h, room temp. [j] TsOH, C_6H_6, reflux, 2 h.

accompanied by simultaneous lactonization to the bicyclic lactone **14**, mp 127–128°. Examination of the 250-MHz NMR spectrum of lactone **14** in carbon tetrachloride easily



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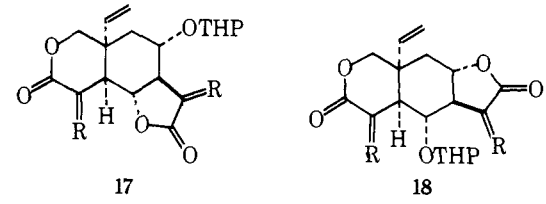
confirmed the assigned structure: δ 5.12 (triplet, 1 H, J_{ab} = J_{bc} = 11 Hz) and 4.94 (triplet of doublets, 1 H, J_{cd} = J_{de} = 11 Hz, J_{df} = 4.5 Hz). Acetate hydrolysis (77%) followed by lactonization (83%) provided a 2.5:1 mixture of bisnorvernolepin (**15**) and bisnorvernomenin (**16**) which, without separation, were converted to their respective tetrahydropyranyl ethers.

Bis-α-hydroxymethylation of the tetrahydropyranyl ethers of **15** and **16** was performed by generation of their respective dilactone enolates with lithium diisopropylamide in tetrahydrofuran containing 10% hexamethylphosphoramide followed by addition of formaldehyde as described previously.[9] Mesylation of the crude adducts **17** and **18** (R = H, CH_2OH) followed by β-elimination employing 1,5-diazabicyclo[5.4.0]undec-5-ene in benzene at room temperature gave **17** and **18** (R = $=CH_2$) in 16% overall yield.



Hydrolysis (60% aqueous acetic acid, 3 h, 45°) of the tetrahydropyranyl ethers afforded (71%) crude vernolepin (**1**) and vernomenin (**2**) as a mixture (ca. 3:1). Vernolepin and vernomenin were cleanly separated by preparative layer chromatography on 0.25-mm silica gel plates (one elution with chloroform–acetone (3:1)). (±)-Vernolepin, mp 210–211°, was identical with a sample of natural vernolepin,[10] mp 181–182°, by thin layer chromatographic and spectral comparisons. (±)-Vernomenin, mp 186–188°, was identical according to spectral comparisons with spectra kindly provided by Professor S. M. Kupchan.

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References and Notes

(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); S. M. Kupchan, R. J. Hemingway, D. Werner, and A. Karim, *J. Org. Chem.*, **34**, 3903 (1969).
(2) P. A. Grieco, J. A. Noguez, and Y. Masaki, *Tetrhedron Lett.*, 4213 (1975), and references cited therein.
(3) Cf. D. H. R. Barton, R. H. Hesse, M. M. Pechet, and E. Rizzardo, *J. Am. Chem. Soc.*, **95**, 2748 (1973).
(4) Compound **3** was prepared from its corresponding cis isomer by equilibration with sodium methoxide in methanol. The preparation of the cis isomer is described in ref 2.
(5) All intermediates were characterized by ir and NMR (60 and 250 MHz) spectroscopy and the spectral data are fully consistent with the structures assigned. All intermediates gave satisfactory combustion analyses or exact mass data. Yields reported are for chromatographically pure substances unless indicated otherwise.
(6) For a recent review of selenium chemistry see K. B. Sharpless, K. M. Gordon, R. F. Lauer, D. W. Patrick, S. P. Singer, and M. W. Young, *Chem. Scr.*, in press.
(7) This reaction was developed in our laboratory by Dr. T. Oguri. Complete details concerning a variety of α-substituted epoxy ketones will be reported in due course.
(8) K. B. Sharpless and M. W. Young, *J. Org. Chem.*, **40**, 947 (1975); P. A. Grieco, Y. Masaki, and D. Boxler, *J. Am. Chem. Soc.*, **97**, 1597 (1975).
(9) P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1317 (1972).
(10) We are indebted to Professor S. M. Kupchan (University of Virginia) for providing us with a sample of natural vernolepin.
(11) Fellow of the Alfred P. Sloan Foundation, 1974–1976.
(12) Andrew Mellon Predoctoral Fellow.

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Reaction Rate Difference in the Laser Excitation of Different Vibrational Modes of CF_2ClCF_2Cl

Sir:

When a molecular vibrational mode of a gaseous system is excited by a laser tuned to the frequency of that mode, intermolecular collisions and intramolecular mode coupling act to transfer the excitation to other vibrational and translational modes. If the tranfer rates are sufficiently rapid,