Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; O, 15.17. Found: C, 75.91; H, 8.74; O, 15.07.

(±)-*trans*-3-Hydroxy-1-*n*-pentyl-6,6,9-trimethyl-6a,7,10,10a-tetrahydrodibenzo[*b,d*]pyran (4b). A solution of 2.48 g of ketone **1c** in 50 ml of ether was added dropwise to a refluxing solution of 3.2 M methylmagnesium bromide in 50 ml of ether and the heating continued for 18 h. The mixture was poured onto ice and acidified with 0.5 N hydrochloric acid. The aqueous layer was extracted with ether and the combined organic phase and extracts washed with water and saturated brine solution, dried over anhydrous sodium sulfate, and evaporated. Crystallization of the residue from cyclohexane–acetone gave 980 mg of solid alcohol. Chromatography of the mother liquor, 1.6 g, on 40 g of Florisil and elution with 10:1 benzene–ether yielded an additional 380 mg of alcohol. A mixture of 380 mg of the latter and 120 mg of *p*-toluenesulfonic acid in 50 ml of benzene with the presence of a Dean-Stark water separator was refluxed for 2 h. It then was poured into a 5% sodium bicarbonate solution and separated. The aqueous layer was washed with ether and the combined organic solutions dried and evaporated. This gave 200 mg of 10:1 (±)-Δ^8-*abn*-THC (**4b**) and an isomer: *m/e* 314; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3, J = 8 Hz, pentyl Me), 1.04 (s, 3, 6α-Me), 1.34 (s, 3, 6β-Me), 1.66 (s, 3, 9-Me), 0.8–2.0 (m, 12, methylenes, methines), 5.45 (m, 1, olefinic H), 6.14, 6.27 (t, 1, J = 3 Hz, aromatic H); spectra identical with those of **4b** obtained by the condensation of citral with olivetol (vide infra).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.97; H, 9.39.

A solution of 2.80 g of boron trifluoride etherate in 10 ml of dry benzene was added slowly with stirring to a solution of 3.60 g of olivetol (5-*n*-pentylresorcinol) and 3.60 g of citral in 20 ml of benzene and the mixture stirred at room temperature under nitrogen for 18 h. Upon the addition of water it was extracted with ether and the extract washed successively with 2 N sodium hydroxide and with water and dried over anhydrous sodium sulfate. Evaporation of the ether yielded 5.87 g of an orange oil whose GPC analysis revealed ten main peaks including one for unreacted citral. Chromatography of the oil on 250 g of Florisil and elution with 750 ml of hexane, 750 ml of 20:1 hexane–ether, and 1.8 l. of 9:1 hexane–ether led in the middle fractions of the last solvent pair to 480 mg (7% yield) of (±)-Δ^8-*abn*-THC (**4b**) of at least 73% purity (by GPC, the major impurity being (±)-*trans*-Δ^8-THC), spectra and GPC retention time identical with those of **4b** above.

Registry No.—**1a,** 52195-11-6; **1b,** 60761-08-2; **1c,** 60734-16-9; **2,** 60761-09-3; **3,** 1972-08-3; **4a,** 5957-75-5; **4b,** 41408-34-8; **5,** 6087-73-6; **6a,** 16849-52-8; **6b,** 60705-74-0; **6c,** 60705-75-1; **7,** 60705-76-2; **14a,** 108-95-2; **14b,** 95-48-7; **14c,** 88-18-6; **14d,** 90-05-1; **15a,** 108-39-4; **15b,** 150-19-6; **16a,** 106-44-5; **16b,** 150-76-5; **17a,** 576-26-1; **17b,** 128-39-2; **18,** 100-66-3; benzyl bromide, 100-39-0; ethyl formate, 109-94-4; methyl vinyl ketone, 78-94-4.

References and Notes

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(7) The authors are indebted to Dr. R. Mechoulam for a sample of this substance.
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(15) G. E. Maciel and J. J. Natterstad, *J. Chem. Phys.* **42,** 2752 (1965).
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(19) Thus, for example, the H(2) and H(4) shifts of 6.17 and 6.30 ppm, respectively, for a deuteriochloroform solution of **4b** are altered to 6.72 and 6.80 ppm, respectively, in pentadeuteriopyridine solution. The perturbation of two hydrogen shifts is indicative of the presence of two methines ortho to the phenolic hydroxy group and thus distinguishes the structure pattern of **4b** from that of **4a.**
(20) The spectrum of the phenoxide ion determined in ethanol/sodium ethoxide solution has been reported previously.[21] The chemical shifts found in the present study show exact agreement for the ipso carbon resonance and minor deviations ($\leq$1 ppm) for the ortho and meta carbon resonances. The para carbon resonance observed here appears 2.5 ppm upfield from that given in the earlier study.
(21) G. E. Maciel and R. V. James, *J. Am. Chem. Soc.,* **86,** 3893 (1964).
(22) A ^{1}H NMR spectroscopic method that distinguishes positional isomers utilizing aromatic solvent shifts (cf. ref 18 and 19) has appeared recently [A. Arnone, R. Bernardi, L. Merlini and S. Servi, *Gazz.Chim. Ital.,* **105,** 1127 (1975)].

(±)-Deoxyvernolepin. A Cytotoxic Vernolepin Prototype

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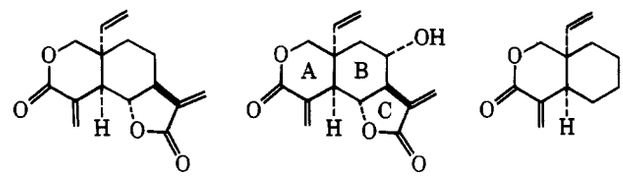
Received July 7, 1976

The totally synthetic *trans*-decalone **4** possessing four chiral centers has been converted into (±)-deoxyvernolepin (**1**) via a sequence of transformations involving (a) cleavage of ring A, (b) introduction of the angular vinyl substituent by elimination of the *o*-nitrophenyl selenoxide derived from selenide **28,** and (c) construction of the two α-methylene units via bis-α-hydroxymethylation of bisnordeoxyvernolepin followed by β-elimination. (±)-Deoxyvernolepin was tested as an inhibitor of the growth of CCRF-CEM human lymphoblastic leukemia cells in culture. Deoxyvernolepin was found to be at least an order of magnitude more potent than natural vernolepin.

We wish to disclose the details of the investigation which led to the total synthesis of deoxyvernolepin (**1**)[3] during the course of a program which had as its ultimate goal the total synthesis of vernolepin (**2**).[4] Deoxyvernolepin possesses both the ring A α-methylene-δ-valerolactone unit and the ring C α-methylene-γ-butyrolactone unit of vernolepin while lacking only the C-8 hydroxyl. The synthesis of deoxyvernolepin established the feasibility of bis-α-methylenation, indicating

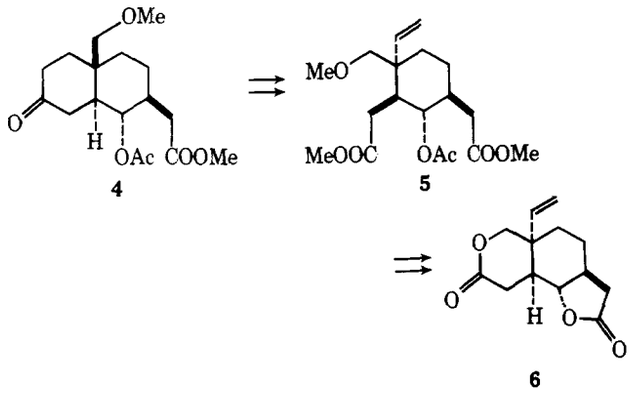


1 2 3

that such a process could be postponed until the final stages of a synthesis, and provided the needed synthetic methodology which set the stage for the successful completion of the total synthesis of vernolepin.[5] The key step in the synthetic route to **1** involves bis-α-hydroxymethylation of a dilactone enolate. In addition to the synthesis of **1** we report that the bifunctional α-methylene lactone system of deoxyvernolepin exhibits cytotoxicity against tumor cells in vitro. The studies revealed that *deoxyvernolepin is at least an order of magnitude more potent than natural vernolepin (vide infra).*

Our initial approach to deoxyvernolepin (Scheme I) centered around (a) construction of the *trans*-decalone **4** with all four chiral centers established, (b) cleavage of ring A with formation of the vinylcyclohexane derivative **5**, and (c) bislactonization of **5** to the tricyclic dilactone **6** (bisnordeoxyvernolepin) which would set the stage for bis-α-methylenation[6] employing the α-hydroxymethylation[7a] procedure introduced by us some years ago in conjunction with the synthesis of the vernolepin model **3**.[7b]

Scheme I



The preparation of decalone **4** (Scheme I) is outlined in Chart I. Hydroboration of the methyl ether of octalin **7** gave, in addition to the expected[8] β-oriented alcohol **12**, appreciable amounts (ca. 40%) of the tertiary alcohol[9] **12′** which upon treatment with 5% HCl in THF could be converted to octalone **13** and recycled. Collins oxidation[12] of the desired alcohol **12** proceeded smoothly in 96% yield to the *cis*-decalone **8**. That ketone **8** possessed the cis arrangement was demonstrated by its conversion to the thermodynamically more stable trans isomer **8′** via equilibration with sodium methoxide in refluxing methanol. At equilibrium the ratio of trans to cis was approximately 7:3. Introduction of the acetic acid side chain at C-7 (steroid numbering) in compound **8** was accomplished in a straightforward manner: (a) carbomethoxylation with formation of β-keto ester **9**, (b) alkylation of the sodium enolate of **9** with methyl bromoacetate, and (c) decarboxylation using barium hydroxide. A similar sequence of reactions for the introduction of an acetic acid unit adjacent to a carbonyl was recently employed in a total synthesis of (±)-isoalantolactone.[13] Reduction (sodium/2-propanol) and esterification of keto acid **10** generated the crystalline hydroxy ester **11**, mp 94–95 °C. During the course of the above chemical transformations equilibration at C-5 takes place (vide infra). Acetylation and deketalization of **11** produced the desired decalone **4**, mp 120 °C. The 250-MHz NMR spectrum of compound **4** exhibited a triplet centered at δ 4.75 for H_b with $J_{ab} = J_{bc} =$ 11 Hz, indicating the required axial relationship between the three protons. Further support for the stereochemical assignment of structure **4** came from NOE measurements. Irradiation of the AB quartet centered at δ 3.53 ($-CH_2OMe$) resulted in a 14% enhancement of the H_b signal.

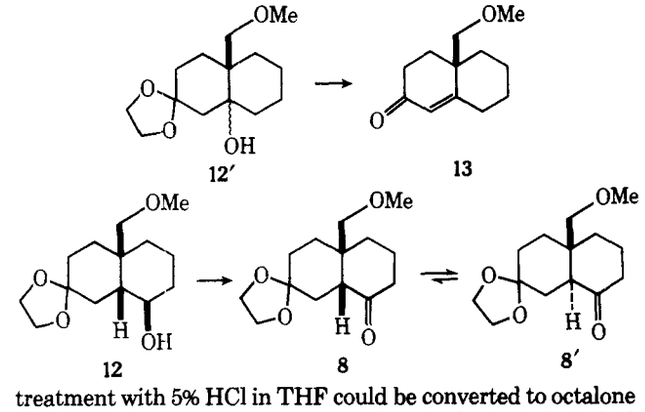
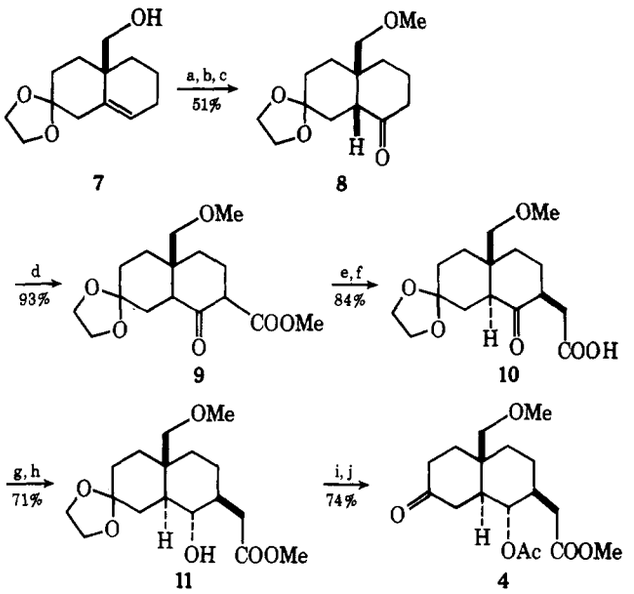
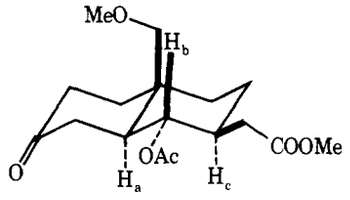


Chart I. Synthesis of the Key Intermediate *trans*-Decalone 4

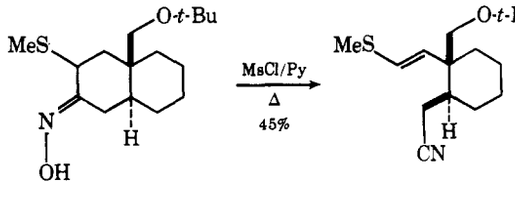


a, NaH, MeI, THF; b, BH_3·THF/OH^-, H_2O_2; c, CrO_3·2Py, CH_2Cl_2; d, NaH, $(MeO)_2CO$, dioxane; e, NaH, $BrCH_2COOMe$, dioxane; f, $Ba(OH)_2$·$8H_2O$, reflux; g, Na, *i*-PrOH; h, CH_2N_2, Et_2O; i, Ac_2O, Py; j, 5% HCl, THF



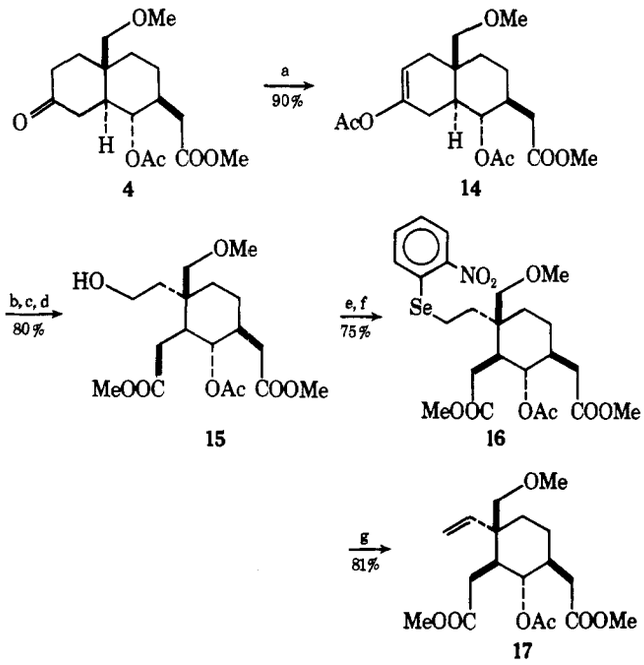
4

Having completed the synthesis of decalone **4**, which established the stereochemical requirements about the key asymmetric carbon atoms C-5, C-6, C-7, and C-10, attention was turned to the transformation of **4** to the tricyclic dilactone **6** (Scheme I). Specific cleavage of the C-2, C-3 carbon–carbon bond of the decalone derivative **4** with formation of an olefin between carbon atoms 1 and 2, and an ester moiety at C-3, so as to produce the highly functionalized cyclohexane derivative **5**, would upon bislactonization provide the desired tricyclic dilactone ring system. Having previously employed in the synthesis of **3**[7b] the second-order Beckman fragmentation of methylthio oximes[14] and obtained only moderate yields of cleavage product (eq 1), we turned our attention to the



(1)

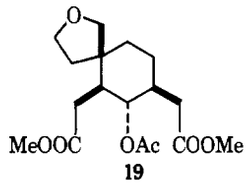
Chart II. Conversion of Decalone 4 to the Vinylcyclohexane Derivative 17



a, CH_2=C(OAc)CH_3, TsOH; b, O_3, MeOH–CH_2Cl_2 (2:3); c, BH_4^-, OH^-; d, CH_2N_2, Et_2O; e, MsCl, Py, 0°C; f, *o*-$O_2NC_6H_4SeCN$,[22] BH_4^-, DMF, room temperature; g, 50% H_2O_2, THF

cleavage of the $\Delta^{2,3}$ enol acetate **14** derived from **4** (Chart II). Compound **4** upon enol acetylation with isopropenyl acetate under thermodynamically controlled conditions[15] resulted in exclusive formation of the crystalline $\Delta^{2,3}$ enol acetate **14**. It was to our advantage that none of the $\Delta^{3,4}$ isomer was formed.[16] it appears that the α-acetoxy function at C-6 interacts unfavorably with the C-4 proton of the $\Delta^{3,4}$ isomer. We have observed such effects with other α substituents at C-6.

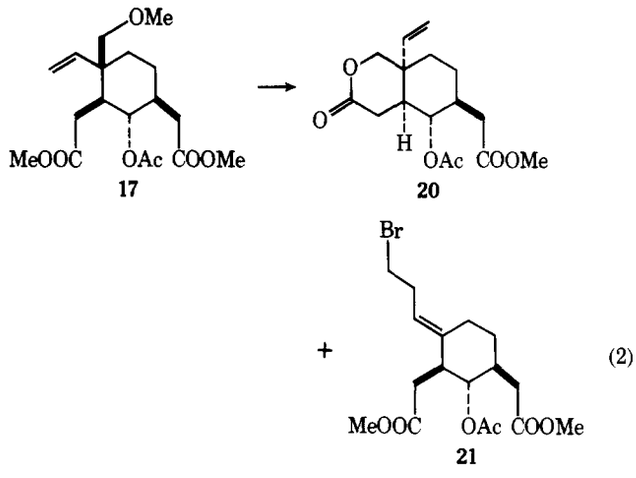
Ozonolysis of **14** followed by a reductive workup and esterification resulted in an excellent yield of the cyclohexane derivative **15** possessing the all-trans arrangement of substituents. The hydroxyethyl side chain in compound **15** is potentially convertible into the required angular vinyl substituent employing the facile elimination of alkyl *o*-nitrophenylselenoxides recently introduced by Sharpless.[19] During the conversion of **15** to the *o*-nitrophenyl selenide **16** via the corresponding mesylate (**18**),[20–22] there was observed formation of the tetrahydrofuran derivative **19** in yields ranging from 0 to 11% (see Experimental Section). We believe that the



19

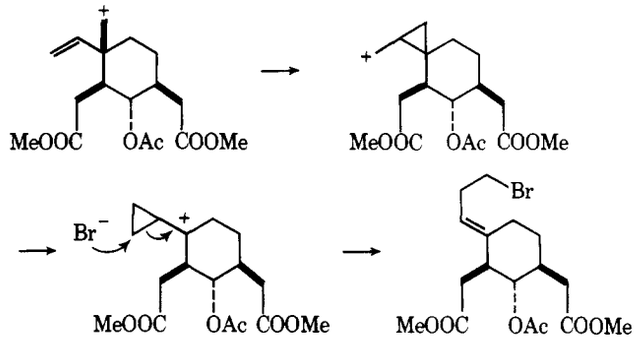
formation of **19** takes place via assisted displacement of the mesylate function followed by cleavage of the O–CH_3 bond by a nucleophile (presumably cyanide). Elimination of the corresponding *o*-nitrophenylselenoxide obtained by oxidation of selenide **16** established the angular vinyl group which was evident by NMR and IR analysis.

Attempted cleavage of the methyl ether **17** with boron tribromide (−78 °C) resulted in formation of lactone **20** in yields of 4–10%. The major product of the reaction (ca. 80%) was the homoallylic bromide **21** which apparently arises from cleavage of the "wrong" carbon–oxygen bond with formation of a homoallyl cation. A mechanism for the observed rearrangement



(2)

Scheme II



(**17** → **21**) is illustrated in Scheme II.[23] This result is surprising in view of previous work in our laboratory[17] in which we demonstrated that compound **22** undergoes smooth demethylation with boron tribromide providing in excellent yield the crystalline δ-lactone **23**. During the total synthesis of vernolepin we observed[5] that the more substituted methyl ether **24** similarly underwent smooth cleavage of the methyl ether with concomitant lactonization. No product derived from cleavage of the "wrong" carbon–oxygen bond was detected. It was indeed surprising in the case of **24** to find that the product was not exclusively the desired lactone **25**, but roughly an equal mixture of the desired compound **25** and a bromine-containing compound **26** in which the C-6 acetate function was replaced by a bromine atom with retention of

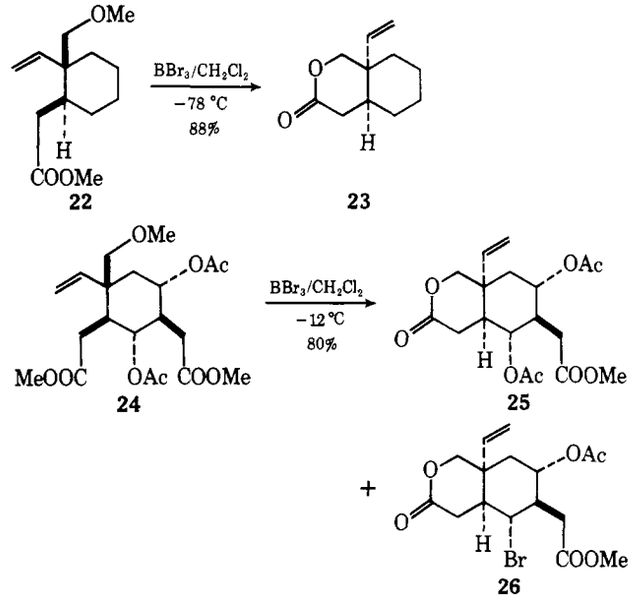
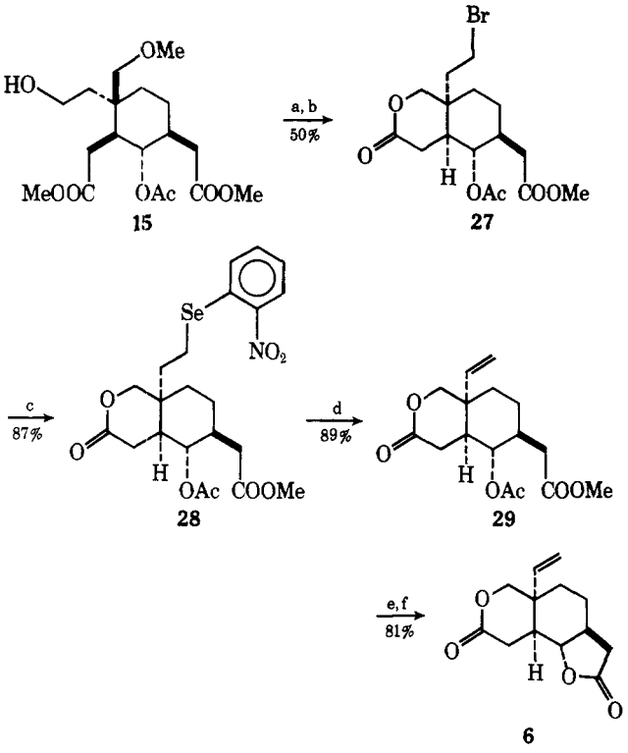


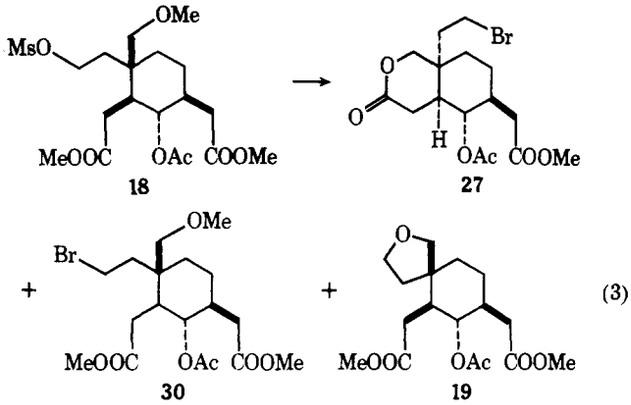
Chart III. Synthesis of Bisnordeoxyvernolepin (6)



a, MsCl, Py, 0°C; b, BBr_3, CH_2Cl_2, −78°C; c, *o*-$O_2NC_6H_4$-$SeCN$,[20,22] BH_4^-, DMF; d, 50% H_2O_2, THF; e, K_2CO_3, MeOH; f, TsOH, C_6H_6, reflux

configuration.[24] At present we have no reasonable explanation for the formation of the homoallylic bromide **21**.

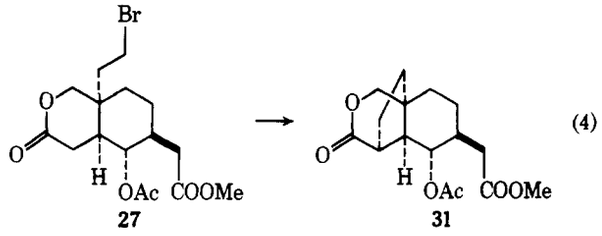
It therefore became apparent after many unsuccessful attempts at cleavage of the methyl ether **17** that any successful synthesis of deoxyvernolepin would require cleavage of the methyl ether prior to generation of the angular vinyl substituent (Chart III). Treatment of the mesylate **18** derived from the hydroxyethyl compound **15** with boron tribromide (eq 3)



(3)

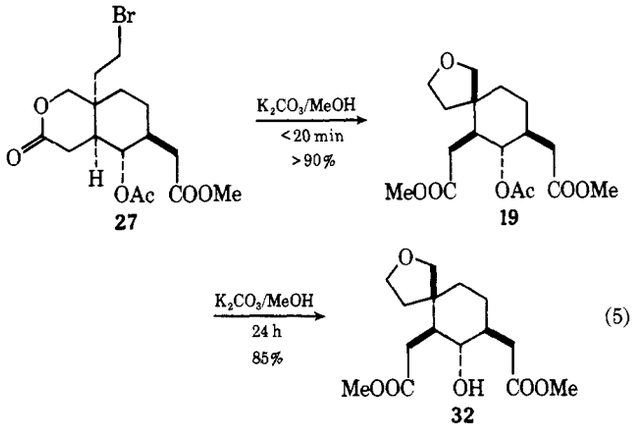
gave, in addition to the desired bromo lactone **27** (ca. 50%), the bromo ether **30** (13%) along with a trace of the tetrahydrofuran derivative **19**. In this particular reaction lactone closure competes with tetrahydrofuran ring formation.

Having thus succeeded in preparing a potential vinyl precursor we focused our attention on dehydrobromination of compound **27** with 1,5-diazabicyclo[5.4.0]undec-5-ene in benzene at room temperature. The reaction proceeded smoothly and in excellent yield, but not to the expected olefinic compound **29** (eq 4). There was obtained a tricyclic compound which has been tentatively assigned structure **31** on the basis of NMR, IR, and high-resolution mass spectra data (see Experimental Section).



(4)

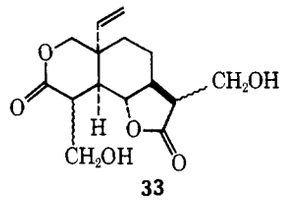
In an alternate approach to convert **27** to bisnordeoxyvernolepin (**6**), we attempted to first cleave the C-6 acetate function of **27** followed by γ-lactone formation. Treatment of compound **27** with anhydrous potassium carbonate in methanol under standard conditions for cleavage of an acetate resulted in a very facile reaction (eq 5) with formation of a new



(5)

compound which was less polar than the starting material. The compound was identified as the tetrahydrofuran derivative **19** on the basis of NMR, IR, MS, and TLC comparisons with a sample of **19** prepared earlier (eq 3). After prolonged treatment (20 h) with potassium carbonate in methanol, the hindered acetate function of **19** was cleaved.[26] In order to circumvent the problems associated with the above approaches (eq 4 and 5), we prepared the *o*-nitrophenyl selenide **28** from the bromo lactone **27** under conditions employed earlier for the preparation of **16**. Oxidation of **28** followed by elimination of the resultant selenoxide provided cleanly the olefinic compound **29** which was smoothly converted in the standard manner to the tricyclic dilactone **6**.

With bisnordeoxyvernolepin in hand, utilization and modification of the α-hydroxymethylation procedure[7a] paved the way for the completion of the total synthesis of deoxyvernolepin (**1**). Bis-α-hydroxymethylation of dilactone **6** in tetrahydrofuran containing 10% hexamethylphosphoramide gave the bis-α-hydroxymethylated adduct **33**. The use of hexamethylphosphoramide was essential in order to solubilize



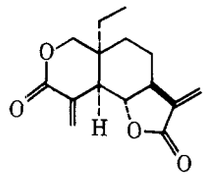
the dilactone enolate. In the absence of hexamethylphosphoramide only very poor yields of adduct **33** could be realized. Treatment of the mesylate derived from **33** with pyridine at elevated temperatures afforded crystalline deoxyvernolepin (**1**), mp 169–170 °C.

The synthetic deoxyvernolepin prepared above was tested,[27] along with natural vernolepin[28] and dihydrodeoxyvernolepin (**34**),[29] as inhibitors of the growth of CCRF-CEM human lymphoblastic leukemia cells in culture.[30] These cells have been characterized[31] as having an absolute nutritional

Table I. Growth Inhibition of CCRF-CEM Human Lymphoblastic Leukemia Cells in Culture by Unsaturated Lactones[27]

Compd	ID_{50}, μM
Dihydrodeoxyvernolepin (34)[29]	0.034
Deoxyvernolepin (1)	0.034
Vernolepin (2)[28]	0.43

requirement for exogenous L-cysteine. The use of CCRF-CEM cells to assay the growth-inhibitory properties of deoxyvernolepin and vernolepin was based on the expectation that these bis-α-methylene lactone systems would function as Michael acceptors[32] and thus scavenge cysteine.[33] The data in Table I indicate that deoxyvernolepin and dihydrodeoxyvernolepin are more active than vernolepin by at least one order of magnitude.



34

Experimental Section[34]

2,2-Ethylenedioxy-10-methoxymethyl-Δ⁸-octalin. To a suspension of 28.8 g (0.60 mol) of 50% sodium hydride (washed with hexane prior to use) in 650 ml of dry tetrahydrofuran at 0 °C was added dropwise a solution of 2,2-ethylendioxy-10-hydroxymethyl-Δ⁸-octalin (7,[35] 100 g, 0.45 mol) in 220 ml of dry tetrahydrofuran. The reaction mixture was warmed to room temperature and stirring was continued for 1 h after which time the reaction mixture was cooled to 0 °C. Methyl iodide (170 g, 1.2 mol) was added dropwise and stirring was continued after addition was complete for 16 h (room temperature). The solvent was removed under reduced pressure on a rotary evaporator and the resulting residue was treated with water and the product isolated by ether extraction.[36] The crude product (102 g, 95%) was homogeneous by TLC analysis on silica gel (benzene/ethyl acetate, 4:1; R_f 0.67) and was used directly in the next reaction. An analytical sample was obtained by column chromatography on silica gel (hexane/ether, 7:3) followed by distillation: bp 95 °C (bath temperature) (0.45 mm); IR (film) 1660 cm^{-1} (C=C); NMR (60 MHz) (CCl_4) δ 5.35 (bs, 1 H, C=CH), 3.80 (s, 4 H, $-OCH_2CH_2O-$), 3.25 (bs, 5 H, $-CH_2OCH_3$).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.34; H, 9.20.

***cis*-2,2-Ethylenedioxy-10-methoxymethyl-8-decalone (8).** To a solution of 34.0 g (0.14 mol) of 2,2-ethylenedioxy-10-methoxymethyl-Δ⁸-octalin in 600 ml of dry tetrahydrofuran cooled to 0 °C was added dropwise 149.6 ml (0.15 mol) of a 1.02 M tetrahydrofuran solution of borane under an atmosphere of nitrogen. The reaction mixture was stirred for 6 h at room temperature, cooled to 0 °C, and then treated with 4.6 ml of water, followed by 56 ml of 3 N aqueous sodium hydroxide and 56 ml of 30% hydrogen peroxide. After stirring for an additional 6 h at room temperature, the tetrahydrofuran was removed under reduced pressure on a rotary evaporator. The product was isolated from the resulting heterogeneous mixture by extraction with ether.[36] The residue amounted to 38.0 g of an oil which was chromatographed on 1000 g of silica gel. Elution with hexane/ethyl acetate (2:1) gave 15.8 g (43%) of the tertiary alcohol 12′ [R_f 0.73 (hexane/ethyl acetate, 1:1). Elution with ethyl acetate gave 20.3 g (56%) of *cis*-2,2-ethylenedioxy-10β-methoxymethyl-8β-decalol (12) [R_f 0.38 (hexane/ethyl acetate, 1:1)] as an oil: IR (film) 3450 cm^{-1}; NMR (60 MHz) ($CDCl_3$) δ 3.98 (m, 5 H, $-OCH_2CH_2O-$, CHOH), 3.38 (bs, 5 H, $-CH_2OCH_3$).

Collins oxidation of this alcohol (17.0 g, 0.066 mol) in 95 ml of dry methylene chloride was carried out in the following manner. To a flask equipped with a mechanical stirrer containing dry methylene chloride (715 ml) and dry pyridine (62.8 g, 0.79 mol) cooled to 0 °C under nitrogen was carefully added portionwise 39.7 g (0.39 mol) of chromium trioxide. After 15 min, the reaction mixture was warmed to room temperature and stirring was continued for 45 min. The methylene chloride solution of the alcohol was added, all at once, to the vigorously stirred reaction mixture. After 20 min, the organic layer was decanted and the remaining black tar was washed with 2 × 100 ml of ether. The remaining residue was dissolved in 600 ml of 5% aqueous sodium hydroxide and washed with 4 × 200 ml of ether. The combined organic layers were washed with 5% aqueous sodium hydroxide until the solution was light yellow followed by washing with water and brine. The organic layer was dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo gave 16.1 g (96%) of 8 which was homogeneous by TLC analysis [silica gel (hexane/ethyl acetate, 3:1)], R_f 0.61: IR (film) 2950, 2875, 2825, 2800, 1705, 1481, 1458, 1431, 1390, 1360, 1310, 1290, 1230, 1200, 1170, 1100, 1030 cm^{-1}; NMR (60 MHz) (CCl_4) δ 3.88 (s, 4 H, $-OCH_2CH_2O-$), 3.30 (s, 3 H, OCH_3), 3.10 (AB q, 2 H, CH_2O). An analytical sample was prepared by distillation [110 °C (bath temperature) (0.15 mm)]. On standing, the sample crystallized, mp 59–61 °C.

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.98; H, 8.81.

Carbomethoxylation of Ketone 8. A solution of 2.66 g (10.5 mmol) of ketone 8 in 4.0 ml of dry dioxane was added dropwise over 45 min to a stirred suspension of 1.05 g (20.9 mmol) of 50% sodium hydride (washed with hexane prior to use) and 4.64 g (51.6 mmol) of dimethyl carbonate in 9.0 ml of dry dioxane heated to 80–85 °C under nitrogen. After addition of the ketone, the reaction mixture was stirred at 80–85 °C for an additional 4 h followed by cooling to room temperature (6 h). The reaction mixture was cooled to 0 °C and acidified with a slight excess of 50% aqueous acetic acid, and the solvent was evaporated under reduced pressure. The residue was diluted with water and the product isolated by ether extraction.[36] The crude product (3.45 g) was purified on 40 g of silica gel. Elution with hexane/ethyl acetate (7:3) gave 3.02 g (93%) of ketone 9 as a mixture of isomers which was used directly in the next reaction: IR (film) 1740 (m), 1705 (m), 1650 (s), 1610 cm^{-1} (s); NMR (60 MHz) (CCl_4) δ 3.85 (s, 4 H, $-OCH_2CH_2O-$), 3.70 (s, 3 H, $COOCH_3$), 3.25 (s, 3 H, OCH_3), 3.10 (AB q, 2 H, $-CH_2O-$).

***trans*-2,2-Ethylenedioxy-10β-methoxymethyl-8-oxo-7β-decalylacetic Acid (10).** To a suspension of 233 mg (4.85 mmol) of a 50% sodium hydride dispersion (washed with pentane prior to use) in 5.0 ml of dry dioxane was added dropwise 1.01 g (3.23 mmol) of keto ester 9 in 5 ml of dry dioxane. After ca. 15 min, methyl bromoacetate (1.09 g, 7.1 mmol) was added and the reaction mixture was heated at 65 °C for ca. 45 min.

The reaction mixture was cooled in an ice water bath and acidified with 50% aqueous acetic acid. The solvent was concentrated in vacuo and the product was isolated by ether extraction.[36] There was obtained 1.07 g (86%) of alkylated material which was used directly in the next reaction.

To a solution of the above keto ester (726 mg, 1.89 mmol) in 8 ml of ethanol was added a solution of $Ba(OH)_2 \cdot 8H_2O$ (2.98 g, 9.46 mmol) in 20 ml of water. The reaction mixture was refluxed for 24 h. The solvent was removed under reduced pressure. The resulting residue was diluted with water and acidified with 5% hydrochloric acid. The product was isolated by ether extraction.[36] There was obtained after removal of the solvent in vacuo 575 mg (98%) of crystalline keto acid 10: IR ($CHCl_3$) 3700–2200, 1700 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 9.86 (s, 1 H), 3.96 (s, 4 H), 3.21 (s, 5 H). Recrystallization from ether/hexane gave analytically pure β-keto acid, mp 143–144 °C.

Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.46; H, 7.66.

Methyl *trans*-2,2-Ethylenedioxy-10β-methoxymethyl-8α-hydroxy-7β-decalylacetate (11). Sodium (36 g) in small portions was added over a 1.5-h period to a refluxing solution of keto acid 10 (4.88 g, 15.6 mmol) in 340 ml of 2-propanol. After refluxing for 4 h, 50 ml of 2-propanol was added to react with the remaining sodium metal (ca. 2 h). After cooling (0 °C), the mixture was neutralized with aqueous acetic acid and the solution was concentrated in vacuo. The residue was dissolved in ether and extracted with 5% aqueous potassium carbonate solution. The aqueous layer was neutralized with acetic acid. Isolation of the product by ether extraction[36] gave 5.2 g of crude acid. An analytical sample was obtained by crystallization from acetone, mp 178–179 °C.

Anal. Calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 60.90; H, 8.18.

Esterification of the above carboxylic acid (5.2 g) with diazomethane gave, after crystallization from carbon tetrachloride/hexane, 3.1 g of pure hydroxy ester 11, mp 92–93 °C. Chromatography of the mother liquors on 10 g of silica gel [elution with hexane–ethyl acetate (7:3)] gave an additional 542 mg of pure product (total yield 71%): IR ($CHCl_3$) 3450, 2915, 2860, 2800, 1725, 1440, 1435, 1355, 1270, 1182, 1160, 1085, 1058, 1025, 990, 968, 940, 918, 880, 848, 808 cm^{-1}; NMR (60 MHz) (CCl_4) δ 3.88 (bs, 5 H, $-OCH_2CH_2O-$, CHO), 3.62 (s, 3 H,

$-COOCH_3$), 3.30 (bs, 5 H, $-CH_2OCH_3$). Recrystallization from carbon tetrachloride/hexane provided an analytically pure sample of decalol **11**, mp 94–95 °C.

Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.18; H, 8.59. Found: C, 62.01; H, 8.62.

Methyl *trans*-10β-Methoxymethyl-2-oxo-8α-acetoxy-7β-decalylacetate (4). A solution of alcohol **11** (1.5 g, 4.57 mmol) in 12 ml of dry pyridine was treated with 12 ml of acetic anhydride at room temperature. After 18 h, the solvent was removed under reduced pressure. After isolation by ether extraction,[36] the product [1.6 g (98%), IR (film) 2920, 2870, 2700, 1730, 1441, 1435, 1362, 1238, 1182, 1141, 1091, 1055, 1010, 970, 960, 925, 800, 750 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 4.76 (t, 1 H, J = 12.5 Hz), 3.97 (s, 4 H), 3.70 (s, 3 H), 3.51 (AB q, 2 H, J = 10 Hz, $\Delta\nu_{AB}$ = 13.7 Hz), 3.38 (s, 3 H), 2.14 (s, 3 H)] was deketalized in 18 ml of a 2:1 mixture of tetrahydrofuran/5% hydrochloric acid. After ca. 19 h at room temperature, the product was isolated by extraction[36] with ethyl acetate which gave 1.41 g of the crude decalone **4**. Crystallization from carbon tetrachloride/hexane gave 1.05 g (74%) of pure crystalline **4**: mp 120 °C; IR ($CHCl_3$) 3010, 2950, 2925, 2815, 1730, 1710, 1485, 1455, 1435, 1375, 1240, 1205, 1108, 1025, 975, 940 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 4.75 (t, 1 H, J = 11 Hz), 3.59 (s, 3 H), 3.53 (AB q, 2 H, J = 9 Hz, $\Delta\nu_{AB}$ = 15.6 Hz), 3.34 (s, 3 H), 2.00 (s, 3 H).

Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.31; H, 8.24.

Enolacetylation of Decalone 4. A mixture of decalone **4** (696 mg, 2.14 mmol) and 22 ml of isopropenyl acetate containing 130 mg of p-toluenesulfonic acid was refluxed (bath temperature, 96 °C) for 9 h. Upon cooling the reaction mixture, solid sodium bicarbonate was added to neutralize the acid present. The solvent was evaporated in vacuo on a rotary evaporator and the remaining residue was taken up in ether and washed with brine. The organic layer was dried (sodium sulfate) and the solvent evaporated leaving 1.07 g of crude product which crystallized on standing (780 mg, 98%). Recrystallization from ethyl acetate/hexane provided pure enol acetate, mp 120 °C: IR ($CHCl_3$) 2924, 2880, 2810, 1730, 1690, 1480, 1435, 1368, 1311, 1230, 1150, 1120, 1100, 1055, 1020, 970, 936, 905, 851 cm^{-1}; NMR (60 MHz) δ (CCl_4) 5.20 (m, 1 H), 4.80 (m, 1 H), 3.60 (s, 3 H), 3.40 (s, 2 H), 3.30 (s, 3 H), 2.03 (s, 3 H), 1.98 (s, 3 H).

Anal. Calcd for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 62.13; H, 7.69.

Ozonolysis of Enol Acetate 14. A solution of enol acetate **14** (459 mg, 1.25 mmol) in 150 ml of methylene chloride cooled to −78 °C was treated with 1 equiv of ozone. After addition of ozone, 100 ml of absolute methanol was added at −78 °C. Stirring was continued at that temperature for 15 min followed by addition of 47.4 mg (1.25 mmol) of sodium borohydride. After 15-min intervals for ca. 1 h, an equal amount of sodium borohydride was added (−78 °C). The reaction mixture was warmed to room temperature (ca. 45 min) and 2.2 ml of 1 N aqueous sodium hydroxide was added. After an additional 30 min, the solvent was removed under reduced pressure and the residue was taken up in water and washed with ether. The aqueous layer was cooled (0 °C), acidified carefully with 37% hydrochloric acid, and extracted exhaustively with ethyl acetate. The combined organic layers were evaporated to leave a solid (414 mg) which was dissolved in ether and treated (0 °C) with an ethereal solution of diazomethane. There was obtained 395 mg of crude diester which was purified on 7.0 g of silica gel. Elution with hexanes/ethyl acetate (3:2) followed by ethyl acetate gave 372 mg (80%) of pure **15**: IR ($CHCl_3$) 3450, 1730 cm^{-1}; NMR (250 MHz) δ ($CDCl_3$) 4.94 (t, 1 H, J = 10 Hz), 3.76 (m, 2 H), 3.71 (s, 6 H), 3.40 (s, 3 H), 3.38 (AB q, 2 H, J = 9 Hz, $\Delta\nu_{AB}$ = 49.2 Hz), 2.05 (s, 3 H).

Anal. Calcd for $C_{18}H_{30}O_8$: C, 57.74; H, 8.08. Found: C, 57.63; H, 8.07.

Preparation of *o*-Nitrophenyl Selenide 16. Methanesulfonyl chloride (156 mg, 1.36 mmol) was added to a solution of alcohol **15** (430 mg, 1.14 mmol) in 6.2 ml of dry pyridine cooled to 0 °C. After 30 min at 0 °C, the reaction temperature was warmed to 25 °C where stirring was continued for an additional 30 min. The solvent was removed under high vacuum and the residue was taken up in ether and washed with water. The combined ether extracts were dried over anhydrous magnesium sulfate. Filtration followed by removal of the solvent in vacuo gave 484 mg (94%) of crude mesylate: IR (film) 1725, 1340, 1165 cm^{-1}; NMR (60 MHz) δ ($CDCl_3$) 4.80 (m, 1 H, **CH**OAc), 4.32 (t, 2 H, $MsOCH_2$), 3.61 (s, 6 H), 3.25 (bs, 5 H, CH_2OCH_3), 2.99 (s, 3 H, CH_3SO_2), 1.95 (s, 3 H, OAc).

The above crude mesylate (484 mg) in 5.0 ml of dry dimethylformamide was added dropwise to a solution of *o*-nitrophenylselenium anion prepared by addition of sodium borohydride (108 mg) to *o*-nitrophenyl selenocyanate[22] (340 mg, 1.50 mmol) in 7.5 ml of dry dimethylformamide cooled to 15 °C. After 20 h, the reaction mixture was taken up in ether and washed with water. The aqueous layer was further extracted with ether. The combined organic washes were dried (anhydrous magnesium sulfate) and evaporated in vacuo, leaving 742 mg of crude selenide. Purification on 120 g of silica gel using hexane/ether (2:1) gave in order of elution 17 mg (5%) of the tetrahydrofuran derivative **19** (identical in all respects with a sample prepared below) and 482 mg of pure *o*-nitrophenyl selenide **16** (75% overall yield from alcohol **15**): IR ($CHCl_3$) 1730, 1590, 1565, 1518, 1336 cm^{-1}; NMR (60 MHz) ($CDCl_3$) δ 8.20 (d, 1 H), 7.40 (m, 3 H), 4.81 (m, 1 H), 3.60 (s, 6 H), 3.35 (s, 3 H), 3.25 (bs, 2 H), 2.78 (m, 2 H), 1.92 (s, 3 H).

Anal. Calcd for $C_{24}H_{33}NO_9Se$: C, 51.61; H, 5.96. Found: C, 51.54; H, 5.90.

***trans*-2-Acetoxy-*trans*-4-vinyl-*cis*-4-methoxymethyl-*cis*, *cis*-1,3-cyclohexanediacetic Acid Dimethyl Ester (17).** A solution of 720 mg (1.29 mmol) of *o*-nitrophenyl selenide (**16**) in 17 ml of tetrahydrofuran cooled to 0 °C was treated dropwise with 0.35 ml of 50% hydrogen peroxide. After addition was complete, the reaction mixture was warmed to room temperature and stirring was continued for 20 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in ether and washed with water. The aqueous layer was extracted exhaustively with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. There was obtained 505 mg of crude olefin. Purification on silica gel [elution with hexane/ethyl acetate (10:1)] gave 370 mg (81%) of crystalline compound. Recrystallization from ether/hexane gave pure olefin **17**, mp 69–71 °C: IR ($CHCl_3$) 3080, 1735, 1638 cm^{-1}; NMR (250 MHz) δ (CCl_4) 5.06–5.75 (typical vinyl eight-line pattern, 3 H), 4.90 (t, 1 H, **CH**OAc), 3.55 (s, 6 H), 3.45 (AB q, 2 H, J = 10 Hz, $\Delta\nu_{AB}$ = 33.5 Hz), 3.30 (s, 3 H, OCH_3), 1.88 (s, 3 H, OAc).

Anal. Calcd for $C_{18}H_{28}O_7$: C, 60.66; H, 7.92. Found: C, 60.54; H, 7.89.

Methyl *cis*-10α-(β-Bromomethyl)-2-oxo-3-oxa-8α-acetoxy-7β-decalylacetate (27). Methanesulfonyl chloride (100 μl, 1.3 mmol) was added to a solution of alcohol **15** (400 mg, 1.07 mmol) in 6.0 ml of anhydrous pyridine cooled to 0 °C. The reaction mixture was stirred for 30 min at room temperature and was then taken up in ether and washed with cold 5% aqueous hydrochloric acid, water, and brine. The ether layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure, providing 475 mg (98%) of crude mesylate which was used immediately in the next reaction.

To a solution of 370 mg (0.818 mmol) of crude mesylate in 30 ml of dry methylene chloride cooled to −78 °C was added dropwise with stirring 1.5 ml of boron tribromide. The reaction mixture was gradually warmed to 0 °C over a period of ca. 1 h. Stirring was continued for an additional 2 h at 0 °C followed by quenching with 12 ml of ether. After 10 min, 12 ml of water was added and stirring was continued at 0 °C for 10 min. The reaction mixture was taken up in ethyl acetate and washed with brine. After drying over anhydrous magnesium sulfate and evaporation of the solvent in vacuo, there was obtained 330 mg of material. Chromatography (ether/hexane, 2:3) of the crude product gave in order of elution 46 mg (13%) of bromo compound **30** [homogeneous on TLC analysis (silica gel, ether, R_f 0.80)] [IR ($CHCl_3$) 3010, 2950, 2930, 2860, 2810, 1732, 1438, 1379, 1210, 1160, 1110, 1020, 975 cm^{-1}; NMR (60 MHz) (CCl_4) δ 4.85 (bt, 1 H), 3.65 (s, 3 H), 3.60 (s, 3 H), 3.35 (s, 3 H), 3.2–3.6 (m, 5 H, $-CH_2Br$, $-CH_2OMe$), 1.95 (s, 3 H)]; a trace of the tetrahydrofuran derivative **19** [R_f 0.57 (ether)] (identical in all respects with a sample prepared below); and 160 mg (50%) of pure crystalline bromo lactone **27** [homogeneous on TLC (silica gel, ether, R_f 0.38)]. Recrystallization from ether/hexane (1:1) gave analytically pure bromo lactone **27**, mp 98–99 °C: IR ($CHCl_3$) 3010, 2950, 2930, 2860, 1730, 1438, 1375, 1209, 1175, 1070, 1020 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 4.89 (t, 1 H, J = 11 Hz, CHOAc), 4.24 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 119.4 Hz), 3.69 (s, 3 H, OCH_3), 3.42 (m, 2 H, CH_2Br), 2.12 (s, 3 H, CH_3CO).

Anal. Calcd for $C_{16}H_{23}BrO_6$: C, 49.11; H, 5.92. Found: C, 49.28; H, 6.02.

***o*-Nitrophenyl Selenide 28.** To a solution of 190 mg (0.84 mmol) of *o*-nitrophenyl selenocyanate[22] in 17.0 ml of dry dimethylformamide at 0 °C was added 42 mg (1.1 mmol) of sodium borohydride. After 10 min, a solution of bromo lactone **27** (220 mg, 0.56 mmol) in 4.0 ml of dry DMF was added dropwise at 0 °C to the deep blood red reaction mixture. Stirring was continued for ca. 20 h at room temperature. Isolation by ether extraction[36] provided 403 mg of crude product. Washing with ether gave 250 mg (87%) of crystalline selenide, mp 154–155 °C: IR ($CHCl_3$) 3000, 2935, 1730, 1590, 1562, 1510, 1438, 1370, 1330, 1300, 1205, 1095, 1070, 1022, 910, 885, 850 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 8.24 (d, 1 H, J = 8 Hz), 7.54 (t, 1 H, J = 8 Hz), 7.43

(d, 1 H, J = 8 Hz), 7.30 (t, 1 H, J = 8 Hz), 4.88 (t, 1 H, J = 11 Hz), 4.26 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 101.3 Hz), 3.64 (s, 3 H), 2.08 (s, 3 H). Recrystallization from benzene/ether (1:1) gave analyically pure selenide **28,** mp 156–157 °C.

Anal. Calcd for $C_{22}H_{27}NO_8Se$: C, 51.57; H, 5.31. Found: C, 51.73; H, 5.19.

Methyl *cis*-10α-Vinyl-2-oxo-3-oxa-8α-acetoxy-7β-decalylacetate (29). A solution of selenide **28** (240 mg, 0.46 mmol) in 12.0 ml of tetrahydrofuran cooled to 0 °C was treated dropwise with 50% hydrogen peroxide (165 μl). After addition was complete, the reaction mixture was stirred at room temperature for 18 h. The solvent was concentrated in vacuo and the product isolated by ether extraction.[36] Purification of the crude product on silica gel (ether/hexane, 3:2) gave 130 mg (89%) of crystalline **29.** Recrystallization from ether/hexane (1:1) provided analytically pure lactone **29,** mp 96–98 °C: IR ($CHCl_3$) 3080, 3020, 2950, 2930, 2850, 1730, 1638, 1490, 1439, 1400, 1370, 1205, 1121, 1000, 980, 930 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 5.8–5.2 (typical vinyl pattern, 8 lines, 3 H), 4.92 (t, 1 H, J = 11 Hz), 4.43 (AB q, 2 H, J = 13 Hz, $\Delta\nu_{AB}$ = 66.7 Hz), 3.68 (s, 3 H), 2.10 (s, 3 H).

Anal. Calcd for $C_{16}H_{22}O_6$: C, 69.04; H, 7.97. Found: C, 68.97; H, 7.95.

Bisnordeoxyvernolepin (6). To a solution of 130 mg (0.42 mmol) of acetoxy lactone 29 in 8.0 ml of anhydrous methanol was added 116 mg (0.84 mmol) of anhydrous potassium carbonate. After 2.5 h at room temperature, the reaction was quenched with 10% aqueous hydrochloric acid and the mixture was evaporated in vacuo. The crude product (117 mg), isolated by ethyl acetate extraction,[36] was dissolved in 20 ml of benzene containing 40 mg of *p*-toluenesulfonic acid and was refluxed for 1.25 h. Isolation by ethyl acetate extraction[36] gave 108 mg of crude crystalline product. Washing of the crude product with ether gave 70 mg of pure **6.** Chromatography (silica gel, ether/hexane, 3:1) of the mother liquor gave an additional 10 mg of pure bisnordeoxyvernolepin (total yield, 81%). Recrystallization from benzene/hexane (1:1) gave analytically pure bisnordeoxyvernolepin, mp 112–113 °C: IR ($CHCl_3$) 3080, 3020, 2925, 2850, 1787, 1735, 1640, 1490, 1460, 1450, 1430, 1401, 1360, 1302, 1285, 1260, 1203, 1160, 1150, 1120, 1085, 1055, 1002, 938, 875, 850, 815 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 5.8–5.3 (typical vinyl pattern, 3 H), 4.35 (AB q, J = 12 Hz, 2 H, $\Delta\nu_{AB}$ = 42.3 Hz), 4.02 (t, 1 H, J = 11 Hz).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.96; H, 6.77.

Deoxyvernolepin (1). A solution of dry diisopropylamine (77 μl, 0.55 mmol) in dry tetrahydrofuran (1.0 ml) cooled to 0 °C was treated dropwise with *n*-butyllithium (0.30 ml of a 1.58 M solution in hexane). After 15 min, the resultant solution of lithium diisopropylamide was cooled to −78 °C and treated dropwise over 30 min via a syringe pump with a solution of bisnordeoxyvernolepin **6** (50 mg, 0.21 mmol) in 2.0 ml of dry tetrahydrofuran containing 0.3 ml of dry hexamethylphosphoramide. After addition was complete, stirring was continued at −78 °C for 10 min, followed by warming to −20 °C. Formaldehyde [generated by depolymerization of paraformaldehyde (200 mg) at 150 °C (bath temperature)] was passed into the cooled (−20 °C) reaction vessel with the aid of a stream of nitrogen. After complete depolymerization (ca. 20 min) the reaction mixture was stirred for an additional 30 min (−20 °C). The reaction was quenched by the addition of 2.0 ml of 5% hydrochloric acid. Isolation of the product by ethyl acetate extraction left 572 mg of very crude product still containing hexamethylphosphoramide. The crude mixture of diols from above (572 mg) was diluted with 0.3 ml of dry pyridine and treated at 0–5 °C with methanesulfonyl chloride (58 mg, 2.4 equiv). Stirring at 5 °C was continued for 8 h. After isolation of the product by ethyl acetate extraction, there was obtained 81 mg of crude dimesylate which was used directly in the next reaction.

The mixture of crude dimesylate (81 mg) was dissolved in 4.0 ml of dry pyridine and refluxed for 17 h. After cooling to room temperature the reaction mixture was diluted with 30 ml of ethyl acetate and washed with water, 5% hydrochloric acid, saturated sodium bicarbonate, and brine. The organic layer was dried ($MgSO_4$) and the solvent was evaporated in vacuo, leaving 42 mg of crude material. Chromatography on 700 mg of silica gel [elution with ethyl acetate/hexane (2:3)] gave 21 mg of pure, crystalline deoxyvernolepin, mp 169–170 °C. The overall yield was 38%. Deoxyvernolepin exhibited the following spectral characteristics: IR ($CHCl_3$) 3015, 2940, 2910, 2850, 1770, 1720, 1670, 1620, 1405, 1340, 1305, 1287, 1250, 1210, 1160, 1130, 1080, 1065, 1010, 990, 950 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 6.71 (s, 1 H), 6.17 (d, J = 2.5 Hz, 1 H), 5.91 (s, 1 H), 5.50 (d, J = 2.5 Hz, 1 H), 5.3–5.8 (typical vinyl pattern, 8 lines, 3 H), 4.40 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 81.2 Hz), 3.97 (t, 1 H, J = 11 Hz), 3.00 (d, 1 H, J = 11 Hz).

Anal. Calcd for $C_{15}H_{16}O_4$: 260.0949. Found: 260.0955.

Reaction of Compound 27 with Potassium Carbonate in Methanol. A suspension of anhydrous potassium carbonate (6 mg, 0.04 mmol) in methanol (0.9 ml) containing bromo lactone 27 (21 mg, 0.05 mmol) was stirred at room temperature for 20 min. Neutralization of the reaction mixture with 10% hydrochloric acid and isolation of the product by ethyl acetate extraction[36] gave 18 mg (99%) of **19:** IR ($CHCl_3$) 3030, 2960, 2940, 2855, 1735, 1440, 1379, 1348, 1245, 1212, 1165, 1120, 1100, 1080, 1050, 1025, 980 cm^{-1}; NMR (250 MHz) (CCl_4) δ 4.43 (t, 1 H, J = 11 Hz), 3.70 (m, 2 H), 3.63 (s, 3 H), 3.60 (s, 3 H), 3.48 (AB q, 2 H, J = 9 Hz, $\Delta\nu_{AB}$ = 53.2 Hz), 1.89 (s, 3 H).

Anal. Calcd for $C_{17}H_{26}O_7$: C, 59.64; H, 7.65. Found: C, 59.50; H, 7.61.

Reaction of Compound 27 with DBU. A mixture of bromo lactone **27** (21 mg, 0.05 mmol) in 2.1 ml of dry benzene containing 75 mg of 1,5-diazabicyclo[5.4.0]undec-5-ene was stirred at room temperature for 72 h. The reaction mixture was diluted with ethyl acetate and washed with 5% hydrochloric acid, and the product isolated by extraction with ethyl acetate.[36] There was obtained 11 mg of crude product. Purification on silica gel [elution with ethyl acetate/hexane (5:2)] gave 7 mg of pure, crystalline **31,** mp 139–140 °C: IR ($CHCl_3$) 1735 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 4.88 (t, 1 H, J = 11 Hz), 4.22 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 109.3 Hz), 3.68 (s, 3 H), 2.82 (bs, 1 H), 2.08 (s, 3 H).

Anal. Calcd for $C_{16}H_{22}O_6$: *m/e* 310.1416. Found: *m/e* 310.1424.

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Registry No.—**1,** 60872-71-1; **2,** 18542-37-5; **4,** 60872-72-2; **6,** 60872-73-3; **7,** 60815-97-6; **7** methyl ether, 60815-98-7; **8,** 60815-99-8; **9,** 60816-00-4; **10,** 60872-74-4; **11,** 60872-75-5; **11** free acid, 60816-01-5; **11** acetate, 60816-02-6; **12,** 60816-03-7; **12′,** 60816-04-8; **14,** 60872-76-6; **15,** 60872-77-7; **15** mesylate, 60816-05-9; **16,** 60816-06-0; **11,** 60816-07-1; **19,** 60816-08-2; **27,** 60872-78-8; **28,** 60872-79-9; **29,** 60816-09-3; **30,** 60816-10-6; **31,** 60840-35-9; **34,** 60816-11-7; *o*-nitrophenyl selenocyanate, 51694-22-5.

References and Notes

(1) Fellow of the Alfred P. Sloan Foundation, 1974–1976.
(2) Postdoctoral fellow supported by a fellowship from the Universidad Nacional Autonoma de Mexico and the Banco de Mexico, S. A.
(3) For a preliminary account of this work see P. A. Grieco, J. A. Noguez, and Y. Masaki, *Tetrahedron Lett.*, 4213 (1975).
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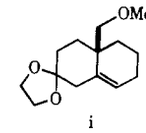
(8) We expected the cis-fused β-decalol **12** to predominate owing to the axial oxygen of the ketal moiety in compound i which effectively blocks the α face of the double bond [cf. M. Nussim, T. Mazur, and F. Sondheimer, *J. Org. Chem.*, **29,** 1120 (1964)].



i

(9) Marshall,[10] during the hydroboration of olefin ii, observed, in addition, the expected product iii (50%), the anti-Markownikoff product iv (10%), and the ketal cleavage products v (40%). We observed no evidence of products derived from cleavage of the ketal.[11] We speculate that the large percentage of anti-Markownikoff product **12′** obtained from i is due to directed hydroboration by the β-methoxymethyl function in the angular position.
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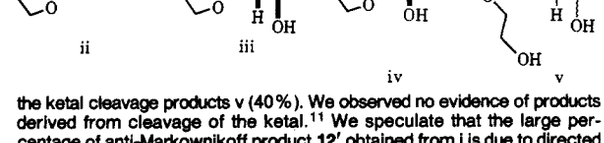

ii iii iv v

(11) Cf. C. H. Heathcock and R. Ratcliffe, *J. Am. Chem. Soc.*, **93**, 1746 (1971).
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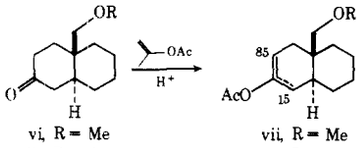
(16) We found previously[17] that decalone vi gave ca. 15% of the $\Delta^{3,4}$ isomer vii. Heathcock[18] has made a similar observation with decalone viii.



vi, R = Me
viii, R = Ac
vii, R = Me
ix, R = Ac

(17) P. A. Grieco, J. J. Reap,and J. A. Noguez, *Synth. Commun.*, **5**, 155 (1975); P. A. Grieco, K. Hiroi, J. J. Reap, and J. A. Noguez, *J. Org. Chem.*, **40**, 1450 (1975).
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(20) The *o*-nitrophenylselenium anion is generated by treatment of *o*-nitrophenyl selenocyanate[21,22] with sodium borohydride in dimethylformamide.[3] For a facile one step conversion of alcohols to alkyl aryl selenides, see P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, **41**, 1485 (1976).
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(22) Previous reports[19,21] have reported *o*-nitrophenyl selenocyanate as light brown crystals, mp 139–141[19] and 142 °C.[21] We have found that the crude crystalline material obtained from the procedure of Bauer[21] can be sublimed at 100 °C (0.2 mmHg) providing yellow crystals of *o*-nitrophenyl selenocyanate, mp 144 °C.
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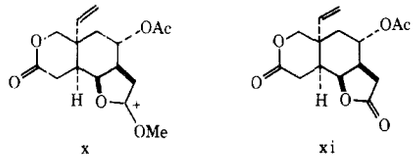
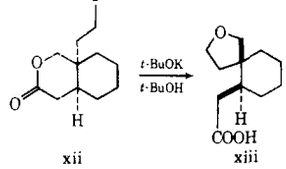
(24) We speculate that compound **26** is formed via the intermediacy of species x which arises through displacement of the C-6 acetate by the neighboring ester function followed by attack of bromide ion. We were unable to detect any of the cis-fused tricyclic dilactone xi which would have arisen from displacement at methyl instead of C-6. Complete details, including proof of structure for compound **26**, will be reported in due course.



x

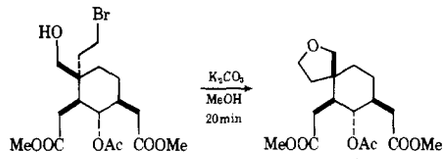
xi

(25) Heathcock[18] has observed a similar transformation on the iodoethyl lactone xii. Treatment of xii with *t*-BuOK/*t*-BuOH gave in excellent yield the spirotetrahydrofuran derivative xiii which presumably arises from a ketene intermediate.



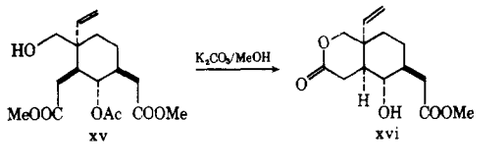
xii xiii

(26) Apparently compound **27** upon initial treatment with potassium carbonate in anhydrous methanol results in formation of the hydroxy ester xiv which spontaneously cyclizes to the spirotetrahydrofuran derivative **19**. In the



xiv 19

conversion of **29** to bisnordeoxyvernolepin (**6**) the initially formed hydroxy ester xv relactonizes upon workup providing hydroxy ester xvi.



xv xvi

(27) We are indebted to Drs. Andre Rosowsky and Herbert Lazarus (Sidney Farber Cancer Center and Departments of Biological Chemistry and Pathology, Harvard Medical School) for carrying out these tests.
(28) We are indebted to Dr. S. Morris Kupchan (University of Virginia) for a sample of natural vernolepin.
(29) For the synthesis and biological evaluation of dihydrodeoxyvernolepin and a variety of mono- and bifunctional α-methylene lactone derivatives, see P. A. Grieco, J. A. Noguez, Y. Masaki, K. Hiroi, M. Nishizawa, A. Rosowsky, S. Oppenheim, and H. Lazarus, *J. Med. Chem.*, in press.
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(34) Melting points were determined on a Fisher-Johns hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded at either 60 MHz (Varian A-60A or T-60 spectrometer) or at 250 MHz as indicated. Chemical shifts are reported in part per million (δ) relative to Me_4Si (δ_{Me_4Si} 0.0 ppm) as an internal standard. Low-resolution mass were recorded on an LKB-9000 spectrometer. High-resolution spectra were recorded on a Varian MAT CH-5DF instrument. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Tetrahydrofuran and dimethoxyethane were distilled from lithium aluminum hydride; dimethylformamide (DMF), hexamethylphosphoramide (HMPA), dimethyl sulfoxide (DMSO), and pyridine were distilled from calcium hydride. Diethyl ether and dioxane were distilled from sodium. Methylene chloride was passed through a column of alumina prior to use.
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(36) The products were isolated by extraction of the aqueous layer with several portions of the indicated solvent. The combined organic extracts were washed with water followed by saturated brine. The organic layer was usually dried with either anhydrous sodium sulfate or anhydrous magnesium sulfate. Filtration followed by removal of the solvent in vacuo (water aspirator) employing a rotary evaporator provided the products.