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Sesquiterpene Lactones: Total Synthesis of (±)-Vernolepin and (±)-Vernomenin[1,2]

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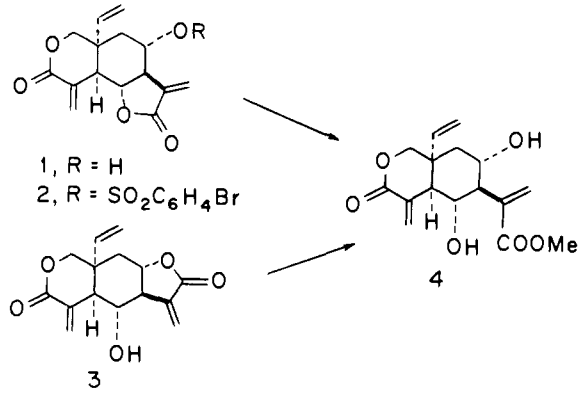
Abstract: Vernolepin (**1**) and vernomenin (**3**), the major constituents of *Vernonia hymenolepis*, have been synthesized in racemic form from *trans*-2,2-ethylenedioxy-10β-methoxymethyl-8-decalone (**20**).

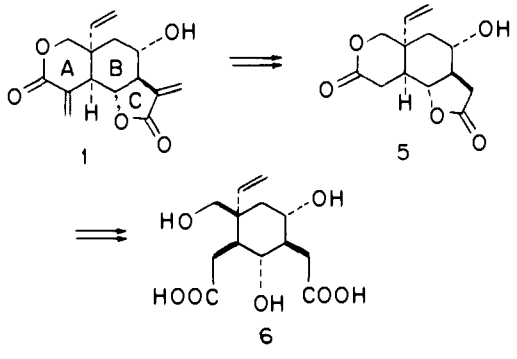
It was during the course of searching for tumor inhibitory compounds from plant sources that Professor S. Morris Kupchan and co-workers obtained an alcoholic extract of *Vernonia hymenolepis*, native to Ethiopia, which exhibited inhibitory activity in vitro. A systematic study aimed at isolation and structure elucidation revealed two novel elemanolide dilactones: vernolepin (**1**), the major active principle, and vernomenin (**3**), a closely related dilactone.



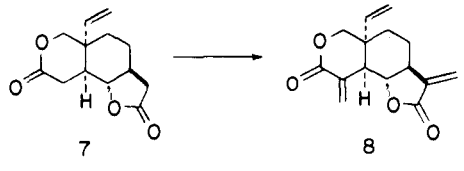
The structure of vernolepin, mp 181–182 °C, was established by x-ray crystallographic examination of the *p*-bromobenzenesulfonate ester **2**.[4] Pure crystalline vernolepin showed significant in vivo inhibitory activity against the Walker intramuscular carcinosarcoma 256 and in vitro cytotoxicity against KB cell culture. Vernomenin was isolated as an amorphous solid whose NMR signals in pyridine-d_5 were similar to those of vernolepin. Treatment of vernomenin with methanolic hydrochloric acid gave the methanol adduct **4**, mp 174–175 °C, which was identical in all respects with a sample of the methanol adduct obtained from vernolepin under identical conditions, thus indicating that both differ only in the attachment of the ring C γ-lactone unit.[5]

Retrosynthetic analysis of the vernolepin molecule (Scheme I) reveals the need for a simultaneous introduction of the two

Scheme I



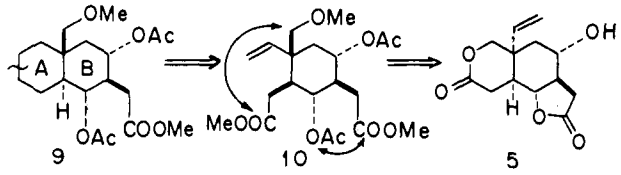
reactive α-methylene units during the latter stages of the synthesis. It is without question that the α-methylene-γ-butyrolactone and to a lesser extent the α-methylene-δ-valerolactone contribute to vernolepin's biological activity.[6] The extreme ease with which α-methylene lactones react with thiols and other biological nucleophiles is well documented.[7] It is primarily for the reasons set forth above that we initiated some years ago a program designed to explore methods for the construction of both α-methylene-γ- and -δ-lactones,[8] as well as to examine the feasibility of bis-α-methylenation in dilactone systems (cf. **7** → **8**).[9]



As indicated in Scheme I, cleavage of the two lactone units of the tricyclic dilactone **5** generates a cyclohexane derivative

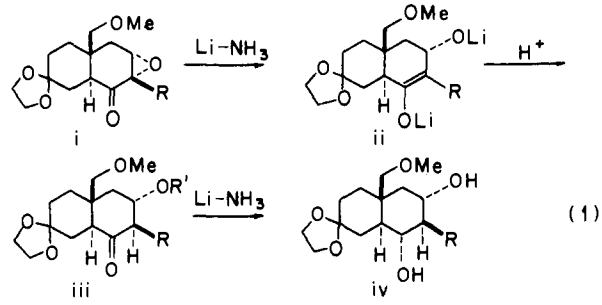
(**6**) possessing five chiral centers, in which five of the six substituents are equatorial. It is the stereospecific synthesis of such a fully substituted, fully protected cyclohexane ring system which represents the stereochemical challenge associated with the approach to vernolepin outlined below.

In principle, one can immediately reduce the problem of constructing five chiral centers to one involving only "three chiral centers" if the highly functionalized cyclohexane derivative **6** is incorporated into ring B of a *trans*-decalin derivative (e.g., **9**). Since there is ample precedent in the literature



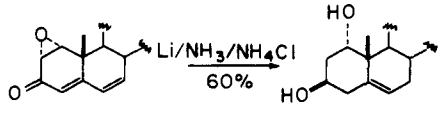
for generating and controlling the trans-ring fusion of C-5 and C-10 in functionalized decalin systems, what would be required is the establishment of three chiral centers at C-6, C-7, and C-8. The advantages of employing a *trans*-decalin derivative are obvious. Cleavage of the C-2, C-3 bond of a suitably functionalized ring A derivative of **9** with conversion of C-1 and C-2 into an olefin or some other functional moiety readily convertible into an olefin, and simultaneous formation of a carboxylic acid unit at C-3, would generate a cyclohexane ring system (**10**) possessing functionality for conversion to vernolepin via bislactonization (as indicated by the arrows) with formation of bisnorvernolepin (**5**). The conversion of C-3 during the cleavage reaction to a nitrile or an aldehyde unit would also be potentially attractive.

In addition to methods for the cleavage of ring A (vide infra) a more serious problem involves the introduction of appropriate functionality at C-6, C-7, and C-8. Our immediate goal was the construction of the fully functionalized, key intermediate decalone **11** (Chart I). The approach involved the reduction (lithium–liquid ammonia) of an appropriately substituted epoxy ketone in the presence of a proton source (eq 1). The



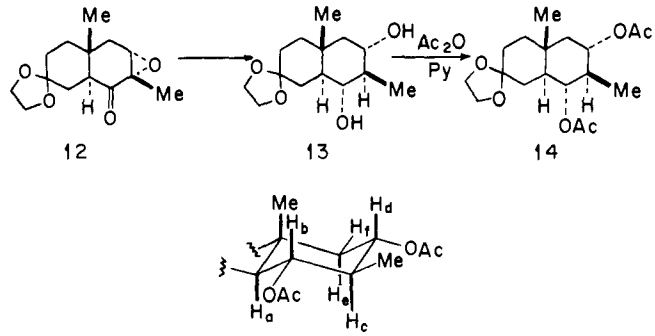
(1)

success of the above reaction scheme is highly dependent upon (a) the direction of protonation of the regiospecifically generated enolate ii, and (b) whether the intermediate aldol-like species iii undergoes reduction of the carbonyl with formation of the desired equatorial hydroxyl faster than β-elimination. In an elegant experiment (eq 2) Barton and co-workers[10]



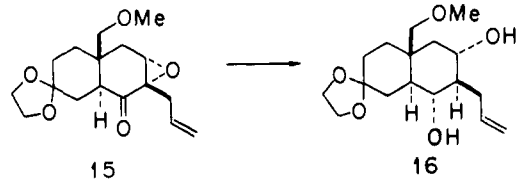
(2)

provided evidence which strongly suggested that the intermediate aldol-like species iii should undergo primarily reduction and not β elimination. The direction of protonation of the intermediate enolate ii remained a question. Initially the model epoxy ketone **12** was treated with a large excess of lithium–ammonium chloride (ca. 1:1) in liquid ammonia–tetrahydrofuran (ca. 1:1) at −33 °C (see experimental details). Workup provided in >95% yield a crystalline diol (**13**), mp

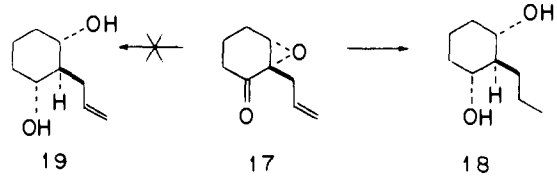


128–129 °C. Rigorous confirmation of the structure assigned to **13** was obtained from its diacetate **14**, mp 104–105 °C, whose 250-MHz NMR spectrum (CCl_4) exhibited in addition to a doublet at δ 0.87 (3 H), a triplet (1 H), at δ 4.56 ($J_{ab} = J_{bc}$ = 12 Hz) and a triplet of doublets (1 H) centered at δ 4.71 ($J_{cd} = J_{de}$ = 12 Hz, J_{df} = 6 Hz).

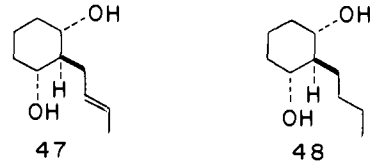
The initial synthetic scheme called for the preparation of compound **15** and its conversion to diol **16.** The allyl moiety



attached to C-7 represents a latent acetic acid unit, which is required for ring C formation during the latter stages of the synthesis. The use of the allyl group in place of the acetic acid side chain avoids carrying the carboxylic acid function through the critical stages during construction of the chiral centers at C-6, C-7, and C-8. In addition, the synthesis of the required epoxyketo carboxylic acid is not so straightforward. Preliminary experiments at −33 °C with the allylated epoxycyclohexanone **17** revealed formation of a major diol with the all-equatorial relationship of substituents; however, none of the desired diol **19** was isolated. Even at −78 °C the terminal



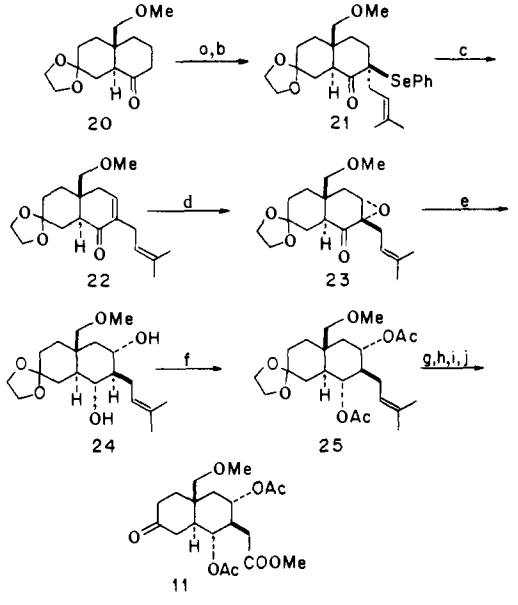
double bond was completely reduced, giving rise again to diol **18** with no trace of compound **19.** In general, nonconjugated carbon–carbon double bonds are resistant to reduction by dissolving metals in liquid ammonia. Terminal olefins may be reduced (tetrasubstituted olefins being the least susceptible to reduction) in solutions of lithium in alkylamines; however, the reaction is slow and yields are variable.[11a] In addition, terminal double bonds have been found to undergo reduction with sodium and methanol[11b] in liquid ammonia. For example, 1-hexene gave a 41% yield of hexane with sodium and methanol in ammonia.[11b] It is of interest to note that no reduction occurred when ammonium bromide was substituted for methanol. Substitution of a crotyl moiety for the allyl group gave rise to a 3:1 mixture of the desired olefin containing diol (**47**) and the fully reduced product **48.**[12] Complete retention



of the olefinic linkage was achieved by utilizing a prenyl group in place of the original allyl unit.

Having established the need for a prenyl group as the latent two-carbon appendage attached to C-7, we set out to prepare the epoxy ketone **23** (Chart I), which represents an intermediate along the synthetic pathway to the *trans*-decalone derivative **11**. The *trans*-decalone **20**, readily available from the corresponding *cis*-decalone[9] by equilibration with sodium methoxide in methanol, was employed as the starting material because it guarantees two of the five asymmetric centers. Of prime importance to the success of the reaction scheme outlined in Chart I is the preparation of the α-epoxy ketone **23** from dienone **22**. Dienone **22** was prepared from the *trans*-decalone **20** via kinetic enolate formation followed by trapping with phenylselenenyl chloride.[13] Treatment of the resultant β-keto selenide with lithium diisopropylamide in tetrahydrofuran containing hexamethylphosphoramide (HMPA) followed by addition of prenyl bromide gave an 83% overall yield of the crystalline selenide **21**, mp 157–158 °C. In the absence of HMPA no alkylation occurred after 1 day at room temperature. The selenoxide derived from compound **21** can, in principle, undergo two modes of elimination with formation of either the desired endocyclic dienone **22** or the exocyclic dienone **26**. Selenoxide formation with 2.5 equiv of 30% hydrogen peroxide in tetrahydrofuran was accompanied by facile elimination of phenylselenenic acid and formation of dienone **22**, mp 90.5–91.0 °C, in 65% isolated yield. Less than 20% of the undesired exocyclic dienone **26** was obtained. In addition, a few percent of an unidentified product was isolated.[14]

Chart I. The Synthesis of *trans*-Decalone 11



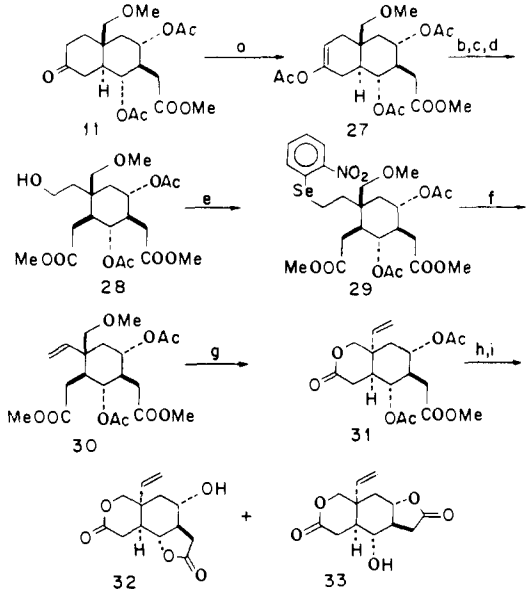
o, LDA, THF(-78°); PhSeCl/THF, 1hr; b, LDA, THF-HMPA(9:1), 0°; prenyl bromide, rt, 20 hr; c, 30% H_2O_2, THF, 0°; d, t-BuOOH(excess), triton B, THF, rt, 20 hr; e Li, NH_4Cl, NH_3-THF, -33°, 20 min; f, Ac_2O, Py, rt; g, O_3, CH_2Cl_2(-78°); h, Jones reagent; i, CH_2N_2, Et_2O; j, HCl-THF.

Attempted epoxidation of 22 with basic hydrogen peroxide led to none of the desired α-epoxide or β-epoxide. This was indeed surprising, since reaction of **22** with *tert*-butyl hydroperoxide in *tetrahydrofuran* containing triton B[16] gave a single epoxide, which had the correct α orientation (vide infra). As one might have anticipated, none of the β-epoxide could be detected. β-Epoxide formation would require a serious 1,3-diaxial interaction between the angular methoxymethyl group and the incoming *tert*-butyl hydroperoxide anion. Treatment of epoxy ketone 23 with a large excess of lithium–ammonium chloride in liquid ammonia–tetrahydrofuran at reflux gave the dihydroxy decalin **24**, whose diacetate **25** exhibited in its 250-MHz NMR spectrum (CCl_4) a triplet centered at δ 4.85 (J = 12 Hz) and a triplet of doublets located at δ 4.93 ($J_{ax,ax}$ = 12 Hz, $J_{ax,eq}$ = 5 Hz).

The latent acetic acid side chain attached to C-7 was unmasked in a straight-forward manner with ozone followed by direct treatment of the ozonide with Jones reagent and esterification. Deketalization gave rise to the key intermediate decalone **11**, which set the stage for fragmentation of ring A. The NMR spectrum of decalone **11** at 250 MHz was in complete accord with the all-trans, all-equatorial orientation of the substituents about ring B. During the removal of the ketal with 5% hydrochloric acid in tetrahydrofuran, some acetate cleavage occurred thus requiring treatment with acetic anhydride in pyridine in order to realize a >90% yield of keto diacetate **11**.

Having assembled all the asymmetric carbon atoms we turned our attention to the next stage of the synthetic scheme (Chart II), which requires cleavage of the C-2, C-3 bond of decalone **11** and eventual construction of bisnorvernolepin (**32**) and bisnorvernomenin (**33**). At some point in the latter half of the synthesis the cleavage of the methyl ether must be considered. From previous work on model systems, it was not obvious at what point cleavage should be carried out (vide infra).

Chart II. Synthesis of Bisnorvernolepin and Bisnorvernmenin

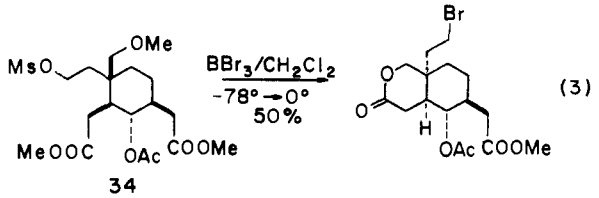


o, isopropenyl acetate, TsOH, reflux; b, O_3, CH_2Cl_2-MeOH(1:1), -78°; c, $NoBH_4$, -78°; d, CH_2N_2, Et_2O; e, g-$O_2NC_6H_4SeCN$, Bu_3P, THF, rt; f, 50% H_2O_2, THF, 24 hr, rt; g, BBr_3, CH_2Cl_2, -78°→-12°; h, K_2CO_3, MeOH; i, TsOH, C_6H_6, reflux.

Early model studies[9,17] indicated that the ozonolytic cleavage of the Δ^2-enol acetate of decalone **11** was the method of choice for cleaving the C-2, C-3 bond in ring A. Treatment of decalone **11** with isopropenyl acetate at reflux in the presence of an acid catalyst gave exclusively (78%) the crystalline Δ^2-enol acetate **27**, mp 133–134 °C. The exclusive formation of the Δ^2 isomer is attributed to an unfavorable interaction which exists in the Δ^3-enol acetate between the C-4 proton and

the C-6 α-acetoxy function. Ozonolysis of **27,** followed by treatment with sodium borohydride and esterification, gave the cyclohexane derivative **28.**

During the synthesis of deoxyvernolepin[9] it was observed that the cleavage of the methyl ether function was best carried out on methyl ether **34** (eq. 3). We therefore prepared the



(3)

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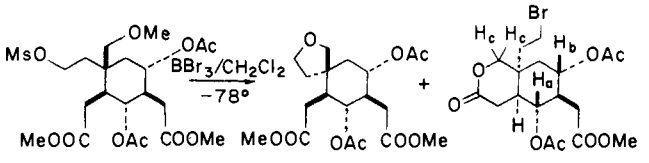
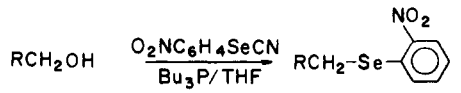
mesylate (**35**) of the hydroxyethyl compound **28** and subjected it to treatment with excess boron tribromide in methylene chloride (−78 °C). We were surprised to find as the major product the spirotetrahydrofuran derivative **36.** A disappointingly low yield (<2%) of the desired lactone **37** was iso-



35 36(80%) 37(trace)

lated on one occasion. We have never been able to reproduce the formation of compound **37.** The structure of compound **37** was corroborated by its 250-MHz NMR (CCl_4) spectrum, which revealed a one-proton triplet centered at δ 5.04 (J = 11.5 Hz, H_a), a one-proton triplet of doublets centered at δ 4.91 ($J_{ax,ax}$ = 11 Hz, $J_{ax,eq}$ = 5 Hz, H_b), an AB quartet centered at δ 4.24 (2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 100.1 Hz, H_c), a three-proton singlet at δ 3.68, and a multiplet at δ 3.43 (2 H, CH_2Br).

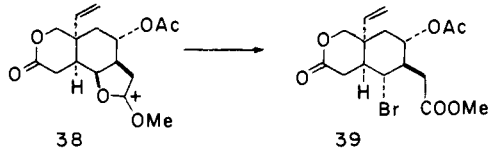
Despite the lack of success in cleaving the methyl ether in the deoxyvernolepin series in the presence of the terminal double bond,[9b] we set out to prepare the olefinic derivative **30.** Initially, compound **30** was prepared from the intermediate hydroxyethyl derivative **28** via a three-step sequence: (a) mesylate formation; (b) displacement of the mesylate by *o*-nitrophenylselenium anion prepared by treatment of *o*-nitrophenylseleno cyanate in dimethylformamide with sodium borohydride;[9,18] and (c) oxidation and elimination of *o*-nitrophenylselenenic acid. Steps a and b usually required long reaction times (1.5 days) and proceeded at best in 77% overall yield. Utilization of the one-step procedure for the conversion of alcohols to arylalkyl selenides (eq 4)[19] proceeded in <30 min



(4)

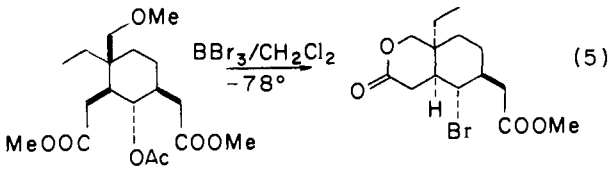
in 91% yield.

Initial attempts at cleavage of the methyl ether of compound **30** with boron tribromide were discouraging due to the persistent formation at varying temperatures of the bromo lactone **39** with no apparent formation of lactone diacetate **31.** Bromo



38 39

lactone **39** presumably arises from intermediate **38.** We previously had observed during the total synthesis of dihydrodeoxyvernolepin[20] a similar loss of the C-6 acetate function with introduction of a bromine atom with retention of configuration during cleavage of methyl ether **40** (eq 5). Fortu-



(5)

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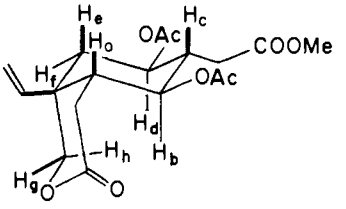
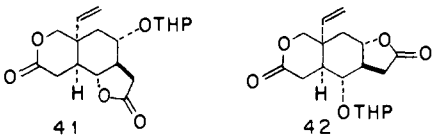
nately, in the case of compound **30,** when this reaction was carried out at −12 °C after initial mixing of reagents at −78 °C, sufficient quantities of the desired lactone **31**,[21] mp 127–128 °C, could be isolated in order to complete the total synthesis of vernolepin. Examination of the detailed 250-MHz NMR spectrum of lactone **31** in carbon tetrachloride readily



31

confirmed the structural assignment: δ 5.12 (triplet, 1 H, J_{ab} = J_{bc} = 11 Hz), 4.94 (triplet of doublets, 1 H, J_{cd} = J_{de} = 11 Hz, J_{df} = 4.5 Hz), and 4.47 (AB quartet, 2 H, J_{gh} = 12.5 Hz, $\Delta\nu_{AB}$ = 66.8 Hz).

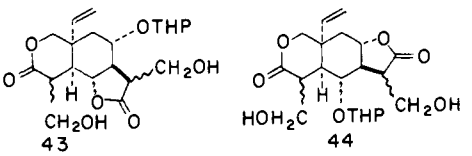
Acetate hydrolysis followed by lactonization provided a readily separable mixture of bisnorvernolepin (**32**) and bisnorvernomenin (**33**), which were converted into their respective tetrahydropyranyl ethers **41** and **42.** Since it had been re-



41 42

ported[5] that vernolepin and vernomenin can be easily separated chromatographically, we proceeded with the mixture of **32** and **33.**

Recent progress on methods for the construction of α-methylene-γ- and -δ-lactones[8] provided us with a variety of ways to introduce the two required α-methylene units. Having previously demonstrated that gaseous formaldehyde readily reacts with lactone enolates, providing a facile route to α-hydroxymethyl lactones,[22] and that such a process can be applied to dilactone systems,[9,20] we set out to prepare the dilactone enolates of **41** and **42.** Generation of the dilactone enolates in tetrahydrofuran at −78 °C under conditions employed for monolactones resulted in a heterogeneous reaction medium from which only very poor yields of the bis-α-hydroxymethylated adducts **43** and **44** could be isolated. Utilization of hex-

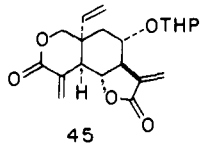


43 44

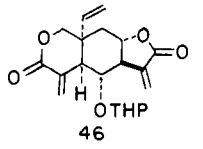
amethylphosphoramide as a co-solvent provided a homogeneous solution of the dilactone enolates at low temperature, which underwent smooth bis-α-hydroxymethylation. Mesylation of adducts **43** and **44** generated the corresponding mesylates, which were heated in pyridine. Unfortunately, no vernolepin THP-ether or vernomenin THP-ether could be isolated. It is of interest to note that this same procedure, when it was applied to the synthesis of deoxyvernolepin, provided directly a 32% yield of crystalline deoxyvernolepin.

We have previously observed the cleavage of tetrahydropyranyl ethers by pyridinium methanesulfonate in refluxing

pyridine[23] and speculate that the tetrahydropyranyl ethers **45** and **46** undergo cleavage accompanied by decomposition of



45



46

the vernolepin and vernomenin produced at such high temperatures. Elimination of the mesylates derived from **43** and **44** with diazabicyclo[5.4.0]undec-5-ene in benzene at room temperature provided the tetrahydropyranyl ethers of vernolepin and vernomenin, which were smoothly hydrolyzed in aqueous acetic acid. Chromatography of the crude product afforded (±)-vernolepin, mp 210–211 °C, and (±)-vernomenin, mp 186–188 °C. Synthetic vernolepin was found to be identical by IR, NMR, and TLC comparison with a sample of natural vernolepin kindly provided by Professor Kupchan. Synthetic vernomenin was found to be consistent with IR and NMR spectra of natural vernomenin supplied by Professor Kupchan.

Experimental Section

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 spectra 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.

***trans*-2,2-Ethylenedioxy-10β-methoxymethyl-8-decalone (20).** To a solution of 65.5 g (1.21 mol) of commercially available sodium methoxide in 400 mL of absolute methanol was added 35.67 g (140 mmol) of *cis*-2,2-ethylenedioxy-10-methoxymethyl-8-decalone in 200 mL of absolute methanol. The mixture was heated at reflux for 4 h, cooled, and diluted with 60 mL of water. The methanol was removed under reduced pressure on a rotary evaporator and the product was isolated by extraction with ether.[24] Chromatography of the crude product (34.2 g) on 1500 g of silica gel (elution with ether–hexanes 1:3) gave 20.70 g (58%) of pure decalone **20** (R_f 0.43, ether–hexanes, 1:1) [IR (CCl_4) 2948, 2876, 2805, 1708, 1480, 1446, 1431, 1395, 1361, 1318, 1294, 1270, 1259, 1235, 1195, 1170, 1105, 1031, 1010, 984, 968, 946, 921, 895, 860 cm^{-1}; NMR δ (CCl_4) 3.16 (ABq, 2 H, J = 10 Hz, $\Delta\nu_{AB}$ = 16.2 Hz), 3.26 (s, 3 H), 3.84 (br s, 4 H)] and 11.19 g (31%) of recovered *cis*-decalone (R_f 0.38). An analytical sample of **20** was prepared by distillation [130 °C (bath temperature) (0.10 mmHg)], which crystallized on standing, mp 59 °C.

Anal. ($C_{14}H_{22}O_4$): C, H.

***trans*-2,2-Ethylenedioxy-7α-(3-methyl-2-butenyl)-7β-phenylselenenyl-10β-methoxymethyl-8-decalone (21).** To a solution of 5.3 mL (37.8 mmol) of diisopropylamine in 45 mL of anhydrous tetrahydrofuran (THF) cooled to −78 °C was added dropwise 22.0 mL (34.6 mmol) of a 1.57 M solution of *n*-butyllithium in hexane. After 30 min at −78 °C, a solution of 8.0 g (31.5 g mmol) of decalone **20** in 25.0 mL of dry tetrahydrofuran was added dropwise. After an additional 5 min at −78 °C, a solution of 6.63 g (34.6 mmol) of phenylselenenyl chloride in 25.0 mL of tetrahydrofuran was added dropwise. Stirring at −78 °C was continued for 3 h followed by warming to 25 °C over 1 h. The reaction was quenched by the dropwise addition of water. The solvent was removed in vacuo and the product was isolated by ether extraction.[24] The crude product (13.5 g) was chromatographed on 500 g of silica gel. Elution with ether–hexanes, 1:2, gave 11.6 g (90%) of pure keto selenide [IR ($CHCl_3$) 3000, 2946, 2880, 2810, 1695, 1578, 1476, 1444, 1436, 1358, 1290, 1260, 1202, 1178, 1089, 1020, 999, 970, 942, 888, 855 cm^{-1}; NMR δ (CCl_4) 3.30 (s, 3 H), 3.91 (br s, 4 H), 7.0–7.7 (m, 5 H)], which was used directly in the next reaction.

To a solution of 7.8 mL (55.5 mmol) of diisopropylamine in 70 mL of dry THF at 78 °C was added dropwise 29.4 mL (46.2 mmol) of a 1.57 M solution of *n*-butyllithium in hexane. After warming to 0 °C (ca. 15 min), 9.7 mL (55.5 mmol) of dry hexamethylphosphoramide was added followed by dropwise addition of 17.2 g (42.0 mmol) of the above keto selenide (obtained from two runs) in 40 mL of dry THF. Stirring was continued at 0 °C for 5 min, followed by the addition of 6.5 mL (55.5 mmol) of 1-bromo-3-methyl-2-butene in one portion. After 22 h at 25 °C the reaction mixture was cooled to 0 °C and quenched with 1.5 mL of water. The THF was removed under reduced pressure on a rotary evaporator and the product was isolated by ether extraction.[24] The crude crystalline product was washed with hexanes, leaving 12.2 g (61%) of pure crystalline decalone **21** [IR ($CHCl_3$) 3000, 2975, 2945, 2880, 1698, 1578, 1491, 1478, 1445, 1436, 1377, 1355, 1302, 1291, 1209, 1178, 1095, 1065, 1025, 1000, 975, 945, 930, 851 cm^{-1}; NMR δ (CCl_4) 1.61 (br s, 3 H), 1.73 (br s, 3 H), 3.17 (s, 3 H), 3.86 (br s, 4 H), 5.17 (br t, 1 H), 7.1–7.8 (m, 5 H)], which was homogeneous on TLC (R_f 0.55, ether–hexanes, 1:1). Recrystallization from ether provided an analytical sample of pure **21**, mp 157–158 °C.

Anal. ($C_{25}H_{34}O_4Se$); C, H.

***trans*-7,7-Ethylenedioxy-2-(3-methyl-2-butenyl)-10β-methoxymethyl-Δ^{2,3}-octal-1-one (22).** To a solution of 4.0 g (8.38 mmol) of keto selenide **21** in 50 mL of tetrahydrofuran containing 14 drops of glacial acetic acid at 0 °C was added dropwise 4.4 mL (51.0 mmol) of 30% aqueous hydrogen peroxide. After stirring at 0 °C for 30 min followed by 60 min at 25 °C, the reaction mixture was cooled to 0 °C and was quenched by the addition of 12.8 g (51.6 mmol) of sodium thiosulfate in water. The solvent was removed under reduced pressure and the product was isolated by ether extraction.[24] The crude enone (3.85 g) was chromatographed on 400 g of silica gel. Elution with ether–hexanes, 1:1, gave in order of elution 1.74 g (65%) of crystalline octalone **22** (R_f 0.57, ether–hexanes, 1:1) [IR ($CHCl_3$) 2999, 2960, 2920, 2872, 2800, 1665, 1442, 1375, 1362, 1290, 1209, 1174, 1155, 1090, 1033, 1015, 978, 946, 928, 905, 860, 840 cm^{-1}; NMR δ (CCl_4) 1.62 (br s, 3 H), 1.69 (br s, 3 H) 3.26 (s, 3 H), 3.86 (br s, 4 H), 5.13 (br t, 1 H), 6.38 (br d, 1 H)] and 630 mg (23%) of the exocyclic dienone **26** (R_f 0.47). An analytical sample of **22** was prepared by recrystallization from hexanes, mp 90.5–91 °C.

Anal. ($C_{19}H_{28}O_4$): C, H.

Epoxidation of Octalone 22. To a solution of 2.13 g (6.66 mmol) of octalone **22** in 66 mL of tetrahydrofuran at 25 °C was added 6.6 mL of triton B followed by 6.6 mL of *tert*-butyl hydroperoxide. After 15 h at 25 °C, the solvent was removed in vacuo and the product was isolated by ethyl acetate extraction.[24] There was obtained 1.87 g (83%) of epoxide **23** [IR (CCl_4) 1705, 1668 cm^{-1}; NMR δ (CCl_4) 3.21 (s, 3 H), 3.87 (s, 4 H), 5.00 (br t, 1 H)], which was homogeneous by TLC analysis (R_f 0.77, ether–benzene, 1:1).

***trans*-1α,3α-Dihydroxy-2β-(3-methyl-2-butenyl)-7,7-ethylenedioxy-10β-methoxymethyldecalin (24).** To a solution of 3.96 g (11.8 mmol) of keto epoxide **23** in 419 mL of dry tetrahydrofuran and 602 mL of anhydrous liquid ammonia at −33 °C was added in one portion 602 mg (86 mmol) of lithium wire cut up into small pieces. After the entire solution had been deep blue for 1 min, 5.15 g of ammonium chloride was added at once. After 20 min at reflux an additional 602 mg of lithium was added to the reaction flask, whose contents turned deep blue after approximately 1 min. The reaction was quenched with 5.15 g of ammonium chloride. The solvents were carefully evaporated under reduced pressure and the product was isolated by ethyl acetate extraction.[24] Chromatography (elution with ether–benzene, 1:2) of the crude product on 300 g of silica gel gave 3.03 g (76%) of diol **24** [IR (CCl_4) 3620, 3500, 2920, 2865, 2800, 1445, 1090 cm^{-1}; NMR δ (CCl_4) 1.72 (br s, 6 H), 3.30 (s, 3 H), 3.86 (s, 4 H), 5.30 (br t, 1 H)], which was homogeneous by TLC analysis (R_f 0.14, ether–benzene, 1:1). An analytical sample was prepared by distillation [155–160 °C (bath temperature) (0.14 mmHg)].

Anal. ($C_{19}H_{32}O_5$): C, H.

Preparation of Diacetate 25. A solution of 3.59 g (10.5 mmol) of diol **24** in 50 mL of pyridine and 39 mL of acetic anhydride was stirred for 12 h at 25 °C. Standard workup gave 4.48 g (100%) of pure **25** [IR

(CCl_4) 2955, 2925, 2880, 2805, 1736, 1450, 1435, 1374, 1360, 1313, 1295, 1235, 1180, 1160, 1113, 1090, 1021, 978, 960, 943, 895 cm^{-1}; NMR (250 MHz) δ (CCl_4) 1.54 (s, 3 H), 1.74 (s, 3 H), 1.98 (s, 3 H), 2.04 (s, 3 H), 3.40 (ABq, 2 H, J = 10 Hz, $\Delta\nu_{AB}$ = 36.7 Hz, $-CH_2OCH_3$), 3.43 (s, 3 H, $-OCH_3$), 3.87 (s, 4 H, $-OCH_2CH_2O-$), 4.85 (t, 1 H, J = 12 Hz, $-CHOAc$), 4.93 (td, 1 H, $J_{ax,ax}$ = 12 Hz, $J_{ax,eq}$ = 5 Hz, $-CHOAc$), 5.05 (br t, 1 H, $-CH{=}CMe_2$)], which was homogeneous on TLC analysis (R_f 0.64, ether–benzene, 1:1). An analytical sample was prepared by distillation [90 °C (bath temperature) (0.20 mmHg)].

Anal. ($C_{23}H_{36}O_7$): C, H.

Methyl *trans*-10β-Methoxymethyl-2-oxo-6α,8α-diacetoxy-7β-decalylacetate (11). A solution of 1.56 g (3.68 mmol) of olefin **25** in 31 mL of methylene chloride cooled to −78 °C was treated with a saturated precooled (−78 °C) solution of ozone in 124 mL of methylene chloride (ca. 4.96 mmol of ozone). After 10 min the reaction mixture was warmed to −10 °C, where stirring was continued for 1 h. The solvent was removed under reduced pressure and the residue was dissolved in 18.6 mL of reagent grade acetone, cooled to 0 °C, and treated dropwise with 4 mL of standard Jones reagent. After 30 min at 0 °C followed by 30 min at 25 °C, the excess Jones reagent was destroyed by the addition of 2-propanol. The solvent was removed in vacuo and the intermediate carboxylic acid was isolated by ether extraction.[24] Removal of the solvent left 1.53 g of crude acid which was dissolved in 75 ml of ether and esterified at 0 °C with an ethereal solution of diazomethane. Evaporation of the ether provided 1.61 g of crude ester, which was dissolved in 16 mL of tetrahydrofuran containing 8.1 mL of 5% hydrochloric acid. After 20 h at 25 °C the solvent was removed under reduced pressure, affording 1.42 g of crude keto ester **11** containing a small amount of deacetylated material. The crude mixture was dissolved in 7.4 mL of pyridine and was treated with 5 mL of acetic anhydride. After 12 h at 25 °C, the solvent was removed under high vacuum and the crude product was chromatographed on 150 g of silica gel. Elution with ether–hexanes, 5:3, gave 1.05 g (74% overall) of pure decalone **11:** IR (CCl_4) 3080, 3030, 2948, 2920, 2860, 2810, 1740, 1718, 1480, 1455, 1434, 1418, 1362, 1320, 1295, 1224, 1200, 1162, 1109, 1042, 1021, 967, 900 cm^{-1}; NMR (250 MHz) δ (CCl_4) 2.05 (s, 3 H), 2.10 (s, 3 H), 3.52 (s, 3 H, $-CH_2OCH_3$), 3.67 (ABq, 2 H, J = 9 Hz, $\Delta\nu_{AB}$ = 25.4 Hz, $-CH_2OCH_3$), 3.68 (s, 3 H), 5.04 (t, 1 H, J = 11 Hz, $-CHOAc$), 5.14 (td, 1 H, $J_{ax,ax}$ = 11 Hz, $J_{ax,eq}$ = 5 Hz, $-CHOAc$). An analytical sample was prepared by recrystallization from hexanes, mp 127–128 °C.

Anal. ($C_{19}H_{28}O_8$): C, H.

Enolacetylation of Decalone 11. A solution of 4.11 g (10.7 mmol) of decalone **11** in 140 mL of isopropenyl acetate containing 250 mg of *p*-toluenesulfonic acid was refluxed under nitrogen. After 9 h the reaction mixture was cooled to 25 °C and the excess isopropenyl acetate was removed under reduced pressure. The resulting residue was chromatographed on 200 g of silica gel. Elution with hexane–ether, 1:1, gave 3.56 g (78%) of crystalline enol acetate **27**, mp 132–133 °C: IR (CCl_4) 2975, 2920, 2855, 2810, 1741, 1695, 1450, 1434, 1365, 1230, 1170, 1152, 1125, 1110, 1090, 1043, 1020, 962, 910 cm^{-1}; NMR (250 MHz) δ (CCl_4) 1.94 (s, 3 H), 1.98 (s, 3 H), 2.04 (s, 3 H), 3.38 (s, 3 H, $-CH_2OCH_3$), 3.38 (ABq, 2 H, J = 9 Hz, $\Delta\nu_{AB}$ = 34.8, $-CH_2OCH_3$), 3.57 (s, 3 H), 4.8–5.1 (m, 3 H). Recrystallization from hexane–ether provided pure enol acetate, mp 133–134 °C.

Anal. ($C_{21}H_{30}O_9$): C, H.

2α,6α-Diacetoxy-4α-(β-hydroxyethyl)-4β-methoxymethyl-1β,3β-cyclohexanediacetic Acid Dimethyl Ester (28). A solution of 3.55 g (8.33 mmol) of enol acetate **27** in 300 mL of methanol cooled to −78 °C was treated with 312 mL of a saturated methylene chloride solution of ozone (ca. 12.5 mmol of ozone). After 15 min 380 mg (10 mmol) of sodium borohydride was added at −78 °C. At 15-min intervals for ca. 45 min an equal amount of sodium borohydride was added (−78 °C). The reaction was warmed to room temperature and the solvents were removed under reduced pressure on a rotary evaporator. The residue was dissolved in water and washed with ether. The aqueous layer was cooled to 0 °C and acidified carefully with 5% hydrochloric acid. The intermediate monocarboxylic acid, isolated by ethyl acetate extraction,[24] was dissolved in ether and treated (0 °C) with an ethereal solution of diazomethane. There was obtained 3.34 g of crude diester **28**, which was purified on 600 g of silica gel. Elution with benzene–ether, 3:7, gave 2.16 g of diacetate **28** as an oil, which was homogeneous on TLC analysis (hexane–ethyl acetate, 1:2): IR (CCl_4) 2975, 2920, 2865, 1740, 1435, 1365, 1295, 1259, 1228, 1109, 1020, 962 cm^{-1}; NMR (250 MHz) δ (CCl_4), 5.12 (t, 1 H, J = 11 Hz), 4.98 (td, 1 H, $J_{ax,eq}$ = 4.5, $J_{ax,ax}$ = 11 Hz), 3.70 (s, 3 H), 3.67 (s, 3 H), 3.48 (s, 3 H), 3.38 (s, 2 H), 2.04 (s, 3 H), 1.98 (s, 3 H).

Anal. ($C_{20}H_{32}O_{10}$): C, H.

Two-Step Procedure for the Preparation of *o*-Nitrophenylselenide 29. A solution of 682 mg (1.78 mmol) of alcohol **28** in 20 mL of dry pyridine was treated with 1.0 mL of methanesulfonyl chloride at room temperature for 5 h. Standard workup gave 808 mg (100%) of crude mesylate [IR (CCl_4) 1735, 1362, 1175 cm^{-1}; NMR δ (CCl_4) 2.95 (s, 3 H), 4.29 (t, 2 H, J = 7 Hz)], which was used directly in the next reaction.

The above crude mesylate (808 mg) in 7.0 mL of dry dimethylformamide was added dropwise to a solution of *o*-nitrophenylselenium anion prepared by the addition of sodium borohydride (179 mg) to *o*-nitrophenyl selenocyanate[25] (539 mg, 2.38 mmol) in 14.0 mL of dry dimethylformamide cooled to 15 °C. After 20 h at 25 °C the product was isolated by ether extraction.[24] Purification of the crude product on 100 g of silica gel using benzene–ether, 3:2, gave 713 mg (73%) of pure (homogeneous by TLC analysis) selenide **29:** IR (CCl_4) 2980, 2918, 2850, 1739, 1588, 1563, 1558, 1512, 1441, 1430, 1360, 1330, 1300, 1225, 1170, 1105, 1035, 1020, 962 cm^{-1}; NMR (250 MHz) δ (CCl_4) 8.26 (d, 1 H, J = 8 Hz), 7.56 (d, 1 H, J = 8 Hz), 7.48 (t, 1 H, J = 8 Hz), 7.30 (t, 1 H, J = 8 Hz), 5.18 (t, 1 H, J = 11 Hz), 5.04 (td, 1 H, $J_{ax,ax}$ = 11 Hz, $J_{ax,eq}$ = 4.5 Hz), 3.76 (s, 6 H), 3.52 (s, 3 H), 3.47 (s, 2 H), 2.14 (s, 3 H), 2.08 (s, 3 H).

Direct One-Step Preparation of Selenide 29. A solution of 49 mg (0.11 mmol) of alcohol **28** in 500 μL of tetrahydrofuran at 25 °C was treated with 39 mg (0.17 mmol) of *o*-nitrophenyl selenocyanate[25] in 500 μL of tetrahydrofuran and 43 μL of tri-*n*-butylphosphine. After 30 min the product was isolated by extraction with ether.[24] Chromatography of the crude product on 20 g of silica gel (elution with hexane–ether, 1:2) gave 63 mg (91%) of pure **29** as a yellow foam. The NMR and IR spectra were completely identical with the spectra recorded above in the two-step process.

2α,6α-Diacetoxy-4β-methoxymethyl-4α-vinyl-1β,3β-cyclohexanediacetic Acid Dimethyl Ester (30). A solution of 713 mg (1.16 mmol) of *o*-nitrophenyl selenide **29** in 20 mL of tetrahydrofuran cooled to 0 °C was treated dropwise with 350 μL of 50% hydrogen peroxide. After addition was complete, the reaction was warmed to room temperature and stirring was continued for 18 h. The reaction mixture was concentrated in vacuo and the product was isolated by extraction with ether.[24] The crude olefin (504 mg) was purified on 150 g of silica gel. Elution with benzene–ether, 2:1, gave 425 (89%) of pure olefin **30** as an oil which was homogeneous by TLC analysis (benzene–ether, 1:1). The IR and NMR spectra exhibited the following characteristics: IR (CCl_4) 2985, 2935, 2915, 2860, 1738, 1430, 1360, 1290, 1225, 1168, 1108, 1020, 962, 920, 891 cm^{-1}; NMR (250 MHz) δ (CCl_4) 5.69 (q, 1 H), 5.22 (t, 1 H, J = 10 Hz), 5.1–5.2 (m, 2 H), 5.05 (td, 1 H, $J_{ax,ax} \simeq$ 10 Hz, $J_{ax,eq} \simeq$ 4.5), 3.70 (s, 6 H), 3.53 (br s, 5 H, $-CH_2OCH_3$), 2.08 (s, 3 H), 2.03 (s, 3 H).

Anal. ($C_{20}H_{30}O_9$): C, H.

Boron Tribromide Cleavage of Methyl Ether 30. A solution of 384 mg (0.93 mmol) of methyl ether **30** in 24 mL of methylene chloride cooled to −78 °C was treated with 865 μL (9.3 mmol) of boron tribromide. After 30 min the reaction was warmed to −12 °C, where stirring was continued for 4 h. The reaction was quenched at −12 °C by the addition of 3 mL of ether. The reaction mixture was warmed to room temperature and was stirred an additional 30 min followed by addition of water. Isolation of the product by ethyl acetate extraction[24] gave 405 mg of crude material which was chromatographed on 80 g of silica gel. There was obtained in order of elution (hexane–ether, 2:5) 45 mg of bromo compound **39**, mp 134–135 °C [IR ($CHCl_3$) 1738 cm^{-1}; NMR (250 MHz) δ (CCl_4) 5.3–5.8 (m, 3 H, typical $-CH{=}CH_2$ pattern), 5.00 (td, 1 H, $J_{ax,ax}$ = 11 Hz, $J_{ax,eq}$ = 5 Hz, $-CHOAc$), 4.52 (t, 1 H, J = 11 Hz, $-CHBr$), 4.46 (ABq, 2 H, J = 13 Hz, $\Delta\nu_{AB}$ = 61.6 Hz, OCH_2-), 3.75 (s, 3 H), 2.08 (s, 3 H); mass spectrum, calcd for $C_{16}H_{21}O_6{}^{81}Br$, 390.0501; found, 390.0503] and 136 mg (40%) of crystalline lactone **31**, mp 122–123 °C [IR (CCl_4) 1743, 1430, 1368, 1258, 1228, 1190, 1062, 1020, 970, 909 cm^{-1}; NMR (250 MHz) δ (CCl_4) 5.3–5.8 (m, 3 H, typical vinyl pattern, $-CH{=}CH_2$), 5.12 (t, 1 H, J_{ab} = J_{bc} = 11 Hz), 4.94 (td, 1 H, J_{cd} = J_{de} = 11 Hz, J_{df} = 4.5 Hz), 4.47 (ABq, 2 H, J = 12.5 Hz, $\Delta\nu_{AB}$ = 66.8 Hz), 3.70 (s, 3 H), 2.15 (s, 3 H), 2.05 (s, 3 H)].

Anal. ($C_{18}H_{24}O_8$): C, H.

Bisnorvernolepin (32) and Bisnorvernomenin (33). To a solution of 130 mg (0.36 mmol) of diacetate **31** in 4.0 mL of methanol was added 146 mg (1.06 mmol) of anhydrous potassium carbonate. After 3 h at

25 °C, the reaction was quenched by the addition of 5% aqueous hydrochloric acid and the solvent was evaporated in vacuo. Isolation of the product by extraction with ethyl acetate[24] gave 100 mg (98%) of crystalline 2α,6α-dihydroxy-4α-vinyl-4β-hydroxymethyl-1β,3β-cyclohexanediacetic acid δ-lactone methyl ester,[21] mp 186–187 °C.

Anal. ($C_{14}H_{20}O_6$): C, H.

A suspension of the above diol (85 mg, 0.30 mmol) in 9 mL of benzene containing 8 mg of *p*-toluenesulfonic acid was heated at reflux for 90 min. The reaction mixture was directly purified on 5 g of silica gel. Elution with methylene chloride–acetone, 5:2, gave 62.5 mg (83%) of a 2.5:1 mixture of bisnorvernolepin (**32**) and bisvernomenin (**33**).

(±)-Vernolepin (1) and (±)-Vernomenin (3). A solution of bisnorvernolepin and bisnorvernomenin (62.5 mg, 0.25 mmol) from above in 2.5 mL of dry methylene chloride containing 10 mg of *p*-toluenesulfonic acid was treated at 0 °C with 34 μL of dihydropyran. After 3.5 h at 0 °C the reaction was quenched by the addition of solid sodium bicarbonate and the product was isolated by extraction with ether.[24] The crude product upon chromatography on 25 g of silica gel (elution with ether–hexane, 8:1) gave 59 mg of a mixture of pure THP-ethers **41** and **42**, which was directly subjected to hydroxymethylation.

To a solution of lithium diisopropylamide [prepared from 71 mg (0.70 mmol) of diisopropylamine and 0.45 mL (0.70 mmol) of *n*-butyllithium (hexane) in 1.5 mL of anhydrous tetrahydrofuran cooled to −78 °C] at −78 °C was slowly added over a period of 1 h a solution of 59 mg (0.20 mmol) of lactones **41** and **42** in 1.5 mL of dry tetrahydrofuran containing 126 mg of dry hexamethylphosphoramide. After an additional 10 min at −78 °C, the reaction was warmed to −20 °C. Formaldehyde [generated by depolymerization of paraformaldehyde at 160 °C] was passed into the reaction mixture with the aid of a stream of nitrogen over a 10-min period. After an additional 10 min the reaction was quenched by the addition of aqueous ammonium chloride solution. The product was isolated by exhaustive extraction with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuo, leaving crude product (**43** and **44**) still containing HMPA, which was used directly in the next reaction.

The above mixture of diols **43** and **44** was dissolved in 1.2 mL of pyridine, cooled to 5 °C, and treated with 88 mg (0.77 mmol) of methanesulfonyl chloride for 14 h. The reaction mixture was taken up in ethyl acetate and brine. Extraction of the products with ethyl acetate gave 235 mg of crude material which was dissolved in 2 mL of benzene containing 116 mg (0.77 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene. After 1 h at 25 °C the reaction mixture was poured directly onto a column of 20 g of silica gel. Elution with hexanes–ether, 1:2, gave 10 mg (16%) of a mixture of the tetrahydropyranyl ethers **45** and **46** as a colorless syrup.

The above mixture of **45** and **46** (10 mg) was dissolved in 1.0 mL of 60% aqueous acetic acid and stirred at 45 °C for 3 h. The mixture was neutralized with aqueous sodium bicarbonate and the product was isolated by extraction with ethyl acetate.[24] The crude product (9 mg) was purified on silica gel by preparative thin layer chromatography employing chloroform–acetone, 3:1. Elution of the band at R_f 0.31 with ethyl acetate gave 1.5 mg of (±)-vernomenin, which crystallized from chloroform, mp 186–188 °C: IR ($CHCl_3$) 3600, 3440, 3045, 2930, 1777, 1728, 1675, 1625, 1408, 1300, 1262, 1170, 1132, 1110, 1062, 1050, 1020, 982, 960, 938 cm^{-1}; NMR (250 MHz) δ ($CDCl_3$) 6.74 (s, 1 H), 6.27 (d, 1 H, J = 2.5 Hz), 6.08 (d, 1 H, J = 2.5 Hz), 5.86 (s, 1 H), 5.3–5.8 (m, 3 H, $-CH{=}CH_2$), 4.44 (ABq, 2 H, J = 13.5 Hz, $\Delta\nu_{AB}$ = 30.1 Hz), 4.0 (m, 2 H); high-resolution mass spectrum, calcd for $C_{15}H_{16}O_5$, 276.0998; found, 276.1004. Elution of the band at R_f 0.22 with ethyl acetate gave 4 mg of crystalline (±)-vernolepin, mp 206–208 °C. Recrystallization from chloroform gave pure (±)-vernolepin, mp 210–211 °C: IR (KBr) 3450, 2925, 1765, 1729, 1622, 1488, 1410, 1366, 1305, 1285, 1271, 1251, 1166, 1138, 1055, 975 cm^{-1}; NMR (250 MHz) δ ($CDCl_3$) 6.74 (d, 1 H, J = 1 Hz), 6.25 (d, 1 H, J = 3 Hz), 6.06 (d, 1 H, J = 3 Hz), 5.97 (d, 1 H, J = 1 Hz), 5.3–5.8 (m, 3 H, typical 8 line pattern for $-CH{=}CH_2$), 4.37 (ABq, 2 H, J = 13.5 Hz, $\Delta\nu_{AB}$ = 41.9 Hz), 4.12 (m, 1 H), 3.99 (t, 1 H, J = 12 Hz), 2.94 (d, 1 H, J = 12 Hz), 2.65 (m, 1 H), 1.96 (dd, 1 H, J = 14 Hz, J = 4.5 Hz), 1.68 (dd, 1 H, J = 14 Hz, J = 12 Hz), 1.59 (s, 2 H, OH); high resolution mass spectrum, calcd for $C_{15}H_{16}O_5$, 276.0998; found, 276.0996.

***trans*-1α,3α-Diacetoxy-2β,10β-dimethyl-7,7-ethylenedioxydecalin (14).** A solution of 17 mg (0.067 mmol) of epoxyketone **12** in 3.5 mL of anhydrous liquid ammonia containing 2.5 mL of dry tetrahydrofuran was treated at reflux with 3.4 mg (0.48 mmol) of lithium metal. After ca. 1 min the blue color persisted and the reaction mixture was treated with 29 mg (0.54 mmol) of solid ammonium chloride. After 5 min an additional 3.4 mg of lithium metal was added. The reaction was quenched by the addition of 23 mg of ammonium chloride after 5 min. The solvents were removed under reduced pressure and the residue was dissolved in 20 mL of ether. The ether layer was washed with water and brine. The aqueous layer was extracted with two 15-ml portions of ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo, leaving 21 mg of a light yellow viscous oil. Purification on 8 g of silica gel (elution with ether) gave 18.3 mg (100%) of diol **13** as a colorless viscous oil, which crystallized on standing. Recrystallization from ether gave pure diol **13** as a white powder, mp 128–129 °C: IR ($CHCl_3$) 3640 cm^{-1}.

Anal. ($C_{14}H_{24}O_4$): C, H.

Treatment of 7.5 mg (0.029 mmol) of the above diol (**13**) in 0.4 mL of benzene with 120 μL of pyridine and 60 μL of acetic anhydride for 20 h at room temperature gave 11 mg of crude diacetate **14.** Purification on a column of silica gel (8 g) using ether–hexane, 1:2, afforded 10 mg of a colorless solid. Recrystallization from pentane gave pure diacetate **14**, mp 104–105 °C, as colorless needles: IR (CCl_4) 1740 cm^{-1}; NMR (250 MHz) δ (CCl_4) 0.87 (d, 3 H, J = 6.5 Hz), 1.08 (s, 3 H), 1.99 (s, 3 H), 2.06 (s, 3 H), 3.85 (s, 4 H), 4.56 (t, 1 H, J = 12 Hz), 4.71 (td, 1 H, $J_{cd} = J_{de}$ = 12 Hz, J_{df} = 6 Hz).

Anal. ($C_{18}H_{28}O_6$): C, H.

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(1) For a preliminary account of this work see P. A. Grieco, M. Nishizawa, S. D. Burke, and N. Marinovic, *J. Am. Chem. Soc.*, **98**, 1612 (1976).
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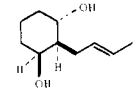

systems related to epoxy ketone **17** similar losses in stereospecificity with as much as 10–15% of the products possessing stereochemistry shown in compound v.
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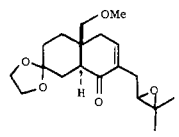
phenylseleninic acid and further oxidation with hydrogen peroxide to benzeneperoxyseleninic acid, which brings about epoxidation of the tri-



vi

substituted olefinic linkage. Details of this and other reactions will be reported shortly.[15]

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Marine Natural Products. Xenicin: a Diterpenoid Possessing a Nine-Membered Ring from the Soft Coral, *Xenia elongata*[1]

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Abstract: The structure of a new diterpenoid, xenicin (**1**), isolated from a soft coral, *Xenia elongata*, has been determined by single crystal x-ray diffraction. Xenicin possesses a nine-membered carbocyclic ring trans-fused to a dihydropyran ring. The crystals are monoclinic, space group $C2$, four molecules per unit cell with dimensions a = 17.704 (3), b = 9.061 (2), c = 18.656 (4) Å; β = 113.33 (2)°. The intensity data (3015) were collected on an automatic diffractometer. The structure, determined by direct methods, was refined by least-squares methods. The final R was 0.046 for all the data.

In our continuing research on the chemistry of soft corals (alcyonaceans) we have isolated a diterpenoid, xenicin (**1**), having a new skeleton in which the only carbocyclic ring present is nine membered. The cyclononene ring itself occurs in only one diterpenoid isolated previously[2] and among sesquiterpenoids is restricted to a few compounds related to caryophyllene.[3] Other investigations of soft corals have resulted in the discovery of new sesquiterpenes,[4] diterpenes,[5] and sterols.[6] The diterpenes previously reported from alcyonaceans have a cembrene skeleton[5a-f] or one easily derived from it by cyclization.[5g]

Results and Discussion

Xenicin, mp 141.5–142.3 °C, $[\alpha]^{23.5}_D$ −36.7° (0.6, $CHCl_3$), was obtained by adsorption chromatography from the hexane soluble portion of an aqueous 2-propanol extract of *Xenia elongata* collected near Heron Island, Australia. Interestingly, specimens of *X. elongata* from Picnic Bay, Magnetic Island, Australia and from the Fiji Islands did not contain any of this new diterpenoid. High resolution mass spectral and elemental analysis established the formula $C_{28}H_{38}O_9$ for **1**. Its infrared spectrum lacked hydroxyl absorption, but displayed a strong, broad band centered at 1735 cm^{-1} (acetate) with a shoulder at 1700 cm^{-1}. The NMR spectrum contained signals for four acetates and three vinyl methyl groups in addition to downfield multiplets corresponding to nine protons from which some partial structural information could be gleaned, but from which it was not possible to deduce a complete structure. Preliminary hydrolytic and catalytic reduction experiments did not yield encouraging results. The complete structure of xenicin was elucidated by single crystal x-ray diffraction and is shown in **1**. This formula also connotes the absolute configuration derived from crystallographic data.

A stereoview[7] of xenicin is shown in Figure 1. Bond distances, bond angles, and torsion angles are given in Figures 2, 3, and 4. Xenicin possesses a dihydropyran ring trans-fused to a nine-membered carbocyclic ring and represents the first member of a hitherto unknown skeletal system.[8] The nine-membered ring contains a trans double bond with a torsion angle of −158° and an exocyclic double bond. Bond lengths and torsion angles indicate that the nine-membered ring is slightly strained. No short intermolecular distances were found in the crystal structure.

The NMR chemical shift assignments and proton couplings in **1**, confirmed by double irradiation experiments at 100 and 220 MHz, are shown in Table I. The enol ether proton H(3) exhibits allylic coupling to H(4a), but not to the conformationally mobile H(12). At 220 MHz (benzene-d_6) the H(9) signal is clearly visible as a broadened triplet, J = 7 Hz, indicating a coupling of nearly 7 Hz with one of the C(10) protons and only a very small coupling to the other as would be suggested by the conformation of crystalline **1**.