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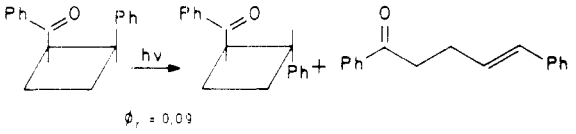

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Stereoselective Synthesis of Racemic Elemanolide Dilactones Related to Vernolepin

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A synthesis of 8-deoxy-9β-hydroxyvernolepin (**16**), an isomer of the elemanolide sesquiterpene dilactone vernolepin, is described. The synthesis employs the monoketal of 1,4-cyclohexanedione as the starting point and proceeds via symmetrical intermediates. Introduction of the requisite acetic acid side chains is achieved via symmetrical dialkylation of the enamine derivative of the aforementioned ketone using 1,3-dichloro-2-propene as an acetic acid chloride equivalent. The second (ketal protected) carbonyl grouping is employed to introduce the geminal hydroxymethyl, vinyl substituents after reduction and protection of the 4-ketone grouping. This is accomplished by carbethoxylation and alkylation of the resulting β-keto ester enolate with ethyl iodoacetate to give a single keto diester of the proper relative stereochemistry at the four contiguous chiral centers. The stereochemistry was confirmed through conversion of this intermediate to bisnordihydro-8-deoxyvernolepin (**21**), a substance of known stereochemistry.

The cytotoxic tumor inhibitory elemanolide sesquiterpene, vernolepin, has occasioned a considerable expenditure of creative synthetic effort in laboratories throughout the world since Kupchan and his associates first described its isolation and structure some ten years ago.[1] Impressive progress has been recorded. Several imaginative total syntheses have evolved[2] and numerous reports describing potential solutions for one or more of the various synthetic problems posed by the vernolepin family have appeared.[3]

Efforts in our own laboratory over the past few years have been directed toward straightforward, efficient stereoselective syntheses of dilactones related to vernolepin. The approach described herein was designed with total synthesis in mind, but unforeseen difficulties at the penultimate stages have thus far kept us from that goal. Nonetheless, the basic plan and the evolved chemistry contain elements of intrinsic interest and applicability to synthetic chemistry which prompt this report.

In our synthetic analysis of vernolepin (Scheme I), we noted that transposition of the C-8 hydroxyl grouping to C-9 (structure I) greatly simplified synthetic and stereochemical problems by permitting the use of a symmetrical intermediate such as III. Furthermore, the expected conformational rigidity imposed by the trans,anti arrangement (all equatorial) of the three substituents in this intermediate and consideration of stereochemical factors controlling enolate alkylations led us

Scheme I

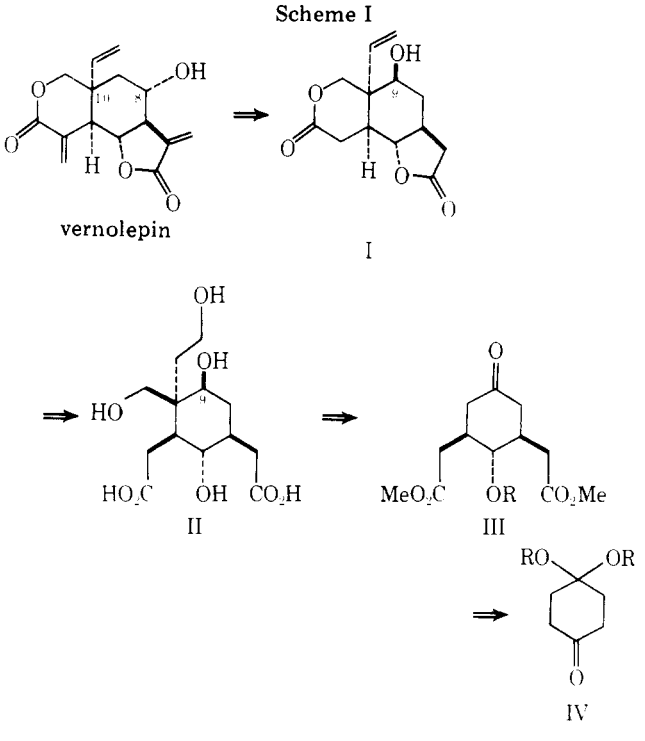
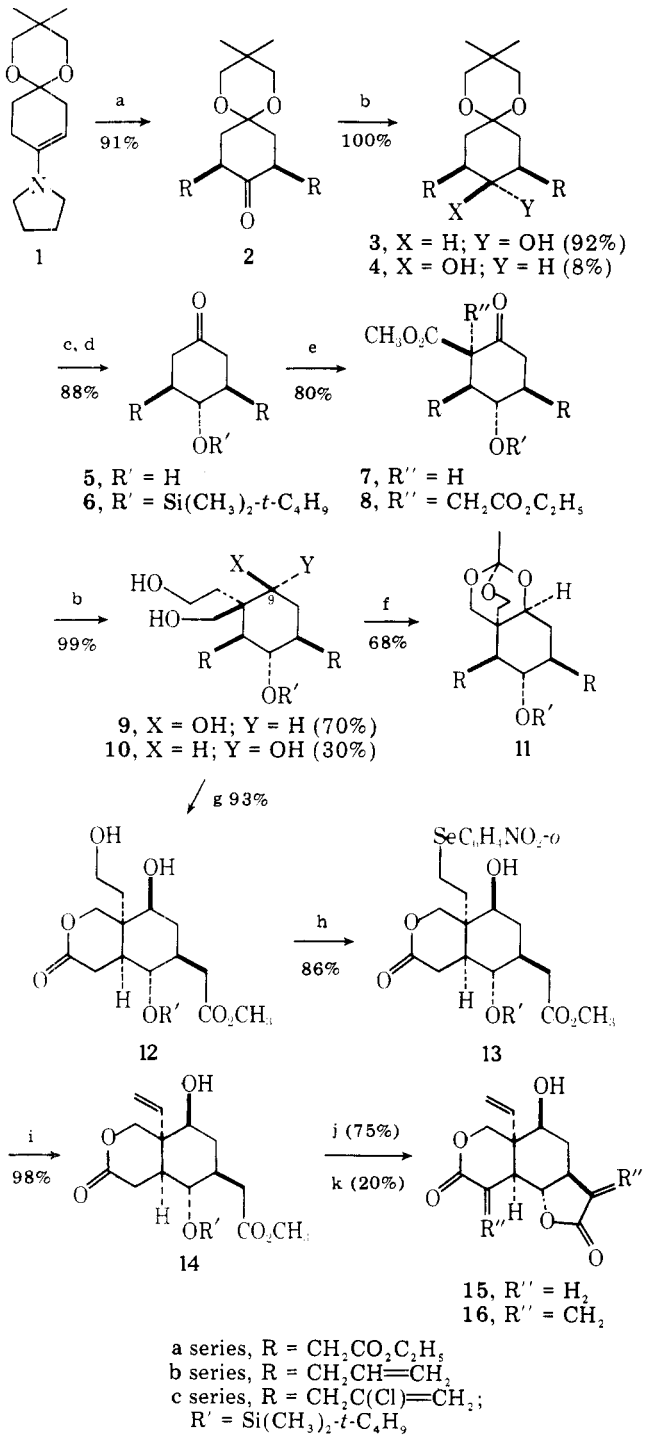


Chart I[a,b]



a series, R = $CH_2CO_2C_2H_5$
b series, R = $CH_2CH{=}CH_2$
c series, R = $CH_2C(Cl){=}CH_2$;
R′ = $Si(CH_3)_2$-t-C_4H_9

[a] (a) RX, NaI, EtOH; H_2O. (b) $LiAlH_4$, ether, −78 °C. (c) HCl, acetone. (d) $ClSi(CH_3)_2$-t-C_4H_9, imidazole, $(CH_3)_2NCHO$. (e) NaH, $(CH_3O)_2CO$, dioxane; HOAc; NaH, $ICH_2CO_2C_2H_5$, C_6H_6, $(CH_3)_2NCHO$ (f) $CH_3C(OC_2H_5)_3$, p-TsOH, THF. (g) O_3, CH_3OH, −78 °C; $(CH_3)_2S$, C_5H_5N. (h) o-$O_2NC_6H_4SeCN$, $(n\text{-}C_4H_9)_3P$, THF. (i) H_2O_2, THF. (j) $(n\text{-}C_4H_9)_4N^+F^-$, C_6H_6. (k) $[(CH_3)_2N{=}CH_2]^+I^-$, $LiN(i\text{-}C_3H_7)_2$, THF; CH_3I, dioxane, $NaHCO_3$. [b] Yields and ratios are shown for c series.

to believe that the requisite geminal substituents could be introduced stereoselectively (III → II). Finally, cyclohexanones such as III appeared to be readily derivable from known monoketals of cyclohexane-1,4-dione.[4] Thus the choice of dilactone I as the initial target allows for rapid construction of the carbon skeleton and permits application of well-established conformational principles for stereochemical control. In addition, we felt that transposition of oxygen from C-9 to C-8 should be possible using available methodology, thus allowing for an eventual total synthesis of vernolepin itself.

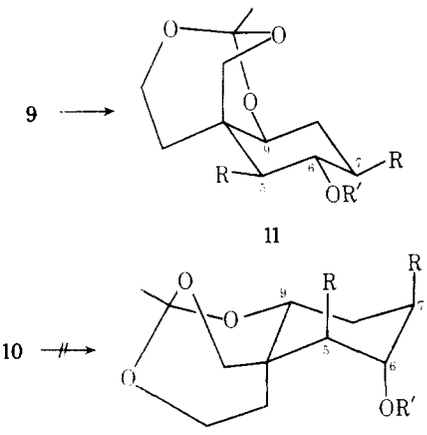
Chart I outlines the initial results of our synthetic studies. Three parallel routes to lactone **12** were initially explored using different side chain substituents (**a, b,** and **c** series). While the **c** series eventually proved most suitable, certain observations in the **a** and **b** series deserve mention. Enamine **1** (derived from the corresponding ketal ketone[5]) could be smoothly bis alkylated to the cyclohexanones **2a** and **2b** with ethyl bromoacetate and allyl bromide, respectively,[6] but with 1,3-dichloro-2-propene as the alkylating agent, the *monoalkylated* ketone (**2**; R, R = H, $CH_2C(Cl){=}CH_2$) predominated. This problem was solved using a catalytic amount of sodium iodide, whereupon the dialkylated ketone could be obtained in over 90% yield.

Reduction of ketone **2c** with lithium aluminum hydride in ether at −78 °C afforded the epimeric alcohols **3c** and **4c** in the ratio 92:8. Similar reduction of ketone **2b** led to a 94:6 mixture of alcohols **3b** and **4b.** Reduction at room temperature proved less selective, leading to an 80:20 mixture of **3b** and **4b.** In the **a** series, keto diester **2a** could not be reduced stereoselectively using various hydride reagents, catalytic hydrogenation, or Meerwein–Pondorff conditions.[6b] Dissolving metal reduction of the diacid **2** (R = CH_2CO_2H) appeared to proceed in the desired sense,[7] but complications in product isolation and problems encountered in subsequent steps forced us to abandon the **a** series in favor of the less direct **b** and **c** series.

We assumed that the substituents in ketones **2a–c** attain the thermodynamically preferred cis arrangement during the course of the enamine alkylation and subsequent hydrolysis.[8] This assumption coupled with the expectation of a preferred trans alcohol orientation in the lithium aluminum hydride reductions of ketones **2b** and **2c** found excellent support in the NMR spectra of alcohols **3b** and **3c,** and **4b** and **4c** thus derived.

Hydrolysis of the 92:8 mixture of hydroxy ketals **3c** and **4c** in aqueous acetone gave the highly crystalline hydroxy ketone **5c** in 88% overall yield. Condensation of the derived *tert*-butyldimethylsilyl ether[9] **6c** with dimethyl carbonate in dioxane using sodium hydride as the base proceeded smoothly below 50 °C to yield keto ester **7c.** At higher temperatures, or when potassium hydride was used, a substantial amount of propargyl-substituted keto ester arising from dehydrochlorination of the vinylic chloride side chain was isolated (**8,** R, R = $CH_2C{\equiv}CH$, $CH_2C(Cl){=}CH_2$). Models suggest that this undesired elimination reaction could follow an intramolecular pathway with the enolate of ketone **6c** or keto ester **7c** serving as an internal base. Under optimized conditions, the crude β-keto ester **7c** could be directly alkylated with ethyl iodoacetate, affording keto diester **8c** in 80% overall yield as a crystalline solid. None of the epimeric keto diester appeared to be formed in this reaction. We would expect the relatively bulky iodoacetate to preferentially approach the intermediate β-keto ester enolate from the face opposite the adjacent chloroallyl side chain leading to the isomer shown.

The next phase of our studies involved conversion of the acetic ester substituent of ketone **8** to a vinyl grouping, reduction of the ketone and ester carbonyls, and oxidative cleavage of the side chain double bonds. Reduction of keto diester **8b** with borohydride reagents, alkoxyaluminohydrides, or lithium aluminum hydride itself produced a nearly 1:1 mixture of C-9 alcohol epimers. Our best results were obtained with lithium aluminum hydride at −78 °C, whereupon a 70:30 mixture of triols **9b** and **10b** was secured. The chloro analogue **8c** behaved identically. Separation of the isomeric triols **9** and **10** and proof of stereochemistry were achieved through treatment of the mixture with triethyl orthoacetate and *p*-toluenesulfonic acid in tetrahydrofuran. The major epimers



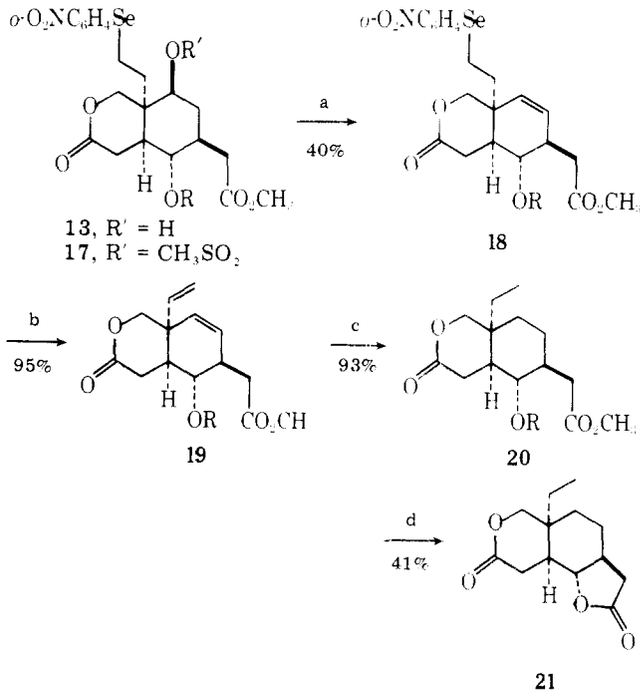
9b and **9c** readily formed nonpolar bridged orthoacetates **11b** and **11c**, which were easily separated through column chromatography from polar products arising from triols **10b** and **10c**. Conformational analysis clearly indicates that these minor triols must adopt either an energetically disfavored boat cyclohexane conformation or a chair conformation in which the three contiguous substituents at C-5, C-6, and C-7 become axially oriented in order to form a bridged orthoacetate. The major triols **9b** and **9c**, on the other hand, suffer no such constraints and can readily yield orthoacetates **11b** and **11c** via low energy equatorially substituted chair conformers. Treatment of orthoacetates **11b** and **11c** with acidic methanol followed by potassium carbonate to saponify the resulting acetates afforded the pure triols **9b** and **9c** quantitatively. Alternatively, triols **9b, 9c** and **10b, 10c** could be easily separated using preparative high-pressure liquid chromatography.

Our initial exploration of the foregoing sequence (**2** → **9, 10**) was conducted using the allyl-substituted intermediates (**b** series). However, it became necessary to consider alternative acetic acid equivalents after numerous attempts to oxidatively cleave the double bonds of diene **9b, 11b,** and several derivatives failed to afford the desired diacid (II) or related lactone (e.g., **12**) in even modest yield. The problem seemed to stem from interactions between the triol, or suitably protected (orthoacetate, triacetate) triol groupings, and the side chains in partially oxidized intermediates. For example, the crude dialdehyde **9** (R = CH_2CHO), obtained via osmium tetroxide–sodium periodate cleavage of diene **9b,** yielded only a trace of diacid or lactone acid upon silver oxide oxidation. On one occasion, lactone ester **12** was formed in 18% yield from orthoacetate **11b** through ozonolysis, silver oxide treatment of the crude ozonide, orthoacetate hydrolysis, and esterification of the acidic products with diazomethane. Subsequent attempts to repeat this sequence resulted in substantially lower yields of useful products. Triol **9b** and its triacetate derivative fared even worse.

Since the aldehyde to acid conversion was the apparent source of our difficulty, we considered the use of allyl derivatives which might afford a carboxylic acid derivative directly upon oxidative cleavage, thereby circumventing this capricious step. The 2-chloroallyl grouping seemed perfectly suited to our needs, especially since the requisite alkylating agent, 2,3-dichloropropene, was readily available. Furthermore, the expected ozonolysis product, an acid chloride,[10] could be expected to afford lactone ester **12** in situ under appropriate conditions. To our great satisfaction, this proved to be the case.[11] Not only did ozonolysis of diene **9c** proceed cleanly to give lactone ester **12** in 89–93% yield, but yields in the steps leading to **9c** equaled or surpassed those in the **b** series and the intermediates were more highly crystalline.

The angular β-hydroxyethyl substituent of diol lactone **12** was efficiently converted to a vinyl grouping by the method

Chart II[a]



R = $Si(CH_3)_2$-*t*-C_4H_9

[a] (a) Al_2O_3, CH_2Cl_2. (b) H_2O_2, THF. (c) 5% Pd–C, H_2, C_2H_5OH. (d) $(n\text{-}C_4H_9)_4N^+F^-$, C_6H_6.

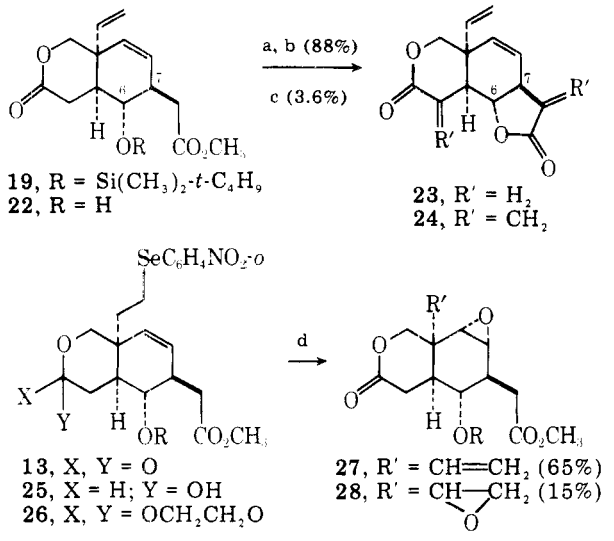
of Grieco.[12a] Accordingly, treatment with 2 equiv of *o*-nitrophenyl selenocyanate and tributylphosphine in tetrahydrofuran afforded selenide **13** in 86% yield. Oxidation with 30% hydrogen peroxide at room temperature was accompanied by selenoxide elimination,[12b] leading to the crystalline lactone **14** in 98% yield. The richly detailed 270-MHz NMR spectrum of this lactone fully supported our stereochemical assignment.[13]

Cleavage of the silyl ether moiety of **14** by tetrabutylammonium fluoride[9] in benzene gave the crystalline dilactone **15** in 75% yield, provided the methanol formed in the lactonization stage of the reaction was removed through codistillation. Otherwise, a mixture of hydroxy ester (**14**, R′ = H) and lactone **15** resulted. Bis α-methylenation was achieved by Danishefsky's method[14] using dimethyl(methylene)ammonium iodide to alkylate the dilactone enolate followed by methylation of the resulting bis(dimethylaminomethyl) dilactone [(**15**, R″ = H, $CH_2N(CH_3)_2$)] with methyl iodide and elimination of the bis methiodide thereby produced with sodium bicarbonate. This sequence led to the highly crystalline elemanolide dilactone **16**, albeit in yields of 20% or less. The majority of the product consisted of an intractable tarry substance.

While the spectral characteristics of lactone **14** confirmed our presumptive stereochemical assignment for keto diesters **8b** and **8c**, we felt that a rigorous proof would be desirable. Of the possibilities considered, direct correlation of lactone **13** with the dilactone **21** (Chart II) previously prepared by Grieco[15] seemed most straightforward. Treatment of the derived methanesulfonate **17** with activated alumina as described by Posner[16] afforded the olefin **18** in 40% yield. Selenoxide elimination gave the crystalline diene **19** in 95% yield. Hydrogenation over palladium-on-carbon in ethanol produced the tetrahydro derivative **20**, which was subjected to the tetrabutylammonium fluoride cleavage–lactonization procedure. Lactone **21** thus secured proved identical with an authentic sample, thereby confirming our stereochemical assignments.

Interestingly, attempts at direct conversion of the unsatu-

Chart III[a]



[a] (a) $(n\text{-}C_4H_9)_4N^+F^-$, C_6H_6, HOAc. (b) *p*-TsOH, C_6H_6. (c) $[(CH_3)_2N{=}CH_2]^+I^-$, $LiN(i\text{-}C_3H_7)_2$, THF; CH_3I, dioxane; $NaHCO_3$. (d) *m*-$ClC_6H_4CO_3H$.

rated silyl ether ester **19** to γ-lactone **23** via fluoride cleavage and methanol codistillation led to extensive decomposition. Even at room temperature, loss of material was substantial and hydroxy ester **22** was formed in low yield. Presumably, the cyclohexene double bond causes an increase in the C-6 alkoxide/C-7 acetic ester dihedral angle of the desilylated intermediate, thereby rendering γ-lactonization more difficult and the resultant γ-lactone **23** more strained than in the previous examples (**15** and **21**). Adding 1 equiv of acetic acid to the fluoride cleavage reaction solved the problem. Hydroxy ester **22** was then formed nearly quantitatively. Treatment with *p*-toluenesulfonic acid in benzene converted this hydroxy ester to lactone **23** in 88% yield (Chart III).[13] Attempts to prepare anhydrovernolepin **24** from dilactone **23** proved unsatisfactory. Application of the aforementioned Danishefsky procedure[14] afforded a high melting (>260 °C) solid with the expected spectral characteristics, but the yield was less than 4%.[13] Again, increased torsional strain in the γ-lactone grouping may be responsible for the apparent base instability of diene dilactone **23** and the resultant poor yield in the α-methylenation sequence.

We explored several schemes for conversion of unsaturated ester **13** to vernolepin, but none showed promise. Treatment of **13** with 9-BBN followed by alkaline hydrogen peroxide led only to lactol **25**. The ortho ester derivative **26**[14] failed to react with excess 9-BBN at room temperature, while complex mixtures resulted at elevated temperatures. Olefin **13** also proved resistant to oxymercuration under a variety of conditions.[17] *m*-Chloroperoxybenzoic acid did not epoxidize the double bond of **13** at 0 °C, even after 24 h. However, upon warming to room temperature, reaction occurred to give epoxide **27** (65%), diepoxide **28** (15%), and diene **19** (20%). Thus the double bond of **13** must be effectively shielded by the *o*-nitrophenyl selenide, or the derived selenoxide, so that epoxidation cannot take place before elimination of the selenoxide moiety, a process known to occur near room temperature.[12b] Conceivably, the epoxidation may involve *o*-nitroperoxybenzeneselenic acid,[18] produced through oxidation of the *o*-nitrobenzeneselenic acid formed in the elimination reaction. This point was not pursued.

Experimental Section[19,20]

***cis*-2,6-Bis(2-chloro-2-propenyl)-4,4-(2,2-dimethyl-1,3-propylenedioxy)cyclohexanone (2c).** To a flame-dried 500-mL round-bottom flask equipped with a magnetic stirring bar, heating mantle, Dean–Stark trap, and reflux condenser connected to an argon bubbler system were added 49.0 g (0.250 mol) of keto ketal IV (R,R = $CH_2C(CH_3)_2CH_2$), 250 mL of benzene, and 31.5 mL (0.375 mol) of pyrrolidine. The resulting solution was refluxed with azeotropic removal of water for 8 h. The cooled contents were concentrated under reduced pressure and 3.75 g (25.0 mmol) of sodium iodide, 125 mL (0.075 mol) of diisopropylethylamine, 70 mL (0.750 mol) of 2,3-dichloro-1-propene, and 100 mL of absolute ethyl alcohol were added. The resulting solution was refluxed under argon for 36 h, 80 mL of water was added, and reflux was continued for 24 h. The contents of the cooled flask were transferred with water and ether to a separatory funnel and extracted with ether. The combined organic extracts were washed with 10% HCl, water, and saturated salt solution. Drying over anhydrous $MgSO_4$, filtration, and concentration under reduced pressure gave 85.0 g of a light brown solid. Recrystallization from methyl alcohol and chromatography of the mother liquors afforded 79.0 g (91%) of crystalline cis-dialkylation product **2c**; mp 122–123 °C; λ_{max}^{film} 1715, 1620, 1140, 1100, and 905 cm^{-1}; δ (Me_4Si, $CDCl_3$) 5.20 (m, 4 H), 3.57 (d, 4 H, *J* = 4 Hz), 2.0–3.2 (m, 10 H), and 1.00 (s, 6 H).

Anal. Calcd for $C_{17}H_{24}Cl_2O_3$: C, 58.80; H, 6.96. Found: C, 58.51; H, 6.88.

***t*-2,*t*-6-Bis(2-chloro-2-propenyl)-4,4-(2,2-dimethyl-1,3-propylenedioxy)cyclohexan-*r*-1-ol (3c).** To a 3-L two-neck round-bottom flask equipped with a magnetic stirring bar, addition funnel, and reflux condenser connected to an argon bubbler system were added 7.9 g (0.208 mol) of lithium aluminum hydride and 1 L of anhydrous ether. The flask was cooled to −78 °C in a dry ice–ethyl alcohol bath and a solution of 72.0 g (0.208 mol) of ketone **2** in 500 mL of anhydrous ether was added over a 1-h period. After stirring for an additional 2 h at −78 °C, the reaction was carefully quenched by adding 8.0 mL of water, 8.0 mL of 15% NaOH solution, and 24.0 mL of water to the vigorously stirred solution while warming to room temperature. Filtration and thorough washing of the white solid with ether followed by concentration of the combined filtrate afforded 72.5 g (~100%) of a white crystalline solid which was shown by high-pressure liquid chromatography to consist of a 92:8 mixture of the equatorial and axial alcohols **3c** and **4c**, respectively. Recrystallization of a small sample from hexane gave white needles: mp 158.5–159.5 °C; λ_{max}^{film} 3450, 1640, 1370, 1160, and 1120 cm^{-1}; δ (Me_4Si, $CDCl_3$) 5.23 (m, 4 H), 3.50 (d, 4 H, *J* = 3 Hz), 3.10 (m, 1 H), 1.6–3.0 (m, 10 H), and 0.95 (s, 6 H).

***t*-3,*t*-5-Bis(2-chloro-2-propenyl)-*r*-4-hydroxycyclohexanone (5c).** To a 2-L round-bottom flask equipped with a magnetic stirring bar and reflux condenser connected to an argon bubbler system were added 72.5 g (0.208 mol) of crude alcohol **3c** (containing 8% of alcohol **4c**), 1 L of acetone, 300 mL of water, and 0.5 mL of concentrated HCl solution. The resulting solution was heated at reflux for 48 h under argon. Solid sodium bicarbonate (5 g) was added to the cooled solution and the acetone was removed under reduced pressure, affording a crystalline solid. Filtration and recrystallization from hot aqueous methyl alcohol gave 49 g (88% overall yield from **2c**) of white needles: mp 121.5–122 °C; λ_{max}^{film} 3400, 1620, 1140, 1100, and 910 cm^{-1}; δ (Me_4Si, $CDCl_3$) 5.21 (m, 4 H), 3.50 (m, 1 H), 3.0 (m, 2 H), and 2.0–2.8 (m, 8 H).

Anal. Calcd for $C_{12}H_{16}Cl_2O_2$: C, 54.77; H, 6.13. Found: C, 54.90; H, 5.90.

***r*-4-(*tert*-Butyldimethylsiloxy)-*t*-3,*t*-5-bis(2-chloro-2-propenyl)cyclohexanone (6c).** To a 500-mL round-bottom flask equipped with a magnetic stirring bar, heating mantle, and condenser connected to an argon bubbler system were added 50.0 g (0.190 mol) of hydroxy ketone **5c**, 42.6 g (0.285 mol) of *tert*-butyldimethylsilyl chloride, 32.3 g (0.475 mol) of imidazole, and 60.0 mL of dry dimethylformamide.[9] The resulting solution was heated at 50 °C for 5 days. The cooled contents of the flask were poured into 500 mL of 10% HCl solution and extracted with ether. The combined organic layers were washed with water and brine. Drying over anhydrous $MgSO_4$, filtration, and concentration under reduced pressure gave 70.9 of a solid. Recrystallization from hexane gave 67.9 g (95%) of white needles: mp 115–116 °C; λ_{max}^{film} 3100, 1720, 1630, 1260, 1120, and 1080 cm^{-1}; δ (Me_4Si, $CDCl_3$) 5.20 (m, 4 H), 3.50 (t, 1 H, *J* = 7 Hz), 1.5–3.0 (m, 10 H), 0.92 (s, 9 H), and 0.14 (s, 6 H).

Anal. Calcd for $C_{18}H_{30}Cl_2O_2Si$: C, 57.28; H, 8.01. Found: C, 57.39; H, 7.95.

Ethyl 2-[*r*-4-(*tert*-Butyldimethylsilyloxy)-*t*-2-(carbomethoxy)-*t*-3,*t*-5-bis(2-chloro-2-propenyl)-1-oxocyclohex-*c*-2-yl]acetate (8c). To a 250-mL flame-dried three-neck round-bottom flask equipped with a magnetic stirring bar, addition funnel, glass stopper, and reflux condenser connected to an argon bubbler system was added 4.00 g (95.0 mmol) of 57% sodium hydride dispersion. The

sodium hydride was triturated with four 10-mL portions of hexane under an atmosphere of argon, 110 mL of dimethyl carbonate and 0.40 mL (10 mmol) of methyl alcohol were added, and the resulting suspension was heated to 50 °C. A solution of 14.5 g (38.4 mmol) of ketone **6c** was added to the stirred reaction mixture over a 1-h period and stirring at 50 °C under argon was continued for 12 h. A solution of 6.0 g (0.10 mol) of glacial acetic acid in 30 mL of water was carefully added to the cooled solution and the contents of the flask were poured into ether. The aqueous layer was removed and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give 16.6 g (~100%) of crude carbomethylated ketone **7c**: λ_{max}^{film} 3090, 1755, 1720, 1655, 1620, 1610, and 1250 cm^{-1}.

To a 500-mL flame-dried round-bottom flask equipped with a magnetic stirring bar, reflux condenser, addition funnel, glass stopper, and reflux condenser connected to an argon bubbler system was added 1.69 g (40.0 mmol) of a 57% sodium hydride dispersion. After the sodium hydride was triturated with four 5-mL portions of hexane, 100 mL of dry dimethyl formamide and 100 mL of benzene were added. A solution of 16.6 g of crude carbomethoxy ketone **7c** in 50 mL of benzene was added over a 15-min period. After hydrogen evolution had ceased, 8.6 g (40.0 mmol) of ethyl iodoacetate was added and the solution was stirred at room temperature for 12 h. The mixture was poured into water and extracted with ether. The combined organic extracts were washed with water and brine. Drying over anhydrous $MgSO_4$ and concentration gave 18.0 g of crude alkylation product. Chromatography over 500 g of silica gel gave 13.9 g (80%) of keto diester **8c**: mp 81–82 °C; λ_{max}^{film} 1735, 1640, 1260, 1200, 1080, 880, and 840 cm^{-1}; δ (Me_4Si, $CDCl_3$) 5.16 (m, 4 H), 4.08 (q, 2 H, J = 7 Hz), 3.72 (s, 3 H), 3.70 (m, 1 H), 3.45 (d, 1 H, J = 18 Hz), 2.97 (d, 1 H, J = 18 Hz), 2.0–2.9 (m, 8 H), 1.23 (t, 3 H, J = 7 Hz), 0.93 (s, 9 H), 0.13 (s, 3 H), and 0.11 (s, 3 H).

Anal. Calcd for $C_{21}H_{38}Cl_2O_6Si$: C, 55.27; H, 7.34. Found: C, 55.35; H, 7.28.

Triol Mixture 9c and 10c. To a 1-L three-neck round-bottom flask equipped with a magnetic stirring bar, addition funnel, glass stopper, and reflux condenser connected to an argon bubbler system were added 2.66 g (70 mmol) of lithium aluminum hydride and 450 mL of anhydrous ether. The stirred suspension was cooled to −78 °C in a dry ice–acetone bath and a solution of 14.6 g (28 mmol) of keto diester **8c** was added over a 30-min period. After stirring at −78 °C for 2 h and at reflux for 6 h, the reaction was carefully quenched with 2.66 mL of water, 2.66 mL of 15% NaOH solution, and 8.0 mL of water. Filtration and thorough ether washing of the precipitate followed by concentration of the combined filtrate under reduced pressure gave 12.9 g (~100%) of triol mixture **9c** and **10c** as a viscous oil.

The isomeric triols **9c** and **10c** could be separated by medium-pressure preparative liquid chromatography with 2% ethyl alcohol–ethyl acetate using the recycling technique. Isomer **9c** (7.32 g), mp 152–153 °C, was obtained in 57% yield: λ_{max}^{film} 3300, 1640, 1250, and 1100 cm^{-1}; δ (Me_4Si, $CDCl_3$) 5.23 (m, 4 H), 3.86 (m, 5 H), 3.31 (t, 1 H, J = 10 Hz), 2.0–3.0 (m, 10 H), 1.00 (s, 9 H), and 0.08 (s, 6 H).

Anal. Calcd for $C_{21}H_{38}Cl_2O_4Si$: C, 55.62; H, 8.45. Found: C, 55.76; H, 8.53.

Bridged Ortho Ester 11c. To a 250-mL round-bottom flask equipped with a magnetic stirring bar and argon inlet were added 12.9 g of crude triol mixture **9c** and **10c**, 15 mL of triethyl orthoacetate, 50 mL of dry tetrahydrofuran, and 200 mg of *p*-toluenesulfonic acid. After 15 min, 1.0 g of solid $NaHCO_3$ was added and the volatile components were removed under reduced pressure. Chromatography of the residue on 700 g of silica gel with 5% ethyl acetate in hexane gave 9.26 g (68% overall yield from keto diester **8c**) of crystalline ortho ester **11c**: mp 45–48 °C; λ_{max}^{film} 3090, 1640, 1255, 1080, 855, 770 cm^{-1}; δ (Me_4Si, $CDCl_3$) 5.2 (m, 4 H), 3.80 (m, 5 H), 3.40 (t, 1 H, J = 8 Hz), 1.3–2.5 (m, 10 H), 1.30 (s, 3 H), 0.94 (s, 9 H), 0.13 (s, 3 H), and 0.11 (s, 3 H).

Anal. Calcd for $C_{23}H_{38}Cl_2O_4Si$: C, 57.85; H, 8.02. Found: C, 58.13; H, 7.89.

Methyl 2-[*r*-6-(*tert*-Butyldimethylsilyloxy)-*t*-9-hydroxy-*c*-10-(2-hydroxyethyl)-2-oxa-3-oxo-*c*-5*H*-decal-*t*-7-yl]acetate (12). To a 500-mL three-neck round-bottom flask equipped with a magnetic stirring bar, glass stopper, gas dispersion tube, and gas outlet adapter connected to a drying tube was added a solution of 6.45 g (14.0 mmol) of triol **9** in 250 mL of freshly distilled methyl alcohol. The stirred solution was cooled to −78 °C (dry ice–ethyl alcohol bath) and a stream of ozone in oxygen gas, which was dried by passing it through a dry ice trap, was bubbled into the solution until a light blue color persisted.

Dimethyl sulfide (5.10 mL, 70.0 mmol) and pyridine (5.60 mL, 70.0 mmol) were added via syringe and the flask was sealed and allowed to gradually warm up to room temperature and stirred for 12 h.

The methyl alcohol and excess dimethyl sulfide were removed under reduced pressure. The residue was taken up in ethyl acetate and dilute HCl and extracted with ethyl acetate. The combined organic layers were washed with 10% HCl solution and brine. Drying over $MgSO_4$, filtration, and concentration under reduced pressure gave a white solid whose IR spectrum showed some carboxylic acid present.

The solid, dissolved in 40 mL of tetrahydrofuran, was treated with an ethereal diazomethane solution. After standing for 2 h, the solution was concentrated and the residue was recrystallized from ethyl acetate–hexane to give 5.20 g (89%) of lactone ester diol **12**: mp 156–157 °C; λ_{max}^{KBr} 3250, 1730, 1260, 1205, 1090, 1060, 1020, and 830 cm^{-1}; δ (Me_4Si, $CDCl_3$) (270 MHz) 4.48 (d, 1 H, J = 13 Hz), 4.33 (d, 1 H, J = 13 Hz), 3.93–3.86 (m, 3 H), 3.68 (s, 3 H), 3.50 (t, 1 H, J = 10 Hz), 2.83 (d of d, 1 H, J^1 = 18 Hz, J^2 = 2 Hz), 2.74 (d of d, 1 H, J^1 = 15 Hz, J^2 = 3 Hz), 2.52 (d of d, 1 H, J^1 = 18 Hz, J^2 = 6.6 Hz), 2.11 (d of d, 1 H, J^1 = 15 Hz, J^2 = 9 Hz), 2.08–1.33 (m, 6 H), 0.90 (s, 9 H), 0.12 (s, 3 H, CH_3Si–), and 0.07 (s, 3 H).

Anal. Calcd for $C_{20}H_{36}O_7Si$: C, 57.63; H, 8.71. Found: C, 57.91; H, 8.78.

Methyl 2-[*r*-6-(*tert*-Butyldimethylsilyloxy)-*t*-9-hydroxy-*c*-10-[2-(*o*-nitrophenyl)selenoethyl]-2-oxa-3-oxo-*c*-5*H*-decal-*t*-7-yl]acetate (13). To a flame-dried 15-mL two-neck round-bottom flask equipped with a magnetic stirring bar, septum cap, and 25-mL Hershberg addition funnel capped with a gas inlet tube connected to a mercury bubbler were added 416 mg (1.00 mmol) of lactone ester diol **12**, 303 mg (1.50 mmol) of tri-*n*-butylphosphine, and 8 mL of dry tetrahydrofuran. A solution of 339 mg (1.50 mmol) of *o*-nitrophenyl selenocyante in 5 mL of dry tetrahydrofuran was added dropwise over a 30-min period and the resulting deep red solution was stirred at room temperature for 8 h.[12a] The reaction mixture was placed directly on a column of 150 g of silica gel which was eluted with 50% ethyl acetate in hexane to yield 498 mg (83%) of the selenide **13** as a fine yellow powder. A small sample recrystallized from ethyl acetate–hexane had: mp 190.5–191.5 °C; λ_{max}^{KBr} 3450, 1730, 1585, 1510, 1335, 1260, 835, 770, and 715 cm^{-1}; δ (Me_4Si, $CDCl_3$) (270 MHz) 8.34 (d, 1 H, J = 8 Hz), 7.64–7.23 (m, 3 H), 4.53 (d, 1 H, J = 13 Hz), 4.25 (d, 1 H, J = 13 Hz), 4.03 (d of d, 1 H, J^1 = 10 Hz, J^2 = 5 Hz), 3.70 (s, 3 H), 3.56 (t, 1 H, J = 10 Hz), 3.07–2.52 (m, 6 H), 2.34–1.50 (m, 6 H), 0.90 (s, 9 H), 0.12 (s, 3 H), and 0.06 (s, 3 H).

Anal. Calcd for $C_{26}H_{39}NO_8SiSe$: C, 51.99; H, 6.54; N, 2.33. Found: C, 52.10; H, 6.82; N, 2.20.

Methyl 2-[*r*-6-(*tert*-Butyldimethylsilyloxy)-*t*-9-hydroxy-2-oxa-3-oxo-*c*-10-vinyl-*c*-5*H*-decal-*t*-7-yl]acetate (14). To a 25-mL round-bottom flask containing 600 mg (1.00 mmol) of *o*-nitrophenyl selenide **13**, 15 mL of tetrahydrofuran, and a magnetic stirring bar was added 1.36 mL (12.0 mmol) of 30% hydrogen peroxide solution. The mixture was stirred at room temperature for 12 h and transferred with ethyl acetate to a separatory funnel containing saturated $NaHCO_3$ solution. After vigorous mixing, the aqueous layer was removed and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure, affording 398 mg (100%) of vinylic lactone **14** as a light tan solid. A small sample recrystallized from ethyl acetate–hexane had: mp 141–142 °C; λ_{max}^{film} 3600–3300, 3110, 1740, 1660, 1260, 1160, and 930 cm^{-1}; δ (Me_4Si, $CDCl_3$) (270 MHz) 5.71–5.43 (m, 3 H), 4.54 (q, 2 H, J = 13 Hz), 3.73 (d of d, 1 H, J^1 = 10 Hz, J^2 = 5 Hz), 3.69 (s, 3 H), 3.57 (t, 1 H, J = 10 Hz), 2.83 (d, 1 H, J = 18 Hz), 2.76 (d, 1 H, J = 16 Hz), 2.49 (d of d, 1 H, J^1 = 18 Hz, J^2 = 6.6 Hz), 2.20 (d of d, 1 H, J^1 = 16 Hz, J^2 = 8.5 Hz), 2.08–1.90 (m, 2 H), 1.81 (s, 1 H), 1.72 (t, 1 H, J = 9 Hz), 1.52 (q, 1 H, J = 13 Hz), 0.90 (s, 9 H), 0.13 (s, 3 H), and 0.08 (s, 3 H).

Anal. Calcd for $C_{20}H_{34}O_6Si$: C, 60.27; H, 8.60. Found: C, 60.26; H, 8.39.

Bisnor-9-hydroxy-8-deoxyvernolepin (15). To a 100-mL flame-dried two-neck round-bottom flask equipped with a magnetic stirring bar, glass stopper, Dean–Stark trap, and condenser with a gas exit to a mercury bubbler were added 522 mg (2.00 mmol) of tetra-*n*-butylammonium fluoride and 50 mL of dry benzene.[9] The apparatus was charged with argon and heated to reflux in an oil bath. A 5-mL forerun of benzene was used to remove any last traces of water. A solution of 556 mg (1.40 mmol) of silyl ether **14** in 10 mL of dry *p*-dioxane was added through the stoppered neck. The pink solution quickly turned dark brown and an oily gum precipitated. Slow reflux with removal of solvent was maintained for 30 min with a total of 25 mL being distilled.

The cooled solution was concentrated under reduced pressure. The gummy residue was treated with 50 mL of ethyl acetate and 5 mL of brine to which 5 drops of concentrated HCl had been added. Vigorous stirring produced a two-phase system which was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$,

concentrated, and filtered over 20 g of silica gel with ethyl acetate to give 400 mg of a yellow oil.

Preparative high-pressure liquid chromatography on Porasil A using 2% methyl alcohol in ethyl acetate gave 250 mg (0.99 mmol, 71%) of dilactone **15**. A small sample recrystallized from acetone–cyclohexane as a fine, white powder: mp 139–140 °C; λ_{max}^{KBr} 3600–3200, 1780, 1730, and 100 cm^{-1}; δ (Me_4Si, $CDCl_3$) 5.30 (m, 3 H), 4.52 (d, 1 H, J = 13 Hz), 4.30 (d, 1 H, J = 13 Hz), 3.72 (m, 2 H), and 1.5–2.7 (m, 8 H).

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90: H, 6.39. Found: C, 61.68; H, 6.38.

9β-Hydroxy-8-deoxyvernolepin (16). To a 50-mL, two-neck, flame dried, round-bottom flask equipped with a magnetic stirring bar, argon inlet, and a glass stopper was added 900 mg (4.86 mmol) of dimethyl(methylene)ammonium iodide.[21] The Mannich salt was triturated with three 8-mL portions of dry tetrahydrofuran and dried by passing argon over the residue and by heating at 80 °C in vacuo (0.05 torr) for 2 h. The evacuated flask was cooled to room temperature and filled with dry argon, and the glass stopper was replaced by a septum cap.

The dilactone enolate of **15** was prepared while the Mannich salt was drying. A solution of 0.56 mL (4.0 mmol) of diisopropylamine in 10 mL of dry tetrahydrofuran was added to a 25-mL flame-dried argon-filled two-neck round-bottom flask equipped with an argon inlet, a 25-mL Hershberg addition funnel, magnetic stirring bar, and septum cap. The flask was cooled to −78 °C and 1.9 mL (3.9 mmol) of 2.0 M *n*-butyllithium in hexane was added via syringe over a period of 2 min. After 30 min, a solution of 54 mg (0.21 mmol) of dilactone **15** and 0.525 mL of dry HMPA in 5 mL of dry THF was added over a period of 1 h. Stirring was continued for 15 min after addition was complete. The resulting solution was added via syringe to the previously prepared vigorously stirred Mannich salt at −78 °C. Stirring was continued at −78 °C for 30 min then at room temperature for 90 min.

The reaction mixture was acidified to pH 2 with 10% aqueous HCl (~7 mL). After 1 min, solid Na_2CO_3 was added until the solution became basic (pH 9). Water was added and the mixture was extracted with ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo, affording 1.5 g of a yellow oil.

To this oil in a 50-mL round-bottom flask was added 6 mL of *p*-dioxane and 15 mL of methyl iodide. The mixture was refluxed under argon for 18 h. The volatiles were removed under reduced pressure and the gummy solid was triturated with three 15-mL portions of ether to afford 750 mg of a yellow solid.

To the solid was added 40 mL of ethyl acetate and 10 mL of water containing 800 mg (9.55 mmol) of sodium bicarbonate. The mixture was stirred vigorously for 30 min, the organic layer was removed via pipet, and three similar extractions were performed. The combined organic extracts were dried over Na_2SO_4 and concentrated to give 180 mg of a yellow oil. Filtration over 10 g of silica gel with ethyl acetate gave 18 mg of an oil which was subjected to preparative liquid chromatography with ethyl acetate on μ-Porasil affording 12.5 mg of crystalline **16**: mp 209.5–210.5 °C; λ_{max}^{KBr} 3600–3100, 1760, 1710, 1665, 1615, and 1165 cm^{-1}; δ (Me_4Si, $CDCl_3$) (270 MHz) 6.70 (s, 1 H), 6.19 (d, 1 H, J = 3 Hz), 5.87 (s, 1 H), 5.78–5.44 (m, 4 H), 4.69 (d, 1 H, J = 15 Hz), 4.54 (d, 1 H, J = 15 Hz), 3.98 (t, 1 H, J = 11 Hz), 3.90 (d of d, 1 H, J^1 = 11 Hz, J^2 = 5.5 Hz), 2.90 (d, 1 H, J = 11 Hz), 2.68 (t of d, 1 H, J^t = 11 Hz, J^d = 2 Hz), 2.44 (d of t, 1 H, J^d = 13 Hz, J^t = 2 Hz), and 1.75 (q, 1 H, J = 12 Hz).

Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.19; H, 5.83.

Methyl 2-[*r*-6-(*tert*-Butyldimethylsilyloxy)-*c*-10-[2-(*o*-nitrophenyl)selenoethyl]-2-oxa-3-oxo-*c*-5*H*-8-octal-*t*-7-yl]-acetate (18). To a 50-mL flame-dried round-bottom flask equipped with a magnetic stirring bar and argon inlet were added 1.20 g (2.00 mmol) of alcohol **13**, 30 mL of dichloromethane, 0.50 mL (4.00 mmol) of triethylamine, and 0.32 mL (4.00 mmol) of methanesulfonyl chloride. The resulting solution was stirred at 0 °C for 1 h. The mixture was poured into 15 mL of 10% HCl solution and extracted with dichloromethane. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. Concentration under reduced pressure afforded 1.40 g (~100%) of the crude mesylate **17**: λ_{max}^{film} 1730, 1585, 1510, 1335, 1260, and 1180 cm^{-1}.

The crude mesylate was dissolved in 35 mL of dichloromethane and added via syringe to a vigorously stirred suspension of 20 g of Woelm alumina (W-200 activity super I preheated to 400 °C for 48 h at 0.05 torr) and the resulting slurry was stirred at room temperature for 24 h.[16] Ethyl alcohol (5 mL, 95%) was added, the mixture was filtered and the alumina was repeatedly washed with dichloromethane. Concentration under reduced pressure gave 680 mg of a red oil. Preparative thick-layer chromatography using 35% ethyl acetate in hexane afforded 466 mg (40%) of seleno olefin **18**.

Methyl 2-[*r*-6-(*tert*-Butyldimethylsilyloxy)-2-oxa-3-oxo-*c*-10-vinyl-*c*-5*H*-8-octal-*t*-7-yl]acetate (19). To a stirred solution of 70 mg (0.12 mmol) of selenide **18** in 3.0 mL of tetrahydrofuran under argon was added 0.15 mL (1.3 mmol) of 30% H_2O_2 and the resulting solution was stirred at room temperature for 6 h.[12b] The solvent was removed under reduced pressure and the residue was taken up in ethyl acetate and washed with saturated $NaHCO_3$ solution and with brine. After standing over $MgSO_4$, the organic layer was concentrated in vacuo to give 47 mg of crude crystalline diene **19**. Recrystallization from hexane gave needles: mp 59–60 °C; λ_{max}^{film} 3040, 2970, 2940, 2905, 2865, 1740, 1635, 1260, and 1100 cm^{-1}; δ (Me_4Si, $CDCl_3$) 6.10–5.04 (m, 5 H), 4.19 (s, 2 H), 3.70 (s, 3 H), 3.0–2.4 (m, 4 H), 2.4–1.8 (m, 2 H), 0.90 (s, 9 H), 0.12 (s, 3 H), and 0.09 (s, 3 H).

Anal. Calcd for $C_{20}H_{32}O_5Si$: C, 63.12; H, 8.48. Found: C, 62.94; H, 8.46.

Methyl 2-[*r*-6-(*tert*-Butyldimethylsilyloxy)-*c*-10-ethyl-2-oxa-3-oxo-*c*-5*H*-decal-*t*-7-yl]acetate (20). To a 50-mL two-neck Morton flask equipped with a magnetic stirring bar and septum cap was added 100 mg of 5% palladium-on-carbon and 5.0 mL of absolute ethyl alcohol. The flask was affixed to an atmospheric hydrogenation apparatus and was charged with hydrogen. The mixture was vigorously stirred and after 30 min, a solution of 47 mg (0.12 mmol) of diene **19** in 2.0 mL of absolute ethyl alcohol was added via syringe. The hydrogen level was noted and vigorous stirring was again initiated. After 5 min, 1 equiv of gas was absorbed while further consumption was slow. After 12 h, the solution was filtered and the catalyst was washed thoroughly. Concentration of the filtrate afforded 43 mg (93%) of a clear oil that crystallized upon treatment with hexane. Recrystallization from this solvent gave colorless needles: mp 55–56 °C; λ_{max}^{film} 2970, 2940, 2865, 1740, 1260, 1200, and 1080 cm^{-1}; δ (Me_4Si, $CDCl_3$) 4.39 (d, 1 H, J = 12 Hz), 3.95 (d, 1 H, J = 12 Hz), 3.70 (s, 3 H), 3.0–2.4 (m, 4 H), 2.4–1.2 (m, 8 H), 0.90 (s, 12 H), 0.12 (s, 3 H), and 0.09 (s, 3 H).

Anal. Calcd for $C_{20}H_{36}O_5Si$: C, 62.46; H, 9.44. Found: C, 62.47; H, 9.41.

Bisnor-8-deoxydihydrovernolepin (21). To a flame-dried 25-mL two-neck round-bottom flask equipped with a magnetic stirring bar, glass stopper, Dean–Stark trap, and a condenser connected to a bubbler system were added 39 mg (0.15 mmol) of tetra-*n*-butylammonium fluoride and 6 mL of dry benzene.[9] The stirred solution was brought to reflux by heating in an oil bath and a small amount of benzene was distilled to ensure anhydrous conditions. A solution of 43 mg (0.11 mmol) of silyl ether **20** and 24 mg (0.25 mmol) of *tert*-amyl alcohol in 2.0 mL of dry dioxane was added quickly through the stoppered neck and slow distillation was maintained for 30 min. The cooled mixture was poured into ethyl acetate and washed with brine acidified with a few drops of concentrated HCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give 35 mg of a golden oil. Chromatography over 1.5 g of silica gel with 50% ethyl acetate–hexane gave 25 mg of an oil which afforded 9.3 mg of white crystals, mp 148.5–149 °C (lit.[15] 149–150 °C), upon trituration with ether. Preparative liquid chromatography of the mother liquors (50% EtOAc–hexane, μ-Porasil) gave an additional 1.5 mg of bis lactone **21** (41% overall yield). The infrared and NMR spectra of this substance were identical to those supplied by Dr. P. A. Grieco:[22] λ_{max}^{film} 1785, 1740 cm^{-1}; δ (Me_4Si, $CDCl_3$) 4.34 (d, 1 H, J = 12 Hz), 3.97 (d, 1 H, J = 12 Hz), 3.95 (t, 1 H, J = 11 Hz), 2.85 (d of d, 1 H, J^1 = 18 Hz, J^2 = 1 Hz), 2.75 (d of d, 1 H, J^1 = 18 Hz, J^2 = 7 Hz), 2.62 (d of d, 1 H, J^1 = 16 Hz, J^2 = 6.5 Hz), 2.34 (d of d, 1 H, J^1 = 16 Hz, J^2 = 13 Hz), 2.1–1.9 (m, 2 H), 1.7–1.4 (m, 6 H), and 0.95 (t, 1 H, J = 7 Hz).

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Registry No.—**2c**, 64921-06-8; **3c**, 69225-40-7; **4c**, 69257-09-6; **5c**, 69225-41-8; **6c**, 69225-42-9; **7c**, 69225-43-0; **8c**, 69225-44-1; **9c**, 69307-83-1; **10c**, 69257-10-9; **11c**, 69258-27-1; **12**, 69225-45-2; **13**, 69225-46-3; **14**, 69225-47-4; **15**, 69225-48-5; **15** dienolate, 69225-49-6; **15** [R″ = H, $CH_2N(CH_3)_2$], 69225-50-9; **15** [R″ = H, $CH_2N^+(CH_3)_2$] diodide, 69225-51-0; **16**, 69225-52-1; **17**, 69225-53-2; **18**, 69257-98-3; **19**, 69225-54-3; **20**, 69238-68-2; **21**, 69257-11-0; **22**, 69225-55-4; **23**, 69225-56-5; **27**, 69225-57-6; **28**, 69225-58-7; IV, 69225-59-8; pyrrolidine, 127-75-1; 2,3-dichloro-1-propene, 78-88-6; *tert*-butyldimethylsilyl chloride, 18162-48-6; dimethyl carbonate, 616-38-6; ethyl iodoacetate, 623-48-3; triethyl orthoacetate, 78-39-7; dimethyl (meth-

ylene) ammonium iodide, 33797-51-2; o-nitrophenyl selenocyanate, 51694-22-5.

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(20) Experiments in the "**c** series" only are described in this section. A detailed account of the analogous "**a** series and **b** series" experiments is available from the Ph.D. thesis of G. A. Flynn.[13]

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Stereochemistry of the Enantioselective Electrolytic Pinacolization of α,β-Unsaturated Racemic Ketones. 2. Substituted 1,9,10,10a-Tetrahydro-3(2*H*)-phenanthrones†

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The electrochemical pinacolization of racemic ketones of the title series shows in many cases a remarkable phenomenon of enantiomeric recognition, called enantioselectivity. The relative configuration of the obtained diol (established by X-ray diffraction analysis) and the steric effects of the substituents on this selectivity indicate that the molecules are selectively absorbed on the electrode by their rear face and give information about the kind of approach of the two activated species during the pinacolization.

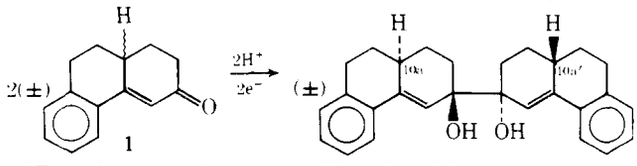
We have shown in a first paper[1] on the hydrodimerization on a mercury cathode of α,β-unsaturated, polycyclic, racemic ketones that the reaction is very selective in a number of cases. The more selective results are observed in a neutral aqueous–alcoholic medium, as in the case of the (±)-1,9,10,10a-tetrahydro-3(2*H*)-phenanthrone (**1**, Scheme I).

By reduction of the corresponding resolved ketones (+)-**1** and (−)-**1**, we have found that the new C–C bond in the racemic diol appears between two like ketones. Its carbons C(10a) and C(10a′) have the same absolute configuration. Such an enantiomeric recognition has been called *enantioselectivity*.[1] A reaction between two like ketones (*R* + *R* or *S* + *S*), giving a *homodiol*, has a lower free energy of activation than a reaction between two opposite ketones (*R* + *S* or *S* + *R*), corresponding to the formation of a *heterodiol*.

Other examples of enantioselectivity are known in cases of chemical[2,3] and more particularly of electrochemical reactions in both oxidative[4] and reductive[5] processes.

In fact, the stereochemical problem of the reaction shown

Scheme I. Phenomenon of Enantioselectivity[a]



[a] Reaction is carried out at pH 6 (C_2H_5OH/CH_3COOH) with a potential (*V*) of −1.4 V on a mercury cathode.

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