Unit.
(15) D. H. Nugteren, D. A. vanDorp, S. Bergstrom, M. Hamberg, and B. Samuelsson, *Nature (London)*, **212**, 38 (1966).
(16) G. L. Bundy, E. G. Daniels, F. H. Lincoln, and J. E. Pike, *J. Am. Chem. Soc.*, **94**, 2124 (1972).
(17) E. Änggard and B. Samuelsson, *J. Biol. Chem.*, **239**, 4097 (1964); G. L. Bundy, W. P. Schneider, F. H. Lincoln, and J. E. Pike, *J. Am. Chem. Soc.*, **94**, 2023 (1972).

The Total Synthesis of *dl*-Vernolepin and *dl*-Vernomenin

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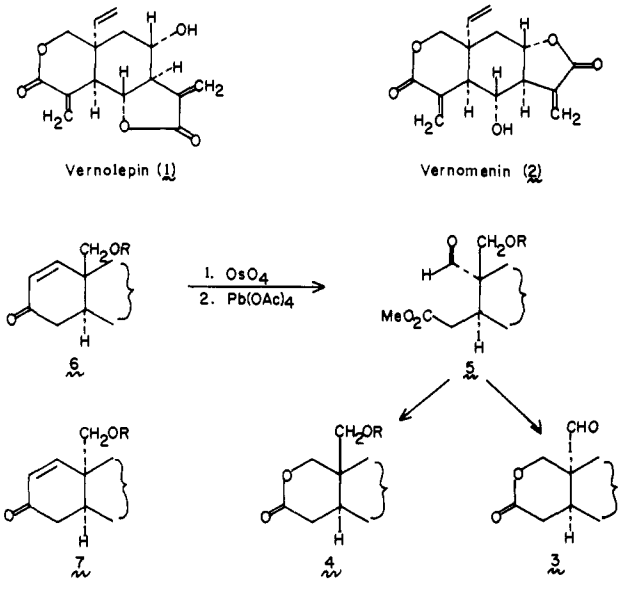
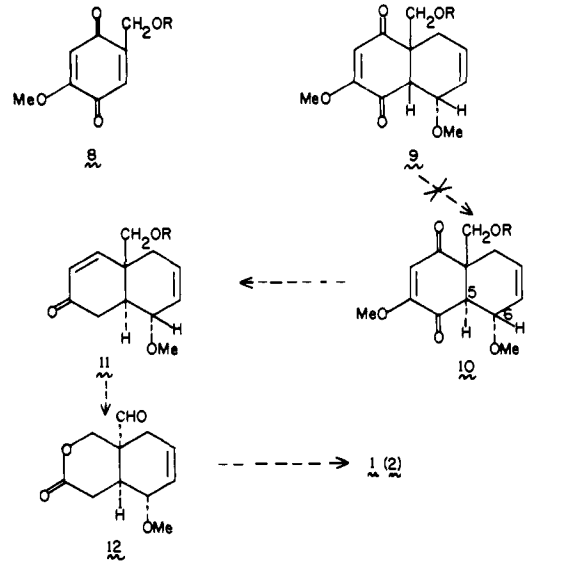
Abstract: The total syntheses of the racemates of the bis-α-methylenelactonic sesquiterpenes, vernolepin and vernomenin, have been achieved. These tumor inhibitors were synthesized in 17 steps starting with dienone ester **29**, itself the result of two Diels–Alder reactions. The key elements of the total syntheses were (i) the use of an angular carboxyl group to establish three centers of asymmetry in the B ring (**29** → **37**), (ii) the conversion of a cis-fused cyclohexenone to a cis δ-lactone (**37** → **41**), (iii) the protection of a δ-lactone as an ethylene glycol mixed orthoester (**41** → **42**), (iv) the opening of a very hindered epoxide to control the stereochemistry of the C ring (**52** → **54**), and (v) the bis-α-methylenation of the bisnor precursor (**55** → **1** and **56** → **2**) using dimethyl(methylene)ammonium iodide.

Background

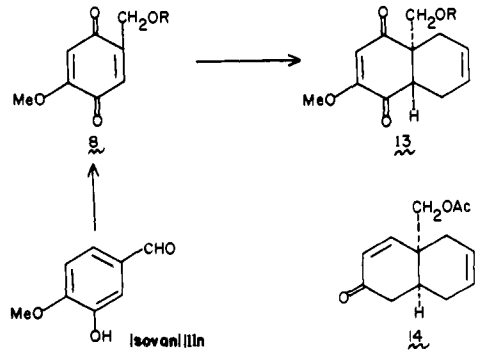
In a previous paper,[1] we described an approach to the total synthesis of the tumor inhibitors vernolepin (**1**) and vernomenin (**2**).[2-4] Our route to the valerolactone segment involved oxidative degradation of a cyclohexenone using the indicated reactions. If one employed a precursor of the type **6**, model studies indicated that one could derive either the cis lactone **3** or a trans lactone **4** by suitable manipulations of the intermediate aldehydo ester **5**. An obvious corollary involved the supposition that one could derive the desired **3** from either a trans-fused enone **6** or a cis-fused enone **7**.



The synthetic scheme to bicyclic Δ^1-enones, which was available, was provided in characteristically elegant form by the Woodward school in the context of its classical total synthesis of steroids.[5] Translated to our needs, this involved recourse to a para quinone of the type **8** which was easily available in copious quantity from isovanillin, as previously described.[1] Cycloaddition of **8** with 1-methoxybutadiene gave, as expected from the maxim of cis-endo addition,[6] the adduct **9**. It was our intention to transform **9**, by equilibration,[5] to the trans epimer **10**. The further elaboration of **10** in the direction of vernolepin and vernomenin was to be achieved via intermediates **11** and **12**. Unfortunately, even after repeated experimentation, we were unable to effect the transformation of **9** → **10**.

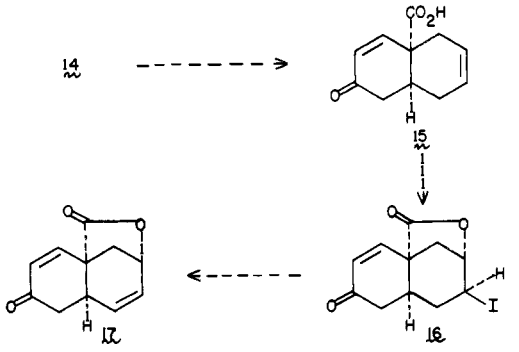


At this juncture we faced a serious dilemma. If we were to use a cis-based Diels–Alder approach involving quinone **8**, we could not incorporate the oxygen functionality to establish the



required arrangement of the B ring, since a 1-oxygenated butadiene would give an adduct of the type **9.** Alternatively, if we used 1,3-butadiene itself, we could obtain adduct **13** and thence, by analogy with Woodward,[5] hexalone **14.**[7] However, we then faced the discouraging prospect of constructing the necessary regio- and stereochemical B-ring functionality without any built-in guidance.

Fortunately, a formally acceptable solution presented itself in the form of hexalone **15.** In principle, iodolactonization of **15** would give **16,** and this might be converted to **17.** System **17** was seen to be provided with sufficient implements for further progress.



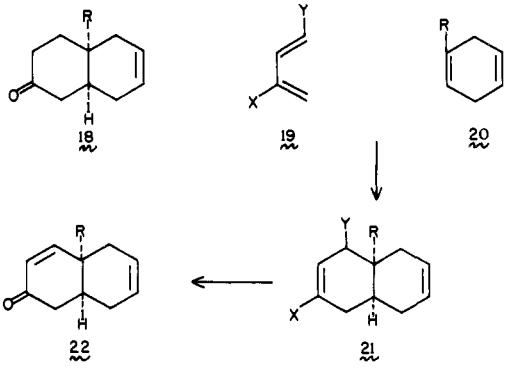
Now a troublesome practical issue had to be addressed. Using the established methodology we were able to reach adduct **13** in three steps from isovanillin. Compound **13** was indeed transformed to **14** in five additional steps.[7] Thus, approximately ten steps in all would be required to reach the desired **15,** which was the starting point on a still uncertain journey.

Results

(i) A New Strategy for the Synthesis of Cyclohexenones. The Synthesis of Dienone Lactone 17. Faced with the unsatisfactory state of affairs of the known art, we formulated a simple proposal to reach cis-fused Δ^1-3-octalone derivatives bearing angular carboxy functionality. The problem, of course, arises from the tendency of cis-fused decalones of the type **18** to enolize toward the junction.

This tendency is, in fact, well documented only in the steroid series.[8] The enolization tendencies of simple bicyclic ketones appear to be less specific, based on fragmentary data in the literature.[9a,b] However, random enolization would complicate even the formal, classical solution of blocking at C_4, followed by functionalization of C_1–C_2, and deblocking. Furthermore, Robinson annelation strategies[10] which have had a major impact on the synthesis of bicyclic systems, are not well suited for the incorporation of Δ^7 unsaturation in the context of the required hexalone **15.**

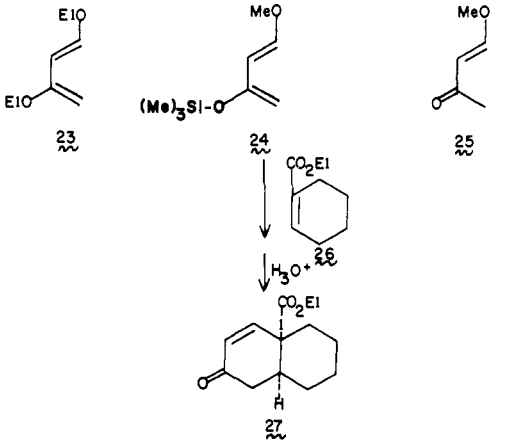
Our proposal, designed to overcome these difficulties, is described below. Diels–Alder reaction of a 1,3-dioxygenated dienone (**19**) with a generalized dienophile **20** would give **21.**



System **21,** being an enol derivative bearing a leaving group on the β-carbon,[11,12] might be expected to unravel to give **22.**

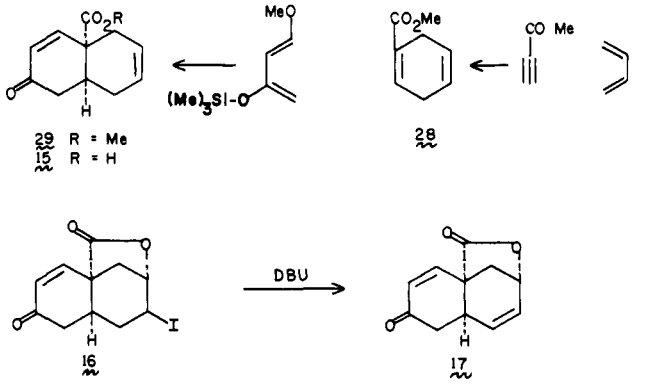
The simplest specific diene which might accommodate this scenario would be a 1,3-dialkoxybutadiene. In fact, 1,3-diethoxybutadiene **23** has been reported,[13] but its preparation is quite complex. In the light of several unsuccessful attempts in our laboratory to prepare the elusive **23,**[14] we studied the possibility of using an equivalent system, **24.** In the event,[15a] **24** was readily prepared by the enol silylation of the commercially available 4-methoxy-3-buten-2-one (**25**).

We have previously described the excellent and highly specific reactivity of diene **24** in several contexts.[15a,b] A crucial finding was that **24** gave cycloaddition products with a variety of otherwise sluggish "dienophiles". Included among these was 1-carbethoxycyclohexene (**26**), a substance which had heretofore resisted all attempted Diels–Alder reactions.[16a] Grudgingly (180–190 °C), **26** succumbed to cycloaddition with **24** to give, after acidic unraveling, the otherwise unknown octalone **27.** The stage was now set for reaching the desired **15.**



Two consecutive Diels–Alder reactions were marshalled. Cycloaddition of 1,3-butadiene with methyl propiolate afforded, as described,[16b] adduct **28.** This now functioned as a dienophile toward diene **24** to give, after acid treatment, hexalone **29.** Using mesitylene as a solvent, under reflux for 100 h, we obtained **29** in 43% yield. Saponification of **29** gave **15,** mp 88.5–89 °C, in nearly quantitative yield. Treatment of **15** with base and iodine afforded iodolactone **16,** mp 143.5–144.5 °C dec, in 88% yield.

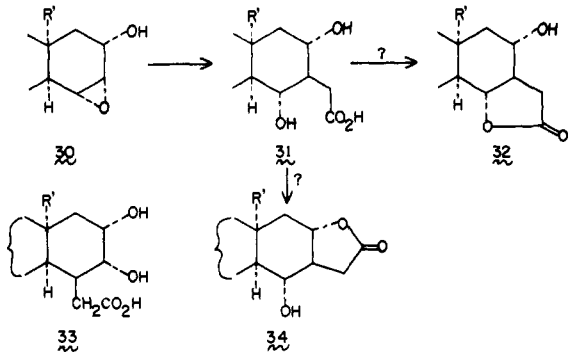
In subsequent developmental work, more suitable to large-scale operations, we reached iodolactone **16** in 49% yield from **28,** without purification of **29** or **15.** Based on the yields realized in going from pure **29** → **15** → **16,** the yield of the critical Diels–Alder reaction of **24** + **28** → **29** must be ca. 60%. Treatment of **16** with diazabicycloundecene (DBU) smoothly afforded dienone lactone **17,** mp 154–155 °C in 87% yield.



Formation of Epoxy Aldehyde 43. Iodolactonization had thus been used to provide a useful stereochemical bias for the proper placement of an α-oxygen atom at C-8 (steroid numbering). Our next objective was the placement of an α oxygen at C-6. A 6α,7α-oxido linkage was perceived to be the setting in which this oxygen would be introduced and, temporarily, housed. At a critical juncture, to be defined by trial and error, the 7α-oxido bond was to be severed upon backside (β)attack by an equivalent of acetic acid carbanion, "$\overline{C}H_2$-CO_2H". In this manner, the elements for the butyrolactone (ring C) were to be introduced in the required (i.e., trans) stereochemical sense.

In examining transformation of **30** → **32** which formalizes the plan, two contentious issues present themselves. The first relates to the conversion of **30** → **31.** In principle, at least, this reaction must compete with **30** → **33,** an outcome which would have most unfortunate consequences for a synthesis of either vernolepin or vernomenin.

Even if intermediate **31** is conceded, one must face the possibility of alternative modes of lactonization (**31** → **32** → vernolepin (**1**) vs. **31** → **34** → vernomenin (**2**). A plan which simultaneously addressed both of these problems was to be developed, and will be described shortly.



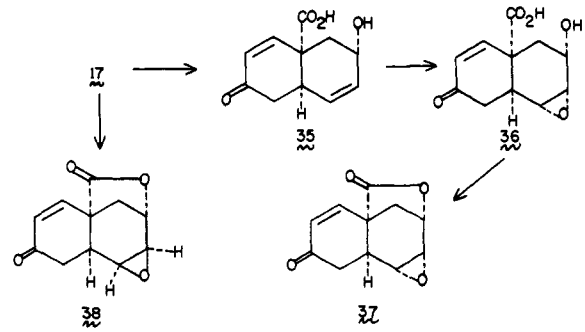
For the moment, our attentions turned to epoxy lactone **37.** Again, we sought to exploit forces potentially contained in **17** to encourage a favorable outcome. Accordingly, **17** was treated with base. Acidic workup afforded a 99% yield of the hydroxy acid **35,** mp 121-122 °C. Under Henbest type of stereochemical guidance,[17a] the allylic alcohol suffered rapid and clean epoxidation with 1.1 equiv of *m*-chloroperoxybenzoic acid (MCPBA) to afford the hydroxy epoxy acid **36,** mp 117-118 °C. It was deemed to be inconvenient to continue the synthesis with the complex functions now found in the B ring. Compound **36** was, therefore, subjected to the action of anhydrous sodium acetate in hot acetic anhydride. Thereby, the nicely crystalline lactone **37,** mp 125-126 °C, was in hand.

Operationally, the conversion of **17** → **37** was most easily executed without purifying **35** and **36.** The yield in going from pure **17** → pure **37** was 76%.

That the steps of saponification (**17** → **35**) and relactonization (**36** → **37**) were, in fact, vital to the achievement of α-epoxidation, was now demonstrated by studying the action of peroxy acids on **17** itself. In contrast to the case of **35, 17** reacted very slowly with MCPBA. Dienone **17** did react with *p*-nitroperoxybenzoic acid to afford an epoxide, mp 171-172 °C, which we formulate as **38.** Compounds **37** and **38** differed widely in chromatographic and spectral properties. The stereochemistry of the two compounds was originally surmised from the method of their preparation, with some support from their NMR spectra (see Experimental Section).

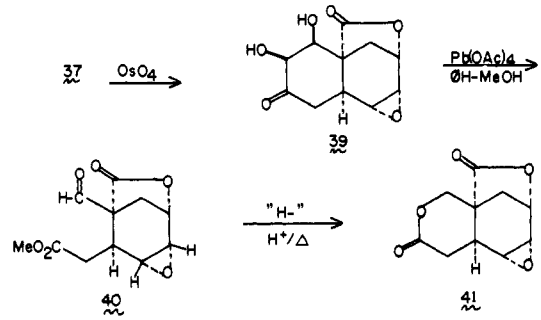
In retrospect it is clear that these assignments were correct because **37** lent itself to eventual conversion to *dl*-vernolepin (vide infra). We did not observe the formation of **37** in the direct epoxidation of **17.** Apparently the concave (β) face of the hexalin constitutes a target requiring lower activation energy for attack by per acids than the convex (α) face bearing the lactone ring.[18]

Of greater practical importance was the fact that epoxidation of hydroxy acid **35** apparently occurs exclusively in the desired α direction. The stereochemistry of the B ring had now been properly arranged.



Happily, the electron-deficient enone had survived the removal, in effect, of four electrons from the B ring (**15–37**), without noticeable damage. The time was now at hand to disassemble this enone and to constitute, from its surviving remnants, the A ring valerolactone.

Fortunately, the conjugated double bond did yield to the action of osmium tetroxide-barium chlorate[19,20] in aqueous tetrahydrofuran at 50 ° for 72 h. There was thus obtained, in 84% yield, a keto diol, mp 215.5-216.5 °C dec. Given the outcome of epoxidation of system **17,** we formulate the stereochemistry of the diol as 1β, 2β as shown in **39.** This diol was subjected to the action of lead tetraacetate in benzene-methanol[21] to give **40,** mp 168.5-169.5 °C, in 86% yield. Treatment of **40** with lithium tri-*tert*-butoxyaluminum hydride gave a hydroxymethyl methyl ester[22] as well as some epoxy dilactone **41.** Complete lactonization was forcibly achieved by treatment of the crude reduction product with Amberlite resin to give **41.** The yield of crude **41** from **39** was nearly quantitative. It was this crude material, virtually homogeneous by NMR analysis, rather than the crystalline material, mp 172-173 °C, which was used in subsequent steps. The crystalline version of **41,** which was obtained in only ca. 40-50% yield, offered no apparent advantages in subsequent operations.

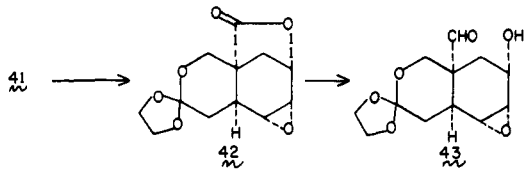


While this work was in progress, the results of some model studies indicated to us that epoxide opening by a two-carbon equivalent of acetic acid carbanion would probably not be feasible in the presence of ester-type groupings. Furthermore, in studying the chemistry of compound **41,** it became apparent that the δ-lactone appeared to contain the more labile carbonyl function.

A remarkable reaction was now discovered. Treatment of dilactone **41** with ethylene glycol in the presence of *p*-toluenesulfonic acid-benzene, containing magnesium sulfate, afforded modest yields (ca. 66%) of the crystalline mono orthoester **42,** mp 203-204 °C. We are still at a loss to account for this kinetonic like behavior of the δ-lactone in lending itself to dioxolane formation. While the formation of orthoesters of 2-oxa-3-keto steroids was reported by a La Roche group,[23] the

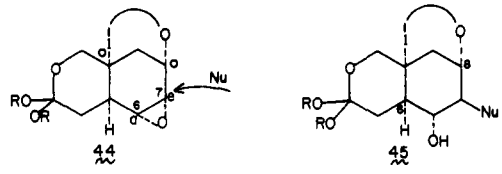
facility of derivatization in the case of **41** → **42**, stands in sharp contrast to the severe conditions employed in the reported case.

With this welcomed stroke of good luck at our disposal, we could then safely operate on the γ-lactone. Reduction of **42** with diisobutylaluminum hydride afforded the hydroxy aldehyde **43**, mp 111–112 °C in 94% yield. Though homogeneous on the basis of TLC analysis, the NMR spectrum of **43** ($CDCl_3$ solution) indicated it to contain ca. 10–20% of its hemiacetal ring-chain tautomer.



Formation of Hemiacetal 50. An Unfortunate Detour. Before describing the transformations by which **43** was converted to vernolepin and vernomenin, we relate the results of a most surprising series of experiments which were addressed to the potential problems which are inherent in the transformation of **30** → **31** and **31** → **32**, alluded to above. We sought to bring to fruition a strategy which simultaneously addressed the potentially competitive process **30** → **33** and **31** → **34**.

We reasoned that if a bridge were constructed spanning the angular position and the C-8 oxygen, the direction of opening of the epoxide linkage under nucleophilic attack could be predicted to occur in the desired fashion. Thus, the existence of a bridge in **44** demands that its foundations be axially joined to the B ring. In turn, the C-oxido bond must be "axial" and the C-7 bond "equatorial". In that event, nucleophilic attack at C-7 could be predicted from the dictum of trans-diaxial opening of epoxides.[24] There would thus be produced specie **45**. Furthermore, the G-6 and C-8 oxygens in **45** are differentiated, and this difference might lend itself to the regiospecific preparation of either lactone type, **32** or **34**, for vernolepin or vernomenin, respectively.



Further encouragement was had when treatment of **43** with trimethyl orthoformate afforded a near-quantitative yield of the orthoester mixed acetal **46**, mp 142–143 °C. Thus, in addition to producing the expected bridge, the trimethyl orthoformate had effected clean transorthoesterification to produce, in the A ring, a dimethoxy orthoester. Nonetheless, compound **46** appeared to embody all the features required for the regio- (and stereo-) specific syntheses of **1** and **2**.

As our acetic acid equivalent, we chose to employ the Creger–Silbert dianion, i.e., $LiCH_2CO_2Li$.[25] We reasoned that forceful conditions may well be necessary, since the nucleophile must invert the epoxide bond at C-7 through axial attack from the concave face of the oxadecalin.

In actual practice, a solution of **46** in tetrahydrofuran containing, initially, 14 equiv of dilithioacetate was heated at 55–60 °C for 36 h. Careful acidification with Amberlite acid resin, followed by esterification with diazomethane, and silica gel chromatography gave a 40–55% yield of a crystalline hydroxy lactone ester, mp 139–140 °C. The alcohol was acylated with pyridine–acetic anhydride to afford a crystalline acetate, mp 157–158 °C.

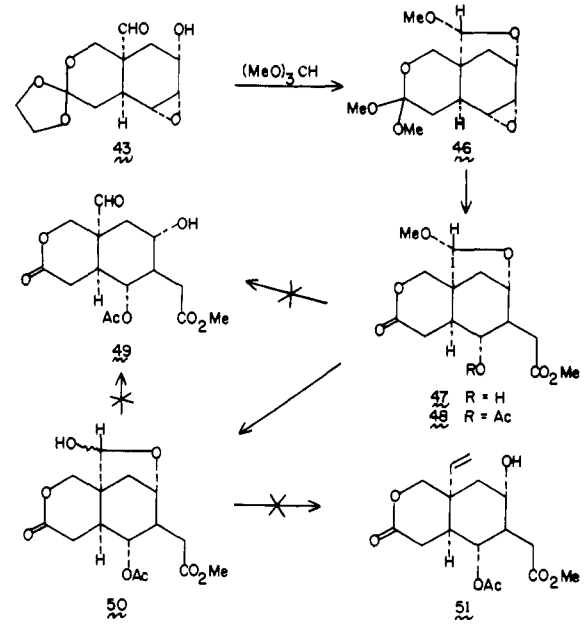
One need not debate the structure of this acetate, for the matter was decisively proven through a crystallographic analysis, kindly conducted by Drs. J. Springer and J. Clardy of Iowa State University.[26] The structure of the acetate is **48** and the alcohol is, therefore, **47**.

The crystal structure confirmed what was suspected from analysis of the high-field NMR spectrum of **48**. The B ring exists as a boat and the OAc and CH_2CO_2Me substituents are quasi-equatorial. This is apparently a lower energy conformation than a B-ring chair form, wherein five interactive axial substituents must be accommodated.

It was therefore a matter of some surprise to find that treatment of **48** with aqueous HCl afforded, not the hydroxy aldehyde **49**, but an amorphous foam, whose NMR spectrum clearly defined it to be the hemiacetal **50**. No "aldehyde" hydrogen was evident in the NMR spectrum of this material. The hemiacetal (as opposed to hydroxy aldehyde) nature of **50** was solvent insensitive and survived heating in toluene. *This was most surprising since ring-chain tautomerism to the hydroxyaldehyde would allow for a B-ring chair conformation in which all the substituents were equatorial.*

Even more disturbing was the finding that treatment of **50** with triphenylmethylenephosphorane under a variety of conditions failed to provide any detectable amounts of **51**. Depending on the nature of the reaction conditions, we obtained either recovered **50** or material which had undergone more deep-seated changes than simple Wittig olefination if, indeed, any such reaction had occurred at all.

This attempt at a fully "rational" synthesis, which sought to address the vernolepin–vernomenin isomerism issue, was thus defeated with success virtually "in hand".



(ii) Synthesis of Bisnorvernolepin and Bisnorvernomenin. We were now obliged to return to **43**. It seemed prudent to take advantage of the demonstrable (NMR) aldehydo character of this intermediate, for the purpose of obtaining the angular vinyl group. Indeed, compound **43** underwent smooth olefination through the action of methylenetriphenylphosphorane, to afford the crystalline **52**, mp 134.5–135.5 °C, in 87% yield.

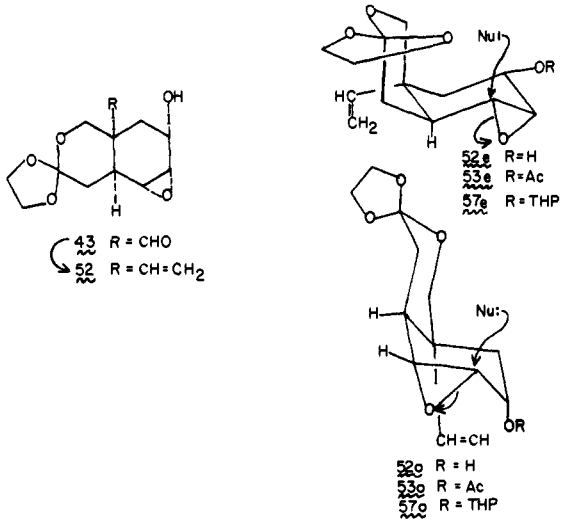
It was now proposed to attempt the opening of the epoxide on this substrate. In principle, **52** was subject to the usual conformational mobility and ambiguity of cis-fused decalins. Of the two chair–chair conformers, it is seen that **52a**, under the influence of trans-diaxial opening, would suffer desired ring opening at C-7. Conversely, **52e** would be expected to suffer opening at C-6.

The high-field proton spectrum of the derived acetate, **53**,

mp 78–79 °C, indicates it to exist largely, in the **53e** conformation. It is particularly clear that the C-5α hydrogen is equatorial to the A ring, since it shows a strong *W* coupling (1.4 Hz) to the α(equatorial) hydrogen of the AB system at position 2.

However, it appeared possible that although conformer **52e** (by extension) could well predominate at equilibrium, the activation energy for axial attack at C-6 by an incoming nucleophile might be greater than corresponding attack at C-7, in conformer **52a.** It is seen that the trajectory for nucleophilic attack at C-6 in **52e** demands a high-energy incursion into the van der Waals radius of the axial oxygen of the orthoester. Such an incursion is not involved in attack at C-7, in the alternate (higher energy) conformer **52a.**

Prediction of the behavior of such systems is the subject of the Curtin–Hammett principle.[24] By Curtin–Hammett considerations, favorable attack at C-7 was, at least, not excluded.



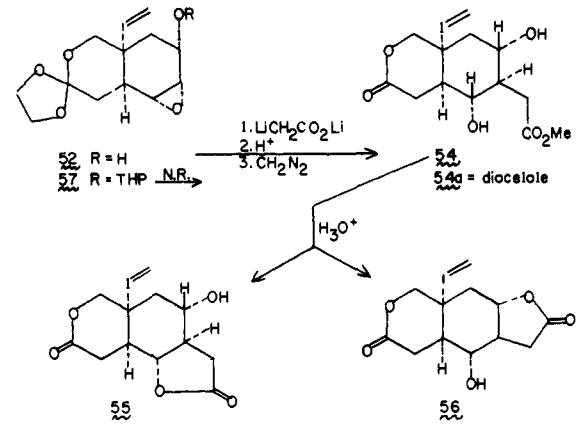
In practice, treatment of **52** with excess dilithioacetate followed by acidification and esterification with diazomethane afforded a crystalline dihydroxy lactone ester, mp 186–187 °C, in 56% yield. Several lines of evidence now converged to tell us that this compound is indeed represented by structure **54.**

Compound **54** had been produced in the Grieco synthesis of vernolepin and vernomenin. Spectral comparison was most readily achieved at the stage of **54a,** the precursor of **54** in the Grieco synthesis but a tangent in our route.

Treatment of our **54** with pyridine–acetic anhydride produced **54a.** The NMR spectrum of **54a,** thus obtained, was identical with a spectrum as kindly compared by Professor Grieco. The mass spectra of the two substances were also identical.[28]

Furthermore, as expected (and feared), treatment of **54** with pTsOH–C_6H_6 afforded a 2:1 mixture of two γ-lactones. These were separated by careful chromatography on silica gel. The NMR spectrum of the major component (R_f 0.23, silica gel, EtOAc), mp 179–180 °C, was consistent with its being bisnorvernolepin (**55**). The minor component, obtained in homogeneous, but amorphous form, could be formulated as bisnorvernomenin (**56**) (R_f 0.36, silica gel, EtOAc). While meaningful spectral comparisons with the mixture of **55** and **56** were not definitive at this stage, the infrared and mass spectra of the homogeneous compounds were independently conclusive. Of course, rigorous assignment of the two structures required the completion of the total synthesis in a fashion wherein each bisnor compound maintained its structural integrity.

We shall return to this question shortly. For the moment, we digress once again to describe another attempt to control



the regiochemistry of the vernolepin–vernomenin isomerism.

In principle, a solution was "at hand" in the form of compound **52.** The plan was simply to cover the hydroxyl group with a protecting group which would be stable to the nucleophilic conditions of epoxide opening, but could readily be discharged at a suitable point wherein the oxygens at C-6 and C-8 would be differentiated.

Indeed, compound **52** was smoothly converted to its OTHP derivative **57.** Unfortunately, in our hands, **57** resisted all efforts at epoxide opening with dilithioacetate under forcing conditions. Starting material was obtained in ca. 80% yield from the neutral portion of the reaction mixture. There was no evidence for the formation of any product, desired or undesired, from epoxide opening.

We surmise that the required conformer **57a** for epoxide opening in the desired sense is energetically unaccessible, perhaps owing to the extremely unfavorable consequences of placing a large OTHP group in a 1,3-diaxial relationship to the angular vinyl function. This, combined with the "orthoester effect" which deters axial attack at C-6 in **57e,** effectively insulates **57** from nucleophilic opening by the dianion at C-6 or C-7.[29]

Bis-α-methylenation of 55 and 56. Completion of the Total Synthesis of *dl*-Vernolepin (1) and *dl*-Vernomenin (2). With the synthesis of the bisnor compounds **55** and **56** achieved, we were now ready to address the final problem, i.e., the introduction of the two methylene groups α to the lactones. We had always felt that, in principle, such a transformation would fall within the scope of the feasible. Accordingly, we did not attempt to further modify our synthesis in such a manner as to provide prearranged implements (β-ketoesters, etc.) to simplify the bis-α-methylenation. Given the difficulties of reaching even the unadorned dilactones **55** and **56,** we did not, in retrospect, have reason to regret this assumption.

The field of α-methylenation of lactones has not suffered, particularly of late, from synthetic neglect. Indeed, two excellent reviews[30,31] have underscored the dramatic progress which has been recorded in this area. Given the widespread occurrence of such systems in natural products of real (or fanciful) therapeutic significance,[32] the attention which this subject has engendered need not be regarded as excessive.

As regards vernolepin (**1**) and vernomenin (**2**), a central discovery was made in 1975 by Grieco and co-workers.[33] They found that 8-deoxybisnorvernolepin could be successfully converted to 8-deoxyvernolepin via bis-α-methylenation. The particular method which they employed, (i) hydroxymethylation, (ii) mesylation, and (iii) β-elimination, was perhaps strategically less important than the overall demonstration of the feasibility of executing these steps concurrently.[33]

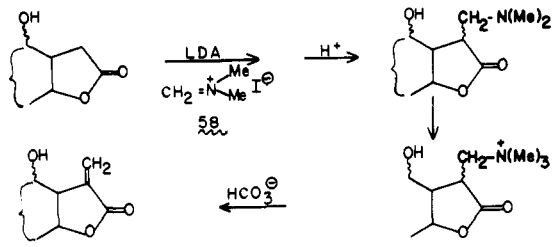
Moreover, in their synthesis of vernolepin (**1**) and vernomenin (**2**),[2] the Grieco group had, in fact, converted a mixture of **55** and **56,** via their OTHP derivatives into the final

natural products. Needless to say, this finding was crucial to our own thinking.

We perceived a possible improvement if the free alcohol groups could be carried through the α-methylenation without formal protection deprotection. In our own early explorations, the conversion of **55** → **55** OTHP was achieved in only 70% yield. The stability of vernolepin to acid treatment has never been fully clarified,[34] but we were not confident that vernolepin (**1**) could be redeemed, without loss, from its OTHP derivative.

It is in this area that a possibility for improvement on the hydroxymethylation methodology seemed likely. It will be noted that the aldol condensation of a lactone enolate with formaldehyde produces a β-hydroxy ester. These are classically eliminated only after further activation (OH → OSO_2R).[35] To avoid sulfonylation of the neighboring alcohol, it was protected prior to the bis-hydroxymethylation step.[2,33,35]

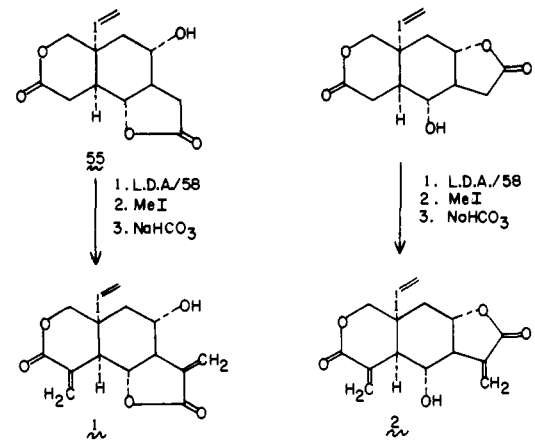
We have already[4] described the applicability of Eschenmoser's dimethyl(methylene)ammonium iodide (**58**)[36,37] with respect to this problem. The advantages of this reagent for the case at hand were: (i) the relative ease of delivering known amounts of electrophiles for small-scale work, (ii) the possibility of operating with a nonprotected hydroxyl, (iii) the ease of elimination to produce the α-methylene lactone, and (iv) the maintenance of the individuality of the two isomeric lactone precursors.



Compound **55** was treated with lithium diisopropylamide (LDA) in THF containing hexamethylphosphoric triamide (HMPA). A homogeneous solution could thus be maintained. To this was added the salt **58**[36] as a THF slurry. After reaction and suitable workup, the resultant product was treated with excess methyl iodide. From this one could liberate *dl*-vernolepin (**1**) by treatment with aqueous sodium bicarbonate. The yield of vernolepin (**1**), mp 210–211 °C, was 31%. The chromatographic mobility of *dl*-vernolepin was identical with that of a sample of the natural product, kindly provided by the late Professor S. M. Kupchan. Moreover, the richly detailed 250-MHz NMR spectra of the two compounds were identical. The solution infrared spectra and low-resolution mass spectra were identical. The total synthesis of *dl*-vernolepin (**1**) had thus been achieved.

Compound **56** was treated in a similar way. There was thus obtained an 18% yield of *dl*-vernomenin (**2**), mp 183–184 °C. The solution ($CHCl_3$) infrared spectrum of *dl*-vernomenin was identical with a spectrum of vernomenin kindly furnished by Professor Kupchan. The richly detailed 250-MHz NMR spectrum was similar to, but clearly different from, that of vernolepin. While a reference sample of naturally derived **2** was no longer available, the 250-MHz NMR spectrum was consistent with the 60-MHz spectrum furnished by Professor Kupchan. The mass spectrum of the synthetic material was in full accord with that which would be expected of vernomenin. The total synthesis of *dl*-vernomenin (**2**) had thus been achieved.

In summary, *dl*-vernolepin (**1**) was obtained in 1.2% yield in 19 steps from 1,3-butadiene. Similarly, *dl*-vernomenin was obtained in 0.4% yield in 19 steps from the same precursor. While these overall yields are certainly not such as to promote complacency, it is felt that the lessons learned here may be used to simplify the solutions to other problems in organic synthesis. Such activities are the basis of continuing research in our laboratory.



Experimental Section[38]

Diels–Alder Reaction of 24 with 28. Preparation of Dienone 29 and Its Direct Conversion to Iodolactone 16. To a solution of methyl 2,5-dihydrobenzoate (**28**,[16b] 55 g, 0.40 mol) in 32 ml of mesitylene, was added diene **24**[15] (83 g, 0.48 mol). The solution was heated under reflux for 24 h, at which time 83 g (0.48 mol) more of **24** was added and reflux continued for another 24 h. An additional 42 g (0.24 mol) of **24** was added and reflux was continued for another 48 h. The reaction mixture was cooled and the volatiles removed under high vacuum at 70 °C on a rotary evaporator. The dark residue was dissolved in 1300 ml of ether and cooled to 0 °C, whereupon 50 g of *p*-toluenesulfonic acid (0.26 mol) was added with vigorous mechanical stirring. After 1 h of stirring at 0 °C, the volatiles were removed until a volume of about 300 ml remained. This was placed onto a short column of 500 g of silica gel and quickly eluted with ether. The eluents were evaporated to a volume of approximately 1600 ml and washed with 4 × 200 ml of ice-cold 1 N NaOH by pouring it through the ether slowly and separating without agitation. (Shaking the layers at this stage may lead to a difficultly separable emulsion.) The combined ether solutions were dried over anhydrous $MgSO_4$ and evaporated in vacuo to afford 63 g (76% recovery) of relatively pure **29** (~90% by NMR analysis).

To the crude adduct, dissolved in 60 ml of tetrahydrofuran, was added a solution of 16.50 g (0.41 mol) of NaOH in 460 ml of water. The solution was stirred at room temperature for 18 h and acidified with aqueous HCl. This was extracted with 6 × 300 ml of methylene chloride. The organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo, giving an oil which was dissolved in 1000 ml of water containing 60 g (0.71 mol) of $NaHCO_3$. After dissolution appeared complete, the aqueous phase was extracted with 300 ml of methylene chloride, which was discarded.

The aqueous solution was cooled to 0 °C and a solution of 190 g of iodine and 660 g of potassium iodide was added. The solution was stirred (mechanically) with exclusion of light, for 1 h at 0 °C and for 48 h at room temperature.

A yellow precipitate was filtered and washed with ca. 2 L of ether. The precipitate was dried overnight to afford 56.30 g of iodolactone **16**. The filtrate was extracted overnight with 2 L of ethyl acetate. The organic phase was extracted with aqueous sodium thiosulfate solution and dried over $MgSO_4$. Evaporation afforded an additional 5.71 g of **16**. The total weight of **16**, thus obtained from **28** without column chromatography, was 62.01 g (49%).

Chromatography of crude **29** (judged to be 90% pure by NMR snalysis; see above) on silica gel and elution with 5% ether–benzene gave a 43% isolated yield of homogeneous **29** of the following spectral and analytical properties: λ_{max} ($CHCl_3$) 5.81, 6.01 μ; δ($CDCl_3$ 250 MHz) 1.8–2.9 (m, ca. 7), 3.73 (s, 3), 5.70 (m, 2), 5.98 (d, J = 10.8 Hz, 1), 6.84 (d, J = 10.8 Hz, 1) ppm.

Anal. ($C_{12}H_{14}O_3$) C, H.

Preparation of Dienone Acid 15. To a solution of pure **29** (22.50 g, 0.11 mol) in 20 ml of tetrahydrofuran was added a solution of 5.25 g (0.131 mol) of NaOH in 125 ml of water. The solution was stirred at room temperature for 18 h. The brown solution was acidified with

aqueous HCl and extracted with 5 × 100 ml of methylene chloride. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo, giving 20.97 g (100%) of **15** as a glassy solid, used as such in subsequent experiments. A small sample, allowed to cool for a long time, crystallized, mp 88–89 °C: λ_{max} ($CHCl_3$) 2.90–3.60 (br), 5.82, 5.87 μ; δ ($CDCl_3$, 250 MHz) 1.7–2.6 (m, 7), 5.73 (s, 2), 6.07 (d, J = 10 Hz, 1), 6.91 (d, J = 10 Hz, 1), 10.2 (s, 1) ppm.

Anal. ($C_{11}H_{12}O_3$) C, H.

Iodolactonization of 15. To dienone acid **15** (29.00 g, 0.151 mol) was added a solution of sodium bicarbonate (31.20 g, 0.367 mol) in 650 ml of water. Dissolution was aided by agitation and gentle warming. To this solution of the sodium salt of **15**, cooled to 0 °C, were added, with vigorous mechanical stirring, iodine (89 g, 0.350 mol) and potassium iodide (330 g, 1.77 mol) in 575 ml of water. After 1 h of stirring at 0 °C, the solution was warmed to room temperature and stirred mechanically, in darkness for 48 h. The slurry was filtered and the precipitate was dried via suction. The solid was washed well with ether (~1 L) to afford **16** as a light yellow powder (39.86 g, 83%). The aqueous residue was extracted with 2 × 600 ml of ethyl acetate. The combined organic phases were virtually decolorized by extraction with aqueous thiosulfate solution, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue crystallized upon trituration with 10 ml of 1:1 ether/ethyl acetate to afford another 2.57 g of darker colored iodolactone, for a total yield of 88% of **16**, mp 143.5–144.5 °C dec: λ_{max} ($CHCl_3$) 5.63, 5.94 μ δ (d_5-pyridine, 250 MHz) 2.0–3.4 (m, ca. 7), 4.51 (s, 1), 5.00 (t, J_t = 5 Hz, 1), 6.21 (d, J = 10 Hz, 1), 6.90 (d, J = 10 Hz, 1) ppm.

Anal. ($C_{11}H_{11}O_3I$) C, H.

Preparation of Dienonelactone 17. To a stirred suspension of **16** (15.00 g, 0.047 mol) in 1250 ml of dry benzene was added 17.90 g (0.118 mol = 2.5 equiv) of diazabicycloundecene in 20 ml of dry benzene. The suspension was stirred vigorously at room temperature under N_2 for 24 h. The slurry was filtered through a thin Celite bed and the bed was washed with 2 × 500 ml of ethyl acetate. The combined filtrates were evaporated in vacuo to afford a partly crystalline residue. Ether and small amounts of acetone were added until the crystals became mobile. These were filtered and washed with 100 ml of ether to afford 6.01 g of **17** as off-white crystals. The combined filtrates were concentrated and rapidly passed through 150 g of Florisil using 1:1 benzene/ethyl acetate. Upon evaporation of the eluents, an additional 1.80 g of **17** was obtained. The total yield of **17** (mp 154–155 °C) was 87%: λ_{max} ($CHCl_3$) 5.64, 5.93 μ; δ (d_5-pyridine, 250 MHz) 2.2–3.2 (m, ca. 5), 4.87 (t, J_t = 5.5 Hz, 1), 5.71 (d of d, J_{AB} = 10 Hz, J_{AX} = 3 Hz, 1) 6.27 (m, 2 containing d, J = 10 Hz at 6.3 ppm), 7.0 (d, J = 10 Hz, 1) ppm.

Formation of Hydroxy Acid 35. To a suspension of dienone lactone **17** (9.25 g, 0.049 mol) in 15 ml of tetrahydrofuran at 0 °C under N_2 was added a solution prepared from 2.25 g (0.056 mol) of NaOH in 75 ml of water. The solution slowly became homogeneous and stirring was continued at room temperature for 1 h. The dark solution was acidified with aqueous HCl and extracted with 5 × 250 ml of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of the volatiles afforded 10.13 g (99%) of hydroxy acid **35**, mp 121–122 °C. λ_{max} ($CHCl_3$) 2.80–4.10, 5.89, 5.95 μ; δ (d_5-pyridine, 250 MHz) 2.4–3.3 (m, ca. 5), 3.66 (s, 1), 4.58 (br s, 1), 5.60 (d, J = 11 Hz, 1), 6.08 (d, J = 11 Hz, 1), 6.22 (d, J = 10 Hz, 1), 7.10 (d, J = 11 Hz, 1) ppm.

Anal. ($C_{11}H_{12}O_4$) C, H.

Preparation of 36. A solution of **35** (10.13 g, 0.049 mol) in 77 ml of benzene and 77 ml of *p*-dioxane was prepared by gentle warming on a water bath. The solution was cooled to 0 °C, whereupon *m*-chloroperoxybenzoic acid (10.43 g, 0.060 mol) was added. Solution occurred almost immediately. After 15 min at 0 °C, the solution was warmed to room temperature and stirred for 10 h under N_2. The volatiles were evaporated completely in vacuo and the semisolid residue was dissolved in 150 ml of saturated $NaHCO_3$. After acidification to pH 5 and extraction with 2 × 125 ml of ethyl acetate, the aqueous phase was further acidified pH ≃1 and extracted with 5 × 300 ml of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo giving a semisolid which was shown by NMR analysis to be a mixture of *m*-chlorobenzoic acid and epoxy hydroxy acid **36**. The recovered weight was 14.46 g (134% of the theoretical). This was not purified further. (The pure epoxy hydroxy acid **36** could be isolated at this stage chromatographically (Florisil, 1:1 benzene/ethyl acetate) if desired. This compound was, however, best prepared by hydrolysis of the lactone **37**; vide infra.) The 14.46 g of crude **36** was dissolved in 180 ml of acetic anhydride, and 2.25 g of anhydrous sodium acetate was added. The solution was stirred under N_2, as the temperature was gradually raised to 80 °C. This temperature was maintained for 3 h. After the solution was cooled to room temperature, the sodium acetate was filtered off and washed with 15 ml of acetic anhydride. The combined acetic anhydride solutions were evaporated completely in vacuo. The solid was leached with 2 × 200 ml and then 2 × 100 ml portions of ether by pulverizing finely and stirring followed by filtration. This removes the *m*-chlorobenzoic acid but not the highly insoluble lactone **37**. After final filtration, 7.60 g (76%) of pure **37**, mp 215–216 °C, was obtained: λ_{max} (KBr) 5.68, 6.01 μ; δ (d_5-pyridine, 250 MHz) 2.3–3.1 (m, ca. 6), 3.52 (t, $J_t \cong$ 4 Hz, 1), 5.12 (m, 1), 6.22 (d, J = 10 Hz, 1), 6.84 (d, J = 10 Hz, 1) ppm.

Anal. ($C_{11}H_{10}O_4$) C, H.

Formation of Epoxy Hydroxy Acid 36. To a suspension of lactone **37** (100 mg, 0.5 mmol) in 1.5 ml of THF at 0 °C was added a solution of 23 mg (0.6 mmol) of sodium hydroxide in 8 ml of THF. The system was stirred for 15 min at 0 °C and for 1 h at room temperature. Acidification and extraction with ethyl acetate afforded 109 mg (100%) of **36**, mp 117–118 °C: λ_{max} ($CHCl_3$) 2.80–4.20, 5.88, 5.97 μ; δ (d_5-pyridine, 250 MHz), 2.2–3.6 (m, ca. 7), 4.24 (q, J = 5 Hz, 1), 4.40 (q, J = 4 Hz, 1), 5.40 (s, 1), 6.25 (d, J = 8.5 Hz, 1), 7.04 (d, J = 8.5 Hz, 1) ppm.

Anal. ($C_{11}H_{12}O_5$). Found: *m/e* 224.06852.

Formation of β-Epoxide 38. To a solution of dienone **17** (85 mg, 0.45 mmol) in 10 ml of ethylene dichloride containing 10 mg of 4,4′-thiobis-6-(*tert-butyl-σ*-cresol)[39] was added 250 mg (1.37 mmol) of *p*-nitroperoxybenzoic acid. The solution was heated at 90 °C under N_2 for 20 h, cooled to room temperature, and filtered. The volatiles of the filtrate were removed in vacuo and the residue was rapidly chromatographed on 15 g of Florisil. Elution with 20% ethyl acetate in hexane afforded 36 mg (39%) of β-epoxide **38**, mp 171–172 °C: λ_{max} ($CHCl_3$) 5.66, 5.96 μ; δ ($CDCl_3$, 60 MHz) 1.9–2.6 (m, 2), 2.7 (br s, 3), 3.1–3.4 (m, 1), 3.7 (t, J = 3 Hz, 1), 5.2 (d of d, 1), 6.2 (d, J = 11 Hz, 1), 6.6 (d, J = 11 Hz, 1) ppm.

Anal. ($C_{11}H_{10}O_4$) C, H.

Formation of Keto Diol 39. To a solution of 2.50 g (0.010 mol) of OsO_4 and 2.92 g (0.009 mol) of barium chlorate in 90 ml of water and 7 ml of tetrahydrofuran was added compound **37** (3.30 g, 0.016 mol). The temperature was raised to 47 °C and stirring was continued for 5 h under N_2. At this time, 2.92 g (0.009 mol) more of barium chlorate was added, and stirring at 47 °C was continued for 3 days under N_2. During this time the reaction mixture became homogeneous. The volatiles (water, tetrahydrofuran, OsO_4) were removed completely in vacuo. The dry salts were leached with 10 × 500 ml of hot ethyl acetate. Evaporation of the combined filtrates afforded a white solid which was washed with 2 × 30 ml of chloroform and filtered to afford 3.22 g (84%) of keto diol **39** as a white solid, mp 215–216.5 °C dec: λ_{max} (KBr) 3.00, 5.75 μ.

Anal. ($C_{11}H_{12}O_6$) C, H.

Preparation of Aldehyde 40. To a suspension of **39** (6.00 g, 0.025 mol) in 925 ml of absolute methanol and 925 ml of dry benzene was added 60.00 g (0.125 mol, 5.73 equiv) of freshly recrystallized lead tetraacetate. The solution became homogeneous after several minutes, turning orange at the same time. After 20 min, a precipitate formed which dissolved after ca. 1 h. The color of the solution became deep red and turned colorless over a period of 6 h while being stirred at room temperature under N_2. After 6.5 h, the solvents were removed in vacuo to give an oil which was treated with 300 ml of water. The aqueous phase was extracted with 10 × 500 ml of ethyl acetate which were combined and dried over anhydrous Na_2SO_4. Evaporation in vacuo left a solid which, upon trituration with 25 ml of ether, afforded 5.14 g (86%) of crystalline aldehyde **40**, mp 168.5–169.5 °C: λ_{max} ($CHCl_3$) 3.65, 5.61, 5.78 μ; δ (d_5-pyridine, 250 MHz) 2.24 (d, J = 11 Hz, 1), 2.56 (d of d, J_{AB} = 13 Hz, J_{AX} = 6 Hz, 1), 2.7–3.7 (m, containing a 3 H s at 3.53), 5.09 (t, J_t = 4 Hz, 1) 9.97 (s, 1) ppm.

Formation of Dilactone 41. A solution of aldehyde-ester **40** (6.00 g, 0.0250 mol) in 480 ml of dry tetrahydrofuran was cooled to −10 °C under N_2. To this was added, with stirring, 6.42 g (0.253 mol, 1.01 equiv) of lithium tri-*tert*-butoxyaluminum hydride. Analysis by TLC showed the reaction to be complete within 20 min. After 55 min, the volatiles were removed in vacuo and 300 ml of ethyl acetate followed by 10 ml of glacial acetic acid was added. The suspension was stirred for 1 min and the filtrate evaprated in vacuo. The semisolid residue was leached with 8 × 800 ml of ethyl acetate. The filtrate was con-

centrated in vacuo to afford a glassy solid residue.

To the glassy solid were added 1.3 L of benzene and 15.0 g of Amberlite 105 (H^+ form) resin. After refluxing over a Dean-Stark trap for 6.5 h with vigorous stirring, the hot benzene was filtered and the resin washed with 2 × 900 ml of portions of hot ethyl acetate. The combined filtrates were evaporated in vacuo to afford an oily residue (4.86 g, 93%) whose NMR spectrum indicated it to be essentially pure dilactone **41.** This compound could be crystallized from acetone-tetramethylsilane to afford a solid, mp 172–173 °C. The oil, **41,** was usually used directly in the next step: λ_{max} ($CHCl_3$) 5.59, 5.72 μ; δ (d_5-pyridine, 250 MHz) 2.24 (d of d, J_{AB} = 14 Hz, J_{AX} = 5.4 Hz, 1), 2.39 (d, J_{BA} = 14 Hz, 1), 2.7–3.2 (m, ca. 4), 3.53 (t, J = 4.54 Hz, 1), 4.38 (d, J = 12 Hz, 1), 4.74 (d, J = 12 Hz, 1), 5.13 (t, J_t = 5.4 Hz, 1) ppm.

Anal. ($C_{10}H_{10}O_5$) C, H.

Formation of Ethylene Orthoester 42. To a solution, made from oily dilactone **41** (1.15 g, 5.48 mmol), in 12 ml of distilled ethylene glycol, was added 700 ml of benzene. The mixture was vigorously stirred as 12 g of anhydrous $MgSO_4$, 700 mg of Dowex 50W-X8[40] (H^+ form), and 120 mg (0.63 mmol) of *p*-toluenesulfonic acid were added in succession. The mixture was heated to reflux under *vigorous agitation* (with occasional breaking up of the lumps of the $MgSO_4$ into a powder with a metal spatula). Reflux under a Dean-Stark separator, with *vigorous agitation*, was continued for 4.5 h. Analysis (TLC, ethyl acetate) showed completion of the reaction at this time. Ethyl acetate (300 ml) was added and the mixture was heated to reflux and filtered. The lumps of $MgSO_4$ were pulverized in a mortar and pestle and leached with two 700-ml portions of hot ethyl acetate. The combined filtrates were washed with 2 × 100 ml of 3:3:4 saturated NaCl/H_2O/saturated $NaHCO_3$, then with 100 ml of saturated NaCl. The organic solution was dried over anhydrous Na_2SO_4. Evaporation left an oil which easily crystallized upon trituration with ether to afford 921 mg (66%) of orthoester **42,** mp 203–204 °C: λ_{max} ($CHCl_3$) 5.63 μ; δ (d_5-pyridine, 250 MHz) 1.9–2.2 (m, ca. 3), 2.37 (d, J = 12 Hz, 1), 2.85 (d, J = 3 Hz, 1), 2.97 (d of d, J_{AB} = 13.5 Hz, J_{AX} = 5.7 Hz, 1) 3.45 (t, J_t = 3 Hz, 1), 3.80 (d, J = 12 Hz, 1), 3.9–4.2 (m, ca. 4), 4.36 (d, J = 12 Hz, 1), 5.01 (t, J_t = 5.7 Hz, 1) ppm.

Anal. ($C_{12}H_{14}O_6$) C, H.

Preparation of Hydroxyaldehyde 43. To a solution of orthoester **42** (230 mg, 0.9 mmol) in 13 ml of dry dimethoxyethane was added 26 ml of dry toluene. Any undissolved orthoester can be dissolved by gentle warming of the flask.[41] The solution, maintained under N_2, was cooled to −76 °C under N_2 and diisobutylaluminum hydride was added via syringe. The reducing agent was administered as follows:

Time, min	DIBAH added, mmol
0	1.35
20	0.71
40	0.50
60	0.40

After TLC analysis indicated the absence of starting material, 9.5 ml of saturated $NaHCO_3$ was added via syringe at −76 °C (some foaming occurs at this point).

The slurry was stirred vigorously at −76 °C for 10 min then at room temperature for 15 min. The volatiles were removed in vacuo, and 3 ml of saturated $NaHCO_3$ followed by 100 ml of ethyl acetate was added. The solution was filtered and the precipitate washed with 6 × 100 ml of ethyl acetate. The combined washings were extracted with 2 × 20 ml of 1:1 saturated NaCl/saturated $NaHCO_3$, dried quickly over anhydrous $MgSO_4$, and evaporated in vacuo to afford 218 mg (94%) of **43** as an oil which crystallized slowly, mp 111–112 °C: λ_{max} ($CHCl_3$) 5.84 μ; δ (d_5-pyridine, 250 MHz) 1.9–2.3 (m), 2.72 (m), 3.15 (2t), 3.43 (d), 3.58 (t), 3.9–4.5 (m), 4.74 (t), 5.53 (s), 9.80 (s) ppm.

Anal. ($C_{12}H_{16}O_6$) C, H.

Formation of Vinyl Alcohol 52. A suspension of dry (120 °C, 1 mm, 24 h) methyltriphenylphosphonium bromide (4.64 g, 13 mmol) in 50 ml of dry dimethoxyethane under N_2 was cooled to 0 °C, whereupon 8.68 ml (12.4 mmol) of 1.43 M *n*-BuLi in hexane was added. The solution was stirred at 0 °C for 1.0 h and allowed to settle before use.

To a solution of aldehyde-alcohol **43** (325 mg, 1.27 mmol) in 8 ml of dry dimethoxyethane under N_2 at 0 °C was added via syringe 6 ml (ca. 1 equiv) of the supernatant **43a** ("salt free") Wittig reagent prepared as described above. A white precipitate formed immediately. After the mixture was stirred for 45 min, 6 ml more of the supernatant "salt free" Wittig reagent was added. The reaction was stirred at room temperature for 2 h. Saturated $NaHCO_3$ (8 ml) was added and the volatiles were removed in vacuo. The solids were leached with 7 × 200 ml of ethyl acetate. The combined filtrates were evaporated, and the residue was chromatographed on 80 g of Florisil. Elution with 15% acetate in hexane and evaporation of the proper (R_f (silica gel-ethyl acetate) 0.57) fractions gave 280 mg (87%) of **52** as a crystalline solid, mp 134.5–135.5 °C: λ_{max} ($CHCl_3$) 2.90 μ.

Anal. ($C_{13}H_{18}O_5$) C, H.

Preparation of Vinyl Acetate 53. To 5.0 mg (0.02 mmol) of **52** in 0.5 ml of acetic anhydride was added 0.5 ml of pyridine. The solution was stirred at room temperature for 12 h, whereupon the volatiles were removed in vacuo completely to afford 5.8 mg (99%) of **53,** mp 79–80 °C: λ_{max} ($CHCl_3$) 5.81 μ; δ ($CDCl_3$) 250 MHz (see text).

Preparation of Dihydroxy Ester 54. To a solution of 2.33 g (23.0 mmol) of dry diisopropylamine in 12.5 ml of dimethoxyethane under nitrogen at −42 °C (dry ice/3-pentanone) was added 16.13 ml (23.0 mmol) of 1.43 M *n*-butyllithium over a period of 10 min. The solution was stirred at −42 °C for 15 min, whereupon a solution of 670 mg (11.2 mmol) of dry[44] acetic acid in 1 ml of dimethoxyethane was added. The suspension was heated to 43 °C with stirring and maintained at that temperature for 90 min.

To a solution of 120 mg (0.47 mmol) of epoxide **52** in 4 ml of dimethoxyethane was added via syringe 30 ml (ca. 15 equiv) of the suspension prepared as described above. The reaction mixture was stirred at 55 °C for 40 h under nitrogen. After the mixture was cooled to −10 °C (ice-salt-acetone), 6 ml of water was added and the dimethoxyethane was removed in vacuo. Water (4 ml) was added and the solution was extracted with 2 × 10 ml of ethyl acetate. The combined organic layers were extracted with 2 × 10 ml of 2% NaOH. The combined aqueous layers were added to 20 ml of ethyl acetate, and Dowex 50W-X8 (H^+ form) was added until the aqueous layer was acidic. The resin was filtered off and washed with 2 × 100 ml of ethyl acetate. The combined organic-aqueous filtrate and washings were evaporated to near dryness in vacuo whereupon 20 ml of acetone and 20 ml of ethyl acetate followed by excess diazomethane were added. The solution was stirred for 20 min, filtered through Celite, and evaporated in vacuo. The oil (160 mg) was chromatographed on 20 g of silica gel. Elution with 3:2 benzene/ethyl acetate afforded 75 mg (56%) of diol ester **54,** mp 186–187 °C: R_f (silica gel-EtOAc) 0.30; λ_{max} (KBr) 5.75 μ; δ (d_5-pyridine, 250 MHz) 1.7–2.1 (m, 3), 2.47 (m, 1), 2.88 (d of d, J_{AB} = 18 Hz, J_{AX} = 7.4 Hz, 1), 3.11 (d of d, J_{AB} = 16 Hz, J_{AX} = 6 Hz, 1), 3.24 (d of d, J_{BA} = 16 Hz, 1), 3.47 (d, J_{BA} = 18 Hz, 1), 3.63 (s, 3), 3.91 (t, J_t = 10.4 Hz), 4.03 (t of d, J_t = 10.4 Hz, J_d = 5 Hz, 1), 4.38 (d, J = 13 Hz, 1), 4.66 (d, J = 13 Hz, 1), 5.13 (d, J = 11 Hz, 1), 5.30 (d, J = 17.4 Hz, 1), 5.79 (d of d, J_{d1} = 17.4 Hz, J_{d2}, 11 Hz, 1) ppm.

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

Formation of Diacetate 54a. To a solution of 11 mg (0.039 mmol) of **54** in 1 ml of acetic anhydride was added 1 ml of pyridine. The solution was stirred at room temperature under N_2 for 12 h. The volatiles were removed in vacuo. The residual oil readily crystallized upon trituration with *n*-pentane to afford 13 mg (93%) of the diacetate **54a,** mp 129–130 °C: λ_{max} ($CHCl_3$) 5.75 μ; δ ($CDCl_3$, 250 MHz) identical with the spectrum of an authentic sample[2] as compared by Professor P. A. Grieco.

Formation of Bisnorvernolepin (55) and Bisnorvernomenin (56). To a solution of **54** (270 mg, 0.95 mmol) in 300 ml of benzene was added 30 mg (0.16 mmol) of *p*-toluenesulfonic acid. The solution was refluxed over a Dean-Stark trap for 90 min, whereupon 500 ml of ethyl acetate was added. The solution was extracted with 25 ml of saturated $NaHCO_3$, then with 25 ml of saturated NaCl. Drying over anhydrous $MgSO_4$ and removal of the volatiles in vacuo gave 282 mg of an oil which, when dissolved in 10 ml of 4:1 ether/methylene chloride, slowly deposited 135 mg of crystals of pure bisnorvernolepin (**55**) in 57% yield. The residue from the wash, shown to be rich in bisnorvernomenin (**56**) (TLC analysis), was chromatographed on 60 g of silica gel using 55% ethyl acetate in hexane to afford 58 mg (25%) of pure bisnorvernomenin (**56**) as a foam. A mixed fraction (29 mg) was also obtained which was rechromatographed to give 16 mg (7%) of bisnorvernomenin (**56**) and 11 mg (5%) of bisnorvernolepin (**55**). The isolated yield of **55** was 61% and that of **56** was 31%.

55: R_f (silica gel-ethyl acetate) 0.23; mp 179–180 °C; λ_{max} (KBr) 2.92, 5.61, 5.81 μ; δ ($CDCl_3$, 250 MHz).[45]

Anal. ($C_{13}H_{16}O_5$) C, H. Found: *m/e* 252.0994.

56: R_f (silica gel–ethyl acetate) 0.36, amorphous; λ_{max} ($CHCl_3$) 2.88, 5.63, 5.82 μ; δ ($CDCl_3$, 250 MHz).[45]

Anal. ($C_{13}H_{16}O_5$) C, H. Found: *m/e* 252.1004.

Preparation of *dl*-Vernolepin (1). To a solution of dry diisopropylamine (0.783 g, 7.8 mmol) in 20 ml of dry ($LiAlH_4$ distilled) tetrahydrofuran at −76 °C under nitrogen was added, via syringe, over a period of 10 min, *n*-butyllithium (5.43 ml of 1.43 M hexane, 7.8 mmol). The solution was stirred for 20 min at −76 °C, whereupon 12 ml of solution was removed via syringe and discarded. To the remaining solution was added dropwise, over a period of 1 h (Hershberg dropping funnel), a solution of bisnorvernolepin (**55**, 55 mg, 0.22 mmol) in 5 ml of tetrahydrofuran containing 525 μL of dry hexamethylphosphoric triamide. After addition was complete, the solution was stirred at −76 °C for 15 min. The temperature was raised to −42 °C and maintained there for 15 min.

To the solution, as described above, was added at −42 °C a suspension of **58** (900 mg, 4.86 mmol) dried at 80 °C under 0.5 mmHg vacuum, then washed with 2 × 10 ml of dry tetrahydrofuran just prior to use) in 10 ml of dry tetrahydrofuran. The resulting suspension became homogeneous over a period of several minutes. The solution was stirred at −42 °C for 45 min, then warmed to room temperature, and stirring was continued for an additional 30 min. Dilute (10% w/v) hydrochloric acid was added until the solution was acidic. Solid potassium carbonate was then added until the solution was slightly basic. The mixture was diluted with 3 ml of water and extracted with 4 × 90 ml of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo, leaving an oil.

To the crude oil were added 6 ml of *p*-dioxane and 15 ml of methyl iodide. The mixture was heated at 90 °C under nitrogen with vigorous stirring for 18 h. The volatiles were removed in vacuo, and the gummy solid was treated with 8 × 10 ml of ether to afford 790 mg of a mobile yellow solid. The ether washings were saved and treated below.

To the solid was added 10 ml of water containing 800 mg (0.0090 mol) of sodium bicarbonate and 40 ml of ethyl acetate. The mixture was stirred vigorously for 30 min. The organic layer was separated and 25 ml more of ethyl acetate was added. Vigorous stirring was continued for 30 min more. The organic layers were combined, dried over anhydrous Na_2SO_4, and evaporated to afford 200 mg of residue. Tlc analysis showed vernolepin (R_f 0.55, ethyl acetate) upon comparison and cospotting with an authentic sample. Chromatography on 25 g of silica gel, using 40% hexane in ethyl acetate, afforded, after washing with ether, 17.3 mg (29%) of pure vernolepin, mp 209–211 °C.

The oil, obtained from the ether washings of the crude "methiodide", was subjected to the same elimination conditions given above (800 mg, $NaHCO_3$, 9 ml of H_2O, 2 × 40 ml of ethyl acetate). Chromatography of the recovered material on 30 g of silica gel and elution with 40% hexane in ethyl acetate afforded 85 mg of a yellow oil which upon rechromatography on 1 g of silica gel using 40% hexane in ethyl acetate as the eluent, afforded an additional 1.2 mg (2%) of vernolepin as a crystalline solid: total yield 31%; λ_{max} (KBr) 2.80, 5.66, 5.80 μ. The infrared spectrum ($CHCl_3$) was identical with that of an authentic sample kindly provided by the late Dr. S. M. Kupchan. The 250-MHz NMR spectra of the natural and synthetic vernolepin were also identical and are available as Supplementary Material.

Preparation of *dl*-Vernomenin (2). To a solution of dry diisopropylamine (0.045 g, 5.8 mmol) in 14 ml of dry tetrahydrofuran at −76 °C under nitrogen, was added via syringe, over a period of 10 min, *n*-butyllithium (4.07 ml of 1.43 M hexane). The solution was stirred for 20 min at −76 °C, whereupon 9.0 ml of the solution was removed via syringe and discarded. To the remaining solution was added dropwise, over a period of 1 h (Hershberg dropping funnel), a solution of 45 mg (0.00018 mol) of bisnorvernomenin (**56**) (45 mg = 0.18 mmol) in 4.0 ml of dry tetrahydrofuran, containing 410 μL of dry hexamethylphosphoric triamide. After addition was complete, the solution was stirred at −76 °C for 15 min. The temperature was raised to −42 °C and maintained there for 15 min.

To the solution, as prepared above, was added at −42 °C, at once, a suspension of **58** (700 mg, 3.76 mmol dried at 80 °C under 0.5 mmHg vacuum, then washed with 3 × 3 ml of dry tetrahydrofuran just prior to use) which had been stirred in 8 ml of dry tetrahydrofuran at room temperature for 1 h. The resulting suspension became homogeneous over a period of several minutes. The solution was stirred at −42 °C for 45 min, then warmed to room temperature and stirred for 30 additional min. Dilute (10% w/v) hydrochloric acid was added until the solution was acidic. Solid potassium carbonate was then added until the solution was slightly basic. The mixture was diluted with 2 ml of water and extracted with 4 × 60 ml of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated.

To the crude oil were added 6 ml of *p*-dioxane and 15 ml of methyl iodide. The mixture was heated at 90 °C under nitrogen for 17 h, whereupon the volatiles were removed in vacuo and the gummy solid was treated with 4 × 8 ml of ether to give 285 mg of a yellow solid. The ether washings were saved and treated below.

To the solid was added 8 ml of water containing 0.350 g (0.0042 mol) of sodium bicarbonate and 30 ml of ethyl acetate. The mixture was stirred vigorously for 30 min, whereupon the organic layer was separated and 30 ml more of ethyl acetate was added. Vigorous stirring was continued for 30 min. The organic layer was separated and the combined organics dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was chromatographed on 20 g of silica gel using 60% hexane in ethyl acetate to afford 7.2 mg (15%) of *dl*-vernomenin (**2**), mp 183–184 °C.

The oil, recovered from the ether washing above, was treated in an identical manner (350 mg of $NaHCO_3$, 8 ml of H_2O, 2 × 40 ml of ethyl acetate). Chromatography on 25 g of silica gel and elution with 40% hexane in ethyl acetate afforded 1.7 mg (3%) of *dl*-vernomenin (**2**): total yield 18%. The infrared spectrum ($CHCl_3$) was identical with that of a spectrum (provided by Professor Kupchan) of authentic vernomenin. The NMR spectrum (250 MHz) corresponded closely with a spectrum (60 MHz) provided by Professor Kupchan; the figure is available as Supplementary Material.

Acknowledgment. This research was supported by PHS Grants CA-12107-12 and CA-12107-13, the Hoffmann-La Roche Foundation, and an unrestricted grant from the Ciba-Geigy Corp. NMR (250 MHz) measurements were obtained from facilities supported by PHS Grant RR-00292-07. We wish to thank Professor Paul A. Grieco for a sample of **54a** and several spectral comparisons. We also wish to thank Professor Paul Dowd (ref 36) for valuable discussions and Dr. Patrick McCurry of Carnegie-Mellon University for valuable consultations on NMR analyses. Further, the cooperation of the late Professor S. M. Kupchan in providing an authentic sample of natural vernolepin and spectra of vernomenin is gratefully acknowledged.

Supplementary Material Available: 250-MHz spectra of authentic and synthetic vernolepin and synthetic vernomenin, NMR spectra of **55** and **56**, and computer printout of crystal structure of **48** (6 pages). Ordering information is given on any current masthead page.

References and Notes

(1) For the structure and biological properties of vernolepin, see S. M. Kupchan, R. Hemingway, D. Werner, A Karim, A. McPhail, and G. Sim, *J. Am. Chem. Soc.*, **90**, 3596 (1968). For the biological properties of vernolepin and related compounds, see S. M. Kupchan, M. Eakin, and A. Thomas, *J. Med. Chem.*, **14**, 1147 (1971). For previous synthetic studies in the vernolepin area, see ref. 3 and 9b and bibliographies therein. For the general conceptual framework on which our synthesis is based, see S. Danishefsky, P. F. Schuda, and K. Kato, *J. Org. Chem.*, **41**, 1081 (1976).

(2) The first total synthesis of vernolepin and vernomenin was achieved in a memorable way by P. A. Grieco and associates; see P. A. Grieco, M. Nishizawa, S. D. Burke, and N. Marinovic, *J. Am. Chem. Soc.*, **98**, 1612 (1976).

(3) For a communication of our synthesis of bisnorvernolepin and bisnorvernomenin, see S. Danishefsky, T. Kitahara, P. F. Schuda, and S. J. Etheredge, *J. Am. Chem. Soc.*, **98**, 3028 (1976).

(4) For a communication on the use of dimethyl(methylene)ammonium iodide for bis-α-methylenation, see S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *J. Am. Chem. Soc.*, **98**, 6715 (1976).

(5) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

(6) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(7) These results arose from the Ph.D. thesis of Samuel Mazza, University of Pittsburgh, 1975. The experimental procedures for reaching adduct **13** and then acetoxydienone **14** are provided in that thesis.

(8) L. Velluz, J. Valls, and G. Nomine, *Angew. Chem., Int. Ed. Engl.*, **4**, 181 (1965).

(9) (a) J. A. Marshall, G. L. Bundy, and W. I. Fanta, *J. Org. Chem.*, **33**, 3913 (1968). (b) For a recent example of enolization of a cis-fused decalone in a direction which would be favorable for the introduction of a 1,2-double bond, seen C. V. Chavdarian, S. L. Woo, R. D. Clark, and C. H. Heathcock, *Tetrahedron Lett.*, 1769 (1976).

(10) M. E. Jung, Tetrahedron Report No. 8, *Tetrahedron*, **32**, 3 (1976).

(11) M. Stiles and A. Longroy, *Tetrahedron Lett.*, 337 (1961); M. Stiles and A.

Longroy, *J. Org. Chem.*, **32**, 1095 (1967).
(12) E. Wenkert and D. P. Strike, *J. Am. Chem. Soc.*, **86**, 2044 (1964).
(13) O. Shavrygena and S. M. Maken, *Khim. Farm. Zh.*, **3**, 17 (1969); *Chem. Abstr.*, **71**, 124112Y (1969). Subsequent to our work,[15a,b] there appeared a description of the use of 1,3-bis(trimethylsilyloxy)-1,3-butadiene: T. Ibuka, Y. Mori, and Y. Inubushi, *Tetrahedron Lett.*, 3169 (1976).
(14) Unpublished results of S. Mazza, University of Pittsburgh.
(15) (a) S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974); (b) *J. Org. Chem.*, **40**, 538 (1975).
(16) (a) Cf. R. L. Kronenthal and E. I. Becker, *J. Am. Chem. Soc.*, **79**, 1095 (1957); (b) A. A. Petrov and K. B. Rall, *Zh. Obshch. Khim.*, **26**, 1588 (1956).
(17) (a) H. B. Henbest and R. A. Wilson, *J. Chem. Soc.*, 1958 (1957). (b) For the possibility of favorable guidance by a proximate carboxyl, see S. A. Cerefice and E. K. Fields, *J. Org. Chem.*, **41**, 355 (1976).
(18) For a possibility of electronic deactivation of expoxidation by a neighboring lactone, see ref 6.
(19) L. Blahay, J. Weichet, J. Zracek, and B. Kakac, *Collect. Czech. Chem. Commun.*, **25**, 237 (1960).
(20) A. S. Kende, T. V. Bentley, R. A. Mader, and D. Ridge, *J. Am. Chem. Soc.*, **96**, 4332 (1974).
(21) R. Hirschmann, N. G. Steinberg, and R. Walker, *J. Am. Chem. Soc.*, **84**, 1270 (1962).
(22) The hydroxy ester was not purified. Its existence could be inferred from the formation of a new substance (TLC analysis) which still exhibited a methyl ester resonance in its NMR spectrum and which cyclized to give **41**.
(23) R. A. Le Mahieu and R. W. Kierstead, *Tetrahedron Lett.*, 5111 (1970).
(24) See E. Eliel, "The Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962.
(25) P. L. Creger, *J. Org. Chem.*, **37**, 1907 (1972).
(26) We thank Professor Jon Clardy and Dr. James Springer of Iowa State University for these measurements. A copy of the computer printout of the crystal structure is available as Supplementary Material. This measurement also defines the stereochemistry of the anomeric methoxyl to be, as shown, in structures **46**, **47**, and **48**.
(27) Obviously, one cannot quantitatively define ground-state conformational populations from such measurement, but it would appear that conformation **53e** nicely accounts for the observed NMR data. The extrapolatibility of these results to the case of **52**, R = H, is unclear.
(28) We thank Professor P. A. Grieco of the University of Pittsburgh for comparing the two spectra and for a small reference sample of **54a**. The latter was valuable both in providing a mass spectrum and in demonstrating that our Wittig reactions on **50** were all unsuccessful. This was done by acetylating our reaction mixtures and finding no clear TLC spots corresponding to **54a**.
(29) For a discussion of the possible directing effect of a proximate Li^+ in these reactions, see S. Danishefsky, M. Tsai, and T. Kitahara, *J. Org. Chem.*, **42**, 394 (1977).
(30) P. A. Grieco, *Synthesis*, 67 (1975).
(31) R. B. Gammill, C. A. Wilson, and T. A. Bryson, *Synth. Commun.*, **5**, 245 (1975).
(32) S. M. Kupchan, M. Eakin, and A. Thomas, *J. Med. Chem.*, **14**, 1147 (1971).
(33) P. A. Grieco, J. A. Noguez, and Y. Masaki, *Tetrahedron Lett.*, 4213 (1975).
(34) S. M. Kupchan, R. Hemingway, D. Werner, and A. Karim, *J. Org. Chem.*, **34**, 3903 (1969).
(35) P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1317 (1972).
(36) J. Schreiber, M. Haag, N. Hashimoto, and A. Eschenmoser, *Angew. Chem., Int. Ed. Engl.*, **10**, 330 (1971). The use of this reagent for lactone methylenation was first suggested to us by Professor Paul Dowd of the University of Pittsburgh. His suggestions are gratefully acknowledged.
(37) Cf. G. Kinast and L. F. Tietze, *Angew. Chem., Int. Ed. Engl.*, **15**, 239 (1976).
(38) Melting points are uncorrected. Combustion analyses were conducted by Galbraith Associates. Infrared spectra were obtained on Perken-Elmer Model 137 or 237 spectrophotometers. High-resolution mass spectra were obtained on a Varian Associates CH-5 instrument by direct insertion. NMR spectra were measured in the indicated solvents with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ) from the Me_4Si resonance. Pictures of all the infrared and NMR spectra described in this paper are found in the Ph.D. thesis of Paul F. Schuda, University of Pittsburgh, 1977. Pictures of the NMR spectra of bisnorvernolepin (**55**) and bisnorvernomenin (**56**) are available as Supplementary Material.
(39) Cf. Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and H. Kakoi, *Chem. Commun.*, 64 (1972).
(40) The commercially available resin (100 g) was treated with 200 ml of dilute HCl. After filtration, the resin was washed with methanol, acetone, chloroform, benzene, and ether to remove soluble impurities. It was dried for 30 min by vacuum desiccation prior to use.
(41) (a) It is crucial that all the starting material, **42**, be dissolved prior to administration of the DIBAH and that the reducing agent be added in the manner indicated. Starting **42** is not easily separated from **43**. Also, higher reaction temperatures or the use of excessive reducing agent leads to formation of an orthoester diol.
(42) The NMR spectrum of a solution of homogeneous **43** indicates the presence of 10–20% of hemiacetal ring–chain tautomer. The chemical shifts given are for the major, hydroxy aldehyde component.
(43) (a) Curiously, if one adds at this stage the bulk suspension of Wittig reagent, this yield is sharply reduced. (b) This chromatography is complicated by the fact that triphenylphosphine oxide has only a slightly lower R_f value than the desired **52**. In some runs, some mixed fractions containing these two compounds were obtained, thereby necessitating partial rechromatography to reach the indicated yield of pure product.
(44) The acetic acid was prepared prior to use by treatment with potassium permanganate and distillation followed by treatment with triacetyl borate and distillation to remove traces of water.
(45) The NMR spectrum of this compound is available as Supplementary Material.

Peptide Synthesis Using the Four-Component Condensation (Ugi Reaction)

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Abstract: Applications of the "four-component condensation" (4CC) or "Ugi reaction" to peptide fragment coupling were studied with syntheses of protected di-, tri-, and tetrapeptides. The most suitable solvents were alcohols, including methanol, 1-butanol, trifluoroethanol, and hexafluoro-2-propanol, as shown by syntheses of Ac-Gly-[*N*-Bzl-DL-Val]-Gly-OBu-*t* in 60–80% yields. The efficacy of several aldehydes in 4CC fragment condensation and subsequent cleavage of the auxiliary substituents was examined by syntheses of model dipeptide Pht-Gly-Gly-OR (R = H, Bu-*t*, Me) and tetrapeptide Z-Gly-Ala-Leu-Gly-OR (R = H, Bu-*t*) derivatives. 2-Nitrobenzaldehyde (photolytic cleavage), 2,4-dimethyloxybenzaldehyde, 1-*tert*-butyloxycarbonyl-3-formylindole (acidolytic cleavage), and 4-pyridinecarboxaldehyde (electrolytic cleavage) proved to be effective along with cyclohexyl isonitrile. As an example, Z-Gly-Ala-Leu-Gly-OBu-*t* was synthesized from Z-Gly-Ala-OH and H-Leu-Gly-OBu-*t* and shown to be indistinguishable from material prepared by conventional procedures.

Present methods permit solution synthesis[1] of homogeneous peptides with up to 50 amino acid residues[2] but condensation of peptides of this size to obtain proteins with over 100 residues has not yet progressed beyond the pioneering stage. The remarkable ribonuclease *S*-protein synthesis by Hirschmann et al.[3] remains to be as yet the only preparation of a peptide of over 100 residues. This synthesis underscored the problem. The yield of the final coupling of a 44- with a 60-residue peptide was ca. 3%. Other efforts in enzyme synthesis have yet to be completed.[2,4,5] Difficulties arise from the second-order kinetics of peptide coupling and from the 100- to 1000-fold lower molar concentrations due to the increased