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Studies in the Synthesis of Vernolepin. A Diels–Alder Approach to the Angularly Functionalized AB System

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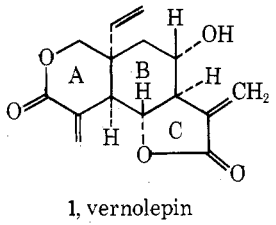
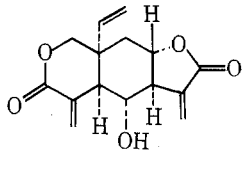
In model systems it has been demonstrated that the sequence (i) osmium tetroxide–barium chlorate, (2) lead tetraacetate–methanol–benzene, (3) lithium tri-*tert*-butoxyaluminum hydride may be used to convert conjugated cyclohexenones to valerolactones with excision of the α-carbon of the enone. A regiospecific and stereospecific Diels–Alder reaction of 2-methoxy-5-hydroxymethyl-1,4-benzoquinone (**25**) with 1-methoxy-1,3-butadiene (**26**) gave 2,8 β-dimethoxy-4aα-hydroxymethyl-5,8α-dihydronaphthalene-1,4-(8aαH,4aH)-dione (**27**). This was converted in five steps to 2β-formyl-2α-acetoxymethyl-4α,5α-oxido-6β-methoxycyclohexane-1β-acetic acid methyl ester (**43**). Treatment of the latter with lithium tri-*tert*-butoxyaluminum hydride gave a 19% yield of 8aα-acetoxymethyl-5β-methoxy-6α,7α-oxido-4aα-2-oxa-3-decalone (**45**) and a 46% yield of 4-acetoxymethyl-6-*exo*-methoxy-7-*endo*-hydroxy-2-oxabicyclo[3.2.1]octane-2-*exo*-acetic acid methyl ester (**46**). The stereochemistry of all intermediates and products is proven by taking advantage of intramolecular reactions.

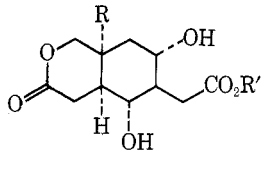
A successful synthesis of the tumor inhibitor vernolepin (**1**)[1a,b] must provide simultaneous solutions to several novel structural problems. We perceive the most formidable of the obstacles to be the construction of the B ring in a stereochemical arrangement which allows for the elaboration of the C ring in its required form. An ancillary problem, whose seriousness cannot now be evaluated, involves the differentiation of the hydroxylactonic arrangements between vernolepin (**1**) and the related system, vernomenin (**2**).[1a,b] For instance, the data emanating from the structure elucidation do not allow for a confident prediction as to the mode of lactonization of a hypothetical precursor of the type **3**.



1, vernolepin



2, vernomenin



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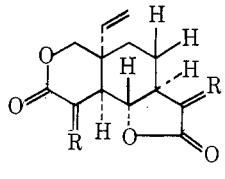
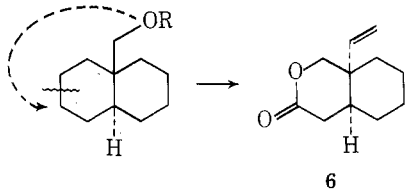


4, R = H
5, R = CH_2
(deoxyvernolepin)

The results of a variety of studies directed to the conversions of lactones to their α-methylene derivatives, most notably those of Grieco and co-workers,[2a,b,3] hold out the hope that the introduction of these functions may be postponed until the final stages of the synthetic effort. Particularly noteworthy in this respect is the transformation of **4** → **5** achieved by Grieco.[4] This work is clearly the most advanced synthttic contribution to the vernolepin problem thus far recorded.

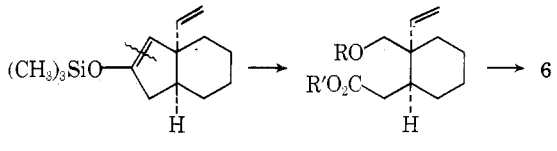
A successful synthesis must also deal with the construction of the cis-fused 2-oxa-3-decalone system bearing an angular function, susceptible of conversion to a vinyl group. Previous approaches directed toward the synthesis of **6** may be classified into two strategies. The approaches of Grieco[4,5a–c] and Marshall[6a,b] involve utilization of a trans-fused decalin, bearing latent hydroxymethyl functionality in the angular position. The C_2–C_3 bond is then cleaved. Carbons 1 and 2 become the vinyl group. The angular hydroxymethyl unit joins with an unravelled C_3 acyl group to afford a cis-fused 2-oxa-3-decalone.

Grieco[4,5] and Marshall[6] routes



6

Heathcock route[7]



7

A spectacular approach, due to Heathcock and Clark,[7] involves the simultaneous elaboration of a cis-fused hydrindene system (7) bearing an angular vinyl group and an endocyclic double bond which is part of a site specifically generated silyl enol ether. An ozonolysis–reduction sequence provides the elements for construction of a cis-fused 2-oxa-3-decalone.

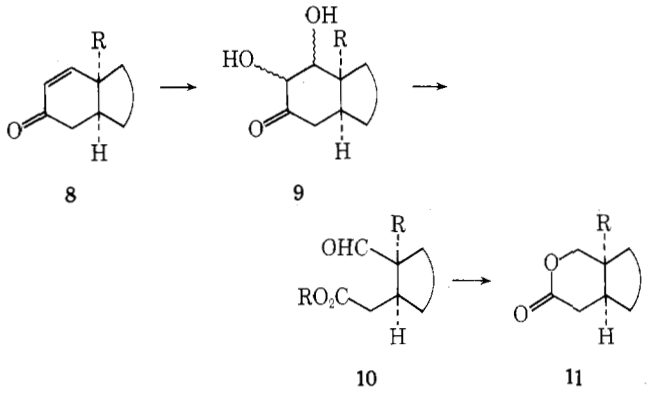
Our approach to this problem centered on the use of cis-fused hydronaphthalenes of the type 8.[8] A favorable element of this strategy appeared to be the availability of the required precursors by a Diels–Alder route. Woodward has demonstrated[9] the convertability of a methoxybenzoquinone adduct of 1,3-butadiene to a Δ^1-3-ketobicyclic system. It was our expectation that a Diels–Alder route lent itself well to variations of angular and ring B functionality in a fashion which might be conducive to attainment of the proper framework for attaching ring C.

The feasibility of oxidative cleavage of a conjugated cyclohexenone system, with excision of the α carbon and formation of a 4-acylbutyric acid derivative, is well known and has, in fact, been utilized in several total synthesis operations.[10a,b] The most commonly employed version of this reaction involves systems in which the β carbon of the enone is substituted and becomes a ketone after oxidation.

For our purposes, the oxidative cleavage must be performed on a substrate in which the β carbon is unsubstituted and is to be converted to an aldehyde. The success of the scheme depends rather critically on the preservation of the distinction in the oxidation levels of carbons 1 and 3 in precursor 8. Transformation of 8 to the secoacylaldehyde system, 10, and reduction of the latter would give the desired 11.

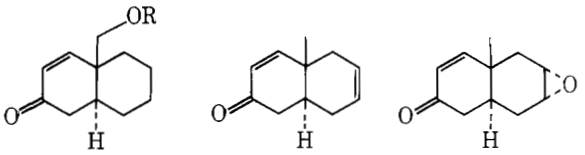
Fortunately, for our planning, there existed several precedents for the feasibility of converting 8 → 9 and, indeed for converting 8 → 10 and 10 → 11. The total synthesis of reserpine[11a] as well as modifications thereof[11b,c] provided a setting in which transformations of the type 8 → 9 and 9 → 10 (R = H) were studied. Furthermore, the conversion of Δ^1-3-keto steroids to 2-oxa-3-keto steroids[12a–c] involves the overall transformation of 8 → 11[13] via an intermediate of the type 10.

The route which we describe here involves a three-step sequence for transforming the bicyclenone to the bicyclic lactone. Glycolation is achieved by reaction of the enone with osmium tetroxide followed by oxidative or reductive work-up. The keto glycol 9 is cleaved by the action of lead tetraacetate in methanol–benzene.[12a] This reaction produces directly, and in high yield, the aldehyde methyl ester 10 (R = Me). Reaction of the general system 10 with lithium tri-*tert*-butoxyaluminum hydride provides the desired lactone, 11.[14] In the cases described below, the lactonization is spontaneous.



8 9 10 11

The method has been applied on a model basis to bicyclenenones 13a and 14. Compound 13a was prepared by



13, R = H 12 14
13a, R = Ac

acetylation of the known alcohol 13, prepared by the route of Mukharji.[15] Compound 14 was obtained by epoxidation of Woodward's dienone 12.[9] Although satisfactory combustion data were not obtained for this monoepoxide, its spectral properties (see Experimental Section) attest to its structure and homogeneity.

Our interest in demonstrating the viability of the transformations of the type 8 → 11 in the presence of an epoxide stems from the possibility that such a linkage may be of utility in elaborating the C ring of vernolepin. Thus, the opening of an epoxide by 1 equiv of $^-CH_2CO_2R$ constitutes a very promising route to trans-fused δ-lactones.

Reaction of 13 with osmium tetroxide in pyridine followed by cleavage with sodium bisulfite[12a] gave an 82% yield of the keto glycol 15, mp 99–100 °C. Treatment of 15 with lead tetraacetate in methanol–benzene[12a] afforded a quantitative yield of the crude aldehyde methyl ester 16. Substantial decomposition was encountered in attempted chromatographic purification of 16 on silica gel. Accordingly, the crude material, whose NMR spectrum was highly supportive of its structure, was used in the next step.

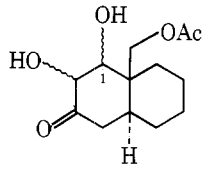
Upon reduction of compound 16 with lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran a 62% (from 15) yield of the trans-fused acetoxylactone, 17, was obtained. It is interesting to note that, in principle, compound 16 lends itself to nonreductive transformation into a cis-fused lactone by utilizing the carbon bearing the acetate function as C_4 of the 2-oxadecalone. This strategy merges into the Grieco[5] and Marshall[6] pathways discussed earlier.

The formalism was reduced to practice by treatment of 16 with methanolic sodium hydroxide. The cis-fused 10-formyl-2-oxa-3-decalone (18) was obtained in 72% yield (from 15). It is seen that a cis- or trans-fused 4a acetoxymethyl functionalized 2-oxa-3-decalone.

Having demonstrated the basic viability of the approach, we tested its compatibility with internal epoxide functionality. Osmylation of 14 utilizing a catalytic amount (0.16 equiv) of osmium tetroxide in an aqueous solution containing barium chlorate[16] gave the crystalline keto glycol 19, mp 118–119 °C. As before, oxidative cleavage to aldehyde methyl ester 20 was achieved in high yield by the action of 19 with lead tetraacetate in methanol–benzene. Again, as before, reductive cyclization (lithium tri-*tert*-butoxyaluminum hydride) of 20 gave the trans-fused epoxyoxadecalone 21, mp 128–129 °C.

With the results of these model studies in hand we undertook a study of a route which held out some promise for reaching vernolepin itself. Although, as will be seen, the scheme did not prove serviceable in terms of the total synthesis objective, the work is suggestive of other pathways which might prove more successful. Furthermore, it is illustrative of the value of the Diels–Alder route for the synthesis of Δ^1-3-octalones bearing greater functionality than had been previously described.

We defined the trans-fused bicyclenone 22 as our intermediate objective. It was assumed that 22 could be converted to aldehyde methyl ester 23. Cleavage of the acetate function of 23 and nonreductive lactonization (cf. 16 → 18) would give the cis-fused oxadecalone 24 bearing an angular formyl group. It will be noted that, in principle, "back-



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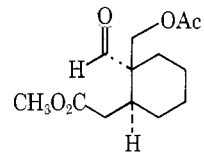

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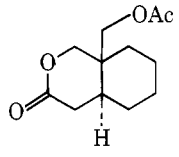

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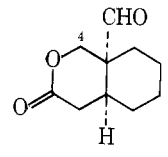

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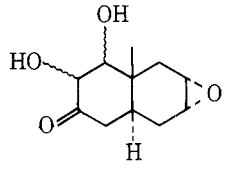

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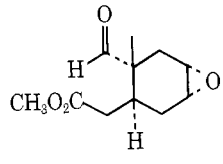

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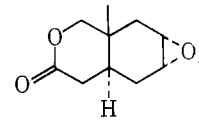

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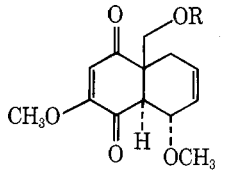
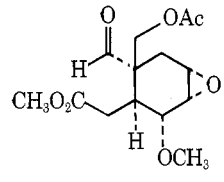


22, R = H or OAc



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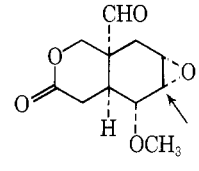
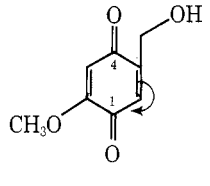


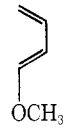
24

side" attack by a $^{-}CH_2CO_2R$ equivalent upon the epoxide bond at carbon 6 (see arrow) in structure **24** or a related congener[17] would give rise to a product in which the stereochemistry of the B ring has been properly arranged.

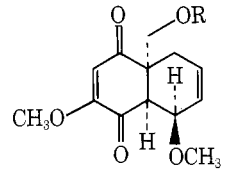
Our plan for reaching the trans-fused **22** involved a projected Diels–Alder reaction of **25** with 1-methoxybutadiene (**26**). It was anticipated that the major adduct would be **27.** This prediction follows from the supposition that of the ketonic groups in structure **25,** the one which is vinylogously conjugated to the ester (i.e., C_4 carbonyl) will be less electron deficient and thus less influential than the C_1 carbonyl in its orientational influence upon reaction with the electron-rich **26.**



25



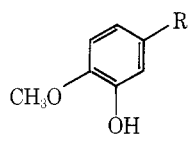
26



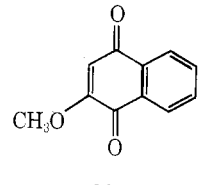
27, R = H
27a, R = Ac

It was further hoped that a cis product of the type **27** would be susceptible to epimerization, thus providing access to the trans series (cf. **22**).

Reduction of isovanillin (**28**) with sodium borohydride gave the known[18] phenol **29,** mp 132–133 °C. Upon treatment with Fremy's salt, **29,** suffered smooth oxidation,



28, R = CHO
29, R = CH_2OH



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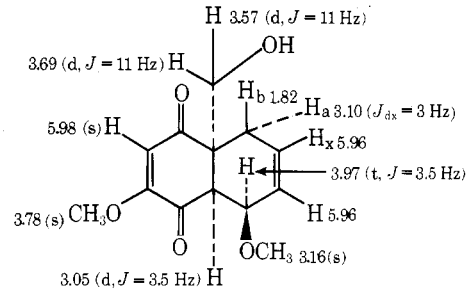
thereby giving the required *p*-quinone **25,** 147–147.5 °C. In the event, Diels–Alder reaction of **25a** with **26** gave a 93% yield of crystalline **27,** mp 150–151 °C. We could find no evidence for the formation of any detectable amounts of positional or stereochemical isomers of **27.**

The most salient feature of the NMR spectrum (250 MHz) which resolves the orientational issue in **27** is the appearance of the allylic hydrogen on the carbon bearing the methoxyl (δ 3.97 ppm) as a triplet, $J_{H_8-H_{8a}} = 3.5$, $J_{H_8}-J_{H_7} = 3.5$ Hz. Correspondingly, the junction hydrogen at C_{8a} is seen as a doublet, δ 3.1 ppm, $J_{H_{8a}-H_8} = 3.5$ Hz. The observed ABX (δ_{H_B} 1.82; δ_{H_A} 3.10, $J_{AB} = 21$, $J_{BX} = <1$, $J_{AX} = 3$ Hz) rather than ABXY pattern for the allylic protons also defines the orientational issue. The remaining resonances are fully consistent with the proposed structure and are indicated.



27

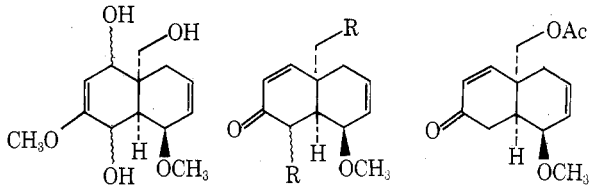
The stereochemical arrangement of **27** could not be argued altogether persuasively from the NMR spectrum. However, it was assumed that the cis junction expected from the Diels–Alder reaction had not undergone epimerization under the reaction conditions. Furthermore, the stereochemistry of the methoxyl group was assigned in the manner indicated on the basis of the principle of endo addition. As will be shown, both of these assumptions were, in fact, correct.

Unfortunately, all attempts to achieve the transformation of **27** or its derived acetate **27a,** mp 126–127 °C, to systems of the type **22** were without success. Even under mildly basic conditions (potassium acetate–methanol) either **27** or **27a** were converted to naphthoquinone **30,**[19] mp 183–184 °C, by the sum of β-elimination of methanol, retro-aldolization of the angular hydroxymethyl function (preceded by saponification in the case of **27a**), and air oxidation. Attempted epimerization of **27a** with diazabicycloundecene (DBU), in the hope of avoiding this unravelling, led to a complex mixture of components which was not separated. Conceivably β-elimination of methanol is the first step in this decomposition route.[20] The use of the nonnucleophilic base sodium hydride on **27b** also resulted in extensive decomposition.

It is noted that the relative configuration of the hydrogens at C_{8a} and C_8 in the cis system **27** does not correspond to that required for vernolepin. An inversion of the oxygen stereochemistry at C_8 is thus required. Such inversion need not have been necessary if the sequence of **27** → **22** → **24** could have been achieved. Nevertheless, it was of interest to continue the synthesis in the cis series in the hope that such an inversion would be possible in the new target system **44** (vide infra).

Reaction of **27** with lithium aluminum hydride in tetrahydrofuran gave tetrahydro product **31,** mp 169–170 °C, in 60% yield. The α-ketol **32,** mp 100–101 °C, was obtained in 88% yield upon reaction of **31** with aqueous acid.[9] The acetoxydienone **32a,** mp 92–92.5 °C, was produced in near-quantitative yield by acetylation of **32** with pyridine and

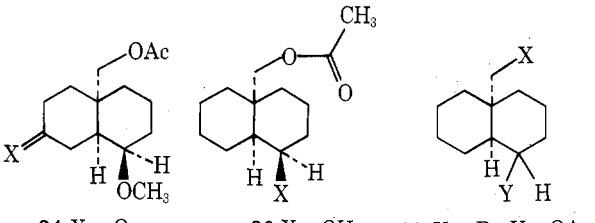
acetic anhydride. Reductive removal of the 4-acetoxy function was smoothly achieved (80%) by treatment of **32a** with chromous chloride in aqueous acetone.[20b] The required enone **33**, mp 84–84.5 °C, was thus available.



31 **32**, R = OH; **32a**, R = OAc **33**

Before relating the results of experiments directed toward elaboration of the *cis*-2-oxa-3-decalone system, a series of transformations which defines the stereochemistry of centers 4a, 8, and 8a in compounds **27**, **31**, **32**, and **33** is described.

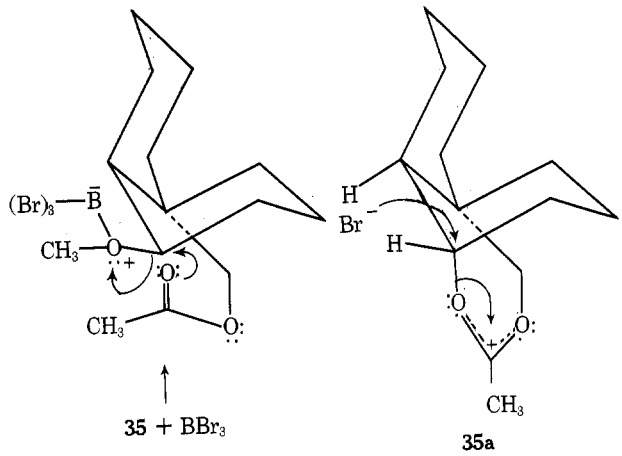
Catalytic reduction of **33** gives the tetrahydro product, **34**. The latter was transformed by a modified (Hirata conditions)[21] Clemmensen reduction to give the acetoxy ether **35**. Our next objective was the demethylation of **35**. It was expected that compound **36** would, upon deoxygenation of the secondary alcohol and saponification, afford **4a** hydroxymethyldecalin which is well known in both cis and trans forms.



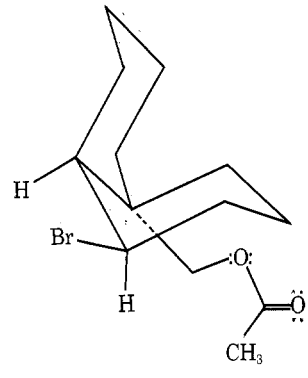
34, X = O; **35**, X = H_2 **36**, X = OH; **37**, X = Br; **39**, X = H **38**, X = Br; Y = OAc **40**, X = OH; Y = H

Accordingly, **35** was treated with boron tribromide in dichloromethane at 0 °C. Rather than the expected **36** there was obtained in 64% yield a compound of the formula $C_{13}H_{21}BrO_2$ whose infrared, NMR, and mass spectral properties defined it to be an acetoxy bromide. The uncertainty as to whether this compound was **37** or **38** was easily resolved in favor of the former. Thus, reaction of the acetoxy bromide with tri-*n*-butyltin hydride gave **39**. The latter was saponified to give the known[22] *cis*-4a-hydroxymethyldecalin (**40**). The material thus prepared was identical with an authentic sample of **40**. For further comparison, acetylation of authentic **40** gave an acetate identical with **39**.

In addition to establishing the cis junction stereochemistry, we believe that this sequence also provides supporting evidence for a trans relationship between the methoxyl at position 1 and the angular acetoxymethyl group in compound **35** and thus in Diels–Alder adduct **27** as well as in compounds **31–35**. The conversion of **35** → **37** may be interpreted in terms of participation of the well-situated neighboring acetoxy function on the coordinated methoxyl group. Attack of bromide at the secondary carbon affords **37** rather than the alternate possibility, **36**, which would have been derived by attack at the neopentyl center of the acetoxonium species **35a**. The conversion of **35** → **35a** in preference to the usual demethylation (i.e., formation of **36**) is readily (though not uniquely) explained by the proposed configurational arrangement. By this view, the stereochemistry of **37** may also be formulated as shown, though this is not essential to our argument.



35 + BBr_3 **35a**



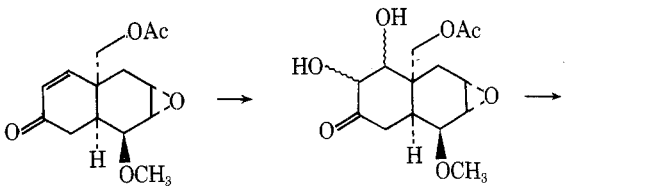
37

We now return to the conversion of **33** to a *cis*-3-oxa-2-decalone system. Reaction of **33** with *m*-chloroperbenzoic acid gave, in 64% yield, epoxy enone **41**, mp 107–108 °C. Though the reaction was slow and inefficient, necessitating long reaction times and large excesses of MCPBA,[23] there was no evidence for the formation of a diastereometric monoepoxide. The convex mode of epoxidation of **33**, which would have been predicted on the basis of precedent,[11a] would give rise to the stereochemistry shown in **41**. The correctness of this assignment of **41** will be proven by the subsequent (damaging) transformation of **43** → **46**.

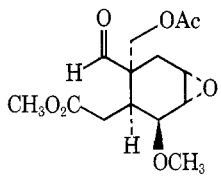
Osmylation of **41** followed by reductive work-up gave glycol **42**,[24] mp 183–184 °C, in 65% yield. Treatment of **42** with lead tetraacetate in benzene–methanol gave a quantitative yield of aldehyde ester **43**, albeit in crude form.

Reaction of **43** with lithium tri-*tert*-butoxyaluminum hydride in THF at 0 °C gave rise to a complex mixture which contained two principal products. The expected compound **45** was obtained but only in 20% yield. The major product of this reaction (46%) is a hydroxy ester [λ_{max} ($CHCl_3$) 2.95, 5.76 μ] whose molecular weight (*m/e* 302) indicates it to be a dihydro version of **43**. This compound, as well as **45**, presumably arises from **44a**, the dihydrometallic derivative of **43**.

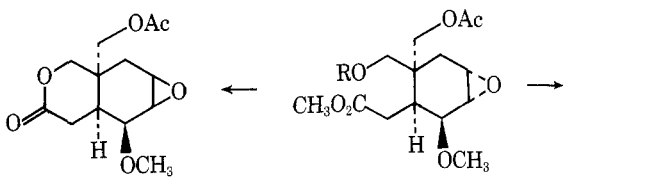
The *m/e* 302 compound did not undergo ring closure to give **45** under a variety of vigorous reaction conditions (heating in pyridine; reflux in benzene containing *p*-TsOH, etc). This nonreaction led us to tentatively reject the assignment of **44** to this substance. Oxidation of this dihydro product produced a ketone, $C_{14}H_{22}O_7$ (*m/e* 300), isomeric with aldehyde **43**. The NMR spectrum (250 MHz) of the ketone in conjunction with its origin and the origin of its precursor lead to the unambiguous assignments of **47** and **46**, respectively, to these compounds. Particularly decisive was the presence of isolated ABX and two AB systems in the NMR spectrum of **47**. The ABX defines with precision the point of attachment of the bridged ether.[25]



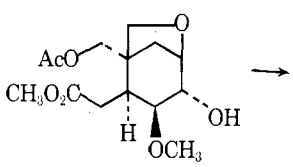
41 42



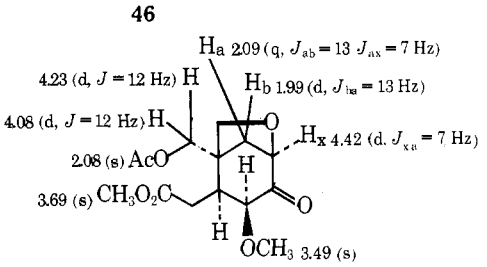
43



45 44, R = H
44a, R = Met



46



47

Apparently, intramolecular epoxide opening by the alkoxide elaborated after metal hydride reduction of aldehyde **43** competes all too effectively with intramolecular acylation. This internal alkylation does, however, serve to define the stereochemistry of the epoxides in compounds **41–43** as well as the target system, **45.**

While in principle, it might be imagined that the ratio of lactonization to epoxide opening would be a function of the metal ion found in **44a,** in practice reduction of **43** with sodium borohydride gave a similar ratio of **45:46.** In view of the consideration that **45** (vide supra) does not constitute an ideal intermediate for vernolepin in that inversion of the oxygen function at C_5 would, in any case, be required, this question was not pursued further.

Nevertheless we extract from these results the information that a cis-fused octalone bearing epoxide functionality in the B ring constitutes a viable precursor of a cis-fused 2-oxa-3-decalone system provided that reaction of the type **44** → **46** is prevented. In view of our recently developed easy access to the required octalones,[25] this approach to vernolepin is particularly attractive and is receiving intensive study in our laboratory.

Experimental Section[26]

Preparation of 4aβ-Acetoxymethyl-4a,5,6,7,8,8aα-hexahydronaphthalen-2(1*H*)-ONE (13a). To 320 mg (1.80 mmol) of hydroxy enone **13**[15] were added 5 ml of acetic anhydride and 5 ml of pyridine. The solution was stirred at room temperature under N_2 for 12 h. Evaporation of the volatiles afforded an oil which crystallized to afford 395 mg of crystalline **13a:** mp 51.5–52 °C (from ether); λ_{max} ($CHCl_3$) 55, 5.96 μ; δ ($CDCl_3$), 1.3–2.4 (m, 11), 2.0 (s, 3), 4.2 (d, J = 12 Hz, 1), 4.4 (d, J = 12 Hz, 1), 5.9 (d, J = 10 Hz, 1), 6.7 ppm (d, J = 10 Hz, 1).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.30; H, 8.21.

Preparation of 3ϵ,4ϵ-Dihydroxy-4aβ-acetoxymethyl-3,4,-4a,5,6,7,8,8aα-octahydronaphthalen-2(1*H*)-one (15). To a solution of 440 mg (1.98 mmol) of enone **13a** in 2 ml of pyridine was added a solution of 5.2 ml of 10% (w/v) OsO_4 in tetrahydrofuran. The solution was stirred at room temperature under N_2 for 18 h. A solution of 1.40 g of $NaHSO_3$ in 20 ml of water was added and stirring continued for 30 min. The solution was extracted with 6 × 75 ml of methylene chloride. Drying over anhydrous sodium sulfate followed by removal of the volatiles and trituration with 1:1 petroleum ether–ether afforded 413 mg (82%) of the keto glycol **15** as a light green, crystalline solid (mp 99–100 °C from ether): λ_{max} ($CHCl_3$) 2.92, 5.78, 5.82 μ; δ ($CDCl_3$) 1.3–2.4 (m, 11), 2.0 (s, 3), 4.0–4.7 ppm (m, 4).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.64; H, 7.69.

Preparation of 2β-Acetoxymethyl-2α-formylcyclohexane-1β-acetic Acid Methyl Ester (16). To a solution of 400 mg (1.56 mmol) of **15** in 63 ml of absolute methanol and 31 ml of benzene was added 2.10 g (4.74 mmol) of lead tetraacetate (freshly recrystallized from glacial acetic acid). The reaction mixture turned yellow upon mixing. After several hours the mixture turned colorless. Stirring under N_2 was continued for 18 h. The volatiles were removed in vacuo and the residual oil dissolved in 50 ml of water and was extracted with 4 × 60 ml of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo to give 400 mg of a light yellow residue, which was taken to be compound **16:** λ_{max} ($CHCl_3$) 3.52, 3.70, 5.75 μ; δ ($CDCl_3$) 1.2–2.8 (m, 11), 2.0 (s, 3), 3,6 (s, 3), 4.2 (broadened s, 2), 9.4 ppm (s, 1).

Preparation of *trans*-4a-Acetoxymethyl-3-oxadecal-2-one (17). To a solution of 240 mg (0.94 mmol) of aldehyde ester **16** in 13 ml of dry tetrahydrofuran (distilled from $LiAlH_4$) at 0 °C was added 300 mg (1.19 mmol) of lithium tri-*tert*-butoxyaluminum hydride. The solution was allowed to warm to room temperature and stirred under N_2 at room temperature for 1 h. The solution was poured into ca. 15 ml of ice water and acidified with 1% HCl. The aqueous solution was extracted with 4 × 50 ml of ethyl acetate. These were combined and dried over anhydrous Na_2SO_4. The volatiles were removed in vacuo leaving 202 mg of a residual oil which was chromatographed on 15 g of silicic acid using 3:2 benzene–ethyl acetate for elution. Lactone **17,** 134 mg (63%), was obtained as an oil (R_f 0.45, 3:2 PhH–EtOAc): λ_{max} ($CHCl_3$) 5.77 μ (br); δ ($CDCl_3$) 1.2–2.6 (m, 11), 2.2 (s, 3), 3.4–4.6 ppm (m, 4).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.84; H, 8.26.

Preparation of *cis*-4a-Formyl-3-oxadecal-2-one (18). To a solution of 390 mg (1.52 mmol) of aldehyde ester **16** in 5.6 ml of absolute methanol at room temperature was added 3.50 ml of a 5% KOH in methanol solution. The solution was stirred at room temperature for 13 min and diluted with 33 ml of water. Acidification with 5% HCl and extraction with 6 × 30 ml of EtOAc followed by drying over anhydrous Na_2SO_4 and removal of the volatiles afforded 270 mg of a viscous oil. The oil was chromatographed on 20 g of silicic acid using 3:2 benzene–ethyl acetate for elution. There was obtained 200 mg (72%) of lactone **18** as an oil (R_f 0.40, 3:2 PhH–EtOAc): λ_{max} ($CHCl_3$) 3.48, 3.68, 5.72 μ (br); δ ($CDCl_3$) 1.2–2.8 (m, 11), 4.4 (d, J = 15 Hz, 1), 4.6 (d, J = 15 Hz, 1), 9.5 ppm (s, 1).

Preparation of 4aβ-Methyl-6α,7α-oxido-4a,5,6,7,8,8aα-hexahydronaphthalen-2-(1*H*)-one (14). To a solution of 3.47 g (0.02 mmol) of *m*-chloroperbenzoic acid in 20 ml of CH_2Cl_2 under N_2 at 0 °C was added 2.52 g (0.02 mmol) of dienone **12.** The mixture was stirred at 0 °C for 2 h. The CH_2Cl_2 solution was stirred with 20 ml of 10% Na_2SO_3 for 30 min. The organic layer was washed with 10% $NaHCO_3$, water, and saturated NaCl successively and dried over anhydrous Na_2SO_4. Upon evaporation of the volatiles in vacuo there was obtained 2.65 g of a residue which was chromatographed on 40 g of silicic acid using $CHCl_3$ for elution. Epoxy enone **14,** 2.09 g (77%), was obtained as an oil (R_f 0.13, $CHCl_3$): λ_{max} ($CHCl_3$) 5.93 μ; δ ($CDCl_3$) 1.02 (s, 3), 1.7–2.3 (m, 7), 3.2 (br s, 2), 5.8 (d, J = 10 Hz, 1), 6.5 ppm (d, J = 10 Hz, 1).

Preparation of 3ϵ,4ϵ-Dihydroxy-6α,7α-oxido-4aβ-methyl-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(1*H*)-one (19).[24] To a solution of 255 mg (1.10 mmol) of $Ba(ClO_3)_2 \cdot 2H_2O$ in 13.5 ml of

water under N_2 added 1.00 g (4.00 mmol) of epoxide. To the stirred suspension was added 1.70 ml of a 10% (w/v) solution of OsO_4 in tetrahydrofuran. The black suspension was stirred at room temperature for 5 h. Another 525 mg (2.10 mmol) of $Ba(ClO_3)_2 \cdot 2H_2O$ was added and stirring was continued for 43 h. During this time the solution became clear. A solution of saturated NaCl (28 ml) was added and the aqueous mixture was extracted with 6 × 50 ml of chloroform. The organic layers were combined and dried. The solvents were evaporated to leave 1.08 g of a oil which crystallized upon trituration with ether. There was thus obtained 602 mg (53%) of compound **19** as light gray crystals.

Chromatography of the 406 mg of mother liquors on 25 g of silica gel using 7:3 chloroform–acetone as an eluent afforded an additional 40 mg of **19**, mp 118–119 °C (R_f 0.35, 7:3 $CHCl_3$–Me_2CO): λ_{max} ($CHCl_3$) 2.77, 5.83 μ; δ ($CDCl_3$) 1.18 (br s, 3), 1.6–2.8 (m, 9), 3.22 ppm (br s, 2).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.96; H, 7.58.

Formation of 2β-Methyl-2α-formyl-4α,5α-oxidocyclohexane-1β-acetic Acid Methyl Ester (20). To a solution containing 91 ml of absolute methanol, 46 ml of benzene, and 500 mg (2.40 mmol) of glycol **19** was added 3.20 g (7.20 mmol) of $Pb(OAc)_4$ (freshly recrystallized from glacial acetic acid). The mixture turned orange-yellow immediately. Within 1 h the mixture had turned colorless. It was allowed to stir under N_2 for 14 h. The solvents were evaporated in vacuo and the resulting oil dissolved in 40 ml of water. The water solution was extracted with 4 × 120 ml of ethyl acetate. The ethyl acetate extracts were washed with 25 ml of saturated brine. The brine solution was extracted once more with 120 ml of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4. After evaporation of the solvents and the acetic acid in vacuo, the residual oil, 500 mg (100%), taken to be aldehyde ester **20**, was used in the next step: λ_{max} ($CHCl_3$) 3.42, 3.60, 5.74 μ (br); δ ($CDCl_3$) 1.0 (s, 3), 1.5–2.6 (m, 7), 3.2 (br s, 2), 3.6 (s, 3), 9.3 ppm (s, 1).

Preparation of *trans*-4aβ-Methyl-6α,7α-oxido-3-oxadecal-2-one (21). To a solution containing 465 mg (2.20 mmol) of crude aldehyde ester 20 in 22 ml of dry (distilled from $LiAlH_4$) tetrahydrofuran at 0 °C was added 581 mg (3.90 mmol) of $LiAl(O\text{-}t\text{-}Bu)_3H$ with stirring. The mixture was allowed to stand for 10 min at 0 °C and then allowed to warm to room temperature. It was stirred under N_2 at room temperature for 1 h. The reaction mixture was poured into ice water (~20 ml) and acidified with 1% HCl. The solution was extracted with 4 × 100 ml of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4. The solvents were evaporated to afford an oil which upon trituration with ether afforded 210 mg (53%) of **21** as off-white crystals, mp 128–129 °C. The mother liquors from the trituration were chromatographed using 15 g of silicic acid and 9:1 chloroform–acetone as an eluent. This afforded another 30 mg (7.5%) of lactone **21** (R_f, 9:1 $CHCl_3$–Me_2CO, 0.45): λ_{max} ($CHCl_3$) 5.76 μ; δ ($CDCl_3$) 1.0 (s, 3), 1.5–2.7 (m, 7), 3.2 (m, 2), 3.9 (d, J = 11 Hz, 1), 4.0 ppm (d, J = 11 Hz, 1).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.74; H, 7.96.

Preparation of 3-Hydroxy-4-methoxybenzyl Alcohol (29). To an ice-cold solution containing 50.00 g (0.33 mmol) of isovanillin (**28**) and 500 ml of absolute ethanol was added dropwise with stirring over a period of 10 min a solution of 12.50 g (0.33 mmol] of sodium borohydride in 312 ml of absolute ethanol. The color changed from light yellow to turbid white during the addition. The reaction mixture was allowed to warm to room temperature over 45 min. The solution was acidified with 5% HCl. The reaction mixture was extensively extracted with chloroform. The organic extracts were combined and dried over anhydrous Na_2SO_4. Evaporation of the solvents afforded a white solid which was washed with a small amount of ether and sucked dry after filtration to give 41.60 g (83.9%) of a white, crystalline solid: mp 132–133 °C (lit.[18] 132 °C); λ_{max} ($CHCl_3$) 2.84 μ; δ ($CDCl_3$) 3.90 (br s, 1), 3.92 (s, 3), 4.6 (s, 2), 5.6 (s, 1), 6.6–7.0 ppm (m, 3).

Preparation of 2-Methoxy-5-hydroxymethyl-1,4-benzoquinone (25). A solution of 11.80 g (0.08 mmol) of phenol **29** dissolved in a minimum amount of $CHCl_3$ and ether was added to a vigorously stirred solution of 45 g (0.19 mmol) of Fremy's salt[27] in 2000 ml of H_2O and 200 ml of 1/6 M KH_2PO_4 at 0 °C. The mixture was stirred at 0 °C for 30 min and extracted with 3 × 300 ml of methylene chloride. The aqueous solution was saturated with solid KCl and again extracted with 3 × 200 ml of methylene chloride. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to afford brownish yellow crystals which upon washing with ether gave 9.56 g (74%) of quinone **25** as a bright yellow, crystalline compound: mp 147–147.5 °C; λ_{max} ($CHCl_3$) 2.80 (br), 5.92, 6.02, 6.19 μ; δ ($CDCl_3$) 2.2 (br s, 1), 3.8 (s, 3), 4.5 (br s, 2), 5.8 (s, 1), 6.6 ppm (t, J = 1.6 Hz, 1).

Anal. Calcd for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 56.98; H, 4.72.

Diels–Alder Reaction of 25 with 1-Methoxy-1,3-butadiene (26). Formation of Adduct 27. A solution of 7.50 g (0.045 mmol) of quinone **25** and 7.50 g (0.089 mmol) of diene (Aldrich) **26** in 150 ml of absolute methanol was heated under reflux under N_2 for 3 h. The reaction mixture was orange at the outset and after a time turned light yellow. The solution was cooled to ambient and the volatiles were evaporated in vacuo. A yellow, crystalline residue was obtained which when washed with a small amount of ether afforded 9.54 g (86%) of **27** as a light yellow, crystalline solid. Cooling of the ether solution afforded 980 mg of impure **27** which was recrystallized from benzene to give an additional 820 mg of adduct (7%) **27**: mp 150–151 °C; λ_{max} ($CHCl_3$) 2.78, 5.84, 6.00, 6.17 μ; δ ($CDCl_3$) (see structure **27**).

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 62.06, H, 6.40.

Preparation of 2,8β-Dimethoxy-4aα-hydroxymethyl-1,4,-4a,5,8,8aα-hexahydronaphthalene-1ε,4ε-diol (31). To a suspension of 6.25 g (0.16 mmol) of $LiAlH_4$ in 50 ml of dry (distilled from $LiAlH_4$) tetrahydrofuran was added with stirring and external cooling a solution of 6.00 g (0.024 mmol) of adduct **27** in 140 ml of dry tetrahydrofuran over a period of 30 min. After addition was complete, the mixture was refluxed under N_2 for 5 h and then allowed to stand overnight. A solution of saturated NH_4Cl was slowly added until the excess $LiAlH_4$ was neutralized. Solid anhydrous Na_2SO_4 (20 g) was then added followed by 700 ml of CH_2Cl_2. The mixture stirred for 30 min. The salts were filtered and washed with 3 × 700 ml of methylene chloride and 2 × 700 ml of ethyl acetate. The combined filtrates were evaporated to afford a white solid which, upon washing with a small amount of ether, gave 3.88 g (60%) of pure **31** as white crystals, mp 169–170 °C, λ_{max} (KBr) 2.75 μ.

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.80; H, 8.08.

Preparation of 1ε-Hydroxy-4aα-hydroxymethyl-8β-methoxy-4a,5,8,8aα-tetrahydronaphthalen-2(1*H*)-one (32). To a solution of 3.51 g (0.014 mmol) of triol **31** in 35 ml of methylene was added 35 ml of 10% H_2SO_4 (w/v). The two-phase system was stirred vigorously under N_2 for 2.5 h at room temperature. The solution was poured into 150 ml of saturated KCl and then extracted with 6 × 30 ml of methylene chloride and with 3 × 300 ml of ether. The organic layers were combined and dried over anhydrous Na_2SO_4. Evaporation of the solvents left a clear oil. To the oil was added 6 ml of 1:1 ether–CH_2Cl_2. The insoluble portion was removed. The solvents were evaporated from the filtrate and this residue crystallized from ether–hexane to afford 2.70 g (88%) of pure **32**, mp 100–101 °C, λ_{max} ($CHCl_3$) 2.75, 5.86 μ.

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.30; H, 7.20.

Preparation of 1ε-Acetoxy-4aα-acetoxymethyl-8β-methoxy-4a,5,8,8aα-tetrahydronaphthalen-2(1*H*)-one (32a). To a solution of 2.71 g (0.012 mmol) of diol in 40 ml of pyridine was added 40 ml of acetic anhydride. The mixture was stirred under N_2 for 12 h at room temperature. The liquids were evaporated in vacuo and a viscous oil remained which crystallized to afford 3.64 g (98%) of a yellowish solid: mp 92–92.5 °C; λ_{max} ($CHCl_3$) 5.68, 5.82 μ; δ ($CHCl_3$) 2.1 (s, 3), 2.2 (s, 3), 2.4 (br s, 2), 2.7 (t, J = 10 Hz, d, J = 3 Hz, 1), 3.3 (s, 3), 3.8 (t, J = 10 Hz, 1), 4.0 (d, J = 11 Hz, 1), 4.2 (d, J = 11 Hz, 1), 5.8–6.4 ppm (m, 5).

Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 61.90; H, 6.23.

Preparation of 4aα-Acetoxymethyl-8β-methoxy-4a,5,8,8aα-tetrahydronaphthalen-2(1*H*)-one (33). To a vigorously stirred solution of 0.8 g of $HgCl_2$ in 10 ml of water was added 10 g of Zn dust. Th mixture was stirred for 5 min and the aqueous solution decanted. To the moist residue was added 20 ml of water and 2 ml of concentrated HCl. The flask was flushed with CO_2 (from dry ice) for 5 min. Finely pulverized chromium(III) chloride (5.0 g) was added with vigorous stirring and CO_2 was continuously allowed to flush through the system. After several minutes the green color turned to a royal blue. The mixture was stirred under CO_2 for 1 h at room temperature at which time it was ready for use. The reagent was used immediately. A flask containing a solution of 3.08 g (0.010 mmol) of the enone diacetate in 600 ml of acetone was flushed for 10 min with CO_2 (from dry ice). A solution of $CrCl_2$ as

prepared above (1200 ml) was introduced via syringe while CO_2 still passed over the system. The solution was stirred at room temperature for 55 min whereupon it was extracted with 6 × 500 ml of ether. The organic layer was evaporated to approximately 150 ml and then washed with 10% $NaHCO_3$. The ether was dried over anhydrous Na_2SO_4. Concentration of the ether afforded 1.78 g (71%) of **33** as pure white needles and 0.72 g of an oil which had essentially the same TLC as the crystals. Chromatography of the oil on 20 g of silicic acid and elution with 9:1 chloroform–acetone afforded an additional 226 mg (9%) of crystalline enone monoacetate: mp 84–84.5 °C; λ_{max} ($CHCl_3$) 5.70, 5.91 μ; δ ($CDCl_3$) 2.1 (s, 3), 2.1 (m, 2), 2.28 (d of d, J_{AB} = 18, J_{AC} = 14 Hz, 1), 2.61 (d of d, J_{BA} = 18, J_{BC} = 5 Hz, 1), 2.76 (d of t, J_{CA} = 14, J_{CB} = 5 Hz), 4.00 (br s, 1), 4.10 (d, J = Hz, 1), 4.13 (d, J = 11 Hz, 1), 5.72–5.78 (m, 2), 5.98 (d J = 10 Hz, 1), 6.70 ppm (d, J = 10 Hz, 1).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.12; H, 7.18.

Preparation of 4aα-Acetoxymethyl-8β-methoxy-3,4,4a,5,-6,7,8,8aα-octahydronaphthalen-2(1*H*)-one (34). A solution of 800 mg (3.20 mmol) of acetoxyenone **33** in 40 ml of ethyl acetate was hydrogenated on a glass hydrogenator at atmospheric pressure over 80 mg of 10% Pd/C for 18 h. The mixture was filtered through Celite and the catalyst washed with three 100-ml portions of ethyl acetate. The ethyl acetate was evaporated in vacuo. The residual oil crystallized upon standing to afford 812 mg (99%) of **34:** mp 69–70 °C (from ether); λ_{max} ($CHCl_3$) 5.78, 5.87 μ; δ ($CDCl_3$) 1.2–2.4 (m, 13), 2.1 (s, 3), 3.2–3.4 (m, 1), 3.2 (s, 3), 4.4 ppm (br s, 3).

Preparation of 4aα-Acetoxymethyl-8β-methoxy-8aα-decahydronaphthalene (35). To a solution of 710 mg (2.80 mmol) of decalone **34** in 50 ml of anhydrous ether at 0 °C was added slowly, in small portions, 3.00 g (46.15 mmol) of activated (0.5% HCl) Zn over a period of 10 min. The mixture was stirred vigorously at 0 °C for 1 h. The Zn was filtered and washed with three 50-ml portions of anhydrous ether. The combined ether layers were washed with 3 × 25 ml of saturated $NaHCO_3$, and then with water. After drying over sodium sulfate the solution was concentrated in vacuo to afford 665 mg of **35** which was used without further purification: λ_{max} (film) 5.77 μ; δ ($CDCl_3$) 1.3–2 (m, 15), 2.1 (s, 3), 4.1 ppm (m, 3).

Formation of 4aα-Acetoxymethyl-8β-bromo-8aα-decahydronaphthalene (37). To a solution of 900 mg (3.75 mmol) of **35** in 20 ml of CH_2Cl_2 (which had been passed through a column of neutral alumina) at 0 °C was then added a solution of 1.80 g (7.17 mmol) of BBr_3 in 3 ml of CH_2Cl_2. The solution was stirred at 0 °C under N_2 for 1.5 h. To this system was added 30 ml of water and stirring was continued for 15 min. The reaction mixture was diluted with 100 ml of CH_2Cl_2 and the aqueous layer well extracted. The organic layers were combined, washed with saturated brine, and dried over anhydrous Na_2SO_4. Removal of the volatiles afforded an oil (820 mg). TLC analysis showed four spots (7% ethyl acetate in *n*-hexane). Chromatography of the oil on 30 g of silicic acid using 7% ethyl acetate in *n*-hexane afforded 466 mg (46%) of the acetoxy bromide **37** (R_f 0.35, 4% ethyl acetate in *n*-hexane): λ_{max} (film) 5.70 μ; δ ($CDCl_3$) 1.3–2.0 (15), 2.1 (s, 3), 4–4.2 ppm (m, 3).

Preparation of *cis*-4a-Acetoxymethyldecalin (39). To a solution of 39 mg (0.13 mmol) of acetoxy bromide **37** in 0.5 ml of benzene at 5 °C was added 60 mg (0.21 mmol) of tri-*n*-butyltin hydride. The solution was stirred under N_2 at room temperature for 24 h. Four drops of concentrated HCl were added and stirring continued overnight at room temperature under N_2. Anhydrous Na_2SO_4 was added, the mixture filtered, and the Na_2SO_4 washed with 20 ml of $CHCl_3$. The combined organic solutions were evaporated in vacuo to an oil. Preliminary chromatography was conducted on 2 g of silicic acid using *n*-hexane as eluent. However, slight amounts of tin compounds containing tin still remained. Preparative TLC using 5% ether in *n*-hexane afforded 14 mg (52%) of compound **39** as an oil: λ_{max} (film) 5.76 μ; δ ($CDCl_3$) 1.5 (m, 17), 2.1 (s, 3), 4.1 ppm (s, 2).

Saponification of 39. Formation of *cis*-4a Hydroxymethyldecalin (40). To a solution of 13 mg (0.06 mmol) of **39** in 1 ml of anhydrous methanol was added a solution of 8 mg (0.15 mmol) of KOH in 1 ml of methanol. After 10 min at room temperature the solution was poured into 1 ml of water and extracted with four 5-ml portions of $CHCl_3$. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo to yield 10 mg (98%) of an oil which crystallized at −78 °C from petroleum ether to afford pure **40:** mp 59–60 °C (lit.[22] 59.4–60.2 °C); NMR spectrum ($CDCl_3$) δ 1–1.8 (m, 18), 3.6 ppm (s, 2). The NMR spectrum of this material was identical with that of the authentic sample. Also, acetylation as the authentic alcohol gave an acetate, the NMR and infrared spectra of which were identical with those of **39** in all respects.

Preparation of 4aα-Acetoxymethyl-6α,7α-oxido-8β-methoxy-4a,5,6,7,8,8aα-hexahydronaphthalen-2(1*H*)-one (41). To a solution of 3.04 mg (0.018 mmol) of *m*-chloroperbenzoic acid in 150 ml of methylene chloride was added 4.00 g (0.016 mmol) of enone acetate. The mixture was stirred at room temperature under N_2 for 24 h. On the basis of TLC analysis of the reaction progress, an additional 3.04 g of peracid was added at 24-h intervals for the next 3 days. After a total reaction time of 96 h, the solution was treated with 350 ml of 10% sodium sulfite for 30 min. The CH_2Cl_2 layer was extracted with 5% $NaHCO_3$, then with H_2O, and finally with saturated NaCl. The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated to give a yellow oil. This, on trituration with 1:1 ether–petroleum ether, gave 2.77 g (64%) of **41:** mp 107–108 °C; λ_{max} ($CHCl_3$) 5.71, 5.92 μ; δ ($CDCl_3$) 1.8–4.0 (m, 8), 2.0 (s, 3), 3.4 (s, 3). 4.1 (d, 2), 6.0 (d, J = 9 Hz, 1), 6.8 ppm (d, J = 9 Hz, 1).

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.18. Found: C, 62.59; H, 6.60.

Osmylation of Enone 41. Formation of 3ϵ,4ϵ-Dihydroxy-4aα-acetoxymethyl-6α,7α-oxido-8β-methoxy-3,4,4a,5,6,7,8,8a-α-octahydronaphthalen-2(1*H*)-one (42). To a solution of 400 mg (1.12 mmol) of $Ba(ClO_3)_2 \cdot 2H_2O$ in 11.75 ml of water was added 450 mg of (1.69 mmol) of enone **41.** To this was added 0.10 ml of a solution of 10% OsO_4 in tetrahydrofuran and the reaction mixture stirred under N_2 for 5 h. The solution turned black during this time. An additional 400 mg (1.12 mmol) of $Ba(ClO_3)_2 \cdot 2H_2O$ was added and the solution slowly became turbid. After an additional 15 h of stirring under N_2, 10 ml of water and 25 ml of freshly prepared 10% $NaHSO_3$ were added and the solution stirred for 5 min. Extraction with 6 × 50 ml of methylene chloride, drying the organic layers over anhydrous Na_2SO_4, and evaporation of the volatiles in vacuo afforded an oil. Upon trituration with 5 ml of 1:1 petroleum ether–ether, 285 mg (63%) of glycol **42** was obtained as a white, crystalline solid. The dark residues were chromatographed on 7 g of silicic acid using 7:3 $CHCl_3$–acetone to afford an additional 11 mg (3%) of **42:** mp 183–184 °C (R_f 0.24, 7:3 $CHCl_3$–Me_2CO); λ_{max} ($CHCl_3$) 2.93 (br), 5.83 μ; *m/e* 300 (P).

Preparation of 2β-Formyl-2α-acetoxymethyl-4α,5α-oxido-β-methoxycyclohexane-1β-acetic Acid Methyl Ester (43). To a solution of 200 mg (0.67 mmol) of **42** in 35 ml of absolute methanol and 16 ml of benzene was added 900 mg (2.03 mmol) of $Pb(OAc)_4$ (freshly recrystallized from glacial acetic acid). The solution turned dark yellow immediately. After several hours it turned colorless, and was combined under N_2 for 15 h. The volatiles were removed in vacuo and the resulting oil dissolved in 20 ml of water. The aqueous solution was extracted with 4 × 120 ml of ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo, leaving 200 mg of oily **43:** λ_{max} (liquid film) 3.55, 3.70, 5.76 μ; δ ($CDCl_3$) 2.0 (s, 3), 2.1–2.8 (m, 5), 3.1–3.6 (m, 3), 3.5 (s, 3), 3.7 (s, 3), 4.1 (br s, 2), 9.7 ppm (s, 1).

Reduction of 43. Formation of 8aα-Acetoxymethyl-5β-methoxy-6α,7α-oxido-4aα,2-oxa-3-decalone (45) and 4-Acetoxymethyl-6-*exo*-methoxy-7-*endo*-hydroxy-2-oxabicyclo[3.2.1]-octane-5-*exo*-acetic Acid Methyl Ester (46). To a solution of 400 mg (1.33 mmol) of **43** in 27 ml of dry tetrahydrofuran at −78 °C under N_2 was added 400 mg (1.57 mmol) of $LiAl(O\text{-}t\text{-}Bu)_3H$. The solution was stirred at −78 °C under N_2 for 7 min and allowed to warm to room temperature. The volatiles were removed in vacuo. To the semisolid mass was added 25 ml of 1% HCl. The aqueous system was extracted with 4 × 150 ml of ethyl acetate. The combined ethyl acetate layers were dried over anhydrous Na_2SO_4 and evaporated to afford 750 mg of a yellow, oily residue. The oil was slowly chromatographed on 32 g of silicic acid using 9:1 chloroform–acetone. From the chromatography was recovered 380 mg from which 71 mg (20%) of lactone **45** as an oil (R_f 0.38, 9:1 $CHCl_3$–Me_2CO) and 184 mg (46%) of bridged ether **46** were obtained (R_f 0.20, 9:1 $CHCl_3$–Me_2CO), mp 125 °C (sublimes). **46:** λ_{max} ($CHCl_3$) 2.97, 5.75 μ (br); δ ($CDCl_3$) 1.76 (d of d, J_{AB} = 12, J_{AX} = 6 Hz, 1), 2.18 (d, J_{BA} = 12 Hz), 1.88 (br s, 1), 2.07 (s, 3), 2.40 (d of d, J_{AB} = 15, J_{AX} = 5 Hz, 1), 2.59 (d, J_{BA} = 15 Hz), 2.63–2.73 (m, 2), 3.31 (s and m, 4), 3.37 (s, 1), 3.40 (br t, 1), 3.70 (s, 1), 3.93–4.10 (m, 4), 4.34 ppm (t, J_{XA} = 6 Hz, 1). **45:** λ_{max} ($CHCl_3$) 5.78 μ (br); δ ($CDCl_3$) 1.76 (d of d, J_{AB} = 15, J_{AX} = 3 Hz, 1), 1.97 (d of d, J_{BA} = 15, J_{BX} = 2 Hz, 1), 2.01 (s, 3), 2.32 (m, 1), 2.38 (d of d, J_{AB} = 14, J_{AX} = 6 Hz, 1), 2.54 (d of d, J_{BA} = 14, J_{BX} = 6 Hz), 3.19 (m, 1), 3.23 (m, 1), 3.41 (s, 3), 3.63 (m, 1), 3.86 (d, J = 9 Hz, 1), 3.89 (d, J = 9 Hz), 3.96 (d, J = 9 Hz), 4.01 ppm (d, J = 9 Hz).

Oxidation of Alcohol of 46. Formation of Ketone 47.[28] To a

solution of 21.5 mg (0.09 mmol, l 1.5 equiv) of pyridinium chlorochromate[28] in 1.5 ml of methylene chloride was added a solution of 20 mg (0.06 mmol) of alcohol in 2 ml of methylene chloride. The solution was stirred at room temperature under N_2 and monitored by TLC (9:1 $CHCl_3$–acetone). After 4 h almost no alcohol was left. The solution was transferred to a column of 4 g of Florisil and filtered using 50 ml of methylene chloride, then 50 ml of 9:1 methylene chloride–acetone. The volatiles were removed in vacuo to yield an oil which was chromatographed via preparative TLC to afford 13 mg of ketone (67%) as an oil (R_f 0.64, 9:1 $CHCl_3$–acetone).

Attempted Epimerization of 27. Formation of 2-Methoxynaphtho-1,4-quinone (30).[29] To a solution of 294 mg (1.00 mmol) of **27** in 7 ml of methanol was added 98 ml (1.00 mmol) of potassium acetate. The solution was refluxed under air ebullition for 2 h.[29] Additional methanol was added as necessary to maintain a volume of approximately 7 ml. The dark mixture was cooled to room temperature and air ebullition continued for 2 h. The mixture was poured into 60 ml of $CHCl_3$ and extracted with 20 ml of water. The aqueous layer was extracted with 5 × 10 ml of chloroform. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to afford a solid residue. Washing with 1:1 ether–petroleum ether afforded 163 mg (87%) of **30:** mp 183–184 °C (lit.[19] 181–182 °C); λ_{max} ($CHCl_3$) 5.92, 6.03, 6.19, 6.23, 6.32 μ; δ ($CDCl_3$) 3.9 (s, 3), 6.2 (s, 1), 7.6–8.3 ppm (m, 4).

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Registry No.—**1,** 18542-37-5; **12,** 17429-21-9; **13,** 24778-90-3; **13a,** 57951-73-2; **14,** 57951-74-3; **15,** 57951-75-4; **16,** 57951-76-5; **17,** 57951-77-6; **18,** 57951-78-7; **19,** 57951-79-8; **20,** 57951-80-1; **21,** 57951-81-2; **25,** 50827-56-0; **26,** 3036-66-6; **27,** 57951-82-3; **28,** 621-59-0; **29,** 4383-06-6; **30,** 2348-82-5; **31,** 57951-83-4; **32,** 57951-84-5; **32a,** 57951-85-6; **33,** 57951-86-7; **34,** 57951-87-8; **35,** 57951-88-9; **37,** 57951-89-0; **39,** 57951-90-3; **40,** 57951-91-4; **41,** 57951-92-5; **42,** 57951-93-6; **43,** 57951-94-7; **45,** 57951-95-8; **46,** 57951-96-9; **47,** 57951-97-0.

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(26) Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer 137 Infracord spectrophotometer. NMR spectra were at 60 MHz on Varian A-60D or Varian T-60 spectrometers. The spectra of **21, 25, 32, 45,** and **46** were measured at 250 MHz. Spectra were measured in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ) from Me_4Si. Low-resolution mass spectra were measured on an LKB-9000 system by direct insertion. High-resolution mass spectra were measured on a Varian CH_5 system. TLC measurements were conducted on Merck silica gel plates 60F-254.
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