warm to room temperature and filtered and the filtrate evaporated in vacuo by a benzene azeotrope. The crude product was purified by column chromatography on silica gel with a $CHCl_3$ eluant to give the pure mesylate. This material (54 mg, 0.16 mmol) was dissolved in dry glyme (1 mL), NaI (112 mg, 0.75 mmol) and Zn (98 mg, 1.5 mmol) were added, and the reaction mixture was stirred under a nitrogen atmosphere at 65 °C for 1.5 h. Then the mixture was filtered and the filtrate evaporated to dryness in vacuo. The residue was purified by column chromatography on silica gel by using *n*-hexane and then *n*-hexane/ethyl acetate (99:1) as eluants to give material that was crystallized from MeOH–H_2O to give **8** (18 mg, 43% from **6**): mp 94–98 °C; UV (MeOH), 202 (ε 10 904) nm; ^1H NMR (CD_2Cl_2, 90 MHz) δ 0.95 (1 H, m), 1.23 (3 H, d, J = 6.5 Hz), 1.50–2.60 (15 H, m), 4.85 (1 H, m), 5.21 (1 H, dd, J = 10, 15 Hz), 5.63 (1 H, d, J = 15.6 Hz), 5.74 (1 H, m), and 7.33 (1 H, dd, J = 5, 11.9, 15.6 Hz); ^{13}C NMR (CD_2Cl_2, 22.5 MHz) δ 21, 25.6, 27, 32.3, 34.9, 35.1, 35.7, 40, 47.6, 50.3, 71.7, 120.8, 130, 138, 151.1, and 166.8; MS, m/z (% rel intensity) 248.1777 calcd, 248.177 found (20, M^+), 206 (37), 161 (22), 152 (39), 121 (57), 79 (83), and 40 (100).

The isomer **9** was prepared from **7** by using the same procedures: colorless oil; UV (MeOH), 201 (ε 3280) nm; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.18 (3 H, d, J = 6.5 Hz), 1.30–2.60 (14 H, m), 2.98 (2 H, d, J = 8 Hz), 4.81 (1 H, m), and 5.00–5.68 (4 H, m); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 20.6, 23.4, 28, 31.3, 32.2 (2 resonances), 33.9, 40.7, 51.2, 51.5, 71.3, 123.2, 131.5, 133.7, 138.5, and 166.7; MS, m/z (% rel intensity) 248 (2, M^+), 206 (10), 152 (20), 121 (35), 120 (35), 80 (77), and 40 (100).

Acknowledgment. We thank Mario Gonzales, University of Wisconsin, for ^2H NMR spectra, Prof. S. Nozoe, Tohoku University, for a culture of *Eupenicillium brefeldianum*, and Prof. Barry Trost for stimulating discussions. This research was supported by a grant from the National Institutes of Health (GM 25799).

Registry No. **1**, 20350-15-6; **2**, 62989-90-6; **3**, 73899-78-2; **4**, 95192-01-1; **5**, 95192-02-2; **6**, 95216-31-2; **7**, 95216-32-3; **8**, 95192-03-3; **9**, 95192-04-4.

Synthetic Studies toward Aflavinine: A Synthesis of 3-Desmethylaflavinine via a [2 + 2 + 2] Annulation

Samuel Danishefsky,* Samuel Chackalamannil, Peter Harrison, Michael Silvestri, and Philip Cole

Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511. *Received October 15, 1984*

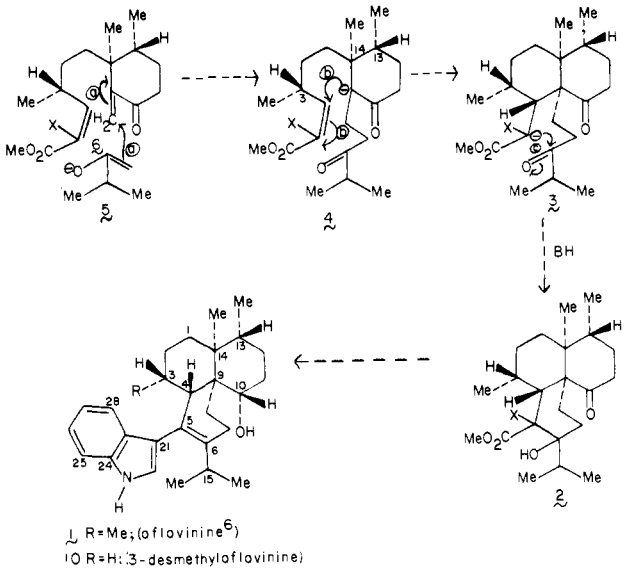
Abstract: Several systems containing two electrophilic olefins have been synthesized. In each case, one of the olefins was an α-methylene ketone while the other was an α,β-unsaturated ester. In each case the α-methylene ketone was attacked by the external nucleophile which was the regiospecific lithium enolate derived from 2-(trimethylsiloxy)-3-methylbut-1-ene. Michael addition to the β-carbon of the α-methylene ketone was followed by intramolecular Michael addition to the enoate. The ester enolate thus produced reacted in an intramolecular aldol-like reaction with the isopropyl ketone to complete the closure of a six-membered ring from the three C_2 units (see Scheme I). The stereochemistry of this process has been investigated in some detail, and an application to the synthesis of 3-desmethylaflavinine (**10**) is described.

Background

Aflavinine (**1**) is a structurally novel indolic diterpenoid which was isolated from a strain of Aspergillus flavus.[1] Other structurally related indolic diterpenoids, such as aflatrem, paspalinine, paspaline, paspalicine, and paxilline have tremorogenic properties.[2,3] The small amount of homogeneous aflavinine which was isolated was apparently not subjected to biological evaluation. Hence, there is no reliable information on its neurological activity, if any.[4]

There exist no data in the literature pertaining to the chemical behavior of aflavinine. The information content of the spectroscopic measurements on aflavinine was too fragmentary to encourage even a meaningful hypothesis as to its structure and stereochemistry. It was to the province of X-ray crystallography that one had to turn for the structural elucidation.[1] Not unlike the case with many of the newer natural products available from natural sources in grudgingly small quantities, a plan for the total synthesis of aflavinine (**1**) would have to make do without the benefit of any information as to the chemical "personality" of its final target.

Scheme I



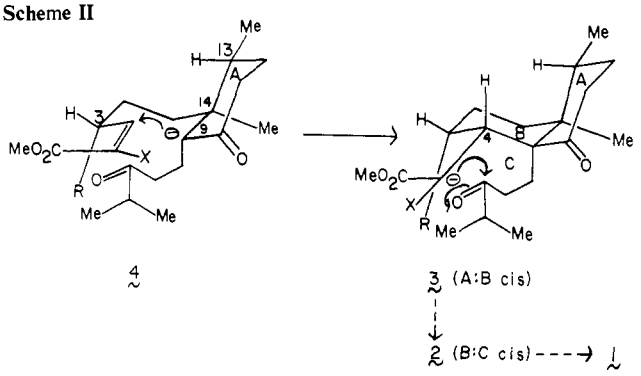
Synthetic Rationale

Our interest in such a total synthesis arose from a perception that the basic ring system could be assembled from an intriguing

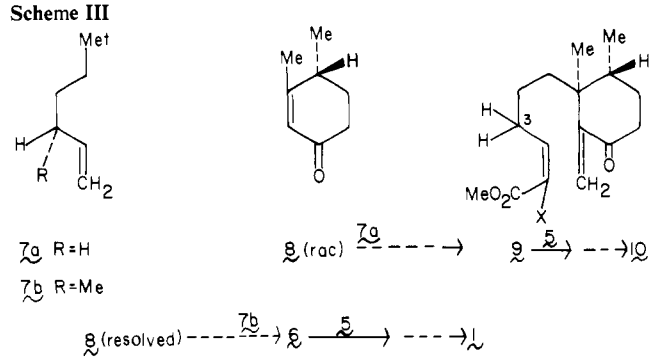
(1) Gallagher, R. T.; McCabe, T.; Hirotsu, K.; Clardy, J.; Nicholson, J.; Wilson, B. J. *Tetrahedron Lett.* **1980**, *21*, 243.
(2) Gallagher, R. T.; Clardy, J.; Wilson, B. J. *Tetrahedron Lett.* **1980**, *21*, 239.
(3) (a) Gallagher, R. T.; Finer, J.; Clardy, J.; Leutwiler, A.; Weibel, F.; Werner, A.; Arigoni, D. *Tetrahedron Lett.* **1980**, *21*, 235. (b) Springer, J. P.; Clardy, J. *Tetrahedron Lett.* **1980**, *21*, 231. (c) Cole, R. J.; Kirksey, J. W.; Wells, J. M. *Can. J. Microbiol.* **1974**, *20*, 1159.
(4) For a report on the biological activity of a hydroxylated aflavinine see: Cole, R. J.; Dorner, J. W.; Springer, J. P.; Cox, R. H. *J. Agric. Food Chem.* **1981**, *29*, 293.

0002-7863/85/1507-2474$01.50/0

Scheme II



Scheme III



process which we have termed a "[2 + 2 + 2] annulation".[5a,b] The notion is formally a very simple one. It was hoped that a monocyclic array such as **6** containing two electrophilic double bonds could be assembled. Though for the moment we leave the precise nature of X in structure **6** unspecified, it was anticipated that the electrophilicity of the β-carbon of the α,β-unsaturated ketone would be greater than that of the corresponding carbon of the α,β-unsaturated ester. Accordingly, it would be expected that attack by the primary enolate **5**, derived from methyl isopropyl ketone, upon the biselectrophile **6** (see arrows "a"), would generate, in the first instance, the enolate **4**. The carbanionic site in **4** would be well positioned for intramolecular Michael addition to the α,β-unsaturated ester linkage (see arrows "b"), generating enolate **3**. Again, the carbanionic center in **3** is strategically disposed to attack the proximal ketone in an aldol-like process (see arrows "c"). The fate of the resultant product **2** could well be a function of the nature of the as yet unspecified "X" and of the configurational relationship of the hydroxyl and X-bearing carbon centers. However, the projection that a product of the type **2** could be converted to aflavinine did not appear to be unduly optimistic.

An interesting feature of the scheme is that it involves two kinetically generated enolates, **4** and **3**. *The Generation of either of these species from the action of bases on their corresponding conjugate acids could well prove difficult.* The viability of the plan presented in Scheme I would rest on the hope that the connectivity of the kinetically generated intermediates would not be disrupted through proton transfers or other unanticipated side reactions.

Furthermore, it seemed at least possible that the stereochemical relationships required for a synthesis of aflavinine could be accommodated within this construct. Already in the monocyclic array **4**, it would be necessary for the stereogenic[7] centers bearing the secondary methyl groups at carbons 3 and 13[6] to have been properly "matched", both in relation to one another and in relation to the quaternary center at C_{14}. Given the manageability of this requirement, attention can be focused on the likely prospects for the interlocking of the rings. It seemed reasonable to suppose that the side chain at C_{14} in compound **4** would be oriented in an equatorial conformation and that it would attack the enolate at C_9[6] from an axial direction due to the usual stereoelectronic considerations. This would ensure a cis fusion of the A and B rings in the bicyclic intermediate **3**. *It was further hoped that the B ring would be produced in a chair conformation with the side chain projecting from C_4 in an equatorial sense, i.e., cis (vis-a-vis the B ring) to the axially disposed side chain projecting from C_8.* In such a case, closure of the C ring would afford the cis fused B:C system **2**, which would eventually be converted to aflavinine. The stereochemical rationale is implied in Scheme II.

It was envisioned that the synthesis of biselectrophile **6** would proceed via the addition of an organometallic reagent **7b** to 3,4-dimethylcyclohex-2-ene-1-one (**8**).[8] While such an approach, based on the precedent of Ziegler,[9] held out strong hope for establishing the required cis relationship of the methyl groups at carbons 13 and 14, in the desired target **6**, it did not offer a rational basis to control the configuration of the distal center at C_3 relative to these proximal centers. Indeed, barring a most unlikely mutual kinetic resolution, the coupling of racemic **7b** with **8** would be expected to produce two diastereomers. Even if the separation of the components of such a mixture could be managed, the assignment of relative stereochemistry to these C_3 epimers might prove to be very difficult. Avoidance of these problems would require the coupling of optically pure versions of **7b** and **8**. The decision was, therefore, made to postpone the need for optically resolved fragments until many of the uncertainties implicit in the [2 + 2 + 2] annulation could be experimentally evaluated. Accordingly, the target became the biselectrophile **9** which, lacking the distal stereogenic center at C_3, could be assembled from **7a** and the readily available racemic **8**. A [2 + 2 + 2] annulation, using the "nor" compound **9**, could provide the basis for a synthesis 3-desmethylaflavinine (**10**). It was hoped that the findings in such a study could be applied to the synthesis of aflavinine (**1**) itself. These projections are summarized in Scheme III, wherein the attractiveness of the 3-desmethyl compound as a model target becomes apparent.

Discussion of Results

The first subgoal became the synthesis of biselectrophile **9** (X = Br). The starting materials were the readily available enone **8**[8] and the commercially available bromide **11**. The Grignard reagent **11a**, generated from **11**, reacted with **8** in a 1:1 solution of diethyl ether–dimethyl sulfide, containing copper(I) iodide. The metalloenolate thus generated was quenched by reaction with methyl chloroformate to produce enol carbonate **12** in ca. 72% yield. Reaction of **12** with ozone under carefully controlled conditions was followed by workup with dimethyl sulfide. The crude aldehyde thus generated was treated with methanol containing trace amounts of *p*-toluenesulfonic acid to afford a crude dimethyl acetal **13**.

Compound **13** reacted with 3.5 equiv of methyllithium in THF in −78 °C. The lithium enolate **13a**, generated in situ, was quenched by reaction with freshly prepared dimethyl methyleneammonium chloride,[10a,b] thereby producing the crude Mannich base **14**, whence, by acidic treatment, the crude aldehyde **15** was obtained. Upon reaction of **15** with the sodium salt of methyl (dimethylphosphonyl)bromoacetate,[11] a 2:3 *E*:*Z* mixture of isomers

(5) (a) Danishefsky, S.; Chackalamannil, S.; Silvestri, M.; Springer, J. *J. Org. Chem.* **1983**, *48*, 3615. (b) Danishefsky, S.; Harrison, P.; Silvestri, M.; Segmuller, B. *J. Org. Chem.* **1984**, *49*, 1319.

(6) The numbering scheme in this discussion section is intended to simplify discourse by maintaining a fixed designation for a particular carbon throughout a series of structures. It follows the crystallographic numbering adopted by Springer.[5a] Proper I.U.C. Names are provided for each compound in the Experimental Section.

(7) Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319.

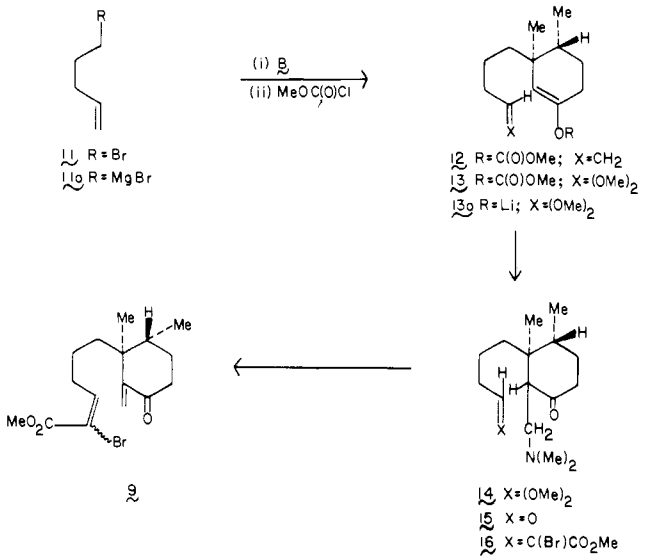
(8) Dauben, W. G.; Shaffer, G. W.; Vietmeyer, V. D. *J. Org. Chem.* **1968**, *33*, 4060.

(9) Ziegler, F. E.; Reid, G. R; Studt, W. L.; Wender, P. A. *J. Org. Chem.* **1977**, *42*, 1991.

(10) (a) Kinast, G. Tietze, L.-F. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 239. (b) For the first example of the reaction of an enolate with a homogeneous imminium salt, see: Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6715.

(11) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

Scheme IV



16 was produced (Scheme IV). Oxidative unveiling of the α-methylene ketone group through exposure of **16** to *m*-chloroperoxybenzoic acid provided the desired biselectrophile **9**. As noted, the intermediates between enol carbonate **12** and biselectrophile **9** were not fully characterized, and the yields of the individual steps are not known. The overall yield for the six-step conversion from **12** to the *E*:*Z* mixture **9** was 30–35%.

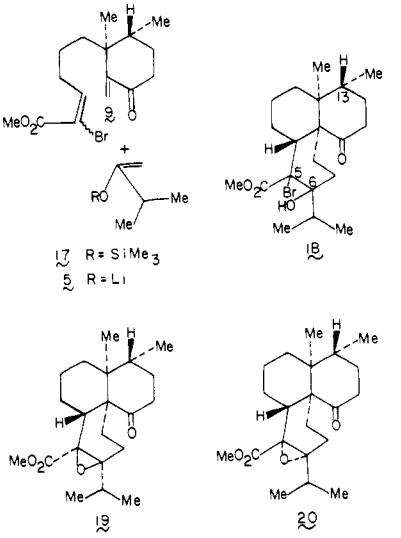
Several features of this scheme merit comment. Clearly, the bromoenoate segment of the side chain of **9** could not have been readily accommodated per se within an organometallic reagent. One possibility would have involved the masking of the functionality in a more sophisticated and less accessible version of nucleophile **11a**. More attractive was the prospect of installing the required substituents subsequent to conjugate addition of the simple Grignard reagent **11a**.

It was also unlikely that the desired neopentyllithium enolate **13a** would be operationally accessible by deprotonation of its conjugate acid. Therefore, it was necessary to *store* the site-specific enolate available from the original addition of the copper species derived from **11a** to the enone **8**. We have previously[12] described the enol carbonate device of specific enolate storage as one which allows for considerable latitude[13] for oxidative operations at distal isolated double bonds. It was the aflavinine problem which prompted that solution.

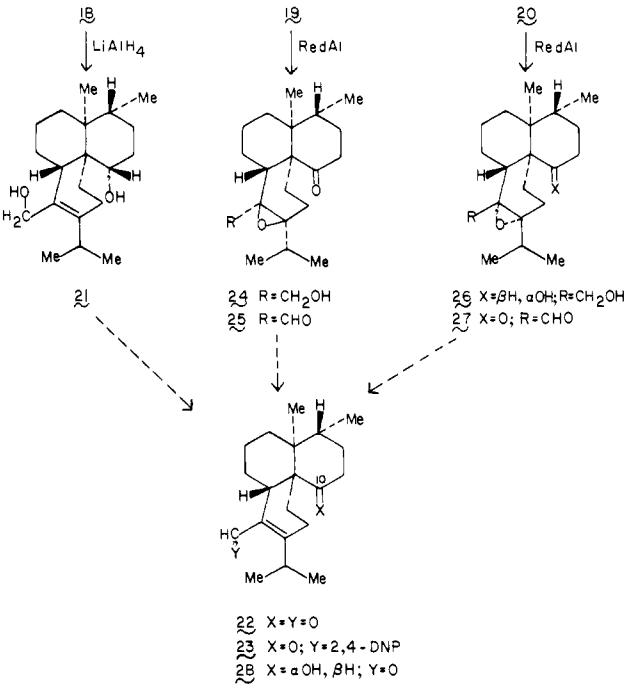
The relative stereochemistry shown in structure **12** was not actually known at this point.[14] However, the analogy to the celebrated case of Ziegler[9] was such that the required "*cis*-dimethyl" stereochemistry would be expected. Subsequent findings were to validate this surmise. The opportunity to test the feasibility of the [2 + 2 + 2] annulation was at hand.

It was anticipated that the reaction of methyllithium with silyl enol ether **17**[15] (itself readily available from methyl isopropyl ketone) would provide a convenient, fully aprotic source of enolate **5**. In practice, reaction of 3.5 equiv of **17** with 2.5 equiv of methyllithium was used to generate the presumed **5**. This substance, at −78 °C in 1,2-dimethoxyethane, was treated with 1 equiv of the biselectrophile isomers **9**. The temperature was maintained

Scheme V



Scheme VI



at −78 °C for 1 h and allowed to rise to ambient temperature over ca. 30 min. After conventional workup, the formation of a mixture of products was indicated. Chromatography on silica gel afforded three homogeneous substances.

The least polar product (25% yield) corresponded to a 1:1 adduct of biselectrophile **9** and methyl isopropyl ketone. Infrared and NMR spectral examination indicated that both of the olefinic linkages of the α,β-unsaturated carbonyl groups of **9** (Scheme V) had been consumed, and its infrared spectrum pointed to the presence of a hydroxyl function. On this basis, the compound was assigned to a gross structure corresponding to that shown in formula **18**. In addition, there were isolated two more polar products (one in 7% yield and the other in 15% yield) which correspond, in their empirical formulas, to compound **18**-HBr. These compounds were provisionally assigned to be the epoxides corresponding to **19** and **20**. Subsequent experiments allowed for the assignments of the individual epoxides.

We next describe experiments which confirm these formulations of gross structure. Moreover, the results demonstrate that the three compounds share a common stereochemical backbone in the tricyclic system and that this backbone corresponds to the cis/cis stereochemistry present in aflavinine. Toward this goal,

(12) Danishefsky, S.; Kahn, M.; Silvestri, M. *Tetrahedron Lett.* **1982**, *23*, 703.

(13) Although the terminal olefin of **12** undergoes selective cleavage to the aldehyde on ozonolysis, similar treatment of the more hindered olefin **38** gave only low yields of the corresponding aldehyde, possibly due to competitive oxidation of the enol carbonate. The relative reactivity of the olefinic linkage of enol carbonates and isolated double bonds would have to be evaluated on a case-to-case basis.

(14) The presence of a small amount of an isomeric species is suggested in the NMR spectrum of **12**, although the material appears homogeneous on chromatography.

(15) Cf.: Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464.

we were much helped by a fortuitous finding. Reaction of the bromohydrin **18** with lithium aluminum hydride in ether gave rise (58%) to compound **21** in which reductions of the ketone and ester functions had been accompanied by reductive elimination of the bromohydrin (Scheme VI). Oxidation of this compound with pyridinium dichromate afforded the enal **22** in 90% yield. This product is transformed to a mono 2,4-dinitrophenylhydrazone, mp 243–244 °C. We have already reported[5a] that a single crystal X-ray determination of this 2,4-DNP revealed its structure and stereochemistry to be that shown in structure **23**.[16a] Of course, these data do not speak to the question of the configurations of carbons 5 and 6[6] (bearing the bromine and hydroxy functions in compound **18**) and that of carbon 10 in compounds **21** and **28** (vide infra), but they do define the crucial issues of the stereochemistry of the interlocking of the tricyclic system, and the relationship of the stereogenic center at C_{13} to these functions.

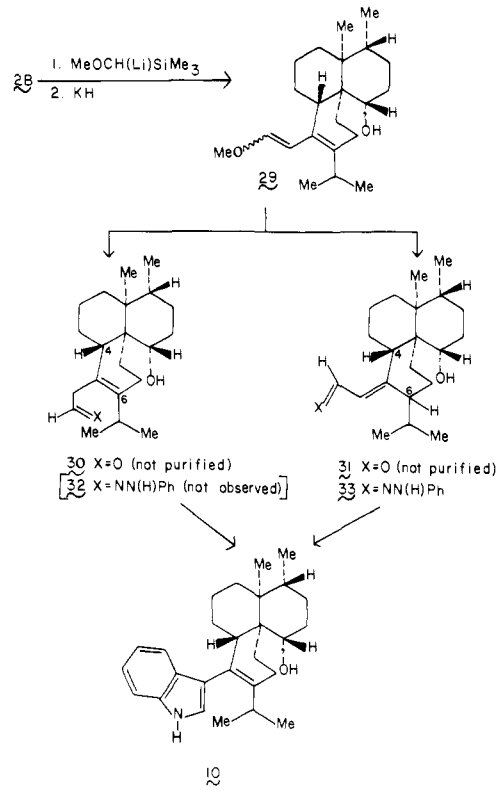
A single crystal X-ray determination[16b] on the minor epoxide, mp 142–143 °C, also revealed its structure to be that shown in structure **19**, wherein the backbone stereochemistry of the ABC tricyclic ring system is the same as that in the bromohydrin **18**. Each of the epoxides was reduced with "RedAl".[17] Under these conditions, the minor epoxide **19** afforded compound **24** in which, surprisingly, the ester had undergone reduction in preference to the ketone. Reoxidation of this product with PCC[18] gave rise to the epoxy keto aldehyde **25** in 95% yield. Deoxygenation of the epoxy function was accomplished through reaction of **25** with excess trimethyliodosilane in CCl_4 at 0 °C in the presence of triethylamine.[19] There was thus obtained the keto enal **22** in 87% yield.[20]

That the major epoxide from the [2 + 2 + 2] annulation of compound **9** is properly represented as structure **20**, with the same backbone stereochemistry as that of **18** and **19**, was demonstrated by its transformation to the same keto enal **22**. Thus, upon treatment with RedAl, compound **20** is converted to **26** which, after reoxidation with PCC, suffers conversion to the stereoisomeric epoxy keto aldehyde **27**. Reaction of **27** with trimethyliodosilane, as described above for epoxide **25**, afforded compound **22** in 77% overall yield.[20]

Although the formation of three products, arising from a common intermediate analogous to the generalized structure **3**, was an inconvenience from the standpoint of synthetic practicality, the fact that the three compounds shared the same backbone stereochemical arrangement required for aflavinine and converged to a common, synthetically relevant, intermediate was encouraging. For this specific purpose, the intermediate hydroxy enal **28** would be most convenient. This compound was readily accessible (80% yield) by oxidation of enediol **21**[20] with activated manganese dioxide. The NMR spectrum of compound **28** revealed the hydroxyl group to be in an axial conformation[21] in that the carbinylmethine proton at C_{-10} appears as a triplet, δ 3.64 (J = 1.5 Hz).

Aldehyde **28** reacted with the lithium derivative of (methoxymethyl)trimethylsilane. The adduct thus generated was subjected to the action of KH according to the protocols of Magnus.[22] There was obtained an *E*:*Z* mixture of methyl dienol ethers **29**, which, upon hydrolysis with 70% perchloric acid, gave rise to a mixture of β,γ- (**30**) and α,β-unsaturated (**31**) aldehydes. The separation of these compounds would probably have been difficult since they appeared to be quite labile. Fortunately, such a separation proved to be unnecessary.

Scheme VII



It was our intention to prepare the phenylhydrazones of these compounds with the expectation that a Fischer indolization, of at least the phenylhydrazone derived from **30**, would produce the aflavinine-type product. Ordinarily, of course, the Fischer indolization is achieved by heating a phenylhydrazone in the presence of protic or Lewis acids.[23] In the case at hand, matters progressed in an unusual way.

Treatment of the mixture of **30** and **31** with phenylhydrazine, followed by aqueous workup, produced two products. One was 3-desmethylaflavinine (**10**) in 36% yield (based on the prehomologated enal **28**). The other was the phenylhydrazone **33** of the homologated conjugated enal **31** (24% yield). This compound was then subjected to conditions (acetic acid, reflux, 12 h) which more nearly resemble those associated with the Fischer process.[23] Interestingly, there was thus obtained a 48% yield of the same target product, **10**.

The spontaneous indolization of the β,γ-unsaturated aldehyde phenylhydrazone is remarkable. Presumably, the β,γ-unsaturation promotes tautomerization of the hydrazone linkage of system **32** to its active dienylhydrazine form. Also, the presence of this additional double bond may well facilitate the bond reorganization phase of the Fischer reaction.

The convertibility of hydrazone **33** to the same noraflavinine **10** could not have been predicted in advance since tautomerization via deprotonation from C_4 leading to other products could have been competitive with the required deprotonation at C_6.[6] The feasibility of this indolization in the series at hand allows for the exploitation of both homologated isomers, **30** and **31**, for the desmethylaflavinine synthesis as shown in Scheme VII.

The groundwork for a total synthesis of aflavinine itself seemed to be secure. As discussed above, the surest method to interface the stereochemistrry at C_3[6] with that of the rest of the molecule would involve the proper matching of an optically pure organo-

(16) (a) Bond distances, bond angles, and thermal parameters for compound **23** are available in the Microfilm Edition corresponding to ref 5a. They are also available from: Chackalamannil, S. Ph.D. Dissertation, Yale University, New Haven, CT, 1985. (b) All crystallographic data for compound **19** are available in: Chackalamannil, S. Ph.D. Dissertation, Yale University, New Haven, CT, 1985.

(17) Bažant, V.; Čapka, M.; Černý, M.; Chvalovský, V.; Kochloefl, K.; Kraus, M.; Málek, J. *Tetrahedron Lett.* **1968**, 3303.

(18) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(19) Denis, J. N.; Magnane, R.; Van Eenoo, M.; Krief, A. *Nouv. J. Chem.* **1979**, *3*, 705.

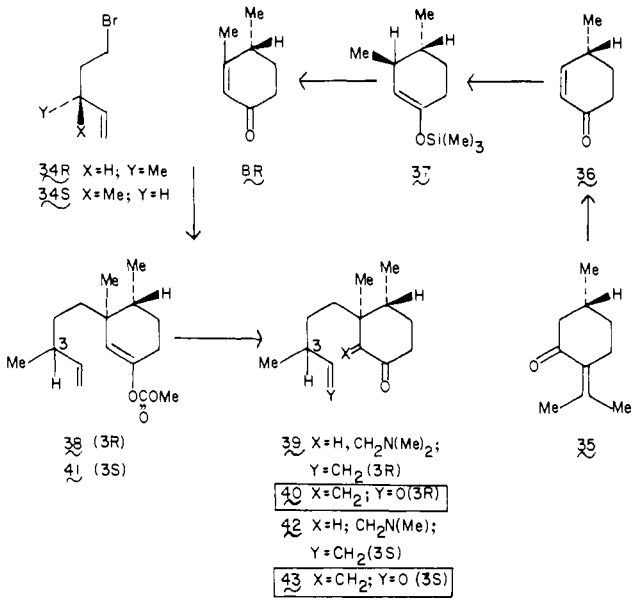
(20) The experimental procedure for the conversion of the two epoxides **19** and **20** to compound **22** is provided in the Microfilm Edition of this paper. The experimental procedures for convergence of these compounds with the common synthetic intermediate **28** are available in: Chackalamannil, S. Ph.D. Dissertation, Yale University, New Haven, CT, 1985.

(21) X-ray structures of **23**[16a] and **19**[16b] indicate a chair conformation for the A ring such that an axial hydroxyl at C_{10} has the α-configuration.

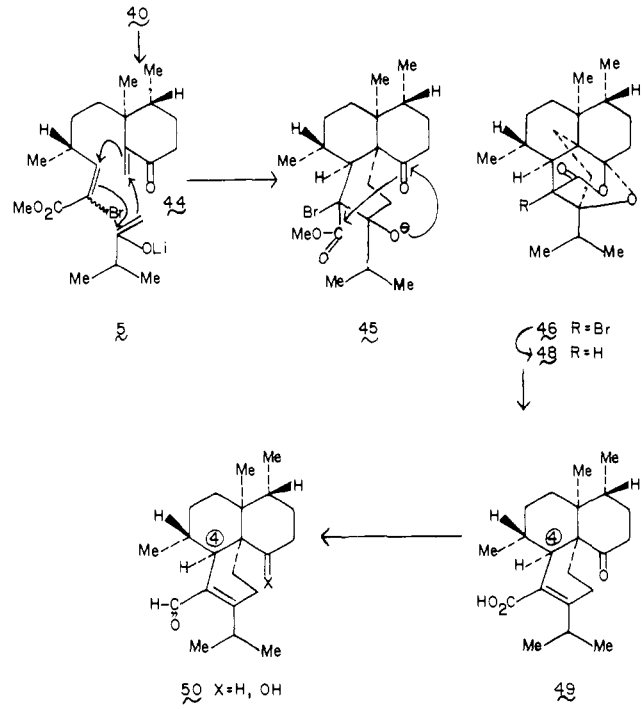
(22) Magnus, P.; Roy, G. *J. Chem. Soc., Chem. Commun.* **1979**, 822.

(23) Robinson, B. *Chem. Rev.* **1963**, 373.

Scheme VIII



Scheme IX



metallic fragment (cf. **7b**) with an optically pure enone **8** (see Scheme III). Since the absolute configuration of aflavinine was not known, the enantiomeric series in which to conduct operations could be selected by considerations of synthetic convenience. Toward this end, one could draw from the experiments of Ireland[24] to prepare either bromide (*R*)-**34** or (*S*)-**34** from the commercially available antipodal citronellols. For the enone subunit, advantage could be taken of the commercial availability of (*R*)-pulegone[25] (**35**). The "matched" partner for the aflavinine synthesis would be bromide (*R*)-**34**.

The conversion of (*R*)-pulegone to (*R*)-4-methylcyclohex-2-ene-1-one (**36**) for the purposes of this project has already been described.[26] Reaction of **36** with lithium dimethylcuprate in ether at 0 °C, followed by quenching of the metalloenolate thus generated with chlorotrimethylsilane, generated silyl enol ether **37**. Reaction of **37** with palladium acetate[27] afforded the (*R*)-antipode of enone **8** (henceforth to be called (*R*)-**8**) in 60% overall yield.

As above (cf. bromide **11**), a Grignard reagent was prepared from bromide (*R*)-**34** (Scheme VIII). Reaction of this Grignard reagent with antipode (*R*)-**8** under the influence of cuprous iodide–dimethyl sulfide generated a metalloenolate which was quenched by reaction with methyl chloroformate. There was thus obtained the optically pure enol carbonate **38** in 72% yield. Reaction of **38** (1 equiv) with methyllithium (3.3 equiv) generated a site-specific enolate which was quenched by the action of dimethylmethyleneammonium chloride[10] (4.4 equiv), to afford the crude Mannich base **39**. Ozonolysis of this product in methanol–methylene chloride containing sodium bicarbonate, followed by treatment of the resultant product with dimethyl sulfide, gave directly enone aldehyde **40** in 49% overall yield (based on enol carbonate **38**). Apparently, ozone converts the Mannich base to a labile oxidation product, possibly the corresponding *N*-oxide. Given the ready transformation in the desmethyl series of Mannich base **16** to enone **9** through the action of MCPBA, this interpretation seems particularly likely.

For reasons which will soon become evident, it was also of interest to investigate the epimeric (mismatched) series wherein the configuration at C_3 was inappropriate for a synthesis of aflavinine. For this purpose, the antipodal bromide (*S*)-**34** was converted to its Grignard reagent which was combined with enone (*R*)-**8** under the same conditions as those employed for bromide (*R*)-**34**. In this fashion, there was obtained the enol carbonate **41** which was converted, as before, to the 3*S* Mannich base **42** and thence to 3*S* enone aldehyde **43**. The aldehyde function in both **40** and **43** underwent selective Emmons-like reaction with the sodium salt of methyl (dimethylphosphonyl)bromoacetate[11] to produce ca. 60–70% yields of the biselectrophiles **44** and **52**, respectively, as *E*:*Z* mixtures. These biselectrophiles served as substrates to investigate the stereochemical consequences of the [2 + 2 + 2] annulation reaction.

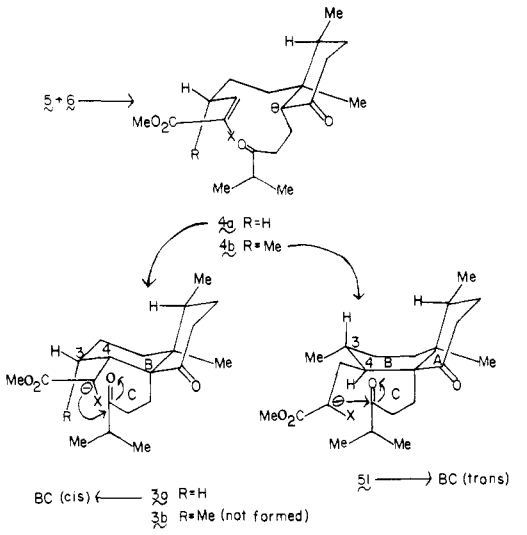
The lithium enolate **5** (derived as before from silyl enol ether **17**) in dimethoxyethane at −78 °C reacted with the "matched" *E*:*Z* biselectrophile mixture **44**. The temperature was allowed to rise to ca. 25 °C where it was maintained for 24 h. Conventional workup afforded a single identifiable product, mp 149.5–150 °C, in 30% yield.

It soon became very clear that this process had taken a different course from that observed in the desmethyl series. The empirical formula of this crystalline product corresponded to its being a 1:1 adduct of **5** and **44** minus LiOMe. Indeed, the most striking features of its NMR spectrum was the absence of resonances ascribable to the protons of an OMe group. Its infrared spectrum was not inconsistent with the presence of a δ-lactone. These data suggested the possibility of a structure corresponding in gross terms to that shown in **46**. Such a product could well arise from a set of bond reorganizations implied in the formalism **5** + **44** → **45** → **46** (Scheme IX). It was striking that no such lactonization had been observed with the desmethyl substrate **9**, wherein bromohydrin **18** and the two epoxides **19** and **20** were produced. The possibility loomed that the different dispositions of the primary [2 + 2 + 2] annulation products from the two series might reflect differences in their backbone stereochemistry, rather than merely the presence or absence of a methyl group at C_3. *As has been previously reported, this concern over stereochemistry was unfortunately not misplaced. A single crystal X-ray determination*[5b,28] *revealed that this product is properly represented by structure* ***46****, wherein the configuration at* C_4 *is epimeric with that found in aflavinine.*

Before the stereochemical facts were known, some further transformations were achieved in this series. Treatment of the bromo lactone with zinc in acetic acid afforded two isomeric

(24) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988.
(25) Fregda, A. *Tetrahedron.* **1960**, *8*, 126.
(26) Silvestri, M. G. *J. Org. Chem.* **1983**, *48*, 2419.
(27) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(28) Detailed crystallographic information for compound **46** is available in the Microfilm Edition corresponding to ref 5b and from: Chackalamannil, S. Ph.D. Dissertation, Yale University, New Haven, CT, 1985.

Scheme X

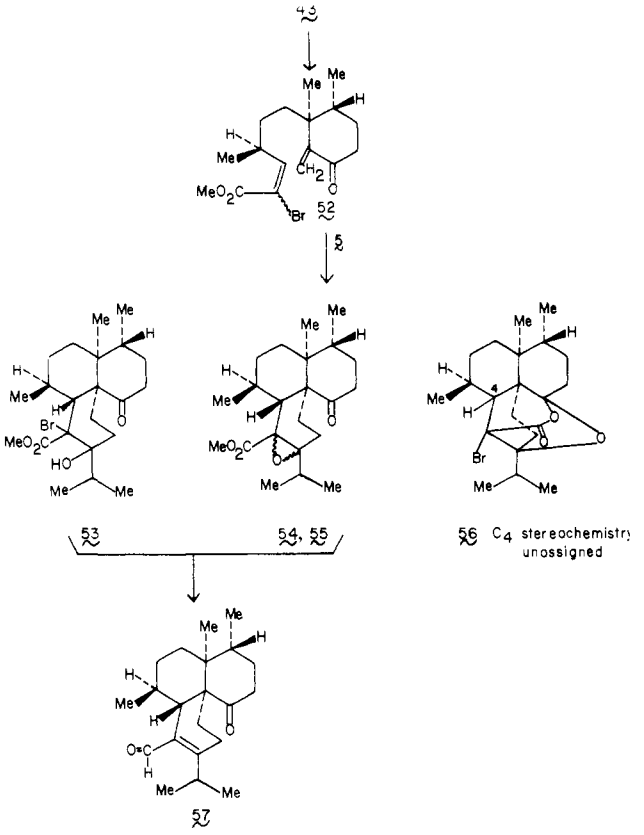


reductive debromination products. The minor product (ca. 30%) was neutral, while the major product (65%) was an unsaturated acid. Esterification of the acid with diazomethane, followed by reduction with lithium aluminum hydride in THF, and partial oxidation with MnO_2, afforded a hydroxy enal. In light of the known stereochemistry of compound **46**, the neutral reductive debromination product can be represented as structure **48** and its isomeric acid as **49**. Accordingly, the hydroxy enal is drawn as **50**, wherein the configuration of the secondary hydroxyl group in this series is not rigorously known.

While the remarkable variation in the stereochemical outcome which was engendered by the presence of the methyl group at C_3 was not expected, a reasonable interpretation could be advanced. In the reaction of enolate **5** with both the "nor" biselectrophile **9** and with the 3*R* biselectrophile **44**, the AB system emerges cis-fused. This outcome was contemplated in conformation diagram **4** (see Scheme II) wherein it was also projected that cyclization would occur in the chair sense to afford structure **3a** with the enolate side equatorial to the B ring. Apparently, this situation pertains in the case of **4a** (R = H) which leads to **3a** (Scheme X). *The same outcome in the instance of* ***4b*** *(R = Me) would produce a bicyclic system* ***3b****, wherein a potentially* serious **1,3-diaxial repulsion between the methyl group and the oxopentyl side chain would emerge.** This source of destabilization might lead to a preference for cyclization to a boatlike B ring, represented as structure **51**, in which the enolate side chain at C_4 and the methyl group at C_3 are related in a trans sense. If this structure undergoes aldolization, the resultant product would have the cis A/B, trans B/C stereochemistry.

It was of interest to probe the validity of this hypothesis further. It seemed that if the main factor which disfavors the formation of stereoisomer **3b** is the presence of the 1,3-diaxial repulsion between the methyl group at C_3 and side chain at C_9, the stereochemical result should be different in the C_3 epimeric series derived from the (*S*)-**34** bromide. For this purpose, compound **43** (Scheme VIII)[29] was converted to the C_3S (mismatched) biselectrophile **52** by reaction with the bromine-substituted Wadsworth–Emmons reagent[11] as before. The *E*:*Z* isomer mixture **52** was subjected to reaction with lithium enolate **5** under the same conditions as were employed with "nor" *E*:*Z* isomers **9** and with the "matched" *E*:*Z* isomers **44** (Scheme IX). Workup as before,

Scheme XI



followed by chromatography on silica gel, produced four homogeneous products. There was obtained a bromohydrin in 6%, to which we assign the structure **53**. There were also obtained two epoxides, **54** (10%) and **55** (13%). In addition, there was obtained, in 5% yield, a bromo lactone **56**.

That compounds **53**, **54**, and **55** share an identical backbone stereochemistry was established by their convergence to keto enal **57** by methods entirely analogous[29] to those used to achieve the convergence of compounds **18**, **19**, and **20** to the common enal **22**. Furthermore, the NMR spectral properties of keto enals **57** and **22** were virtually identical with the exception of the presence of resonances for an additional secondary methyl group in the former compound.

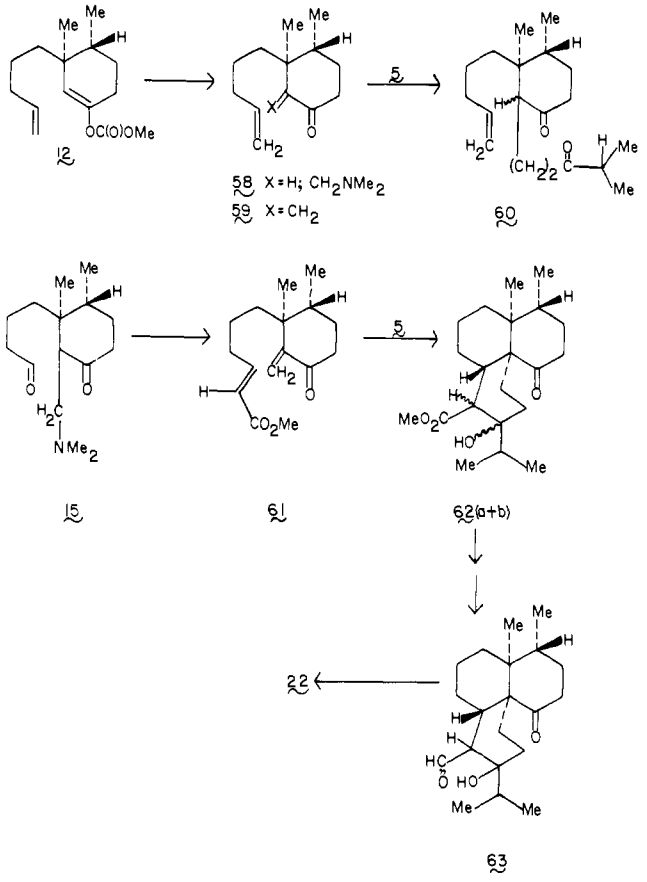
The stereochemistry of the bromo lactone **56** remains unproven. Since bromo lactone **46** (Scheme VIII) has the 4*S* configuration, it would be tempting to formulate compound **56** in a similar way. However, no objective basis for the assignment exists.

In spite of the uncertainty of the stereochemistry of compound **56** which constitutes ca. 15% of the annulation products, the basic hypothesis advanced to explain the difference in stereochemical outcome between nor substrate **9** and the (3*R*)-methyl substrate **44** is supported. Thus, substrate **52**, where the C_3 methyl group in the kinetically produced chair/chair bicyclic system would be equatorial, behaves substantially the same way as nor substrate **9**. This finding strongly argues for the critical influence of the putative C_3 axial methyl group in disfavoring the formation of stereoisomer **3b** from monocyclic **4b** (see Scheme X). The results for the 3*S* series are summarized in Scheme XI.

Although three instances of the [2 + 2 + 2] annulation reaction had now been demonstrated, the combined yields of the cyclization products were all in the range of only 30–45%. It was of interest to learn something about the origin of the yield problem. Unfortunately, aside from the various annulation products discussed above, the remaining materials seemed to be polymeric, and their spectral properties were uninformative. Under the conditions described above, no monocyclic product arising from only the first Michael addition (cf. structure **4**) or any bicyclic product (cf. structure **3**) wherein the sequential Michael reactions had not been followed by aldolization (see Scheme II) was isolated. One in-

(29) The preparation of compounds **41**, **42**, and **43** in the "mismatched" series involves procedures which were identical with those employed for compounds **38**, **39**, and **40** in the "matched" series. The procedures and spectral properties for the "matched" isomers are given in the Experimental Section of this paper. The corresponding information for compounds **41**, **42**, and **43** is given in the supplementary material of this paper. The details of the convergence of mismatched epoxy annulation products **54** and **55** to keto enone are available from: Chackalamannil, S. Ph.D. Dissertation, Yale University, New Have, CT, 1985. Addition analytical and spectroscopic data pertinent to these compounds are found in this thesis.

Scheme XII



terpretation of these negative findings is that the yield-limiting step was in fact the initial Michael addition. This proposition was tested.

Thus, the Mannich base **58**, prepared directly from enol carbonate **12** in the usual way, was treated with MCPBA to produce the previously described[30] α-methylene ketone **59** (Scheme XII). This compound seemed to be a reasonable model substrate for probing the quality of the first Michael step, by insulating this reaction from subsequent intramolecular reactions. In the event, reaction of enone **59** with the lithium enolate **5** under the usual conditions produced an 87% yield of the adducts **60** which were separated into homogeneous components of undetermined configuration. To the extent that the reliability of compound **59** as a model for the biselectrophiles is accepted, the first Michael addition step does not appear to be yield-limiting.

It will also have been noted that in the three cases described thusfar, the second Michael acceptor of the biselectrophile was an α,β-unsaturated α-bromo ester. Such a substrate was used under the theory that electrophilicity might well be improved by the presence of a bromine at the α-carbon. It was of interest to check the feasibility of the [2 + 2 + 2] annulation process where the second Michael acceptor was a simple enoate. Toward that end, the Mannich base aldehyde **15** prepared in crude form as described above [Scheme IV] was subjected to an Emmons condensation with the sodium salt of methyl (diethylphosphonyl)acetate to produce a crude enoate which, on treatment with MCPBA, afforded biselectrophile **61** in 30% overall yield.

Reaction of **61** with enolate **5** under the now standard conditions was followed by chromatography on silica gel. There was thus obtained a 34% yield of a 3:2 mixture of two stereoisomeric β-hydroxy esters, formulated as **62a** and **62b**. The configurations of the stereogenic centers[7] bearing the carbomethoxy and tertiary alcohol functions are not determined for either isomer. However, it was shown that the major and less polar isomer **62a** contains the A/B cis–B/C cis stereochemistry of aflavinine. Reduction of **62a** with lithium aluminum hydride, followed by oxidation with pyridinium chlorochromate, afforded the β-hydroxyaldehyde **63**. Reaction of **63** with *p*-TsOH in benzene under reflux afforded, albeit in very low yield, the now well-known keto enal **22**. Thus, from a yield standpoint, as well as from the standpoint of ease of introduction of the required unsaturation in the C ring, the bromine on the enoate was quite helpful. However, the precise reasons for the yield benefit on the annulation process are not rigorously known.

In summary, though the total synthesis of aflavinine itself has not been accomplished, the feasibility of the [2 + 2 + 2] annulation has been demonstrated in several contexts. It is likely that the principles governing the stereochemistry of the process gathered in this work will find applications in other systems. Future studies involving applications of other sorts of systems containing multiple electrophiles to various problems in organic synthesis are planned. It is also hoped that through suitable modifications in the designs described above, a total synthesis of aflavinine will be feasible.

Experimental Section

Methyl (*trans*-3,4-Dimethyl-3-(4-pentenyl)-1-cyclohexen-1-yl)carbonate (12). To a stirred suspension of magnesium turnings (2.65 g, 109.0 mmol) in 15 mL of ether was added a solution of 5-bromo-1-pentene (13.04 g, 87.57 mmol) in ether (10 mL) such that gentle refluxing was maintained. After completion of the addition, the mixture was stirred at room temperature for 15 min.

The above solution was added dropwise (via a syringe pump), over 65 min, to a solution of 3,4-dimethyl-cyclohex-2-ene-1-one[8] (**8**) (7.80 g, 62.90 mmol) and copper(I) iodide (1.90 g, 10.0 mmol) in 120 mL of dimethyl sulfide–ether (1:1 v/v) maintained at ice bath temperature. After completion of the addition, the reaction mixture was allowed to warm to room temperature and then cooled again to 0 °C. To this was added methyl chloroformate (20.80 g, 220 mmol). Cooling was discontinued after 2 h, and the suspension was stirred at ambient temperature for an additional 12 h. The volatiles were removed under reduced pressure, and the residue was taken up in 400 mL of dichloromethane. This solution was washed successively with saturated ammonium chloride solution (300 mL), 10% sodium carbonate (2 × 300 mL), water (300 mL), and brine (300 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated. The residue was purified by chromatography on silica gel. Elution with 4% ethyl acetate in hexanes afforded 11.40 g (72%) of enol carbonate **12**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.82 (s, 3 H), 0.82 (d, J = 7 Hz, 3 H), 1.36–2.38 (m, 11 H), 3.74 (s, 3 H), 4.78–5.07 (m, 2 H), 5.15 (s, 1 H), 5.45–5.98 (m, 1 H); IR (neat) 1750 cm^{-1}; MS, *m/e* 183, 139, 109, 107.

Methyl (*trans*-3-(4,4-Dimethoxybutyl)-3,4-dimethyl-1-cyclohexen-1-yl)carbonate (13). The enol carbonate **12** (7.170 g, 28.45 mmol) was dissolved in 320 mL of dichloromethane–methanol (4:1 v/v). A gentle stream of ozone was passed through the solution at −78 °C. When monitoring of the reaction by TLC indicated that all starting material had been consumed (ca. 4 h), the flow of ozone was discontinued, and the solution was purged with nitrogen. Dimethyl sulfide (250 mL) was added, and the mixture was stirred for 24 h. Evaporation of the volatiles under reduced pressure left a residue which was dissolved in 70 mL of absolute methanol. This solution was stirred at room temperature for 1 h in the presence of *p*-toluenesulfonic acid (250 mg). This solution was diluted with dichloromethane (200 mL) and washed successively with 5% sodium bicarbonate solution (150 mL) and water (150 mL). The organic phase was dried over magnesium sulfate and concentrated to give 7.51 g (88%) of crude acetal **13**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.90 (s, 3 H) 0.90 (d, J = 6 Hz, 3 H), 1.00–2.40 (m, 11 H), 3.31 (s, 6 H), 3.70 (s, 3 H), 4.32 (t, J = 6 Hz, 1 H), 5.20 (s, 1 H); IR (neat) 1745 cm^{-1}; MS, *m/e* 300 (M^+), 269, 268, 161, 139.

((1α,6β)-2-[(Dimethylamino)methyl]-1,6-dimethyl-3-oxocyclohexanyl)butanal (15). (i) **Preparation of (Dimethylmethylene)immonium Chloride.**[10a] (Tetramethyldiamino)methane (Aldrich) (10.20 g, 100 mmol) was dissolved in 50 mL of ether. To this solution, which was cooled under argon in a dry ice–acetone bath, was added freshly distilled acetyl chloride (7.20 g, 92 mmol). The bath was removed and the mixture allowed to warm to room temperature. The white suspension was diluted with 250 mL of ether and filtered under argon pressure. The white solid so obtained was dried by passing argon through and transferred under anhydrous atmosphere. A suspension of this solid in 120 mL of THF and cooled under argon to −78 °C was used in the next experiment.

(30) Danishefsky, S.; Kahn, M.; Silvestri, M. *Tetrahedron Lett.* **1982**, *23*, 1419. See also: Kahn, M. Ph.D. Dissertation, Yale University, New Haven, CT, 1983. This thesis also contains additional spectroscopic and analytical information on α-methylene ketone **30**.

(il) **Conversion of 13 to 15.** Enol carbonate **13** (4.61 g, 15.33 mmol) was dissolved in 60 mL of THF and cooled under argon to −78 °C, and methyllithium (41.0 mL, 53.6 mmol) was added. This was stirred at −78 °C for 15 min and cannulated into the suspension of (dimethylmethylene)immonium chloride described above. The bath was removed, and the reaction was stirred for 2 h. Undissolved suspensions were separated by filtration, and the volatiles were evaporated in vacuo. The crude residue was dissolved in 50 mL of 0.65 N HCl and extracted with ether (20 mL). The aqueous acidic solution was cooled and basified by careful addition of solid sodium carbonate. The free Mannich base **15** present was extracted into dichloromethane (4 × 50 mL), and the combined organic phases were washed with water, dried over magnesium sulfate, and concentrated in vacuo, leaving a residue of 3.50 g of crude aldehyde **15** which was used in the next reaction: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.80 (s, 3 H), 0.40–3.90 (m, 17 H), 2.2 (s, 6 H), 9.8 (m, 1 H); IR (neat) 1710 cm^{-1}; MS, *m/e* 253 (M^+), 182.

Methyl 2-Bromo-6-[(1α,6β)-2-[(dimethylamino)methyl]-1,6-dimethyl-3-oxocyclohexyl]-2-hexenoate (16). Sodium hydride (55%, 546 mg, 12.51 mmol) was suspended in 10 mL of dry glyme and cooled in an ice bath, and methyl (dimethylphosphonyl)bromoacetate[11] (3.56 g, 13.64 mmol) dissolved in 5 mL of glyme was added. After discontinuation of the cooling, the reaction mixture was stirred for 20 min. To this mixture was added the aldehyde **15** (2.88 g, 11.37 mmol), dissolved in 13 mL of glyme. The mixture was stirred at room temperature for 2 h. To this was added 30 mL of dichloromethane and water (30 mL). The aqueous phase was extracted with dichloromethane (3 × 25 mL), and the combined organic phases were washed with water (60 mL), dried over magnesium sulfate, and concentrated in vacuo to give 4.51 g of crude enoate **16**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.79 (s, 3 H), 1.00 (d, J = 6 Hz, 3 H), 2.16 (s, 6 H), 1.10–2.60 (m, 14 H), 3.80 (s, 3 H), 6.65 (t, J = 7.5 Hz, 0.4 H), 7.26 (t, J = 7.5 Hz, 0.6 H); IR ($CHCl_3$) 1708, 1720 cm^{-1}; MS, *m/e* 387 (M^+), 389 (M + 2)$^+$, 357, 359.

Methyl 2-Bromo-6-[(1α,6β)-1,6-dimethyl-2-methylene-3-oxocyclohexyl]-2-hexenoate (9). The material from the above experiment was dissolved in 25 mL of dichloromethane. To this solution was added *m*-chloroperbenzoic acid (85%, 4.50 g, 27.51 mmol). The solution was stirred at room temperature for 15 min and poured on a column packed with silica gel (ca. 60 g). Elution with ethyl acetate/hexanes/triethylamine (70:25:5) yielded the bromo ester 9 in impure form.

Rechromatography on silica gel and elution with 15% ethyl acetate in hexanes gave 1.64 g of 9 as a 3:2 *E*:*Z* mixture (34% based on enol carbonate **12**): ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.03 (s, 3 H), 0.80–2.70 (m, 14 H), 3.80 (s, 3 H), 5.08 (s, 1 H), 5.81 (s, 1 H), 6.61 (t, J = 7.5 Hz, 0.4 H), 7.24 (t, J = 7.5 Hz, 0.6 H); IR ($CHCl_3$) 1720, 1690 cm^{-1}; MS, *m/e* 342 (M^+), 346 (M + 2), 327, 329.

Formation of Methyl 4-Bromododecahydro-3-hydroxy-7a,8-dimethyl-3-(1-methylethyl)-11-oxo-1*H*-benzo[*d*]naphthalyl-4-carboxylate (18), Methyl (1aα,1bβ,4aα,5α,8a(*S),10aα)-decahydro-4a,5-dimethyl-10a-(1-methylethyl)-8-oxo-3*H*-benzo[4a,5]naphth[1,2-*b*]oxirenyl-1a(9*H*)-carboxylate (19), and Methyl (1aα,1bα,4aβ,5β,8a(*R**),10aα)-Decahydro-4a,5-dimethyl-10a-(1-methylethyl)-8-oxo-3*H*-benzo[4a,5]naphth[1,2-*b*]oxirenyl-1a(9*H*)-carboxylate (20).** To a solution of the silyl enol ether **17** (212 mg, 1.34 mmol) in 4 mL of monoglyme, cooled in a dry ice-acetone bath, was added a solution of methyllithium in ether (1.2 M, 1.074 mmol). After 2 min, the dry ice–acetone bath was replaced by an ice bath. The clear solution so obtained was stirred for 20 min prior to use.

A solution of 9 (107 mg, 0.31 mmol) in 10 mL of glyme was cooled in a dry ice–acetone bath under argon and 3.0 mL of the above enolate solution (ca. 0.62 mmol) was added. The reaction mixture was stirred at −78 °C for 1 h, cooling was discontinued, and the mixture was stirred at room temperature for 10 h. To this was added 15 mL of saturated ammonium chloride solution and 15 mL of ether. The layers were separated, and the aqueous phase was extracted with ether [2 × 15 mL). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. Chromatography of the residue on silica gel (12% ethyl acetate in hexanes) yielded, in ascending order of polarity, the bromohydrin **18** (34 mg, 25%) as an oil, the α-epoxy ester **20** (16 mg, 15%) mp 138–139 °C (crystallized from pentane), and the β-epoxy ester **19** (7 mg, 7%) mp 142–143 °C (crystallized from pentane). **18**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.64 (d, J = 7.0 Hz, 3 H), 0.77 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.92 (s, 3 H), 3.71 (s, 3 H), 0.60–2.40 (m, 16 H), 3.02–3.07 (m, 1 H); IR ($CHCl_3$) 3550, 1715 cm^{-1}; MS, *m/e* 428 (M^+), 430 (M + 2)$^+$, 223. **20**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.61 (s, 3 H), 0.76 (d, J = 7.0 Hz, 3 H), 0.81 (d, J = 6.6 Hz, 3 H), 0.99 (d, J = 7.0 Hz, 3 H), 1.00–2.00 (m, 12 H), 2.20 (m, 1 H), 2.40–2.70 (m, 2 H), 3.24–3.40 (m, 2 H), 3.76 (s, 3 H); IR ($CHCl_3$) 1740, 1720, 1690 cm^{-1}; MS, *m/e* 348 (M^+), 333, 305, 260. Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.48, H, 8.95. **19**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.55 (s, 3 H), 0.76 (d, J = 7.0 Hz, 3 H), 0.93 (d, J = 7.0 Hz, 3 H), 0.97 (d, J = 7.0 Hz, 3 H), 1.00–2.25 (m, 14 H), 2.55 (m, 1 H), 2.87–3.00 (m, 1 H), 3.26 (dd, J = 12, 3.5 Hz, 1 H), 3.75 (s, 3 H); IR ($CHCl_3$) 1725, 1695 cm^{-1}; MS, *m/e* 348 (M^+), 330, 305, 298, 273, 245, 205. Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.51; H, 9.02.

(4aα,7aβ,8β,11a(*R))-2,4a,5,6,7,7a,8,9,10,11-decahydro-7a,8-dimethyl-3-(1-methylethyl)-11-oxo-1*H*-benzo[*d*]naphthalene (21).** To a solution of the bromohydrin **18** (140 mg, 0.33 mmol) in a 4 mL of ether was added lithium aluminum hydride (270 mg, 7.10 mmol). The reaction mixture was stirred at room temperature for 30 min and diluted with 30 mL of ether. Excess of lithium aluminum hydride was quenched by cautious addition of a saturated solution of sodium potassium tartarate. The granular precipitate was filtered, and the filtrate was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by chromatography on silica gel (elution with 25% ethyl acetate in hexanes) to give 55 mg (55%) of diol **21**, mp 170–171 °C (crystallized from pentane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (d, J = 8.0 Hz, 3 H), 0.97 (s, 3 H), 0.98 (d, J = 6.0 Hz, 3 H), 1.00 (d, J = 6.0 Hz, 3 H), 0.70–2.25 (m, 17 H), 2.39 (dd, J = 12.0 Hz, 4.0 Hz, 1 H), 2.93 (septet, J = 6.0 Hz, 1 H), 3.88 (d, J = 12.0 Hz, 1 H), 3.95 (s, 1 H), 4.281 (d, J = 12.0 Hz, 1 H); IR ($CHCl_3$) 3600 cm^{-1}; MS, *m/e* 288, 270, 260, 245, 227, 201, 160. Anal. Calcd for $C_{34}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.57; H, 11.23.

(4aα,7aβ,8β,11a(*R))-2,4a,5,6,7,7a,8,9,10,11-Decahydro-7a,8-dimethyl-3-(1-methylethyl)-11-oxo-1*H*-benzo[*d*]naphthalyl-4-carboxaldehyde (22).** To a solution of **21** (40 mg, 0.13 mmol) in 2.5 mL of dichloromethane was added pyridinium dichromate (Aldrich) (250 mg, 0.66 mmol). The suspension was stirred at room temperature until monitoring by TLC indicated that the starting material had been consumed (ca. 45 min). The reaction mixture was diluted with ether (10 mL) and filtered through a small column of silica gel. The filtrate was concentrated in vacuo, and the residue was purified by chromatography on silica gel. Elution with 12% ethyl acetate in hexanes yielded keto enal **22** (36 mg, 90%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.63 (s, 3 H), 0.84 (d, J = 6.7 Hz, 3 H), 1.04 (d, J = 6.7 Hz, 3 H), 1.08 (d, J = 6.7 Hz, 3 H), 1.30–2.30 (m, 12 H), 2.56–2.85 (m, 3 H), 3.58 (septet, J = 6.7 Hz, 1 H), 3.65 (dd, J = 10.5, 3.0 Hz, 1 H), 10.10 (s, 1 H); IR (CH_2Cl_2) 1685, 1645, 1605 cm^{-1}: MS, *m/e* 302 (M^+), 284, 259, 241, 217.

(4aα,7aβ,8β,11a(*R))-2,4a,5,6,7,7a,8,9,10,11-Decahydro-7a,8-dimethyl-3-(1-methylethyl)-11-oxo-1*H*-benzo[*d*]naphthalyl-4-carboxaldehyde 4-[(2,4-Dinitrophenyl)hydrazone (23).** To a solution of the enal **22** (16 mg, 0.05 mmol) in 2 mL of absolute ethanol was added 2,4-dinitrophenylhydrazine (20 mg, 1 mmol), followed by 0.1 mL of 10% sulfuric acid solution. The reaction mixture was stirred for 30 min, and the volatiles were removed by rotary evaporation. The residue was purified by chromatography on silica gel. Elution with 15% ethyl acetate in hexanes afforded 24 mg (94%) of the phenylhydrazone **23** which was crystallized from methanol–dichloromethane, mp 244 °C dec: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.67 (s, 3 H), 0.92 (d, J = 6.7 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H), 1.05 (d, J = 6.8 Hz, 3 H), 1.15–2.88 (m, 15 H), 3.08 (septet, J = 6.8 Hz, 1 H), 3.87 (dd, J = 11.5, 3.0 Hz, 1 H), 7.90 (d, J = 9.5 Hz, 1 H), 8.22 (s, 1 H), 8.40 (dd, J = 10.0, 2.5 Hz, 1 H), 9.16 (d, J = 2.5 Hz, 1 H), 9.86 (s, 1 H); IR (CH_2Cl_2) 3250, 1680, 1620 cm^{-1}; MS, *m/e* 482 (M^+), 483, 469, 447, 368. Anal. Calcd for $C_{26}H_{34}N_4O_5$: C, 64.71; H, 7.10; N, 11.61. Found: C, 64.70; H, 7.20; N, 11.88.

(4aα,7aβ,8β,11α,11a(*R))-2,4a,5,6,7,7a,8,9,10,11-Decahydro-11-hydroxy-7a,8-dimethyl-3-(1-methylethyl)-1*H*-benzo[*d*]-naphthalyl-4-carboxaldehyde (28).** A solution of allylic alcohol **21** (33 mg, 0.11 mmol) in 3 mL of dichloromethane was stirred with activated manganese dioxide (brown, Aldrich) (470 mg, 5.40 mmol) for 11 h. The suspension was diluted with dichloromethane (15 mL) and filtered, and the filtrate was concentrated in vacuo. Chromatography of the residue on silica gel (18% ethyl acetate in hexanes) yielded the previously prepared aldehyde **28** (28 mg, 80%): IR (CH_2Cl_2) 3600, 1660 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (d, J = 6.0 Hz, 3 H), 0.97 (s, 3 H), 1.11 (d, J = 6.0 Hz, 3 H), 1.14 (d, J = 6.0 Hz, 3 H), 1.00–2.40 (m, 15 H), 3.03 (dd, J = 12.0, 3 Hz, 1 H), 3.64 (t, J = 1.5 Hz, 1 H), 3.69 (septet, J = 6.0 Hz, 1 H), 10.18 (s, 1 H); MS, *m/e* 304 (M^+), 286, 261, 243, 225, 201.

(4aα,7aβ,8β,11α,11a(*R))-2,4a,5,6,7,7a,8,9,10,11-Decahydro-11-hydroxy-4-(2-methoxyethenyl)-7a,8-dimethyl-3-(1-methylethyl)-1*H*-benzo[*d*]naphthalene (29).** To a solution of (methoxymethyl)trimethylsilane (Petrarch) (204 mg, 1.73 mmol) in 3 mL of tetrahydrofuran, cooled under argon to −78 °C, was added a solution of *sec*-butyllithium in cyclohexane (1.05 mL, 1.35 mmol). The reaction mixture was stirred at −78 °C for 10 min and then at −25 °C for 35 min. To this was added a solution of the enal **28** (48 mg, 0.16 mmol) in 2 mL of tetrahydrofuran. The reaction mixture was stirred for 30 min, gradually allowing to warm to room temperature. To this was added a saturated solution of ammonium chloride (15 mL) and ether (15 mL). The layers were separated, and the aqueous phase was extracted with ether (2 × 15 mL). The

combined organic layers were washed with water (25 mL), dried over magnesium sulfate, and concentrated in vacuo.

The crude product from the above experiment was dissolved in 3 mL of tetrahydrofuran. To this was added potassium hydride (24% suspension in oil, 200 mg, 1.2 mmol). The suspension was stirred at room temperature for 45 min. Dilution with ether (25 mL) was followed by quenching by cautious addition of a saturated ammonium chloride solution (25 mL). The aqueous layer was extracted with ether (2 × 25 mL). The combined organic layers were washed with water (40 mL), dried over magnesium sulfate, and concentrated in vacuo. The crude residue so obtained was subjected to chromatography on a short column of silica gel (7% ethyl acetate in hexanes) to give 48 mg (92%) of enol ethers **29** as an *E*:*Z* mixture (9:1). **29** (major isomer): ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.80 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 3.9 Hz, 3 H), 0.93 (d, J = 3.9 Hz, 3 H), 0.95 (s, 3 H), 1.10–2.20 (m, 15 H), 2.76 (m, 1 H), 3.59 (s, 3 H), 4.06 (m, 1 H), 4.90 (d, J = 9.5 Hz, 1 H), 5.74 (d, J = 9.5 Hz, 1 H); IR (CH_2Cl_2) 3625, 3575 cm^{-1}; MS, m/e 332 (M^+), 314, 299.

3-Desmethylaflavinine (10). To a solution of enol ethers **29** (48 mg, 0.14 mmol) in 1.5 mL of ether, cooled under argon in an ice bath, was added 0.3 mL of 70% perchloric acid. The reaction mixture was stirred at 0 °C for 15 min, and phenylhydrazine (164 mg, 1.52 mmol) was added. This was followed, after 10 min, by addition of 2 mL of absolute ethanol and a few molecular sieves (4 Å). The cooling bath was removed, and the reaction mixture was stirred at ambient temperature for 8 h. The mixture was diluted with dichloromethane (20 mL) and filtered. The filtrate was washed with water (20 mL) and the aqueous phase extracted with dichloromethane (20 mL). The combined organic layers were washed with water (25 mL), dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by chromatography on silica gel (15% ethyl acetate in hexanes) to give the 3-desmethylaflavinine **10** (22 mg, 36% overall based on enal **28**), mp 173–175 °C (crystallized from methanol–dichloromethane) and the phenylhydrazone **33** (15 mg, 24% overall based on enal **28**). **10**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.76 (d, J = 6.7 Hz, 3 H), 0.81 (d, J = 6.9 Hz, 3 H), 0.91 (d, J = 6.9 Hz, 3 H), 1.01 (s, 3 H), 0.85–2.33 (m, 16 H), 2.45 (septet, J = 7.0 Hz, 1 H), 4.50 (s, 1 H), 6.87 (d, J = 2 Hz, 1 H), 7.11 (dd, J = 8.0 Hz, 1 H), 7.20 (dd, J = 8.0, 8.0 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 1 H), 7.43 (d, J = 8.0 Hz, 1 H), 8.03 (s, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 16.14, 18.43, 19.85, 20.80, 20.91, 21.30, 22.11, 26.00, 30.27, 31.09, 31.28, 31.62, 33.15, 38.83, 42.15, 42.30, 70.93, 111.45, 119.69, 119.83, 120.09, 121.97, 122.12, 122.25, 128.23, 136.26, 139.76; IR (CH_2Cl_2) 3560, 3450 cm^{-1}; MS, m/e 391 (M^+), 373, 358, 348, 330; UV λ_{max} (ϵ) 226 [28 900), 276 (5000), 284 (5500), 292 (5070). **33**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.82 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 7.0 Hz, 3 H), 0.93 (s, 3 H), 1.00 (d, J = 7.0 Hz, 3 H), 0.80–2.35 (m, 16 H), 3.22 (dd, J = 11.5, 2.5 Hz, 1 H), 3.90 (s, 1 H), 6.05 (d, J = 9.0 Hz, 1 H), 6.80–7.30 (m, 6 H), 7.81 (d, J = 9.0 Hz, 1 H); IR (CH_2Cl_2) 3600, 1600 cm^{-1}; MS, m/e 408 (M^+), 316, 281, 134.

Conversion of α,β-Unsaturated Phenylhydrazone 33 to 10. A solution of the phenylhydrazone **33** (22 mg, 0.06 mmol) in 3 mL of glacial acetic acid was heated at 100 °C for 12 h. This was cooled and added to 10 mL of heptane, and the volatiles were removed in vacuo. The residue was dissolved in dichloromethane (2 mL) and passed through a small plug of silica gel. Elution with 15% ethyl acetate in hexanes afforded a product which was further purified by HPLC (Waters, μ-porasil). Elution with 9% ethyl acetate in hexanes yielded 11 mg (50%) of 3-desmethylaflavinine (**10**).

(+)-(*R*)-3,4-Dimethylcyclohex-2-ene-1-one ((*R*)-8). Ethereal methyllithium (1.15 M, 46.4 mL, 72 mmol) was added dropwise to a suspension of copper(I) iodide (6.86 g, 36 mmol) in ether (150 mL) and stirred at 0 °C under nitrogen. After 45 min, (+)-(*R*)-4-methylcyclohex-2-ene-1-one (**36**) (1.98 g, 18 mmol) in ether (5 mL) was added dropwise over a period of 30 min and stirring continued at 0 °C for 45 min. Chlorotrimethylsilane (15.6 g, 144 mmol) was added, followed by triethylamine (14.5 g, 144 mmol). The resultant mixture was stirred for 2 h at room temperature, diluted with hexane (300 mL), washed with ice-cold saturated aqueous sodium bicarbonate (3 × 200 mL), and brine (200 mL), dried over sodium sulfate, filtered, and concentrated in vacuo.

The residue in acetonitrile (150 mL) was stirred at room temperature with palladium(II) acetate (4.05 g, 18 mmol), for 12 h. The mixture was diluted with ether (150 mL), filtered through celite, concentrated in vacuo, and subjected to flash chromatography (60 g silica, 30 mm column, 1:4 ethyl acetate/hexanes as eluant) to give enone (*R*)-**8** as a colorless oil, 1.34 g (57%): IR (CCl_4) 3030–2800, 1680, 1620 w cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.19 (d, J = 7 Hz, 3 H), 1.95 (br s, 3 H), 1.56–2.20 (m, 3 H), 2.20–2.68 (m, 2 H), 5.80 (br s, 1 H); MS, m/e (%) 124 (38, M^+), 96 (100); $[\alpha]^{20}_D$ +125.2° (*C* 2.5, $CHCl_3$).

(3*S*,4*R*)-3,4-Dimethyl-3-(3(*R*)-methyl-4-pentenyl)-1-cyclohexen-1-yl)carbonate (38). An ethereal (10 mL) solution of pentenyl bromide ((*R*)-(**34**) (3.26 g, 20 mmol) was added dropwise to magnesium turnings (583 mg, 24 mmol) such that gentle reflux was maintained. After addition was complete, the reaction mixture was allowed to cool. The supernatant was drawn off and added (together with ether washings of the remaining magnesium), over a period of 1 h, to a stirred solution of enone (*R*)-**8** (1.98 g, 16 mmol) and copper(I) iodide (456 mg, 2.4 mmol) in 1:1 ether/dimethyl sulfide (30 mL), at 0 °C under nitrogen. After stirring for 1 h at room temperature, the reaction mixture was recooled to 0 °C and treated with methyl chloroformate (7.42 mL, 96 mmol). Stirring was continued for 90 min at 0 °C and 4 h at room temperature. The reaction mixture was concentrated in vacuo and taken up in methylene chloride (50 mL) and saturated aqueous ammonium chloride (50 mL), and the organic layer was separated and washed with saturated aqueous sodium carbonate (4 × 25 mL) and then dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography (200 g silica, 40-mm column, 6:94 ethyl acetate/hexane) gave 3.18 g (75%) colorless oil. IR (neat) 3010 w, 2960–2750, 1750, 1665 w, 1610 w cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.85 (m, 6 H), 0.97 (d, J= 7 Hz, 3 H), 1.25 (m, 4 H), 1.60 (m, 3 H), 2.13 (m, 3 H), 3.78 (s, 3 H), 4.86 (br d, J = 10 Hz, 1 H), 4.89 (br d, J = 17 Hz, 1 H), 5.17 (br s, 1 H), 5.64 (ddd, J = 17, 10, 7 Hz, 1 H); MS, m/e (%) 183 (61), 139 (81), 109 (100).

(3*S*,4*R*)-2-[(Dimethylamino)methyl]-3,4-dimethyl-3(3(*R*)-methyl-4-pentenyl)cyclohexanone (39). Ethereal methyllithium (1.41 M, 28.1 mL, 39.6 mmol) was added to a solution of enol carbonate **38** (3.18 g, 12.0 mmol) in THF (40 mL) and stirred at 0 °C under nitrogen. After 5 min, the solution was added to a suspension of *N*,*N*-dimethylmethyleneammonium chloride (vide supra) (52.8 mmol) in THF (60 mL) and also stirred at 0 °C under nitrogen, and the reaction mixture was allowed to warm to room temperature. After 4 h, the reaction mixture was diluted with 1 N aqueous hydrochloric acid (100 mL). The organic layers was separated and extracted with additional hydrochloric acid (2 × 60 mL), and the combined aqueous layers were basified with sodium carbonate and back-extracted with methylene chloride (100 mL, 2 × 60 mL). The chlorocarbon extracts were washed with brine (60 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo to yield the crude amino ketone **39** as a colorless oil, in quantitative yield. IR (CCl_4) 3050 w, 3000–2700, 1710, 1630 w cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.51–1.40 (m, 9 H), 1.10–2.63 (m, 13 H), 2.19 (br s, 6 H), 4.91 (m, 2 H), 5.65 (m, 1 H); MS, m/e (%) 265 (4, M^+), 264 (7), 236 (19), 73 (100).

(2*R*)-4-[(1*S*,6*R*)-1,6-Dimethyl-2-methylene-3-oxocyclohexyl]-2-methylbutanal (40). Ozone was passed through a solution of crude amino ketone **39** (12 mmol) in methanol (40 mL) and methylene chloride (160 mL) stirred over sodium bicarbonate at −78 °C, until a Sudan Red 7B end-point was reached. The mixture was purged with nitrogen, treated with dimethyl sulfide (15 mL), and allowed to warm to room temperature. After 12 h, the mixture was washed with water (2 × 120 mL) and brine (120 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the residue (60 g silica, 30-mm column, with 15:85 ethyl acetate/hexane as eluant) gave enone aldehyde **40** as a colorless oil, yield 1.353 g (51%). IR ($CHCl_3$) 3020–2780, 2680, 1715, 1680, 1600 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.94 (d, J = 7 Hz, 3 H), 0.98 (s, 3 H), 1.01 (d, J = 8 Hz, 3 H), 1.17–2.53 (m, 10 H), 5.03 (br s, 1 H), 5.74 (br s, 1 H), 9.60 (d, J = 2 Hz, 1 H); MS, m/e (%) 222 (4, M^+), 194 (7), 177 (27), 149 (100).

Methyl (4*R*)-2-Bromo-6-[(1*S*,6*R*)-1,6-dimethyl-2-methylidene-3-oxocyclohexyl]-4-methyl-2-hexenoate (44). Methyl (dimethylphosphonyl)bromoacetate (219 mg, 0.84 mmol) was added to a suspension of 60% sodium hydride dispersion (34 mg, 0.84 mmol) in DME (5 mL) and stirred at 0 °C under nitrogen. The mixture was stirred for 40 min at room temperature and then added under nitrogen to a stirred DME (5 mL) solution of enone aldehyde **40** (125.3 mg, 0.56 mmol). After a further hour, the mixture was poured into water (40 mL) and extracted with ether (3 × 20 mL). The organic layers were washed with water (20 mL) and brine (20 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography (8 g silica, 10-mm-diameter column, 15:85 ethyl acetate/hexane) of the residue gave bromo ester **44** (as a mixture of *E*:*Z* isomers), as a colorless oil (131.8 mg, 65.4%). IR $CHCl_3$) 3040–2850, 1715, 1685, 1605 w cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.98 (m, 9 H), 1.15–1.43 (m, 4 H), 1.56–2.10 (m, 3 H), 2.40 (m, 2 H), 3.01 (m, 1 H), 3.76 (br s, 3 H), 5.05 (br s, 1 H), 5.77 (br s, 1 H), 6.33 and 6.98 (ratio 3.5:1; d, J = 10.5 Hz and d, J = 9.5 Hz, respectively, total 1 H); MS, m/e (%) 358 (1.6, M^+ for ^{81}Br), 357 (3.8), 356 (1.5, M^+ for ^{79}Br), 355 (3.7), 343 (5.3), 341 (5.5), 277 (25), 245 (33), 217 (28), 137 (100).

(−)-(3*S*,4a*R*,7*R*,7a*S*,10*R*,11*S*,11a*S*,12*R*)-12-Bromodecahydro-7,7a,10-trimethyl-3-(1-methylethyl)-4a,3,11-(epoxyethanylylidene)-1*H*,4a*H*-naphtho[1,8-*ab*]pyran-13-one (46). Ethereal methyllithium (1.41 M, 0.71 mL, 1.00 mmol) was added to silyl enol ether **17** (0.25 mL,

1.25 mmol) in DME (4.1 mL) and stirred at −78 °C under nitrogen. The resulting solution was stirred for 5 min at −78 °C and 25 min at 0 °C. A portion (1.92 mL, 0.38 mmol, 1.2 equiv) was then added to a DME (5 mL) solution of the bromo ester **44** (114.6 mg, 0.32 mmol) and stirred at −78 °C. Stirring was continued for 30 min at −78 °C and then for 24 h at room temperature. After quenching with saturated aqueous ammonium chloride (35 mL), the mixture was extracted with ether (35 mL, 3 × 18 mL). The combined extracts were washed with brine (35 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash chromatography of the residue (6 g of silica, 10-mm column, 1:9 ethyl acetate/hexane as eluant) gave bromo lactone **46** as colorless prisms, 39.4 mg (30%); mp 149.5–150 °C; IR ($CHCl_3$) 2980–2800, 1755 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$), δ 0.80 (s, 3 H), 0.87 (d, J = 6.5 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 6 H), 1.10–2.06 (m, 15 H), 1.16 (d, J = 6.0 Hz, 3 H), 2.20 (septet, J = 6.8 Hz, 1 H); MS, m/e (%) 412 (20, M^+ for ^{81}Br), 410 (17, M^+ for ^{79}Br), 331 (33), 314 (89), 312 (85), 287 (80), 233 (100); $[\alpha]^{20}_D$ −190° (c 1.4, $CHCl_3$).

(3*S*,4a*R*,7*R*,7a*S*,10*R*,11*R*,11a*S*,12*S*)-Decahydro-7,7a,10-trimethyl-3-(1-methylethyl)-4a,3,11-(epoxyethanylylidene)-1*H*,4a*H*-naphtho(1,8-*ab*)pyran-13-one (48) and (−)-(4a*S*,5*R*,7a*S*,8*R*,11a*S*)-2,4a,5,6,7,7a,8,9,10,11-Decahydro-5,7a,8-trimethyl-3-(1-methylethyl)-11-oxo-1*H*-benzo[*d*]naphthalene-4-carboxylic Acid (49). Bromo lactone **46** (91.6 mg, 0.22 mmol) was stirred in acetic acid (5 mL) with freshly activated (washed sequentially with 1 N aqueous hydrochloric acid, water, methanol, and finally acetic acid) zine dust (about 100 mg) for 1 h. The mixture was filtered through celite and the solid washed with methylene chloride (25 mL). The filtrate was washed with water (2 × 15 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. Separation by flash chromatography (6 g of silica, 10-mm-diameter column, 3:97 ethyl acetate/methylene chloride as eluant) gave the less polar lactone **48**, 25.3 mg (34.2%), and the more polar keto acid **49**, 48.4 mg (65.4%), both as colorless prisms; mp 171.5–172 and 181–183 °C, respectively. Lactone **48**: IR ($CHCl_3$) 3000–2800, 1745 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.82 (s, 3 H), 0.91 (m, 12 H), 1.05–1.90 (m, 15 H), 1.84 (septet, J = 7 Hz, 1 H), 2.93 (d, J = 4 Hz, 1 H); MS, m/e (%) 332 (1, M^+), 314 (100), 288 (56). Keto acid **49**: IR ($CHCl_3$) 3300–2700 br, 3000–2800, 1725, 1670 cm^{-1}; ^1H NMR (500 MHz, $CHCl_3$) δ 0.84 (d, J = 6.9 Hz, 3 H), 0.99 (d, J = 6.8 Hz, 3 H), 1.01 (d, J = 5.6 Hz, 3 H), 1.13 (m, 1 H), 1.17 (s, 3 H), 1.19 (m, 1 H), 1.31 (d, J = 7.5 Hz, 3 H), 1.36 (m, 1 H), 1.56 (m, 1 H), 1.68 (m, 4 H), 2.00 (m, 2 H), 2.16 (dt, J = 14.4, 3.8 Hz, 1 H), 2.30 (m, 2 H), 2.50 (ddd, J = 14.0, 5.7, 2.5 Hz, 1 H), 2.78 (m, 1 H), 3.11 (septet, J = 6.8 Hz, 1 H), 9.04 (br s, 1 H); MS, m/e (%) 332 (10, M^+), 314 (100), 286 (20), 243 (17), 201 (50); $[\alpha]^{20}_D$ +70.8 [c 1.44, $CHCl_3$).

(+)-Methyl (4a*S*,5*R*,7a*S*,8*R*,11a*S*)-2,4a,5,6,7,7a,8,9,10,11-Decahydro-5,7a,8-trimethyl-3-(1-methylethyl)-11-oxo-1*H*-benzo[*d*]naphthalyl-4-carboxylate. Ethereal diazomethane was added in portions over about 40 min to a solution of keto acid **49** (48.4 mg, 0.15 mmol) in ether (5 mL). After concentration in vacuo, the crude product was purified by flash chromatography (4 g of silica, 10-mm-diameter column, 15:85 ethyl acetate/hexane as eluant) to give the methyl ester as a colorless oil, 40.4 mg (80.1%). IR ($CHCl_3$) 3030–2800, 1705 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.83 (d, J = 6.6 Hz, 3 H), 0.86 (d, J = 7.3 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.98 (s, 3 H), 1.04–1.27 (m, 2 H), 1.20 (d, J = 7.1 Hz, 3 H), 1.43–2.48 (m, 13 H), 2.68 (m, 1 H), 3.74 (s, 3 H); MS, m/e (%) 346 (5, M^+) 314 (100), 286 (21), 243 (18), 201 (55); $[\alpha]^{20}_D$ +67.4° [c 0.90, $CHCl_3$].

(−)-(4a*R*,5*R*,7a*S*,8*R*,11a*S*)-2,4a,5,6,7,7a,8,9,10,11-Decahydro-11-hydroxy-4-(hydroxymethyl)-5,7a,8-trimethyl-3-(1-methylethyl)-1*H*-benzo[*d*]naphthalene. Ethereal lithium aluminum hydride (1 M, 0.13 mL, 0.13 mmol) was added under nitrogen to a THF (1 mL) solution of the foregoing keto ester (9.0 mg, 0.026 mmol) and the resulting solution stirred for 1 h at room temperature and 2 h at reflux. The cooled mixture was treated with a 1:1 mixture of sodium sulfate decahydrate and celite and filtered, and the solid was washed well with ether. Concentration of the eluate in vacuo was followed by flash chromatography (1 g of silica, pipet column, 15:85 ethyl acetate/methylene chloride as eluant), affording the diol as a crystalline solid, yield 8.3 mg (100%): IR ($CHCl_3$) 3380 br, 3000–2800 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.67 (m, 1 H), 0.82–2.40 (m, 13 H), 0.89 (d, J = 5.9 Hz, 3 H), 0.95–1.04 (m, 12 H), 2.65 (td, J = 13.5, 4.3 Hz, 1 H), 3.09 (septet, J = 6.8 Hz, 1 H), 3.24 (br s, 2 H), 3.51 (t, J = 3.0 Hz, 1 H), 4.16 (d, J = 11.7 Hz, 1 H), 4.53 (d, J = 11.7 Hz, 1 H); MS, m/e (%) 320 (1.5, M^+), 302 (65), 287 (29), 259 (100); $[\alpha]^{20}_D$ −152.9° [c 0.86, $CHCl_3$).

(−)-(4a*S*,5*R*,7a*S*,8*R*,11a*S*)-2,4a,5,6,7,7a,8,9,10,11-Decahydro-11-hydroxy-5,7a,8-trimethyl-3-(1-methylethyl)-1*H*-benzo[*d*]naphthalyl-4-carboxaldehyde (50). The foregoing diol (8.3 mg, 0.026 mmol) was stirred in methylene chloride (1 mL) with manganese dioxide (90 mg) for 20 h and then filtered through celite, the solid being washed thoroughly with 1:9 ethyl acetate/methylene chloride. The filtrate was concentrated in vacuo and subjected to flash chromatography (1 g of silica, pipet column, 3:97 ethyl acetate/methylene chloride as eluant) to give crystalline hydroxy enal **50**, 7.2 mg (84%); mp 130–133 °C: IR ($CHCl_3$) 3450, 2980–2800, 1645, 1590 w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.49 (m, 1 H), 0.63 (d, J = 7.0 Hz, 3 H), 0.90 (s, 3 H), 0.95 (d, J = 7.8 Hz, 3 H), 0.96 (d, J = 7.4 Hz, 3 H), 0.99–1.36 (m, 5 H), 1.02 (d, J = 7.0 Hz, 3 H), 1.63 (m, 2 H), 1.87 (m, 2 H), 2.00 (dd, J = 14.1, 8.4 Hz, 1 H), 2.20 (dt, J = 15.1, 4.4 Hz, 1 H), 2.26 (dd, J = 15.1, 5.3 Hz, 1 H), 2.70 (m, 2 H), 3.09 (m, 1 H), 3.44 (septet, J = 7.0 Hz, 1 H), 4.28 (dd, J = 4, 2 Hz, 1 H), 10.19 (s, 1 H); MS, m/e (%) 318 (22, M^+), 300 (100), 285 (33), 257 (65); $[\alpha]^{20}_D$ −58.2° (c 0.72, $CHCl_3$).

Methyl (4*S*)-2-Bromo-6[(1*S*,6*R*)-1,6-dimethyl-2-methylene-3-oxocyclohexyl]-4-methyl-2-hexenoate (52). To a suspension of sodium hydride (60% in oil, 122 mg, 3.05 mmol) in **4** mL of glyme, kept in a bath at 20 °C, was added, dropwise, methyl (dimethylphosphonyl)bromoacetate (vide supra) (1.08 g, 4.14 mmol). The clear solution so obtained was stirred at room temperature for 5 min and then added to a solution of 43[29] (300 mg, 1.35 mmol) in 2 mL of glyme. The reaction mixture was stirred at room temperature for 30 min and quenched by addition of 15 mL of saturated ammonium chloride solution followed by 15 mL of ether. The aqueous phase was extracted with ether (2 × 15 mL). The combined organic layers were washed with water, dried over magnesium sulfate, and concentrated in vacuo. The residue so obtained was subjected to chromatography on silica gel. Elution with 12% ethyl acetate in hexanes gave 290 mg (60%) of **52**. ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (d, J = 7.5 Hz, 3 H), 1.01 (s, 3 H), 1.02 (d, J = 5.6 Hz, 3 H), 0.95–2.15 (m, 10 H), 3.82 (s, 0.64 H), 3.84 (s, 0.36 Hz), 5.10 (d, J = 1.2 Hz, 1 H), 5.83 (d, J = 1.2 Hz, 1 H), 6.40 (d, J = 10.4 Hz, 0.64 H), 7.05 (d, J = 10.4 Hz, 0.36 H); IR (CCl_4) 1735, 1720, 1690 cm^{-1}; MS, m/e 356 (M^+), 358 (M + 2), 341, 343. Anal. Calcd for $C_{17}H_{25}BrO_3$: C, 57.15; H, 7.05; Br, 22.36. Found: C, 56.93; H, 7.02 Br, 22.08.

Reaction of Unsaturated Bromo Ester 52 with Enolate 5. To a solution of silyl enol ether **17** (222 mg, 1.40 mmol) in 4 mL of glyme, cooled in a dry ice–acetone bath under argon, was added a solution of methyllithium in ether (1.5 M, 0.94 mmol). Approximately 2 min after addition, the dry ice–acetone bath was replaced by an ice bath. The reaction mixture was stirred at 0 °C for 20 min prior to use.

A 2.4-mL (0.48 mmol) aliquot of the above enolate solution was added to a solution of bromo ester **52** (96 mg, 0.27 mmol) in 2 mL of glyme, cooled in a dry ice–acetone bath. The reaction mixture was stirred at −78 °C for 75 min and then at room temperature for 10 h. To this was added a solution of saturated ammonium chloride (15 mL), followed by 15 mL of ether. The layers were separated, and the aqueous phase was extracted with ether (2 × 15 mL). The combined organic layers were washed with water (20 mL), dried over magnesium sulfate, and concentrated in vacuo. The residue was processed by chromatography on silica gel. Elution with 8% ethyl acetate in hexanes yielded the following products: bromo lactone **56** (6 mg, 5%), bromohydrin **53** (7 mg, 6%), epoxy ester **54** (less polar) (13 mg, 13%), and epoxy ester **55** (polar) (10 mg, 10%). **53**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.65 (d, J = 6.9 Hz, 3 H), 0.76 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.94 (s, 3 *H*), 1.07 (d, J = 6.3 Hz, 3 H), 0.70–2.30 (m, 14 H), 2.40 (septet, J = 6.9 Hz, 1 H), 2.85 (dd, J = 10.9, 2.18 Hz, 1 H), 3.70 (s, 3 H); IR (CCl_4) 3575, 1715 cm^{-1}; MS, m/e 442 (M^+), 444 (M + 2)$^+$, 223. **54** (less polar diastereomer): ^1H NMR (250 MHz, $CDCl_3$) δ 0.61 (s, 3 H), 0.73 (d, J = 7.0 Hz, 3 H), 0.81 (d, J = 6.8 Hz, 3 H), 0.99 (d, J = 6.8 Hz, 3 H), 1.03 (d, J = 6.3 Hz, 3 H), 1.25–2.70 (m, 14 H), 3.25–3.40 (m, 1 H), 3.04 (d, J = 10.2 Hz, 1 H), 3.76 (s, 3 H); IR (CCl_4) 1745, 1720, 1700 cm^{-1}; MS, m/e 362 (M^+), 274, 205. **55** (more polar diastereomer): ^1H NMR (250 MHz, $CDCl_3$) δ 0.53 (s, 3 H), 0.77 (d, J = 6.7 Hz, 3 H), 0.93 (d, J = 6.9 Hz, 3 H), 1.02 (d, J = 6.3 Hz, 3 H), 1.08 (d, J = 6.7 Hz, 3 H), 1.30–2.26 (m, 13 H), 2.54 (septet, J = 6.7 Hz, 1 H), 3.00–3.14 (m, 1 H), 3.28 (d, J = 9.4 Hz, 1 H), 3.75 (s, 3 H); IR (CCl_4) 1740, 1700 cm^{-1}; MS, m/e 362 (M^+), 287, 205. **56**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.81 (s, 3 H), 0.88 (d, J = 6.5 Hz, 3 H), 0.96 (d, J = 6.7 Hz, 3 H), 1.17 (d, J = 6.0 Hz, 3 H), 1.30 (d, J = 6.0 Hz, 3 H), 1.15–3.30 (m, 16 H); IR (CCl_4) 1770 cm^{-1}; MS, m/e 410 (M^+), 412 (M + 2)$^+$, 312.

(4a*S*,5*S*,7a*S*,8*R*,11a*S*)-2,4a,5,6,7,7a,8,9,10,11-Decahydro-5,7a,8-trimethyl-3-(1-methylethyl)-11-oxo-1*H*-benzo[*d*]naphthalyl-4-carboxaldehyde (57). To a solution of the bromohydrin **53** (10 mg, 0.02 mmol) in 0.5 mL of ether was added a solution of lithium aluminum hydride in ether (1 M, 0.1 mmol). The reaction mixture was stirred at room temperature for 3 h and quenched by addition of a solution of sodium potassium tartarate. The suspension so obtained was diluted with ether (8 mL) and filtered. The filtrate was dried over magnesium sulfate and concentrated in vacuo. The crude product so obtained was purified by chromatography on silica gel (20% ethyl acetate in hexanes) to yield 4 mg (55% of theory) of enediol which was submitted to the next experiment: ^1H NMR (250 MHz, $CDCl_3$) δ 0.78 (d, J = 6.7 Hz, 3 H), 0.84 (d, J = 6.4 Hz, 3 H), 0.95 (s, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 1.02 (d,

J = 6.9 Hz, 3 H), 1.10–2.25 (m, 13 H), 2.99 (septet, J = 6.9 Hz, 1 H), 3.49 (dd, J = 11.7, 6.7 Hz, 1 H), 3.94 (s, 1 H), 4.53 (d, J = 10.8 Hz, 1 H); IR (CCl_4) 3600–3100 cm^{-1}; MS, m/e 302, 284, 259, 241, 217, 215. A solution of the enediol (4 mg, 0.01 mmol) in 0.5 mL of dichloromethane was stirred with pyridinium dichromate (10 mg, 0.03 mmol) for 30 min. The slurry was diluted with dichloromethane (3 mL) and filtered through a small column of silica gel. The product so obtained was processed by chromatography on silica gel (12% ethyl acetate in hexanes) to give 3.5 mg (88%) of enal **57**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.62 (s, 3 H), 0.73 (d, J = 6.3 Hz, 3 H), 0.85 (d, J = 6.7 Hz, 3 H), 1.05 (d, J = 6.9 Hz, 3 H), 1.08 (d, J = 6.9 Hz, 3 H), 1.20–2.86 (m, 14 H), 3.47 (dd, J = 10.7, 2.0 Hz, 1 H), 3.61 (septet, J = 6.9 Hz, 1 H), 10.23 (s, 1 H); IR (CCl_4) 1700, 1660 cm^{-1}; MS, m/e 316 (M^+), 273, 255, 228.

(3α,4β)-3,4-Dimethyl-2-methylene-3-(4-pentenyl)cyclohexanone (59). To a solution of crude Mannich base **58** (1.100 g, 4.4 mmol) in 15 mL of dichloromethane was added *m*-chloroperbenzoic acid (85%, 1.340 mg, 6.6 mmol). The reaction mixture was stirred at room temperature for 20 min and poured on to a column packed with silica gel. Elution with 8% ethyl acetate in hexanes yielded 720 mg (88% of theory) of **59**: ^1H NMR (90 MHz, $CDCl_3$] δ 0.98 (d, J = 6.0 Hz, 3 H), 1.03 (s, 3 H), 1.00–2.60 (m, 17 H), 4.80–5.15 (m, 2 H), 5.05 (d, J = 2.0 Hz, 1 H), 5.73 (d, J = 2.0 Hz, 1 H), 5.50–6.00 (m, 1 H); IR (CCl_4) 1690 cm^{-1}; MS, m/e 206 (M^+), 191, 177, 149, 84.

[3α,4β]-3,4-Dimethyl-2-(4-methyl-3-oxopentyl)-3-(4-pentenyl)cyclohexanone (60). To a solution of the silyl enol ether **17** (vide supra) (1.364 g, 8.63 mmol) in 20 mL of glyme, cooled under argon in a dry ice–acetone bath, was added methyllithium (1.4 M, 6.90 mmol). The reaction mixture was stirred at −78 °C for 5 min and then the dry ice–acetone bath was replaced by an ice bath. The clear solution so obtained was stirred at 0 °C for 20 min prior to use.

The above enolate solution (10.0 mL, ca. 2.5 mmol) was added to a solution of **59** (200 mg, 0.97 mmol) in 5 mL of glyme, cooled under argon in a dry ice–acetone bath. The reaction mixture was stirred at −78 °C for 2 h and then at room temperature for 5 h. To this mixture was added saturated ammonium chloride (40 mL), followed by 50 mL of ether. The layers were separated, and the aqueous phase was extracted into ether (2 × 40 mL). The combined organic layers were washed with water, dried over magnesium sulfate, and concentrated in vacuo. The crude product so obtained was purified by chromatography on neutral alumina (10% ethyl acetate in hexanes) to yield 254 mg (87%) of diastereomers **60** (3:2). **60** (less polar diastereomer): ^1H NMR (250 MHz, $CDCl_3$) δ 0.85 (s, 3 H), 0.98 (d, J = 6.7 Hz, 3 H), 1.07 (d, J = 6.9 Hz, 6 H), 1.15–2.65 (m, 17 H), 4.91–5.20 (m, 2 H), 5.70–5.90 (m, 1 H); IR (CCl_4) 1705 cm^{-1}; MS m/e 292 (M^+), 223, 149. **60** (more polar diastereomer): ^1H NMR (250 MHz, $CDCl_3$) δ 0.57 (s, 3 H), 0.86 (d, J = 6.8 Hz, 3 H), 1.05 (d, J = 3.3 Hz, 3 H), 1.08 (d, J= 3.3 Hz, 3 H), 1.30–2.71 (m, 13 H), 4.95–5.08 (m, 2 H), 5.78–5.93 (m, 1 H); IR (CCl_4) 1705 cm^{-1}; MS, m/e 292 (M^+), 223, 149.

Methyl *trans*-6-[(1α,6β)-1,6-Dimethyl-2-methylene-3-oxocyclohexyl]-2-hexenoate (61). To a suspension of sodium hydride (60% in oil, 288 mg, 7.2 mmol) in 20 mL of glyme was added, dropwise, a solution of trimethyl phosphonoacetate (Aldrich) (1.310 g, 7.19 mmol) in 10 mL of glyme. The viscous solution so obtained was stirred at room temperature for 30 min. To this was added a solution of aldehyde **15** (1.40 g, 5.55 mmol) in 5 mL of glyme. The reaction mixture was stirred at room temperature for 3 h. The volatiles were evaporated in vacuo, the residue so obtained was dissolved in 50 mL of dichloromethane, and 40 mL of saturated ammonium chloride solution was added. The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with water (50 mL), dried over magnesium sulfate, and concentrated in vacuo. The crude residue so obtained was dissolved in dichloromethane (15 mL). To this was added *m*-chloroperbenzoic acid (85%, 2.00 g, 11.59 mmol). The reaction mixture was stirred at room temperature for 15 min and then poured on to a column packed with silica gel. Elution with hexanes/ethylacetate/triethylamine (7.0:2.5:0.5) gave crude ester **61**. Rechromatography on silica gel (12% ethyl acetate in hexanes) yielded 435 mg (30%) of **61**: ^1H NMR (90 MHz, $CDCl_3$) δ 1.03 (d, J = 7.0 Hz, 3 H), 1.04 (s, 3 H), 1.00–2.60 (m, 11 H), 3.71 (s, 3 H), 5.08 (d, J = 2.0 Hz, 1 H), 5.78 (d, J = 2.0 Hz, 1 H), 5.70 (d, J = 16.5 Hz, 1 H), 5.91 (dd, J = 16.5, 6.5 Hz, 1 H); IR (CH_2Cl_2) 1720, 1680 cm^{-1}; MS, m/e 264 (M^+), 242, 207, 123.

Methyl Dodecahydro-3-hydroxy-7a,8-dimethyl-3-(1-methylethyl)-11-oxo-1*H*-benzo[*d*]naphthalyl-4-carboxylate (62a and b). To a solution of the silyl enol ether **17** (611 mg, 3.87 mmol) in 7 mL of glyme, cooled under argon in a dry ice–acetone bath was added a solution of methyllithium (1.3 M, 3.09 mmol). After 5 min, the dry ice–acetone bath was replaced by an ice bath. The reaction mixture was stirred at 0 °C for 20 min prior to use.

A 4.3-mL aliquot of the above solution was added to a solution of **61** (114 mg, 0.43 mmol) in 2.0 mL of glyme and cooled in a dry ice–acetone bath. The reaction mixture was stirred at −78 °C for 1 h and then at ambient temperature for 10 h. To this was added 20 mL of saturated ammonium chloride solution and 20 mL of ether. The layers were separated, and the aqueous phase was extracted with ether (2 × 20 mL). The combined organic layers were washed with water (30 mL), dried over magnesium sulfate, and concentrated in vacuo. The residue thus obtained was subjected to chromatography on silica gel (8% ethyl acetate in hexanes) to yield 48 mg (26%) of **62a** (less polar diastereomer) and 12 mg (8%) of **62b** (more polar diastereomer). **62a** (less polar diastereomer): ^1H NMR (250 MHz, $CDCl_3$) δ 0.64 (d, J = 6.7 Hz, 3 H), 0.69 (d, J = 6.7 Hz, 3 H), (250 (s, 3 H), 1.09 (d, J = 7.4 Hz, 3 H), 1.40–2.23 (m, 18 H), 2.55–2.69 (m, 1 H), 3.49 (s, 3 H); IR (CH_2Cl_2) 3575, 1690 cm^{-1}; MS, m/e 350 (M^+), 332, 307, 275, 223. **62b** (more polar diasteromer): ^1H NMR (250 MHz, $CDCl_3$) δ 0.78 (d, J = 6.2 Hz, 3 H), 0.87 (d, J = 4.2 Hz, 3 H), 0.90 (d, J = 4.2 Hz, 3 H), 0.92 (s, 3 H), 0.90–2.85 (m, 18 H), 3.68 (s, 3 H); IR (CH_2Cl_2) 3550, 1700 cm^{-1}; MS, m/e 350 (M^+), 332, 318, 289, 275, 223.

(4aα,7aβ,8β,11a*R)-Dodecahydro-3-hydroxy-7a,8-dimethyl-3-(1-methylethyl)-11-oxo-1*H*-benzo[*d*]naphthalyl-4-carboxaldehyde (63).** To a solution of compound **62a** (28 mg, 0.08 mmol) in 3 mL of tetrahydrofuran was added lithium aluminum hydride (15 mg, 0.39 mmol). The reaction mixture was heated under reflux for 2 h, cooled, and quenched by addition of water. The suspension so obtained was diluted with ether (40 mL) and filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in 1 mL of dichloromethane, and pyridinium chlorochromate (40 mg, 0.18 mmol) was added. The reaction mixture was stirred for 30 min, diluted with dichloromethane (5 mL), and filtered through a column of silica gel. Chromatography of the product so obtained on silica gel (20% ethyl acetate in hexanes) yielded 15 mg (59%) of aldehyde **63**: ^1H NMR (250 MHz, $CDCl_3$) δ 0.87 (d, J= 6.8 Hz, 3 H), 0.88 (d, J = 6.8 Hz, 3 H), 1.18 (s, 3 H), 1.31 (d, J = 7.4 Hz, 3 H), 1.00–2.45 (m, 16 H), 2.73–2.89 (m, 1 H), 3.69 (dd, J = 11.3, 3.7 Hz, 1 H), 9.98 (d, J= 3.67 Hz, 1 H); IR (CH_2Cl_2) 3500, 1700 cm^{-1}; MS, m/e 320 (M^+), 302, 287, 277, 259, 223.

Conversion of 63 to 22. A solution of **63** (15 mg, 0.05 mmol) in 5 mL of benzene was refluxed with *p*-toluenesulfonic acid (5 mg) for 45 min. The reaction mixture was cooled and directly purified by chromatography on silica gel (15% ethyl acetate in hexanes) to afford 1.1 mg (8% of theory) of unsaturated aldehyde **22**.

Acknowledgment. This work was supported by PHS Grant HL 25848. P. H. gratefully acknowledges financial support of the Science and Engineering Research Council (England) through a Postdoctoral Fellowship, funded in part by NATO. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE7916210. We also express appreciation to Dr. Michael Kahn for his development of the enol carbonate methodology (ref 12 and 30) and to Drs. James Springer and Brigitte Segmuller for their previously reported crystallographic determinations.

Supplementary Material Available: The synthesis of "mismatched" intermediates **41**, **42**, and **43**, the convergence of nor products **19**, **20**, and **63** to enal **22**, and the synthesis of model Mannich base **59** (4 pages). Ordering information is given on any current masthead page.