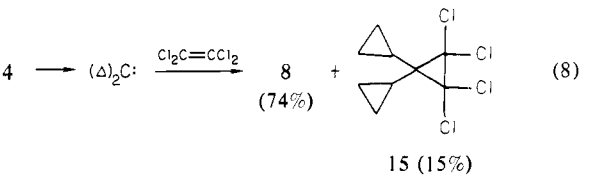
the positive end of the H–C dipole.

Although the above model (**21**) is useful, it is very likely, in view of the feeble acidity of chloroform, that the real process is a concerted one rather than a two-step reaction through an ion pair. We suggest that insertion of singlet dicyclopropylcarbene into the CH bond of chloroform is a nonsynchronous concerted process, involving charge separation in the sense of **21** but with a geometry resembling **23**. Significant conjugative stabilization of positive charge by the cyclopropyl substituents may account for the present finding that dicyclopropylcarbene inserts into the C–H bond of chloroform whereas other singlet carbenes prefer to abstract chlorine instead.[10]

Finally, dicyclopropylcarbene from **4** can be trapped in a cycloaddition reaction with an alkene. Tetrachloroethylene (neat) intercepted about 15% of the carbene before it could undergo ring expansion to **8** (eq 8).

In summary, **4** appears to be the most convenient source of dicyclopropylcarbene that is currently available, for it is readily accessible and it decomposes under mild conditions in the absence of metallic or acid/base catalysts. The reaction of dicyclopropylcarbene with chloroform suggests that the carbene is relatively nucleophilic.



15 (15%) (8)

Acknowledgment. Financial support for this work came from a grant provided by the Natural Sciences and Engineering Research Council of Canada. We are grateful to two referees for valuable suggestions.

Registry No. 4, 86310-10-3; **8**, 22693-18-1; **11**, 86310-11-4; **12**, 86310-12-5; **13**, 86310-13-6; **14**, 86310-14-7; **15**, 86310-15-8; **16**, 86310-16-9; $(c\text{-}C_3H_5)_2CO$, 1121-37-5; $H_2NNHCOCH_3$, 1068-57-1; $(c\text{-}C_3H_5)_2C{=}NNHCOCH_3$, 83313-96-6; $(c\text{-}C_3H_5)_2C{:}$, 86310-17-0; CCl_4, 56-23-5; $CHCl_3$, 67-66-3; $Cl_2C{=}CCl_2$, 127-18-4.

Total Synthesis of (±)-Spiniferin-1, a Naturally Occurring 1,6-Methano[10]annulene

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Contribution from the Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208. *Received February 24, 1983*

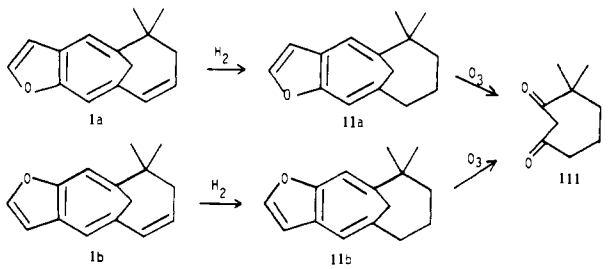
Abstract: Total syntheses of (±)-spiniferin-1 (Ia), a natural furanosesquiterpene with a 1,6-methano[10]annulene carbon skeleton, and the dihydro derivative IIa are described. A key transformation in each synthesis entails catalyzed electrocyclic ring opening of a methanonaphthalenone (**10** and **48**, with acid and base, respectively). For the dihydro compound IIa, completion of the synthesis was achieved, after Wittig homologation to the bis(enol ether) **13**, by acid-catalyzed furan cyclization. However, analogous cyclization of the dehydro counterpart, bis(enol ether) **57**, led to multiple decomposition products. The acid lability of spiniferin-1 and its synthetic precursors led to the examination of various base-promoted internal Wittig and aldol-type furan cyclizations. Specifically, the ester aldehyde **56** was found to give a mixture of (±)-spiniferin-1 (Ia), the furan ester **59**, and the furan acid **60** upon base treatment followed by acidification. Acid **60** afforded (±)-spiniferin-1 through Cu-promoted decarboxylation in quinoline.

In their extensive studies on marine natural products, Cimino et al. isolated an unstable furanosesquiterpene, spiniferin-1, from the sponge *Pleraplysilla spinifera*, found in the Bay of Naples.[1] The instability of spiniferin-1 made classical chemical investigation difficult. However, two key transformations, hydrogenation to a dihydro derivative and ozonolysis of this derivative to 4,4-dimethylcycloheptane-1,3-dione (III), provided the clues that, together with perceptive spectral analysis, proved instrumental to the ultimate structure assignment as Ia or the furano isomer Ib (Scheme I). The former was preferred on biogenetic grounds.

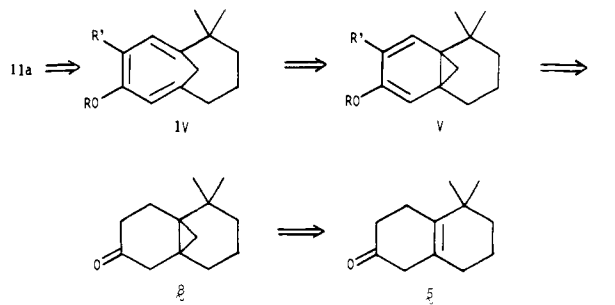
The formulation of spiniferin-1 as a substituted 1,6-methano[10]annulene, a substance conceived and elegantly synthesized by Vogel in his brilliant studies on Hückel aromaticity,[2] was profoundly interesting to us as a conceptual link between theoretical and natural products chemistry. For the present, spiniferin-1 represents the sole known sesquiterpene with this unusual carbon skeleton. While the proposed structure seemed fully consistent with the reported spectral data, we felt that rational chemical synthesis would provide desirable verification of both the carbon skeleton and the furan orientation.

We selected IIa, the favored structure for dihydrospiniferin-1,[1] as an initial synthetic target.[3] Our plan (Scheme II) employed a norcaradiene–cycloheptatriene-type electrocyclic rearrangement to introduce the methanoannulene structural unit.[4] An analogous rearrangement was used by Vogel in his efficient synthesis of the parent aromatic system.[2] Of course, such reactions are reversible,

Scheme I



Scheme II



† National Science Foundation predoctoral fellow, 1979–1982. The results described in this manuscript are recorded in: Conrow, R. E. Ph.D. Dissertation, submitted to Northwestern University, Evanston, IL, June 1983.

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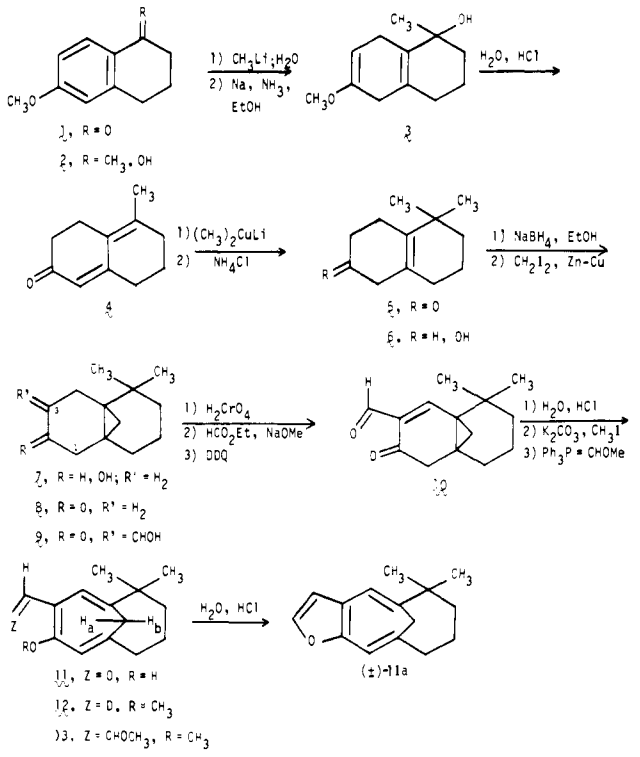
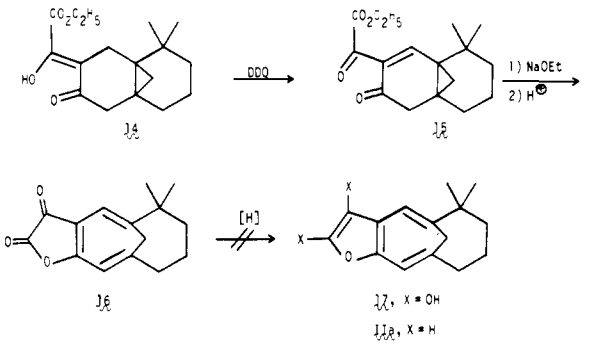
Scheme III



Scheme IV



and we had no assurances that the annulene IV could be generated in this way. However, the proposed plan offered several options for dealing with such an event. In the first place, we could incorporate substituents R and R′ in a prefuran tricyclic V that would facilitate the rearrangement to IV.[4,5] Alternatively, since spectral data show IIa to be the favored valence-bond isomer of dihydrospiniferin-1,[1] we could direct our synthetic route toward a furano-fused V (R, R′ = CH=CH), the disfavored isomer, and let the rearrangement occur spontaneously, as in the Vogel synthesis.[2]

We prepared enone **5** some years ago in connection with studies on the regiochemistry of conjugate additions to extended dienones.[6] Dienone **4**, the progenitor of enone **5** (Scheme III), was obtained in modest yield via Birch reduction of 6-methoxy-1-tetralone (**1**) followed by Oppenauer oxidation, addition of methyllithium, and acid-catalyzed hydrolysis–elimination.[6] In the present work we found it more expedient to initiate the sequence by addition of methyllithium to tetralone **1** and then effect Birch reduction of the resultant alcohol **2** thereby circumventing the Oppenauer oxidation step. Dienone **4**, available in 71% yield by this modified sequence, reacted cleanly with lithium dimethylcuprate to give enone **5** in 85% yield.

Attempted Simmons–Smith cyclopropanation of enone **5** with methylene iodide and zinc–copper couple in ether led to a mixture of conjugated ketone and other unidentified (decomposition) products. Evidently, the steric inaccessibility of the double bond and the acid lability of the β,γ-enone system render this approach unworkable. The related alcohol **6** reacted more readily[7] affording the cyclopropane **7** in 50% yield upon treatment with methylene iodide and a zinc–copper couple prepared from cuprous chloride.[8] Unfortunately, this conversion proved capricious and failed completely when purified cuprous chloride was used. After numerous trials using various alternative procedures we discovered that the reaction was best carried out at high concentration with excess reagent using a couple prepared from *cupric* chloride. Even then, varying amounts of inseparable starting olefin **6** remained. However, epoxidation of the unreacted olefin with *m*-chloroperoxybenzoic acid allowed easy separation of cyclopropane **7** by chromatography. Jones oxidation[9] completed the synthesis of ketone **8**.

It was now necessary to introduce a substituent at C-3 of ketone **8** for later elaboration to the furan ring. Unsaturation was also required at this center in preparation for the planned norcaradiene rearrangement. Both transformations could be effected via enolate chemistry. Attempts at regioselective conversion of ketone **8** to a single C-3 enolate under various kinetic and thermodynamic conditions were unpromising.[10a] However, Claisen condensation of ketone **8** with ethyl formate cleanly afforded the hydroxymethylene derivative **9**. This regiochemical outcome, well precedented in related steroid and decalone systems,[10b] reflects a thermodynamic preference for the less crowded of the two possible regioisomeric products. In addition to serving as one of the eventual furan carbons, the hydroxymethylene substituent of **9** also facilitated reaction with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[11a] to afford keto aldehyde **10**.

Methanoannulene **11**, the next plateau in our synthetic sequence, was reached with unexpected ease. We had originally planned to carry out the pericyclic rearrangement of keto aldehyde **10** under basic conditions hoping to gain electronic acceleration through an anion effect,[5] possibly enhanced by the increased electron delocalization in the vinylogous carboxylate product. However, to our astonishment, keto aldehyde **10** was completely transformed to the rearranged product **11** by passage through a column of silica gel! Dilute aqueous hydrochloric acid served equally well as a catalyst. The ^{1}H NMR spectrum of rearranged

(1) Cimino, G.; De Stefano, S.; Minale, L.; Trivellone, E. *Tetrahedron Lett.* **1975**, 3727–3730. Minale, L.; Cimino, G.; De Stefano, S.; Sodano, G. *Fortschr. Chem. Org. Naturst.* **1976**, *33*, 1–72. Cimino, G. In "Marine Natural Products Chemistry"; Faulkner, D. J., Fenical, W. H., Eds.; Plenum: New York, 1977; pp 71–74. Cimino, G.; De Stefano, S.; Minale, L.; Trivellone, E. *Experientia* **1978**, *34*, 1425–1427. For a review of furanosesquiterpenes, see: Hikino, H.; Konno, C. *Heterocycles* **1976**, *4*, 817–870.

(2) Vogel, E.; Roth, H. D. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 228–229. Vogel, E. *Pure Appl. Chem.* **1982**, *54*, 1015–1039.

(3) Marshall, J. A.; Conrow, R. E. *J. Am. Chem. Soc.* **1980**, *102*, 4274–4275.

(4) For an alternative approach to this ring system, see: Knox, L. H.; Velarde, E.; Cross, A. D. *J. Am. Chem. Soc.* **1963**, *85*, 2533–2535; *Ibid.* **1965**, *87*, 3727–3736. Bentley, P. H.; Todd, M.; McCrae, W.; Maddox, M. L.; Edwards, J. A. *Tetrahedron* **1972**, *28*, 1411–1425.

(5) Marvell, E. N. "Thermal Electrocyclic Reactions"; Academic Press: New York, 1980; pp 283–289. Steigerwald, M. L.; Goddard, W. A., III; Evans, D. A. *J. Am. Chem. Soc.* **1979**, *101*, 1994–1997.

(6) Marshall, J. A.; Ruden, R. A.; Hirsch, L. K.; Phillippe, M. *Tetrahedron Lett.* **1971**, 3795–3798.

(7) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1–131, cf. p 24.

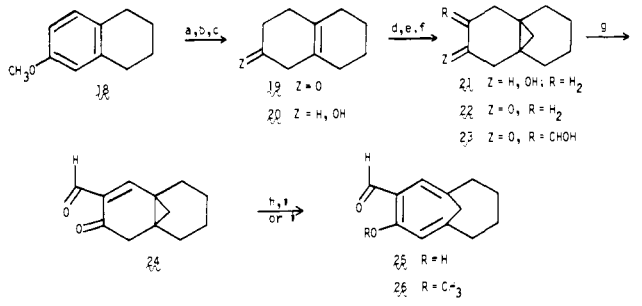
(8) Rawson, R. J.; Harrison, I. T. *J. Org. Chem.* **1970**, *35*, 2057–2058.

(9) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39–45. Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547–1549.

(10) (a) Ketone **8** gave nearly 1:1 mixtures of the two isomeric enol ethers upon treatment with various bases followed by trimethylsilyl chloride. The enolate produced by adding excess lithium diisopropylamide yielded a 2:1 mixture of C-3 and C-1 phenylselenides upon treatment with phenylselenyl chloride. Direct addition of phenylselenyl chloride to ketone **8** in ethyl acetate gave only the C-1 phenylselenide. (b) Cf. House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, 1972; p 752, compare p 776. (c) Johnson, W. S.; Posvic, H. *J. Am. Chem. Soc.* **1947**, *69*, 1361–1366.

(11) (a) Shimizu, Y.; Mitsuhashi, H.; Caspi, E. *Tetrahedron Lett.* **1966**, 4113–4116. Edwards, J. A.; Calzada, M. C.; Ibáñez, L. C.; Cabezas Rivera, M. E.; Urquiza, R.; Cardona, L.; Orr, J. C.; Bowers, A. *J. Org. Chem.* **1964**, *29*, 3481–3486. (b) Liotta, D.; Barnum, C.; Puleo, R.; Zima, G.; Bayer, C.; Kezar, H. S., III *J. Org. Chem.* **1981**, *46*, 2920–2923.

Scheme V



aldehyde **11** contained a sharp doublet (J = 10 Hz) at δ 3.08, the downfield half (H_b) of an AB quartet attributable to the methano bridge protons. A similar doublet (δ 3.04, J = 10 Hz) was noted by Cimino et al. in the ^{1}H NMR spectrum of dihydrospiniferin-1.[1] The close correspondence of these characteristic signals, though not conclusive, was certainly encouraging.

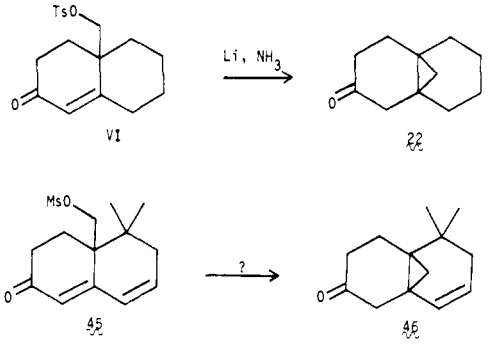
We were now ready to extend aldehyde **11** by one carbon preparatory to furan annulation. Since **11** is a vinylogous carboxylic acid we decided to first protect the enolic hydroxyl group. This was easily done using methyl iodide and potassium carbonate in *N*,*N*-dimethylformamide (DMF). A crystalline methyl ether was thereby obtained whose ^{13}C NMR spectrum was consistent with the desired structure **12**. Introduction of the final (furan) carbon was achieved through condensation of aldehyde **12** with (methoxymethylene)triphenylphosphorane.[12] The resulting diether **13**, upon treatment with 10% aqueous hydrochloric acid, afforded an array of polar intermediates that slowly gave way to a single nonpolar product over a period of several days. The conversion was accelerated by concentrated hydrochloric acid but the nonpolar product was itself somewhat acid unstable. This product was identified as (±)-dihydrospiniferin-1 through comparison of its ^{13}C and ^{1}H NMR spectra with those of an authentic specimen. The structure was secured.

We briefly examined a potentially more direct route to dihydrospiniferin-1 involving simultaneous introduction of both furano carbons via condensation of ketone **8** with diethyl oxalate to give oxalo ketone **14** (Scheme IV). Dehydrogenation with DDQ afforded the enone **15**. This enone was unchanged by acid but cleanly rearranged upon treatment with sodium ethoxide to a base-soluble intermediate. Acidification afforded lactone **16**, a bright orange crystalline substance. Unfortunately, exposure of lactone **16** to a variety of reducing agents in an attempt to effect conversion to **17** or the lactone tautomer gave complex mixtures. No single product could be isolated, and not even a trace of dihydrospiniferin-1 could be detected by thin-layer chromatography (TLC).

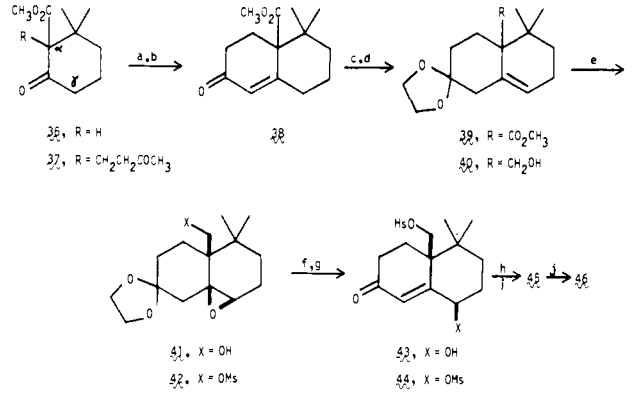
Possible conversions of (±)-dihydrospiniferin-1 (IIa) to (±)-spiniferin-1 (Ia) were also briefly examined without success. Both *N*-bromosuccinimide (NBS) and DDQ caused extensive degradation of IIA. Enol ether **12**, while unaffected by DDQ, was totally destroyed by NBS. Clearly such heavy-handed tactics could not be employed on these fragile substances. The synthesis of (±)-spiniferin-1 would require a lighter touch.

Before attempting a de novo synthesis of spiniferin-1 we wished to further study the surprisingly facile norcaradiene-type rearrangement observed with enones **10** and **15**. It was of particular interest to assess the contribution of the *gem*-dimethyl moiety as a possible steric driving force for cyclopropane bond cleavage.[4] Enone **24** was selected as a prototype system. Its synthesis, outlined in Scheme V, commenced with methoxytetralin **18**. Birch reduction followed by mild hydrolysis afforded enone **19**. Reduction with sodium borohydride gave unsaturated alcohol **20** which underwent Simmons–Smith cyclopropanation nearly quantitatively under our modified conditions to give the tricyclic alcohol **21**.[13] Jones oxidation and formylation of the resulting ketone **22** yielded the formyl ketone **23**. Dehydrogenation via the two-step selenoxide process[11b] then afforded the formyl enone **24**. This material readily gave the methanoannulene **25** upon treatment with dilute hydrochloric acid in ethyl acetate. We were also able to effect cleavage of formyl enone **24** with potassium carbonate in DMF. When this reaction was carried out in the presence of methyl iodide, the enol ether **26** was obtained directly. This base-promoted cleavage–alkylation was to prove useful in systems to be described (e.g., **52**) where the methanoannulene is especially acid labile.

Scheme VI



Scheme VII



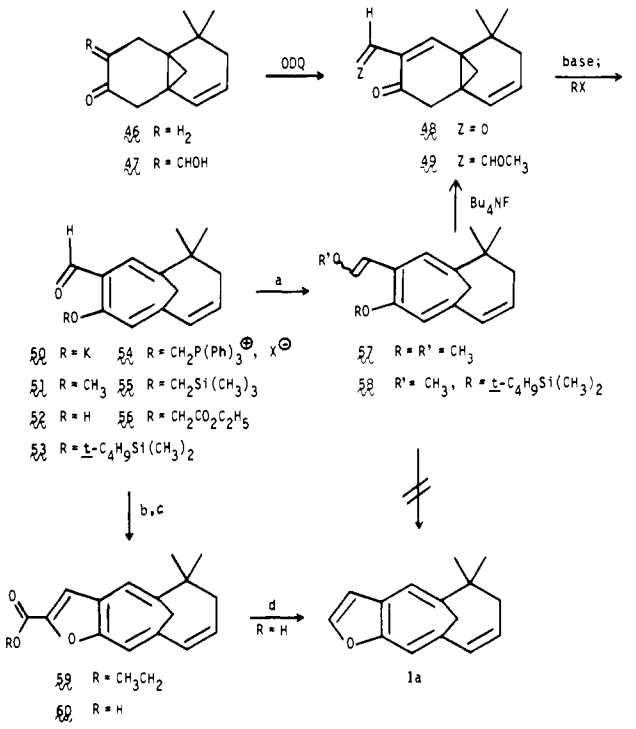
The ultimate application of our formyl norcarenone ring-expansion route to methanoannulenes was directed at (±)-spiniferin-1 (Ia) itself. We envisioned an approach quite similar to the one employed for the dihydro derivative IIa (Scheme III). However, our experience there taught us that Simmons–Smith cyclopropanation of tetrasubstituted double bonds with flanking *gem*-dimethyls (**6** → **7**) was sluggish and capricious, a consequence no doubt of adverse steric factors. Thus the preparation of the analogous unsaturated cyclopropyl ketone **46** along similar lines was perceived as unworkable. Accordingly, we turned our attention to intramolecular cyclopropanation strategies for the synthesis of this enone. Our approach[14] was based on Stork and Tsuji's finding that enone tosylate VI (Scheme VI) undergoes internal alkylation to cyclopropane **22** upon reduction with lithium in liquid ammonia.[15] We felt that the dienone analogue **45** might

(12) Schow, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760–3765. Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150–6151. Wittig, G.; Böll, W.; Krück, W.-H. *Chem. Ber.* **1962**, *95*, 2514–2525.

(13) This reaction was reported to proceed in ca. 61% yield under conventional Simmons–Smith conditions: Starr, J. E.; Eastman, R. H. *J. Org. Chem.* **1966**, *31*, 1393–1402.

(14) A solvolysis scheme patterned after that successfully used in steroidal systems (Bonet, J. J.; Wehrli, H.; Schaffner, K. *Helv. Chim. Acta* **1962**, *45*, 2615–2618) gave an interesting assortment of products. Details may be found in the Ph.D. Dissertation of R. Conrow.[+]

Scheme VIII



a) $Ph_3P{=}CHOCH_3$ b) $KN(SiMe_3)_2$ c) acidify base soluble product from step b d) Cu_2O, 1,10-phenanthroline, quinoline, 180°C.

follow a similar reduction pathway to give cyclopropyl enone **46**.

Dienone **45** was eventually[16] prepared as shown in Scheme VII from keto ester **36**.[17] This sterically hindered β-keto ester proved unreactive toward methyl vinyl ketone under the usual Robinson annulation conditions.[18,19] However, Michael addition could be effected by using a catalytic amount of potassium methoxide in tetrahydrofuran (THF). The resulting mixture of Michael adduct **37** and derived ketol intermediates[20] afforded enone **38** in 65% yield upon heating with methanolic potassium carbonate. Ketalization with ethylene glycol in refluxing benzene followed by reduction of ester **39** with lithium aluminum hydride in refluxing ether gave the alcohol **40** in ca. 80% yield, after purification by preparative liquid chromatography to remove a small amount of byproduct whose genesis could be traced to Michael addition at the γ position of β-keto ester **36**.

Epoxidation of unsaturated alcohol **40** with *m*-chloroperoxybenzoic acid afforded the epoxy ketal alcohol **41**. Acidic hydrolysis led to partial loss of the CH_2OH grouping (deformylation). Therefore, alcohol **41** was first converted to mesylate **42**, which was hydrolyzed to hydroxy enone **43**. Treatment of **43** with methanesulfonyl chloride in pyridine yielded a mixture of the dimesylate **44** and dienone mesylate **45**. Brief exposure of the mixture to calcium carbonate in *N,N*-dimethylacetamide (DMA) at 100 °C completed the elimination process giving dienone **45** (Scheme VI) in 65% overall yield from unsaturated ketal alcohol **40**. Despite its indirect course, this route to dienone **45** is reasonably efficient. Owing to the instability of the intermediates **42–44**, the sequence was best performed without interruption.

Having invested no small effort in the preparation of dienone mesylate **45**,[21] we were pleased to find that lithium-in-ammonia reduction afforded the easily purified cyclopropyl enone **46** in 55% yield. Thus, the stage was set for completion of the total synthesis.

With cyclopropyl enone **46** in hand, the road to spiniferin-1 looked straight and narrow (Scheme VIII). Formylation with ethyl formate–sodium methoxide afforded the hydroxymethylene derivative **47** as a mixture of *E* and *Z* isomers in high yield. Dehydrogenation required careful control of experimental conditions but proceeded readily with DDQ in dioxane containing a trace of acetic acid[22] to give the formyl enone **48**. This enone proved remarkably acid sensitive. Attempts to effect ring cleavage with aqueous hydrochloric acid, as for **10**, caused extensive decomposition. Fortunately, the base-promoted alternative proved successful. Treatment with either potassium *tert*-butoxide or potassium hexamethyldisilazide in THF rapidly gave rise to a dark red solution of enolate **50**. Careful acidification afforded aldehyde **52**, which rapidly decomposed upon standing. This instability was of no immediate concern, however, since direct methylation of enolate **50** with methyl iodide yielded the stable enol ether derivative **51**, which was cleanly transformed to the desired bis(enol ether) **57** upon condensation with methoxymethylenetriphenylphosphorane.

The final acid-catalyzed conversion of bis(enol ether) **57** to (±)-spiniferin-1 was given many trials under a variety of conditions but none succeeded. Not even a faint nonpolar spot could be detected by TLC analysis. Hoping to use neighboring-group participation to assist the furan ring closure we prepared the silyl enol ether **53** by treatment of the potassium enolate **50** with *tert*-butyldimethylsilyl chloride. Wittig condensation, as before, afforded the methyl enol ether **58**. This substance likewise decomposed upon exposure to various acids. Desilylation with tetrabutylammonium fluoride in aqueous THF led not to the desired mono(enol ether) **58** (R = H) but gave instead the ring-closed enone **49**.[4] Thus the vinylogous acid structure of **52** is a seemingly crucial factor in its preference for the cycloheptatriene valence-bond isomer.[23] Ketone **49**, like its congeners, yielded an array of decomposition products upon acid treatment but no trace of nonpolar, spiniferin-like material could be detected.

The apparent acid lability of intermediates **49**, **57**, **58**, and, presumably, spiniferin-1 itself prompted a change in our furan synthetic strategy to an approach using basic reaction conditions. It may be noted that spiniferin-1 is a hypothetical cyclodehydration product of the methyl enol ether aldehyde **51**. While it is unlikely that such a transformation could be realized with ether **51** itself, a modified version using the phosphonium-substituted methyl enol ether **54** is well within reason. Our successful conversion of aldehyde **51** to the enol ether **57** attested to the feasibility of an intermolecular Wittig condensation and gave us reason to explore intramolecular variants.

Attempts to synthesize the phosphonium compound **54** failed owing to the low nucleophilicity of the enolate **50** and the unreactivity and insolubility of the halomethylphosphonium precursors.[24] However, the analogous (trimethylsilyl)methyl ether **55** was readily obtained by treatment of the formyl enone **48** with potassium carbonate in hexamethylphosphoric triamide (HMPA)

(15) Stork, G.; Tsuji, J. *J. Am. Chem. Soc.* **1961**, *83*, 2783–2784. Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1964**, *87*, 275–286.

(16) A number of initially promising but ultimately unsuccessful routes were examined. A description of these studies may be found in the Ph.D. Dissertation of R. Conrow.†

(17) Sum, F. W.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431–1441.

(18) Jung, M. E. *Tetrahedron* **1976**, *32*, 3–31.

(19) The Wichterle variant was likewise unsuccessful: Wichterle, O.; Procházka, J.; Hofman, J. *Collect. Czech. Chem. Commun.* **1948**, *13*, 300–315. In the course of these studies, we developed an improved preparation of the Wichterle reagent: Conrow, R. E.; Marshall, J. A. *Synth. Commun.* **1981**, *11*, 419–422.

(20) Cf.: Marshall, J. A.; Fanta, W. I. *J. Org. Chem.* **1964**, *29*, 2501–2505.

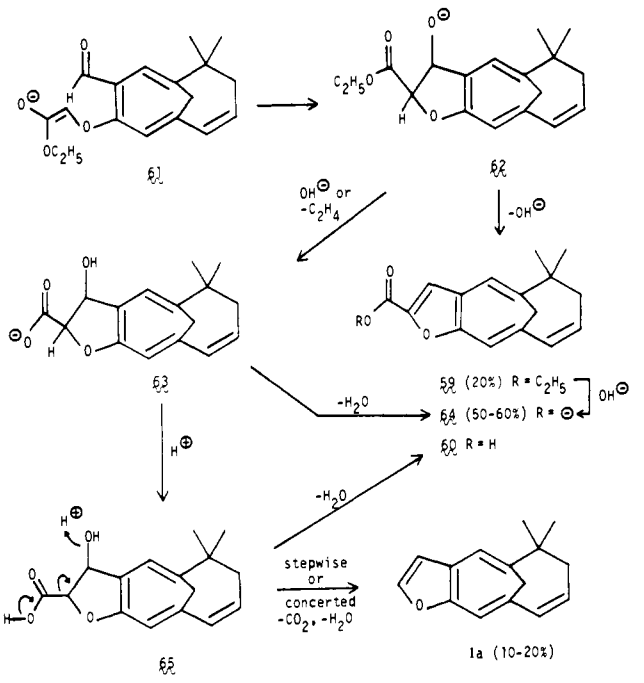
(21) A number of seemingly more direct routes involving dehydrogenation and dehydrohalogenation of enone **38** and derivatives thereof were examined, but none succeeded. A detailed discussion may be found in the Ph.D. Dissertation of R. Conrow.†

(22) Meyer, W. L.; Manning, R. A.; Schindler, E.; Schroeder, R. S.; Shew, D. C. *J. Org. Chem.* **1976**, *41*, 1005–1015. Dehydrogenation of hydroxymethylene ketone **47** via selenenylation and selenoxide elimination gave no significant improvement in yield.

(23) A related shift in a steroidal norcarenone–cycloheptadienone equilibrium through preferential derivatization of the cycloheptadienone partner has been described.[4]

(24) Attempts at conversion of salicylaldehyde to the ether with $Ph_2P(O)CH_2I$ under a variety of conditions (Me_2SO, DMF, 18-crown-6 using KO-*t*-Bu or NaH as base) were not successful. Cf.: Seyferth, D. *J. Organomet. Chem.* **1966**, *5*, 167–174. Warren, S. *Chem. Ind.* (*London*) **1980**, 824–828.

Scheme IX



followed by (trimethylsilyl)methyl iodide. Various trials at internal Peterson olefination[25] of this aldehyde did not produce (±)-spiniferin-1, even in quantities detectable by TLC analysis. Attempted formation of a silyl-stabilized anion with *n*-butyl-, *sec*-butyl-, or *tert*-butyllithium gave only intermolecular addition products. The use of tetramethylethylenediamine as a cosolvent suppressed these unwanted carbonyl addition reactions but then only starting material was recovered. Lithium tetramethylpiperidide[26] also failed to give a useful product, as did cesium fluoride in refluxing 1,2-dimethoxyethane.[27]

Successful implementation of the internal Wittig approach was realized in modified form through the use of aldehyde ester **56**, prepared by quenching enolate **50** with ethyl iodoacetate. Treatment with excess potassium hexamethyldisilazide in THF–HMPA at −78 °C followed by warming to room temperature and addition of water afforded the ester **59** upon extraction with ether, but only in 20% yield. Acidification of the basic aqueous phase with aqueous tartaric acid gave two products that together accounted for the remaining material. The major product, a highly labile acid, was identified as **60** (spiniferin-1-carboxylic acid) and the minor product, much to our surprise, was (±)-spiniferin-1! The acid **60**, as expected, afforded (±)-spiniferin-1 upon heating with copper(I) oxide and 1,10-phenanthroline in quinoline.[28] The ester **59** could be saponified to acid **60** and likewise converted to (±)-spiniferin-1. While the overall yields of these products seemed to be high their rapid deterioration seriously hampered additional chemical investigations. The richly detailed ^{1}H NMR spectrum of a freshly prepared sample of racemic spiniferin-1 matched that of the natural product even to the presence of several extraneous peaks in the 0.9–1.3-ppm region attributed to "lipidic impurities" by the Italian workers.[1] We ascribe these peaks to air oxidation products. Synthetic spiniferin-1 decomposed upon standing in air or upon treatment with even weak acids such as acetic or tartaric. The nature of these decomposition products was not investigated.

A possible rationale for the unusual reaction leading from aldehyde ester **56** to (±)-spiniferin-1 is outlined in Scheme IX. We presume that aldol-type addition occurs first to give the β-alkoxy ester **62**. Elimination of water (or hydroxide) proceeds as expected to give the ester **59**. The alkoxy ester **62** could also give rise to the hydroxy carboxylate **63** either via saponification (hydroxide is generated in the conversion of **62** to **59**) or E2 elimination of ethylene. Dehydration of **63** could account for the eventual isolation of the furan carboxylic acid **60**. Since **63** and **64** are both carboxylic acid salts they would be water soluble and thus separate from the neutral ester **59** in the workup protocol employed here. At this stage any spiniferin-1 that had formed would have been detectable by TLC, but none was seen. We can therefore rule out spontaneous decarboxylation of a β-lactone intermediate as a possible genesis.[29]

Acidification of the alkaline aqueous solution would produce spiniferin-1-carboxylic acid **60** and hydroxy acid **65**. The latter could either dehydrate to give additional spiniferin-1-carboxylic acid **60** or it could undergo acid-promoted decarboxylation to (±)-spiniferin-1. The attendant loss of water would not have to be concerted since the derived carbocation would be well delocalized. Unfortunately, spiniferin-1-carboxylic acid and spiniferin-1 are both highly labile compounds, and our limited supplies of aldehyde ester **56** did not permit a thorough examination of the cyclization reaction that produced them. We hope to carry out additional studies at a later date.

Experimental Section[30]

1,2,3,4-Tetrahydro-6-methoxy-1-methyl-1-naphthalenol (2). A 150-mL (255 mmol) portion of 1.7 M ethereal methyllithium–lithium bromide complex was added to 600 mL of dry ether and cooled to 0 °C, and a solution of 30.0 g (170 mmol) of 6-methoxy-1-tetralone in 125 mL of dry tetrahydrofuran was added dropwise with cooling and stirring over

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(26) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582–584.
(27) Chan, T. H.; Massuda, D. *Tetrahedron Lett.* **1975**, 3383–3386. Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452–6454.
(28) Cohen, T.; Schambach, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 3189–3190.
(29) Adam, W.; Baeza, J.; Liu, J.-C. *J. Am. Chem. Soc.* **1972**, *94*, 2000–2006.
(30) (a) The apparatus and methods described by G. W. Kramer, M. M. Midland, and A. B. Levy [Brown, H. C. "Organic Syntheses via Boranes"; Wiley: New York, 1975; pp 191–202] were used to maintain an argon or nitrogen atmosphere in the reaction flask. (b) Isolation of reaction products was accomplished by pouring the reaction mixture into water and thoroughly extracting with the specified solvent. The combined organic extracts were washed with water until neutral. Pyridine was removed by washing with saturated aqueous copper(II) sulfate. The resulting organic solution was washed with saturated aqueous sodium chloride (brine), then dried over anhydrous magnesium sulfate (unless otherwise specified), and filtered, and the solvents were removed by distillation at reduced pressure on a Büchi Rotovapor. (c) Anhydrous solvents were obtained by distillation from sodium benzophenone ketyl (diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, and dioxane), calcium hydride (dichloromethane and hexamethylphosphoramide), barium oxide (triethylamine, *N,N*-dimethylacetamide, and *N,N*-dimethylformamide), or sodium (benzene and toluene). (d) Infrared spectra were determined with a Perkin-Elmer 137 or 727B spectrophotometer. Infrared absorption maxima are reported in wavenumbers (cm^{-1}) and are standardized by reference to the 1601-cm^{-1} peak of polystyrene. (e) Proton magnetic resonance spectra were recorded on Varian T-60, EM-360A, or Hitachi/Perkin-Elmer R20B, IBM NR-80, and Varian EM-390 spectrometers. Carbon-13 spectra were recorded at 20 MHz on Varian CFT-20 or IBM NR-80 Fourier transform spectrometers. All samples were prepared as dilute solutions in deuteriochloroform ($CDCl_3$). Chemical shifts (δ) are reported downfield from tetramethylsilane (Me_4Si), in parts per million (ppm) of the applied field. Peak multiplicities are abbreviated: singlet s, doublet d, triplet t, quartet q, and multiplet m. Coupling constants (*J*) are reported in hertz (Hz). When necessary, proton assignments were made using single-frequency off-resonance decoupling. (f) Melting points were determined on a Fisher–Johns hot stage or a Thomas–Hoover capillary apparatus and are uncorrected. Boiling points are uncorrected. (g) Gas chromatography–mass spectral analysis (GC/MS) was performed on a Finigan 4021 instrument. High-resolution mass spectra (HRMS) were determined at the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE. (h) Combustion microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, IL. (i) Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F254 of 0.25 mm thickness, supplied by Brinkmann Instruments, were used. (j) Analytical gas–liquid chromatography (GLC) was performed with a Hewlett-Packard 5710A instrument equipped with a flame ionization detector and Model 3380A integrator, employing nitrogen as the carrier gas. (k) Analytical high-performance liquid chromatography (HPLC) was performed on an IBM LC/9533 chromatograph equipped with an IBM LC/9540 data integrator. Preparative liquid chromatography (LC) was performed on a Waters Prep LC/System 500 instrument equipped with silica gel columns. Column chromatography was performed using E. Merck silica gel 60 (230–400 ASTM mesh) according to the procedure of: Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

a 2-h period. After standing at room temperature overnight the mixture was poured cautiously into stirred ice water. Isolation of the crude product with ether afforded 32.0 g (98%) of dark red-brown oil containing 8% of starting ketone **1** (NMR analysis), which was chromatographically inseparable from alcohol **2**. This material was used without further purification: IR (film) ν 3450, 2950, 1610, 1265, 1250, 1040 cm^{-1}; NMR (60 MHz ^1H) δ 1.47 (s, C-1 CH_3), 1.6–2.1 (m), 2.68 (br s, OH), 3.65 (s, CH_3O), 6.4–6.8 (m, H-5, H-7), 7.32 (d, J = 8 Hz, H-8).

4,6,7,8-Tetrahydro-5-methyl-2(3*H*)-naphthalenone (4). The procedure of Miller and Nash was employed.[31] To a mechanically stirred solution of 31.7 g (165 mmol) of tetralol **2** and 315 mL of absolute ethanol in 1.0 L of liquid ammonia was added sodium metal in pieces until the blue color persisted for several minutes. A total of 15.0 g (0.65 mol) of sodium was added. The ammonia was allowed to evaporate overnight through a mercury bubbler, and the residue was poured into brine and extracted twice with diethyl ether. The combined ethereal extracts were vigorously stirred overnight with an equal volume of 10% aqueous HCl. Isolation of the crude product with ether afforded 22.5 g of an orange-red oil that was purified by preparative liquid chromatography[30] (25% ethyl acetate–hexane) to afford 19.0 g (71%) of dienone **4** as a clear yellow oil: IR (film) ν 2950, 1665, 1625, 1585, 1230 cm^{-1}; NMR (60 MHz ^1H) δ 1.82 (s, CH_3), 1.5–3.0 (m), 5.58 (d, J = 1 Hz, H-1).

3,4,5,6,7,8-Hexahydro-5,5-dimethyl-2(1*H*)-naphthalenone (5). The procedure of Marshall et al. was employed.[6] To a cooled (0 °C) mechanically stirred suspension of 31.3 g (164 mmol) of copper(I) iodide in 1.0 L of dry diethyl ether was added 183 mL (311 mmol) of 1.7 M ethereal methyllithium–lithium bromide complex. The resulting clear cuprate solution was stirred for 15 min, and a solution of 14.82 g (91.4 mmol) of dienone **4** in 50 mL of diethyl ether was added. The solution was stirred for 0.5 h and was then quenched with 1 L of saturated aqueous ammonium chloride. Concentrated aqueous ammonia (500 mL) was added to dissolve the precipitated solids. Isolation of the crude product with ether afforded 16.18 g of an oil that was purified by preparative liquid chromatography[30] (10% ethyl acetate–hexane) to afford 13.9 g (85%) of ketone **5** as a pale yellow oil: IR (film) ν 2960, 1725, 1460, 1200 cm^{-1}; NMR (60 MHz ^1H) δ 1.00 (s, CH_3), 1.2–2.1 (m), 2.37 (s, 4H), 2.68 (s, H-1).

1,2,3,4,5,6,7,8-Octahydro-5,5-dimethyl-2-naphthalenol (6). To a stirred, cooled (0 °C) solution of 14.85 g (83.3 mmol) of ketone **5** in 150 mL of absolute ethanol was added 1.18 g (31.2 mmol) of sodium borohydride. The resulting solution was stirred for 1 h, the cooling bath was removed, the stirred solution was allowed to warm to room temperature, 50 mL of 10% aqueous sodium hydroxide was added, and the reaction mixture was concentrated under reduced pressure. Isolation of the crude product with ether gave 14.74 g of off-white solid that was purified by recrystallization from 15 mL of hexane to give 10.10 g (67%) of alcohol **6** as a white solid. Preparative liquid chromatography (25% ethyl acetate–hexane) followed by short-path distillation (Kugelrohr oven, 110–130 °C at 0.9 torr) afforded an additional 2.43 g (16%) of white solid, combined yield 83%: IR (film) ν 3400, 3050 (w), 2930, 1460, 1440, 1360, 1065 cm^{-1}; NMR (60 MHz ^1H) δ 0.92 (s, CH_3), 1.2–2.5 (m), 3.78 (br m, C*H*OH).

The analytical sample was secured by a second recrystallization from hexane: white crystals, soften 42–47 °C, 68 °C, mp 78–80 °C. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.07; H, 11.09.

Octahydro-5,5-dimethyl-4a,8a-methanonaphthalen-2-ol (7). To a stirred suspension of 8.80 g (0.135 mol) of zinc dust in 20 mL of dry ether was added 1.80 g of finely ground anhydrous copper(II) chloride. The resulting suspension was stirred and heated to reflux for 15 min, whereupon a dark gray zinc–copper couple was formed. The mixture was cooled (0 °C), and 20 mL of dry ether was added followed by 12.11 g (67.2 mmol) of the homoallylic alcohol **6**. Then 1 mL of diiodomethane was added dropwise, and the reaction mixture was warmed until spontaneous reflux began whereupon 5.4 mL (67 mmol) of diiodomethane was added in portions to sustain reflux. The volume was reduced by ca. $^1/_3$ by passing a stream of argon through the flask, and the resulting mixture was heated to reflux for 2 h. Analytical GLC showed only ca. 10% conversion to product.

The mixture was cooled, 17.6 g of zinc dust, 20 mL of dry ether, and 5.4 mL of diiodomethane was added, and the reaction mixture was again heated to reflux for 1 h. Analytical GLC showed ca. 60% conversion to product. The mixture was cooled, an additional 30 mL of dry ether, 17.6 g of zinc dust, and 5.4 mL of diiodomethane were added, and the mixture was heated overnight. A 1-g portion of unpurified (light green) copper(I) chloride was added, and heating was continued for 0.5 h. Analytical GLC showed ca. 90% conversion to product.

The mixture was diluted with ether, Celite was added, the suspension was filtered, and the precipitate was washed with ether. The filtrate was poured slowly into saturated aqueous ammonium chloride (exothermic), the layers were separated, and the organic layer was extracted with saturated ammonium chloride, saturated aqueous sodium bicarbonate, water, and brine. A 5-g (30 mmol) portion of *m*-chloroperoxybenzoic acid was added to consume any remaining olefin, and after 1 h, the solution was extracted with 10% aqueous sodium hydroxide, water, and brine and was dried over anhydrous potassium carbonate. The mixture was filtered and the solvents were evaporated to give 12.7 g of an oil that was purified by preparative LC[30] (25% ethyl acetate–hexane) followed by short-path distillation (Kugelrohr oven, 66–80 °C at 0.35 torr) to afford 8.35 g (64%) of cyclopropyl alcohol **7** as a viscous oil: IR (film) ν 3350, 3050 (w), 2960, 2860, 1470, 1370, 1070 cm^{-1}; NMR (60 MHz ^1H) δ 0.38 (AB, J = 4 Hz, $\Delta\nu$ = 11 Hz, cyclopropane CH_2), 0.87 (s), 1.00 (s) (CH_3), 1.0–2.4 (m), 3.5 (m, C*H*OH). Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.52; H, 11.58.

Hexahydro-5,5-dimethyl-4a,8a-methanonaphthalen-2(1*H*)-one (8). To a mechanically-stirred solution of 8.00 g (41.2 mmol) of alcohol **7** in 80 mL of acetone was added 11 mL of Jones reagent[9] dropwise over 1 h. Isolation of the crude product with ether[30] gave 7.43 g of a yellow oil that was purified by preparative liquid chromatography[30] (15% ethyl acetate–hexane) and short-path distillation (Kugelrohr oven, 110–130 °C at 0.15 torr) to afford 6.29 g (79.5%) of ketone **8** as a clear colorless oil: IR (film) ν 3050 (w), 2930, 1710, 1475, 1460 cm^{-1}; NMR (60 MHz ^1H) δ 0.43 (s, cyclopropane CH_2), 0.97 (s), 1.07 (s) (CH_3), 1.1–1.8 (m), 1.8–2.4 (m, H-3), 2.47 (s, H-1). Anal. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.05; H, 10.75.

Hexahydro-3-(hydroxymethylene)-5,5-dimethyl-4a,8a-methanonaphthalen-2(1*H*)-one (9). The method of Johnson and Posvic was employed.[10c] Sodium methoxide (47 mmol) was freshly prepared by dissolving 1.08 g (47 mmol) of sodium metal in 20 mL of methanol, concentrating the resulting solution under reduced pressure, and evaporating the residue to dryness by heating at ca. 200 °C with a "heat gun" under vacuum. The cooled flask was filled with argon, and 20 mL of dry benzene was added. The resulting suspension was stirred and cooled (0 °C), and then a solution of 4.50 g (23.4 mmol) of ketone **8** and 3.8 mL (47 mmol) of ethyl formate in 5 mL of benzene was added. The cooling bath was removed after 5 min, and the reaction mixture was stirred for 1 h. The resulting thick orange paste was allowed to stand at room temperature for 13 h, whereupon it was diluted with ether and extracted with cold water and then with two portions of cold 5% aqueous sodium hydroxide. The combined aqueous extracts were washed once with ether, then cooled in ice, and acidified with concentrated aqueous HCl. The resulting suspension was thoroughly extracted with ether; the combined ethereal extracts were washed twice with water and once with brine and were dried over anhydrous magnesium sulfate. Filtration and removal of solvents under reduced pressure afforded 4.77 g (92.5%) of crude hydroxymethylene ketone **9** as a yellow solid: mp 77–78 °C after 2 recrystallizations from hexane; IR (film) ν 2960, 2940, 1655, 1595, 1235 cm^{-1}; NMR (60 MHz ^1H) δ 0.47 (AB, J = 5 Hz, $\Delta\nu$ = 7.5 Hz, cyclopropane CH_2), 0.97 (s), 1.08 (s) (CH_3), 0.8–2.0 (m), 2.48 (AB, J = 14 Hz, $\Delta\nu$ = 14 Hz, H-1), 2.52 (s, H-4), 7.78 (br s, C*H*OH), 14.05 (br s, OH). A satisfactory analytical sample of this material could not be prepared even after repeated recrystallization.

3,4,5,6,7,8-Hexahydro-8,8-dimethyl-3-oxo-4a,8a-methanonaphthalene-2-carboxaldehyde (10). To a solution of 200 mg (0.91 mmol) of hydroxymethylene ketone **9** in 5 mL of benzene, open to the atmosphere, was added 227 mg (1.00 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone with swirling. After 30 min, the rection mixture was poured into ether, and the organic layer was extracted twice with 5% aqueous NaOH, followed by back extraction with ether. The combined organic layers were washed with water and brine and dried ($MgSO_4$). Filtration and evaporation under reduced pressure gave 53 mg (27%) of formyl enone **10** as an oil: IR (film) ν 2975, 2950, 2875, 1695, 1680, 1600, 1240 cm^{-1}; NMR (60 MHz ^1H) δ 0.50 (d, J = 4 Hz, cyclopropane CH_2), 1.17 (s, CH_3), 2.75 (AB, J = 18 Hz, $\Delta\nu$ = 13 Hz, H-4), 8.22 (s, H-1), 9.78 (s, CHO).

4-Hydroxy-10,10-dimethylbicyclo[4.4.1]undeca-1,3,5-triene-3-carboxaldehyde (11). To a solution of hydroxymethylene ketone **9** (4.165 g, 18.9 mmol) in benzene (100 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (4.51 g, 19.8 mmol). The resulting deep red solution was swirled and allowed to stand at room temperature for 30 min whereupon a yellow precipitate formed. The mixture was filtered, the solvent was removed under reduced pressure, the residue was triturated with 25% ethyl acetate–hexane, and the resulting suspension was filtered. The filtrate was concentrated and purified by column chromatography on silica gel (25% ethyl acetate–hexane, 100-mL fractions). To each fraction containing enone **10** or the isomeric enol aldehyde **11** was added 3 drops (ca. 0.15 mL) of concentrated aqueous HCl with swirling. After 22 h, the acidified fractions were combined, neutralized with solid sodium bicarbonate, and dried over anhydrous magnesium sulfate. Filtration and

(31) Miller, R. B.; Nash, R. D. *J. Org. Chem.* **1973**, *38*, 4424–4427.

removal of solvents under reduced pressure afforded 3.39 g of a viscous brown oil that was purified by column chromatography on silica gel (50% ethyl acetate–hexane) to afford 3.105 g (75%) of enol aldehyde **11** as a viscous red oil: IR (film) ν 3600–2400 (br), 2975, 2950, 1630, 1600, 1515, 1365, 1280, 1195 cm^{-1}; NMR (60 MHz ^{1}H) δ 1.07 (s), 1.25 (s), (CH_3), 1.0–2.8 (m), 3.05 (d, J = 10 Hz, H-11b), 5.78 (s, H-5), 5.98 (s, H-2), 9.48 (s, CHO), 13.32 (br s, OH); NMR (20 MHz ^{13}C) δ 197.0 (d, CHO), 170.3 (s, C-4), 146.1 (s, C-3), 135.2 (s, C-6), 117.1 (d, C-2), 116.7 (s, C-1), 114.2 (d, C-5), remaining resonances 41.8, 37.2, 36.7, 36.0, 28.5, 26.9, 24.7.

4-Methoxy-10,10-dimethylbicyclo[4.4.1]undeca-1,3,5-triene-3-carboxaldehyde (12). To a stirred solution of enol aldehyde **11** (1.62 g, 7.42 mmol) in dry dimethylformamide (8.0 mL) were added finely ground anhydrous potassium carbonate (2.7 g, 19.5 mmol) and methyl iodide (0.92 mL, 14.8 mmol). The reaction mixture was stirred for 2.5 h and then filtered. The crude product was isolated from the filtrate by ether extraction to give 1.65 g of yellow solid that was purified by column chromatography on silica gel (25% ethyl acetate–hexane) to afford 1.27 g (74%) of methoxy aldehyde **12** as a yellow crystalline solid: IR (film) ν 2940, 1650, 1615, 1390, 1275, 1145 cm^{-1}; NMR (60 MHz ^{1}H) δ 1.03 (s), 1.23 (s) (CH_3), 1.3–2.7 (m), 3.08 (d, J = 10 Hz, H-11b), 3.77 (s, CH_3O), 5.80 (s, H-5), 6.28 (s, H-2), 10.28 (s, CHO); NMR (20 MHz ^{13}C) δ 191.1 (d, CHO), 168.2 (s, C-4), 144.0 (s, C-3), 134.3 (s, C-6), 123.2 (s, C-1), 114.6 (d, C-2), 111.2 (d, C-5), 58.2 (q, CH_3O), remaining resonances 41.5, 37.2, 37.0, 36.6, 28.4, 26.7, 24.6. The analytical sample, yellow crystals, mp 127–128.5 °C, was secured by recrystallization from aqueous acetone. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.63; H, 8.80.

3-Methoxy-4-(2-methoxyethenyl)-7,7-dimethylbicyclo[4.4.1]undeca-1,3,5-triene (13). The procedure of Schow and McMorris was employed.[12] To a stirred suspension of oil-free potassium hydride (0.98 g) in dry toluene (17 mL) was added *tert*-amyl alcohol (2.7 mL) dropwise. The resulting thick suspension was diluted with 4 mL of toluene. Titration with aqueous potassium hydrogen phthalate using phenolphthalein indicator showed the suspension to be 0.78 M in potassium *tert*-amylate.

To a stirred suspension of dry (methoxymethyl)triphenylphosphonium chloride (1.30 g, 3.79 mmol) in 5.5 mL of dry toluene was added 4.85 mL of the above potassium *tert*-amylate suspension. The resulting red ylide solution was stirred until all solids dissolved. To this stirred, clear red solution was added methoxy aldehyde **12**. After 45 min the bis(enol ether) **13** was isolated with ether and was filtered through 20 g of silica gel (50% ethyl acetate–hexane). Removal of solvent under reduced pressure gave 559 mg (113%) of diether **13** as a red-orange oil. NMR analysis of this product showed ca. 15% of triphenylphosphine oxide; the corrected yield of bis(enol ether) is thus 98%. This material was used without further purification: IR (film) ν 2930, 1640, 1600, 1465, 1440, 1370, 1280, 1230, 1145, 1090 cm^{-1}; NMR (60 MHz ^{1}H) δ 1.00 (s), 1.27 (s) (CH_3), 1.3–2.6 (m), 2.93 (d, J = 10 Hz, H-11b), 3.57 (s), 3.62 (s) (CH_3O), 5.62 (br s, H-2, H-5), 5.4–6.5 (m, C*H*=C*H*OCH_3).

In later experiments it was found that a better quality potassium *tert*-amylate solution was produced by refluxing a ca. 1 M solution of *tert*-amyl alcohol in toluene with a small excess of potassium metal.

1,2-Dihydrospiniferin-1 (IIa). To a stirred solution of 651 mg (2.30 mmol) of diether **13** (92% pure by NMR analysis) in 10 mL of ether was added 10 mL of 10% aqueous HCl. The reaction mixture was stirred vigorously for 25 h. Additional ether (7 mL) and concentrated (12 M) aqueous HCl (4 mL) were added, and the mixture was further stirred for 25 h. Isolation of the crude product with ether gave 453 mg of a brown oil that was purified by column chromatography on silica gel (5% ethyl acetate–hexane), affording 242 mg (49%) of the furan IIa as a yellow-orange oil: IR (film) ν 2930, 1465, 1440, 1275, 1150, 1095, 740 cm^{-1}; NMR (60 MHz ^{1}H) δ 1.03 (s), 1.30 (s) (CH_3), 1.0–2.6 (m), 3.13 (d, J = 10 Hz, H-11b), 6.16 (s, H-6, H-9), 6.45 (d, J = 2 Hz, H-12), 7.20 (d, J = 2 Hz, H-13); NMR (20 MHz ^{13}C) δ 153.3 (C-8), 140.3 (C-13), 132.5 (C-10), 129.4 (C-5), 125.4 (C-7), 112.2 (C-9), 110.0 (C-12), 109.2 (C-6), 42.1 (C-3), 37.8 (C-4), 36.8 (C-1), 35.0 (C-11), 29.2 (C-15), 27.1 (C-14), 25.9 (C-2).

The identity of this material was confirmed through comparison of its ^{1}H and ^{13}C NMR spectra with those of an authentic specimen.

1,2,3,4,5,6,7,8-Octahydro-2-naphthalenol[32] (20). To a stirred solution of 20 g (104 mmol) of 6-methoxytetralin (85% purity) and 60 mL of absolute ethanol in 450 mL of liquid ammonia (distilled through KOH) was added 16.7 g (0.73 mol) of sodium over a 35-min period, whereupon the blue color persisted. The ammonia was allowed to evaporate through a mercury bubbler. Isolation of the crude product with ether afforded 19.7 g (97%) of a yellow oil. NMR analysis of this material showed it to contain 15% of an aromatic contaminant present in the starting material and 8% of the starting tetralin. This material was used without further purification: IR (film) ν 2940, 2830, 1700, 1670, 1220 cm^{-1}; NMR (60 MHz ^{1}H) δ 1.0–2.2 (m), 2.58 (br s, H-5, H-8), 3.47 (s, CH_3O), 4.55 (t, J = 2 Hz, H-7).

To a stirred solution of 19.7 g of the above crude dienol ether in 200 mL of isopropyl alcohol and 10 mL of water was added 20.0 g of anhydrous oxalic acid. After stirring for 10 min, the solution was poured into saturated aqueous sodium bicarbonate. Isolation of the crude product with ether afforded 17.8 g (99%) of yellow oil that was used without further purification: IR (film) ν 2940, 1720, 1445 cm^{-1}; NMR (60 MHz ^{1}H) δ 1.0–2.1 (m), 2.4 (br d, 4 H), 2.72 (s, H-1).

To a stirred, cooled (0 °C) solution of 17.9 g of the above crude ketone **19** in 200 mL of absolute ethanol was added 1.69 g of sodium borohydride. The solution was stirred for 2.5 h, and then 80 mL of 10% aqueous sodium hydroxide was added. The resulting mixture was concentrated under reduced pressure. Isolation of the crude product with ether afforded 18.1 g of a yellow oil that was purified by column chromatography on silica gel (25% ethyl acetate–hexane) and short-path distillation (Kugelrohr oven, 60–78 °C at 0.7 torr), yielding 13.15 g of white solid: IR (film) ν 3350, 2925, 2835, 1440, 1055, 1040 cm^{-1}; NMR (60 MHz ^{1}H) δ 1.3–2.2 (m), 3.83 (br s, C*H*OH). The yield from 6-methoxytetralin is 85% overall.

Octahydro-4a,8a-methanonaphthalen-2-ol (21). To a stirred suspension of 25.8 g (0.394 mol) of zinc dust in 60 mL of dry ether under argon was added 2.65 g (19.7 mmol) of finely ground anhydrous copper(II) chloride. The mixture was stirred and heated to reflux for 30 min to form the zinc–copper couple. The suspension was cooled to room temperature and 12.0 g (78.9 mmol) of alcohol **20** was added followed by 16 mL (199 mmol) of diiodomethane at a dropwise rate sufficient to maintain reflux. After $^1/_3$ of the diiodomethane was added, application of external heat became necessary. The total time of addition was 1.5 h. The reaction mixture was heated to reflux for an additional 2.7 h and was then allowed to stand at room temperature for 2 h. Ether and Celite were added, the resulting suspension was filtered through a pad of Celite with suction, and the filtrate was poured cautiously into saturated aqueous ammonium chloride. Isolation of the crude product with ether was followed at once by short-path distillation (Kugelrohr oven, 55–85 °C at 0.7 torr) to afford 12.3 g (94%) of cyclopropyl alcohol **21**[13] as a colorless oil: IR (film) ν 3330, 3050 (w), 2930, 2850, 1450, 1050 cm^{-1}; NMR (60 MHz ^{1}H) δ 0.35 (s, cyclopropane CH_2), 0.8–2.2 (m), 3.47 (m, C*H*OH).

Hexahydro-4a,8a-methanonaphthalen-2(1*H*)-one (22). To a cooled (0 °C), mechanically stirred mixture of 12.0 g (72.3 mmol) of cyclopropyl alcohol **21**, 20 g of Celite 545, and 120 mL of acetone was added 24 mL of Jones reagent (8 N H_2CrO_4 in water)[9] dropwise over 30 min, whereupon an orange color persisted. After stirring for an additional 15 min, the mixture was filtered with suction, the precipitate was washed with acetone and ether, and the filtrate was concentrated under reduced pressure. Isolation of the crude product with ether afforded 10.22 g of yellow oil that was purified by column chromatography on silica gel (25% ethyl acetate–hexane), yielding 9.19 g (77%) of cyclopropyl ketone **22** as a volatile oil: IR (film) ν 3050 (w), 2940, 2880, 1715, 1455 cm^{-1}; NMR (60 MHz ^{1}H) δ 0.47 (AB, J = 5 Hz, $\Delta\nu$ = 7.5 Hz, cyclopropane CH_2), 1.0–1.9 (m), 2.1 (m, H-3), 2.47 (s, H-1).

Hexahydro-3-(hydroxymethylene)-4a,8a-methanonaphthalen-2(1*H*)-one (23). The method employed for the synthesis of hydroxymethylene ketone **9** was followed. To a stirred, cooled (0 °C) suspension of 58.2 mmol of freshly prepared sodium methoxide and 15 mL of dry benzene was added a solution of 4.78 g (29.1 mmol) of ketone **22** and 4.7 mL (58.2 mmol) of ethyl formate in 10 mL of dry benzene. The cooling bath was removed after 1 h, and the resulting thick orange paste was allowed to stand at room temperature for 26 h. Workup (as detailed above for **9**) gave 5.33 g (95%) of hydroxymethylene ketone **23** as an orange oil: IR (film) ν 3060 (w), 2950, 2870, 1655, 1600 cm^{-1}; NMR (60 MHz ^{1}H) δ 0.37 (AB, J = 5 Hz, $\Delta\nu$ = 17 Hz), 0.66 (s, cyclopropane CH_2), 1.0–2.0 (m), 2.48 (br s, H-1, H-4), 7.88 (br s, C*H*OH), 14.10 (br s, OH).

3,4,5,6,7,8-Hexahydro-3-oxo-4a,8a-methanonaphthalene-2-carboxaldehyde (24). To a stirred solution of 1.84 g (9.57 mmol) of hydroxymethylene ketone **23** in 30 mL of dry toluene was added 1.92 g (10.0 mmol) of phenylselenenyl chloride. The resulting red solution was stirred for 3 min, and then 0.81 mL (10.0 mmol) of dry pyridine was added. After 5 min, the yellow suspension was filtered with the aid of 9 mL of toluene. The filtrate was stirred and maintained at room temperature (water bath), 2.05 mL (20.1 mmol) of 30% aqueous hydrogen peroxide was added in small portions, and the reaction mixture was stirred for an additional 0.5 h. Isolation of the crude product with ether gave 1.78 g of an oil that was purified by column chromatography on silica gel (25% ethyl acetate–hexane) to afford 944 mg (52%) of formyl enone **24** as an oil: IR (film) ν 3070 (w), 2950, 2860, 1720, 1695, 1675, 1600, 1455, 1345, 1260, 1200 cm^{-1}; NMR (60 MHz ^{1}H) δ 0.73 (cyclopropane CH_2), 0.9–2.4 (m), 2.73 (AB, J = 17 Hz, $\Delta\nu$ = 21 Hz), 8.03 (s, H-1), 9.81 (s, CHO).

(32) House, H. O.; Blankley, C. J. *J. Org. Chem.* **1968**, *33*, 53–60.

4-Hydroxybicyclo[4.4.1]undeca-1,3,5-triene-3-carboxaldehyde (25). To a stirred solution of 70 mg of formyl enone **24** in 10 mL of ethyl acetate was added 1 drop of 12 M aqueous HCl. The reaction mixture was stirred for 70 min, and the product was isolated with ethyl acetate to afford 72 mg of the enol **25** as a yellow oil: IR (film) ν 2940, 2860, 1630, 1600, 1525, 1375, 1305 cm^{-1}; NMR (60 MHz ^1H) δ 1.33 (d, J = 10 Hz, H-11a), 1.0–2.9 (m), 3.02 (d, J = 10 Hz, H-11b), 5.88 (s, H-5), 6.06 (s, H-2), 9.45 (s, CHO), 13.30 (s, OH).

4-Methoxybicyclo[4.4.1]undeca-1,3,5-triene-3-carboxaldehyde (26). To a stirred solution of 86 mg (0.45 mmol) of formyl enone **24** in 0.45 mL of dry dimethylformamide was added 190 mg (1.37 mmol) of anhydrous potassium carbonate and 0.06 mL (0.96 mmol) of methyl iodide. The reaction mixture was stirred for 1 h, and the product was isolated with ether to afford 77 mg (83%) of aldehyde **26** as a yellow oil that slowly solidified: IR (film) ν 2930, 2840, 1650, 1620, 1600, 1390, 1295, 1230, 1160 cm^{-1}; NMR (90 MHz ^1H) δ 1.0–2.9 (m), 1.25 (d, J = 10 Hz, H-11a), 3.05 (d, J = 10 Hz, H-11b), 3.83 (s, CH_3O), 5.83 (s, H-5), 6.31 (s, H-2), 10.42 (s, CHO).

Charomtography on silica gel with ether afforded the analytical sample, mp 120–122 °C. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.40; H, 7.92.

4a-Carbomethoxy-4,4a,5,6,7,8-hexahydro-5,5-dimethyl-2(3*H*)-naphthalenone (38). To a stirred, cooled (0 °C) solution of 13.47 g (73.1 mmol) of keto ester **36** and 0.50 g (7.3 mmol) of potassium methoxide in 25 mL of dry tetrahydrofuran was added 6.0 mL of distilled methyl vinyl ketone (MVK) over a 1-h period. The resulting solution was stirred for 10 min, and an additional 1.5 mL of MVK [for a total of 7.5 mL (92.4 mmol)] was added over 30 min. The reaction mixture was stirred with cooling for 1 h. Isolation of the crude product with ether and ethyl acetate afforded 19.5 g of a viscous oil, consisting of the Michael adduct **37** and various aldol products according to NMR and IR spectral analysis.

To a solution of 19.3 g of this material in 150 mL of methanol was added 10.5 g (76 mmol) of anhydrous potassium carbonate. The mixture was heated to reflux for 90 min and was cooled overnight. Isolation with ether, followed by addition of benzene and rotary evaporation to remove residual water, gave 17.9 g of an oil. Preparative liquid chromatography[30] (20% ethyl acetate–hexane) followed by bulb-to-bulb distillation (Kugelrohr oven, 108–137 °C at 0.004 torr) gave 11.14 g (65%) of keto ester **38** as a pale yellow oil: IR (film) ν 2930, 1725, 1670, 1615, 1260, 1205, 1155 cm^{-1}; NMR (90 MHz ^1H) δ 0.96 (s), 1.00 (s) (CH_3), 1.0–2.6 (m), 2.7–3.2 (m, H-8), 3.74 (s, CH_3O), 5.91 (d, J = 3 Hz, H-1); GC/MS, m/e (M^+) = 236. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.18; H, 8.75.

4a-Carbomethoxy-3,4,4a,5,6,7-hexahydro-5,5-dimethyl-2(1*H*)-naphthalenone Ethylene Ketal (39). A mixture of 14.4 g (60.9 mmol) of enone **38**, 7 mL (125 mmol) of ethylene glycol, and 47 mg of *p*-toluenesulfonic acid monohydrate in 300 mL of benzene was heated to reflux with continuous water removal (Dean-Stark trap) for 19 h. The reaction mixture was poured into saturated aqueous sodium bicarbonate, and the crude product was isolated with ether (drying with K_2CO_3). Bulb-to-bulb distillation (Kugelrohr oven, 115–135 °C at 0.04 torr) afforded 15.7 g (92%) of ketal ester **39** as a colorless oil: IR (film) ν 2940, 1725, 1675 (w), 1200, 1115, 1080 cm^{-1}; NMR (90 MHz ^1H) δ 0.83 (s), 0.98 (s) (CH_3), 1.1–2.6 (m), 3.70 (s, CH_3O), 3.93 (s, OCH_2CH_2O), 5.57 (br t, J = 3 Hz, H-8); GC/MS, m/e (M^+) = 280.

3,4,4a,5,6,7-Hexahydro-4a-hydroxymethyl-5,5-dimethyl-2(1*H*)-naphthalenone Ethylene Ketal (40). To a cooled (0 °C) stirred suspension of 3.1 g (82 mmol) of lithium aluminum hydride in 150 mL of dry ether was added a solution of 15.3 g (54.6 mmol) of ketal ester **39** in 75 mL of dry ether over 10 min. The reaction mixture was heated to reflux for 18.5 h and then cooled to 0 °C, and 3.1 mL of water was cautiously added, followed by 4.7 mL of 10% aqueous sodium hydroxide solution and 7.7 mL of water. Potassium carbonate was added, the mixture was filtered, and the precipitate was thoroughly washed with ethyl acetate. Evaporation of the solvents gave 15 g of an oil that was purified by preparative liquid chromatography[30] (35% ethyl acetate–hexane) to afford 12.0 g (87%) of alcohol **40** as a viscous oil that slowly solidifed: IR (film) ν 3500, 2925, 1655 (w), 1115, 1080, 1055, 1020 cm^{-1}; NMR (90 MHz ^1H) δ 0.89 (s), 0.99 (s) (CH_3), 1.0–2.1 (m), 2.34 (AB, J = 15 Hz, $\Delta\nu$ = 24 Hz, H-1), 3.68 (AB, J = 12 Hz, $\Delta\nu$ = 12 Hz, CH_2OH), 3.93 (s, OCH_2CH_2O), 5.58 (m, H-8); GC/MS, m/e (M^+) = 252.

The analytical sample, mp 77–78 °C, was secured by two recrystallizations from hexane. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.23; H, 9.68.

Octahydro-4aβ-hydroxymethyl-8β,8aβ-epoxy-5,5-dimethyl-2(1*H*)-naphthalenone Ethylene Ketal (41). To a stirred, cooled (0 °C) solution of 7.4 g (29.3 mmol) of alcohol **40** in 120 mL of dry dichloromethane was added 4.2 g (50 mmol) of sodium bicarbonate. To the resulting suspension was added 6.50 g (nominally 37.6 mmol) of *m*-chloroperoxybenzoic acid (Aldrich, 80–85% pure). After stirring for 1 h, the reaction mixture was washed with water and saturated aqueous sodium carbonate. Isolation with dichloromethane (drying with K_2CO_3) afforded 7.5 g (95%) of epoxy alcohol **41** as a white solid: IR (film) ν 3450, 2920, 1370, 1105, 1065, 1045 cm^{-1}; NMR (90 MHz ^1H) δ 0.90 (s), 1.03 (s) (CH_3), 1.1–2.1 (m), 2.3 ($^1/_2$ of AB, J = 13 Hz, H-1), 2.93 (t, J = 2.5 Hz, H-8), 3.84 (s, CH_2OH), 3.90 (s, OCH_2CH_2O). Recrystallization from hexane afforded the analytical sample, mp 97–99 °C. Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.01. Found: C, 67.07; H, 8.80.

Octahydro-4aβ-[(mesyloxy)methyl]-8β,8aβ-epoxy-5,5-dimethyl-2(1*H*)-naphthalenone Ethylene Ketal (42). The procedure of Crossland and Servis[33] was employed. To a stirred, cooled (0 °C) solution of 7.4 g (27.6 mmol) of epoxy alcohol **41** in 100 mL of dry dichloromethane was added 5.8 mL (42 mmol) of triethylamine, followed by 2.7 mL (35 mmol) of methanesulfonyl chloride over 5 min. The cooling bath was removed and the reaction mixture was stirred for 45 min, whereupon a precipitate formed. The reaction mixture was again cooled to 0 °C and was quenched with water. The crude product was isolated with dichloromethane (drying with K_2CO_3); during solvent evaporation, the bath temperature was kept below 37 °C. There was thus obtained 9.5 g (99%) of the crude epoxy mesylate **42** as a pale brown solid: IR (film) ν 2940, 1360, 1350, 1180, 960 cm^{-1}; NMR (90 MHz ^1H) δ 0.93 (s), 1.03 (s) (CH_3), 1.1–2.1 (m), 2.17 ($^1/_2$ of AB, J = 13 Hz, H-1), 2.93 (t, J = 2.5 Hz, H-8), 3.03 (s, CH_3SO_2), 3.92 (s, OCH_2CH_2O), 4.44 (AB, J = 10 Hz, $\Delta\nu$ = 25 Hz, CH_2OMs). This unstable compound was used at once without further purification.

4,4a,5,6,7,8-Hexahydro-8β-hydroxy-4aβ-[(mesyloxy)methyl]-5,5-dimethyl-2(3*H*)-naphthalenone (43). To a stirred solution of 9.5 g (27.4 mmol) of epoxy mesylate **42** in 110 mL of acetone was added 30 mL of 10% aqueous hydrochloric acid. The reaction mixture was stirred for 50 min and the crude product was isolated with ethyl acetate. During solvent evaporation, the bath temperature was kept below 38 °C. There was thus obtained 8.3 g (100%) of the crude hydroxy mesylate **43** as a viscous oil: IR (film) ν 3400, 2940, 1690 (sh), 1655, 1355, 1340, 1180, 1075, 960, 940 cm^{-1}; NMR (90 MHz ^1H) δ 0.98 (s), 1.03 (s) (CH_3), 1.0–2.7 (m), 3.02 (s, CH_3SO_2), 4.33 (t, J = 2 Hz, H-8), 4.68 (AB, J = 9 Hz, $\Delta\nu$ = 34 Hz, CH_2OMs), 6.06 (s, H-1). This unstable compound was used at once without further purification.

4,4a,5,6,7,8-Hexahydro-8β-mesyloxy-4aβ-[(mesyloxy)methyl]-5,5-dimethyl-2(3*H*)-naphthalenone (44). To a stirred solution of 8.3 g (27.4 mmol) of hydroxy mesylate **43** in 45 mL of dry pyridine, maintained at 29–30 °C (water bath) was added 8.5 mL (110 mmol) of methanesulfonyl chloride over 10 min. The reaction mixture was stirred for 75 min and was then pipetted into 1.2 kg of rapidly stirred ice water. The resulting mixture was allowed to warm to 20 °C, the crude product was isolated with ethyl acetate, and the dried organic extracts were partially concentrated and then purified by elution through Florisil with ethyl acetate. During solvent evaporation, the bath temperature was kept below 40 °C. There was thus obtained 8.7 g of an oil, whose spectra showed it to be a 1:2 mixture of the dienone mesylate **45** and the dimesylate **44**: IR (film) ν 2930, 1685, 1625 (w), 1350, 1180, 965, 900 cm^{-1}; NMR (90 MHz ^1H) δ 0.99 (s), 1.04 (s) (CH_3), 1.2–2.9 (m), 3.05 (s, 6 H, CH_3SO_2), 4.50 (AB, J = 9 Hz, $\Delta\nu$ = 17 Hz, CH_2OMs), 5.25 (br t, J = 2 Hz, H-8), 6.22 (s, H-1). This material was used at once without further purification.

4,4a,5,6-Tetrahydro-4a-[(mesyloxy)methyl]-5,5-dimethyl-2(3*H*)-naphthalenone (45). To a solution of 8.6 g of the above 2:1 mixture of dimesylate **44** and dienone mesylate **45** in 86 mL of *N,N*-dimethylacetamide was added 4.3 g of calcium carbonate. The mixture was heated on the steam bath with mechanical stirring for 1.5 h. The crude product was isolated with ethyl acetate and was purified by preparative LC[30] (60% ethyl acetate–hexane) to afford 5.3 g of the dienone mesylate **45** as a yellow oil. The overall yield for five steps from the alcohol **40** is thus 65%. IR (film) ν 2950, 1655, 1620, 1590, 1360, 1180, 965, 840 cm^{-1}; NMR (90 MHz ^1H) δ 0.97 (s), 1.10 (s) (CH_3), 1.8–2.8 (m), 2.98 (s, CH_3SO_2), 4.32 (AB, J = 10 Hz, $\Delta\nu$ = 8 Hz, CH_2OMs), 5.91 (s, H-1), 6.2 (br s, 2 H, H-7 and H-8); MS (direct injection), m/e (M^+) = 284.

3,4,5,6-Tetrahydro-5,5-dimethyl-4a,8a-methanonaphthalen-2(1*H*)-one (46). The procedure of Stork et al.[15] was modified. Ammonia was passed through KOH and $CaSO_4$ drying towers, and 300 mL was condensed into a 500-mL flask equipped with two cold finger condensers (−78 °C) and a mechanical stirrer. Lithium wire (990 mg, 140 mmol) was added in ca. 5-mm pieces with stirring. The resulting deep-blue solution was stirred for 45 min and was then cooled to −78 °C (dry ice–acetone bath). After 30 min, a solution of 2.37 g (8.33 mmol) of dienone mesylate **45** in 15 mL of dry tetrahydrofuran was added dropwise via syringe over 10 min. The resulting solution was stirred for 10 min

(33) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195–3196.

and was then quenched with solid ammonium chloride. The cooling bath was removed and the ammonia was allowed to escape through a mercury bubbler. The crude product was isolated with ether (eight–ten water washes were required to remove all the ammonia) to give 1.72 g of an oil. This material was purified by column chromatography on silica gel (16% ethyl acetate–hexane) to afford 871 mg (55%) of ketone **46** as a volatile, waxy white solid: IR (film) ν 3010 (w), 2940, 2850, 1715, 1645 (w), 1475, 1365, 940, 710 cm^{-1}; NMR (90 MHz ^1H) δ 0.70 ($^1/_2$ of AB, J = 6 Hz, cyclopropane CH), 1.00 (s), 1.10 (s) (CH_3), 1.7–2.5 (m), 2.64 (AB, J = 17 Hz, $\Delta\nu$ = 10.5 Hz, H-1), 5.37 (m, H-7), 5.73 (dd, J = 10, 3 Hz, H-8); GC/MS, m/e (M^+) = 190.

Chromatography on silica gel with ether afforded the analytical sample, mp 43–44 °C. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.08; H, 9.62.

3,4,5,6-Tetrahydro-3-(hydroxymethylene)-5,5-dimethyl-4a,8a-methanonaphthalen-2(1*H*)-one (47). The method of Johnson and Posvic was employed.[10c] To a stirred suspension of 16.3 mmol of freshly prepared sodium methoxide (as detailed above in the preparation of compound **9**) in 8 mL of dry benzene was added a solution of 779 mg (4.09 mmol) of ketone **46** and 1.3 mL (16 mmol) of ethyl formate in 8 mL of dry benzene. The resulting thick orange suspension was stirred for 17 h. Workup (as detailed above for compound **9**) afforded 862 mg (96.5%) of hydroxymethylene ketone **47** as a yellow-orange semisolid: IR (film) ν 3000 (w), 2940, 2850, 1640, 1580, 1465, 1410, 1360, 1195 cm^{-1}; NMR (90 MHz ^1H) δ 0.78 (AB, J = 5 Hz, $\Delta\nu$ = 17 Hz, cyclopropane CH_2), 1.00 (s), 1.11 (s) (CH_3), 1.83 (m, H-6), 2.64 (AB, J = 14 Hz, $\Delta\nu$ = 19 Hz, H-1 or H-4), 2.69 (s, H-1 or H-4), 5.44 (m, H-7), 5.83 (m, H-8), 8.05 (s) and 8.41 (s) (isomeric C*H*OH, 3:1 ratio), 14.17 (br s) and 14.63 (br s) (isomeric CHO*H*, 3:1 ratio); GC/MS, m/e (M^+) = 218 (two isomers, 3:1 ratio).

3,4,7,8-Tetrahydro-8,8-dimethyl-3-oxo-4a,8a-methanonaphthalene-2-carboxaldehyde (48). The procedure of Meyer et al.[22] was modified. To a stirred solution of 862 mg (3.95 mmol) of hydroxymethylene ketone **47** in 8 mL of dry dioxane was added 41 mg of acetic acid, followed by a solution of 990 mg (4.34 mmol) of **DDQ** in 13 mL of dry dioxane. The reaction mixture was stirred for exactly 3 min and was then diluted with 45 mL of hexane and filtered. The filtrate was diluted with hexane and was extracted 3 times with saturated aqueous sodium bicarbonate, twice with water and once with brine, dried over magnesium sulfate, and filtered and evaporated to give 475 mg of a yellow oil. The crude product was purified by column chromatography on silica gel (25% ethyl acetate–hexane) to afford 433 mg (51%) of formyl enone **48** as a yellow oil: IR (film) ν 3020 (w), 2940, 2850, 1720 (m), 1695, 1680, 1600, 1360, 1235 cm^{-1}; NMR (90 MHz ^1H) δ 0.70 ($^1/_2$ of AB, J = 4 Hz, cyclopropane CH), 1.00 (s), 1.33 (s) (CH_3), 1.89 (m, H-7), 2.89 (AB, J = 18 Hz, $\Delta\nu$ = 24 Hz, H-4), 5.50 (m, H-6), 5.89 (d, J = 10 Hz, H-5), 8.32 (s, H-1), 9.97 (s, CHO); GC/MS, m/e (M^+) = 216; HRMS, m/z 216.1151 ($C_{14}H_{16}O_2$ requires 216.1150). This material always contained a small amount of the ring-expanded enolic isomer **52**.

10,10-Dimethyl-4-[(*tert*-butyldimethylsilyl)oxy]bicyclo[4.4.1]undeca-1,3,5,7-tetraene-3-carboxaldehyde (53). To a stirred solution of 39 mg (0.18 mmol) of formyl enone **48** in 1 mL of dry tetrahydrofuran (THF) was added 0.20 mL (0.20 mmol) of 1.0 M potassium hexamethyldisilazide in THF.[34] The resulting dark red-brown enolate solution was stirred for 5 min, and 50 mg (0.33 mmol) of *tert*-butyldimethylchlorosilane was added. The mixture was stirred until the dark color faded to yellow (several minutes). The crude product was obtained by filtering the reaction mixture through Florisil under pressure and eluting with 25% ethyl acetate–hexane, followed by concentration under reduced pressure and removal of excess silyl chloride under vacuum. There was thus obtained 62 mg (100%) of crude siloxy aldehyde **53**: IR (film) ν 2910, 2840, 1665, 1595, 1550, 1470, 1400, 1365, 1270, 1260 cm^{-1}; NMR (90 MHz ^1H) δ 0.81 (s), 1.40 (s) (CH_3), 0.89 (s, *t*-Bu), 2.13 (dd, J = 16, 9 Hz), 2.74 (dt, J = 16, 3 Hz) (H-9), 3.53 (d, J = 10 Hz, H-11b), 5.60 (m, H-8), 5.84 (s, H-5), 6.26 (dt, J = 11, 3 Hz, H-7), 6.53 (s, H-2), 10.50 (s, CHO). This material was labile to hydrolysis upon standing and was used at once.

10,10-Dimethyl-4-[(trimethylsilyl)methoxy]bicyclo[4.4.1]undeca-1,3,5,7-tetraene-3-carboxaldehyde (55). A suspension of 46 mg (0.21 mmol) of formyl enone **48**, 0.36 mL (3.1 mmol) of (iodomethyl)trimethylsilane, and 120 mg (0.87 mmol) of anhydrous potassium carbonate in 0.40 mL of dry hexamethylphosphoramide was stirred for 11 h. Isolation of the crude material with ether followed by column chromatography on silica gel (17% ethyl acetate–hexane) afforded 42 mg (65%) of the siloxy aldehyde **55** as a yellow solid, mp 133–135 °C: IR (film) ν 2930, 1645, 1400, 1370, 1265, 1255, 1165 cm^{-1}; NMR (90 MHz ^1H) δ 0.16 (s, Me_3Si), 0.82 (s), 1.35 (s) (CH_3), 2.07 (dd, J = 9, 16 Hz), 2.71 (dt, J = 16, 3 Hz) (H-9), 3.50 (d, J = 10 Hz, H-11b), 3.70 (AB, J = 13 Hz, $\Delta\nu$ = 25 Hz, Me_3SiCH_2O), 5.55 (m, H-8), 6.00 (s, H-5), 6.28 (dd, J = 3, 10 Hz, H-7), 6.61 (s, H-2), 10.44 (s, CHO); GC/MS, m/e (M^+) = 302; HRMS, m/z = 302.1692 ($C_{18}H_{26}O_2Si$ requires 302.1702).

10,10-Dimethyl-4-[(carbethoxy)methoxy]bicyclo[4.4.1]undeca-1,3,5,7-tetraene-3-carboxaldehyde (56). To a stirred solution of 92 mg (0.425 mmol) of formyl enone **48** in 1.7 mL of dry tetrahydrofuran (THF) was added 0.41 mL (0.45 mmol) of 1.09 M potassium hexamethyldisilazide in THF[34] [freshly titrated against (±)-10-camphorsulfonic acid in 50% aqueous ethanol with phenolphthalein as indicator]. After 5 min, the dark red-brown enolate solution was quenched with a solution of 0.20 mL (1.70 mmol) of ethyl iodoacetate in 1.2 mL of dry 1,2-dimethoxyethane, whereupon a precipitate formed within minutes. The mixture was stirred for 20 min, and the crude product was isolated with ether and was purified at once by column chromatography on silica gel (25% ethyl acetate–hexane) to afford 106 mg (82.5%) of the carbethoxy aldehyde **56** as a yellow oil: IR (film) ν 2940, 1760, 1670, 1375, 1220, 1170, 1150 cm^{-1}; NMR (90 MHz ^1H) δ 0.73 (d, J = 9 Hz, H-11a), 0.82 (s), 1.40 (s) (CH_3), 1.27 (t, J = 7 Hz, CH_3CH_2O), 2.11 (dd, J = 9, 17 Hz), 2.74 (dt, J = 17, 3 Hz) (H-9), 3.53 (d, J = 9 Hz, H-11b), 4.22 (q, J = 7 Hz, CH_3CH_2O), 4.67 (s, EtO_2CCH_2O), 5.59 (m, H-8), 5.88 (s, H-5), 6.28 (dd, J = 3, 12 Hz, H-7), 6.67 (s, H-2), 10.53 (s, CHO); HRMS, m/z = 302.1516 ($C_{18}H_{22}O_4$ requires 302.1518).

13-Carbethoxyspiniferin-1 (59), 13-Carboxyspiniferin-1 (60), and Spiniferin-1 (Ia). To a stirred, cooled (−78 °C) solution of 103 mg (0.34 mmol) of the carbethoxy aldehyde **56** in 2.2 mL of dry tetrahydrofuran (THF) and 0.7 mL of dry hexamethylphosphoramide was added via syringe 0.60 mL (0.65 mmol) of 1.09 M potassium hexamethyldisilazide in THF. The cooling bath was removed, and the solution was stirred for 30 min to reach room temperature.

The dark solution was diluted with ether and washed twice with water. The combined aqueous extracts were washed once with ether, and the combined organic solutions were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified at once by column chromatography on silica gel (10% ethyl acetate–hexane) to afford 19 mg (20%) of 13-carbethoxyspiniferin-1 (**59**) as a white solid: IR (film) ν 2930, 1710, 1570, 1480, 1370, 1330, 1310, 1205, 1170 cm^{-1}; NMR (90 MHz ^1H) δ 0.83 (d, J = 10 Hz, H-11a), 0.83 (s), 1.42 (s) (CH_3), 1.38 (t, J = 7 Hz, CH_3CH_2O), 2.10 (dd, J = 16 Hz, 9 Hz), 2.85 (dt, J = 16 Hz, 3 Hz) (H-3), 3.62 (d, J = 10 Hz, H-11b), 4.37 (q, J = 7 Hz, CH_3CH_2O), 5.47 (m, H-2), 6.33 (m, H-1), 6.36 (s, H-6 or H-9), 6.43 (s, H-6 or H-9), 7.33 (s, H-12); GC/MS: m/e (M^+) = 284. Chromatography on silica gel (1:2 ether–hexane) afforded the analytical sample, mp 97–102 °C. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.94; H, 7.19.

The aqueous extracts from above were acidified with 10% aqueous tartaric acid, whereupon a precipitate formed. Brine was added, and the aqueous solution was extracted 3 times with ether. The combined organic extracts were washed with water, aqueous sodium bicarbonate, and brine, dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified immediately by column chromatography on silica gel (10% ethyl acetate–hexane) to afford 7 mg (10%) of synthetic spiniferin-1 (Ia) as an oil: IR (film) ν 3000 (w), 2940, 2900, 1470, 1270, 1150, 1095, 815, 745 cm^{-1}; NMR (90 MHz ^1H) δ 0.77 (d, J = 10 Hz, H-11a), 0.81 (s), 1.42 (s) (CH_3), 2.07 (dd, J = 17, 9 Hz), 2.87 (dt, J = 17, 3 Hz) (H-3), 3.65 (d, J = 10 Hz, H-11b), 5.41 (m, H-2), 6.30 (d, J = 10 Hz, H-1), 6.35 (s, H-6 or H-9), 6.38 (s, H-6 or H-9), 6.59 (d, J = 2 Hz, H-12), 7.33 (d, J = 2 Hz, H-13); GC/MS, m/e (M^+) = 212.

The ^1H NMR spectrum of this material was identical with that of natural spiniferin-1.

The combined water and bicarbonate extracts from above were acidified with 10% aqueous hydrochloric acid and were extracted twice with ethyl acetate. The combined organic extracts were washed with water until neutral and with brine, dried ($MgSO_4$), filtered, and concentrated to afford 43 mg of a brown oil. The ^1H NMR spectrum of this material indicated 13-carboxyspiniferin-1 (**60**) to be the major component. This component was found to deteriorate upon even brief storage.

After standing overnight, the crude (deteriorated) material was purified by column chromatography on silica gel (1:1 ethanol–hexane eluant) to afford 4 mg (4.5%) of 13-carboxyspiniferin-1 (**60**): IR (film) ν 3600–2200 (br), 2900, 1685, 1570, 1485, 1235, 1215, 1175, 820 cm^{-1}; NMR (90 MHz ^1H) δ 0.89 (s), 1.48 (s) (CH_3), 2.17 (dd, J = 16, 9 Hz), 2.93 (dt, J = 16, 3 Hz) (H-3), 3.73 (d, J = 11 Hz, H-11b), 5.60 (m, H-2), 6.44 (dt, J = 10, 3 Hz, H-1), 6.50 (s, H-6 or H-9), 6.57 (s, H-6 or H-9), 7.1 (br s, OH), 7.59 (s, H-12).

Saponification and Decarboxylation of 13-Carbethoxyspiniferin-1 (59). To a stirred solution of 9 mg (0.03 mmol) of ester **59** in 1.2 mL of methanol and 0.5 mL of water was added 94 mg (1.7 mmol) of potassium hydroxide. The reaction mixture was stirred at room temperature for 45

(34) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913–3918. In our experience, heating the KH–hexamethyldisilazane–THF mixture to reflux was necessary to achieve a reasonable rate of metalation.

min and was then acidified with 10% aqueous tartaric acid. Isolation of the crude product with ethyl acetate afforded 9 mg of 13-carboxyspiniferin-1 (**60**) as an oil, whose IR and NMR spectra were identical with those recorded above. This unstable compound was used immediately.

The method of Cohen and Schambach[28] was employed for the decarboxylation of the furoic acid **60**. A stirred mixture of 8 mg of **60**, 40 mg of 1,10-phenanthroline, and 30 mg of copper(I) oxide in 0.25 mL of distilled quinoline under an argon atmosphere was placed in a preheated (170–180 °C) oil bath. After the mixture was stirred for 5 min, the mixture was cooled and the product was isolated directly by chromatography on silica gel (10% ethyl acetate–hexane) to afford 5 mg of spiniferin-1 (Ia), whose IR and NMR spectra were identical with those recorded above.

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Total Synthesis of 11-Deoxydaunomycinone

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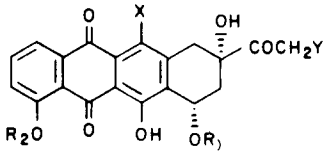
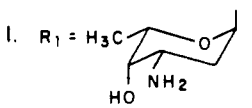
Abstract: An efficient regiospecific synthesis of 11-deoxydaunomycinone (**2a**) is described. Key elements of the synthesis were the use of bicyclooctenol **3a** as a precursor to the acetyl-substituted naphthalenone **6** which served as a synthon for the A and B rings of **2a**. Condensation of **6** with the anion of the methoxy(phenylsulfonyl)isobenzofuranone **7** regiospecifically furnished the tetracyclic product **8**, which was transformed to the tetrahydronaphthacenone **9** in a single step. The eight-step preparation of **9** was achieved in 20% overall yield.

The aklavin type anthracyclines 11-deoxydaunorubicin (**1a**) and 11-deoxyadriamycin (**1b**) possess significant anticancer activity

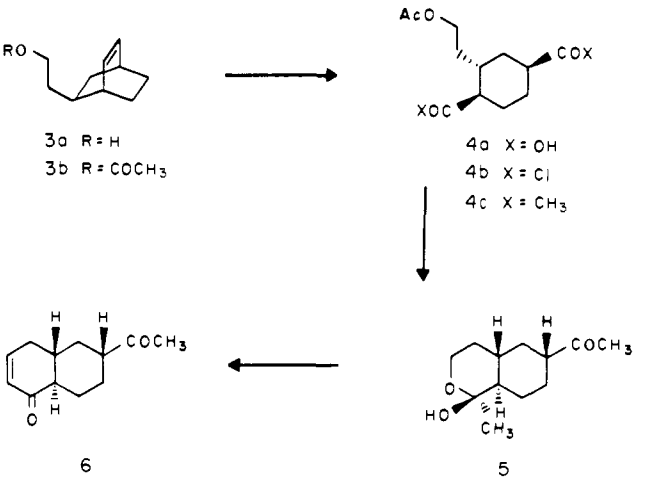




a. $R_2 = CH_3$, X = Y = H
b. $R_2 = CH_3$, X = H, Y = OH
c. $R_2 = CH_3$, X = OH, Y = H
d. $R_2 = CH_3$, X = Y = OH
e. R_2 = X = Y = H

and are less cardiotoxic[2] than the clinically important rhodomycins,[3] daunorubicin (**1c**) and adriamycin (**1d**). The potential advantages associated with these compounds have prompted interest in their preparations, and several total syntheses of the aglycone fragment **2a**[4,5] of 11-deoxydaunorubicin (**1a**) and one of 11-deoxycarminomycinone (**2e**)[6] have been published.

Scheme I



We report here an efficient and preparatively useful route to the acetyl-substituted naphthacene **9**, an established[4] late-stage intermediate to 11-deoxydaunomycinone (**2a**). This reaction sequence has enabled us to perform laboratory preparation of multigram quantities of **9**, with absolute control over the regiochemical integrity, in 20% overall yield from the bicyclooctene **3a**. In addition, only one intermediate required chromatographic purification; the others were purified by either distillation or recrystallization.

Previously, we demonstrated that the A and B rings of 11-deoxyanthracyclinones could be introduced as a large single fragment through use of 1(4*H*)-naphthalenones.[7] However, the absence of methods for preparing appropriately substituted naphthalenones seriously limited the scope of this strategy. We have now developed a synthesis of the acetyl-substituted naphthalenone **6** that is efficient and permits the practical preparation of the tetracyclic product **9**.

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