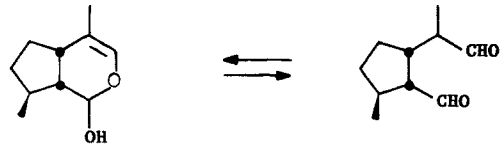
A Total Synthesis of Plumericin, Allamcin, and Allamandin. 1. Basic Strategy

Barry M. Trost,* Michael K.-T. Mao, James M. Balkovec, and Peter Buhlmayer

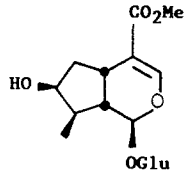
Contribution from the McElvain Laboratories of Organic Chemistry, Department of Chemistry, University of Wisconsin—Madison, Madison, Wisconsin 53706. *Received December 2, 1985*

Abstract: As part of a basic study directed toward a synthesis of the allamanda and plumeria type of iridoids, methodology was investigated to introduce the requisite lactone and the carboxylic acid of these molecules onto a basic building block such as *cis*-bicyclo[3.3.0]oct-7-en-2-one. Elaboration of a spirolactone from a saturated ketone with simultaneous introduction of additional substitution at the α-position of the ketone evolved into a general substitutive spiroannulation. In this approach, the oxaspiropentane formed by condensation of cyclopropyldiphenylsulfonium fluoroborate with a ketone is isomerized to a vinylcyclopropanol. Addition of an electrophile such as Br^+ or OH^+ effects functionalization at the carbon which was originally α to the carbonyl group and initiates formation of the spirocyclobutanone which can easily be converted to the spirolactone by a Baeyer–Villiger oxidation. The stereocontrol depends upon the choice of electrophile. Elaboration of the saturated lactone into an α-(hydroxyalkyl)-α,β-unsaturated lactone necessitated development of a new approach to magnesium enolates of sulfenylated lactones. Grignard reagents effect clean monodesulfenylation of bissulfenylated lactones to produce magnesium enolates which condense with aldehydes in virtually quantitative yield. This approach to the aldol condensation of sulfenylated carbonyl compounds extends to ketones upon addition of a catalytic amount of copper bromide–dimethyl sulfide complex. Introduction of the carboxylic acid carbon takes advantage of the [2.3]sigmatropic rearrangement of allyl tri-*n*-butylstannylmethyl ethers induced by *n*-butyllithium. These methods set the stage for an attack on this family of iridoids.

The monoterpenoid natural products are a large, structurally diverse class of C-10 compounds that occur in a wide variety of plant and animal species. A subgroup of this class, the cyclopentanoid monoterpenes, has been under extensive investigation during the past 30 years.[1] Most of the members of this subgroup contain a cyclopentanopyran ring system, and the name "iridoid" was suggested[2] due to the structural similarity of these compounds to one of the simplest members, iridodial (**1**). Another common



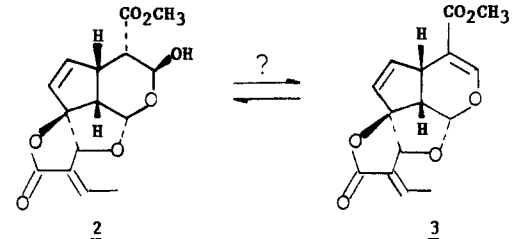
IRIDODIAL 1



LOGANIN 2

structural feature of this subgroup is a 7,8-seco ring, these natural products being termed the secoiridoids. These compounds possess a wide range of physiological activity. Various plants containing iridoids have been used in a variety of folk medicines for centuries as a bitter tonic, an expectorant, a purgative, and as a treatment for certain skin diseases.[1j] Among the isolated iridoids, demonstrated biological activities include antibiotic (genepic acid, genipinic acid, plumericin, fulvoplumierin, udoteatrial), antifungal (plumericin, fulvoplumierin), hypotensive (oleuropein), analgesic (harpagoside), diuretic (catalposide), antipsychotic (gentianine), purgative (geniposide), tumor inhibitory (allamandin, plumericin, allamcin, pentstemide), and antiviral properties (elenolic acid).[3] These terpenoids are also important as a defensive secretion for a variety of ants,[4] an attractant for certain beetles,[5] and a plant defensive mechanism as an insect antifeedant.[6] Nepetalactone, found in catnip, is a potent attractant for cats.[7]

We were attracted by the synthetic challenge posed by allamandin (**2**)[8,9] and the related iridoid plumericin (**3**)[8-10,11a,12] the



2 3

latter simply being an anhydro form of the former for which chemical interconversion should be feasible. The recognition of the relationship between the lactol ring of the iridoids in the form of its dialdehyde and a vicinally substituted cyclopentane or cyclopentene (eq 1) has made the bicyclo[3.3.0]octane system a

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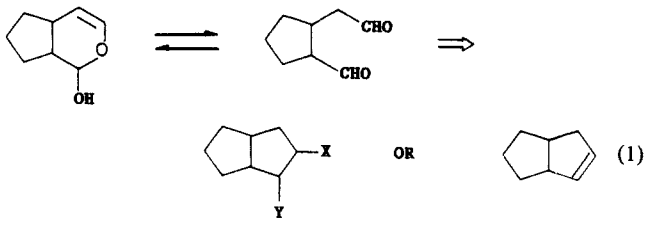
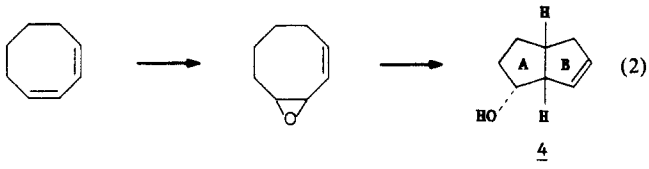


(1)

favorite framework onto which must be placed the appropriate substitution for iridoid synthesis.[13] In this paper, we wish to record our initial studies directed toward elaborating allamandin and plumericin.

The basic ring system chosen as our starting material is bicyclo[3.3.0]oct-7-en-*endo*-2-ol (**4**)[14-16] because (1) it offers differ-

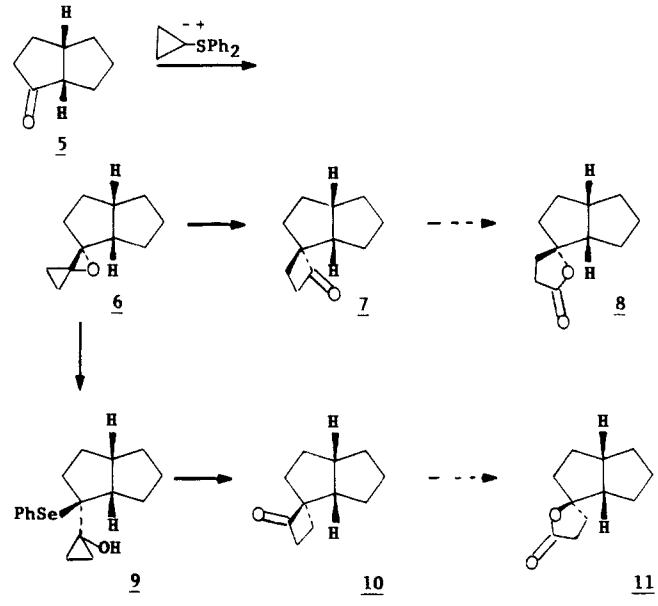


(2)

4

ential functionality in each five-membered ring to allow each ring to be elaborated independently, (2) it is readily available in high yield from cycloocta-1,3-diene, and (3) an opportunity for asymmetric synthesis may exist if a method for obtaining the epoxide optically pure may be found. Viewing the alcohol-containing ring of **4** (i.e., A) as the remaining cyclopentyl ring in **2** and **3** and the olefin bearing ring (B) as becoming the pyranyl ring, our problems for structural elaboration require developing a method for stereocontrolled spiroannulation of an alkylidenebutyrolactone ring onto the oxygen-bearing carbon of ring A simultaneous with the introduction of a double bond as well as inserting a carbon at the allylic position of ring B and maintaining the location of the double bond.[17]

Substitutive Spiroannulation. Using our previously described spiroannulation technique[18-20] based upon the readily available oxaspiropentanes such as **6** derived from ketone **5**, direct Lewis acid-catalyzed rearrangement (eq 3) produces cyclobutanone **7**

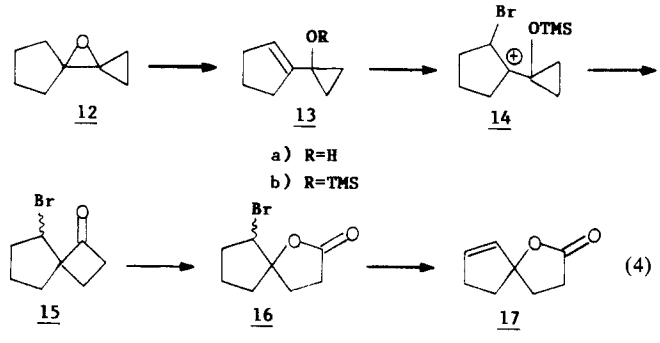


5 **6** **7** **8** **9** **10** **11**

(3)

(**7**:**10** = 96:4) which corresponds to the γ-butyrolactone of incorrect stereochemistry for **2** and **3**. Our stereoreversal procedure[21] in which the oxaspiropentane is opened with sodium phenylselenide to give **9** followed by MCPBA oxidation to induce ring enlargement does give predominantly the cyclobutanone **10** (eq 3, **10**:**7** = 88:12) whose corresponding lactone **11** would possess the stereochemistry of **3** and **4**. However, this method does not provide for introduction of the additional double bond.

We therefore decided to develop an alternative approach that could provide for introduction of a double bond as well as provide the correct stereochemistry. In this strategem, the oxaspiropentane such as **12**, available from cyclopentanone, is isomerized to the



12 **13** **14** **15** **16** **17**

(4)

vinylcyclopropanol **13a** with base.[18] Quenching the reaction with TMS–Cl provides the silyl ether **13b** directly. Use of a Br⊕ equivalent to induce rearrangement puts the proper structural elements into place for formation of an unsaturated spirolactone. Because of the sensitivity of such vinylcyclopropanols to acid-catalyzed rearrangement to cyclobutanone, a Br⊕ source free of HBr such as dioxane–bromine complex is mandated. Because of the chemical instability of **15**, it is immediately subjected to Baeyer–Villiger oxidation to give the bromolactone **16** as a 1:1 stereoisomeric mixture as determined by NMR spectroscopy which may be separated by TLC. Completion of the sequence occurs upon refluxing a benzene solution of **16** with DBU to give the desired unsaturated spirolactone **17**.

While the lack of stereocontrol looks ominous, we must consider whether the nature of the substrate may play a role. The bicyclic system **19**, available in identical fashion as above from the ketone **18**,[26] which in turn is obtained by Swern oxidation of **5**, provides a more valid test of the stereocontrol as well as chemoselectivity.

(13) For some recent examples, see: (a) Sakan, T.; Abe, K. *Tetrahedron Lett.* **1968**, 2471. (b) Sakan, T.; Murai, F.; Isoe, S.; Hyeon, S. B.; Hayashi, Y. *Nippon Kagaku Zasshi* **1969**, *90*, 507. (c) Matthews, R. S.; Whitesell, J. K. *J. Org. Chem.* **1975**, *40*, 3312. (d) Au-Yeung, B.-W.; Fleming, I. *Chem. Commun.* **1977**, *81*. (e) Whitesell, J. K.; Matthews, R. S.; Helbing, A. M. *J. Org. Chem.* **1978**, *43*, 784. (f) Obara, H.; Kimura, H.; Suzuki, M.; Onodera, J. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3610. (g) Whitesell, J. K.; Matthews, R. S.; Minton, M. A.; Helbing, A. M. *J. Am. Chem. Soc.* **1981**, *103*, 3468. (h) Hiroi, K.; Muira, H.; Kotsuji, K.; Sato, S. *Chem. Lett.* **1981**, 559. (i) Callant, P.; Ongena, R.; Vandewalle, M. *Tetrahedron* **1981**, *37*, 2085. (j) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1981**, *103*, 5972. (k) Fleming, I. *Tetrahedron Suppl.* **1981**, 13. (l) Hewson, A. T.; MacPherson, D. T. *Tetrahedron Lett.* **1983**, *24*, 5807. (m) Kon, K.; Isoe, S. *Helv. Chim. Acta* **1983**, *66*, 755. (n) Wender, P. A.; Dreyer, G. B. *Tetrahedron Lett.* **1983**, *24*, 4543. (o) Caille, J. C.; Bellamy, F.; Guiland, R. *Tetrahedron Lett.* **1984**, *25*, 2345. (p) Ritterskamp, P.; Demuth, M.; Schaffner, K. *J. Org. Chem.* **1984**, *106*, 1092. (q) Trost, B. M.; Nanninga, T. N. *J. Am. Chem. Soc.* **1985**, *107*, 1293.

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(15) Apparu, M.; Barrelle, M. *Tetrahedron* **1978**, *34*, 1541. Whitesell, J. K.; Matthews, R. S.; Wang, P. K. S. *Synth. Commun.* **1977**, *7*, 355.

(16) This compound served as the starting material for Whitesell's synthesis of sarracenin, see ref 25e.

(17) For preliminary reports of portions of this work, see: Trost, B. M.; Mao, M. K.-T. *Tetrahedron Lett.* **1980**, *21*, 3523. Trost, B. M.; Buhlmayer, P.; Mao, M. *Tetrahedron Lett.* **1982**, *23*, 1443. Trost, B. M.; Mao, M. K.-T. *J. Am. Chem. Soc.* **1983**, *105*, 6753.

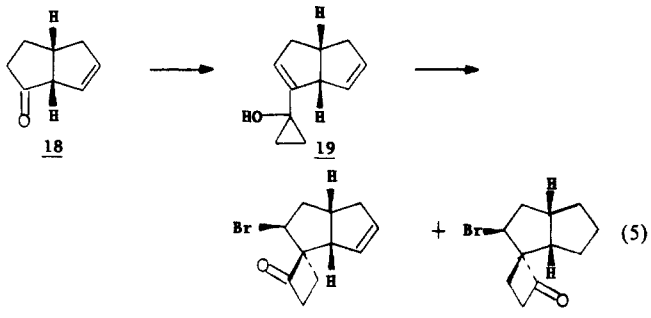
(18) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 289, 5311. Trost, B. M.; Kurozumi, S. *Tetrahedron Lett.* **1974**, *1929*. For alternative approaches, see: Girard, C.; Amice, P.; Barnier, J. P.; Conia, J. M. *Tetrahedron Lett.* **1974**, 3329. Girard, C.; Conia, J. M. *J. Chem. Res.* **1978**, 183. Salaun, J.; Allivier, J. *Nouv. J. Chim.* **1981**, *5*, 587.

(19) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321.

(20) For alternative reagents, see: Trost, B. M.; Keeley, D. E. *J. Am. Chem. Soc.* **1976**, *98*, 248. Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1979**, *99*, 3088. Halanzy, S.; Lucchetti, J.; Krief, A. *Tetrahedron Lett.* **1978**, 3971. Cohen, T.; Matz, J. R. *Ibid.* **1981**, *22*, 2455. Gadwood, R. C. *Ibid.* **1984**, *25*, 5851.

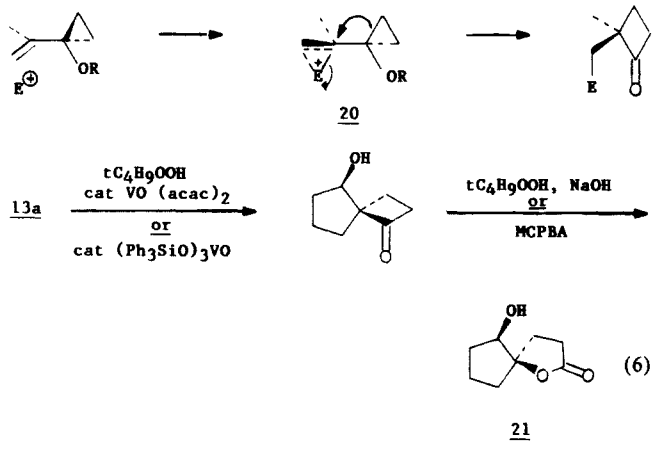
(21) Trost, B. M.; Scudder, P. H. *J. Am. Chem. Soc.* **1977**, *99*, 7601.

Again, a diastereomeric mixture of bromocyclobutanones results (eq 15). Nevertheless, the vinylcyclopropanol reacts

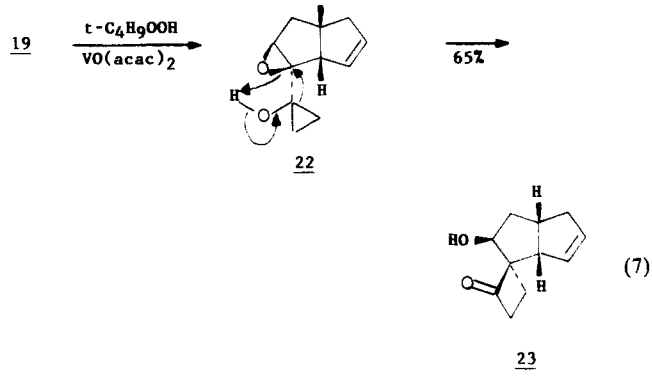


exclusively—indicative of the activating influence of the cyclopropanol fragment on the conjugating double bond.

A bridged electrophile as in **20** should force migration trans to the electrophile and thereby improve the distereoselectivity. Indeed, treating **13a** with *tert*-butyl hydroperoxide in the presence of a catalytic amount of vanadyl acetoacetonoate[23] in toluene at −10 °C gives essentially a single hydroxycyclobutanone (eq 6).

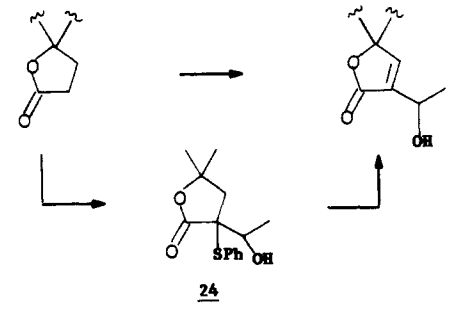


Alternatively, tris(triphenylsilyl)vanadate[24] may be used as a catalyst. Baeyer–Villiger oxidation with MCPBA or basic *tert*-butyl hydroperoxide produces a homogeneous hydroxyl lactone **21**. Application of this hydroxylation to **19** produces the corresponding hydroxycyclobutanone **23** as an 8:1 diastereomeric mixture (eq 7). The fact that the methine proton adjacent to

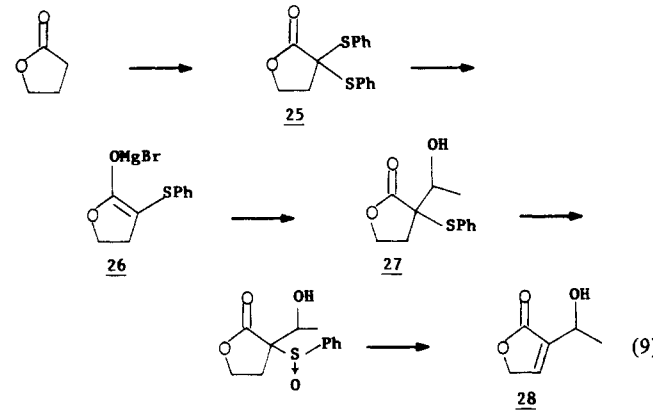


the hydroxyl group exhibits identical coupling patterns [dd, J = 8.5 and 6.0 at δ 4.4 (minor) and δ 4.2 (major)] suggests the stereochemistry at this center is the same in both. The high field shift of the carbon of the β-methylene group of the cyclobutanone in the ^{13}C spectrum of the major isomer (δ 18.5) indicates this carbon is cis to the adjacent ring as depicted.[21] The good diastereoselectivity can be ascribed to the stereocontrolled acid-catalyzed rearrangement of epoxide **22** to the desired hydroxycyclobutanone. In contrast to the use of *tert*-butyl hydroperoxide catalyzed by vanadyl acetoacetonoate, MCPBA gives only a 2:1 diastereomeric mixture—presumably because of the presence of an acid, *m*-chlorobenzoic acid, which induces formation of an open cyclopropyl carbinyl cation.

Desulfenylative Enolization: A Base Free Route to Enolates of β-Keto Sulfides. The formation of a 2-(1′-hydroxyethyl)butenolide from the saturated lactone as in eq 8 is required in the elaboration



of **2** and **3**. The aldol product of a β-keto sulfide and acetaldehyde as in **24** constitutes an ideal intermediate. Sulfenylation of **17**[25,26] provides initially the α-phenylthio lactone and also its corresponding sulfoxide by subsequent oxidation. All attempts to effect an aldol condensation failed.[27] The source of this failure is attributed to the enolate generation step. In order to assure a favorable aldol equilibrium, a more covalent metal such as zinc or magnesium is preferred; however, a direct method for the formation of a zinc or magnesium enolate is normally possible with only highly acidic systems like 1,3-dicarbonyl compounds. α-Halocarbonyl compounds can serve as precursors of such enolates upon treatment with metal (O) but would not be a viable approach to sulfenylated enolates. The usual facility with which lactones undergo bissulfenylation offered a new opportunity to generate the requisite enolates.[26,28,29] Bissulfenylation of γ-butyrolactone (LDA, $PhSSO_2Ph$) gives an 87% yield of **25**. The



ease with which a nucleophile like thiolate desulfenylates such bissulfenylated carbonyl compounds suggests that other nucleophiles like Grignard reagents would preferentially desulfenylate **25** to produce a clean solution of the magnesium enolate **26** with only an innocuous thioether as a byproduct. Indeed, treating **25**

(22) Billimoria, J. D.; Maclagan, N. F. *J. Chem. Soc.* **1954**, 3257.
(23) Sheng, M. N.; Zajacek, J. G. *J. Org. Chem.* **1968**, *33*, 588. Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136. For a review, see: Sheldon, R. A. In *Aspects of Homogeneous Catalysis*; Manfred, C., Ed.; Monotipia Rossi-Santi-Milano, Vol. IV, p 19. Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.
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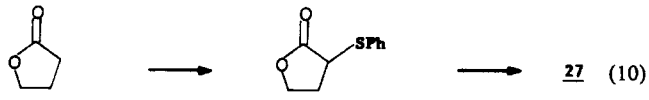
(25) For reviews, see: Trost, B. M. *Acc. Chem. Res.* **1978**, *11*, 453. *Chem. Rev.* **1978**, *78*, 363.
(26) Trost, B. M.; Salzmann, T. N. *J. Am. Chem. Soc.* **1973**, *95*, 6840. Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.
(27) However, see: Kunieda, N.; Nokami, J.; Kinoshita, M. *Tetrahedron Lett.* **1974**, 3997. Kunieda, N.; Nokami, J.; Kinoshita, M. *Tetrhedron Lett.* **1975**, 2841. Bonjouklian, R.; Ganem, B. *Tetrahedron Lett.* **1977**, 2835. Hoye, T.; Kurth, M. J. *J. Org. Chem.* **1967**, *32*, 1901.
(28) Trost, B. M.; Rigby, J. *J. Org. Chem.* **1978**, *43*, 2938.
(29) Bissulfenylation of ketones,[26,30] esters,[26,30b,c] lactams,[31] imino ethers,[32] and nitriles[33] are also known.

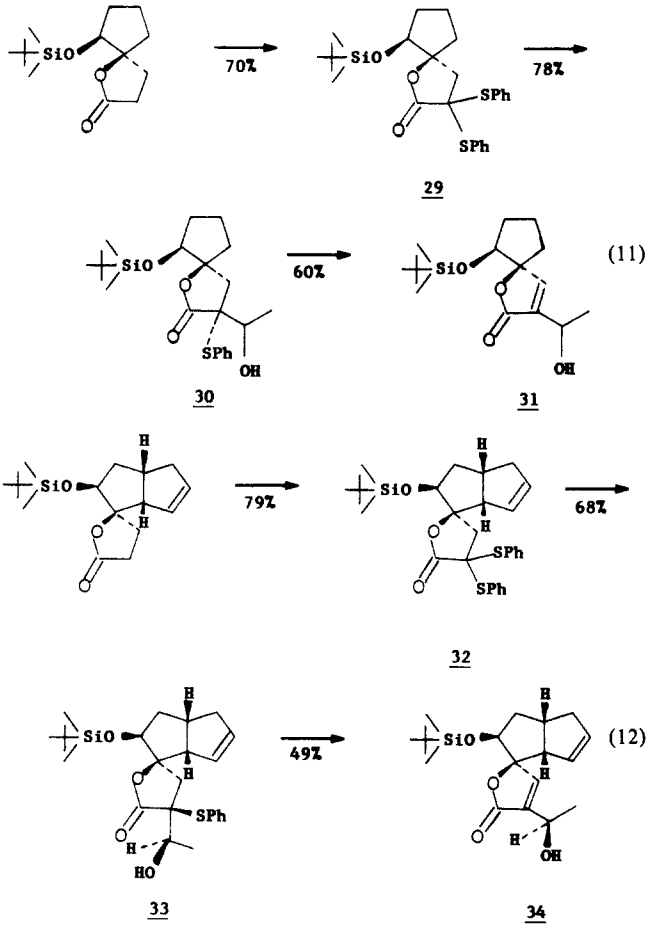
with ethylmagnesium bromide followed by acetaldehyde gives a 98% yield of the aldol adduct **27**. For comparison in this case, γ-butyrolactone may be monosulfenylated but in only 55% yield. Aldol condensation via the zinc enolate (LDA then $ZnCl_2$) to give **27** proceeds in 67% yield. Thus, **27** is available in 85% yield via the method outlined in eq 9 but in only 37% yield via the one of eq 10. Oxidation with MCPBA followed by thermolysis to



27 (10)

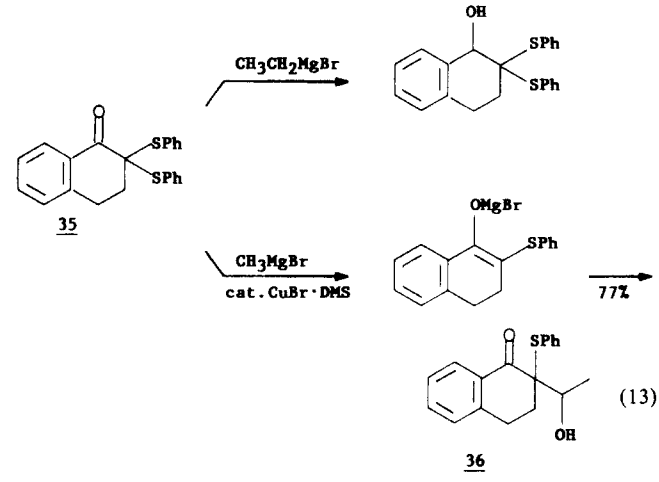
butenolide **28** completes the sequence.[26] The regioselectivity of the sulfoxide elimination is noteworthy. In a similar substrate lacking the hydroxyl group in the side chain, 10–20% elimination in an exocyclic fashion is observed.[34] As pointed out previously, the polar effect of the hydroxyl group enhances the elimination away from itself.[26,35]

This same approach applies to the *tert*-butyldimethylsilyl ether of lactones **21** (eq 11) and **23** (eq 12) although the yields have



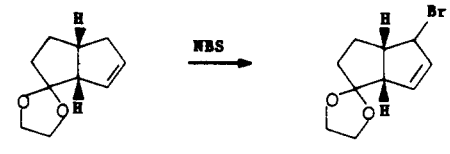
not been optimized in these cases. It is interesting to note that **30** appears to be a mixture of only two of four possible isomers. Since **31** is also a mixture of only two isomers, the former compound must consist of both epimeric alcohols but must be only one isomer at the sulfur-bearing carbon. The depicted stereochemistry of this center corresponds to attack on the face of the enolate by acetaldehyde away from the silyloxy group—an argument simply reflecting steric approach control. In the case of **33**, again only two isomers are seen in a surprisingly high 6:1 ratio. The diastereomer depicted for the major isomer which is a crystalline solid, mp 119–121 °C is based on (1) approach of the acetaldehyde on the less hindered face of the enolate as determined from inspection of molecular models and (2) chelation-controlled aldol reaction.

The extension to ketone enolates would expand utility of the approach. The bissulfenylated ketone **35**, available in 70% yield from α-tetralone, surprisingly suffers reduction upon exposure to ethylmagnesium bromide. Anticipating that such a reduction



involves a β-hydride transfer from the Grignard reagent, switching the Grignard reagent to one lacking such hydrogens should preclude such a process. Phenylmagnesium bromide leads to no reaction, and methylmagnesium bromide produces only 10% of the desired aldol product **36**. Increasing the thiophilicity of the metal by simply adding a catalytic amount of cuprous bromide–dimethyl sulfide complex[37,38] smoothly generates the desired enolate as determined by the isolation of a 77% yield of the aldol product.

Allylic Alkylation. The final structural problem to resolve is introduction of a one carbon unit without allyl inversion in **5**. Initially, attention was focused on the simplest strategy of displacement of an allylic bromide as in **38**; however, bromide displacement failed.



37 **38**

An alternative strategy envisions use of a [3.3] or [2.3] rearrangement of an allylic alcohol such as **39**, which is readily available by MCPBA epoxidation (87%) and lithium diisopropylamide iosomerization (81%). Use of Ireland conditions for an ester enolate Claisen rearrangment with either **40a** or **40b** fails.[39] On the other hand, a [2.3]sigmatropic rearrangement

(30) (a) Hayashi, S.; Fumkawa, M.; Fujimo, Y.; Matsukura, H. *Chem. Pharm. Bull.* **1969**, *17*, 419. (b) Watanabe, M.; Shirai, K.; Kumamoto, T. *Chem. Lett.* **1975**, 855. (c) Kumamoto, T.; Kobayashi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 866. (d) Mukaiyama, T.; Kobayashi, S.; Kamro, K.; Takei, H. *Chem. Lett.* **1972**, 237. (e) Trost, B. M.; Salzmann, T. N. *J. Org. Chem.* **1975**, *40*, 148. (f) Schultz, A. G.; Lee, Y. K.; Berger, M. H. *J. Am. Chem. Soc.* **1977**, *99*, 8065. (g) Nagao, Y.; Kaneko, K.; Kawabata, K.; Fujita, E. *Tetrahedron Lett.* **1978**, 5021.

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(33) Brattesani, D. N.; Heathcock, C. H. *Tetrahedron Lett.* **1974**, 2279.

(34) Trost, B. M.; Leung, K. K. *Tetrahedron Lett.* **1975**, 4197.

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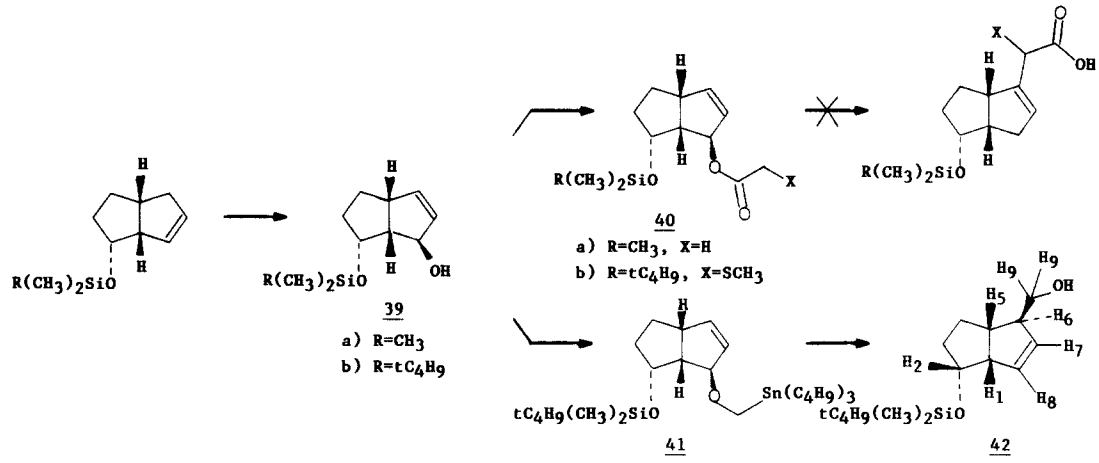
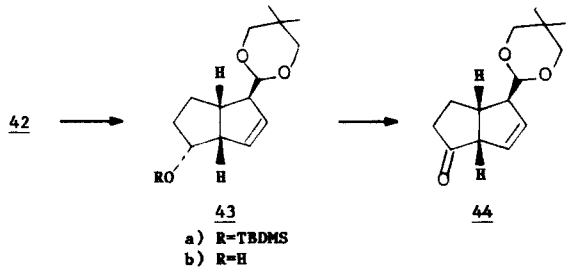
(37) Normant, J. F.; Cahiez, G.; Bourgain, M.; Chuit, C.; Villieras, J. *Bull. Soc. Chim. Fr.* **1974**, 1656. Alexakis, A.; Noumant, J.; Villieras, J. *Tetrahedron Lett.* **1976**, 3461. Westmijze, H.; Kleijn, H.; Vermeer, P. *Tetrahedron Lett.* **1977**, 2023. Marfat, A.; McGuirk, P. R.; Kramer, R.; Helquist, P. *J. Am. Chem. Soc.* **1977**, *99*, 253.

(38) For generation of enolates using stoichiometric organocopper chemistry and α-heteroatom-substituted ketones, see: (bromide) Posner, G. H.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 3076. (chloride) Depres, J.-P.; Greene, A. E. *J. Org. Chem.* **1980**, *45*, 2037. (sulfoxide) Posner, G. H.; Mallamo, J. P.; Miura, K. *J. Am. Chem. Soc.* **1981**, *103*, 2886. (sulfone) Posner, G. H.; Kogan, T. P.; Hulce, M. *Tetrahedron Lett.* **1984**, *25*, 383.



(14)

of the lithiomethyl ether derived by transmetalation of **41** with *n*-butyllithium[40] proceeds in almost quantitative yield to give the alcohol **42** (eq 14).[41] To complete the synthesis of a suitable precursor for the substitutive spiroannulation, **42** is subjected to Swern oxidation,[42] and the resultant aldehyde is ketalized to give

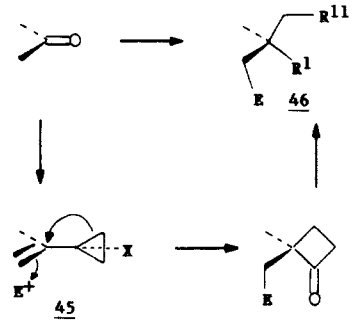


(15)

43. Desilylation with aqueous acid followed by another Swern oxidation completes the synthesis of the bicyclic ketone **44**. This eleven step synthesis of **44** proceeds in 21% overall yield from cycloocta-1,3-diene.

Discussion

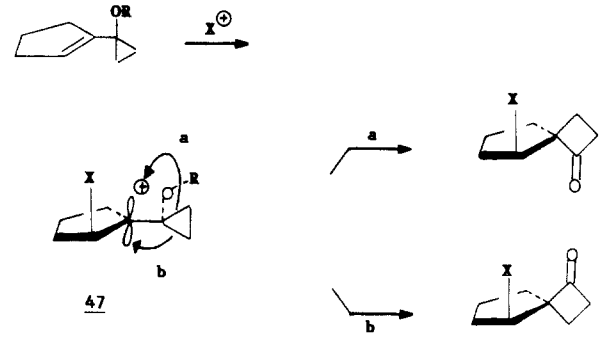
The substitutive spiroannulation offers a new dimension to the spiroannulation reactions previously developed.[43] In the broadest sense a simple ketone may be functionalized simultaneously at the α-carbon as well as the carbonyl carbon with stereocontrol as summarized in eq 16. Such a concept can extend to a variety



(16)

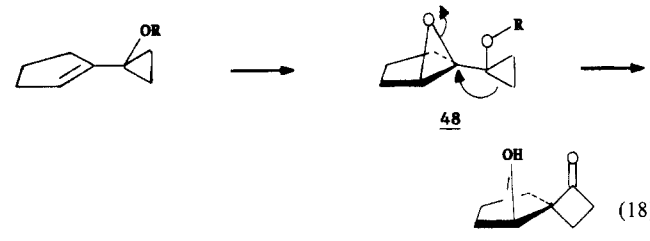
of cyclopropyl systems but would always benefit if X in **45** is an electron-releasing heteroatom as in our case where it is oxygen.[44-47]

The stereocontrol in these reactions is exceptionally sensitive to the electrophile. With bromine and peracids, open ions as depicted in **47**, eq 17, may be responsible for the diastereomeric



(17)

mixtures observed. The neutral conditions for epoxidation feasible with the transition metal-catalyzed reactions permit ring enlargement of the cyclopropane concommitant with epoxide opening as depicted in **48** to give clean stereochemistry (eq 18). While



(18)

our use of tris(triphenylsilyl)vanadate was dictated by solubility considerations, its success herein merits further consideration of the catalytic properties of this vanadium ester. Even in these cases, the epoxides such as **48** are not observed. Obviously, their rearrangement is very facile—a fact that attests to the strong driving force for relief of strain energy. The resultant β-functionalized cylclobutanones then possess all the versatility of the cyclobutanones such as ring expansion to γ-butyrolactones as practiced here but also to cyclopentanones[18,42] or larger rings as well as ring cleavage reactions[43,48] giving the general structural equivalent represented by **46**. In addition, since the electrophile

(39) For use of such a strategy with a lactate ester see Whitesell's synthesis of sarracenin, ref 25e.
(40) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927.
(41) A detailed NMR analysis of **42** is summarized in Table I which appears in the appendix in the microfilm edition.
(42) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.
(43) For reviews, see: Trost, B. M. *Acc. Chem. Res.* **1974**, *7*, 85. *Pure Appl. Chem.* **1975**, *43*, 563. *Gazz. Chim. Ital.* **1984**, *114*, 139. *Top. Curr. Chem.*, in press.
(44) For pioneering work with the parent vinylcyclopropanol, see: Wasserman, H. H.; Hearn, M. J.; Cochoy, R. E. *J. Org. Chem.* **1980**, *45*, 2874.
(45) For a proton as an electrophile see ref 30 and 55 as well as Salaun, J.; Garnier, B.; Conia, J. *Tetrahedron* **1974**, *30*, 1413. Bourelli-Wargnier, F. *Tetrahedron Lett.* **1974**, 1589.
(46) For carbon electrophiles see ref 55 and Trost, B. M.; Brandi, A. *J. Am. Chem. Soc.* **1984**, *106*, 5041.
(47) For a review, see: Conia, J.; Robson, M. J. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 473.
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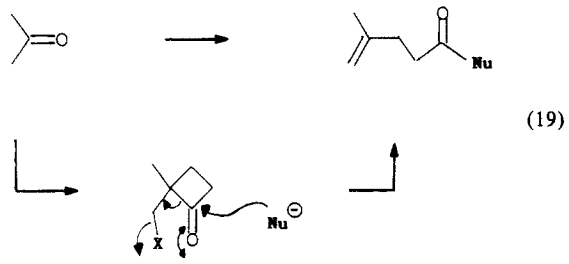
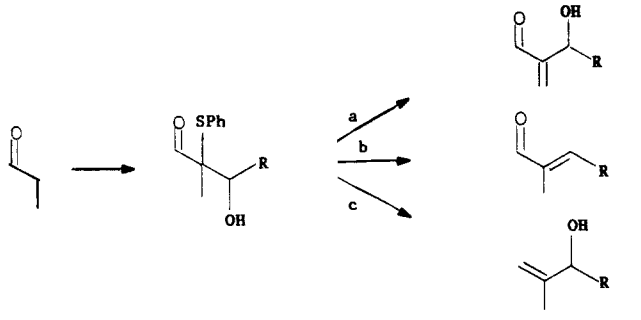
can be a leaving group such as Br or made into a leaving group as in the case of OH, a fragmentation as depicted in **49** is also possible (eq 19). The secoalkylation sequence now extends to all ketones not just α,β-epoxy or cyclopropyl ketones.[43,49]



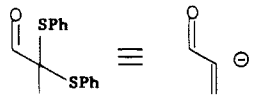
(19)

49

The new enolate generation sequence corresponds to an efficient approach to elaborate α-(hydroxyalkyl)-α,β-unsaturated systems as shown in eq **20a**. In this way, the bissulfenylated carbonyl compounds correspond to a synthon for **50**.[50]

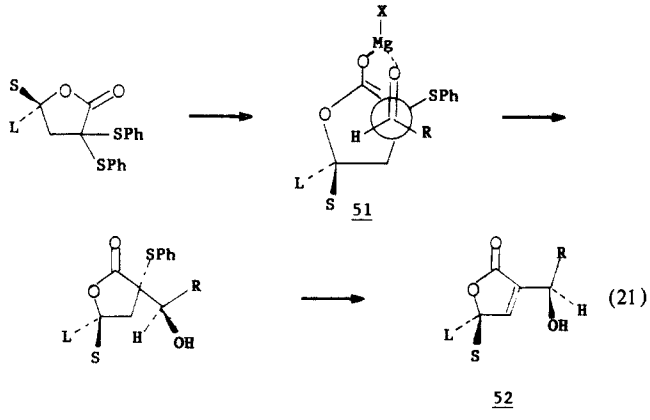


(20)



50

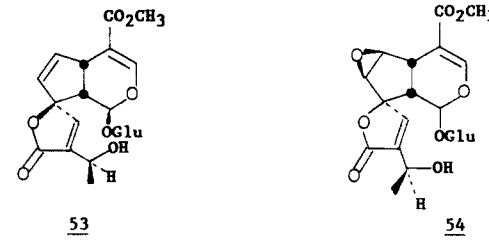
A bonus arises in the case of the bicyclic ketone series where **33** (eq 12) is predominantly one diastereomer. Attack on the enolates of such lactones trans to the bulkier group at C(4) has previously been observed.[51] Combining diastereofacial selectivity with a chelation model for the aldol condensation[52] as in **51** (eq 21) suggests that the stereochemistry present at C(4) is transmitted



(21)

51 52

via C(2) to the side chain C(2′). Since the stereochemistry at C(2) is subsequently obliterated, the net effect is to control 1,4-stereochemistry. The use of the carbon-bearing sulfur as a temporary diastereochemical relay point to transmit stereochemical information over longer distances may be a helpful general technique. We had previously noted a similar effect in the case of an α-sulfonyl macrolactone.[53] Using such a principle, this synthetic strategy extrapolates to iridoids such as plumieride[23,48] **53** and plumepoxide[23] **54** as well as others such as allamcidin[23] whose stereochemistry has yet to be established.



53 54

In addition, β-hydroxy- and β-keto sulfides can also be equivalents of olefins. The sequence then corresponds to paths b and c of eq 20. The efficiency of the aldol reaction under these conditions is believed to reflect the absence of any amines, the normal byproducts in most enolate generating reactions. Such amines can serve as alternative complexing agents for metals such as magnesium and thereby inhibit their ability to function effectively as Lewis acids in the aldol condensation. While it is clear that the presence of such amines in most cases has little deleterious effect, their presence cannot be ignored in those cases which may be particularly difficult. The need sometimes to resort to enol acetates and enol silyl ethers as enolate precursors is presumably a reflection of this problem. The lower reactivity of the enolates of β-keto sulfides may be the source of their sensitivity to cleanliness of the reaction mixtures in aldol condensations.

In the particular case of lactones, this method has an additional advantage. Controlling the sulfenylation so that it stops at the monosulfenylation stage can be tedious. On the other hand, bissulfenylation is simple and proceeds in high yield. Thus, the ability to use the bissulfenylated lactone directly for enolate generation increases the efficiency of this approach.

We believe these methods may be of general utility. Their development was crucial in the ultimate successful execution of an efficient synthesis of the allamandin family of iridoids.

Experimental Section

General Methods. All reactions were run under an inert atmosphere, the apparatus was flamed dried immediately prior to use, and the solvents were freshly distilled. For details see microfilm edition.

Preparation of 2-(1′-Hydroxycyclopropyl)-*cis*-bicyclo[3.3.0]oct-2,7-diene (19). *cis*-Bicyclo[3.3.0]oct-7-en-2-one (**18**) (2.04 g, 16.7 mmol) was dissolved in 15 mL of Me_2SO with 5.5 g (17.5 mmol) of cyclopropyldiphenylsulfonium fluoroborate and stirred until a clear solution was obtained. Powdered potassium hydroxide (1.22 g, 21.7 mmol) was added in 4 portions over a period of 45 min. The solution was stirred for a total of 5 h at room temperature to give a yellow cloudy solution. It was extracted with 3 × 80 mL of pentane. The pentane extracts were combined and washed with 60 mL of saturated aqueous sodium bicarbonate solution to remove traces of remaining Me_2SO. After drying over sodium sulfate and concentrating in vacuo at 0 °C, the crude oil was purified by Kugelrohr distillation (70 °C at 1.5 mmHg) to give 2 g (75%) of oxaspiropentane as a colorless oil: NMR ($CDCl_3$) δ 5.9–5.6 (m, 2 H), 3.2–1.4 (m, 8 H), 1.1–0.9 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 131.19, 129.10, 73.83, 62.35, 52.96, 40.76, 40.38, 31.99, 31.60, 3.33 ppm; calcd for $C_{11}H_{14}O$ 162.1045, found 162.1041.

To 33 mmol of lithium diethylamide in 20 mL of pentane at −78 °C was added 2.0 g (12.4 mmol) of oxaspiropentane in 10 mL of pentane. The reaction was warmed to room temperature for 3.5 h and poured into 30 mL of cold (0 °C) saturated aqueous ammonium chloride solution. It was extracted with 3 × 80 mL of ether, and the extracts were dried (anhydrous sodium sulfate) and concentrated in vacuo. Crude product was purified by preparative TLC (20% ethyl acetate in hexane) to yield 1.4 g (70%) of cyclopropanol **19**: NMR (CCl_4) δ 5.9–5.7 (m, 1 H), 5.7–5.5 (m, 1 H), 5.2 (d of d, J = 4, 2 Hz, 1 H), 3.7–3.5 (m, 1 H),

(49) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 4777. Trost, B. M.; Frazer, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 6124. Trost, B. M.; Bogdanowicz, M. J.; Frazee, W. J.; Salzmann, T. N. *J. Am. Chem. Soc.* **1980**, *102*, 7910.

(50) Smith, A. B., III.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855.

(51) Takano, S.; Yonaga, M.; Morimoto, M.; Ogasowara, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 305.

(52) For a review, see: Heathcock, C. H. In *Comprehensive Carbanion Chemistry*; Durst, T., Buncel, E., Eds.; Elsevier: Amsterdam, 1983; Vol. II.

(53) Trost, B. M.; Brickner, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 568.

3.1–2.4 (m, 3 H), 2.4–1.9 (m, 3 H) 0.8 (pt, J = 2 Hz, 2 H), 0.7 (pt, J = 2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 147.23, 131.84, 129.35, 122.83, 58.08, 54.38, 40.36, 40.19, 14.80, 13.97 ppm; IR (CCl_4) 3590, 3400, 1580 cm^{-1}; calcd for $C_{11}H_{14}O$ 162.1045, found 162.1044.

Preparation of 3-Bromo-*cis*-bicyclo[3.3.0]oct-7-ene-2-spiro(2′-oxocyclobutane). To 79 mg (0.49 mmol) of vinylcyclopropanol **19** in a mixture of 1 mL of dichloromethane and 0.2 mL of triethylamine at −78 °C was added 180 mg (0.73 mmol) of bromine–dioxane[22] complex in 1 portion. A precipitate started appearing immediately. After stirring for 0.5 h, it was poured into 10 mL of saturated aqueous sodium sulfite solution and extracted with 3 × 20 mL of ether. The ether extracts were combined and dried over sodium sulfate. The solution was filtered and concentrated in vacuo. Purification by preparative TLC (50% ethyl acetate in hexane) yielded 88 mg (75%) of product (R_f 0.83). NMR shows a triplet at δ 3.4 and a doublet of doublets at δ 4.0, each with an integration of 0.5 proton which indicates the product consists of a mixture of stereoisomers in approximately 1:1 ratio: NMR (CCl_4) δ 5.8–5.4 (m, 2 H), 4.3 (t, J = 6 Hz, 0.5 H), 4.0 (d of d, J = 12, 8 Hz, 0.5 H), 3.6–1.8 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 207.52, 133.65, 132.33, 128.13, 128.02, 77.62, 59.46, 55.76, 53.88, 51.34, 44.06, 43.39, 43.23, 42.18, 41.85, 39.64, 38.76, 37.49, 23.24, 17.80; IR (CCl_4) 1775, 1450, 1390 cm^{-1}; calcd for $C_{11}H_{13}OBr$ 240.0150, found 240.0121.

Preparation of Spiro[4.3]-1-oxo-5-hydroxyoctane. Method A. To vinylcyclopropanol **13a** (400 mg, 3.22 mmol) in 2.5 mL of toluene at −10 °C was added dry (see notes in preparation of **23**) *tert*-butyl hydroperoxide (0.9 mL, approximately 9.7 mmol) followed immediately by the addition of 26 mg (approximately 3%) of vanadium(IV) oxide bis(2,4-pentanedionate). A purple color appeared immediately. After stirring for 2.75 h at −10 °C, the color of the reaction faded somewhat, and TLC indicated no starting material remained. The reaction was worked up by pouring into 10 mL of cold (0–5 °C) saturated sodium bisulfite solution and extracted with 3 × 30 mL of ethyl acetate. The ethyl acetate extracts were combined, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Crude product was purified by preparative TLC (50% ethyl acetate in hexane) to yield 190 mg (42%) of clear oil: NMR ($CDCl_3$) δ 4.3 (t, J = 5 Hz, 1 H), 3.4 (ps, 1 H), 3.0 (t, J = 9 Hz, 2 H), 2.7–1.6 (m, 8 H); IR (CCl_4) 3620, 3580, 1765 cm^{-1}; calcd for $C_8H_{12}O_2$ 140.0837, found 140.0838.

Method B. Dry *tert*-butyl hydroperoxide (0.7 mL, 7.2 mmol) was added to 300 mg (2.41 mmol) of vinylcyclopropanol **13a** in 2 mL of toluene at room temperature followed immediately by 64 mg (3%) of tris(triphenylsilyl) vanadate.[24] After stirring for 50 min at room temperature, TLC indicated no starting material remained, and the reaction was worked up as in method A. Similar purification by preparative TLC gave 150 mg (44%) of product.

Preparation of Spiro[4.4]-6-hydroxy-1-oxanonan-2-one (21) Method A.[54] A 72% aqueous *tert*-butyl hydroperoxide (0.94 mL, 7 mmol) solution was added dropwise to 330 mg (2.35 mmol) of spiro[4.3]-1-oxo-5-hydroxyoctane in 10 mL of THF at 0 °C followed by 0.5 mL of 10% aqueous sodim hydroxide solution. The solution was stirred at 0 °C for 1 h, then poured into 10 mL of saturated aqueous sodium bisulfite solution, and extracted with 3 × 20 mL of ethyl acetate. The organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo. Purification by preparative TLC (50% ethyl acetate in hexane, R_f 0.34) yielded 160 mg (44%) of product: NMR ($CDCl_3$) δ 4.1 (t, J = 5.5 Hz, 1 H), 3.9 (br s, 1 H) 2.8–2.5 (m, 2 H), 2.5–1.6 (m, 8 H); IR (CCl_4) 3420, 1770 cm^{-1}; calcd for $C_8H_{12}O_3$ 156.0786, found 156.0783.

Method B. Solid sodium bicarbonate (662 mg, 7.9 mmol) was added in 1 portion to 850 mg (6 mmol) of spiro[4.3]-1-oxo-5-hydroxyoctane dissolved in 10 mL of methylene chloride at 0 °C followed by 1.6 g (7.9 mmol) of 85% MCPBA. After stirring at 0 °C for 1 h, the solution was poured into a mixture of 10 mL of saturated aqueous sodium bicarbonate and 2 mL of saturated sodium sulfite solution and extracted with 3 × 50 mL of ethyl acetate. The organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. The remaining residue was purified by preparative TLC (50% ethyl acetate in hexane) to yield 660 mg (60%) of the product as a clear oil.

Preparation of (1*S,2*R**)-3-Hydroxy-*cis*-bicyclo[3.3.0]oct-7-ene-2-spiro(2′-oxocyclobutane) (23). Method A.** Dry *tert*-butyl hydroperoxide (1.18 mL, 12.34 mmol) in 2 mL of toluene was added to 1 g (6.17 mmol) of a vinylcyclopropane **19** in 8 mL of dry toluene at −10 °C followed immediately by the addition of 32 mg (0.12 mmol) of vanadium(IV) oxide bis(2,4-pentanedionate). A purple solution was obtained. The reaction was stirred at −10 °C for 3 h and poured into 20 mL of cold (5–10 °C) saturated aqueous sodium bisulfite solution. Extraction was done with 3 × 60 mL of ethyl acetate. The extracts were combined, dried over sodium sulfate, and concentrated in vacuo. Purification by preparative TLC (20% ethyl acetate in hexane) gave 590 mg (65%) of product (R_f 0.21). The NMR spectrum shows two absorption patterns of doublet of doublets at δ 4.4–4.0 in approximately 1:8 ratio indicating the product was contaminated by 10–15% of a minor isomer: NMR ($CDCl_3$) δ 5.8–5.6 (m, 1 H), 5.6–5.4 (m, 1 H), 4.3 (d of d, J = 8.5, 6.0 Hz, 0.11 H), 4.1 (d of d, J = 7.6, 5.8 Hz, 0.89 H), 3.5–3.3 (m, 1 H), 3.0–1.5 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 214.43., 132.55, 128.84, 79.17, 76.85, 53.61, 43.23, 41.30, 41.02, 36.88, 18.49 ppm; IR (CCl_4) 3610, 3500, 1775 cm^{-1}. calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0983.

Note. The dryness of *tert*-butyl hydroperoxide is critical for the success of this reaction. The method employed to dry *tert*-butyl hydroperoxide was as follows: a 75-mL portion of aqueous 72% *tert*-butyl hydroperoxide in a 125-mL Erlenmeyer flask was shaken with approximately 10 g of powdered anhydrous sodium sulfate at room temperature for 1–2 min and then decanted. This procedure was repeated with another 5 g of powdered anhydrous sodium sulfate followed by 3 × 5 g of magnesium sulfate. The final solution was filtered through a glass funnel equipped with a glass wool plug to remove traces of remaining solid to give approximately 20 mL of viscous solution. This solution solidifies and can be stored below −10 °C for prolonged periods. During usage, this material is melted at room temperature, and the desired amount can be syringed out and mixed with the appropriate amount of solvent (if necessary, this solution can be further dried with a small amount of magnesium sulfate before use).

Preparation of 2,2-Bis(phenylthio)-γ-butyrolactone (25). γ-Butyrolactone (500 mg, 5.8 mmol) was added to a solution of 6.96 mmol of lithium diethylamide at −78 °C, and the resultant solution was stirred for 1 h at −78 °C. A solution of 3 g (12.2 mmol) of phenyl (phenylthio)sulfonate in 7 mL of THF was added, and the reaction was raised to −25 °C and stirred for another hour. It was poured into 50 mL of saturated aqueous ammonium chloride solution and extracted with 3 × 50 mL of ether. The ether extracts were dried (anhydrous sodium sulfate), and solvent was removed in vacuo. Purification by preparative TLC (20% ethyl acetate in hexane) gave 1.53 g (87%) of the bissulfide (R_f 0.33): NMR ($CDCl_3$) δ 7.7–7.5 (m, 4 H), 7.4–7.2 (m, 6 H), 4.1 (t, J = 6 Hz, 2 H), 2.4 (t, J = 6 Hz, 2 H); IR (CCl_4) 1780, 1470, 1440, and 1370 cm^{-1}; calcd for $C_{16}H_{14}O_2S_2$ 302.0435, found 302.0439.

Preparation of 2-(1′-Hydroxyethyl)-2-(phenylthio)-γ-butyrolactone (27) from 25. To 300 mg (0.99 mmol) of 2,2-bis(phenylthio)-γ-butyrolactone dissolved in 2 mL of THF at −10 °C was added dropwise 0.77 mL (1.49 mmol) of ethylmagnesium bromide (2 M in ether). The resultant solution was stirred for 2 h at −10 °C to give a white precipitate. Acetaldehyde was distilled into the enolate solution, and a clear solution returned. After stirring for 10 min at −10 °C, the solution was poured into 25 mL of saturated aqueous ammonium chloride solution and extracted with 3 × 50 mL of ether. The ether layers were combined and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and preparative TLC (20% ethyl acetate in hexane) purification gave 230 mg (98%) of aldol adduct. While mass and infrared spectra show the product obtained is identical with the adduct obtained below from direct aldol condensation of 2-(phenylthio)-γ-butyrolactone and acetaldehyde, NMR integration of the methyl group absorptions at δ 1.3 (d) and δ 1.2 (d) show the product consists of two diastereomers in the ratio of 2:1: NMR ($CDCl_3$) δ 7.6–7.1 (m, 5 H), 4.2–3.8 (m, 3 H), 3.5 (br s, 0.5 H), 2.8 (br s, 0.5 H), 2.4–2.3 (m, 1 H), 2.2–1.8 (m, 1 H), 1.3 (d, J = 6.5 Hz, 1.5 H), 1.2 (d, J = 6.5 Hz, 1.5 H); IR (CCl_4) 3600, 3500, 1760, 1440, 1370 cm^{-1}; calcd for $C_{12}H_{14}O_3S$ 238.0664, found 238.0656.

Preparation of 2-(1′-Hydroxyethyl)-Δ^{2,3}-butenolide (28). MCPBA (208 mg, 0.98 mmol) was added to a solution of 230 mg (0.97 mmol) of aldol adduct **27** in 10 mL of dichloromethane at −78 °C. When TLC indicated the absence of starting material (1 h), 100 mL of ether was added, and the resulting solution was washed with a mixture of 30 mL of saturated aqueous sodium bicarbonate and 10 mL of saturated aqueous sodium sulfite solution. The organic layer was separated, dried (anhydrous sodium sulfate), and concentrated in vacuo to give the corresponding sulfoxide as an oil.

The oil was immediately mixed with 2 mL of carbon tetrachloride and added dropwise to 13 mL of refluxing carbon tetrachloride (pot temperature: 80 °C) containing 490 mg (4.8 mmol) of solid calcium carbonate. After refluxing for 1 h, the solution was cooled and filtered through a pad of fluorosil under aspirator pressure. The solvent was removed in vacuo, and purification by preparative TLC (50% ethyl acetate) gave 78.6 mg (64% overall for 2 steps) of product: NMR ($CDCl_3$) δ 7.25 (q, J = 1.3 Hz, 1 H), 4.7 (t, J = 1.3 Hz, 2 H), 4.7–4.4 (m, 1 H), 2.9 (br s, 1 H), 1.4 (d, J = 7 Hz, 3 H); IR ($CDCl_3$) 3600, 3500, 1760, 1450, 1350 cm^{-1}; calcd for $C_6H_8O_3$ 128.0473, found 128.0473.

Preparation of Spiro[4.4]-6-(*tert*-butyldimethylsilyloxy)-3,3-bis(phenylthio)-1-oxanonan-2-one (29). The *tert*-butyldimethylsilyl ether of spirolactone **21** (150 mg, 0.555 mmol) dissolved in 1.5 mL of THF was

(54) Cf. Grieco, P. A.; Oguri, T.; Wang, C.-L. J.; Williams, E. *J. Org. Chem.* **1977**, *42*, 4113.

added to 1.22 mmol of LDA in 0.5 mL of THF at −78 °C, and the resultant solution was stirred for 1.5 h at −78 °C. Phenyl (phenylthio)sulfonate (347 mg, 1.3 mmol) in 1 mL of THF was added, and the solution was warmed to −25 °C and stirred for 5 h. It was poured into 10 mL of saturated aqueous ammonium chloride solution and extracted with 3 × 20 mL of ether. After the ether layer was dried (sodium sulfate), filtered, and concentrated in vacuo, the residue was purified by preparative TLC (20% ethyl acetate in hexane) to give 190 mg (70%) of bissulfenylated adduct: NMR (CCl_4) δ 7.7–7.2 (m, 10 H), 4.0–3.8 (m, 1 H), 2.5 (AB pattern, J = 15 Hz, 2 H), 2.0–1.4 (m, 6 H), 0.9 (s, 9 H), 0.02 (s, 6 H); IR (CCl_4) 1770, 1470, 1440 cm^{-1}; calcd for $C_{22}H_{25}O_3SiS_2$ (M^+ − tert-butyl group) 429.1014, found 429.1015.

Preparation of Spiro[4.4]-6-(*tert*-butyldimethylsilyloxy)-3-(1′-hydroxyethyl)-1-oxanon-3-en-2-one (31). Ethylmagnesium bromide (1.8 M in ether, 0.3 mL, 0.53 mmol) was added dropwise to 187 mg (0.38 mmol) of bissulfenylated lactone in 2 mL of THF at −10 °C. After stirring for 2 h during which time a white precipitate formed, gaseous acetaldehyde was bubbled into the reaction mixture until a clear solution was obtained. After stirring for another 5 min at −10 °C, the solution was poured into 10 mL of saturated aqueous ammonium chloride solution and extracted with 3 × 10 mL of ether. The ether extracts were dried (sodium sulfate), and the solvent was removed in vacuo. The crude oil was purified by preparative TLC to give 127 mg (78%) of aldol adduct **30**. NMR shows a methyl group absorption as two doublets, at 1.3 and 1.2 in approximately 1:1 ratio indicating that the product consists of a mixture of two diastereomers: NMR ($CDCl_3$) δ 7.6–7.2 (m, 5 H), 3.9 (t, J = 6 Hz, 1 H), 3.9–3.7 (q, J = 6 Hz, 1 H), 2.8 (br s, 1 H), 2.1 (AB pattern, J = 15 Hz, 2 H), 2.1–1.5 (m, 6 H), 1.3 (d, J = 6 Hz, 1.5 H), 1.2 (d, J = 6 Hz, 1.5 H), 0.9 (s, 4.5 H), 0.8 (s, 4.5 H), 0.2 (s, 3 H), 0.1 (s, 3 H); IR (CCl_4) 3450, 1760, 1460, 1440 cm^{-1}; MS, m/e (rel intensity) 367 [M^+ − 45] (0.4), 366 (1), 365 (7), 323 (2), 322 (5), 321 (30), 319 (7), 293 (13), 211 (37), 171 (29), 167 (12), 159 (16), 157 (100), 135 (27), 129 (11).

MCPBA (85%, 72.7 mg, 0.36 mmol) was added in 1 portion to 126 mg (0.3 mmol) of aldol adduct **30** in 1 mL of dichloromethane at −78 °C. After stirring at −78 °C for 3 h, the mixture was poured into a solution composed of 10 mL of saturated aqueous sodium bicarbonate and 2 mL of saturated aqueous sodium sulfite followed by extraction with 3 × 20 mL of dichloromethane. The organic extracts were dried (sodium sulfate) and concentrated in vacuo to give an oil which is unstable to silica gel and prolonged storage. Thus it was employed immediately without purification as described below.

The oil was dissolved in 5 mL of carbon tetrachloride and added dropwise slowly over a period of 10–15 min to 10 mL of refluxing carbon tetrachloride containing 300 mg (3 mmol) of solid calcium carbonate (oil bath temperature: 90–95 °C). After completion of the addition, the solution was refluxed for another hour, cooled, and filtered through a sintered glass funnel containing a pad of fluorosil under aspirator pressure. The solvent was removed in vacuo, and the crude material was purified by preparative TLC (20% ethyl acetate in hexane) to give 55 mg (60% overall for two steps) of oil (R_f 0.26): NMR ($CDCl_3$) δ 7.28 (d, J = 1.5 Hz, 0.5 H), 7.2 (d, J = 1.5 Hz, 0.5 H), 4.7 (q of t, J = 6.6 Hz, 1.5 Hz, 1 H), 4.1 (d of d, J = 5, 3 Hz, 1H), 3.0 (bs, 1H), 2.4–1.6 (m, 6 H), 1.55 (d, J = 6.6 Hz, 1.5 H) 1.5 (d, J = 6.6 Hz, 1.5 H), 0.9 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 171.8, 149.3, 137.6, 137.2, 96.4, 79.6, 62.7, 33.0, 25.7, 21.5, 18.1, −2.9; IR ($CHCl_3$) 3600, 3450, 1750 cm^{-1}. Anal. Calcd for $C_{16}H_{28}O_4Si$: C, 61.49, H, 9.03. Found: C, 61.71; H, 8.82.

Preparation of (1*S,2*R**)-*exo*-3-(*tert*-Butyldimethylsilyloxy)-*cis*-bicyclo[3.3.0]oct-7-ene-2-spiro-4′-(α,α-bis(phenylthio))-γ-butyrolactone (32).** The *tert*-butyldimethylsilyl ether of spirolactone **23** (257 mg, 0.83 mmol) in 2 mL of THF was added dropwise to 2.5 mmol of LDA in 1.5 mL of THF at −78 °C. After stirring at −78 °C for 1.5 h, 585 mg (2.34 mmol) of phenyl (phenylthio)sulfonate, dissolved in a mixture of 1 mL of THF and 0.1 mL of HMPA, was added dropwise to the reaction. The resulting solution was warmed to −20 °C and stirred for 4 h. After workup as before the product was purified by preparative TLC (30% ethyl acetate in hexane) to yield 348 mg (79%) of a viscous oil: NMR ($CDCl_3$) δ 7.8–7.5 (m, 4 H), 7.5–7.2 (m, 6 H), 5.8–5.6 (m, 1 H), 5.4–5.2 (m, 1 H), 3.6 (d of d, J = 11, 7 Hz), 3.3–3.1 (m, 1 H), 3.0–1.9 (m, 4 H), 2.5 (AB pattern, J = 15 Hz, 2 H), 1.5 (d of d, J = 13, 7 Hz, 1 H), 0.9 (s, 9 H), 0.02 (s, 6 H); IR (CCl_4) 1775 cm^{-1}. Anal. Calcd for $C_{29}H_{36}O_3SiS_2$: C, 66.37; H, 6.92. Found: C, 66.60; H, 7.06.

Preparation of (1*S,2*R**)-*exo*-3-(*tert*-Butyldimethylsilyloxy)-*cis*-bicyclo[3.3.0]oct-7-ene-2-spiro-4′-[α-(1-hydroxyethyl)-α-(phenylthio)-γ-butyrolactone] (33).** Ethylmagnesium bromide (2 M in ether, 0.24 mL, 0.48 mmol) was added dropwise to 84.5 mg (0.16 mmol) of bissulfenylated lactone **32** in 1 mL of THF at −10 °C. After addition of acetaldehyde and workup as described for preparation of **30**, preparative TLC purification (20% ethyl acetate in hexane) gave 50 mg (68%) of product. The product consists of two diastereomers with different R_f values (0.42, 0.30; 20% ethyl acetate in hexane) in an approximately 6:1 ratio. NMR spectroscopy shows that while the major isomer (white solid, mp 119–121 °C, R_f 0.42) has a quartet at δ 4.1 and a doublet of doublets at δ 3.7, the minor isomer (an oil, R_f 0.3) has the doublet of doublets at δ 4.0 and the corresponding quartet at 3.8: NMR ($CDCl_3$) (major isomer) δ 7.8–7.3 (m, 5 H), 5.9–5.7 (m, 1 H), 5.6–5.4 (m, 1 H), 4.1 (q, J = 7 Hz, 1 H), 3.7 (d of d, J = 11, 7 Hz), 3.3 (br s, 1 H), 3.3–3.0 (m, 1 H), 3.0–1.9 (m, 4 H), 2.0 (AB pattern, J = 15 Hz, 2 H), 1.8–1.5 (m, 1 H), 1.25 (d, J = 7 Hz, 3 H), 0.9 (s, 9 H), 0.01 (s, 6 H); IR (CCl_4) 3540, 1760, 1470, 1440, 1365 cm^{-1}; Anal. Calcd for $C_{25}H_{36}O_4SSi$: C, 65.17; H, 7.55; S, 6.96. Found: C, 65.28; H, 7.92; S, 7.07.

Preparation of (1*S,2*R**)-*exo*-3-(*tert*-Butyldimethylsilyloxy)-*cis*-bicyclo[3.3.0]oct-7-ene-2-spiro-4′-[α-(1-hydroxyethyl)-$\Delta^{\alpha,\beta}$-butenolide] (34).** As described in the preparation of **32**, 122 mg (0.265 mmol) of aldol **33** in 5 mL of dichloromethane were oxidized to the sulfoxide with 108 mg (0.53 mmol) of 85% MCPBA. The crude sulfoxide was thermolyzed in 10 mL of hot carbon tetrachloride (bath temperature 90 °C) containing 265 mg of solid calcium carbonate to give, after purification by preparative TLC (33% ethyl acetate in hexane), 45 mg (49% overall for 2 steps) of **34**: NMR ($CDCl_3$) δ 7.0 (d, J = 1.5 Hz, 1 H), 6.0–5.8 (m, 1 H), 5.7–5.5 (m, 1 H), 4.7 (q of d, J = 7, 1.5 Hz, 1 H), 4.1 (d of d, J = 11, 7 Hz, 1 H), 3.3–1.9 (m, 5 H), 1.7 (d of d, J = 12, 7 Hz, 1 H), 1.5 (d, J = 7 Hz, 3 H), 0.8 (s, 9 H), 0.02 (s, 6 H); IR (CCl_4) 1750 cm^{-1}. Anal. Calcd for $C_{19}H_{30}O_4Si$: C, 65.10; H, 8.63. Found: C, 65.06; H, 8.54.

Preparation of 2,2-Bis(phenylthio)-1-tetralone (35). Prewashed sodium hydride (3 times with pentane to remove oil) (428 mg, 17.8 mmol) was added to 790 mg (5.9 mmol) of 1-tetralone in 10 mL of THF at 0 °C. After 10 min, 4.45 g (17.8 mmol) of phenyl (phenylthio)sulfonate (4.45 g, 17.8 mmol) was added in 1 portion, and the resulting solution was stirred for 16 h at room temperature. The solution was poured into 50 mL of saturated aqueous ammonium chloride solution and extracted with 2 × 50 mL of ether. After the ether extracts were combined, dried (magnesium sulfate), and concentrated in vacuo, the remaining residue was purified by preparative TLC (20% ethyl acetate in hexane) to yield 1.5 g (70%) of bissulfenylated **35** as an oil: NMR (CCl_4) δ 7.6–7.0 (m, 14 H), 3.0 (br t, J = 6 Hz, 2 H), 2.3 (br t, J = 6 Hz, 2 H); IR (CCl_4) 1680, 1600, 1470 cm^{-1}; calcd for $C_{22}H_{18}OS_2$: 362.0799, found 362.0794.

Preparation of 2-(1′-Hydroxyethyl)-2-(phenylthio)-1-tetralone (36). Methylmagnesium bromide (0.09 mL, 0.27 mmol, 3 M in ether) was added dropwise to a solution of 65 mg (0.18 mmol) of bissulfenylated ketone **35** in 0.6 mL of THF containing approximately 2 mg (5 mol %) of cuprous bromide–dimethyl sulfide complex. After reaction with gaseous acetaldehyde and workup as described above, purification by preparative TLC (20% ethyl acetate in hexane) gave 41.2 mg (77%) of product. NMR integration of the methyl group absorption at δ 1.3(d) and δ 1.05(d) of product showed the product consisted of two diastereomers in the ratio of 3.5:1: NMR (CCl_4) δ 8.0–7.2 (m, 9 H), 4.2 (q, J = 7 Hz, 0.8 H), 4.0 (q, J = 7 Hz, 0.2 H), 3.6–3.2 (m, 1 H), 3.0–2.4 (m, 2 H), 2.2–1.9 (m, 2 H), 1.3 (d, J = 7 Hz, 2.3 H), 1.05 (d, J = 7 Hz, 0.7 H); IR (CCl_4) 3600, 3500, 1675, 1600, 1450 cm^{-1}; calcd for $C_{18}H_{18}O_2S$ 298.1027, found 298.1029.

Preparation of *endo*-2-(*tert*-Butyldimethylsiloxy)-*cis*-bicyclo[3.3.0]-oct-7-ene. Bicyclo alcohol **5** (40.4 g, 0.325 mol) in 25 mL of DMF was added slowly at 0 °C to a mixture of 51.43 g (0.341 mol) of (*tert*-butyldimethyl)chlorosilane and 24.3 g (0.358 mol) of imidazole in 250 mL of DMF. After the addition was completed, the cold bath was removed, and the reaction was stirred for 3 h at room temperature. It was poured into 300 mL of water and extracted with 3 × 250 mL of pentane. The pentane extracts were combined and dried over anhydrous sodium sulfate. Filtration followed by concentration in vacuo gave an oil (77.3 g, quantitative yield) (R_f 0.7, 20% ethyl acetate in hexane) which was pure enough (single spot on TLC) to be employed in subsequent reactions without further treatment: NMR ($CDCl_3$) δ 5.7–5.6 (m, 1 H), 5.55 (dt, J = 6, 2 Hz, 1 H), 4.1 (pq, J = 6 Hz, 1 H), 3.2–3.0 (m, 1 H), 2.7–1.2 (m, 7 H), 0.9 (s, 9 H), 0.02 (s, 6 H); calcd for $C_{14}H_{26}OSi$ 238.1753, Found 238.1741.

Preparation of *endo*-2-(*tert*-Butyldimethylsilyloxy)-*exo*-8-hydroxy-bicyclo[3.3.0]oct-6-ene (39b). To a suspension of 202 g (1 mol) of 85% MCPBA and 124.7 g (1.5 mol) of powdered sodium bicarbonate in 1.7 L of dichloromethane at 0 °C was added over a 1-h period 237 g (0.99 mol) of the above silyl ether. After stirring 4 h at room temperature, the resulting solution was filtered through a sintered glass funnel under aspirator pressure, and the remaining solid was washed with an additional 200 mL of dichloromethane. The filtrate was washed with 1 L of 0.1 N aqueous sodium hydroxide solution, and the aqueous layer was back extracted with 1 L of dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude oil was purified by vacuum distillation (88–92 °C at 0.5

mmHg) to yield 220 g (87%) of epoxide: NMR (CCl_4) δ 4.5–4.3 (m, 1 H), 3.45 (t, J = 2 Hz, 1 H), 3.5 (d, J = 2 Hz, 1 H), 2.6 (d of d, J = 8, 6 Hz, 1 H), 2.5–2.5 (m, 2 H), 2.1–1.3 (m, 5 H), 0.9 (s, 9 H), 0.05 (s, 3 H), 0.02 (s, 3 H). Anal. Calcd for $C_{14}H_{26}O_2Si$: C, 66.08; H, 10.30; M_r 254.1702. Found: C, 65.82; H, 9.90; M_r 254.1704.

A solution of 220 g (0.866 mol) of epoxide in 200 mL of ether was added to a solution of 2.6 mol of LDA in 1.5 L of ether at 0 °C. After stirring 4 h at room temperature, the reaction was quenched by pouring into 1 L of saturated aqueous ammonium chloride solution with 300 g of crushed ice. The ether layer was separated, and the aqueous layer was further extracted with 2 × 0.7 L of ether. The combined organic layers were dried (magnesium sulfate), filtered, and concentrated in vacuo. Vacuum distillation (80–83 °C at 0.3 mmHg) yielded 196.5 g (90%) of alcohol **39b** (R_f 0.33, 20% ethyl acetate in hexane): NMR (CCl_4) δ 5.6 (m, 2 H), 4.9 (ps, 1 H), 4.2–4.0 (m, 1 H), 3.2–3.0 (m, 1 H), 2.2 (td, J = 8, 2 Hz, 1 H), 1.6–1.2 (m, 6 H), 0.9 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H); IR (CCl_4) 3600, 3450 cm^{-1}. Anal. Calcd for $C_{14}H_{26}O_2Si$: C, 66.08; H, 10.30. Found: C, 66.04; H, 10.21.

Preparation of *exo*-8-(Tri-*n*-butylstannyl)methoxy-*endo*-2-(*tert*-butyldimethylsiloxy)-*cis*-bicyclo[3.3.0]oct-6-ene (41). Allyl alcohol **39b** (52.3 g, 0.206 mol) was added to a solution of 102 g (0.237 mol) of iodomethyl-tri-*n*-butyltin[55] in 50 mL of THF at 0 °C. Potassium hydride (12 g, 0.3 mol, prewashed with 3 × 50 mL of pentane), vigorously stirred in a separate flask with 90 mL of THF, was transferred very slowly through a transfer needle into the reaction at 0 °C over a period of 1.5 h. After the addition was completed and gas evolution ceased, the milky white solution was warmed to room temperature and stirred for an additional 6 h. It was carefully poured into 800 mL of cold (0 °C) saturated aqueous ammonium chloride solution and extracted with 3 × 600 mL of pentane. The pentane extracts were dried (sodium sulfate) and concentrated in vacuo to give an oil. Purification by column chromatography (20% ethyl acetate in hexane, R_f 0.7) yielded 91.2 g (80%) of colorless oil: NMR (CCl_4) δ 5.9–5.7 (m, 2 H), 4.58 (ps, 1 H), 4.2–4.0 (m, 1 H), 3.6 (s, 2 H), 3.2–3.0 (m, 1 H), 2.4 (br t, J = 8 Hz, 1 H), 1.6–1.0 (m, 16 H), 1.0–0.7 (m, 15 H), 0.9 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H). Anal. Calcd for $C_{20}H_{54}O_2SiSn$: C, 58.25; H, 9.77; Si, 5.04. Found: C, 58.24; H, 9.35; Si, 4.87.

Preparation of *exo*-6-(Hydroxymethyl)-*endo*-2-(*tert*-butyldimethylsilyloxy)-*cis*-bicyclo[3.3.0]oct-7-ene (42). A solution of 91.2 g (0.164 mol) of tin compound **41** in 50 mL of hexane was added slowly into 437 mL of a hexane solution of *n*-butyllithium at −78 °C. The resulting solution was mechanically stirred at −78 °C for 2 h and poured into 800 mL of ice cold saturated aqueous ammonium chloride solution. This mixture was extracted with 3 × 600 mL of ether. The ether phase was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification by silica gel dry column (20% ethyl acetate in hexane) gave 44 g (quantitative yield) of pure product.

Note. It was later found that this two-step 2,3-sigmatropic reaction[40] could be accomplished in a single step without isolating the tin intermediate. Typically, the tin intermediate in THF solution was transferred slowly through a cannula into 4 equiv (based on the starting alcohol) of *n*-butyllithium at −78 °C and mechanically stirred for 2 h. Similar workup conditions and purification provide 72–76% overall yield: NMR ($CDCl_3$) δ 5.77 (ddd, J = 5.5, 2.5, 1.5 Hz, 1 H), 5.67 (ddd, J = 5.5, 2, 2 Hz), 4.16 (m, 1 H), 3.53 (d of AB pattern, J = 11, 5.5 Hz, 2 H), 3.17 (m, 1 H), 2.59 (m, 1 H), 2.36 (tt, J = 8, 2.5 Hz, 1 H), 1.8–1.1 (m, 5 H), 0.8 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H); IR (CCl_4) 3620, 3450 cm^{-1}; calcd for $C_{11}H_{19}O_2Si$ (M − C_4H_9) 211.1154, found 211.1135.

Preparation of *endo*-2-(*tert*-Butyldimethylsilyloxy)-*cis*-bicyclo[3.3.0]oct-7-en-*exo*-6-carboxyaldehyde 2′,2′-Dimethyl-1′,3′-propanediol Acetal (43a). A solution of 5.26 g (19.6 mmol) of alcohol **42** in 14 mL of dichloromethane was added slowly at −78 °C to a mixture prepared by dropwise addition of 3.06 mL (43.12 mmol) of Me_2SO to 1.9 mL (21.56 mmol) of oxalyl chloride in 40 mL of dichloromethane. At −78 °C, 13.7 mL (98 mmol) of triethylamine was added, and the resulting solution was stirred for another 20 min at −78 °C. It was poured into 100 mL of water, and the mixure was extracted with 3 × 300 mL of pentane. The pentane extracts were combined and washed with an additional 100 mL of water prior to drying over anhydrous sodium sulfate. The solvent was removed in vacuo to give a light yellow oil (5.3 g) which was employed without further purification: NMR (CCl_4) δ 9.4 (d, J = 2 Hz, 1 H), 6.0–5.6 (m, 2 H), 4.4–4.0 (m, 1 H), 3.4–3.1 (m, 2 H), 3.0–1.1 (m, 6 H), 0.9 (s, 9 H), 0.02 (s, 6 H).

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Crude aldehyde (5.3 g, approximately 19.6 mmol) and 4.08 g (39.2 mmol) of 2,2-dimethyl-1,3-propanediol in 50 mL of dichloromethane were stirred at room temperature until a clear solution was obtained. Approximately 6.6 g (54.8 mmol) of anhydrous magnesium sulfate (activated by heating occasionally with a Bunsen burner under vacuum (0.1 mmHg) for 0.5 h) was added to the solution, and the resulting suspension was cooled to 0 °C. Boron trifluoride etherate (1.8 mL, 25.5 mmol) was added dropwise and stirred for 30 min at 0 °C. It was poured into 50 mL of cold (5–10 °C) saturated aqueous sodium bicarbonate solution, and the solution was extracted with 3 × 200 mL of ether. The ether extracts were combined and dried over sodium sulfate. The solvent was removed in vacuo to give a solid which was purified by dissolving in a minimal amount of acetone and then recrystallized from hot water. Off-white crystals (mp 64–65 °C) (R_f 0.54, 20% ethyl acetate in hexane) were obtained (5.6 g, 81% overall yield for 2 steps): NMR (CCl_4) δ 5.65 (ps, 2 H), 4.1 (d, J = 7.2 Hz, 1 H), 4.0–4.2 (m, 1 H), 3.4 (AB pattern, J = 11 Hz, 4 H), 3.1 (t of d, J = 7.2, 4 Hz, 1 H), 2.6–2.4 (m, 2 H), 1.7–1.3 (m 4 H), 1.15 (s, 3 H), 0.9 (s, 9 H), 0.7 (s, 3 H), 0.1 (s, 6 H). Anal. Calcd for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.30; M_r 352.2434. Found: C, 68.16; H, 10.24; M_r 352.2431.

Preparation of *cis*-Bicyclo[3.3.0]oct-7-en-*endo*-2-ol-*exo*-6-carboxaldehyde 2′,2′-Dimethyl-1′,3′-propanediol Acetal (43b). Method A. From 43a. Acetal **43a** (3 g, 8.9 mmol) was added to a mixture of 20 mL of glacial acetic acid, 10 mL of water, and 15 mL of THF. The resulting solution was stirred at room temperature for 29 h when TLC indicated no starting material remained. The solution was cooled to 0 °C, and excess solid sodium bicarbonate was added over a period of 0.5 h to neutralize the acetic acid. It was poured into 50 mL of water and extracted with 3 × 150 mL of ether. The organic layers were dried (magnesium sulfate) and concentrated in vacuo to give an oil which was purified by silica gel dry column (20% ethyl acetate in hexane, R_f 0.15) to yield 1.86 g (87%) of product: NMR ($CDCl_3$) δ 5.9–5.7 (m, 2 H), 4.25 (d, J = 7.2 Hz, 1 H), 4.3–4.1 (m, 1 H), 3.5 (AB pattern, J = 11 Hz, 4 H), 3.3–3.1 (m, 1 H), 2.8–2.5 (m, 2 H), 2.0–1.2 (m, 5 H), 1.2 (s, 3 H), 0.73 (s, 3 H); IR (CCl_4) 3600, 3500 cm^{-1}; calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1568.

Method B. From 42. Crude aldehyde (31.4 g, approximately 118 mmol) was obtained by the oxidation of alcohol **42** as described previously. It was mixed with 24.5 g (236 mmol) of 2,2-dimethyl-1,3-propanediol in 300 mL of dichloromethane and stirred at room temperature until a clear solution was obtained (large crystals of 2,2-dimethyl-1,3-propanediol were crushed into smaller pieces before use to faciliate this dissolution process). The solution was cooled to 0 °C, and boron trifluoride etherate (18.9 mL, 153 mmol) was added slowly and stirred for 5 min at 0 °C. This reaction was warmed to room temperature and stirred for 0.5 h when TLC indicated the reaction was completed. It was poured into 500 mL of cold (5–10 °C) saturated aqueous sodium bicarbonate solution and stirred until gas evolution ceased. Ethyl acetate (500 mL) was added and shaken vigorously. The organic layer was separated and washed with 200 mL of water. Aqueous layers were back extracted with 300 mL of ethyl acetate. The ethyl acetate extracts were combined, dried (sodium sulfate), and concentrated in vacuo. Similar purification by silica gel dry column yielded 19.4 g of desired alcohol (69% overall for the 3 steps).

Preparation of *cis*-Bicyclo[3.3.0]oct-7-en-2-one-*exo*-6-carboxaldehyde 2′,2′-Dimethyl-1′,3′-propanediol Acetal (44). Hydroxyacetal **43b** (12.4 g, 52.06 mmol) in 30 mL of dichloromethane was oxidized by the Swern oxidation as described above by using 14.8 mL (0.208 mol) of Me_2SO, 9.08 mL (0.104 mol) of oxalyl chloride in 130 mL of dichloromethane followed by 36.2 mL (0.26 mol) of triethylamine. After the usual workup, purification by silica gel dry column (20% ethyl acetate in hexane, R_f 0.29) gave 11.1 g (90% yield) of a colorless oil: NMR (CCl_4) δ 5.7 (ps, 2 H), 4.2 (d, J = 7 Hz, 1 H), 3.5 (AB pattern, J = 11 Hz, 4 H), 3.3–3.1 (m, 1 H), 3.0–2.6 (m, 2 H), 2.3–2.0 (m, 2 H), 2.0–1.4 (2 H), 1.2 (s, 3 H), 0.73 (s, 3 H); IR (CCl_4) 1740 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; M_r 236.1412. Found: C, 71.13; H, 8.53; M_r 236.1410.

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Supplementary Material Available: Table I, ^1H NMR decoupling and assignment of **42**, general experimental, and experimental details for preparation of **5**, **6**, **7**, **10**, **13a**, **16**, **17**, **18**, silylation of **21**, and **27** (8 pages). Ordering information is given on any current masthead.