32.2, 27.1, 26.8, 26.4, 25.5, 21.4, 21.4, 20.8, 20.3 ppm; IR (film) 1720 cm^{-1}.

(3a*R,4a*S**,8a*S**)-3,3a,4,4a,6,7,8,8a,9,10-Decahydro-3a,8a-dimethyl-1-isopropylbenz[*f*]azulen-5(2*H*)-one (61).** To a solution of sodium methoxide (4.35 mmol) in methanol (5 mL) was added 126 mg (0.46 mmol) of ketone **60** in 1 mL of dry methanol. The mixture was stirred at rt for 16 h and diluted with 1 mL of saturated aq NH_4Cl. Standard ethereal workup provided 126 mg of an inseparable 1:1 mixture of ketones **60** and **61**: ^1H NMR (300 MHz) δ 0.73 (s, 1.5 H), 0.92 (s, 1.5 H), 0.97 (s, 1.5 H), 1.01 (s, 1.5 H), 0.85–1.05 (m, 12 H), 1.10–2.43 (m, 17 H), 2.53–2.64 (m, 1 H).

(3a*R,4a*R**,8a*S**)-2,3,3a,4,4a,5,6,7,8,8a,9,10-Dodecahydro-3a,8a-dimethyl-1-isopropyl-5-methylenebenz[*f*]azulene (62).** To a solution of 126 mg of a 1:1 mixture of ketones **60** and **61** (0.46 mmol) at −78 °C was added 1.4 mL of commercially available (trimethylsilylmethyl)lithium (1.39 mmol, 1.0 M in THF, Aldrich). The resulting mixture was stirred at −78 °C for 30 min and then slowly allowed to warm to rt over a 4-h period. Standard ethereal workup afforded 154 mg of a crude residue, which was purified by chromatography on silica gel (elution with H:E, 7:1) to give 70 mg (42.5% actual yield, or 85% based on **61**) of a β-hydroxy silane. This alcohol was homogeneous by TLC analysis (H:E, 7:1, R_f(alcohol) = 0.20, R_f(**60**) = 0.30): ^1H NMR (300 MHz) δ 0.86 (s, 3 H), 0.90 (d, 3 H, J = 7.0 Hz), 0.97 (s, 3 H), 0.98 (d, 3 H, J = 7.0 Hz), 1.13–1.28 (m, 4 H), 1.45–2.38 (m, 13 H), 2.61 (hept, 1 H, J = 7.0 Hz). Further elution gave 48 mg of unreacted ketone **60**.

To a solution of aq HF (4 drops, 50%) in 10 mL of THF was added 70 mg of the above β-hydroxy silane (0.194 mmol), and the mixture was stirred at rt for 1 h. The reaction mixture was then partitioned between pentane (50 mL) and saturated aq $NaHCO_3$ (10 mL). The aq layer was extracted thoroughly with pentane (3 × 50 mL), and then combined organic extracts were washed with brine, dried over anhyd $MgSO_4$, and filtered. Concentration followed by chromatographic purification gave 46 mg of diene **62** (88%), which was homogeneous by TLC analysis (H:E, 7:1, R_f (alcohol) = 0.75, R_f(**62**) = 0.95): ^1H NMR (300 MHz) δ 0.67 (s, 3 H), 0.93 (d, 3 H, J = 6.8 Hz), 0.95 (d, 3 H, J = 6.8 Hz), 1.09 (s, 3 H), 0.8–2.46 (m, 26 H), 2.61 (hept, 1 H, J = 7.0 Hz), 4.53 (br s, 1 H), 4.76 (d, 1 H, J = 1.5 Hz).

Preparation of Sulfoxide 63. Ethylaluminum dichloride (140 μL of a 1.5 M solution in toluene, 0.14 mmol) was added to a solution of diene **62** (27 mg, 0.10 mmol) and *p*-toluenesulfinyl chloride[58] (17.4 mg, 0.1 mmol) in 1 mL of ether at 0 °C. The solution was allowed to warm to rt and stirred for a total of 15 h. Standard ethereal workup gave 43 mg of an oily residue. Chromatography on silica gel (elution with hexanes) gave 33 mg (90%) of tetrasubstituted sulfoxide **63**, which was homogeneous by TLC analysis: ^1H NMR (300 MHz) δ 0.80–1.05 (m, 13 H), 1.10–2.40 (m, 15 H), 2.50–2.65 (m, 1 H), 2.95 (d, 1 H, J = 13 Hz), 4.40 (d, 1 H, J = 13 Hz), 7.45–7.68 (m, 5 H).

Acknowledgment. Support from the National Institute of General Medical Sciences through research grant 1 R01 GM39752 is gratefully acknowledged. G.M. expresses his gratitude to Dr. Christopher Shiner for helpful discussion regarding the preparation of silane **9**.

Abbreviations. Aqueous (aq), hexanes:ether (H:E), triethylamine (TEA).

Supplementary Material Available: NMR spectra of compounds studied and X-ray diffraction data for **37** (77 pages). Ordering information is given on any current masthead page.

Intramolecular Additions of Allylsilanes to Conjugated Dienones. Direct Stereoselective Syntheses of (±)-Neolemnanyl Acetate and (±)-Neolemnane†,1

George Majetich,* Derric Lowery, Vikram Khetani, Jee-Seop Song, Kenneth Hull, and Clay Ringold

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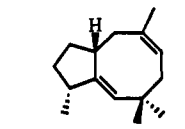
Received October 17, 1990

The total synthesis of the marine sesquiterpenes neolemnanyl acetate (**1**) and neolemnane (**2**) is reported. An intramolecular allylsilane addition to a conjugated dienone is used to assemble the basic 6,8-fused skeleton. Functionalization of the cyclooctane ring was achieved by means of a regiospecific photooxygenation.

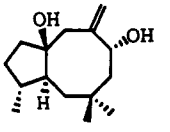
The identification of many biologically active natural products containing eight-membered rings has recently stimulated considerable interest in the development of methodology for the construction of cyclooctane rings. Recently, many model studies have been recorded in this area[2] and in rarer cases total syntheses of natural products containing eight-membered rings have been achieved (Chart I).[3,4]

The usefulness of butenyl dienone cyclizations[5] for the synthesis of fused cyclohexanes or cyclooctane rings is detailed in an accompanying paper[6] and is generalized in Scheme I. Note that one can direct the reactivity along two distinctly different pathways by the simple choice of reaction catalyst.[7a] For example, cyclization of trienone vi using ethylaluminum dichloride directly afforded (±)-nootkatone (vii) in 65% yield.[7b] In sharp contrast to this result, treatment of vi with fluoride ion gave fused

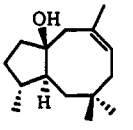
Chart I



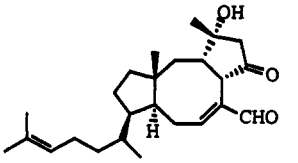
Precapnelladiene (i)



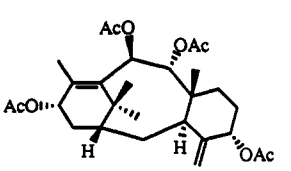
Poitediol (ii)



Dactylol (iii)



Ophiobolin C (iv)

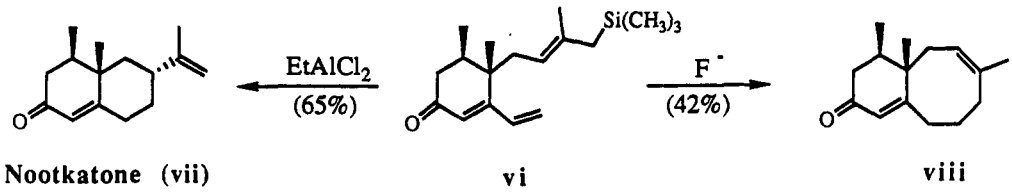


Taxusin (v)

†Dedicated to Professor Paul A. Grieco on the occasion of his receipt of The 1991 ACS Award for Creative Work in Synthetic Organic Chemistry.

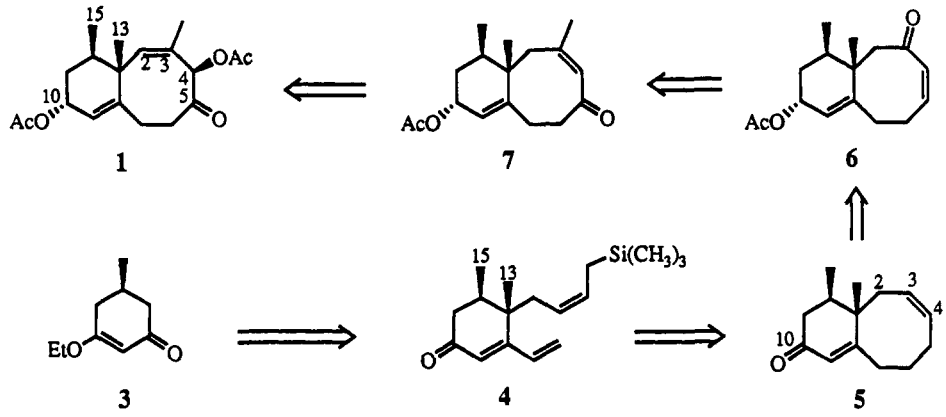
0022-3263/91/1956-3988$02.50/0

Scheme I



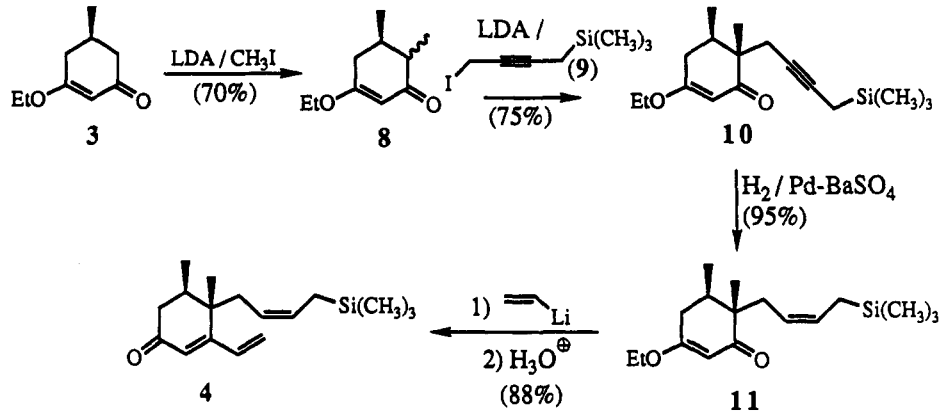
Nootkatone (vii) vi viii

Scheme II



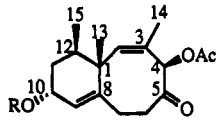
1 7 6 3 4 5

Scheme III



3 8 10 4 11

cyclooctane viii, which has most of the salient features of neolemnanyl acetate (1) and neolemnane (2).[8] These sesquiterpenes were first isolated from extracts of the Pacific soft-coral *Lemnalia africana* by Fenical and Clardy



neolemnanyl acetate (1) R = Ac

neolemnane (2) R = H

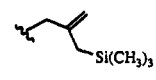
(1) (a) Taken in part from the Ph.D. Dissertation of Derric Lowery, The University of Georgia, 1989. (b) Taken in part from the Ph.D. Dissertation of Kenneth Hull, The University of Georgia, 1988.

(2) For a comprehensive listing of cyclooctane-forming reactions prior to 1987, see: Fuchs, P. L.; Hardinger, S. A. *J. Org. Chem.* **1987**, *52*, 2739 and references cited therein.

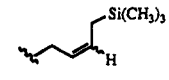
(3) Each of the cyclooctanoids shown in Chart I has been synthesized. Precapnelladiene (i): (a) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 6868. (b) *Ibid.* **1985**, *107*, 7352. (c) Mehta, G.; Murthy, A. N. *J. Org. Chem.* **1987**, *52*, 2875. Poitediol (ii): (d) Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 3869. Dactylol (iii): (e) Gadwood, R. C. *J. Chem. Soc., Chem. Commun.* **1985**, 123. (f) Hayasaka, K.; Matsumoto, T.; Ohtsuka, T.; Shirahama, H. *Tetrahedron Lett.* **1985**, *26*, 873. (g) Paquette, L. A.; Ham, W. H. *J. Am. Chem. Soc.* **1987**, *109*, 3025. Ophiobolin C (iv): (h) Kishi, Y.; Rowley, M.; Tsukamoto, M. *J. Am. Chem. Soc.* **1989**, *111*, 2735. Taxusin (v): (i) Harusawa, S.; Holton, R. A.; Juo, R. R.; Kim, H. B.; Lowenthal, R. E.; Williams, A. D.; Yogai, S. *J. Am. Chem. Soc.* **1988** *110*, 6558.

(4) For the synthesis of other cyclooctanoids, see the following. Stegnancin: (a) Kende, A. S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1976**, *98*, 267. (b) Ziegler, F. E.; Chliwner, I.; Fowler, K. W.; Kanfer, S. J.; Kuo, S. J.; Sinha, N. D. *J. Am. Chem. Soc.* **1980**, *102*, 790. (c) Koga, K.; Ishiguro, T.; Tomioka, K. *Tetrahedron Lett.* **1980**, *21*, 2973. *epi*-Precapnelladiene: (d) Birch, A. M.; Pattenden, G. *J. Chem. Soc., Perkin Trans. I* **1983**, 1913; (e) *J. Chem. Soc., Chem. Commun.* **1980**, 1195. Pleuromutilin: (f) Gibbons, E. G. *J. Am. Chem. Soc.* **1982**, *104*, 1767. (g) Paquette, L. A.; Wiedeman, P. E. *Tetrahedron Lett.* **1985**, *26*, 1603. (h) Paquette, L. A.; Bulman-Page, P. C. *Ibid.* **1985**, *26*, 1607. (i) Paquette, L. A.; Bulman-Page, P. C.; Weideman, P. E. *Ibid.* **1985**, *26*, 1611. Albolic acid: (j) Kataoka, H.; Kato, N.; Ohbuchi, S.; Takashita, H.; Tanaka, S. *J. Chem. Soc., Chem. Commun.* **1988**, 354. Ceroplastol I: Arvinitis, A.; Boeckman, R. K.; Voss, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 2737.

(5) We have developed several methods to produce six-, seven-, and eight-membered rings based on the intramolecular addition of an allylsilane to a 3-vinylcycloalkenone. For convenience sake, we use the following conventions to describe these various cyclizations: (1) the suffix "dienone" describes the 3-vinylcycloalkenone unit; (2) a locant for the allylsilane appendage is stated; (3) the nature of the allylsilane side chain is defined either as an isoalkenyl or *n*-alkenyl substituent; and (4) geometric isomers or substitutions are ignored.

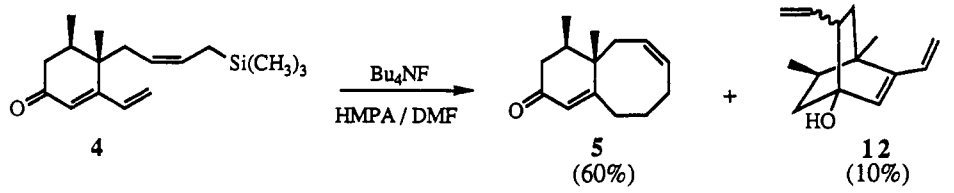


isoalkenyl



n-alkenyl

Scheme IV



4 5 (60%) 12 (10%)

in 1981 and have irregular terpenoid structures.[9] Accordingly, we chose to illustrate our cyclooctane annulation through the synthesis of these natural products.[10]

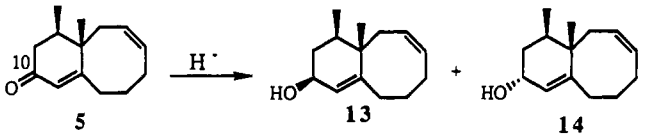
Synthetic Plan

Scheme II presents a straightforward retrosynthetic analysis of 1, which exploits our model studies of butenyl dienone cyclizations. Close examination of the cyclization product (e.g. 5) reveals that the six-membered ring requires only the stereospecific reduction of the C(10) carbonyl. We expected that the C(3),C(4) double bond of 5 would allow the preparation of enone 6 and then trisubstituted enone 7. The use of enone 7 as a key intermediate requires the efficient migration of the C(3),C(4) double bond to C(2),C(3) as well as the stereospecific introduction of a C(4)-hydroxyl group. We chose first to synthesize neolemnanyl acetate and therefore delayed the need to differentiate the C(4) and C(10) hydroxyls, which a neolemnane synthesis requires.

Discussion of Results

Our first priority was the construction of trienone 4, the cyclization precursor leading to the neolemnanyl skeleton. The starting material for the synthesis of 1 was enol ether 3, conveniently prepared from dihydroorcinol (Scheme III).[11,12] From the work of Stork and Danheiser,[13] we knew that the *cis*-C(13),C(15)-dimethyl relationship found in trienone 4 could be achieved by successive alkylations and that the relative stereochemistry of the asymmetric centers could be established by the alkylation order.[14] Thus methylation of 3 under kinetic conditions yielded enol ether 8. The silicon-containing iodide 9 was prepared in 74% overall yield from 4-(trimethylsilyl)-2-butyn-1-ol[15] by means of the Finkelstein method. Enol ether 8 was alkylated under kinetic conditions with 9 to yield an 8:1 mixture of diastereomers of which 10 was the major isomer. Enone 10 was isolated by column chromatography as a viscous oil in 75% yield.

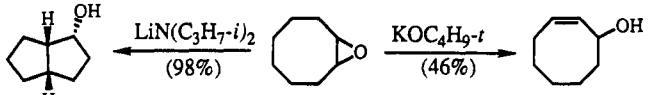
Scheme V



5 13 14

$LiAlH_4$	(85%)	(10%)
$LiBH(sec\text{-}Bu)_3$	(19%)	(76%)

Scheme VI



16 15 17

Selective reduction of the acetylenic functionality to a cis olefin with a modification of the traditional Lindlar procedure afforded 11 in 95% yield. Conversion of 11 into dienone 4 was achieved through the 1,2-addition of vinyllithium to the carbonyl group, followed by subsequent hydrolysis of the diastereomeric enol ethers to yield the target trienone in 88% yield. Yields for the analogous procedure with vinylmagnesium bromide are approximately 10% lower.

Cyclization of 4 under fluoride ion catalysis yielded the 6,8-fused bicyclic enone 5 in 60% yield (Scheme IV) while bicyclic alcohol 12, resulting from the 1,2-addition of the allylsilane, accounted for 10% of the isolated reaction products. The yield of this annulation was improved when the DMF was removed by distillation, instead of aqueous workup, prior to column chromatography. This modification allowed the reaction to be carried out on up to 7 g of substrate in 51% yield.

The next objective was to generate the axial allylic alcohol from the cyclohexenone system. In accordance with the observations of Henbest[16a] and Dauben[16b] we expected the reduction of 5 with $LiAlH_4$ to provide only 13 on the basis that rigid cyclic α,β-unsaturated ketones afford the thermodynamically more stable equatorial alcohol upon reduction. Indeed, treatment of enone 5 with lithium aluminum hydride provided the equatorial alcohol 13 in 85% yield (Scheme V). It was clear that the introduction of the axial allylic alcohol would require a bulkier source.[17] The use of L-Selectride afforded a 4:1 ratio (axial:equatorial) of the C(10) epimeric alcohols in 95% combined yield. These alcohols were separable by column chromatography.

Since the reduction described above gave a 19% yield of 13, we attempted to invert the C(10) stereochemistry of this material. However, subjection of 13 to the Mitsu-

(6) Majetich, G.; Hull, K.; Casares, A. M.; Khetani, V. "Cyclooctane or Cyclohexane Annulations Based on Intramolecular Additions of Allylsilanes to Conjugated Dienones", *J. Org. Chem.*, first of three papers in this issue.

(7) (a) For a preliminary report of this work, see: Majetich, G.; Hull, K.; Desmond, R. *Tetrahedron Lett.* **1985**, *26*, 2751. (b) Majetich, G.; Behnke, M.; Hull, K. *J. Org. Chem.* **1985**, *50*, 3615.

(8) The systematic numbering sequence shown for this new ring system is based on the biogenetic relationship of neolemnane and neolemnanyl acetate to the nardosinane (lemnalane) sesquiterpenoids.[9]

(9) (a) Izac, R. R.; Fenical, W.; Tagle, B.; Clardy, J. *Tetrahedron* **1981**, *37*, 2569. (b) Izac, R. R.; Schneider, P.; Swain, M.; Fenical, W. *Tetrahedron Lett.* **1982**, *23*, 817. (c) Bowden, B. F.; Coll, J. C.; Mitchell, S. J. *Aust. J. Chem.* **1980**, *33*, 885.

(10) For a preliminary account of our synthesis of neolemnanyl acetate, see: Majetich, G.; Lowery, D.; Khetani, V. *Tetrahedron Lett.* **1990**, *31*, 51.

(11) (a) All structures drawn herein represent racemates, with only one enantiomer shown. (b) The spectroscopic data obtained for all new compounds were fully consistent with the assigned structures. (c) Reaction conditions have not been optimized. (d) All yields are isolated yields.

(12) Crossly, A. W.; Renouf, N. *J. Chem. Soc.* **1915**, 602.

(13) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

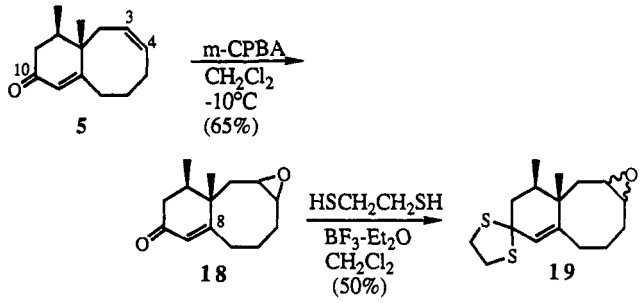
(14) This strategy has also been utilized in a short synthesis of nootkatone. See: (a) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley-Interscience: New York, 1983; Vol. V, p 184. For related applications, see: (b) ref 7b. (c) Majetich, G.; Defauw, J.; Ringold, C. *J. Org. Chem.* **1988**, *53*, 50.

(15) Mastalerz, H. *J. Org. Chem.* **1984**, *49*, 4094.

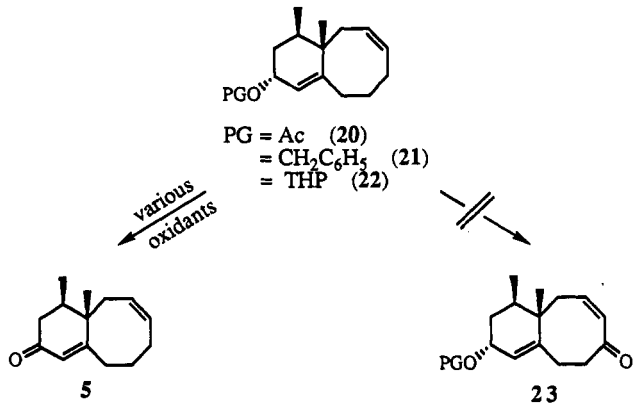
(16) (a) Henbest, H. B.; McEntee, J. *J. Chem. Soc.* **1961**, 4478. (b) Ashcraft, A. C.; Dauben, W. G. *J. Am. Chem. Soc.* **1963**, *85*, 3673.

(17) (a) Krishnamerthy, S.; Brown, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 3383 and references cited therein. (b) Dauben, W. G.; Ashmore, J. W. *Tetrahedron Lett.* **1978**, 4487.

Scheme VII



Scheme VIII



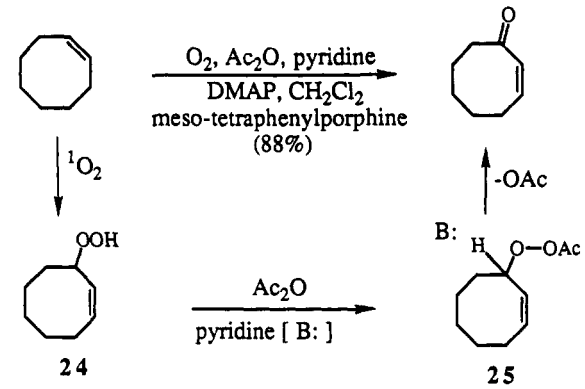
nobu methodology[18] yielded a 1:1 mixture of allylic esters, presumably through solvolysis of the intermediate allylic oxyphosphonium salt. Additionally, conversion of **13** to the corresponding allylic mesylate followed by treatment with cesium acetate gave similar results,[19] which suggests that the axial allylic acetate is prone to solvolysis.

The isomerization of epoxides to allylic alcohols in medium sized rings (8–10 members) is a highly substrate- and/or catalyst-dependent conversion.[20] For example, *cis*-cyclooctene epoxide undergoes a transannular cyclization under strongly basic conditions to afford a 5,5-fused system (**15** → **16**), while weaker bases such as potassium *tert*-butoxide give allylic alcohol **17** (Scheme VI).[21]

We felt that the unsaturated nature of C(8) in our system precluded transannular side reactions and therefore we chose to prepare epoxide **19** (Scheme VII). The relatively stable dithiolane protecting group was employed because protected cyclohexenol derivatives underwent elimination under strongly basic conditions. The use of a dithiolane required that we oxidize the C(3),C(4) double bond using *m*-chloroperbenzoic acid prior to masking the C(10) carbonyl. Subsequent thioketalization[22] of **18** using ethanedithiol in the presence of boron trifluoride etherate furnished substrate **19** in only 33% yield. Unfortunately, epoxide **19** either decomposed or failed to react with bases under all experimental conditions examined.[23]

The failure of the epoxide-opening strategy led us to investigate the selective oxidation of the C(5)-allylic methylene (Scheme VIII). However, all attempts to oxidize acetate **20** or other protected variants such as **21** or **22**, with common procedures [SeO_2,[24] PCC,[25] PDC, or $Cr(CO)_6$[26]] resulted in the facile regeneration of dienone **5**.

Scheme IX

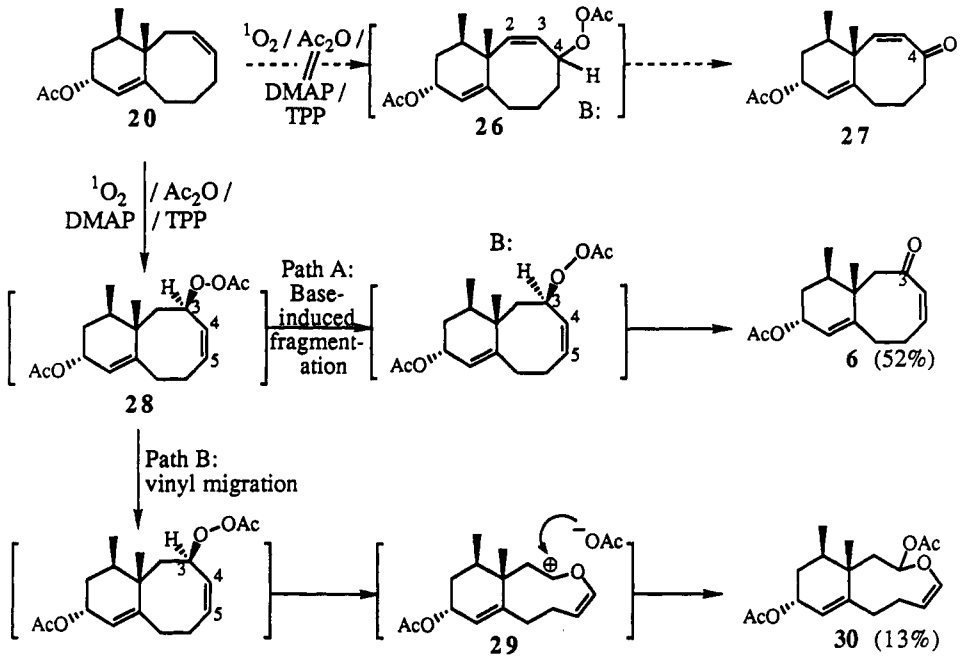


The use of singlet oxygen is an attractive method for oxidizing aliphatic or cyclic olefins to the corresponding α,β-unsaturated enones.[27] This conversion is usually carried out in a stepwise fashion and involves the isolation of either the hydroperoxide or the allylic alcohol, prior to further oxidation. Problems caused by isolating the oxidized intermediates can be avoided by means of an in situ photooxygenation–elimination procedure developed by Mihelich and Eickhoff.[28] This one-pot procedure is typified by the oxidation of cyclooctene to cyclooctenone as illustrated in Scheme IX. Reaction of cyclooctene with singlet oxygen, produced using *meso*-5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP) as the photosensitizer, gives allylic hydroperoxide **24**, which is acetylated in situ to provide an allylic peracetate (e.g. **25**). Base-promoted fragmentation of this peracetate intermediate furnishes cyclooctenone in 88% yield.

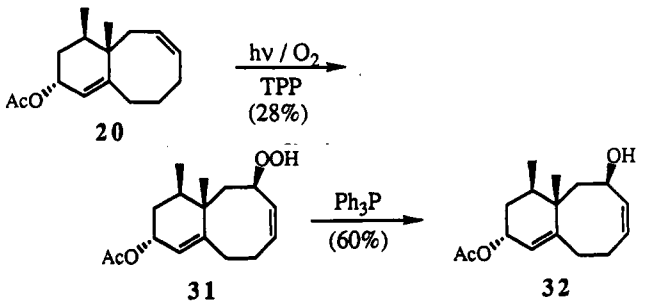
In Mihelich and Eickhoff's study, the regiospecificity of the oxidation is not an issue. Such selectivity, however, becomes a concern when more complex substrates are studied. Because singlet oxygen photooxidations are thought to proceed through a concerted ene reaction mechanism,[27,29] oxidation of **20** must occur at either C(3) or C(4) (cf. **28** → **6** and **26** → **27**, Scheme X). We felt that formation of peracetate **26** was unlikely due to steric considerations. Indeed, photooxygenation of acetate **20** afforded enone **6** in 52% yield, along with 20% of unreacted **20** and a 13% yield of enol ether **30**, the product of a Hock fragmentation.[30] The origin of enol ether **30**

(18) For a comprehensive review of this methodology, see: Mitsunobu, O. *Synthesis* **1981**, 22.
(19) (a) Desai, R. J.; Huffman, J. W. *Synth. Commun.* **1983**, *13*, 553. (b) Ikegami, S.; Okabe, H.; Torisawa, Y. *Chem. Lett.* **1984**, 1555.
(20) For a review on epoxide transformations, see: Smith, J. G. *Synthesis* **1976**, 777.
(21) Sheng, M. N. *Synthesis* **1972**, 194.
(22) Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172.
(23) For representative experimental conditions, see: (a) White, P. D.; Whitesell, J. K. *Q. Rev.* **1975**, *29*, 602. (b) Giguere, R. J.; Hoffmann, H. M. R.; Ilsemann, G. *J. Org. Chem.* **1982**, *47*, 4948. (c) Imaeda, H.; Ishii, Y.; Itoh, K.; Sakai, S. *J. Organomet. Chem.* **1969**, *19*, 299. (d) Murata, S.; Noyori, R.; Suzuki, M. *J. Am. Chem. Soc.* **1982**, *101*, 2738. (e) See also ref 21.
(24) (a) Carver, J. R.; Trachtenberg, E. N. *J. Org. Chem.* **1970**, *35*, 1646. (b) Neilsen, S. D.; Wiberg, K. B. *J. Org. Chem.* **1964**, *29*, 3353.
(25) Parrish, E. J.; Chitracorn, S.; Wei, T. S. *Synth. Commun.* **1986**, *16*, 1371.
(26) Pearson, A. J.; Chen, Y. S.; Hsu, S. Y.; Ray, T. *Tetrahedron Lett.* **1984**, *25*, 1235.
(27) For a review of the chemistry and synthetic applications of singlet oxygen through 1985, see: (a) *Singlet Oxygen. Reaction Modes and Products Part I*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL 1985; Vol. II. (b) *Singlet Oxygen Reactions with Organic Compounds and Polymers*; Ranby, B., Rabek, J. F. Eds.; John Wiley & Sons: New York, 1978.
(28) Mihelich, E. D.; Eickhoff, D. J. *J. Org. Chem.* **1983**, *48*, 4135.
(29) The mechanism of singlet oxygen reactions has the subject of extensive study. For relevant reviews, see: (a) Frimer, A. A.; Stephenson, L. M. "The Singlet Oxygen "Ene" Reaction", in ref 27a, pp 68–92. (b) Gollnick, K. "Mechanism and Kinetics of Chemical Reactions of Singlet Oxygen with Organic Compounds", in ref 27b, pp 111–134. For experimental evidence supporting an alternative mechanism, see: (c) Fenical, W.; Kearns, D. R.; Radlick, P. *J. Am. Chem. Soc.* **1969**, *91*, 3396, 7771.
(30) (a) Hock, H.; Lang, S. *Ber. Dtsch, Chem. Ges.* **1942**, *75*, 300; (b) **1944**, *77*, 257. (c) Hock, H.; Kropf, H. *Angew. Chem.* **1957**, 313. (d) Criegee, R. *Liebigs Ann.* **1948**, 560, 127. (e) Herz, W.; Juo, R.-R. *J. Org. Chem.* **1985**, *50*, 618.

Scheme X



Scheme XI



can be traced to peracetate **28** in which a migration of the vinyl unit, analagous to that in the Baeyer–Villiger reaction, generates an oxygen-stabilized carbonium ion species (e.g. **29**) that is eventually trapped by the acetate ion in solution to afford the nine-membered acetal. The formation of **30** was significantly decreased by using minimal solvent while the use of excess (or stronger) base had little influence on the product distribution.

In view of the Hock fragmentation product resulting from rearrangement of the allylic peracetate intermediate, we investigated the stepwise conversion of **20** to **6**. Standard photooxidation of **20** afforded hydroperoxide **31** in 28% yield (Scheme XI) while reduction of **31** with triphenylphosphine in ether at 0 °C gave allylic alcohol **32** in 60% yield. Although oxidation of **32** gave enone **6** in 95% yield, this three-reaction sequence was less efficient and therefore deemed impractical.

Preparation of trisubstituted enone **7**, the next pivotal synthetic intermediate, required the seemingly trivial 1,2-addition of a methyl anion equivalent to the C(3)-carbonyl of **6**, followed by the oxidative rearrangement of tertiary allylic alcohol **33**.[31] Since methyllithium readily adds to cyclooctenone, we expected enone **6** to behave similarly. However, treatment of **6** with excess methyllithium or methylmagnesium bromide [>4 equiv] under conditions ranging from −78 °C to lengthy periods of reflux failed to provide **33** (Scheme XII). Surprisingly, the C(10)-acetate was stable under these vigorous conditions (cf. **6** → **36**, Scheme XIV).

This lack of reactivity of **6** was puzzling because Dreiding stereomodels indicated that the C(3)-carbonyl was unhindered. We therefore assumed that enolization of the enone was precluding 1,2-addition and to test this, we treated **6** with 4.0 equiv of methyllithium at room temperature for 4 h and then quenched the reaction with 4.1 equiv of chlorotrimethylsilane (TMSCl). However, the isolated product was not the expected silyl enol ether but ketone **34** resulting from the Michael addition of chloride ion produced by the reaction of TMSCl with methyllithium. Moreover, the excess TMSCl promotes the Michael reaction[32] as was confirmed by treating enone **6** with 1 equiv of lithium chloride and a catalytic amount of TMSCl. We also examined whether cesium chloride,[33] lithium perchlorate,[34] or boron trifluoride etherate could activate enone **6** toward 1,2-addition. However, these activating agents either had no influence or caused **6** to decompose.

In the past decade, organotitanium and organozirconium reagents[35] have been shown to be superior to traditional Grignard reagents for additions to sterically hindered and/or enolizable ketones. The high reactivity and low basicity of zirconium reagents is illustrated by the efficient conversion of ethyl acetoacetate to diol **35**, whereas exposure to typical Grignard reagents results only in enolization (Scheme XIII).

We were pleased to find that reaction of enone **6** with tetramethylzirconium gave tertiary alcohol **33** in high yield (Scheme XIV). This conversion was empirically observed to require 2 equiv of the zirconium reagent to proceed to completion; however, reaction times in excess of 30 s also

(31) For a recent review of oxidative rearrangement reactions, see: Schlecht, M. "Oxidative Rearrangement Reactions" in *Comprehensive Organic Chemistry*; Pergamon Press, 1991; Vol. 7.

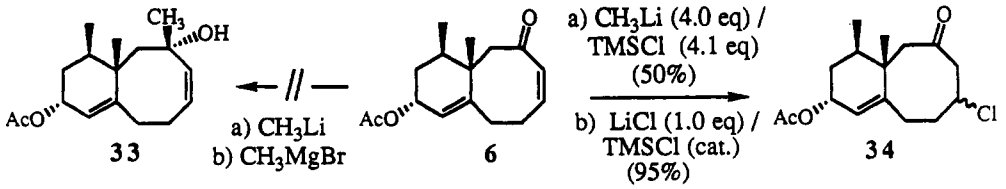
(32) Use of chlorotrimethylsilane greatly enhances the rate of conjugate or 1,2-addition of copper reagents. See: Matsuzawa, S.; Isaka, M.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 1975 and references cited therein.

(33) Imamoto, T.; Kusumoto, T.; Yokayama, M. *J. Chem. Soc., Chem. Commun.* **1982**, 1042.

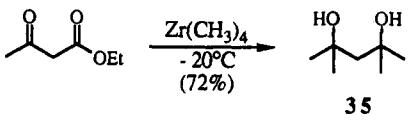
(34) Bogdanowicz, M. J.; Trost, B. M. *J. Am. Chem. Soc.* **1971**, *93*, 3773.

(35) (a) Reetz, M. T.; Steinbach, R.; Westermann, J. *Chem. Ber.* **1985**, *118*, 1421. (b) Peter, R.; Reetz, M. T.; Steinbach, R.; Wenderoth, B.; Westermann, J.; Urz, R. *Angew. Chem.* **1982**, *94*, 133. (c) Jung, A.; Reetz, M. T. *J. Am. Chem. Soc.* **1983**, *105*, 4833.

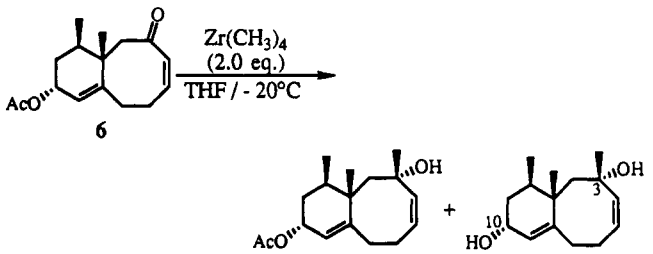
Scheme XII



Scheme XIII

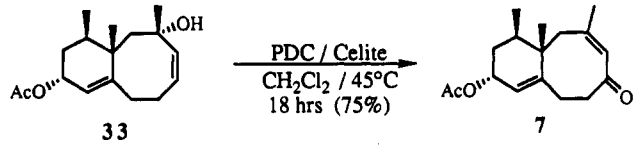


Scheme XIV



Reaction Time	33	36
20 seconds	86%	---
30 seconds	77%	13%
5 minutes	---	50%

Scheme XV



led to deacetylation of the C(10) alcohol (cf. **36**). Formation of diol **36** was inconsequential since the secondary C(10)-hydroxyl could be selectively acetylated by using standard conditions to regenerate **33** in quantitative yield. It is noteworthy that the cyclic nature of organozirconium reactions[35c] precludes conjugate addition of the methyl group in the preparation of **33** and accounts for the stereochemistry of the newly formed C(3) chiral center.

The final step in preparing enone **7** was the oxidative rearrangement of **33**. This oxidation proceeds smoothly using pyridinium dichromate to furnish enone **7** in 75% yield (Scheme XV).[36]

Three manipulations remained to complete our synthesis: (1) the migration of the C(3),C(4) double bond to C(2),C(3); (2) the stereospecific hydroxylation of C(4);[37] and (3) acetylation of the C(4)-hydroxyl group. Our first strategy relied on the generation of through-conjugated silyl dienol ether **37** (Scheme XVI). In previous research photolysis of 3-alkylcyclooctenones[38a] and the base-promoted isomerizations of 3-methylcycloalkenones[38b,39] afforded the corresponding β,γ-substituted cyclooctenones (Scheme XVII).[40-42] These studies suggested that deconjugation of **7** would lead to β,γ-enone **39**, which contains a relatively acidic allylic methylene unit positioned next to the carbonyl, thus facilitating the specific formation of dienol silyl ether **37** (e.g. **39** → **37**). With this strategy in mind enone **7** was irradiated (365 nm, 7 h in cyclohexane) at ambient temperature to yield a single product, identified as the exocyclic isomer (**40**, Scheme XVIII). This result was confusing because photoisomerizations proceed via free radical pathways and the exocyclic olefin is clearly the result of the less stable primary radical.[43] Identical results were obtained whether the allylic alcohol in the six-membered ring was protected or not.

The formation of the exocyclic olefin under photolytic conditions led us to study base-catalyzed isomerizations. Attempts to generate and trap the endocyclic dienolate derived from **7** using standard thermodynamic conditions also failed.[44] For example, subjection of **7** to excess DBN in refluxing benzene for up to 5 days afforded only recovered starting material.[41,42]

Babler and others discovered that ketalization of cyclic enones occurs with deconjugation of the enone.[45] Ketalization of **7** using ethylene glycol in refluxing benzene with a catalytic quantity of *p*-toluenesulfonic acid did migrate the C(3),C(4) double bond; however, the isolated product (**41**) contained not only an exocyclic olefin but also a heteroannular diene (Scheme XIX). Ketalization conditions could not be developed to avoid the elimination of the C(10)-acetate.[46] Thus we were forced to devise another route to complete the functionalization of the eight-membered ring.

If enone **7** was stereospecifically epoxidized from the β-face, the resulting epoxide would have the required stereochemistry at C(4) (Scheme XX). Moreover, this epoxide could be opened with a Lewis acid to form a

(36) For the use of PCC in these oxidations, see: Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682. For the 1,3-oxidative rearrangement of dienols using PDC, see: Majetich, G.; Condon, S.; Hull, K.; Ahmad, S. *Tetrahedron Lett.* **1989**, *30*, 1033.

(37) (a) Gallucci, J. C.; Lin, H. S.; Paquette, L. A. *Tetrahedron Lett.* **1987**, *28*, 1363. (b) Hassner, A.; Pinnick, H. W.; Reuss, R. H. *J. Org. Chem.* **1975**, *40*, 3427.

(38) For a study of the photochemical deconjugation reaction of 3-alkylcyclooctenone derivatives, see: (a) Pirrung, M. C.; Webster, N. J. G. *J. Org. Chem.* **1987**, *52*, 3603. For related studies with 3-alkyl-2-cyclohexen-1-ones, see: (b) Weedon, A. C. In *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum: New York, 1984; pp 61-143.

(39) (a) Heap, N.; Whitham, G. H. *J. Chem. Soc. B* **1966**, 164. (b) Whitham, G. H.; Zaidlewicz, M. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1509.

(40) Whitham has suggested that the effectiveness of conjugation between the carbonyl and the double bond of a medium ring enone decreases with increasing ring size.[39] This work was extended by Hirsch and co-workers,[41] who have proposed that this decreased conjugation results in the increased stability of the deconjugated system relative to the conjugated system, because the π-system of the isolated double bond can be more effectively bonded while making fewer conformational demands on the ring system.

(41) (a) Hirsch, J. A.; Mease, R. C. *J. Org. Chem.* **1984**, *49*, 2925. (b) Eskola, P.; Hirsch, J. A. *Medium-Ring Systems. Synthesis and Isomerizations of Medium-Ring 3-Methylenecycloalkanones and 3-Methylcycloalkenones*, in press.

(42) Boll, W. A.; Schubart, R.; Vogel, E. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 510.

(43) (a) Barltrop, J. A.; Willis, J. *Tetrahedron Lett.* **1968**, 4987. (b) See also ref 38a. Recent work suggests that the photochemical deconjugation reaction of 3-alkyl-2-cyclohexenones requires the presence of catalytic amounts of a weak acid in order to proceed. See: (c) Rudolph, A.; Weedon, A. C. *J. Am. Chem. soc.* **1989**, *111*, 8756.

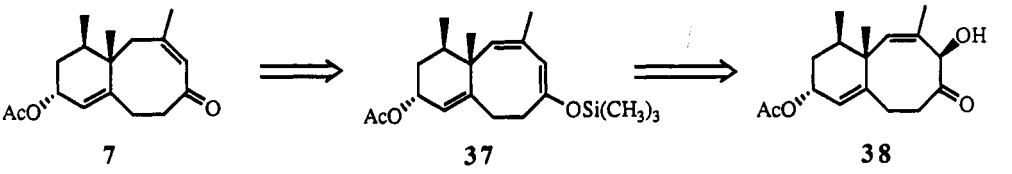
(44) For other reagents and conditions examined, see: (a) Meinwald, J.; Hendry, L. *J. Org. Chem.* **1971**, *36*, 1446. (b) Shibasaki, M.; Mase, T.; Ikegami, S. *J. Am. Chem. Soc.* **1986**, *108*, 2090.

(45) (a) Babler, J. H.; Malak, N. C.; Coghlan, M. J. *J. Org. Chem.* **1978**, *43*, 1821 and references cited therein. (b) Santelli, M. *C. R. Hebd. Seances Acad. Sci.* **1965**, *261*, 3150.

(46) The use of 1,3-propanediol, or its silylated analogue,[47] gave only the exocyclic olefin.

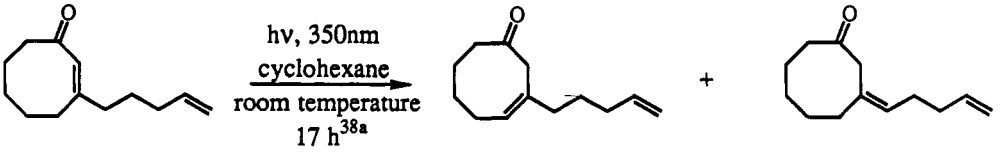
(47) Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.

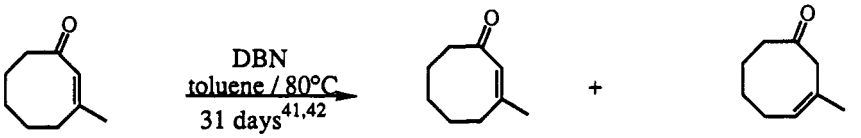
Scheme XVI



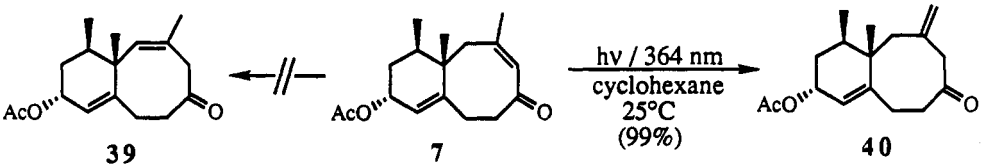
7 37 38

Scheme XVII



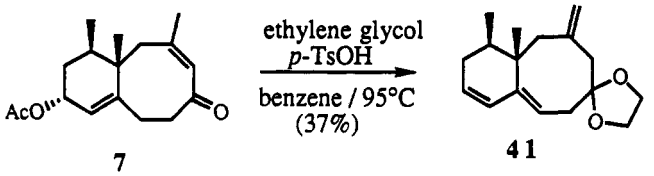


Scheme XVIII



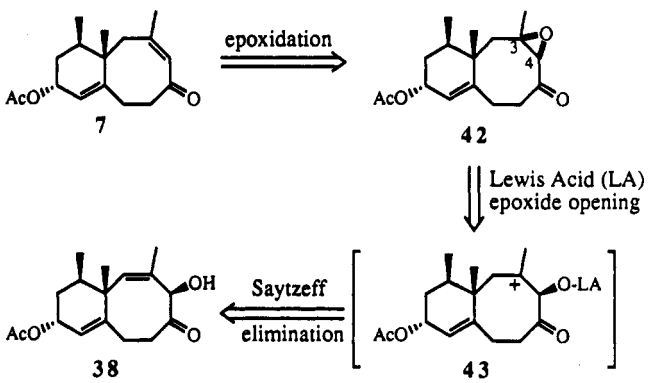
39 7 40

Scheme XIX



7 41

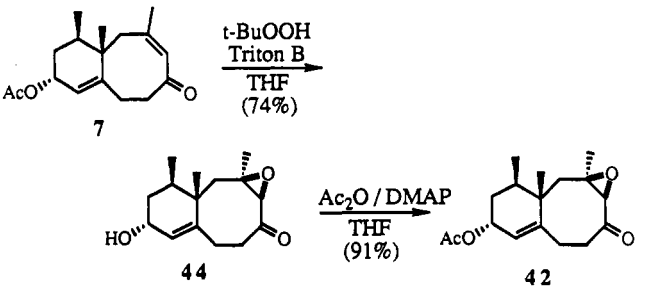
Scheme XX



7 42 38 43

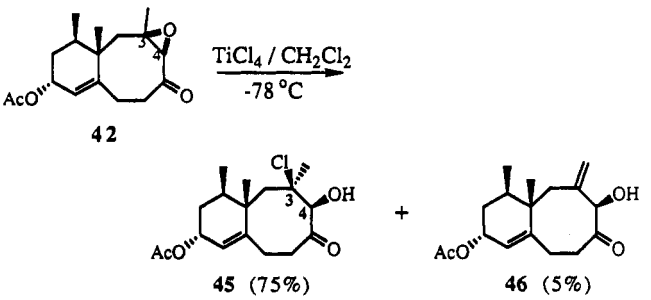
tertiary carbonium ion (43), capable of producing the more-substituted C(2),C(3) double bond upon Saytzeff elimination.[48] Epoxidation of 7 using the bulky *tert*-butyl hydroperoxide anion, which is strongly influenced by steric effects,[49] yielded a single epoxide, which was assigned as the desired isomer 44 (Scheme XXI). Although the acetate protecting group was lost because of the basic conditions used, reprotection of the epoxy alcohol posed no difficulty.

Scheme XXI



7 44 42

Scheme XXII

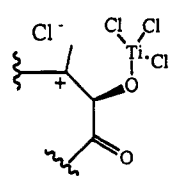


42 45 (75%) 46 (5%)

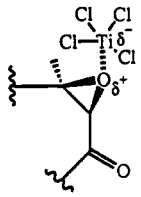
On several occasions we noted that the C(10)-acetate was sensitive to moderately acidic or basic conditions; hence, the safest approach to open the C(3),C(4)-epoxide would be to begin with mild Lewis acids and to proceed accordingly. Although we tried weak Lewis acids such as $(CH_3)_3Al$,[20] ZnI_2,[50a] $MgBr_2$,[50b] $Ti(i\text{-}OPr)_4$,[50c] TMSi/DBU,[50d] and DATMP,[23c] only strong Lewis acids such as titanium

(48) House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 5083.
(49) (a) Finnegan, R. A.; Yang, N. C. *J. Am. Chem. Soc.* **1958**, *80*, 5845. (b) Burke, S. D.; Grieco, P. A.; Marinovic, N.; Nishizawa, M.; Oguri, T. *J. Am. Chem. Soc.* **1977**, *99*, 5773.
(50) (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (b) Filler, R.; Horwitz, J. P.; Naqvi, S. M. *J. Am. Chem. Soc.* **1957**, *79*, 6283. (c) Hashimoto, K.; Kaji, K.; Masaki, Y.; Serizawa, Y. *Bull. Chem. Soc. Japan* **1984**, *57*, 3476. (d) Frazier, K.; Kraus, G. *J. Org. Chem.* **1980**, *45*, 2579.

Scheme XXIII



(ix) via S_N1



(x) via S_N1

tetrachloride or ethylaluminum dichloride were effective.[51] For example, treatment of epoxide **42** with excess titanium tetrachloride in tetrahydrofuran at −78 °C led to the formation of chlorohydrin **45** as a single diastereomer in 75% yield (Scheme XXII) with allylic alcohol **46** isolated as a minor side product (≤5%). The relative stereochemistry of the chlorine in **45** is based on the assumption that the substitution occurs via an S_N1 mechanism from the sterically more accessible face of **45** or via an S_Ni displacement of the C(3)-oxygen bond by the chlorine ligand of the coordinated Lewis acid as illustrated in Scheme XXIII.[52] The failure of chlorohydrin **45** to regenerate epoxide **42** upon treatment with various bases supports our stereochemical assignment.

The formation of allylic alcohol **46**, although seemingly a setback, substantiated our belief that a teritary carbonium ion, *in the absence of nucleophiles*, would undergo an E_1 elimination. We decided to use silver salts to form carbonium ion **43**. The real question, in light of the preference of cyclooctenones to exist out of conjugation, was whether the olefin formed would be endocyclic or exocyclic. As a precaution the C(3)-hydroxyl group was acetylated.[53]

Four silver salts of varying strengths were investigated. Reaction of chloride **47** with silver nitrate afforded only recovered starting material,[54a] whereas silver tetrafluoroborate[54b] and silver trifluoromethanesulfonate[54c] proved to be too harsh and resulted in either decomposition of **47** or the formation of multiple products, none of which was shown to be neolemnanyl acetate. Fortunately, treatment of **47** with silver trifluoroacetate in refluxing benzene furnished a separable mixture of neolemnanyl acetate (**1**) and its exocyclic isomer **48** in 35% yield each (Scheme XXIV). The spectral and chromatographic properties of synthetic (±)-neolemnanyl acetate were identical with those of an authentic sample prepared by acetylating neolemnane. In an attempt to isomerize the exocyclic double bond, a 1:1 mixture of **1** and **48** was treated with rhodium trichloride and heated.[55-57] Unfortunately, the isomer ratio was not affected, while prolonged exposure gave elimination of the C(10)-acetate unit.

Having prepared neolemnanyl acetate, our attention turned to neolemnane. Although selective deprotection of the C(10)-acetate of neolemnanyl acetate would directly afford neolemnane, hydrolysis gave only alcohol **38** (Scheme XXIV). The use of protecting groups to differentiate the C(4)- and C(10)-allylic alcohols ultimately permitted the preparation of neolemnane (Scheme XXV). The formate protecting group was chosen on the basis of its compatibility with titanium tetrachloride [necessary for opening the C(2),C(3)-epoxide] and its capability to be removed selectively even in the presence of the C(4)-acetate.[58,59] Addition of epoxy alcohol **44** to acetic formic anhydride, prepared from anhydrous formic acid and acetic anhydride, gave formate ester **49** in 95% yield after standing at room temperature for 18 h. These conditions precluded solvolysis of the C(10) alcohol and preserved the stereochemistry of this chiral center. Reaction of epoxide **49** with $TiCl_4$ gave chlorohydrin **50** in good yield. The C(4)-hydroxyl group was then acetylated in 75% overall yield from epoxide **49**. Dehydrohalogenation of tertiary chloride **51** with silver trifluoroacetate yielded a separable mixture of cyclooctenones **52** and **53** in 67% yield in a 1:2 ratio, respectively. Finally, the formate protecting group was selectively removed with $KHCO_3$/aqueous methanol to afford neolemnane (**2**). The NMR (300 MHz), infrared and mass spectra as well as the chromatographic properties of synthetic (±)-neolemnane were identical with those of a sample kindly furnished by Professor William Fenical, thus confirming the first total syntesis of this sesquiterpene.

The above syntheses showcase the utility of 4-butenyl dienone cyclizations for the efficient assembly of polycylic cyclooctanoids. Additional applications of this methodology are forthcoming.

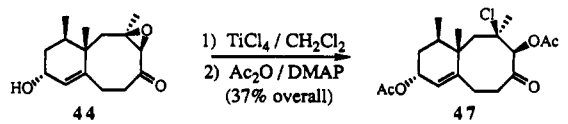
Experimental Section

General.[60] All reactions were run under an inert atmosphere of nitrogen and monitored by TLC analysis until the starting material was completely consumed. Unless otherwise indicated, all ethereal workups consisted of the following procedure: the reaction was quenched at rt with saturated aqueous ammonium chloride. The organic solvent was removed under reduced pressure on a rotary evaporator and the residue was taken up in ether, washed with brine, and dried over anhyd $MgSO_4$. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 1 Torr to constant weight, afforded a crude residue, which was purified by flash chromatography using NM

(51) Boron trifluoride etherate failed to react with epoxide **42**. For successful epoxide openings using $BF_3{\cdot}Et_2O$, see: Blackett, B. N.; Coxon, J. M.; Hartshorn, M. P.; Richards, K. E. *Tetrahedron* **1969**, *25*, 4999.

(52) For an example of nucleophilic epoxide opening with retention of configuration at the site of bond formation, see: (a) Hayashi, M. Yamamoto, M.; *Jpn. Kokai Tokkyo Koho* **1986**, 5. For examples of Lewis acid mediated epoxide openings with inversion, see: (b) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560. (c) Chong, J. M.; Sharpless, K. B.; *Ibid.* **1985**, *50*, 1563.

(53) Bis-acetate **47** was prepared from alcohol **44** in two steps but in only 37% overall yield.



44 **47**

(54) (a) Ayer, R. P.; Cromwell, N. H.; Foster, P. W. *J. Am. Chem. Soc.* **1960**, *82*, 130. (b) Brugger, M.; Eschenmoser, A.; Peter, H.; Schreiber, J. *Helv Chim. Acta* **1963**, *46*, 577. (c) Booth, B. L.; Haszeldine, R. N.; Khosrow, L. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2887.

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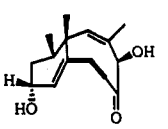
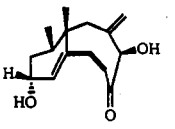
(56) For successful examples of medium-sized ring double isomerizations, see: (a) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 6868; (b) **1985**, *107*, 7352. (c) Mehta, G.; Murthy, A. N. *J. Chem. Soc., Chem. Commun.* **1984**, 1058. (d) Mehta, G.; Murthy, A. N. *J. Org. Chem.* **1987**, *52*, 2875.

(57) Based on MM3 calculations on diols **48** and **49**, enone **48** is more stable by more than 11 kcal.



(**48**) 19.98 kcals



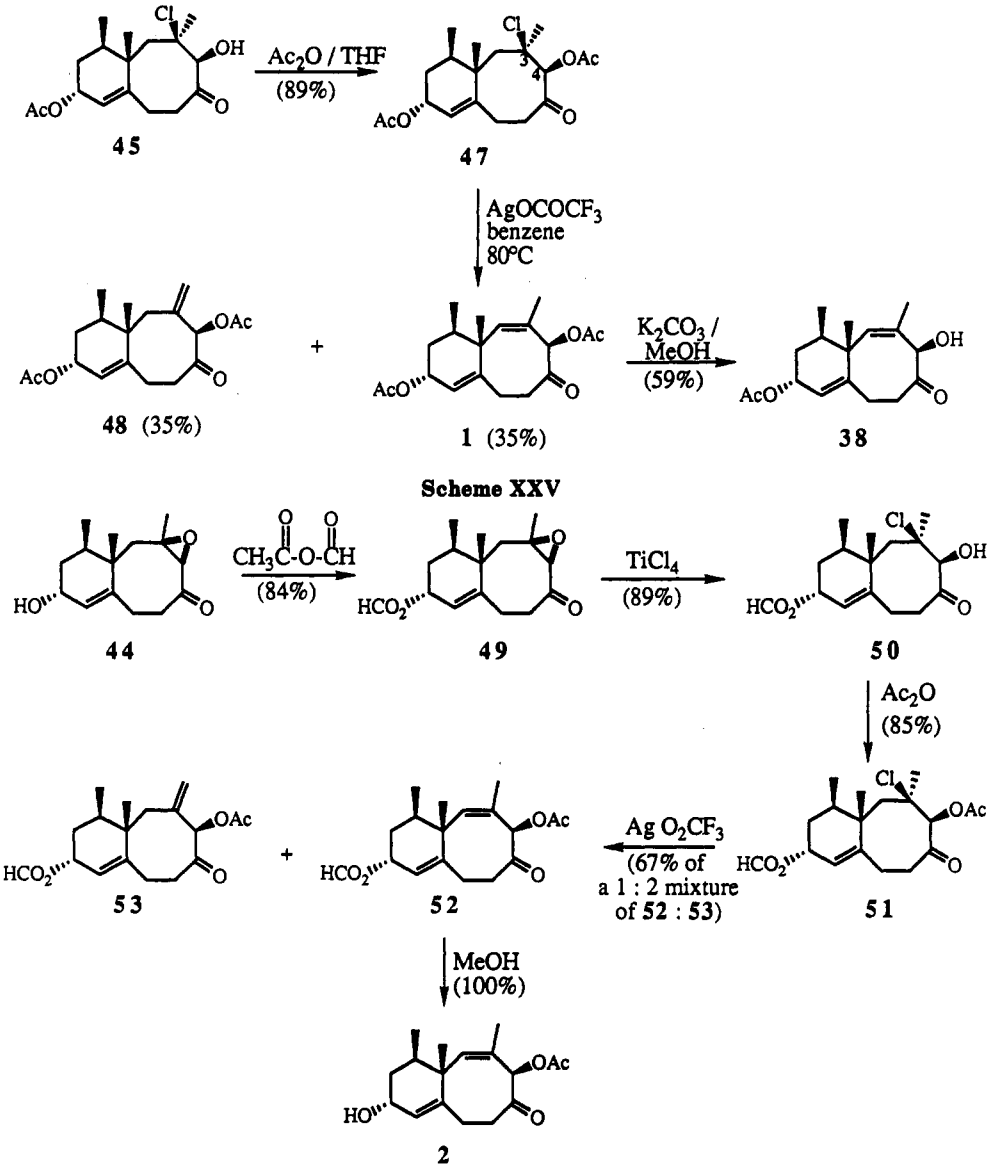
(**49**) 8.22 kcals

(58) (a) Loewenthal, H. J. E. *Tetrahedron* **1959**, *6*, 269. (b) Reber, F.; Lardon, A.; Reichstein, T. *Helv. Chim. Acta* **1954**, *37*, 45.

(59) Various silyl or benzyl ethers were shown to be incompatible with these requirements.

(60) For a general description of the experimental procedures employed in this research, see: ref 6.

Scheme XXIV



Scheme XXV

silica gel 60 (230–400 mesh ASTM) and distilled reagent-grade solvents. Unless otherwise indicated, all NMR spectra were obtained with $CDCl_3$ as solvent.

4-(Trimethylsilyl)-2-butynyl Iodide (9). To a solution of 4.45 g (31.3 mmol) of 4-(trimethylsilyl)-2-butyn-1-ol[15] in 125 mL of dry THF and 4.80 mL (3.48 g, 34.5 mmol) of TEA at 0 °C was added dropwise 2.67 mL (3.95 g, 34.5 mmol) of methanesulfonyl chloride over a 5-min period; a thick precipitate formed. The mixture was stirred for 2 h with gradual warming to rt. Filtration followed by careful evaporation of the solvent in vacuo afforded the crude mesylate, which was used directly in the next reaction without further purification.

The crude mesylate (ca. 31.3 mol) was diluted with freshly distilled acetone (200 mL) and cooled to 0 °C. Anhyd NaI (7.00 g, ca. 47.0 mmol) was added, resulting in the formation of a thick yellow precipitate. The mixture was stirred for 2 h at 0 °C and then warmed to rt. The reaction mixture was filtered and the filtrate was concentrated in vauo to afford 9.50 g of crude iodide, which was purified on silica gel (elution with petroleum ether) to give 5.81 g (74%) of iodide **9**, which was homogeneous by TLC analysis (H:E, 9:1, R_f(alcohol) = 0.05, R_f(**9**) = 0.75): ^{1}H NMR (90 MHz) δ 0.18 (s, 9 H), 1.54 (t, 2 H, J = 2 Hz), 3.75 (t, 2 H, J = 2 Hz) ppm; IR (film) 2220 cm^{-1}.

3-Ethoxy-5-methyl-2-cyclohexen-1-one (3). A mixture of 42 g (0.25 mol) of 5-methylcyclohexane-1,3-dione[12] in 700 mL of absolute ethanol and 3 g (7% catalyst) of p-toluenesulfonic acid was refluxed for 9 h. After cooling the reaction mixture to rt, 1 mL of a saturated aq solution of $NaHCO_3$ was added. The solvent was removed in vacuo and the residue was diluted with 300 mL of ether. The ethereal phase was washed with cold aq 10% $NaHCO_3$ solution until the washing measured pH 9. The resulting organic phase was washed with brine, dried over anhyd $MgSO_4$, filtered, and concentrated to give 42.3 g of residue. The crude oil was distilled to give 37.1 g (83%) of **3** (bp 90–95 °C at 2 mmHg), which was homogeneous by TLC analysis (acetone:chloroform, 1:1, R_f(dione) = 0.39, R_f(**3**) = 0.76): ^{1}H NMR (90 MHz, CCl_4) δ 1.12 (d, 3 H, J = 4.5 Hz), 1.38 (t, 3 H, J = 7.5 Hz), 1.80–2.50 (m, 5 H), 3.88 (q, 2 H, J = 7.5 Hz), 5.09 (s, 1 H).

5,6-Dimethyl-3-ethoxy-2-cyclohexen-1-one (8). To a solution of LDA, prepared from 6.3 g (62.3 mmol) of diisopropylamine in 52 mL of freshly distilled THF and 43.0 mL (62.3 mmol) of n-butyllithium (1.45 M in hexane) at −78 °C, was added a solution of 8.0 g (51.9 mmol) of 5-methyl-3-ethoxy-2-cyclohexen-1-one (**3**) in 30 mL of THF over a 30-min period. After stirring an additional hour at −78 °C, 8.11 g (57.1 mmol) of methyl iodide was added. The reaction mixture was stirred at −78 °C for 1 h was then allowed to slowly warm to rt over an 8-h period. Standard ethereal workup afforded a crude residue, which was purified by distillation (103 °C/5 mmHg) to give 6.17 g (70%) of **8**. Enone **8** was homogeneous by TLC analysis (H:E, 2:3, R_f(**3**) = 0.43, R_f(**8**) = 0.61): ^{1}H NMR (90 MHz, CCl_4) δ 1.06 (d, 6 H, J = 6 Hz), 1.35 (t, 3 H, J = 5 Hz), 1.45–2.25 (m, 4 H), 3.80 (q, 2 H, J = 7 Hz), 5.03 (s, 1 H); IR (film) 1675, 1610 cm^{-1}; ^{13}C NMR (62.89 MHz) 201.8 (s), 175.6 (s), 101.4 (d), 63.9 (t), 34.7 (t), 31.7 (d), 19.6 (d), 13.9 (q), 12.7 (q), 10.9 (q) ppm. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.35; H, 9.60.

5,6-Dimethyl-3-ethoxy-6-[4-(trimethylsilyl)-2-butynyl]-2-cyclohexen-1-one (10). To a solution of LDA prepared from 4.9 mL (35.7 mmol) of diisopropylamine in 30 mL of THF and 13.0 mL (32.5 mmol) of *n*-butyllithium (2.5 M in hexanes) at −78 °C was added a solution of 5.0 g (29.8 mmol) of 5,6-dimethyl-3-ethoxy-2-cyclohexen-1-one in 20 mL of THF containing 6.2 mL (35.7 mmol) of HMPA over a 90-min period. After an additional 20 min at −78 °C, iodide **9** (7.5 g, 29.8 mmol) was added, and the reaction mixture was allowed to warm slowly to rt over a 12-h period. The dark solution was quenched with saturated aq NH_4Cl. Standard ethereal workup gave 8.4 g of an oily residue. Purification on silica gel (elution with H:E, 5:1) afforded 6.5 g (75%) of the alkylated enone **10**, which was homogeneous by TLC analysis (H:E, 1:1, R_f(**8**) = 0.25, R_f(**10**) = 0.50): ^{1}H NMR (270 MHz, CCl_4) δ 0.00 (s, 9 H), 1.00 (s, 3 H), 1.08 (d, 3 H, J = 8 Hz), 1.22 (t, 3 H, J = 7 Hz), 1.28 (t, 2 H, J = 7 Hz), 1.85–2.70 (m, 5 H), 3.80 (q, 2 H, J = 7 Hz), 5.00 (s, 1 H) ppm; ^{13}C NMR (62.89 MHz) 202.8 (s), 174.7 (s), 101.1 (d), 79.3 (s), 75.1 (s), 64.0 (t), 47.7 (s), 34.1 (t), 33.0 (d), 25.8 (t), 17.4 (q), 15.0 (q), 14.1 (t), 7.0 (t), −2.1 (q); IR (film) 2225, 1650, 1610 cm^{-1}.

(*Z*)-5,6-Dimethyl-3-ethoxy-6-[4-(trimethylsilyl)-2-butenyl]-2-cyclohexen-1-one (11). Enone **10** (9.0 g, 31 mmol) was dissolved in 200 mL of pyridine/methanol (1:3, v/v) and 500 mg of 5% palladium on barium sulfate was added. The mixture was placed under hydrogen at atmospheric pressure and stirred for 6 h at rt. The mixture was diluted with 100 mL of ether and the catalyst was removed by filtration. The filtrate was concentrated in vacuo to yield 9.13 g of crude product, which was chromatographed on silica gel (elution with H:E, 5:1) to give 8.61 g (95%) of dienone **11**, which was homogeneous by TLC analysis (H:E, 1:1, R_f(**10**) = 0.75, R_f(**11**) = 0.78): ^{1}H NMR (270 MHz) δ −0.05 (s, 9 H), 0.94 (d, 3 H, J = 8 Hz), 0.97 (s, 3 H), 1.32 (t, 3 H, J = 7 Hz), 1.48 (t, 2 H, J = 8 Hz), 2.02–2.57 (m, 5 H), 3.84 (q, 2 H, J = 7 Hz), 5.02–5.14 (m, 1 H), 5.25 (s, 1 H), 5.34–5.49 (m, 1 H); ^{13}C NMR (62.89 MHz) 204.1 (s), 174.7 (s), 127.3 (d), 123.0 (d), 101.4 (d), 63.9 (t), 47.7 (s), 34.2 (t), 33.0 (t), 32.9 (d), 18.5 (t), 18.2 (q), 15.3 (q), 14.1 (q), −1.8 (q) ppm; IR (film) 1650, 1640, 1610 cm^{-1}; mass spectrum, m/z 294 (M^+). Anal. Calcd for $C_{17}H_{30}O_2Si$: C, 69.33; H, 10.27. Found: C, 69.01; H, 9.98.

(*Z*)-4,5-Dimethyl-4-[4-(trimethylsilyl)-2-butenyl]-3-vinyl-2-cyclohexen-1-one (4). A solution of 2.17 g (7.38 mmol) of dienol ether **11** in 30 mL of THF at 0 °C was treated dropwise with 6.4 mL (15 mmol) of vinyllithium (2.3 M in THF) over a 5-min period. The reaction mixture was stirred for 1 h with slow warming to rt. Standard ethereal workup provided 3.10 g of crude alcohol, which was used directly in the next reaction.

The crude alcohol was dissolved in 40 mL of THF at rt and treated with 35 drops of 10% hydrochloric acid. The reaction mixture was stirred for 30 min and then concentrated in vacuo. Standard ethereal workup provided 2.90 g of crude conjugated dienone **4**. The crude oil was chromatographed on silica gel (elution with H:E, 10:1) to afford 1.79 g (88%) of conjugated dienone **4**, which was homogeneous by TLC analysis (H:E, 2:1, R_f(**11**) = 0.55, R_f(**4**) = 0.80): ^{1}H NMR (250 MHz) δ 0.02 (s, 9 H), 0.96 (d, 3 H, J = 6 Hz), 1.06 (s, 3 H), 1.33–1.58 (m, 2 H), 2.13–2.46 (m, 3 H), 2.32 (t, 2 H, J = 9 Hz), 4.97–5.11 (m, 1 H), 5.35 ($^1/_2$ ABX dq, 1 H, J_{AB} = 10.9 Hz, J_{AX} = 1.5 Hz, J_{BX} = 1.47 Hz), 5.42–5.55 (m, 1 H), 5.67 ($^1/_2$ ABX dq, 1 H, J_{AX} = 10.9 Hz, J_{AX} = 1.5 Hz, J_{BX} = 1.47 Hz), 6.13 (s, 1 H), 6.49 (dd, 1 H, J = 17 Hz, 11 Hz); ^{13}C NMR (62.89 MHz) 199.7 (s), 166.5 (s), 134.8 (d), 128.8 (d), 124.7 (d), 122.2 (d), 120.3 (t), 42.3 (t), 41.7 (s), 34.4 (t), 34.3 (d), 19.9 (q), 19.2 (t), 16.0 (q), −1.5 (q) ppm; IR (film) 1655 cm^{-1}; mass spectrum, m/z 276 (M^+).

(4*R,4a*S**)-4,4a,5,8,9,10-Hexahydro-4,4a-dimethyl-2-(3*H*)-benzocyclooctenone (5).** A reaction vessel containing 4A molecular sieves was flame-dried under vacuum (5 min) and placed under nitrogen. A solution of 250 mg (0.15 equiv) of anhyd TBAF in 20 mL of DMF was added to the flask and stirred for 20-min, followed by addition of 3.40 mL (19.2 mmol) of HMPA. A solution of 1.77 g (6.41 mmol) of conjugated dienone **4** in 10 mL of DMF was added dropwise by syringe pump at rt over a 2.5-h period. The resulting mixture was stirred an additional 12 h. The reaction mixture was quenched by addition of water (25 mL). Standard ethereal workup furnished 1.9 g of a crude oily residue. Purification on silica gel (elution with H:E, 7:1) provided 130 mg (10%) of the 1,2-adduct, 3,6-diethenyl-4,7-dimethylbicyclo[2.2.2]oct-2-en-1-ol (**12**), which was homogeneous by TLC analysis (H:E, 2:1, R_f(**4**) = 0.80, R_f(**12**) = 0.70): ^{1}H NMR (90 MHz, CCl_4) δ 0.80 (d, 3 H, J = 6 Hz), 1.01 (s, 3 H), 1.10–2.20 (m, 7 H), 4.70–5.20 (m, 4 H), 5.05 (br s, 1 H), 5.40–6.15 (m, 2 H) ppm; IR (film) 3600–3200 cm^{-1}.

Continued elution provided 784 mg (60%) of **5**, which was homogeneous by TLC analysis (H:E, 2:1, R_f(**5**) = 0.55): ^{1}H NMR (250 MHz) δ 1.02 (s, 3 H), 1.03 (d, 3 H, J = 6 Hz), 1.13–1.46 (m, 3 H), 1.95–2.59 (m, 8 H), 5.52–5.64 (m, 1 H), 5.68–5.82 (m, 1 H), 5.87 (s, 1 H); ^{13}C NMR (62.89 MHz) 199.3 (s), 175.1 (s), 132.0 (d), 129.3 (d), 128.2 (d), 46.5 (s), 41.6 (t), 33.9 (t), 33.8 (d), 32.8 (t), 31.1 (t), 27.3 (t), 18.7 (q), 15.8 (q) ppm; IR (film) 1665, 1640, 1610 cm^{-1}; mass spectrum, m/z 204 (M^+). Anal. Calcd for $C_{14}H_{20}C$: C, 82.29; H, 9.87. Found: C, 82.10; H, 10.05.

(2*S,4*R**,4a*S**)-2,3,4,4a,5,8,9,10-Octahydro-4,4a-dimethylbenzocyclooctadien-2-ol (13).** To a solution of 11 mg (0.29 mmol) of $LiAlH_4$ suspended in 3 mL of dry THF at −78 °C was added dropwise 50 mg (0.24 mmol) of enone **5** dissolved in 1 mL of THF over a 3-min period. The resulting mixture was allowed to slowly warm to 0 °C over a 3-h period. The reaction mixture was quenched by dropwise addition of water. Standard ethereal workup afforded 60 mg of an oily residue. The crude oil was chromatographed on silica gel (elution with H:E, 6:1) to yield 5 mg (10%) of the axial alcohol **14**, which was homogeneous by TLC analysis (H:E, 1:1, R_f(**5**) = 0.65, R_f(**14**) = 0.62): ^{1}H NMR (270 MHz) δ 0.88 (s, 3 H), 0.98 (d, 3 H, J = 7 Hz), 1.25–1.40 (m, 1 H), 1.50 (br s, 1 H), 1.48–1.68 (m, 1 H), 1.84–2.26 (m, 6 H), 2.39 (dd, 2 H, J = 9 Hz, 10 Hz), 4.04 (m, 1 H), 5.56–5.65 (m, 1 H), 5.62 (d, 1 H, J = 5.6 Hz), 5.70–5.80 (m, 1 H); ^{13}C NMR (62.89 MHz) 152.0 (s), 131.6 (d), 128.7 (d), 126.2 (d), 64.2 (d), 45.3 (s), 35.7 (t), 32.9 (t), 32.6 (t), 31.9 (t), 27.6 (d), 27.5 (t), 19.3 (q), 16.0 (q) ppm; IR (film) 3500–3150 cm^{-1}; mass spectrum, m/z 206 (M^+). Anal. Calcd for $C_{14}H_{22}O$: C, 81.49; H, 10.75. Found: C, 81.27; H, 10.57.

Continued elution provided 42.9 mg (85%) of the equatorial alcohol **13**, which was homogeneous by TLC analysis (H:E, 1:1, R_f(**13**) = 0.59): ^{1}H NMR (250 MHz) δ 0.92 (s, 3 H), 0.97 (d, 3 H, J = 8 Hz), 1.71–2.38 (m, 9 H), 4.25 (dd, 1 H, J = 9.0, 7 Hz), 5.42 (d, 1 H, J = 1.3 Hz), 5.48–5.59 (m, 1 H), 5.68–5.78 (m, 1 H); ^{13}C NMR (62.89 MHz) 149.0 (s), 131.7 (d), 129.3 (d), 128.5 (d), 67.9 (d), 45.1 (s), 37.3 (t), 32.9 (t), 32.7 (t), 32.3 (t), 31.9 (d), 27.5 (t), 20.7 (q), 16.2 (q) ppm; IR (film) 3550-3300 (broad) cm^{-1}; mass spectrum, m/z 206 (M^+).

(2*R,4*R**,4a*S**)-2,3,4,4a,5,8,9,10-Octahydro-4,4a-dimethylbenzocyclooctadien-2-ol (14).** To a solution of 750 mg (3.68 mmol) of enone **5** in 20 mL of dry THF at −70 °C was added dropwise 7.35 mL (7.35 mmol) of L-Selectride (1 M in THF, Aldrich) over a 3-min period. The reaction mixture was stirred for 2 h at −70 °C and then allowed to slowly warm to 0 °C over a 3-h period. Standard ethereal workup provided 900 mg of a crude oil. Purification on silica gel (elution with H:E, 6:1) yielded 575 mg (76%) of the axial alcohol **14**, which was identical with that previously characterized.

Continued elution yielded 143 mg (19%) of the equatorial alcohol **13**, which was identical with that previously characterized.

(4*R,4a*S**)-6,7-Epoxy-4,4a,5,6,7,8,9,10-octahydro-4,4a-dimethylbenzocycloocten-2(3*H*)-one (18).** To a cold solution (−5 °C) of 100 mg of enone **5** (0.49 mmol) in 5 mL of freshly distilled CH_2Cl_2 was added 0.132 g of *m*-CPBA (0.735 mmol) in two equal portions over a period of 30 min. The resultant solution was allowed to warm to rt over a period of 6 h then quenched with 2 mL of saturated aq $NaHCO_3$. The layers were separated and the aq layer was extracted with ether (3 × 50 mL). The combined organic phases were extracted with saturated aq $NaHCO_3$ (30 mL) and brine (20 mL) followed by drying over anhyd $MgSO_4$. Concentration in vacuo provided a crude yellow oil, which was purified via column chromatography (elution with H:E, 2:1) to give 69.5 mg (64%) of epoxide **18** as a pale yellow oil, which was homogeneous by TLC analysis (H:E, 3:2, R_f = 0.24): ^{1}H NMR (250 MHz) δ 1.00 (s, 3 H), 1.07 (d, 3 H, J = 6.6 Hz), 1.12–1.38 (m, 2 H), 1.41–1.59 (m, 2 H), 2.15–2.51 (m, 4 H), 2.80–2.99 (m, 2 H), 5.91 (s, 1 H); ^{13}C NMR (62.89 MHz) 198.8, 173.7, 129.0, 55.5, 52.9, 41.8, 41.5, 34.0, 33.4, 32.6, 29.9, 26.5, 18.8, 15.6 ppm.

(4*R,4a*S**)-6,7-Epoxy-4,4a,5,6,7,8,9,10-octahydro-4,4a-dimethylspiro[3*H*-benzocyclooctene-2,2′-[1,3]dithiolane] (19).** To a solution of 69 mg of epoxide **18** (0.31 mmol) in 2 mL of freshly distilled methanol at rt was added 47 μL of ethanedithiol (0.56

mmol) and 46 μL of boron trifluoride etherate, respectively. The resultant solution was allowed to stir at rt for 2 h followed by quenching with 2 mL of water. Standard ethereal workup provided a yellow oil. Purification via column chromatography (elution with H:E, 3:1) yielded 30.8 mg (33%) of thioketal **19** as a foul smelling yellow oil, which was homogeneous by TLC analysis (H:E, 3:2, R_f = 0.59): ^{1}H NMR (90 MHz) δ 0.85 (s, 3 H), 0.99 (d, 3 H, J = 5 Hz), 1.09–1.42 (m, 2 H), 1.43–2.30 (m, 9 H), 2.45–2.93 (m, 2 H), 3.05–3.40 (m, 4 H), 5.51 (s, 1 H); ^{13}C NMR (62.89 MHz) 147.3, 130.2, 65.5, 55.8, 53.8, 45.4, 39.9, 39.6, 39.5, 34.3, 32.4, 32.0, 29.8, 26.8, 20.3, 15.9 ppm.

(2*R,4*R**,4a*S**)-2,3,4,4a,5,8,9,10-Octahydro-2-(acetyloxy)-4,4a-dimethylbenzocyclooctadiene (20).** To a solution of alcohol **14** (0.38 g, 2.1 mmol) in 20 mL of dry THF were added 0.22 mL of Ac_2O (2.4 mmol) and 5.0 mg of DMAP. The resulting mixture was allowed to stir at rt for 12 h. Standard ethereal workup yielded a crude yellow oil. Purification via column chromatography (elution with H:E, 5:1) yielded 410 mg (90%) of **20**, which was homogeneous by TLC analysis (H:E, 1:1, R_f(**20**) = 0.75): ^{1}H NMR (250 MHz) δ 0.84 (s, 3 H), 0.93 (d, 3 H, J = 7.5 Hz), 1.25–2.0 (m, 6 H), 2.05 (s, 3 H), 2.06–2.27 (m, 3 H), 2.38 (dd, 1 H, J = 16.8 Hz, 12 Hz), 5.09 (m, 1 H), 5.53 (d, 1 H, J = 5.45 Hz), 5.56–5.80 (m, 3 H); ^{13}C NMR (62.89 MHz) 171.1 (s), 154.1 (s), 131.4 (d), 128.4 (d), 122.2 (d), 67.7 (d), 44.9 (s), 32.8 (t), 32.7 (t), 32.5 (t), 31.7 (t), 28.6 (q), 27.4 (t), 21.5 (d), 19.4 (q), 15.8 (q) ppm; IR (film) 1720 cm^{-1}; mass spectrum, m/z 188 (M − 60).

(2*R,4*R**,4a*S**)-2,3,4,4a,5,6,9,10-Octahydro-2-(acetyloxy)-4,4a-dimethyl-6-oxobenzocyclooctadiene (6).** This experiment was carried out in a three-neck 25-mL round-bottom flask equipped with a dry ice condenser, a gas bubbler inlet, and a rubber septum. A solution of 86 mg of acetate **20** (0.34 mmol), 2 mg of TPP, 34 μL of Ac_2O (0.36 mmol), 14 μL of pyridine (0.17 mmol), 2 mg of DMAP, and 10 mL of dry CH_2Cl_2 was irradiated for 12 h at rt with a Sylvania 150W/120V lamp while vigorously bubbling O_2 through the solution. The reaction mixture was quenched with 5 mL of water and the aq phase was extracted with ether (3 × 30 mL). The combined organic phases were washed with saturated aq $NaHCO_3$, 2 M HCl (30 mL), and saturated aq copper sulfate and concentrated in vacuo to give a crude red oil (due to the presence of the TPP). Purification via column chromatography (elution with H:E, 7:1) gave 17 mg (20%) of unreacted **6** and 14.5 mg (13%) of enol ether **30**, which was homogeneous by TLC analysis (H:E, 1:1, R_f(**30**) = 0.59): ^{1}H NMR (250 MHz) δ 0.86 (s, 3 H), 0.92 (d, 3 H, J = 7.5 Hz), 1.50–1.70 (m, 2 H), 1.89 ($^1/_2$ ABX dq, J_{AB} = 15 Hz, J_{AX} = 9 Hz, J_{BX} = 0 Hz), 2.05 (s, 3 H), 2.09 (s, 3 H), 2.10–2.22 (m, 1 H), 2.26 ($^1/_2$ ABX dq, 1 H, J_{AB} = 15 Hz, J_{AX} = 9 Hz, J_{BX} = 0 Hz), 2.30–2.40 (m, 2 H), 2.70–2.90 (m, 2 H), 4.75–4.81 (m, 1 H), 5.05–5.15 (m, 1 H), 5.55 (d, 1 H, J = 9 Hz), 5.71 (d, 1 H, J = 5 Hz), 6.32 (d, 1 H, J = 5 Hz); ^{13}C NMR (62.89 MHz) 171.0 (s), 170.2 (s), 148.7 (s), 143.0 (d), 121.2 (d), 114.3 (d), 95.2 (d), 67.1 (d), 42.6 (t), 39.8 (s), 32.5 (t), 30.4 (q), 27.3 (t), 23.8 (t), 21.3 (d), 21.1 (q), 19.1 (q), 16.1 (q) ppm; IR (film) 1750, 1720, 1655 cm^{-1}; mass spectrum, m/z 263 (M − 59).

Continued elution proved 47.4 mg (52%) of enone **6**, which was homogeneous by TLC analysis (H:E, 1:1, R_f(**6**) = 0.43): ^{1}H NMR (300 MHz) δ 0.96 (d, 3 H, J = 4.8 Hz), 0.98 (s, 3 H), 1.60 (m, 2 H), 1.88 (m, 1 H), 2.00 (s, 3 H), 2.24 (ddd, 1 H, J = 14.3 Hz, 11.6 Hz, 8.1 Hz), 2.38–2.49 (m, 1 H), 2.65 ($^1/_2$ AB q, 1 H, J = 13.2 Hz), 2.79 (ddd, 1 H, J = 10.6 Hz, 9.9 Hz, 1.6 Hz), 2.90–3.05 (m, 1 H), 3.08 ($^1/_2$ AB q, 1 H, J = 13.2 Hz), 5.00–5.05 (m, 1 H), 5.54 (d, 1 H, J = 5.1 Hz), 6.02 (dt, 1 H, J = 12.0 Hz, 1.9 Hz), 6.42 (ddd, 1 H, J = 12.0 Hz, 9.3 Hz, 7.5 Hz); ^{13}C NMR (62.89 MHz) 201.0 (s), 171.0 (s), 147.4 (s), 142.6 (d), 134.2 (d), 126.3 (d), 67.1 (d), 52.5 (t), 40.9 (s), 32.5 (t), 32.4 (t), 31.5 (d), 26.8 (t), 21.4 (q), 19.6 (q), 15.3 (q) ppm; IR (film) 1720, 1680, 1640 cm^{-1}; mass spectrum, m/z 218 (M − 43). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.24; H, 8.46. Found: C, 73.20; H, 8.56. NOTE: Photooxygenations using more than 500 mg of acetate **20** gave increased yields of enol ether **30**.

(2*R,4*R**,4a*S**)-2,3,4,4a,5,6,9,10-Octahydro-2-(acetyloxy)-4,4a-dimethyl-6-hydroxybenzocyclooctadiene (32).** A solution of 98 mg of acetate **20** (0.39 mmol), 2 mg of TPP, and 10 mL of dry CH_2Cl_2 was irradiated for 4 h at rt with a Sylvania 150W/120V lamp while vigorously bubbling O_2 through the solution (apparatus described in preceding experimental). The reaction mixture was concentrated in vacuo to give a crude red oil. Purification via column chromatography (elution with H:E, 4:1) gave 31.7 mg (28%) of (2*R**,4*R**,4a*S**)-2,3,4,4a,5,6,9,10-octahydro-2-acetoxy-4,4a-dimethyl-benzocyclooctadien-6-yl hydroperoxide (**31**), which was was homogeneous by TLC analysis (H:E, 1:1, R_f(**31**) = 0.75): ^{1}H NMR (250 MHz) δ 0.84 (s, 3 H), 0.92 (d, 3 H, J = 7.1 Hz), 1.68 (dd, 2 H, J = 11.3 Hz, 3.6 Hz), 1.72–2.35 (m, 6 H), 2.06 (s, 3 H), 2.51–2.71 (m, 1 H), 4.42–4.55 (m, 1 H), 5.12–5.22 (m, 1 H), 5.61 (d, 1 H, J = 5.1 Hz), 5.70–5.80 (m, 1 H), 5.85–6.02 (m, 1 H), 8.22 (br s, 1 H); ^{13}C NMR (62.89 MHz) 171.1 (s), 152.3 (s), 133.5 (d), 130.2 (d), 124.4 (d), 81.4 (d), 67.5 (d), 40.5 (s), 40.2 (t), 32.4 (t), 31.9 (t), 30.2 (t), 28.9 (d), 21.5 (q), 20.1 (q), 15.6 (q) ppm.

Triphenylphosphine (29.6 mg, 0.11 mmol) was added to a solution of 31 mg of hydroperoxide **31** (0.11 mmol) in 4 mL of dry ether at rt, and the resulting solution was allowed to stir for 15 min. The reaction mixture was diluted with 1 mL of cold water and then worked up to provide a pale yellow oil. Purification via column chromatography (elution with H:E, 2:1) gave 18 mg (60%) of **32**, which was was homogeneous by TLC analysis (H:E, 1:1, R_f(**32**) = 0.25): ^{1}H NMR (250 MHz) δ 0.87 (s, 3 H), 0.94 (d, 3 H, J = 7.5 Hz), 1.56–1.65 (m, 1 H), 1.67–1.75 (m, 2 H), 1.90–2.02 (m, 4 H), 2.05 (s, 3 H), 2.21 (dd, 2 H, J = 7.1 Hz, 3.0 Hz), 2.48–2.65 (m, 1 H), 4.16–4.28 (m, 1 H), 5.17 (q, 1 H, J = 4.3 Hz), 5.58 (d, 1 H, J = 4.7 Hz), 5.61–5.71 (m, 1 H), 5.79 (dd, 1 H, J = 10.1 Hz, 6.3 Hz).

Preparation of 6 from 32. Allylic alcohol **32** (18 mg, 0.06 mmol) was dissolved in 12 mL of dry CH_2Cl_2 containing 10 mg of 4A molecular sieves. To this solution was added 39 mg (0.18 mmol) of pyridinium chlorochromate, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with 20 mL of CH_2Cl_2 and washed with brine (50 mL). The resulting solution was dried over anhyd $MgSO_4$ and filtered. Evaporation of the solvent and purification by column chromatography (elution with H:E, 1:1) afforded 16.9 mg (95%) of enone **6**, which was identical with the product obtained from the photooxygenation of **20**.

(4*R,4a*S**,10*R**)-2,3,4,4a,5,6,7,8,9,10-Decahydro-2-acetoxy-8-chloro-4,4a-dimethyl-6-oxobenzocyclooctene (34).** Methyllithium (1.4 M in diethyl ether, 64 μL, 0.089 mmol) was added dropwise to a cold solution (0 °C) of enone **6** (15 mg, 0.06 mmol) in 3 mL of dry THF. The resulting solution was allowed to stir at 0 °C for a 10-min period, followed by the addition of 7.6 μL of chlorotrimethylsilane (0.06 mmol). After being warmed to rt and stirred for 5 h, the reaction mixture was quenched with 2 drops of cold water. Standard ethereal workup yielded a crude yellow oil, which was purified via column chromatography (elution with H:E, 3:1) to provide 18 mg (50%) of ketone **34**, which was was homogeneous by TLC analysis (H:E, 1:1, R_f(**34**) = 0.60): ^{1}H NMR (250 MHz) δ 0.93 (s, 3 H), 0.97 (d, 3 H, J = 5.2 Hz), 1.60–1.90 (m, 5 H), 2.07 (s, 3 H), 2.08–2.32 (m, 2 H), 2.53 (d, 1 H, J = 13.0 Hz), 2.68–3.09 (m, 3 H), 4.46–4.50 (m, 1 H), 5.12–5.22 (m, 1 H), 5.73 (d, $^1/_2$ H, J = 5.2 Hz), 5.78 (d, $^1/_2$ H, J = 5.2 Hz); ^{13}C NMR (62.89 MHz) 207.8, 207.8, 170.8, 170.7, 149.8, 148.8, 124.2, 123.2, 66.7, 66.6, 56.5, 54.1, 53.2, 52.4, 50.5, 49.5, 42.8, 42.6, 41.1, 40.7, 33.4, 32.4, 32.1, 31.7, 29.0, 27.2, 21.4, 21.3, 20.0, 18.2, 15.9, 15.2 ppm; IR (film) 1770, 1750, 1730, 1705 cm^{-1}; mass spectrum, m/z 298 (M$^+$). These data represent a mixture of diastereomers.

(2*R,4*S**,4a*S**,6*S**)-2,3,4,4a,5,6,9,10-Octahydro-2-(acetyloxy)-4,4a,6-trimethyl-6-hydroxybenzocyclooctadiene (33).** Methyllithium (1.68 mL, 2.35 mmol, 1.4 M in diethyl ether) was added dropwise to a cold suspension (−20 °C) of 137 mg (0.58 mmol) of $ZrCl_4$ in 1 mL of freshly distilled THF. The resulting mixture was stirred at −20 °C for 20 min and then a solution of 77 mg of enone **6** (0.29 mmol) in 2 mL of THF was added in a single portion. The resulting solution was stirred for 30 s at −20 °C and then quenched by the addition of 1 mL of water. Standard ethereal workup afforded a pale yellow oil, which was purified by column chromatography (gradient elution, H:E, 5:1 to 1:1) to give 63 mg (77%) of crystalline alcohol **33**, which was homogeneous by TLC analysis (H:E, 1:2, R_f(**33**) = 0.79): ^{1}H NMR (300 MHz) δ 0.86 (s, 3 H), 0.95 (d, 3 H, J = 6.8 Hz), 1.27 (s, 3 H), 1.56 (dd, 1 H, J = 11.2 Hz, 3.7 Hz), 1.56–1.68 (m, 1 H), 1.97 ($^1/_2$ AB q, 1 H, J = 15.6 Hz), 2.03 (s, 3 H), 2.09 ($^1/_2$ AB q, 1 H, J = 15.6 Hz), 2.00–2.20 (m, 3 H), 2.40–2.70 (m, 3 H), 5.05–5.15 (m, 1 H), 5.28–5.59 (m, 3 H); ^{13}C NMR (62.89 MHz) 171.0 (s), 150.9 (s), 138.0 (d), 124.6 (d), 124.1 (d), 73.9 (s), 67.7 (d), 48.8 (t), 41.0 (s), 34.7 (t),

32.9 (t), 32.7 (q), 30.7 (q), 24.0 (t), 21.4 (q), 21.1 (q), 15.9 (q) ppm; IR (film) 3520–3150 (br) cm^{-1}; mass spectrum, m/z 218 (M – 60); mp 74–75 °C.

Continued elution provided 9.0 mg (13%) of (2*R**,4*S**,4a*S**,6*S**)-2,3,4,4a,5,6,9,10-octahydro-2,6-dihydroxy-4,4a,6-trimethylbenzocyclooctadiene (**36**), which was homogeneous by TLC analysis (H:E, 1:2, R_f(**36**) = 0.22): ^{1}H NMR (300 MHz) δ 0.86 (s, 3 H), 0.97 (d, 3 H, J = 6.6 Hz), 1.28 (s, 3 H), 1.43–1.68 (m, 2 H), 1.54 (dd, 1 H, J = 15 Hz, 6.0 Hz), 1.54–1.68 (m, 1 H), 1.96 ($^1/_2$ AB q, 1 H, J = 18 Hz), 2.0–2.2 (m, 4 H), 2.40–2.70 (m, 3 H), 3.96–4.08 (m, 1 H), 5.28–5.44 (m, 1 H), 5.50–5.13 (m, 2 H); ^{13}C NMR (62.89 MHz) 148.0 (s), 138.0 (d), 128.3 (d), 124.8 (d), 74.1 (s), 64.3 (d), 48.7 (t), 41.2 (s), 36.3 (t), 34.1 (t), 33.1 (d), 29.7 (q), 24.2 (t), 21.3 (q), 16.2 (q) ppm; IR (film) 3700–3100 (br) cm^{-1}; mass spectrum, m/z 218 (M – 18). NOTE: On occasion, the crude reaction mixture of **33** and **36** was directly acetylated to give only alcohol **33** after workup.

(1*R,3*R**,10a*S**)-1,2,3,5,9,10a-Hexahydro-3-(acetyloxy)-1,9,10a-trimethylbenzocycloocten-7(6*H*)-one (7).** To a magnetically stirred slurry of pyridinium dichromate (0.35 g, 0.94 mole) and 300 mg of Celite in 5 mL of freshly distilled CH_2Cl_2 was added in a single portion a solution of 65 mg of acetate **33** (0.235 mmol) in 10 mL of CH_2Cl_2 at rt. The resulting solution was then heated to 45 °C and allowed to stir for 18 h. The reaction mixture was then cooled and diluted with ether, and the solids were filtered off. The organic layer was washed with water and the aq washings were back extracted with ether (3 × 30 mL). The combined organic extracts were washed with brine, dried over anhyd $MgSO_4$, and concentrated in vacuo to afford a pale brown solid. Purification via column chromatography (elution with H:E, 3:1) yielded 48.7 mg (75%) of enone **7** as a white crystalline solid, which was homogeneous by TLC analysis (H:E, 1:2, R_f(**7**) = 0.45): ^{1}H NMR (250 MHz) δ 0.98 (d, 3 H, J = 5.8 Hz), 1.00 (s, 3 H), 1.53–1.65 (m, 2 H), 1.73–1.95 (m, 1 H), 1.98 (s, 3 H), 2.05 (s, 3 H), 2.31 ($^1/_2$ AB q, 1 H, J = 12.7 Hz), 2.25–2.45 (m, 1 H), 2.61 (dt, 2 H, J = 28.0 Hz, 13.8 Hz), 3.05–3.20 (m, 1 H), 3.11 ($^1/_2$ AB q, 1 H, J = 12.7 Hz), 4.98–5.06 (m, 1 H), 5.63 (d, 1 H, J = 5.4 Hz), 6.05 (s, 1 H); ^{13}C NMR (62.89 MHz) 201.0 (s), 170.7 (s), 153.8 (s), 147.2 (s), 131.7 (d), 126.4 (d), 66.4 (d), 42.7 (s), 41.7 (t), 41.0 (t), 32.4 (t), 30.0 (d), 30.0 (q), 29.8 (t), 21.4 (q), 18.9 (q), 15.7 (q) ppm; IR (film) 1725, 1710, 1650 cm^{-1}; mass spectrum, m/z 216 (M – 60); mp 110–111 °C. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.87; H, 8.76. Found: C, 73.99; H, 9.00.

(1*R,3*R**,10a*S**)-1,2,3,5,8,9,10,10a-Octahydro-3-(acetyloxy)-1,10a-dimethyl-9-methylenebenzocycloocten-7(6*H*)-one (40).** A solution of enone **7** (11 mg, 0.04 mmol) in 5 mL of freshly distilled cyclohexane was irradiated at 364 nm for 7 h at rt. The reaction mixture was concentrated in vacuo to give a crude yellow oil, which was purified via column chromatography (elution with H:E, 3:1) to furnish 10.8 mg (99%) of enone **40**. Enone **40** was homogeneous by TLC analysis (H:E, 1:2 R_f(**40**) = 0.58): ^{1}H NMR (250 MHz) δ 0.84 (s, 3 H), 0.90 (d, 3 H, J = 6.8 Hz), 1.34–1.50 (m, 1 H), 1.52–1.84 (m, 2 H), 2.07 (s, 3 H), 2.27 (br s, 2 H), 2.29–2.52 (m, 2 H), 2.55–2.68 (m, 2 H), 2.86 ($^1/_2$ AB q, 1 H, J = 15.0 Hz), 3.64 ($^1/_2$ AB q, 1 H, J = 15.0 Hz), 4.89 (d, 2 H, J = 7.8 Hz), 5.14–5.24 (m, 1 H), 5.84 (d, 1 H, J = 5.2 Hz); ^{13}C NMR (62.89 MHz) 211.8 (s), 170.8 (s), 151.5 (s), 140.9 (s), 122.6 (d), 116.5 (t), 67.0 (d), 48.6 (t), 48.5 (t), 42.0 (t), 40.2 (s), 32.6 (t), 28.6 (q), 27.2 (t), 21.4 (d), 20.1 (q), 15.2 (q) ppm; IR (film) 1970, 1840, 1810, 1730, 1705 cm^{-1}; mass spectrum, m/z 276 (M^+).

(4*S,4a*S**)-3,4,4a,5,6,7,8,9-Octahydro-4,4a-dimethyl-6-methylenebenzocyclooctadiene-8-spiro-2′-[1,3]-dioxolane (41).** A solution of 19 mg of enone **7** (0.7 mmol), 12 μL of ethylene glycol (0.21 mmol), 1 mg of *p*-toluenesulfonic acid, and 7 mL of dry benzene was refluxed at 90 °C for 30 min. The reaction mixture was cooled and then diluted with 20 mL of ether and 20 mL of saturated aq $NaHCO_3$. Standard ethereal workup, followed by purification via column chromatography (elution with hexanes/ether, 5:1), yielded 6 mg (37%) of a pale yellow oil, which was homogeneous by TLC analysis (H:E, 1:2, R_f(**41**) = 0.67): ^{1}H NMR (250 MHz) δ 0.91 (s, 3 H), 0.93 (d, 3 H, J = 7.0 Hz), 1.62–1.86 (m, 3 H), 1.95–2.38 (m, 3 H), 2.29 ($^1/_2$ AB q, 1 H, J = 15.0 Hz), 2.50 (t, 1 H, J = 12.5 Hz), 2.78 ($^1/_2$ AB q, 1 H, J = 15.0 Hz), 3.86–4.50 (m, 4 H), 4.87 (d, 2 H, J = 2.0 Hz); ^{13}C NMR (62.89 MHz) 144.2, 131.1, 122.2, 121.4, 116.5, 111.0, 64.4, 63.7, 44.4, 44.1, 40.0, 28.6, 27.8, 18.0, 13.4 ppm; IR (film) 1650 cm^{-1}; mass spectrum, m/z 216 (M^+); UV (MeOH) λ_{max} = 243 nm (ε = 1.04).

(1*R,3*R**,10a*S**)-8,9-Epoxy-1,2,3,5,8,9,10,10a-octahydro-3-hydroxy-1,9,10a-trimethylbenzocycloocten-7(6*H*)-one (44).** To a solution of 61.1 mg of acetate **7** (0.22 mmol) in 2 mL of THF at 0 °C were added 0.201 mL of 40% Triton B in methanol (0.44 mmol) and 0.1 mL of 90% *tert*-butyl hydroperoxide in methanol (0.885 mmol). The resulting solution was allowed to warm to rt over a 6-h period and then quenched with saturated aq NH_4Cl. Standard ethereal workup provided 91 mg of a crude residue. Purification via column chromatography (elution with H:E, 3:1) gave 41 mg (74%) of a white amorphous solid (**44**), which was homogeneous by TLC analysis (H:E, 2:5, R_f(**44**) = 0.20): ^{1}H NMR (250 MHz) δ 0.84 (s, 3 H), 0.98 (d, 3 H, J = 6.8 Hz), 1.52 (s, 3 H), 1.55–1.72 (m, 1 H), 2.00 ($^1/_2$ AB q, 1 H, J = 15.1 Hz), 2.01 (br s, 1 H), 2.28 ($^1/_2$ AB q, 1 H, J = 15.1 Hz), 2.28–2.45 (m, 5 H), 3.05–3.18 (m, 1 H), 3.12 (s, 1 H), 4.03–4.11 (m, 1 H), 5.67 (d, 1 H, J = 5.3 Hz); ^{13}C NMR (62.89 MHz) 209.5 (s), 146.4 (s), 131.4 (d), 66.9 (d), 63.2 (d), 61.8 (s), 41.9 (t), 35.8 (t), 35.0 (t), 29.3 (s), 28.1 (q), 28.0 (t), 27.3 (d), 20.0 (q), 16.0 (q) ppm; IR (film) 3600–3100 (br) cm^{-1}; mass spectrum, m/z 222 (M – 28); mp 121–122 °C. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.95; H, 8.86. Found: C, 71.78; H, 8.85.

(1*R,3*R**,8*R**,9*R**,10a*S**)-8,9-Epoxy-1,2,3,5,8,9,10,10a-octahydro-3-(acetyloxy)-1,9,10a-trimethylbenzocycloocten-7(6*H*)-one (42).** To a stirred solution of 60 mg of epoxy ketone **44** (0.24 mmol) in 1 mL of dry THF were added an excess of Ac_2O (1 mL) was 1 mg of DMAP. The resulting solution was allowed to stir at rt for 12 h and then quenched by the addition of 1 mL of cold water. Standard ethereal workup afforded 71 mg of a yellow oil. Purification via column chromatography (elution with H:E, 5:1) provided 63.7 mg (91%) of a white amorphous solid, which was homogeneous by TLC analysis (H:E, 1:4, R_f(**44**) = 0.50): ^{1}H NMR (250 MHz) δ 0.84 (s, 3 H), 0.99 (d, 3 H, J = 6.4 Hz), 1.54 (s, 3 H), 1.59–1.63 (m, 2 H), 1.77 ($^1/_2$ AB q, 1 H, J = 15.2 Hz), 2.07 (s, 3 H), 2.25–2.53 (m, 4 H), 2.29 ($^1/_2$ AB q, 1 H, J = 15.2 Hz), 2.88–2.97 (m, 1 H), 3.19 (s, 1 H), 5.08–5.12 (m, 1 H), 5.74 (d, 1 H, J = 5.72 Hz); ^{13}C NMR (62.89 MHz) 207.6 (s), 170.6 (s), 148.5 (s), 126.7 (d), 66.6 (d), 66.4 (d), 60.9 (s), 41.0 (t), 40.9 (t), 37.4 (t), 32.2 (t), 29.6 (s), 28.9 (q), 26.7 (d), 21.3 (q), 20.0 (q), 15.7 (q) ppm; IR (film) 1765, 1745, 1690, 1600, 1300, 1280, 1250 cm^{-1}; mass spectrum, m/z 250 (M – 42); mp 72–73 °C.

(1*R,3*R**,8*R**,9*R**,10a*S**)-1,2,3,5,8,9,10,10a-Octahydro-3-(acetyloxy)-9-chloro-8-hydroxy-1,9,10a-trimethylbenzocycloocten-7(6*H*)-one (45).** To a solution of epoxy ketone **42** (34 mg, 0.11 mmol) in 2 mL of dry CH_2Cl_2 under nitrogen at –78 °C was added 51 μL of $TiCl_4$ (0.46 mmol) dropwise over a 60-s period. The resulting solution was allowed to stir at 78 °C for 5 min and then quenched with 5 mL of wet ether, followed by the addition of 2 mL of cold water. The resulting heterogeneous solution was separated and the aq layer was extracted with ether (3 × 30 mL). The combined organic phases were washed with brine, dried over anhyd $MgSO_4$, filtered, and concentrated in vacuo to provide 57 mg of a crude yellow oil. Further purification via column chromatography (elution with H:E, 5:1) afforded 28.7 mg of chloro alcohol **45** (75%) as a clear yellow amorphous solid, which was homogenous by TLC analysis (H:E, 1:4, R_f(**45**) = 0.68): ^{1}H NMR (300 MHz) δ 0.96 (s, 3 H), 1.04 (d, 3 H, J = 6.8 Hz), 1.68 (dd, 2 H, J = 9.0 Hz, 3.0 Hz), 1.94 (s, 3 H), 2.08 (s, 3 H), 2.26–2.48 (m, 2 H), 2.53 ($^1/_2$ AB q, 1 H, J = 16.0 Hz), 2.57 ($^1/_2$ AB q, 1 H, J = 16.0 Hz), 2.67 (t, $^1/_2$ H, J = 6.98 Hz), 2.74 (t, 1 H, J = 5.6 Hz), 2.81 (t, $^1/_2$ H, J = 6.88 Hz), 3.02–3.12 (m, 1 H), 3.73 (d, 1 H, J = 6.4 Hz), 4.59 (d, 1 H, J = 6.4 Hz), 5.09–5.17 (m, 1 H), 5.78 (d, 1 H, J = 5.6 Hz); ^{13}C NMR (67.41 MHz) 208.1, 170.7, 149.5, 124.3, 79.3, 75.5, 66.5, 48.4, 42.4, 32.6, 31.1, 29.2, 27.8, 21.4, 21.2, 15.6 ppm; IR (film) 3600–3200 (br) cm^{-1}; mass spectrum, m/z 250 (M – 78); mp 138–139 °C.

Continued elution afforded 1.6 mg (4.7%) of (1*R**,3*R**,8*R**,10a*S**)-1,2,3,5,8,9,10,10a-octahydro-3-(acetyloxy)-1,10a-dimethyl-8-hydroxy-9-methylenebenzocycloocten-7(6*H*)-one (**46**) as a clear yellow oil, which was homogeneous by TLC analysis (H:E, 1:4, R_f(**46**) = 0.29): ^{1}H NMR (300 MHz) δ 0.86 (s, 3 H), 0.90 (d, 3 H, J = 6.4 Hz), 1.44–1.78 (m, 5 H), 2.08 (s, 3 H), 2.20 ($^1/_2$ AB q, 1 H, J = 17.9 Hz), 2.26–2.50 (m, 1 H), 2.44 ($^1/_2$ AB q, 1 H, J = 17.9 Hz), 2.67–2.83 (m, 1 H), 3.02 (d, 1 H, J = 8.3 Hz), 4.89 (d, 1 H, J = 8.3 Hz), 5.07 (br s, 1 H), 5.16–5.22 (m, 1 H), 5.41 (br s, 1 H), 5.84 (d, 1 H, J = 5.7 Hz).

(1R*,3R*,8R*,9R*,10aS*)-1,2,3,5,8,9,10,10a-Octahydro-8-chloro-3,8-bis(acetyloxy)-1,9,10a-trimethylbenzocycloocten-7(6H)-one (47). A solution of 31.5 mg of alcohol **45** (0.96 mmol), 0.9 mL of Ac_2O and 0.2 mL of pyridine was stirred at rt for 8 h. The reaction mixture was diluted with 2 mL of cold water and allowed to stir for 10 min at rt. The resulting solution was diluted with ether and the layers were separated. Standard ethereal workup gave 47 mg of a crude yellow oil. Purification via column chromatography (elution with H:E, 3:1) gave 31.7 mg (89%) of diacetate **47** as a white amorphous powder, which was homogeneous by TLC analysis (H:E, 1:4, R_f(**47**) = 0.73): ^{1}H NMR (300 MHz) δ 0.91 (s, 3 H), 1.02 (d, 3 H, J = 6.8 Hz), 1.67 (dd, 2 H, J = 8.0 Hz, 2.8 Hz), 1.87 (s, 3 H), 2.03 (s, 3 H), 2.19 (s, 3 H), 2.28–2.58 (m, 3 H), 2.43 ($^1/_2$ AB q, 1 H, J = 14.2 Hz), 2.55 ($^1/_2$ AB q, 1 H, J = 14.2 Hz), 2.69–2.95 (m, 2 H), 5.12–5.16 (m, 1 H), 5.46 (br s, 1 H), 5.91 (d, 1 H, J = 5.5 Hz); ^{13}C NMR (67.41 MHz) 203.4 (s), 171.2 (s), 169.9 (s), 149.2 (s), 124.0 (d), 80.6 (d), 71.9 (s), 66.0 (d), 47.5 (t), 44.6 (t), 42.2 (s), 33.0 (q), 30.9 (t), 29.9 (t), 28.9 (q), 26.0 (d), 21.2 (q), 20.4 (q), 15.8 (q) ppm; IR (film) 1715, 1705, 1670 cm^{-1}; mass spectrum, m/z 335 (M – 35).

(1R*,3R*,8R*,10aS*)-1,2,3,5,8,9,10,10a-Octahydro-3,8-bis(acetyloxy)-1,10a-dimethyl-9-methylenebenzocycloocten-7(6H)-one (48). A solution of 1.8 mg of alcohol **46** (0.006 mmol), 0.5 mL of Ac_2O, and 0.1 mL of pyridine was stirred at rt for 8 h. The reaction mixture was diluted with 2 mL of cold water and 5 mL of ether. The heterogenous solution was stirred for 20 min at rt. Standard ethereal workup gave 2.9 mg of a crude yellow oil. Purification via column chromatography (elution with H:E, 3:1) gave 1.5 mg (74%) of crystalline diacetate **48**, which was homogeneous by TLC analysis (H:E, 1:4, R_f(**48**) = 0.80): ^{1}H NMR (300 MHz) δ 0.88 (s, 3 H), 0.92 (d, 3 H, J = 5.9 Hz), 1.55–1.82 (m, 2 H), 2.01 (s, 3 H), 2.13 (s, 3 H), 2.25–2.50 (m 4 H), 2.70 (dt, 1 H, J = 12.6 Hz, 3.5 Hz), 2.98 (td, 1 H, J = 13.0 Hz, 6.4 Hz), 5.08 (br s, 1 H), 5.15–5.23 (m, 1 H), 5.39 (br s, 1 H), 5.71 (br s, 1 H), 5.94 (d, 1 H, J = 5.5 Hz); ^{13}C NMR (67.41 MHz) 208.5, 170.9, 170.2, 150.3, 138.2, 123.8, 114.9, 76.9, 66.7, 53.8, 46.9, 41.0, 40.3, 29.5, 28.4, 26.8, 21.2, 20.0, 15.3 ppm; mp 91–92 °C.

Neolemnanyl Acetate (1). To a solution of diacetate **47** (9.8 mg, 0.026 mmol) in 2 mL of freshly distilled benzene at rt was added silver trifluoroacetate (23 mg, 0.106 mmol) in a single portion. The resulting solution was heated to 80 °C for 6 h. The reaction mixture was then cooled, diluted with 1 mL cold water, and allowed to stir for 5 min. The organic layer was extracted with ether (3 × 30 mL). The ethereal extracts were combined, washed with brine, dried over anhyd $MgSO_4$, filtered, and concentrated in vacuo to afford a clear yellow oil. Purification by column chromatography (elution with H:E, 20:1) yielded 3.0 mg (35%) of **1**, which was homogeneous by TLC analysis (H:E, 1:4, R_f(**1**) = 0.69): ^{1}H NMR (300 MHz) δ 0.98 (d, 3 H, J = 6.86 Hz), 1.00 (s, 3 H), 1.70 (d, 2 H, J = 1.2 Hz), 1.70–1.83 (m, 4 H), 2.01 (s, 3 H), 2.11 (s, 3 H), 2.14–2.50 (m, 2 H), 2.63–2.68 (m, 2 H), 5.18–5.26 (m, 1 H), 5.51 (s, 1 H), 5.87 (d, 1 H, J = 5.2 Hz), 6.38 (s, 1 H); ^{13}C NMR (67.41 MHz) 202.2, 171.0, 169.7, 152.9, 138.1, 127.1, 121.1, 76.5, 66.7, 44.2, 43.9, 34.3, 32.6, 29.6, 28.1, 21.1, 20.4, 18.1, 16.6 ppm. This data is identical with the 300-MHz NMR spectrum of authentic neolemnanyl acetate.

Continued elution afforded 3.0 mg (35%) of **48**.

(1R*,3R*,8R*,10aS*)-1,2,3,5,8,10a-Hexahydro-3-(acetyloxy)-8-hydroxy-1,9,10a-trimethylbenzocycloocten-7(6H)-one (38). To a solution of 2 mg of neolemnanyl acetate in 1 mL of anhyd methanol was added 0.8 mg of anhyd K_2CO_3. The resulting solution was allowed to stir at 0 °C for 12 h. Standard ethereal workup afforded 1.9 mg of a pale yellow oil. Purification via column chromatography (elution with H:E, 1:1) provided 1.0 mg (59%) of alcohol **38**, which was homogeneous by TLC analysis (H:E, 1:4, R_f(**38**) = 0.69): ^{1}H NMR (250 MHz) δ 0.84 (s, 3 H), 0.97 (d, 3 H, J = 6.8 Hz), 1.51 (s, 3 H), 1.63 (m, 2 H), 1.84 ($^1/_2$ AB q, 1 H, J_{AB} = 15.4 Hz), 2.27 ($^1/_2$ AB q, 1 H, J_{AB} = 15.4 Hz), 2.22–2.45 (m, 4 H), 2.97 (m, 1 H), 3.16 (s, 1 H), 5.22 (m, 1 H), 5.69 (d, 1 H, J = 5.7 Hz), 8.07 (s, 1 H); ^{13}C NMR (62.89 MHz) 207.7, 160.6, 149.1, 126.3, 66.5, 66.3, 60.9, 41.2, 41.0, 36.6, 32.2, 28.9, 28.8, 27.0, 19.9, 15.6 ppm.

(1R*,3R*,8R*,9R*,10aS*)-8,9-Epoxy-1,2,3,5,8,9,10,10a-octahydro-3-(formyloxy)-1,9,10a-trimethylbenzocycloocten-7(6H)-one (49). Anhyd formic acid (0.5 mL) was added to 1.0 mL of Ac_2O. The resultant solution was stirred for 15 min and then added to a stirred solution of 70 mg of epoxy ketone **44** (0.28 mmol) in 0.1 mL of pyridine at rt. The resulting solution was allowed to stir at rt for 12 h and then quenched by the addition of 1 mL of cold water. Standard ethereal workup afforded 71 mg of a yellow oil. Purification via column chromatography (elution with H:E, 5:1) provided 65 mg (84%) of crystalline formate **49**, which was homogeneous by TLC analysis (H:E, 1:1, R_f(**49**) = 0.47): ^{1}H NMR (300 MHz) δ 0.84 (s, 3 H), 0.97 (d, 3 H, J = 6.9 Hz), 1.51 (s, 3 H), 1.63 (m, 2 H), 1.84 ($^1/_2$ AB q, 1 H, J_{AB} = 15.4 Hz), 2.27 ($^1/_2$ AB q, 1 H, J_{AB} = 15.4 Hz), 2.22–2.45 (m, 4 H), 2.97 (m, 1 H), 3.16 (s, 1 H), 5.22 (m, 1 H), 5.69 (d, 1 H, J = 5.7 Hz), 8.07 (s, 1 H); ^{13}C NMR (67.41 MHz) 207.7, 160.6, 149.1, 126.3, 66.5, 66.3, 60.9, 41.2, 41.0, 36.6, 32.2, 28.9, 28.8, 27.0, 19.9, 15.6 ppm; IR (film) 2950, 1715 cm^{-1}; mass spectrum, m/z 278 (M$^+$); mp 104–105 °C.

(1R*,3R*,8R*,9R*,10aS*)-1,2,3,5,8,9,10,10a-Octahydro-9-chloro-3-(formyloxy)-8-hydroxy-1,9,10a-trimethylbenzocycloocten-7(6H)-one (50). To a solution of epoxy ketone **49** (34 mg, 0.12 mmol) in 2 mL of dry CH_2Cl_2 under nitrogen at –78 °C was added 51 μL of $TiCl_4$ (0.46 mmol) dropwise over a 60-s period. The resulting solution was allowed to stir at –78 °C for 5 min and then quenched with 5 mL of wet ether, followed by the addition of 2 mL of cold water. Standard ethereal workup provided 47 mg of a crude yellow oil. Further purification via column chromatography (elution with H:E, 5:1) afforded 34.2 mg of chloro alcohol **50** (89%) as a amorphous yellow solid, which was homogenous by TLC analysis (H:E, 1:4, R_f(**50**) = 0.68): ^{1}H NMR (300 MHz) δ 0.94 (s, 3 H), 1.03 (d, 3 H, J = 6.8 Hz), 1.71 (m, 2 H), 1.92 (s, 3 H), 2.3–2.5 (m, 2 H), 2.54 (d, 2 H, J = 8.1 Hz), 2.6–2.8 (m, 2 H), 3.06 (m, 1 H), 3.77 (br d, 1 H, J = 6.4 Hz), 4.54 (d, 1 H, J = 6.4 Hz), 5.29 (m, 1 H), 5.77 (d, 1 H, J = 5.58 Hz), 8.03 (s, 1 H); ^{13}C NMR (62.89 MHz) 207.8 (s), 160.6 (d), 150.4 (s), 123.5 (d), 79.1 (s), 75.8 (s), 66.2 (d), 66.2 (d), 48.2 (t), 42.5 (t), 32.4 (t), 31.0 (d), 29.1 (q), 27.5 (t), 21.1 (q), 15.5 (q) ppm; IR (film) 2940, 1710 cm^{-1}; mass spectrum, m/z 250 (M – 64); mp 94–95 °C.

(1R*,3R*,8R*,9R*,10aS*)-1,2,3,5,8,9,10,10a-Octahydro-8-(acetyloxy)-9-chloro-3-(formyloxy)-1,9,10a-trimethylbenzocycloocten-7(6H)-one (51). A solution of 34 mg of alcohol **50** (0.10 mmol), 1.0 mL of Ac_2O, and 0.1 mL of pyridine was stirred at rt for 8 h. The reaction mixture was diluted with 2 mL of cold water and 5 mL of ether. The heterogeneous solution was stirred for 20 min at rt. The layers were separated and the aq phase was extracted with ether (3 × 30 mL). The combined organic phases were washed with 20 mL of saturated aq $NaHCO_3$ and 10 mL of brine. Concentration of the dried ethereal extracts (dried over anhyd $MgSO_4$) gave 45 mg of a crude yellow oil. Purification via column chromatography (elution with H:E, 3:1) gave 32.7 mg (85%) of acetate **51** as an amorphous white solid, which was homogeneous by TLC analysis (H:E, 1:4, R_f(**51**) = 0.80): ^{1}H NMR (300 MHz) δ 0.91 (s, 3 H), 1.01 (d, 3 H, J = 6.8 Hz), 1.69 (m, 2 H), 1.85 (s, 3 H), 2.17 (s, 3 H), 2.3–2.6 (m, 3 H), 2.43 ($^1/_2$ AB q, 1 H, J_{AB} = 15.8 Hz), 2.53 ($^1/_2$ AB q, 1 H, J_{AB} = 15.8 Hz), 2.7–2.9 (m, 2 H), 5.27 (m, 1 H), 5.42 (s, 1 H), 5.90 (d, 1 H, J = 5.4 Hz), 8.02 (s, 1 H); ^{13}C NMR (67.41 MHz) 203.1 (s), 169.9 (s), 160.6 (d), 149.7 (s), 123.7 (d), 80.5 (s), 71.5 (s), 65.9 (d), 65.9 (d), 47.3 (t), 44.1 (t), 32.3 (t), 30.3 (q), 28.6 (d), 25.9 (t), 21.0 (q), 20.3 (q), 15.6 (q) ppm; IR (film) 2950, 1745, 1725, 1715 cm^{-1}; mass spectrum, m/z 321 (M – 35); mp 116–117 °C.

(1R*,3R*,8R*,10aS*)-1,2,3,5,8,9,10,10a-Octahydro-8-(acetyloxy)-3-(formyloxy)-1,10a-dimethylbenzocycloocten-7(6H)-one (52). To a solution of acetate **51** (20 mg, 0.056 mmol) in 3 mL of freshly distilled benzene at rt was added 18 μL of TEA, followed by the addition of 50.6 mg of silver trifluoroacetate (0.224 mmol) in a single portion. The resulting solution was heated to 70 °C for 4 h. The reaction mixture was then cooled, diluted with 1 mL cold water, and allowed to stir for 5 min. The organic layer was extracted with ether (3 × 30 mL). The ethereal extracts were combined, washed with brine, dried over anhyd $MgSO_4$, filtered, and concentrated in vacuo to afford a clear yellow oil. Purification by column chromatography (elution with H:E, 20:1) yielded 4.1 mg (22%) of formate **52**, which was homogeneous by TLC analysis (H:E, 1:1, R_f(**52**) = 0.52): ^{1}H NMR (300 MHz) δ 0.99 (d, 3 H, J = 6.8 Hz), 1.02 (s, 3 H), 1.71 (s, 3 H), 1.79 (m, 2 H), 2.12 (s, 3 H), 2.19 (ddd, 1 H, J = 13.4 Hz, 9.3 Hz, 7.0 Hz), 2.31 (ddd, 1 H, J = 11.6 Hz, 6.8 Hz, 4.7 Hz), 2.47 (br td, 1 H, J = 13.4 Hz, 4.7 Hz), 2.67 (m, 2 H), 5.39 (m, 1 H), 5.51 (s 1 H), 5.89 (d, 1 H, J = 5.1 Hz), 6.35 (s, 1 H), 8.04 (s, 1 H); ^{13}C NMR (67.41 MHz) 202.0, 169.8,

160.9, 153.8, 137.8, 127.4, 120.6, 76.1, 66.7, 44.1, 43.9, 34.2, 32.6, 28.1, 20.8, 20.5, 18.1, 16.5 ppm; IR (film) 2920, 1745, 1720, 1710 cm^{-1}; mass spectrum, m/z 320 (M^+).

Continued elution provided 8.0 mg of **53** (45%), which was homogeneous by TLC analysis (H:E, 1:1, R_f(**53**) = 0.48): ^1H NMR (300 MHz) δ 0.88 (s, 3 H), 0.92 (d, 3 H, J = 6.8 Hz), 1.74 (m, 2 H), 2.07 (m, 1 H), 2.14 (s, 3 H), 2.3-2.5 (m, 4 H), 2.71 (td, 1 H, J = 12.5 Hz, 3.9 Hz), 2.99 (dt, 1 H, J = 12.5 Hz, 6.3 Hz), 5.09 (s, 1 H), 5.35 (m, 1 H), 5.40 (s, 1 H), 5.56 (s, 1 H), 5.92 (d, 1 H, J = 5.3 Hz), 8.04 (s, 1 H); ^{13}C NMR (67.41 MHz) 208.5, 170.1, 160.8, 151.2, 137.8, 123.1, 115.1, 66.5, 46.2, 40.7, 40.3, 32.4, 29.6, 28.4, 26.7, 20.4, 20.1, 15.2 ppm; IR (film) 2920, 1740, 1720, 1710 cm^{-1}; mass spectrum, m/z 274 (M - 46).

Neolemnane (2). To a solution of 4.0 mg of **53** (0.012 mmol) in 2 mL of freshly distilled, dry methanol was added 0.1 mg of anhyd K_2CO_3. The resulting solution was stirred at 0 °C for 2 h and then quenched with 0.5 mL of water. Standard ethereal workup afforded 5 mg of a pale yellow oil. Purification by column chromatography (elution with H:E, 5:1) yielded 3.5 mg (95%) of **2**, which was homogeneous by TLC analysis (H:E, 1:4, R_f(**2**) = 0.35): ^1H NMR (300 MHz) δ 0.97 (d, 3 H, J = 6.8 Hz), 1.01 (s, 3 H), 1.68 (s, 3 H), 1.74 (m, 2 H), 2.13 (s, 3 H), 2.23 (m, 2 H), 2.43 (m, 1 H), 2.66 (m, 2 H), 4.19 (m, 1 H), 5.51 (s, 1 H), 5.86 (d, 1 H, J = 4.8 Hz), 6.80 (s, 1 H); ^{13}C NMR (67.41 MHz) 202.3 (s), 170.6 (s), 149.7 (s), 138.7 (d), 127.2 (s), 125.7 (d), 75.7 (d), 63.8 (d), 44.2 (s), 43.4 (t), 35.7 (t), 34.2 (d), 28.3 (t), 20.7 (q), 20.6 (q), 18.0 (q), 16.5 (q) ppm; IR (film) 3450, 2940, 1740, 1720, 1450, 1370, 1270, 1240, 1060, 1035, 1010, 930, 890, 750 cm^{-1}; mass spectrum, m/z 292 (M^+). These spectral data are identical with those of authentic neolemnane kindly provided by Professor William Fenical.

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Abbreviations. Aqeuous (aq), hexanes: ether (H:E), tetrabutylammonium fluoride (TBAF), and triethylamine (TEA).

Supplementary Material Available: NMR spectra of compounds studied (41 pages). Ordering information is given on any current masthead page.

Oxidation of 3,4-Di-*tert*-butylthiophene 1,1-Dioxide

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The oxidation of 3,4-di-*tert*-butylthiophene 1,1-dioxide (**4**) by a variety of reagents under various conditions was investigated in detail. Oxidation of **4** with peracids (MCPBA, trifluoroperacetic acid) affords the thiete 1,1-dioxide **6** and the sulfone **7**, both in moderate yield. The formation of these compounds can be explained as being the result of an acid-catalyzed rearrangement of the initial product, epoxy sulfone **5** via the carbocation **8**. Under basic conditions the rearrangement is suppressed and thus **5** can be isolated in good yield. Treatment of **5** with BF_3·Et_2O affords **6** and the sultine **10**. Oxidation of **4** with alkaline H_2O_2 involves a smooth Michael addition of HOO^- to give the hydroperoxide **17** in high yield. This represents the first example of the formation of an isolable β-hydroperoxy sulfone, a species which has been hypothesized to be an intermediate in the formation of epoxy sulfones by the oxidation of α,β-unsaturated sulfones with alkaline H_2O_2. Thermal decomposition of **17** affords the ketone **19** quantitatively. Reduction of **17** with $NaBH_4$ gives the alcohol **20**. On treatment with base, both **17** and **20** undergo ring opening to yield the alkene **18** in good yield.

Introduction

It is well known that the oxidation of α,β-unsaturated sulfones with HOO^-,[1,2] t-$BuOO^-$,[2] ClO^-,[3] and m-$ClC_6H_4CO_3^-$[2] represents a convenient route to α,β-epoxy sulfones. To our knowledge, however, only one report describes the oxidation of thiophene 1,1-dioxides, a type of cyclic α,β-unsaturated sulfone. Thus, the oxidation of benzo[*b*]thiophene 1,1-dioxide with alkaline hydrogen peroxide affords 3-oxo-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide (**1**), whereas the oxidation of the 3-alkyl- or 3-phenyl-substituted derivatives produces the corresponding 3-hydroxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxides (**2**).[4] We recently developed[5] a simple synthesis of a sterically congested molecule, 3,4-di-*tert*-butylthiophene (**3**), and described its oxidation to 3,4-di-*tert*-butylthiophene 1,1-dioxide (**4**). This method enables the preparation of **3** and **4** in large quantities. We since became interested in developing methods for converting such heterocycles to other sterically congested molecules, those in which two bulky *tert*-butyl groups occupy adjacent positions.[6] With this in mind, we investigated the oxidation of **4** to determine the general behavior of thiophene 1,1-dioxides toward oxidizing agents and in expectation of obtaining the sterically congested epoxy sulfone **5**, which is representative of a new ring system.

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