Synthesis of (±)-7,8-Epoxy-4-basmen-6-one by a Transannular Cyclization Strategy

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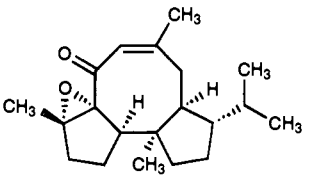
Abstract: A synthetic route to the cembranoid natural product (±)-7,8-epoxy-4-basmen-6-one (**1**) is described employing as key steps the cationic macrocyclization of the acid chloride derived from **15** to provide the ketone **16** and the photochemical transannular radical cyclization of the ester **41** to form the tricyclic hydrocarbon **50**. Product **50** was transformed into **1** in ten steps. Transition-state molecular modeling studies were found to provide accurate predictions of the structural and stereochemical outcomes of cyclization reactions explored experimentally in the development of the synthetic route to **1**. These investigations should prove valuable in the development of transannular cyclization as a strategy for synthetic simplification.

Introduction and Retrosynthetic Analysis

The use of transannular bond-forming reactions in synthesis, proceeding via cationic, free-radical, carbenoid, or other intermediates, has been limited.[1] This is likely due to the perceived difficulty of constructing the macrocyclic precursors necessary to execute such a strategy and to the problem of predicting the regiochemical and stereochemical outcomes of such reactions. Because many methods are now available for the efficient synthesis of medium and large rings, in many cases the problem of precursor synthesis no longer presents a serious concern.[2] Furthermore, as computational methods and transition-state molecular modeling progress, it is anticipated that predictive power will emerge, allowing these reactions to be incorporated with confidence in synthetic planning.

In this work we explore the use of a transannular free-radical cyclization reaction as the key step in a synthesis of the complex cembranoid natural product 7,8-epoxy-4-basmen-6-one (**1**).[3,4] While free-radical cyclization reactions have been studied in depth in acyclic systems,[5] little is known of the factors that govern the outcome of transannular free-radical cyclization



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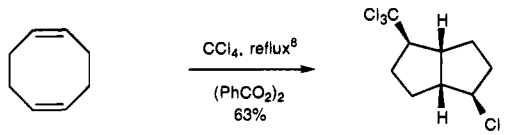
reactions. In this regard, it is instructive to consider the cyclization reaction of eq 1. It is now a paradigm of organic

(1)

chemistry that 5-*exo-trig* cyclization of 5-hexenyl radicals is a facile process whereas 5-*endo-trig* closure of 4-pentenyl radicals is so slow as to be considered "forbidden".[6,7] Thus, the feasibility of the cyclization reaction of eq 1, which is at once a 5-*exo-trig* and a 5-*endo-trig* closure, cannot be predicted on the basis of acyclic precedent. It is, in fact, observed that 1,5-cyclooctadiene reacts with molecules such as carbon tetrachloride to form substituted [3.3.0]bicyclooctanes (eq 2) stereo-



(2)

selectively in a free-radical chain process.[8] The related transformations of eqs 3 and 4 illustrate the potential of

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(1) For recent examples, see: (a) Begley, M. J.; Pattenden, G.; Smithies, S.-A. J.; Walter, D. S. *Tetrahedron Lett.* **1994**, *35*, 2413, 2417. (b) Curran, D. P.; Shen, W. *Tetrahedron* **1993**, *49*, 755. (c) Hitchcock, S. A.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4843. (d) Winkler, J. D.; Sridar, V. *J. Am. Chem. Soc.* **1986**, *108*, 1708. (e) Mehta, G.; Rao, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 8015. (f) Gonzalez, A.; Galindo, A.; Palenzuela, J. A.; Mansilla, H. *Tetrahedron Lett.* **1986**, *27*, 2771. (g) Shizuri, Y.; Yamaguchi, S.; Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 57.

(2) (a) Nishitani, K.; Konomi, T.; Mimaki, Y.; Tsunoda, T. *Heterocycles* **1993**, *36*, 1957. (b) Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 9345. (c) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593. (d) Marshall, J. A.; DeHoff, B. S.; Crooks, S. L. *Tetrahedron Lett.* **1987**, *28*, 527. (e) Nicolau, K. C.; Chakraborty, T. K.; Daines, R. A.; Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1986**, 413. (f) Marshall, J. A.; DeHoff, B. S. *Tetrahedron Lett.* **1986**, *27*, 4873. (g) Deslongchamps, P.; Brillon, D. *Tetrahedron Lett.* **1986**, *27*, 1131. (h) Deslongchamps, P. *Aldrichim. Acta* **1984**, *17*, 59. (i) Deslongchamps, P.; Lamothe, S.; Lin, H.-S. *Can. J. Chem.* **1984**, *62*, 2395. (j) Still, W. C.; Mobilio, D. *J. Org. Chem.* **1983**, *48*, 4875. (k) Takahashi, T.; Nemoto, H.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 2005, 3485. (l) McMurry, J. E.; Matz, J. R. *Tetrahedron Lett.* **1982**, *23*, 2723. (m) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 6112. (n) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

(3) Wahlberg, I.; Eklund, A.-M.; Nishida, T.; Enzell, C. R.; Berg, J.-E. *Tetrahedron Lett.* **1983**, *24*, 843.

(4) Previous work directed toward the synthesis of **1**: (a) Kang, H.-J.; Paquette, L. A. *J. Am. Chem. Soc.* **1990**, *112*, 3252. (b) Paquette, L. A.; Kang, H.-J. *J. Am. Chem. Soc.* **1991**, *113*, 2610.

(5) (a) Beckwith, A. L. J.; Schiesser, C. J. *Tetrahedron Lett.* **1985**, *26*, 373. (b) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545. (c) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. (d) Beckwith, A. L. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 484. (e) Beckwith, A. L. J.; Serelis, A. K.; Easton, C. J. *J. Chem. Soc., Chem. Commun.* **1980**, 482.

(6) For an explanation of terminology, see: Baldwin, J. E. *J. Chem. Soc., Chem. Commun.*, **1976**, 734.

(7) (a) Surzur, J.-M. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1982; Vol. 2. (b) Stork, G. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergammon Press: New York, 1983. (c) Hart, D. J. *Science* **1984**, *223*, 883.

(8) (a) Dowbenko, R. *Tetrahedron* **1964**, *20*, 1843. (b) Dowbenko, R *J. Am. Chem. Soc.* **1964**, *86*, 946. (c) Gancarz, R. A.; Kice, J. J. *J. Org. Chem.* **1981**, *46*, 4899.

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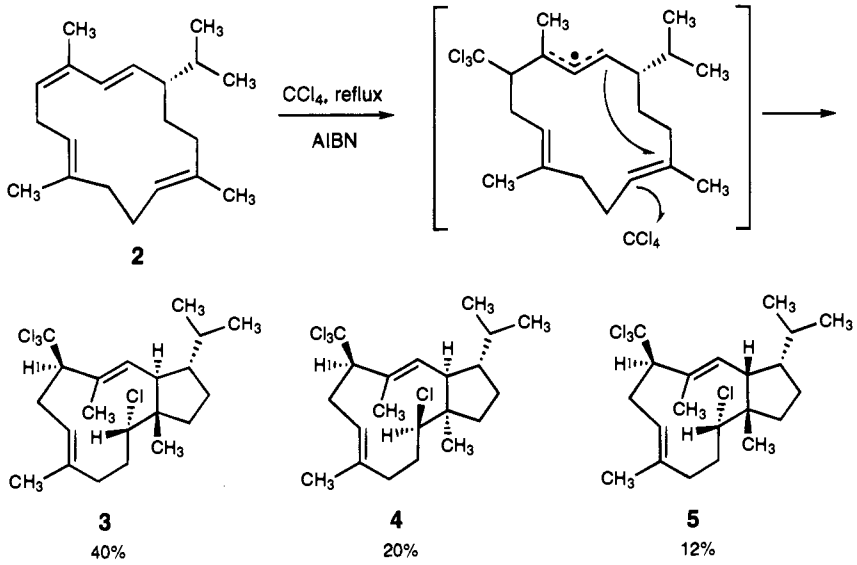
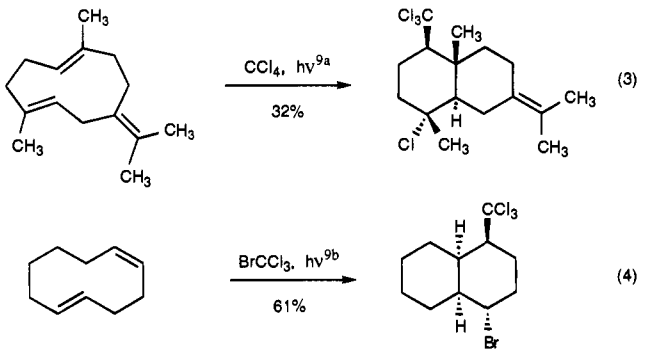
Scheme 1. Radical Cyclization of Cembrene and Products



transannular free-radical cyclization reactions to form *cis*- and *trans*-decalin systems as well.[9] These reactions follow a 6-*endo*-



trig/6-*exo-trig* closure pathway, rather than the 5-*exo-trig*/7-*endo-trig* pathway which might have been predicted on the basis of acyclic precedent.

In the course of retrosynthetic analysis of **1**, we were drawn to consider the use of a transannular free-radical cyclization strategy. This arose, in part, from biogenetic considerations, where it has been postulated that **1** may be derived from a (macrocyclic) cembranoid precursor by sequential transannular cyclizations.[3] Although it is likely that cationic intermediates would be involved in this hypothetical transformation in nature,[10] the bicyclopentyl substructure within **1** leads naturally to consideration of the use of free-radical intermediates in the construction of the basmene skeleton. It is a useful exercise to consider how such a transannular cyclization might occur within cembrene (**2**) itself. Addition of a radical to the C5 terminus of the diene produces an allylic radical that might undergo transannular addition to C12 in a 5-*exo-trig*/11-*endo-trig* cyclization reaction. To complete the tricyclic skeleton, the resultant C11-centered radical must undergo transannular 5-*endo-trig*/8-*exo-trig* closure onto C7. The latter addition appears tenuous on the basis of stereoelectronic considerations (5-*endo-trig* component of the closure) and due to the strain of the developing *trans*-cyclooctene ring in the transition state. Implicit in this analysis is the assumption that the conjugated diene group of **2** adopts an *s-trans* orientation in the initial addition reaction. Examination of the crystal conformation of cembrene[11] (Figure 1) suggests that if the transition state for the first proposed closure reaction were to resemble the solid-state structure, then the required 5-*exo-trig*/11-*endo-trig* cyclization mode would prevail, given that the C2–C12–C11 angle of 90.9° is nearer the optimum attack trajectory of 107°[5] than are any of the alternative cyclization modes.

It was possible to explore this conjecture experimentally and thus gain valuable information for the implementation of a transannular free-radical cyclization strategy in the synthesis of **1**. Stirring a solution of commercial cembrene and 2,2′-azobis(2-methylpropionitrile) (AIBN) in carbon tetrachloride at reflux for 56 h afforded a mixture of the bicyclic products **3**, **4**, and **5** in 72% combined yield (Scheme 1). These products presumably arise by the addition of trichloromethyl radical to the C5 terminus of the diene, cyclization of the resultant allylic radical onto C12, as proposed, and chlorine atom abstraction from the solvent to terminate the addition reaction. The stereochemistry of **3** and **4** was assigned tentatively on the basis of difference nuclear Overhauser effect (NOE) and $^1H-^1H$ COSY NMR experiments, while that of **5** was determined unambiguously by single-crystal X-ray analysis (Figure 2).

These results were encouraging for the synthetic planning of **1**, for they demonstrated that the model allylic radical is completely selective for the 5-*exo-trig*/11-*endo-trig* ring closure. The stereochemical outcome of this cyclization was less of a concern, for it was anticipated that the actual macrocyclic precursor constructed for the synthesis of **1** would exhibit

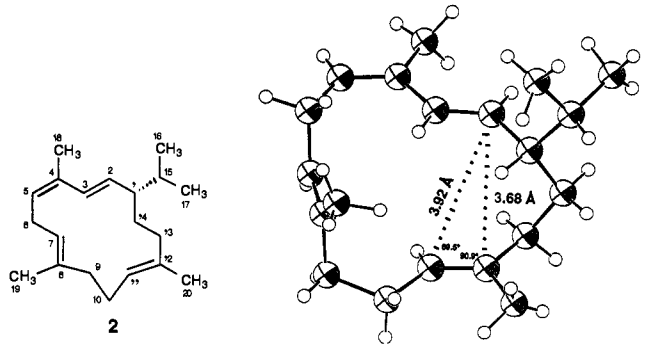


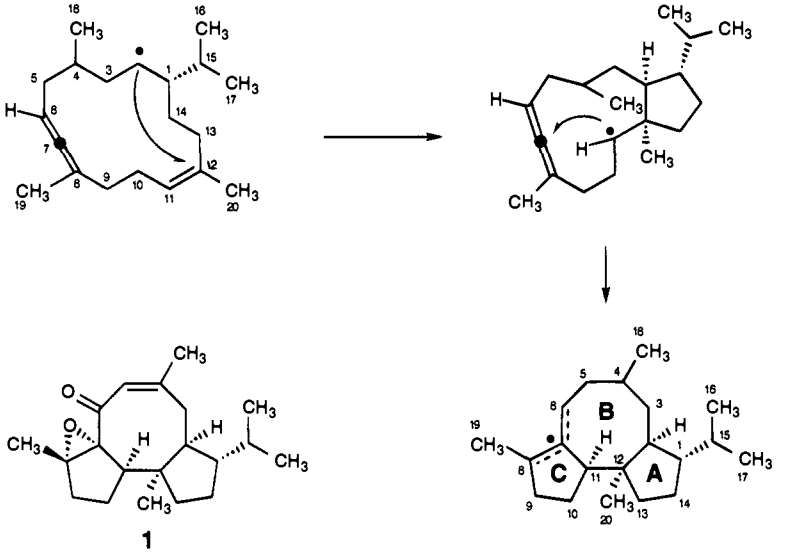
Figure 1. X-ray structure of cembrene.

(9) (a) Sam, T. W.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1971**, 970. (b) Traynham, J. G.; Hsieh, H. H. *J. Org. Chem.* **1973**, *38*, 868.

(10) Dauben, W. G.; Hubben, J. P.; Thiessen, W. E. *J. Org. Chem.* **1979**, *44*, 669.

(11) Drew, M. G. B.; Templeton, D. H.; Zalkin, A. *Acta Crystallogr., Sect. B* **1969**, *25*, 261. Note that all atoms in Figure 1 are presented as isotropic ellipsoids.

Scheme 2. Proposed Tandem Radical Cyclization



different stereoselectivity, as discussed below. For the reasons outlined above, it was not surprising that intermolecular capture of the transient C11 radical with chlorine from the solvent was faster than a second 5-*endo-trig*/8-*exo-trig* closure.

In designing a macrocyclic precursor appropriate for a synthesis of **1**, several problems identified in the cembrene model cyclization were addressed. An allene was incorporated into the macrocycle in order to make favorable a second (serial) transannular cyclization (Scheme 2). The trajectory (kinetics) and thermodynamics for radical addition are greatly improved by this modification in comparison to the disfavorable second closure reaction of the cembrene model system.[12] The latter cyclization also likely suffers from the development of strain due to the formation of a *trans*-cyclooctene ring; therefore, the four diastereomeric macrocyclic radicals **7**−**10**, each of which lacks the C3 olefin, were proposed for study in addition to the radical **6** (Figure 3). The diastereomers **7**−**10** were chosen in order to investigate the influence of the stereochemistry of the macrocycle upon the stereochemical outcome of the cyclization reaction. These macrocyclic precursors (**6**−**10**) each contain a C11 *cis*-olefin in contrast to the C11 *trans*-olefin found in the cembrene model system. This modification was expected to lead to the formation of an A ring with correct stereochemistry for a synthesis of **1** by favoring a chair-like local conformation of C1, C2, and C11−C14 (vide infra). In addition to the proposed experimental studies, transition-state molecular modeling was pursued in order to assess its value as a tool for planning syntheses that utilize a transannular radical cyclization strategy.

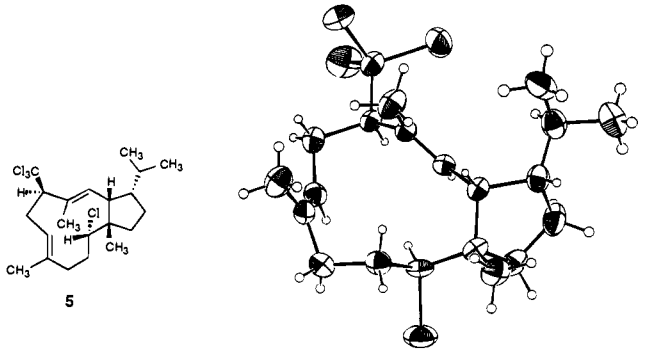


Figure 2. X-ray structure of cembrene cyclization product **5**.

Construction of a Macrocyclic Free-Radical Precursor

The following sequence has provided a concise synthetic route to the proposed macrocyclic precursors for free-radical cyclization studies (Scheme 3). Addition of a freshly prepared solution of lithium acetylide (1.5 equiv)[13] in tetrahydrofuran (THF) to commercially available neryl acetone (**11**) in THF at −78 °C afforded the acetylenic alcohol **12** in 99% yield. The use of freshly prepared lithium acetylide (from purified acetylene gas and *n*-butyllithium in THF at −78 °C) was essential in order to obtain reproducibly high yields of **12**; commercially available lithium acetylide−ethylenediamine complex proved inferior.[14] The transformation of **12** to the corresponding mesylate was accomplished using triethylamine (2.0 equiv) and methanesulfonyl chloride (1.5 equiv) in dichloromethane at 0 °C for 0.5 h.[15] This thermally sensitive mesylate was stored briefly at 0 °C as a solution in THF (1 M); warming the neat mesylate above 0 °C resulted in its rapid and sometimes violent

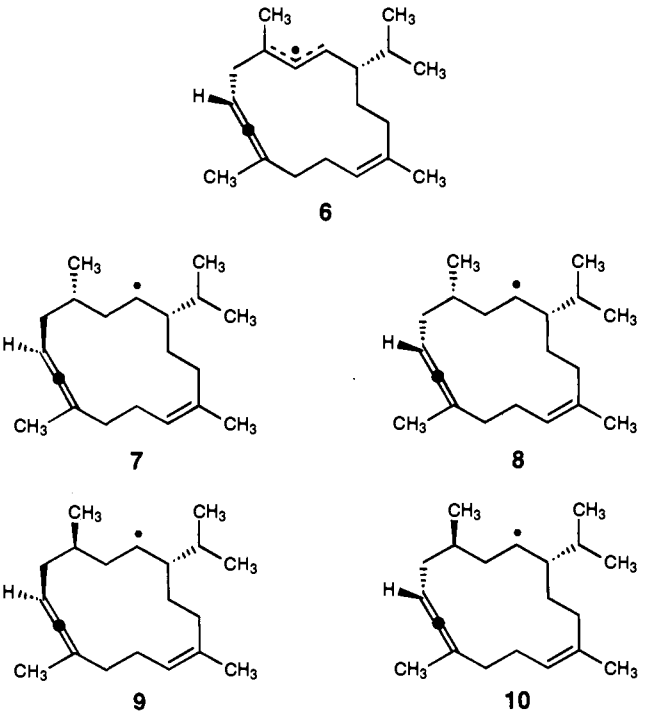
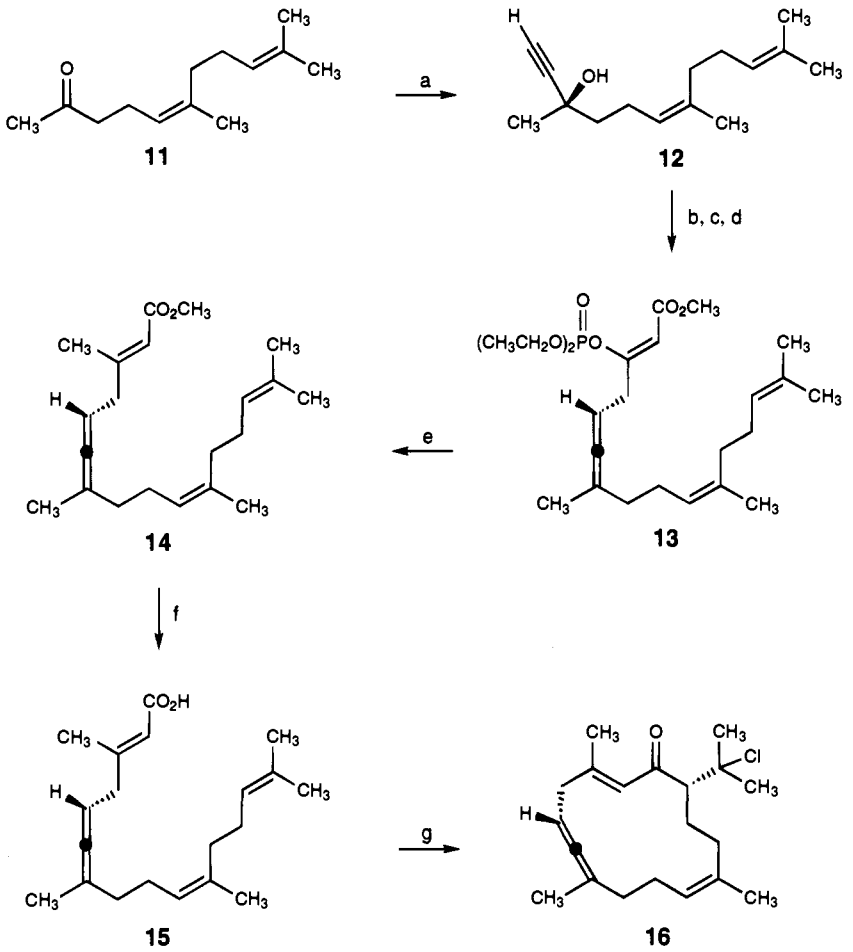


Figure 3.

Scheme 3[a]



[a] Reagents and conditions: (a) 1.5 equiv of LiC≡CH, THF, −78 °C, 30 min, 99%; (b) 2.0 equiv of Et_3N, 1.5 equiv of CH_3SO_2Cl, CH_2Cl_2, 0 °C, 30 min; (c) 1.5 equiv of $CH_3COCH_2CO_2CH_3$, 1.5 equiv of NaH, 1.5 equiv of *n*-BuLi, 0.75 equiv of CuI, THF, 0 °C; → −78 °C, then 1.0 equiv of mesylate from **12**; (d) 2.0 equiv of $(EtO)_2POCl$, −78 → 0 °C, 2 h, 85% from **12**; (e) 3.5 equiv of CH_3Li, 2.3 equiv of CuI, Et_2O, −78 → 0 °C, 10 h, 96%; (f) NaOH, H_2O, *t*-BuOH, 70%; (g) 7.4 equiv of $(COCl)_2$, benzene, 23 °C; 1.2 equiv of $SnCl_4$, CH_2Cl_2, −78 °C, 60%.

decomposition. A deep red-brown organocopper reagent was prepared from the dianion of methyl acetoacetate (1 equiv, formed by sequential deprotonations of methyl acetoacetate with sodium hydride and *n*-butyllithium in THF at 0 °C[16]) and high-purity cuprous iodide[17] (0.5 equiv) in THF at 0 °C for 1 h. After the organocopper reagent was cooled to −78 °C, the cold mesylate solution was added, resulting in the stereocontrolled formation of an allenyl β-keto ester enolate. This enolate was trapped in situ by the addition of diethyl chlorophosphate (−78 → 0 °C) to produce the (*Z*)-enol phosphate **13** in 85% yield from **12**. Treatment of **13** with lithium dimethylcuprate (2.3 equiv) in diethyl ether (−78 → 0 °C)[18] led to its clean conversion to the ester **14** in 96% yield.

Attempted saponification of **14** under a variety of conditions formed, in addition to the desired carboxylic acid **15**, a product arising from the isomerization of the allene to form a conjugated triene, presumably arising by deprotonation at the doubly allylic (C5) position. Acidic hydrolysis conditions also resulted in destruction of the allene functional group. After extensive experimentation, a heterogeneous hydrolysis method was found to give superior yields with minimal amounts of rearrangement. Thus, vigorous stirring of **14** in a biphasic mixture of aqueous sodium hydroxide (1 N) and *tert*-butyl alcohol at 75 °C for 24 h afforded, after acidic workup, the acid **15** in 70% yield.

Treatment of the acid **15** with oxalyl chloride (7.4 equiv) in benzene at 23 °C for 30 min and concentration of the reaction mixture in vacuo afforded the corresponding acid chloride. Macrocyclization of this acid chloride was accomplished using a modification of the methodology developed by Kato et al. This methodology, which has been used in the synthesis of various cembranoids, leads stereoselectively to the formation of 14-membered rings in a variety of terpenoid systems.[19] Addition of stannic chloride (1.2 equiv) to a solution of the crude acid chloride from **15** in dichloromethane (0.005 M) at −78 °C produced the chloro ketone **16** in 60% yield as a 10:1

(12) Leading references, intramolecular radical additions to allenes: (a) Apparu, M.; Crandall, J. K. *J. Org. Chem.* **1984**, *49*, 2125. (b) Pattenden, G.; Robertson, G. M. *Tetrahedron* **1985**, *41*, 4001. (c) Crandall, J. K.; Mualla, M. *Tetrahedron Lett.* **1986**, *27*, 2243. (d) Belotti, D.; Cossy, J.; Pete, J. P.; Portella, C. *J. Org. Chem.* **1986**, *51*, 4196. (e) Crandall, J. K.; Ayers, T. A. *Tetrahedron Lett.* **1991**, *32*, 3659.

(13) Midland, M. M.; McLoughlin, J. I.; Werley, R. T., Jr. *Org. Synth.* **1990**, *68*, 14.

(14) Beumel, O. F., Jr.; Harris, R. F. *J. Org. Chem.* **1964**, *29*, 1872.

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

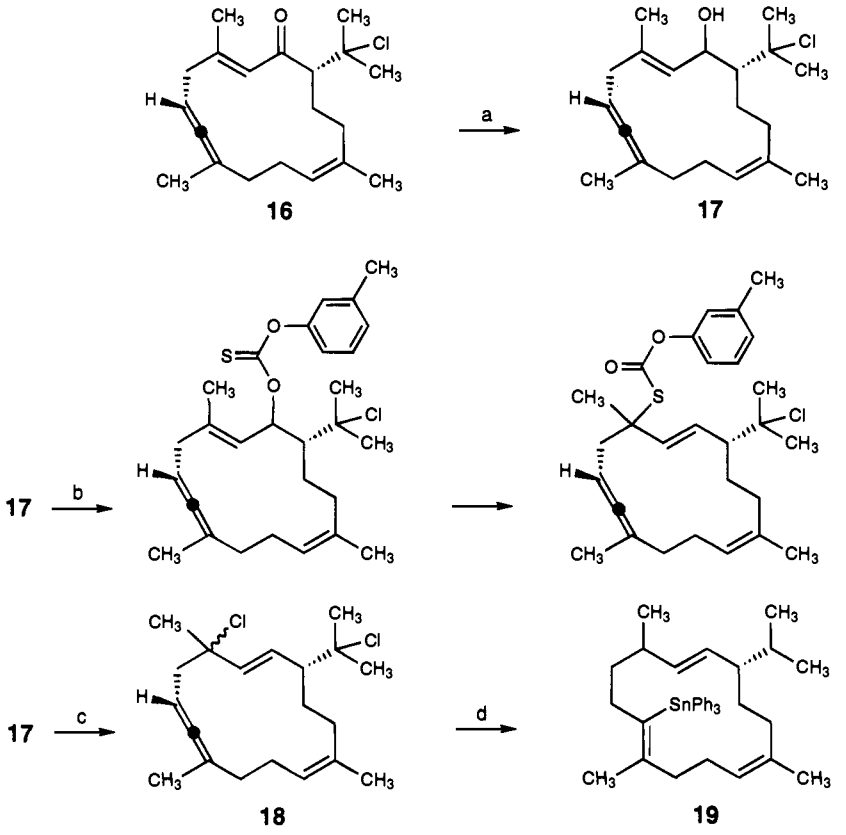
(16) (a) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082. (b) Sum, F.-W.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431. (c) Weiler, L. *J. Am. Chem. Soc.* **1970**, *92*, 6702.

(17) Copper(I) iodide, 99.999%, available from the Aldrich Chemical Company, Milwaukee, WI.

(18) This procedure involved modifications to the methods in ref 16 (see Experimental Section).

(19) (a) Kato, T.; Kobayashi, T.; Kumagai, T.: Kitihara, Y. *Synth. Commun.* **1976**, *6*, 365. (b) Kato, T.; Suzuki, M.; Kobayashi, T.; Moor. B. P. *J. Org. Chem.* **1980**, *45*, 1126. (c) Aoki, M.; Tooyama, Y.; Uyehara, T.; Kato, T. *Tetrahedron Lett.* **1983**, *24*, 2267. (d) Kobayashi, T.; Kumazawa, S.; Kato, T.; Kitahara, Y. *Chem. Lett.* **1977**, 301. (e) Kato, T.; Suzuki, M.; Nakazima, Y.; Shimizu, K.; Kitahara, Y. *Chem. Lett.* **1977**, 705.

Scheme 4[a]



[a] Reagents and conditions (Ph = phenyl): (a) 5.0 equiv of DIBAL, 5.0 equiv of *n*-BuLi, toluene, −78 → 0 °C, 43%; (b) *p*-CH3PhOC(=S)Cl, pyridine, CH_2Cl_2, 0 °C; (c) $(COCl)_2$, CH_3CN, −10 °C; (d) Ph_3SnH, AIBN, toluene, reflux.

ratio of diastereomers.[20] The macrocycle **16** has proven to be a versatile synthetic intermediate, providing access to all of the free-radical substrates examined in this study. Stereochemical assignments for **16** and for the free-radical precursors **6**−**10** were determined rigorously by X-ray crystallographic analysis of a subsequent intermediate (vide infra).

Transannular Cyclizations: Allylic Radicals

The first series of transannular free-radical cyclization reactions that was investigated centered on attempts to generate the allylic radical **6** or a closely related species as an intermediate (Scheme 4). Treatment of the macrocyclic ketone **16** with the 1:1 complex of diisobutylaluminum hydride (DIBAL) and *n*-butyllithium (5.0 equiv) in toluene at −78 °C[21] formed the allylic alcohol **17** as a single diastereomer (stereochemistry not determined) in modest yield (43%). Initial attempts to generate an allylic radical from the alcohol **17** focused on Barton deoxygenation methodology[22] but were precluded by our inability to generate the requisite allylic thionocarbonate derivatives. Thus, the treatment of **17** with *p*-tolyl chlorothionoformate and pyridine in dichloromethane afforded the transposed thionocarbonate as a single diastereomer (stereochemistry not determined), presumably via a [3,3] sigmatropic rearrangement. As an alternative means of generating the desired allylic radical intermediate, the trialkyltin hydride-mediated reduction of the corresponding allylic chlorides (**18**) was investigated. An epimeric mixture of the tertiary allylic chlorides **18** (ca. 2:1, stereochemistry not determined) was formed in high yield upon addition of oxalyl chloride to a solution of **17** in acetonitrile at −10 °C.[23] Treatment of chlorides **18** with excess triphenyltin hydride and AIBN in toluene at reflux afforded a product formulated as **19** (single diastereomer, stereochemistry not determined) on the basis of spectroscopic data. In this product, triphenyltin hydride has added to the allene group, and both chlorides have been reduced. This result demonstrated that the cyclization of the allylic radical in this system was slow relative to intermolecular trapping by trialkyltin hydride and, at the same time, it revealed the potential incompatibility of the allene functional group with reactions involving trialkyltin radicals as intermediates.[24]

Efforts to bring about the desired allylic radical cyclization then turned toward methods that do not involve trialkyltin radicals as intermediates. A further problem, the facility of chloride elimination within the intermediates containing the 2-chloro-2-propyl appendage, was also addressed at this point, by the use of substrates containing the 2-prop-2-enyl appendage from the outset. Treatment of the ketone **16** with a suspension of silver(I) carbonate in 2,2,4-trimethylpentane at 95 °C smoothly produced the olefin **20** in 97% yield (Scheme 5). It was essential that 2,2,4-trimethylpentane be used as solvent in the latter procedure; no reaction was observed when toluene or THF were used as the solvent. The use of silver(I) tetrafluoroborate in place of silver(I) carbonate was found to form the corresponding tertiary fluoride, while neither silver(I) trifluoromethanesulfonate nor silver(I) hexafluoroantimonate (in the

(20) The product of chloride elimination (2-propenyl derivative) was also observed (typically <10%). Neither this impurity nor the minor diastereomer of enone **16** were routinely separated from **16**, because all three compounds are processed identically in subsequent steps and converge upon common intermediates.

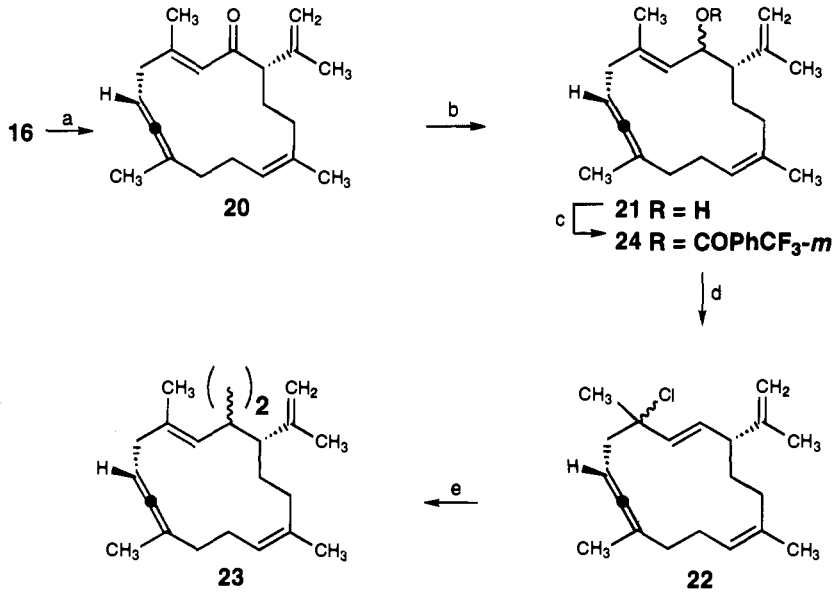
(21) Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1717.

(22) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(23) This product was used in crude form due to the lability of the tertiary chloride during silica gel chromatography.

(24) Such a complication was not unanticipated; for a recent study of tin-centered radical additions to allenes, see: Mitchell, T. N.; Schneider, U. *J. Organomet. Chem.* **1991**, *405*, 195.

Scheme 5[a]



[a] Reagents and conditions: (a) 3.0 equiv of Ag_2CO_3, 2,2,4-trimethylpentane, 95 °C, 97%; (b) 5.0 equiv of DIBAL, toluene, −78 → 0 °C, 86%; (c) 5.0 equiv of *m*-CF_3PhCOCl, 10 equiv of pyridine, CH_2Cl_2, 23 °C, 75%; (d) $SOCl_2$, CH_2Cl_2, 0 °C; (e) 5.0 equiv of SmI_2, THF, 23 °C.

presence of 2,6-lutidine) produced an observable reaction. The reduction of the ketone **20** with DIBAL in toluene at −78 °C proceeded cleanly, affording the alcohols **21** (4:1 ratio of diastereomers, stereochemistry not determined) in 86% yield. Treatment of the major diastereomer (purified by flash column chromatography on silica gel) with thionyl chloride in dichloromethane at 0 °C produced the allylic chloride **22** (single epimer, stereochemistry not determined) in good yield. The minor diastereomer **21** was transformed under the same reaction conditions to the epimeric allylic chloride **22**. Addition of freshly prepared samarium(II) iodide[25] to a solution of either one of the epimeric chlorides **22** in THF at 23 °C afforded a mixture of the four diastereomeric dimerization products **23**, in approximately equal amounts, with no detectable cyclization products.[26] The use of an inverse addition procedure also led to dimerization.

As a mechanistically distinct protocol for the generation of radicals that did not involve trialkyltin radical intermediates, the photochemical reduction of *m*-(trifluoromethyl)benzoate esters, developed by Saito and co-workers, was investigated.[27] Acylation of either epimeric alcohol **21** with *m*-(trifluoromethyl)-benzoyl chloride and pyridine in dichloromethane at 23 °C afforded the corresponding ester **24** in good yield. Irradiation of a solution of either one of the epimeric esters **24** (0.002 M) in THF−water (10:1 v/v) containing *N*-methylcarbazole (MCZ, 1.1 equiv) and 1,4-cyclohexadiene (0.2 M, this modification of the Saito deoxygenation protocol is discussed below) as a hydrogen atom source with a medium-pressure mercury vapor lamp (Pyrex filtered) for 1 h at 55 °C afforded a complex mixture of nonpolar products which proved to be quite sensitive to autoxidation. The crude mixture of products showed none of the spectroscopic features characteristic of the desired tricyclic cyclization products, as later determined. Although the latter method failed to produce the desired tricyclic products in the present case, this chemistry was to prove critical for later successful cyclization reactions.

(25) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

(26) Precedent for the formation of dimers during the reduction of allylic and benzylic halides using samarium(II) iodide can be found in ref 25.

(27) Saito, I.; Ikehira, H.; Kasatani, R.; Watanabe, M.; Matsuura, T. *J. Am. Chem. Soc.* **1986**, *108*, 3115.

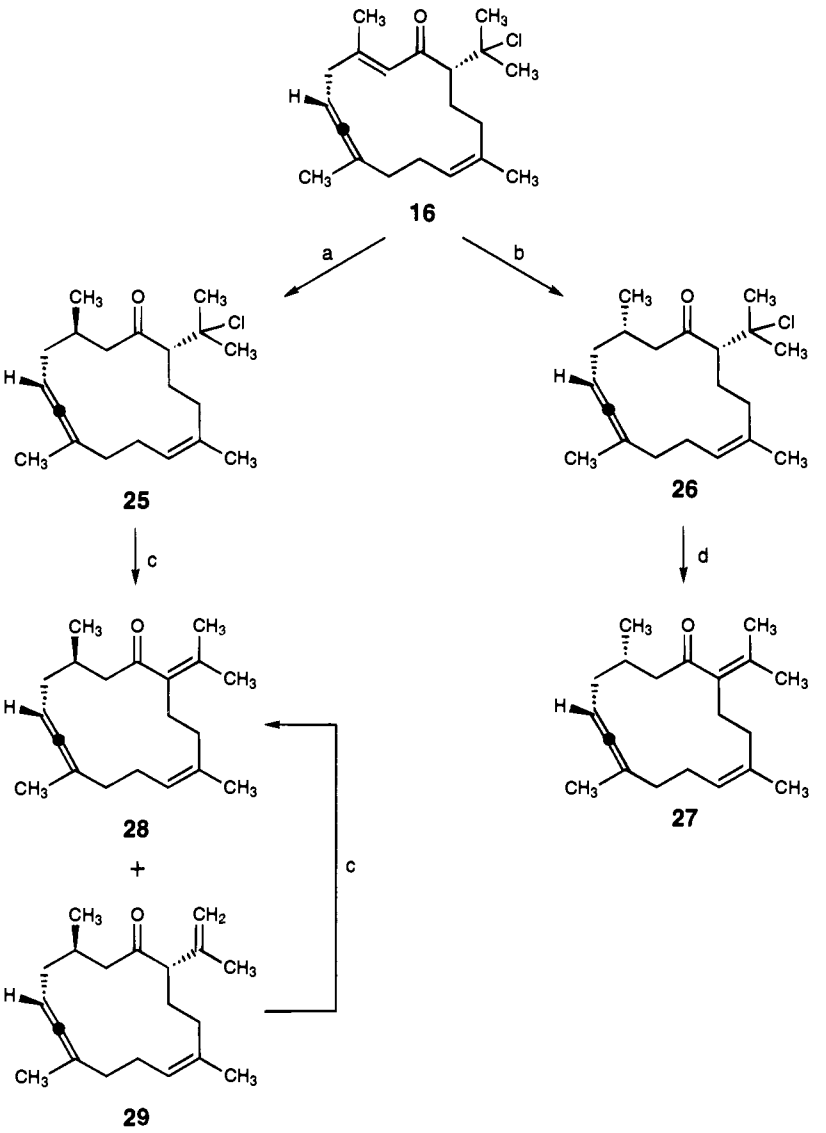
Transannular Cyclizations: Secondary Radicals

The allylic radical cyclizations attempted above were each thought to suffer from developing strain in the transition state for cyclization due to the C3−C4 *trans*-olefin. The corresponding C3−C4 saturated intermediates, radicals **7**−**10**, were therefore considered for study (Figure 3). In addition to alleviating a potential source of strain in the transition state for cyclization, saturation of the C3−C4 olefin should increase the reactivity of the secondary radical. Intermediates **7**−**10** introduce a further complication in the analysis of the cyclization reaction, however, in that the configuration of the methyl-bearing and the isopropyl-bearing stereogenic centers (C4 and C1, respectively) was predicted to play a critical role in the outcome of the cyclization reaction. For this reason, each of the four possible diastereomers (**7**−**10**) was studied. These diastereomers were prepared from the common intermediate **16**. With the appropriate choice of reducing agent, it was possible to set the C4-stereogenic center with either configuration. Thus, treatment of **16** with lithium tri-*sec*-butylborohydride in THF at −78 °C afforded the ketone **25** (mp 53−55 °C) in 91% yield,[28] while the reaction of **16** and DIBAL in THF at 0 °C afforded predominantly the diastereomer **26** (stereoselectivity 2:1, **26**:**25**, 50% isolated yield of **26**, mp 69 °C, Scheme 6). Stereochemical assignments were secured by X-ray crystallographic analysis of the diastereomer **26** (Figure 4).

Reductive removal of the tertiary chlorides within ketones **25** and **26** was accomplished, in each case, by a two-step procedure involving initial treatment with hot DBU in THF to induce elimination of the chloride. Chloroketone **26** afforded the α,β-unsaturated ketone **27** in 82% yield, whereas chloro ketone **25** afforded a separable mixture of the α,β-unsaturated ketone **28** (mp 44 °C) and the 2-propenyl (β,γ-unsaturated) ketone **29** (single diastereomer, stereochemistry not determined) in a 4:1 ratio (80% combined yield). The latter mixture was shown to represent the thermodynamic product distribution; thus, it was possible to convert the minor product **29** into the major, conjugated product **28** by its resubjection to the reaction conditions.

(28) Ganem, B.; Fortunato, J. M. *J. Org. Chem.* **1975**, *40*, 2846. (b) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194.

Scheme 6[a]



[a] Reagents and conditions: (a) 2.0 equiv of Li(*sec*-Bu)$_3$BH, THF, −78 °C, 2 h, 91%; (b) 2.0 equiv of DIBAL, THF, 0 °C, 30 min, **26**:**25** (2:1) 75%; (c) DBU−THF (1:3, v/v), reflux, 24 h, **28**:**29** (4:1) 80%; (d) DBU−THF (1:10, v/v), reflux, 23 h, 82%.

Initial attempts to induce conjugate reduction of the enone **28** proved problematic. Lithium or potassium tri-*sec*-butylborohydride afforded only 1,2-reduction products, and lithium in liquid ammonia led to reduction of the allene functional group. Sodium borohydride in pyridine and zinc in acetic acid also failed to reduce the conjugated carbon−carbon double bond. The reduction of enones with samarium(II) iodide in THF is reported to produce mixtures of 1,2- and 1,4-reduction products; in the present case, however, the treatment of **28** with samarium(II) iodide (2.5 equiv) in THF containing methanol at 23 °C for 1 h afforded only the 1,4-reduction product **30** (mp 36 °C) as a single diastereomer in 99% yield (Scheme 7). The analogous reduction conducted with the epimeric enone **27** produced a separable mixture of the diastereomeric 1,4-reduction products **31** (mp 62 °C) and **32** (mp 31−33 °C) in a ratio of 1.6:1, respectively (99% combined yield). For clarity in presentation, these racemic products are each depicted with the 1*S* configuration. The fourth and final diastereomer, ketone **33**, was produced by treating a solution of the ketone **30** in toluene with DBU at reflux for 48 h; a thermodynamic distribution of the epimeric ketones **33** and **30** was formed in a 2:1 ratio (mp 49 and 36 °C, respectively, separable by flash column chromatography) in 81% combined yield.

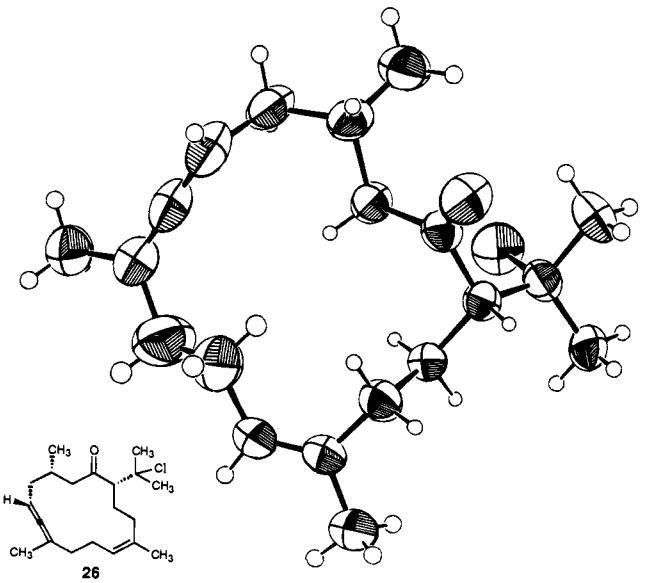
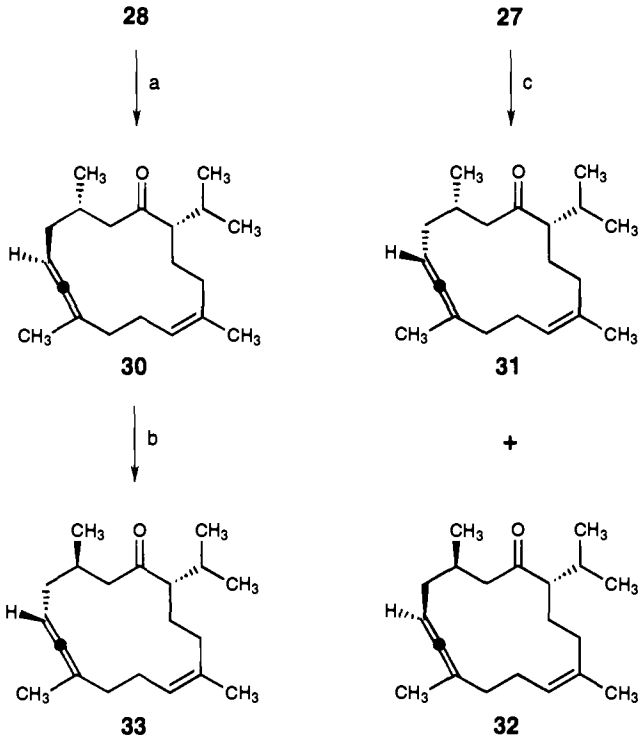


Figure 4. X-ray structure of chloroketone **26**.

Generation of stable radical precursors from the four diastereomeric ketones was accomplished by reduction of the

Scheme 7[a]



[a] Reagents and conditions: (a) 2.5 equiv of SmI_2, Sm metal, THF, 5.0 equiv of CH_3OH, 23 °C, 1 h, 99% (racemic product **30** is now depicted as the 1*S* enantiomer); (b) DBU–toluene (1:3, v/v), reflux, 48 h, **33**:**30** (2:1), 81%; (c) 4.2 equiv of SmI_2, Sm metal, 10 equiv of CH_3OH, THF, 23 °C, 1 h, mixture of epimers, 1.6:1 ratio, 99%.

ketones to their corresponding alcohols **34**–**37** (lithium aluminum hydride (LAH) in THF at −78 °C) and acylation of the resulting alcohols with *m*-(trifluoromethyl)benzoyl chloride and pyridine in dichloromethane at 0 °C (Scheme 8). In each case, epimeric mixtures at C2 were produced; however, this was found, not surprisingly, to be of no consequence in the subsequent generation of C2-centered radicals. The radicals were generated in each case by photolysis of the epimeric mixture of *m*-(trifluoromethyl)benzoate esters **38**–**41**, using conditions outlined above for substrate **24**.

Thus, irradiation of a solution of diastereomer **38** (0.002 M) in THF–water (10:1) and 1,4-cyclohexadiene (0.2 M) with a Pyrex-filtered medium pressure mercury vapor lamp at 40 °C for 7 h gave a mixture of nonpolar tricyclic products. The incorporation of 1,4-cyclohexadiene, which represents a modification of the method of Saito et al.,[27] led to an improved yield of tricyclic products, with optimal results achieved at a concentration of 0.2 M. To facilitate the separation and characterization of the nonpolar product mixture, and to provide a means for further synthetic transformations, the crude reaction mixture was epoxidized with *m*-chloroperoxybenzoic acid (MCPBA) in dichloromethane at 0 °C for 2.3 h. The major products of this cyclization–epoxidation sequence could be separated by chromatography on silica gel and were identified as the cyclopentyl epoxide **42** (8%) and the cyclooctenyl epoxide **43** (6%) (Scheme 9, stereochemistry established below). Because an extensive series of ^1H NMR experiments failed to establish conclusively the stereochemistry of these products at this stage, the decision was made to attempt to complete the synthesis of **1** from **43** in order to compare synthetic and authentic materials.

Exposure of the epoxide **43** to excess lithium diethylamide in ether at 23 °C for 15 h afforded the allylic alcohol **44** in 58% yield (Scheme 10).[29] Epoxidation of **44** with MCPBA in dichloromethane buffered with solid sodium bicarbonate[30] produced the epoxy alcohol **45** (mp 88 °C, 41%), which was oxidized to the epoxy ketone **46** (mp 69 °C) in 86% yield under Swern conditions.[31] Metalation of **46** with lithium diisopropylamide (LDA) in THF at −78 °C followed by the addition of trimethylsilyl chloride formed the corresponding trimethylsilyl enol ether which, upon treatment with phenylselenenyl chloride, produced a single α-phenylselenenyl ketone diastereomer. Oxidation of this phenylselenide with MCPBA at −78 °C and warming of the resultant selenoxide to 23 °C afforded the enone **47**. Comparison of ^1H NMR spectroscopic data from synthetic **47** with data from natural **1** showed clearly that **47** was different from **1**. Extensive NOE and COSY ^1H NMR data from intermediates **44**–**46** strongly supported the stereochemical assignments shown within structure **47** for the synthetic substance.

From this assignment, and given the requirement for *syn* elimination in the transformation of **43** to **44**, the stereochemistry of the radical cyclization products from the substrate **38** may be assigned tentatively as shown within structures **48** and **49** (Scheme 9). Thus, the cyclization of radical diastereomer **7** had proceeded with improper stereochemistry at both C2 and C12. This outcome was encouraging, nonetheless, as it had demonstrated that the tandem radical cyclization in a macrocyclic precursor was effective for the construction of 5–8–5 tricyclic ring systems like that found in the target molecule **1**.

It was anticipated that altering the stereocenters within the macrocyclic precursor would have a profound effect on the cyclization outcome; this proposal was verified experimentally. Irradiation of the epimeric esters **41** (under conditions described above for the cyclization of **38**) at 55 °C for 4 h produced a mixture of three tricyclic products in approximately equal amounts (cyclopentene **50** and epimeric cyclooctenes **51**, 51% combined yield, Scheme 11) which differed from the products derived from substrate **38**. Epoxidation of the product mixture with MCPBA afforded the crystalline epoxide **52** (mp 69 °C) as one component of the product mixture. Analysis of the latter product by X-ray crystallography established the stereostructure shown within Figure 5. The tricyclic epoxide **52** possesses the stereochemical configuration found within the A ring of the natural product **1**; the stereochemistry at C11, however, is epimeric with that found within **1**. The three components of the radical cyclization product mixture (**50** and epimers **51**) were shown to be allylic stereoisomers by the fact that the mixture could be transformed into the single isomer **50** upon irradiation in thiophenol–heptane (1:3, v/v, AIBN catalysis, 23 → 62 °C) for 2 h (93%). Similarly, each pure stereoisomer **51** (obtained by careful chromatography on silica gel) was transformed into product **50** under these conditions. Together, these results establish the identity of products **50** and **51** and show that the tandem radical cyclization of **41** proceeded essentially by a single pathway, producing the intermediate **53**. The three tricyclic products arose from hydrogen atom trapping of **53** at either allylic terminus; the two cyclooctenyl products resulted from trapping of the intermediate allylic radical at the *re* and *si* faces of the C8 allylic terminus.

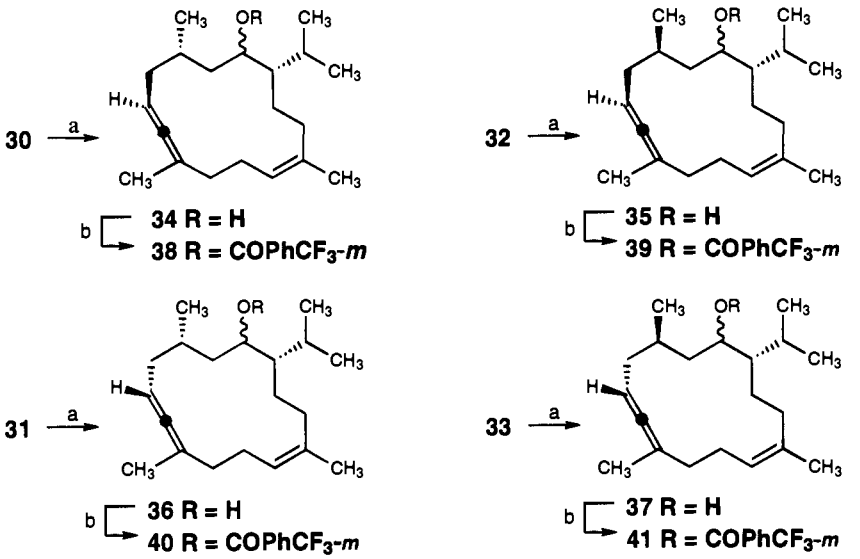
The conclusion that the cyclization reaction proceeded essentially by a single reaction pathway is supported by ^{13}C NMR analysis of the crude mixture of cyclic products where exactly 60 signals were observed for the three 20-carbon

(29) (a) Cope, A. C.; Heeren, J. K. *J. Am. Chem. Soc.* **1965**, *87*, 3125. (b) For a review, see: Smith, J. G. *Synthesis* **1984**, 629.

(30) Epoxidation done without buffer resulted in epoxide ring opening and incorporation of *m*-chlorobenzoate into the product.

(31) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

Scheme 8[a]



[a] Reagents and conditions (Ph = phenyl): (a) 1–5 equiv of $LiAlH_4$, THF, −78 °C, 2–5 h, 90–99%; (b) 5 equiv of *m*-$CF_3PhCOCl$, excess pyridine, CH_2Cl_2, 0 °C, 7–24 h, 65–99%.

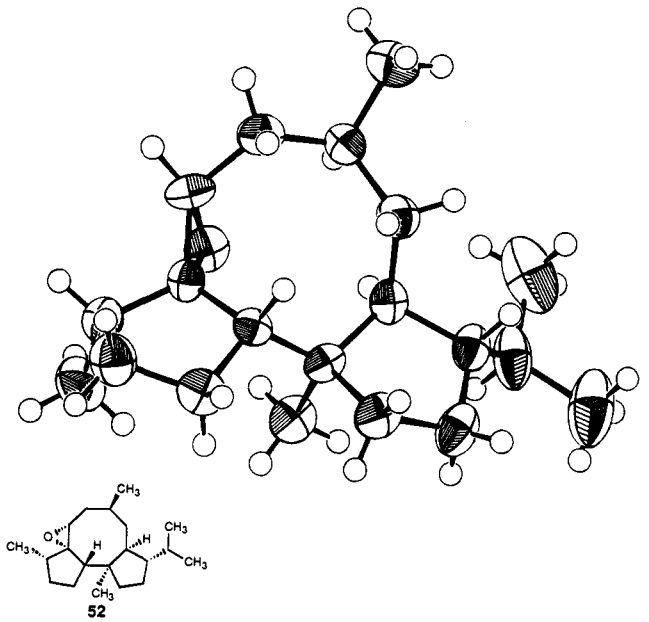


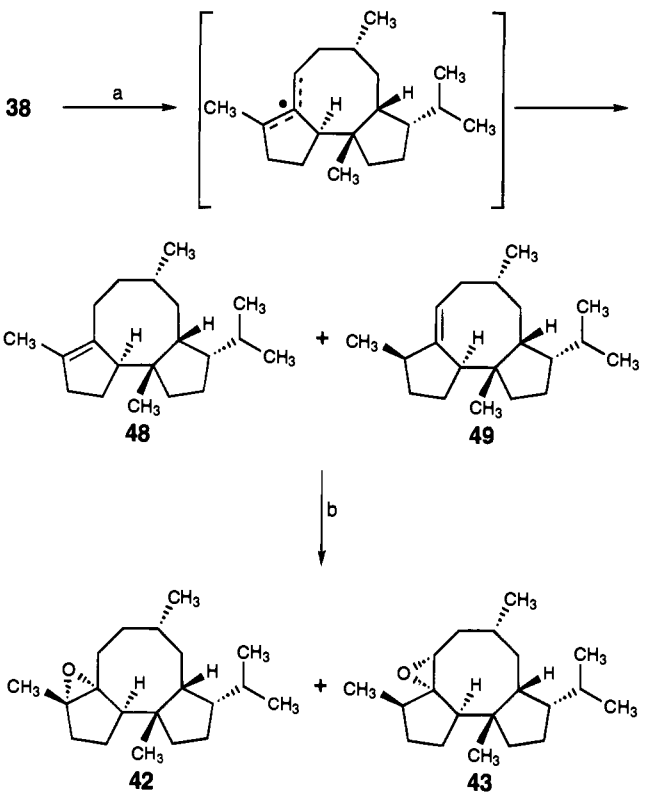
Figure 5. X-ray structure of epoxide **52**.

isomers. Treatment of the product mixture with thiophenol/AIBN and analysis of this reaction product by ^{13}C NMR showed exactly 20 signals for the single product **50**.

Further information regarding the effect of macrocycle precursor stereochemistry on the cyclization outcome was obtained from cyclization studies of the diastereomers **39** and **40**. Irradiation of the epimeric esters **39**, as above, produced an inseparable mixture of nonpolar products. ^1H NMR analysis of the crude product mixture showed that the same products from the cyclization of esters **41** (**50** and **51**) constituted the major components of this mixture, although they were formed in lower yield (ca. 40%). Cyclization of esters **40**, as above, and epoxidation of the crude reaction mixture afforded a complex product mixture which appeared to contain tricyclic components. Because of the large number of products formed in this reaction, further characterization of the mixture was not pursued.

(32) Houk, K. N.; Paddon-Row, M. N.; Spellmeyer, D. C.; Rondan, N. G.; Nagase, S. *J. Org. Chem.* **1986**, *51*, 2874.

Scheme 9[a]



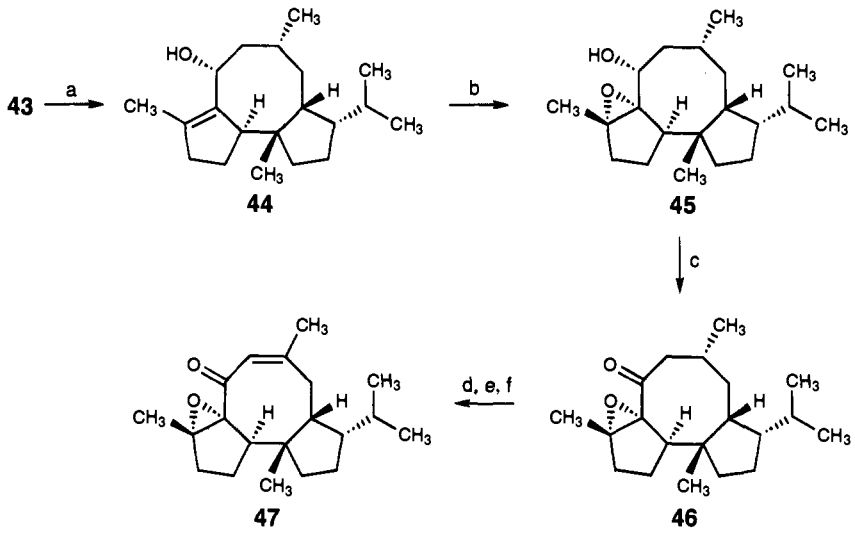
[a] Reagents and conditions: (a) 1.1 equiv of *N*-methylcarbazole, 1,4-cyclohexadiene (0.2 M), THF–H_2O (10:1 v/v), *hν*, 40 °C, 7 h; (b) 3.0 equiv of MCPBA, CH_2Cl_2, 0 °C, 2.3 h; **42** and **43**, 8% and 6%, respectively, from **38**.

Transition-State Molecular Modeling Studies

In an effort to better understand the results of the cyclization experiments summarized above, transition-state molecular modeling was conducted. Modeling of free-radical cyclization reactions has been investigated extensively for hydrocarbon substrates.[5a,32] Spellmeyer and Houk have developed a force-field model for radical additions to alkenes[33] that is now incorporated in the program MACROMODEL.[34] Each of the

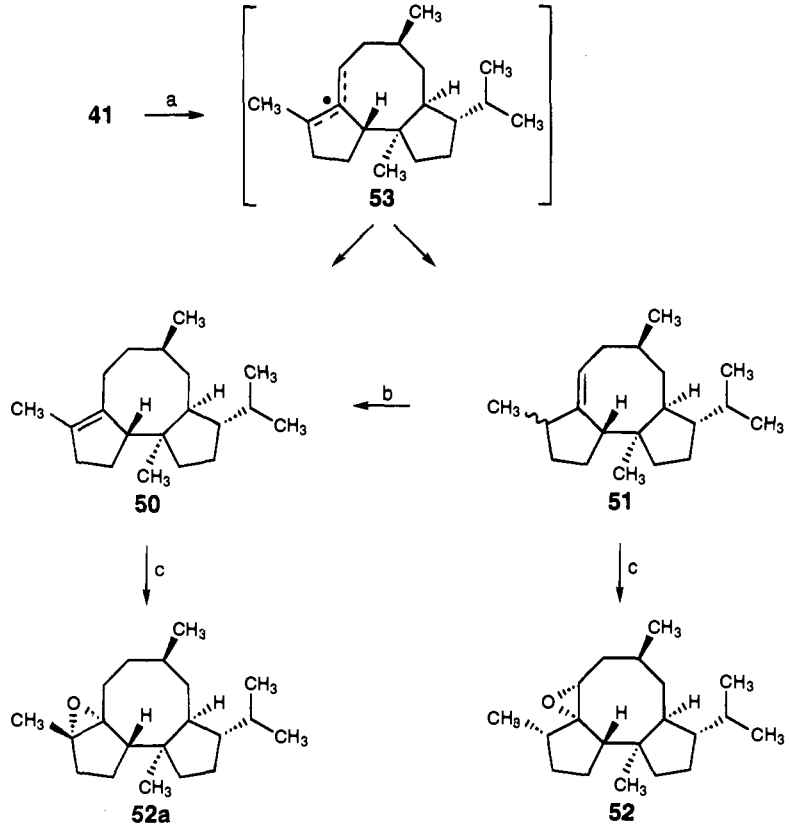
(33) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

Scheme 10[a]



[a] Reagents and conditions (Ph = phenyl): (a) excess $LiNEt_2$, Et_2O, 23 °C, 15 h, 58%; (b) 3.0 equiv of MCPBA, 5.0 equiv of $NaHCO_3$, CH_2Cl_2, −14 → −5 °C, 3.5 h, 41%; (c) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 → −14 °C, 86%; (d) excess Et_3N, $(CH_3)_3SiCl$, excess LDA, THF, −78 °C, 30 min; (e) excess PhSeCl, pyridine, CH_2Cl_2, −78 °C, 10 min; (f) MCPBA, CH_2Cl_2, −78 °C, 40 min; excess $(CH_3)_2S$, −78 → 23 °C, 2.5 h.

Scheme 11[a]



[a] Reagents and conditions (Ph = phenyl): (a) 1.1 equiv of *N*-methylcarbazole, 1,4-cyclohexadiene (0.2 M), THF−H_2O (10:1 v/v), *hv*, 55 °C, 4 h, 51%; (b) PhSH−heptane (1:3, v/v), AIBN, *hv* 23 → 62 °C, 2 h, **50**:other cyclopentenyl isomers (4:1), 93%; (c) 3.0 equiv of MCPBA, 5.0 equiv of $NaHCO_3$, CH_2Cl_2, 0 °C (products other than **52** resulting from the epoxidation of the cyclooctenes **51** are not shown).

radical diastereomers **7**−**10** is capable of forming four diastereomeric products within the 5-*exo-trig*/11-*endo-trig* cyclization manifold (Figure 6). Each of the 16 transition structures leading to these products was subjected to an internal-coordinate Monte Carlo conformational search employing the MACROMODEL

(34) Macromodel V3.5X: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440. Parameters have been implemented in the MM2* force field.

(35) (a) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379. (b) Saunders, M.; Houk, K. N.; Wu, Y.-D.; Still, W. C.; Lipton, M.; Chang, G.; Guida, W. C. *J. Am. Chem. Soc.* **1990**, *112*, 1419.

(36) Monte Carlo conformational searches were done using one closure bond in the forming eleven-membered ring while varying the remaining six torsions. The energy window for saved structures and for subsequent structure selection was set to 50 kJ/mol. Typically, 1000 conformations were generated and minimized for each of the transition structures studied; conformational searching routines were sometimes terminated before 1000 structures had been processed if convergence to a global minimum was demonstrated reproducibly and repetitively at an earlier point.

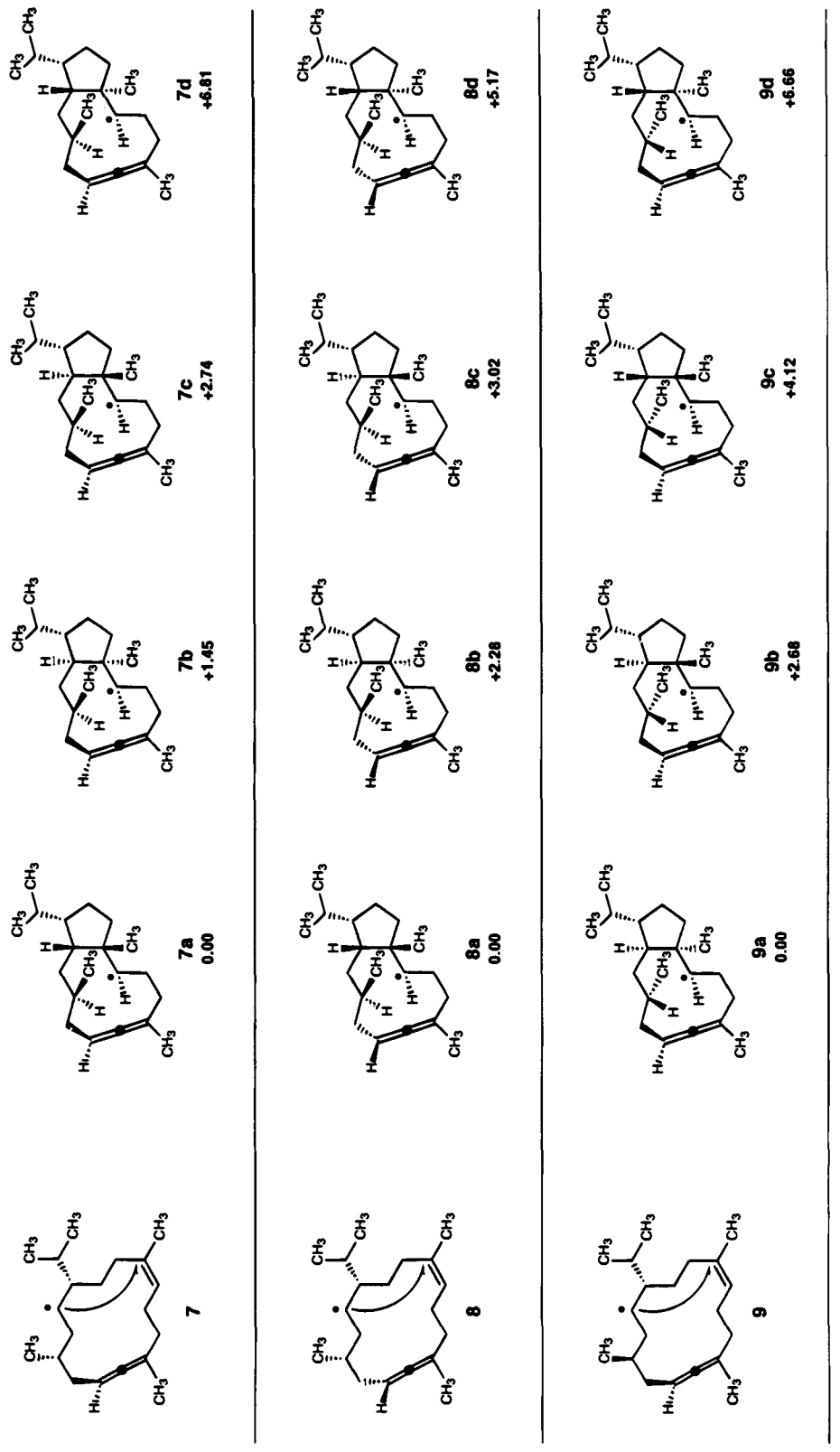


Figure 6. Values shown are relative energies (kcal/mol, as compared to structure **a** in each series) for the transition structures leading to the indicated products for each of the diastereomers.

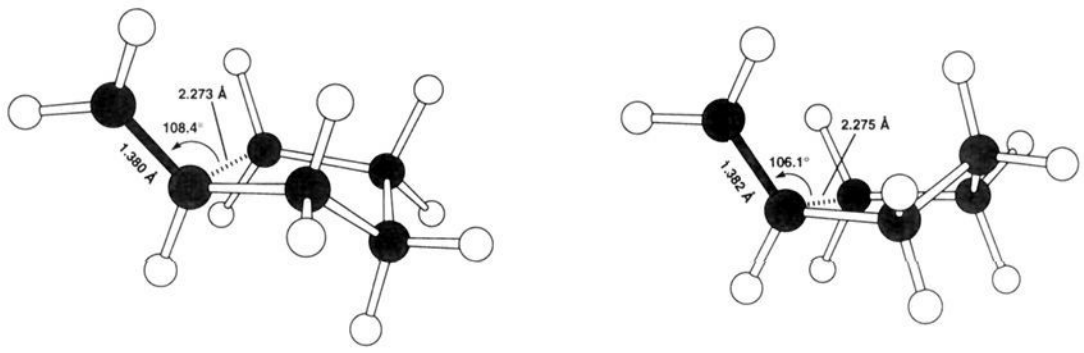


Figure 7. Calculated chair (left) and boat (right) transition structures for the 5-*exo-trig* cyclization of the 5-hexenyl radical.

program with the MM2* force field.[35] This search was used to generate various starting conformations of a given transition structure for subsequent energy minimization and the location of a global minimum.[36] Steric energies (kcal/mol) calculated for the 16 transition structures (Figure 6) are presented as values relative to the steric energy calculated for structure **a** in each series. For each macrocyclic radical diastereomer, the four transition structures **a**−**d** are rank-ordered energetically, from most to least favored (left to right, respectively, Figure 6). This analysis predicts that both diastereomers **9** and **10** will undergo cyclization to form products (**9a** and **10a**, respectively) with the same relative stereochemistry in the A ring as that found within epoxybasmenone (**1**). The steric energy differences among the four possible transition structures for cyclization of **10** show that the transition structure leading to **10a** is favored by more than 3.8 kcal/mol over the three alternative pathways, leading to **10b**, **10c**, and **10d**. Similarly, the cyclization of **9** to **9a** is found to be favored by more than 2.6 kcal/mol over any other pathway. Relative energy differences of this magnitude strongly suggest that the cyclizations of **9** and **10** will proceed stereoselectively to form the intermediates **9a** and **10a**, respectively.[37] Calculations were also done for each of the possible alternative 5-*exo-trig* and 6-*endo-trig* cyclization modes of the C2 macrocyclic radicals onto the C6, C7, and C11 positions. These alternative cyclizations were calculated to be significantly higher in energy (>6.0 kcal/mol) than the favored 5-*exo-trig* cyclization of C2 onto the C12 position.

Calculations for the cyclization of macrocyclic radicals **9** and **10** were in excellent agreement with experimental results. In the photochemical cyclizations of esters **39** and **41** (precursors to radicals **9** and **10**, respectively), each of the observed tricyclic products possessed the same A-ring configuration as that of **1**. Although both substrates afforded the desired A-ring configuration, esters **41** were more attractive from a synthetic standpoint given their ease of preparation as compared with esters **39** and the efficiency of their cyclizations.

The calculations predict that the preferred 5-*exo-trig*/11-*endo-trig* cyclization mode within radical diastereomers **7** and **8** will produce an A ring with unnatural stereochemistry (intermediates **7a** and **8a**, respectively). The formation of these intermediates is calculated to be favored over the next-best isomers **7b** and **8b**, respectively, each possessing the natural A-ring stereochemistry, by 1.45 and 2.28 kcal/mol, respectively. Experimental results from the photochemical cyclization of esters **38** (precursors to radical **7**) were in agreement with the calculations. The product mixture from the cyclization of esters **40** was too complex to draw meaningful conclusions regarding the stereochemistry of this cyclization reaction.

It is interesting to note that the diastereomer pair **7** and **8** and the pair **9** and **10** are both predicted to transform identically in the cyclization that forms the A ring, suggesting that the allene is not a dominant stereochemical controlling element in this system. The configuration of C4 would appear to be critical, however, for inversion of this center alters the cyclization outcome (cf. **8** and **10**, **7** and **9**).

The following analysis provides a rationale for the results of both calculation and experiment in relation to the configuration of the C4 stereocenter. In the case of the 5-*exo-trig* cyclization of the 5-hexenyl radical, affording the cyclopentyl carbinyl radical, a chair-like transition structure has been calculated to be favored over a boat-like transition structure by 1.0 kcal/mol;[32,33] three-dimensional representations of these calculated transition structures are shown in Figure 7. The calculated transition structures for the favored cyclization of **10** (to give **10a**, Figure 8) and for the favored cyclization of **9** (to give **9a**, Figure 9) both exhibit local geometries corresponding to the chair-like cyclization of the 5-hexenyl radical. In each case, the isopropyl group occupies a pseudoequatorial position within the chair transition structure, as does the C4 methyl group. Inversion of the allene stereocenter (**9** → **10**) does induce a

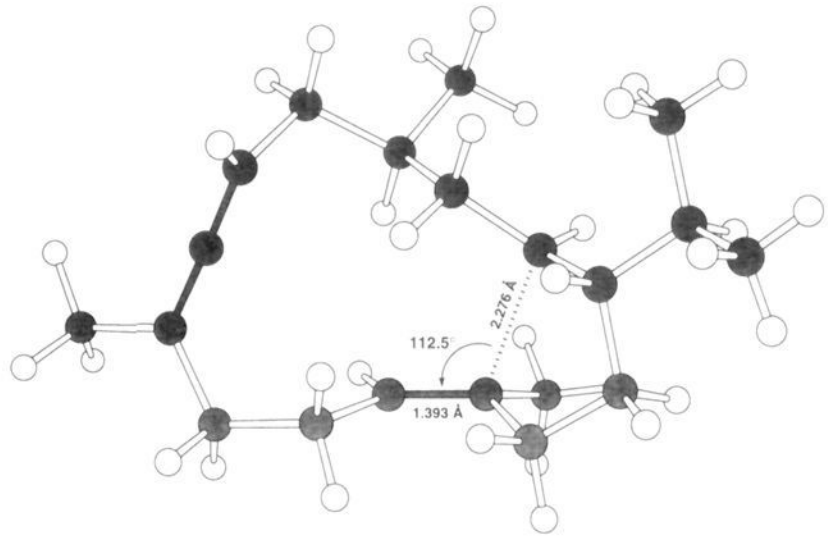


Figure 8. Calculated transition structure for the cyclization of **10** to give **10a**.

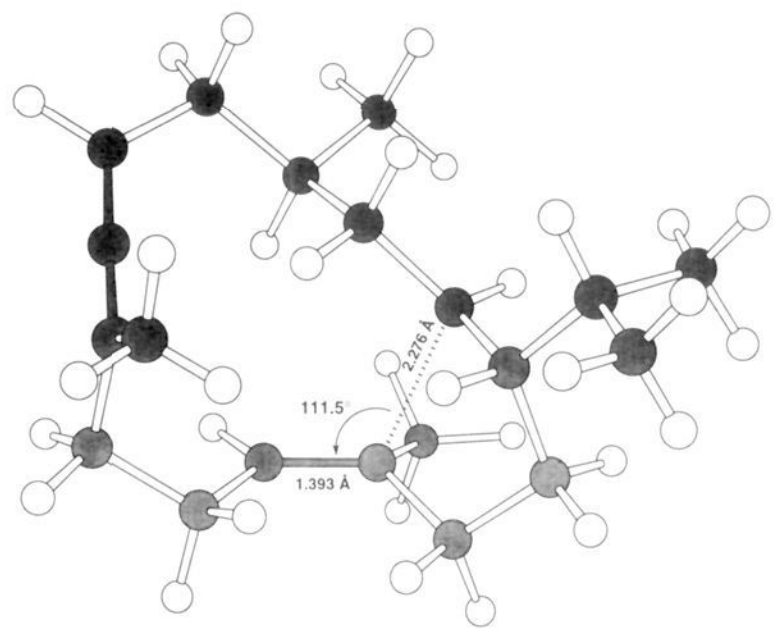


Figure 9. Calculated transition structure for the cyclization of **9** to give **9a**.

(37) Based upon a Boltzmann distribution at 323 K, a relative energy difference of 3.82 kcal/mol between two transition structures corresponds to an estimated 384:1 ratio of products; minor products will likely be present only in trace amounts.

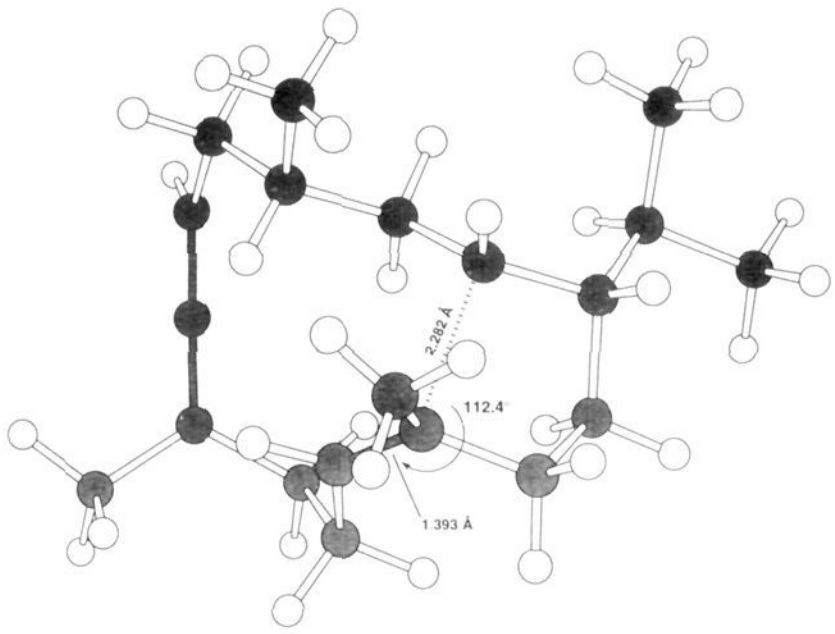


Figure 10. Calculated transition structure for the cyclization of **7** to give **7a**.

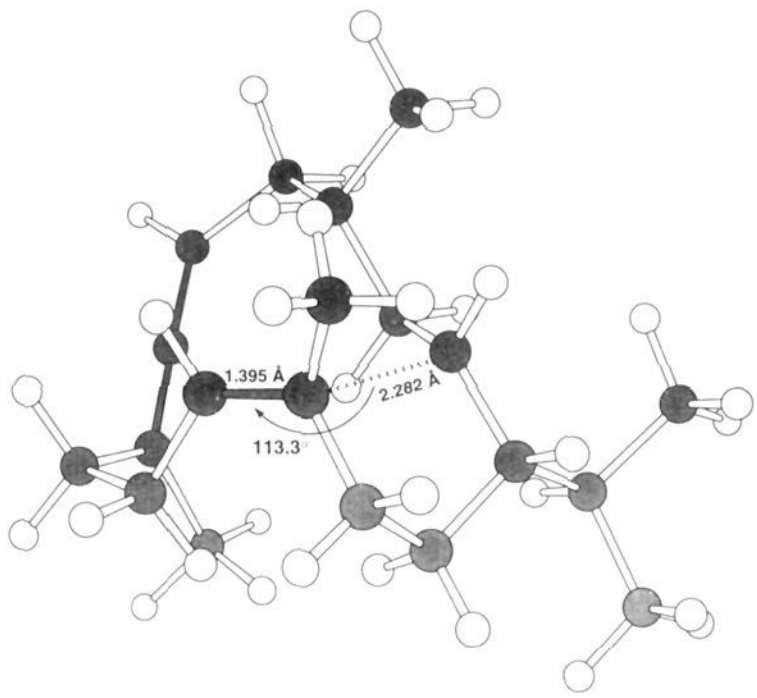


Figure 11. Calculated transition structure for the cyclization of **8** to give **8a**.

conformational change in the most-favored transition structures, but the chair-like local conformation is maintained (Figures 8 and 9). In contrast, epimerization of the C4 stereocenter would produce a strongly destabilizing transannular interaction between the C4 methyl group and the C11 hydrogen atom in a chair-like conformation. Thus, it is not surprising that the calculations show a boat-like transition structure in which the isopropyl group and the C4 methyl group occupy pseudoequatorial positions (Figures 10 and 11, respectively), to be favored by ≥1.45 kcal/mol (**7a**) over transition structures leading to **7b**, **7c**, and **7d** in the cyclization of **7**, and by ≥2.28 kcal/mol (**8a**) in the case of **8**. Alternative cyclization products **7b**−**d** and **8b**−**d** are each calculated to proceed through distorted chair-like transition structures in which unfavorable steric interactions existing within normal chair-like transition structures are minimized.

Additional transition-structure modeling was done for the second transannular radical cyclization step for both of the intermediates **9a** and **10a**.[38] In this cyclization there are only two feasible diastereomeric products, both of which result from attack of the C11 radical on the central carbon of the allene. Both **9a** and **10a** are calculated to favor the same tricyclic product, structure **53**, in which C11 is epimeric with respect to **1**, over the alternative and desired product **54** by relative energies of 1.64 and 3.29 kcal/mol, respectively (Figure 12). This analysis is in agreement with the experimental observations in the cyclizations of **38** and **41** (vide supra). A three-dimensional representation of the favored calculated transition structure for the cyclization of **10a** to **53** is shown in Figure 13.

It is interesting to note that molecular modeling shows that the desired product **55** is inherently more strained than the observed stereoisomeric product **50**, suggesting that factors producing strain in the ground state structure **55** may also contribute to produce strain within the transition structure giving rise to the radical intermediate **54** as well (Figure 14).

In summary, the formation of tricyclic products from **10** is believed to occur as depicted in Scheme 12, where **10** undergoes 5-*exo-trig* cyclization via transition structure $\mathbf{A}^{\ddagger}$ to form **10a**. Avoiding the sterically congested, bowl-shaped transition structure $\mathbf{B}^{\ddagger}$ (which would lead to the natural configuration at the C11 stereocenter as shown in structure **54**), **10a** undergoes conformational isomerization to **10a′** prior to cyclization via the transition structure $\mathbf{C}^{\ddagger}$ to form intermediate **53**. The three products observed experimentally from the cyclization of **41** (the cyclopentene product **50** and the two C8-epimers **51**) arise

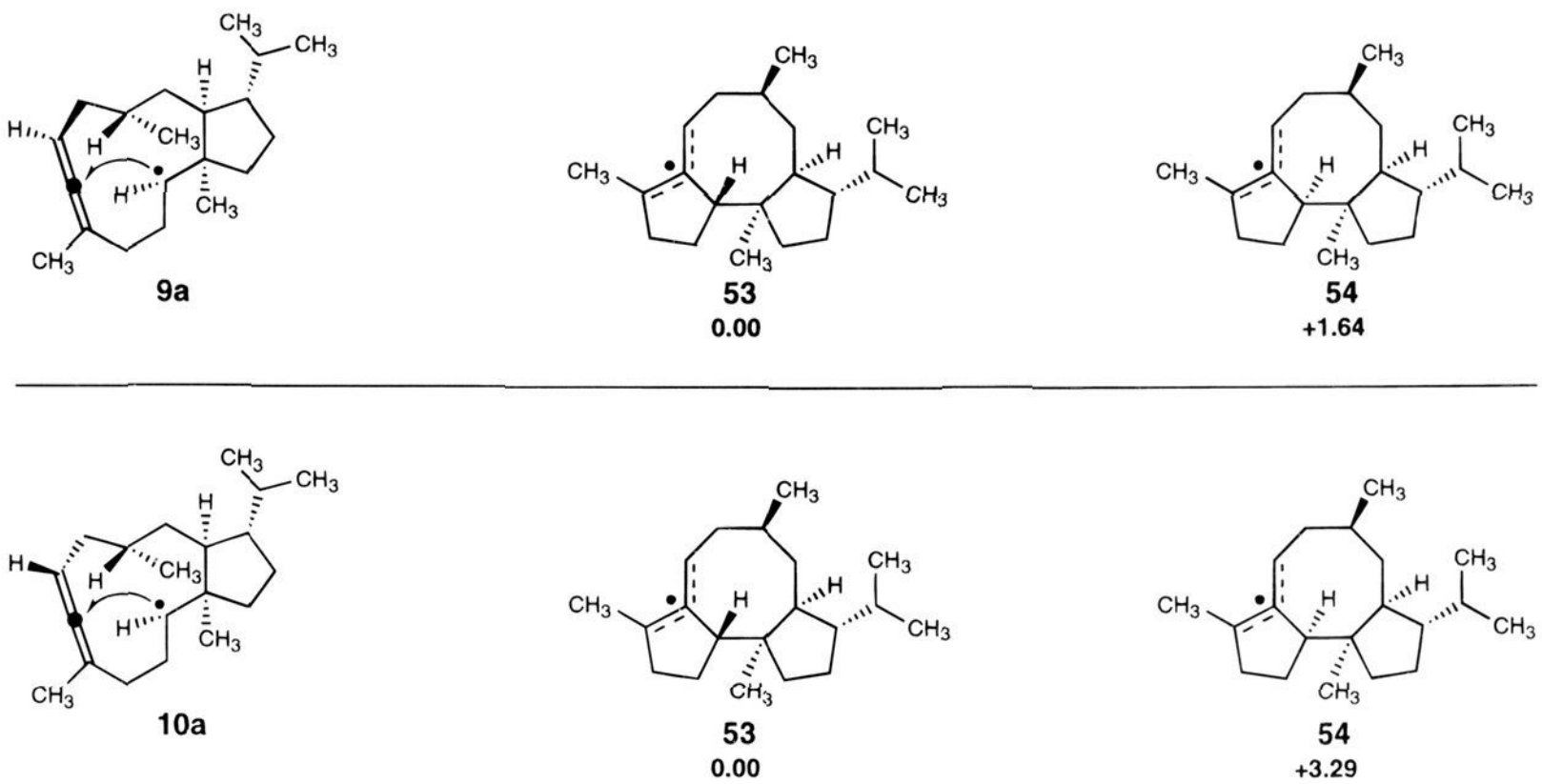
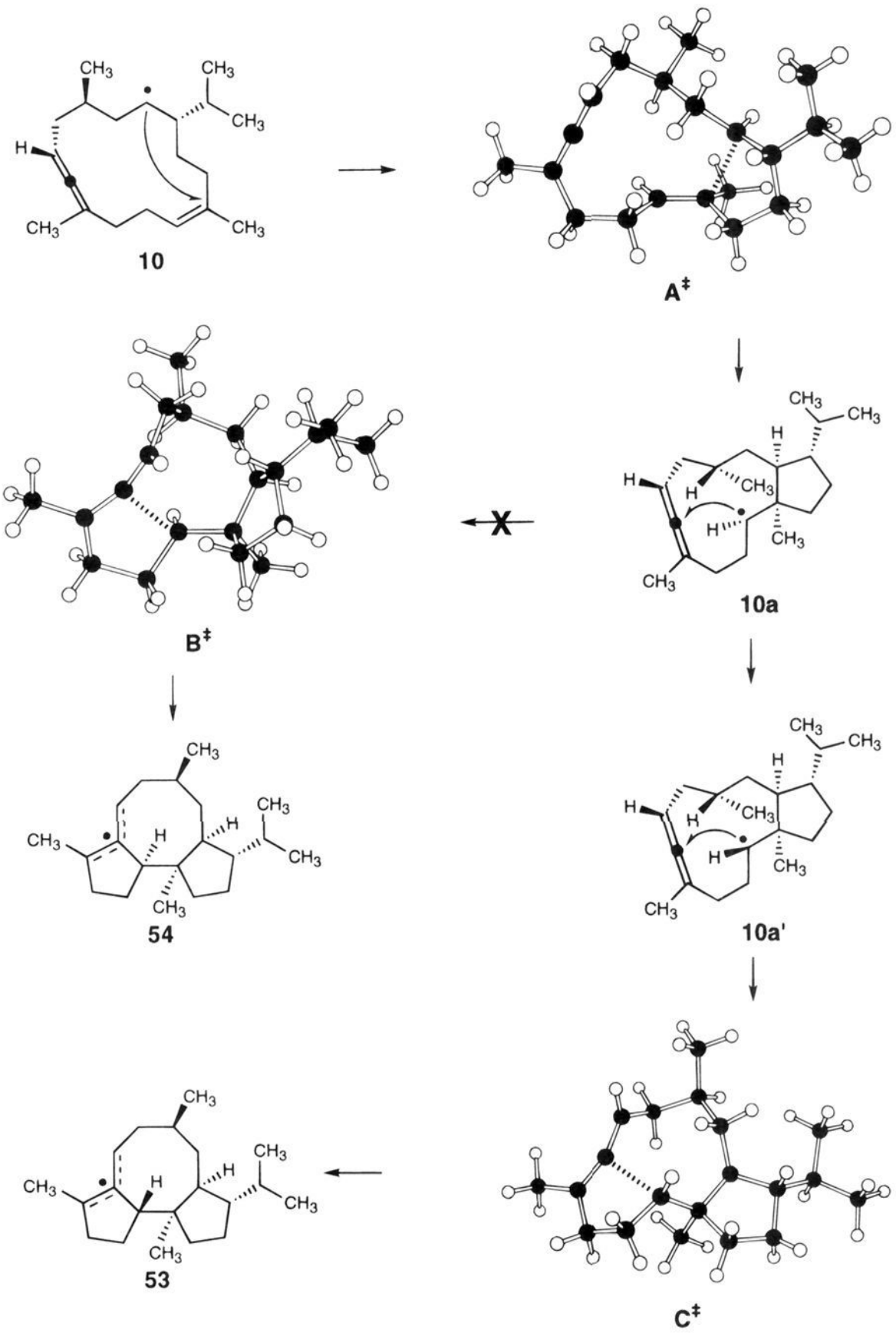


Figure 12. Values shown are relative energies kcal/mol) for the transition structures leading from **9a** and from **10a** to the indicated products.

Scheme 12. Formation of Tricyclic Products from **10**



from the trapping of the allylic radical **53** at either allylic terminus by hydrogen atom abstraction.

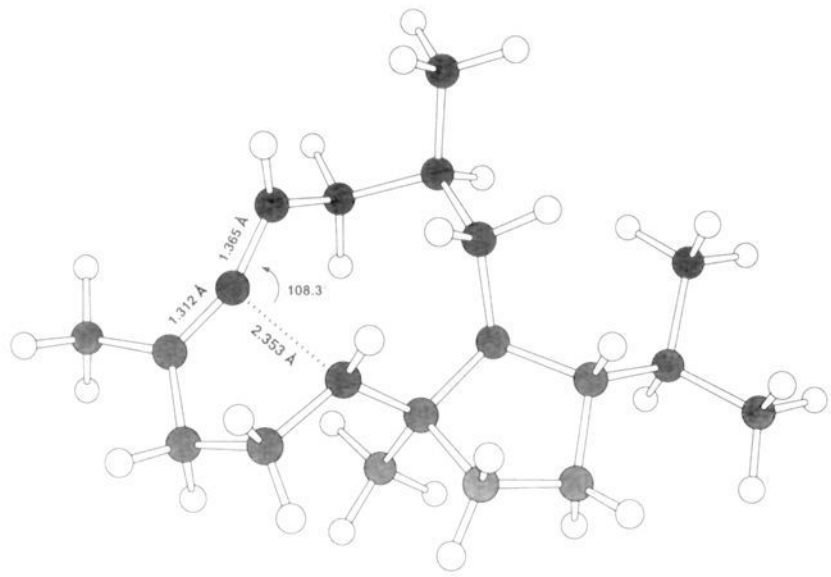


Figure 13. Calculated transition structure for the second (serial) cyclization of **10a** to give **53**.

Completion of the Synthesis of (±)-7,8-Epoxy-4-basmen-6-one

Photochemical cyclization of *m*-(trifluoromethyl)benzoate esters **41** and thiophenol-catalyzed olefinic isomerization of the resulting tricyclic products (vide supra) provides the pure tricyclic product **50** in about 50% yield for the two steps. To complete the synthesis of **1** it was necessary to invert the configuration of C11 within intermediate **50** and to introduce

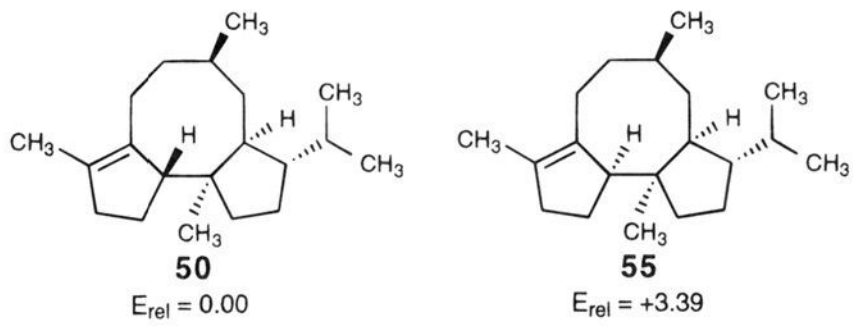
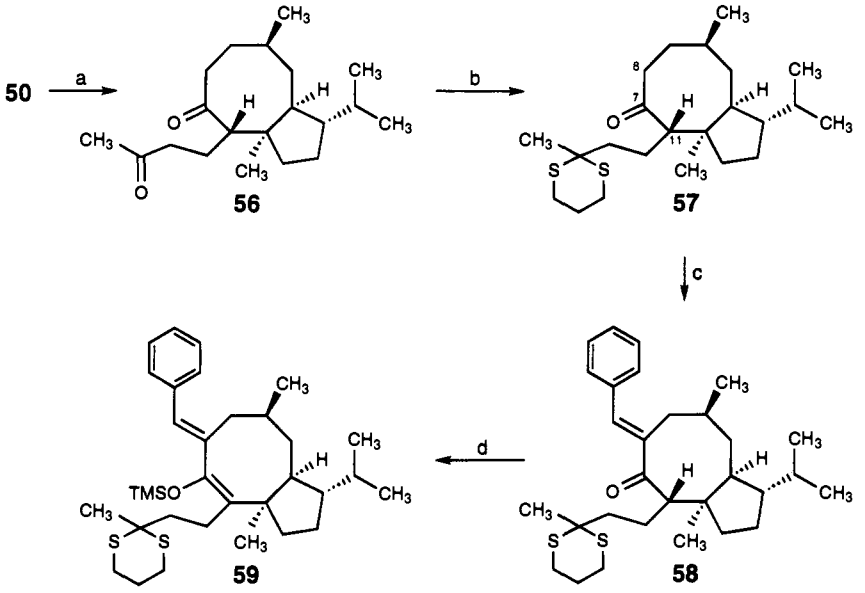


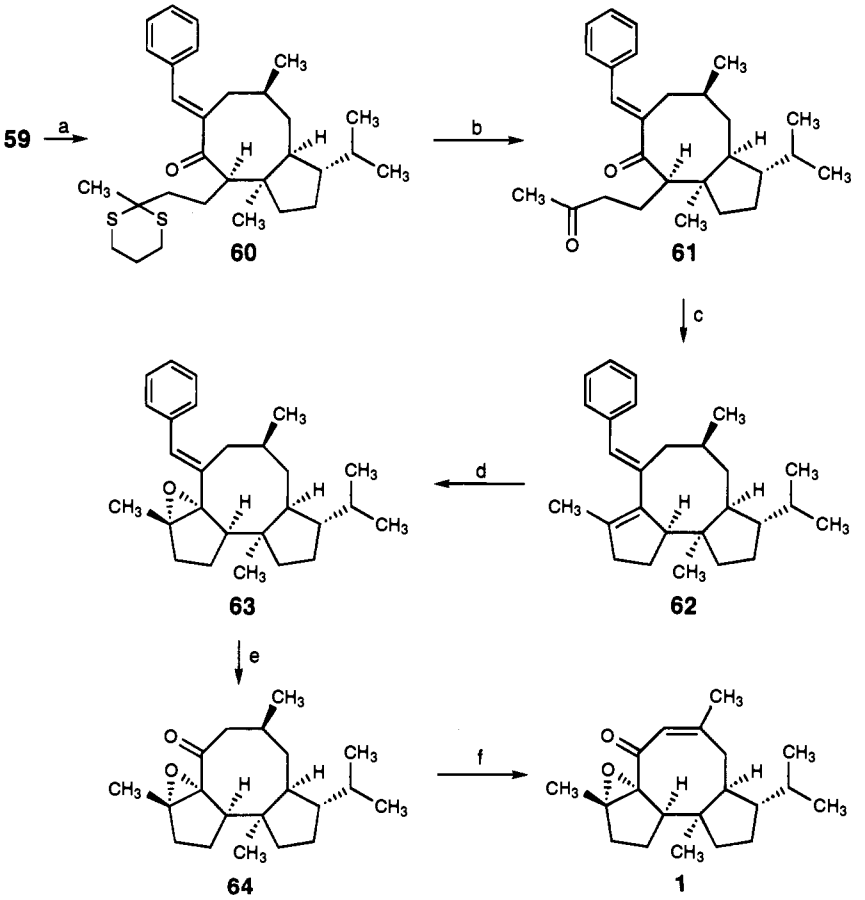
Figure 14. Comparison of calculated relative steric energies (kcal/mol) for observed alkene **50** and desired alkene **55**.

Scheme 13[a]



[a] Reagents and conditions (Ph = phenyl, TMS = $(CH_3)_3Si$): (a) 5.0 equiv of $NaIO_4$, 0.050 equiv of RuO_2, CCl_4:CH_3CN:H_2O (1:1:1.5), 23 °C, 1 h, 68%; (b) 10 equiv of $HS(CH_2)_3SH$, 0.74 equiv of BF_3·EtO_2, CH_2Cl_2, 23 °C, 98%; (c) excess PhCHO, catalytic NaOH, EtOH, 23 °C, 96%; (d) excess TMS-I, excess Et_3N, CH_2Cl_2, 50 °C, 96%.

Scheme 14[a]



[a] Reagents and conditions: (a) HCl (37% aq), CH_3OH, 23 °C, 10 min, **60:58** (2:1), 99%; (b) CH_3CN:CH_3I:H_2O (4:2:1), 23 °C, 17 h, 96%; (c) $TiCl_3$·$(DME)_{1.5}$, DME, reflux, 3.5 h, 73%; (d) 4.3 equiv of MCPBA, 20 equiv of $NaHCO_3$, CH_2Cl_2, −14 °C, 1 h, 96%; (e) 10 equiv of $NaIO_4$, 0.16 equiv of RuO_2, CCl_4:CH_3CN:H_2O (1:1:1.5), 23 °C, 15 min, 93%; (f) 6.5 equiv of LDA, THF, 0 °C, 8 min; 14 equiv of PhSeCl, 0 °C, 10 min; H_2O_2 (30% aq), pyridine, CH_2Cl_2, 23 °C, 20 min, 75%.

the requisite functionality in the B and C rings. Toward this end, **50** was treated with ruthenium tetroxide (formed in situ from ruthenium dioxide and sodium periodate)[39] in a biphasic mixture of carbon tetrachloride and aqueous acetonitrile at 23 °C for 1 h to produce the diketone **56**, followed by selective thioketalization of the acyclic carbonyl group with 1,3-propanedithiol in dichloromethane using boron trifluoride diethyl etherate as catalyst (23 °C, 5 min) to afford the dithiane **57** in

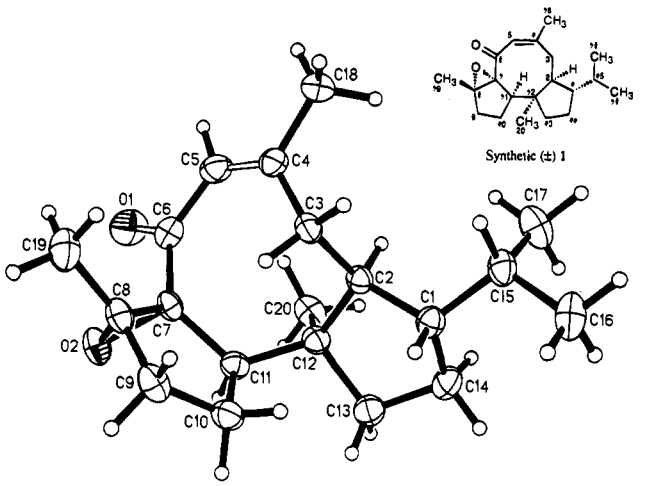


Figure 15. X-ray structure of synthetic epoxybasmenone (±**1**).

67% yield for the two steps (Scheme 13). Epimerization of **57** at C11 was envisioned to occur by kinetic protonation of the appropriate (C7−C11) enolate. Initial experiments suggested that the C6−C7 enolate and enol derivatives were both kinetically and thermodynamically preferred. The C6 position was therefore blocked by condensation of the ketone **57** with benzaldehyde, employing sodium hydroxide as catalyst (ethanol, 23 °C, 24 h) to form the enone **58** in 96% yield.[40] Deprotonation of **58** proved to be difficult. Lithium diethylamide, lithium diisopropylamide, and lithium tetramethylpiperidide in THF were all ineffective as bases, and attempts using titanium tetrachloride−triethylamine in dichloromethane, potassium *tert*-butoxide in *tert*-butyl alcohol, and numerous other reagents resulted in decomposition of the starting material. Removal of the C11 proton was accomplished in high yield and without the use of strong base by the initial conversion of **58** to the corresponding trimethylsilyl enol ether **59** employing excess trimethylsilyl iodide and triethylamine in dichloromethane at 50 °C in a sealed tube. Other silylating reagents, e.g., trimethylsilyl trifluoromethanesulfonate, proved unreactive toward **58**. Attempted hydrolysis of the trimethylsilyl enol ether **59** with tetrabutylammonium fluoride in THF (−78 → 0 °C) gave a complex mixture of products that was not identified. Treatment with milder fluoride sources such as potassium fluoride in methyl alcohol at 0 °C and triethylamine hydrofluoride in THF at 0 °C led to similar results. Camphorsulfonic acid in THF−water (10:1 v/v) also gave complex product mixtures. Treatment of **59** with methyllithium in diethyl ether and in DME failed to produce the lithium enolate (no reaction was observed). The reaction of a solution of the silyl enol ether **59** in diethyl ether with an ethereal solution of anhydrous HCl at 0 °C, however, produced the original ketone **58** as the major product, along with lesser amounts of **60**, the desired C11 epimer of **58** (Scheme 14). Lower reaction temperatures and the use of different organic solvents (hexanes, formamide, 1,3-dioxane, 1,1,1-trifluoroethanol) had little effect on the selectivity of the hydrolysis reaction. A critical parameter in the acidic hydrolysis reaction was found to be the presence of water in the hydrolysis mixture. Thus, treatment of trimethylsilyl enol ether **59** with 37% aqueous hydrochloric acid solution (0.40 mL) in methyl alcohol (6.0 mL) at 23 °C for 10 min afforded **60** (now the major product) as a crystalline solid (mp 162 °C, 95% for the two steps, 2:1 **60**:**58**). The minor epimer **58** was easily removed by trituration with hexanes and was routinely recycled (Scheme 14).

Removal of the dithiane protecting group within **60** was readily accomplished with methyl iodide (4 M) in 25% aqueous acetonitrile at 23 °C for 17 h, providing the crystalline diketone **61** (mp 99 °C) in 96% yield.[41] Subjection of **61** to freshly prepared titanium trichloride−DME complex and zinc−copper couple in refluxing DME for 3.5 h led to smooth carbonyl coupling to furnish the sensitive diene product **62** in 73% yield.[42] The use of other than freshly prepared reagents in the reaction required longer reaction times (in excess of 24 h) and led to inferior yields of carbonyl coupling products. Epoxidation of **62** with MCPBA afforded the acid-labile allylic epoxide **63**, which was treated directly with ruthenium tetroxide to form the epoxy ketone **64** in 89% yield for the two steps.

Conversion of the ketone **64** to the natural product **1** was accomplished by deprotonation of **64** with LDA in THF at 0 °C and quenching of the resultant enolate with phenylselenenyl chloride, forming a single α-phenylseleno ketone diastereomer. Direct treatment of this product with 30% aqueous hydrogen peroxide in dichloromethane buffered with pyridine[43,44] at 23 °C for 20 min provided racemic **1** as a crystalline solid (mp 122 °C; lit. mp for (+)-**1**: 109−110 °C) in 75% yield from **64**. Synthetic (±)-**1** provided spectral data indistinguishable from that obtained from the natural substance (^{1}H NMR, ^{13}C NMR, FTIR, and HRMS), and the structure was established unequivocally by X-ray crystallographic analysis (Figure 15).

Conclusion

An efficient strategy for the formation of the basmene ring system by a macrocyclic free-radical cyclization reaction has been demonstrated with the synthesis of (±)-**1**. The conversion of the acetylenic alcohol **12** to the enol phosphate **13** employing an organocopper reagent derived from methyl acetoacetate introduced the allene functional group stereoselectively and in high yield. Cationic cyclization of **15** was both efficient and stereocontrolled, the latter an interesting outcome attributable to the presence of the allene functional group. In the key step of the synthesis, the serial transannular radical cyclization reaction of **41** by a photochemical method provided the tricyclic product **50** stereoselectively. Transition-state molecular modeling was examined objectively as a tool to predict the outcome of complex transannular radical cyclization reactions. Examination of calculated transition structures helped rationalize experimental observations and led to informative conclusions regarding the observed stereoselectivities in the tandem tran-

(38) Because the MM2* force field included with MACROMODEL version 3.5X did not contain proper parameters for radical additions to the central carbon of allenes, an *ab initio* calculation was done to locate the transition structure for such a reaction. The transition structure for methyl radical addition to the central carbon of allene was located and optimized at the UHF/6-31G* level using the GAUSSIAN 92 program (GAUSSIAN 92, Revision B, M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1992). Frequency calculations were performed to verify that the geometry was a saddle point with a single negative force constant (imaginary frequency). These data were then used to modify the bond lengths and angles used in the radical addition substructure in the MM2* force field as necessary to achieve the proper transition structure geometry for addition to allene (see supplementary material).

(39) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

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(41) Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1977**, 68.

(42) (a) McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748. (b) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513.

(43) Oxidation performed without pyridine buffer resulted in increased side-reactions and lower yields of the desired enone.

(44) (a) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Org. Chem.* **1974**, *39*, 2133. (b) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137. (c) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

sannular radical cyclizations studied. The agreement between theory and experiment in this work is encouraging for future applications of transition-state molecular modeling in the design of synthetic schemes employing transannular radical cyclization strategies.

Experimental Section

General Procedures. All reactions were performed in round-bottom flasks that were flame-dried under a vacuum of ≤1 Torr. Flasks were fitted with rubber septa and Teflon-coated magnetic stirring bars, and all reactions were run under a positive pressure of argon which was dried by passage through a tower containing anhydrous potassium hydroxide pellets. All non-aqueous liquids and solutions were transferred via stainless steel cannulas or glass syringes fitted with stainless steel needles, except where otherwise noted. Flash column chromatography was performed using 230–400 mesh silica gel as described by Still et al.[45] Medium-pressure liquid chromatography was performed using 230–400 mesh silica gel with a constant pressure solvent pump used to control the elution rate. Thin-layer chromatography was carried out using commercially available glass plates coated with a 0.25 mm layer of 230–400 mesh silica gel containing a 254 nm fluorescent indicator. Organic solutions were concentrated by rotary evaporator at ~25 Torr (water aspirator). Photolyses of (trifluoromethyl)benzoate esters were performed in Pyrex vessels irradiated with a 400 W medium-pressure mercury vapor lamp. Photochemical equilibrations of alkene mixtures were performed in Pyrex vessels irradiated with a 250 W sunlamp. In both cases, the reaction temperatures were maintained by placing the reaction vessels in a temperature-controlled water bath. The lamps and reaction vessels were surrounded with aluminum foil to improve the efficiency of the photochemical reactions.

Materials. Commercial reagents were used as received, with the following exceptions. Tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), and diethyl ether were distilled from sodium benzophenone ketyl immediately prior to use. Dichloromethane, diisopropylamine, diisopropylethylamine, triethylamine, diethylamine, acetonitrile, *tert*-butyl alcohol, benzene, toluene, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) were distilled from calcium hydride. Trimethylacetaldehyde was distilled at 760 Torr. Methanesulfonyl chloride was distilled from phosphorus pentoxide at 760 Torr. High-purity cuprous iodide (99.999%) was purchased from Aldrich Chemical Co. Titanium trichloride–DME complex and zinc–copper couple were prepared immediately prior to use as described in the literature.[42] Samarium diiodide was prepared as described in the literature from samarium metal (40 mesh) and 1,2-diiodoethane (purified by washing with aqueous sodium thiosulfate solution and recrystallization).[25] The molarities of methyllithium (diethyl ether) and *n*-butyllithium (hexanes) solutions were accurately determined by titration using diphenylacetic acid indicator (average of five trials).[46]

Instrumentation. Infrared (IR) spectra were obtained with a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad), and assignment (when appropriate). Proton and carbon nuclear magnetic resonance (^1H NMR and ^{13}C NMR) spectra were recorded with a Bruker AM-500 (^1H, 500 MHz; ^{13}C, 125 MHz), JEOL JX-400 (^1H, 400 MHz; ^{13}C, 100 MHz), General Electric QE-300 (^1H, 300 MHz; ^{13}C, 75 MHz), or JEOL FX-90Q (^1H, 90 MHz, ^{13}C, 22.5 MHz) NMR spectrometer. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26; C_6D_5H, δ 7.20). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment (H#). Assignments of epimeric mixtures are indicated by H# designation for the major epimer and by H#′ for the minor epimer. Elemental analyses were performed in the analytical laboratories of the Arnold and Mabel Beckman Laboratories of Chemical Synthesis. High-resolution mass spectra were obtained from the University of California, Riverside Mass Spectrometry Facility and from the Midwest Center for Mass Spectrometry at the University of Nebraska, Lincoln. X-ray crystallographic analyses were obtained from the Arthur Amos Noyes Laboratory of Chemical Physics X-ray Facilities, Division of Chemistry and Chemical Engineering, California Institute of Technology, and from the University of California, Irvine Department of Chemistry X-ray Laboratory.

Cyclization of Cembrene (2). Tetrachlorides 3, 4, and 5. A solution of cembrene (202 mg, 0.741 mmol, 1.00 equiv) and AIBN (24.0 mg, 0.146 mmol, 0.197 equiv) in carbon tetrachloride (29.0 mL) was heated at reflux for 56 h. The reaction solution was then cooled to 23 °C and concentrated on a rotary evaporator. Flash chromatography of the residue (100% hexanes) afforded a mixture of the three diastereomeric tetrachlorides **3**, **4**, and **5** (3.2:1.7:1.0 ratio, respectively; 228 mg, 72% combined yield) as a viscous oil, along with trace amounts of recovered cembrene (**2**). Repeated medium-pressure liquid chromatography (100% hexanes) of the product mixture provided pure samples of each of the bicyclic products for spectroscopic analyses (**3** and **4** as viscous oils, and **5** as a crystalline solid, mp 60–61 °C). The relative stereochemical configuration of **5** was established unequivocally by X-ray crystallographic analysis of crystals grown from a solution of **5** in hexanes (see supplementary material). **3**: R_f 0.34, 100% hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (dd, 1H, J = 10.5, 1.2 Hz), 5.20 (t, 1H, J = 7.7 Hz), 3.74 (d, 1H, J = 6.8 Hz), 3.32 (dd, 1H, J = 10.8, 2.2 Hz), 2.71 (dd, 1H, J = 11.7, 7.7 Hz), 2.41 (ddd, 1H, J = 13.2, 10.9, 8.0 Hz), 1.90–2.18 (m, 5H), 1.89 (d, 3H, J = 1.2 Hz, $-CH_3$), 1.77 (s, 3H, $-CH_3$), 1.33–1.85 (m, 6H), 1.14 (s, 3H, H-20), 0.84 (d, 3H, J = 6.7 Hz, $-CH(CH_3)_2$), 0.79 (d, 3H, J = 6.7 Hz, $-CH(CH_3)_2$); IR (neat film) 2955 (s), 2870 (s), 1462 (m), 1455 (m), 1385 (m), 1019 (w), 906 (w), 867 (w), 803 (m), 788 (m), 756 (m), 649 (m); HRMS (EI) *m/z* calcd for $C_{21}H_{32}{}^{35}Cl_4$ (M^+) 424.1258, found 424.1250. **4**: R_f 0.30, 100% hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ 5.25 (dd, 1H, J = 11.3, 1.3 Hz), 4.78 (dd, 1H, J = 10.5, 1.2 Hz), 3.89 (d, 1H, J = 10.2 Hz), 3.30 (dd, 1H, J = 10.4, 7.2 Hz), 2.83 (dd, 1H, J = 15.0, 6.7 Hz), 2.27 (dd, 1H, J = 11.4, 6.5 Hz), 1.86 (s, 3H, $-CH_3$), 1.78 (s, 3H, $-CH_3$), 1.50–2.20 (m, 9H), 1.40 (m, 2H), 1.00 (s, 3H, $-CH_3$), 0.87 (m, 6H, H-16,17); IR (neat film) 2956 (s), 2870 (s), 1462 (m), 1455 (m), 1446 (m), 1385 (m), 1367 (m), 781 (m), 751 (m), 642 (m); HRMS (EI) *m/z* calcd for $C_{21}H_{32}{}^{35}Cl_4$ (M^+) 424.1258, found 424.1258. **5**: R_f 0.29, 100% hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ 5.04 (d, 1H, J = 12.0 Hz), 5.01 (m, 1H), 4.08 (d, 1H, J = 10.3 Hz), 3.26 (dd, 1H, J = 10.2 Hz), 2.70 (m, 2H), 2.51 (dd, 1H, J = 13.1, 10.1 Hz), 2.12 (dd, 1H, J = 13.1, 10.1 Hz), 1.97 (dd, 1H, J = 13.4, 6.6 Hz), 1.72 (s, 3H, $-CH_3$), 1.63 (s, 3H, $-CH_3$), 1.40 (m, 2H), 1.60–1.95 (m, 5H), 1.23 (dd, 1H, J = 14.6, 10.2 Hz), 1.10 (s, 3H, $-CH_3$), 0.81 (d, 3H, J = 6.6 Hz, $-CH(CH_3)_2$), 0.80 (d, 3H, J = 6.4 Hz, $-CH(CH_3)_2$); IR (neat film) 2934 (s), 2869 (s), 1454 (m), 1426 (m), 1380 (m), 780 (s), 646 (s); HRMS (EI) *m/z* calcd for $C_{21}H_{32}{}^{35}Cl_4$ (M^+) 424.1258, found 424.1257.

Alcohol 12. Acetylene gas (6.00 g, 231 mmol, 1.50 equiv) was purified by first passing a stream of the gas through a condenser cooled to −78 °C to remove residual acetone. The stream of gas from the condenser was bubbled directly through sulfuric acid (98%) and passed through a tower containing dry potassium hydroxide. The purified acetylene gas was dissolved in THF (500 mL) at −78 °C. Following an argon purge of the atmosphere above the reaction, a solution of *n*-butyllithium (2.50 M, 92.4 mL, 231 mmol, 1.50 equiv) in THF (25 mL, precooled to −78 °C) was added to the vigorously stirred solution of acetylene slowly via cannula, keeping the dispensing tip of the cannula below the surface of the acetylene solution at all times in order to prevent formation of the acetylene dianion. After the mixture was stirred for 20 min at −78 °C, neryl acetone **11** (30.0 g, 0.154 mmol, 1.00 equiv) was added dropwise over 20 min, and the resulting solution was stirred for an additional 30 min at −78 °C. Saturated aqueous ammonium chloride solution (10 mL) was then added slowly at −78 °C. Excess acetylene gas evolved as the reaction was allowed to warm slowly to 23 °C. The reaction mixture was then diluted with hexanes (100 mL), and the layers were separated. The aqueous layer was extracted with hexanes (3 × 100 mL), and the combined organic layers were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (100% dichloromethane) provided the propargyl alcohol **12** (33.7 g, 99%) as a colorless, viscous

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oil: R_f 0.32, 100% dichloromethane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (m, 2H, H-6,10), 2.44 (s, 1H, H-1), 2.19 (s, 1H, $-OH$), 2.12–2.30 (m, 2H, $-CH_2-$), 2.06 (m, 4H, $-CH_2-$), 1.69 (m, 8H, H-12,13, $-CH_2-$), 1.60 (s, 3H, H-14), 1.49 (s, 3H, H-15); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 135.8, 131.4, 124.4, 124.3, 87.6, 71.3, 68.0, 43.4, 31.8, 29.6, 26.4, 25.6, 23.3, 23.2, 17.5; IR (neat film) 3430 (m), 3309 (m), 2966 (s), 2929 (s), 2857 (m), 2099 (w), 1450 (s), 1376 (s), 1113 (m), 909 (m), 835 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{24}O$ (M^+) 220.18272, found 220.18236. Calcd for $C_{15}H_{24}O$: C, 81.75; H, 10.97. Found: C, 81.69; H, 10.84.

Enol Phosphate 13. Methanesulfonyl chloride (0.530 mL, 6.81 mmol, 1.5 equiv) was added dropwise to a solution of alcohol **12** (1.00 g, 4.54 mmol, 1.00 equiv) and triethylamine (1.27 mL, 9.11 mmol, 2.00 equiv) in dichloromethane (12 mL) at 0 °C. The resulting white suspension was stirred for 30 min at 0 °C. Ice was added to the reaction mixture, and the organic layer was washed sequentially at 0 °C with aqueous hydrochloric acid solution (1.0 N, 25 mL), water (25 mL), and saturated aqueous sodium bicarbonate solution (25 mL). The organic layer was dried over sodium sulfate and concentrated at 0 °C to afford the thermally sensitive mesylate, which was stored briefly as a solution in THF (10 mL) at −78 °C.

Methyl acetoacetate (0.730 mL, 6.81 mmol, 1.50 equiv) was added slowly to a suspension of sodium hydride (163 mg, 6.81 mmol, 1.50 equiv) in THF (25 mL) at 0 °C, resulting in the evolution of hydrogen gas. After 15 min, a solution of *n*-butyllithium in hexanes (2.50 M, 2.72 mL, 6.81 mmol, 1.50 equiv) was introduced into the cold reaction solution by dropwise addition. After 15 min of additional stirring at 0 °C, cuprous iodide (1.30 g, 6.81 mmol, 1.50 equiv) was added, producing a homogeneous, deep reddish-brown solution over a period of 40 min at 0 °C. The solution of mesylate in THF (10 mL) was added dropwise via cannula to the organocopper reagent (precooled to −78 °C), and the reaction mixture was stirred for 2.3 h at −78 °C. The reaction solution was warmed to −35 °C, diethyl chlorophosphate (1.31 mL, 9.08 mmol, 2.00 equiv) was added, and the mixture was stirred for 8 h at −35 °C. The reaction mixture was poured into a mixture of saturated aqueous ammonium chloride solution (200 mL) and saturated aqueous potassium carbonate solution (50 mL), and the biphasic mixture was stirred open to the air at 23 °C for 2 h. The deep blue aqueous phase was discarded, and the organic layer was washed twice with a mixture of saturated aqueous ammonium chloride solution (40 mL) and saturated aqueous potassium carbonate solution (10 mL). The organic layer was dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (30% ethyl acetate in hexanes) afforded the enol phosphate **13** (1.74 g, 85%) as a viscous oil: R_f 0.31, 40% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 5.66 (s, 1H, H-3), 5.27 (m, 2H, H-1,11), 5.14 (m, 1H, H-6), 4.19 (m, 4H, H-22), 3.43 (s, 3H, H-18), 3.30 (m, 2H, H-5), 2.24 (dd, 2H, J = 14.6, 7.3 Hz), 2.17 (m, 4H), 1.97 (td, 2H, J = 8.3, 2.8 Hz), 1.78 (d, 3H, J = 1.3 Hz, H-19), 1.73 (br s, 3H, H-20), 1.63 (s, 3H, H-16), 1.62 (s, 3H, H-17), 1.10 (m, 6H, H-21); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 163.8, 160.6 (d, J_{C-O-P} = 7.3 Hz), 135.1, 131.0, 124.3, 123.9, 104.7 (d, $J_{C-C-O-P}$ = 7.3 Hz), 100.4, 83.9, 64.5 (d, 2C, J_{C-O-P} = 6.2 Hz), 50.7, 35.3, 33.8, 31.6, 26.2, 25.4 (d, $J_{C-C-O-P}$ = 15.9 Hz), 25.3, 23.0, 18.6, 17.2, 15.7 (d, 2C, $J_{C-C-O-P}$ = 7.1 Hz); IR (neat film) 2966 (s), 2915 (s), 2856 (s), 1967.2 (w), 1733 (s), 1666 (s), 1436 (m), 1371 (m), 1356 (m), 1284 (s), 1199 (s), 1146 (m), 1035 (s), 986 (s), 821 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{24}H_{39}O_6P$ (M^+) 454.2484, found 454.2482. Calcd for $C_{24}H_{39}O_6P$: C, 63.42; H, 8.65. Found: C, 63.41, H, 8.65.

Methyl Ester 14. Methyllithium (52.7 mL, 74.9 mmol, 3.45 equiv) was added to a suspension of cuprous iodide (9.51 g, 49.9 mmol, 2.30 equiv) in diethyl ether (300 mL) at 0 °C, producing initially a bright yellow suspension and then a colorless solution with a yellow precipitate upon completion of the addition. After the mixture had been stirred for 45 min at 0 °C, all precipitate had dissolved, and the colorless solution was cooled to −78 °C. A solution of the enol phosphate **13** (9.92 g, 21.8 mmol, 1.00 equiv) in diethyl ether (40 mL) was added to the cuprate solution at −78 °C, and the resulting mixture was allowed to warm to 0 °C over a period of 4 h. The reaction was poured into a 1:1 mixture of saturated aqueous ammonium chloride and saturated aqueous potassium carbonate (500 mL), and the resulting mixture was allowed to stir for 1 h at 23 °C exposed to air. The deep blue aqueous phase was separated and discarded, and the organic phase was washed twice with a 1:1 mixture of saturated aqueous ammonium chloride solution and saturated aqueous potassium carbonate solution (250 mL). The organic layer was washed with saturated aqueous sodium thiosulfate solution (125 mL), filtered through a medium porosity glass frit to remove a fine precipitate, and concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes) provided the methyl ester **14** (6.63 g, 96%) as a viscous oil: R_f 0.55, 20% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (d, 1H, J = 1.2 Hz, H-3), 5.13 (m, 2H, H-1,11), 4.97 (m, 1H, H-6), 3.69 (s, 3H, H-21), 2.77 (d, 2H, J = 7.1 Hz, H-5), 2.18 (d, 3H, J = 1.2 Hz, H-18), 1.90–2.12 (m, 8H, H-9,10,13,14), 1.68 (br s, 9H, H-16,17,20), 1.60 (br s, 3H, H-19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 167.1, 158.7, 135.4, 131.4, 124.7, 124.3, 115.6, 99.9, 86.6, 50.6, 41.2, 34.3, 32.0, 26.6, 26.0, 25.6, 23.3, 19.0, 18.7, 17.5; IR (neat film) 2965 (s), 2916 (s), 2855 (s), 1965 (w), 1723 (s), 1652 (s), 1435 (s), 1377 (m), 1356 (m), 1284 (m), 1220 (s), 1148 (s), 1042 (m), 838 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{21}H_{32}O_2$ (M^+) 316.2402, found 316.2403.

Acid 15. Freshly prepared aqueous sodium hydroxide solution (1.0 N, 200 mL, excess) was added to a solution of the ester **14** (8.35 g, 26.4 mmol, 1.00 equiv) in *tert*-butyl alcohol (250 mL), and the biphasic reaction mixture was heated to 75 °C with vigorous stirring. After 7 h, the reaction mixture was cooled to 0 °C and acidified to pH = 2 with aqueous hydrochloric acid (1.0 N). Hexanes (200 mL) was added to the reaction mixture, and the organic phase was separated. The aqueous phase was saturated with solid sodium chloride and extracted with 50% ethyl acetate in hexanes (2 × 200 mL). The combined organic layers were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes) afforded the acid **15** (5.59 g, 70%) as a viscous oil: R_f 0.49, 40% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.09 (br s, 1H, $-CO_2H$), 5.77 (d, 1H, J = 1.0 Hz, H-3), 5.13 (m, 2H, H-1,11), 4.98 (m, 1H, H-6), 2.80 (d, 2H, J = 7.1 Hz, H-5), 2.19 (d, 3H, J = 1.2 Hz, H-18), 1.93-2.10 (m, 8H, H-9,10,13,14), 1.68 (s, 9H, H-16,17,20), 1.61 (s, 3H, H-19); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 172.6, 162.4, 135.3, 131.3, 124.6, 124.2, 115.6, 99.9, 86.4, 41.5, 34.2, 31.9, 26.5, 25.9, 25.6, 23.3, 19.0, 18.9, 17.5; IR (neat film) 2965 (s), 2925 (s), 2855 (s), 2575 (m), 1965 (w), 1691 (s), 1642 (s), 1439 (s), 1376 (m), 1292 (m), 1252 (s), 1167 (m), 932 (m), 873 (m), 839 (m), 710 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_2$ (M^+) 302.2246, found 302.2247. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.39; H, 9.91.

Enone Chloride 16. Oxalyl chloride (8.81 g, 69.4 mmol, 7.37 equiv) was added to a solution of the acid **15** (2.85 g, 9.42 mmol, 1.00 equiv) in benzene (50.0 mL), and the resulting solution was stirred at 23 °C for 20 min (gas evolution was observed for the first 2 min following the addition), after which time the volatile components were removed in vacuo (~0.1 Torr). The residue was dissolved in dichloromethane (1.0 L, 0.0094 M) and the resulting solution was cooled to −78 °C whereupon stannic chloride solution in dichloromethane (1.00 M, 10.9 mL, 10.9 mmol, 1.16 equiv) was added. The resulting deep red solution was stirred for 30 min at −78 °C and then transferred directly into a solution of saturated aqueous sodium bicarbonate (750 mL) at 23 °C, and the resulting biphasic mixture was stirred for 30 min. The organic phase was washed sequentially with saturated aqueous sodium bicarbonate solution (3 × 500 mL) and saturated aqueous sodium chloride solution (2 × 500 mL) and filtered through a short column of Celite to remove traces of insoluble material. The filtrate was dried over sodium sulfate and concentrated. Purification of the residue by flash chromatography (50% toluene in hexanes) gave a mixture of four products (1.78 g, 60%, typically not separated) containing **16** (84% by ^{1}H NMR), in combination with minor amounts of its C1-epimer (8%), and lesser amounts of the corresponding products of chloride elimination (8%). **16**: R_f 0.53, 100% toluene; ^{1}H NMR (400 MHz, C_6D_6) δ 6.50 (d, 1H, J = 1.2 Hz, H-3), 5.24 (dd, 1H, J = 6.7 Hz, 6.7 Hz, H-11), 5.06 (m, 1H, H-6), 2.96 (d, 1H, J = 10.7 Hz, H-1), 2.58 (dd, 1H, J = 7.5, 16.5 Hz, H-5), 2.38 (dd, 1H, J = 16.5, 6.1 Hz, H-5), 2.19 (d, 3H, J = 1.0 Hz, H-18), 1.80–2.15 (m, 8H, H-8,9,-12,13), 1.71 (d, 3H, J = 1.2 Hz, $-CH_3$), 1.65 (s, 3H, $-CH_3$), 1.61 (m, 6H, H-19, $-CH_3$); ^{13}C NMR (22.5 MHz, C_6D_6) δ 203.6, 158.4, 134.9, 128.3, 126.3, 126.1, 101.3, 87.5, 72.1, 63.8, 40.3, 34.6, 31.6, 30.3, 29.9, 28.3, 27.5, 22.9, 20.4, 18.6; IR (neat film) 2971 (s), 2937 (s), 2852 (s),

1964 (w), 1683 (s), 1616 (s), 1456 (s), 1387 (s), 1372 (s), 1213 (s), 1178 (s), 1119 (s), 1087 (s), 873 (m), 831 (m), 763 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{29}OCl$ (M^+) 320.1907, found 320.1908.

Allylic Alcohol 17. A solution of *n*-butyllithium in hexanes (2.50 M, 0.872 mL, 2.18 mmol, 10.0 equiv) was added to a solution of diisobutylaluminum hydride (310 mg, 2.18 mmol, 10.0 equiv) in a mixture of toluene (4.0 mL) and hexanes (2.0 mL), and the mixture was stirred for 50 min at 0 °C and then cooled to −78 °C. A solution of the enone **16** (68.4 mg, 0.218 mmol, 1.00 equiv) in toluene (2.0 mL) was added to the hydride solution dropwise over a period of 5 min. After 45 min at −78 °C, excess reducing reagent was quenched slowly by the addition of methyl alcohol (1.0 mL). The reaction mixture was warmed to 0 °C, and aqueous hydrochloric acid solution (0.50 N, 30 mL) was added. The clear aqueous and organic layers were separated. The organic layer was washed with a 1:1 mixture of aqueous hydrochloric acid solution (0.50 N) and saturated aqueous sodium chloride solution (50 mL), and the aqueous layer was washed with diethyl ether (2 × 25 mL). The combined organic layers were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (5% ethyl acetate in hexanes, grading to 10% ethyl acetate in hexanes) afforded the allylic alcohol **17** (29.4 mg, 43%) as a single epimer (viscous oil, stereochemistry not determined), along with lesser amounts of recovered starting material **16** (17.0 mg, 25%). **17**: R_f 0.08, 100% toluene; ^{1}H NMR (400 MHz, C_6D_6) δ 5.51 (dd, 1H, *J* = 7.4, 1.0 Hz, H-3), 5.35 (t, 1H, *J* = 7.1 Hz, H-11), 5.25 (m, 1H, H-6), 4.99 (dd, 1H, 7.4, 2.9 Hz, H-2), 2.72 (dd, 1H, *J* = 13.7, 10.5 Hz, H-5), 2.52 (dd, 1H, *J* = 13.7, 5.1 Hz, H-5), 1.80−1.95 (m, 3H, $-CH_2-$), 1.95−2.40 (m, 6H, $-CH_2-$), 1.76 (d, 3H, *J* = 1.2 Hz, H-18), 1.71 (d, 3H, *J* = 2.9 Hz, H-19), 1.66 (s, 3H, $-CH_3$), 1.63 (s, 3H, $-CH_3$), 1.59 (s, 3H, $-CH_3$), 1.27 (d, 1H, *J* = 2.0 Hz, −O*H*); IR (neat film) 3458 (br), 2973 (s), 2933 (s), 1962 (w), 1714 (s), 1674 (s), 1451 (s), 1372 (s), 1115 (br) cm^{-1}.

Dichlorides 18. A solution of the allylic alcohol **17** (10.0 mg, 0.0310 mmol, 1.00 equiv) in acetonitrile (2.0 mL) at −10 °C was treated with oxalyl chloride (13.1 μL, 0.150 mmol, 5.00 equiv), and the mixture was stirred for 1 h at −10 °C. Aqueous phosphate buffer solution (pH 7, 0.10 N, 5 mL) was added, and the mixture was extracted with ethyl acetate (10 mL). The organic layer was dried over sodium sulfate and concentrated, providing the crude dichlorides **18** (11.8 mg, 97%) as a viscous oil. Attempted purification by flash column chromatography afforded a pure sample of **18** as a mixture of C4-epimers (4.4 mg, 36%, 2:1 ratio, stereochemistry not determined), with the remainder of the chloride undergoing hydrolysis on silica to produce the corresponding allylic alcohol. **18** (major epimer): R_f 0.78, 20% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 6.25 (d, 1H, *J* = 15.9 Hz, H-3), 5.66 (m, 1H, H-6), 5.37 (m, 1H, H-11), 5.30 (dd, 1H, *J* = 15.9, 9.5 Hz, H-2), 2.77 (dd, 1H, *J* = 14.2, 3.7 Hz, H-5), 2.15 (dd, *J* = 14.2, 11.0 Hz, H-5), 2.07 (m, 1H, H-1), 1.85−2.45 (m, 8H, $-CH_2-$), 1.75 (s, 3H, H-20), 1.63 (d, 3H, *J* = 2.9 Hz, H-19), 1.58 (s, 3H, H-18), 1.49 (s, 3H, H-16), 1.39 (s, 3H, H-17). **18** (minor epimer): R_f 0.78, 20% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 5.90 (dd, 1H, *J* = 15.1, 8.3 Hz, H-2), 5.84 (d, 1H, *J* = 15.1 Hz, H-3), 5.37 (m, 1H, H-11), 4.91 (m, 1H, H-6), 2.79 (dd, 1H, *J* = 12.2, 3.7 Hz, H-5), 2.15 (dd, 1H, *J* = 12.2, 10.7 Hz, H-5), 1.85−2.45 (m, 9H, $-CH_2-$), 1.77 (s, 3H, H-20), 1.61 (d, 3H, *J* = 2.7 Hz, H-19), 1.58 (s, 3H, H-18), 1.50 (s, 3H, H-16), 1.39 (s, 3H, H-17); IR (mixture of epimers, neat film) 3000 (s), 2960 (s), 1970 (w), 1460 (s), 1385 (s), 1225 (m), 1120 (s), 985 (s), 805 (m) cm^{-1}; MS (EI) found *m/z* 340 (M^+).

Vinyl Stannane 19. Triphenyltin hydride (27.8 mg, 0.079 mmol, 3.00 equiv) and AIBN (1.0 mg, catalytic) were added to a solution of the dichlorides **18** (9.0 mg, 0.026 mmol, 1.0 equiv) in toluene (0.60 mL), and the resulting mixture was heated at reflux for 4 h. The volatile components of the mixture were then removed in vacuo (~1 Torr) to give a viscous yellow residue. Purification by preparative thin-layer chromatography (TLC) on silica gel (20% toluene in hexanes) afforded the vinyl stannane **19** (5.3 mg, 32%) as the predominant component of a mixture of overlapping compounds. Further purification by preparative TLC (20% carbon tetrachloride in hexanes) gave **19** (1.2 mg), along with decomposition products formed during the elution on silica gel, as a viscous oil: R_f 0.53, 20% toluene in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 6H, Ar-**H**), 7.36 (m, 9H, Ar-**H**), 5.22 (m, 2H, H-3, 11), 5.11 (t, 1H, *J* = 8.3 Hz, H-6), 2.51 (m, 1H), 1.92−2.40 (m, 8H), 1.78 (s, 3H, $-CH_3$), 1.70 (m, 2H), 1.68 (s, 3H, $-CH_3$), 1.54 (s, residual H_2O), 1.25−1.40 (m, 4H), 0.85 (d, 3H, *J* = 6.6 Hz, $-CH_3$), 0.81 (d, 3H, *J* = 6.6 Hz, $-CH_3$), 0.63 (d, 3H, *J* = 6.6 Hz, $-CH_3$); HRMS (EI) *m/z* calcd for $C_{38}H_{48}{}^{120}Sn$ (M^+) 624.2778, found 624.2793.

Enone 20. Silver(I) carbonate (893 mg, 3.24 mmol, 3.00 equiv) was added in one portion to a deoxygenated solution of the enone **16** (347 mg, 1.08 mmol, 1.00 equiv) in 2,2,4-trimethylpentane (45 mL), and the resulting solution was heated at 75 °C for 8.5 h with vigorous stirring. The reaction mixture was cooled to 23 °C and washed with a 1:1 mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous ammonium chloride solution (3 × 100 mL). The organic layer was dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes) gave the enone **20** (297 mg, 97%) as a viscous oil: R_f 0.38, 100% toluene; ^{1}H NMR (400 MHz, C_6D_6) δ 6.30 (s, 1H, H-3), 5.18 (t, 1H, *J* = 5.5 Hz, H-11), 5.12 (m, 1H, H-6), 4.92 (s, 1H, H-16), 4.86 (d, 1H, *J* = 1.2 Hz, H-16), 3.09 (dd, 1H, *J* = 12.0, 2.4 Hz, H-1), 2.52 (dd, 1H, *J* = 14.2, 6.6 Hz, H-5), 2.41 (dd, 1H, *J* = 14.2, 5.9 Hz, H-5), 2.22 (d, 3H, *J* = 1.0 Hz, H-18), 1.79−2.18 (m, 8H, $-CH_2-$), 1.72 (s, 3H, $-CH_3$), 1.65 (s, 3H, $-CH_3$), 1.59 (d, 3H, *J* = 2.7 Hz, H-19); IR (neat film) 3083 (w), 2965 (s), 2939 (s), 2815 (s), 1964 (w), 1684 (s), 1641 (s), 1617 (s), 1441 (s), 1377 (s), 1359 (m), 1224 (m), 1200 (m), 1114 (m), 1063 (m), 894 (s) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{28}O$ (M^+) 284.2140, found 284.2130.

Allylic Alcohols 21. A solution of diisobutylaluminum hydride in hexanes (1.0 M, 1.06 mL, 1.06 mmol, 5.00 equiv) was added dropwise to a solution of the enone **20** (60.0 mg, 0.211 mmol, 1.00 equiv) in toluene (15 mL) at −78 °C. The reaction mixture was slowly warmed to 0 °C over a period of 2.5 h and then poured into a 1:1 mixture of saturated aqueous sodium potassium tartrate solution and saturated aqueous potassium carbonate solution (600 mL). The biphasic mixture was stirred vigorously until the two layers appeared homogeneous. The organic layer was separated, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography afforded the allylic alcohols **21** as a lower R_f major epimer (41.8 mg) and a higher R_f minor epimer (10.4 mg), both as slurries of solids in viscous oils (86% overall yield). **21** (major epimer): R_f 0.07, 100% toluene; ^{1}H NMR (400 MHz, C_6D_6) δ 5.36 (d, 1H, *J* = 8.8 Hz, H-3), 5.18 (m, 2H, H-6,10), 4.93 (m, 1H, H-16), 4.90 (m, 1H, H-16), 4.26 (m, 1H, H-2), 2.77 (dd, 1H, *J* = 16.3, 3.4 Hz, H-5), 2.51 (dd, 1H, *J* = 16.3, 7.0 Hz, H-5), 2.00−2.30 (m, 7H), 1.70−1.78 (m, 2H), 1.68−1.70 (m, 12H, $-CH_3$), 1.47 (d, 1H, *J* = 3.0 Hz, −O*H*); IR (neat film) 3430 (br), 2965 (s), 2920 (s), 1964 (w), 1650 (m), 1444 (s), 1375 (s), 1030 (m), 990 (m), 890 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O$ (M^+) 286.2297, found 286.2289. **21** (minor epimer): R_f 0.13, 100% toluene; ^{1}H NMR (400 MHz, C_6D_6) δ 5.59 (dd, 1H, *J* = 7.8, 0.7 Hz, H-3), 5.31 (m, 1H, H-6), 5.25 (m, 1H, H-11), 4.96 (m, 1H, H-16), 4.91 (m, 1H, H-16), 4.53 (m, 1H, H-2), 2.78 (dd, 1H, *J* = 13.2, 9.0 Hz, H-5), 2.49 (dd, 1H, *J* = 13.2, 5.9 Hz, H-5), 1.90−2.40 (m, 7H), 1.85 (m, 3H, $-CH_3$), 1.74 (s, 3H, $-CH_3$), 1.73 (m, 2H), 1.71 (d, 3H, *J* = 2.7 Hz, H-19), 1.61 (s, 3H, $-CH_3$), 1.24 (d, 1H, *J* = 3.0 Hz, −O*H*); IR (neat film) 3404 (br), 2965 (s), 2909 (s), 1962 (w), 1662 (w), 1640 (m), 1441 (s), 1376 (s), 1255 (m) 1227 (m), 1011 (s), 890 (s) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O$ (M^+) 286.2297, found 286.2289.

Chloride 22. Thionyl chloride (39 μL, 0.54 mmol, 30 equiv) was added to a solution of the alcohol **21** (major, low R_f epimer, 5.2 mg, 0.018 mmol, 1.00 equiv) in dichloromethane (1.0 mL) at −78 °C. After the mixture was stirred for 20 min at −78 °C, the reaction was warmed to 0 °C and held at that temperature for 10 min. The reaction mixture was partitioned between hexanes (10 mL) and saturated aqueous sodium chloride solution (10 mL). The organic phase was separated, washed with saturated aqueous sodium chloride solution (10 mL), dried over sodium sulfate, and concentrated. The crude chloride **22** (5.0 mg) was obtained as a viscous oil that was not purified further because of the facility with which it underwent elimination of hydrogen chloride upon exposure to silica gel: R_f 0.70, 10% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (d, 1H, *J* = 15.6 Hz, H-3), 5.67 (m, 1H, H-6), 5.38 (m, 1H, H-11), 5.33 (dd, 1H, *J* = 15.9, 9.0 Hz, H-2), 4.86 (s, 1H, H-16), 4.82 (m, 1H, H-16), 2.80 (dd, 1H, *J* = 14.3, 3.5 Hz, H-5), 2.58 (m, 1H), 2.42 (m, 1H), 2.29 (m, 1H), 2.20 (dd, 1H, 14.3, 10.7 Hz, H-5), 1.99 (m, 1H), 1.71 (s, 3H, $-CH_3$), 1.69 (s, 3H, $-CH_3$), 1.64 (s, 3H, $-CH_3$), 1.61 (s, 3H, $-CH_3$), 1.30−1.80 (m, 5H); IR (neat

film) 2967 (s), 2929 (s), 1964 (w), 1736 (w), 1643 (m), 1449 (s), 1375 (s), 1197 (m), 972 (m), 891 (s) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{29}Cl$ (M^+) 304.1958, found 304.1950.

Dimeric Macrocycles 23. Samarium diiodide (0.10 M in THF, 1.9 mL, 0.15 mmol, 5.0 equiv) was added dropwise to a solution of the allylic chloride **22** (9.0 mg, 0.030 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. After 40 min, hexanes (10 mL) was added to the reaction mixture, and the resulting solution was washed with aqueous hydrochloric acid solution (0.10 N, 3 × 25 mL). The organic layer was dried over sodium sulfate and concentrated. Purification of the residue by repeated preparative thin-layer silica gel chromatography (100% hexanes, eluting twice and drying between elutions) gave the four diastereomeric dimeric products **23** in near equimolar quantities, each as a viscous oil. **23** (diastereomer with R_f 0.37, 10% ethyl acetate in hexanes): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (d, 1H, J = 15.9 Hz, H-3), 5.61 (d, 1H, J = 15.6 Hz, H-3), 5.14 (m, 4H, H-6,11), 4.69 (m, 4H, H-16), 2.40 (m, 4H), 2.20 (m, 1H), 1.90–2.15 (m, 6H), 1.60–1.80 (m, complex overlapping signals), 1.74 (s, 3H, $-CH_3$), 1.71 (s, 3H, $-CH_3$), 1.68 (s, 6H, $-CH_3$), 1.63 (s, 6H, $-CH_3$), 1.04 (s, 3H, $-CH_3$), 1.03 (s, 3H, $-CH_3$); IR (neat film) 2965 (s), 2926 (s), 2855 (s), 1961 (w), 1642 (m), 1450 (m), 1373 (s), 984 (m), 887 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{40}H_{58}$ (M^+) 538.4539, found 538.4553. **23** (diastereomer with R_f 0.41, 10% ethyl acetate in hexanes): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (d, 1H, J = 15.6 Hz, H-3), 5.45 (d, 1H, J = 15.8 Hz, H-3), 5.30 (m, 1H, H-11), 5.11 (m, 2H, H-6,11), 4.94 (m, 1H, H-6), 4.70 (m, 2H, H-16), 4.69 (s, 1H, H-16), 4.68 (s, 1H, H-16), 2.58 (m, 1H), 2.40 (m, 3H), 2.00–2.30 (m, 5H), 1.60–1.80 (m, complex overlapping signals), 1.73 (s, 3H, $-CH_3$), 1.68 (s, 9H, $-CH_3$), 1.66 (d, 3H, J = 2.9 Hz, H-19), 1.63 (d, 3H, J = 2.7 Hz, H-19), 1.04 (s, 3H, $-CH_3$), 1.01 (s, 3H, $-CH_3$); IR (neat film) 2964 (s), 2925 (s), 2854 (s), 1960 (w), 1711 (m), 1643 (m), 1450 (m), 1371 (s), 983 (m), 887 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{40}H_{58}$ (M^+) 538.4539, found 538.4559. **23** (diastereomer with R_f 0.46, 10% ethyl acetate in hexanes): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (d, 1H, J = 15.6 Hz, H-3), 5.43 (d, 1H, J = 16.1 Hz, H-3), 5.30 (dd, 1H, J = 16.4, 6.4 Hz, H-11), 5.13 (m, 2H, H-6, 11), 4.94 (m, 1H, H-6), 4.69 (m, 4H, H-16), 2.60 (m, 1H), 2.43 (m, 2H), 1.95–2.35 (m, 9H), 1.80–1.94 (m, complex overlapping signals), 1.75 (s, 3H, $-CH_3$), 1.68 (m, 9H, $-CH_3$), 1.65 (d, 3H, J = 2.7 Hz, H-19), 1.63 (d, 3H, J = 2.9 Hz, H-19), 1.02 (s, 3H, $-CH_3$), 1.01 (s, 3H, $-CH_3$); IR (neat film) 2965 (s), 2925 (s), 2854 (s), 1962 (w), 1710 (m), 1643 (m), 1450 (m), 1371 (s), 983 (m), 887 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{40}H_{58}$ (M^+) 538.4539, found 538.4569. **23** (diastereomer with R_f 0.50, 10% ethyl acetate in hexanes): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22–5.42 (m, 4H, H-3, 11), 4.93 (m, 2H, H-6), 4.71 (s, 2H, H-16), 4.68 (m, 2H, H-16), 2.58 (m, 2H), 2.20 (m, 4H), 1.60–1.90 (m, complex overlapping signals), 1.69 (s, 3H, $-CH_3$), 1.68 (s, 9H, $-CH_3$), 1.65 (s, 3H, $-CH_3$), 1.64 (s, 3H, $-CH_3$), 1.02 (s, 3H, $-CH_3$), 1.00 (s, 3H, $-CH_3$); IR (neat film) 2965 (s), 2925 (s), 2854 (s), 1962 (w), 1711 (m), 1643 (m), 1441 (m), 1372 (s), 983 (m), 888 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{40}H_{58}$ (M^+) 538.4539, found 538.4585.

Ester 24. 3-(Trifluoromethyl)benzoyl chloride (53 μL, 0.35 mmol, 5.00 equiv) and pyridine (57 μL, 0.70 mmol, 10.0 equiv) were added to a solution of the alcohol **21** (major low R_f epimer, 20.0 mg, 0.0698 mmol, 1.00 equiv) in dichloromethane (3.0 mL) at 23 °C. After being stirred for 50 min at 23 °C, the reaction mixture was diluted with hexanes (10 mL) and the resulting solution was washed with saturated aqueous sodium chloride solution (3 × 10 mL). The organic layer was dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (5% ethyl acetate in hexanes) gave the ester **24** (23.9 mg, 75%) as a viscous oil: R_f 0.70, 20% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, C_6D_6) δ 8.56 (s, 1H, H-28), 8.15 (d, 1H, J = 7.8 Hz, H-25), 7.28 (d, 1H, J = 7.8 Hz, H-23), 6.81 (t, 1H, J = 7.8 Hz, H-24), 5.96 (d, 1H, J = 10.7, 1.2 Hz, H-2), 5.35 (d, 1H, J = 9.5 Hz, H-3), 5.18 (m, 2H, H-6, 11), 4.96 (d, 1H, J = 2.0 Hz, H-16), 4.87 (m, 1H, H-16), 2.70 (dd, 1H, J = 16.1, 3.4 Hz, H-5), 2.39–2.52 (m, 2H), 2.20–2.31 (m, 2H), 2.11–2.19 (m, 2H), 1.98 (d, 3H, J = 0.5 Hz, H-18), 1.80 (m, 2H), 1.69 (m, 9H, $-CH_3$), 1.67 (m, 1H), 1.41 (m, 1H); IR (neat film) 2955 (s), 1791 (s), 1724 (s), 1616 (m), 1333 (s), 1254 (s), 1171 (s), 1126 (s), 1072 (s), 929 (m), 752 (s), 742 (s), 695 (s) cm^{-1}.

Chloro Ketone 25. Lithium tri-*sec*-butylborohydride (1.00 M, 11.1 mL, 11.1 mmol, 2.00 equiv) was added to a solution of the enone **16** (1.78 g, 5.55 mmol, 1.00 equiv, 10:1 ratio of diastereomers at C1, including 10% 2-propenyl chloride elimination products) in THF (100 mL) at −78 °C. After the mixture was stirred for 2.5 h, excess hydride was quenched by the addition of a solution of acetic acid (2.54 mL, excess) in THF (10 mL). Oxidation of the intermediate borate esters was effected by the addition of 10% aqueous sodium hydroxide solution (50 mL) and 30% aqueous hydrogen peroxide solution (20 mL) to the reaction mixture. The resulting biphasic mixture was stirred at 23 °C for 3.3 h. The aqueous layer was separated and extracted with hexanes (2 × 100 mL). The combined organic layers were washed sequentially with saturated aqueous sodium chloride solution (100 mL) and saturated aqueous sodium thiosulfate solution (100 mL) and dried over sodium sulfate. The solution was **partially** concentrated to a volume of approximately 25 mL behind a protective blast shield. [**Caution:** Organic peroxides are known to be shock sensitive and potentially explosive in neat form.] Methyl alcohol (50 mL) and dimethyl sulfide (15 mL) were added and the resulting solution was stirred at 23 °C until peroxides were no longer detected by enzymatic peroxide test strips (typically about 12 h). Concentration of the solution and purification of the residue by filtration through a short column of silica gel (100% toluene) gave the chloro ketone **25** (1.63 g, 91%, 10:1 ratio of diastereomers at C1, including 10% 2−propenyl chloride elimination products) as a viscous oil. A sample of pure **25** was obtained for analysis by flash chromatography (100% toluene), providing **25** as a crystalline solid: mp 53−55 °C; R_f 0.47, 50% toluene in hexanes; ^{1}H NMR (400 MHz, C_6D_6) δ 5.28 (t, 1H, J = 7.1 Hz, H-11), 5.13 (m, 1H, H-6), 2.82 (m, 1H, H-1), 2.76 (dd, 1H, J = 19.2, 4.0 Hz, H-3), 2.56 (m, 1H, H-4), 2.39 (dd, 1H, J = 19.2, 8.2 Hz, H-3), 2.31 (ddd, 1H, J = 15.6, 6.2, 3.0 Hz, H-5), 1.70–2.20 (m, 9H), 1.67 (br s, 3H, H-20), 1.64 (d, 3H, J = 2.9 Hz, H-19), 1.54 (s, 3H, H-16), 1.53 (s, 3H, H-17), 0.98 (d, 3H, J = 6.6 Hz, H-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 202.1, 135.7, 125.0, 100.5, 87.2, 71.5, 62.5, 53.6, 35.1, 34.9, 30.5, 30.3, 30.0, 28.0, 27.7, 26.7, 22.4, 20.6, 18.6; IR (neat film) 2956 (s), 2928 (s), 1960 (w), 1711 (s), 1457 (m), 1388 (m), 1371 (s), 1118 (m) cm^{-1}; HRMS (CI, NH_3) *m/z* calcd for $C_{20}H_{32}OCl$ (MH^+) 323.2142, found 323.2149.

Chloro Ketone 26. A solution of diisobutylaluminum hydride in THF (1.0 M, 3.12 mL, 3.12 mmol, 2.00 equiv) was added to a solution of the enone **16** (500 mg, 1.56 mmol, 1.00 equiv) in THF (50 mL), and the resulting solution was stirred for 30 min at 0 °C. Excess hydride was quenched by the dropwise addition of water (0.120 mL). The reaction mixture was partitioned between hexanes (50 mL) and a 1:1 mixture of saturated aqueous sodium potassium tartrate solution and saturated aqueous potassium carbonate solution (100 mL). The aqueous layer was separated and extracted with hexanes (2 × 50 mL). The combined organic layers were washed with a 1:1 mixture of saturated aqueous sodium potassium tartrate solution and saturated aqueous potassium carbonate solution (2 × 100 mL), dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (35% toluene in hexanes) provided pure samples of the chloro ketone **26** (374 mg, 50%) as a crystalline solid (mp 69 °C) and the epimeric chloro ketone **25** (187 mg, 25%) as a crystalline solid (mp 53−55 °C). The relative stereochemical configuration of **26** was established unequivocally by X-ray crystallographic analysis of crystals grown in methyl alcohol (see supplementary material). **26**: R_f 0.33, 50% toluene in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 5.27 (t, 1H, J = 6.7 Hz, H-11), 4.99 (m, 1H, H-6), 2.99 (d, 1H, J = 17.8 Hz, H-3), 2.55–2.62 (m, 2H, H-3, 14), 1.80–2.30 (m, 10H), 1.70 (s, 3H, H-20), 1.66 (d, 3H, J = 2.7 Hz, H-19), 1.62 (m, 1H), 1.52 (s, 3H, H-16), 1.47 (s, 3H, H-17), 1.06 (d, 3H, J = 5.6 Hz, H-18); IR (neat film) 3406 (w), 2959 (s), 2928 (s), 1958 (w), 1703 (s), 1453 (m), 1389 (m), 1372 (m), 1215 (m), 1114 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{31}OCl$ (M^+) 322.2064, found 322.2061. Calcd. for $C_{20}H_{31}OCl$: C, 74.38; H, 9.68. Found: C, 74.52; H, 9.40.

Enone 27. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 2.0 mL, excess) was added to a solution of the chloro ketone **26** (250 mg, 0.774, 1.00 equiv) in THF (20 mL) at 23 °C, and the resulting solution was heated at reflux for 23 h. The reaction mixture was cooled to 23 °C and diluted with hexanes (100 mL). The resulting solution was washed with saturated aqueous citric acid solution (100 mL), and the aqueous

layer was separated and extracted with hexanes (50 mL). The organic layers were combined and washed sequentially with saturated aqueous citric acid solution (2 × 100 mL) and saturated aqueous sodium bicarbonate solution (100 mL). The organic layer was dried over sodium sulfate and concentrated. Purification by flash column chromatography (50% toluene in hexanes) gave the enone **27** (180 mg, 82%) as a crystalline solid: mp 88 °C; R_f 0.23, 50% toluene in hexanes; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22 (td, 1H, J = 7.8, 1.4 Hz, H-11), 4.95 (m, 1H, H-6), 3.27 (dd, 1H, J = 17.7, 1.4 Hz, H-3), 2.39 (m, 1H), 1.91−2.29 (m, 10H), 1.82 (s, 3H, H-16), 1.78 (s, 3H, H-17), 1.74 (q, 3H, J = 1.2 Hz, H-20), 1.69 (d, 3H, J = 2.8 Hz, H-19), 1.65 (m, 1H), 0.99 (d, 3H, J = 6.3 Hz, H-18); IR (neat film) 2911 (s), 1956 (w), 1680 (s) cm^{-1}; HRMS (CI, NH_3) *m/z* calcd for $C_{20}H_{31}O$ (MH^+) 287.2375, found 287.2357.

Enone 28. A solution of the chloro ketone **25** (1.00 g, 3.10 mmol, 1.00 equiv) in a mixture of THF (15 mL) and DBU (5 mL) was heated at reflux for 24 h. The reaction mixture was cooled to 0 °C and poured into saturated aqueous citric acid solution (100 mL) at 0 °C. The resulting mixture was washed with hexanes (2 × 100 mL), and the combined organic layers were washed sequentially with saturated aqueous citric acid solution (100 mL) and saturated aqueous sodium bicarbonate solution (100 mL). The organic layer was dried over sodium sulfate and concentrated. Purification by flash column chromatography (50% toluene in hexanes) provided the α,β-unsaturated ketone **28** (567 mg, 64%), as a crystalline solid (mp 44 °C) and lesser amounts of the 2-propenyl elimination product **29** (145 mg, 16%), also a crystalline solid (mp 35 °C), in the equilibrium ratio of 4:1, respectively. The ketone **29** could be recycled under identical conditions, giving rise to the same thermodynamic distribution of products. **28**: R_f 0.24, 50% toluene in hexanes; ^{1}H NMR (400 MHz, C_6D_6) δ 5.28 (t, 1H, J = 7.5 Hz, H-11), 5.15 (m, 1H, H-6), 2.89 (dd, 1H, J = 18.2, 4.5 Hz, H-3), 2.62 (m, 1H, H-4), 1.90−2.45 (m, 11H, $-CH_2-$), 1.86 (s, 3H, H-16), 1.73 (d, 3H, J = 1.2 Hz, H-20), 1.67 (d, 3H, J = 2.9 Hz, H-19), 1.57 (s, 3H, H-17), 1.04 (d, 3H, J = 6.8 Hz, H-18); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 202.4, 136.6, 136.4, 135.8, 124.9, 99.6, 86.9, 47.3, 35.8, 34.8, 31.7, 29.2, 27.9, 27.1, 23.6, 22.3, 20.9, 19.4, 19.0; IR (neat film) 2917 (s), 2850 (s), 1959 (w), 1678 (s), 1631 (m), 1435 (m), 1369 (m), 1132 (m), 1013 (m), 760 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O$ (M^+) 286.2297, found 286.2300. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.59; H, 10.46. **29**: R_f 0.56, 100% toluene; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (t, 1H, J = 6.6 Hz, H-11), 4.90 (m, 1H, H-6), 4.76 (m, 1H, H-16), 4.72 (m, 1H, H-16), 2.96 (dd, 1H, J = 11.8, 1.6 Hz), 2.61 (dd, 1H, J = 18.3, 3.5 Hz), 1.62−2.38 (m, 11H), 1.57 (m, 9H), 1.24 (m, 1H), 0.87 (d, 3H, J = 6.7 Hz, H-18); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3, 201.7, 145.1, 133.8, 126.1, 113.3, 100.0, 86.6, 57.0, 45.8, 34.9, 34.4, 28.8, 28.2, 26.3, 25.8, 22.4, 20.3, 20.3, 17.7; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O$ (M^+) 286.2297, found 286.2307.

Ketone 30. Samarium diiodide (0.100 M in THF, 50.0 mL, 5.00 mmol, 2.60 equiv) and methyl alcohol (0.400 mL, 9.88 mmol, 5.14 equiv) were added sequentially to a solution of the enone **28** (550 mg, 1.92 mmol, 1.00 equiv) in THF (50 mL) at 23 °C, and the resulting solution was stirred at 23 °C for 1 h. Excess reductant was quenched by admitting air to the stirring reaction mixture until the characteristic deep blue color of samarium diiodide dissipated, producing a yellow solution. The reaction mixture was partitioned between hexanes (50 mL) and aqueous hydrochloric acid solution (0.50 N, 50 mL). The aqueous layer was separated and extracted with hexanes (50 mL), and the combined organic layers were washed sequentially with aqueous hydrochloric acid (0.50 N, 2 × 50 mL) and aqueous sodium bicarbonate (50 mL). The organic phase was dried over sodium sulfate and concentrated. Purification by flash column chromatography (10% ethyl acetate in hexanes) provided the ketone **30** (550 mg, 99%) as a crystalline solid: mp 36 °C; R_f 0.50, 100% toluene; ^{1}H NMR (500 MHz, C_6D_6) δ 5.30 (t, 1H, J = 7.6 Hz, H-11), 5.21 (m, 1H, H-6), 2.82 (dd, 1H, J = 18.3, 4.2 Hz, H-3), 2.49 (m, 1H, H-4), 2.18−2.30 (m, 4H), 2.08 (dd, 1H, J = 18.3, 8.2 Hz, H-3), 1.74−2.03 (m, 6H), 1.68 (s, 3H, H-20), 1.65 (d, 3H, J = 2.8 Hz, H-19), 1.63 (m, 1H, H-15), 1.33 (m, 1H), 1.06 (d, 3H, J = 6.8 Hz, H-18), 0.84 (d, 3H, J = 6.8 Hz, H-16), 0.82 (d, 3H, J = 6.8 Hz, H-17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0, 201.7, 135.9, 124.7, 100.5, 87.8, 62.3, 43.1, 35.5, 34.7, 30.4, 30.1, 28.6, 27.2, 26.7, 23.3, 21.3, 20.6, 20.5, 18.9; IR (neat film) 2959 (s), 2927 (s), 1963 (w), 1703 (s), 1463 (m), 1454 (m), 1371 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{32}O$ (M^+) 288.2453, found 288.2444.

Ketones 31 and 32. Samarium diiodide (0.100 M in THF, 24.8 mL, 2.48 mmol, 4.18 equiv) and methyl alcohol (0.250 mL, 6.20 mmol, 10.4 equiv) were added to a solution of the enone **27** (170 mg, 0.593 mmol, 1.00 equiv) in THF (30 mL), and the resulting solution was stirred at 23 °C for 5.5 h. The excess reductant was quenched by admitting air to the reaction as it was stirred until the characteristic deep blue color of samarium diiodide dissipated, producing a yellow solution. The reaction was partitioned between hexanes (50 mL) and aqueous hydrochloric acid solution (0.50 N, 50 mL). The aqueous layer was extracted with hexanes (50 mL), and the combined organic layers were washed sequentially with aqueous hydrochloric acid solution (0.50 N, 2 × 50 mL), aqueous sodium bicarbonate solution (50 mL), saturated aqueous sodium thiosulfate solution (50 mL), and saturated sodium chloride solution (50 mL). The organic phase was dried over sodium sulfate and concentrated. Purification by flash column chromatography (10% ethyl acetate in hexanes) afforded the ketones **31** and **32** (170 mg, 99%) as a mixture of epimers in a 1.6:1 ratio. The mixture of epimers was separated by flash column chromatography (30% toluene in hexanes) to give pure **31** (mp 31−33 °C) and **32** (mp 62 °C), both as crystalline solids. **31**: R_f 0.40, 50% toluene in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 5.25 (t, 1H, J = 6.6 Hz, H-11), 5.11 (m, 1H, H-6), 2.91 (dd, 1H, J = 18.7, 3.4 Hz, H-3), 2.38 (m, 1H, H-4), 2.30 (m, 1H), 2.11−2.19 (m, 4H), 1.98−2.07 (m, 3H), 1.87−1.93 (m, 3H), 1.70 (m, 1H), 1.68 (m, 6H, H-19,20), 1.45 (m, 1H), 0.99 (d ,3H, J = 6.7 Hz, H-18), 0.92 (d, 3H, J = 6.7 Hz, H-16), 0.83 (d, 3H, J = 6.8 Hz, H-17); IR (neat film) 2959 (s), 2929 (s), 2872 (s), 1960 (w), 1708 (s), 1462 (m), 1455 (m), 1371 (m), 1044 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{32}O$ (M^+) 288.2453, found 288.2459. **32**: R_f 0.30, 50% toluene in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 5.27 (t, 1H, J = 6.6 Hz, H-11), 5.04 (m, 1H, H-6), 2.84 (d, 1H, J = 15.6 Hz, H-3), 2.32 (m, 1H), 1,86−2.23 (m, 9H), 1.60−1.72 (m, 3H), 1.69 (m, 6H, H-19,20), 1.49 (m, 1H), 1.04 (d, 3H, J = 6.4 Hz, H-18), 0.86 (d, 3H, J = 6.7 Hz, H-16), 0.83 (d, 3H, J = 6.6 Hz, H-17); IR (neat film) 2960 (s), 2928 (s), 2861 (s), 1959 (w), 1704 (s), 1462 (m), 1454 (m), 924 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{32}O$ (M^+) 288.2453, found 288.2450.

Ketone 33. The ketone **30** (591 mg, 2.05 mmol) was dissolved in toluene (20 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (10 mL), and the resulting solution was heated at reflux for 46 h. The reaction mixture was cooled to 0 °C and poured into saturated aqueous citric acid solution (100 mL). The aqueous phase was separated and washed with hexanes (100 mL), and the combined organic phases were washed sequentially with saturated aqueous citric acid solution (2 × 100 mL) and saturated aqueous sodium bicarbonate solution (100 mL). The organic phase was dried over sodium sulfate and concentrated. Purification by flash column chromatography (33% toluene in hexanes) provided the ketone **33** (325 mg, 55%) as a crystalline solid (mp 49 °C) and recovered starting material **30** (153 mg, 26%). **33**: R_f 0.57, 100% toluene; ^{1}H NMR (400 MHz, C_6D_6) δ 5.23 (m, 1H, H-11), 5.10 (m, 1H, H-6), 2.74 (dd, 1H, J = 19.0, 4.9 Hz, H-3), 2.51 (m, 1H, H-4), 2.43 (m, 1H, H-1), 2.35 (ddd, 1H, J = 16.0, 6.1, 3.2 Hz, H-5), 2.18 (ddd, 1H, J = 10.2, 5.9, 2.0 Hz, H-13), 1.89−2.12 (m, 9H), 1.66 (br s, 3H, H-20), 1.62 (d, 3H, J = 2.9 Hz, H-19), 1.32 (m, 1H, H-14), 1.00 (d, 3H, J = 6.8 Hz, H-18), 0.87 (d, 3H, J = 6.6 Hz, H-16), 0.77 (d, 3H, J = 6.8 Hz, H-17); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9, 201.7, 135.0, 125.3, 100.3, 86.8, 56.0 (2C), 47.8, 35.1, 34.6, 29.0, 28.3, 28.1, 26.2, 22.8, 21.4, 20.7, 18.1, 17.9; IR (neat film): 2960 (s), 2930 (s), 2872 (s), 1963 (w), 1707 (s), 1454 (m), 1370 (m) cm^{-1}; HRMS (EI) calcd for $C_{20}H_{32}O$ (M^+) 288.2453, found 288.2451.

Alcohol 34. A solution of lithium aluminum hydride in THF (0.92 M, 0.942 mL, 0.866 mmol, 1.00 equiv) was added slowly to a solution of the ketone **30** (250 mg, 0.866 mmol, 1.00 equiv) in THF (25 mL) at −78 °C, and the resulting solution was stirred for 3 h at −78 °C. Additional lithium aluminum hydride solution in THF (0.92 M, 0.600 mL, 0.552 mmol, 0.637 equiv) was added, and the reaction mixture was stirred for 1 h at −78 °C. Water (55 μL) was added cautiously to the reaction mixture, followed by the sequential addition of 15% aqueous sodium hydroxide solution (55 μL) and water (165 μL). The organic layer was filtered through a short column of silica gel and concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes) provided an epimeric mixture of

alcohols **34** (250 mg, 99%, 2.5:1 ratio, stereochemistry not determined) as a viscous oil: R_f 0.04, 5% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 5.33 (t, 1H, J = 7.7 Hz, H-11), 5.31 (t, 1H, J = 7.7 Hz, H-11′), 5.27 (m, 1H, H-6′), 5.20 (m, 1H, H-6), 3.93 (m, 1H, H-2′), 3.50 (t, 1H, J = 9.5 Hz H-2), 2.56 (td, 1H, J = 13.2, 4.1 Hz), 2.28–2.43 (m), 2.06–2.29 (m), 2.00 (m), 1.78 (m), 1.80 (s, 3H, H-20′), 1.79 (s, 3H, H-20), 1.67 (m), 1.53 (m), 1.42 (m), 1.29 (m), 1.05 (d, 3H, J = 6.8 Hz, $-CH_3$′), 1.00 (d, 3H, J = 6.8 Hz, $-CH_3$′), 0.98 (d, 3H, J = 6.9 Hz, $-CH_3$), 0.95 (d, 3H, J = 6.5 Hz, $-CH_3$′), 0.93 (d, 3H, J = 6.9 Hz, $-CH_3$), 0.87 (d, 3H, J = 6.8 Hz, $-CH_3$); IR (neat film) 3358 (br), 2956 (s), 2930 (s), 2870 (s), 1963 (w), 1462 (m), 1440 (m), 1385 (m), 1376 (m), 1068 (w) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{34}O$ (M^+) 290.2610, found 290.2597.

Alcohols 35. A solution of lithium aluminum hydride in THF (0.92 M, 0.40 mL, 0.37 mmol, 4.00 equiv) was added slowly to a solution of the ketone **32** (26.0 mg, 0.0901 mmol, 1.00 equiv) in THF (5.5 mL) at −78 °C, and the resulting solution was stirred for 2 h at −78 °C. Water (14 μL) was added cautiously to the reaction mixture, followed by the sequential addition of 15% aqueous sodium hydroxide solution (14 μL) and water (42 μL). The reaction was partitioned between hexanes (10 mL) and a 1:1 mixture of saturated aqueous potassium carbonate solution and saturated sodium potassium tartrate solution (50 mL). The aqueous layer was separated and extracted with hexanes (10 mL), and the combined organic layers were washed with a 1:1 mixture of saturated aqueous potassium carbonate solution and saturated sodium potassium tartrate solution (2 × 50 mL). The organic layer was dried over sodium sulfate and concentrated, providing an epimeric mixture of alcohols **35** (24.9 mg, 95%, 4:1 ratio, stereochemistry not determined) as a viscous oil with some slurry of solid present: R_f 0.31, 10% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 5.30 (m, 2H, H-11, 11′), 5.05 (m, 2H, H-6, 6′), 3.97 (d, 1H, J = 13.2 Hz, H-2′), 3.56 (m, 1H, H-2), 2.39 (m), 2.25 (m), 2.17 (m), 2.00 (m), 1.82–1.98 (m), 1.81 (d, 3H, J = 1.2 Hz, H-20′), 1.78 (d, 3H, J = 1.2 Hz, H-20), 1.71 (d, 3H, J = 3.0 Hz, H-19′), 1.68 (d, 3H, J = 3.2 Hz, H-19), 1.65 (m), 1.50 (m), 1.40 (m, 1H), 1.18 (d, 3H, J = 6.9 Hz, $-CH_3$), 1.14 (m), 1.13 (d, 3H, J = 6.7 Hz, $-CH_3$′), 0.99 (d, 3H, J = 6.7 Hz, $-CH_3$′), 0.97 (d, 3H, J = 7.0 Hz, $-CH_3$), 0.93 (d, 3H, J = 6.6 Hz, $-CH_3$′), 0.90 (d, 3H, J = 6.9 Hz, $-CH_3$), 0.75 (m), 0.66 (m, 1H); IR (neat film) 3447 (br), 2956 (s), 2870 (s), 1963 (w), 1465 (m), 1437 (m), 1368 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{34}O$ (M^+) 290.2610, found 290.2620.

Alcohols 36. A solution of lithium aluminum hydride in THF (0.92 M, 0.32 mL, 0.30 mmol, 5.0 equiv) was added slowly to a solution of the ketone **31** (17.0 mg, 0.0589 mmol, 1.00 equiv) in THF (6.0 mL) at −78 °C, and the resulting solution was stirred for 4.0 h at −78 °C. Water was added cautiously until hydrogen gas evolution had ceased. The reaction was diluted with hexanes (10 mL) and washed sequentially with saturated sodium potassium tartrate solution (3 × 50 mL) and saturated aqueous sodium chloride solution (50 mL). The organic layer was dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes) gave an epimeric mixture of alcohols **36** (15.3 mg, 90%, 3:1 ratio, stereochemistry not determined) as a viscous oil: R_f 0.23 and 0.19, 10% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 5.34 (t, 1H, J = 7.2 Hz, H-11′), 5.27 (t, 1H, J = 7.2 Hz, H-11), 5.10 (m, 2H, H-6,6′), 3.90 (m, 1H, H-2), 3.76 (d, 1H, J = 10.7 Hz, H-2′), 2.63 (td, 1H, J = 12.8, 4.4 Hz), 2.52 (m, 1H), 2.35 (q, 2H, J = 7.7 Hz), 2.20–2.30 (m), 1.96–2.19 (m), 1.80–1.95 (m), 1.79 (m, 6H, H-20,20′), 1.73 (d, 3H, J = 3.0 Hz, H-19), 1.71 (d, 3H, J = 2.9 Hz, H-19′), 1.68 (m), 1.51–1.62 (m), 1.47 (m, 1H), 1.42 (s, 1H), 1.32 (m, 1H), 1.22 (m), 1.06–1.18 (m), 1.03 (d, 3H, J = 6.8 Hz, $-CH_3$), 1.01 (d, 3H, J = 6.8 Hz, $-CH_3$), 0.97 (d, 3H, J = 6.7 Hz, $-CH_3$), 0.96 (d, 3H, J = 6.3 Hz, $-CH_3$′), 0.92 (d, 3H, J = 6.7 Hz, $-CH_3$), 0.92 (d, 3H, J = 6.8 Hz, $-CH_3$); IR (neat film): 3398 (br), 2956 (s), 2929 (s), 2871 (s), 1960 (w), 1461 (m), 1384 (m), 1375 (m), 1021 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{34}O$ (M^+) 290.2610, found 290.2609.

Alcohols 37. A solution of lithium aluminum hydride in THF (0.92 M, 3.96 mL, 3.64 mmol, 5.00 equiv) was added slowly to a solution of the ketone **33** (210 mg, 0.728 mmol, 1.00 equiv) in THF (30 mL) at −78 °C, and the resulting solution was stirred for 18 h at −78 °C. The reaction was warmed to 0 °C for 2 h, and water was added cautiously until hydrogen gas evolution had ceased. The reaction was diluted with hexanes (30 mL) and washed with a 1:1 mixture of saturated aqueous potassium carbonate solution and saturated sodium potassium tartrate solution (100 mL). The aqueous layer was separated and extracted with hexanes (30 mL), and the combined organic layers were washed with a 1:1 mixture of saturated aqueous potassium carbonate solution and saturated sodium potassium tartrate solution (2 × 100 mL). The organic layer was dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes) gave an epimeric mixture of alcohols **37** (210 mg, 99%, 2.5:1 ratio stereochemistry not determined) as a viscous oil: R_f 0.36 and 0.29, 10% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (t, 1H, J = 7.1 Hz, H-11′), 5.17 (t, 1H, J = 7.4 Hz, H-11), 5.05 (m, 1H, H-6), 4.98 (m, 1H, H-6′), 3.93 (d, 1H, J = 11.1 Hz, H-2), 3.66–3.71 (m, 2H, H-2', −O*H*), 1.72–2.28 (m, 16H), 1.66 (s, 3H, H-20), 1.65 (s, 3H, H-20′), 1.64 (d, 3H, J = 3.0 Hz, H-19), 1.63 (d, 3H, J = 2.8 Hz, H-19′), 1.55–1.70 (m, 2H), 1.20–1.47 (m, 12H), 1.00 (d, 3H, J = 6.7 Hz, H-18′), 0.94 (d, 3H, J = 6.9 Hz, $-CH_3$), 0.93 (d, 3H, J = 6.6 Hz, $-CH_3$), 0.92 (d, 3H, J = 7.0 Hz, $-CH_3$), 0.83 (d, 3H, J = 6.7 Hz, $-CH_3$′), 0.82 (d, 3H, J = 6.7 Hz, $-CH_3$′), 0.77 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 201.6, 136.9, 135.0, 125.1, 124.1, 99.7, 99.0, 87.9, 86.4, 70.8, 69.8, 50.8, 47.2, 41.9, 40.6, 37.3, 34.2, 34.1, 34.1, 33.4, 30.2, 30.1, 28.7, 27.7, 27.5, 27.4, 26.0, 25.8, 23.6, 23.2, 22.5, 22.3, 21.0, 20.9, 20.8, 19.4, 19.2, 18.9, 17.5; IR (neat film) 3480 (br), 2955 (s), 2929 (s), 2871 (s), 1962 (s), 1462 (m), 1376 (m), 1213 (w), 968 (w), 832 (w) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{34}O$ (M^+) 290.2610, found 290.2617.

Esters 38. 3-(Trifluoromethyl)benzoyl chloride (0.730 mL, 4.81 mmol, 6.21 equiv) and pyridine (0.830 mL, 10.3 mmol, 13.3 equiv) were added to a solution of the alcohols **34** (225 mg, 0.775 mmol, 1.00 equiv, 2.5:1 ratio of epimers) in dichloromethane (25 mL) at 23 °C. After being stirred for 1.5 h, the reaction mixture was partitioned between pentane (25 mL) and saturated aqueous sodium bicarbonate solution (2 × 50 mL). The organic layer was separated and washed sequentially with aqueous hydrochloric acid solution (50 mL) and saturated aqueous sodium bicarbonate solution (50 mL). The organic layer was dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (3% ethyl acetate in hexanes) provided an epimeric mixture of esters **38** (355 mg, 99%, 2.5:1 ratio, stereochemistry not determined) as a viscous oil: R_f 0.44, 5% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 8.62 (s, 1H, H-28), 8.60 (s, 1H, H-28′), 8.22 (d, 1H, J = 7.8 Hz, H-25), 8.15 (d, 1H, J = 7.8 Hz, H-25′), 7.33 (d, 1H, J = 7.3 Hz, H-23), 7.31 (d, 1H, J = 7.8 Hz, H-23′), 6.87 (t, 1H, J = 7.8 Hz, H-24), 6.85 (t, 1H, J = 7.8 Hz, H-24′), 5.82 (t, 1H, J = 7.0 Hz, H-2′), 5.67 (m, 1H, H-2), 5.37 (t, 1H, J = 7.5 Hz, H-11), 5.33 (t, 1H, J = 7.5 Hz, H-11′), 5.20 (m, 2H, H-6,6′), 2.63 (m, 1H), 2.51 (m, 1H), 2.36 (m, 1H), 2.15–2.30 (m), 2.07–2.14 (m), 1.89–2.04 (m), 1.80 (s, 3H, H-20′), 1.75 (d, 3H, J = 2.9 Hz, H-19), 1.74 (s, 3H, H-20), 1.69 (d, 3H, J = 2.9 Hz, H-19′), 1.56–1.70 (m), 1.20–1.30 (m), 1.01 (d, 3H, J = 6.1 Hz, $-CH_3$), 0.98 (d, 3H, J = 6.8 Hz, $-CH_3$), 0.97 (d, 3H, J = 6.5 Hz, C**H**$_3$), 0.92–1.0 (m, 9H, $-CH_3$′); IR (neat film) 2960 (s), 2932 (s), 2875 (s), 1963 (w), 1721 (s), 1617 (w), 1463 (m), 1456 (m), 1442 (m), 1378 (m), 1370 (m), 1256 (s), 1170 (s), 1133 (s), 1086 (s), 1072 (s), 926 (w), 819 (w), 757 (s), 696 (s) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{28}H_{37}O_2F_3$ (M^+) 462.2746, found 462.2739.

Esters 39. 3-(Trifluoromethyl)benzoyl chloride (0.219 mL, 1.45 mmol, 17.6 equiv) and pyridine (0.167 mL, 2.06 mmol, 25.0 equiv) were added to a solution of the alcohols **35** (24.0 mg, 0.0826 mmol, 1.00 equiv, 4:1 ratio of epimers) in dichloromethane (5 mL) at 23 °C. After being stirred for 7 h at 23 °C, the reaction mixture was partitioned between hexanes (20 mL) and saturated aqueous sodium bicarbonate solution (3 × 25 mL). The organic layer was separated, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (2.5% ethyl acetate in hexanes) provided an epimeric mixture of esters **39** (31.2 mg, 82%, 4:1 ratio, stereochemistry not determined) as a viscous oil: R_f 0.52, 5% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6), δ 8.66 (s, 1H, H-28), 8.60 (s, 1H, H-28′), 8.22 (d, 1H, J = 7.8 Hz, H-25), 8.14 (d, 1H, J = 7.8 Hz, H-25′), 7.34 (d, 1H, J = 7.8 Hz, H-23), 7.28 (d, 1H, J = 7.8 Hz, H-23), 6.90 (t, 1H, J = 7.8 Hz, H-24), 6.82 (t, 1H, J = 7.8 Hz, H-24′), 5.90 (d, 1H, J = 12.2 Hz, H-2′), 5.79 (m, 1H, H-2), 5.33 (m, 2H, H-11, 11′), 5.10 (m, 1H, H-6), 4.84 (m, 1H, H-6′), 2.78 (m, 1H), 2.51 (m, 1H), 2.23–

2.39 (m), 1.86−2.22 (m), 1.81 (s, 1H), 1.73 (m, 6H, H-20,20′), 1.71 (d, 3H, J = 3.2 Hz, H-19), 1.68 (m, 3H, J = 3.0 Hz, H-19′), 1.42−1.65 (m), 1.25 (m), 1.13 (d, 3H, J = 6.7 Hz, −CH_3′), 1.08 (d, 3H, J = 6.7 Hz, −CH_3′), 0.94 (m, 12H, −CH_3, C$\mathbf{H}_3$′); IR (neat film): 2959 (s), 2932 (s), 2875 (s), 1963 (w), 1721 (s), 1617 (w), 1463 (m), 1455 (m), 1442 (m), 1334 (s), 1300 (m), 1254 (s), 1170 (s), 1133 (s), 1086 (s), 1072 (s), 925 (m), 819 (w), 756 (s), 696 (s) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{28}H_{37}O_2F_3$ (M^+) 462.2746, found 462.2763.

Esters 40. 3-(Trifluoromethyl)benzoyl chloride (78 μL, 0.52 mmol, 10 equiv) and pyridine (83 μL, 1.0 mmol, 20 equiv) were added to a solution of the alcohols **36** (15.0 mg, 0.0515 mmol, 1.00 equiv, 3:1 ratio of epimers) in dichloromethane (5 mL) at 23 °C. After being stirred for 24 h at 23 °C, the reaction mixture was partitioned between hexanes (20 mL) and saturated aqueous potassium carbonate solution (3 × 25 mL). The organic layer was separated, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (2% ethyl acetate in hexanes) provided an epimeric mixture of the esters **40** (15.6 mg, 65%, 3:1 ratio, stereochemistry not determined) as a viscous oil: R_f 0.03, 100% hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 8.64 (s, 1H, H-28′), 8.59 (s, 1H, H-28), 8.22 (d, 1H, J = 7.9 Hz, H-25′), 8.17 (d, 1H, J = 7.8 Hz, H-25), 7.32 (m, 2H, H-23,-23′), 6.85 (t, 1H, J = 7.8 Hz, H-24), 6.84 (t, 1H, J = 7.8 Hz, H-24′), 5.70 (m, 2H, H-2,2′), 5.35 (t, 1H, J = 6.9 Hz, H-11′), 5.28 (t, 1H, J = 6.8 Hz, H-11), 5.06 (m, 1H, H-6), 5.01 (m, 1H, H-6′), 2.83 (m, 1H), 2.62 (m, 2H), 2.20−2.41 (m), 1.98−2.08 (m), 1.81 (m, 6H, H-20,19′), 1.74 (s, 3H, H-20′), 1.72 (d, 3H, J = 3.0 Hz, H-19), 1.40−1.60 (m), 1.10 (m, 1H), 1.07 (d, 3H, J = 6.4 Hz, −CH_3), 1.04 (d, 3H, J = 6.8 Hz, −CH_3′), 0.97 (m, 12H, −CH_3, −CH_3′); IR (neat film) 2959 (s), 2931 (s), 2875 (s), 1960 (w), 1721 (s), 1617 (w), 1463 (m), 1441 (m), 1370 (m), 1334 (s), 1300 (m), 1256 (s), 1170 (s), 1133 (s), 1086 (s), 1072 (s), 925 (m), 757 (s), 696 (s) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{28}H_{37}O_2F_3$ (M^+) 462.2746, found 462.2757.

Esters 41. 3-(Trifluoromethyl)benzoyl chloride (0.544 mL, 3.61 mmol, 5.00 equiv) and pyridine (0.584 mL, 7.22 mmol, 10.0 equiv) were added to a solution of the alcohols **37** (210 mg, 0.722 mmol, 1.00 equiv, 2.5:1 ratio of epimers) in dichloromethane (10 mL) at 23 °C. After being stirred for 36 h at 23 °C, the reaction mixture was partitioned between hexanes (20 mL) and saturated aqueous sodium bicarbonate solution (3 × 50 mL). The organic layer was separated, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (2% ethyl acetate in hexanes) provided an epimeric mixture of the esters **41** (322 mg, 97%, 2.5:1, stereochemistry not determined) as a viscous oil: R_f 0.42 and 0.31, 5% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 8.62 (s, 1H, H-28′), 8.61 (s, 1H, H-28), 8.21 (d, 1H, J = 7.9 Hz, H-25), 8.18 (d, 1H, J = 7.9 Hz, H-25′), 7.32 (d, 1H, J = 7.8 Hz, H-23), 7.32 (d, 1H, J = 7.8 Hz, H-23′), 6.88 (t, 1H, J = 7.8 Hz, H-24), 6.87 (t, 1H, J = 5.6 Hz, H-24′), 5.95 (d, 1H, J = 12.0 Hz, H-2′), 5.91 (d 1H, J = 11.8 Hz, H-2), 5.41 (m, 2H, H-11,11′), 5.20 (m, 1H, H-6), 5.08 (m, 1H, H-6′), 1.20−2.90 (m, 30H), 1.77 (br s, 3H, H-20), 1.71 (br s, 3H, H-20′), 1.69 (d, 3H, J = 3.0 Hz, H-19), 1.68 (d, 3H, J = 2.9 Hz, H-19′), 1.07 (d, 3H, J = 3.7 Hz, −CH_3), 1.06 (d, 3H, J = 3.6 Hz, −CH_3), 1.03 (d, 3H, J = 6.9 Hz, −CH_3′), 0.92 (d, 3H, J = 6.6 Hz, −CH_3), 0.92 (d, 3H, J = 7.0 Hz, −CH_3′), 0.87 (d, 3H, J = 6.9 Hz, −CH_3′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 201.6, 165.3, 164.9, 136.7, 134.7, 132.7, 131.8, 131.6, 131.2 (q, 2C, $^2J_{C-F}$ = 32.3 Hz), 129.2 (q, 1C, $^4J_{C-F}$ = 1.5 Hz), 129.0, 129.0, 126.7 (q, 2C, $^3J_{C-F}$ = 4.0 Hz), 126.5 (q, 2C, $^3J_{C-F}$ = 3.7 Hz), 125.9, 124.7, 123.7 (q, 2C, $^1J_{C-F}$ = 272.4 Hz), 100.1, 99.5, 88.2, 85.8, 74.5, 74.4, 50.0, 45.7, 40.1, 38.0, 36.8, 34.8, 34.6, 34.3, 32.8, 31.6, 29.9, 28.9, 28.7, 28.7, 27.7, 26.3, 23.6, 23.0, 22.6, 21.8, 21.2, 20.7, 20.3, 19.8, 19.2, 18.5, 17.7, 14.0; IR (neat film) 2959 (s), 2932 (s), 1964 (w), 1721 (s), 1617 (m), 1462 (m), 1443 (m), 1334 (s), 1256 (s), 1170 (s), 1133 (s), 1086 (s), 1072 (s), 921 (m), 819 (m), 756 (s), 695 (s) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{28}H_{37}O_2F_3$ (M^+) 462.2746, found 462.2737.

Epoxides 42 and 43. A vigorously stirred solution of the esters **38** (360 mg, 0.778 mmol, 1.00 equiv), *N*-methylcarbazole (141 mg, 0.778 mmol, 1.00 equiv), and 1,4-cyclohexadiene (1,4-CHD, 7.36 mL, 77.8 mmol, 100 equiv, 0.200 M) in THF−water (350 mL, 10:1 v/v) was deoxygenated by purging the resulting solution with argon for 10 min at 23 °C. The Pyrex reaction vessel was irradiated with a 400 W medium-pressure mercury vapor lamp at 40 °C for 7 h. After being cooled to 23 °C, the reaction mixture was diluted with hexanes (100 mL) and washed with saturated sodium bicarbonate solution (3 × 100 mL). The combined organic layers were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (100% hexanes) provided a mixture of co-eluting alkene products (170 mg). The crude mixture of alkenes (170 mg, 0.620 mmol, 1.00 equiv) was dissolved in dichloromethane (2.5 mL) and the resulting solution was cooled to 0 °C. Sodium bicarbonate powder (270 mg, 3.21 mmol, 3.30 equiv) was added, followed by *m*-chloroperoxybenzoic acid (65%, 500 mg, 1.88 mmol, 3.04 equiv). The reaction was stirred at 0 °C for 2.3 h, after which excess oxidant was quenched by the addition of saturated aqueous sodium thiosulfate solution (10 mL). After being stirred for 40 min at 0 °C, the mixture was diluted with hexanes (10 mL), and the layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate solution (2 × 10 mL), dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (100% toluene) afforded separately the epoxide **42** (13.2 mg, 6% for the two steps) and the epoxide **43** (17.8 mg, 8% for two steps), both as viscous oils. **42**: R_f 0.34, 100% toluene; ^{1}H NMR (500 MHz, C_6D_6) δ 2.72 (d, 1H, J = 8.8 Hz, H-11), 2.56 (m, 1H), 2.36 (m, 1H, H-4), 2.15 (m, 1H), 2.08 (m, 1H), 1.83 (m, 2H, H-10,15), 1.25−1.60 (m, 9H), 1.27 (s, 3H, H-19), 1.15 (m, 1H), 0.95 (m, 2H), 0.94 (d, 3H, J = 6.9 Hz, H-16), 0.88 (d, 3H, J = 6.4 Hz, H-18), 0.82 (s, 3H, H-20), 0.79 (d, 3H, J = 6.8 Hz, H-17); IR (neat film) 2954 (s), 2870 (s), 1461 (m), 1379 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{34}O$ (M^+) 290.2610, found 290.2612. **43**: R_f 0.41, 100% toluene; ^{1}H NMR (500 MHz, C_6D_6) δ 3.24 (t, 1H, J = 2.4 Hz, H-6), 2.35 (d, 1H, J = 8.6 Hz, H-11), 2.12 (m, 3H), 2.03 (m, 1H), 1.89 (m, 1H, H-4), 1.79 (dd, 1H, J = 13.4, 8.4 Hz), 1.70 (m, 2H), 1.53 (m, 1H), 1.40 (m, 2H), 1.22−1.39 (m, 6H), 0.98 (d, 3H, J = 7.4 Hz, H-19), 0.95 (d, 3H, J = 6.8 Hz, H-16), 0.86 (d, 3H, J = 6.7 Hz, H-18), 0.83 (d, 3H, J = 6.7 Hz, H-17), 0.78 (s, 3H, H-20); IR (neat film) 2954 (s), 2870 (s), 1462 (m), 1377 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{34}O$ (M^+) 290.2610, found 290.2610.

Allylic Alcohol 44. A solution of lithium diethylamide in diethyl ether (0.268 M) was prepared immediately prior to use by adding a solution of *n*-butyllithium in hexanes (1.37 M, 5.00 mL, 6.85 mmol) to a solution of diethylamine (0.780 mL, 7.54 mmol) in diethyl ether (20 mL) at 0 °C. The resulting solution was stable for more than 24 h at 0 °C.

A freshly prepared solution of lithium diethylamide in diethyl ether (0.268 M, 10.0 mL, 2.68 mmol, excess) was added to a solution of the epoxide **43** (6.0 mg, 0.021 mmol, 1.0 equiv) in diethyl ether (1.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then warmed to 23 °C and held at that temperature for 15 h. Hexanes (25 mL) was added to the reaction mixture, and the resulting solution was washed sequentially with aqueous hydrochloric acid solution (1.0 N, 25 mL) and saturated aqueous sodium bicarbonate solution (25 mL). The organic layer was dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes) provided the allylic alcohol **44** (3.5 mg, 58%) as a viscous oil. No elimination to the corresponding cyclooctenyl allylic alcohol was observed in the complex mixture of minor products. Alcohol **44**: R_f 0.37, 20% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, C_6D_6) δ 4.82 (s, 1H, H-6), 2.95 (d, 1H, J = 8.3 Hz, H-11), 2.39 (m, 1H, H-3), 2.38 (m, 2H), 1.93 (dd, 1H, J = 14.6, 3.9 Hz), 1.63−1.89 (m, 4H), 1.61 (m, 1H), 1.58 (s, 3H, H-19), 1.52 (m, 1H), 1.30−1.44 (m, 4H), 1.10 (d, 3H, J = 65.7 Hz, −CH_3), 0.95−1.08 (m, 2H), 0.94 (s, 3H, H-20), 0.93 (d, 3H, J = 6.9 Hz, −CH_3), 0.78 (d, 3H, J = 6.8 Hz, −CH_3), 0.58 (s, 1H, −O*H*); IR (neat film) 3394 (br), 2953 (s), 2925 (s), 2869 (s), 1709 (w), 1456 (m), 1385 (m), 1376 (m), 1028 (w), 1009 (w) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{34}O$ (M^+) 290.2610, found 290.2612.

Epoxy Alcohol 45. Sodium bicarbonate powder (24 mg, 0.28 mmol, 5.0 equiv) and *m*-chloroperoxybenzoic acid (65%, 9.6 mg, 0.036 mmol, 3.0 equiv) were added to a solution of the allylic alcohol **44** (3.5 mg, 0.012 mmol, 1.00 equiv) in dichloromethane (12 mL) at −14 °C. After being stirred for 2 h at −14 °C, additional sodium bicarbonate powder (5.0 mg, 0.060 mmol, 5.0 equiv) and *m*-chloroperoxybenzoic acid (65%, 3.0 mg, 0.012 mmol, 1.0 equiv) were added to the reaction mixture, and the resulting solution was stirred for 3.3 h at −14 °C. Excess oxidant was quenched by the addition of saturated aqueous sodium

thiosulfate solution (12 mL) to the reaction, and the biphasic mixture was stirred for 1 h. The organic layer was separated and washed with saturated aqueous sodium bicarbonate solution (2 × 25 mL), dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (5% ethyl acetate in hexanes) afforded the sensitive epoxy alcohol **45** (1.5 mg, 41%) as a crystalline solid: mp 88 °C; R_f 0.45, 20% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 4.77 (td, 1H, J = 10.3, 5.4 Hz, H-6), 2.80 (d, 1H, J = 9.9 Hz, $-OH$), 2.61 (d, 1H, J = 8.5 Hz, H-11), 2.19 (m, 1H, H-4), 1.83−1.97 (m, 2H), 1.77 (dd, 1H, J = 13.0, 8.5 Hz), 1.63−1.71 (m, 3H), 1.62 (s, 3H, H-19), 1.48 (m, 2H), 1.08−1.40 (m, 7H), 0.89 (d, 3H, J = 6.9 Hz, $-CH_3$), 0.86 (d, 3H, J = 6.4 Hz, $-CH_3$), 0.73 (s, 3H, H-20), 0.71 (d, 3H, J = 6.8 Hz, $-CH_3$); IR (neat film) 3506 (br), 2956 (s), 2834 (s), 1458 (m), 1421 (m), 1386 (m), 1379 (m), 1234 (m), 1031 (m), 1010 (m), 748 (m) cm^{-1}.

Epoxy Ketone 46. Dimethyl sulfoxide (0.10 mL, 1.4 mmol, 300 equiv) was added dropwise to a solution of oxalyl chloride (60 μL, 0.69 mmol, 150 equiv) in dichloromethane (3.0 mL) at −78 °C, and the resulting solution was stirred for 10 min at −78 °C. A solution of the epoxy alcohol **45** (1.4 mg, 0.0046 mmol, 1.00 equiv) in dichloromethane (1.5 mL) was added, and the mixture was stirred for 40 min at −78 °C, then for 40 min at −14 °C. The reaction mixture was partitioned between a 1:1 mixture of hexanes and water (10 mL), and the layers were separated. The aqueous layer was extracted with hexanes (10 mL), and the organic phases were combined. The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and dried over sodium sulfate. Concentration and purification of the residue by flash column chromatography (2% ethyl acetate in hexanes) provided the epoxy ketone **46** (1.2 mg, 86%) as a crystalline solid: mp 69 °C; R_f 0.48, 10% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 2.83 (dd, 1H, J = 14.8, 5.0 Hz, H-5), 2.78 (d, 1H, J = 8.1 Hz, H-11), 2.52 (m, 1H, H-4), 2.16 (dd, 1H, J = 14.8, 11.6 Hz, H-5), 1.80 (s, 3H, H-19), 1.64−1.72 (m, 3H), 1.48−1.56 (m, 2H), 1.12−1.43 (m, 8H), 0.87 (d, 3H, J = 6.9 Hz, $-CH_3$), 0.78 (d, 3H, J = 6.8 Hz, $-CH_3$), 0.71 (d, 3H, J = 6.4 Hz, $-CH_3$), 0.69 (s, 3H, H-20); IR (neat film): 3372 (w), 2957 (s), 2929 (s), 2873 (s), 1695 (s), 1456 (m), 1413 (m), 1388 (m), 1379 (m), 1011 (m), 873 (m), 858 (m), 747 (m) cm^{-1}; HRMS (EI) m/z calcd for $C_{20}H_{32}O_2$ (M^+) 304.2402; found 304.2397.

Basmenone 47. An activated silylating reagent was prepared by adding trimethylsilyl chloride (TMSCl, 5.2 mL, 41 mmol) to triethylamine (9.0 mL, 64 mmol); the resulting suspension was stirred for 20 min at 23 °C. Centrifugation produced a homogeneous, colorless supernatant solution. Lithium diisopropylamide (LDA) solution in THF was prepared immediately prior to use by adding a solution of n-butyllithium in hexanes (1.37 M, 1.7 mL, 2.4 mmol) to a solution of diisopropylamine (0.40 mL, 2.9 mmol) in THF (8.0 mL) at −78 °C. The solution (0.238 M) was warmed to 0 °C for 20 min and stored at −78 °C until needed.

The supernatant solution of TMSCl−triethylamine (0.10 mL, 400 equiv) and the solution of LDA in THF (0.10 mL, 33 equiv) were added sequentially to a solution of the epoxy ketone **46** (0.2 mg, 0.7 μmol, 1.00 equiv) in THF (2.0 mL) at −78 °C. The reaction mixture was stirred for 15 min at −78 °C and excess silylating agent was quenched by the addition of a 1:1 (v/v) mixture of triethylamine and methanol (0.25 mL). After being stirred for 15 min at −78 °C, the reaction mixture was partitioned between hexanes (10 mL) and 4% aqueous sodium bicarbonate solution (10 mL). The organic layer was separated, dried over sodium sulfate, and concentrated to give the corresponding labile trimethylsilyl enol ether as a viscous oil. The crude trimethylsilyl enol ether (R_f 0.62, 10% ethyl acetate in hexanes) was immediately dissolved in dichloromethane (1.0 mL), and the resulting solution was cooled to −78 °C. Pyridine (0.10 mL, excess) and phenylselenenyl chloride (20 mg, excess) were added sequentially to the cold reaction solution. The reaction was warmed to 23 °C for 10 min and poured into a 1:1 mixture of hexanes and 4% aqueous sodium bicarbonate solution (10 mL), and the layers were separated. The organic layer was washed with saturated aqueous sodium chloride solution (10 mL) and dried over sodium sulfate. Concentration and purification of the residue by flash column chromatography (2% ethyl acetate in hexanes) provided the α-phenylseleno ketone as a single diastereomer (stereochemistry not determined), R_f 0.42, 10% ethyl acetate in hexanes. Sodium bicarbonate powder (5.0 mg, excess) and m-chloroperoxybenzoic acid (3.0 mg, excess) were added to a solution of the α-phenylseleno ketone in dichloromethane (0.50 mL), and the resulting mixture was stirred for 40 min at −78 °C . Methyl sulfide (0.20 mL, excess) was added to quench any excess oxidant, and the resulting biphasic mixture was stirred for 2.5 h at 23 °C. The reaction was partitioned between hexanes (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The organic layer was separated, dried over sodium sulfate, and concentrated. Purification of the residue by preparative thin-layer chromatography on silica gel (5% ethyl acetate in hexanes) afforded the basmenone **47** (<0.2 mg) as a viscous oil: R_f 0.17, 5% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (s, 1H, H-5), 2.48 (d, 1H, J = 9.3 Hz, H-11), 2.20 (d, 1H, J = 20.2 Hz, H-3), 2.08 (dd, 1H, J = 20.2, 10.0 Hz, H-3), 1.86 (dd, 1H, J = 13.8, 9.3 Hz), 1.83 (s, 3H, H-18), 1.78 (m, 1H), 1.72 (s, 3H, H-19), 1.50−1.70 (m, obscured by residual H_2O), 1.34−1.46 (m, 2H), 1.21−1.30 (m, obscured by residual hydrocarbons), 0.88 (s, 3H, H-20), 0.86 (d, 3H, J = 6.9 Hz, H-16), 0.69 (d, 3H, J = 6.9 Hz, H-17); HRMS (EI) m/z calcd for $C_{20}H_{30}O_2$ (M^+) 302.2246, found 302.2242.

Alkenes 50 and 51. A solution of the esters **41** (90.0 mg, 0.195 mmol, 1.00 equiv), N-methylcarbazole (39.0 mg, 0.215 mmol, 1.10 equiv), and 1,4-cyclohexadiene (1,4-CHD, 1.80 mL, 19.0 mmol, 100 equiv, 0.200 M) in THF−water (99.0 mL, 10:1 v/v) was deoxygenated by bubbling argon through the vigorously stirred solution for 5 min at 23 °C. The reaction solution was irradiated in a Pyrex vessel with a 400 W medium-pressure mercury vapor lamp for 4 h at 55 °C. The reaction was cooled to 23 °C and diluted with hexanes (100 mL), and the resulting mixture was washed with saturated sodium bicarbonate solution (3 × 100 mL). The organic layer was dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (100% hexanes) provided a co-eluting mixture of cyclopentene **50** and epimeric cyclooctenes **51** (26.9 mg, 51%, ~1:1:1 molar ratio) as a viscous oil.

A solution of the mixture of the three alkene products **50** and **51** (~1:1:1 molar ratio, 145 mg, 0.529 mmol, 1.00 equiv, obtained by combining purified products from several prior cyclization reactions of esters **41**), thiophenol (4.0 mL), and 2,2′-azobis(2-methylpropionitrile) (AIBN, 100 mg, 0.609 mmol, 1.15 equiv) in heptane (10 mL) was deoxygenated by three cycles of sequential freezing (liquid nitrogen) and thawing in vacuo (~0.1 Torr). The deoxygenated solution was irradiated in a Pyrex vessel with a 250 W sunlamp beginning at a temperature of 23 °C and steadily warming to 62 °C over a period of 2 h, after which the volatile components of the mixture were removed in vacuo (~0.1 Torr). Purification of the residue by repeated flash column chromatography (2 × 100% hexanes) provided cyclopentene **50** (107 mg, 74%) as a viscous oil, along with a co-eluting mixture of isomeric cyclopentenes (27.5 mg, 19%) which were recycled under identical reaction conditions to give additional **50**. Cyclopentene **50**: R_f 0.66, 100% hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 2.98 (m, 1H, H-11), 2.66 (dd, 1H, J = 14.9, 10.4 Hz, H-6), 2.30 (m, 2H), 1.90 (m, 1H), 1.78 (m, 2H), 1.67 (dd, 3H, J = 2.0, 1.0 Hz, H-19), 1.00−1.70 (m, 12H), 1.02 (d, 3H, J = 6.6 Hz, H-16), 0.96 (d, 3H, J = 6.6 Hz, H-17), 0.96 (d, 3H, J = 6.6 Hz, H-18), 0.83 (s, 3H, H-20); ^{13}C NMR (100 MHz, C_6D_6) δ 1138.8, 131.1, 61.6, 53.8, 51.9, 46.2, 44.4, 39.3, 38.4, 37.1, 36.0, 35.1, 27.6, 25.3, 25.2, 25.1, 22.3, 21.5, 21.0, 14.1; IR (neat film) 2951 (s), 2868 (s), 1453 (m), 1383 (m), 1376 (m), 1366 (m) cm^{-1}; HRMS (EI) m/z calcd for $C_{20}H_{34}$ (M^+) 274.2661, found 274.2661. Inseparable mixture of cyclopentene **50** and epimeric cyclooctenes **51**: R_f 0.66, 100% hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 5.51−6.00 (m), 2.98 (m), 2.53−2.69 (m), 2.40−2.47 (m), 2.24−2.36 (m), 1.20−1.90 (m), 1.67 (dd, J = 2.0, 1.0 Hz, $-CH_3$), 1.16 (d, J = 6.5 Hz, $-CH_3$), 1.09 (d, J = 7.1 Hz, $-CH_3$), 1.07 (bs, $-CH_3$), 1.06 (d, 6.4 Hz, $-CH_3$), 1.03 (d, J = 6.5 Hz, $-CH_3$), 1.03 (d, J = 6.5 Hz, $-CH_3$), 1.02 (d, J = 6.6 Hz, $-CH_3$), 1.00−1.06 (m, $-CH_3$), 0.96 (d, J = 6.6 Hz, $-CH_3$), 0.96 (d, J = 6.6 Hz, $-CH_3$), 0.96 (s, $-CH_3$), 0.95 (d, J = 6.7 Hz, $-CH_3$), 0.94 (d, J = 6.6 Hz, $-CH_3$), 0.83 (s, $-CH_3$); ^{13}C NMR (100 MHz, C_6D_6) δ 152.0, 151.5, 138.9, 131.2, 117.2, 116.9, 61.7, 57.5, 57.2, 54.0, 53.9, 53.1, 52.1, 52.0, 50.1, 46.6, 46.3, 44.5, 44.0, 43.7, 41.1, 40.9, 40.8, 40.6, 39.5, 38.5, 38.0, 37.2, 36.6, 36.3, 36.1, 35.1, 34.1, 33.5, 32.3, 31.8, 31.5, 30.9, 28.1, 27.6, 27.5, 26.2, 25.9, 25.3, 25.3, 25.2, 24.4, 23.6, 23.2, 22.7, 22.6, 22.4, 22.3,

21.6, 21.0, 20.9, 20.2, 19.4, 18.8, 14.0; IR (neat film) 2951 (s), 2868 (s), 1453 (m), 1383 (m), 1376 (m), 1366 (m) cm^{-1}.

Epoxides 52 and 52a. Sodium bicarbonate powder (84.0 mg, 1.00 mmol, 6.00 equiv) and *m*-chloroperoxybenzoic acid (86.4 mg, 0.501 mmol, 3.00 equiv) were added sequentially to a solution of the alkene products **50** and **51** (45.8 mg, 0.167 mmol, 1.00 equiv) in dichloromethane (10 mL) at 0 °C, and the resulting mixture was stirred for 4 h at 0 °C. Excess oxidant was quenched by the addition of saturated aqueous sodium thiosulfate solution (10 mL) and vigorous stirring for 2 h at 0 °C. The reaction mixture was partitioned between hexanes (10 mL) and saturated aqueous sodium bicarbonate solution (50 mL). The organic layer was separated, washed with saturated aqueous sodium bicarbonate solution (50 mL), dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (50% toluene in hexanes) provided samples of the major product epoxides **52** (15.4 mg, 32%) and **52a** (16.2 mg, 34%) as viscous oils containing small amounts of impurities, along with several minor epoxide products (2.1 mg, 4%). Further purification of epoxide **52** by preparative thin-layer chromatography on silica gel (30% toluene in hexanes) afforded pure **52** (5.6 mg) as a crystalline solid (mp 60–62 °C), along with a fraction of **52** still containing trace impurities (6.7 mg). The relative stereochemical configuration of epoxide **52** was established unequivocally by X-ray crystallographic analysis of crystals from ethyl alcohol (see supplementary material). **52**: R_f 0.65, 100% toluene; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.78 (dd, 1H, J = 7.9, 2.6 Hz, H-6), 1.96 (t, 1H, J = 8.4 Hz, H-11), 1.88 (ddd, 1H, J = 14.7, 7.9, 1.7 Hz, H-5), 1.85 (m, 4H, H-2, 10, 13, 14), 1.78 (m, 1H, H-4), 1.64 (m, 1H, H-3), 1.50–1.63 (m, 5H), 1.42 (m, 2H), 1.25 (m, 1H, H-2), 1.22 (m, 1H), 1.18 (s, 3H, H-20), 1.13 (m, 1H), 1.00 (d, 3H, J = 7.1 Hz, $-CH_3$), 1.00 (d, 3H, J = 6.6 Hz, $-CH_3$), 0.94 (d, 3H, J = 7.0 Hz, $-CH_3$), 0.92 (d, 3H, J = 6.6 Hz, $-CH_3$); IR (neat film) 2954 (s), 2870 (s), 1460 (m), 1450 (m), 1374 (m), 1365 (m), 1320 (w), 1075 (w), 935 (w), 914 (w) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{34}O$ (M^+) 290.2610, found 290.2602. **52a**: R_f 0.19, 100% toluene; ^{1}H NMR (500 MHz, C_6D_6) δ 2.49 (d, 1H, J = 8.7 Hz, H-11), 1.80–1.92 (m, 2H), 1.78 (m, 1H), 1.69 (dd, 1H, J = 14.6, 8.8 Hz), 1.48–1.64 (m, 5H), 1.46 (m, 1H), 1.44 (m, 2H, H-4,15), 1.35 (m, 2H), 1.30 (s, 3H, H-19), 1.15–1.22 (m, 4H), 0.99 (d, 3H, J = 6.6 Hz, $-CH_3$), 0.94 (d, 3H, J = 6.3 Hz, $-CH_3$), 0.93 (d, 3H, J = 6.6 Hz, $-CH_3$), 0.69 (s, 3H, H-20); IR (neat film) 2953 (s), 2869 (s), 1459 (s), 1381 (m), 1309 (w), 867 (w) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{34}O$ (M^+) 290.2610, found 290.2596.

Diketone 56. Sodium periodate (234 mg, 1.10 mmol, 5.00 equiv) was added to a biphasic mixture the alkene **50** (56.6 mg, 0.206 mmol, 1.00 equiv) in carbon tetrachloride (5.0 mL), acetonitrile (5.0 mL), and water (7.5 mL) at 23 °C, and the resulting mixture was stirred at 23 °C until all of the periodate had dissolved. Ruthenium dioxide (1.5 mg, 0.011 mmol, 0.050 equiv) was added in one portion, and the reaction was stirred vigorously for 1 h at 23 °C, producing a yellow biphasic reaction mixture. The mixture was diluted with dichloromethane (25 mL), and the layers were separated. The aqueous layer was washed with dichloromethane (10 mL), and the organic layers were combined. The organic layers were dried over sodium sulfate and concentrated. The residue was purified immediately by flash column chromatography (20% ethyl acetate in hexanes) to provide the diketone **56** (43.0 mg, 68%) as a viscous oil: R_f 0.34, 20% ethyl acetate in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97 (dd, 1H, J = 11.5, 2.7 Hz, H-11), 2.38–2.53 (m, 2H), 2.30 (ddd, 1H, J = 14.5, 10.5, 1.6 Hz), 2.16 (1H, ddd, 14.5, 8.0, 1.5 Hz), 2.07 (s, 3H, H-19), 1.92 (m, 1H), 1.55–1.76 (m, 6H), 1.15–1.48 (m, 7H), 0.93 (d, 3H, J = 6.6 Hz, $-CH_3$), 0.92 (d, 3H, J = 6.5 Hz, $-CH_3$), 0.82 (d, 3H, J = 6.5 Hz, $-CH_3$), 0.72 (s, 3H, H20); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.6, 208.9, 59.9, 52.8, 52.6, 46.5, 44.4, 42.6, 42.4, 38.5, 36.4, 34.3, 31.3, 29.8, 26.9, 24.5, 22.5, 22.2, 21.5, 20.4; IR (neat film) 2953 (s), 2870 (s), 1714 (s), 1694 (s), 1462 (s), 1455 (s), 1416 (m), 1384 (s), 1366 (s), 1163 (m), 1115 (m), 872 (w) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{34}O_2$ (M^+) 306.2559, found 306.2560.

Dithiane 57. 1,3-Propanedithiol (0.218 mL, 2.17 mmol, 10.0 equiv) and boron trifluoride etherate (0.020 mL, 0.16 mmol, 0.74 equiv) were added sequentially to a solution of the diketone **56** (66.4 mg, 0.217 mmol, 1.00 equiv) in dichloromethane (10 mL) at 23 °C. After being stirred for 15 min at 23 °C, the reaction solution was diluted with hexanes (10 mL) and washed with 5% aqueous sodium hydroxide solution (3 × 10 mL). The organic layer was dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes) afforded the dithiane **57** (84.1 mg, 98%) as a viscous oil: R_f 0.42, 20% ethyl acetate in hexanes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90 (dd, 1H, J = 9.3, 2.3 Hz, H-11), 2.68–2.87 (m, 6H, H-21,22,23), 2.48 (ddd, 1H, J = 16.1, 8.4, 1.6 Hz, H-6), 2.29 (ddd, 1H, J = 16.1, 10.3, 1.5 Hz, H-6), 1.78–1.98 (m, 6H), 1.18–1.77 (m, 10H), 1.53 (s, 3H, H-19), 0.92 (d, 3H, J = 6.3 Hz, $-CH_3$), 0.88 (d, 3H, J = 6.5 Hz, $-CH_3$), 0.80 (d, J = 6.5 Hz, $-CH_3$), 0.72 (s, 3H, H-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.5, 59.9, 53.7, 52.6, 49.1, 46.7, 44.3, 42.6, 40.0, 38.7, 36.1, 34.3, 31.3, 27.4, 26.8, 26.4, 26.3, 25.1, 24.5, 22.7, 22.6, 22.2, 20.3; IR (neat film) 2952 (s), 2870 (s), 1694 (s), 1455 (m), 1422 (m), 1383 (m), 1369 (m), 1275 (w), 908 (w), 860 (w), 736 (w) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{34}OS_2$ (M^+) 396.2521, found 396.2515.

Enone 58. Benzaldehyde (0.400 mL, 3.94 mmol, 67.8 equiv) and solid sodium hydroxide (10.0 mg, 0.250 mmol, 4.31 equiv) were added to a solution of the ketone **57** (23.0 mg, 0.0580 mmol, 1.00 equiv) in anhydrous ethyl alcohol (3.0 mL) at 23 °C. The reaction was stirred for 40 h at 23 °C in a vessel that was shielded from light to avoid facile photochemical isomerization of the benzylidene double bond to a corresponding mixture of geometric isomers. The reaction was diluted with hexanes (10 mL) and washed with saturated aqueous sodium bicarbonate solution (3 × 10 mL). The organic layer was dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (100% toluene) gave the enone **58** (26.9 mg, 96%) as a viscous oil: R_f 0.48, 20% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 7.83 (s, 1H, H-21), 7.32 (d, 2H, J = 7.4 Hz, H-23,-23′), 7.15 (dd, 2H, J = 7.4, 7.4 Hz, H-24,24′), 7.06 (tt, 1H, J = 7.4, 1.1 Hz, H-25), 3.42 (dd, 1H, J = 11.4, 2.5 Hz, H-11), 2.82 (m, 1H), 2.74 (d, 1H, J = 14.0 Hz), 2.58–2.65 (m, 2H), 2.40–2.54 (m, 3H), 2.04 (dd, 1H, J = 14.0, 11.7 Hz), 1.85–1.95 (m, 2H), 1.78 (s, 3H, H-19), 1.73–1.80 (m, 2H), 1.52–1.62 (m, 4H), 1.40–1.47 (m, 2H), 1.29–1.36 (m, 2H), 1.12–1.23 (m, 2H), 0.98 (d, 3H, J = 6.6 Hz, $-CH_3$), 0.86 (s, 3H, H-20), 0.83 (d, 3H, J = 6.5 Hz, $-CH_3$), 0.82 (d, 3H, J = 6.5 Hz, $-CH_3$); ^{13}C NMR (75 MHz, C_6D_6) δ 203.9, 141.2, 136.8, 136.6, 132.7, 129.9 (2C), 128.8 (2C), 128.4, 61.4, 53.5, 51.7, 49.8, 47.2, 46.9, 40.7, 38.0, 37.9, 35.8, 35.7, 28.1, 27.8, 26.6, 25.5, 25.0, 23.5, 22.6, 22.1, 21.4; IR (neat film) 2953 (s), 2870 (s), 1676 (s), 1597 (s), 1493 (m), 1454 (s), 1421 (m), 1382 (m), 1368 (m), 1274 (m), 1230 (m), 1205 (m), 1170 (m), 1115 (s), 1070 (m), 736 (s), 696 (s) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{30}H_{44}OS_2$ (M^+) 484.2834, found 484.2830.

Trimethylsilyl Enol Ether 59. Triethylamine (0.59 mL, 4.2 mmol, 55 equiv) and trimethylsilyl iodide (0.44 mL, 3.1 mmol, 40 equiv) were added sequentially to a solution of the dithiane **58** (37.2 mg, 0.0767 mmol, 1.00 equiv) in dichloromethane (5.0 mL) at 23 °C. The reaction mixture was deoxygenated by two cycles of sequential freezing and thawing in vacuo (~1 Torr), and the reaction mixture was sealed under vacuum in a pressure reactor and heated to 50 °C behind a protective blast shield. After 13 h at 50 °C, the reaction mixture was cooled to 23 °C, and additional trimethylsilyl iodide (0.12 mL, 0.84 mmol, 11 equiv) was added. The reaction was deoxygenated as above and heated at 50 °C for 24 h. The reaction solution was cooled to 23 °C and diluted with hexanes (10 mL). The reaction mixture was washed with a 1:1 mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution (2 × 50 mL). Concentration of the organic layer gave the trimethylsilyl enol ether **59** (41.0 mg, 96%) as a viscous oil: R_f 0.42, 10% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 7.46 (dd, 2H, J = 7.6, 0.5 Hz, H-23), 7.23 (t, 2H, J = 7.7 Hz, H-24), 7.09 (t, 1H, J = 7.5 Hz, H-25), 6.64 (s, 1H, H-21), 2.87 (dd, 1H, J = 12.4, 5.4 Hz), 2.62–2.81 (m, 3H), 2.59 (m, 6H), 2.30 (td, 1H, J = 12.5, 3.5 Hz), 2.17 (m, 1H, H-4), 2.10 (m, 1H), 1.99 (t, 1H, J = 11.9 Hz), 1.88 (s, 3H, H-19), 1.84 (m, 1H), 1.75 (m, 1H), 1.62 (m, 2H), 1.36 (m, 3H), 1.29 (s, 3H, H-20), 1.20 (d, 1H, J = 13.8 Hz), 1.00 (d, 3H, J = 5.8 Hz, $-CH_3$), 0.94 (d, 3H, J = 6.4 Hz, $-CH_3$), 0.89 (d, 3H, J = 5.9 Hz, $-CH_3$), 0.32 (s, 9H, $-Si(CH_3)_3$); ^{13}C NMR (100 MHz, C_6D_6) δ 149.4, 141.2, 137.6, 131.0, 128.8, 128.5, 127.2, 124.4, 62.7, 54.1, 50.3, 50.1, 47.0, 41.6, 38.0, 37.3, 35.8, 29.8, 28.4, 28.2, 26.8, 26.7, 25.8, 24.8, 24.3, 22.9, 21.5, 1.2; IR (neat film) 2953 (s), 2867 (s), 1626 (w), 1453 (m), 1368 (m), 1250 (s), 1196 (m), 1126

(w), 1099 (m), 1041 (m) , 922 (m), 902 (m), 886 (m), 875 (m), 843 (s), 753 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{33}H_{52}OS_2Si$ (M^+) 556.3229, found 556.3224.

Dithiane 60. Thirty seven percent aqueous hydrochloric acid (0.250 mL) was added dropwise to a vigorously stirred solution of the trimethylsilyl enol ether **59** (42.0 mg, 0.0754 mmol, 1.00 equiv) in methyl alcohol (7.0 mL) at 23 °C. After 3 min at 23 °C, the solution became cloudy, and a white precipitate formed. After 10 min, the reaction was diluted with ethyl acetate (10 mL), and the resulting solution was washed with saturated sodium bicarbonate solution (2 × 50 mL). The aqueous layers were combined and washed with dichloromethane (25 mL). The organic layers were combined, dried over sodium sulfate, and concentrated to give a partially crystalline mixture of **60** and **58** (36.2 mg, 99%, 1.8:1 ratio, respectively). The undesired epimer **58** was removed by trituration with hexanes to provide pure **60** as a crystalline solid: mp 162 °C; R_f 0.25, 10% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 7.59 (s, 1H, H-21), 7.29 (d, 2H, J = 7.7 Hz, H-23), 7.14 (t, 2H, J = 7.6 Hz, H-24), 7.07 (t, 1H, J = 7.0 Hz, H-25), 3.17 (d, 1H, J = 9.8 Hz, H-11), 2.86 (d, 2H, J = 4.2 Hz), 2.48−2.64 (m, 3H), 2.37−2.47 (m, 2H), 2.10−2.23 (m, 2H), 1.99 (t, 1H, J = 10 Hz), 1.80−1.91 (m, 2H), 1.68 (s, 3H, H-19), 1.50−1.62 (m, 5H), 1.38−1.46 (2H), 1.11(m, 2H), 1.08 (s, 3H, H-20), 1.04 (d, 1H, J = 12 Hz), 0.90 (d, 3H, J = 6.4 Hz, $-CH_3$), 0.85 (d, 3H, J = 6.4 Hz, $-CH_3$), 0.78 (d, 3H, J = 6.8 Hz, $-CH_3$); ^{13}C NMR (100 MHz, C_6D_6) δ 209.1, 143.6, 137.0, 134.6, 129.5, 128.6, 127.8, 58.8, 56.3, 54.4, 50.3, 49.6, 43.3, 40.6, 35.0, 34.4, 33.2, 31.1, 29.8, 28.0, 27.2, 26.7, 26.7, 26.6, 25.5, 22.6, 22.4, 20.8; IR (neat film) 2953 (s), 2870 (s), 1687 (s), 1683 (s), 1615 (m), 1463 (s), 1446 (s), 1383 (m) 1367 (m), 1275 (w), 1168 (m), 1072 (m), 739 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{30}H_{44}OS_2$ (M^+) 484.2834, found 484.2848.

Diketone 61. Methyl iodide (3.0 mL, excess) was added to a solution of the dithiane **60** (19.0 mg, 0.0392 mmol, 1.00 equiv) in acetonitrile (6.0 mL) and water (1.5 mL), and the resulting biphasic mixture was stirred at 23 °C for 17 h. Diethyl ether (10 mL) was added, and the resulting mixture was washed with a 1:1 mixture of saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution (2 × 50 mL). The organic layer was dried over sodium sulfate and concentrated to provide the clean diketone **61** (14.9 mg, 96%) as a crystalline solid: mp 99 °C; R_f 0.37, 20% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 7.54 (s, 1H, H-21), 7.31 (d, 2H, J = 7.4 Hz, H-23), 7.16 (t, 2H, J = 7.6 Hz, H-24), 7.08 (t, 1H, J = 7.4 Hz, H-25), 3.23 (dd, 1H, J = 11.6, 2.2 Hz, H-11), 2.83 (d, 2H, J = 4.3 Hz), 2.20−2.27 (m, 1H), 1.97−2.17 (m, 4H), 1.81 (m, 1H, H-4), 1.66 (s, 3H, H-19), 1.37−1.62 (m, 5H), 1.12 (m, 2H), 1.09 (s, 3H, H-20), 1.03 (dd, 1H, J = 16.1, 3.8 Hz), 0.89 (d, 3H, J = 6.6 Hz, $-CH_3$), 0.85 (d, 3H, J = 6.6 Hz, $-CH_3$), 0.74 (d, 3H, J = 6.9 Hz, $-CH_3$); ^{13}C NMR (100 MHz, C_6D_6) δ 208.8, 206.1, 143.5, 136.9, 134.5, 129.4, 128.6, 127.9, 58.7, 54.5, 54.4, 50.1, 43.2, 41.4, 34.9, 34.2, 33.0, 31.1, 29.7, 29.3, 27.2, 25.1, 22.7, 22.4, 20.7; IR (neat film) 2955 (s), 2871 (s), 1715 (s), 1681 (s), 1615 (m), 1462 (m), 1365 (m), 1159 (m), 1073 (m), 699 (m) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{27}H_{38}O_2$ (M^+) 394.2872, found 394.2869.

Diene 62. 1,2-Dimethoxyethane (DME, 4.0 mL) was added to a mixture of zinc−copper couple (196 mg, excess) and $TiCl_3$·$(DME)_{1.5}$ (208 mg, excess) in a schlenk-type flask under argon. The resulting mixture was heated at reflux for 1.5 h, whereupon a solution of the diketone **61** (14.9 mg, 0.0378 mmol, 1.00 equiv) in DME (1.50 mL) was added to the reaction mixture. The resulting mixture was heated at reflux for 3.5 h. The reaction mixture was cooled to 23 °C, hexanes (6.0 mL) was added, and the resulting slurry was filtered through a short column of silica gel. The filtrate was concentrated, and the residue was purified by flash column chromatography (100% hexanes), providing the diene **62** (10.0 mg, 73%) as a viscous oil: R_f 0.70, 20% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 7.34 (d, 2H, J = 7.6 Hz, H-23), 7.25 (t, 2H, J = 7.6 Hz, H-24), 7.10 (t, 1H, J = 7.6 Hz, H-25), 6.33 (s, 1H, H-21), 3.17 (m, 1H), 2.65 (dt, 1H, J = 15.2, 2.0 Hz), 2.42 (dd, 1H, J = 15.2, 11.0 Hz), 2.11−2.26 (m, 3H), 2.03 (m, 1H), 1.90 (m, 1H), 1.81 (s, 3H, H-19), 1.49−1.77 (m, 7H), 1.41 (m, 1H), 1.27 (m, 1H), 1.23 (s, 3H, H-20), 0.93 (d, 3H, J = 6.6 Hz, $-CH_3$), 0.85 (d, 3H, J = 6.7 Hz, $-CH_3$), 0.81 (d, 3H, J = 6.7 Hz, $-CH_3$); IR (neat film) 3056 (w), 3021 (w), 2952 (s), 2867 (s), 2834 (s), 1940 (w), 1598 (w), 1574 (m), 1493 (m), 1453 (s), 1445 (s), 1384 (s), 1375 (s), 1367 (s), 1154 (w), 1073 (w), 1030 (w), 914 (w), 863 (w), 756 (s), 697 (s) cm^{-1}; HRMS (EI) *m/z* calcd for $C_{27}H_{38}$ (M^+) 362.2974, found 362.2957.

Allylic Epoxide 63. Sodium bicarbonate powder (42 mg, 0.50 mmol, 20 equiv) and *m*-chloroperoxybenzoic acid (85%, 22 mg, 0.13 mmol, 5.0 equiv) were added sequentially to a solution of the diene **62** (9.0 mg, 0.025 mmol, 1.0 equiv) in dichloromethane (5.0 mL) at −14 °C. After the mixture was stirred for 1.5 h at −14 °C, excess oxidant was quenched by the addition of saturated aqueous sodium thiosulfate solution (10 mL) at 0 °C. After being stirred for 1 h at 0 °C, the reaction mixture was diluted with hexanes (10 mL), and the layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate solution (2 × 15 mL) and dried over sodium sulfate. Concentration of the organic layer afforded the sensitive allylic epoxide **63** (9.0 mg, 96%) as a viscous oil: R_f 0.23, 5% ethyl acetate in hexanes. The epoxide **63** was found to undergo facile spontaneous elimination to the corresponding allylic alcohol, so only limited ^{1}H NMR analysis was possible: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22−7.40 (m, 5H, H-23, 24, 25), 5.83 (s, 1H, H-21), 3.13 (t, 1H, J = 9.0 Hz), 2.18 (m, 1H), 1.67−1.95 (m, 6H), 1.54−1.62 (m, 2H), 1.44−1.51 (m, 3H), 1.43 (s, 3H, H-19), 1.20−1.29 (m, 2H), 0.96−1.04 (m, 2H), 0.95 (d, 3H, J = 6.6 Hz, $-CH_3$), 0.87 (s, 3H, H-20), 0.86 (d, 3H, J = 6.6 Hz, $-CH_3$), 0.81 (d, 3H, J = 6.6 Hz, $-CH_3$).

Epoxy Ketone 64. *m*-Chloroperoxybenzoic acid (18.7 mg, 0.12 mmol, 4.25 equiv) was added to a mixture of the diene **62** (9.0 mg, 0.025 mmol, 1.0 equiv) and sodium bicarbonate powder (42 mg, 0.50 mmol, 20 equiv) in dichloromethane (5.0 mL) at −14 °C. After the mixture was stirred for 1.5 h at −14 °C, saturated aqueous sodium thiosulfate solution (5.0 mL) was added to quench excess oxidant, and the resulting biphasic mixture was stirred for 1 h at 0 °C. Hexanes (10 mL) was added to the reaction mixture, and the layers were separated. The organic phase was washed with saturated sodium bicarbonate solution (2 × 10 mL), dried over sodium sulfate, and concentrated. The crude allylic epoxide (9.0 mg, 0.024 mmol, 1.0 equiv) was immediately dissolved in a biphasic mixture of carbon tetrachloride (2.0 mL), acetonitrile (2.0 mL), and water (3.0 mL). Sodium periodate (51 mg, 0.24 mmol, 10 equiv) was added to the epoxide solution and allowed to dissolve completely. Ruthenium dioxide (0.50 mg, 0.0038 mmol, 0.16 equiv) was added, and the resulting biphasic mixture was stirred vigorously for 15 min at 23 °C, producing a yellow biphasic mixture. The reaction was diluted with dichloromethane (10 mL) and the dark green organic layer was separated. The aqueous layer was washed with dichloromethane (10 mL), and the combined organic layers were dried over sodium sulfate and concentrated. Immediate purification by flash column chromatography (10% ethyl acetate in hexanes) afforded the epoxy ketone **64** (6.7 mg, 89% for two steps) as a viscous oil: R_f 0.21, 10% ethyl acetate in hexanes; ^{1}H NMR (500 MHz, C_6D_6) δ 2.79 (dd, 1H, J = 14.8, 4.7 Hz, H-5), 2.76 (dd, 1H, J = 9.1, 4.6 Hz, H-11), 2.42 (m, 1H, H-4), 2.11 (dd, 1H, J = 14.8, 9.4 Hz, H-5), 1.50−1.78 (m, 9H), 1.48 (s, 3H, H-19), 1.43 (m, 1H), 1.34 (m, 1H), 1.19 (m, 1H), 1.13 (m, 1H), 0.93 (d, 3H, J = 6.5 Hz, $-CH_3$), 0.93 (s, 3H, H-20), 0.78 (d, 3H, J = 6.6 Hz, $-CH_3$), 0.74 (d, 3H, J = 6.6 Hz, $-CH_3$); IR (neat film) 2956 (s), 2871 (s), 1704 (s), 1456 (s), 1383 (m), 1329 (m), 1272 (w), 1258 (w), 1215 (w), 1072 (w) cm^{-1}; HRMS (FAB, 3-NBA Matrix) *m/z* calcd for $C_{20}H_{33}O_2$ (MH^+) 305.2481, found 305.2487.

Synthetic (±)-7,8-Epoxy-4-basmen-6-one (±1). A solution of lithium diisopropylamide (LDA) in THF was prepared immediately prior to use by adding a solution of *n*-butyllithium in hexanes (2.51 M, 0.960 mL, 2.41 mmol) to a solution of diisopropylamine (0.400 mL, 2.85 mmol) in THF (8.50 mL) at −78 °C. The solution (0.240 M) was warmed to 0 °C for 10 min and stored at −78 °C.

The freshly prepared LDA solution in THF (0.70 mL, 0.17 mmol, 6.5 equiv) was added to a solution of the epoxy ketone **64** (8.0 mg, 0.026 mmol, 1.0 equiv) in THF (2.5 mL) at 0 °C. The reaction was stirred for 8 min at 0 °C, and phenylselenenyl chloride (70 mg, 0.37 mmol, 14 equiv) was added in one portion. After being stirred for 10 min at 0 °C, the reaction mixture was partitioned between hexanes (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The organic layer was separated, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography provided the corresponding sensitive α-phenylseleno ketone, which was

immediately dissolved in dichloromethane (8.0 mL) buffered with pyridine (0.20 mL, 2.5 mmol, 94 equiv) at 23 °C. Thirty percent aqueous hydrogen peroxide solution (2.0 mL) was added to the α-phenylselenoketone solution at 23 °C. After being stirred vigorously for 30 min at 23 °C, the reaction mixture was diluted with hexanes (25 mL) and washed with water (3 × 25 mL). The organic layer was dried over sodium sulfate and concentrated. Flash column chromatography of the residue (25% ethyl acetate in hexanes) provided pure (±)-**1** (5.9 mg, 75%) as a crystalline solid: mp 122 °C. The stereochemical configuration of (±)-**1** was established unequivocally by X-ray crystallographic analysis of crystals from hexanes (see supplementary material). Synthetic (±)-**1**: R_f 0.40, 40% ethyl acetate in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (br s, 1H, H-5), 2.68 (t, 1H, J = 12.5 Hz, H-2), 2.61 (m, 1H, H-11), 2.00−2.12 (m, 2H), 1.99 (d, 3H, J = 1.0 Hz, H-18), 1.88−1.97 (m, 3H), 1.68−1.75 (m, 2H), 1.52−1.62 (m, 2H), 1.31−1.49 (m, 3H), 1.30 (s, 3H, H-19), 1.16 (s, 3H, H-20), 0.96 (d, 3H, J = 6.7 Hz, H-16), 0.81 (d, 3H, J = 6.7 Hz, H-17); ^{13}C NMR/DEPT (75 MHz, $CDCl_3$) δ 195.08 (C), 157.36 (C), 129.89 (CH), 74.46 (2C), 54.68 (CH), 53.35 (CH), 47.56 (C), 47.27 (CH), 41.65 (CH_2), 34.35 (CH_3), 33.69 (CH_2), 32.46 (CH_2), 27.52 (CH), 27.52 (CH_3), 27.25 (CH_2), 22.54 (CH_3), 22.35 (CH_2), 15.82 (CH_3), 14.98 (CH_3); IR (neat film) 2955 (s), 2875 (s), 1651 (s), 1462 (m), 1436 (m), 1385 (m), 1375 (m), 1276 (m), 1180 (w), 1141 (w), 1070 (w), 1008 (m), 924 (w), 892 (w), 868 (w), 660 (w) cm^{-1}; HRMS (FAB, 3-NBA Matrix) m/z calcd for $C_{20}H_{33}O_2$ (MH^+) 303.2324, found 303.2334.

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Supplementary Material Available: Thermal ellipsoid plots with experimental procedures and crystal structure data for compounds analyzed by X-ray crystallography (51 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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