Enantioselective Double Michael Addition/Cyclization with an Oxygen-Centered Nucleophile as the First Step in a Concise Synthesis of Natural (+)-Asteriscanolide

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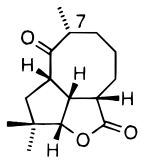
Abstract: The total synthesis of (+)-asteriscanolide (**1**) starting from 2-bromo-4,4-dimethylcyclopentenone has been accomplished. The synthetic route features two key steps. The first step is an unprecedented Michael−Michael reaction sequence that involves a heteronucleophile and proceeds with complete asymmetric induction. The two five-membered rings of the target molecule are thereby generated enantioselectively in a single laboratory step. The second step is based on utilization of ring-closing metathesis to provide an eight-membered ring in which a conjugated 1,3-diene unit resides. Other features of the synthetic stratagem involve the utilization of singlet oxygen in a regiocontrolled ene reaction, the fully stereocontrolled hydrogenation of a dienone, and a chemoselective ruthenium tetraoxide oxidation.

(+)-Asteriscanolide (**1**) has captured the attention of the organic chemical community since San Feliciano et al. first reported its isolation from *Asteriscus aquaticus* L and structure determination in 1985.[1] The attraction offered by **1** is chiefly structural. Its sesquiterpenoid framework consists of a rather



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uncommon bicyclo[6.3.0]undecane ring system bridged by a butyrolactone fragment. The challenge offered by the construction of its cyclooctanoid core[2] has been approached from several directions. The only prior enantioselective synthesis of **1** has been described by the Wender group, their stratagem featuring the deployment of a Ni(0)-promoted [4 + 4] cycloaddition in the pivotal step.[3] The route utilized by Booker-Milburn and coworkers to produce the 7-desmethyl derivative involved the sequential application of intramolecular [2 + 2] photocycloaddition, Curtius rearrangement, and oxidative fragmentation steps on arrival at the cyclooctane lactone stage.[4] Several other innovative strategies have been less rewarding.[5−10]

Despite the entropic and enthalpic factors that impede the preparation of eight-membered rings,[11] the issue of the feasible application of ring-closing metathesis (RCM)[12] in the construction of asteriscanolide attracted our attention. In recent years, it has become increasingly apparent that polar functional groups such as ethers,[13] amides,[14] urethanes,[15] sulfonamides,[16] and esters[17] greatly facilitate the assembly of cyclooctyl derivatives. This phenomenon has been interpreted by Fürstner and coworkers to be a function of the relay properties of these heteroatoms "which help to assemble the reacting sites within the coordination sphere of the metal and thus confer bias to cyclization over competing intermolecular metathesis events".[18] In the absence of these internal ligands, the formation of eight-membered rings via metathesis has been documented much less frequently.[19]

Nonetheless, we looked forward to the successful involvement of RCM as a key element of our synthetic protocol because of the pronounced restriction in the degrees of conformational freedom available to the projected triene precursor (Scheme 1). Beyond this, the issue of involving a conjugated diene in an RCM reaction was unprecedented when this work was originated and held specific interest.[20] We hoped that in this way we could also evaluate the possibility of deriving the three stereogenic centers resident therein in their proper absolute configuration

(1) San Feliciano, A.; Barrero, A. F.; Medarde, M.; Miguel del Corral, J. M.; Aramburu, A.; Perales, A.; Fayos, J. *Tetrahedron Lett.* **1985**, *26*, 2369.

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(4) Booker-Milburn, K. I.; Cowell, J. K.; Harris, L. J. *Tetrahedron* **1997**, *53*, 12319.

(5) Mehta, G.; Murty, A. N. *J. Org. Chem.* **1990**, *55*, 3568.

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(9) Cheung, Y. Y.; Krafft, M. E.; Juliano-Capucao, C. A. *Book of Abstracts*, 216th ACS National Meeting, Boston, August 23−27, 1998; American Chemical Soceity: Washington, DC, 1998; ORGN-238.

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(11) Table 2 in the 1998 review by S. K. Armstrong [*J. Chem. Soc., Perkin Trans. 1* **1998**, 371] dramatically points to the dearth of eight-membered ring examples as of that date.

(12) For recent reviews, consult: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833. (c) Fürstner, A. *Topics Catal.* **1997**, *4*, 285. (d) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037. (e) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792. (f) Philips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999,** *32*, 75. (g) Pariya, C.; Jayaprakash, K. N.; Sarkar, A. *Coord. Chem. Rev.* **1998**, *168*, 1. (h) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A: Chem.* **1998**, *133*, 29. (i) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (j) Ivin, K. J. *J. Mol. Catal. A: Chem.* **1998**, *133*, 1. (k) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211.

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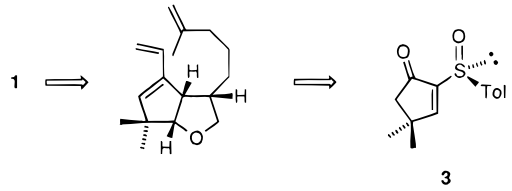
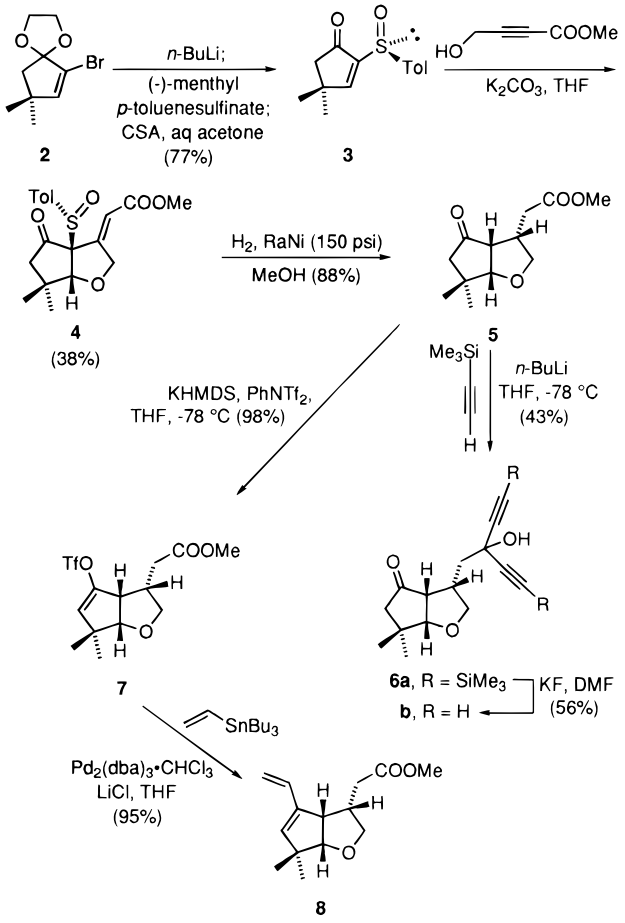
Scheme 1



by chirality transfer from the enantiodefined sulfoxide substituent in cyclopentenone **3**. The success of this tactic was dependent on the operation of a highly enantioselective Michael addition to **3** by an oxygen-centered heteronucleophile. Although the Posner vinyl sulfoxide system has been scrutinized in detail for its ability to capture carbanions and organometallic reagents enantioselectively,[21] the literature describes no comparable evaluation of the magnitude and direction of possible stereoinduction attainable during the conjugate addition of alcohols to such acceptors.[22] This facet of the problem added significantly to the general interest in the total synthesis goal that otherwise held promise to deliver **1** in concise fashion. In this paper, we document the successful realization of a short route that gives rise to the natural dextrorotatory enantiomer of asteriscanolide.

Scheme 2



Results and Discussion

Our synthesis was initiated as projected with ketalization of the known 2-bromo-4,4-dimethylcyclopentenone.[23] Although all attempts to accomplish the preparation of **2** by stirring in ethylene glycol and a catalytic quantity of *p*-toluenesulfonic acid in dichloromethane at room temperature as recommended by Ladlow and Pattenden[24] were uniformly unsuccessful, recourse to more forcing conditions[25] provided **2** in 77% yield. Arrival at **3** was modeled after the earlier work of Posner et al. involving the parent cyclopentenone[26] and involved halogen−metal exchange with subsequent condensation of the vinyllithium reagent with (*S*)-(−)-menthyl *p*-toluenesulfinate[27,28] (Scheme 2).

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(20) More recently, the right-hand sector of sanglifehrin, which contains a 22-membered ring, was elaborated by RCM of a precursor that featured a diene moiety: Cabrejas, L. M. M.; Rohrbach, S.; Wagner, D.; Kallen, J.; Zenke, G.; Wagner, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2443.

(21) Posner, G. H. In *Asymmetric Synthesis, Volume 2*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Chapter 8.

(22) In addition, a single report on the involvement of amines as heteronucleophiles in these processes has appeared: Matsuyama, H.; Itoh, N.; Yoshida, M.; Kamigata, N.; Sasaki, S.; Iyoda, M. *Chem Lett.* **1997**, 375. In this study, 2-(*p*-tolylsulfinyl)cinnamates served as the Michael acceptors.

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(25) Smith, A. B., III; Branca, S. J.; Guaciaro, M. A.; Wovkulich, P. M.; Korn, A. *Organic Syntheses*; Wiley: New York, 1990; Collect Vol. VII, p 271.

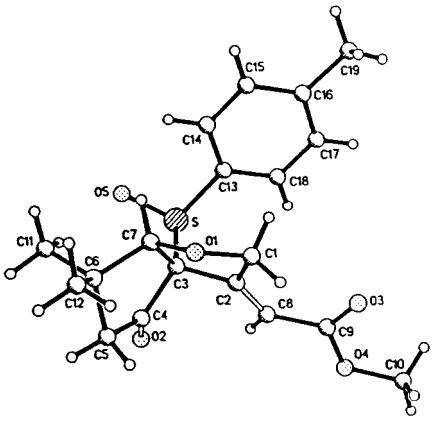
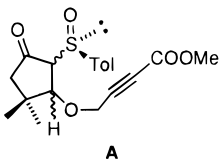


Figure 1. Computer-generated perspective model of the final X-ray model of **4**.

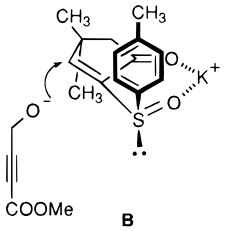
Considerable experimentation was devoted to investigating the way in which the Michael reaction of methyl 4-hydroxy-2-butynoate[29] with **3** could be exploited such that a second-stage conjugate addition would follow and give rise directly to the bicyclic ester **4**.[30] Initially, attention was directed to the use of DBN and DBU over a wide range of temperatures, with and without the co-addition of potential Lewis acid promoters such as $La(OTf)_3$, $Ti(O\textit{i}\text{-}Pr)_4$, $CeCl_3$, and $LiBF_4$. Several general conclusions emerged. Temperatures above −40 °C resulted in the onset of rapid and uncontrolled reactions, as shown also in the presence of larger amounts of base. In general, Lewis acid catalysts did not help matters to any measurable extent, with one exception. In an experiment involving the use of 3 equiv of lithium tetrafluoroborate in acetonitrile containing 0.03 equiv of DBU (−40 °C, 7 h), monoadduct **A** was formed efficiently as a mixture of diastereomers. Proper conditions for bringing about the further cyclization of **A** were not uncovered.



A

In the event, the desired conversion to **4** was found to occur when the reaction was promoted with potassium carbonate in THF at room temperature.[31] The major product, isolated in 38% yield, was shown to be the required **4** on the basis of an X-ray crystallographic analysis (Figure 1). Our prior knowledge of the *S* configuration at sulfur in **3** makes possible the assignment of absolute configuration to **4** as shown in the illustrated formula.

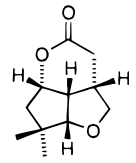
With the configurational assignments secure, it is evident that the butynoate adds to **3** from the *a*-surface with asymmetric induction, paralleling closely the outcome of organometallic conjugate additions to (*S*)-(+)-2-(*p*-toluenesulfinyl)-2-cyclopentenone.[26,32] These events can be concisely rationalized in terms of a chelate model such as **B**, although other rotamers may play an equally influential role in the stereodirective outcome. The significant issues here are twofold: (a) the



B

Michael addition of a heteroatom-centered nucleophile is seemingly subject to forces not dissimilar to those involving carbon, and (b) the initial product of 1,4-conjugate addition is capable of intramolecular addition to the triple bond. The overall consequence is the one-step fully controlled conversion of **3** to **4**, the tandem process offsetting to a reasonable degree the modest yield realized for this pivotal transformation.

Now that the chiral sulfoxide auxiliary had served its intended purpose, we sought to address the issue of the reductive desulfurization of **4**. Our expectation that hydrogenation of **4** in the presence of Raney nickel would result in carbon−sulfur bond cleavage concomitant with saturation of the olefinic linkage was readily reduced to practice. Evidence that the newly generated stereogenic centers in **5** were properly installed was gained simply by encouraging overreduction to occur. An increase in hydrogen pressure to 1000 psi was sufficient to reduce the ketone carbonyl as well. This step was followed by in situ intramolecular cyclization to give lactone **9** (65% yield), an event that could not materialize had a different diastereomer been initially produced.



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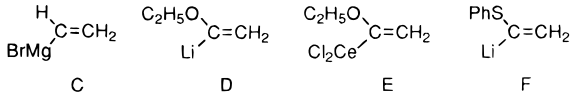
Before embarking on the metathesis phase of the synthesis, it seemed appropriate to investigate the regioselectivity of nucleophilic additions to **5**. Quite unexpectedly, exposure of **5** to the organometallic reagents exemplified by **C**−**F** gave no evidence of adduct formation. The keto ester was invariably



C **D** **E** **F**

recovered unscathed. When the inspection of molecular models gave no suggestion of overwhelming steric hindrance to attack at the ketone carbonyl, suspicion arose that **5** was especially prone to enolization. Considerable credence was lent to this hypothesis when it was discovered that recourse to an excess of the "slimmer" lithium trimethylsilylacetylide reagent gave **6a**, the result of twofold addition to the ester carbonyl. This ester functionality, which is sterically shielded, was nevertheless attacked to the exclusion of the ketone when the size of the nucleophile was reduced to a suitable level.

(26) Earl, R. A.; Townsend, L. B. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 334.

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(28) Hulce, M.; Mallamo, J. P.; Frye, L. L.; Kogan, T. P.; Posner, G. H. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 495.

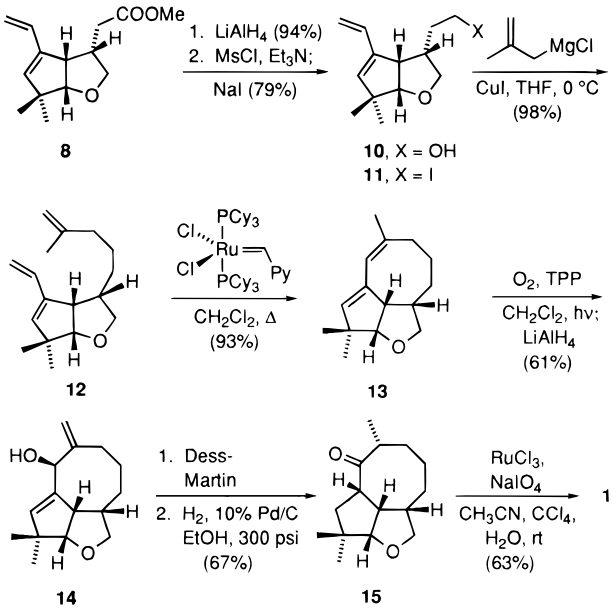
(29) Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173.

(30) Nitro olefins and particularly 1-nitrocyclohexene have been shown to be particularly conducive to this type of double Michael addition/cyclization: Yakura, T.; Yamada, S.; Shima, M.; Iwamoto, M.; Ikeda, M. *Chem. Pharm. Bull.* **1998**, *46*, 744.

(31) The use of potassium carbonate in refluxing THF has been shown to be effective in bringing about the condensation of acyloins with dimethyl acetylenedicarboxylate to give 4-hydroxy-4,5-dihydrofurans: Jauch, J.; Schurig, V. *Tetrahedron Lett.* **1991**, *32*, 4687.

(32) Posner, G. G.; Mellamo, J. P.; Miura, K. *J. Am. Chem. Soc.* **1981**, *103*, 2886.

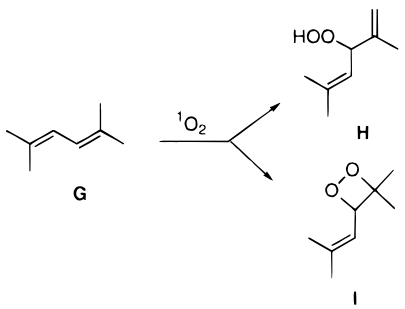
Scheme 3



This property of **5** played nicely into our hands. Thus, the generation of enol triflate **7** was straightforwardly accomplished in near-quantitative yield.[33] The use of **7** as the coupling partner for tributylvinylstannane in a Stille coupling[34] proceeded smoothly to deliver diene **8** very efficiently. This important compound was reduced to the primary carbinol **10** and subsequently transformed into iodide **11** by deployment of conventional methods (Scheme 3). Copper-catalyzed substitution[35] of iodide by methallylmagnesium chloride proceeded with the anticipated level of regioselectivity and without any visible degradation to provide **12** (98%).

As previously indicated, the time had now come to involve **12** in a ring-closing metathesis reaction. Our reservations with regard to the efficiency of this cyclization were quickly dismissed when the generation of **13** was seen to proceed in 93% yield. Evidently, the limited conformational flexing available to the side chains in **12** serves to facilitate their conjoining via a ruthenium carbenoid.

With this critical step accomplished, the next consideration was to achieve suitable oxygenation of the double bond internal and not external to the eight-membered ring. When preliminary studies involving epoxidation and hydroboration options were found not to conform to our goals, we turned to singlet oxygen as the potential reagent of choice.[36] The decision was made to take a lead from Hasty and Kearns's careful investigation of the photooxygenation of 2,5-dimethyl-2,4-hexadiene (**G**).[37]



These workers demonstrated the ene reaction of **G** to be strongly dependent on solvent. In aqueous methanol, the conversion to dioxetane **I** is very much favored (**I**:**H** = 5.5). A change in solvent to dichloromethane (**I**:**H** = 0.1) or to acetonitrile (**I**:**H** = 0.01) alters the ratio toward hydroperoxide **H** by a factor larger than 500. On this basis, we elected to explore the photooxygenation of **13** in CH_2Cl_2 solution containing 5,10,-15,20-tetraphenyl-21*H*,23*H*-porphine (TPP) as sensitizer. In this way, we were able to reach a hydroperoxide, direct hydride reduction of which gave rise to sensitive diallylic carbinol **14** in 61% overall yield. Detailed spectroscopic analysis established that the major product of this reaction occurred with conversion of the original methyl substituent into an exocyclic methylene group. The hydroxyl functionality in **14** was assigned the *b* configuration in order to conform to the substantial spatial demands of the singlet oxygen ene transition state[36] and assumed preferred approach of the reagent to the less congested convex surface of the diene segment. Since oxidation to the ketone level is next to be implemented, only minor importance is associated with this deduction.

As the projected route continued, we made recourse to the Dess−Martin periodinane[38] for generation of the dienone in preparation for exhaustive hydrogenation. Here it is critical that saturation of the pair of double bonds proceed from the exterior surface of the semispherical compound, for proper introduction of the final two stereogenic centers is dependent on this differentiation. The decision to proceed in this direction was rewarded by the isolation of a single tetrahdyro ketone. That this penultimate intermediate was, indeed, **15** was confirmed by its regioselective oxidation to crystalline (+)-**1** with ruthenium tetraoxide.[39] The spectral data of the fully synthetic keto lactone were identical to those reported by San Feliciano et al. for authentic **1**. In addition, the $[\alpha]^{22}_D$ of our material is +8.5 (*c* 0.019, $CHCl_3$), a value closely comparable to the +12.1 originally registered.[1]

Summary

The chemistry detailed herein defines a concise 13-step strategy for the synthesis of (+)-asteriscanolide (**1**). In the recapitulation of this venture, it is important to emphasize that the convergent merging of the readily available enantiopure cyclopentenone sulfoxide **3** and methyl 4-hydroxy-2-butynoate proved to be especially profitable in that it resulted in a series of highly enantioselective bonding events. The capture by a cyclic Michael acceptor such as **3** of a heteronucleophile has not been previously described. In the present setting, the first-stage Michael addition proceeds with a strong kinetic bias for α-attack as a direct consequence of precoordination. The stereochemical course of the second conjugate addition is inextricably linked to that manifested during prior C−O bond formation, thereby ultimately providing a substrate properly configured and functionalized for eventual arrival at the target. Use of the Stille coupling protocol constituted a productive step in paving the way for critical adaptation of ring-closing metathesis. A key finding was that a conjugated diene typified by **13** can be produced in this manner with exceptional efficiency.

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The tricyclic conjugated diene **13** served in turn as a reliable platform for directing the regioselectivity of the singlet oxygen ene process and the stereoselectivity of the subsequent catalytic hydrogenation. The remarkable success of this sequence of reactions was matched in the final RuO_4 oxidation that established the butyrolactone ring.

A particularly rewarding aspect of this undertaking was *the ability to start with **3** and to install all of the requisite stereochemistry inherent to asteriscanolide without recourse to resolution*. In this study, the feasibility of generating dienes by RCM has been demonstrated, and an original means was developed for assembly of the unusual framework of the target structure. We anticipate that the present route will prove adaptable to diversely functionalized intermediates and lend itself to the rational synthesis of other structurally complex medium-ring natural products.

Experimental Section

General Information. Tetrahyrofuran and ether were distilled from sodium benzophenone ketyl under nitrogen just prior to use. For dichloromethane and dimethyl sulfoxide, the drying agent was calcium hydride. All reactions were performed under a nitrogen atmosphere. Analytical thin-layer chromatography was carried out on E. Merck silica gel 60 F_{245} aluminum-backed plates. The 230−400 mesh size of the same absorbent was utilized for all chromatographic purifications. The organic extracts were dried over anhydrous $MgSO_4$. ^{1}H and ^{13}C NMR spectra were recorded on Bruker instruments at 300 and 75 MHz, respectively. Infrared spectra were recorded with a Perkin-Elmer 1320 spectrometer. The high-resolution mass spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center.

4,4-Dimethyl-2-[(*S*)-*p*-tolylsulfinyl]-2-cyclopenten-1-one (3). A solution of 2-bromo-4,4-dimethylcyclopentenone[23] (3.00 g, 15.9 mmol), ethylene glycol (3.64 mL, 65.2 mmol), and camphorsulfonic acid (42 mg, 0.18 mmol) in benzene (50 mL) was heated to reflux under a Dean−Stark trap and maintained at this temperature overnight with azeotropic removal of water. The solvent was removed under reduced pressure, the residue was taken up in ethyl acetate (200 mL), and this solution was washed with water, saturated $NaHCO_3$ solution, and brine prior to drying and concentration. Chromatography on silica gel (elution with 15:1 hexanes/ethyl acetate) followed by Kugelrohr distillation afforded 2.79 g (75%) of **2** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (s, 1 H) 4.18 (m, 2 H), 3.96 (m, 2 H), 1.99 (s, 2 H), 1.14 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 122.0, 117.1, 65.4, 49.7, 41.7, 28.3.[13]

A 250-mL flask containing a magnetic stirring bar was charged with anhydrous THF (25 mL) and cooled to −78 °C prior to the introduction of *n*-butyllithium (14.1 mL of 1.6 M in hexanes, 23 mmol) and freshly distilled **2** (4.765 g, 20.44 mmol) dissolved in THF (10.8 mmol) via cannula under positive N_2 pressure. The clear yellow solution was stirred for 3.5 h and transferred via cannula to a cold (−78 °C) vigorously stirred mixture of (−)-menthyl (5*S*)-*p*-toluenesulfinate (8.65 g, 30.4 mmol) in THF (180 mL). The cooling bath was removed, 50 mL of saturated KH_2PO_4 solution was added, and the reaction mixture was warmed to room temperature. The THF was removed under reduced pressure, and the product was extracted into $CHCl_3$. The combined organic layers were dried and concentrated to leave a residue, purification of which by chromatography on silica gel (elution with 40% ethyl acetate in hexane) returned 2.97 g of the sulfinate and provided 4.63 g (77%) of the sulfoxide acetal as a white crystalline solid: mp 116.5−117.5 °C (from CH_2Cl_2/hexanes); IR ($CHCl_3$, cm^{-1}) 1317, 1234, 1025; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 8.1 Hz, 2 H), 7.29 (d, J = 8.1 Hz, 2 H), 6.52 (s, 1 H), 3.87−3.59 (m, 4 H), 2.40 (s, 3 H), 2.07 (d, J = 13.5 Hz, 1 H), 2.01 (d, J = 13.5 Hz, 1 H), 1.20 (s, 3 H), 1.18 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 145.0, 141.6, 140.4, 129.6 (2 C), 125.8 (2 C), 117.7, 65.3, 65.0, 52.6, 41.4, 28.2 (2 C), 21.4; HRMS (EI) *m*/*z* (M^+) calcd 292.1133, obsd 292.1125; $[\alpha]^{22}_D$ +98.8 (*c* 0.026, $CHCl_3$).

Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.72; H, 6.89. Found: C, 65.59; H, 6.89.

A solution of acetal (3.87 g, 13.2 mmol) and camphorsulfonic acid (0.37 g, 1.3 mmol) in acetone (50 mL) and water (10 mL) was stirred at room temperature for 15 h, treated with K_2CO_3 (0.37 g, 2.7 mmol), and stirred 30 min longer. The mixture was concentrated under reduced pressure, the brown oily biphasic residue was taken up in ether (40 mL), and the ethereal solution was washed with water, saturated $NaHCO_3$ solution, and brine prior to drying and solvent evaporation. Flash chromatography of the residue on silica gel (elution with 60% ethyl acetate in hexanes) furnished **3** as white crystals: mp 93.5−94 °C (from 10:1 ethyl acetate/ether); IR ($CHCl_3$, cm^{-1}) 1706, 1592, 1295, 1042; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1 H), 7.64 (d, J = 8.1 Hz, 2 H), 7.28 (d, J = 8.1 Hz, 2 H), 2.46 (d, J = 18.8 Hz, 1 H), 2.39 (s, 3 H), 2.33 (d, J = 18.8 Hz, 1 H), 1.32 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 171.3, 148.7, 142.2, 139.2, 130.0 (2 C), 125.1 (2 C), 51.9, 40.5, 27.9, 27.6, 21.5; HRMS (EI) *m*/*z* (M^+) calcd 248.0871, obsd 248.0876; $[\alpha]^{22}_D$ +212 (*c* 0.025, $CHCl_3$).

Anal. Calcd for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.49. Found: C, 67.53; H, 6.40.

Methyl (3a*S*,6a*R*)-4,5,6,6a-Tetrahydro-6,6-dimethyl-4-oxo-3a-[(*S*)-*p*-tolylsulfinyl]-2*H*-cyclopenta[*b*]furan-D$^{3(3aH),\alpha}$-acetate (4). A THF solution (50 mL) of **3** (5.00 g, 20.1 mmol) and methyl 4-hydroxy-2-butynoate (5.00 g, 43.8 mmol) was treated with K_2CO_3 (5.50 g, 39.8 mmol) at room temperature for 5 h, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (elution with 10% ethyl acetate in hexanes) to furnish **4** (2.77 g, 38%) as a colorless solid: mp 109−110 °C (from 3:2:2 methanol/THF/ethanol); IR (film, cm^{-1}) 1747, 1714, 1651; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 8.1 Hz, 2 H), 7.31 (d, J = 8.1 Hz, 2 H), 6.34 (m, 1 H), 4.77 (dd, J = 17.7, 2.4 Hz, 1 H), 4.70 (s, 1 H), 3.76 (s, 3 H), 3.65 (dd, J = 17.7, 2.8 Hz, 1 H), 2.40 (d, J = 16.9 Hz, 1 H), 2.41 (s, 3H), 2.26 (d, J = 16.9 Hz, 1 H), 1.24 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.4, 165.6, 152.6, 143.4, 135.7, 129.9 (2 C), 125.5 (2 C), 115.0, 85.7 83.8, 74.1, 53.2, 51.8, 38.6, 26.5, 23.1, 21.5; HRMS (EI) *m*/*z* (M^+) calcd 362.1188, obsd 362.1198; $[\alpha]^{22}_D$ −14.5 (*c* 0.020, $CHCl_3$).

Anal. Calcd for $C_{19}H_{22}O_5S$: C, 62.96; H, 6.12. Found: C, 62.97; H, 6.11.

Methyl (3a*S*,3a*R*,6a*S*)-Hexahydro-6,6-dimethyl-4-oxo-2*H*-cyclopenta[*b*]furan-3-acetate (5). Into a stainless steel autoclave were placed 4.20 g (11.6 mmol) of **4**, 10 mL of THF, 40 mL of methanol, and 42 g of Raney nickel (as a 50% water slurry), which had previously been washed several times with water and methanol. Stirring was initiated, and the apparatus was pressurized to 150 psi with hydrogen. After 4 h, the reaction mixture was filtered through Celite. The pad was washed with copious amounts of CH_2Cl_2, and the combined filtrates were concentrated to leave a residue that was chromatographed on silica gel. Elution with 9:1 hexanes/ethyl acetate afforded 2.30 g (88%) of **5** as a colorless oil: IR (neat, cm^{-1}) 1736, 1466, 1172; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (d, J = 3.3 Hz, 1 H), 4.03 (m, 1 H), 3.67 (s, 3 H), 3.42 (m, 1 H), 2.94 (m, 2 H), 2.68 (dd, J = 17.1, 6.4 Hz, 1 H), 2.26 (dd, J = 17.1, 7.8 Hz, 1 H), 2.23 (d, J = 17.5 Hz, 1 H), 2.00 (d, J = 17.5 Hz, 1 H), 1.20 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.6, 172.6, 90.2, 73.2, 53.8, 51.6 (2 C), 39.0, 38.2, 32.7, 26.9, 22.9; HRMS (EI) *m*/*z* (M^+) calcd 226.1205, obsd 226.1213; $[\alpha]^{23}_D$ −77.0 (*c* 0.087, $CHCl_3$).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.58; H, 8.08.

(3*S*,3a*R*,6a*S*)-3-(2-Ethynyl-2-hydroxy-3-butynyl)hexahydro-6,6-dimethyl-4*H*-cyclopenta[*b*]furan-4-one (6b). Freshly distilled trimethylsilylacetylene (0.39 mL, 2.7 mmol) was taken up in dry THF (5 mL) under N_2, cooled to 0 °C, treated with *n*-butyllithium (1.40 mL of 2.04 M in hexanes, 2.85 mmol), stirred for 15 min, and cooled to −78 °C. A solution of **5** (200 mg, 2.21 mmol) in dry THF (3 mL) was slowly introduced, and the reaction mixture was stirred for 3 h at this temperature before being quenched with saturated NH_4Cl solution. The separated aqueous phase was extracted with ether (2 × 10 mL), and the combined organic layers were washed with water and brine, dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 25:1 hexanes/ethyl acetate) afforded 112 mg (43%) of **6a**, which was directly desilylated.

A solution of **6a** (143 mg, 0.49 mmol) in DMF (5 mL) was treated with potassium fluoride (45 mg, 0.74 mmol), stirred for 20 min, and quenched with saturated $NaHCO_3$ solution. After 10 min, the product was extracted into ether (4 × 10 mL), and the combined organic phases were washed with water (4 × 10 mL) and brine prior to drying and solvent evaporation. Chromatography of the residue on silica gel (elution with 20:1 hexanes/ethyl acetate) gave **6b** (60 mg, 56%) as a colorless oil: IR (neat, cm^{-1}) 3287, 1732; ^1H NMR (300 MHz, $CDCl_3$) δ 4.16 (m, 2 H), 3.37 (t, J = 9.9 Hz, 1 H), 3.15 (m, 1 H), 3.03 (m, 1 H), 2.55 (s, 2 H), 2.28 (dd, J = 5.6, 4.1 Hz, 1 H), 2.25 (d, J = 14.5 Hz, 1 H), 2.10 (d, J = 14.5 Hz, 1 H), 2.06 (dd, J = 5.6, 5.2 Hz, 1 H), 1.20 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.3, 90.3, 84.5, 82.8, 73.6, 72.0, 71.1, 62.4, 54.8, 52.2, 40.8, 39.4, 38.9, 26.9, 23.0; HRMS (EI) m/z (M^+) calcd 246.1256, obsd 246.1247.

Methyl (3*S*,3a*S*,6a*S*)-3,3a,6,6a-Tetrahydro-6,6-dimethyl-4-vinyl-2*H*-cyclopenta[*b*]furan-3-acetate (8). To a THF solution (25 mL) of **5** (802 mg, 3.54 mmol) at −78 °C was added potassium hexamethyldisilazide (7.09 mL of 0.5 N in toluene, 3.54 mmol), followed by *N*-phenyl triflimide (1.40 g, 3.92 mmol) in THF (5 mL) 20 min later. The reaction mixture was stirred for 3 h at −78 °C, quenched with saturated NH_4Cl solution, and extracted with ether (3 × 50 mL). The combined organic phases were dried and concentrated to leave a residue that was purified by flash chromatography on silica gel (elution with 5% ethyl acetate in hexanes). In addition to the recovery of unreacted **5** (83 mg, 10%), 1.12 g (98% based on consumed **5**) of **7** was isolated, which was used directly.

Enol triflate **7** (994 mg, 2.77 mmol) was dissolved in THF (20 mL), treated with tributylvinylstannane (1.62 mL, 5.54 mmol), lithium chloride (706 mg, 16.7 mmol), and $Pd_2(dba)_3{\cdot}CHCl_3$ (64 mg, 0.57 mmol), stirred at 20 °C for 15 h, diluted with saturated $NaHCO_3$ solution (20 mL), and extracted with ether (3 × 50 mL). The combined organic phases were dried and concentrated to leave a residue that was subjected to flash chromatography on silica gel (elution with 5% ethyl acetate in hexanes). Diene ester **8** was isolated as a colorless liquid (622 mg, 95%): IR (neat, cm^{-1}) 1725, 1425, 1155; ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (dd, J = 17.6, 10.7 Hz, 1 H), 5.50 (s, 1 H), 5.13 (d, J = 17.6 Hz, 1 H), 5.06 (d, J = 10.7 Hz, 1 H), 4.16 (d, J = 8.0 Hz, 1 H), 3.74 (d, J = 3.2 Hz, 2 H), 3.67−3.60 (m, 1 H), 3.64 (s, 3 H), 2.85−2.70 (m, 1 H), 2.35 (dd, J = 16.6, 3.3 Hz, 1 H), 2.16 (dd, J = 16.6, 11.4 Hz, 1 H), 1.07 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 143.3, 136.9, 134.0, 114.9, 90.8, 74.2, 52.0, 51.6, 46.7, 37.7, 33.7, 30.2, 21.4; HRMS (EI) m/z (M^+) calcd 236.1412, obsd 236.1390; $[\alpha]^{22}_D$ −7.2 (*c* 0.028, $CHCl_3$).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.07; H, 8.52.

(2a*S*,4a*S*,7a*S*,7b*S*)-Hexahydro-3,3-dimethyl-1*H*-2,5-dioxacyclopent-[*cd*] inden-6-(2a*H*)-one (9). A 50% slurry of Raney nickel in water (1.01 g) was washed with methanol (3 × 5 mL) and transferred in methanol (5.8 mL) to **4** (69 mg, 0.30 mmol). This mixture was stirred under 1000 psi of hydrogen for 12 h at room temperature and filtered through Celite. After rinsing of the filter cake with THF (250 mL), the combined filtrates were concentrated, and the residue was subjected to flash chromatography on silica gel. Elution with 50% ethyl acetate in hexanes gave **9** (38 mg, 65%) as a colorless crystalline solid: mp 72−74 °C (from THF−hexanes); IR (neat, cm^{-1}) 1744, 1468, 1402, 1368; ^1H NMR (300 MHz, $CDCl_3$) δ 5.00 (m, 1 H), 3.85 (d, J = 6.4 Hz, 1 H), 3.72 (dd, J = 9.1, 5.1 Hz, 1 H), 3.65 (dd, J = 9.1, 2.1 Hz, 1 H), 3.00 (m, 1 H), 2.76 (m, 1 H), 2.61 (dd, J = 16.0, 5.8 Hz, 1 H), 2.43 (dd, J = 16.1, 10.2 Hz, 1 H), 1.97 (dd, J = 12.8, 7.1 Hz, 1 H), 1.77 (dd, J = 12.8, 9.9 Hz, 1 H), 1.15 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 92.7, 80.6, 73.2, 45.4, 42.4, 39.2, 36.9, 32.2, 26.7, 22.9; HRMS (EI) m/z (M^+) calcd 196.1099, obsd 196.1081; $[\alpha]^{23}_D$ +10.5 (*c* 0.087, $CHCl_3$).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.43; H, 8.27.

(3*S*,3a*S*,6a*S*)-3,3a,6,6a-Tetrahydro-6,6-dimethyl-3-(4-methyl-4-pentenyl)-4-vinyl-2*H*-cyclopenta[*b*]furan (12). A THF (30 mL) solution of **8** (622 mg, 2.63 mmol) was treated with lithium aluminum hydride (100 mg, 2.63 mmol) at 20 °C for 30 min, quenched with 3 N NaOH solution at 0 °C, and filtered. After the filter cake had been rinsed with CH_2Cl_2 (2 × 20 mL), the combined filtrates were concentrated to leave alcohol **10** as a colorless liquid (525 mg, 94%).

A solution of **10** (585 mg, 2.81 mmol) in CH_2Cl_2 (20 mL) was treated with triethylamine (0.78 mL, 5.62 mmol) and methanesulfonyl chloride (0.33 mL, 4.21 mmol) at 0 °C for 1.5 h, diluted with saturated $NaHCO_3$ solution (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried and evaporated to leave the mesylate that was dissolved in acetone, added to acetone (50 mL) containing sodium iodide (4.21 g, 28.1 mmol) and $NaHCO_3$ (500 mg), stirred for 15 h at 20 °C, diluted with saturated $Na_2S_2O_3$ solution (100 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic solutions were dried and concentrated to leave a residue, purification of which by flash chromatography on silica gel (elution with 5% ethyl acetate in hexanes) gave 702 mg (79% for two steps) of iodide **11** as a colorless oil that was used directly.

To magnesium turnings (3.25 g, 0.134 mmol) that had been dried under a flow of N_2 for 15 h[40] was added dry THF (25 mL), followed by the introduction of methallyl chloride (2.50 mL, 25.2 mmol) slowly over 1.5 h at 0 °C. This Grignard solution was added to a THF (10 mL) solution of copper(I) iodide (421 mg, 2.21 mmol) at 0 °C and stirred for 10 min before being treated with a solution of **11** (702 mg, 2.21 mmol) in THF (5 mL). The reaction mixture was stirred for 4 h at 0 °C and quenched with saturated NH_4Cl solution at this temperature. The precipitated white solid was filtered off and rinsed with CH_2Cl_2 (2 × 20 mL). The combined filtrates were concentrated and subjected to flash chromatography on silica gel (elution with 5% ethyl acetate in hexanes) to yield 531 mg (98%) of **12** as a colorless oil: IR (neat, cm^{-1}) 1435, 1355, 1080; ^1H NMR (300 MHz, $CDCl_3$) δ 6.42 (dd, J = 17.5, 10.7 Hz, 1 H), 5.48 (s, 1 H), 5.13 (dd, J = 17.5, 1.3 Hz, 1 H), 5.03 (dd, J = 10.7, 1.4 Hz, 1 H), 4.65 (d, J = 10.6 Hz, 2 H), 4.18 (d, J = 7.9 Hz, 1 H), 3.70 (d, J = 4.4 Hz, 2 H), 3.57 (t, J = 8.1 Hz, 1 H), 2.25−2.15 (m, 1 H), 2.10−1.85 (m, 2 H), 1.68 (s, 3 H), 1.55−0.95 (series of m, 4 H), 1.062 (s, 3 H), 1.057 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0, 142.3, 137.3, 134.2, 114.1, 109.6, 90.6, 73.1, 52.7, 46.6, 41.8, 37.8, 30.0, 28.2, 27.1, 22.4, 21.3; HRMS (EI) m/z (M^+) calcd 246.1984, obsd 246.1978; $[\alpha]^{22}_D$ −3.0 (*c* 0.070, $CHCl_3$).

(2a*S*,9a*S*,9b*S*)-1,2a,3,7,8,9,9a,9b-Octahydro-3,3,6-trimethyl-2-oxacycloocta[*cd*]pentalene (13). To a refluxing CH_2Cl_2 (750 mL) solution of Grubbs's catalyst (152 mg, 10 mol %) was added **12** (424 mg, 1.72 mmol) dissolved in CH_2Cl_2 (10 mL). The reaction mixture was refluxed for 7 h, an additional 10% of catalyst was introduced, and this procedure was repeated again after 24 h. Following a total reflux period of 48 h, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (elution with 5% ethyl acetate in hexanes). In addition to 46 mg (11%) of recovered **12**, 313 mg (93% based on unreacted **12**) of **13** was isolated as a colorless oil: IR (neat, cm^{-1}) 1435, 1350, 1195, 1075; ^1H NMR (300 MHz, C_6D_6) δ 6.11 (s, 1 H), 5.34 (s, 1 H), 4.32 (d, J = 6.4 Hz, 1 H), 3.83 (dd, J = 8.1, 7.1 Hz, 1 H), 3.68 (t, J = 7.4 Hz, 1 H), 3.20 (dd, J = 10.6, 8.2 Hz, 1 H), 2.85−2.70 (m, 1 H), 2.07−1.90 (m, 1 H), 1.70−1.15 (series of m, 5 H), 1.65 (d, J = 1.0 Hz, 3 H), 1.20 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 141.4, 137.4, 134.3, 126.2, 93.0, 74.0, 54.2, 47.1, 44.1, 31.5, 30.1, 26.5, 26.4, 24.6, 22.4; HRMS (EI) m/z (M^+) calcd 218.1671, obsd 218.1679; $[\alpha]^{22}_D$ +21.1 (*c* 0.070, $CHCl_3$).

(2a*S*,5*S*,9a*S*,9b*S*)-1,2a,3,5,6,7,8,9,9a,9b-Decahydro-3,3-dimethyl-6-methylene-2-oxacycloocta[*cd*]pentalen-5-ol (14). Dry oxygen was passed through a CH_2Cl_2 (5 mL) solution of **13** (69 mg, 0.32 mmol) and TPP sensitizer (5 mg) with concurrent radiation from a tungsten halogen lamp for 40 min. The reaction mixture was directly chromatographed on silica gel, elution with 10% ethyl acetate in hexanes affording the hydroperoxide. This material was immediately reduced with lithium aluminum hydride (70 mg, 1.8 mmol) in THF (10 mL) at 20 °C for 30 min and quenched with 3 N NaOH solution at 0 °C. The white solid was filtered off and rinsed with CH_2Cl_2 (2 × 20 mL). The combined filtrates were concentrated to give 45 mg (61%) of **14** as an unstable colorless oil (1.9:1 epimeric mixture) that was immediately oxidized: IR (neat, cm^{-1}) 3400, 1630, 1435, 1350; ^1H NMR (300 MHz, $CDCl_3$) δ 6.29 (s, 0.34 H), 5.58 (s, 0.66 H), 5.53 (s, 0.34 H), 5.14 (s,

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0.66 H), 4.90 (s, 0.66 H), 4.72 (s, 0.66 H), 4.25 (m, 1 H), 3.98 (s, 0.68 H), 3.95−3.75 (m, 1.34 H), 3.58 (t, J = 8.3 Hz, 0.66 H), 3.40 (dd, J = 8.4, 6.7 Hz, 0.66 H), 3.12 (dd, J = 10.8, 8.3 Hz, 0.34 H), 2.84 (m, 0.34 H), 2.50−1.20 (series of m, 7.66 H), 1.04 (s, 2 H), 1.01 (s, 3 H), 0.96 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 144.4, 142.9, 139.8, 136.9, 136.0, 125.1, 112.7, 92.5, 92.3, 76.6, 75.9, 73.4, 68.2, 53.5, 51.6, 46.8, 46.1, 43.4, 42.9, 30.6, 30.4, 29.6, 29.4, 27.1, 26.9, 26.7, 24.0, 21.5, 21.3; HRMS (EI) *m*/*z* (M^+) calcd 234.1620, obsd 234.1617.

(2a*S*,4a*S*,6*R*,9a*S*,9b*S*)-Decahydro-3,3,6-trimethyl-2-oxacycloocta-[*cd*] pentalen-5(1*H*)-one (15). A solution of **14** (43 mg,0.18 mmol) in CH_2Cl_2 (5 mL) was oxidized with the Dess−Martin periodinane (156 mg, 0.37 mmol) at room temperature for 30 min and subjected directly to flash chromatography on silica gel. Elution with 10% ethyl acetate in hexanes gave the dienone, which was dissolved in ethanol (3 mL), treated with 10% palladium on charcoal (20 mg), and hydrogenated at 300 psi for 1 h. The insolubles were separated by filtration and rinsed with CH_2Cl_2 (2 × 20 mL). Concentration of the filtrate followed by flash chromatography on silica gel (elution with 5% ethyl acetate in hexanes) provided 29 mg (67%) of **15** as a white solid: mp 83−85 °C; IR (neat, cm^{-1}) 1690, 1445, 1360, 1060; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (dd, J = 6.9, 1.1 Hz, 1 H), 3.83 (t, J = 7.8 Hz, 1 H), 3.35 (m, 1 H), 3.20−3.09 (m, 2 H), 2.56−2.43 (m, 2 H), 2.40−2.22 (m, 1 H), 2.00 (t, J = 12.8 Hz, 1 H), 1.90−1.65 (m, 2 H), 1.65−1.43 (m, 2 H), 1.37−1.20 (m, 1 H), 1.12−1.00 (m, 1 H), 1.10 (d, J = 6.8 Hz, 3 H), 1.09 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.5, 94.4, 74.9, 50.7, 48.7, 45.8, 44.2, 41.7, 40.5, 28.7, 25.9, 23.2, 23.1, 22.3, 13.5; HRMS (EI) *m*/*z* (M^+) calcd 236.1776, obsd 236.1777; $[\alpha]^{22}_D$ +4.9 (*c* 0.020, $CHCl_3$).

(+)-Asteriscanolide (1). A mixture of **15** (29 mg, 0.12 mmol), ruthenium trichloride (26 mg, 0.12 mmol), and sodium periodate (263 mg, 1.23 mmol) in 2:2:1 $CH_3CN-CCl_4-H_2O$ (2.5 mL) was stirred for 5 h, diluted with CH_2Cl_2 (5 mL), dried, and filtered. After solvent evaporation, the residue was subjected to flash chromatography on silica gel. Elution with 20% ethyl acetate in hexanes gave 19 mg (63%) of **1** as a white solid: mp 156−158 °C; IR (neat, cm^{-1}) 1755, 1685, 1450, 1360; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (dd, J = 5.3, 1.1 Hz, 1 H), 3.73 (ddd, J = 11.1, 9.7, 5.3 Hz, 1 H), 3.20 (ddd, J = 13.0, 11.1, 6.8 Hz, 1 H), 2.71 (ddd, J = 12.4, 9.7, 4.7 Hz, 1 H), 2.57−2.35 (m, 2 H), 2.18 (d, J = 13.0, 13.0 Hz, 1 H), 2.05−1.20 (series of m, 6 H), 1.20 (s, 3 H), 1.12 (d, J = 6.8 Hz, 3 H), 1.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 178.1, 91.1, 50.4, 46.0, 45.9, 43.4, 41.0, 38.6, 28.3, 24.8, 23.2 (2 C), 22.7, 13.5; HRMS (EI) *m*/*z* (M^+) calcd 250.1569, obsd 250.1557; $[\alpha]^{22}_D$ +8.5 (*c* 0.019, $CHCl_3$).

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Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra of **1** as well as tables giving the crystal data and structure refinement information, bond lengths and bond angles, atomic and hydrogen coordinates, and isotropic and anisotropic displacement coordinates for **4** (PDF). This information is available free of charge via the Internet at http://pubs.acs.org.

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