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Formal Synthesis of (±)-Guanacastepene A

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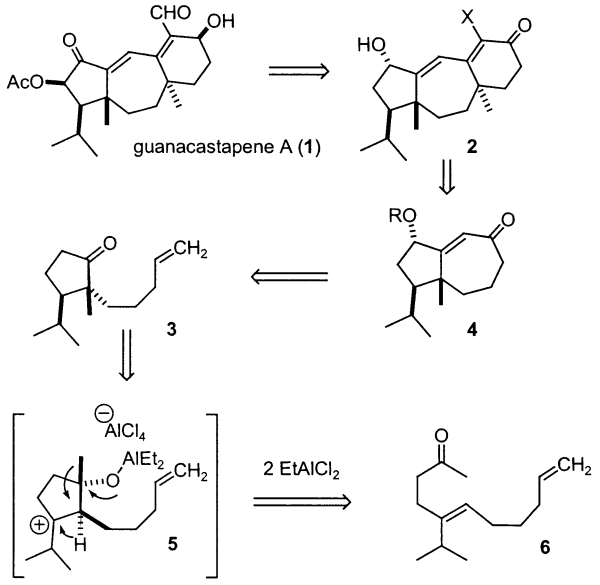
A 17 step synthesis of **55**, a late intermediate in Danishefsky's guanacastepene A synthesis, has been completed in 4% overall yield. Key features include the use of vinylmagnesium bromide in the Pd-catalyzed coupling with triflate **13** to give triene **16** without the formation of Heck products, a novel extension of the Stork−Jung vinylsilane Robinson annulation that provides tricyclic 2-hydroxymethylcyclohexenone **42** from **23b** in four steps and 51% yield, the ability to obtain almost exclusively α′-alkylation of **35ba** by the proper choice of protecting groups, and the ability to obtain the desired β-alcohol selectively by reduction of keto alcohol **42** rather than keto ester **53**.

Introduction

Guanacastepene A (**1**), a novel diterpene antibiotic isolated in 2000 by Clardy and co-workers from an unidentified fungus growing on the tree *Daphnopsis americana*, shows excellent activity toward methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*.[1a] Further biological studies established that guanacastepene A has moderate activity against Gram-positive bacteria, poor activity against Gram-negative bacteria, and hemolytic activity against human red blood cells.[1b] The structure of **1** was determined by X-ray crystallography; the ^{1}H and ^{13}C NMR spectra indicate that the cycloheptene exists as a mixture of two slowly equilibrating conformers, which causes difficulties in interpreting the NMR spectra of guanacastepene A (**1**) and related compounds. In 2001, the same group reported a series of congeners, guanacastepenes B−O, from the same source.[1c]

Although guanacastepene A is unlikely to be developed into a useful therapeutic agent due to its hemolytic activity against human red blood cells, its biological activity, novel carbon skeleton, and highly functionalized upper half make it a challenging and important synthetic target. Not surprisingly, synthetic studies have been reported by a number of groups,[2−9] and Danishefsky recently reported the first total synthesis of (±)-guanacastepene A.[10]

SCHEME 1



Our retrosynthetic analysis (Scheme 1) suggested that guanacastepene A (**1**) can be obtained by elaboration of the tricyclic dienone **2**, in which X is a precursor of the aldehyde group of **1**. We envisioned that the cyclohexenone ring of **2** can be formed by methylation and a modified Robinson annulation on hydroazulenone **4**. The cycloheptenone of **4** will be prepared from 2,2,3-trisub-

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(1) (a) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116−2117. (b) Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256−261. (c) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900−9901.

(2) For a preliminary communication on the synthesis of **23** see: (a) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569−572. (b) Snider, B. B.; Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123−9126.

(3) (a) Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399−2401. (b) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6789−6791.

(4) Magnus, P.; Waring, M. J.; Ollivier, C.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 4797−4950, 6977.

(5) (a) Mehta, G.; Umarye, J. D. *Org. Lett.* **2002**, *4*, 1063−1066. (b) Mehta, G.; Umarye, J. D.; Gagliardini, V. *Tetrahedron Lett.* **2002**, *43*, 6975−6978.

(6) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063−2066.

(7) (a) Nguyen, T. M.; Lee, D. *Tetrahedron Lett.* **2002**, *42*, 4033−4037. (b) Nguyen, T. M.; Seifert, R. J.; Mowrey, D. R.; Lee, D. *Org. Lett.* **2002**, *4*, ASAP.

(8) Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4*, 3363−3366.

(9) Boyer, F.-D.; Hanna, I. *Tetrahedron Lett.* **2002**, *43*, 7469−7472.

(10) (a) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2185−2188. (b) Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2188−2191.

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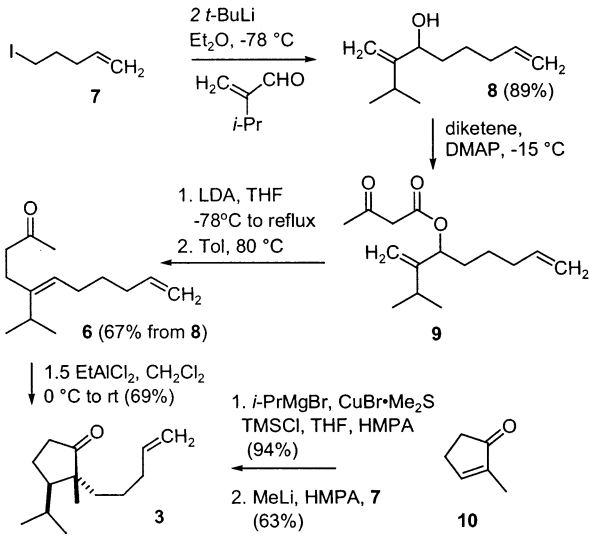
SCHEME 2

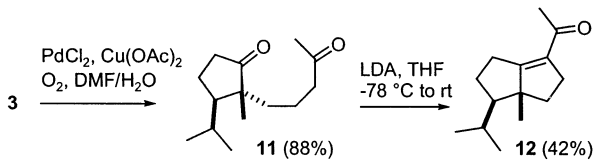


situted cyclopentanone **3**. We thought that cyclopentanone **3** could be prepared stereospecifically by the $EtAlCl_2$-initiated cyclization of γ,δ-unsaturated ketone **6**. Several years ago we reported a new method for cyclopentanone annulation by treatment of γ,δ-unsaturated ketones with excess $RAlCl_2$.[11] This reaction was used to make fused ring systems, but should also be suitable for the stereospecific construction of **3** by cyclization of **6** to give zwitterion **5**, which should undergo concerted 1,2-hydride and methyl shifts to give **3** stereospecifically. We chose to carry out this reaction on **6** with a synthetically versatile terminal double bond, since previous studies indicated that isolated double bonds are compatible with the acidic conditions required for this cyclization.[11]

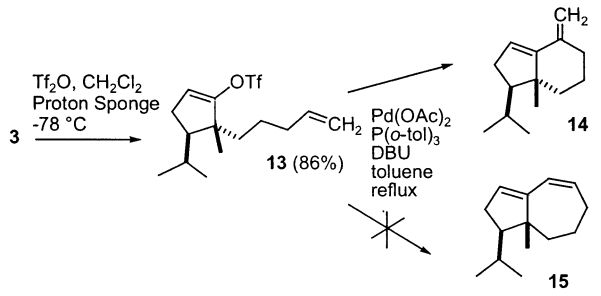
Results and Discussion

4-Pentenyllithium, prepared by halogen−metal exchange[12] of 5-iodo-1-pentene (**7**) with 2 equiv of *t*-BuLi in THF at −78 °C, was added to 2-isopropylacrolein[13] to afford 89% of allylic alcohol **8**. Reaction of **8** with diketene and DMAP provided acetoacetate **9** (see Scheme 2). Enolate-accelerated Carroll rearrangement by the procedure of Wilson[14] was effected by treating **9** with 2 equiv of LDA in THF at −78 °C and heating at reflux to give the β-keto acid. Decarboxylation by heating in toluene at 80 °C provided dienone **6** in 67% yield from alcohol **8**. We were delighted to find that treatment of γ,δ-unsaturated ketone **6** with 1.5 equiv of $EtAlCl_2$ in CH_2Cl_2 at 0 °C with gradual warming to room temperature over 24 h gave 69% of cyclopentanone **3** as the only cyclic product. Cyclopentanone **3** has also been prepared from 2-methyl-2-cyclopentenone (**10**) by Danishefsky[3a] using the method of Piers.[15] Addition of isopropyl cuprate and trapping with TMS chloride afforded the trimethylsilyl enol ether.

SCHEME 3



SCHEME 4



Regeneration of the enolate with MeLi in THF and HMPA and alkylation with **7** afforded 59% of **3**.

Initially, we planned to form the cycloheptenone by an intramolecular aldol reaction, which has been used successfully to form related hydroazulenones.[16] Diketone **11** was prepared in 88% yield by Wacker oxidation of **3** with $PdCl_2$, $Cu(OAc)_2 \cdot H_2O$, and O_2 (1 atm) in DMF (see Scheme 3).[17] Unfortunately, no reaction occurred on treatment of diketone **11** with pyrrolidine at 80 °C[16a] or KOH in MeOH.[16b] The aldol reaction was eventually achieved by reaction of diketone **11** with LDA in THF at −78 to 0 °C to give 42% of acetylhydropentalene **12**, rather than the desired hydroazulenone.

We then unsuccessfully explored sequences involving nucleophilic addition to the carbonyl group of cyclopentanone **3**. Enolization was the only reaction, even with unhindered nucleophiles such as *n*-BuLi and $CeCl_3$. The carbonyl group is very hindered by the three substituents, while the α-position is unhindered. We decided to take advantage of the facile enolization of **3** by exploring Pd-insertion reactions of enol triflate **13** (see Scheme 4).

Reaction of cyclopentanone **3** with Tf_2O and Proton Sponge afforded enol triflate **13** in 86% yield. A Heck reaction of enol triflate **13** using $Pd(OAc)_2$, $P(o\text{-tol})_3$, and DBU in toluene at reflux gave only the 6-exo product **14** and none of the desired 7-endo product hydroazulene **15**. No **15** was obtained under a variety of conditions, including those that have been reported to favor the formation of endo products in Heck reactions.[18] The formation of **14** rather than **15** probably results from the steric constraints of the bicyclic ring system. With a different ring system, Martin observed only the undesired 7-endo product, rather than the desired 6-exo product.[19]

We then decided to prepare hydroazulene **15** by a ring-closing metathesis (RCM) of triene **16** (see Scheme 5).

(11) (a) Snider, B. B.; Cartaya-Marin, C. P. *J. Org. Chem.* **1984**, *49*, 153−157. (b) Snider, B. B.; Kirk T. C. *J. Am. Chem. Soc.* **1983**, *105*, 2364−2368.

(12) Negishi, E.-i.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406−5409.

(13) Riehs, G.; Urban, E. *Tetrahedron* **1996**, *52*, 1221−1230.

(14) Wilson, S. R.; Price, M. F. *J. Org. Chem.* **1984**, *49*, 722−725. Wilson, S. R.; Augelli, C. E. *Organic Syntheses;* Wiley: New York, 1993; Collect. Vol. 8, pp 235−240.

(15) Piers, E.; Renaud, J.; Rettig, S. J. *Synthesis* **1998**, 590−602.

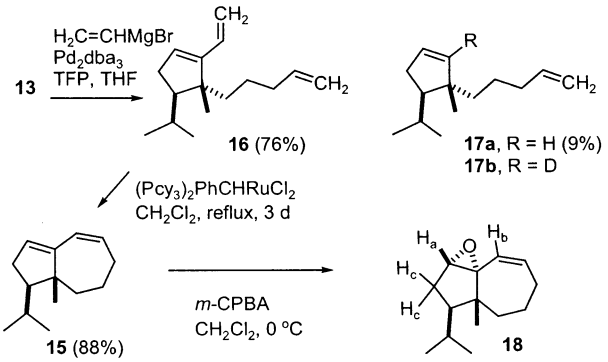
(16) (a) Ravi Kumar, V. T.; Swaminathan, S.; Rajagopalan, K. *J. Org. Chem.* **1985**, *50*, 5867−5869. (b) Money, T.; Wong, M. K. C. *Tetrahedron* **1996**, *52*, 6307−6324.

(17) Smith, A. B., III.; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765−8768.

(18) (a) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834−7835. (b) Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genet, J. *Tetrahedron Lett.* **1996**, *37*, 2003−2006. (c) Brombrun, A.; Sageot, O. *Tetrahedron Lett.* **1997**, *38*, 1057−1060.

(19) Lee, K. L.; Goh, J. B.; Martin, S. F. *Tetrahedron Lett.* **2001**, *42*, 1635−1638.

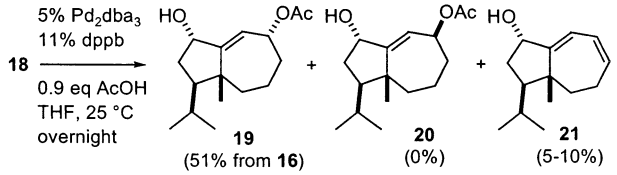
SCHEME 5



Formation of triene **16** from enol triflate **13** proved to be quite challenging, due to the facility of the intramolecular 6-exo Heck reaction that formed **14**. For instance, treatment of triflate **13** with 5 equiv of tributylvinyltin, Pd_2dba_3 (0.02 equiv), and tri-2-furylphosphine (TFP) (0.04 equiv) in THF gave a 9:1 mixture of Heck product **14** and triene **16**, even though these conditions were developed by Farina to accelerate Stille coupling.[20] Only the Heck product was obtained from the Suzuki coupling with potassium vinyltrifluoroboronate.[21] Transfer of the vinyl group from tin or boron to the cyclopentenylpalladium intermediate is slower than the intramolecular Heck reaction. We then tried to prepare triene **16** without the competing Heck reaction by Cu-catalyzed coupling of vinylmagnesium bromide with triflate **13**.[22] Unfortunately, we obtained only traces of triene **16**, in agreement with previous reports that cuprate coupling with enol triflates can be problematic.[23] Finally, we concluded that Pd-catalyzed coupling of vinylmagnesium bromide with enol triflate **13** should be faster than the intramolecular Heck reaction.[24]

We were pleased to find that treatment of triflate **13** with vinylmagnesium bromide and $Pd(Ph_3P)_4$ in THF at reflux gave a 9:1 mixture of triene **16** and Heck product **14**. The formation of the Heck product can be completely suppressed using catalyst conditions optimized for Stille coupling.[20] Treatment of **13** with vinylmagnesium bromide (2 equiv), Pd_2dba_3 (0.02 equiv), and TFP (0.08 equiv) in THF at 0 °C to room temperature gave an 84:16 mixture of triene **16** and the reduction product **17**, which can be separated on silica gel impregnated with 20% silver nitrate to give 76% of pure **16** and 14% of 90% pure **17a**. Quenching the coupling reaction with D_2O provided a similar mixture of **16** and **17b**, in which deuterium has been incorporated at the carbon that was substituted with the triflate in **13**. Although the D_2O quenching experiment established that the hydrogen comes from water, the mechanism for the formation of **17** is not clear. Reaction at −78 °C significantly slowed the transfer of the vinyl group and gave some Heck product. Other ligands (Ph_3As) or catalysts ($PdCl_2dppf$)[25] gave more byproducts.

SCHEME 6



The RCM[26] of the 84:16 mixture of **16** and **17a** required more than 20% of Grubbs' first generation catalyst. Only 2% of **17a** was recovered, suggesting that **17a** consumed the catalyst. RCM of pure **16** required only 6% of Grubbs' catalyst to provide 88% of a 95:5 mixture of the volatile hexahydroazulene **15** and styrene after filtration through silica gel.

Treatment of hydroazulene **15** with *m*-CPBA at 0 °C in CH_2Cl_2 and saturated aqueous $NaHCO_3$ gave epoxide **18** as a single stereoisomer. A 1D NOESY spectrum of epoxide **18** with irradiation of the epoxide hydrogen H_a at δ 3.26 showed a larger cross-peak to the alkene hydrogen H_b at δ 5.50 than to the cyclopentane methylene hydrogens H_c at δ 2.06 and 1.33. The distances calculated by conformational searching with MMX minimization[27] in **18** are $H_a-H_b = 2.80$ Å and $H_a-H_c = 2.62$ and 2.69 Å. The calculated distances in the stereoisomer in which epoxidation occurred from the more hindered β-face are $H_a-H_b = 3.37$ Å and $H_a-H_c = 2.54$ and 2.83 Å. In this isomer the NOE between the epoxide hydrogen H_a and the alkene hydrogen H_b should be much smaller than those to the cyclopentane methylene hydrogens H_c.

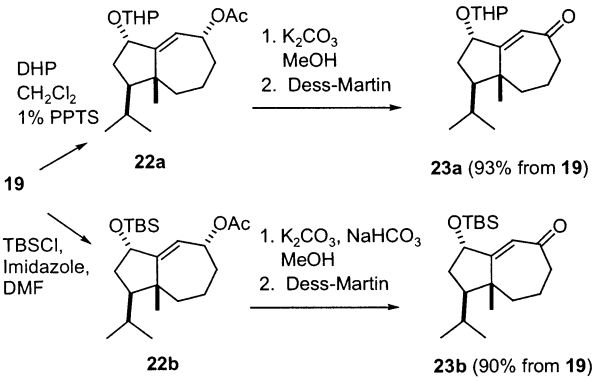
Opening the epoxide ring of **18** with AcOH using catalytic $Pd(Ph_3)_4$, which was reported by Deardorff[28] to give only the cis acetoxy alcohol, gave a 30% yield of a 1:1 mixture of **19** and **20** (see Scheme 6). Reaction of **18** with Pd_2dba_3 and dppb as reported by Trost[29] with only 0.9 equiv of acetic acid in concentrated solution gave a 6:1 mixture of hydroxy acetate **19** and elimination product **21**, from which **19** was isolated in 51% overall yield from triene **16**. Excess acetic acid decreased the yield of elimination product **21** but gave a mixture of stereoisomers **19** and **20** in lower yield. In the absence of Pd catalyst, a large excess of acetic acid gave a 1:1 mixture of **19** and **20** in low yield.

The cyclopentanol of **19** was protected with both THP and TBS groups to give **22a** and **22b**, respectively (see Scheme 7). Saponification of the acetate and Dess−Martin oxidation gave the protected hydroazulenones **23a** and **23b** in 93% and 90% yield, respectively, for the three-step sequence.

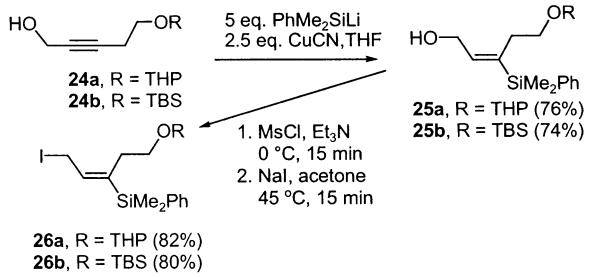
We recently reported[2b] the development of a novel extension of the Stork−Jung vinylsilane Robinson an-

(20) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.
(21) Molander, G.; Rivero, M. R. *Org. Lett.* **2001**, *4*, 107−109.
(22) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313−4316.
(23) (a) Lipshutz, B. H.; Vivian, R. W. *Tetrahedron Lett.* **1999**, *40*, 2871−2874. (b) Lipshutz, B. H.; Elworthy, T. R. *J. Org. Chem.* **1990**, *55*, 1695−1696. (c) Hirama, M.; Nakamine, T.; Itô, S. *Tetrahedron Lett.* **1988**, *29*, 1197−1198.
(24) Murahashi, S.-I.; Yamamura, M.; Yanagisawa, K.-i.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979**, *44*, 2408−2417.
(25) Busacca, C. A.; Erikson, M. C.; Fiaschi, R. *Tetrahedron Lett.* **1999**, *40*, 3101−3104.
(26) (a) Schneider, M. F.; Junga, H.; Blechert, S. *Tetrahedron* **1995**, *51*, 13003−13014. (b) Fürstner, A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3012−3043. (c) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3007.
(27) MMX calculations were carried out using PCMODEL version 7.5 with conformational searching.
(28) (a) Deardorff, D. R.; Myles, D. C.; MacFerrin, K. D. *Tetrahedron Lett.* **1985**, *26*, 5615−5618. (b) Deardorff, D. R.; Myles, D. C. *Organic Synthesis*; Wiley & Sons: New York, 1993; Collect. Vol. 8, pp 13−19.
(29) Trost, B. M.; Ito, N.; Greenspan, P. D. *Tetrahedron Lett.* **1993**, *34*, 1421−1424.

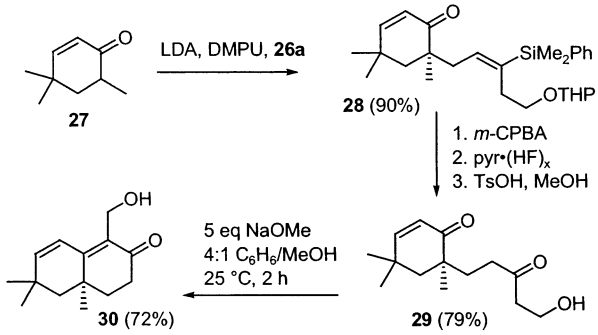
SCHEME 7



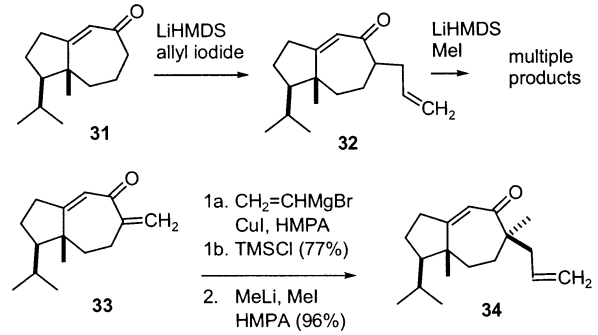
SCHEME 8



SCHEME 9



SCHEME 10



nulation procedure[30] for the annulation of 2-hydroxymethyl-2-cylohexenones onto cycloalkenones.[2b] Addition of phenyldimethylsilylcuprate[31] to propargylic alcohol **24a**[32] gave 76% of the desired phenyldimethylsilyl allylic alcohol **25a** and only 1−2% of the regioisomer (see Scheme 8). CuCN-catalyzed addition of $PhMe_2SiLi$•Et_2Zn as described by Oshima[33] gave 94% of a difficultly separable 84:16 mixture of **25a** and the regioisomer. Formation of the mesylate of **25a** with MsCl and Et_3N and displacement with NaI in acetone at 45 °C provided 82% of the desired functionalized dimethylphenylsilyl allylic iodide **26a**.

Alkylation of the enolate of **27** with **26a** provided 90% of **28**, which was epoxidized with *m*-CPBA (see Scheme 9). Protodesilylation of the crude epoxide and cleavage of the THP group with pyr•$(HF)_x$ and TsOH gave 79% of hydroxy dione **29**. Aldol reaction and dehydration was most effectively carried out with 5 equiv of NaOMe in 4:1 benzene/MeOH to give 72% of hydroxy dienone **30**.[2b] These conditions minimize the formation of byproducts.[2b] This procedure introduces the required functionality and was particularly appealing since the alkylation of **23** with methyl iodide and **26a** can be carried out in either order, increasing the likelihood that we could introduce the correct stereochemistry at the ring fusion carbon.

While this work was in progress, Danishefsky reported studies on the alkylation of the related hydroazulenone **31** (see Scheme 10).[3b] Allylation of **31** proceeded cleanly at the α′-position to give **32**, but a second alkylation with MeI was frustrated by difficulties in generating the α′-enolate of **32**. The desired product **34** was finally obtained as a single stereoisomer by a longer route involving addition of vinylmagnesium bromide and CuI to **33**, trapping the enolate as the TMS enol ether (77%), regeneration of the enolate with MeLi, and alkylation with MeI and HMPA (96%). These results indicate that the second alkylation occurs from the bottom face so that our first alkylation should be carried out with **26a** and our second alkylation with MeI. We were optimistic that we would not have the same problems with the second enolization because of the oxygen substituent at the γ-position of **23**.

Alkylation of the enolate of THP-protected hydroazulenone **23a** with **26a** (see Scheme 11) afforded 90% of **35aa**, but methylation of the enolate of **35aa** gave a 1:1 mixture of **36aa** and **37aa**, which was formed by enolization at the γ-position, methylation in the α-position, and reconjugation of the β,γ-unsaturated ketone. We were very disappointed to find that the tetrahydropyranyloxy group did not prevent enolization at the γ-position. We thought that changing the protecting group to a TBS ether might give better regioselectivity, since the OTHP might be coordinating to the lithium atom of LDA and directing enolization to the γ-position.[34]

We were delighted to find that alkylation of the enolate of **23b** with **26a** provided 94% of **35ba** and that methylation of the enolate of **35ba** now gave ∼90% of the desired product **36ba** as a single stereoisomer contaminated with less than 5% of regioisomer **37ba**. The stereochemistry at the newly formed quaternary center of **36ba** was tentatively assumed by analogy to **34**.

We thought that if one OTBS protecting group is good, two might be better. We therefore prepared **26b** analo-

(30) (a) Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682−3684. (b) Stork, G.; Jung, M. E.; Colvin, E.; Noel, Y. *J. Am. Chem. Soc.* **1974**, *96*, 3684−3686.

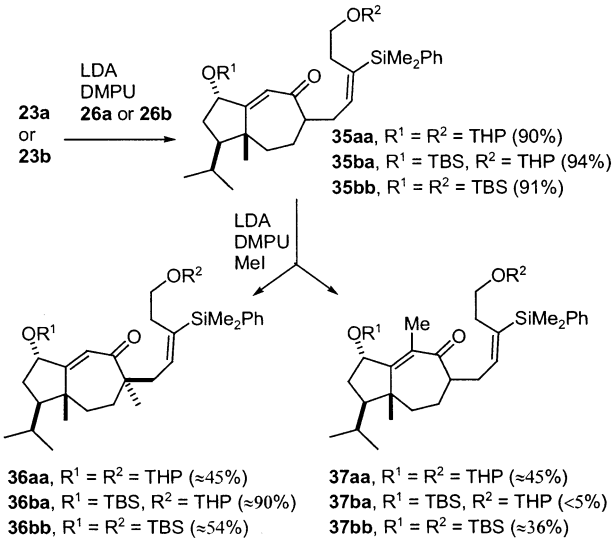
(31) Betzer, J.-F.; Pancrazi, A. *Synlett* **1998**, 1129−1131.

(32) Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S.; Kageyama, M.; Tamura, T. *J. Org. Chem.* **1989**, *54*, 2817−2825.

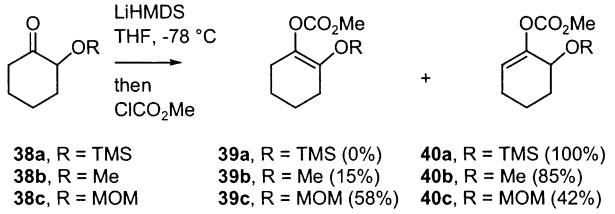
(33) Wakamatsu, K.; Nonaka, T.; Okuda, Y.; Tückmantel, W.; Oshima, K.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1986**, *42*, 4427−4436.

(34) (a) Paquette, L. A.; O'Neil, S. V.; Guillo, N.; Zeng, Q.; Young, D. G. *Synlett.* **1999**, 1857−1866 and **2000**, 428.

SCHEME 11



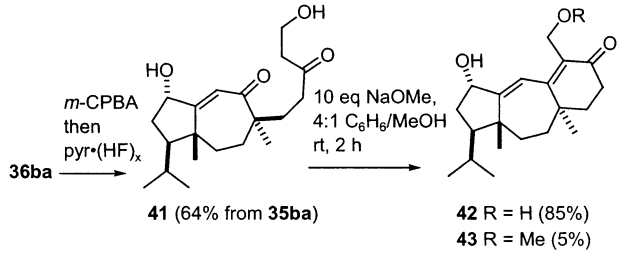
SCHEME 12



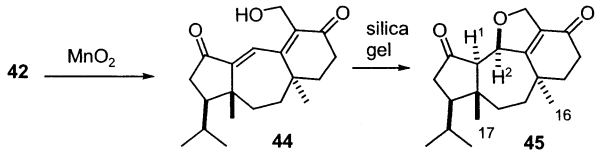
gously to **26a** from **24b**,[35] as shown in Scheme 8. Alkylation of **23b** with **26b** provided 91% of **35bb**. However, methylation of the enolate of **35bb** afforded a 6:4 mixture of **36bb** and **37bb**. *Therefore, the choice of both protecting groups is crucial for the successful* α′*-alkylation of* **35ba**. The OTBS on the cyclopentane retards enolization at the γ-position. The OTHP group on the side chain may facilitate enolization at the α′-position by coordination to the lithium. Use of 1.6 equiv of LDA decreased the regioselectivity in the methylation of **35ba**, giving more than 15% of **37ba**. Uncoordinated LDA may enolize **35ba** less regioselectively, competing with the OTHP-coordinated LDA that selectively enolizes at the α′-position.

We briefly examined the ability of an acetal to direct enolization in a simpler system (see Scheme 12). Hanessian reported that enolization of 2-trimethylsilyloxycyclohexanone (**38a**) with LiHMDS and trapping with methyl chloroformate gave exclusively enol carbonate **40a**.[36] A similar reaction with 2-methoxycyclohexanone (**38b**) afforded an 85:15 mixture of **40b** and **39b**. We prepared 2-(methoxymethoxy)cyclohexanone (**38c**) by Dess−Martin oxidation of the alcohol[37] with the expectation that the MOM ether would help direct enolization toward the oxygen-substituted carbon. Enolization and trapping under Hanessian's conditions gave a 42:58 mixture of **40c** and **39c**. The MOM ether does direct enolization to the oxygen-substituted carbon to give **39c**

SCHEME 13



SCHEME 14



(58%), but enolization at the methylene group to give **40c** (42%) is still significant. However, enolization of **38c** with LDA in THF at −78 °C afforded an 88:12 mixture of **40c** and **39c**, indicating the choice of base has a major effect on the regioselectivity of the enolization. Similar ratios of products were formed using TMSCl to trap the enolates.

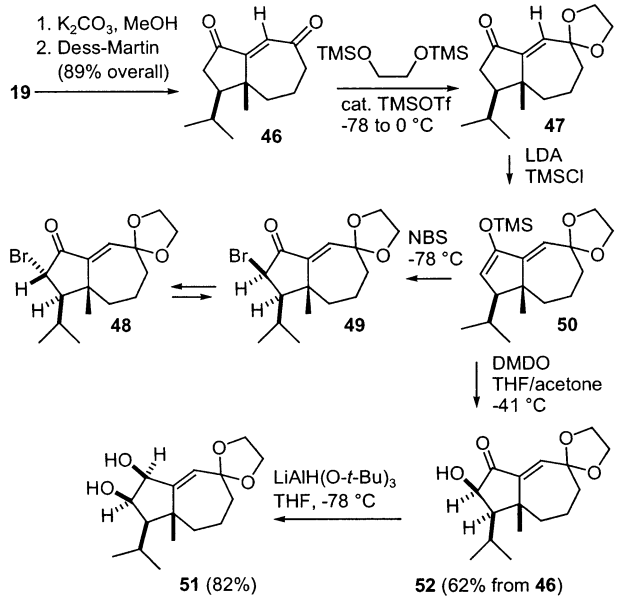
Epoxidation of the vinylsilane of **36ba** and protodesilylation with pyr•$(HF)_x$ formed the ketone and hydrolyzed the THP and TBS groups to give diketone diol **41** in 64% overall yield from **35ba** (see Scheme 13). Cyclization of **41** with 10 equiv of NaOMe in 4:1 mixture of benzene/MeOH provided 85% of the tricyclic dihydroxy dienone **42** and only 5% of **43**. With the proper choice of protecting groups, this novel extension[2b] of the Stork−Jung vinylsilane Robinson annulation regio- and stereospecifically converted **23b** to **42**, which has the complete guanacastepene skeleton, in four steps and 51% overall yield!

Reduction of **42** gave a 4:1 mixture of triol isomers. On the basis of our model study,[2b] we expected that the major isomer was the undesired α-alcohol (see below). Since carrying out a Mitsunobu reaction on the free triol was problematic, we explored other approaches. Oxidation of **42** with MnO_2 at room temperature provided hydroxy dione **44** as the major product, 10−20% of the diketone aldehyde, and 5% of deacetoxy-*epi*-guanacastepene G (**45**) (see Scheme 14).[1c] Hydroxy dione **44** is unstable and cyclized partially in the presence of weak acids, such as silica gel or acetic acid, or weak bases to give a mixture of **44** and **45**. Stirring with silica gel in CH_2Cl_2 for 2 d gave what appears to be a 4:1 equilibrium mixture of **45** and **44**.

The stereochemistry of **45** was assigned on the basis of coupling constants and NOEs. The coupling constant between H_1 and H_2 in **45** is 4.9 Hz, which fits well with the value of 5.1 Hz calculated by MMX.[27] The calculated value for the guanacastepene G stereochemistry, in which H_1 is β, is 11 Hz; the published spectrum of guanacastepene G shows a large coupling constant.[1c] The calculated value for the isomer in which both H_1 and H_2 are β is 1.9 Hz. Strong NOEs between H_1 and both H_2 and Me_{16} confirmed the assignment. MMX calculations[27] suggest that **45** with a trans ring fusion is 1.1 kcal/mol more stable than the isomer with the cis ring fusion of

(35) Argenti, L.; Bellina, F.; Carpita, A.; Rossi, E.; Rossi, R. *Synth. Commun.* **1994**, *24*, 2281−2297.
(36) Hanessian, S.; Sakito, Y.; Dhanoa, D.; Baptistella, L. *Tetrahedron* **1989**, *45*, 6623−6630.
(37) Gras, J.-L.; Guérin, A. *C. R. Acad. Sci., Ser. 2* **1985**, *301*, 379−381.

SCHEME 15



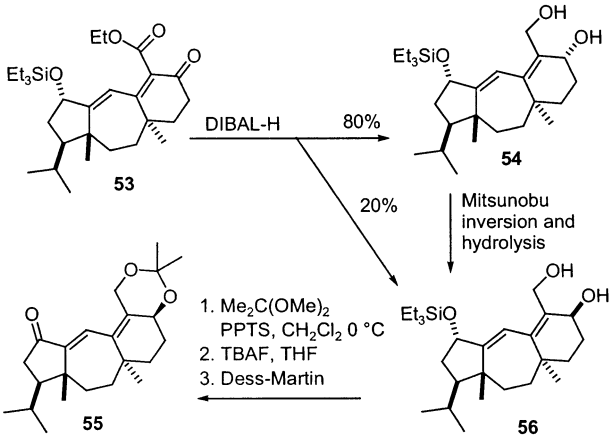
guanacastepene G. Therefore, either the acetoxy group of guanacastepene G perturbs the relative stability of the two isomers or guanacastepene G is formed by kinetically controlled protonation of the enol/enolate formed by addition of the alcohol to the enone. Sorensen has observed a similar cyclization on silica gel of an analogue lacking the isopropyl group to give a tetracyclic compound with guanacastepene G stereochemistry.[6]

We then examined functionalization of the cyclopentane before annulation of the cyclohexane ring. Hydrolysis of the acetate of **19** and Dess−Martin oxidation of the resulting diol gave diketone **46** in 89% yield (see Scheme 15). Selective protection of the cycloheptenone with 1 equiv of 1,2-bis(trimethylsilyloxy)ethane[38] and 5% of TMSOTf gave **47** as the only product. The alkene absorption at δ 6.51 is consistent with the β-H of an α,β-unsaturated ketone. Comparison of the IR spectrum of **47** (1724, 1651 cm^{-1}) with that of **46** (1727, 1673, 1634 cm^{-1}) indicated that a conjugated cyclopentanone is still present. The coupling patterns and chemical shifts of the protons adjacent to the cyclopentanone are similar in **46** and **47**.

Enolization of **47** with LDA and trapping with TMSCl gave **50** cleanly. We prepared the bromo cyclopentanone with the expectation that we would obtain the α-isomer, which could be converted to the desired β-acetate by nucleophilic substitution. Surprisingly, reaction of **50** with NBS in THF at −78 °C gave exclusively the unstable β-bromocyclopentanone **49**. Partial isomerization of **49** to **48** was observed in pyridine[39] or on silica gel. The vicinal coupling constant between the cyclopentane methine hydrogens is 6.7 Hz in **49** and 12.8 Hz in **48**, which is very close to 12.7 Hz reported by Tius for a similar α-bromocyclopentanone.[8]

Since bromination of **50** occurred from the apparently more hindered top face, we thought that hydroxylation of **50** should give the desired β-hydroxy cyclopentanone

SCHEME 16



52. Oxidation of **50** with DMDO[40] at −41 °C gave the epoxide, which was opened by washing with 5% KH_2PO_4/H_2O solution to give **52** in 62% overall yield from **46**. The coupling constant between the cyclopentane methine hydrogens is 6.1 Hz, which is comparable to those of a similar β-acetate reported by Mehta[5b] (6.3 Hz) and the two conformers of guanacastepene A (7.5 and 8.5 Hz).[1a] Mehta reported a 12.6 Hz coupling constant in a similar α-acetate.[5b] Reduction of **52** with LiAlH(O-*t*-Bu)$_3$ provided 82% of cis diol **51**.

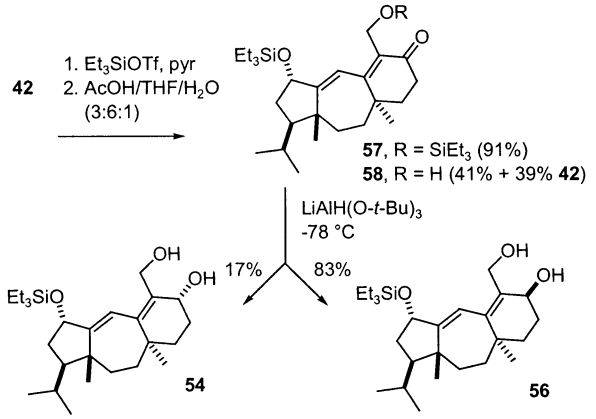
At this point in our investigations, Danishefsky and co-workers published the first total synthesis of guanacastepene A (see Scheme 16).[10] Triethylsilyloxy keto ester **53**, which is very similar to our keto diol **42**, was prepared from **34**. Reduction of both the ketone and ester groups gave a difficultly separable 4:1 mixture of **54** and **56**. The formation of α-alcohol **54** as the major isomer is consistent with our results on the reduction of model **30**.[2b] A Mitsunobu reaction and hydrolysis were employed to convert the major isomer **54** to the desired β-alcohol **56**. Protection of the diol of **56** as the acetonide, liberation of the alcohol, and Dess−Martin oxidation gave cyclopentanone **55**. Hydroxylation of the silyl enol ether prepared from **55** with DMDO occurred selectively from the β-face to introduce the hydroxy group with the desired stereochemistry. Acetylation, cleavage of the acetonide, and oxidation to the aldehyde completed the synthesis of **1**. The selective hydroxylation of the enol ether formed from **55** from the β-face is analogous to the selective bromination and hydroxylation of **50** from the β-face, although in neither case does examination of models predict this high degree of selectivity.

Since Danishefsky's conversion of **56** to guanacastepene A (**1**) is very efficient, we decided it would be appropriate to complete a formal synthesis of guanacastepene by elaboration of keto diol **42** to **54** and **56**. Protection of both alcohols of **42** gave 91% of bis TES ether **57** (see Scheme 17). Selective hydrolysis of the primary TES ether with 3:6:1 AcOH/THF/H_2O at room temperature for 3 h[41] gave 41% of the desired triethylsilyloxy keto alcohol **58** and 39% of the diol **42**, which

(38) Hwu, J. R.; Wetzel, J. M. *J. Org. Chem.* **1985**, *50*, 3948−3950.
(39) Hiroi, K.; Yamada, S. *Chem. Pharm. Bull.* **1973**, *21*, 54−61.

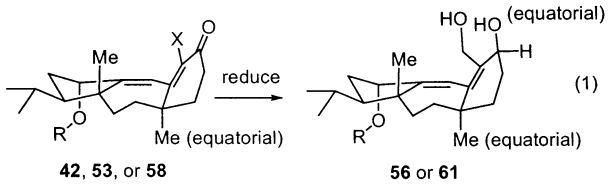
(40) (a) Adam, W.; Hadjiarapoglou, L.; Wang, X. *Tetrahedron Lett.* **1989**, *30*, 6497−6500. (b) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.
(41) Clive, D. L. J.; Bo, Y.; Tao, Y.; Daigneault, S.; Wu, Y.-J., Meignan, G. *J. Am. Chem. Soc.* **1998**, *120*, 10332−10349.

SCHEME 17



can be recycled. We were surprised and delighted to find that reduction of **58** with LiAlH(O-*t*-Bu)$_3$ in THF at −78 °C gave a 5:1 mixture of the desired β-alcohol **56** and the undesired α-alcohol **54**, whose spectra are identical to those of Danishefsky's intermediates.

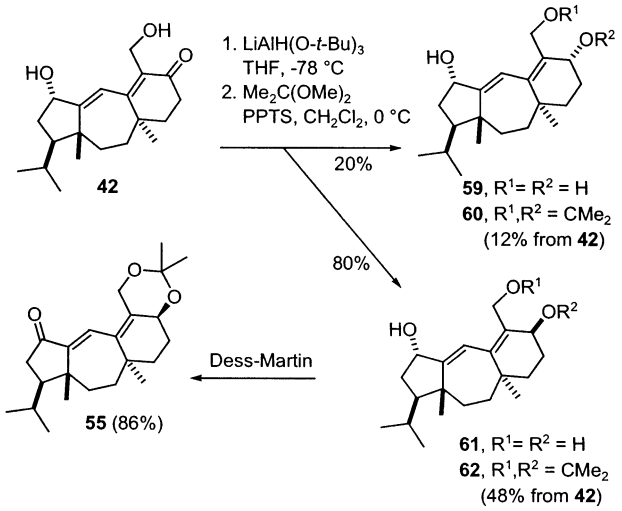
Reductions of keto ester **53** *and keto alcohol* **58** *both proceed with good selectivity, but in the opposite direction!* We do not have a good explanation for this, but note that there is no inherent contradiction, since the ketone of **53** is reduced before the ester so that these reactions are not proceeding through a common intermediate. The primary alcohol of **58** and ester of **53** clearly have very different directing effects on the reduction. We have previously noted very different stereoselectivities in the reductions of keto esters and keto alcohols in the synthesis of allocyathin B$_2$.[42] MMX calculations[27] indicate that the most stable conformation of both **53** and **58** has the cyclohexanone ring in a chair conformer with an equatorial methyl group and an axial cycloheptene ring (see eq 1). Therefore, the β-alcohol in the desired product



56 is equatorial, rather than axial. This conformation is accessible in **53** and **58** with a medium-sized ring fused to the cyclohexenone, but is not accessible in decalin **30**.

We do not need to carry out the Mitsunobu inversion, since reduction of **58** selectively gave the desired β-alcohol **56**. There is therefore no need to protect the cyclopentanol of **42**. Reduction of **42** with LiAlH(O-*t*-Bu)$_3$ in THF at −78 °C provided a difficultly separable 4:1 mixture of the desired β-alcohol **61** and α-alcohol **59** (see Scheme 18). L-Selectride was less selective, giving a 2:1 mixture. Protection of the 4:1 mixture as the acetonide with 2,2-dimethoxypropane and PPTS in CH_2Cl_2 at 0 °C afforded a readily separable mixture of **62** (48% from **42**) and **60** (12% from **42**). Dess−Martin oxidation of **62** yielded 86% of acetonide ketone **55**. The ^{1}H and ^{13}C NMR spectra of both **55** and **62** are identical to those of Danishefsky's

SCHEME 18



intermediates. This completes an efficient formal synthesis of guanacastepene A (**1**) in which protected ketone **55** was prepared in only seven steps from hydroazulenone **23b**. Hydroazulenone **23b** was made in eight steps from cyclopentanone **3**, which can be prepared in two steps from 2-methyl-2-cyclopentenone.

In conclusion, we have developed a short and efficient (17 steps, 4% overall yield) route to the key tricyclic acetonide ketone **55**, which should make guanacastepene A (**1**) more readily available for further study. Noteworthy features include the EtAlCl$_2$-induced stereospecific cyclization of ketone **6** to give cyclopentanone **3**, use of vinylmagnesium bromide in the Pd-catalyzed coupling with triflate **13** to give triene **16** without the formation of Heck products, a novel extension of the Stork−Jung vinylsilane Robinson annulation to prepare tricyclic 2-hydroxymethylcyclohexenone **42** in four steps and 51% yield, the ability to obtain almost exclusively α′-alkylation of **35ba** with the proper choice of protecting groups, and the ability to obtain the desired β-alcohol selectively by reduction of keto alcohol **42** rather than keto ester **53**.

Experimental Section

General Procedures. NMR spectra were recorded at 400 MHz in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in δ, coupling constants in hertz, and IR spectra in cm^{-1}.

5-Iodo-1-pentene (7). 5-Bromo-1-pentene (0.8 mL, 6.71 mmol) was added to a solution of NaI (2.0 g, 13.3 mmol) in acetone (22 mL). The reaction mixture was heated at 60 °C for 2 h. The mixture was cooled to room temperature, diluted with water (100 mL), and extracted with pentane. The pentane layers were combined, washed with brine, dried over Na_2SO_4, and concentrated to give 1.27 g (96%) of 5-iodo-1-pentene (**7**): ^{1}H NMR 5.75 (ddt, 1, J = 17.2, 10.4, 6.8), 5.08 (dd, 1, J = 17.2, 1.6), 5.02 (dd, 1, J = 10.4, 1.6), 3.19 (t, 2, J = 7.0), 2.17 (dt, 2, J = 6.8, 7.0), 1.91 (tt, 2, J = 7.0, 7.0).

2-Methyl-3-methylene-8-penten-4-ol (8). *t*-BuLi (8.25 mL, 14.03 mmol of a 1.7 M solution in pentane) was added dropwise to a solution of **7** (1.31 g, 6.68 mmol) in Et_2O (33.4 mL) at −78 °C. The reaction mixture was stirred for 5 min at −78 °C and then warmed to room temperature for 1 h. The resulting solution was added dropwise to a solution of 2-isopropylacrolein[13] (662 mg, 6.35 mmol) in Et_2O (20 mL) at −78 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was quenched with saturated

(42) Snider, B. B.; Vo, N. H.; O'Neil, S. V. *J. Org. Chem.* **1998**, *63*, 4732−4740.

NH_4Cl solution and extracted with Et_2O. The Et_2O extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated, providing 961 mg (89%) of alcohol **8** that was used without further purification. An analytical sample was prepared by flash chromatography on silica gel (80:1 hexanes/EtOAc): ^{1}H NMR 5.78 (ddt, 1, J = 17.2, 10.4, 6.8), 5.01 (s, 1), 4.94 (dd, 1, J = 17.2, 2.0), 4.93 (dd, 1, J = 10.4, 2.0), 4.80 (s, 1), 4.09−4.05 (m, 1), 2.24 (qq, 1, J = 6.8, 6.8), 2.11−2.01 (m, 2), 1.67−1.35 (m, 4), 1.06 (d, 3, J = 6.8), 1.03 (d, 3, J = 6.8); ^{13}C NMR 159.2, 138.7, 114.6, 106.9, 74.3, 35.6, 33.6, 30.2, 25.1, 23.2, 22.7; HRMS (CI/CH_4/NH_3) calcd for $C_{11}H_{22}N$ [(M + NH_4 − H_2O)$^+$] 168.1752, found 168.1744.

2-Methyl-3-methylene-8-penten-4-yl Acetoacetate (9). Diketene (0.5 mL, 6.51 mmol) was added to a solution of **8** (961 mg, 5.71 mmol) and DMAP (6 mg, 0.051 mmol) in Et_2O (19 mL) at −15 °C. The solution was warmed to room temperature and stirred overnight. The mixture was washed with 0.01 M NaOH until the dark orange color of the Et_2O layer was removed, resulting in a pale yellow Et_2O layer. The Et_2O layer was washed with brine, dried over Na_2SO_4, and concentrated to give 1.32 g (92%) of **9** as an orange oil that was used without further purification: ^{1}H NMR 5.75 (ddt, 1, J = 17.2, 10.4, 6.8), 5.23 (t, 1, J = 6.4), 4.99 (s, 1), 4.98 (dd, 1, J = 17.2, 2.0), 4.96 (dd, 1, J = 10.4, 2.0), 4.93 (s, 1), 3.43 (s, 2), 2.24 (s, 3), 2.26−2.21 (m,1), 2.07−2.01 (m, 2), 1.67−1.61 (m, 2), 1.40−1.33 (m, 2), 1.06 (d, 3, J = 6.8), 1.03 (d, 3, J = 6.8).

5-(1-Methylethyl)-5*E*,10-undecadien-2-one (6). *n*-BuLi (21.14 mL, 0.053 mol) was added to (*i*-Pr)$_2$NH (7.85 mL, 0.056 mol) in THF (53.0 mL) at 0 °C. The resulting solution was stirred for 30 min and then cooled to −78 °C. Acetoacetate **9** (4.44 g, 0.018 mol) in THF (20 mL) was added dropwise to the LDA solution at −78 °C. The reaction mixture was warmed to room temperature and stirred for 4 h, heated at reflux for 1 h, cooled to room temperature, concentrated *without heating*, and taken up in water. The water layer was then washed with Et_2O. The Et_2O layer was further washed with 0.01 M NaOH. The combined aqueous layers were diluted with CH_2Cl_2. Then, 1 M HCl was added slowly to this H_2O/CH_2Cl_2 mixture with rapid stirring. Upon complete acidification, the two layers separated. The CH_2Cl_2 layer was separated and the water layer was further extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with brine, dried over Na_2SO_4, and concentrated *without heating*. The residue was dissolved in toluene (20 mL) and heated at 80 °C for 1 h. The solution was concentrated and purified by flash chromatography on silica gel (80:1 hexanes/EtOAc) to give 2.25 g (60% from 2-isopropylacrolein) of **6**: ^{1}H NMR 5.78 (ddt, 1, J = 17.2, 10.4, 6.8), 5.00−4.98 (m, 1), 4.96−4.91 (m, 2), 2.81 (sp, 1, J = 6.8), 2.52 (t, 2, J = 8.0), 2.18 (t, 2, J = 8.0), 2.13 (s, 3), 2.05−1.97 (m, 4), 1.42−1.35 (m, 2), 0.95 (d, 6, J = 6.8); ^{13}C NMR 208.7, 143.1, 138.8, 112.9, 114.3, 43.1, 33.3, 29.8, 29.3, 28.3, 26.6, 24.5, 21.0 (2); HRMS (DEI) calcd for $C_{14}H_{25}O$ (MH^+) 209.1954, found 209.1896.

(2α,3*β*)-2-Methyl-3-(1-methylethyl)-2-(4-pentenyl)cyclopentanone (3). A solution of **6** (272 mg, 1.31 mmol) in dry CH_2Cl_2 (26.2 mL) was cooled to 0 °C and evacuated under vacuum for 1−2 min and then purged with N_2. $EtAlCl_2$ (1.97 mL, 1.97 mmol, 1 M in heptane) was added dropwise to the solution of **6** at 0 °C. The mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for 24 h. The reaction mixture was then poured into ice water and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were combined washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel deactivated with 1% water (80:1 hexanes/EtOAc) gave 185 mg (69%) of **3**: ^{1}H NMR 5.76 (ddt, 1, J = 17.2, 10.4, 6.8), 4.99 (dd, 1, J = 17.2, 1.2), 4.94 (dd, 1, J = 10.4, 1.2), 2.39−2.31 (m, 1), 2.09−1.96 (m, 4), 1.82−1.64 (m, 3), 1.51−1.36 (m, 3), 1.10−1.00 (m, 1), 1.01 (d, 3, J = 6.8), 0.94 (d, 3, J = 6.8), 0.89 (s, 3); ^{13}C NMR 224.4, 138.5, 114.6, 52.0, 48.3, 37.7, 37.1, 34.2, 29.4, 24.3, 23.6, 22.1, 21.4, 18.3; IR (neat) 2933, 2871, 1738; HRMS (DEI) calcd for $C_{14}H_{25}O$ (MH^+) 209.1905, found 209.1910.

(4α,5*β*)-5-Methyl-4-(1-methylethyl)-5-(4-pentenyl)-1-cyclopenten-1-yl Trifluoromethanesulfonate (13). Tf_2O (4.208 mL, 25 mmol) was added to a mixture of **3** (4.165 g, 20 mmol), Proton Sponge (6.856 g, 32 mmol), and dry CH_2Cl_2 (50 mL) under N_2 at −78 °C. The cold bath was then removed and the mixture was stirred for 3 h while it slowly warmed up to room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution in water (10 mL). Most of the CH_2Cl_2 in the mixture was removed under reduced pressure and the residue was poured into brine (160 mL), which was extracted five times with hexanes. The organic layers were combined, dried over Na_2SO_4, and concentrated to give 7.45 g of crude **13**. Flash chromatography on 75 g of silica gel deactivated with 1% water (hexanes) gave 5.850 g (86%) of unstable **13** as a colorless liquid: ^{1}H NMR 5.79 (ddt, 1, J = 17.2, 10.4, 6.8), 5.56 (t, 1, J = 3.2), 5.02 (dd, 1, J = 17.2, 1.2), 4.97 (dd, 1, J = 10.4, 1.2), 2.38 (ddd, 1, J = 15.2, 8.0, 3.2), 2.07−1.98 (m, 3), 1.90−1.84 (m, 1), 1.77−1.68 (m, 1), 1.54−1.45 (m, 2), 1.27−1.20 (m, 2), 1.05 (s, 3), 0.97 (d, 3, J = 6.8), 0.89 (d, 3, J = 6.8); ^{13}C NMR 153.7, 138.4, 118.5 (q, 1, J_{C-F} = 319), 114.7, 111.9, 48.6, 48.0, 36.5, 34.0, 30.9, 29.2, 23.9, 22.2, 21.4, 18.9; IR (neat) 2957, 2871, 1737.

(4α,5*β*)-1-Ethenyl-5-methyl-4-(1-methylethyl)-5-(4-pentenyl)-1-cyclopentene (16). Vinylmagnesium bromide (26 mL, 26 mmol, 1 M in THF) was added to a solution of **13** (4.420 g, 13 mmol) in dry THF (10 mL) under N_2 at 0 °C. A premixed solution of Pd_2dba_3 (239 mg, 0.26 mmol) and tri(*o*-furyl)-phosphine (242 mg, 1.04 mmol) in dry THF (5 mL) was added via syringe dropwise. The solution turned blue-purple and was stirred for 20 min while it slowly warmed up to room temperature. An additional portion of catalyst may be needed, depending on the quality of the Grignard reagent. The mixture was cooled to 0 °C, quenched with water, and extracted three times with pentane. The organic layers were combined, dried over Na_2SO_4, and concentrated to give 3.25 g of an 84:16 crude mixture of **16** and **17a**. Flash chromatography on 80 g of silica gel impregnated with 20% of $AgNO_3$ (49:1 then 19:1 hexanes/Et_2O) gave 2.156 g (76%) of pure triene **16** as a colorless liquid and (9:1 hexanes/Et_2O) 392 mg (14%) of 90% pure diene **17a**.

Data for **16**: ^{1}H NMR 6.12 (dd, 1, J = 17.7, 11.6), 5.79 (ddt, 1, J = 17.1, 10.4, 6.7), 5.73 (t, 1, J = 3.1), 5.38 (d, 1, J = 17.7), 5.02−4.90 (m, 3), 2.33 (ddd, 1, J = 16.5, 7.9, 3.1), 2.04−1.93 (m, 3), 1.83 (ddd, 1, J = 8.8, 8.8, 8.8), 1.77−1.67 (m, 1), 1.61−1.48 (m, 2), 1.48−1.37 (m, 1), 1.21−1.10 (m, 1), 0.98 (d, 3, J = 6.1), 0.97 (s, 3), 0.89 (d, 3, J = 6.1); ^{13}C NMR 149.2, 139.2, 131.9, 126.2, 114.2, 113.5, 50.9, 50.1, 37.9, 35.0, 34.5, 29.3, 24.0, 22.8, 22.5, 20.6.

Data for **17a**: ^{1}H NMR 5.81 (ddt, 1, J = 17.1, 10.4, 6.7), 5.56 (ddd, 1, J = 5.8, 2.5, 2.5), 5.47 (ddd, 1, J = 5.8, 2.4, 1.2), 4.99 (br d, 1, J = 17.1), 4.93 (br d, 1, J = 10.4), 2.36 (dddd, 1, J = 16.6, 8.0, 2.8, 1.2), 2.09−1.96 (m, 3), 1.74−1.56 (m, 2), 1.51−1.38 (m, 3), 1.38−1.27 (m, 1), 0.97 (d, 3, J = 6.7), 0.89 (s, 3), 0.89 (d, 3, J = 6.7); ^{13}C NMR 141.5, 139.1, 127.0, 114.2, 52.2, 49.4, 41.0, 37.1, 34.6, 29.5, 24.7, 22.83, 22.79, 20.5; IR (neat) 1641, 910, 736; HRMS (EI) calcd for $C_{14}H_{24}$ (M^+) 192.1878, found, 192.1877.

The alkene region of the crude ^{1}H NMR spectrum of a reaction quenched with D_2O was the same, except that the signal at δ 5.47 was missing and the 5.8 Hz coupling constant of the signal at δ 5.56 was replaced with a 1 Hz coupling to deuterium as a 1:1:1 triplet, indicating the presence of **17b**.

(1α,8aα)-1,2,6,7,8,8a-Hexahydro-8a-methyl-1-(1-methylethyl)azulene (15). A solution of bis(tricyclohexylphosphine)-benzylidineruthenium(IV) dichloride (Grubbs' catalyst) (222 mg, 0.27 mmol) in dry CH_2Cl_2 (4 mL) was added to **16** (1.965 g, 9.0 mmol) in dry CH_2Cl_2 (90 mL) under N_2 at 40 °C. The reaction was monitored using 20% impregnated $AgNO_3$ silica gel TLC plates (20:1 hexanes/Et_2O). The solution was stirred at 40 °C for 1 d. Another portion (222 mg, 0.27 mmol) of catalyst was added and stirring was continued for 2 d. When TLC showed that only a slight amount of starting material was left, the reaction mixture was carefully concentrated and

purified using flash chromatography on 40 g of silica gel deactivated with 1% water (pentane) to give 1.59 g (88%) of 95% pure **15** (contaminated with 5% styrene formed from Grubbs' catalyst) as a colorless liquid: ^{1}H NMR 6.03 (br d, 1, J = 12.0), 5.54 (ddd, 1, J = 12.0, 6.2, 3.2), 5.45 (br s, 1), 2.42−2.30 (m, 2), 2.20−2.08 (m, 1), 2.08−1.98 (m, 2), 1.82−1.56 (m, 4), 1.56−1.44 (m, 1), 1.01 (d, 3, J = 6.4), 0.96 (s, 3), 0.92 (d, 3, J = 6.4); ^{13}C NMR 152.0, 129.4, 127.6, 125.5, 58.6, 50.5, 41.3, 35.7, 31.9, 29.3, 23.5, 22.9, 22.0, 18.6.

(1α,3*β*,3a*β*,8aα)-3,3a-Epoxy-1,2,3,3a,6,7,8,8a-octahydro-8a-methyl-1-(1-methylethyl)azulene (18). *m*-CPBA (77%, 1.698 g, 7.6 mmol) was added to a biphasic mixture of **15** (95% pure, 1.59 g, ∼8 mmol) in CH_2Cl_2 (10 mL), and saturated aqueous sodium bicarbonate (10 mL) at 0 °C. The heterogeneous mixture was stirred vigorously for 30 min and then quenched with saturated Na_2SO_3 solution in H_2O (2 mL). The mixture was stirred for another 30 min while slowly warming up to room temperature. The CH_2Cl_2 layer was separated and the aqueous layer was extracted two more times with CH_2Cl_2. The CH_2Cl_2 layers were combined and washed with saturated $NaHCO_3$ solution in H_2O (5 mL) and then brine (5 mL). The CH_2Cl_2 solution was dried over Na_2SO_4 and concentrated to give 1.65 g of crude epoxide **18** that was carried on without purification: ^{1}H NMR 6.13 (ddd, 1, J = 10.8, 5.5, 5.5), 5.53 (d, 1, J = 10.8), 3.29 (s, 1), 2.42−2.32 (m, 1), 2.27−2.16 (m, 1), 2.10 (dd, 1, J = 13.4, 6.7), 1.87−1.76 (m, 3), 1.76−1.66 (m, 1), 1.56−1.46 (m, 1), 1.40−1.33 (m, 1), 1.30−1.25 (m, 1), 0.94 (s, 3), 0.92 (d, 3, J = 6.7), 0.86 (d, 3, J = 6.7); ^{13}C NMR 139.9, 125.4, 69.7, 62.9, 52.1, 44.4, 39.9, 32.2, 30.1, 29.2, 24.2, 23.0, 22.6, 18.0.

(1*β*,3α,3aα,7*β*)-7-Acetoxy-1,2,3,3a,4,5,6,7-octahydro-3a-methyl-3-(1-methylethyl)azulen-1-ol (19). Epoxide **18** (1.65 g, ∼8 mmol) in dry THF (15 mL) was added to a premixed solution of Pd_2dba_3 (366 mg, 0.40 mmol), dppb (375 mg, 0.88 mmol), and AcOH (412 μL, 7.2 mmol) in dry THF (15 mL) under N_2 at room temperature. The solution was stirred overnight and TLC showed that only a slight amount of starting material was left. The mixture was concentrated and purified by flash chromatography on silica gel. Elution with 19:1 hexanes/EtOAc gave impure **21**. Elution with 9:1 and then 4:1 hexanes/EtOAc gave 1.218 g (51%, 3 steps from **16**) of pure **19** as a colorless oil: ^{1}H NMR 5.70 (br s, 1, $W_{1/2}$ = 6), 5.55 (ddd, 1, J = 11.6, 2.4, 2.4), 4.32 (d, 1, J = 4.9), 2.06 (s, 3), 2.02 (ddd, 1, J = 14.5, 5.5, 2.4), 1.95−1.87 (m, 2), 1.87−1.75 (m, 3), 1.65 (qqd, 1, J = 6.7, 6.7, 6.7), 1.58−1.47 (m, 2), 1.45 (br, 1, OH), 1.34 (ddd, 1, J = 13.4, 13.4, 3.1), 0.98 (d, 3, J = 6.7), 0.96 (s, 3), 0.91 (d, 3, J = 6.7); ^{13}C NMR 170.3, 157.3, 129.2, 74.3, 73.1, 55.0, 47.4, 39.5, 36.2, 34.0, 27.6, 24.0, 22.3, 22.0, 21.3, 16.6; IR (neat) 3520−3400, 1737, 1246; HRMS (DCI NH_3/CI) calcd for $C_{16}H_{30}NO_3$ (MNH_4^+) 284.2226, found 284.2233.

Data for **21**: ^{1}H NMR 5.91−5.87 (m, 1), 5.86 (d, 1, J = 11.6), 5.82 (d, 1, J = 11.6), 4.46 (d, J = 4.9), 2.42−2.36 (m, 2), 2.06 (ddd, 1, J = 13.4, 4.3, 4.3), 1.92 (dd, 1, J = 12.5, 5.2), 1.82−1.64 (m, 3), 1.56 (br, 1, OH), 1.45 (ddd, 1, J = 13.4, 11.3, 6.1), 1.02 (d, J = 6.1), 0.94 (d, 3, J = 6.7), 0.83 (s, 3).

(1*β*,3α,3aα,7*β*)-7-Acetoxy-1,2,3,3a,4,5,6,7-octahydro-3a-methyl-3-(1-methylethyl)-1-(*tert*-butyldimethylsilyloxy)-azulene (22b). DMF (0.8 mL, 2.0 mmol) was added to a mixture of **19** (1.332 g, 5.0 mmol), TBSCl (0.829 g, 5.5 mmol), and imidazole (0.749 g, 11 mmol) under N_2 at room temperature. The mixture was stirred overnight and water was added. The mixture was extracted three times with hexanes. The organic layers were combined and concentrated to give 1.956 g of crude **22b** that was carried on without further purification. An analytical sample was prepared by flash chromatography on silica gel (49:1 hexanes/EtOAc) to give pure **22b** as a colorless oil: ^{1}H NMR 5.55 (ddd, 1, J = 11.6, 3.1, 2.4), 5.49 (br s, 1), 4.25 (d, 1, J = 4.9), 2.02 (s, 3), 1.95−1.83 (m, 3), 1.83−1.72 (m, 2), 1.69 (dd, 1, J = 12.5, 5.8), 1.62 (qqd, 1, J = 6.7, 6.7, 6.7), 1.54 (ddd, 1, J = 12.2, 12.2, 2.4), 1.45 (ddd, 1, J = 12.8, 12.8, 4.9), 1.35 (ddd, 1, J = 13.4, 13.4, 2.4), 0.96 (d, 3, J = 6.7), 0.96 (s, 3), 0.88 (d, 3, J = 6.7), 0.88 (s, 9), 0.064 (s, 3), 0.060 (s, 3); ^{13}C NMR 170.5, 156.1, 127.8, 74.4, 73.2, 54.8, 46.8, 39.1, 37.5, 33.9, 27.7, 25.8 (3 C), 24.0, 22.4, 22.2, 21.4, 18.0, 16.8, −4.1, −4.5; IR (neat) 1740, 1246, 1064; HRMS (DCI/NH_3) calcd for $C_{22}H_{44}NO_3Si$ (MNH_4^+) 398.3090, found 398.3079.

(1*β*,3α,3aα,7*β*)-1,2,3,3a,4,5,6,7-octahydro-3a-methyl-3-(1-methylethyl)-1-(*tert*-butyldimethylsilyloxy)azulene-7-ol. K_2CO_3 (1.382 g, 10 mmol) and $NaHCO_3$ (0.835 g, 10 mmol) were added to a solution of crude **22b** (1.956 g, from 5 mmol of **19**) in MeOH (10 mL). The mixture was stirred at room temperature for 2 h and then concentrated to remove the MeOH. Saturated NH_4Cl solution in water was added until the pH = 8. The mixture was extracted three times with diethyl ether. The organic layers were combined, dried over Na_2SO_4, and concentrated to give 1.709 g of the crude alcohol that was carried on without further purification. An analytical sample was prepared by flash chromatography on silica gel (19:1 hexanes/EtOAc) to give the pure alcohol as a white solid: mp 86−87 °C; ^{1}H NMR 5.60 (br s, 1), 4.55 (dddd, 1, J = 11.6, 5.0, 2.4, 2.4), 4.25 (d, 1, J = 4.9), 1.92−1.84 (m, 2), 1.84−1.73 (m, 3), 1.69 (dd, 1, J = 12.8, 5.5), 1.61 (qqd, 1, J = 6.7, 6.7, 6.7), 1.54 (d, 1, J = 5.0, OH), 1.53 (ddd, 1, J = 11.6, 11.6, 3.0), 1.45 (ddd, 1, J = 12.8, 12.8, 4.9), 1.34 (ddd, 1, J = 13.4, 12.8, 3.0), 0.96 (d, 3, J = 6.7), 0.91 (s, 3), 0.88 (d, 3, J = 6.7), 0.88 (s, 9), 0.072 (s, 3), 0.066 (s, 3); ^{13}C NMR 155.1, 131.9, 74.4, 70.7, 54.8, 46.8, 39.2, 38.1, 37.5, 27.7, 25.8 (3 C), 24.0, 22.40, 22.39, 18.0, 16.7, −4.1, −4.5; IR (neat) 3500−3200, 1664; HRMS (DCI/NH_3) calcd for $C_{20}H_{42}NO_2Si$ (MNH_4^+) 356.2985, found 356.2998.

(1*β*,3α,3aα)-1,2,3,4,5-Hexahydro-3a-methyl-3-(1-methylethyl)-1-(*tert*-butyldimethylsilyloxy)-7(6*H*)-azuleneone (23b). To a solution of the above crude alcohol (1.709 g, from 5.0 mmol of **19**) in CH_2Cl_2 (10 mL) was added pyridine (1.35 mL, 15.0 mmol) under N_2 at 0 °C. A solution of Dess−Martin reagent (2.332 g, 5.5 mmol) in CH_2Cl_2 (10 mL) was then added via syringe. The mixture was stirred for 20 min while slowly warming up to room temperature. Sodium thiosulfate solution (10% in water) was added and the mixture was stirred for additional 30 min until the layers appeared clear. The layers were separated, and the water layer was extracted two times with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated to give 1.895 g of crude **23b**. Flash chromatography on silica gel (49:1 then 30:1 hexane/Et_2O) gave 1.515 g (90%, three steps from **19**) of pure **23b** as a colorless oil: ^{1}H NMR 5.91 (d, 1, J = 1.2), 4.56 (br dd, 1, J = 11.6, 4.9), 2.67 (ddd, 1, J = 15.9, 7.6, 4.3), 2.55 (ddd, 1, J = 15.9, 8.5, 4.9), 2.08 (ddd, 1, J = 13.7, 7.3, 2.7), 1.99−1.87 (m, 1), 1.88−1.70 (m, 5), 1.67 (qqd, 1, J = 6.7, 6.7, 6.7), 1.06 (s, 3), 0.99 (d, 3, J = 6.7), 0.91 (d, 3, J = 6.7), 0.90 (s, 9), 0.09 (s, 6); ^{13}C NMR 205.0, 170.6, 124.0, 73.3, 54.4, 48.9, 44.4, 39.5, 36.6, 28.4, 25.8 (3 C), 23.7, 21.9, 21.6, 20.2, 18.1, −4.6, −4.7; IR (neat) 1670; HRMS (DCI NH_3/CI) calcd for $C_{20}H_{37}O_2Si$ (MH^+) 337.2563, found 337.2572.

(2*E*)-3-(Dimethylphenylsilyl)-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]penten-1-ol (25a). To a suspension of 788 mg (8.8 mmol) of CuCN in 4 mL of dry THF under N_2 at −78 °C was added 17.6 mL (17.6 mmol) of 1 M $LiSi(Me)_2Ph$[43] in THF. The mixture was stirred at 0 °C for 30 min and cooled to −78 °C. A solution of 736 mg (4 mmol) of 5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2-pentyn-1-ol (**24a**)[32] in 4 mL of dry THF was added dropwise. The mixture was warmed to −20 °C and stirred overnight. Brine (20 mL) was added slowly and 10 mL of EtOAc was added. The mixture was stirred vigorously for about 1 h until the organic layer became clear. The aqueous layer was extracted three times with 10 mL of EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated to give 3.244 g of crude **25a**. Flash chromatography on silica gel (20:1, then 10:1 hexanes/EtOAc) gave 56 mg (4%) of a 3:1 mixture of **25a** and the regioisomer, followed by 972 mg (76%) of pure **25a** as a colorless oil: ^{1}H NMR 7.53−7.49 (m, 2), 7.36−

(43) Trost, B. M.; Tour, J. M. *J. Org. Chem.* **1989**, *54*, 484−486.

7.31 (m, 3), 6.29 (dd, 1, J = 6.7, 6.7), 4.36 (dd, 1, J = 3.4, 3.4), 4.25−4.13 (m, 2), 3.71 (ddd, 1, J = 11.0, 8.5, 3.1), 3.62 (ddd, 1, J = 9.8, 6.1, 6.1), 3.42 (ddd, 1, J = 11.0, 4.6, 4.6), 3.15 (ddd, 1, J = 9.8, 7.3, 5.5), 2.75 (dd, 1, J = 5.8, 5.8, OH), 2.60−2.44 (m, 2), 1.80−1.60 (m, 2), 1.49−1.44 (m, 4), 0.40 (s, 3), 0.39 (s, 3); ^{13}C NMR 142.4, 139.9, 138.0, 133.9 (2 C), 129.1, 127.8 (2 C), 98.8, 66.0, 62.0, 58.3, 30.1, 29.8, 25.2, 19.3, −2.8, −3.1; IR (neat) 3600−3300, 1616, 1029; HRMS (DEI) calcd for $C_{18}H_{29}O_3Si$ (MH^+) 321.1886, found 321.1872.

(2*E*)-1-Iodo-3-(dimethylphenylsilyl)-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]pentene (26a). To pure **25a** (641 mg, 2.0 mmol) in 4 mL of dry CH_2Cl_2 under N_2 at 0 °C was added 0.558 mL (4.0 mmol) of Et_3N and 168 μL (2.2 mmol) of MsCl. The mixture was stirred at 0 °C for 15 min. Water and citric acid were added until the pH was 3−4, and the aqueous layer was separated and discarded. The organic layer was washed with water three times, dried over Na_2SO_4, and concentrated to give 851 mg of crude mesylate.

The crude mesylate was dissolved in 8 mL of dry acetone under N_2 and 445 mg (3.0 mmol) of NaI in 4 mL of dry acetone was added while the mixture stirred vigorously. The mixture was heated at 45 °C for 15 min and cooled to room temperature. Water (10 mL) and a small amount of $Na_2S_2O_3$ were added. Acetone was removed under reduced pressure and the aqueous layer was extracted three times with hexanes. The combined organic layers were dried (Na_2SO_4) and concentrated to give 890 mg of crude **26a** as a yellow oil, which was used directly in the next step. The oil turns red slowly in air at room temperature but can be kept at −4 °C under N_2 for a week without significant change. Although the red color usually does not affect the chemistry significantly, freshly made crude **26a** is usually used in the next step. An analytical sample was prepared by flash chromatography on silica gel (25:1 hexanes/EtOAc) to give pure **26a** as a colorless oil: ^{1}H NMR 7.51−7.46 (m, 2), 7.37−7.32 (m, 3), 6.22 (t, 1, J = 8.5), 4.45 (dd, 1, J = 3.4, 3.4), 4.01 (d, 2, J = 8.5), 3.77 (ddd, 1, J = 11.0, 8.2, 3.4), 3.61 (ddd, 1, J = 9.8, 8.5, 6.1), 3.44 (ddd, 1, J = 11.0, 4.4, 4.4), 3.27 (ddd, 1, J = 9.8, 7.8, 7.3), 2.60−2.46 (m, 2), 1.82−1.72 (m, 1), 1.65 (dddd, 1, J = 12.8, 12.8, 3.1, 3.1), 1.57−1.45 (m, 4), 0.37 (s, 6); ^{13}C NMR 140.4, 139.5, 137.7, 134.0 (2 C), 129.1, 127.8 (2 C), 98.7, 65.5, 62.1, 30.5, 29.6, 25.4, 19.5, 1.2, −3.12, −3.18; IR (neat) 2940, 2869, 1032.

(1*β*,3α,3aα)-6-[(2*E*)-3-(Dimethylphenylsilyl)-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentyl]-1,2,3,3a,4,5-hexahydro-3a-methyl-3-(1-methylethyl)-1-(*tert*-butyldimethylsilyloxy)-7(6*H*)-azuleneone (35ba). To 3.15 mL of freshly made LDA (1 M in THF, 3.15 mmol) under N_2 at −78 °C was added a solution of **23b** (1.013 g, 3 mmol) in 5 mL of dry THF. The solution was stirred at −78 °C for 20 min and dry DMPU (527 μL, 6.6 mmol) was added. The mixture was stirred at −78 °C for another 10 min and was added via cannula to a stirred solution of pure **26a** (2.073 g, 4.5 mmol) in 10 mL of dry THF at −78 °C under N_2. The solution was stirred overnight while slowly warming to room temperature. Water was added and the solution was extracted three times with hexanes. The combined organic layers were washed with 5 mL of brine and dried (Na_2SO_4). Concentration gave 2.64 g of crude **35ba**. Flash chromatography on silica gel (20:1 hexanes/EtOAc) gave recovered **26a** (0.368 g, 0.8 mmol) and 1.802 g (94%) of pure **35ba** as a colorless oil: ^{1}H NMR 7.50−7.46 (m, 2), 7.34−7.28 (m, 3), 5.90 (d, 1, J = 1.8), 5.83 (dd, 1, J = 6.7, 6.7), 4.60 (ddd, 1, J = 8.5, 3.6, 1.8), 4.46−4.42 (m, 1), 3.81−3.73 (m, 1), 3.58−3.48 (m, 1), 3.43 (ddd, 1, J = 10.4, 5.2, 5.2), 3.24−3.15 (m, 1), 2.74 (dddd, 1, J = 7.3, 7.3, 6.7, 6.7), 2.56 (ddd, 1, J = 14.7, 6.1, 6.1), 2.55−2.40 (m, 2), 2.36 (ddd, 1, J = 14.7, 7.9, 7.3), 2.02−1.90 (m, 2), 1.88−1.81 (m, 1), 1.81−1.60 (m, 6), 1.60−1.43 (m, 5), 1.07 (s, 3), 0.99 (d, 3, J = 6.1), 0.92 (d, 3, J = 6.1), 0.91 (s, 9), 0.34 (s, 6), 0.087 (s, 3), 0.084 (s, 3); ^{13}C NMR 205.9, 170.5, 142.0, 138.78 (0.5 C), 138.76 (0.5 C), 136.58 (0.5 C), 136.54 (0.5 C), 134.0 (2 C), 128.8, 127.6 (2 C), 123.4, 98.62 (0.5 C), 98.59 (0.5 C), 72.9, 66.6, 62.1, 53.91 (0.5 C), 53.89 (0.5 C), 52.1, 48.3, 36.8, 36.3, 31.1, 30.6, 30.24 (0.5 C), 30.19 (0.5 C), 28.7, 26.8, 25.9 (3 C), 25.4, 23.6, 21.9, 19.5, 19.0, 18.2, −2.72, −2.75 (0.5 C), −2.77 (0.5 C), −4.6, −4.7; IR (neat) 1669, 1610; HRMS (FAB DCM/NBA) calcd for $C_{38}H_{62}O_4NaSi_2$ (MNa^+) 661.4084, found 661.4095.

(1*β*,3α,3aα,6α)-3a,6-Dimethyl-6-[(2*E*)-3-(dimethylphenylsilyl)-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentyl]-1,2,3,3a,4,5-Hexahydro-3-(1-methylethyl)-1-(*tert*-butyldimethylsilyloxy)-7(6*H*)-azuleneone (36ba). To 2.94 mL of freshly made LDA (1 M in THF, 2.94 mmol) under N_2 at −78 °C was added a solution of **35ba** (1.80 g, 2.8 mmol) in 4 mL of dry THF. The solution was stirred for 30 min at −78 °C and another 40 min while slowly warming to room temperature. The solution was cooled again to −78 °C and dry DMPU (495 μL, 6.2 mmol) was added. The mixture was stirred at −78 °C for 15 min and dry MeI (0.374 mL, 6.0 mmol) was added. The solution was stirred overnight while slowly warming to room temperature. Water was added and the solution was extracted three times with hexanes. The combined organic layers were washed with 5 mL of brine and dried (Na_2SO_4). Concentration gave 2.03 g of crude **36ba**, which was used for the next step.

An analytical sample was prepared by flash chromatography on silica gel (25:1 hexanes/EtOAc) to give a trace of **37ba**, followed by pure **36ba** as a colorless liquid: ^{1}H NMR 7.50−7.46 (m, 2), 7.34−7.28 (m, 3), 5.90 (dd, 1, J = 7.0, 7.0), 5.81 (d, 1, J = 1.8), 4.51 (ddd, 1, J = 5.2, 5.2, 1.8), 4.46−4.42 (m, 1), 3.82−3.74 (m, 1), 3.57−3.49 (m, 1), 3.43 (ddd, 1, J = 10.4, 5.2, 5.2), 3.24−3.16 (m, 1), 2.53 (ddd, 1, J = 14.7, 3.7, 3.0), 2.52−2.42 (m, 1), 2.47 (dddd, 1, J = 7, 7, 7, 7), 2.37 (dd, 1, J = 14.7, 7.9), 2.00−1.83 (m, 3), 1.82−1.69 (m, 4), 1.69−1.57 (m, 2), 1.57−1.43 (m, 5), 1.15 (s, 3), 0.98 (d, 3, J = 6.7), 0.95 (s, 3), 0.90 (s, 9), 0.89 (d, 3, J = 6.7), 0.342 (s, 3), 0.336 (s, 3), 0.08 (s, 6); ^{13}C NMR 209.0, 166.8, 140.8, 138.8, 137.0, 133.9 (2 C), 128.8, 127.6 (2 C), 122.5, 98.7, 72.7, 66.8, 62.1, 53.0, 51.0, 48.2, 38.0, 37.3, 34.4, 31.1, 30.6, 30.17 (0.5 C), 30.15 (0.5 C), 28.7, 25.8 (3 C), 25.4, 24.7, 23.6, 22.1, 21.2, 19.5, 18.1, −2.65 (0.5 C), −2.68 (0.5 C), −2.71 (0.5 C), −2.75 (0.5 C), −4.6, −4.7; IR (neat) 1674, 1643, 1611; HRMS (FAB DCM/NBA) calcd for $C_{39}H_{64}O_4NaSi_2$ (MNa^+) 675.4241, found 675.4221.

Data for **37ba**: ^{1}H NMR 7.49−7.44 (m, 2), 7.34−7.28 (m, 3), 5.73 (dd, 1, J = 6.1, 4.3), 4.61 (br d, 1, J = 4.3), 4.44−4.39 (m, 1), 3.79−3.71 (m, 1), 3.56−3.45 (m, 1), 3.45−3.37 (m, 1), 3.20−3.11 (m, 1), 2.64−2.53 (m, 2), 2.53−2.33 (m, 3), 2.04−1.94 (m, 1), 1.89−1.67 (m, 6), 1.76 (s, 3), 1.67−1.44 (m, 6), 1.39 (ddd, 1, J = 12.8, 12.8, 4.9), 0.98 (d, 3, J = 6.7), 0.88 (d, 3, J = 6.7), 0.88 (s, 3), 0.88 (s, 9), 0.33 (s, 6), 0.10 (s, 3), 0.09 (s, 3); ^{13}C NMR 214.2, 156.03 (0.5 C), 155.99 (0.5 C), 141.2 (0.5 C), 141.18 (0.5 C), 138.44 (0.5 C), 138.42 (0.5 C), 137.36 (0.5 C), 137.34 (0.5 C), 133.9 (2 C), 131.3, 128.8, 127.6 (2 C), 98.50 (0.5 C), 98.47 (0.5 C), 71.6, 66.4, 61.90 (0.5 C), 61.89 (0.5 C), 55.4, 52.70 (0.5 C), 52.68 (0.5 C), 47.2, 36.9, 35.9, 30.74 (0.5 C), 30.71 (0.5 C), 30.5, 30.2, 27.5, 27.2, 25.7 (3 C), 25.4, 23.8, 22.4, 22.1, 19.40 (0.5 C), 19.37 (0.5 C), 17.9, 17.3, −2.77 (0.5 C), −2.83, −2.87 (0.5 C), −3.9, −4.8; IR (neat) 1677, 1612.

(1*β*,3α,3aα,6α)-3a,6-Dimethyl-6-(5-hydroxy-3-oxopentyl)-1,2,3,3a,4,5-hexahydro-3-(1-methylethyl)-1-(*tert*-butyldimethylsilyloxy)-7(6*H*)-azuleneone (41). To a solution of 762 mg (77%, 3.4 mmol) of *m*-CPBA in 5 mL of CH_2Cl_2 was added dropwise a solution of crude **36ba** (2.03 g, from 2.8 mmol of **35ba**) in 5 mL of CH_2Cl_2 while stirring at 0 °C. The solution was stirred at CH_2Cl_2 for 30 min and at room temperature for another 1 h. Saturated Na_2SO_3 solution (5 mL) and $NaHCO_3$ solution (10 mL) in water were added, and the mixture was stirred vigorously for 1 h. The organic layer was separated and the water layer was extracted three times with hexanes. The combined organic layers were dried (Na_2SO_4) and concentrated to give 2.13 g of crude epoxide.

The crude epoxide (2.13 g, from 2.8 mmol of **35ba**) was dissolved in 5 mL of dry CH_2Cl_2 and transferred to a dry polyethylene tube equipped with a rubber septum. To this solution was added dropwise 0.5 mL of pyr·$(HF)_x$ at 0 °C while stirring vigorously. The mixture was stirred for 5 min and another 0.5 mL of pyr·$(HF)_x$ was added. The mixture was

slowly warmed to room temperature and additional pyr·$(HF)_x$ (0.5 mL × 2) was added in about 10 min until TLC showed that the hydrolysis of the THP group was complete. Solid Na_2CO_3 and water in small portions were carefully added to the mixture at 0 °C until the pH of the solution was 8. The aqueous layer was extracted four times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated to give 897 mg of crude **41**. Flash chromatography on deactivated silica gel (1% H_2O) (2:1 then 1:2 hexanes/EtOAc) gave 625 mg (64%, 2 steps from **35ba**) of pure **41** as a colorless oil: ^{1}H NMR 5.88 (d, 1, J = 1.2), 4.52 (br d, 1, J = 6.1), 3.86 (t, 2, J = 5.5), 2.71 (t, 2, J = 5.5), 2.54−2.47 (m, 2), 2.06−1.95 (m, 3), 1.92−1.73 (m, 7), 1.65 (qqd, 1, J = 6.7, 6.7, 6.7), 1.54−1.47 (m, 1), 1.17 (s, 3), 1.00 (d, 3, J = 6.7), 0.96 (s, 3), 0.92 (d, 3, J = 6.7); ^{13}C NMR 211.7, 208.9, 167.1, 123.6, 72.9, 57.9, 53.8, 49.7, 48.6, 44.4, 38.7, 36.4, 34.2, 32.7, 32.1, 28.2, 24.2, 23.7, 22.1, 20.9; IR (neat) 3600−3200, 1707, 1654; HRMS (DCI NH_3/CI) calcd for $C_{20}H_{34}NO_3$ (M + NH_4^+ − H_2O) 336.2539, found 336.2540.

(1α,3*β*,8a*β*,10aα)-1,2,3,8,8a,9,10,10a-Octahydro-3-hydroxy-5-hydroxymethyl-8a,10a-dimethyl-1-(1-methylethyl)benz[*f*]azulen-6(7*H*)-one (42). To a solution of pure **41** (349 mg, 1 mmol) in 10 mL of benzene was added 5 mL of 1 M NaOMe in MeOH (5 mmol) under N_2 at room temperature while the mixture stirred vigorously. The mixture was stirred for 2 h and 10 mL of saturated $NaHCO_3$ aqueous solution was added. MeOH and benzene were removed under reduced pressure. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated to give 368 mg of crude **42**. Flash chromatography on deactivated silica gel (1% H_2O) (2:1 then 1:1 hexanes/EtOAc) gave 281 mg (85%) of pure **42** as a white solid: ^{1}H NMR 6.32 (s, 1), 4.51 (d, 1, J = 3.7), 4.33 (d, 1, J = 12.8), 4.23 (d, 1, J = 12.8), 2.89 (br s, 1, OH), 2.62−2.45 (m, 2), 2.06−1.46 (m, 9), 1.62 (qqd, 1, J = 6.7, 6.7, 6.7), 1.20 (s, 3), 0.98 (d, 3, J = 6.7), 0.91 (d, 3, J = 6.7), 0.87 (s, 3); ^{13}C NMR 200.3, 163.0 (br), 161.7, 133.6, 120.0 (br), 73.2 (br), 58.1, 53.5 (br), 47.7 (br), 38.3 (br), 36.7 (br), 36.6, 36.0, 33.9, 33.2 (br), 28.2, 25.3, 23.7, 22.3, 20.0 (br); IR (neat) 3600−3200, 1652, 1589; HRMS (DCI NH_3/CI) calcd for $C_{20}H_{31}O_3$ (MH^+) 319.2273, found 319.2278.

(1α,8a*β*,10aα)-1,8,8a,9,10,10a-Hexahydro-5-hydroxymethyl-8a,10a-dimethyl-1-(1-methylethyl)benz[*f*]azulen-3,6(2*H*,7*H*)-dione (44) and Deacetoxy-epi-guanacastepene G (45). To a solution of pure **42** (9.7 mg, 0.03 mmol) in 1 mL CH_2Cl_2 was added MnO_2 (40 mg, 0.6 mmol) at room temperature. When TLC analysis showed that most of the starting material had disappeared (∼4 h), the reaction was quenched with EtOAc, and MnO_2 was filtered off and washed with EtOAc. The combined organic layers were concentrated to give 10 mg of crude **44** containing about 5% of **45** and about 15% of the diketone aldehyde. Flash chromatography on silica gel (19:1 hexanes/EtOAc) gave 1 mg of pure diketone aldehyde, followed by 6 mg (60%) of a 1:3 mixture of **45** and **44** as a colorless oil. Stirring with silica gel in CH_2Cl_2 for 2 d increased the ratio of **45** and **44** to about 4:1, but never completed the cyclization.

Partial data for **45**: ^{1}H NMR 5.51 (ddd, 1, J = 5.5, 5.5, 4.9), 4.72 (dd, 1, J = 12.2, 5.5), 4.66 (dd, 1, J = 12.2, 5.5), 2.73−2.62 (m, 1), 2.57 (d, 1, J = 4.9), 2.49−2.39 (m, 2), 2.25−2.03 (m, 5), 1.74 (qqd, 1, J = 6.7, 6.7, 6.7), 1.70−1.51 (m, 2), 1.20 (s, 3), 1.04 (d, 3, J = 6.7), 0.91 (d, 3, J = 6.7), 0.87 (s, 3); HRMS (EI) calcd for $C_{20}H_{28}O_3$ (M^+) 316.2038, found 316.2043.

A COSY experiment showed δ 5.51 (C_2–H) was coupled to δ 4.72 (J = 5.5 Hz), 4.66 (J = 5.5 Hz), and 2.57 (C_1–H, J = 4.9 Hz). Irradiation of the proton at δ 5.51 showed a strong NOE signal at δ 2.57 and a weak NOE signal at δ 1.20 (Me-16). Irradiation of the proton at δ 1.20 showed only an NOE signal at δ 2.57 and no NOE signal at δ 5.51, 1.04, or 0.91.

Partial data for **44**: ^{1}H NMR 7.12 (br, 1), 4.26 (d, 2, J = 6.1), 1.17 (s, 3), 1.05 (d, 3, J = 6.7), 1.03 (s, 3), 0.95 (d, 3, J = 6.7).

Data for diketone aldehyde: ^{1}H NMR 10.25 (s, 1), 7.28 (s, 1), 2.68−2.59 (m, 2), 2.55 (d, 1, J = 18.3, 7.3), 2.26−1.95 (br, 1), 2.20 (dd, 1, J = 18.3, 12.5), 2.12−2.02 (m, 2), 1.90−1.70 (br, 2), 1.78 (qqd, 1, J = 6.7, 6.7, 6.7), 1.73−1.63 (m, 2), 1.26 (s, 3), 1.05 (d, 3, J = 6.7), 1.01 (br, 3), 0.95 (d, 3, J = 6.7).

(1*β*,3α,3aα,7*β*)-1,2,3,3a,4,5,6,7-Octahydro-3a-methyl-3-(1-methylethyl)azulene-1,7-diol. K_2CO_3 (553 mg, 4 mmol) was added to a solution of **19** (520 mg, 2.0 mmol) in MeOH (5 mL). The mixture was stirred at room temperature for 20 min and then concentrated to remove the MeOH. Saturated NH_4Cl solution in water was added until pH 8. The mixture was extracted six times with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated to give 468 mg of crude diol that was carried on without further purification. An analytical sample was prepared by recrystallization from EtOAc to give pure diol as a white solid: mp 165−166 °C; ^{1}H NMR 5.81 (br, 1), 4.56 (br d, 1, J = 10.0), 4.31 (br d, 1, J = 4.9), 1.99 (ddd, 1, J = 13.4, 4.9, 2.4), 1.96−1.73 (m, 5), 1.64 (qqd, 1, J = 6.7, 6.7, 6.7), 1.64−1.60 (m, 1), 1.59−1.46 (m, 2), 1.36−1.27 (m, 2), 0.98 (d, 3, J = 6.7), 0.92 (s, 3), 0.91 (d, 3, J = 6.7); ^{13}C NMR 156.6, 133.2, 74.5, 70.7, 55.2, 47.5, 39.7, 38.3, 36.2, 27.7, 24.0, 22.3, 22.2, 16.6; IR (KBr) 3500−3200.

(3α,3aα)-2,3,3a,4,5,6-Hexahydro-3a-methyl-3-(1-methylethyl)-1,7-azulenedione (46). To a solution of crude diol (460 mg, from 2.0 mmol of **19**) in CH_2Cl_2 (10 mL) was added pyridine (1.35 mL, 15.0 mmol) under N_2 at 0 °C. A solution of Dess−Martin reagent (2.12 g, 5.0 mmol) in CH_2Cl_2 (10 mL) was then added via syringe. The mixture was stirred for 1 h at room temperature. Sodium thiosulfate solution (10% in water, 5 mL) was added and the mixture was stirred for an additional 30 min until the layers appeared clear. The layers were separated and the water layer was extracted two times with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated to give 510 mg of crude **46**. Flash chromatography on deactivated silica gel (1% H_2O) (49:1 then 24:1 hexane/Et_2O) gave 392 mg (89%, two steps from **19**) of pure **46** as a colorless oil: ^{1}H NMR 6.46 (s, 1), 2.75 (ddd, 1, J = 14.7, 6.7, 4.3), 2.59 (ddd, 1, J = 14.7, 10.2, 5.9), 2.56 (dd, 1, J = 18.9, 7.3), 2.34 (ddd, 1, J = 14.0, 6.1, 3.1), 2.26 (dd, 1, J = 18.9, 12.8), 2.12−2.00 (m, 1), 1.99−1.90 (m, 1), 1.85 (qqd, 1, J = 6.7, 6.7, 6.7), 1.76 (ddd, 1, J = 15.3, 12.2, 3.1), 1.72 (dd, 1, J = 12.8, 7.3), 1.16 (s, 3), 1.08 (d, 3, J = 6.7), 0.97 (d, 3, J = 6.7); ^{13}C NMR 206.0, 204.5, 154.6, 127.9, 50.6, 48.0, 45.1, 40.0, 38.8, 28.2, 24.1, 21.9, 20.3, 20.2; IR (KBr) 1727, 1673, 1634; HRMS (DCI NH_3/CI) calcd for $C_{14}H_{24}NO_2$ (M + NH_4^+) 238.1807, found 238.1804.

(3α,3aα)-7,7-Ethylenedioxy-3,3a,4,5,6,7-hexahydro-3a-methyl-3-(1-methylethyl)-1(2*H*)-azulenone (47). To a solution of pure **46** (353 mg, 1.6 mmol) in CH_2Cl_2 (5 mL) was added 1,2-bis(trimethylsilyloxy)ethane (392 μL, 1.6 mmol) and TMSOTf (15 μL, 0.08 mmol) under N_2 at −78 °C. The solution was stirred for 4 h while slowly warming up to 0 °C. Saturated $NaHCO_3$ solution (10% in water, 2 mL) was added. The layers were separated, and the water layer was extracted three times with hexanes. The organic layers were combined, dried over Na_2SO_4, and concentrated to give 440 mg of crude **47** that was carried on without further purification. An analytical sample was prepared by flash chromatography on deactivated silica gel (1% H_2O) (19:1 hexanes/EtOAc) to give pure **47** as a white solid: mp 60−62 °C; ^{1}H NMR 6.51 (d, 1, J = 1.2), 4.04−3.98 (m, 2), 3.98−3.86 (m, 2), 2.45 (dd, 1, J = 18.3, 7.9), 2.18 (ddd, 1, J = 15.9, 6.0, 2.4), 2.17 (dd, 1, J = 18.3, 13.1), 2.11 (ddddd, 1, J = 13.4, 11.6, 11.6, 2.4, 2.4), 1.93 (dddd, 1, J = 14.0, 6.1, 2.4, 1.2), 1.81 (ddd, 1, J = 14.6, 11.6, 2.4), 1.80 (qqd, 1, J = 6.7, 6.7, 6.7), 1.72 (ddddd, 1, J = 11.6, 6.1, 6.0, 2.4, 2.4), 1.57 (ddd, 1, J = 13.1, 7.9, 6.7), 1.48 (ddd, 1, J = 13.4, 13.4, 2.4), 1.20 (s, 3), 1.04 (d, 3, J = 6.7), 0.93 (d, 3, J = 6.7); ^{13}C NMR 206.3, 148.3, 134.9, 108.2, 64.6, 64.5, 51.0, 47.0, 40.4, 39.7, 37.8, 28.1, 24.2, 22.1, 19.8, 18.5; IR (KBr) 1724, 1651; HRMS (DCI NH_3/CI) calcd for $C_{16}H_{25}O_3$ (MH^+) 265.1804, found 265.1794.

(3α,3aα)-7,7-Ethylenedioxy-3,3a,4,5,6,7-hexahydro-3a-methyl-3-(1-methylethyl)-1-(trimethylsilyloxy)-azulenene (50). To freshly made LDA (1 M in THF, 2.40 mL, 2.40 mmol) under N_2 at −78 °C was added a solution of crude **47** (440 mg, from 1.6 mmol of **46**) in dry THF (3 mL). The solution was stirred for 30 min at −78 °C and dry TMSCl (407 μL, 3.2 mmol) was added. The mixture was stirred for another 1 h while slowly warming up to room temperature. Water was added and the mixture was extracted three times with hexanes. The organic layers were combined, dried over Na_2SO_4, and concentrated to give 695 mg of crude **50** that was carried on without further purification. Partial data for **50**: ^{1}H NMR 5.54 (s, 1), 5.08 (d, 1, J = 2.4), 4.03−3.86 (m, 4), 2.10 (ddddd, 1, J = 14.7, 12.8, 12.8, 1.8, 1.8), 2.04−2.00 (m, 1), 1.98−1.88 (m, 2), 1.80 (ddd, 1, J = 12.8, 12.8, 3.1), 1.76−1.61 (m, 2), 1.61−1.52 (m, 1), 1.24 (s, 3), 0.98 (d, 3, J = 6.7), 0.93 (d, 3, J = 6.7), 0.22 (s, 9).

(2α,3α,3aα)-2-Bromo-7,7-ethylenedioxy-3,3a,4,5,6,7-hexahydro-3a-methyl-3-(1-methylethyl)-1(2*H*)-azulenone (49). To a solution of crude **50** (44 mg, from 0.1 mmol of **46**) in THF (1 mL) was added a solution of NBS (1.35 mL, 15.0 mmol) in 1 mL of THF under N_2 at −78 °C. The mixture was stirred for 30 min while slowly warming up to room temperature. Saturated $NaHCO_3$ solution in water was added and the mixture was stirred for an additional 5 min. The mixture was extracted three times with hexanes. The organic layers were combined, dried over Na_2SO_4, and concentrated to give 55 mg of crude **49** that is very unstable and decomposes on silica gel. **49** also partially isomerized on silica gel or in pyridine to **48**.

Partial data for **49**: ^{1}H NMR 6.78 (d, 1, J = 1.2), 4.45 (d, 1, J = 6.7), 4.10−3.90 (m, 4), 2.26−2.13 (m, 2), 2.05 (dqq, 1, J = 10, 6.7, 6.7), 1.93−1.86 (m, 1), 1.80 (ddd, 1, J = 12.8, 12.8, 3.1), 1.73−1.64 (m, 2), 1.37 (dd, 1, J = 10, 6.7), 1.26 (s, 3), 1.13 (d, 3, J = 6.7), 1.06 (d, 3, J = 6.7). A COSY experiment showed coupling (J = 6.7 Hz) between δ 4.45 (CHBr) and δ 1.37, coupling (J = 10 Hz) between δ 1.37 and δ 2.05, and coupling (J = 6.7 Hz) between δ 2.05 and the two methyl groups of the isopropyl side chain (δ 1.13 and δ 1.06). Irradiation of the proton at δ 4.45 showed NOE signals at δ 1.37 and δ 1.06, but no NOE signal at δ 2.05.

Partial data for **48**: ^{1}H NMR 6.71 (d, 1, J = 1.8), 4.49 (d, 1, J = 12.8).

(2α,3α,3aα)-7,7-Ethylenedioxy-3,3a,4,5,6,7-hexahydro-2-hydroxy-3a-methyl-3-(1-methylethyl)-1(2*H*)-azulenone (52). To a solution of crude **50** (434 mg, from 1.0 mmol of **46**) in dry THF (10 mL) was added DMDO[40b] (0.1 M in acetone, 30 mL, 3.0 mmol) under N_2 at −78 °C. The mixture was warmed to −40 °C and stirred for 2 h. The solvent was removed under reduced pressure to give 480 mg of residue. The residue was dissolved in 2 mL of CH_2Cl_2. NaH_2PO_4 solution (5% in water) was added and the mixture was stirred vigorously for 30 min. The layers were separated and the water layer was extracted two times with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated to give 300 mg of crude **52**. Flash chromatography on deactivated silica gel (1% H_2O) (19:1 then 9:1 hexane/EtOAc) gave 173 mg (62%, 3 steps from **46**) of pure **52** as a white solid: mp 136−137 °C; ^{1}H NMR 6.65 (d, 1, J = 1.2), 4.06 (dd, 1, J = 6.1, 2.4), 4.05−4.00 (m, 2), 3.99−3.87 (m, 2), 2.41−2.37 (br, 1, OH), 2.25 (ddd, 1, J = 14.0, 6, 2.4, 2.4), 2.18 (dqq, 1, J = 10.4, 6.1, 6.1), 2.14 (ddddd, 1, J = 14.6, 13.4, 12.2, 2.4, 2.4), 1.92 (dddd, 1, J = 14.0, 6, 2.4, 1.2), 1.80 (ddd, 1, J = 14.0, 12.2, 3.0), 1.69 (ddddd, 1, J = 14.6, 6, 6, 3.0, 2.4), 1.44 (s, 3), 1.42 (ddd, 1, J = 14.0, 13.4, 2.4), 1.36 (dd, 1, J = 10.4, 6.1), 1.10 (br d, 6, J = 6.1); ^{13}C NMR 206.1, 147.7, 138.6, 108.2, 73.8, 64.7, 64.5, 56.0, 46.7, 40.4, 37.6, 24.6, 23.4, 23.3, 20.1, 19.7; IR (KBr) 3500−3300, 1711, 1637; HRMS (DCI NH_3/CI) calcd for $C_{16}H_{25}O_4$ (MH^+) 281.1753, found 281.1755. A COSY experiment showed coupling (J = 6.1 Hz) between δ 4.46 (CHOH) and 1.36, coupling (J = 10.4 Hz) between δ 1.36 and 2.18, and coupling (J = 6.1 Hz) between δ 2.18 and 1.10 (the two methyl groups of the isopropyl side chain). Irradiation of the proton at δ 4.46 showed NOE signals at δ 1.36 and 1.10 but no NOE signal at δ 2.18.

(1α,2α,3α,3aα)-7,7-Ethylenedioxy-1,2,3,3a,4,5,6,7-octahydro-3a-methyl-3-(1-methylethyl)-1,2-azulenediol (51). To a solution of **52** (112 mg, 0.4 mmol) in 2 mL of dry THF was added 0.90 mL of 1.0 M $LiAlH(O\text{-}t\text{-}Bu)_3$ in THF (0.90 mmol) under N_2 at −78 °C. The solution was stirred for 3 h while warming to room temperature slowly. H_2O was added and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated to give 120 mg of crude **51**. Flash chromatography on deactivated silica gel (1% H_2O) (9:1 then 6:1 hexanes/EtOAc) gave 92 mg (82%) of pure **51** as a white solid: mp 115−116 °C; ^{1}H NMR 5.78 (br, 1), 4.30 (ddd, 1, J = 7.3, 4.9, 2.4), 4.11 (m, 1), 4.01−3.88 (m, 4), 2.35−2.30 (br, 1, OH), 2.21−2.18 (br, 1, OH), 2.18−2.06 (m, 2), 2.02 (ddd, 1, J = 13.4, 5.8, 2.4), 1.87 (ddd, 1, J = 13.4, 5, 5), 1.78 (ddd, 1, J = 13.4, 12.8, 3.1), 1.66−1.58 (m, 1), 1.48 (s, 3), 1.32 (ddd, 1, J = 13.4, 12.8, 1.8), 1.12 (dd, 1, J = 10.4, 3.7), 1.06 (d, 3, J = 6.7), 1.02 (d, 3, J = 6.7); ^{13}C NMR 158.5, 127.5, 108.9, 75.0, 73.3, 64.4, 63.7, 57.0, 46.9, 40.1, 37.8, 24.7, 23.33, 23.28, 20.7, 20.3; IR (neat) 3700−3100, 1670 (weak); HRMS (DCI NH_3/CI) calcd for $C_{16}H_{27}O_4$ (MH^+) 283.1909, found 283.1917.

(1α,3*β*,8a*β*,10aα)-1,2,3,8,8a,9,10,10a-Octahydro-8a,10a-dimethyl-1-(1-methylethyl)-3-triethylsilyloxy-5-triethylsilyloxymethyl-benz[*f*]azulen-6(7*H*)-one (57). To a solution of pure **42** (64 mg, 0.2 mmol) in 1 mL CH_2Cl_2 were added pyridine (90 μL, 1 mmol) and TESOTf (113 μL, 0.5 mmol) under N_2 at 0 °C. The mixture was stirred for 30 min and 1 mL of saturated $NaHCO_3$ aqueous solution was added. The mixture was extracted three times with hexanes. The combined organic layers were dried (Na_2SO_4) and concentrated to give 138 mg of crude **57**. Flash chromatography on silica gel (49:1 hexanes/EtOAc) gave 99.6 mg (91%) of pure **57** as a colorless liquid: ^{1}H NMR 6.34 (s, 1), 4.48 (br, 1), 4.45 (d, 1, J = 10.7), 4.12 (d, 1, J = 10.7), 2.47−2.53 (m, 2), 2.03−1.71 (m, 6), 1.71−1.48 (m, 3), 1.59 (qqd, 1, J = 6.7, 6.7, 6.7), 1.19 (s, 3), 0.97 (t, 9, J = 7.9), 0.96 (d, 3, J = 6.7), 0.93 (t, 9, J = 7.9), 0.89 (d, 3, J = 6.7), 0.84 (s, 3), 0.62 (q, 6, J = 7.9), 0.58 (q, 6, J = 7.9); ^{13}C NMR 197.6, 165.1, 159.6, 134.0 (br), 73.5 (br), 55.7, 47.0 (br), 37.7, 36.0, 34.1, 28.4, 25.6, 23.7, 22.3, 6.87 (3 C), 6.80 (3 C), 5.0 (3 C), 4.4 (3 C), 6 carbons were too broad to be observed; IR (neat) 1669, 1588.

(1α,3*β*,8a*β*,10aα)-1,2,3,8,8a,9,10,10a-Octahydro-5-hydroxymethyl-8a,10a-dimethyl-1-(1-methylethyl)-3-(triethylsilyloxy)benz[*f*]azulen-6(7*H*)-one (58). Pure **57** (66 mg, 0.12 mmol) was dissolved in 1 mL of 3:6:1 H_2O/THF/AcOH at room temperature. The solution was stirred for 3 h and monitored by TLC. When most of the starting material was consumed, the reaction was quenched with solid Na_2CO_3 and water. The mixture was extracted three times with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated to give 68 mg of crude mixture of **58** and **42**. Flash chromatography on deactivated silica gel (1% H_2O) (19:1 then 9:1 hexanes/EtOAc) gave 21 mg (41%) of pure **58** as a colorless oil. Elution with 1:1 hexanes/EtOAc gave 15 mg (39%) of recovered **42**.

Data for **58**: ^{1}H NMR 6.13 (s, 1), 4.49 (br, 1), 4.30 (dd, 1, J = 12.2, 6.1), 4.24 (dd, 1, J = 12.2, 7.3), 2.98 (dd, 1, OH, J = 7.3, 6.1), 2.60−2.46 (m, 2), 2.08−1.46 (m, 10), 1.19 (s, 3), 0.98 (t, 9, J = 7.9), 0.96 (d, 3, J = 6.7), 0.89 (d, 3, J = 6.7), 0.86 (s, 3), 0.62 (q, 6, J = 7.9); ^{13}C NMR 200.7, 163.8, 160.6, 133.5 (br), 118.0 (br), 72.7 (br), 58.9, 47.3 (br), 37.6, 35.7, 34.1, 28.5, 25.4, 23.7, 22.3, 6.9 (3 C), 5.0 (3 C), 4 carbons were too broad to be observed; IR (neat) 3600−3300, 1655, 1592; HRMS (DCI NH_3/CI) calcd for $C_{26}H_{45}O_3Si$ (MH^+) 433.3138, found 433.3153.

(1α,3*β*,6*β*,8a*β*,10aα)- and (1α,3*β*,6α,8a*β*,10aα)-1,2,3,6,7,8,8a,9,10,10a-Decahydro-5-hydroxymethyl-8a,10a-dimethyl-1-(1-methylethyl)-3-(triethylsilyloxy)benz[*f*]azulen-6-ol (54 and 56). To a solution of **58** (10.8 mg, 0.025 mmol) in 0.5 mL of dry THF was added 0.06 mL of 1.0 M $LiAlH(O\text{-}t\text{-}Bu)_3$

in THF (0.06 mmol) under N_2 at −78 °C. The solution was stirred for 3 h while warming to room temperature slowly. The aqueous layer was extracted four times with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated to give 12 mg of crude **56** containing 17% of **54**. Flash chromatography on deactivated silica gel (1% H_2O) (9:1 hexanes/EtOAc) gave 1 mg of impure **54** and 7.5 mg (69%) of 90% pure **56** as a colorless oil.

Data for **56**: ^{1}H NMR 5.93 (s, 1), 4.43−4.33 (br, 2), 4.33 (br d, 1, J = 12), 4.21 (br d, 1, J = 12), 2.39 (br, 1, OH), 2.09 (br, 1, OH), 1.96−1.85 (m, 1), 1.85−1.65 (m, 5), 1.65−1.46 (m, 2), 1.59 (qqd, 1, J = 6.7, 6.7, 6.7), 1.46−1.33 (br, 2), 1.32−1.20 (br, 1), 0.99 (s, 3), 0.96 (t, 9, J = 7.9), 0.96 (d, 3, J = 6.7), 0.88 (s, 3), 0.88 (d, 3, J = 6.7), 0.60 (q, 6, J = 7.9); ^{13}C NMR 157.3, 142.0 (br), 73.8 (br), 68.6 (br), 62.8 (br), 46.6 (br), 37.8, 37.2 (br), 33.8 (br), 28.2, 25.6, 23.8, 22.4, 6.90 (3 C), 5.05 (3 C), 7 carbons were too broad to be observed. The spectra are identical to those provided by Prof. Danishefsky.

Partial data for **54**: ^{1}H NMR 6.20 (s, 1), 4.44−4.33 (m, 3), 4.11 (d, 1, J = 12), 1.08 (s, 3), 0.78 (s, 3).

(1α,3*β*,6*β*,8a*β*,10aα)- and (1α,3*β*,6α,8a*β*,10aα)-1,2,3,6,7,8,8a,9,10,10a-Decahydro-5-hydroxymethyl-8a,10a-dimethyl-1-(1-methylethyl)-3,6-benz[*f*]azulenediol (59 and 61). To a solution of **42** (100 mg, 0.3 mmol) in 4 mL of dry THF was added 1.05 mL of 1.0 M LiAlH(O-*t*-Bu)$_3$ in THF (1.05 mmol) under N_2 at −78 °C. The solution was stirred for 3 h while warming to room temperature slowly. Saturated NH_4Cl solution in H_2O was added until the pH of the solution was 7. The aqueous layer was extracted six times with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated to give 95 mg of crude **61** containing 20% of **59**, which was used for the next step. An analytical sample was prepared by flash chromatography on deactivated silica gel (1% H_2O) (1:1 then 1:2 hexanes/EtOAc) to give pure **61** as a white solid.

Data for **61**: ^{1}H NMR 6.12 (s, 1), 4.44−4.35 (br, 2), 4.33 (br d, 1, J = 12), 4.24 (br d, 1, J = 12), 2.42 (br, 1, OH), 2.14 (br, 1, OH), 1.96−1.73 (m, 6), 1.73−1.50 (br, 2), 1.62 (qqd, 1, J = 6.7, 6.7, 6.7), 1.48−1.35 (br, 1), 1.38 (ddd, 1, J = 14.7, 4.3, 3.7), 1.31 (br, 1), 1.25 (br, 1), 1.00 (s, 3), 0.98 (d, 3, J = 6.7), 0.91 (d, 3, J = 6.7), 0.90 (s, 3); ^{13}C NMR 158.5, 36.7, 28.1, 25.6 (br), 23.8, 22.4; IR (neat) 3600−3100; HRMS (FAB DCM/NBA) calcd for $C_{20}H_{32}O_3Na$ (MNa^+) 343.2249, found 343.2254.

Data for **59**: ^{1}H NMR 6.21 (s, 1), 4.44−4.30 (m, 3), 4.11 (dd, 1, J = 12, 5), 2.39 (d, 1, J = 5, OH), 2.21 (t, 1, J = 5, OH), 2.02−1.66 (m, 8), 1.61 (qqd, 1, J = 6.7, 6.7, 6.7), 1.56−1.36 (br, 2), 1.31 (d, 1, J = 3, OH), 1.31−1.25 (br, 1), 1.08 (s, 3), 0.98 (d, 3, J = 6.7), 0.90 (d, 3, J = 6.7), 0.87 (s, 3).

(1α,3*β*,6α,8a*β*,10aα)-1,2,3,6,7,8,8a,9,10,10a-Decahydro-5-hydroxymethyl-8a,10a-dimethyl-1-(1-methylethyl)-3,6-benz[*f*]azulenediol Acetonide (62). To a solution of a crude 4:1 mixture of **61** and **59** (95 mg, from 0.3 mmol of **42**) in dry CH_2Cl_2 (10 mL) were added 2,2-dimethoxypropane (738 μL, 6 mmol) and PPTS (15 mg, 0.06 mmol) under N_2 at 0 °C. The mixture was stirred at 0 °C for 30 min and monitored by TLC. When only a slight amount of starting material was left, the reaction was quenched with saturated $NaHCO_3$ solution. The two layers were separated, and the water layer was extracted twice with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated to give 115 mg of crude **62** containing 20% of **60**. Flash chromatography on silica gel (24:1 then 15:1 hexane/Et_2O) gave 54 mg (48% from **42**) of pure **62** as a colorless oil, followed by 15 mg (12% from **42**) of 90% pure **60** as a colorless oil.

Data for **62**: ^{1}H NMR 5.87 (s, 1), 4.38−4.32 (m, 2), 4.26 (d, 1, J = 15.3), 4.11 (d, 1, J = 15.3), 2.25 (ddd, 1, J = 14.0, 13.4, 3.0), 1.91−1.78 (m, 4), 1.78−1.68 (m, 2), 1.63 (qqd, 1, J = 6.7, 6.7, 6.7), 1.58−1.44 (m, 3), 1.44 (s, 3), 1.37 (s, 3), 1.34 (br s, 1, OH), 1.28 (ddd, 1, J = 14.0, 3.6, 3.6), 0.99 (s, 3), 0.98 (d, 3, J = 6.7), 0.91 (d, 3, J = 6.7), 0.88 (s, 3); ^{13}C NMR 158.0, 134.0, 133.4, 121.6, 99.6, 74.6, 67.6, 60.3, 55.0, 46.6, 38.1, 37.3, 36.5, 35.7, 34.4, 27.9, 26.6, 25.1, 25.0, 23.9, 23.7, 22.4, 17.0; IR (neat) 1670; HRMS (FAB) calcd for $C_{23}H_{35}O_3$ ($M - H^+$) 359.2586, found 359.2577. The spectra are identical to those provided by Prof. Danishefsky.

Data for **60**: ^{1}H NMR 5.87 (s, 1), 4.41 (d, 1, J = 15.3), 4.40−4.32 (br, 2), 4.13 (d, 1, J = 15.3), 1.92−1.74 (m, 6), 1.64 (qqd, 1, J = 6.7, 6.7, 6.7), 1.60−1.45 (m, 4), 1.46 (s, 3), 1.43−1.34 (m, 1), 1.38 (s, 3), 1.24 (br, 1), 1.05 (s, 3), 0.98 (d, 3, J = 6.7), 0.91 (d, 3, J = 6.7), 0.86 (s, 3); ^{13}C NMR 160.1, 133.6, 120.8 (br), 99.3, 74.7 (br), 67.3, 60.5, 37.0 (br), 36.5, 28.0, 25.5, 23.9, 23.5 (br), 22.4.

(1α,6α,8a*β*,10aα)-1,6,7,8,8a,9,10,10a-Octahydro-6-hydroxy-5-hydroxymethyl-8a,10a-dimethyl-1-(1-methylethyl)benz[*f*]azulen-3(2*H*)-one Acetonide (55). To a solution of pure **62** (37 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) was added pyridine (45 μL, 0.5 mmol) under N_2 at 0 °C. A solution of Dess−Martin reagent (170 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) was then added via syringe. The mixture was stirred for 30 min while slowly warming up to room temperature. Sodium thiosulfate solution (10% in water) was added and the mixture was stirred for an additional 30 min until the layers appeared clear. The layers were separated, and the water layer was extracted two times with hexanes. The organic layers were combined, dried over Na_2SO_4, and concentrated to give 45 mg of crude **55**. Flash chromatography on silica gel (24:1 then 30:1 hexane/Et_2O) gave 32 mg (86%) of pure **55** as a colorless oil: ^{1}H NMR 6.82 (s, 1), 4.26 (d, 1, J = 15.3), 4.35 (m, 1), 4.11 (d, 1, J = 15.3), 2.49 (dd, 1, J = 18.0, 7.6), 2.26 (ddd, 1, J = 14.0, 14.0, 1.8), 2.14 (dd, 1, J = 18.0, 12.7), 1.91−1.79 (m, 4), 1.82−1.56 (m, 4), 1.43 (s, 3), 1.39−1.32 (m, 1), 1.35 (s, 3), 1.04 (d, 3, J = 6.7), 1.01 (s, 3), 0.95 (s, 3), 0.93 (d, 3, J = 6.7); ^{13}C NMR 205.4, 146.4, 139.7, 133.1, 129.4, 100.1, 67.6, 60.1, 51.4, 46.0, 41.2, 38.1, 36.9, 36.4, 33.8, 28.5, 26.9, 25.0, 24.5, 24.1, 23.9, 22.3, 17.9; HRMS (EI 70 eV) calcd for $C_{23}H_{34}O_3$ (M^+) 358.2508, found 358.2503. The spectra are identical to those provided by Prof. Danishefsky.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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