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Construction of the Tricyclic 5−7−6 Scaffold of Fungi-Derived Diterpenoids. Total Synthesis of (±)-Heptemerone G and an Approach to Danishefsky's Intermediate for Guanacastepene A Synthesis

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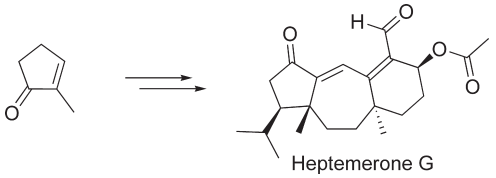

An efficient and operationally simple synthesis of the neodolestane diterpenoids (±)-heptemerone G and (±)-guanacastepene A is reported. The common tricyclic scaffold (±)-**4** was prepared from 2-methylcyclopent-2-en-1-one via 23 isolated intermediates in 5.1% yield. The key features include a novel annulation sequence combining tandem conjugate addition, methylenation, and metathesis reaction and completely diastereoselective transformation of the azulene derivative **23** into rings AB building block **32**. Stereochemistry of alkylation of both saturated *trans*-azulene enolate **38** and its α,β-unsaturated counterpart **48** was examined. Rather surprisingly, a different facial selectivity was recorded. Several synthetic methods were modified or developed, including an alternative methodology for the Wharton-type rearrangement, ketalization of epimerizable ketone under mild conditions, and efficient alkylation of a ketone via its kinetic enolate.

Introduction

The microbial and fungi-derived terpenoids distinguished by the presence of medium ring in their structure are important synthetic targets.[1,2] Recently, the attention of several laboratories has been focused on the neodolastane diterpenoids that were isolated from an endophytic fungus CR115 growing in branches of the *Daphnopsis americana* tree (Guanacaste Conservation Area, Costa Rica).[3,4] The first identified representative of this family, guanacastepene A (**1**, Figure 1), has a tricyclic structure with linearly fused five-, seven-, and six-membered rings. The "northern" edge of the molecule is highly polar, while the opposite edge is hydrophobic and bears two quaternary carbon atoms and an isopropyl group. A remarkable structural property of guanacastepene A consists of the noticeable conformational flexibility of the seven-membered ring. Along with the conformer "frozen" in a crystal lattice and registered by the X-ray analysis another conformer with only a slightly higher

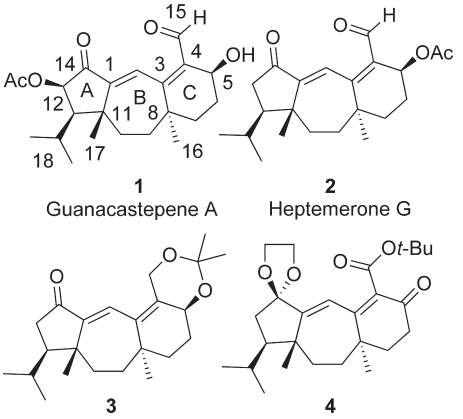

FIGURE 1. Structures of guanacastepene A, heptemerone G, and the key synthetic intermediates.

(1) (a) Brase, S.; Encinas, A.; Keck, J.; Nising, C. F. *Chem. Rev.* **2009**, *109*, 3903–3990. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963–3007. (c) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757–5821.

(2) For a review on synthesis guanacastepenes and related diterpenoids, see: (a) Maifeld, S. V.; Lee, D. *Synlett* **2006**, 1623–1644. (b) Hiersemann, M.; Helmboldt, H. *Top. Curr. Chem.* **2004**, *243*, 73–136.

(3) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, S. *J. Am. Chem. Soc.* **2000**, *122*, 2116–2117.

(4) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900–9901.

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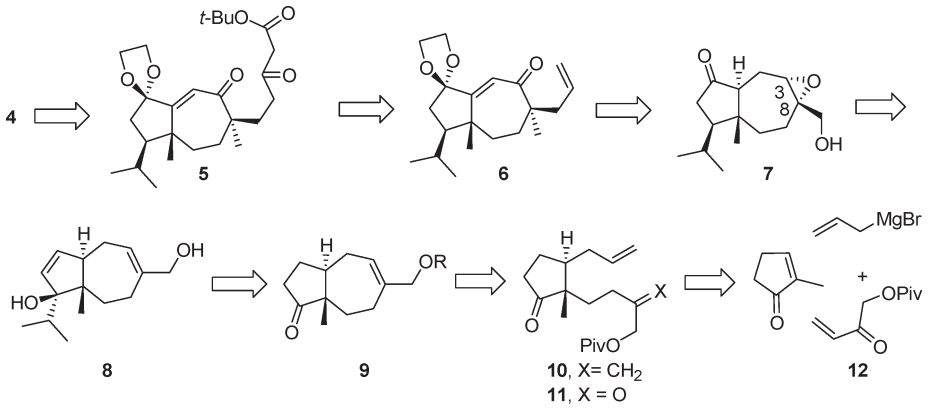
SCHEME 1. Main Features of the Proposed Scheme for the Synthesis of 4



energy exists in a solution, as evidenced by the NMR spectra.[3] Structurally closely related terpenoids have been isolated from a broth of a submerged culture *Coprinus heptemerus*.[5] The major representative of this group, heptemerone G (**2**), differs from **1** by the absence of the acetoxy substituent in ring A and by the nature of the substituent at C-5.

The interest in the synthesis of guanacastepene and heptemerone has been stimulated not only by their fascinating structure. The crude fermentation extracts of fungi from *Daphnopsis* as well as isolated guanacastepene A, were found to be highly active against drug-resistant strains of *Staphylococcus aureus* and *Enterococcus faecalis*. However, further development of guanacastepene A as a drug is limited by its hemolytic activity against human red blood cells.[6] Extracts of *Coprinus heptemerus* and heptemerone G inhibit germination of the rice blast fungal pathogen *Magnaporthe grisea* without interfering with the mycelia growth and show other biological activities.[7] Henceforth, a new class of diterpenoids with antibacterial and antifungal activities has been opened for the chemical and pharmacological exploration.

The first total synthesis of guanacastepene A was reported by Danishefsky and co-workers.[8−10] Syntheses of **1** have also been accomplished by Shipe and Sorensen,[11] and formal total syntheses of **1** were reported by Hanna,[12] Snider,[13] and Mehta[14] and their respective co-workers. Guanacastepene C was synthesized by Mehta,[14] guanacastepene N by Overman,[15] and guanacastepene E by Trauner.[16] To date, only one representative of the heptemerone family, i.e., heptemerone B, has been synthesized.[16] Several approaches to advanced intermediates for guanacastepene synthesis have also been developed.[2,17]

Now we report the first total synthesis of (±)-heptemerone G (**2**) and, en route, a new synthetic approach to compound **3** (which is a guanacastepene A precursor in the Danishefsky's synthesis) via the versatile tricyclic intermediate **4**.[18] The nature and location of functional groups in **4** were devised to ensure the selective reduction of carbonyl group at C-5 and further site-selective transformations.

Results and Discussion

The key features of our retrosynthetic plan for preparing of intermediate **4** are shown in Scheme 1. The bicyclic ketoester **5** was chosen as the immediate precursor to **4**. A smooth Knoevenagel-type annulation was anticipated since the enolization of ring carbonyl group would be blocked. The preparation of **5** from the bicyclic intermediate **6** would involve an oxidation of the allyl group to the propionaldehyde moiety, followed by an addition of the *tert*-butyl acetate anion and reoxidation. These routine operations would be carried out under neutral or alkaline conditions compatible with the presence of the acetal function.

The hydroxy epoxide moiety in **7** would serve as a starting point for installation of the carbonyl group at C-3 and for alkylation at C-8. The intermediate **7** would be prepared from **8** by (1) site-selective epoxidation of the less sterically shielded double bond (C-3−C-8) followed by protection of the primary hydroxy group, (2) oxidation of the tertiary allylic alcohol function with the oxygen transposition, and (3) hydrogenation of the double bond and removal of the hydroxy group protection.

The intermediate **8** would be prepared from **9** by dehydrogenation followed by addition of isopropyllithium to the corresponding α,β-unsaturated ketone. A procedure for synthesis of **9** was projected as follows: a set of tandem

(5) Valdivia, C.; Kettering, M.; Anke, H.; Thines, E.; Sterner, O. *Tetrahedron* **2005**, *61*, 9527–9532.
(6) 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.
(7) Kettering, M.; Valdivia, C.; Sterner, O.; Anke, H.; Thines, E. *J. Antibiot*. **2005**, *58*, 390–396.
(8) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2185–2188.
(9) Lin, S. N.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188–2191.
(10) Mandal, M.; Yun, H. D.; Dudley, G. B.; Lin, S. N.; Tan, D. S.; Danishefsky, S. J. *J. Org. Chem*. **2005**, *70*, 10619–10637.
(11) Shipe, W. D.; Sorensen, E. J. *J. Am. Chem. Soc*. **2006**, *128*, 7025–7035.
(12) Boyer, F. D.; Hanna, I. *Tetrahedron Lett*. **2002**, *43*, 7469–7472.
(13) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem*. **2003**, *68*, 1030–1042.
(14) Mehta, G.; Pallavi, K.; Umarye, J. D. *J. Chem. Soc., Chem. Commun*. **2005**, 4456–4458.
(15) Iimura, S.; Overman, L. E.; Paulini, R.; Zakarian, A. *J. Am. Chem. Soc*. **2006**, *128*, 13095–13101.
(16) Miller, A. K.; Hughes, C. C.; Kennedy-Smith, J. J.; Gradl, S. N.; Trauner, D. *J. Am. Chem. Soc*. **2006**, *128*, 17057–17062.
(17) Recent works include: (a) Fang, X. J.; Tong, X. F. *Tetrahedron Lett*. **2010**, *51*, 317–320. (b) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc*. **2009**, *131*, 6614–6617. (c) Malik, C. K.; Ghosh, S. *Org. Lett*. **2007**, *9*, 2537–2540. (d) McGowan, C. A.; Schmieder, A. K.; Roberts, L.; Greaney, M. F. *Org. Biomol. Chem*. **2007**, *5*, 1522–1524. (e) Srikrishna, A.; Dethe, D. H. *Org. Lett*. **2004**, *6*, 165–168.
(18) For preliminary communication on this work, see: (a) Michalak, K.; Michalak, M.; Wicha, J. *Tetrahedron Lett*. **2008**, *49*, 6807–6809. (b) Michalak, K.; Michalak, M.; Wicha, J. *Tetrahedron Lett*. **2010**, *51*, 4344–4346.

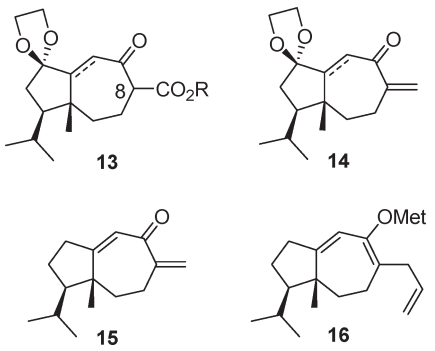


FIGURE 2. Plausible Intermediates for Generation of a Quaternary Stereogenic Center at C-8.

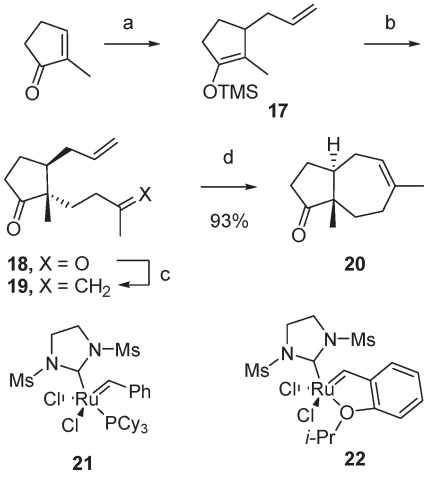
Michael−Michael−Mukaiyama conjugate additions of allylmagnesium bromide, 2-methylcyclopent-2-en-1-one, and the novel methyl vinyl ketone derivative **12** would afford adduct **11**. The side-chain carbonyl group in the latter would be subjected to the regioselective Wittig methylenation, and the 1,8-diene **10** would be submitted to the ring-closing metathesis reaction.[19,20]

The bulky pivaloyloxy group in **12** was expected to prevent sequential Mukaiyama−Michael addition and polymerization reactions that are notorious when unsubstituted methyl vinyl ketone is used.[21] The conjugate addition steps may, in principle, accommodate also the future attempt of synthesis of enantiomerically enriched intermediates.[22]

The stereochemical aspects of the proposed construction of quaternary stereogenic center in **6** are of special note. It was thought that the intermediate **7** would be transformed into **6** via either keto ester **13** (Figure 2) or α-methylidene ketone **14**. Mehta et al.[23] have shown that the methylation of a keto ester similar to **13** occurs stereoselectively in the *trans*-relationship to the angular methyl group. Conjugate addition of vinyl anion to **15** and methylation of **16** (Met = Li) were studied in detail by Danishefsky[8,10] and later by Snider.[13] Notably, azulene derivatives bearing a double bond at the ring junction position were a main subject of all discussed literature reports on methylation. Initially, we have underestimated the effect that the double bond may have on the steric course of this reaction.

The projected annulation procedure was initially examined in the synthesis of the simpler azulene derivative **20** (Scheme 2). The copper-catalyzed addition of allylmagnesium bromide to 2-methylcyclopent-2-en-1-one and trapping of the resulting enolate with the trimethylsilyl chloride was performed by analogy to the procedure reported by

SCHEME 2. Development of a Procedure for an α,β-Unsaturated Ketone Annulation[a]



[a]Key: (a) allylmagnesium bromide, CuI, LiBr, THF, −78 °C, and then TMSCl, Et_3N, 74%; (b) 2-methyl-2-vinyl-1,3-dioxolane, TMSOTf (cat.), CH_2Cl_2, −78 °C, and then acetone and water, rt, 48%; (c) $Ph_3P^+MeBr^-$, *n*-BuLi, THF−hexanes, rt, 3 h, 62%; (d) Grubbs' catalyst **21**, benzene, reflux, 2 h, 93%.

Booker−Milburn and Thompson,[25] giving **17** in 74% yield. Interestingly, the recently reported[26] indium chloride−trimethylsilyl chloride catalyzed Hosomi−Sakurai addition of allylsilane to 2-methylcyclopent-2-en-1-one afforded 3-allyl-2-methylcyclopentan-1-one in excellent yield. However, all our attempts to obtain the trimethylsilyl enol ether **17** following this route failed.

Silyl enol ether **17** was treated with 2-methyl-2-vinyl-1,3-dioxolane (which is the preferred synthetic equivalent of methyl vinyl ketone in the Mukaiyama−Michael addition[21,27]) and a Lewis acid catalyst to provide the respective adduct. The best results were obtained with trimethylsilyl triflate[20,28] as the catalyst (1.5 mol %), and the crude product was hydrolyzed in wet acetone. The diketone **18**, obtained in a 48% yield, was subjected to reaction with methylidenetriphenylphosphorane generated in situ from methyltriphenylphosphonium bromide and butyllithium. As expected, only the less sterically shielded carbonyl group was affected to give the methylidene derivative **19** in a 62% yield. The ring-closing metathesis of 1,8-diene **19** catalyzed by the Grubbs' dihydroimidazolylidene ruthenium complex[29] **21** in benzene at reflux temperature afforded the azulene derivative **20** in 93% yield.

The Michael acceptor **12** was prepared from readily accessible but-3-ene-1,2-diol[30] by selective acylation of the primary hydroxy group with pivaloyl chloride[31] followed by the oxidation of secondary hydroxy group with the Jones'

(19) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. Michalak, K.; Michalak, M.; Wicha, J. *Molecules* **2005**, *10*, 1084–1100. Michalak, M.; Wicha, J. *Synlett* **2005**, 2277–2280.

(20) Michalak, K.; Michalak, M.; Wicha, J. *Tetrahedron Lett.* **2005**, *46*, 1149–1153.

(21) Marczak, S.; Michalak, K.; Urbanczyk-Lipkowska, Z.; Wicha, J. *J. Org. Chem.* **1998**, *63*, 2218–2223. and references quoted therein..

(22) For leading references, see: (a) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192–1194. (b) Bernardi, A.; Karamfilova, K.; Sanguinetti, S.; Scolastico, C. *Tetrahedron* **1997**, *53*, 13009–13026. (c) Gorobets, E.; Stepanenko, V.; Wicha, J. *Eur. J. Org. Chem.* **2004**, 783–799. (d) Tanis, S. P.; Robinson, E. D.; McMills, M. C.; Watt, W. *J. Am. Chem. Soc.* **1992**, *114*, 8349–8362.

(23) Mehta, G.; Umarye, J. D.; Srinivas, K. *Tetrahedron Lett.* **2003**, *44*, 4233–4237.

(24) For some early literature reports on cycloheptanone alkylation, see: (a) Crews, P. *J. Chem. Soc., Chem. Commun.* **1971**, 583–584. (b) Pearson, A. J.; Bansal, H. S. *Tetrahedron Lett.* **1986**, *27*, 287–290.

(25) Booker-Milburn, K. I.; Thompson, D. F. *Tetrahedron* **1995**, *51*, 12955–12962.

(26) Lee, P. H.; Lee, K.; Sung, S. Y.; Chang, S. *J. Org. Chem.* **2001**, *66*, 8646–8649. Lee, P. H.; Seomoon, D.; Kim, S.; Nagaiah, K.; Damle, S. V.; Lee, K. *Synthesis* **2003**, 2189–2193.

(27) Narasaka, K.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779–783.

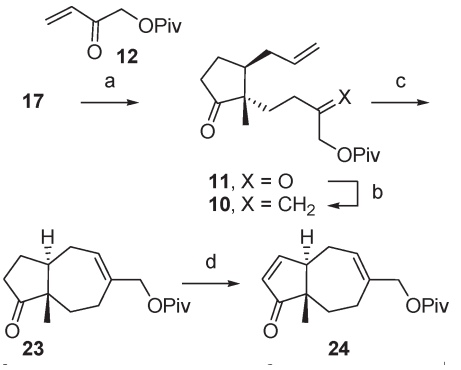
(28) Michalak, K.; Wicha, J. *Pol. J. Chem.* **2004**, *78*, 205–215.

(29) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

(30) Rama Rao, A. R.; Bose, D. S.; Gurjar, M. K.; Ravindranathan, T. *Tetrahedron* **1989**, *45*, 7031–7040.

(31) Dallanoce, C.; De Amici, M.; Carrea, G.; Secundo, F.; Castellano, S.; De Micheli, C. *Tetrahedron: Asymmetry* **2000**, *11*, 2741–2751.

SCHEME 3. Synthesis of the Azulene Derivative 24[a]



[a]Key: (a) TMSOTf, CH_2Cl_2, −78 °C, 79%; (b) $Ph_3P^+MeBr^-$, *n*-BuLi, THF−hexanes, 83%; (c) **21** or **22** (2−4 mol %), CH_2Cl_2, reflux, 96−100%; (d) (1) TMSCl, NaI, Et_3N, MeCN, reflux, (2) *o*-iodoxybenzoic acid (IBX), 4-methoxypyridine *N*-oxide (MPO), DMSO, rt, chromatography, 84% in two steps.

reagent. The reaction of silyl enol ether **17** and the α,β-unsaturated ketone **12** in the presence of trimethylsilyl triflate afforded the adduct **11** in a 79% yield (Scheme 3). Regioselective methylenation of **11** gave the 1,8-diene **10** with the pivaloyl group unaffected (83% yield). The ring-closing metathesis reaction of **10** was carried out using the catalyst **21** or the Hoveyda−Blechert modified catalyst[32] **22** in refluxing CH_2Cl_2 to afford **23** in a 96% yield. The larger scale metathesis reactions were preferentially carried out by periodic portionwise additions of the diene **10** and the catalyst **22** to the refluxing reaction mixture, which allowed us to limit the total amount of solvent to 1.5 L per 20 g of the product (see the Experimental Section).

Ketone **23** was dehydrogenated via its trimethylsilyl enol ether with a combination of 2-iodoxybenzoic acid (IBX) and 4-methoxypyridine *N*-oxide (MPO) in DMSO at ambient temperature.[33] The product **24** was isolated in an 84% yield after careful chromatography, along with some unconsumed starting material.

The α,β-unsaturated ketone **24** in THF at −78 °C was treated with a freshly prepared isopropyllithium in hexanes to afford **8** (Scheme 4). The two double bonds in compound **8** differ significantly with respect to the steric shielding. Indeed, the reaction of **8** with the 3-chloroperoxybenzoic acid (3 equiv) in dichloromethane at −78 to 0 °C selectively produced the monoepoxide **25**. This sparingly soluble product could be purified by chromatography followed by crystallization; however, it was more convenient to purify the monobenzoate **26** prepared from the crude product (85% yield in two steps). The allylic alcohol moiety in **26** was oxidized with pyridinium chlorochromate (PCC) in dichloromethane to provide the α,β-unsaturated ketone **27** with the oxygen function transposed[34] (82% yield).

The catalytic hydrogenation of the double bond in **27** was carried out using palladium catalyst in ethyl acetate at 80 bar (ca. 20 h). Initially, the stock Degussa 10% palladium-on-carbon was used, which provided pure dihydro product **28** in virtually quantitative yield. When the hydrogenation was repeated with new batches of the Degussa catalyst or with the Fluka 10% palladium-on-carbon catalyst, a small amount of a side product (more polar) was also formed. Satisfactory results were consistently obtained using 10% palladium-on-calcium carbonate in the presence of powdered sodium hydrogen carbonate. The crude hydrogenation product **28** was subjected to hydrolysis with methanolic potassium hydroxide to give the crystalline, easy to purify epoxy alcohol **7**. The structure of this product was confirmed by X-ray analysis.[18]

The primary hydroxy group in **7** could be oxidized to the carbaldehyde group. However, our initial attempts to transform either **7** or the respective epoxy-aldehyde into the earlier discussed β-ketoester structure (**13**, Figure 2) were discouraging. Consequently, we concentrated our attention on the preparation of the methylidene alcohol **31** (Scheme 5).

The free-radical variation of the Wharton rearrangement[35] was examined as a means to effect reduction of epoxy alcohol **7** into **31**. Alcohol **7** on treatment with thiocarbonyldiimidazole (TCDI) gave the derivative **29** almost quantitatively. Reduction of **29** with tributyltin hydride−AIBN (cat.) in refluxing benzene furnished **31**, but the yield was low, and several side products were formed.[36] To circumvent the difficulties, the synthesis of iodide **30** was attempted in anticipation of a facile reduction of the iodo epoxy functionality.[37] After some experimentation, an extremely mild method for conversion of alcohols into iodides was successfully applied: the already prepared imidazolide **29** was heated with methyl iodide at reflux temperature[38] in the presence of sodium hydrogen carbonate and some copper turnings. Iodide **30** thus formed, unstable and difficult to handle, was purified by a flash chromatography and then immediately reduced with zinc dust in refluxing ethanol. The methylidene alcohol **31** was obtained as the sole product. Eventually, an alternate preparation of **31** from **7** via the respective tosylate, the Finkelstein exchange, and zinc reduction without purification of the intermediates was developed. This method was used in synthetic runs at multigram scale giving the product in 92% overall yield.

In an attempt to protect the oxo group, **31** was subjected to reaction with ethylene glycol in the presence of pyridinium *p*-toluenesulfonate (PPTS) in refluxing benzene in a flask equipped with a Dean−Stark adapter for water removal. A mixture of products was obtained that could not be separated by chromatography. Oxidizing the crude mixture with active manganese dioxide[39] in ether followed by chromatography gave the required derivative **32** (Scheme 6). However, the reproducibility of results was poor, and the reaction yields were notoriously low. When the ketalization product

(32) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179. Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973–9976.

(33) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996–999.

(34) Babler, J. H.; Coghlan, M. J. *Synth. Commun.* **1976**, *6*, 469–474. Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682–685. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2650.

(35) Barton, D. H. R.; Hay Motherwell, R. S.; Motherwell, W. B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2363–2367. Wharton, P.; Bohlen, D. *J. Org. Chem.* **1961**, *26*, 3615–3616.

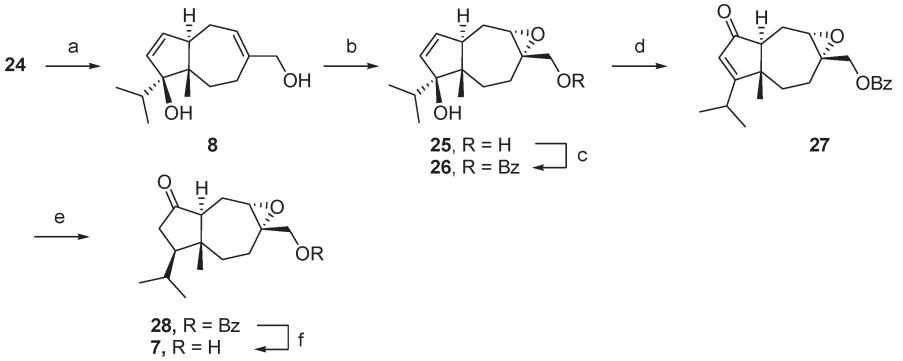
(36) For some examples of skeletal rearrangements of epoxy alcohol thioimidazolides, see: Goto, M.; Miyoshi, I.; Ishii, Y.; Ogasawara, Y.; Kakimoto, Y. I.; Nagumo, S.; Nishida, A.; Kawahara, N.; Nishida, M. *Tetrahedron* **2002**, *58*, 2339–2350. and references quoted therein..

(37) Logusch, E. W. *Tetrahedron Lett.* **1979**, *20*, 3365–3366. Oikawa, Y.; Nishi, T.; Yonemitsu, O. *J. Chem. Soc., Perkin Trans. 1* **1985**, 7–17.

(38) Barton, D. H. R.; Stick, R. V.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2112–2116.

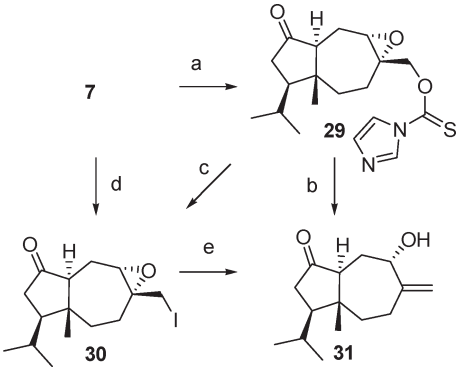
(39) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094–1111.

SCHEME 4. Diastereoselective Transformations of 24 into 7[a]



[a]Key: (a) *i*-PrLi, THF−hexanes, −78 °C, 84%; (b) *m*-CPBA, CH_2Cl_2, −78 °C → rt; (c) BzCl, Py, CH_2Cl_2, rt, 85% from **8**; (d) PCC, CH_2Cl_2, rt, 82%; (e) H_2−Pd/$CaCO_3$, $NaHCO_3$, EtOAc, 80 bar; (f) KOH, MeOH, rt, 94% from **27**.

SCHEME 5. Wharton-Type Reductive Rearrangement of Epoxy Alcohol 7[a]



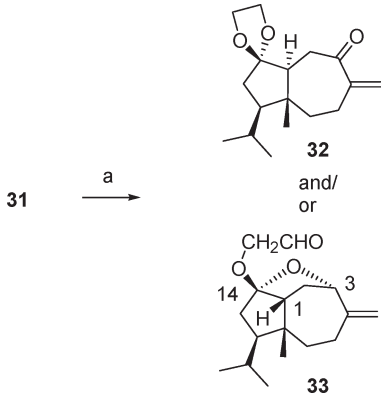
[a]Key: (a) thiocarbonyldiimidazole (TCDI), benzene, 60 °C, 98%; (b) Bu_3SnH, AIBN (cat.), benzene, reflux. 32%; (c) MeI, $NaHCO_3$, Cu wire, 60 °C (sealed ampule), 83%; (d) (1) TsCl, Py, 0 °C, (2) NaI, acetone, reflux; (e) Zn dust, anhyd EtOH, reflux, 97%; 92% from **7** via the tosylate without intermediate purification.

was subjected to the oxidation with Dess−Martin periodinane[40] in dichloromethane another product was isolated (up to 80% yield). The ^{1}H NMR spectrum of this product indicated the presence of an aldehyde proton (δ 9.69−9.67 ppm, m) and deshielded methylidene group protons [δ 4.20 (dd, J = 17.9, 1.4 Hz, 1H) and 4.06 (dd, J = 17.9, 1.0 Hz, 1H)]. The structure of internal acetal−aldehyde **33** was assigned to this product. It was evident that under the ketalization conditions the epimerization at ring junction (C-1) occurred. The subsequent intramolecular acetalization with the tetrahydrofuran ring closing was a dominant process reflecting the close proximity of the oxo group (C-14) and the hydroxy group (C-3).

Careful acetylation of hydroxy-ketone **31** with acetic anhydride and DMAP in methylene chloride at room temperature gave the acetate **34** (Scheme 7) contaminated with another product, presumably its *cis*-azulene epimer (10−15% by ^{1}H NMR). No ketal was isolated in an attempted reaction of acetoxy ketone **34** with ethylene glycol and PPTS in refluxing benzene. After considerable experimentation, we were gratified to find

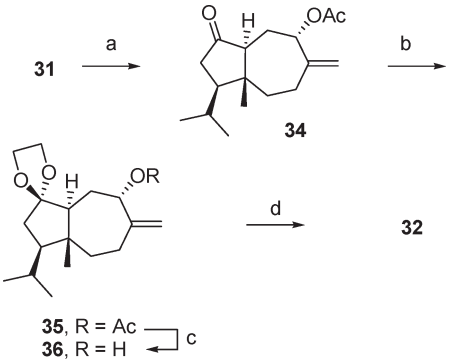
(40) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

SCHEME 6. Attempted Ketalization of 31 Followed by Oxidation of the Crude Product[a]



[a]Key: (a) ethylene glycol, PPTS, benzene, reflux and then oxidation with MnO_2 or with Dess−Martin periodinane.

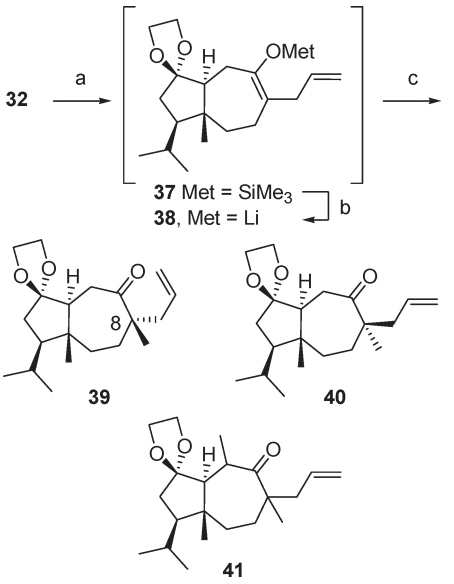
SCHEME 7. Protection of Enolizable Ketone 31 under Mild Conditions and the Synthesis of Intermediate 32[a]



[a]Key: (a) Ac_2O, DMAP, CH_2Cl_2, rt, 89% (85−90% pure); (b) ethylene glycol, $(MeO)_3CH$, *p*-TSA·H_2O, rt; (c) KOH, MeOH, 96% from **34**; (d) MnO_2, Et_2O, 84%.

that treatment of a suspension of **34** in ethylene glycol with *p*-toluenesulfonic acid as the catalyst and methyl orthoformate as the water scavenger afforded the respective ethylene ketal **35** as the sole product. Hydrolysis of the acetate function in the crude ketal provided **36** in 98% yield. Manganese dioxide

SCHEME 8. Unsuccessful Attempt at Construction of the Guanacastepene Quaternary Stereogenic Center C-8[a]



[a]Key: (a) CH_2=CHMgBr, CuI, HMPA, TMSCl, THF, −78 °C → rt; (b) MeLi, THF-Et_2O, 0 °C; (c) MeI, HMPA, and chromatography, **39** and **40**, 72% in a ratio of 90:10, **41**, 14%.

oxidation of **36** led to methylidene ketone **32** (84% yield) that was used immediately in the next step.

With an expeditious approach to the methylidene ketone **32** in hand, the construction of the stereogenic center at C-8 and the final annulation could be approached. At this juncture of the synthetic route we thought we could benefit from the experience gathered by Danishefsky and co-workers who have applied a similar methylidene ketone as an intermediate in their guanacastepene A synthesis.[10,41] These authors treated their methylidene ketone intermediate with vinylmagnesium bromide in the presence of copper(I) iodide and trimethylsilyl chloride[42] to generate dienolate silyl enol ether (Figure.2, 16, Met = TMS). The dienol silyl ether was then transmetalated with methyllithium[43] to generate **16**, Met = Li, which was subsequently quenched with methyl iodide and HMPA.

No obvious difference in the facial selectivity was predicted from the inspection of the Dreiding molecular models of the reported dienolate (**16**, Met = Li) and our projected enolate **38** (Scheme 8). However, when methylidene ketone **32** was subjected to the alkylation procedure, little similarity to the reported outcome was observed. The crude product was separated by column chromatography into two fractions. The more mobile, minor fraction was homogeneous and was identified as the allyl dimethyl derivative **41** (Scheme 8, 14% yield). The major fraction appeared homogeneous by TLC and HPLC, but analysis of its ^{1}H NMR spectra and HPLC−HRMS analysis indicated the presence of two epimeric allyl methyl derivatives in a ratio of 9:1 (72% yield).

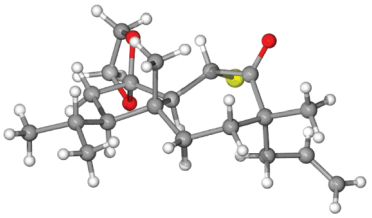
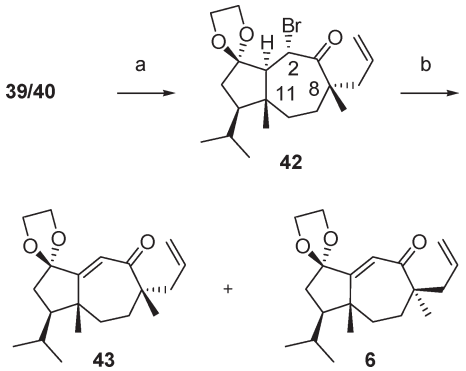


FIGURE 3. ORTEP diagram of the X-ray structure of **42**.

SCHEME 9. Preparation of Bromide 42 and Stereochemical Correlations[a]



[a]Key: (a) (1) LDA, THF−hexanes, −78 °C, (2) TMSCl, (3) NBS, THF, −78 °C, crystallization, 78%; (b) KO*t*-Bu, THF, **43**/**6**, 9:1, 67% from **39**/**40** via nonisolated bromides.

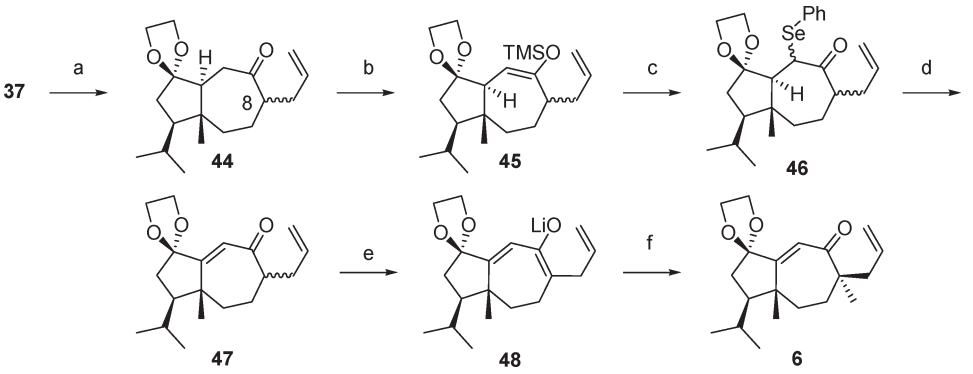
Elucidation of the structure of these products was based on the single-crystal X-ray analysis of the bromide **42** (Scheme 9) and the complementing chemical correlations. Thus, the mixture, without separation, was converted into the respective trimethylsilyl enol ethers that were subsequently treated with *N*-bromosuccinimide in THF at −78 °C. Crystalline and homogeneous by ^{1}H NMR bromide was obtained in 77% yield after recrystallization of the crude product. The structure of this highly unstable derivative was solved by a low-temperature single-crystal X-ray analysis.[44] The striking feature of the revealed structure, **42** (Figure 3), was the *β*-orientation of the newly introduced methyl group in a *cis*-relationship to the angular methyl group. The bromine substituent at C-2 was in the α-orientation (it should be noted that epimerization of α-bromo ketones may occur under mild conditions[13,45]). The azulene rings were joined in *trans*-fashion, in accordance with our previous assumption.

Dehydrobromination of pure **42** with potassium *tert*-butoxide gave the enone **43**. When the crude bromides generated from the mixture of monomethylated products were subjected to an analogous dehydrobromination procedure, the enone **43** was accompanied by its minor epimer. The structure **6** was assigned to this epimer, and consequently, the structures **39** and **40** to the monomethylated products, **39** being the major one.

In a modified approach to the construction of the stereogenic center at C-8, the silyl enol ether **37**, prepared from **32** as described previously, was treated with tetrabutylammonium fluoride to afford the ketone **44** (Scheme 10).

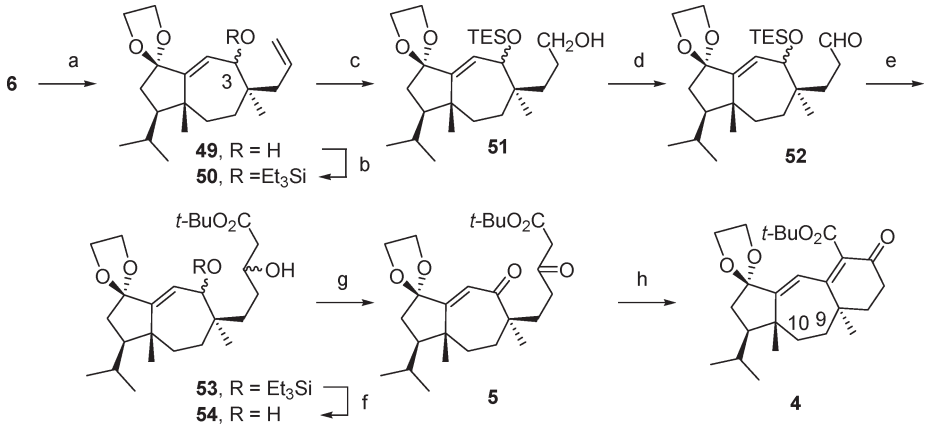
(41) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6789–6791.
(42) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019–6022. Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368–3370. Frantz, D. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 3288–3295.
(43) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464–4465.
(44) Selected X-ray structure data are included in the Supporting Information.
(45) Hiroi, K.; Yamada, S. I. *Chem. Pharm. Bull. Jpn.* **1973**, *21*, 54–61.

SCHEME 10. Synthesis of the Intermediate 6[a]



[a]Key: (a) $Bu_4NF \cdot 3H_2O$, 92% from **32**; (b) LDA, THF−hexanes, −78 °C and then TMSCl; (c) PhSeCl, Py, CH_2Cl_2, 73% from **44**; (d) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, −78 °C, 89%; (e) LHMDS, THF, 0 °C; (f) MeI, HMPA, −20 °C → rt, 98% from **47** (>99% pure).

SCHEME 11. Synthesis of the Key Tricyclic Intermediate 4[a]



[a]Key: (a) $NaBH_4-CeCl_3 \cdot 7H_2O$, MeOH, −20 °C; (b) TESCl, imidazole, DMAP, CH_2Cl_2, 90% from **6**; (c) (1) 9-BBN, THF, 0 °C → rt, (2) H_2O_2−NaOH, 97%; (d) tetra-*n*-propylammonium perruthenate (TPAP)−NMO, 4 Å MS, CH_2Cl_2, 95%; (e) LDA, CH_3CO_2t-Bu, THF−hexanes, −78 °C → rt; (f) $Bu_4NF \cdot 3H_2O$, THF, 91% from **52**; (g) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2; (h) EtONa−EtOH, 80% from **54**.

This product was epimerically pure according to its ^1H and ^{13}C NMR spectra. However, no effort was made to determine the configuration at C-8 since this center was to be destroyed in further steps. The "kinetic" lithium enolate was generated from **44** with LDA and then trapped with trimethylsilyl chloride. The trimethylsilyl derivative **45** was transformed into phenyl selenide **46** in the usual way and, hence, through the respective selenoxide(s), into enone **47**.[46]

Dienolate **48**, generated from **47** and lithium hexamethyldisilazanide (LHMDS), was allowed to react with methyl iodide in the presence of HMPA. The single product was obtained in 98% yield. HPLC−MS analysis of this product indicated that it is at least 99% pure and established its identity with **6**.

In summing up experiments on the construction of the stereogenic center at C-8, the methylation of lithium dienolate **48** was completely site- and diastereoselective, affording **6** (Scheme 10). Alkylation of the lithium enolate **38** was less selective leading to a mixture of **39** and **40** in a ratio of 9:1, along with the dimethyl derivative **41**. Formation of **41** could be attributed to the harsh conditions of enolate generation. The main difference in alkylation of **48** and **38** consisted in the stereochemical outcome. While methylation of the dienolate **48** occurred *trans* to the angular methyl group, consistent with the reported observations,[10,13,23] the methylation of enolate **38** indicated the opposite facial selectivity. The computational explanation of this apparent discrepancy in alkylation of unsaturated and saturated azulenone derivatives has been already published.[47]

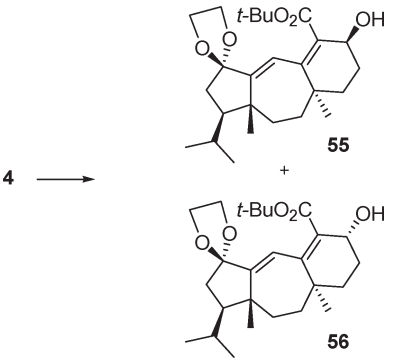
In order to protect the α,β-unsaturated ketone function for further transformations, **6** was reduced following the Luche protocol,[48] and the resulting alcohol **49**, without purification, was transformed into its triethylsilyl ether to give **50** in a 97% yield (Scheme 11). The terminal double bond in **50** was subjected to hydroboration−oxidation procedure to afford the primary alcohol **51**. Oxidation of **51** with Dess−Martin periodinane[40] turned out to be sluggish. Gratifyingly, the tetra-*n*-propylammonium perruthenate

(46) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137–6139. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447. Ryu, I.; Murai, S.; Niwa, I.; Sonda, N. *Synthesis* **1977**, 874–876.

(47) Wang, H.; Michalak, K.; Michalak, M.; Jiménez-Osés, G.; Wicha, J.; Houk, K. N. *J. Org. Chem.* **2010**, *75*, 762–766.

(48) Luche, J.-L.; Rodriguez-Hahn, L.; Crabbe, P. *Chem. Commun.* **1978**, 601–602.

SCHEME 12. Reduction of the Keto Group in 4



(TPAP)−*N*-methylmorpholine *N*-oxide (NMO)[49] oxidation afforded the aldehyde **52** in excellent yield.

The addition of lithium *tert*-butyl acetate[50] (generated from *tert*-butyl acetate and LDA in THF−hexanes at −78 °C) to **52** afforded the adduct **53** that was desilylated without purification. A mixture of diols **54**, thus obtained, was oxidized with freshly prepared Dess−Martin periodinane to the dione **5** that was decomposing on attempted isolation. However, when crude **5** was treated with sodium ethoxide in absolute ethanol at room temperature the tricyclic derivative **4** was formed smoothly (80% yield from diol **54**). It was pleasing to see this intermediate as beautiful crystals (mp 145−146 °C, hexane) amenable for storing, after struggling through several stages with unstable oily intermediates. The ^{1}H NMR spectra taken in $CDCl_3$ at 25 °C fully confirmed the structure of **4**. In the ^{13}C NMR spectra of **4** some resonances were significantly broadened which presumably reflects the presence of two conformers in a dynamic equilibrium (flexibility in the region of the C9−C10 bond).[3,5]

The keto group in keto-ester **4** was site- and stereoselectively reduced by several reducing agents to afford a mixture of alcohols **55** and **56** (both crystalline) that were easy to separate by chromatography (Scheme 12). The composition of the mixture could be determined directly from the ^{1}H NMR spectrum by integration of well-separated signals at δ 1.25 and 1.09 ppm (singlets, 3H) for **55** and **56**, respectively. The results of the experiments are compiled in Table 1. Thus, reduction with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ (the Luche protocol) affords **55** and **56** in a ratio of 5:4 (isolated products), whereas $NaBH_4$ alone proved somewhat more selective (**55**:**56** as 2:1). The same selectivity was observed with L-Selectride in THF at −78 °C. DIBAL in CH_2Cl_2 at −78 °C afforded a slight excess of the undesired 5α-isomer **56**. LiAl(O-*t*-Bu)$_3$ in THF at −78 °C to rt afforded the isomers **55** and **56** in a ratio of 3:2. $LiAlH_4$ in THF at −78 °C proved to be more selective, giving the isomers in a ratio of 3:1. Lowering the temperature to −93 °C permitted us to obtain alcohol **55** in 77% yield along with **56**, 12%. Noteworthy, the reduction with $LiAlH_4$ was solvent dependent; in Et_2O at −78 °C, the product ratio of 1:1 was observed.

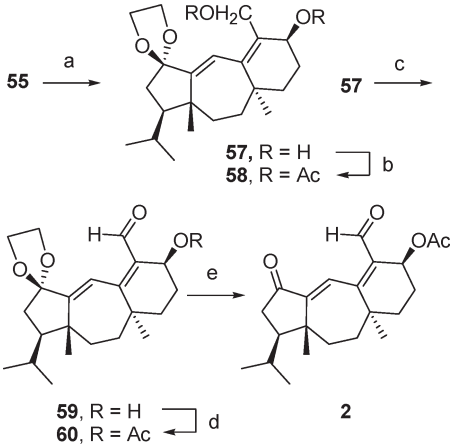
The hydroxy ester **55** was reduced further with $LiAlH_4$ at room temperature to give the diol **57** (Scheme 13), which decomposed upon attempted purification by chromatography.

TABLE 1. Reduction of the Keto Group in 4: Epimer Ratio 55:56 Estimated by ^{1}H NMR (Integration of 3H singlets δ 1.25 and 1.09)

reagent	conditions	**55**/**56** ratio
$NaBH_4$	THF-MeOH, −78 °C→ rt	2:1
$CeCl_3\ 7H_2O$, $NaBH_4$	MeOH, −20 °C	5:4[a]
DIBAL-H	CH_2Cl_2, −78 °C	4:5
L-Selectride	THF, −78 °C	2:1
LiAl(O*t*-Bu)$_3$	THF, −78 °C → rt.	3:2
$LiAlH_4$	Et_2O, −78 °C	1:1
$LiAlH_4$	THF, −78 °C	3:1
$LiAlH_4$	THF, −93 °C	6.5:1[a]

[a]Ratio of isolated products.

SCHEME 13. Concluding Steps in the Synthesis of Heptemerone G (2)[a]



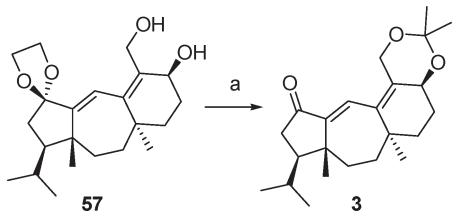
[a]Key: (a) $LiAlH_4$, THF, rt; (b) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 94% from **55**; (c) $PhI(OAc)_2$−TEMPO, CH_2Cl_2, 67% from **55**; (d) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 94%; (e) PPTS (cat.) aq acetone, rt, 94%.

While the diol **57** could be transformed into diacetate **58** almost quantitatively, all attempts to selectively hydrolyze the primary acetoxy group in **58** failed. Eventually, the procedure developed by Danishefsky et al.[10,51] for a similar diol was employed. Thus, oxidation of **57** with $PhI(OAc)_2$−2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) provided the hydroxy aldehyde **59** in 60−70% yield (Scheme 13). The hydroxy group in **59** was then acetylated using acetic anhydride in the presence of triethylamine and DMAP in dichloromethane. The crystalline and easy to purify acetate **60** was obtained (94%). Finally, the ethylene ketal protective group in **60** was hydrolyzed using PPTS in wet acetone. The product was purified by chromatography to give heptemerone G (**2**, 94% yield). Its HRMS, IR, UV, and ^{1}H, and ^{13}C NMR spectra fully corroborated its assigned structure. The ^{1}H and ^{13}C NMR in DMSO-d_6 at 100 °C of **2** showed the signals in full agreement with reported data.[5] No spectrum of the natural product was available for a direct comparison.

The crude diol **57**, immediately after preparation, was dissolved in acetone and treated with a catalytic amount of *p*-toluenesulfonic acid monohydrate. Compound **3** (Scheme 14) was obtained in 95% yield as a crystalline solid showing the expected HRMS spectra and ^{1}H, ^{13}C NMR spectra in a full agreement with those reported.[10] Since an efficient three-step transformation of **3** into the guanacastepene A (**1**) has

(49) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.
(50) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318–2320. Rathke, M. W.; Sullivan, D. F. *J. Am. Chem. Soc.* **1973**, *95*, 3050–3051.
(51) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977.

SCHEME 14. Synthesis of Guanacastepene A Precursor 3[a]



[a]Key: (a) acetone, *p*-TSA·H_2O, rt, 95%.

been reported,[10] the formal total synthesis of (±)-**1** has been thus accomplished.

In conclusion, a synthesis of a versatile tricyclic intermediate for neodolestane triterpenoids (**4**), the first total synthesis of (±)-heptemerone G (**2**), and a formal total synthesis of (±)-guanacastepene A were developed. The intermediate **4** was prepared from 2-methylcyclopent-2-en-1-one in 5.1% yield via 23 isolated intermediates. The synthetic route includes a new efficient sequence for 2-methylcyclopent-2-en-1-one annulation and a stereoselective alkylation of an azulene related ketone and is concluded with a straightforward construction of the six-membered ring. An unprecedented effect of the double bond on face selectivity was observed in the construction of a quaternary stereogenic center in azulene-related derivatives.

Experimental Section

[(3-Allyl-2-methylcyclopent-1-en-1-yl)oxy]trimethylsilane (17). Freshly prepared allylmagnesium bromide (1 M in Et_2O, 110 mL) was added dropwise, within 15 min, to a solution of anhyd LiBr (10.95 g, 127.4 mmol) and CuI (24.2 g, 127.4 mmol) in THF (220 mL), stirred at −78 °C. The dark brown solution was stirred for 30 min at −78 °C and then 2-methylcyclopent-2-en-1-one (**11**, 4.08 g, 42.5 mmol) was added, followed by TMSCl (16.7 mL, 131.7 mmol). Stirring was continued for 1 h at −78 °C, and then Et_3N (26.6 mL, 191.1 mmol) was added. The mixture was allowed to warm to rt, and then the next portion of Et_3N (26.6 mL, 191.1 mmol) was added. The mixture was diluted with hexanes (500 mL) and set aside for 15 min. The solution was decanted from the solids and washed with $NaHCO_3$ solution. The organic layer was collected, washed with water and brine, and dried (Na_2SO_4). The solvent was evaporated, and the residue was distilled (98−102 °C/15 mmHg) to give **17** (6.60 g, 74%): ^{1}H NMR (200 MHz) 5.88−5.65 (m, 1H), 5.15−4.90 (m, 2H), 2.62−2.42 (m, 1H), 2.38−2.10 (m, 4H), 2.05−1.80 (m, 2H), 1.54−1.40 (m, 3H), 0.17 (s, 9H); ^{13}C NMR (50 MHz) 146.0, 137.1, 115.8, 115.6, 44.2, 38.5, 32.5, 25.7, 10.3, 0.6. Anal. Calcd for $C_{12}H_{22}OSi$ (210.14): C, 68.51; H, 10.54. Found: C, 68.76; H, 10.50.

(2*S,3*S**)-3-Allyl-2-(4-hydroxy-3-oxobutyl)-2-methylcyclopentan-1-one Pivalate (11).** Enone **12** (see the Supporting Information, 3.93 g, 23.1 mmol) and TMSOTf (418 μL, 2.3 mmol) were consecutively added to a solution of silyl enol ether **17** (4.86 g, 23.1 mmol) in anhyd CH_2Cl_2 (40 mL), stirred at −78 °C. Stirring at −78 °C was continued for 72 h, and then the reaction was quenched with water (2 mL). The mixture was allowed to warm to rt, and then powdered $NaHCO_3$ (1.5 g) was added portionwise. The solution was diluted with hexanes (60 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was chromatographed on silica gel (240 g of silica gel, EtOAc−hexanes, 7.5:92.5−15:85) to give **11** (5.63 g, 79%): ^{1}H NMR (400 MHz) 5.80−5.68 (m, 1H), 5.08−4.96 (m, 2H), 4.58 (s, 2H), 2.49 (ddd, J = 15.9, 10.3, 5.5 Hz, 1H), 2.41−2.18 (m, 4H), 2.11−1.98 (m, 2H), 1.95−1.76 (m, 4H), 1.69 (ddd, J = 14.4, 10.3, 5.5 Hz, 1H), 1.22 (s, 9H), 0.83 (s, 3H); ^{13}C NMR (50 MHz) 222.7, 203.6, 177.7, 136.3, 116.3, 67.7, 50.0, 43.7, 38.6, 36.9, 34.2, 33.6, 28.5, 27.0, 24.5, 17.0; HRMS calcd for $C_{18}H_{28}O_4$ (M^+) 308.1988, found 308.1999.

(2*S,3*S**)-3-Allyl-2-[3-(hydroxymethyl)but-3-enyl]-2-methylcyclopentan-1-one Pivalate (10).** A solution of *n*-BuLi (2.5 M in hexanes, 34.75 mL, 86.9 mmol) was added dropwise to a suspension of methyltriphenylphosphonium bromide (38.1 g, 106.7 mmol) in THF (500 mL), stirred at rt. The mixture was stirred for 30 min, and then it was cooled to −78 °C. Dione **11** (13.45 g, 43.7 mmol) in THF (200 mL) was added slowly via a cannula, and stirring was continued for 1 h. Water (6 mL) was then added, and the mixture was allowed to warm to −20 °C. The solution was diluted with hexanes (1 L) and set aside for 1 h at rt. The solid (triphenylphosphine oxide) was filtered off, and the filtrate was evaporated. The residue was chromatographed on silica gel (150 g, EtOAc−hexanes, 5:95) to give **10** (11.14 g, 83%): ^{1}H NMR (200 MHz) 5.95−5.76 (m, 1H), 5.18−4.85 (m, 4H), 4.50 (s, 2H), 2.50−1.35 (m, 11H), 1.22 (s, 9H), 0.88 (s, 3H); ^{13}C NMR (50 MHz) 222.7, 178.0, 144.0, 136.5, 116.2, 111.8, 66.4, 42.5, 38.8, 37.2, 34.6, 33.8, 27.9, 27.2, 24.7, 17.6; HRMS calcd for $C_{19}H_{30}O_3Na$ ($M + Na^+$) 329.2087, found 329.2080.

(3a*S,8a*S**)-6-(Hydroxymethyl)-8a-methyl-3,3a,4,7,8,8a-hexahydroazulen-1(2*H*)-one pivalate (23).** (a) A solution of diene **10** (2.35 g, 7.62 mmol) in CH_2Cl_2 (70 mL) was added to a solution of Grubbs' catalyst **21** (130 mg, 0.15 mmol, 2 mol %) in CH_2Cl_2 (700 mL), and the mixture was heated under reflux for 2 h (TLC indicated the substrate consumption). After cooling, the solvent was evaporated, and the residue was chromatographed on silica gel (100 g, EtOAc−-hexanes, 1:9) to give **23** (2.05 g, 96%): ^{1}H NMR (200 MHz) 5.87−5.70 (m, 1H), 4.40 (s, 2H), 2.55−1.05 (m, 11H), overlapping 1.20 (s, 9H), 0.88 (s, 3H); ^{13}C NMR (50 MHz) 222.3, 178.2, 136.8, 128.0, 71.1, 50.7, 45.8, 38.8, 35.9, 33.0, 29.1, 27.2, 25.2, 24.8, 12.8; HRMS calcd for $C_{17}H_{26}O_3$ (M^+) 278.1882, found 278.1870.(b) The Hoveyda−Blechert−Grubbs' catalyst **22** (407 mg, 0.65 mmol, 2 mol %) was added to a solution of diene **10** (9.98 g, 32.6 mmol) in CH_2Cl_2 (1.5 L), and the mixture was heated under reflux for 4 h. New portions of **10** (6.01 g, 19.6 mmol) and of the catalyst (250 mg, 0.40 mmol) were then added, and heating was continued for 2 h. Next, portions of **10** (6.12 g, 20 mmol) and the catalyst (254 mg, 0.41 mmol) were added, and the mixture was heated under reflux for subsequent 4 h. After cooling, the solvent was evaporated and the residue was chromatographed on silica gel (300 g, EtOAc−hexanes, 1:9) to give **23** (20.08 g, 100%).

(3a*R,8a*S**)-6-(Hydroxymethyl)-8a-methyl-4,7,8,8a-tetrahydroazulen-1(3a*H*)-one Pivalate (24).** A mixture of ketone **23** (18.02 g, 64.8 mmol), NaI (20.0 g, 133 mmol), TMSCl (17.0 mL, 134 mmol), Et_3N (37.0 mL, 266 mmol), and acetonitrile (180 mL) was heated under reflux for 1.5 h. After being cooled to 0 °C, the solution was diluted with hexanes (700 mL), and saturated aq $NaHCO_3$ (500 mL) and water (500 mL) were added. The organic layer was separated, washed with water and brine, and dried (Na_2SO_4). The solvent was evaporated to give the silyl enol ether that was used for the next step without purification. A mixture of IBX (28.0 g, 100 mmol), MPO (12.5 g, 100 mmol), and DMSO (250 mL) was stirred for 30 min (until clear solution has formed) and then added to the silyl enol ether. The mixture was vigorously stirred at rt for 16 h, and then it was diluted with CH_2Cl_2 (200 mL) and poured into saturated aq Na_2SO_3 (500 mL). The product was extracted with hexane (700 mL). The organic extract was washed with water and brine and dried (Na_2SO_4), and the solvent was evaporated. The residue was chromatographed on silica gel (600 g, EtOAc−hexanes, 5:95, ca. 13 L) to give unchanged **23** (2.94 g, 16%) and enone **24** (15.10 g, 84%): ^{1}H NMR (200 MHz) 7.34 (dd, J = 5.9, 1.9 Hz, 1H), 6.08 (dd, J = 5.9, 2.9 Hz, 1H), 5.77 (br d, J = 6.6 Hz, 1H), 4.40 (br s, 2H), 2.94−2.78 (m, 1H), 2.60−1.76 (m, 5H), 1.65−1.42 (m, 1H), 1.18 (s, 9H), 0.99 (s, 3H); ^{13}C NMR (50 MHz)

213.6, 178.2, 162.8, 135.3, 131.2, 127.2, 71.7, 51.4, 51.0, 38.8, 30.9, 28.5, 27.2, 26.6, 18.4; HRMS calcd for $C_{17}H_{24}O_3$ (M^+) 276.1725, found 276.1735.

(1*S,3a*R**,8a*S**)-6-(Hydroxymethyl)-1-isopropyl-8a-methyl-1,3a,4,7,8,8a-hexahydro-1-azulenol (8).** Freshly prepared *i*-PrLi (0.54 M in hexanes, 120 mL, 64.80 mmol) was added dropwise, within 20 min, to a solution of enone **24** (5.12 g, 18.53 mmol) in THF (150 mL), stirred at −78 °C. Stirring at −78 °C was continued for 30 min, and then the reaction was quenched with saturated aq NH_4Cl (12.5 mL). The mixture was allowed to warm to rt, diluted with EtOAc (500 mL), and poured into water (1 L). The organic layer was separated, washed with water and brine, and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel (200 g, EtOAc−hexanes, 3:7, ca. 3 L) to give **8** (3.64 g, 84%): ^{1}H NMR (200 MHz) 5.78−5.65 (m, 1H), 5.62 (dd, J = 6.0, 1.0 Hz, 1H), 5.55 (dd, J = 6.0, 2.5 Hz, 1H), 3.94 (s, 2H), 2.56−2.44 (m, 1H), 2.38−1.58 (m, 9H), 0.98 (d, J = 6.6 Hz, 3H), 0.91 (s, 3H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz) 140.3, 135.3, 134.3, 125.2, 90.7, 70.5, 53.2, 51.9, 33.2, 31.9, 29.7, 27.1, 19.3, 18.7, 15.1; HRMS calcd for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1771.

(1a*S,2a*R**,5*S**,5a*S**,7a*S**)-7a-(Hydroxymethyl)-5-isopropyl-5a-methyl-1a,2,2a,5,5a,6,7,7a-octahydroazulen[5,6-*b*]oxiren-5-ol (25).** Diene **8** (5.37 g, 20.4 mmol) was dissolved in CH_2Cl_2 (500 mL), and the solution was cooled to −78 °C (part of the material precipitated). *m*-CPBA (70%, 11.3 g, 40.8 mmol) was added in one portion to the mixture stirred at −78 °C. After 16 h, the slurry was allowed to warm to 0 °C (in ca. 2 h), and saturated aq Na_2SO_3 (150 mL) was added. The mixture was allowed to warm to rt, and then it was partitioned between EtOAc (200 mL) and water (150 mL). The organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 200 mL, shaking was continued until white crystals disappeared from the aq layer). The combined organic extract was dried ($MgSO_4$), and the solvent was evaporated to give crude sparingly soluble epoxide **25** (8.6 g, containing some *m*-chlorobenzoic acid). An analytical sample was chromatographed on silica gel (30 g, EtOAc−hexanes, 3:7, and then MeOH−CH_2Cl_2, 1:1) and crystallized from acetone−diisopropyl ether: mp 172−175 °C; ^{1}H NMR (400 MHz, CD_3OD) 5.63 (dd, J = 5.9, 1.5 Hz, 1H), 5.52 (dd, J = 5.9, 2.9 Hz, 1H), 3.45 (d, J = 11.9 Hz, 1H), 3.42 (d, J = 11.9 Hz, 1H), 3.07 (d, J = 4.8 Hz, 1H), 2.65−2.58 (m, 1H), 2.27 (ddd, J = 15.6, 4.8, 3.3 Hz, 1H), 2.17−2.03 (m, 2H), 1.98−1.86 (m, 2H), 1.76−1.57 (m, 2H), 0.96 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) 136.0, 134.7, 97.3, 91.6, 69.1, 66.1, 61.2, 53.7, 35.0, 29.2, 29.1, 25.7, 19.6, 19.5, 15.9. Anal. Calcd for $C_{15}H_{24}O_3$ (236.14): C, 71.39; H, 9.59. Found: C, 71.24; H, 9.73.

(1a*S,2a*R**,5*S**,5a*S**,7a*S**)-7a-(Benzoxymethyl)-5-isopropyl-5a-methyl-1a,2,2a,5,5a,6,7,7a-octahydroazulen[5,6-*b*]oxiren-5-ol (26).** The crude **25** (8.5 g), prepared from **8** as described above, was suspended in CH_2Cl_2 (200 mL). Pyridine (9.9 mL, 123 mmol) and then benzoyl chloride (7.1 mL, 61 mmol) were added, and the mixture was stirred at rt for 1 h . The reaction was then quenched with methanol (15 mL). After 15 min, the mixture was partitioned between EtOAc (200 mL), hexanes (200 mL), and water (200 mL). The organic layer was separated, washed with 2% aq HCl, water, and brine, and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel (200 g) eluting first with EtOAc−hexanes, 15:85, to remove methyl benzoate and then with EtOAc−hexanes, 1:4. Benzoate **26** was obtained (6.93 g, 85% from **8**): ^{1}H NMR (200 MHz) 8.15−8.05 (m, 2H), 7.65−7.36 (m, 3H), 5.62 (dd, J = 6.0, 1.8 Hz, 1H), 5.57 (dd, J = 6.0, 2.7 Hz, 1H), 4.36 (d, J = 11.7 Hz, 1H), 4.16 (d, J = 11.7 Hz, 1H), 3.13 (d, J = 4.7 Hz, 1H), 2.75−2.62 (m, 1H), 2.42−1.42 (m, 7H), 0.99 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.83 (s, 3H); ^{13}C NMR (50 MHz): 166.1, 134.8, 134.3, 133.1, 129.6, 128.4, 90.6, 70.1, 62.3, 60.3, 52.3, 46.8, 33.3, 28.0, 27.9, 25.0, 19.2, 18.7, 14.9; HRMS calcd for $C_{22}H_{28}O_4Na$ (M + Na^+) 379.1880, found 379.1872

[(1a*S,2a*S**,5a*S**,7a*S**)-7a-Hydroxymethyl-5-isopropyl-5a-methyl-2,2a,5a,6,7,7a-hexahydroazulen[5,6-*b*]oxiren-3(1a*H*)-one Benzoate (27).** PCC (16.8 g, 78 mmol) was added to a stirred solution of **26** (6.93 g, 19.5 mmol) in CH_2Cl_2 (250 mL) at rt. After 16 h, the mixture was diluted with Et_2O (150 mL) and hexanes (450 mL) and filtered through a pad of Celite. The filtrate was evaporated, and the residue was chromatographed on silica gel (70 g, EtOAc−hexanes, 1:4) to give **27** (waxy solid, 5.67 g, 82%): ^{1}H NMR (200 MHz) 8.14−7.94 (m, 2H), 7.66−7.38 (m, 3H), 5.77 (d, J = 0.6 Hz, 1H), 4.37 (d, J = 11.8 Hz, 1H), 4.19 (d, J = 11.8 Hz, 1H), 3.28 (d, J = 4.6 Hz, 1H), 2.84−1.35 (m, 8H), 1.16 (d, J = 6.8 Hz, 3H), 1.11 (d, J = 6.8 Hz, 3H), 0.96 (s, 3H); ^{13}C NMR (50 MHz) 207.1, 192.5, 166.0, 133.2, 129.6, 128.4, 124.5, 70.0, 62.0, 59.7, 53.9, 49.2, 31.2, 27.4, 24.7, 23.4, 23.0, 22.2, 20.3; HRMS calcd for $C_{22}H_{26}O_4Na$ (M + Na^+) 377.1723, found 377.1718.

[(1a*S,2a*S**,5*R**,5a*R**,7a*S**)-7a-(Hydroxymethyl)-5-isopropyl-5a-methyloctahydroazulen[5,6-*b*]oxiren-3(1a*H*)-one benzoate (28).** A mixture of enone **27** (1.86 g, 5.25 mmol), Pd/$CaCO_3$ (10%, 419 mg), powdered $NaHCO_3$ (2.0 g), and EtOAc (50 mL) was stirred at under hydrogen at 80 bars of pressure for 20 h and then filtered through a pad of Celite. The solvent was evaporated to give **28** (1.84 g): ^{1}H NMR (400 MHz) 8.10−8.00 (m, 2H), 7.66−7.54 (m, 1H), 7.48−7.41 (m, 2H), 4.38 (d, J = 11.8 Hz, 1H), 4.17 (d, J = 11.8 Hz, 1H), 3.21 (d, J = 5.3 Hz, 1H), 2.61 (ddd, J = 16.3, 5.5, 2.8 Hz, 1H), 2.61 (ddd, J = 19.4, 8.8, 1.1 Hz, 1H), 2.26−1.87 (m, 5H), 1.80−1.47 (m, 4H), 1.03 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.70 (s, 3H); ^{13}C NMR (100 MHz) 216.9, 166.1, 133.2, 129.7, 128.4, 69.2, 61.6, 58.6, 57.9, 51.1, 44.5, 40.1, 35.1, 28.9, 24.1,24.0, 22.3, 21.8, 11.6; HRMS calcd for $C_{22}H_{28}O_4Na$ (M + Na^+) 379.18798, found 379.18616.

(1a*S,2a*S**,5*R**,5a*R**,7a*S**)-7a-(Hydroxymethyl)-5-isopropyl-5a-methyloctahydroazulen[5,6-*b*]oxiren-3(1a*H*)-one (7).** The benzoate **28** (541 mg, 1.5 mmol) in MeOH (10 mL) was added to a solution of KOH (1.48 g, 26.5 mmol) in MeOH (40 mL) and stirred at rt. After 30 min, the mixture was diluted with water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extract was washed with brine (1 × 20 mL), dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (EtOAc−hexanes, 3:7) to give alcohol **7** (370 mg, 94% from **27**): mp 65−68 °C (Et_2O−hexanes): ^{1}H NMR (400 MHz) 3.61 (dd, J = 12.1, 4.8 Hz, 1H), 3.53 (d, J = 12.1, 7.9 Hz, 1H), 3.26 (d, J = 5.4 Hz, 1H), 2.60 (ddd, J = 16.2, 5.4, 2.7 Hz, 1H), 2.45 (ddd, J = 19.7, 8.6, 1.3 Hz, 1H), 2.25−2.19 (m, 1H), 2.09−1.89 (m, 4H), 1.81−1.55 (m, 5H), 1.04 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.69 (s, 3H); ^{13}C NMR (50 MHz) 217.1, 66.3, 63.9, 57.9, 57.4, 51.1, 44.5, 40.0, 35.3, 28.9, 24.2, 23.7, 22.2, 21.7, 11.7; HRMS calcd for $C_{15}H_{24}O_3$ (M^+) 252.1725, found 252.1723. Anal. Calcd for $C_{15}H_{24}O_3$ (236.14): C, 71.39; H, 9.59. Found: C, 71.34; H, 9.61.

***O*-[(1a*S**,2a*S**,5*R**,5a*R**,7a*S**)-7a-(Hydroxymethyl)-5-isopropyl-5a-methyloctahydroazuleno[5,6-*b*]oxiren-3(1a*H*)-one] Imidazol-1-yl Thiocarbonate (29).** A mixture of TCDI (142 mg, 1.13 mmol), **7** (201 mg, 0.57 mmol), and benzene (8 mL) was heated at 60 °C for 1.5 h and cooled, and the solvent was evaporated. The residue was chromatographed on silica gel (5 g, EtOAc−hexanes, 2:3) to give **29** as a yellow oil (200 mg, 98%): ^{1}H NMR (400 MHz) 8.42−8.37 (m, 1H), 7.65 (dd, J = 1.8, 1.4 Hz, 1H), 7.08 (dd, J = 1.8, 0.8 Hz, 1H), 4.73 (d, J = 11.8 Hz, 1H), 4.46 (d, J = 11.8 Hz, 1H), 3.19 (d, J = 5.4 Hz, 1H), 2.65 (ddd, J = 16.4, 5.4, 2.6 Hz, 1H), 2.47 (ddd, J = 19.4, 8.7, 1.2 Hz, 1H), 2.27−2.02 (m, 4H), 1.95 (dd, J = 19.4, 11.3 Hz, 1H), 1.82−1.50 (m, 3H) overlapping 1.77 (dd, J = 16.4, 12.2 Hz, 1H), 1.05 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 0.72 (s, 3H); ^{13}C NMR (50 MHz) 216.5, 183.5, 136.6, 130.6, 117.9, 77.5, 60.9, 58.9, 57.7, 51.0, 44.5, 40.0, 35.0, 29.0, 24.1, 24.0, 22.3, 21.7, 11.6; HRMS calcd for $C_{19}H_{26}N_2O_3SNa$ (M + Na^+) 385.1556, found 385.1550.

(1a*S,2a*S**,5*R**,5a*R**,7a*R**)-7a-(Iodomethyl)-5-isopropyl-5a-methyloctahydroazuleno[5,6-*b*]oxiren-3(1a*H*)-one (30).** (a) A mixture of **29** (156 mg, 0.43 mmol), MeI (2 mL), $NaHCO_3$ (90 mg), and Cu wire (24 mg) was heated in a sealed ampule at 60 °C (bath temperature) for 16 h. The mixture was filtered, and volatile material was evaporated. The residue was chromatographed on silica gel (5 g, EtOAc−hexanes, 1:9) to afford iodide **30** (130 mg, 83%): ^{1}H NMR (400 MHz) 3.22 (d, J = 9.9 Hz, 1H), 3.12 (d, J = 5.4 Hz, 1H), 3.07 (d, J = 9.9 Hz, 1H), 2.56−2.34 (m, 3H), 2.20−1.88 (m, 4H), 1.78−1.42 (m, 4H), 1.04 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.70 (s, 3H); ^{13}C NMR (100 MHz) 216.9, 63.8, 62.7, 57.8, 51.0, 44.4, 39.9, 35.4, 28.9, 25.7, 24.1, 22.2, 22.2, 15.3, 11.5; HRMS calcd for $C_{15}H_{23}O_2INa$ ($M + Na^+$) 385.0639, found 385.0639. (b) Tosyl chloride (3.68 g, 19.3 mmol) was added portionwise to a solution of alcohol **7** (1.21 g, 4.82 mmol) in pyridine (30 mL), stirred at 0 °C. Stirring at 0 °C was continued for 6 h, and then water (4 mL) was added. The mixture was allowed to warm to rt, and then it was diluted with EtOAc (200 mL) and poured into water (200 mL). Hexane (50 mL) was added, and the layers were separated. The organic layer was washed with 1% aq tartaric acid, water, and brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was dried in high vacuum for 1 h to give the crude tosylate. This product was dissolved in acetone (30 mL), NaI (1.45 g, 9.7 mmol) was added, and the mixture was heated under reflux for 20 min. After cooling, the mixture was diluted with EtOAc (50 mL) and concentrated under vacuum to ca. half of its volume. The residue was partitioned between water containing some Na_2SO_3 and EtOAc−hexanes (200 mL, 1:1). The organic layer was separated, washed with water and brine, and dried (Na_2SO_4). The solvent was evaporated to give crude iodide **30** (1.72 g) that was immediately used for the next step.

(3*R,3a*R**,7*S**,8a*S**)-7-Hydroxy-3-isopropyl-3a-methyl-6-methyleneoctahydroazulen-1(2*H*)-one (31).** (a) (n-Bu)$_3$SnH (112 μL, 0.393 mmol) in benzene (4 mL) was added via syringe pump, within 30 min, to a refluxing under argon solution of imidazolide **29** (28.5 mg, 0.079 mmol) and AIBN (1.3 mg, 10 mol %, 0.0078 mmol) in benzene (4 mL). After 15 min, the mixture was cooled, and the solvent was evaporated. The residue was chromatographed on silica gel (2 g, hexanes and then EtOAc−hexanes, 3:7) to give **31** (5.9 mg, 32%): ^{1}H NMR (200 MHz) 5.08 (br s, 1H), 4.92 (br s, 1H), 4.52−4.42 (m, 1H), 2.55−2.30 (m, 3H), 2.20−1.46 (m, 9H), 1.03 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H), 0.76 (s, 3H); ^{13}C NMR (50 MHz) 217.7, 152.1, 111.6, 72.2, 57.0, 53.0, 45.2, 42.9, 41.0, 29.8, 29.7, 29.5, 23.5, 22.7, 14.3; HRMS calcd for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1785. (b) Zinc powder (246.9 mg, 3.80 mmol) was added to a solution of iodide **30** (136.5 mg, 0.38 mmol) in anhyd EtOH (15 mL), stirred under argon, and the mixture was heated under reflux for 2 h. After cooling, the mixture was filtered through pad of Celite, and the filtrate was evaporated. The residue was chromatographed on silica gel (5 g, EtOAc−hexanes, 3:7) to give **31** (86.1 mg, 97%). (c) The crude iodide **30** (1.72 g), prepared from **7** as described above, was dissolved in anhyd EtOH (55 mL). Zinc powder (3.01 g, 46.0 mg atom) was added, and the suspension was vigorously stirred and heated under reflux for 1 h. After cooling, the mixture was diluted with EtOAc−hexanes, 1:1 (100 mL) and filtered through a pad of Celite. The filtrate was evaporated, and the residue was chromatographed on silica gel (30 g, EtOAc−hexanes, 1:4) to give **31** (1.04 g, 92% from **7**).

(3*R,3a*R**,7*S**,8a*S**)-7-Hydroxy-3-isopropyl-3a-methyl-6-methyleneoctahydroazulen-1(2*H*)-one acetate (34).** Ac_2O (5 mL) and DMAP (10 mg) were added to a solution of **31** (2.33 g, 9.86 mmol) in CH_2Cl_2 (100 mL), stirred at rt. After 8 h, the mixture was partitioned between EtOAc−hexanes, 1:1 (100 mL), and water (100 mL). The organic layer was separated, washed with aq $NaHCO_3$ (2 × 30 mL), water, and brine, and dried (Na_2SO_4). The solvent was evaporated to give **34** (2.44 g, 89%) contaminated with a minor side product (less than 10% by ^{1}H NMR): ^{1}H NMR (200 MHz) 5.52−5.45 (m, 1H), 4.98−4.91 (m, 2H), 2.54−1.46 (m, 12H), 2.06 (s, 3H), 1.04 (d, J = 6.2 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.79 (s, 3H); separated signal of the side product (an isomer): 4.81 (br s); ^{13}C NMR (100 MHz) 217.0, 170.0, 147.6, 112.2, 73.9, 57.7, 53.0, 45.3, 43.0, 40.8, 29.9, 29.6, 27.3, 23.6, 22.7, 21.2, 14.1; HRMS calcd for $C_{17}H_{27}O_3$ (M^+) 279.1960, found 279.1970.

(3*R,3a*R**,7*S**,8a*S**)-3-Isopropyl-3a-methyl-6-methyleneoctahydro-2*H*-spiro[azulene-1,2′-[1,3]dioxolan]-7-ol acetate (35).** Trimethyl orthoformate (5 mL) was added in five portions every 20 min to a vigorously stirred suspension of **34** (2.44 g, 8.77 mmol) in ethylene glycol (75 mL) containing p-TSA·H_2O (150 mg). Stirring was continued for additional 2.5 h, and Et_3N (2 mL) was added. The mixture was diluted with EtOAc (100 mL) and then partitioned between water (300 mL) and hexanes (150 mL). The organic layer was separated, washed with water (2 × 50 mL) and brine (50 mL), and dried (Na_2SO_4). The solvent was evaporated to give acetate **35** as a waxy solid (2.74 g): ^{1}H NMR (200 MHz) 5.47 (br t, J = 4.4 Hz, 1H) 4.93 (br s, 1H), 4.87 (br s, 1H), 3.95−3.76 (m, 4H), 2.42−2.26 (m, 1H), 2.22−1.24 (m, 10H), 2.07 (s, 3H) 0.95 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR (50 MHz) 170.3, 148.2, 115.7, 111.7, 75.16, 64.9, 63.6, 55.1, 53.1, 45.6, 42.0, 41.9, 30.2, 29.3, 27.5, 23.8, 22.4, 21.3, 13.2; HRMS calcd for $C_{17}H_{23}O_3$ ($M^+ - C_2H_4O$) 278.18819, found 278.18934.

(3*R,3a*R**,7*S**,8a*S**)-3-Isopropyl-3a-methyl-6-methyleneoctahydro-2*H*-spiro[azulene-1,2′-[1,3]dioxolan]-7-ol (36).** KOH (1.03 g) was added to a stirred solution of crude **35** (2.74 g) in MeOH (50 mL). After 6 h, the mixture was partitioned between Et_2O (150 mL)−hexanes (100 mL) and water (250 mL). The organic layer was separated, washed with water and brine, and dried (Na_2SO_4). The solvent was evaporated to give **36** (2.35 g, 96% from **34**): ^{1}H NMR (200 MHz) 5.06 (br s, 1H), 4.88 (s, 1H), 4.42 (br s, 1H), 3.98−3.66 (m, 4H), 2.42−2.26 (m, 1H), 2.12−1.20 (m, 11H), 0.95 (d, J = 6.6 Hz, 3H), 0.85 (s, 3H), 0.82 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50 MHz) 153.1, 115.8, 110.3, 72.5, 64.8, 63.4, 55.4, 51.9, 45.3, 43.3, 42.0, 29.8, 29.7, 29.4, 23.5, 22.4, 13.4; HRMS calcd for $C_{17}H_{28}O_3$ (M^+) 280.20384, found 280.20335.

(3*R,3a*R**,8a*S**)-3-Isopropyl-3a-methyl-6-methyleneoctahydro-7*H*-spiro[azulene-1,2′-[1,3]dioxolan]-7-one (32).** Active MnO_2 (Fluka, 5.50 g) was added to a vigorously stirred solution of alcohol **36** (1.09 g (4.63 mmol) in Et_2O (55 mL) at rt. After 1 h, the mixture was filtered through a pad of Celite, and the solid was washed with Et_2O (3 × 20 mL). The combined filtrates were evaporated to give **32** (905 mg, 84%): ^{1}H NMR (200 MHz) 5.84 (d, J = 2.0 Hz, 1H), 5.32−5.20 (m, 1H), 4.00−3.62 (m, 4H), 2.74−1.22 (m, 11H), 0.99 (s, 3H), 0.97 (d, J = 7.6 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz) 204.1, 149.2, 122.7, 115.1, 65.1, 63.7, 55.6, 53.1, 45.1, 44.3, 42.4, 37.0, 29.7, 28.9, 23.5, 22.7, 12.5; HRMS calcd for $C_{17}H_{26}O_3$ (M^+) 278.18819, found 278.18682. (This crude product was used for the next step immediately after the preparation.)

(3*R,3a*R**,6ξ*,8a*S**)-6-Allyl-3-isopropyl-3a-methyloctahydro-7*H*-spiro[azulene-1,2′-[1,3]dioxolan]-7-one (44).** Vinylmagnesium bromide (0.95 M, 3.6 mL, 3.4 mmol) was added dropwise to a stirred suspension of CuI at −78 °C (320 mg, 1.68 mmol) in THF (4 mL). The mixture was stirred at −44 °C (dry ice actonitrile bath) for 1 h and then cooled again to −78 °C and treated with HMPA (0.89 mL, 5.1 mmol). To the thus-prepared solution of magnesium cuprate was added via cannula a cooled to −78 °C mixture of **32** (233 mg, 0.84 mmol, preliminarily dried by azeotrpic distillation of benzene, 5 mL) and TMSCl (freshly distilled, 0.63 mL, 5 mmol) in THF (4 mL). The substrate flask was washed with THF (2 mL). After 0.5 h, Et_3N (0.85 mL, 6.1 mmol) was added, and the mixture was allowed to warm to rt. The mixture was then cooled to 0 °C and satd aq solution of NH_4Cl and NH_4OH (pH = 8, 5, and 5 mL) was added. The mixture was

then partitioned between hexanes (80 mL) and satd aq NH_4Cl-NH_4OH (pH = 8, 5, and 30 mL) (the mixture was shaken until the precipitate has completely dissolved, ca. 20 min). The layers were separated and the aqueous layer was extracted with hexanes (50 mL). The combined hexane extract was washed with satd aq NH_4Cl-NH_4OH, water, and brine, and dried (Na_2SO_4). The solvent was evaporated, the residue (silyl enol ether **37**) was dissolved in THF (5 mL), and $Bu_4NF \cdot 3H_2O$ (320 mg, 1.02 mmol) was added. The mixture was stirred at rt for 15 min, diluted with Et_2O (5 mL), and poured into water (50 mL). The mixture was extracted with hexanes (50 mL), and the hexane extract was washed with water and brine and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel (5 g, EtOAc–hexanes, 95:5) to give **44** (235 mg, 92% from **32**): ^{1}H NMR (200 MHz): 5.80–5.58 (m, 1H), 5.03–4.90 (m, 2H), 3.97–3.63 (m, 4H), 2.66–1.13 (m, 14 H), 0.94 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H), 0.72 (s, 3H); ^{13}C NMR (50 MHz) 213.7, 136.5, 116.3, 115.6, 65.0, 63.7, 54.9, 52.0, 51.1, 45.8, 43.0, 41.1, 39.0, 35.3, 28.4, 27.9, 24.1, 22.2, 12.1; HRMS calcd for $C_{19}H_{30}O_3$ (M^+) 306.21950, found 306.21861.

(3*R,3a*R**,6ξ,*8ξ,*8a*S**)-6-Allyl-3-isopropyl-3a-methyl-8-(phenylseleno)octahydro-7*H*-spiro[azulene-1,2′-[1,3]dioxolan]-7-one (46).** Ketone **44** (235 mg, 0.76 mmol) in THF (4 mL) was added to a stirred solution of LDA at −78 °C prepared from $(i\text{-Pr})_2NH$ (0.42 mL, 3 mmol), *n*-BuLi (2.5 M in hexanes, 0.92 mL, 2.3 mmol), and THF (5 mL). After 0.5 h, TMSCl (0.29 mL, 2.29 mmol) was added dropwise, and stirring at −78 °C was continued for 15 min. The mixture was allowed to warm to rt (in ca. 15 min), and Et_3N (1 mL) was added and then cooled again to 0 °C. Saturated aq $NaHCO_3$ (4 mL) was added, and the mixture was poured into water (50 mL) and extracted with hexanes (70 mL). The organic layer was separated, washed with water, and dried (Na_2SO_4). The solvent was evaporated, and the residue (400 mg, silyl enol ether **45**) was dissolved in dry CH_2Cl_2 (7 mL) containing pyridine (0.58 mL, 7.2 mmol). The solution was cooled to −78 °C, and PhSeCl (168 mg, 0.87 mmol) in CH_2Cl_2 (0.5 mL) was added. The mixture was stirred at −78 °C for 0.5 h, and then it was allowed to warm to rt. Saturated aq $NaHCO_3$ (2 mL) was added, and the mixture was poured into water (50 mL) and extracted with Et_2O–hexanes (1:2, 70 mL). The organic extract was washed with water and brine and dried (Na_2SO_4), and the solvent was evaporated. The residue was chromatographed on silica gel (10 g, EtOAc–hexanes, 95:5) to give **46** as an amorphous solid (257 mg, 73%): ^{1}H NMR (200 MHz) 7.58–7.44 (m, 2H), 7.32–7.16 (m, 3H), 5.78–5.56 (m, 1H), 5.08–4.92 (m, 2H), 4.26–3.78 (m, 5H), 2.95–2.78 (m, 1H), 2.45–1.14 (m, 11H), 0.94 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H), 0.71 (s, 3H); ^{13}C NMR (50 MHz) 205.4, 136.5, 134.8, 128.9, 128.0, 116.3, 115.4, 65.9, 63.4, 55.3, 53.8, 50.0, 48.1, 47.2, 42.0, 40.7, 35.9, 29.8, 27.1, 24.7, 21.4, 11.9; HRMS calcd for $C_{25}H_{34}O_3{}^{80}Se$ (M^+) 462.16732, found 462.16878.

(3*R,3a*R**,6ξ*)-6-Allyl-3-isopropyl-3a-methyl-2,3,3a,4,5,6-hexahydro-7*H*-spiro[azulene-1,2′-[1,3]dioxolan]-7-one (47).** *m*-CPBA (70%, 137 mg, 0.56 mmol) was added to a stirred at −78 °C solution of **46** (257 mg, 0.56 mmol) in CH_2Cl_2 (15 mL) containing solid $NaHCO_3$ (0.25 mg). After 0.5 h, Et_3N (0.5 mL) was added, followed by satd aq Na_2SO_3 (4 mL), and stirring at rt was continued for 20 h. The mixture was partitioned between Et_2O (20 mL)–hexanes (50 mL) and water (50 mL). The organic layer was separated, washed with water and brine, and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel (10 g, EtOAc–hexanes, 1:9) to give **47** (150 mg, 89%): ^{1}H NMR (200 MHz) 5.97 (s, 1H), 5.85–5.64 (m, 1H), 5.08–4.92 (m, 2H), 4.10–3.96 (m, 4H), 2.65–2.48 (m, 2H), 2.34–1.46 (m, 9H), 1.03 (s, 3H), 0.98 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50 MHz) 206.2, 162.7, 136.7, 125.2, 116.4, 112.1, 65.6, 64.1, 53.3, 52.2, 47.5, 39.0, 38.1, 34.9, 27.4, 27.0, 24.2, 21.9, 21.0; HRMS calcd for $C_{19}H_{28}O_3$ (M^+) 304.20384, found 304.20331.

(3*R,3a*R**,6*R**)-6-Allyl-3a,6-dimethyl-3-isopropyl-2,3,3a,4,5,6-hexahydro-7*H*-spiro[azulene-1,2′-[1,3]dioxolan]-7-one (6).** LHMDS (1 M in THF, 1.62 mL, 1.62 mmol) was added dropwise to a stirred at 0 °C solution of enone **47** (165 mg, 0.54 mmol) in THF (8 mL), and stirring was continued at rt for 2 h (to generated dienolate **48**). The mixture was then cooled to −20 °C, and HMPA (0.283 mL, 1.62 mmol) and MeI (0.20 mL, 3.24 mmol) were consecutively added. The mixture was stirred at rt for 1 h, and then it was diluted with hexanes (70 mL) and washed with water (50 mL) and brine (50 mL). The organic solution was dried (Na_2SO_4), and the solvent was evaporated. The residue was chromatographed on silica gel (10 g, EtOAc–hexanes, 8:92) to give **6** (170 mg, 98%): ^{1}H NMR (400 MHz) 5.87 (s, 1H), 5.86–5.75 (m, 1H), 5.07–5.01 (m, 2H), 4.08–3.90 (m, 4H), 2.24 (ddt, J = 7.6, 13.9, 1.0 Hz, 1H), 2.05 (dd, J = 6.7, 13.3 Hz, 1H), 2.03–1.88 (m, 3H), 1.75 (t, J = 13.1 Hz, 1H), 1.66 (dq, J = 13.5, 6.6 Hz, 1H), 1.59–1.47 (m, 2H), 1.13 (s, 3H), 1.02 (s, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz) 208.9, 162.1, 135.1, 123.5, 117.7, 112.1, 65.5, 64.1, 52.0, 50.1, 77.4, 43.1, 38.6, 34.0, 32.1, 27.8, 24.0, 23.7, 22.1, 21.2; HRMS calcd for $C_{20}H_{30}O_3$ (M^+) 318.21950, found 318.21825.

HPLC analysis of **6**, Nucleosil 50/5 mμ, 25 cm, EtOAc–hexanes, 5:95, Shimadzu SPD-6A, shows one pick, t_R = 8.55 min. No other compounds were recorded at the detection level (1%).

HPLC analysis of **6** at the reversed-phase column, HPLC/MS system, Waters SYMMETRY C_{18} 4.6 × 250 mm, Shimadzu Prominence LC-20 chromatograph conjugated with mass spectrometer (4000 Q TRAP Applied Biosystems), MeOH–water, 8:2. Compound showed one pick, t_R = 18.01 min, mass determination: 319.3 $[M + H]^+$, 341.3 $[M + Na]^+$, 420.7 $[M + TEA]^+$, 659.7 $[2M + Na]^+$.

(3*S*,3a*R*,6*R*,7ξ)-6-Allyl-3-isopropyl-3a,6-dimethyl-3,3a,4,5,6,7-hexahydro-2*H*-spiro[azulene-1,2′-[1,3]dioxolan]-7-ol (49). $CeCl_3 \cdot 7H_2O$ (556 mg, 1.49 mmol) was added to a stirred at −20 °C solution of **6** (325 mg, 1.02 mmol) in MeOH (18 mL). After the solid has dissolved (ca. 2 min), $NaBH_4$ (57 mg, 1.5 mmol) was added in three portions within 20 min, and stirring was continued for 30 min. The solution was partitioned between EtOAc–hexanes (1:1, 100 mL) and water (100 mL). The organic layer was washed with water and brine and dried (Na_2SO_4). The solvent was evaporated to give crude **49** (335 mg): ^{1}H NMR (200 MHz) 6.04–5.78 (m, 1H), 5.56 (d, J = 3.2 Hz, 1H), 5.15–4.96 (m, 2H), 4.39 (br s, 1H), 4.10–3.78 (m, 4H), 2.30–1.10 (m, 10H), 0.98 (s, 3H), 0.94 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.86 (s, 3H); ^{13}C NMR (50 MHz) 150.1, 135.3, 130.2, 117.4, 112.3, 74.0, 65.4, 63.5, 52.7, 45.9, 45.4, 39.8, 38.5, 33.7, 27.7, 24.1, 22.4, 17.3, 16.3; HRMS calcd for $C_{20}H_{32}O_3$ (M^+) 320.23515, found 320.23624.

7-*O*-Triethylsilyl (3*S*,3a*R*,6*R*,7ξ)-6-Allyl-3a,6-dimethyl-3-isopropyl-3,3a,4,5,6,7-hexahydro-2*H*-spiro[azulene-1,2′-[1,3]dioxolan]-7-ol (50). Triethylsilyl chloride (0.44 mL, 2.62 mmol) was added dropwise to a stirred at rt solution of the described above alcohol **49** (335 mg, 1.05 mmol), imidazole (535 mg, 7.86 mmol), and DMAP (7 mg, 0.06 mmol) in CH_2Cl_2 (15 mL). The mixture was left for 16 h and then it was partitioned between hexanes (100 mL) and water (70 mL). The organic extract was washed with water and brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel (18 g, hexanes–EtOAc, 98:2) to give **50** (397 mg, 90% from **6**): ^{1}H NMR (200 MHz) 5.94–5.72 (m, 1H), 5.54 (d, J = 3.4 Hz, 1H), 5.10–5.92 (m, 2H), 4.34 (d, J = 3.4 Hz, 1H), 4.12–3.82 (m, 4H), 2.19 (dd, J = 13.4, 7.2 Hz, 1H), 2.03 (dd, J = 13.4, 7.8 Hz, 1H), 1.93 (dd, J = 12.6, 5.8 Hz, 1H), 1.72–1.20 (m, 7H), 1.02–0.80 (m, 21H), 0.67–0.53 (m, 6H); ^{13}C NMR (50 MHz) 149.3, 135.8, 131.3 (br), 116.9, 112.5, 75.2, 65.4, 63.6, 52.4(br), 45.6(br), 42–46(br), 40.1, 38.7, 33.6 (br), 33.1(br), 27.8, 24.1, 22.4, 16–18(br), 7.0, 5.2; HRMS calcd for $C_{26}H_{46}O_3Si$ (M^+) 434.32162, found 434.32234.

7-*O*-Triethylsilyl (3*S*,3a*R*,6*R*,7ξ)-6-(3-Hydroxypropyl)-3a,6-dimethyl-3-isopropyl-3,3a,4,5,6,7-hexahydro-2*H*-spiro[azulene-1,2′-[1,3]dioxolan]-7-ol (51). 9-BBN (0.5 M in THF, 5.5 mL, 2.75 mmol) was added dropwise to a stirred at 0 °C solution of **50** (397 mg, 0.92 mmol) in THF (15 mL). The mixture was allowed to warm to rt in 2 h, stirred for additional 1.5 h, and then it was cooled to 0 °C again. Aqueous NaOH (3 M, 3.1 mL, 9.3 mmol) and H_2O_2 (30%, 0.94 mL) were consecutively added. The mixture was stirred for 10 min and then addition of aq NaOH (3 M, 3.1 mL, 9.3 mmol) and H_2O_2 (30%, 0.94 mL) was repeated. The mixture was allowed to warm to rt and partitioned between Et_2O−hexanes (1:1, 140 mL) and water (70 mL). The organic extract was washed with water and brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel (20 g, hexanes−EtOAc, 9:1) to give **51** (400 mg, 97%): ^{1}H NMR (200 MHz) 5.43 (d, J = 3.6 Hz, 1H), 4.35 (d, J = 3.6 Hz, 1H), 4.10−3.76 (m, 4H), 3.59 (t, J = 6.4 Hz, 2H), 1.92 (dd, J = 6.0, 12.6 Hz, 1H), 1.78−1.20 (m, 11H), 1.00−0.76 (m, 21H), 0.64−0.50 (m, 6H); ^{13}C NMR (50 MHz) 149.1, 131.3(br), 112.4, 74.9, 72.2, 65.3, 64.0, 63.5, 52.3 (br), 45.5 (br), 37−35 (br), 34.7, 33.5 (br), 32.9 (br), 27.8, 27.4, 27.0, 25.2, 24.1, 22.6, 22.4, 18−16(br), 6.9, 5.1; HRMS calcd for $C_{26}H_{48}O_4Si$ (M^+) 452.33219, found 452.33017.

3-{(3*S*,3a*R*,6*R*,7ξ)-3-Isopropyl-3a,6-dimethyl-7-triethylsilyloxy-3,3a,4,5,6,7-hexahydro-2*H*-spiro[azulene-1,2′-[1,3]dioxolan]-6-yl}-propanal (52). TPAP (31 mg, 0.088 mmol) was added to a stirred mixture of alcohol **51** (400 mg, 0.88 mmol), NMO (205 mg, 1.75 mmol), powdered 4 Å molecular sieves (1.2 g), and CH_2Cl_2 (20 mL) at rt under argon. After 20 min, the mixture was quickly filtered through silica gel (5 g, EtOAc−hexanes, 1:9), collecting 10 mL fractions. Fractions containing the product were combined to give **52** (377 mg, 95%): ^{1}H NMR (200 MHz) 9.77 (t, J = 2.0 Hz, 1H), 5.54 (d, J = 3.6 Hz, 1H), 4.36 (d, J = 3.6 Hz, 1H), 4.10−3.84 (m, 4H), 2.40 (t, J = 2.0 Hz, 2H), 1.94 (dd, J = 12.4, 5.6 Hz, 1H), 1.88−1.22 (m, 9H), 1.08−0.56 (m, 21 H), 0.67−0.52 (m, 6H); ^{13}C NMR (50 MHz) selected signals, 203.1, 112.3, 74.9, 65.4, 63.5, 41.9, 39.3, 39.0, 27.8, 27.1, 25.6, 24.7, 24.1, 22.4, 6.9, 5.1; HRMS calcd for $C_{26}H_{46}O_4Si$ (M^+) 450.31654, found 450.31570.

***tert*-Butyl 3ξ-Hydroxy-5-{(3*S*,3a*R*,6*R*,7ξ)-3a,6-dimethyl-7-triethylsilyloxy-3-isopropyl-3,3a,4,5,6,7-hexahydro-2*H*-spiro[azulene-1,2′-[1,3]dioxolan]-6-yl}pentanoate (53).** *tert*-Butyl acetate (0.556 mL, 4.15 mmol) was added dropwise to a stirred at −78 °C solution of LDA prepared from (*i*-Pr)$_2$NH (0.582 mL, 4.16 mmol) and *n*-BuLi (2.5 M in hexanes, 1.33 mL, 3.3 mmol) in THF (15 mL). Stirring was continued for 0.5 h, aldehyde **52** (377 mg, 0.84 mmol) in THF (5 mL) was added via syringe, and the flask and the syringe were washed with THF (2 × 2 mL). Stirring was continued for 45 min, the mixture was allowed to warm to rt, and the reaction was quenched with satd aq $NaHCO_3$ (20 mL). The mixture was partitioned between Et_2O (70 mL) and water (70 mL). The organic extract was washed with water and brine and dried (Na_2SO_4). The solvent was evaporated to give adduct **53** (473 mg): ^{1}H NMR (200 MHz) 5.53 (d, J = 3.6 Hz, 1H), 4.33 (d, J = 3.6 Hz, 1H), 4.10−3.80 (m, 4H), 3.09 (dd, J = 4.0, 8.8 Hz, 1H), 2.54−2.20 (m, 2H), 1.92 (dd, J = 5.8, 12.6 Hz, 1H), 1.78−1.12 (m, 10H), 1.46 (s, 9H), 1.02−0.76 (m, 12 H), 0.66−0.52 (m, 6H); ^{13}C NMR (50 MHz) selected signals, 172.6, 112.4, 81.2, 69.2, 65.3, 63.5, 42.2, 42.1, 39.4, 38.7, 36.6, 30.4, 28.1, 27.8, 24.7, 24.1, 22.4, 7.0, 5.1; HRMS calcd for $C_{32}H_{58}O_6NaSi$ ([M + Na]$^+$) 589.38949, found 589.38688.

***tert*-Butyl 3ξ-Hydroxy-5-[(3*S*,3a*R*,6*R*,7ξ)-3a,6-dimethyl-7-hydroxy-3-isopropyl-3,3a,4,5,6,7-hexahydro-2*H*-spiro[azulene-1,2′-[1,3]dioxolan]-6-yl]pentanoate (54).** The crude adduct **53** (473 mg) was dissolved in THF (15 mL), $Bu_4NF\cdot 3H_2O$ (393 mg, 1.25 mmol) was added, and the solution was stirred for 0.5 h. The solvent was evaporated, and the residue was dissolved in a small volume of CH_2Cl_2 and transferred to a silica gel column (15 g). The column was eluted with EtOAc−hexanes, 4:6, to give **54** as a mixture of diastereomers (342 mg, 91% from **52**): ^{1}H NMR (200 MHz) 5.59 (dd, J = 1.8, 3.0 Hz, 1H), 4.47 (br s, 1H), 4.16−3.80 (m, 4H), 3.55 (br s, 0.3H), 3.39 (br s, 0.4H), 2.90 (br s, 0.3H), 2.50−2.36 (m, 3H), 1.93 (dd, J = 5.2, 12.2 Hz, 1H), 1.86−1.10 (m, 12H), 1.45 (s, 9H), 0.99 (s, 3H), 0.94 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.85 (s, 3H); ^{13}C NMR (50 MHz) selected signals, 172.6, 172.4, 149.8, 149.6, 130.4, 112.3, 81.4, 73.1, 72.3, 69.0, 68.5, 65.5, 63.4, 52.8, 45.4, 42.4, 41.7, 39.1, 39.0, 38.6, 36.6, 35.6, 33.7, 33.2, 29.4, 28.1, 27.7, 24.7, 24.1, 22.4, 18.3, 16.2; HRMS calcd for $C_{26}H_{44}O_6Na$ ([M + Na]$^+$) 475.30301, found 475.30083.

***tert*-Butyl 3-Oxo-5-{(3*S*,3a*R*,6*R*,7ξ)-3a,6-dimethyl-3-isopropyl-7-oxo-3,3a,4,5,6,7-hexahydro-2*H*-spiro[azulene-1,2′-[1,3]dioxolan]-6-yl}pentanoate (5).** $NaHCO_3$ (1130 mg) and freshly prepared Dess−Martin reagent (790 mg, 1.86 mmol) were added at rt to a vigorously stirred solution of diol **54** (211 mg, 0.47 mmol) in CH_2Cl_2 (45 mL). After 15 min, satd aq Na_2SO_3 (20 mL) was added, stirring was continued for 5 min, and the mixture was partitioned between Et_2O−hexanes (1:1, 140 mL) and water (70 mL). The organic extract was washed with water and brine and dried (Na_2SO_4). The solvent was evaporated to give a crude dione **5** (199 mg): ^{1}H NMR (200 MHz) 5.84 (s, 1H), 4.10−3.85 (m, 4H), 3.37 (s, 2H), 2.60 (t, J = 7.6 Hz, 2H), 2.10−1.20 (m, 10H), 1.47(s, 9H), 1.16 (s, 3H), 1.03 (s, 3H), 0.99 (d, J = 6.2 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz) selected signals, 162.1, 123.4, 112.0, 65.6, 64.0, 52.1, 50.6, 49.7, 47.3, 38.5, 33.9, 32.7, 32.4, 28.0, 27.8, 24.1, 22.1, 21.1; HRMS calcd for $C_{26}H_{40}O_6$ (M^+) 448.28249, found 448.28108.

(1*S*,8a*R*,10a*R*)-5-*tert*-Butoxycarbonyl-8a,10a-dimethyl-1-isopropyl-6-oxo-1,6,7,8,8a,9,10,10a-octahydrobenzo[*f*]azulene-2*H*-spiro-3.2′[1,3]dioxolane (4). The crude dione **5** (199 mg), immediately after its preparation, was dissolved in absolute EtOH (30 mL), and EtONa in EtOH [17 mL of a solution prepared by dissolving of sodium (3.60 g) in absolute EtOH (90 mL)] was added at rt. The mixture was stirred at rt for 2.5 h, and then it was partitioned between Et_2O−hexanes (1:1, 200 mL) and water (250 mL). The aqueous layer was extracted with Et_2O−hexanes (1:1, 50 mL). The combined organic extracts were washed with water and brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on silica gel (10 g, EtOAc−hexanes, 85:15) to give **4** (160 mg, 80% from **54**): mp 145−146 °C (hexanes); IR (film) 1727, 1671 cm^{-1}; UV (EtOH) 283.3 nm; ^{1}H NMR (500 MHz) 6.17 (s, 1H), 4.01−3.88 (m, 4H), 2.58−2.43 (m, 2H), 2.00 (dd, J = 6.3, 13 Hz, 1H), 1.96−1.62 (m, 9H), 1.49 (s, 9H), 1.19 (s, 3H), 1.02 (s, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (50 MHz) selected signals, 194.9, 165.7, 158.1, 133.6, 119.4, 112.2, 82.1, 65.5, 63.7, 38.4, 36.0, 33.7, 29.7, 28.1, 28.0, 27.8, 25.2, 24.1, 22.2. Anal. Calcd for $C_{26}H_{38}O_5$ (430.59): C, 72.53; H, 8.90. Found: C, 72.55; H, 9.03.

(1*S*,6*S*,8a*R*,10a*R*)-5-*tert*-Butoxycarbonyl-8a,10a-dimethyl-6-hydroxy-1-isopropyl-1,6,7,8,8a,9,10,10a-octahydrobenzo[*f*]azulene-2*H*-spiro-3.2′[1,3]dioxolane (55) and (1*S*,6*R*,8a*R*,10a*R*)-5-*tert*-Butoxycarbonyl-8a,10a-dimethyl-6-hydroxy-1-isopropyl-1,6,7,8,8a,9,10,10a-octahydrobenzo[*f*]azulene-2*H*-spiro-3.2′[1,3]dioxolane (56). A solution of $LiAlH_4$ (48 mg, 1.26 mmol) in THF (2 mL) was added slowly to a stirred solution of **4** (60 mg, 0.14 mmol) in THF (10 mL) in a 50 mL round-bottom flask deeply immersed in a bath cooled to −93 °C. Stirring at −93 °C was continued for 30 min, satd aq Na_2SO_4 (0.3 mL) was added, and the cooling bath was removed. The mixture was allowed to warm to rt, and then the precipitate was filtered off and washed with Et_2O. The combined filtrates were evaporated. The residue was chromatographed on silica gel (20 g, CH_2Cl_2−Et_2O, 98:2, containing a drop of Et_3N per 100 mL of the mixture) to give **55** (46 mg, 77%) and **56** (7 mg, 12%).

55: mp 112−113 °C (hexanes); ^{1}H NMR (500 MHz) 6.19 (br s, 1H), 4.46 (br s, 1H), 4.05−3.89 (m, 4H), 1.96 (dd, J = 6.1, 12.7 Hz, 1H), 1.88−1.75 (m, 4H), 1.67−1.58 (m, 4H), 1.54−1.45 (m, 3H),

1.49 (s, 9H), 1.25 (s, 3H), 0.98 (s, 3H), 0.96 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz) selected signals 169.0, 122.7, 112.6, 81.9, 65.4(br), 63.3(br), 38.5, 28.0, 28.0, 27.9, 26.5(br), 24.0, 22.3. HRMS calcd for $C_{26}H_{40}O_5$ (M^+) 432.28757, found 432.28943. Anal. Calcd for $C_{26}H_{40}O_5$ (433.29): C, 72.19; H, 9.32. Found: C, 71.94; H, 9.40

56: mp 93−96 °C (from the mass); ^{1}H NMR (500 MHz) 6.18 (s, 1H), 4.40 (br s, 1H), 4.06−3.88 (m, 4H), 1.95 (dd, J = 5.7, 12.5 Hz, 1H), 1.92−1.27 (m, 12H), 1.49 (s, 9H), 1.09 (s, 3H), 0.96 (d, J = 6.6 Hz, 3H), 0.94 (s, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz) selected signals 150.5, 122.8, 112.6. 82.0, 65.6 (br), 65.3 (br), 63.0 (br), 45.7 (br), 38.5, 36.8, 34.6 (br), 28.1, 27.9, 26.1 (br), 24.0, 22.4; HRMS calcd for $C_{26}H_{40}O_5$ (M^+) 432.28757, found 432.28808.

(1*S*,6*S*,8a*R*,10a*R*)-8a,10a-Dimethyl-6-hydroxy-5-hydroxymethyl-1-isopropyl-1,6,7,8,8a,9,10,10a-octahydrobenzo[*f*]azulene-2*H*-spiro-3.2′[1,3]dioxolane (57). $LiAlH_4$ (10 mg, 0.26 mmol) was added to a solution of **55** (38.9 mg, 0.093 mmol) in THF (5 mL), stirred at rt. After 30 min, the reaction was quenched with satd aq Na_2SO_4, the mixture was filtered, and the solid was washed with Et_2O. The combined filtrates were evaporated to give **57** (32.7 mg, 100%): ^{1}H NMR (600 MHz) 6.11 (s, 1H), 4.36 (br s, 1H), 4.32 (d, J = 12.6 Hz, 1H), 4.23 (d, J = 12.6 Hz, 1H), 4.06−3.90 (m, 4H), 1.96 (dd, J = 6.1, 12.6 Hz, 1H), 1.92−1.32 (m, 12H), 0.97 (s, 6H), 0.96 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H); ^{13}C NMR (150 MHz) selected signals, 152.8, 121.2, 112.5, 65.5, 63.4, 38.4, 29.7, 27.9, 25.5, 24.0, 22.3; HRMS calcd for $C_{22}H_{34}O_4$ (M^+) 362.24571, found 362.24447. This product decomposed upon attempted chromatography or storage.

(1*S*,6*S*,8a*R*,10a*R*)-8a,10a-Dimethyl-5-formyl-6-hydroxy-1-isopropyl-1,6,7,8,8a,9,10,10a-octahydrobenzo[*f*]azulene-2*H*-spiro-3.2′[1,3]dioxolane (59). $PhI(OAc)_2$ (59 mg, 0.18 mmol) and TEMPO (12 mg. 0.077 mmol) were added to a solution of freshly prepared **57** (22.2 mg, 0.061 mmol) in CH_2Cl_2 (12 mL), stirred at rt. After 30 min, the mixture was diluted with Et_2O (30 mL), washed consecutively with satd aq Na_2SO_3 (15 mL), water, and brine, and dried. The solvent was evaporated, and the residue was chromatographed on silica gel (4.5 g, EtOAc−hexanes, 2:8 and then 3:7) to give **59** (14.8 mg, 67%): ^{1}H NMR (500 MHz) 10.02 (s, 1H), 6.56 (d, J = 1.4 Hz, 1H), 4.60 (t, J = 5.4 Hz, 1H), 4.08−3.94 (m, 4H), 2.01 (dd, J = 6.2, 12.9 Hz, 1H), 1.90−1.80 (m, 3H), 1.69−1.47 (m, 9H), 1.10 (s, 3H), 1.02 (s, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz) selected signals 194.5, 157.2, 136.2, 118.6, 112.1, 65.6, 63.7, 38.4, 29.7, 27.8, 25.9, 25.4, 24.0, 22.3; HRMS calcd for $C_{22}H_{32}O_4$ (M^+) 360.23006, found 360.22913.

(1*S*,6*S*,8a*R*,10a*R*)-6-Acetoxy-8a,10a-dimethyl-5-formyl-1-isopropyl-1,6,7,8,8a,9,10,10a-octahydrobenzo[f]azulene-2*H*-spiro-3.2′[1,3]dioxolane (60). Ac_2O (0.06 mL, 0.64 mmol) was added dropwise to a stirred at rt solution of **59** (14.8 mg, 0.041 mmol) in CH_2Cl_2 (5 mL) containing DMAP (0.1 mg) and Et_3N (0.25 mL, 1.8 mmol). The solution was stirred for 4 h, and then MeOH (0.05 mL) was added followed (after 5 min) by Et_2O (10 mL). The mixture was partitioned between hexane−Et_2O (1:1, 20 mL). The organic layer was separated and washed with aq $NaHCO_3$ (2 × 15 mL) and brine, and the solvent was evaporated. The residue was chromatographed on silica gel (1.2 g, EtOAc−hexanes, 8:2) to give acetate **60** (15.6 mg, 94%): mp 153−155 °C (from the mass); ^{1}H NMR (500 MHz) 9.96 (s, 1H), 6.52 (s, 1H), 5.75 (br s, 1H), 4.06−3.91 (m, 4H), 2.04 (dd, J = 6.4, 13.5 Hz, 1H), 2.01 (s, 3H), 1.95−1.53 (m, 12H), 1.36 (br d, J = 11.2, 1H), 1.10 (s, 3H), 1.06 (s, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz) selected signals 191.5, 170.3, 132.4, 118.6, 112.1, 65.4, 64.0, 38.6, 27.9, 25.0, 24.2, 24.0, 22.2, 21.2; HRMS calcd for $C_{24}H_{34}O_5$ (M^+) 402.24062, found 402.24129.

Heptemerone G (2). Water (0.03 mL) and PPTS (1.7 mg) were added to a stirred at rt solution of **60** (13.1 mg, 0.033 mmol) in acetone (3 mL). The mixture was left for 16 h, and then the solvent was evaporated at rt. The residue was dried in high vacuum and chromatographed on silica gel (1.3 g, EtOAc−hexanes, 1:7) to give **2** (11 mg, 94%): IR (film) 1738 (with shoulder), 1681, 1642, 1610, 1236 cm^{-1}; UV (MeOH) 281.4 nm; ^{1}H NMR (500 MHz) 9.88 (br s, 1H), 7.34 (s, 1H), 5.75 (s, 1H), 2.54 (dd, J = 7.6, 18.6 Hz, 1H), 2.19 (dd, J = 12.9, 18.5 Hz, 1H), 2.01 (s, 3H) overlapping 2.06−2.00 (m, 1H), 1.97−1.67 (m, 6H), 1.64−1.56 (m, 2H), 1.37 (br d, J = 8.2 Hz, 1H), 1.09 (s, 6H), 1.06 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H); ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) 9.76 (s, 1H), 7.26 (s, 1H), 5.64 (br s, 1H), 2.44 (dd, J = 7.7, 18.4 Hz, 1H), 2.25 (dd, J = 12.7, 18.4 Hz, 1H), 2.00 (ddd, J = 1.5, 10.6, 14.7 Hz, 1H), 1.96 (s, 3H), 1.86−1.68 (m, 7H), 1.62 (ddd, J = 1.5, 8.7, 14.4 Hz, 1H), 1.43−1.38 (m, 1H), 1.08 (s, 3H), 1.05 (s, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) 203.0, 190.0 (split), 168.8, 161.3, 149.6, 133.3, 125.5, 63.0, 48.1, 45.9, 38.5, 35.9, 32.2, 31.4, 27.1, 24.4, 23.3, 23.2, 21.2, 20.2, 19.7; HRMS calcd for $C_{22}H_{30}O_4$ (M^+) 358.21441, found 358.21384.

The chemical shifts and coupling constants in the ^{1}H NMR spectrum of the synthetic material (in DMSO-d_6, 100 °C) match those reported for the natural product.[5] Chemical shifts in the ^{13}C NMR match those reported, but in our spectrum the signal at δ 190 ppm occurred as a doublet with J = ca. 0.5 Hz. No spectrum of natural heptemerone G was available from the authors for direct comparison.

8α,11β-Dimethyl-12β-isopropyl-5β,15-isopropylidenedioxy-14-keto-($\Delta^{1,2}\Delta^{3,4}$)-tricycle (3). $LiAlH_4$ (10 mg, 0.26 mmol) was added to a solution of **55** (9.1 mg, 0.021 mmol) in THF (3 mL) stirred at rt. After 30 min, the reaction was quenched with satd aq Na_2SO_4, the mixture was diluted with Et_2O (5 mL) and filtered, and the solid was washed with Et_2O (5 × 2 mL). The combined filtrates were evaporated to give **57** (11 mg). This product was immediately dissolved in dry acetone (3 mL) and treated with p-TsOH·H_2O (1.5 mg). The mixture was stirred at rt for 2 h, diluted with Et_2O (10 mL) and hexanes (10 mL), and poured into water. The organic layer was separated, washed with water and brine, and dried. The solvent was evaporated, and the residue was chromatographed on silica gel (1.3 g, EtOAc−hexanes, 7:93) to give **3** (7.2 mg, 95%): mp 70−73 °C (from the mass); IR 1716, 1640, 1621 cm^{-1}; UV 293.17 nm; ^{1}H NMR (500 MHz) 6.81 (br s, 1H), 4.39−4.31 (m, 2H), 4.07 (dt, J = 16.0, 1.9 Hz, 1H), 2.48 (dd, J = 7.6, 18.0 Hz, 1H), 2.26 (dt, J = 1.8, 14.0 Hz, 1H), 2.14 (dd, J = 13.4, 18.1 Hz, 1H), 1.95 (ddd, J = 2.7, 5.0, 14.3 Hz, 1H), 1.92−1.85 (m, 1H), 1.83−1.71 (m, 2H), 1.68−1.55 (m, 5H), 1.43 (s, 3H), 1.35 (s, 3H), 1.04 (d, J = 6.6 Hz, 3H), 1.01 (s, 3H), 0.95 (s, 3H), 0.93 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz) 205.4, 146.5, 139.7, 133.2, 129.5, 100.1, 67.6, 60.1, 51.5, 46.1, 41.2, 38.2, 36.9, 36.4, 33.9, 28.5, 26.9, 25.1, 24.5, 24.2, 23.9, 22.3, 17.9; HRMS calcd for $C_{23}H_{34}O_3$ (M^+) 358.25080, found 358.25208.

The ^{1}H and ^{13}C NMR spectra of our crystalline material are identical (a direct comparison) with those reported for an oily material.[10]

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Supporting Information Available: Complete experimental procedures and spectral data for previously unreported compounds; ^{1}H and ^{13}C NMR spectra for all synthetic intermediates and target products; IR spectra for selected compounds; X-ray crystal structure coordinates for **42**. This material is available free of charge via the Internet at http://pubs.acs.org.