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Synthesis of Pinguisane-Type Sesquiterpenoids Acutifolone A, Pinguisenol, and Bisacutifolones by a Diels–Alder Dimerization Reaction

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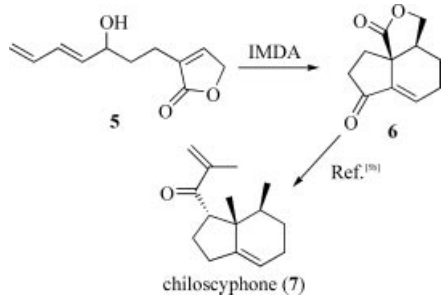
The total synthesis of pinguisane-type sesquiterpenoids, acutifolone A (**1**) and pinguisenol (**2**), has been achieved by using the Mukaiyama aldol reaction as the key step. The intermolecular Diels–Alder reaction of these monomeric natural products successfully led to stereoselective dimerization, leading to bisacutifolones A (**3**) and B (**4**). Theoretical calculations revealed that the dimerization reaction proceeded through the most stable transition state.

Introduction

A number of sesquiterpenoids possessing a variety of biological activities such as antitumor and antimicrobial activities have been isolated from liverwort.[1] Chemical and biological research groups throughout the world have shown considerable interest in their complicated and attractive structures. In recent years, Asakawa and co-workers have isolated a series of pinguisane-type sesquiterpenoids such as acutifolone A (**1**),[2] pinguisenol (**2**),[3] bisacutifolone A (**3**), and bisacutifolone B (**4**).[2] These natural products have in common all-*cis* substituents at four stereogenic centers in the bicyclo[4.3.0]nonane framework. Although three groups have reported the total synthesis of **2**,[4] possessing the simplest pinguisane skeleton, the total synthesis of the other congeners has not been achieved, probably owing to more complicated structures. Generally, the synthetic approaches adopted by other groups applied propargylsilane-terminated cyclization[4a,4b] or orthoester Claisen reactions coupled with Cu/$CuSO_4$-catalyzed cyclopropanation.[4c] Against such a background, we have previously reported a synthesis of optically active[5a] and racemic[5b] **6**, an important precursor of a variety of sesquiterpenoids, by using the intramolecular Diels–Alder reaction (IMDA)[5a] and its application to the total synthesis of chiloscyphone (**7**) (Scheme 1).[5b,5c] Along this line, in the investigation presented herein, we carried out a synthetic study of pinguisane-type sesquiterpenoid **1** as well as the formal synthesis of **2**. In addition, we attempted the synthesis of the dimeric derivatives bisacutifolones A (**3**) and B (**4**), isolated nearly at the same time as monomeric **1** and **2**. The synthesis of **3** and **4** has not been reported so far.[6] In biogenesis, these dimeric structures should be assembled by Diels–Alder re-



Scheme 1. Total synthesis of chiloscyphone (**7**) by intramolecular Diels–Alder reaction.

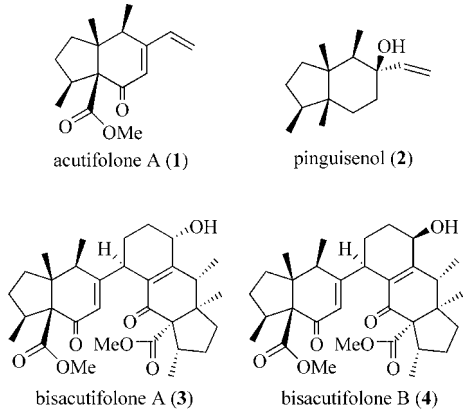


Figure 1. Pinguisane-type sesquiterpenoids isolated from liverwort.

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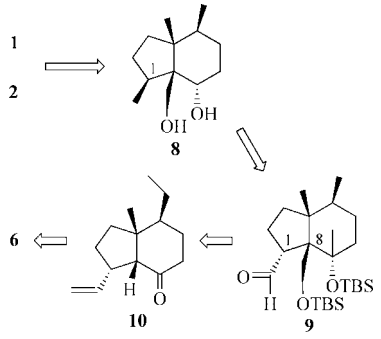
actions. Based on such a hypothesis, we attempted a plausible biomimetic approach to the bisacutifolones **3** and **4**. The regioselectivity of the coupling reaction was elucidated by theoretical calculations. We disclose herein the details of the synthesis of **1**–**4** from racemic **6** (Figure 1).

Results and Discussion

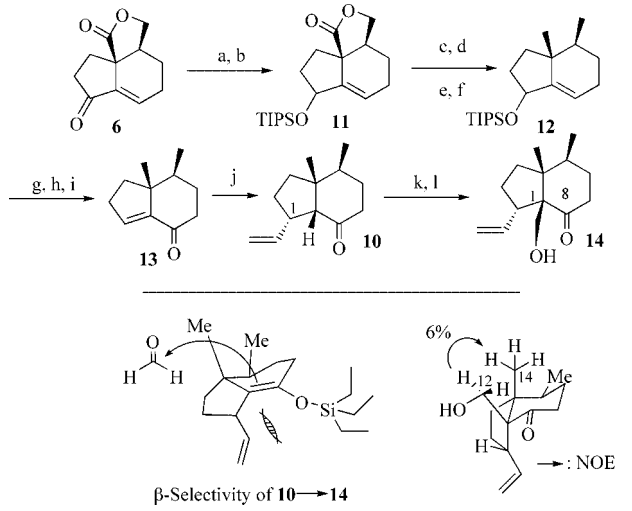
Synthesis of 1 and 2

In the retrosynthetic analysis of the pinguisane-type sesquiterpenoids (Scheme 2), compounds **1** and **2** would be synthesized from the common intermediate **8**. The β-methyl group at the C-1 position of **8** would be constructed by isomerization of the α-aldehyde **9**. The hydroxymethyl derivative at the C-8 position of **9** might be constructed stereoselectively by the Mukaiyama aldol reaction of **10**, which would be produced by stepwise manipulation of **6**.



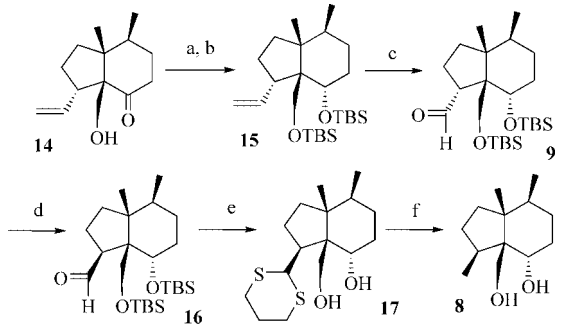
Scheme 2. Retrosynthetic analysis.

At the outset, starting from **6**, the stereoselective construction of **14**, carrying the C-8 hydroxymethyl function, was examined (Scheme 3). The common intermediate **6** was reduced under Luche conditions[7] and protected with a TIPS group to furnish **11**. Reduction of the lactone moiety gave the corresponding diol, which was converted into a cyclic sulfide and reduced with Raney Ni W-4[8] to produce **12**. After exposure of the trisubstituted olefin in **12** to sequential hydroboration and oxidation, elimination of the siloxy group furnished the α,β-unsaturated ketone **13**. Stereoselective Michael addition of a vinyl group gave **10** as a single isomer owing to the steric hindrance caused by the dimethyl moiety on the β face (Scheme 3). The ketone moiety of **10** was converted into the corresponding TES enol ethers (desired tetrasubstituted olefin/trisubstituted isomer = 72:28) which was submitted to the Mukaiyama aldol reaction,[9] giving alcohol **14** as a single isomer. This stereoselective addition was effectively controlled by the steric hindrance at the neighboring C-1 position resulting from the α-face vinyl moiety. The stereochemistry of **14** was unambiguously confirmed by NOE correlation between 12-H and 14-H (Scheme 3). A combination of aqueous HCHO and Lewis acid [$Sc(OTf)_3$ or $Yb(OTf)_3$] played an essential role in the successful hydroxymethylation whereas other conditions did not give the desired reaction. Furthermore, a low reaction concentration (2.7 mmol in a 56 mL solution) increased the product yield to 88% (conversion yield). The undesired trisubstituted TES ether was recovered as **10** without coupling with HCHO under these reaction conditions; presumably, this yield refers to the conversion of the tetrasubstituted TES ether in the isomeric mixture.



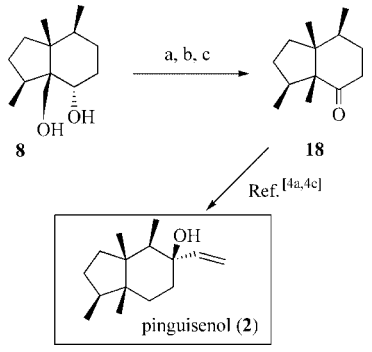
Scheme 3. Reagents and conditions: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$/MeOH, –70 °C; (b) TIPSOTf, 2,6-lutidine/CH_2Cl_2, 0 °C, 99% in 2 steps; (c) DIBAL-H/CH_2Cl_2, 0 °C; (d) MsCl, pyr, 0 °C; (e) Na_2S/DMF, room temp.; (f) Raney Ni W-4/THF, room temp., 65% in 4 steps; (g) 1. $BH_3 \cdot$THF/THF, 0 °C, then H_2O_2, NaOH, room temp.; (h) TFAA, DMSO, Et_3N/CH_2Cl_2, –65 °C; (i) DBU/PhMe, 0 °C, 60% in 3 steps; (j) CH_2=CHMgBr, CuI/THF, –78 °C, 79%; (k) TESCl, Et_3N, LiI/CH_2Cl_2, 40 °C; (l) HCHO (aq.) $Sc(OTf)_3$/THF, 65 °C, 88% in 2 steps.

The construction of the *all-cis* tetramethyl moiety is outlined in Scheme 4. After stereoselective reduction of the ketone **14** with $LiAlH(OtBu)_3$, TBS protection of the corresponding hydroxy group gave **15**. Oxidative cleavage of the olefin furnished the α-aldehyde **9** which isomerized under basic conditions to give the β-aldehyde **16**. Manipulation of the protecting groups in **16** provided dithiane **17** which, on desulfurization with Raney Ni W-4, provided diol **8**.



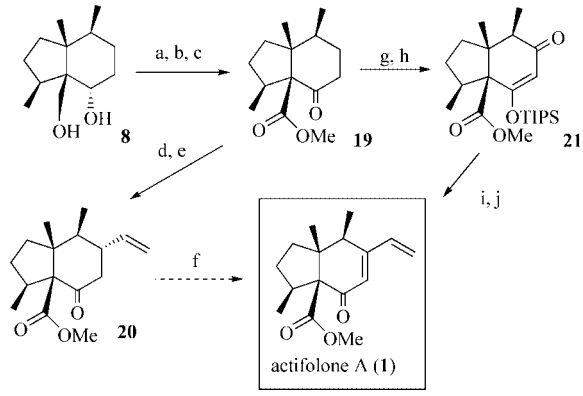
Scheme 4. Reagents and conditions: (a) $LiAlH(OtBu)_3$/THF, 0 °C; (b) TBSOTf, 2,6-lutidine/CH_2Cl_2, 0 °C, 96% in 2 steps; (c) OsO_4, Me_3NO/acetone, H_2O, 0 °C, then $NaIO_4$, room temp., 71%; (d) DBU/PhH, 50 °C, 99%; (e) $HS(CH_2)_3SH$, $BF_3 \cdot OEt_2$/CH_2Cl_2, 0 °C, 93%; (f) Raney Ni W-4/THF, reflux, 78%.

Exhaustive oxidation of **8** with PDC gave the corresponding keto aldehyde which, on selective conversion into a monodithiane and reduction, gave **18**, the known synthetic intermediate in the synthesis of **2** (Scheme 5). All the spectroscopic data for **18** were identical to those reported in the literature.[4c]



Scheme 5. Reagents and conditions: (a) PDC/DMF, room temp.; (b) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2/CH_2Cl_2$, –78 °C; (c) Raney Ni W-4/THF, reflux, 65% in 3 steps.

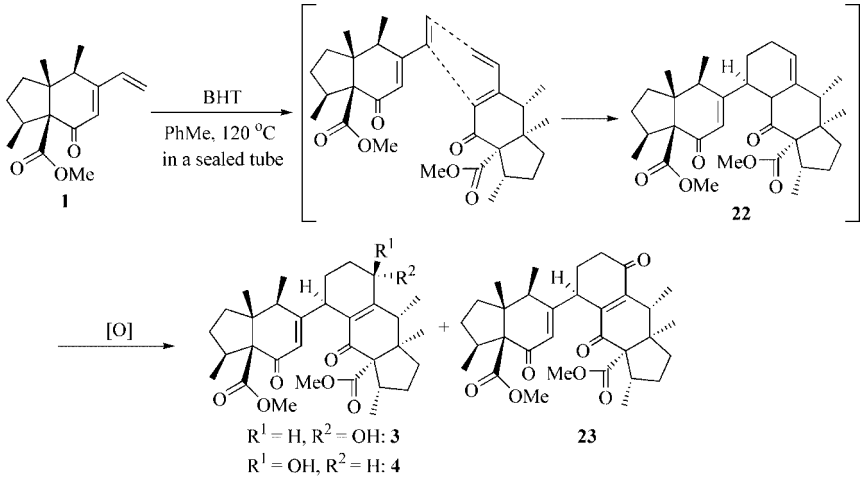
The total synthesis of **1** from **8** is displayed in Scheme 6. After sequential oxidation (PDC, $NaClO_2$) and esterification of **8**, the introduction of the diene moiety into **19** was investigated. Compound **19** was oxidized with 2-iodoxybenzoic acid (IBX)[10] and the resulting enone reacted with CH_2=CHMgCl in the presence of CuI to provide **20**. Unfortunately, production of the target **1** was unsuccessful by oxidative olefination of **20** with IBX or the Ito–Saegusa protocol.[11] Therefore, ketone **19** was converted into a TIPS enol ether, which was submitted to Corey's allylic oxidation protocol[12] to furnish the β-siloxy unsaturated ketone **21**. After 1,2-addition of the Grignard reagent in the presence of $CeCl_3$,[13] removal of the TIPS group under acidic conditions provided **1**. The spectroscopic data of **1** are in agreement with reported data.[2]



Scheme 6. Reagents and conditions: (a) PDC/DMF, room temp.; (b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene/*t*BuOH/H_2O, 0 °C; (c) $TMSCHN_2$/MeOH, 0 °C, 54% in 3 steps; (d) IBX/DMSO/THF, 80 °C; (e) CH_2=CHMgCl, CuI/THF, –78 °C, 75% in 2 steps; (f) IBX or TMSOTf, Et_3N, then $Pd(OAc)_2$; (g) TIPSOTf, 2,6-lutidine/CH_2Cl_2, room temp.; (h) TBHP, 20% $Pd(OH)_2$/C, Cs_2CO_3, O_2/CH_2Cl_2, 0 °C; (i) CH_2=CHMgCl, $CeCl_3$/THF, 0 °C; (j) CSA/MeOH, room temp., 82% in 2 steps.

Synthesis of 3 and 4

Biomimetic Diels–Alder dimerization of **1** was attempted in an effort to produce the dimeric derivatives **3** and **4** (Scheme 7). Whereas no coupling product was obtained under acidic (TsOH, TFA, or Et_2AlCl) or neat conditions, the desired reaction proceeded by heating **1** in a sealed tube in the presence of 2,6-di-*tert*-butyl-4-methylphenol ("butylated hydroxytoluene", BHT) to give a mixture of **3**, **4**, and the over-oxygenated **23** in 30, 35, and 11% yields, respectively. Their structures were spectroscopically determined by ^1H and ^{13}C NMR after purification. Although dimerization and successive oxidation progressed smoothly, the plausible dimeric intermediate **22** was not obtained owing to rapid autoxidation of the newly generated olefinic moiety, similar to the oxidation mechanisms of steroids.[14]



Scheme 7. Synthesis of **3** and **4** by a Diels Alder dimerization reaction.

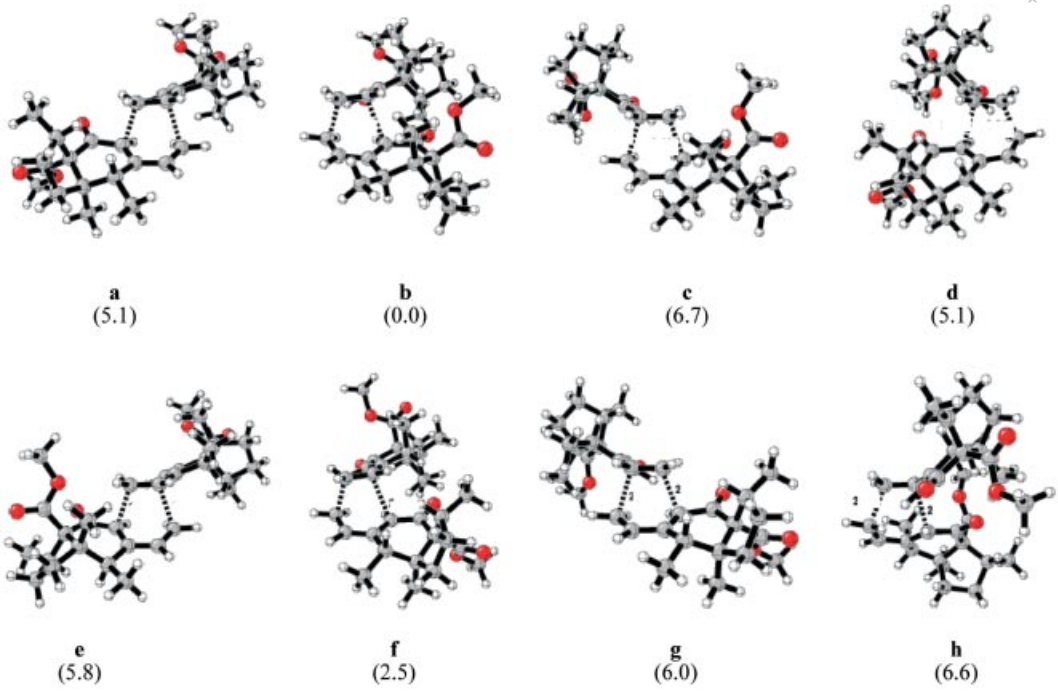
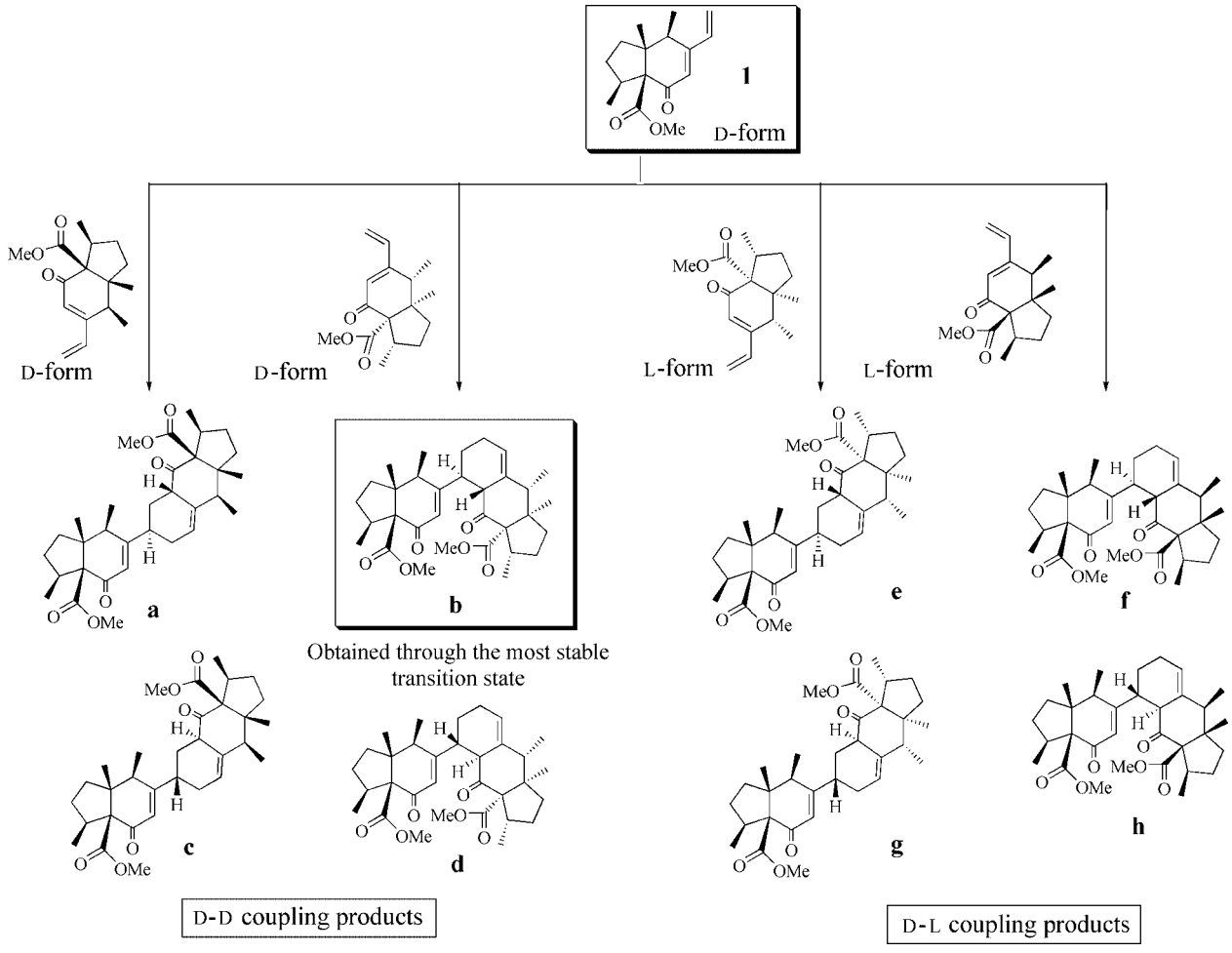


Figure 2. Eight transition-state structures (**a**–**h**) for the dimerization of **1** determined at the RHF/3-21G level.



Scheme 8. Dimerization of D-D and D-L combinations of **1** (the racemate of **1** was employed).

Transition-State Analysis of the Dimerization Reaction

To further understand the stereoselectivity of the dimerization reaction, we performed a computational analysis of the transition states of the Diels–Alder reaction. The transition-state geometries were optimized at the RHF/3-21G level (Figure 2). Each structure was confirmed to be the lowest energy for the rotatable side-chain conformations by AM1 calculations. Single-point energy calculations were performed at the B3LYP/6-31G* level to estimate the relative stabilities (kcal/mol) of the transition states (Figure 2). All calculations were performed by using the GAUSSIAN03 program package.[15] Among the eight potential dimerization products (**a**–**h**),[16] isomer **22** (**b** in Scheme 8), having the lowest transition-state energy (**b** in Figure 2), seems to be a precursor of **3**, **4**, and **23** (Scheme 7). This observation indicates that the dimerization is affected by the chirality of the monomer. In other words, we need to consider all possible combinations of chiral monomers: D-D, L-L, and D-L. In addition, there are combinations of regioselectivity and reacting face that also need to be considered. Nevertheless, **22** (**b**) is considered to be the sole product of the Diels–Alder reaction and the calculations revealed the transition state leading to **22** (**b**) to be the most stable among the eight possible isomeric transition states. We had expected to obtain **b** and **e**, which would be produced with the least steric hindrance because the β face of **1** is a convex face (Scheme 8). However, the dimerization reaction produced **b** as the sole product and the theoretical study also agrees with the experimental result.

Conclusions

We have accomplished the stereoselective total synthesis of **1** and **2**. The synthetic intermediate **6** may be widely used for the synthesis of related sesquiterpenoids. Biomimetic dimerization of **1** by Diels–Alder reaction successfully produced **3** and **4**. The stereoselectivity of the reaction was supported by calculation of the energy levels of eight transition-state structures.

Experimental Section

General: IR spectra were recorded with a JASCO Model A-202 spectrophotometer. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz on a JEOL JNM GX-400 spectrometer in a deuteriochloroform ($CDCl_3$) solution using tetramethylsilane as an internal standard. High-resolution mass spectra were obtained with a Hitachi M-80 B GC-MS spectrometer operating at an ionization energy of 70 eV. Silica gel column chromatography was carried out by using Kanto Chemical silica 60 N (spherical, neutral, 63–210 μm). Thin-layer chromatography (TLC) was carried out on 0.25 mm precoated silica gel plates of Silica Gel 60 F254 (E. Merck, Darmstadt). The reaction was monitored by either UV (254 nm) or 5% phosphomolybdic acid in EtOH. Work-up procedure: A mixture was partitioned between EtOAc and H_2O. The organic layers were washed with saturated aqueous $NaHCO_3$ (acidic mixture) or aqueous NH_4Cl (basic mixture), brine, dried (Na_2SO_4), and then concentrated in vacuo.

(1*S,5*S**,10*R**)-10-(Triisopropylsiloxy)-3-oxatricyclo[7.3.0.0^{1,5}]dodec-8-en-2-one (11):** $NaBH_4$ (390 mg, 10 mmol) was added to a solution of **6** (1.35 g, 7.0 mmol) and $CeCl_3 \cdot 7H_2O$ (3.90 g, 11 mmol) in MeOH (70 mL) at –70 °C; the resulting mixture was stirred at the same temperature for 50 min. After the addition of 1 M HCl, work up gave a crude product. 2,6-Lutidine (1.22 mL, 11 mmol) and TIPSOTf (2.10 mL, 7.8 mmol) were added to the crude product in CH_2Cl_2 (70 mL) at 0 °C; the mixture was stirred at the same temperature for 2 h. After the addition of 1 M HCl followed by work up, purification by silica gel column chromatography (hexane/EtOAc, 10:1) gave **11** (2.44 g, 99% in two steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 2941, 2864, 1774 cm^{-1}. ^{1}H NMR: δ = 5.94 (m, 1 H), 4.74 (m, 1 H), 4.41 (dd, J = 5.6, 8.8 Hz, 1 H), 3.99 (d, J = 8.8 Hz, 1 H), 2.25 (m, 1 H), 2.15–2.05 (complex, 5 H), 1.74 (m, 1 H), 1.65 (m, 1 H), 1.47 (m, 1 H), 1.04 (s, 21 H) ppm. ^{13}C NMR: δ = 177.5, 141.4, 126.1, 74.3, 70.7, 50.8, 40.3, 34.1, 33.3, 24.8, 23.7, 18.2, 18.1, 17.7, 12.5, 12.3 ppm. HRMS: calcd. for $C_{20}H_{34}O_3Si$ [M]$^+$ 350.2277; found 350.2266.

(4*S,1*R**,3a*R**)-(3a,4-Dimethyl-2,3,3a,4,5,6-hexahydro-1*H*-inden-1-yloxy)triisopropylsilane (12):** DIBAL-H (1.0 M solution in PhMe, 25 mL, 25 mmol) was added to a solution of **11** (2.31 g, 6.6 mmol) in CH_2Cl_2 (25 mL) at 0 °C; the mixture was stirred at the same temperature for 20 min. After the addition of 3 M HCl, the resulting slurry was worked up. A mixture of the crude product and MsCl (2.00 mL, 26 mmol) in pyridine (10 mL) was stirred at 0 °C for 1 h. After the addition of 1 M HCl, the mixture was worked up. The crude residue and Na_2S (5.15 g, 66 mmol) in DMF (66 mL) was stirred at room temperature for 8 h. After the addition of H_2O, the resulting slurry was worked up (a 1:1 mixture of EtOAc/hexane was used for extraction). The crude residue and Raney Ni W-4 (ca. 5 g) in THF (25 mL) was stirred at room temperature for 1 h. The reaction mixture was filtered through a Celite pad and washed with EtOAc. The filtrate was concentrated in vacuo. Purification by silica gel column chromatography (hexane) gave **12** (1.38 g, 65% in four steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 2925, 2866 cm^{-1}. ^{1}H NMR: δ = 5.55 (m, 1 H), 4.56 (m, 1 H), 2.07–1.77 (complex, 8 H), 1.42 (m, 1 H), 1.06 (s, 21 H), 1.02 (s, 3 H), 0.89 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR: δ = 151.4, 120.8, 76.0, 39.4, 38.1, 33.6, 29.7, 26.7, 25.6, 25.5, 19.4, 18.1, 16.7, 12.3 ppm. HRMS: calcd. for $C_{20}H_{38}OSi$ [M]$^+$ 322.2692; found 322.2699.

(7*S,7a*R**)-7,7a-Dimethyl-1,2,5,6,7,7a-hexahydro-4*H*-inden-4-one (13):** $BH_3 \cdot$THF (1.0 M solution in THF, 11 mL, 11 mmol) was added to a solution of **12** (1.25 g, 3.9 mmol) in THF (7 mL) at 0 °C; the resulting solution was stirred at room temperature for 12 h. 3 M NaOH (5 mL) and a 35% H_2O_2 solution (5 mL) were added to this mixture at 0 °C; the resulting mixture was stirred at room temperature for 1 h. After the addition of H_2O, the resulting slurry was worked up. A solution of DMSO (1.1 mL, 16 mmol) in CH_2Cl_2 (5 mL) was added to a solution of TFAA (1.10 mL, 7.8 mmol) in CH_2Cl_2 (60 mL) at –65 °C; the resulting mixture was stirred at the same temperature for 10 min. A solution of the crude product in CH_2Cl_2 (5 mL) was added to this reaction mixture at –65 °C; the resulting solution was stirred at the same temperature for another 1 h. Et_3N (2 mL) was added to this reaction mixture; the resulting mixture was stirred at 0 °C for another 15 min. After the addition of 1 M HCl, the resulting slurry was worked up. A mixture of the crude and DBU (1.20 mL, 8.0 mmol) in PhMe (75 mL) was stirred at 0 °C for 1 h. After the addition of 1 M HCl, the resulting slurry was worked up. Purification by silica gel column chromatography (hexane/EtOAc, 15:1) gave **13** (380 mg, 60% in 3 steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 2956, 2875, 1684, 1618 cm^{-1}. ^{1}H NMR: δ = 6.43 (t, J = 2.4 Hz, 1 H), 2.49–2.42 (complex, 2 H), 2.39–2.23 (complex, 2 H), 1.93 (dd, J = 7.0, 11.8 Hz, 1 H), 1.79–

1.71 (complex, 4 H), 0.95 (d, J = 6.0 Hz, 3 H), 0.91 (s, 3 H) ppm. ^{13}C NMR: δ = 200.2, 149.8, 136.0, 50.3, 41.2, 40.8, 40.2, 29.8, 28.9, 17.3, 15.9 ppm. HRMS: calcd. for $C_{11}H_{16}O$ $[M]^+$ 164.1201; found 164.1212.

(5*S,9*S**,1*R**,6*R**)-5,6-Dimethyl-9-vinylbicyclo[4.3.0]nonan-2-one (10):** CH_2=CHMgBr (1.32 M solution in THF, 8.4 mL, 11 mmol) was added to a mixture of CuI (211 mg, 1.1 mmol) in THF (15 mL) at –20 °C; the resulting mixture was stirred at the same temperature for 30 min. A solution of **13** (720 mg, 4.4 mmol) in THF (3 mL) was added to this reaction mixture at –78 °C; the resulting mixture was stirred at the same temperature for another 5 min. After the addition of saturated aqueous NH_4Cl and NH_4OH, the resulting slurry was worked up. Purification by silica gel column chromatography (hexane/EtOAc, 20:1) gave **10** (670 mg, 79%) as a colorless oil. IR (film): $\tilde{\nu}$ = 2956, 2873, 1701 cm^{-1}. ^{1}H NMR: δ = 5.78 (m, 1 H), 5.00–4.94 (complex, 2 H), 3.07 (m, 1 H), 2.53 (d, J = 10.8 Hz, 1 H), 2.37 (m, 1 H), 2.14 (m, 1 H), 1.91–1.86 (complex, 2 H), 1.81–1.56 (complex, 4 H), 1.44 (m, 1 H), 0.94 (s, 3 H), 0.93 (d, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR: δ = 214.0, 139.7, 115.3, 65.5, 47.7, 47.1, 42.2, 39.3, 35.8, 30.0, 29.4, 21.5, 16.3 ppm. HRMS: calcd. for $C_{13}H_{20}O$ $[M]^+$ 192.1514; found 192.1502.

(5*S,9*S**,1*R**,6*R**)-1-(Hydroxymethyl)-5,6-dimethyl-9-vinylbicyclo-[4.3.0]nonan-2-one (14):** Et_3N (0.70 mL, 5.0 mmol) and LiI (610 mg, 4.6 mmol) were added to a mixture of **10** (520 mg, 2.7 mmol) in CH_2Cl_2 (27 mL) at room temperature. TESCl (0.70 mL, 4.2 mmol) was added to this reaction mixture at 40 °C; the resulting mixture was stirred at the same temperature for 24 h. After the addition of saturated aqueous $NaHCO_3$, the resulting slurry was worked up. A 35% aqueous solution of formaldehyde (14 mL) and $Sc(OTf)_3$ (66.1 mg, 0.13 mmol) was added to the crude residue in THF (42 mL) at 65 °C; the resulting mixture was stirred at the same temperature for 2 h. After the addition of saturated aqueous $NaHCO_3$, the resulting slurry was worked up. Purification by silica gel column chromatography (hexane/EtOAc, 20:1→10:1) gave **14** (325 mg, 88% conversion in two steps) and **10** (200 mg, 38%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3483, 2956, 2875, 1678 cm^{-1}. ^{1}H NMR: δ = 5.78 (m, 1 H), 5.04 (d, J = 16.8 Hz, 1 H), 4.98 (d, J = 10.4 Hz, 1 H), 3.94 (dd, J = 3.2, 10.8 Hz, 1 H), 3.38–3.28 (complex, 3 H), 2.35 (m, 1 H), 2.25 (m, 1 H), 1.98–1.47 (complex, 7 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.84 (s, 3 H) ppm. ^{13}C NMR: δ = 219.3, 141.2, 115.3, 66.0, 65.9, 51.8, 48.2, 42.4, 36.6, 34.2, 28.9, 28.4, 16.1, 14.7 ppm. HRMS: calcd. for $C_{14}H_{22}O_2$ $[M]^+$ 222.1620; found 222.1618.

***tert*-Butyl{[(2*S**,5*S**,9*S**,1*R**,6*R**)-2-(*tert*-butyldimethylsiloxy)-5,6-dimethyl-9-vinylbicyclo[4.3.0]nonyl]methoxy}dimethylsilane (15):** A mixture of **14** (202 mg, 0.91 mmol) and $LiAlH(OtBu)_3$ (670 mg, 2.9 mmol) in THF (9.0 mL) was stirred at 0 °C for 1 h. After the addition of 1 M HCl, the resulting slurry was worked up. 2,6-Lutidine (0.60 mL, 5.2 mmol) and TBSOTf (0.60 mL, 2.6 mmol) were added to the crude residue in CH_2Cl_2 (4.5 mL) at 0 °C; the resulting mixture was stirred at the same temperature for 20 min. After the addition of 1 M HCl, the resulting slurry was worked up. Purification by silica gel column chromatography (hexane) gave **15** (394 mg, 96% in 2 steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 2954, 2927, 2883, 2858, 1631 cm^{-1}. ^{1}H NMR: δ = 6.54 (m, 1 H), 4.92 (dd, J = 1.8, 17.4 Hz, 1 H), 4.84 (dd, J = 1.8, 11.0 Hz, 1 H), 3.84 (d, J = 10.0 Hz, 1 H), 3.62 (dd, J = 5.2, 11.4 Hz, 1 H), 3.50 (d, J = 10.0 Hz, 1 H), 2.74 (m, 1 H), 1.88–1.15 (complex, 9 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.83 (s, 3 H), 0.78 (d, J = 6.8 Hz, 3 H), 0.04 (s, 6 H), 0.03 (s, 6 H) ppm. ^{13}C NMR: δ = 144.6, 110.6, 73.3, 70.7, 56.5, 48.6, 48.2, 36.6, 34.7, 32.6, 29.0, 26.7, 26.0, 25.8, 18.2, 18.1, 16.8, 15.0, –2.8, –3.5, –4.9, –5.5 ppm. HRMS: calcd. for $C_{22}H_{43}O_2Si_2$ $[M - C_4H_9]^+$ 395.2802; found 395.2782.

(2*S,5*S**,1*R**,6*R**,7*R**)-5-(*tert*-Butyldimethylsiloxy)-6-(*tert*-butyldimethylsiloxymethyl)-1,2-dimethylbicyclo[4.3.0]nonane-7-carbaldehyde (9):** OsO_4 (0.04 M solution in tBuOH, 1.0 mL, 0.04 mmol) was added to a mixture of **15** (394 mg, 0.87 mmol) and Me_3NO (300 mg, 2.7 mmol) in acetone (4.5 mL) and H_2O (1.5 mL) at 0 °C; the resulting mixture was stirred at the same temperature for 6 h. $NaIO_4$ (600 mg, 2.8 mmol) was added to this mixture at 0 °C; the resulting mixture was stirred at room temperature for 2 d. After the addition of saturated aqueous Na_2SO_3, the resulting slurry was worked up. Purification by silica gel column chromatography (hexane/EtOAc, 20:1→4:1) gave **9** (281 mg, 71%) as a colorless oil. IR (film): $\tilde{\nu}$ = 2954, 2929, 2881, 2858, 1712 cm^{-1}. ^{1}H NMR: δ = 10.32 (s, 1 H), 3.98 (d, J = 10.0 Hz, 1 H), 3.66 (dd, J = 5.2, 11.2 Hz, 1 H), 3.62 (d, J = 10.0 Hz, 1 H), 2.85 (t, J = 8.2 Hz, 1 H), 2.28 (m, 1 H), 1.87–1.12 (complex, 8 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.85 (s, 3 H), 0.78 (d, J = 6.8 Hz, 3 H), 0.07 (s, 6 H), 0.06 (s, 6 H) ppm. ^{13}C NMR: δ = 206.4, 72.5, 70.4, 59.9, 58.2, 48.9, 36.1, 34.2, 33.2, 28.4, 25.9, 20.2, 18.1, 16.6, 14.9, –3.4, –4.9, –5.5 ppm. HRMS: calcd. for $C_{25}H_{50}O_3Si_2$ $[M]^+$ 454.3298; found 454.3296.

(2*S,5*S**,7*S**,1*R**,6*R**)-5-(*tert*-Butyldimethylsiloxy)-6-(*tert*-butyldimethylsiloxymethyl)-1,2-dimethylbicyclo[4.3.0]nonane-7-carbaldehyde (16):** A mixture of **9** (159 mg, 0.35 mmol) and DBU (1.0 mL, 6.7 mmol) in PhH (30 mL) was stirred at 50 °C for 2 d. After the addition of 1 M HCl, the resulting slurry was worked up. Purification by silica gel column chromatography (hexane/EtOAc, 20:1) gave **16** (157 mg, 99%) as a colorless powder. IR (KBr): $\tilde{\nu}$ = 2954, 2927, 2856, 1711 cm^{-1}. ^{1}H NMR: δ = 9.95 (d, J = 1.6 Hz, 1 H), 4.16 (d, J = 10.8 Hz, 1 H), 3.61 (d, J = 10.8 Hz, 1 H), 3.51 (dd, J = 5.6, 11.2 Hz, 1 H), 3.12 (t, J = 9.2 Hz, 1 H), 2.12–2.04 (complex, 2 H), 1.83–1.13 (complex, 7 H), 0.88 (s, 3 H), 0.87 (s, 9 H), 0.85 (s, 9 H), 0.81 (d, J = 6.8 Hz, 3 H), 0.04 (s, 6 H), 0.01 (s, 6 H) ppm. ^{13}C NMR: δ = 206.1, 72.3, 65.1, 57.4, 52.7, 50.1, 36.4, 35.3, 31.8, 29.1, 25.9, 22.3, 18.1, 18.0, 16.9, 13.9, –3.9, –4.7, –5.8 ppm. HRMS: calcd. for $C_{25}H_{50}O_3Si_2$ $[M]^+$ 454.3298; found 454.3294.

(2*S,5*S**,9*S**,1*R**,6*R**)-9-(1,3-Dithian-2-yl)-1-(hydroxymethyl)-5,6-dimethylbicyclo[4.3.0]nonan-2-ol (17):** $BF_3{\cdot}OEt_2$ (0.25 mL, 2.0 mmol) and 1,3-propanedithiol (0.1 mL, 1 mmol) were added to a solution of **16** (157 mg, 0.35 mmol) in CH_2Cl_2 (3.5 mL) at 0 °C; the resulting mixture was stirred at the same temperature for 2 h. After the addition of 5% NaOH, the resulting slurry was worked up (Et_2O was used for extraction). Purification by silica gel column chromatography (hexane/EtOAc, 1:1) gave **17** (101 mg, 93%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3375, 2933 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 70 °C): δ = 5.00 (d, J = 2.0 Hz, 1 H), 4.22 (d, J = 4.4 Hz, 1 H), 3.92 (d, J = 4.4 Hz, 1 H), 3.89 (d, J = 4.0 Hz, 1 H), 3.80 (t, J = 4.8 Hz, 1 H), 3.74 (dd, J = 4.8, 11.2 Hz, 1 H), 2.97 (m, 1 H), 2.86–2.73 (complex, 4 H), 2.04–1.15 (complex, 11 H), 0.86 (s, 3 H), 0.75 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 70 °C): δ = 69.2, 61.8, 54.7, 50.2, 47.7, 45.2, 34.2, 33.3, 31.3, 30.0, 29.6, 28.9, 25.1, 22.4, 16.3, 14.5 ppm. HRMS: calcd. for $C_{16}H_{28}O_2S_2$ $[M]^+$ 316.1531; found 316.1518.

(2*S,5*S**,9*S**,1*R**,6*R**)-1-(Hydroxymethyl)-5,6,9-trimethylbicyclo-[4.3.0]nonan-2-ol (8):** A mixture of **17** (101 mg, 0.32 mmol) and Raney Ni W-4 (ca. 500 mg) in THF (15 mL) was stirred at refluxing temperature for 3 h. The reaction mixture was filtered through a Celite pad and washed with EtOAc. The filtrate was concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 2:1) gave **8** (52.9 mg, 78%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3429, 2956, 2875 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, a mixture of conformers at 100 °C): δ = 4.08–3.96 (m, 1 H), 3.88–3.61 (complex, 2 H), 2.72–2.52 (m, 1 H), 2.01–1.81 (m, 1 H), 1.71–1.19 (complex, 7 H), 1.14, 1.08 (2 × d, J = 7.0 Hz, 3 H), 0.82, 0.72 (2 × s, 3 H),

0.74–0.73 (2×d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 °C): δ = 73.3, 70.8, 65.2, 62.9, 48.4, 47.9, 36.9, 34.5, 34.1, 33.3, 33.2, 32.7, 30.2, 29.1, 29.0, 28.7, 27.7, 17.7, 16.0, 15.5, 13.9, 13.0 ppm. HRMS: calcd. for $C_{13}H_{25}O_2$ [M + H$^+$] 213.1849; found 213.1875.

(5*S,9*S**,1*R**,6*R**)-1,5,6,9-Tetramethylbicyclo[4.3.0]nonan-2-one (18):** A mixture of **8** (10.4 mg, 0.049 mmol) and PDC (80 mg, 0.21 mmol) in DMF (0.5 mL) was stirred at room temperature for 18 h. After the addition of H_2O, the resulting slurry was partitioned between EtOAc/hexane (1:1) and H_2O. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. BF_3·OEt_2 (0.050 mL, 0.40 mmol) and 1,3-propanedithiol (0.020 mL, 0.20 mmol) were added to the crude residue in CH_2Cl_2 (0.5 mL) at –78 °C; the resulting mixture was stirred at the same temperature for 10 min. After the addition of 5% NaOH, the resulting slurry was worked up (Et_2O was used for extraction). The crude residue and Raney Ni W-4 (ca. 50 mg) in THF (1 mL) was stirred at refluxing temperature for 1 h. The reaction mixture was filtered through a Celite pad and washed with EtOAc. The filtrate was concentrated in vacuo. Purification by silica gel column chromatography (hexane/EtOAc, 15:1) gave **18** (6.2 mg, 65% in three steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 2957, 1699 cm^{-1}. ^{1}H NMR: δ = 2.82–2.59 (complex, 2 H), 2.20 (m, 1 H), 2.16–1.91 (complex, 2 H), 1.83–1.78 (complex, 2 H), 1.65–1.26 (complex, 3 H), 0.91 (d, J = 6.4 Hz, 3 H), 0.86 (s, 3 H), 0.80 (s, 3 H), 0.78 (d, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR: δ = 216.4, 61.5, 54.2, 41.0, 37.6, 35.7, 34.3, 31.3, 30.9, 16.8, 16.7, 14.8, 11.7 ppm. HRMS: calcd. for $C_{13}H_{22}O$ [M]$^+$ 194.1671; found 194.1681.

Methyl (1*S,5*S**,9*S**,6*R**)-5,6,9-Trimethyl-2-oxobicyclo[4.3.0]nonane-1-carboxylate (19):** A mixture of **8** (52.9 mg, 0.25 mmol) and PDC (500 mg, 1.3 mmol) in DMF (2.5 mL) was stirred at room temperature for 18 h. After the addition of H_2O, the resulting slurry was partitioned between EtOAc/hexane (1:1) and H_2O. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. $NaClO_2$ (120 mg, 1.1 mmol) was added to a mixture of the crude residue, NaH_2PO_4 (400 mg, 2.6 mmol) in *t*BuOH (2.0 mL), H_2O (0.50 mL), and 2-methyl-2-butene (0.30 mL, 2.8 mmol) at 0 °C; the resulting mixture was stirred at the same temperature for 30 min. After the addition of 1 M HCl, the resulting slurry was worked up ($CHCl_3$ was used for extraction). To the crude residue in MeOH (2 mL) was added $TMSCHN_2$ (2 M solution in Et_2O, 1.0 mL, 2.0 mmol) at 0 °C; the resulting solution was stirred at the same temperature for 1 h. The mixture was concentrated in vacuo and purification by silica gel column chromatography (hexane/EtOAc, 10:1) gave **19** (31.9 mg, 54% in three steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 2952, 2877, 1730, 1703 cm^{-1}. ^{1}H NMR: δ = 3.67 (s, 3 H), 2.60 (m, 1 H), 2.46–2.35 (complex, 2 H), 1.84–1.58 (complex, 7 H), 1.09 (d, J = 6.8 Hz, 3 H), 0.98 (s, 3 H), 0.95 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR: δ = 209.9, 170.9, 72.5, 52.4, 51.0, 41.6, 38.0, 37.3, 36.2, 30.9, 28.2, 18.2, 16.4, 15.5 ppm. HRMS: calcd. for $C_{14}H_{22}O_3$ [M]$^+$ 238.1569; found 238.1556.

Methyl (1*S,7a*S**,4*R**,3a*R**)-1,3a,4-Trimethyl-5-oxo-7-(triisopropylsiloxy)-2,3,3a,4,5,7a-hexahydro-1*H*-indene-7a-carboxylate (21):** 2,6-Lutidine (0.050 mL, 0.43 mmol) and TIPSOTf (0.050 mL, 0.19 mmol) were added to a mixture of **19** (10.0 mg, 0.040 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C; the resulting mixture was stirred at room temperature for 2 h. After the addition of saturated aqueous $NaHCO_3$, the resulting slurry was worked up ($CHCl_3$ was used for extraction). 20% $Pd(OH)_2$/C (10 mg) and TBHP (5.1 M solution in isooctane, 0.15 mL, 0.77 mmol) were added to a mixture of the crude and Cs_2CO_3 (40.2 mg, 0.12 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C under argon; the resulting mixture was vigorously stirred at the same temperature for 3 h under O_2. The mixture was filtered through a short column ($CHCl_3$). The filtrate was concentrated in vacuo and purification by silica gel column chromatography (hexane/EtOAc, 10:1) gave **21** (12.8 mg, 75% in two steps) as a colorless oil. IR (film): $\tilde{\nu}$ = 2947, 2870, 1732, 1662, 1610 cm^{-1}. ^{1}H NMR: δ = 5.35 (s, 1 H), 3.65 (s, 3 H), 2.67 (m, 1 H), 2.55 (q, J = 6.8 Hz, 1 H), 2.04 (m, 1 H), 1.88 (m, 1 H), 1.81–1.62 (complex, 2 H), 1.30 (d, J = 6.8 Hz, 3 H), 1.10–1.07 (complex, 21 H), 1.06 (d, J = 6.8 Hz, 3 H), 0.81 (s, 3 H) ppm. ^{13}C NMR: δ = 199.9, 172.2, 171.1, 106.8, 66.7, 53.6, 50.7, 45.2, 42.3, 34.7, 31.1, 18.5, 18.0, 17.9, 17.8, 16.6, 12.7, 9.0 ppm. HRMS: calcd. for $C_{23}H_{40}O_4Si$ [M]$^+$ 408.2696; found 408.2683.

Acutifolone A (1): $CeCl_3$·$7H_2O$ (135 mg, 0.36 mmol) was placed in a round-bottomed flask. The flask was evacuated and heated at 140 °C for 2 h. The resulting solid was dissolved in THF (1.0 mL) and the mixture was stirred at room temperature for 30 min. A solution of **21** (14.5 mg, 0.036 mmol) in THF (1.0 mL) was added to this mixture at 0 °C; the resulting mixture was stirred at the same temperature for another 10 min. CH_2=CHMgCl (1.3 M solution in THF, 1.00 mL, 1.3 mmol) was added to this mixture at 0 °C; the resulting mixture was stirred at the same temperature for another 2 h. After the addition of saturated aqueous NH_4Cl, the resulting slurry was worked up. The crude residue and CSA (8.4 mg, 0.036 mmol) in MeOH (1.0 mL) was stirred at room temperature for 10 min. After the addition of saturated aqueous $NaHCO_3$, the resulting slurry was worked up. Purification by silica gel column chromatography (hexane/EtOAc, 15:1) gave acutifolone A (**1**) (7.6 mg, 82% in two steps) as a colorless powder. IR (KBr): $\tilde{\nu}$ = 2927, 1736, 1662 cm^{-1}. ^{1}H NMR: δ = 6.45 (dd, J = 10.4, 17.6 Hz, 1 H), 5.98 (s, 1 H), 5.68 (d, J = 17.6 Hz, 1 H), 5.45 (d, J = 10.4 Hz, 1 H), 3.67 (s, 3 H), 2.62 (q, J = 6.8 Hz, 1 H), 2.21 (m, 1 H), 1.73–1.51 (complex, 4 H), 1.25 (d, J = 6.8 Hz, 3 H), 1.18 (d, J = 6.8 Hz, 3 H), 1.10 (s, 3 H) ppm. ^{13}C NMR: δ = 196.9, 171.1, 160.2, 136.7, 124.3, 120.0, 67.4, 51.2, 49.9, 45.8, 41.0, 38.5, 31.5, 23.4, 18.1, 15.7 ppm. HRMS: calcd. for $C_{16}H_{22}O_3$ [M]$^+$ 262.1569; found 262.1596.

Bisacutifolones A (3) and B (4): A solution of **1** (8.5 mg, 0.032 mmol) and BHT (8.0 mg, 0.036 mmol) in PhMe (0.2 mL) was heated in a sealed tube at 120 °C for 24 h. After being cooled to room temperature, the residue was purified by silica gel column chromatography (hexane/EtOAc, 10:1→2:1) to give **3** (2.6 mg, 30%), **4** (3.1 mg, 35%), and **23** (1.0 mg, 11%) as colorless oils.

Spectroscopic Data for Bisacutifolone A (3): IR (film): $\tilde{\nu}$ = 3483, 2949, 2870, 1732, 1658 cm^{-1}. ^{1}H NMR: δ = 5.54 (d, J = 2.0 Hz, 1 H), 4.35 (m, 1 H), 3.66 (s, 2×3 H), 3.58 (m, 1 H), 2.91 (m, 1 H), 2.57 (q, J = 6.8 Hz, 1 H), 2.18–1.66 (complex, 13 H), 1.28 (d, J = 6.8 Hz, 3 H), 1.26 (d, J = 6.8 Hz, 3 H), 1.06 (d, J = 6.8 Hz, 3 H), 1.00 (s, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 0.89 (s, 3 H) ppm. ^{13}C NMR: δ = 195.3, 195.1, 171.2, 171.1, 168.0, 159.7, 133.3, 124.0, 69.6, 69.0, 67.4, 52.5, 51.1, 49.5, 43.7, 40.9, 40.8, 40.7, 40.5, 37.0, 36.0, 31.5, 30.8, 29.5, 24.6, 23.2, 19.4, 18.3, 14.6, 13.8, 13.1 ppm. HRMS: calcd. for $C_{32}H_{44}O_7$ [M]$^+$ 540.3087; found 540.3081.

Spectroscopic Data for Bisacutifolone B (4): IR (film): $\tilde{\nu}$ = 3460, 2949, 2875, 1732, 1657 cm^{-1}. ^{1}H NMR: δ = 5.76 (d, J = 2.0 Hz, 1 H), 4.29 (m, 1 H), 3.66 (s, 3 H), 3.65 (s, 3 H), 3.48 (m, 1 H), 2.91 (m, 1 H), 2.59 (m, 1 H), 2.17 (m, 1 H), 1.97–1.74 (complex, 10 H), 1.66–1.53 (complex, 3 H), 1.28 (d, J = 7.3 Hz, 3 H), 1.16 (d, J = 7.3 Hz, 3 H), 1.07 (d, J = 6.8 Hz, 3 H), 1.02 (s, 3 H), 1.00 (d, J = 6.3 Hz, 3 H), 0.90 (s, 3 H) ppm. ^{13}C NMR: δ = 195.3, 195.2, 171.2, 171.1, 168.8, 158.9, 133.3, 124.3, 69.5, 66.9, 65.7, 52.5, 51.1, 51.0, 48.2, 44.8, 42.2, 40.8, 40.6, 40.2, 37.2, 36.1, 31.7, 30.8, 28.9, 25.1,

24.2, 19.4, 18.3, 14.7, 13.9, 13.2 ppm. HRMS: calcd. for $C_{32}H_{44}O_7$ $[M]^+$ 540.3087; found 540.3083.

Spectroscopic Data for Compound 23: IR (film): $\tilde{\nu}$ = 2951, 2875, 1732, 1666 cm^{-1}. ^1H NMR: δ = 5.71 (s, 1 H), 3.87 (t, J = 5.9 Hz, 1 H), 3.66 (s, 2×3 H), 3.00 (m, 1 H), 2.83 (m, 1 H), 2.68 (m, 1 H), 2.50 (m, 1 H), 2.35 (m, 1 H), 2.09–1.58 (complex, 11 H), 1.32 (d, J = 6.8 Hz, 3 H), 1.09 (d, J = 7.3 Hz, 3 H), 1.07 (s, 3 H), 1.04 (d, J = 6.8 Hz, 3 H), 1.03 (d, J = 6.8 Hz, 3 H), 0.93 (s, 3 H) ppm. ^{13}C NMR: δ = 198.8, 196.8, 194.7, 170.8, 170.5, 164.4, 150.4, 145.0, 125.3, 69.3, 66.6, 52.3, 51.2, 51.1, 48.1, 45.4, 43.1, 41.3, 40.9, 36.9, 36.5, 35.2, 35.1, 31.7, 30.9, 27.3, 24.6, 19.7, 19.4, 14.7, 13.8, 13.7 ppm. HRMS: calcd. for $C_{32}H_{42}O_7$ $[M]^+$ 538.2931; found 538.2915.

Comparison of Transition-State Energies by Ab Initio Calculations: Eight transition-state structures were optimized at the RHF/3-21G level. Each structure was confirmed to be the lowest energy for rotatable side-chain conformations using AM1 calculations. Single-point energy calculations were performed at the B3LYP/6-31G* level to evaluate the relative stabilities (kcal/mol) of the transition states. All the calculations were carried out by using the GAUSSIAN03 program package.[15]

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[16] The Diels–Alder reaction of racemic **1** provided the enantiomeric products (L-L and L-D) **a**–**h**; their structures have been omitted.

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