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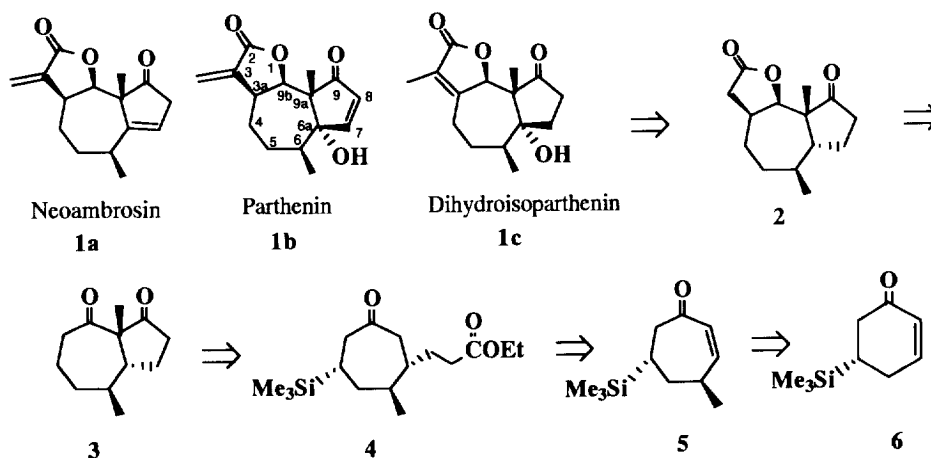
Enantioselective Synthesis of Neoambrosin, Parthenin, and Dihydroisoparthenin

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Abstract: Enantioselective synthesis of the titled ambrosanolides is described. Use of the trimethylsilyl group as an anchor contributed to the stereoselective introduction of two methyl groups.

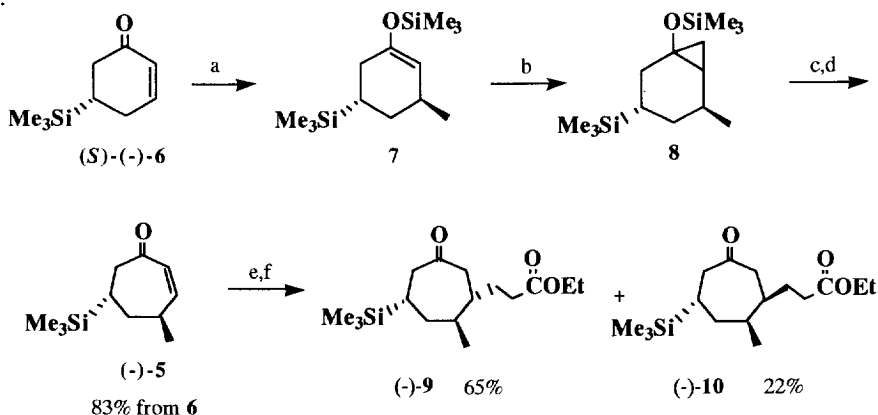
The pseudoguaianolide sesquiterpene lactones have contiguous chiral centers on the flexible seven-membered ring portion of the bicyclo[5.3.0]decane framework, and therefore have been the challenging and attractive synthetic targets for many years.¹⁾ In connection with our studies on enantioselective synthesis of terpenes using 5-trimethylsilyl-2-cyclohexenone (**6**) as a chiron, we were interested in the structural and stereochemical complexities in conjunction with the once presumed potential for use as therapeutic agents. We designed enantioselective synthesis of ambrosanolide neoambrosin (**1a**)²⁾, parthenin (**1b**)³⁾, and dihydroisoparthenin (**1c**)^{3a,4)} which have two methyl groups with *cis* relationship. Homochiral keto lactone **2** can be considered as a key intermediate for an enantioselective access to the ambrosanoides. Actually, in the racemic version, **1b** was synthesized from **2**.⁵⁾ Our synthetic route adopted stepwise introduction of functional groups to an unsaturated 7-membered ring, and as a stereocontrol strategy, the trimethylsilyl group anchoring method⁶⁾ was examined.



Scheme 1.

We envisioned that the presence of the trimethylsilyl group of **6** enable stereoselective introduction of the methyl group to 6 position of **1**, and subsequent stereocontrol at 6a position and angular methyl group at 9a.

Stereoselective introduction of the methyl group to (*S*)-(-)-**6** was carried out by the same method for its enantiomer⁷⁾ to give enol silyl ether **7**. Cyclopropanation of the enol silyl ether⁸⁾ followed by oxidative ring opening with FeCl₃⁹⁾ and dehydrochlorination afforded cycloheptenone (-)-**5** in 83% overall yield from (*S*)-(-)-**6**.

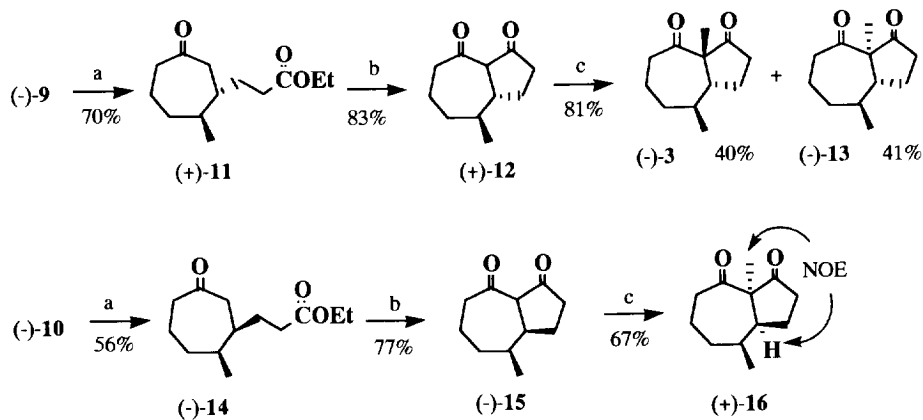


Scheme 2. a) MeMgI, CuBr·Me₂S, Me₃SiCl, HMPA, THF, -78 °C; b) CH₂I₂, ZnEt₂, PhMe, 0 °C; c) FeCl₃, DMF, 0 °C-rt; d) NaOAc, MeOH, reflux; e) Zn[(CH₂)₂CO₂Et, CuCN·2LiCl, Me₃SiCl; f) KF, MeOH.

For cyclopentane annulation, introduction of C3 unit to (-)-**5** by 1,4-addition was examined. Titanium (IV) chloride catalyzed 1,4-addition of allylsilane proceeded smoothly to give a 2:1 mixture (determined by 500 MHz ¹H NMR) of diastereomers in 83% combined yield, however, the diastereomers could not be separated by column chromatography. 1,4-Addition of zinc homoenolate, which was generated from ethyl 3-iodopropionate, in the presence of CuCN·2LiCl and Me₃SiCl¹⁰⁾ gave an easily separable 3:1 mixture of diastereoisomers [(*-*)-**9** and (*-*)-**10**] in 87% combined yield. The stereostructures of (*-*)-**9** and (*-*)-**10** were established by the total synthesis of clavukerin A and its epimer.¹¹⁾ The reaction of the homoenolate generated from (1-ethoxy)cyclopropyl trimethylsilyl ether¹²⁾ gave almost the same results. In this system, stereo control with the Me₃Si group turned out to be less effective. To test the anchoring effect of the Me₃Si group on angular methyl introduction step, two types of bicyclo[5.3.0]decane-2,10-diones, the one with a Me₃Si group (Scheme 4), and the other without a Me₃Si group (Scheme 3) were subjected to methylation.

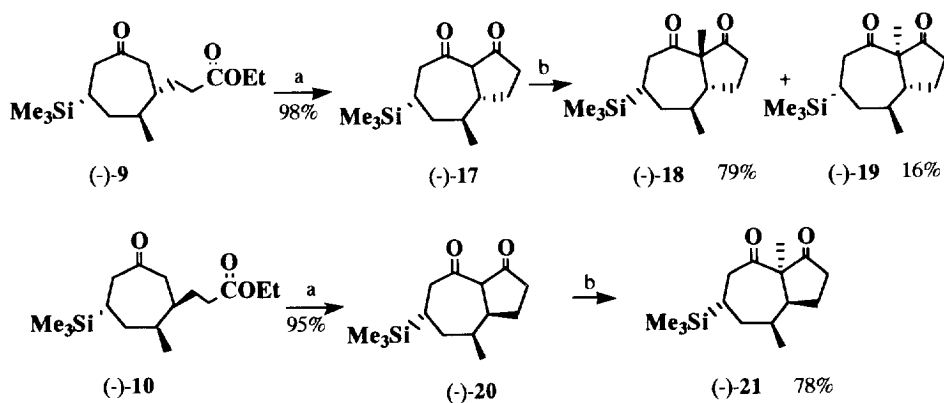
Treatment of (-)-**9** with excess bromine followed by reduction with zinc and hydrogenation gave desilylated product (+)-**11** in 70% overall yield. The Claisen condensation with *t*-BuOK in THF gave dione (+)-**12**, which exists as an enolketone in CDCl₃, in 83% yield. Initial trial for *in situ* methylation of the potassium salt of the diketone under refluxing conditions resulted in a failure. Methylation of (+)-**12** in refluxing acetone with excess of methyl iodide and anhydrous potassium carbonate gave an easily separable 1:1 mixture of diastereoisomers, (-)-**3** and (-)-**13**, in 81% combined yield. In a similar manner, (-)-**14** was obtained from (-)-**10** in 56% yield. Claisen condensation of (-)-**14** gave (-)-**15** (77%) whose methylation gave (+)-**16** as an exclusive product in 67% yield. The ¹H and ¹³C NMR data of (-)-**3** were virtually identical with

those previously reported for (\pm)-**3**.⁵) Thus, the structure of (-)-**13** was deduced as depicted in Scheme 3. NOE experiment revealed the cis relationship of the ring junction of (+)-**16**.



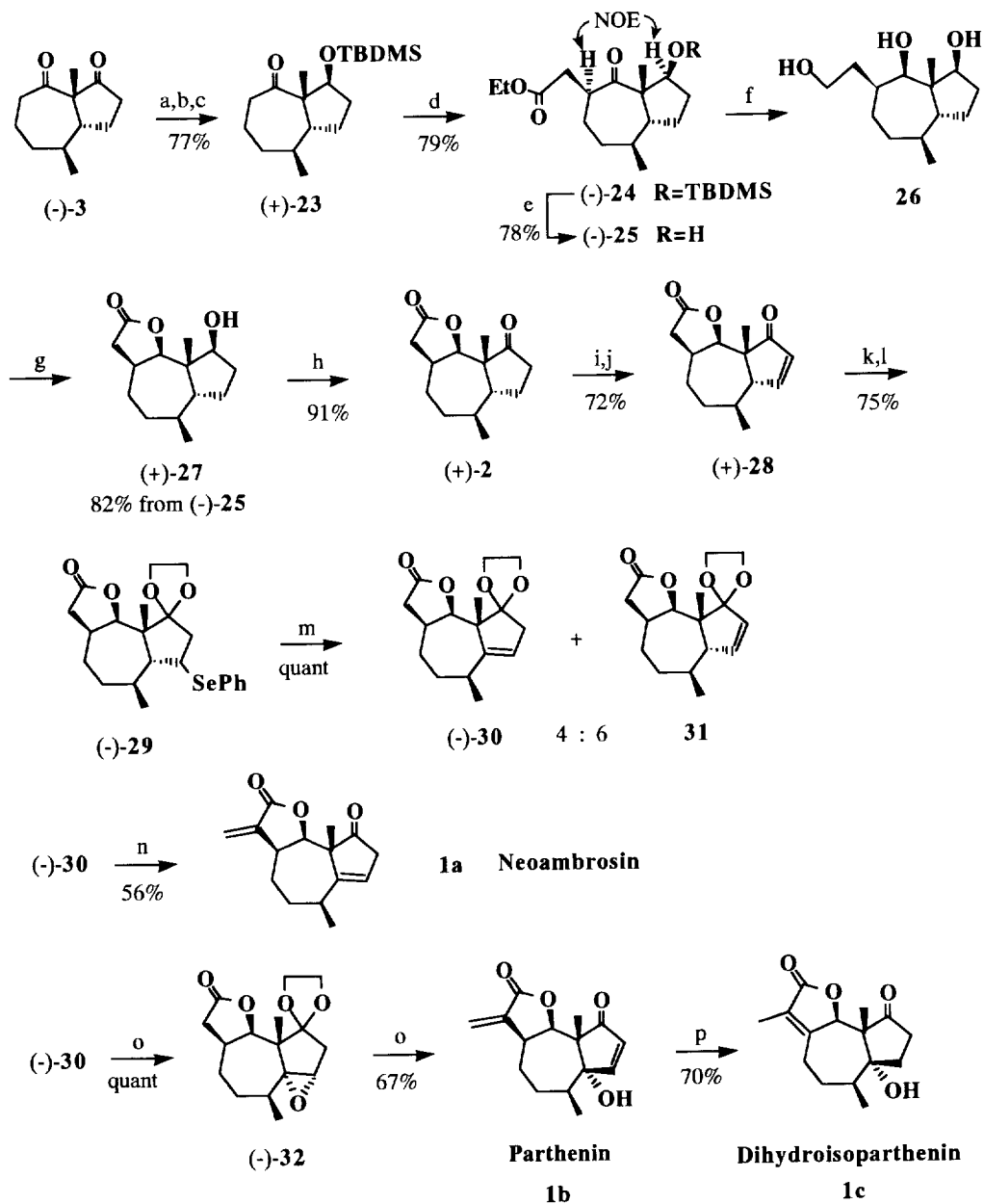
Scheme 3. a) Br_2 , CCl_4 ; Zn, EtOH; H_2 , Pd-C; b) *t*-BuOK, THF, 0 °C; c) MeI, K_2CO_3 , acetone, reflux.

The Dieckmann-type condensation of (-)-**9** gave diketone (-)-**17** in 98% yield. In this case also the *in situ* methylation was unsuccessful. Methylation of (-)-**17** under the same conditions used for (+)-**12** gave (-)-**18** (79%) and (-)-**19** (16%). Thus the presence of the trimethylsilyl group contributes the stereoselectivity in the methylation. The structure of (-)-**18** was confirmed by the transformation into (-)-**3** (93%). In the same way, (-)-**10** was converted to (-)-**20** (95%) and subjected methylation to give (-)-**21** (78%) as a sole product. The structure of (-)-**21** was confirmed by the transformation into (+)-**16**. Consequently, the following sequence of operations for the conversion of the major isomer (-)-**9** to desired (-)-**3** turned out to be the best choice: (-)-**9** → (-)-**17** (98%) → (-)-**18** (79%) → (-)-**3** (93%).



Scheme 4. a) *t*-BuOK, THF, 0 °C; b) MeI, acetone, reflux.

Although the trial for selective reduction of diketone (-)-**3** was unsuccessful, selective protection of one hydroxy group of diol derivative obtained by the reduction of (-)-**3** with excess DIBAH (80% yield) gave the corresponding TBDMS ether in 96% yield. Oxidation with PDC gave (+)-**23** quantitatively. The relative stereochemistry of (+)-**23** was confirmed after removal of the TBDMS group by comparison of its ^1H and ^{13}C NMR with those of racemic one.⁵⁾ After the treatment with LDA, (+)-**23** was alkylated with ethyl iodoacetate at -78 °C in the presence of HMPA to give (-)-**24** in 79% yield. The structure of (-)-**24** was determined by the NOE enhancement between depicted two protons. To convert (-)-**24** to a lactone derivative, chemoselective reduction of the ketone to hydroxy group was examined. Reduction with NaBH_4 in MeOH at 0 °C-rt resulted in a recovery of the starting keto ester. Use of DIBAH in ether at -78 °C resulted in a reduction of ester to aldehyde and the ketone remained intact. These results should be ascribed to the steric bulkiness of TBDMS ether. Therefore, to release the steric hindrance, removal of TBDMS group was first carried out. Trials for direct conversion of hydroxy keto ester (-)-**25** into lactone (+)-**27** resulted in a failure due to the formation of triol **26** as a by-product. Reduction of (-)-**25** with excess DIBAH (5 eq) gave triol **26** which was oxidized with O_2 in the presence of PtO_2 ¹³⁾ gave (+)-**27** in 82% overall yield from (-)-**25**. Jones oxidation of (+)-**27** gave the key intermediate (+)-**2** in 91% yield. The ^1H NMR data of (+)-**2** showed good agreement with those of reported for (\pm)-**2** whose structure was confirmed by X-ray analysis, however, the ^{13}C NMR data were apparently different.⁵⁾ The results of X-ray analysis on (+)-**2**¹⁴⁾ were consistent with the depicted structure. These seemingly inconsistent results can be explained by the fact that the chemical shifts of ^{13}C NMR of (+)-**2** are concentration dependent which suggest the strong self-association ability of this type of compounds. Such disagreement of ^{13}C NMR spectra data between optically active and racemic ones was observed on **28** also. In a racemic series, the conversion of **2** to **30** is already reported.⁵⁾ Initially, we applied the method to the subsequent transformations but sometimes the harsh reaction conditions caused decomposition of products. Therefore, we examined mild methods. Silylation of (+)-**2** with TMSOTf and Et_3N at room temperature followed by treatment with stoichiometric amount of $\text{Pd}(\text{OAc})_2$ in CH_3CN at room temperature gave (+)-**28** in 72% overall yield. 1,4-Addition of benzeneselenol to (+)-**28** and subsequent acetalization gave (-)-**29** in 75% overall yield. The oxidative elimination of phenylseleno group with NaIO_4 gave a 4:6 mixture of the desired (-)-**30** and **31** in quantitative yield. Though the undesired compound **31** is a major product, **31** can be recycled via conversion into (+)-**28** (quantitative yield). The isolation of (-)-**30** from the mixture was carried out by careful column chromatography or by chromatographical separation after selective hydrolysis of **31** to (+)-**28** in an acidic media. The introduction of exo-methylene group to (-)-**30** by usual method followed by deacetalization gave neoambrosin (**1a**) in 56% overall yield from (-)-**30**. The synthesis of parthenin (**1b**) from (-)-**30** was carried out according to Heathcock's method.⁵⁾ The epoxidation of (-)-**30** gave (-)-**32** in quantitative yield and parthenin (**1b**) was obtained in 67% overall yield from (-)-**32**. Transformation of parthenin (**1b**) into dihydroisoparthenin (**1c**) was achieved in 70% yield according to Herz's method.^{3a)}



Scheme 5. a) DIBAH, THF, -78 °C; b) TBDMSCl, imidazole, DMF, 0 °C; c) PDC, CH₂Cl₂, π; d) LDA, ICH₂CO₂Et, HMPA, THF, -78 °C; e) AcOH-H₂O-THF, 100 °C; f) DIBAH, THF; g) PtO₂, O₂; h) Jones ox.; i) TMSOTf, Et₃N; j) Pd(OAc)₂; k) PhSeH, AcOH; l) (TMSOCH₂)₂, TMSOTf, 0 °C; m) NaIO₄, MeOH-H₂O, 0 °C; n) ref. 15; o) ref. 5; p) ref. 3a.

The spectral (^1H NMR, ^{13}C NMR and IR) and physical data of synthesized **1a-c** were in full agreement with those of reported. The optical rotation of synthesized **1a-c** showed good agreement with those of natural ones, however, the sign of synthesized **1b** was opposite. The CD spectrum of synthesized **1c** was consistent with the structure of natural dihydroisoparthenin. These results led us to the conclusion that the reported sign of $[\alpha]_{\text{D}}$ value of natural **1b** is in error.

Experimental

General Procedures. All solvents were dried and stored over molecular sieves. All reactions were carried out under Ar. Infrared spectra were recorded on a Hitachi 260-50. ^1H - and ^{13}C -NMR spectra were recorded on a Hitachi R-24B, JEOL JNM-FX-90Q, or a JEOL JNM-EX 270 in CDCl_3 otherwise noted. Specific rotation was measured on a Horiba SEPA-200 in CHCl_3 otherwise noted. CD spectrum was recorded on a JASCO J-500C Spectropolarimeter. Melting points were obtained on a Mitamura Riken melting-point apparatus and are uncorrected.

(3*S*, 5*S*)-3-Methyl-1-trimethylsiloxy-5-trimethylsilyl-1-cyclohexene (7). To a mixture of (-)-5-trimethylsilyl-2-cyclohexenone [(-)-**6**] (8.6 g, 51 mmol) and $\text{CuBr}\cdot\text{Me}_2\text{S}$ (0.52 g, 5 mol%) in THF (500 ml) cooled to $-78\text{ }^\circ\text{C}$ were added HMPA (17.9 ml, 102 mmol) and chlorotrimethylsilane (19.6 ml, 153 mmol). After the addition of 1 M solution of MeMgI (100 ml) over a period of 2 h, the reaction mixture was stirred at that temperature further 10 minutes, and then Et_3N (21.3 ml, 153 mmol) was added. The reaction mixture was warmed to room temperature and extracted with hexane and then with ether. The organic layers were combined, washed with brine, and dried over MgSO_4 . After removal of the solvent under reduced pressure, distillation of the residue gave **7** (26.2 g, 92%): oil; bp $75\text{--}82\text{ }^\circ\text{C}/3\text{ mmHg}$; IR (neat) $1665\text{ cm}^{-1}(\text{C}=\text{O})$; ^1H NMR δ -0.01 (s, 9 H), 0.18 (s, 9 H), 0.94 (d, $J=6.9\text{ Hz}$, 3 H), 1.22-2.47 (m, 9 H), 4.86 (d, $J=1.7\text{ Hz}$, 1 H).

(4*S*,6*S*)-4-Methyl-6-trimethylsilyl-2-cycloheptenone [(-)-5**]:** To a cooled ($0\text{ }^\circ\text{C}$) mixture of **7** (27.4 g, 107 mmol) in toluene (100 ml) and 1M solution of Et_2Zn in hexane (160 ml) was added CH_2I_2 (11.3 ml, 140 mmol), and the resulting solution was stirred further 1.5 h at that temperature. After quenching with aq. NH_4Cl , the mixture was stirred at $0\text{ }^\circ\text{C}$ for 10 min, filtrated through a short pad of celite. The organic layer was washed with aq. NH_4Cl and then with water. Concentration under reduced pressure gave 28.1 g of a crude oil which was used in the following reaction without further purification. To a cooled ($0\text{ }^\circ\text{C}$) solution of Fe (III) chloride (24.2 g, 150 mmol) in dry DMF (68.8 ml) was added the crude oil (13.5 g, 50 mmol) in dry DMF (31.6 ml)- CH_2Cl_2 (1.3 ml) over a period of 1 h. Stirring was continued for 0.5 h at $0\text{ }^\circ\text{C}$ and 2 h at room temperature. The reaction mixture was poured into cooled 1M hydrochloric acid and extracted with hexane 7 times. The combined organic layer was washed with cold 1M hydrochloric acid, saturated NaHCO_3 solution, and brine. The organic layer was dried over MgSO_4 . After filtration, saturated NaOAc in MeOH (200 ml) was added to the filtrate and the volatiles were removed with rotary evaporator. To the residue was added MeOH (200 ml) and the mixture was refluxed for 2 h. Usual workup followed by column chromatography on silica gel (hexane:AcOEt=40:1) gave (-)-**5** (8.96 g, 91%): oil; $[\alpha]_{\text{D}}^{19}$ -207.3° (c 1.0); IR (neat) $1660\text{ cm}^{-1}(\text{C}=\text{O})$; ^1H NMR δ 0.0 (s, 9 H), 0.90-1.30 (m, 1 H), 1.26 (d, $J=6\text{ Hz}$, 3 H), 1.46-1.85 (m,

2 H), 2.20-3.05 (m, 3 H), 5.85 (dd, $J=11$, 1 Hz, 1 H), 6.25 (dd, $J=11$, 4 Hz, 1 H); ^{13}C NMR δ -3.4, 18.1, 21.2, 33.6, 34.8, 43.5, 131.2, 151.4, 205.6. Anal. Calcd for $\text{C}_{11}\text{H}_{20}\text{OSi}$: C, 67.28; H, 10.27. Found: C, 67.26; H, 10.48.

(4*S*,6*S*)-3-[2-(Ethoxycarbonyl)ethyl]-4-methyl-6-trimethylsilylcycloheptanone [(-)-9**, (-)-**10**].** A mixture of Zn powder (3.14 g, 48 mmol) and 1,2-dibromoethane in THF (4 ml) was heated at 65 °C for 2 min. Chlorotrimethylsilane (0.2 ml, 1.6 mmol) was added to the mixture at rt and the mixture was stirred for 10 min. To the reaction mixture was added ethyl iodopropionate (10.7 g, 47 mmol) in dry THF (25 ml) at 30 °C, and the resulted solution was stirred at 35-40 °C for 24 h. To the cooled (-10 °C) slurry were added LiCl (83.3 g, 80 mmol) and CuCN (3.58 g, 40 mmol) in dry THF (40 ml). After being stirred for 10 min the mixture was cooled to -78 °C. After addition of a mixture of (-)-**5** (2.94 g, 15 mmol) and chlorotrimethylsilane (10.3 ml, 81.5 mmol) in dry ether (20 ml) over a period of 1 h, stirring was continued at -78 °C for 3 h. The reaction mixture was warmed to room temperature over a period of 3 h, and stirred at room temperature overnight. Usual workup and purification by column chromatography (hexane:AcOEt=8:1) afforded (-)-**9** (2.9 g, 65%) and (-)-**10** (0.98 g, 22%). (-)-**9**: mp 39-39.5 °C (pentane); $[\alpha]_{\text{D}}^{22}$ -50.1° (c 0.99); IR (neat) 1695, 1735 cm^{-1} (C=O); ^1H NMR δ 0.0 (s, 9 H), 1.03 (d, $J=6$ Hz, 3 H), 1.25 (t, $J=7$ Hz, 3 H), 1.2-2.9 (m, 13 H), 4.05 (q, $J=7$ Hz, 2 H); ^{13}C NMR δ -3.6, 14.3, 14.9, 19.1, 29.1, 32.0, 32.2, 35.5, 39.6, 42.7, 45.0, 60.2, 173.4, 214.3. Anal. Calcd For $\text{C}_{16}\text{H}_{30}\text{O}_3\text{Si}$: C, 64.38; H, 10.13. Found: C, 64.66; H, 10.33. (-)-**10**: oil; $[\alpha]_{\text{D}}^{26}$ -52.68° (c 1.1); IR (neat) 1710, 1745 cm^{-1} (C=O); ^1H NMR δ 0.0 (s, 9 H), 0.83 (d, $J=7$ Hz, 3 H), 1.25 (t, $J=7$ Hz, 3 H), 0.8-2.7 (m, 13 H), 4.08 (q, $J=7$ Hz, 2 H); ^{13}C NMR δ -3.5, 11.7, 14.3, 17.8, 30.1, 32.5, 35.5, 37.5, 38.4, 43.9, 45.2, 60.4, 173.3, 213.8. Anal. Calcd For $\text{C}_{16}\text{H}_{30}\text{O}_3\text{Si}$: C, 64.38; H, 10.13. Found: C, 64.16; H, 10.06.

(3*S*,4*S*)-3-[2-(Ethoxycarbonyl)ethyl]-4-methylcycloheptanone [(+)-11**].** To a solution of (-)-**9** (4.0 g, 13.4 mmol) in CCl_4 (10 ml) was added a 1M solution of Br_2 in CCl_4 (40 ml) at room temperature. After being stirred for 2 h, the solution was quenched with saturated aq. NaHCO_3 and solid Na_2SO_3 . After usual workup, the crude product was dissolved in EtOH (40 ml). A mixture of the solution and activated Zn powder (2.0 g, 3 mmol) was heated to 60 °C for 0.5 h and then cooled to room temperature. The reaction mixture was filtrated through a short pad of celite, and the filtrate was concentrated to 20 ml. To the solution was added 10% Pd/C (0.8 g), and stirring under H_2 (1 atm) was continued for 24 h. Usual workup and purification by column chromatography (hexane:AcOEt=85:15) gave (+)-**11** (2.12 g, 70%): oil; $[\alpha]_{\text{D}}^{26}$ +19.76° (c 2.7); IR (neat) 1705, 1730 cm^{-1} (C=O); ^1H NMR δ 1.02 (d, $J=5$ Hz, 3 H), 1.25 (t, $J=7$ Hz, 3 H), 1.2-2.0 (m, 8 H), 2.15-2.70 (m, 6 H), 4.05 (q, $J=7$ Hz, 2 H); ^{13}C NMR δ 14.3, 20.5, 29.4, 31.3, 35.0, 38.1, 41.2, 43.7, 45.5, 60.3, 173.4, 213.6. Anal. Calcd For $\text{C}_{13}\text{H}_{22}\text{O}_3$: C, 68.99; H, 9.80. Found: C, 68.99; H, 10.05.

(3*R*,4*S*)-3-[2-(Ethoxycarbonyl)ethyl]-4-methylcycloheptanone [(-)-14**].** Yield 56%; oil; $[\alpha]_{\text{D}}^{24}$ -3.55° (c 4.0); IR (neat) 1700, 1740 cm^{-1} (C=O); ^1H NMR δ 0.95 (d, $J=7$ Hz, 3 H), 1.25 (t, $J=7$ Hz, 3 H), 1.2-3.0 (m, 14 H), 4.05 (q, $J=7$ Hz, 2 H); ^{13}C NMR δ 14.3, 15.1, 21.0, 27.3, 32.2,

35.3, 37.1, 38.4, 43.8, 45.9, 60.24 173.3, 213.5. Anal. Calcd For C₁₃H₂₂O₃: C, 68.99; H, 9.80. Found: C, 69.05; H, 10.12.

(6*S*,7*R*)-6-Methylbicyclo[5.3.0]decane-2,10-dione [(+)-12]. To a cooled (0 °C) solution of *t*-BuOK (22 mmol) in THF (10 ml) was slowly added a solution of (+)-**11** (1.0 g, 4.4 mmol), and the mixture was stirred for 15 min. Usual workup and column chromatography (hexane:AcOEt=94:6) gave (+)-**12** (645 mg, 81%): oil; $[\alpha]_D^{21} +43.44^\circ$ (c 1.2); IR (neat) 1640, 1610 cm⁻¹ (C=O, C=C); ¹H NMR δ 0.95 (d, J=6 Hz, 3 H), 1.0-2.8 (m, 12 H), 14-15 (br s, 1 H); ¹³C NMR δ 20.6, 24.1, 27.7, 36.0, 37.2, 39.3, 40.4, 45.8, 113.8, 183.4, 204.9. Anal. Calcd For C₁₁H₁₆O₂: C, 73.30; H, 8.95. Found: C, 72.98; H, 9.14.

(6*S*,7*S*)-6-Methylbicyclo[5.3.0]decane-2,10-dione [(-)-15]. Yield 77%; oil; $[\alpha]_D^{15} -60.80^\circ$ (c 1.5); IR (neat) 1645, 1610 cm⁻¹ (C=O, C=C); ¹H NMR δ 0.80 (d, J=6 Hz, 3 H), 1.3-3.3 (m, 12 H), 12.5-13.5 (br s, 1 H); ¹³C NMR δ 11.8, 18.2, 24.8, 34.6, 35.6, 37.3, 38.7, 43.5, 111.1, 186.5, 199.9. Anal. Calcd For C₁₁H₁₆O₂: C, 73.30; H, 8.95. Found: C, 72.83; H, 9.23.

(6*S*,7*R*)-1,6-Dimethylbicyclo[5.3.0]decane-2,10-dione [(-)-3, (-)-13]. A mixture of (+)-**12** (111 mg, 0.62 mmol), MeI (1.2 g, 8.45 mmol), acetone (5 ml), and anhydrous K₂CO₃ (530 mg, 3.84 mmol) was heated under reflux for 5 h. Usual workup and column chromatography (hexane:AcOEt=4:1) gave (-)-**(1*R*,6*S*,7*R*)-3** (48 mg, 40%) and (-)-**(1*S*,6*S*,7*R*)-13** (49 mg, 41%). (-)-**(1*R*,6*S*,7*R*)-3**: mp 77-77.5 °C (hexane); $[\alpha]_D^{12} -65.12^\circ$ (c 0.8); IR (KBr) 1705, 1745 cm⁻¹ (C=O); ¹H NMR δ 1.05 (d, J=6.6 Hz, 3 H), 1.41 (s, 3 H), 1.2-2.9 (m, 12 H); ¹H NMR (CCl₄) δ 1.02 (d, J=6.6 Hz, 3 H), 1.29 (s, 3 H), 1.4-2.8 (m, 12 H); ¹³C NMR δ 21.5, 23.5, 23.9, 26.6, 32.1, 37.8, 38.3, 40.5, 52.8, 210.4, 218.6. Anal. Calcd For C₁₂H₁₈O₂: C, 74.19; H, 9.34. Found: C, 73.90; H, 9.65. (-)-**(1*S*,6*S*,7*R*)-13**: mp 75-76.5 °C (hexane); $[\alpha]_D^{15} -9.45^\circ$ (c 0.7); IR (neat) 1690, 1760 cm⁻¹ (C=O); ¹H NMR δ 1.05 (d, J=6 Hz, 3 H), 1.29 (s, 3 H), 1.4-2.70 (m, 12 H); ¹H NMR (CCl₄) δ 1.02 (d, J=6 Hz, 3 H), 1.15 (s, 3 H), 1.2-2.65 (m, 12 H); ¹³C NMR δ 16.0, 19.9, 22.0, 23.5, 32.9, 37.0, 37.9, 42.7, 50.0, 63.9, 209.4, 213.1. Anal. Calcd For C₁₂H₁₈O₂: C, 74.19; H, 9.34. Found: C, 74.24; H, 9.43.

(1*S*,6*S*,7*S*)-1,6-Dimethylbicyclo[5.3.0]decane-2,10-dione [(+)-16]. Yield 67%; mp 49-50 °C (pentane); $[\alpha]_D^{20} +137.6^\circ$ (c 1.1); IR (KBr), 1715, 1740 cm⁻¹ (C=O); ¹H NMR δ 1.07 (d, J=6.9 Hz, 3 H), 1.29 (s, 3 H), 1.51-1.61 (m, 3 H), 1.82-1.93 (m, 2 H), 2.01-2.18 (m, 1 H), 2.21-2.35 (m, 1 H), 2.38-2.62 (m, 3 H); ¹³C NMR δ 19.7, 20.8, 22.9, 24.7, 30.8, 33.8, 37.4, 42.5, 51.5, 66.2, 208.2, 216.6. Anal. Calcd For C₁₂H₁₈O₂: C, 74.19; H, 9.34. Found: C, 73.72; H, 10.02.

(4*S*,6*S*,7*R*)-6-Methyl-4-trimethylsilylbicyclo[5.3.0]decane-2,10-dione [(-)-17]. Yield 98%; mp 60-61.5 °C (pentane); $[\alpha]_D^{21} -44.0^\circ$ (c 1.0); IR (neat) 1620, 1660 cm⁻¹ (C=O); ¹H NMR δ 0.0 (s, 9 H), 0.93 (d, J=6 Hz, 3 H), 1.16-2.62 (m, 11 H), 13.9 (br s, 1 H); ¹³C NMR δ 0.0, 22.7, 23.4, 31.3, 37.7, 39.9, 41.0, 41.9, 46.0, 117.4, 183.6, 210.2. Anal. Calcd For C₁₄H₂₄O₂Si: C, 66.61; H, 9.58. Found: C, 66.71; H, 9.86.

(4*S*,6*S*,7*R*)-1,6-Dimethyl-4-trimethylsilylbicyclo[5.3.0]decane-2,10-dione [(-)-18, (-)-19]. (**1*S*,4*S*,6*S*,7*R*)-18**: yield 79%; mp 68-69 °C (pentane); [α]_D²¹ -122.0° (*c* 1.1); IR (KBr) 1690, 1740 cm⁻¹ (C=O); ¹H NMR δ 0.0 (s, 9 H), 0.97 (d, *J*=5 Hz, 3 H), 1.23 (s, 3 H), 1.36-2.43 (m, 10 H); ¹³C NMR δ 0.0, 21.7, 22.4, 26.7, 28.9, 34.5, 38.5, 41.2, 46.9, 54.4, 69.3, 210.9, 220.0. Anal. Calcd For C₁₅H₂₆O₂Si: C, 67.61; H, 9.84. Found: C, 67.32; H, 9.87. (**1*R*,4*S*,6*S*,7*R*)-19**: yield 16%; mp 84-85 °C (pentane); [α]_D²¹ -83.1° (*c* 1.1); IR (KBr) 1690, 1745 cm⁻¹ (C=O); ¹H NMR δ 0.0 (s, 9 H), 0.92 (d, *J*=6 Hz, 3 H), 1.10 (s, 3 H), 1.22-2.56 (m, 10 H); ¹³C NMR δ 0.0, 17.9, 19.7, 22.1, 27.3, 35.9, 37.0, 41.2, 46.0, 52.0, 68.0, 213.2, 216.7. Anal. Calcd For C₁₅H₂₆O₂Si: C, 67.61; H, 9.84. Found: C, 67.56; H, 9.92.

(4*S*,6*S*,7*S*)-6-Methyl-4-trimethylsilylbicyclo[5.3.0]decane-2,10-dione [(-)-20]. Yield 95% (crude). The crude product was used in the next alkylation. IR (KBr) 1640 cm⁻¹ (C=O); ¹H NMR δ -0.01 (s, 1 H), 0.76 (d, *J*=6.9 Hz, 3 H), 0.92-0.99 (m, 1 H), 1.50-1.67 (m, 2 H), 1.82-2.10 (m, 3 H), 2.26-2.50 (m, 4 H), 3.11-3.17 (m, 1 H); ¹³C NMR δ -3.5, 11.7, 15.9, 24.6, 35.0, 35.2, 38.5, 40.0, 43.8, 110.8, 189.5, 197.0.

(1*R*,4*S*,6*S*,7*S*)-1,6-Dimethyl-4-trimethylsilylbicyclo[5.3.0]decane-2,10-dione [(-)-21]. Yield 78%; [α]_D²⁸ -16.6° (*c* 1.5); IR (neat) 1740, 1700 cm⁻¹ (C=O); ¹H NMR δ -0.01 (s, 9 H), 0.88-0.95 (m, 1 H), 1.00 (d, *J*=6.6 Hz, 3 H), 1.28 (s, 3 H), 1.47-1.55 (m, 2 H), 1.86-1.99 (m, 1 H), 2.03-2.10 (m, 3 H), 2.27-2.36 (m, 2 H), 2.49-2.54 (m, 2 H); ¹³C NMR δ -3.7, 18.0, 19.6, 21.3, 21.9, 31.0, 31.6, 36.4, 39.6, 50.8, 64.7, 210.9, 217.4.

Transformation of (-)-18 into (-)-3 by Desilylation. A solution of (-)-18 (405 mg, 1.52 mmol) and Br₂ (3.5 ml) in CCl₄ (18.5 ml) was left at room temperature overnight. The solution was poured into saturated NaHCO₃ and Na₂SO₃ solution and extracted with CH₂Cl₂. After removal of the solvent, the residue was dissolved into glacial acetic acid (12 ml). To the solution was added zinc powder (400 mg) and the mixture was stirred at room temperature for 20 min. The mixture was slowly poured into cooled saturated NaHCO₃ solution. Filtration through a short pad of celite, extraction of the filtrate with ether, and removal of the solvent gave a crude product. To a solution of the crude product in EtOH (20 ml) was added 10% Pd/C and the mixture was stirred for 1 h under H₂ (1 atm). To the reaction mixture were added saturated NaHCO₃ solution and ether. Filtration, extraction with ether, concentration, and purification by column chromatography (hexane:AcOEt=10:1) gave (-)-3 (275 mg, 93%).

(1*S*,6*S*,7*R*,10*S*)-10-*t*-Butyldimethylsiloxy-1,6-dimethylbicyclo[5.3.0]decane-2-one [(+)-23]. To a cooled (-78 °C) solution of (-)-3 (194 mg, 1.0 mmol) in THF (10 ml) was added 1 M DIBAH (2.5 ml), and the solution was stirred 10 min. After addition of aq. NH₄Cl, the mixture was warmed to room temperature, filtrated through a short pad of celite, and extracted with ether. Usual workup and purification by column chromatography (hexane:AcOEt=4:1) gave (**1*R*,6*S*,7*R*,10*S*)-2,10-Dihydroxy-1,6-dimethylbicyclo[5.3.0]decane** (159 mg, 80%): mp 73-74 °C (hexane); [α]_D¹⁶ +22.8° (*c* 1.1); IR (KBr) 3100-3650 cm⁻¹ (OH); ¹H NMR δ 0.88 (d, *J*=6.6 Hz, 3 H), 0.94 (s, 3 H), 1.15 (dt, *J*=5.6,12.5 Hz, 1 H),

1.23-1.37 (m, 1 H), 1.40-1.83 (m, 9 H), 1.87-1.96 (m, 1 H), 2.66 (br s, 1 H), 2.95 (br s, 1 H), 3.80 (d, $J=5.9$ Hz, 1 H), 4.32 (dd, $J=5.9, 11.2$ Hz, 1 H); ^{13}C NMR δ 22.7, 23.4, 24.3, 28.5, 31.1, 31.7, 36.7, 38.1, 48.5, 56.8, 75.8, 76.2. To a cooled (0 °C) solution of the above diol (251 mg, 1.26 mmol) in DMF (12.6 ml) were added imidazole (95 mg, 1.39 mmol) and chloro-*t*-butyldimethylsilane (190 mg, 1.26 mmol), and the mixture was stirred at 0 °C for 22 h. Usual workup and purification by column chromatography (hexane:AcOEt=30:1) gave **(1*R*,6*S*,7*R*,10*S*)-10-*t*-Butyldimethylsiloxy-2-hydroxy-1,6-dimethylbicyclo[5.3.0]decane** (378 mg, 96%): oil; IR (neat) 3650, 3250-3600 cm^{-1} (OH); ^1H NMR δ 0.05 (s, 6 H), 0.86 (d, $J=6.6$ Hz, 3 H), 0.87 (s, 3H), 0.88 (s, 9 H), 0.98-1.11 (m, 1 H), 1.21-1.84 (m, 12 H), 3.71 (q, $J=5.0$ Hz, 1 H), 4.41 (dd, $J=10.5, 5.9$ Hz, 1 H); ^{13}C NMR δ -5.0, -4.2, 18.0, 23.4, 23.9, 24.7, 25.9, 29.0, 30.4, 32.5, 36.7, 39.0, 49.3, 56.9, 75.7, 76.2. To a solution of the above TBDMS ether (306 mg, 0.98 mmol) in CH_2Cl_2 (27 ml) was added PDC (2.0 g, 5.3 mmol), and the mixture was stirred at room temperature for 3 h. Usual workup and purification by preparative TLC (hexane:ether=3:1) gave **(+)-23** (304 mg, quant): mp 50-51 °C (pentane); $[\alpha]_{\text{D}}^{20} +76.4^\circ$ (c 0.4); IR (neat), 1690 cm^{-1} (C=O); ^1H NMR δ 0.0 (s, 3 H), 0.04 (s, 3 H), 0.84 (s, 9 H), 0.87 (d, $J=6.6$ Hz, 3 H), 0.92-1.23 (m, 2 H), 1.25 (s, 3 H), 1.38-1.57 (m, 4 H), 1.61-1.68 (m, 1 H), 1.73-1.89 (m, 3 H), 2.28 (ddd, $J=4.3, 5.0, 11.2$ Hz, 1 H), 2.83 (dt, $J=5.3, 11.2$ Hz, 1 H), 2.83 (dt, $J=5.3, 11.2$ Hz, 1 H), 4.70 (dd, $J=6.3, 10.6$ Hz, 1 H); ^{13}C NMR δ -4.9, -4.7, 18.0, 22.2, 22.8, 25.8, 25.9, 27.7, 32.8, 36.4, 39.0, 39.3, 55.7, 59.3, 74.3, 214.6. Anal. Calcd For $\text{C}_{18}\text{H}_{34}\text{O}_2\text{Si}$: C, 69.62; H, 11.04. Found: C, 69.20; H, 10.96.

(1*S*,3*S*,6*S*,7*R*,10*S*)-10-*t*-Butyldimethylsiloxy-3-[2-(ethoxycarbonyl)methyl]-1,6-dimethylbicyclo[5.3.0]decane-2-one [(-)-24]. To a cooled (-78 °C) solution of LDA (1.62 mmol) in THF (10 ml) was added (+)-23 (315 mg, 1.2 mmol) in THF (10 ml), and stirred for 1 h. After addition of a mixture of ethyl iodoacetate (181 ml, 1.56 mmol) and HMPA (315 mg, 1.0 mmol) in THF (10 ml) over a period of 40 min, the reaction mixture was left to warm to room temperature. Usual workup and purification by column chromatography gave (-)-24 (316 mg, 79%): oil; $[\alpha]_{\text{D}}^{16} -35.5^\circ$ (c 1.1); IR (neat) 1695, 1740 cm^{-1} (C=O); ^1H NMR δ -0.04 (s, 3 H), 0.02 (s, 3 H), 0.88 (s, 9 H), 0.91 (d, $J=6.9$ Hz, 3 H), 1.07 (s, 3 H), 1.24 (t, $J=7.1$ Hz, 3 H), 1.28-2.06 (m, 10 H), 2.35 (dd, $J=6.9, 16.8$, 1 H), 2.73 (dd, $J=6.9, 16.8$ Hz, 1 H), 3.19 (ddt, $J=4.3, 6.9, 11.2$ Hz, 1 H), 4.10 (q, $J=7.3$ Hz, 2 H), 4.45 (dd, $J=6.3, 9.6$ Hz, 1 H); ^{13}C NMR δ -5.0, -4.6, 14.2, 18.0, 20.4, 21.1, 25.7, 28.6, 29.0, 30.5, 34.5, 35.6, 36.7, 44.0, 54.5, 59.7, 60.3, 77.2, 172.6, 214.4.

(1*S*,3*S*,6*S*,7*R*,10*S*)-3-[2-(Ethoxycarbonyl)ethyl]-10-hydroxy-1,6-dimethylbicyclo[5.3.0]decane-2-one [(-)-25]. A solution of (-)-24 (981 mg, 2.48 mmol) in AcOH-H₂O-THF (3:1:1) was heated at 110 °C for 4 h. After cooling to room temperature, the volatiles were removed under reduced pressure. Purification of the residue by column chromatography (hexane:AcOEt=25:1) gave unreacted (-)-24 (163 mg, 17%) and (-)-25 (545 mg, 78%). (-)-25: oil; $[\alpha]_{\text{D}}^{22} -53.7^\circ$ (c 1.1); IR (neat) 3550 (OH), 1740 and 1700 (C=O) cm^{-1} ; ^1H NMR δ 0.91 (d, $J=6.3$ Hz, 3 H), 1.09 (s, 3 H), 1.23 (t, $J=7.3$ Hz, 3 H), 1.09-1.85 (m, 9 H), 1.93-2.12 (m, 1 H), 2.06 (d, $J=9.2$ Hz, 1 H), 2.34 (dd, $J=3.1, 17.6$ Hz, 1 H), 3.07 (dd, $J=11.4, 17.6$ Hz, 1 H), 3.39 (m, 1 H), 4.08 (q, $J=7.3$ Hz, 2 H), 4.79 (dd, $J=6.6, 11.2$ Hz, 1 H); ^{13}C NMR δ 14.1, 18.9, 21.5, 27.7, 28.7, 30.6, 31.4, 36.9, 37.1, 40.8, 55.6, 61.0, 61.4, 77.9, 173.7, 216.2.

(3aS,6S, 6aR,9S,9aS,9bR)-9-Hydroxy-6,9a-dimethyl-3,3a,4,5,6,6a,7,8,9,9a,9b-decahydroazureno[4,5-b]furan-2-one [(+)-27]. To a cooled (-78 °C) solution of (-)-25 (149 mg, 0.53 mmol) in THF (14 ml) was added 0.93 M solution of DIBAH in hexane (2.9 ml, 2.7 mmol) and the solution was stirred at that temperature for 1 h. After addition of 2 M HCl, the mixture was warmed to room temperature and extracted with CH₂Cl₂ (8x30 ml). Removal of the solvent gave an oil which was used for the next step without further purification. Under oxygen atmosphere, to a mixture of platinum black prepared from PtO₂ (149 mg, 0.53 mmol)¹³ and H₂O (25 ml) was added a H₂O (12 ml)-acetone (5 ml) solution of the above oil. The mixture was heated to reflux and stirred at that temperature for 1 h. After cooling to room temperature, the mixture was filtered through celite and the filtrate was extracted with CH₂Cl₂. Removal of the solvent and purification of the residue by column chromatography (hexane:AcOEt=5:3) gave (+)-27 (103 mg, 82 %): mp 106-107 °C (hexane-ether); [α]_D²² +52.0° (c 0.7); IR (KBr) 3510 (OH), 1780 (C=O) cm⁻¹; ¹H NMR δ 0.84 (d, J=5.9 Hz, 3 H), 1.09 (s, 3 H), 1.13-1.37 (m, 2 H), 1.45-2.00 (m, 9 H), 2.29 (dd, J=11.9, 17.8 Hz, 1 H), 2.62 (dd, J=9.9, 17.8 Hz, 1 H), 2.80 (m, 1 H), 4.02 (dd, J=5.6, 11.2 Hz, 1 H), 4.81 (d, J=8.9 Hz, 1 H); ¹³C NMR δ 17.6, 21.0, 27.1, 27.3, 29.8, 33.8, 35.2, 35.4, 37.4, 47.4, 51.6, 83.0, 90.4, 176.4. Anal. Calcd For C₁₄H₂₂O₃: C, 70.56; H, 9.31. Found: C, 70.53; H, 9.36.

(3aS,6S,6aR,9aR,9bR)-6,9a-Dimethyl-3,3a,4,5,6,6a,7,8,9a,9b-decahydroazureno[4,5-b]furan-2,9-dione [(+)-2]. To a stirred solution of (+)-27 (214 mg, 0.9 mmol) in acetone (20 ml) was slowly added the Jones reagent until (+)-27 was consumed. After addition of 2-propanol, the mixture was poured into a 2 M HCl solution. Extraction with CH₂Cl₂, removal of the solvent, and purification of the residue by column chromatography (hexane:AcOEt=2:1) gave (+)-2 (193 mg, 91%): mp 103-105 °C (hexane-ether); [α]_D²³ +47.4° (c 1.1); IR (KBr) 1780, 1740 cm⁻¹ (C=O); ¹H NMR δ 1.05 (d, J=6.3 Hz, 3 H), 1.35 (s, 3 H), 1.30-1.88 (m, 6 H), 1.94 (m, 1 H), 2.12 (m, 1 H), 2.22 (dd, J=4.1, 17.5 Hz, 1 H), 2.39 (m, 2 H), 2.82 (dd, J=9.4, 17.5 Hz, 1 H), 2.90 (m, 1 H), 4.76 (d, J=6.9 Hz, 1 H); ¹³C NMR δ 22.5, 23.6, 25.3, 29.8, 30.4, 34.1, 36.3, 36.9, 38.4, 50.6, 55.6, 85.2, 176.7, 217.8. Anal. Calcd For C₁₄H₂₀O₃: C, 71.16; H, 8.53. Found: C, 70.96; H, 8.28.

(3aS,6S,6aS,9aR,9bR)-6,9a-Dimethyl-3,3a,4,5,6,6a,9a,9b-octahydroazureno[4,5-b]furan-2,9-dione [(+)-28]. A mixture of (+)-2 (175 mg, 0.74 mmol), Et₃N (0.19 ml, 1.3 mmol), and trimethylsilyl triflate (0.22 ml, 1.1 mmol) in toluene (6.6 ml) was stirred at room temperature for 4.5 h. After dilution with CH₂Cl₂, the mixture was washed with saturated NaHCO₃ solution and dried over Na₂SO₄. Filtration and evaporation gave a crude enol silyl ether. A mixture of the enol silyl ether and Pd(OAc)₂ (166 mg, 0.74 mmol) in CH₃CN (4.5 ml) was stirred at room temperature for 1 h. Filtration through a short pad of silica gel followed by purification by column chromatography (hexane: AcOEt=1:1) gave (+)-28 (126 mg, 72%): mp 156-157.5 °C (hexane-ether); [α]_D²² +54.4° (c 0.7); IR (KBr) 1780, 1700 cm⁻¹ (C=O); ¹H NMR δ 1.08 (d, J=6.3 Hz, 3 H), 1.26 (s, 3 H), 1.35-1.95 (m, 5 H), 2.29 (dd, J=10.8, 17.5 Hz, 1 H), 2.56 (ddd, J=1.7, 3.0, 9.9 Hz, 1 H), 2.69 (dd, J=9.9, 17.5 Hz, 1 H), 2.83 (m, 1 H), 4.77 (d, J=8.6 Hz, 1 H), 6.15 (dd, J=1.7, 5.9 Hz, 1 H), 7.68 (dd, J=3.0, 5.9 Hz, 1 H); ¹³C NMR δ 20.6, 21.2, 27.4, 34.1, 35.0, 35.6,

37.5, 51.7, 56.4, 81.2, 130.5, 164.7, 176.1, 210.2. Anal. Calcd For C₁₄H₁₈O₃: C, 71.77; H, 7.74. Found: C, 71.14; H, 7.57.

(3aS,6S,6aR,9aR,9bR)-6,9a-Dimethyl-7-phenylseleno-3,3a,4,5,6,6a,7,8,9a,9b-decahydroazureno[4,5-b]furan-2,9-dione 9-Ethylen Acetal [(-)-29]. A mixture of diphenyldiselenide (241 mg, 1.03 mmol) and NaBH₄ (83 mg, 2.19 mmol) in EtOH (4 ml) was stirred at room temperature under Ar until a clear solution was obtained. To the cooled (0 °C) solution were added glacial acetic acid (0.22 ml, 3.84 mmol) and (+)-**28** (241 mg, 1.03 mmol) in degassed CH₂Cl₂ (8.5 ml). After being stirred at 0 °C for 1.5 h, the solution was poured into a saturated NaHCO₃ solution. Extraction with CH₂Cl₂ and concentration of the organic layer gave a crude selenol adduct which was used without further purification. A mixture of the crude adduct, 1,2-bis(trimethylsiloxy)ethane (0.76 ml, 3.09 mmol), and trimethylsilyl triflate (0.11 ml, 0.58 mmol) in dry CH₂Cl₂ was stirred at 0 °C overnight. After addition of Et₃N (0.34 ml), the mixture was poured into a saturated NaHCO₃ solution and extracted with CH₂Cl₂. Removal of the solvent and purification by column chromatography (hexane:AcOEt=3:1) gave (-)-**29** (335 mg, 75%); IR (KBr) 1770 cm⁻¹ (C=O); ¹H NMR δ 1.02 (s, 3 H), 1.14 (d, J=5.6 Hz, 3 H), 1.25-1.45 (m, 1 H), 1.60-1.90 (m, 5 H), 1.90 and 1.94 (2d, J=13.2 Hz, 1 H), 2.00 and 2.14 (2d, J=13.2 Hz, 1 H), 2.24 and 2.28 (2d, J=17.8 Hz, 1 H), 2.51 and 2.55 (2d, J=17.8 Hz, 1 H), 2.78 (m, 1 H), 3.32 (m, 1 H), 3.74-4.08 (m, 4 H), 5.25 (d, J=9.6 Hz, 1 H), 7.24-7.65 (m, 5 H); ¹³C NMR δ 20.1, 20.6, 26.6, 31.7, 35.5, 36.1, 37.6, 38.3, 42.1, 51.2, 55.3, 64.8, 65.3, 77.2, 81.1, 117.8, 128.2, 128.5, 129.0, 136.2, 176.9.

(3aS,6S,9aR,9bR)-6,9a-Dimethyl-3,3a,4,5,6,8,9a,9b-octahydroazureno[4,5-b]furan-2,9-dione 9-Ethylen Acetal [(-)-30] and (3aS,6S,6aS,9aR,9bR)-6,9a-Dimethyl-3,3a,4,5,6,6a,9a,9b-octahydroazureno[4,5-b]furan-2,9-dione 9-Ethylen Acetal [31]. To a cooled (-10 °C) solution of (-)-**29** (64 mg, 0.15 mmol) in MeOH (7 ml) was slowly added a solution of NaO₄ (500mg, 2.35 mmol) in H₂O (3 ml). The mixture was stirred at -10 °C for 3 h and at room temperature for 0.5 h. After addition of saturated Na₂SO₃ and NaHCO₃ solutions, the mixture was extracted with CH₂Cl₂. Removal of the solvent and purification by tlc (hexane:ether=1:2) gave a 4 to 6 mixture of (-)-**30** and **31** (42 mg, 100%). (-)-**30**: [α]_D²⁹ -26.4° (c 0.56); IR (KBr) 1780 cm⁻¹ (C=O); ¹H NMR δ 1.18 (d, J=7.3 Hz, 3 H), 1.28 (s, 3 H), 1.58-1.90 (m, 4 H), 2.36 (dd, J=7.6, 17.5 Hz, 1 H), 2.43-2.50 (m, 2 H), 2.64 (dd, J=9.2, 17.5 Hz, 1 H), 2.70-2.98 (m, 2 H), 3.90-4.10 (m, 4 H), 4.68 (d, J=7.6 Hz, 1 H), 5.53 (t, J=2.3 Hz, 1 H); ¹³C NMR δ 17.6, 22.9, 26.1, 28.5, 36.2, 37.2, 39.2, 40.1, 56.8, 64.9, 64.9, 82.8, 120.0, 125.0, 149.9, 177.4.

Neoambrosin (1a). A mixture of (-)-**30** (20 mg, 0.07 mmol) and a 2M solution of MMC (methyl methoxymagnesium carbonate) in DMF (4 ml) was heated at 140 °C for 3 h. To the cooled (-10 °C) solution was added 5% HCl. Extraction with CH₂Cl₂ and concentration of the organic layer gave a crude carboxylic acid. A mixture of the crude acid, NaOAc (51 mg), diethylamine (0.5 ml), formalin (1.5 ml), and acetic acid (2 ml) was stirred at 110 °C for 15 min. After being cooled to 0 °C, the mixture was diluted with CH₂Cl₂ and washed with water, 5% HCl, and saturated NaHCO₃ solution. The organic layer was concentrated and the residue was dissolved into MeOH (2.0 ml)-3M HCl (1.3 ml). After 1.5 h at 15 °C, the solution was poured

into a cold saturated NaHCO₃ solution. Extraction with CH₂Cl₂, concentration of the organic layer, and purification by tlc (ether:hexane=1.5:1) gave **1a** (10 mg, overall 56%): [α]_D²⁵ -68.7° (c 0.4) [lit.^{2a}] [α]_D -66° (c 2)]; IR (KBr) 1750 cm⁻¹ (C=O); ¹H NMR δ 1.17 (d, J=7.3 Hz, 3 H), 1.20 (s, 3 H), 1.60-2.20 (m, 4 H), 2.82 (dd, J=2.3, 23.0 Hz, 1 H), 2.90 (m, 1 H), 3.13 (dd, J=2.3, 23.0 Hz, 1 H), 3.35 (m, 1H), 4.42 (d, J=8.9 Hz, 1 H), 5.52 (d, J=3.3 Hz, 1 H), 5.96 (t, J=2.3 Hz, 1 H), 6.27 (d, J=3.3 Hz, 1 H); ¹³C NMR δ 15.1, 21.2, 24.0, 30.1, 38.8, 39.9, 43.5, 58.5, 79.8, 119.9, 124.3, 138.8, 149.3, 169.8, 213.8.

(3aS,6S,6aR,7S,9aR,9bR)-6a,7-Epoxy-6,9a-dimethyl-3,3a,4,5,6,6a,7,8,9a,9b-decahydroazureno[4,5-b]furan-2,9-dione 9-Ethylen Acetal [(-)-32]. To a solution of a mixture of (-)-**30** and **31** (4 to 6 mixture, 51 mg) in CH₂Cl₂ was added *m*-CPBA (40 mg, 0.23 mmol) and the mixture was stirred at room temperature for 2 h. The mixture was diluted with CH₂Cl₂, and the solution was washed with cold saturated NaHCO₃ and Na₂SO₃ solutions. Removal of the solvent and purification by column chromatography (hexane:AcOEt=4:1) gave recovered **31** (36 mg, quant) and (-)-**32** (23 mg, quant): mp 196-197.5 °C (hexane-ether); [α]_D²⁰ -52.6° (c 1.6); IR (KBr) 1780 cm⁻¹ (C=O); ¹H NMR δ 1.22 (d, J=7.6 Hz, 3 H), 1.23 (s, 3 H), 1.60-2.07 (m, 5 H), 2.16 (s, 2 H), 2.36 (dd, J=12.4, 17.8 Hz, 1 H), 2.63 (dd, J=9.6, 17.8 Hz, 1 H), 3.03 (m, 1 H), 3.23 (s, 1 H), 3.75-4.17 (m, 4 H), 5.13 (d, J=9.6 Hz, 1 H); ¹³C NMR δ 14.4, 18.4, 24.5, 28.5, 36.1, 38.5, 38.9, 38.9, 54.8, 58.6, 64.5, 65.6, 69.5, 81.4, 116.1, 176.9.

Parthenin (1b). A mixture of (-)-**32** (64 mg, 0.22 mmol) and a 2 M solution of MMC in DMF (4 ml) was heated at 140 °C for 3 h. To the cooled (-10 °C) solution was added 5% HCl. Extraction with CH₂Cl₂ and concentration of the organic layer gave crude a carboxylic acid. A mixture of the crude acid, NaOAc (51 mg), diethylamine (0.5 ml), formalin (1.5 ml), and acetic acid (2 ml) was stirred at 110 °C for 15 min. After being cooled to 0 °C, the mixture was diluted with CH₂Cl₂ and washed with water, 5% HCl, and saturated NaHCO₃ solution. The organic layer was concentrated and the residue was dissolved into MeOH (4.5 ml)-conc. HCl (1.5 ml). After 12 h, the solution was poured into cold saturated NaHCO₃ solution. Extraction with CH₂Cl₂, concentration of the organic layer, and purification by tlc (ether) gave **1b** (38 mg, overall 67%): mp 165-166.5 °C (hexane-AcOEt); [α]_D²⁴ -7.1° (c 0.4) [lit.^{3a}] [α]_D²⁵ +7.02° (c 2.71)]; IR (KBr) 3400 (OH), 1730, 1710 (C=O) cm⁻¹; ¹H NMR δ 1.13 (d, J=7.6 Hz, 3 H), 1.29 (s, 3 H), 1.62-2.42 (m, 6 H), 3.51 (m, 1 H), 5.01 (d, J=7.9 Hz, 1 H), 5.60 (d, J=2.6 Hz, 1 H), 6.20 (d, J=5.7 Hz, 1 H), 6.29 (d, J=2.6 Hz, 1 H), 7.52 (d, J=5.7 Hz, 1 H); ¹³C NMR δ 17.4, 18.4, 28.4, 29.8, 40.5, 44.2, 59.1, 78.9, 84.3, 121.9, 131.6, 140.4, 163.4, 171.0, 210.9.

Dihydroisoparthenin (1c): A mixture of **1b** (13 mg, 0.05 mmol) and Pd/C in ethanol (2 ml) was stirred under H₂ (1 atm) for 1.5 h. Filtration through a short pad of celite, concentration of the filtrate, and purification by tlc (ether) gave **1c** (9 mg, 70%): mp 192.5-193.0 °C (hexane-AcOEt); [α]_D²⁴ +15.8° (c 0.1) [lit.^{3a}] [α]_D²⁵ +16.6° (c 0.783)]; IR (KBr) 3330 (OH), 1740, 1720 (C=O) cm⁻¹; ¹H NMR δ 0.85 (s, 3 H), 1.11 (d, J=7.6 Hz, 3 H), 1.27-1.45 (m, 1 H), 1.75-1.90 (m, 1 H), 1.83 (s, 3 H), 2.05-2.87 (m, 7 H), 5.40 (s, 1 H); ¹³C NMR δ 8.4, 11.1, 18.2, 23.3, 30.2, 32.7, 33.3, 43.3, 57.5, 81.7, 84.1, 123.5, 162.7, 175.3, 215.5. CD (c 3.4x10⁻³, dioxane, 25° C) [θ]₃₃₅ 0, [θ]₃₁₀ +1911, [θ]₂₈₂ 0, [θ]₂₆₉ -332, [θ]₂₆₄ 0.

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