Total Synthesis of (−)-Dendrobine via α-Carbonyl Radical Cyclization

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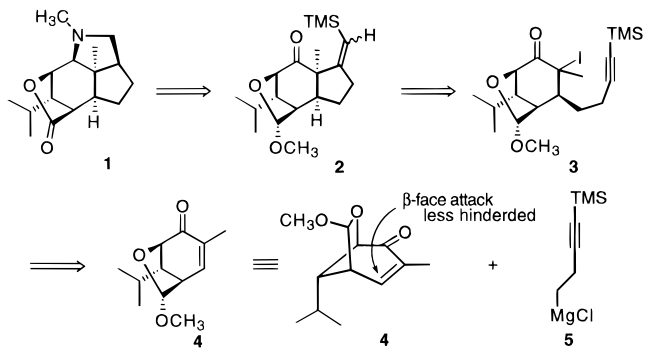
Abstract: An efficient total synthesis of enantiomerically pure (−)-dendrobine (**1**) is accomplished based on an α-carbonyl radical cyclization reaction. (*S*)-carvotanacetone (**6**) was converted to bicyclic acetal-enone **4** in five steps. CuI-mediated conjugate addition of 4-(trimethylsilyl)-3-butynylmagnesium chloride to **4** followed by treatment with TMSCl afforded trimethylsilyl enol ether **10**. Iodination of **10** with NaI and *m*-CPBA gave iodoketone **3**. Intramolecular radical cyclization of **3**, effected with Bu_3SnH and AIBN, furnished tricyclic ketone **2**. Removal of the TMS group of **2** and oxidation of the resulting cyclic acetal **12** with *m*-CPBA and BF_3 etherate gave peroxy compound **13**. Compound **13** was treated with DBU to yield lactone **14**. Hydroboration of **14** with basic H_2O_2 oxidation gave diol **17**. Conversion of **17** to the corresponding azido alcohol **19** followed by Jones oxidation furnished azido ketone **20**. Treatment of **20** with PPh_3 followed by reduction with $NaBH_3CN$ afforded amine **21**. Crude amine **21** was methylated to give enantiomerically pure (−)-dendrobine (**1**).

(−)-Dendrobine (**1**) is the major alkaloid isolated from an ornamental orchid "Jinchai Shihu" (Dendrodium *nobile Lindl*) that is used in traditional Chinese herbal medicine as a tonic.[1] Due to its interesting physiological activity and intricate molecular structure, dendrobine is a challenging target for total synthesis. Several successful total syntheses[2] and formal syntheses[3] of dendrobine have been reported. Among these, only two formal syntheses[3c−f] were asymmetric syntheses. In our previous report, we described an α-carbonyl radical cyclization reaction for synthesis of fused-bicyclic ketones with a *cis*-ring juncture.[4] Herein, we report an application of this method to asymmetric total synthesis of enantiomerically pure (−)-dendrobine (**1**). The retro-synthetic analysis is outlined in Scheme 1. The *cis*-ring juncture of (−)-dendrobine (**1**) might be established by an α-carbonyl radical cyclization (**3** → **2**). Iodoketone **3** would be generated from **4** according to our method.[4] Conjugate addition of Grignard reagent **5** to the less hindered *β*-face of bicyclic acetal-enone **4** might give the desired stereochemistry in **3**. Chiral bicyclic acetal-enone **4** would be prepared from (*S*)-carvotanacetone (**6**).[5]

Scheme 1



Thus our synthesis started from the chiral starting material **6**. According to the method of Takazawa,[6] compound **6** was treated sequentially with methylmagnesium chloride, ferric chloride, and chlorotrimethylsilane and then a mixture of trimethyl orthoformate and boron trifluoride etherate to give acetal **7** (55%), Scheme 2. Reaction of **7** with lithium diisopropylamide (LDA) and chlorotrimethylsilane generated the corresponding trimethylsilyl enol ether, which without purification was reacted with *m*-chloroperoxybenzoic acid (*m*-CPBA) to give siloxyenone **8** (71%).[7] Compound **8** was then treated with *p*-toluenesulfonic acid (PTSA) to effect cyclization to afford bicyclic acetal-enones **4** (79%) and **9** (14%). The latter was isolated and converted to **4** on treatment with PTSA in refluxing dichloromethane (55% yield with 25% **9** recovered). Cuprous iodide-mediated conjugate addition of Grignard reagent **5** to **4** followed by trapping the resulting enolate with chlorotrimethylsilane yielded **10** with desired stereochemistry which was confirmed in the next step of the synthesis, Scheme 3. At this point, the addition of Grignard reagent **5** to the enone moiety of **4** was expected to proceed from the less hindered *β*-face of

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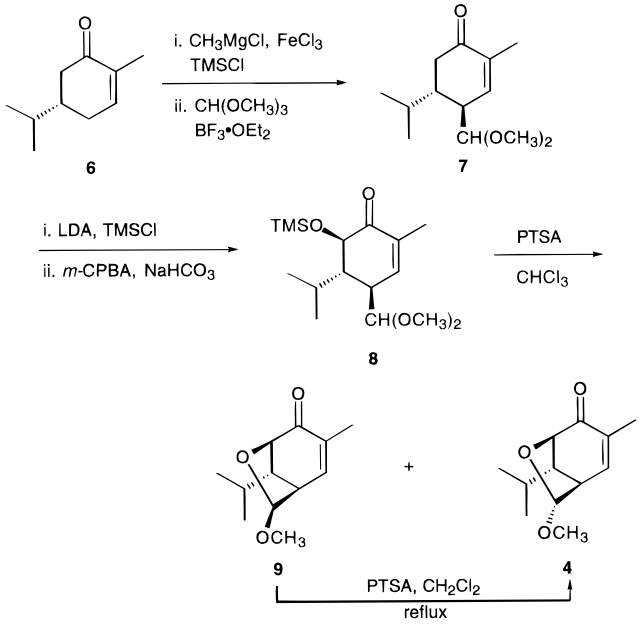
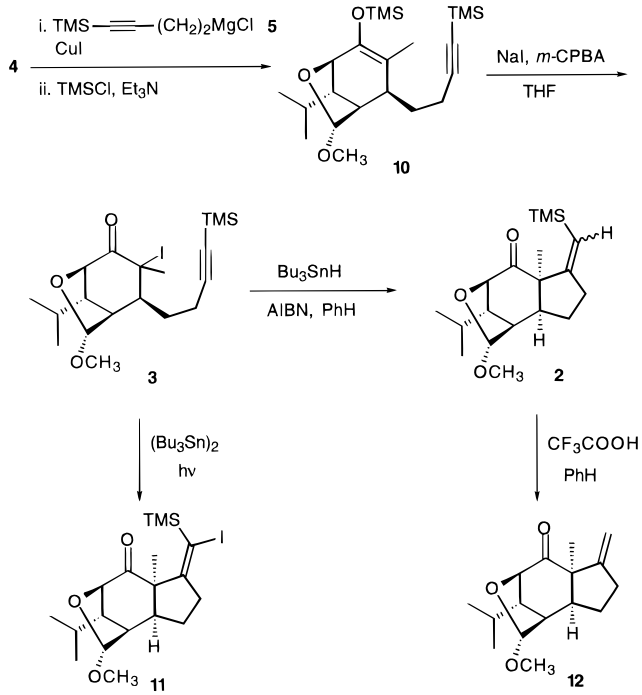
S0002-7863(96)04343-0 CCC: $14.00

Scheme 2



Scheme 3



4, as the bulky isopropyl group was locked at the axial position in the bicyclic structure of **4** and shielded the α face. Reaction of crude **10** with an iodination reagent, generated by mixing sodium iodide and *m*-CPBA in THF,[8] gave iodoketone **3** (82% from **4**). Compound **3** was then treated with tributyltin hydride and AIBN by slow addition to effect radical cyclization. The tricyclic ketone **2** (*E*:*Z*, 1:9) was obtained as a viscous liquid in 69% yield with a minor amount (25%) of the uncyclized reduction product.

In order to determine the stereochemistry of **2**, iodoketone **3** was also cyclized with atom transfer cyclization method[9] to produce a crystalline product **11**. The stereochemistry of **11** was determined by single-crystal X-ray analysis, Figure 1. Compounds **2** and **11** presumably were formed via similar radical cyclization mechanisms.[9] Hence, the stereochemistry

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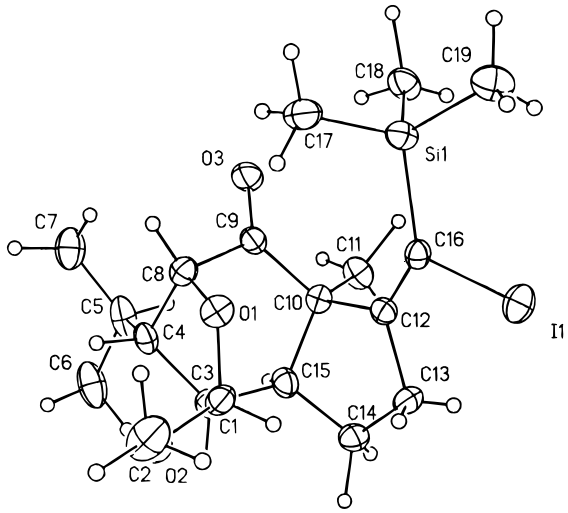

Figure 1. Molecular drawing of compound **11** generated by SHELXTL PLUS.

of **2** is believed to be the same as that of **11**. The trimethylsilyl group was then removed from **2** by treatment with trifluoroacetic acid to give **12** (84%).

In order to convert the cyclic acetal group in **12** to a lactone, compound **12** was oxidized with *m*-CPBA in the presence of boron trifluoride etherate according to Grieco's method,[10] Scheme 4. However a labile peroxy compound **13** was obtained instead of the desired lactone **14**. The expected spontaneous elimination of carboxylic acid from **13** occurred very slowly at room temperature. Apparently intramolecular abstraction of the peroxy-acetal proton by the carbonyl oxygen in **13**, through a six-membered transition state,[10] is difficult due to the steric hinderance. Thus, peroxy compound **13** was treated with a base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), to effect elimination and produced lactone **14** (62% from **12**). Stereoselective hydroboration of **14** with borane dimethyl sulfide complex followed by basic hydrogen peroxide oxidation afforded diol **17**. It is noteworthy that hydroboration occurred from the less hindered α-face to give **15** that was followed by internal delivery of hydride[11] from the β-face *via* intermediate **16** to afford diol **17** after oxidation by basic hydrogen peroxide. Diol **17** was then treated with methanesulfonyl chloride and triethylamine to give mesylate **18**. Crude product **18** was further reacted with sodium azide and 18-crown-6 in DMF to afford azido alcohol **19** (80% from **17**). Compound **19** was oxidized by Jones reagent[12] to afford azido ketone **20** (94%). Treatment of **20** with triphenylphosphine followed by reduction of the imine moiety with sodium cyanoborohydride from the less hindered α-face afforded amine **21**. The crude amine **21** was immediately methylated with paraformaldehyde and formic acid to give enantiomerically pure (−)-dendrobine (**1**) (42% from **20**). ^{1}H NMR, ^{13}C NMR, and MS spectra of **1** were identical to the spectra provided by Professor Livinghouse.[2g] The optical rotation[13] of **1** is in satisfactory agreement with those reported.[14]

In summary, we have demonstrated that the combination of conjugate addition and α-carbonyl radical cyclization is a

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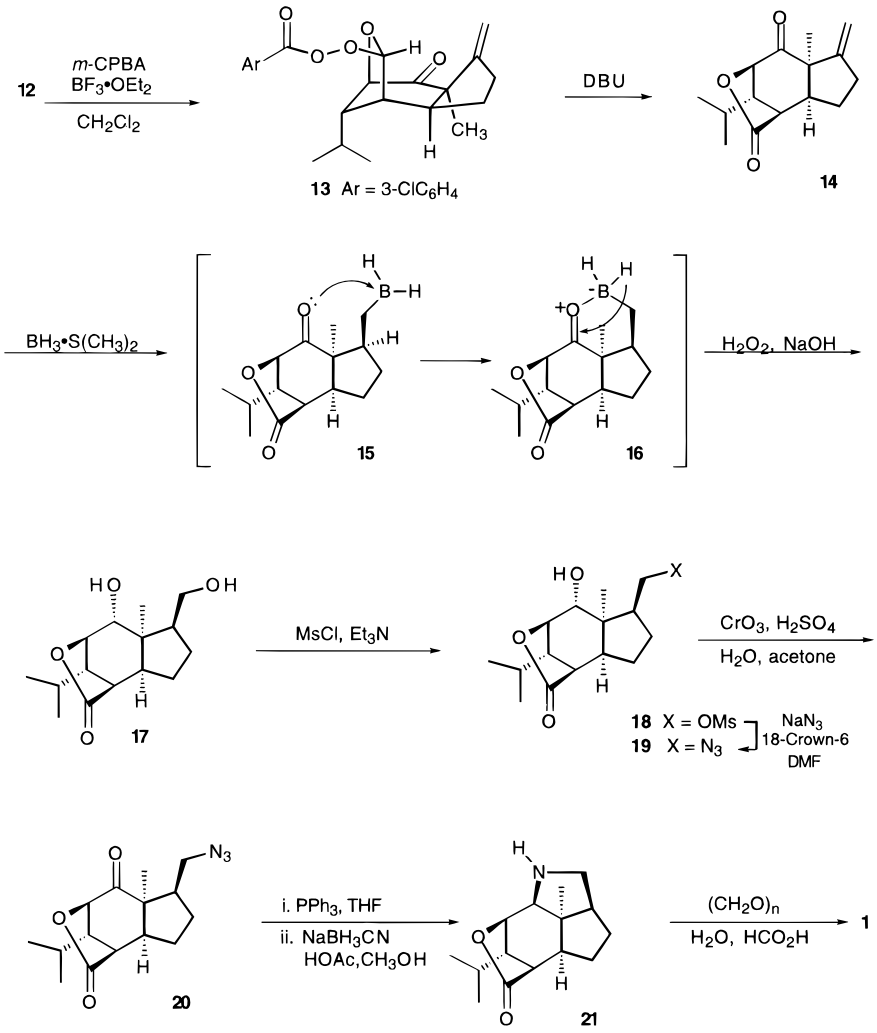
(14) An authentic sample was not available for comparison.

Scheme 4



straightforward and highly efficient method for synthesis of a complex natural product. Total synthesis of enantiomerically pure (−)-dendrobine (**1**) from (*S*)-carvotanacetone (**6**) has been accomplished. In this synthesis six stereogenic centers were induced, each in a stereoselective manner, from a single chiral center of the starting material. Stereoselective hydroboration (**14** to **17**) is highly efficient, in which an internal hydride delivery mechanism was proposed. The formation of peroxy compound **13** from the oxidation of the cyclic acetal moiety of **12** was unexpected. However this provides proof for the oxidation mechanism proposed by Grieco.[10] Applications of this sequence of conjugate addition and α-carbonyl radical cyclization to total syntheses of other natural products are currently under investigation in our laboratories.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR were recorded on a Varian Gemini-300, Varian Unity-400, or a Bruker AM-400 spectrometer. Mass spectra were recorded on a JEOL SX-102A or HX-110 mass spectrometer. IR spectra were recorded on a Bomem MB-100 FT spectrometer. Melting points were determined with a Büchi 530 melting-point apparatus and were uncorrected. Optical rotations were measured on a JASCO DIP-360 polarimeter. Single crystal X-ray analysis was performed on a Siemens SMART CCD diffractometer. Elemental analyses were performed by the Southern Regional Instrument Center of National Science Council at National Cheng Kung University, Tainan, Taiwan.

(4*R*,5*S*)-4-(Dimethoxymethyl)-5-isopropyl-2-methyl-2-cyclohexen-1-one (7). To a suspension of anhydrous ferric chloride (1.68 g, 10.4 mmol) in THF (40 mL) at −20 °C was added methylmagnesium chloride (20% in THF, 7 mL, 19.3 mmol) dropwise. After stirring for 15 min, a solution of **6** (10 g, 66.3 mmol) in THF (130 mL) was added over 2 h and stirred at −20 °C for 30 min. To this reaction mixture, another portion of methylmagnesium chloride (20% in THF, 25 mL, 68.8 mmol) was added over 1 h. After stirring for 30 min, chlorotrimethylsilane (11.5 mL, 91.1 mmol) and triethylamine (12.6 mL, 91.1 mmol) were added. The mixture was poured into a saturated $NaHCO_3$ solution (150 mL) at 0 °C. The resulting mixture was filtered through a short pad of Celite. The aqueous layer was extracted with hexane (3 × 100 mL). The combined organic layer was washed with brine and dried (K_2CO_3). Concentration gave a residue (14.7 g). To the residue (14.7 g) was added a solution of trimethyl orthoformate (11 mL, 100.7 mmol) in CH_2Cl_2 (130 mL). After cooling to −78 °C, BF_3·OEt_2 (11 mL, 87.5 mmol) was added dropwise. After stirring for 1 h at −78 °C, the reaction mixture was quenched with saturated $NaHCO_3$ (100 mL) and allowed to warm to room temperature. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layer was dried ($MgSO_4$). Concentration and silica-gel chromatography (ethyl acetate−hexane, 1:20) gave **7** (8.2 g, 55%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74−6.69 (m, 1 H), 4.39 (d, J = 4.9 Hz, 1 H), 3.38 (s, 6 H), 2.63−2.57 (m, 1 H), 2.47 (dd, J = 16.4, 4.7 Hz, 1 H), 2.22 (dd, J = 16.4, 8.9 Hz, 1 H), 2.02−1.95 (m, 1 H), 1.86−1.76 (m, 1 H), 1.73 (s, 3 H), 0.87 (d, J = 6.9 Hz, 3 H), 0.83 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 200.0, 144.0, 136.1, 105.5, 56.0, 54.6, 42.4, 41.4, 37.3, 28.3, 20.9, 17.8, 15.8; IR (neat) 1674 cm^{-1}; HRMS calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1561. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.8. Found: C, 68.76; H, 9.76. $[\alpha]^{25}_D$ −109 (*c* 0.95, $CHCl_3$).

(4*R*,5*S*,6*R*)-4-(Dimethoxymethyl)-5-isopropyl-2-methyl-6-(trimethylsiloxy)-2-cyclohexen-1-one (8). To a solution of diisopropyl-

amine (2.7 mL, 19.3 mmol) in THF (20 mL) was added *n*-BuLi (1.6 M in hexane, 12 mL, 19.2 mmol) at −20 °C. After warming to 0 °C, the solution was stirred for 30 min and then cooled to −78 °C. To this mixture a solution of **7** (3.34 g, 14.8 mmol) in THF (20 mL) was added dropwise at −78 °C. After stirring for 30 min chlorotrimethylsilane (2.1 mL, 16.6 mmol) and triethylamine (2.2 mL, 15.9 mmol) were added. The reaction mixture was allowed to warm to room temperature and poured into a saturated $NaHCO_3$ solution (100 mL) at 0 °C. The aqueous layer was extracted with hexane (3 × 70 mL). The combined organic layer was washed with brine and dried (K_2CO_3). Concentration gave a crude silyl enol ether (4.41 g). The crude silyl enol ether (4.41 g) was then dissolved in CH_2Cl_2 (50 mL). To the resulting solution was added $NaHCO_3$ (6.22 g, 17.4 mmol) at room temperature and a solution of *m*-CPBA (3.06 g, 17.8 mmol) in CH_2Cl_2 (20 mL) at −20 °C. After stirring for 20 min, a saturated $Na_2S_2O_3$ solution (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was washed with a saturated $NaHCO_3$ solution and dried ($MgSO_4$). Concentration and silica-gel chromatography (ethyl acetate−hexane, 1:30) gave **8** (3.29 g, 71%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (d, J = 4.0 Hz, 1 H), 4.61 (d, J = 6.3 Hz, 1 H), 3.98 (d, J = 6.2 Hz, 1 H), 3.38 (s, 3 H), 3.35 (s, 3 H), 2.56−2.50 (m, 1 H), 2.05−2.00 (m, 1 H), 1.75−1.68 (m, 1 H), 1.73 (s, 3 H), 0.91 (t, J = 6.6 Hz, 6 H), 0.09 (s, 9 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.1, 143.4, 133.8, 106.6, 74.7, 55.01, 54.95, 47.5, 42.1, 28.5, 21.2, 20.0, 16.0, 0.2; IR ($CHCl_3$) 1678 cm^{-1}; HRMS calcd for $C_{16}H_{30}O_4Si$ 314.1913, found 314.1904. Anal. Calcd for $C_{16}H_{30}O_4Si$: C, 61.11; H, 9.61. Found: C, 61.09; H, 9.58. $[\alpha]^{22}_D$ −87.0 (*c* 1.22, $CHCl_3$).

(1*R*,5*R*,7*R*,8*S*)-8-Isopropyl-7-methoxy-3-methyl-6-oxabicyclo-[3.2.1]oct-2-en-4-one (4) and (1*R*,5*R*,7*S*,8*S*)-8-Isopropyl-7-methoxy-3-methyl-6-oxabicyclo[3.2.1]oct-2-en-4-one (9). To a solution of **8** (3.29 g, 10.5 mmol) in $CHCl_3$ (60 mL) was added PTSA monohydrate (5 mg, 0.03 mmol). The reaction mixture was stirred for 6 h at room temperature and diluted with CH_2Cl_2 (100 mL). The organic solution was washed with a $NaHCO_3$ solution (20 mL) and dried ($MgSO_4$). Concentration and silica-gel chromatography (ethyl acetate−hexane, 1:20) gave **4** (1.73 g, 79%) and **9** (0.31 g, 14%) as white solids. Recrystallization (hexane−CH_2Cl_2) of **4** and **9** both gave colorless crystals. Data of **4**: mp 56.0−56.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71−6.68 (m, 1 H), 4.75 (s, 1 H), 4.30 (d, J = 6.0 Hz, 1 H), 3.41 (s, 3 H), 2.81 (dd, J = 6.4, 3.6 Hz, 1 H), 2.57−2.49 (m, 1 H), 1.73 (d, J = 1.2 Hz, 3 H), 1.59−1.49 (m, 1 H), 0.91 (d, J = 6.4 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 196.1, 139.9, 136.9, 106.9, 84.0, 56.7, 55.2, 46.1, 23.8, 21.7, 21.2, 14.5; IR ($CHCl_3$) 1691 cm^{-1}; HRMS calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1269. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.60; H, 8.60. $[\alpha]^{22}_D$ −220.2 (*c* 0.95, $CHCl_3$). Data of **9**: mp 73.5−74.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66−6.60 (m, 1 H), 5.26 (d, J = 4.3 Hz, 1 H), 4.20 (d, J = 6.6 Hz, 1 H), 3.38 (s, 3 H), 3.02 (dt, J = 9.1, 4.5 Hz, 1 H), 2.23−2.14 (m, 1 H), 1.83 (s, 3 H), 1.60−1.47 (m, 1 H), 0.85 (d, J = 8.8 Hz, 6 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 197.1, 140.8, 137.5, 108.6, 84.6, 58.9, 57.0, 43.6, 24.2, 21.7, 20.7, 14.9; IR ($CHCl_3$) 1684 cm^{-1}; HRMS calcd for $C_{12}H_{18}O_3$ 210.1256, found 210.1265. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.56; H, 8.70. $[\alpha]^{20}_D$ −216.4 (*c* 1.21, $CHCl_3$).

Conversion of 9 to 4. To a solution of **9** (75 mg, 0.36 mmol) in dichloromethane (7 mL) was added PTSA monohydrate (7 mg, 0.04 mmol). The reaction mixture was heated to reflux for 1 h. After cooling to room temperature, a saturated $NaHCO_3$ solution was added. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was dried ($MgSO_4$). Concentration and silica-gel chromatography (ethyl acetate−hexane, 1:5) gave **4** (41 mg, 55%) and **9** (18 mg, 25%).

(1*R*,2*S*,5*R*,7*R*,8*S*)-8-Isopropyl-7-methoxy-3-methyl-4-(trimethylsiloxy)-2-(4-(trimethylsilyl)-3-butynyl)-6-oxabicyclo[3.2.1]oct-3-ene (10). To a suspension of magnesium (820 mg, 34.2 mmol) in refluxing THF (10 mL) was added a solution of 4-chloro-1-(trimethylsilyl)-1-butyne (3.84 g, 23.9 mmol) and 1,2-dibromoethane (0.2 mL, 2.32 mmol) in THF (34 mL) dropwise over a period of 4 h. The reaction mixture was heated for 30 min and cooled to −78 °C. CuI (1.93 g, 10.1 mmol) was added. After stirring at −78 °C for 30 min, compound **4** (1.95 g, 9.28 mmol) in THF (31 mL), chlorotrimethylsilane (1.0 mL, 7.6 mmol), and triethylamine (1.1 mL, 8.0 mmol) were added dropwise in sequence. The reaction mixture was allowed to warm to room temperature and stirred for 12 h and was then poured into a saturated $NaHCO_3$ solution (30 mL). The mixture was stirred and filtered with Celite to remove black solid. The Celite with filtered solid was washed with hexane (100 mL). After separating the organic layer, the aqueous layer was extracted with hexane (2 × 60 mL). The combined organic layer was washed with brine and dried (K_2CO_3). Concentration gave crude product **10** (4.8 g) that was used for the next step without purification. A small sample of crude **10** was purified by silica-gel chromatography (ethyl acetate−hexane, 1:50) gave **10** as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 1H), 4.02 (d, 1H, J = 4.4 Hz), 3.35 (s, 3 H), 2.51−2.21 (m, 5H), 2.04−1.91 (m, 2H), 1.55−1.39 (m, 1 H), 1.51 (s, 3 H), 1.00 (d, J = 6.7 Hz, 3 H), 0.92 (d, J = 6.5 Hz, 3H), 0.20 (s, 9 H), 0.14 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.4, 113.9. 106.0, 105.0, 85.5, 79.4, 55.0, 49.2, 43.6, 35.3, 27.4, 24.7, 22.0, 21.5, 17.2, 12.2, 0.0, −0.2; IR (neat) 2170 cm^{-1}; HRMS calcd for $C_{22}H_{40}O_3Si_2$: 408.2516, found 408.2513.

(1*S*,2*S*,5*R*,7*R*,8*S*)-3-Iodo-8-isopropyl-7-methoxy-3-methyl-2-(4-(trimethylsilyl)-3-butynyl)-6-oxabicyclo[3.2.1]octan-4-one (3). To a solution of crude product **10** (4.6 g) and NaI (4.62 g, 30 mmol) in THF (100 mL) was added a solution of *m*-CPBA (87%, 5.63 g, 28 mmol) in THF (50 mL) dropwise at 0 °C. After warming to room temperature and stirring for 20 min, the reaction mixture was diluted with Et_2O (150 mL) and quenched with a saturated $Na_2S_2O_3$ solution (150 mL). The organic layer was separated, washed with a saturated $NaHCO_3$ solution and brine, and dried ($MgSO_4$). Concentration and silica-gel chromatography (ethyl acetate−hexane, 1:50) gave **3** (3.54 g, 82% from **4**) as a brown liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (s, 1 H), 4.47 (d, J = 5.6 Hz, 1 H), 3.38 (s, 3H), 2.50−2.41 (m, 2 H), 2.36−2.24 (m, 2 H), 2.05 (s, 3 H), 1.95−1.85 (m, 1 H), 1.80−1.70 (m, 1 H), 1.31−1.21 (m, 1 H), 1.12−1.01 (m, 1 H), 0.97 (d, J = 6.4 Hz, 3 H), 0.91 (d, J = 6.0 Hz, 3 H), 0.09 (s, 9 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 204.8, 105.3, 103.0, 87.3, 83.2, 55.0, 50.6, 46.0, 43.9, 40.5, 34.8, 30.8, 25.0, 21.0, 18.2, 0.1; IR (neat) 2173, 1716 cm^{-1}; HRMS calcd for $C_{19}H_{31}IO_3Si$ 462.1089, found 462.1082.

(1*R*,2*S*,6*R*,8*R*,10*R*,11*S*)-11-Isopropyl-10-methoxy-6-methyl-5-[(*Z* and *E*)-1-(trimethylsilyl)methylidene]-9-oxatricyclo[6.2.1.0^{2,6}]-undecan-7-one (2). To a solution of **3** (3.07 g, 6.65 mmol) in refluxing benzene (333 mL) was added a solution of tributyltin hydride (2.16 g, 7.44 mmol) and AIBN (87 mg, 0.53 mmol) in benzene (93 mL) with a syringe pump over 6 h. After the addition, the reaction mixture was heated at reflux for 1 h, then cooled to room temperature, and concentrated. The residue was dissolved into ethyl acetate (70 mL). A KF solution (2.88 g, 49.7 mmol) in water (5 mL) was added. The resulting solution was stirred for 10 h and filtered to remove white solid. The filtrate was washed with saturated $NaHCO_3$ solution (2 × 50 mL). The organic layer was dried ($MgSO_4$). Concentration and silica-gel chromatography (ethyl acetate−hexane, 1:40) gave the uncyclized reduction product (555 mg, 25%) and cyclized product **2** (1.55 g, 69%) as a mixture of *E* and *Z* isomers (*E*:*Z* = 1:9): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (t, J = 2.0 Hz, 0.9 H), 5.15 (t, J = 2.4 Hz, 0.1 H), 4.89 (s, 0.9 H), 4.77 (s, 0.1 H), 4.22 (d, J = 6.2 Hz, 0.9 H), 4.12 (d, J = 6.0 Hz, 0.1 H), 3.33 (s, 2.7 H), 3.29 (s, 0.3 H), 2.88−2.52 (m, 2 H), 2.46−2.36 (m, 1 H), 2.28−2.10 (m, 3 H), 1.85−1.62 (m, 1 H), 1.35−1.10 (m, 1 H), 1.19 (s, 2.7 H), 1.13 (s, 0.3 H), 0.92 (d, J = 6.5 Hz, 3 H), 0.88 (d, J = 6.4 Hz, 3 H), 0.05 (s, 8.1 H), 0.04 (s, 0.9 H); ^{13}C NMR (75 MHz, $CDCl_3$) of *Z* isomer: δ 210.3, 163.6, 121.2, 105.3, 84.3, 58.8, 54.7, 53.5, 49.3, 48.6, 37.7, 26.0, 25.4, 24.5 , 21.1, 20.8, 0.9; IR (neat) 1715 cm^{-1}; HRMS calcd for $C_{19}H_{32}O_3Si$ 336.2121, found 336.2126. Anal. Calcd for $C_{19}H_{32}O_3Si$: C, 67.81; H, 9.58. Found: C, 67.73; H, 9.53.

(1*R*,2*S*,6*R*,8*R*,10*R*,11*S*)-5-[(*E*)-1-Iodo-1-(trimethylsilyl)methylidene]-11-isopropyl-10-methoxy-6-methyl-9-oxatricyclo[6.2.1.0^{2,6}]undecan-7-one (11). To a solution of **3** (302 mg, 0.65 mmol) and iodoethane (0.2 mL) in benzene (5 mL) was added bis(tributyltin) (208 mg, 0.36 mmol) and AIBN (5 mg, 0.03 mmol). The reaction mixture was irradiated with a sun lamp (300 W) to reflux for 1 h. Et_2O (50 mL) and a solution of KF (189 mg, 3.25 mmol) in water (10 mL) was added. The mixture was stirred for 30 min, then filtered, and extracted with Et_2O (3 × 50 mL). The combined organic layer was dried ($MgSO_4$). Concentration and silica-gel chromatography (ethyl acetate−hexane,

1:40) gave **11** (220 mg, 73%). Recrystallization (ethyl acetate−hexane) gave colorless crystals, mp 128.0−129.0 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 (s, 1 H), 4.29 (d, J = 6.3 Hz, 1 H), 3.37 (s, 3 H), 3.04−2.81 (m, 2 H), 2.50−2.40 (m, 2 H), 2.31−2.14 (m, 2 H), 1.77−1.69 (m,1 H), 1.24 (s, 3 H), 1.24−1.12 (m, 1 H), 0.91 (d, 6 H, J = 7.2 Hz), 0.28 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 164.8, 107.1, 105.2, 84.4, 60.3, 54.8, 53.9, 51.5, 50.7, 49.1, 25.7, 24.22, 24.18, 20.7, 20.5, 3.7; IR ($CHCl_3$) 1710 cm^{-1}; MS (EI) *m/z* 462 (M^+, 13), 335 (100), 305 (24), 193 (30), 175 (34). Anal. Calcd for $C_{19}H_{31}IO_3Si$: C, 49.35; H, 6.76. Found: C, 49.39; H, 6.78. Single-crystal X-ray analysis of **11** was performed. All crystallographic calculation were carried out with Siemens SHELXTL PLUS-VMS system. Crystal data of **11**: $C_{19}H_{31}IO_3Si$, MW = 462.4 g/mol, orthorombic crystal system, space group $P2_12_12$, Z = 8, a = 16.377(2) Å, b = 29.029(2) Å, c 8.932(2) Å, V = 4234(1) Å^3, D_c = 1.451 Mg/m^3. A total of 7468 independent reflections were collected of which 6746 were considered observed [$I > 3.0\sigma(I)$, (R = 6.09%)]. The structure was solved by direct methods and refined to an R value 0.0448. Absolute structure was determined with η = 0.98(4).

(1*R*,2*S*,6*R*,8*R*,10*R*,11*S*)-11-Isopropyl-10-methoxy-6-methyl-5-methylene-9-oxatricyclo[6.2.1.0^{2,6}]undecan-7-one (12). To a solution of **2** (219 mg, 0.65 mmol) in benzene (5 mL) was added CF_3CO_2H (0.25 mL, 3.3 mmol). The reaction mixture was stirred for 20 min and then concentrated to give a residue. Silica-gel chromatography (ethyl acetate−hexane, 1:15) gave **12** (144 mg, 84%) as a white solid. Recrystallization (CH_2Cl_2) gave colorless crystals, mp 94−94.5 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (s, 1 H), 4.83 (t, J = 2.2 Hz, 1 H), 4.73 (t, J = 2.6 Hz, 1 H), 4.19 (d, J = 6.0 Hz, 1 H), 3.35 (s, 3 H), 2.79−2.54 (m, 2 H), 2.45 (ddd, J = 11.8, 6.0, 3.8 Hz, 1 H), 2.31−2.14 (m, 3 H), 1.86−1.73 (m, 1 H), 1.42−1.24 (m, 1 H), 1.21 (s, 3 H), 0.98 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.7, 154.6, 106.0, 105.3, 83.5, 57.2, 54.8, 52.6, 48.8, 45.9, 31.7, 26.8, 26.4, 24.5, 21.3, 21.0; IR (neat) 1716 cm^{-1}; HRMS calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1729. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.70; H, 9.15. $[\alpha]^{19}_D$ −50.9 (c 0.99, $CHCl_3$).

(1*S*,2*S*,6*R*,8*R*,10*R*,11*S*)-10-(3-Chloroperoxybenzoyl)-11-isopropyl-6-methyl-5-methylene-9-oxatricyclo[6.2.1.0^{2,6}]undecan-7-one (13). To a solution of **12** (97 mg, 0.37 mmol) in CH_2Cl_2 (30 mL) was added molecular sieve (3 Å, 1 g) and a solution of *m*-CPBA (80%, 100 mg, 0.56 mmol) and $BF_3{\cdot}OEt_2$ (0.047 mL, 0.37 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred for 3.5 h. After filtration with Celite, the solution was washed with a saturated $Na_2S_2O_3$ solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was washed with a saturated $NaHCO_3$ solution, brine, and dried ($MgSO_4$). Concentration gave crude peroxy compound **13** as a brown solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (br s, 1 H), 7.83 (d, J = 7.9 Hz, 1 H), 7.56 (d, J = 7.9 Hz, 1 H), 7.38 (t, J = 7.9 Hz, 1 H), 5.72 (s, 1 H), 4.85 (br s, 1 H), 4.74 (br s, 1 H), 4.36 (d, J = 5.9 Hz, 1 H), 2.84−2.51 (m, 4 H), 2.46−2.37 (m, 1 H), 2.37−2.20 (m, 1 H), 1.83−1.79 (m, 1 H), 1.44−1.30 (m, 1 H), 1.25 (s, 3 H), 1.02 (d, J = 6.0 Hz, 3 H), 0.94 (d, J = 6.0 Hz, 3 H); IR (neat) 1765, 1718 cm^{-1}; MS (EI) *m/z* 404 (M^+, <1), 248 (18), 156 (30), 139 (36), 94 (100), 79 (54); HRMS calcd for $C_{22}H_{25}{}^{35}ClO_5$ and $C_{22}H_{25}{}^{37}ClO_5$ 404.1390 and 406.1379, found 404.1388 and 406.1397.

(1*R*,2*S*,6*R*,8*R*,11*S*)-11-Isopropyl-6-methyl-5-methylene-9-oxatricyclo[6.2.1.0^{2,6}] undecane-7,10-dione (14). To a solution of crude peroxy compound **13** from the previous stage in CH_2Cl_2 (5 mL) was added DBU (0.17 mL, 1.1 mmol). The reaction mixture was stirred at room temperature for 1 h. A saturated $NaHCO_3$ solution (10 mL) was added. The reaction mixture was extracted with Et_2O (2 × 10 mL). The combined organic layer was washed with brine and dried (Na_2SO_4). Concentration and silica-gel chromatography (ethyl acetate−hexane, 1:15) gave **14** (57 mg, 62% from **12**). Recrystallization (CH_2Cl_2) gave colorless crystals, mp 161.5−162 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.91 (t, J = 2.2 Hz, 1 H), 4.74 (t, J = 2.6 Hz, 1 H), 4.56 (d, J = 5.6 Hz, 1 H), 2.76−2.49 (m, 3 H), 2.47−2.37 (m, 2 H), 2.25−2.00 (m, 2 H), 1.55−1.38 (m, 1 H), 1.28 (s, 3 H), 0.97 (d, J = 6.5 Hz, 3 H), 0.93 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.7, 177.5, 152.8, 108.3, 83.9, 58.1, 54.4, 46.4, 44.8, 30.6, 26.6, 25.7, 24.7, 20.6, 19.5; IR (neat) 1785, 1714 cm^{-1}; HRMS calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1414. Anal. Calcd for $C_{15}H_{20}O_3$: C 72.55, H 8.12. Found: C, 72.57; H, 8.13. $[\alpha]^{29}_D$ +55.9 (c 1.34, $CHCl_3$).

(1*R*,2*S*,5*S*,6*R*,7*R*,8*R*,11*S*)-7-Hydroxy-5-(hydroxymethyl)-11-isopropyl-6-methyl-9-oxatricyclo[6.2.1.0^{2,6}]undecan-10-one (17). To a solution of **14** (45 mg, 0.18 mmol) in THF (5 mL) was added $BH_3{\cdot}S(CH_3)_2$ (1.38 M in THF, 1.30 mL, 1.79 mmol) dropwise at room temperature. The reaction mixture was stirred at room temperature, stirred for 4.5 h, and then cooled to 0 °C. Methanol (2 mL) was added dropwise. The mixture was concentrated to give a residue. THF (5 mL) was added. To the resulting solution was added a mixture of NaOH (3 M, 2 mL, 6 mmol) and H_2O_2 (30%, 2 mL, 23 mmol) at room temperature. The reaction mixture was stirred for 12 h and brine (10 mL) was added. The mixture was extracted with Et_2O (3 × 15 mL). The combined organic layer was dried ($MgSO_4$). Concentration and silica-gel chromatography (ethyl acetate−hexane, 1:1) gave **17** as a white solid (29 mg, 60%). Recrystallization ($CHCl_3$−MeOH) gave colorless crystals, mp 155.5−156 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (dd, J = 4.8, 2.8 Hz, 1 H), 4.47 (d, J = 2.8 Hz, 1 H), 3.74 (A of ABX, J_{AB} = 11.1, J_{AX} = 9.4 Hz, 1 H), 3.62 (B of ABX, J_{AB} = 11.1, J_{BX} = 6.0 Hz, 1 H), 2.35 (t, J = 4.6 Hz, 1 H), 2.31−2.07 (m, 4 H), 2.07−1.88 (m, 3 H), 1.88−1.77 (m, 1 H), 1.77−1.66 (m, 1 H), 1.43−1.30 (m, 1 H), 1.27 (s, 3 H), 1.06 (d, J = 6.4 Hz, 3 H), 0.91 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 179.6, 81.4, 66.8, 64.2, 55.8, 51.1, 45.4, 44.8, 44.5, 30.5, 29.0, 28.7, 24.4, 21.24, 21.19; IR (neat) 3417, 1761 cm^{-1}; HRMS calcd for $C_{15}H_{24}O_4$ 268.1674, found 268.1680. Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.04; H, 9.10. $[\alpha]^{17}_D$ +10.9 (c 1.32, CH_3OH).

(1*R*,2*S*,5*S*,6*R*,7*R*,8*R*,11*S*)-5-(Azidomethyl)-7-hydroxy-11-isopropyl-6-methyl-9-oxatricyclo[6.2.1.0^{2,6}]undecan-10-one (19). To a solution of **17** (35 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (0.018 mL, 1.3 mmol) and methanesulfonyl chloride (0.011 mL, 0.14 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1.5 h and diluted with Et_2O (20 mL). The mixture was washed with a saturated $NaHCO_3$ solution and brine. The organic layer was separated and dried (Na_2SO_4). Filtration with Celite and concentration gave crude product **18**. The crude product **18**, unstable on exposure to silica-gel chromatography, was used for the next step without purification. Data of crude **18**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (dd, J = 4.4, 3.1 Hz, 1 H), 4.37 (dd, J = 10.3, 8.0 Hz, 1 H), 4.27 (dd, J = 5.7, 3.1 Hz, 1 H), 4.10 (dd, J = 10.3, 7.0 Hz, 1 H), 3.00 (s, 3 H), 2.41 (d, J = 5.7 Hz, 1 H), 2.36 (t, J = 4.4 Hz, 1 H), 2.28−2.19 (m, 1 H), 2.19−2.06 (m, 2 H), 2.06−1.93 (m, 2 H), 1.91−1.81 (m, 2 H), 1.57−1.45 (m, 1 H), 1.26 (s, 3 H), 1.05 (d, J = 6.4 Hz, 3 H), 0.90 (d, J = 6.8 Hz, 3 H); MS (EI) *m/z* 347 (M^+, 1), 207 (60), 151 (21), 113 (32), 95 (100), 94 (30). To a solution of crude **18** in DMF (10 mL) was added NaN_3 (62 mg, 1.2 mmol) and 18-crown-6 (40 mg, 0.15 mmol). The reaction mixture was heated to 100 °C and stirred for 1.5 h. After cooling to room temperature, water (10 mL) was added. The mixture was extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with brine (20 mL) and dried ($MgSO_4$). Concentration and silica-gel chromatography (ethyl acetate−hexane, 1:5) gave **19** (31 mg, 80%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (dd, J = 3.8, 2.9 Hz, 1 H), 4.27 (d, J = 2.9 Hz, 1 H), 3.38 (A of ABX, J_{AB} = 12.6, J_{AX} = 8.7 Hz, 1 H), 3.31 (B of ABX, J_{AB} = 12.6, J_{BX} = 7.0 Hz, 1 H), 2.35 (t, J = 4.5 Hz, 1 H), 2.19−2.05 (m, 2 H), 2.05−1.91 (m, 3 H), 1.91−1.76 (m, 2 H), 1.71 (br, 1 H), 1.54−1.39 (m, 1 H), 1.26 (s, 3 H), 1.06 (d, J = 6.1 Hz, 3 H), 0.91 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 80.8, 67.2, 53.4, 52.9, 50.9, 45.1, 45.0, 44.4 , 29.9, 29.8, 28.7, 24.4, 21.23, 21.17; IR (neat) 3481, 2102, 1763 cm^{-1}; MS (FAB) *m/z* 294 (M^+ + H, 53), 266 (100), 251 (51), 222 (42), 154 (71), 137 (83), 95 (53), 81 (52); $[\alpha]^{29}_D$ −49.9 (c 1.31, $CHCl_3$).

(1*R*,2*S*,5*S*,6*R*,8*R*,11*S*)-5-(Azidomethyl)-11-isopropyl-6-methyl-9-oxatricyclo[6.2.1.0^{2,6}]undecane-7,10-dione (20). To a solution of **19** (42 mg, 0.14 mmol) in acetone was added Jones reagent (0.5 mL), prepared from CrO_3 (13.36 g), concentrated H_2SO_4 (11.5 mL) and water (25 mL), dropwise at room temperature. The reaction mixture was stirred for 1.5 h. Isopropyl alcohol (1 mL) and water (20 mL) was added to quench the reaction. The mixture was extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution brine and dried ($MgSO_4$). Concentration and silica

gel chromatography (ethyl acetate−hexane, 1:5) gave **20** (30 mg, 94%) as a white solid. Recrystallization (CH_2Cl_2) gave colorless crystals, mp 108−108.5 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (d, J = 5.6 Hz, 1 H), 3.32 (A of ABX, J_{AB} = 12.0, J_{AX} = 4.7 Hz, 1 H), 3.01 (B of ABX, J_{AB} = 12.0, J_{BX} = 10.3 Hz, 1 H), 2.62 (t, J = 4.8 Hz, 1 H), 2.44−2.30 (m, 2 H), 2.12−1.98 (m, 4 H), 1.72−1.50 (m, 2 H), 1.37 (s, 3 H), 0.98 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 207.7, 177.3, 83.3, 55.6, 53.9, 53.3, 53.1, 45.8, 44.8, 30.9, 29.6, 28.7, 24.5, 20.9, 19.5; IR (neat) 2097, 1790, 1714 cm^{-1}; MS (FAB) *m/z* 292 (M^+ + H, 6), 264 (100), 249 (16), 171 (69), 137 (20), 91 (46); $[\alpha]^{25}_D$ +18.9 (*c* 1.62, $CHCl_3$).

(1*S*,4*S*,7*S*,8*R*,11*R* 12*R*,13*S*)-13-Isopropyl-12-methyl-10-oxa-2-azatetracyclo[5.4.1.1^{8,11}.0^{4,12}]tridecan-9-one (21). To a solution of **20** (64 mg, 0.22 mmol) in THF (5 mL) was added Ph_3P (69 mg, 0.26 mmol). The reaction mixture was stirred at room temperature for 12 h. To this mixture was added CH_3OH (4 mL), HOAc (0.14 mL, 2.45 mmol), and $NaBH_3CN$ (70 mg, 1.1 mmol). The resulting mixture was stirred for 12 h. Dilute HCl (1 M, 10 mL) was added. After stirring for 1 h, the mixture was washed with Et_2O (10 mL). The aqueous layer was basified on adding NaOH solution (3 M, 10 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined CH_2Cl_2 layer was dried ($MgSO_4$). Concentration gave crude product **21** (42 mg). The crude product was used for the next step without purification. Data of crude **21**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.61 (dd, J = 5.3, 3.5 Hz, 1 H), 3.18 (dd, J = 11.4, 8.5 Hz, 1 H), 2.86 (d, J = 3.5 Hz, 1 H), 2.83 (dd, J = 11.4, 6.9 Hz, 1 H), 2.47−2.43 (m, 1 H), 2.35−2.20 (m, 1 H), 2.20−2.00 (m, 5 H), 1.89−1.71 (m, 2 H), 1.55−1.39 (m, 1 H), 1.34 (s, 3 H), 0.96 (d, J = 6.4 Hz, 3 H), 0.95 (d, J = 6.4 Hz, 3 H); MS (EI) *m/z* 249 (M^+, 38), 206 (100), 193 (31), 163 (27), 150 (44), 95 (29), 82 (58).

(−)-Dendrobine (1). To crude product **21** (42 mg) was added water (5 mL), HCOOH (3.3 g, 72 mmol), and paraformaldehyde (180 mg, 6.0 mmol). The reaction mixture was stirred and heated at 120 °C for 12 h. After cooling to room temperature, the reaction mixture was basified on adding a NaOH solution (3 M, 30 mL) and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layer was dried ($MgSO_4$). Concentration and silica-gel chromatography (ethyl acetate−hexane−methanol, 25:25:1) gave **1** (24 mg, 42% from **20**) as a white solid. Recrystallization (hexane−Et_2O, 2:1) gave colorless crystals, mp 133.0−133.5 °C, lit.[13] mp 134.6−136 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (dd, J = 5.6, 3.2 Hz, 1 H), 3.13 (t, J = 8.6 Hz, 1 H), 2.67 (dd, J = 8.4, 7.6 Hz, 1 H), 2.64 (d, J = 2.8 Hz, 1 H), 2.48 (s, 3 H), 2.43 (t, J = 5.0 Hz, 1 H), 2.34 (m, 1 H), 2.15−1.96 (m, 4 H), 1.88−1.73 (m, 2 H), 1.59−1.47 (m, 1 H), 1.36 (s, 3 H), 0.95 (d, J = 6.4 Hz, 3 H), 0.94(d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 79.1, 66.9, 62.0, 53.7, 52.5, 51.5, 43.9, 43.1, 36.5, 32.8, 32.7, 30.8, 24.5, 21.1, 20.4; IR (neat) 1767 cm^{-1}; MS (EI) *m/z* 263 (M^+, 38), 220 (100), 206 (14), 178 (10), 96 (17); HRMS calcd for $C_{16}H_{25}NO_2$ 263.1885, found 263.1880; $[\alpha]^{21}_D$ −46.7 (*c* 1.38, CH_3OH), lit.[13] $[\alpha]^4_D$ −48.4 (*c* 1.98, CH_3OH).

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Supporting Information Available: X-ray crystallographic data and molecular drawing of **11**, ^{1}H NMR spectra of **1**−**4**, **7**−**14**, and **17**−**21**, and ^{13}C NMR spectra of **1**−**4**, **7**−**9**, **11**, **12**, **14**, **17**, **19**, and **20** (38 pages). See any current masthead page for ordering and Internet access instructions.

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