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Synthesis of (−)-Chamobtusin A from (+)-Dehydroabietylamine

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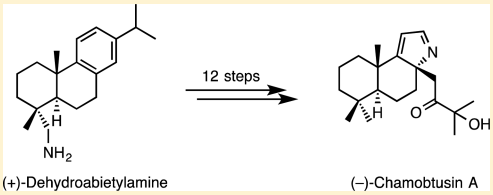
Supporting Information

ABSTRACT: Chamobtusin A, a unique diterpene alkaloid isolated from *Chamaecyparis obtusa* cv. tetragon, is considered to be biosynthesized from an abietane diterpenoid. On the basis of this biosynthetic hypothesis, ferruginol (**15**) was synthesized from (+)-dehydroabietylamine and then biomimetically transformed into (−)-chamobtusin A in 6 steps (12 steps from (+)-dehydroabietylamine).

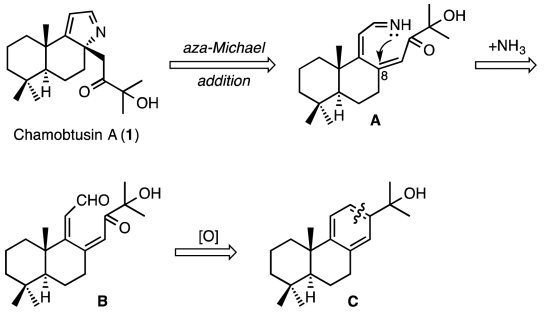


INTRODUCTION

The family Cupressaceae, which has a worldwide distribution, is abundant in natural products such as terpenes, flavones, and lignans. During the search for new bioactive compounds in this family, Tan and co-workers isolated the novel diterpene alkaloid chamobtusin A (**1**) from *Chamaecyparis obtusa* cv. tetragon.[1] Although no remarkable biological activity of **1** has been reported to date, its unique structure having a 2*H*-pyrrole ring has intrigued synthetic chemists. In 2010, we achieved the first total synthesis of (±)-**1** by using a presumed biomimetic aza-cyclization.[2] Following our synthesis, Aoyagi et al. accomplished the asymmetric[3a] as well as racemic[3b] synthesis of **1**.

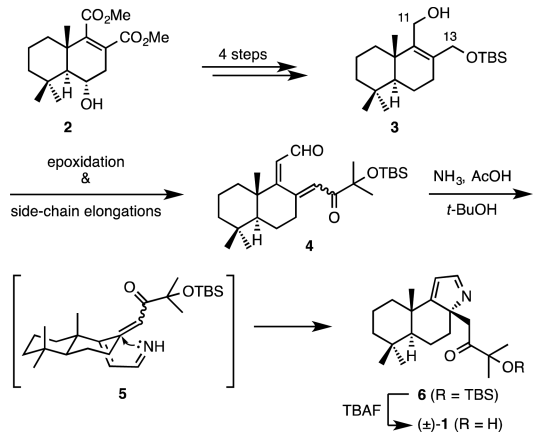
Our proposed biosynthetic pathway of **1** is shown in Scheme 1. Oxidative cleavage of the benzene ring of **C**[4] with a well-known abietane skeleton would generate keto aldehyde **B**. In the presence of ammonia, **B** would be converted into imine **A** and subsequent aza-Michael addition to C8 would produce **1**.

Scheme 1. Presumed Biosynthesis of 1



On the basis of this hypothesis, the biomimetic aza-cyclization was employed as a key reaction in our synthesis of (±)-**1**, as outlined in Scheme 2.[2] Our racemic synthesis commenced with the transformation of the known alchohol **2**[5] into **3** through a four-step sequence. Compound **4**, a precursor for intramolecular aza-cyclization, could be obtained from **3** through epoxidation of the double bond followed by side-chain elongations at C11 and C13 (chamobtusin A numbering). Imine formation, as shown in **5**, and subsequent intramolecular aza-Michael addition smoothly proceeded from both geometrical isomers of **4** by treatment with ammonia in the presence of acetic acid to afford **6** (65% from the *E* isomer, 60% from the *Z* isomer). Finally, the TBS group was removed with TBAF to give (±)-**1**.

Scheme 2. Our Racemic Synthesis of 1[2]



Thus, the remaining task for us is to synthesize optically active **1** from an abietane diterpenoid through a biomimetic pathway. In this article, we describe the synthesis of (−)-chamobtusin A starting from (+)-dehydroabietylamine.

RESULTS AND DISCUSSION

Scheme 3 illustrates our retrosynthetic analysis for the synthesis of an optically active form of **1**. The 2*H*-pyrrole ring of **1** would be elaborated from keto aldehyde **D** in the same manner as was used in our racemic synthesis. Keto aldehyde **D** would be accessed from **E** by selective cleavage of the C12−C13 bond. Commercially available (+)-dehydroabietylamine (**F**) was

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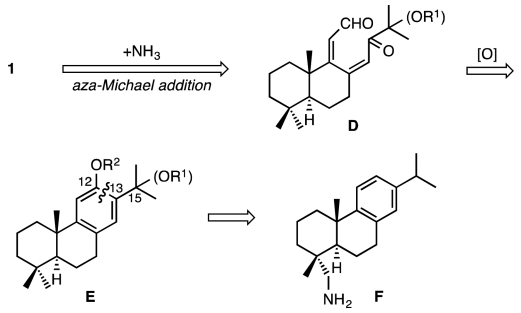
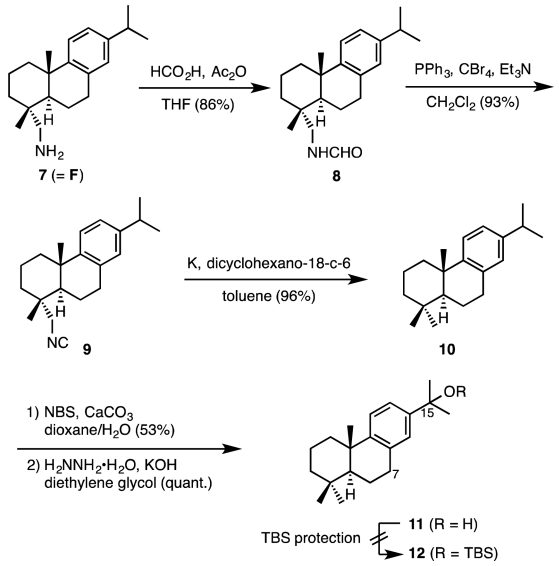
Scheme 3. Retrosynthetic Analysis



considered to be suitable for a starting material, which would be converted into **E** in a straightforward manner. Key points in this strategy are when to introduce a hydroxy group at C15 and how to cleave the C12−C13 bond selectively.

The synthesis started with deamination[6] of (+)-dehydroabietylamine (**7** = **F**) (Scheme 4). Amine **7** was converted to

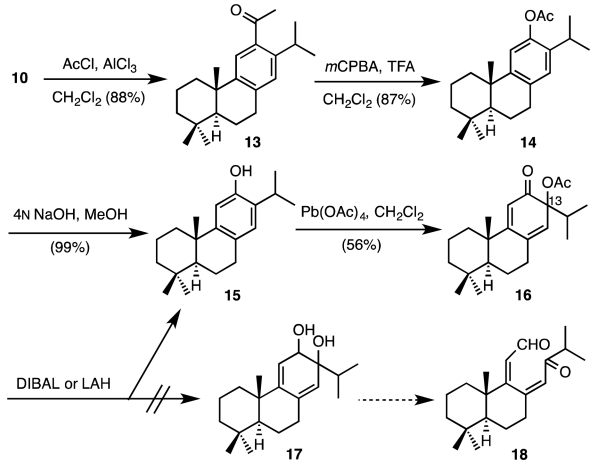
Scheme 4. Preparation of 10 and Attempt To Introduce a TBSoxy Group at C15



formamide **8** by treatment with acetic-formic anhydride in 86% yield. Dehydration of formamide proceeded under Appel's conditions[7] (PPh_3, CCl_4, Et_3N) to give **9** in 93% yield. The resulting isocyano group was removed by treatment with potassium and dicyclohexano-18-crown-6 in toluene[8] to afford dehydroabietane **10**. With **10** in hand, we then investigated the feasibility of introduction of a C15 hydroxy group at an earlier stage. Benzylic oxidation[9] (at C7 and C15) of **10** followed by modified Wolff−Kishner reduction[10] of a ketone at C7 successfully introduced a hydroxy group at C15 to afford the alcohol **11**. Disappointingly, the hydroxy group of **11** was prone to dehydration, and even the TBS ether **12** could not be obtained under various conditions. This result suggested that a hydroxy group at C15 should be installed at a later stage.

Having faced the instability of the oxygen functionality at C15, we next turned our attention to the oxidative cleavage of the C12−C13 bond. At first, we attempted the 1,2-glycol cleavage (**17** → **18**), as shown in Scheme 5. Friedel−Crafts acylation of **10** gave **13**, which was then converted to the acetate **14** by Baeyer−Villiger oxidation in 77% yield over two

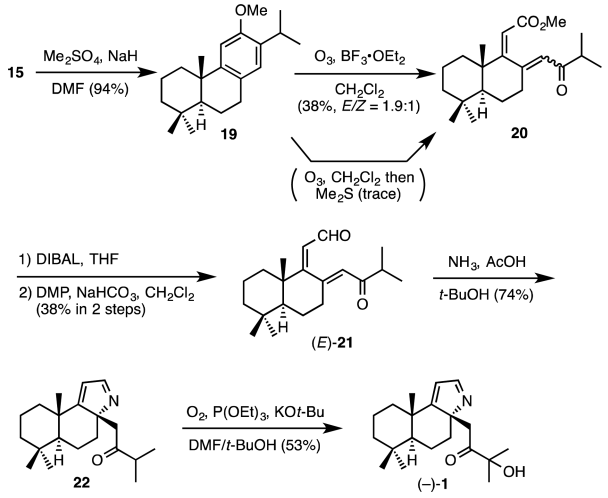
Scheme 5. First Attempt to Cleave the C12−C13 Double Bond



steps.[11] The hydrolysis of **14** smoothly proceeded to give the phenol **15** (=ferruginol)[12] in 99% yield. After extensive experimentation, the acetate **16** could be obtained by using a Wessely oxidation ($Pb(OAc)_4$).[13] On the other hand, a hydroxy group could not be introduced at C13 by using other oxidants ($(PhSeO)_2O$,[14] hypervalent iodine(III) reagent,[15] MoO_5·Py·HMPA[16]). Reduction of **16** to the glycol **17** was then examined, but disappointingly, treatment with DIBAL or LAH resulted in regeneration of **15**.

Next, we focused on ozonolysis[17] for the selective cleavage of the C12−C13 bond (Scheme 6). The phenol **15** was converted

Scheme 6. Completion of the Synthesis



to the methyl ether **19** by treatment with dimethyl sulfate and sodium hydride in DMF. Standard ozonolysis of **19** in dichloromethane at −78 °C afforded a trace amount of the desired product **20**, in which reaction the addition of boron trifluoride[18] suppressed the overoxidation to raise the yield of **20** (*E*/*Z* = 1.9/1) up to 38%. *E*/*Z* mixtures of **20** were subjected to DIBAL reduction to give the corresponding diol. The crude product was then oxidized with Dess−Martin periodinane to afford (*E*)-**21** as a single isomer in a moderate yield. On the other hand, a Swern oxidation as well as a TPAP oxidation provided *E*/*Z* mixtures of **21** (Swern, 38%; TPAP, 21%), but the reproducibility of these reactions was poor. Imine

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formation and subsequent intramolecular aza-Michael addition of (*E*)-**21** proceeded under the same conditions as were used in our racemic synthesis to afford **22** in 74% yield. Finally, a hydroxy group was successfully introduced at C15 by aerobic oxidation[19] to give (−)-**1** in 53% yield, whose spectroscopic data and optical rotation agreed with those of natural chamobtusin A.

In conclusion, we have succeeded in the biomimetic transformation of ferruginol (**15**), which was synthesized from (+)-dehydroabietylamine, into (−)-chamobtusin A in six steps. Key steps of the synthesis include a boron trifluoride assisted selective ozonolysis of the C12−C13 bond and a late-stage installation of a hydroxy group at C15.

EXPERIMENTAL SECTION

General Procedures. Dry tetrahydrofuran (THF) and toluene were distilled from sodium−benzophenone ketyl before use. Anhydrous methylene chloride (CH_2Cl_2) was distilled from phosphorus pentoxide (P_2O_5) and stored under an argon atmosphere. IR spectra were measured with an FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature. Chemical shifts (δ) were referenced to the residual solvent peak as the internal standard ($CDCl_3$, δ_H 7.26, δ_C = 77.0; C_6D_6, δ_H 7.15, δ_C 128.4; CD_3OD, δ_H 3.30, δ_C 49.0). Column chromatography was performed using 0.060−0.200 mm silica gel. TLC was carried out using a 0.25 mm plate. Preparative TLC was carried out using a 0.5 mm plate.

(+)-(1*R*,4a*S*,10a*R*)-1-(Formamidomethyl)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (8). An equimolar mixture of formic acid (4.10 mL, 95.5 mmol) and acetic anhydride (9.00 mL, 95.5 mmol) was heated at 65 °C for 10 min. After it was cooled to 0 °C, this solution was added to (+)-dehydroabietylamine (18.2 g, 63.7 mmol) in THF (200 mL). After it was stirred at room temperature for 20 min, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was successively washed with saturated aqueous $NaHCO_3$, water, and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (1/1) gave **8** (17.2 g, white solid, 86%): $[\alpha]_D^{19}$ = +36.7 (*c* 1.05, $CHCl_3$). Mp: 43−46 °C. IR (ν_{max} (Nujol), cm^{-1}): 3291, 2241, 1663, 1544, 1497, 1456, 1384, 1231, 1039, 909, 822, 771, 732. ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm): 0.96 (3H, s), 1.22 (3H, s), 1.22 (6H, d, *J* = 6.9 Hz), 1.33−2.04 (8H, m), 2.30 (1H, m), 2.82 (1H, sep, *J* = 6.9 Hz), 2.78−2.91 (2H, m), 3.13 (1H, dd, 14.1, 6.9 Hz), 3.29 (1H, dd, *J* = 14.1, 6.9 Hz), 5.55 (1H, br), 6.90 (1H, brs), 7.00 (1H, dd, *J* = 8.1, 1.5 Hz), 7.16 (1H, d, *J* = 8.1 Hz), 8.19 (1H, d, *J* = 1.5 Hz).^{13}C NMR δ (125 MHz, $CDCl_3$) ppm: 18.8, 18.9, 19.1, 24.2, 25.4, 30.2, 33.6, 36.4, 37.5, 37.6, 38.5, 45.3, 48.5, 124.1, 124.3, 127.1, 134.9, 145.9, 147.3, 161.5. ESI-TOFMS *m*/*z* calcd. for $C_{21}H_{31}NNaO$ [M + Na]$^+$ 336.2298, found 336.2331.

(+)-(1*R*,4a*S*,10a*R*)-1-Isocyanomethyl-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (9). To a solution of **8** (26.8 mg, 85.0 mmol) in CH_2Cl_2 (1.0 mL) were added triphenylphospine (63.0 mg, 0.239 mmol), triethylamine (83.0 mL, 0.595 mmol) and carbon tetrabromide (85.0 mg, 0.255 mmol), and stirring was continued under argon at 0 °C for 10 min. The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane-ethyl acetate (1:1) gave **9** (23.3 mg, orange oil, 93%): $[\alpha]_D^{20}$ = +10.3 (*c* 1.02, $CHCl_3$). IR (ν_{max} (Nujol), cm^{-1}): 2143, 1497, 1456, 1387, 822. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 0.99 (3H, s), 1.23 (3H, s), 1.23 (6H, d, *J* = 6.9 Hz), 1.40−1.88 (8H, m), 2.32 (1H, dt, *J* = 12.9, 3.3 Hz), 2.83 (1H, sep, *J* = 6.9 Hz), 2.92 (2H, dd, *J* = 8.1, 4.8 Hz), 3.17 (1H, d, *J* = 14.7 Hz), 3.33 (1H, d, *J* = 14.7 Hz), 6.90 (1H, d, *J* = 1.2 Hz), 7.01 (1H. dd. *J* = 8.1, 1.2 Hz), 7.18 (1H, d, *J* = 8.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$; δ, ppm): 18.3, 18.7, 19.2, 24.2, 25.3, 30.2, 33.7, 36.1, 37.1, 37.7, 38.3, 45.2, 53.9, 124.2, 124.5, 127.0, 134.5, 146.0, 146.7, 157.1. ESI-TOFMS (*m*/*z*): calcd for $C_{21}H_{29}NNa$ [M + Na]$^+$ 318.2192, found 318.2211.

(+)-(4a*S*,10a*S*)-7-Isopropyl-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (10). To a solution of **9** (14.1 mg, 48.0 mmol) in toluene (1.0 mL) were added dicyclohexano-18-c-6-ether (35.0 mg, 95.0 mmol) and potassium (56.0 mg, 1.43 mmol), and stirring was continued under argon at room temperature for 80 min. The reaction mixture was quenched by the addition of isopropyl alcohol. After it was stirred for 2 h, the reaction mixture was poured into water and extracted with Et_2O. The organic layer was successively washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane gave **10** (11.1 mg, white crystal, 96%): $[\alpha]_D^{20}$ = +48.3 (*c* 1.00, $CHCl_3$). Mp: 34−35 °C. IR (ν_{max} (Nujol), cm^{-1}): 1497, 1457, 1374, 1038, 888, 821. ^{1}H NMR δ(300 MHz, $CDCl_3$) ppm: 0.93 (3H, s), 0.94 (3H, s), 1.18 (3H, s), 1.23 (6H, d, *J* = 6.9 Hz), 1.32−2.17 (8H, m), 2.27 (1H, m), 2.83 (1H, sep, *J* = 6.9 Hz), 2.78−2.97 (2H, m), 6.89 (1H, s), 6.99 (1H, d, *J* = 8.4 Hz). 7.18 (1H, d, *J* = 8.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$; δ, ppm): 19.3, 19.6, 21.8, 24.2 (2C), 25.1, 30.7, 33.6, 33.7, 37.7, 39.1, 41.9, 50.6, 124.0, 124.5, 127.0, 135.1, 145.6, 147.8. ESI-TOFMS (*m*/*z*): calcd for $C_{20}H_{30}Na$ [M + Na]$^+$ 293.2240, found 293.2264.

(+)-(4a*S*,10a*S*)-6-Acetyl-7-isopropyl-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (13). To a solution of **10** (406 mg, 1.50 mmol) and AcCl (373 mL, 5.25 mmol) in CH_2Cl_2 (7.5 mL) was added $AlCl_3$ (125 mg, 4.50 mmol) at 0 °C under argon. After it was stirred for 3 min at room temperature, the reaction mixture was poured into ice-cold 3 N HCl and extracted with Et_2O. The organic layer was successively washed with saturated aqueous $NaHCO_3$, water, and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (20/1) gave **13** (337 mg, white solid, 88%): $[\alpha]_D^{20}$ = +62.5 (*c* 1.01, $CHCl_3$). Mp: 95−98 °C. IR (ν_{max} (Nujol), cm^{-1}): 1683, 1557, 1457, 1353, 1262, 1218, 771. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 0.78 (3H, s), 0.80 (3H, s), 1.03 (3H, s), 1.04 (3H, d, *J* = 6.9 Hz), 1.97 (3H, d, *J* = 6.9 Hz), 1.10−1.79 (8H, m), 2.13 (1H, m), 2.40 (3H, s), 2.61−2.84 (2H, m), 3.33 (1H, sep, *J* = 6.9 Hz), 6.89 (1H, s), 7.11 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$; δ, ppm): 19.1, 19.4, 21.8, 24.3, 24.5, 25.1, 28.8, 30.6, 30.7, 33.5, 33.7, 37.7, 39.0, 41.8, 50.5, 124.7, 127.1, 136.4, 139.3, 144.9, 147.4, 203.6. ESI-TOFMS (*m*/*z*): calcd for $C_{22}H_{32}NaO$ [M + Na]$^+$ 335.2345, found 335.2332.

(+)-(4a*S*,10a*S*)-6-Acetoxy-7-isopropyl-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (14). **13** (63.8 mg, 0.204 mmol) and *m*-chloroperbenzoic acid (ca. 65%, 63.8 mg 1.22 mmol) were dissolved in CH_2Cl_2 (1.5 mL). At 0 °C, trifluorocetic acid (15.0 mL, 0.204 mmol) was added dropwise to the mixture. After it was stirred overnight at room temperature, the reaction mixture was diluted with CH_2Cl_2, poured into 5% aqueous Na_2SO_3, and extracted with CH_2Cl_2. The organic layer was successively washed with saturated aqueous $NaHCO_3$, water, and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (50/1) gave **14** (58.0 mg, yellow oil, 87%): $[\alpha]_D^{21}$ = +54.6 (*c* 0.96, $CHCl_3$). IR (ν_{max} (Nujol), cm^{-1}): 1760, 1496, 1457, 1366, 1205, 1164, 1015, 913, 772. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 0.92 (3H, s), 0.94 (3H, s), 1.16 (3H, d, *J* = 7.2 Hz), 1.18 (3H, s), 1.19 (3H, d, *J* = 7.2 Hz), 1.24−1.88 (8H, m), 2.16 (1H, m), 2.30 (3H, s), 2.76−2.94 (3H, m), 6.83 (1H, s), 6.94 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$; δ, ppm): 19.3, 19.4, 21.2, 21.8, 23.2, 23.3, 25.0, 27.3, 30.2, 33.5, 33.6, 37.8, 39.0, 41.9, 50.2, 118.1, 127.1, 133.3, 136.8, 146.3, 149.0, 170.2. ESI-TOFMS (*m*/*z*): calcd for $C_{22}H_{32}NaO_2$ [M + Na]$^+$ 351.2295, found 351.2274.

(+)-(4a*S*,10a*S*)-6-Hydroxy-7-isopropyl-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (15). To a solution of **14** (6.65 g, 20.2 mmol) in MeOH (70 mL) was added 4 N NaOH (150 mL), and stirring was continued at room temperature for 2 h. The reaction mixture was poured into 3 N HCl and extracted with Et_2O. The organic layer was successively washed with saturated aqueous $NaHCO_3$, water, and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed

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over silica gel. Elution with hexane/ethyl acetate (10/1) gave **15** (5.74 g, white amorphous, 99%): $[\alpha]_D^{22}$ = +55.7 (*c* 0.91, $CHCl_3$) (lit.[12a] $[\alpha]_D^{20}$ = +45.6 (*c* 2.5, $CHCl_3$)). IR (ν_{max} (Nujol), cm^{-1}): 3336, 1507, 1458, 1417, 1374, 1323, 1221, 1164, 1001, 908, 891, 771, 734. ^1H NMR (300 MHz, $CDCl_3$; *δ*, ppm): 0.93 (3H, s), 0.95 (3H, s), 1.18 (3H, s), 1.24 (3H, d, *J* = 6.9 Hz), 1.25 (3H, d, *J* = 6.9 Hz), 1.28−1.90 (8H, m), 2.16 (1H, m), 2.72−2.91 (2H, m), 3,12 (1H, sep, *J* = 6.9 Hz), 4.59 (1H, br), 6.64 (1H, s), 6.85 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$; *δ*, ppm): 19.4, 19.5, 21.8, 22.7, 23.0, 25.0, 27.0, 30.0, 33.5, 33.6, 37.7, 39.1, 41.9, 50.6, 111.2, 126.8, 127.5, 131.6, 148.9, 150.9. ESI-TOFMS (*m*/*z*): calcd for $C_{20}H_{30}NaO$ $[M + Na]^+$ 309.2189, found 309.2190.

(+)-(4a*S*,10a*S*)-7-Isopropyl-6-methoxy-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (19). To a solution of sodium hydride (530 mg, 12.2 mmol) in DMF (30 mL) was added a solution of **15** (2.32 g, 8.10 mmol) in DMF (30 mL) at 0 °C. After the mixture was stirred for 30 min, dimethyl sulfate (3.84 mL, 40.5 mmol) was added and stirring was continued for 10 min. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was successively washed with 3 N HCl, saturated aqueous $NaHCO_3$, water, and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (20/1) gave **19** (2.28 g, colorless oil, 94%): $[\alpha]_D^{22}$ = +61.9 (*c* 0.81, $CHCl_3$). IR (ν_{max} (Nujol), cm^{-1}): 1613, 1573, 1499, 1463, 1404, 1374, 1323, 1249, 1207, 1165, 1104, 969, 909, 892, 735. ^1H NMR (300 MHz, $CDCl_3$; *δ*, ppm): 0.95 (3H, s), 0.97 (3H, s), 1.22 (3H, s), 1.23 (6H, d, *J* = 6.6 Hz), 1.20−1.92 (8H, m), 2.28 (1H, m), 2.75−2.91 (2H, m), 3.25 (1H, sep, *J* = 6.6 Hz), 3.82, (3H, s), 6.75 (1H, s), 6.87 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$; *δ*, ppm): 19.4, 19.6, 21.8, 22.9, 23.1, 25.0, 26.6, 30.0, 33.6, 33.7, 38.1, 39.1, 41.9, 50.7, 55.8, 106.7, 126.6, 127.1, 134.3, 148.3, 155.2. ESI-TOFMS (*m*/*z*): calcd for $C_{21}H_{32}NaO$ $[M + Na]^+$ 323.2345, found 323.2326.

Methyl 2-[(4a*S*,8a*S*)-5,5,8a-Trimethyl-2-(3-methyl-2-oxobutylidene)-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-ylidene]-acetate (20). At−78 °C, a stream of ozone was bubbled through a solution of **19** (17.0 mg, 56.6 mmol) and $BF_3{\cdot}OEt_2$ (8.00 mL, 62.3 mmol) in CH_2Cl_2 (2.0 mL) for 15 min. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (7/1) gave **20** (7.2 mg, yellow oil, 38%, *E*/*Z* = 1.9/1). Two isomers were separated by preparative TLC for instrumental analyses. (*E*)-**20**: $[\alpha]_D^{21}$ = −43.8 (*c* 1.02, $CHCl_3$). IR (ν_{max} (Nujol), cm^{-1}): 1728, 1685, 1612, 1462, 1371, 1173, 1055, 487, 473, 454, 436, 415. ^1H NMR (300 MHz, C_6D_6; *δ*, ppm): 0.65 (6H, s), 0.82 (3H, s), 1.05 (6H, d, *J* = 7.2 Hz), 0.54−1.55 (9H, m), 1.99 (1H, ddt, *J* = 5.7, 1.8, 13.2 Hz), 2.35 (1H, sep, *J* = 7.2 Hz), 3.42 (3H, s), 4.40 (1H, m), 5.51 (1H, s), 5.97 (1H, d, *J* = 1.8 Hz). ^{13}C NMR (125 MHz, C_6D_6; *δ*, ppm): 18.5, 18.7, 19.7, 20.0, 22.3, 23.8, 31.2, 33.7, 34.5, 37.5, 42.5, 43.9, 51.3, 53.8, 111.5, 123.6, 155.9, 167.8, 168.0, 203.9. ESI-TOFMS (*m*/*z*): calcd for $C_{21}H_{32}NaO_3$ $[M + Na]^+$ 355.2244, found 355.2253: (*Z*)-**20**: $[\alpha]_D^{25}$ = +36.5 (*c* 1.11, $CHCl_3$). IR (ν_{max} (Nujol), cm^{-1}): 1727, 1644, 1612, 1458, 1389, 1178, 1048, 855, 668. ^1H NMR (300 MHz, C_6D_6; *δ*, ppm): 0.70 (3H, s), 0.71 (3H, s), 1.08 (3H, d, *J* = 7.2 Hz), 1.11 (3H, d, *J* = 7.2 Hz), 1.12 (3H, s), 0.84−1.58 (9H, m), 2.19−2.27 (2H, m), 2.47 (1H, sep, *J* = 7.2 Hz), 3.41 (3H, s), 5.72 (1H, s), 6.04 (1H, s). ^{13}C NMR (125 MHz, C_6D_6; *δ*, ppm): 17.8, 18.9, 19.7, 22.4, 25.2, 33.9, 34.8, 37.1, 40.2, 41.3, 42.7, 45.1, 51.0, 55.7, 110.8, 122.8, 153.3, 165.4, 167.0, 201.8. ESI-TOFMS (*m*/*z*): calcd for $C_{21}H_{32}NaO_3$ $[M + Na]^+$ 355.2244, found 355.2253.

(−)-(2*E*)-2-[(4a*S*,8a*S*)-5,5,8a-trimethyl-2-(3-methyl-2-oxobutylidene)-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-ylidene]-acetaldehyde (21). To a solution of **20** (19.6 mg, 59.0 mmol) in THF (0.5 mL) was added 1.03 M DIBAL in hexane (286 mL, 0.295 mmol) at −10 °C. After it was stirred for 5 min, the reaction mixture was quenched with MeOH and a saturated aqueous Rochelle's salt solution and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude product was used for the next step without purification. To a solution of the crude alcohol in CH_2Cl_2 (1.0 mL) were added Dess−Martin periodinane (75.0 mg, 0.177 mmol) and $NaHCO_3$ (25.0 mg, 0.295 mmol) at room temperature, and stirring was continued for 4 h. The reaction mixture was diluted with Et_2O, poured into 5% aqueous $Na_2S_2O_3$ solution, and extracted with Et_2O. The organic layer was washed with brine, dried over sodium sulfate, and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (10/1) gave (*E*)-**21** (6.7 mg, yellow oil, 38% in two steps): $[\alpha]_D^{19}$ = −87.4 (*c* 0.98, $CHCl_3$). IR (ν_{max} (Nujol), cm^{-1}): 1674, 1604, 1462, 1378, 1117, 1051, 861. ^1H NMR (300 MHz, C_6D_6; *δ*, ppm): 0.63 (3H, s), 0.67 (3H, s), 0.73 (3H, s), 0.92 (3H, d, *J* = 6.6 Hz), 0.93 (3H, d, *J* = 6.6 Hz), 0.69−1.50 (9H, m), 1.62 (1H, ddt, *J* = 6.0, 2.1, 13.8 Hz), 2.15 (1H, sep, *J* = 6.6 Hz), 4.16 (1H, ddd, *J* = 13.8, 4.2, 2.1 Hz), 5.73 (1H, d, *J* = 2.1 Hz), 5.77 (1H, d, *J* = 7.2 Hz), 9.85 (1H, d, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, C_6D_6; *δ*, ppm): 18.3, 18.5, 19.5, 20.2, 22.3, 23.4, 31.4, 33.6, 34.6, 37.2, 42.2, 42.3, 43.6, 53.0, 123.4, 127.3, 153.4, 174.3, 192.3, 203.3. ESI-TOFMS (*m*/*z*): calcd for $C_{20}H_{30}NaO_2$ $[M + Na]^+$ 325.2138, found 325.2129.

(−)-3-Methyl-1-[(3a*S*,5a*S*,9a*S*)-6,6,9a-trimethyl-4,5,5a,6,7,8,9,9a-octahydro-3a*H*-benzo[*e*]indol-3a-yl]butan-2-one (22). At room temperature, a stream of ammonia gas was bubbled through a solution of (*E*)-**21** (42.1 mg, 0.139 mmol) and AcOH (3.0 mL) in *t*-BuOH (5.0 mL) for 5 min, and stirring was continued for 2 h. The reaction mixture was concentrated in vacuo, and the residue was chromatographed over silica gel. Elution with ethyl acetate gave **22** (31.0 mg, yellow oil, 74%): $[\alpha]_D^{20}$ = −221 (*c* 1.02, $CHCl_3$). IR (ν_{max} (Nujol), cm^{-1}): 1709, 1604, 1517, 1465, 1381, 1235, 1138, 835, 455, 432, 413. ^1H NMR (300 MHz, C_6D_6; *δ*, ppm): 0.70 (3H, s), 0.77 (3H, s), 0.95 (3H, d, *J* = 6.9 Hz), 1.04 (3H, s), 1.08 (3H, d, *J* = 6.9 Hz), 0.49−1.65 (10H, m), 2.41 (1H, d, *J* = 13.2 Hz), 2.67 (1H, sep, *J* = 6.9 Hz), 2.79 (1H, dt, *J* = 12.6, 3.0 Hz), 2.99 (1H, d, *J* = 13.2 Hz), 5.61 (1H, s), 7.78 (1H, s). ^{13}C NMR (125 MHz, C_6D_6; *δ*, ppm): 18.0, 18.5, 18.6, 19.2, 19.9, 22.1, 34.2, 34.2, 38.3, 39.1, 40.4, 42.1, 42.6, 45.9, 58.1, 81.8, 117.3, 162.6, 183.1, 210.8. ESI-TOFMS (*m*/*z*): calcd for $C_{20}H_{31}NNaO$ $[M + Na]^+$ 324.2298, found 324.2308.

(−)-3-Hydroxy-3-methyl-1-[(3a*S*,5a*S*,9a*S*)-6,6,9a-trimethyl-4,5,5a,6,7,8,9,9a-octahydro-3a*H*-benzo[*e*]indol-3a-yl]butan-2-one (Chamobtusin A, 1). To a solution of **22** (43.2 mg, 0.143 mmol) in *t*-BuOH/DMF (1/2, 1.5 mL) were added triethyl phosphite (48.0 mL, 0.286 mmol) and *t*-BuOK (18.0 mg, 0.157 mmol) at 0 °C, and stirring was continued under oxygen for 1 h. The reaction mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with ethyl acetate gave **1** (24.0 mg, yellow crystal, 53%): $[\alpha]_D^{20}$ = −297 (*c* 0.22, CH_3OH). Mp: 139−144 °C. IR (ν_{max} (KBr), cm^{-1}): 3154, 2925, 1723, 1607, 1521, 1476, 1390, 1242, 1182, 1054, 969, 831, 707. ^1H NMR (500 MHz, CD_3OD; *δ*, ppm): 0.65−0.76 (2H, m), 0.89 (3H, s), 0.98 (3H, s), 1.16 (3H, s), 1.20 (3H, s), 1.21 (3H, s), 1.08−1.87 (8H, m), 2.62 (1H, dt, *J* = 13.0, 3.0 Hz), 3.39 (1H, d, *J* = 17.5 Hz), 3.53 (1H, d, *J* = 17.5 Hz), 6.10 (1H, s), 7.96 (1H, s). ^{13}C NMR (125 MHz, CD_3OD; *δ*, ppm): 17.5, 19.7, 20.5, 22.3, 26.9, 34.4, 35.0, 38.9, 41.6, 42.3, 42.7, 43.4, 59.8, 78.1, 80.9, 118.2, 165.9, 184.7, 213.7. ESI-TOFMS (*m*/*z*): calcd for $C_{20}H_{31}NNaO_2$ $[M + Na]^+$ 340.2247, found 340.2249.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02328.

^1H and ^{13}C NMR spectra of compounds **8**−**10**, **13**−**15**, **19**−**22**, and **1** (PDF)

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Notes

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