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The first total synthesis and determination of the absolute configuration of chapecoderin A, B and C

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Abstract—The *seco*- and rearranged-labdanes, chapecoderins A **1**, B **2**, and C **3** have been synthesized for the first time starting from (*S*)-(+)-Wieland-Miescher ketone analogue **11**. Their absolute configurations have been determined as depicted in the structures **1**, **2** and **3**.

1. Introduction

Brazilian plants are known to be a rich source of biologically active natural products. In their search for new pharmaceutical agents, Kobayashi and coworkers[1] isolated a new *seco*-labdane type diterpenoid, chapecoderin A **1**, and two new rearranged labdane type diterpenoids, chapecoderin B **2** and C **3** from the leaves of the Brazilian medicinal plant *Echinodorus macrophyllus* (Kunth) Micheli (Alismataceae) which have been used to treat difficulties in urination, hepatitis and rheumatism (Fig. 1). Chapecoderins B **2** and C **3** exhibit cytotoxicity against murine lymphoma L1210 cells with IC_{50} values of 7.2 and 6.0 μg/mL, respectively, while no significant bioactivity was observed in chapecoderin A **1**.

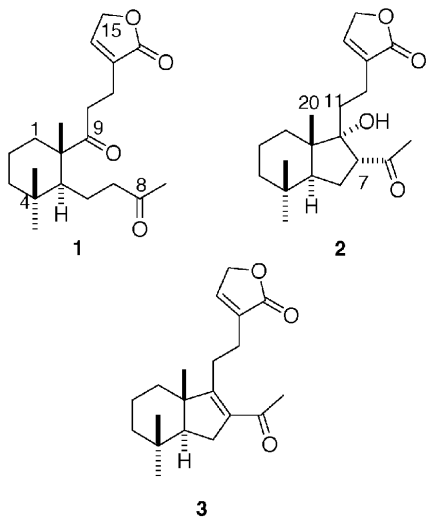

Figure 1.

Their structures were elucidated based on modern NMR techniques and relative stereochemistries were assigned by extensive NOESY correlations unambiguously by Kobayashi et al.[1] Chapecoderins A **1**, B **2** and C **3** possess a characteristic α,β-unsaturated butenolide moiety in the side chain in common. Biosynthetically, chapecoderin C **3** may be derived through dehydration of chapecoderin B **2** which in turn was formed from chapecoderin A **1** through intramolecular aldol condensation. However, their absolute stereochemistries are yet to be clarified. Potential bioactivity and new *seco*- and rearranged-labdane structures as well as our recent interests towards a synthetic study of *seco*-norsesquiterpenoids[2] **4** and **5** (Fig. 2) prompted us to investigate the total synthesis of chapecoderins A **1**,[3] B **2** and C **3**.

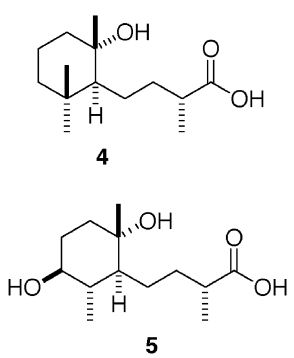

Figure 2.

Keywords: Total synthesis; Labdane diterpenoid; Absolute stereochemistry.
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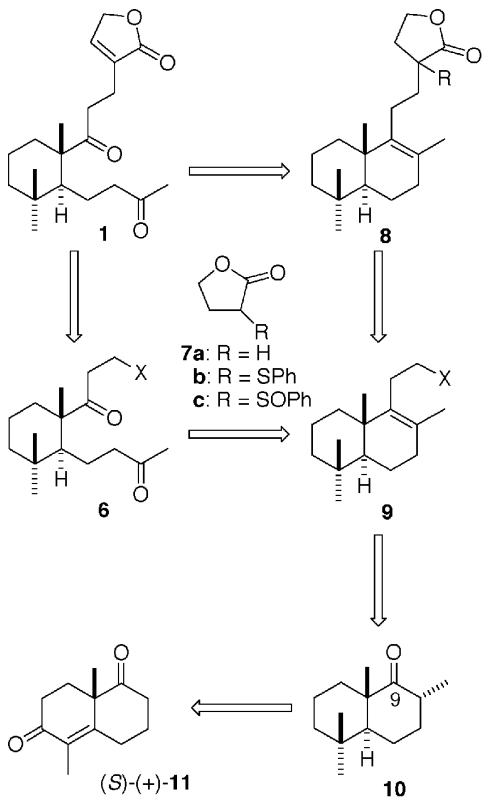


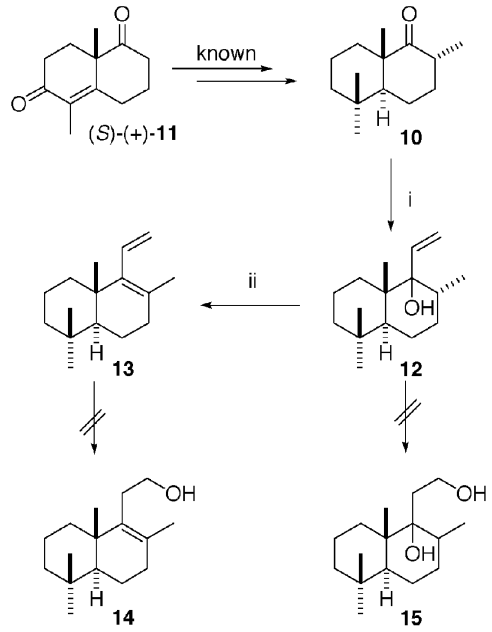
Scheme 1.

Our synthetic design is outlined in Scheme 1. Since enantioselective construction of a substituted cyclohexane ring is not facile due to its conformational flexibility, a route by cleavage of a properly substituted decaline framework was designed. The butenolide ring might be introduced by nucleophilic reaction of γ-butyrolactone derivatives **7** with electrophiles **6** which would be obtained by cleavage of tetrasubstituted olefin **9**. The olefin **9** in turn would be synthesized from the known decalone **10**[2b,4] which has been derived from optically pure Wieland-Miescher ketone analogue **11**.[5] One of the major issues of the present synthetic design is the timing of introduction of the butenolide ring and cleavage of the tetrasubstituted olefin. There are several plausible routes to install the butenolide moiety to the decaline framework by (1) alkylation of α-phenylthio-γ-butyrolactone **7b**, (2) aldol condensation of γ-butyrolactone **7a**, or (3) 1,4-conjugate addition of α-phenylsulfinyl-γ-butyrolactone **7c**.

2. Results and discussion

(*S*)-(+)-Wieland-Miescher ketone analogue **11** was employed as a starting material though there was no knowledge on the absolute stereochemistries of chapecoderins A **1**, B **2** and C **3** (Scheme 2). According to our previously reported procedure,[2b] (*S*)-(+)-Wieland-Miescher ketone analogue **11**[5] was transformed into the decalone **10**.

Initially, introduction of a two carbon unit at C-9 and subsequent manipulation were investigated. Addition of vinylmagnesium bromide to the ketone **10** gave in 90% yield a diastereomeric mixture of alcohol **12** (5.7:1) which



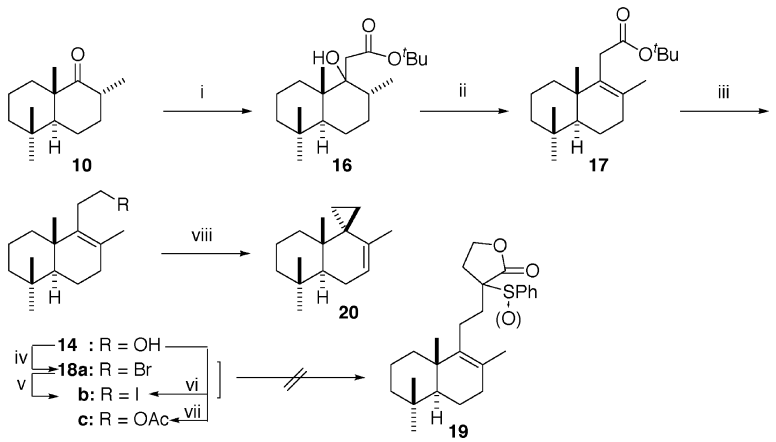
Scheme 2. Reagents, conditions and yields: (i) vinylmagnesium bromide, THF, room temperature, 90%; (ii) $SOCl_2$, DMAP, pyridine, 0 °C, 68%.

was dehydrated with thionyl chloride ($SOCl_2$) to diene **13**[4] in 68% yield. Attempts of selective hydroxylation of the terminal olefin of **12** or **13** resulted in recovery of the starting materials by using bulky reagents such as diisoamylborane or 9-borabicyclo[3.3.1]nonane, while hydroboration by borane-THF complex provided a small amount of the desired primary alcohol **14**.

As an alternative two-carbon addend, reaction of the enolate of *tert*-butyl acetate was investigated in the presence of HMPA to give ester **16** as a mixture of diastereomers (Scheme 3) in 89% yield. Subsequent dehydration by $SOCl_2$ gave unsaturated ester **17** in 97% yield. Reduction of the ester **17** with lithium aluminum hydride (LAH) provided primary alcohol **14** quantitatively. Bromination of the alcohol **14** with carbon tetrabromide and triphenylphosphine (PPh_3) gave in 94% yield bromide **18a** which was further elaborated into iodide **18b** in 96% yield. Since the substitution reaction of the bromide **18a** with sodium iodide required several repeated reactions for complete conversion into iodide **18b**, direct iodination of the alcohol **14** was investigated. Cerium chloride mediated iodination[6] provided the iodide **18b** in 70% yield. Interestingly, an attempt to prepare the more reactive trifluoromethanesulfonate derivative of the alcohol **14** afforded predominantly cyclopropane **20** in 98% yield even at −78 °C.

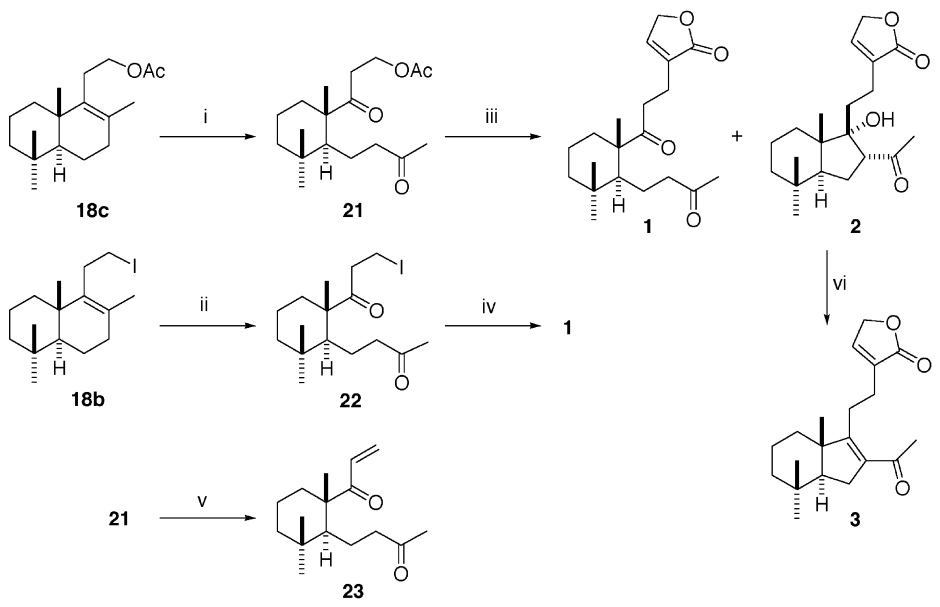
Then, substitution of α-phenylthio- or α-phenylsulfinyl-γ-butyrolactone **7b** or **7c** with the halide **18a** or **18b** were investigated,[7] which resulted in recovery of halides by various combinations of reagents, reaction conditions and substrates. Since the model experiment employing benzyl bromide was successful, the low reactivity of halide **18a** or **18b** might prevent the present reaction.

Although aldol reaction of the aldehyde derived from alcohol **14** with the enolate of lactone **7a** proceeded smoothly, subsequent transformations were unsatisfactory.



Scheme 3. Reagents, conditions and yields: (i) LDA, HMPA, CH_3CO_2t-Bu, −78 °C, 89%; (ii) $SOCl_2$, DMAP, pyridine, room temperature, 97%; (iii) LAH, Et_2O, room temperature, quant; (iv) CBr_4, PPh_3, $CHCl_3$, room temperature, 94%; (v) NaI, acetone, reflux, repeated 3 times, 96%; (vi) NaI, $CeCl_3{\cdot}7H_2O$, CH_3CN, 70%; (vii) acetic anhydride, DMAP, pyridine, room temperature, 88%; (viii) Tf_2O, pyridine, CH_2Cl_2, −78 °C, 98%.

To this end, the order and method of introduction of the butenolide moiety were exchanged (Scheme 4). Ozonolysis of the iodide **18b** provided diketone **22** in 41% yield. While the acetate **18c**, obtained by acetylation of the alcohol **14** in 88% yield (Scheme 3), was also cleaved by ozonolysis in 52% yield in dichloromethane (DCM). The yield was soon improved to 75% by carrying out the reaction in methanol at −20 °C in 0.01 M concentration. The higher yield in dilute solution may be due to preventative formation of polymeric peroxides during the bond reorganization from molozonide to ozonide. Such polymeric peroxides are difficult to decompose to carbonyl compounds. Methanol plays a role in stabilizing intermediates by adding to intermediary zwitter ions.[8] Treatment of the acetoxy diketone **21** and the α-phenylsulfinyl-γ-butyrolactone **7c** with DBU in benzene at room temperature followed by gradual warming to 60 °C furnished chapecoderin A **1** in 39% yield accompanied by 18% of chapecoderin B **2**. The reaction proceeded via three consecutive processes; β-elimination of acetic acid to vinylketone **23** followed by conjugate addition of the α-phenylsulfinyl-γ-lactone **7c** and subsequent elimination of phenylsulfinic acid to chapecoderin A **1**. No other stereoisomers of chapecoderin B **2** were found, which indicates intramolecular aldol condensation proceeded in the desired manner to afford the thermodynamically stable isomer. Vinylketone **23** was actually isolated by treatment of the acetoxy diketone **21** with DBU in 80% yield. The diketo-iodide **22** also provided chapecoderin A **1** in 19% yield by the treatment with α-phenylsulfinyl-γ-lactone **7c** in the presence of potassium carbonate and tetrabutylammonium iodide in DME. Base catalyzed intramolecular aldol condensation of chapecoderin A **1** was difficult due to the instability of the butenolide moiety. Dehydration of chapecoderin B **2** by $SOCl_2$ in the presence of DMAP in pyridine afforded chapecoderin C **3** in 52% yield. Alternatively, treatment of chapecoderin A **1** with pyrrolidine/benzoic acid provided chapecoderin C **3** in 24% yield.



Scheme 4. Reagents, conditons and yields: (i) O_3/O_2, CH_3OH, −20 °C, Me_2S, 75%; (ii) O_3/O_2, DCM, Me_2S, −78°C, 41%; (iii) **7c**, DBU, benzene, room temperature→60 °C, **1**, 39%, **2**, 18%; (iv) **7c**, K_2CO_3, n-Bu_4NI, DME, 0→98 °C, 19%; (v) DBU, benezene, 80%; (vi) $SOCl_2$, pyridine, DMAP, 52%.

Spectral data of the synthetic compounds were identical with those of natural chapecoderin A **1**, B **2** and C **3** kindly supplied by Professors Kobayashi and Shigemori. Since the values and signs of optical rotation of the synthetic compounds were the same as natural compounds, the absolute stereostructures of chapecoderins A **1**, B **2** and C **3** were unambiguously determined as depicted in the structures **1**, **2** and **3**.

Thus, we have completed the first total synthesis of chapecoderin A **1** in 23% overall yield in 8 steps from the known ketone **10**, as well as the total syntheses of chapecoderins B **2** and C **3**, thereby establishing absolute stereochemistries of these natural products.

3. Experimental

3.1. General

Mp was determined with a Yanaco MP hot-stage apparatus and is uncorrected. IR spectra were recorded on a Shimadzu FT/IR-4200 spectrophotometer in carbon tetrachloride unless otherwise indicated. ^{1}H NMR spectra were obtained for solutions in deuteriochloroform with Varian Gemini 200H (200 MHz) and Unity 500plus (500 MHz) instruments with tetramethylsilane as internal standard. *J*-values are in Hz. ^{13}C NMR spectra were obtained for solutions in deuteriochloroform with Varian Gemini 200H (50 MHz), JEOL EX-270 (67.5 MHz) and Unity 500plus (125 MHz) instruments. Mass spectral data were obtained with a JEOL GC-Mate spectrometer. Specific rotations were measured with a Horiba SEPA-200 spectrophotometer for solutions in methanol unless otherwise indicated.

3.1.1. (1*S*,2*RS*,3*R*,6*S*)-1,3,7,7-Tetramethyl-2-vinylbicyclo[4.4.0]decan-2-ol (12).[4] To a stirred solution of the decalone **10** (59 mg, 0.28 mmol) in THF (2.8 mL) was added a solution of vinylmagnesium bromide (590 μL, 0.98 M in THF, 0.56 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 90 min at room temperature, the reaction was quenched by addition of aq. ammonium chloride. Products were extracted with ethyl acetate four times. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:10) and subsequent MPLC (eluent: ethyl acetate–*n*-hexane=1:6) provided allyl alcohol **12** (major less polar diastereomer; 51 mg, 76%, minor more polar diastereomer, 9 mg, 13%) as a colorless oil.

More polar diastereomer had $[\alpha]_D^{20}$ −4.82 (*c* 0.39); IR 3625, 2944, 1736, 1460 cm^{-1}; ^{1}H NMR δ (200 MHz) 0.73 (d, 3H, *J*=6.6 Hz), 0.86 (s, 3H), 0.87 (s, 3H), 1.08 (s, 3H), 0.95–1.78 (m, 11H), 1.90 (m, 1H), 5.22 (dd, 1H, *J*=7.3, 1.9 Hz), 5.29 (m, 1H), 6.23 (dd, 1H, *J*=16.5, 11.7 Hz); ^{13}C NMR (67.5 MHz) δ 14.7, 15.9, 18.7, 21.8, 22.0, 31.9, 32.8, 33.4, 33.9, 35.9, 42.0, 42.4, 48.5, 80.8, 115.2, 138.3.

Less polar diastereomer had $[\alpha]_D^{20}$ −5.62 (*c* 1.10); IR 3617, 2946, 1709, 1462 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.72 (d, 3H, *J*=6.7 Hz), 0.84 (s, 3H), 0.88 (s, 3H), 0.98 (s, 3H), 1.10–1.80 (m, 11H), 1.90 (m, 1H), 5.12 (dd, 1H, *J*=4.7, 1.8 Hz), 5.19 (dd, 1H, *J*=2.9, 1.8 Hz), 5.83 (dd, 1H, *J*=17.9, 10.3 Hz); ^{13}C NMR (67.5 MHz) δ 16.2, 17.0, 18.6, 21.7, 22.1, 30.9, 32.4, 33.4, 33.8, 34.1, 41.6, 41.9, 45.5, 79.4, 113.7, 141.9. Anal. calcd for $C_{16}H_{28}O$: C, 81.3; H, 11.9. Found: C, 81.1; H, 11.9.

3.1.2. (1*S*,6*S*)-1,3,7,7-Tetramethyl-2-vinylbicyclo[4.4.0]-dec-2-ene (13).[4] To a stirred solution of the alcohol **12** (39 mg, 0.16 mmol) in pyridine (1.6 mL) was added 4-dimethylaminopyridine (DMAP) (6 mg, 0.049 mmol) and thionyl chloride ($SOCl_2$) (8 μL, 0.25 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 2.5 h, the reaction was quenched by addition of water. Product was extracted with ethyl acetate twice. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:20) gave diene **13** (28 mg, 68%) as a colorless oil; $[\alpha]_D^{20}$ +66.2 (*c* 1.02); IR 3079, 2944, 918 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.84 (s, 3H), 0.88 (s, 3H), 1.00 (s, 3H), 1.05–1.80 (m, 9H), 1.56 (s, 3H), 2.06 (m, 2H), 4.89 (dd, 1H, *J*=17.5, 2.8 Hz) 5.22 (dd, 1H, *J*=11.1, 2.8 Hz), 6.12 (dd, 1H, *J*=17.5, 11.1 Hz); ^{13}C NMR (67.5 MHz) δ 19.0, 19.1, 20.1, 21.2, 21.7, 33.3, 33.4, 33.6, 37.7, 38.2, 41.9, 51.3, 118.2, 126.7, 135.1, 141.9; exact mass calcd for $C_{16}H_{26}$, 218.2035, found 218.2032.

3.1.3. *tert*-Butyl 2-((1*S*,2*RS*,3*R*,6*S*)-2-hydroxy-1,3,7,7-tetramethylbicyclo[4.4.0]dec-2-yl)acetate (16). To a stirred solution of LDA prepared from diisopropylamine (305 μL, 2.3 mmol) and *n*-BuLi (1.4 mL, 2.3 mmol, 1.64 M in *n*-hexane) in THF (5 mL) at 0 °C was added a solution of *tert*-butyl acetate (338 μL, 2.5 mmol) in THF (0.5 mL) at −78 °C under nitrogen atmosphere. After being stirred for 20 min, a solution of HMPA (209 μL, 1.2 mmol) in THF (0.5 mL) was added and the resulting solution was stirred for 10 min. To the solution was added the decalone **10** (211 mg, 1.0 mmol) in THF (4 mL). After being stirred for 3 h, the reaction was quenched by addition of aq. ammonium chloride. Product was extracted with ethyl acetate three times and the combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:5) and subsequent MPLC purification (eluent: ethyl acetate–*n*-hexane=1:10) provided hydroxy-ester **16** as a mixture of diastereomers (293 mg, 89%) as a colorless oil.

More polar diastereomer had IR 3459, 2980, 2899, 1705, 1462, 1370, 1152 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.84 (s, 3H), 0.86 (s, 3H), 0.87 (s, 3H), 0.91 (d, 3H, *J*=3.2 Hz), 1.46 (s, 9H), 0.90–2.05 (m, 12H), 2.36 (d, 1H, *J*=16.1 Hz), 2.58 (d, 1H, *J*=16.1 Hz), 5.05 (s, 1H).

Less polar diastereomer had $[\alpha]_D^{20}$ +13.2 (*c* 1.00); IR 3459, 2980, 2870, 1705, 1462, 1370, 1154 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.81 (s, 3H), 0.82 (s, 3H), 0.84 (s, 3H), 0.88 (d, 3H, *J*=2.0 Hz), 1.45 (s, 9H), 0.80–1.80 (m, 12H), 2.21 (d, 1H, *J*=15.9 Hz), 2.49 (d, 1H, *J*=15.9 Hz), 4.89 (s, 1H); ^{13}C NMR (50 MHz) δ 15.9 (q), 16.7 (q), 18.8 (t), 21.6 (t), 21.9 (q), 27.9 (q), 31.2 (t), 32.5 (t), 33.1 (s), 33.6 (q), 36.7 (t), 41.4 (t), 43.1 (s), 44.7 (d), 77.0 (d), 81.5 (s), 174.9 (s).

Anal. calcd for $C_{20}H_{30}O_3$: C, 74.0; H, 11.2. Found: C, 74.3; H, 11.3.

3.1.4. *tert*-Butyl 2-((1*S*,6*S*)-1,3,7,7-tetramethylbicyclo[4.4.0]dec-2-en-2-yl)acetate (17). To a stirred solution of the hydroxy-ester **16** (293 mg) in pyridine (9 mL) was added DMAP (33 mg, 0.27 mmol) and $SOCl_2$ (198 μL, 2.7 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 3 h at room temperature, the reaction was quenched by addition of water. Product was extracted with ethyl acetate four times. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:5) and subsequent MPLC purification (eluent: ethyl acetate–*n*-hexane=1:10) afforded unsaturated ester **17** (269 mg, 97%) as a colorless oil; $[\alpha]_D^{20}$ +72.6 (*c* 1.00); IR 2967, 1734, 1368, 1150 cm^{-1}; ^1H NMR (200 MHz) δ 0.83 (s, 3H), 0.88 (s, 3H), 0.92 (s, 3H), 1.43 (s, 9H), 1.57 (s, 3H), 0.80–2.30 (m, 11H), 2.87 (d, 1H, *J*=16.1 Hz), 3.05 (d, 1H, *J*=16.1 Hz); ^{13}C NMR (125 MHz) δ 18.96 (t), 19.7 (q), 20.1 (q), 21.6 (q), 28.0 (q), 33.2 (q), 33.3 (s), 33.6 (t), 36.2 (t), 36.3 (t), 38.5 (t), 41.5 (t), 51.4 (d), 79.9 (s), 129.7 (s), 134.3 (s), 172.2 (s); MS (EI) *m/z* 306 (M^+, 12), 250 (78), 235 (64), 191 (86), 175 (30), 139 (28), 109 (37), 57 (100); exact mass calcd for $C_{20}H_{34}O_2$, 306.2559, found 306.2564.

3.1.5. 2-((1*S*,6*S*)-1,3,7,7-Tetramethylbicyclo[4.4.0]dec-2-en-2-yl)ethan-1-ol (14). To a stirred solution of the unsaturated ester **17** (26 mg, 0.083 mmol) in diethyl ether (1.0 mL) was added LAH (6 mg, 0.16 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 3 h at room temperature, the reaction was quenched by addition of wet diethyl ether. Organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography (eleunt: ethyl acetate–*n*-hexane=1:1) followed by MPLC purification (eluent: ethyl acetate–*n*-hexane=1:1) to give alcohol **14** (21 mg, quant.) as a colorless oil; $[\alpha]_D^{20}$ −41.81 (*c* 1.00); IR 3636, 2943, 1368, 1072 cm^{-1}; ^1H NMR (200 MHz) δ 0.83 (s, 3H), 0.88 (s, 3H), 0.95 (s, 3H), 1.60–2.10 (m, 11H), 1.61 (s, 3H), 2.30 (m, 2H), 3.60 (t, 2H, *J*=7.5 Hz); ^{13}C NMR (50 MHz) δ 18.95 (t),18.96 (t) 19.9 (q), 20.0 (q), 21.6 (q), 31.4 (q), 33.3 (q), 33.3 (s), 33.6 (t), 37.1 (t), 38.6 (s), 41.7 (t), 51.6 (d), 62.6 (t), 128.5 (s), 136.1 (s); exact mass calcd for $C_{16}H_{28}O$, 236.2140, found 236.2146.

3.1.6. (1*S*,6*S*)-2-(2-Bromoethyl)-1,3,7,7-tetramethylbicyclo[4.4.0]dec-2-ene (18a). To a stirred solution of the alcohol **14** (83 mg, 0.36 mmol) in chloroform (2.0 mL) was added triphenylphosphine (PPh_3) (189 mg, 0.72 mmol) and carbon tetrabromide (CBr_4) (239 mg, 0.72 mmol) and the solution was stirred for 11 h at room temperature under nitrogen atmosphere. Extra PPh_3 (95 mg, 0.36 mmol) and CBr_4 (120 mg, 0.36 mmol) were added and stirring was continued for 1 h. Evaporation of the solvent followed by column chromatography of the residue (eluent: ethyl acetate–*n*-hexane=1:20) and subsequent MPLC (eluent: ethyl acetate–*n*-hexane=1:20) provided bromide **18a** (102 mg, 94%) as a colorless oil; $[\alpha]_D^{20}$ +45.5 (*c* 0.91); IR 2930, 1389, 1206 cm^{-1}; ^1H NMR (200 MHz) δ 0.82 (s, 3H), 0.88 (s, 3H), 0.90 (s, 3H), 1.59 (s, 3H), 0.80–2.10 (m, 11H), 2.35–2.72 (m, 2H), 3.20–3.45 (m, 2H); MS (EI) *m/z* 298 (M^+, 6.6), 235 (59), 203 (87), 109 (77), 69 (98), 55 (100); exact mass calcd for $C_{16}H_{27}Br$ 298.1296, found 298.1295.

3.1.7. (1*S*,6*S*)-2-(2-Iodoethyl)-1,3,7,7-tetramethylbicyclo[4.4.0]dec-2-ene (18b). *Method 1*. To a stirred solution of the bromide **18a** (86 mg, 0.29 mmol) in acetone (2.8 mL) was added sodium iodide (65 mg, 0.43 mmol) and the solution was heated at reflux for 15 h. Evaporation of the solvent followed by column chromatography of the residue (eluent: ethyl acetate–*n*-hexane=1:20) gave almost a 1:1 inseparable mixture of the bromide **18a** and iodide **18b**. A solution of the residue and sodium iodide (86 mg, 0.57 mmol) in acetone (5 mL) was refluxed for 14 h. After evaporation of the solvent followed by column chromatography gave a 1:3 mixture of the bromide **18a** and the iodide **18b**. The same procedure was repeated once again to give the iodide **18b** (96 mg, 96%).

Method 2. To a stirred solution of the alcohol **14** (33 mg, 0.14 mmol) in acetonitrile (2.0 mL) was added sodium iodide (25 mg, 0.17 mmol) and cerium chloride heptahydrate (78 mg, 0.21 mmol) under nitrogen atmosphere and the resulting solution was heated at reflux temperature for 10 h. After being cooled to room temperature, the resulting slurry was diluted with ethyl acetate. After addition of 0.5 M HCl (1.5 mL), the organic layer was washed with aq. sodium hydrogen carbonate twice and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:1) and subsequent MPLC (eluent: ethyl acetate–*n*-hexane=1:20) provided the iodide **18b** (34 mg, 70%) as a colorless oil; $[\alpha]_D^{20}$ +10.8 (*c* 1.12); IR 2965, 1468, 1165 cm^{-1}; ^1H NMR (200 MHz) δ 0.83 (s, 3H), 0.88 (s, 3H), 0.92 (s, 3H), 1.56 (s, 3H), 0.80–2.10 (m, 11H), 2.40–2.70 (m, 2H), 2.97–3.14 (m, 2H); ^{13}C NMR (67.5 MHz) δ 5.3, 19.0, 19.1, 19.9, 20.1, 21.7, 22.7, 31.7, 33.3, 33.4, 33.7, 37.2, 38.7, 41.7, 51.8, 129.0, 140.9; MS (EI) *m/z* 346 (M^+, 27), 203 (99), 191 (98), 107 (100); exact mass calcd for $C_{16}H_{27}I$, 346.1158, found 346.1163.

3.1.8. (1*S*,6*S*)-1,3,7,7-Tetramethylspiro[bicyclo[4.4.0]-decane-2,1′-cyclopropane]-3-ene (20). To a stirred solution of the alcohol **14** (19.5 mg, 0.083 mmol) in anhydrous DCM (1.0 mL) was added anhydrous pyridine (20 μL, 0.25 mmol) and trifluoromethanesulfonic anhydride (208 μL, 0.12 mmol) at −78 °C under nitrogen atmosphere. After being stirred for 2 h at −78 °C, the reaction was quenched by addition of phosphate buffer (pH 7). Product was extracted with *n*-hexane and the organic layer was washed with water, aq. sodium hydrogen carbonate, water, and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography of the residue (eluent: *n*-hexane) provided cyclopropane **20** (18 mg, 98%) as a colorless oil; $[\alpha]_D^{20}$ −88.8 (*c* 1.08); IR 2965, 2849, 1549, 1335, 1389 cm^{-1}; ^1H NMR (200 MHz) δ 0.40–0.55 (m, 2H), 0.64–0.78 (m, 2H), 0.80–1.72 (m, 7H), 0.87 (s, 3H), 0.89 (s, 3H), 0.96 (s, 3H), 1.39 (m, 3H), 1.87–2.21 (m, 2H), 5.45 (m, 1H); ^{13}C NMR (50 MHz) δ 5.5 (t), 8.6 (t), 18.4 (t), 19.0 (q), 19.3 (q), 22.1 (q), 24.3 (t), 32.5 (q), 32.9 (t), 33.1 (s), 33.2 (s), 34.9 (s), 42.5 (t), 47.8 (d), 121.2 (d), 135.1 (s); MS (EI) *m/z* 218 (M^+, 13), 119 (68), 55 (48), 44 (100), 41 (82); exact mass calcd for $C_{16}H_{26}$, 218.2035, found 218.2029.

3.1.9. 4-[(1*S*,6*S*)-6-(3-Iodopropanoyl)-2,2,6-trimethylcyclohexyl]butan-2-one (22). To a stirred solution of the iodide **18b** (68 mg, 0.19 mmol) in DCM (3.0 mL) was passed O_3/O_2 at −78 °C for 2 h. After addition of dimethylsulfide (2.0 mL), the resulting solution was stirred for 1 h at −78 °C and allowed to stand overnight until ambient temperature. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:1) and subsequent MPLC (eluent: ethyl acetate–*n*-hexane=1:3) afforded *seco*-iodide **22** (29 mg, 41%) as a colorless oil; $[\alpha]_D^{20}$ +13.50 (*c* 0.51); IR 2932, 1717, 1462, 1356, 1327, 1267, 1165 cm^{-1}; ^1H NMR (200 MHz) δ 0.92 (s, 3H), 0.93 (s, 3H), 1.10–1.79 (m, 9H), 1.22 (s, 3H), 2.10 (s, 3H), 2.32–2.67 (m, 2H), 3.07–3.18 (m, 2H), 3.29 (t, 2H, *J*=6.4 Hz); ^{13}C NMR (67.5 MHz) δ−2.9, 17.1, 18.1, 22.4, 22.6, 30.1, 33.5, 34.4, 37.2, 41.2, 41.6, 45.8, 47.4, 52.9, 208.8, 213.8; MS (EI) *m/z* 378 (M^+, 3.8), 195 (31), 177 (100), 149 (38). exact mass calcd for $C_{16}H_{27}O_2I$, 378.1056, found 378.1060.

3.1.10. 2-((1*S*,6*S*)-1,3,7,7-Tetramethylbicyclo[4.4.0]dec-2-en-2-yl)ethyl acetate (18c). To a solution of the alcohol **14** (28 mg, 0.12 mmol) in dry pyridine (2.0 mL) was added DMAP (1.4 mg, 0.012 mmol) and acetic anhydride (35 μL, 0.35 mmol) under nitrogen atmosphere and the solution was stirred at room temperature for 1 h. The reaction was quenched by addition of water and product was extracted with ethyl acetate twice. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:1) and subsequent MPLC (eluent: ethyl acetate–*n*-hexane=1:2) gave acetate **18c** (29 mg, 88%) as a colorless oil; $[\alpha]_D^{20}$ +32.6 (*c* 1.02); IR 2965, 2940, 1742, 1237, 1030 cm^{-1}; ^1H NMR (200 MHz) δ 0.83 (s, 3H), 0.88 (s, 3H), 0.94 (s, 3H), 1.62 (s, 3H), 0.95–1.74 (m, 9H), 1.80–2.14 (m, 2H), 2.05 (s, 3H), 2.15–2.48 (m, 2H), 4.00 (t, 2H, *J*=7.9 Hz); ^{13}C NMR (50 MHz) δ 18.9 (t), 19.0 (t), 19.9 (q), 20.0 (q), 21.6 (q), 31.4 (t), 33.3 (q), 33.3 (s), 33.6 (t), 37.1 (t), 38.6 (s), 41.7 (t), 51.6 (d), 62.6 (t), 128.5 (s), 136.1 (s). Anal. calcd for $C_{18}H_{30}O_2$: C, 77.7; H, 10.9. Found: C, 77.5; H, 11.2.

3.1.11. 3-[(1′*S*,2′*S*)-1′,3′,3′-Trimethyl-2′-(3″-oxobutyl)-cyclohexyl]-3-oxopropyl acetate (21). To a solution of the acetate **18c** (26 mg, 0.095 mmol) in anhydrous methanol (10 mL) was passed into O_3/O_2 at −20 °C for 35 min. After flushing the solution with N_2, dimethylsulfide (2.0 mL) was added and the resulting solution was stirred at −20 °C for 2 h. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:2) and subsequent MPLC (eluent: ethyl acetate–*n*-hexane=7:8) afforded *seco*-acetate **21** (22 mg, 75%) as a colorless oil; $[\alpha]_D^{20}$ −56.7 (*c* 1.00); IR 2953, 2872, 1745, 1719, 1238 cm^{-1}; ^1H NMR (200 MHz) δ 0.92 (s, 3H), 0.93 (s, 3H), 1.22 (s, 3H), 1.28–1.75 (m, 9H), 2.02 (s, 3H), 2.10 (s, 3H), 2.46 (m, 2H), 2.82 (td, 2H, *J*=6.5, 4.1 Hz), 4.00 (t, 2H, *J*=7.9 Hz); ^{13}C NMR (50 MHz) δ 17.1 (q), 18.6 (t), 20.9 (q), 22.2 (t), 22.5 (q), 29.9 (q), 33.3 (q), 34.3 (s), 36.7 (t), 37.2 (t), 41.0 (t), 45.5 (t), 47.3 (d), 52.9 (s), 59.9 (t), 170.9 (s), 208.9 (s), 213.8 (s). Anal. calcd for $C_{18}H_{30}O_4$: C, 69.6; H, 9.7. Found: C, 69.6; H, 10.0.

3.1.12. Chapecoderin A (1). To a stirred solution of the acetate **21** (54 mg, 0.173 mmol) in benzene (1.7 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (31 μL, 0.208 mmol) and the solution was stirred for 1 h at room temperature under nitrogen atmosphere. To the solution were added γ-lactone **7c** (55 mg, 0.266 mmol) and DBU (39 μL, 0.260 mmol) and the resulting solution was stirred for 1 h. The solution was then heated at 60 °C for 2 h. The reaction was quenched by addition of 1 M HCl and extracted with ethyl acetate four times. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:2) and subsequent MPLC (eluent: ethyl acetate–*n*-hexane=2:1) furnished chapecoderin A (**1**) (23 mg, 39%) and chapecoderin B (**2**) (10 mg, 18%) as amorphous solids.

Chapecoderin A **1** had $[\alpha]_D^{23}$ +6.0 (*c* 0.86) {lit. $[\alpha]_D^{23}$+5.5 (*c* 0.86)}; IR 2934, 1765, 1717, 1699, 1072 cm^{-1}; ^1H NMR (500 MHz) δ 0.91 (s, 3H), 0.92 (s, 3H), 1.16–1.22 (m, 2H), 1.22 (s, 3H), 1.31–1.38 (m, 1H), 1.40–1.43 (m, 1H), 1.46–1.52 (m, 2H), 1.53–1.63 (m, 2H), 1.73 (t, 1H, *J*=4.9 Hz), 2.10 (s, 3H), 2.44 (t, 2H, *J*=8.2 Hz), 2.56 (td, 2H, *J*=7.0, 1.4 Hz), 2.76 (dt, *J*=18.2, 6.9 Hz), 2.87 (dt, *J*=18.2, 7.3 Hz), 4.76 (dd, 2H, *J*=2.0, 1.5 Hz), 7.17 (t, *J*=1.5 Hz); ^{13}C NMR (125 MHz) δ 17.1 (q), 18.1 (t), 20.2 (t), 22.2 (t), 22.5 (q), 29.8 (q), 33.4 (q), 34.3 (q), 34.9 (t), 37.1 (t), 41.1 (t), 45.5 (t), 47.6 (d), 53.5 (s), 70.1 (t), 132.9 (s), 145.7 (d), 174.1 (s), 208.9 (s), 215.2 (s).

Peaks at 30.0 (C-7) and 19.5 (C-20) ppm in original paper[1] were mistyped and should be corrected to 45.8 and 17.3 ppm, respectively, according to private communication from Professor Shigemori.

Chapecodeirn B (**2**) had $[\alpha]_D^{23}$ −11.9 (*c* 0.31) {lit. $[\alpha]_D^{23}$ −4.6 (*c* 0.38)}; ^1H NMR (500 MHz) δ 0.72 (s, 3H), 0.82 (s, 3H), 0.84 (s, 3H), 1.12 (m, 1H), 1.34 (m, 2H), 1.40 (m, 1H), 1.52 (m, 1H), 1.54 (m, 1H), 1.75 (m, 1H), 1.78 (m, 1H), 1.80 (s, 3H), 2.04 (dt, 1H, *J*=5.0, 12.4 Hz), 2.27 (dd, 1H, *J*=8.1, 12.7 Hz), 2.29 (m, 1H), 2.47 (td like), 2.56 (dd, 1H, *J*=5.0, 12.1 Hz), 3.77 (s, 2H), 5.90 (s, 1H); ^{13}C NMR (125 MHz) δ 16.1, 19.8, 21.0, 21.4, 27.1, 31.1, 31.2, 33.2, 33.6, 35.6, 41.5, 49.4, 51.4, 53.7, 69.4, 84.7, 134.4, 143.6, 173.8, 215.5. Inconsistency of value of optical rotations may arise from different purity of synthetic chapecoderin B (**2**).

3.1.13. Chapecoderin C (3). To a stirred solution of chapecoderin B (**2**) (21 mg, 0.06 mmol) and DMAP (2.3 mg, 0.018 mmol) in pyridine (0.6 mL) was added $SOCl_2$ (7 μL, 0.9 mmol) at 0 °C under nitrogen atmosphere and the resulting solution was stirred for 1.5 h at 0 °C. The reaction was quenched by addition of water and extracted with ethyl acetate twice. The combined organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by MPLC (eluent: ethyl acetate–*n*-hexane=2:1) furnished chapecoderin C (**3**) (10 mg, 52%) as an amorphous solid; $[\alpha]_D^{23}$ +11.6 (*c* 1.10) {lit. $[\alpha]_D^{23}$ +5.7 (*c* 1.10)}; ^1H NMR (500 MHz) δ 0.78 (s), 0.87 (s), 0.92 (s), 1.05 (td, *J*=13.1, 3.8 Hz), 1.24 (td, *J*=13.1, 3.8 Hz), 1.34 (dd, *J*=6.6, 11.7 Hz), 1.38 (td, *J*=3.8, 13.1 Hz), 1.48 (m), 1.57 (tq, *J*=3.8, 13.1 Hz), 1.70 (td, *J*=3.8,13.1 Hz), 1.94 (s), 2.10

(dd, J=6.6, 14.0 Hz), 2.15 (dd, J=11.7, 14.0 Hz), 2.36 (dt, J=4.2, 11.5 Hz), 2.50 (m), 2.67 (m), 2.93 (dt, J=5.2, 11.5 Hz), 3.86 (s), 6.37 (s); ^{13}C NMR (125 MHz) δ 16.8, 19.9, 21.4, 25.3, 25.7, 29.6, 30.8, 32.9, 33.0, 34.4, 41.6, 50.1, 57.6, 69.5, 133.9, 135.3, 144.3, 165.9, 173.6, 197.4.

3.1.14. 1-[(1′*S*,2′*S*)-1′,3′,3′-Trimethyl-2′-(3″-oxobutyl)-cyclohexyl]prop-2-en-1-one (23). A solution of diketo-acetate **21** (30 mg, 0.096 mmol) and DBU (22 μL, 0.145 mmol) in benzene (1 mL) was stirred at room temperature for 1 h under nitrogen atmosphere. The reaction was quenched by addition of 1 M HCl. Product was extracted with ethyl acetate four times. The combined organic layer was washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate–*n*-hexane=1:1) afforded vinyl-ketone **23** (19 mg, 80%) as a colorless oil which had IR 2938, 1721, 1690, 1609, 1399, 1356, 1161 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.94 (s, 6H), 1.20 (s, 3H), 1.15–1.8 (m, 9H), 2.06 (s, 3H), 2.23–2.58 (m, 2H), 5.67 (dd, 1H, J=10.3, 1.1 Hz), 6.34 (dd, 1H, J=16.9, 1.1 Hz), 6.91 (dd, 1H, J=16.9, 10.3 Hz); ^{13}C NMR (50 MHz) δ 17.0 (q), 18.0 (t), 21.9 (t), 22.5 (q), 29.8 (q), 33.2 (q), 34.4 (s), 35.8 (t), 41.1 (t), 44.9 (t), 47.3 (d), 51.5 (s), 128.5 (t), 131.4 (d), 205.0 (s), 208.9 (s).

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