Synthesis of both enantiomer of akolactone B and (+)-ancepsenolide

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Abstract: The syntheses of (+)- and (–)-akolactone B and (+)-ancepsenolide was accomplished using Pd-catalyzed carbonylation. As to the absolute configuration of akolactone B, making a comparison of the optical rotation of both enantiomers of synthetic akolactone B and the natural compound suggests that the absolute configuration at the 4-position of akolactone B is *R*.

Key words: lactones, stereoselective synthesis, natural product, absolute configuration, carbonylation

1. Introduction

The substructures of α,β-unsaturated butanolide are seen in bioactive natural products such as annonaceous acetogenins.[1] Akolactone B (**1**), an α,β–unsaturated butanolide derivative, has shown cytotoxicity toward human tumorial cell lines, has been isolated by Chen and co-workers from the stem bark of *Litsea akoensis* in 1998.[2] The isolated material was determined to be α,β-unsaturated-γ-lactone, connected with a *trans*-olefinic group at the C-2 position and conjugated *trans*-diene at terminal one. However, its stereochemistry at the C-4 chiral center has not been determined yet. Synthesis of **1** has not been reported either. (+)-Ancepsenolide (**2**) was isolated from *Pterogorgia anceps*,[3] *P. citrina*,[4] and *P. guadalupensis*,[5] respectively. Several syntheses of (+)-ancepsenolide (**2**) have been reported.[6] Iriye and co-worker reported the synthesis of **2** using (*S*)-(−)-2-[(*R*)-*O*-MEM-mandeloyloxy]propanal.[6a] In this synthesis, the yield of each transformation was not good. Recently Baati and co-workers reported the synthesis of **2** using a-substituted butenolide as a key intermediate.[6b] This synthesis suffered from the low yield of palladium-catalyzed reduction of enol triflate. In the previous report, we described the synthesis of both enantiomers of akolactone A and the determination of its absolute configuration at C-4

position.[7] Herein we wish to report the total synthesis of both enantiomer of akolactone B (**1**) and (+)-ancepsenolide (**2**) using Pd-catalyzed carbonylation and spontaneous lactonization. We also wish to describe determination of the absolute configuration of natural akolactone B (Figure 1).

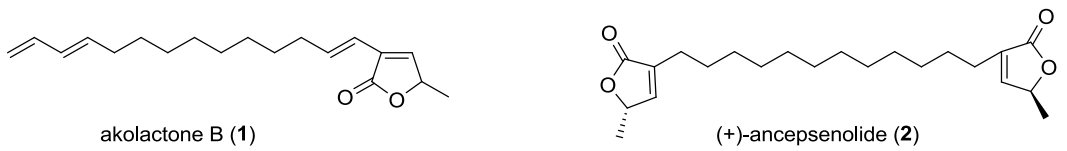
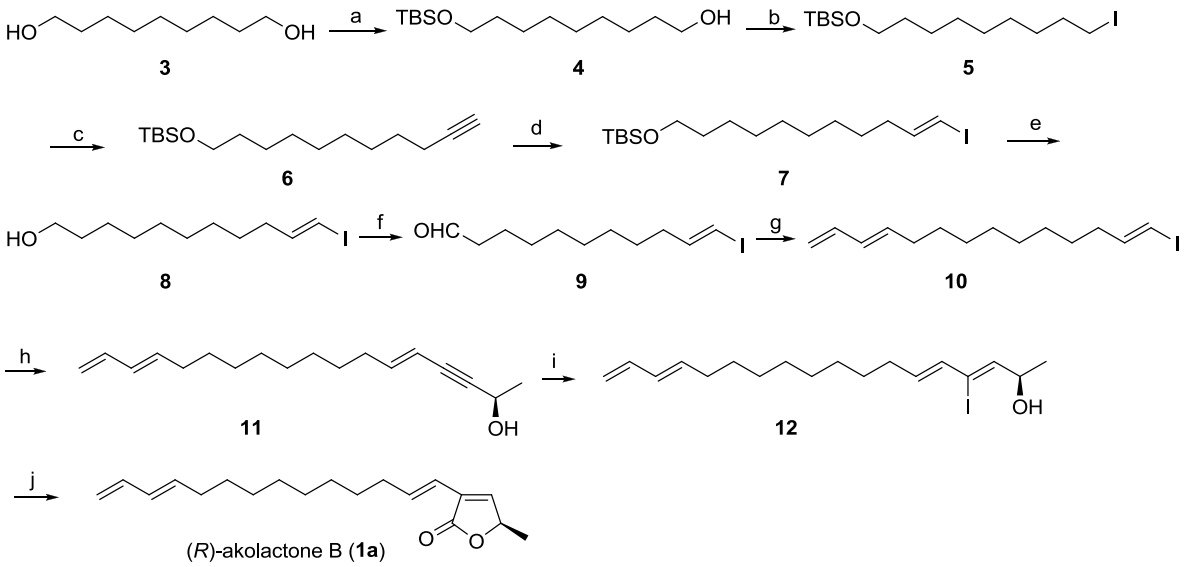


Figure 1. The structures of akolactone B (**1**) and (+)-ancepsenolide (**2**).

2. Results and Discussion

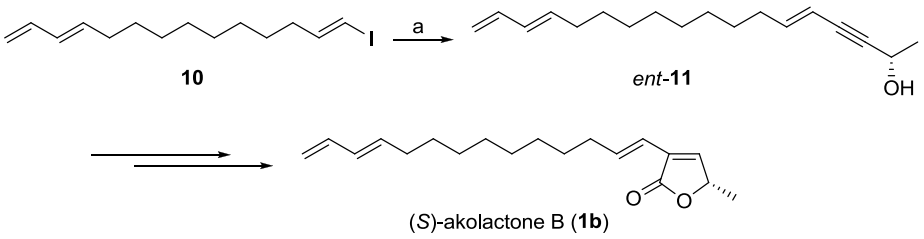
The synthetic method used for both enantiomers of akolactone B is shown in Scheme 1. We chose 1,9-nonanediol (**3**) as a starting material. 9-*tert*-Butylsilyloxynonan-1-ol (**4**) was prepared by protecting one of the hydroxy groups of 1,9-nonanediol (**3**) with *tert*-butyldimethylsilyl chloride in the presence of imidazole.[8] Transformation of compound **4** to **7** was performed as described below according to the procedure reported by Hegedus and co-workers except that hydrozirconated product was treated with iodine instead of NIS which is rather expensive reagent.[9] Mesylation followed by iodination of hydroxy group of **3** using NaI in the presence of sodium bicarbonate gave iodide **5**.[10] Alkynylation of **5** with lithium acetylide ethylenediamine complex furnished terminal alkyne **6**. Hydrozirconation using Schwarz reagent followed by treatment with iodine afforded vinyl iodide **7**.[11] Deprotection of the TBS group of **7** with TBAF afforded primary alcohol **8**. Alcohol **8** was also synthesized by Suginome and co-workers using 11-hydroxy-1-uncenyl boronic acid as a key intermediate.[12] The yield of this synthesis (38% in 5 steps) was little bit higher than ours (34% in 5 steps), however, the experimental procedure of our synthesis was simpler than that of the reported synthesis. Oxidation of the primary alcohol **8** with SO_3 · pyridine and DMSO afforded aldehyde **9**. Horner-Wadsworth-Emmons reaction using diethyl allylphosphonate gave **10**. The Sonogashira cross-coupling reaction of **10** with (*R*)-(+)-3-butyn-2-ol using pyrrolidine as a base furnished **11**.[13] Regioselective hydroalumination of **11** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®) and successive treatment with EtOAc and iodine gave vinyl iodide **12**. Pd-catalyzed carbonylation and spontaneous lactonization of **12** with 1 atmosphere of CO in the presence of 5 mol% of $Cl_2Pd(PPh_3)_2$, K_2CO_3 and Et_3N in the presence of hydrazine at 40 °C afforded (*R*)-(−)-akolactone B (**1a**) in a 63% yield.[14] The ^{1}H- and ^{13}C-NMR, and IR spectra of synthetic **1a** were in good agreement with the reported values.[2] The optical rotation of synthetic **1a** ($[\alpha]^{18}_D$ = −38.1, *c* 1.10, $CHCl_3$) is larger than those of the reported value for naturally occurring akolactone B {$[\alpha]^{27}_D$ = −10.0, (*c* 0.10, $CHCl_3$)}. Taking into account that optical rotation of natural product was measured in low concentration, the difference may be due to experimental error or contamination of impurity (Scheme 1).[2] We also synthesized (*S*)-(+)-akolactone B (**1b**) using (*S*)-(−)-3-

butyn-2-ol (Scheme 2). The optical rotation of **1b** was +35.8 (*c* 0.500, $CHCl_3$). On the basis of these results, we assigned the absolute configuration of natural akolactone B at the C-4 position to be *R*.



Scheme 1. Synthesis of (*R*)-akolactone B (**1a**).

Regents and conditions: (a) TBSCl, imidazole, CH_2Cl_2, 58%; (b) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C; (ii) NaI, $NaHCO_3$, acetone, 93%; (c) lithium acetylide ethylenediamine complex, DMSO, 83%; (d) Cp_2ZrHCl, THF, 81%; (e) TBAF, THF, 94%; (f) SO_3 pyridine, DMSO, 84%; (g) diethyl allylphosphonate, *n*-BuLi, THF-HMPA, 46%; (h) (*R*)-3-bytyn-2-ol, $Cl_2Pd(PPh_3)_2$, CuI, pyrrolidine, 79%; (i) (i) Red-Al®, THF; (ii) EtOAc, (iii) I_2, THF, 75%; (j) $Cl_2Pd(PPh_3)_2$, CO, K_2CO_3, Et_3N, NH_2NH_2, THF, 40 °C, 63%.

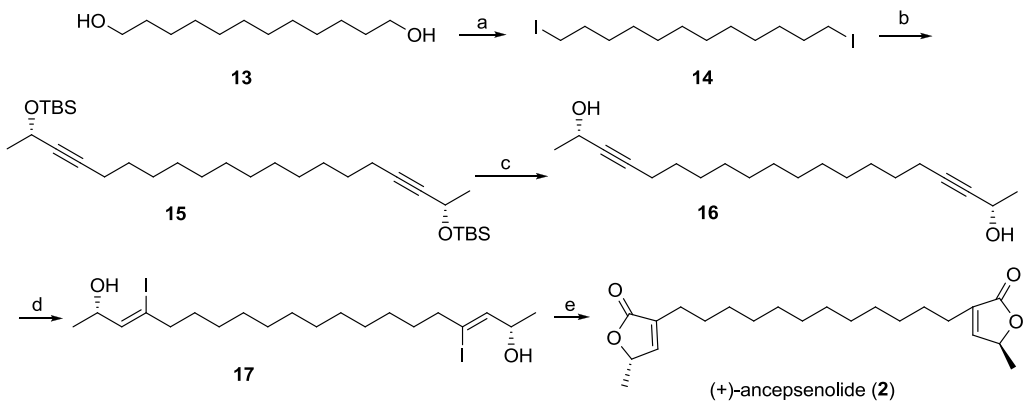


Scheme 2. Synthesis of (*S*)-akolactone B (**1b**).

Regents and conditions: (a) (*S*)-3-bytyn-2-ol, $Cl_2Pd(PPh_3)_2$, CuI, pyrrolidine, 86%

As to the synthesis of (+)-ancepsenolide, we selected 1,12-dodecanediol (**13**) as a starting material. Mesylation followed by iodination of both of the hydroxy groups of **13** using NaI gave diiodide **14**. Diiodide **14** was also prepared by Ainscow and co-workers from cyclododecanone through 5 steps.[15] Our synthetic procedure was much more efficient than that of the reported. Alkynylation of **14** with TBS protected (*S*)-(−)-3-butyn-2-ol afforded alkyne **15**. Removal of the TBS group of **15** with TBAF followed by regioselective hydroalumination using Red-Al® and successive treatment with EtOAc and iodine gave vinyl iodide **17**. Pd-catalyzed carbonylation and spontaneous lactonization of **17** with 1 atmosphere of CO in the presence of 5 mol% of $Cl_2Pd(PPh_3)_2$, K_2CO_3

and Et_3N in the presence of hydrazine at 40 °C afforded (+)-ancepsenolide (**2**) in 79% yield.[14] The ^1H- and ^{13}C-NMR, IR spectra and physicochemical data of synthetic **2** were in good agreement with those of the reported values (Scheme 3).[6]



Scheme 3. Synthesis of (+)-ancepsenolide (**2**).

Regents and conditions: (a) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C;; (ii) NaI, acetone, 84%; (b) (*S*)-3-(*tert*-butuldimethylsilyloxy)but-1-yn, *n*-BuLi, THF-HMPA, 94%; (c) TBAF, THF, 61%; (d) (i) Red-Al®, THF; (ii) EtOAc, (iii) I_2, THF, 86%; (e) $Cl_2Pd(PPh_3)_2$, CO, K_2CO_3, Et_3N, NH_2NH_2, THF, 40 °C 79%.

3. Conclusion

In conclusion, we accomplished the syntheses of both enantiomer of akolactone B and (+)-ancepsenolide using Pd-catalyzed carbonylation and lactonization. A comparison of the optical rotation of both enantiomers of akolactone B and the natural compound suggests that the absolute configuration at the 4-position of akolactone B is *R*.

4. Experimental

4.1. General. All melting points were uncorrected. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX 500 FT-NMR spectrometer in $CDCl_3$ at 500 and 125 MHz, respectively. Chemical shifts were relative to tetramethylsilane as an internal standard. The coupling constants were given in Hz. Mass spectra were obtained on JEOL JMS-HX211A and JMS-HX110A mass spectrometer. IR spectra were recorded with JASCO FT-IR 480 Plus infrared spectrometer. Optical rotations were determined with a JASCO DIP-1000 polarimeter.

4.1.1. 9-*tert*-Butyldimethylsilyloxynonan-1-ol (4). To a solution of 1,9-nonanediol (0.50 g, 3.12 mmol) in CH_2Cl_2 (15 mL) were added imidazole (212 mg, 3.12 mmol) and TBSCl (470 mg, 3.12 mmol). After the reaction

had been stirred for 30 min, the reaction was quenched with water and the mixture was extracted with ethyl acetate. The organic layer was successively washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (hexane:AcOEt = 5:1) to give **4** (1.00 g, 58%) as a colorless oil. The spectral data of **4** were identical with those of the reported values.[8]

4.1.2. 9-(*tert*-Butyldimethylsilyloxy)-1-iodononane (5). To a solution of **4** (4.68 g, 17.1 mmol) and Et_3N (4.75 mL, 34.1 mmol) in CH_2Cl_2 (35 mL) was added MsCl (1.72 mL, 22.2 mmol) at 0 °C. The reaction mixture was stirred for 30 min at this temperature. After the reaction had been completed, the mixture was extracted with ether. The organic solution was successively washed with saturated aqueous NH_4Cl, water, and brine, dried over $MgSO_4$, and concentrated. The crude product was dissolved in acetone (20 mL) and NaI (4.30 g, 51.3 mmol) and $NaHCO_3$ (4.30 g, 51.3 mmol) was added to this solution. After being stirred for 16 h, the reaction was quenched with water. The organic materials were extracted with ether and organic layer was successively washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (hexane:AcOEt = 20:1) to give **5** (6.14 g, 93%) as a pale yellow oil. The spectral data of **5** were identical with those of the reported values.[10]

4.1.3. 11-(*tert*-Butyldimethylsilyloxy)undec-1-yne (6). To a suspension of lithium acetylide ethylenediamine complex (1.12 g, 10.9 mmol) in DMSO (18 mL) was added **5** (3.50 g, 9.10 mmol) at 0° C. After stirring for 1h, the mixture was diluted with ether and the reaction was quenched with saturated aqueous NH_4Cl. The organic layer was successively washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (hexane:AcOEt = 20:1) to give **6** (2.13 g, 83%) as a colorless oil. The spectral data of **6** were identical with those of the reported values.[9]

4.1.4. (*E*)-11-(*tert*-Butyldimethylsilyloxy)-1-iodoundec-1-ene (7). To a solution of **6** (3.10 g, 11.1 mmol) in THF (55 mL) was added Cp_2ZrHCl (3.60 g, 13.3 mmol). After stirring for 3h, I_2 (5.60 g, 22 mmol) in THF (10 mL) was added to the mixture at 0°C and the resulting mixture was stirred for 30 min at room temperature. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ and the mixture was filtered through Celite and the solvent was concentrated. The residue was purified with silica gel column chromatography (hexane:AcOEt = 20:1) to afford **7** (3.70 g, 81%) along with **8** (14%). The spectral data of **7** were identical with those of the reported values.[9]

4.1.5. (*E*)-11-Iodoundec-10-en-1-ol (8). To a solution of **7** (581 mg, 1.41 mmol) in THF (14. mL) was added TBAF (1.0 mol/L solution in THF, 1.41 mL, 1.41 mmol) at 0 °C. The reaction mixture was stirred for 17 h at room temperature. The mixture was extracted with ether. The organic layer was successively washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (hexane:AcOEt = 5:1) to give **8** (394 mg, 94%) as a pale yellow oil. The spectral data of **8** were identical with those of the reported values.[12]

4.1.6. (*E*)-11-Iodoundec-10-enal (9). To a solution of **8** (395 mg, 1.33 mmol) in CH_2Cl_2 (1.6 mL) and DMSO (0.9 mL) were added Et_3N (0.9 mL, 6.65 mmol) and sulfer trioxide pyridine complex (423 mg, 2.66 mmol). After stirring for 1.5 h, the reaction was quenched with water and the organic materials were extracted with ethyl acetate. The organic layer was washed with saturated aqueous NH_4Cl, brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (hexane:EtOAc = 20:1) to give **9** (330 mg, 84%) as a pale yellow oil. This compound was immediately used for the next step. ^{1}H-NMR ($CDCl_3$) δ:1.25-1.40 (10H, m), 1.62 (2H, m), 2.05 (2H, td, *J* = 7.0, 1.0 Hz), 2.42 (2H, t, *J* = 7.0 Hz), 5.97 (1H, dd, *J* = 15.0, 1.0 Hz), 6.50 (1H, dt, *J* = 15.0, 7.0 Hz), 9.76 (1H, s).

4.1.7. (3*E*,13*E*)-14-Iodotetradeca-1,3,13-triene (10). To a solution of diethyl allylphosphonoacetate (0.23 mL, 1.34 mmol) in THF (22 mL) at −78 °C was added *n*-BuLi (1.6 mol/L solution in hexane, 0.83 mL, 1.34 mmol). After stirring for 15 min at this temperature, **9** (330 mg, 1.12 mmol) in THF-HMPA (1:1, 4 mL) was added dropwise. The mixture was stirred for 1.5 h at −70 °C. After the reaction had been completed, the mixture was extracted with ether. The organic layer was washed with saturated aqueous NH_4Cl, brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (hexane) to give **10** (163 mg, 46%) as a pale yellow oil. IR (film) ν_{max}cm^{-1}: 3006, 2925, 2852, 1652, 1604, 1457, 1436, 1002, 947, 897. ^{1}H-NMR ($CDCl_3$) δ:1.25-1.40 (12H, m), 2.00-2.10 (4H, m), 4.95 (1H, d, *J* = 10.5 Hz), 5.08 (1H, d, *J* = 15.5 Hz), 5.70 (1H, dt, *J* = 15.0, 7.0 Hz), 5.97 (1H, d, *J* = 14.0 Hz), 6.05 (1H, dd, *J* = 15.5 Hz, 7.0 Hz), 6.31 (1H, dt, *J* = 17.0, 10.5 Hz), 6.50 (1H, dt, *J* = 14.0, 7.0 Hz); ^{13}C-NMR ($CDCl_3$) δ: 28.33, 28.89, 29.14, 29.27, 29.35, 32.53, 36.04, 74.29, 114.61, 130.85, 135.57, 137.34, 146.79. HREIMS: calcd. for $C_{14}H_{23}I$, 318.0845; found, 318.0850.

4.1.8. (2*R*,5*E*,17*E*)-Octadeca-5,15,17-trien-3-yn-2-ol (11). To a solution of **10** (130 mg, 0.41 mmol) in pyrrolidine (1.2 mL) were added (*R*)-3-butyn-1-ol (0.03 mL, 0.41 mmol), $Cl_2Pd(PPh_3)_2$ (13 mg, 0.018 mmol), and CuI (7 mg, 0.037 mmol) and the resultant mixture was stirred for 15 h. After the reaction had been completed, the mixture was extracted with ether. The organic layer was washed with saturated aqueous NH_4Cl, brine, dried

over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (hexane:AcOEt = 5:1) to give **11** (77 mg, 79%) as a pale yellow oil. $[\alpha]^{19}_D$ +15.9 (*c* 1.23, $CHCl_3$), IR (film) $\nu_{max}cm^{-1}$: 3322, 2925, 2853, 1653, 1456, 1172, 1078, 1003, 954, 896. ^{1}H-NMR ($CDCl_3$) δ:1.25-1.60 (12H, m), 1.46 (3H, d, *J* = 6.5 Hz), 1.79 (1H, brs, -OH), 2.05-2.12 (4H, m), 4.63 (1H, m), 4.95 (1H, d, *J* = 10.5 Hz), 5.08 (1H, d, *J* = 16.0 Hz), 5.49 (1H, dd, *J* = 16.0, 1.8 Hz), 5.72 (1H, dt, *J* = 15.0, 7.0 Hz), 6.03 (1H, dd, *J* = 15.0, 10.5 Hz), 6.14 (1H, dt, *J* = 16.0, 7.0 Hz), 6.31 (1H, dt, *J* = 17.0, 10.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 24.41, 28.63, 29.04, 29.14, 29.33, 29.37, 32.52, 33.04, 58.84, 82.86, 89.32, 108.72, 114.60, 130.84, 135.59, 137.34, 145.55. HREIMS: calcd. for $C_{18}H_{28}O$, 260.2140; found, 260.2143.

4.1.9. (2*R*,3*Z*,5*E*,15*E*)-4-Iodooctadeca-3,5,15,17-tetraen-2-ol (12). To a solution of **11** (117 mg, 0.45 mmol) in THF (1.5 mL) was added sodium bis(2-methoxyethoxy) aluminum hydride (0.2 mL, 65% in toluene, 0.7 mmol) was added at 0 °C. The reaction mixture was stirred for 1 h at rt, before ethyl acetate (0.13 mL, 1.4 mmol) was added. After the mixture had been cooled at −78 °C, a solution of iodine (345 mg, 1.4 mmol) in THF (2 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature, the reaction was quenched with a saturated aqueous $Na_2S_2O_3$. The mixture was extracted with ether. The organic layer was successively washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by preparative TLC (hexane:AcOEt = 5:1) to give **12** (131 mg, 75%) as a pale yellow oil. $[\alpha]^{19}_D$ +8.60 (*c* 1.69, $CHCl_3$), IR (film) $\nu_{max}cm^{-1}$: 3331, 2971, 2925, 2852, 1651, 1602, 1125, 1058, 1002, 948, 896. ^{1}H-NMR ($CDCl_3$) δ: 1.20-1.45 (12H, m), 1.38 (3H, d, *J* = 7.5 Hz), 1.92 (1H, brs), 2.05-2.10 (2H, m), 2.16-2.22 (2H, m), 4.67-4.70 (1H, m), 4.95 (1H, d, *J* = 10.5 Hz), 5.08 (1H, d, *J* = 17.0 Hz), 5.67-5.73 (2H, m), 5.83 (1H, d, *J* = 7.5 Hz), 5.99-6.07 (2H, m), 6.31 (1H, dt, *J* = 17.0, 7.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 22.00, 29.13, 29.16, 29.38, 31.93, 32.52, 72.37, 105.95, 114.58, 130.82, 131.10, 135.57, 137.32, 140.23, 140.53. HREIMS: calcd. for $C_{18}H_{29}IO$, 388.1263; found, 388.1265.

4.1.10. (*R*)-(−)-Akolactone B (1a). To a solution of **12** (50 mg, 0.13 mmol) in THF were added K_2CO_3 (36 mg, 0.26 mmol), NH_2NH_2 (10 mg), and Et_3N (0.02 mL, 0.13 mmol) under CO atmosphere. The mixture was stirred for 16 h at 40 °C. After cooling, the mixture was filtered through Celite and the solvent was concentrated. The residue was purified with preparative TLC (hexane:AcOEt = 5:1) to afford **1a** (23 mg, 63%) as a pale yellow oil. $[\alpha]^{18}_D$ −38.1 (*c* 1.10, $CHCl_3$), {natural akolactone B, $[\alpha]^{27}_D$ = −10.0, (*c* 0.10, $CHCl_3$)}.[2a] IR (film) $\nu_{max}cm^{-1}$: 3030, 2925, 2853, 1755, 1318, 1082, 1003. ^{1}H-NMR ($CDCl_3$) δ: 1.20-1.50 (12H, m), 1.43 (3H, d, *J* = 6.5 Hz), 2.05-2.08 (2H, m), 2.13-2.18 (2H, m), 4.95 (1H, d, *J* = 10.0 Hz), 5.02 (1H, qd, *J* = 6.5, 1.5 Hz), 5.08 (1H, d, *J* = 17.0 Hz), 5.71 (1H, dt, *J* = 15.0, 7.5 Hz), 6.00-6.05 (1H, m), 6.09 (1H, d, *J* = 16.0 Hz), 6.31 (1H, dt, *J* = 17.0, 10.0 Hz), 6.79 (1H, dt, *J* = 16.0, 7.0 Hz), 7.03 (1H, d, *J* = 1.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 19.18, 28.74, 29.14, 29.16, 29.20, 29.38 (2×C), 32.53, 33.41, 76.91, 114.58, 118.28, 129.41, 130.82, 135.62, 137.35, 138.84, 146.83, 172.06. HREIMS: calcd. for $C_{19}H_{28}O_2$, 288.2089; found, 288.2086.

4.1.11. (*S*)-(+)-Akolactone B (1b). $[\alpha]^{19}_{D}$ +35.8 (*c* 0.500, $CHCl_3$). The ^{1}H- and ^{13}C-NMR, and IR spectra were identical with those of **1a**. HREIMS: calcd. for $C_{19}H_{28}O_2$, 288.2089; found, 288.2091.

4.1.12. 1,12-Diiododododecane (14). To a solution of 1,12-dodecanediol (1.06 g, 5.23 mmol) and Et_3N (2.9 mL, 20.9 mmol) in CH_2Cl_2 (17 mL) was MsCl (1.01 mL, 13.1 mmol) at 0^o C. The reaction mixture was stirred for 5 h at 0^o C. After the reaction had been completed, the mixture was extracted with ether. The organic layer was successively washed with saturated aqueous NH_4Cl, water, and brine, dried over $MgSO_4$, and concentrated. The crude product was dissolved in acetone (20 mL) and NaI (3.90 g, 26 mmol) was added to this solution. After being stirred for 16h, the reaction was quenched with water. The organic materials were extracted with ether and organic layer was successively washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (hexane:AcOEt = 20:1) to give **14** (1.85 g, 84%) as a colorless solid. The ^{1}H NMR spectral data of **14** were identical with those of reported value.[15]

4.1.13. (2*S*,19*S*)-2,19-bis-(*tert*-Butyldimethylsilyoxy)eicosa-3,17-diyne (15). To a solution of (*S*)-3-(*tert*-butyldimethylsilyloxy)but-1-yne (923 mg, 5.0 mmol) in THF (7.4 mL) was added *n*-BuLi (1.6 mol/L solution in hexane, 4.0 mL, 6.54 mmol) at −78 ^{o}C. After being stirred for 1.5 h at 0 ^{o}C, **14** (920 mg, 2.18 mmol) in HMPA (1.5 mL) and THF (2.0 mL) was added. The reaction mixture was allowed to warm to room temperature, the reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (hexane:AcOEt = 20:1) to give **15** (1.10 g, 94%) as a pale yellow oil. $[\alpha]^{18}_{D}$ −5.41 (*c* 1.44, $CHCl_3$), IR (film) ν_{max}cm^{-1}: 2928, 2856, 1463, 1252, 1101, 1087, 833, 777. ^{1}H-NMR ($CDCl_3$) δ: 0.11 (6H, s), 0.12 (6H, s), 0.90 (18H, s), 1.20-1.27 (16H, m), 1.38 (6H, d, *J* = 6.5 Hz), 1.46-1.50 (4H, m), 2.17 (4H, dt, *J* = 7.0, 2.0 Hz), 4.50 (2H, qd, *J* = 6.5, 2.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: –4.91, –4.59, 18.29, 18.65, 25.84, 28.64, 28.84, 29.14, 29.54, 29.60, 53.41, 59.22, 82.72, 83.72. HREIMS: calcd. for $C_{32}H_{62}O_2Si_2$, 534.4288; found, 534.4293.

4.1.14. (2*S*,19*S*)-Eicosa-3,17-diyne-2,19-diol (16). To a solution of **15** (967 mg, 1.8 mmol) in THF (5.5. mL) was added TBAF (1.0 mol/L solution in THF, 3.6 mL, 3.6 mmol) at 0 ^{o}C. The reaction mixture was stirred for 14 h at room temperature. The mixture was extracted with ether. The organic layer was successively washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (hexane:AcOEt = 2:1) to give **16** (337 mg, 61%) as a colorless solid. Mp. 58-59^{o}C, $[\alpha]^{21}_{D}$ –26.2 (*c* 0.635, $CHCl_3$), IR (KBr) ν_{max}cm^{-1}: 3324, 2980, 2918, 2848, 1470, 1149, 1075, 891. ^{1}H-NMR ($CDCl_3$) δ: 1.20-1.50 (20H, m), 1.43 (6H, d, *J* = 6.5 Hz), 1.79 (2H, brs), 2.46 (4H, dt, *J* = 7.0, 2.0 Hz), 4.47 (2H, q, *J* = 6.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 18.59, 24.72, 28.58, 28.79, 29.06, 29.44, 29.52, 58.56, 82.16, 84.71. HREIMS: calcd. for $C_{20}H_{34}O_2$, 306.2559; found, 306.2561.

4.1.15. (2*S*,19*S*)-4,17-Diiodoeicosa-3,17-diene-2,19-diol (17). To a solution of **16** (149 mg, 0.49 mmol) in THF (10 mL) was added sodium bis(2-methoxyethoxy) aluminum hydride (0.8 mL, 65% in toluene, 4.1 mmol) was added at 0 °C. The reaction mixture was stirred for 3 h at rt, before ethyl acetate (0.4 mL, 3.9 mmol) was added at 0 °C. After the mixture had been cooled at −78°C, a solution of iodine (1.11 g, 4.4 mmol) in THF (7 ml) was added dropwise. The reaction mixture was allowed to warm to rt, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The mixture was extracted with ether. The organic layer was successively washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by preparative TLC (hexane:AcOEt = 5:1) to give **17** (234 mg, 86%) as a pale yellow oil. $[\alpha]^{18}_D$ −0.030 (*c* 1.25, $CHCl_3$), IR (film) $\nu_{max}cm^{-1}$: 3326, 2970, 2925, 2852, 1644, 1366, 1247, 1114, 1065, 941, 867. ^{1}H-NMR ($CDCl_3$) δ: 1.20-1.35 (16H, m), 1.31 (6H, d, *J* = 6.5 Hz), 1.45-1.50 (4H, m), 1.79 (2H, brs), 2.46 (4H, dt, *J* = 1.0, 7.0 Hz), 4.47 (2H, m), 5.60 (2H, d, *J* = 7.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 22.01, 28.12, 29.07, 29.28, 29.46, 29.53, 45.12, 72.83, 109.50, 137.97. HREIMS: calcd. for $C_{20}H_{36}I_2O_2$, 562.0805; found, 562.0803.

4.1.15. (+)-Ancepsenolide (2). To a solution of **17** (30 mg, 0.053 mmol) in THF were added K_2CO_3 (30 mg, 0.21 mmol), NH_2NH_2 (one drop), and Et_3N (0.03 mL, 0.21 mmol) under CO atmosphere. The mixture was stirred for 44 h at 40 °C. After cooling, the mixture was diluted with EtOAc, washed with satrated aqueous NH_4Cl, brine, dried over $MgSO_4$, and concentrated. The residue was purified with preparative TLC (toluene:AcOEt = 4:1) to afford **3** (15 mg, 79%) with monolactonized product. Mp. 96-97°C, (lit., 96.0-97.9°C).[4] $[\alpha]^{18}_D$ +47.1 (*c* 1.28, $CHCl_3$), {lit., $[\alpha]^{27}_D$ = +45.53, (*c* 0.43, $CHCl_3$)}.[6a] IR (KBr) $\nu_{max}cm^{-1}$: 3076, 2913, 2849, 1743, 1652, 1472, 1326, 1205, 1121, 1085, 1035, 884. ^{1}H-NMR ($CDCl_3$) δ: 1.20-1.60 (20H, m), 1.41 (6H, d, *J* = 7.0 Hz), 2.25-2.28 (4H, m), 5.00 (2H, qd, *J* = 7.0, 1.5 Hz), 6.99 (2H, d, *J* = 1.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 19.20, 25.15, 27.37, 29.15, 29.27, 29.46, 29.53, 77.40, 134.28, 148.87, 173.91. HREIMS: calcd. for $C_{22}H_{34}O_4$, 362.2457; found, 362.2455.

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