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Enantioselective total synthesis of (+)-sarcodictyenone

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Abstract

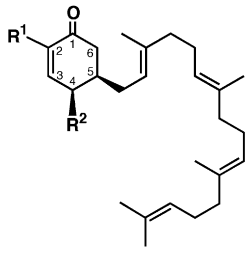
The first enantioselective total synthesis of (+)-sarcodictyenone is described [4.3% overall yield from (5*R*,6*R*)-6-methyl-5-trimethylsily-2-cyclohexenone]. This work establishes the absolute stereochemistry of the natural product.

Keywords: (+)-Sarcodictyenone; Terpenoid; Asymmetric synthesis; Hydroxycyclohexenone

1. Introduction

(+)-Sarcodictyenone [(+)-**1**] isolated from the Mediterranean stolonifer *Sarcodictyon roseum* of temperate waters is the first example of a natural product, which has a terpenylated optically active 4-hydroxy-2-cyclohexenone framework. The relative structure of (+)-**1** was assigned by ^{1}H NMR, ^{13}C NMR, IR, and HRMS, however, the absolute stereochemistry has not been determined yet since the attempt to clarify the absolute configuration by CD spectroscopy was unsuccessful.[1]

More recently, analogous natural products eunicenone A and B, whose absolute stereochemistry has been elucidated as shown in Figure 1, have been isolated from the Caribbean gorgonian genus *Eunicea*.[2] The enantioselective total synthesis of eunicenone A has already been reported by Corey et al. in 2001.[2] We planned to clarify the absolute chemistry of (+)-sarcodictyenone [(+)-**1**] by the enantioselective total synthesis.



(+)-sarcodictyenone [(+)-**1**] R^1 = Me, R^2 = OH
eunicenone A R^1 = COOMe, R^2 = OH
eunicenone B R^1 = COOH, R^2 = OAc

Figure 1. Structures of sarcodictyenone and its analogues.

2. Results and discussion

Initial straightforward attempt to introduce the geranylgeranyl side chain via 1,4-addition of geranylgeranyl-MgBr to enantiomerically pure enone (−)-**2**[3] resulted in failure, i.e., lack of diastereo- and regio-selectivity was observed. Thus we examined the introduction of the geranylgeranyl group via alkylation as shown in Scheme 1. Enone (−)-**2** was converted into hydroxysulfone **3** by the conjugate addition of benzenethiol, reduction with DIBAH followed by oxidation with *m*-CPBA. Dianion formation with *n*-BuLi followed by alkylation with geranylgeranylbromide (GG-Br) gave **4** in 88% overall yield from (−)-**2** as a mixture of three diastereoisomers. Swern oxidation of **4** and subsequent elimination of

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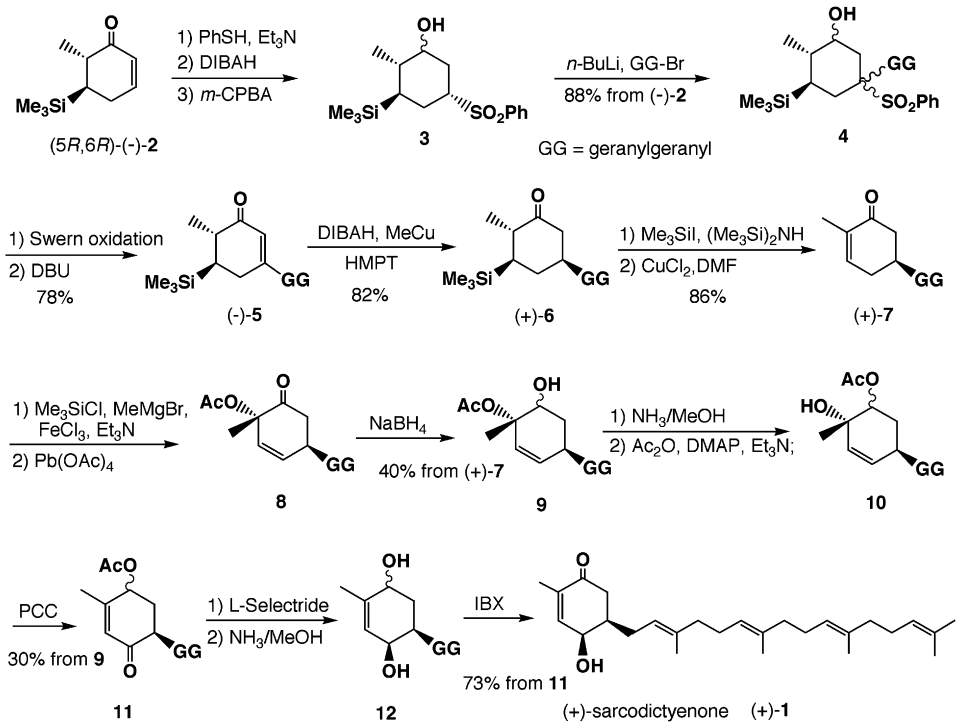

Scheme 1. Synthesis of (+)-sarcodictyenone.

phenylsulfinic acid by base treatment gave (−)-**5** (78%). Diastereoselective conjugate reduction of (−)-**5** with DIBAH in the presence of MeCu in THF−HMPT[4] gave (+)-**6**, whose diastereo homogeneity was confirmed by ^{13}C NMR, in 82% yield.[5] Removal of the trimethylsilyl group was carried out by $CuCl_2$ treatment[9] of the regioselectively formed enol silyl ether, which was prepared from (+)-**6** by Miller's method,[10] to give (+)-**7** in 86% yield. Introduction of the γ-hydroxy group to (+)-**7** by applying reported methods[11] was unsuccessful.

Oxidative introduction of acetoxy group to α-position of the carbonyl group via the corresponding trimethylsilyl dienol ether[12] was accomplished by the treatment with lead tetraacetate. Since the product **8** was susceptible to silica gel, reduction of the crude product with sodium borohydride was carried out to give **9** in 40% overall yield from (+)-**7**. Removal of the acetyl group with methanolic ammonia and monoacetylation with acetic anhydride gave **10** whose PCC oxidation[13] gave enone **11** in 30% overall yield from **9**. Stereoselective reduction of **11** with L-Selectride, removal of the acetyl group, and sterically controlled partial oxidation of diol **12** with IBX[14] gave (+)-sarcodictyenone (73% overall yield from **11**) whose specific rotation and spectral data were in good agreement with those of reported for natural one.

3. Conclusion

The first enantioselective total synthesis of (+)-sarcodictyenone has been accomplished [18 steps from (−)-**2**, 4.3% overall yield]. By this synthesis the absolute stereochemistry of natural (+)-sarcodictyenone was determined as (4*R*,5*R*).

4. Experimental

4.1. General method

Infrared (IR) spectra were measured on a JASCO-FT/IR-350 spectrometer and recorded in wave number (cm^{-1}). ^1H and ^{13}C NMR spectra were recoded in $CDCl_3$ solution on a JEOL JEM-EX270 or AL-300 or Bruker AM-400 spectrometer. Chemical shifts (δ) are reported in parts per million downfield from TMS as internal standard, and coupling constants (*J*) are reported in hertz. High and low resolution EI mass spectral data were obtained on a JEOL JMS-SX 102A and JMS-AX 505W spectrometers. Optical rotations were measured with a HORIBA SEPA-300 polarimeter. Analytical- and preparative-thin-layer chromatography (TLC and p-TLC) were performed on Merck 60 F_{254} and 60 PF_{254} pre-coated silica gel plates, respectively. Visualization was preformed by ultraviolet light and/or staining with ceric ammonium molybdate. Flash chromatography was performed on a column with WAKO C-300 silica gel.

4.2. Materials

All solvents were obtained commercial sources and used without purification unless otherwise indicated. THF and ether were distilled over sodium benzophenone ketyl under Ar before use. CH_2Cl_2, DIA, DMF, DMPU, DMSO, HMPA, hexane, NEt_3, TMEDA, and toluene were distilled from calcium hydride or sodium hydride. All non-aqueous reactions were performed under Ar atmosphere with oven-dried glassware.

*4.2.1. (1R,2R,3R,5S)-5-Benzenesulfonyl-2-methyl-3-trimethylsilylcyclohexanol (**3a**) and (1S,2R,3R,5S)-5-benzenesulfonyl-2-methyl-3-trimethylsilylcyclohexanol (**3b**)*

A mixture of (−)-(5*R*,6*R*)-6-methyl-5-trimethylsilyl-2-cyclohexenon (1.97 g, 10.8 mmol), Et_3N (1 mL), and benzenethiol (1.13 mL, 11.0 mmol) in hexane (10 mL) was stirred at room temperature for 1 h. The solvent was removed under reduced pressure to give (2*R*,3*R*,5*S*)-5-benzenesulfanyl-2-methyl-3-trimethylsilylcyclohexanone as an oil, which was used in the next step without purification. IR (neat) 1730 (C=O) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.02 (s, 9H), 1.13 (d, 3H, J=6.6 Hz), 1.43 (dt, 1H, J=10.5 Hz), 1.09–1.99 (m, 2H), 2.31 (dq, 1H, J=6.6, 10.5 Hz), 2.53 (dd, 1H, J=4.5, 14.4 Hz), 2.69 (dd, 1H, J=4.5, 14.4 Hz), 3.91 (quintet, 1H, J=4.5 Hz), 7.21–7.33 (m, 3H), 7.36–7.46 (m, 2H).

To a solution of the crude cyclohexanone derivative in dry THF (65 mL) was added DIBAL (1.01 M in toluene, 12.8 mL, 13.8 mmol) at −78 °C under Ar. After 1.5 h stirring, aq NH_4Cl was added to the mixture. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to give a 10:1 mixture of (1*R*,2*R*,3*R*,5*S*)-5-benzenesulfanyl-2-methyl-3-trimethylsilylcyclohexanol and (1*S*,2*R*,3*R*,5*S*)-5-benzenesulfanyl-2-methyl-3-trimethylsilylcyclohexanol as a colorless oil. To a solution of the crude mixture in CH_2Cl_2 (100 mL) was added *m*-CPBA (4.12 g, 23.8 mmol) at 0 °C under Ar. The mixture was stirred for 1.5 h and diluted with ether. After addition of aq $NaHCO_3$, the organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with $Na_2S_2O_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (hexane/AcOEt=2:1) afforded a mixture of **3a** and **3b** (10:1) as a colorless oil [3.22 g, 91% from (−)-(5*R*,6*R*)-6-methyl-5-trimethylsilyl-2-cyclohexenone]. Analytical samples were obtained by careful flash column chromatography.

*4.2.1.1. Compound **3a**.* IR (neat) 3500 (OH) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.01 (s, 9H), 1.01 (d, 3H, J=6.6 Hz), 1.13 (q, 1H, J=6.6 Hz), 1.60–1.70 (m, 1H), 1.84 (dq, 1H, J=2.9, 6.6 Hz), 1.91–2.10 (m, 3H), 2.40–2.64 (m, 1H), 3.03–3.12 (m, 1H), 3.67–3.73 (m, 1H), 7.55–7.71 (m, 3H), 7.84–7.90 (m, 2H).

*4.2.1.2. Compound **3b**.* IR (neat) 3500 (OH) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ −0.01 (s, 9H), 0.99–1.08 (m, 1H), 1.07 (d, 3H, J=6.6 Hz), 1.40–1.58 (m, 2H), 1.62–1.73 (m, 2H), 2.07 (dt, 1H, J=3.8, 15.8 Hz), 2.34 (dt, 1H, J=3.8, 14.0 Hz), 3.33 (quintet, 1H, J=3.8 Hz), 3.90 (dt, 1H, J=3.8, 8.6 Hz), 7.53–7.68 (m, 3H), 7.84–7.90 (m, 2H); HRMS calcd for $C_{16}H_{26}O_3SiS$: 326.1372. Found: *m*/*z* 326.1382.

*4.2.2. 5-Benzenesulfonyl-5-geranylgeranyl-2-methyl-3-trimethylsilylcyclohexanol (**4a–c**)*

To a solution of a mixture (10:1) of **3a** and **3b** (1.48 g, 4.50 mmol) in dry THF (10 mL) was added *n*-BuLi (1.57 M in hexane, 6.1 mL, 9.57 mmol) at −78 °C under Ar. The mixture was gradually warmed to 0 °C over 1 h, then geranylgeranylbromide freshly prepared from geranylgeraniol (1.45 g, 5 mmol) was added. After stirring for 30 min at the same temperature, the reaction was quenched with aq NH_4Cl. The mixture was extracted twice with AcOEt and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (hexane/AcOEt,=5:1) afforded a ca. 30:2:1 mixture of three diastereomers **4a–c** (2.77 g, 97%) as a colorless oil. Separation of the diastereomers was carried out by careful flash column chromatography (hexane/AcOEt=7:1).

*4.2.2.1. Compound **4a**.* IR (neat) 3470 (OH) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (s, 9H), 1.08 (d, 3H, J=6.3 Hz), 1.28–1.50 (m, 3H), 1.47 (s, 3H), 1.58 (s, 6H), 1.59 (s, 3H), 1.67 (s, 3H), 1.83–2.24 (m, 14H), 2.17 (t, 2H, J=6.3 Hz), 2.39 (d, 1H, J=16.2 Hz), 3.60–3.72 (m, 1H), 4.45 (br d, 1H, J=11.9 Hz), 4.94–5.15 (m, 4H), 7.54–7.72 (m, 3H), 7.90–7.95 (m, 2H).

*4.2.2.2. Compound **4b**.* ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 9H), 1.23 (s, 3H), 1.10–1.15 (m, 1H), 1.36–1.74 (m, 3H), 1.47 (s, 3H), 1.58 (s, 6H), 1.59 (s, 3H), 1.68 (s, 3H), 1.86–2.23 (m, 16H), 2.37 (ddd, 1H, J=3.1, 4.5, 14.7 Hz), 4.06–4.18 (m, 1H), 4.98–5.15 (m, 4H), 7.53–7.69 (m, 3H), 7.84–7.87 (m, 2H).

*4.2.2.3. Compound **4c**.* ^1H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 9H), 0.46–0.56 (m, 1H), 1.04 (d, 3H, J=6.3 Hz), 1.47–1.84 (m, 4H), 1.58 (s, 6H), 1.60 (s, 6H), 1.68 (s, 3H), 1.92–2.13 (m, 14H), 2.42 (br d, 2H, J=6.3 Hz), 3.19 (dt, 1H, J=4.6, 10.2 Hz), 5.04–5.15 (m, 3H), 5.18–5.28 (m, 1H), 7.50–7.66 (m, 3H), 7.82–7.85 (m, 2H).

*4.2.3. (5R,6R)-3-Geranylgeranyl-6-methyl-5-trimethylsilyl-2-cyclohexenone (−)-**5***

To a solution of DMSO (680 μL, 9.58 mmol) in dry CH_2Cl_2 (60 mL) was added oxalyl chloride (414 μL, 4.79 mmol) at −60 °C under Ar. After stirring for 5 min at the same temperature, a mixture of **4a–c** (993 mg, 1.66 mmol) in dry CH_2Cl_2 (10 mL) was added to the solution. The mixture was stirred for 15 min at the same temperature. NEt_3 (1.7 mL, 12.8 mmol) was added and the reaction mixture was slowly warmed to a room temperature. After stirring for 40 min, the reaction was quenched by adding H_2O. The organic layer was separated and the aqueous layer was extracted with hexane. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to give a diastereomeric mixture of 5-benzenesulfonyl-5-geranylgeranyl-2-methyl-3-trimethylsilylcyclohexanone as an oil.

To a solution of the crude oil in CH_2Cl_2 (10 mL) was added DBU (1.2 mL, 7.96 mmol) at room temperature. After stirring for 20 min, the mixture was diluted with CH_2Cl_2, filtered through a short pad of silica gel and concentrated. Purification by flash column chromatography (hexane/AcOEt=20:1) gave 588 mg (78% yield) of (−)-**5** as an oil. $[\alpha]_D$ −35.6 (*c* 1.3, $CHCl_3$); IR (neat) 1672 (C=O) cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ 0.045 (s, 9H), 1.19 (d, 3H, J=6.8 Hz), 1.12 (m, 1H), 1.60–1.63 (m, 12H), 1.68 (s, 3H), 1.98–2.15 (m, 14H), 2.29–2.35 (m, 1H), 2.87 (d, 2H, J=6.8 Hz), 5.09–5.12 (m, 4H), 5.82 (s, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −1.96, 16.03, 16.12, 16.23, 17.70, 25.71, 26.58, 26.65, 26.79, 29.31, 30.28, 36.23, 39.73, 42.12, 118.72, 123.88, 124.20, 124.42, 124.53, 131.26, 134.97, 135.36, 139.12, 164.20, 202.76; HRMS calcd for $C_{30}H_{50}OSi$: 454.3631. Found: *m/z* 454.3637.

*4.2.4. (2R,3R,5R)-5-Geranylgeranyl-2-methyl-3-trimethylsilylcyclohexanone (+)-**6***

To a pre-cooled (−50 °C) solution of CuI (882 mg, 4.61 mmol) in dry THF (21 mL) was added methyllithium (1.05 M in ether, 4.4 mL, 4.61 mmol) under Ar. After stirring for 30 min at the same temperature, HMPA (4.2 mL) and DIBAL (1.01 M in toluene, 4.6 mL, 4.65 mmol) were added. After 40 min stirring at the same temperature, (−)-**5** (420 mg, 0.92 mmol) in dry THF (10 mL) was added. Then the mixture was warmed to −10 °C and stirred for 12 h. The reaction mixture was treated with hexane and saturated aq NH_4Cl. The resulting mixture was filtered through a short pad of Celite. After separation of the organic layer, the aqueous layer was extracted with AcOEt. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (hexane/AcOEt=20:1) afforded (+)-**6** (346 mg, 82% yield) as a colorless oil. $[\alpha]_D$ +32.00 (*c* 3.0, $CHCl_3$); IR (neat) 1740 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.081 (s, 9H), 0.85 (dq, 1H, J=2.7, 14 Hz), 1.04 (d, 3H, J=6.6 Hz), 1.20–1.28 (m, 2H), 1.62 (s, 12H), 1.70 (s, 3H), 1.84 (d, 2H, J=12 Hz), 1.98–2.06 (m, 14H), 2.25 (m, 1H, J=6.3, 6.4 Hz), 2.43 (dt, 1H, J=2.4, 12 Hz), 5.14–5.12 (m, 4H); HRMS calcd for $C_{30}H_{52}OSi$: 456.3787. Found: *m/z* 456.3768.

*4.2.5. (5S)-5-Geranylgeranyl-2-methyl-2-cyclohexenone (+)-**7***

To a solution of (+)-**6** (446 mg, 0.98 mmol) in dry CH_2Cl_2 (10 mL) at room temperature were added hexamethyldisilazane (412 μL, 1.96 mmol) and TMSI (172 μL, 1.27 mmol). After 1 h stirring at the same temperature, the reaction was quenched with aq $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with hexane. The combined organic layers were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated to give 504 mg of trimethylsilyl ether as an oil. A solution of the crude oil and $CuCl_2$ (395 mg, 2.94 mmol) in DMF (5 mL) was stirred at room temperature under Ar for 2 h and then heated at 60 °C for 30 min. The reaction was quenched by the addition of cold H_2O. The reaction mixture was extracted twice with hexane, and the combined organic extracts were washed three times with water, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by p-TLC (hexane/AcOEt=15:1) afforded (+)-**7** [322 mg, 86% from (+)-**6**] as a colorless oil. $[\alpha]_D$ +23.8 (*c* 2.0, $CHCl_3$); IR (neat) 1670 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 12H), 1.69 (s, 3H), 1.60–1.77 (m, 1H), 1.77 (s, 3H), 1.98–2.17 (m, 16H), 2.38 (dd, 1H, J=4.5, 17 Hz), 2.53 (dd, 1H, J=1.7, 12 Hz), 5.11–5.12 (m, 4H), 6.70 (dd, 1H, J=1.0, 4.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.78, 15.99, 16.05, 16.21, 17.68, 25.70, 26.56, 26.63, 26.72, 26.77, 32.15, 33.89, 36.32, 39.73, 39.82, 44.37, 121.09, 124.04, 124.20, 124.38, 131.26, 134.93, 135.15, 135.54, 137.32, 144.90, 200.25; HRMS calcd for $C_{27}H_{42}O_3$: 382.3236. Found: *m/z* 382.3263.

*4.2.6. 2-Acetoxy-5-geranylgeranyl-2-methyl-3-cyclohexenone **8***

A solution of dry $FeCl_3$ (20 mg, 0.12 mmol) in dry THF (2 mL) was cooled to −20 °C under Ar and a solution of MeMgBr (2.04 mL, 1.86 mmol, 0.91 M in THF) was added slowly. The reaction mixture was stirred for 20 min at −20 °C and (+)-**7** (100 mg, 0.26 mmol) in dry THF (1 mL) was added dropwise over a period of 5 min. After stirring for 20 min at the same temperature, the reaction mixture was warmed to 0 °C and added TMSCl (252 μL, 1.86 mmol), NEt_3 (156 μL, 1.1 mmol), and DMPU (156 μL, 1.24 mmol). The mixture was stirred overnight at room temperature and then aq $NaHCO_3$ was added. The mixture was extracted three times with ether and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give 122 mg of the corresponding dienol silyl ether as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 9H), 1.61 (s, 12H), 1.69 (s, 3H), 1.63–1.69 (m, 1H), 1.94–2.10 (m, 14H), 2.19 (dd, 1H, J=1.5, 8.4 Hz), 2.37–2.45 (m, 1H), 5.12–5.15 (m, 4H), 5.37 (dd, 1H, J=3.6, 9.3 Hz), 5.71 (dd, 1H, J=1.8, 9.0 Hz). The dienol silyl ether was used in the next step immediately.

To a solution of $Pb(OAc)_4$ (340 mg, 0.76 mmol) in CH_2Cl_2 (30 mL) was added the crude dienol silyl ether (122 mg) in CH_2Cl_2 (10 mL) at −78 °C under Ar. After stirring for 30 min at the same temperature, the reaction was quenched by adding hexane. The resulting mixture was filtered through a short pad of silica gel and concentrated to afford **8** (58 mg) as an oil, which was used in the next step immediately without further purification, since this compound was found to be relatively unstable. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 3H), 1.60 (s, 12H), 1.69 (s, 3H), 2.03 (s, 3H), 1.98–2.08 (m, 14H), 2.14–2.32 (m, 1H), 2.67 (ddd, 1H, J=0.9, 4.5, 15 Hz), 2.87 (m, 1H), 5.11–5.14 (m, 4H), 5.54 (dd, 1H, J=2.7, 10 Hz), 5.91 (dt, 1H, J=1.6, 9.7 Hz).

*4.2.7. 5-Geranylgeranyl-2-methyl-3-cyclohexene-1,2-diol 2-acetate **9***

To a solution of the crude **8** (58 mg) in MeOH (10 mL) was added $NaBH_4$ (200 mg) at 0 °C under Ar. After stirring overnight at room temperature, the reaction was quenched by adding H_2O. The mixture was extracted three times with AcOEt and the combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by p-TLC (hexane/AcOEt=5:1) afforded **9** [46 mg, 40% from (+)-**7**] as a colorless oil. IR (neat) 1713 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 3H), 1.60 (s, 12H), 1.68 (s, 3H), 1.47–1.68 (s, 3H), 1.68–2.10 (m, 1H), 2.00–2.03 (m, 14H), 2.07 (s, 3H), 2.28 (m, 1H, J=5.0 Hz), 4.00 (dd, 1H, J=3.5, 13 Hz), 4.62 (s, 1H), 5.12 (m, 4H), 5.62 (s, 2H).

*4.2.8. 5-Geranylgeranyl-2-methyl-3-cyclohexene-1,2-diol 1-acetate **10***

Compound **9** (44 mg, 0.10 mmol) was dissolved in MeOH/NH_3 (1 mL). After overnight at room temperature, the solution was concentrated to give (5*S*)-5-geranylgeranyl-2-methyl-3-cyclohexene-1,2-diol as a colorless oil. IR (neat) 3400 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.60 (s, 12H), 1.68 (s, 3H), 1.59–1.68 (m, 1H), 2.03 (s, 3H), 1.98–2.06 (m, 15H), 2.27–2.38 (m, 1H), 3.79 (dd, 1H, *J*=3.6, 13 Hz), 5.11 (br s, 4H), 5.48 (d, 1H, *J*=10 Hz), 5.54 (dd, 1H, *J*=2.0, 10 Hz); HRMS calcd for $C_{27}H_{44}O_2$: 400.3341. Found: *m/z* 400.3340.

To a solution of the crude diol, NEt_3 (61 μL, 0.45 mmol), and DMAP in dry THF (1 mL) was added acetic acid anhydride (20 μL, 0.22 mmol) at room temperature under Ar. After 20 min stirring, the reaction was quenched by the addition of MeOH. The resulting mixture was poured into H_2O, and the mixture was extracted twice with AcOEt, and the combined organic layers were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated to give **10** (42 mg) as an oil, which was used without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.60 (s, 12H), 1.68 (s, 3H), 1.68–1.80 (m, 1H), 1.98–2.09 (m, 15H), 2.12 (s, 3H), 2.35–2.47 (m, 1H), 4.93 (dd, 1H, *J*=3.8, 13 Hz), 5.18 (br s, 4H), 5.50 (d, 1H, *J*=10 Hz), 5.56 (dd, 1H, *J*=1.9, 10 Hz).

*4.2.9. (6R)-4-Acetoxy-6-geranylgeranyl-3-methyl-2-cyclohexenone **11***

To a solution of **10** (42 mg) in CH_2Cl_2 (5 mL) was added PCC (300 mg) at room temperature. The mixture was stirred overnight and quenched by the addition of hexane. The resulting mixture was filtered and concentrated. Purification by p-TLC (hexane/AcOEt=10:1) afforded **11** (13 mg, 30% from **9**) as an oil. IR (neat) 1747, 1638 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 12H), 1.68 (s, 3H), 1.68–1.72 (m, 1H), 1.90 (s, 3H), 2.13 (s, 3H), 2.29–2.41 (m, 1H), 2.54–2.61 (m, 1H), 5.09–5.11 (m, 4H), 5.70 (m, 1H), 5.92 (s, 1H); HRMS calcd for $C_{29}H_{44}O_3$: 440.3290. Found: *m/z* 440.3293.

*4.2.10. (4R,5R)-5-Geranylgeranyl-2-methyl-2-cyclohexene-1,4-diol **12***

To a solution of **11** (6.7 mg, 0.015 mmol) in dry THF (1 mL) was added L-Selectride (15 μL, 0.015 mmol, 1.0 M in toluene) at −78 °C under Ar. After 20 min stirring at the same temperature, the reaction was quenched by the addition of MeOH. The resulting mixture was poured into H_2O, and the mixture was extracted three times with AcOEt. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to give a colorless oil. IR (neat) 1740 (C=O), 3400 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 12H), 1.63 (s, 3H), 1.68 (s, 3H), 1.60–1.68 (m, 1H), 2.03–2.06 (m, 16H), 2.08 (s, 3H), 3.98–3.99 (m, 1H), 5.08–5.19 (m, 4H), 5.29 (t, 1H, *J*=8.8 Hz), 5.77 (dt, 1H, *J*=1.5, 5.0 Hz); HRMS calcd for $C_{29}H_{46}O_3$: 442.3447. Found: *m/z* 442.3454.

The crude product was dissolved in MeOH/NH_3 (1 mL). After 3 days at room temperature, the solution was concentrated to give **12** as a colorless oil. IR (neat) 3400 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 12H), 1.69 (s, 3H), 1.60–1.69 (m, 1H), 1.81 (s, 3H), 1.87–2.14 (m, 16H), 3.97 (t, 1H, *J*=3.5 Hz), 4.03 (t, 1H, *J*=7.3 Hz), 5.11–5.20 (m, 4H), 5.68 (dd, 1H, *J*=1.4, 3.4 Hz); HRMS calcd for $C_{27}H_{44}O_2$: 400.3341. Found: *m/z* 400.3344.

*4.2.11. (+)-Sarocdictyenone (+)-**1***

To a solution of the crude **12** in THF (0.5 mL) and DMSO (0.5 mL) was added IBX (100 mg, 0.35 mmol) at room temperature. After 30 min stirring, the reaction was quenched with H_2O. The mixture was extracted twice with AcOEt. The combined organic extracts were washed twice with water, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by p-TLC (hexane/AcOEt=5:1) afforded (+)-**1** (2.4 mg, 73% from **11**) as a colorless oil. $[\alpha]_D$ +51.9 (*c* 0.08, EtOH) [lit.[1] $[\alpha]_D$ +52.0 (*c* 0.17, EtOH)]; IR (neat) 3400 (OH), 1682 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 12H), 1.68 (s, 3H), 1.80 (s, 3H), 1.98–2.08 (m, 14H), 2.26 (ddd, 1H, *J*=6.6, 13.5 Hz), 2.36 (dd, 1H, *J*=3.6, 16 Hz), 2.52 (dd, 1H, *J*=10, 16 Hz), 4.36 (br s, 1H), 5.08–5.17 (m, 4H), 6.70 (dd, 1H, *J*=1.7, 5.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 16.0, 16.1, 16.2, 17.7, 25.7, 26.5, 26.6, 26.8, 29.0, 39.2, 39.7, 39.8, 40.3, 66.4, 121.2, 124.1, 124.2, 124.4, 131.7, 135.3, 135.5, 137.3, 138.1, 143.5, 199.8; HRMS calcd for $C_{27}H_{42}O_2$: 398.3185. Found: *m/z* 398.3200.

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References and notes

1. D'Ambrosio, M.; Guerriero, A.; Fabbri, D.; Pietra, F. *Helv. Chim. Acta* **1986**, *69*, 1581–1584.
2. Isolation and the total synthesis of closely related marine natural products, see: Shin, J.; Fenical, W. *Tetrahedron* **1993**, *49*, 9277–9284; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2001**, *123*, 1872–1877.
3. Asaoka, M.; Aida, T.; Sonoda, S.; Takei, H. *Tetrahedron Lett.* **1989**, *30*, 7075–7078.
4. Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537–540.
5. Conjugate reduction of (−)-**5** with Et_3SiH[6] or $[(Ph_3P)CuH]_6$[7] under reported conditions resulted in recovery of the starting enone. With $Ph_2SiH_2/ZnCl_2$ in the presence of cat. $Pd(PPh_3)_4$,[8] crude (+)-**6** was obtained in a good yield, however, contaminated unidentified side products could not be removed. The configuration of (+)-**6**, (2*R*,3*R*,5*R*), was assigned by comparison of the spectral data with those of (2*R*,3*R*,5*S*)-isomer which was obtained in a fair yield via conjugate addition of geranylgeranyl-MgBr to (−)-**2**[3] in the presence of a catalytic amount of $CuBr\cdot SMe_2$ at −100 °C. (2*R*,3*R*,5*S*)-5-Geranylgeranyl-2-methyl-3-trimethylsilylcyclohexanone: ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 9H), 0.97–1.15 (m, 1H), 1.09 (d, 3H, *J*=6.6 Hz), 1.59 (s, 12H), 1.68 (s, 3H), 1.60–1.74 (m, 2H), 1.90–2.48 (m, 18H), 5.03–5.15 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.63, 15.87, 16.00,

16.26, 17.67, 25.68, 26.63, 26.70, 26.74, 29.51, 29.83, 32.02, 38.91, 39.71, 39.86, 45.73, 45.99, 122.01, 124.10, 124.22, 124.39, 131.23, 134.90, 135.08, 136.82, 214.86.

6. Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731–3733.
7. Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291–293; Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1988**, *29*, 3749–3752.
8. Keinan, E.; Greenspoon, N. *Tetrahedron Lett.* **1985**, *26*, 1353–1356.
9. Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Org. Chem.* **1980**, *45*, 2022–2024; Asaoka, M.; Shima, K.; Takei, H. *J. Chem. Soc., Chem. Commun.* **1988**, 430–431.
10. Miller, R. D.; Mckean, D. R. *Synthesis* **1979**, 730–732.
11. Miyasita, M.; Suzuki, T.; Yoshikoshi, A. *J. Org. Chem.* **1985**, *50*, 3377–3380; Rong-Bao, Z.; Yu-Lin, W. *Acta Chim. Sin. Engl. Ed.* **1989**, 86–87.
12. Krafft, M. E.; Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 7619–7621.
13. Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682–685.
14. Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.