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The first total synthesis of (−)-sinulariol-B and three other cembranoids

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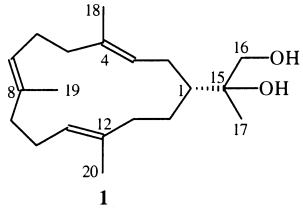
Abstract

The first total synthesis of (−)-sinulariol-B, a marine cembrandiol, was achieved from geraniol. Three other cembranoids were also synthesized from (−)-sinulariol-B.

1. Introduction

Cembranoids, a 14-membered cyclic diterpene family, have become of interest to synthetic chemists and biologists because of their unusual structures and wide range of biological activities.[1,2] Sinulariol-B **1**, sinulariol-D **2**, sinularial-A **3** and sinularic acid-A **4** were isolated in 1987 and 1988 from the southern Japan soft coral *Sinularia mayi*.[3,4] Their geometrical structures and configurations were confirmed to be 3*E*, 7*E*, 11*E* and 1*R*, respectively, but the absolute configuration C_{15} of sinulariol-B was not determined. In our previous work,[5] we have reported the synthesis of (±)-sinulariol-B. For determining the absolute configuration and finding a new method to synthesize sinulariol-D, sinularial-A and sinularic acid-A, the total synthesis of (−)-sinulariol-B **1** was studied. Herein we wish to describe the details of their total syntheses.



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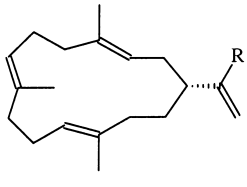

2 R=CH_2OH
3 R=CHO
4 R=COOH

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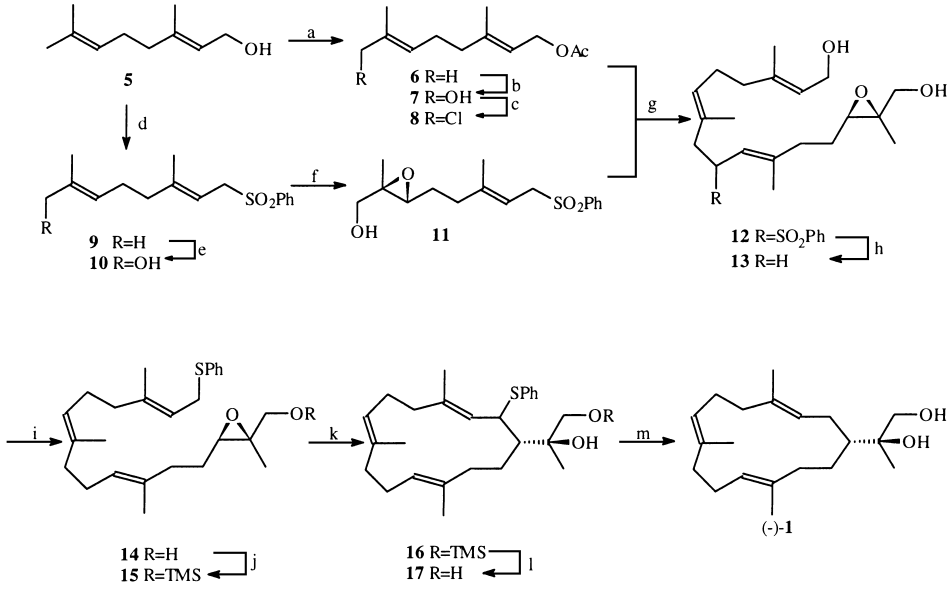
2. Results and discussion

Our strategy involved three key steps: (1) the Sharpless asymmetric epoxidation of **10**; (2) the coupling of sulfone **11** with allylic chloride **8** by sulfone-stabilized carbanionic alkylation; and (3) the macrocyclization of precursor **15** by *intramolecular* thioether-stabilized carbanionic alkylation.

The synthesis began with geraniol **5**. Acetylation of **5** with Ac_2O in pyridine[6] gave the acetate **6** in 98% yield, which was converted into the alcohol **7** in 73% yield by selective oxidation with SeO_2/*t*-BuOOH according to the Sharpless procedure.[7] Reaction of the alcohol **7** with the insoluble complex of NCS and Ph_3P in dry THF[8] yielded the allyl chloride **8**. The sulfone **9** was prepared in 75% yield from geraniol using the Grieco procedure[9] and then transformed into the sulfonyl alcohol **10** in 78% yield. Using the Sharpless asymmetric epoxidation,[10] sulfonyl alcohol **10** was converted to the epoxide **11** in 98% yield and 99% ee (determined by ^1H NMR with its (*R*)-(−)-acetylmandelic acid derivative).

Alkylation of the anion of sulfone **11** with the allylic chloride **8** took place smoothly in anhydrous THF at −78°C, and the acetyl group was removed from the product without damage to the rest of the molecule by treatment with anhydrous K_2CO_3 in dry MeOH to give the sulfonyl diol **12** in 85% yield. The sulfonyl group was reductively removed from **12** by the reaction with 6% Na(Hg) at 20°C to yield the diol **13** in 76% yield.[11,12] We found that removal of the sulfonyl group with 6% Na(Hg) was better than by Li–$EtNH_2$.[5] It did not need low temperatures for a long time. The yield was high, and most importantly, the double bonds did not rearrange. From the alcohol **13**, the cyclization precursor **15** was conveniently obtained after two steps.

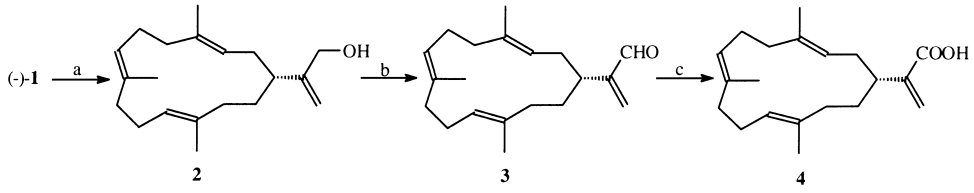


a). Ac_2O, Py, DMAP, 20°C, 98%; b). SeO_2, *t*-BuOOH, CH_2Cl_2, 20°C, 73%; c). Ph_3P, NCS, THF, 20°C, 85%; d). PBr_3, Et_2O then $PhSO_2Na$, DMF, 20°C, 75%; e). Se_2O, *t*-BuOOH, CH_2Cl_2, 20°C, 78%; f). $Ti(O^iPr)_4$, D-(-)-DET, TBHP, CaH_2, Silica gel, Molecular sieves 4Å, CH_2Cl_2, 98%; g). LDA, -78°C then K_2CO_3-MeOH, 20°C, 85%; h). 6% Na(Hg), Na_2HPO_4, MeOH, 20°C, 76%; i). Ph_3P, NCS, THF, r.t., then PhSLi 76%; j). TMSCl, imidazole, DMF, 98%; k). LDA, -78°C, Dabco, 54%; l). *n*-$Bu_4N^+F^-$, ~100%; m). Li-$EtNH_2$, -78°C, 70%.

The next key step was cyclization by intramolecular thioether-stabilized carbanionic alkylation. Slow addition of **15** over 48 h in dry THF to a cooled (−78°C), well-stirred solution of LDA and DABCO[13] in dry THF gave the intermediate **16**. After deprotection of **16** in the usual way, the thiophenyl diol **17** was

obtained in 54% yield after two steps and then reduced with Li–$EtNH_2$ at −78°C to yield (−)-sinulariol-B in 70% yield.

The spectral data and specific rotation of synthetic compound **1** showed good agreement with natural products.[3] The absolute stereochemistry of the synthetic compound at C_1 and C_{15} should be 1*R*,15*S*, and therefore the absolute stereochemistry of the naturally occurring material should have the 15*S*-configuration too.



a). $SOCl_2$, Py, 15°C, 3h, 49%; b). MnO_2, *n*-hexane, 15°C, 10h, 92%; c). $Ca(ClO)_2$-H_2O, 15°C, 65%

From (−)-sinulariol-B, sinulariol-D was obtained by treatment with $SOCl_2$ in pyridine. Oxidation of sinulariol-D with MnO_2 gave sinularial-A, which was converted into sinularic acid-A in 65% yield by treatment with $Ca(ClO)_2$.[14]

In summary, we have accomplished the total synthesis of natural products (1*R*,15*S*)-(−)-**1**, (*R*)-(+)-**2**, (*R*)-(+)-**3** and (*R*)-(+)-**4** from geraniol, and the absolute configuration C_{15} of sinulariol-B was assigned to be 15*S*.

3. Experimental

3.1. General

Melting points were determined on a Kofler apparatus, and are uncorrected. IR spectra were recorded on a FT-170SX (film) spectrometer. ^{1}H NMR spectra were measured on a Bruker AC-80 or AM-400 spectrometer using $CDCl_3$ as a solvent and TMS as an internal standard. Mass spectra were measured on a VG ZAB-HS spectrometer by direct inlet at 70 eV, and signals given in m/z with relative intensity (%) in brackets. Elemental analyses were determined on a Vario EL instrument. Optical rotation measurements were carried out on a Perkin–Elmer 141 polarimeter. All solvents were distilled prior to use. All anhydrous solvents were prepared by standard methods. All reactions were conducted under an argon atmosphere unless otherwise noted, and monitored by TLC. All products prepared were purified by flash column chromatography on silica gel (200–300 mesh) purchased from Qingdao Marine Chemical Company. Geraniol was purchased from Aldrich Chemical Company, Inc.

3.2. 3,7-Dimethyl-2E,6-octadien-1-yl acetate **6**

A mixture of geraniol **5** (4.00 g, 26.0 mmol) and acetic anhydride (2.7 mL, 28.6 mmol) and a catalytic amount of 4-(dimethylamino)pyridine in pyridine (5 mL) was stirred at 20°C for 6 h, then poured into water and extracted with ether (3×50 mL). The combined ether layer was washed successively with 2N HCl, 10% aqueous $NaHCO_3$, water and brine, then dried over $MgSO_4$ and concentrated. The resulting oil was purified by flash column chromatography on silica gel using petroleum ether:acetone (25:1, v/v) as an eluent to yield the acetate **6** (5.00 g, 98%) as a colorless oil. ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.67 (s, 6H, $2CH_3$), 1.71 (s, 3H, CH_3), 2.04 (s, 3H, CH_3CO), 2.00–2.40 (m, 4H, $2CH_2$), 4.59 (d, 2H, *J*=7.2 Hz,

CH_2OAc), 4.95–5.30 (m, 2H, 2CH=). Anal. calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27; found: C, 73.56; H, 10.34.

3.3. 3,7-Dimethyl-8-hydroxy-2E,6E-octadien-1-yl acetate **7**

To a suspension of SeO_2 (550 mg, 5.0 mmol) and 70% *t*-BuOOH (6.8 mL, 50 mmol) in CH_2Cl_2 (30 mL) was added the acetate **6** (4.90 g, 25.0 mmol) in CH_2Cl_2 (20 mL). After being stirred at 20°C for 15 h, the reaction mixture was diluted with ether (150 mL) and washed successively with 10% aqueous KOH, saturated aqueous $NaHSO_3$, water and brine, then dried over $MgSO_4$, and concentrated. The resulting oil was purified by flash column chromatography on silica gel using petroleum ether:acetone (15:1, v/v) as an eluent to give the alcohol **7** (3.87 g, 73%) as a colorless oil. IR (film): ν_{max} 3437, 1738, 1670, 1021; ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.67 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 2.03 (s, 3H, CH_3CO), 2.00–2.40 (m, 4H, $2CH_2$), 3.95 (s, 2H, OCH_2), 4.58 (d, 2H, *J*=7.2 Hz, CH_2OAc), 5.00–5.35 (m, 2H, 2CH=). Anal. calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50; found: C, 67.67; H, 9.45.

3.4. 3,7-Dimethyl-8-chloro-2E,6E-octadien-1-yl acetate **8**

Triphenylphosphine (5.42 g, 20.7 mmol) in THF (25 mL) was added dropwise to a stirring solution of *N*-chlorosuccinimide (2.76 g, 20.7 mmol) in THF (20 mL) under an atmosphere of argon. After 30 min the alcohol **7** (3.85 g, 18.2 mmol) in THF (15 mL) was added slowly over 10 min to the resulting suspension of solids, and the mixture was stirred at 20°C until it became clear and homogeneous (about 5 h). The resulting dark mixture was diluted with ether (200 mL), washed successively with saturated aqueous $NaHCO_3$, water and brine, then dried over $MgSO_4$, and concentrated. Flash column chromatography over silica gel using petroleum ether:acetone (20:1, v/v) as an eluent gave the chloride **8** (3.56 g, 85%) as a colorless oil. ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.69 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.03 (s, 3H, CH_3CO), 1.80–2.20 (m, 4H, $2CH_2$), 3.97 (s, 2H, CH_2Cl), 4.58 (d, 2H, *J*=7.2 Hz, CH_2OAc), 5.05–5.40 (m, 2H, 2CH=). Anal. calcd for $C_{12}H_{19}ClO_2$: C, 62.47; H, 8.30; found: C, 62.32; H, 8.25.

3.5. 3,7-Dimethyl-1-(phenylsulfonyl)-2E,6-octadiene **9**

Phosphorus tribromide (2.4 mL, 25.0 mmol) was added dropwise into an anhydrous ether solution (65 mL) of geraniol **5** (3.50 g, 22.7 mmol) under ice-bath cooling, and then the mixture was stirred for 3 h at 20°C. After the reaction was quenched with saturated aqueous $NaHCO_3$, the ether layer was washed twice with brine, dried over $MgSO_4$, and concentrated to give an oil. The oil was added into sodium benzenesulfonate (3.72 g, 22.7 mmol) dissolved in dry DMF (45 mL), and the mixture was stirred at room temperature under argon in the dark for 24 h. After addition of brine, the organic substances were extracted with ether, and the usual workup gave an oil. Flash column chromatography on silica gel using petroleum ether:acetone (12:1, v/v) as an eluent gave the sulfone **9** (4.73 g, 75%) as a colorless oil. IR (film): ν_{max} 1655, 1585, 1300, 1140; ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.31 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.95–2.20 (m, 4H, $2CH_2$), 3.80 (d, 2H, *J*=7.9 Hz, CH_2SO_2), 5.07 (t, 1H, *J*=7.2 Hz, CH=), 5.17 (t, 1H, *J*=7.8 Hz, CH=), 7.45–8.00 (m, 5H, ArH). Anal. calcd for $C_{16}H_{22}SO_2$: C, 69.03; H, 7.96; found: C, 69.43; H, 7.90.

3.6. 3,7-Dimethyl-1-(phenylsulfonyl)-8-hydroxy-2E,6E-octadiene **10**

To a suspension of SeO_2 (367 mg, 3.31 mmol) and 70% *t*-BuOOH (4.5 mL, 33.1 mmol) in CH_2Cl_2 (30 mL) was added the sulfone **9** (4.60 g, 16.5 mmol) in CH_2Cl_2 (15 mL). After being stirred at 20°C for 25 h, the reaction mixture was poured into water and extracted with ether (3×60 mL). The combined organic layers were washed successively with 10% aqueous KOH, saturated aqueous $NaHSO_3$, water and brine, then dried over $MgSO_4$, and concentrated to give an oil. Flash column chromatography on silica gel using petroleum ether:acetone (10:1, v/v) as an eluent yielded the alcohol **10** (3.78 g, 78%) as a colorless oil. IR (film): ν_{max} 3440, 1658, 1587, 1312, 1150; ^{1}H NMR (80 MHz, $CDCl_3$): δ 1.39 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.90–2.40 (m, 4H, $2CH_2$), 3.85 (d, 2H, *J*=7.9 Hz, CH_2SO_2), 4.02 (s, 2H, OCH_2), 5.00–5.45 (m, 2H, 2CH=), 7.35–8.00 (m, 5H, ArH); EIMS m/z: 294 (M^+, 2%), 279 (5), 276 (3), 212 (73), 77 (100). Anal. calcd for $C_{16}H_{22}SO_3$: C, 65.28; H, 7.53; found: C, 65.12; H, 7.49.

3.7. 3,7-Dimethyl-1-(phenylsulfonyl)-6R,7R-epoxy-8-hydroxy-2E-octene **11**

To a suspension of $Ti(O^iPr)_4$ (2.85 g, 10 mmol), CaH_2 (150 mg), powdered and freshly activated 4 Å molecular sieves (400 mg) and silica gel (200 mg) in anhydrous CH_2Cl_2 (20 mL) was added dropwise a solution of D-(−)-DET (2.47 g, 12 mmol) in anhydrous CH_2Cl_2 (20 mL) at −20°C with stirring. After being stirred for an additional 10 min at −20°C, the solution of the alcohol **10** (2.94 g, 10.0 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise to the above reaction mixture. The mixture was further stirred for 15 min at that temperature and then cooled to −40°C, followed by the addition of a solution of *tert*-BuOOH in toluene (3.2 M, 6.3 mL, 20 mmol). The resulting mixture was stirred for a further 5 h at that temperature before being allowed to warm to −30°C. The reaction was then quenched by the addition of 10% aqueous tartaric acid (40 mL). The mixture was allowed to warm to room temperature gradually and was stirred for a further 1 h prior to extraction with CH_2Cl_2 (3×40 mL). The combined organic phase was washed with water and brine, then dried over $MgSO_4$. Evaporation of the solvent followed by flash column chromatography on silica gel using petroleum ether:acetone (5:1, v/v) as an eluent afforded the epoxide **11** (3.04 g, 98%) as a colorless oil. $[\alpha]_D^{20}$=+8.3 (*c* 1.0, $CHCl_3$); IR (film): ν_{max} 3400, 1650, 1250, 1150; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.80–2.20 (m, 4H, $2CH_2$), 2.94 (t, 1H, *J*=6.1 Hz, epoxy H), 3.47 (d, 2H, *J*=12.1 Hz, OCH), 3.64 (d, 2H, *J*=12.1 Hz, OCH), 3.76 (d, 2H, *J*=7.8 Hz, CH_2SO_2), 5.22 (t, 1H, *J*=7.8 Hz, CH=), 7.40–7.65 (m, 5H, ArH); EIMS m/z: 310 (M^+, 1%), 295 (5), 292 (3), 151 (19), 141 (85), 77 (100). Anal. calcd for $C_{16}H_{22}SO_4$: C, 61.91; H, 7.14; found: C, 61.75; H, 7.18.

3.8. Determination of the enantiomeric excess of **11**

To a solution of dicyclohexylcarbodiimide (DCC, 16 mg, 78 μmol) and the epoxide **11** (20 mg, 65 μmol) in 0.5 mL of dry CH_2Cl_2 was added (*R*)-(−)-acetylmandolic acid (15 mg, 77 μmol) and a catalytic amount of 4-(dimethylamino)pyridine. After stirring at room temperature for 24 h, the solution was evaporated in vacuo and the residue was directly chromatographed using petroleum ether:acetone (4:1) to yield the ester (31 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.80–2.20 (m, 4H, $2CH_2$), 2.21 (s, 3H, CH_3CO), 2.84 (t, 1H, *J*=6.1 Hz, epoxy H), 3.81 (d, 2H, *J*=7.8 Hz, CH_2SO_2), 4.02 (d, 1H, *J*=12.0 Hz, OCH), 4.19 (d, 1H, *J*=12.0 Hz, OCH), 5.20 (t, 1H, *J*=7.8 Hz, CH=), 5.93 (s, 1H, CH), 7.40–7.90 (m, 10H, ArH).

3.9. 2,6,10,14-Tetramethyl-2R,3R-epoxy-8-(phenylsulfonyl)-6E,10E,14E-hexadecatrien-1,16-diol **12**

To a cooled (−78°C), well-stirred solution of 1.6 M LDA in hexane (7.5 mL, 12.0 mmol) in anhydrous THF (40 mL) was added dropwise the sulfone **11** (1.77 g, 5.71 mmol) in dry THF (12 mL) under an argon atmosphere. After 40 min, the allylic chloride **8** (1.32 g, 5.71 mmol) in dry THF (12 mL) was added. The reaction mixture was allowed to warm to room temperature in 2 h and then saturated aqueous NH_4Cl (20 mL) was added. The usual workup gave an oil, which was added to anhydrous K_2CO_3 (480 mg) suspended in dry methanol (40 mL), and the mixture was stirred at 20°C for 2 h. After addition of water, the organic substances were extracted with ethyl acetate (3×50 mL). The extracts were washed with water and brine, then dried over $MgSO_4$, and concentrated. The resulting oil was passed through a short pad of silica gel using petroleum ether:acetone (2:1, v/v) as an eluent to give the sulfonyl diol **12** (2.24 g, 85%) as a colorless oil. $[\alpha]_D^{20}$=+7.8 (*c* 1.0, $CHCl_3$); IR (film): ν_{max} 3421, 1640, 1252, 1151; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.80–2.30 (m, 10H, 5CH_2), 2.98 (t, 1H, *J*=5.9 Hz, epoxy H), 3.53 (d, 2H, *J*=12.0 Hz, OCH), 3.69 (d, 2H, *J*=12.0 Hz, OCH), 3.78 (m, 1H, $CHSO_2$), 4.13 (d, 2H, *J*=7.1 Hz, OCH_2), 4.95 (t, 1H, *J*=6.9 Hz, CH=), 5.10 (t, 1H, *J*=6.8 Hz, CH=), 5.36 (t, 1H, *J*=6.9 Hz, CH=), 7.30–7.60 (m, 5H, ArH); EIMS m/z: 462 (M^+, 1%), 477 (2), 444 (2), 135 (65), 93 (67), 43 (100). Anal. calcd for $C_{26}H_{38}O_5S$: C, 67.50; H, 8.28; found: C, 67.32; H, 8.25.

3.10. 2,6,10,14-Tetramethyl-2R,3R-epoxy-6E,10E,14E-hexadecatrien-1,16-diol **13**

To a solution of the sulfonyl diol **12** (2.20 g, 4.76 mmol) and sodium hydrogenphosphate (2.70 g, 19 mmol) in dry methanol (20 mL) was added portionwise 6% Na(Hg) powder (9.13 g, 23.8 mmol) at 20°C. After the reaction was complete, the reaction mixture was diluted with water and extracted with Et_2O. The organic layer was washed with saturated aqueous NH_4Cl, water and brine, then dried over $MgSO_4$. Evaporation of the solvent followed by flash column chromatography on silica gel using petroleum ether:acetone (4:1, v/v) as an eluent yielded the diol **13** (1.16 g, 76%) as a colorless oil. $[\alpha]_D^{20}$=+8.1 (*c* 2.3, $CHCl_3$); IR (film): ν_{max} 3440 (br), 1644, 1250, 1020, 920; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (s, 3H, CH_3), 1.62 (s, 6H, 2CH_3), 1.67 (s, 3H, CH_3), 1.80–2.45 (m, 12H, 6CH_2), 2.97 (t, 1H, *J*=6.0 Hz, epoxy H), 3.58 (d, 2H, *J*=12.1 Hz, OCH), 3.72 (d, 2H, *J*=12.1 Hz, OCH), 4.10 (d, 2H, *J*=7.0 Hz, OCH_2), 5.08 (t, 1H, *J*=6.8 Hz, CH=), 5.14 (t, 1H, *J*=6.7 Hz, CH=), 5.39 (t, 1H, *J*=6.9 Hz, CH=); EIMS m/z: 322 (M^+, 1%), 135 (32), 123 (15), 95 (72), 69 (45), 43 (100). Anal. calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63; found: C, 74.28; H, 10.69.

3.11. Preparation of **13** by Li–Et_2N

Sulfonyl diol **12** (700 mg, 1.52 mmol) in dry THF (2 mL) was added at −78°C to a solution of lithium wire (630 mg, 91 mmol) in dry $EtNH_2$ (10 mL, dried over sodium). The mixture was stirred at −78°C for 4 h and some solid NH_4Cl and some methanol were added. The solution was allowed to warm to room temperature, then poured into water, and extracted with Et_2O (3×20 mL). The combined organic layers were washed with water and brine, then dried over $MgSO_4$, and concentrated to give an oil, which was purified by flash column chromatography on silica gel using petroleum ether:acetone (4:1, v/v) as an eluent to yield diol **13** (380 mg, 78%) as a colorless oil.

3.12. 2,6,10,14-Tetramethyl-2R,3R-epoxy-16-(thiophenyl)-6E,10E,14E-hexadecatrien-1-ol **14**

Triphenylphosphine (1.02 g, 3.90 mmol) in THF (10 mL) was added dropwise to a stirring solution of *N*-chlorosuccinimide (520 mg, 3.90 mmol) in THF (8 mL) under an argon atmosphere. After 30 min, the diol **13** (1.10 g, 3.42 mmol) in THF (8 mL) was added dropwise in 10 min to the resulting suspension, the mixture was stirred at 20°C until it became clear and homogeneous (about 5 h), and then PhSLi (500 mg, 3.78 mmol) in THF (5 mL) was added. After 3 h, the reaction mixture was poured into water and extracted with ether (3×40 mL). The combined organic layers were washed successively with 2N KOH, water and brine, then dried over $MgSO_4$, and concentrated to yield an oil, which was purified by flash column chromatography on silica gel using petroleum ether:acetone (25:1, v/v) as an eluent to give the alcohol **14** (1.08 g, 76%) as a colorless oil. $[\alpha]_D^{20}$=+11.8 (*c* 1.7, $CHCl_3$); IR (film): ν_{max} 3640 (br), 1644, 1450, 1390, 1160, 720, 690; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.80–2.40 (m, 12H, $6CH_2$), 3.00 (t, 1H, *J*=6.1 Hz, epoxy H), 3.51 (d, 2H, *J*=7.6 Hz, CH_2S), 3.56 (d, 2H, *J*=12.0 Hz, OCH), 3.68 (d, 2H, *J*=12.0 Hz, OCH), 5.08 (t, 1H, *J*=6.8 Hz, CH=), 5.14 (t, 1H, *J*=6.7 Hz, CH=), 5.35 (t, 1H, *J*=6.9 Hz, CH=), 7.20–7.50 (m, 5H, ArH); EIMS m/z: 414 (M^+, 1%), 287 (7), 161 (13), 135 (42), 107 (52), 93 (100), 81 (89). Anal. calcd for $C_{26}H_{38}SO_2$: C, 75.32; H, 9.24; found: C, 75.40; H, 9.16.

3.13. 2,6,10,14-Tetramethyl-1-(trimethylsiloxy)-2R,3R-epoxy-16-(thiophenyl)-6E,10E,14E-hexadecatriene **15**

To a mixture of the alcohol **14** (1.05 g, 2.54 mmol) and imidazole (345 mg, 5.07 mmol) in dry DMF (5 mL) was added trimethylchlorosilane (303 mg, 2.79 mmol). After being stirred at 50°C for 10 h under an atmosphere of argon, the reaction mixture was cooled to room temperature, then diluted with brine, and extracted with ether (3×40 mL). The combined organic layers were washed successively with 10% aqueous $NaHCO_3$, water and brine, then dried over $MgSO_4$, and concentrated. The resulting oil was purified by flash column chromatography on silica gel using petroleum ether:acetone (30:1, v/v) as an eluent to yield **15** (1.21 g, 98%) as a colorless oil. $[\alpha]_D^{20}$=+4.8 (*c* 1.8, $CHCl_3$); IR (film): ν_{max} 2940, 1650, 1458, 1401, 1150, 720, 690; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 9H, $3CH_3$), 1.31 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.66 (s, 6H, $2CH_3$), 1.70–2.24 (m, 12H, $6CH_2$), 2.98 (t, 1H, *J*=6.1 Hz, epoxy H), 3.54 (d, 2H, *J*=7.9 Hz, CH_2S), 3.60 (d, 2H, *J*=12.3 Hz, OCH), 3.74 (d, 2H, *J*=12.3 Hz, OCH), 5.07 (t, 1H, *J*=6.9 Hz, CH=), 5.15 (t, 1H, *J*=6.8 Hz, CH=), 5.31 (t, 1H, *J*=6.8 Hz, CH=), 7.25–7.45 (m, 5H, ArH); EIMS m/z: 486 (M^+, 2%), 471 (5), 456 (2), 377 (7), 161 (27), 135 (42), 93 (100). Anal. calcd for $C_{29}H_{46}O_2SSi$: C, 71.55; H, 9.53; found: C, 71.67; H, 9.48.

3.14. 4,8,12-Trimethyl-1R-(15S,16-dihydroxyl-isopropyl)-2-(thiophenyl)-cyclotetradeca-3E,7E,11E-triene **17**

To a mixture of 1.6 M LDA–hexane solution (1.36 mL, 2.18 mmol) and DABCO (80 mg, 0.74 mmol) in anhydrous THF (40 mL) was added the precursor **15** (300 mg, 0.62 mmol) in anhydrous THF (40 mL) at −78°C via syringe pump over 48 h under an atmosphere of argon. After 3 h, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature, and then poured into saturated aqueous NH_4Cl and extracted with ether (3×100 mL). The extracts were washed with water and brine, then dried over $MgSO_4$, and concentrated to give crude product **16**, to which was added *n*-$Bu_4N^+F^-$ in THF (1N, 2 mL). After being stirred at 15°C for 24 h under argon, the reaction mixture was diluted with ethyl acetate (100 mL), and washed with water and brine, then dried over $MgSO_4$,

and concentrated. The resulting oil was purified by flash column chromatography on silica gel using petroleum ether:acetone (10:1, v/v) as an eluent to yield **17** (139 mg, 54% from **15**) as colorless needles. Mp 92–93°C; IR (KBr): ν_{max} 3360–3100 (br), 1665, 1385, 890, 840, 690, 660; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.70–2.10 (m, 13H, CH, 6CH_2), 3.55 (d, 1H, *J*=11.8 Hz, CH_2O), 3.66 (d, 1H, *J*=11.8 Hz, CH_2O), 3.81 (dd, 1H, *J*=8.6 and 10.8 Hz, CHSPh), 4.89 (t, 1H, *J*=6.6 Hz, CH=), 4.99 (t, 1H, *J*=6.7 Hz, CH=), 5.08 (t, 1H, *J*=6.7 Hz, CH=), 7.25–7.50 (m, 5H, ArH); EIMS m/z: 414 (M^+, 2%), 305 (8), 304 (4), 287 (5), 153 (20), 93 (48), 81 (100), 71 (74). Anal. calcd for $C_{26}H_{38}O_2S$: C, 75.31; H, 9.24; found: C, 75.55; H, 9.18.

*3.15. 4,8,12-Trimethyl-1*R*-(15*S*,16-dihydroxyl-isopropyl)-cyclotetradeca-3*E*,7*E*,11*E*-triene **1***

A mixture of **17** (130 mg, 0.31 mmol) in dry THF (1 mL) was added at −78°C to a solution of lithium (130 mg, 18.7 mmol) in dry $EtNH_2$ (10 mL). The mixture was stirred at −78°C for 3.5 h and a small amount of NH_4Cl and methanol were added. The solution was allowed to warm to room temperature, then poured into water, and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with water and brine, then dried over $MgSO_4$, and concentrated to give a crude product, which was purified by flash column chromatography on silica gel using petroleum ether:acetone (5:1, v/v) as an eluent to yield (−)-sinulariol-B **1** (66 mg, 70%) as colorless needles. Mp 60–62°C [lit.[3], 61–63°C]; $[\alpha]_D^{15}$=−50 (*c* 0.24, $CHCl_3$) [lit.[3], −52 (*c* 1.12, $CHCl_3$)]; IR (KBr): ν_{max} 3260 (br), 1650, 1384, 1370; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.50–2.30 (m, 15H, 7CH_2, CH), 3.43 (d, 1H, *J*=11.1 Hz, OCH), 3.55 (d, 1H, *J*=11.1 Hz, OCH), 4.91 (t, 1H, *J*=6.8 Hz, CH=), 4.99 (t, 1H, *J*=6.7 Hz, CH=), 5.10 (t, 1H, *J*=6.8 Hz, CH=); EIMS m/z: 306 (M^+, 8%), 291 (15), 288 (6), 275 (45), 257 (42), 189 (35), 93 (70), 40 (100).

*3.16. 2-[1*R*,4,8,12-Trimethyl-3*E*,7*E*,11*E*-cyclotetradecatrien-1-yl]-prop-2-en-1-ol **2***

To a solution of the diol **1** (60.0 mg, 0.20 mmol) in pyridine (10 mL) at 15°C was added dropwise $SOCl_2$ (0.29 mL, 4.0 mmol). The reaction mixture was stirred at that temperature for 3 h. After addition of 10% aqueous NaCl, the organic substance was extracted with ether (3×20 mL). The combined organic layers were washed with 2N HCl, water and brine, then dried over $MgSO_4$. Evaporation of the solvent followed by flash column chromatography on silica gel using petroleum ether:acetone (12:1, v/v) as an eluent yielded (+)-sinulariol-D **2** (18.3 mg, 49%) as a colorless oil. $[\alpha]_D^{15}$=+13.2 (*c* 0.60, $CHCl_3$) [lit.[4], +14 (*c* 0.84, $CHCl_3$)]; IR (KBr): ν_{max} 3348, 1644, 895; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57 (s, 6H, 2CH_3), 1.60 (s, 3H, CH_3), 1.45–2.35 (m, 15H, 7CH_2, CH), 4.09 (s, 2H, CH_2O), 4.92 and 5.09 (br s, each 1H, CH_2=), 4.97 (t, 1H, *J*=5.7 Hz, CH=), 5.07 (t, 1H, *J*=6.1 Hz, CH=), 5.18 (t, 1H, *J*=6.5 Hz, CH=); EIMS m/z: 288 (M^+, 16%), 273 (16), 270 (6), 257 (41), 255 (14), 147 (25), 93 (75), 40 (100).

*3.17. 2-[1*R*,4,8,12-Trimethyl-3*E*,7*E*,11*E*-cyclotetradecatrien-1-yl]-propenal **3***

To a suspension of active MnO_2 (151 mg, 1.74 mmol) in *n*-hexane (5 mL) was added dropwise a solution of the alcohol **2** (25.0 mg, 0.087 mmol) in *n*-hexane (2 mL) at 15°C. After the reaction mixture was stirred for an additional 12 h, ether (30 mL) was added to the mixture which was then filtered through a short column of silica gel. Evaporation of the solvent followed by flash column chromatography on silica gel using petroleum ether:acetone (20:1, v/v) as an eluent yielded aldehyde **3** (22.9 mg, 92%) as a colorless oil. $[\alpha]_D^{15}$=+11.5 (*c* 0.46, $CHCl_3$) [lit.[4], +12.5 (*c* 0.64, $CHCl_3$)]; IR (KBr): ν_{max} 2701, 1696, 1620, 940; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.60 (s, 3H, CH_3),

1.40–2.40 (m, 14H, 7CH_2), 2.61 (m, 1H, CH), 4.97 (t, 1H, *J*=6.7 Hz, CH=), 5.07 (t, 1H, *J*=6.9 Hz, CH=), 5.17 (t, 1H, *J*=6.9 Hz, CH=), 6.03 and 6.24 (s, each 1H, CH_2=), 9.56 (s, 1H, CHO); EIMS m/z: 286 (M^+, 21%), 271 (8), 255 (40), 147 (21), 93 (79), 40 (100).

*3.18. 2-[1*R*,4,8,12-Trimethyl-3*E*,7*E*,11*E*-cyclotetradecatrien-1-yl]-propenoic acid **4***

To a solution of 67% $Ca(ClO)_2$ (14.8 mg, 0.070 mmol) in water (1 mL) and a drop of glacial acetic acid was added the aldehyde **3** (20 mg, 0.070 mmol) in acetonitrile (4 mL) at 15°C. After the reaction mixture was stirred for 20 h at that temperature, the mixture was extracted with Et_2O (3×50 mL). The combined organic layers were washed with water and brine, then dried over $MgSO_4$. Evaporation of the solvent followed by flash column chromatography on silica gel using petroleum ether:acetone (4:1, v/v) as an eluent yielded the acid **4** (13.7 mg, 65%) as a colorless oil. $[\alpha]_D^{15}$=+18.2 (*c* 0.25, $CHCl_3$) [lit.[4], +19.7 (*c* 0.71, $CHCl_3$)]; IR (KBr): ν_{max} 3600–2700 (br), 1698, 1624, 951; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.40–2.40 (m, 14H, 7CH_2), 2.60 (m, 1H, CH), 4.98 (t, 1H, *J*=6.5 Hz, CH=), 5.07 (t, 1H, *J*=6.7 Hz, CH=), 5.18 (t, 1H, *J*=7.0 Hz, CH=), 5.64 and 6.35 (s, each 1H, CH_2=); EIMS m/z: 302 (M^+, 1%), 287 (3), 257 (30), 219 (14), 119 (53), 93 (74), 40 (100).

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