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Enantioselective total synthesis of (+)-3,4-epoxycembrene-A

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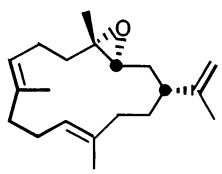
Abstract—A concise and efficient total synthesis of (+)-3,4-epoxycembrene-A **1**, an epoxy cembrane diterpenoid from tropical marine soft coral, is described. The synthesis features the use of an intramolecular McMurry coupling and Sharpless asymmetric epoxidation as key steps.

1. Introduction

Cembranoids, a family of 14-membered cyclic diterpenoid natural products existing in both terrestrial and, more prevalently, in marine organisms,[1] are of great interest to synthetic organic chemists and biologists alike because of their unique structures and wide ranging biological activities.[2]



(+)-3,4-Epoxycembrene-A

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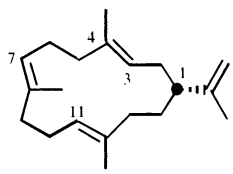

***R*-(−)-Cembrene-A**

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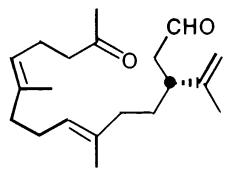

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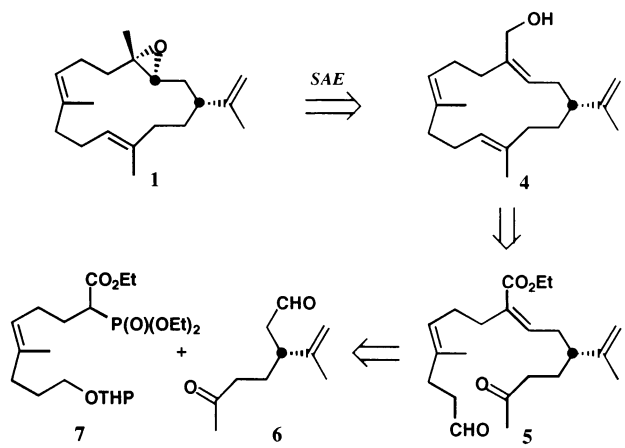
(+)-3,4-Epoxycembrene-A **1**, a naturally occurring epoxy derivative of cembrane diterpene *R*-(−)-cembrene-A **2**,[3] was first isolated by Bowden and co-workers[4] in 1981 from the Australian marine soft coral *Sinularia facile* and more recently from the Formosan soft coral *Nephthea brassica* as a potent cytotoxic constituent against A549, HT-29, KB and P-388 cell lines by Duh and co-workers.[5] The absolute configuration of **1** was determined as (1*R*,3*S*,4*S*) by means of spectroscopic techniques and chemical degradation. Earlier investigation[6] of an unidentified Southern Pacific soft coral by Faulkner et al. in 1978 also led to the isolation of the 3,4-epoxy derivative of cembrene-A **2**, which is clearly a diastereomer of **1**, having a different configuration at the epoxy functionality.

The total synthesis of **1** and natural *R*-(−)-cembrene-A **2** starting from the chiral pool with *R*-(+)-limonene and employing the low valent titanium mediated intramolecular pinacol coupling of the corresponding *sec*-keto aldehyde precursor **3** has been achieved previously in our laboratory.[7] In a continuation of our studies on the enantioselective synthesis of cembrenoids,[8] we herein disclose a more general and



Scheme 1.

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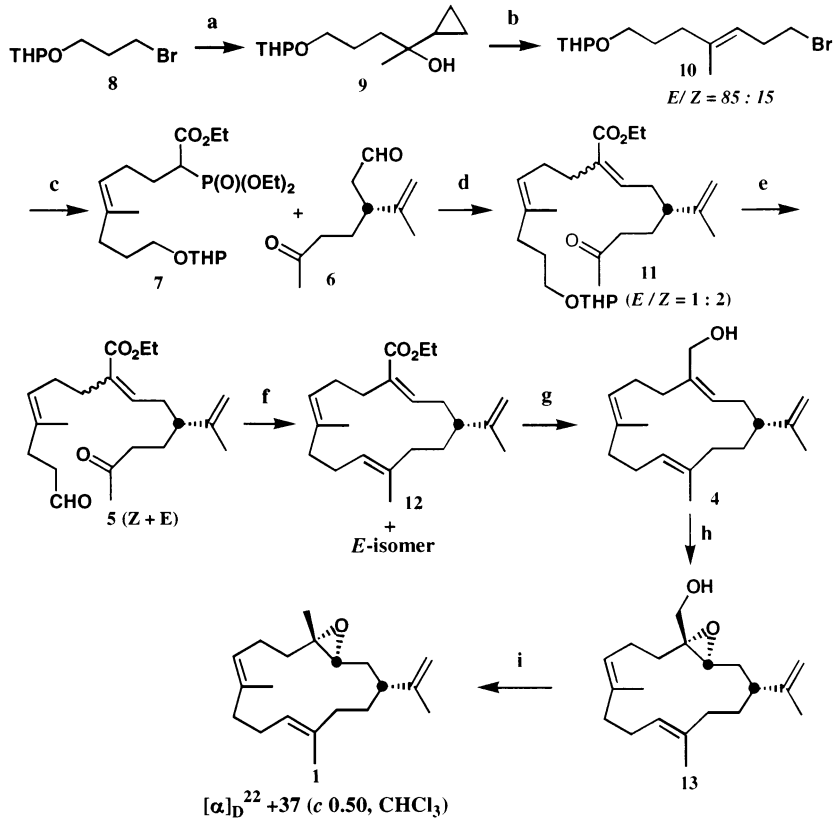

Scheme 2. *Reagents and conditions*: (a) Li, THF, methyl cyclopropylketone **8**, rt, 1 h, 84%; (b) LiBr, TMSCl, CH_2Cl_2, rt, 2 h, 79%; (c) NaH, $(EtO)_2P(O)CH_2CO_2Et$, DMF, 60°C, 6 h, 79%; (d) *n*-BuLi, **7**, −78°C, 0.5 h, −78°C to −20°C, 0.5 h, then **6**, −20°C, 2 h, 70%; (e) i) *p*-TsOH, MeOH, rt, 2 h; ii) PCC, NaOAc, CH_2Cl_2, rt, 2 h, 85%; (f) $TiCl_3$, Zn–Cu, DME, reflux, 6 h, 41%; (g) Dibal-H, CH_2Cl_2, −78°C, 1 h, 92%; (h) $Ti(O^iPr)_4$, D-(−)-DET, *t*-BuOOH, CH_2Cl_2, −20°C, 8 h, 90%; (i) i) Ph_3P, imidazole, pyridine, I_2, Et_2O–CH_3CN, 0°C, 2 h; ii) $NaBH_3(CN)$, HMPA–THF, 60°C, 24 h, 77%.

efficient enantioselective synthesis of (+)-3,4-epoxycembrene-A **1** using a chiral pool protocol and Sharpless asymmetric epoxidation (SAE) for the introduction of three chiral centers (Scheme 1).

The synthesis of (+)-3,4-epoxycembrene-A **1** is detailed in Scheme 2. Addition of the lithium derivative of bromide **8** to cyclopropyl methyl ketone[9] led to cyclopropyl carbinol **9** in 84% yield, which was treated with LiBr in the presence of TMSCl in CH_2Cl_2 at room temperature using a procedure developed by Balme,[10] to give the homoallylic bromide **10** in 82% yield in a ratio of 85:15 for (*E*)- and (*Z*)-geometric isomers as determined by proton NMR.[11] Alkylation of bromide **10** with triethyl phosphonoacetate (NaH, DMF)[12] gave the phosphono ester **7** in 79% yield. Horner–Emmons coupling[13] of phosphono ester **7** and keto aldehyde **6** (derived from *R*-(+)-limonene by ozonolysis[14]) mediated by *n*-BuLi led to ester **11** in 70% yield as a mixture of geometric isomers ((*Z*)-:(*E*)- = 2:1, determined by ^{1}H NMR). Saponification of **11** and subsequent PCC oxidation[15] (85%, two steps) gave the keto aldehyde **5**, which was added slowly to a slurry of low valent titanium reagent (prepared by the in situ reduction of $TiCl_3$ with a Zn–Cu couple[16]) in DME under reflux for 6 hours to afford[17] the desired carbocyclic ester **12** as readily separable (*E*)- and (*Z*)-isomers (in a 1:2 ratio) by silica gel column chromatography in a combined yield of 41%. The McMurry olefination of the (*Z*)-geometric isomer of dicarbonyl compound **5** led to predominant formation of the desired 11(*E*)-isomer **12** (the isomers were found to have formed in an (*E*)-:(*Z*)- ratio of 5:2, as determined by ^{1}H NMR) presumably resulting from the preferred conformation of the macrocyclic ring.[18] Reduction of ester **12** with Dibal-H in ether gave allylic alcohol **4**[19] in 92% yield, which was subjected to the Sharpless asymmetric epoxidation[20] with D-(−)-DET to afford epoxy alcohol **13** in 90% yield and 95% d.e. as determined by high resolution ^{1}H NMR (400 MHz) analysis of the corresponding Mosher's ester[21] (Scheme 2). Standard iodination[22] of **13** (Ph_3P, imidazole, pyridine, I_2) and subsequent reductive dehalogenation[23] of the corresponding iodide intermediate with $NaBH_3CN$ in HMPA afforded the title compound **1**, which has shown identical spectroscopic properties (^{1}H, ^{13}C NMR) with those of the natural product. The specific rotation of the synthetic **1** was comparable to that of the natural product.[4] Thus, the absolute configuration of the 3,4-epoxy function of natural **1** is assigned as (3*S*,4*S*).

The synthesis described here is concise, efficient and applicable to other members of the cembrenoid family. This should enable us to synthesize the other three

diastereomers of **1** and determine the absolute configuration of the natural 3,4-epoxy derivative of cembrene-A isolated by Faulkner et al. about two decades ago.

2. Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer in $CDCl_3$ solution using TMS as an internal reference. IR spectra were obtained using a FT-170SX spectrophotometer. LRMS 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. HRMS were determined on a Bruker Daltonics APEX II 47e Fourier Transfer spectrometer with ESI ionization methods. Optical rotation measurements were carried out on a Jasco 20C polarimeter. All solvents were freshly purified and dried by standard techniques prior to use. Organic extractive phases were dried over anhydrous $MgSO_4$. Purification of products was performed by Flash Column Chromatography (FCC) on silica gel (200–300 mesh) purchased from Qing Dao Marine Chemical Co. and eluting with a solvent mixture (v/v) of petroleum ether (PE) and ethyl acetate (EA).

2.1. 5-Tetrahydropyranoxy-2-cyclopropyl-2-pentanol 9

One-third of a solution of the bromide **8** (4.44 g, 20 mmol) and methyl cyclopropyl ketone (2.1 mL, 21 mmol) in anhydrous THF (20 mL) was added to lithium wire (840 mg, 120 mmol) in THF (60 mL) under an atmosphere of argon at 0°C. The remainder of the solution was added over 30 min and the reaction mixture was stirred at room temperature for 1 h. Excess lithium was removed by filtration and the resulting filtrate was diluted with Et_2O (300 mL). The organic phases were washed with saturated aqueous ammonium chloride (30 mL), saturated aqueous $NaHCO_3$ (30 mL), water, brine, and then dried. Evaporation of the solvent in vacuum was followed by FCC (PE:EA 4:1) to afford the alcohol **9** (3.84 g, 84%) as a colorless oil. IR (film): ν_{max} = 3476, 2935, 2864, 1455, 1350, 1323, 1124, 1076, 1031, 986, 869 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.56 (1 H, t, J = 3.5 Hz, CH-O), 3.90–3.84 (1 H, m, CH-O), 3.76–3.70 (1 H, m, CH-O), 3.55–3.48 (2 H, m, CH_2-O), 1.93 (1 H, s, OH), 1.83–1.61 (2 H, m, CH_2), 1.61–1.35 (2 H, m, CH_2), 1.07 (3 H, s, CH_3), 0.94–0.74 (1 H, m, CH), 0.39–0.21 (4 H, m, 2 CH_2); LRMS (EI) m/z: 201 (3.9%, M−15), 171 (1), 153 (0.3), 143 (2.6), 129 (1.2), 101 (18), 85 (100), 67 (9), 55 (18), 41 (17).

2.2. (3*E*)-4-Methyl-7-tetrahydropyranoxy-1-bromo-3-heptene 10

To a solution of LiBr (2.08 g, 24 mmol) in CH_2Cl_2 (15 mL) was added TMSCl (2.8 mL, 22 mmol) in CH_2Cl_2 (5 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 10 min and a solution of the alcohol **9** (4.56 g, 20 mmol) in CH_2Cl_2 (10 mL) was added over 20 min. After stirring for 2 h, the reaction mixture was filtered and the residue was washed with Et_2O (3×50 mL). The combined organic phases were evaporated in vacuum and the crude product was purified by FCC (PE:EA 15:1) to afford the bromide **10** (4.56 g, 79%) as a colorless oil, in a ratio of 85:15 for the (*E*)- and (*Z*)-isomers. IR (film): ν_{max} = 2941, 2869, 1663, 1443, 1351, 1266, 1202, 1122, 1075, 1032, 984 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.22 (0.15 H, t, J = 6.9 Hz, *Z*-CH=), 5.18 (0.85 H, t, J = 6.9 Hz, *E*-CH=), 4.57 (1 H, t, J = 3.1 Hz, CH-O), 3.89–3.81 (1 H, m, CH-O), 3.77–3.61 (1 H, m, CH-O), 3.51–3.27 (4 H, m, CH_2-O, CH_2Br), 2.71–2.45 (2 H, m, CH_2), 2.21–2.02 (2 H, m, CH_2), 1.88–1.50 (8 H, m, 4 CH_2), 1.65 (3 H, s, CH_3); LRMS (EI) m/z: 188 (0.4%, M−THPOH), 147 (0.1), 126 (1.2), 109 (11), 95 (2), 85 (100), 81 (12), 67 (31), 55 (18), 43 (36).

2.3. Ethyl (5*E*)-6-methyl-9-tetrahydropyranoxy-2-(diethylphosphono)-5-nonenoate 7

To a stirred suspension of NaH (60%, 553 mg, 13.82 mmol) in anhydrous DMF (6 mL) was added dropwise a solution of ethyl (diethylphosphono)acetate (2.76 mL, 13.82 mmol) in DMF (8 mL). The mixture was stirred at room temperature for 2 h and a solution of the bromide **10** (3.34 g, 11.51 mmol) was added. The resulting solution was stirred at 60°C for 6 h and partitioned between Et_2O (20 mL) and H_2O (10 mL). The reaction mixture was extracted with AcOEt (3×50 mL). The organic phases were washed with H_2O, brine, and dried. Evaporation of the solvent was followed by FCC (PE:EA 1:1) to afford the phosphono ester **7** (3.93 g, 79%) as a colorless oil. IR (film): ν_{max} = 2939, 2870, 1735, 1444, 1389, 1256, 1027, 968 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.08 (1 H, t, J = 7.2 Hz, CH=), 4.56 (1 H, t, J = 3.5 Hz, CH-O), 4.25–4.10 (6 H, m, 3 CH_2-O), 3.90–3.84 (1 H, m, CH-O), 3.76–3.70 (1 H, m, CH-O), 3.55–3.48 (2 H, m, CH_2-O), 3.12–3.01 (1 H, m, CH), 2.17–1.93 (8 H, m, 4 CH_2), 1.93–1.77 (2 H, m, CH_2), 1.77–1.64 (2 H, m, CH_2), 1.58 (3 H, s, CH_3), 1.36–1.26 (9 H, m, 3 CH_3); LRMS (EI) m/z: 389 (0.1%, M), 350 (2.4), 332 (1.3), 307 (2.1), 287 (1.4), 261 (0.6), 259 (1.1), 224 (100), 197 (38), 169 (9), 152 (38), 123 (13), 85 (43), 67 (20), 41 (27).

2.4. (4*E*)-11*R*-Isopropenyl-4-methyl-1-tetrahydropyranoxy-8-ethoxycarbonyl-14-oxo-4,8-quindecadiene 11

To a stirred solution of phosphono ester **7** (1.13 g, 2.60 mmol) in THF (20 mL) was added *n*-BuLi (1.63 mL, 1.6 M in *n*-hexane, 2.60 mmol) in anhydrous THF (10 mL) over 5 min under an atmosphere of argon at −78°C. The resulting solution was stirred at −78°C for 0.5 h and then warmed to −20°C. A solution of aldehyde **6** (524 mg, 3.12 mmol) in THF (10 mL) was added over 10 min. The resulting mixture was stirred at −20°C for 2 h, the saturated aqueous NH_4Cl (10 mL) was then added. The mixture was extracted with Et_2O (3×50 mL). The organic phases were washed with water, brine and dried. Evaporation of the solvent in vacuum was followed by FCC (PE:EA 8:1) to give **11** as a mixture of (*E*)- and (*Z*)-isomers (in an (*E*)-:(*Z*)- ratio of ca. 1:2) (810 mg, 70%) as a colorless oil. IR (film): ν_{max} = 2928, 2856, 1713, 1644, 1447, 1369, 1263, 1197, 1032, 894

cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.67 (0.33 H, t, $J=7.2$ Hz, *trans*-CH=), 5.78 (0.67 H, t, $J=7.2$ Hz, *cis*-CH=), 5.11 (1 H, t, $J=7.1$ Hz, CH=), 4.80, 4.70 (2 H, s, CH_2=), 4.57 (1 H, t, $J=3.5$ Hz, CH-O), 4.23–4.17 (2 H, m, CH_2-O), 3.90–3.84 (1 H, m, CH-O), 3.74–3.68 (1 H, m, CH-O), 3.55–3.48 (2 H, m, CH_2-O), 3.43–3.39 (1 H, m, CH-O), 2.40–2.33 (3 H, m, CH, CH_2), 2.33–2.25 (2 H, m, CH_2), 2.25–2.21 (2 H, m, CH_2), 2.13 (3 H, s, CH_3), 2.12–1.95 (2 H, m, CH_2), 1.87–1.64 (6 H, m, 3 CH_2), 1.55–1.44 (4 H, m, 2 CH_2), 1.61 (3 H, s, CH_3), 1.26 (3 H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.6, 167.8, 146.2/145.7, 140.2, 135.2, 132.8/132.4, 123.5, 112.7, 98.8, 67.3, 62.2, 60.0, 46.9/46.4, 41.4, 36.1, 34.7, 33.1/32.7, 30.8, 30.0/29.7, 28.2, 27.7, 27.0/26.5, 25.5, 19.6, 18.0, 15.9, 14.3; LRMS (EI) m/z: 402 (0.05%, M–EtOH), 367 (0.8), 346 (0.2), 318 (1.3), 300 (0.5), 251 (2.4), 223 (0.8), 205 (4.6), 187 (2.7), 147 (4), 119 (5), 95 (94), 85 (100), 43 (29); HRMS (ESI): calcd for $C_{27}H_{44}NaO_5$: 471.3081, found for [M+Na]$^+$: 471.3074.

2.5. (4*E*)-11*R*-Isopropenyl-4-methyl-8-ethoxycarbonyl-14-oxo-4,8-quindecadienal 5

A mixture of tetrahydropyranyl ether **11** (1.08 g, 2.41 mmol) and *p*-TsOH (5 mg) in methanol (10 mL) was stirred vigorously at room temperature for 2 h. To the reaction mixture was added water (4 mL). The resulting mixture was extracted with Et_2O (3×50 mL). The organic phases were washed with H_2O, brine, and dried. Evaporation of the solvent in vacuum gave the crude product, which without further purification, was taken in CH_2Cl_2 (25 mL) and treated with NaOAc (100 mg), silica gel (650 mg, 200–300 mesh) and PCC (1.30 g, 6.03 mmol). The resulting suspension mixture was stirred for 2 h at room temperature, and diluted with Et_2O (50 mL). The combined ether extracts were washed with saturated aqueous $NaHCO_3$ solution (10 mL), water, brine and dried. Evaporation of the solvent in vacuum was followed by FCC (PE:EA 6:1) to give the keto aldehyde **5** (in an (*E*)-:(*Z*)- ratio of ca. 1:2) (742 mg, 85%) as a colorless oil. IR (film): $\nu_{max}=3071$, 2970, 2933, 1715, 1642, 1445, 1375, 1267, 1193, 892 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (1 H, s, CHO), 6.67 (0.33 H, t, $J=7.2$ Hz, *trans*-CH=), 5.92 (0.67 H, t, $J=7.2$ Hz, *cis*-CH=), 5.13 (1 H, t, $J=7.1$ Hz, CH=), 4.79, 4.69 (2 H, s, CH_2=), 4.23–4.17 (2 H, q, $J=7.1$ Hz, CH_2-O), 2.38–2.17 (3 H, m, CH, CH_2), 2.14 (3 H, s, CH_3), 2.17–2.05 (10 H, m, 5 CH_2), 1.79–1.50 (4 H, m, 2 CH_2), 1.59 (3 H, s, CH_3), 1.31 (3 H, t, $J=7.1$ Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.8, 202.5, 167.9, 146.2, 140.5/140.3, 133.7, 125.6/124.5, 122.7, 112.7, 60.0, 46.9, 42.3/42.1, 41.3, 34.8/34.6, 33.1, 31.8, 30.0, 27.9, 26.4, 18.0, 16.0, 14.3; LRMS (EI) m/z: 316 (0.2%, M–EtOH), 298 (0.5), 273 (1.3), 255 (0.8), 233 (3.3), 218 (3), 205 (9), 187 (2), 147 (19), 125 (12), 107 (21), 93 (34), 55 (45), 43 (100); HRMS (ESI): calcd for $C_{22}H_{34}NaO_4$: 385.2349, found for [M+Na]$^+$: 385.2345.

2.6. Ethyl (1*Z*,7*E*,11*E*)-4*R*-isopropenyl-7,11-dimethyl-1,7,11-cyclotetradecatriene-1-carboxylate 12

To anhydrous DME (30 mL) was added $TiCl_3$ (1.8 g, 11.7 mmol) at −78°C with vigorous stirring under an argon atmosphere. After removal of the cooling bath, the resulting suspension was treated with a Zn–Cu couple (2.6 g, 40.6 mmol) and heated to reflux for 2 h. A dilute solution of keto aldehyde **5** (200 mg, 0.552 mmol) in anhydrous DME (24 mL) was added via syringe slowly over 6 h. After the reaction mixture was refluxed for an additional 2 h, the mixture was cooled to room temperature and 20% aqueous K_2CO_3 solution (5 mL) was added. The resulting suspension was extracted with Et_2O (4×50 mL) and the combined organic phases were washed with saturated aqueous $NaHCO_3$ solution, water, brine and dried. The solvent was evaporated in vacuum and the evaporation residue was subjected to FCC to give the cyclized esters **12** and **12a** (75 mg, 41%) as colorless oils. The (*E*)- and (*Z*)-isomers (formed in a ratio of 1:2) were separated by silica gel (300–400 mesh) column chromatography (PE:Et_2O 100:1). **12**: $[\alpha]_D^{25}$ −20.7 (*c* 0.9, $CHCl_3$); IR (film): $\nu_{max}=2929$, 2859, 1710, 1642, 1447, 1376, 1273, 1198, 1164, 890 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (1 H, t, $J=6.4$ Hz, CH=), 5.04 (1 H, t, $J=6.9$ Hz, CH=), 4.94 (1 H, t, $J=6.7$ Hz, CH=), 4.68, 4.62 (2 H, s, CH_2), 4.14 (2 H, q, $J=5.3$ Hz, CH_2O), 2.75–2.57 (2 H, m, CH_2), 2.37–1.96 (13 H, m, 6 CH_2, CH), 1.62 (3 H, s, CH_3), 1.59 (3 H, s, CH_3), 1.50 (3 H, s, CH_3), 1.26 (3 H, t, $J=5.3$ Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 148.5, 141.8, 140.5, 126.1, 125.2, 124.2, 122.4, 110.7, 59.9, 47.6, 45.3, 40.0, 39.4, 34.1, 30.2, 25.8, 23.8, 19.4, 17.8, 17.0, 14.3; LRMS (EI) m/z: 330 (1%, M), 315 (10), 287 (11), 269 (4), 257 (30), 233 (13), 201 (17), 187 (22), 161 (31), 147 (41), 121 (63), 107 (90), 79 (100), 67 (99), 53 (63); HRMS (ESI): calcd for $C_{22}H_{34}NaO_2$: 353.2451, found for [M+Na]$^+$: 353.2448. **(*E*)-isomer 12a**: $[\alpha]_D^{25}$ −6.9 (*c* 1.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.71 (1 H, t, $J=4.3$ Hz, CH=), 5.21 (1 H, t, $J=7.8$ Hz, CH=), 5.12 (1 H, t, $J=7.8$ Hz, CH=), 4.80, 4.74 (2 H, s, CH_2), 4.18 (2 H, q, $J=7.2$ Hz, CH_2-O), 2.46–1.92 (15 H, m, 7 CH_2, CH), 1.70 (3 H, s, CH_3), 1.67 (3 H, s, CH_3), 1.53 (3 H, s, CH_3), 1.28 (3 H, t, $J=7.2$ Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 148.2, 141.6, 140.6, 126.2, 125.5, 124.6, 123.1, 110.8, 60.1, 45.5, 44.4, 39.8, 36.1, 31.0, 29.3, 26.9, 25.6, 20.0, 18.8, 16.8, 14.3.

2.7. (1*E*,7*E*,11*Z*)-4*R*-Isopropenyl-7,11-dimethyl-1,7,11-cyclotetradecatriene-1-methanol 4

To a solution of ester **12** (50 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) under an argon atmosphere was added dropwise Dibal-H (0.3 mL, 1 M in toluene, 0.30 mmol) at −78°C. The mixture was stirred at −78°C for 1 h. Methanol (0.1 mL) was added to decompose the reagent and the reaction mixture was extracted with Et_2O (3×50 mL). The combined ether extracts were washed with 5% aqueous NaOH solution (2×10 mL), saturated aqueous $NaHCO_3$ solution (10 mL), water, brine and dried. Evaporation of the

solvent in vacuum was followed by FCC (PE:EA 4:1) to give the allylic alcohol **4** (40 mg, 92%) as a colorless oil. $[\alpha]_D^{28}$ −76.8 (*c* 0.2, $CHCl_3$); IR (film): ν_{max} = 3332, 2924, 2852, 1643, 1439, 1376, 1009, 888 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.35 (1 H, t, *J* = 7.5 Hz, CH=), 5.01 (1 H, t, *J* = 7.2 Hz, CH=), 4.99 (1 H, t, *J* = 7.1 Hz, CH=), 4.73, 4.66 (2 H, s, CH_2=), 4.12 (2 H, s, CH_2-O), 2.35–2.27 (3 H, m, CH_2, CH), 2.21–1.98 (10 H, m, 5 CH_2), 1.66 (3 H, s, CH_3), 1.59 (3 H, s, CH_3), 1.56 (3 H, s, CH_3), 1.41–1.32 (2 H, m, CH_2); LRMS (EI) *m*/*z*: 288 (4.3%, M), 273 (4), 270 (4.6), 257 (19), 245 (5.2), 227 (5), 213 (3.3), 199 (8), 187 (13), 173 (13), 159 (21), 147 (27), 133 (40), 121 (67), 107 (74), 93 (100), 81 (79), 79 (73), 68 (72), 67 (87), 55 (49), 41 (42); HRMS (ESI): calcd for $C_{20}H_{32}NaO$: 311.2345, found for $[M+Na]^+$: 311.2343.

2.8. (7*E*,11*E*)-1*R*-1-Isopropenyl-8,12-dimethyl-3*S*,4*S*-epoxy-7,11-cyclotetradecadiene-4-methanol 13

To a mixture of $Ti(O^iPr)_4$ (0.041 mL, 0.14 mmol), CaH_2 (1 mg), 4 Å molecular sieves (3 mg) and silica gel (1 mg) in CH_2Cl_2 (2 mL) was added D-(−)-DET (0.029 mL, 0.17 mmol) under an argon atmosphere at −20°C. After stirring for 10 min, the allylic alcohol **4** (40 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) was added. The reaction mixture was stirred for additional 10 min and *t*-BuOOH (0.089 mL, 3.16 M in toluene, 0.28 mL) was added at −40°C. After stirring for 6 h at −20°C, 10% aqueous tartaric acid solution (1 mL) was added and the mixture stirred for 1 h, the mixture was diluted by Et_2O (50 mL), washed with 5% aqueous NaOH solution (2×10 mL), saturated $NaHCO_3$ solution (15 mL), water, brine and dried. Evaporation of the solvent in vacuum was followed by FCC (PE:EA 3:1) to give the epoxy alcohol **13** (38 mg, 90%) as a colorless oil. $[\alpha]_D^{28}$ −40.5 (*c* 0.2, $CHCl_3$); IR (film): ν_{max} = 3437, 3071, 2927, 2857, 1644, 1447, 1377, 1035, 890 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.08 (1 H, t, *J* = 7.2 Hz, CH=), 5.06 (1 H, t, *J* = 7.1 Hz, CH=), 4.75, 4.71 (2 H, s, CH_2=), 3.73 (1 H, dd, *J* = 6.6, 11.0 Hz, CHO), 3.55 (1 H, dd, *J* = 4.4, 11.0 Hz, CHO), 3.02 (1 H, t, *J* = 7.2 Hz, epoxy H), 2.33–1.95 (11 H, m, 5 CH_2, CH), 1.72 (3 H, s, CH_3), 1.67 (3 H, s, CH_3), 1.58 (3 H, s, CH_3), 1.49–1.32 (4 H, m, 2 CH_2); LRMS (EI) *m*/*z*: 304 (0.6%, M), 286 (0.9), 273 (3.3), 255 (4.2), 243 (1.8), 215 (2.2), 187 (5.6), 173 (7), 161 (12), 147 (17), 135 (34), 93 (100), 121 (34), 107 (60), 93 (75), 81 (100), 79 (70), 67 (74), 55 (64), 41 (55); HRMS (ESI): calcd for $C_{20}H_{32}NaO_2$: 327.2295, found for $[M+Na]^+$: 327.2303.

2.9. (1*R*,3*S*,4*S*)-Epoxycembrene-A 1

To a stirred solution of epoxy alcohol **13** (32 mg, 0.105 mmol) in dry Et_2O–CH_3CN (5:3, 2 mL) were added successively Ph_3P (41 mg, 0.16 mmol), imidazole (11 mg, 0.16 mmol), pyridine (0.025 mL, 0.32 mmol) and I_2 (40 mg, 0.16 mmol) at 0°C. The resulting mixture was stirred for 0.5 h at 0°C, diluted with Et_2O (50 mL) and washed with 20% aq. $Na_2S_2O_3$ solution, water, brine, and dried. Evaporation of the solvent in vacuum was followed by FCC (PE:EA 70:1) purification of the crude oil to give the epoxy iodide (39 mg, 89%) as a colorless oil. To a solution of epoxy iodide (23 mg, 0.06 mmol) in a mixture of THF (0.8 mL) and HMPA (0.15 mL) was added $NaBH_3CN$ (12 mg, 0.18 mmol) at room temperature. The reaction mixture was stirred for 24 h at 60°C under an argon atmosphere. The resulting mixture was diluted with Et_2O (5 mL), washed with water, brine, and dried. Evaporation of the solvent in vacuum was followed by FCC (PE:EA 60:1) to give the epoxide **1** (14 mg, 87%) as a colorless oil. $[\alpha]_D^{22}$ +37 (*c* 0.50, $CHCl_3$), [lit.:[4] $[\alpha]_D$ +49 (*c* 0.22, $CHCl_3$)]; IR (film): ν_{max} = 3070, 2960, 2927, 2857, 1644, 1448, 1378, 1066, 889 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.08 (1 H, t, *J* = 7.2 Hz, CH=), 5.06 (1 H, t, *J* = 7.1 Hz, CH=), 4.75, 4.63 (2 H, s, CH_2=), 2.84 (1 H, dd, *J* = 3.1, 10.4 Hz, epoxy H), 2.33–1.98 (11 H, m, 5 CH_2, CH), 1.67 (3 H, s, CH_3), 1.63 (3 H, s, CH_3), 1.62 (3 H, s, CH_3), 1.45–1.30 (4 H, m, 2 CH_2), 1.26 (3 H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 135.2, 133.3, 124.2, 124.0, 110.8, 63.3, 61.0, 40.4, 39.6, 38.3, 34.7, 33.7, 29.8, 24.4, 23.7, 18.5, 17.0 (2 C), 15.9; LRMS (EI) *m*/*z*: 288 (1.8%, M), 273 (2.8), 255 (2.1), 245 (1.8), 231 (1.9), 205 (3.6), 189 (4), 175 (5), 163 (11), 147 (15), 135 (31), 121 (42), 107 (74), 93 (84), 81 (95), 67 (100), 57 (69), 55 (56), 43 (57), 41 (69).

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