New Synthesis of Macrolide Pheromones of the Flat Grain Beetle, *Cryptolestes pusillus* Schönherr†

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(Z)-3-Dodecen-12-olide **1** and (5Z,13S)-5-tetradecen-13-olide **2**, the macrolide pheromones of the flat grain beetle, were synthesized by employing the acetylene zipper reaction in the key steps.

The flat grain beetle, *Cryptolestes pusillus* Schönherr, is a worldwide pest of diverse stored products. Millar *et al.* have recently isolated and identified two macrolides (**1** and **2**) from the volatiles and frass of this insect.¹⁾ (Z)-3-Dodecen-12-olide **1** was the major volatile produced and was active alone. (5Z,13S)-5-Tetradecen-13-olide **2** was not active alone, but synergized the response to **1**.¹⁾ Oehlschlager's synthesis of both **1** and **2** confirmed the proposed structures (**1** and **2**).²⁾

It occurred to us that the acetylene zipper reaction³⁾ might be advantageously employed in synthesizing both **1** and **2**, this idea being realized as shown in the scheme. Multipositional isomerization of alkynes with potassium 3-aminopropylamide (KAPA)³⁾ was used as the key steps, (**4** to **5a** and **12b** to **13**) in our new syntheses of **1** and **2**.

Our synthesis of **1** started from propargyl alcohol **3**. A dianion of **3** prepared from **3** and 2 equivalents of *n*-butyllithium in tetrahydrofuran and hexamethylphosphoric triamide was alkylated with *n*-heptyl bromide to give **4** in a yield of 63%. Treatment of **4** with 6.5 equivalents of KAPA in 3-aminopropylamine gave **5a** in a 91% yield.³⁾ The terminal hydroxyl group of **5a** was protected as a (2'-methoxyethoxy)methyl ether (MEM ether) to give **5b** in

an 88% yield. Treatment of **5b** with *n*-butyllithium and ethylene oxide gave **6** in an 86% yield. The alcohol **6** was oxidized with Jones chromic acid to give **7a** in a 77% yield. Removal of the MEM protecting group of **7a** was effected with 40% perchloric acid in tetrahydrofuran (1:1) to give a hydroxy acid **7b** in a quantitative yield. Semi-hydrogenation of **7b** with P-2 nickel⁴⁾ gave an olefinic acid **8**²⁾ in a 76% yield. Finally, cyclization of **8** with triphenylphosphine and 2,2-dipyridyl disulfide in xylene according to Corey⁵⁾ yielded **1** in a 32% yield. The spectral data of our **1** were in good accord with those previously reported for the natural¹⁾ and synthetic²⁾ **1**. The overall yield of **1** from **3** was 7.5% in 8 steps. The Oehlschlager synthesis was reported to give an overall yield of 3.6~6.2% from 1,8-octanediol in 8 steps.²⁾

For the synthesis of **2**, Oehlschlager *et al.* employed (*S*)-(–)-propylene oxide as the chiral source. However, our choice was to use ethyl (*S*)-3-hydroxybutanoate **9**, since we had a simple and reliable method for preparing **9**.⁶⁾ Reduction of ethyl acetoacetate with the thermophilic yeast, *Saccharomyces bailii* KI 0116, gave **9** of 97.7% *e.e.*⁷⁾ This ester **9** was converted to a tosylate **10** in an overall yield of 70% by a known method.⁸⁾ Treatment of **10**

† Pheromone Synthesis. Part 85. Part 84, see K. Mori and H. Watanabe, *Tetrahedron*, **42**, 295 (1986). The experimental part of this work was taken from the B. Sc. theses of T. S. and H. H. (March, 1985).

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with lithium bromide in acetone gave **11** in a 90% yield. Alkylation of 1-hexyne with **11** by employing *n*-butyllithium as a base furnished **12a**, which was treated with *p*-toluenesulfonic acid in methanol to give **12b** in a 75% yield from **11**. This was submitted to the acetylene zipper reaction, which was known to proceed without racemization at the carbon atom bearing the hydroxyl group.⁹⁾ The action of 10 equivalents of KAPA on **12b** gave the desired terminal alkyne **13** in a 91% yield. For the next alkylation step, **14** was prepared by protecting the hydroxyl group of the known tetramethylene iodohydrin¹⁰⁾ in the conventional manner. To a dianion derived from **13** was added **14** to give **15a** in a 70% yield. The secondary hydroxyl group of **15a** was then acetylated to **15b** (97%), and its tetrahydropyranyl (THP) protective group was removed by warming at 30°C with aqueous acetic acid–tetrahydrofuran to give **15c** in a quantitative yield. Oxidation of **15c** with Jones chromic acid afforded an acid **16a** in an 80% yield. Treatment of **16a** with potassium carbonate

in methanol gave a crystalline acid **16b**, mp 30.5–31.5°C, in an 85% yield. This was reduced with P-2 nickel⁵⁾ to give an olefinic acid **17** in a 90% yield. Cyclization of **17** to **2** was carried out according to Oehlschlager²⁾ to give **2** in a 53% yield by employing 2-chloro-*N*-methylpyridinium iodide as the lactonization reagent.¹¹⁾ The spectral data of our **2**, $[\alpha]_D^{23} + 54.4^\circ$ (CHCl₃) [lit.²⁾ $[\alpha]_D^{32} + 49.6^\circ$ (CHCl₃)], were identical to the reported data of the natural¹⁾ and synthetic **2**.²⁾ Especially, the 400 MHz ¹H-NMR spectrum of our synthetic **2** was in complete accord with that of the natural product.¹⁾ The overall yield of **2** from the known tosylate **10**⁸⁾ was 13.5% in 11 steps. The overall yield of the Oehlschlager synthesis was 15.1% from 5-hexyn-1-ol in 9 steps.²⁾

In conclusion, we synthesized both **1** and **2** from readily available starting materials.

EXPERIMENTAL

All boiling points and melting point were uncorrected. IR spectra were measured on a Jasco A-102 spectrometer

as films. NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer, unless otherwise stated. Mass spectra were recorded on a JEOL DX-303 spectrometer at 70 eV. Optical rotations were measured on a Jasco DIP-140 polarimeter, and GLC analyses were performed on a Yanaco G-180 gas chromatograph.

2-Decyn-1-ol 4. A solution of *n*-butyllithium in *n*-hexane (1.59 M, 220 ml, 350 mmol) was added dropwise to a stirred and cooled solution of **3** (10.0 g, 160 mmol) in dry tetrahydrofuran (THF, 160 ml) and dry hexamethylphosphoric triamide (HMPA, 130 ml) at between -40 and -10°C under argon. The solution was stirred for 25 min at 0°C , before a solution of *n*-heptyl bromide (30.3 g, 170 mmol) in dry HMPA (150 ml) was added over 50 min to the stirred and cooled mixture, keeping the temperature below 0°C . After the addition, the temperature was raised to room temperature, and the mixture was stirred for 30 min at room temperature. A small amount of ice-cooled water was added to the stirred mixture, which was then poured into water and extracted with ether. The ether solution was washed with water and brine, dried over MgSO_4 and concentrated *in vacuo* to give 35.0 g of crude **4**. This was chromatographed over silica gel (Fuji Davison BW 820 MH, 100 g). Elution with *n*-hexane-ethyl acetate (6:1) gave an oil. This was distilled to give 17.2 g (63%) of **4**, bp $83^{\circ}\text{C}/0.77\text{ mmHg}$, n_{D}^{20} 1.4548; IR $\nu_{\text{max}}\text{ cm}^{-1}$ 3340 (s), 2280 (w), 2210 (w), 1015 (s); NMR δ (CDCl_3) 0.87 (3H, br. t, $J \approx 7\text{ Hz}$), 1.05–1.90 (10H, m), 1.95–2.30 (2H, m), 2.23 (1H, s, $-\text{OH}$, D_2O exchangeable), 4.28 (2H, t, $J = 4.2\text{ Hz}$). *Anal.* Found: C, 78.03; H, 11.94. Calcd. for $\text{C}_{10}\text{H}_{18}\text{O}$: C, 77.87; H, 11.76%.

9-Decyn-1-ol 5a. Potassium hydride (a 21.8% suspension in mineral oil, 35 ml, 190 mmol) was washed three times with dry pentane under argon. Freshly distilled 1,3-diaminopropane (160 ml) was then added at room temperature, and the mixture was stirred for 1.5 hr at room temperature. The mixture was cooled to 0°C and to this was rapidly added **4** (4.5 g, 29 mmol). After the addition, the temperature was raised to room temperature and the mixture was stirred for 30 min at room temperature. The mixture was again cooled to 0°C and quenched by the addition of ice-cooled water. The mixture was poured into ice-cooled 6 N-HCl aq. and extracted with ether. The ether solution was successively washed with water, 2 N-HCl aq., sat. NaHCO_3 aq. and brine, dried over MgSO_4 and concentrated *in vacuo* to give 6.0 g of crude **5a**. This was distilled to give 4.1 g (91%) of **5a**, bp $70^{\circ}\text{C}/0.55\text{ mmHg}$; IR $\nu_{\text{max}}\text{ cm}^{-1}$ 3340 (s), 3320 (s), 2120 (m), 1055 (s); NMR δ (CCl_4) 1.10–1.25 (12H, m), 1.73 (1H, t, $J = 3.0\text{ Hz}$), 1.90–2.28 (2H, m), 2.54 (1H, br. s), 3.45 (2H, t, $J = 4.6\text{ Hz}$). *Anal.* Found: C, 78.35; H, 11.91. Calcd. for $\text{C}_{10}\text{H}_{18}\text{O}$: C, 77.87; H, 11.76%.

9-Decyn-1-ol MEM ether 5b. To a stirred and ice-cooled solution of **5a** (3.4 g, 23 mmol) and dry diisopropylamine (8.5 ml, 48 mmol) in CH_2Cl_2 (73 ml) was added MEM chloride (5.1 ml, 46 mmol) at 0°C . After the addition, the temperature was raised to room temperature and the mixture was stirred for 10 hr at room temperature. The mixture was successively washed with water, 10% $\text{Na}_2\text{S}_2\text{O}_3$ aq., sat. NaHCO_3 aq. and brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was distilled to give 4.8 g (88%) of **5b**, bp $109^{\circ}\text{C}/1.1\text{ mmHg}$; IR $\nu_{\text{max}}\text{ cm}^{-1}$ 3220 (s), 2125 (w), 1120 (s), 1050 (s); NMR δ (CCl_4) 1.10–1.75 (12H, m), 1.84 (1H, t, $J = 2.7\text{ Hz}$), 1.94–2.32 (2H, m), 3.29 (3H, s), 3.40–3.60 (6H, m), 4.56 (2H, s). *Anal.* Found: C, 69.38; H, 10.81. Calcd. for $\text{C}_{14}\text{H}_{26}\text{O}_3$: C, 69.30; H, 10.70%.

3-Dodecyn-1,12-diol 12-MEM ether 6. A solution of *n*-butyllithium in *n*-hexane (1.54 M, 14.3 ml, 22 mmol) was added dropwise to a stirred and ice-cooled solution of **5b** (2.5 g, 10 mmol) in dry HMPA (11 ml), keeping the temperature below 10°C . Then, a solution of ethylene oxide in THF (4.0 M, 2.9 ml, 22 mmol) was added to the stirred and cooled mixture at 0°C . After the addition, the temperature was gradually raised to room temperature, and the mixture was stirred for 4.5 hr at room temperature. The mixture was next quenched with ice-cooled water, and extracted with ether. The ether solution was successively washed with brine, water and brine, dried over MgSO_4 and concentrated *in vacuo* to give 3.62 g of an oil. This was chromatographed over silica gel (Fuji Davison BW 820 MH, 40 g). Elution with *n*-hexane-ethyl acetate (9:1 ~ 4:1) gave the recovery of **5b** (0.5 g). Further elution with *n*-hexane-ethyl acetate (3:1) gave 2.0 g (86.3%, based on the **5b** consumed) of **6**, IR $\nu_{\text{max}}\text{ cm}^{-1}$ 3450 (s), 1110 (s), 1045 (s); NMR δ (CDCl_3) 1.10–1.80 (12H, m), 2.00–2.50 (5H, m), 3.35 (3H, s), 3.42–3.80 (8H, m), 4.67 (2H, s). HR-MS (m/z) 286.2228. Calcd. for $\text{C}_{16}\text{H}_{30}\text{O}_4$: 286.2145.

12-Hydroxy-3-dodecynoic acid 12-MEM ether 7a. A solution of **6** (3.3 g, 12 mmol) in acetone (140 ml) was added dropwise over 4 hr to a stirred and ice-cooled solution of chromium trioxide (4.3 g, 43 mmol) in 1.5 N- H_2SO_4 aq. (70 ml). After the addition, the mixture was stirred for 2 hr at room temperature. The excess chromic acid was destroyed by the addition of solid $\text{Na}_2\text{S}_2\text{O}_3$, and the mixture was extracted with ether. The ether solution was washed three times with brine, and concentrated *in vacuo*. The residue was mixed with ether (100 ml) and extracted twice with 1 N-NaOH aq. From the residual ether solution, **6** (0.35 g) was recovered. The aqueous solution was acidified with 6 N- H_2SO_4 aq. to pH 2 and extracted with ether. The ether solution was washed with brine, dried over MgSO_4 and concentrated *in vacuo* to give 2.4 g (77%, based on the **6** consumed) of crude **7a** as an oil. IR $\nu_{\text{max}}\text{ cm}^{-1}$ 3700–2400 (br. s), 2245 (w), 1715 (s), 1170 (s), 1115 (s), 1050 (s). This was employed in the next step without further purification.

12-Hydroxy-3-dodecenoic acid 7b. A mixture of 40% perchloric acid (12 ml) and THF (12 ml) was added to neat **7a** (2.4 g, 8.0 mmol) with stirring and ice-cooling. The mixture was stirred vigorously for 3 hr at room temperature. Then, the mixture was adjusted to pH 3 by the addition of 3-N NaOH aq., and extracted with ether. The ether solution was washed with brine, dried over MgSO_4 and concentrated *in vacuo* to give 1.8 g (quantitative) of crude **7b**, IR ν_{max} cm^{-1} 3700~2400 (br. s), 2240 (w), 1720 (s); NMR δ (CDCl_3) 1.20~1.90 (12H, m), 2.00~2.40 (2H, m), 3.26 (2H, m), 4.13 (2H, t, $J=6.0$ Hz), 5.58 (2H, br. s). This was employed in the next step without further purification.

12-Hydroxy-(Z)-3-dodecenoic acid 8. According to the reported procedure,²⁾ **7b** (1.7 g) afforded **8** (1.3 g, 75.8%). Its IR and NMR spectra were identical with those reported.²⁾

(Z)-3-Dodecenolide 1. **1** was prepared from **8** according to the reported procedure,²⁾ but with slight modification. Triphenylphosphine (262 mg, 1 mmol) and 2,2'-dipyridyl disulfide (220 mg, 1 mmol) were dissolved in dry xylene (8 ml) under argon. To this was added a solution of **8** (100 mg, 0.47 mmol) in dry xylene (2 ml). The mixture was stirred for 1 hr at room temperature and diluted with dry xylene (150 ml). This solution was added dropwise over 6 hr to stirred dry xylene (200 ml) under reflux, the stirring and refluxing being continued for 1 hr after the addition. After cooling, the mixture was diluted with *n*-hexane (400 ml) and directly chromatographed over silica gel (Fuji Davison BW 820 MH, 150 g). The silica gel column was washed with *n*-hexane to remove the xylene and other less-polar impurities. Further elution with *n*-hexane-ethyl acetate gave a crude oil (100 mg). This was further purified by preparative TLC (Merck Kieselgel 60 F₂₅₄ Art. 5715) to give 30 mg (32%) of **1**, IR ν_{max} cm^{-1} 3040 (m), 2950 (s), 2880 (s), 1740 (s), 1650 (sh), 1455 (s), 1400 (w), 1380 (m), 1350 (m), 1300 (s), 1250 (s), 1210 (sh), 1180 (s), 1145 (s), 1115 (s), 1060 (m), 1025 (m), 980 (m), 860 (w), 770 (m), 735 (m), 700 (m); NMR δ (CDCl_3) 1.10~1.90 (12H, m), 1.90~2.40 (2H, m), 3.06 (2H, d, $J=6.2$ Hz), 4.13 (2H, t, $J=5.1$ Hz), 5.50~5.58 (2H, m); GLC (column, PEG 20M, 50 m $\times$ 0.25 mm at 180°C; carrier gas, nitrogen, 1.15 kg/cm²): t_R 5.52 min (96.7%); MS (m/z) 196 (M^+ , 14%), 178 (7%), 136 (14%), 121 (8%), 112 (21%), 95 (26%), 81 (48%), 67 (65%), 53 (100%). HR-MS (m/z) 196.1476. Calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_2$: 194.1464. Anal. Found: C, 73.50; H, 10.24. Calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_2$: C, 73.43; H, 10.27%. Its IR, NMR and MS spectra were identical with those reported.^{1,2)}

(S)-(+)-3-Tetrahydropyranyloxybutyl bromide 11. (S)-3-Tetrahydropyranyloxybutan-1-ol tosylate **10** was prepared from **9** (97.7% *e.e.*)^{6,7)} according to the reported procedure.⁸⁾ NaHCO_3 (9.9 g, 117 mmol) and LiBr (9.9 g, 114 mmol) were added to a solution of **10** (25.0 g, 76 mmol) in dry acetone (250 ml), the mixture being stirred

overnight at room temperature. Then, the mixture was stirred and heated under reflux for 2 hr, and again stirred overnight at room temperature. Ether (200 ml) was added to the mixture and the mixture was filtered through Celite. The filter cake was washed with THF, the combined filtrate and washings were concentrated *in vacuo*. The residue was diluted with ether (200 ml) and successively washed with water, 10% $\text{Na}_2\text{S}_2\text{O}_3$ aq., sat. NaHCO_3 aq. and brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was chromatographed over silica gel (Fuji Davison BW 820 MH, 180 g). Elution with *n*-hexane-ethyl acetate (15:1) gave an oil, which was distilled to give 16.2 g (90%) of **11**, bp 64~75°C/0.55 mmHg, $n_D^{21.2}$ 1.4703; $[\alpha]_D^{21.3} + 50.8^\circ$ ($c=1.10$, CHCl_3); IR ν_{max} cm^{-1} 1135 (s), 1075 (s), 1030 (s), 990 (s); NMR δ (CCl_4) 1.10 and 1.22 (total 3H, each d, $J=6.0$ Hz), 1.30~1.70 (6H, m), 1.70~2.20 (2H, m), 3.20~4.10 (5H, m), 4.60 (1H, br. s). HR-MS (m/z) 236.0357. Calcd. for $\text{C}_9\text{H}_{17}\text{O}_2\text{Br}$: 236.0412.

(S)-(+)-5-Decyn-2-ol THP ether 12a. A solution of *n*-butyllithium in *n*-hexane (1.62 M, 50.3 ml, 82 mmol) was added dropwise over 15 min to a stirred and cooled solution of 1-hexyne (6.1 g, 74 mmol) in dry THF (74 ml) at between -20 and -10°C under argon. The mixture was then stirred for 20 min at 0°C, before a solution of **11** (15.9 g, 67 mmol) in dry HMPA (107 ml) was added over 25 min the stirred and cooled mixture, keeping the temperature below 0°C. After stirring for 15 min at 0~5°C, the mixture was quenched by the addition of ice-cooled water (20 ml), and poured into water (250 ml). The mixture was extracted with *n*-hexane, the *n*-hexane solution being washed with water and brine, dried over MgSO_4 and concentrated *in vacuo* to give 16.8 g of crude **12a**. A small portion was distilled to give an analytical sample, bp 110°C/1.4 mmHg, $n_D^{19.5}$ 1.4569; $[\alpha]_D^{18.4} + 11.9^\circ$ ($c=1.245$, CHCl_3); IR ν_{max} cm^{-1} 1135 (s), 1080 (s), 1020 (s); NMR δ (CDCl_3) 0.87~1.90 (18H, m), 1.90~2.30 (4H, m), 3.10~4.00 (3H, m), 4.60 (1H, br. s). Anal. Found: C, 75.54; H, 10.89. Calcd. for $\text{C}_{15}\text{H}_{26}\text{O}_2$: C, 75.58; H, 11.00%.

(S)-(+)-5-Decyn-2-ol 12b. **12a** (16.6 g, 70 mmol) was dissolved in MeOH (330 ml), and *p*-toluenesulfonic acid (1.1 g, 7.0 mmol) was added to the solution. The mixture was then stirred overnight at room temperature. An additional amount (0.3 g, 1.9 mmol) of *p*-toluenesulfonic acid was added to the mixture, and stirring was continued for another 3 hr. To this was added solid NaHCO_3 (7.0 g, 83 mmol), and the mixture was stirred for a further 2 hr at room temperature. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was diluted with water (300 ml) and extracted with ether. The ether solution was washed with brine and sat. NaHCO_3 aq., dried over MgSO_4 and concentrated *in vacuo*. The residue was distilled to give 7.8 g (75% from **11**) of **12b**, bp 77°C/4 mmHg, $n_D^{19.0}$ 1.4525; $[\alpha]_D^{22.0} + 17.3^\circ$ ($c=1.00$, CHCl_3); IR ν_{max} cm^{-1} 3320 (s), 1080 (s); NMR δ (CCl_4) 0.90 (3H, br. t, $J \approx 7$ Hz), 1.14 (3H, d, $J=6.0$ Hz), 1.25~

1.80 (6H, m), 1.85~2.40 (4H, m), 3.50~4.00 (1H, m). *Anal.* Found: C, 77.77; H, 11.82. Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76%.

(S)-(+)-9-Decyn-2-ol **13**. Potassium hydride (a 35% suspension in mineral oil, 35 ml, 310 mmol) was washed three times with dry pentane under argon. Freshly distilled 1,3-diaminopropane (260 ml) was added at room temperature, and the mixture was stirred for 1.5 hr at room temperature. Then, the mixture was cooled to 0°C and to this was rapidly added **12b** (5.0 g, 32 mmol). After the addition, the temperature was raised to room temperature and the mixture was stirred for 30 min at room temperature. The mixture was again cooled to 0°C and quenched by the addition of sat. NH_4Cl aq. The mixture was poured into ice-cooled water (500 ml) and neutralized by the addition of conc. HCl aq. (ca. 1000 ml). This solution was extracted with ether, before the ether solution was washed with water, sat. $NaHCO_3$ aq. and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled to give 4.6 g (91%) of **13**, bp 81°C/3.2 mmHg, $n_D^{21.5}$ 1.4487; $[\alpha]_D^{21.2} + 9.4^\circ$ ($c = 1.02$, $CHCl_3$); IR ν_{max} cm^{-1} 3400 (s), 3330 (s), 2130 (w); NMR δ ($CDCl_3$) 1.17 (3H, d, $J = 7.0$ Hz), 1.20~1.80 (10H, m), 1.63 (1H, br. s), 1.91 (1H, t, $J = 2.3$ Hz), 2.00~2.40 (2H, m), 3.50~3.90 (1H, m). *Anal.* Found: C, 77.82; H, 11.56. Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76%.

4-Iodo-1-butanol THP ether **14**. 4-Iodo-1-butanol was obtained according to the reported procedure,¹⁰ IR ν_{max} cm^{-1} 3350 (s), 1050 (s), 1025 (s). 4-Iodo-1-butanol (10 g, 50 mmol) and dihydropyran (6.26 g, 74 mmol) were dissolved in dry CH_2Cl_2 (66 ml), and pyridinium *p*-toluenesulfonate (1.24 g, 4.9 mmol) was added to the stirred solution at room temperature. The mixture was stirred for 4 hr at room temperature. After adding ether (20 ml), the mixture was washed with water and 10% $Na_2S_2O_3$ aq., dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled to give 8.9 g (63%) of **14**, bp 95°C/1.0 mmHg, $n_D^{15.2}$ 1.5060; IR ν_{max} cm^{-1} 1180 (m), 1135 (s), 1125 (s), 1080 (s), 1035 (s); NMR δ ($CDCl_3$) 1.30~2.30 (10H, m), 3.10~4.20 (6H, m), 4.64 (1H, br. s). HR-MS (m/z) 284.0247. Calcd. for $C_9H_{17}O_2I$: 284.0274.

(S)-(+)-5-Tetradecyne-1,13-diol 1-THP ether **15a**. A solution of *n*-butyllithium (1.50 M, 4.53 ml, 6.80 mmol) was added dropwise over 10 min to a stirred and cooled solution of **13** (500 mg, 3.25 mmol) in dry THF (5 ml) at between -15 and -14°C under argon. The solution was stirred for 5 min at -15°C, before HMPA (2 ml) was added over 5 min to the stirred and cooled mixture, keeping its temperature below -10°C. The stirring was continued for 3 hr at between -18 and -5°C. Then, a solution of **14** (968 mg, 3.41 mmol) in HMPA (5 ml) was added over 30 min to the mixture with stirring and cooling at -15°C. After the addition, the temperature was gradually raised over 2 hr to room temperature. The mixture was cooled

to -15°C and quenched by the addition of water (20 ml) below 0°C, and then extracted with ether. The ether solution was washed with 10% $Na_2S_2O_3$ aq. and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Merck Kieselgel 60, Art 9385, 25 g). Elution with *n*-hexane-ether (4:1) gave the recovery of **13** (112 mg). Further elution with the same solvent gave 550 mg (70.4% based on the **13** consumed) of **15a**, $n_D^{18.4}$ 1.4730; $[\alpha]_D^{18.4} + 3.2^\circ$ ($c = 1.81$, $CHCl_3$); IR ν_{max} cm^{-1} 3450 (s), 1140 (s), 1125 (s), 1080 (s), 1040 (s), 1025 (s); NMR δ ($CDCl_3$) 1.19 (3H, d, $J = 6.2$ Hz), 1.30~2.00 (21H, m), 2.00~2.40 (4H, m), 3.20~4.00 (5H, m), 4.60 (1H, br. s). *Anal.* Found: C, 73.31; H, 11.12. Calcd. for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04%.

(S)-(+)-13-Acetoxy-5-tetradecyn-1-ol THP ether **15b**. Acetic anhydride (1.12 g, 11 mmol) was added to a stirred solution of **15a** (360 mg, 1.16 mmol) in pyridine (0.87 g, 10.6 mmol). The mixture was stirred for 15 hr at room temperature, before being diluted with ice-cooled water and extracted with ether. The ether solution was successively washed with water, sat. $CuSO_4$ aq., sat. $NaHCO_3$ aq. and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel (Fuji Davison BW 820 MH, 10.5 g). Elution with *n*-hexane-ether (40:1~4:1) gave 396 mg (97%) of **15b**, $n_D^{19.5}$ 1.4620; $[\alpha]_D^{19.5} + 0.7^\circ$ ($c = 1.045$, $CHCl_3$); IR ν_{max} cm^{-1} 1740 (s), 1245 (s), 1140 (s), 1125 (s), 1080 (s), 1040 (s), 1025 (s); NMR δ (CCl_4) 1.16 (3H, d, $J = 6.0$ Hz), 1.25~1.90 (20H, m), 1.95 (3H, s), 2.00~2.50 (4H, m), 3.00~4.00 (4H, m), 4.52 (1H, br. s), 4.64~5.05 (1H, m). *Anal.* Found: C, 71.75; H, 10.28. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30%.

(S)-(+)-13-Acetoxy-5-tetradecyn-1-ol **15c**. **15b** (100 mg, 0.28 mmol) was dissolved in a mixture of acetic acid (3.2 ml), water (0.8 ml) and THF (1.6 ml), and the mixture was stirred for 24 hr at 25~30°C. Then, the mixture was diluted with water (10 ml) and neutralized by the addition of 10% Na_2CO_3 aq., before being extracted with ether. The ether solution was successively washed with water, sat. $NaHCO_3$ aq. and water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel (Fuji Davison BW 820 MH, 2 g). Elution with *n*-hexane-ether (4:1~1:1) gave 76 mg (quantitative) of **15c**. Distillation of this gave an analytical sample, bp 130~135°C/0.37 mmHg, $n_D^{21.1}$ 1.4605; $[\alpha]_D^{22.5} + 0.9^\circ$ ($c = 1.175$, $CHCl_3$); IR ν_{max} cm^{-1} 3450 (m), 1740 (s), 1720 (sh), 1250 (s), 1060 (s), 1035 (s); NMR δ ($CDCl_3$) 1.17 (3H, d, $J = 6.0$ Hz), 1.25~1.85 (14H, m), 2.03 (3H, s), 1.85~2.40 (4H, m), 3.65 (3H, t, $J = 6.0$ Hz), 4.75 (1H, m). *Anal.* Found: C, 71.25; H, 10.42. Calcd. for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52%.

(S)-(+)-13-Acetoxy-5-tetradecynoic acid **16a**. Jones chromic acid (8 N, 5 ml) was added dropwise to a solution of **15c** (1.50 g, 5.60 mmol) in acetone (70 ml) with stirring

and cooling at 0~5°C, stirring being continued for 15 min at 0~5°C. The excess chromic acid was destroyed by the addition of isopropyl alcohol (8 ml). The temperature was then raised to room temperature, and the mixture was stirred for 1 hr at room temperature. The mixture was diluted with 10% sodium chloride solution (250 ml), and extracted with ether. The ether solution was washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was chromatographed over silica gel (Fuji Davison BW 820 MH, 30 g), elution with *n*-hexane-ether (8:1~2:1) giving 1.27 g (80.4%) of **16a**, $n_D^{22.5}$ 1.4593; $[\alpha]_D^{23.2} + 0.5^\circ$ ($c=1.05$, CHCl_3); IR ν_{max} cm^{-1} 3730~2350 (br. s), 1740~1700 (s), 1245 (s); NMR δ (CCl_4) 1.16 (3H, d, $J=6.0$ Hz), 1.33 (12H, br. s), 1.70~2.60 (6H, m), 1.95 (3H, s), 4.60~5.00 (1H, m), 10.73 (1H, br. s). *Anal.* Found: C, 67.69; H, 9.27. Calcd. for $\text{C}_{16}\text{H}_{26}\text{O}_4$: C, 68.05; H, 9.28%.

(*S*)-(+)-13-Hydroxy-5-tetradecynoic acid **16b**. **16a** (1.22 g, 4.32 mmol) was dissolved in methanol (31 ml). To this was added solid K_2CO_3 (6.6 g, 47.5 mmol) and the mixture was stirred overnight at room temperature. Then, the mixture was acidified with 2.5N-HCl aq. to pH 3, and extracted with ether. The ether solution was washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was dissolved in toluene (5 ml) and concentrated *in vacuo*, this operation being repeated three times to remove the acetic acid and water. The residue was recrystallized from *n*-pentane-ether to give 880 mg (84.6%) of **16b**, mp 30.5~31.5°C; $[\alpha]_D^{23.2} + 6.0^\circ$ ($c=1.06$, CHCl_3); IR ν_{max} cm^{-1} : 3800~2300 (br. s), 1710 (s); NMR δ (CDCl_3) 1.16 (3H, d, $J=6.0$ Hz), 1.34 (10H, br. s), 1.60~2.60 (8H, m), 3.50~4.00 (1H, m), 5.01 (2H, br. s). *Anal.* Found: C, 69.90; H, 10.28. Calcd. for $\text{C}_{14}\text{H}_{24}\text{O}_3$: C, 69.96; H, 10.07%.

(*S,Z*)-(+)-13-Hydroxy-5-tetradecenoic acid **17**. NaBH_4 (250 mg, 13.2 mmol) was dissolved in 95% EtOH (6 ml) containing 2N-NaOH aq. (0.32 ml). After stirring for a while, the mixture was filtered. A portion (1.25 ml) of the filtrate was added dropwise to a vigorously stirred mixture of nickel acetate tetrahydrate (250 mg, 1.0 mmol) in dry EtOH (20 ml) under hydrogen. Ethylenediamine (0.20 ml, 2.98 mmol) was added to the resulting black suspension. A solution of **16b** (850 mg, 3.50 mmol) in 95% EtOH (10 ml) was then added dropwise to the suspension of P-2 nickel under hydrogen. The mixture was stirred for 2.5 hr at room temperature, before it was diluted with brine (80 ml), acidified with 2N-HCl aq. to pH 3, and extracted with ether. The ether solution was washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Merck Kieselgel 60, Art 9385, 30 g). Elution with *n*-hexane-ethyl acetate-acetic acid (75:25:1) gave 766 mg (89.4%) of **17**, $n_D^{22.5}$ 1.4650; $[\alpha]_D^{22.6} + 6.4^\circ$ ($c=1.225$, CHCl_3); IR ν_{max} cm^{-1} 3700~2300 (br. s), 1710 (s), 1245 (m); NMR δ (CDCl_3) 1.17 (3H, d, $J=6.0$ Hz), 1.25~1.60 (10H, m), 1.60~2.50 (8H, m), 3.50~4.00 (1H, m), 5.20~5.50 (2H, m), 6.10 (2H, br. s). *Anal.* Found: C, 69.29; H, 10.77. Calcd. for

$\text{C}_{14}\text{H}_{26}\text{O}_3$: C, 69.38; H, 10.81%.

(*5Z,13S*)-5-Tetradecen-13-olide **2**. According to the reported procedure,²¹ **17** (500 mg) afforded **2** (280 mg, 60.5%), which was distilled to give 245 mg (52.9%) of **2**, bp 69.0~75.0°C/0.1 mmHg, $n_D^{23.0}$ 1.4728; $[\alpha]_D^{23.0} + 54.4^\circ$ ($c=1.275$, CHCl_3) [lit.²¹ $[\alpha]_D^{32} + 49.6^\circ$ ($c=4.62$, CHCl_3)]; IR ν_{max} cm^{-1} 2950 (s), 2880 (s), 1735 (s), 1460 (s), 1420 (m), 1380 (m), 1350 (m), 1330 (m), 1295 (m), 1248 (s), 1208 (s), 1190 (m), 1160 (m), 1135 (s), 1105 (m), 1040 (m), 1018 (m), 995 (w), 975 (w), 938 (w), 902 (w), 878 (w), 860 (w), 838 (w), 802 (w), 710 (m); NMR δ (JEOL JMN FX-400, 400 MHz, CDCl_3) 1.22 (3H, d, $J=5.5$ Hz), 1.25~1.68 (13H, m), 1.70~1.78 (1H, m), 1.78~1.98 (2H, m), 2.15~2.38 (2H, m), 2.23 (1H, m), 2.44 (1H, m), 4.94~5.03 (1H, m), 5.31 (1H, m), 5.40 (1H, m); MS (m/z) 225 ($\text{M}^+ + 1$, 7%), 224 (M^+ , 41%), 206 (3%), 181 (9%), 168 (9%), 164 (16%), 150 (12%), 140 (17%), 137 (10%), 126 (48%), 110 (41%), 95 (54%), 81 (98%), 67 (100%), 55 (71%); GLC (column, OV-101, 50 m $\times$ 0.25 mm at 208°C; carrier gas, nitrogen, 1.15 kg/cm²): t_R 40.81 min (99.2%). *Anal.* Found: C, 74.62; H, 10.91. Calcd. for $\text{C}_{14}\text{H}_{24}\text{O}_2$: C, 74.95; H, 10.78%. Its NMR mass spectra were identical with those of natural **2**.¹⁾

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