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A NEW SYNTHESIS OF (-)-α-MULTISTRIATIN, THE PHEROMONE OF THE SMALLER EUROPEAN ELM BARK BEETLE†

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Abstract -- (-)-α-Multistriatin[(1S,2R,4S,5R)-2,4-dimethyl-5-ethyl-6,8-dioxabicyclo-[3.2.1]octane] was synthesized from (Z)-2-butene-1,4-diol monobenzyl ether by employing the Sharpless asymmetric epoxidation and the regioselective epoxide cleavage with Me_3Al as the key-steps.

The smaller European elm bark beetle, Scolytus multistriatus Marsham is the principal vector of Dutch elm disease in Europe and in the United States. Its aggregation pheromone was characterized as a mixture of (1S,2R,4S,5R)-(-)-α-multistriatin **A**(=1), (3S,4S)-(-)-4-methyl-3-heptanol **B** and (-)-α-cubebene **C** by Silverstein and his co-workers.[1] The structure of (-)-α-multistriatin as depicted in **1** was confirmed by a number of syntheses of its racemate[2,3] as well as the correct enantiomer. The existing eight different syntheses[4-11] of optically active α-multistriatin **1** started from D-glyceraldehyde acetonide(Mori[5]), (R)-citronellol (Kocienski[6]), D-glucose(Weiler[7] and Fraser-Reid[8]), (S)-malic acid (Larcheveque[11]) and optically active intermediates obtained either by resolution[4,9] or by asymmetric epoxidation.[10]

Although the chiral syntheses of **1** served to establish the absolute configuration of the natural α-multistriatin, only very few of them were successful in affording the enantiomerically pure (-)-**1**. The syntheses reported by Weiler[7] and Larcheveque[11] were successful enough to furnish the pure enantiomer of **1**. Herein we report a new synthesis of the enantiomerically pure (-)-**1** by employing the Sharpless asymmetric epoxidation[12] of **2** to **3a** and the regioselective ring-cleavage of the resulting epoxy alcohol **3a** with Me_3Al[13-15] to give **4a** as the major product. This epoxidation-methylation technique was previously employed by us in the synthesis of (3S,4S)-(-)-**B**[16] and also in the synthesis of brassinolide, a steroidal plant-growth promotor.[17]

(Z)-2-Butene-1,4-diol monobenzyl ether **2** was chosen as our starting material. Asymmetric epoxidation of **2**, using (-)-diisopropyl D-tartrate, t-BuOOH and $Ti(i\text{-}PrO)_4$, gave in 86% yield the optically active epoxy alcohol (2R,3S)-**3a**, which was previously prepared by a multi-step synthesis from D-tartaric acid.[18] As the specific rotation of our **3a** revealed it to be of ca. 89% e.e., we converted it to the corresponding 3,5-dinitrobenzoate **3b**. Recrystallization of **3b** afforded pure **3b** in 73% yield from the crude **3a**. Alkaline hydrolysis of the purified **3b** gave pure **3a**, whose enantiomeric purity was estimated to be ca. 100% by the ^1H NMR analysis at 400 MHz of the corresponding (R)- and (S)-α-methoxy-α-trifluoromethylphenylacetate(MTPA ester).[19]

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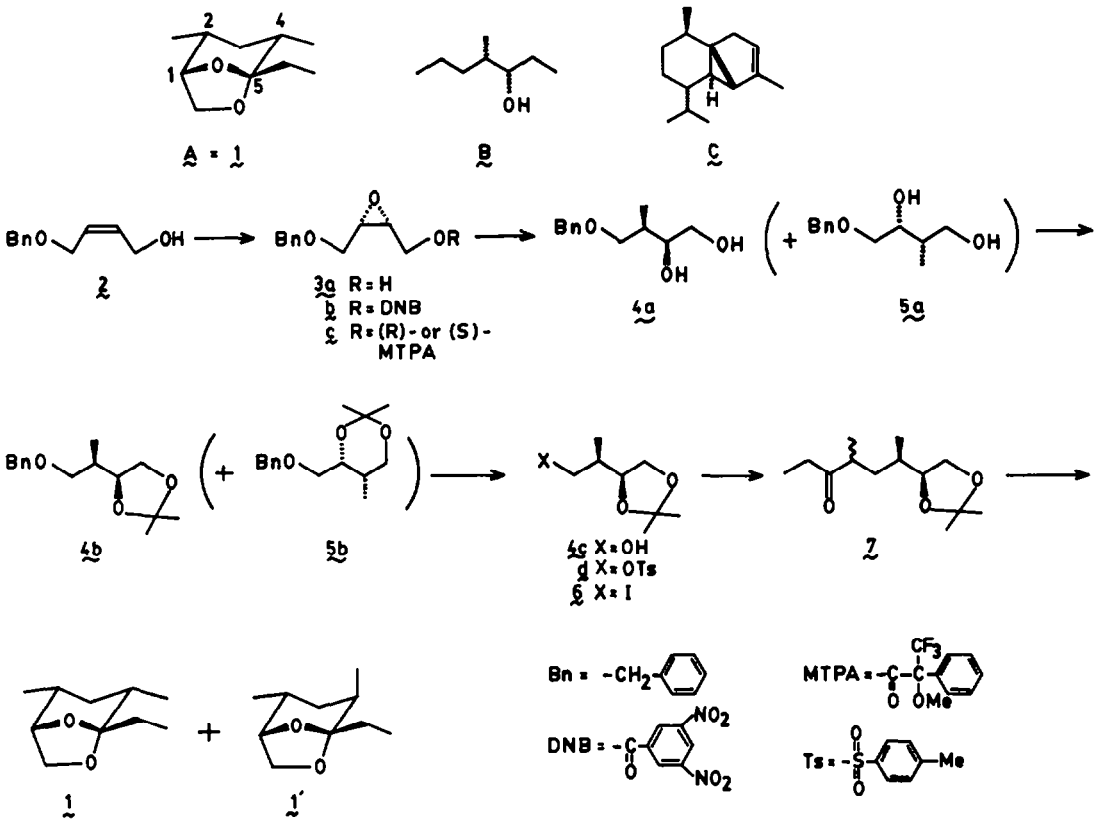

The regioselective ring-cleavage of the epoxy alcohol **3a** was executed by treatment with Me_3Al in n-pentane/CH_2Cl_2(10:1) to give the desired 1,2-diol (2S,3R)-**4a** as the major product contaminated with a small amount of the undesired 1,3-diol (2S,3R)-**5a**.[cf.20] Because it was difficult to separate the diol mixture of **4a** and **5a** by conventional chromatographic techniques, it was immediately converted to the mixture of the corresponding acetonides **4b** and **5b** by treatment with acetone and p-TsOH. The mixture was separable by chromatographic means, and the ratio of **4b** to **5b** was estimated to be 94:6 by GLC analysis. Pure **4b** was obtained in 73% yield from **3a** after chromatographic purification. Removal of the benzyl protective group of **4b** by hydrogenolysis over Pd-C gave an acetonide alcohol **4c**. The later steps to α-multistriatin **1** were carried out in a similar manner as described by us for the synthesis of δ-multistriatin.[21] The acetonide alcohol **4c** was converted to an iodide **6** in 86% yield *via* the corresponding tosylate **4d**. Lithium enolate of diethyl ketone generated by lithium diisopropylamide(LDA) in THF was alkylated with **6** to give **7** in 46% yield as a diastereomeric mixture at C-4. Finally, treatment of **7** with aq HCl-MeCN gave in 85% yield a mixture of (-)-α-multistriatin **1** and (-)-γ-multistriatin **1'** in a ratio of 81:19 as revealed by GLC analysis. This mixture was further purified by preparative GLC to give pure (-)-α-multistriatin **1**, $[\alpha]_D^{23.5}$ -46°(n-hexane) [lit.[4] for the natural pheromone: $[\alpha]_D^{25}$ -47°; lit.[7] $[\alpha]_D^{24}$ -46°(hexane); lit.[11] $[\alpha]_D^{22}$ -45°(hexane)].

In summary, a new synthesis of (1S,2R,4S,5R)-(-)-α-multistriatin was achieved to secure an enantiomerically pure sample. After the completion of this work, another synthesis of **4b** was reported without full experimental details.[22]

EXPERIMENTAL

All m.ps and b.ps were uncorrected. IR spectra were measured as Nujol mulls(solid) or as films(liquid) on a Jasco IRA-102 spectrometer. ^{1}H NMR spectra were recorded with TMS as an internal standard at 60 MHz on a Hitachi R-24A spectrometer or at 400 MHz on a Bruker AM-400 spectrometer. ^{13}C NMR spectra were recorded with TMS as an internal standard at 100 MHz on a Bruker AM-400 spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. Mass spectra were recorded on a JEOL DX-303 spectrometer at 70 eV.

(2R,3S)-4-Benzyloxy-2,3-epoxy-1-butanol **3a**. To stirred and cooled dry CH_2Cl_2(400 ml) at -20°~ -25°C under Ar were added $Ti(i\text{-}PrO)_4$ (11.9 ml, 40 mmol), (-)-diisopropyl D-tartrate (9.37 g, 40 mmol), 2 (6.65 g, 38 mmol) and a soln of t-BuOOH in CH_2Cl_2 (4.5 M, 18 ml, 80 mmol) in this order. This mixture was left to stand for 40 hr at -20°C. The temp was raised to room temp and the reaction mixture was diluted with ether (500 ml) and sat Na_2SO_4 (12 ml) aq. The mixture was stirred vigorously for 2 hr at room temp, and filtered. The filtrate was concentrated in vacuo and the residue (16.8 g) was chromatographed over SiO_2 to give 6.33 g (86 %) of **3a**. $[\alpha]_D^{25}$ +25° (c=1.0, $CHCl_3$). This was converted to the corresponding 3,5-dinitrobenzoate for further purification.

(2R,3S)-4-Benzyloxy-2,3-epoxy-1-butyl 3,5-dinitrobenzoate **3b**. To a stirred and ice-cooled soln of **3a** (11.7g, 60 mmol) in dry ether-pyridine (200 ml/80 ml) was added 3,5-dinitrobenzoyl chloride (18.5g, 80 mmol) and the mixture was stirred for 30 min at 0°~-5°C. It was then poured into water and extracted with EtOAc. The org layer was washed with water, N-HCl aq, sat $NaHCO_3$ aq, water and brine, dried($MgSO_4$) and concentrated in vacuo. The residue(25 g) was repeatedly recrystallized from ether-CH_2Cl_2(10:1) to give 17.1 g (73 %) of **3b** with a constant optical rotation. m.p. 99-99.5°C ; $[\alpha]_D^{24}$ +37° (c=1.0, $CHCl_3$); ν_{max} 3120(w), 3100(w), 1730(s), 1625(w), 1538(m), 1345(s), 1275(m), 1165(m), 1100(m), 740(m), 700(m) cm^{-1}; δ ($CDCl_3$) 3.2~3.6 (2H, m), 3.6~3.9 (2H, m, 3.70, 3.79), 4.60 (2H, s),~4.4~4.8 (2H, m), 7.38 (5H, s), 9.32 (3H, s). (Found : C, 55.64; H, 4.18; N, 7.28. Calc for $C_{18}H_{16}O_8N_2$: C, 55.67; H, 4.15; N, 7.21 %).

Hydrolysis of **3b** to **3a**. To a stirred and ice-cooled soln of **3b** (18.4g, 47 mmol) in THF-EtOH (1:1, 200 ml) was added dropwise N-KOH aq (56 ml, 56 mmol). After the addition, the mixture was stirred for 1 hr at room temp. Then the mixture was diluted with sat $NaHCO_3$ aq and concentrated in vacuo. The residue was extracted with ether. The ether soln was washed with sat $NaHCO_3$ aq, water and brine, dried($MgSO_4$) and concentrated in vacuo. The residue was purified by SiO_2 chromatography and distilled to give 9.0 g(98 %) of pure **3a**. b.p 135°C / 0.35 Torr ; n_D^{22} 1.5208 ; $[\alpha]_D^{22}$ +28° (c=0.96, $CHCl_3$); ν_{max} 3450(s), 3040(w), 3000(w), 1090(s), 1025(m), 740(m), 700(m) cm^{-1}; δ($CDCl_3$) 2.78 (1H, t, J=6 Hz), 2.9~3.2 (2H, m), 3.35~3.65 (4H, m), 4.43 (2H, s), 7.20 (5H, s). (Found : C, 67.73 ; H, 7.22. Calc for $C_{11}H_{14}O_3$: C, 68.02 ; H, 7.27 %).

(2S,3R)-4-Benzyloxy-3-methylbutane-1,2-diol acetonide **4b**. To a stirred soln of **3a** (6.87g, 35.4 mmol) in distilled n-pentane (700 ml) was added dropwise Me_3Al in hexane (1.0 M, 138 ml, 138 mmol) at room temp under Ar. After the addition of Me_3Al, 70 ml of CH_2Cl_2 was added. The mixture was stirred for 24 hr at room temp, diluted with CH_2Cl_2 and washed with cold N-HCl. The aq layer was extracted with EtOAc. The combined org soln was washed with water, sat $NaHCO_3$ aq, water and brine, dried ($MgSO_4$) and concentrated in vacuo to give 7.57 g of the crude mixture of 1,2-diol **4a** and 1,3-diol **5a**. ν_{max} 3400(s), 1090(s) cm^{-1}. This was employed for the next step without further purification. The crude **4a+5a** was dissolved in a stirred soln of p-TsOH·H_2O(30 mg) in acetone(100 ml) and the mixture was stirred for 6 hr at room temp. The mixture was diluted with sat $NaHCO_3$ aq and extracted with ether. The org soln was washed with water, sat $NaHCO_3$ aq and brine, dried($MgSO_4$) and concentrated in vacuo. The residue (9.4 g) was chromatographed over SiO_2 and distilled to give 6.49 g (73 % from **3a**) of **4b**, b.p. 118-121°C / 0.45 Torr; n_D^{24} 1.4833; $[\alpha]_D^{24}$ -1.0° (c=0.94, $CHCl_3$); ν_{max} 1380 (s), 1215 (m), 1100 (m), 1060 (s), 738 (m), 700 (m) cm^{-1}; δ(CCl_4) 0.96 (3H, d, J=7 Hz), 1.27 (3H, s), 1.29 (3H, s), 1.6~2.2 (1H, m), 3.27 (2H, d, J=6 Hz), 3.4 ~ 4.1 (3H, m), 4.42 (2H, s), 7.29 (5H, s); GLC (column, 10%-PEG, 2m x 4mm, at 190°C const; carrier gas, N_2, 50ml/min) Rt 12.7 min (**4b**). Rt of **5b** was 15.9 min. (Found : C, 72.33 ; H, 8.86. Calc for $C_{15}H_{22}O_3$: C, 71.97 ; H, 8.86 %). Further elution gave a small amount of 1,3-acetonide **5b**.

(2S,3R)-3-Methylbutane-1,2,4-triol 1,2-acetonide **4c**. 10 % Pd-C (1.20 g) and $NaHCO_3$ (100 mg) were added to a soln of **4b** (3.95 g, 15.8 mmol) in 95% EtOH (300 ml) and the suspension was vigorously stirred under H_2 at room temp. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue (2.41 g) was distilled to give 2.30 g (91 %) of **4c**, b.p. 88~92°C / 0.35 Torr; n_D^{24} 1.4352; $[\alpha]_D^{24}$ -1.8° (c=1.1, $CHCl_3$); ν_{max} 3450 (s), 1370 (m), 1215 (m), 1060 (s), 1040 (s), 855 (m) cm^{-1}; δ(CCl_4) 0.91 (3H, d, J=7 Hz), 1.28 (3H, s), 1.33 (3H, s), 1.4~2.0 (1H, m), 2.65 (1H, s), 3.4 (2H, d, J=6 Hz), 3.5~4.2 (3H, m, 3.53, 3.62, 3.70, 3.78, 3.86, 3.94, 4.02). (Found: C, 59.88; H, 10.06. Calc for $C_8H_{16}O_3$: C, 59.98; H, 10.07 %).

(2S,3R)-4-Tosyloxy-3-methylbutane-1,2-diol acetonide **4d**. To a stirred and ice-cooled soln of **4c** (2.67 g, 16.7 mmol) in dry pyridine (30 ml) was added p-TsCl (6.37 g, 33.4 mmol) and the mixture was stirred at 0°C for 2 hr and then at room temp for 8 hr. The mixture was poured into ice-water and extracted with ether. The ether soln was washed with N-HCl aq, water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue (5.06 g) was chromatographed over SiO_2 to give 4.80 g (92 %) of (2S,3R)-**4d**, n_D^{24} 1.4950; $[\alpha]_D^{24}$ -7.7° (c=1.1, $CHCl_3$); ν_{max} 1595 (m), 1360 (s), 1210 (m), 1175 (s), 1060 (m), 965 (s), 810 (m) cm^{-1}; δ(CCl_4) 0.91 (3H, d, J=6.5Hz), 1.21 (3H, s), 1.25 (3H, s), 1.85 (1H, q.t, J=6.5, 6 Hz), 2.43 (3H, s), 3.45 (1H, t, J=9 Hz), 3.65~4.20 (2H, m), 3.80 (2H, d, J=6 Hz), 7.28 (2H, d, J=9 Hz), 7.73 (2H, d, J=9 Hz). (Found : C, 57.29 ; H, 7.01. Calc for $C_{15}H_{22}O_5S$: C, 57.31 ; H, 7.05 %).

(2S,3S)-4-Iodo-3-methylbutane-1,2-diol acetonide **6**. NaI (5.22 g, 34.8 mmol) and $NaHCO_3$ (1 g) were added to a soln of **4d** (3.64 g, 11.6 mmol) in dry acetone (50 ml) and the mixture was stirred under Ar for 2 days. The mixture was poured into water and extracted with ether(x3). The ether soln was washed with water, 10 % $Na_2S_2O_3$ aq, water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by SiO_2 chromatography followed by distillation to give 2.94 g (94 %) of **6**, b.p. 87~90°C / 5 Torr; n_D^{23} 1.4941; $[\alpha]_D^{23}$ -6.6° (c=0.92, C_6H_6); ν_{max} 1450 (w), 1380 (m), 1375 (m), 1210 (m), 1150 (m), 1065 (s), 885 (m) cm^{-1}; δ(CCl_4) 1.05 (3H, d, J=6 Hz), 1.32 (3H, s), 1.38 (3H, s), 1.4~2.0 (1H, m), 2.94 (1H, dd, J=7, 10 Hz), 3.21 (1H, dd, J=7, 10 Hz), 3.37~4.2 (3H, m, 3.4, 3.55, 3.71, 3.84, 3.94, 4.02, 4.08, 4.18). (Found : C, 35.73 ; H, 5.68. Calc for $C_8H_{15}O_2I$: C, 35.58 ; H, 5.60 %).

(2S,3R,5RS)-3,5-Dimethyl-6-oxooctane-1,2-diol acetonide **7**. A soln of LDA was prepared by the addition of 1.62 M n-BuLi (in n-hexane, 9.0 ml) to a stirred soln of i-Pr_2NH (2.1 ml, 15 mmol) in dry THF (10 ml) at -65°C under Ar. The soln was stirred for 1 hr at this temp. A soln of Et_2CO (1.6 ml) in THF (15 ml) was added to the stirred and cooled LDA soln at -65--60°C. After stirring for 1 hr at -40°C, a soln of **6** (0.70 g, 2.6 mmol) in THF (15 ml) was added at -40°C with stirring. After gradually warming to room temp, the stirring was continued for 2 days. The mixture was poured into ice-brine and extracted with ether. The org soln was washed with N-HCl aq, water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated in vacuo to give a crude oil (1.17 g). This was chromatographed over SiO_2. Elution with n-hexane-EtOAc (20:1) gave a small amount of recovered starting material **6** and further elution gave 0.29 g of crude **7**, which was distilled to give 0.27 g (46 %) of **7** as a stereoisomeric mixture at C-5, b.p. 85-90°C / 4 Torr; n_D^{24} 1.4401; $[\alpha]_D^{23}$ +14.9° (c=1.02, $CHCl_3$); ν_{max} 1710 (s), 1460 (m), 1375 (m), 1210 (m), 1160 (m), 1065 (m), 855 (m) cm^{-1}; GLC (column, 10%-PEG, 2m x 4mm at 100°C (+2°C/min); carrier gas, N_2, 0.4 kg/cm^2): R_t 13.4 min(48 %), 14.5 min(52 %).

(1S,2R,4S,5R)-2,4-Dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (α-multistriatin) **1**. A soln of **7** (300 mg) in MeCN-10% HCl aq (4.7 ml/2.3 ml) was stirred overnight at room temp. The soln was saturated with NaCl by the addition of powdered NaCl, poured into brine and extracted with ether. The ether extract was washed with water, sat $NaHCO_3$ aq and brine, dried($MgSO_4$) and concentrated under atm press to give crude (-)-**1** as the major product. This was chromatographed over SiO_2 and distilled to give 202 mg (85 %) of **1** which contains a small amount of **1'**. The ratio of **1** and **1'** was 81:19 on glc (column, 10%-PEG, 2m x 4mm, 80°C const, carrier gas, N_2 0.7 kg/cm^2, R_t 18.0 min(**1**, 81%), 19.8 min(**1'**, 19%). b.p. 100-105°C / 45 Torr; n_D^{19} 1.4454; $[\alpha]_D^{19}$ -44° (c=0.84, ether); (Found : m/z 170.1275 Calc. for $C_{10}H_{18}O_2$: 170.1307). GC-MS (70 eV) 55 (27 %), 57 (100 %), 59 (28 %), 69 (13 %), 71 (18 %), 74 (20 %), 81 (20 %), 83 (17 %), 96 (25 %), 97 (17 %), 128 (15 %), 141 (19 %), 170 (M^+, 6 %), 171 (M+1, 1 %). This was further purified by preparative GLC (column, 10%-PEG, 4m x 6mm, at 100°C (+2°C/min), carrier gas N_2 0.1 ml/min) to give purified (-)-**1**, n_D^{24} 1.4501; $[\alpha]_D^{23.5}$ -46° (c=0.99, n-hexane); ν_{max} 2956 (s), 2920 (s), 2880 (s), 1484 (w), 1460 (m), 1440 (w), 1378 (m), 1362 (m), 1341 (w), 1312 (w), 1282 (w), 1245 (m), 1203 (m), 1176 (s), 1125 (m), 1110 (m), 1093 (w), 1055 (m), 1032 (s), 1000 (w), 988 (m), 957 (m), 915 (m), 896 (s), 820 (w), 784 (w), 760 (w) cm^{-1}; NMR (400 MHz, $CDCl_3$) δ = 0.81 (6H, d, J=6.7 Hz), 0.93 (3H, t, J=7.5 Hz), 1.02 (1H, ddd, J=13.4, 11.7, 11.7 Hz), 1.60 (1H, dddd, J=13.4, 5.0, 5.0, 1.5 Hz), 1.71 (2H, q, J=7.5 Hz), 1.79 (1H, ddq, J=11.7, 5.0, 6.7 Hz), 1.99-2.06 (1H, m), 3.68 (1H, ddd, J=7.0, 5.0, 0.5 Hz), 3.88 (1H, d, J=7.0 Hz), 4.21 (1H, m) ^{13}C NMR (100 MHz, $CDCl_3$) δ = 7.22, 16.42, 16.62, 22.16, 33.21, 34.93, 37.29, 65.22, 78.88, 110.44 GLC (column, PEG 20M, 50m x 0.25mm, at 110°C (+3°C/min), carrier gas N_2 1.0 kg/cm^2) R_t 1048 sec.(>98%, (-)-**1**), 1072 sec.(<2%, (-)-**1'**).

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