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SYNTHESIS OF BOTH THE ENANTIOMERS OF *ENDO*-BREVICOMIN, THE AGGREGATION PHEROMONE OF *DRYOCOETES AUTOGRAPHUS*†

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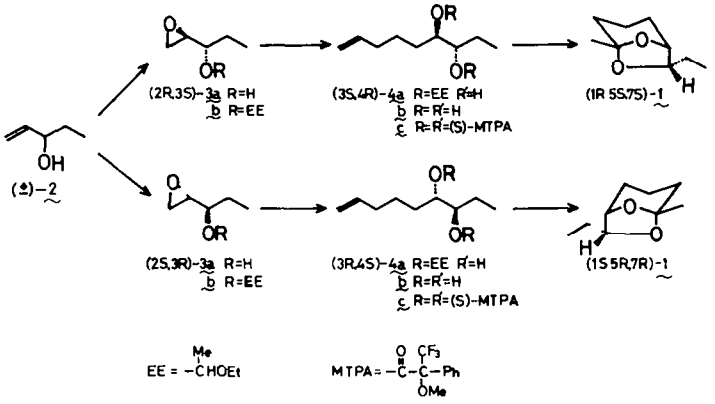
Abstract—(1*R*,5*S*,7*S*)-(+)-*endo*-Brevicomin (7-ethyl-5-methyl-6,8-dioxabicyclo[3 2 1]octane) and its (1*S*,5*R*,7*R*)-(−)-isomer were synthesised employing the Sharpless asymmetric epoxidation as the key-step

endo-Brevicomin **1** was first isolated[1] and synthesised[2] by Silverstein *et al* as a biologically inactive component of the frass of the western pine beetle, *Dendroctonus brevicomis* Very recently Kohnle and Vite[3] found that the aggregation of female and male beetles of the scolytid *Dryocoetes autographus* on Norway spruce was enhanced by *endo*-brevicomin **1** released by the male beetle upon feeding in the phloem tissue of suitable host material In cooperation with Professor Vite, we became interested in synthesising the enantiomers of **1** so as to find the stereochemistry–pheromone activity relationship Although a number of syntheses of (±)-**1** have been recorded to date,[4–11] there is only one paper reporting the synthesis of (+)- and (−)-**1** [12] That chiral synthesis of **1**, however, was not stereoselective [12] Herein we describe a simple and enantioselective synthesis of both (1*R*,5*S*,7*S*)-(+)- and (1*S*,5*R*,7*R*)-(−)-**1** in highly optically pure state (96–97% e e)

treated with ethyl vinyl ether in the presence of pyridinium *p*-toluenesulfonate (PPTS) to give (2*R*,3*S*)-**3b** in 23% overall yield from (±)-**2** A Grignard reagent prepared from 3-butenyl bromide was added to the epoxide **3b** in the presence of Cu_2Br_2[14] to effect the C-chain elongation yielding (3*S*,4*R*)-**4a** as a crude oil Acid hydrolysis of **4a** with dil HCl–THF yielded a crystalline diol (3*S*,4*R*)-**4b**, m.p 81–82°, $[\alpha]_D^{21}$ + 11 6° ($CHCl_3$), in 54% yield from **3b** Recrystallisation of (3*S*,4*R*)-**4b** from n-hexane improved its chemical and optical purities (96% e e , see later) Finally the Wacker oxidation of (3*S*,4*R*)-**4b** with $PdCl_2$–$CuCl_2$ in 1,2-dimethoxyethane (DME)[7 15 16] gave (1*R*,5*S*,7*S*)-*endo*-brevicomin **1**, $[\alpha]_D^{21}$ + 78 8° (ether) [lit [12] $[\alpha]_D$ 74° (ether)], in 53 7% yield The overall yield of (+)-**1** from (±)-**2** was 7% Similarly, by using diisopropyl D-(−)-tartrate, (2*S*,3*R*)-**3a** was obtained from (±)-**2** The epoxide (2*S*,3*R*)-**3a** was converted to (3*R*,4*S*)-**4b**, m p 81–82°, $[\alpha]_D^{21}$ − 11 5°



Scheme 1

The first step of the synthesis was the kinetic resolution of (±)-1-penten-3-ol **2** by enantioselective epoxidation using diisopropyl tartrate according to the procedure of Martin *et al* [13] Employing diisopropyl L-(+)-tartrate as the chiral source and interrupting the reaction after 15 hr at −20° in the presence of t-BuOOH and Ti(i-PrO)$_4$, an optically active epoxy alcohol (2*R*,3*S*)-**3a** was obtained as a crude oil This was ($CHCl_3$), via **3b** and **4a** The Wacker oxidation of (3*R*,4*S*)-**4b** gave (1*S*,5*R*,7*R*)-*endo*-brevicomin, **1**, $[\alpha]_D^{21}$ − 75 9° (ether) [lit [12] $[\alpha]_D$ − 76 7° (ether)] in 4 5% overall yield from (±)-**2** The IR and ^{1}H-NMR data of the enantiomers of *endo*-brevicomin coincided with those of (±)-*endo*-brevicomin previously synthesised by us [8]

The optical purity of (3*S*,4*R*)-**4b** and that of (3*R*,4*S*)-**4b** were estimated to be 96 and 97%, respectively, by the HPLC analyses of the corresponding bis-(*S*)-α-trifluoromethylphenylacetate (MTPA ester)[17] **4c** On the basis of these analyses, the optical purity of our (+)-**1** and that of (−)-**1** were assumed to be 96–97%, since no racemisation was anticipated in the course of the Wacker reaction

† Pheromone Synthesis—Part 75 Part 74, K Mori, T Uematsu, K Yanagi and M Minobe, *Tetrahedron* **41** (1985) The experimental part of this work was taken from the forthcoming doctoral dissertation of Y -B Seu

In conclusion, both the enantiomers of *endo*-brevicomin were synthesised in five steps from the commercially available starting material (±)-**2**. The biological activity of our materials is now being tested by Professor J P Vite of Freiburg University. According to his preliminary results, (1*R*,5*S*,7*S*)-**1** attracted *Dryocoetus autographus*, while (1*S*,5*R*,7*R*)-**1** was inactive.

EXPERIMENTAL

All m.ps and b.ps were uncorrected. IR spectra were measured as Nujol mulls (solid) or as films (liquid) on a Jasco A-102 spectrometer. NMR spectra were recorded at 60 MHz as CCl_4 soln with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated. Optical rotations were measured on a Jasco DIP 140 polarimeter.

1,2-Epoxy-3-pentanol EE *ether* **3b**

(a) (2S,3R)-*Isomer*. To a stirred and cooled dry CH_2Cl_2 (1000 ml) at −23° under Ar were added Ti(i-PrO)$_4$ (29.8 ml, 100 mmol), diisopropyl D-(−)-tartrate (25.5 ml, 120 mmol), (±)-**2** (10.26 ml, 100 mmol) and t-BuOOH in CH_2Cl_2 (3.37 M, 26.81 ml, 100 mmol) in this order. The mixture was left to stand for 15 hr at −20°. The temp was raised to room temp and diluted with ether (1000 ml) and sat Na_2SO_4 aq (30 ml). The mixture was stirred for 2 hr, and filtered. The filtrate was concentrated *in vacuo* to give 56.2 g of an oil containing **3a**. This was dissolved in dry CH_2Cl_2 (150 ml). To this were added ethyl vinyl ether (300 ml) and PPTS (3 g) under ice-cooling. The mixture was stirred for 20 hr at room temp. It was then diluted with ether. The ether soln was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 92 g of a crude oil. This was chromatographed over SiO_2. The oily (2*S*,3*R*)-**3b** was distilled to give 2.03 g (23.4%) of **3b**, b.p. 102°/58 mm, n_D^{21} 1.4146, $[\alpha]_D^{21}$ +6.15° (*c* = 1.06, $CHCl_3$), ν_{max} 1130 (s), 1095 (s), 1080 (s), 1055 (s) cm^{-1}, δ 0.7–1.9 (11H, m), 2.4–2.8 (2H, m), 2.9–3.7 (3H, m), 4.4–4.9 (1H, m). (Calc for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.72; H, 10.54%.)

(b) (2R,3S)-*Isomer*. In the same manner as described above except that diisopropyl L-(+)-tartrate was used, 10.26 ml (100 mmol) of (±)-**2** yielded 2.06 g (24%) of (2*R*,3*S*)-**3b**, b.p. 115°/70 mm, n_D^{20} 1.4142, $[\alpha]_D^{20}$ −6.12° (*c* = 1.03, $CHCl_3$). (Calc for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.71; H, 10.55%.) The IR and ^{1}H-NMR spectra of (2*R*,3*S*)-**3b** were identical with those of (2*S*,3*R*)-**3b**.

8-Nonene-3,4-diol **4b**

(a) (3R,4S)-*Isomer*. A soln of CH_2=$CHCH_2CH_2MgBr$ in THF was prepared from CH_2=$CHCH_2CH_2Br$ (4.78 g, 35.4 mmol) and Mg (1.03 g, 42.5 mg atom) in dry THF (35 ml). This was added dropwise to a stirred and cooled suspension of Cu_2Br_2 (473.4 mg, 1.65 mmol) in THF (10 ml) at −30° under Ar. The stirring was continued for 10 min. A soln of (2*S*,3*R*)-**3b** (1.914 g, 11 mmol) in dry THF (10 ml) was added dropwise to the stirred and cooled mixture at −30°. The stirring was continued overnight with gradual raising of the temp to 5°. The mixture was poured into sat NH_4Cl soln, filtered to remove inorganic material and extracted with ether. The extract was dried ($MgSO_4$) and concentrated *in vacuo* to give crude **4a** (3.536 g). The crude product **4a** (3.536 g) in THF (7 ml) was added to a stirred and cooled mixture of N HCl (15 ml) and THF (15 ml). After stirring for 2.5 hr, the mixture was neutralised with sat $NaHCO_3$ aq and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallised from n-hexane to give 584 mg (33.6%) of (3*R*,4*S*)-**4b**, m.p. 81–82°, $[\alpha]_D^{21}$ −11.5° (*c* = 0.92), ν_{max} 3320 (s), 3225 (s), 1640 (w), 1065 (s), 985 (m), 970 (s), 910 (s) cm^{-1}, δ 0.97 (3H, t, J = 6 Hz), 1.20–1.80 (6H, m), 1.80–2.20 (2H, m), 2.61 (2H, br s, —OH), 3.20–3.80 (2H, m), 4.60–5.30 (2H, m), 5.30–6.10 (1H, m). (Calc for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.04; H, 11.65%.)

(b) (3S,4R)-*Isomer*. In the same manner as described above 2.061 g of (2*R*,3*S*)-**3b** gave 995 mg (54%) of (3*S*,4*R*)-**4b**, m.p. 81–82°, $[\alpha]_D^{21}$ +11.6° (*c* = 1.00, $CHCl_3$). (Calc for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.48; H, 11.56%.) The IR and ^{1}H-NMR spectra of (3*S*,4*R*)-**4b** were identical with those of (3*R*,4*S*)-**4b**.

endo-Brevicomin (*7-ethyl-5-methyl-6,8-dioxabicyclo*[3.2.1]-*octane* **1**

(a) (1S,5R,7R)-*Isomer*. $CuCl_2$ (637.3 mg, 4.74 mmol) and $PdCl_2$ (150.2 mg, 0.85 mmol) were added to 1,2-dimethoxyethane (DME, 5 ml), and the mixture was stirred for 1 hr at room temp. A soln of (3*R*,4*S*)-**4b** (740 mg, 4.74 mmol) in DME (4 ml) was added slowly to the stirred mixture. The stirring was continued for 6 hr. Then the reaction mixture was diluted with water and extracted with ether. The aq layer was acidified with dil HCl (0.5 N, 3.5 ml) to pH 2, left to stand overnight, and extracted with ether. The combined ether soln was washed with water and brine, dried (Na_2SO_4) and concentrated under atm. press. The residue was further purified by SiO_2 chromatography and distillation to give 428.4 mg (58.7%) of (1*S*,5*R*,7*R*)-**1**, b.p. 96°/77 mm, n_D^{21} 1.4420, $[\alpha]_D^{21}$ −75.9° (*c* = 0.717, ether), ν_{max} 2950 (s), 2880 (s), 2750 (w), 2680 (w), 1465 (m), 1375 (s), 1345 (m), 1335 (w), 1325 (w), 1305 (w), 1285 (w), 1255 (m), 1235 (s), 1195 (m), 1190 (m), 1170 (s), 1140 (w), 1120 (w), 1105 (s), 1100 (m), 1080 (w), 1065 (w), 1050 (w), 1030 (s), 1000 (s), 965 (m), 940 (w), 900 (m), 865 (m), 850 (s), 815 (w), 805 (w), 790 (w), 780 (w) cm^{-1}, ^{1}H-NMR (100 MHz, $CDCl_3$) 0.98 (3H, t, J = 7.5 Hz), 1.45 (3H, s), 1.50–2.20 (8H, m), 3.98 (1H, dt, J_1 = 4 Hz, J_2 = 7.5 Hz), 4.12–4.30 (1H, m), ^{13}C-NMR δ (25 MHz, $CDCl_3$) 11.01, 17.59, 21.96, 23.71, 25.05, 34.51, 76.57, 81.68, 107.00, GLC (Column, PEG 20M, 2 m × 2 mm at 100–200° (+10°/min), Carrier gas, N_2, 0.8 kg/cm^2) R_t 4.0 min (100%), MS *m/z* 156.1147 (Calc for $C_9H_{16}O_2$: 156.1151.)

(b) (1R,5S,7S)-*Isomer*. In the same manner as described above, 436 mg of (3*S*,4*R*)-**3b** gave 231.5 mg (53.7%) of (1*R*,5*S*,7*S*)-**1**, b.p. 100°/80 mm, n_D^{21} 1.4422, $[\alpha]_D^{21}$ +78.8° (*c* = 0.5, ether), GLC (Column, PEG 20M, 2 m × 2 mm at 100–200° (+10°/min), Carrier gas, N_2, 0.8 kg/cm^2) R_t 4.1 min (99.7%), MS *m/z* 156.1154 (Calc for $C_9H_{16}O_2$: 156.1151.) GC-MS (70 eV) *m/z* 52 (13%), 53 (19%), 55 (44%), 57 (51%), 58 (30%), 59 (15%), 67 (45%), 68 (92%), 69 (24%), 70 (13%), 71 (100%), 72 (17%), 81 (79%), 83 (23%), 85 (41%), 86 (90%), 97 (24%), 98 (100%), 99 (48%), 113 (44%), 114 (100%), 115 (13%), 127 (10%), 156 (27%, M$^+$), 157 (4%, M + 1). The IR, ^{1}H-NMR and ^{13}C-NMR spectra of (1*R*,5*S*,7*S*)-**1** were identical with those of (1*S*,5*R*,7*R*)-**1**.

Determination of the optical purity of **4b**

(a) (3R,4S)-**4b**. To a soln of (3*R*,4*S*)-**4b** (7.9 mg) and 4-(N,N-dimethylamino)pyridine (3.4 mg) in dry CH_2Cl_2 (0.8 ml), were added MTPA chloride (26 μl) prepd from (*S*)-MTPA and Et_3N (0.2 ml). After 5 hr an additional amount (13 μl) of MTPA chloride was added. The mixture was stirred overnight at room temp. After conventional work-up, (3*R*,4*S*)-**4c** was isolated by prep. TLC (Merck SiO_2, developed with n-pentane–ether 2:1, R_f 0.74). HPLC analysis of (3*R*,4*S*)-**4c** (Column, Nucleosil 5-50, 25 cm × 4.6 mm, solvent, n-hexane–$ClCH_2CH_2Cl$ 3:1, press. 50 kg/cm^2) R_t 16.9 min (98.5%), 18.4 min (1.5%). The optical purity of (3*R*,4*S*)-**4b** was therefore 97.0%.

(b) (3S,4R)-**4b**. In the same manner as described above, HPLC analysis of (3*S*,4*R*)-**4c** was carried out under the same condition. R_t 17.2 min (1.9%), 18.8 min (98.1%). The optical purity of (3*S*,4*R*)-**4b** was therefore 96.2%.

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