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SYNTHESIS AND BIOACTIVITY OF OPTICALLY ACTIVE FORMS OF 1-METHYL-2-CYCLOHEXEN-1-OL, AN AGGREGATION PHEROMONE OF DENDROCTONUS PSEUDOTSUGAE[†1)]

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Abstract -- Both the enantiomers of 1-methyl-2-cyclohexen-1-ol, an aggregation pheromone of the female Douglas-fir beetle, were synthesized from the enantiomers of seudenol (3-methyl-2-cyclohexen-1-ol). The enantiomers were less active than the racemate of 1-methyl-2-cyclohexen-1-ol as an aggregation pheromone.

The female Douglas-fir beetle (Dendroctonus pseudotsugae Hopkins) releases numerous aggregation pheromones such as frontalin, 3-methyl-2-cyclohexen-1-one, verbenone, seudenol (3-methyl-2-cyclohexen-1-ol), trans-verbenol and 3-penten-1-ol.[1] 1-Methyl-2-cyclohexen-1-ol **1** was also isolated from the female Douglas-fir beetle, identified as such, synthesized as a racemate, and shown by bioassays to be an aggregation pheromone.[1,2] The enantiomeric composition of the natural **1**, however, is still unknown. We became interested in synthesizing both the enantiomers of **1** so as to know whether only one enantiomer is responsible for the beetle aggregation or both the enantiomers are responsible. In spite of the simple structure of **1** with a single chiral center at the quaternary carbon atom, a synthesis of the pure enantiomers of **1** was not an easy task because of the allylic and tertiary nature of the OH group of **1**, which makes the conventional optical resolution of (±)-**1** difficult. This paper describes how we have solved the problem and prepared both the enantiomers of **1**.

As the direct optical resolution of (±)-**1** was difficult, we adopted the strategy to prepare the optically active **1** by reductive cleavage of the epoxy ring of an

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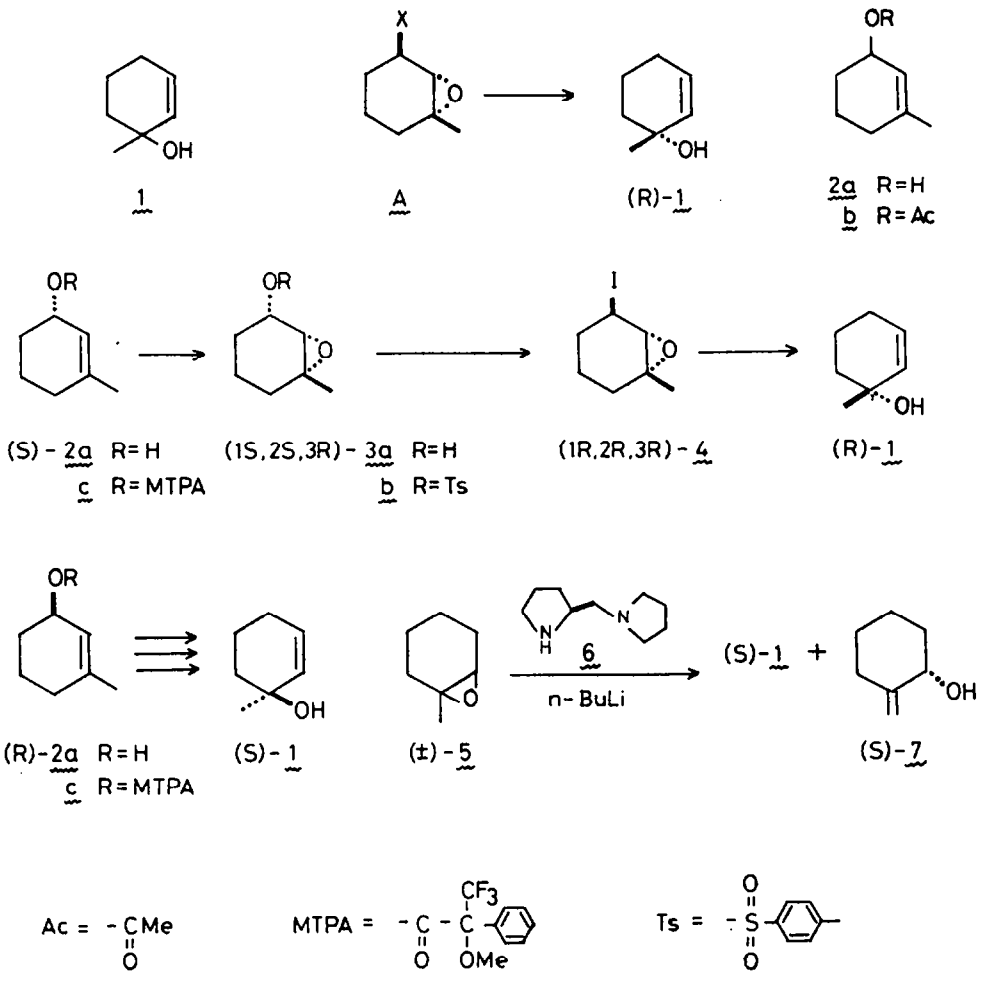

epoxy halide such as **A**. For the preparation of **A**, an epoxy alcohol **3a** is a suitable precursor. The epoxide **3a** is in principle obtainable by the Sharpless asymmetric epoxidation (under the condition of kinetic resolution) of (±)-seudenol **2a**. However, the reported kinetic resolution of 2-cyclohexen-1-ol to give the product of only 30 % e.e.[3] made us not to attempt that reaction. The alternative choice was to prepare the enantiomers of **3a** by the OH-directed epoxidation of seudenol enantiomers **2a**. To obtain seudenol enantiomers **2a**, we at first attempted enzymic hydrolysis of (±)-seudenol acetate **2b** expecting kinetic resolution.[cf.4] Hydrolysis of (±)-**2b** with lipases M, A, F and P (Amano Pharmaceutical Co.), lipase MY (Meito Sangyo Co.) and pig pancreas lipase (PPL, Sigma Chemical Co.) with 0.1 M phosphate buffer (pH 7) at 37° for 3 h yielded only racemic seudenol (±)-**2a**. The biochemical method was thus inadequate. The next attempt was the asymmetric reduction of 3-methyl-2-cyclohexen-1-one with a modified LAH reagent,[5] but we could obtain seudenol **2a** of unsatisfactory optical purity. We therefore decided to employ our classical procedure for the synthesis of seudenol enantiomers involving the optical resolution of (±)-3-iodo-2-cyclohexen-1-ol.[6] Consequently (S)-seudenol **2a**, $[\alpha]_D^{20}$ -92.2° ($CHCl_3$), was prepared, whose enantiomeric purity was shown to be 88 % e.e. by comparing its $[\alpha]_D$ value with that of (R)-**2a** (+93.9°). (R)-Seudenol **2a**, $[\alpha]_D^{20}$ +93.9° ($CHCl_3$), was also

prepared and shown to be of 90 % e.e. by the 400 MHz ^{1}H NMR analysis of its α-methoxy-α-trifluoromethylphenylacetate (MTPA ester)[7] **2c** (see Experimental).

Epoxidation of (S)-seudenol **2a** with MCPBA furnished the epoxy alcohol (1S,2S,3R)-**3a** in quantitative yield. An inferior result was obtained when the oxidation was carried out with t-BuOOH and $VO(acac)_2$[8] due to the difficulty in isolating highly volatile **3a**. The epoxy alcohol **3a** on treatment with p-TsCl in C_5H_5N afforded the corresponding crystalline tosylate (1S,2S,3R)-**3b** in 62 % yield. Treatment of (1S,2S,3R)-**3b** with NaI in DMF in the presence of $NaHCO_3$ gave a crystalline epoxy iodide (1R,2R,3R)-**4** in 75 % yield. The mother liquor contained **4** and its (1S,2R,3R)-isomer as revealed by its NMR analysis (see Experimental). The latter must have been generated by the further attack of I^- on **4** resulting in the Walden inversion at C-1. Reduction of (1R,2R,3R)-**4** to (R)-**1** was executed by treating the epoxy iodide **4** with Zn and NH_4Cl aq in EtOH to give the desired (R)-**1**, $[\alpha]_D^{22}$ +74.5° (ether), in 71 % yield. The overall yield of (R)-**1** from (S)-**2a** was 33 % in 4 steps. Similarly, (R)-seudenol **2a** gave (S)-**1**, $[\alpha]_D^{23}$ -75.4° (ether), in 16 % overall yield in 4 steps. Attempts were made to directly measure the enantiomeric purity of the enantiomers of **1** by their NMR measurements in the presence of a chiral shift reagent, but did not give useful results. The use of complexation GLC was more promising as a tool to determine the enantiomeric purity of **1**.[9,10] Prof. Schurig kindly analyzed our (S)-**1** by that technique, and found it to be of ca. 90 % e.e. This e.e. value was in good accord with that of the starting material (R)-**2a** (90 % e.e.). In the case of (R)-**1**, however, the complexation GLC analysis was not so successful. It was estimated to be of also ca. 90 % e.e. by comparing its $[\alpha]_D$ value with that of (S)-**1**.

After the completion of the above described work, we tried another attempt to synthesize (S)-**1**. An asymmetric transformation of cyclohexene oxide to optically active 2-cyclohexen-1-ol of 90 % e.e. by the epoxide cleavage with chiral lithium amides was reported recently by Asami.[11] Following his procedure, (±)-1-methylcyclohexene oxide **5** was treated with (S)-2-(1-pyrrolidino)methylpyrrolidine **6** and n-BuLi. A 1:1 mixture of alcohols (S)-**1** and (S)-**7** was obtained in 52.5 % yield, which was separated by prep GLC. The desired product (S)-**1** possessed a shorter retention time, and was estimated to be of ca. 80 % e.e. based on its specific rotation, $[\alpha]_D^{24}$ -67.2° (ether). The structure (S)-**7** was assigned to the alcohol, $[\alpha]_D^{24}$ -18.0° (ether), with a longer retention time on the basis of its ^{1}H NMR spectrum showing a signal due to $=CH_2$ (δ 4.76 and 4.90, each 1H, br.s) and that due to CHOH (δ 3.92-4.24, 1H, m). The enantiomeric purity of **7** was not determined. Asami's procedure was indeed a very convenient one to prepare the optically enriched **1**, but it could not afford the highly enantiomerically pure enantiomers of **1** suitable for biological studies.

The field test of the enantiomers of 1-methyl-2-cyclohexen-1-ol **1** was carried out in British Columbia, Canada. The data as shown in Table 1 are not very enlightening, unfortunately, due to the minute amounts of the samples. It was impossible to test various release rate, etc. To do anything worthwhile in the field, >100 mg of each enantiomer is necessary. As it is not so easy at present to secure

Table 1. Attractiveness of the enantiomers of 1-methyl-2-cyclohexen-1-ol 1 to the Douglas-fir beetle, Dendroctonus pseudotsugae

Replicate	Numbers of the insect attracted by											
	(±)-Frontalin (control)			(±)-Frontalin +(R)-(+)-1			(±)-Frontalin +(S)-(-)-1			(±)-Frontalin +(±)-1		
	♂	♀	Total	♂	♀	Total	♂	♀	Total	♂	♀	Total
1	4	1	5	4	4	8	4	7	11	6	6	12
2	0	1	1	2	1	3	1	3	4	3	4	7
3	0	0	0	0	1	1	0	2	2	0	2	2
4	6	9	15	2	6	8	3	5	8	9	12	21
Sum Total	10	11	21	8	12	20	8	17	25	18	24	42

Twenty mg of each enantiomer of **1** was obtained for field bioassay. The experiment was set up as a time-replicated Latin square near Merritt, British Columbia, Canada. Four Lindgren funnel traps[12] were baited with (±)-frontalin released at 0.4 mg/24 h from one 30 µl glass capillary. One trap served as a control, while the other traps were baited with one 5 µl glass capillary of (+)-**1**, (-)-**1** or one capillary of each enantiomer, respectively. The release rate of each enantiomer of **1**, estimated at 25 µg/24 h, was thus held constant. The data were analyzed by analysis of variance after transformation to $x'=\log(x+1)$ to correct for heterogeneity of variances. No significant differences between treatments, analysis of variance ($p<0.05$).

>100 mg of pure enantiomers, decisive field tests will become possible only after the development of a more efficient synthesis of the enantiomers of **1**. The tentative conclusion drawn from the present field test was the fact that the the enantiomers of **1** were less attractive to the Douglas-fir beetle than the racemate (±)-**1**.

The results also show that at the very low release rate used, **1** does not significantly synergize frontalin. However, for females and total catch, the treatment effect was significant at 7.7 % and at 5.3 %, respectively. It is possible that further bioassays using higher release rates would reveal a synergistic effect by **1** on frontalin.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils or as nujol mulls for solids on a Jasco A-102 spectrometer. ^{1}H NMR spectra were recorded at 60 MHz 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.

Seudenol **2a**. (i) (S)-Isomer: b.p. 78-79°/21 Torr; n_D^{22} 1.4777; $[\alpha]_D^{20}$ -92.2° (c=0.50, $CHCl_3$). [lit.[6] b.p. 83-85°/23 Torr; n_D^{20} 1.4807; $[\alpha]_D^{20}$ -93.9° ±0.4° (c=0.524, $CHCl_3$)].
(ii) (R)-Isomer: b.p. 82-85°/22 Torr; n_D^{22} 1.4787; $[\alpha]_D^{22}$ +93.9° (c=0.76, $CHCl_3$). [lit.[6] b.p. 83-85°/23.5 Torr; n_D^{22} 1.4804; $[\alpha]_D^{20}$ +93.5±0.4° (c=0.491, $CHCl_3$)].

Determination of the enantiomeric purity of (R)-seudenol **2a**. According to the reported procedure,[7] MTPA ester **2c** was prepared from (R)-**2a**. ^{1}H NMR (Jeol JNM-GX 400, 400 MHz, TMS, $CDCl_3$) δ 3.55 (95 %), 3.57 (5 %). Therefore the optical purity of (R)-**2a** was determined to be 90 % e.e.

2,3-Epoxy-3-methyl-1-cyclohexanol **3a**. (i) (1S,2S,3R)-Isomer. A) A soln of MCPBA (80 % purity, 0.81 g) in dry CH_2Cl_2 (18

ml) was added dropwise to a soln of (S)-2a (0.41 g) in CH_2Cl_2 (25 ml) over 15 min at -1–0° with stirring. The stirring was continued for further 15 min at this temp. It was then diluted with CH_2Cl_2, washed with 10 % Na_2CO_3 soln and brine, dried ($MgSO_4$) and concentrated in vacuo at low temp to give 0.47 g (quantitative) of 3a, vmax 3410 cm^{-1}; δ (CCl_4) 1.30 (3H, s), 1.35–2.20 (7H, m), 3.00 (1H, br.d, J=4 Hz), 3.80 (1H, m). This was employed in the next step without further purification. B) To a refluxing soln of (S)-2a (0.4 g) and $VO(acac)_2$ (14 mg) in C_6H_6 (10 ml), 70 % t-BuOOH (0.6 ml) was added dropwise with stirring during 7 min. The mixture was further stirred and heated under reflux for 20 min. It was then diluted with ether. The ether-C_6H_6 layer was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated to afford crude 3a (0.2 g). Purification of this by column chromatography (Woelm neutral Al_2O_3, activity grade III) and by distillation resulted in much loss of 3a. (ii) (1R,2R,3R)-Isomer. Similary by epoxidation with MCPBA, (R)-2a (0.78 g) gave 0.90 g of (1R,2R,3S)-3a.

2,3-Epoxy-3-methylcyclohexyl tosylate 3b. (i) (1S,2S,3R)-Isomer. To a soln of (1S,2S,3R)-3a (1.1 g) in C_5H_5N (10 ml), p-TsCl (1.6 g) was added with stirring at 0°. The stirring was continued for 6.5 h at this temp. The mixture was then diluted with ice-water and extracted with ether. The ether soln was washed with sat $CuSO_4$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 1.5 g (62 %) of crystalline 3b. This was recrystallized from EtOAc-n-hexane to give an analytical sample, m.p. 74–76°; $[\alpha]_D^{23}$ -51.8° (c=0.58, $CHCl_3$); vmax (KBr) 1600 (w), 1360 (m), 1180 (s), 930 (s), 875 (m), 815 (m) cm^{-1}; δ ($CDCl_3$) 1.30 (3H, s), 1.35–2.00 (6H, m), 2.44 (3H, s), 3.02 (1H, m), 4.60–5.10 (1H, m), 7.33 (2H, d, J=8 Hz), 7.85 (2H, d, J=8 Hz). (Found: C, 59.60; H, 6.25. Calc for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.42 %). (ii) (1R,2R,3S)-Isomer. Similarly as described above, (1R,2R,3S)-3a (0.90 g) gave 1.30 g (51 % from 2a) of crystalline 3b as needles from EtOAc-n-hexane, m.p. 76°; $[\alpha]_D^{23}$ +48.8° (c=0.60, $CHCl_3$). Its IR and NMR spectra were identical with those of (1S,2S,3R)-3b.

2,3-Epoxy-3-methylcyclohexyl iodide 4. (i) (1R,2R,3R)-Isomer. To a stirred soln of (1S,2S,3R)-3b (1.05 g) in DMF (9 ml) were added NaI (1.5 g) and $NaHCO_3$ (1.7 g), and the mixture was stirred and heated at 75–80° for 25 min. After cooling, the mixture was diluted with water (50 ml), and extracted with ether. The ethereal extract was washed with $Na_2S_2O_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to afford crude 4 as a low melting solid (0.83 g, 93 %). This was recrystallized from n-pentane to give pure 4 (0.67 g, 75 %), m.p. 47–48°; $[\alpha]_D^{22}$ -139° (c=0.64, ether); vmax 1125 (s), 895 (s) cm^{-1}; δ (CCl_4) 1.25 (3H, s), 1.35–2.20 (6H, m), 3.08 (1H, br.d, J=3 Hz), 4.20–4.55 (1H, m). (Found: C, 35.51; H, 4.56. Calc for $C_7H_{11}OI$: C, 35.31; H, 4.66 %). The mother liquor after removal of 4 was concentrated to give 0.16 g (18 %) of an oil, whose ^1H NMR spectrum revealed the presence of 4 and its (1S,2R,3R)-isomer in 1:1 ratio as shown by the presence of two singlets (CH_3C) at δ (100 MHz, $CDCl_3$) 1.30 and 1.35 in 1:1 ratio. (ii) (1S,2S,3S)-Isomer. In the same manner as described above, (1R,2R,3S)-3b (0.85 g) gave 0.68 g (95 %) of crude 4, which was recrystallized from n-pentane to give 0.46 g (64 %) of pure 4, m.p. 47–48°; $[\alpha]_D^{21}$ +144° (c=0.76, ether). Its spectral data were identical with those of (1R,2R,3R)-4.

1-Methyl-2-cyclohexen-1-ol 1. (i) (R)-Isomer. To a stirred and ice-cooled soln of (1R,2R,3R)-4 (0.50 g) in 99 % EtOH (2 ml) were added Zn dust (0.55 g) and sat NH_4Cl soln (5 drops) at 0–5°. The mixture was warmed up and stirred for 20 min at room temp. It was then diluted with ether and filtered. The ethereal extract was washed with sat $NaHCO_3$ soln and brine, dried (K_2CO_3) and concentrated in vacuo. The residue was distilled to give 0.17 g (71 %) of (R)-1, b.p. 58°/16 Torr; n_D^{22} 1.4708; $[\alpha]_D^{22}$ +74.5° (c=0.47, ether); vmax 3380 (s), 3040 (m), 2975 (m), 2940 (s), 2875 (m), 2840 (m), 1650 (w), 1450 (m), 1435 (m), 1395 (m), 1370 (m), 1325 (m), 1250 (w), 1220 (w), 1180 (s), 1125 (s), 1100 (s), 1060 (w), 1020 (m), 1000 (m), 960 (m), 910 (s), 845 (m), 635 (s) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.29 (3H, s), 1.45–2.05 (7H, m), 5.55–5.90 (2H, m); MS: m/z 112 (M^+, 11.8 %), 97 (base peak, 100.0 %), 94 (10.0 %), 91 (9.4 %), 84 (36.0 %), 79 (46.6 %), 77 (19.0 %), 74 (19.4 %), 69 (61.2 %); GLC (Column, OV-101, 50 m x 0.25 mm at 100°; Carrier gas, N_2, 1.1 kg/cm^2): Rt 9.7 min (100 %). (Found: m/z 112.0890. Calc for $C_7H_{12}O$: 112.0888). Due to the high volatility of 1, the combustion analysis could not be performed. (ii) (S)-Isomer. In the same manner as described above, (1S,2S,3S)-4 (0.24 g) gave 55 mg (50 %) of (S)-1, b.p. 62°/22 Torr; n_D^{22} 1.4707; $[\alpha]_D^{23}$ -75.4° (c=0.40, ether). This was gas chromatographically pure and its IR, NMR and mass spectra coincided with those of (R)-1. (Found: m/z 112.0803. Calc for $C_7H_{12}O$: 112.0888).

Conversion of (±)-1-methylcyclohexane oxide to (S)-1 and (S)-2-methylene-1-cyclohexanol 7. To a stirred and cooled soln of 6 (2.55 g) in THF (50 ml) was added n-BuLi (1.43 M in n-hexane, 7 ml) at 0° under N_2. The mixture was stirred at 0° for 30 min and then cooled to -78°. A soln of (±)-5 (1.12 g) in THF (25 ml) was then added to the stirred mixture and the stirring was continued for 2 h at -78°. It was slowly brought to room temp and kept at room temp for 16 h. The mixture was diluted with ice-sat NH_4Cl soln and extracted with ether. The ether soln was washed with brine, dried (K_2CO_3) and concentrated in vacuo. The residue was chromatographed over Al_2O_3 (ICN Biochemicals, grade II). Elution with n-pentane gave the recovered 5 (0.15 g). Elution with ether gave a mixture of (S)-1 and (S)-7 (1.02 g). This was distilled to give 0.59 g (52.5 %) of the mixture: GLC (Column, 5 % FFAP, 2 m x 4 mm at 100° + 2°/min; Carrier gas, N_2, 1 kg/cm^2) Rt 8.6 min (1, ca. 50 %), 14.2 min (7, ca. 50 %). The mixture was separated by prep GLC (Column, 5 % FFAP, 1 m x 4 mm at 90°; Carrier gas, N_2, 1 kg/cm^2). The separated 1, $[\alpha]_D^{24}$ -67.2° (c=0.08, ether), thus obtained was 99 % pure by GLC analysis and the identity with an authentic sample of 1 was proved by GLC co-injection. Its spectral properties were also identical with those of the authentic 1. The separated 7 thus obtained was 99 % pure by GLC analysis and showed the following properties: $[\alpha]_D^{24}$ -18.0° (c=0.08, ether); vmax 3400 (s), 1660 (w), 905 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.40–2.10 (9H, m), 3.90–4.24 (1H, m), 4.76 (1H, br.s), 4.90 (1H, br.s); MS: m/z 112 (M^+, 83.7 %), 97 (base peak, 100.0 %), 84 (60.2 %), 83 (65.6 %), 79 (43.4 %), 74 (55.6 %). (Found: m/z 112.0843. Calc for $C_7H_{12}O$: 112.0888). Due to the high volatility of 7, the combustion analysis could not be performed.

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