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A NATURAL PRODUCT WAS SHOWN TO BE OF LOW OPTICAL PURITY: SYNTHESIS OF (2S,5R,6E,8E)-2,5-EPOXY-6,8-MEGASTIGMADIENE, ITS (6Z,8E)-ISOMER AND (2S,6R,7S,8E)-2,7-EPOXY-4,8-MEGASTIGMADIENE, THE CONSTITUENTS OF OSMANTHUS ABSOLUTE[†]

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Abstract -- The title compounds were synthesized from (S)-3-hydroxy-2,2-dimethylcyclohexanone. (6E,8E)-2,5-Epoxy-6,8-megastigmadiene isolated as a minor constituent of Osmanthus absolute was shown to be of only ca. 11 % e.e. enriched in (2S,5R)-(+)-isomer.

In 1978 Kaiser and Lamparsky reported the isolation and identification of three new bicyclic oxa-compounds (**1**~**3**) of the megastigmane type in the Osmanthus absolute.[1,2] Osmanthus fragrans Lourd (Japanese name: kinmokusei) is well known among oriental people by virtue of the soft fragrance of its flowers. The total content of **1** and **2** was 0.02 % in the ratio of 5:1 in the Osmanthus absolute, and **1** was reported to show a strong odor like tomato leaves.[1] The content of **3** in the Osmanthus absolute was only a trace amount.[2] Owing to the difficulty in obtaining sufficient amounts of the naturally occurring **1**~**3**, their absolute configurations remained unknown. In the case of (6E,8E)-2,5-epoxy-6,8-megastigmadiene **1**, its specific rotation was recorded as $[\alpha]_D^{20}$ +17.7° (c=1.037, $CHCl_3$).[1] Herein we report the clarification of its absolute configuration by synthesizing (2S,5R)-**1**. Unexpectedly our synthesis of (2S,5R)-**1** revealed the low optical purity of the naturally occurring **1**.

As shown in the Scheme our synthesis started from 2,2-dimethyl-1,3-cyclohexanedione **4**. Reduction of **4** with baker's yeast yielded (S)-3-hydroxy-2,2-dimethylcyclohexanone **5**.[3,4] This ketol **5** served as the starting material for various optically active isoprenoids such as (S)-2-hydroxy-β-ionone **6**,[4] karahana lactone **11**,[5] dihydroactinidiolide **12**[6] and polygodial.[7] Since our synthesis of (S)-**6** from **4** was so efficient as to give (S)-**6** of 96 % e.e.,[4] we decided to employ **6** as the key intermediate to synthesize **1**, **2** and **3**. With regard to the conversion of (S)-**6** to the target molecules, we essentially followed the route developed by Kaiser and Lamparsky in their conversion of (±)-**6** to (±)-**1**, (±)-**2** and (±)-**3**.[1,2]

Treatment of (S)-**6** with hot isopropenyl acetate in the presence of p-TsOH gave **7**, whose LAH reduction yielded **8**. Cyclization of **8** to a mixture of (2S,5R)-**1** and (2S,5R)-**2** was effected by heating a C_6H_6 soln of **8** in the presence of p-TsOH. The crude mixture was

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[†] Carotenoids and Degraded Carotenoids -- 6. For Part 5, see M. Yanai, T. Sugai and K. Mori, Agric. Biol. Chem. **49**, 2373 (1985). This work was presented by K. M. as a part of his lecture at the 11th Conference of Isoprenoids, Jachranka, Poland (September 20, 1985).

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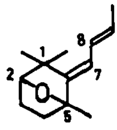
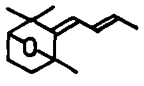


1



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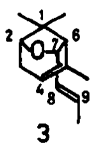
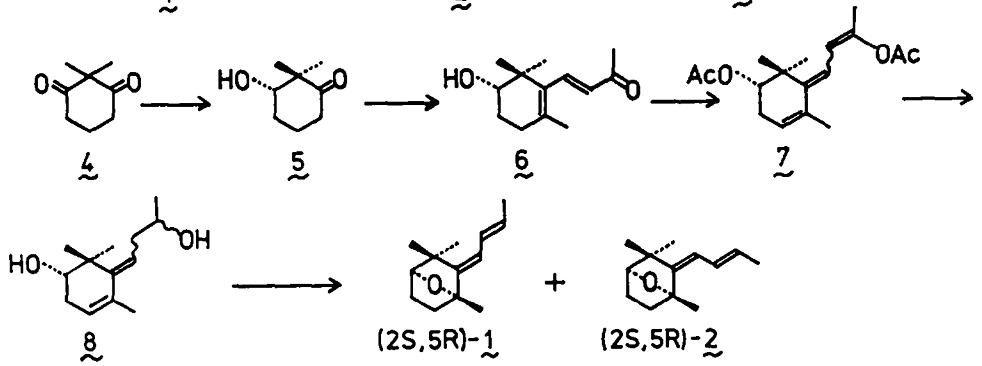
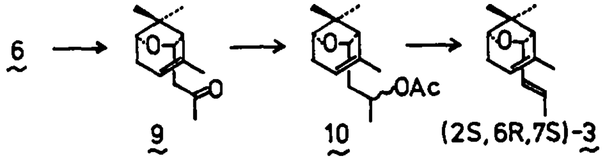


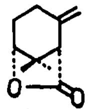
3



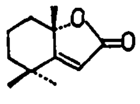
4 5 6 7 8 (2S,5R)-1 (2S,5R)-2



9 10 (2S,6R,7S)-3



(-)-11



(+)-12

purified by SiO_2 chromatography to give a mixture of **1** and **2** in a ratio of 82.5:17.5. Final purification of the mixture by prep HPLC furnished pure (2S,5R)-**1** (19.8 % from **6**) and (2S,5R)-**2** (4.2 % from **6**). The synthetic (2S,5R)-**1** was obtained as needles with fruity and camphor-like odor, m.p. 19.5~20.5°, $[\alpha]_D^{24}$ +159.5° ($CHCl_3$), whose spectral properties were in good accord with the published data for the natural **1**.[1] Assuming that no racemization took place in the course of the cyclization of **8**, optically pure (2S,5R)-**1** should show the $[\alpha]_D$ value of 166°, since we started from (S)-**6** of 96 % e.e. The natural **1**, however, was reported to show m.p. 31~32° and $[\alpha]_D^{20}$ +17.7° ($CHCl_3$). This means that the optical purity of the natural **1** was only ca. 11 %. The oily (2S,5R)-**2** also showed a large specific rotation value, $[\alpha]_D^{24}$ +260.7° ($CHCl_3$), and its spectral properties were same as those published for the natural **2**. Since no $[\alpha]_D$ value was reported for the natural **2**, we could not estimate its optical purity.

For the synthesis of (2S,6R,7S)-**3**, (S)-**6** was heated with NaOEt-EtOH to effect deconjugation followed by Michael addition to give **9** in 45 % yield. Reduction of **9** with LAH was followed by acetylation of the product to give **10**. Pyrolysis of **10** at 500° under N_2 gave a crude oil containing **3**. This was purified by SiO_2 chromatography and prep HPLC to give (2S,6R,7S)-**3** (9.9 % from **9**), $[\alpha]_D^{24}$ +10.9° ($CHCl_3$), whose spectral properties were in accord with the published data for the natural **3**.[2] In this case, too, because of the unavailability of the $[\alpha]_D$ value of the natural **3**,[2] it was impossible to estimate the optical purity of the natural **3**.

In summary, we synthesized (2S,5R)-**1**, (2S,5R)-**2** and (2S,6R,7S)-**3** starting from (S)-**5**. An important conclusion drawn from this work was the fact that the naturally occurring **1** was only of ca. 11 % optical purity. Many chemists take it for granted that the natural products are optically pure. A number of exceptions was found even in our own works. Recent two examples were (-)-karahana lactone **11**[5] and (+)-dihydroactinidiolide **12**[6]. (-)-Karahana lactone **11**, $[\alpha]_D^{23}$ -3.06° ($CHCl_3$), was isolated as a constituent of Japanese hop "Shinshu-wase", Humulus lupulus.[8] Only after our synthesis of (1S,5R)-**11**, $[\alpha]_D^{22}$ -236° ($CHCl_3$), the natural **11** was shown to be of 1.3 % e.e.[5] A naturally occurring sample of (+)-dihydroactinidiolide **12**, m.p. 40~41°, $[\alpha]_D^{15}$ +7.1°, isolated from Actinidia polygama[9] was shown to be a mixture of the two enantiomers by our synthesis of pure (S)-(+)-**12**, m.p. 67~68°, $[\alpha]_D^{24}$ +120.9° ($CHCl_3$). At the time when the isolation works of **1**, **11** and **12** were carried out,[1,8,9] there was no method available for the determination of the enantiomeric excess of a small amount of the natural product. Now many ingenious methods are available utilizing NMR, GLC or HPLC techniques.[10] Accordingly, it is recommended that the enantiomeric excess of a natural product should be determined at the time of its isolation as is the case in pheromone chemistry.[10]

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films on a Jasco IRA-102 spectrometer. ^1H NMR spectra were recorded with TMS as an internal standard at 60 MHz on a Hitachi R-24A spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. Fuji-Davison BW-820 MH gel was used for SiO_2 column chromatography.

(S)-2,9-Diacetoxy-4,6,8-megastigmatriene **7**. To a soln of (S)-**6** ($[\alpha]_D^{24}$ -28.7° (c=1.07, EtOH); lit.[4] $[\alpha]_D^{24}$ -28.3° (c=1.03, EtOH), 1.534 g, 7.38 mmol) in isopropenyl acetate (31 ml) was added p-TsOH·H_2O (15 mg), and the mixture was stirred and heated under reflux for 40 min. After confirming the disappearance of (S)-**6** by TLC, the mixture was poured into sat $NaHCO_3$ soln and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give 2.14 g (quantitative) of crude **7**. This was directly used in the next step.

(S)-4,6-Megastigmadiene-2,9-diol **8**. A soln of crude **7** (2.14 g) in dry ether (43 ml) was added dropwise over 20 min to a stirred suspension of LAH (557 mg, 14.7 mmol) in dry ether at room temp. After the addition, the mixture was stirred and heated under reflux for 1 h. It was then cooled, and the excess LAH was destroyed by the dropwise addition of water with stirring and ice-cooling. The insoluble material was filtered off. The ether soln was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give crude **8** (1.66 g, quantitative). This was employed in the next step without further purification.

(2S,5R,6E,8E)-(+)-2,5-Epoxy-6,8-megastigmadiene **1** and its (6Z,8E)-(+)-isomer **2**. To a soln of crude **8** (1.66 g) in C_6H_6 (331 ml) was added p-TsOH·H_2O (10 mg). The mixture was stirred and heated under reflux with continuous removal of water employing a Dean-Stark water separater. After cooling, the mixture was washed with $NaHCO_3$ soln and brine, dried ($MgSO_4$), and concentrated in vacuo to give 1.55 g of an oil. This was chromatographed over SiO_2 (155 g). Elution with n-hexane-ether (30:1) gave 670 mg of a mixture of **1** and **2** (**1**:**2**=82.5:17.5 as analyzed by GLC). Final purification was achieved by prep HPLC (Waters 7000A: Column Develosil 60-5, 25 cm x 8 mm x 2 + 25 cm x 10 mm x 2; Solvent, n-hexane:EtOAc=87.5:12.5; Flow rate, 3.0 ml/min; RI detecter) to give 280 mg (19.8 % from **6**) of **1** and 60 mg (4.2 % from **6**) of **2**. **1** showed the following properties: b.p. 68~69°/1.0 Torr; $n_D^{23.5}$ 1.5013; m.p. 19.5~20.5° (needles from n-pentane); $[\alpha]_D^{24}$ +159.5° (c=1.06, $CHCl_3$); νmax 3070 (m), 3000 (s), 2950 (s), 2890 (m), 1660 (w), 1630 (w), 1470 (m), 1455 (m), 1420 (w), 1390 (s), 1365 (m), 1330 (m), 1295 (w), 1285 (m), 1240 (m), 1215 (m), 1200 (m), 1190 (m), 1165 (w), 1120 (m), 1085 (w), 1025 (s), 1005 (s), 985 (m), 970 (s), 945 (m), 875 (s), 850 (m), 830 (m), 780 (w), 725 (m), 695 (m), 675 (m) cm^{-1}; δ ($CDCl_3$) 1.20 (6H, s), 1.45 (3H, s), 1.73 (3H, d, J=6 Hz), 1.37~2.38 (4H, m), 3.80 (1H, d, J=3 Hz), 5.50 (1H, dq, J=16, 6 Hz), 5.60 (1H, d, J=10 Hz), 6.20 (1H, dd, J=16, 10 Hz); MS: m/z 192 (M^+, 28 %), 177 (4 %), 149 (13 %), 136 (8 %), 123 (31 %), 121 (19 %), 109 (25 %), 93 (15 %), 91 (20 %), 81 (19 %), 69 (60 %), 43 (100 %), 29 (11 %); GLC (Column, PEG-20M, 25 m x 0.25 mm at 70~220° (+3°/min); Carrier gas N_2, 1.0 ml/min): Rt 23.9 min (single peak). (Found: C, 80.80; H, 10.41. Calc for $C_{13}H_{20}O$; C, 81.20; H, 10.48 %). **2** showed the following properties: b.p. 85~90° (bath temp)/2.5 Torr; $n_D^{23.5}$ 1.5017; $[\alpha]_D^{24}$ +260.7° (c=1.05 $CHCl_3$); νmax 3050 (m), 2975 (s), 2930 (s), 2860 (s), 1660 (w), 1620 (w), 1460 (s), 1450 (s), 1375 (s), 1355 (m), 1310 (m), 1290 (m), 1275 (w), 1250 (w), 1230 (w), 1215 (m), 1180 (m), 1115 (s), 1080 (m), 1015 (s), 1005 (s), 990 (s), 975 (m), 960 (s), 925 (m), 900 (w), 875 (m), 850 (w), 830 (m), 770 (m), 720 (w), 695 (w), 675 (m) cm^{-1}; δ ($CDCl_3$) 1.03 (3H, s), 1.10 (3H, s), 1.70 (3H, s), 1.75 (3H, d, J=7 Hz), 1.30~1.95 (4H, m), 3.85 (1H, d, J=4 Hz), 5.50 (1H, dq, J=16, 7 Hz), 5.60 (1H, d, J=10 Hz), 6.20 (1H, dd, J=16, 10 Hz); MS: m/z 192 (M^+, 38 %), 177 (7 %), 149 (14 %), 136 (12 %), 123 (48 %), 109 (36 %), 91 (34 %), 69 (85 %), 43 (100 %), 29 (16 %); GLC (Column, PEG-20M, 25 m x 0.25 mm at 70~220° (+3°/min); Carrier gas, N_2, 1.0 ml/min): Rt 22.6 min (99.3 %). (Found: C, 80.84; H, 10.43. Calc for $C_{13}H_{20}O$: C, 81.20; H, 10.48 %).

(2S,6R,7S)-(+)-2,7-Epoxy-dihydro-α-ionone **9**. A soln of (S)-**6** (2.093 g, 10.1 mmol) in 0.5 % NaOEt in EtOH (63 ml) was stirred and heated under reflux for 1 h under Ar. After cooling, the mixture was poured into water and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give an oil (2.16 g). This was chromatographed over SiO_2 (216 g). Elution with n-hexane-ether (3:1) gave 940 mg (45 %) of **9**, $n_D^{23.5}$ 1.4924; $[\alpha]_D^{23}$ +34.3° (c=1.014, $CHCl_3$); νmax 2880 (s), 1710 (s), 1040 (s) cm^{-1}; δ ($CDCl_3$) 1.07 (3H, s), 1.18 (3H, s), 1.59 (3H, s), 1.80~2.45 (2H, m), 1.94 (1H, d, J=4 Hz), 2.18 (3H, s), 2.48 and 2.84 (2H, dd, J=16, 7 Hz), 4.40~4.85 (1H, m), 5.30 (1H, br.s). This was employed in the next step without further purification.

(2S,6R,7S)-2,7-Epoxy-dihydro-α-ionyl acetate **10**. A soln of **9** (940 mg, 4.52 mmol) in dry ether (30 ml) was added dropwise to a stirred suspension of LAH (172 mng, 4.52 mmol) in dry ether (86 ml) under Ar. The mixture was stirred and heated under reflux for 1 h. The excess LAH was destroyed by the addition of H_2O. The insoluble material was filtered off. The ether soln was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give 962 mg of an oil. This was dissolved in dry C_5H_5N (10 ml). Ac_2O (960 mg, 9.4 mmol) was added to the C_5H_5N soln, and the mixture was stirred overnight at room temp. It was then diluted with water and extracted with ether. The ether soln was washed with dil HCl, water, sat $NaHCO_3$ soln, water and brine, dried ($MgSO_4$), and concentrated in vacuo to give 1.12 g (quantitative) of crude **10**, νmax 2850 (s), 1740 (s), 1375 (s), 1250 (s), 1055 (s) cm^{-1}; δ ($CDCl_3$) 1.04 (3H, s), 1.12 (3H, s), 1.23 (3H, d, J=6 Hz), 1.65 (3H, seemingly t, J=2 Hz), 1.75~2.35 (4H, m), 2.00 (3H, s), 3.55 (1H, br. s), 4.25 (1H, m), 4.75~5.25 (1H, m), 5.30 (1H, br.s). This was employed in the next step without further purification.

(2S,6R,7S,8E)-(+)-2,7-Epoxy-4,8-megastigmadiene 3. A pyrolysis apparatus consisting of a pyrex glass tube (50 cm x 5 cm) containing many pieces of pyrex glass tubes (5~10 mm x 5 mm) was heated at 500°. A soln of crude **10** (1.12 g, 4.44 mmol) in *n*-hexane (112 ml) was added dropwise with N_2 stream (300 ml/min) to the pyrolysis apparatus. The recovered *n*-hexane soln was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give an oil (635 mg). This was chromatographed over SiO_2 (65 g). Elution with *n*-hexane-ether (20:1) gave 533 mg of an oil containing 3. This was further purified by prep HPLC (Waters 7000A; Column Develosil 60-5, 25 cm x 8 mm x 2 + 25 cm x 10 mm x 2; Solvent, *n*-hexane:EtOAc=9:1; Flow rate, 3.0 ml/min) to give 203 mg of a fraction containing 3. This was purified again by HPLC (Solvent, *n*-hexane:EtOAc=97.5:2.5) to give 86 mg (9.9 % from 9) of 3, n_D^{24} 1.4775; $[\alpha]_D^{24}$ +10.9° (c=1.075, $CHCl_3$); νmax 3020 (m), 2980 (s), 2945 (s), 2900 (s), 2850 (m), 2750 (w), 1675 (w), 1475 (m), 1455 (m), 1445 (m), 1430 (m), 1380 (m), 1365 (m), 1355 (w), 1330 (w), 1315 (w), 1305 (w), 1265 (w), 1240 (m), 1220 (m), 1185 (w), 1135 (m), 1090 (w), 1065 (s), 1050 (s), 1025 (m), 1005 (s), 975 (s), 945 (m), 930 (m), 885 (m), 860 (m), 840 (w), 830 (w), 790 (w), 750 (w) cm^{-1}; δ ($CDCl_3$, 100 MHz) 1.07 (3H, s), 1.19 (3H, s), 1.62 (3H, m), 1.70 (3H, d, J=5 Hz), 1.82 (1H, d, J=4 Hz), 2.03~2.32 (2H, m), 3.66 (1H, br.s), 4.62 (1H, dd, J=7, 4 Hz), 5.18~5.40 (1H, m), 5.50 (1H, dd, J=15, 7.5 Hz), 5.75 (1H, dq, J=15, 6 Hz); MS: *m/z* 192 (M^+, 4 %), 134 (2 %), 122 (56 %), 107 (100 %), 93 (4 %), 91 (15 %), 79 (5 %), 77 (4 %), 65 (2 %), 55 (2 %), 53 (2 %); GLC (Column, PEG-20M, 25 m x 0.25 mm at 70~220° (+3°/min); Carrier gas, N_2, 1.0 ml/min): Rt 24.2 min (single peak). (Found: C, 80.35; H, 10.26. Calc for $C_{13}H_{20}O$: C, 81.20; H, 10.48 %). MS: *m/z* 192.1556 (M^+, Calc for $C_{13}H_{20}O$: 192.1515).

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