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A NEW SYNTHESIS OF THE ENANTIOMERS OF IPSDIENOL, THE PHEROMONE OF THE *IPS* BARK BEETLES†

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Abstract —— The enantiomers (~96% e.e.) of ipsdienol (2-methyl-6-methylene-2,7-octadien-4-ol, **1a**) were synthesized from the enantiomers of serine (**5**) in 16-21% overall yield in 8 steps.

Ipsdienol (**1a**) was first isolated by Silverstein et al. as a component of the aggregation pheromone of the bark beetle, *Ips paraconfusus*.[1] The absolute configuration of (+)-**1a** isolated by them in 1966[1] was determined to be *S* by Mori's synthesis of (*R*)-(-)-**1a** in 1976.[2] Since then interesting relationships between biological activity and absolute configuration of ipsdienol have been clarified, which can be summarized as follows. Firstly, there are species-specific differences in response to the enantiomers of **1a**. Thus, both *Ips calligraphus* and *Ips avulsus* responds to (*R*)-**1a**, while *Ips paraconfusus* is attracted by the (*S*)-enantiomer.[3] Secondly, the male *Ips pini* in California produces (*R*)-**1a**, and this isomer inhibits the attractive pheromone response in *Ips paraconfusus*.[4] Thirdly, (*S*)-**1a** interrupts the response of the Californian *Ips pini* to (*R*)-**1a**.[5] Fourthly, in the east coast of the U.S.A., *Ips pini* responds to (*S*)-**1a**, while the (*R*)-isomer is active in the Pacific coast. This strange phenomenon was studied at the receptor cell level by electrophysiological method to reveal the existence of two distinct types of receptor cells: one keyed to (*R*)-**1a** and the other keyed to the (*S*)-isomer.[6] Finally, further detailed studies on the enantiomeric purity of **1a** in *Ips pini* showed a considerable inter- and intrapopulation variation in the enantiomeric excess (e.e.) of **1a** produced by the insect.[7]

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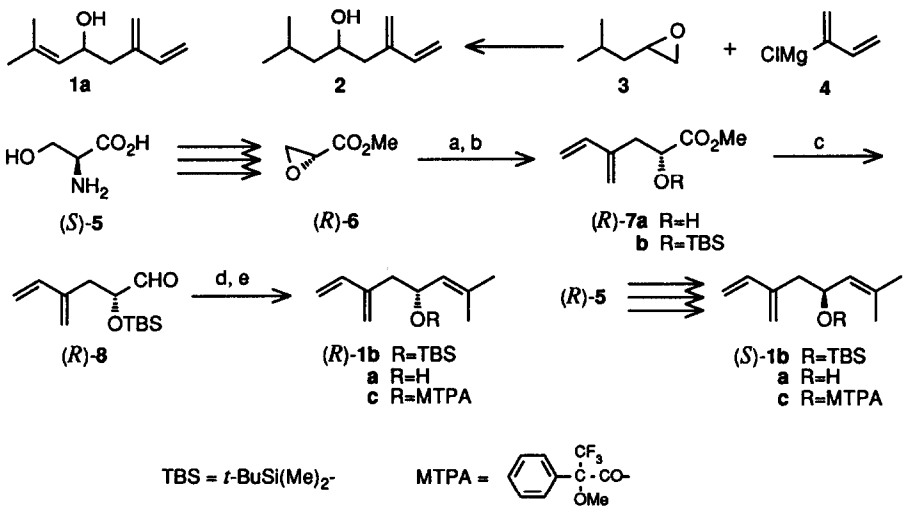
†In memory of the late Professor Toshio Goto, the former Regional Editor of *Tetrahedron*, who deceased on August 29, 1990. Pheromone Synthesis, Part 128. Part 127, Mori, K.; Nagano, E. *Liebigs Ann. Chem.*, in press. The experimental part of this work was taken from a part of the forthcoming doctoral dissertation of H. T. (March, 1993).

Due to their biologically interesting properties as mentioned above, there is a need to develop an efficient synthesis of the enantiomers of ipsdienol (**1a**). Very recent work of Brown and Randad was an attempt along this line, culminating into the synthesis of highly pure enantiomers of **1a**.[8] All other attempts to prepare (*R*)- and/or (*S*)-**1a** either gave enantiomerically impure materials or were inefficient and/or time-consuming.[2,9-14] We herein report a new synthesis of the enantiomers of **1a** (~96% e.e.) starting from the readily available enantiomers of serine (**5**). The synthetic route as showen in Scheme 1 is an extention of our previous synthesis of ipsenol enantiomers (**2**) by the reaction of **3** with the Grignard reagent **4** derived from chloroprene.[10] The key-step was the cleavage of the epoxy ring of **6** with **4** to give **7a**.



Scheme 1. Synthesis of (*R*)- and (*S*)-Ipsdienol.

Reagents: (a) **4**, CuBr•Me_2S/THF (70%); (b) TBSCl, imidazole/DMF (74%); (c) $(i\text{-Bu})_2$AlH/toluene; (d) $Me_2C{=}PPh_3$/DME (70% from **7b**); (e) $(n\text{-Bu})_4$NF/THF (92%).

The epoxy ester (*R*)-**6** was prepared in 63% yield from (*S*)-serine (**5**) according to Larchevêque and Petit.[15] The Grignard reagent **4** was added to (*R*)-**6** in the presence of copper(I) bromide to give (*R*)-**7a**, whose hydroxy group was protected as *t*-butyldimethylsilyl ether (*R*)-**7b**. This was reduced with diisobutylaluminum hydride to give (*R*)-**8**, the Wittig reaction of which with isopropylidene triphenylphosphorane yielded (*R*)-ipsdienol *t*-butyldimethylsilyl ether (**1b**). Finally, treatment of (*R*)-**1b** with tetra-*n*-butylammonium fluoride in THF gave (*R*)-(-)-ipsdienol (**1a**), $[\alpha]_D^{24}$ -15.3° (MeOH) [lit.[8] $[\alpha]_D^{23}$ -13.11° (MeOH); lit.[9] $[\alpha]_D^{20}$ -12° (MeOH)]. The overall yield of (*R*)-**1a** was 33% in 5 steps from (*R*)-**6**, or 21% in 8 steps from (*S*)-serine. Similarly, (*S*)-(+)-ipsdienol (**1a**), $[\alpha]_D^{24}$ +15.7° (MeOH) [lit.[8] $[\alpha]_D^{23}$ +13.18° (MeOH); lit.[9] $[\alpha]_D^{20}$ +11.0° (MeOH)], was prepared in 26% overall yield from (*S*)-**6** or in 16% overall yield from (*R*)-serine.

The enantiomeric purity of our products [(*R*)- and (*S*)-**1a**] was determined as ~96% e.e. by the HPLC analysis of the corresponding (*R*)- and (*S*)-α-methoxy-α-trifluoromethylphenylacetates (MTPA esters)[16] according to Kubo et al.[12] The observed specific rotations (-15.3° and +15.7°) of our enantiomers of **1a** were the highest of those ever have been observed, although Mori et al previously estimated the maximum specific rotation of **1a** as 13.2-13.9°.[10] The values reported in the present work must be considered as the maximum rotation of (*R*)- and (*S*)-**1a**.

In conclusion, we achieved a short and efficient synthesis of the highly pure enantiomers of ipsdienol starting from serine.

EXPERIMENTAL

All b.ps were uncorrected. IR spectra were measured as films on a Jasco IRA-102 spectrometer. ^{1}H NMR spectra were recorded as $CDCl_3$ soln with TMS as an internal standerd at 100 MHz on a Jeol FX-100 spectrometer unless otherwise stated. Optical rotations were measured on a Jasco DIP-140 polarimeter.

Methyl 2-Hydroxy-4-methylene-5-hexenoate **7a**

(a) *(R)-Isomer.* The Grignard reagent **4** was prepared from chloroprene (13.5 g, 15.3 mmol) and Mg (3.60 g, 16.9 mmol) in dry THF (100 ml) under Ar. The reaction was initiated by adding a trace of I_2 and $ZnCl_2$ (0.34 g, 2.5 mmol). The soln of **4** in THF was taken up in another flask in which CuBr-Me_2S (0.63 g, 3.1 mmol) was placed at -70 °C under Ar. To this mixture a soln of (*R*)-**6** (3.02 g, 29.6 mmol) in dry THF (20 ml) was added dropwise, and the stirring was continued at -78 °C for 2 hr. After having been quenched with sat NH_4Cl aq, this mixture was extracted with Et_2O. The Et_2O soln was washed with H_2O and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on SiO_2 to give 3.23 g (70%) of (*R*)-**7a**, IR vmax 3500 (s, OH), 1740 (s, CO_2Me), 1595 (m, 1,3-diene), 1440 (m), 1100 (s), 905 (s) cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 2.3-2.9 (3 H, OH, 3-CH_2), 3.68 (3 H, s, CO_2CH_3), 4.20 (1 H, m, 2-CH), 4.99 (1 H, d, J = 11 Hz, *cis*-6-H), 5.07 (2 H, br s, 4-=CH_2), 5.20 (1 H, d, J = 17 Hz, *trans*-6-H), 6.32 (1 H, dd, J = 11, 17 Hz, 5-H). This material was used for the next step without further purification.

(b) *(S)-Isomer.* In the same manner as described above, (*S*)-**6** (10.3 g, 101 mmol) was converted to 8.75 g (56%) of (*S*)-**7a**, Its IR spectrum was identical with that of (*R*)-**7a**; ^{1}H NMR δ 2.51 (1 H, dd, J = 8, 14 Hz, 3-H), 2.67 (1 H, J = 7 Hz, OH), 2.77 (1 H, dd, J =5, 14 Hz, 3-H), 3.77 (3 H, s, CO_2CH_3), 4.37 (1 H, ddd, J = 5, 7, 8 Hz, 2-CH), 5.10 (1 H, d, J = 11 Hz, *cis*-6-H), 5.18 (2 H, br s, 4-=CH_2), 5.28 (1 H, d, J = 18 Hz, *trans*-6-H), 6.41 (1 H, dd, J = 11, 18 Hz, 5-H). This material was used for the next step without further purification.

Methyl 2-t-Butyldimethylsilyloxy-4-methylene-5-hexenoate **7b**

(a) *(R)-Isomer.* A mixture of (*R*)-**7a** (5.91 g, 37.9 mmol), TBSCl (8.57 g, 54.9 mmol) and imidazole (7.74 g, 114 mmol) in dry DMF (30 ml) was stirred at room temp overnight. It was then poured into H_2O and extracted with *n*-hexane. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), and

concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 followed by distillation to give 7.56 g (74%) of (*R*)-**7b**, b.p. 91-92 °C/4 Torr; n_D^{19} 1.4510; $[\alpha]_D^{24}$ +9.51° (*c* 1.22, MeOH); IR vmax 1760 (s, CO_2Me), 1740 (m, CO_2Me), 1595 (m, diene), 1255 (m, TBS), 1130 (s), 945 (m), 900 (m), 835 (s), 780 (s) cm^{-1}; ^1H NMR δ 0.00 (3 H, s, Si-CH_3), 0.04 (3 H, s, Si-CH_3), 0.88 (9 H, s, *t*-butyl), 2.46 (1 H, dd, *J* = 8, 14 Hz, 3-H), 2.76 (1 H, ddd, *J* = 1, 5, 14 Hz, 3-H), 3.72 (3 H, s, CO_2CH_3), 4.34 (1 H, dd, *J* = 5, 8 Hz, 2-CH), 5.12 (3 H, m, 4-=CH_2, *cis*-6-H), 5.27 (1 H, d, *J* = 18 Hz, *trans*-6-H), 6.37 (1 H, dd, *J* = 11, 18 Hz, 5-H). (Calcd for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69. Found: C, 62.30; H, 9.76%.)

(b) *(S)-Isomer*. In the same manner as described above, (*S*)-**7a** (8.73 g, 55.9 mmol) was converted to 10.79 g (71%) of (*S*)-**7b**, b.p. 91 °C/1.7 Torr; n_D^{27} 1.4499; $[\alpha]_D^{28}$ -9.20° (*c* 1.04 MeOH); Its IR and ^1H NMR spectra were identical with those of (*R*)-**7b**. (Calcd for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69. Found: C, 61.73; H, 9.64%.)

4-t-Butyldimethylsilyloxy-2-methyl-6-methyleneocta-2,7-diene **1b**

(a) *(R)-Isomer*. To a stirred and cooled soln of (*R*)-**7b** (2.65 g, 9.80 mmol) in dry toluene (15 ml), (*i*-Bu)$_2$AlH (1.02 M in toluene, 9.9 ml, 10.1 mmol) was added dropwise at -78 °C under Ar. After stirring for 1 hr at -78 °C, the mixture was quenched with sat Rochelle salt aq, filtered through Celite, and extracted with Et_2O. The Et_2O layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give crude (*R*)-**8**, IR vmax 1735 (s, CHO), 1595 (m, diene), 1250 (s, TBS) cm^{-1}. This crude (*R*)-**8** was directly used for the next step of the Wittig reaction. A soln of *n*-BuLi (1.57 N in hexane, 13.7 ml, 21.5 mmol) was added dropwise to a stirred and ice-cooled suspension of $(CH_3)_2CHPh_3PI$ (10.4 g, 24 mmol) in dry DME (70 ml) under Ar. The mixture was stirred for 1 hr at 0 °C and allowed to settle. The salt-free supernatant (50 ml) was taken up in another flask, and a soln of (*R*)-**8** in dry DME (15 ml) was added dropwise to that soln at -15 °C under Ar. It was then stirred for 2 hr at -15 °C. After having been quenched with sat NH_4Cl aq, this was filtered through Celite, diluted with H_2O and extracted with Et_2O. The Et_2O soln was washed with H_2O and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 followed by distillation to give 1.58 g (61%) of (*R*)-**1b**, b.p. 86-88 °C/2.5 Torr; n_D^{15} 1.4573; $[\alpha]_D^{22}$ -15.7° (*c* 1.10, pentane); IR vmax 2950 (s, C-H), 2870 (s, C-H), 1595 (m, diene), 1250 (m, TBS), 1070 (s), 900 (s), 835 (s), 775 (s) cm^{-1}; ^1H NMR δ 0.00 (3 H, s, Si-CH_3), 0.02 (3 H, s, Si-CH_3), 0.87 (9 H, s, *t*-butyl), 1.59 (3 H, d, *J* = 1 Hz, C=C-CH_3), 1.69 (3 H, d, *J* = 1 Hz, C=C-CH_3), 2.25 (1 H, dd, *J* = 6, 14 Hz, 5-H), 2.43 (1 H, dd, *J* = 8, 14 Hz, 5-H), 4.47 (1 H, ddd, *J* = 6, 7, 8 Hz, 4-CH), 4.9-5.4 (5 H, m, allylic-H without 7-H), 6.37 (1 H, dd, *J* = 11, 18 Hz, 7-H). (Calcd for $C_{16}H_{30}OSi$: C, 72.11; H, 11.35. Found: C, 72.05; H, 11.20%.)

(b) *(S)-Isomer*. In the same manner as described above, (*S*)-**7b** (10.7 g, 39.6 mmol) was converted to 7.61 g (72%) of (*S*)-**1b**, b.p. 87-88 °C/3 Torr; n_D^{21} 1.4543; $[\alpha]_D^{21}$ +15.8° (*c* 1.19, pentane); Its IR and ^1H NMR spectra were identical with those of (*R*)-**1b**. (Calcd for $C_{16}H_{30}OSi$: C, 72.11; H, 11.35. Found: C, 72.21; H, 11.41%.)

Ipsdienol **1a**

(a) *(R)-Isomer*. (*n*-Bu)$_4$NF soln (1.0 M in THF, 23 ml, 23 mmol) was added to a stirred soln of (*R*)-**1b** (4.05 g, 15.2 mmol) in dry THF (8 ml). After stirring at room temp for 5 hr, it was then poured into H_2O and

extracted with Et_2O. The Et_2O soln was washed with H_2O, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on SiO_2 followed by distillation to give 2.18 g (92%) of (*R*)-**1a**. An analytical sample was obtained by further distillation, b.p. 90-92 °C/11 Torr; n_D^{24} 1.4845; $[\alpha]_D^{24}$ -15.3° (*c* 0.97, MeOH); IR vmax 3440 (s, OH), 3080 (w), 2970 (m), 2850 (s), 1800 (w), 1665 (w), 1630 (w), 1590 (s), 1440 (m), 1385 (m), 1320 (w), 1250 (w), 1200 (w), 1160 (w), 1020 (s), 1005 (w), 990 (s), 960 (w), 895 (s), 870 (w), 835 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (1 H, s, OH), 1.68 (3 H, d, *J* = 1.2 Hz, C=C-CH_3), 1.73 (3 H, br d, *J* = 1.2 Hz, C=C-CH_3) 2.38 (1 H, dd, *J* = 8.2, 14.1 Hz, 5-H), 2.45 (1 H, dd, *J* = 5.2, 14.1 Hz, 5-H), 4.52 (1 H, ddd, *J* = 5.2, 8.2, 8.2 Hz, 4-CH), 5.10 (1 H, s, 6-=CH) 5.11 (1 H, d, *J* = 10.5 Hz, *cis*-8-H) 5.14 (1 H, br s, 6-=CH), 5.21 (1 H, dqq, *J* = 8.2, 1.2, 1.2 Hz, 3-CH), 5.28 (1 H, d, *J* = 17.5, *trans*-8-H), 6.41 (1 H, dd, *J* = 10.5, 17.5 Hz, 7-H); GLC (column, PEG-20M, 4 mmϕ ×200 cm at 100 °C; carrier gas, N_2, 50 ml/min): t_R 3 min 46 sec (>99%). (Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.76; H, 10.72%.)

(b) *(S)-Isomer*. In the same manner as described above, (*S*)-**1b** (6.53 g, 24.5 mmol) was converted to 3.51 g (92%) of (*S*)-**1a**, b.p. 76-79 °C/6 Torr; n_D^{24} 1.4822; $[\alpha]_D^{24}$ +15.7° (*c* 0.99 MeOH); Its IR spectrum was identical with that of (*R*)-**1a**; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (1 H, d, *J* = 3.0 Hz, OH), 1.68 (3 H, d, *J* = 1.2 Hz, C=C-CH_3), 1.73 (3 H, br d, *J* = 1.2 Hz, C=C-CH_3) 2.38 (1 H, dd, *J* = 8.2, 14.1 Hz, 5-H), 2.45 (1 H, dd, *J* = 5.2, 14.1 Hz, 5-H), 4.52 (1 H, dddd, *J* = 3.0, 5.2, 8.2, 8.2 Hz, 4-CH), 5.10 (1 H, br s, 6-=CH) 5.11 (1 H, d, *J* = 10.5 Hz, *cis*-8-H) 5.14 (1 H, br s, 6-=CH), 5.18-5.23 (1 H, m, 3-CH), 5.28 (1 H, d, *J* = 17.5, *trans*-8-H), 6.41 (1 H, dd, *J* = 10.5, 17.5 Hz, 7-H); GLC (column, PEG-20M, 4 mmϕ ×200 cm at 100 °C; carrier gas, N_2, 50 ml/min): t_R 3 min 51 sec (>99%). (Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.52; H, 10.59%.)

Determination of the Enantiomeric Purity of ***1a***

(*R*)-**1a** was converted to the corresponding MTPA ester **1c** and analyzed by HPLC [column, Senshu pak-Silica 1251-N, 4.6 mmϕ × 250 mm; solvent, pentane-acetone (1000:1); flow rate, 1.0 ml/min]: t_R -21 min [<2%, (*S*)-MTPA ester of (*S*)-**1a**], 22.0 min [>98%, (*S*)-MTPA ester of (*R*)-**1a**]. The optical purity of (*R*)-**1a** was >96% e.e. In the same manner the optical purity of (*S*)-**1a** was determined to >96% e.e.

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