39. A Facile Synthesis of Optically Pure (−)-(*S*)-Ipsenol Using a Chiral Titanium Complex[1])

by **Konrad Oertle***, **Harry Beyeler**, **Rudolf O. Duthaler**, **Willi Lottenbach**, **Martin Riediker**[2]), and **Eginhard Steiner**

Central Research Laboratories, *Ciba-Geigy AG*, CH-4002 Basel

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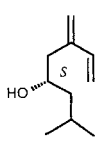
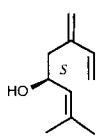
A stereocontrolled synthetic route to optically pure (−)-(*S*)-ipsenol (**1**), the pheromone of *Pityokteines curvidens* and various other bark-beetle species is described. Key step of the synthesis is an enantioselective aldol reaction using a chiral titanium-cabrohydrate complex *(Scheme 1)*. The carboxylate function of the optically pure β-hydroxy acid **5** thus obtained in mol quantities is then elaborated to the diene moiety by standard methodology *(Scheme 2)*.

Various species of bark beetles are important pests to coniferous forests throughout the world. Among these are beetles of the genus *Ips*. In 1965 *Silverstein et al.* [2] isolated and characterized two new terpene alcohols from frass produced by *Ips paraconfusus* in ponderosa pine: (−)-(*S*)-ipsenol (= 2-methyl-6-methylideneoct-7-en-4-ol; **1**) and (+)-(*S*)-ipsdienol (= 2-methyl-6-methylideneocta-2,7-dien-4-ol; **2**). The absolute configurations were established by *Mori* in 1976 by chemical correlation [3].



1 (-)-Ipsenol



2 (+)-Ipsdienol

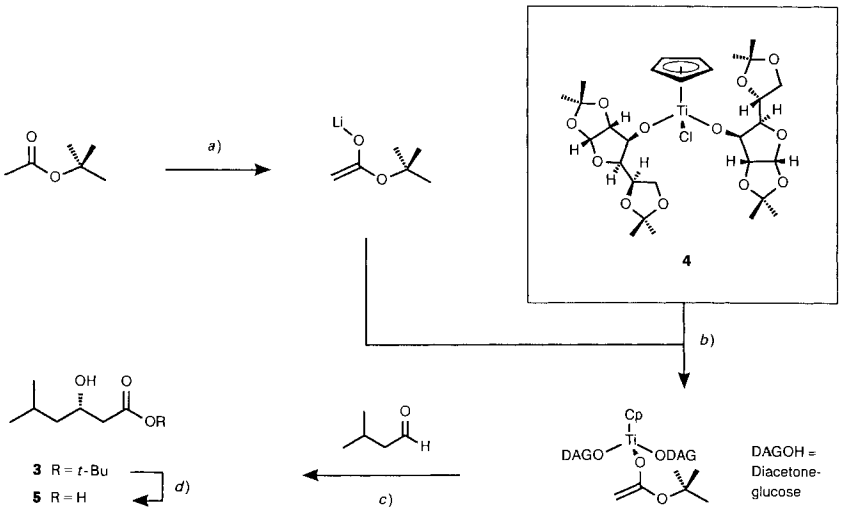
Later, it was found that (−)-(*S*)-ipsenol is also an aggregation pheromone of other *Ips* as well as of *Pityokteines* species [4]. In the last couple of years, the population of *Pityokteines curvidens* in forests of Central Europe increased drastically. One way to reduce damage by these bark beetles in silver fir trees is to catch the insects in special traps with the aid of their aggregation pheromone. For this purpose[3]), larger amounts (50 g) of (−)-(*S*)-ipsenol of high optical purity (≥ 99.5% ee) were needed. Several syntheses of ipsenol, in racemic [2c] [5] and optically pure form [3] [6], have been published in the past. However, all reported enantioselective procedures have shortcomings in that the product

[1]) Part 6 of 'Enatioselective Syntheses with Titanium-Carbohydrate Complexes'; part 5, see [1].

[2]) Present address: Research Laboratories, Plastics Division, *Ciba-Geigy Corp.*, Ardsley, New York 10502, USA.

[3]) Field tests were carried out at the *Swiss Federal Institute for Forests, Snow, and Landscape*, CH-8903 Birmensdorf, Switzerland, by Dr. *J. K. Maksymov*. The results will be published elsewhere.

Scheme 1



a) Lithium dicyclohexylamide/Et_2O, −70°. *b*) **4** (0.155M in toluene), −70 to −30°. *c*) 1) 3-Methylbutanal at −30°, warming to r.t.; 2) 45% NH_4F/25% NaCl, filtration, 0.1N HCl, extraction (Et_2O), distillation (60–64°/0.3 Torr). *d*) 2N aq. NaOH/MeOH 1:2, 50°, evaporation of MeOH, addition of H_2O and HCl (conc.), filtration, recrystallisation (cyclohexane).

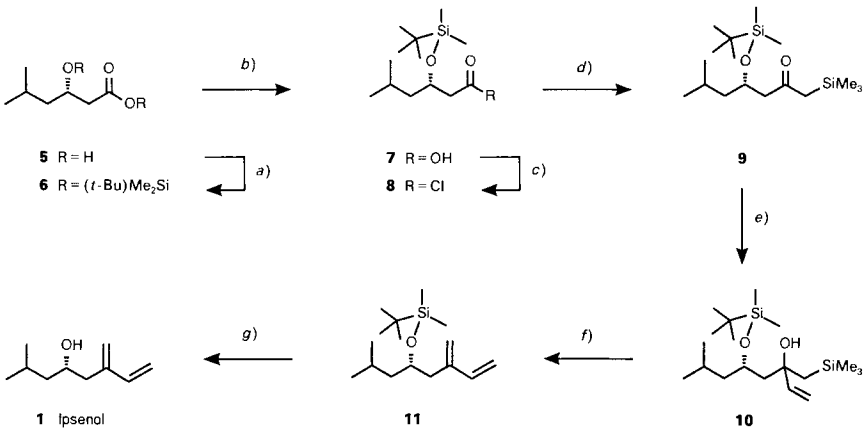
is either obtained in insufficient optical purity, or only small amounts can be synthesised conveniently. Since we were unable to separate racemic ipsenol into its optical antipodes on a preparative scale, we decided to develop an improved synthetic access to this pheromone in optically pure form.

A suitable starting material for the synthesis of **1** is *tert*-butyl (3*S*)-3-hydroxy-5-methylhexanoate (**3**), as it is obtained conveniently by aldol reaction [7b] using the chiral titanium complex **4**, a procedure developed recently in our laboratories [7]. Saponification and recrystallisation from cyclohexane affords the hydroxy acid **5** in high optical purity (≥ 99% ee) and 38% overall yield on a 2-mol scale *(Scheme 1)*[4]).

The subsequent transformation of the carboxylate function of **5** follows, with some modifications, the silicon-directed diene synthesis described by *Jenkins* and coworkers [13] *(Scheme 2)*. The hydroxy acid **5** is treated with 2.5 equiv. of (*tert*-butyl)chloro-(dimethyl)silane in the presence of imidazole in DMF at room temperature to give the bis-silylated product **6**. Selective hydrolysis of the silyl ester **6** in THF/aq. $NaHCO_3$ solution at room temperature gives (3*S*)-3-[(*tert*-butyl)dimethylsilyloxy]-5-methylhex-

[4]) While this aldol reaction is probably the most direct access to optically pure β-hydroxy acid **5** – other enantioselective aldol methods involve either sophisticated reagents [8] or the introduction and removal of chiral auxiliaries and extremely low temperatures (−100°) [9] – such aldols can also be obtained from the corresponding β-keto esters by enantioselective catalytic hydrogenation [10] or by hydride reduction [11]. Since the racemate of **5** crystallizes as a conglomerate of enantiomers [7b], a separation of this racemate by direct crystallisation [12] (without chiral auxiliary) should also be possible and, maybe, this is the most feasible procedure for obtaining bulk quantities of (+)- or (−)-**5**.

Scheme 2



a) 2.5 Equiv. (*t*-Bu)Me_2SiCl, imidazole/DMF, r.t. *b*) $NaHCO_3$/THF/H_2O, r.t. *c*) 1-Chloro-*N*,*N*-2-trimethylprop-1-enylamine [14]/CH_2Cl_2, 0°. *d*) 1) 1 Equiv. Cu_2I_2, Me_3SiCH_2MgCl/Et_2O, −60 to 0°; 2) 1 equiv. NH_4Cl, 0°. *e*) CH_2 = CHMgBr/THF, −7 to 0°. *f*) Sat. NaOAc/AcOH, 55°. *g*) 2.5 Equiv. $Bu_4NF \cdot 3\,H_2O$, r.t.

anoic acid (**7**) in 98% yield[5]). The crude acyl chloride **8**, obtained by reaction of **7** with 1-chloro-*N*,*N*,2-trimethylprop-1-enylamine [15], is treated at −60 to 0° with [(trimethylsilyl)methyl]magnesium chloride/Cu_2I_2 in Et_2O following the procedure of *Akiba* and coworkers [16]. Careful workup by quenching the reaction at 0° with 1 equiv. of aq. NH_4Cl solution gives the β-keto-silane **9**. Crude **9** is treated at −7 to 0° with 2 equiv. of vinylmagnesium bromide in THF (6 h). The vinyl alcohol **10** is then subjected without further purification to *Peterson* olefination [8]: reaction with a saturated NaOAc/AcOH solution at 55° affords silyl-protected (−)-(*S*)-ipsenol (**11**), the overall yield for the four steps **7** to **11** being 46.5%. Deprotection of **11** is achieved with 2.5 equiv. of $[(Bu)_4N]F \cdot 3H_2O$ in THF (15 h) and yields, after purification by chromatography and distillation, 70–90% of optically pure (−)-(*S*)-ipsenol (**1**). In this way, 56.04 g of **1** have been prepared in one batch from 160.6 g of β-hydroxy-acid **5** (33% from **5**, 13% from AcO(*t*-Bu)).

We like to thank Ms. *H. Landert* for her skillful assistance in the laboratory.

Experimental Part

1. *(3S)-3-Hydroxy-5-methylhexanoic Acid* (**5**). 1.1. *Small Scale.* To a soln. of dicyclohexylamine (7.25 g, 40 mmol) in dry Et_2O (130 ml), BuLi (21.8 ml of a 1.6M soln. in hexane, 35 mmol) was added at −25° (Ar). After 20 min at −25° and cooling to −74°, a soln. of AcO(*t*-Bu) (3.48 g, 30 mmol) 35 ml of Et_2O was added within 45 min. The mixture was stirred for 30 min at −74° before 425.5 ml of 0.094M **4** (*ca.* 40 mmol) in toluene [7a], which had been precooled to −74°, was added within 1 h *via* canula. After 30 min at −74°, the mixture was warmed to −30° (30 min), kept for 1 h at −30 to −33°, and recooled to −74° (35 min). Then, 3-methylbutanal (3.88 g, 45 mmol) in 40 ml

[5]) This synthetic sequence has been carried out with equal success using thexyl-dimethylsilyl protection [14].

of Et_2O was slowly added (45 min). After stirring for 2 h at −74°, the reaction was quenched by the addition of 45% aq. NH_4F soln. (150 ml), and stirring was continued for 30 min at r.t. The precipitated titanium compounds were removed by filtration (*Celite*), and the aq. phase of the filtrate was separated and extracted with Et_2O (2 ×). The org. phases were washed with sat. NaCl soln. (2 ×), dried ($MgSO_4$), and evaporated. The residue (38.1 g) was suspended in 0.1N HCl (300 ml) and the mixture stirred for 1.5 h at r.t. Extraction with Et_2O (3 ×), washing of the org. phases with H_2O, drying ($MgSO_4$), and distillation (5-cm *Vigreux* column, 41–45°/0.002 Torr) of the residue of the organic phase afforded 4.92 g (81%) of tert-*butyl-(3S)-3-hydroxy-5-methylhexanoate* (**3**). $[\alpha]_D = +14.8$, $[\alpha]_{365} = +47.0$ (*c* = 1, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.92 (*d*, *J* = 7.5, 3 H–C(6), CH_3–C(5)); 1.16 (*ddd*, *J* = 13, 9, 4.5) and 1.4–1.55 (*m*) (2 H–C(4)); 1.46 (*s*, $(CH_3)_3C$); 1.7–1.9 (*m*, 7 main peaks, H–C(5)); 2.30 (*dd*, *J* = 16, 9) and 2.41 (*dd*, *J* = 16, 3.5) (2 H–C(2)); 2.3–3.0 (br. OH–C(3)); 4.03 (*tdd*, *J* = 9, 4.5, 3.5, H–C(3)). Anal. calc. for $C_{11}H_{22}O_3$ (202.29): C 65.31, H 10.97; found: C 65.59, H 11.10.

At r.t./*ca.* 150 Torr, 4.69 g of **3** were stirred for 1 h in 40 ml of CF_3COOH. After addition of toluene (70 ml), the volatile material was evaporated. Repeated addition of toluene (2 × 50 ml) and evaporation gave 3.76 g of crude **5**. An anal. sample (*ca.* 10 mg) of this material in CH_2Cl_2 (2 ml) and isopropyl isocyanate (1 ml) was heated in a sealed ampule to 100° (1 h). After cooling, the volatile material was removed in a stream of dry Ar, and the residue was redissolved in CH_2Cl_2 (5 ml). Analysis on a chiral cap.-GLC column (*Chirasil-L-Val*® [17], 50 m, 190°, carrier 90 kPa): (3*S*)-enantiomer (t_R 9.35 min) 97%, (3*R*)-enantiomer (t_R 9.58 min) 3%; 94% ee.

The remaining crude **5** was dissolved in CH_3OH (5 ml) and 2N NaOH (15 ml) and extracted with Et_2O. The Et_2O layer was washed with 2N NaOH (2 × 10 ml) and discarded. The combined aq. phases were acidified with conc. HCl soln. (pH 2), saturated with NaCl, and extracted with AcOEt (3 × 150 ml). Washing of the org. phases with sat. NaCl soln. (4 ×), drying ($MgSO_4$), evaporation and recrystallisation of the residue (3.37 g) from hot cyclohexane (30 ml) afforded 2.97 g (83%, 67% based on AcO(*t*-Bu)) of **5**. M.p. 82–83°. Optical purity ≥ 99.5% (capillary GLC, see above). $[\alpha]_D = +14.2$, $[\alpha]_{365} = +49$ (*c* = 1, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.94 (*d*, *J* = 7.5, 3 H–C(6), CH_3–C(5)); 1.23 (*ddd*, *J* = 13.5, 9, 4.5) and 1.52 (*ddd*, *J* = 13.5, 9, 5.5) (2 H–C(4)); 1.7–1.9 (*m*, 7 main peaks, H–C(5)); 2.46 (*dd*, *J* = 16, 9) and 2.56 (*dd*, *J* = 16, 4) (2 H–C(2)); 4.12 (*tdd*, *J* = 9, 4.5, 4, H–C(3)); 5.3–8.0 (br. CO_2H, OH). Anal. calc. for $C_7H_{14}O_3$ (146.19): C 57.51, H 9.65; found C 57.58, H 9.77.

1.2. *Large Scale.* 1.2.1. *Chloro(cyclopentadienyl)bis(1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-O-yl) titanium* (**4**). Cyclopentadienyltitanium trichloride (440 g, 2 mol) was placed into a 20-l flask equipped with dropping funnel (gas inlet), cooler (gas-bubbler), thermometer, and mechanical stirrer (anchor paddle impeller) which had been flushed thoroughly with Ar. After the addition of dry toluene (10 l) and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (1.04 kg, 4 mol, freshly sublimed), a soln. of Et_3N (414 g, 4.1 mol) in 1.5 l of toluene was added from the dropping funnel within 1.5 h. Immediate precipitation of $Et_3N \cdot HCl$ was accompanied by a raise in temp. from r.t. to 32°. The mixture was stirred for 5 h and filtered under Ar through a fritted funnel. Washing with toluene (2 × 500 ml) afforded 11.5 kg (12.9 l) of a clear yellow soln. of **4** in toluene (*ca.* 0.155M).

1.2.2. *Acid* **5**. To a soln. of dicyclohexylamine (362.6 g, 2.0 mol) in 5 l of Et_2O (dist. from Na), placed into a 30-l stainless-steel vessel, BuLi (1.25 l of a 1.6M soln. in hexane, 2.0 mol) was added at −50° within 1 h. The mixture was cooled to −70°, and a soln. of AcO(*t*-Bu) (232.4 g, 2.0 mol) in dry toluene (1 l) was added simultaneously with 12.9 l of **4** (*ca.* 0.155M in toluene, see above) within 5 h. The cooling bath was removed, and when the temp. reached −30°, a soln. of 3-methylbutanal (172.3 g, 2.0 mol) in Et_2O (1 l) was added slowly. Stirring was continued, while the temp. slowly reached 23° (overnight, *ca.* 16 h). The reaction was then quenched by the addition of 45% aq. NH_4F (3.25 l) and 25% NaCl soln. (5 l). After stirring for 1 h, the precipitated material was removed by filtration using Et_2O (3 l) for washing. The aq. phase of the filtrate was separated and extracted with Et_2O (2 × 1.5 l). After evaporation of solvents, the residue (1.828 kg) was suspended in 0.1N HCl (15 l), and the mixture was stirred vigorously overnight (*ca.* 16 h, r.t.). The resulting emulsion was extracted with Et_2O (4 × 5 l), the extracts were washed with H_2O (5 l), dried (Na_2SO_4), and evaporated. Distillation of the residue over a vacuum-jacketed *Vigreux* column (55 cm) afforded 193.4 g (48%) of **3**. B.p. 60–64°/0.3 Torr.

To a soln. of **3** (202 g, 1 mol) in CH_3OH (220 ml) 2N NaOH (1 l) was added. After heating for 7 h to 50°, the two-phase mixture had become homogeneous. Concentration by evaporation of solvent on a rotary evaporator at 30° until some material precipitated was followed by addition of H_2O (150 ml) and acidification by slow addition of conc. HCl soln. (250 ml) with cooling (5°, 45 min). The precipitated product was collected by filtration, washed with cyclohexane (400 ml), and dried under vacuum at 40°. This crude material (119.9 g; m.p. 86–87°) was dissolved in boiling cyclohexane (3 l). The soln. was cleared by filtration through a paper filter placed in a heated funnel using 100 ml of cyclohexane for flushing. Cooling to 12°, collection of the crystals by filtration, and drying at 50° (vacuum) afforded 115.7 g (79%) of **5**. M.p. 87–87.5°. Optical purity ≥ 99% as determined by capillary GLC (see above). Extraction of the acidified aq. mother liquor after filtration with Et_2O yielded another crop (17.4 g, 11%) of **5** of lower optical purity (61.5% ee).

2. *(3S)-3-[(*tert*-Butyl)dimethylsilyloxy]-5-methylhexanoic Acid* (**7**). To a soln. of **5** (160.6 g, 1.1 mol) and imidazole (217.9 g, 3.2 mol) in DMF (350 ml) cooled to 10°, (*tert*-butyl)chloro(dimethyl)silane (393.1 g, 97%, 2.53 mol) was added at such a rate that the temp. did not exceed 30° (*ca.* 15 min) using 150 ml of DMF for flushing. After stirring for 21 h at r.t., hexane (250 ml) was added followed by careful addition of H_2O (750 ml). The aq. phase was separated and extracted with hexane (4 × 100–150 ml). The org. extracts were washed with H_2O (50 ml) and sat. NaCl soln. (100 ml), dried ($MgSO_4$), and the solvent was evaporated (40°). The residue (464.5 g), consisting mainly of bis-silylated derivative **6**, was dissolved in THF (1.2 l), H_2O (300 ml), and sat. $NaHCO_3$ soln. (400 ml). The resulting mixture was stirred for 19 h at r.t., diluted with H_2O (1.8 l), and acidified to pH 2 by careful addition of 2N HCl (300 ml, *ca.* 1 h). The aq. phase was separated and extracted with Et_2O (2 × 200 ml, 2 × 100 ml). The org. layers were washed with H_2O (100 ml) and sat. NaCl soln. (3 × 50 ml), dried ($MgSO_4$), and evaporated (40°). The residue was freed from (*tert*-butyl)dimethylsilanol by careful evaporation (bath temp. 41–99°/0.3–0.05 Torr; caution, foams): 280.4 g (98%) of **7** as slightly yellow viscous oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.05, 0.06 (2*s*, $(CH_3)_2Si$); 0.85 (*s*, $(CH_3)_3CSi$); 0.89 (*d*, *J* = 6, 3 H–C(6), CH_3–C(5)); 1.34 (*ddd*, *J* = 12, 7.5, 6) and 1.42 (*ddd*, *J* = 12, 7, 6), 2 H–C(4)); 1.55–1.7 (*m*, 7 main peaks, H–C(5)); 2.43 (*dd*, *J* = 14, 6.5) and 2.50 (*dd*, *J* = 14, 5.5) (2 H–C(2)); 4.1–4.2 (*m*, 5 main peaks, H–C(3)); 12.5–12.8 (br., CO_2H).

3. *(2'S)-2-{2'[(*tert*-Butyl)dimethylsilyloxy]-4'-methylpentyl}buta-1,3-diene* (**11**). 3.1. *(3S)-3-[(*tert*-Butyl)-dimethylsilyloxy]-5-methylhexanoyl Chloride* (**8**). To a soln. of **7** (279.6 g, 1.075 mol) in CH_2Cl_2 (600 ml), 1-chloro-*N*,*N*,2-trimethylprop-1-enylamine [15] (190 ml, 1.345 mol) was added at 0–4° within 20 min (Ar, mechanical stirrer, cooling with dry-ice/acetone). The mixture was warmed to r.t. (2 h) and the volatile material removed by evaporation at reduced pressure (5–30°/1 Torr). The residue, crude **8** containing some *N*,*N*-dimethylisobutyramide, was used without purification for the next step.

3.2. *(4S)-4-[(*tert*-Butyl)dimethylsilyloxy]-6-methyl-1-(trimethylsilyl)heptan-2-one* (**9**). To a stirred suspension of Mg turnings (41.32 g, 1.7 mol) in dry Et_2O (200 ml), a soln. of (chloromethyl)trimethylsilane (208.54 g, 1.7 mol) in Et_2O (300 ml) was added at such a rate that gentle boiling was maintained (2 h; the reaction had to be started by the addition of a few drops of 1,2-dibromoethane and heating). The mixture was boiled under reflux for additional 1.5 h, cooled to r.t., transferred to a dropping funnel *via* canula (Ar pressure), and slowly added (1 h) at −60° to a soln./suspension of crude **8** (see above) and Cu_2I_2 (227 g, 1.12 mol) in Et_2O (1.6 l) with efficient stirring using *ca.* 100 ml of Et_2O for flushing. The mixture was warmed to 0° within 1.5 h and quenched at this temp. by careful addition of sat. NH_4Cl soln. (300 ml, 10 min, cooling with dry-ice/acetone). The inorg. salts were separated by filtration and washed with Et_2O (750 ml). The filtrate was dried ($MgSO_4$), the solvent evaporated, and the residue freed from inorg. material by repeated dissolving in benzene, filtration, and evaporation. The crude **9** thus obtained (470.1 g) was used without further purification for the next step.

3.3. *(5S)-5-[(*tert*-Butyl)dimethylsilyloxy]-7-methyl-3-[(trimethylsilyl)methyl]oct-1-en-3-ol* (**10**). Vinyl bromide (224.1 g, 2.095 mol) was condensed with cooling into dry THF (350 ml), and the resulting soln. was added with Ar pressure to a well stirred suspension of Mg turnings (50.92 g, 2.095 mol) in dry THF (100 ml) at a rate that the temp. was kept between 40 and 60° (1.5 h). During this addition, the mixture was diluted with THF (4 × 250 ml). After heating under reflux for 5 h, the mixture was cooled to r.t., and precipitated material was dissolved by the addition of THF (400 ml). The contents of the flask were then transferred within 1 h by Ar pressure *via*-glass-tubes to a soln. of crude **9** (469.5 g, see above) in THF (800 ml) cooled to −7 to 0°. The mixture was warmed to r.t. (2 h) and stirred for 3 h at r.t. For workup, the mixture was divided into two halfs, each being transferred to a mixture of sat. NH_4Cl soln. (650 ml), sat. NaCl soln. (1 l), 2N HCl (500 ml), and ice (350 g). After acidification to pH 5 with 2N HCl and saturation with NaCl, each half was extracted with Et_2O (200 ml). Washing of the org. layers with sat. NaCl soln. to neutrality, drying ($MgSO_4$), and evaporation afforded 408.3 g crude **10** (mixture of epimers) which was used directly for the next step.

3.4. Peterson *Olefination*. AcOH saturated with NaOAc (1.1 l) was added to crude **10** (407.9 g, see above), and the resulting suspension was heated for 2.5 h to 50–55° with efficient stirring. The cooled mixture was diluted with H_2O (2 l) and extracted with hexane (500 ml, 4 × 100 ml). The org. phase was washed with sufficient sat. $NaHCO_3$ soln. to ensure complete removal of AcOH (4 × 50 ml) and with sat. NaCl soln. (3 × 50 ml), dried ($MgSO_4$), and evaporated, after the addition of *ca.* 1 g of 4-(*tert*-butyl)catechol as polymerisation inhibitor. Chromatography (1.25 kg of silica gel, hexane) and distillation (61–64°/0.1 Torr) over a short *Vigreux* column (10 cm) into a recipient containing 4-(*tert*-butyl)catechol (1 g) afforded 134.15 g (46.5% based on **7**) of diene **11**. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.03, 0.035 (2*s*, $(CH_3)_2Si$); 0.86, 0.90 (2*d*, *J* = 6.5, 3 H–C(5'), CH_3–C(4')); 0.88 (*s*, $(CH_3)_3CSi$); 1.27 (*ddd*, *J* = 12, 5, 2) and 1.35 (*dd*, *J* = 12, 7) (2 H–C(3')); 1.73 (*hept.*, *J* = 6.5, H–C(4')); 2.3–2.4 (*m*, 2 main peaks, 2 H–C(1')); 3.87 (*quint.*, *J* = 6, H–C(2')); 5.01, 5.07 (2*m*, $w_{1/2} \approx 5$, 2 H–C(1)); 5.06 (*d*, *J* = 11) and 5.31 (*d*, *J* = 17) (2 H–C(4)); 6.35 (*dd*, *J* = 17, 11, H–C(3)).

4. *(4S)-2-Methyl-6-methyleneoct-7-en-4-ol* (**1**). A soln. of **11** (133.88 g, 0.499 mol) in THF (250 ml) was added to a soln. of $[(Bu)_4N]F \cdot 3H_2O$ (437 g, 1.385 mol) in THF (1.75 l). The mixture was stirred for 15 h at r.t. and for 2 h at 55°. After dilution with H_2O (2.5 l), the mixture was extracted with Et_2O (3 × 250 ml, 2 × 100 ml). The org. phases were washed with 3/4-sat. NaCl soln. (3 × 75 ml), dried ($MgSO_4$), and 35°, after the addition of 4-(*tert*-butyl)catechol (*ca.* 1 g). The residue (146.5 g) was passed through alumina (900 g, neutral, act. III) with CH_2Cl_2. Distillation over a 10-cm *Vigreux* column (77–80°/11 Torr), rechromatography (alumina III/CH_2Cl_2 and silica gel/hexane, hexane/Et_2O, CH_2Cl_2/Et_2O, and Et_2O) and redistillation as above afforded 56.04 g (72.8%) of **1**, stabilised with 4-(*tert*-butyl)catechol. The course of purification was followed by capillary GLC (*SE 54*, 15 m, 80–220°, 10°/min carrier 30 kPa), t_R 3.73 min (99%). The optical purity ($\geq$ 99% ee) was determined by reaction of derivatives with isopropyl isocyanate in CH_2Cl_2 at 100° as described above for **5** and capillary GLC of the resulting carbamate on a chiral column (*Chirasil-L-Val*® [17], 50 m, 110°, carrier 60 kPa): t_R 49.2 min ((4*R*)-enantiomer) and 50.1 min ((4*S*)-enantiomer). $[\alpha]_D = -17.7$, $[\alpha]_{365} = -31.7$ (*c* = 1, EtOH; [2a]: $[\alpha]_D = -17.5$ (*c* = 1, EtOH)). ^{1}H-NMR (300 MHz, $CDCl_3$): 0.92, 0.96 (2*d*, *J* = 6.0, 3 H–C(1), CH_3–C(2)); 1.28 (*ddd*, *J* = 4.0, 8.0, 13.0) and 1.48 (*ddd*, *J* = 5.0, 8.0, 13.0) (2 H–C(3)); 1.70 (br., OH), 1.82 (*m*, H–C(2)); 2.22 (*dd*, *J* = 8.0, 13.0) and 2.50 (*dd*, *J* = 4.0, 13.0) (2 H–C(5)); 3.83 (*dddd*, *J* = 4.0, 4.0, 8.0, 8.0, H–C(4)); 5.10 and 5.18 (*m*, $w_{1/2} \approx 3$, CH_2 = C(6)); 5.12 (*d*, *J* = 10.5) and 5.26 (*d*, *J* = 17.0) (2 H–C(8)); 6.40 (*dd*, *J* = 10.5, 17.0, H–C(7)).

REFERENCES

[1] R. O. Duthaler, P. Herold, S. Wyler-Helfer, M. Riediker, *Helv. Chim. Acta* **1990,** *73,* submitted.

[2] a) R. M. Silverstein, J. O. Rodin, D. L. Wood, L. E. Browne, *Tetrahedron* **1966,** *22,* 1929; b) R. M. Silverstein, J. O. Rodin, D. L. Wood, *Science* **1966,** *154,* 509; c) C. A. Reece, J. O. Rodin, R. G. Brownlee, W. G. Duncan, R. M. Silverstein, *Tetrahedron* **1968,** *24,* 4249.

[3] K. Mori, *Tetrahedron* **1976,** *32,* 1101.

[4] a) C. M. Harring, J. P. Vité, *Naturwissenschaften* **1975,** *62,* 488; b) J. P. Vité, R. Hedden, K. Mori, *ibid.* **1976,** *63,* 42; c) M. C. Birch, D. M. Light, K. Mori, *Nature (London)* **1977,** *270,* 738; d) C. M. Harring, *Z. Angew. Entom.* **1978,** *85,* 281; e) M. C. Birch, D. M. Light, D. L. Wood, L. E. Browne, R. M. Silverstein, B. J. Bergot, G. Ohloff, J. R. West, J. C. Young, *J. Chem. Ecol.* **1980,** *6,* 703.

[5] a) St. Karlsen, P. Froyen, L. Skattebol, *Acta Chem. Scand., Ser. B* **1976,** *30,* 664; b) A. Hosomi, Y. Araki, H. Sakurai, *J. Org. Chem.* **1983,** *48,* 3122; c) L. S. Hegedus, S. Varaprath, *Organometallics* **1982,** *1,* 259; d) A. Garcia Martinez, J. L. Marco Contelles, *Synthesis* **1982,** 742; e) Y. N. Bubnov, M. Y. Etinger, *Tetrahedron Lett.* **1985,** *26,* 2797.

[6] a) K. Mori, *Tetrahedron Lett.* **1975,** *26,* 2187; b) K. Mori, T. Takigawa, T. Matsuo, *Tetrahedron* **1979,** *35,* 933; c) N. Ikeda, I. Arai, H. Yamamoto, *J. Am. Chem. Soc.* **1986,** *108,* 483.

[7] a) M. Riediker, R. O. Duthaler, *Angew. Chem.* **1989,** *101,* 488; *ibid. Int. Ed.* **1989,** *28,* 494; b) R. O. Duthaler, P. Herold, W. Lottenbach, K. Oertle, M. Riediker, *Angew. Chem.* **1989,** *101,* 490; *ibid. Int. Ed.* **1989,** *28,* 495; c) G. Bold, R. O. Duthaler, M. Riediker, *Angew. Chem.* **1989,** *101,* 491; *ibid. Int. Ed.* **1989,** *28,* 497; d) M. Riediker, A. Hafner, U. Piantini, G. Rihs, A. Togni, *Angew. Chem.* **1989,** *101,* 493; *ibid. Int. Ed.* **1989,** *28,* 499.

[8] a) S. Masamune, T. Sato, B.-M. Kim, T. A. Wollmann, *J. Am. Chem. Soc.* **1986,** *108,* 8279; b) E. J. Corey, R. Imwinkelried, St. Pikul, Y. B. Xiang, *ibid.* **1989,** *111,* 5493; c) Sh. Kobayashi, T. Sano, T. Mukaiyama, *Chem. Lett.* **1989,** 1319.

[9] M. Braun, *Angew. Chem.* **1987,** *99,* 24; *ibid. Int. Ed.* **1987,** *26,* 24.

[10] a) M. Nakahata, M. Imaida, H. Ozaki, T. Harada, A. Tai, *Bull. Chem. Soc. Jpn.* **1982,** *55,* 2186; b) R. Nojori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **1987,** *109,* 5856.

[11] D. F. Taber, P. B. Deker, M. D. Gaul, *J. Am. Chem. Soc.* **1987,** *109,* 7488.

[12] A. Collet, M.-J. Brienne, J. Jacques, *Chem. Rev.* **1980,** *80,* 215.

[13] a) P. A. Brown, P. R. Jenkins, *J. Chem. Soc., Perkin Trans. 1* **1986,** 1303; b) P. A. Brown, R. V. Bonnert, P. R. Jenkins, M. R. Selim, *Tetrahedron Lett.* **1987,** *28,* 693.

[14] a) K. Oertle, H. Wetter, *Tetrahedron Lett.* **1985,** *26,* 5511; b) *ibid.* **1985,** *26,* 5515.

[15] B. Haveaux, A. Dekoker, M. Rens, A. R. Sidani, J. Toye, L. Ghosez, *Org. Synth. Coll. Vol. VI* **1980,** 282.

[16] Y. Yamamoto, K. Ohdoi, M. Nakatani, K. Akiba, *Chem. Lett.* **1984,** 1967.

[17] W. A. König, I. Benecke, N. Lucht, E. Schmidt, J. Schulze, S. Sievers, *J. Chromatogr.* **1983,** *270,* 555.