Organic Chemistry

Terpenes in organic synthesis
14.* Synthesis of *S*-(+)-hydroprene from (+)-β-citronellene

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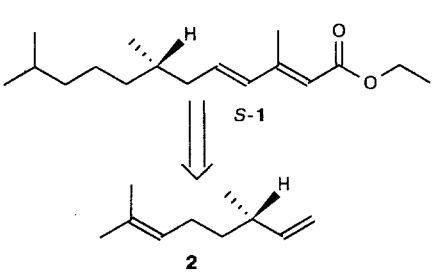
A seven-step synthesis of *S*-(+)-hydroprene (*S*-**1**) in ~20 % overall yield starting from *S*-(+)-3,7-dimethyl-1,6-octadiene (**2**) of 55±10 % optical purity is described. The introduction of an optical enhancement step in the synthetic sequence at the stage of *S*-(−)-3,7-dimethyl-1-octanol (**9**) raises the optical purity of *S*-**1** from ~50 % to ~80 %.

Key words: technical grade β-citronellene; *S*-2,6-dimethyl-7-octen-3-one, Wolff–Kizhner reduction; *S*-3,7-dimethyl-1-octanol, enantiomeric enrichment.

The mixture of $C_{10}H_{18}$ hydrocarbons resulting from the thermolysis of *cis*-pinane, known as «technical grade β–citronellene» (TGC), is an inexpensive starting material for the synthesis of chiral pheromones or juvenoids with asymmetric centers in both the *R*- and in *S*-configuration.[1,2] Here we report our synthesis of ethyl 7*S*,2*E*,4*E*-3,7,11-trimethyldodeca-2,4-dienoate (*S*-**1**), a juvenoid with a morphogenetic potency nearly twice as high as that of its racemic counterpart known as hydroprene. Earlier,[3] *S*-**1** was obtained in three steps from the valuable perfumery chemical, *S*-(−)-citronellol. The latter is manufactured by hydroalumination—oxygenation of individual *S*-(+)-3,7-dimethyl-1,6-octadiene (**2**, (+)-β-citronellene), the main component of the dextrorotatory TGC which is obtained from (+)-α-pinene in two steps.[4] Optical purity (OP) of diolefin **2** in TGC depends mainly on that of the starting (+)-α-pinene, which ranges from 40 to 70 per cent in turpentine oils of East European origin, and is normally within 55±10 %.



Recently,[5] a novel six-step synthesis of *S*-**1** from *S*-(−)-citronellol was recorded, where that intermediate was prepared by direct hydroalumination of dextrorotatory TGC, i.e. a mixture of isomeric hydrocarbons. However, the presence of other terminal alkenes along with **2** in the TGC prompted us to consider an alternative and possibly more unambiguous procedure for the chemoselective separation of **2** from the rest of the $C_{10}H_{18}$ hydrocarbons.

This procedure is based on the selective monoepoxidation of diolefin **2** in the presence of other com-

* For part 13, see. ref.[1]

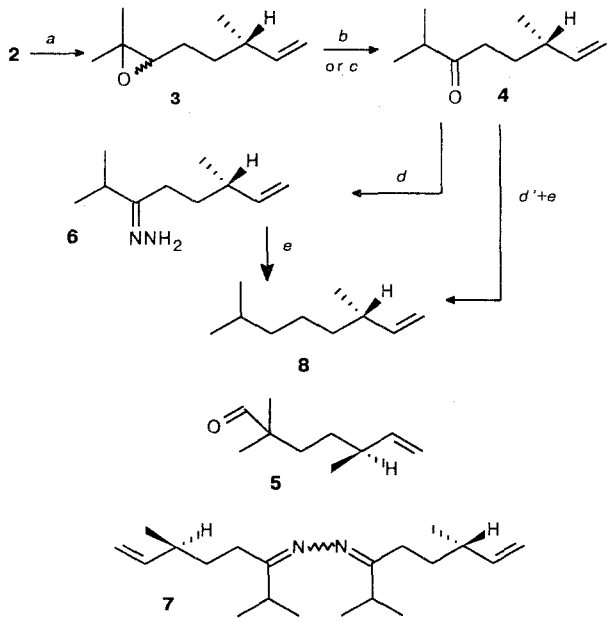
Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 342—348, February, 1993.

1066-5285/93/4202-0300$12.50

ponents of TGC (cf.[2]) to give 3*R*/*S*,6*S*-2,3-epoxy-2,6-dimethyl-7-octene (**3**), which can be further isomerized to *S*-(+)-2,6-dimethyl-7-octen-3-one (**4**) without separating the epoxide from the unreacted hydrocarbons. Lithium perchlorate, known to catalyze the isomerization of **3** to **4** (cf.[6]), was found to be quite suitable for this purpose. This makes it possible to prepare ketone **4** directly from TGC and thus to avoid the tedious isolation of **2** from its mixture with isomeric hydrocarbons. The yield of ketone **4** from TGC (based on the content of **2** in it as determined by GC analysis) amounts to 42—48 %. A side product with additional absorbance at ν 2720 cm^{-1} in the IR spectrum was tentatively identified as *S*-2,2,5-trimethylhept-6-enal (**5**); the ratio **4** : **5** in the reaction mixture is ~7 : 1 (GC data). The optical rotation of **4** thus obtained ($[\alpha]_D^{28}$ +6.1°, in $CHCl_3$) corresponds to OP ~60 % (cf.[6]).

The isomerization of epoxide **3** catalyzed by $BF_3 \cdot OEt_2$ (0.25 eqv) in benzene proceeds more selectively to give ketone **4** in 80 % yield. Unfortunately, this modification is less suitable for the preparation of **4** directly from the mixture of **3** with unreacted hydrocarbons of TGC, as the latter tend to polymerize and/or to co-polymerize with **3** on treatment with $BF_3 \cdot OEt_2$ to give viscous tars, from which the desired ketone **4** cannot be isolated without losses. In this case it is more expedient to isolate epoxide **3** by vacuum rectification (70 % yield based on the content of **2** in the starting TGC) before isomerization.

Scheme 1



a. AcO_2H/AcONa; *b*. $LiClO_4$/petroleum ether, Δ;
c. $BF_3 \cdot OEt_2$/PhH; *d*. NH_2NH_2/MeOH;
d'. $NH_2NH_2/N(CH_2CH_2OH)_3$, Δ;
e. $KOH/N(CH_2CH_2OH)_3$, Δ.

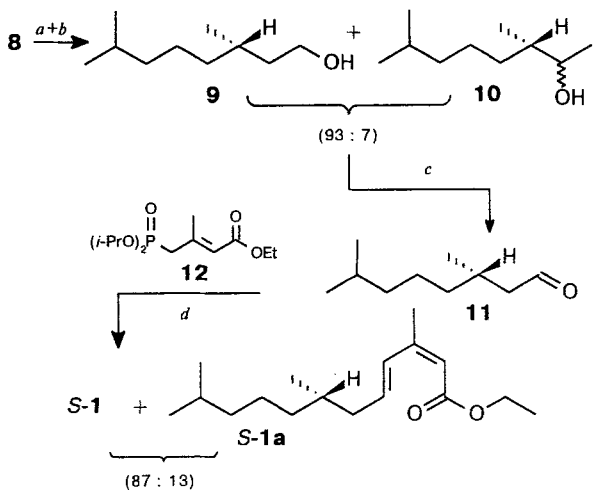
The reaction of ketone **4** with hydrazine hydrate (85 %) in MeOH afforded an oily hydrazone (**6**) in 90 % yield, which was characterized by IR and ^1H NMR spectra (ν 3300, 1680, and 1460 cm^{-1}; a broad singlet at 4.8 ppm, 2 H, $=NNH_2$). An attempt to purify the crude hydrazone **6** by vacuum distillation resulted in the corresponding azine (**7**), the content of which in the distillate amounted to 70 mass. % as judged from elemental analysis, the ^1H NMR spectrum, and TLC. As the formation of **7** from **6** is easily provoked by moisture, the next step of the synthesis, the Wolff—Kizhner reduction of ketone **4** to *S*-(+)-3,7-dimethyl-1-octene (**8**), could not be performed successfully by means of the conventional Huang-Minlon technique. The careful choice of reaction conditions led us to an optimum procedure which combines elements of the two known methods[7,8] and stipulates that both the crude hydrazone **6** and triethanolamine, which is used as the solvent, be thoroughly dried with KOH prior to hydrazone decomposition. In this case the highest yield of alkene **8** from **6** (80.9 %) is achieved at the molar ratio **6** : KOH = 1 : 8. At ratios 1 : 2 and even 1 : 5 the formation of **8** is accompanied by that of the azine **7** (up to 35 % from **6**) while at 1 : 10 the viscosity of the reaction mixture prevents effective distillation of the olefin from it. Under these conditions ketone **4** can be transformed into alkene **8** without isolating the intermediate **6**, if the solution of **4** in triethanolamine is first treated with hydrazine hydrate and the excess NH_2NH_2 and water are distilled from the solution, after which 8 eqv of powdered KOH are added and the mixture is heated until the evolution of N_2 has stopped. In this way the yield of **8** from **4** amounts to 65.4 % while in the two-step sequence **4**→**6**→**8** the yield is ~72 % (Scheme 1).

Hydroboration of alkene **8** with B_2H_6 *in situ*, at 0—20°C is fast (100 % conversion in 30 min). If immediately followed by oxidative work-up with alkaline H_2O_2 it affords a mixture of isomeric 3,7-dimethyloctanols, **9** and **10**, in the proportion 80 : 20. This ratio was raised to the equilibrium value (93 : 7) when, after the completion of hydroboration (20°C, 30 min), the reaction mixture was kept at 65°C for 1.5 h. The yield of *S*-(−)-3,7-dimethyl-1-octanol (**9**) contaminated with ~7 mass. % of 2*R*/*S*,3*S*-3,7-dimethyl-2-octanol (**10**) was in this case 82.9 %. The mixture of alcohols was then oxidized with pyridinium chlorochromate/CH_2Cl_2 in the presence of anhydrous AcONa to give *S*-3,7-dimethyloctanal (**11**) in 74 % yield.*

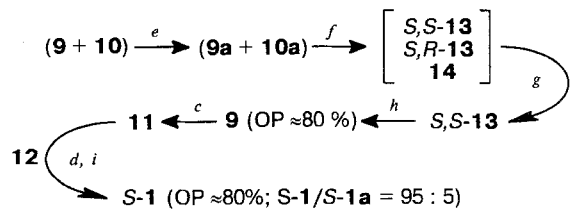
The reaction of aldehyde **11** with diisopropyl 3-ethoxycarbonyl-2-methyl-2-propenylphosphonate (**12**) under the conditions of phase transfer catalysis described earlier[1] gave a mixture of the target juvenoid *S*-**1** with its less active 2*Z*,4*E*-diastereomer (*S*-**1a**) in the proportion

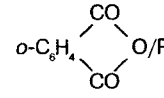
* If anhydrous AcONa is not added, the yield of the aldehyde decreases, due to the formation of 3,7-dimethyloctanoic acid and of some non-polar products.

Scheme 2



Enantiomeric enrichment



a. $NaBH_4$—$BF_3 \cdot OEt_2$/THF(0→20°C, 0.5 h+35°C, 1.5 h);
b. H_2O_2—NaOH;
c. PCC—$AcONa/CH_2Cl_2$;
d. KOH/PhH/18-C-6;
e. 
f. *S*-PEA/MeOH. *g*. Fractional crystallization (n-C_5H_{12}, MeOH (aq));
h. NaOH/MeOH—H_2O;
i. Chromatography (SiO_2/n-C_6H_{14}—AcOEt).

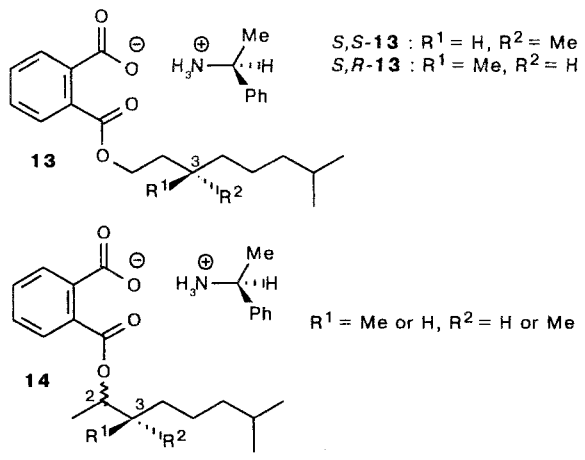
~87 : 13 (^{1}H NMR and GC data) in 80 % yield. Column chromatography of this product over silica gel using hexane—AcOEt (95 : 5) afforded a sample with $[\alpha]_D^{20}$ +2.1° (MeOH). Comparison with the values of $[\alpha]_D^{25}$ in MeOH reported earlier[3] for *S*-**1** and its *R*-enantiomer (+2.9° for a sample of *S*-**1** with OP = 69.6 % and −3.8° for a sample of *R*-**1** with OP 97.8 %) shows that our sample of *S*-**1** obtained from **2** is likely to be of ~50–55 % optical purity. This is comparable to the OP range for diolefin **2** in the starting TGC and for the (+)-α-pinene used to produce it.

The overall yield of *S*-**1** (with admixture of *S*-**1a**), based on the content of **2** in TGC, amounts to 19.6 % if the synthesis is carried out with isolation of all intermediates along the path **2**→**3**→**4**→**6**→**8**→**11**→*S*-**1** (Scheme 1,2). This path may be shortened by excluding the isolation of intermediates **3** and **6**, but at the expense of the yield which in this case is only 13.5 %. Although alcohol **9** could be transformed into aldehyde **11** simply by vapor-phase catalytic dehydrogenation (cf.[9]), we were not tempted by that possibility as the optimum yield of **11** from **9** did not exceed 50 %.

In order to improve upon the OP of *S*-(+)-hydroprene we undertook enantiomeric enrichment of its chiral precursor **9**. This alcohol was converted to the acidic monoalkyl phthalate (**9a**) which was subsequently treated with *S*-(−)-1-phenylethylamine (*S*-PEA) to yield a salt. The latter was submitted to fractional crystallization first from pentane and then from aqueous MeOH; the course of diastereomeric enrichment was monitored by specific rotation at λ 546 nm.

The initial sample of alcohol **9** (containing 7 mass. % of the isomeric secondary alcohol **10**) showed $[\alpha]_{546}^{19}$ −2.52° (MeOH). The oily phthalate **9a**, obtained from it in 98 % yield, turned out to contain an admixture of isomeric acidic phthalates (**10a**) derived from **10**. Consequently, the ammonium salt formed by the crude phthalate (**9a** : **10a** ~ 93 : 7) with *S*-PEA was both sterically and chemically heterogeneous. This salt (or, rather, mixture of salts), a slowly melting powdery solid, was characterized by its ^{1}H NMR spectrum and $[\alpha]_{546}^{19}$ −5.09° (MeOH). *A priori*, in addition to the two salts derived from *S*-PEA and *S*-(−)- and *R*-(+)-3,7-dimethyl-1-octanols (*S*,*S*-**13** and *R*,*S*-**13**, respectively), it would contain four minor diastereomers derived from *S*-PEA and 2*R*/*S*,3*S*- and 2*R*/*S*, 3*R*-3,7-dimethyl-2-octanols (**14**). Judging by the chemical composition of diolefin **2** (OP 55±10 %) from which this sample was obtained, the initial ratio of components *S*,*S*-**13**, *S*,*R*-**13** and **14** in the salt should be close to ~74 : 19 : 7.

The salt (i.e., the mixture of *S*,*S*-**13**, *R*,*S*-**13**, and **14**) was heated with a fixed amount of pentane, the undissolved part of it (residue **A**) was separated by filtration, and the crystals deposited by the filtrate on standing (precipitate **A**) were recrystallized from pentane. The fraction thus obtained, with mp 96–98°C and $[\alpha]_{546}^{19}$ −5.28° (precipitate **A1**), was recrystallized fron aqueous



MeOH, a small precipitate was separated by filtration, and the mother liquor was evaporated to dryness to afford a residue which was dissolved in the smallest volume of pentane. The crystalline deposit from this solution with $[\alpha]_{546}^{19}$ −5.77° (precipitate **A2**) accounted for 12.2 % of the initial amount of the salt. On heating with the same volume of pentane as was used to obtain it from the initial batch, residue **A** dissolved only partially. The remainder (residue **B**) was filtered off, and the crystals which were deposited from the filtrate (precipitate **B**) were recrystallized from pentane. This fraction (precipitate **B1**), with mp 97—98°C and $[\alpha]_{546}^{19}$ −4.96°, was recrystallized from aqueous MeOH, the crystals were separated, and the mother liquor was evaporated to dryness. After dissolution in pentane and re-precipitation the residue gave crystals with $[\alpha]_{546}^{19}$ −6.17° (precipitate **B2**); the yield of this fraction was 9.8 %. Finally, residue **B** (also ~10 % of the initial salt), which was almost insoluble in boiling pentane, showed $[\alpha]_{546}^{19}$ −7.0°. In total, the three fractions with noticeably stronger negative rotation than the initial salt (precipitate **A2** + precipitate **B2** + the bulk of precipitate **B** insoluble in boiling pentane) comprise ~32 % of the initial amount of the salt.

Since the specific rotation of *S,S*-**13** is determined by the contributions of both of its components, *S*-PEA and *S*-3,7-dimethyl-1-octanol, while that of *S,R*-**13** reflects the superposition of contributions from *S*-PEA and *R*-(+)-3,7-dimethyl-1-octanol, the content of alcohol **9** in precipitates **A2** and **B2** and in residue **B** is obviously higher than in the initial sample of **9** taken for enantiomeric enrichment and, respectively, in the initial mixture of diastereomeric salts.

The three most levorotatory fractions (precipitate **A2** + precipitate **B2** + residue **B**) were combined and treated with NaOH in aqueous MeOH to give chromatographically pure alcohol **9** in 98 % yield. Its OP was ~81 % ($[\alpha]_D^{19}$ −4.93° in MeOH; for a sample of **9** with OP ~100 % $[\alpha]_D^{20}$ −6.10° in MeOH was reported[10]). On the other hand, alkaline decomposition of fractions which were «dextrorotatory» with respect to the initial mixture of salts (*S,S*-**13**, *S,R*-**13**, and **14**) afforded samples of alcohols with a higher content of minor isomer **10** than in the starting material. Hence, enantiomeric enrichment of alcohol **9** can be effectively combined with its separation from **10**.

Enantiomerically enriched and chemically pure **9** was then oxidized to give aldehyde **11** of the same optical purity with $[\alpha]_D^{22}$ −11.0° (in $CHCl_3$, cf.[11]). The latter was condensed with phosphonate **12** as indicated above, and the product of condensation, consisting of *S*-**1** and its diastereomer *S*-**1a** (*S*-**1** : *S*-**1a** = 86 : 14), was chromatographed over SiO_2. Two main fractions were collected with ratios *S*-**1** : *S*-**1a** = 70 : 30 ($[\alpha]_D^{19}$ +3.02°) and *S*-**1** : *S*-**1a** = 95 : 5 ($[\alpha]_D^{19}$ +3.22°). It follows from these data that the specific rotation of *S*-**1** should be somewhat higher than that of *S*-**1a**. A comparison of $[\alpha]_D$ values for two samples of *S*-**1** possessing 90 % geometrical purity before and after enantiomeric enrichment with the values of $[\alpha]_D$ reported earlier[3] for *S*-(+)-hydroprene of ~69.6 % optical purity ($[\alpha]_D^{20}$ +2.9°) and for *R*-(−)-hydroprene of 97.8 % optical purity ($[\alpha]_D^{20}$ −3.8°)* shows that the operation of enantiomeric enrichment increased the OP of *S*-**1** from ~55±10 % to 77.3—82.8 %.

The morphogenetic activity of our sample of *S*-(+)-hydroprene (OP ~80 %, diastereomeric purity 90 %) was assayed on 4-th instar larvae and young pupae of the yellow-fever mosquito *Aedes aegypti*. In the whole range of concentrations (from 10^{-3} mg L^{-1} to 10^{0} mg L^{-1}) *S*-**1** displayed higher potency than the corresponding racemate, (±)-**1**. Thus, 50 % inhibition of the pupa-to-imago metamorphosis occurs for *S*-**1** at IC_{50} = 0.005 mg L^{-1} while for (±)-**1** IC_{50} = 0.010 mg L^{-1}. These results are in keeping with the corresponding values of IC_{50} for *A. aegypti* reported earlier.[3]

Experimental

All boiling and melting points are uncorrected. GC analyses were performed on a LKhM-8MD instrument equipped with a 150×0.3 cm stainless steel column (5 % SE-30 on Chromatone N-AW-DMCS) and a flame ionization detector; N_2 was used as the carrier gas. ^{1}H-NMR spectra were recorded with a Bruker WM-250 spectrometer (250 MHz). IR spectra were measured with an UR-20 spectrophotometer («Carl Zeiss»). Optical rotations were measured on a Jasco DIP-360 polarimeter. *S*-(−)-1-phenylethylamine with $[\alpha]_D$ −30° (EtOH) and chemical purity > 99 % («Fluka Chemie AG») was used in the enantiomeric enrichment step.

***S*-(+)-2,6-Dimethyl-7-octen-3-one (4).** A three-neck flask equipped with a mechanical stirrer, a thermometer, and a dropping funnel with pressure equalization arm was charged with 321.3 g of freshly distilled Ac_2O (3.15 mol) and then warmed to 35—40°C with stirring. This was followed by the addition of 124 g (113 mL) of 30 % H_2O_2 aq over 1.5 h during the course of which the temperature was kept at 35—40°C by external cooling. Stirring at this temperature was continued for 4 h, after which the clear solution was left overnight. The AcO_2H content determined iodometrically was within 27—30 %. To the 30 % solution of peracetic acid thus obtained (~1.12 mol of AcO_2H) 16.4 g of anhydrous AcONa (0.2 mol) were added and the mixture was cooled to 0°C with stirring. Then 230 g of technical grade β-citronellene were added gradually with stirring (0°C, 3 h). The content of diolefin **2** in TGC was ~60 mass. % (GC data), i.e., 230 g of TGC corresponded to 138 g of chemically pure **2** (1.0 mol). After the addition of **2** had been completed, the stirring was continued for three more hours at 18—20°C, while the course of epoxidation was checked by GC every 45 min. The bulk of the AcONa was carefully separated by vacuum filtration (ace Buchner funnel, porosity ~150 μ) and the filtrate was diluted water with (150 mL). The upper layer was separated, washed with a 10 % aqueous solution of $NaHCO_3$ (3×100 mL) and with water (100 mL), and dried over $MgSO_4$. This work-up afforded a mixture of epoxide **3** with unreacted hydrocarbons of TGC which was

* All values of $[\alpha]_D$ for hydroprene were determined in MeOH.

further used to prepare ketone **4** by one of the two following procedures.

Procedure A (without isolation of epoxide **3**). 245 g of this mixture containing ~60 % mass. % of epoxide **3** and ~40 mass. % of the remaining $C_{10}H_{18}$ hydrocarbons (GC data) were dissolved in 750 mL of freshly distilled dry petroleum ether (boiling range 50–70°C), and the solution was boiled for 7 h with 12 g of finely powdered anhydrous $LiClO_4$ (10 mol. % with respect to **3**). The formation of ketone **4** was monitored by GC. The reaction mixture was treated with enough water to dissolve the precipitate of $LiClO_4$, and the organic layer was separated, washed with a 20 % aqueous solution of $NaHCO_3$ and with water, and dried over $MgSO_4$. According to GC analysis (isothermic, 80°C), the reaction product consisted of 60–65 mass. % of ketone **4** (R_t 7.7 min), 8–10 mass. % of aldehyde **5** (R_t 8.7 min, identified by its IR absorbtion at ν 2720 cm^{-1}), and of high-boiling products with $R_t \geq 15$ min. The remaining hydrocarbons of TGC were distilled from the reaction mixture (water aspirator), and the residue was fractionated using a 30 cm×1.5 cm (i.d.) Vigreux column at 72–72.5°C (12 Torr) to give ketone **4** as a colorless oil with n_D^{25} 1.4337 and $[\alpha]_D^{28}$ +6.1° (*c* 0.8, in $CHCl_3$) (ref.[6] $[\alpha]_D^{20}$ +10.1°, in $CHCl_3$). Yield 94.3 g (61 % based on the content of **3** in the starting mixture). IR spectrum (in CCl_4), ν (cm^{-1}): 3070, 1710, 1640, 1380, 912. ^1H NMR spectrum (in $CDCl_3$), δ: 0.98 (d, 3 H, MeCH, J = 7 Hz); 1.07 (d, 6 H, Me_2CH, J = 7 Hz); 2.1 (m, 1 H, $MeCHCH{=}CH_2$); 2.42 (t, 2 H, CH_2CO, J = 7 Hz); 2.62 (hpt, 1 H, Me_2CHCO, J = 7 Hz); 4.91 dd + 4.99 dd + 5.62 m (3 H, $CH_2{=}CH$, ABC system). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}(%)): 154 $[M]^+$ (8), 139 $[M-Me]^+$ (1), 111 $[M-C_3H_7]^+$ (16), 83 $[M-Me_2CHCO]^+$ (21), 71 $[Me_2CHCO^+$ (59), 55 $[C_4H_7]^+$ (100).

Procedure B (with isolation of epoxide **3**). 245 g of the mixture of epoxide **3** (~60 mass. %) with unreacted $C_{10}H_{18}$ hydrocarbons were fractionated using a 45 cm×1.4 cm (i.d.) Widmer column, and the fraction boiling within 80–90°C (12 Torr) was collected, which contained 93 mass. % of **3** (GC data); n_D^{21} 1.4351, $[\alpha]_D^{28}$ +8.5° (*c* 0.73, in $CHCl_3$). Yield 103 g (70 % based on the content of diolefin **2** in the TGC used). ^1H NMR spectrum (in $CDCl_3$), δ: 0.96 (d, 3 H, MeCH, J = 7 Hz); 1.21 (m, 6 H, Me_2CO); 1.45 (m, 4 H); 2.20 (m, 1 H, $MeCHCH{=}CH_2$, J = 7 Hz); 2.65 (m, 1 H, HCO); 4.93 dd + 4.97 dd + 5.60 m (3 H, $CH_2{=}CH$, ABC system). Ref.[6] $[\alpha]_D^{20}$ +9.43° (in $CHCl_3$).*

A three-neck flask equipped with a mechanical stirrer, a condenser and a dropping funnel, was charged with 40 g of epoxide **3** (0.26 mol based on 93 % content) in 50 mL of dry benzene. Then 9.1 g of freshly distilled $BF_3 \cdot OEt_2$ (25 mol % with respect to **3**) were added dropwise with stirring at 5–10°C, and the stirring was continued for 0.5 h. The reaction was quenched by careful addition of saturated aqueous $NaHCO_3$ (100 mL) and the resulting emulsion was stirred for an additional 45–50 min until it turned a light pink. The organic layer was separated, and the aqueous layer was extracted with pentane (2×25 mL). The combined organic layers were washed with H_2O and dried over $MgSO_4$. The solvents were removed through an efficient Vigreux column, and the residue was fractionated in a vacuum to afford (72°C, 12 Torr) a sample of ketone **4** with the same constants and spectra as in procedure **A**.**

* A sample of diolefin **2** with $[a]_D^{20}$ +11.9° (in $CHCl_3$) was used to obtain epoxide **3** (ref.[6]).

** Unlike procedure **A**, the crude reaction product obtained on treatment of epoxide **3** with $BF_3 \cdot OEt_2$ displayed no absorbtion at n 2720 cm^{-1} in the IR spectrum.

S*-(+)-3,7-Dimethyl-1-octene (8). Procedure *C (with isolation of hydrazone **6**). A mixture of ketone **4** (20 g, 0.13 mol), 85 % hydrazine hydrate (45 g, 0.9 mol) and MeOH (90 mL) was refluxed for 4 h. The course of the reaction was monitored by TLC. When the reaction was completed, water and MeOH were removed from the resulting solution at 80°C (bath) under reduced pressure (10 Torr). The turbid liquid residue was treated with 1–2 g of solid KOH to salt out the organic phase and the lower layer was separated from it and extracted with pentane (3×20 mL). The extract was mixed with the organic layer and the resulting solution was dried over K_2CO_3 and evaporated to give 19.6 g of a chromatographically pure (TLC) colorless liquid which was identified by its IR and ^1H NMR spectra as hydrazone **6**. Yield 90 %. IR spectrum (in $CHCl_3$), ν (cm^{-1}): 3420, 3300, 1680, 1490. ^1H NMR spectrum (in $CDCl_3$), δ: 0.92–1.05 (dd, 9 H, $MeCHCH{=}CH_2$ and $Me_2CHC{=}NN{=}$); 2.1 (m, 3 H, $MeCHCH{=}CH_2$ and $CH_2C{=}NN{=}$); 2.62 (hpt, 1 H, $Me_2CHC{=}NN{=}$); 4.8 (br.s, 2 H, NNH_2); 4.91 dd + 4.92 dd + 5.62 ddd (3 H, $CH_2{=}CH$, ABC system). An attempt to isolate hydrazone **6** by vacuum distillation (bp 114°C/18 Torr) resulted mainly in the corresponding azine **7**, a light yellow liquid with higher R_f on Silufol plates than that of **6**. As follows from the integral intensities of characteristic signals in the ^1H NMR spectrum, the content of **7** in the distillate amounts to ~70 %. ^1H NMR spectrum (in $CDCl_3$), δ: 0.97 (d, ≤6 H); 1.11 (d, ≤12 H); 1.36 (m, ≤2 H); 2.08 (m, ≤2 H); 2.20 (m, ≤4 H, $(CH_2C{=}N)_2$); 2.51 (m, ≤2 H, $(Me_2CHC{=}N)_2$); 4.92 m–5.65 m (6 H, $CH_2{=}CH$, ABC system). Found (%): C 76.45; H 14.71; N 9.97. For $C_{20}H_{36}N_2$ calculated (%): C 78.95; H 14.71; N 9.97. For hydrazone **6** ($C_{10}H_{20}N_2$) calculated (%): C 71.43; H 11.91; N 16.67.

A Claisen flask (capacity 250 mL), connected with a receiver through a descending condenser, was charged with 98 % triethanolamine (110 mL) and 43.9 g (0.8 mol) of powdered KOH. The mixture was heated (oil bath) to form a clear solution. The solution was cooled to r.t., then 16.5 g of hydrazone **6** (0.098 mol) were added dropwise and the heating was resumed at a rate of 50°C/h. The decomposition of **6** began at 120°C. The mixture was heated to 150–160°C for one hour (intense evolution of N_2) and was kept at 160°C for 7 h to complete the reaction. The hydrocarbon **8** thus formed gradually accumulated in the receiver. The pot was cooled to r.t. and the viscous residue was immediately extracted with pentane (3×20 mL). The collected product and the extract were combined, washed with 5 % hydrochloric acid (2×15 mL) and with H_2O to neutrality, dried over $MgSO_4$ and filtered. Pentane was removed using a 25 cm × 1.4 cm Vigreux column and the residue was distilled under reduced pressure to afford pure alkene **8**, bp 146–146.5°C (200 Torr), n_D^{25} 1.4149, $[\alpha]_D^{28}$ +6.9° (*c* 0.80, in $CHCl_3$). Yield 11.1 g (80.9 %). IR spectrum (in $CHCl_3$), ν (cm^{-1}): 3065, 1380, 1365, 910. ^1H NMR spectrum (in $CDCl_3$), δ: 0.98 (d, 6 H, Me_2CH, J = 7 Hz); 1.01 (d, 3 H, MeC(3), J = 7 Hz); 2.05 (m, 1 H, HC(3)); 4.91 (dd, 1 H, J_{AC} = 17 Hz, J_{AB} = 2.5 Hz) + 4.93 (dd, 1 H, J_{AB} = 2.5 Hz, J_{BC} = 9 Hz) + 5.62 (ddd, 1 H, J_{AC} = 17 Hz, J_{BC} = 9 Hz, $J_{2,3}$ = 6.5 Hz) ($CH_2{=}CHCH$, ABC system).

Procedure D (without isolation of hydrazone **6**). A distilling flask equipped with a Vigreux column which was connected to a receiver through a descending condenser was charged with 4.7 g of ketone **4** (0.03 mol), 9.9 g of hydrazine hydrate (0.3 mol), and triethanolamine (50 mL). The mixture was heated at 110°C for 2 h to complete the transformation of **4** into hydrazone **6** (TLC control). The excess of hydrazine was removed from the reaction medium at 45°C (50 Torr), with the bath temperature not exceeding 65°C. Powdered KOH (13.4 g,

0.24 mol) was added to the resulting solution. On heating to 120–130°C (oil bath) a slow evolution of gas ensued, which became intense at 160–180°C. The mixture was heated for three additional hours before the elimination of N_2 was complete, and the hydrocarbon that accumulated in the receiver was washed with H_2O (2×10 mL), dried over $MgSO_4$, and distilled at 146°C (200 Torr). The sample of hydrocarbon **8** thus obtained was in all respects identical to that described above. Yield 2.8 g (55 %). The viscous residue in the pot was carefully diluted with water until two layers emerged, the upper layer was dissolved in 15 % aqueous HCl and the pH of the solution was adjusted to 2. The acidic solution was extracted with Et_2O, and washed and dried as above to afford an additional amount of **8** (0.5 g) with the same constants. This raised the overall yield of olefin **8** from ketone **4** to 65.4 %.

***S*-(–)-3,7-Dimethyl-1-octanol (9).** A mixture of $NaBH_4$ (2.28 g, 0.06 mol) and olefin **8** (8.4 g, 0.06 mol) in dry THF (45 mL) was stirred and cooled to 0°C, after which 5.53 mL of $BF_3 \cdot OEt_2$ (0.045 mol) were added. The reaction was left to warm to 20°C and the stirring was continued at r.t. for another 30 min. GC analysis (isothermic, 130°C) revealed the disappearance of **8** and the presence of two products with R_t 6.0 and 7.1 min in a ratio of ~20 : 80 respectively. The mixture was heated to 65°C and stirred for another 90 min, then cooled to 5°C and treated with 30 % H_2O_2 (18.5 mL, 0.18 mol) and 3 *N* NaOH (20 mL) and stirred at 65°C for 2 h. The reaction mass was filtered through a pad of neutral Al_2O_3 (12 g) on a porous funnel, and the solvent was evaporated using a small Vigreux column to afford 8.1 g of colorless oil. Vacuum distillation gave mainly alcohol **9** with bp 138–138.5°C (56 Torr), n_D^{25} 1.4335 and $[\alpha]_D^{25}$ −2.41°(*c* 1.78, in MeOH). IR spectrum (in $CHCl_3$), ν (cm^{-1}): 3320, 1380, 1365, 1045. ^1H NMR spectrum (in $CDCl_3$), δ: 0.95 (d, 6 H, $\underline{Me}_2CH$, *J* = 7 Hz); 0.97 (d, 3 H, MeC(3), *J* = 7 Hz); 1.69 (br.s, 1 H, OH); 1.07–1.66 (m, 10 H); 3.7 (m, 2 H, $C\underline{H}_2OH$). In the sample thus obtained the ratio of components with R_t 6.0 and 7.1 min amounted to ~7 : 93. A minor component, alcohol **10**, could be detected in the ^1H NMR spectrum due to a weak multiplet at 3.83 ppm and a weak broad doublet at 1.30 ppm which were indicative of the $C\underline{H}_3C\underline{H}OH$ fragment.

This sample of alcohol **9** was used in the next step of synthesis without further purification.

***S*-(–)-3,7-Dimethyloctanal (11).** To a vigorously stirred suspension of pyridinium chlorochromate (15 g, 0.07 mol) and anhydrous AcONa (1.1 g, 0.014 mol) in dry CH_2Cl_2 (60 mL) 5.6 g of alcohol **9** (0.035 mol) were added in one portion, and the stirring at r.t. was continued for 2 h. The reaction mixture was diluted with 100 mL of dry Et_2O and left to settle. The supernatant was decanted from the black tar and the latter was thoroughly washed with dry Et_2O (3×25 mL) until it became a disperse solid. The supernatant and the ethereal washings were combined, filtered through a pad of SiO_2 (10 g) and evaporated using a Vigreux column. The residue was distilled to give aldehyde **11** as the only product; bp 121–122°C (30 Torr), n_D^{25} 1.4230; $[\alpha]_D^{22}$ −7.1° (*c* 0.9, in $CHCl_3$). IR spectrum (in $CHCl_3$), ν (cm^{-1}): 2710, 1709, 1385, 1365. ^1H NMR spectrum (in $CDCl_3$), δ: 0.85 (d, 6 H, $\underline{Me}_2CH$, *J* = 7 Hz); 0.98 (d, 3 H, MeC(3), *J* = 7 Hz); 1.1–1.65 (m, 7 H, $3CH_2$+CH); 2.1–2.45 (m, 3 H, =$C\underline{H}C\underline{H}_2CHO$); 9.45 (s, 1 H, CHO).

***S*-(+)-Hydroprene (*S*-1).** To a vigorously stirred mixture of diisopropyl 3-ethoxycarbonyl-2-methyl-2-propenylphosphonate (**12**) (2.92 g, 0.010 mol), powdered KOH (1.12 g, 0.020 mol) and 18-crown-6 (0.5 g, 1.17 mmol) in 30 mL of dry benzene, a solution of aldehyde **11** (1.56 g, 0.010 mol) in 10 mL of benzene was added dropwise at ~20°C. The system was stirred for 4 h to complete the reaction (GC monitoring) and then poured into a beaker containing 80 mL of icy water. The layers were quickly separated and the lower alkaline layer was extracted with benzene (3×25 mL). The extracts and the upper organic layer were combined, washed with water (2×20 mL), and dried over $MgSO_4$. Benzene was removed by distillation, the residue was dissolved in 30 mL of hexane, and the solution was filtered through a funnel with 3 g of neutral Al_2O_3. The filtrate was evaporated and the residue was distilled in a vacuum to give a sample of *S*-(+)-hydroprene with bp 112–114°C (0.1 Torr) and n_D^{25} 1.4805. IR spectrum (in $CHCl_3$), ν (cm^{-1}): 1710, 1640, 1610, 1380, 1270. ^1H NMR spectrum (in $CDCl_3$), δ: 0.85 (dd, 9 H, $\underline{Me}_2CH$ and MeC(7)); 1.0–1.7 (m, 8 H); 1.25 (t, 3 H, $\underline{Me}CH_2O$, *J* = 7 Hz); 1.8–2.2 (m, 2 H, $H_2C(6)$); 1.95 (d, 0.4 H, MeC(3) in *S*-**1a**, *J* = 1.5 Hz); 2.20 (d, 2.6 H, MeC(3) in *S*-**1**, *J* = 1.5 Hz); 4.09 m + 4.13 q (2 H, $Me\underline{C}H_2O$, *J* = 7 Hz); 5.5 (br.s, ~0.15 H, HC(2) in *S*-**1a**); 5.6 (br.s, ~0.85 H, HC(2) in *S*-**1**); 6.04 (m, ~0.15 H, HC(5) in *S*-**1a**); 7.62 (d, ~0.15 H, HC(4) in *S*-**1a**). The ratio of the integral intensities of the diagnostic signals from *S*-**1** and *S*-**1a** practically coincided with the ratio of *S*-**1** and *S*-**1a** determined by GC (~87 : 13). Column chromatography of this sample on 10 g of SiO_2 using a hexane–AcOEt (100 : 0→95 : 5) gradient elution system afforded a product with an enhanced ratio of *S*-**1** and *S*-**1a** (≥95 : 5) and $[\alpha]_D^{19}$ +2.1° (*c* 1.8, in MeOH).

Enantiomeric enrichment and purification of alcohol 9. A sample of alcohol **9** (3.40 g, 20 mmol) obtained as described above and containing ~7 % by weight of isomeric alcohol **10** ($[\alpha]_{546}^{19}$ −2.52°, in MeOH) was treated with a solution of freshly sublimed phthalic anhydride (2.96 g, 20 mmol) and 4-dimethylaminopyridine (80 mg, 2 mol. %) in dry pyridine (7 mL). The reaction mixture was left for 12 h at 18–20°C and then poured onto a mixture of crushed ice (50 mL) with conc. HCl (5 mL). The oil precipitate was separated, the acidic aqueous layer was extracted with $CHCl_3$ (2×15 mL), and the extract was added to the oil. The combined organic phase was washed with H_2O and dried over $MgSO_4$. The solvents were removed in a vacuum at 40°C (bath temperature), leaving a monoalkyl phthalate derived from alcohol **9** (**9a**), contaminated by the isomeric phthalate (**10a**); this product was obtained as a colorless oil which did not crystallize on standing or trituration. Yield 6.0 g (98 %). IR spectrum (in $CHCl_3$), ν (cm^{-1}): 3400–2950, 3090, 1780, 1730, 1695, 1380, 1260, 1120. ^1H NMR spectrum (in $CDCl_3$), δ: 0.85 (d, 6 H, $\underline{Me}_2CH$, *J* = 7 Hz); 0.92 (d, 3 H, MeC(7), *J* = 7 Hz); 1.05–1.35 (m, 7 H); 1.55–1.80 (m, 3 H); 4.35 (q, 2 H, $C\underline{H}_2OCOAr$); 7.55 (m, 4 H, ArH); 11.9 (s, 1 H, COOH). Found (titrimertically): MW 309.5; 312.2. Calculated for $C_{18}H_{26}O_4$: MW 316.

To a stirred solution of this mixture of phthalates **9a** and **10a** (6.0 g, 19.6 mmol) in 10 mL of MeOH, *S*-(–)-1-phenylethylammine (2.37 g, 19.6 mmol) was added dropwise. No crystals appeared on standing for 24 h at 0–5°C. On evaporation to constant weight the solution left a colorless solid consisting of the salts formed by *S*-PEA with phthalates **9a** and **10a**, $[\alpha]_{546}^{19}$ −5.09° (*c* 1.5, in MeOH). Yield 8.21 g (98 %). This residue was boiled for 1 h with 60 mL of pentane, and the tepid supernatant was quickly filtered from the solid residue and left for a few hours. The crystals deposited on standing (2.0 g, precipitate **A**) were separated by filtration and dried in a vacuum dessicator. The bulk of the initial mixture of salts, which did not dissolve in pentane (residue **A**, 5.6 g), was boiled once more with 60 mL of pentane and the insoluble part of it

(residue **B**, 0.8 g) was separated by filtration, dried (vacuum dessicator), and boiled again with 180 mL of pentane. This time only 10 mg of salt passed in solution. The almost insoluble residue **B** (0.79 g) was a colorless crystalline powder with mp 97—98°C and $[\alpha]_{546}^{19}$ −7.0° (*c* 1.30, in MeOH).

Precipitate **A** (2.0 g, m.p. 96—98°C) was recrystallized once more from pentane to give 1.4 g of crystals (precipitate **A1**) with unchanged m.p and $[\alpha]_{546}^{19}$ −5.28° (*c* 1.42, in MeOH). This substance dissolved easily on heating in MeOH—H_2O (4 : 1, v/v); a tiny crop of crystals deposited by the solution after 24 h of standing was removed by filtration. The filtrate, which contained the bulk of precipitate **A1**, was evaporated in a vacuum to constant weight and recrystallized from pentane to afford 1.0 g of crystals (precipitate **A2**) with m.p. 97—98°C and $[\alpha]_{546}^{19}$ −5.77° (*c* 1.42, in MeOH). The filtrate left after the separation of residue **B** from the supernatant, deposited crystals after 12 h of standing. The crystals were collected by filtration, dried in a vacuum, and recrystallized again from pentane, which gave 1.0 g of crystals with mp 96—98°C and $[\alpha]_{546}^{19}$ −4.96° (*c* 1.57, in MeOH). This fraction (precipitate **B1**) was dissolved in MeOH—H_2O (4 : 1, v/v) on heating, the crystals deposited on standing (~0.2 g) were removed by filtration, the mother liquor was evaporated to dryness, and the residue was recrystallized once more from pentane to yield 0.8 g of crystals (precipitate **B2**) with mp 97—98°C and $[\alpha]_{546}^{19}$ −6.17° (*c* 1.49, in MeOH). The crystalline fractions with $[\alpha]_{546}^{19}$ −7.0°, −6.17°, and −5.77° (i.e., residue **B** + precipitate **B2** + precipitate **A2**, altogether 2.6 g or 32 % by weight of the initial mixture of salts *S,S*-**13**, *S,R*-**13** and **14**) were combined and dissolved in a minimum amount of MeOH. To this solution 15 mL of 25 % solution of NaOH in aqueous MeOH (MeOH : H_2O = 4 : 1) were added dropwise. The reaction mixture was stirred for 4 h at 55—60°C and then poured onto 50 mL of crushed ice. The products were extracted with Et_2O (3×15 mL), the extract was washed with 5 % hydrochloric acid (3×10 mL) and water (3×10 mL), dried over $MgSO_4$ and evaporated using a Vigreux column. The residue was distilled to give chromatographically pure alcohol **9** (R_t 7.1 min) with $[\alpha]_D^{19}$ −4.93° (*c* 1.58, in MeOH). Yield 0.8 g (87 %). Ref.[10]: $[\alpha]_D^{20}$ −6.10° (in MeOH).

Enantiomerically enriched *S*-(+)-hydroprene. Alcohol **9** thus obtained was oxidized with [PyH]CrO_3Cl in CH_2Cl_2 in the presence of AcONa to give aldehyde **11** (R_t 4.25 min at 130°C) of similar optical purity with $[\alpha]_D^{22}$ −11.0° (*c* 0.9, in $CHCl_3$) and with the same spectral data as the sample of ~50 % OP described above. Yield 0.55 g (70 %). This specimen on condensation with phosphonate **12** followed by filtration through a pad of Al_2O_3 and column chromatography on SiO_2, afforded a sample of *S*-(+)-hydroprene with $[\alpha]_D^{19}$ +3.22° (*c* 1.58, in MeOH) which contained *S*-**1** and *S*-**1a** in a ratio of ≥95 : 5 (GC and ^1H NMR data). Yield 0.12 g (11.7 %). The less polar eluates gave another fraction (0.33 g) with $[\alpha]_D^{19}$ +3.02° (*c* 1.6, in MeOH) in which the ratio *S*-**1**/*S*-**1a** was ~70 : 30.

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Received March 12, 1992