Large-Scale Preparation of Pure (+)-(1*S*,2*R*,5*S*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol

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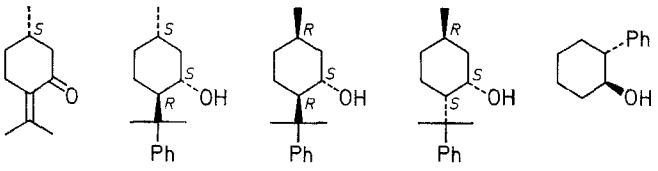
A procedure is described for the preparation of (*S*)-(−)-pulegone, (−)-**1**, starting from (*S*)-(−)-citronellol, (−)-**6**, in a preparative scale. Compound (−)-**1** can easily be converted into (+)-(1*S*,2*R*,5*S*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanol: (+)-**2**["(+)-8-phenylmenthol"] by a procedure described in literature, which was simplified essentially. Now (+)-**2** is accessible in larger amounts and thus is available as an efficient chiral auxiliary in stoichiometric asymmetric syntheses.

Among the chiral auxiliaries in asymmetric syntheses 5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanol **(2)**, correspondingly known as "8-phenylmenthol", occupies a preferred position.[1] As a matter of fact, in contrast to (−)-**2**, the enantiomer (+)-**2** is not readily available. Thus the complementary chiral information in asymmetric syntheses cannot be established directly. Amazingly, 8-phenylmenthol **2** has been described already in 1975[2] in form of its (+)-enantiomer, (+)-**2**. However, the (−)-enantiomer (−)-**2** is in fact the one that was mainly applied later on as a chiral auxiliary in many successful asymmetric syntheses.[1,3] This is because (*R*)-(+)-pulegone, (+)-**1**, precursor for (−)-**2**, is readily accessible from the "chiral pool",[4] whereas (*S*)-(−)-pulegone, (−)-**1**, is not.[5] Consequently the use of suitable substitutes for (+)-**2** has been introduced in organic syntheses. Some of them induce the same chirality with approximately as high efficiency as (+)-**2**.[3,6,7,8] Such substitutes are for example isomers of the 8-phenylmentholsystem, like (+)-8-phenylisomenthol (+)-**3**[3] and (+)-8-phenylneomenthol (+)-**4**.[7] The starting compound for (+)-**3** and (+)-**4** is again (*R*)-(+)-pulegone, (+)-**1**. Since the asymmetric induction of these compounds is mainly below that of (+)-**2**,[3,7] compounds like *trans*-2-substituted cyclohexanols, e.g. (+)-**5**, have also been recommended as suitable substitutes for (+)-**2**.[6,8] Compound **5**, which is available in both enantiomeric forms, turns out to be an efficient auxiliary in a number of ground-state reactions.[8] In photochemical oxetane formation, however, only a low diastereoisomeric excess can be achieved.[9]

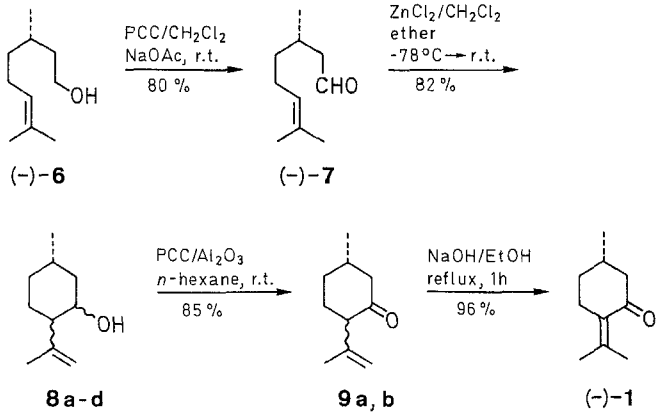


(−)-1 (+)-2 (+)-3 (+)-4 (+)-5

On the other hand, experimental tricks, like change of educt geometry,[1,10] or alternatively, the simple isomerization of one intermediate,[11] allow both product enantiomers to be obtained starting from the auxiliary with the same configuration. Although there is no doubt that the application of these methods has been successful in a few cases,[8,10,11] it is still desirable to have both enantiomers of a chiral auxiliary at ones disposal.

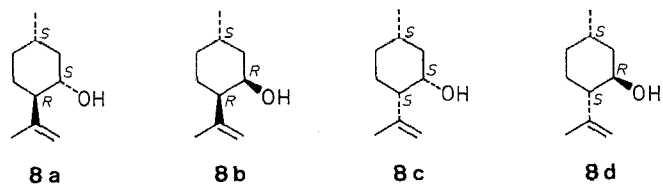
Superficially, there is no demand for synthetic procedures for the preparation of (+)-**2**, which is already described in literature;[2,12-15] but, in accordance with our experiences, all of the known methods that include the one-pot procedure of Corey and coworkers[15] for the preparation of (+)-**2** turn out not to be reproducible,[6,7] especially not for synthetic purposes.[16]

To overcome this drawback, we reinvestigated the pulegone-synthesis starting from citronellol **(6)** (Scheme **A**), which was originally described in 1896[14] with a very low yield.



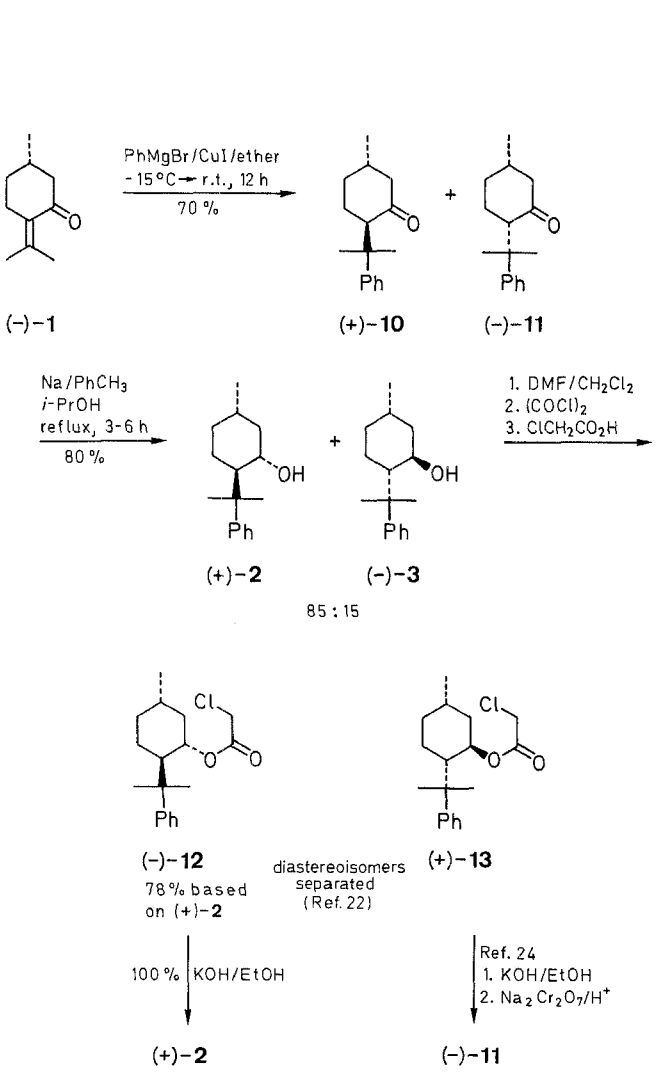
Scheme **A**

By optimizing the single reaction steps of the original Tiemann–Schmidt route, we have now succeeded in the preparation of (−)-pulegone, (−)-**1**, from (−)-citronellol, (−)-**6**, in a reproducible overall yield of 53%. Our synthesis can be scaled up to 100 g.[17] The cyclization of (−)-**7** has already been investigated,[18] since isopulegol **(8a)** represents an intermediate for industrial menthol production. However, the application of catalytic amounts of Zinc(II) chloride (10 mol-% based on **7** in ether/dichloromethane)[19] was found to be a selective and preparatively simple procedure to convert **7** in high yields into the isomers of isopulegol **8**. Only small amounts of condensation products of **7** are formed. The isolated isopulegol mixture consists (according to GC, and HPLC) of 77% of (+)-isopulegol, (+)-**8a**, 11% of (−)-neoisopulegol, (−)-**8b**, and 12% of (−)-neoisoisopulegol, (−)-**8c**; (−)-isoisopulegol, (−)-**8d**; was found in traces only.



8a **8b** **8c** **8d**

In the course of Corey's procedure,[2] (−)-**1** is converted, in a cuprate-catalyzed addition of phenylmagnesium bromide, into the isomeric 8-phenylmenthone mixture (+)-**10** and (−)-**11**. Earlier investigations of the cuprate-catalyzed addition of Grignard reagents to **1** have been published by C. Djerassi[20] in 1964. The resulting kinetic 1:1 mixture of the isomeric phenylmenthones (+)-**10** and (−)-**11** can be reduced on the basis of our experiences without prior equilibration[3,21] to the diastereoisomeric alcohols (+)-**2** and (−)-**3**. After separation of the diastereoisomeres via their chloroacetic acid esters[22] (−)-**12** and (+)-**13**, which can be prepared by a simplified Stadler method,[23] the collected fractions of the minor isomer (+)-**13** can be converted by saponification and oxidation with sodium chromate under phase-transfer conditions[24] into the menthone isomere (−)-**11**. The latter yields, after further reduction, again a mixture of the diastereoisomeric alcohols (+)-**2** and (−)-**3**. Along this line the minor isomer (−)-**3** is finally converted into the desired (+)-**1** completely. With this procedure the large-scale preparation of (+)-**2** is now possible. On the other hand, (−)-pulegone, (−)-**1**, itself represents an interesting chiral molecule,[25] which promises further applications in natural product syntheses.



IR spectra were recorded with a Perkin-Elmer 377 spectrophotometer, ^{1}H-NMR spectra on a Varian EM-390 (90 MHz) and a Varian VXR-300 (300 MHz), spectrometers, ^{13}C-NMR spectra on a Varian VXR-300 (74 MHz) spectrometer using $CDCl_3$ as solvent. Melting points (not corrected) were measured on a Büchi apparatus (Dr. Tottoli); specific rotations, on a Perkin-Elmer 241 instrument. HPLC was performed with a Abimed-Gilson apparatus: pump 303, module 803, R.I. detector (Bischoff LCD 202), columns, 7 μ Li-Chrosorb Si 60 (2.2 × 26 cm, prep.); eluent: EtOAc/cyclohexane (1:9). All solvents were purified by standard methods before use.

(*S*)-(−)-Citronellal (−)-7:
Compound (−)-**6**{$[\alpha]_D^{20}$ − 4,7° (neat)} is oxidized as described in Ref. 26 with pyridinium chlorochromate (PCC) in an acetate buffered dichloromethane solution to give (−)-**7**; yield: 80%, $[\alpha]_d^{20}$ − 12.0° (neat).

Cyclization of (−)-7 to Isomeric 2-Isopropenyl-5-methylcyclohexanols (8a–d):
The cyclization is carried out in a nitrogen atmosphere. $ZnCl_2$ (8.0 g, 42 mmol; Merck), which is heated before use 12 h at 200 °C (0.01 Torr), is dissolved in ether (200 mL). The $ZnCl_2$/ether solution is diluted with CH_2Cl_2 (800 mL) and cooled to − 78 °C. To the stirred solution, (−)-**7** (80 g, 0.52 mol), dissolved in CH_2Cl_2 (800 mL) and cooled to − 78 °C, is added in one portion. The mixture is stirred for 2 h at − 78 °C and then allowed to come to room temperature within two h. To complete the reaction, stirring is continued overnight at room temperature. Finally the mixture is washed with dil. aq. ammonia (3 × 75 mL) to destroy the zinc catalyst. After drying ($MgSO_4$) the organic layer is evaporated, and the remaining oil is distilled to give a mixture of isomeric isopulegols **8**; yield: 66 g (82%); bp 40–44 °C/0.01 Torr (the mixture consists, according to GC and HPLC, of 77% of (+)-**8a**, to 11% of (−)-**8b** and 12% of (−)-**8c**; (−)-**8d** was found in traces only).

Oxidation of the mixture of 8a–d to Isomeric 2-Isopropenyl-5-methylcyclohexanones (9a, b):
The oxidation is carried out with PCC on alumina (neutral, Machery & Nagel), which is prepared as described in Ref. 27. To the reagent [1230 g ≙ 1.0 mol Cr(VI)]suspended in *n*-hexane (1500 mL), the isomeric isopulegols **8a–d** (60 g, 0.39 mol), dissolved in *n*-hexane (300 mL), are added in one portion. The heterogenous mixture is stirred for 14 h at room temperature; then the adsorbed reagent is separated and washed with ether (5 × 250 mL). Solvent is removed (*attention*; the isomeric isopulegones **9a, b** are extremely volatile oils). Either the crude product can be isomerized directly, or it can be distilled to isolate the isopulegone mixture **9a, b**;[28] *yield: 54.0 g (92%, crude product), 50.4 g* (85%, distilled product); bp 28–29 °C/0.01 Torr.

Isomerization of the Isopulegone Mixture 9a, b to (*S*)-2-Isopropylidene-5-methylcyclohexanone, (−)-1:
The crude mixture of **9a, b** is isomerized with catalytical amounts of sodium hydroxide in boiling EtOH, as described in Ref. 15, to give (−)-**1**; yield: 51.8 g (96%, based on the crude mixture of **9**); bp 43 °C/0.01Torr; $[\alpha]_D^{20}$ − 23.0° (neat).

(2*R*,5*S*)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone, (+)-10, and Its 2*S*-Isomer, (−)-11:
To cooled Grignard solution (− 15 °C), prepared from Mg filings (11 g, 0.45 mol) and phenyl bromide (71 g, 0.45 mol) in ether (300 mL), is added CuI (6 g, 32 mmol, Aldrich). After stirring the mixture for 30 min at this temperature, a solution of (−)-**1** (40 g, 0.26 mol) in ether (100 mL) is added dropwise. The resulting mixture is allowed to warm and is stirred for 12 h at room temperature. The mixture is then cooled in ice and treated with H_2O (50 mL) followed by a solution of NH_4Cl (10 g) in H_2O (200 mL) and conc. HCl (30 mL). The organic layer is separated, and the aqueous solution is extracted with ether (3 × 60 mL). The combined organic phase is washed with sat. aq. $NaHCO_3$ and dried ($MgSO_4$). The solvent is removed, and the residue is distilled to obtain the isomeric 8-phenylmenthones (+)-**10** and (−)-**11** [(+)-**10**/(−)-**11** ≈ 1:1 by HPLC and ^{13}C-NMR]; yield: 42 g (70%); bp 92–93 °C/0.01 Torr.

(1*S*,2*R*,5*S*)-5-Methyl-2-(1-methyl-1-phenylethyl(cyclohexanol (+)-2 and Its 1*R*,2*S*,5*S*-Isomer, (−)-3:
The isomeric 8-phenylmenthones (+)-**10** and (−)-**11** are reduced without prior equilibration.[21] To a stirred suspension of Na (23 g, 1 mol) in boiling toluene (700 mL), a solution of (+)-**10** and (−)-**11** (42 g, 0.18 mol) in 2-propanol (80 g) is added dropwise. The resulting mixture is stirred and refluxed until the Na is dissolved (3–6 h). After cooling to *ambient temperature, the stirred mixture is treated with a solution of* NaH_2PO_4 (20 g) in H_2O (100 mL) followed by dil. HCl [conc. HCl (120 mL) in H_2O (400 mL)]. The organic layer is separated and the aqueous phase is extracted with ether (200 mL). After drying ($MgSO_4$) the combined organic phase is evaporated, and the remaining oil is distilled to obtain a mixture of (+)-**2** and (−)-**3** [(+)-**2**/(−)-**3** = 85:15 by HPLC and ^{13}C-NMR]; yield: 33.5 g (80%); bp 82–83 °C/0.01 Torr.

(1*S*,2*R*,5*S*)-1-Chloroacetoxy-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexane, (−)-12, and Its 1*R*,2*S*,5*S*-Isomer, (+)-13:
Oxalyl chloride (24.1 g, 0.19 mol) is added dropwise to a solution of DMF (40 mL, 0.52 mol) in CH_2Cl_2 (400 mL) at − 15 °C. After 15 min, chloroacetic acid (18 g, 0.19 mol) is added and stirring is continued until the precipitate dissolves (~ 30 min). The mixture is warmed and stirred for 1 h at room temperature. Subsequently the mixture of (+)-**2** and (−)-**3** (44 g, 0.19 mol) obtained above, dissolved in CH_2Cl_2 (100 mL) is added dropwise at − 15 °C and stirring is continued for 12 h at room temperature. The mixture is cooled (ice-bath) and treated with an 10% aq. $NaHCO_3$ (200 mL). The separated organic layer is washed with sat. aq. $NaHCO_3$ solution (100 mL) and dried ($MgSO_4$) before the solvent is evaporated. The purification of the residue is carried out as described in Ref. 22 to give (−)-**12** and (+)-**13**; yield: 38 g (78% based on the amount of (+)-**2** in the original mixture); mp 82 °C; $[\alpha]_D^{20}$ − 21.2° (c = 1.2, CCl_4).

Saponification of Ester (−)-12 to (+)-2:
The ester (−)-**12** is saponified quantitatively to the alcohol (+)-**2** by the procedure described in Ref. 22; yield: 28 g (≈ 100%); bp 84–85 °C/0.01 Torr; $[\alpha]_D^{20}$ − 32° (c = 0.43, $CHCl_3$); ee > 98% as determined by GC.

The obtained ^{1}H-NMR, ^{13}C-NMR, IR and MS spectra of all prepared compounds are identical with those of the corresponding enantiomeric ones. The microanalyses were in agreement with the calculated values: C ± 0.20, H ± 0.25.

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