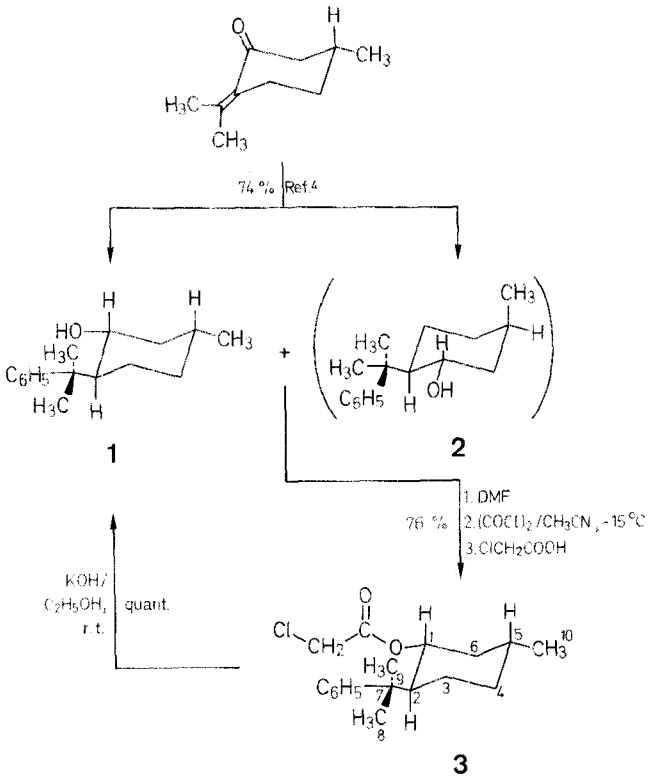
## Preparation of Pure (−)-(1*R*,2*S*,5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclehexanol in Larger Amounts

Heinz HERZOG, Hans-Dieter SCHARF*

Institut für Organische Chemie der RWTH Aachen, Prof.-Pirlet-Str. 1, D-5100 Aachen, Federal Republic of Germany

A method is described for the separation of (−)-(1*R*,2*S*,5*R*)-1-(1-methyl-1-phenylethyl)-5-methylcyclohexanol (**1**; 8-phenylmenthol) in preparative amounts in the form of its chloroacetate **3** from the accompanying diastereomer **2**, which is formed according to Corey's synthesis.

Compound **1** has proved to be a versatile chiral terpene alcohol[1], particularly used as a face differentiating agent[2] in asymmetric organic synthesis. In both ground state[1] and excited state[3] reactions, extremely high d.e. values were reported. This fact is of special interest in natural product synthesis[1,3c]. The Corey synthesis[4] of **1**, starting from (+)-pulegone results in a mixture of **1** and **2** (ratio: 85/15, as shown by $^{13}$C-N.M.R. and H.P.L.C.-analysis) in 74% overall yield.




The separation of **1** from **2** in larger amounts is, in practice, the main problem[5] since chromatographic methods (C.C., H.P.L.C.) in this case are not practicable. The derivatisations of **1** by means of phenylglyoxylic acid[3] or hippuric acid[6] were also not satisfactory. The most efficient procedure, in our opinion, is the conversion of the reaction mixture of **1** and **2** (85/15) to the chloroacetic acid esters, according to the method of Stadler[7]. This allows the separation by crystallisation of ester **3** (m.p. 82 °C) and its subsequent saponification to **1** in 46% overall yield.

I.R. spectra were recorded with a Perkin-Elmer 377 instrument; $^1$H-N.M.R., Varian EM 390; $^{13}$C-N.M.R., Varian CFT 20; melting points (not corrected), Büchi apparatus (D. Tottoli); specific rotations, Perkin-Elmer 241 instrument. All solvents were purified by standard methods before use.

**Esterification of the Mixture of 1 and 2:**

Oxalyl chloride (16.1 ml, 0.19 mol) in acetonitrile (30 ml) is added dropwise to solution of dimethylformamide (40 ml) in acetonitrile (250 ml) at −15 °C under nitrogen. After 15 min, chloroacetic acid (17.9 g, 0.19 mol) is added with stirring and stirring is continued until the precipitate dissolves (~30 min). The mixture (44 g, 0.19 mol) of **1** {85% by H.P.L.C. and $^{13}$C-N.M.R.; $[\alpha]_D^{21}$: −29.4° (*c* 0.32, $CHCl_3$)} and **2** {15% by H.P.L.C. and $^{13}$C-N.M.R.: $[\alpha]_D^{21}$: +26.1° (*c* 0.28, $CHCl_3$)} dissolved in acetonitrile (30 ml) is added and the mixture is stirred at room temperature for 6 h. The mixture is then cooled to 0 °C, pyridine (15 ml) in acetonitrile (30 ml) is added dropwise, and the mixture is stirred for 1 h. Dichloromethane (400 ml) is added, the solution is washed with sodium carbonate solution (300 ml) and water (300 ml), extracted with dichloromethane (300 ml). The extract is dried with magnesium sulfate (+ charcoal) and the solvent is evaporated. The residue is cooled to −25 °C and mixed with an equal volume of 1/1 ether/pentane. After 5–10 h, the crystals are filtered, washed with pentane and the mother liquor is again evaporated and cooled. A total of 3 crops of the ester **3** are thus obtained; yield: 38 g (76% based on the amount of **1** in the original mixture); m.p. 82 °C; $[\alpha]_D^{23}$: +21.2° (*c* 1.2, $CCl_4$).

$C_{18}H_{25}ClO_2$ (308.8) calc. C 70.00 H 8.16 found 69.85 8.21

I.R. (KBr): $\nu$ = 3060–3020 ($C_6H_5$): 1740 (C=O); 1180 (C–O); 700 $cm^{-1}$ (C–Cl).

$^1$H-N.M.R. ($CDCl_3$): $\delta$ = 0.89 (d, $J$ = 6 Hz, 10-$CH_3$); 0.9–2.2 (m, 8 H, cyclohexyl); 1.22, 1.33 (2 s, 3 H each, 8-$CH_3$, 9-$CH_3$); 3.03 (d, $J$ = 14.7 Hz, 1 H, ClCHH—); 3.32 (d, $J$ = 14.7 Hz, 1 H, ClCHH—); 4.88 (dt, $J$ = 4.0 Hz, 10.0 Hz, 1 H, CHO); 7.1–7.3 ppm (m, 5 $H_{arom}$).

$^{13}$C-N.M.R. ($CDCl_3$): $\delta$ = 21.75 (C-10); 22.77 (C-8); 26.23 (C-3); 29.72 (C-9); 31.28 (C-5); 34.44 (C-4); 39.44 (C-7); 40.47 ($CH_2Cl$); 41.51 (C-6); 50.30 (C-2); 75.80 (C-1); 125.14 (*para*); 125.32 (*ortho*); 128.01 (*meta*); 155.70 (C-1 of $C_6H_5$); 166.47 ppm (COO).

The chiral alcohol **1** can be stored indefinitely as its chloroacetate **3**. The latter should be saponified when the alcohol is required. The alcohol itself is unstable and decomposes even in a refrigerator.

**Saponification of Ester 3:**

The ester **3** (38 g, 0.12 mol) is stirred with potassium hydroxide (13.8 g, 0.25 mol) dissolved in ethanol (1000 ml) at room temperature overnight. The ethanol is evaporated and toluene (800 ml) is added. The mixture is washed with water (400 ml) and the toluene phase is dried with magnesium sulfate. Evaporation and final distillation gives the alcohol **1**; yield: 27–28 g (~ 100%); b.p. 84–85°C/0.05 torr; $[\alpha]_D^{21}$: –29.4° (*c* 0.32, $CHCl_3$).

$C_{16}H_{24}O$ (232.4) calc. C 82.70 H 10.41 found 82.68 10.52

I.R. ($CDCl_3$): $\nu$ = 3550–3100 (OH); 3080–3020 ($C_6H_5$); 1595 $cm^{-1}$ ($C_6H_5$).

$^1$H-N.M.R. ($CDCl_3$): $\delta$ = 0.88 (d, $J$ = 6 Hz, 3 H, 10-$CH_3$); 1.02–2.00 (m, 8 H, cyclohexyl); 1.22 (s, 1 H, OH); 1.30, 1.43 (2 s, 3 H, each, 8-$CH_3$, 9-$CH_3$); 3.50 (dt, $J$ = 4.5 Hz, 10 Hz, 1 H, CHOH); 7.05–7.50 ppm (m, 5 $H_{arom}$).

$^{13}$C-N.M.R. ($CDCl_3$): $\delta$ = 21.99 (C-10); 24.90 (C-8); 26.56 (C-4); 28.21 (C-9); 31.51 (C-5); 34.80 (C-3); 39.82 (C-7); 45.50 (C-6); 54.11 (C-2); 72.66 (C-1); 125.66 (*para*); 125.76 (*ortho*); 128.34 (*meta*); 151.28 ppm (C-1 of $C_6H_5$).

Received: August 21, 1985

* Address for correspondence.


1 Kipphardt, H., Enders, D. *Merck Kontakte*, **1985**, (2), 37 and references cited therein.

2 Helmchen, G., Schmierer, R. *Angew. Chem.* **1981**, *93*, 208; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 205.

3 (a) Herzog, H., Koch, H., Scharf, H.-D., Runsink, J. *Tetrahedron* **1986**, in press.
(b) Runsink, J., Koch, H., Nehrings, A., Scharf, H.-D. *J. Chem. Soc., Perkin Trans. 2* **1986**, in press.
(c) Nehrings, A., Scharf, H.-D., Runsink, J. *Angew. Chem.* **1985**, 97, 882; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 877.
(d) Koch, H., Runsink, J., Leismann, H., Scharf, H.-D. *Chem. Ber.* **1985**, *118*, 1485.
(e) Koch, H., Runsink, J., Scharf, H.-D. *Tetrahedron Lett.* **1983**, *24*, 3217.

4 Corey, E.J., Ensley, H. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

5 Oppolzer, W. *Angew. Chem.* **1984**, *96*, 840; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876.

6 Kober, R., Papadopoulos, K., Miltz, W., Enders, D., Steglich, W., Reuter, H., Puff, H. *Tetrahedron* **1985**, *41*, 1693.

7 Stadler, P.A. *Helv. Chim. Acta* **1978**, *61*, 1675.