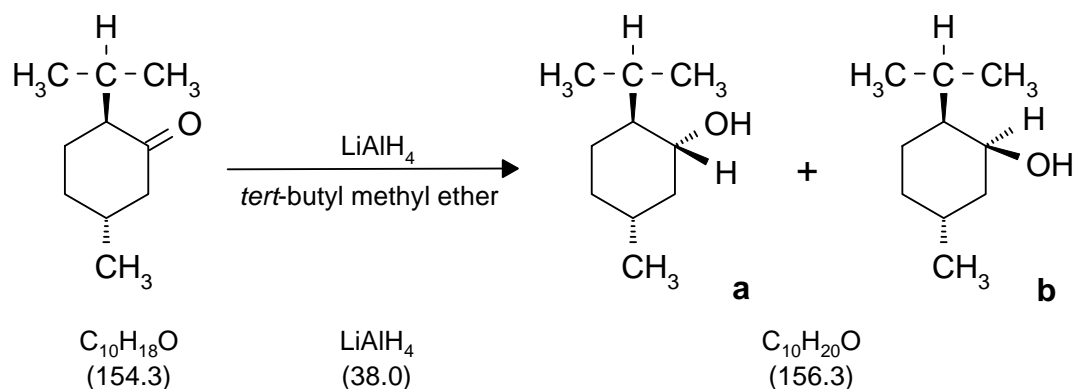


## 2022 Reduction of L-(–)-menthone with lithium aluminium hydride to an isomeric mixture of (–)-menthol and (+)-neomenthol



### Classification

#### Reaction types and substance classes

reaction of the carbonyl group in ketones, reduction, stereoselective addition  
ketone, alcohol, complex metal hydride, natural product

#### Work methods

working with moisture exclusion, stirring with KPG stirrer, adding dropwise with an addition funnel, heating under reflux, filtering, evaporating with rotary evaporator, distilling under reduced pressure, use of a cooling bath, heating with oil bath

### Instruction (batch scale 100 mmol)

#### Equipment

500 mL three-neck flask, metal reflux condenser, drying tube, protective gas supply, KPG-stirrer, addition funnel with pressure balance, suction flask, Buechner funnel, rotary evaporator, distillation apparatus, heatable magnetic stirrer, magnetic stir bar, vacuum pump, cooling bath, oil bath

#### Substances

L-(–)-menthone (bp 85-66 °C/16hPa), $[\alpha]_D^{20} = -29.6^\circ$	15.4 g (100 mmol)
lithium aluminium hydride	5.32 g (140 mmol)
tert-butyl methyl ether (dry) (bp 55 °C)	240 mL
aqueous sodium hydroxide solution (15%)	6 mL
potassium carbonate for drying	

#### Reaction

The reaction apparatus, consisting of a 500 mL three-neck flask, KPG-stirrer, metal reflux condenser with drying tube and an addition funnel with pressure balance, must be completely

dry and preferably rinsed with nitrogen. 160 mL of dry *tert*-butyl methyl ether are filled into the flask and 5.32 g (140 mmol) lithium aluminium hydride are added at once. The mixture is stirred for 5 minutes and then a solution of 15.4 g (100 mmol) L-(–)-menthone in 60 mL dry *tert*-butyl methyl ether is added dropwise under stirring, so that the ether is moderately boiling. Then the mixture is stirred and heated under reflux for further 2 hours.

### Work up

Under stirring, the mixture is cooled down in a cooling bath (for safety reasons no ice bath because of  $\text{LiAlH}_4$ ) to about 0 °C. Then **very carefully** 6 mL water are added dropwise through an addition funnel, then 6 mL of a 15% sodium hydroxide solution and then again 16 mL water to decompose the excessive lithium aluminium hydride. Thereby the reaction mixture is foaming under gas evolution, and it boils. A colourless, viscous precipitate is formed. After the addition has been finished, the mixture is stirred for further 30 minutes and then sucked off over a Buechner funnel. If the filtrate is not clear, it is filtered again. Then, the filtrate is dried with potassium carbonate. The drying agent is sucked off, washed with 20 mL *tert*-butyl methyl ether and the solvent is evaporated at a rotary evaporator. A colourless oily residue remains as crude product.

Crude yield: 13.8 g; GC-purity 98%; ratio menthol to neomenthol 73 : 27

The crude product is distilled under reduced pressure (about 20 hPa).

Yield: 12.5 g (80.0 mmol, 80%); bp 102-104 °C (20 hPa);  $[\alpha]_D^{20} = -28.1^\circ$ . Purity and ratio of the isomers are the same as described for the crude product (see analytics).

### Waste management

#### Recycling

The evaporated *tert*-butyl methyl ether is collected and redistilled.

#### Waste disposal

Waste	Disposal
solid residue from lithium aluminium hydride hydrolysis	solid waste, free from mercury
distillation residue	organic solvents, halogen free
potassium carbonate	solid waste, free from mercury

#### Time

7 hours

#### Break

After the hydrolysis of the lithium aluminium hydride and sucking off the precipitation and before distillation.

#### Degree of difficulty

Difficult

## Instruction (batch scale 10 mmol)

### Equipment

100 mL three-neck flask, metal reflux condenser, drying tube, protective gas supply, KPG-stirrer, addition funnel with pressure balance, suction flask, Buechner funnel, rotary evaporator, small distillation apparatus, heatable magnetic stirrer, magnetic stir bar, vacuum pump, cooling bath, oil bath

### Substances

L-(–)-menthone (bp 85-66 °C/16hPa), $[\alpha]_D^{20} = -29.6^\circ$	1.54 g (10.0 mmol)
lithium aluminium hydride	532 mg (14.0 mmol)
<i>tert</i> -butyl methyl ether (dry) (bp 55 °C)	70 mL
aqueous sodium hydroxide solution (15%)	1 mL
potassium carbonate for drying	

### Reaction

The reaction apparatus, consisting of a 100 mL three-neck flask, KPG-stirrer, metal reflux condenser with drying tube and an addition funnel with pressure balance, must be completely dry and preferably rinsed with nitrogen. 40 mL of dry *tert*-butyl methyl ether are filled into the flask and 532 mg (14.0 mmol) lithium aluminium hydride are added at once. The mixture is stirred for 5 minutes and then a solution of 1.54 g (10.0 mmol) L-(–)-menthone in 20 mL dry *tert*-butyl methyl ether is added dropwise under stirring, so that the ether is moderately boiling. Then the mixture is stirred and heated under reflux for further 2 hours.

### Work up

Under stirring, the mixture is cooled down in a cooling bath (for safety reasons no ice bath because of  $\text{LiAlH}_4$ ) to about 0 °C. Then **very carefully** 1 mL water is added dropwise through an addition funnel, then 1 mL of a 15% sodium hydroxide solution and then again 4 mL water to decompose the excessive lithium aluminium hydride. Thereby the reaction mixture is foaming under gas evolution, and it boils. A colourless, viscous precipitate is formed. After the addition has been finished, the mixture is stirred for further 30 minutes and then sucked off over a Buechner funnel. If the filtrate is not clear, it is filtered again. Then, the filtrate is dried with potassium carbonate. The drying agent is sucked off, washed with 10 mL *tert*-butyl methyl ether and the solvent is evaporated at a rotary evaporator. A colourless oily residue remains as crude product.

Crude yield: 1.35 g; GC-purity 98%; ratio menthol to neomenthol 73 : 27

The crude product is distilled in a small distillation apparatus at reduced pressure (about 20 hPa).

Yield: 1.05 g (6.72 mmol, 67%); bp 102-104 °C;  $[\alpha]_D^{20} = -28.1^\circ$ . Purity and ratio of the isomers are the same as described for the crude product (see analytics).

**Waste management****Recycling**

The evaporated *tert*-butyl methyl ether is collected and redistilled.

**Waste disposal**

Waste	Disposal
solid residue from lithium aluminium hydride hydrolysis	solid waste, free from mercury
distillation residue	organic solvents, halogen free
potassium carbonate	solid waste, free from mercury

**Time**

6 hours

**Break**

After the hydrolysis of the lithium aluminium hydride and sucking off the precipitation and before distillation

**Degree of difficulty**

Difficult

**Analytics****Reaction monitoring**

In principle, the reaction can be followed either with GC or TLC, for safety reasons no samples should be taken during reaction.

**TLC**

TLC-conditions:

adsorbant:	TLC-aluminium foil silica gel 60 F <sub>254</sub>
eluent:	petroleum ether (40-60 °C) / acetic acid ethyl ester 1:1
visualizing reagent	vanillin
R <sub>f</sub> (menthone)	0.80
R <sub>f</sub> (menthol/neomenthol)	0.62

**GC**

Sample preparation:

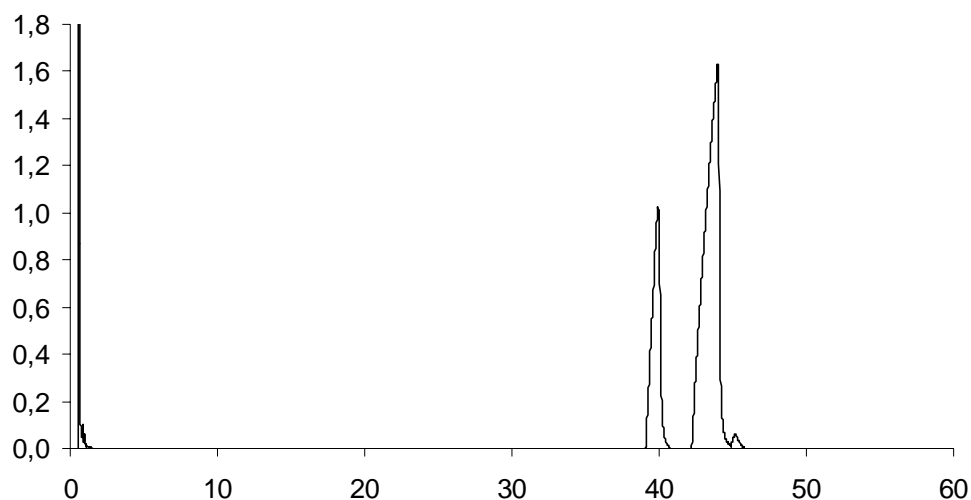
40 mg substance are dissolved in 1 mL dichloromethane.

GC-conditions :

column:	Zebtron ZB-1, length 15 m, internal diameter 0.25 mm, film 0.25 µm, (Phenomenex, Torrance, CA, USA)
inlet:	injector temperature 260 °C; split injection 20:1; injected volume 0.1 µL
carrier gas:	He, pre-column pressure 100 kPa
oven:	40 °C isotherm
detector:	FID, 260 °C, H <sub>2</sub> 30 mL/min; synth air 361 mL/min; make-up-gas N <sub>2</sub> , 14.9 mL/min (59 kPa)
integration:	integrator 4290 (Thermo Separation Products)

Percent concentration was calculated from peak areas.

## GC of the crude product



Retention time (min)	Substance	Peak area%
39.9	neomenthol	26.7
44.0	menthol	72.3
45.1	unknown	1.0

The peak at 45.1 min could not be assigned, it does not originate from isomenthol, which was injected for comparison.

The GCs of the crude product and the pure product are virtually identic.

The ratio of menthol to neomenthol from the GC peak areas is **73 : 27**.

## Optical rotation of the pure product

optical rotation of the pure components according to literature:

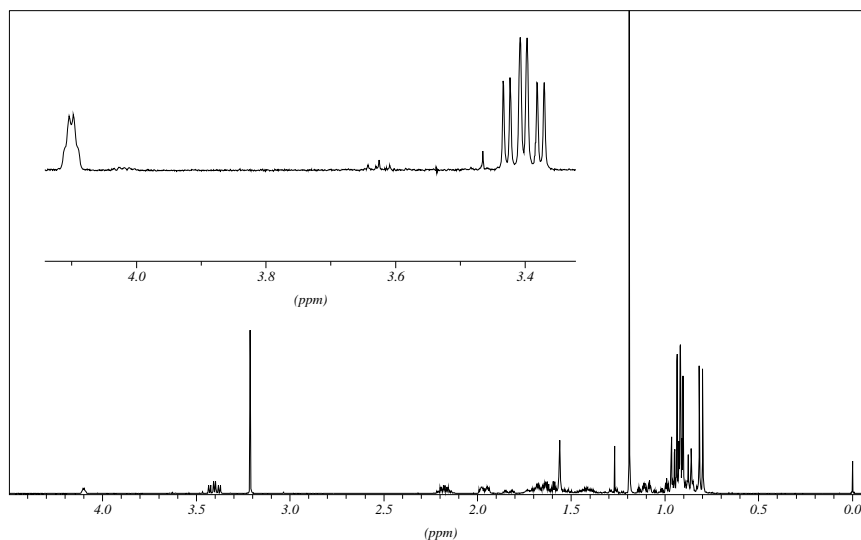
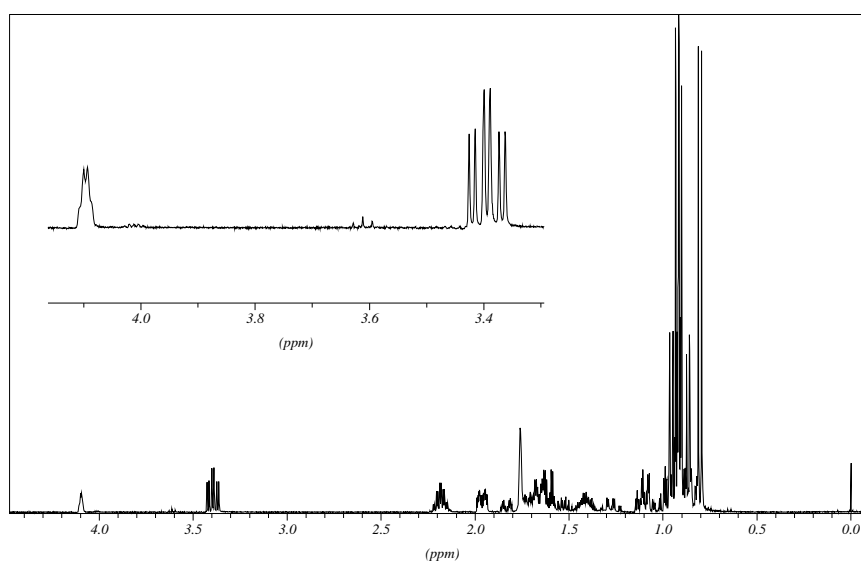
$[\alpha]_D^{20}$  (menthol):  $-59.6^\circ$  (ethanol)

$[\alpha]_D^{20}$  (neomenthol):  $+19.8^\circ$  (ethanol)

optical rotation of the pure product from a 3% solution in ethanol:

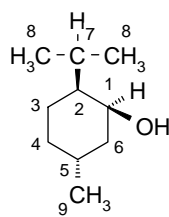
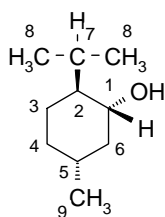
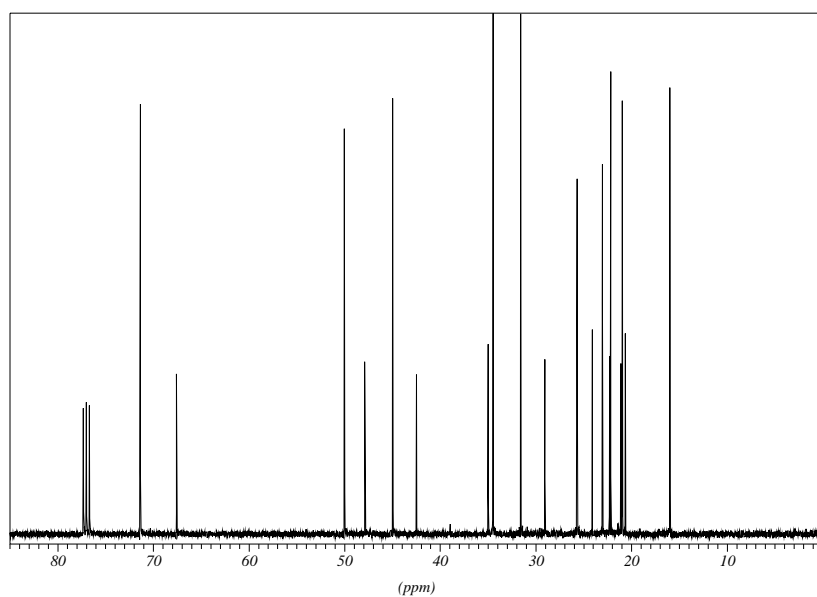
$[\alpha]_D^{20} = -28.10^\circ$

result: ratio of menthol to neomenthol = **69 : 31**.

**$^1\text{H}$  NMR spectrum of the crude product (400 MHz,  $\text{CDCl}_3$ )** **$^1\text{H}$  NMR spectrum of the pure product (400 MHz,  $\text{CDCl}_3$ )**

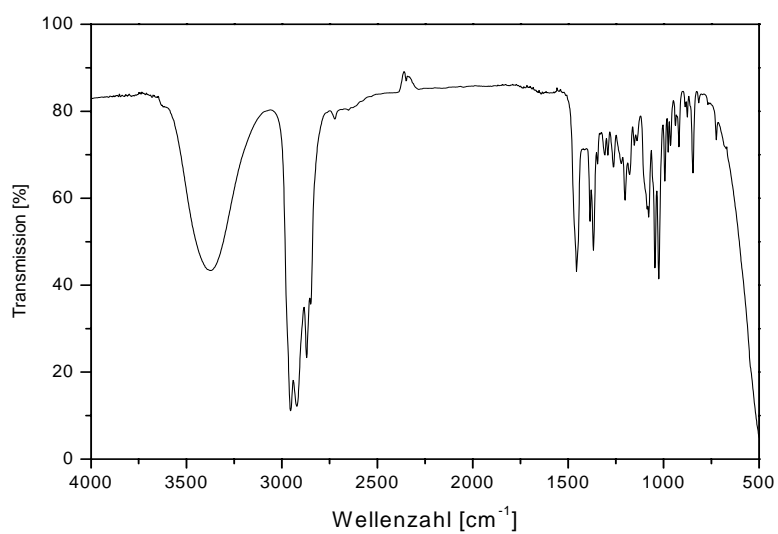
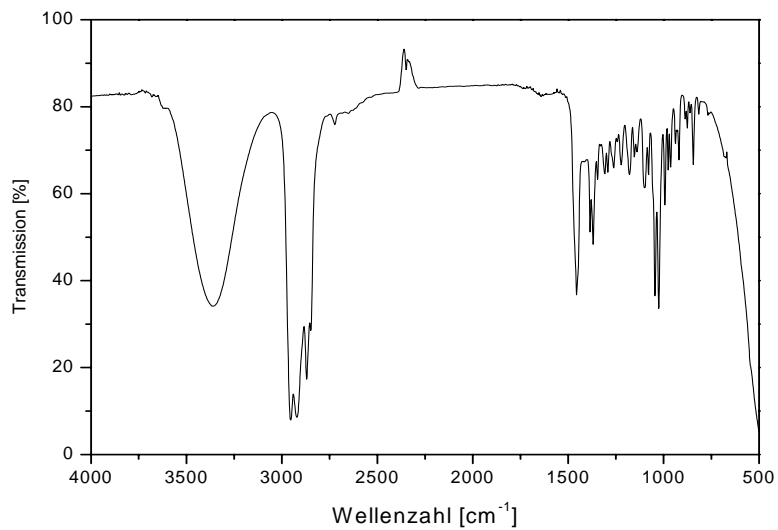
$\delta$ (ppm)	Multiplicity	rel. intensity	Assignment
3.40	m	72	CH – OH (menthol)
4.10	m	28	CH – OH (neomenthol)
0.7 – 2.3	m		other protons from menthol and neomenthol

Peaks at 1.19 and 3.20 ppm in the crude product originate from the *tert*-butyl methyl ether.

**$^{13}\text{C}$  NMR spectrum of the pure product (400 MHz,  $\text{CDCl}_3$ )**

Menthol		Neomenthol	
$\delta$ (ppm)	Assignment	$\delta$ (ppm)	Assignment
71.36	C-1	67.57	C-1
50.01	C-2	47.88	C-2
44.97	C-6	42.50	C-6
34.48	C-4	34.99	C-4
31.57	C-5	29.05	C-5
25.67	C-7	25.72	C-7
23.02	C-3	24.09	C-3
22.15	C-9	22.28	C-9
20.95	C-8	21.10	C-8
15.97	C-8	20.64	C-8

The lines at 76.5-77.5 ppm originate from the solvent.

**IR spectrum of the crude product (film)****IR spectrum of the pure product (film)**

(cm <sup>-1</sup> )	Assignment
3360	O – H – valence
2970 – 2860	C – H – valence, alkane