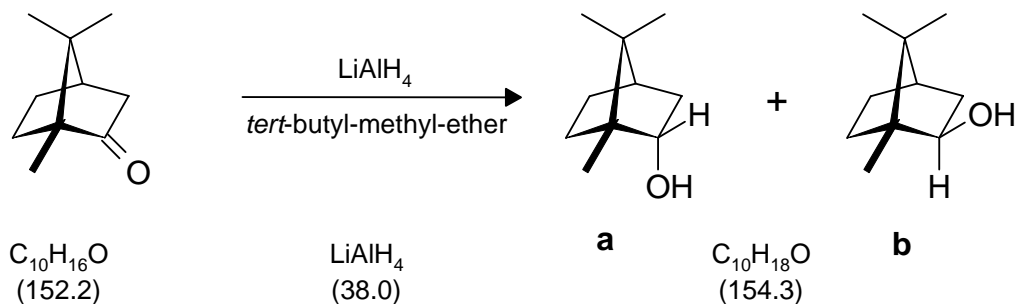


## 2023 Reduction of D-(+)-camphor with lithium aluminium hydride to an isomeric mixture of (+)-borneol and (-)-isoborneol



### 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, sublimating, 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, sublimation apparatus, heating plate, vacuum pump, cooling bath, oil bath

#### Substances

D-(+)-camphor, $[\alpha]_D^{20} = +44.0^\circ$ (mp $179^\circ\text{C}$ )	15.2 g (100 mmol)
lithium aluminium hydride	5.32 g (140 mmol)
<i>tert</i> -butyl methyl ether, dry (bp $55^\circ\text{C}$ )	280 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 15.2 g (100 mmol) D-(+)-camphor in 100 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 until reflux for further 3 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 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 a second time. 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 crystalline residue remains as crude product.

Crude yield: 13.4 g; mp 209-210 °C; GC-purity over 99%; ratio isoborneol to borneol 87 : 13

1.00 g of the crude product is sublimated at reduced pressure (about 20 hPa) and an oil bath temperature of about 100 °C. 1.00 g crude product results in 0.970 g sublimated pure product. Yield of sublimated product extrapolated to the total volume of crude product: 13.0 g (84.2 mmol, 84%); mp 211-213 °C;  $[\alpha]_D^{20} = -24.090^\circ$

The product consists of isoborneol and borneol in the ratio of 87 : 13 and shows less than 0.1% impurities (GC, see analytics).

### Comments

If the reaction is carried out with racemic camphor, it proceeds as described for the D-(+)-camphor. The product consists of the racemates of borneol and isoborneol, the single enantiomers can be visualized with a chiral GC-column (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
residue from sublimation	solid waste, free from mercury
potassium carbonate	solid waste, free from mercury

### Time

6 hours until sublimation

### Break

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

**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, sublimation apparatus, heating plate, vacuum pump, cooling bath, oil bath

**Substances**

D-(+)-camphor, $[\alpha]_D^{20} = +44.0^\circ$ (mp 179 °C)	1.52 g (10.0 mmol)
lithium aluminium hydride	532 mg (14.0 mmol)
<i>tert</i> -butyl methyl ether, dry (bp 55 °C)	90 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 1.52 g (10.0 mmol) D-(+)-camphor in 40 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 3 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 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 a second time. 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 crystalline residue remains as crude product.

Crude yield: 1.31 g; mp 209-210 °C; GC-purity 99%; ratio isoborneol to borneol 87 : 13

The crude product is sublimated at reduced pressure (about 20 hPa) and an oil bath temperature of about 100 °C.

Yield of sublimated pure product: 1.27 g (8.23 mmol, 82%); mp 211-213 °C;  $[\alpha]_D^{20} = -24.09^\circ$

The product consists of isoborneol and borneol in a ratio of 87 : 13 and shows less than 0.1% impurities (GC, see analytics).

### Comments

If the reaction is carried out with racemic camphor, it proceeds as described for the D-(+)-camphor. The product consists of the racemates of borneol and isoborneol, the single enantiomers can be visualized with a chiral GC-column (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
residue from sublimation	solid waste, free from mercury
potassium carbonate	solid waste, free from mercury

### Time

5 hours until sublimation

### Break

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

### 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> (camphor)	0.75
R <sub>f</sub> (borneol/isoborneol)	0.70

**GC**

## GC-conditions I:

Sample preparation: 10 mg substance are dissolved in 1 mL *tert*-butyl methyl ether.

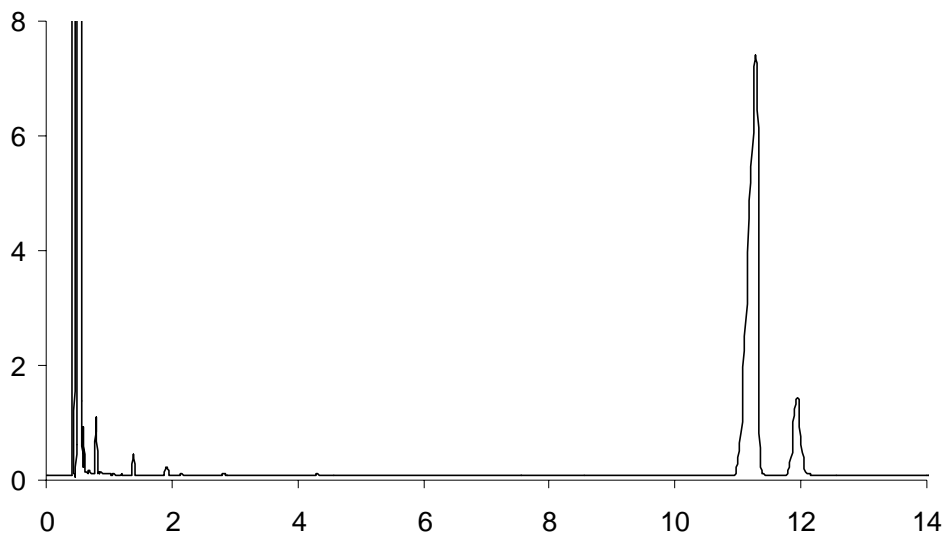
column: Zebtron ZB-1, length 15 m, internal diameter 0.25 mm, film 0.25  $\mu$ m,  
(Phenomenex, Torrance, CA, USA)  
inlet: injector temperature 270 °C; split injection 21:1; injected volume 0.3  $\mu$ L  
carrier gas: He, pre-column pressure 100 kPa  
oven: 60 °C isotherm  
detector: FID, 250 °C, H<sub>2</sub> 29 mL/min; synth air 333 mL/min;  
integration: Integrator 4290 (Thermo Separation Products)

## GC-conditions II:

Sample preparation: 50 mg substance are dissolved in 1 mL *tert*-butyl methyl ether.

chiral column: Cyclosil B, length 2 x 30 m, internal diameter 0.32 mm, film 0.25  $\mu$ m,  
(J & W Scientific, Folsom, CA, USA)  
inlet: injector temperature 260 °C; split injection 4.9; injected volume 0.13  $\mu$ L  
carrier gas: H<sub>2</sub>, pre-column pressure 100 kPa  
oven: 70 °C (45 min isotherm), 0.3 °C/min to 110 °C (25 min)  
detector: FID, 300 °C, H<sub>2</sub> 25.1 mL/min; synth air 393 mL/min  
integration: integrator 4290 (Thermo Separation Products)

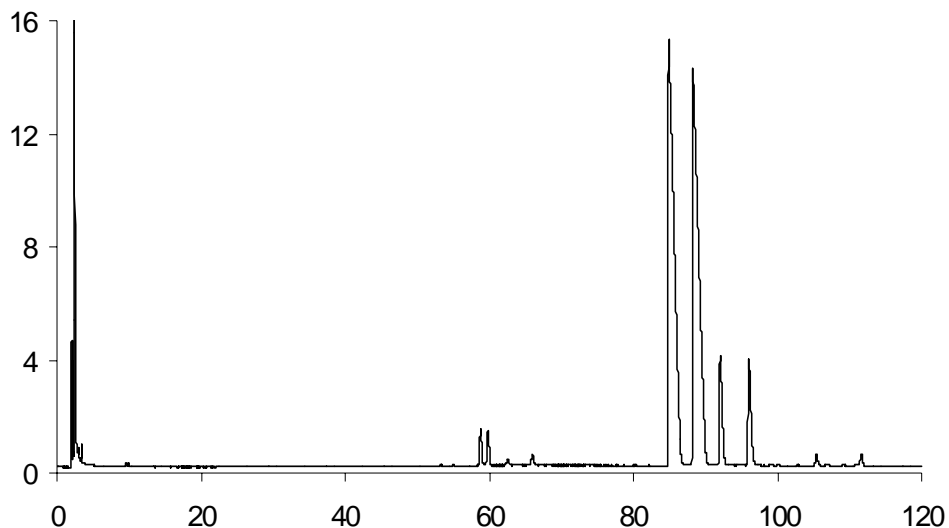
Percent concentration was calculated from peak areas.

**GC of the product from D-(+)-camphor (GC-conditions I)**

Retention time (min)	Substance	Peak area %
11.3	isoborneol	87.5
11.9	borneol	12.5
9.8	camphor	0.0

The GCs of the crude product and the pure product are virtually identical, they show less than 0.1% impurities. The peaks below a retention time of 2 minutes originate from the solvent and its impurities.

### GC of the product from racemic camphor (GC-conditions II)



Retention time (min)	Substance	Peak area %
58.8	(-)-camphor	1.27
59.8	(+)-camphor	1.30
84.9	(+)-isoborneol	42.4
88.3	(-)-isoborneol	42.5
92.0	(-)-borneol	5.4
96.0	(+)-borneol	5.4
others	not identified	1.7

From the peak areas results a ratio of isoborneol to borneol = **89 : 11**.

### Optical rotation of the pure product

optical rotation of the pure components (literature values):

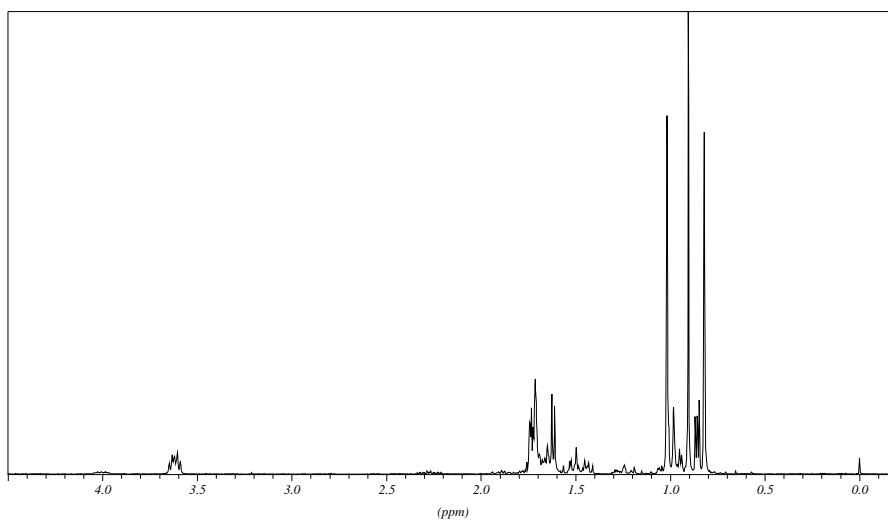
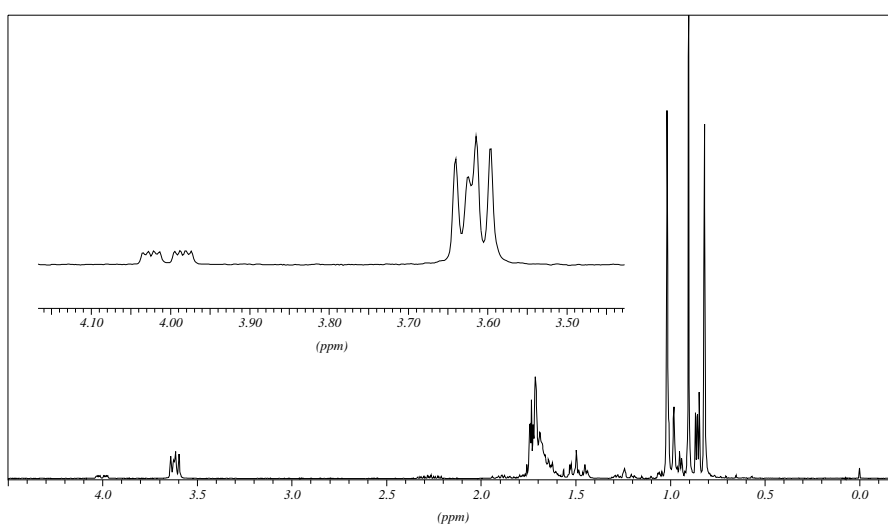
$$[\alpha]_D^{20} \text{ (isoborneol): } -34.6^\circ \text{ (ethanol)}$$

$$[\alpha]_D^{20} \text{ (borneol): } +37.7^\circ \text{ (ethanol)}$$

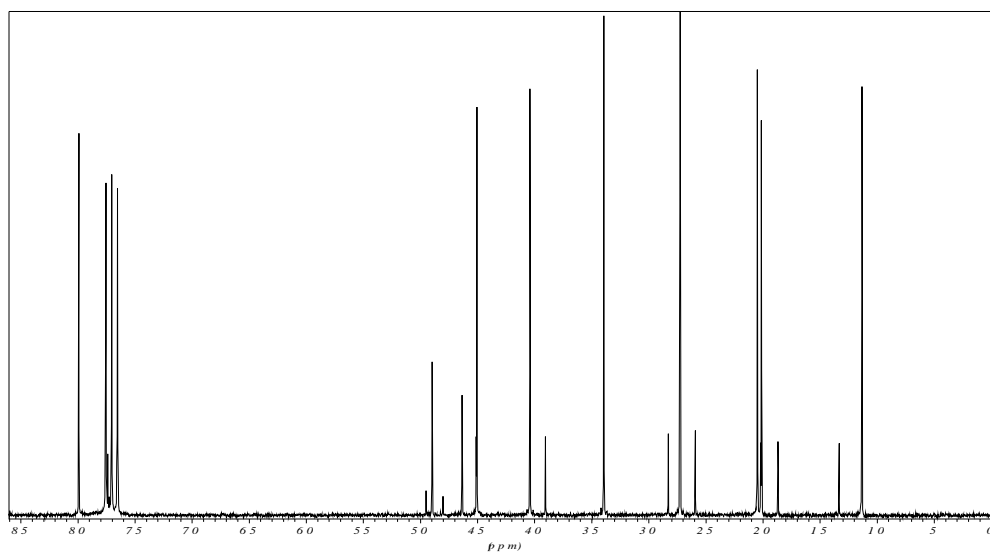
optical rotation of the pure product measured from a 3% solution in ethanediol:

$$[\alpha]_D^{20} = -24.090^\circ$$

result: ratio of isoborneol to borneol = **85 : 15**.

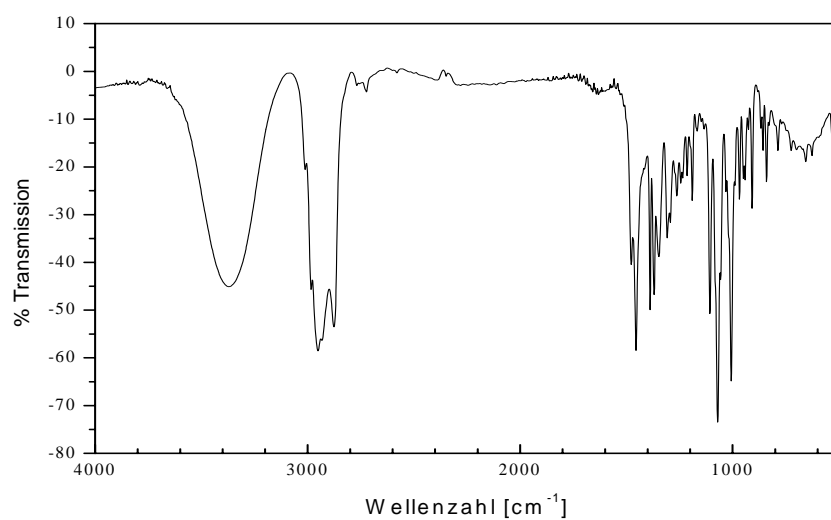
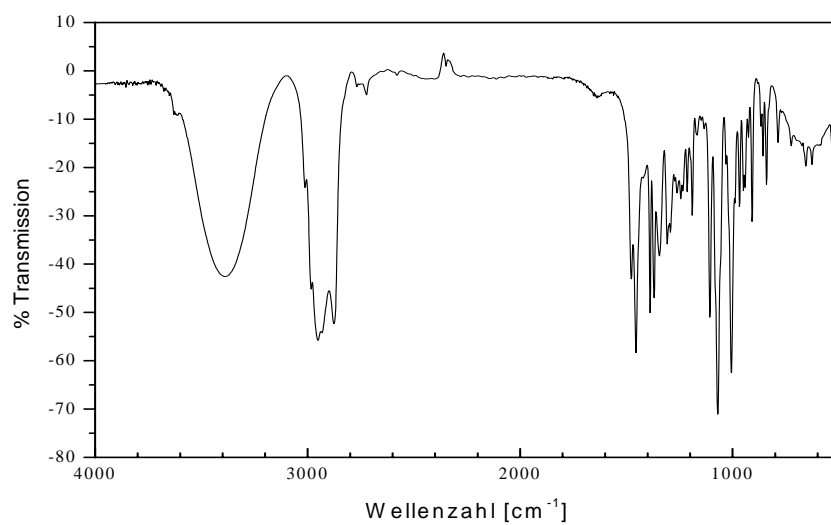
**$^1\text{H}$  NMR spectrum of the crude product (250 MHz,  $\text{CDCl}_3$ )** **$^1\text{H}$  NMR spectrum of the pure product (250 MHz,  $\text{CDCl}_3$ )**

$\delta$ (ppm)	Multiplicity	Rel. Intensity	Assignment
0.82	s		$\text{CH}_3$ (isorneol)
0.91	s		$\text{CH}_3$ (isorneol)
1.02	s		$\text{CH}_3$ (isorneol)
3.58-3.65	m	<b>86</b>	$\text{CH} - \text{OH}$ (isorneol)
3.96-4.40	m	<b>14</b>	$\text{CH} - \text{OH}$ (borneol)
0.8-2.4	m		other ring protons in isorneol and borneol and $\text{CH}_3$ in borneol

**$^{13}\text{C}$  NMR spectrum of the pure product (250 MHz,  $\text{CDCl}_3$ )**

$\delta$ (ppm) Isoborneol	$\delta$ (ppm) Borneol	Assignment
79.92	77.37	CH(OH)
48.97	49.50	$\text{C}_{\text{quart}}$
46.35	48.03	$\text{C}_{\text{quart}}$
45.05	45.11	CH
40.41	39.04	$\text{CH}_2$
33.92	28.29	$\text{CH}_2$
27.25	25.93	$\text{CH}_2$
20.49	20.20	$\text{CH}_3 - \text{C} - \text{CH}_3$
20.12	18.69	$\text{CH}_3 - \text{C} - \text{CH}_3$
11.33	13.34	$\text{CH}_3$ at the bridge head C
76.5-77.5		solvent.



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

(cm <sup>-1</sup> )	Assignment
3370	O – H – valence
2983–2876	C – H – valence, alkane