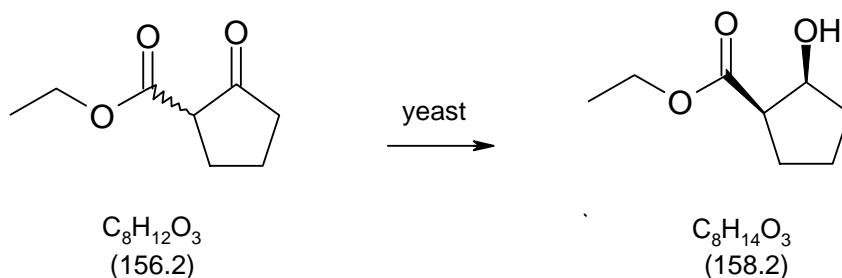


## 4024 Enantioselective synthesis of (1R,2S)-cis-hydroxycyclopentane-carboxylic acid ethyl ester



### Classification

#### Reaction types and substance classes

reduction, stereoselective reduction

carboxylic acid ester, ketone, alcohol, enzyme, natural product

#### Work methods

stirring with magnetic stir bar, adding dropwise with an addition funnel, working with a thermostat, filtering, evaporating with rotary evaporator, extracting, perforating, rectifying, use of a distillation column, distilling under reduced pressure, heating with oil bath, stirring with a propeller stirrer

for batch scale 100 mmol additional:

stirring with a propeller stirrer

### Instruction (batch scale 10 mmol)

#### Equipment

2 L round bottom flask, addition funnel, thermostat, rotary evaporator, heatable magnetic stirrer, magnetic stir bar, distillation apparatus, 10 cm packed column, suction flask, Buechner funnel (Ø 15 cm), apparatus for continuous extraction of liquids, oil bath

#### Substances

fresh yeast (baker's yeast)	78.0 g
cyclopentanone-2-carboxylic acid ethyl ester (purity > 95%) (bp 109 °C, 20 hPa; product from NOP 4023)	1.56 g (10.0 mmol)
water (boiled)	750 mL
diethyl ether (bp 35 °C)	500 mL
Celite 545 (filter help)	
sodium sulfate for drying	

**Reaction**

78.0 g fresh yeast are suspended under slowly stirring and in portions in a 2 L round bottom flask in 750 mL cold boiled water and brought to a temperature of 30 °C. After the complete suspension of the yeast, 1.56 g (10.0 mmol) cyclopentanone-2-carboxylic acid ethyl ester are added dropwise with an addition funnel within 30 minutes. The flask is covered with aluminium foil or a wad of cotton wool and the reaction mixture is slowly stirred at 30 °C for two days.

**Work up**

To the reaction solution 1 g Celite is added and the mixture is stirred for one hour. A Buechner funnel (Ø 15 cm) is charged with a 2 cm layer of moisted Celite and the solution is filtered through the moisted filter medium into a suction flask. The filtrate is extracted in an apparatus for continuous extraction of liquids with 500 mL diethyl ether. The extract is dried over sodium sulfate, the drying agent is filtered off and the solvent is evaporated at a rotary evaporator. The residue is distilled under reduced pressure (about 20 hPa) over a 10 cm packed column.

1. fraction 50-90 °C: fore-run

2. fraction 94-112 °C: product

Further fractions are not obtained.

The product fraction is again distilled under reduced pressure over the same column. A uniform fraction is obtained at 110 °C (15 hPa).

Yield: 0.55 g (3.5 mmol, 35%);  $n_D^{20} = 1.4578$ , optical rotation: +15.1° (c = 1, CHCl<sub>3</sub>)

**Comments**

If not fermenting yeast suspensions are used, the batch can possibly be fungous. The filtered solution can not be stored for long and should therefore be immediately extracted. Therefore the used water must be boiled before. During reaction, all reaction containers should be as completely as possible covered.

During the extraction, the volume of the aqueous phase increases by 5-7%! To secure a continuous extraction, an appropriate reserve volume must be available in the extraction apparatus.

**Waste management****Recycling**

The evaporated diethyl ether is collected and redistilled.

**Waste disposal**

Waste	Disposal
filter residue with Celite	solid waste, free from mercury,
aqueous phase from extraction	solvent water mixtures, halogen free
fore-run from distillation	organic solvents, halogen free
distillation residue	organic solvents, halogen free
sodium sulfate	solid waste, free from mercury

**Time**

Preparation of reaction solution: 1 hour

Stirring: two days

Work up: 4 hours

**Break**

Before distillation

**Degree of difficulty**

Medium

**Instruction (batch scale 100 mmol)****Equipment**

10 L beaker, addition funnel, stirring motor with propeller stirrer, thermostat, rotary evaporator, heatable magnetic stirrer, magnetic stir bar, distillation apparatus, 10 cm packed column, suction flask, Buechner funnel ( $\varnothing$  26 cm), apparatus for continuous extraction of liquids, oil bath

**Substances**

fresh yeast (baker's yeast)	780 g
cyclopentanone-2-carboxylic acid ethyl ester (purity > 95%) (bp 109 °C/20 hPa; product from NOP 4023)	15.6 g (100 mmol)
water (boiled)	5 L
diethyl ether (bp 35 °C)	1 L
Celite 545 (filter help)	
sodium sulfate for drying	

**Reaction**

780 g fresh yeast are suspended under slowly stirring and in portions in a 10 L beaker in 5 L cold boiled water and brought to a temperature of 30 °C. After the complete suspension of the yeast, 15.6 g (100 mmol) cyclopentanone-2-carboxylic acid ethyl ester are added dropwise with an addition funnel within 30 minutes. The beaker is covered with aluminium foil and the reaction mixture is slowly stirred at 30 °C for two days.

**Work up**

To the reaction solution 200 g Celite are added and the mixture is stirred for one hour. A Buechner funnel ( $\varnothing$  26 cm) is charged with a 2 cm layer of moisted Celite and the solution is filtered through the moisted filter medium into a suction flask. If a smaller Buechner funnel is used, the mixture has to be filtered in several portions with a fresh filter medium for each filtration. The filtrate is extracted in an apparatus for continuous extraction of liquids with 1 L diethyl ether. After about 20 hours the extraction is completed. The extract is dried over sodium sulfate, the drying agent is filtered off and the solvent is evaporated at a rotary

evaporator. The residue is distilled under reduced pressure (about 20 hPa) over a 10 cm packed column.

1. fraction 50-90 °C: fore-run

2. fraction 94-112 °C: product

Further fractions are not obtained.

The product fraction is again distilled under reduced pressure over the same column. A uniform fraction is obtained at 110 °C (15 hPa).

Yield: 8.69 g (55.3 mmol, 55%);  $n_D^{20} = 1.4578$ , optical rotation: +15.1° (c = 1, CHCl<sub>3</sub>)

### Comments

If not fermenting yeast suspensions are used, the batch can possibly be fungous. The filtered solution can not be stored for long and should therefore be immediately extracted. Therefore the used water must be boiled before. During reaction, all reaction containers should be as completely as possible covered.

During the extraction, the volume of the aqueous phase increases by 5-7%! To secure a continuous extraction, an appropriate reserve volume must be available in the extraction apparatus.

### Waste management

#### Recycling

The evaporated diethyl ether is collected and redistilled.

#### Waste disposal

Waste	Disposal
filter residue with Celite	solid waste, free from mercury,
aqueous phase from extraction	solvent water mixtures, halogen free
fore-run from distillation	organic solvents, halogen free
distillation residue	organic solvents, halogen free
sodium sulfate	solid waste, free from mercury

### Time

Preparation of reaction solution: 1 hour

Stirring: two days

Work up: 5 hours

### Break

Before distillation

### Degree of difficulty

Difficult

## Analytics

### Reaction monitoring with TLC or GC

Sample preparation:

10 mL reaction solution are separated from the yeast through zentrifugation or filtration over Celite. The filtrate is extracted with 10 mL diethyl ether. The extract is dried with sodium sulfate and analyzed with TLC or GC.

TLC-conditions:

adsorbant: TLC-aluminium foil (Kieselgel 60)  
 eluent: cyclohexane/diethyl ether 10 : 4  
 visualizing: After the solvent is evaporated, the chromatogram is dipped in a 2% ninhydrin solution and then dried with a hot-air dryer.  
 The educt is red-violet, the product blue-grey.

R<sub>f</sub> (educt) 0.74

R<sub>f</sub> (product) 0.40

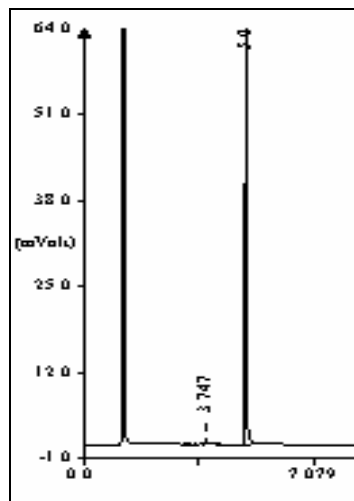
## GC

GC-conditions:

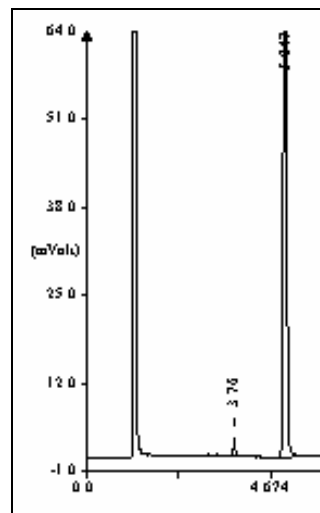
column: DB-1, 28 m, internal diameter 0.32 mm, film 0.25 µm  
 inlet: on-column-injection  
 carrier gas: hydrogen (40 cm/s)  
 oven: 100 °C isotherme  
 detector: FID, 270 °C

Percent concentration was calculated from peak areas.

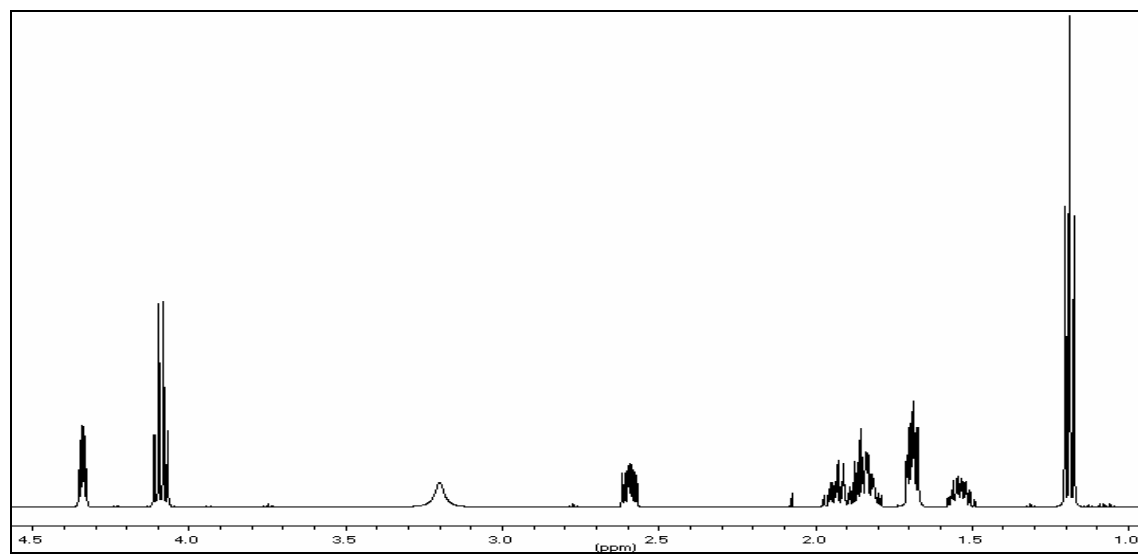
### GC of the product after 1st distillation



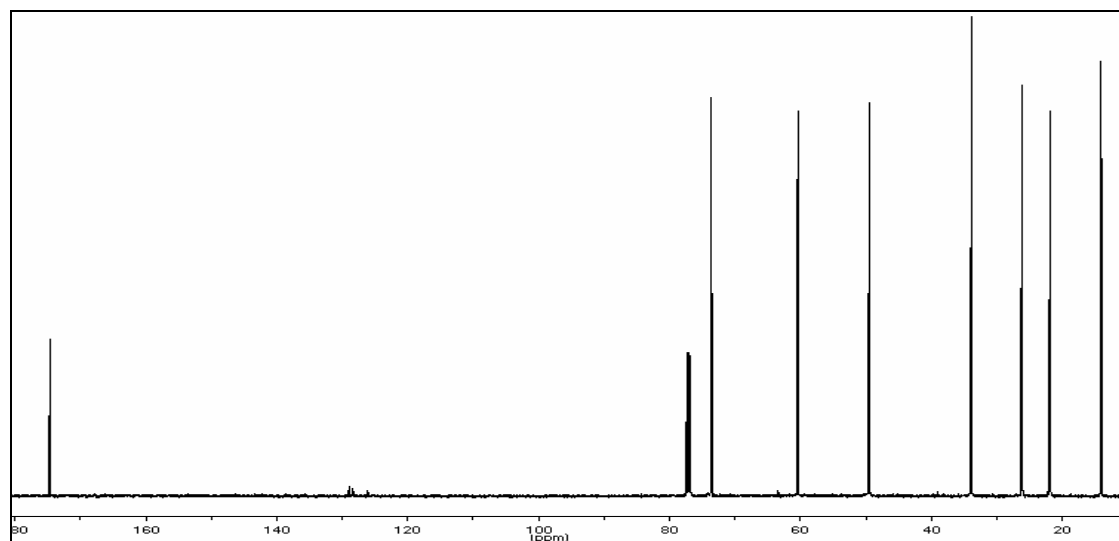
### GC of the product after 2<sup>nd</sup> distillation



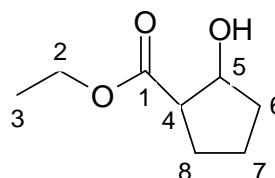
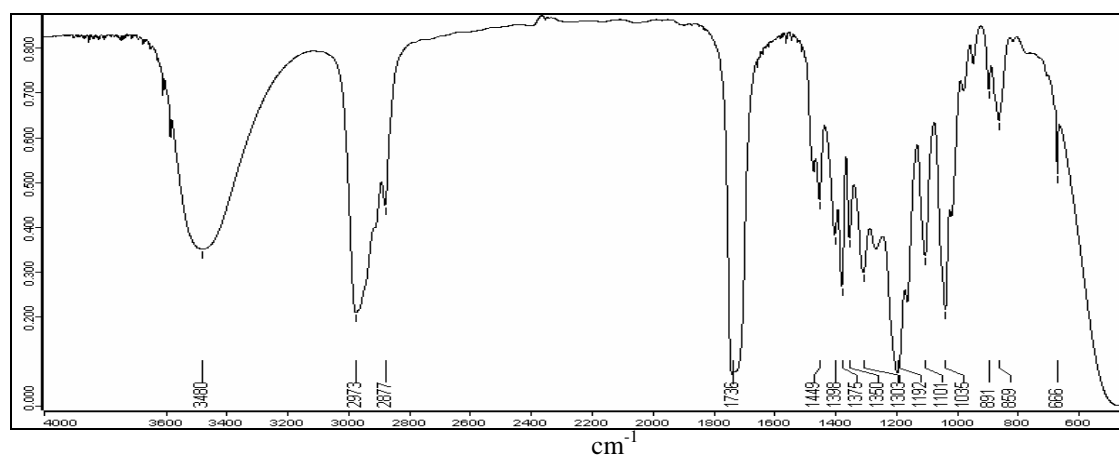
Retention time (min)	Substance	Peak area %	
		After 1st distillation	After 2nd distillation
5.1	Produkt	98.9	99.4

**$^1\text{H}$  NMR spectrum of the pure product (500 MHz,  $\text{CDCl}_3$ )**

$\delta$ (ppm)	Multiplicity	Number of H	Assignment
1.19	t	3	$\text{O-CH}_2\text{-CH}_3$
1.5 – 2.0	m	6	$\text{CH}_2$ Ring
2.54 - 2.65	m	1	$\text{CH-CO}$
3.2	br.s	1	$\text{OH}$
4.08	q	2	$\text{O-CH}_2$
4.34	m	1	$\text{HO-CH}$

**$^{13}\text{C}$  NMR spectrum of the pure product (125.8 MHz,  $\text{CDCl}_3$ )**

$\delta$ (ppm)	Assignment
174.6	C-1
73.6	C-5
60.4	C-2
49.5	C-4
33.9	C-6
26.1	C-8
21.8	C-7
14.0	C-3
76.5-77.5	solvent

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

( $\text{cm}^{-1}$ )	Assignment
3480	O-H-valence
2973, 2877	C-H-valence, alkane
1736	C=O-valence, ester