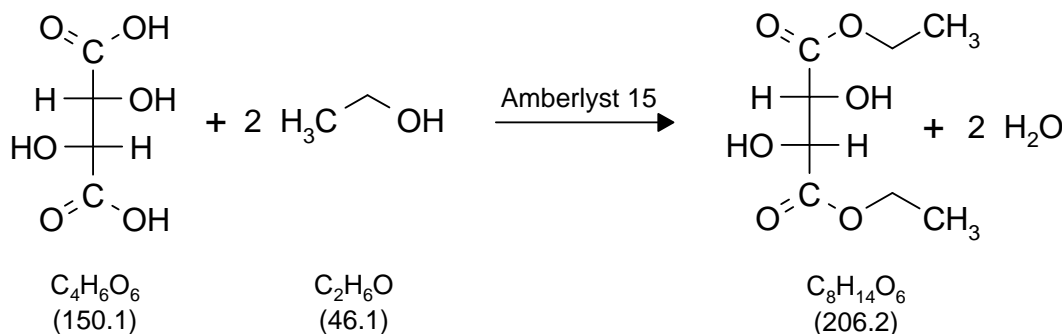


2011 Acid catalyzed reaction of L-(+)-tartaric acid with ethanol to L-(+)-tartaric acid diethyl ester



Classification

Reaction types and substance classes

reaction of the carbonyl group in carboxylic acids, esterification

carboxylic acid, alcohol, carboxylic acid ester, ion exchanger, acid catalyst

Work methods

heating under reflux, filtering, evaporating with rotary evaporator, distilling under reduced pressure, stirring with magnetic stir bar, heating with oil bath, use of an ice cooling bath

Instruction (batch scale 100 mmol)

Equipment

250 mL round-bottom flask, reflux condenser, drying tube, heatable magnetic stirrer, magnetic stir bar, electronic temperature control, rotary evaporator, glass funnel (large), distillation apparatus, vacuum pump, oil bath, ice bath

Substances

L-(+)-tartaric acid (mp 170 °C)	15.0 g (100 mmol)
ethanol (bp 78 °C) (dry)	57.6 g (73.0 mL, 1.25 mol)
Amberlyst 15 (strongly acidic ion exchanger)	1.0 g

Reaction

In a dry 250 mL round-bottom flask with magnetic stir bar and reflux condenser with drying tube 1.0 g Amberlyst 15, 57.6 g (73.0 mL, 1.25 mol) dry ethanol and 15.0 g (100 mmol) L-(+)-tartaric acid are heated under stirring for 48 hours under reflux. The stirrer should stir only at a slow rate, so that a delay in boiling is avoided; too strong stirring can cause, that the amberlyst is crushed and then can hardly be filtered.

Work up

The reaction mixture is cooled in an ice bath, finally without stirring, so that the amberlyst sediments well. The solution is filtered over a large folded filter into a round bottom flask. The excessive ethanol is rapidly and as completely as possible evaporated at a rotary evaporator, finally at about 20 hPa. The crude product in form of a slightly oily colourless liquid remains as residue.

Crude yield: 19.1 g

The crude product is transferred into a 50 mL round bottom flask and is fractional distilled at about 10^{-1} hPa in a small distillation apparatus. Normally, the product distills at a very constant boiling temperature, the single fractions hardly vary in their refractive index. The pressure must be low enough to avoid an oil bath temperature above 165 °C. Above this temperature decomposition reactions occur whereby volatile substances are formed.

Yield: 15.7 g (76.1 mmol, 76%); bp 95-98 °C ($2 \cdot 10^{-1}$ hPa), colourless liquid; GC-purity 98.4%; $[\alpha]_D^{20} = + 8.1^\circ$ (undiluted)

3.30 g of a viscous light yellow mass remains as residue, which solidifies during cooling down to a glassy solid, but is soluble in warm water.

Comments

Under the influence of acids, tartaric acid can cleave off water and then CO₂ and so react to pyruvic acid. Under the here described reaction conditions no CO₂ is formed. With barium hydroxide solution in a bubble counter on the reflux condenser no CO₂ could be detected.

Waste management**Recycling**

The evaporated ethanol is collected and redistilled.

Waste disposal

Waste	Disposal
distillation residue	dissolve in warm water, then: solvent water mixtures, halogen free
Amberlyst 15	solid waste, free from mercury

Time

4-5 hours without the time for heating under reflux (filtration of amberlyst takes possibly a long time)

Break

After the evaporation of ethanol

Degree of difficulty

Easy

Instruction (batch scale 500 mmol)

Equipment

1 L round bottom flask, reflux condenser, drying tube, heatable magnetic stirrer, magnetic stir bar, electronic temperature control, rotary evaporator, glass funnel (large), distillation apparatus, vacuum pump, oil bath, ice bath

Substances

L-(+)-tartaric acid (mp 170 °C)	75.0 g (500 mmol)
Ethanol (bp 78 °C) (dry)	288 g (365 mL, 6.25 mol)
Amberlyst 15 (strongly acidic ion exchanger)	5.0 g

Reaction

In a dry 1 L round bottom flask with magnetic stir bar and reflux condenser with drying tube 5.0 g Amberlyst 15, 288 g (365 mL, 6.25 mol) dry ethanol and 75.0 g (500 mmol) L-(+)-tartaric acid are heated under stirring for 48 hours under reflux. The stirrer should stir only at a slow rate, so that a delay in boiling is avoided; too strong stirring can cause, that the amberlyst is crushed and then can hardly be filtered.

Work up

The reaction mixture is cooled in an ice bath, finally without stirring, so that the amberlyst sediments well. The solution is filtered over a large folded filter into a round bottom flask. The excessive ethanol is rapidly and as completely as possible evaporated at a rotary evaporator, finally at about 20 hPa. The crude product in form of a slightly oily colourless liquid remains as residue.

Crude yield: 95.5 g

The crude product is transferred into a 250 mL round bottom flask and is fractional distilled at about 10^{-1} hPa. Normally, the product distills at a very constant boiling temperature, the single fractions hardly vary in their refractive index. The pressure must be low enough to avoid an oil bath temperature above 165 °C. Above this temperature decomposition reactions occur whereby volatile substances are formed.

Yield: 78.5 g (381 mmol, 76%); bp. 95-98 °C ($2 \cdot 10^{-1}$ hPa), colourless liquid; GC-purity 98.4%; $[\alpha]_D^{20} = + 8.1^\circ$ (undiluted)

16.5 g of a viscous light yellow mass remains as residue, which solidifies during cooling down to a glassy solid, but is soluble in warm water.

Comments

Under the influence of acids, tartaric acid can cleave off water and then CO₂ and so react to pyruvic acid. Under the here described reaction conditions no CO₂ is formed. With barium hydroxide solution in a bubble counter on the reflux condenser no CO₂ could be detected.

Waste management**Recycling**

The evaporated ethanol is collected and redistilled.

Waste disposal

Waste	Disposal
distillation residue	dissolve in warm water, then: solvent water mixtures, halogen free
Amberlyst 15	solid waste, free from mercury

Time

4-5 hours without the time for heating under reflux (filtration of amberlyst takes possibly a long time)

Break

After the evaporation of ethanol

Degree of difficulty

Easy

Instruction (batch scale 20 mmol)**Equipment**

50 mL round bottom flask, reflux condenser, drying tube, heatable magnetic stirrer, magnetic stir bar, electronic temperature control, rotary evaporator, glass funnel, micro distillation apparatus, vacuum pump, oil bath, ice bath

Substances

L-(+)-tartaric acid (mp 170 °C)	3.0 g (20 mmol)
ethanol (bp 78 °C) (dry)	11.5 g (14.6 mL, 0.250 mol)
Amberlyst 15 (strongly acidic ion exchanger)	0.2 g

Reaction

In a dry 50 mL round bottom flask with magnetic stir bar and reflux condenser with drying tube 0.2 g Amberlyst 15, 11.5 g (14.6 mL, 0.250 mol) dry ethanol and 3.0 g (20 mmol) L-(+)-tartaric acid are heated under stirring for 48 hours under reflux. The stirrer should stir only at a slow rate, so that a delay in boiling is avoided; too strong stirring can cause, that the amberlyst is crushed and then can hardly be filtered.

Work up

The reaction mixture is cooled in an ice bath, finally without stirring, so that the amberlyst sediments well. The solution is filtered over a folded filter into a round bottom flask. The excessive ethanol is rapidly and as completely as possible evaporated at a rotary evaporator, finally at about 20 hPa. The crude product in form of a slightly oily colourless liquid remains as residue.

Crude yield: 3.82 g

The crude product is transferred into a 10 mL round bottom flask and is fractional distilled at about 10^{-1} hPa in a small distillation apparatus. Normally, the product distills at a very constant boiling temperature, the single fractions hardly vary in their refractive index. The pressure must be low enough to avoid an oil bath temperature above 165 °C. Above this temperature decomposition reactions occur whereby volatile substances are formed.

Yield: 2.85 g (13.8 mmol, 69%); bp. 95-98 °C ($2 \cdot 10^{-1}$ hPa), colourless liquid; GC-purity 98.4%; $[\alpha]_D^{20} = + 8.1^\circ$ (undiluted)

0.920 g of a viscous light yellow mass remains as residue, which solidifies at cooling down to a glassy solid, but is soluble in warm water.

Comments

Under the influence of acids, tartaric acid can cleave off water and then CO_2 and so react to pyruvic acid. Under the here described reaction conditions no CO_2 is formed. With barium hydroxide solution in a bubble counter on the reflux condenser no CO_2 could be detected.

Waste management

Recycling

The evaporated ethanol is collected and redistilled.

Waste disposal

Waste	Disposal
distillation residue	dissolve in warm water, then: solvent water mixtures, halogen free
Amberlyst 15	solid waste, free from mercury

Time

3 hours without the time for heating under reflux

Break

After the evaporation of ethanol

Difficulty

Easy

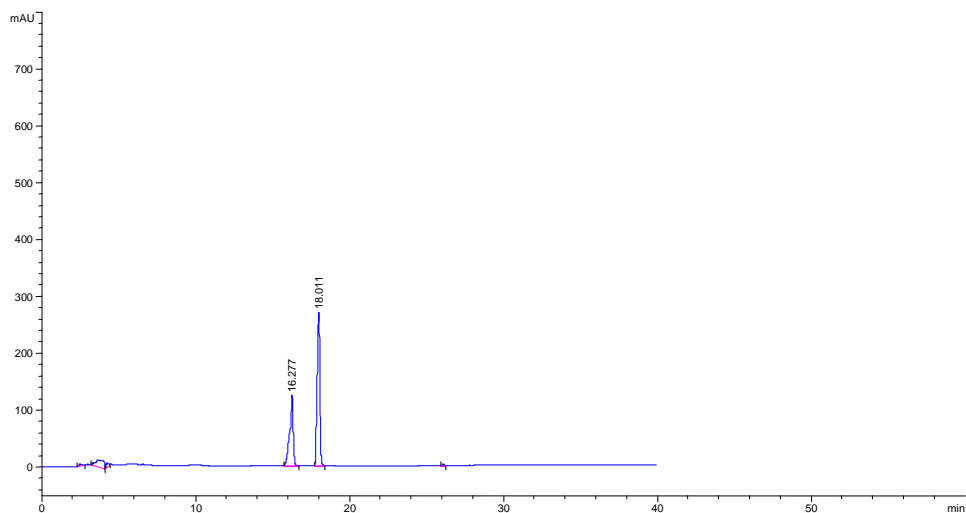
Analytics

Reaction monitoring with HPLC

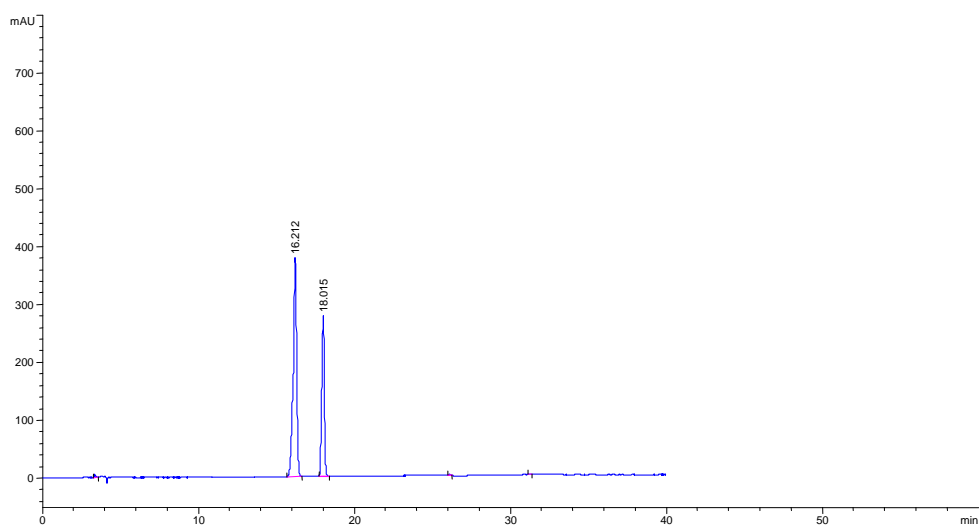
Under the used HPLC-conditions, tartaric acid could not be clearly analyzed in presence of tartaric acid diethyl ester and. Therefore the tartaric acid diethyl ester was analyzed quantitatively by using acetanilide as internal standard (tracer) in the samples.

Sample preparation and HPLC-conditions see next page.

HPLC of a sample after 6 hours reaction time



HPLC of a sample after 96 hours reaction time



Retention time (min)	Substance
16.2	tartaric acid diethyl ester
18.0	acetanilide (tracer)

Sample preparation for batch scale 100 mmol:

Instead of the 250 mL one-neck flask a two- or three-neck flask is used for the reaction, so that the samples could be taken through the second neck. For each sample the lab jack with the oil bath is lowered. When the reaction solution has stopped boiling, the stirrer is switched off, one waits 1 minute, until the amberlyst has sedimented in the flask. Using a pipette, one takes 5 mL from the solution and fills it into a test tube, which is closed immediately and cooled in the ice bath. Then it is stored in the freezer until measuring.

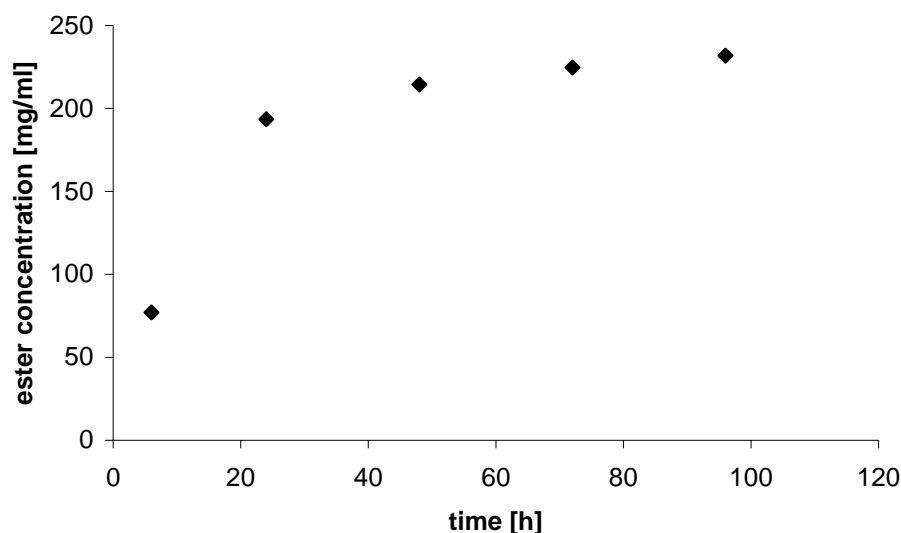
As tracer solution serves a solution of 1.11 mg acetanilide in 10 mL dry ethanol.

Shortly before the measuring, the sample solution is diluted 1:20 with ethanol and 1 mL of the diluted sample solution is mixed with 1 mL of the tracer solution. 15 μ L of this solution are injected.

HPLC-conditions:

column: Phenomenex Luna C18; Particle size 3 μ m, length 150 mm, internal diameter 4.6 mm
 column temperature: 25 $^{\circ}$ C
 injection volume: 15 μ L
 gradient: 0 min 3% MeOH + 97% H₂O
 30 min 98% MeOH + 2% H₂O
 40 min 98% MeOH + 2% H₂O
 flow: 0.6 mL/min
 wave length: 220 nm

Concentration of tartaric acid diethyl ester in the HPLC-sample solutions in dependence to the reaction time



Reaction monitoring through preparative work up after different reaction times

Reaction time (h)	Batch scale (mmol)	Isolated yield(%)
3	100	4
24	500	55
48	500	76
48	100	76
72	100	73

Determination of the tartaric acid diethyl ester in the isolated crude product with HPLC

(work up after 48 hours)

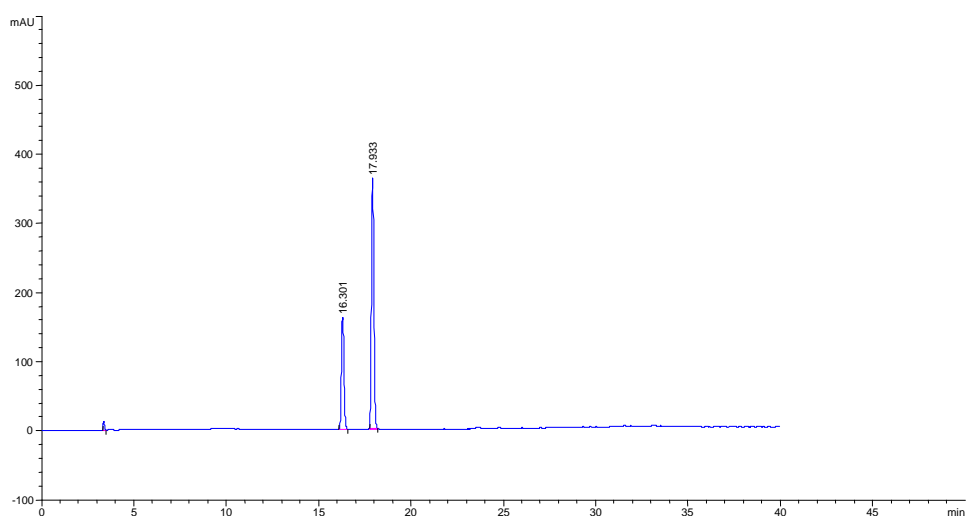
The concentration of tartaric acid diethyl ester in the crude product was analyzed quantitatively. Acetanilide was used as internal standard.

Sample preparation:

For the tracer solution 1 mg acetanilide is dissolved in 10 mL methanol. From the crude product a solution of 2 mg per mL methanol is prepared. For measuring 1 mL tracer solution and 1 mL sample solution are mixed. 15 μ L from this solution are injected.

HPLC- conditions as described under reaction monitoring with HPLC

HPLC of the isolated crude product



Retention time (min)	Substance
16.3	tartaric acid diethyl ester
17.9	acetanilide (tracer)

Result of the quantitative evaluation from different batches:

The mass of tartaric acid diethyl ester found in the crude product is equivalent on average to a yield of 75% (variation +/- 7%).

GC

Sample preparation: 11.4 mg substance are dissolved in 0.5 mL dichloromethane, injected volume: 0.2 μ L.

GC-conditions:

column: Zebron ZB-1, length 15 m, internal diameter 0.25 mm, Film 0.25 μ m, (Phenomenex, Torrance, CA, USA)

inlet: injector temperature 250 $^{\circ}$ C; split injection; injected volume 0.2 μ L

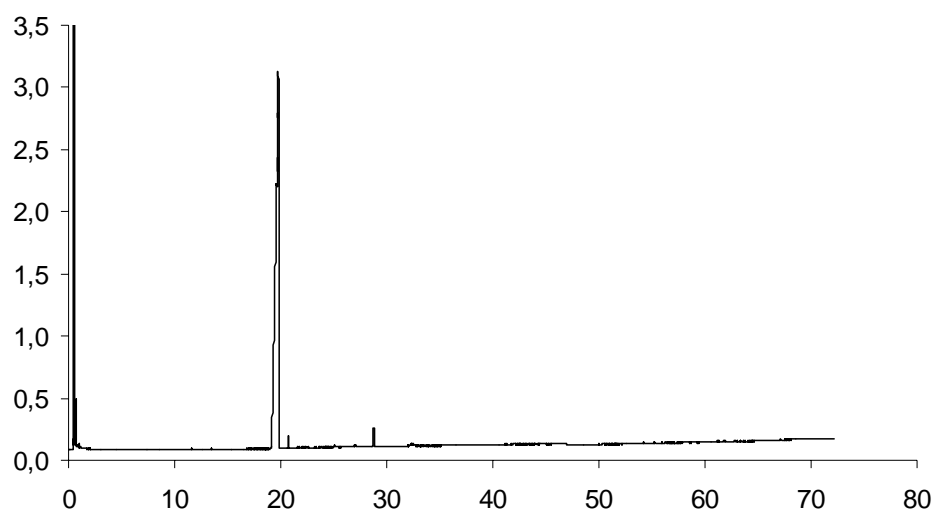
carrier gas: He, pre-column pressure 90 kPa

oven: start temperature 30 $^{\circ}$ C (4 min), 20 $^{\circ}$ C/min to 240 $^{\circ}$ C (7 min)

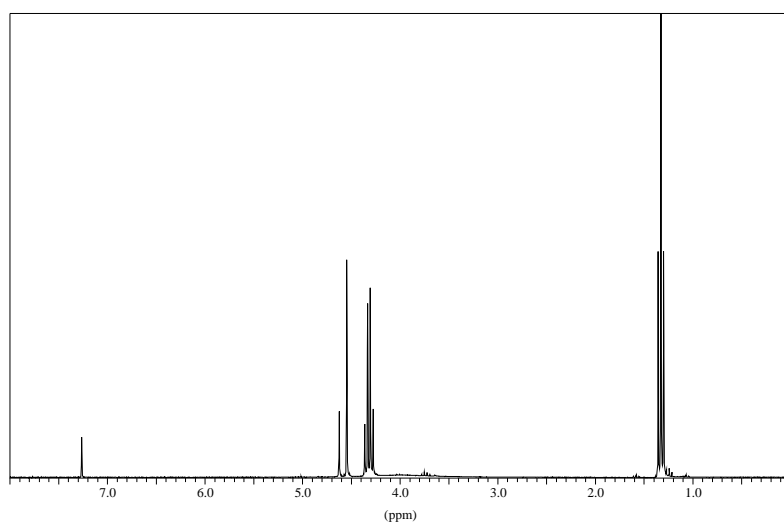
detector: FID, 230 $^{\circ}$ C, H₂ 30.8 mL/min; synth. air 361 mL/min; make-up-gas N₂, flow 14.9 mL/min (59 kPa)

integration: integrator 4290 (Thermo Separation Products)

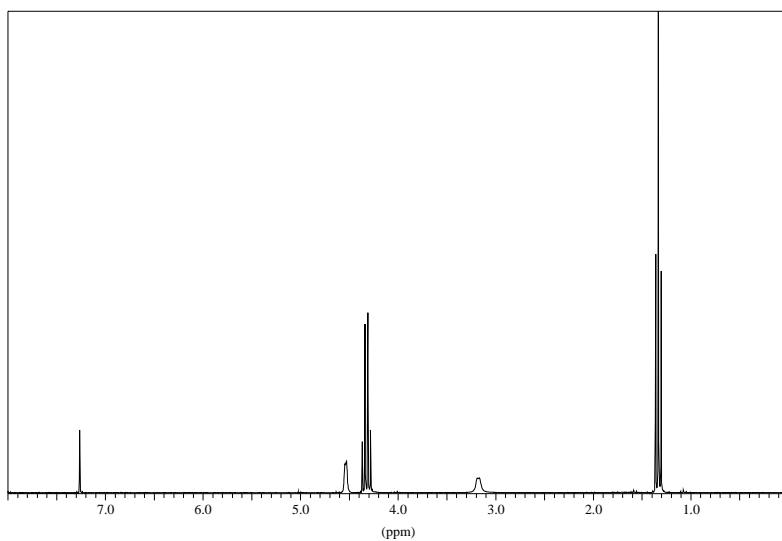
Percent concentration was calculated from peak areas.

GC of the pure product

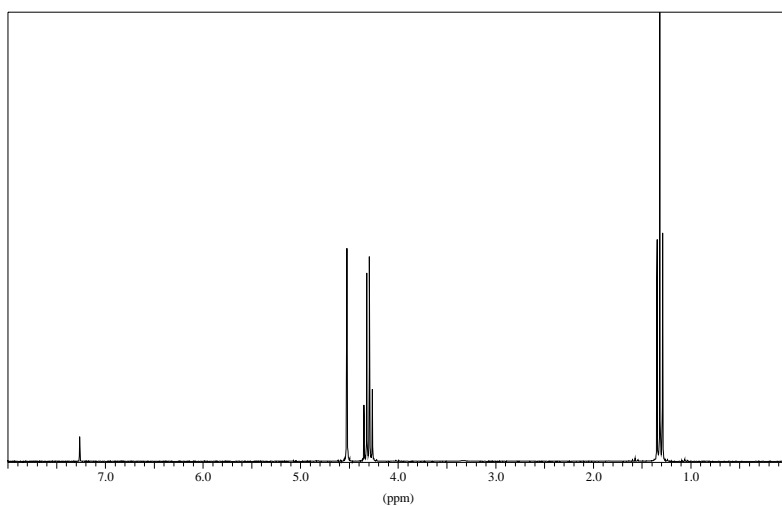
Retention time(min)	Substance	Peak area %
19.8	tartaric acid diethyl ester	98.4
28.8	unidentified	1.6

¹H NMR spectrum of the pure product (250 MHz, CDCl₃)

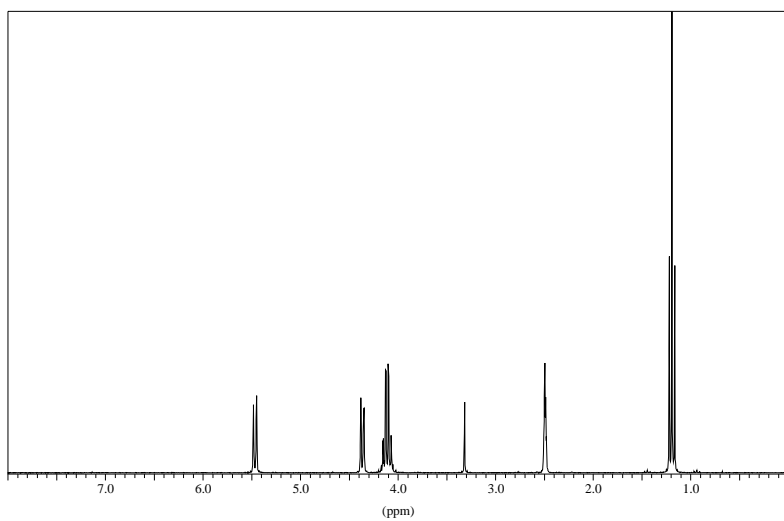
δ (ppm)	Multiplicity	Number of H	Assignment
1.33	T	6	CH ₃
4.32	Q	4	CH ₂
4.54	S	2	CH – OH
4.62	S		OH
7.26			solvent.

^1H NMR spectrum of the pure product (250 MHz, CDCl_3)

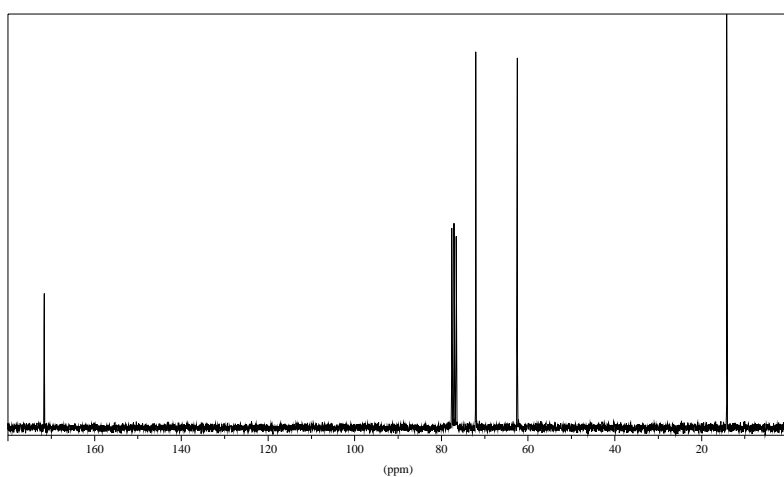
δ (ppm)	Multiplicity	Number of H	Assignment
1.33	t	6	CH_3
3.18	m	2	OH
4.32	q	4	CH_2
4.54	s	2	CH – OH
7.26			solvent

 ^1H NMR spectrum of the pure product (250 MHz, CDCl_3) (after shaking with D_2O)

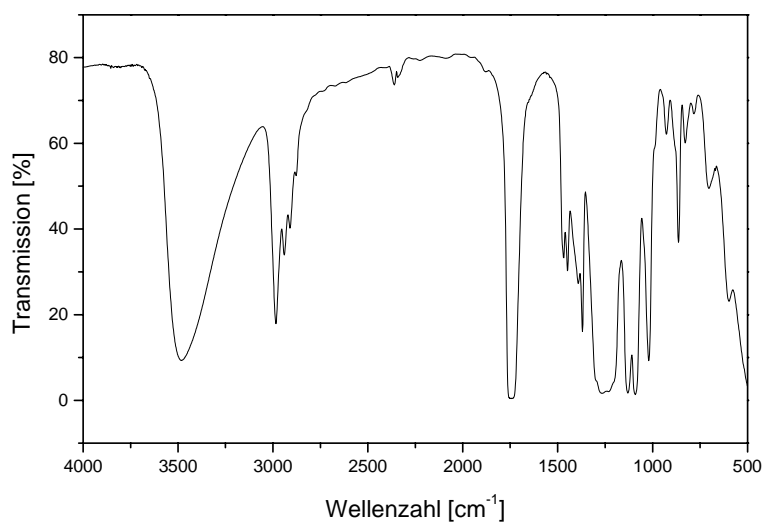
δ (ppm)	Multiplicity	Number of H	Assignment
1.33	t	6	CH_3
4.32	q	4	CH_2
4.54	s	2	CH – OH
7.26			solvent

^1H NMR spectrum of the pure product (250 MHz, DMSO-D_6)

δ (ppm)	Multiplicity	Number of H	Assignment
1.19	t	6	CH_3
2.49	m		DMSO
3.32	s		H_2O
4.31	q	4	CH_2
4.37	d	2	$\text{CH} - \text{OH}$
5.47	d	2	$\text{CH} - \text{OH}$

 ^{13}C NMR spectrum of the pure product (250 MHz, CDCl_3)

δ (ppm)	Assignment
14.14	CH_3
62.48	CH_2
72.05	$\text{CH} - \text{OH}$
171.59	$\text{CO} - \text{O}$
76.5-77.5	solvent

IR spectrum of the pure product (film)

(cm ⁻¹)	Assignment
3500	O – H – valence
2985, 2940, 2910,	C – H – valence, alkane
1745	C = O – valence

The IR-spectrum of the crude product does not differ from that of the pure product.