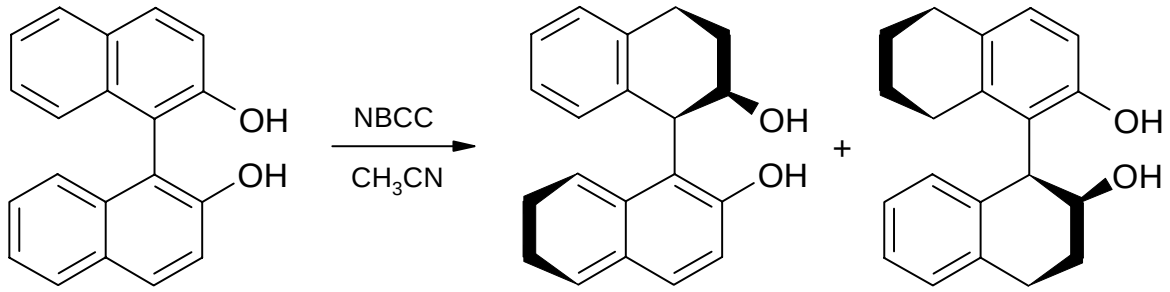
4014 Enantiomeric resolution of (R)- and (S)-2,2'-dihydroxy-1,1'-binaphthyl ((R)- and (S)-1,1-bi-2-naphthol)



$C_{20}H_{14}O_2$ (286.3) | $C_{26}H_{29}ClN_2O$ (421.0) | *R*-enantiomer | *S*-enantiomer

Classification

Reaction types and substance classes
enantiomeric resolution
naphthol

Work methods
heating under reflux, stirring with magnetic stir bar, evaporating with rotary evaporator, filtering, extracting, shaking out, recrystallizing, use of an ice cooling bath, heating with oil bath

for batch scale 100 mmol additional:
column chromatography

Instruction (batch scale 10 mmol)

Equipment
100 mL round bottom flask, heatable magnetic stirrer, magnetic stir bar, reflux condenser, suction flask, Buechner funnel (Ø 5.5 cm), separating funnel, rotary evaporator, ice bath, oil bath

Substances

1,1'-bi-2-naphthol (racemate) (mp 215-218 °C, product from NOP 4016)	2.86 g (10.0 mmol)
(-)-N-benzylcinchonidinium chloride (NBCC) (product from NOP 4012)	2.32 g (5.50 mmol)
acetonitrile (bp 82 °C)	50 mL
methanol (bp 65 °C)	30 mL

acetic acid ethyl ester (bp 77 °C)	90 mL
2 M hydrochloric acid	60 mL
sodium chloride	about 7 g (for 20 mL saturated aqueous solution)
sodium carbonate	
sodium sulfate for drying	

Reaction

2.86 g (10.0 mmol) 1,1'-bi-2-naphthol and 2.32 g (5.50 mmol) NBCC are filled in a 100 mL round bottom flask. 30 mL acetonitrile are added and the mixture is heated under stirring for 3 hours under reflux.

Work up

Initially, the reaction solution is cooled down to room temperature and then cooled in an ice bath for 30 minutes. The crystals are sucked off over a Buechner funnel and washed two times with 10 mL acetonitrile each. Filtrate and washing solutions are combined, from this solution the *S*-enantiomer is isolated. The *R*-enantiomer is isolated from the filter residue.

Isolation of (*R*)-1,1'-bi-2-naphthol:

The filter residue (4.22 g) is heated in 20 mL methanol under stirring for 2 hours under reflux and then cooled down to room temperature. The crystals are sucked off over a Buechner funnel and are washed with 10 mL methanol.

Crude yield: 3.03 g

To the crude product 40 mL acetic acid ethyl ester and 20 mL 2 M hydrochloric acid are added and the mixture is stirred for 1 hour at room temperature. Then the organic phase is separated with a separating funnel and shaken out again with 20 mL 2 M hydrochloric acid. The combined acidic aqueous phases are stored for the moment. The organic phase is dried over sodium sulfate. After filtering off the drying agent the solvent is evaporated at a rotary evaporator. As product remains a crystalline residue.

Yield: 1.15g (4.02 mmol, 80%); light-brown solid, mp 206-208 °C; $[\alpha]_D^{20}$ = +32 °(THF, c = 1)

The NBCC is recovered from the acidic aqueous phase (see below).

Isolation of (*S*)-1,1'-bi-2-naphthol:

The solvent is evaporated from the combined acetonitrile phases at the rotary evaporator.

Crude yield: 1.78 g

To the crude product 50 mL acetic acid ethyl ester and 20 mL 2 M hydrochloric acid are added and the mixture is stirred for 15 minutes at room temperature. Then the organic phase is separated with a separating funnel, shaken out with 20 mL saturated sodium chloride solution and dried over sodium sulfate. After filtering off the drying agent the solvent is evaporated at a rotary evaporator. As product remains a crystalline residue.

Yield: 1.30 g (4.54 mmol, 91%); light-brown solid, mp 204-205 °C;$[\alpha]_D^{20}$ = -32 °(THF, c = 1)

Recovering of (-)-N-benzylcinchonidinium chloride (NBCC):
The aqueous acidic phase from the isolation of (*R*)-1,1'-bi-2-naphthol is adjusted to pH 8 in a tall beaker under stirring with sodium carbonate (Attention: gas development!). NBCC precipitates as white solid. The crystals are sucked off, washed with 10 mL water and dried.
Yield: 1.70 g (72%); $[\alpha]_D^{20}$ = -172 ° (H_2O, c = 0.4)

Waste management

Recycling
The evaporated acetonitrile and the evaporated acetic acid ethyl ester are collected and redistilled.

Waste disposal

Waste	Disposal
methanol	organic solvents, halogen free
aqueous phases	neutralize, then: solvent water mixtures, containing halogen
sodium sulfate	solid waste, free from mercury

Time
7-8 hours

Break
Before work up and after heating with methanol

Degree of difficulty
Medium

Instruction (batch scale 100 mmol)

Equipment
500 mL round-bottom flask, heatable magnetic stirrer, magnetic stir bar, reflux condenser, suction flask, Buechner funnel (Ø 10 cm), separating funnel, rotary evaporator, chromatography column (length 30 cm, Ø 3 cm), ice bath, oil bath

Substances

1,1'-bi-2-naphthol (racemate) (mp 215-218 °C, product from NOP 4016)	28.6 g (100 mmol)
(-)-N-benzylcinchonidinium chloride (NBCC) (product from NOP 4012)	23.2 g (550 mmol)
acetonitrile (bp 82 °C)	325 mL
methanol (bp 65 °C)	160 mL
acetic acid ethyl ester (bp 77 °C)	1050 mL
2 M hydrochloric acid	280 mL
sodium chloride	about 35 g (for 100 mL saturated aqueous solution)

sodium carbonate
sodium sulfate for drying

Reaction
28.6 g (100 mmol) 1,1'-Bi-2-naphthol and 23.2 g (5.50 mmol) NBCC are filled in a 500 mL round bottom flask. 250 mL acetonitrile are added and the mixture is heated under stirring for 4 hours under reflux.

Work up
Initially, the reaction solution is cooled down to room temperature and then cooled in an ice bath for 30 minutes. The crystals are sucked off over a Buechner funnel and washed two times with 25 mL acetonitrile each. Filtrate and washing solutions are combined, from this solution the *S*-enantiomer is isolated. The *R*-enantiomer is isolated from the filter residue.

Isolation of (*R*)-1,1'-bi-2-naphthol:
The filter residue (41.8 g) is heated in 100 mL methanol under stirring for 2 hours under reflux and then cooled down to room temperature. The crystals are sucked off over a Buechner funnel and are washed with 30 mL methanol.
Crude yield: 36.9 g

To the crude product 200 mL acetic acid ethyl ester and 100 mL 2 M hydrochloric acid are added and the mixture is stirred for 1 hour at room temperature. Then the organic phase is separated with a separating funnel and shaken out again with 80 mL 2 M hydrochloric acid. The combined acidic aqueous phases are stored for the moment. The organic phase is dried over sodium sulfate. After filtering off the drying agent the solvent is evaporated at a rotary evaporator. As product remains a crystalline residue.
Yield: 12.5g (43.7 mmol, 87%); brown inhomogeneous solid

For further purification, the product is dissolved in about 100 ml acetic acid ethyl ester, filtered over a silica gel column (3cm x 30 cm) and the column is eluted with further 150 mL acetic acid ethyl ester. The solvent is evaporated at a rotary evaporator and the residue is dried.
Yield: 11.4 g (39.8 mmol, 80%); light-brown solid, mp 202-204 °C;$[\alpha]_D^{20}$ = + 34°(THF, c = 1)

The NBCC is recovered from the acidic aqueous phase (see below).

Isolation of (*S*)-1,1'-bi-2-naphthol:
The solvent is evaporated from the combined acetonitrile phases at a rotary evaporator.
Crude yield: 18.1 g

To the crude product 350 mL acetic acid ethyl ester and 100 mL 2 M hydrochloric acid are added and the mixture is stirred for 15 minutes at room temperature. Then the organic phase is separated with a separating funnel, shaken out with 100 mL saturated sodium chloride solution and dried over sodium sulfate. After filtering off the drying agent the solvent is evaporated at a rotary evaporator. As product remains a crystalline residue.
Yield: 13.9 g (48.6 mmol, 97%); brown inhomogeneous solid

For further purification, the product is dissolved in about 100 ml acetic acid ethyl ester, filtered over a silica gel column (3 cm x 30 cm) and the column is eluted with further 150 mL acetic acid ethyl ester. The solvent is evaporated at a rotary evaporator and the residue is dried.

Yield: 13.2 g (46.1 mmol, 92%); light-brown solid, mp 203-204 °C;$[\alpha]_D^{20}$ = -36 °(THF, c = 1)

Recovering of (-)-N-benzylcinchonidinium chloride (NBCC):

The aqueous acidic phase from the isolation of (*R*)-1,1'-bi-2-naphthol is adjusted to pH 8 in a tall beaker under stirring with sodium carbonate (Attention: gas development!). NBCC precipitates as white solid. The crystals are sucked off, washed with 30 mL water each and dried.

Yield: 21.7 g (94%); $[\alpha]_D^{20}$ = -163 ° (H_2O, c = 0.4)

Waste management

Recycling

The evaporated acetonitrile and the evaporated acetic acid ethyl ester are collected and redistilled.

Waste disposal

Waste	Disposal
methanol	organic solvents, halogen free
aqueous phases	neutralize, then: solvent water mixtures,containing halogen
sodium sulfate	solid waste, free from mercury

Time

8-9 hours

Break

Before work up and after heating with methanol

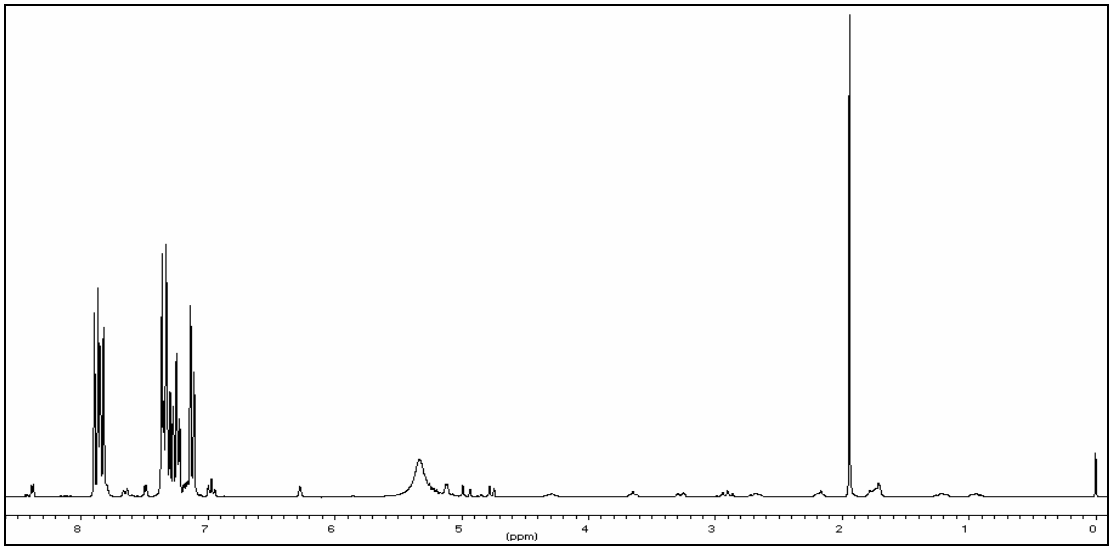
Before chromatography

Degree of difficulty

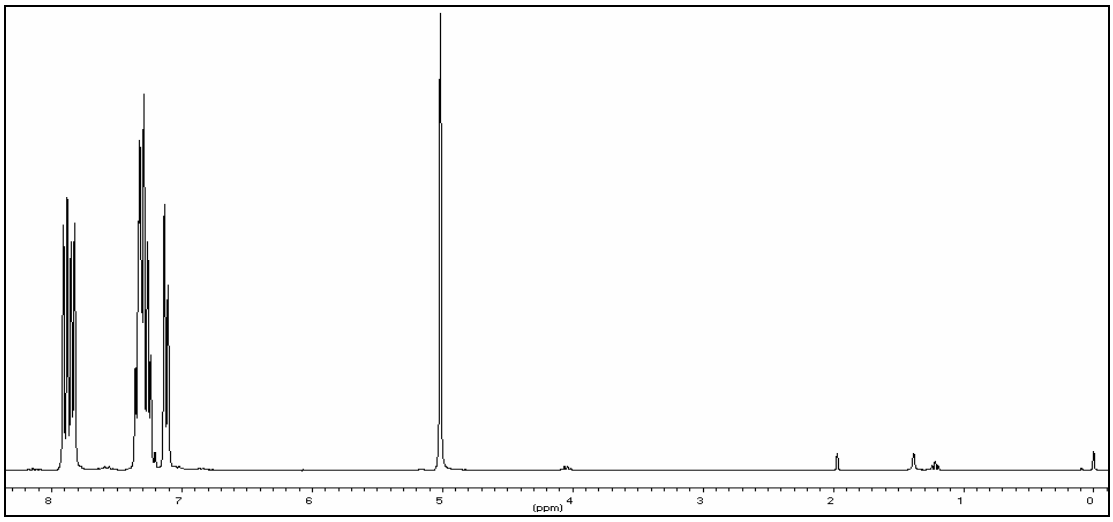
Medium

Analytics

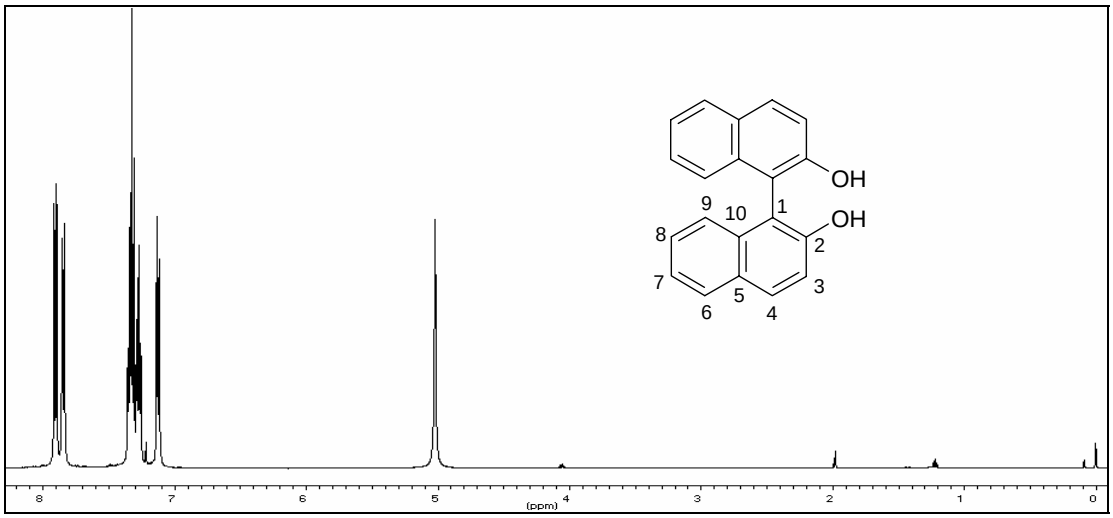
^{1}H NMR spectrum of the crude product (*S*)-1,1'-bi-2-naphthol (300 MHz, $CDCl_3$)



^{1}H NMR spectrum of the pure product (*S*)-1,1'-bi-2-naphthol (300 MHz, $CDCl_3$)

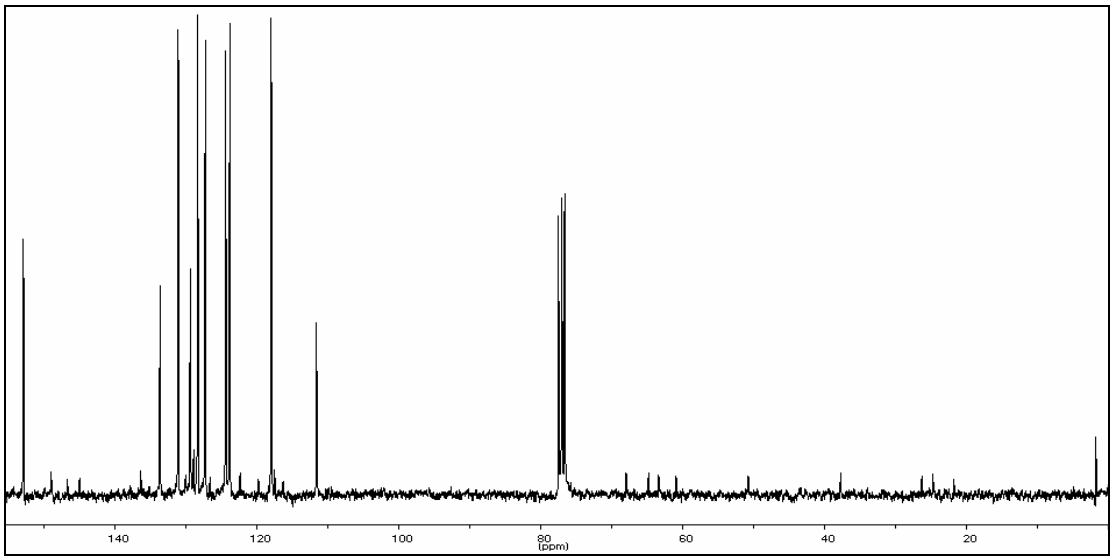


^{1}H NMR spectrum of the pure product (*R*)-1,1'-bi-2-naphthol (500 MHz, $CDCl_3$)

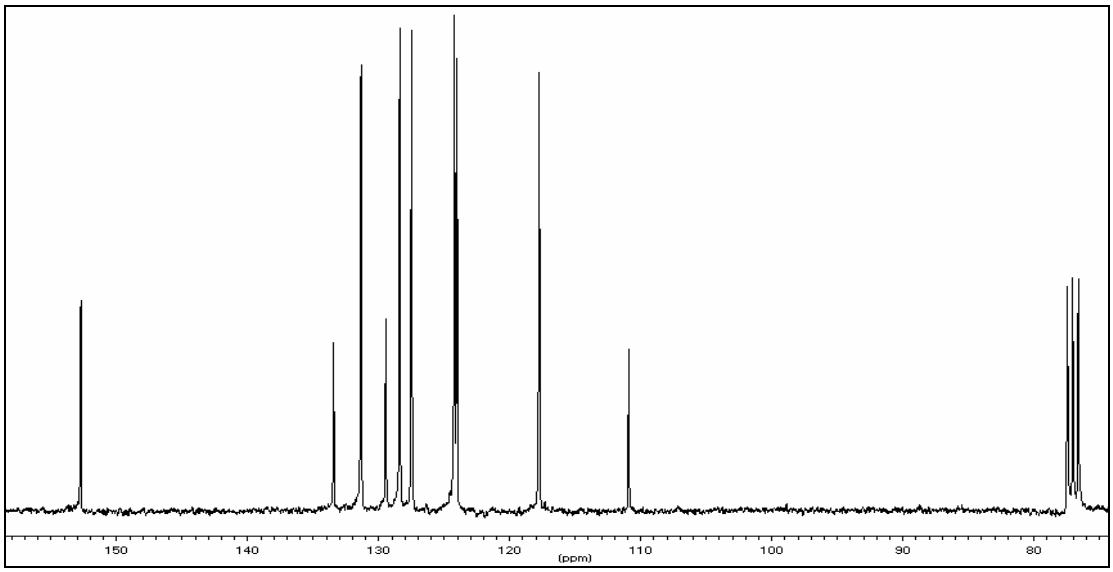


δ (ppm)	Multiplicity	Number of H	Assignment
5.05	s	2	OH
7.12	d	2	3-H
7.38-7.19	m	6	7-H, 8-H, 9-H
7.83	d	2	4-H (6-H)
7.89	d	2	6-H (4-H)

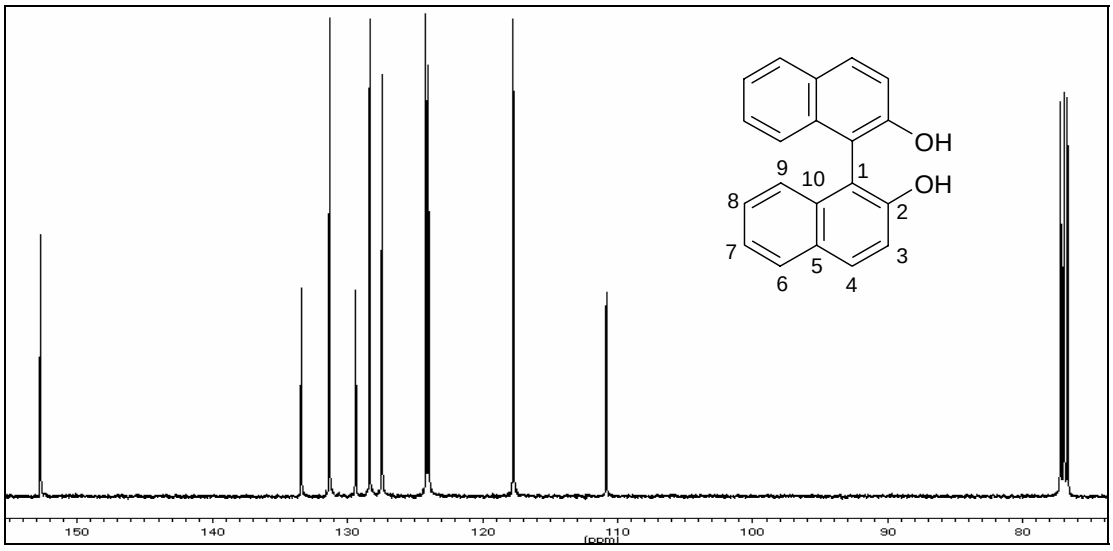
^{13}C NMR spectrum of the crude product (*S*)-1,1'-bi-2-naphthol (75.5 MHz, $CDCl_3$)



^{13}C NMR spectrum of the pure product (*S*)-1,1'-bi-2-naphthol (75.5 MHz, $CDCl_3$)



^{13}C NMR spectrum of the pure product (*R*)-1,1'-bi-2-naphthol (125.8 MHz, $CDCl_3$)



δ (ppm)	Assignment
152.7	C-2
133.4	C-10
131.3	C-5
129.4	C-4
128.3	C-6
127.4	C-8
124.2	C-9
124.0	C-7
117.7	C-3
110.9	C-1
76.5-77.5	solvent