Crystallization-Induced Chiral Inversion As The Key Step for Synthesis of (*S*)-2-Acetylthio-3-phenylpropanoic Acid From *L*-Phenylalanine

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Supporting Information

General Methods.

All starting materials and catalysts were purchased from commercial sources and were used without further purification. Magnetic resonance spectra were recorded using a Bruker DRX 360 spectrometer, with chemical shifts internally referenced to (^{1}H NMR/ ^{13}C NMR): CD_2Cl_2 at 5.32ppm/ 53.8ppm, $CDCl_3$ at 7.25ppm/ 77.0ppm. Reactions were monitored as a function of time by HPLC. HPLC analyses were performed on a HP1100 HPLC instrument using a Phenomenex LUNA 5µ C18 column (250 x 4.60mm) and acetonitrile/water/TFA phase. UV detection was set at 220, 230 and 254nm. The e.e.% was determined by chiral HPLC against authentic samples. Chiral HPLC methods are as following:

For 2-bromo-3-phenylpropanoic acid:

Method 1

Column: Chiralcel AD 250 x 4.6mm, from Daicel Chemical Industries. Mobile phase: Mobile Phase: 96.9% of hexane, 3% of absolute ethanol and 0.1% TFA. Flow rate: 2 mL/min. Detector: UV at 220 nm. Retention time: (*S*)-2-bromo-3-phenylpropanoic acid (**4**), 6.4 min; (*R*)-2-bromo-3-phenylpropanoic acid (**3**), 5.3 min.

Method 2

Column: Chiralpak AD 250 x 4.6mm; Mobile phase: 97.9% of hexane, 2% of isopropanol and 0.1% TFA. Flow rate: 1 mL/min. Detector: UV at 215 nm. Retention time: (*S*)-2-bromo-3-phenylpropanoic acid (**4**), 22.2 min; (*R*)-2-bromo-3-phenylpropanoic acid (**3**), 23.7 min.

(See attached HPLC chromatographs on pages 4-6).

For 2-acetylthio-3-phenylpropanoic acid:

Column: Chiralpak AD 250 x 4.6mm; Mobile phase: 97.9% of hexane, 2% of absolute ethanol and 0.1% TFA. Flow rate: 1 mL/min. Detector: UV at 230 nm. Retention time: (R)-2-acetylthio-3-phenylpropanoic acid, 7.89min; (S)-2-acetylthio-3-phenylpropanoic acid (**1**), 8.45min.

(See attached HPLC chromatograph on page 7)

(1) Preparation of (*S*)-2-bromo-3-phenylpropanoic acid (4) from L-phenylalanine

In a 1L jacketed reactor equipped with mechanical stirring and thermometer, 48% HBr (408.2g, 2.42mol), water (150mL) and toluene (168mL) were charged at 15°C under nitrogen flow. The mixture temperature was brought to 0°C and L-phenylalanine (100g, 0.605 moles) was added. The mixture was cooled to -5°C. A solution of sodium nitrite (54.3g, 0.787mol) in water (102mL) was added dropwise to the reaction mixture over 2 hours. After the addition, the reaction mixture was stirred for 3 hours, and then the temperature was brought to 15°C, and stirring was kept on for another hour. The mixture was then left to stand for 30 minutes, and the phases were separated. The organic layer was diluted with 260mL toluene, and first washed with water (twice, 150mL each), then with brine (150mL). The organic phase was then separated and dried over $MgSO_4$. After removal of solvent, a total of 126.5g of product were obtained. The product was 97% pure by HPLC area, and had 94.7% e.e. ^{1}H NMR ($CDCl_3$) δ 11.0 (s, 1H), 7.1-7.3 (m, 5H), 4.48 (dd, 1H), 3.51 (m, 1H), 3.30 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 175.4, 136.7, 129.6, 129.2, 127.9, 45.1, 41.2.

(2) Preparation of (*R*)-2-Bromo-3-phenylpropanoic Acid (3) from (*S*)-2-Bromo-3-phenylpropanoic Acid (4)

Under nitrogen, 2-bromoacid **4** (8.97g, 97% pure, 38.0mmol) and TEAB (780mg, 3.67mmol) were charged into a 500mL round bottom flask equipped with a magnetic stir bar and a condenser. Acetonitrile (200mL) was then added. The mixture was then heated to 55°C. (*R*)-Bornylamine (6.0g, 97% pure, 38.0mmol) was dissolved in 50mL acetonitrile. This solution was added through a syringe pump to the bromo acid reaction mixture at 55°C over a period of 24 hours. The reaction was monitored by chiral HPLC. After 48hrs, of acid reached ~96%. The mixture was cooled to rt. The amine-acid salt (**5**) obtained after filtration, washing (with 20mL acetonitrile) and vacuum drying weighed 11.3g (29.6mmol, 78.0% yield). IR: KBr 1634, 1526, 1393. ^{1}H NMR (DMSO-d6) δ 7.28 (s, 5H), 4.32 (m, 1H), 3.22 (m, 2H), 2.78 (m, 1H), 2.21 (m, 2H) 1.61 (m, 2H), 1.35 (m, 1H), 1.08 (m, 2H), 0.91 (s, 3H), 0.87 (s, 6H). Elemental analysis: Theory 59.69% C; 7.38% H, 3.66% N, 20.90% Br; Found 59.49% C, 7.41% H, 3.63% N, 21.21% Br.

The amine-acid salt **5** was mixed with 50mL of water and 60mL of MTBE. The pH of the mixture was then adjusted to between 1 and 2 with methanesulfonic acid, and was then stirred for 15 min. Layers were separated, and the aqueous layer was extracted with 20mL MTBE once, then with 10mL MTBE twice. (*R*)-Bornylamine was recycled by first adjusting the pH of the aqueous solution to between 10 and 13, then extracting the free amine into MTBE. After removal of solvent, 4.31g of (*R*)-bornylamine was obtained (97% pure by ^{1}H NMR, 92.1% yield). The organic layers were combined and washed with 5mL water, then with 10mL brine, and then dried over $MgSO_4$. Bromo acid **3** was obtained in quantitative yield and 96.4% e.e. after solvent

evaporation under reduced vacuum. Alternatively, the bromo acid solution in MTBE could be used directly to synthesize (S)-2-acetylthio-3-phenylpropanoic acid (**1**). ^{1}H NMR ($CDCl_3$) δ 11.3 (s, 1H), 7.1-7.3 (m, 5H), 4.48 (dd, 1H), 3.52 (m, 1H), 3.30 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 175.35, 136.73, 129.57, 129.17, 127.91, 45.11, 41.15.

(3) Preparation of (*S*)-2-Acetylthio-3-phenylpropanoic acid (1)

(R)-2-Bromo-3-phenylpropanoic acid **3** (~29.6mmol) solution in MTBE (~30mL) was transferred into a 100mL 3-neck round bottom flask equipped with mechanical stirring and thermometer. KSAc (3.54g, 30.4mmol) was slowly added to the flask over 5 minutes. A water bath was used to keep the reaction temperature below 30°C. The mixture was stirred for 24 hours. Water (10g) was added, and the mixture was stirred for 10 minutes. Layers were separated, the organic layer was washed with 6 wt% $Na_2S_2O_3$ solution (twice, 10g each time), and then washed with brine (10g). After removal of solvent, oily product was obtained which solidified on cooling to 0°C. A total of 6.40g of the product was obtained (83.3 M% product, 16.7M% MTBE by ^{1}H NMR, 87.1% yield after correction for MTBE), and the e.e. of the product was 92.4%.

The e.e. of the acid could be further improved by the following recrystallization step: Crude **1** (8.29g, 88.4%) was dissolved in MTBE (4mL). The solution of acid in MTBE was then heated to 45 ^{o}C. Heptanes (~25mL) was added dropwise to the warm solution until cloudy. The slurry was seeded with **1** crystals, and slowly cooled to r.t. without agitation. The addition of heptanes was continued (~15 mL) with agitation over 30 min. The mixture was then cooled to 0-5°C. After filtration, the wet cake was washed with 5mL cold heptane. After drying in vacuum, 5.5g product **1** was obtained (66% yield, 98.7% e.e., 98.2% pure). ^{1}H NMR ($CDCl_3$) δ 10.5-11 (s, 1H), 7.23-7.32 (m, 5 H), 4.47 (t, J = 7.2 Hz, 1 H), 3.28-3.34 (m, 1 H), 3.01-3.07 (m, 1 H), 2.35 (s, 3 H).

Data File D:\HPCHEM\1\DATA\01140003\001-0701.D Sample Name: racemic BrAcid
racemic bromohydrocinnamic acid

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Acq. Operator   : Jason G. Chen                      Inj :   1
Acq. Instrument : Instrument 1                Inj Volume : 1 µl
Acq. Method     : C:\HPCHEM\1\METHODS\CHIRALAD.M
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                  (modified after loading)
Analysis Method : D:\HPCHEM\1\METHODS\CHIRALAD.M
Last changed    : 7/22/04 6:39:09 PM by JC
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Normal phase chiral separation of acids
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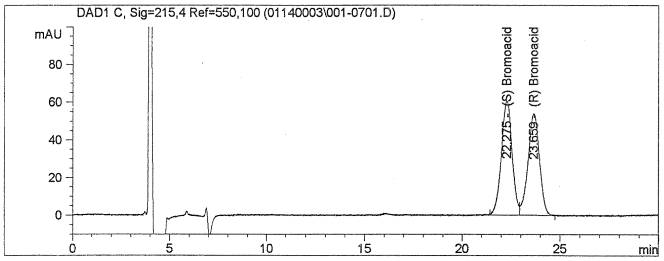


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Dilution              :      1.0000


Signal 1: DAD1 C, Sig=215,4 Ref=550,100

Peak RetTime  Type   Width     Area      Area     Name
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----|-------|------|-------|----------|--------|--------------------
   1  22.275 BV      0.5886 2325.28076  51.3263 (S) Bromoacid
   2  23.659 VP      0.6236 2205.10815  48.6737 (R) Bromoacid

Totals :                   4530.38892 100.0000

 Results obtained with enhanced integrator!
2 Warnings or Errors :

Warning : Invalid calibration curve, ((S) Bromoacid)
Warning : Invalid calibration curve, ((R) Bromoacid)

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HP1100 DAD 1 7/22/04 6:39:13 PM JC Page 1 of 1

Data File D:\HPCHEM\1\DATA\01170001\009-0103.D Sample Name: 1917-80-sm
starting material, (2s)bracide from Kenny. In MTBE

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Sample Name     : 1917-80-sm                         Vial :   9
Acq. Operator   : Jason G. Chen                       Inj :   3
Acq. Instrument : Instrument 1                Inj Volume : 1 µl
Acq. Method     : C:\HPCHEM\1\METHODS\CHIRALAD.M
Last changed    : 1/12/00 3:52:23 PM by Jason G. Chen
Analysis Method : D:\HPCHEM\1\METHODS\CHIRALAD.M
Last changed    : 7/22/04 6:39:09 PM by JC
                  (modified after loading)
Normal phase chiral separation of acids
==========================================================================
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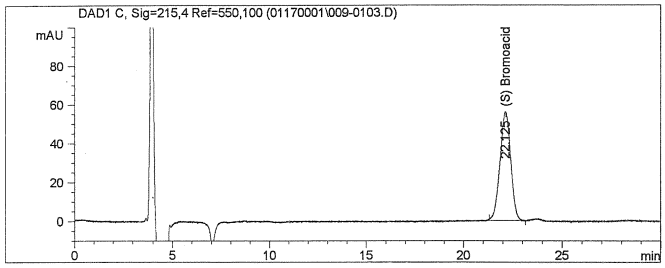


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Calib. Data Modified  :      Thursday, July 22, 2004 6:23:27 PM
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 C, Sig=215,4 Ref=550,100

Peak RetTime  Type   Width     Area      Area     Name
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   1  22.125 BP      0.5757 2123.48535 100.0000 (S) Bromoacid
   2  23.700         0.0000    0.00000   0.0000 (R) Bromoacid

Totals :                    2123.48535 100.0000

 Results obtained with enhanced integrator!
2 Warnings or Errors :

Warning : Calibrated compound(s) not found
Warning : Invalid calibration curve, ((S) Bromoacid)

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HP1100 DAD 1 7/22/04 6:41:07 PM JC Page 1 of 1

Data File D:\HPCHEM\1\DATA\01140003\005-0101.D Sample Name: 1907-50-1
Using TEAB as PTC. exp 35

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Sample Name     : 1907-50-1                         Vial :   5
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Acq. Instrument : Instrument 1                Inj Volume : 1 µl
Acq. Method     : C:\HPCHEM\1\METHODS\CHIRALAD.M
Last changed    : 1/12/00 3:52:23 PM by Jason G. Chen
Analysis Method : D:\HPCHEM\1\METHODS\CHIRALAD.M
Last changed    : 7/22/04 6:39:09 PM by JC
                  (modified after loading)
Normal phase chiral separation of acids
==========================================================================
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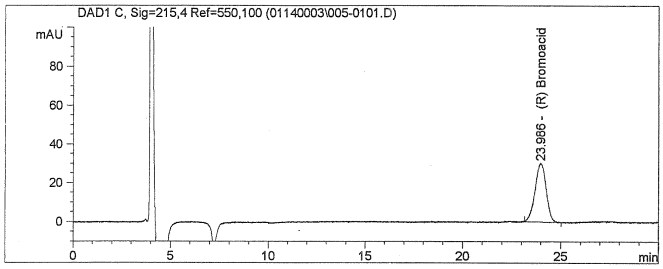


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Calib. Data Modified  :      Thursday, July 22, 2004 6:23:27 PM
Multiplier            :      1.0000
Dilution              :      1.0000

Signal 1: DAD1 C, Sig=215,4 Ref=550,100

Peak RetTime  Type   Width     Area     Area     Name
  #   [min]          [min]   [mAU*s]       %
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   1  22.200        0.0000    0.00000   0.0000 (S) Bromoacid
   2  23.986 BP     0.6051 1207.52954 100.0000 (R) Bromoacid

Totals :                  1207.52954 100.0000

 Results obtained with enhanced integrator!
2 Warnings or Errors :

Warning : Calibrated compound(s) not found
Warning : Invalid calibration curve, ((R) Bromoacid)

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                          *** End of Report ***
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Sample Information

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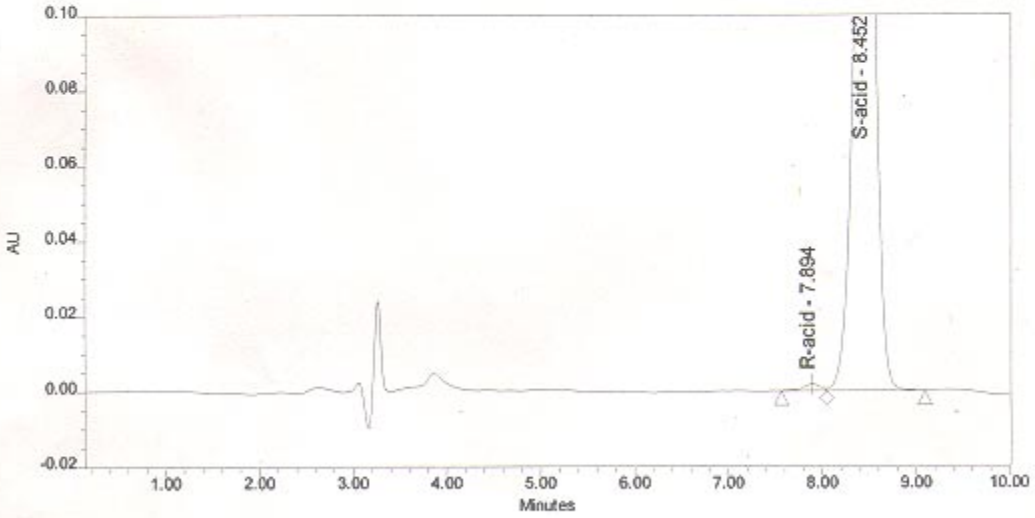
Injection Volume	10.00 ul	Processing Method	Omapatrilat_L5S3_1129
Channel	996	Date Processed	11/29/99 2:43:02 PM
Run Time	10.0 Minutes		
sample_description	1903-40		



Peak Results

	Name	RT	Area	Height	% Area
1	R-acid	7.89	21935	1787	0.7
2	S-acid	8.45	3097588	219202	99.3