# One-pot racemization process of 1-phenyl-1,2,3,4-tetrahydroisoquinoline - a key intermediate for the antimuscarinic agent solifenacin

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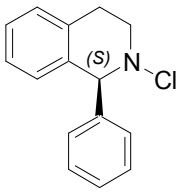
**Supporting information**

**CONTENTS**

## I. General Remarks

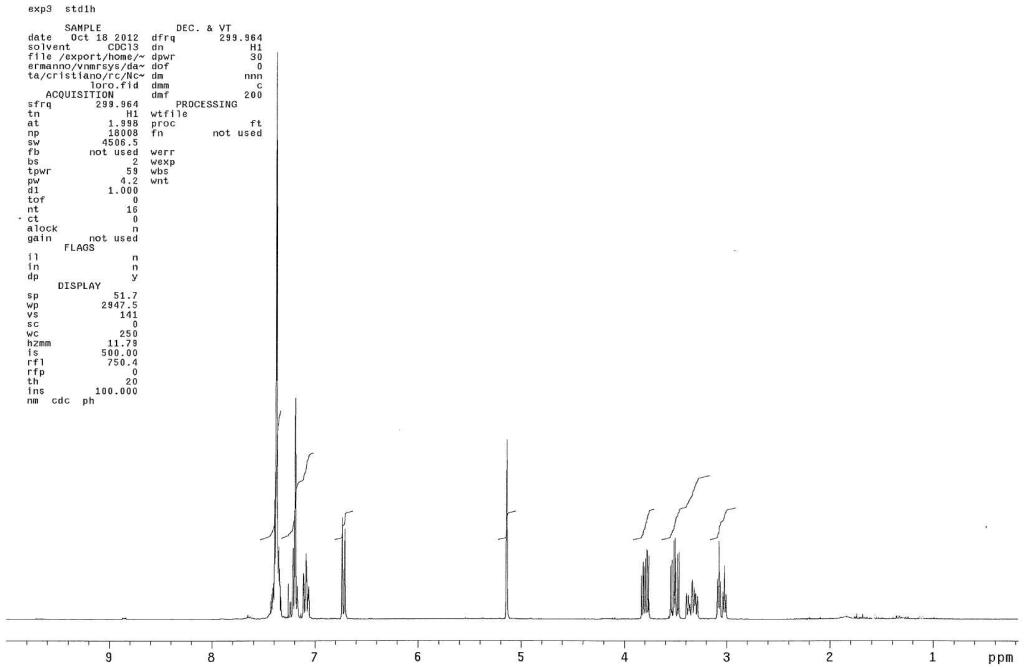
$^{1}H$ NMR spectra were recorded on a Varian Gemini 300 operating at 300 MHz and $^{13}C$ NMR at 75 MHz. Chemical shifts are reported in ppm relative to residual solvent ($CHCl_3$ or DMSO) as internal standard. ESI-MS analyses were acquired using TSQ Quantum di ThermoFinnigan, Rodano. The melting points were determined by DSC analysis. The DSC curves were recorded and integrated with the aid of a TA Instruments DSC 2010 apparatus. The enatiomer mixtures of **3** were prepared by mixing the solid racemate with the solid (*S*)-enantiomer. The TGA curves were recorded with the aid of a TA instruments TGA Q50 apparatus. Optical rotations were determined in a 1 a 1 dm cell of 1 ml capacity using a Perkin-Elmer 241 polarimeter. Enantiomeric excesses of **3** were determined by HPLC after conversion into acetamide using a Kromasil AmyCoat column (250x4.6 mm i.d.) as chiral stationary phase at 220 nm.

All the analytical data refer to crude products excepting those referring to (*S*)-**3** used as starting material and to (*S*)-**3** recovered from the resolutions with tartaric acid.

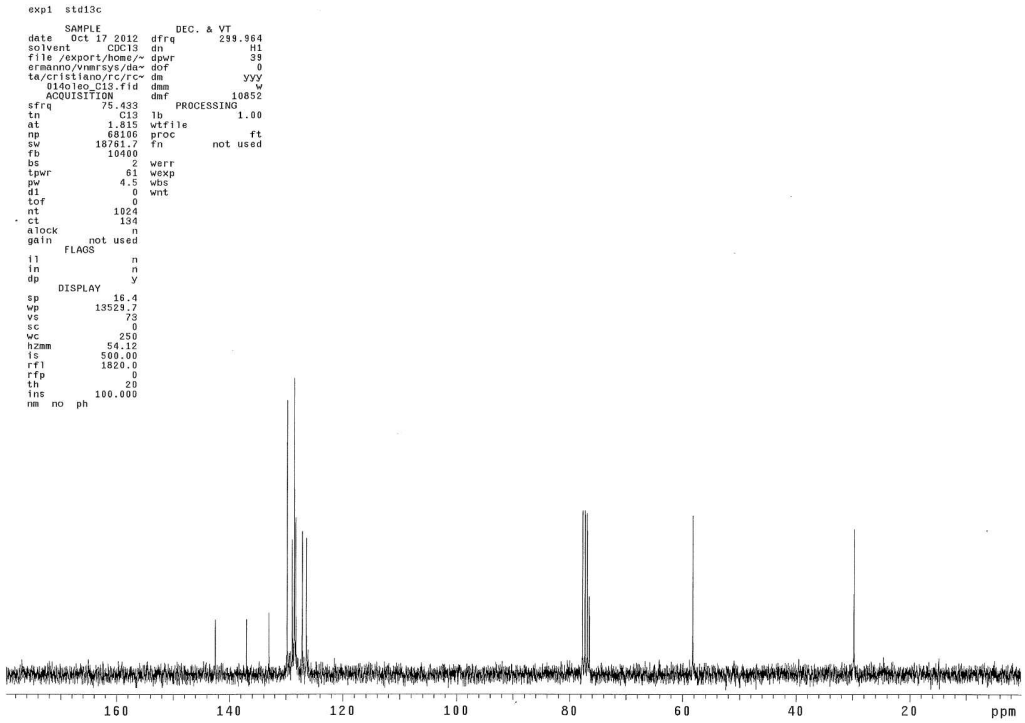



**(*S*)-N-chloro-1-phenyl-1,2,3,4-tetrahydroisoquinoline [(*S*)-7].**

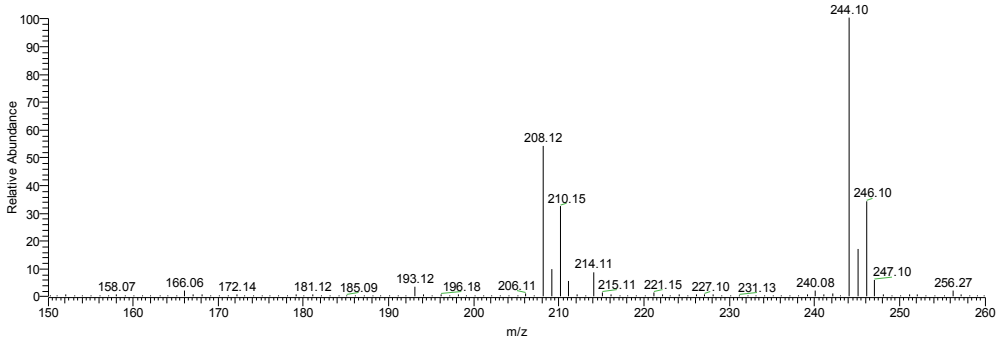
$^{1}$H NMR (300 MHz, $CDCl_3$)



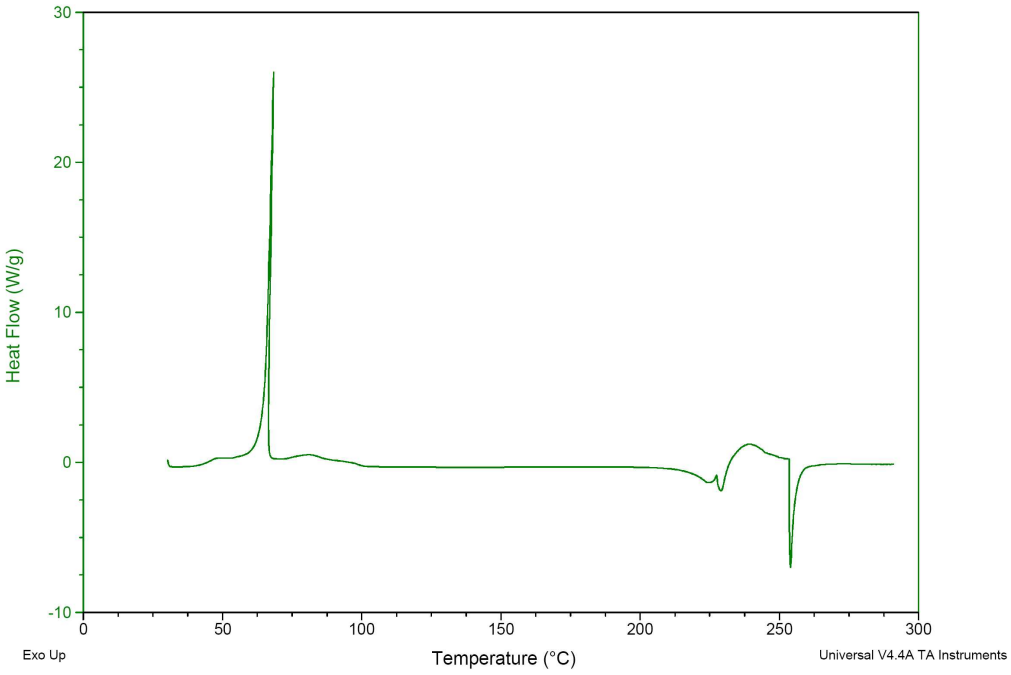

$^{13}$C NMR(75 MHz, $CDCl_3$



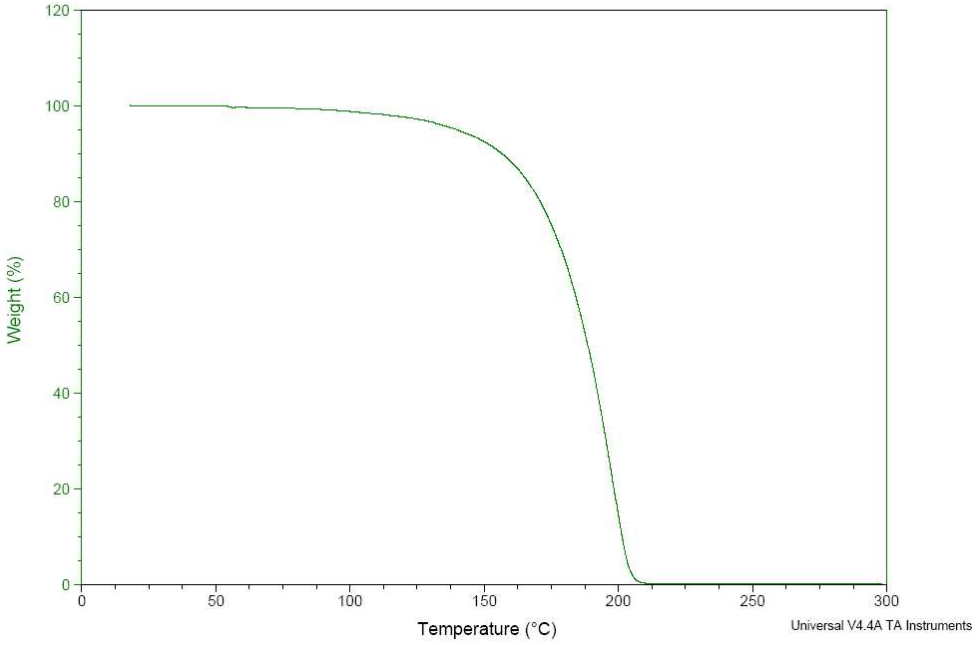
Mass spectrum of (*S*)-**7**

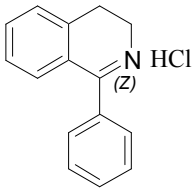



DSC trace of (*S*)-**7**



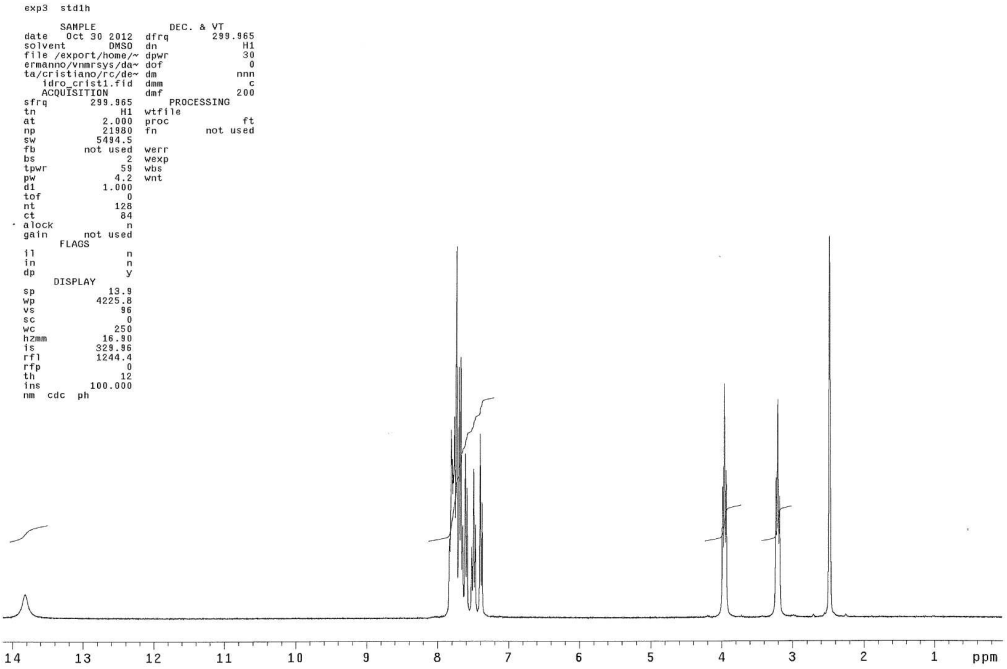

TGA curve of (*S*)-**7**



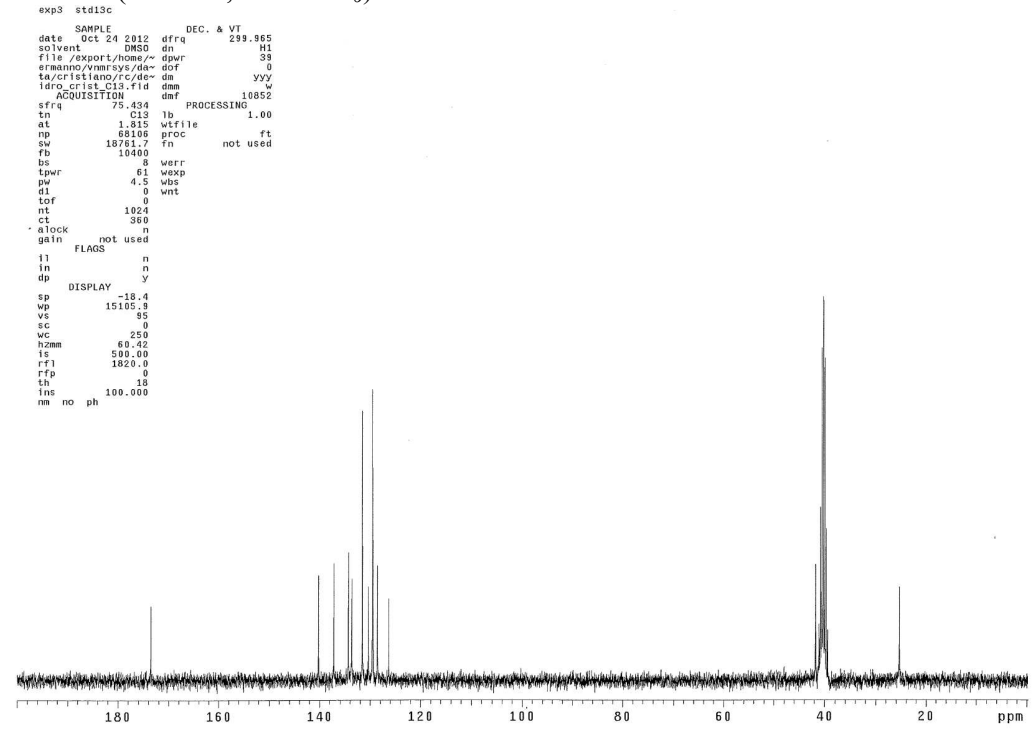



**1-phenyl-3,4-dihyhydroisoquinoline HCl [2·HCl]**.

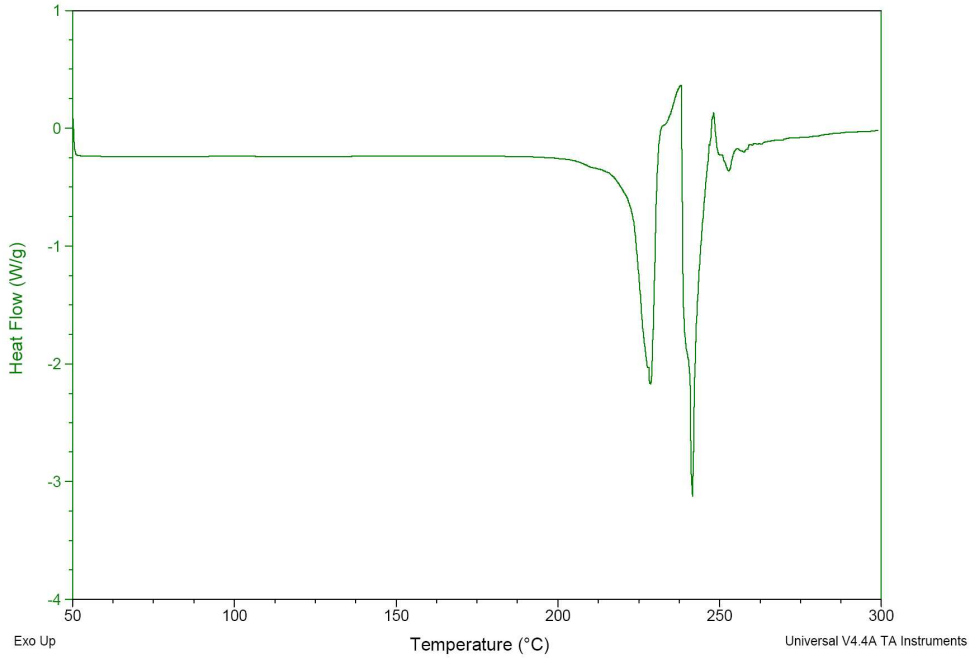
$^{1}$H NMR (300 MHz, DMSO-$d_6$)



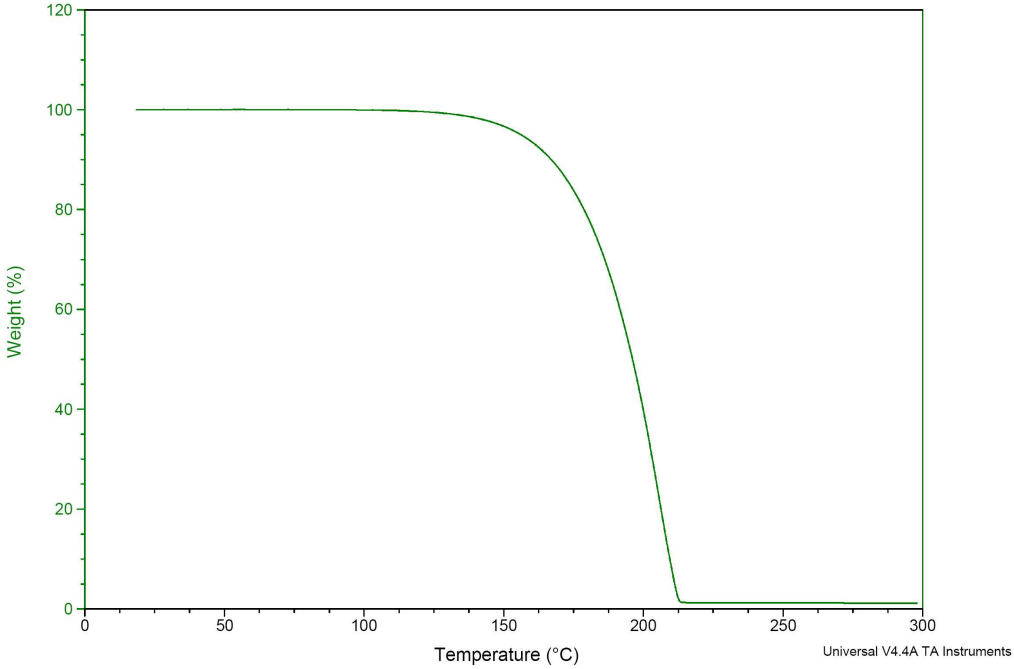

$^{13}$C NMR(75 MHz, DMSO-$d_6$)

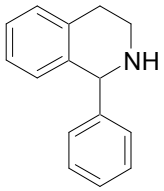


DSC trace of **2**·HCl



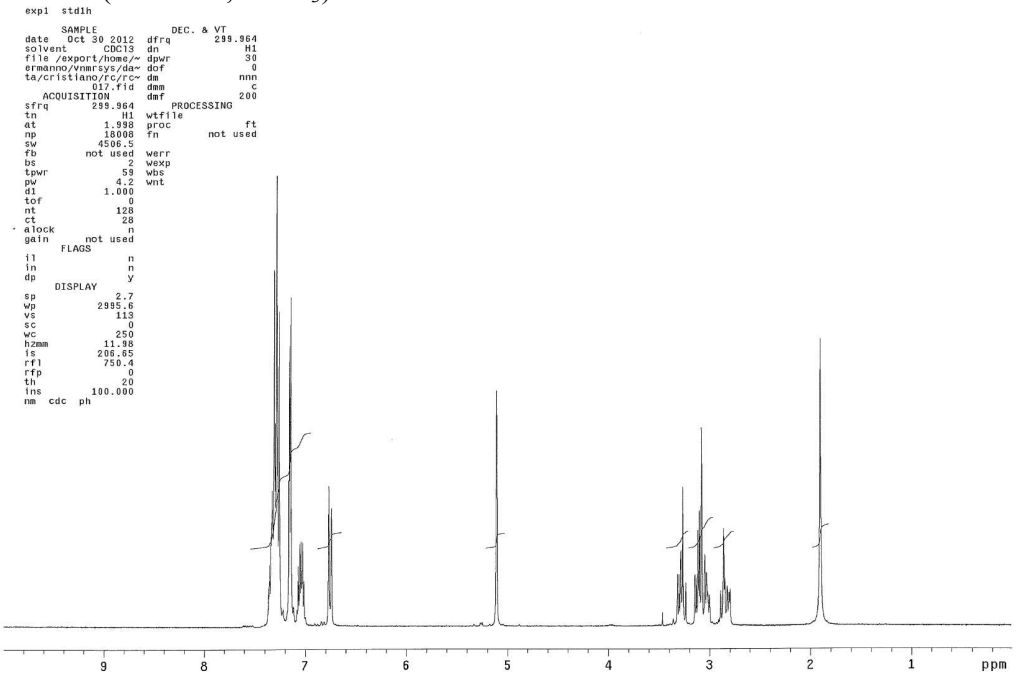

TGA trace of **2**·HCl



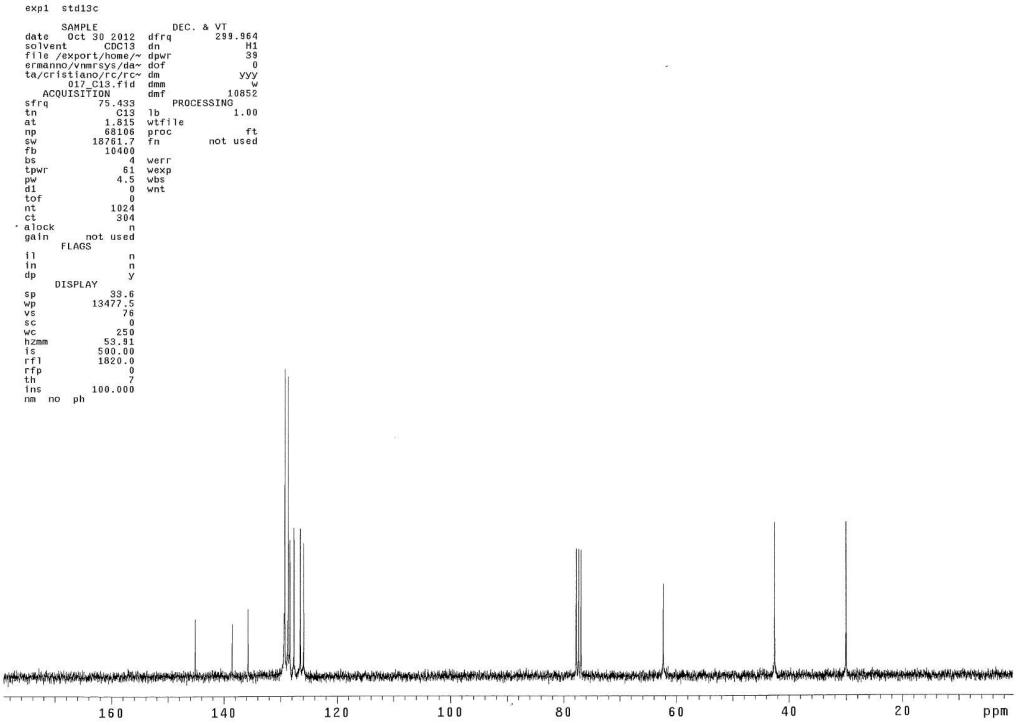



**1-phenyl-1,2,3,4-tetrahydroisoquinoline [*rac*-3]**.

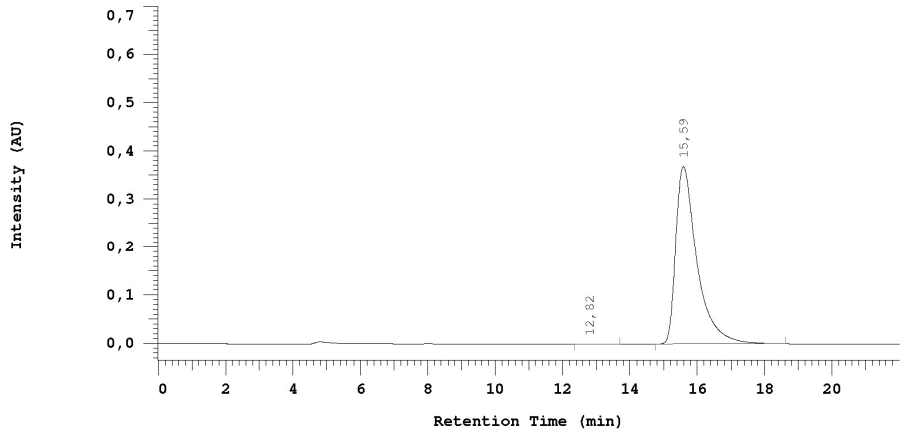
$^{1}$H NMR (300 MHz, $CDCl_3$)




$^{13}$C (75 MHz, $CDCl_3$)



Enantiomeric composition of starting material (*S*)-**3**




Acquisition Method: fase diretta chirale
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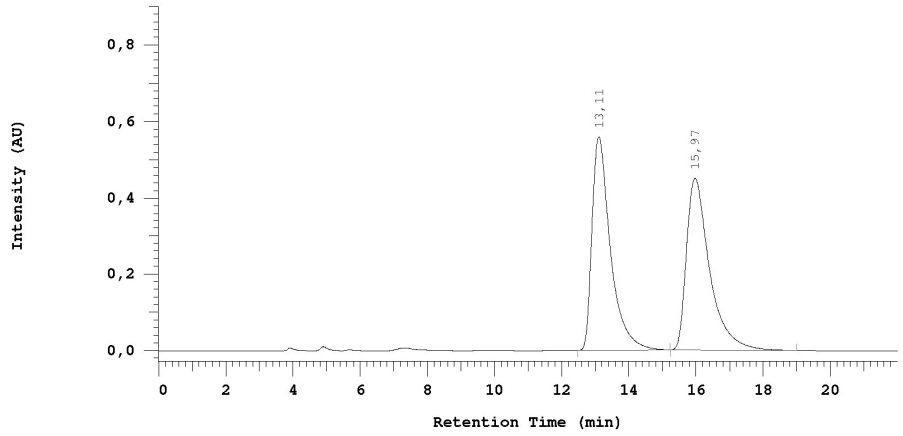
Method Description: esano:IsPrOH 9:1 220 nm F=0,8
Peak Quantitation: AREA
Calculation Method: AREA%

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 12,82 | 3723 | 0,046 | MC |
| 2 | 15,59 | 8058116 | 99,954 | MC |
| | | 8061839 | 100,000 | |

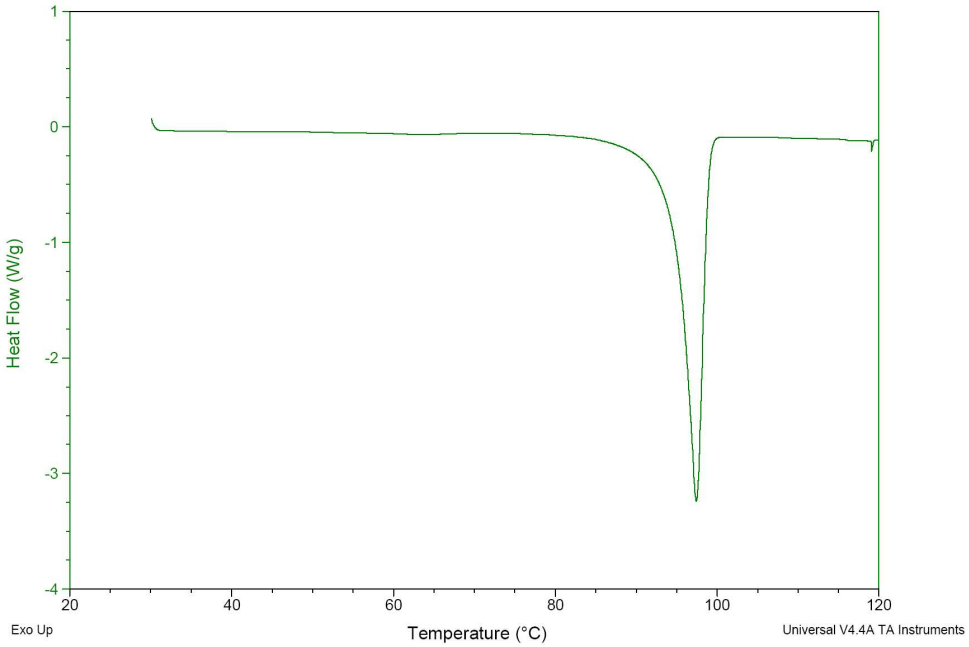
Enantiomeric composition of *rac*-**3** obtained by one-pot racemization of (*S*)-**3**



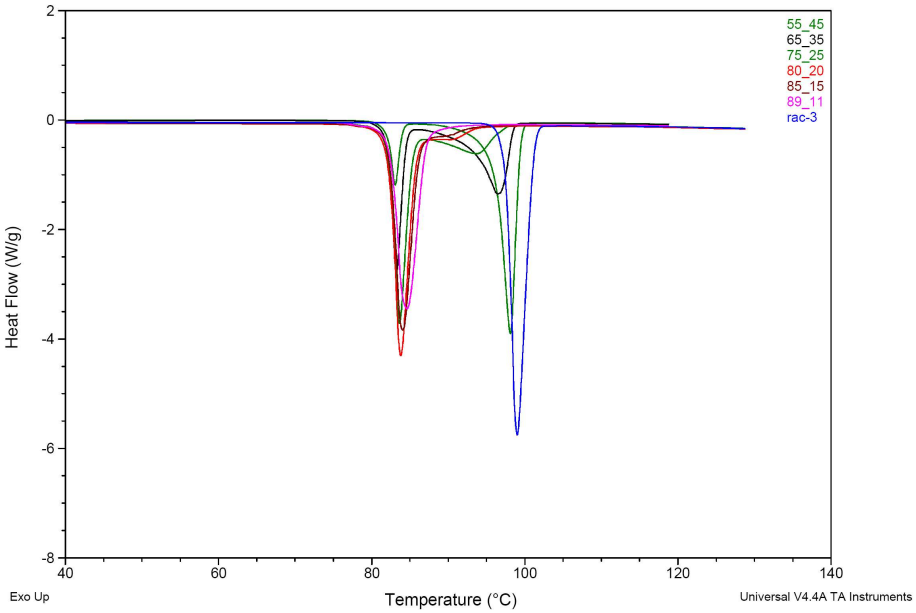

Acquisition Method: fase diretta chirale
Column Type:
Method Description: esano:IsPrOH 9:1 220 nm F=0,8
Peak Quantitation: AREA
Calculation Method: AREA%

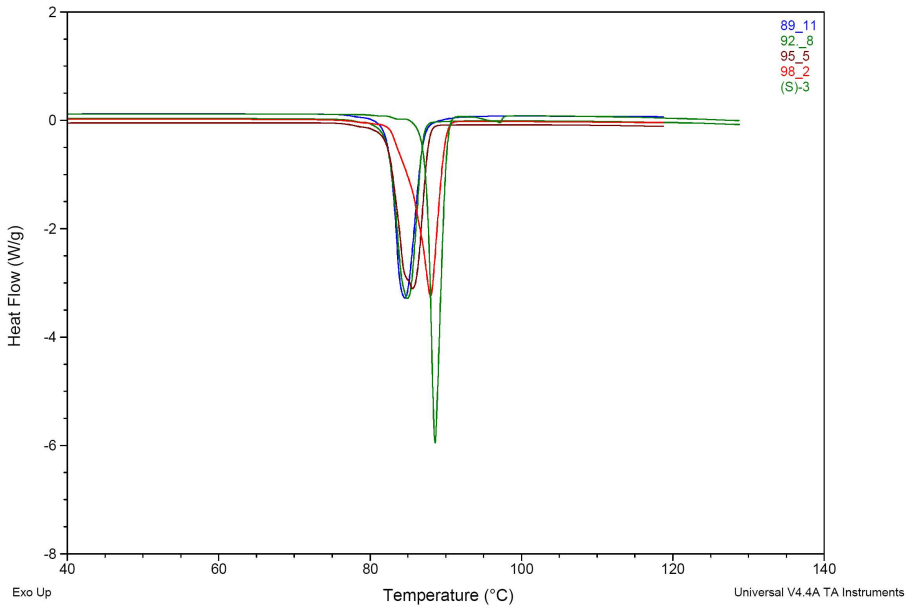
| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 13,11 | 10654908 | 49,836 | MC |
| 2 | 15,97 | 10724958 | 50,164 | MC |
| | | 21379866 | 100,000 | |

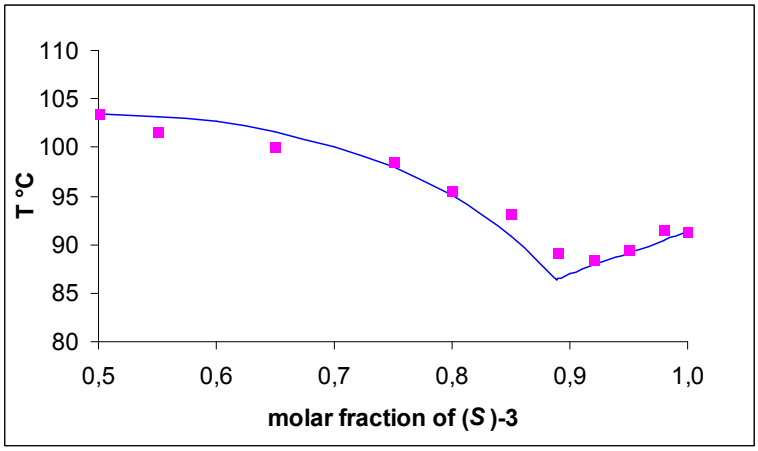
DSC trace of one pot *rac*-**3** obtained by one-pot racemization of (*S*)-**3**



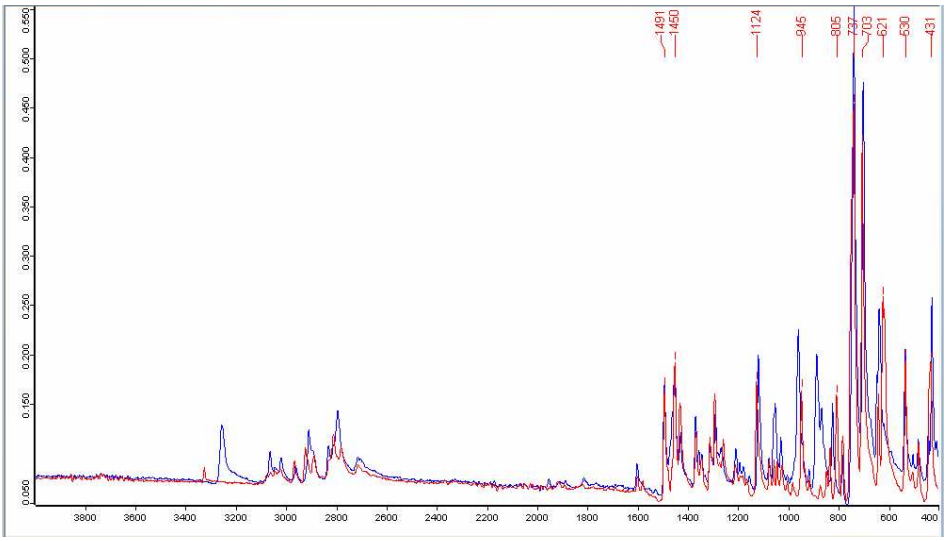
DSC traces of (*S*)-**3**/*rac*-**3** mixtures utilized to construct the binary melting point phase diagram of **3**.



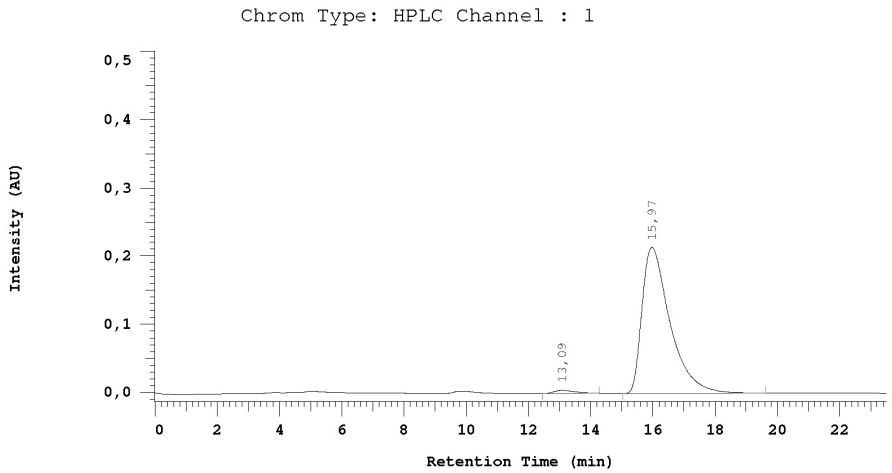



Overlapped IR spectra of *rac*-**3** and (*S*)-**3**



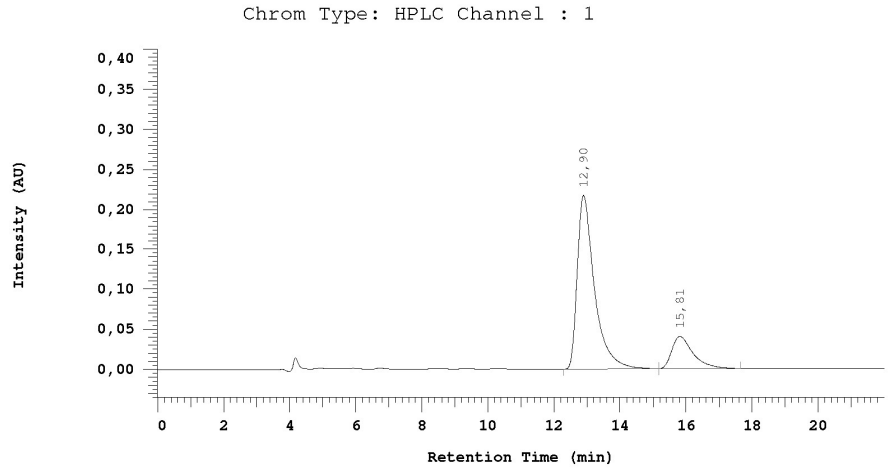
Enantiomeric compositio of (*S*)-**3** obtained by resolution of *rac*-**3** resulting from the one-pot racemization of (*S*)-**3**




Acquisition Method: fase diretta chirale
Column Type:
Method Description: esano:IsPrOH 9:1 220 nm F=0,8
Peak Quantitation: AREA
Calculation Method: AREA%

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 13,09 | 111118 | 1,631 | MC |
| 2 | 15,97 | 6701696 | 98,369 | MC |
| | | 6812814 | 100,000 | |

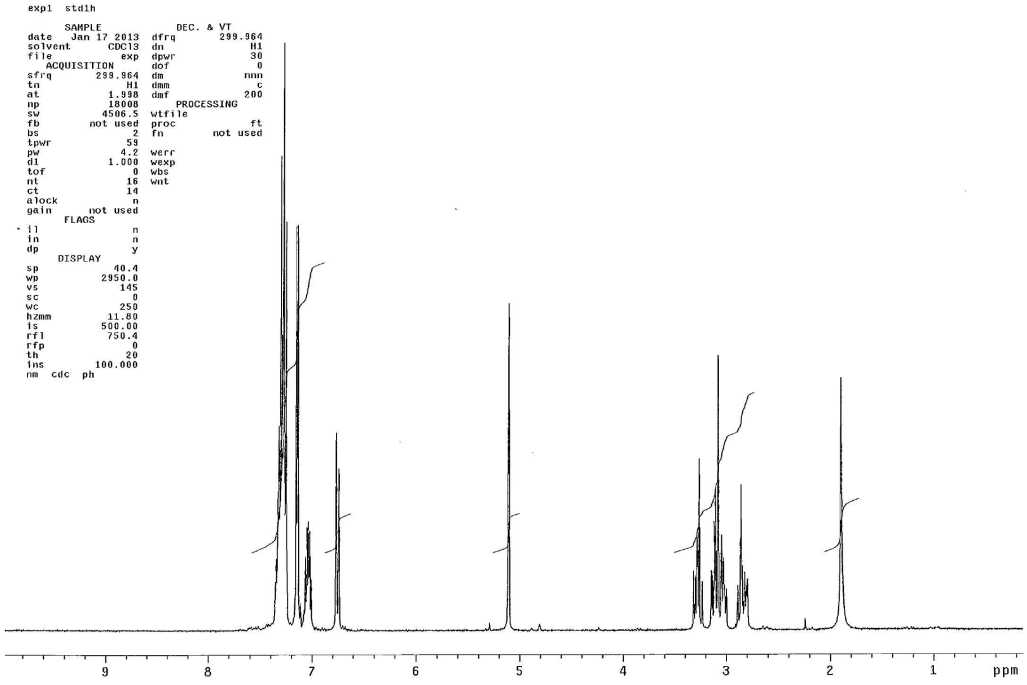
Enantiomerically enriched (*R*)-**3** from the mother liquors of the above resolution



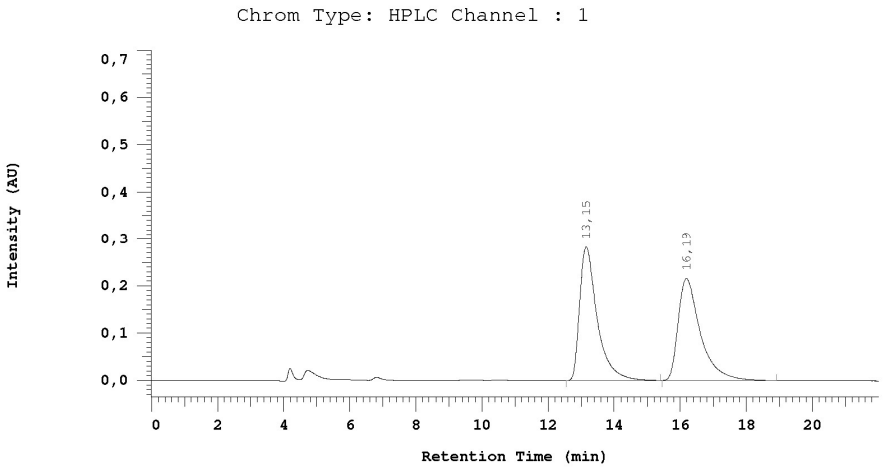

Acquisition Method: fase diretta chirale
Column Type:
Method Description: esano:IsPrOH 9:1 220 nm F=0,8
Peak Quantitation: AREA
Calculation Method: AREA%

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 12,90 | 3941626 | 81,640 | MC |
| 2 | 15,81 | 886445 | 18,360 | MC |
| | | 4828071 | 100,000 | |

$^1$H NMR (300 MHz, $CDCl_3$) of *rac*-**3** obtained by one-pot racemization of *R* enriched **3** resulting from the preceding resolution



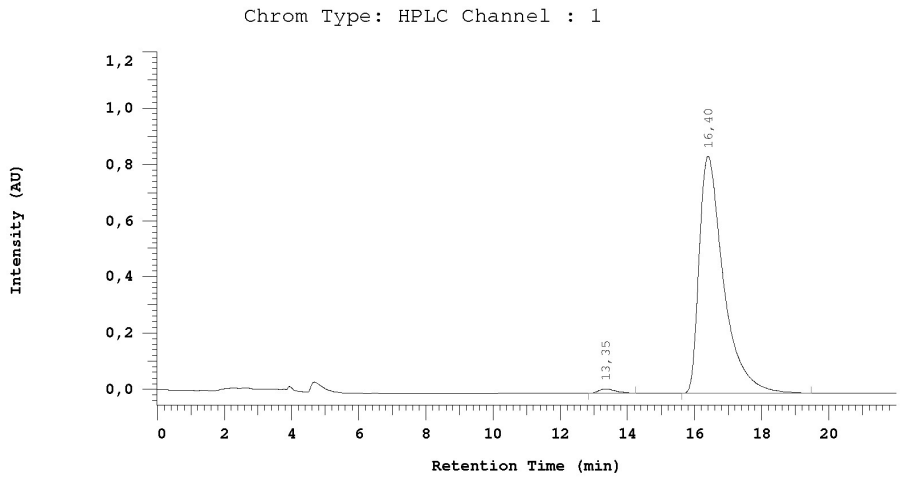

Enantiomeric composition of *rac*-**3** obtained by one-pot racemization of *R* enriched **3** resulting from the preceding resolution




Acquisition Method: fase diretta chirale
Column Type:
Method Description: esano:IsPrOH 9:1 220 nm F=0,8
Peak Quantitation: AREA
Calculation Method: AREA%

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 13,15 | 5221247 | 50,962 | MC |
| 2 | 16,19 | 5024194 | 49,038 | MC |
| | | 10245441 | 100,000 | |

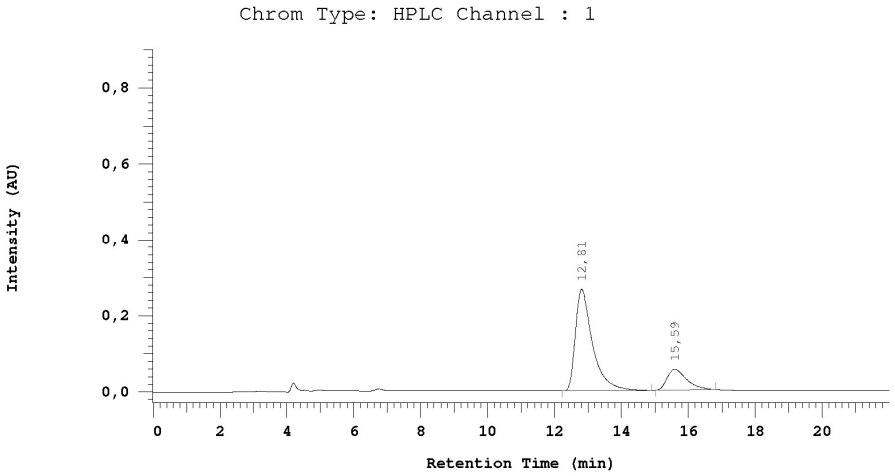
Enantiomeric composition of (*S*)-**3** from the second resolution




Acquisition Method: fase diretta chirale
Column Type:
Method Description: esano:IsPrOH 9:1 220 nm F=0,8
Peak Quantitation: AREA
Calculation Method: AREA%

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 13,35 | 274970 | 1,286 | MC |
| 2 | 16,40 | 21112852 | 98,714 | MC |
| | | 21387822 | 100,000 | |

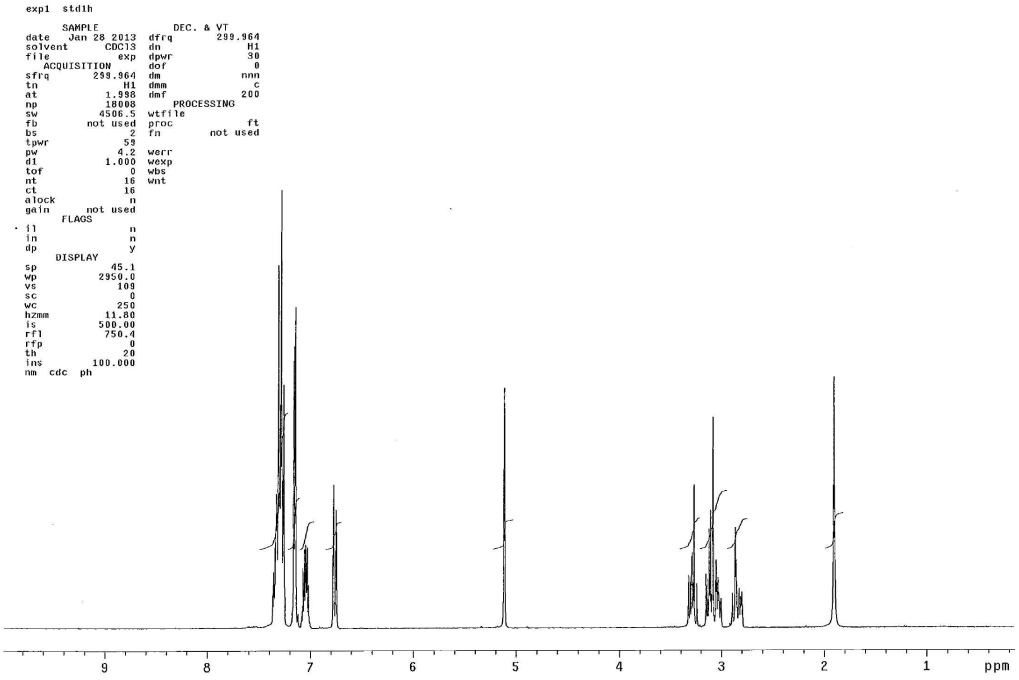
Enantiomerically enriched (*R*)-**3** from the second resolution mother liquors



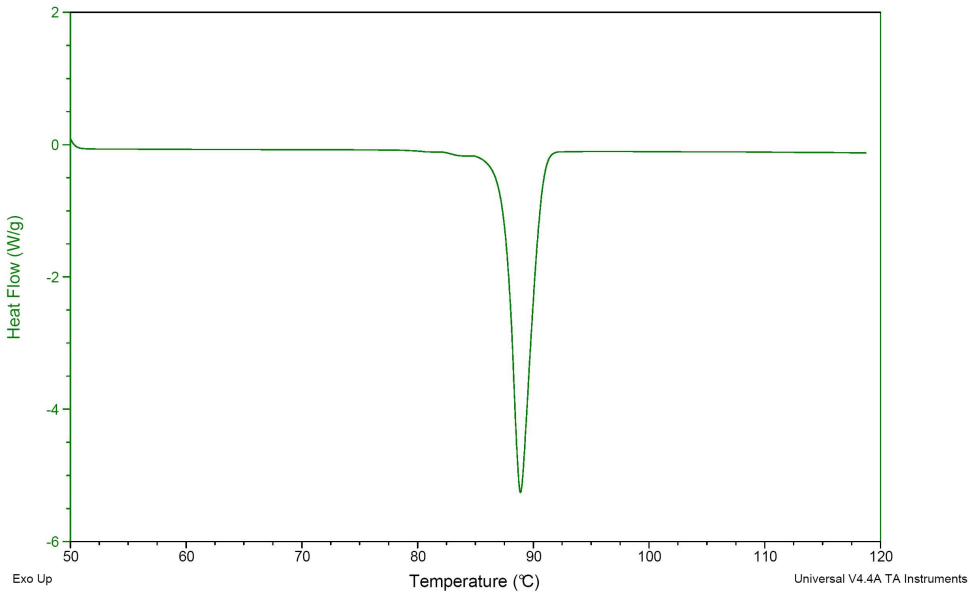

Acquisition Method: fase diretta chirale
Column Type:
Method Description: esano:IsPrOH 9:1 220 nm F=0,8
Peak Quantitation: AREA
Calculation Method: AREA%

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 12,81 | 4769616 | 81,110 | MC |
| 2 | 15,59 | 1110780 | 18,890 | MC |
| | | 5880396 | 100,000 | |

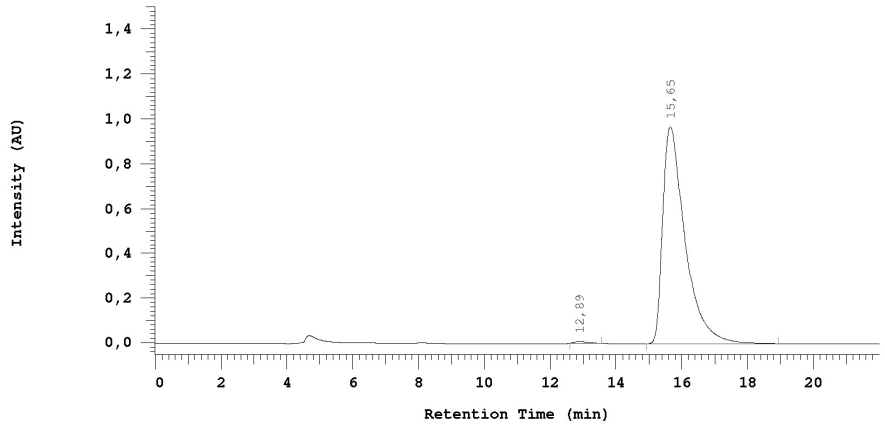
$^1$H NMR (300 MHz, $CDCl_3$) of (*S*)-**3** obtained bringing together the two previously resolved amounts and recrystallizing them from methanol/water




DSC trace of (*S*)-**3** obtained bringing together the two previously resolved amounts and recrystallizing them from methanol/water



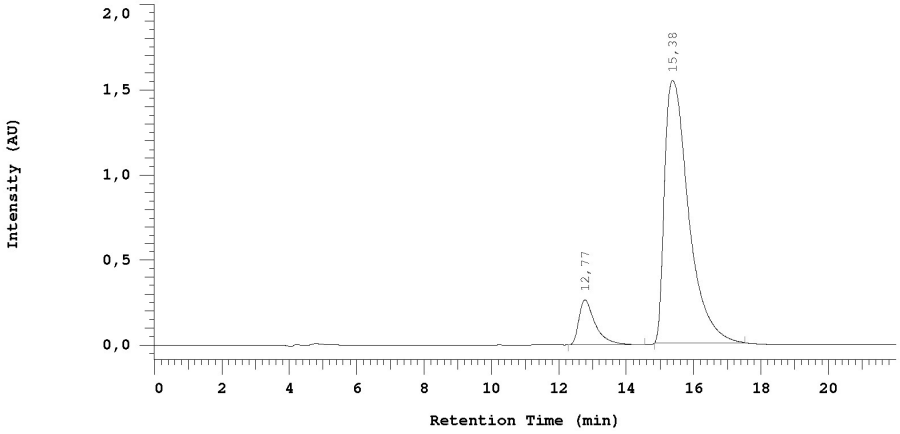
Enantiomeric composition of (*S*)-**3** obtained bringing together the two previously resolved amounts and recrystallizing them from methanol/water




Acquisition Method: fase diretta chirale
Column Type:
Method Description: esano:IsPrOH 9:1 220 nm F=0,8
Peak Quantitation: AREA
Calculation Method: AREA%

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 12,89 | 110472 | 0,480 | MC |
| 2 | 15,65 | 22889700 | 99,520 | MC |
| | | 23000172 | 100,000 | |

Enantiomeric composition of the mother liquors of the recrystallization of (*S*)-**3** ($E^+$)




Acquisition Method: fase diretta chirale
Column Type:
Method Description: esano:IsPrOH 9:1 220 nm F=0,8
Peak Quantitation: AREA
Calculation Method: AREA%

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 12,77 | 4494692 | 10,450 | MC |
| 2 | 15,38 | 38516064 | 89,550 | MC |
| | | 43010756 | 100,000 | |