Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Total synthesis of Fluoxetine & Duloxetine through an *in situ* imine formation/borylation/transimination and reduction approach

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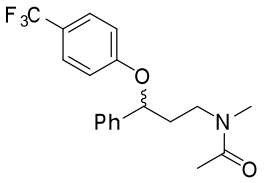
Contents

General experimental

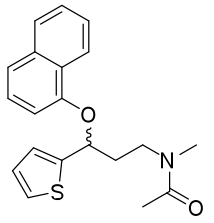
All reagents were used as received from the supplier without further purification, unless stated. All solvents were used as received from the supplier, except THF (freshly distilled) and methanol (stored over molecular sieves). Molecular sieves, 3Å 1-2mm beads, were supplied from Alfa Aesar, and stored at 220 °C. Reactions were monitored by TLC analysis using POLTFRAM® SIL G/UV_{254} (40 x 80 mm) TLC plates. Flash column chromatography was carried out using Silica gel as supplied from Sigma-Aldrich (230-400 mesh, 40-63 μm, 60 Å) and monitored using TLC analysis.^{1}H NMR spectra were recorded on a Varian-Mercury 500 MHz spectrometer, operating at ambient probe temperature unless specified elsewhere. ^{13}C NMR spectra were recorded on a Varian Mercury 500 MHz instrument, operating at 101 MHz, unless specified elsewhere. Deuterated chloroform $CDCl_3$ was used as solvent for all NMR spectra, unless specified elsewhere. NMR peaks are reported as singlet (s), doublet (d), triplet (t), quartet (q), broad (br), combinations thereof, or as a multiplet (m). Mass spectra for liquid chromatography mass spectrometry (LCMS) were obtained using a Waters (UK) TQD mass spectrometer (low resolution ESI+, electrospray in positive ion mode, ES+), Waters (UK) Xevo QTOF mass spectrometer (low and high resolution ASAP+) and a Waters (UK) LCT premier XE (high resolution ESI+, electrospray in positive ion mode, ES+) unless stated elsewhere. HPLC analysis was carried out on an Agilent 1100 series instrument, fitted with a Perkin Elmer series 200 degasser. AS-H-CHIRALCEL column (250 x 4.6 mm) fitted with guard cartridge (50 x 4.6 mm) was used to achieve chiral resolution, unless stated elsewhere. Optical rotations were measured using a JASCO P-1020 polarimeter with $[\alpha]_D$ values given in deg cm^2g^{-1}.

Chiral HPLC

HPLC analysis was carried out on an Agilent 1100 series instrument, fitted with a Perkin Elmer series 200 degasser.



13a Enantiomeric excess determined by HPLC using an AS-H CHIRALCEL column (250 x 4.6 mm) fitted with guard cartridge (50 x 4.6 mm), 25 ^{o}C, 1.0 mL/min, 210 nm, hexane : IPA (9 : 1). t_R (*R*) = 23.6 min; t_R (*S*) = 31.9 min.



13b Enantiomeric excess determined by HPLC using an AS-H CHIRALCEL column (250 x 4.6 mm) fitted with guard cartridge (50 x 4.6 mm), 25 ^{o}C, 1.0 mL/min, 210 nm, hexane : IPA (85 : 15). t_R (*S*) = 29.2 min; t_R (*R*) = 38.2 min.

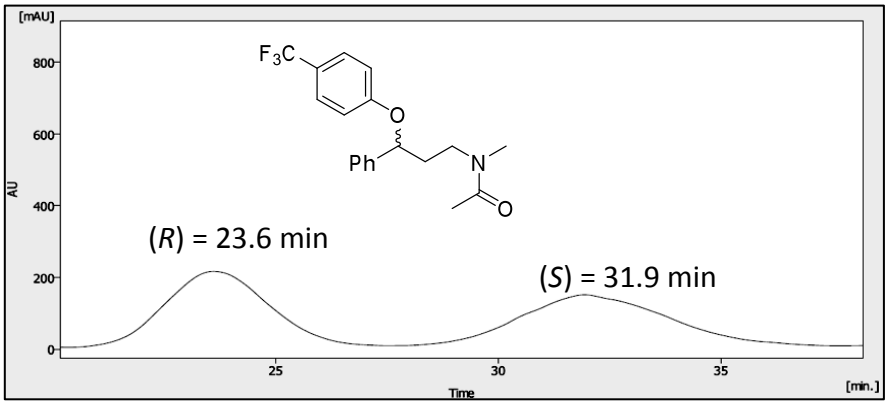


Figure 1 Chiral HPLC of (*rac*)-**13a** showing base-line resolution of each enantiomer.

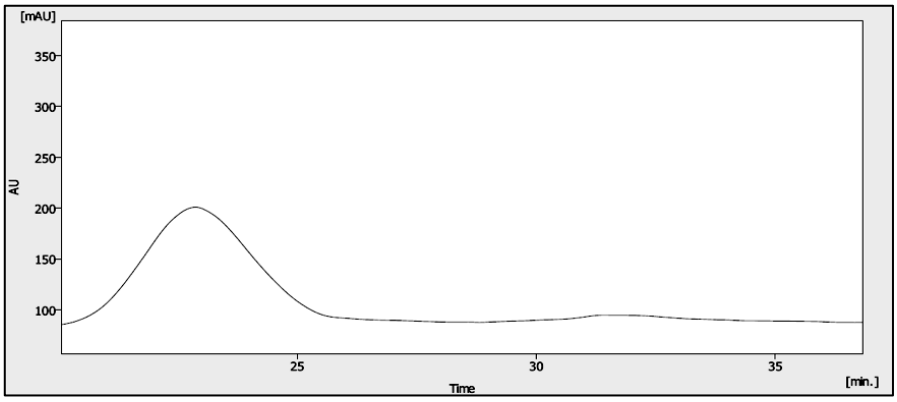


Figure 2 Chiral HPLC of (*R*)-**13a** showing a 98:2 ratio of the major and minor (respectively) enantiomers, thus giving 96% *e.e.* overall.

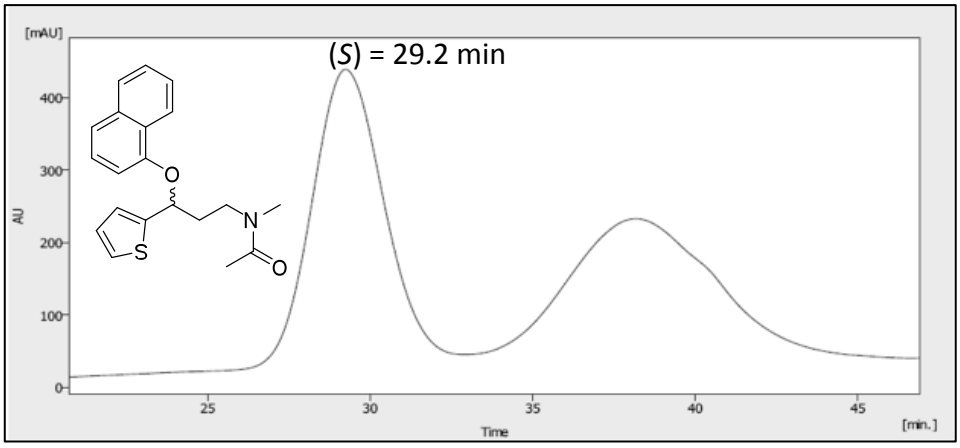


Figure 3 Chiral HPLC of (*rac*)-**13b** showing base-line resolution of each enantiomer.

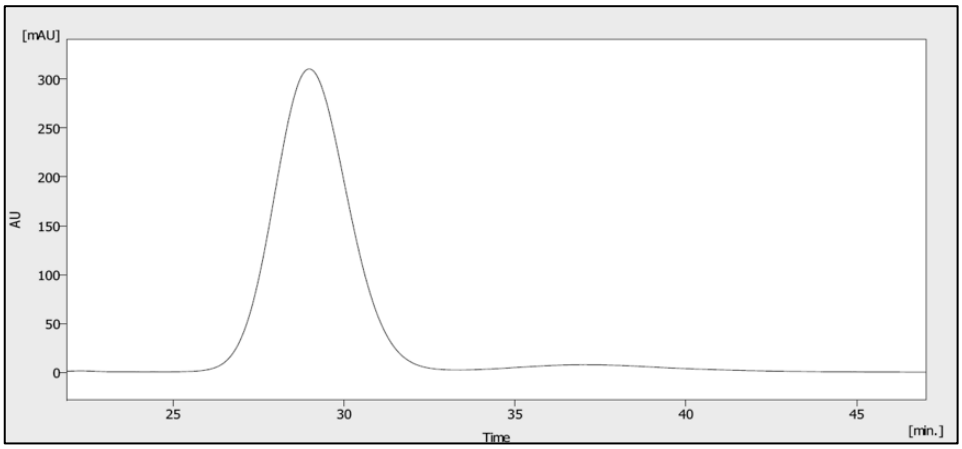
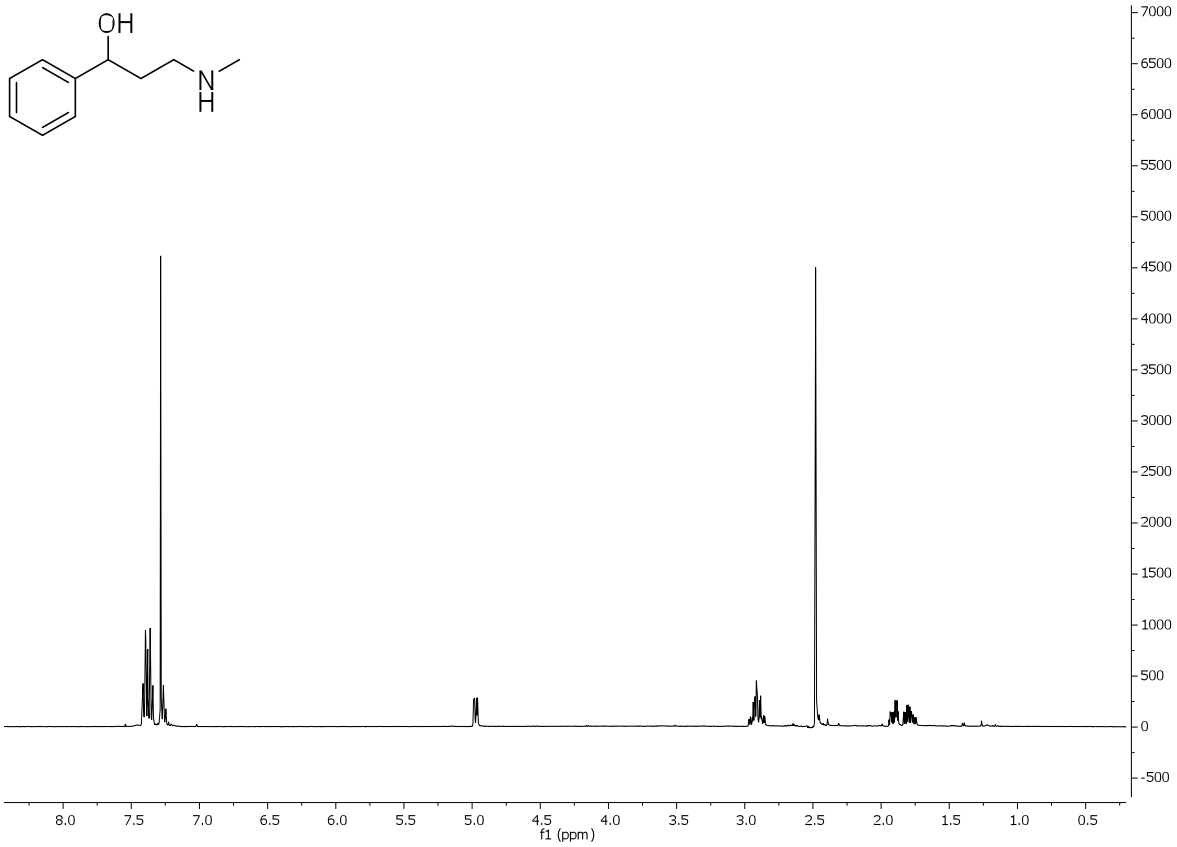
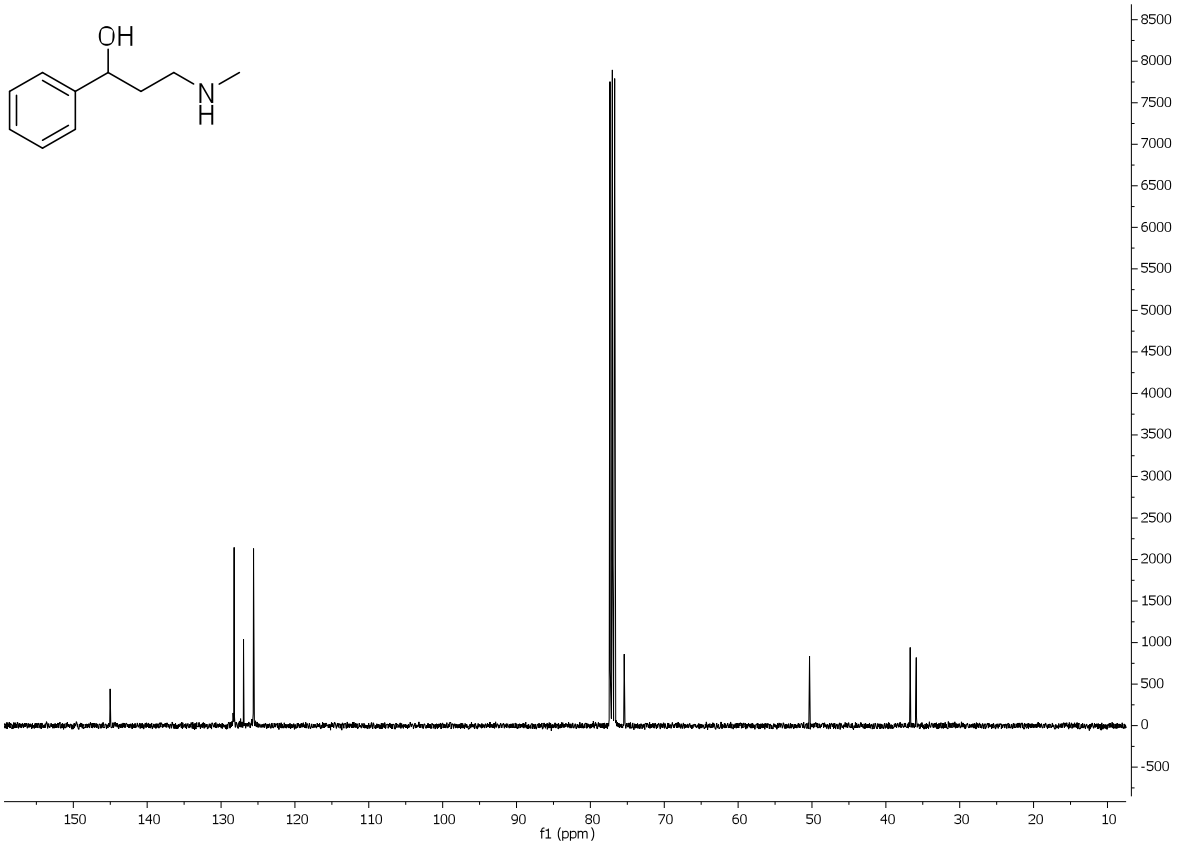
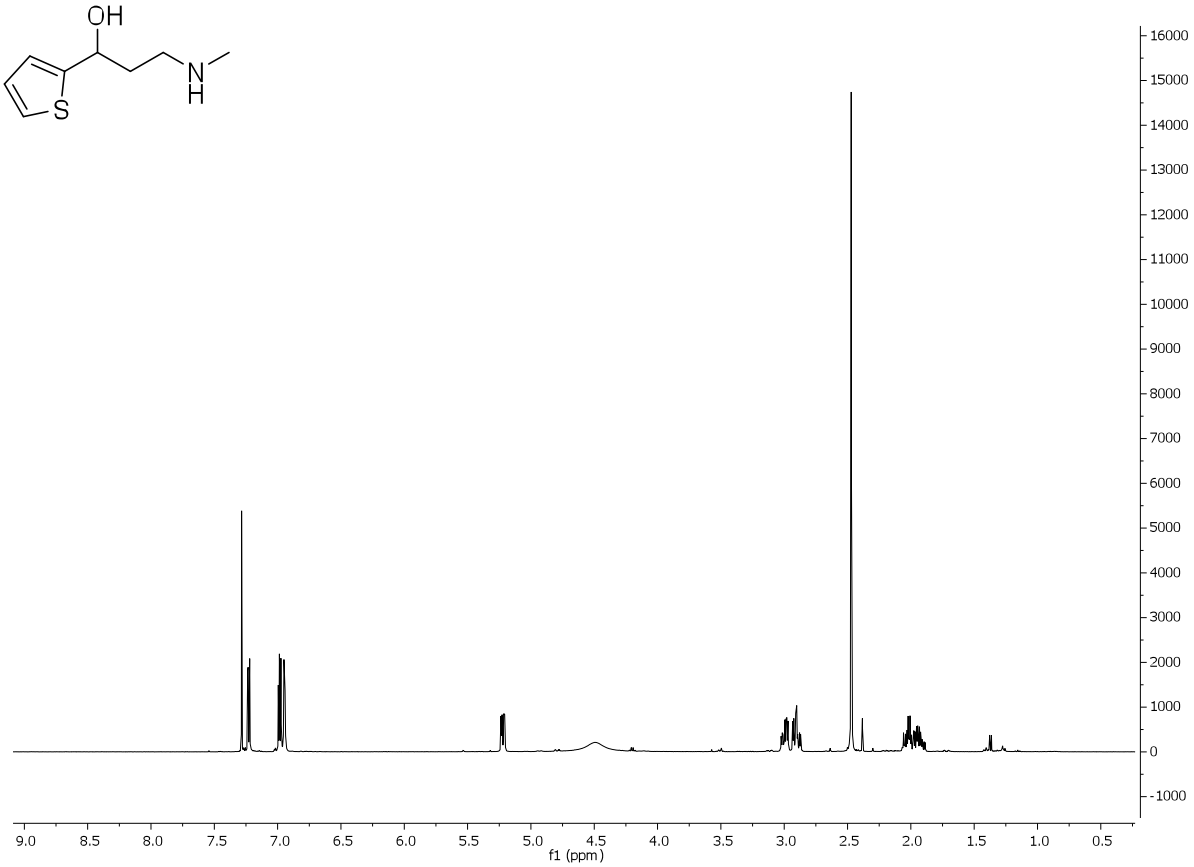


Figure 4 Chiral HPLC of (*R*)-**13b** showing a 97:3 ratio of the major and minor (respectively) enantiomers, thus giving 94% *e.e.* overall.

^{1}H and ^{13}C-NMR



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7000
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3000
2000
1000
0
-1000
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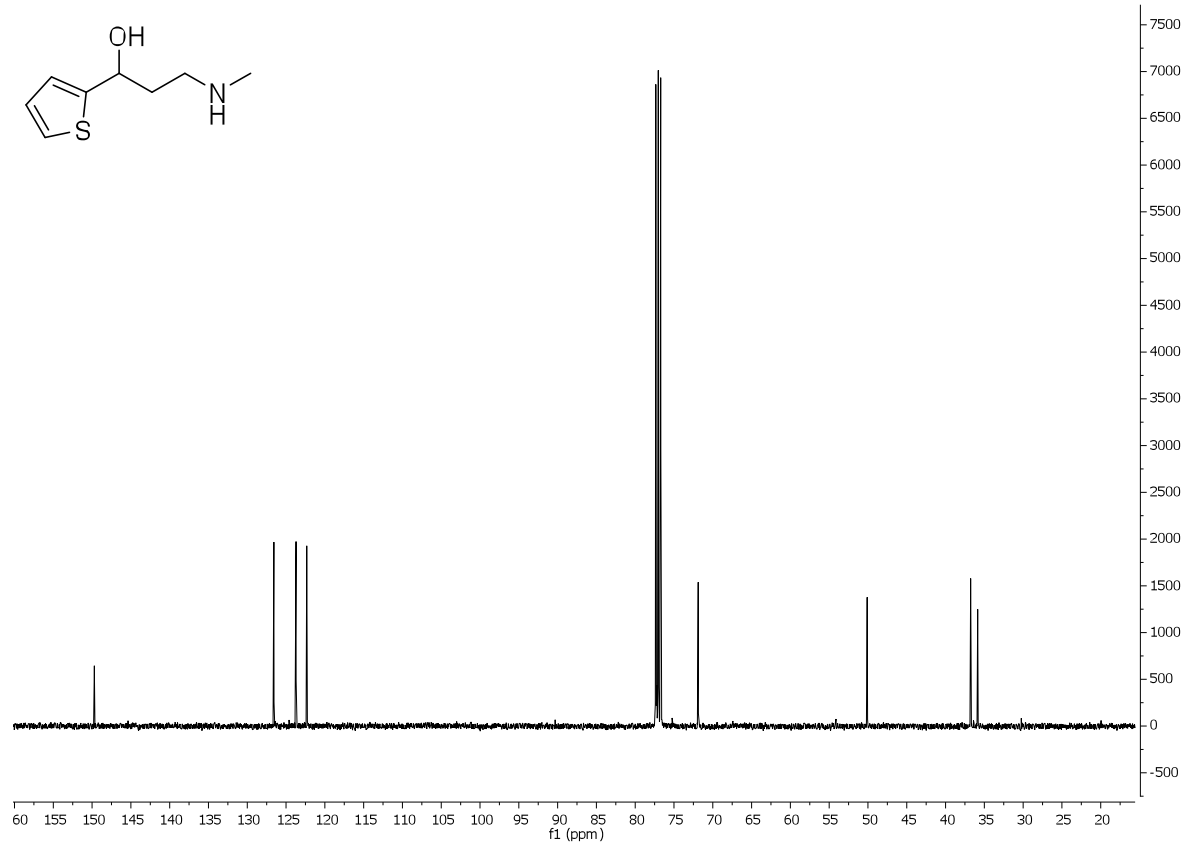
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0
-500
60 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)


F3C
O
N
H
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
8.0
7.5
7.0
6.5
6.0
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3.0
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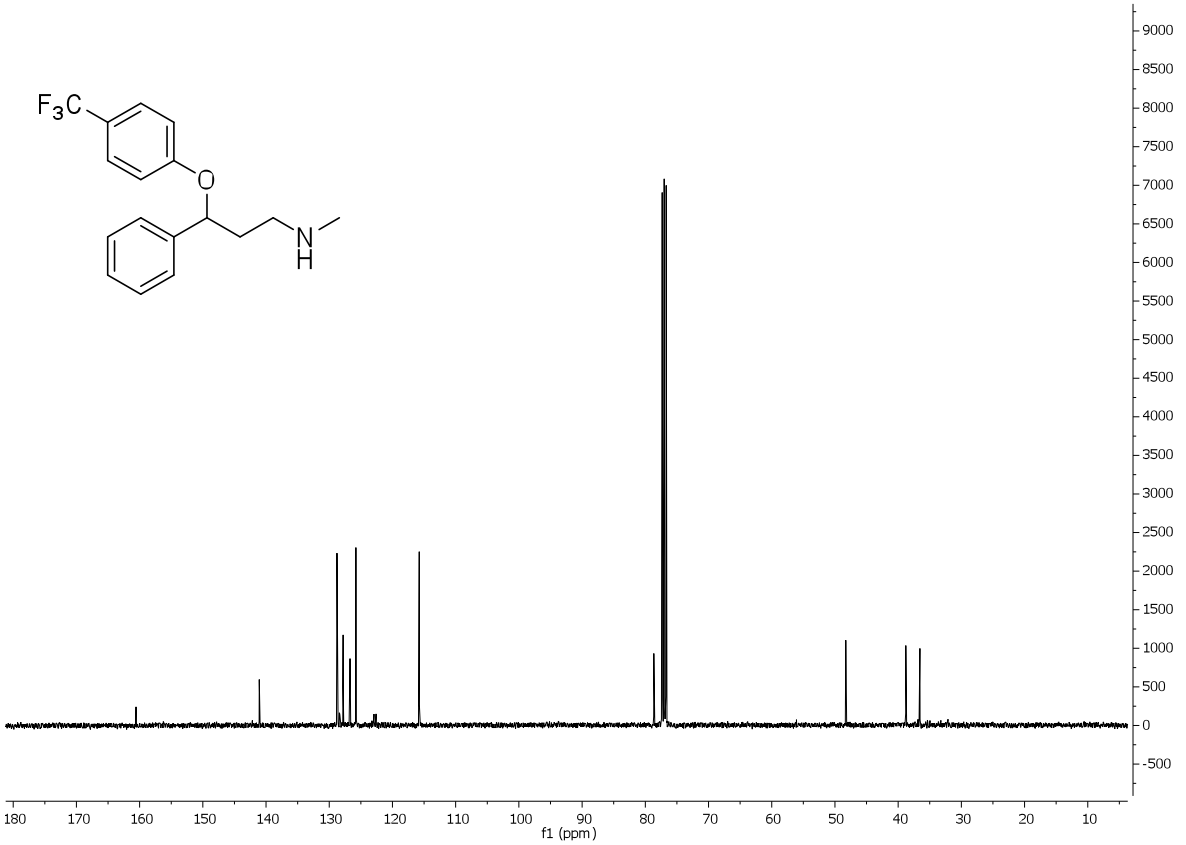
1.5
1.0
0.5
f1 (ppm)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4500
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3000
2500
2000
1500
1000
500
0
-500
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110
100
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80
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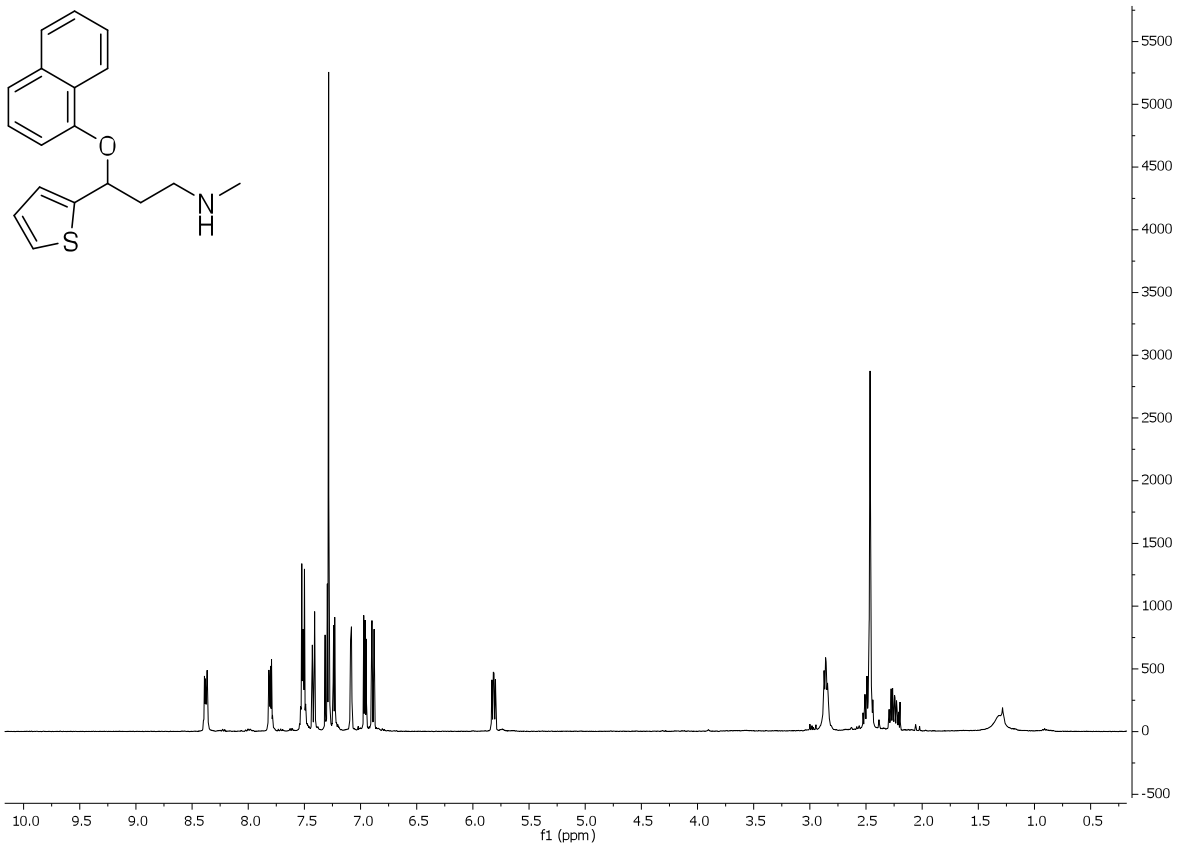
60
50
40
30
20
10
f1 (ppm)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9.0
8.5
8.0
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6.0
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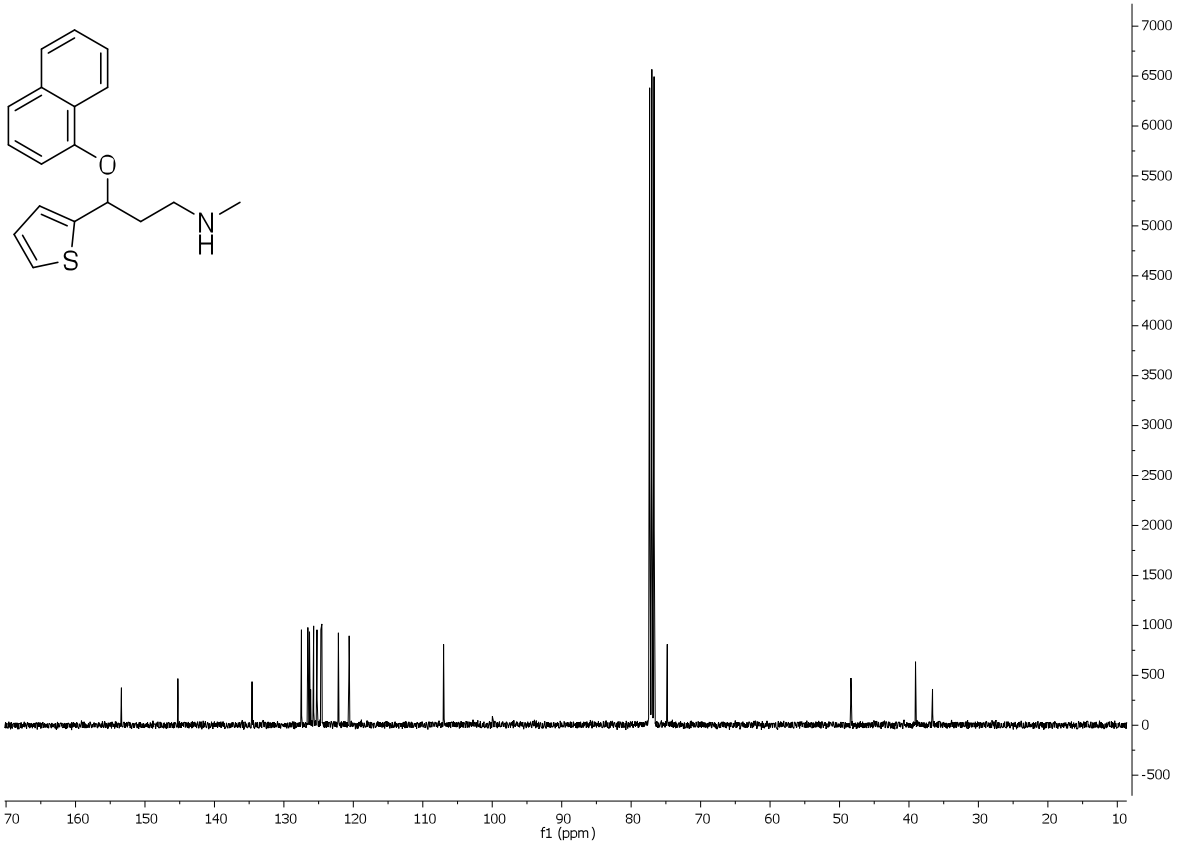
f1 (ppm)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0
-500
70
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140
130
120
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100
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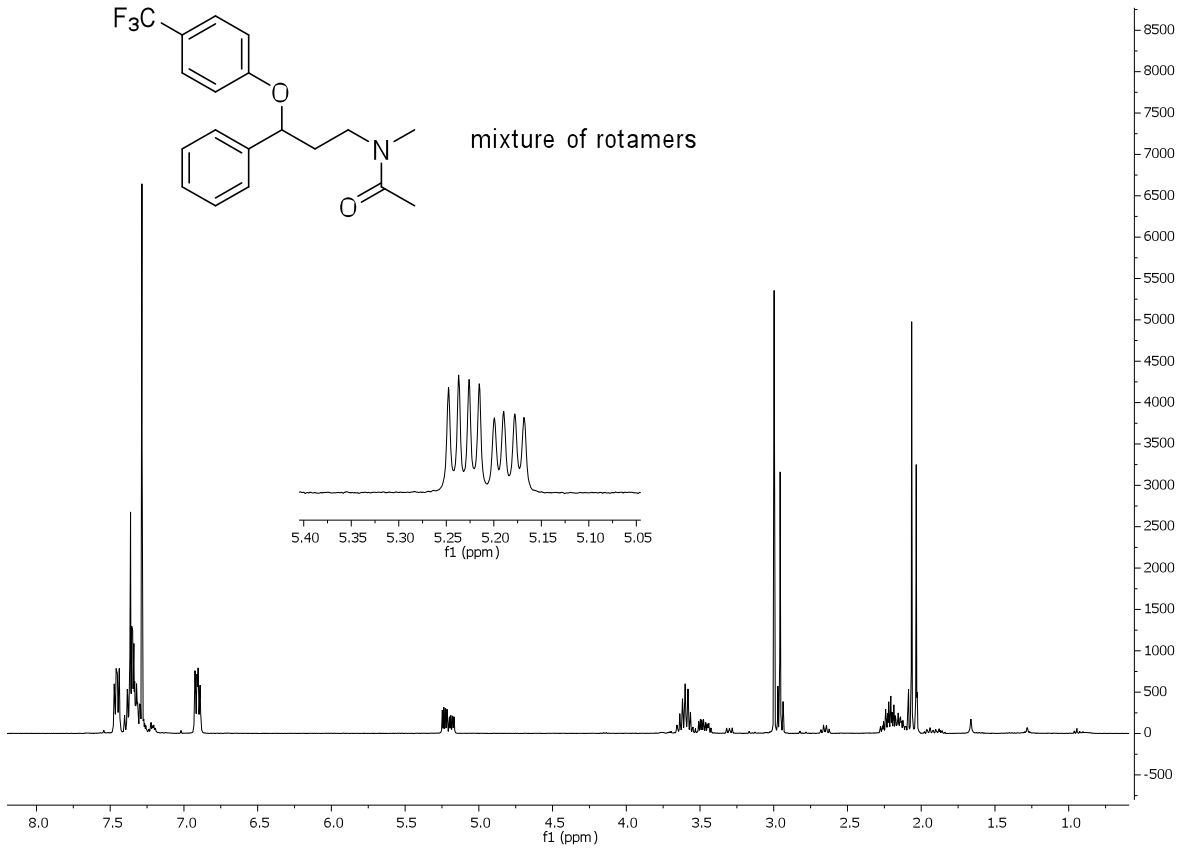
80
70
60
50
40
30
20
10
f1 (ppm)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O
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f1 (ppm)
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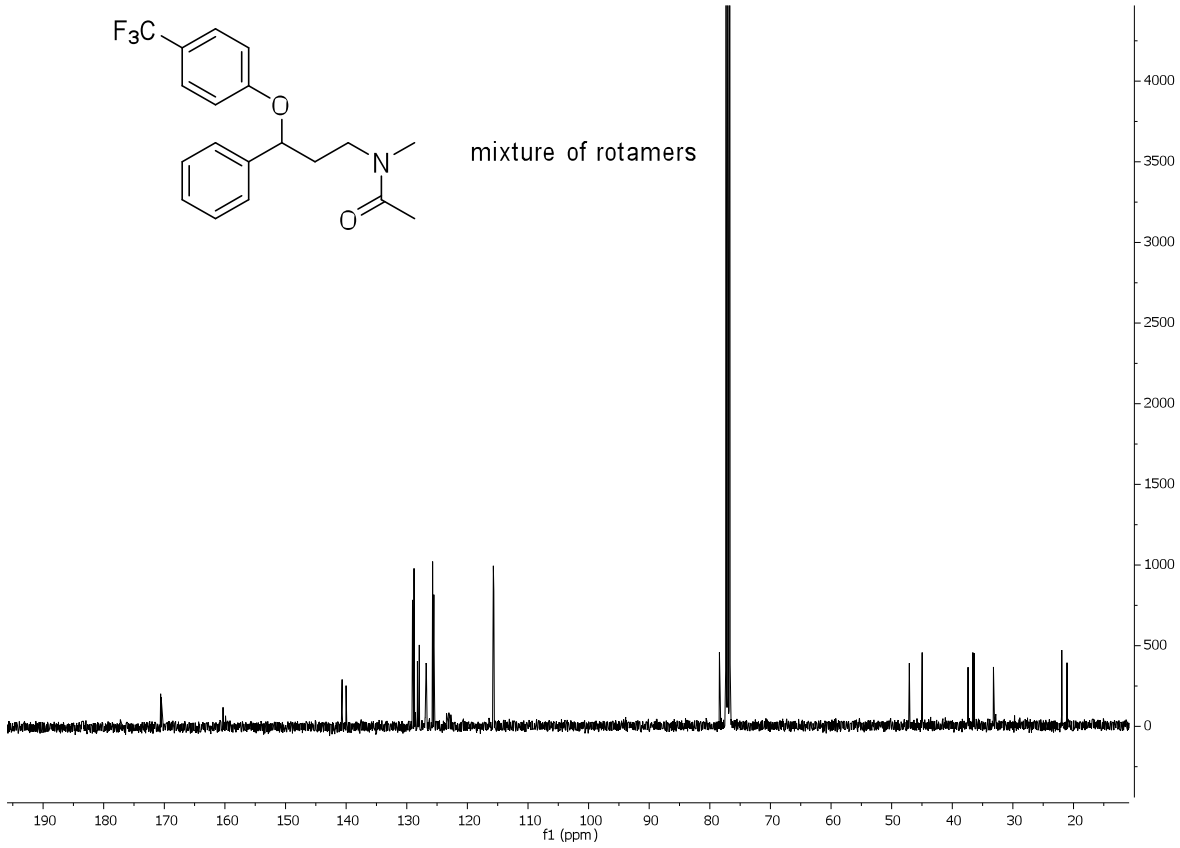
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)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O
mixture of rotamers
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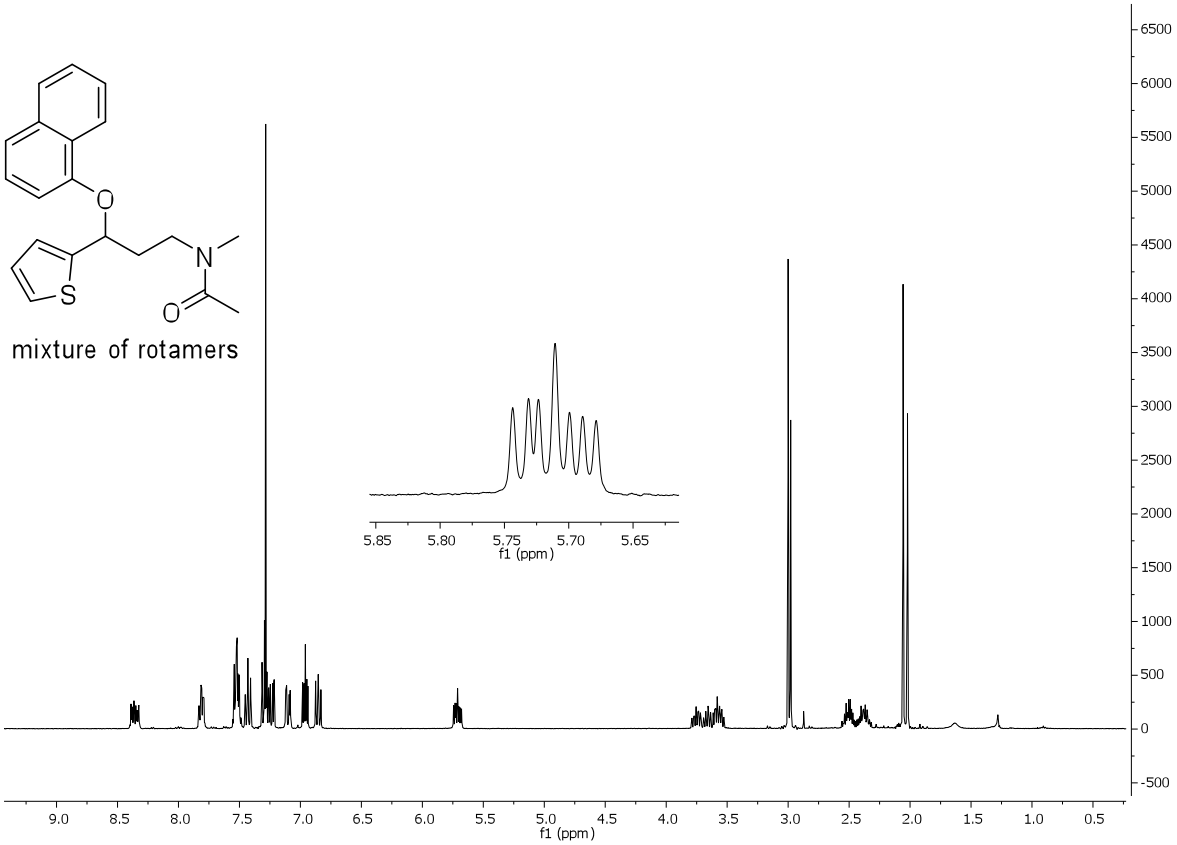
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S
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mixture of rotamers
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f1 (ppm)
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5000
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3500
3000
2500
2000
1500
1000
500
0
-500
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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4.0
3.5
3.0
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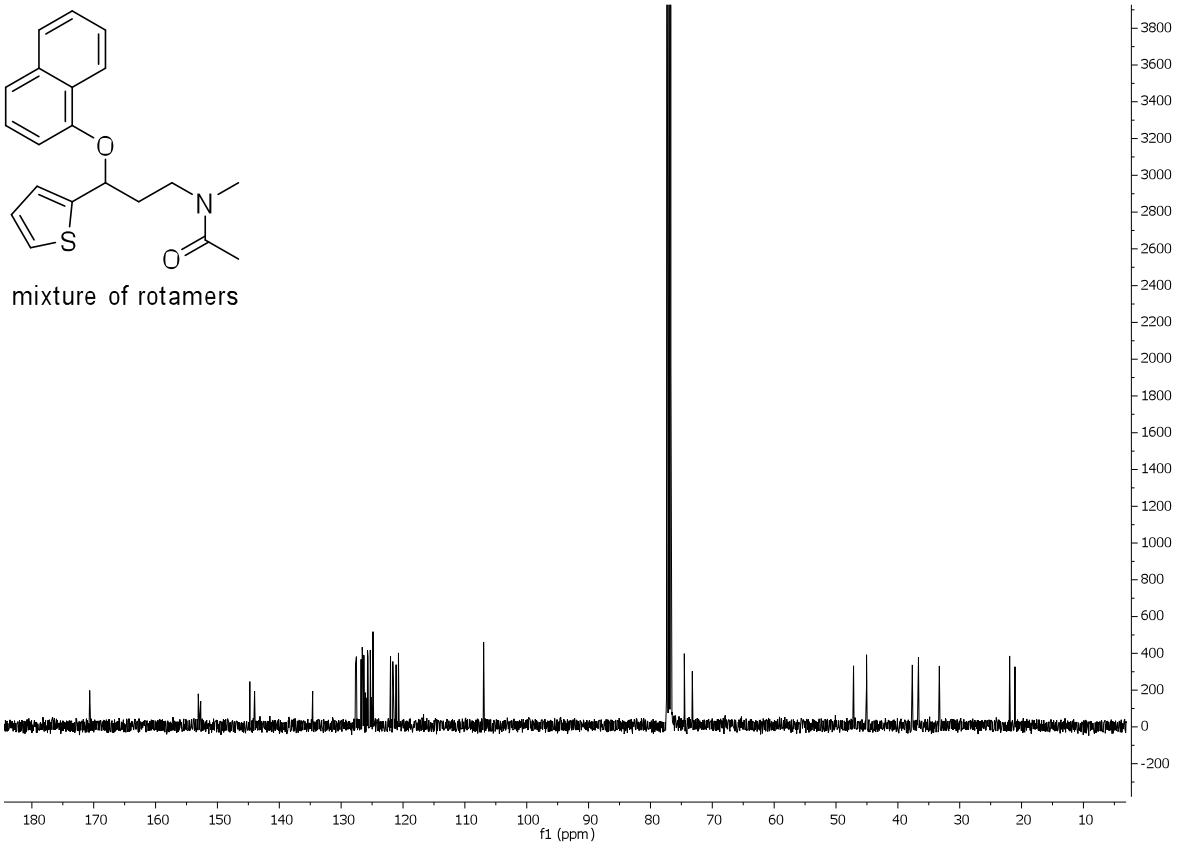
2.0
1.5
1.0
0.5
f1 (ppm)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N
S
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1600
1400
1200
1000
800
600
400
200
0
-200
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140
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100
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80
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60
50
40
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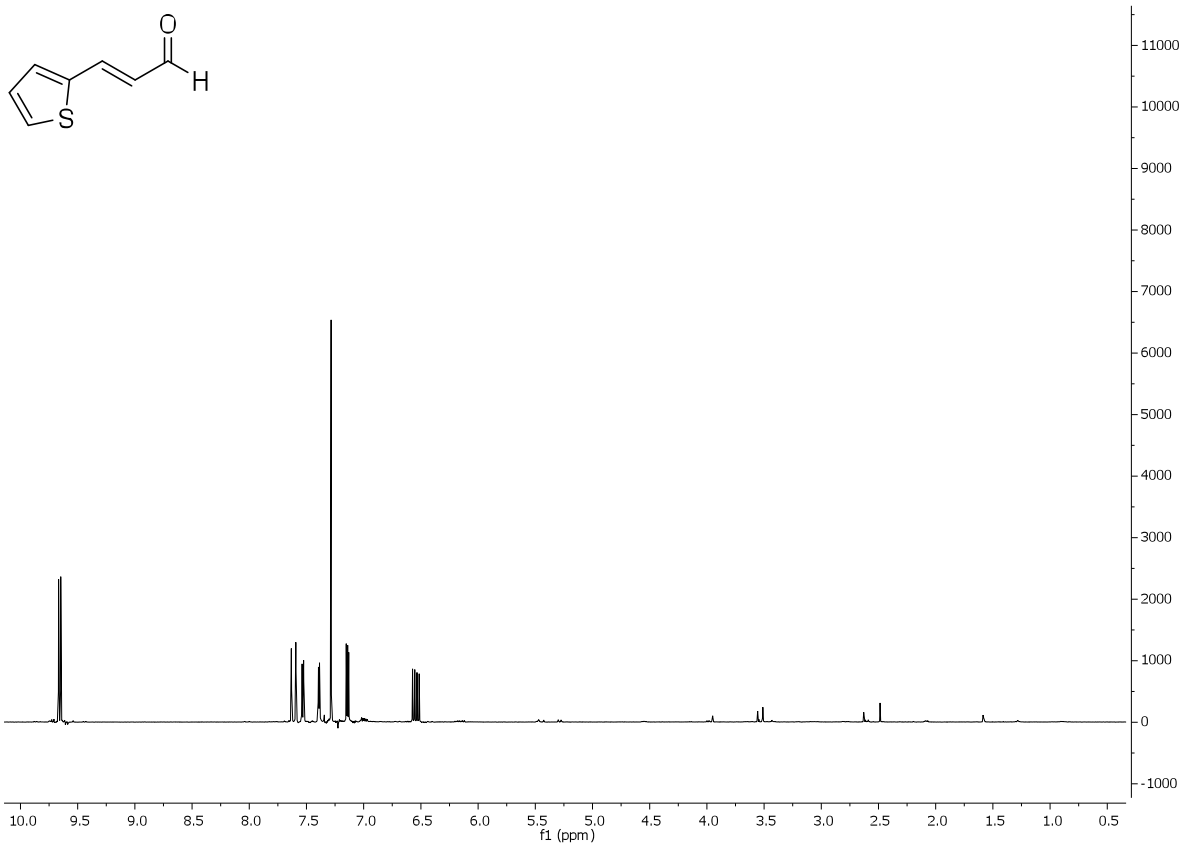
20
10
f1 (ppm)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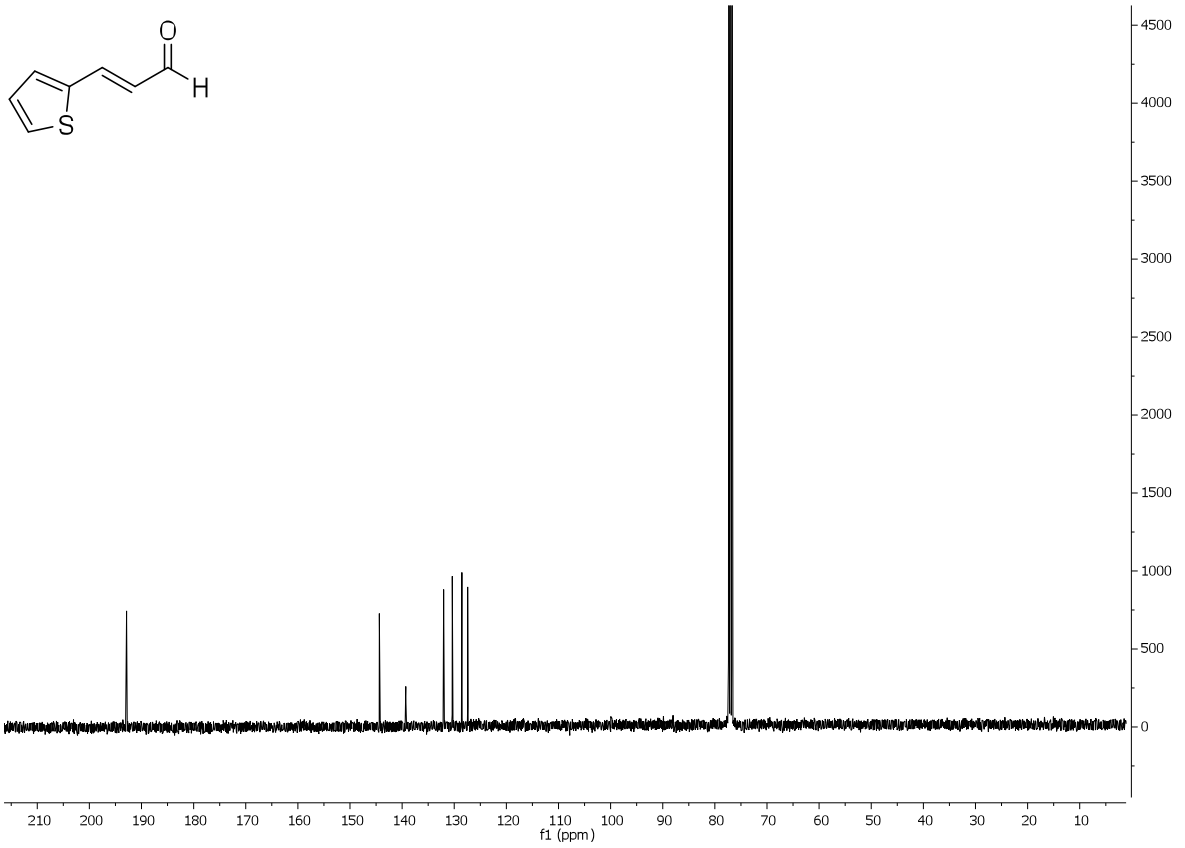
f1 (ppm)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f1 (ppm)