Electronic Supplementary Material (ESI) for RSC Advances.

In situ generation of dihydropyridine for the enantioselective transfer hydrogenation of 1,4-benzoxazines

A. Aillerie, C. Gosset, C. Dumont, V. Skrzypczak, P. Champetter, S. Pellegrini, T. Bousquet,* L. Pélinski*

till.bousquet@univ-lille1.fr and lydie.pelinski@univ-lille1.fr

Table of contents

General considerations

Solvents were not distilled and were used as received from commercial sources. BINOL phosphoric acids and other common reagents were purchased from commercial sources and used without further purification. Flash column chromatography was performed with Macherey-Nagel silica gel (230-400 mesh). Enantiomeric excesses were determined using a Hitachi Elite Lachrom HPLC with a binary pump and a diode array detector. Column conditions are reported in the experimental section below. The chiral HPLC method was calibrated with the corresponding racemic mixtures. Optical rotations were determined at 589 nm (sodium D line) by using a Perkin-Elmer-343 polarimeter. NMR data of dihydrobenzoxazines **2a**,[i,ii] **2b**,[ii,iii,iv] **2c**,[iv] **2d**,[iv,v,vi] **2e**,[i,ii,iv] **2f**,[iii,iv] **2g**[i,iii] were recorded on a Bruker Advance spectrometer (300 MHz for ^{1}H) and are in accordance to literature.

Synthesis of the dihydrobenzoxazines

(*S*)-3-Phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine 2a

To a solution containing the benzoxazine **1a** (50.2 mg, 0.24 mmol), ethyl acetoacetate (154 µL, 1.22 mmol) and the catalyst **3f** (8.4 mg, 0.012 mmol) in toluene (2 mL) were successively added NH_4HCO_3 (68 mg, 0.86 mmol) and the formaldehyde 37 wt. % in H_2O (39 µL, 0.53 mmol). After 48h at 70 °C, the mixture was evaporated under vacuum and the residue was purified over silica gel chromatography (petroleum ether/ethyl acetate: 96/4). The (*S*)-3-Phenyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine **2a** was isolated with 93% yield (48 mg) and 94% ee. $[\alpha]_D^{20}$ = +125.5 (c 0.9 $CHCl_3$). ^{1}H NMR (300 MHz, C*D*Cl_3): δ = 4.02 (dd, *J* = 8.6, 10.6 Hz, 1H), 4.30 (dd, *J* = 3.0, 10.6 Hz, 1H), 4.52 (dd, *J* = 3.0, 8.6 Hz, 1H), 6.67-6.75 (m, 2H), 6.80-6.89 (m, 2H), 7.33-7.44 (m, 5H). ^{13}C NMR (75 MHz, C*D*Cl_3): δ = 54.4, 71.1, 115.5, 116.7, 119.1, 121.6, 127.3, 128.5, 129.0, 134.0, 139.3, 143.7. HPLC conditions: Chiralpak® IB (Hex/EtOH = 75/25, 0.6 mL.min^{-1}), major enantiomer: t_R = 13.98 min, minor enantiomer: t_R = 10.94 min, 94% ee.

(*S*)-6-Methyl-3-phenyl-3,4-dihydro-2*H*-benzo[b][1,4]oxazine 2b

The product was prepared from benzoxazine **1b** (53.5 mg, 0.24 mmol) according to the previous procedure. The (*S*)-6-Methyl-3-phenyl-3,4-dihydro-2*H*-benzo[b][1,4]oxazine **2b** was isolated with 99% yield (53 mg) and 89% ee. $[\alpha]_D^{20}$ = +73.1 (c 0.5 $CHCl_3$). ^{1}H NMR (300 MHz, C*D*Cl_3): δ = 2.25 (s, 3H), 3.99 (dd, *J* = 8.5, 10.5 Hz, 1H), 4.27 (dd, *J* = 3.0, 10.6 Hz, 1H), 4.51 (d, *J* = 6.5 Hz), 6.51-6.54 (m, 2H), 6.76 (d, *J* = 8.40 Hz, 2H), 7.33-7.43 (m, 5H). ^{13}C NMR (75 MHz, C*D*Cl_3): δ = 20.9, 54.5, 71.1, 116.0, 116.4, 119.6, 127.3, 128.4, 133.6, 139.6, 139.5, 141.5. HPLC conditions: Chiralpak® IB (Hex/EtOH = 95/5, 0.5 mL.min^{-1}), major enantiomer: t_R = 18.85 min, minor enantiomer: t_R = 15.90 min, 89% ee.

(*S*)-7-Methyl-3-phenyl-3,4-dihydro-2*H*-benzo[b][1,4]oxazine 2c

The product was prepared from benzoxazine **1c** (53.5 mg, 0.24 mmol) according to the previous procedure. The (*S*)-7-Methyl-3-phenyl-3,4-dihydro-2*H*-benzo[b][1,4]oxazine **2c** was isolated with 89% yield (53 mg) and 91% ee. $[\alpha]_D^{20}$ = +98.2 (c 1 $CHCl_3$). ^{1}H NMR (300 MHz, C*D*Cl_3): δ = 2.25 (s, 3H), 3.99 (dd, *J* = 8.6, 10.6 Hz, 1H), 4.27 (dd, *J* = 3.0, 10.6 Hz, 1H), 4.48 (dd, *J* = 8.5, 10.5 Hz, 1H), 6.57-6.69 (m, 3 H), 7.31-7.42 (m, 5H). . ^{13}C NMR (75 MHz, C*D*Cl_3): δ = 20.7, 54.6, 71.3, 115.5, 117.3, 122.1, 127.3, 128.4, 128.8, 128.9, 131.5, 139.5, 143.6. HPLC conditions: Chiralpak® IB (Hex/EtOH = 95/5, 0.5 mL.min^{-1}), major enantiomer: t_R = 21.86 min, minor enantiomer: t_R = 13.89 min, 91% ee.

(*S*)-6-Chloro-3-phenyl-3,4-dihydro-2*H*-benzo[b][1,4]oxazine 2d

The product was prepared from benzoxazine **1d** (58.3 mg, 0.24 mmol) according to the previous procedure. The (*S*)-6-Chloro-3-phenyl-3,4-dihydro-2*H*-benzo[b][1,4]oxazine **2d** was isolated with 75% yield (44.1 mg) and 93% ee. $[\alpha]_D^{20}$ = +75.2 (c 0.7 $CHCl_3$). ^{1}H NMR (300 MHz, C*D*Cl_3): δ = 3.97 (dd, *J* =

8.4, 10.7 Hz, 1H), 4.28 (dd, *J* = 3.0, 10.6 Hz, 1H), 4.50 (1H, *J* = 3.0, 10.4 Hz), 6.62-6.66 (m, 2H), 6.75-6.78 (m, 1H), 7.32-7.44 (m, 5H). ^{13}C NMR (75 MHz, C*D*Cl$_3$): δ = 54.1, 70.9, 114.9, 117.6, 126.3, 127.2, 128.6, 129.0, 135.0, 138.8, 142.2. HPLC conditions: Chiralpak® IB (Hex/EtOH = 95/5, 0.5 mL.min^{-1}), major enantiomer: t_R = 26.66 min, minor enantiomer: t_R = 24.30 min, 93% ee.

(*S*)-3-(4-Methoxyphenyl)-3,4-dihydro-2*H*-benzo[b][1,4]oxazine 2e

The product was prepared from benzoxazine **1e** (57.4 mg, 0.24 mmol) according to the previous procedure. The (*S*)-3-(4-Methoxyphenyl)-3,4-dihydro-2*H*-benzo[b][1,4]oxazine **2e** was isolated with 99% yield (57.3 mg) and 89% ee. $[\alpha]_D^{20}$ = +77.5 (c 0.8 CHCl$_3$). ^{1}H NMR (300 MHz, C*D*Cl$_3$): δ = 3.82 (s, 3H), 3.98 (dd, *J* = 8.7, 10.6 Hz, 1H), 4.26 (dd, *J* = 3.0, 10.6 Hz, 1H), 4.46 (d, *J* = 8.3 Hz, 1H), 6.65-6.73 (m, 2H), 6.78-6.87 (m, 2H), 6.90-6.95 (m, 2H), 7.30-7.35 (m, 2H). ^{13}C NMR (75 MHz, C*D*Cl$_3$): δ = 53.8, 55.5, 71.2, 114.4, 115.5, 116.7, 119.0, 121.6, 128.4, 131.3, 134.1, 143.7, 159.8. HPLC conditions: Chiralpak® IB (Hex/EtOH = 95/5, 0.5 mL.min^{-1}), major enantiomer: t_R = 36.34 min, minor enantiomer: t_R = 22.13 min, 89% ee.

(*S*)-3-(4-Bromophenyl)-3,4-dihydro-2*H*-benzo[b][1,4]oxazine 2f

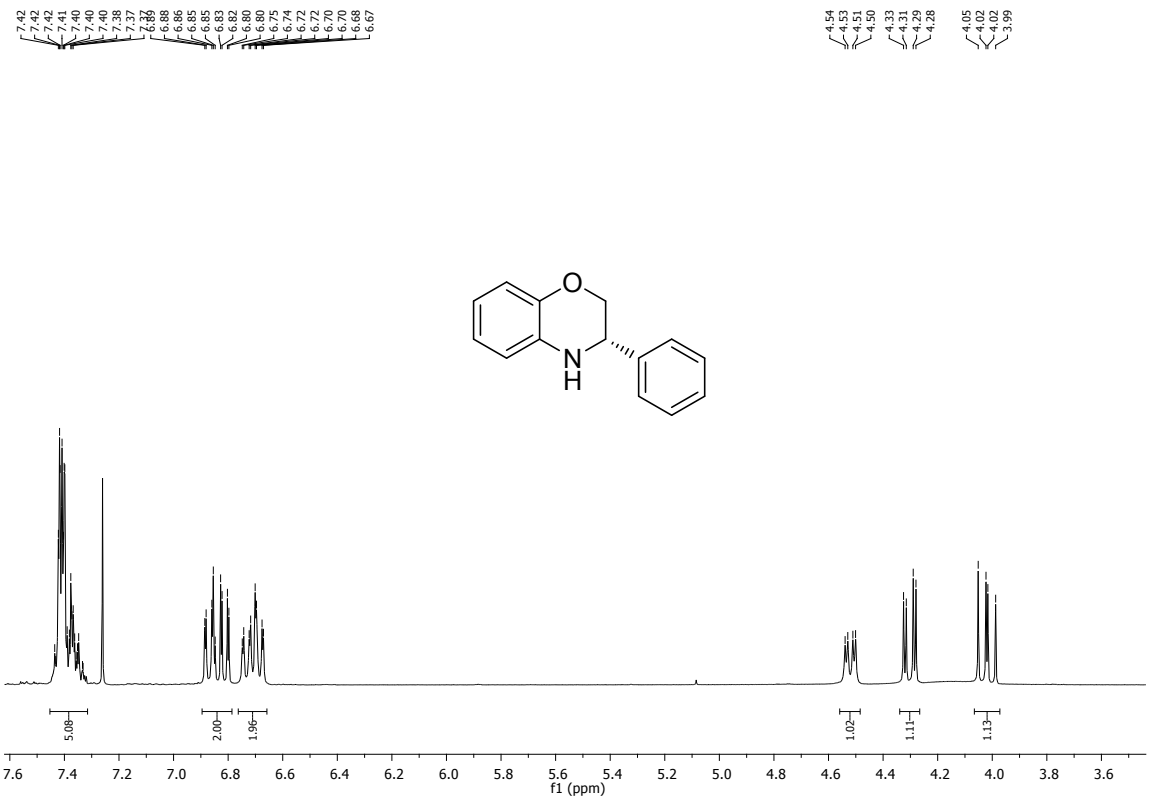
The product was prepared from benzoxazine **1f** (69 mg, 0.24 mmol) according to the previous procedure. The (*S*)-3-(4-Bromophenyl)-3,4-dihydro-2*H*-benzo[b][1,4]oxazine **2f** was isolated with 98% yield (68 mg) and 96% ee. $[\alpha]_D^{20}$ = +99.8 (c 1 CHCl$_3$). ^{1}H NMR (300 MHz, C*D*Cl$_3$): δ = 4.06 (dd, *J* = 8.5, 10.6 Hz, 1H), 4.34 (dd, *J* = 3.0, 10.6 Hz, 1H), 4.57 (dd, *J* = 3.0, 8.5 Hz, 1H), 6.69-6.76 (m, 2H), 6.81-6.91 (m, 2H), 7.35-7.40 (m, 1H), 7.44-7.50 (m, 4H), 7.58-7.64 (m, 4H). ^{13}C NMR (75 MHz, C*D*Cl$_3$): δ =53.8, 70.8, 115.6, 116.8, 119.3, 121.7, 122.3, 129.0, 132.1, 133.7, 138.4, 143.6. HPLC conditions: Chiralpak® IB (Hex/EtOH = 85/15, 0.8 mL.min^{-1}), major enantiomer: t_R = 21.24 min, minor enantiomer: t_R = 10.92 min, 89% ee.

(*S*)-3-([1,1'-Biphenyl]-4-yl)-3,4-dihydro-2*H*-benzo[b][1,4]oxazine 2g

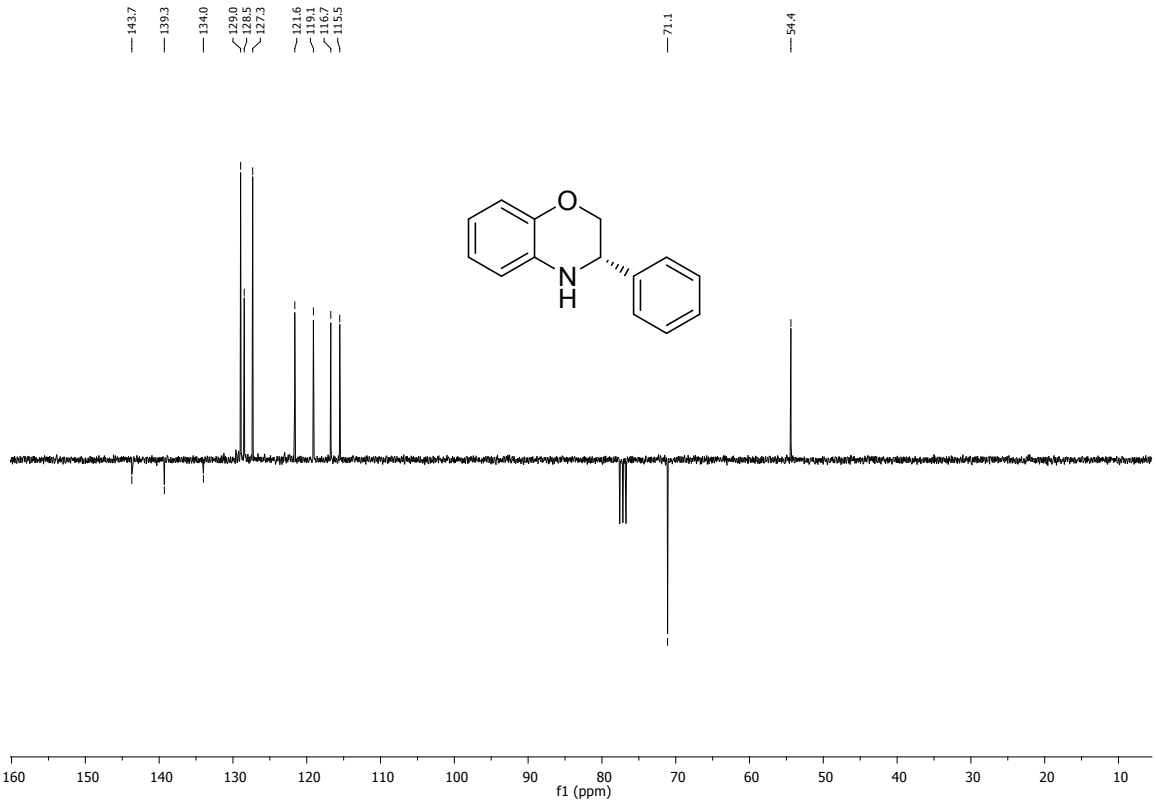
The product was prepared from benzoxazine **1g** (68.4 mg, 0.24 mmol) according to the previous procedure. The (*S*)-3-(4-Bromophenyl)-3,4-dihydro-2*H*-benzo[b][1,4]oxazine **2g** was isolated with 91% yield (63 mg) and 95% ee. $[\alpha]_D^{20}$ = +87.9 (c 0.6 CHCl$_3$). ^{1}H NMR (300 MHz, C*D*Cl$_3$): δ = 4.06 (dd, *J* = 8.5, 10.6 Hz, 1H), 4.34 (dd, *J* = 3.0, 10.6 Hz, 1H), 4.57 (dd, *J* = 3.0, 8.5 Hz, 1H), 6.69-6.76 (m, 2H), 6.81-6.91 (m, 2H), 7.35-7.40 (m, 1H), 7.43-7.51 (m, 4H), 7.58-7.64 (m, 4H). ^{13}C NMR (75 MHz, C*D*Cl$_3$): δ =54.1, 71.1, 115.5, 116.8, 119.1, 121.7, 127.3, 127.6, 127.7, 127.8, 129.0, 134.0, 138.3, 140.8, 141.5, 141.5, 143.7. HPLC conditions: Chiralpak® IB (Hex/EtOH = 75/25, 0.6 mL.min^{-1}), major enantiomer: t_R = 23.32 min, minor enantiomer: t_R = 15.12 min, 95% ee.

^{1}H and ^{13}C NMR spectrums of dihydrobenzoxazines

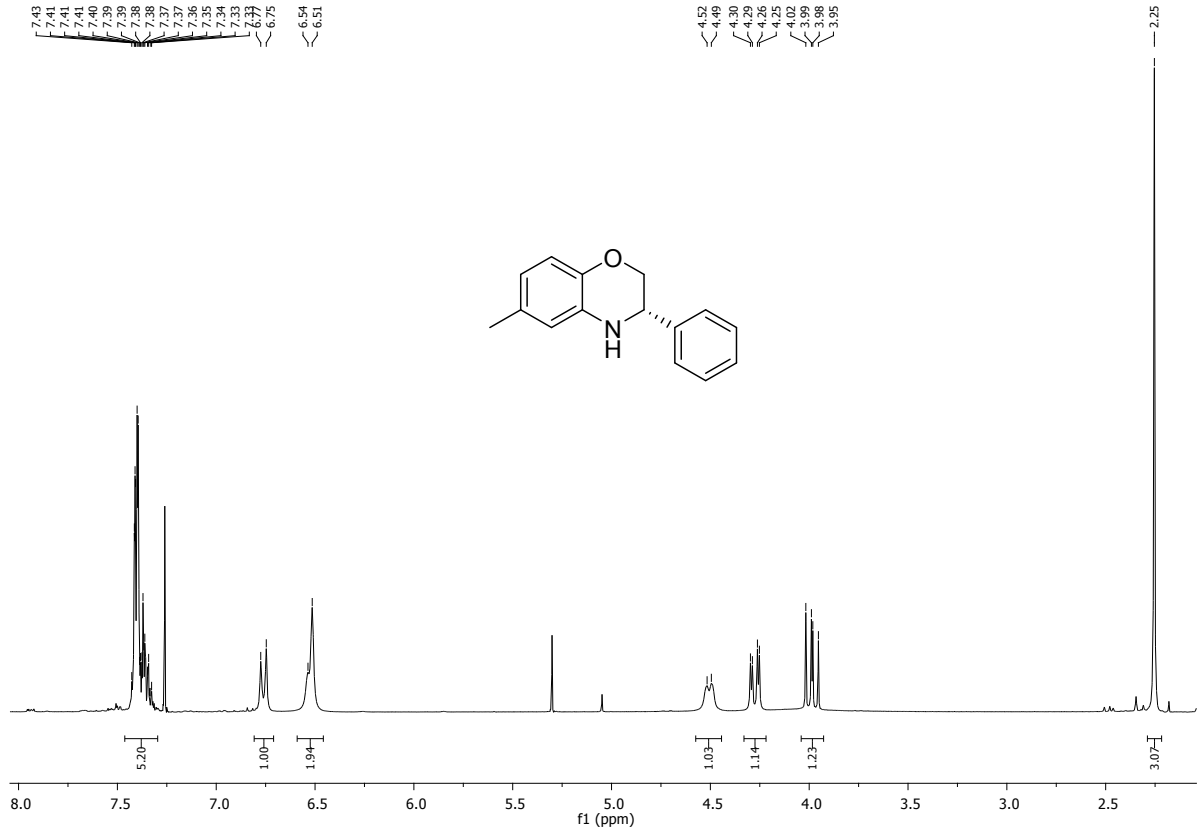
^{1}H NMR spectrum of compound **2a**



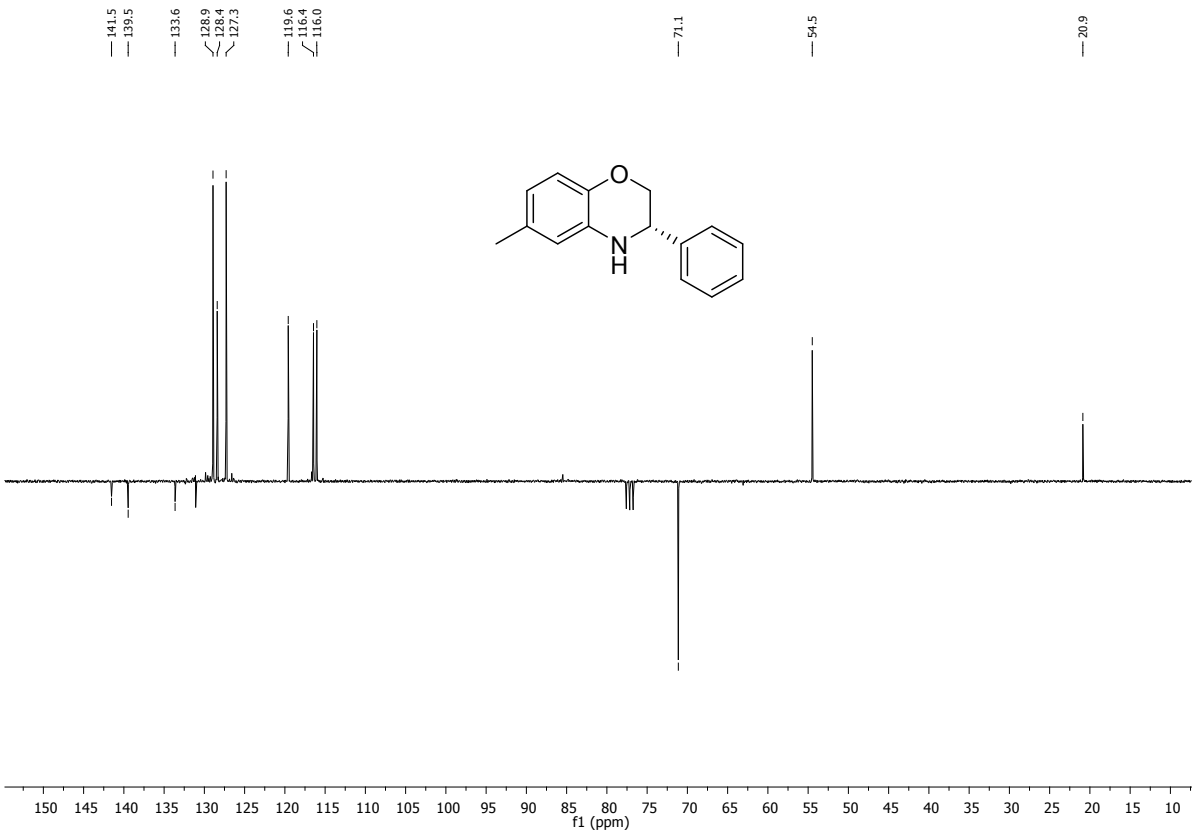
^{13}C NMR spectrum of compound **2a**



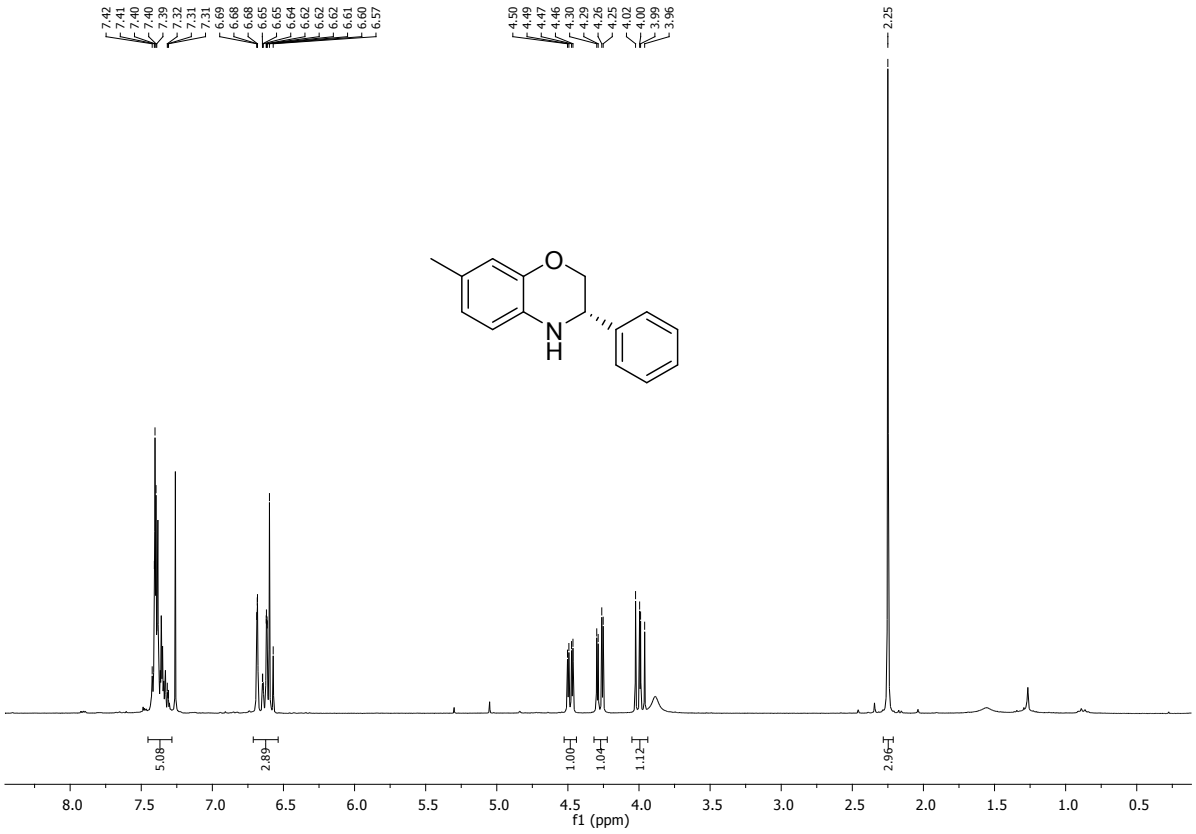
^{1}H NMR spectrum of compound **2b**



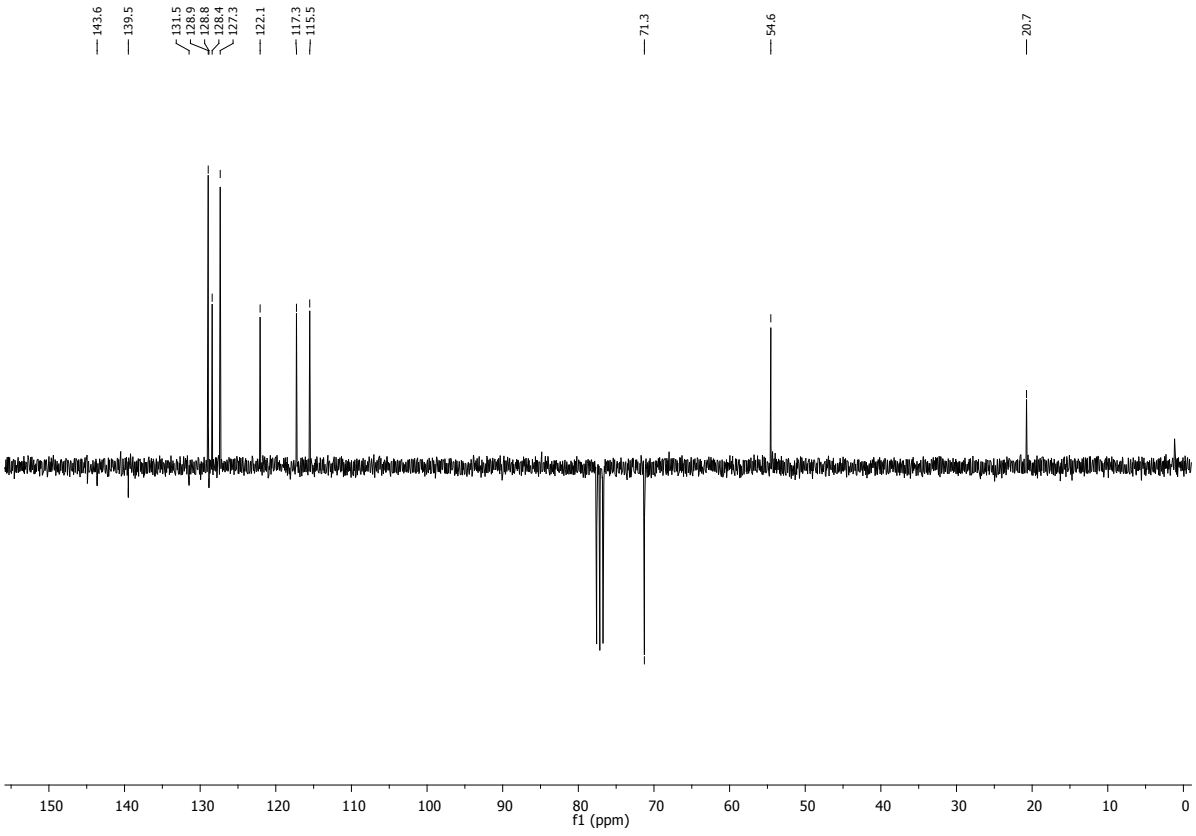
^{13}C NMR spectrum of compound **2b**



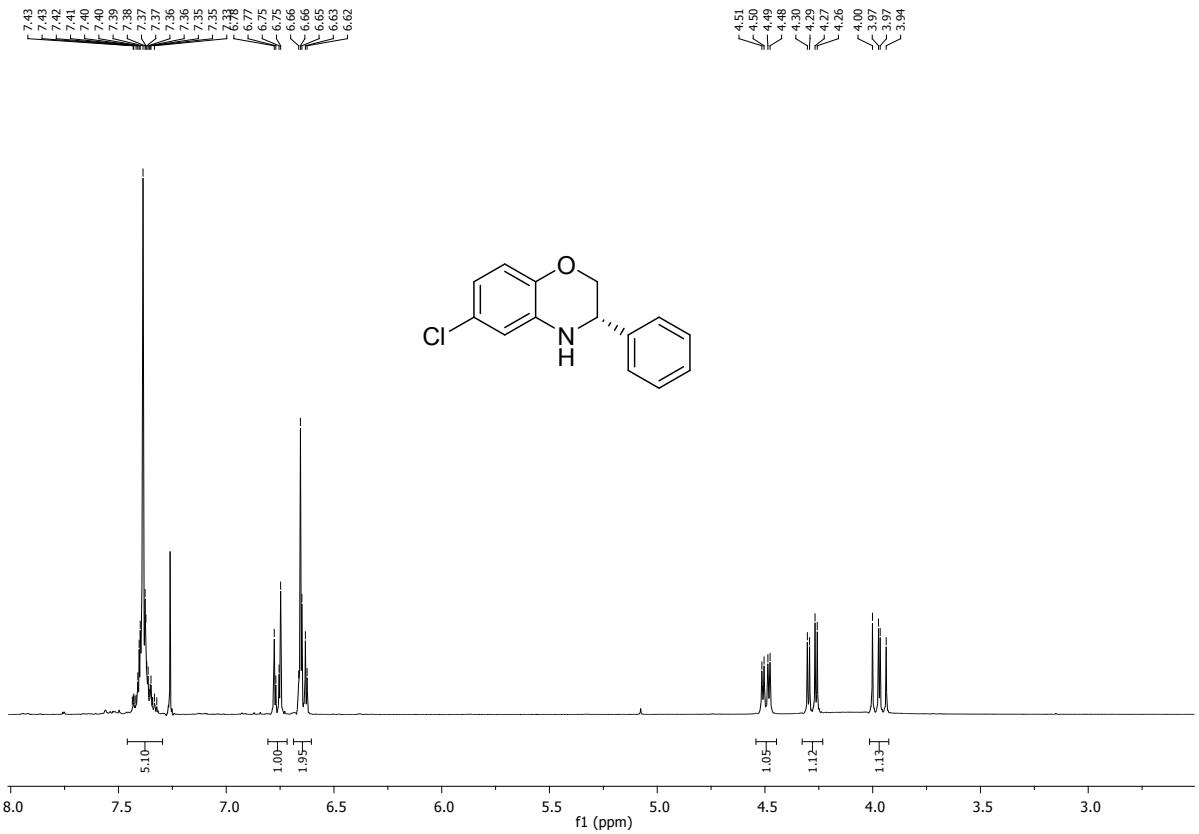
^{1}H NMR spectrum of compound **2c**



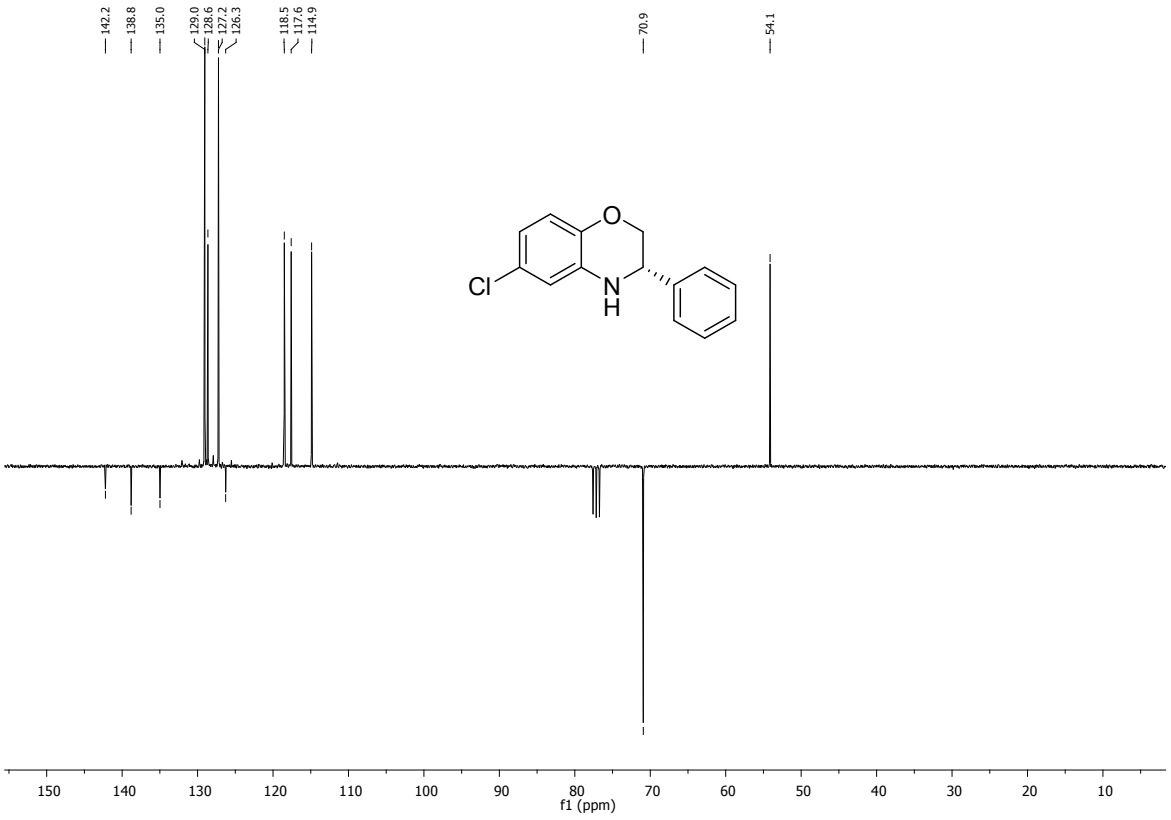
^{13}C NMR spectrum of compound **2c**



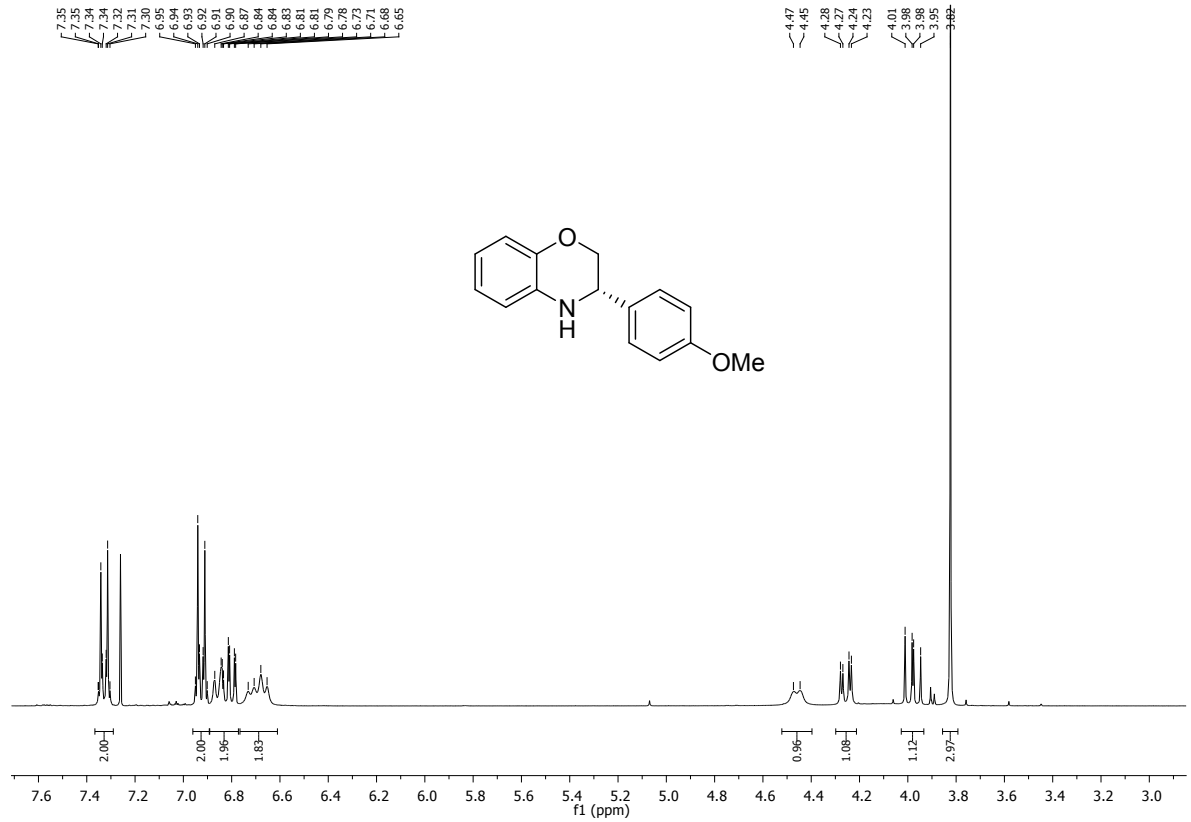
^{1}H NMR spectrum of compound **2d**



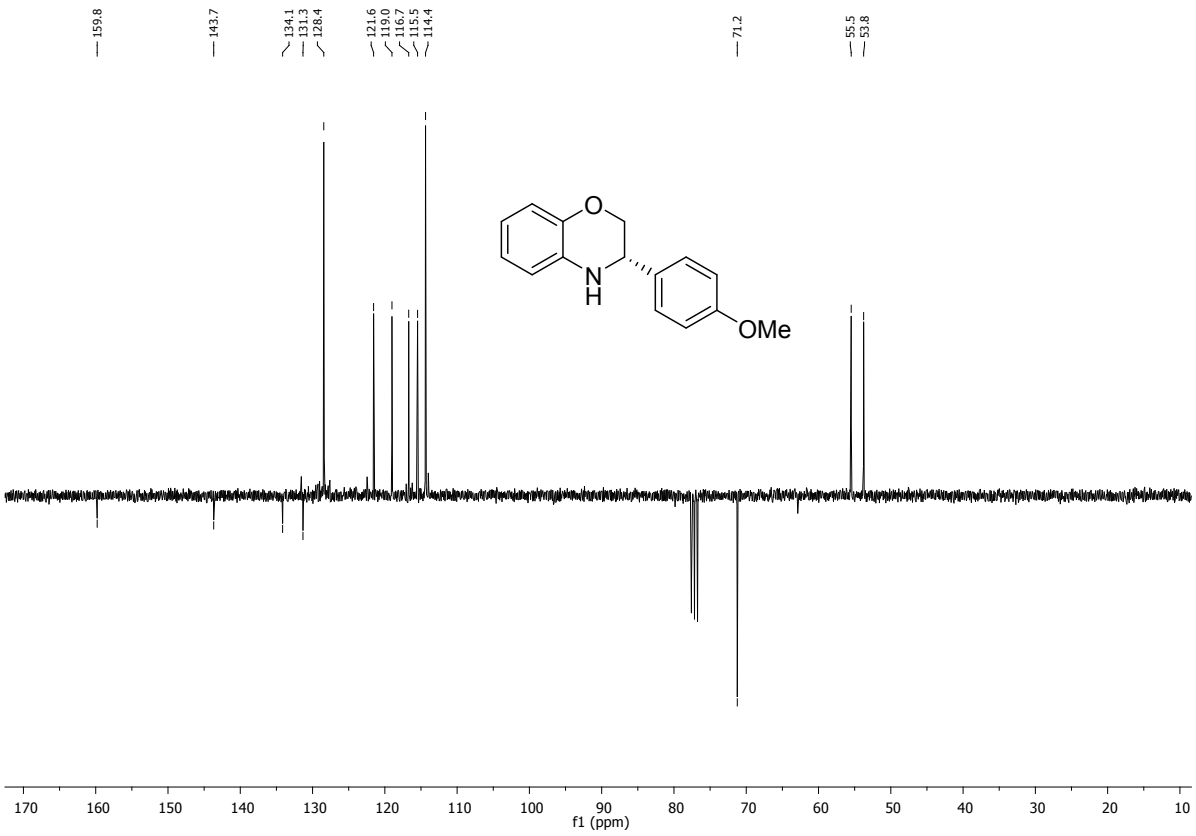
^{13}C NMR spectrum of compound **2d**



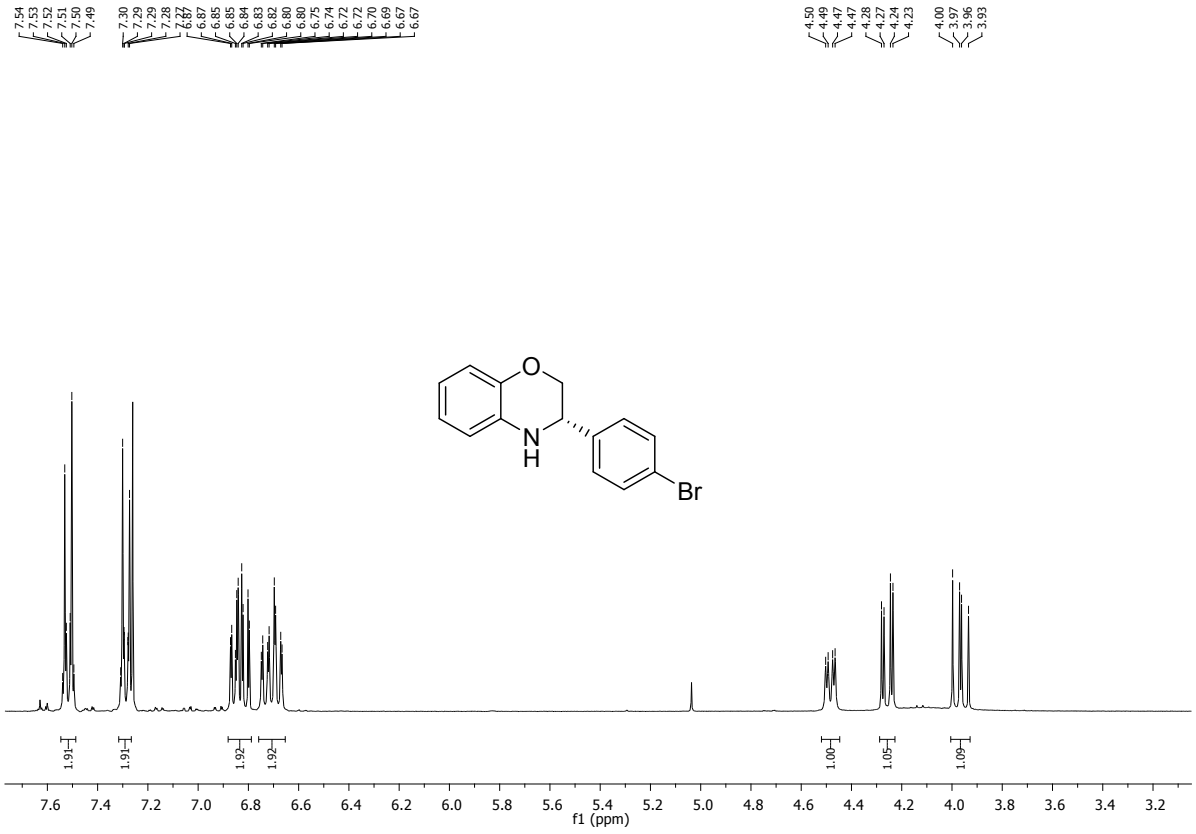
^{1}H NMR spectrum of compound **2e**



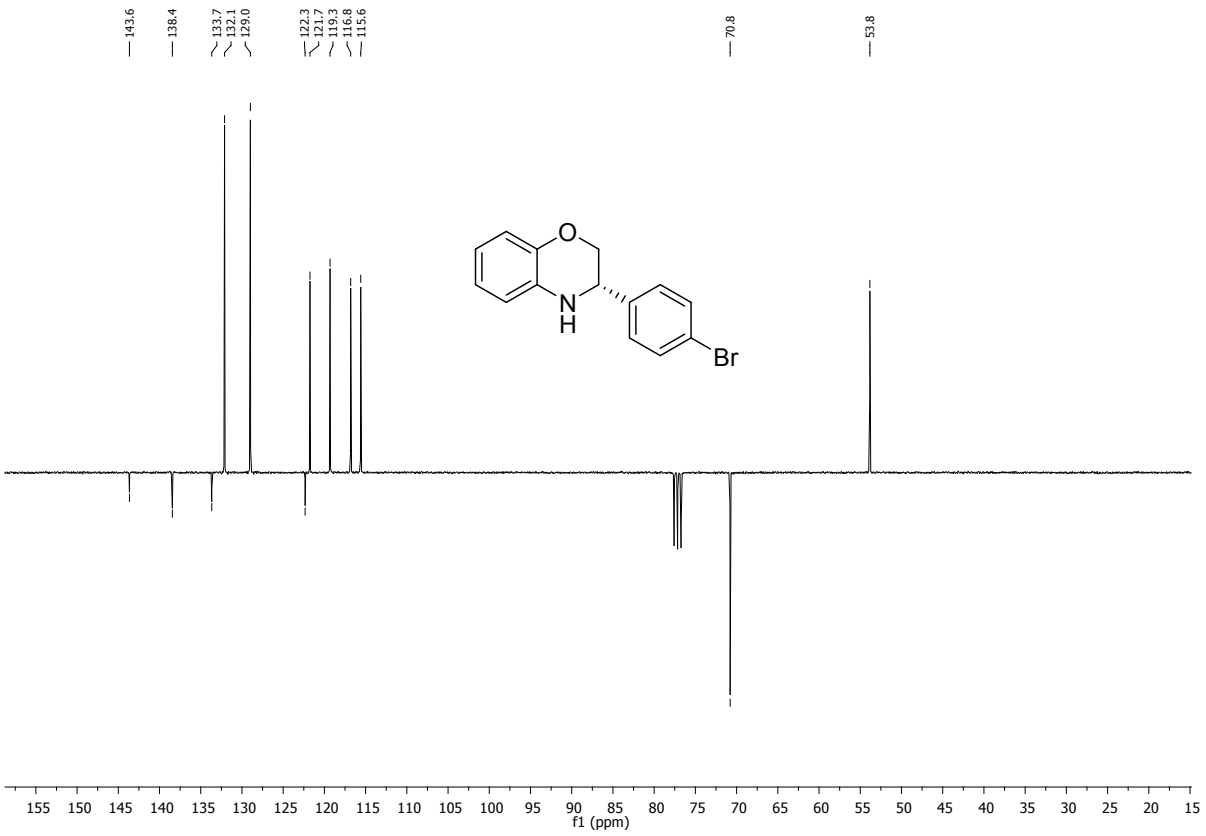
^{13}C NMR spectrum of compound **2e**



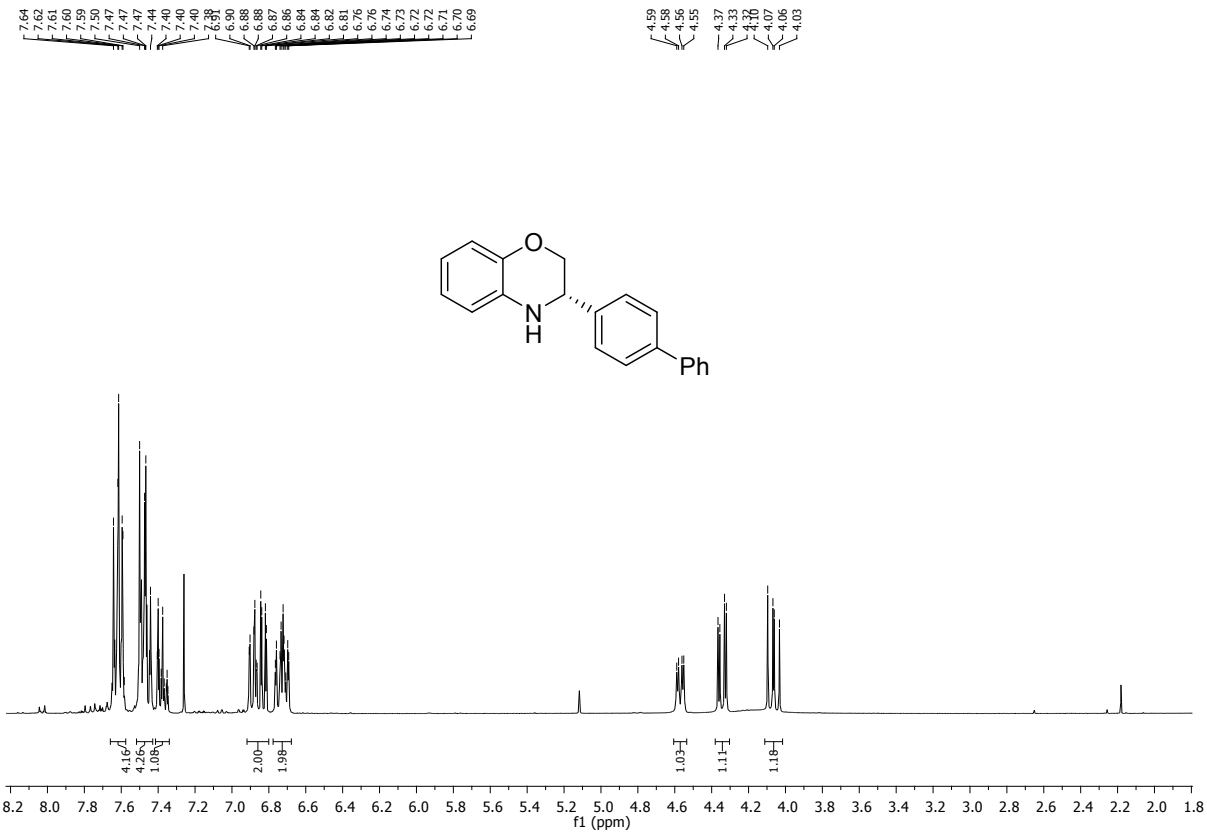
^{1}H NMR spectrum of compound **2f**



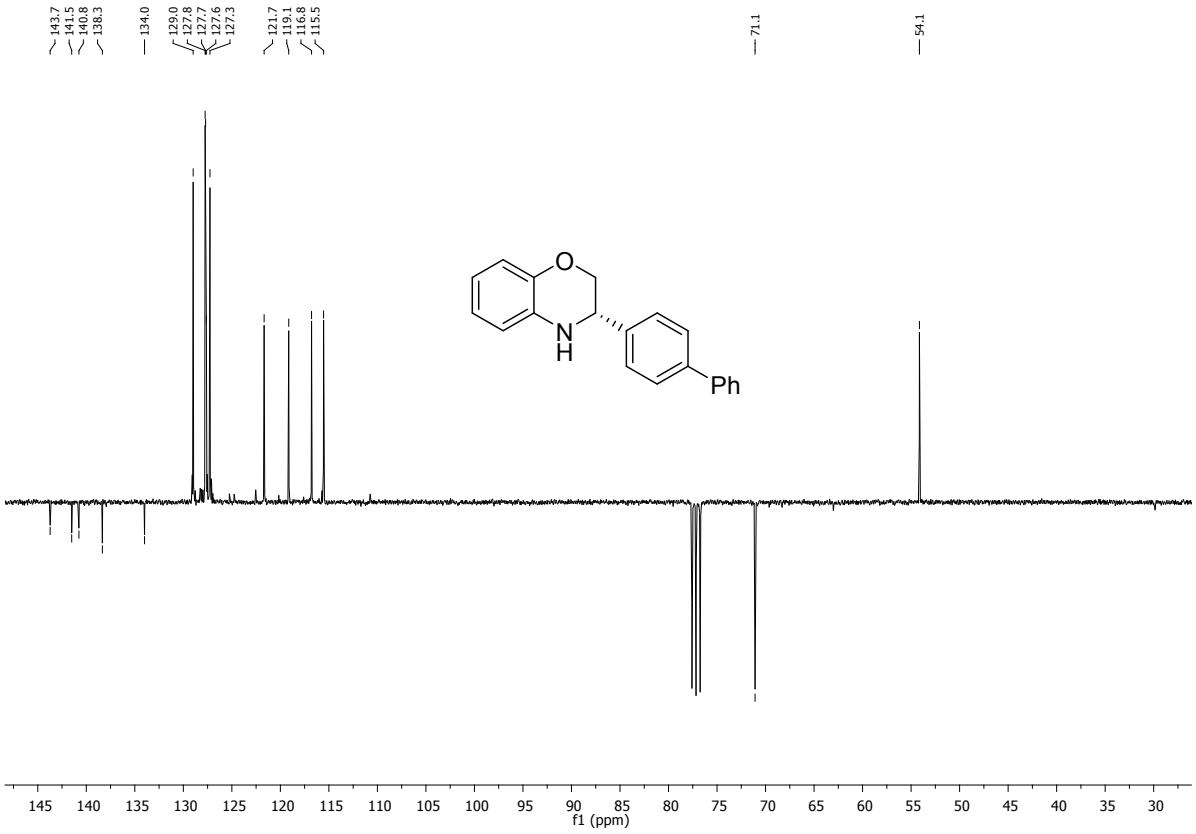
^{13}C NMR spectrum of compound **2f**



^{1}H NMR spectrum of compound **2g**

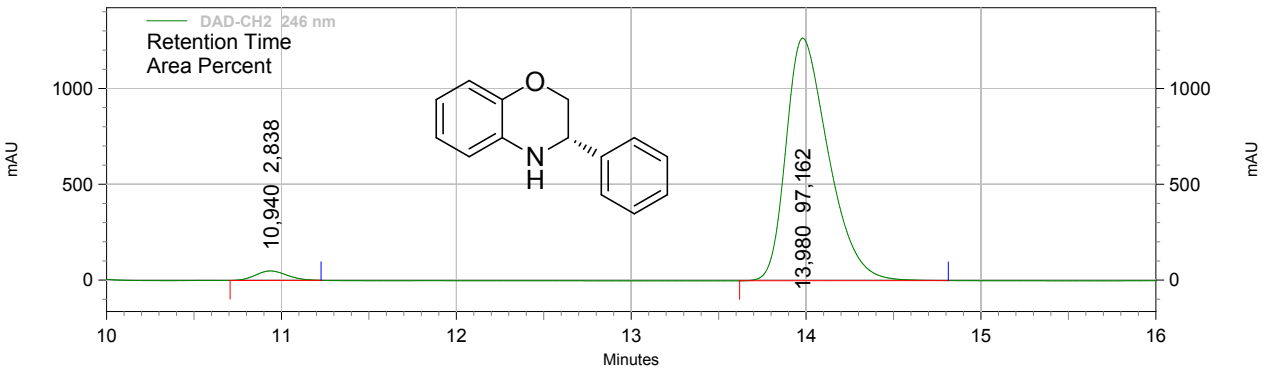


^{13}C NMR spectrum of compound **2g**



HPLC chromatograms of the chiral dihydrobenzoxazines

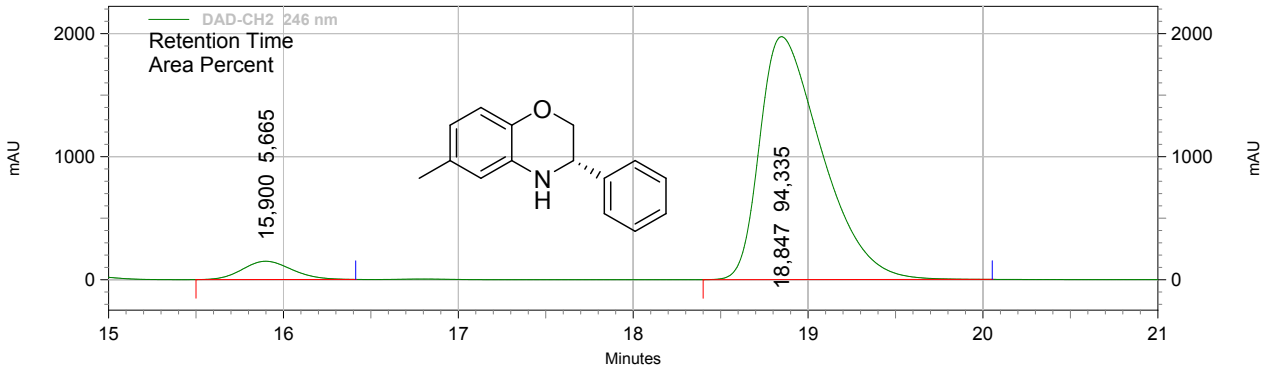
HPLC data of compound **2a**: CHIRALPAK® IB, Hexane/iPrOH 75/25, 0.6 mL.min^{-1}, 20°C, 94% ee



246 nm Results

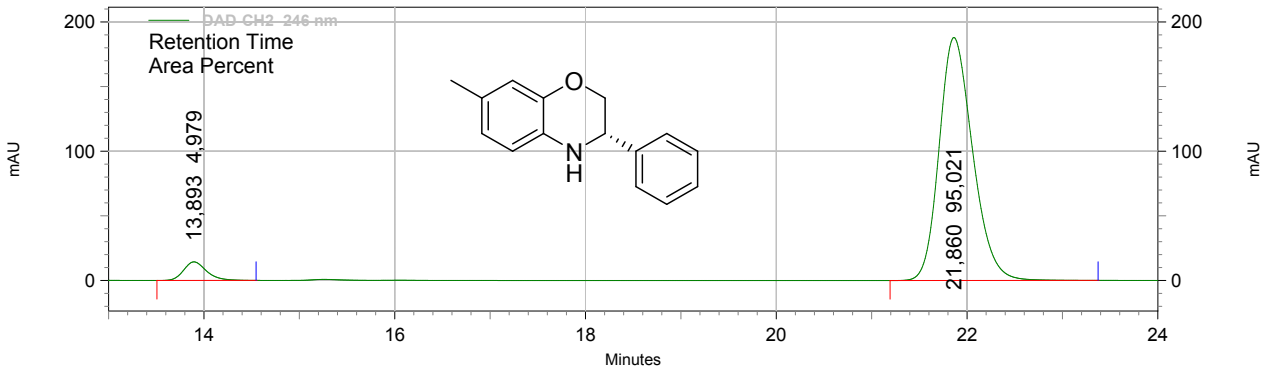
Retention Time	Area	Area %
10.940	2488559	2.84
13.980	85189199	97.16
Totals	87677758	100.00

HPLC data of compound **2b**: CHIRALPAK® IB, Hexane/iPrOH 95/5, 0.5 mL.min^{-1}, 20°C, 89% ee



246 nm Results		
Retention Time	Area	Area %
15.900	11701533	5.66
18.847	194864786	94.34
Totals	206566319	100.00

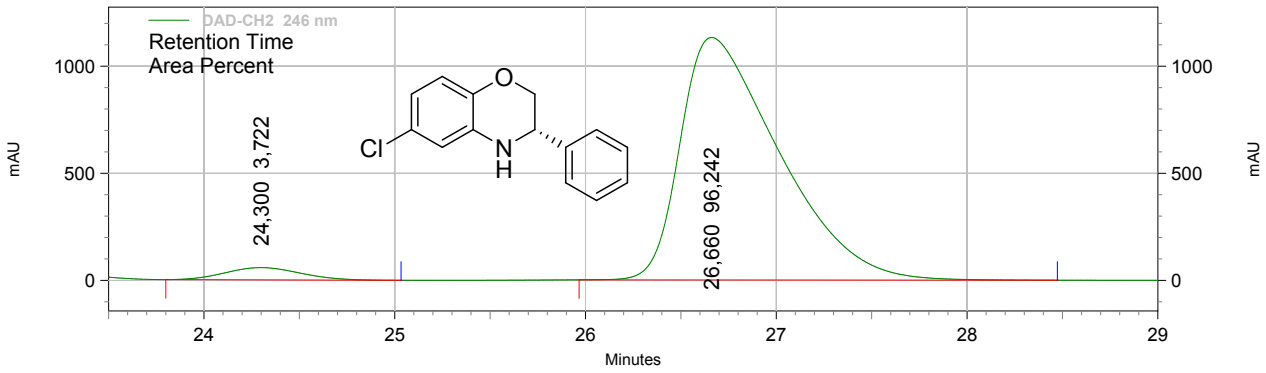
HPLC data of compound **2c**: CHIRALPAK® IB, Hexane/iPrOH 85/15, 0.5 mL.min^{-1}, 20°C, 90% ee



296 nm Results

Retention Time	Area	Area %
13.893	501468	4.77
21.860	10006518	95.23
Totals	10507986	100.00

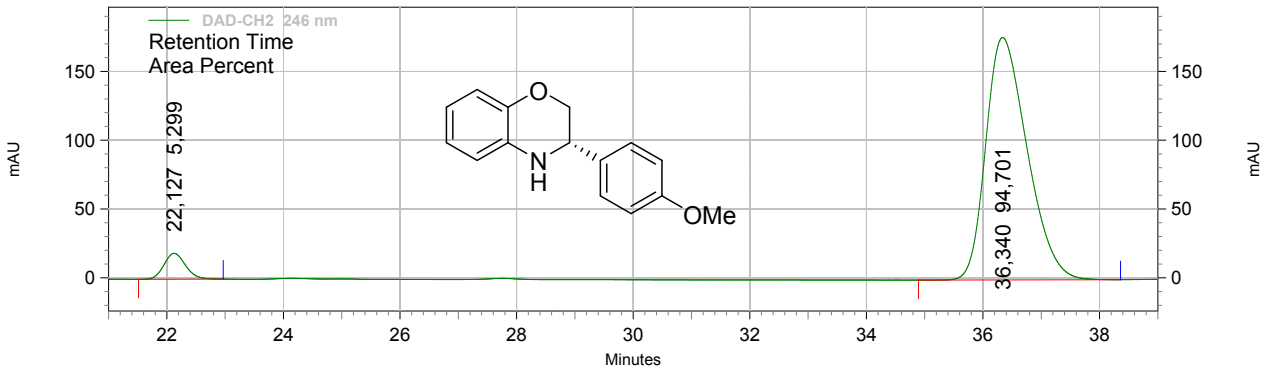
HPLC data of compound **2d**: CHIRALPAK® IB, Hexane/iPrOH 95/5, 0.5 mL.min^{-1}, 20°C, 93% ee



246 nm Results

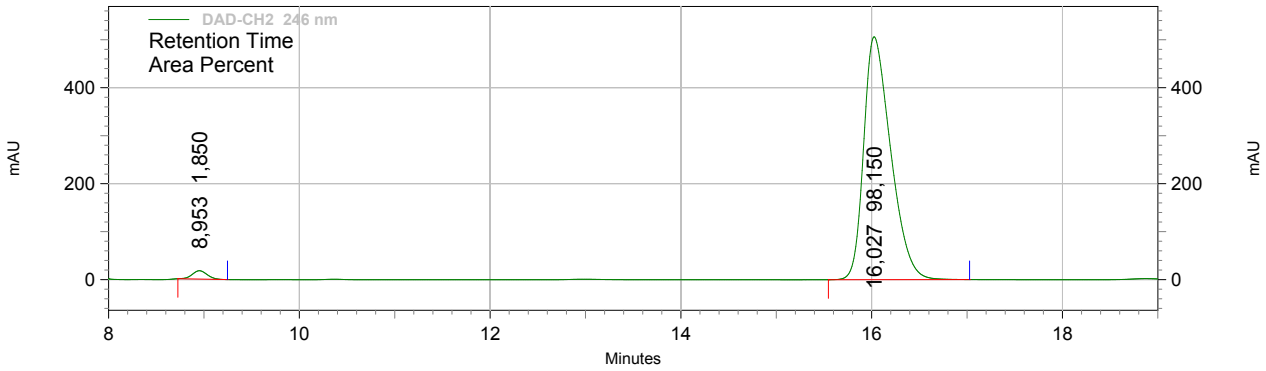
Retention Time	Area	Area %
24.300	6290248	3.72
26.660	162659719	96.28
Totals	168949967	100.00

HPLC data of compound **2e**: CHIRALPAK® IB, Hexane/iPrOH 95/5, 0.5 mL.min^{-1}, 20°C, 89% ee



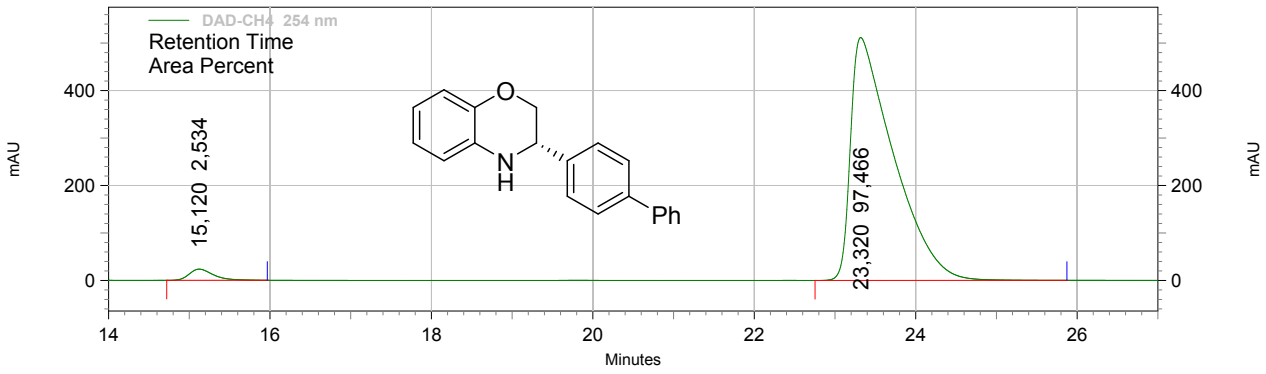
246 nm Results		
Retention Time	Area	Area %
22.127	1937353	5.30
36.340	34624327	94.70
Totals	36561680	100.00

HPLC data of compound **2f**: CHIRALPAK® IB, Hexane/iPrOH 75/25, 0.8 mL.min^{-1}, 20°C, 96% ee



246 nm Results		
Retention Time	Area	Area %
8.953	751190	1.85
16.027	39847954	98.15
Totals	40599144	100.00

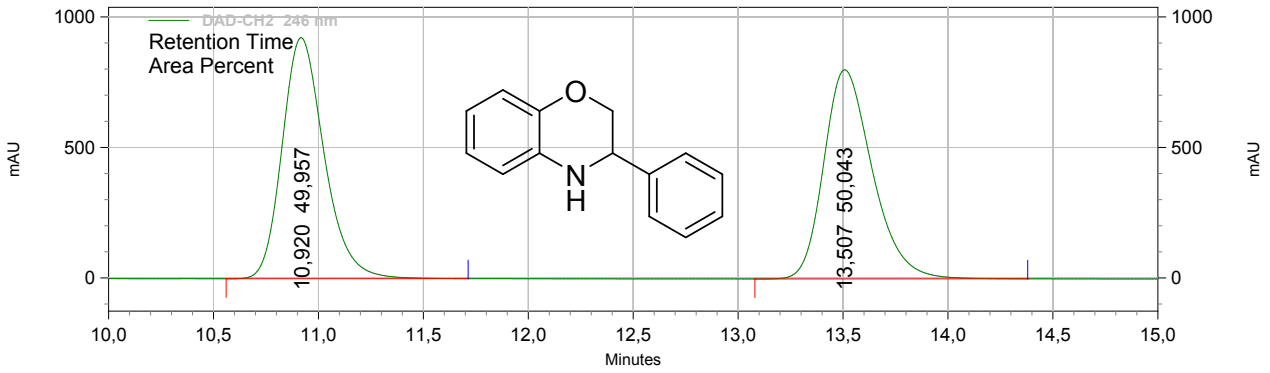
HPLC data of compound **2g**: CHIRALPAK® IB, Hexane/iPrOH 75/25, 0.6 mL.min^{-1}, 20°C, 95% ee



DAD-CH4 254 nm Results		
Retention Time	Area	Area %
15.120	1966869	2.53
23.320	75663567	97.47
Totals	77630436	100.00

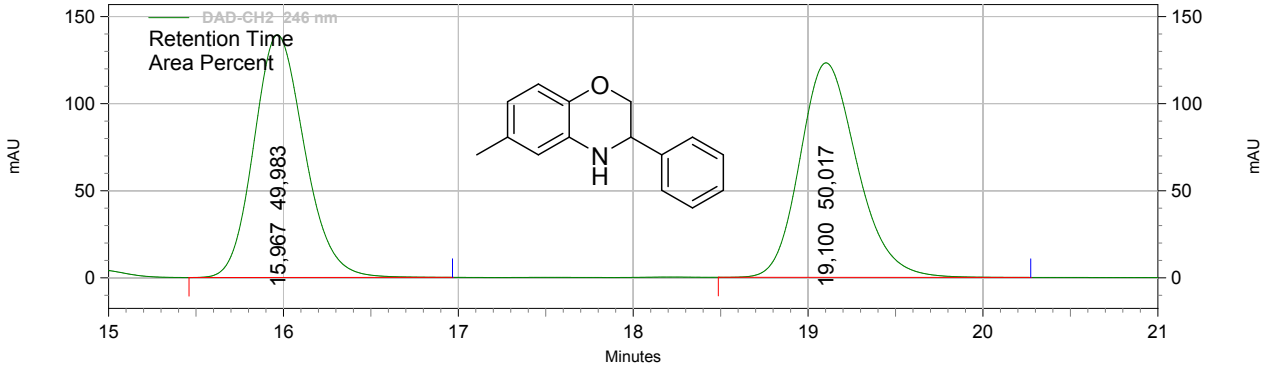
HPLC chromatograms of the racemic dihydrobenzoxazines

HPLC data of compound Rac-**2a**: CHIRALPAK® IB, Hexane/iPrOH 75/25, 0.6 mL.min^{-1}, 20°C



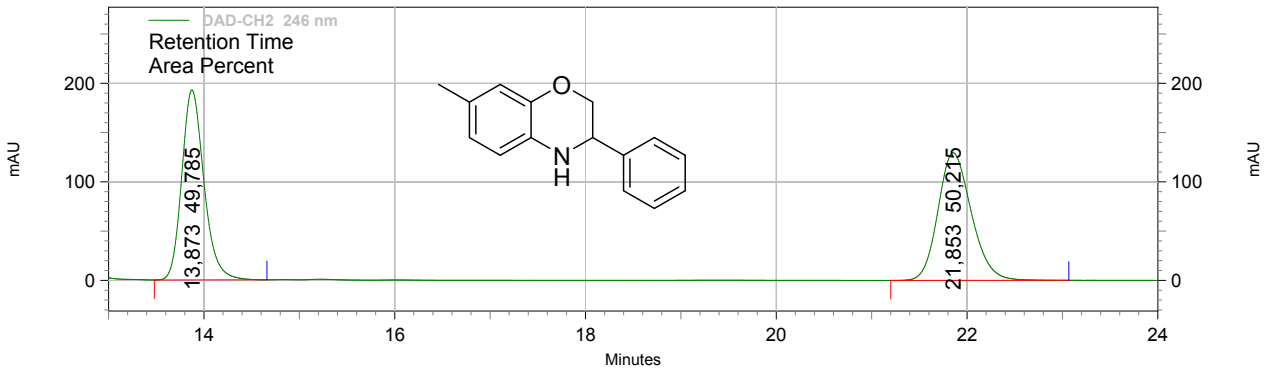
246 nm Results		
Retention Time	Area	Area %
10.920	51460057	49.96
13.507	51549616	50.04
Totals	103009673	100.00

HPLC data of compound Rac-**2b**: CHIRALPAK® IB, Hexane/iPrOH 95/5, 0.5 mL.min^{-1}, 20°C



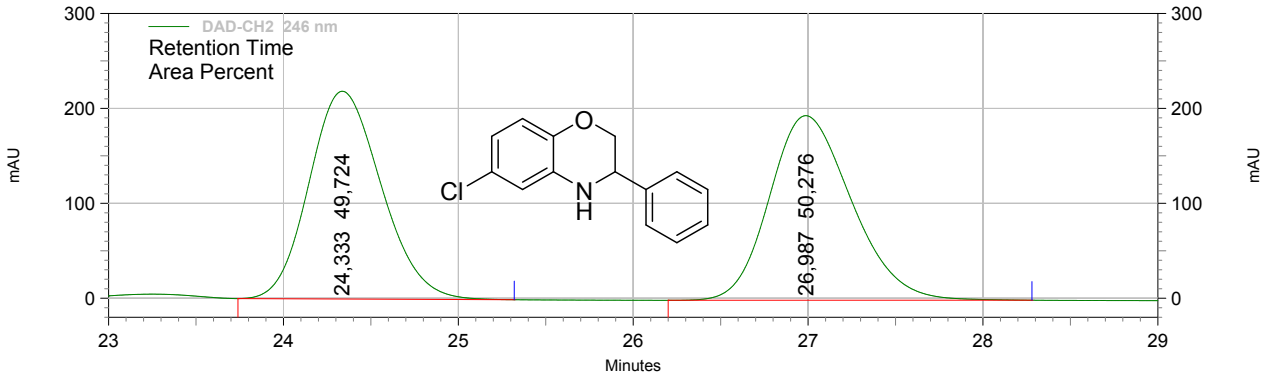
246 nm Results		
Retention Time	Area	Area %
15.967	11205208	49.98
19.100	11212947	50.02
Totals	22418155	100.00

HPLC data of compound Rac-**2c**: CHIRALPAK® IB, Hexane/iPrOH 85/15, 0.5 mL.min^{-1}, 20°C



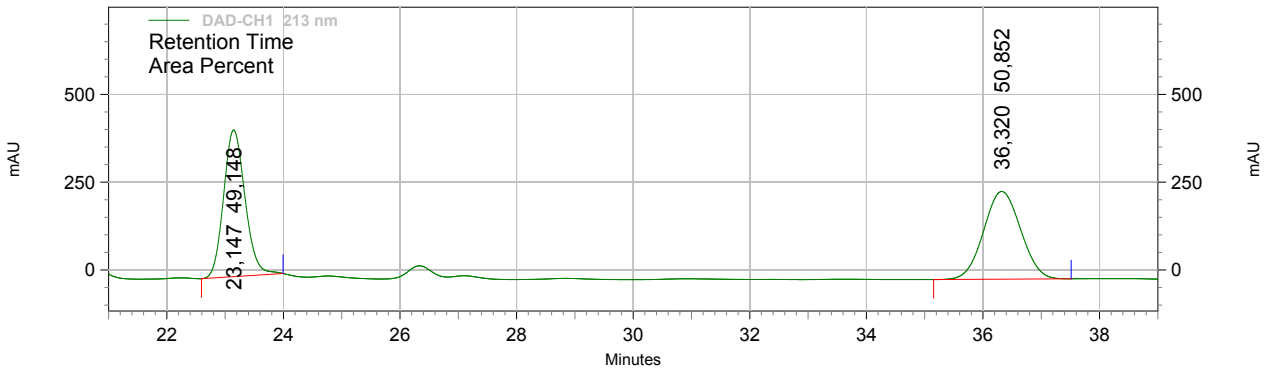
246 nm Results		
Retention Time	Area	Area %
13.873	12456236	49.79
21.853	12563768	50.21
Totals	25020004	100.00

HPLC data of compound Rac-**2d**: CHIRALPAK® IB, Hexane/iPrOH 95/5, 0.5 mL.min^{-1}, 20°C



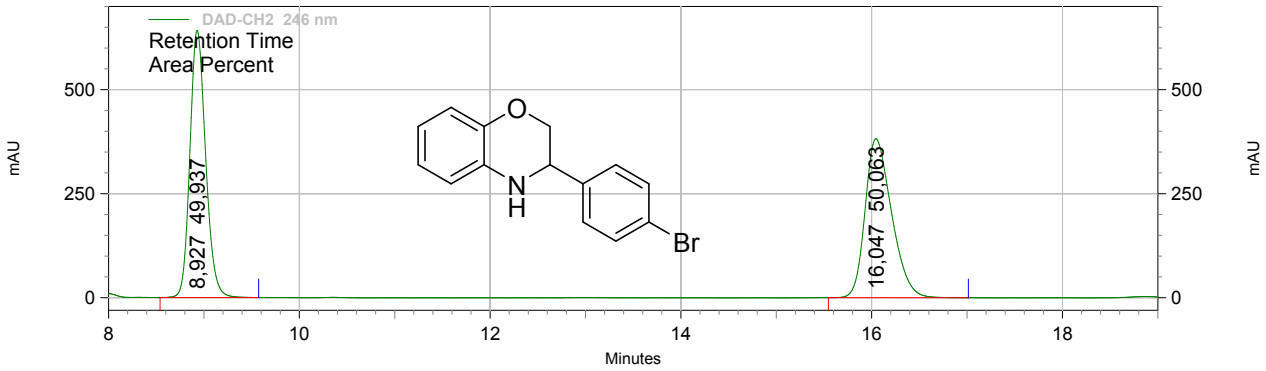
246 nm Results		
Retention Time	Area	Area %
24.333	25102823	49.72
26.987	25381705	50.28
Totals	50484528	100.00

HPLC data of compound Rac-**2e**: CHIRALPAK® IB, Hexane/iPrOH 95/5, 0.5 mL.min^{-1}, 20°C



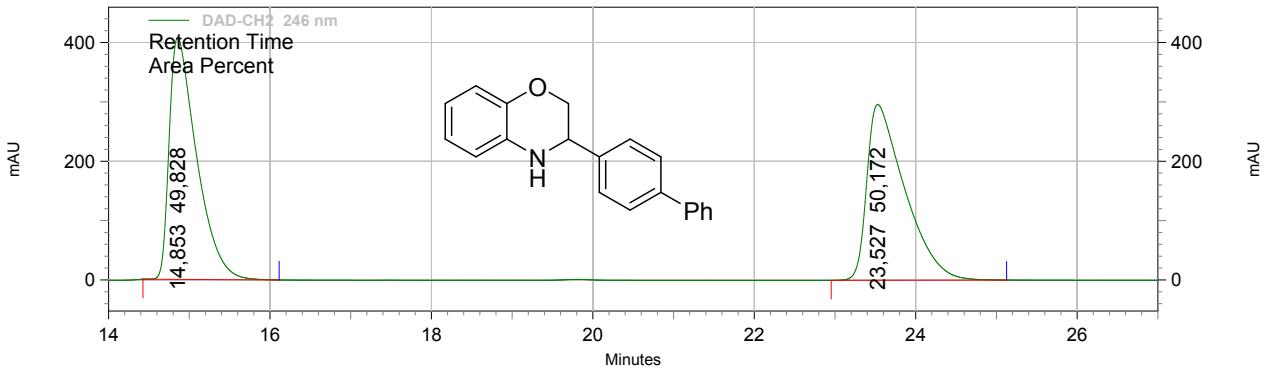
246 nm Results		
Retention Time	Area	Area %
23,147	42620748	49,15
36,320	44098514	50,85
Totals	86719262	100.00

HPLC data of compound Rac-**2f**: CHIRALPAK® IB, Hexane/iPrOH 75/25, 0.8 mL.min^{-1}, 20°C



246 nm Results		
Retention Time	Area	Area %
8.927	29393969	49.94
16.047	29468640	50.06
Totals	58862609	100.00

HPLC data of compound Rac-**2g**: CHIRALPAK® IB, Hexane/iPrOH 75/25, 0.6 mL.min^{-1}, 20°C, 95%



246 nm Results		
Retention Time	Area	Area %
14.853	38358891	49.83
23.527	38623957	50.17
Totals	76982848	100.00

[i] M. Rueping, A. P. Antonchick, A. P. and T. Thiessmann, *Angew. Chem., Int. Ed.*, 2006, **45**, 6751.
[ii] X.-W. Liu, C. Wang, Y. Yan, Y.-Q. Wang and J. Sun, *J. Org. Chem.*, 2013, **78**, 6276
[iii] Y. Zhang, R. Zhao, R. L.-Y. Bao and L. Shi, *Eur. J. Org. Chem.*, 2015, 3344.
[iv] H. Juan, W. Daoyong, Z. Zhuo and H. Xiangping, *Chin. J. Chem.*, 2012, **30**, 2664.
[v] Z.-P. Chen, M.-W. Chen, R.-N. Guo and Y.-G. Zhou, *Org. Lett.*, 2014, **16**, 1406.
[vi] J. L. Núñez-Rico, A. Anton Vidal-Ferran, *Org. Lett.*, 2013, **15**, 2066.