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A Highly Enantioselective Acyl-Mannich Reaction of Isoquinolines with Aldehydes promoted by Proline Derivatives: an Approach to 13-Alkyl-Tetrahydroprotoberberine Alkaloids

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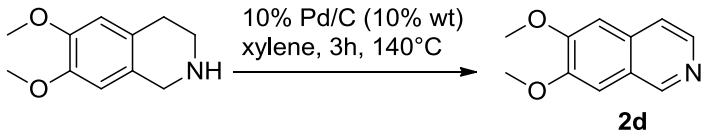
Table of contents:

General methods. ^{1}H NMR spectra were recorded on Varian Gemini 200, Varian Mercury 400 and Inova 600 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, dd = double duplet, dt = double triplet, bs = broad signal, pd = pseudo duplet, pt = pseudo triplet, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on Varian Gemini 200, Varian MR400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: δ= 77.0 ppm). If rotamers are present, the splitted signals are labeled as A (major rotamer) and B (minor rotamer). GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. LC-electrospray ionization mass spectra (ESI-MS) were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. They are reported as: *m/z* (rel. intense). Chromatographic purification was done with 240-400 mesh silica gel. Purification on preparative thin layer chromatography was done on Merck TLC silica gel 60 F_{254} and on Merck TLC aluminum oxide 60 F_{254} neutral. Determination of diastereomeric ratio and of enantiomeric excess was performed on Agilent Technologies 1200 instrument equipped with a variable wave-length UV detector (reference 420 nm), using Daicel Chiralpak® columns (0.46 cm I.D. x 25 cm), Phenomenex® Lux columns and HPLC grade isopropanol and *n*-hexane as eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 1 dm (Na_D line).

Materials. If not otherwise stated, all reactions were carried out in sealed vials in open air without nitrogen atmosphere. Anhydrous solvents were supplied by Aldrich in Sureseal® bottles and were used as received avoiding further purification.

Reagents were purchased from Aldrich and used without further purification unless otherwise stated. The aldehydes **5a** and **5c** were supplied by Aldrich and used after distillation.
The isoquinolines **2e**,[S1] **2f**,[S2] **2g**,[S2] **2i**,[S3] and aldehyde **5e**[S4] were prepared according to literature procedure.

Synthesis of 6,7-dimethoxy-isoquinoline (2d).

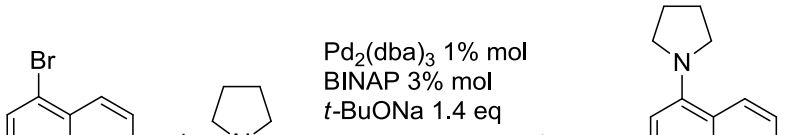


2d

In a 25 mL balloon under nitrogen atmosphere, 10% palladium on carbon (10% wt, 393 mg) and xylene (4 mL) were added. The mixture was refluxed for 1 h (T = 140°C), then it was allowed to cool and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (2.7 mmol, 532 mg) was added. The mixture was refluxed for other 3 hours until complete conversion of the starting material. Then the mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (5 mL) and filtered thought Celite®. After solvent removal under reduced pressure, the crude mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95/5) to give 6,7-dimethoxy-isoquinoline **(2d)** in 77% yield as orange sticky solid.

(**2d**): ^{1}H NMR (200 MHz, $CDCl_3$, 25°C): δ = 4.04 (s, 6H), 7.07 (s, 1H), 7.20 (s, 1H), 7.51 (d, J = 5.5 Hz, 1H), 8.39 (d, J = 5.5 Hz, 1H), 9.05 (s, 1H).

Synthesis of 5-(*N*)-pyrrolidin-isoquinoline (2h).

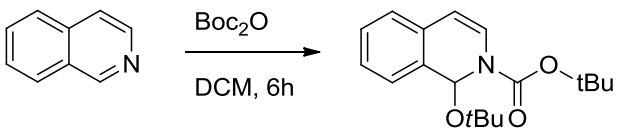


2b 1.2 eq **2h**

In a Schlenck tube were added toluene (0.5 mL), BINAP (0.003 mmol, 1.9 mg) and $Pd_2(dba)_3$ (0.001 mmol, 1.0 mg) under nitrogen atmosphere. The violet solution was stirred at room temperature for 1 hour during which it turned red. Then *t*-BuONa (0.14 mmol, 13.4 mg), pyrrolidine (0.12 mmol, 10 μL) and 5-bromo isoquinoline **2b** (0.1 mmol, 20.8 mg) were added and the temperature was raised to 100°C. The mixture was stirred at this temperature for 12 h, then it was allowed to cool to room temperature and it was filtered through Celite® washing with CH_2Cl_2 (4 x 20 ml). The organic layer was concentrated under reduced pressure and 5-(*N*)-pyrrolydin-isoquinoline (**2h**) was isolated after flash chromatography on silica gel (cyclohexane/ethyl acetate 9/1) in 70 % yield as white sticky solid.

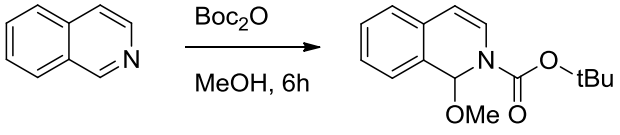
(2h): ^{1}H NMR (200 MHz, $CDCl_3$, 25°C): δ = 1.99–2.09 (m, 4H), 3.46 (t, J = 5.6 Hz, 4H), 7.00-7.06 (m, 1H), 7.44-7.49 (m, 2H), 7.96 (d, J = 5.9 Hz, 1H), 8.43 (d, J = 5.9 Hz, 1H), 9.18 (s, 1H).

Synthesis of adducts 3a and 3b.



2a **3a**

To a solution of **2a** (2.0 mmol, 240 μL) in CH_2Cl_2 (5 mL), Boc_2O (2.0 mmol, 440 μL) was added. The mixture was stirred under at room temperature for 6 h and the solvent was evaporated to give pure **3a** that was stored at -20°C without purification.

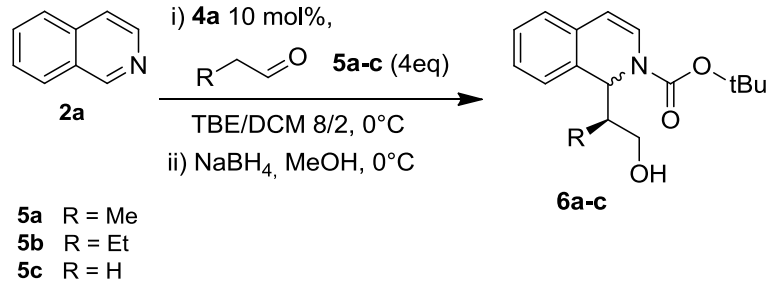


2a **3b**

To a solution of **2a** (2.0 mmol, 240 μL) in MeOH (5 mL), Boc_2O (2.0 mmol, 440 μL) was added. The mixture was stirred under at room temperature for 6 h and the solvent was evaporated to give pure **3b** that was stored at -20°C without purification.

Spectral properties of **3a** and **3b** were according with the literature.[S5]

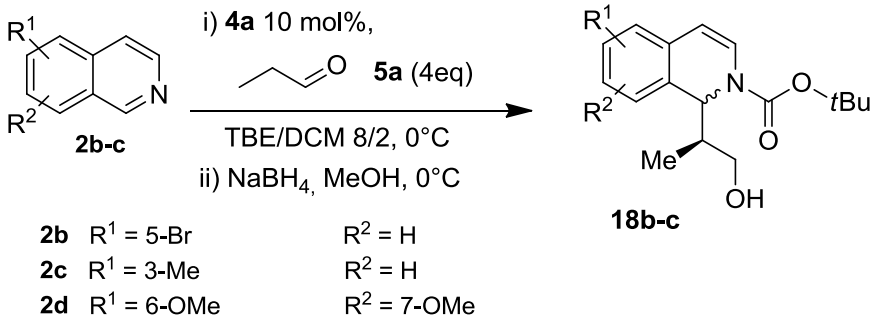
Stereoselective alkylation of isoquinolines activated with Boc_2O.



Entry[a]	Product	Yield[b]	dr[c]	ee%(*syn*)[c]	ee%(*anti*)[c]
1	**6a**	57	88/12	97	93
2[d]	**6a**	80	87/13	97	85
3	**6b**	44(35/9)[e]	79/21	97	93
4	**6c**	26	-	60[f]	-

[a] All reactions were conducted on 0.2 mmol of **2a**, 0.2 mmol Boc_2O, 0.8 mmol of **5a-c** and 0.02 mmol **4a**, in 1 mL of a mixture of TME/DCM 8/2 at 0°C. After 15 hours the mixture was reduced with $NaBH_4$ in MeOH at 0°C. [b] After chromatographic purification. [c] Enantiomeric excesses and diastereomeric ratios were determined by HPLC-analysis after reduction and chromatographic purification. Dr were reported as *syn*/*anti*. [d] Isolated **3b** was used as starting material. [e] The compound **6b** was isolated as pure diastereoisomers after chromatographic purification. In all other cases, the adducts were obtained as inseparable mixture of *syn* and *anti* stereoisomers. The dr for **6b** was determined by ^{1}HNMR of the crude mixture after reduction. [f] Enantiomeric excess of the product.

When isoquinolines **2b**, **2c**, **2d** were reacted with Boc_2O at room temperature, no adducts corresponding to **3a** were isolated. Attempted *in situ* activation of these isoquinolines with Boc_2O according to the procedure described below did not afford any product.



Entry[a]	Product	Yield[b]	dr[c]	ee%(*syn*)[c]	ee%(*anti*)[c]
1	**18b**	0	-	-	-
2	**18c**	0	-	-	-
3	**18d**	0	-	-	-

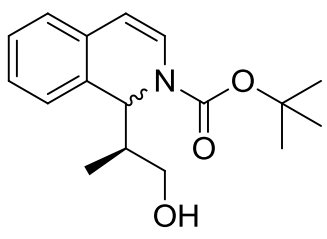
[a] All reactions were conducted on 0.2 mmol of **2a**, 0.2 mmol Boc_2O, 0.8 mmol of **5a-c** and 0.02 mmol **4a**, in 1 mL of a mixture of TME/DCM 8/2 at 0°C. After 15 hours the mixture was reduced with $NaBH_4$ in MeOH at 0°C.

General procedure for the *in situ* activation of isoquinoline with Boc_2O: To a 5 mL vial equipped with a stirring magnetic bar, 1 mL of *t*-BuOMe/CH_2Cl_2 (8/2), isoquinoline **2a** (0.2 mmol, 24 μL) and Boc_2O (0.2mmol, 44 μL) were added. The mixture was stirred at room temperature for 1 h. Then the temperature was lowered to 0°C and aldehyde **5a** (0.8 mmol, 54 μL), Jørgensen catalyst **4a** (0.02 mmol, 12 mg) were added. After 15 hours, a few drops of MeOH and $NaBH_4$ (2 mmol, 76 mg) were added. When complete conversion was obtained (monitored by TLC), water (2 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The collected organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford **6a**.

The racemic products were synthesized with the same procedure except for using pyrrolidine (0.1 mmol, 8.3 μL) instead of **4a** and dichloromethane as reaction solvent.

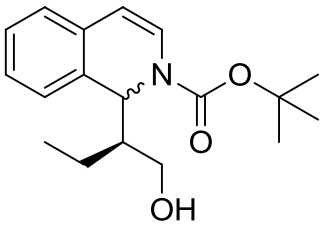
General procedure using 3a or 3b as starting materials: 3a (0.2 mmol, 60.6 mg) was dissolved in 1 mL of *t*-BuOMe/CH_2Cl_2 (8/2). Then the temperature was lowered to 0°C and aldehyde **5a** (0.8 mmol, 54 μL), Jørgensen catalyst **4a** (0.02 mmol, 12 mg) were added. After 15 hours, a few drops of MeOH and $NaBH_4$ (2 mmol, 76 mg) were added. When complete conversion was obtained (monitored by TLC), water (2 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The collected organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford **6a**.
The same procedure was followed using **3b** instead of **3a**.

Note: the enantiomeric excesses and diastereomeric ratios of the compounds remain unaltered after column flash chromatography or after preparative thin layer chromatography on neutral alumina.

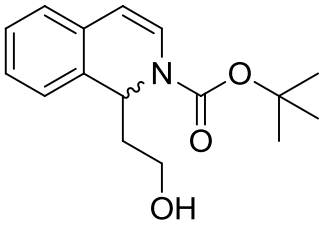


(6a): yellowish oil; 57% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15) as mixture of diastereoisomers in 88/12 ratio (*syn*-**6a**:*anti*-**6a**). *Syn* diastereoisomer ee = 97%; *anti* diastereoisomer ee = 93%. The dr and ee were determined by HPLC analysis Phenomenex® Lux Amylose-2 column: hexane/*i*-PrOH from 93:7 to 90:10 in 20 min., then 90:10, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer τ_{major} = 17.75 min., τ_{minor} = 19.29 min.; *anti* diastereoisomer τ_{major} = 26.41 min., τ_{minor} = 16.94 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 7:1 ratio): δ_{syn}= 0.68 (d, *J* = 6.6 Hz, $3H_A$), 0.96 (d, *J* = 6.6 Hz, $3H_B$), 1.53

(s, $9H_A$), 1.56 (s, $9H_B$), 1.92-2.01 (m, 1H), 3.30 (pt, *J* = 11.2 Hz, 1H), 3.34-3.45 (m, 1H), 4.17-4.24 (m, 1H), 5.61 (d, *J* = 3.2 Hz, 1H), 5.75 (d, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 7.4 Hz, 1H), 7.00-7.07 (m, 1H), 7.10-7.16 (m, 1H), 7.17-7.24 (m, 2H); δ_{anti}= 0.86 (d, *J* = 6.6 Hz, 3H), 1.53 (s, 9H), 1.92-2.01 (m, 1H), 3.30 (pt, *J* = 11.2 Hz, 1H), 3.34-3.45 (m, 1H), 3.60 (d, *J* = 11.2 Hz, 1H), 5.09 (d, *J* = 10.4 Hz, 1H), 5.91 (d, *J* = 7.6 Hz, 1H), 6.73 (dd, J_1 = 7.6 Hz, J_2 = 0.9 Hz, 1H), 7.00-7.07 (m, 1H), 7.08 (d, *J* = 1.2 Hz, 1H), 7.10 (d, *J* = 1.4 Hz, 1H), 7.17-7.24 (m, 1H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ_{syn}= 10.5, 28.2 (3C), 46.6, 54.0, 63.8, 82.3, 109.2, 124.2, 126.4, 126.5, 127.2, 127.4, 131.0, 132.1, 154.0; δ_{anti}= 14.1, 28.1 (3C), 36.7, 55.9, 63.6, 82.4, 109.7, 124.6, 126.3, 126.5, 127.4, 127.6, 130.42, 130.9, 153.4; ESI-MS: *m/z* = 290.4 $[M+H]^+$, 312.3 $[M+Na]^+$; HMRS calcd for $C_{17}H_{23}NO_3$: 289.16779; found 289.16769.

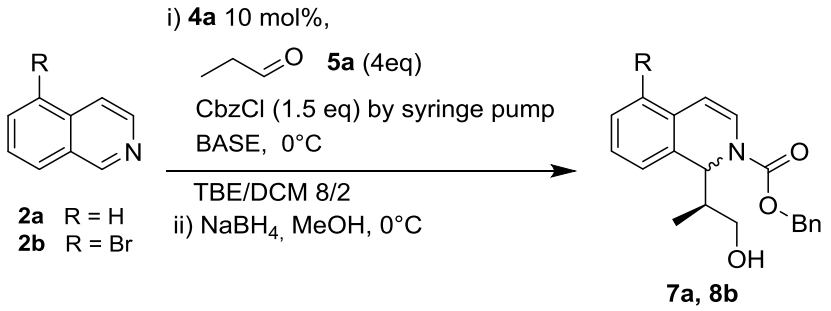


(6b): reddish oil; 44% yield (35% *syn*, 9% *anti*); the title compounds were isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 80/20). *Syn* diastereoisomer ee = 97%; *anti* diastereoisomer ee = 93%. The dr was determined by integration of the NC(1)H signals of the two diastereoisomers in the ^{1}HNMR of the crude mixture after reduction. The ee were determined by HPLC analysis Phenomenex® Lux Amylose-2 column: hexane/*i*-PrOH 95:5, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer τ_{major} = 17.18 min., τ_{minor} = 19.12 min.; *anti* diastereoisomer τ_{major} = 21.86 min., τ_{minor} = 12.70 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 8:1): δ_{syn}= 0.72 (t, *J* = 7.8 Hz, 3H), 1.05-1.14 (m, 1H), 1.34-1.42 (m, 1H), 1.53 (s, $9H_A$), 1.56 (s, $9H_B$), 1.67-1.77 (m, 1H), 3.26-3.33 (m, $1H_A$), 3.37-3.42 (m, $2H_B$), 3.60-3.68 (m, $1H_A$), 4.12-4.18 (dd, J_1 = 10.2 Hz, J_2 = 4.6 Hz, 1H), 5.63 (d, *J* = 3.1 Hz, 1H), 5.77 (d, *J* = 7.5 Hz, 1H), 6.78 (d, *J* =7.5 Hz, 1H), 7.02-7.06 (m, 1H), 7.13-7.17 (m, 1H), 7.18-7.23 (m, 2H); δ_{anti}= 0.77 (t, *J* = 7.1 Hz, 3H), 1.04-1.16 (m, 1H), 1.41-1.57 (m, 2H), 1.53 (s, $9H_A$), 1.56 (s, $9H_B$), 3.22-3.32 (bs, 1H), 3.48 (pd, *J* = 12.3 Hz, 1H), 3.58 (pd, *J* = 12.3 Hz, 1H), 5.12 (d, *J* = 10.1 Hz, 1H), 5.92 (d, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 7.8 Hz,1H), 7.05-7.10 (m, 2H), 7.11-7.26 (m, 2H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ_{syn} (two rotamers A:B, 8:1) = 12.5, 17.9, 28.2 ($3C_A$), 28.4 ($3C_B$), 53.2, 54.0, 61.0, 82.2, 109.5, 124.3, 126.4, 126.6, 127.3, 127.4, 131.2, 132.3, 154.0; δ_{anti}= 11.8, 19.2, 28.2 (3C), 43.0, 55.5, 58.8, 82.4, 110.0, 124.6 (2C), 126.3, 127.6, 128.1, 130.5, 130.9, 153.5; ESI-MS: *m/z* = 304.3 $[M+H]^+$, 326.2 $[M+Na]^+$; HMRS calcd for $C_{18}H_{25}NO_3$: 303.18344; found 303.18359.



(6c): colourless oil; 26% yield; 60% ee; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15). The ee was determined by HPLC analysis Phenomenex® Lux Amylose-2 column: hexane/*i*-PrOH 95:5, flow rate 1.00 mL/min, 40°C, λ = 295 nm: τ_{major} = 12.02 min., τ_{minor} = 19.74 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 9:1 ratio): δ = 1.54 (s, $9H_A$), 1.58 (s, $9H_B$), 1.60-1.71 (m, 1H), 1.85-1.95 (m, 1H), 3.45 (pt, J = 11.3 Hz, 1H), 3.50-3.61 (bs, 1H), 3.61-3.69 (bs, 1H), 5.49 (dd, J_1 = 11.3 Hz, J_2 = 2.3 Hz, 1H), 5.86 (d, J = 7.5 Hz, $1H_A$), 5.93 (d, J = 7.5 Hz, $1H_B$), 6.72 (d, J = 7.8 Hz, $1H_A$), 6.92 (d, J = 7.8 Hz, $1H_B$), 7.04-7.09 (m, 1H), 7.11-7.15 (m, 1H), 7.17-7.22 (m, 2H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ = 28.2 (3C), 37.9, 51.3, 58.0, 82.3, 109.0, 124.1, 124.7, 125.9, 127.3, 127.5, 129.9, 133.4, 153.4; ESI-MS: *m/z* = 276.4 $[M+H]^+$, 298.3 $[M+Na]^+$, 573.5 $[2M+Na]^+$; HMRS calcd for $C_{16}H_{21}NO_3$: 275.15214; found : 275.15228.

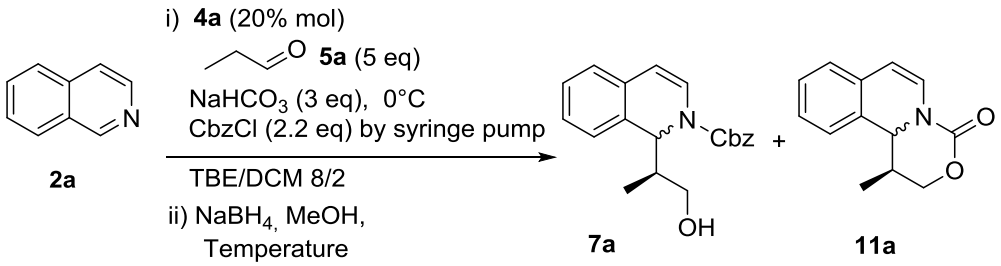
Screening test for the alkylation of isoquinolines activated with CbzCl



Entry[a]	Product	Yield[b]	dr[c]	ee%(*syn*)[c]	ee%(*anti*)[c]	Base
1	**8b**	21	83/27	86	88	$NaHCO_3$
2[d]	**8b**	-	68/32	94	83	$NaHCO_3$
3	**7a**	15	75/25	98	88	$NaHCO_3$
4	**7a**	0	-	-	-	*t*-$Bu_4NOH{\cdot}30H_2O$
5	**7a**	0	-	-	-	K_2HCO_3
6	**7a**	0	-	-	-	Cs_2HCO_3
7	**7a**	traces	-	-	-	$NaHCO_3$ aq.sat.
8[e]	**7a**	42	-	-	-	$NaHCO_3$
9[e]	**7a**	33	-	-	-	$NaHCO_3$[f]

[a] All reactions were conducted on 0.2 mmol of **2a-b**, 0.3 mmol CbzCl, 0.8 mmol of **5a**, 0.6 mmol of base and 0.02 mmol **4a**, in 0.5 mL of a mixture of TME/DCM 8/2. After 15 hours the mixture was reduced with $NaBH_4$ in MeOH at -40°C. [b] After chromatographic purification. [c] Enantiomeric excesses and diastereomeric ratios were determined by HPLC-analysis after reduction and chromatographic purification. Dr were reported as *syn*/*anti*. [d] reaction conducted in presence of 0.02 mmol *p*-$NO_2PhCOOH$. [e] Reaction conducted using 0.45 mmol CbzCl, 1.0 mmol of **5a** and 0.04 mmol **4a**; **11a** was detected in 17% yield after chromatographic purification. [f] Reaction conducted using 1.0 mmol of $NaHCO_3$.

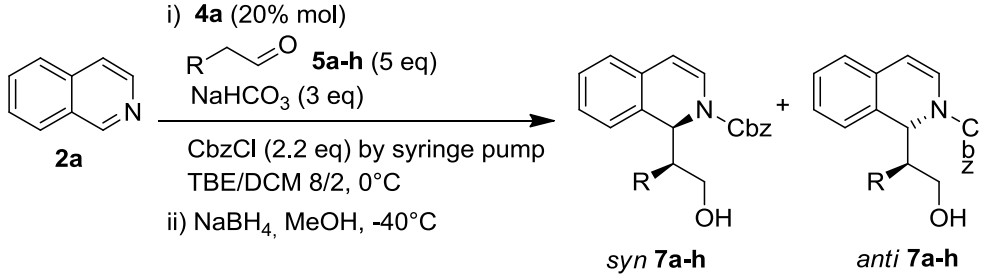
Temperature effect in the reduction step and rate effect in the addition of CbzCl



Entry[a]	Yield[b] **7a**	Yield[b] **11a**	Temperature (°C)	CbzCl addition time (h)
1	42	17	0	15
2	44	8	-20	15
3	traces	-	-20	2
4	42	traces	-30	28
5	53	0	-40	15

[a] All reactions were conducted on 0.2 mmol of 2**a**, 0.45 mmol CbzCl, 1.0 mmol of **5a**, 0.6 mmol of $NaHCO_3$ and 0.04 mmol **4a**, in 0.5 mL of a mixture of TME/DCM 8/2. After the CbzCl addition was completed the mixture was reduced with $NaBH_4$ in MeOH at the indicated temperature. [b] After chromatographic purification.

Stereoselective alkylation of isoquinoline activated with CbzCl with aldehydes



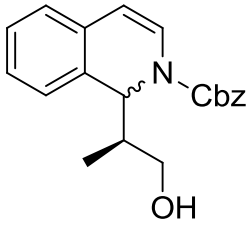
5a R = Me **5e** R = -$(CH_2)_3$Cl
5b R = Et **5f** R = -CH_2-Ph
5c R = H **5g** R = cis-CH_2CH=$CHCH_2CH_3$
5d R = -$(CH_2)_5CH_3$ **5h** R = Ph

General procedure: To a solution of isoquinoline **2a** (0.2 mmol) in 0.5 mL *t*-BuOMe/CH_2Cl_2 (8/2) inside a round-bottomed flask equipped with a stirring magnetic bar and cooled at 0°C, $NaHCO_3$ (0.6 mmol, 51 mg), Jørgensen catalyst **4a** (0.04 mmol, 24 mg) and aldehyde **5a-h** (1.0 mmol) were added. To the mixture a solution of CbzCl (0.45 mmol, 78 µL CbzCl in 1 mL *t*BuOMe/CH_2Cl_2 8/2) was added dropwise by a syringe pump during 15 h. After that 2 mL of an aqueous saturated solution of NH_4Cl were added and the organic layer was extracted with Et_2O (3 x 5 mL). The collected organic layers were dried over $MgSO_4$. The residue was diluted in MeOH and the resulting solution was cooled at -40°C. Then $NaBH_4$ (2 mmol, 76 mg) was added. When complete conversion was obtained (monitored by TLC), HCl 1N was added (at -40°C) until pH = 1. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The

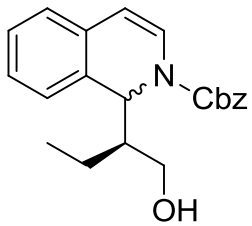
collected organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give **7a-h**.

The racemic products were synthesized with the same procedure except for using pyrrolidine (0.1 mmol, 8.3 μL) instead of **4a**, CH_2Cl_2 as reaction solvent and for conducing the reaction at room temperature.

Note: the enantiomeric excesses and the diasteromeric ratios of the compounds remain unaltered after flash chromatography or after preparative thin layer chromatography on neutral alumina.

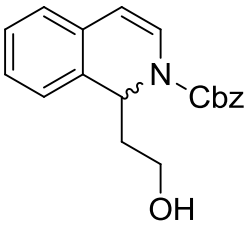


(7a): yellowish oil; 53% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15) as mixture of diastereoisomers in 74/26 ratio (*syn*-**7a**:*anti*-**7a**). *Syn* diastereoisomer ee = 96%; *anti* diastereoisomer ee = 87%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min., flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer τ_{major} = 23.87 min., τ_{minor} = 14.64 min.; *anti* diastereoisomer τ_{major} = 13.79 min., τ_{minor} = 20.95 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_{syn} (two rotamers A:B, 7:1 ratio) = 0.70 (d, *J* = 6.8 Hz, $3H_A$), 0.90 (d, *J* = 6.8 Hz, $3H_B$), 1.89-2.04 (bs, 1H), 3.35-3.48 (bs, 2H), 3.90-4.00 (bs, 1H), 5.22-5.32 (m, 2H), 5.64 (d, *J* = 3.0 Hz, 1H), 5.81 (d, *J* = 7.8 Hz, $1H_A$), 5.99 (d, *J* = 7.8 Hz, $1H_B$), 6.87 (d, *J* =7.8 Hz, 1H), 7.03-7.07 (m, 1H), 7.13-7.17 (m, 1H), 7.20-7.24 (m, 2H), 7.38-7.42 (m, 5H); δ_{anti} = 0.87 (d, *J* = 6.83 Hz, 3H), 1.89-2.04 (bs, 1H), 3.31 (pt, J_1 = 11.7 Hz, J_2 = 11.2 Hz, 2H), 3.59 (d, *J* = 11.7 Hz, 1H), 5.16 (d, *J* = 10.1 Hz, 1H), 5.22-5.32 (m, 2H), 5.95 (d, *J* =7.6 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 7.08-7.12 (m, 2H), 7.20-7.24 (m, 2H), 7.38-7.42 (m, 5H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ_{syn} = 10.5, 46.4, 54.9, 63.8, 68.5, 110.3, 124.5, 125.5, 126.5, 127.4, 127.5, 128.1 (2C), 128.4, 128.6 (2C), 130.6, 132.0, 135.6, 154.9; δ_{anti} = 14.0, 36.0, 56.6, 63.6, 68.5, 110.7, 123.8, 124.7, 126.6, 127.7, 127.8, 128.2 (2C), 128.6 (2C), 128.7, 130.2, 130.8, 135.5, 154.3; ESI-MS: *m/z* = 324.4 $[M+H]^+$, 347.3 $[M+Na]^+$, 669.5 $[2M+Na]^+$; HMRS calcd for $C_{20}H_{21}NO_3$: 323.15214; found 323.15228.

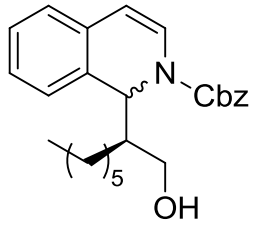


(7b): reddish oil; 51% yield (39% *syn*, 12% *anti*); the title compounds were isolated by preparative thin layer chromatography (cyclohexane/acetone 97/3) on neutral alumina. *Syn* diastereoisomer ee = 98%; *anti* diastereoisomer ee = 98%. The dr was determined by integration of the NC(1)H signals of the two diastereoisomers in the ^{1}HNMR of the crude mixture after reduction. The ee

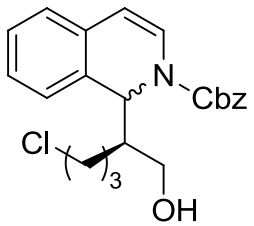
were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min. then 70:30, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer τ_{major} = 25.46 min., τ_{minor} = 16.41 min.; *anti* diastereoisomer τ_{major} = 14.20 min., τ_{minor} = 20.20 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 12:1 ratio): δ_{syn} = 0.73 (t, *J* = 7.8 Hz, $3H_A$), 0.84 (t, *J* = 7.8 Hz, $3H_B$), 1.04-1.19 (m, 1H), 1.32-1.42 (m, 1H), 1.75-1.80 (m, 1H), 3.31 (dd, $J_1 = J_2$ = 10.5 Hz, 1H), 3.56-3.66 (bs, 2H), 3.71-3.80 (bs, 1H), 5.24 (d, *J* = 12.3 Hz, 1H), 5.28 (d, *J* = 12.3 Hz, 1H), 5.66 (d, *J* = 3.1 Hz, 1H), 5.76 (d, *J* = 7.9 Hz, $1H_B$), 5.82 (d, *J* = 7.9 Hz, $1H_A$), 6.85 (d, *J* =7.9 Hz, 1H), 7.03-7.07 (m, 1H), 7.15-7.18 (m, 1H), 7.19-7.24 (m, 2H), 7.35-7.42 (m, 5H); δ_{anti} = 0.73 (t, *J* = 7.1 Hz, $3H_B$), 0.78 (t, *J* = 7.1 Hz, $3H_A$), 1.07-1.19 (m, 1H), 1.42-1.54 (m, 1H), 1.56-1.64 (m, 1H), 3.03-3.11 (bs, 1H), 3.45-3.52 (bs, 1H), 3.55-3.63 (bs, 1H), 5.18 (d, *J* = 9.9 Hz, 1H), 5.24 (d, *J* = 12.2 Hz, 1H), 5.30 (d, *J* = 12.2 Hz, $1H_A$), 5.35 (d, *J* = 12.2 Hz, $1H_B$), 5.97 (d, *J* = 7.5 Hz, $1H_A$), 6.02 (d, *J* = 7.5 Hz, $1H_B$), 6.78 (dd, J_1 = 7.3 Hz, J_2 = 0.9 Hz, $1H_A$), 6.96 (d, *J* = 7.3 Hz, $1H_B$), 7.05-7.10 (m, 2H), 7.13-7.23 (m, 2H), 7.26-7.42 (m, 5H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ_{syn} = 12.4, 18.0, 52.8, 54.8, 60.9, 68.5, 110.6, 124.5, 125.4, 126.6, 127.4, 127.5, 128.2 (2C), 128.4, 128.7 (2C), 130.8, 132.1, 135.6, 154.9; δ_{anti} = 11.8, 19.2, 43.1, 56.1, 58.7, 68.6, 111.1, 123.7, 124.8, 126.5, 127.7, 128.1, 128.3 (2C), 128.5 (2C), 128.6, 130.2, 130.9, 134.6, 154.9; ESI-MS: *m/z* = 338.3 $[M+H]^+$, 360.2 $[M+Na]^+$; 360.50 $[2M+Na]^+$; HMRS calcd for $C_{21}H_{23}NO_3$: 337.16779; found 337.16743.



(7c): colourless oil; 9% yield; 50% ee; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15). The ee was determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min. then 70:30, flow rate 0.70 mL/min, 40°C, λ = 295 nm: τ_{major} = 23.87 min., τ_{minor} = 13.79 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 9:1 ratio): 1.66-1.75 (m, 1H), 1.88-1.97 (m, 1H), 3.33-3.40 (bs, 1H), 3.41-3.50 (dd, $J_1 = J_2$ = 11.7 Hz, 1H), 3.51-3.60 (bs, 1H), 5.23 (d, *J* = 12.4 Hz, $1H_B$), 5.25 (d, *J* = 12.4 Hz, $1H_A$), 5.30 (d, *J* = 12.4 Hz, $1H_A$), 5.34 (d, *J* = 12.4 Hz, $1H_B$), 5.53 (dd, J_1 = 10.9 Hz, J_2 = 3.3 Hz, 1H), 5.90 (d, *J* = 7.8 Hz, $1H_A$), 5.98 (d, *J* = 7.8 Hz, $1H_B$), 6.78 (dd, J_1 = 7.8 Hz, J_2 = 1.0 Hz, $1H_A$), 6.95 (dd, J_1 = 7.8 Hz, J_2 = 1.0 Hz, $1H_B$), 7.06-7.10 (m, 1H), 7.12-7.15 (m, 1H), 7.20-7.24 (m, 2H), 7.35-7.42 (m, 5H); ESI-MS: *m/z* = 310.4$[M+H]^+$, 332.3 $[M+Na]^+$; HMRS calcd for $C_{19}H_{19}NO_3$: 309.13649; found 309.13673.

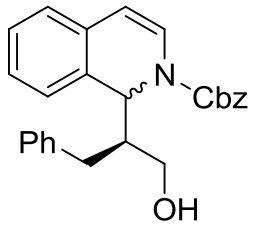


(7d): yellowish oil; 65% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 97/3) as mixture of diastereoisomers in 79/21 ratio (*syn*-**7d**:*anti*-**7d**). The dr ratio was determined by integration of the δ_{major}= 6.86 and δ_{minor}= 6.79 ^{1}H NMR signals relative to the proton on the C3 carbon of the isoquinoline ring. *Syn* diastereoisomer ee = 99%; *Anti* diastereoisomer ee = 96%. The ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 70:30 in 40 min., flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer τ_{major} = 23.20 min., τ_{minor} = 18.94 min.; *anti* diastereoisomer τ_{major} = 16.97 min., τ_{minor} = 17.56 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 10:1 ratio): δ_{syn} = 0.81 (t, *J* = 7.3 Hz, $3H_A$), 0.82 (t, *J* = 7.3 Hz, $3H_B$), 1.03-1.13 (m, 2H), 1.13-1.24 (m, 2H), 1.24-1.42 (m, 6H), 1.78-1.88 (m, 1H), 3.27-3.36 (m, 1H), 3.54-3.62 (bs, 1H), 3.79-3.87 (bs, 1H), 5.23 (d, *J* = 12.2 Hz, 1H), 5.29 (d, *J* = 12.2 Hz, 1H), 5.66 (d, *J* = 3.9 Hz, 1H), 5.83 (d, *J* = 7.8 Hz, $1H_A$), 5.99 (d, *J* = 7.8 Hz, $1H_B$), 6.86 (d, *J* =7.8 Hz, 1H), 7.03-7.07 (m, 1H), 7.14-7.17 (m, 1H), 7.18-7.25 (m, 2H), 7.32-7.46 (m, 5H); δ_{anti} = 0.90 (t, *J* = 6.9 Hz, 3H), 1.03-1.13 (m, 2H), 1.13-1.24 (m, 2H), 1.24-1.42 (m, 6H), 1.78-1.88 (m, 1H), 3.11-3.17 (bs, 1H), 3.27-3.36 (m, 1H), 3.46-3.54 (bs, 1H), 5.24 (d, *J* = 12.2 Hz, 1H), 5.30 (d, *J* = 12.2 Hz, 1H), 5.41 (d, *J* = 7.2 Hz, 1H), 5.75 (d, *J* = 7.8 Hz, $1H_B$), 5.97 (d, *J* = 7.8 Hz, $1H_A$), 6.79 (dd, J_1 = 7.4 Hz, J_2 = 1.1 Hz, 1H), 7.01-7.13 (m, 2H), 7.18-7.25 (m, 2H), 7.32-7.46 (m, 5H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ_{syn} (two rotamers, A:B 5:1 ratio) = 14.0, 22.5, 24.9 ($1C_A$), 25.3 ($1C_B$), 27.5, 29.2, 31.4 ($1C_A$), 33.4 ($1C_B$), 50.7, 54.9 ($1C_A$), 56.4 ($1C_B$), 60.8 ($1C_B$), 61.3 ($1C_A$), 68.4, 110.5, 124.5, 125.4, 126.6, 127.4, 127.5, 128.1 (2C), 128.4, 128.6 (2C), 130.7, 132.1, 135.7, 154.8; δ_{anti} = 14.1, 22.6, 25.7, 27.2, 29.3, 32.1, 41.5, 56.2, 59.5, 68.5, 111.0, 123.7, 124.7, 126.5, 127.4, 127.7, 128.0, 128.2 (2C), 128.5 (2C), 130.7, 132.1, 135.6, 154.2; ESI-MS: *m/z* = 394.2 $[M+H]^+$; HMRS calcd for $C_{25}H_{31}NO_3$: 393.23039; found 393.23068.



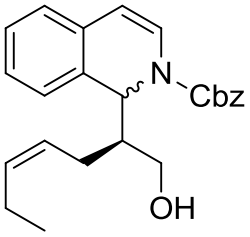
(7e): colourless oil; 13% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 90/10) as mixture of diastereoisomers in 79/21 ratio (*syn*-**7e**:*anti*-**7e**) containing some impurities. Further purification by preparative thin layer chromatography on silica (cyclohexane/ethyl acetate 80/20) lead to pure compound as mixture of diastereoisomers in 53/47 ratio (*syn*-**7e**:*anti*-**7e**). *Syn* diastereoisomer ee = 97%; *anti* diastereoisomer ee = 80%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 70:30 in 40 min., flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer τ_{major} = 32.23 min., τ_{minor} = 26.01 min.; *anti* diastereoisomer τ_{major} = 24.71

min., τ_{minor} = 28.00 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 10:1 ratio): δ_{syn} = 1.18-1.32 (m, 1H), 1.33-1.51 (m, 1H), 1.54-1.76 (m, 2H), 1.76-1.86 (m, 1H), 3.24-3.38 (m, 3H), 3.48-3.58 (m, 1H), 3,74 (dd, J_1 = 9.1 Hz, J_2 = 4.8 Hz, 1H), 5.16-5.41 (m, 2H), 5.66 (d, J = 3.5 Hz, 1H), 5.85 (d, J = 7.5 Hz, $1H_A$), 6.04 (d, J = 7.5 Hz, $1H_B$), 6.87 (dd, J_1 = 7.5 Hz, J_2 = 0.8 Hz, $1H_A$), 7.02 (d, J = 7.5 Hz, $1H_B$), 7.05-7.18 (m, 2H), 7.18-7.29 (m, 2H), 7.32-7.48 (m, 5H); δ_{anti} = 1.18-1.32 (m, 1H), 1.33-1.51 (m, 1H), 1.54-1.76 (m, 2H), 1.76-1.86 (m, 1H), 3.11 (t, J = 7.3 Hz, 1H), 3.35 (t, J = 7.0 Hz, 2H), 3.48-3.58 (m, 2H), 5.19 (d, J = 10.2 Hz, 1H), 5.16-5.41 (m, 2H), 5.97 (d, J = 7.9 Hz, $1H_A$), 6.00 (d, J = 7.9 Hz, $1H_B$), 6.79 (dd, J_1 = 7.9 Hz, J_2 = 1.3 Hz, $1H_A$), 6.97 (d, J = 7.9 Hz, $1H_B$), 7.05-7.18 (m, 2H), 7.18-7.29 (m, 2H), 7.32-7.48 (m, 5H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ_{syn} (two rotamers, A:B 7:1 ratio) = 22.7 ($1C_A$), 24.2 ($1C_B$), 30.8, 44.8, 50.1, 54.7, 61.3, 66.9 ($1C_B$), 68.5 ($1C_A$), 110.5, 124.7, 125.4, 126.6, 127.7, 127.9, 128.2 (2C), 128.4, 128.7 (2C), 130.7, 131.7, 135.5, 154.9; δ_{anti} = 24.1, 30.5, 41.7, 44.8, 55.9, 59.5, 68.6, 111.0, 123.7, 124.9, 126.8, 127.6, 127.9, 128.0 (2C), 128.5, 128.7 (2C), 130.2, 130.3, 135.6, 153.2; ESI-MS: *m/z* = 386.3 $[M(^{35}Cl)+H]^+$, 388.3 $[M(^{37}Cl)+H]^+$, 408.2 $[M(^{35}Cl)+Na]^+$, 410.1 $[M(^{37}Cl)+Na]^+$; HMRS calcd for $C_{22}H_{24}ClNO_3$: 385.14447; found 385.14415.

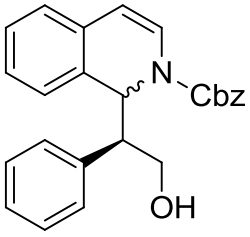


(7f): yellowish oil; 9% yield (7% *syn*, 2% *anti*); the title compound was isolated by column chromatography on silica (cyclohexane/ethyl acetate, gradient elution from 90/10 to 80/20) as separated diastereoisomers in 81/19 ratio (*syn*-**7f**:*anti*-**7f**). *Syn* diastereoisomer ee = 91%; *anti* diastereoisomer ee = 93%. The dr was determined by integration of the NCHC(4)H signals of the two diastereoisomers in the ^{1}HNMR of the crude mixture after reduction. The ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min. then 70:30, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer τ_{major} = 19.50 min., τ_{minor} = 17.22 min.; *anti* diastereoisomer τ_{major} = 25.36 min., τ_{minor} = 23.21 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_{syn} (two rotamers A:B, 7:1 ratio) = 2.13-2.20 (m, 1H), 2.27 (dd, J_1 = J_2 = 13.2 Hz, 1H), 2.53-2.61 (m, $1H_B$), 2.72 (dd, J_1 = 13.2 Hz, J_2 = 1.4 Hz, $1H_A$), 3.20-3.41 (m, 2H), 3.59-3.76 (bs, 1H), 5.22-5.37 (m, 2H), 5.57 (d, J = 5.8 Hz, $1H_B$), 5.78 (d, J = 3.0 Hz, $1H_A$), 5.89 (d, J = 7.7 Hz, $1H_A$), 6.01 (d, J = 7.7 Hz, $1H_B$), 6.86-6.94 (m, 3H), 6.97-7.33 (m, 7H), 7.35-7.46 (m, 5H); δ_{anti} (two rotamers A:B, 9:1 ratio)= 1.91-2.04 (m, 1H), 2.36 (dd, J_1 = J_2 = 12.9 Hz, $1H_B$), 2.44 (dd, J_1 = 12.9 Hz, J_2 = 2.8 Hz, $1H_A$), 2.53 (dd, J_1 = 12.9 Hz, J_2 = 2.8 Hz, $1H_B$), 2.73 (dd, J_1 = J_2 = 12.9 Hz, $1H_B$), 3.12-3.44 (m, 3H), 5.18 (d, J = 21.0 Hz, $1H_B$), 5.25 (d, J = 12.1 Hz, $1H_A$), 5.31 (d, J = 12.1 Hz, $1H_A$), 5.32 (d, J = 10.9 Hz, $1H_A$), 5.36-5.44 (m, $2H_B$), 6.03 (d, J = 7.4 Hz, $1H_A$), 6.07 (d, J = 7.4 Hz, $1H_B$), 6.79 (d, J = 7.4 Hz, $1H_A$), 6.93 (d, J = 7.4 Hz, $1H_B$), 6.95-6.99 (m, 2H), 7.08-7.33 (m,

7H), 7.35-7.46 (m, 5H); ^{13}CNMR (50 MHz, $CDCl_3$, 25°C): δ_{syn} (two rotamers, A:B 8:1 ratio) = 31.8, 52.6, 54.9, 60.7, 68.6, 107.6 ($1C_B$), 110.6 ($1C_A$), 124.7, 125.3, 125.9, 126.6, 127.7, 127.8, 128.2 (2C), 128.3 (2C), 128.5, 128.6 (2C), 128.7 (2C), 130.7, 131.8, 135.6, 140.2, 154.9; δ_{anti} = 32.7, 44.2, 55.9, 58.3, 68.6, 111.0, 123.7, 125.0, 125.7, 126.7, 128.0, 128.1 (2C), 128.2 (2C), 128.5, 128.7 (2C), 129.0, 129.1 (2C), 130.2, 130.5, 135.5, 140.4, 154.3; ESI-MS: *m/z* = 400.2 $[M+H]^+$, 422.3 $[M+Na]^+$, 821.6 $[2M+Na]^+$; HMRS calcd for $C_{26}H_{25}NO_3$: 399.18344; found 399.18361.



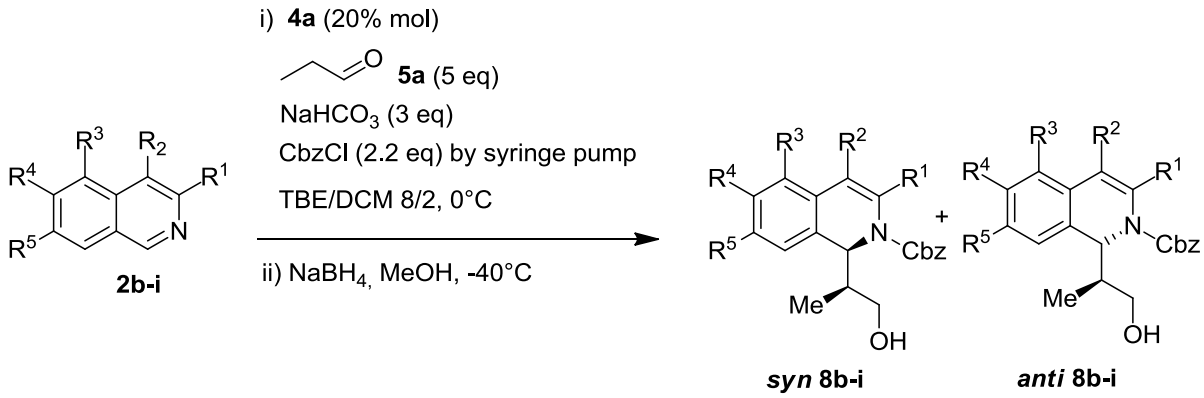
(7g): yellowish oil; 23% yield; the title compound was isolated by column chromatography on silica (cyclohexane/ethyl acetate, gradient elution from 95/5 to 90/10) as mixture of diastereoisomers in 68/32 ratio (*anti*-**7g**:*syn*-**7g**). *Anti* diastereoisomer ee = 94%; *syn* diastereoisomer ee = 81%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 30 min. then 70:30, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *anti* diastereoisomer τ_{major} = 20.39 min., τ_{minor} = 18.82 min.; *syn* diastereoisomer τ_{major} = 12.66 min., τ_{minor} = 16.12 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_{anti} (two rotamers, A:B 9:1 ratio) = 0.86 (t, *J* = 7.6 Hz, 3H), 1.71-1.97 (m, 4H), 2.24-2.38 (m, 1H), 3.11-3.19 (m, 1H), 3.47-3.60 (m, 2H), 5.05-5.17 (m, 1H), 5.19-5.39 (m, 4H), 5.97 (d, *J* = 7.9 Hz, $1H_A$), 6.02 (d, *J* = 7.9 Hz, $1H_B$), 6.78 (d, *J* = 7.9 Hz, 1H), 7.08-7.15 (m, 2H), 7.18-7.26 (m, 2H), 7.33-7.45 (m, 5H); δ_{syn} = 0.85 (t, *J* = 7.6 Hz, 3H), 1.71-1.97 (m, 3H), 1.98-2.12 (m, 2H), 3.28-3.37 (m, 1H), 3.47-3.60 (m, 1H), 3.77-3.82 (bs, 1H), 5.05-5.17 (m, 1H), 5.19-5.39 (m, 3H), 5.66 (d, *J* = 2.7 Hz, 1H), 5.84 (d, *J* = 7.9 Hz, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 7.08-7.15 (m, 2H), 7.18-7.26 (m, 2H), 7.33-7.45 (m, 5H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ_{anti} = 14.1, 20.3, 24.3, 42.5, 55.8, 59.5, 68.6, 111.0, 123.7, 124.8, 126.6, 126.7, 127.8, 127.9, 128.2 (2C), 128.5, 128.7 (2C), 130.2, 130.6, 133.5, 135.6, 154.2; δ_{syn} = 14.0, 20.3, 23.1, 51.2, 54.6, 61.3, 68.4, 110.5, 121.9, 124.6, 125.2, 126.8, 127.5, 127.6, 128.1 (2C), 128.4, 128.7 (2C), 130.7, 131.8, 133.1, 135.7, 154.8; ESI-MS: *m/z* = 378.4 $[M+H]^+$, 400.2 $[M+Na]^+$, 777.5 $[2M+Na]^+$; HMRS calcd for $C_{24}H_{27}NO_3$: 377.19909; found 282.1114.



(7h): the compound was prepared according to the general procedure using DCM as reaction solvent. Yellowish oil; 62% yield; the title compound was isolated after column chromatography on silica (cyclohexane/ethyl acetate 9/1) as mixture of diastereoisomers in 67/32 ratio (*anti*-**7h**:*syn*-**7h**) determined by integration of the COOC$\underline{H_2}$Ph signals of the Cbz groups. *Anti* diastereoisomer ee = 90%; *syn* diastereoisomer ee = 82%. The ees were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 80:20 in 20 min., flow rate

1.0 mL/min, 25°C, λ = 295 nm: *anti* diastereoisomer τ_{major} = 10.79 min., τ_{minor} = 11.87 min.; *syn* diastereoisomer τ_{major} = 13.32 min., τ_{minor} = 14.70 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (*anti:syn* 1:1 mixture): δ_{anti} (two rotamers A:B, 4:1 ratio) = 2.93-3.06 (m, 1H+1H_A), 3.16-3.27 (m, 1H_B), 3.67-3.83 (m, 1H), 3.84-3.93 (m, 1H), 5.27 (d, *J* = 12.5 Hz, 1H), 5.32 (d, *J* = 12.5 Hz, 1H), 5.49 (d, *J* = 10.5 Hz, 1H_B), 5.61 (d, *J* = 10.5 Hz, 1H_A), 5.85 (d, *J* = 7.9 Hz, 1H_B), 5.94 (d, *J* = 7.9 Hz, 1H_A), 6.29 (d, *J* = 7.8 Hz, 1H_A), 6.46 (d, *J* = 7.8 Hz, 1H_B), 6.74-6.82 (m, 2H), 6.98-7.48 (m, 12H); δ_{syn} (two rotamers A:B, 3:1 ratio) = 3.06-3.14 (m, 1H_A), 3.16-3.27 (m, 1H_B), 3.67-3.81 (m, 2H), 3.84-3.93 (m, 1H), 5.13 (d, *J* = 12.5 Hz, 1H), 5.20 (d, *J* = 12.5 Hz, 1H), 5.45 (d, *J* = 7.0 Hz, 1H_A), 5.53 (d, *J* = 7.0 Hz, 1H_B), 5.81 (d, *J* = 5.3 Hz, 1H_A), 5.94 (d, *J* = 7.9 Hz, 1H_B), 6.56 (d, *J* = 7.0 Hz, 1H), 6.84-6.92 (m, 3H), 6.98-7.48 (m, 11H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 6:1 ratio) δ_{anti} = 50.0 (1C_A), 51.2 (1C_B), 56.8 (1C_A), 58.2 (1C_B), 63.0 (1C_A), 63.1 (1C_B), 68.3 (1C_B), 68.5 (1C_A), 110.2 (1C_B), 110.9 (1C_A), 123.3, 124.4, 126.2, 126.9, 127.4, 127.5, 128.0 (2C), 128.2, 128.5, 128.6 (2C), 128.7 (2C), 129.4, 129.8, 130.5, 135.8 (1C_A), 138.1 (1C_B), 139.3 (1C_A), 141.0 (1C_B), 154.0; δ_{syn} = 52.5 (1C_B), 54.6 (1C_A), 56.0 (1C_A), 59.9 (1C_B), 61.7 (1C_A), 62.2 (1C_B), 67.9 (1C_B), 68.2 (1C_A), 109.7, 124.6, 125.0, 126.6, 127.0, 127.1, 127.7 (2C), 127.8, 128.0 (2C), 128.3, 128.6, 129.0, 129.1 (2C), 130.7, 131.1, 135.6, 137.5 (1C_A), 138.2 (1C_B), 154.1; ESI-MS: *m/z* = 386.3 $[M+H]^+$, 408.2 $[M+Na]^+$.

Stereoselective alkylation of isoquinolines activated with CbzCl with propionaldheyde



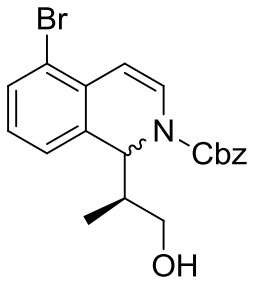
2b	R^1= R^2= R^4= R^5= H; R^3= Br	**2f**	R^1= R^2= R^3= R^5= H; R^4= OMe
2c	R^2= R^3= R^4= R^5= H; R^1= Me	**2g**	R^1= R^2= R^3= R^5= H; R^4= Me
2d	R^1= R^2= R^3= H; R^4= R^5= OMe	**2h**	R^1= R^2= R^4= R^5= H; R^3= Pyrrolidinyl
2e	R^1= R^2= R^4= R^5= H; R^3= allyl	**2i**	R^1= R^3= R^4= R^5= H; R^2= Bn

General procedure: To a solution of isoquinoline **2b-i** (0.2 mmol) in 0.5 mL *t*-BuOMe/CH_2Cl_2 (8/2) inside a round-bottomed flask equipped with a stirring magnetic bar and cooled at 0°C, $NaHCO_3$ (0.6 mmol, 51 mg), Jørgensen catalyst **4a** (0.04 mmol, 24 mg) and aldehyde **5a** (1.0

mmol) were added. To the mixture a solution of CbzCl (0.45 mmol, 78 μL CbzCl in 1 mL *t*BuOMe/CH_2Cl_2 8/2) was added drop wise by a syringe pump during 15 h. After that 2 mL of an aqueous saturated solution of NH_4Cl were added and the organic layer was extracted with Et_2O (3 x 5 mL). The collected organic layers were dried over $MgSO_4$. The residue was diluted in MeOH and the resulting solution was cooled at -40°C. Then $NaBH_4$ (2 mmol, 76 mg) was added. When complete conversion was obtained (monitored by TLC), HCl 1N was added (at -40°C) until pH = 1. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The collected organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give **8b-i**.

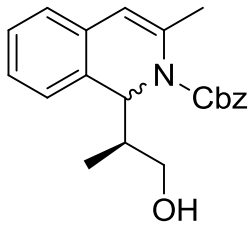
The racemic products were synthesized with the same procedure except for using pyrrolidine (0.1 mmol, 8.3 μL) instead of **4a**, CH_2Cl_2 as reaction solvent and for conducing the reaction at room temperature.

Note: the enantiomeric excesses and the diasteromeric ratios of the compounds remain unaltered after flash chromatography or after preparative thin layer chromatography on neutral alumina.

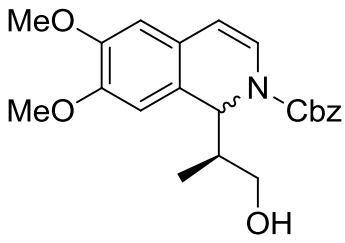


(8b): colourless oil; 40% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15) as mixture of diastereoisomers in 73/27 ratio (*syn*-**8b**:*anti*-**8b**). *Syn* diastereoisomer ee = 95%; *anti* diastereoisomer ee = 88%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min., flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer τ_{major} = 16.16 min., τ_{minor} = 13.42 min.; *anti* diastereoisomer τ_{major} = 12.71 min., τ_{minor} = 14.51 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 7:1 ratio): δ_{syn} = 0.72 (d, J = 7.0 Hz, $3H_A$), 0.86 (d, J = 7.0 Hz, $3H_B$), 1.92-2.02 (bs, 1H), 3.31 (dd, J_1 = 12.1 Hz, J_2 = 10.0 Hz, 1H), 3.37-3.45 (m, 1H), 3.67-3.90 (bs, 1H), 5.27 (s, $2H_A$), 5.28 (s, $2H_B$), 5.60 (d, J = 3.1 Hz, 1H), 6.20 (d, J = 8.0 Hz, $1H_A$), 6.35 (d, J = 8.0 Hz, $1H_B$), 6.96 (d, J = 8.0 Hz, 1H), 7.02-7.10 (m, 2H), 7.34-7.41 (m, 5H), 7.44 (dd, J_1 = 7.3 Hz, J_2 = 1.7 Hz, 1H); δ_{anti} = 0.60 (d, J = 7.0 Hz, $3H_B$), 0.85 (d, J = 7.0 Hz, $3H_A$), 1.92-2.02 (bs, 1H), 3.37-3.45 (m, 1H), 3.58 (dd, J_1 = 12.1 Hz, J_2 = 2.4 Hz, 1H), 3.67-3.90 (bs, 1H), 5.14 (d, J = 10.1 Hz, 1H), 5.18-5.33 (m, 2H), 6.24 (d, J = 8.0 Hz, $1H_B$), 6.31 (d, J = 8.0 Hz, $1H_A$), 6.89 (d, J = 8.0 Hz, 1H), 7.02-7.10 (m, 2H), 7.34-7.41 (m, 5H), 7.47 (dd, J_1 = 6.7 Hz, J_2 = 2.3 Hz, 1H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ_{syn} = 10.7, 43.8 ($1C_B$), 46.1 ($1C_A$), 55.0, 63.5, 68.7, 108.9, 120.1, 125.8, 127.2, 128.2 (2C), 128.3, 128.6, 128.7 (2C), 130.2, 131.6, 134.0, 135.4, 154.7; δ_{anti} = 14.0, 36.5, 56.8, 63.4, 68.7, 109.3, 120.5, 125.5, 127.0,

127.5, 128.2 (2C), 128.5, 128.6 (2C), 129.8, 131.9, 132.5, 135.3, 153.4; ESI-MS: *m/z* = 402.4 $[M(^{79}Br)+H]^+$, 404.3 $[M(^{81}Br)+H]^+$, 425.3 $[M(^{79}Br)+Na]^+$, 427.2 $[M(^{81}Br)+Na]^+$; HMRS calcd for $C_{20}H_{20}BrNO_3$: 401.06266; found 401.06251.

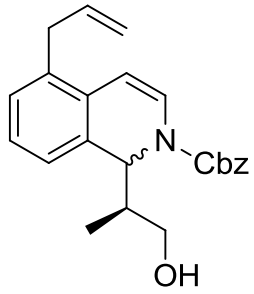


(8c): colourless oil; 23% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15) as mixture of diastereoisomers in 87/13 ratio (*syn*-**8c**:*anti*-**8c**). *Syn* diastereoisomer ee = 99%; *anti* diastereoisomer ee = 94%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 85:15 in 40 min. then 85:15, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer τ_{major} = 41.21 min., τ_{minor} = 30.31 min.; *anti* diastereoisomer τ_{major} = 21.58 min., τ_{minor} = 31.20 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_{syn}= 0.71-0.80 (bs, 3H), 1.96-2.05 (m, 1H), 2.14-2.24 (bs, 3H), 3.37-3.51 (bs, 3H), 5.17 (d, *J* = 12.5 Hz, 1H), 5.26 (d, *J* = 12.5 Hz, 1H), 5.50-5.58 (bs, 1H), 5.94-5.99 (bs, 1H), 7.02-7.10 (m, 1H), 7.13-7.18 (m, 1H), 7.18-7.25 (m, 1H), 7.29-7.34 (m, 1H), 7.34-7.40 (m, 4H), 7.40-7.43 (m, 1H); δ_{anti}= 0.90 (d, *J* = 6.9 Hz, 3H), 1.68-1.76 (bs, 1H), 2.14-2.24 (bs, 3H), 3.37-3.51 (bs, 1H), 3.76-3.81 (bs, 2H), 5.12 (d, *J* = 10.9 Hz, 1H), 5.14-5.28 (m, 2H), 5.99-6.02 (bs, 1H), 7.02-7.10 (m, 1H), 7.13-7.18 (m, 1H), 7.18-7.25 (m, 1H), 7.29-7.34 (m, 1H), 7.34-7.40 (m, 4H), 7.40-7.43 (m, 1H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ_{syn} (two rotamers, A:B 5:1 ratio) = 11.8 ($1C_A$), 13.8 ($1C_B$), 21.7, 29.7 ($1C_A$), 33.8 ($1C_B$), 57.4, 64.0, 65.4 ($1C_B$), 68.4 ($1C_A$), 115.2, 124.2, 126.0, 126.8, 127.0, 127.4, 128.4 (2C), 128.5, 128.6 (2C), 131.4, 133.2, 135.6, 140.9; δ_{anti} = 14.1, 21.7, 35.8, 59.0, 63.8, 68.6, 115.0, 124.2, 126.1, 127.2, 127.5, 127.6, 128.5, 128.6 (2C), 128.7 (2C), 130.8, 132.1, 135.4, 140.9; ESI-MS: *m/z* = 338.3 $[M+H]^+$, 360.4 $[M+Na]^+$, 697.5 $[2M+Na]^+$; HMRS calcd for $C_{21}H_{23}NO_3$: 337.16779; found 337.16789.

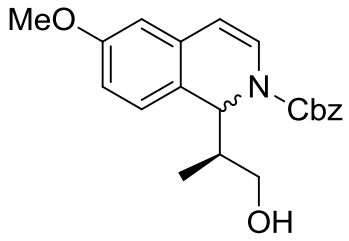


(8d): (Reaction carried out in CH_2Cl_2 as reaction solvent); yellowish oil; 53% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 80/20) as mixture of diastereoisomers in 71/29 ratio (*anti*-**8d**:*syn*-**8d**). *Anti* diastereoisomer ee = 91%; *syn* diastereoisomer ee = 77%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH 80:20, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *anti* diastereoisomer τ_{major} = 19.62 min., τ_{minor} = 25.51 min.; *syn* diastereoisomer τ_{minor} = 21.04 min., τ_{major} = 24.99 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_{anti} (two rotamers A:B, 13:1 ratio) = 0.74 (d, *J* = 7.2 Hz, $3H_B$),0.89 (0.74 rotamer) (d, *J* = 7.2 Hz, $3H_A$),

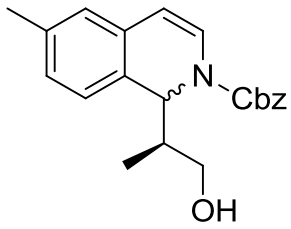
1.86-2.00 (m, 1H), 3.02-3.18 (bs, 1H), 3.38 (dd, J_1 = 12.0 Hz, J_2 = 2.6 Hz, 1H), 3.57 (dd, J_1 = 12.0 Hz, J_2 = 2.6 Hz, 1H), 3.87 (s, 6H), 5.11 (d, J = 9.8 Hz, 1H), 5.23 (d, J = 12.2 Hz, 1H), 5.29 (d, J = 12.2 Hz, 1H), 5.87 5.90 (d, J = 7.9 Hz, $1H_A$), 5.90 (d, J = 7.9 Hz, $1H_B$), 6.63 (s, 1H), 6.65 (s, 1H), 6.70 (dd, J_1 = 7.6 Hz, J_2 = 1.0 Hz, 1H), 7.28-7.42 (m, 5H); δ_{syn} = 0.69 (d, J = 7.2 Hz, 3H), 2.00-2.04 (m, 1H), 3.00-3.02 (bs, 1H), 3.27-3.33 (bs, 1H), 3.48 (dd, J_1 = 10.9 Hz, J_2 = 4.7 Hz, 1H), 3.88 (s, 6H), 5.20 (d, J = 11.9 Hz, 1H), 5.33 (d, J = 11.9 Hz, 1H), 5.60 (d, J = 3.0 Hz, 1H), 5.73 (d, J = 7.9 Hz, 1H), 6.58 (s, 1H), 6.68 (s, 1H), 6.78 (d, J = 7.3 Hz, 1H), 7.16-7.22 (m, 1H), 7.28-7.42 (m, 3H), 7.43-7.48 (m, 1H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ_{anti} = 14.1, 37.3, 55.9, 56.1, 56.3, 63.7, 68.4, 108.1, 110.6, 111.5, 122.2, 123.4, 126.9, 128.1 (2C), 128.4, 128.6 (2C), 135.6, 147.8, 148.4, 154.3; δ_{syn} = 10.3, 46.2, 54.6, 56.1, 56.3, 65.3, 68.4, 107.8, 109.8, 110.2, 123.2, 123.9, 127.6, 128.5 (2C), 128.6 (3C), 135.7, 147.8, 148.4, 154.3; ESI-MS: m/z = 384.4 $[M+H]^+$, 406.4 $[M+Na]^+$, 789.5 $[2M+Na]^+$; HMRS calcd for $C_{22}H_{25}NO_5$: 383.17327; found 383.17338.



(8e): colourless oil; 56% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 80/20) as mixture of diastereoisomers in 81/19 ratio (*syn*-**8e**:*anti*-**8e**). *Syn* diastereoisomer ee = 54%; *anti* diastereoisomer ee = 48%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min., flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer τ_{major} = 16.18 min., τ_{minor} = 12.19 min.; *anti* diastereoisomer τ_{major} = 11.53 min., τ_{minor} = 14.23 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_{syn} (two rotamers A:B, 10:1 ratio) = 0.70 (d, J = 7.3 Hz, $3H_A$), 0.94 (d, J = 7.3 Hz, $3H_B$), 1.97-2.04 (m, 1H), 3.27-3.35 (m, 1H), 3.35-3.47 (m, 3H), 3.83-3.92 (bs, 1H), 4.96 (d, J = 17.0 Hz, 1H), 5.06 (d, J = 9.8 Hz, 1H), 5.21-5.32 (m, 2H), 5.61 (d, J = 2.6 Hz, 1H), 5.89-6.01 (m, 1H), 5.97 (d, J = 7.8 Hz, $1H_A$), 6.15 (d, J = 7.8 Hz, $1H_B$), 6.88 (d, J = 7.8 Hz, 1H), 6.96-7.11 (m, 2H), 7.12-7.19 (m, 1H), 7.33-7.44 (m, 5H); δ_{anti}= 0.86 (d, J = 7.3 Hz, 3H), 1.97-2.04 (m, 1H), 3.01-3.08 (bs, 1H), 3.27-3.35 (m, 1H), 3.35-3.47 (m, 2H), 3.55-3.61 (bs, 1H), 5.00 (d, J = 17.0 Hz, 1H), 5.12 (d, J = 9.8 Hz, 1H), 5.21-5.32 (m, 2H), 5.29 (d, J = 10.6 Hz, 1H), 5.89-6.01 (m, 1H), 6.10 (d, J = 7.8 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.96-7.11 (m, 2H), 7.12-7.19 (m, 1H), 7.33-7.44 (m, 5H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ_{syn} = 10.7, 29.6, 36.8, 46.3, 55.1, 68.5, 107.1, 115.9, 125.0, 125.5, 127.4, 128.2 (2C), 128.5, 128.6 (2C), 128.7, 128.9, 132.5, 133.7, 135.6, 136.7, 154.8; δ_{anti} = 14.1, 22.7, 36.9, 46.4, 56.9, 63.8, 107.6, 115.9, 123.8, 126.3, 126.5, 128.3 (2C), 128.5, 128.6 (2C), 128.8, 128.9, 132.5, 133.7, 135.6, 136.6, 154.8; ESI-MS: m/z = 364.2 $[M+H]^+$, 386.3 $[M+Na]^+$, 749.6 $[2M+Na]^+$; HMRS calcd for $C_{23}H_{25}NO_3$: 363.18344; found 363.18362.

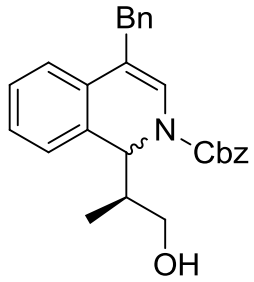


(8f): yellowish oil; 56% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15) as mixture of diastereoisomers in 54/46 ratio (*syn*-**8f**:*anti*-**8f**). *Syn* diastereoisomer ee = 78%; *anti* diastereoisomer ee = 25%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min. then 70:30, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer τ_{major} = 31.40 min., τ_{minor} = 17.33 min.; *anti* diastereoisomer τ_{major} = 16.58 min., τ_{minor} = 25.73 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 10:1 ratio): δ_{syn} = 0.72 (d, *J* = 7.0 Hz, $3H_A$), 0.90 (d, *J* = 7.0 Hz, $3H_B$), 1.87-2.00 (m, 1H), 3.31 (pt, J_1 = 12.5 Hz, J_2 = 10.0 Hz, 1H), 3.35-3.44 (bs, 1H), 3.80 (s, 3H), 3.88-3.95 (bs, 1H), 5.21-5.32 (m, 2H), 5.59 (d, *J* = 3.0 Hz, 1H), 5.77 (d, *J* = 8.2 Hz, $1H_A$), 5.94 (d, *J* = 8.2 Hz, $1H_B$), 6.64 (d, *J* = 3.5 Hz, 1H), 6.76 (dd, J_1 = 15.1 Hz, J_2 = 2.3 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 7.33-7.45 (m, 5H); δ_{anti} = 0.72 (d, *J* = 7.0 Hz, $3H_B$), 0.86 (d, *J* = 7.0 Hz, $3H_A$), 1.87-2.00 (m, 1H), 3.04-3.12 (bs, 1H), 3.35-3.44 (bs, 1H), 3.57 (dd, J_1 = 12.0 Hz, J_2 = 3.6 Hz, 1H), 3.80 (s, 3H), 5.13 (d, *J* = 10.0 Hz, 1H), 5.21-5.32 (m, 2H), 5.89 (d, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 3.5 Hz, 1H), 6.75-6.77 (bs, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 7.33-7.45 (m, 5H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ_{syn} = 10.6, 46.4, 54.5, 55.3, 63.8, 68.5, 109.7, 110.2, 112.8, 124.2, 125.9, 127.4, 128.1, 128.2, 128.6 (2C), 128.7, 131.7, 135.6, 154.8, 159.1; δ_{anti} = 13.9, 37.4, 55.3, 56.2, 63.2, 65.2, 110.0, 110.6, 112.0, 123.2, 124.3, 126.9, 127.5, 128.42, 128.45, 128.5 (2C), 131.3, 135.6, 154.1, 158.9; ESI-MS: *m/z* = 354.4 $[M+H]^+$, 376.3 $[M+Na]^+$, 729.5 $[2M+Na]^+$; HMRS calcd for $C_{21}H_{23}NO_2$: 353.16271; found 353.16277.



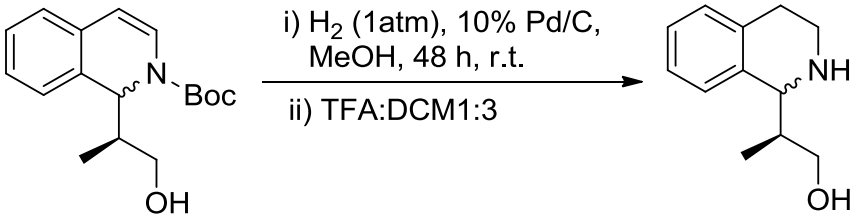
(8g): (Reaction carried out in CH_2Cl_2 as reaction solvent); colourless oil; 68% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15) as mixture of diastereoisomers in 53/47 ratio (*anti*-**8g**:*syn*-**8g**). *Syn* diastereoisomer ee = 88%; *anti* diastereoisomer ee = 92%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min. then 70:30, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer τ_{major} = 27.05 min., τ_{minor} = 14.04 min.; *anti* diastereoisomer τ_{major} = 13.30 min., τ_{minor} = 21.83 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 10:1 ratio): δ_{anti} = 0.70 (d, *J* = 7.0 Hz, $3H_A$), 0.90 (d, *J* = 7.0 Hz, $3H_B$),1.87-2.01 (m, 1H), 2.32 (s, 3H), 3.32 (dd, J_1 = J_2 = 10.2 Hz, 1H), 3.36-3.45 (bs, 1H), 3.90-3.99 (bs, 1H), 5.23-5.32 (m, 2H), 5.60 (d, *J* = 3.0 Hz, 1H), 5.77 (d, *J* = 7.7 Hz, $1H_A$), 5.94 (d, *J* = 7.7 Hz, $1H_B$), 6.87 (d, *J* = 7.7 Hz, 1H), 6.88 (s, 1H), 6.98-7.05 (m, 2H), 7.34-7.41

(m, 5H); δ_{syn} = 0.74 (d, J = 6.9 Hz, $3H_B$), 0.87 (d, J = 6.9 Hz, $3H_A$), 1.87-2.01 (m, 1H), 2.33 (s, 3H), 3.06-3.15 (bs, 1H), 3.36-3.45 (bs, 1H), 3.59 (dd, J_1 = 12.2 Hz, J_2 = 2.5 Hz, 1H), 5.14 (d, J = 10.0 Hz, 1H), 5.23-5.32 (m, 2H), 5.90 (d, J = 7.7 Hz, $1H_A$), 5.93 (d, J = 7.7 Hz, $1H_B$), 6.78 (dd, J_1 = 7.6 Hz, J_2 = 1.0 Hz, 1H), 6.92 (s, 1H), 6.98-7.05 (m, 2H), 7.34-7.41 (m, 5H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ_{anti} (two rotamers, A:B 8:1 ratio) = 10.6, 21.0, 46.3, 54.7, 63.8 ($1C_A$), 65.3 ($1C_B$), 68.4, 110.4, 125.1, 125.4, 126.3, 127.6, 127.9, 128.1, 128.2, 128.6 (2C), 129.1, 130.5, 135.7, 137.0, 154.9; δ_{syn} (two rotamers A:B, 5:1 ratio)= 14.0 ($1C_A$), 14.1 ($1C_B$), 21.1, 37.2, 56.4, 60.2 ($1C_B$), 63.6 ($1C_A$), 63.9, 110.8, 123.8, 125.5, 127.0, 127.3, 127.5, 128.0 (2C), 128.3, 128.4 128.5, 130.0, 135.6, 137.3, 154.2; ESI-MS: m/z = 338.3 $[M+H]^+$, 360.4 $[M+Na]^+$, 697.5 $[2M+Na]^+$; HMRS calcd for $C_{21}H_{23}NO_3$: 337.16779; found 337.16761.



(8i): yellowish oil; 60% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15) as mixture of diastereoisomers in 81/19 ratio (*syn*-**8i**:*anti*-**8i**). *Syn* diastereoisomer ee = 97%; *anti* diastereoisomer ee = 74%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min. then 70:30, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer τ_{major} = 27.42 min., τ_{minor} = 15.48 min.; *anti* diastereoisomer τ_{major} = 13.65 min., τ_{minor} = 24.98 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 8:1 ratio): δ_{syn} = 0.69 (d, J = 7.1 Hz, $3H_A$), 0.92 (d, J = 7.1 Hz, $3H_B$), 1.88-2.03 (m, 1H), 3.33 (pt, J_1 = 11.9 Hz, J_2 = 10.2 Hz, 1H), 3.37-3.47 (m, 1H), 3.72 (d, J = 16.0 Hz, 1H), 3.80 (d, J = 16.0 Hz, 1H), 3.93-4.01 (bs, 1H), 5.22 (d, J = 12.3 Hz, $1H_B$), 5.23 (d, J = 12.3 Hz, $1H_A$), 5.28 (d, J = 12.3 Hz, $1H_A$), 5.32 (d, J = 12.3 Hz, $1H_B$), 5.62 (d, J = 3.2 Hz, 1H), 6.70 (s, $1H_A$), 6.92 (s, $1H_B$), 7.15-7.27 (m, 6H), 7.27-7.33 (m, 3H), 7.33-7.47 (m, 5H); δ_{anti} = 0.73 (d, J = 6.9 Hz, $3H_B$), 0.88 (d, J = 6.9 Hz, $3H_A$), 1.88-2.03 (m, 1H), 3.12-3.21 (bs, 1H), 3.37-3.47 (m, 1H), 3.59-3.66 (m, 1H), 3.72 (d, J = 16.0 Hz, 1H), 3.89 (d, J = 16.0 Hz, 1H), 5.15 (d, J = 10.4 Hz, 1H), 5.24 (d, J = 12.3 Hz, 1H), 5.30 (d, J = 12.3 Hz, 1H), 6.66 (s, $1H_A$), 6.88 (s, $1H_B$), 7.01-7.14 (m, 2H), 7.15-7.27 (m, 4H), 7.27-7.33 (m, 3H), 7.33-7.47 (m, 5H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ_{syn} = 10.7, 36.2, 45.9, 54.9, 63.8, 68.3, 119.0, 122.2, 124.1, 126.3, 126.6, 127.3, 127.5, 127.9 (2C), 128.2, 128.4 (2C), 128.6 (2C), 128.7 (2C), 131.3, 133.0, 135.7, 139.0, 154.9; δ_{anti} = 14.1, 35.9, 37.2, 56.8, 63.6, 68.4, 119.8, 122.2, 122.5, 126.3, 126.7, 126.9, 127.6, 128.0 (2C), 128.3, 128.5 (2C), 128.60 (2C), 128.7 (2C), 129.1, 131.7, 135.6, 139.2, 154.2; ESI-MS: m/z = 414.2 $[M+H]^+$, 436.1 $[M+Na]^+$, 849.2 $[2M+Na]^+$; HMRS calcd for $C_{27}H_{27}NO_3$: 413.19909; found 413.19979.

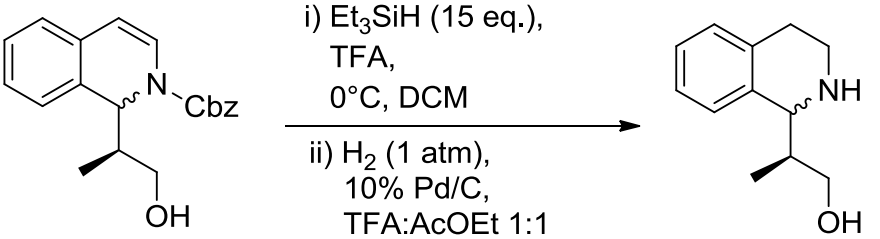
Synthesis of compound 9a



6a, *syn*/*anti* 88/12; ee_{syn} 97%

9a, 71%, *syn*/*anti* 88/12, ee_{syn} 97%

Procedure starting from 6a: To a 25 mL balloon equipped with a magnetic stirring bar, 3 mL MeOH and 10% Pd/C (20% wt, 60 mg), were added and the mixture was stirred under hydrogen atmosphere (1 atm) for 30 min. Then **6a** (0.2 mmol, 58.7 mg) was added and the mixture was stirred under hydrogen atmosphere for 48 hours. After that the mixture was diluted with CH_2Cl_2 (5 mL), filtered trough Celite® and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (7.5 mL) and trifluoroacetic acid (33 mmol, 2.5 mL) was added and the mixture was stirred for 4 h. The solution was concentrated under reduced pressure, water (5 mL) was added and the solution was basified with $NaHCO_3$ and subsequently extracted with Et_2O (3 x 5 mL). The organic layers were collected and washed with HCl 1N (3 x 5 mL). The aqueous layers were collected and basified at 0°C with KOH and subsequently extracted with Et_2O (3 x 5 mL). The collected organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give pure **9a** in 71% yield.



7a, *syn*/*anti* 74/26, ee_{syn} 96%

9a, 76%, *syn*/*anti* 74/26, ee_{syn} 96%

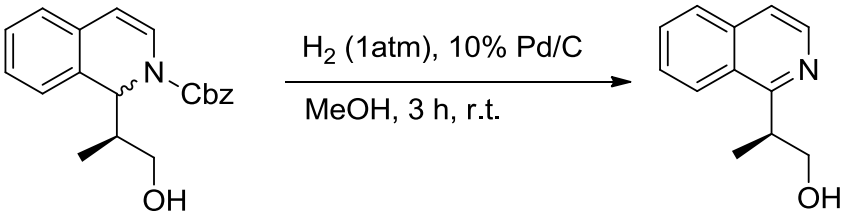
Procedure starting from 7a: To a solution of **7a** (0.24 mmol, 77.5 mg) in CH_2Cl_2 (2 mL) at 0°C, triethylsilane (3.7 mmol, 586 µL) and trifluoroacetic acid (46 mmol, 3.5 mL) were added and the mixture was stirred at 0°C. After 3 hours the solution was concentrated under reduced pressure.

The residue was diluted in AcOEt (1 mL) and trifluoroacetic acid (1 mL). 10% Pd/C (10% wt, 45 mg) was added and the mixture was kept under hydrogen atmosphere (1 atm) for 2 hours. Then the mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite®. The solution was concentrated under reduced pressure, water (5 mL) was added and the solution was basified with

$NaHCO_3$ and subsequently extracted with Et_2O (3 x 5 mL). The organic layers were collected and washed with HCl 1N (3 x 5 mL). The aqueous layers were collected and basified at 0°C with KOH and subsequently extracted with Et_2O (3 x 5 mL). The collected organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give pure **9a** in 76% yield.

(9a): yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_{syn} = 0.91 (d, J = 7.2 Hz, 3H), 2.34-2.44 (m, 1H), 2.29-2.74 (bs, 2H), 2.66-2.75 (m, 1H), 2.81-2.95 (m, 1H), 2.96-3.05 (m, 1H), 3.24-3.34 (m, 1H), 3.76 (dd, J_1 = 10.9 Hz, J_2 = 3.4 Hz, 1H), 4.00 (dd, J_1 = 10.9 Hz, J_2 = 5.0 Hz, 1H), 4.30 (d, J = 2.65 Hz, 1H), 7.07-7.21 (m, 4H); δ_{anti} = 1.22 (d, J = 7.2 Hz, 3H), 2.17-2.27 (m, 1H), 2.29-2.74 (bs, 2H), 2.66-2.75 (m, 1H), 2.81-2.95 (m, 1H), 2.96-3.05 (m, 1H), 3.24-3.34 (m, 1H), 3.45 (ddd, J_1 = 10.8 Hz, J_2 = 4.6 Hz, J_3 = 0.9 Hz, 1H), 3.66 (dd, J_1 = 10.8 Hz, J_2 = 2.4 Hz, 1H), 4.17 (d, J = 4.60 Hz, 1H), 7.07-7.21 (m, 4H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ_{syn} (two rotamers, A:B 10:1 ratio) = 10.7, 29.7 ($1C_A$), 30.2 ($1C_B$), 37.9, 42.3, 59.6, 67.9, 125.3, 126.1, 126.2, 129.5, 135.7, 137.3; δ_{anti} = 15.1, 29.6, 37.8, 41.6, 61.6, 66.1, 125.8, 126.3, 126.4, 129.3, 135.7, 137.3; ESI-MS: m/z = 192.2 $[M+H]^+$; HMRS calcd for $C_{12}H_{17}NO$: 191.13101; found 191.13152.

Synthesis of 1-alkyl isoquinoline 10a



7a, *syn*/*anti* 75/25, ee_{syn} 95%, ee_{anti} 86%

10a, 80%, ee 93%

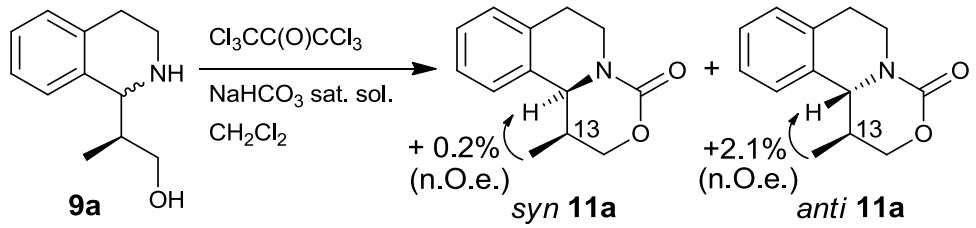
A mixture of 10% Pd/C (10% wt, 15 mg) was stirred under hydrogen atmosphere for 30 min. Then **7a** (0.12 mmol, 39.2 mg) was added and the mixture was stirred under hydrogen atmosphere (1atm) for further 3 hours. The mixture was diluted with CH_2Cl_2 (10 mL) and filtered through Celite®. The solvent was concentrated under reduced pressure to give crude **10a**. The title compound was isolated by column chromatography on silica (cyclohexane/acetone 75/25) as colorless oil (80% yield; 93% ee). The ee was determined by HPLC analysis Daicel Chiralpak® IC column: hexane/*i*-PrOH 90:10, flow rate 0.70 mL/min, 40°C, λ = 214 nm: τ_{major} = 17.48 min., τ_{minor} = 18.40 min.

(8aa): $[\alpha]_D^{20}$=-52.4 (c=1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.48 (d, J = 7.0 Hz, 3H), 3.82-3.90 (m, 1H), 4.04 (dd, J_1 = 10.9 Hz, J_2 = 5.1 Hz, 1H), 4.21 (dd, J_1 = 10.9 Hz, J_2 = 3.1

Hz, 1H), 4.75-4.97 (bs, 1H), 7.52 (d, J = 5.6 Hz, 1H), 7.60 (ddd, J_1 = 8.2 Hz, J_2 = 6.9 Hz, J_3 = 1.1 Hz, 1H), 7.67 (ddd, J_1 = 8.2 Hz, J_2 = 6.9 Hz, J_3 = 1.1 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 8.16 (d, J = 8.2 Hz, 1H), 8.38 (d, J = 5.6 Hz, 1H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C): δ= 17.8, 37.2, 66.3, 119.5, 124.7, 126.4, 127.2, 127.5, 130.0, 136.4, 140.9, 165.3; ESI-MS: *m/z* = 188.1 $[M+H]^+$; HMRS calcd for $C_{12}H_{13}NO$: 187.09971; found 187.09964.

Determination of the relative configuration of 9a

To determine the relative configuration of the obtained products **6**, **7** and **8**, the oxazolidinone **11a** was prepared starting from **9a**. The major and the minor diastereoisomers were separated by preparative TLC and the relative configuration of the stereogenic centers 1 and 2' was determined by NOESY1D NMR analysis.



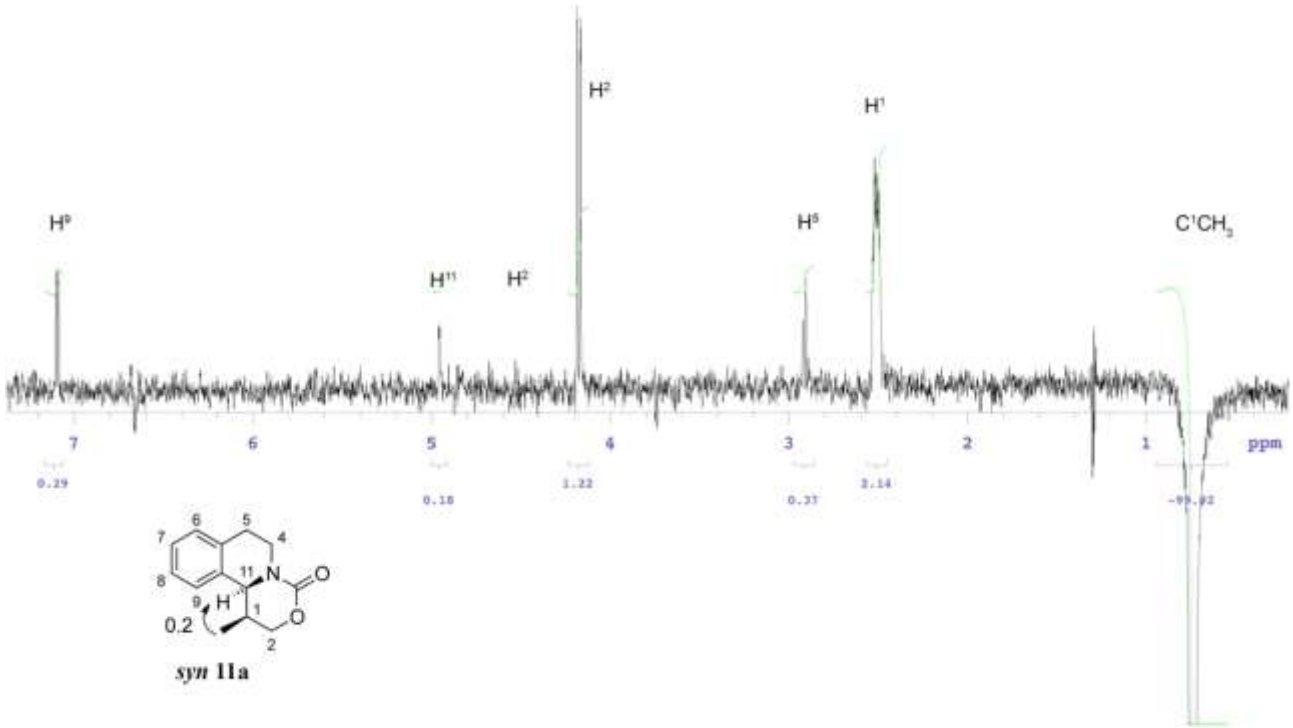
Preparation of the oxazolidinone: In a 5 mL vial equipped with stirring bar, **9a** (dr *syn*:*anti* 2.57:1.0) (0.06 mmol, 12.0 mg) was dissolved in 1 mL of CH_2Cl_2. The solution was cooled to 0°C and 1 mL of a saturated solution of $NaHCO_3$ was added under vigorous agitation. Then triphosgene (0.24 mmol, 56 mg) was added in two portions after a two hours gap. After six hours the reaction was allowed to warm to room temperature overnight. Et_2O (10 mL) and water (1 mL) were added and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified with preparative thin layer chromatography on silica (cyclohexane/AcOEt 6/4) to afford product **11a** in 64% yield.

(11a) ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_{syn} = 0.78 (d, J = 6.8 Hz, 3H), 2.48-2.57 (m, 1H), 2.65-2.74 (m, 1H), 2.89-3.00 (m, 2H), 4.21 (dd, J_1 = 10.7 Hz, J_2 = 1.9 Hz, 1H), 4.52 (dd, J_1 = 10.7 Hz, J_2 = 2.4 Hz, 1H), 4.68-4.73 (m, 1H), 4.99 (d, J = 3.8 Hz, 1H), 7.10-7.29 (m, 4H); δ_{anti} = 1.32 (d, J = 6.9 Hz, 3H), 2.46-2.56 (m, 1H), 2.79 (dt, J_1 = 15.9 Hz, J_2 = 4.9 Hz, 1H), 3.04-3.13 (m, 1H), 3.18-3.26 (m, 1H), 3.98 (dd, J_1 = 10.8 Hz, J_2 = 8.3 Hz, 1H), 4.14 (dd, J_1 = 10.8 Hz, J_2 = 3.8 Hz, 1H), 4.22 (dt, J_1 = 12.7 Hz, J_2 = 5.3 Hz, 1H), 4.32 (d, J = 6.7 Hz, 1H), 7.18-7.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ_{syn} = 16.2, 28.5, 31.9, 43.8, 60.3, 69.3, 126.5, 126.7, 127.5, 129.0, 135.9,

136.5, 153.7; δ_{anti} = 10.2, 29.0, 32.1, 41.3, 58.4, 70.9, 124.1, 125.3, 126.8, 129.3, 133.9, 135.6, 152.8; ESI-MS: *m/z* = 218.1 $[M+H]^+$, 435.2 $[2M+H]^+$, 457.1 $[2M+Na]^+$; HMRS calcd for $C_{13}H_{15}NO_2$: 217.11028; found 217.11014.

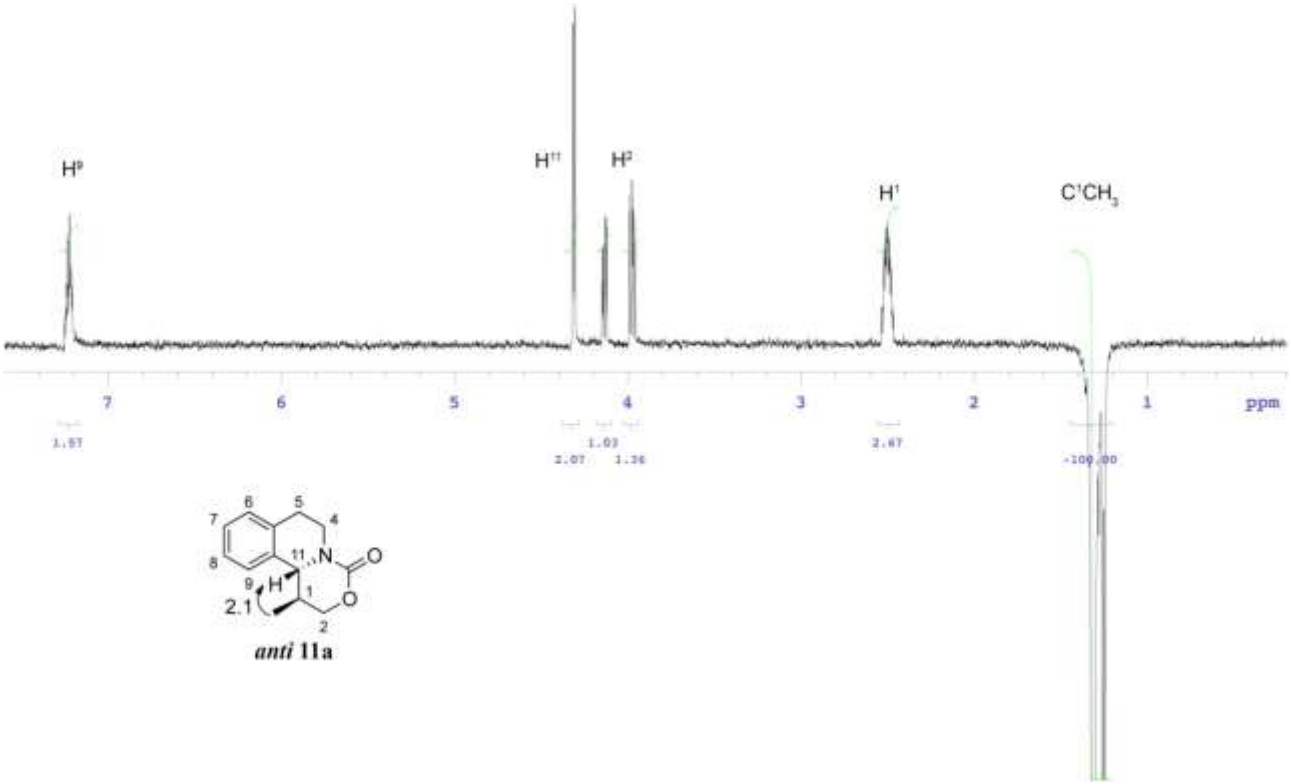
Selective excitation of the C1 methyl signal of the major diastereoisomer, shows a positive n.O.e. on the proton H^{11} that could be estimated 0.2 considered 100 the intensity of the irradiated signal. The same analysis was conducted on the minor diastereoisomer and a positive n.O.e. was observed for the proton H^{11} with an intensity of 2.1 considered 100 the intensity of the irradiated signal. On the basis of this evidence the relative configuration *syn* was assigned to the major diastereoisomer and the relative configuration *anti* was assigned to the minor diastereoisomer.

Figure S1. Major diasteroisomer *syn* **11a** (Obtained 600 MHz in $CDCl_3$ using a DPFGSE-NOE sequence with a 50 Hz 'rsnob' pulse and a mixing time of 2 s)

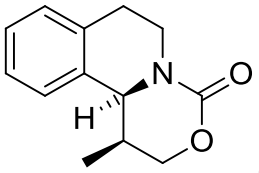


syn **11a**

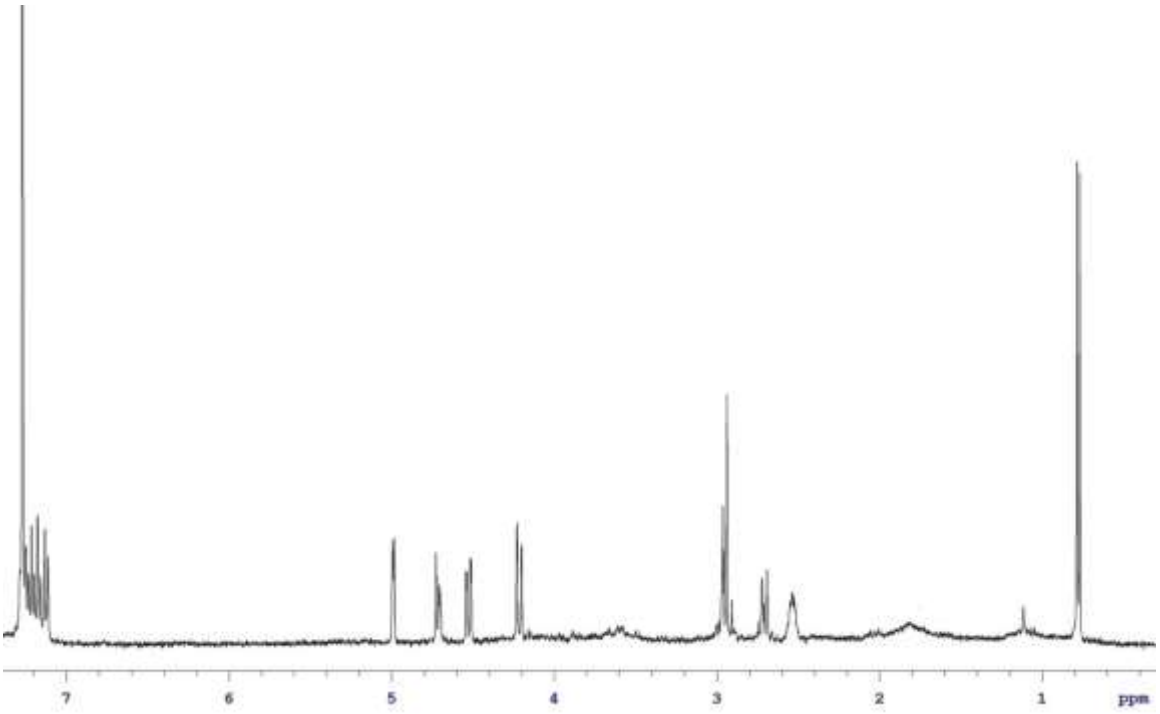
Figure S2. Minor diasteroisomer *anti* **11a** (Obtained 600 MHz in $CDCl_3$ using a DPFGSE-NOE sequence with a 50 Hz 'rsnob' pulse and a mixing time of 2 s)

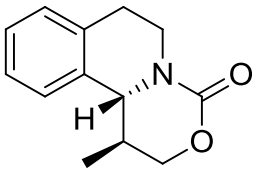


anti **11a**

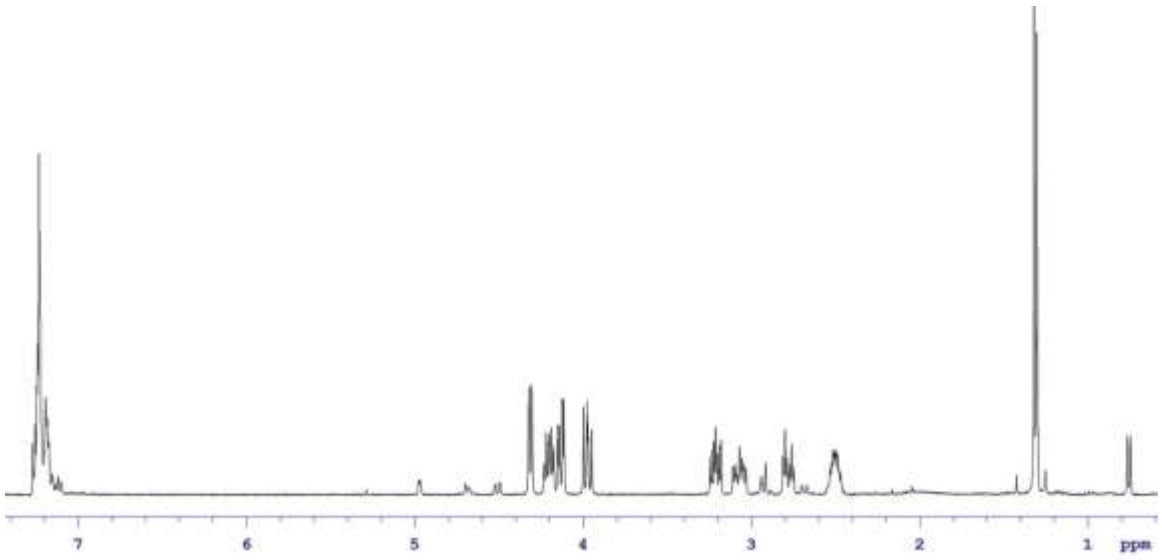


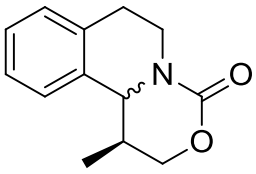
syn-**11a**



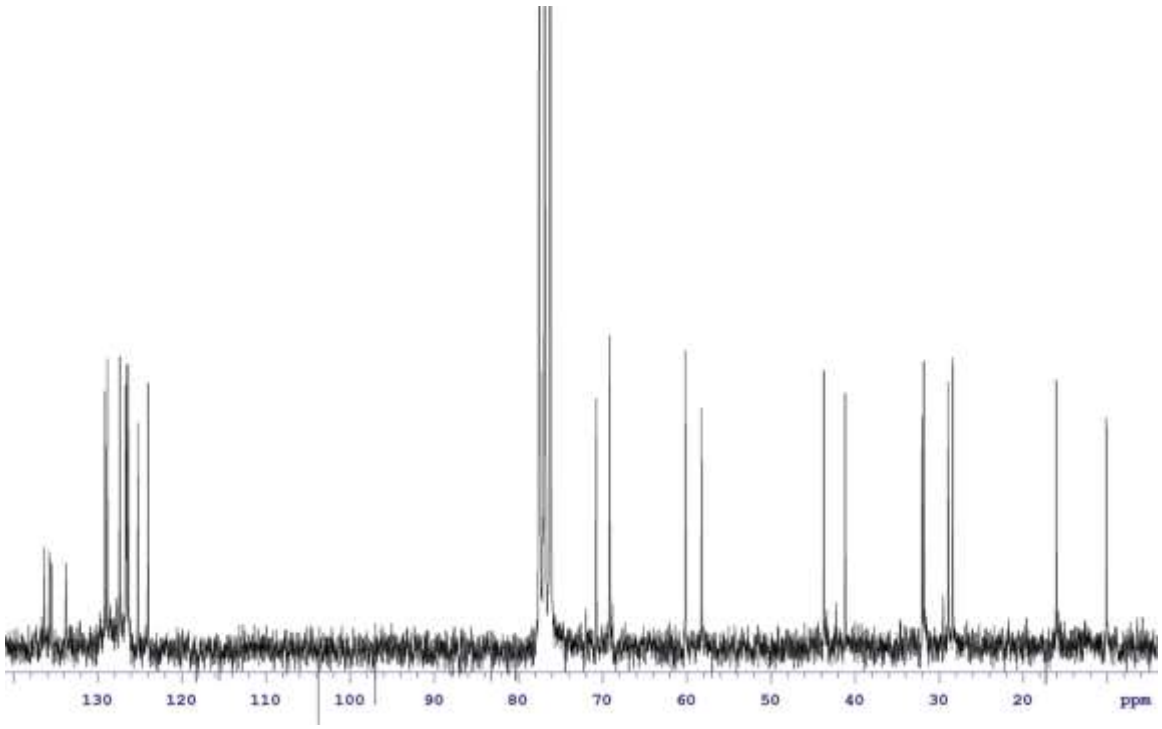


anti-**11a**



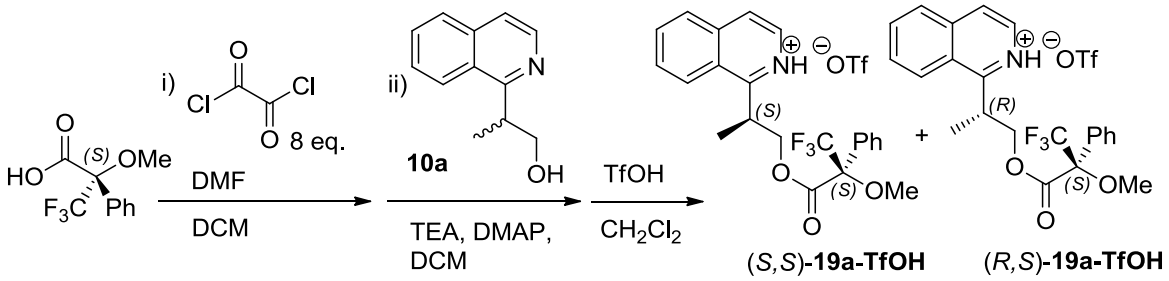


11a, *syn-anti* 1.2:1



Determination of the absolute configuration of 10a

To determinate the absolute configuration of the products **6, 7** and **8** the α-methoxy-α-trifluoromethylphenylacetyl (MPTA) esters of **10a** was prepared. As during the rearomatisation the stereogenic center on the C1 position of the tetrahydroisoquinoline is lost, the obtained result indicates that the remaining stereocenter has the same absolute configuration for both the obtained diastereoisomers. Furthermore, considering that **9a** was obtained with the same relative configuration of the major diastereoisomer starting either from **6a** or from **7a**, the configuration of the stereocenters of the compounds obtained using either Boc_2O or CbzCl is the same.



(**19a-TfOH**). In a Schlenk tube under nitrogen atmosphere equipped with a stirring bar, (*S*)-MPTA (0.2 mmol, 46.8 mg) and DMF (0.005 mmol, 0.3 μL) were dissolved in 400 μL of dichloromethane. Then oxalyl chloride (1.6 mmol, 137 μL) was added and the solution was stirred for 4 hours. Subsequently the solvent and the excess of oxalyl chloride were evaporated under reduced pressure. To the residue a solution of racemic alcohol **10a** (0.1 mmol, 18.7 mg), triethylamine (0.4 mmol, 56 μL) and 4-dimethylaminopyridine (0.02 mmol, 2.5 mg) in dichloromethane (500 μL) were added under nitrogen atmosphere. The mixture was stirred overnight, then a solution of satured $NaHCO_3$ (2 mL) and Et_2O (10 mL) were added and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified with preparative thin layer chromatography on silica (cyclohexane/AcOEt 8/2) to afford product **19a** as 1:1 mixture of the two diastereoisomers.

Mosher ester **19a** was dissolved in DCM (2 mL) and trifluoromethansulfonic acid (0.1 mmol, 9 μL) was added under stirring. After two hours the solvent and the excess of trifluoromethansulfonic acid were evaporated under reduced pressure to afford triflate salt **19a·TfOH** in quantitative yield.

The same procedure was used to obtain Mosher ester **19a·TfOH** as single diastereoisomer (quantitative yield) using active alcohol **10a** (ee 93%) as starting material. The ^{1}HNMR samples

were prepared dissolving **19a·TfOH** in solution of deuterated chloroform and deuterated acetonitrile in a 2.5/1.0 ratio.

The absolute configuration of chiral centers of primary alcohols with a branched methyl at C2 could be determinate by Modified Mosher's method.[S6]

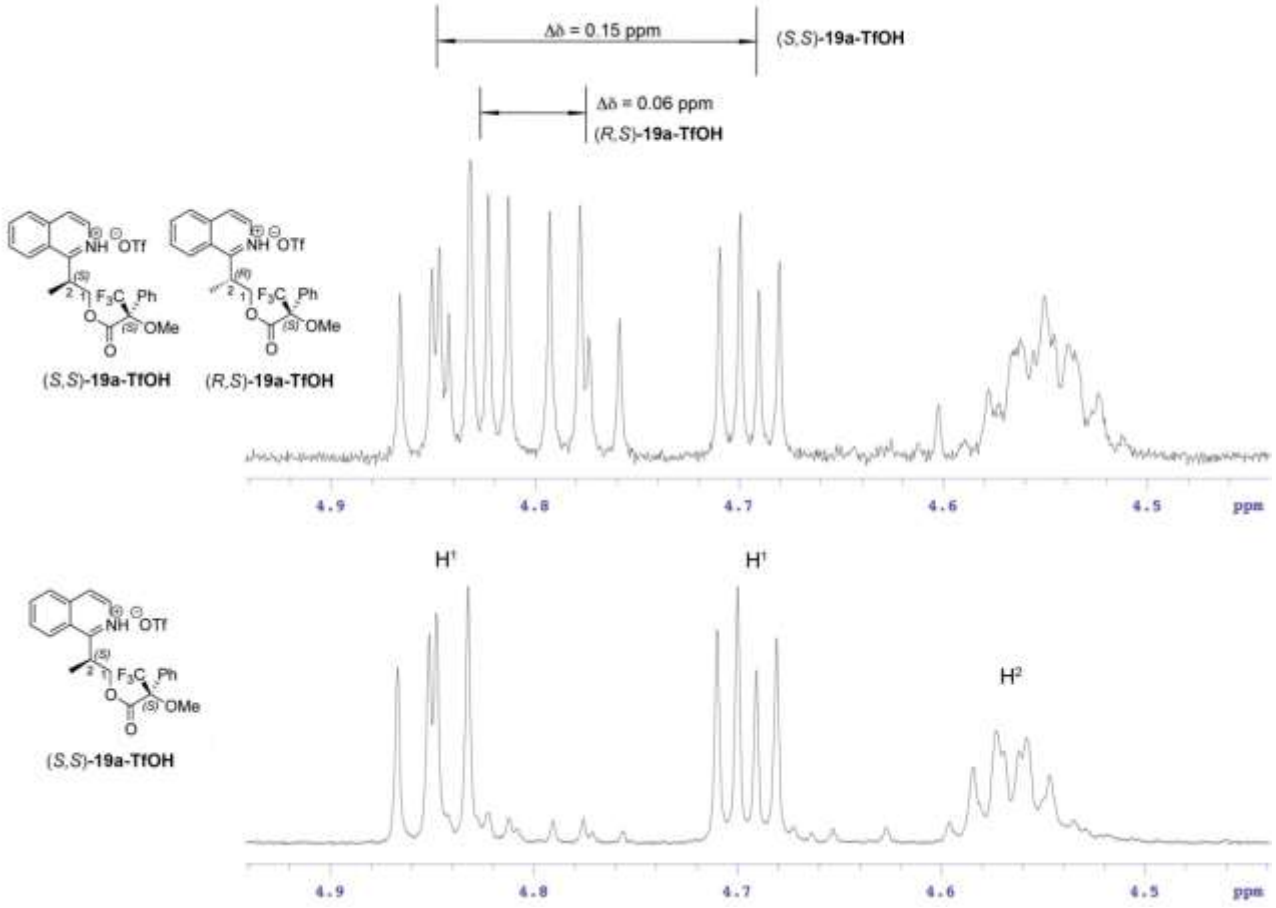
^{1}HNMR spectra of the mixture of (*S*,*S*)-**19a·TfOH** and (*R*,*S*)-**19a·TfOH** showed a clear separation between one of C1 methylene protons relative to the two diasteroisomer.

From the literature, in (*S*)-MPTA ester of a C2 branched primary alcohol the distance between the double doublet signals for the diastereomeric protons on C1 is larger if the absolute configuration of the C2 chiral center is *S*, while it is closer for the *R* stereoisomer. The reverse is also true for the (*R*)-MPTA ester. Considering this, it is possible to attribute the correct diastereoisomer to ^{1}H NMR signals: the double doublet signals for the diastereomeric protons of (*R*,*S*)-**19a·TfOH** were closer (0.06 ppm), while the same signal relative to (*S*,*S*)-**19a·TfOH** were more separated (0.15 ppm).

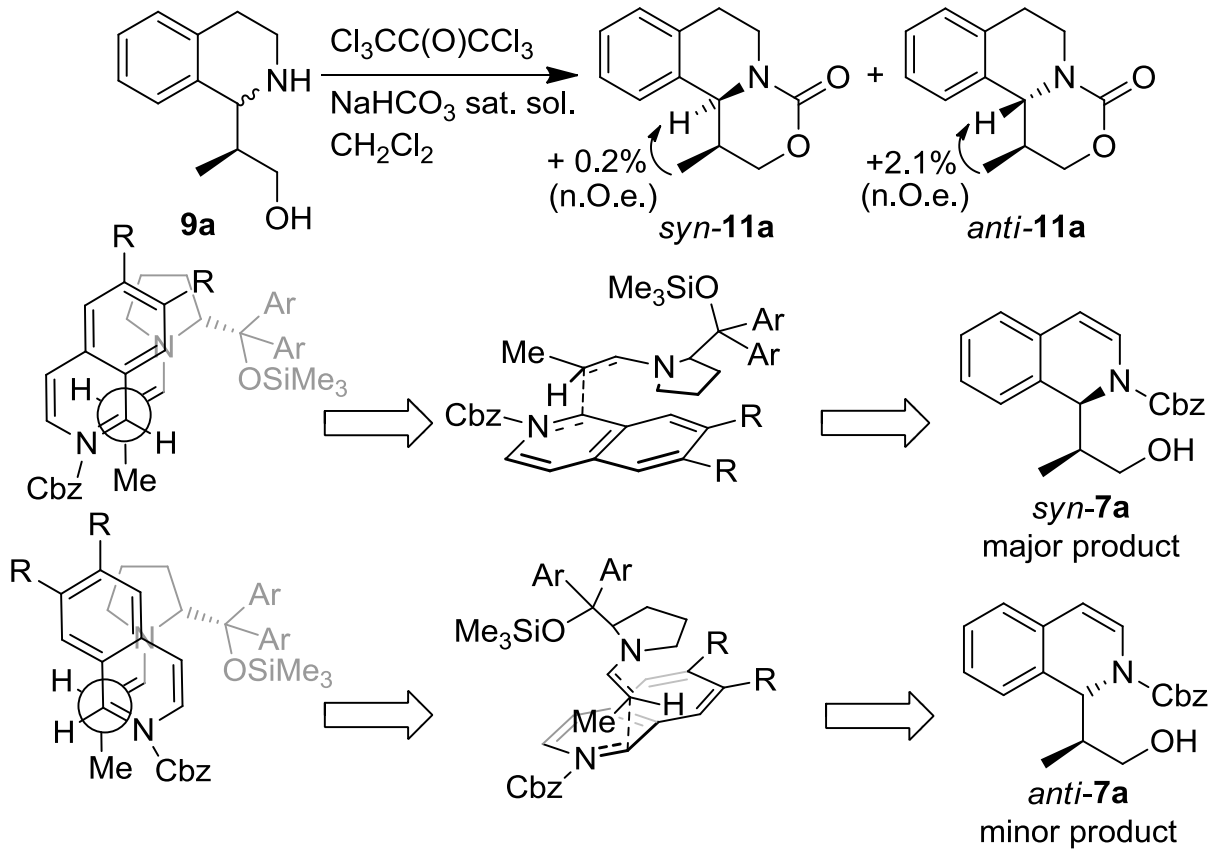
The same analysis was conducted to **19a·TfOH** prepared from enantioriched **7a** (see above) obtained from the organocatalytic alkylation of isoquinoline. Based on the ^{1}H NMR signals it is possible to attribute (*S*) absolute configuration of the stereocenter in the C2 position. In conclusion the absolute configuration of the *syn*-**7a** was assigned (2'*S*,1*S*) while for the *anti*-**7a** was (2'*S*,1*R*). The same absolute configuration were suggested for **6a-c**, **7a-h** and **8b-i**.

Note: free **19a** did not present an adequate splitting of the two diasteroisomeric protons for the assignment of the absolute configuration.

Figure S3. ^{1}H NMR (600 MHz, $CDCl_3/CD_3CN$ 2.5/1, 25°C) spectra of (*S*,*S*)+(*R*,*S*)-**19a·TfOH** above and (*S*,*S*)-**19a·TfOH** below.



Stereochemical proposal for the nucleophilic addition of Jørgensen enamine to isoquinolinium ions.

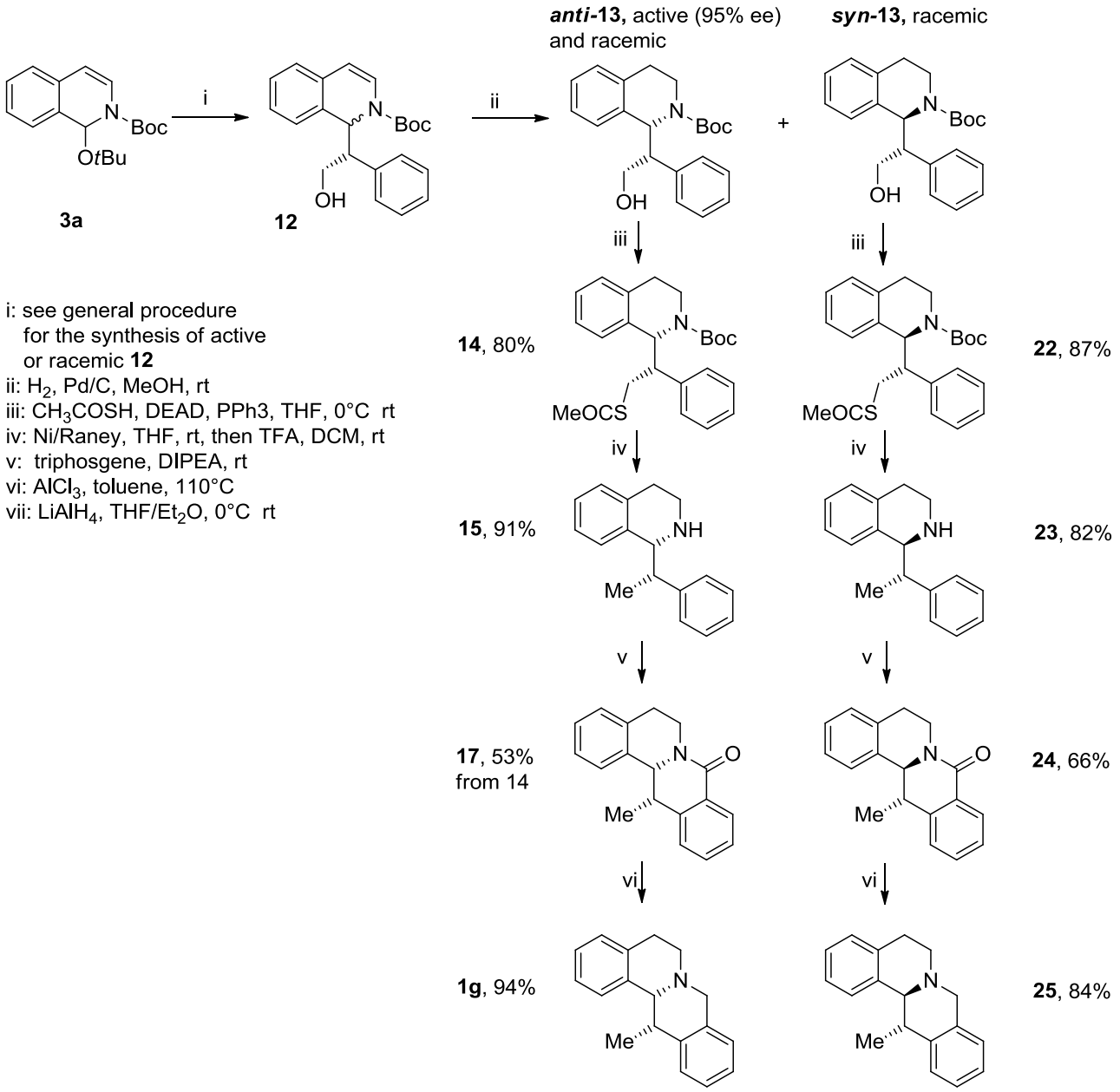


Synthesis of (+)-13-methyl tetrahydroprotoberberine 1g using Boc as activating group.

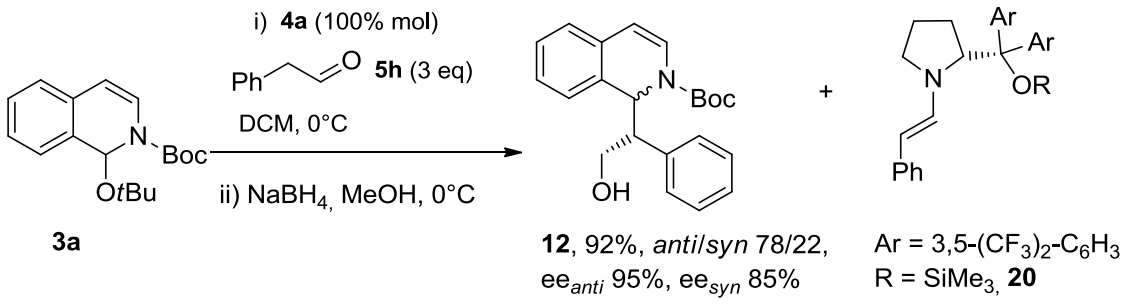
The alkylation reaction of adduct **3a** with phenylacetaldehyde **5h** afforded **12** as mixture of diastereoisomers. After reduction of the enamide double bond, *syn*-**13** and *anti*-**13** were separated. Starting from *anti*-**13**, 13-methyl tetrahydroprotoberberine **1g** was obtained, while *syn*-**13** lead to product **25** (diastereoisomer of **1g**).

Compound **1g** was synthesized in both active and racemic form, while **25** was synthesized in racemic form.

The relative configuration of the enamides **17** and **24** was determined by n.O.e analysis.



Synthesis of active 12.



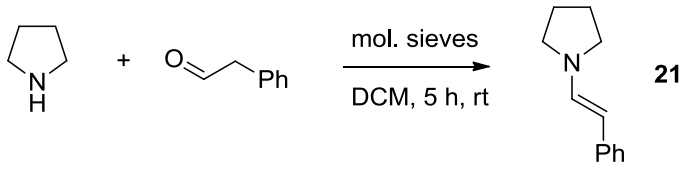
(12): To a 5 mL vial equipped with a magnetic stirring bar, CH_2Cl_2 (1 mL), phenylacetaldehyde **5h** (0.6 mmol, 68 μL) and **4a** (0.2 mmol, 120 mg) were added. After 5 h the reaction mixture was cooled at 0°C and **3a** (0.2 mmol, 60.6 mg) was added. 500 μL MeOH and $NaBH_4$ (1.2 mmol, 48 mg) were added after 16 hours. When reduction reaction was complete (monitored by TLC), the reaction was quenched with aqueous HCl 1M until pH = 1. The mixture was diluted with diethyl ether (3 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 3 mL). The collected organic layers were washed with brine, dried on $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 90/10) to afford **12** (64.7 mg, 92% yield, colourless oil) and enamine **20** as yellowish oil (112 mg, 0.16 mmol, 80% recovered catalyst).

(12): diastereomeric ratio 77/23 (*anti*-**12**:*syn*-**12**); *anti* diastereoisomer ee = 95%; *syn* diastereoisomer ee = 66%. The d.r. and e.e. were determined by HPLC analysis Daicel Chiralcel AD column: hexane/*i*-PrOH 95:5 for 20 min, then gradient elution from 95:5 to 85:5 in 10 min, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *anti* diastereoisomer τ_{major} = 29.93 min., τ_{minor} = 15.60 min.; *syn* diastereoisomer τ_{major} = 19.74 min., τ_{minor} = 24.17 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_{anti} (two rotamers A:B, 9:1 ratio) = 1.57 (s, 9H_A), 1.60 (s, 9H_B), 2.50-2.76 (bs, 1H), 2.98-3.04 (m, 1H), 3.76 (dd, J_1 = 12.2 Hz, J_2 = 2.9 Hz, 1H), 3.93 (dd, J_1 = 12.2 Hz, J_2 = 4.9 Hz, 1H), 5.44 (d, J = 9.8 Hz, 1H_B), 5.59 (d, J = 9.8 Hz, 1H_A), 5.94 (d, J = 7.7 Hz, 1H_A), 5.99 and 5.88 (d, J = 7.7 Hz, 1H_B), 6.27 (d, J = 7.7 Hz, 1H_A), 6.40 (d, J = 7.7 Hz, 1H_B), 6.77 (d, J = 7.7 Hz, 1H), 6.88-6.94 (m, 1H), 6.97-7.34 (m, 7H); δ_{syn}= 1.44 (s, 9H), 2.50-2.76 (bs, 1H), 3.05-3.15 (m, 1H), 3.73-3.76 (m, 1H), 3.88-3.96 (m, 1H), 5.44 (d, J = 7.7 Hz,1H), 5.78 (d, J = 5.6 Hz,1H), 6.52 (d, J = 7.7 Hz,1H), 6.74-6.77 (m,1H), 6.88-6.94 (m, 1H), 6.97-7.34 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ_{anti} (two rotamers A:B, 9:1 ratio) = 27.7 (3C_B), 28.2 (3C_A), 46.3 (1C_B), 49.8 (1C_A), 56.0 (1C_A), 56.5 (1C_B), 61.0 (1C_B), 63.0 (1C_A), 79.9 (1C_B), 82.5 (1C_A), 109.6 (1C_B), 109.9 (1C_A), 124.1 (1C_A), 124.2 (1C_A), 125.2 (1C_B), 125.7 (1C_B), 125.9 (1C_A), 126.2 (1C_B), 126.3 (1C_B), 126.5 (1C_B), 126.7 (1C_A), 127.3 (1C_A), 127.4 (1C_B), 127.5 (1C_A), 127.7 (1C_A), 127.9 (2C_A), 128.0 (2C_B), 128.41 (1C_B), 128.43 (1C_B), 129.5 (1C_A), 130.0 (1C_A), 130.6 (1C_A), 134.6 (1C_B), 134.7 (1C_B), 139.6 (1C_A), 142.3 (1C_B), 153.0 (1C_B), 153.3 (1C_A); δ_{syn} = 28.1 (3C), 54.4, 55.2, 61.8, 81.9, 108.6, 124.4, 125.8, 126.6, 126.8, 126.9, 127.6, 128.3, 128.5, 129.1 (2C), 131.0, 131.2, 137.8, 157.1; ESI-MS: *m/z* = 374.0 $[M+Na]^+$, 390.2 $[M+K]^+$.

(20): ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = -0.14 (s, 9H), 0.33-0.47 (m, 1H), 1.50-1.62 (m, 1H), 1.76-1.86 (m, 1H), 2.11-2.23 (m, 1H), 2.52 (td, J_1 = 9.1 Hz, J_2 = 2.8 Hz, 1H), 2.94 (q, J = 10.5 Hz,

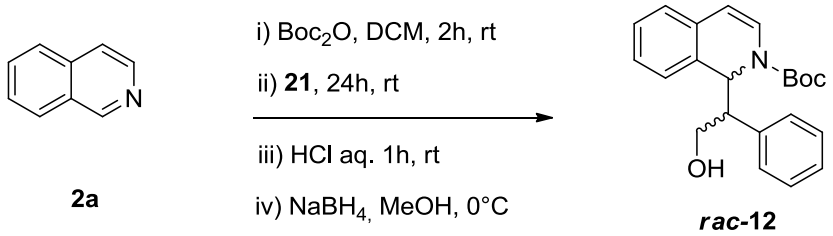
1H), 4.63 (dd, J_1 = 9.1 Hz, J_2 = 1.5 Hz, 1H), 5.12 (d, J = 13.9 Hz, 1H), 6.97-7.25 (m, 4H), 7.74-8.03 (m, 8H).

Preparation of enamine 21.



In a two necked round bottomed flask, molecular sieves 4 Å (1g) were heated under vacuum for 10 minutes. Then the flask was cooled at room temperature and filled with nitrogen. DCM (5 mL), phenylacetaldehyde (10 mmol, 1.11 mL), pyrrolidine (10 mmol, 830 μL) and *p*-toluenesulfonic acid monohydrate (0.1 mmol, 19 mg) were added. After 1 hour the yellow and sluggish solution became clear. After 5 hours the solution was filtered through Celite pad under nitrogen atmosphere and concentrated to give enamine **21** as a yellow oil in quantitative yield. It was used without further purification in the next steps and it can be stored under nitrogen atmosphere for several weeks without any appreciable hydrolysis. Spectroscopic data was according to the literature[S7].

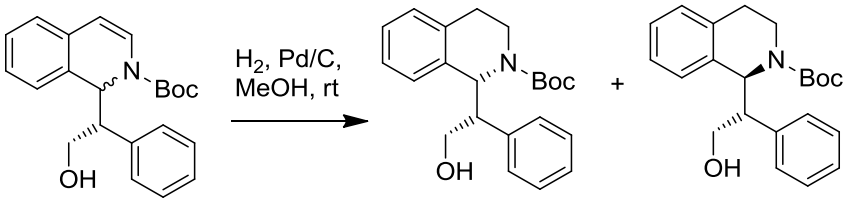
Synthesis of racemic 12



2a ***rac*-12**

To a solution of isoquinoline **2a** (8.67 mmol 1.02 mL) in DCM (5 mL), Boc_2O (8.67 mmol, 2.0 mL) was added. The resulting solution was stirred for 2 hours at room temperature, then enamine **21** (8.67 mmol, 1.5 g) was added. After 24 hours the reaction was quenched with HCl 1M (10 mL) and the mixture was vigorously stirred for 1 hour. The organic phase was separated and the aqueous layer was extracted with DCM (2 x 8 mL). The collected organic layers were dried over Na_2SO_4. The residue was diluted with MeOH (3 mL) and cooled to 0°C, then $NaBH_4$ (13 mmol, 494 mg) was added. After 2 hours complete conversion was observed by TLC analysis and the reaction was quenched by careful addition of HCl 1M until pH = 1. The organic layer was separated and the aqueous layer was extracted with DCM (2 x 10 mL). The collected organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 90/10) to afford racemic **12** (974 mg, 2.77 mmol, 32% yield, diastereomeric ratio *anti-syn* 75:25) as colourless oil.

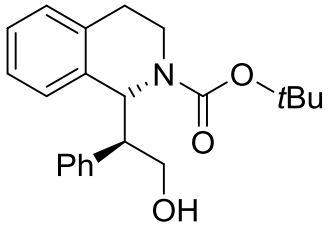
Preparation of compounds 13



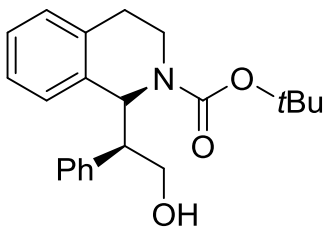
12, 92%, *anti*/*syn* 78/22, ee_{anti} 95%, ee_{syn} 85% ***anti*-13**, 54% ***syn*-13**, 23%

In a 25 mL two necked round bottomed flask, **12** (0.57 mmol, 200 mg), MeOH (5 mL) and 10% Pd/C (50%, 100 mg) were sequentially added and kept under H_2 (1 atm). The reaction mixture was stirred for 16 hours, then it was filtered through Celite pad and was washed with DCM (15 mL). The solvent was removed under reduced pressure to afford a mixture of ***syn*-13** (R_f = 0.4, 8:2 cyclohexane:ethyl acetate) and ***anti*-13** (R_f = 0.2). The two diasteroisomers were separated by column chromatography (cyclohexane/ethyl acetate 85/15).

The same procedure was followed to obtain racemic ***anti*-13** and ***syn*-13**.



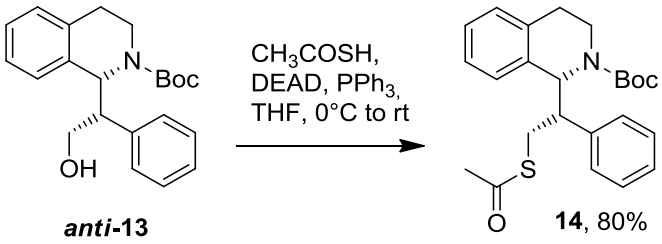
(*anti*-13): sticky white solid, 109 mg, 54% yield; $[\alpha]_D^{20}$ = -37.3 (c=1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 8:1 ratio): δ_{anti} = 1.53 (s, 9H), 2.50-2.61 (m, $2H_B$), 2.79-2.90 (m, $2H_A$), 2.90-2.97 (m, 1H), 3.21-3.30 (m, $1H_B$), 3.40-3.49 (m, $1H_B$), 3.61-3.69 (m, $2H_A$), 3.82 (dd, J_1 = 11.9 Hz, J_2 = 3.0 Hz, 1H), 3.86-3.98 (bs, 1H), 4.07 (dd, J_1 = 11.9 Hz, J_2 = 4.5 Hz, 1H), 5.29 (d, J = 6.2 Hz, $1H_B$), 5.43 (d, J = 10.2 Hz, $1H_A$), 6.31 (d, J = 7.9 Hz, $1H_A$), 6.37 (d, J = 5.7 Hz, $1H_B$), 6.76-6.82 (m, $1H_A$), 6.84-6.92 (m, $1H_B$), 7.02-7.13 (m, 2H), 7.15-7.23 (bs, 4H), 7.25-7.30 (bs 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 8:1 ratio): δ_{anti} = 27.9, 28.4 (3C), 39.6 ($1C_B$), 41.3 ($1C_A$), 53.5 ($1C_A$), 54.2 ($1C_B$), 56.8 ($1C_A$), 58.0 ($1C_B$), 63.8, 80.6, 125.3, 126.8 (2C), 127.6, 128.1 (2C), 128.3, 129.5 (2C), 134.4 ($1C_A$), 134.9 ($1C_B$), 135.4 ($1C_B$), 136.0 ($1C_A$), 139.8 ($1C_B$), 140.6 ($1C_A$), 155.2 ($1C_B$), 156.7 ($1C_A$); ESI-MS: *m/z* = 376.2 $[M+Na]^+$, 392.2 $[M+K]^+$, 729.4 $[2M+Na]^+$.



(*syn*-13) colourless oil, 47 mg, 23% yield; $[\alpha]_D^{20}$ = +4.7 (c=0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ (two rotamers A:B, 9:1 ratio) = 1.50 (s, 9H), 1.85 (dt, J_1 = 16.1 Hz, J_2 = 5.6 Hz, 1H), 2.40-2.50 (m, $1H_A$), 2.51-2.58 (m, $1H_B$), 2.64-2.72 (m, $1H_A$), 2.73-2.84 (m, $1H_B$), 3.34-3.40 (m, 1H), 3.59 (dt, J_1 = 13.1 Hz, J_2 = 5.7 Hz, 1H), 3.81 (dd, J_1 = 11.9 Hz, J_2 = 4.9 Hz, $1H_A$), 3.86-4.05 (m, $2H_B$), 4.10 (t, J = 11.4 Hz, $1H_A$), 4.43-4.63 (bs, 1H), 5.41 (d, J = 4.2 Hz, $1H_B$), 5.65 (d, J = 3.4 Hz, $1H_A$), 6.84 (d, J = 6.8 Hz, 2H), 6.94 (d, J = 7.8 Hz,

1H), 7.09-7.19 (m, 4H), 7.20-7.36 (m, 1H), 7.42 (d, J = 7.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 4:1 ratio): δ_{syn} = 27.8, 28.3 ($3C_A$), 28.5 ($3C_B$), 40.9, 45.8, 54.5, 62.4, 79.5 ($1C_B$), 80.5 ($1C_A$), 126.2, 126.5, 126.9, 127.3, 128.0 (2C), 128.3, 128.9 (2C), 135.3, 136.1, 138.5, 154.8 ($1C_B$), 157.3 ($1C_A$); ESI-MS: m/z = 376.2 $[M+Na]^+$, 392.2 $[M+K]^+$, 729.4 $[2M+Na]^+$.

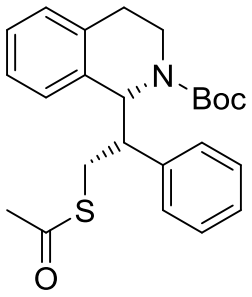
General procedure for the Mitsunobu reaction.



***anti*-13** **14**, 80%

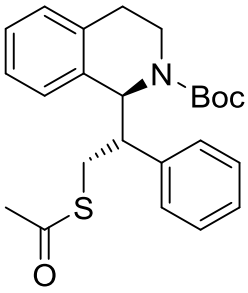
(14). In a 10 mL round bottomed flask under nitrogen atmosphere, triphenyl phosphine (1.21 mmol, 317 mg) was dissolved in 1 mL THF at 0°C. Then diethyl diazodicarboxylate (DEAD) (40% solution in toluene, 1.24 mmol, 568 μL) was slowly added and the solution stirred for 30 min. while its color turned from yellow to orange. A solution of thioacetic acid (1.24 mmol, 90 μL) and ***anti*-13** (0.31 mmol, 109 mg) in 1 mL THF, was rapidly added to the reaction mixture, whose color changed rapidly to dark brown and then to yellow. After 30 min the reaction mixture was allowed to warm to room temperature and stirred for 15 hours. The solvent was evacuated under vacuum, the solid residue dissolved in DCM (3 mL) and revacuated under vacuum for three times to eliminate any trace of thioacetic acid. The crude mixture was purified by column chromatography (cyclohexane/diethyl ether from 95/5 to 90/10) to afford the desired product.

The same procedure was followed to obtain racemic **14.**



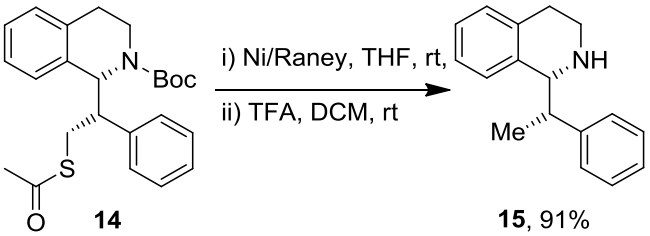
(14): pinkish oil, 80% yield (102.5 mg), $[\alpha]_D^{20}$ = + 42.2 (c=1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ (two rotamers A:B, 1.4:1 ratio) = 1.53 (s, $9H_A$), 1.57 (s, $9H_B$), 2.24 (s, $3H_B$), 2.25 (s, $3H_A$), 2.44-2.56 (m, $2H_B$), 2.68-2.85 (m, $2H_A$), 3.00-3.09 (m, $2H_B$), 3.12-3.24 (m, $2H_A$), 3.49-3.88 (m, 3H), 5.22 (d, J = 9.7 Hz, $1H_B$), 5.35 (d, J = 9.7 Hz, $1H_A$), 6.19 (d, J = 7.9 Hz, $1H_B$),6.30 (d, J = 7.9 Hz, $1H_A$), 6.78-6.96 (m, 2H), 6.98-7.05 (bs, 1H), 7.06-7.18 (m, 2H), 7.21-7.28 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ (two rotamers A:B, 1.4:1 ratio) = 27.5 ($1C_B$), 27.8 ($1C_A$), 28.4 ($3C_A$), 28.5 ($3C_B$), 30.4 ($1C_B$), 30.5 ($1C_A$), 32.2 ($1C_B$), 32.3 ($1C_A$), 39.7 ($1C_B$), 40.8 ($1C_A$), 51.5 ($1C_B$), 52.0 ($1C_A$), 59.6 ($1C_A$), 60.3 ($1C_B$), 79.9 ($1C_A$), 80.3 ($1C_B$), 125.1 ($1C_B$), 125.2 ($1C_A$), 126.9 ($1C_A$), 127.0 ($1C_B$), 127.1 ($1C_A$), 127.3 ($1C_B$), 127.7 ($1C_B$), 127.8 ($1C_A$), 127.9 ($1C_A$), 128.2 ($2C_A$ + $1C_B$), 128.3 ($2C_B$), 128.4 ($1C_B$), 128.9 ($1C_A$), 129.0 ($1C_B$),

129.1 ($1C_A$), 134.7 ($1C_A$), 135.0 ($1C_B$), 135.1 ($1C_B$), 135.7 ($1C_A$), 140.5 ($1C_B$), 140.9 ($1C_A$), 154.9 ($1C_B$), 155.9 ($1C_A$), 195.4 ($1C_B$), 196.0 ($1C_A$); ESI-MS: *m/z* = 434.2 $[M+Na]^+$, 845.2 $[2M+Na]^+$.



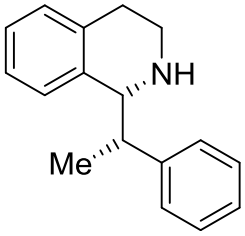
(rac-22): Obtained carrying out the Mitsunobu reaction on **rac-*syn*-13** following the procedure described for **14.** Pinkish oil, 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ (two rotamers A:B, 1.1:1 ratio) = 1.37 (s, $9H_A$), 1.42 rotamer) (s, $9H_B$), 2.25 (s, 3H), 2.51-2.58 (m, 1H), 2.59-2.88 (m, 2H), 3.28-3.42 (m, 2H), 3.43-3.60 (m, $2H_A$), 3.78-3.89 (m, $2H_B$), 5.33 (bs, $1H_A$), 5.50 (bs, $1H_B$), 6.98-7.13 (m, 3H), 7.17-7.30 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C): δ (two rotamers, 1.1:1 ratio) = 27.6 ($1C_B$), 27.9 ($1C_A$), 28.3 (3C), 30.5, 32.4, 38.6 ($1C_A$), 40. ($1C_B$), 51.4 ($1C_A$), 51.9 ($1C_B$), 58.0 ($1C_A$), 59.3 ($1C_B$), 79.5 ($1C_B$), 80.3 ($1C_A$), 125.9, 127.0, 127.7, 127.9, 128.2, 128.6 (3C), 129.0, 134.9 ($1C_B$), 135.2 ($1C_A$), 136.1 ($1C_B$), 135.7 ($1C_A$), 139.2 ($1C_A$), 139.5 ($1C_B$), 154.9 ($1C_A$), 155.4 ($1C_B$), 195.9. ESI-MS: *m/z* = 434.2 $[M+Na]^+$, 845.2 $[2M+Na]^+$.

Preparation of compound 15

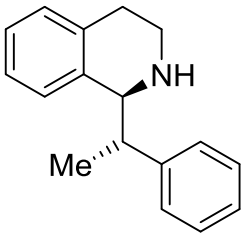


In a round bottomed flask, to a solution of **14** (0.25 mmol, 102.5 mg) in THF (4 mL), Ni/Raney (1.5 g, slurry in water) was added. The reaction mixture was stirred for 16 hours at room temperature until TLC analysis revealed complete conversion. The solution was separated and Nickel/Raney washed 4 times with DCM (5 mL). The collected organic phases were filtered through a Celite pad and concentrated under vacuum. The resulting oil was dissolved in DCM (750 μL) and trifluoroacetic acid (2.5 mL) was added. The solution was stirred at room temperature for 4 hours until complete conversion (monitored with TLC). The solvent was evaporated under reduce pressure and the residue was dissolved in DCM (10 mL) and washed with $NaHCO_3$ sat. sln. until basic pH. The organic layer was separated and the aqueous layer was extracted with DCM (3 x 10 mL). The collected organic layers were dried over Na_2SO_4 and concentrated under vacuum to give pure 14 (49.8 mg, 91% yield). This compound is air sensitive, but it can be stored as its hydrochloride salt at -20°C for several weeks without any appreciable decomposition.

The same procedure was followed to obtain racemic **15.**

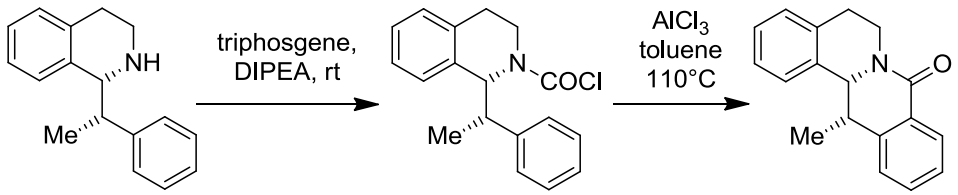


(15): Colourless oil, 49.8 mg, 91% yield, $[\alpha]_D^{20}$ = +31.4 (=1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.18 (d, J = 7.2 Hz, 3H), 1.72-1.80 (bs, 1H), 2.61-2.68 (m, 1H), 2.81 (dt, J_1 = 10.9 Hz, J_2 = 2.7 Hz, 1H), 2.90-3.00 (m, 1H), 3.13-3.20 (m, 1H), 3.50-3.58 (m, 1H), 4.25 (d, J = 3.4 Hz, 1H), 7.08-7.29 (m, 5H), 7.33-7.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 12.7, 30.6, 42.7, 43.7, 61.8, 125.9, 126.1 (2C), 126.6, 128.4 (2C), 128.7 (2C), 129.4, 136.7, 138.0, 144.7; ESI-MS: *m/z* = 238.3 $[M+H]^+$.



(rac-23): Obtained from **22** following the procedure described for **15.** Colorless oil, 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.45 (d, J = 6.7 Hz, 3H), 2.57-2.66 (m, 1H), 2.71-2.81 (m, 1H), 2.82-2.90 (m, 1H), 3.17-3.31 (m, 2H), 3.40 (dq, J_1 = J_2 = 6.7 Hz, 1H), 4.24 (d, J = 6.7 Hz, 1H), 7.06-7.09 (m, 1H), 7.16-7.26 (m, 6H), 7.27-7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 19.3, 29.2, 39.9, 44.0, 61.0, 125.1, 126.2, 126.4, 127.9 (2C), 127.9, 128.3 (2C), 129.1, 135.5, 137.0, 143.2; ESI-MS: *m/z* = 238.3 $[M+H]^+$.

Preparation of compound 17.



15 **16** **17**, 53% from **15**

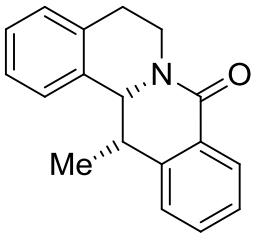
To a solution of **15** (0.20 mmol, 49.8 mg) in DCM (1 mL) under nitrogen atmosphere, triphosgene (0.11 mmol, 33 mg) and DIPEA (0.44 mmol, 76 µL) were subsequently added at room temperature. The reaction mixture was stirred for 16 hours until complete conversion was observed by TLC analysis. The solution was diluted with MeOH (500 µL) and $NaHCO_3$ sat. sln. (3 mL) was added after 10 min.. The organic phase was separated, and the aqueous layer was extracted with DCM (2 x 5 mL). The collected organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum.

The obtained crude product (**16**) was dissolved in toluene (1 mL) in a sealed tube under nitrogen atmosphere and aluminium trichloride (0.36 mmol, 48 mg) was added. The reaction mixture was refluxed for 6 hours (until complete conversion was observed by TLC), was cooled at 0°C and quenched with ice. DCM (3 mL) was added, the organic phase was separated and the aqueous layer

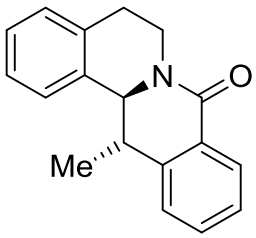
was extracted with DCM (4 x 3 mL). The collected organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum.

The crude mixture was purified by column chromatography (cyclohexane/ethyl acetate from 90/10 to 70/30) to give pure **17** (53% yield, 28 mg).

The same procedure was followed to obtain racemic **17.**

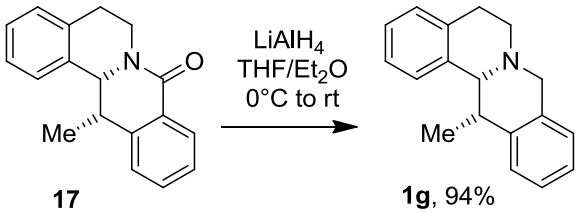


(17): Yellow sticky solid; $[\alpha]_D^{20}$ = +491 (c=1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 0.83 (d, J = 7.0 Hz, 3H), 2.78-2.89 (m, 1H), 2.90-3.03 (m, 2H), 3.21-3.29 (m, 1H), 4.98-5.03 (m, 1H), 5.13 (d, J = 3.4 Hz, 1H), 7.20-7.33 (m, 5H), 7.38 (dt, J_1 = 7.8 Hz, J_2 = 1.3 Hz, 1H), 7.48 (dt, J_1 = 7.3 Hz, J_2 = 1.6 Hz, 1H), 8.16 (dd, J_1 = 7.8 Hz, J_2 = 1.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C): δ_{anti} = 14.7, 29.2, 38.1, 40.8, 58.6, 125.9, 126.3, 126.6, 126.8, 127.1, 127.9, 128.6, 128.8, 131.9, 134.5, 136.2, 144.1, 164.3; ESI-MS: *m/z* = 264.2 $[M+H]^+$, 286.2 $[M+Na]^+$, 549.2 $[2M+Na]^+$.



(rac-24): Obtained from **23** following the procedure described for **17.** Yellow sticky solid, 66% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.44 (d, J = 7.2 Hz, 3H), 2.81-2.91 (m, 1H), 3.10-3.20 (m, 2H), 3.39 (p, J = 6.9 Hz, 1H), 4.63 (d, J = 6.4 Hz, 1H), 4.88-4.98 (m, 1H), 7.14-7.23 (m, 4H), 7.34 (t, J = 7.5 Hz, 2H), 7.47 (dt, J_1 = 7.5 Hz, J_2 = 1.6 Hz, 1H), 8.09 (dd, J_1 = 8.4 Hz, J_2 = 1.7 Hz, 1H); ^{3}C NMR (50 MHz, $CDCl_3$, 25°C): δ = 19.2, 29.3, 36.3, 41.9, 62.2, 125.7, 125.8, 126.3, 127.0, 127.3, 128.3, 128.5, 129.1, 132.1, 135.3, 136.8, 142.3, 164.4; ESI-MS: *m/z* = 264.2 $[M+H]^+$, 286.2 $[M+Na]^+$, 549.2 $[2M+Na]^+$.

Preparation of compound 1g



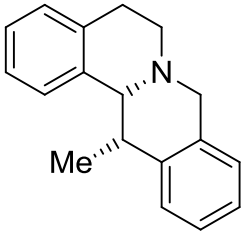
17 **1g**, 94%

In a 10 mL round bottomed flask under nitrogen atmosphere, diethyl ether (600 µL) and $LiAlH_4$ (1 M in THF, 0.11 mmol, 110 µL) were added at 0°C. A solution of **17** (0.07 mmol, 18.8 mg) in THF (750 µL), was added dropwise, and the reaction mixture was allowed to warm to room temperature. After two hours complete conversion was observed by TLC analysis. The reaction mixture was

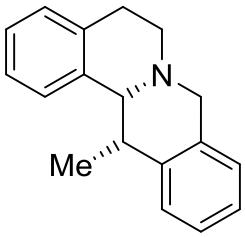
cooled to 0°C and quenched following Fieser Method. The mixture was filtered through a Celite pad and was washed with DCM (15 mL). The collected organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by column chromatography on silica gel (cyclohexane/ethyl acetate from 100/0 to 90/10) to give pure **1g** (94% yield, 16.4 mg). Such compound is air sensitive, but it can be stored as its hydrochloride salt at -20°C without any appreciable decomposition.

The same procedure was followed to obtain racemic **1g.**

The spectroscopic data for **1g** and **25** are according with literature,[S8] confirming the relative configuration assigned for such compounds.



(1g): Colourless oil, $[\alpha]_D^{20}$ = +266 (c=1.0, $CHCl_3$); 95% e.e. determined by HPLC analysis Daicel Chiralcel OD-H column: hexane, flow rate 0.70 mL/min, 40°C, λ = 210 nm: τ_{major} = 21.51 min., τ_{minor} = 15.75 min.; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.00 (d, J = 6.8 Hz, 3H), 2.59-2.74 (m, 2H), 3.14-3.25 (m, 2H), 3.34-3.42 (m, 1H), 3.72 (d, J = 14.7 Hz, 1H), 3.87 (bs, 1H), 4.07 (d, J = 14.7 Hz, 1H), 7.07-7.29 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$, 25°C): δ = 18.3, 29.7, 38.8, 51.1, 58.9, 63.5, 125.7 (2C), 125.8, 126.0, 126.1, 126.2, 128.6, 128.9, 134.1, 136.0, 136.7, 141.5; ESI-MS: m/z = 250.2 $[M+H]^+$; HMRS calcd for $C_{18}H_{19}N$: 249.15175; found 249.15166.



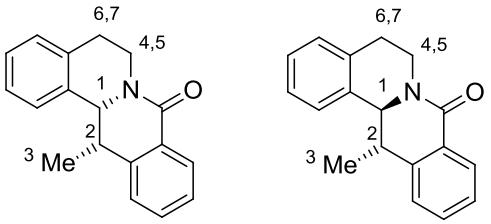
(rac-25). Obtained from **24** following the procedure described for **1g.** The title compound was isolated by column chromatography on silica gel (cyclohexane/ethyl acetate 70/30). Colourless oil, 84% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.53 (d, J = 6.9 Hz, 3H), 2.82-2.91 (m, 1H), 2.96-3.08 (m, 2H), 3.09-3.20 (m, 2H), 3.79 (d, J = 7.4 Hz, 1H), 3.85 (d, J = 15.8 Hz, 1H), 4.23 (d, J = 15.8 Hz, 1H), 7.08 (d, J = 7.3 Hz, 1H), 7.13-7.31 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 22.2, 28.2, 35.0, 46.8, 56.5, 64.8, 125.2, 125.8, 126.5, 126.7, 126.8, 127.0, 127.7, 129.2, 132.8, 133.7, 138.0, 139.3; ESI-MS: m/z = 250.2 $[M+H]^+$.

Organocatalytic alkylation performed with recovered Jørgensen enamine 20

In a 5 mL vial, chiral enamine **20** (0.1 mmol, 70 mg) and phenylacetaldehyde **5h** (0.2 mmol, 22 μL) were dissolved in DCM (500 μL) at 0°C. After 10 minutes, **3a** (0.1 mmol, 30 mg) was added and the solution was stirred for 16 hours at 0°C. Then MeOH (250 μL) and $NaBH_4$ (0.6 mmol, 23 mg) were added and the reaction was stirred until TLC analysis showed complete conversion. The

reaction was quenched with aqueous HCl 1M until pH = 1. The mixture was diluted with diethyl ether (3 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 3 mL). The collected organic layers were washed with brine, dried on $MgSO_4$ and concentrated under reduced pressure. The title compound was purified by column chromatography on silica gel (90:10 cyclohexane/ethyl acetate) to afford product **12** (Rf = 0.4, 8:2 cyclohexane/ethyl acetate, 0.099 mmol, 34.7 mg, 99% yield) and enamine **20** (R_f = 0.7 eluting mixture 8:2 cyclohexane/ethyl acetate, 53 mg, 0.076 mmol, 76% recovered catalyst).

Determination of the relative configurations of amides 17 and 24



17 **24**

The ^{1}HNMR signals of **17** and **24** were assigned by g-COSY experiments of such compounds (Figure S4 and S6).

The relative configuration was established by comparison of the 1DNOESY NMR experiments carried on these two compounds.

Selective excitation of the Me^3 signal of **17**, showed a positive n.O.e on the proton H^1 that could be estimated 0.26 considering 100 the intensity of the irradiated signal (Figure S5).

Instead, when the same experiment was conducted on **24**, the positive n.O.e observed was respectively 1.14 (Figure S7).

On the basis of such results the relative configuration of **17** (referred to the protons H^1 and H^2) was assigned *syn*, while the relative configuration of **24** was assigned *anti*.

Figure S4: g-COSY spectra of **17.**

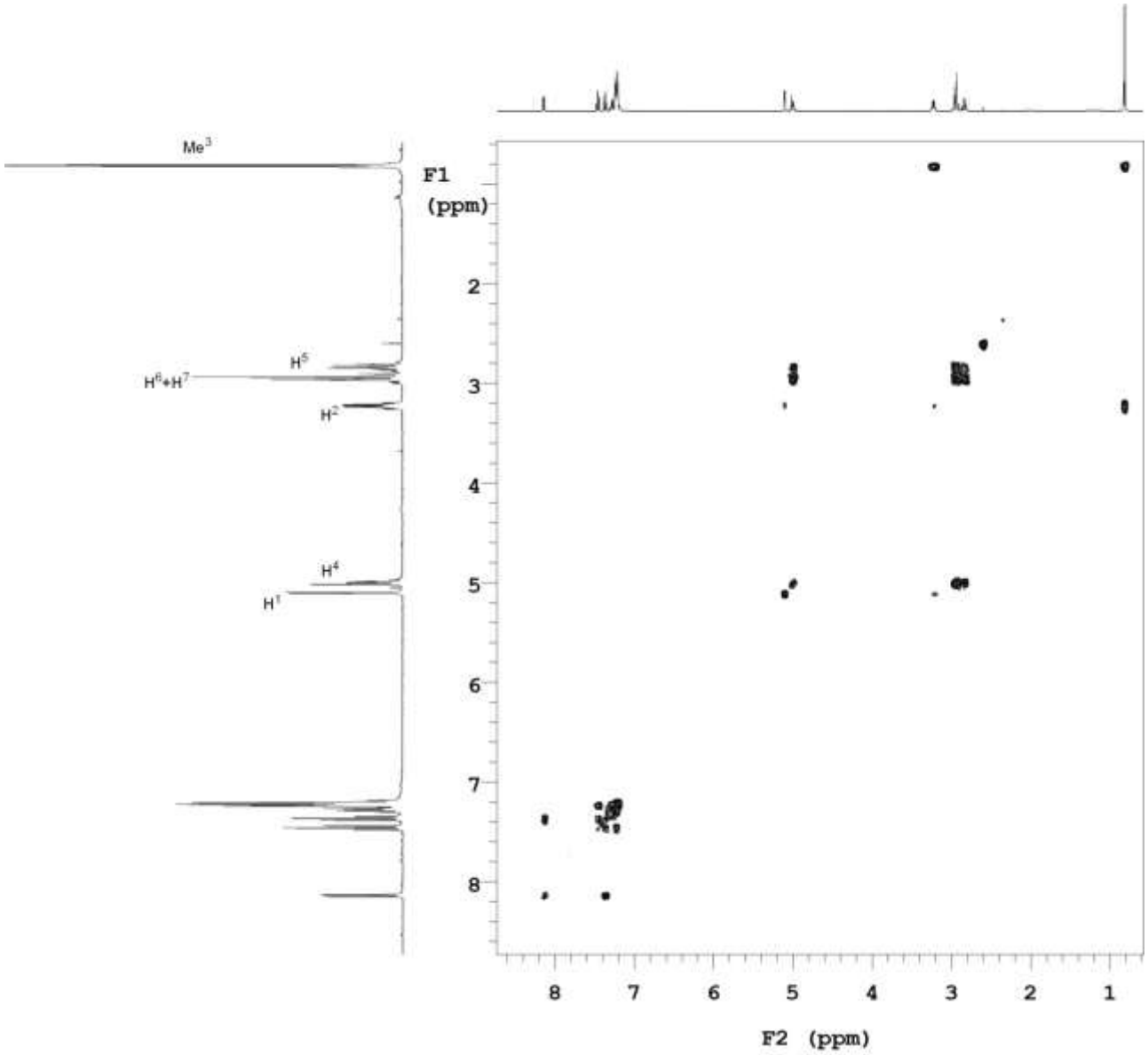


Figure S5. selective n.O.e excitation of Me^3 of **17.**

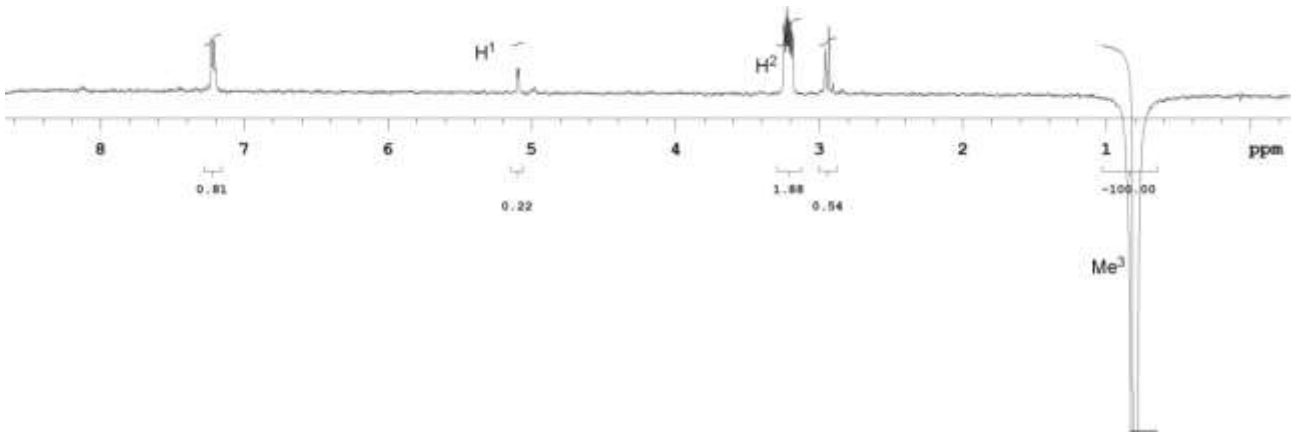


Figure S6: g-COSY spectra of **24.**

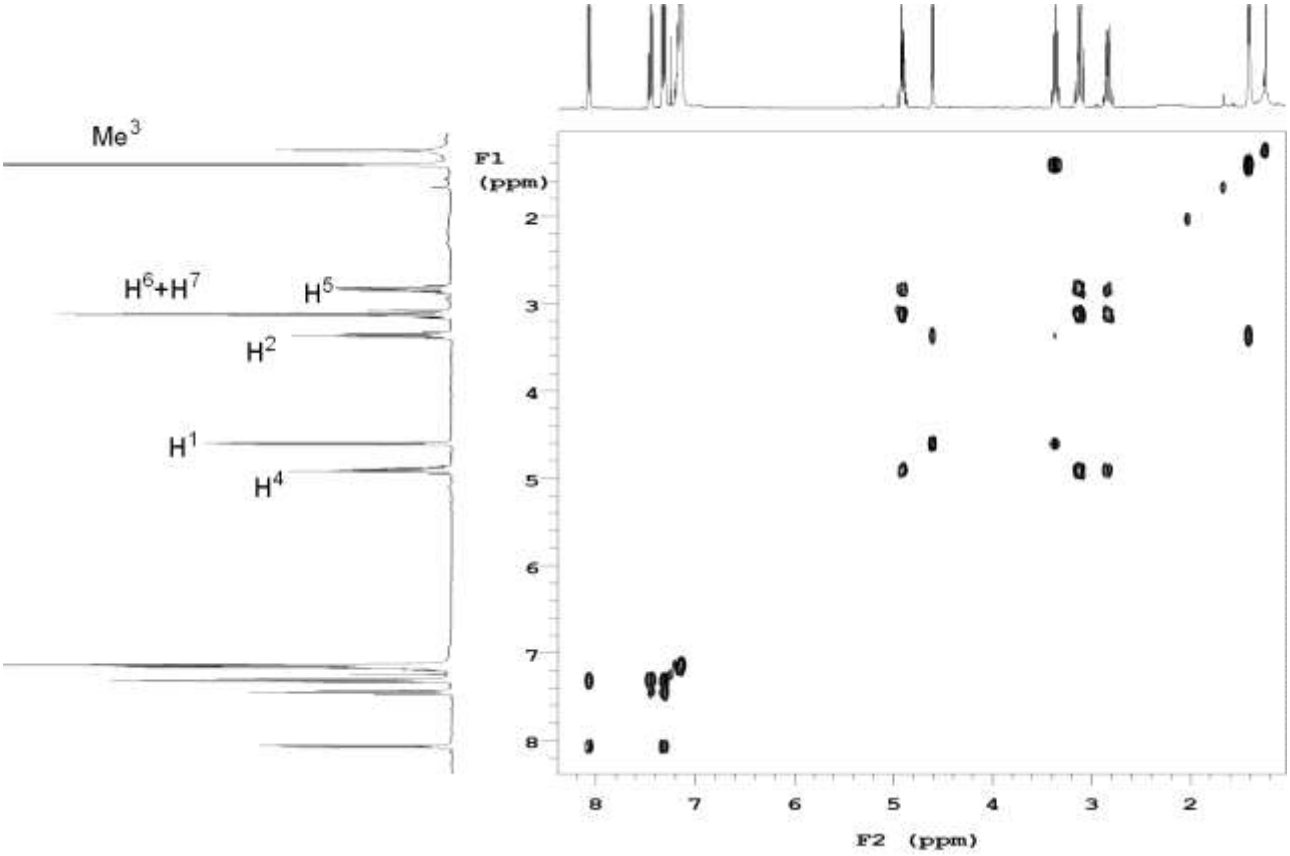
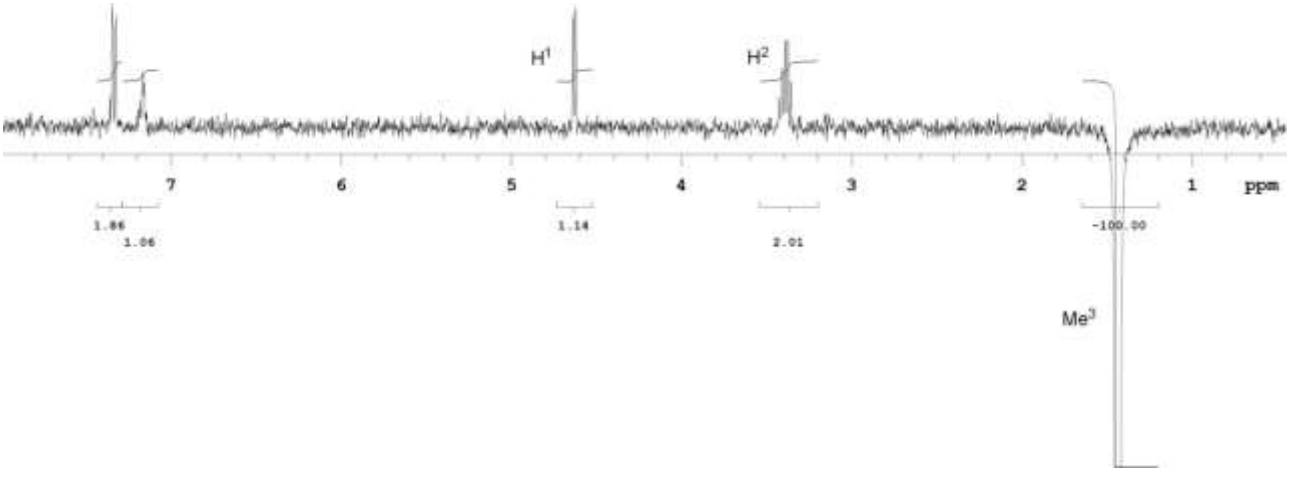
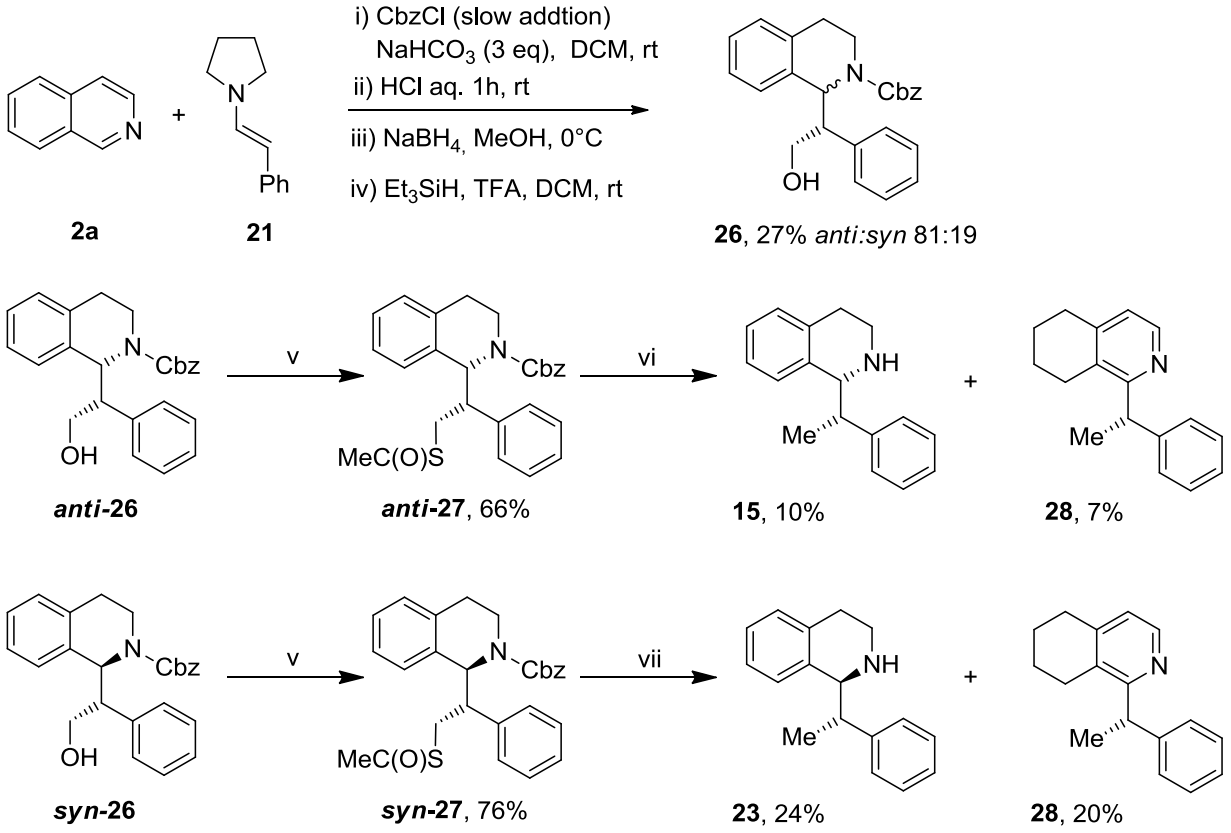


Figure S7. selective n.O.e excitation of Me^3 of **24.**



Attempted synthesis of (+)-13-methyl tetrahydroprotoberberine 1g with Cbz as activating group

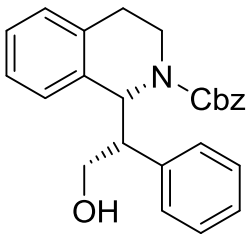


v: CH_3COSH, DEAD, PPh3, THF, 0°C to rt
vi: Ni/Raney, THF, rt, then H_2
vii: Ni/Raney, H_2, THF, rt

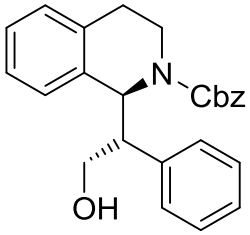
We had first attempted the synthesis of **1g** starting from **7h**. We evaluated the feasibility of this synthetic route on racemic **7h**. After reduction of the enamide double bond, the two diastereoisomers could be separated by column chromatography and we proceeded on parallel synthesis on both ***syn*-26** and ***anti*-26**. The Mitsunobu reaction proceeded smoothly, but the removal of the thioester moiety and of the Cbz protecting group lead to desired product **15** in low yield and to a mixture of by-products, the major of which was pyridine **28**. We suppose that during the reaction with Ni/Raney also the Cbz was removed causing the re-aromatisation to the isoquinoline ring. When the reaction mixture was placed under hydrogen atmosphere the benzene ring was reduced leading to pyridine **28.** In an attempt to avoid the re-aromatisation the reaction was conducted directly under hydrogen atmosphere, but the same mixture of by-products was obtained. Due to the low yields of the desired product **15**, we turned on the Boc as activating agent.

Synthesis of racemic 26

To a stirred solution of isoquinoline (8.00 mmol, 939 μL) and enamine **21** (8.0 mmol, 1.38 g) in DCM (5 mL), a solution of CbzCl (8.00 mmol, 1.15 mL) in DCM (4 mL) was added by syringe pump over the course of 15 hours. After the addition was complete the solution was stirred for 2 more hours, then the HCl 1M (10 mL) was added and the mixture was vigorously stirred for 1 hour. The organic layer was separated and the aqueous layer was extracted with DCM (2 x 8 mL). The collected organic layers were dried over Na_2SO_4 and diluted with MeOH (3 mL). The solution was cooled to 0°C and $NaBH_4$ (13 mmol, 494 mg) was added. After 2 hours complete conversion was observed by TLC analysis and the reaction was quenched by cautious addition of HCl 1M until pH = 1. The mixture was diluted with DCM (3 mL), the organic layer was separated and the aqueous layer was extracted with DCM (2 x 10 mL). The collected organic layers were washed with brine, dried on $MgSO_4$ and concentrated under reduced pressure. The crude product was transferred in a two necked round bottomed flask under nitrogen atmosphere and dissolved in DCM (7 mL), then TFA (15 mL) and triethlysilane (40 mmol, 6.3 mL) were added. The mixture was stirred for 18 hours at room temperature, then solvent was removed under reduce pressure. The residue was dissolved in diethyl ether (20 mL) and washed with $NaHCO_3$ sat. sln. until basic pH. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The collected organic layers were washed with brine, dried on $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 85/15) to give ***anti*-26** (774 mg of 3.5:1 mixture ***anti*-26**: *N*-Cbz pyrrolidine, 672 mg ***anti*-26**, 1.74 mmol, 22% yield) and ***syn*-26** (235 mg of 1.2:1 mixture ***syn*-26**: *N*-Cbz pyrrolidine, 164 mg ***syn*-26,** 0.42 mmol, 5% yield).

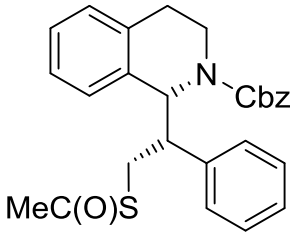


(*anti*-26): Colourless sticky solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 3:1 ratio): δ = 2.41-2.53 (m, $2H_B$), 2.76-2.85 (m, $2H_A$), 3.00-3.06 (m, 1H), 3.20-3.32 (m, 1H), 3.48-3.57 (m, $2H_B$), 3.68-3.76 (m, $2H_A$), 3.86 (dd, J_1 = 11.9 Hz, J_2 = 3.7 Hz, $1H_A$), 3.96-3.92 (m, $2H_B$), 4.06 (dd, J_1 = 11.9 Hz, J_2 = 4.9 Hz, $1H_A$), 5.23 (d, J = 12.2 Hz, 1H), 5.27 (d, J = 12.2 Hz, 1H), 5.39 (d, J = 10.2 Hz, $1H_B$), 5.47 (d, J = 10.2 Hz, $1H_A$), 6.36 (d, J = 7.7 Hz, $1H_A$), 6.42 (d, J = 6.5 Hz, $1H_B$), 6.79-6.86 (m, 1H), 6.88-6.98 (m, 1H), 7.03-7.47 (m, 11H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C) δ_{anti} = 27.6, 41.1, 53.3, 57.4. 63.7, 67.6, 125.5, 126.9, 127.0, 127.7, 127.9 (2C), 128.1 (2C), 128.2, 128.3, 128.6 (2C), 129.5 (2C), 134.2, 135.3, 136.4, 140.1, 157.1; ESI-MS: *m/z* = 388.3 $[M+H]^+$, 797.6 $[2M+Na]^+$.

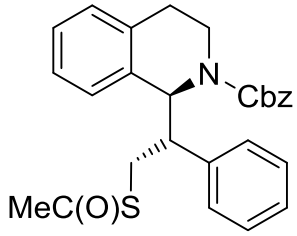


(*syn*-26): Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 4:1 ratio): δ = 1.58-1.81 (bs, 1H), 1.82-1.91 (m, 1H), 2.43-2.57 (m, 1H), 2.69-2.79 (m 1H), 3.27-3.34 (m, $1H_B$), 3.35-3.45 (m, $1H_A$), 3.70 (dt, J_1 = 13.0 Hz, J_2 = 5.2 Hz, 1H), 3.81 (dd, J_1 = 11.8 Hz, J_2 = 5.2 Hz, $1H_A$), 3.84 (dd, J_1 = 11.8 Hz, J_2 = 5.2 Hz, $1H_B$), 3.98-3.91 (m, $1H_B$), 4.10 (dd, J_1 = J_2 = 11.8 Hz, $1H_A$), 5.01 (d, J = 12.2 Hz, $1H_B$), 5.09 (d, J = 12.2 Hz, $1H_B$), 5.20 (d, J = 12.2 Hz, $1H_A$), 5.24 (d, J = 12.2 Hz, $1H_A$), 5.51 (d, J = 6.8 Hz, $1H_B$), 5.70 (d, J = 3.0 Hz, $1H_A$), 6.82 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 7.5 Hz, $1H_A$), 7.00 (d, J = 7.5 Hz, $1H_B$), 7.08-7.21 (m, 4H), 7.24-7.44 (m, 8H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C) δ = 27.6, 40.7, 54.4, 55.0, 62.3, 67.6, 126.2, 126.6, 126.9, 127.1, 127.6 (2C), 127.9 (2C), 128.0, 128.3, 128.4 (2C), 128.7 (2C), 134.8, 135.6, 136.4, 138.1, 157.8; ESI-MS: m/z = 388.3 $[M+H]^+$, 797.6 $[2M+Na]^+$.

The Mitsunobu reaction was performed on ***anti*-26** and ***syn*-26** according to the procedure described for **13** to obtain respectively ***anti*-27** and ***syn*-27.** The products were isolated by column chromatography on silica gel (cyclohexane/diethyl ether from 99/1 to 8/2).



(*anti*-27). Colourless oil, 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B 2:1 ratio): δ = 2.21 (s, $3H_B$), 2.26 (s, $3H_A$), 2.49-2.58 (m, $1H_B$), 2.62-2.71 (m, $1H_A$), 2.74-2.88 (m, 1H), 2.97-3.06 (m, $1H_B$), 3.08-3.22 (m, 1H+$1H_A$), 3.50 (dd, J_1 = 13.5 Hz, J_2 = 5.5 Hz, $1H_B$), 3.59-3.66 (m, $1H_A$), 3.69-3.80 (m, 1H), 3.83-3.92 (m, 1H), 5.14-5.31 (m, 2H+$1H_B$), 5.38 (d, J = 8.7 Hz, $1H_A$), 6.26 (d, J = 8.0 Hz, $1H_A$), 6.28 (d, J = 8.7 Hz, $1H_B$), 6.79-6.90 (m, 2H), 6.92-6.97 (m, 1H), 7.04-7.14 (m, 2H), 7.16-7.26 (m, 3H), 7.29-7.47 (m, 5H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C) (two rotamers A:B 2:1 ratio): δ = 27.3 ($1C_B$), 27.5 ($1C_A$), 30.4 ($1C_B$), 30.5 ($1C_A$), 32.1 ($1C_B$), 32.3 ($1C_A$), 40.2 ($1C_B$), 40.7 ($1C_A$), 51.4 ($1C_B$), 51.7 ($1C_A$), 60.1 ($1C_B$), 60.4 ($1C_A$), 67.2 ($1C_A$), 67.5 ($1C_B$), 125.5 ($1C_B$), 125.2 ($1C_A$), 126.9 ($1C_A$), 127.0 ($1C_B$), 127.1 ($1C_A$), 127.2 ($1C_B$), 127.5 ($1C_B$), 127.6 ($2C_A$+$1C_B$), 127.8 ($1C_A$), 127.9 (2C), 128.0 ($1C_B$), 128.1 (2C), 128.2 ($1C_A$), 128.3 ($1C_B$), 128.4 (2C), 128.5 ($1C_A$), 129.0 ($1C_B$), 134.5 ($1C_A$), 134.6 ($1C_B$), 134.7 ($1C_B$), 135.1 ($1C_A$), 136.4 ($1C_B$), 136.7 ($1C_A$), 140.2 ($1C_B$), 140.4 ($1C_A$), 155.5 ($1C_B$), 156.4 ($1C_A$), 195.3 ($1C_B$), 195.7 ($1C_A$); ESI-MS: m/z = 446.3 $[M+H]^+$, 468.4 $[M+Na]^+$.

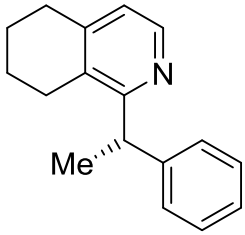


(*syn*-27). Colourless oil, 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B 1.2:1 ratio): δ = 2.23 (s, $3H_B$), 2.28 (s, $3H_A$), 2.44-2.54 (m, $1H_A$), 2.58-2.89 (m, $2H+1H_B$), 3.20-3.30 (m, $1H_B$), 3.31-3.45 (m, 2H), 3.55 (dd, J_1 = 12.5 Hz, J_2 = 5.7 Hz, $1H_A$), 3.63-3.72 (m, $1H_A$), 3.82-3.91 (m, $1H_B$), 4.98 (d, J = 13.0 Hz, $1H_B$), 5.08 (d, J = 13.0 Hz, 1H), 5.14 (d, J = 13.0 Hz, $1H_A$), 5.41 (d, J = 3.6 Hz, $1H_B$), 5.58 (d, J = 4.7 Hz, $1H_A$), 6.96 (d, J = 6.7 Hz, 1H), 7.00-7.13 (m, 2H), 7.14-7.42 (m, 11H); ^{13}CNMR (100 MHz, $CDCl_3$, 25°C) (two rotamers A:B 1.2:1 ratio): δ = 27.5 ($1C_B$), 27.9 ($1C_A$), 30.4 ($1C_B$), 30.5 ($1C_A$), 32.1 ($1C_B$), 32.2 ($1C_A$), 39.5 ($1C_B$), 40.1 ($1C_A$), 51.3 ($1C_B$), 52.0 ($1C_A$), 58.8 ($1C_A$), 59.0 ($1C_B$), 67.1 ($1C_A$), 67.5 ($1C_B$), 125.9 ($1C_B$), 126.1 ($1C_A$), 127.0 ($1C_A$), 127.08 ($1C_B$), 127.09 ($1C_B$), 127.2 ($1C_A$), 127.6 (1C), 127.7 ($1C_B$), 127.8 (1C), 128.0 (1C), 128.1 ($1C_A$), 128.2 (1C), 128.38 (1C), 128.41 ($1C_B$), 128.45 ($1C+1C_A$), 128.48 ($1C_A$), 128.49 ($1C_B$), 128.50 ($1C_A$), 128.6 (1C), 129.0 ($1C_B$), 134.6 ($1C_A$), 134.9 ($1C_B$), 135.3 ($1C_B$), 135.6 ($1C_A$), 136.3 ($1C_B$), 136.8 ($1C_A$), 139.0 ($1C_B$), 139.2 ($1C_A$), 155.6 ($1C_B$), 156.3 ($1C_A$), 195.4 ($1C_B$), 195.7 ($1C_A$); ESI-MS: m/z = 446.3 $[M+H]^+$, 468.4 $[M+Na]^+$.

Reaction with Ni-Raney of compounds *anti*-27 and *syn*-27.

In a two necked round bottomed flask, to a solution of ***anti*-27** (0.34 mmol, 150 mg) in THF (5 mL) and Ni/Raney (2.0 g, slurry in water) was added. The mixture was stirred for 24 hours at room temperature until complete conversion was observed by TLC analysis. The reaction mixture was kept under H_2 atmosphere (1 atm) and stirred for further 16 h. The solution was separated and Nickel/Raney washed 4 times with DCM (5 mL). The collected organic phases were filtered through a Celite pad and concentrated under vacuum. The reaction was subjected to column chromatography on silica gel (cyclohexane/ethyl acetate from 9/1 to 5/5) to give **15** (8.1 mg, 0.034 mmol, 10% yield) and **28** (5.5 mg, 0.023 mmol, 7 % yield).

In a two necked round bottomed flask, to a solution of ***anti*-26** (0.31 mmol, 136 mg) in THF (5 mL) and Ni/Raney (2.0 g, slurry in water) was added. The reaction mixture was kept under H_2 atmosphere (1 atm) and stirred for 24 h at room temperature until complete conversion was observed by TLC analysis. The solution was separated and Nickel/Raney washed 4 times with DCM (5 mL). The collected organic phases were filtered through a Celite pad and concentrated under vacuum. The reaction crude was a complex mixture of products and after column chromatography on silica gel (cyclohexane/ethyl acetate from 9/1 to 5/5) **23** (18 mg, 0.076 mmol, 24% yield) and **28** (15 mg, 0.063 mmol, 20 % yield) were isolated.



28: Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.53-1.86 (m, 4H), 1.70 (d, *J* = 7.0 Hz, 3H), 2.41-2.51 (m, 1H), 2.80-2.69 (m, 3H), 4.36 (q, *J* = 7.0 Hz, 1H), 6.90 (d, *J* = 5.1 Hz, 1H), 7.14-7.19 (m, 1H), 7.21-7.28 (m, 4H), 8.36 (d, *J* = 5.1 Hz, 1H); ESI-MS: *m/z* = 238.3 $[M+H]^+$.

References

S1 U.S. Pat. Appl. Publ., 20030083352, 01 May 2003.

S2 J. B. Hendrickson, C. Rodriguez, *J. Org. Chem.* 1983, **48**, 3344.

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S4 A. C. Cutter, I. R. Miller, J. F. Kelly, R. K. Bellinghan, M. E. Light, R. C. D. Brown, *Org. Lett.*, 2011, **13**, 3988.

S5 Y. Saito, H. Ouchi, H. Takahata, *Tetrahedron*, 2006, **62**, 11529.

S6 a) E. Finamore, L. Minale, R. Riccio, G. Rinaldo, F. Zollo, *J. Org. Chem.* 1991, **56**, 1146-1153; b) F. Dericcardis, L. Minale, R. Riccio, B. Giovannitti, M. Iorizzi, C. Debitus, *Gazz. Chim. Ital.* 1993, **123**, 79-86.

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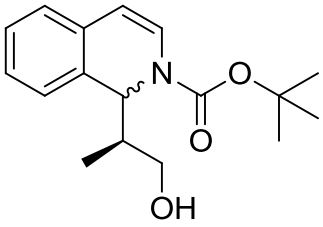
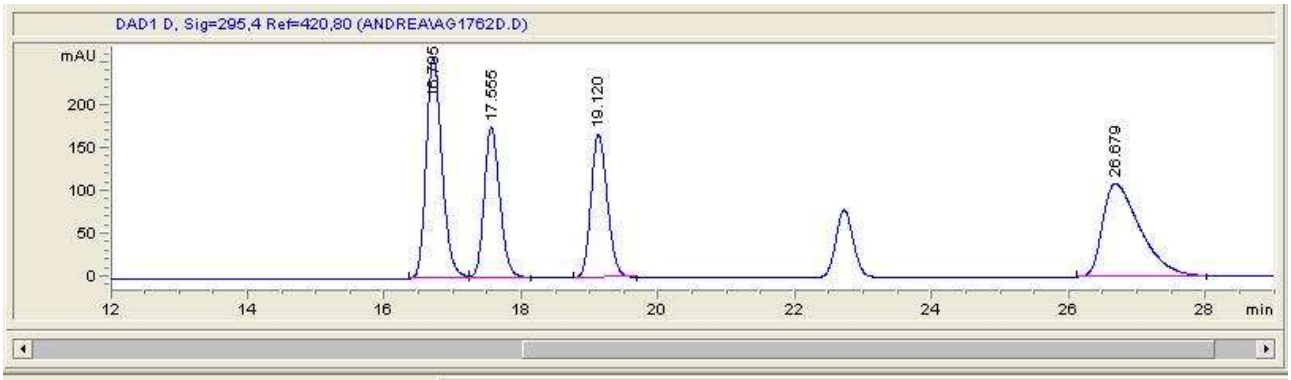
S8 a) I.-S. Cho, S. S.S. Chang, C. Ho, C.-P. Lee, H. L. Ammon, P. S. Mariano, *Heterocycles* 1991, **32**, 2161-2192. b) M. Sugiura, N. Takao, K. Iwasa, Y. Sasaki, *Chem. Pharm. Bull.* 1976, **26**, 1168-1176.

Copies of HPLC traces of compounds 6a-c, 7a-h, 8b-i and 10a



6a

Racemic



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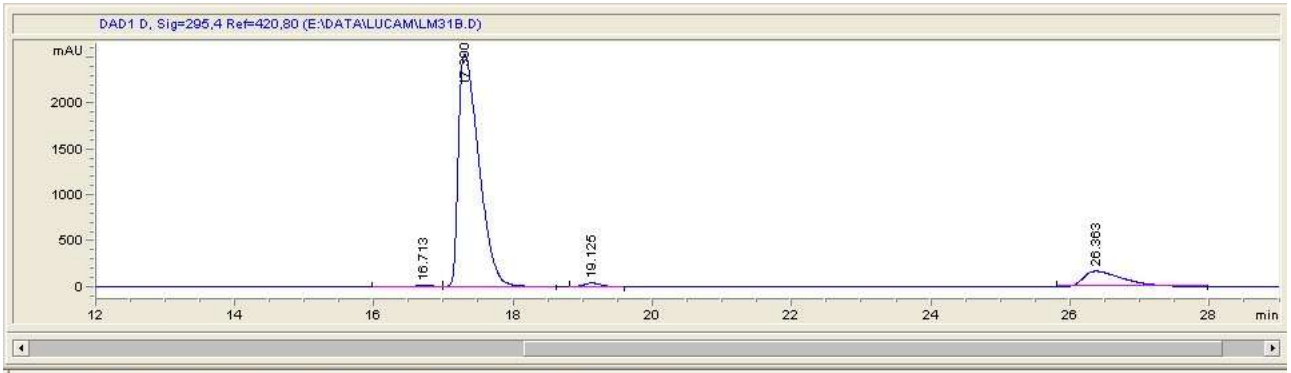
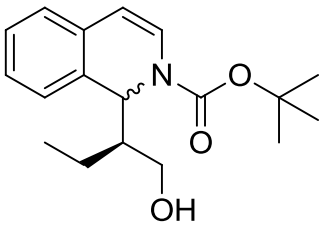
2	17.555	2806.5	175.9	0.2481	20.264	0.803
3	19.12	2773.8	167.6	0.2591	20.028	0.802
4	26.679	4121.7	108.4	0.5775	29.760	0.496

Active

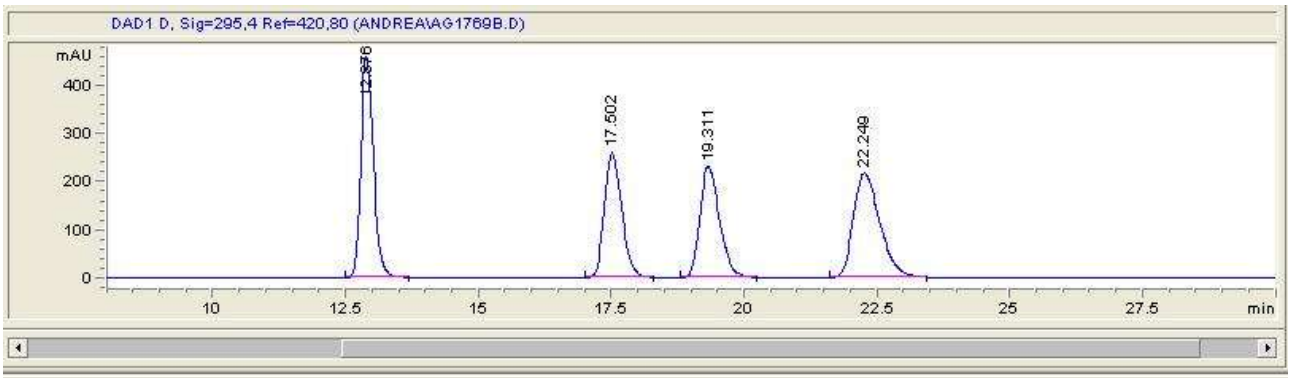


#	Time	Area	Height	Width	Area%	Symmetry
1	16.713	327.4	15.4	0.3073	0.549	1.184
2	17.3	51807.3	2533.5	0.3146	86.828	0.419
3	19.125	700	40.1	0.2755	1.173	0.873
4	26.363	6831.9	168.3	0.6075	11.450	0.418



6b

Racemic



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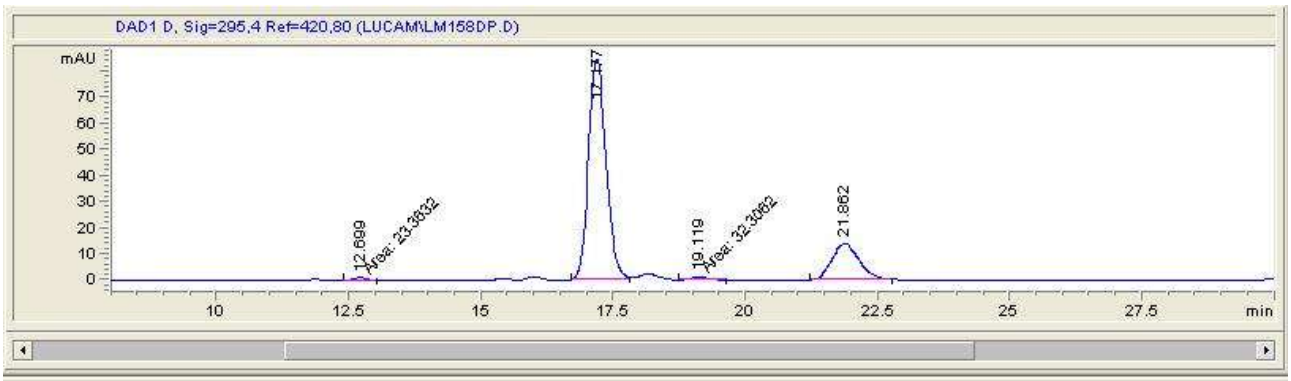
1	12.876	7635.2	462.2	0.2547	28.139	0.736
2	17.502	5953.5	261.1	0.354	21.941	0.758
3	19.311	5955.9	231	0.3989	21.950	0.697
4	22.249	7589.3	218.5	0.5372	27.970	0.674

Active



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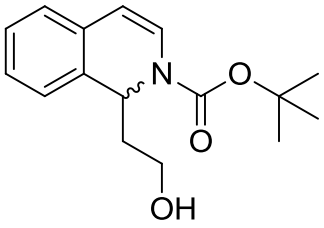
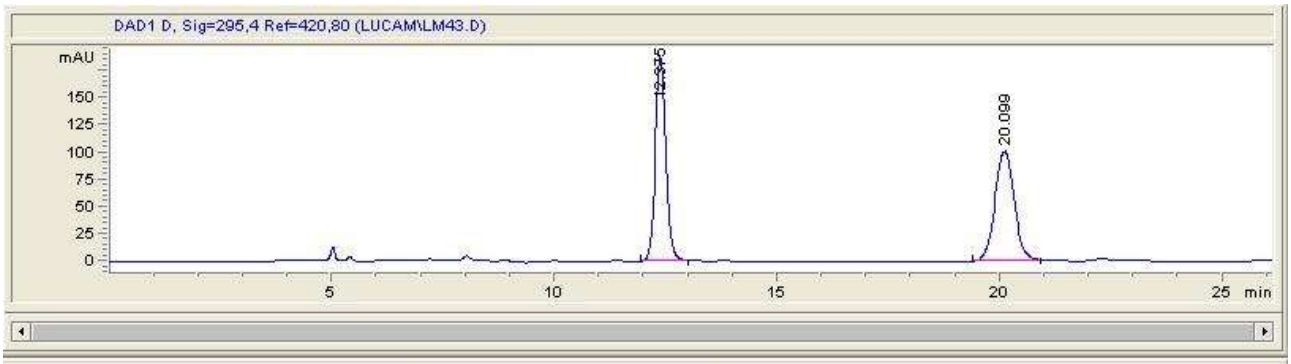
1	12.699	23.4	1.2	0.3328	0.934	0.835
2	17.177	1945.7	84.4	0.3569	77.814	0.819
3	19.119	32.3	1.2	0.439	1.292	0.948
4	21.862	499.1	13.8	0.5326	19.959	0.826



6c

Racemic



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1	12.375	3086	186.9	0.2546	50.495	0.973
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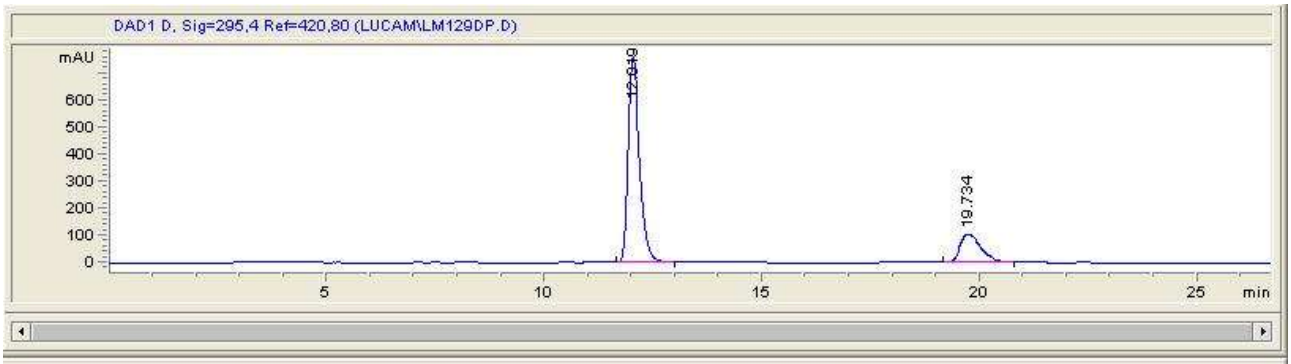
Active



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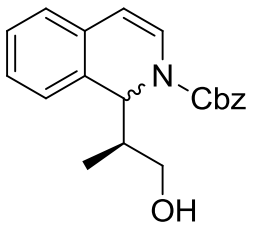
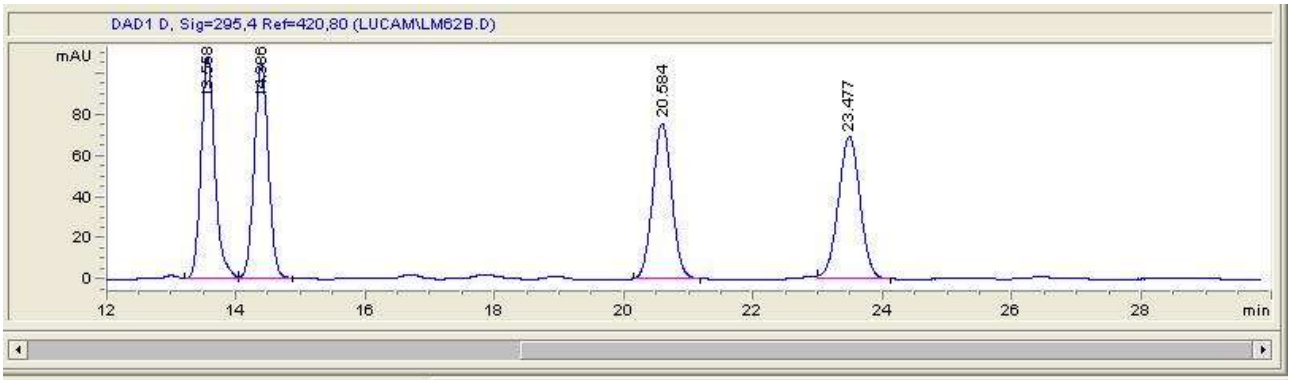


7a

Racemic



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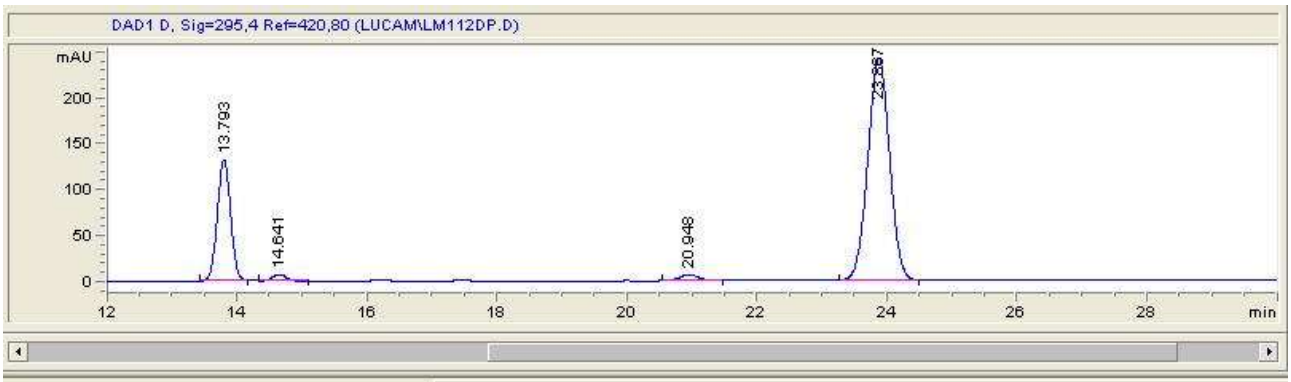
2	14.386	1580.4	104.4	0.2367	24.943	0.95
3	20.584	1554.4	75.7	0.3195	24.532	0.958
4	23.477	1602.6	68.8	0.3636	25.294	0.994

Active



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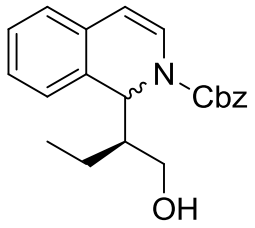
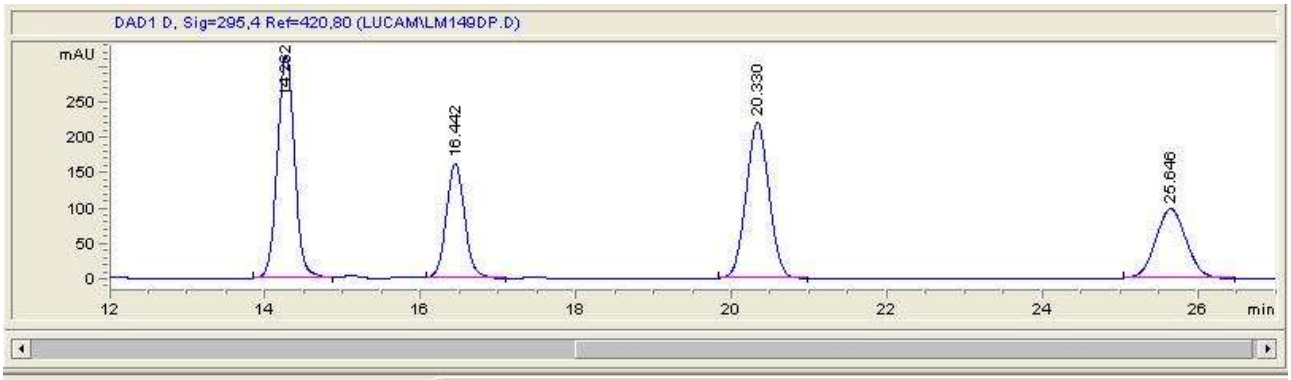
1	13.793	1870.9	132.2	0.2212	24.212	0.966
2	14.641	102.7	7.2	0.227	1.329	0.941
3	20.948	127.7	6.3	0.3087	1.652	0.988
4	23.867	5625.8	241.8	0.3634	72.806	1.005



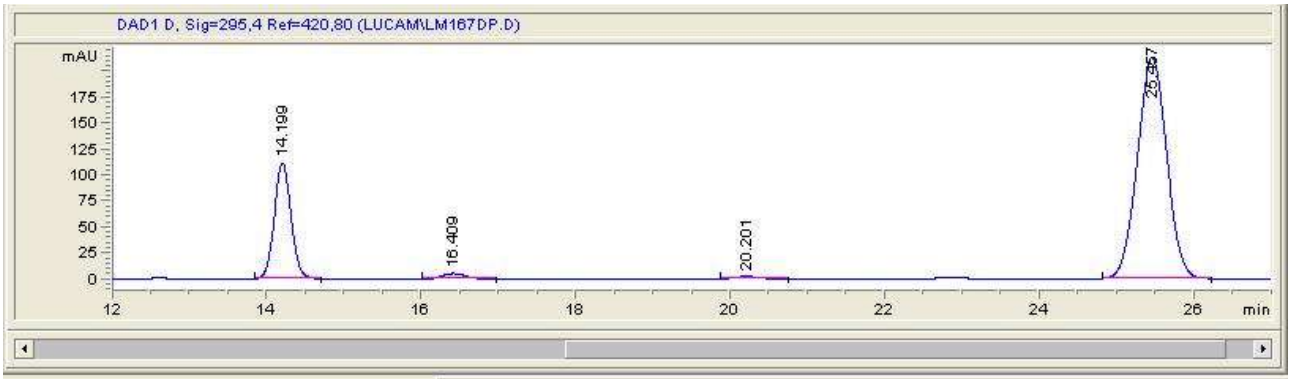
7b

Racemic

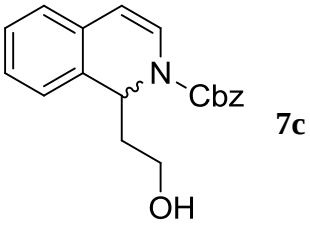


#	Time	Area	Height	Width	Area%	Symmetry
1	14.262	4823.7	314.1	0.2372	32.888	0.948
2	16.442	2633.1	161	0.2528	17.952	0.926
3	20.33	4512.7	220.2	0.3191	30.768	0.959
4	25.646	2697.7	98.4	0.424	18.392	0.946

Active

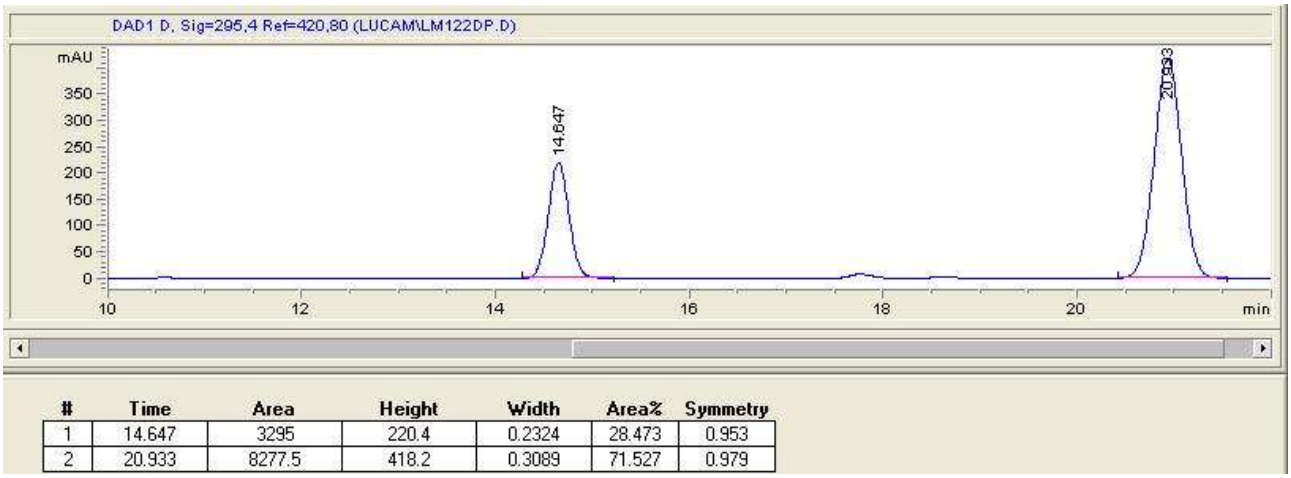


#	Time	Area	Height	Width	Area%	Symmetry
1	14.199	1683.7	111.8	0.2317	22.558	0.928
2	16.409	109.4	5.2	0.3306	1.465	0.847
3	20.201	41.4	2.2	0.3031	0.555	0.952
4	25.457	5629.5	212.9	0.4124	75.422	0.984



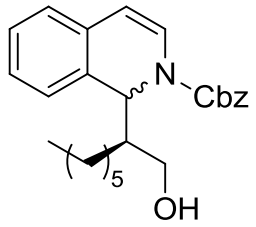
7c

Active



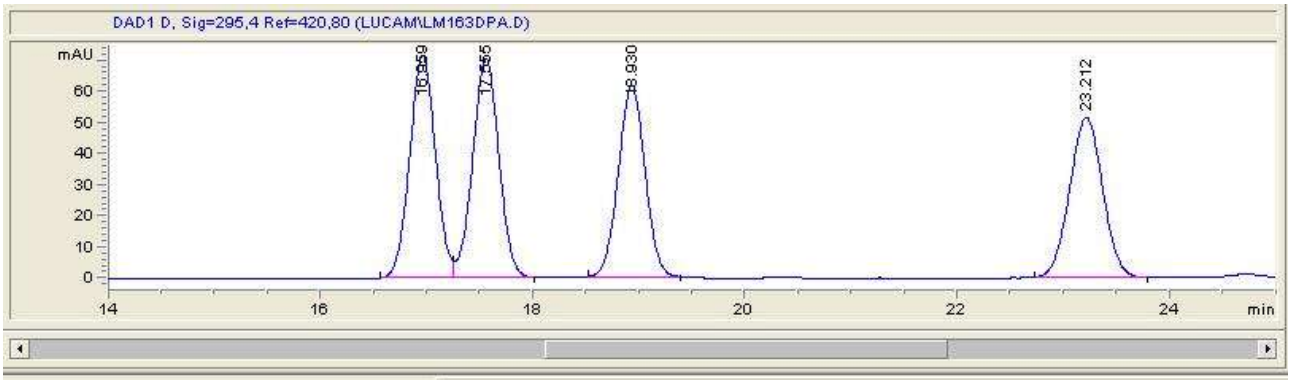
#	Time	Area	Height	Width	Area%	Symmetry
1	14.647	3295	220.4	0.2324	28.473	0.953
2	20.933	8277.5	418.2	0.3089	71.527	0.979

Racemic product was not obtained using either pyrrolidine or racemic Hayashi catalyst **4c**.



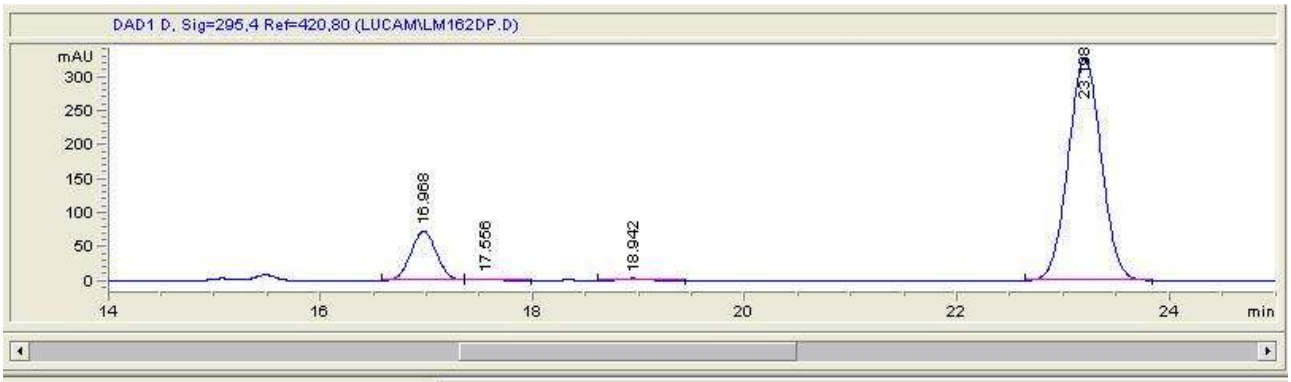
7d

Racemic

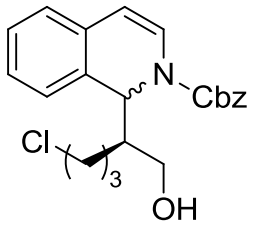


#	Time	Area	Height	Width	Area%	Symmetry
1	16.959	1217.7	71.5	0.2646	26.244	0.971
2	17.555	1216.4	70.7	0.2688	26.214	0.977
3	18.93	1089.2	61.6	0.2744	23.475	0.973
4	23.212	1116.7	51.6	0.3406	24.067	0.983

Active

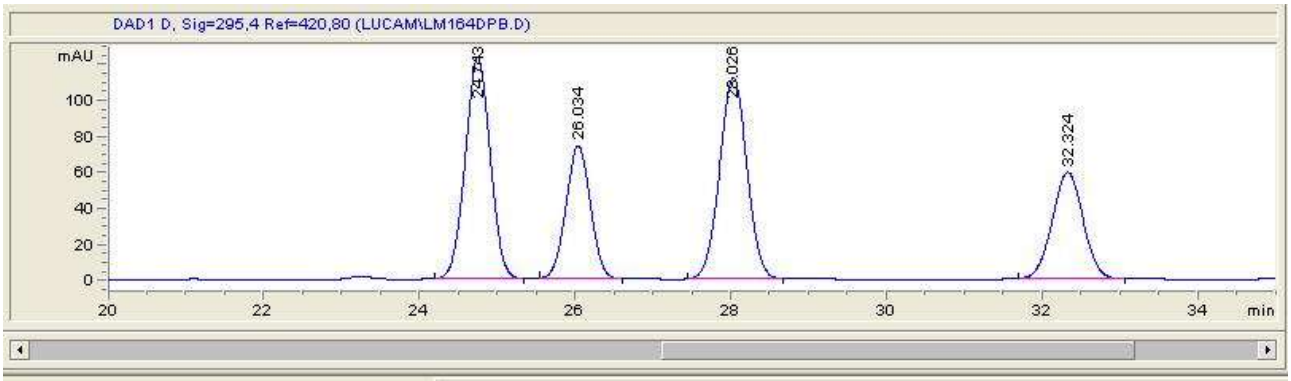


#	Time	Area	Height	Width	Area%	Symmetry
1	16.968	1233.8	72.6	0.2662	14.615	0.965
2	17.556	55.3	3.3	0.2564	0.655	0.961
3	18.942	58.4	3.1	0.2763	0.692	0.741
4	23.198	7094.6	327.4	0.3388	84.038	0.969



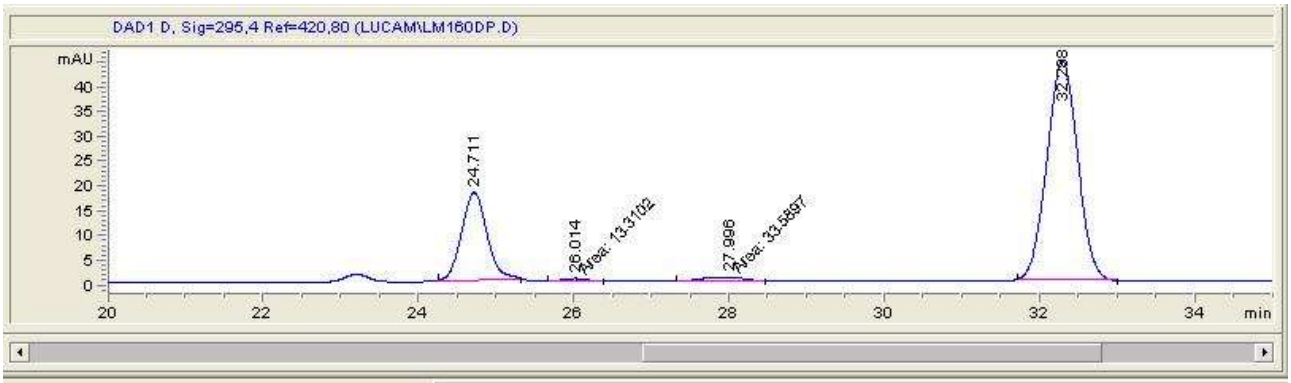
7e

Racemic

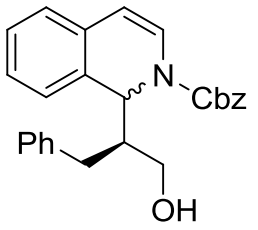


#	Time	Area	Height	Width	Area%	Symmetry
1	24.743	2743.7	123	0.3461	31.402	0.991
2	26.034	1608.5	73.8	0.3383	18.409	0.983
3	28.026	2743.5	111.7	0.3826	31.400	0.986
4	32.324	1641.6	59.2	0.4335	18.789	0.989

Active

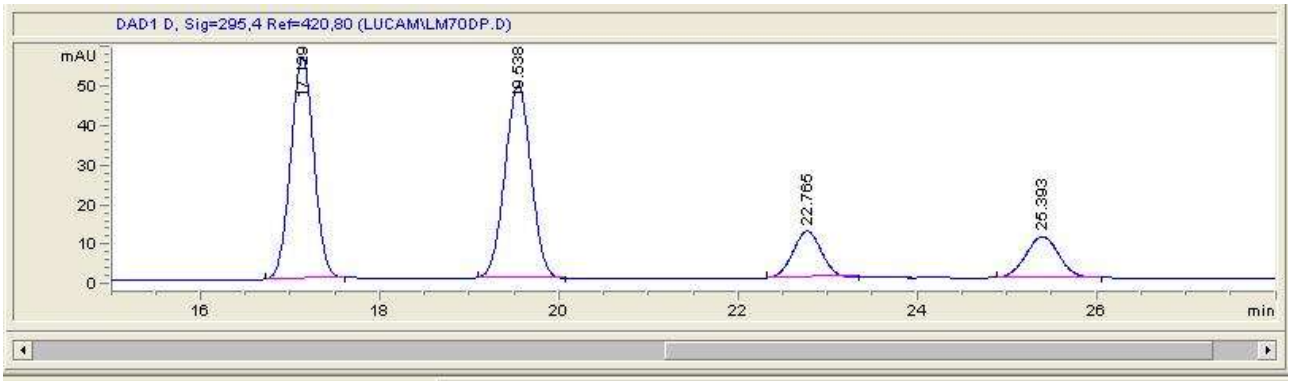


#	Time	Area	Height	Width	Area%	Symmetry
1	24.711	413.8	17.9	0.359	24.520	0.899
2	26.014	13.3	5.9E-1	0.3748	0.789	0.884
3	27.996	33.6	9E-1	0.624	1.990	1.564
4	32.288	1226.9	44.5	0.4278	72.701	0.983



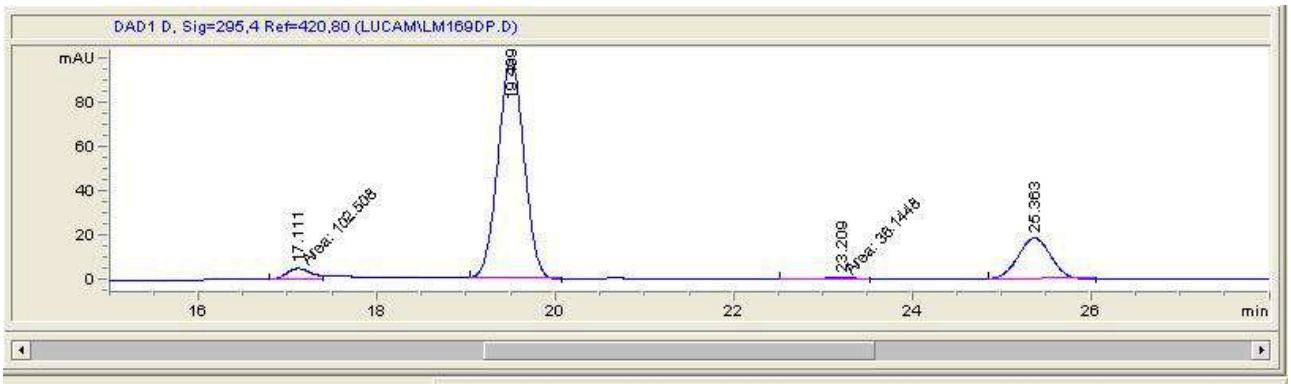
7f

Racemic

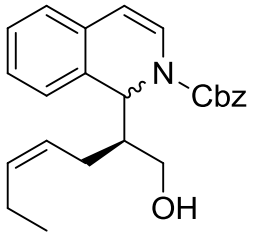


#	Time	Area	Height	Width	Area%	Symmetry
1	17.129	999.6	55.9	0.2805	39.740	0.978
2	19.538	991.3	48.7	0.3155	39.410	0.991
3	22.765	260.5	11.7	0.3477	10.356	0.983
4	25.393	264	10.4	0.3931	10.494	1.005

Active

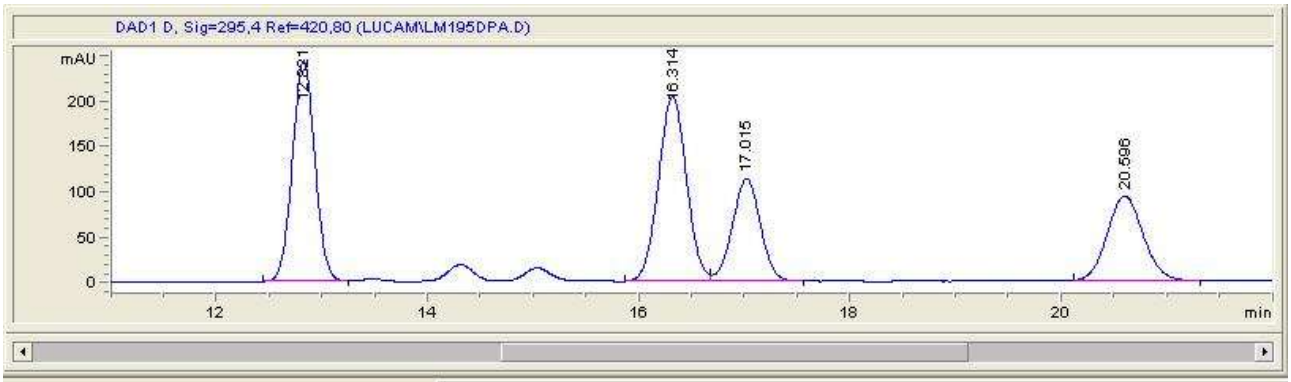


#	Time	Area	Height	Width	Area%	Symmetry
1	17.111	102.5	5.1	0.3382	3.894	0.797
2	19.499	2017.2	99.4	0.3167	76.626	0.984
3	23.209	36.1	9.1E-1	0.6628	1.373	1.624
4	25.363	476.7	18.6	0.4024	18.107	0.988



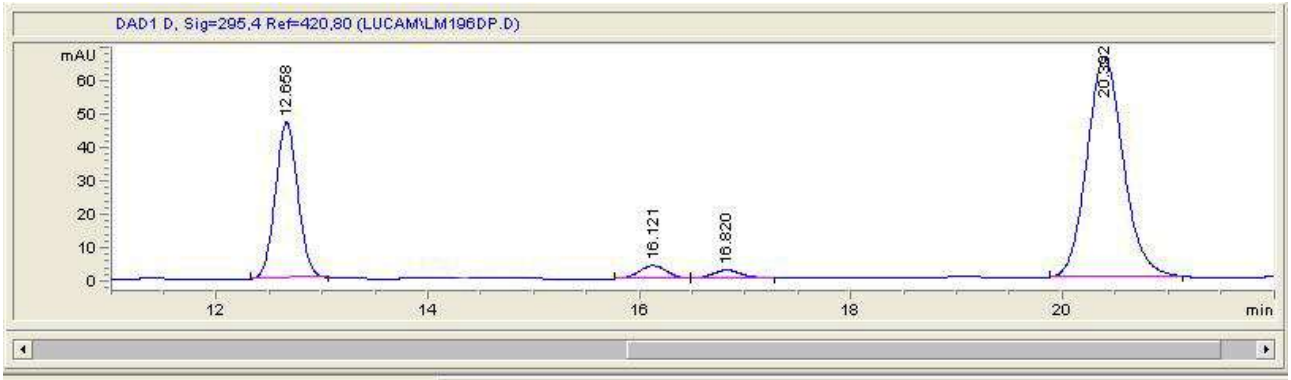
7g

Racemic

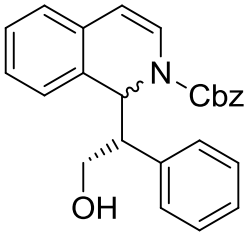


#	Time	Area	Height	Width	Area%	Symmetry
1	12.821	3623.6	243.9	0.2313	30.990	0.958
2	16.314	3766.6	204.1	0.2873	32.213	0.964
3	17.015	2085.7	113.3	0.2867	17.837	0.981
4	20.596	2216.9	93.3	0.3693	18.960	0.897

Active

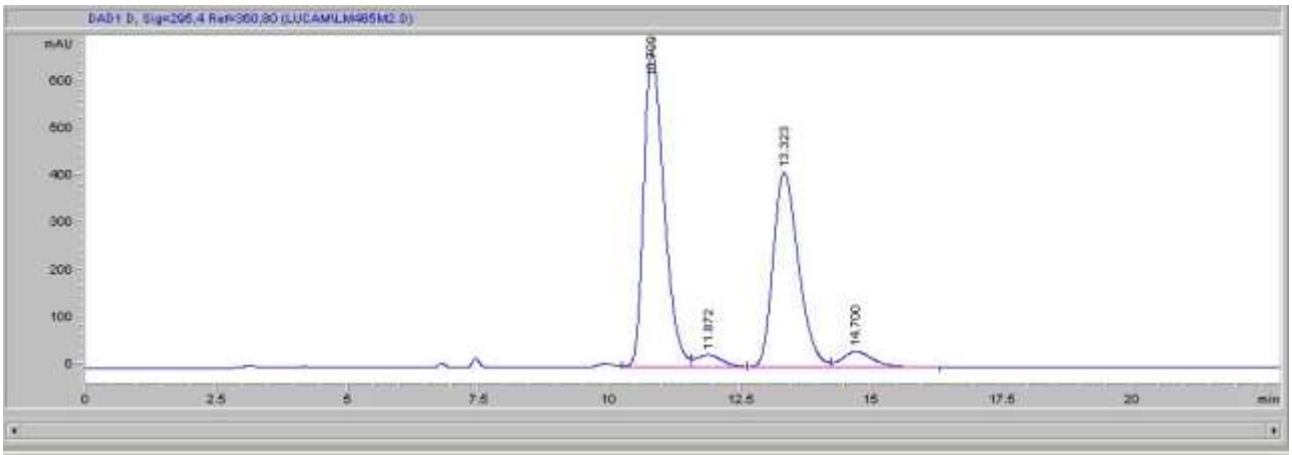


#	Time	Area	Height	Width	Area%	Symmetry
1	12.658	691.3	46.8	0.2283	28.729	0.952
2	16.121	71.5	3.9	0.2808	2.972	0.975
3	16.82	48.3	2.5	0.2935	2.009	0.898
4	20.392	1595.1	66.2	0.3691	66.290	0.88



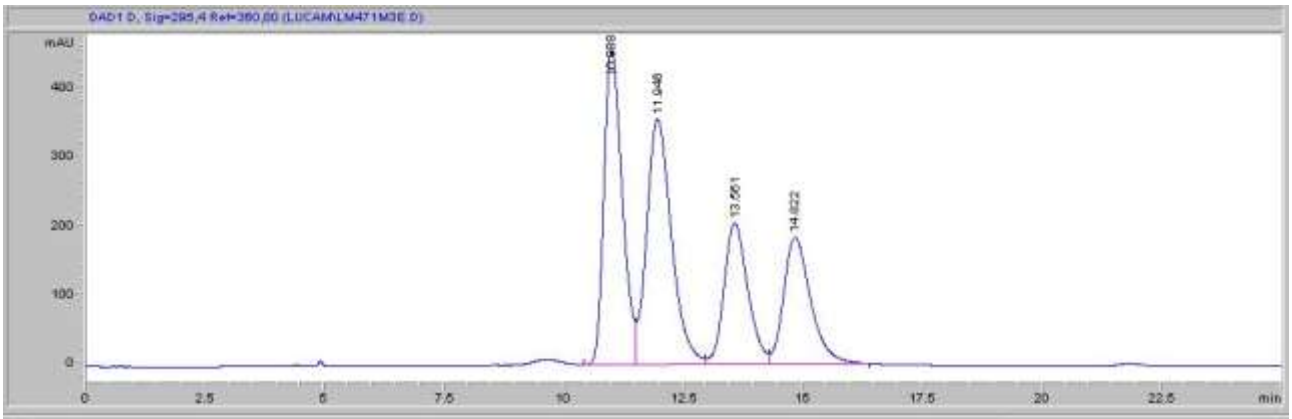
7h

active

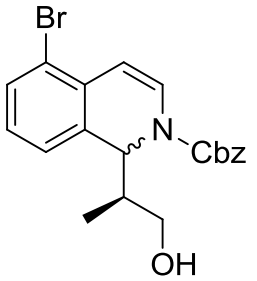


#	Time	Area	Height	Width	Area%	Symmetry
1	10.799	18173.5	669.9	0.4165	52.672	0.645
2	11.872	923.8	26.5	0.519	2.678	0.734
3	13.323	13998.2	413.1	0.5211	40.548	0.715
4	14.7	1415.5	34.2	0.6224	4.102	0.738

racemic

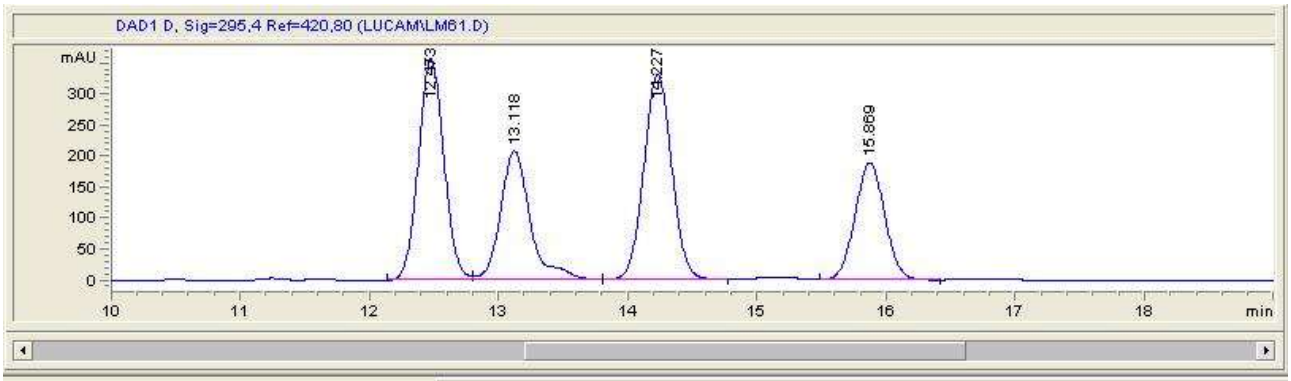


#	Time	Area	Height	Width	Area%	Symmetry
1	10.988	12118.4	458	0.4067	30.743	0.679
2	11.946	12881	358	0.5477	32.678	0.715
3	13.561	7149.2	206.1	0.5326	18.137	0.78
4	14.822	7269.5	184.7	0.5971	18.442	0.682



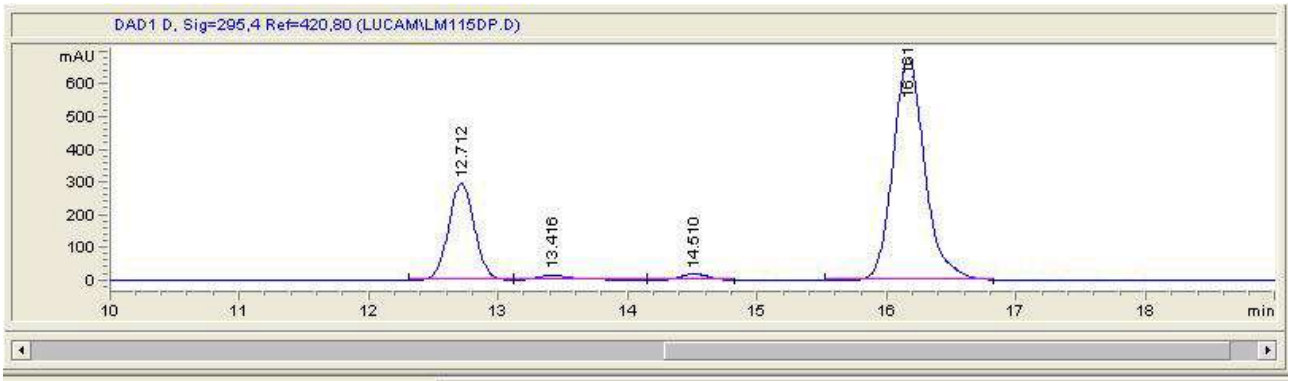
8b

Racemic

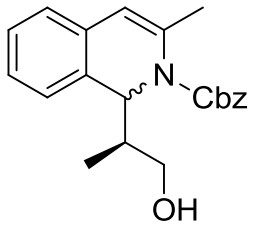


#	Time	Area	Height	Width	Area%	Symmetry
1	12.473	4920	357.8	0.2144	29.879	0.933
2	13.118	3397.3	208.9	0.2457	20.632	0.792
3	14.227	5066.7	333	0.2355	30.770	0.944
4	15.869	3082.2	190.2	0.253	18.719	0.953

Active

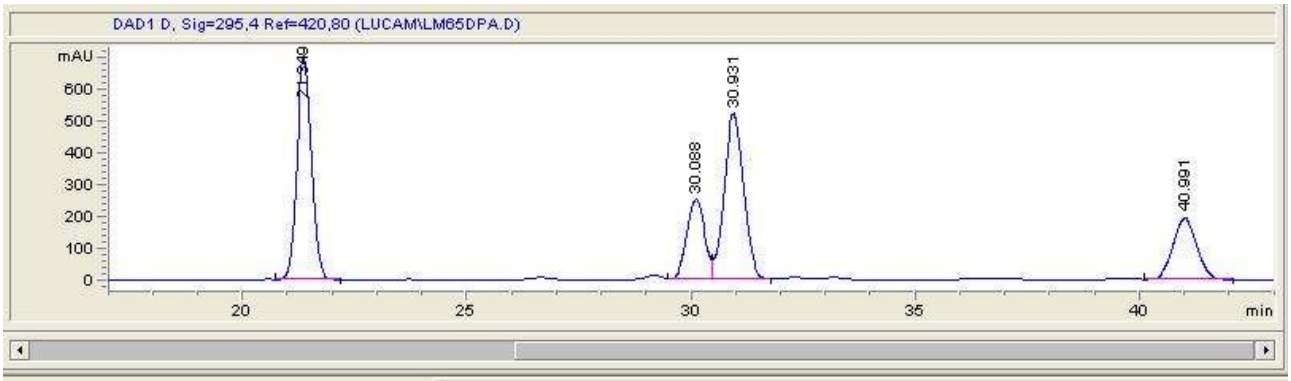


#	Time	Area	Height	Width	Area%	Symmetry
1	12.712	4140.1	296.8	0.2168	25.281	0.948
2	13.416	308.6	14.7	0.3108	1.884	0.624
3	14.51	293.4	19.2	0.2381	1.792	0.959
4	16.161	11634.3	681.6	0.2611	71.043	0.858



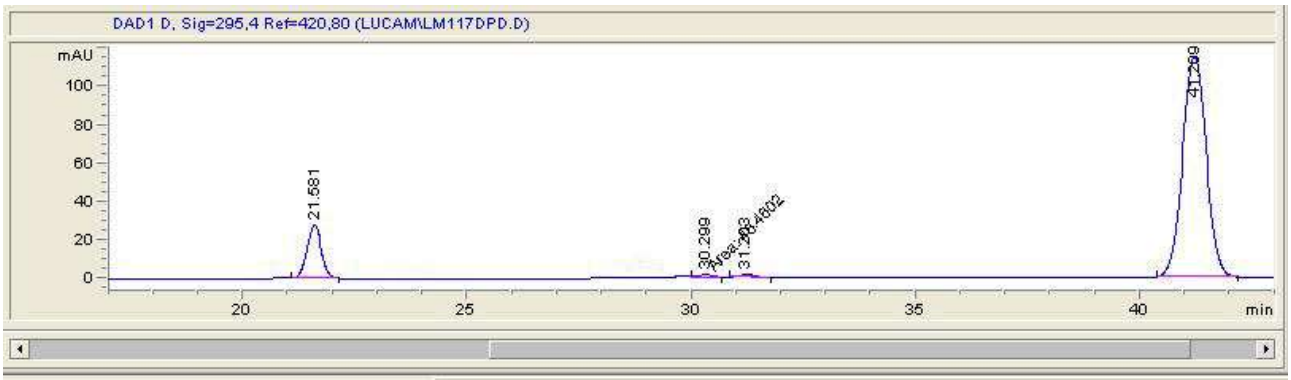
8c

Racemic

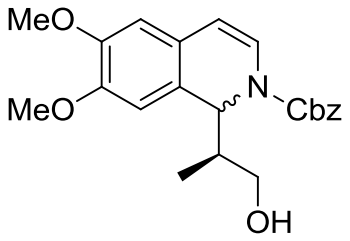


#	Time	Area	Height	Width	Area%	Symmetry
1	21.349	15910.9	701.9	0.3525	34.507	0.904
2	30.088	7113.3	253.5	0.4393	15.427	0.972
3	30.931	15958.9	525.8	0.4741	34.611	0.897
4	40.991	7126.6	194.2	0.572	15.456	0.958

Active

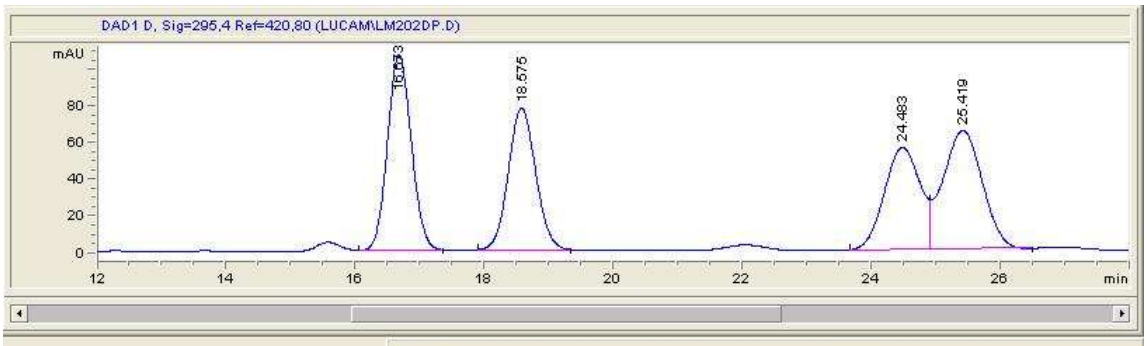


#	Time	Area	Height	Width	Area%	Symmetry
1	21.581	621.6	27.8	0.3487	12.671	0.975
2	30.299	46.5	1.7	0.4576	0.947	0.919
3	31.203	41.4	1.6	0.387	0.843	0.826
4	41.209	4196.6	114.7	0.573	85.539	0.974



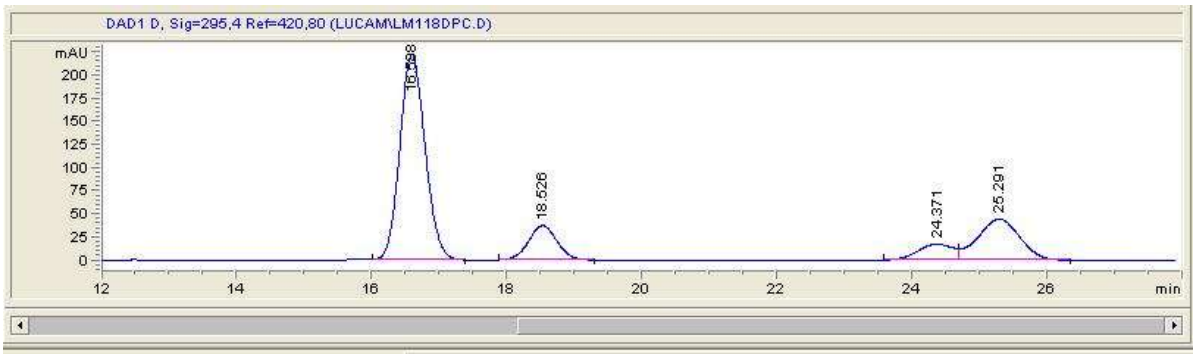
8d

Racemic



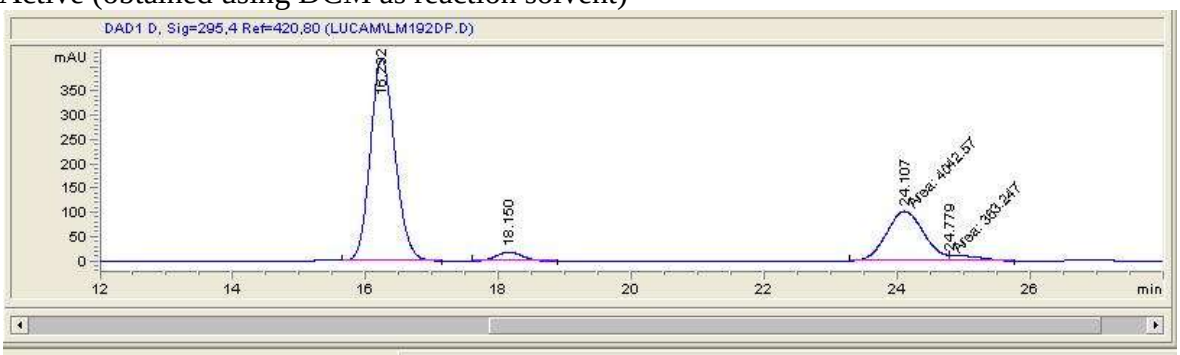
#	Time	Area	Height	Width	Area%	Symmetry
1	16.673	2759.6	106.9	0.3992	27.650	0.889
2	18.575	2307	77.9	0.4597	23.116	0.901
3	24.483	2188.7	55.9	0.5949	21.930	1.002
4	25.419	2725.1	64.7	0.6472	27.304	0.966

Active

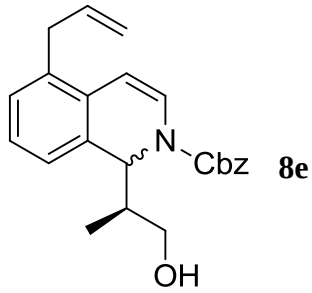


#	Time	Area	Height	Width	Area%	Symmetry
1	16.588	5768.2	222	0.4052	61.132	0.854
2	18.526	1093.4	37.1	0.4578	11.588	0.968
3	24.371	641.9	17.3	0.5474	6.803	1.197
4	25.291	1932.1	44.5	0.667	20.477	1.005

Active (obtained using DCM as reaction solvent)

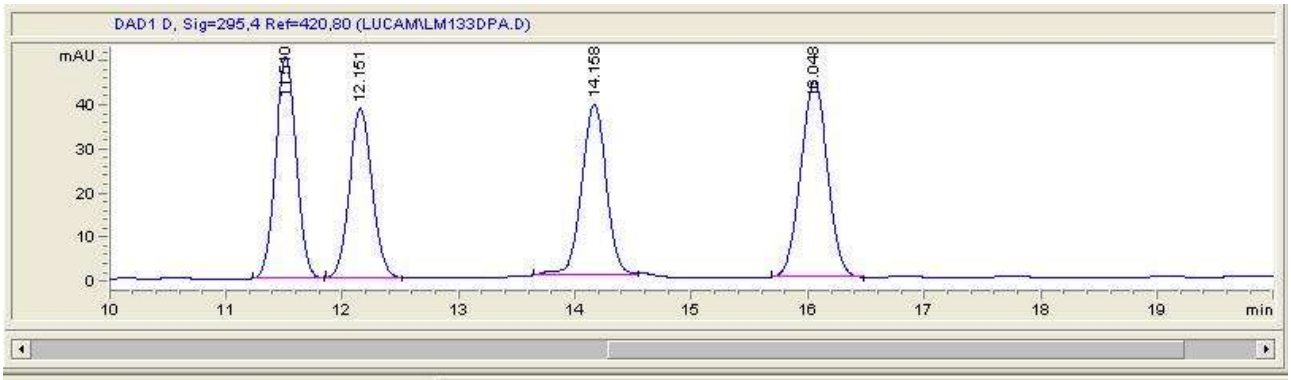


#	Time	Area	Height	Width	Area%	Symmetry
1	16.232	10698	417.5	0.3969	68.479	0.821
2	18.15	518.5	18.6	0.4316	3.319	0.933
3	24.107	4042.6	102.3	0.6588	25.877	0.92
4	24.779	363.2	11.3	0.5344	2.325	0



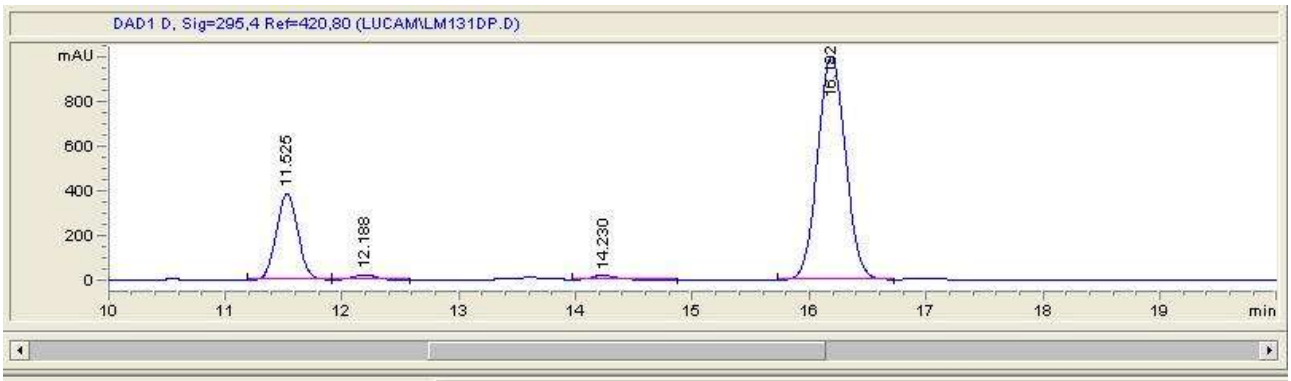
8e

Racemic

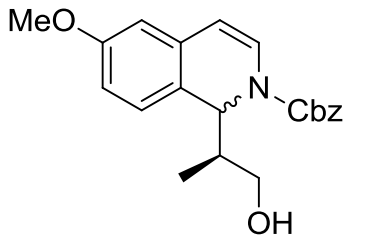


#	Time	Area	Height	Width	Area%	Symmetry
1	11.51	623.1	50.2	0.1947	25.601	0.968
2	12.151	522.4	38.5	0.2123	21.463	0.933
3	14.158	575.7	38.8	0.2311	23.654	1.021
4	16.048	712.7	44.4	0.2511	29.282	0.986

Active

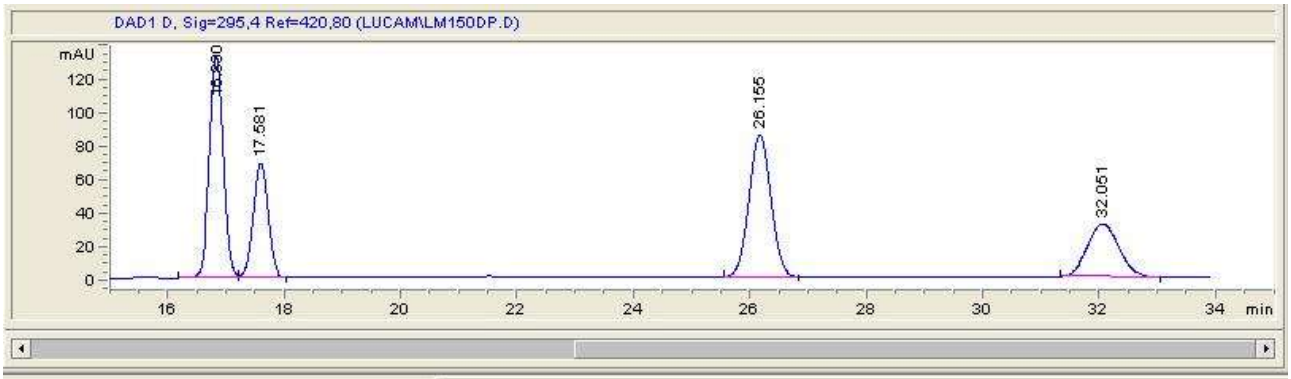


#	Time	Area	Height	Width	Area%	Symmetry
1	11.525	4963.5	387.8	0.1973	22.189	0.926
2	12.188	345.9	23.8	0.2239	1.546	0.978
3	14.23	357.7	20.7	0.2591	1.599	0.721
4	16.182	16702.1	1003.8	0.2601	74.666	0.929



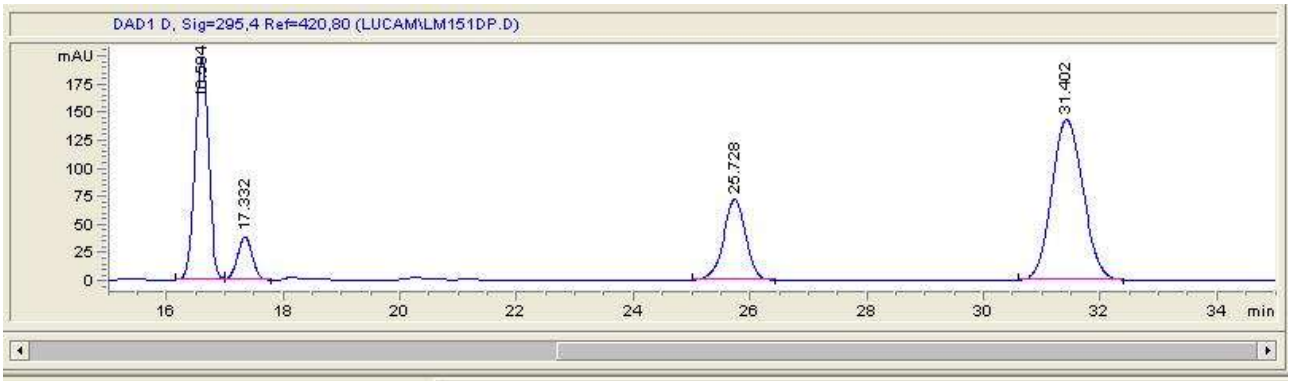
8f

Racemic

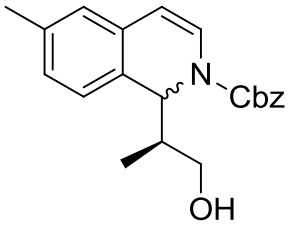


#	Time	Area	Height	Width	Area%	Symmetry
1	16.83	2218.8	132.6	0.2593	32.614	0.994
2	17.581	1206.3	68.6	0.2752	17.731	0.988
3	26.155	2187	84.6	0.4035	32.146	0.94
4	32.051	1191.3	31.7	0.5885	17.510	0.945

Active

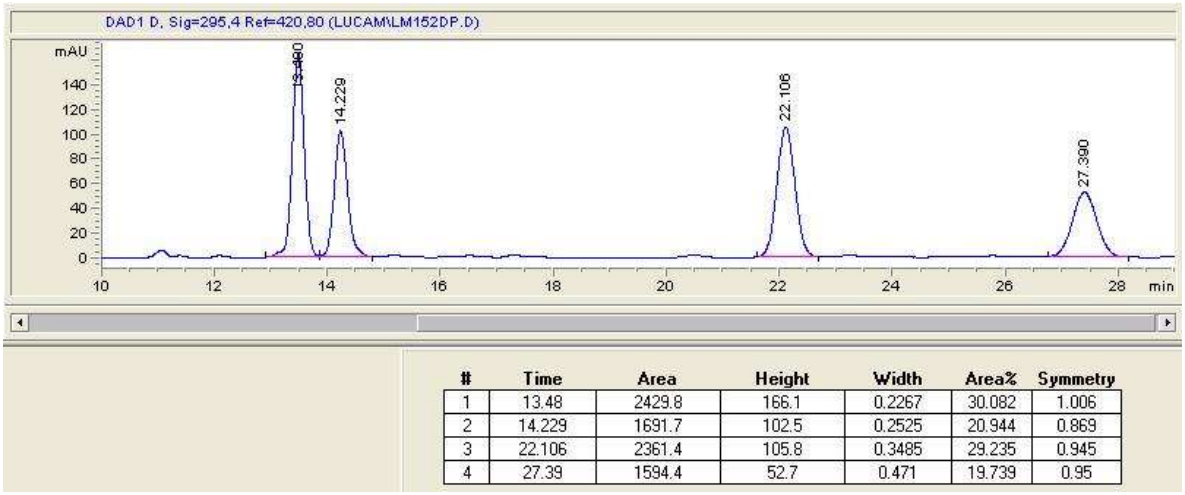


#	Time	Area	Height	Width	Area%	Symmetry
1	16.584	3245.8	198.1	0.2552	29.118	0.968
2	17.332	667.6	38.5	0.2681	5.989	0.996
3	25.728	1931.5	71.6	0.4128	17.327	1.063
4	31.402	5302.1	142.8	0.5812	47.565	0.844



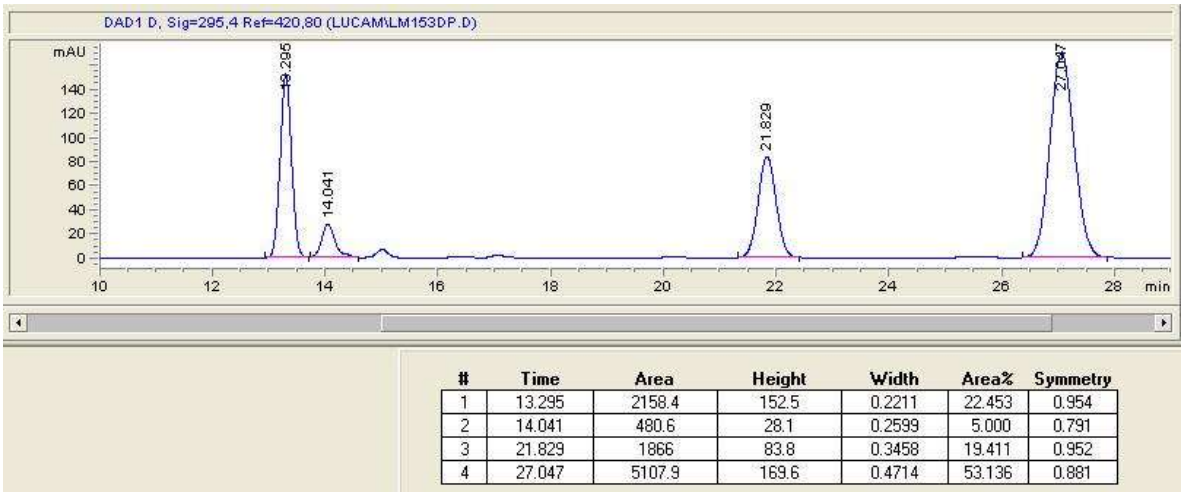
8g

Racemic



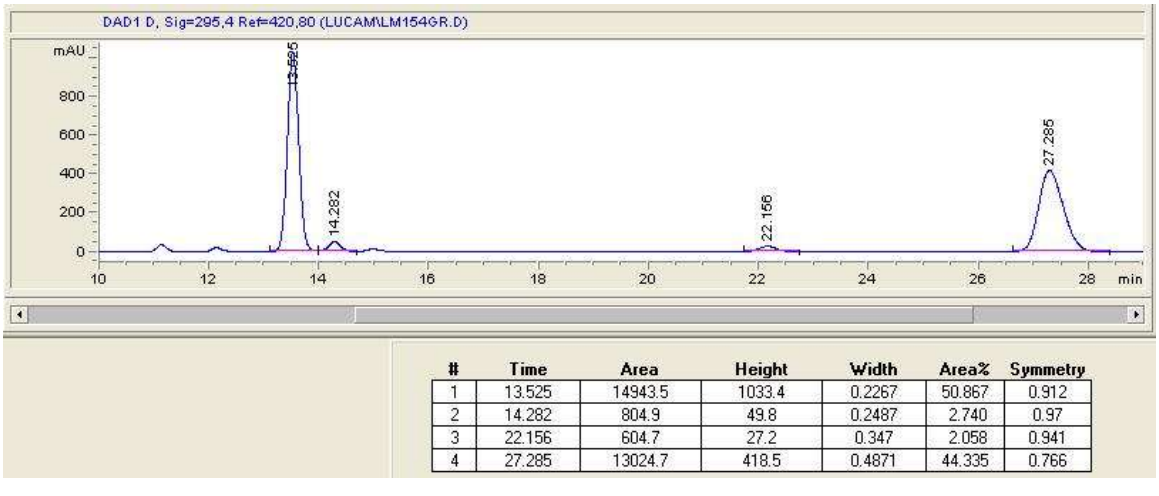
#	Time	Area	Height	Width	Area%	Symmetry
1	13.48	2429.8	166.1	0.2267	30.082	1.006
2	14.229	1691.7	102.5	0.2525	20.944	0.869
3	22.106	2361.4	105.8	0.3485	29.235	0.945
4	27.39	1594.4	52.7	0.471	19.739	0.95

Active

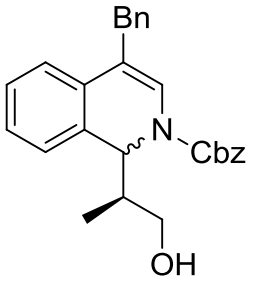


#	Time	Area	Height	Width	Area%	Symmetry
1	13.295	2158.4	152.5	0.2211	22.453	0.954
2	14.041	480.6	28.1	0.2599	5.000	0.791
3	21.829	1866	83.8	0.3458	19.411	0.952
4	27.047	5107.9	169.6	0.4714	53.136	0.881

Active (obtained using DCM as reaction solvent)

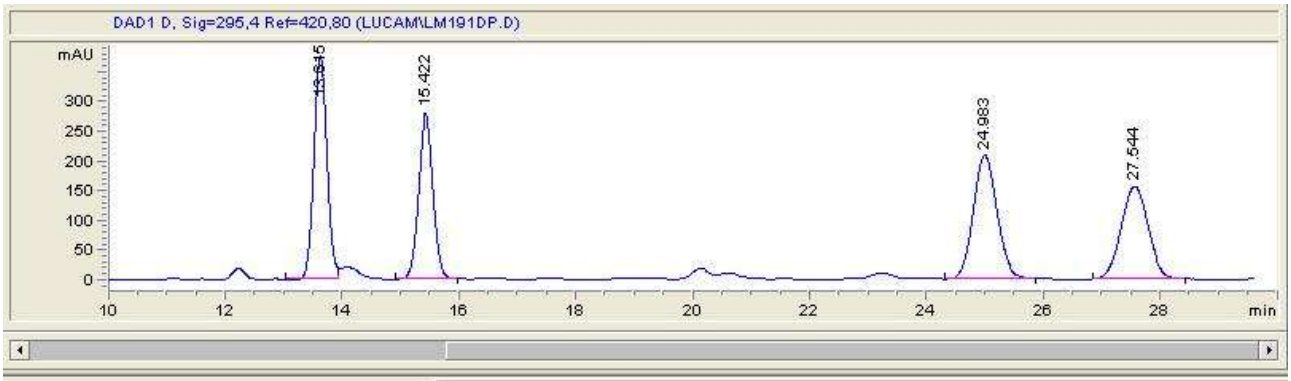


#	Time	Area	Height	Width	Area%	Symmetry
1	13.525	14943.5	1033.4	0.2267	50.867	0.912
2	14.282	804.9	49.8	0.2487	2.740	0.97
3	22.156	604.7	27.2	0.347	2.058	0.941
4	27.285	13024.7	418.5	0.4871	44.335	0.766



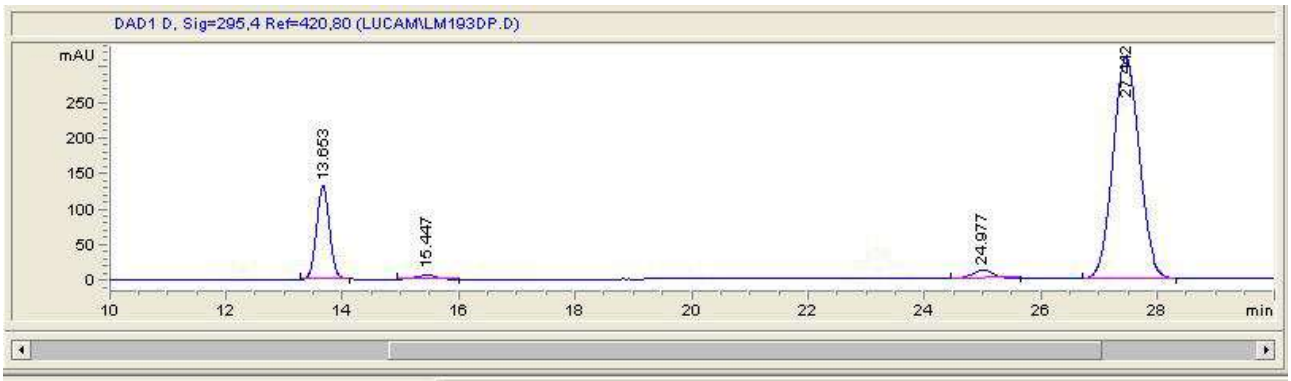
8i

Racemic

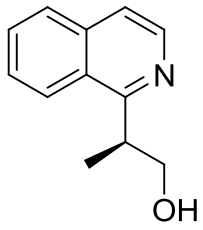


#	Time	Area	Height	Width	Area%	Symmetry
1	13.615	5761.4	376.8	0.2364	26.681	0.925
2	15.422	5008.5	280.3	0.2785	23.194	0.963
3	24.983	5826.7	208.3	0.4343	26.984	0.876
4	27.544	4997.1	156.6	0.4962	23.141	0.941

Active

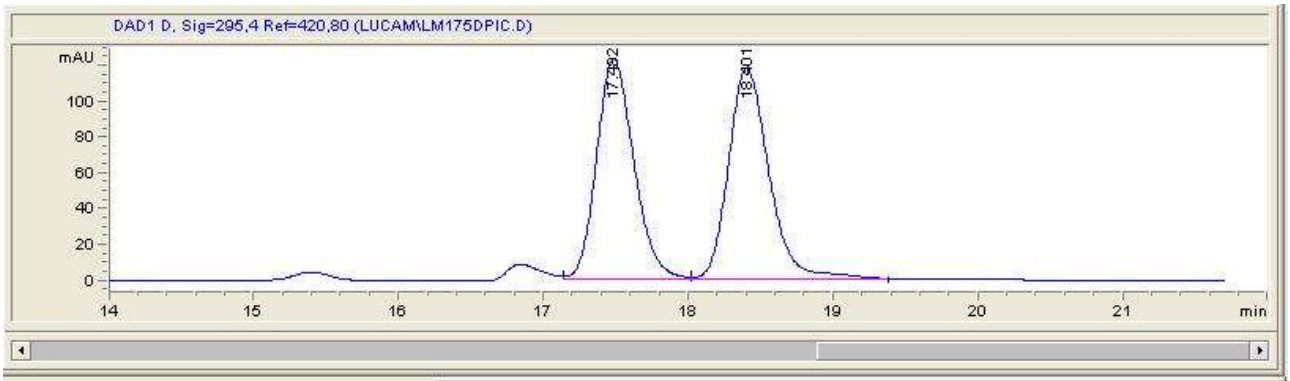


#	Time	Area	Height	Width	Area%	Symmetry
1	13.653	1998.6	131.2	0.2377	16.500	0.949
2	15.447	147.8	6.8	0.3215	1.220	1.447
3	24.977	299.2	11.4	0.408	2.470	0.928
4	27.442	9667	312	0.4835	79.810	0.909



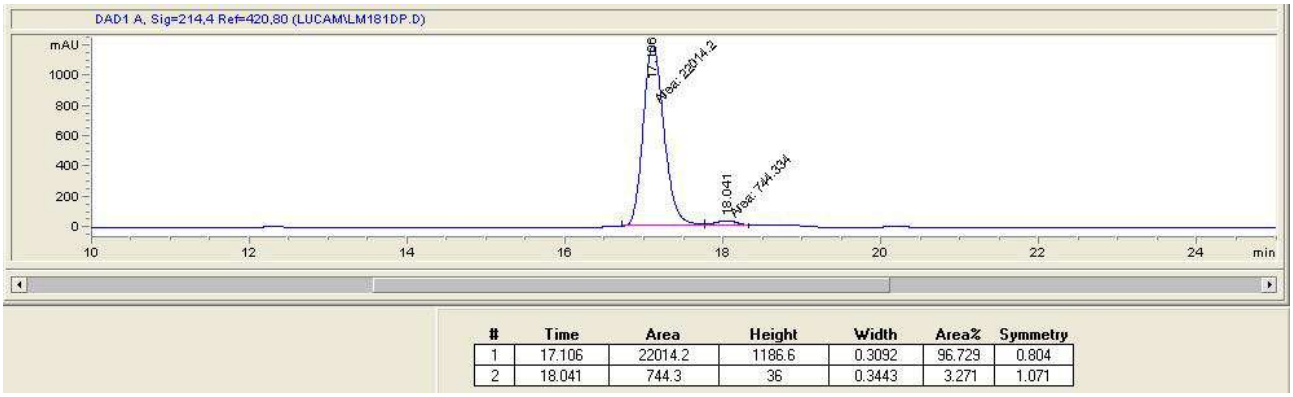
10a

Racemic



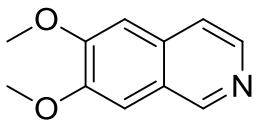
#	Time	Area	Height	Width	Area%	Symmetry
1	17.482	2233.3	123.7	0.2806	49.058	0.798
2	18.401	2319	117.9	0.3015	50.942	0.756

Active

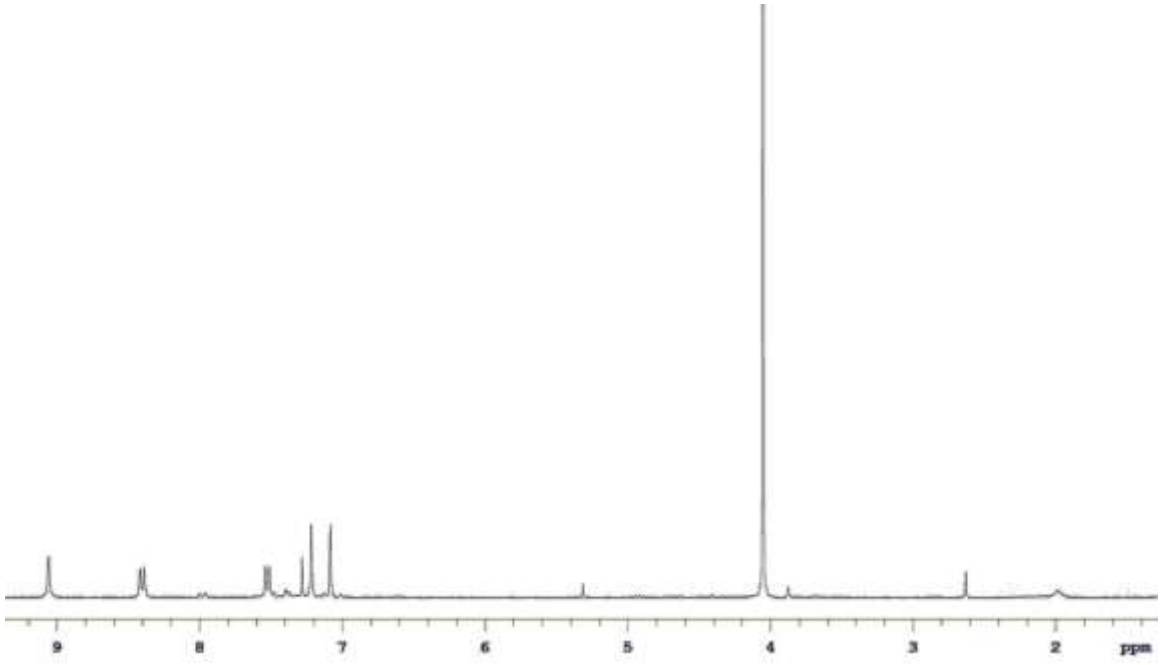


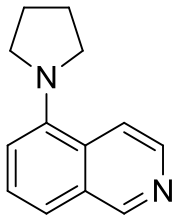
#	Time	Area	Height	Width	Area%	Symmetry
1	17.106	22014.2	1186.6	0.3092	96.729	0.804
2	18.041	744.3	36	0.3443	3.271	1.071

Copies of NMR spectra of compounds 2d, 2h, 6a-c, 7a-h, 8b-I, 9a, 10a

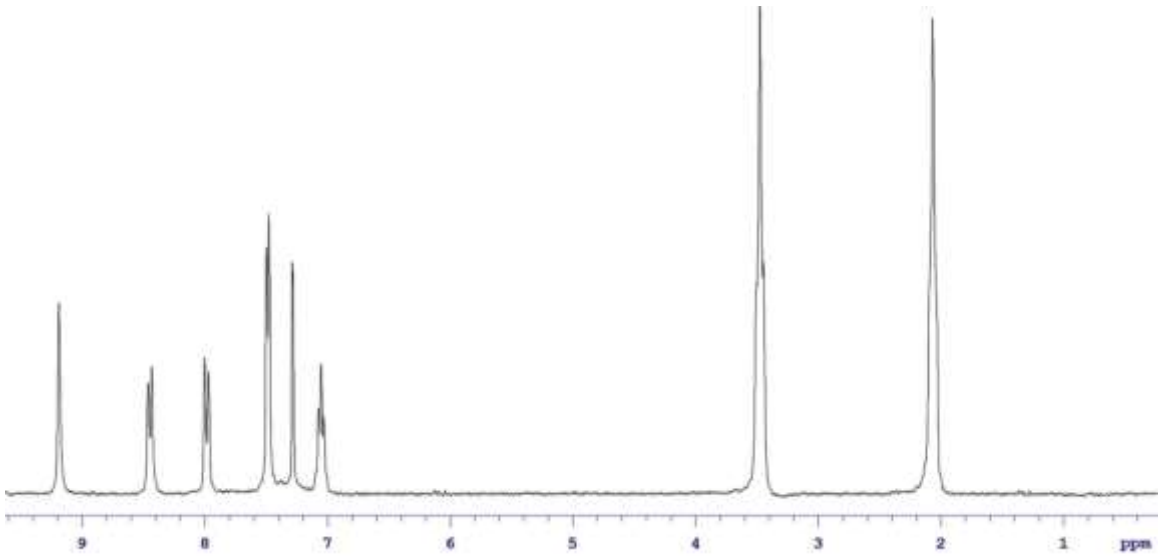


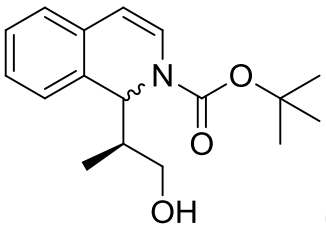
2d



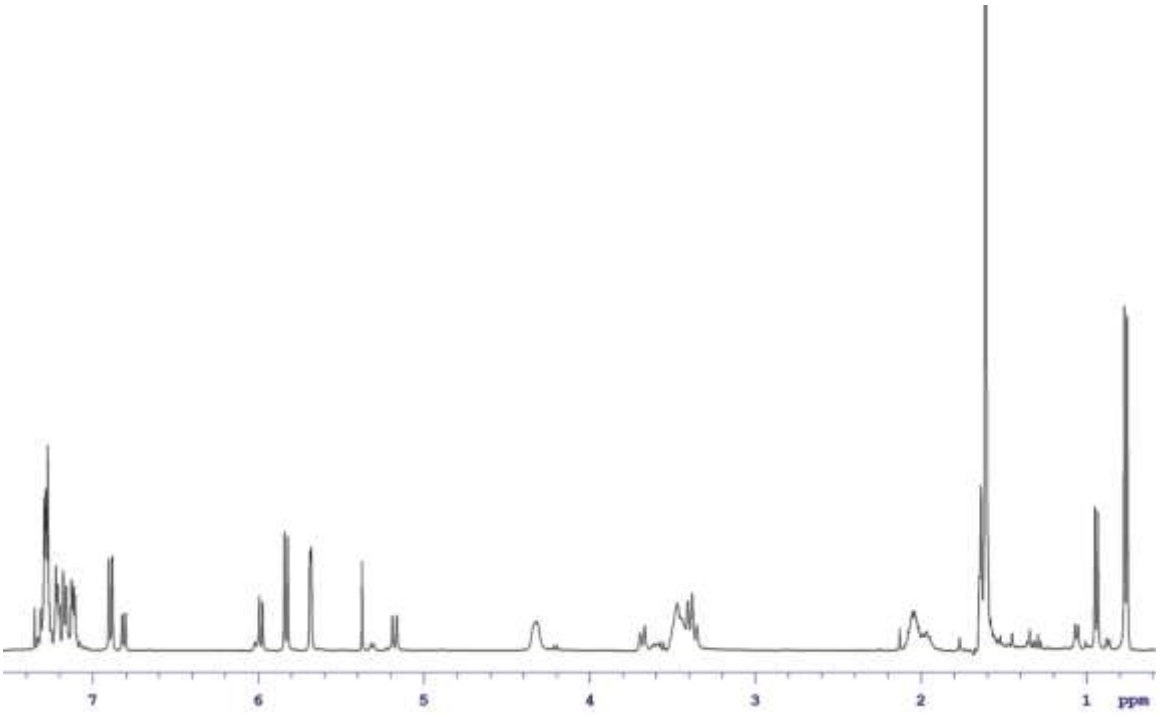


2h




N
O
O
OH

6a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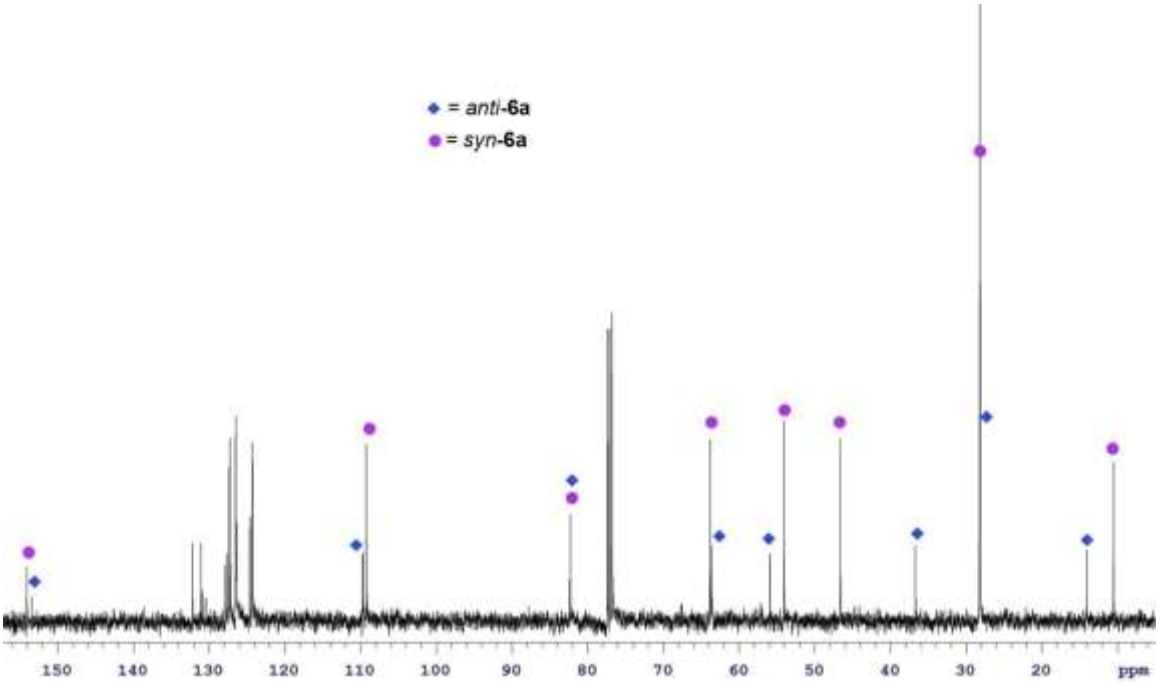
4
3
2
1
ppm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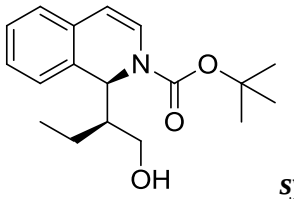
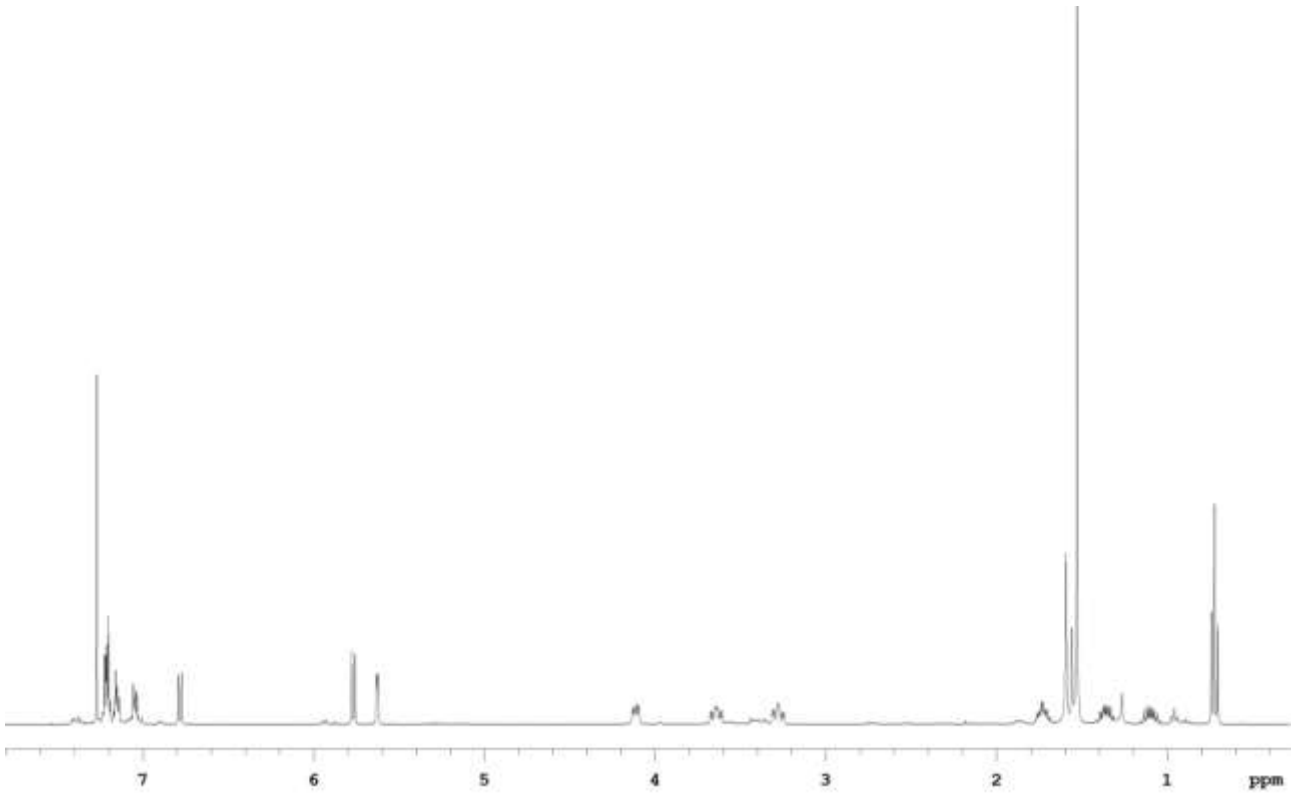
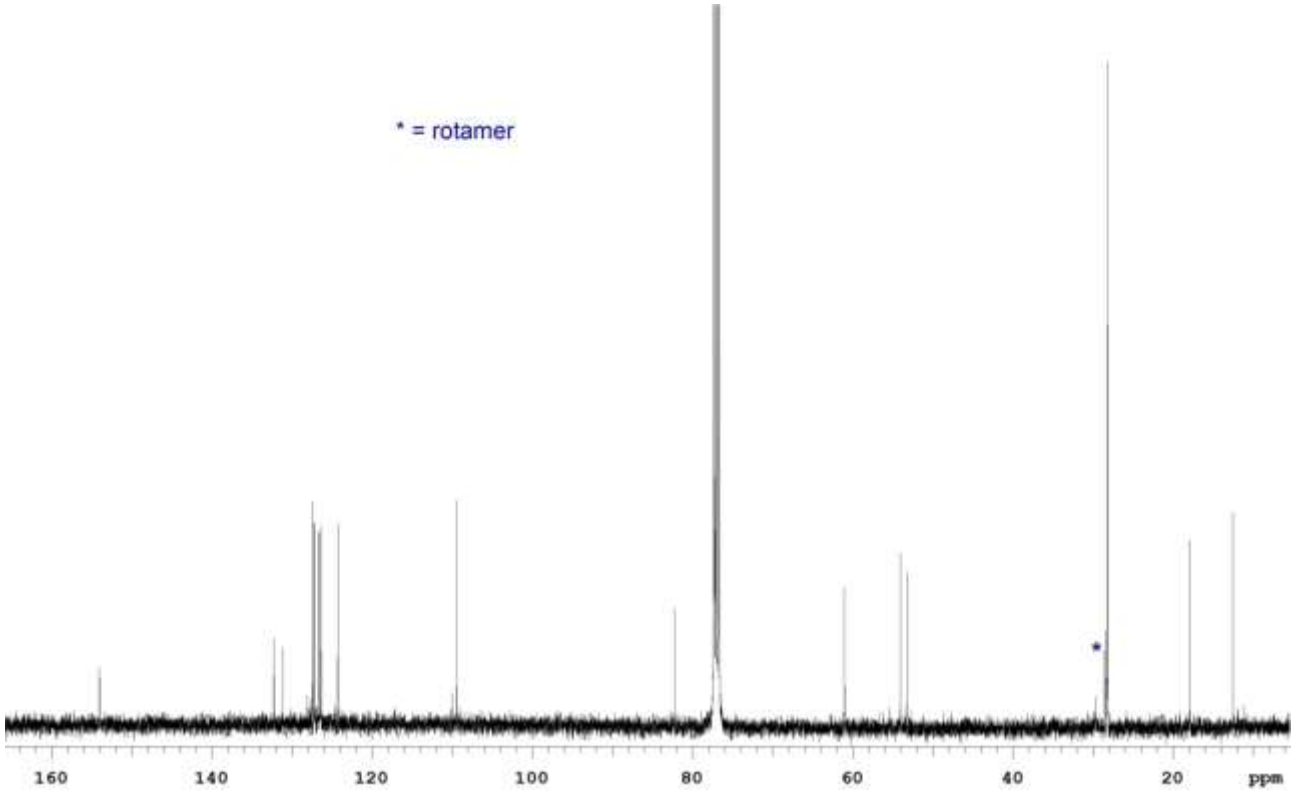
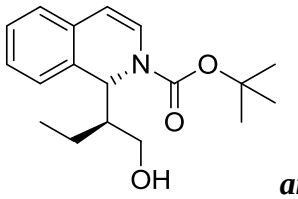


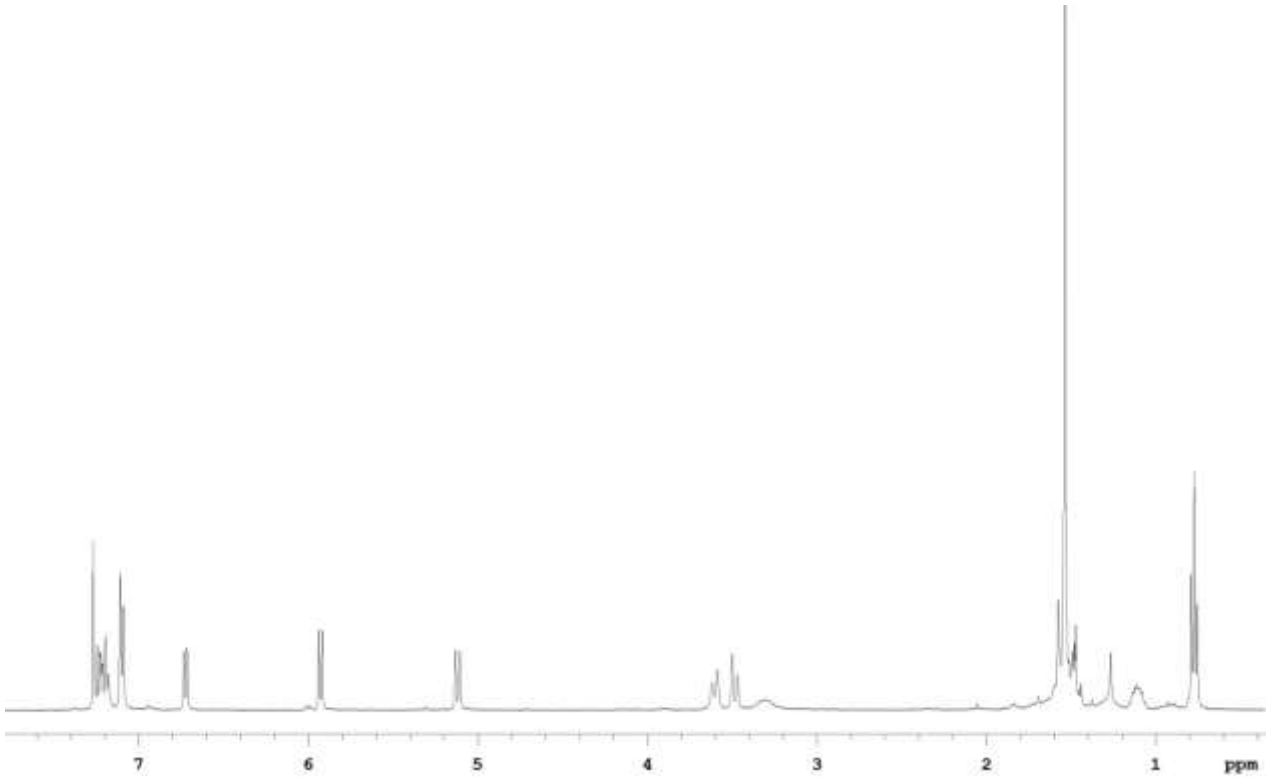
***syn*-6b**






N
O
O
OH

***anti*-6b**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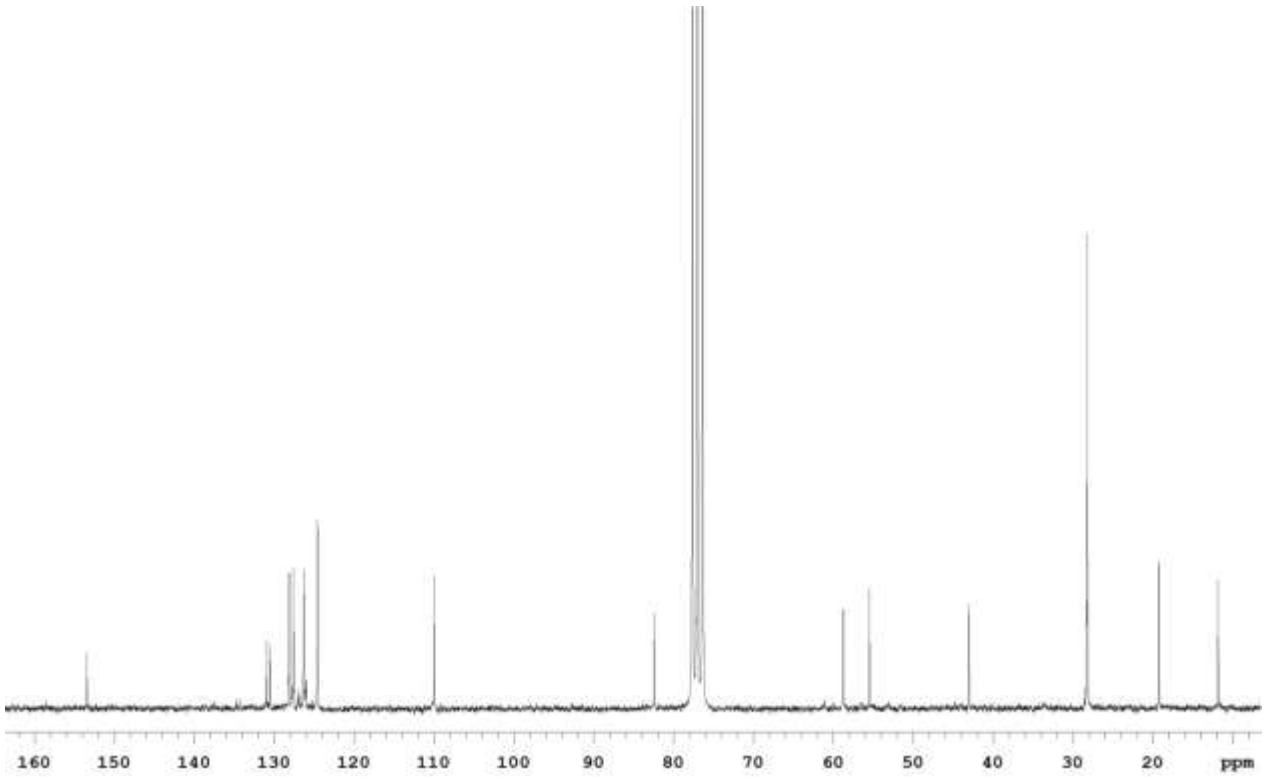
4
3
2
1
ppm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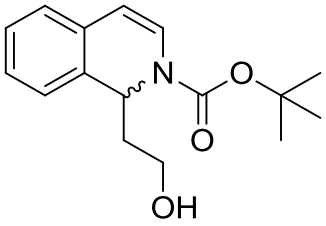
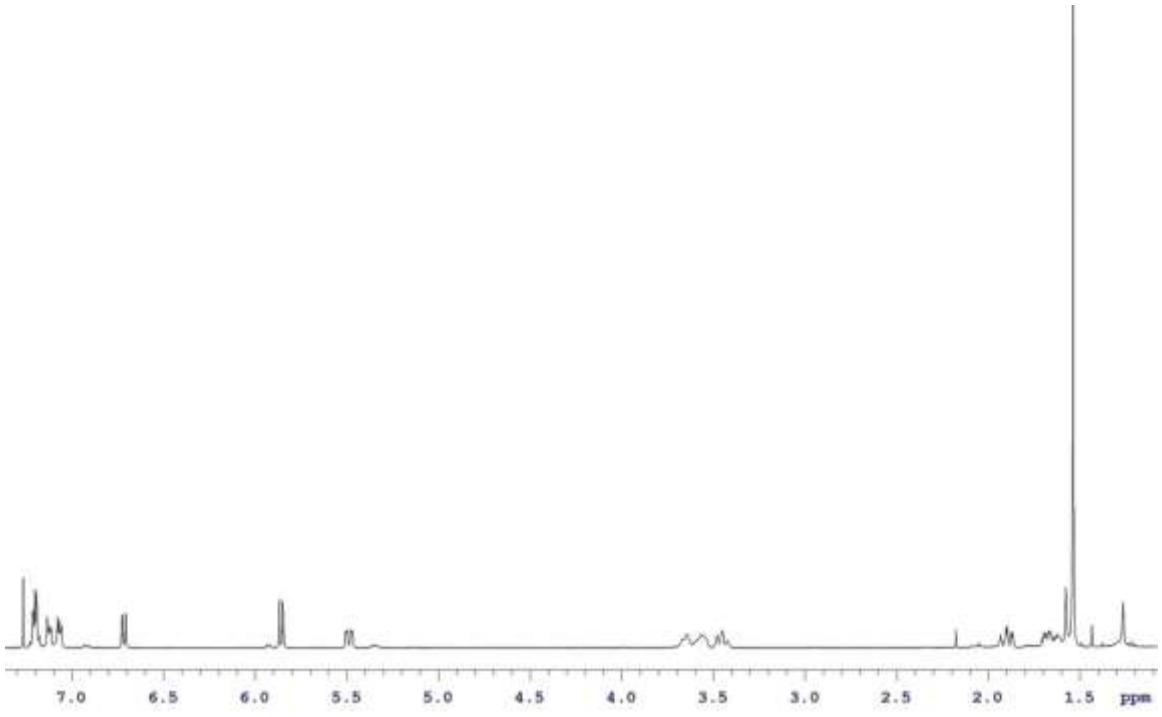
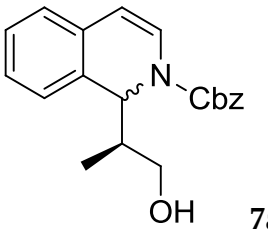
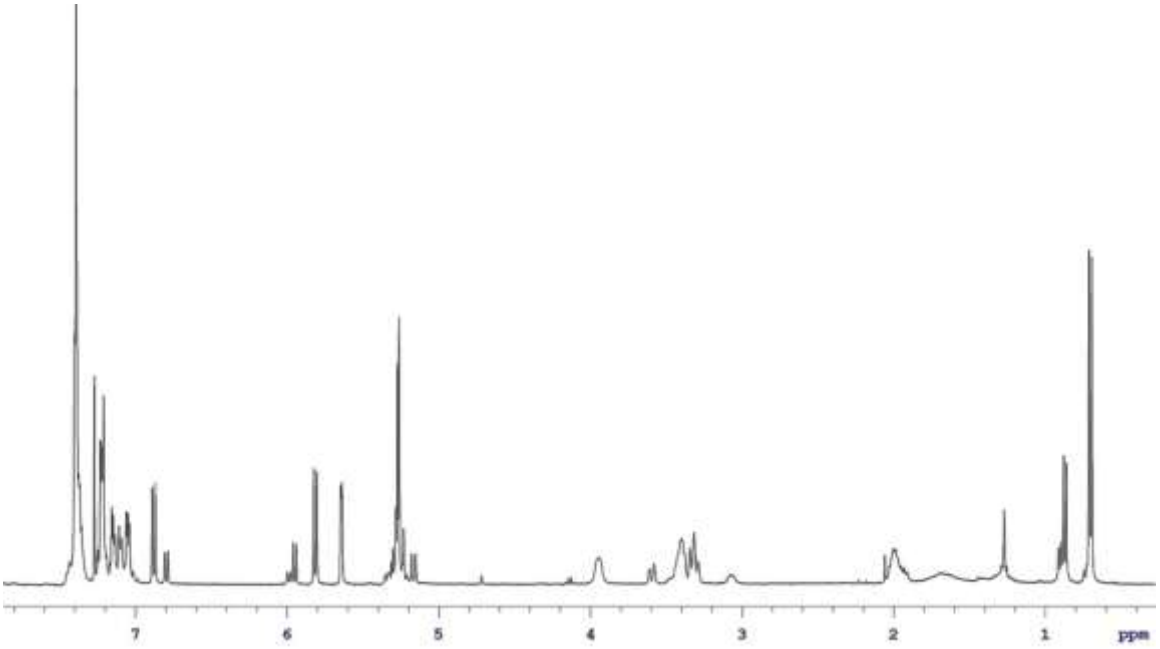


6c




N
Cbz
OH

7a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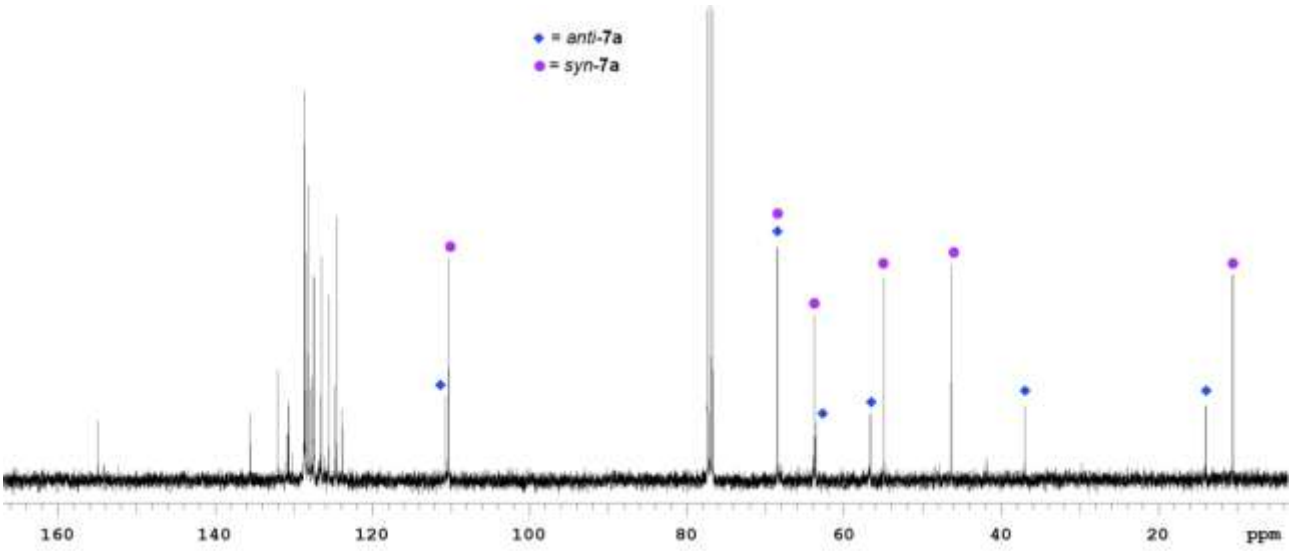
3
2
1
ppm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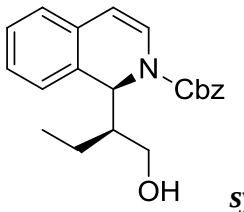
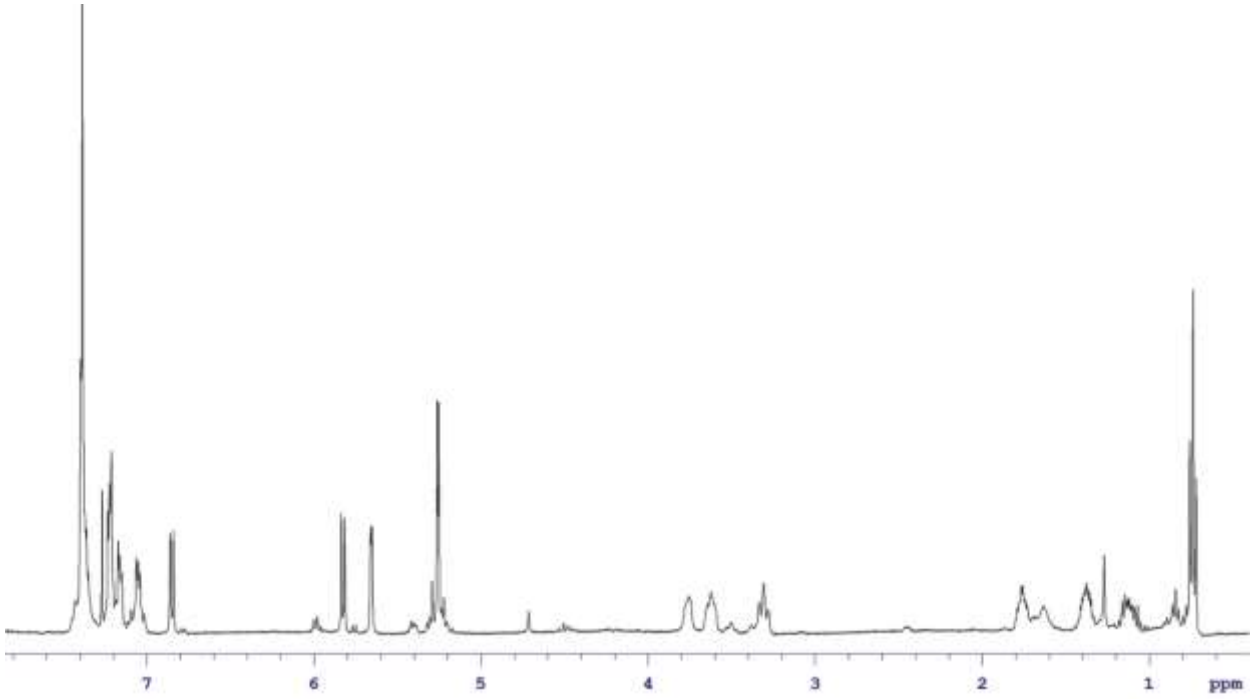
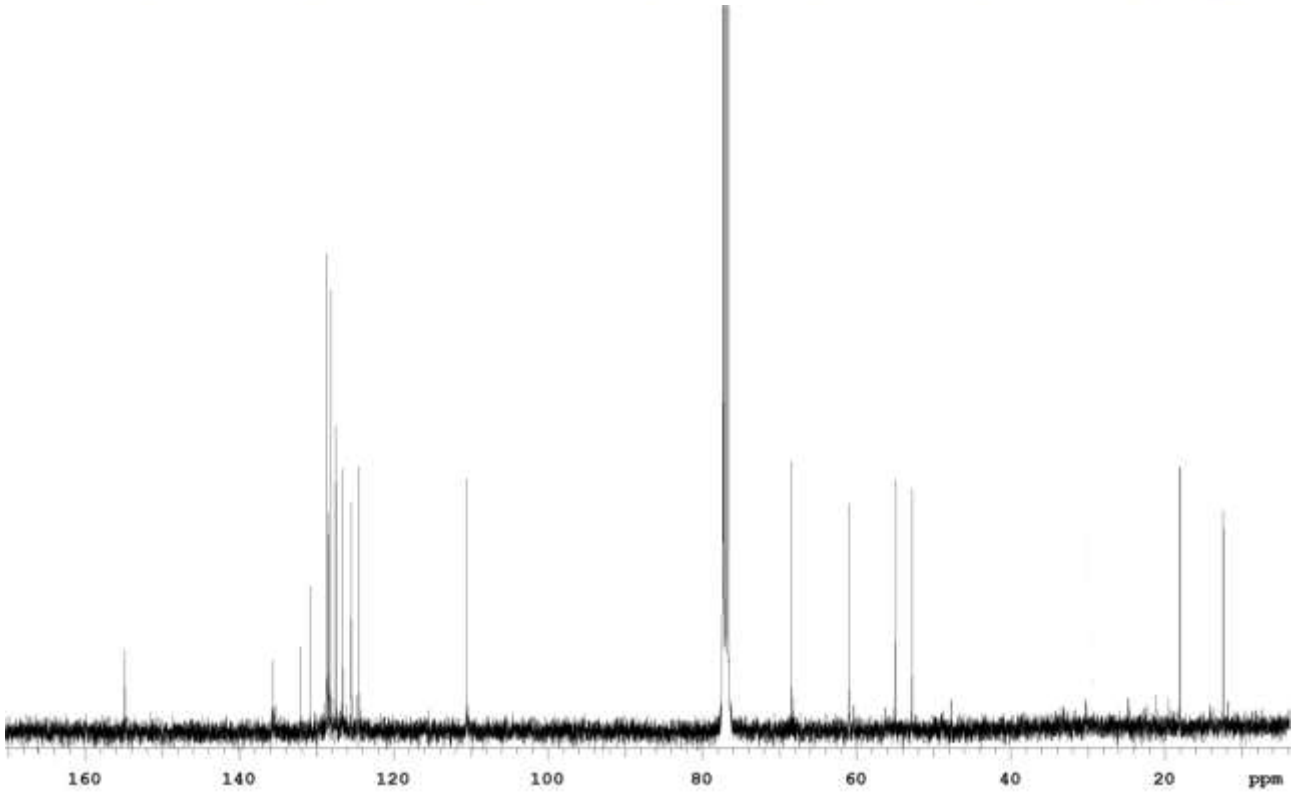
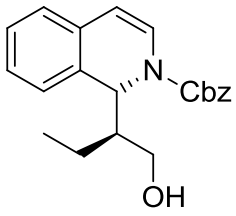


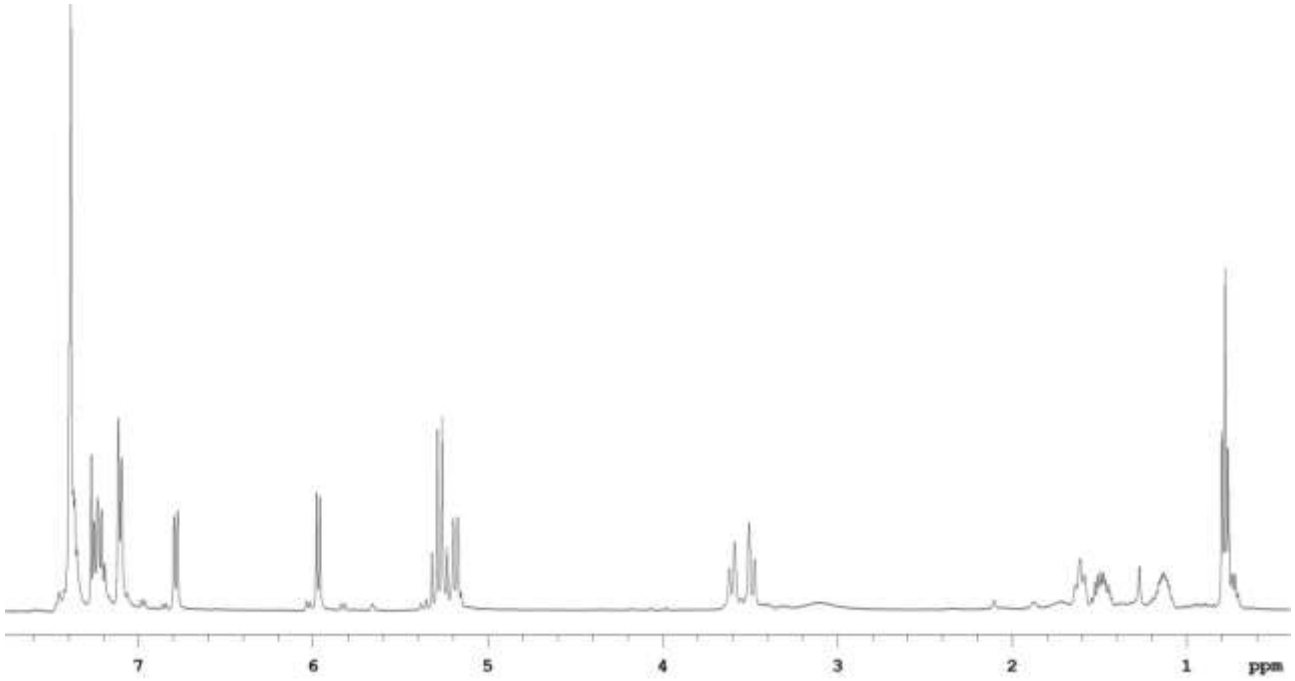
***syn*-7b**






N
Cbz
OH

***anti*-7b**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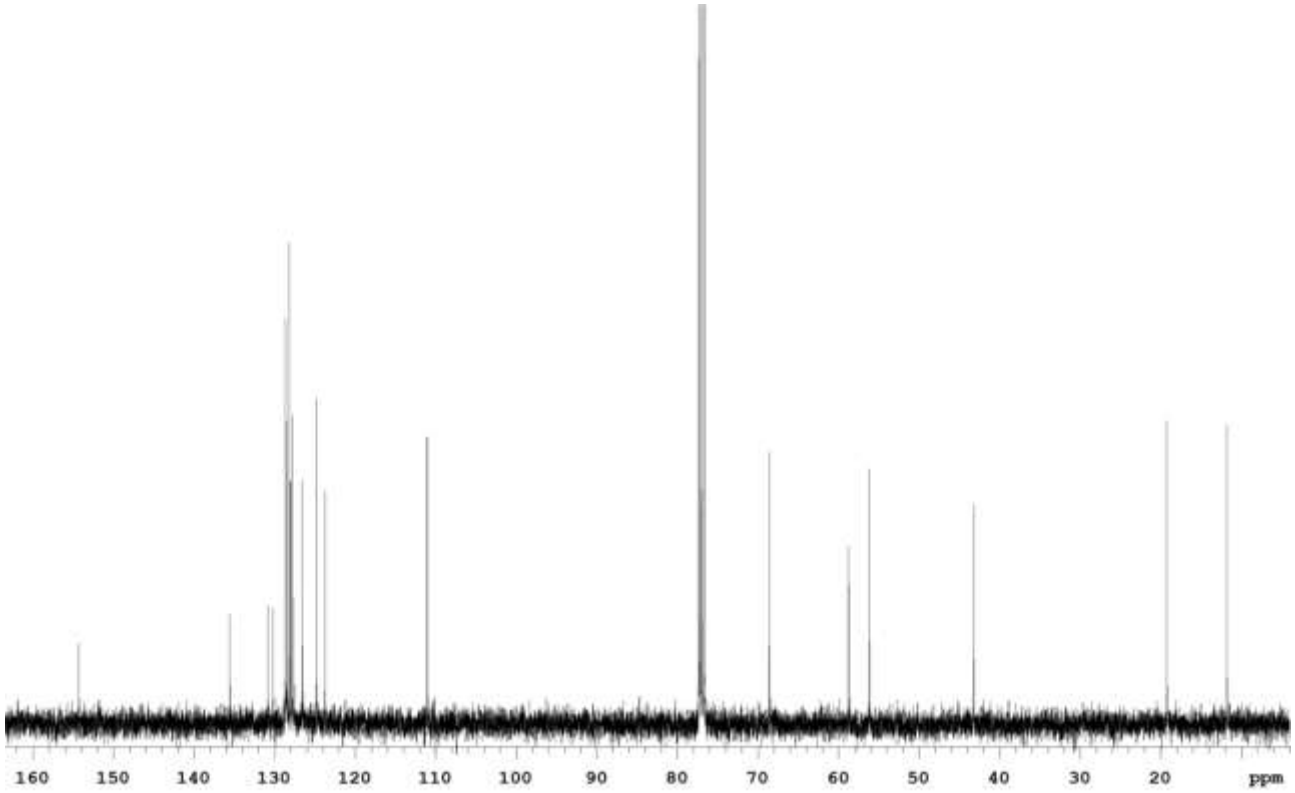
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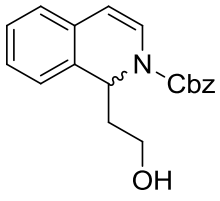

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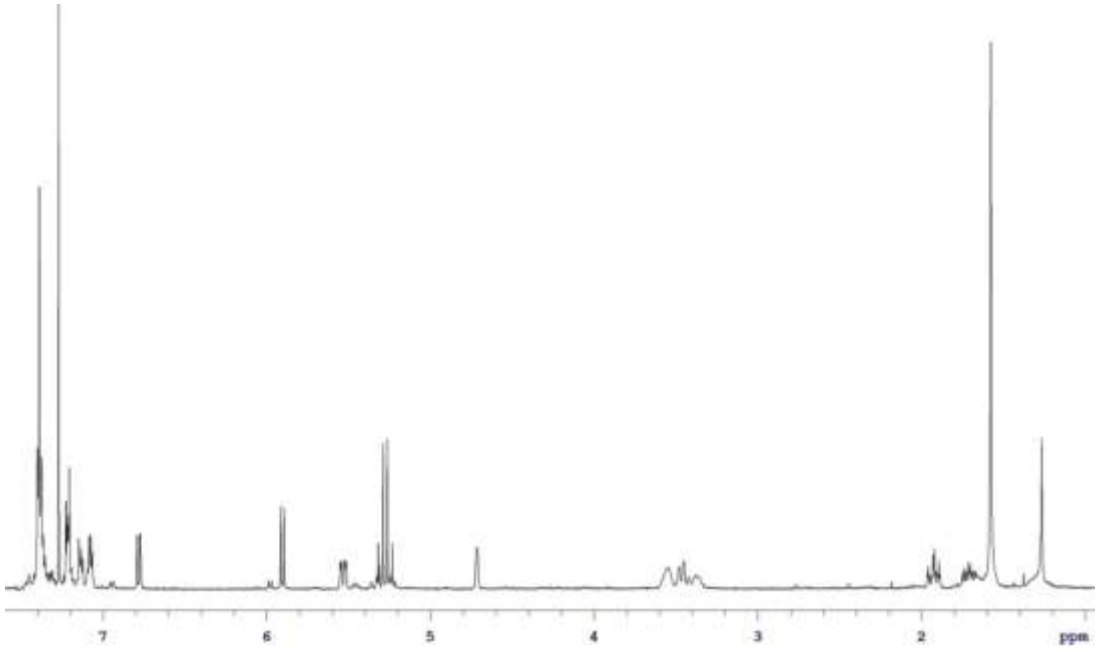

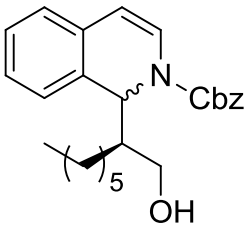
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Cbz
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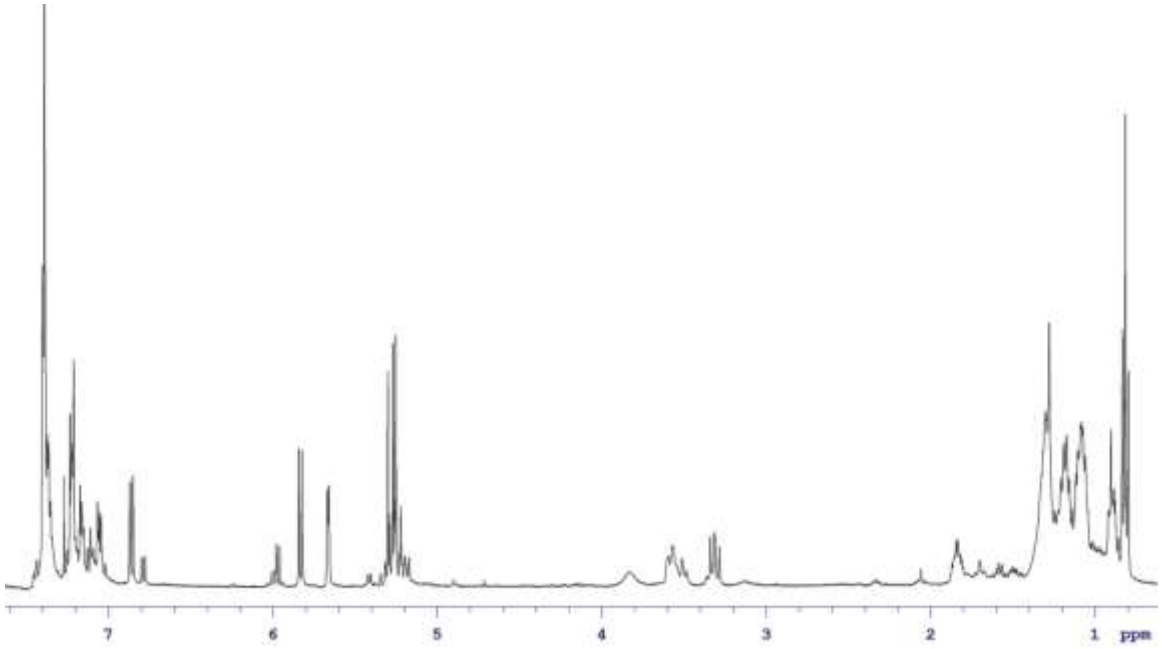
OH

7d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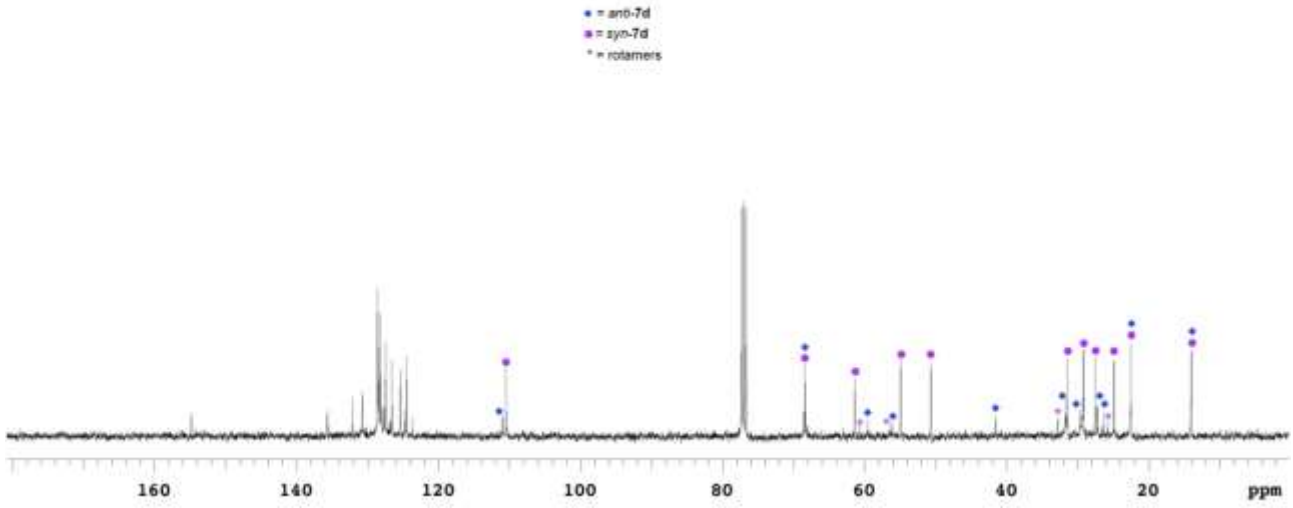
1
ppm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* = rotamers
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80
60
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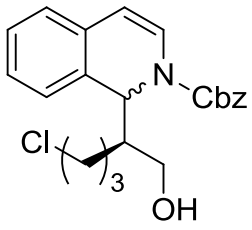
20
ppm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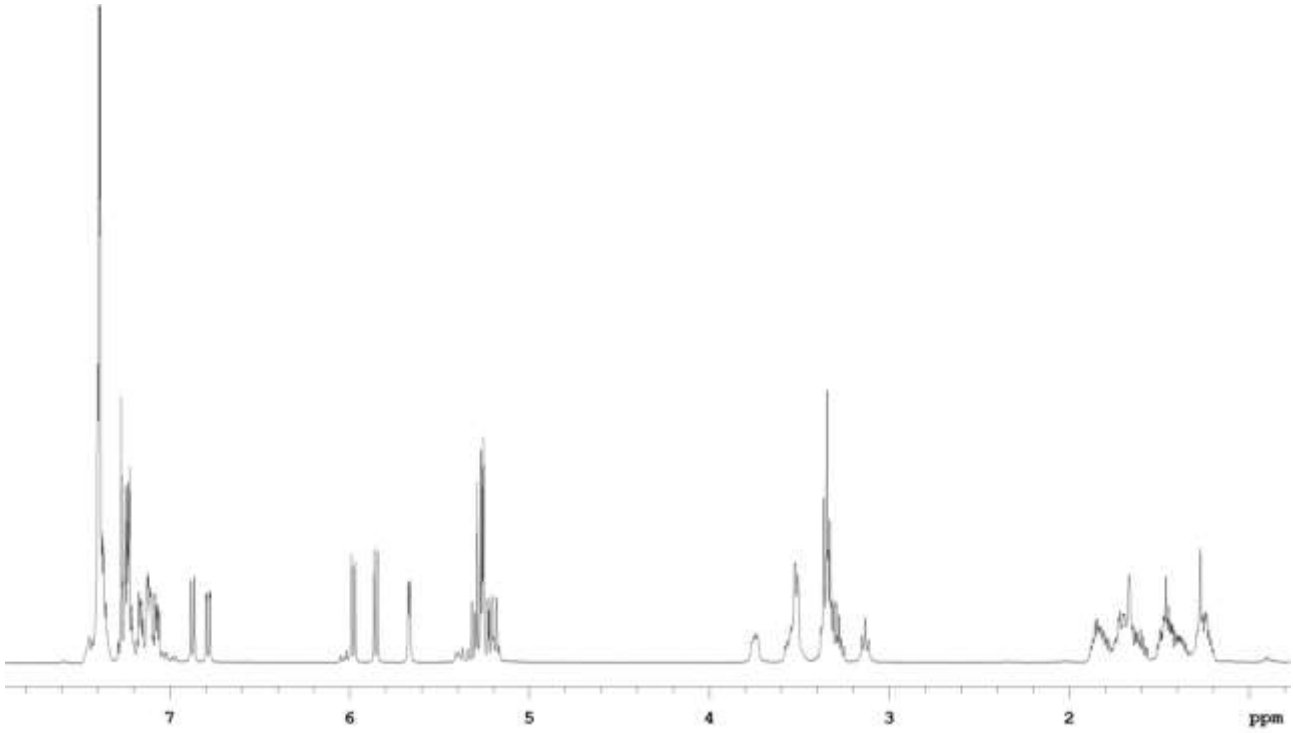
Cbz
Cl
3
OH

7e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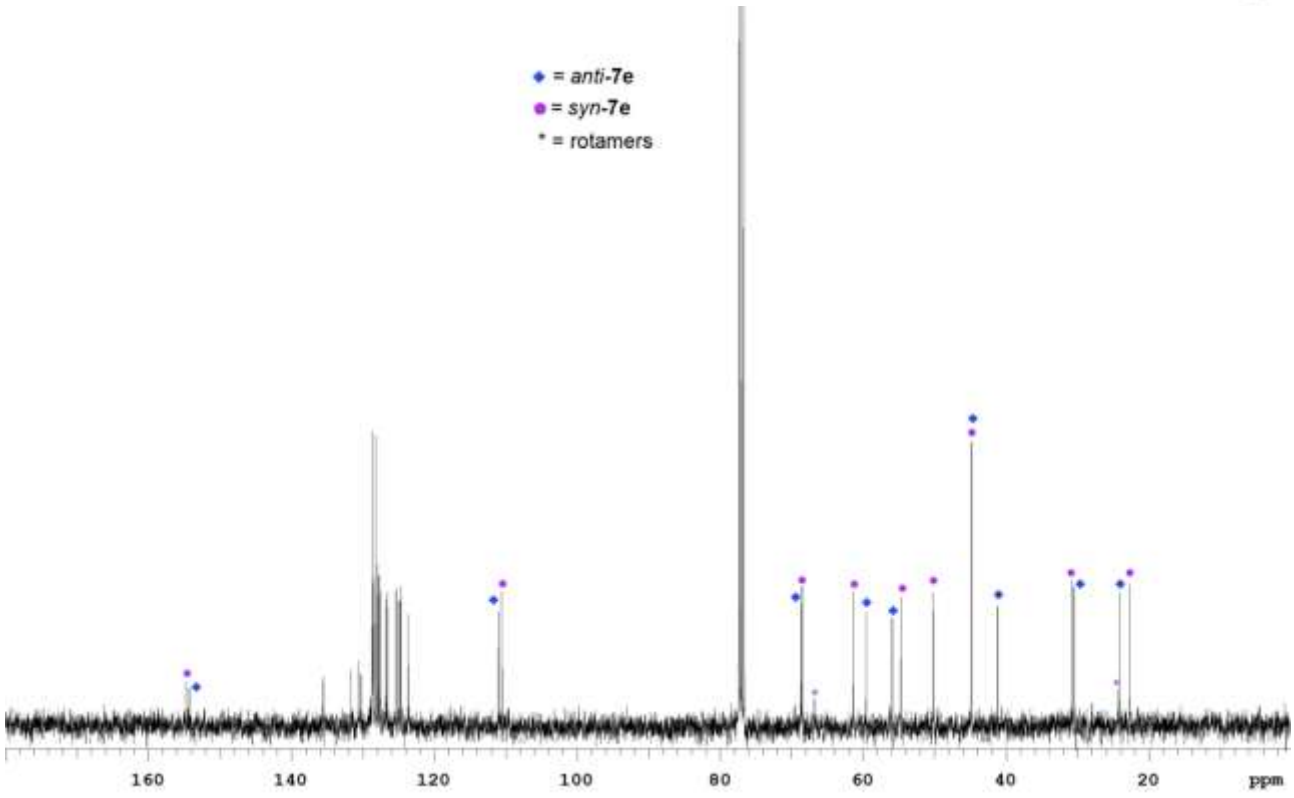
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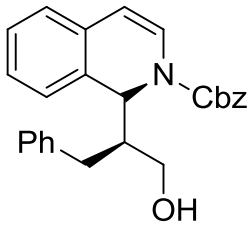
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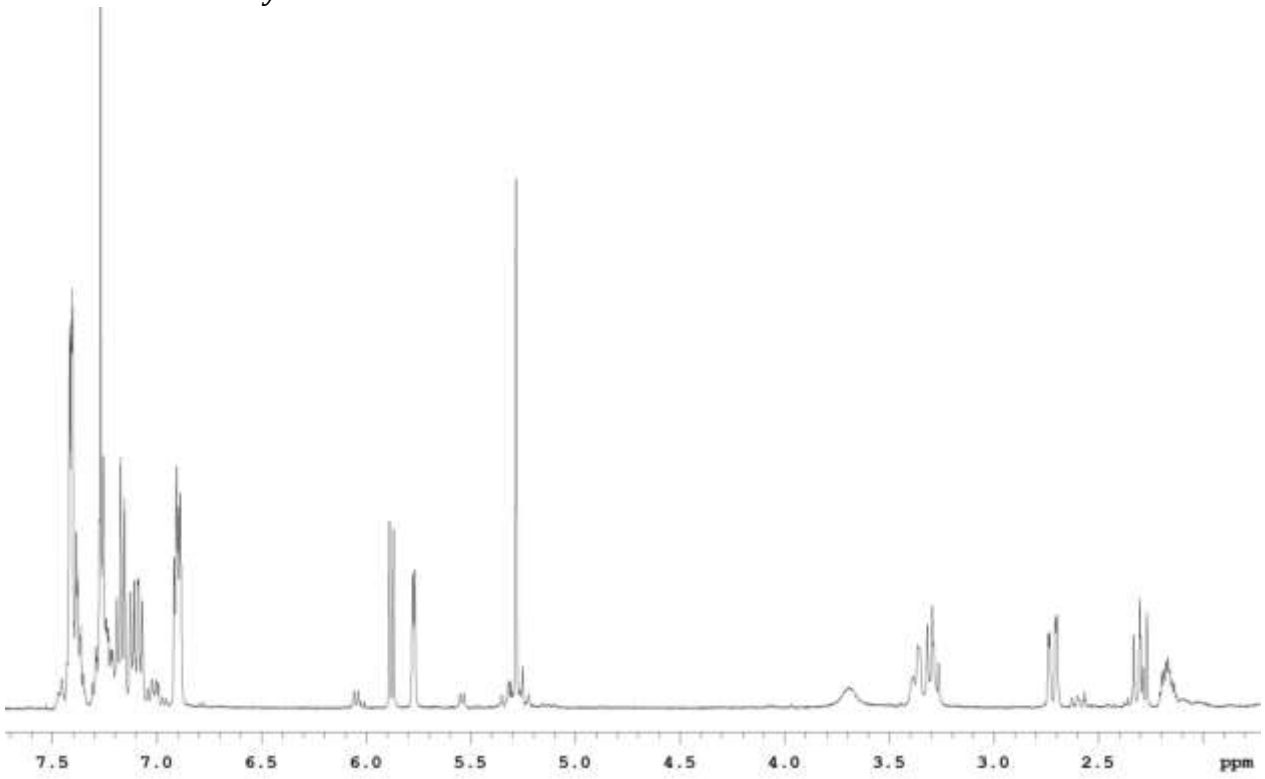
Cbz
Ph
OH

***syn*-7f**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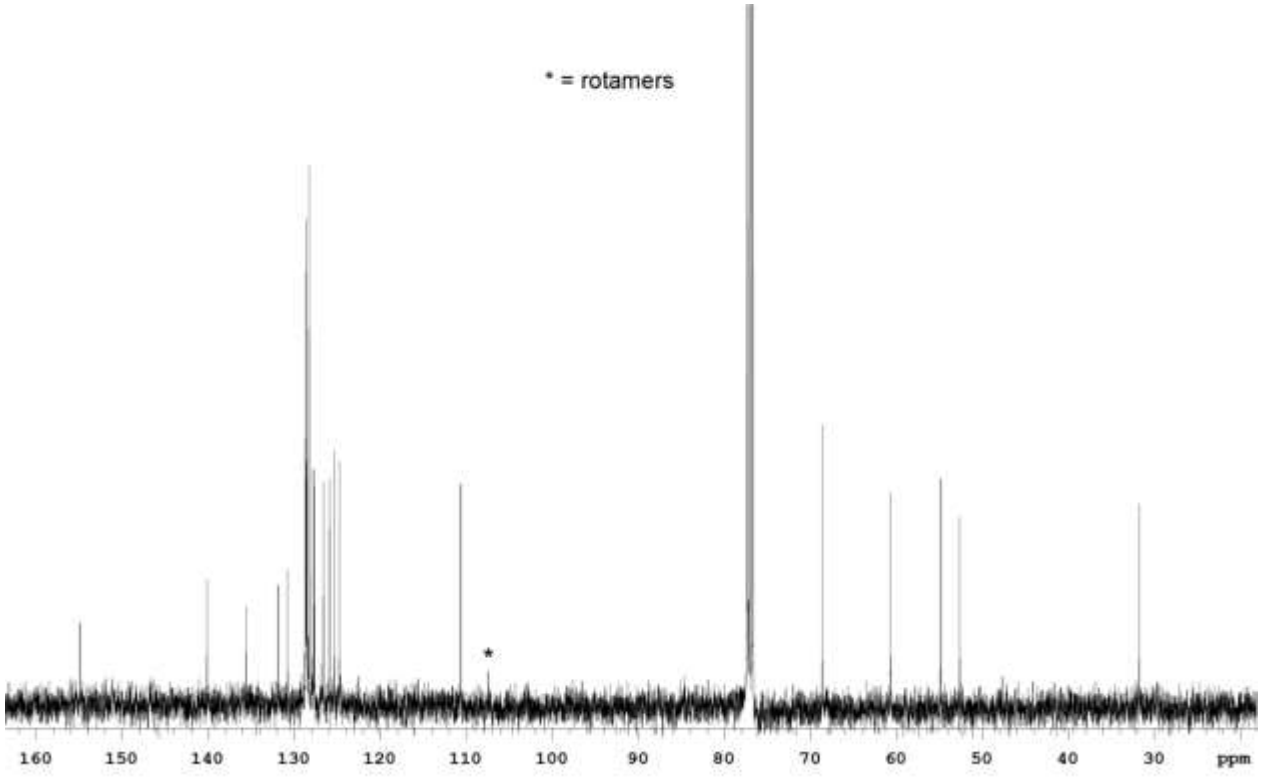
4.5
4.0
3.5
3.0
2.5
ppm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30
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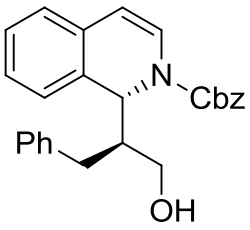
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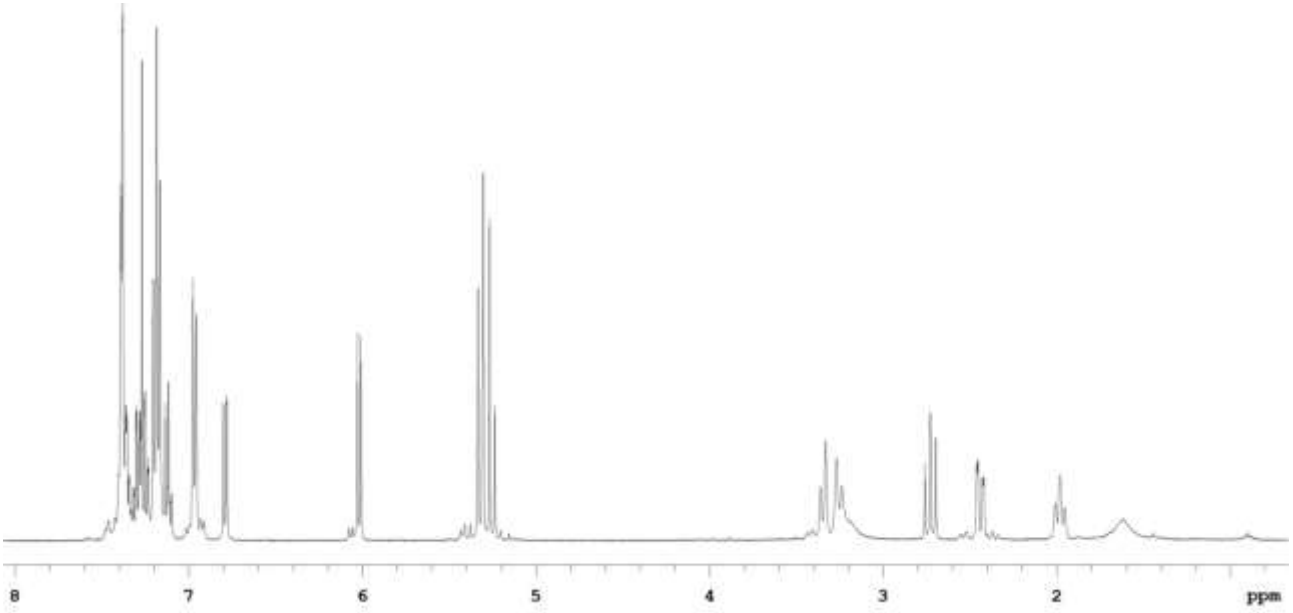
Cbz
Ph
OH

***anti*-7f**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2
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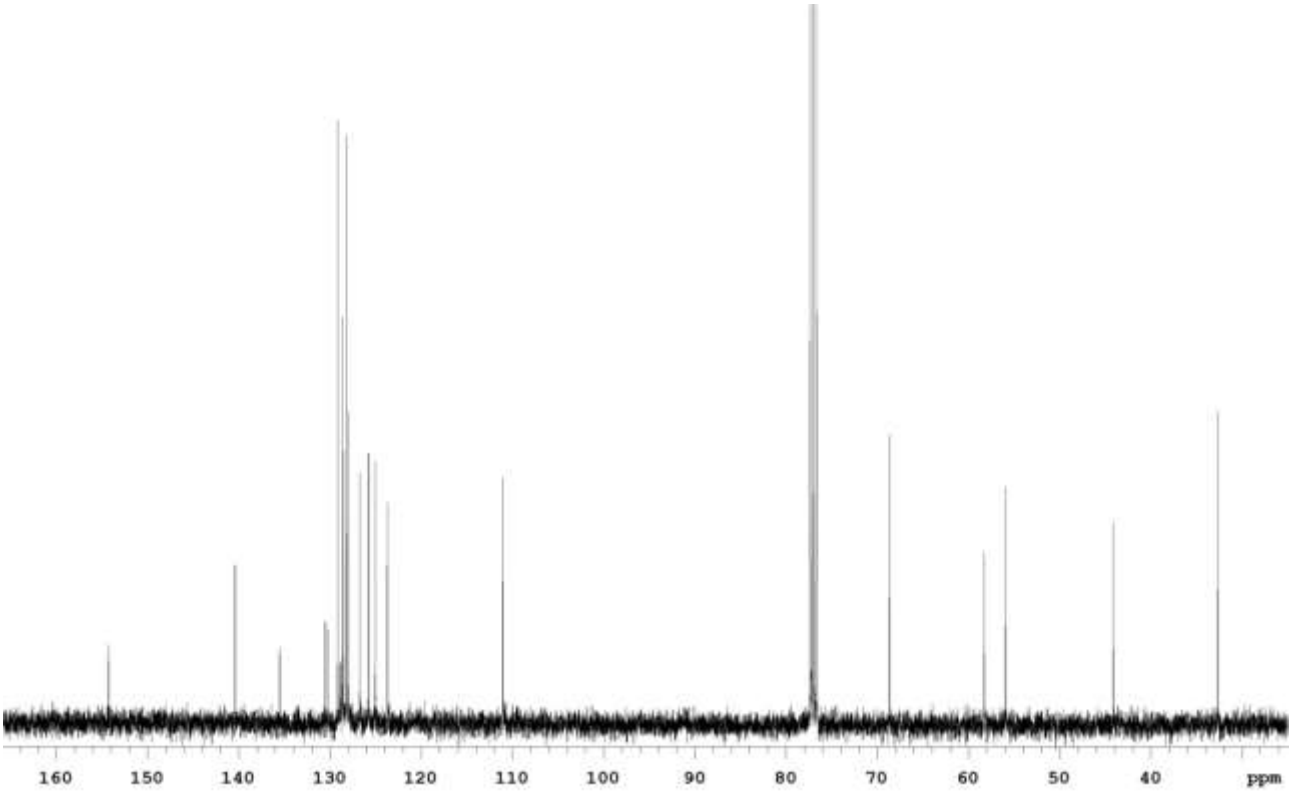
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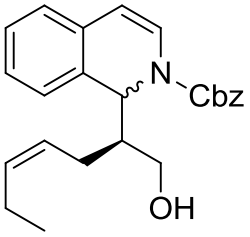
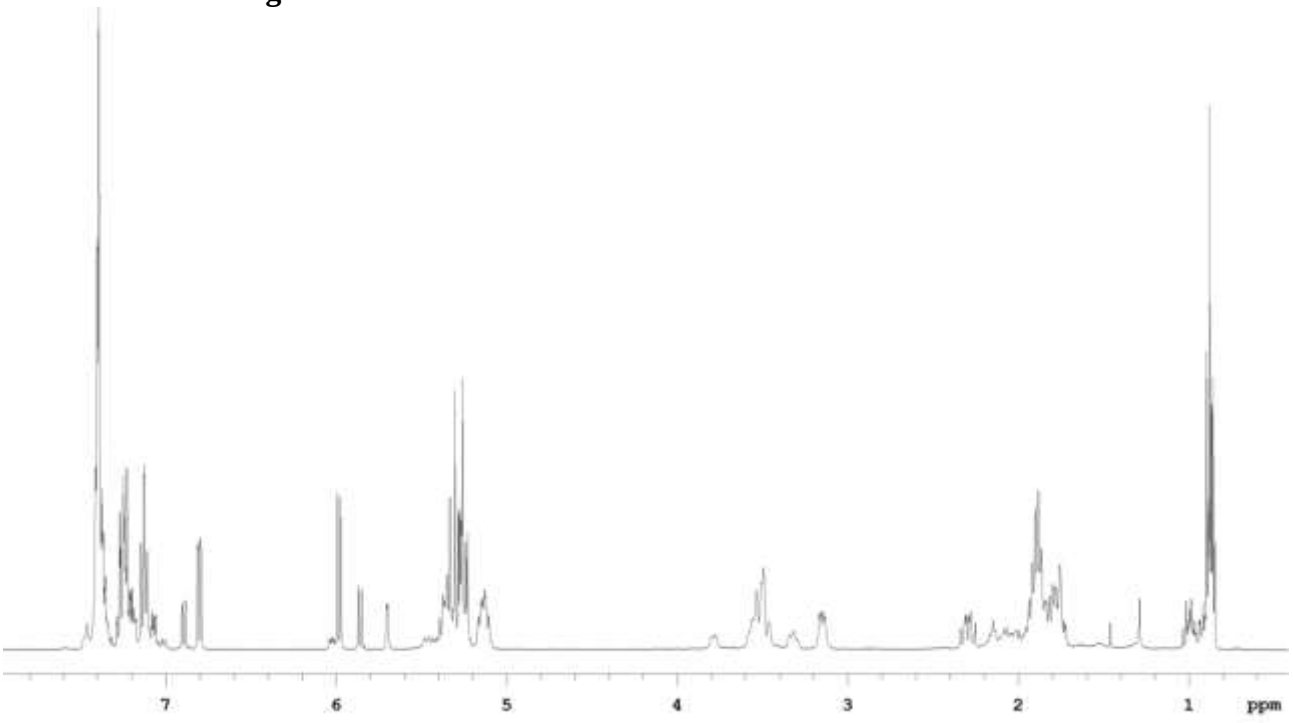

N
Cbz
OH

7g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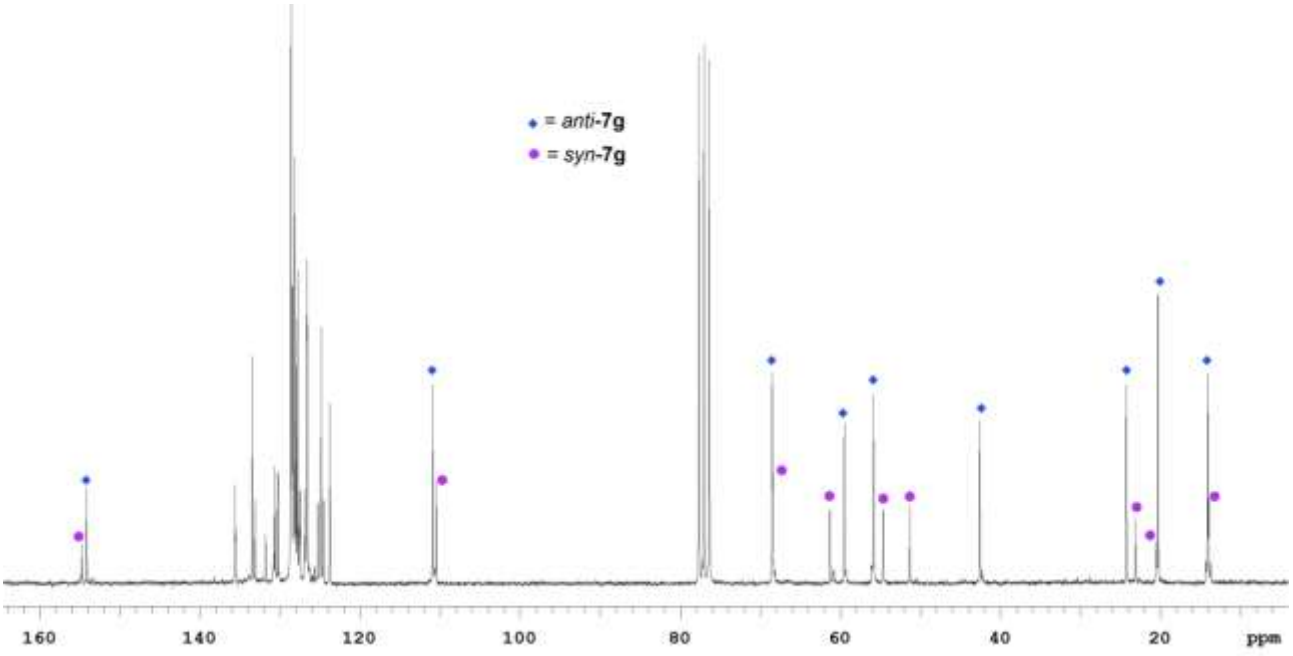
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= syn-7g
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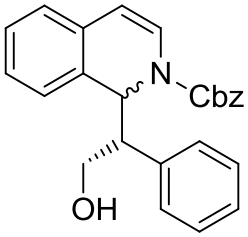
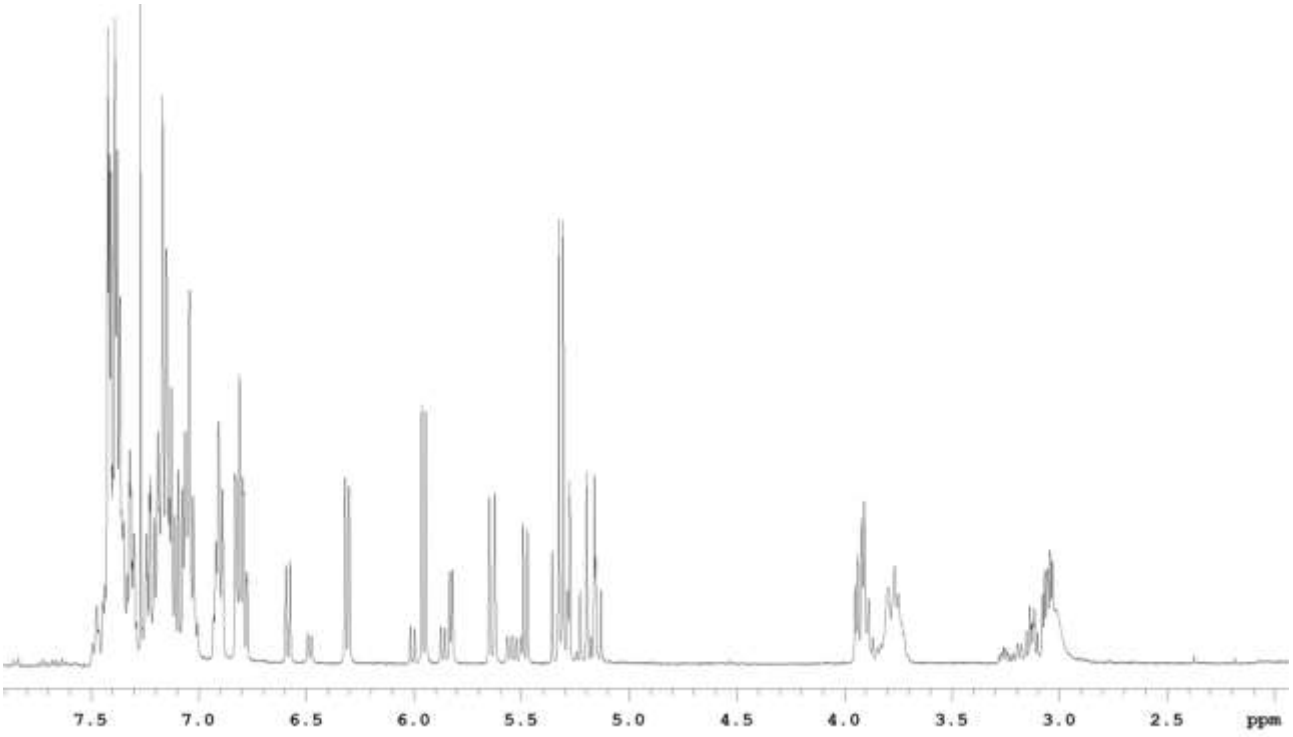

N
Cbz
OH

7h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3.0
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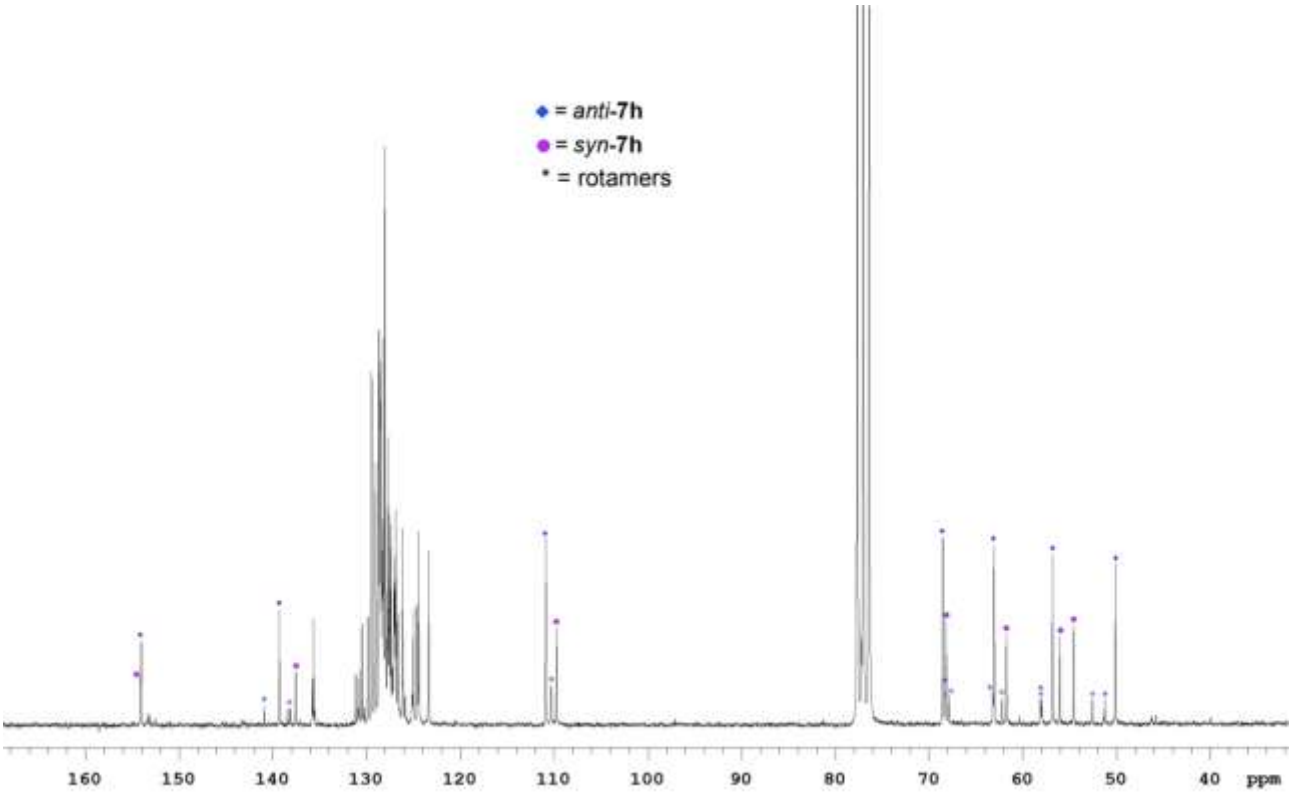
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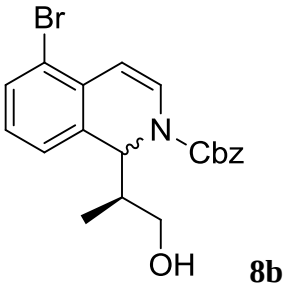
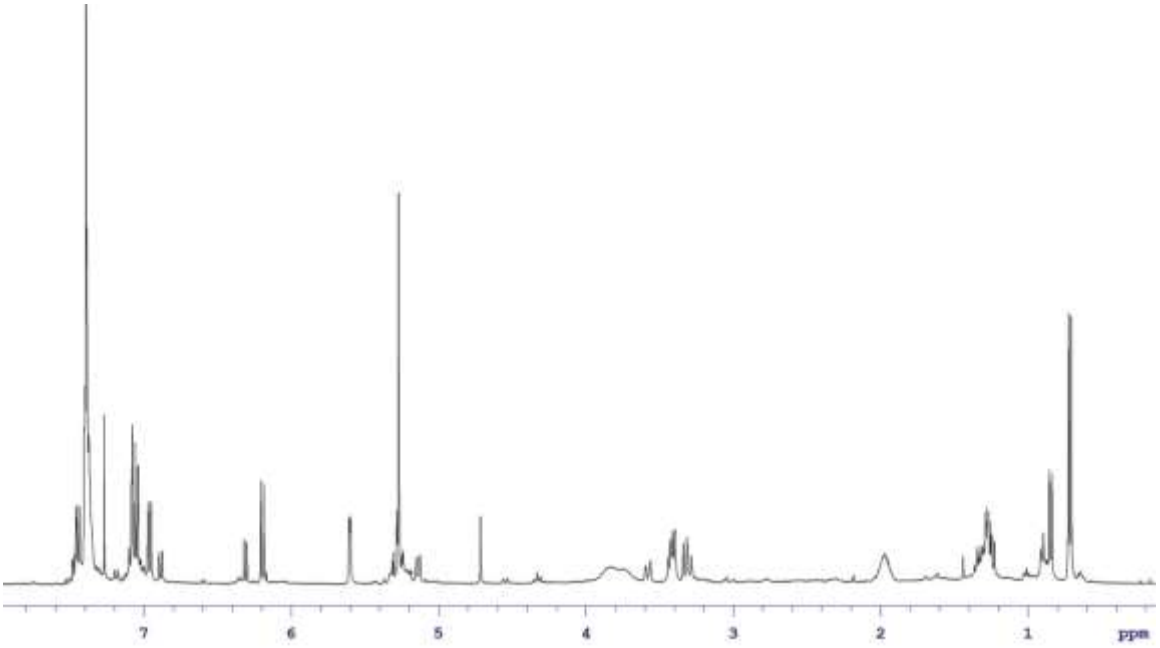
ppm


Br
N
Cbz
OH

8b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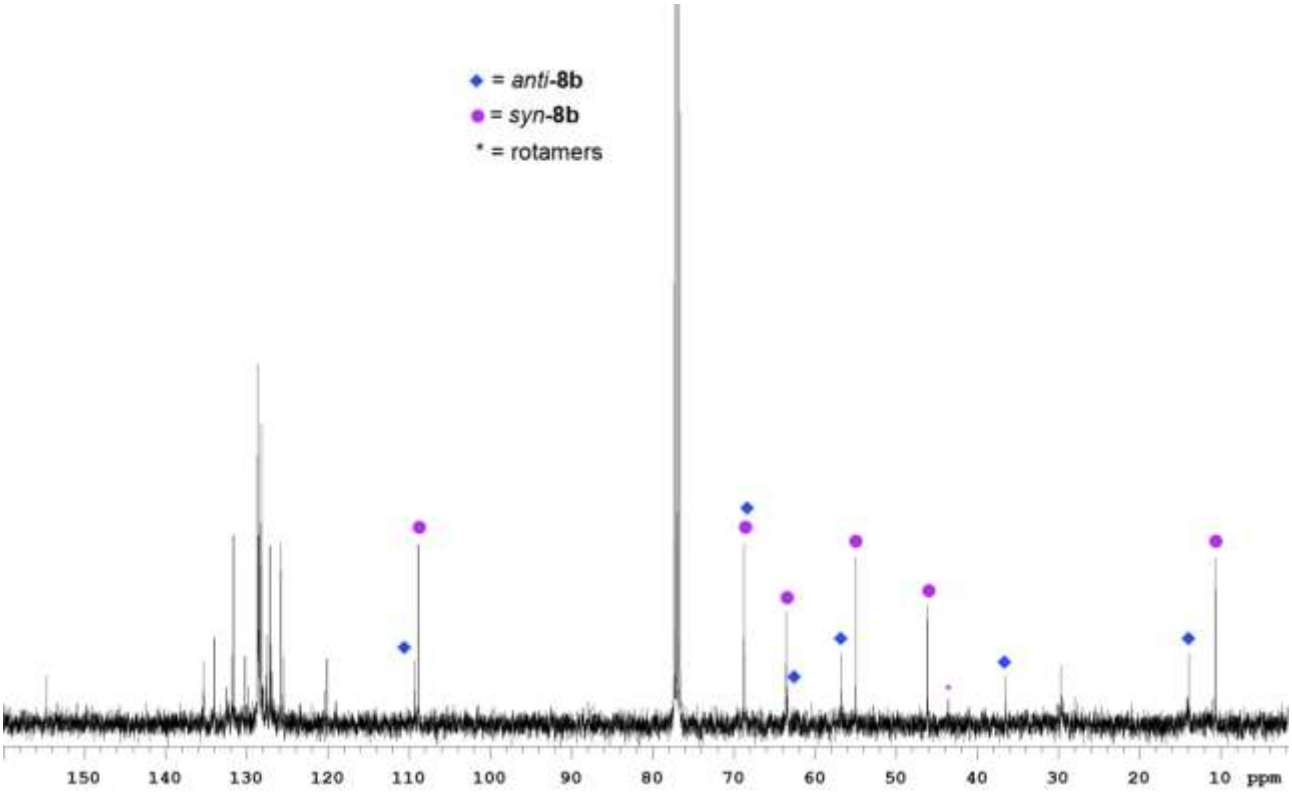
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50
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30
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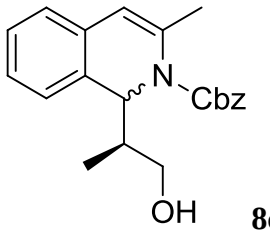
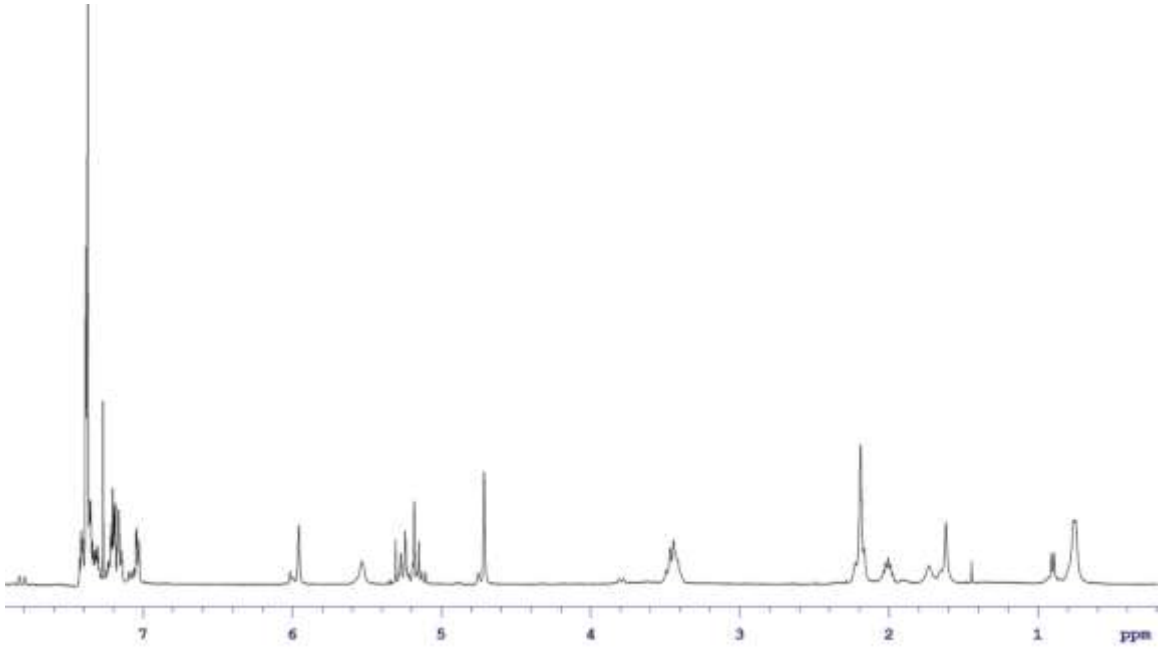
10
ppm


N
Cbz
OH

8c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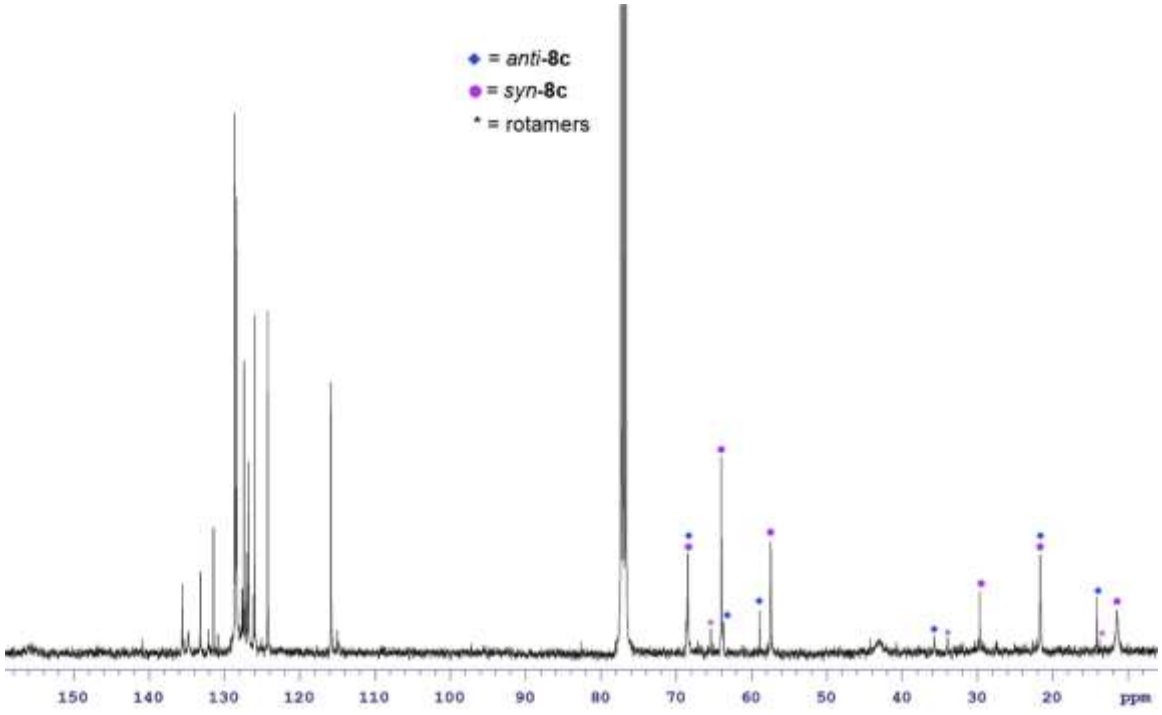
ppm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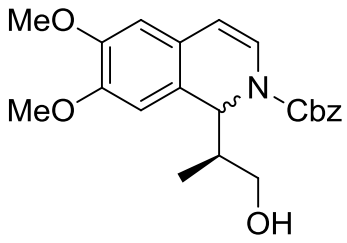
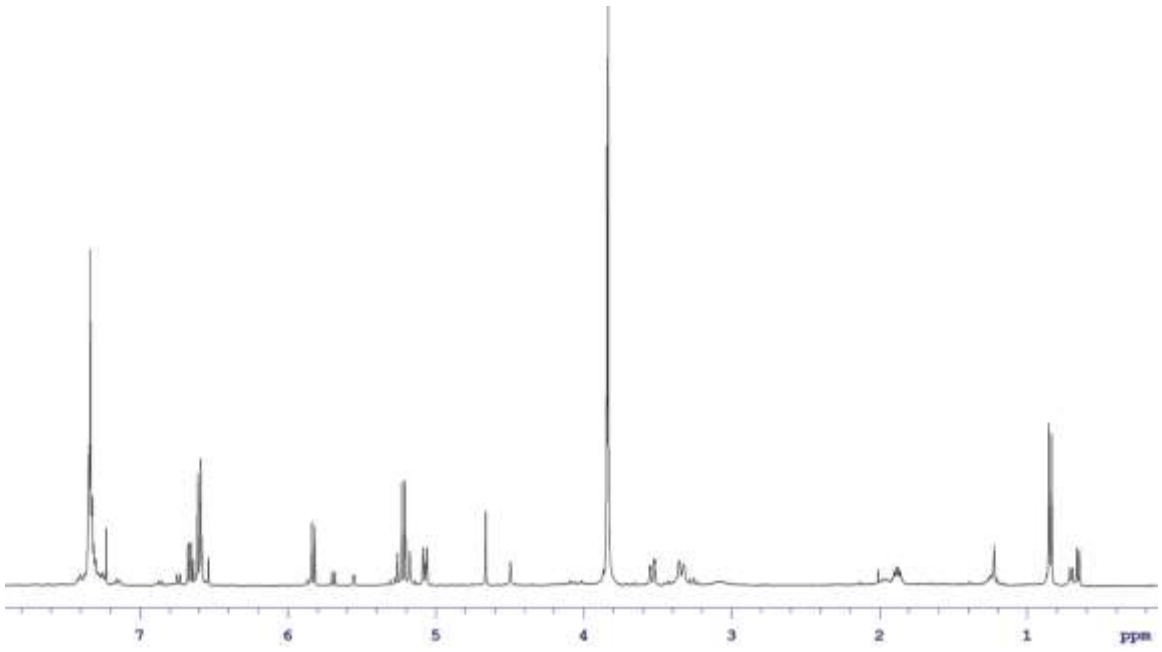
ppm


MeO
MeO
N
Cbz
OH

8d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3
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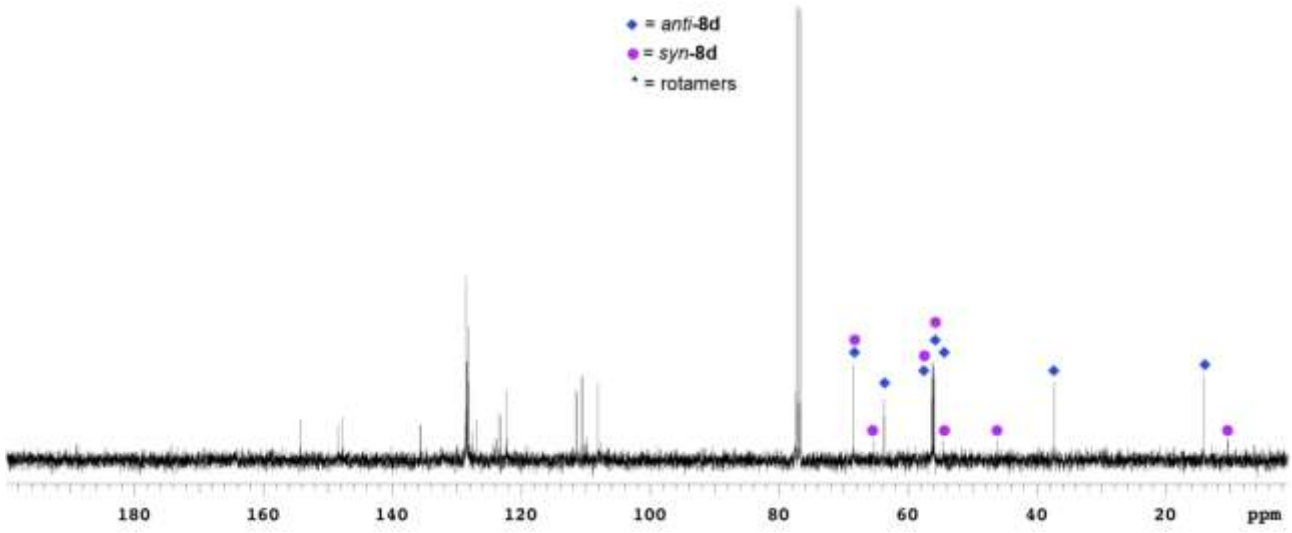
ppm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80
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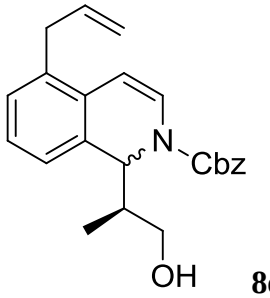
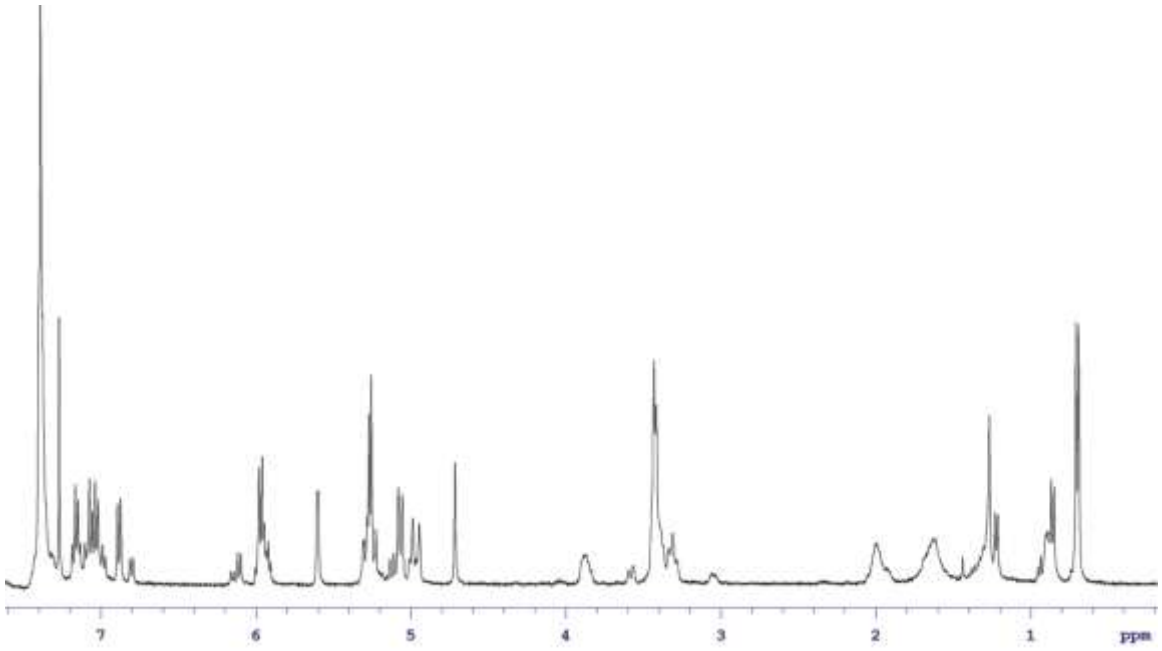
20
ppm


N
Cbz
OH

8e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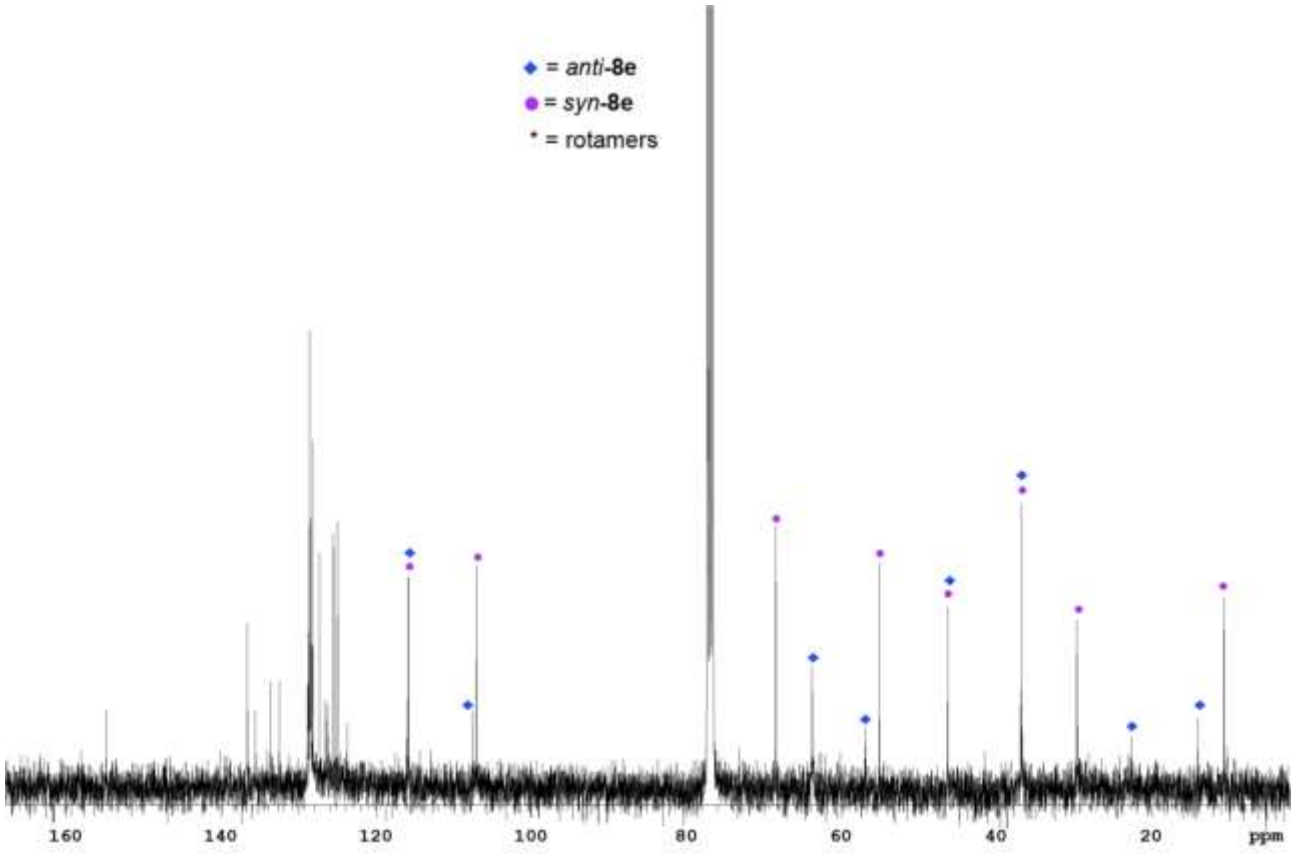
ppm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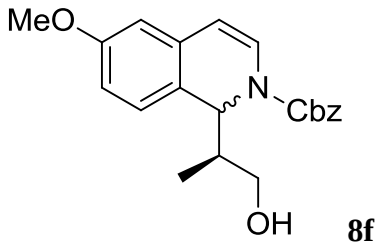
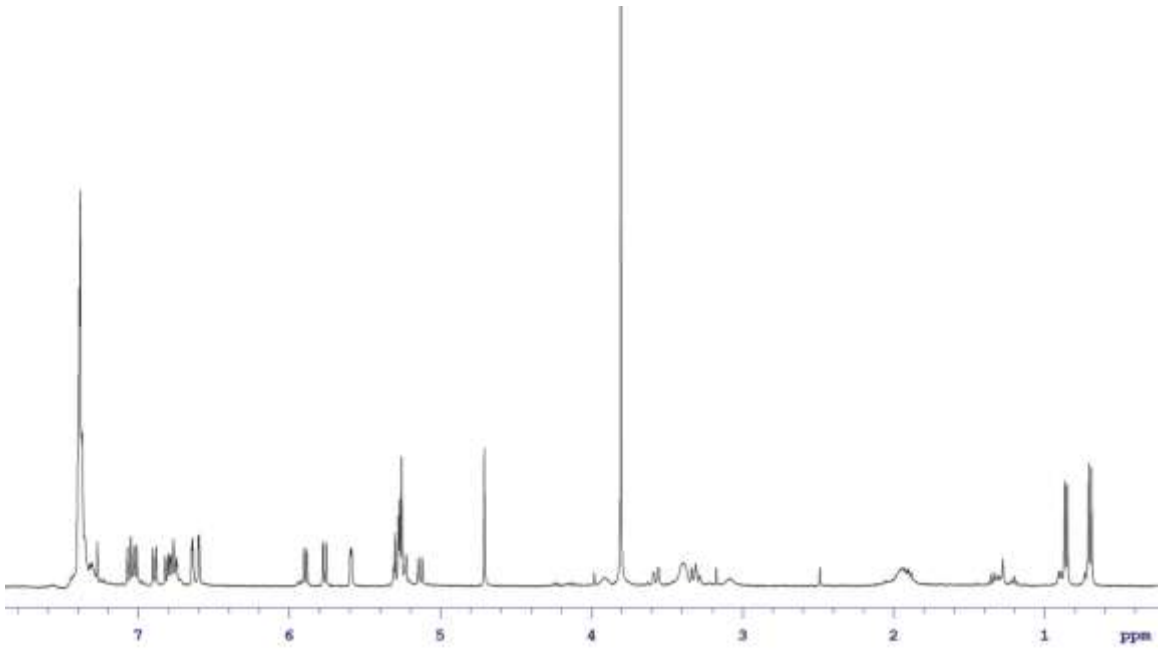
60
40
20
ppm


MeO
N
Cbz
OH

8f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4
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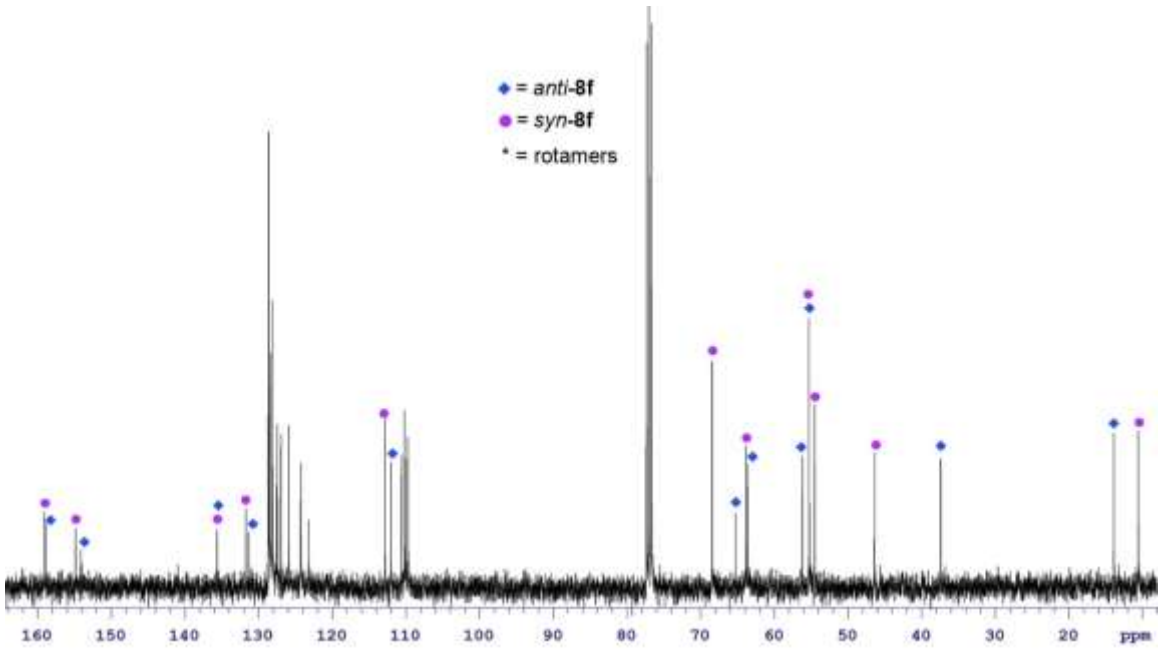
ppm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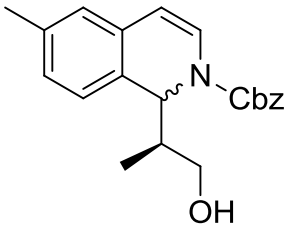
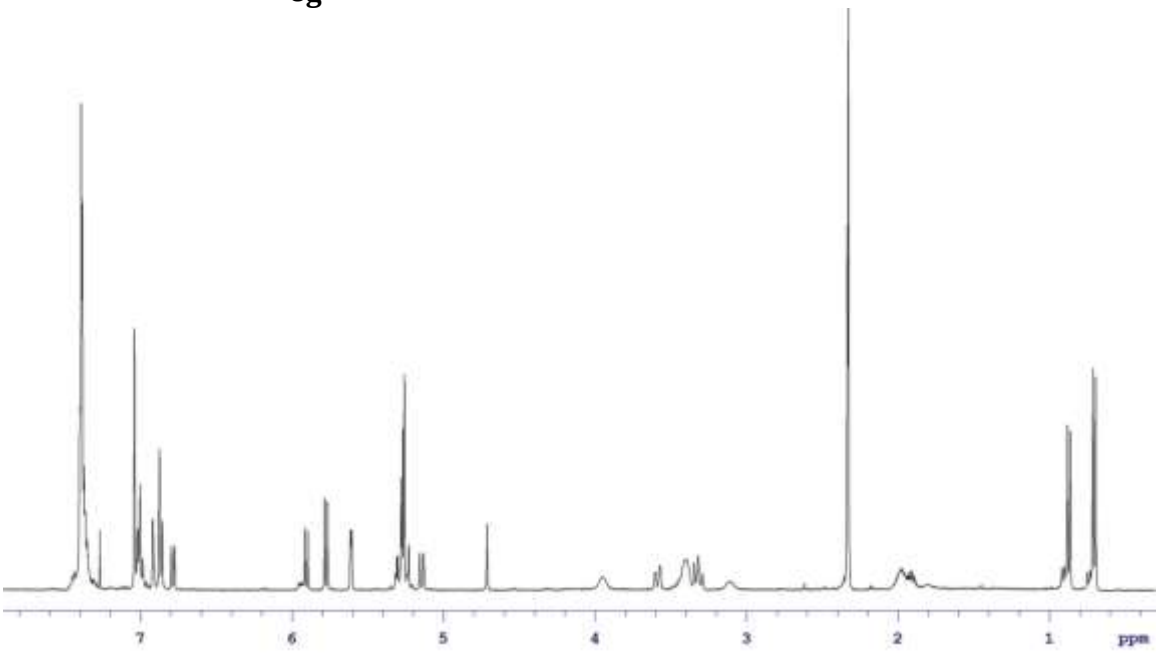
20
ppm


N
Cbz
OH

8g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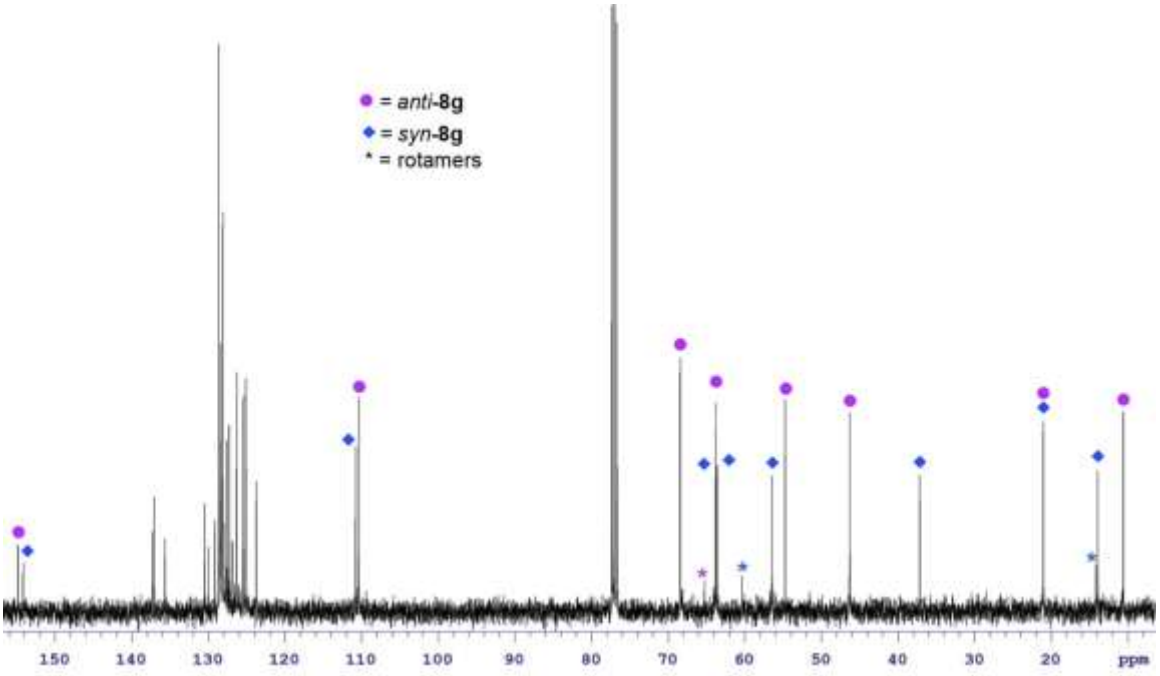
4
3
2
1
ppm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◆ = syn-8g
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120
110
100
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80
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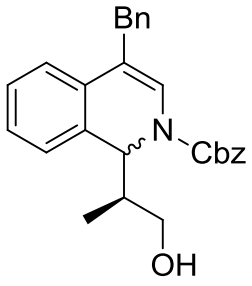
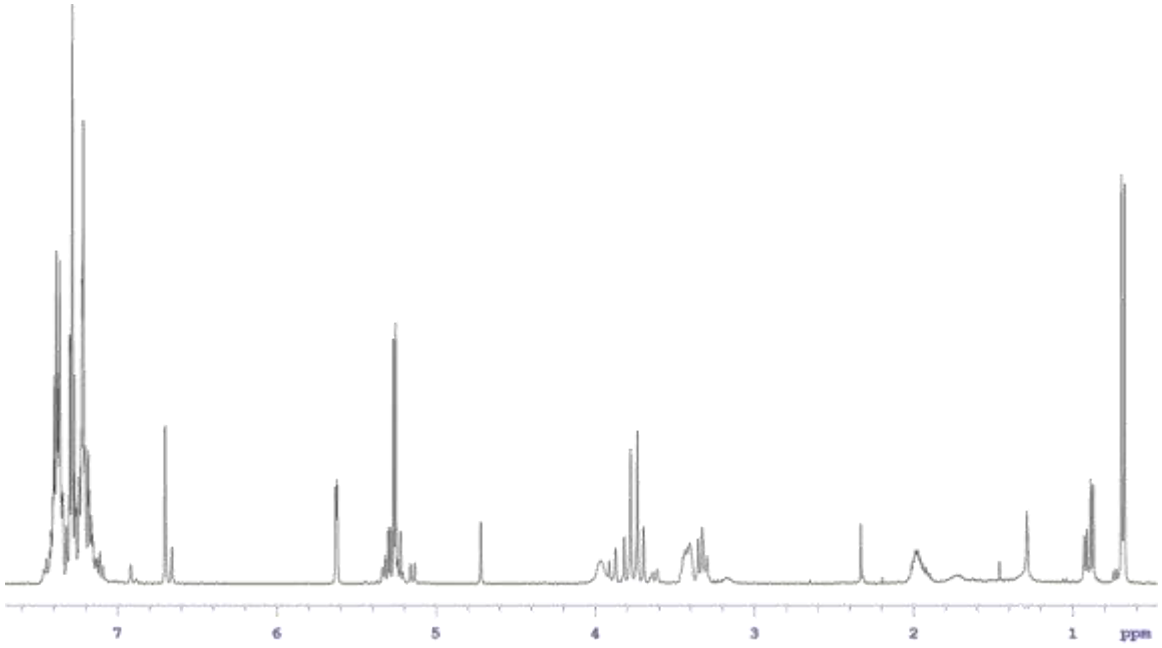
50
40
30
20
ppm


Bn
N
Cbz
OH

8i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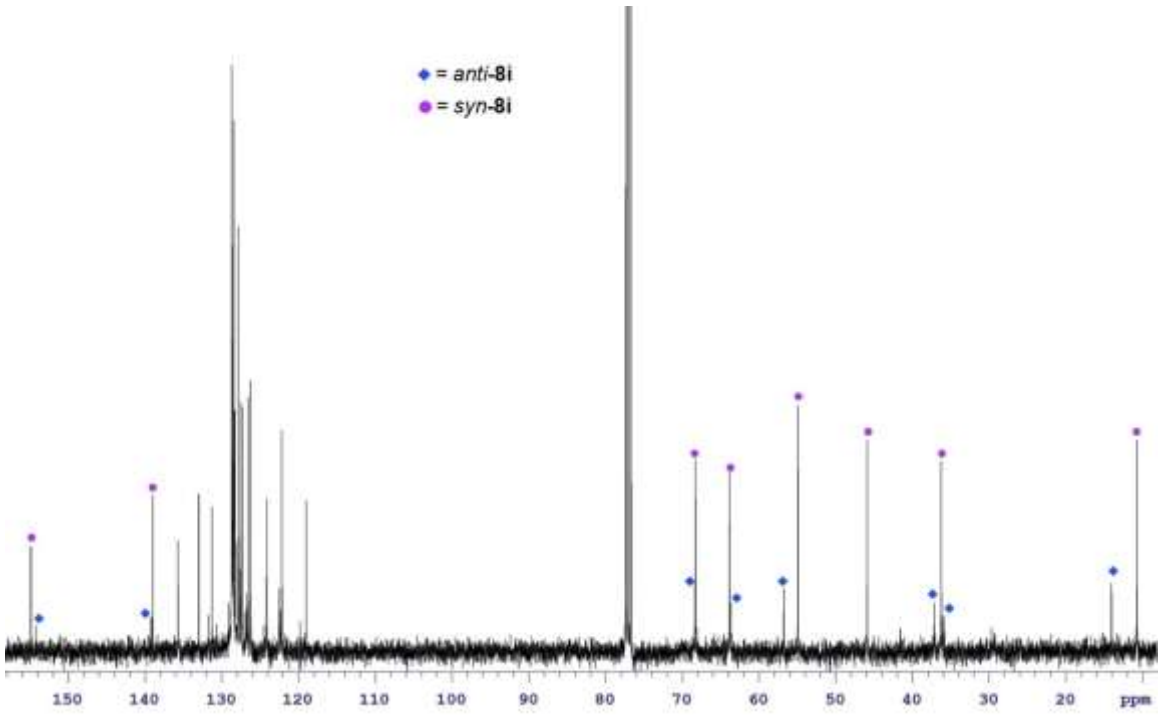
4
3
2
1
ppm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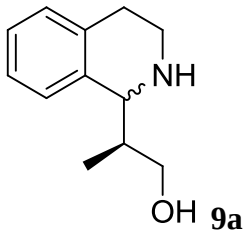
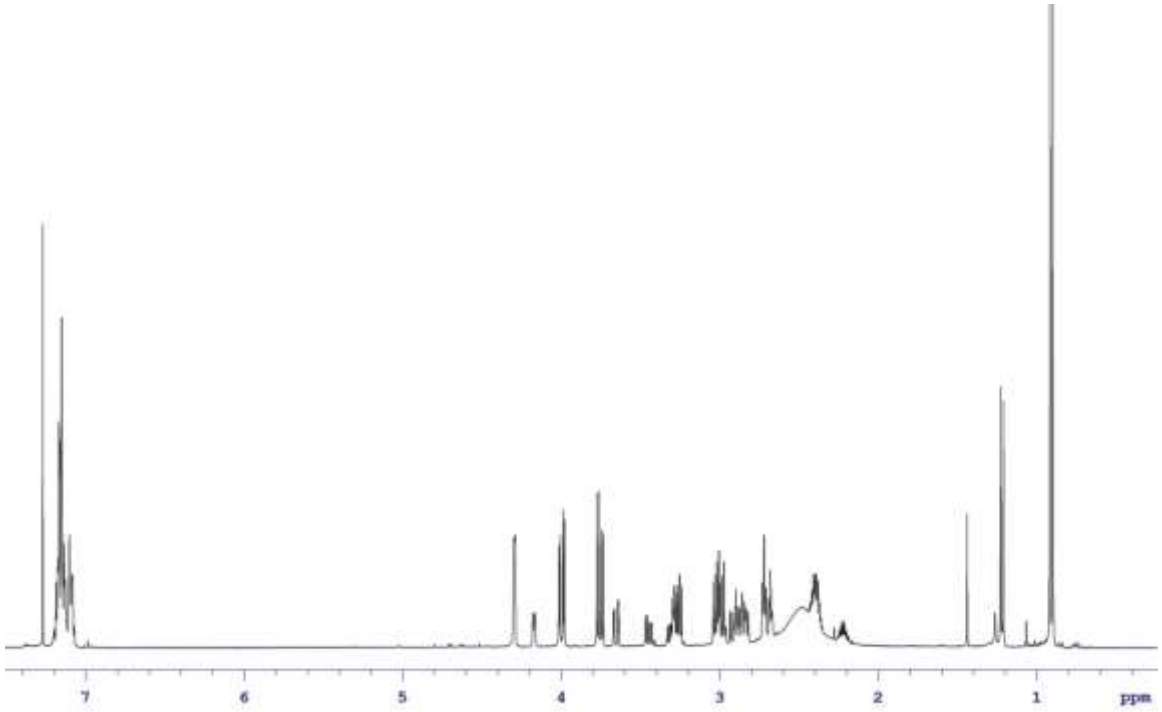
ppm


NH
OH

9a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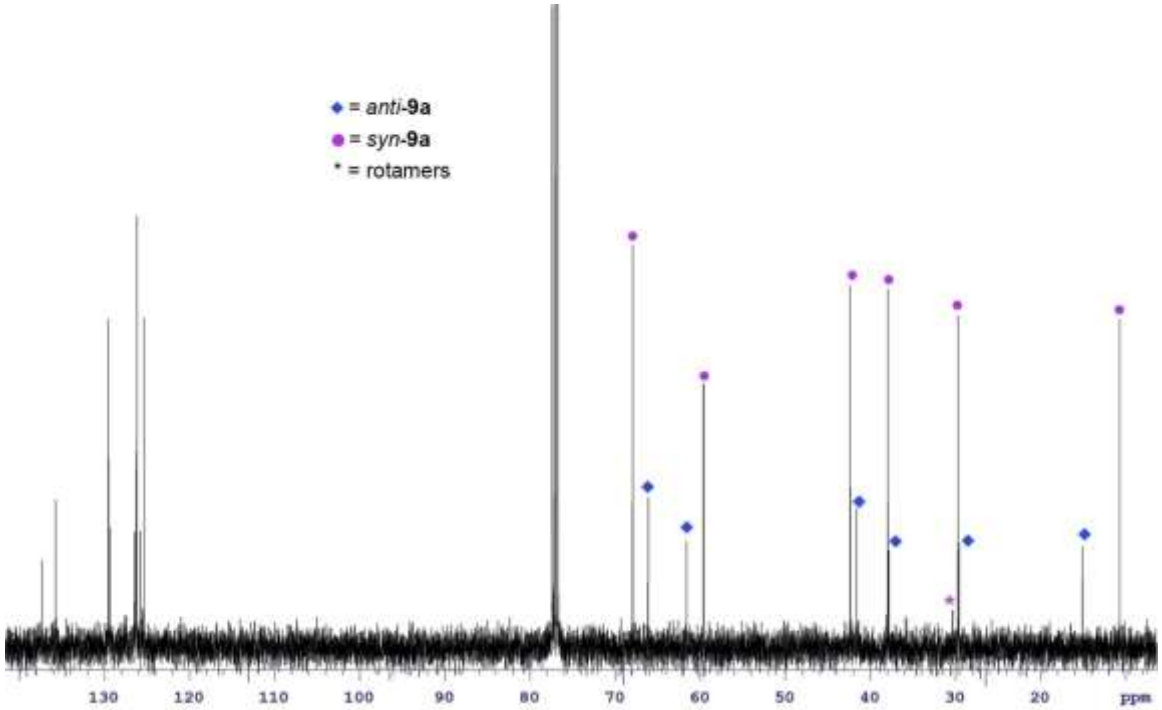
4
3
2
1
ppm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* = rotamers
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120
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100
90
80
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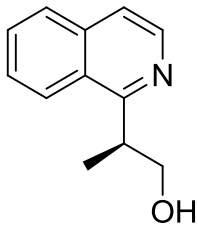
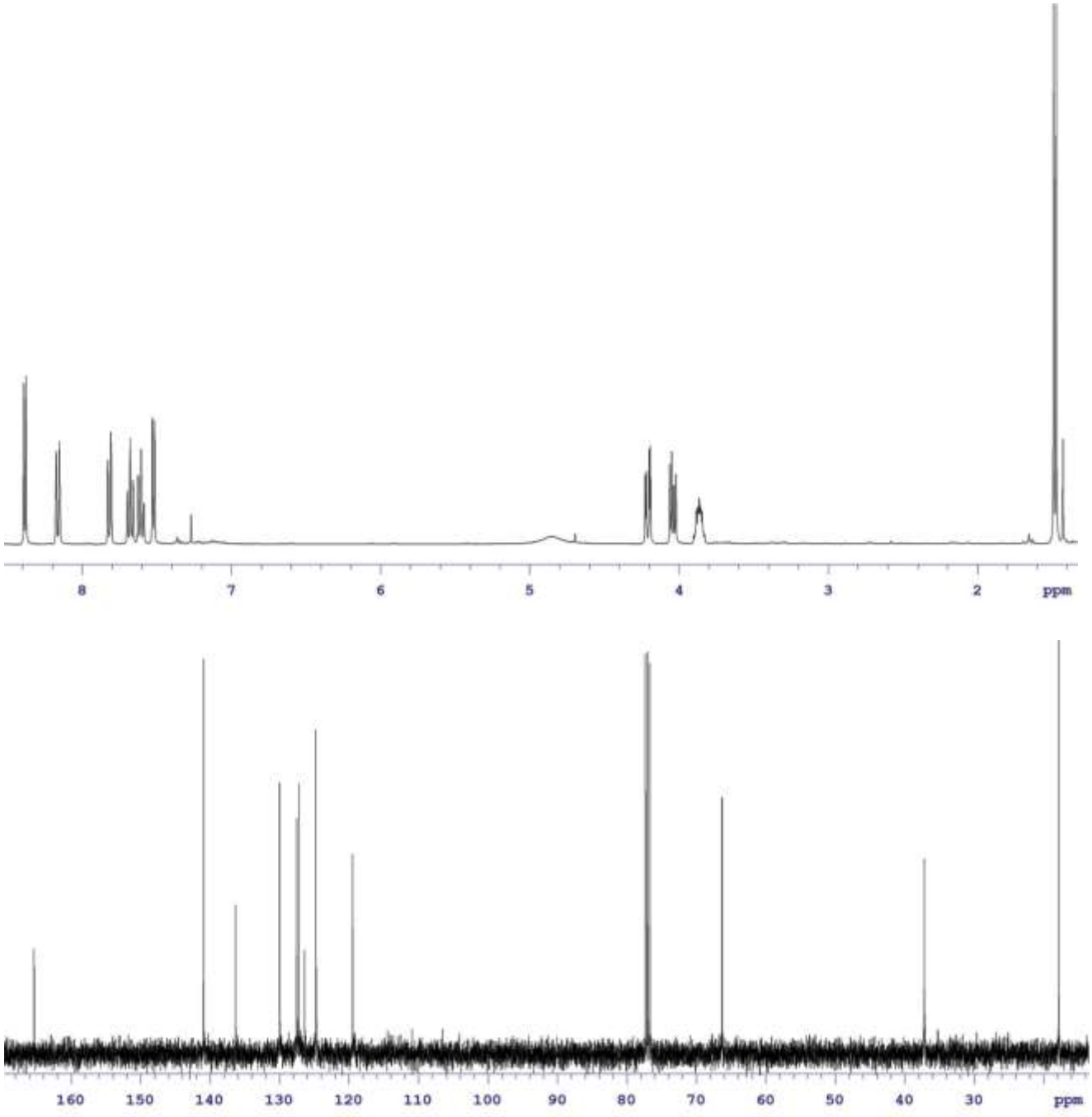
60
50
40
30
20
ppm


N
OH

10a


8
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4
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2
ppm
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120
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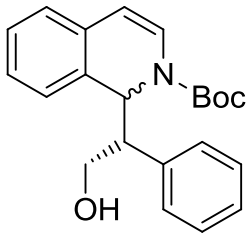
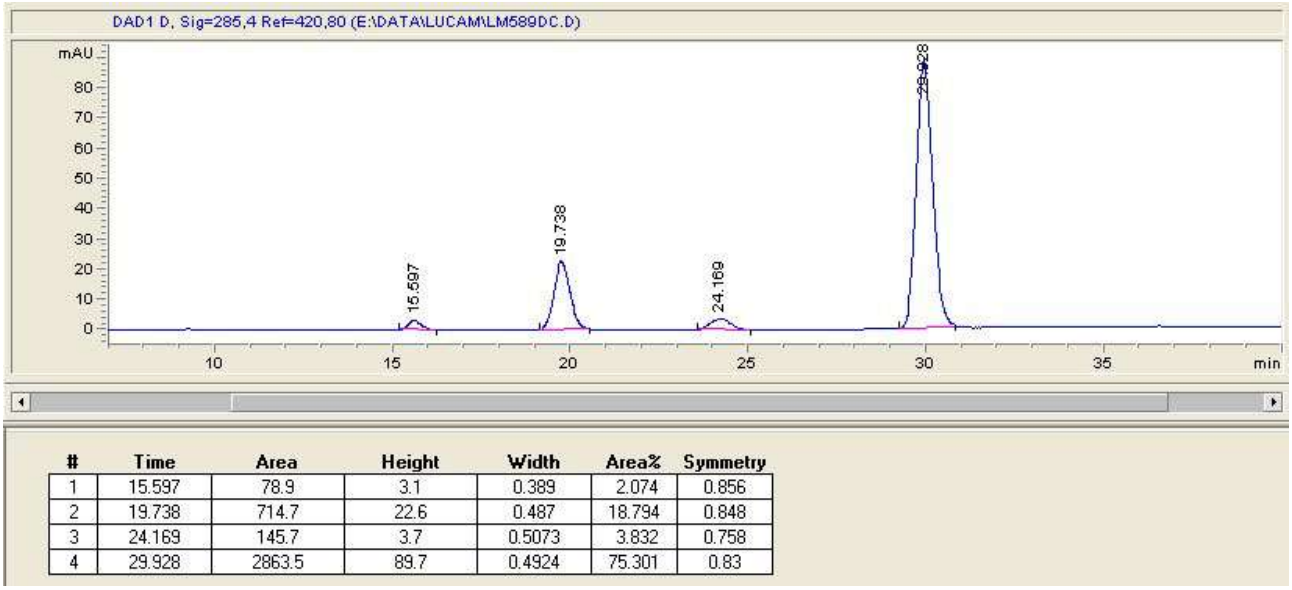
90
80
70
60
50
40
30
ppm

Copies of the HPLC traces of 12 and (+)-1g



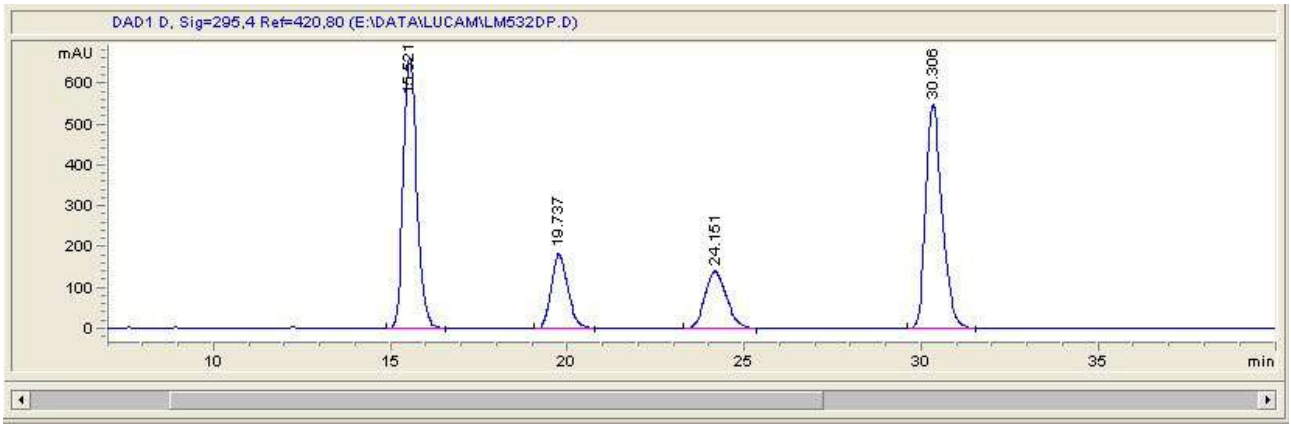
12

active

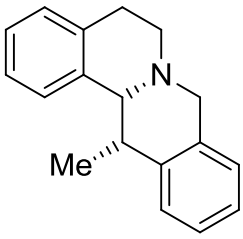


#	Time	Area	Height	Width	Area%	Symmetry
1	15.597	78.9	3.1	0.389	2.074	0.856
2	19.738	714.7	22.6	0.487	18.794	0.848
3	24.169	145.7	3.7	0.5073	3.832	0.758
4	29.928	2863.5	89.7	0.4924	75.301	0.83

racemic

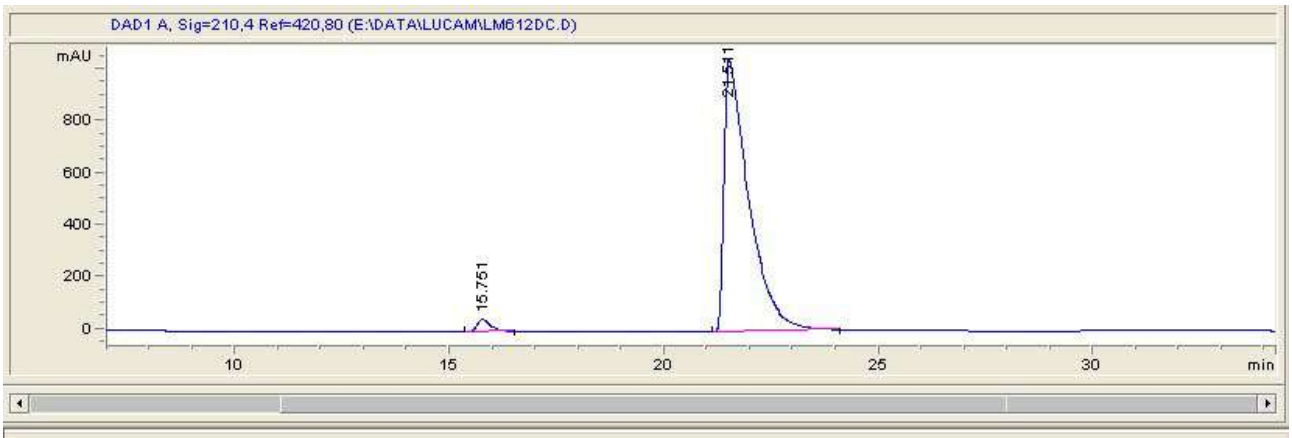


#	Time	Area	Height	Width	Area%	Symmetry
1	15.521	17611.2	664.1	0.4094	37.333	0.804
2	19.737	5964.4	183.6	0.4989	12.644	0.803
3	24.151	5967.3	140.5	0.6556	12.650	0.832
4	30.306	17630.3	547	0.494	37.374	0.703



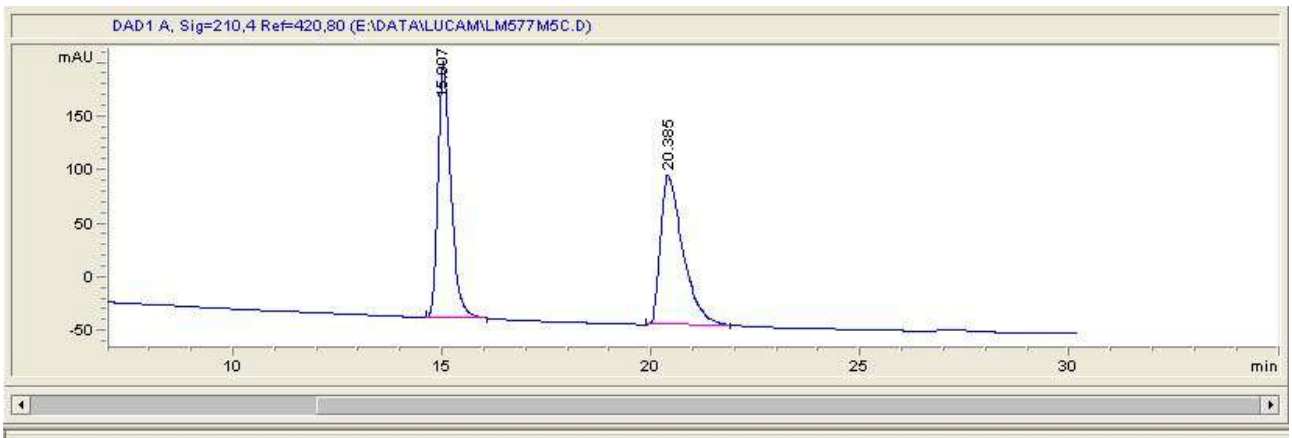
1g

active



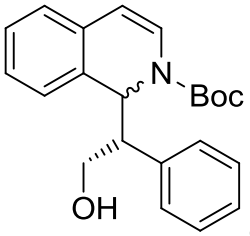
#	Time	Area	Height	Width	Area%	Symmetry
1	15.751	1057.5	48.2	0.3321	2.429	0.612
2	21.511	42483	1045.8	0.5779	97.571	0.261

Racemic

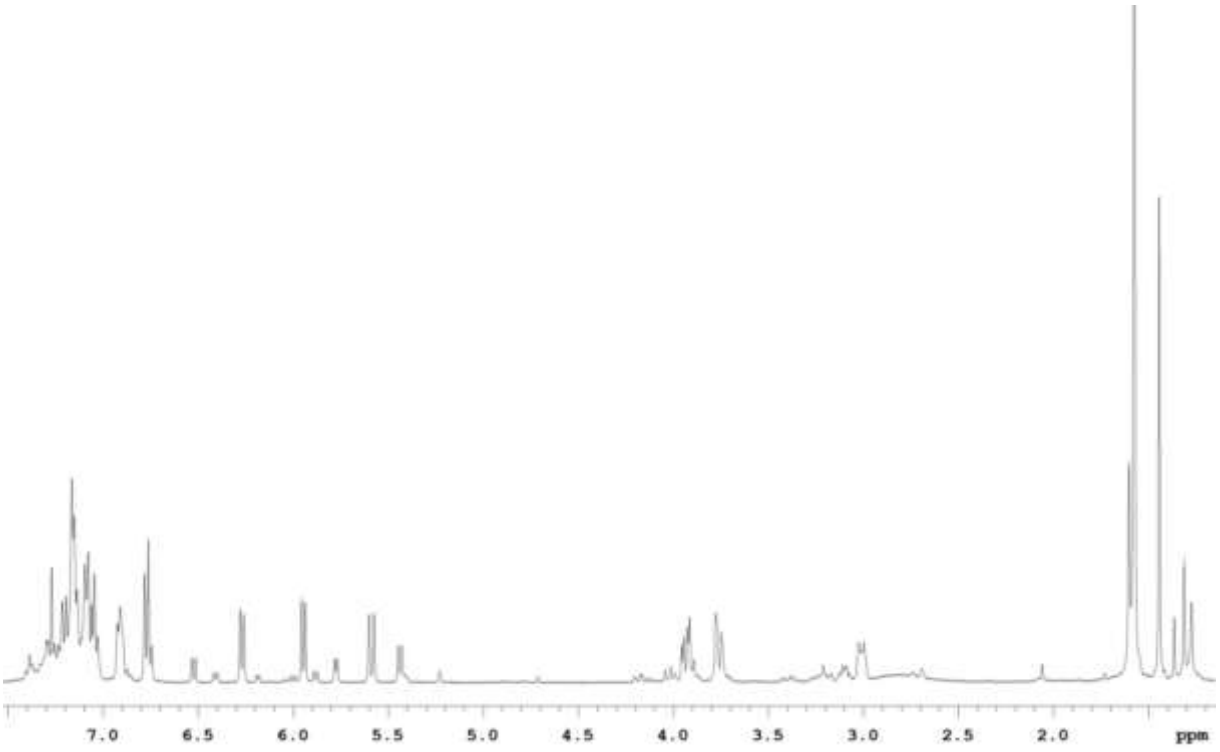


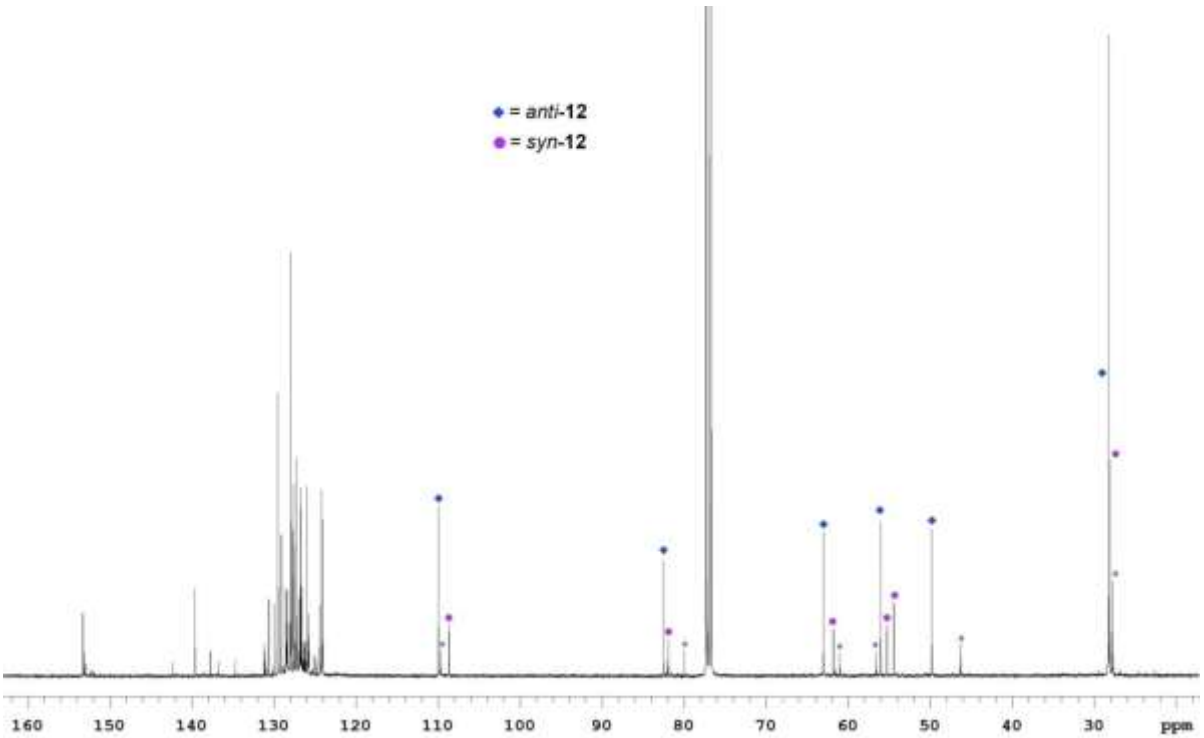
#	Time	Area	Height	Width	Area%	Symmetry
1	15.007	5153.9	239.7	0.3269	49.709	0.632
2	20.385	5214.3	139.1	0.5632	50.291	0.47

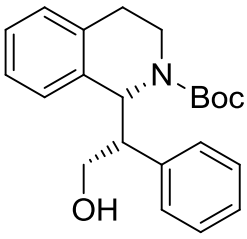
Copies of NMR spectra of (+)-1g, of the intermediates 12-17 and of enamine 20



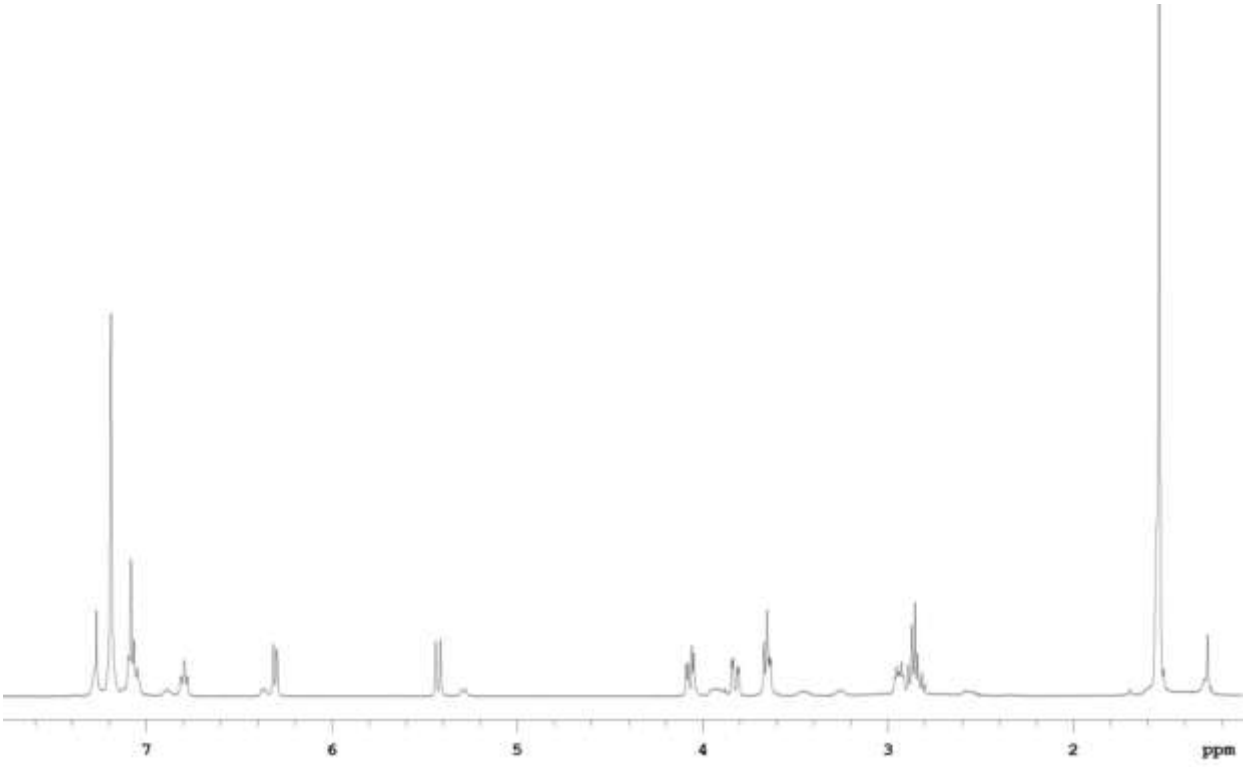
active **12**

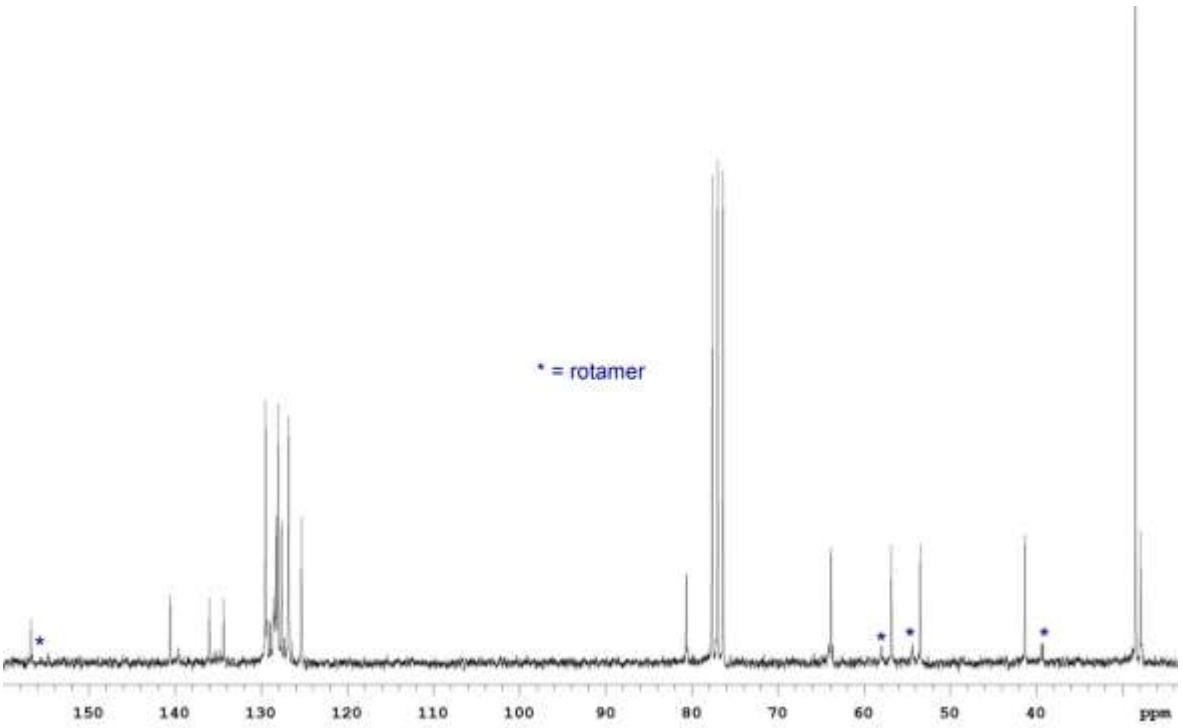





N
Boc
OH

***anti*-13**


7
6
5
4
3
2
ppm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110
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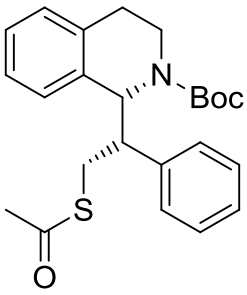
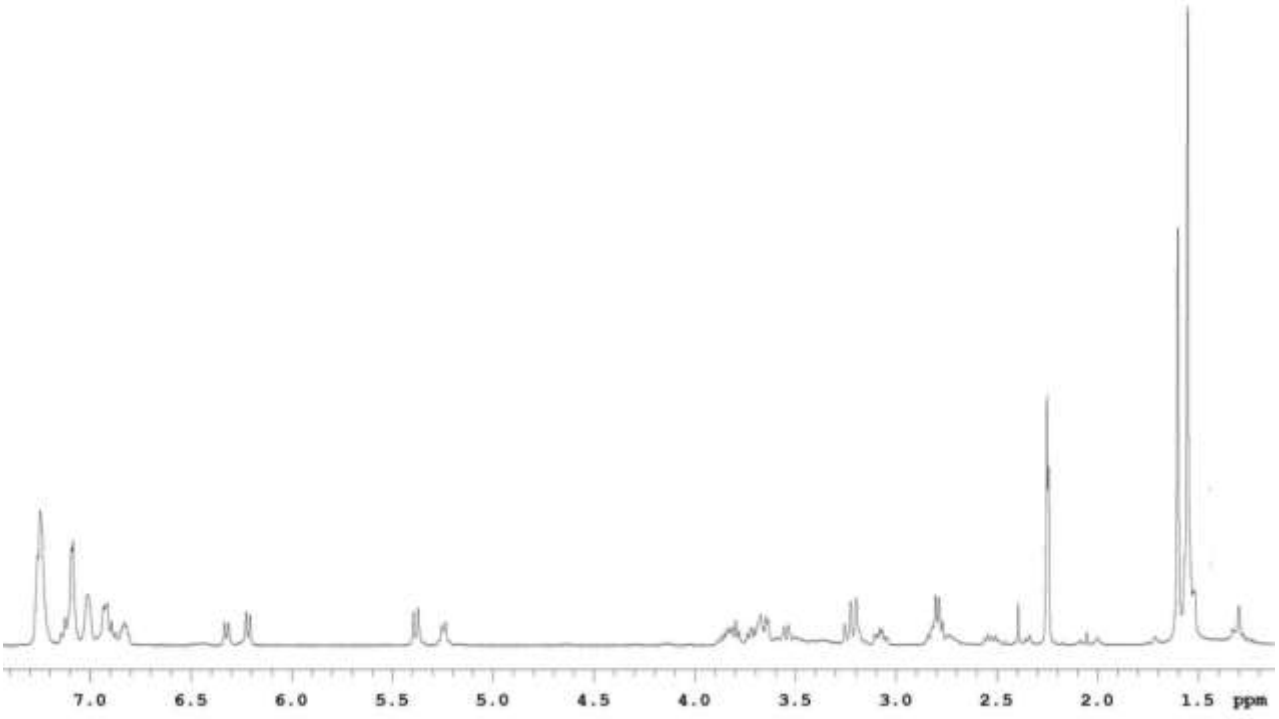
90
80
70
60
50
40
ppm


N
Boc
S
O

14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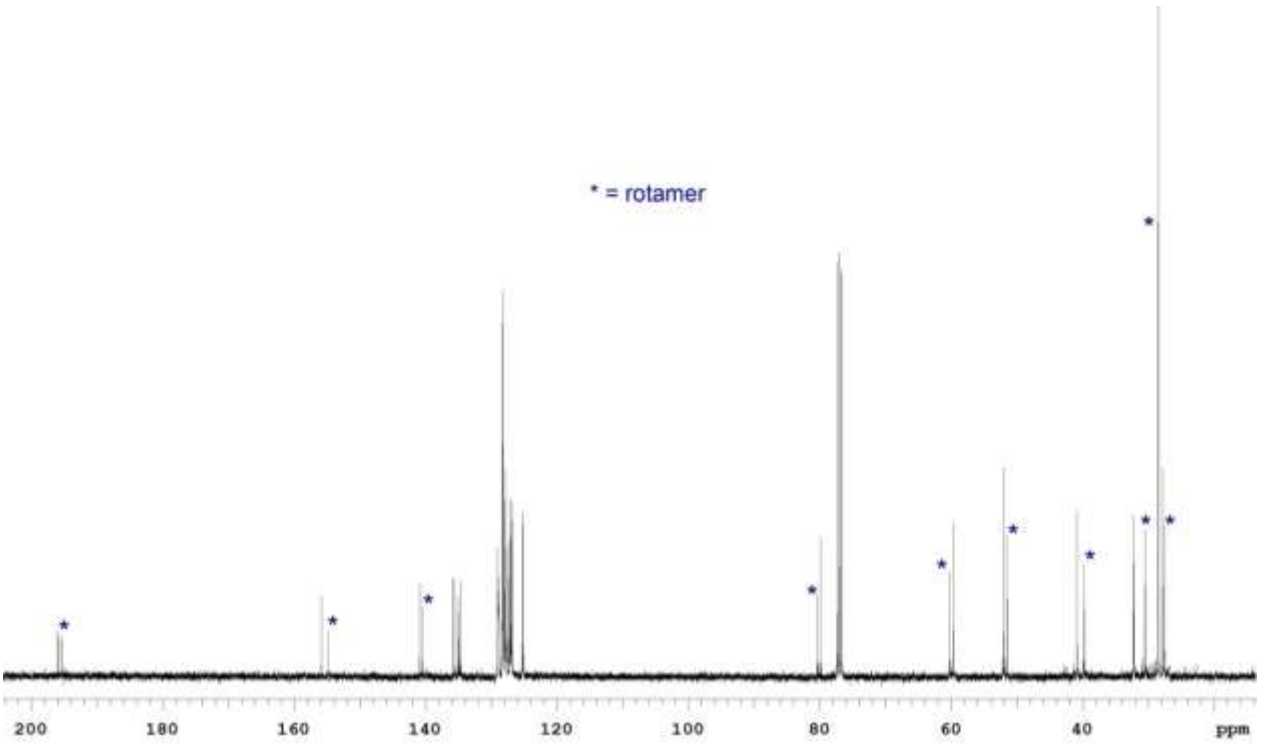
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm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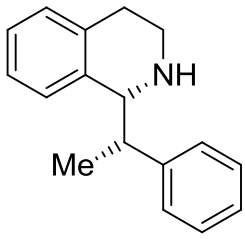
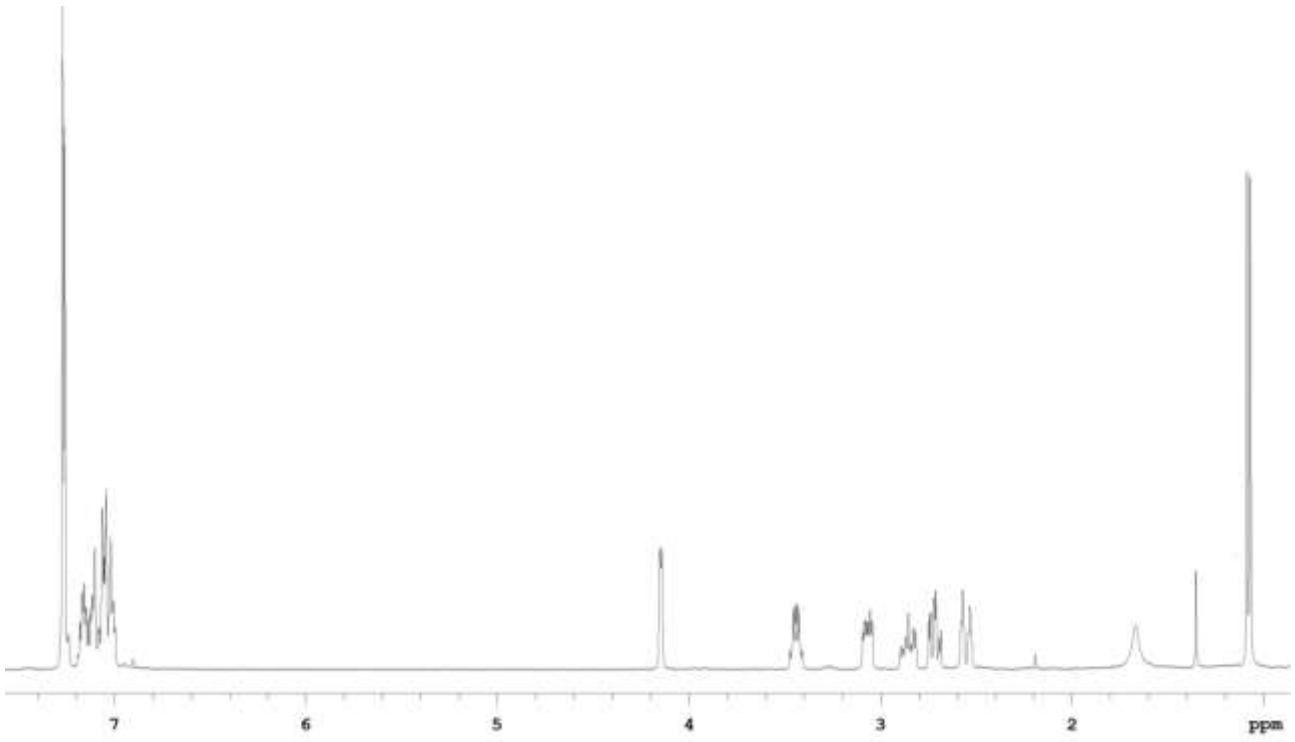
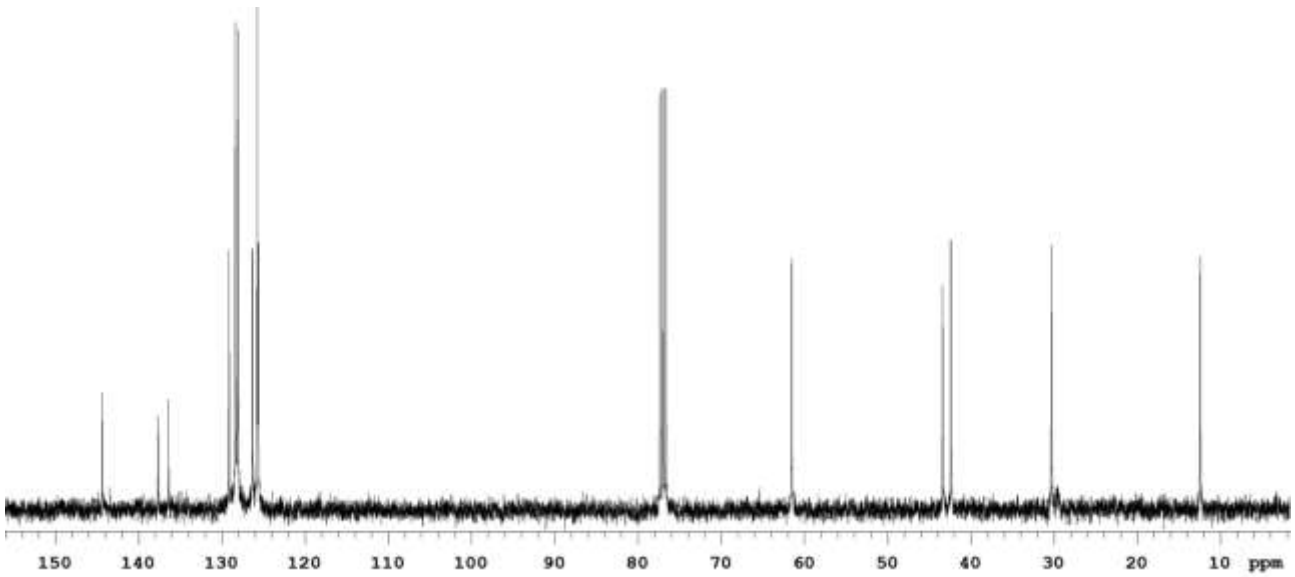
180
160
140
120
100
80
60
40
ppm


NH
Me

15


7
6
5
4
3
2
ppm


150
140
130
120
110
100
90
80
70
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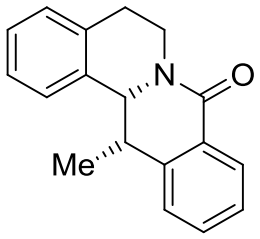
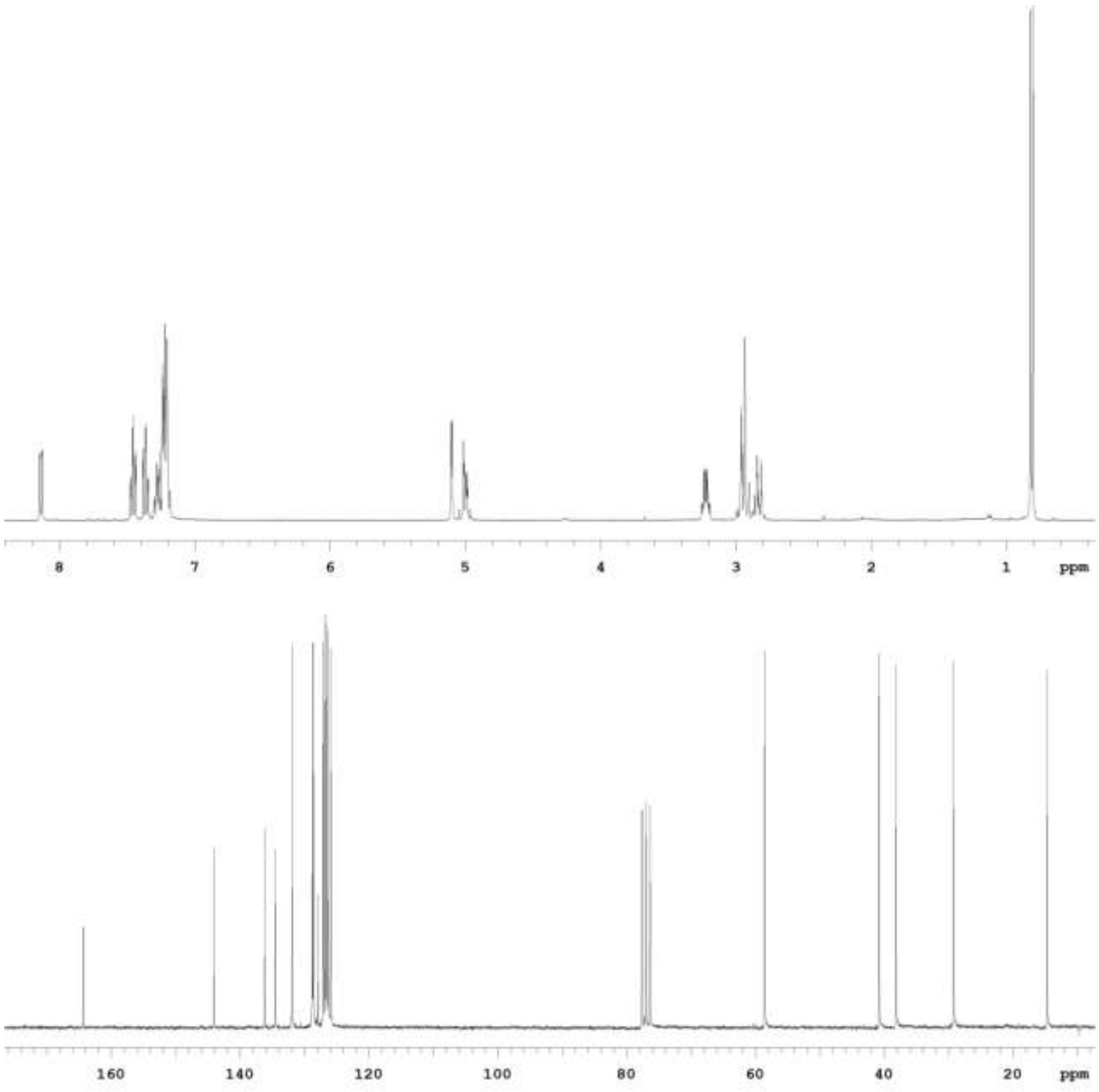
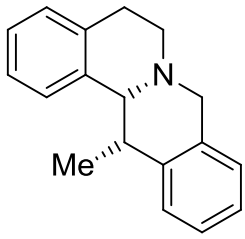
50
40
30
20
10
ppm

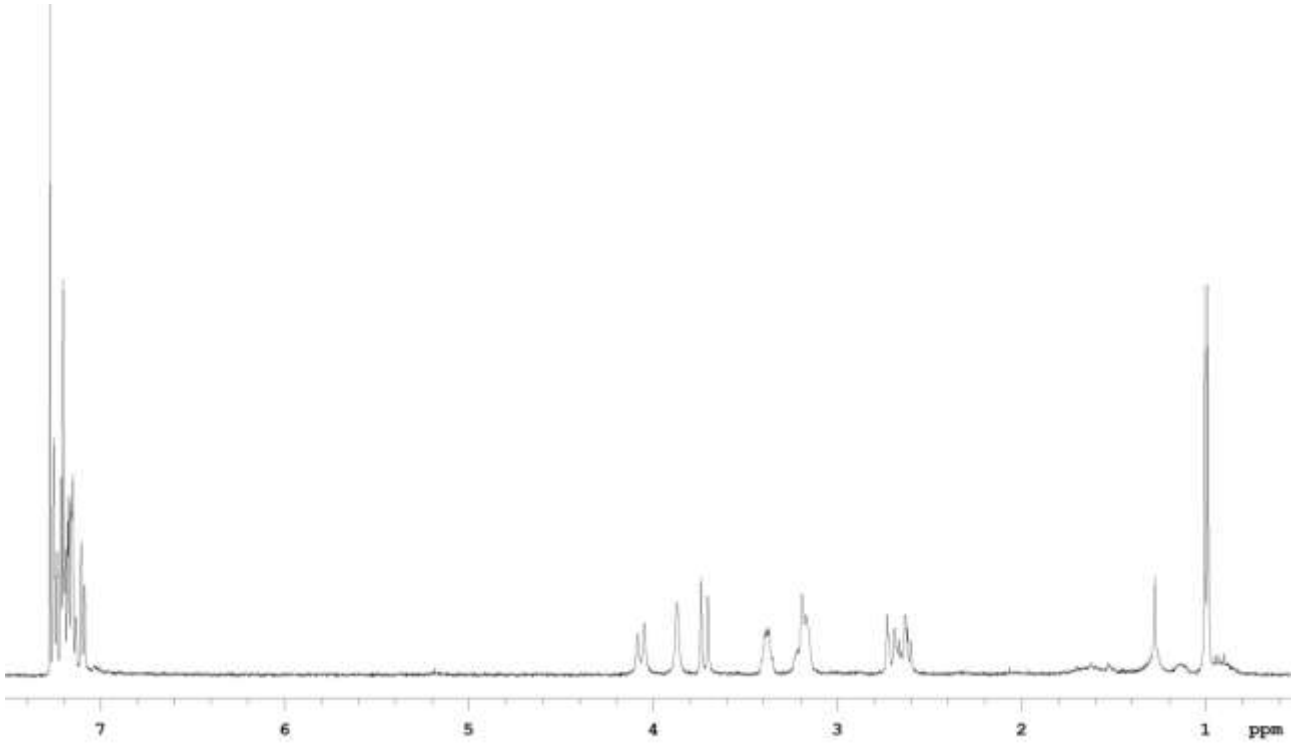


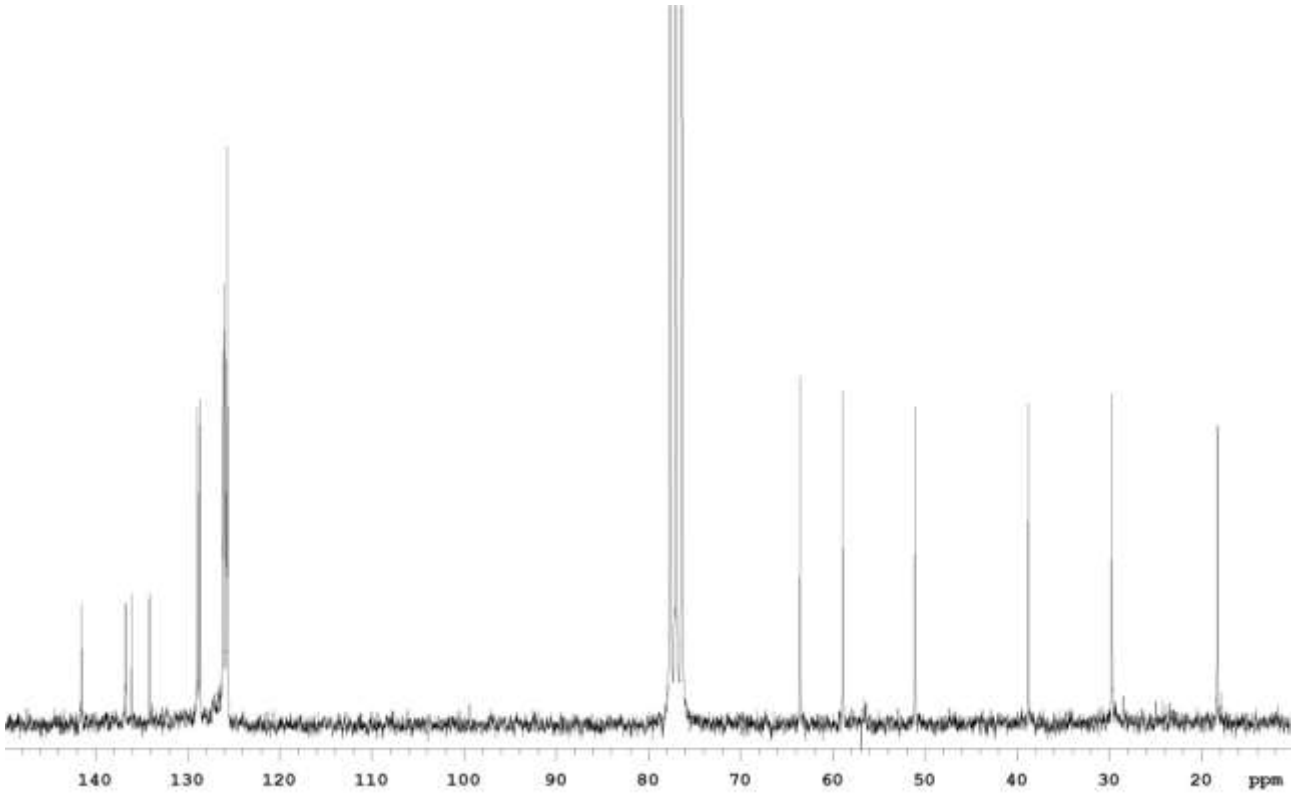
17

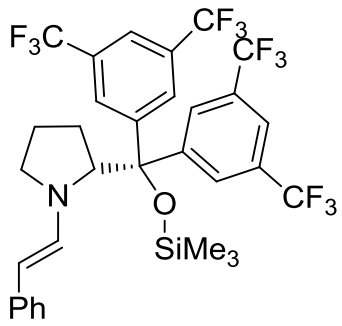




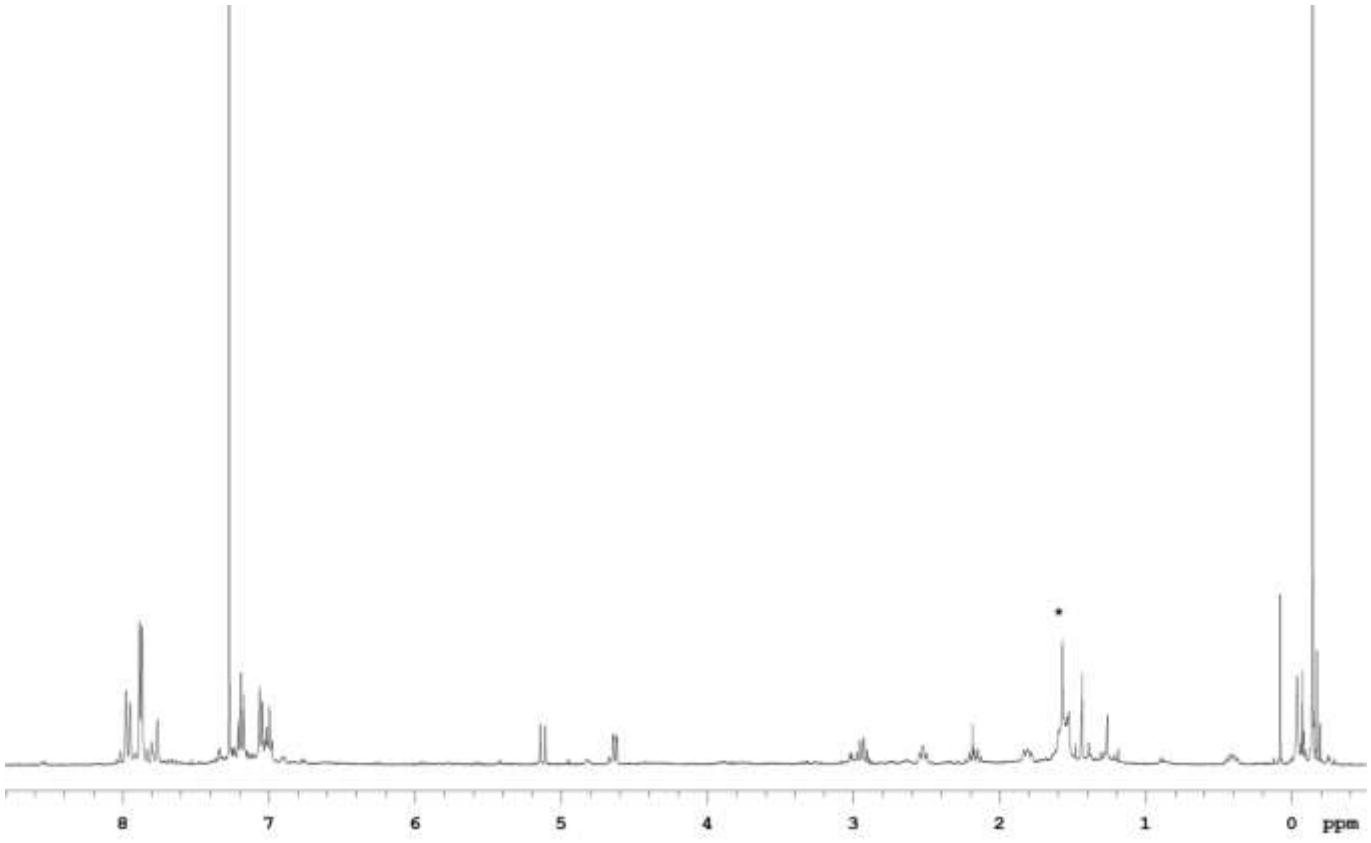
1g





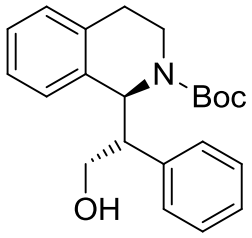


20

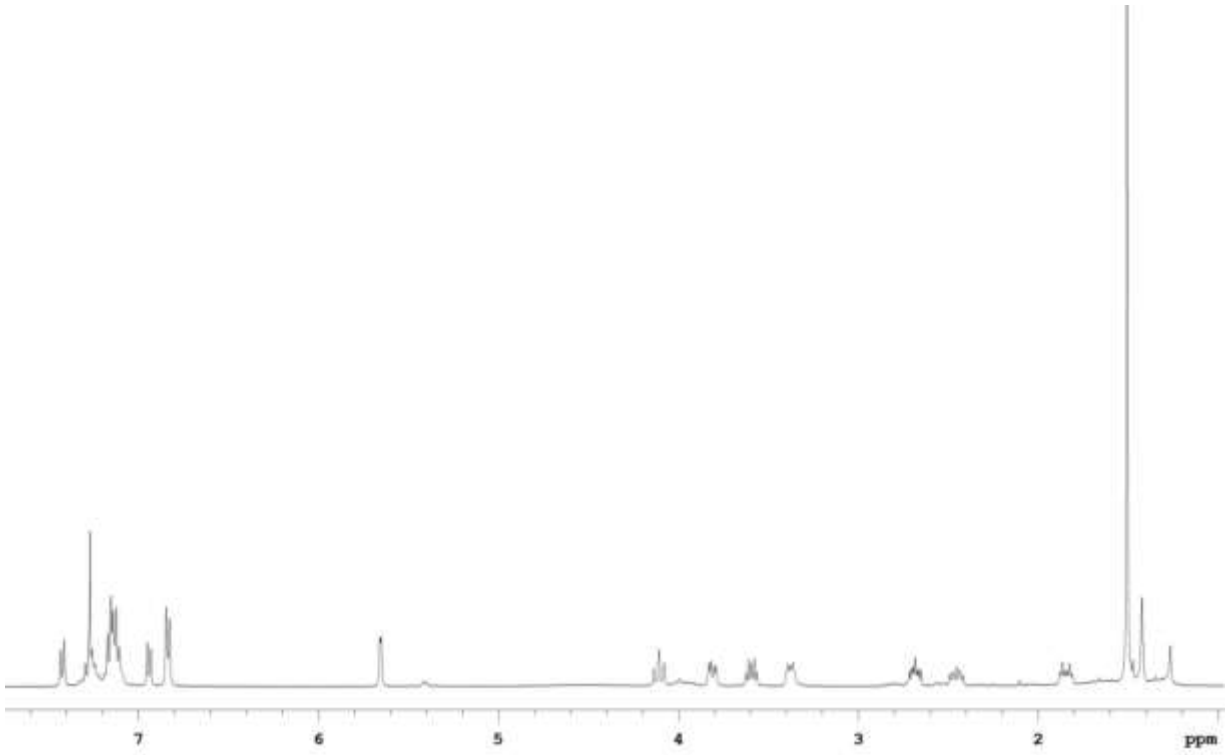


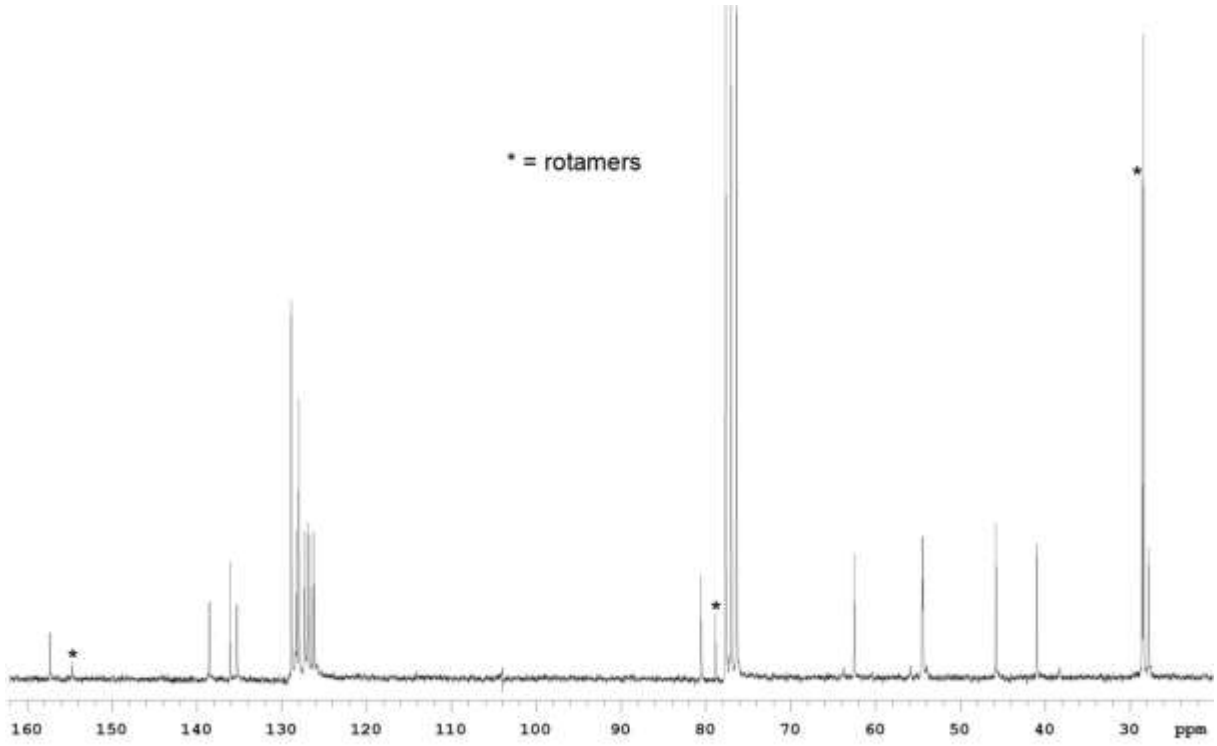
***** 1H signal overlapped with water.

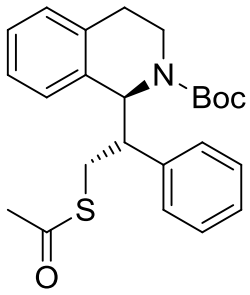
Copies of the NMR spectra of 25 and of the intermediates *syn*-13, 22-24



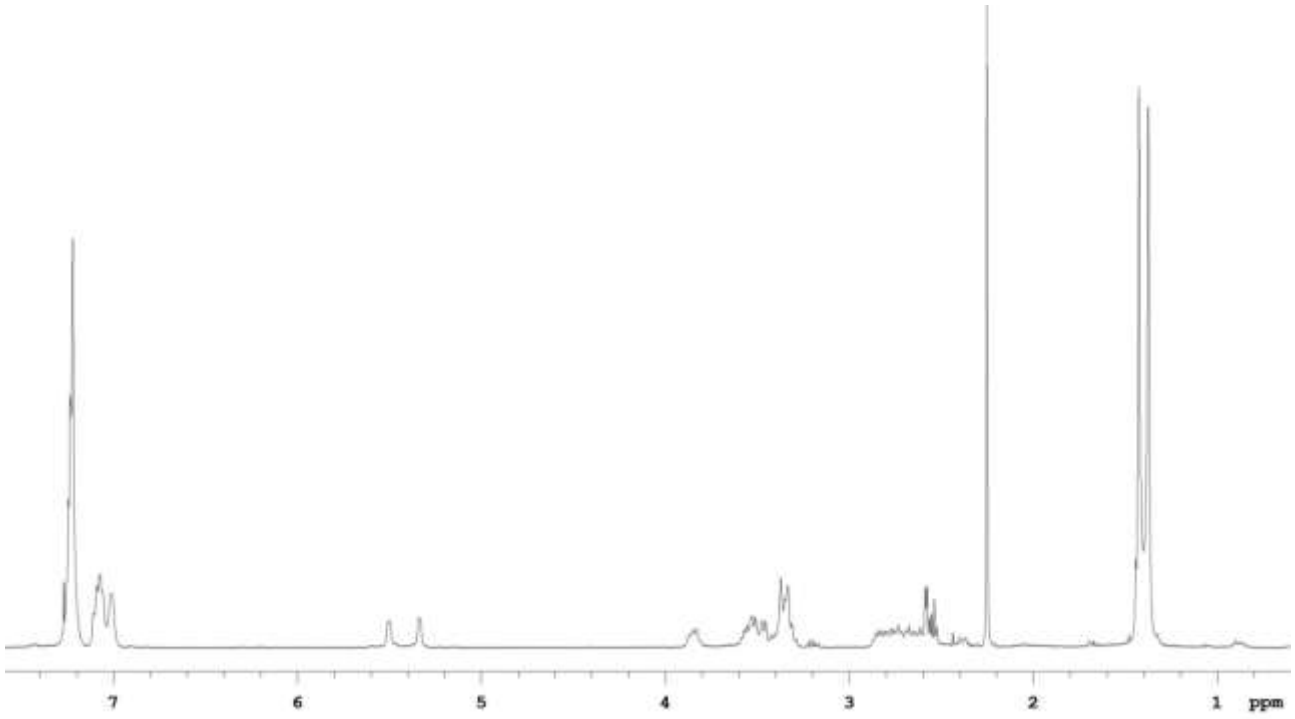
***syn*-13**

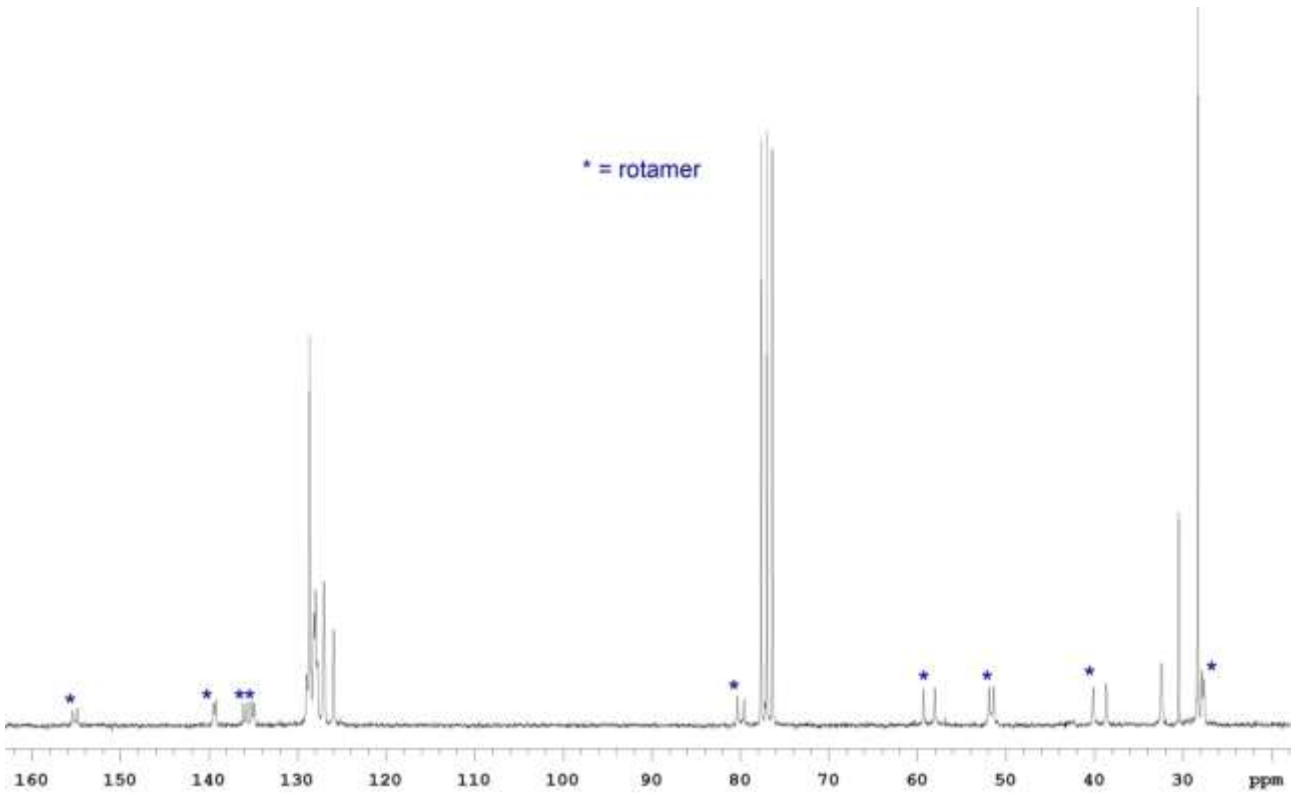





N
Boc
S
O

22


7
6
5
4
3
2
1
ppm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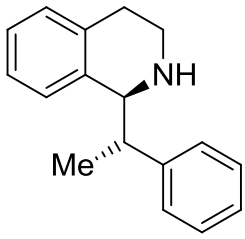
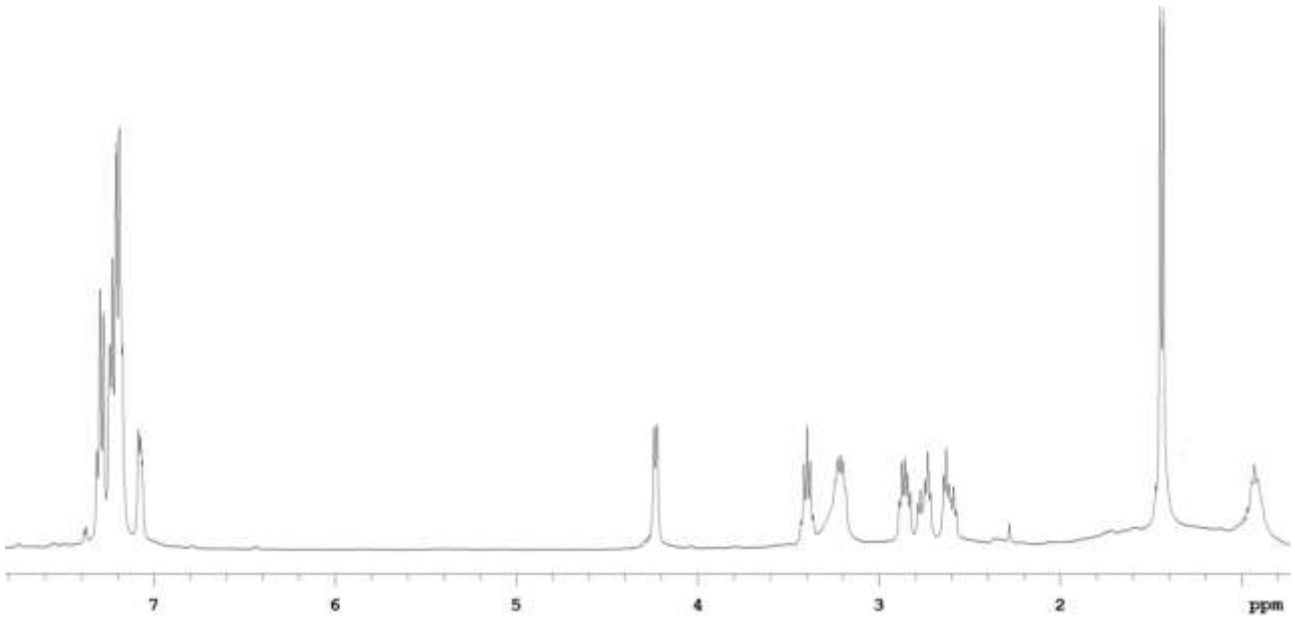
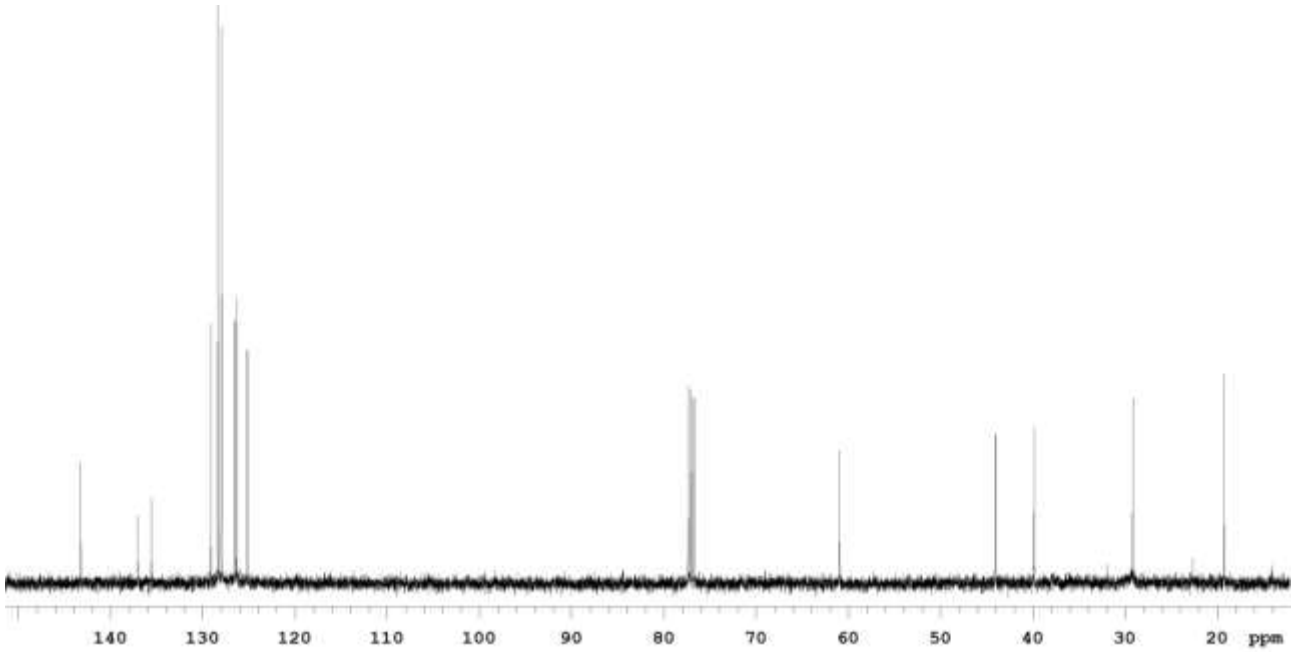
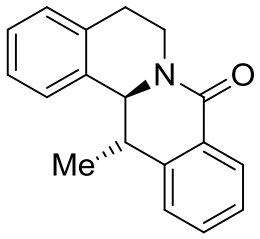
140
130
120
110
100
90
80
70
60
50
40
30
ppm



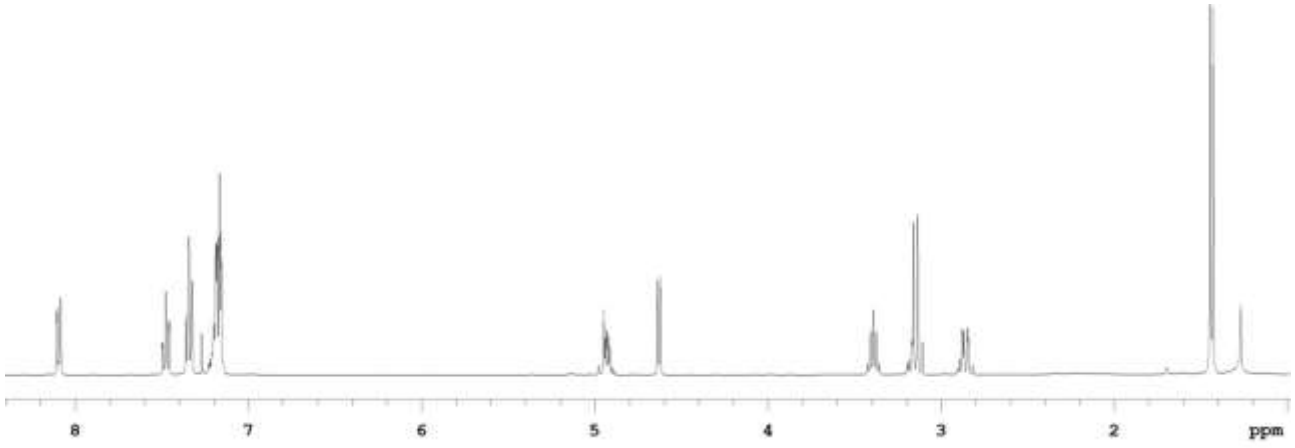
23

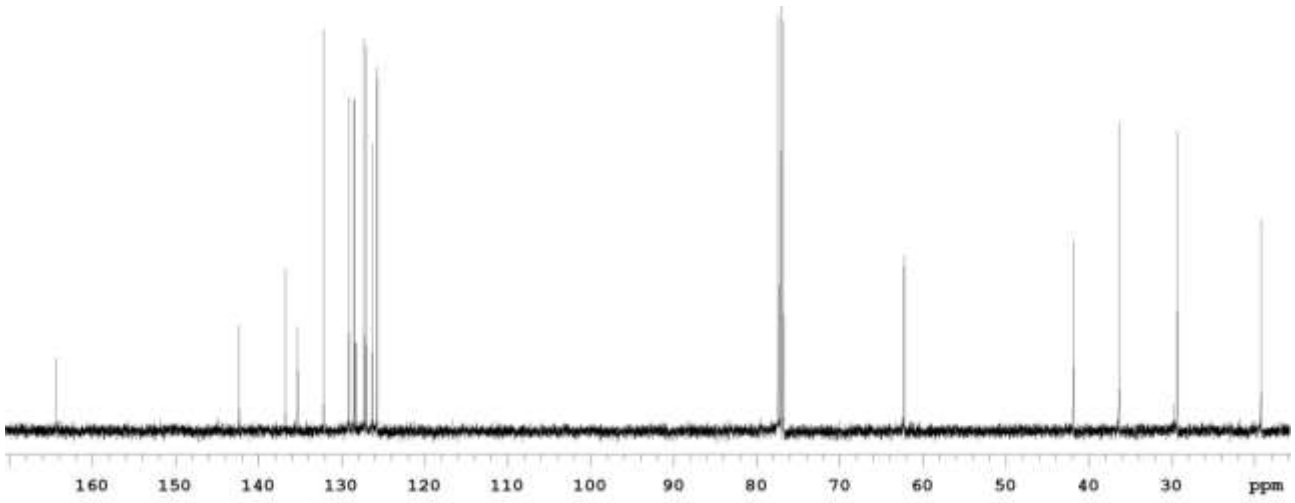


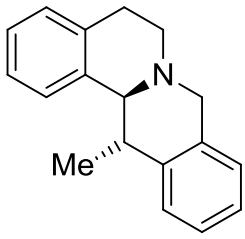



N
O
Me

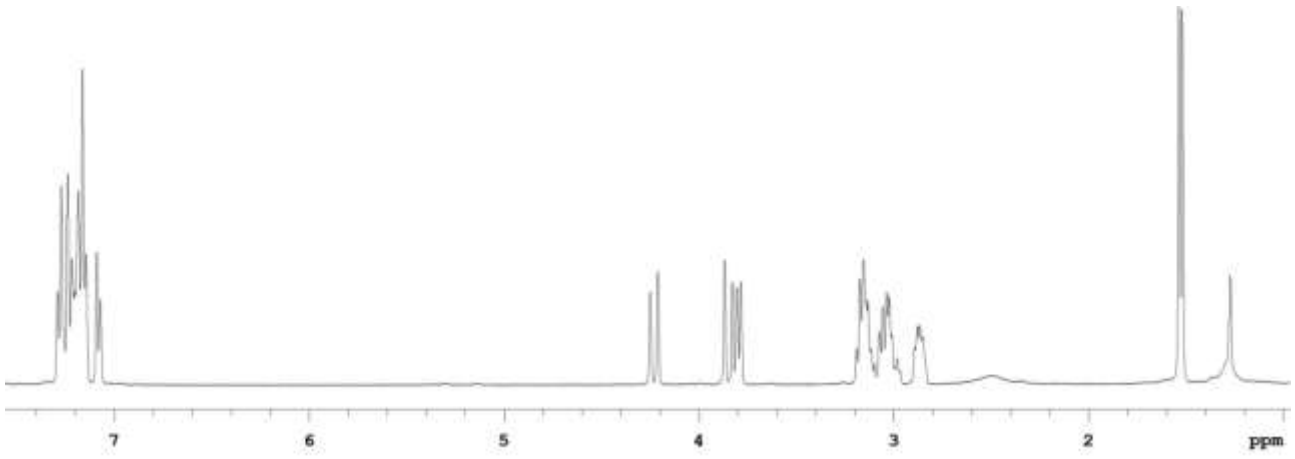
24

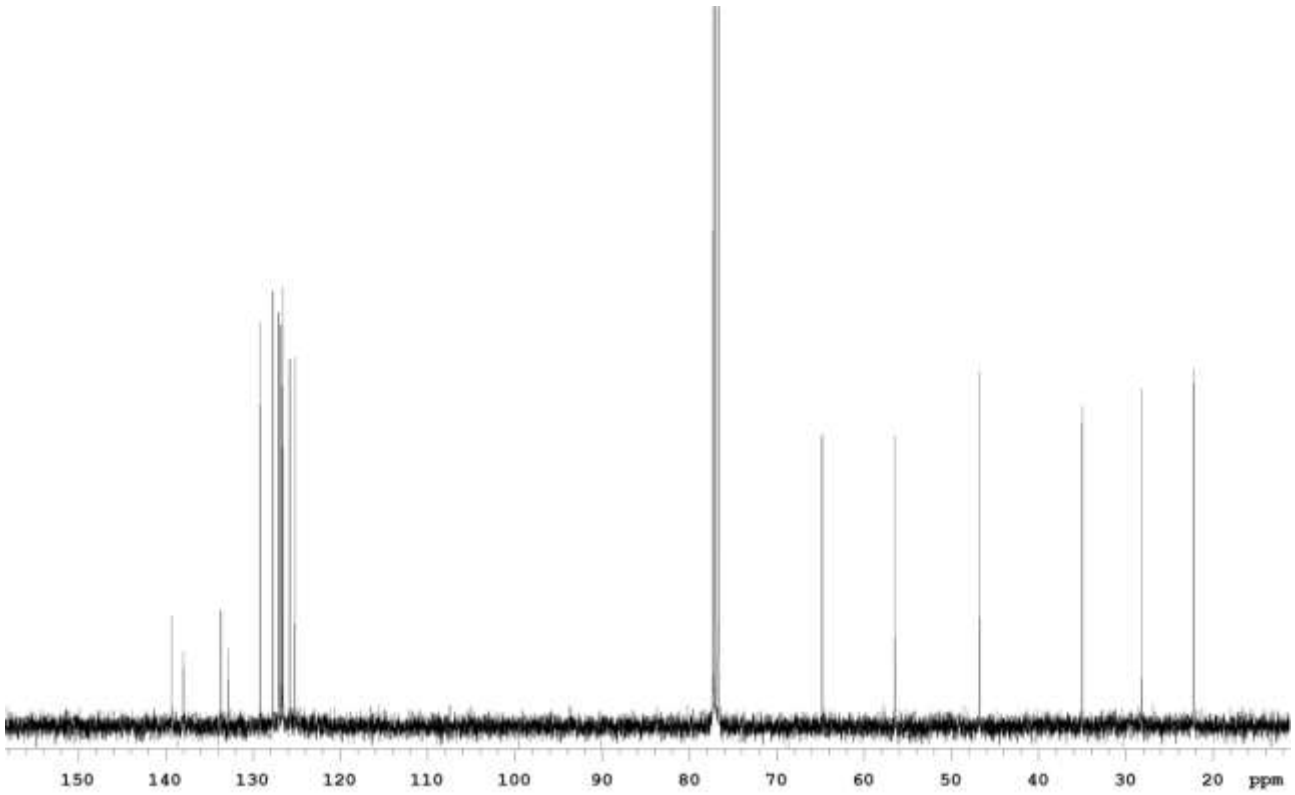

8
7
6
5
4
3
2
ppm


160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

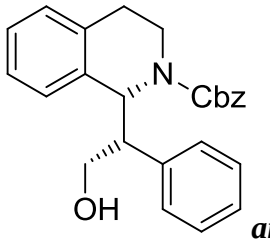


25

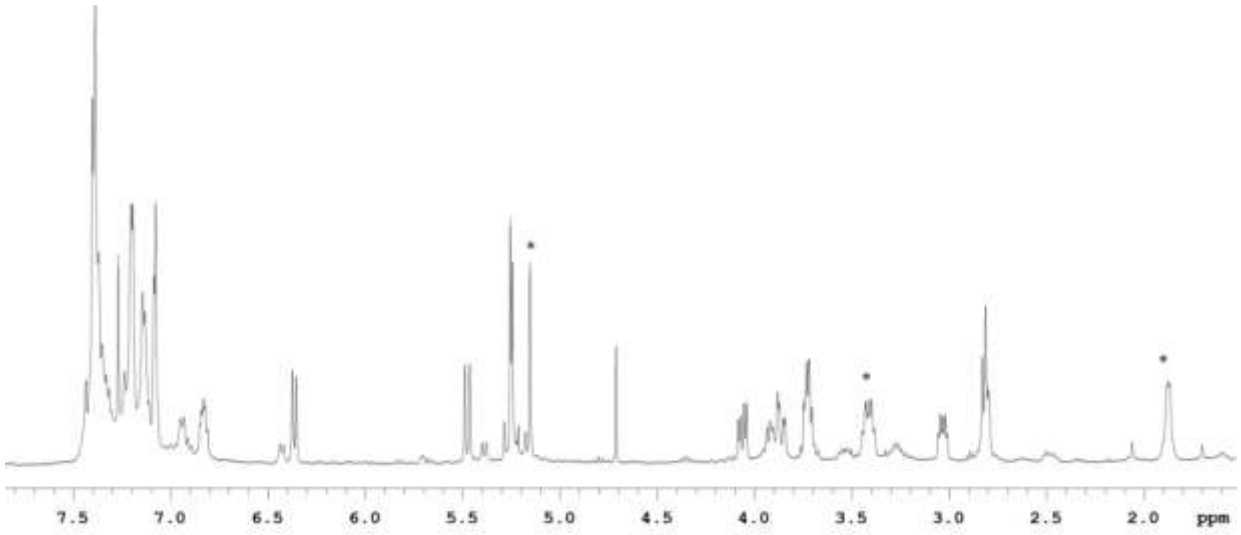




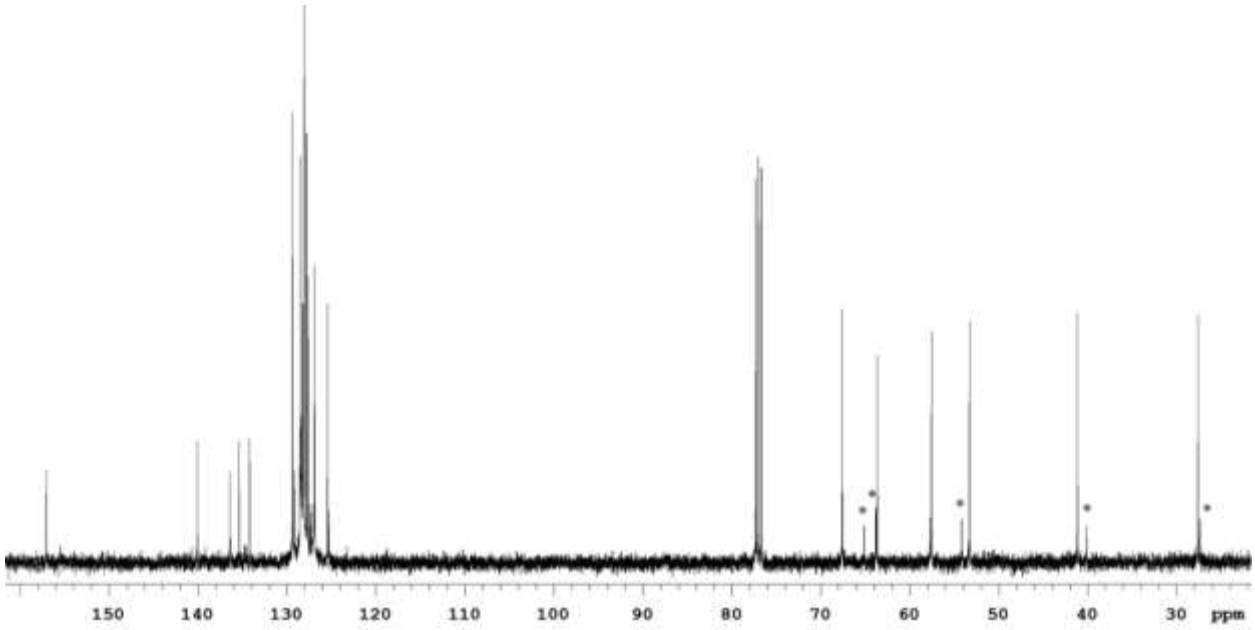
Copies of the NMR spectra of compounds 26-28



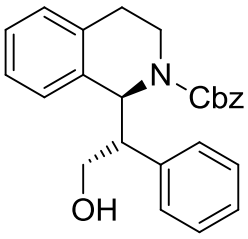
***anti*-26**



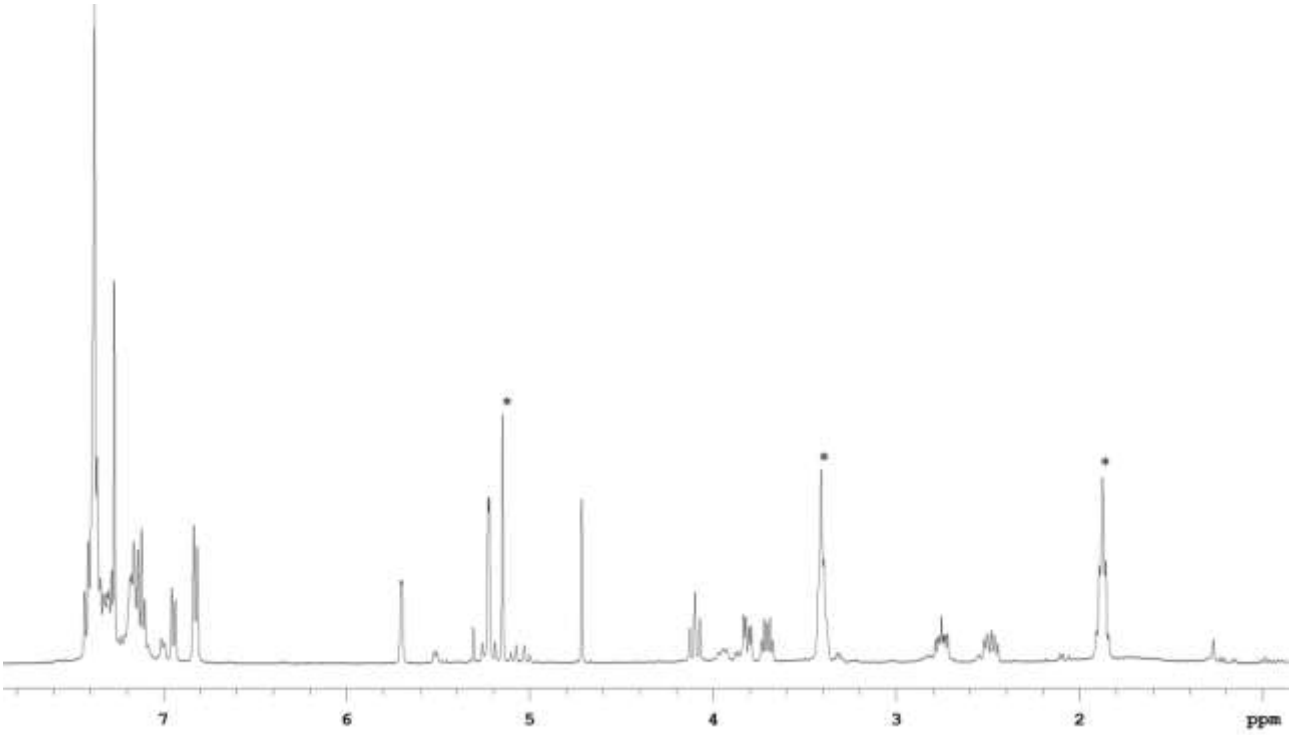
***** (*N*)-Cbz pyrrolidine



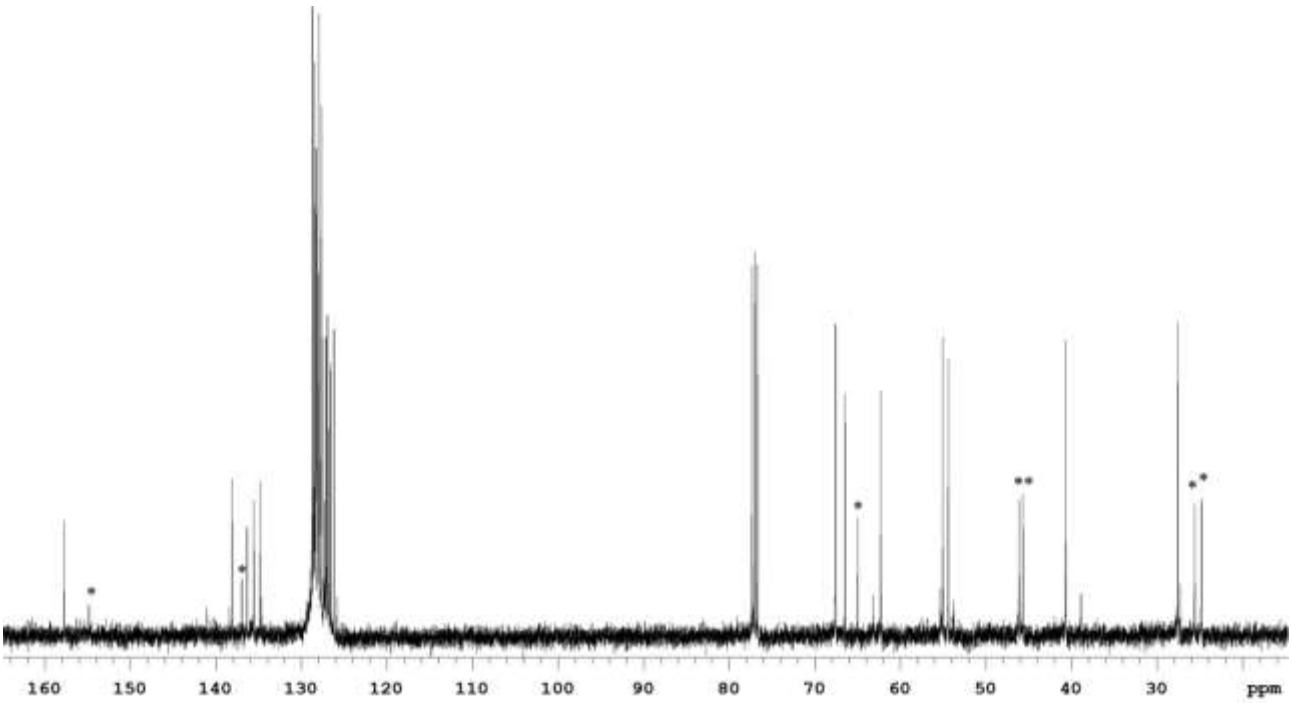
***** (*N*)-Cbz pyrrolidine



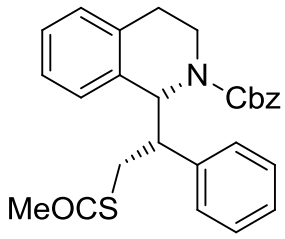
***syn*-26**



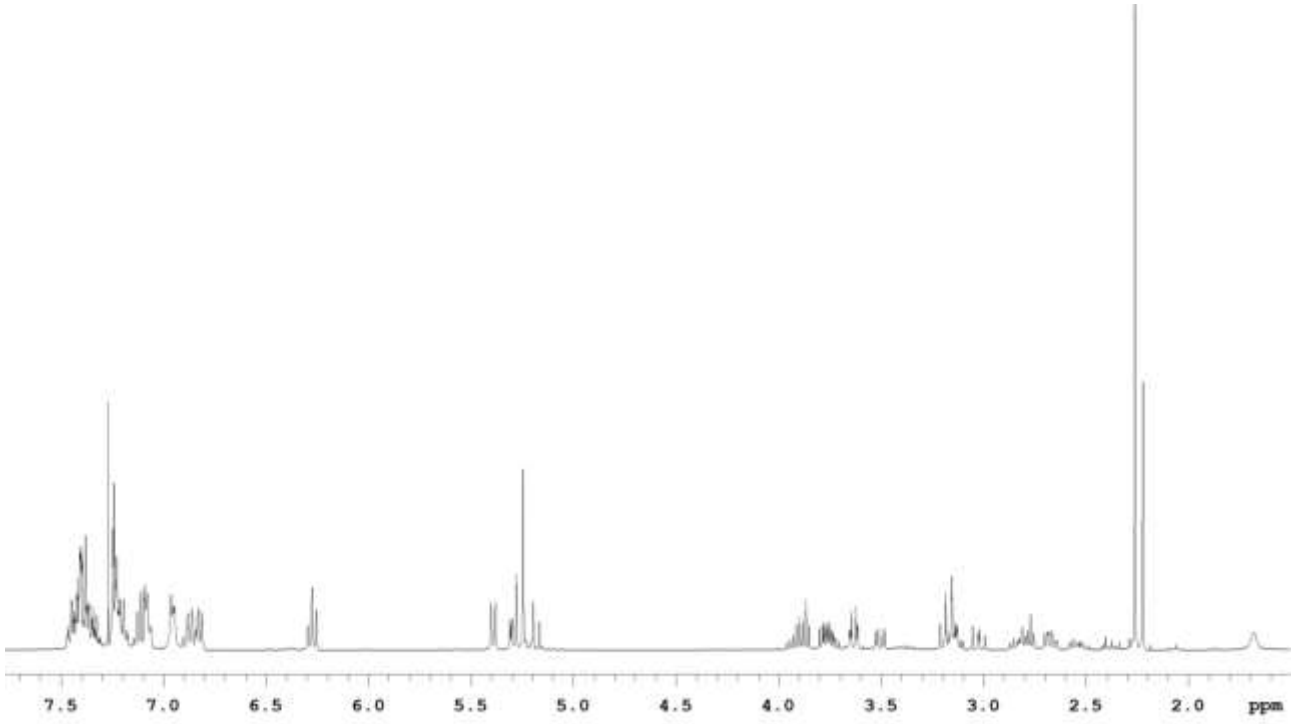
***** (*N*)-Cbz pyrrolidine

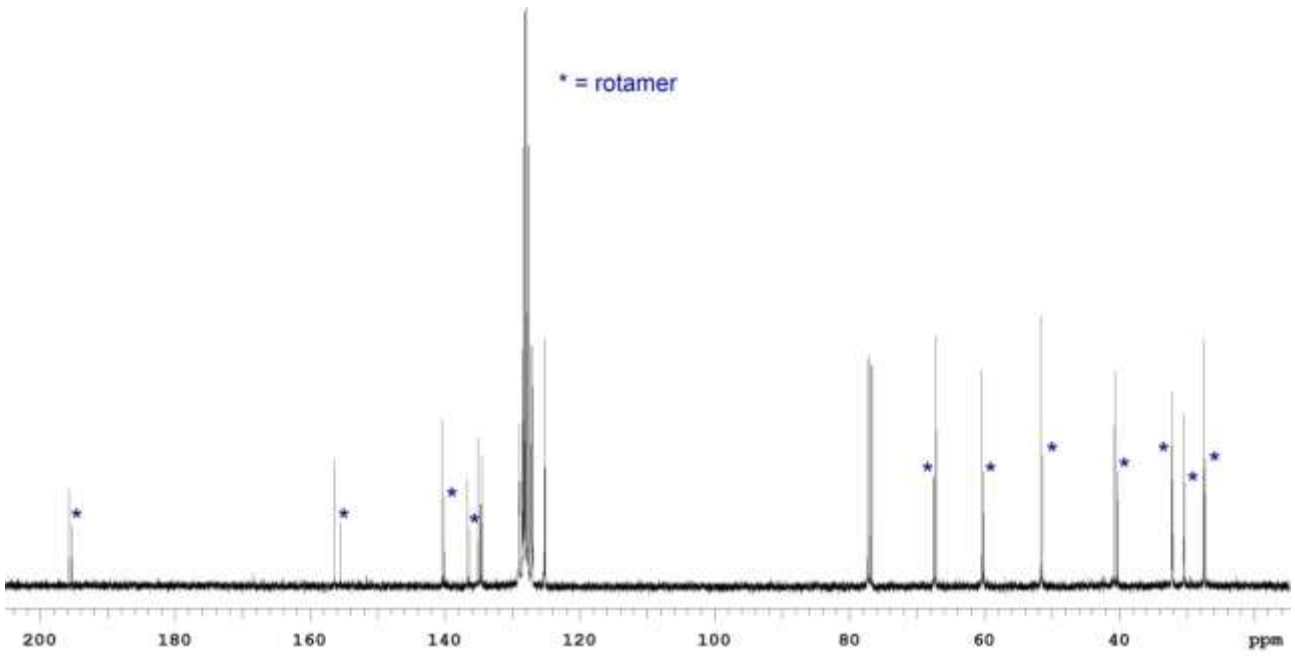


***** (*N*)-Cbz pyrrolidine


N
Cbz
MeOCS

***anti*-27**


7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm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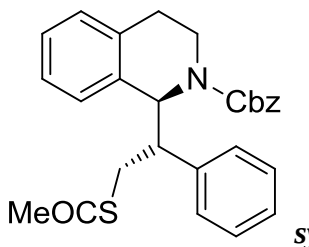
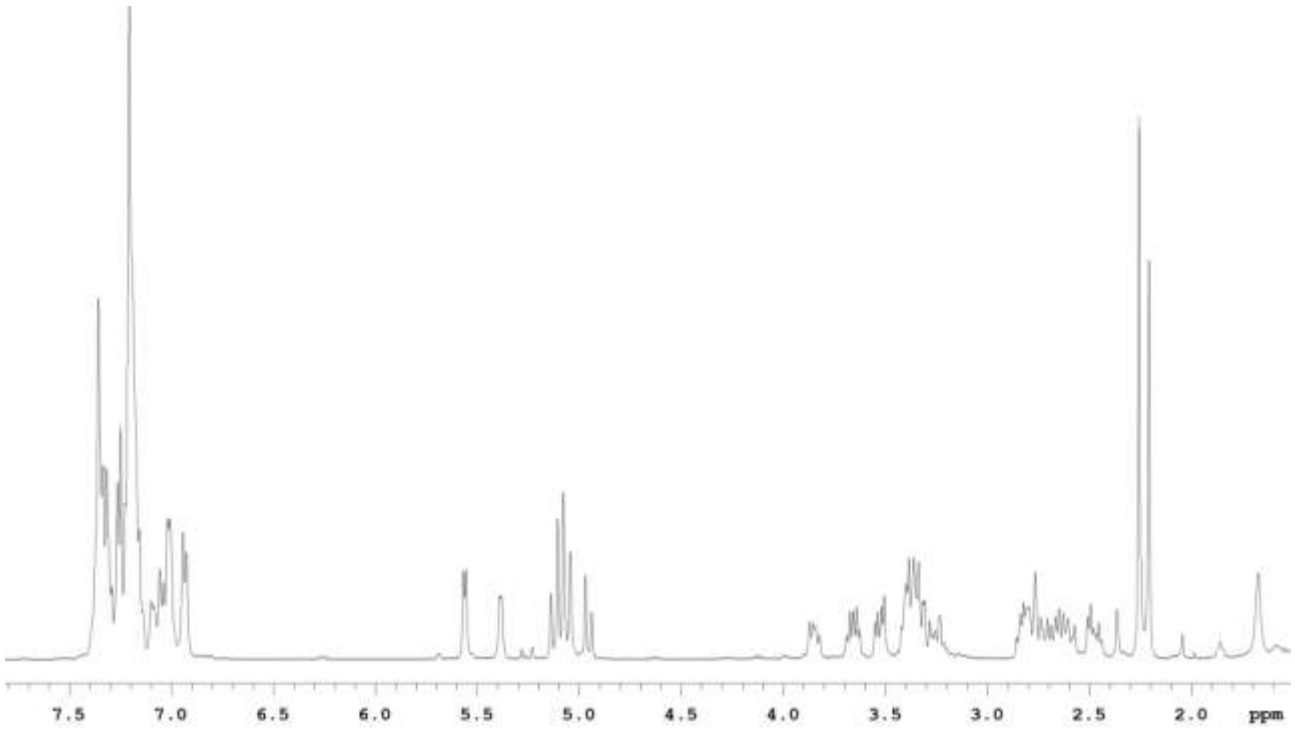
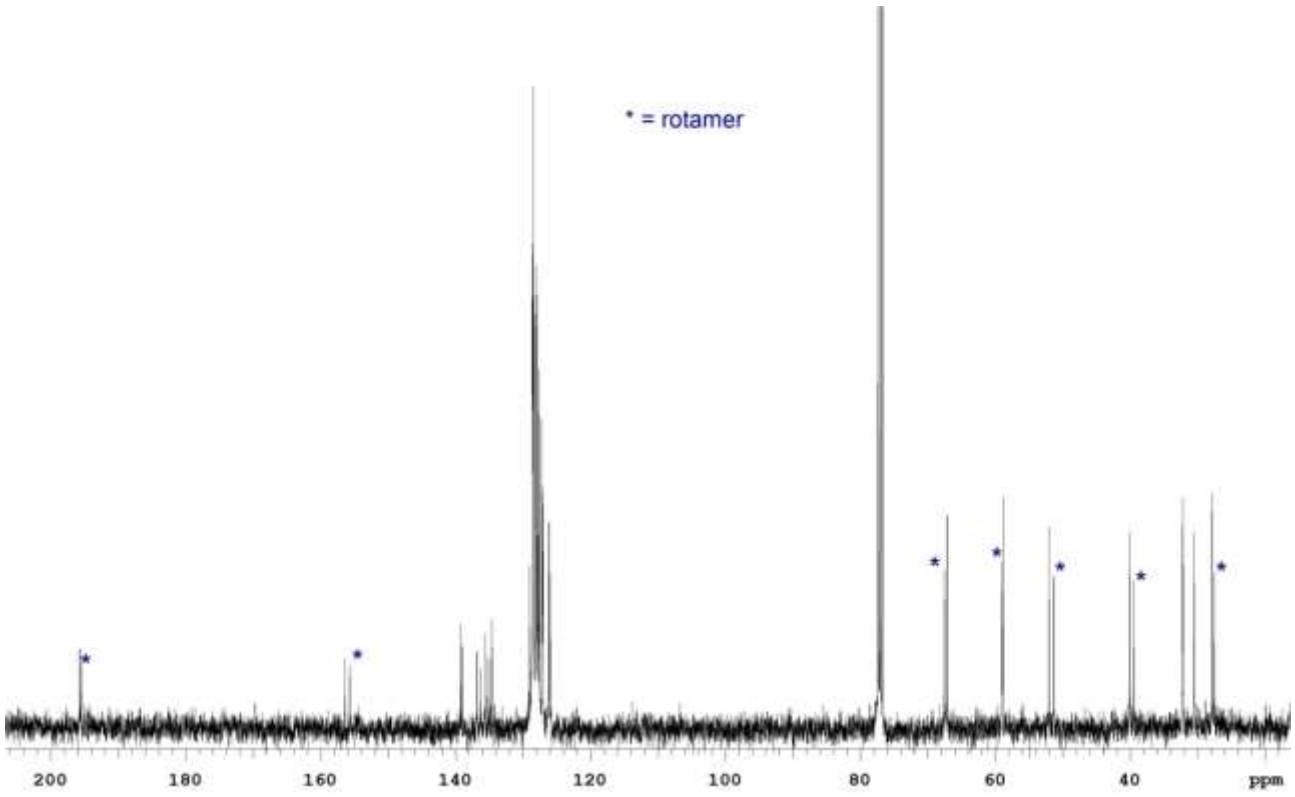
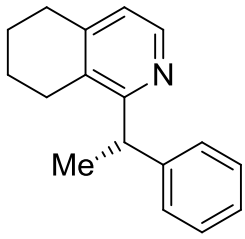
140
120
100
80
60
40
ppm


N
Cbz
MeOCS

***syn*-27**


7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm


* = rotamer
200
180
160
140
120
100
80
60
40
ppm



28