Enantioselective Nitroaldol Reaction of α-Ketoesters Catalyzed by Cinchona Alkaloids

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Supporting Information

General Information. ^{1}H and ^{13}C NMR spectra were recorded on a Varian instrument (400 MHz and 100 MHz, respectively) and internally referenced to tetramethylsilane signal or residual protio solvent signals. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), intergration, coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrometer and are reported in frequency of absorption. Low resolution mass spectra for all the new compounds were performed by 70SE CI+, and were recorded and exact mass spectra on a 70-VSE-B high resolution mass spectrometer. Specific rotations were measured on a Jasco Digital Polarimeter.

High performance liquid chromatography (HPLC) analysis was performed on a Hewlett-Packard 1100 Series instrument equipped with a quaternary pump, using a Daicel Chiralcel OJ, OD Column (250 x 4.6 mm) or Chiralpak AD, AS Column (250 x 4.6 mm). UV absorption was monitored at 220 nm or at 280 nm.

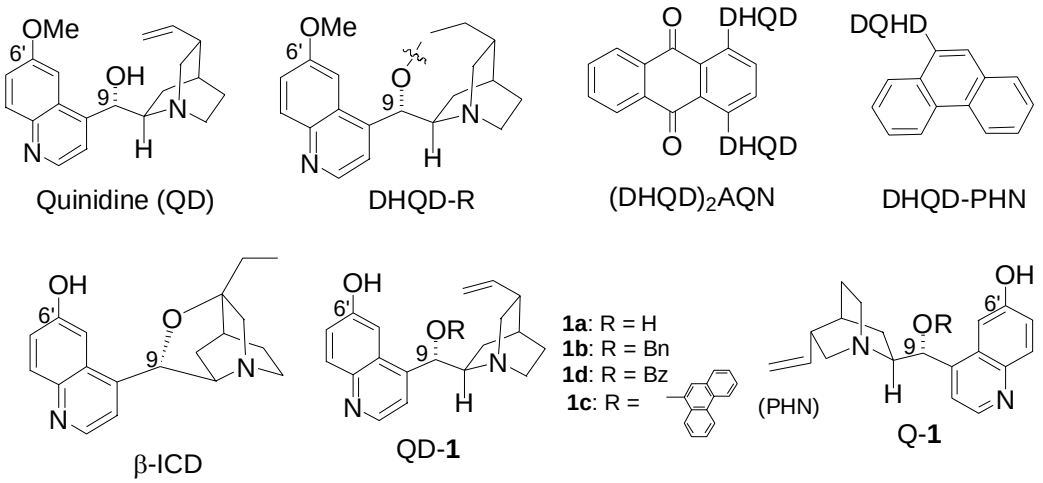
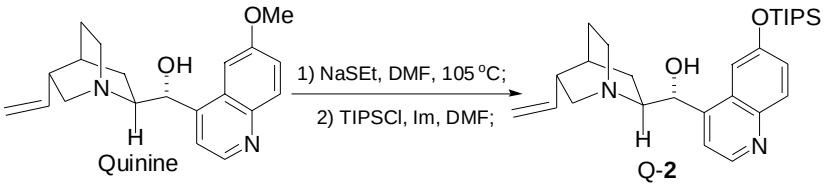


Figure 1. The Structure of Cinchona Alkaloids

Materials: (For structure of α-ketoesters **2**, see Table1, for structure of cinchona alkaloid catalysts, see Figure 1) α-ketoesters **2a, 2b** were prepared according to literature procedures.[1] Other α-ketoesters **2** were commercially available and purified by flash chromatography (silica gel 60, 0.040-0.063 mm, purchased from EM SCIENCE Inc.) before they were used for the nitroaldol reaction. Catalysts QD, DHQD-PHN, $(DHQD)_2AQN$ were purchased from Aldrich company and used without any further purification. C6'-OH catalysts Q-**1a-c** and QD-**1a-c** were prepared following procedures reported from these laboratories, [2] and β-ICD was prepared according to literature procedures.[3] Petroleum ether (36-60 ^oC) for chromatography was purchased from Fisher Company.

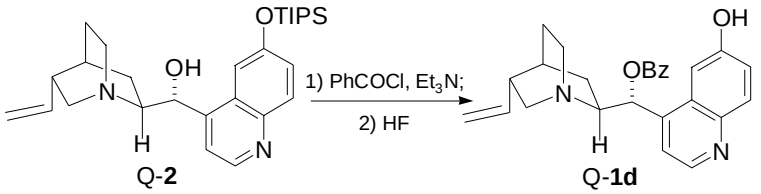
Preparation of catalyst Q-1d:

*6'-OTIPS Quinine derivative Q-**2**:*



A suspension of quinine (3.6 g, 11.46 mmol), NaSEt (90% purity, 5g, 5eq.) in anhydrous DMF (60 mL) was heated at 105 ^{o}C (oil bath temperature) under N_2 for 16 hours. The mixture was cooled to room temperature then pored into sat. NH_4Cl aq. (100 mL) and pH of the aqueous phase was around 7. The mixture was extracted with ethyl acetate (2 x 200 mL). The combined organic phase was washed with aqueous HCl (2N, 4 x 25 mL) and the combined aqueous phase was treated with ammonium hydroxide (20 mL) and the pH of the aqueous phase is 10-11. The mixture was exacted with ethyl acetate (2 x 250 mL), and the combined organic phase was washed with brine, dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was dissolved in anhydrous DMF (50 mL). At room temperature, TIPSCl (4.6 mL, 2 eq.) was added to the solution, followed by addition of imidazole (1.5 g, 2 eq.). The resulting solution was stirred at room temperature for 4h, when TLC analysis indicated that the starting material was completely consumed. The reaction mixture was diluted with ethyl acetate (400 mL) and washed with sat. $NaHCO_3$ aq. (2 x 50 mL), brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by flash chromatography (ethyl acetate to ethyl acetate/MeOH/NH_4OH = 20/2/0.5) to give Q-**2** (4.7g, 90% yield over 2 steps). $[\alpha]_D^{25}$ = -77.2 (c 0.43, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 4.0 Hz, 1H), 7.99 (d, *J* = 6.8 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.46 (s, 1H), 7.33 (dd, *J* = 2.4 Hz, 9.2 Hz, 1H), 5.81-5.72 (m, 1H), 5.43 (d, *J* = 4.8 Hz, 1H), 4.99-4.91 (m, 2H), 3.36-3.32 (m, 1H), 3.22-3.27 (m, 1H), 3.07 (dd, *J* = 10.0 Hz, 1H), 2.68-2.63 (m, 2H), 2.25 (br, 1H), 1.81-1.80 (m, 1H), 1.70-1.64 (m, 4H), 1.48 (br, 1H), 1.37-1.26 (m, 3H), 1.13 (d, *J* = 7.6 Hz, 18H); ^{13}C NMR (100 MHz, DMSO-d6) δ 154.2, 147.65, 147.59, 144.1, 141.9, 131.4, 126.7, 124.9, 118.6, 114.2, 109.9, 72.6, 59.9, 57.0, 43.1, 40.0, 27.8, 27.7, 22.4, 17.9, 12.7; IR ($CHCl_3$) ν 3400-2400(br), 2943, 2866, 1616, 1506, 1457, 1258; HRMS (CI) m/z calcd. for ($C_{28}H_{42}N_2O_2Si$ + H^+): 467.3094, found: 467.3106.

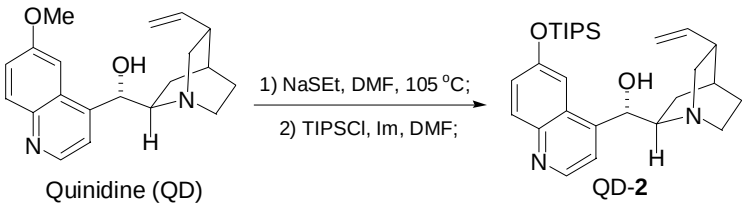
*Catalyst Q-**1d**:*



At room temperature to a solution of Q-**2** (3.3 g, 7 mmol) in anhydrous CH_2Cl_2 (40 mL) was added PhCOCl (0.91 mL, 1.1 eq.) and Et_3N (1.97 mL, 2 eq.). The resulting mixture was stirred at room temperature for 3 hours and TLC analysis indicated that the starting material was completely consumed. The reaction mixture was diluted with CH_2Cl_2 (250 mL) and washed with sat. $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was dissolved in CH_3CN (50 mL). To the resulting solution, HF (48 % aqueous solution, 2.5 mL) was added dropwise through syringe. Afte 15 minutes, TLC analysis showed that the starting material was completely consumed and the reaction mixture was diluted with ethyl acetate (400 mL), washed with sat. $NaHCO_3$ aq. (2 x 50 mL) and brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was purified by flash chromatography. (ethyl acetate/MeOH = 20/1) to give Q-**1d** as a white powder (2.7 g, 73% yield over 2 steps). m.p: 204-207 ^oC; $[\alpha]_D^{25}$ = + 89.3 (c 0.45, $CHCl_3$); ^1H NMR (400 MHz, DMSO-*d6*) δ 10.16 (br, 1H), 8.62 (d, *J* = 4.4 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.59-7.51 (m , 4H), 7.32 (d, *J* = 9.2 Hz, 1H), 6.44 (d, *J* = 7.6 Hz, 1H), 5.99-5.91 (m, 1H), 5.03 (d, *J* = 18.4 Hz, 1H), 4.98 (d, *J* = 11.6 Hz, 1H), 3.50-3.48 (m, 1H), 3.09 (br, 1H), 2.92-2.86 (m, 1H), 2.54-2.43 (m, 2H), 2.24 (br, 1H), 1.96-1.93 (m, 1H), 1.79 (br, 1H), 1.72-1.68 (m, 1H), 1.59-1.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d6) δ165.7, 156.4, 147.3, 144.0, 143.9, 142.9, 134.4, 132.0, 130.0, 129.9, 129.6, 127.6, 122.3, 119.6, 115.1, 105.2, 79.8, 75.3, 59.9, 56.6, 42.4, 27.9, 27.8, 25.3; IR ($CHCl_3$) ν 3500-2300 (br), 2943, 1717, 1540, 1558, 1507, 1268; HRMS (CI) m/z calcd for ($C_{26}H_{26}N_2O_3 + H^+$): 415.2022, found:415.2027.

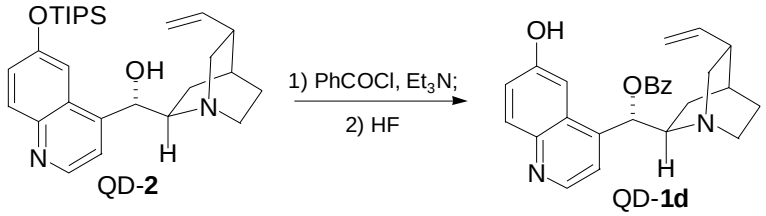
Preparation of catalyst QD-1d

*6'-OTIPS quinidine derivative QD-**2***:



Following same procedure as described for preparation of Q-**2** , QD-**2** was obtained in 75% yield from quinidine (QD). $[\alpha]_D^{25}$ = + 137.8 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 5.2 Hz, 1H), 7.87 (d, *J* = 9.2 Hz, 1H), 7.65 (d, *J* = 4.4 Hz, 1H), 7.37 (d, *J* = 2.8 Hz, 1H), 7.20 (dd, *J* = 2.4 Hz, 9.2 Hz, 1H), 6.50 (br, 1H), 6.02-5.93 (m, 1H), 5.22 (d, 3.6 Hz, 1H), 5.19 (d, *J* = 10.4 Hz, 1H), 4.25 (br, 1H), 3.37-3,31 (m, 3H), 3.14-3.08 (m, 1H), 2.54-2.51 (m, 1H), 2.32 (t, *J* = 12.0 Hz, 1H), 1.93-1.86 (m, 2H), 1.68-1.63 (m, 1H), 1.36 (hept. *J* = 7.2 Hz, 3H), 1.13 (d, *J* = 7.2 Hz, 9H), 1.11 (d, *J* = 7.2 Hz, 9H); 1.00-0.90 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d6) δ 154.4, 147.8, 144.1, 143.7, 136.6, 131.3, 125.6, 124.7, 119.0, 117.3, 110.0, 67.3, 60.2, 49.2, 48.7, 37.6, 27.7, 23.6, 18.5, 18.05, 18.01, 12.8; IR ($CHCl_3$) ν 3217 (br), 2943, 2867, 1617, 1589, 1504, 1456, 1259; HRMS (CI) m/z calcd. for ($C_{28}H_{42}N_2O_2Si + H^+$): 467.3094, found: 467.3103.

*Catalyst QD-**1d** :*

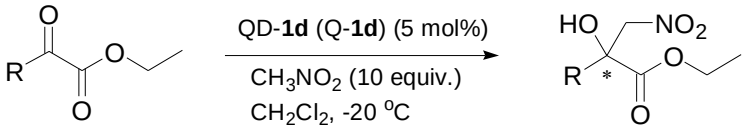


Following the same procedure described above for the preparation of Q-**1d**, QD-**1d** was prepared in 87% yield from QD-**2**. m.p.: 235-237 °C; $[\alpha]_D^{25}$ = - 10 (c 0.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (br, 1H), 8.65 (d, *J* = 4.4 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 2H), 7.92 (d, *J* = 9.6 Hz, 1H), 7.69 (s, 1H), 7.54 (t, *J* = 6.8 Hz, 1H), 7.42-7.40 (m, 3H), 7.20 (d, *J* = 9.2 Hz, 1H), 6.75 (d, *J* = 5.6 Hz, 1H), 6.02-5.93 (m, 1H), 5.08 (d, *J* = 6.4 Hz,

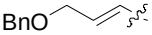
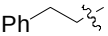
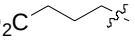
1H), 5.05 (d, *J* = 17.2 Hz, 1H), 3.39 (dd, *J* = 8.4 Hz, 6.4 Hz, 1H), 3.10-3.05 (m, 1H), 3.01-2.95 (m, 1H), 2.84-2.79 (m, 1H), 2.73-2.65 (m, 1), 2.27 (dd, *J* = 7.6 Hz, 8.0 Hz, 1H), 2.01 (t, *J* = 9.6 Hz, 1H), 1.83 (s, 1H), 1.50-1.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 156.4 ,146.1, 143.6, 143.4, 139.8, 133.3, 131.0, 129.7, 129.6, 128.5, 127.3, 122.8, 118.6, 115.1, 105.8, 74.3, 58.8, 49.6, 49.1, 39.2, 27.5, 26.0. 23.0; IR ($CHCl_3$) ν 2500-3500 (br), 3071, 2940, 1723, 1618, 1469, 1452, 1269, 1107; HRMS (ESI) m/z calcd for ($C_{26}H_{26}N_2O_3 + H^+$): 415.2022, found: 415.2026.

General procedure for enantioselective addition of nitromethane to α-ketoesters 2 catalyzed by QD-1d and Q-1d:

Table 2 Enantioselective Nitroaldol Addition of Nitromethane to α-Ketoester **2** Catalyzed by QD-**1d** and Q-**1d** (in brackets). [a]



2 (0.5 mmol) **3**

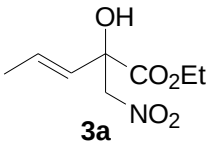
Entry		R	Time / h	yield / % [b]	ee / % [c]
1	**2a**		14 (15)	92 (92)	96 (97)
2	**2b**		24 (24)	98 (99)	94 (95)
3	**2c**	Ph-	35 (46)	96 (96)	95[d] (93)
4	**2d**	4-MeO-Ph-	96 (96)	86 (84)	94 (97)
5	**2e**	4-MeS-Ph-	72 (72)	86 (86)	96 (96)
6	**2f**	4-Cl-Ph-	12 (12)	98 (96)	97[d] (96)
7	**2g**	4-CN-Ph-	9 (11)	96 (98)	94 (97)
8	**2h**	3-Cl-Ph-	11 (11)	91 (96)	95 (95)
9	**2i**	2-Naphthyl-	60 (60)	96 (97)	94 (94)
10	**2j**	Me-	12 (12)	89 (90)	95 (95)
11	**2k**	*n*-Pr-	17 (15)	90 (90)	93 (93)
12	**2l**		14 (11)	88 (89)	95 (94)
13	**2m**		15 (11)	87 (86)	94 (93)

[a] Unless noted, reactions were run with 0.5 mmol of **2,** 5 mmol CH_3NO_2 in 0.5 mLCH_2Cl_2 with 5 mol% QD-**1d**, the results in parentheses were obtained with Q-**1d** to give opposite enantiomer, see Supporting Information for details. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The absolute configuration is determined to be *S,* see Supporting Information for details.

At -20 °C, to a solution of α-ketoester **2** (0.5 mmol), nitromethane (5 mmol) in CH_2Cl_2 (0.5 mL) was added catalyst QD-**1d** or Q-**1d** (5 mol%). The resulting mixture was kept

at the indicated temperature until **2** is completely consumed. The reaction mixture was directly subjected to silica gel flash chromatography using the eluent specified below to afford the desired product in the yields and enantiomeric excess summarized above. The catalyst is recovered in greater than 95% yield by washing the silica gel column with MeOH. The recovered catalyst was identical to that before the reaction by NMR analysis and can be reused without further treatment.

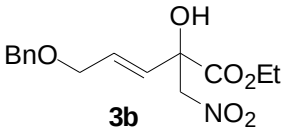
Data for nitroaldol products 3:



3a

(+)-2-Hydroxy-2-nitromethyl-pent-3-enoic acid ethyl ester (3a) This product was obtained as a colorless oil in 92% yield after flash chromatography (elution gradient: ethyl acetate/hexane = 1/15) and 96% ee as determined by HPLC analysis [Daicel chiralpak AD, hexanes:IPA, 90:10, 0.8 ml/min, λ 215 nm, t (major) = 10.03 min, t (minor) = 10.91 min] from a reaction catalyzed by QD-**1d** (5 mol%) at -20 °C for 14 hours. $[\alpha]_D^{25}$ = +56.0 (c 0.93, $CHCl_3$) ;^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (dq, *J* = 15.2 Hz, 6.8 Hz, 1H), 5.45 (dq, *J* = 15.2 Hz, 1.6 Hz, 1H), 4.86 (d, *J* = 14.0 Hz, 1H), 4.48 (d, *J* = 14.0 Hz, 1H), 4.42-4.28 (m, 2H), 3.77 (s, 1H), 1.75 (dd, *J* = 1.2 Hz, 14.0 Hz, 3H), 1.34 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 130.6, 125.7, 79.9, 75.0, 63.2, 17.6, 13.9; these data is in agreement with those reported in literature. [4]

(-)-2-Hydroxy-2-nitromethyl-pent-3-enoic acid ethyl ester (3a) This product was obtained as a colorless oil in 92% yield and 97% ee from a reaction catalyzed by Q-**1d** (5.0 mol %) at -20 °C for 15 hours.

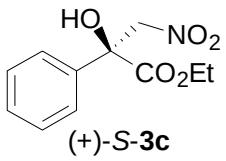


3b

(+)-5-Benzyloxy-2-hydroxy-2-nitromethyl-pent-3-enoic acid ethyl ester (3b) This product was obtained as a colorless oil in 98 % yield after flash chromatography (elution gradient: diethyl ether) and 94 % ee as determined by HPLC analysis [Daicel chiralpak AD, hexanes:IPA, 90:10, 0.8 ml/min, λ 215 nm, t (major) = 17.65 min, t (minor) = 19.99 min] from a

reaction catalyzed by QD-**1d** (5 mol%) at -20 °C for 24 hours. $[\alpha]_D^{25}$ = + 29.8 (c 1.22, $CHCl_3$) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.32 (m, 5H), 6.25 (dt, *J* = 15.2 Hz, 4.8 Hz, 1H), 5.76 (dt, *J* = 15.2 Hz, 1.6 Hz, 1H), 4.88 (dd, *J* = 14.0 Hz, 1.2 Hz, 1H), 4.53 (s, 2H), 4.48 (d, *J* = 13.2 Hz, 1H), 4.41-4.29 (m, 2H), 4.08-4.06 (m, 2H), 3.84 (s, 1H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ171.4, 137.7, 131.5, 128.3, 127.7, 127.6, 125.8, 79.7, 75.1, 72.6, 68.9, 63.3, 13.9; IR ($CHCl_3$) ν 3489 (br), 3031, 2983, 2859, 1742, 1560, 1453, 1378, 1220; HRMS (ESI) m/z calcd for ($C_{15}H_{19}NO_6$ + Na^+): 332.1110, found: 332.1102.

(-)-5-Benzyloxy-2-hydroxy-2-nitromethyl-pent-3-enoic acid ethyl ester (3b) This product was obtained as a colorless oil in 99% yield and 95% ee from a reaction catalyzed by Q-**1d** (5 mol %) at -20 °C for 24 hours.

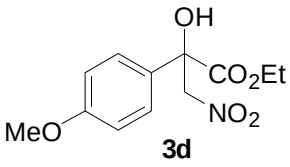


(+)-*S*-**3c**

(+)-*S*-2-Hydroxy-3-nitro-2-phenyl-propionic acid ethyl ester (3c) This product was obtained as a colorless oil in 96% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/19) and 95 % ee as determined by HPLC analysis [Daicel chiralcel OD, hexanes:IPA, 80:20, 1.0 ml/min, λ 220 nm, t (major) = 7.49 min, t (minor) = 9.46 min] from a reaction catalyzed by QD-**1d** (5 mol%) at -20 °C for 35 hours. $[\alpha]_D^{25}$ = + 28.4 (c 1.05, $CHCl_3$) ;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.60 (m, 2H), 7.43-7.40 (m, 3H), 5.26 (d, *J* = 14.0 Hz, 1H), 4.68 (d, *J* = 14.0 Hz, 1H), 4.44-4.31 (m ,2H), 4.22 (s, 1H), 1,34 (dt, *J* = 1.2Hz, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 136.4, 129.0, 128.8, 125.2, 80.7, 75.9, 63.5, 13.8; these data are in agreement with those reported in literature. [4]

The absolute configuration of (+)-3c was determined to be S by converting 3c into β-lactam 5c and comparing the value of the specific rotation of 5c with that reported in the literature. (for details see below preparation of β-lactam **5c** part**).**

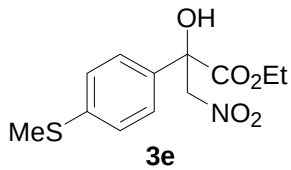
(-)-*R*-2-Hydroxy-3-nitro-2-phenyl-propionic acid ethyl ester (3c) This product was obtained as a colorless oil in 96% yield and 93% ee from a reaction catalyzed by Q-**1d** (5 mol %) at -20 °C for 46 hours.



3d

(+)-2-Hydroxy-2-(4-methoxy-phenyl)-3-nitro-propionic acid ethyl ester (3d) This product was obtained as a white solid in 86% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/10) and 94% ee as determined by HPLC analysis [Daicel chiralpak AS, hexanes:IPA, 80:20, 1.0 ml/min, λ 220 nm, t (major) = 10.90min, t (minor) = 13.49 min] from a reaction catalyzed by QD-**1d** (5 mol%) at -20 °C for 96 hours. M.p.: 70-73 °C; $[\alpha]_D^{25}$ = + 26.9 (c 1.25, $CHCl_3$) ;^{1}H NMR (400 MHz, $CDCl_3$) δ7.51 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.22 (d, *J* = 14.4 Hz, 1H), 4.41-4.31 (m, 2H), 4.65 (d, *J* = 14.4 Hz, 1H), 4.17 (s, 1H), 3.82 (s, 3H), 1.34 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 160.1, 128.3, 126.6, 114.2, 80.8, 75.7, 63.5, 55.3, 13.9; these data are in agreement with those reported in lit. [4]

(-)-2-Hydroxy-2-(4-methoxy-phenyl)-3-nitro-propionic acid ethyl ester (3d) This product was obtained as a colorless oil in 84% yield and 97% ee from a reaction catalyzed by Q-**1d** (5 mol %) at -20 °C for 96 hours.

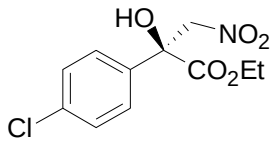


3e

(+)- 2-Hydroxy-2-(4-methylsulfanyl-phenyl)-3-nitro-propionic acid ethyl ester (3e) This product was obtained as a white solid in 86% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/7) and 96% ee as determined by HPLC analysis [Daicel chiralcel OD, hexanes:IPA, 80:20, 1.0 ml/min, λ 220 nm, t (major) = 8.84 min, t (minor) = 12.15 min] from a reaction catalyzed by QD-**1d** (5.0 mol%) at -20 °C for 72 hours. M.p.: 84-86 °C; $[\alpha]_D^{25}$ = + 29.7 (c 1.1, $CHCl_3$) ;^{1}H NMR (400 MHz, $CDCl_3$) δ7.51 (dd, *J* = 2.0 Hz, 6.8 Hz, 2H), 7.25 (d, *J* = 6.8 Hz, 2H), 5.22 (d, *J* = 14.4 Hz, 1H), 4.65 (d, *J* = 14.4 Hz, 1H), 4.43-4.30 (m, 2H), 4.19 (s, 1H), 2.49 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ171.5, 140.2, 132.8, 126.2, 126.6,

80.6, 75.7, 63.6, 15.3, 13.9; IR ($CHCl_3$) ν 3484, 2984, 2924, 1736, 1559, 1493, 1378, 1226; HRMS (ESI) m/z calcd for ($C_{12}H_{15}NO_5S + Na^+$): 308.0569, found: 308.0571.

(-)-2-Hydroxy-2-(4-methylsulfanyl-phenyl)-3-nitro-propionic acid ethyl ester (3e) This product was obtained as a colorless oil in 86 % yield and 96 % ee from a reaction catalyzed by Q-**1d** (5 mol %) at -20 °C for 72 hours.

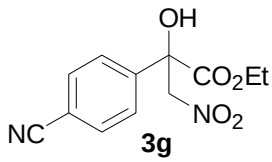


(+)-*S*-**3f**

(+)-*S*-2-(4-Chloro-phenyl)-2-hydroxy-3-nitro-propionic acid ethyl ester (3f) This product was obtained as a colorless oil in 98 % yield after flash chromatography (elution gradient: ethyl acetate/hexane =1/15) and 97 % ee as determined by HPLC analysis [Daicel chiralcel OD, hexanes:IPA, 85:15, 1.0 ml/min, λ 220 nm, t (major) = 7.67 min, t (minor) = 9.17 min] from a reaction catalyzed by QD-**1d** (5 mol%) at -20 °C for 12 hours. $[\alpha]_D^{25} = +24.4$ (c 1.1, $CHCl_3$) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (td, *J* = 2.4 Hz, 8.8 Hz, 2H), 7.39 (td, *J* = 2.4 Hz, 8.8 Hz, 2H), 5.22 (d, *J* = 14.0 Hz, 1H), 4.64 (d, *J* = 14.0 Hz, 1H), 4.44-4.31 (m, 2H), 4.24 (s, 1H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ171.2, 135.2, 134.9, 129.0, 126.7, 80.5, 75.6, 63.7, 13.8; these data are in agreement with those reported in lit. [4]

The absolute configuration of (+)-3f was determined to be S by comparing the specific rotation with that of literature data. $[\alpha]_D^{25} = +21.7$ (c 1.0, CH_2Cl_2) for 96% ee [lit. [4] $[\alpha]_D^{23} = -17.5$ (c 1.02, CH_2Cl_2) 88 % ee for *R* isomer].

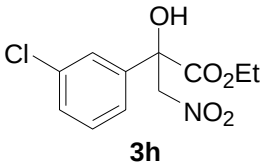
(-)-*R*-2-(4-Chloro-phenyl)-2-hydroxy-3-nitro-propionic acid ethyl ester (3f) This product was obtained as a colorless oil in 96% yield and 96% ee from a reaction catalyzed by Q-**1d** (5 mol %) at -20 °C for 12 hours.



3g

(+)-2-(4-Cyano-phenyl)-2-hydroxy-3-nitro-propionic acid ethyl ester (3g) This product was obtained as a white solid in 96% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/6) and 94% ee as determined by HPLC analysis [Daicel chiralpak AD, hexanes:IPA, 80:20, 0.9 ml/min, λ 220 nm, t (major) = 15.44 min, t (minor) = 13.99 min] from a reaction catalyzed by QD-**1d** (5 mol%) at -20 ^{o}C for 9 hours. M.p.: 97-100 ^{o}C; $[\alpha]_D^{25}$ = + 24.9 (c 1.05, $CHCl_3$) ;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 5.23 (d, *J* = 14.0 Hz, 1H), 4.65 (d, *J* = 14.0 Hz, 1H), 4.47-4.33 (m ,2H), 4.32 (s, 1H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 141.3, 132.6, 126.3, 118.0, 113.3, 80.3, 75.7, 64.2, 13.9; IR ($CHCl_3$) ν 3475 (br), 2985, 2232, 1741, 1561, 1502, 1378, 1229; HRMS (CI) m/z calcd for ($C_{12}H_{12}N_2O_5 + H^+$): 265.0824, found: 265.0831.

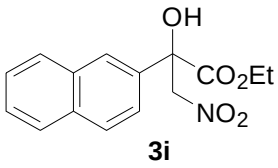
(-)-2-(4-Cyano-phenyl)-2-hydroxy-3-nitro-propionic acid ethyl ester (3g) This product was obtained as a colorless oil in 98% yield and 97% ee from a reaction catalyzed by Q-**1d** (5 mol %) at -20 ^{o}C for 11 hours.



3h

(+)-2-(3-Chloro-phenyl)-2-hydroxy-3-nitro-propionic acid ethyl ester (3h) This product was obtained as a colorless oil in 91 % yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/15) and 95 % ee as determined by HPLC analysis [Daicel chiralcel OD, hexanes:IPA, 85/15, 1.0 ml/min, λ 220 nm, t (major) = 7.86 min, t (minor) = 10.15 min] from a reaction catalyzed by QD-**1d** (5 mol%) at -20 ^{o}C for 11 hours. $[\alpha]_D^{25}$ = + 25.2 (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 1.6 Hz, 1H), 7.51-7.47 (m, 1H), 7.38-7.32 (m, 2H), 5.22 (d, *J* = 14.8 Hz, 1H), 4.65 (d, *J* = 14.8 Hz, 1H), 4.46-4.33 (m, 2H), 4.25 (s, 1H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 138.3, 135.0, 130.1, 129.3, 125.7, 123.4, 80.5, 75.6, 63.9, 13.9; IR ($CHCl_3$) ν 3486 (br), 3073, 2984, 2926, 1739, 1562, 1475, 1416, 1377, 1227; HRMS (ESI) m/z calcd for ($C_{11}H_{12}ClNO_5 + Na^+$): 296.0302, found: 296.0300.

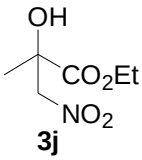
(-)-2-(3-Chloro-phenyl)-2-hydroxy-3-nitro-propionic acid ethyl ester (3h) This product was obtained as a colorless oil in 96% yield and 95% ee from a reaction catalyzed by Q-**1d** (5 mol %) at -20 °C for 11 hours.



3i

(+)-2-Hydroxy-2-naphthalen-2-yl-3-nitro-propionic acid ethyl ester (3i) This product was obtained as a white solid in 96% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/19) and 94% ee as determined by HPLC analysis [Daicel chiralcel OD, hexanes:IPA, 60:40, 1.0 ml/min, λ 280 nm, t(major) = 7.60 min, t(minor) = 19.91 min] from a reaction catalyzed by QD-**1d** (5 mol%) at -20 °C for 60 hours. M.p.: 75-77 °C; $[\alpha]_D^{25}$ = + 47.6 (c 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.89-7.84 (m, 3H), 7.67 (dd, *J* = 2.0 Hz, 8.8 Hz, 1H), 7.56-7.52 (m, 2H), 5.39 (d, *J* = 14.0 Hz, 1H), 4.76 (d, *J* = 14.0Hz, 1H), 4.46-4.33 (m, 2H), 4.34 (s, 1H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ171.6, 133.6, 133.2, 132.9, 128.7, 128.4, 127.5, 127.0, 126.7, 125.0, 122.3, 80.7, 76.2, 63.6, 13.9; IR ($CHCl_3$) ν 3487 (br), 3059, 2983, 1738, 1560, 1415, 1377, 1270, 1224, 1133; HRMS (CI) m/z calcd for ($C_{15}H_{15}NO_5^+$): 289.0950, found: 289.0942.

(-)-2-Hydroxy-2-naphthalen-2-yl-3-nitro-propionic acid ethyl ester (3i) This product was obtained as a colorless oil in 97% yield and 94% ee from a reaction catalyzed by Q-**1d** (5.0 mol %) at -20 °C for 60 hours.

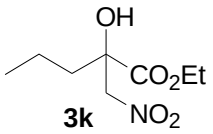


3j

(-)-2-Hydroxy-2-methyl-3-nitro-propionic acid ethyl ester (3j) This product was obtained as a colorless oil in 89% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/6) and 95% ee as determined by HPLC analysis [Daicel chiralpak AS, hexanes:IPA, 95:5, 1.0 ml/min, λ 215 nm, t (major) = 16.90 min, t (minor) = 19.93 min] from a reaction catalyzed by QD-**1d** (5 mol%) at -20 °C for 12 hours. $[\alpha]_D^{25}$ = - 5.1 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.84 (d, *J* = 14.0 Hz, 1H), 4.56 (d, *J* = 14.0 Hz, 1H), 4.40-

4.28 (m, 2H), 3.73 (s, 1H), 1.46 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ173.5, 80.9, 72.4, 63.0, 23.8, 13.9; these data are in agreement with those reported in lit. [4]

(+)-2-Hydroxy-2-methyl-3-nitro-propionic acid ethyl ester (3j) This product was obtained as a colorless oil in90% yield and 95% ee from a reaction catalyzed by Q-**1d** (5.0 mol %) at -20 °C for 12 hours.

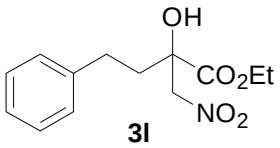


3k

(-)-2-Hydroxy-2-nitromethyl-pentanoic acid ethyl ester (3k) This product was obtained as a colorless oil in 90% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/15) and 93% ee as determined by HPLC analysis [Daicel chiralpak AS, hexanes:IPA, 90:10, 1.0 ml/min, λ 215 nm, t (major) = 8.75 min, t (minor) = 10.84 min] from a reaction catalyzed by QD-**1d** (5.0 mol%) at -20 °C for 17 hours. $[\alpha]_D^{25}$ = - 14.0 (c 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (d, J = 13.2 Hz, 1H), 4.56 (d, J = 13.2 Hz, 1H), 4.41-4.29 (m, 2H), 3.70 (s, 1H), 1.72-1.59 (m, 2H), 1.57-1.45 (m, 1H), 1.34 (t, J = 7.2 Hz, 3H), 1.26-1.14 (m, 1H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 80.8, 75.2, 62.9, 38.6, 16.0, 14.0, 13.8; IR ($CHCl_3$) ν 3505 (br), 2967, 2937, 1739, 1561, 1467, 1380, 1234, 1162; HRMS (CI) m/z calcd for ($C_8H_{15}NO_5 + H^+$): 206.1028, found: 206.1023.

(-)-2-Hydroxy-2-nitromethyl-pentanoic acid ethyl ester (3k) This product was obtained as a colorless oil in 90% yield and 93% ee from a reaction catalyzed by Q-**1d** (5.0 mol %) at -20 °C for 15 hours.

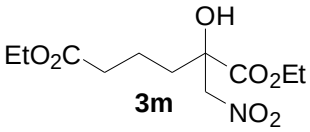
(-)-2-Hydroxy-2-nitromethyl-4-phenyl-butyric acid ethyl ester (3l) This product was obtained as a colorless oil in 88 % yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/15) and 95% ee as determined by HPLC analysis [Daicel chiralpak AS, hexanes:IPA, 90:10, 1.0 ml/min, λ 220 nm, t (major) = 10.75 min, t (minor) = 14.79 min] from a reaction catalyzed by QD-**1d** (5 mol%) at -20 °C for 14 hours.



3l

$[\alpha]_D^{25}$ = - 18.8 (c 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.14 (m, 5H), 4.83 (d, *J* = 13.2 Hz, 1H), 4.58 (d, *J* = 13.2 Hz, 1H), 4.39-4.25 (m, 2H), 3.82 (s, 1H), 2.86-2.79 (m, 1H), 2.53-2.45 (m, 1H), 2.06-1.92 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 140.1, 128.5, 128.2, 126.2, 80.7, 74.9, 63.0, 38.1, 28.9, 14.0; these data are in agreement with those reported in lit. [4]

(+)-2-Hydroxy-2-nitromethyl-4-phenyl-butyric acid ethyl ester (3l) This product was obtained as a colorless oil in 89% yield and 94% ee from a reaction catalyzed by Q-**1d** (5.0 mol %) at -20 °C for 11 hours.

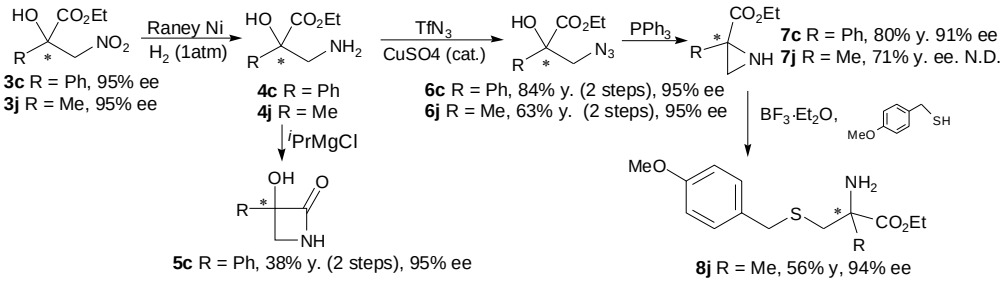


3m

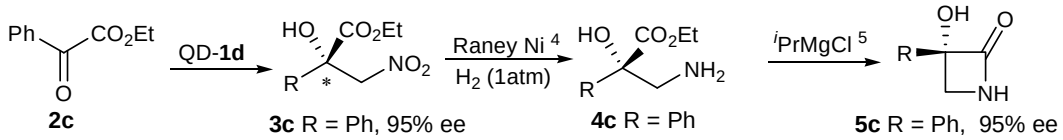
(-)-2-Hydroxy-2-nitromethyl-hexanedioic acid diethyl ester (3m) This product was obtained as a colorless oil in 87% yield after flash chromatography (elution gradient: ethyl acetate/hexane=1/5) and 94% ee as determined by HPLC analysis [Daicel chiralcel OJ, hexanes:IPA, 70:30, 1.0 ml/min, λ 215 nm, t (major) = 17.23min, t (minor) = 12.00 min] from a reaction catalyzed by QD-**1d** (5 mol%) at -20 °C for 15 hours. $[\alpha]_D^{25}$ = - 5.3 (c 1.15, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (d, *J* = 14.0 Hz, 1H), 4.57 (d, *J* = 14.0 Hz, 1H), 4.43-4.30 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.75 (s, 1H), 2.37-2.26 (m, 2H), 1.86-1.73 (m, 2H), 1.70-1.64 (m, 1H), 1.59-1.49 (m, 1H), 1.35 (t, *J* = 6.8 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ172.7, 172.6, 80.7, 75.0, 63.1, 60.4, 35.6, 33.5, 18.2, 14.1, 14.0; IR ($CHCl_3$) ν 3492 (br), 2983, 2939, 1733, 1560, 1419, 1379, 1224; HRMS (ESI) m/z calcd for ($C_{11}H_{19}NO_7$ + Na^+): 300.1059, found: 300.1053.

(+)-2-Hydroxy-2-nitromethyl-hexanedioic acid diethyl ester (3m) This product was obtained as a colorless oil in 86% yield and 93% ee from a reaction catalyzed by Q-**1d** (5 mol %) at -20 °C for 11 hours.

Concise Asymmetric Syntheses of β-lactam 5, aziridines 7 and α-methylcysteine derivative 8 from nitroaldol products 3:



*Synthesis of **3-phenyl-3-hydroxyazetidin-2-one (5c):*** [4, 5]



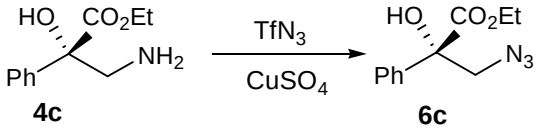
At -20 °C, to a solution of α-ketoester **2c** (1.136g, 6.38 mmol), nitromethane (3.4 mL) in CH_2Cl_2 (6.4 mL) was added catalyst QD-**1d** (132 mg, 5.0 mol%) The resulting mixture was kept at -20 °C for 40 hours when TLC showed **2c** was completely consumed. The reaction mixture was directly subjected to silica gel flash chromatography (EA/Hexanes = 1/15) to furnish **3c** as a clear oil (1.503g, 98% yield) and in 95% ee. The column was washed with MeOH and the catalyst **1d** was recovered almost quantitatively (> 131 mg). The recovered catalyst was shown to be identical to that before the reaction by NMR analysis.

To a solution of **3c** (1.04g, 4.35mmol) obtained from reactions using QD-**1d** in EtOH (25 mL) was added Raney nickel (1.0 g in 10 mL). The resulting reaction mixture was stirred under H_2 at atmospheric pressure for 4 h at room temperature. After the starting material

was completely consumed (monitored by TLC), the reaction mixture was passed through a short pad of celite and the celite was then washed with EtOH (2 x 10 mL). The filtrate was concentrated in vacuo and the residue **4c** was used in next step without further purification (864 mg, 95% yield).

At 0 ^{o}C, to a solution of **4c** (113 mg, 0.54 mmol) in anhydrous THF (2.0 mL) was added ^{i}PrMgCl (2.0 M in THF,1.35 mL, 2.7 mmol) dropwisely via a synringe. The resulting reaction mixture was stirred at room temperature for 19 hours. The reaction was quenched with NH_4Cl aq. (sat. 10.0 mL) and extracted with ethyl acetate (50 mL). The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was purified by flash chromatography (ethyl acetate:hexanes = 1.5:1) to give **5c** as a white powder (36 mg, 37% yield over 3 steps from **2c**). The ee of **5c** was determined to be 95% by HPLC analysis (chiralcel OD, IPA/Hexane = 95/5, 1.0 ml/min, 220 nm, t(major) = 32.27 min, t(minor) = 28.73 min). M.p.: 127-130 ^{o}C; $[\alpha]_D^{25}$ = - 107 ^{o} (c: 0.27 in $CHCl_3$) {lit.[5] $[\alpha]_D^{23}$ = - 57.4^{o}, (c: 0.25 in $CHCl_3$) for 80% ee, ***S*** isomer}. The absolute configuration of **5c** is therefore determined to be **S,** which indicate that the absolute configuration of **3c** obtained with QD-**1d** is ***S.*** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.45 (m, 2H), 7.36-7.26 (m, 3H), 6.89 (br, 1H), 3.56 (d, *J* = 5.6 Hz, 1H), 3.47 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 138.0, 128.6, 128.4, 125.3, 86.9, 54.1. The data is consistent with those reported in the literature.[5]

Synthesis of ***Propionic acid 2-azido-1-hydroxy-1-phenyl-ethyl ester (6c):*** [6]



A mixture of NaN_3 (1.76g, 27 mmol), water (4 mL) and CH_2Cl_2 (2 mL) was cooled to 0 ^{o}C in an ice-water bath. To this mixture under vigorous stirring, Tf_2O (0.75 mL, 4.5

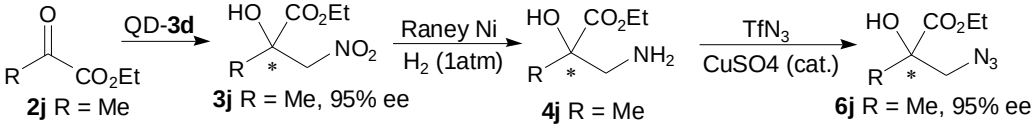
mmol) was added dropwise via a syringe. The resulting mixture was stirred at 0 ^{o}C for 3 h and 1 mL of water was added to the reaction mixture, after which the aqueous and organic phase was separated. The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (2 mL). The combined organic phase was washed with sat. aqueous $NaHCO_3$ (5 mL), after which it was used for the reaction with **4c**.

At room temperature, to a solution of crude **4c** (341 mg, 1.6 mmol, derived from hydrogenation of **3c** as described above) in CH_2Cl_2 (1.5 mL) was added Et_3N (0.63 mL, 4.8 mmol) and an aqueous solution of $CuSO_4$ (12 mg in 0.25 mL of water) consecutively. To the resulting mixture, a solution of TfN_3 in CH_2Cl_2 freshly prepared as described above was added. This is followed by the addition of MeOH (around 1 mL), and the reaction mixture became homogenous. The reaction mixture was stirred at room temperature for 2.5 hours, afterwhich it was poured into sat. $NaHCO_3$ aq. (20 mL). The resulting mixture was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was purified by chromatography (silica gel, ethyl acetate/hexanes = 1/20) to give **6c** as a clear oil (339 mg, 88% yield, 84% yield over 2 steps from **3c**). The ee of **6c** was determined to be 96% by HPLC analysis (chiralcel OJ, IPA/Hexanes = 90/10, 1.0 mL/min, 220nm, t(minor)=10.03 min, t(major)=13.17 min). $[\alpha]_D^{25}$ =-30 ^{o} (c: 1.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 6.8 Hz, 2H), 7.40-7.32 (m, 3H), 4.39-4.25 (m, 2H), 4.01 (s, 1H), 3.84 (d, *J* = 12.4 Hz, 1H), 3.62 (d, *J* = 12.4 Hz, 1H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 138.3, 128.5, 125.3, 79.3, 63.1, 58.4, 14.0; IR ($CHCl_3$) ν 3496, 3063, 2984, 2102, 1732, 1448, 1250; HRMS (ESI) m/z calcd for ($C_{11}H_{13}N3O_3 + Na^+$): 258.0855, found: 258.0860.

*Synthesis of **2-Phenyl-aziridine-2-carboxylic acid ethyl ester (7c):*** [7]

To a solution of **6c** (300 mg, 1.27 mmol) in anhydrous CH_3CN (8.0 mL) was added PPh_3 (501 mg, 1.9 mmol) at room temperature. The mixture was stirred at room temperature for 1.0 h and then refluxed for 14 h under Ar atmosphere. The solvent was removed in vacuo and the residue was purified by chromatography (ethyl acetate/hexanes = 1/15) to give **7c** as a clear oil (196 mg, 80% yield). The ee of **7**c was determined to be 91% ee by HPLC (chiralpak AS plus *R,R*-Whelko, IPA/Hexanes = 90/10, 1.0 ml/min, 220 nm, t(major)= 11.20 min, t(minor)=12.59 min). $[\alpha]_D^{25} = -7.4^{o}$ (c: 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.44 (m, 2H), 7.35-7.27 (m, 3H), 4.26-4.12 (m, 2H), 2.51 (dd, *J* = 2.0 Hz, 10.4 Hz, 1H), 2.00-1.91 (m, 2H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 136.3, 129.1, 127.9, 127.6, 62.2, 41.2, 35.2, 13.9; 3290, 2984, 1717, 1306, 1195; HRMS (CI) m/z calcd for ($C_{11}H_{13}NO_2 + H^+$): 192.1024, found: 192.1018.

Synthesis of azide ***3-Azido-2-hydroxy-2-methyl-propionic acid ethyl ester (6j):*** [4, 6]



At -20 °C, to a solution of α-ketoester **2j** (580 mg, 5 mmol), nitromethane (2.7 mL) in CH_2Cl_2 (5 mL) was added catalyst QD-**1d** (104 mg, 5 mol%). The resulting mixture was kept at -20 °C for 13 hours and TLC showed **2j** is completely consumed. The reaction mixture was directly subjected to silica gel flash chromatography (EA/Hexanes = 1/15) to give **3j** as a clear oil (830 mg, 94% yield). The ee of **3j** was determined to be 95%. The

column was washed with MeOH and the catalyst was recovered almost quantitatively (> 103 mg). The recovered catalyst was shown to be identical to that before the reaction by NMR analysis.

To a solution of **3j** (800 mg, obtained with QD-**1d** in 95% ee) in EtOH (20 mL) was added Raney nickel (1.5 g in 10 mL). The reaction mixture was stirred under H_2 at atmospheric pressure for 4 h at room temperature. After the starting material was completely consumed (monitored by TLC), the reaction mixture was passed through a short pad of celite and celite was washed with EtOH (2 x 10 mL). The filtrate was concentrated in vacuo and the residue **4j** was used directly in next step (600 mg, 90% crude yield).

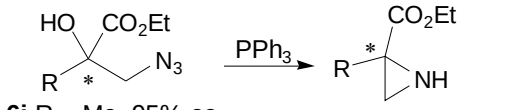
A solution of NaN_3 (3.5 g, 54 mmol) in water (8 mL) and CH_2Cl_2 (3 mL) was cooled to 0 ^oC in an ice-water bath. To this solution under vigorous stirring, Tf_2O (1.51 mL, 9 mmol) was added dropwise via a syringe. The reaction mixture was stirred at 0 ^oC for 3 h, afterwhich the mixture was diluted with water (2 mL). The aqueous and organic phases were separated. The organic phase was collected and the aquous phase was extracted with CH_2Cl_2 (3 mL). The combined organic phase was washed with sat. $NaHCO_3$ aq. (10 mL). This solution was used for the next step.

At room temperature, to a solution of **4j** (475 mg, crude from **3j** as described before) in CH_2Cl_2 (3 mL) was added Et_3N (1.25 mL) and a solution of $CuSO_4$ (24 mg in 0.5 mL H_2O) consecutively. To the resulting mixture, a freshly prepared solution of TfN_3 in CH_2Cl_2 as described above was added. This is followed by the addition of MeOH (around 2.0 mL) afterwhich the solution became homogenous. The resulting mixture was stirred at room temperature for 2.5 hours. The reaction mixture was poured into sat. $NaHCO_3$ aq. (30 mL). The resulting mixture was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue aas purified by chromatography (silica gel, petroleum ether/ether = 9/1) to give **6j** as a clear oil (390 mg, 70% yield, 59% yield over 3 steps from **2j**). The ee of **6j** was determined to be 95% by HPLC analysis: Daicel

chiralpak AS, Hexane:IPA, 97:3, 1.0 mL/min, λ 215 nm t(major)= 8.40 min, t(minor)= 9.52 min); $[\alpha]_D^{25}$ = - 83.3 ^{o} (c: 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31-4.25 (m, 2H), 3.51 (s, 1H), 3.47-3.40 (m, 2H), 1.41 (s, 3H), 1.32 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 75.1, 62.5, 58.4, 23.3, 14.0; IR ($CHCl_3$) ν 3503, 2985, 2939, 2105, 1733, 1456, 1258.

(*Cautious: the product is very volatile, be careful when remove solvent in vacuo*)

Synthesis of aziridine ***2-Methyl-aziridine-2-carboxylic acid ethyl ester (7j):*** [7]



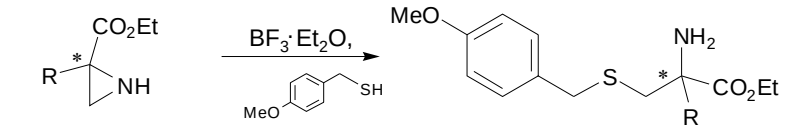
6j R = Me, 95% ee

7j R = Me, ee. N.D.

To a solution of **6j** (188 mg, 1.09 mmol) in anhydrous CH_3CN (4 mL) was added PPh_3 (427 mg, 1.6 mmol) at room temperature. The mixture was stirred at r.t. for 1 h and then refluxed for 9 h under Ar atmosphere. The solvent was removed in vacuo and the residue was purified by chromatography (silica gel, petroleum ether/ether = 5/1) to give **7j** as a clear oil (99 mg, 71% yield). $[\alpha]_D^{25}$ = - 28 ^{o} (c: 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (dq, *J* = 1.6 Hz, 7.2 Hz, 2H), 2.17 (d, *J* = 10.4 Hz, 1H), 1.64 (d, *J* = 4.8 Hz, 1H), 1.42 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 53.4, 34.7, 34.1, 17.9, 14.0; IR ($CHCl_3$) ν 3294, 3070, 2983, 2940, 1724, 1325, 1199; HRMS (CI) m/z calcd for ($C_6H_{11}NO_2 + H^+$): 130.0868, found: 130.0867.

(*Cautious: the product is very volatile, be exremely careful when remove solvent in vacuo*)

Synthesis of ***2-Amino-3-(4-methoxy-benzylsulfanyl)-2-methyl-propionic acid ethyl ester (8j):*** [7]



7j R = Me, ee. N.D.

8j R = Me, 56% y, 94% ee

At 0 ^{o}C, to the solution of **7j** (65 mg, 0.5 mmol) in CH_2Cl_2 (1.5 mL) was added *p*-methoxybenzyl mercaptan (0.21 mL, 1.5 mmol) and boron trifluride diethyl etherate (0.11 mL). The resulting mixture was stirred at 0 ^{o}C for 12 h followed by stirring at room temperature for 24 h. The reaction mixture was poured into sat. $NaHCO_3$ aq. (20 mL) and the mixture was extracted with ethyl acetate (2 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by chromatography (silica gel, petroleum ether/ethyl acetate = 2/1) to give **8j** as a clear oil (80 mg, 56% yield) in 94% ee (determined by HPLC: Daicel chiralcel OD, Hexane:IPA, 80:20, 0.5 mL/min, λ 254 nm, t (minor) = 14.56 min, t (major) = 15.22 min). $\alpha]_D^{25}$ = - 12 ^{o} (c: 1.05 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.20-4.14 (m, 2H), 3.79 (s, 3H), 3.70 (s, 2H), 2.92 (d, *J* = 13.2 Hz, 1H), 2.59 (d, *J* = 13.2 Hz, 1H), 1.85 (br, 2H), 1.34 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ176.3, 158.6, 130.1, 129.9, 113.8, 61.2, 58.6, 55.2, 42.0, 37.1, 26.3, 14.1; IR ($CHCl_3$) ν 3373, 2978, 2933, 1731, 1610, 1512, 1249; HRMS (ESI) m/z calcd for ($C_{14}H_{21}NO_3S + H^+$): 284.1320, found: 284.1315.

References:

1) Jesen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 160-163.
2) (a) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906-9907. (b) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng L. *Angew. Chem.Int. Ed.* **2005**, *44*, 105-108. (c) Liu, X.; Li, H.; Deng, L. *Org. Lett.* **2005**, *7*, 167-169.
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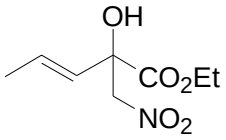
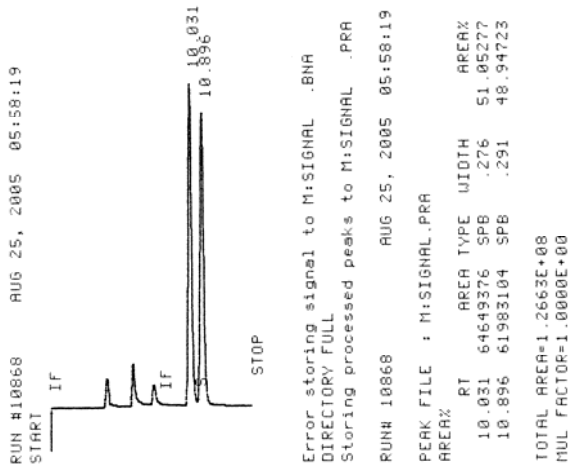
6) a) Liu, Q.; Tor, Y. *Org. Lett.* **2003**, *5*, 2571-2572. b) Nyffeler, P. T.; Liang, C.-H.; Koeller, K. M.; Wong, C.-H *J. Am. Chem. Soc.* **2002**, *124*, 10773-10778.
7) Shao, H.; Zhu, Q.; Goodman, M. *J. Org. Chem.* **1995**, *60*, 790-791.

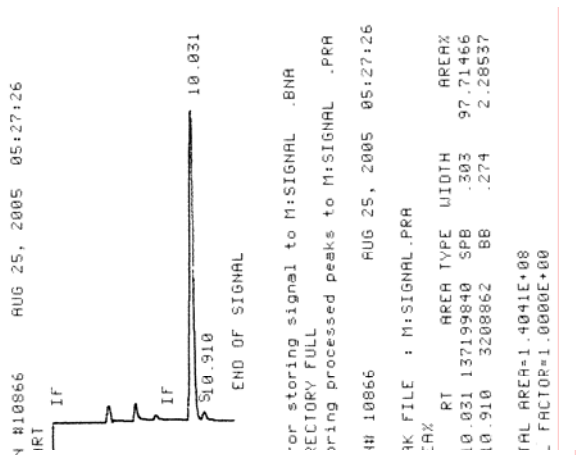
HPLC Conditions: Daicel chiralpak AD, Hexane:IPA, 90:10, 0.80 mL/min, λ 215 nm



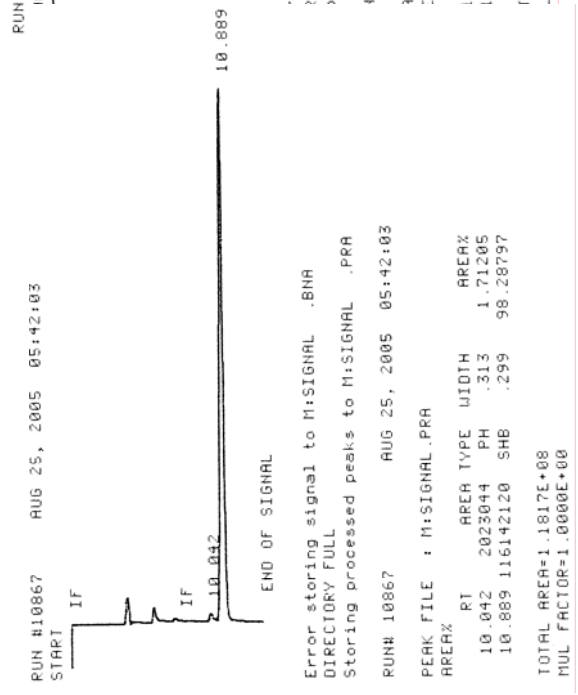
racemic **3a**



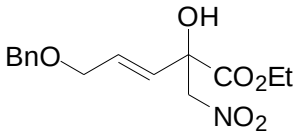
(+)-**3a** 96% ee
Product obtained with QD-**1d**



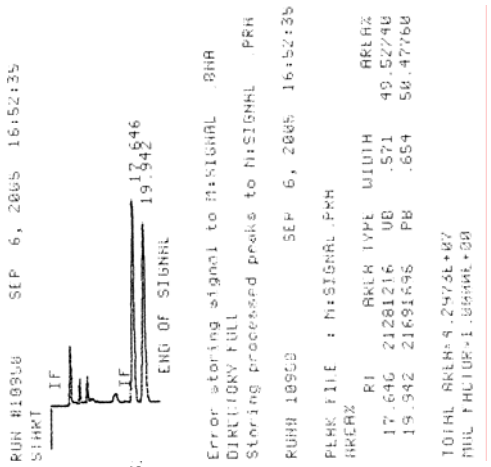
(-)-**3a** 97% ee
Product obtained with Q-**1d**



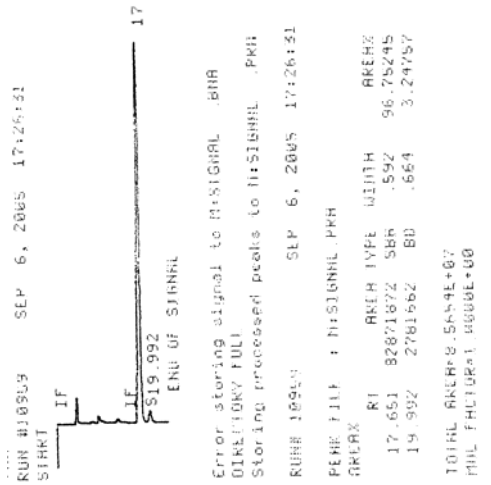
HPLC Conditions: Daicel chiralpak AD, Hexane:IPA, 90:10, 0.80 mL/min, λ 215 nm



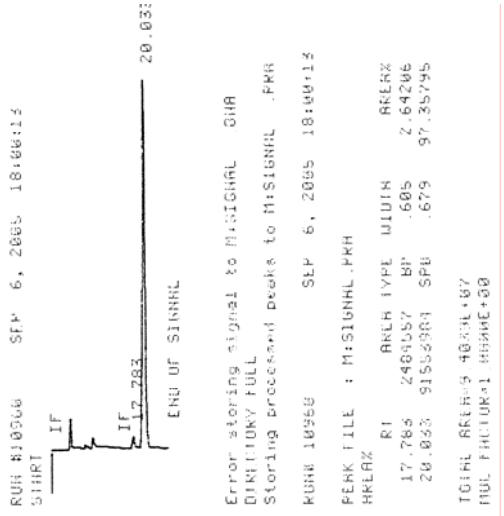
racemic **3b**



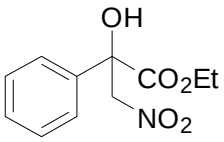
(+)-**3b** 94% ee
Product obtained with QD-**1d**



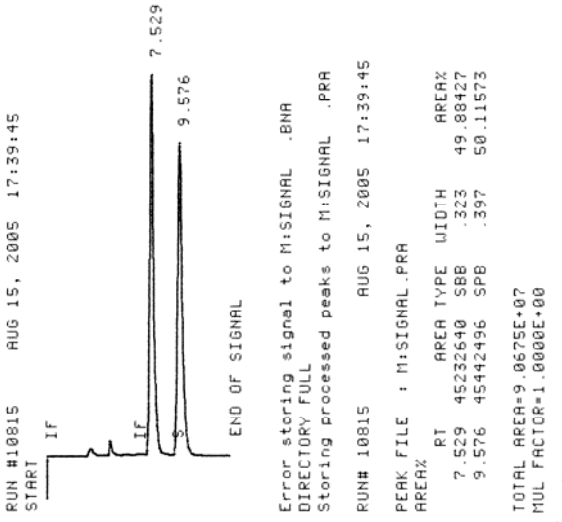
(-)-**3b** 95% ee
Product obtained with Q-**1d**

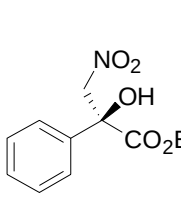


HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 80:20, 1.00 mL/min, λ 220 nm

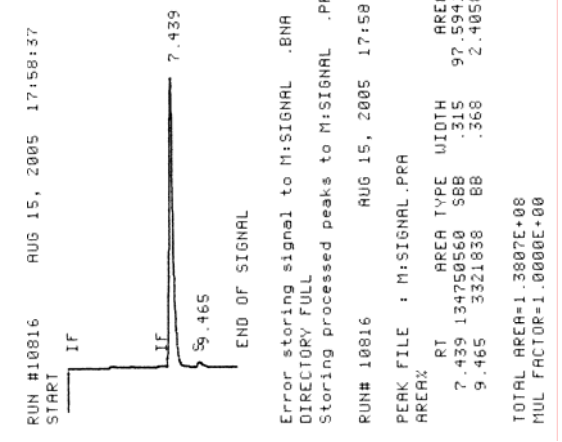


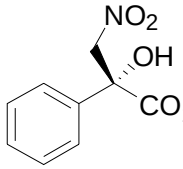
racemic **3c**



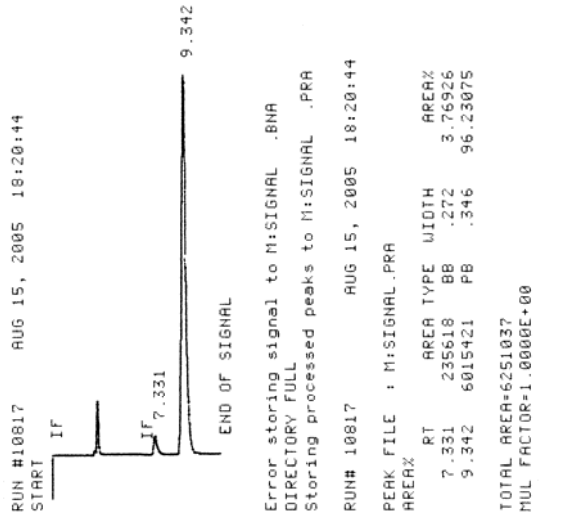


(+)-*S*-**3c** 95% ee
Product obtained with QD-**1d**

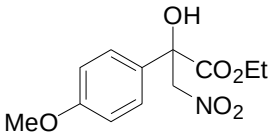




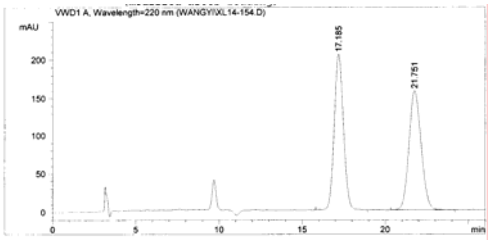
(-)-*R*-**3c** 93% ee
Product obtained with Q-**1d**



HPLC Conditions: Daicel chiralpak AS, Hexane:IPA, 85:15, 1.00 mL/min, λ 220 nm



racemic **3d**

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Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :      1.00000  [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

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----|-------|---|----|----------|----------|--------|
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Totals :                1.57303e4   360.64748
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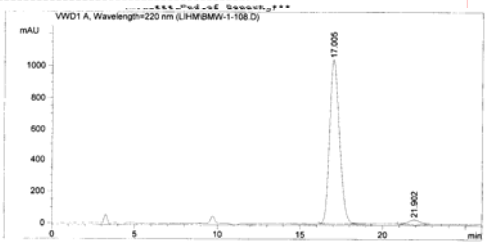
(+)-**3d** 94% ee
Product obtained with QD-**1d**

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Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

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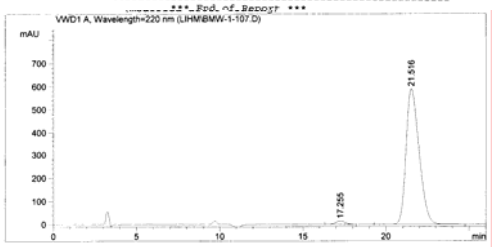
(-)-**3d** 97% ee
Product obtained with Q-**1d**

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Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Sig Type     Area      Height     Area
  #   [min]              mAU   *s   [mAU   ]     %
----|-------|---|----|----------|----------|--------|
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   2  21.516  1   VB   3.20168e4   588.83374  98.2551

Totals :                3.25854e4   603.17529

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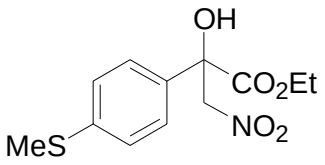
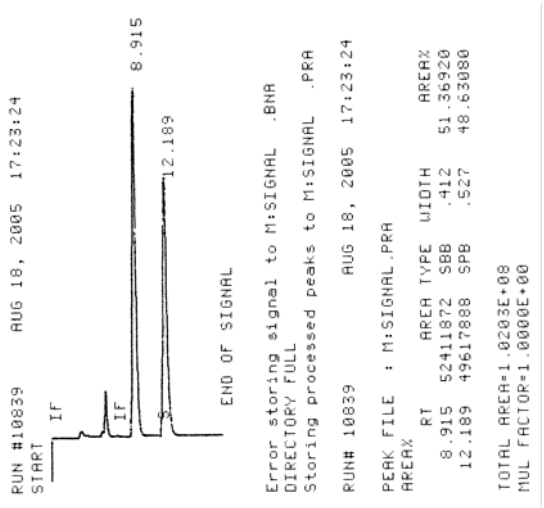
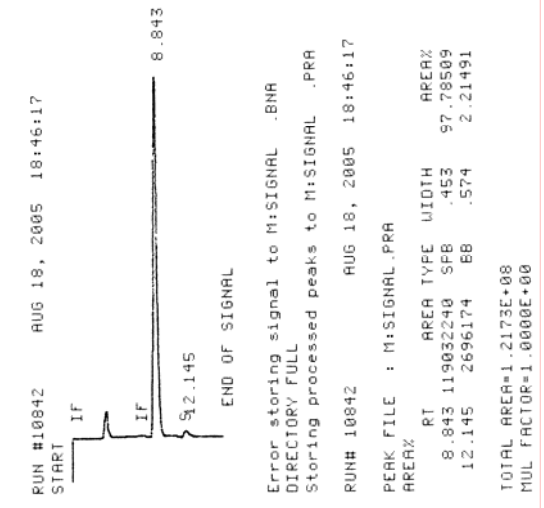
HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 80:20, 1.00 mL/min, λ 220 nm



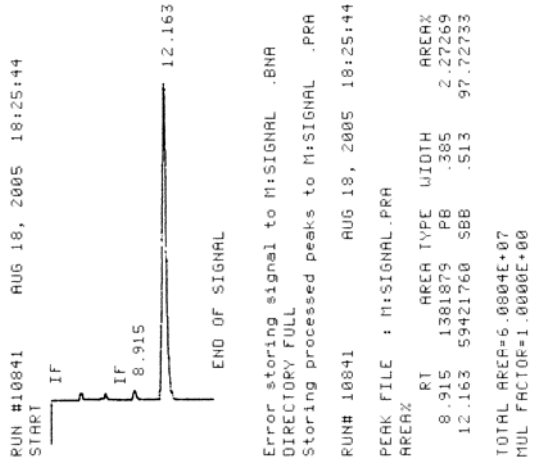
racemic **3e**



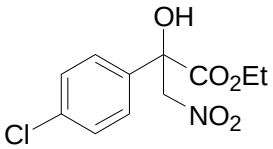
(+)-**3e** 96% ee
Product obtained with QD-**1d**



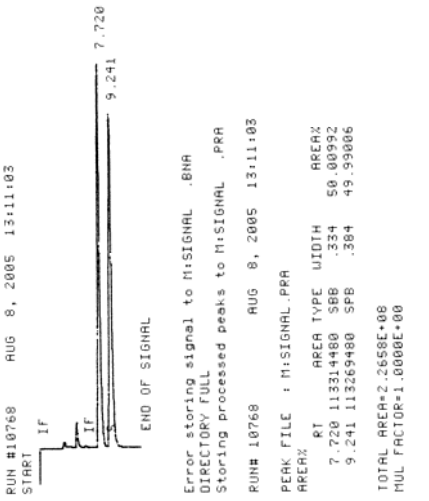
(-)-**3e** 96% ee
Product obtained with Q-**1d**

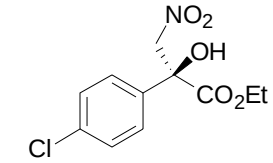


HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 85:15, 1.00 mL/min, λ 220 nm

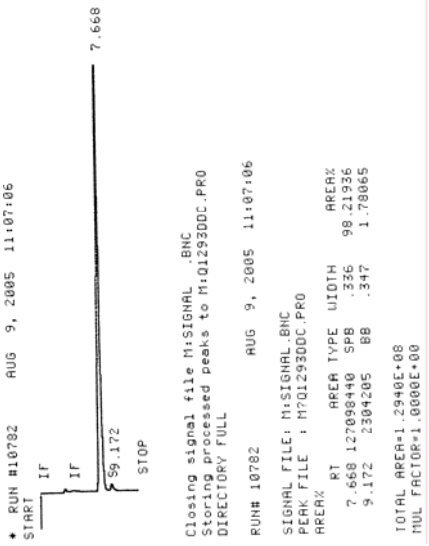


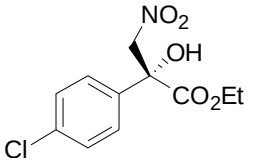
racemic **3f**



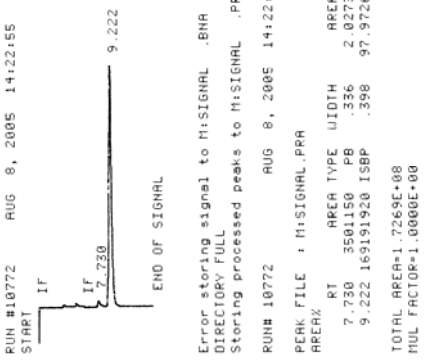


(+)-*S*-**3f** 97% ee
Product obtained with QD-**1d**

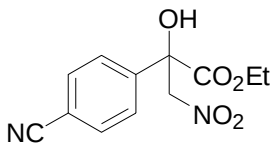




(-)-*R*-**3f** 96% ee
Product obtained with Q-**1d**

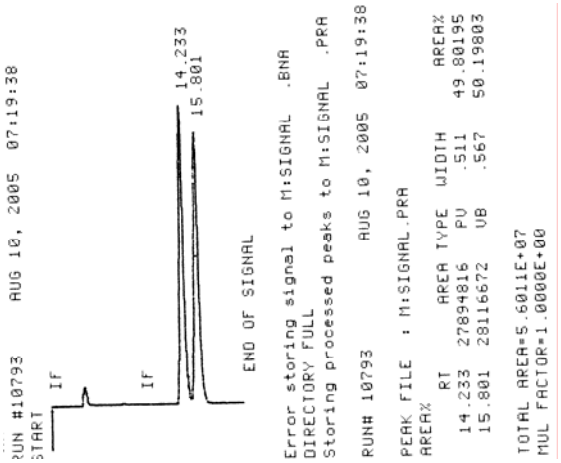


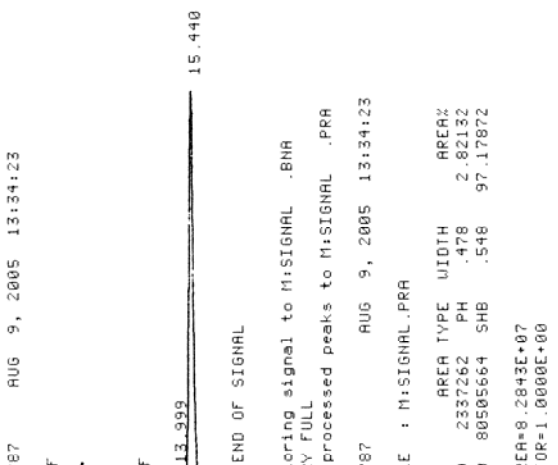
HPLC Conditions: Daicel chiralpak AD, Hexane:IPA, 80:20, 0.90 mL/min, λ 220 nm



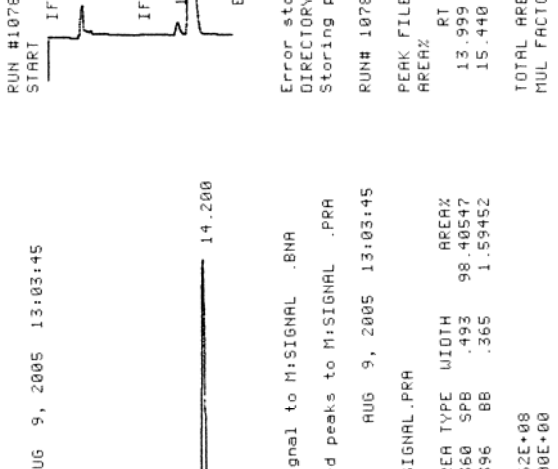
racemic **3g**

(+)-**3g** 94% ee
Product obtained with QD-**1d**

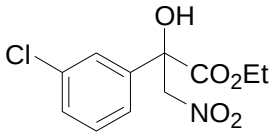




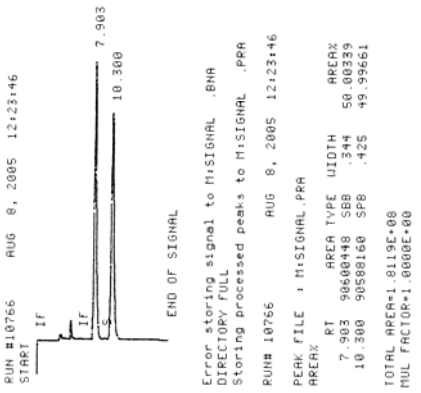
(-)-**3g** 97% ee
Product obtained with Q-**1d**



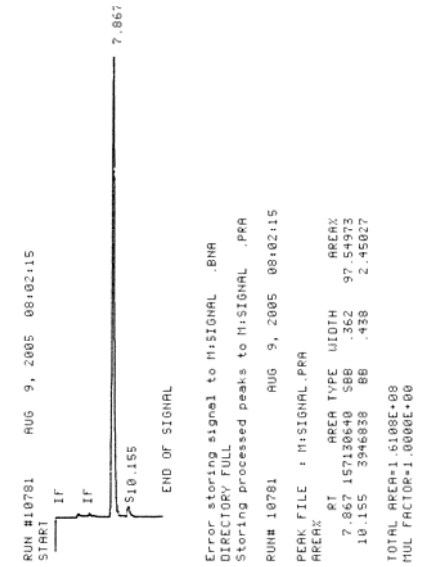
HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 85:15, 1.00 mL/min, λ 220 nm



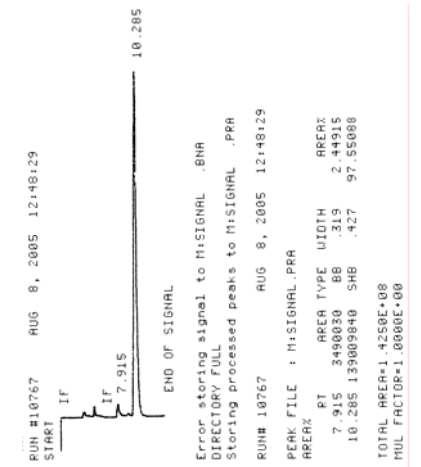
racemic **3h**



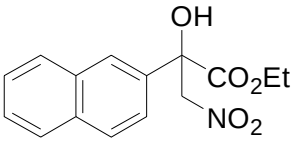
(+)-**3h** 95% ee
Product obtained with QD-**1d**



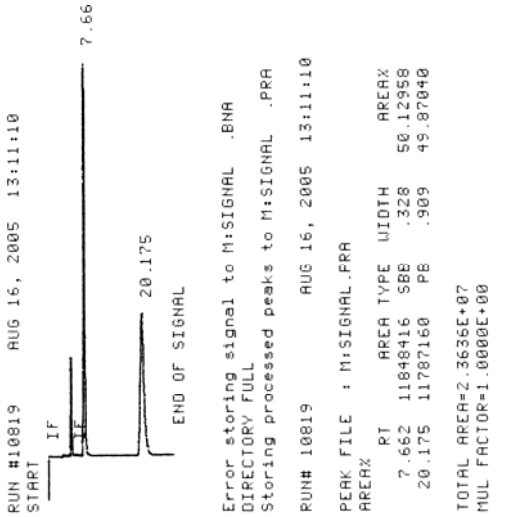
(-)-**3h** 95% ee
Product obtained with Q-**1d**



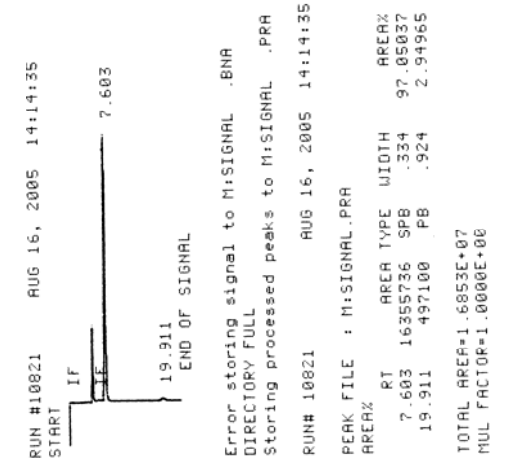
HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 60:40, 1.00 mL/min, λ 280 nm



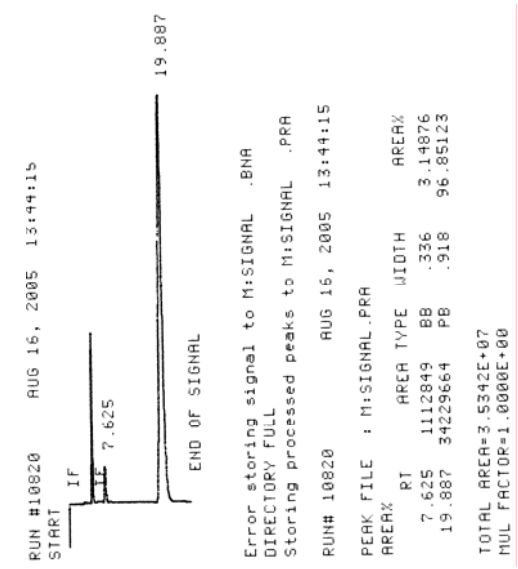
racemic **3i**



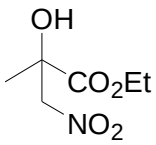
(+)-**3i** 94% ee
Product obtained with QD-**1d**



(-)-**3i** 94% ee
Product obtained with Q-**1d**

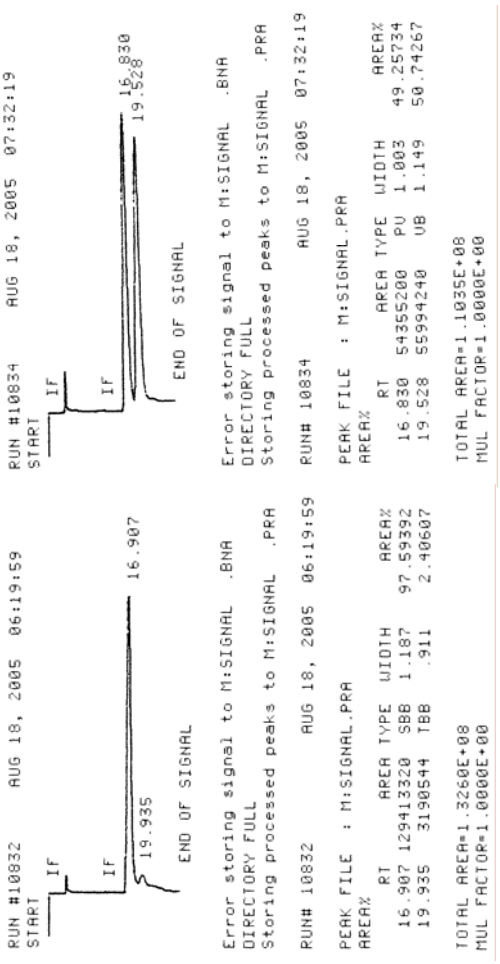


HPLC Conditions: Daicel chiralpak AS, Hexane:IPA, 95:5, 1.00 mL/min, λ 215 nm

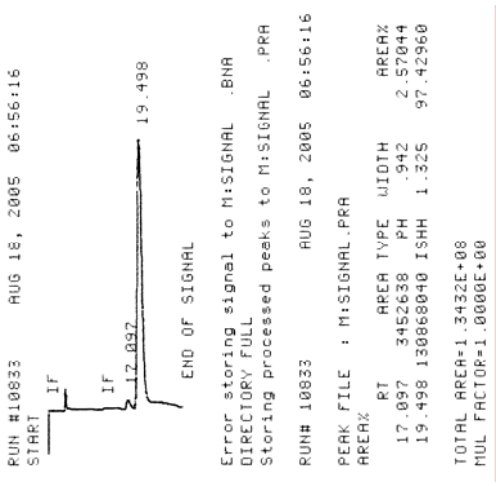


racemic **3j**

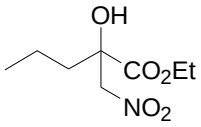
(-)-**3j** 95% ee
Product obtained with QD-**1d**



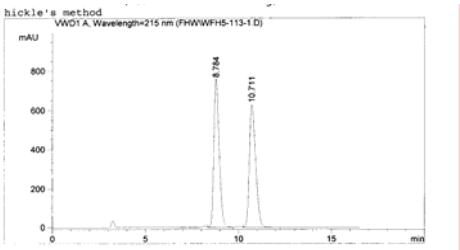
(+)-**3j** 95% ee
Product obtained with Q-**1d**



HPLC Conditions: Daicel chiralpak AS, Hexane:IPA, 90:10, 1.00 mL/min, λ 215 nm



racemic **3k**



Area Percent Report

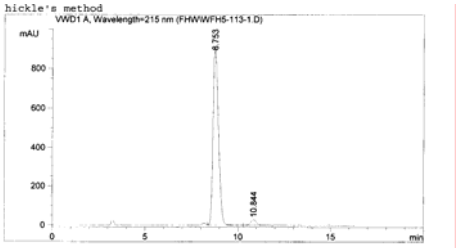
Sorted By : Retention Time
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 1.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=215 nm

Peak #	RetTime [min]	Sig	Type	Area mAU *s	Height [mAU]	Area %
1	8.784	1	VV	1.52245e4	753.39691	50.4358
2	10.711	1	VB	1.49614e4	628.23187	49.5642

Totals : 3.01859e4 1381.62878

(-)-**3k** 93% ee
Product obtained with QD-**1d**



Area Percent Report

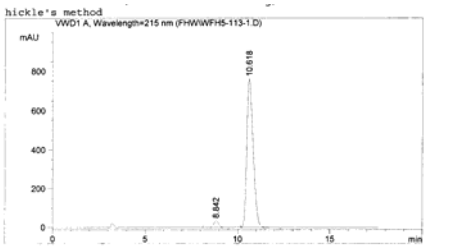
Sorted By : Retention Time
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 1.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=215 nm

Peak #	RetTime [min]	Sig	Type	Area mAU *s	Height [mAU]	Area %
1	8.753	1	VV	1.84167e4	902.78381	96.6691
2	10.844	1	VV	634.57745	28.33386	3.3309

Totals : 1.90512e4 931.11768

(+)-**3k** 93% ee
Product obtained with QD-**1d**



Area Percent Report

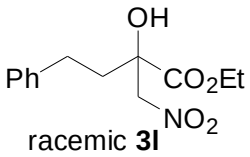
Sorted By : Retention Time
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 1.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=215 nm

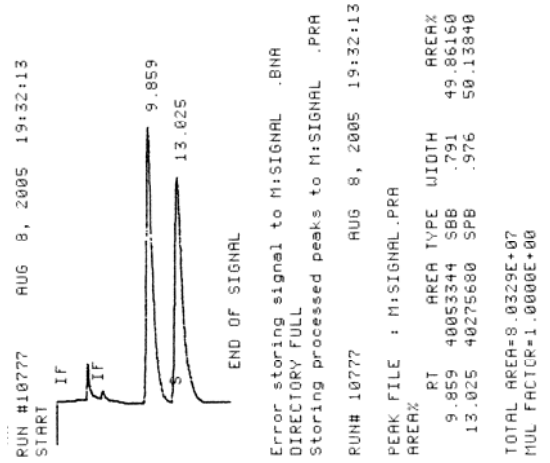
Peak #	RetTime [min]	Sig	Type	Area mAU *s	Height [mAU]	Area %
1	8.842	1	VV	662.42883	36.39874	3.4849
2	10.618	1	VV	1.83462e4	762.05957	96.5151

Totals : 1.90086e4 798.45831

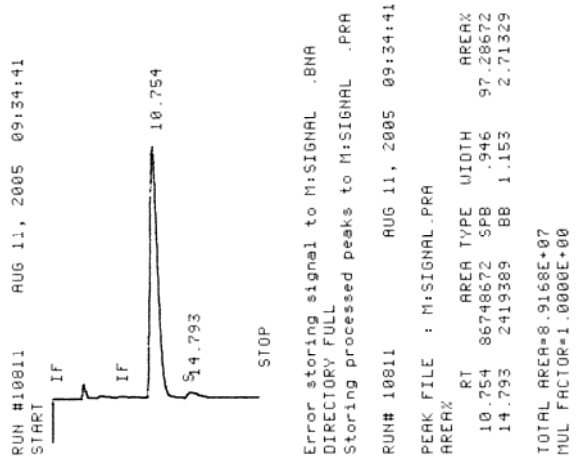
HPLC Conditions: Daicel chiralpak AS, Hexane:IPA, 90:10, 1.00 mL/min, λ 220 nm



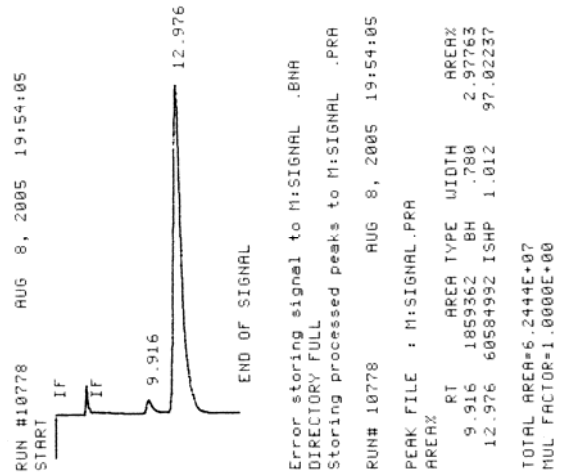
racemic **3l**



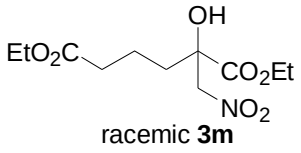
(-)-**3l** 95% ee
Product obtained with QD-**1d**



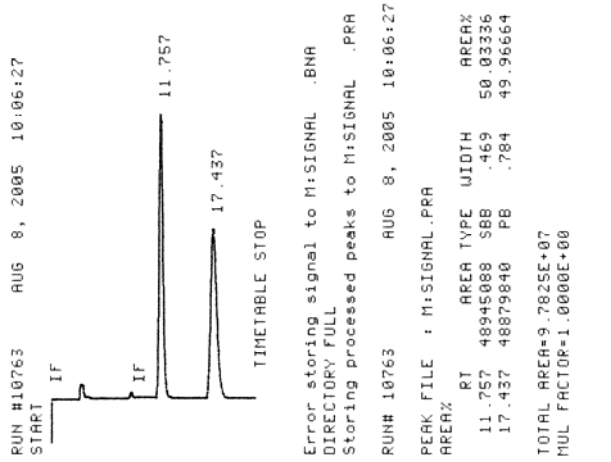
(+)-**3l** 94% ee
Product obtained with Q-**1d**



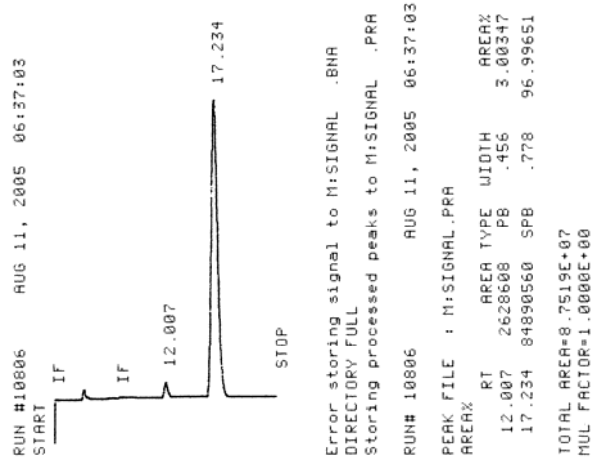
HPLC Conditions: Daicel chiralcel OJ, Hexane:IPA, 70:30, 1.0 mL/min, λ 215 nm



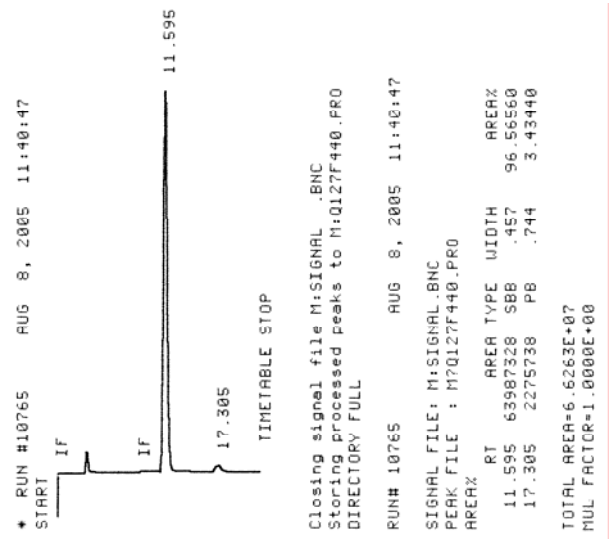
racemic **3m**



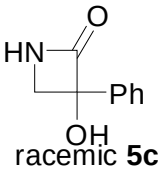
(-)-**3m** 94% ee
Product obtained with QD-**1d**



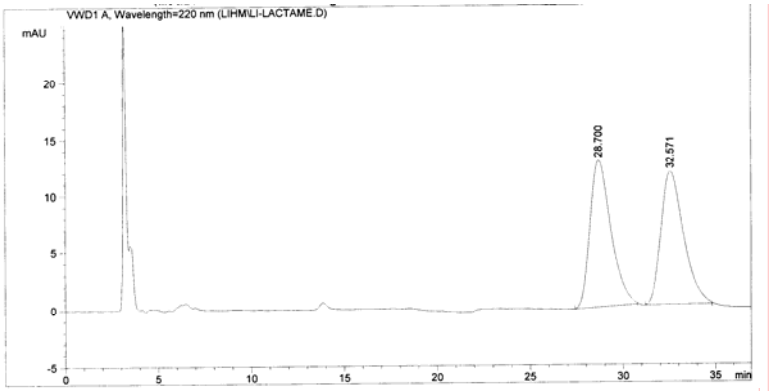
(+)-**3m** 93% ee
Product obtained with Q-**1d**



HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 95:5, 1.00 mL/min, λ 220 nm



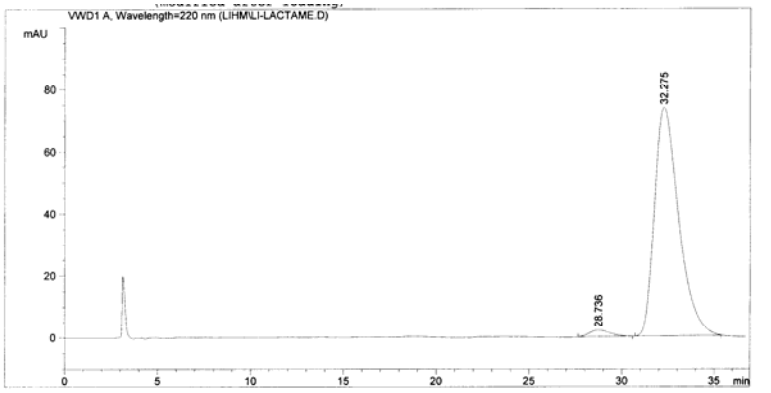
racemic **5c**

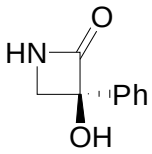


Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	28.700	BB	1.1426	1006.38245	12.86675	50.5199
2	32.571	BB	1.2364	985.66785	11.64612	49.4801
Totals :				1992.05029	24.51287	

*** End of Report ***



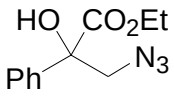


(-)-*S*-**5c** 95% ee

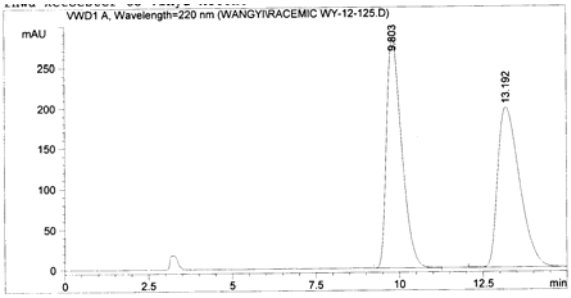
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	28.736	BB	0.9140	167.63673	2.17435	2.4255
2	32.275	BB	1.3818	6743.72607	73.51411	97.5745
Totals :				6911.36281	75.68846	

*** End of Report ***

HPLC Conditions: Daicel chiralcel OJ, Hexane:IPA, 90:10, 1.0 mL/min, λ 220 nm



racemic **6c**

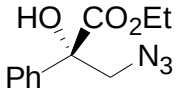


Area Percent Report

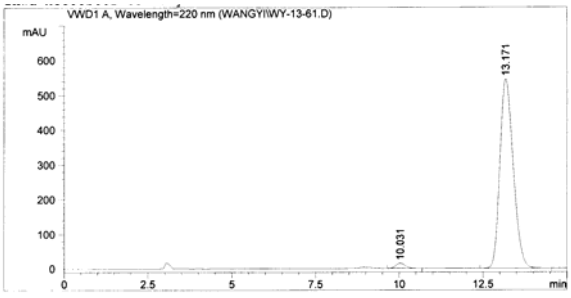
Sorted By : Retention Time
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 1.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Sig	Type	Area mAU *s	Height [mAU]	Area %
1	9.803	1	VB	8949.16211	284.00308	49.8995
2	13.192	1	BB	8985.20703	198.48335	50.1005
Totals :				1.79344e4	482.48643	



(-)-*S*-**6c** 96% ee



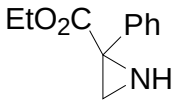
Area Percent Report

Sorted By : Retention Time
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 1.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

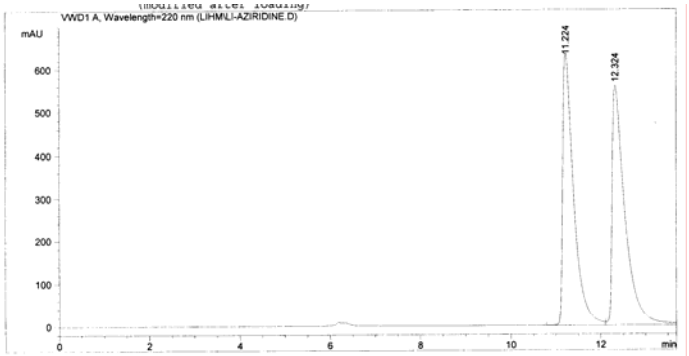
Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Sig	Type	Area mAU *s	Height [mAU]	Area %
1	10.031	1	BB	294.72345	14.97665	1.9095
2	13.171	1	BB	1.51401e4	544.54773	98.0905
Totals :				1.54348e4	559.52438	

HPLC Conditions: Daicel chiralpak AS plus (R, R)-whelk-O 1, Hexane:IPA, 90:10, 1.0 mL/min, λ 220 nm



racemic **7c**



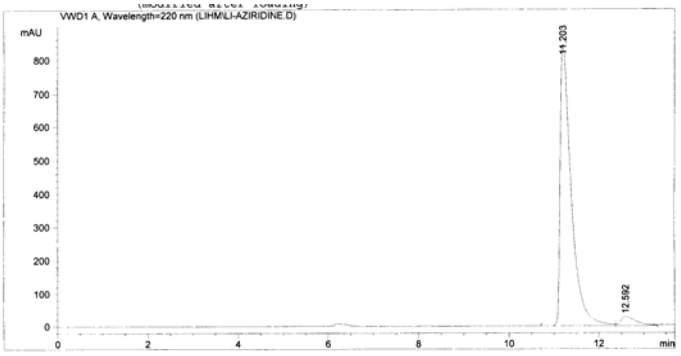
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 1.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.224	BV	0.2501	1.07312e4	633.45020	49.2105
2	12.324	VV	0.2890	1.10755e4	560.03827	50.7895
Totals :				2.18068e4	1193.48846	

(-)-*R*-**7c** 91% ee



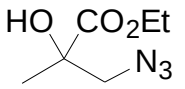
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 1.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

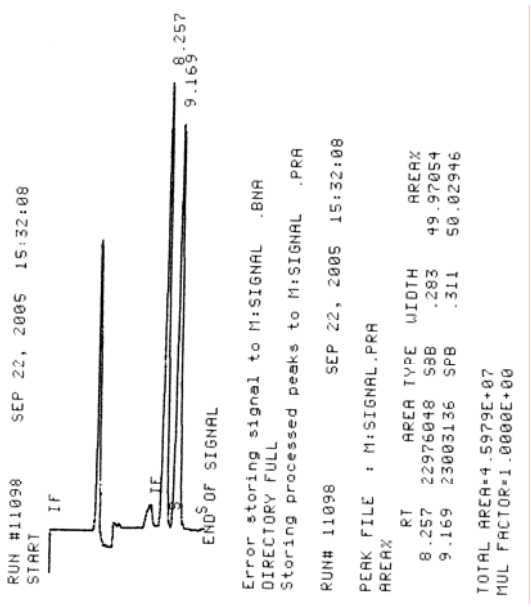
Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	11.203	VV	0.2542	1.45336e4	840.34460	95.4503
2	12.592	VV	0.3295	692.74963	29.79496	4.5497
Totals :				1.52263e4	870.13956	

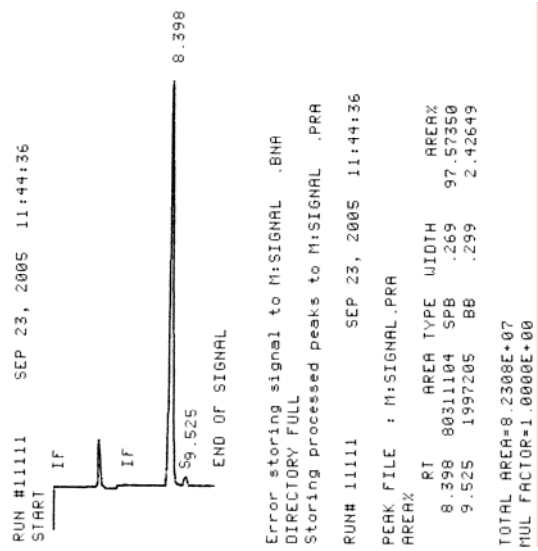
HPLC Conditions: Daicel chiralpak AS, Hexane:IPA, 97:3, 1.0 mL/min, λ 215 nm



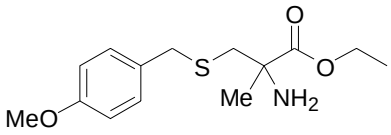
racemic **6j**



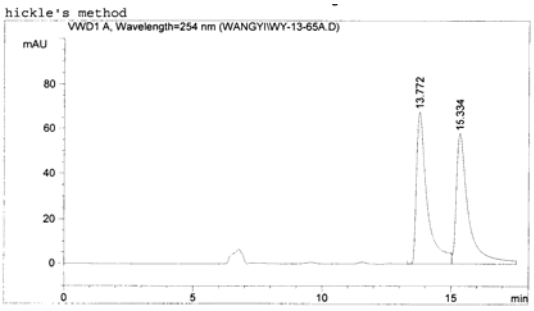
(-)-**6j** 95% ee



HPLC Conditions: Daicel chiralcel OD, Hexane:IPA, 80:20, 0.5 mL/min, λ 254 nm

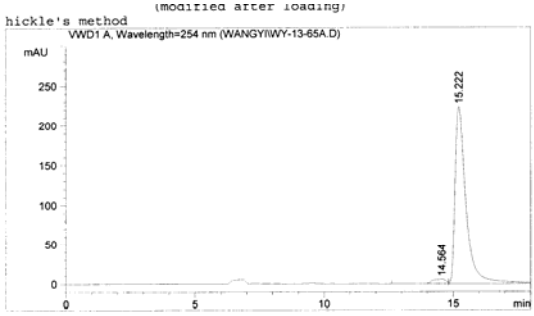


racemic **8j**

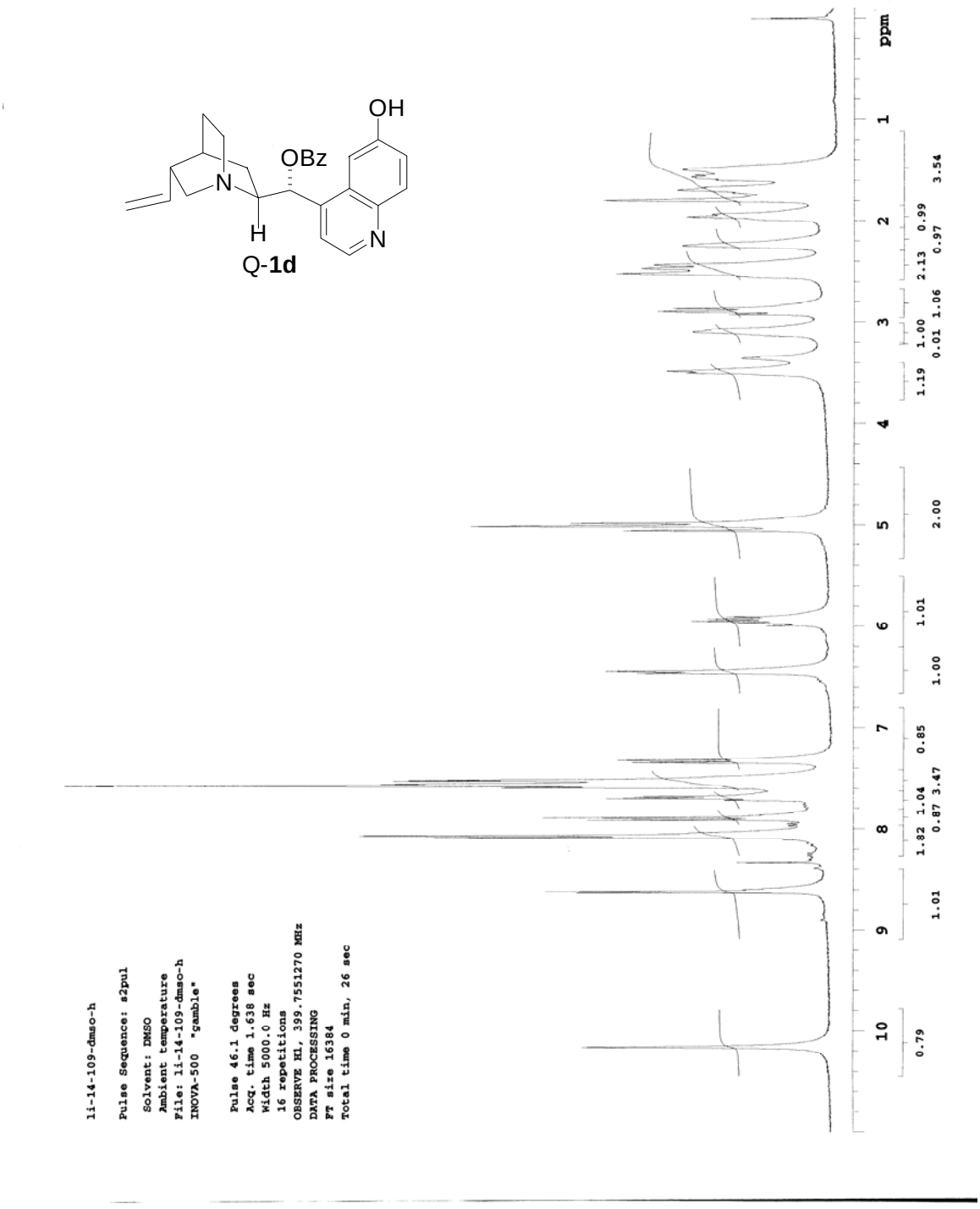


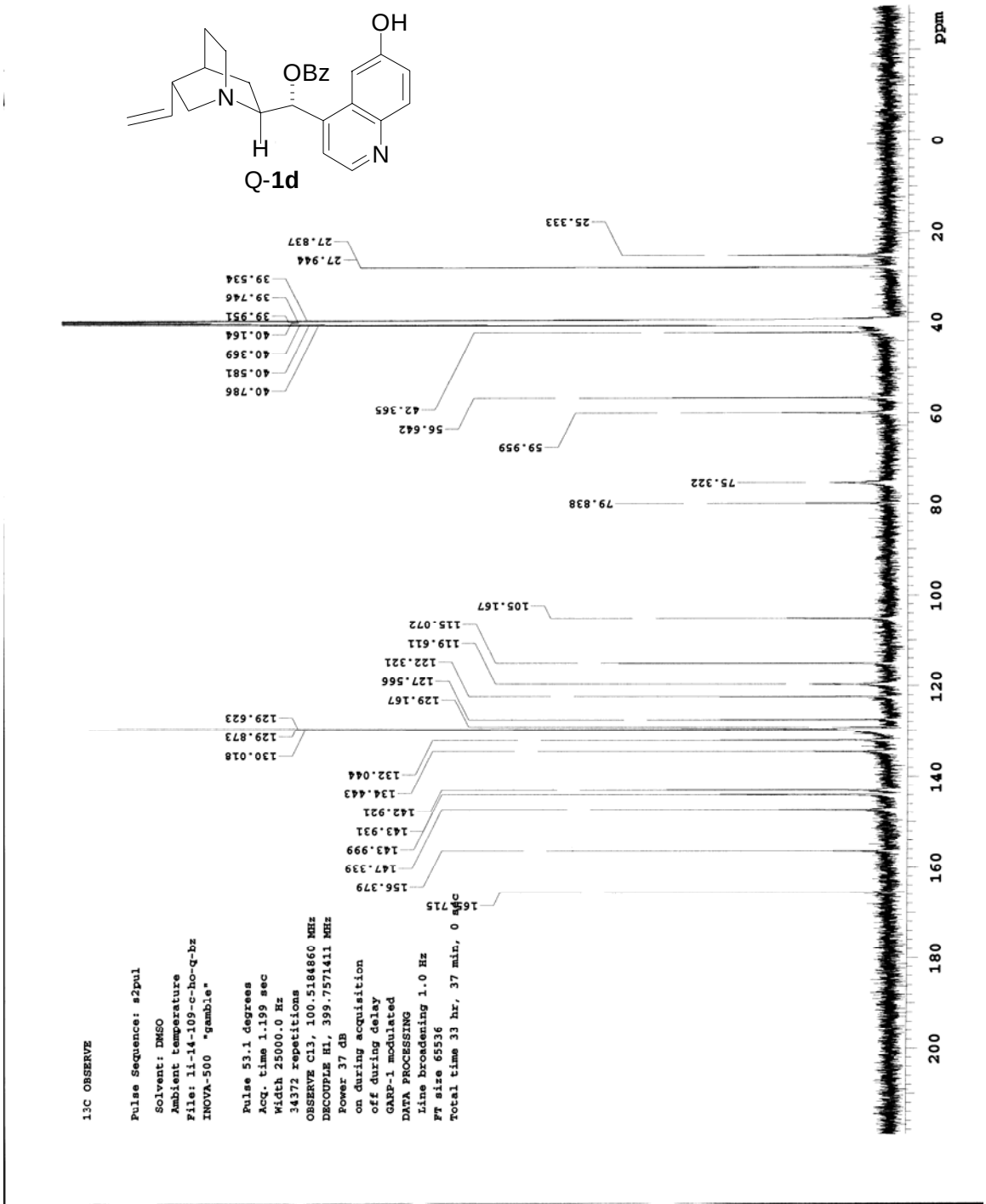

```
================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :      1.00000  [ng/ul]    (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Sig Type     Area      Height      Area
  #   [min]           mAU   *s    [mAU   ]       %
----|-------|---|----|----------|----------|--------|
   1  13.772  1  BV   1961.92175   67.72769  50.8178
   2  15.334  1  VBA  1898.77490   57.90228  49.1822

Totals :              3860.69666  125.62997
```

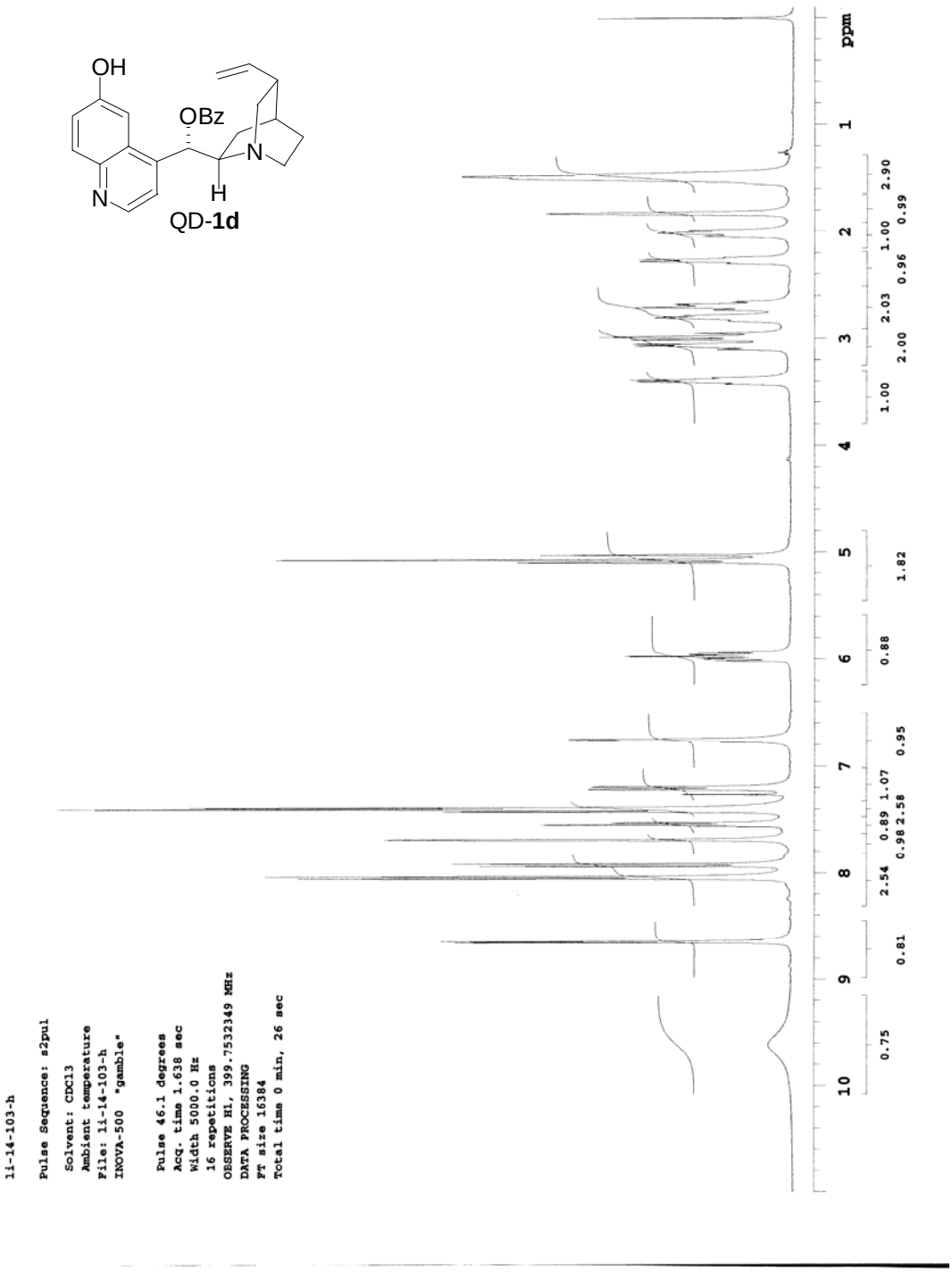
(-)-**8j** 94% ee

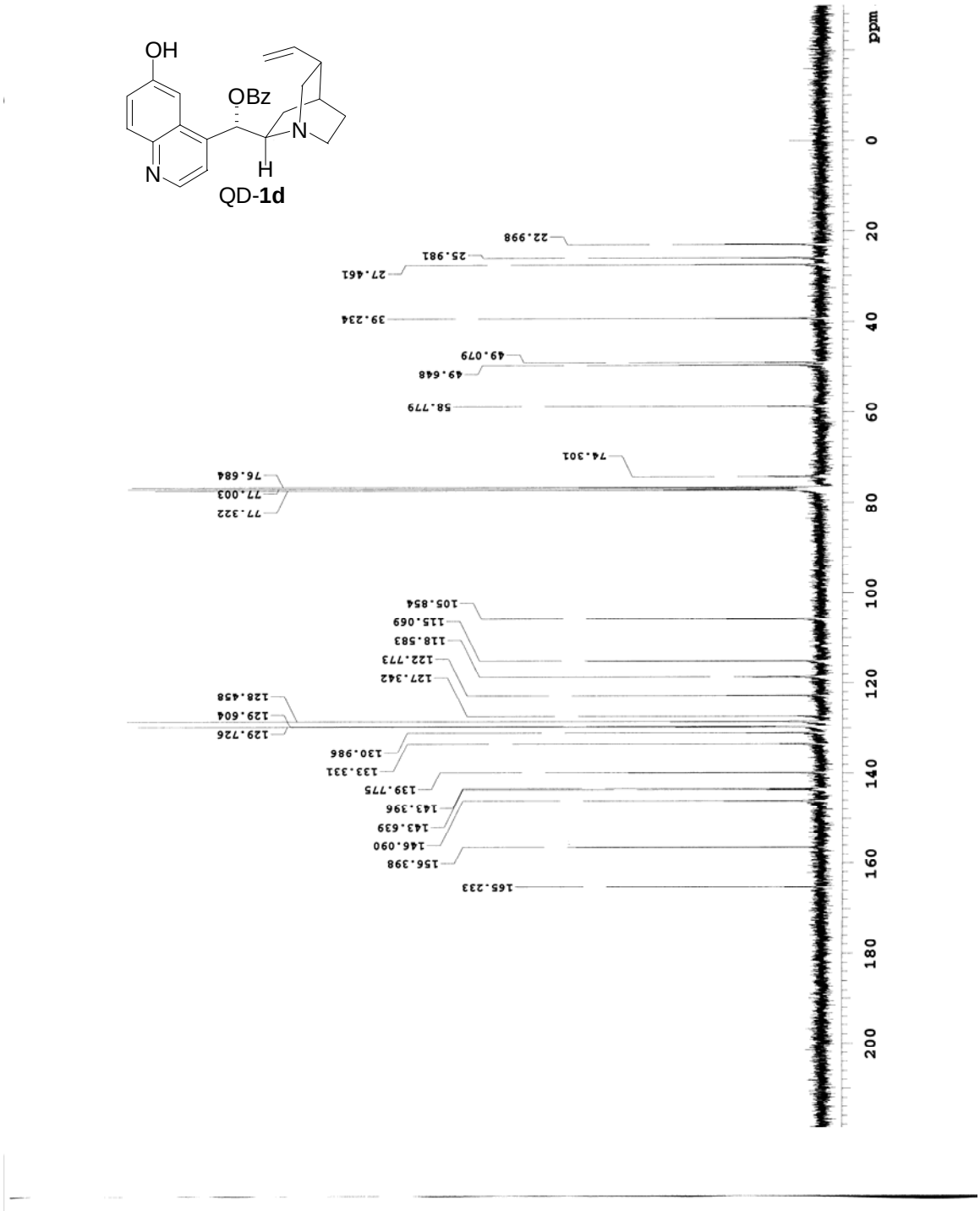


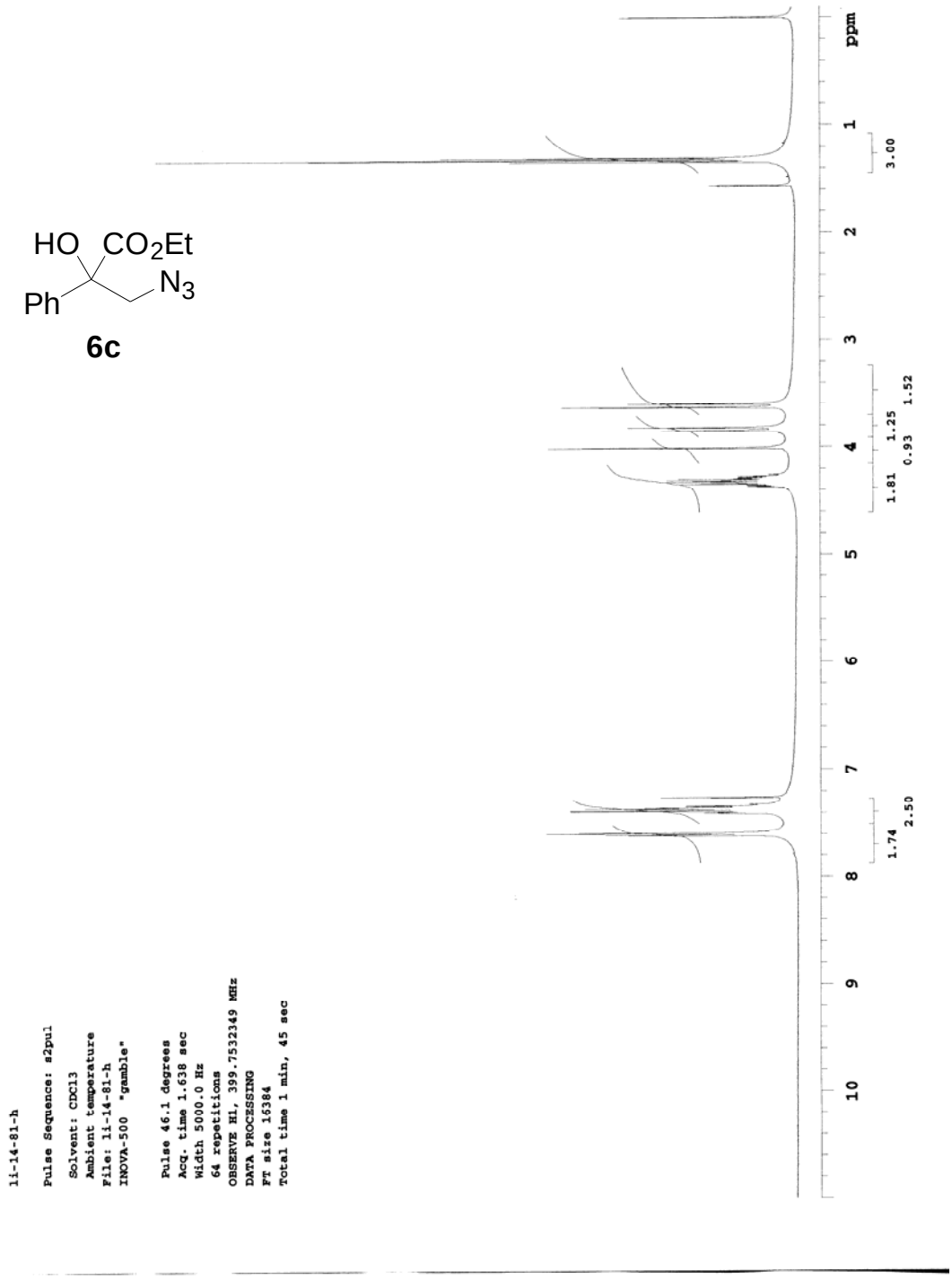

```
================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Retention Time
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount         :      1.00000  [ng/ul]    (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Sig Type     Area      Height      Area
  #   [min]           mAU   *s    [mAU   ]       %
----|-------|---|----|----------|----------|--------|
   1  14.564  1  BV    199.35370    5.47416   2.8939
   2  15.222  1  VBA  6689.34277  223.38412  97.1061

Totals :              6888.69647  228.85828
```

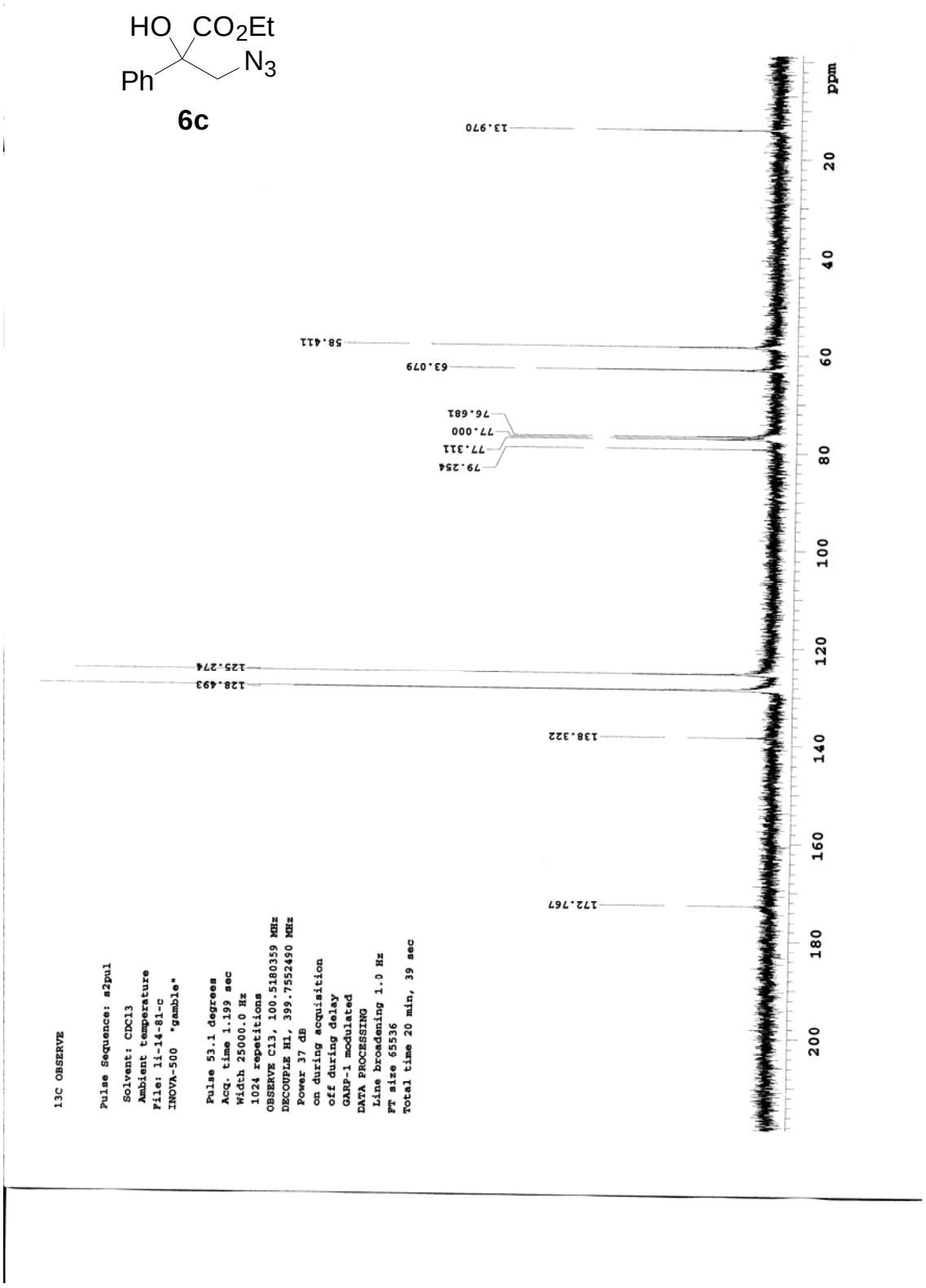

li-14-109-dmso-h
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
File: li-14-109-dmso-h
INOVA-500 "gamble"
Pulse 46.1 degrees
Acq. time 1.638 sec
Width 5000.0 Hz
16 repetitions
OBSERVE H1, 399.7551270 MHz
DATA PROCESSING
FT size 16384
Total time 0 min, 26 sec
OH
OBz
N
H
N
Q-1d
ppm


OH
OBz
N
H
N
Q-1d
25.333
27.837
27.944
39.534
39.746
39.951
40.164
40.369
40.581
40.786
42.365
56.642
59.959
75.322
79.838
105.167
115.072
119.611
122.321
127.566
129.167
129.623
129.873
130.018
132.044
134.443
142.921
143.931
143.999
147.339
156.379
165.715
13C OBSERVE
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
File: li-14-109-c-ho-q-bz
INOVA-500 "gambie"
Pulse 53.1 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
34372 repetitions
OBSERVE C13, 100.5184860 MHz
DECOUPLE H1, 399.7571411 MHz
Power 37 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 33 hr, 37 min, 0 sec
ppm
0
20
40
60
80
100
120
140
160
180
200


OH
OBz
N
N
H
QD-1d
li-14-103-h
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: li-14-103-h
INOVA-500 "gamble"
Pulse 46.1 degrees
Acq. time 1.638 sec
Width 5000.0 Hz
16 repetitions
OBSERVE H1, 399.7532349 MHz
DATA PROCESSING
FT size 16384
Total time 0 min, 26 sec
ppm


OH
OBz
N
N
H
QD-1d
22.998
25.981
27.461
39.234
49.079
49.648
58.779
74.301
76.684
77.003
77.322
105.854
115.069
118.583
122.773
127.342
128.458
129.604
129.726
130.986
133.331
139.775
143.396
143.639
146.090
156.398
165.233
ppm
0
20
40
60
80
100
120
140
160
180
200


li-14-81-h
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: li-14-81-h
INOVA-500 "gamble"
Pulse 46.1 degrees
Acq. time 1.638 sec
Width 5000.0 Hz
64 repetitions
OBSERVE H1, 399.7532349 MHz
DATA PROCESSING
FT size 16384
Total time 1 min, 45 sec
HO
CO2Et
N3
Ph
6c
ppm
3.00
1.81
1.25
0.93
1.52
1.74
2.50


HO
CO2Et
Ph
N3
6c
13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: li-14-81-c
INOVA-500 "gamble"
Pulse 53.1 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
1024 repetitions
OBSERVE C13, 100.5180359 MHz
DECOUPLE H1, 399.7552490 MHz
Power 37 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 20 min, 39 sec
13.970
58.411
63.079
76.681
77.000
77.311
79.254
125.274
128.493
138.322
172.767
ppm
200
180
160
140
120
100
80
60
40
20