Supporting Information

Direct Asymmetric Three-Component Organocatalytic *anti*-selective Mannich Reactions in a Purely Aqueous System

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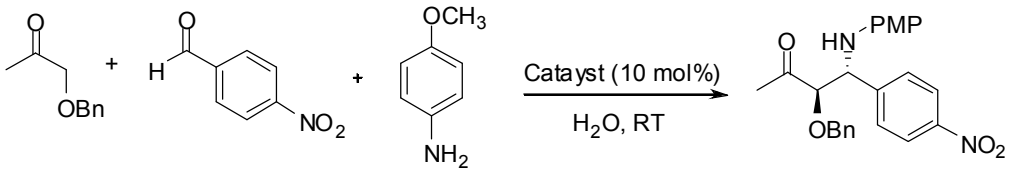
General methods

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 (300MHz) or AMX500 (500MHz) spectrometer. Chemical shifts are reported in parts per million (ppm), and the residual solvent peak was used as an internal reference. Low resolution mass spectra were obtained on a VG Micromass 7035 spectrometer in EI mode, a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL-T mass spectrometer in FAB mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. For thin-layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F_{254}) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with 5% ninhydrin in ethanol, ceric molybdate or $KMnO_4$ solution followed by heating on a hot plate. Flash chromatography separations were performed on Merck 60 (0.040 - 0.063mm) mesh silica gel. All the reactions were performed at ambient temperature. The *anti* to *syn* ratios of the Mannich products were determined by ^{1}H NMR analysis of the crude products. The enantiomeric excesses were determined by chiral-phase HPLC analysis.

Catalysts **4**, **5**, **6** and **7** were commercially available, and catalyst **8** was prepared according to the literature procedure.[1]

Representative procedure for the direct three-component Mannich reaction in water



A mixture of *p*-nitrobenzaldehyde (15.1 mg, 0.1 mmol), *O*-benzyl hydroxyacetone (48 µl, 0.3 mmol), *p*-anisidine (13.5 mg, 0.11 mmol) and catalyst **2b** (3.57 mg, 0.01 mmol) in water (18 µl, 1 mmol) was stirred at room temperature for 24 hours. The reaction mixture was filtered through a small pad of silica gel to remove the catalyst, and washed with ethyl acetate (30 ml). The filtrate was concentrated *in vacuo*, and the crude product was purified by column chromatography using mixtures of hexane/ethyl acetate as eluants (8:1 to 4:1) to afford the Mannich product as a pale yellow oil (38 mg, 90% yield).

Synthesis of the catalysts

2c

***N*-Benzyloxycarbonyl-L-threonine benzyl ester:** This compound was prepared according to the literature procedure.[2]
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19-1.28 (d, J = 6.4 Hz, 3H), 1.80-2.20 (br, 1H), 4.20-4.45 (m, 2H), 5.05-5.30 (m, 4H), 5.60 (br, 1H), 7.30-7.40 (m, 10H); $[\alpha]_D^{20}$ = -11 (c = 8.1, $CHCl_3$).

***N*-Benzyloxycarbonyl-*O*-(*tert*-Butyldimethylsiloxy)-L-threonine benzyl ester**
N-Benzyloxycarbonyl-L-threonine benzyl ester (1.372 g, 4 mmol) was dissolve in minimum amount of anhydrous DMF. To this solution was added TBSCl (0.752 g, 5 mmol) and imidazole (0.544 g, 8 mmol), respectively. After stirring at room temperature for 30 hours, the reaction mixture was diluted with ether and washed with water. The organic layer was dried, filtered and concentrated. The crude product was dissolved in a minimum amount of ethyl acetate, silica gel (10 g) was added under vigorous stirring, followed by a mixture of ethyl acetate and hexanes (50 mL, EtOAc/Hex = 1/10). The above mixture filtered, and the silica gel was further washed with ethyl acetate and hexane (50 mL x 2). The organic solvents were combined and removed *in vacuo* to afford the product as a colorless oil (1.60 g, 87% yield), which was pure enough and used directly in next reaction.
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.016 (s, 6H), 0.82 (s, 9H), 1.19 (d, J = 6.0 Hz, 3H), 4.29-4.35 (dd, J = 1.8 Hz and 10.2 Hz, 1H), 4.42-4.50 (dq, J = 1.8 Hz and 6.3 Hz, 1H), 5.05-5.22 (m, 4H), 5.10-5.15 (d, J = 10.2 Hz, 1H), 7.30-7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.33, -4.44, 17.76, 20.81, 25.57, 60.00, 67.05, 68.71, 128.09, 128.28, 128.35, 128.48, 128.53, 135.12, 136.23, 156.73, 170.67; HRMS (ESI) m/z calcd for ($C_{25}H_{35}NO_5Si$ +Na) 480.2177, found 480.2190.

***O*-(*tert*-Butyldimethylsiloxy)-L-threonine (2c):**
To *N*-benzyloxycarbonyl-*O*-(*tert*-Butyldimethylsilyloxy)-L-threonine benzyl ester (1.4 g, 6 mmol) in methanol (8 mL) was added Pd/C (140 mg, 10 wt%) at room temperature, and the resulting mixture was stirred for 12 hours under an atmosphere of H_2. The mixture was filtered through celite and the filtrate was concentrated to afford the crude product. The crude was dissolved in a minimum amount of methanol, ether was added while the methanol solution was vigorously stirred. The pure **2c** precipitated out as white powder, which was collected and dried (0.58 g, 82% yield).
^{1}H NMR (300 MHz, DMSO) δ 0.009 (s, 3H), 0.032 (s, 3H), 0.83 (s, 9H), 1.16-1.18 (d, J = 6.6 Hz, 3H), 2.95-3.05 (d, J = 2.7 Hz, 1H), 4.29-4.40 (dq, J = 2.7 Hz and 6.6 Hz, 1H).
^{13}C NMR (75 MHz, DMSO) δ –4.45, 18.10, 20.81, 22.03, 26.05, 60.08, 67.05, 171.07.

HRMS (ESI) m/z calcd for ($C_{10}H_{24}NO_3Si$) 234.1520, found 234.1528. $[\alpha]_D^{20}$ = -31.4 (c = 0.65, MeOH).

***O*-(Triisopropylsiloxy)-L-threonine (2a):**
^{1}H NMR (300 MHz, DMSO) δ 1.00 - 1.15 (m, 21H), 1.21-1.24 (d, *J* = 6.6 Hz, 3H), 3.00-3.03 (d, *J* = 1.95 Hz, 1H), 4.50-4.60 (dq, *J* = 1.95 Hz, 6.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ 12.37, 18.34, 22.19, 26.05, 59.93, 67.88, 171.11. HRMS (ESI) m/z calcd for ($C_{13}H_{30}NO_3Si$) 276.1989, found 276.1999. $[\alpha]_D^{20}$ = -20.1 (c = 0.48, MeOH).

***O*-(*tert*-Butyldiphenylsiloxy)-L-threonine (2b):**
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (m, 12H), 3.50 (m, 1H), 4.39 (m, 1H), 7.20-7.30 (m, 6H), 7.60-7.70 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.88, 21.94, 61.44, 69.86, 128.10, 128.28, 130.19, 130.48, 133.20, 134.55, 136.40, 136.54, 171.67. HRMS (ESI) m/z calcd for ($C_{20}H_{27}NO_3Si$+Na) 380.1652, found 380.1658. $[\alpha]_D^{20}$ = -28.9 (c = 0.53, MeOH).

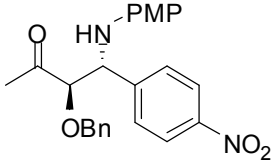
***O*-(Triisopropylsiloxy)-L-serine (1a):**
^{1}H NMR (300 MHz, CD_3OD) δ 1.10 - 1.20 (m, 21H), 0.95 (s, 9H), 3.61-3.68 (dd, *J* = 6.4 Hz and 3.8 Hz, 1H), 4.05-4.25 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ 11.61, 16.88, 56.64, 62.39, 170.14. HRMS (ESI) m/z calcd for ($C_{12}H_{28}NO_3Si$) 262.1833, found 262.1836. $[\alpha]_D^{20}$ = -12.5 (c = 0.61, MeOH).

***O*-(*tert*-Butyldiphenylsiloxy)-L-serine (1b):**
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 - 1.10 (m, 9H), 3.70-4.10 (m, 3H), 4.05-4.25 (m, 2H), 7.05-7.40 (m, 6H), 7.50-7.70 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.68, 27.30, 57.64, 63.39, 172.84. HRMS (ESI) m/z calcd for ($C_{19}H_{26}NO_3Si$) 344.1676, found 344.1678 $[\alpha]_D^{20}$= -32.8 (c = 0.61, MeOH).

***O*-(*tert*-Butyldimethylsiloxy)-L-serine (1c):**
^{1}H NMR (300 MHz, CD_3OD) δ 0.143 (s, 6H), 0.95 (s, 9H), 3.60-3.65 (dd, *J* = 6.3 Hz and 4.3 Hz, 1H), 3.95-4.1 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ –6.90, 17.76, 24.85, 56.50, 62.07, 170.27. HRMS (ESI) m/z calcd for ($C_9H_{22}NO_3Si$) 220.1363, found 220.1369. $[\alpha]_D^{20}$ = -29.3 (c = 0.174, MeOH).

<u>The characterizations of Mannich products:</u>

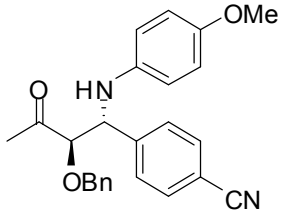
(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-benzyloxy-4-(4-nitrophenyl)butan-2-one (**3**):



Compound **3**: a brown oil; t_r (minor) = 21.1 min, t_r (major) = 26.1 min (Chiralcel AD-H, λ = 280 nm, 15% *i*-PrOH/Hexanes, flow rate = 1.0 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 3H), 3.71 (s, 3H), 4.07 - 4.09 (d, *J* = 5.9 Hz, 1H), 4.36-4.40 (d, *J* = 11.7

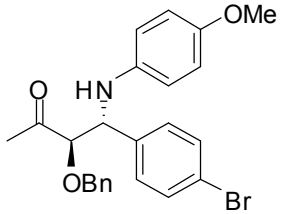
Hz, 1H), 4.66-4.70 (d, *J* = 11.7 Hz, 1H), 4.73-4.75 (d, *J* = 6.1Hz, 1H), 6.43-6.46 (m, 2H), 6.69-6.72 (m, 2H), 7.21-7.25 (m, 2H), 7.37-7.39 (m, 3H), 7.52-7.54 (m, 2H), 8.16-8.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.3, 55.5, 59.5, 73.7, 86.8, 114.7, 115.3, 123.4, 128.0, 128.4, 128.6, 128.7, 136.2, 139.1, 146.6, 147.4, 152.8, 209.8; HRMS (ESI) *m/z* calcd for $C_{24}H_{24}N_2O_5$ $[M+Na]^+$ 443.1577, found 443.1593.

(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-benzyloxy-4-(4-cyanophenyl)butan-2-one (**9**)



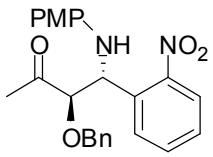
Compound **9**: a yellow oil; t_r (minor) = 27.8 min, t_r (major) = 30.3 min (Chiralcel AS-H, λ = 254 nm, 10% *i*-PrOH/Hexanes, flow rate = 1 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 3H), 3.68 (s, 3H), 4.00-4.02 (d, *J* = 6.3 Hz, 1H), 4.16 (br, 1H), 4.30-4.34 (d, *J* = 11.5 Hz, 1H), 4.61-4.64 (d, *J* = 11.5 Hz, 2H), 6.38-6.41 (d, *J* = 9.1 Hz, 2H), 6.65-6.68 (d, *J* = 9.1 Hz, 2H), 7.17-7.20 (m, 2H), 7.33-7.35 (m, 3H), 7.42-7.44 (d, *J* = 8.0 Hz, 2H), 7.56-7.59 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 55.6, 59.8, 73.7, 86.9, 111.6, 114.8, 115.3, 118.6, 128.1, 128.4, 128.7, 132.1, 136.3, 139.3, 144.7, 152.8, 210; HRMS (ESI) *m/z* calcd for $C_{25}H_{24}N_2O_3$ $[M+Na]^+$ 423.1679, found 423.1686.

(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-benzyloxy-4-(4-bromophenyl)butan-2-one (**10**)



Compound **10**: a brown oil; t_r (minor) =12.5min, t_r (major) = 18.5 min (Chiralcel AD-H, λ = 254 nm, 10% *i*-PrOH/Hexanes, flow rate = 1 mL/min);^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (s, 3H), 3.68 (s, 3H), 4.02-4.77 (m, 4H), 6.43-6.46 (d, *J* = 9.0 Hz, 2H), 6.66-6.69 (d, *J* = 9.0 Hz, 2H), 7.19-7.43 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 55.6, 59.6, 73.7, 87.1, 114.8, 115.3, 121.6, 126.9, 127.9, 128.4, 128.8, 130.8, 136.6, 137.9, 139.7, 152.6, 210.3; HRMS (ESI) *m/z* calcd for $C_{24}H_{24}BrNO_3$ $[M+Na]^+$ 476.0832, found 476.0836.

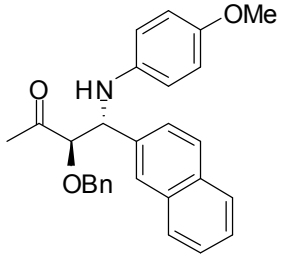
(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-benzyloxy-4-(2-nitrophenyl)butan-2-one (**11**)



Compound **11**: a yellow solid; t_r (minor) = 16.5 min, t_r (major) = 29.2 min (Chiralcel AD-H, λ = 254 nm, 10% *i*-PrOH/Hexanes, flow rate = 1 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 3.67 (s, 3H), 4.14-4.16 (m, 1H), 4.19-4.23 (d, *J* = 12.2 Hz, 1H), 4.46-4.49 (d, *J* = 12 Hz, 1H), 5.65-5.67 (m, 1H), 6.52-6.65 (d, *J* = 8.7 Hz, 2H), 6.67-6.70 (d, *J* = 9.0 Hz, 2H), 7.0 (m, 2H), 7.20-7.26 (m, 3H), 7.39-7.46 (m, 2H), 7.56 (m,1H),

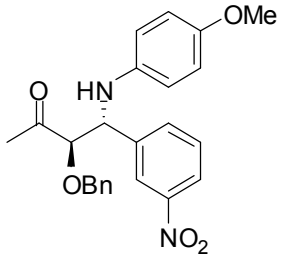
7.88-7.90 (d, *J* = 7.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3, 53.9, 56.6, 72.9, 86.3, 114.9, 115.0, 124.6, 128.1, 128.14, 128.4, 133.0, 134.6, 135.9, 139.4, 150.7, 152.8, 209.2; HRMS (ESI) *m/z* calcd for $C_{24}H_{24}N_2O_5$ $[M+Na]^+$ 443.1577, found 443.1586.

(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-benzyloxy-4-(naphthalen-2-yl)butan-2-one (**12**)



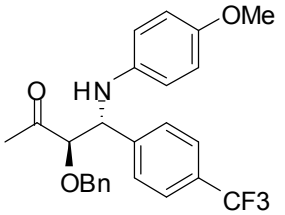
Compound **12**: a yellow solid; t_r (major) = 34.9 min, t_r (minor) = 43.1min (Chiralcel OD-H, λ = 254 nm, 10% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91(s, 3H), 3.67 (s, 3H), 4.17-4.19 (d, *J* = 5.9 Hz, 1H), 4.35-4.39 (d, *J* = 11.9 Hz, 1H), 4.60-4.64 (d, *J* = 11.9 Hz, 1H), 4.79-4.81 (d, *J* = 5.9 Hz, 1H), 6.52-6.56 (d, *J* = 9.1Hz, 2H), 6.66 (d, *J* = 9.1 Hz, 2H), 7.29-7.49 (m, 8H), 7.79-7.82 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 55.6, 60.4, 73.5, 87.5, 114.8, 115.4, 125.4, 125.9, 126.0, 126.2, 127.1, 127.6, 127.9, 128.0, 128.1, 128.3, 128.5, 133.1, 136.4, 140.1, 152.5, 210.7; HRMS (ESI) *m/z* calcd for $C_{28}H_{27}NO_3$ $[M+Na]^+$ 448.1883, found 448.1893.

(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-benzyloxy-4-(3-nitrophenyl)butan-2-one (**13**)



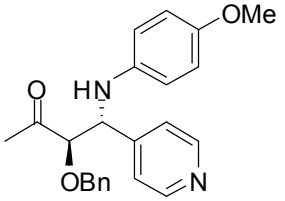
Compound **13**: a brown oil; t_r (minor) = 19.2 min, t_r (major) = 24.9 min (Chiralcel AD-H, λ = 280 nm, 10% *i*-PrOH/Hexanes, flow rate = 1 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3H), 3.71 (s, 3H), 4.04-4.06 (d, *J* = 6.2 Hz, 1H), 4.34-4.38 (d, *J* = 11.7 Hz, 1H), 4.66-4.70 (d, *J* = 11.8 Hz, 1H), 4.80 (d, *J* = 6.0 Hz , 1H), 6.48 (m, 2H), 6.69 (m, 2H), 7.20-7.23 (m, 2H), 7.35-7.38 (m, 3H), 7.47-7.52 (t, 1H), 7.67-7.70 (d, *J* = 7.7 Hz, 1H), 8.13-8.16 (m, 1H), 8.27-8.28 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 55.5, 59.3, 73.6, 86.7, 114.7, 115.2, 122.7, 122.8, 128.0, 128.3, 128.6, 129.2, 134.0, 136.2, 139.2, 141.5, 148.2, 152.7, 209.9; HRMS (ESI) *m/z* calcd for $C_{24}H_{24}N_2O_5$ $[M+Na]^+$ 443.1577, found 443.1586.

(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-benzyloxy-4-(4-trifluoromethylphenyl)butan-2-one (**14**)



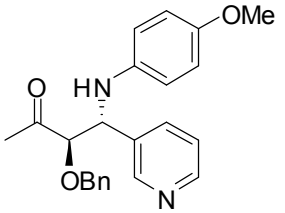
Compound **14**: a brown oil; t_r (minor) = 31.6 min, t_r (major) = 38.3 min (Chiralcel AD-H, λ = 254 nm, 5% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98 (s, 3H), 3.68 (s, 3H), 4.02-4.05 (m, 1H), 4.22-4.35 (m, 1H), 4.61-4.65 (m, 2H), 6.46 (m, 2H), 6.70 (m, 2H), 7.01-7.57 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 55.5, 59.7, 73,7, 87.0, 114.8, 115.3, 125.2, 125.3, 12.5, 128.0, 128.3, 128.6, 130, 136.5, 139.6, 143.2, 152.7, 210.1; HRMS (ESI) *m/z* calcd for $C_{25}H_{24}F_3NO_3$ $[M+Na]^+$ 466.1606, found 466.1610.

(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-benzyloxy-4-(pyridin-4-yl)butan-2-one (**15**)



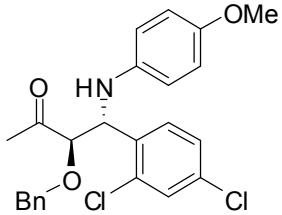
Compound **15**: a dark orange oil; t_r (minor) = 13.1 min, t_r (major) = 18.9 min (Chiralcel AD-H, λ = 254 nm, 15% *i*-PrOH/Hexanes, flow rate = 1 mL/min);^{1}H NMR (300 MHz, $CDCl_3$) δ 2.03 (s, 3H), 3.70 (s, 3H), 4.04-4.07 (d, *J* = 6.1 Hz, 1H), 4.35-4.39 (d, *J* = 11.7 Hz, 1H), 4.63-4.67 (m, 2H), 6.44-6.48 (m, 2H), 6.69-6.72 (d, *J* = 9.0 Hz, 2H), 7.22-7.38 (m, 7H), 8.54-8.56 (d, *J* = 4.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 55.5, 59.2, 73.6, 86.6, 114.7, 115.2, 123.0, 128.0, 128.3, 128.6, 136.3, 139.3, 148.1, 149.7, 152.7, 209.9; HRMS (ESI) *m/z* calcd for $C_{23}H_{24}N_2O_3$ $[M+Na]^+$ 399.1679, found 399.1695.

(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-benzyloxy-4-(pyridin-3-yl)butan-2-one (**16**)



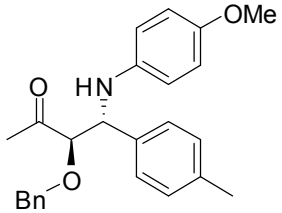
Compound **16**: a brown oil; t_r (major) = 20.3 min, t_r (minor) = 39.4 min (Chiralcel OD-H, λ = 254 nm, 15% *i*-PrOH/Hexanes, flow rate = 1 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.00 (s, 3H), 3.71 (s, 3H), 4.08-4.10 (d, *J* = 5.9 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 4.65-6.68 (d, *J* = 11.5 Hz, 1H), 4.68 (br s, 1H), 6.48-6.51 (d, *J* = 9.0 Hz, 2H), 6.68-6.71(d, *J* = 9.0 Hz, 2H), 7.22-7.38 (m, 6H), 7.66-7.69 (d, *J* = 9.8 Hz, 1H), 8.52-8.54 (d, *J* = 6.4 Hz, 1H), 8.63-8.64 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.3, 55.5, 57.9, 73.6, 86.8, 114.7, 115.4, 123.2, 127.9, 128.2, 128.6, 134.4, 135.3, 136.4, 1393, 148.6, 149.5, 152.7, 210.2; HRMS (ESI) *m/z* calcd for $C_{23}H_{24}N_2O_3$ $[M+Na]^+$ 399.1679, found 399.1690.

(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-benzyloxy-4-(2,4-dichlorophenyl)butan-2-one (**17**)



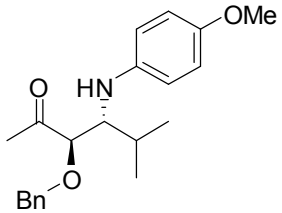
Compound **17**: brown oil; t_r (minor) = 17.7 min, t_r (major) = 22.1 min (Chiralcel AD-H, λ = 254 nm, 10% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (s, 3H), 3.69 (s, 3H), 4.15-4.16 (d, *J* = 8.7 Hz, 1H), 4.31 (br, 1H), 4.36-4.38 (d, *J* = 12.0 Hz, 1H), 4.62-4.64 (d, *J* = 12.0 Hz, 1H), 5.11-5.12 (d, *J* = 5.7 Hz, 1H), 6.44-6.46 (d, *J* = 8.9 Hz, 2H), 6.68 (d, *J* = 9.5 Hz, 2H), 7.19-7.37 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.0, 55.7, 72.9, 85.4, 114.8, 115.2, 127.1, 127.9, 128.1, 128.4, 129.3, 130.2, 134.3, 135.1, 136.6, 139.8, 152.9, 208.5; HRMS (ESI) *m/z* calcd for $C_{24}H_{23}Cl_2NO$ $[M+Na]^+$ 466.0947, found 466.0947.

(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-benzyloxy-4-(4-methylphenyl)butan-2-one (**18**)



Compound **18**: a brown oil; t_r (minor) = 20.6 min, t_r (major) = 33.9 min (Chiralcel AD-H, λ = 254 nm, 10% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.89 (s, 3H), 2.32 (s, 3H), 3.67 (s, 3H), 4.09-4.10 (d, *J* = 5.7 Hz, 1H), 4.36-4.39 (d, *J* = 11.9 Hz, 1H), 4.59-4.62 (d, *J* = 12.0 Hz, 1H), 4.61-4.62 (d, *J* = 6.3 Hz, 1H), 6.49-6.50 (d, *J* = 1.9 Hz, 2H), 6.68 (d, *J* = 1.9 Hz, 2H), 7.12 (m, 2H), 7.22-7.33 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 26.7, 55.7, 59.9, 73.5, 87.4, 114.8, 127.7, 127.8, 128.0, 128.5, 129.2, 135.7, 136.7, 137.3, 140.3, 152.4, 210.8; HRMS (ESI) *m/z* calcd for $C_{25}H_{27}NO_3$ $[M+Na]^+$ 412.1883, found 412.1897.

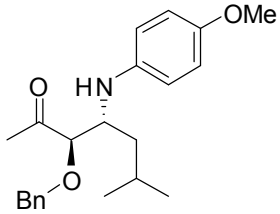
(3*R*,4*R*)-4-(4-Methoxyphenylamino)-3-(benzyloxy)-5-methylhexan-2-one (**19**)



Compound **19**: a pale yellow oil; t_r (major) = 25.8 min, t_r (minor) = 30.1 min (Chiralcel AD-H, λ = 254 nm, 5% *i*-PrOH/Hexanes, flow rate = 0.3 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (m, 6H), 1.97-2.04 (m, 1H), 2.13 (s, 3H), 3.58-3.61 (m, 1H), 3.73 (s, 3H), 3.81-3.83 (d, *J* = 6.2 Hz, 1H), 4.33-4.37 (d, *J* = 11.8 Hz, 1H), 4.57-4.61 (d, *J* = 11.5 Hz, 1H), 6.52-6.55 (d, *J* = 8.5 Hz, 2H), 6.71-6.74 (d, *J* = 8.7 Hz, 2H), 7.32-7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1, 19.7, 20.7, 26.1, 29.7, 55.7, 61.1, 73.3, 86.1, 114.3,

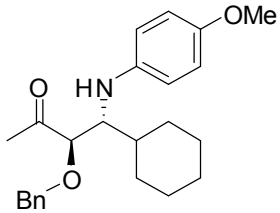
114.9, 127.9, 128.0, 128.4, 137.2, 141.7, 152.2, 211.1; HRMS (ESI) *m/z* calcd for $C_{21}H_{27}NO_3$ $[M+Na]^+$ 364.1883, found 364.1899.

(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-(benzyloxy)-6-methylheptan-2-one (**20**)



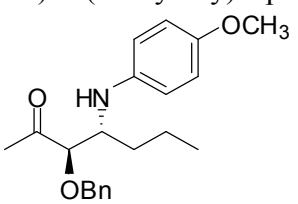
Compound **20**: a yellow oil; t_r (major) = 13.9 min, t_r (minor) = 14.8 min (Chiralcel AD-H, λ = 254 nm, 5% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80-1.10 (m, 6H), 1.44-1.60 (m, 3H), 2.18 (s, 3H), 3.72-3.78 (m, 1H), 3.74 (s, 3H), 4.09 (br s, 1H), 4.31-4.35 (d, *J* = 11.5 Hz, 1H), 4.59-4.62 (d, *J* = 11.5 Hz, 1H), 6.60-6.63 (m, 2H), 6.75-6.78 (m, 2H), 7.26-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 22.7, 24.7, 27.3, 39.4, 55.0, 55.7, 73.8, 85.8, 115.1, 115.4, 127.8, 128.2, 128.5, 137.5, 141.1, 152.5, 211.1; HRMS (ESI) *m/z* calcd for $C_{22}H_{29}NO_3$ $[M+Na]^+$ 378.204, found 378.2034.

(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-(benzyloxy)-4-cyclohexylbutan-2-one (**21**)



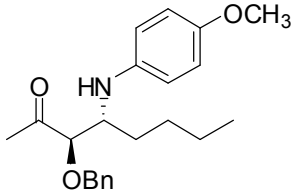
Compound **21**: a pale yellow oil; t_r (minor) = 8.6 min, t_r (major) = 9.5 min (Chiralcel AD-H, λ = 254 nm, 10% *i*-PrOH/Hexanes, flow rate = 1 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00-1.26 (m, 5H), 1.50-1.69 (m, 6H), 2.11 (s, 3H), 3.30 (br s, 1H), 3.58 (br, s, 1H), 3.72 (s, 3H), 3.82-3.84 (d, *J* = 6.3 Hz, 1H), 4.32-4.36 (d, *J* = 11.9 Hz, 1H), 4.59-4.63 (d, *J* = 11.9 Hz, 1H), 6.50-6.53 (m, 2H), 6.70-6.74 (m, 2H), 7.26-7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.1, 26.2, 26.4, 27.1, 27.6, 30.3, 31.0, 40.0, 41.5, 55.7, 60.9, 85.6, 114.0, 114.8, 128.13, 128.19, 128.4, 137.2, 141.7, 152.2, 211.0; HRMS (ESI) *m/z* calcd for $C_{24}H_{31}NO_3$ $[M+Na]^+$ 404.2196, found 404.2203.

(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-(benzyloxy)heptan-2-one (**22**)



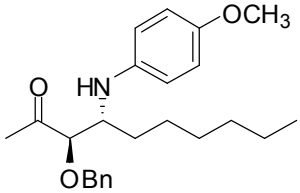
Compound **22**: an orange oil; t_r (major) = 25.1 min, t_r (minor) = 27.6 min (Chiralcel AD-H, λ = 254 nm, 5% *i*-PrOH/Hexanes, flow rate = 0.3 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85-0.92 (m, 3H), 1.10-1.60 (m, 4H), 2.19 (s, 3H), 3.66-3.76 (m, 1H), 3.74 (s, 3H), 3.98-4.00 (d, *J* = 3.8 Hz, 1H), 4.30-4.34 (d, *J* = 11.5 Hz, 1H), 4.59-4.63 (d, *J* = 11.5 Hz, 1H), 6.53-6.56 (d, *J* = 9.0 Hz, 2H), 6.74-6.77 (d, *J* = 9.0 Hz, 2H), 7.26-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 19.2, 27.0, 32.5, 55.6, 56.4, 73.7, 85.7, 113.8, 114.8, 127.8, 128.1, 128.4, 137.1, 141.2, 152.4, 211.3; HRMS (ESI) *m/z* calcd for $C_{21}H_{27}NO_3$ $[M+Na]^+$ 364.1883, found 364.1884.

(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-(benzyloxy)octan-2-one (**23**)



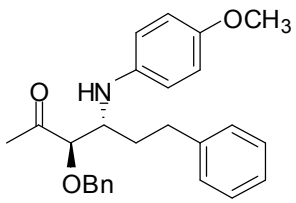
Compound **23**: a dark orange oil; t_r (major) = 16.5 min, t_r (minor) = 18.8 min (Chiralcel AD-H, λ = 254 nm, 5% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81-0.93 (m, 3H), 1.26-1.54 (m, 6H), 2.20 (s, 3H), 3.50-3.76 (m, 1H), 3.74 (s, 3H), 3.99-4.00 (d, *J* = 3.5 Hz, 1H), 4.30-4.34 (d, *J* = 11.5 Hz, 1H), 4.60-4.64 (d, *J* = 11.5 Hz, 1H), 6.54-6.57 (m, 2H), 6.74-6.77 (m, 2H), 7.30-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.5, 27.3, 28.5, 30.2, 55.7, 57.2, 73.7, 85.7, 114.8, 115.3, 127.8, 128.1, 128.4, 137.4, 141.3, 152.4, 211.2; HRMS (ESI) *m/z* calcd for $C_{22}H_{29}NO_3$ $[M+Na]^+$ 378.204, found 378.2043.

(3*R*, 4*R*)-4-(4-Methoxyphenylamino)-3-(benzyloxy)decan-2-one (**24**)



Compound **24**: a dark orange oil; t_r (major) = 34.3 min, t_r (minor) = 40.5 min (Chiralcel AD-H, λ = 254 nm, 5% *i*-PrOH/Hexanes, flow rate = 0.2 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87-0.91 (m, 3H), 1.27-1.68 (m, 10H), 2.23 (s, 3H), 3.74-3.80 (m, 1H), 3.78 (s, 3H), 4.02-4.03 (d, *J* = 3.6 Hz, 1H), 4.33-4.37 (d, *J* = 11.5 Hz, 1H), 4.63-4.67 (d, *J* = 11.5 Hz, 1H), 6.57-6.60 (m, 2H), 6.78-6.81 (m, 2H), 7.29-7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.4, 26.0, 27.1, 29.0, 30.4, 31.6, 55.6, 57.2, 73.7, 84.7, 114.8, 115.0, 127.8, 128.1, 128.4, 137.1, 141.2, 152.1, 212.0; HRMS (ESI) *m/z* calcd for $C_{24}H_{33}NO_3$ $[M+Na]^+$ 406.2353, found 406.2355.

(3R,4R)-4-(4-methoxyphenylamino)-3-(benzyloxy)-6-phenylhexan-2-one (**25**)



Compound **25**: a brown oil; t_r (major) = 14.7 min, t_r (minor) = 25.9 min (Chiralcel AS-H, λ = 254 nm, 10% *i*-PrOH/Hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87-2.08 (m, 2H), 2.14 (s, 3H), 2.58-2.67 (m, 2H), 3.64-3.74 (m, 1H), 3.76(s, 3H), 4.00-4.01 (d, *J* = 3.0 Hz, 1H), 4.31-4.71 (m, 3H), 6.44-6.75 (m, 4H), 7.15-7.36 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.4, 32.1, 32.9, 55.6, 56.2, 75.2, 5.5, 114.9, 115.6, 125.8, 1259, 127.8, 127.9, 128.2, 128.3, 128.4, 137.0, 137.3, 140.7, 141.3, 152.5, 210.7; HRMS (ESI) *m/z* calcd for $C_{26}H_{29}NO_3$ $[M+Na]^+$ 426.2147, found 426.2041.

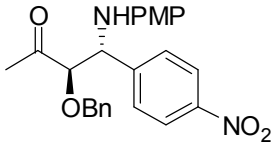
Determination of Configuration

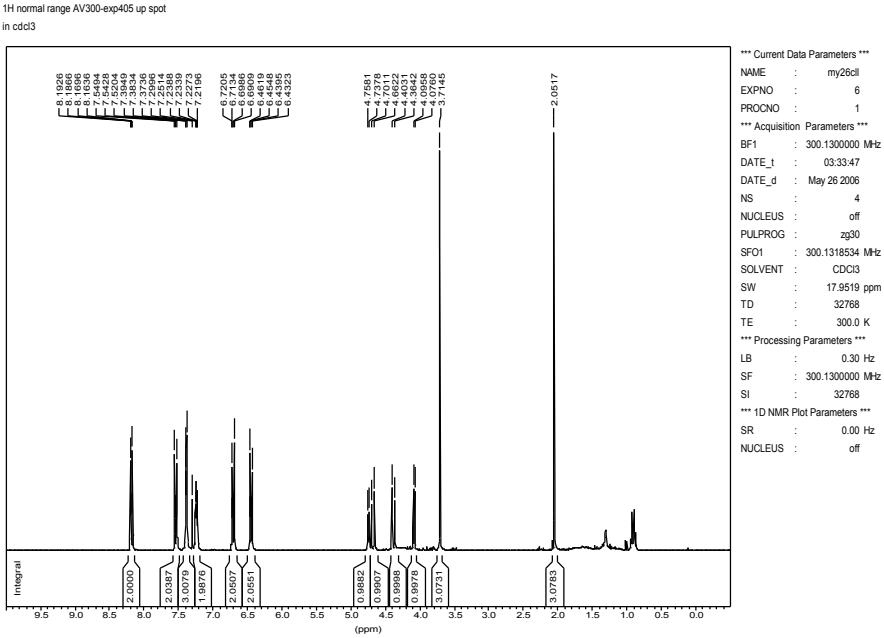
The Mannich products were converted into the corresponding *N*-BOC oxazolidinones using literature procedure.[3] The absolute configurations were then determined based on the comparison with commercially available chiral substances.

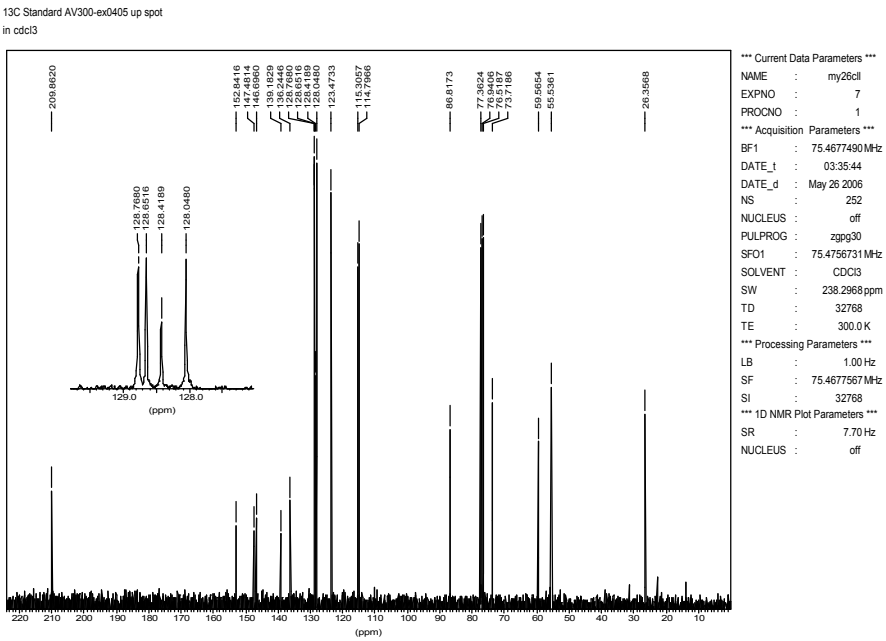
References

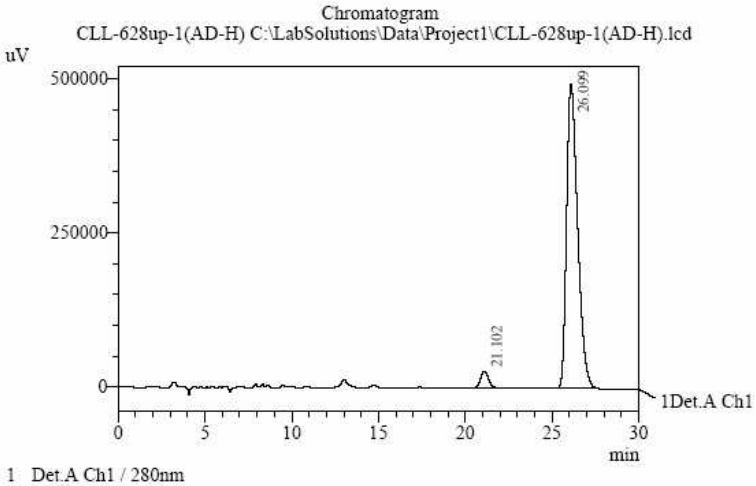
(1) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 958.
(2) Petursson, S. and Baldwin, J. E. *Tetrahedron,* **1998**, *54*, 6001.
(3) List, B.; Pojarliev, P.; Biller, W. T. and Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827.

Selective NMR spectra and HPLC chromatogram





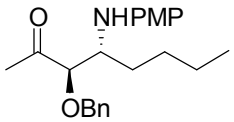


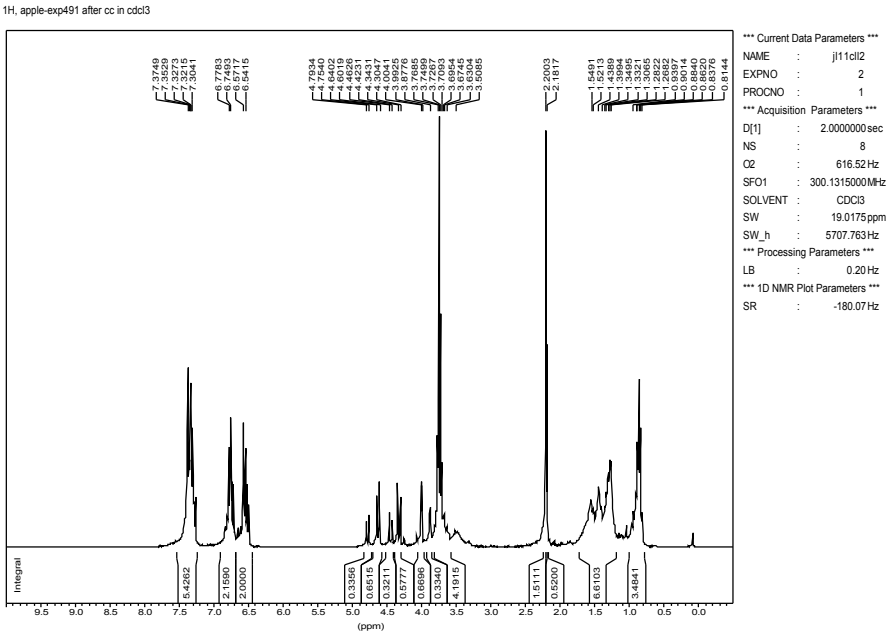


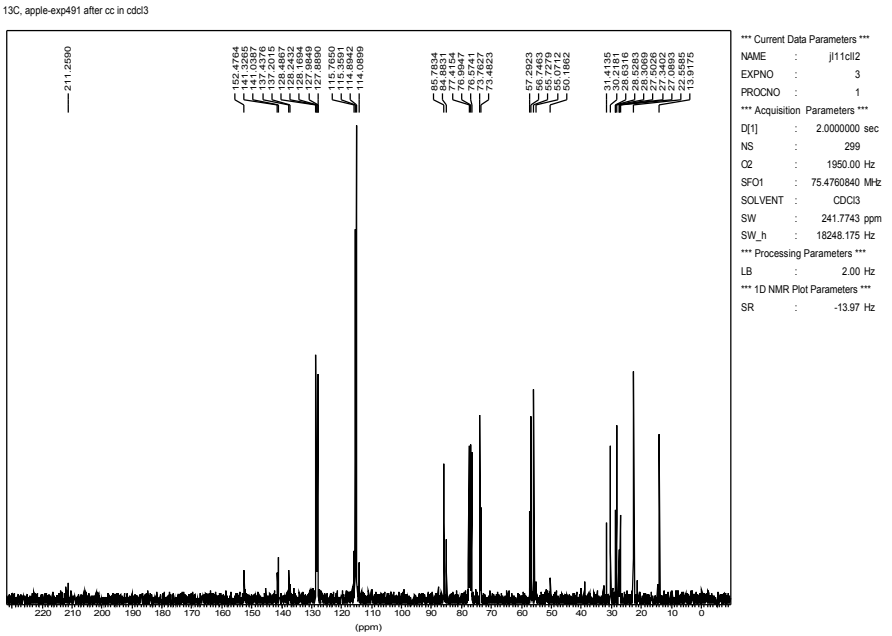
PeakTable

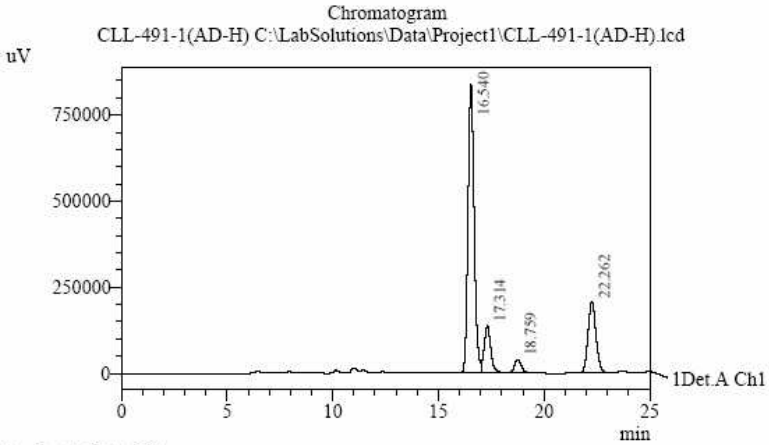
Detector A Ch1 280nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	21.102	838715	26567	3.694	5.104
2	26.099	21863340	493933	96.306	94.896
Total		22702055	520500	100.000	100.000









1 Det.A Ch1 / 254nm

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.540	16932681	839478	64.796	68.729
2	17.314	2952788	136835	11.299	11.203
3	18.759	814847	37970	3.118	3.109
4	22.262	5431943	207154	20.786	16.960
Total		26132260	1221436	100.000	100.000