Supplementary Material (ESI) for Chemical Communications

Direct enantio- and diastereoselective Mannich reactions of malonate and β-keto esters with *N*-Boc and *N*-Cbz aldimines catalysed by a bifunctional cinchonine derivative

A. Louise Tillman[a], Jinxing Ye[b] and Darren J. Dixon[b]*

[a] University Chemical Laboratories, University of Cambridge, Lensfield Road, Cambridge. CB2 1EW. UK.

[b] School of Chemistry, The University of Manchester, Oxford Road, Manchester. M13 9PL. UK; Tel: +44 (0) 161 275 1426; E-mail: darren.dixon@manchester.ac.uk.

SUPPLEMENTARY INFORMATION

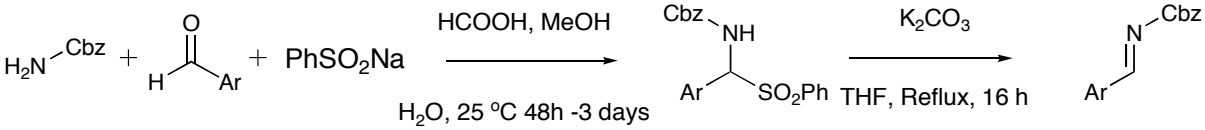
General experimental

Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 Polarimeter and $[\alpha]_D^{25}$ are given in 10^{-1} deg ml / g, concentrations are given in g / 100 ml. IR spectra were recorded on a Perkin-Elmer Spectrum 1 FTIR with an ATR sampling accessory as neat films or compressed solids; only selected absorbances are quoted. HRMS was recorded on Finnigan MAT 900XLT or a Finnigan MAT 95XP at the EPSRC National Mass Spectrometry Service. ^{1}H NMR spectra were recorded at 400 MHz on a Brucker DRX 400 spectrometer at 300 K unless otherwise stated against an internal deuterium lock and are reported (δ_H ± 0.01) / ppm (number of protons, multiplicity, coupling constant (J ±0.1) / Hz, assignment). ^{13}C NMR spectra were recorded on the same instrument at 100 MHz with broadband proton decoupling and are quoted (δ_C ± 0.1) / ppm (assignment).

Flash column chromatography was performed on 9385 silica gel unless otherwise stated. Chiral HPLC analysis was performed on a Hewlett-Packard Series 1090 liquid chromatograph and retention times (r.t.) are given from the solvent front. THF was distilled from calcium hydride, lithium aluminium hydride with triphenylmethane indicator. Chloroform and deuterated chloroform were distilled from $CaCl_2$. All other reagents and solvents were used as provided without purification.

N-Boc imines were prepared by the method reported by Jacobsen.[1]

General two-step procedure for the synthesis of N-Cbz aryl aldimines 4[1] and 17



Step 1

To a rapidly stirred suspension of benzyl carbamate (4.65 g, 0.031 mol) and benzenesulfinic acid sodium salt (10.18 g, 0.062 mol) in methanol / water (30 mL / 60 mL) was added aldehyde (4.78 mL, 0.047 mol) in one portion, followed by formic acid (4.7 mL). The reaction mixture was vigorously stirred for three days and then filtered. The resulting white solid was filtered and washed with water (50 mL) and ether (50 mL) and then dried *in vacuo* to yield clean *sulphone* that was then used without further purification in the next step

Benzenesulfonyl-phenylmethyl-carbamic acid benzyl ester

11.45 g, 0.03 mmol, 97%, from benzaldehyde as a white solid. IR (film) / cm^{-1} υ_{max} = 3330 (N-H), 1694 (C=$O_{carbamate}$), 1519 (Ar), 1494 (Ar), 1308 ($SO_{2\ asymm}$), 1142 ($SO_{2\ symm}$); ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.83 (2H, d, *J* 7.6, SO_2Ph_{ortho}), 7.60 (1H, t, *J* 7.5, SO_2Ph_{para}), 7.45-7.32 (10H, m, Ar), 7.23-7.25 (2H, m, Ar), 6.22 (1H, d, *J* 10.7, N**H**), 5.98 (1H, d, *J* 10.7, C**H**NH), 4.95 (1H, d, *J* 12.1, $CO_2C\mathbf{H}_AH_B$), 4.91 (1H, d, *J* 12.1, $CO_2CH_A\mathbf{H}_B$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c 154.7 (**C**O_2CH_2), 136.5 (**C**, Ar), 135.5 (**C**, Ar), 134.1 (**C**H, Ar), 129.9 (**C**H, Ar), 129.8 (**C**, Ar), 129.4

(**C**H, Ar), 129.0 (**C**H, Ar), 128.8 (**C**H, Ar), 128.8 (**C**H, Ar), 128.6 (**C**H, Ar), 128.4 (**C**H, Ar), 128.2 (**C**H, Ar), 74.6 (NH**C**H), 67.7 (CO_2**C**H_2).

Step 2

Anhydrous potassium carbonate (3.17 g, 22.8 mmol, 6.00 equiv) was placed under vacuum and flame-dried. Once cool, sulphone (3.8 mmol, 1.0 equiv) was added under nitrogen, followed by tetrahydrofuran (42 mL). The reaction mixture was refluxed for 15 hours and then cooled to ambient temperature. The solids were removed via filtration through a fine, glass sinter and the filtrate was concentrated *in vacuo* to yield essentially pure imine **4** in quantitative yield:

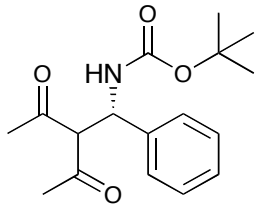
Benzylidene-carbamic acid benzyl ester 4

^{1}H NMR (500 MHz; $CDCl_3$): δ_H 8.79 (1H, s, PhC**H**N), 7.77-7.76 (2H, m, Ph), 7.43-7.39 (1H, m, Ph), 7.33-7.30 (4H, m, Ph), 7.26-7.20 (3H, m, Ph), 5.18 (1H, s, PhC**H$_2$**); ^{13}C NMR (125 MHz; $CDCl_3$): δ_c 171.7 (N**C**O_2), 164.1 (Ph**C**N), 135.8 (**C**H, Ph), 134.4 (**C**H, Ph), 134.4 (**C**H, Ph), 134.3 (**C**H, Ph), 131.0 (**C**H, Ph), 130.7 (**C**H, Ph), 129.4 (**C**H, Ph), 129.0 (**C**H, Ph), 69.3 (CO_2**C**H_2).

General procedure for the addition of 1,3-dicarbonyls to N-acyl imines

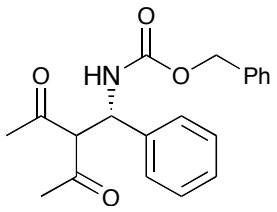
To a solution of imine (0.1 mmol, 1 eq) and catalyst **1** (5.6 mg, 0.01 mmol, 0.1 eq) in toluene (0.4 mL) at –78 ^{o}C was added 1,3-dicarbonyl (0.4 mmol, 4 eq). After three days the reaction was observed to have gone to completion, volatiles were removed *in vacuo* and the residue was purified by flash column chromatography eluting with hexane / acetone (100 / 1 to 3 / 1). This method was used to prepare:

2-Acetyl-3-oxo-1-phenylbutylcarbamic acid tert-butyl ester 6[2]



31 mg, 0.10 mmol, 100% from benzaldehyde *N*-(*tert*-butoxycarbonyl)imine **3** and acetyl acetone **2** as a white solid. Analytical Chiral HPLC (Daicel CHIRALCEL OG, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times 11.96 (4263.33 mAu s), 13.73 min (413.97 mAu s) gives 82% ee; Mpt. 171 - 173 ^{o}C; $[\alpha]_D^{25}$ -26.22 (*c* 0.45, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.34-7.22 (5H, m, Ph), 5.77 (1H, s, br, N**H**), 5.29 (1H, s, br, NHC**H**), 4.20 (1H, d, *J* 5.9, NHCHC**H**), 2.18 (3H, s, CH(COC$\mathbf{H}_3$)$_A$), 2.11 (3H, s, CH(COOC$\mathbf{H}_3$)$_B$), 1.39 (9H, s, C(C$\mathbf{H}_3$)$_3$).

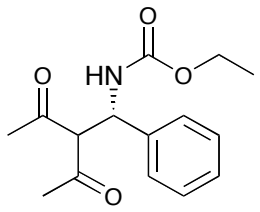
2-Acetyl-3-oxo-1-phenyl-butylcarbamic acid benzyl ester 7



25 mg, 0.07 mmol, 73% from benzaldehyde *N*-(benzyloxycarbonyl)imine **4** and acetyl acetone **2** as a white solid. Analytical Chiral HPLC (Daicel CHIRALCEL OG, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times 13.73 (3248.8 mAu s), 15.94 min (92.24 mAu s) gives 86% ee; Mpt. 100 - 101 ^{o}C; $[\alpha]_D^{25}$ +3.05 (*c* 0.95, $CHCl_3$); IR (film) / cm^{-1} υ_{max} = 3327 (br, N-H), 1697 (C=O), 1603 (Ar), 1497 (Ar); ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.39-7.23 (10H, m, Ar), 6.09 (1H, s, br, N**H**), 5.54 (1H, s, br, C**H**NH), 5.07 (2H, s, C$\mathbf{H}_2$), 4.24 (1H, d, *J* 5.4, NHCHC**H**), 2.17 (3H, s, (C$\mathbf{H}_3$)$_A$) 2.10 (3H, s, (C$\mathbf{H}_3$)$_B$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c 204.3 (CH(**C**OCH$_3$)$_A$), 202.1 (CH(**C**OCH$_3$)$_B$), 155.8 (**C**OOCH$_2$),

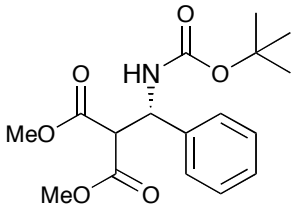
139.4 (NHCH**C**, Ar), 136.1 (OCH_2**C**), 128.8 (**C**H, Ar), 128.4 (**C**H, Ar), 128.1 (**C**H, Ar), 127.9 (**C**H, Ar), 127.8 (**C**H, Ar), 126.3 (**C**H, Ar), 71.5 (**C**HCOCH_3), 67.1 (O**C**H_2), 54.3 (NH**C**H), 30.5 ((**C**H_3)$_A$), 30.0((**C**H_3)$_B$); m/z (ESI-NH_4^+) 357.1807; $C_{20}H_{25}N_2O_4^+$ requires 357.1809.

2-Acetyl-3-oxo-1-phenyl-butylcarbamic acid ethyl ester 8



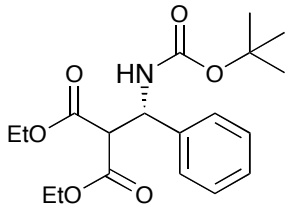
29 mg, 0.1 mmol, 100% from benzaldehyde *N*-(ethoxycarbonyl)imine **5** and acetyl acetone **2** as a white solid. Mpt. 87 - 88 °C; $[\alpha]_D^{25}$ -6.50 (*c* 1.17, $CHCl_3$); IR (film) / cm^{-1} υ_{max} = 3321 (br, N-H), 1697 (C=O), 1603 (Ar), 1506 (Ar) ; ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.35-7.22 (5H, m, Ar), 5.95 (1H, s, br, N**H**), 5.51 (1H, s, br, C**H**NH), 4.22 (1H, d, *J* 6.7, NHCHC**H**), 4.07 (1H, q, *J* 7.1, OC**H**$_2$$CH_3$), 2.18 (3H, s, (C**H**$_3$)$_A$), 2.11 (3H, s, (C**H**$_3$)$_B$), 1.20 (3H, t, *J* 7.1, OCH_2C**H**$_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c 204.4 (CH(**C**OCH_3)$_A$), 202.2 (CH(**C**OCH_3)$_B$), 156.0 (**C**OOCH_2), 139.6 (NHCH**C**, Ar), 128.9 (NHCHC**C**H, Ar), 127.8 (NHCHCCHCH**C**H, Ar), 126.4 (NHCHCCH**C**H, Ar), 71.5 (**C**HCOCH_3), 67.1 (O**C**$H_2$$CH_3$), 54.2 (NH**C**H), 30.5 ((**C**H_3)$_A$), 30.0((**C**H_3)$_B$), 14.6 (OCH_2**C**H_3); m/z (ESI-NH_4^+) 295.1654; $C_{15}H_{23}N_2O_4^+$ requires 295.1652.

2-(tert-Butoxycarbonylamino-phenyl-methyl)-malonic acid dimethyl ester 12



34 mg, 0.1 mmol, 100% from benzaldehyde *N*-(*tert*-butoxycarbonyl)imine **3** and dimethyl malonate **9** as a white solid. Analytical Chiral HPLC (Daicel CHIRALCEL AD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times 18.52 (14748.1 mAu s), 28.44 min (853.36 mAu s) gives 89% ee; Mpt. 89 - 90 ^{o}C; $[\alpha]_D^{25}$ +17.0 (*c* 1.14, $CHCl_3$); IR (film) / cm^{-1} υ_{max} = 3377 (br, N-H), 1736 (C=O_{ester}), 1717 (C=$O_{carbamate}$), 1603 (Ar), 1497 (Ar) ; ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.34-7.22 (5H, m, Ar), 6.13 (1H, s, br, N**H**), 5.48 (1H, s, br, C**H**NH), 3.92 (1H, d, *J* 3.0, NHCHC**H**), 3.74 (3H, s, O(C$\mathbf{H}_3$)$_A$) 3.64 (3H, s, O(C$\mathbf{H}_3$)$_B$), 1.42 (9H, s, br, C(C$\mathbf{H}_3$)$_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c 168.8 (CH(**C**OOCH_3)$_A$), 167.5 (CH(**C**OOCH_3)$_B$), 155.1 (**C**OOC(CH_3)$_3$), 139.1 (NHCH**C**, Ar), 128.6 (CCH**C**H, Ar), 127.6 (CCHCH**C**H, Ar), 126.2 (C**C**H, Ar), 79.8 (**C**(CH_3)$_3$), 56.7 (NHCH**C**H), 53.3 (NH**C**H), 52.8 (O(**C**H_3)$_A$), 52.5 (O(**C**H_3)$_B$), 28.3 (C(**C**H_3)$_3$); m/z (ESI-H$^+$) 338.1594; $C_{17}H_{24}NO_6^+$ requires 338.1598.

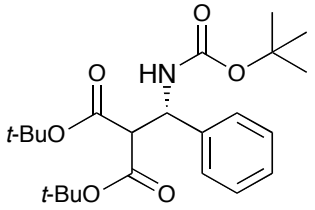
2-(tert-Butoxycarbonylamino-phenyl-methyl)-malonic acid diethyl ester 13



35 mg, 0.096 mmol, 96% from benzaldehyde *N*-(*tert*-butoxycarbonyl)imine **3** and diethyl malonate **10** as a white solid. Analytical Chiral HPLC (Daicel CHIRALCEL AD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times 14.03 min (7687.93 mAu s), 16.74 min (937.56 mAu s) gives 78% ee; Mpt. = 52 – 53 ^{o}C; $[\alpha]_D^{25}$ = +10.0 (c = 0.74, $CHCl_3$); IR (film) / cm^{-1} υ_{max} = 3426 (br, N-H), 1718 (C=O), 1496 (Ar) ; ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.33-7.28 (4H, m, $Ph_{ortho+meta}$), 7.23 (1H, m, Ph_{para}), 6.18 (1H, s, br, N**H**), 5.49 (1H, s, br, C**H**NH), 4.19 (2H, dq, *J* 10.2, 7.1, (OC$\mathbf{H}_2$CH_3)$_A$), 4.08 (2H, dq, *J* 14.0, 7.1, (OC$\mathbf{H}_2$CH_3)$_B$), 3.88 (1H, d, *J* 3.6, NHCHC**H**), 1.41 (9H, s, C(C$\mathbf{H}_3$)$_3$), 1.26 (3H, t, *J* 7.1, (OCH_2C$\mathbf{H}_3$)$_A$), 1.13 (3H, t, *J* 7.1, (OCH_2C$\mathbf{H}_3$)$_B$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c

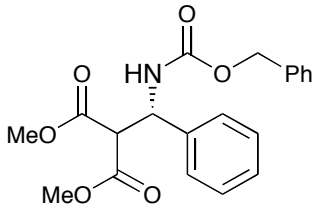
168.0 (CH(**C**OOCH$_2$CH$_3$)$_A$), 167.1 (CH(**C**OOCH$_2$CH$_3$)$_B$), 155.0 (**C**OOC(CH$_3$)$_3$), 139.6 (NHCH**C**, Ar), 128.4 (CCH**C**H, Ar), 127.4 (CCHCH**C**H, Ar), 126.2 (C**C**H, Ar), 79.6 (COO**C**(CH$_3$)$_3$), 61.9 (O(**C**H$_2$CH$_3$)$_A$), 61.5 (O(**C**H$_2$CH$_3$)$_B$), 56.9 (NHCH**C**H), 53.7 (NH**C**H), 27.7 (C(**C**H$_3$)$_3$), 14.0 (O(CH$_2$**C**H$_3$)$_A$), 13.8 (O(CH$_2$**C**H$_3$)$_B$); m/z (ESI-NH$_4^+$) 383.2180; $C_{19}H_{31}N_2O_6^+$ requires 383.2177;.

2-(tert-Butoxycarbonylamino-phenyl-methyl)-malonic acid di-tert-butyl ester 14



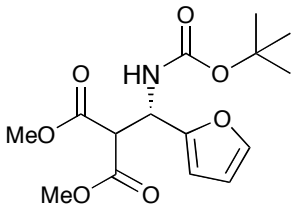
35 mg, 0.096 mmol, 96% from benzaldehyde *N*-(*tert*-butoxycarbonyl)imine **3** and di-*tert*-butyl malonate **11** as a white solid. Analytical Chiral HPLC (Daicel CHIRALCEL AD, 25 cm x 0.46 cm dia., 215nm), hexane / *I*-PrOH (9 / 1, 0.8 ml / min), retention times 9.04 min (8425.35 mAu s), 17.88 min (9776.03 mAu s) gives 7% ee; Mpt. = 60 – 61 ^oC; $[\alpha]_D^{25}$ = +0.94 (c = 0.96, $CHCl_3$); IR (film) / cm^{-1} υ_{max} = 3426 (br, N-H), 1717 (C=O), 1497 (Ar); ^1H NMR (400 MHz; $CDCl_3$): δ_H 7.30-7.26 (4H, m, Ph$_{ortho+meta}$), 7.25-7.20 (1H, m, Ph$_{para}$), 6.25 (1H, s, br, N**H**), 5.40 (1H, s, br, C**H**NH), 3.71 (1H, d, *J* 3.9, NHCHC**H**), 1.45 (9H, s, CH(COOC(C**H**$_3$)$_3$)$_A$), 1.42 (9H, s, NHCOOC(C**H**$_3$)$_3$), 1.41 (9H, s, CH(COOC(C**H**$_3$)$_3$)$_B$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c 167.6 (CH(**C**OOC(CH$_3$)$_3$)$_A$), 166.5 (CH(**C**OOC(CH$_3$)$_3$)$_B$), 155.0 (NH**C**OOC(CH$_3$)$_3$), 140.1 (NHCH**C**, Ar), 128.3 (CCH**C**H, Ar), 127.3 (CCHCH**C**H, Ar), 126.3 (C**C**H, Ar), 82.6 (CH(COO**C**(CH$_3$)$_3$)$_A$), 82.3 (CH(COO**C**(CH$_3$)$_3$)$_B$), 79.3 (NHCOO**C**(CH$_3$)$_3$), 58.5 (NHCH**C**H), 53.5 (NH**C**H), 28.4 (CH(COOC(**C**H$_3$)$_3$)$_A$), 27.8 (CH(COOC(**C**H$_3$)$_3$)$_A$), 27.7 (NHCOOC(**C**H$_3$)$_3$); m/z (ESI-NH$_4^+$) 439.2799; $C_{23}H_{39}N_2O_6^+$ requires 439.2803.

2-(Benzyloxycarbonylamino-phenyl-methyl)-malonic acid dimethyl ester 15



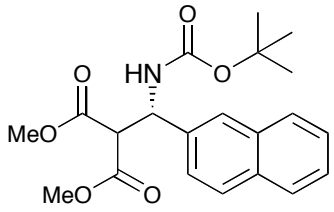
32 mg, 0.086 mmol, 86% from benzaldehyde *N*-(benzyloxycarbonyl)imine **4** and dimethyl malonate **9** as a white solid. Analytical Chiral HPLC (Daicel CHIRALCEL AD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times 21.06 (55676.8 mAu s), 31.14 min (2370.80 mAu s) gives 92% ee; Mpt. 69 - 70 ^{o}C; $[\alpha]_D^{25}$ +9.4 (*c* 1.0, $CHCl_3$); IR (film) / cm^{-1} υ_{max} = 3324 (br, N-H), 1734 (C=O), 1498 (Ar); ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.36-7.27 (10H, m, Ar), 6.44 (1H, d, *J* 7.4, N**H**), 5.55 (1H, dd, *J* 7.4, 3.4, NHC**H**), 5.12 (1H, d, *J* 12.2, COOC$\mathbf{H}_A$H$_B$), 5.08 (1H, d, *J* 12.2, COOCH$_A$$\mathbf{H}_B$), 3.94 (1H, d, *J* 3.4, NHCHC**H**), 3.70 (3H, s, O(C$\mathbf{H}_3$)$_A$) 3.63 (3H, s, O(C$\mathbf{H}_3$)$_B$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c 168.3 (CH(**C**OOCH$_3$)$_A$), 167.3 (CH(**C**OOCH$_3$)$_B$), 155.7 (**C**OOCH$_2$C$_6$H$_5$), 139.0 (NHCH**C**, Ar), 136.4 (OCH$_2$**C**, Ar), 128.7 (OCH$_2$CCH**C**H, Ar), 128.5 (NHCHCCH**C**H, Ar), 128.5 (OCH$_2$CCHCH**C**H, Ar), 128.1 (OCH$_2$C**C**H, Ar), 127.8 (NHCHCCHCH**C**H, Ar), 126.2 (NHCHC**C**H, Ar), 66.9 (O**C**H$_2$), 56.5 (NHCH**C**H), 54.0 (NH**C**H), 52.9 (O(**C**H$_3$)$_A$), 52.6 (O(**C**H$_3$)$_B$); m/z (ESI-H$^+$) 372.1454; $C_{20}H_{22}NO_6^+$ requires 372.1447.

2-(tert-Butoxycarbonylamino-furan-2-yl-methyl)-malonic acid dimethyl ester 18a



31 mg, 0.095 mmol, 95% from 2-furanaldehyde *N*-(*tert*-butoxycarbonyl)imine **16a** and dimethyl malonate **9** as a colourless oil. Analytical Chiral HPLC (Daicel CHIRALCEL AD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times 11.91 min (40471.7 mAu s), 18.1 min (1171.37 mAu s) gives 94% ee; $[\alpha]_D^{25}$ = +3.0 (c = 0.83, $CHCl_3$); IR (film) / cm^{-1} υ_{max} = 3423 (br, N-H), 1720 (C=O), 1497 (Ar); ^1H NMR (400 MHz; $CDCl_3$): δ_H 7.31 (1H, d, *J* 1.8, COC**H**CHCH), 6.29 (1H, dd, *J* 3.2, 1.8, COCHC**H**CH), 6.22 (1H, d, *J* 3.2, COCHCHC**H**), 5.83 (1H, s, br, N**H**), 5.53 (1H, d *J* 4.5, NHC**H**), 4.04 (1H, d, *J* 4.5, NHCHC**H**), 3.75 (3H, s, O(C**H**$_3$)$_A$), 3.72 (3H, s, O(C**H**$_3$)$_B$), 1.44 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c 168.2 (CH(**C**OOCH$_3$)$_A$), 167.3 (CH(**C**OOCH$_3$)$_B$), 155.0 (**C**OOC(CH$_3$)$_3$), 152.2 (O**C**CHCHCH), 142.1 (OC**C**HCHCH), 110.5 (OCCH**C**HCH), 106.7 (OCCHCH**C**H), 80.0 (COO**C**(CH$_3$)$_3$), 54.1 (NHCH**C**H), 52.9 (O(**C**H$_3$)$_A$), 52.6 (O(**C**H$_3$)$_B$), 48.3 (NH**C**H), 28.3 (C(**C**H$_3$)$_3$); m/z (ESI-H^+) 328.1406; $C_{15}H_{22}NO_7^+$ requires 328.1396.

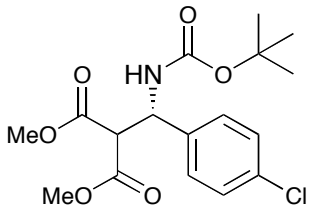
2-(tert-Butoxycarbonylamino-naphthalen-2-yl-methyl)-malonic acid dimethyl ester 18b



33 mg, 0.085 mmol, 85% from 2-naphthaldehyde *N*-(*tert*-butoxycarbonyl)imine **16b** and dimethyl malonate **9** as a white solid. Analytical Chiral HPLC (Daicel CHIRALCEL AD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times 26.31 (15263.9 mAu s), 30.39 min (282.33 mAu s) gives 96% ee; Mpt. = 139 – 140 ^oC; $[\alpha]_D^{25}$ = -1.28 (c = 1.1, $CHCl_3$); IR (film) / cm^{-1} υ_{max} = 3421 (br, N-H), 1735 (C=O$_{ester}$), 1717 (C=O$_{carbamate}$), 1601 (Ar), 1497 (Ar); ^1H NMR (400 MHz; $CDCl_3$): δ_H 7.84-7.79 (3H, m, Ar), 7.76 (1H, s, NHCHCC**H**C), 7.50-7.44 (2H, m, Ar), 7.42 (1H, dd, *J* 8.6, 1.8, NHCHCC**H**CH), 6.28 (1H, s, br,

NH), 5.66 (1H, s, NHC**H**), 4.04 (1H, d, *J* 3.2, NHCHC**H**), 3.76 (3H, s, O(C**H**$_3$)$_A$) 3.61 (3H, s, O(C**H**$_3$)$_B$), 1.43 (9H, s, br, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c 168.4 (CH(**C**OOCH$_3$)$_A$), 167.5 (CH(**C**OOCH$_3$)$_B$), 155.1 (**C**OOC(CH$_3$)$_3$), 136.9 (NHCH**C**, Ar), 133.2 (NHCHCCH**C** , Ar), 132.8 (NHCHCCHCH**C** , Ar), 128.4 (NHCHC**C**HCHC, Ar), 128.0 (NHCHCCHCHC**C**H, Ar), 127.5 (NHCHCCHC**C**H, Ar), 126.2 (NHCHCCH**C**HC, Ar), 126.0 (NHCHC**C**HC, Ar), 125.1 (NHCHCCHCCH**C**H, Ar), 124.1 (CCHCCHCH**C**H, Ar), 79.9 (**C**(CH$_3$)$_3$), 56.6 (NHCH**C**H), 53.6 (NH**C**H), 52.9 (O(**C**H$_3$)$_A$), 52.5 (O(**C**H$_3$)$_B$), 28.3 (C(**C**H$_3$)$_3$); m/z (ESI-H$^+$) 388.1763; $C_{21}H_{26}NO_6^+$ requires 388.1760.

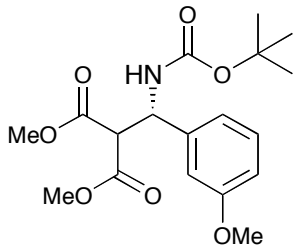
2-[tert-Butoxycarbonylamino-(4-chloro-phenyl)-methyl]-malonic acid dimethyl ester 18c



32 mg, 0.085 mmol, 85% from 4-chlorobenzaldehyde *N*-(*tert*-butoxycarbonyl)imine **16c** and dimethyl malonate **9** as a white solid. Analytical Chiral HPLC (Daicel CHIRALCEL AD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times 20.85 min (122.15 mAu s), 25.84 min (7756.55 mAu s) gives 97% ee; Mpt. = 88 – 89 ^{o}C; $[\alpha]_D^{25}$ = +15.4 (c = 0.36, $CHCl_3$); IR (film) / cm^{-1} υ_{max} = 3417 (br, N-H), 1736 (C=O$_{ester}$), 1717 (C=O$_{carbamate}$), 1597 (Ar), 1492 (Ar); ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.29 (2H, d, *J* 8.4, 2 x ClCC**H**CHC), 7.23 (2H, d, *J* 8.4, 2 x ClCCHC**H**C), 6.13 (1H, s, br, N**H**), 5.44 (1H, s, br, NHC**H**), 3.93 (1H, d, *J* 2.9 NHCHC**H**), 3.75 (3H, s, O(C**H**$_3$)$_A$), 3.65 (3H, s, O(C**H**$_3$)$_B$), 1.41 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c 168.2 (CH(**C**OOCH$_3$)$_A$), 167.3 (CH(**C**OOCH$_3$)$_B$), 155.0 (**C**OOC(CH$_3$)$_3$), 144.1 (ClCCHCH**C**), 138.0 (Cl**C**CHCH), 128.8 (ClC**C**HCH), 127.7 (ClCCH**C**H), 80.0

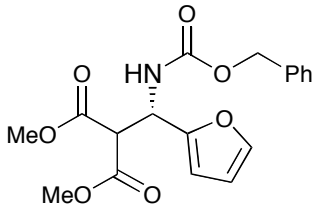
(COO**C**$(CH_3)_3$), 56.5 (NHCH**C**H), 52.9 (NH**C**H), 52.9 (O(**C**$H_3)_A$), 52.6 (O(**C**$H_3)_B$), 28.2 (C(**C**$H_3)_3$); m/z (ESI-H^+) 372.1210; $C_{17}H_{23}NO_6Cl^+$ requires 372.1214.

2-[tert-Butoxycarbonylamino-(3-methoxy-phenyl)-methyl]-malonic acid dimethyl ester –18d



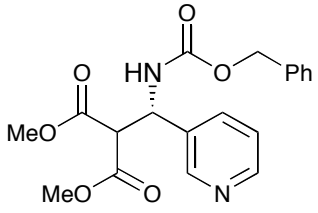
33 mg, 0.089 mmol, 89% from 3-methoxy-benzaldehyde *N*-(*tert*-butoxycarbonyl)imine **16d** and dimethyl malonate **9** as a white solid. Analytical Chiral HPLC (Daicel CHIRALCEL AD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times 31.89 (10893.5 mAu s), 36.00 min (710.35 mAu s) gives 88% ee; Mpt. = 79 - 80 ^oC; $[\alpha]_D^{25}$ = +12.94 (c = 1.43, $CHCl_3$); IR (film) / cm^{-1} υ_{max} = 3414 (br, N-H), 1737 (C=O_{ester}), 1716 (C=$O_{carbamate}$), 1601 (Ar), 1587 (Ar), 1497 (Ar); ^1H NMR (400 MHz; $CDCl_3$): δ_H; 7.23 (1H, t, *J* 7.9, NHCHCCHC**H**), 6.85 (1H, d, *J* 7.7, NHCHCC**H**CH), 6.84 (1H, d, *J* 2.3, NHCHCC**H**$COCH_3$), 6.79 (1H, dd, *J* 8.1, 2.3, NHCHCCHCHC**H**), 6.12 (1H, s, br, N**H**), 5.45 (1H, s, br, NHC**H**), 3.92 (1H, d, *J* 3.5, NHCHC**H**), 3.78 (3H, s, NHCHCCHCOC**H**$_3$) 3.74 (3H, s, CH(COOC**H**$_3)_A$), 3.65 (3H, s, CH(COOC**H**$_3)_B$), 1.42 (9H, s, br, C(C**H**$_3)_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c 168.4 (CH(**C**$OOCH_3)_A$), 167.5 (CH(**C**$OOCH_3)_B$), 159.8 (CCH**C**O C H_3), 155.1 (**C**$OOC(CH_3)_3$), 141.1 (NHCH**C**, Ar), 129.7 (NHCHCCH**C**H, Ar), 118.4 (NHCHC**C**HCH, Ar), 113.0 (C**C**$HCOCH_3$, Ar), 112.1 (NHCHCCHCH**C**H, Ar), 79.8 (**C**$(CH_3)_3$), 56.6 (NHCH**C**H), 55.2 (CCHCO**C**H_3), 53.4 (NH**C**H), 52.9 (CH(COO**C**$H_3)_A$), 52.5 (CH(COO**C**$H_3)_B$), 28.3 (C(**C**$H_3)_3$); m/z (ESI-H^+) 368.1709; $C_{18}H_{26}NO_7^+$ requires 368.1709.

2-(Benzyloxycarbonylamino-furan-2-yl-methyl)-malonic acid dimethyl ester –19a



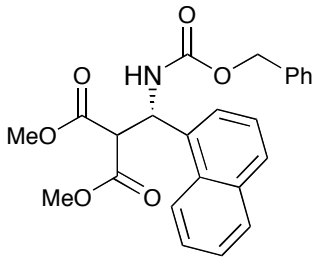
36 mg, 0.096 mmol, 96% from 2-furanaldehyde *N*-(benzyloxycarbonyl)imine **17a** and dimethyl malonate **9** as a colourless oil. Analytical Chiral HPLC (Daicel CHIRALCEL AD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times 26.61 min (7055.17 mAu s), 18.1 min (122.08 mAu s) gives 97% ee; $[\alpha]_D^{25}$ = -2.66 (c = 1.24, $CHCl_3$); IR (film) / cm^{-1} υ_{max} = 3420 (br, N-H), 1726 (C=O), 1499 (Ar); ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.36-7.28 (5H, m, Ar), 7.32 (1H, dd, *J* 1.8, 0.6, NHCHCOC**H**), 6.30 (1H, dd, *J* 3.2, 1.8, NHCHCOCHC**H**), 6.22 (1H, d, *J* 3.2, NHCHCC**H**), 6.17 (1H, d, *J* 9.3, N**H**), 5.60 (1H, dd, *J* 9.3, 4.5, NHC**H**), 5.13 (2H, s, COOC**H**$_2$), 4.05 (1H, d, *J* 4.5, NHCHC**H**), 3.70 (6H, s, 2 x OC**H**$_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c 168.1 (CH(**C**OOCH$_3$)$_A$), 167.0 (CH(**C**OOCH$_3$)$_B$), 155.7 (**C**OOCH$_2$C$_6$H$_5$), 151.7 (O**C**CHCHCH), 142.2 (O**C**HCHCH), 136.3 (OCH$_2$**C**, Ar) 128.4 (OCH$_2$CCH**C**H, Ar), 128.0 (OCH$_2$C**C**H, Ar), 128.0 (OCH$_2$CCHCH**C**H), 110.5 (OCCH**C**H), 106.7 (OC**C**H), 67.1 (**C**H$_2$C$_6$H$_5$), 53.9 (NHCH**C**H), 52.9 (O(**C**H$_3$)$_A$), 52.7 (O(**C**H$_3$)$_B$), 48.8 (NH**C**H); m/z (ESI-Na^+) 384.1057; $C_{18}H_{19}NO_7Na^+$ requires 384.1059.

2-(Benzyloxycarbonylamino-pyridin-3-yl-methyl)-malonic acid dimethyl ester – 19b



30 mg, 0.081 mmol, 81% from 3-pyridine carboxyaldehyde *N*-(benzyloxycarbonyl)imine **17b** and dimethyl malonate **9** as a white solid. Analytical Chiral HPLC (Daicel CHIRALCEL AD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times 20.32 (463.68 mAu s), 25.03 min (5072.91 mAu s) gives 83% ee; Mpt. = 74 - 75 ^{o}C; $[\alpha]_D^{25}$ = +9.33 (c = 1.35, $CHCl_3$); IR (film) / cm^{-1} υ_{max} = 3322 (br, N-H), 1724 (C=O), 1578 (Ar), 1503 (Ar); ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 8.58 (1H, s, NHCHCC**H**N), 8.53 (1H, d, *J* 4.0, NHCHCCHNC**H**), 7.65 (1H, d, *J* 7.9, NHCHCC**H**CH), 7.34 (5H, m, Ar), 7.25 (1H, dd, *J* 7.9, 4.0, NHCHCCHC**H**), 6.47 (1H, d, *J* 7.7, N**H**), 5.57 (1H, dd, *J* 7.7, 3.2, NHC**H**), 5.10 (1H, d, *J* 12.2, COOC**H**$_A$H$_B$), 5.07 (1H, d, *J* 12.2, COOCH$_A$**H**$_B$), 3.93 (1H, d, *J* 3.2, NHCHC**H**), 3.71 (3H, s, O(C**H**$_3$)$_A$) 3.65 (3H, s, O(C**H**$_3$)$_B$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c 168.0 (CH(**C**OOCH$_3$)$_A$), 166.9 (CH(**C**OOCH$_3$)$_B$), 155.6 (**C** O O C H$_2$C$_6$H$_5$), 149.3 (NHCHC**C**HN), 148.1 (NHCHCCHN**C**H), 136.1 (OCH$_2$**C**, Ar), 134.7 (NHCH**C**CHN), 134.2 (NHCHC**C**HCH), 128.5 (OCH$_2$CCH**C**H, Ar), 128.2 (OCH$_2$CCHCH**C**H, Ar), 128.1 (OCH$_2$C**C**H, Ar), 123.4 (NHCHCCH**C**H), 67.2 (O**C**H$_2$), 56.1 (NHCH**C**H), 53.1 (O(**C**H$_3$)$_A$), 52.8 (O(**C**H$_3$)$_B$), 52.1 (NH**C**H); m/z (ESI-H$^+$) 373.1399; $C_{19}H_{21}N_2O_6^+$ requires 373.1400.

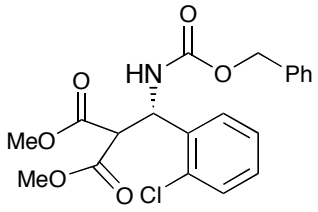
2-(Benzyloxycarbonylamino-naphthalen-1-yl-methyl)-malonic acid dimethyl ester – 19c



42 mg, 0.10 mmol, 100% from 1-naphthaldehyde *N*-(benzyloxycarbonyl)imine **17c** and dimethyl malonate **9** as a colourless oil. Analytical Chiral HPLC (Daicel

CHIRALCEL AD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times 30.11 (21908.8 mAu s), 36.91 min (297.56 mAu s) gives 83% ee; $[\alpha]_D^{25}$ = +40.26 (c = 1.95, $CHCl_3$); IR (film) / cm^{-1} υ_{max} = 3413 (br, N-H), 1723 (C=O), 1600 (Ar), 1506 (Ar), 1500 (Ar); m/z (ESI-H^+) 422.1600; ^1H NMR (400 MHz; $CDCl_3$): δ_H 8.14 (1H, d, *J* 8.4, NHCHCCC**H**), 7.89 (1H, d, *J* 7.9, NHCHCCCHCHCHC**H**), 7.79 (1H, d, *J* 8.1, NHCHCCHCHC**H**), 7.61 (1H, t, *J* 7.7, NHCHCCCHC**H**), 7.53 (1H, t, *J* 7.9, NHCHCCCHCHC**H**), 7.49 (d, *J* 7.5, NHCHCCHCHC**H**), 7.43 (1H, dd, *J* 7.9, 7.5, NHCHCCHC**H**), 7.36-7.32 (5H, m, Ar), 6.87 (1H, d, *J* 9.2, N**H**), 6.38 (1H, dd, *J* 9.2, 3.7, NHC**H**), 5.12 (1H, d, *J* 15.3, $OC\mathbf{H}_AH_B$), 5.09 (1H, d, *J* 15.3, $OCH_A\mathbf{H}_B$), 4.12 (1H, d, *J* 3.7, NHCHC**H**), 3.78 (3H, s, $O(C\mathbf{H}_3)_A$) 3.55 (3H, s, $O(C\mathbf{H}_3)_B$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c 168.5 ($CH(\mathbf{C}OOCH_3)_A$), 167.6 ($CH(\mathbf{C}OOCH_3)_B$), 155.7 ($\mathbf{C}OOCH_2C_6H_5$), 136.5 ($OCH_2\mathbf{C}$, Ar), 134.5 (NHCH**C**, Ar), 133.9 (NHCHCC**C**, Ar), 130.0 (NHCHC**C**, Ar), 129.1 (NHCHCCCHCHCH**C**H, Ar), 128.6 ($OCH_2C\,C\,H\,\mathbf{C}\,H$, Ar), 128.4 (NHCHCCHCH**C**H, Ar), 128.0 ($OCH_2CCHCH\mathbf{C}H$, Ar), 126.9 (**C**H, Ar), 126.9 (**C**H, Ar), 125.8 ($OCH_2C\mathbf{C}H$, Ar), 125.1 (NHCHCCCH**C**H), 123.6 (NHCHCCCHCH**C**H), 122.0 (NHCHCC**C**H, Ar), 67.0 ($O\mathbf{C}H_2$), 56.2 (NHCH**C**H), 53.1 ($O(\mathbf{C}H_3)_A$), 52.5 ($O(\mathbf{C}H_3)_B$), 50.7 (NH**C**H); $C_{24}H_{24}NO_6^+$ requires 422.1604.

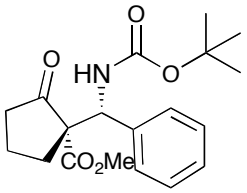
2-(Benzyloxycarbonylamino-2-chloro-phenyl-methyl)-malonic acid dimethyl ester – 19d



38 mg, 0.093 mmol, 93% from 2-chlorobenzaldehyde *N*-(benzyloxycarbonyl)imine **17d** and dimethyl malonate **9** as a colourless oil Analytical Chiral HPLC (Daicel CHIRALCEL AD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times 17.20 (23.20 mAu s), 23.28

min (938.18 mAu s) gives 97% ee; $[\alpha]_D^{25}$ = +32.60 (c = 1.31, $CHCl_3$); IR (film) / cm^{-1} υ_{max} = 3416 (br, N-H), 1726 (C=O), 1601 (Ar), 1587 (Ar), 1499 (Ar); ^1H NMR (400 MHz; $CDCl_3$): δ_H; 7.38-7.30 (6H, m, Ar), 7.25-7.20 (3H, m, Ar), 6.70 (1H, d, *J* 8.8, N**H**), 5.86 (1H, dd, *J* 8.8, 4.1, NHC**H**), 5.12 (1H, d, *J* 12.5, OC$\mathbf{H}_A$$H_B$$C_6H_5$), 5.07 (1H, d, *J* 12.5, OC$H_A$$\mathbf{H}_B$$C_6H_5$), 4.15 (1H, d, *J* 4.1, NHCHC**H**), 3.73 (3H, s, CH(COOC$\mathbf{H}_3$)$_A$), 3.60 (3H, s, CH(COOC$\mathbf{H}_3$)$_B$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c 168.5 (CH(**C**OOCH_3)$_A$), 167.3 (CH(**C**OOCH_3)$_B$), 155.5 (**C**OOC$H_2$$C_6H_5$), 136.3 (**C**, Ar), 136.2 (**C**, Ar), 132.4 (**C**, Ar), 129.9 (**C**H, Ar), 129.2 (**C**H, Ar), 129.5 (**C**H, Ar), 128.1 (**C**H, Ar), 128.1 (**C**H, Ar), 127.8 (**C**H, Ar), 127.0 (**C**H, Ar), 66.9 (OC$\mathbf{H}_2$$C_6H_5$), 53.6 (NH**C**H), 52.9 (CH(COO**C**H_3)$_A$), 52.5 (CH(COO**C**H_3)$_B$), 51.6 (**C**H(COOCH_3)$_2$); m/z (ESI-H^+) 406.0982; $C_{20}H_{21}ClNO_6^+$ requires 406.0979.

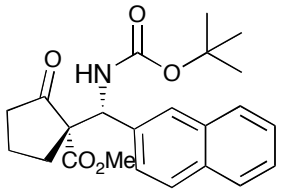
1-(tert-Butoxycarbonylaminophenylmethyl)-2-oxocyclopentanecarboxylicac id methyl ester 21a -Major diastereomer



24.3 mg, 0.07 mmol, 70% from *N*-(*tert*-butoxycarbonyl)imine **3** and methyl cyclopentanone carboxylate **20** as a white solid. Analytical Chiral HPLC (Daicel CHIRALCEL AD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (98 / 2, 0.8 ml / min), retention times of major diastereomer 12.82 (27411.0 mAu s), 14.96 min (2315.16 mAu s) gives 85% ee; Mpt. 64 - 66 ^oC; IR (film) / cm^{-1} υ_{max} = 3387 (br, N-H), 1753 (C=O_{ester}) 1716 (C=O_{ketone}), 1700 (C=$O_{carbamate}$), 1496 (Ar); ^1H NMR (400 MHz; $CDCl_3$): δ_H 7.30–7.29 (4H, m, $Ph_{ortho+meta}$), 7.25-7.23 (1H, m, Ph_{para}), 6.71 (1H, s, br, N**H**), 5.33 (1H, d, *J* 9.4, NHC**H**), 3.65 (3H, s, COOC$\mathbf{H}_3$), 2.57-2.52 (1H, m, CCOC$\mathbf{H}_A$$H_B$), 2.21 (1H, ddd, *J* 18.5, 8.7, 5.9, CC$\mathbf{H}_A$$H_B$), 2.05 (1H, dt, *J*, 13.8, 7.7, COC$H_A$$\mathbf{H}_B$), 1.88 (1H, dt, *J* 18.5, 8.4, CC$H_A$$\mathbf{H}_B$), 1.80-1.71 (1H, m, COC$H_2C\mathbf{H}_A$$H_B$), 1.6-1.45 (1H, m, COC$H_2CH_A$$\mathbf{H}_B$); ^{13}C NMR (100 MHz; d_6-DMSO,

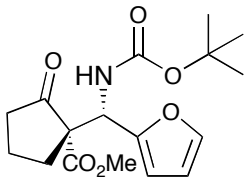
120 °C): δ_c 211.2 (C**C**OCH$_2$), 169.5 (C**C**OOCH$_3$), 155.2 (**C**OOC(CH$_3$)$_3$), 139.7 (**C**, Ph$_{ipso}$), 128.5 (**C**H, Ph), 128.3 (**C**H, Ph), 127.7 (**C**H, Ph$_{para}$), 79.0 (O**C**(CH$_3$)$_3$), 65.8 (NHCH**C**CO), 57.4 (NH**C**H), 52.6 (CCOO**C**H$_3$), 38.1 (CCO**C**H$_2$), 29.2 (C**C**H$_2$), 28.7 (OC(**C**H$_3$)$_3$), 19.0 (COCH$_2$**C**H$_2$); m/z (ESI-Na$^+$) 370.1628; C19H$_{25}$NO$_5$Na$^+$ requires 370.1630.

1-(tert-Butoxycarbonylamino-naphthalen-2yl)-2-oxocyclopentane carboxylicacid methyl ester 21b -Major diastereomer



66 mg, 0.166 mmol, 83% from 2-naphthaldehyde *N*-(*tert*-butoxycarbonyl)imine **16b** and methyl cyclopentanone carboxylate **20** as a white solid. Analytical Chiral HPLC (Daicel CHIRALCEL AD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (98 / 2, 0.8 ml / min), retention times of major diastereomer 12.12 (8494 mAu s), 37.70 min (119483 mAu s) gives 87% ee; Mpt. 139 - 140 °C; IR (film) / cm^{-1} υ_{max} = 3444 (br, N-H), 1751 (C=O$_{ester}$) 1714 (C=O$_{ketone}$), 1698 (C=O$_{carbamate}$), 1494 (Ar); ^{1}H NMR (400 MHz; CDCl$_3$): δ_H 7.81-7.75 (4H, m, Ar), 7.49-7.43 (3H, m, Ar), 6.07 (1H, s, br, N**H**), 5.38 (1H, d, *J* 9.3, NHC**H**), 3.68 (3H, s, COOC**H**$_3$), 2.54 (1H, dt, *J* 13.5, 6.8, CCOC**H**$_A$H$_B$), 2.36-2.28 (2H, m, CC**H**$_2$), 2.06 (1H, dt, *J*, 13.5, 6.9, COCH$_A$**H**$_B$), 2.00-1.89 (2H, m, COCH$_2$C**H**$_2$); ^{13}C NMR (100 MHz; CDCl$_3$): δ_c 210.9 (C**C**OCH$_2$), 169.9 (C**C**OOCH$_3$), 155.3 (**C**OOC(CH$_3$)$_3$), 135.8 (NHCH**C**CH), 133.0 (**C**, Ar), 132.8 (**C**, Ar), 128.1 (**C**H, Ar), 128.0 (**C**H, Ar), 127.4 (**C**H, Ar), 127.3 (**C**H, Ar), 126.1 (**C**H, Ar), 126.1 (**C**H, Ar), 125.7 (**C**H, Ar), 79.9 (O**C**(CH$_3$)$_3$), 65.0 (NHCH**C**CO), 56.0 (NH**C**H), 52.7 (CCOO**C**H$_3$), 37.6 (CCO**C**H$_2$), 30.8 (C**C**H$_2$), 28.3 (OC(**C**H$_3$)$_3$), 18.8 (COCH$_2$**C**H$_2$); m/z (ESI-H$^+$) 397.1886; C$_{28}$H$_{28}$NO$_5^+$ requires 397.1889.

1-(tert-Butoxycarbonylamino-furan-2-yl-methyl)-2-oxocyclopentane carboxylicacid methyl ester 21c -Major diastereomer

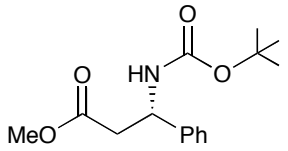


65 mg, 0.194 mmol, 97% from 2-furanaldehyde *N*-(*tert*-butoxycarbonyl)imine **16a** and methyl cyclopentanone carboxylate **20** as a colourless oil. Analytical Chiral HPLC (Daicel CHIRALCEL AD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times of major diastereomer 12.04 (708.82 mAu s), 19.13 min (8354.13 mAu s) gives 84% ee; Mpt 64 - 66 ^{o}C; IR (film) / cm^{-1} υ_{max} = 3377 (br, N-H), 1753 (C=O$_{ester}$) 1725 (C=O$_{ketone+carbamate}$), 1494 (Ar); ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.29 (1H, dd, *J* 1.8, 1.0, NHCHCOC**H**), 6.28 (1H, dd, *J* 3.2, 1.8, NHCHCOCHC**H**), 6.20 (1H, d, *J* 3.2, NHCHCCH), 5.61 (1H, s, br, N**H**), 5.36 (1H, d, *J* 10.2, NHC**H**), 3.71 (3H, s, COOC**H**$_3$), 2.58 (1H, dt, *J* 13.9, 7.2, CCOC**H**$_A$H$_B$), 2.35-2.28 (2H, m, CC**H**$_2$), 2.07-1.99 (1H, m, COCH$_A$**H**$_B$), 1.98-1.89 (2H, m, COCH$_2$C**H**$_2$), 1.41 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ_c 210.5 (C**C**OCH$_2$), 169.6 (C**C**OOCH$_3$), 155.2 (**C**OOC(CH$_3$)$_3$), 151.7 (NHCH**C**O), 141.8 (NHCHCO**C**H), 110.4 (NHCHCOCH**C**H), 108.0 (NHCHC**C**H), 70.0 (O**C**(CH$_3$)$_3$), 64.3 (NHCH**C**CO), 52.8 (CCOO**C**H$_3$), 50.6 (NH**C**H), 37.6 (CCO**C**H$_2$), 30.6 (C**C**H$_2$), 28.2 (OC(**C**H$_3$)$_3$), 18.9 (COCH$_2$**C**H$_2$); m/z (ESI-H$^+$) 337.1524; $C_{17}H_{24}NO_6^+$ requires 337.1525.

Method for dealkyl decarboxylation

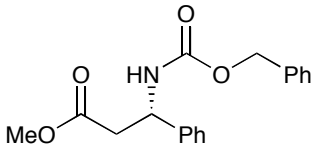
In an NMR tube **12** or **15** was dissolved in d$_6$-DMSO (0.5 mL). 1 drop of water was added and the reaction vessel was heated at 160 ^{o}C for 12 hours. After the reaction was observed to have gone to completion by NMR, the reaction was purified by flash column chromatography eluting with hexane / acetone (100 / 1 to 3 / 1). This method was use to prepare:

3-tert-Butoxycarbonylamino-3-phenyl-propionic acid methyl ester 22[3a]



10.8 mg, 0.038 mmol, 68%, from **13** as a white solid. Analytical Chiral HPLC (Daicel CHIRALCEL OD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times 8.10 (167.57 mAu s), 9.16 min (2894.96 mAu s) gives 89% ee; Mpt 72 ^{o}C; $[\alpha]_D^{25}$ -23.3 (*c* 0.40, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.35-7.24 (5H, m, Ph), 5.43 (1H, s, br, N**H**), 5.10 (1H, s, br, NHC**H**), 3.61 (3H, s, COOC$\mathbf{H}_3$), 2.87 (1H, dd, *J* 15.3, 5.2 NHCHC$\mathbf{H}_A$H$_B$), 2.81 (1H, dd, *J* 15.3, 5.8. NHCHCCH$_A\mathbf{H}_B$), 1.42 (9H, s, C(CH$_3$)$_3$).

3-Benzyloxycarbonylamino-3-phenyl-propionic acid methyl ester 23[3b]



14.8 mg, 0.047 mmol, 90%, from **16** as a white solid. Analytical Chiral HPLC (Daicel CHIRALCEL OD, 25 cm x 0.46 cm dia., 215nm), hexane / *i*-PrOH (9 / 1, 0.8 ml / min), retention times 19.76 (3891.02 mAu s), 24.82 min (165.58 mAu s) gives 92% ee; Mpt. 58 - 60 ^{o}C; $[\alpha]_D^{25}$ -13.7 (*c* 0.19, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$): δ_H 7.35-7.24 (10H, m, Ph), 5.73 (1H, s, br, N**H**), 5.16 (1H, dd, *J* 5.9, 5.3, NHC**H**), 5.12 (1H, d, *J*, 12.3, NHCOOC$\mathbf{H}_A$H$_B$), 5.08 (1H, d, *J* 12.3, NHCOOCH$_A\mathbf{H}_B$), 3.60 (3H, s, COOC$\mathbf{H}_3$), 2.89 (1H, dd, *J* 15.4, 5.2, NHCHC$\mathbf{H}_A$H$_B$), 2.83 (1H, dd, *J* 15.4, 5.9, NHCHCH$_A\mathbf{H}_B$).

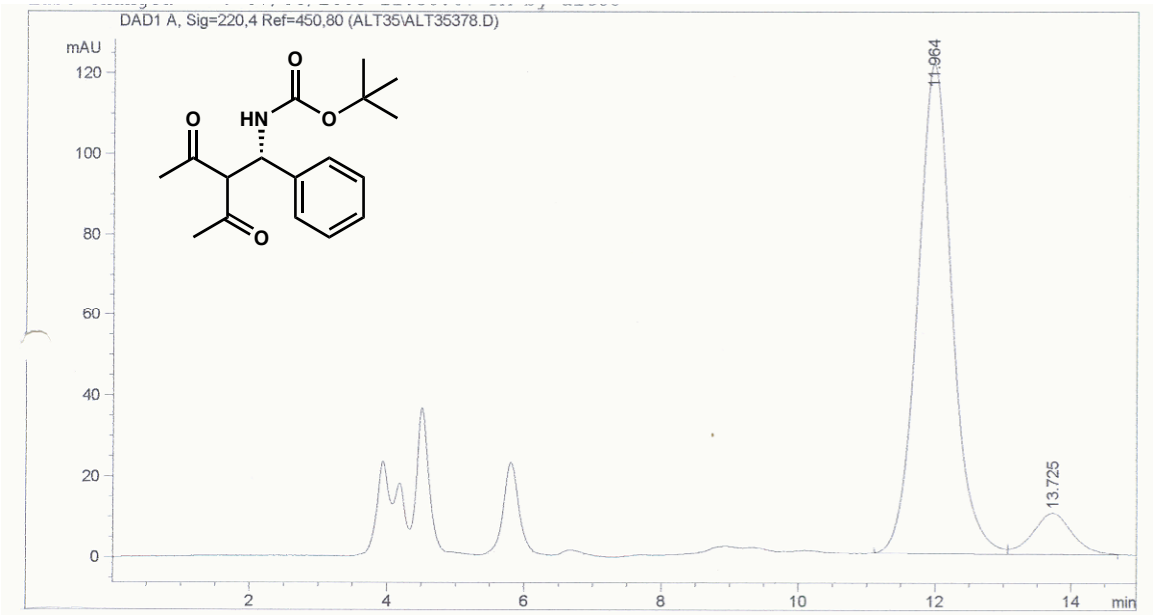
References

1. A.G. Wenzel, E.N. Jacobsen, *J. Am. Chem. Soc.* 2002, **124**, 12964-12965
2. D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* 2004, **126**, 5356-5357
3. a) F. A. Davis, J. M. Szewczyk, *Tetrahedron Lett*. 1998, **39**, 5951-5954. b) L. Crombie, D. Haigh, R. C. F. Jones, A. R. Mat-Zin, *J. Chem. Soc. Perkin Trans.* **1***,* 1993, 2047-2054.

HPLC analysis

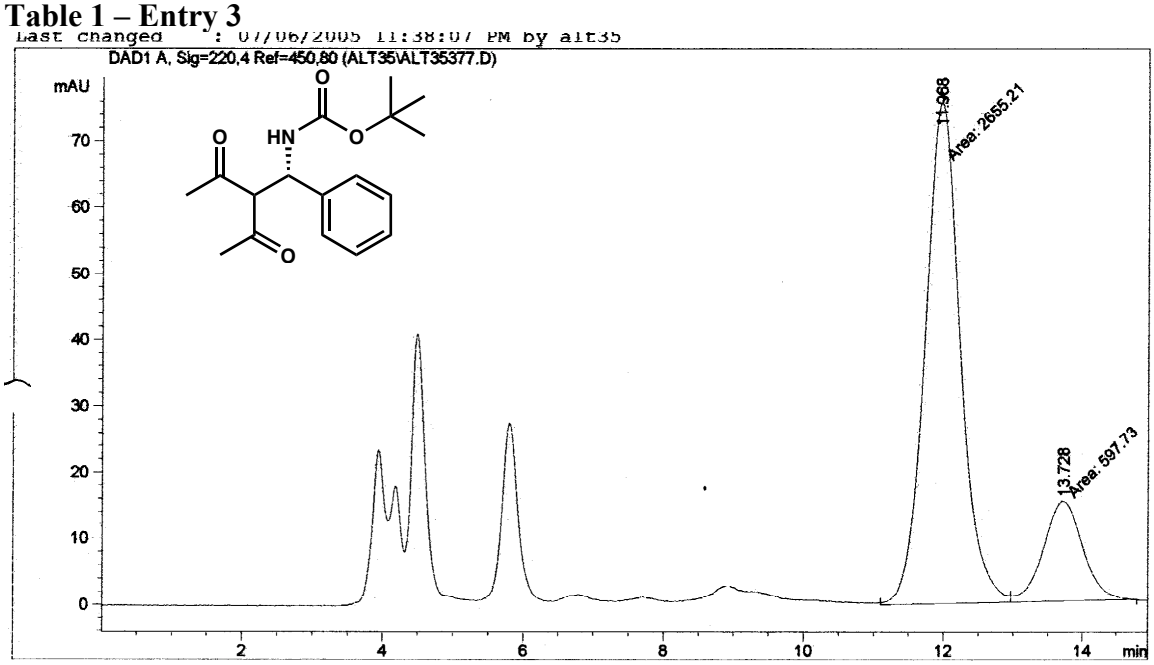
Analytical chiral HPLC data was obtained using Daicel CHIRALCEL AD, OG or OD columns (25 cm x 0.46 cm dia., at wavelengths specified in the traces below). For compounds **6**, **12**-**15**, **18**-**19** the traces were obtained using a Daicel CHIRALCEL AD column eluting with hexane / *i*-PrOH (9 / 1, 0.8 ml / min). For compound **7** the traces were obtained using a Daicel CHIRALCEL OG column eluting with hexane / *i*-PrOH (9 / 1, 0.8 ml / min). For compounds **21** the traces were obtained using a Daicel CHIRALCEL AD column eluting with hexane / *i*-PrOH (98 / 2, 0.8 ml / min). For compounds **22** and **23** the traces were obtained using a Daicel CHIRALCEL OD column eluting with hexane / *i*-PrOH (9 / 1, 0.8 ml / min).

Table 1 – Entry 2



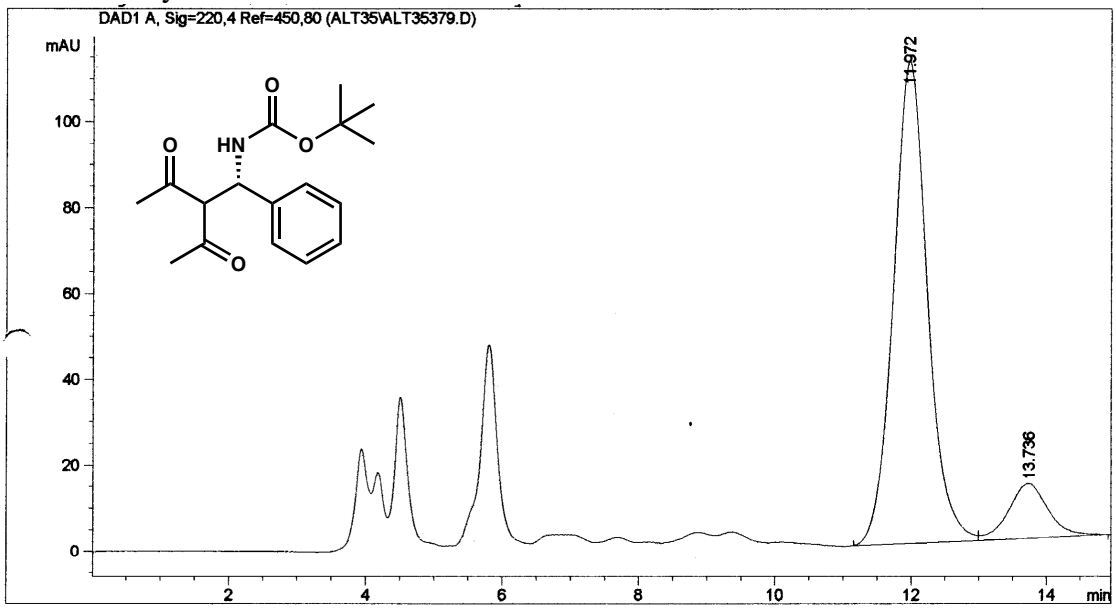
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.964	BB	0.5251	4260.33252	121.26134	91.2023
2	13.725	BB	0.4798	410.96936	10.19605	8.7977

Table 1 – Entry 3



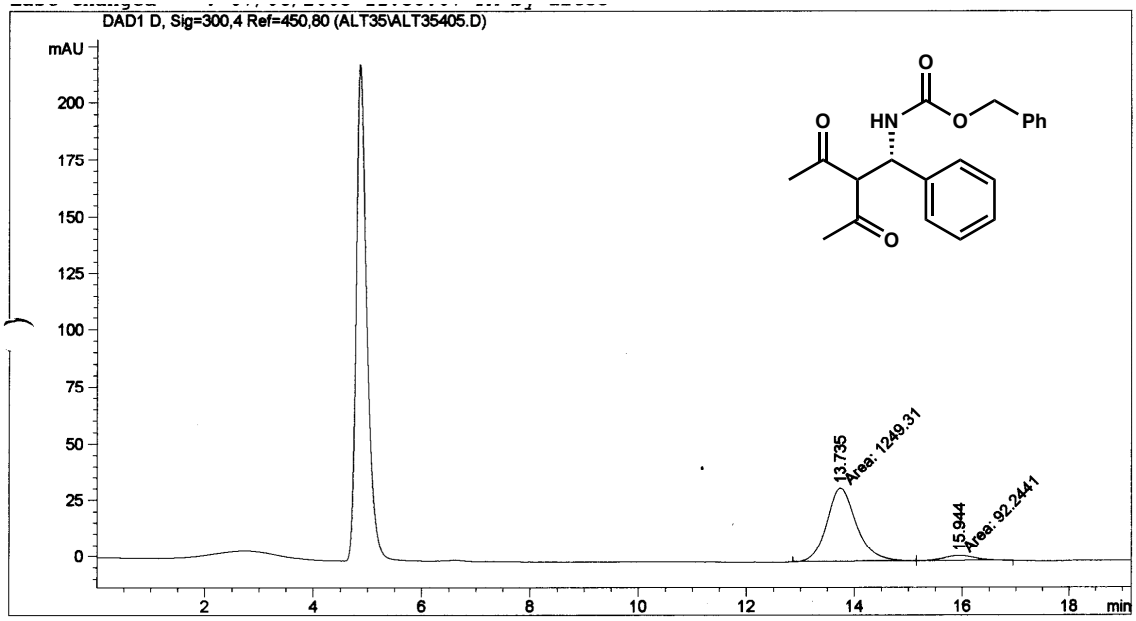
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.968	MF	0.5843	2655.21216	75.74127	81.6249
2	13.728	FM	0.6604	597.73029	15.08570	18.3751

Table 1 – Entry 4



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.972	BB	0.4945	3894.27368	112.21050	88.2445
2	13.736	BB	0.4915	518.77478	12.64461	11.7555

Table 1 - Entry 5



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.735	MF	0.6408	1249.30591	32.49191	93.1241
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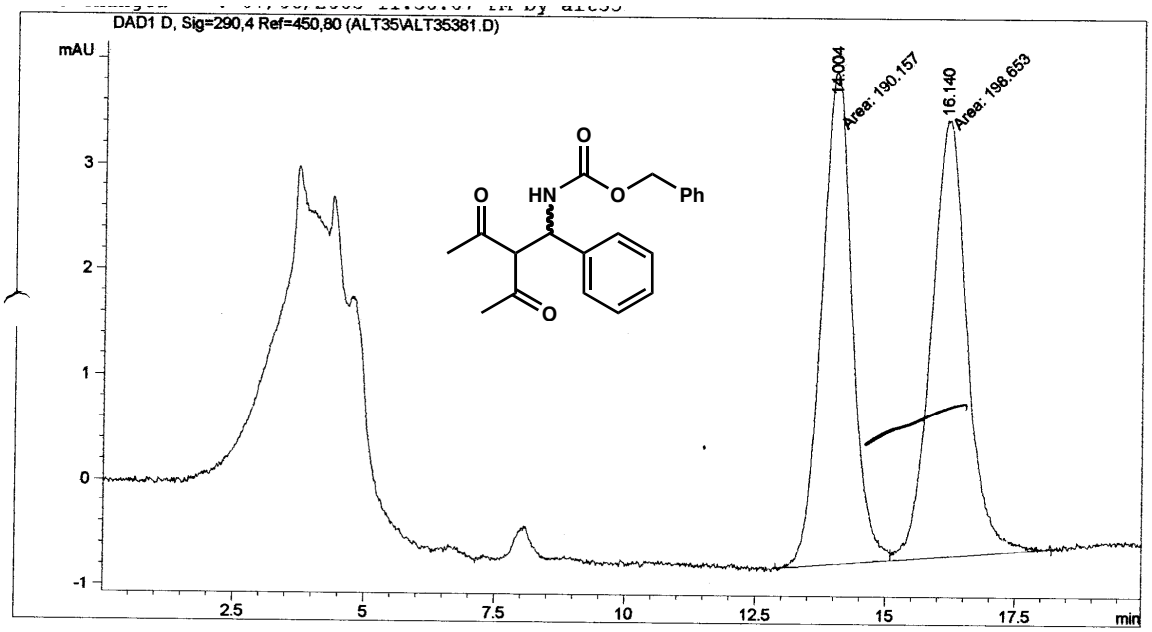
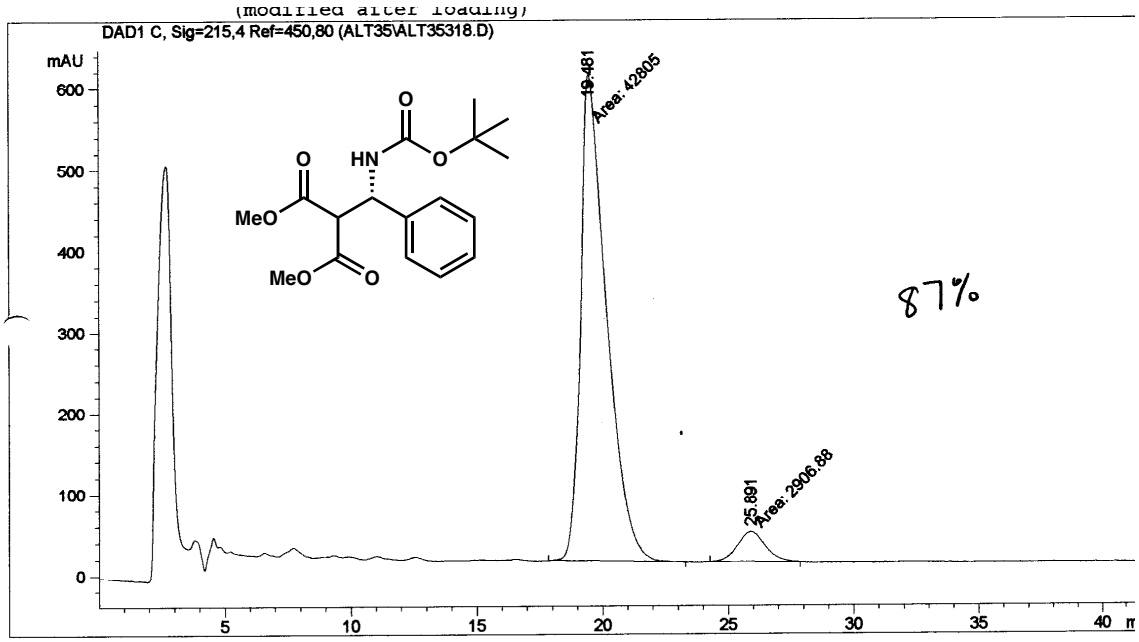


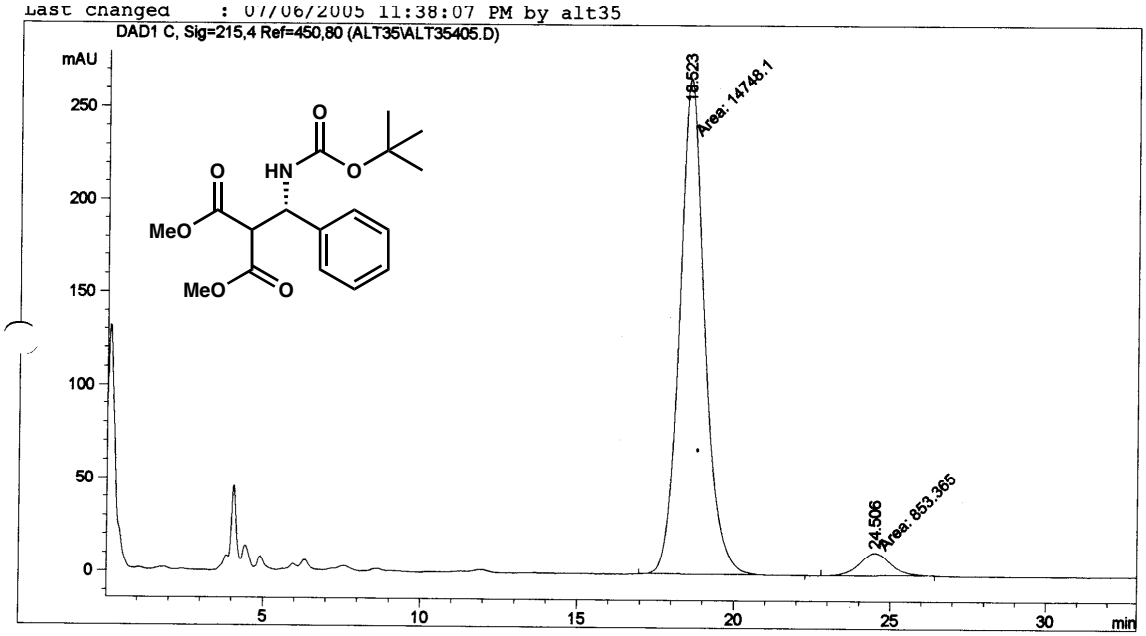
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.004	MF	0.6775	190.15697	4.67815	48.9075
2	16.140	FM	0.8002	198.65263	4.13776	51.0925

Table 2 – Entry 1



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.481	MM	1.1898	4.28050e4	599.60748	93.6409
2	25.891	MM	1.2954	2906.88477	37.40037	6.3591

Table 2 – Entry 2



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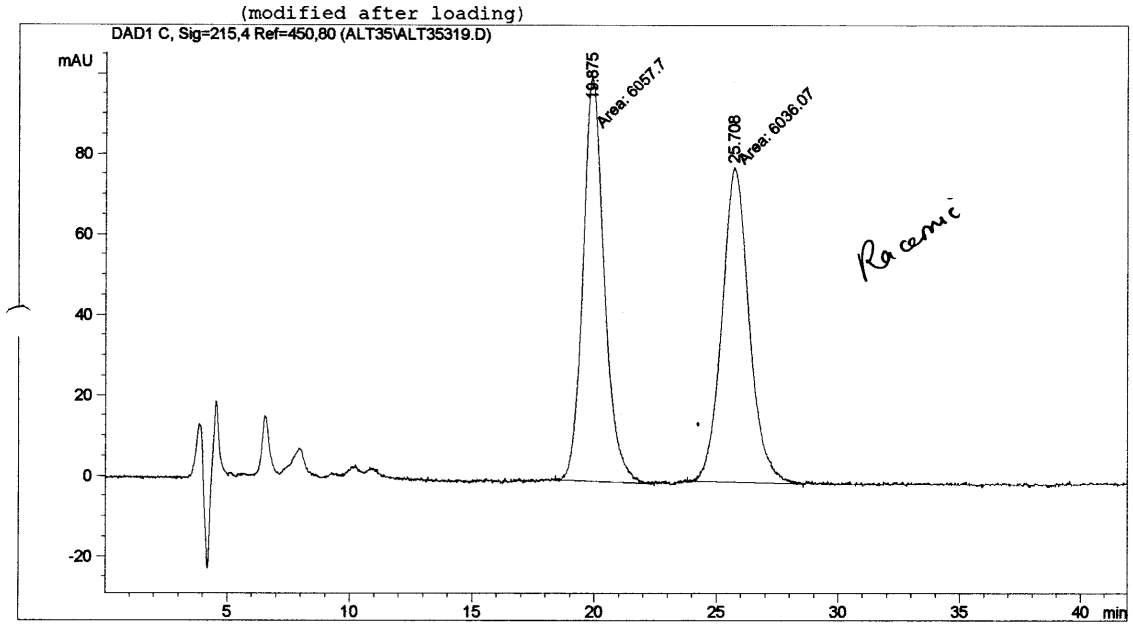
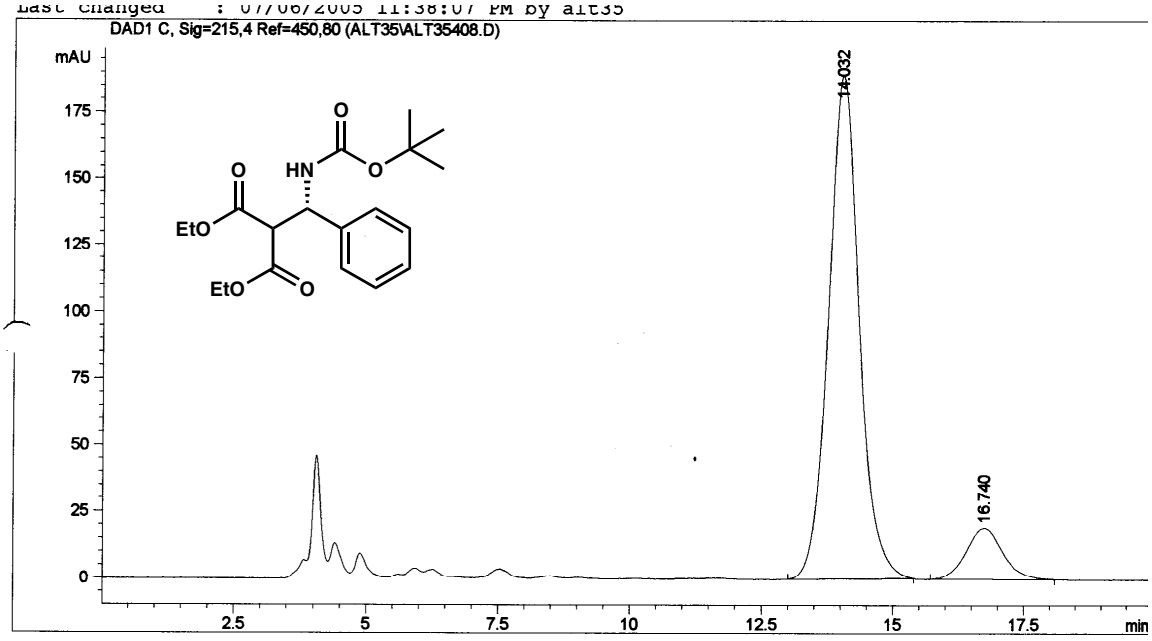
1	18.523	MM	0.9230	1.47481e4	266.30496	94.5302
2	24.506	MM	1.1721	853.36456	12.13405	5.4698



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.875	MM	1.0049	6057.70264	100.47092	50.0894
2	25.708	MM	1.2879	6036.07422	78.11353	49.9106

Table 2 – Entry 3



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1	14.032	BB	0.5632	7687.92920	189.40187	89.1304
2	16.740	BP	0.5851	937.55688	19.22157	10.8696

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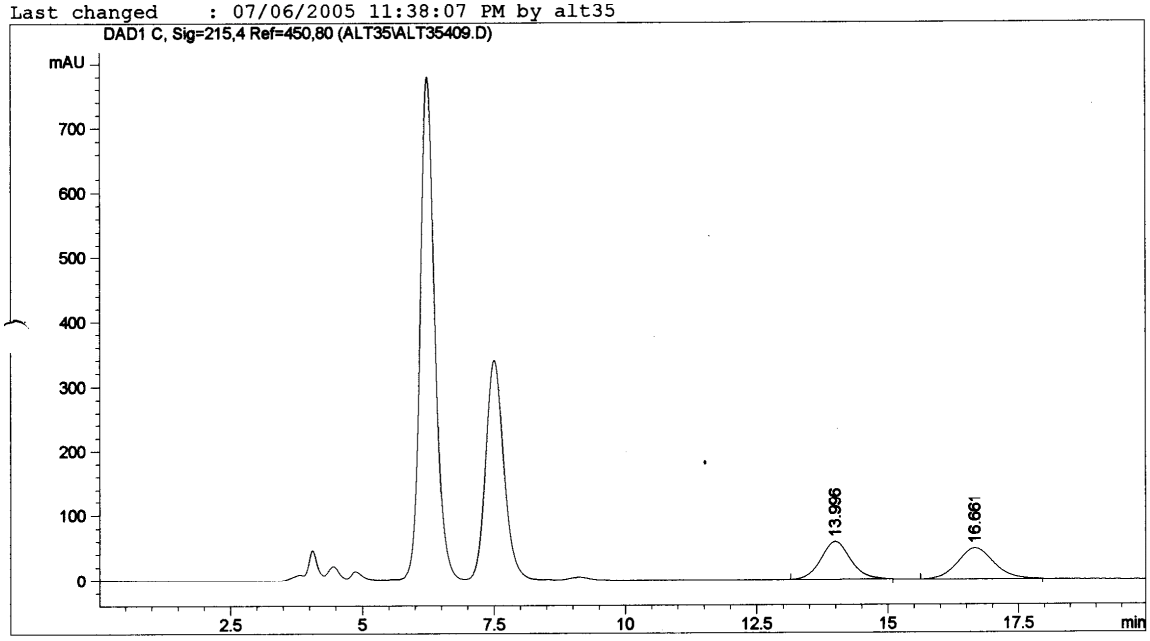

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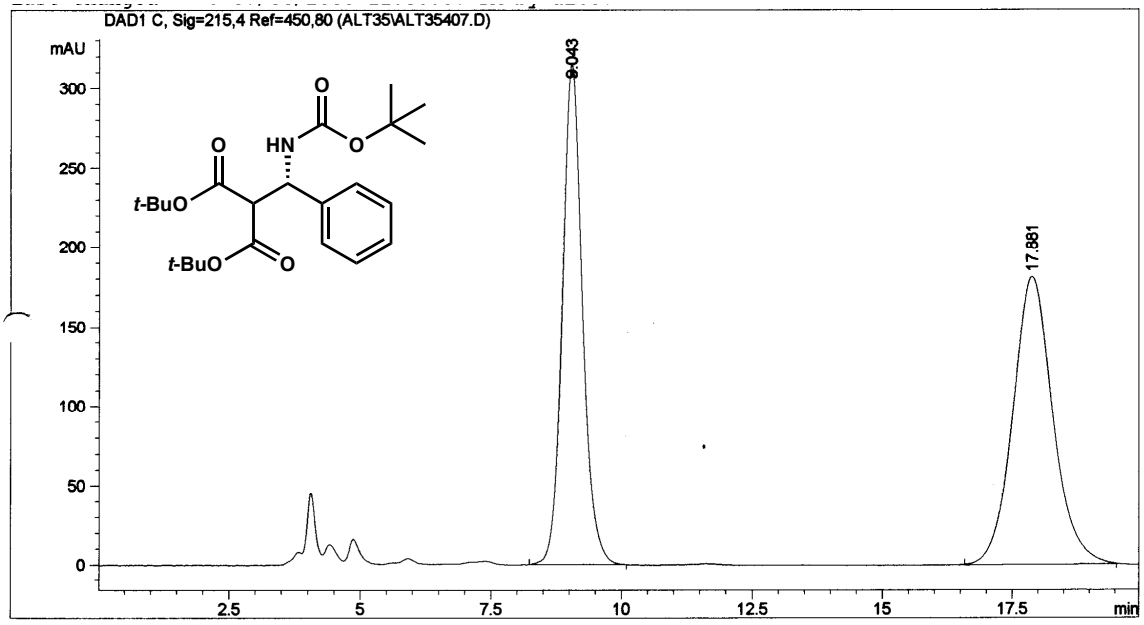
1	13.996	BB	0.5014	2309.57837	57.79316	50.0357
2	16.661	BB	0.5800	2306.28076	47.16818	49.9643

Table 2 – Entry 4



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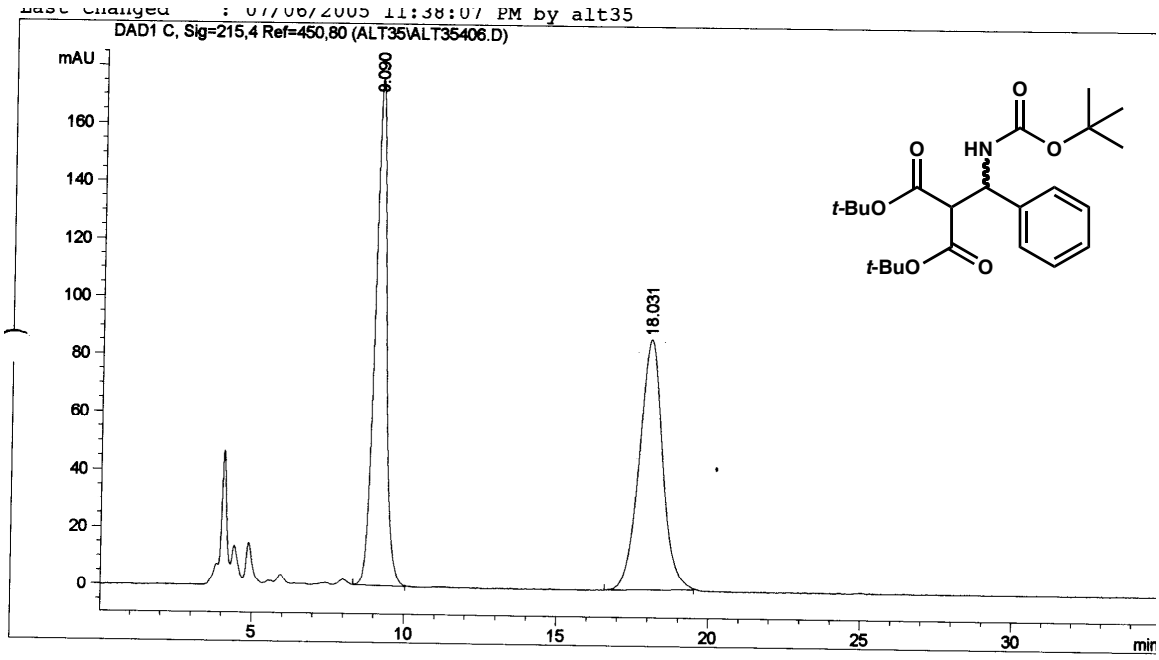
1	9.043	BB	0.4047	8425.35156	315.20044	46.2896
2	17.881	BB	0.7137	9776.03320	180.90126	53.7104



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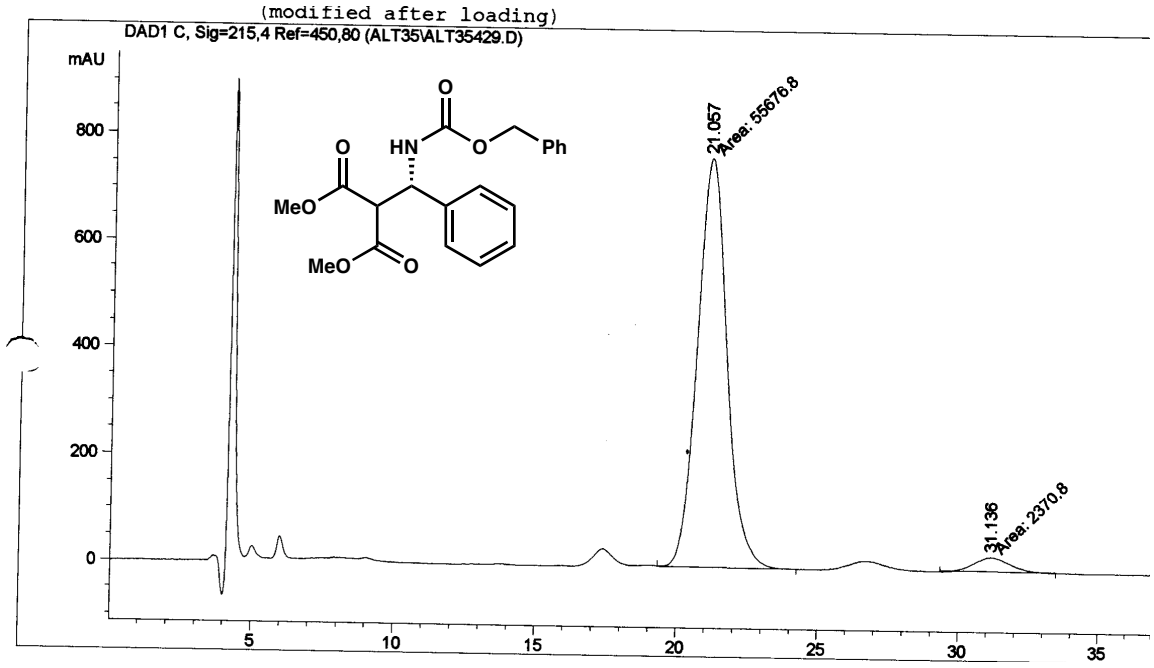
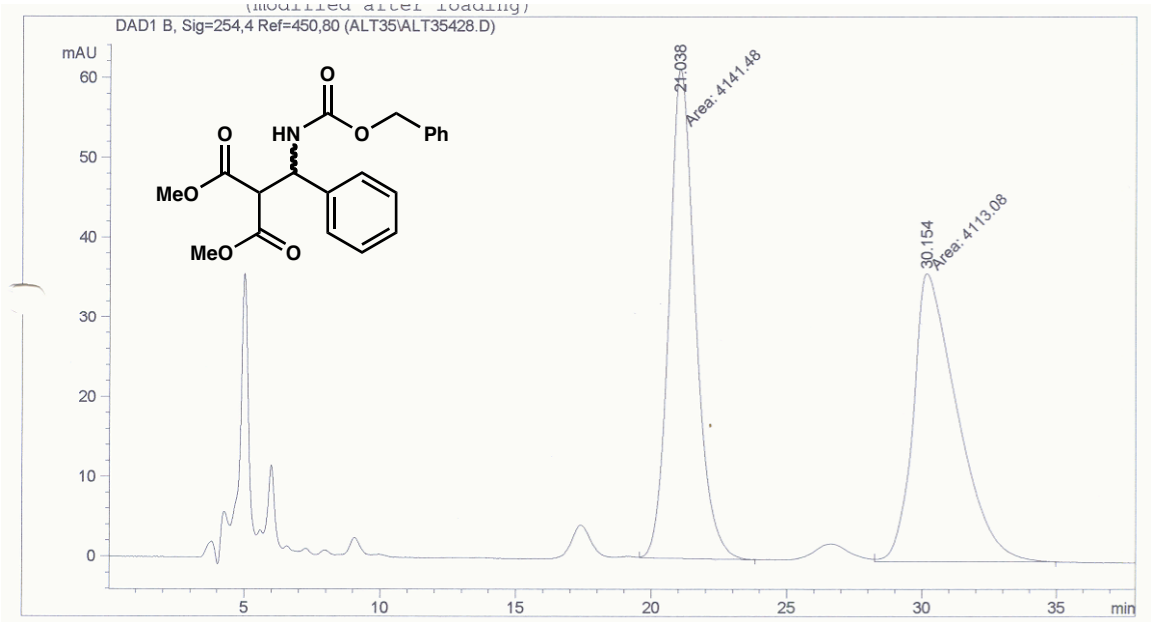
1	9.090	VB	0.3967	4688.23877	176.28735	50.1397
2	18.031	PB	0.6619	4662.10889	86.78384	49.8603

Table 2 – Entry 5



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.057	MM	1.2121	5.5676e4	765.57410	95.9158
2	31.136	MM	1.4798	2370.79565	26.70153	4.0842



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1	21.038	MM	1.1260	4141.48437	61.30132	50.1720
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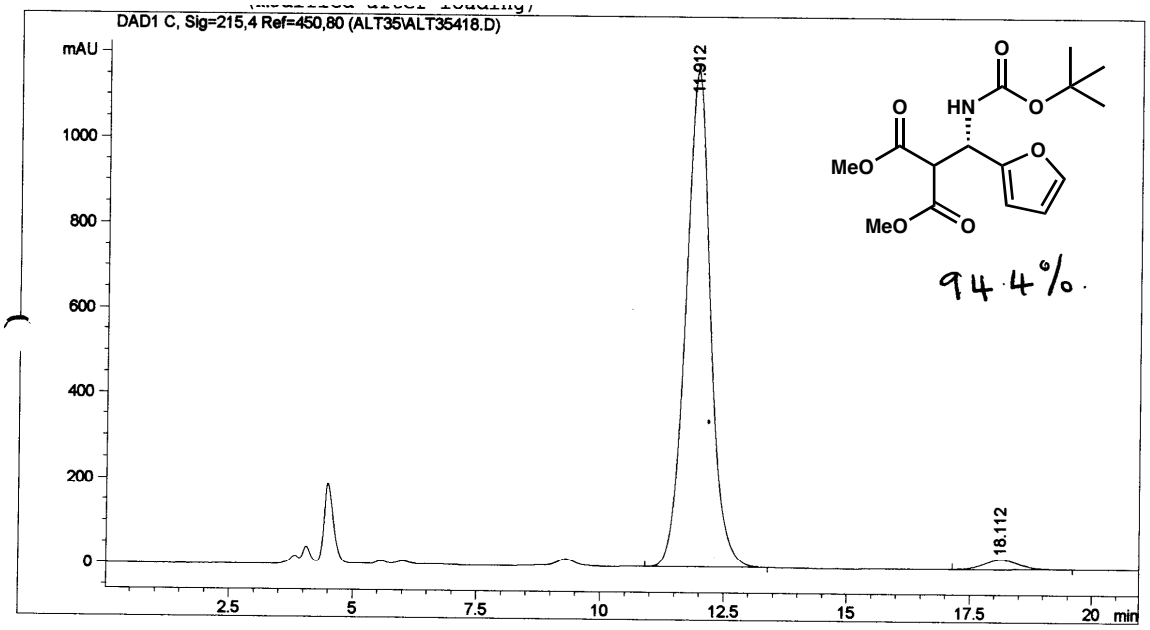
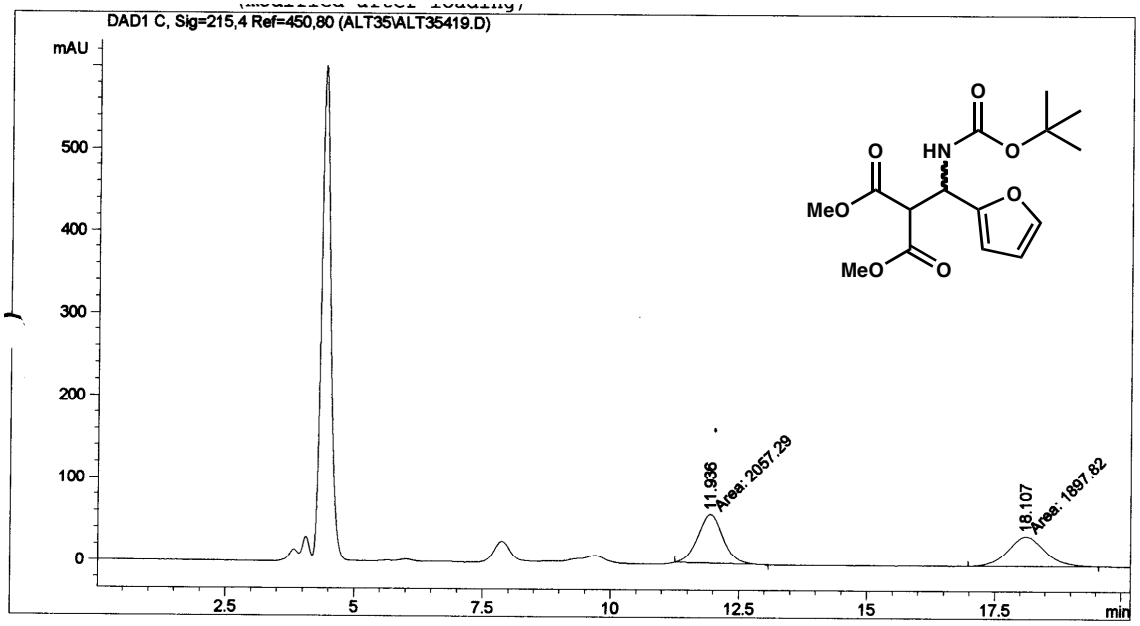
Table 3 – Entry 1



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.912	PB	0.4631	4.04717e4	1164.31152	97.1871
2	18.112	BP	0.6079	1171.37085	22.71992	2.8129



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1	11.936	MM	0.5766	2057.29272	59.46577	52.0160
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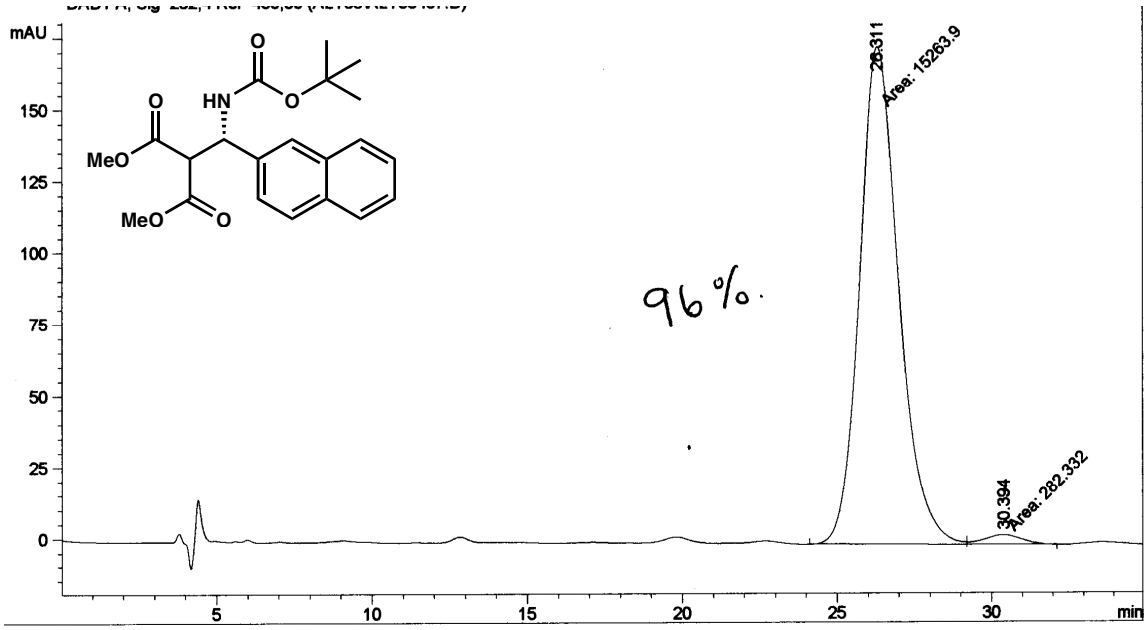
Table 3 – Entry 2



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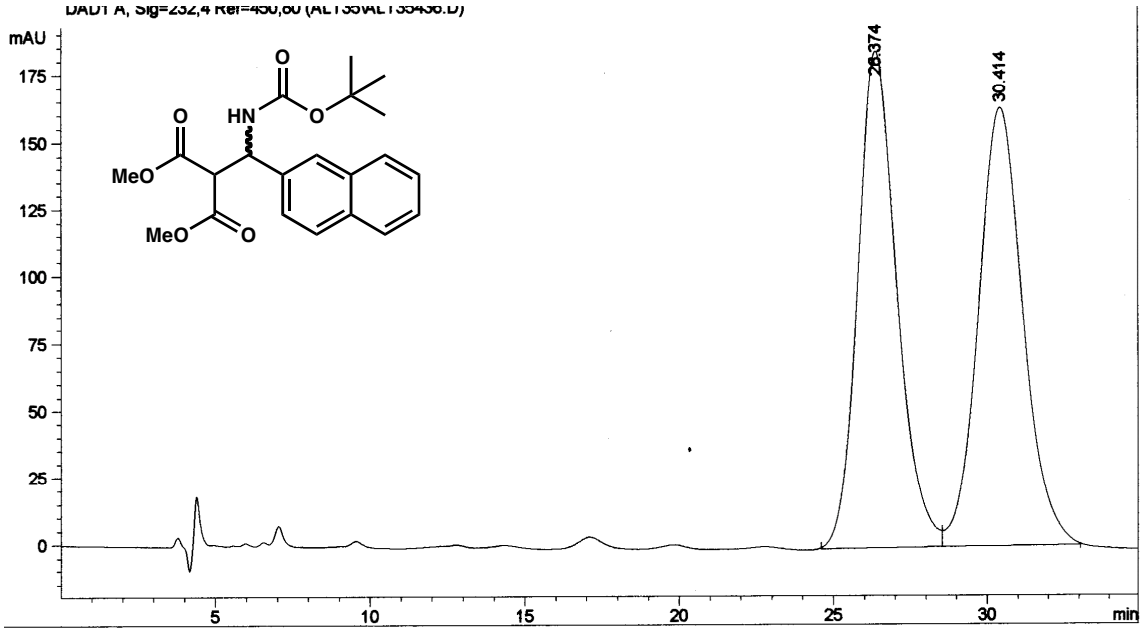

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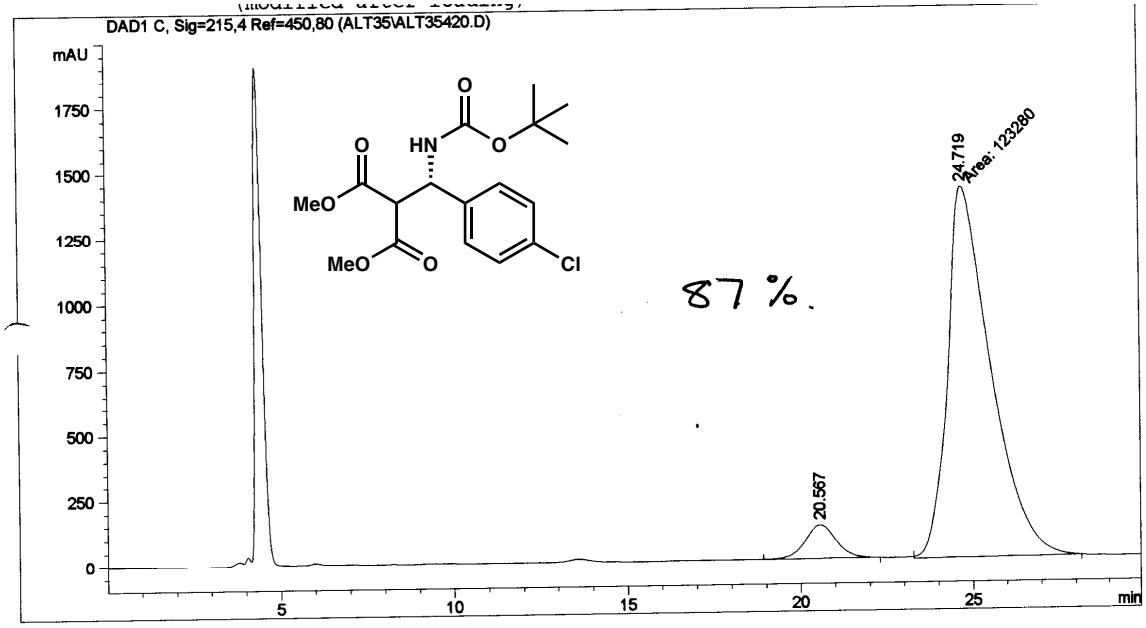
1	26.374	BV	1.0620	1.62730e4	184.90158	49.6567
2	30.414	VB	1.1949	1.64980e4	163.27118	50.3433

Table 3 – Entry 3



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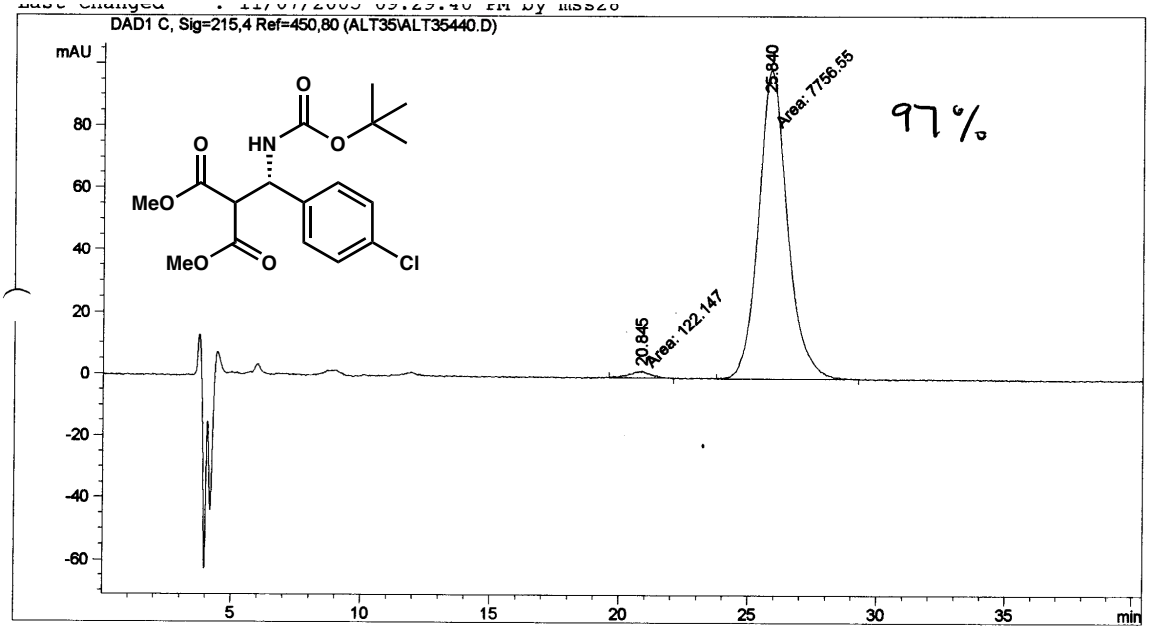

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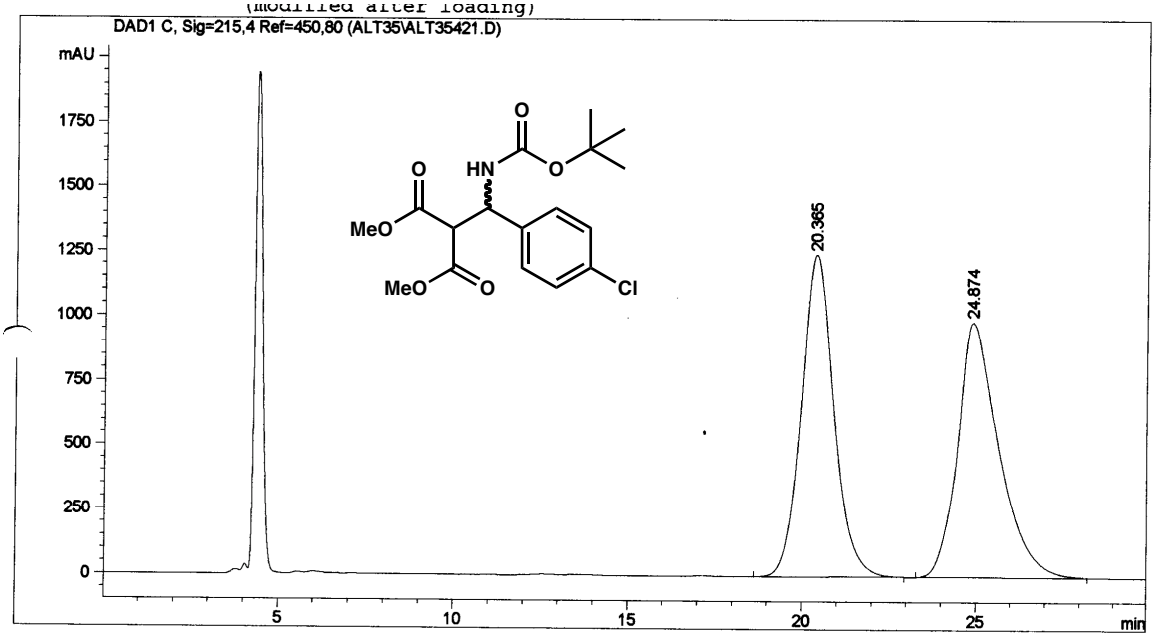
2	25.840	MM	1.2989	7756.54883	99.52971	98.4497



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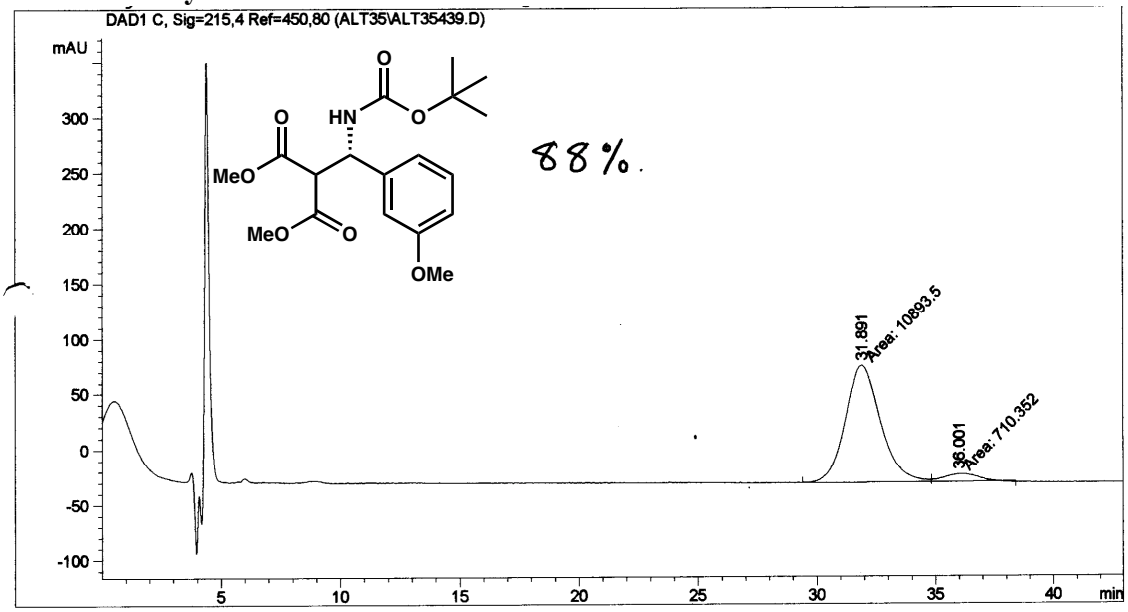
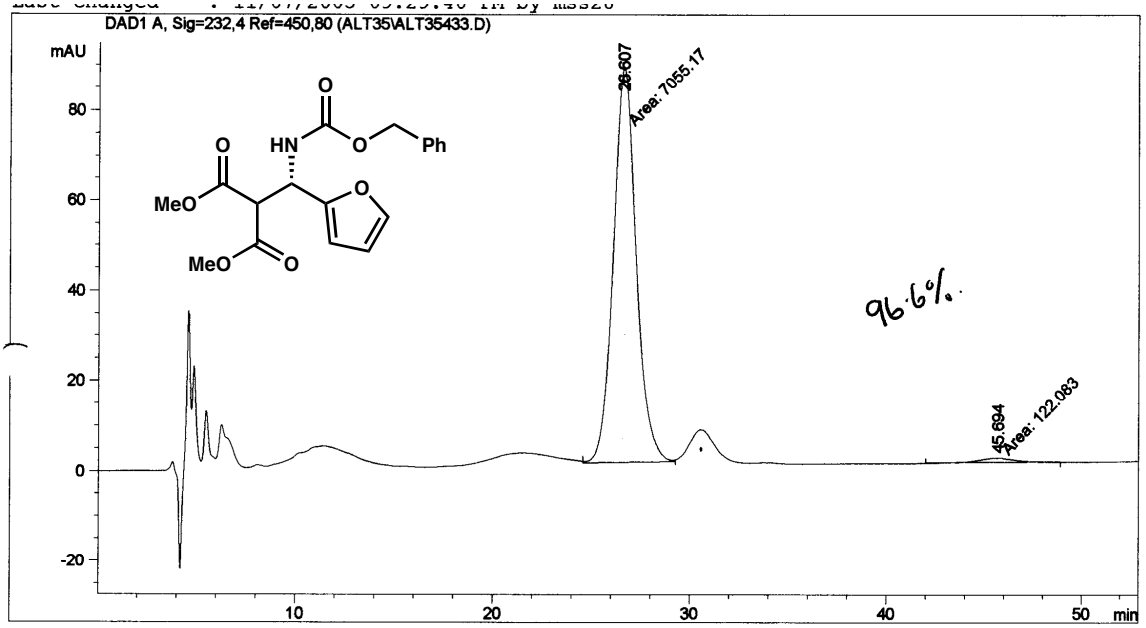
1	20.365	BB	0.7773	8.06904e4	1241.78210	49.7959
2	24.874	BB	0.9866	8.13519e4	984.35327	50.2041

Table 3 – Entry 4

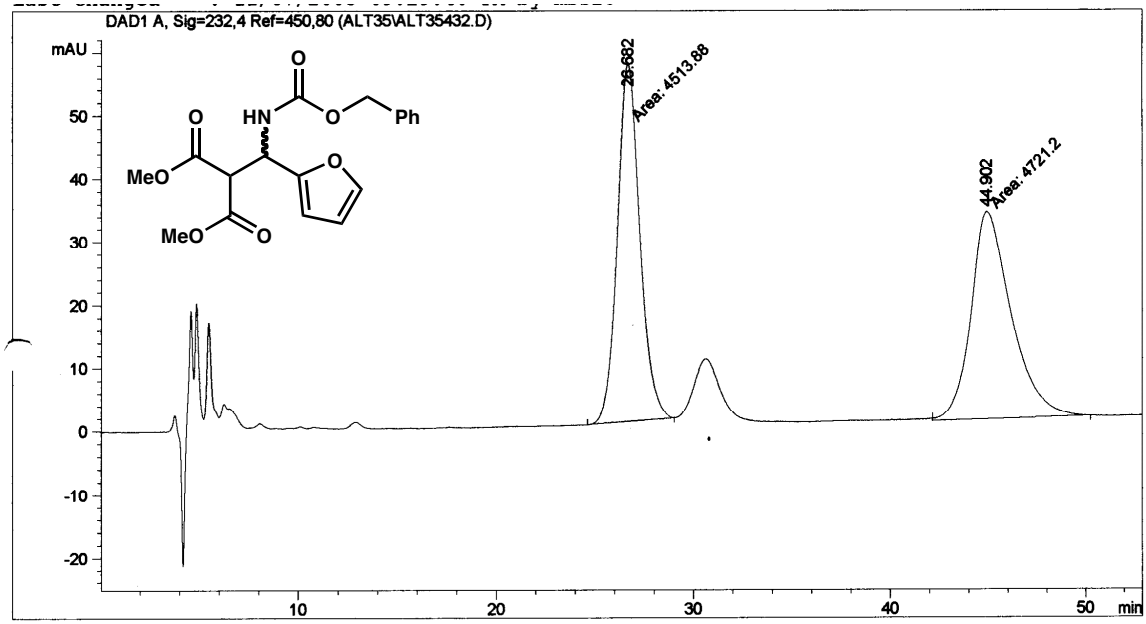


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.891	MF	1.7129	1.08935e4	105.99590	93.8783
2	36.001	FM	1.6685	710.35205	7.09587	6.1217

Table 3 – Entry 5

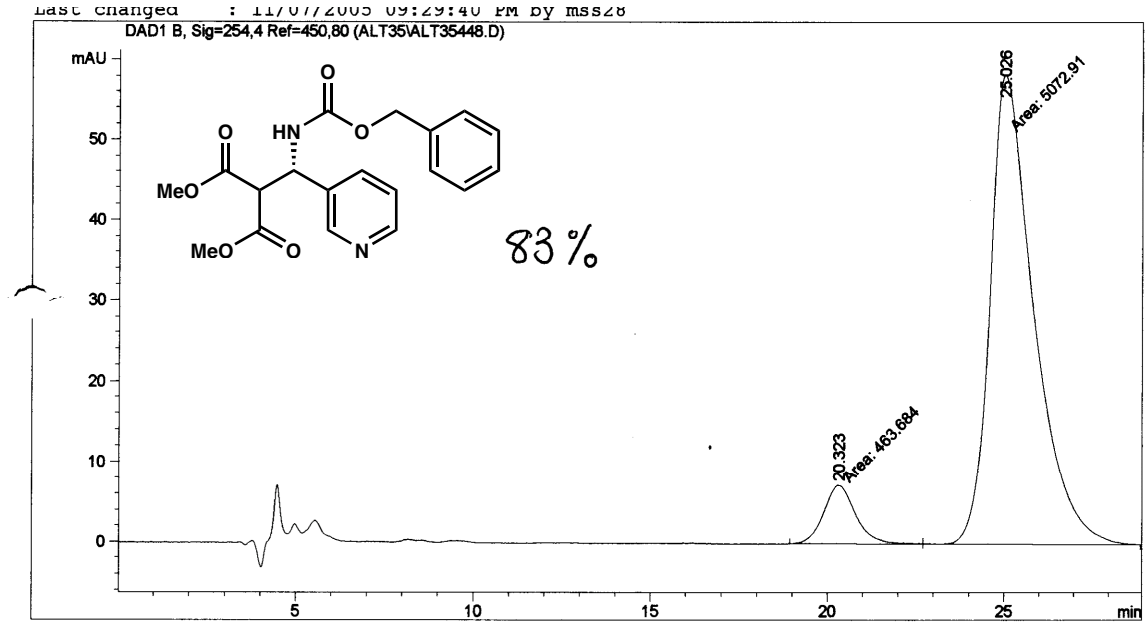


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.607	MM	1.3462	7055.16650	87.34762	98.2990
2	45.694	MM	2.0814	122.08276	9.77555e-1	1.7010

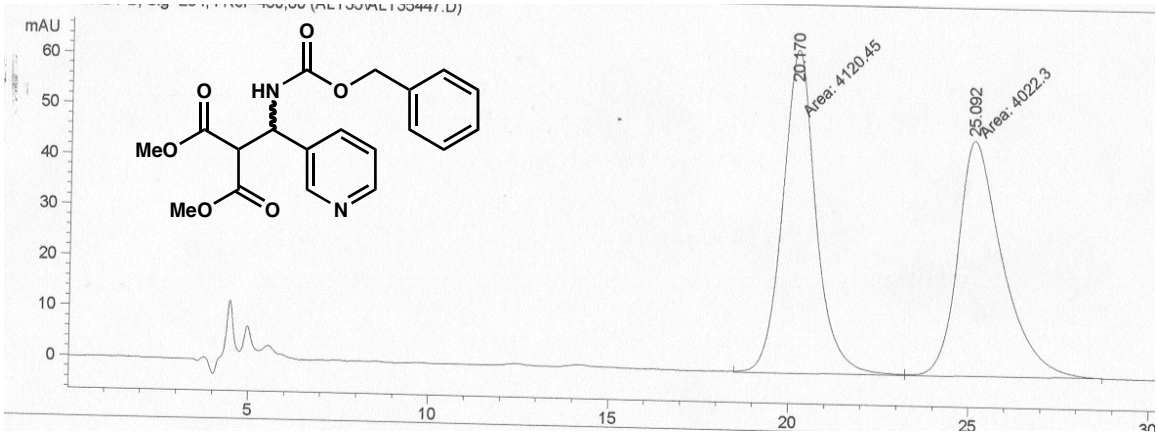


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.682	MM	1.3259	4513.87500	56.73988	48.8775
2	44.902	MM	2.3904	4721.19922	32.91759	51.1225

Table 3 – Entry 6

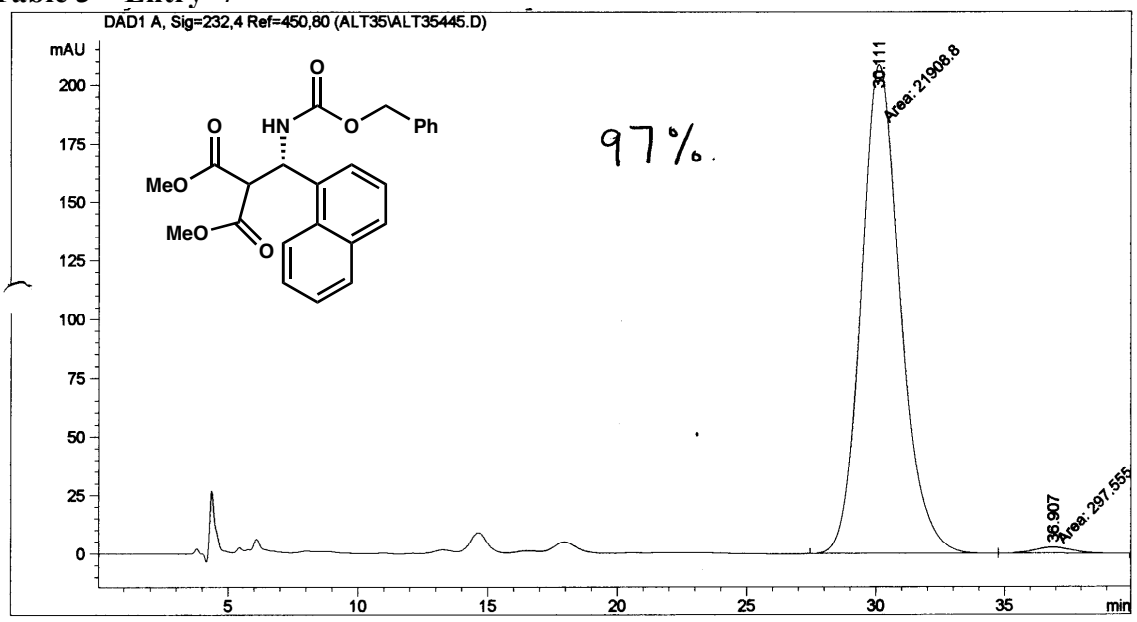


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.323	MF	1.0586	463.68384	7.30061	8.3749
2	25.026	FM	1.4469	5072.90820	58.43264	91.6251

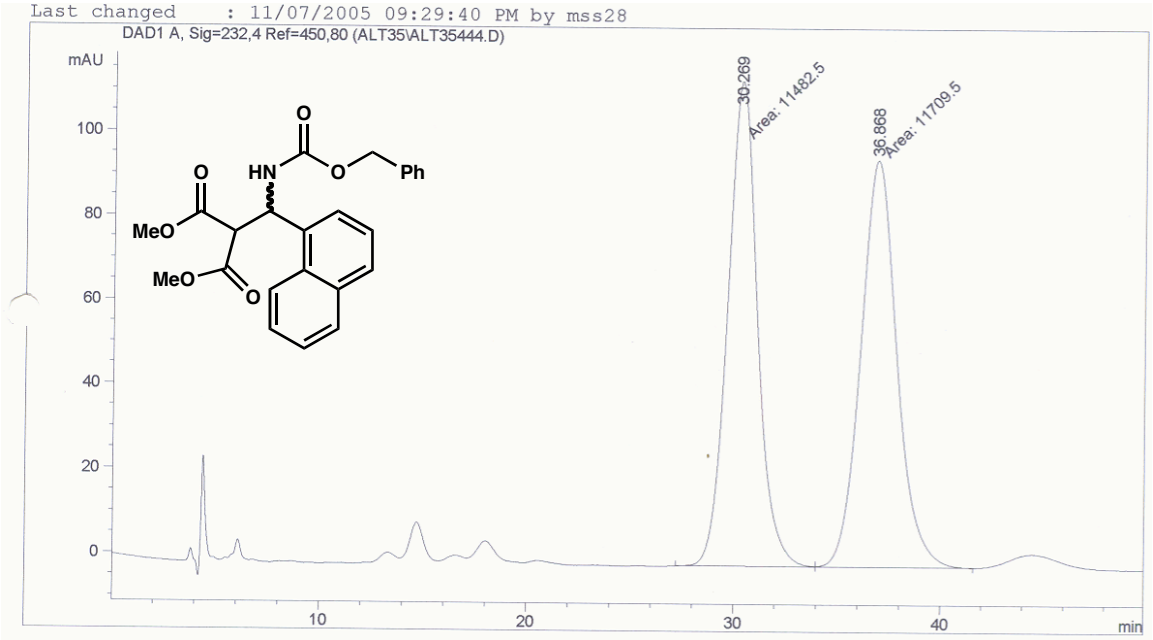


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.170	MF	1.0743	4120.44727	63.92307	50.6027
2	25.092	FM	1.4436	4022.30029	46.43672	49.3973

Table 3 – Entry 7

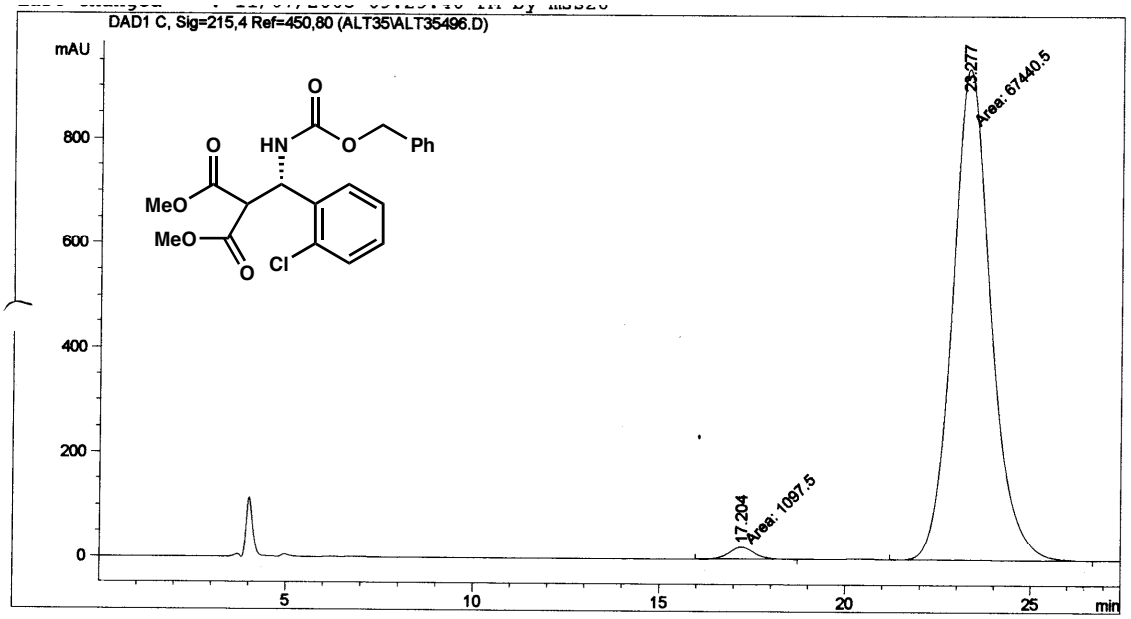


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.111	MF	1.7505	2.19088e4	208.59091	98.6600
2	36.907	FM	1.8058	297.55542	2.74623	1.3400

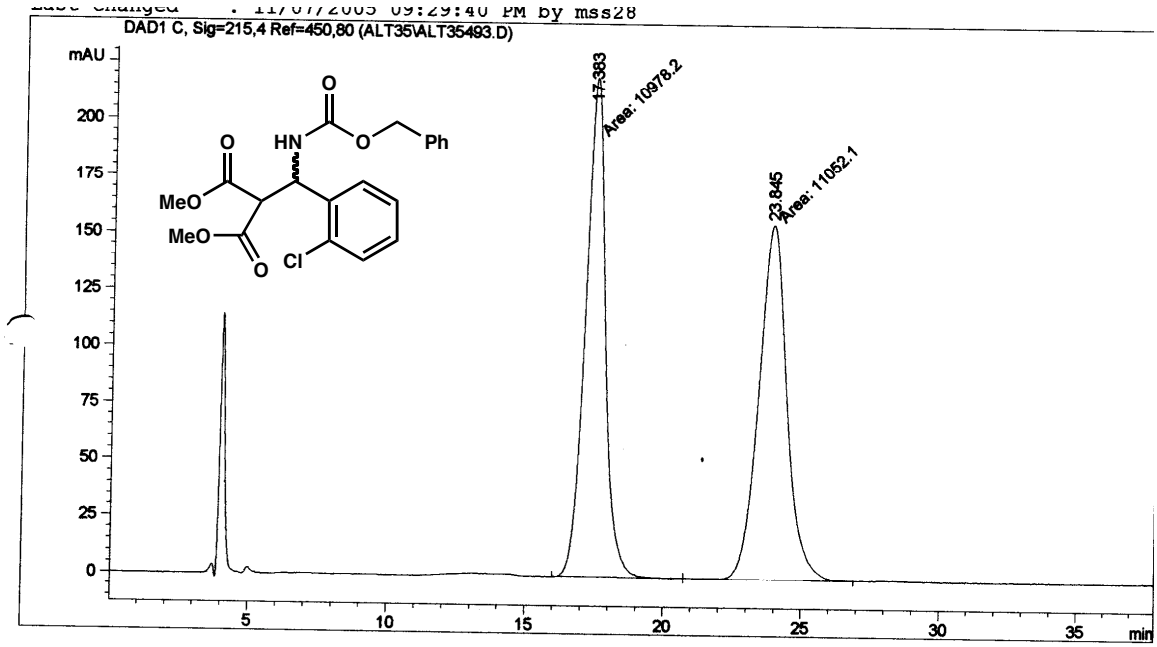


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.269	MF	1.6670	1.14825e4	114.80521	49.5108
2	36.868	FM	2.0261	1.17095e4	96.32027	50.4892

Table 3 – Entry 8

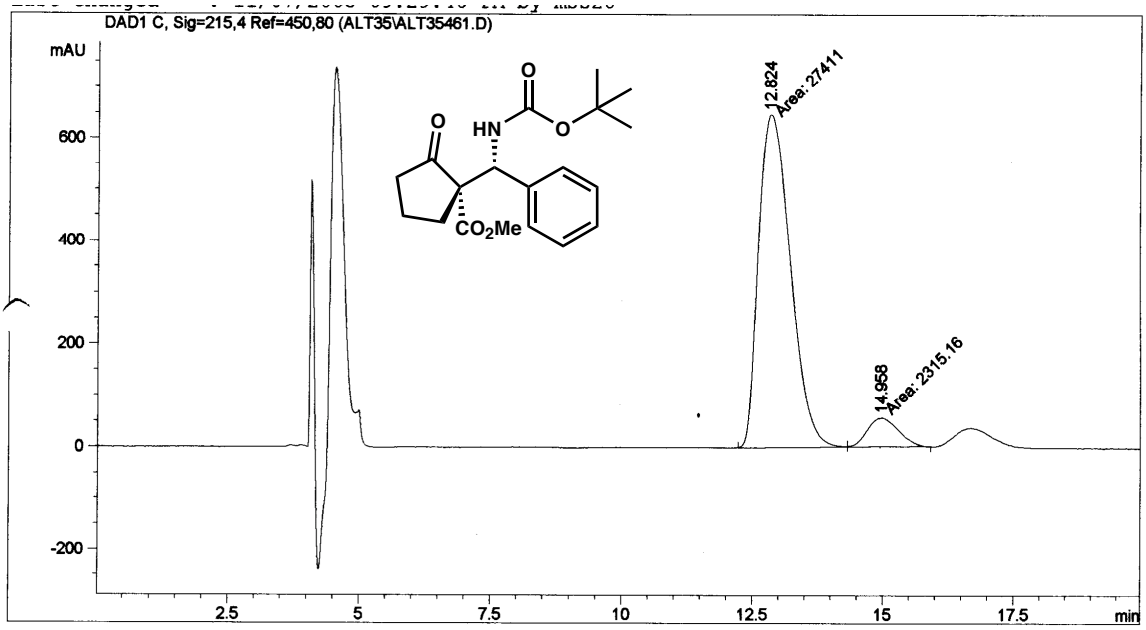


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.204	MM	0.7885	1097.49548	23.19672	1.6013
2	23.277	MM	1.1981	6.74405e4	938.18433	98.3987

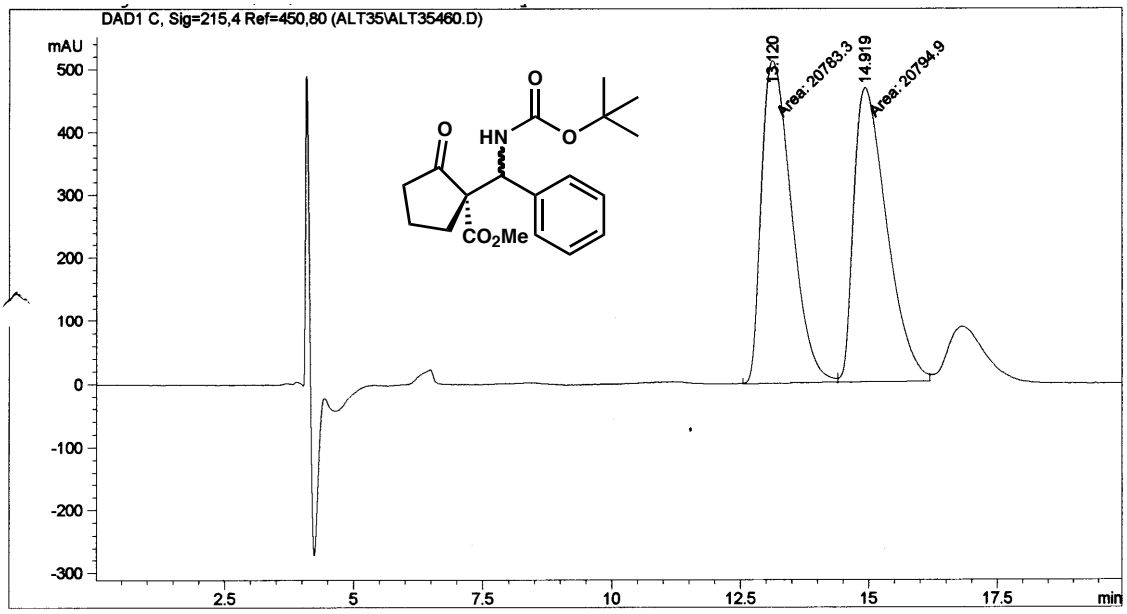


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.383	MF	0.8333	1.09782e4	219.57062	49.8324
2	23.845	FM	1.1800	1.10521e4	156.09680	50.1676

Table 4 – Entry 1

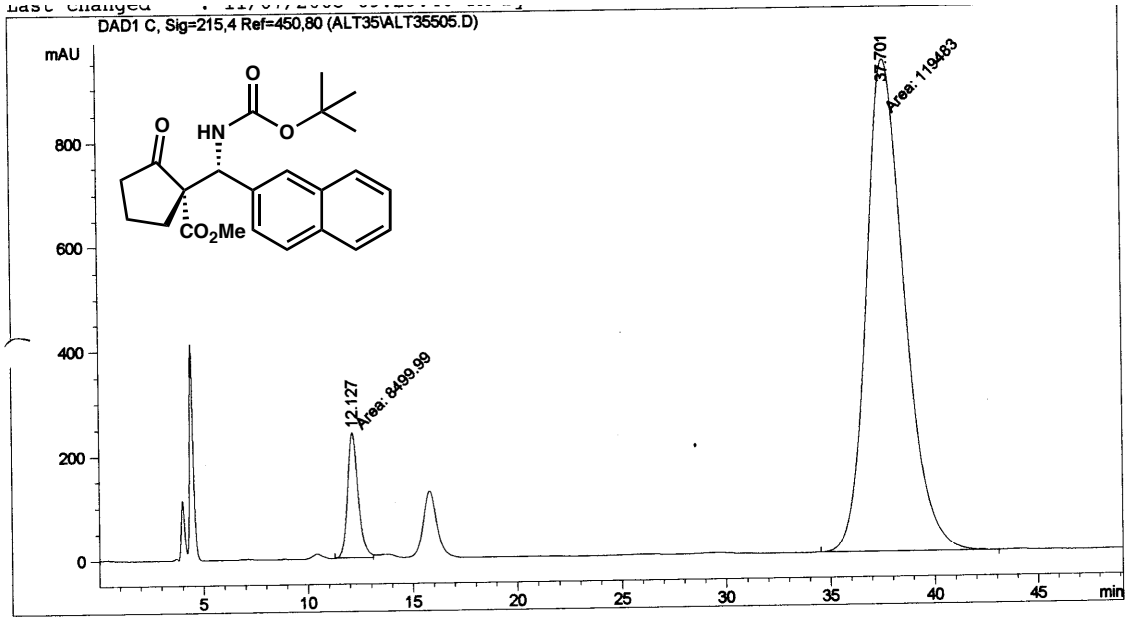


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.824	MF	0.7050	2.74110e4	647.99164	92.2117
2	14.958	FM	0.6889	2315.16138	56.01035	7.7883

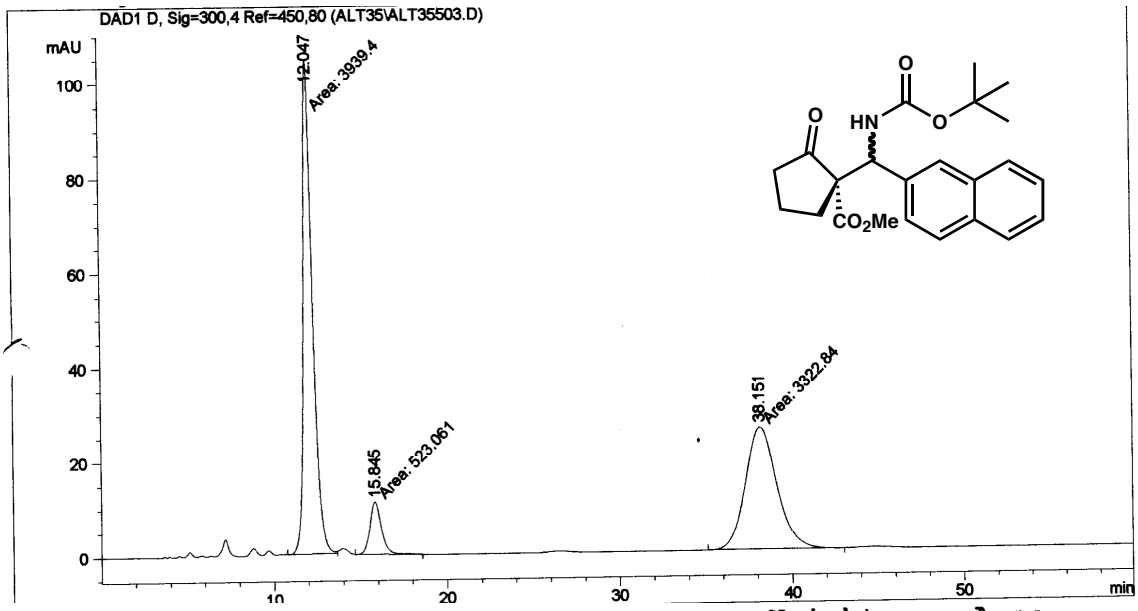


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.120	MF	0.6759	2.07833e4	512.45435	49.9860
2	14.919	FM	0.7427	2.07949e4	466.64969	50.0140

Table 4 – Entry 2

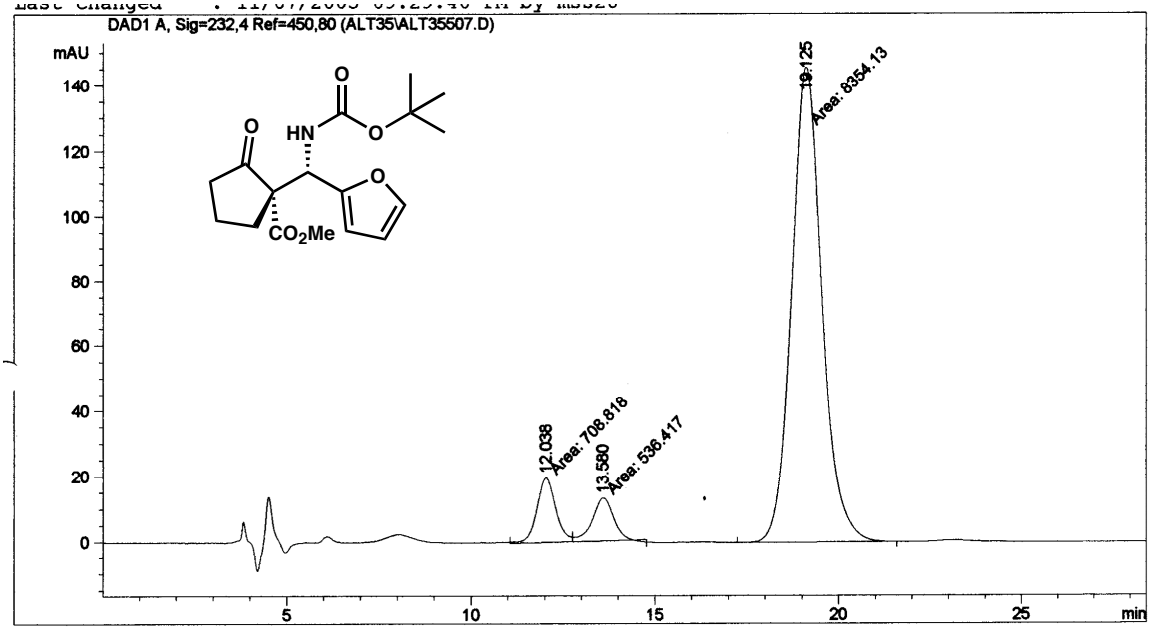


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.127	MM	0.5873	8499.98828	241.20081	6.6415
2	37.701	MM	2.1092	1.19483e5	944.13947	93.3585

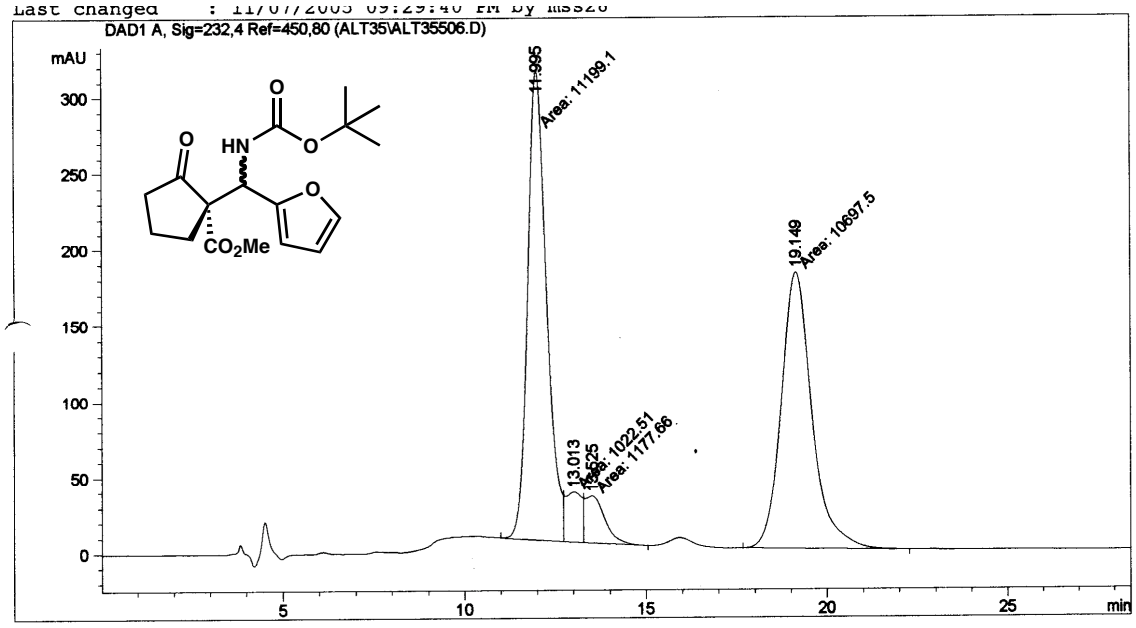


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.047	MM	0.6277	3939.39746	104.60127	50.6004
2	15.845	MM	0.7791	523.06097	11.19004	6.7186
3	38.151	MM	2.1347	3322.84448	25.94360	42.6810

Table 4 – Entry 3

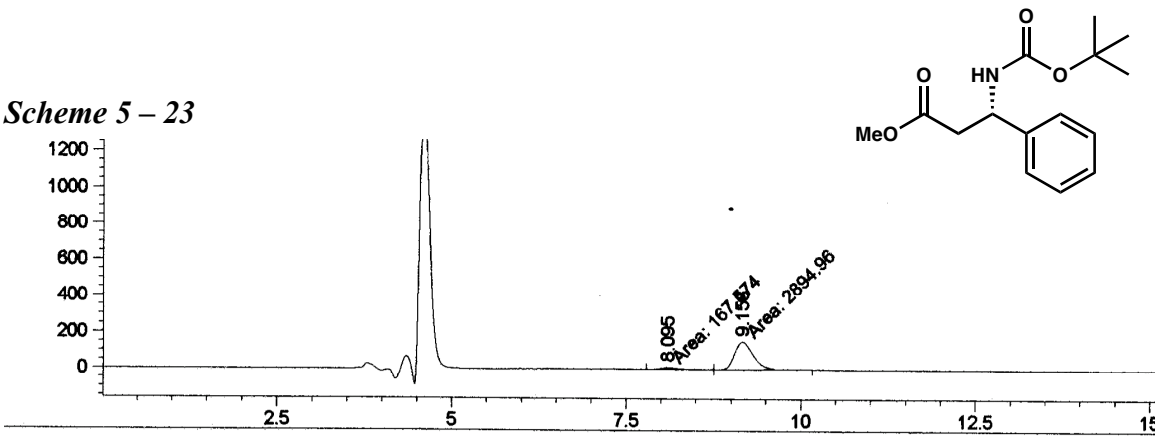


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.038	MF	0.5992	708.81769	19.71531	7.3840
2	13.580	FM	0.6792	536.41736	13.16355	5.5880
3	19.125	MM	0.9552	8354.13379	145.76079	87.0279

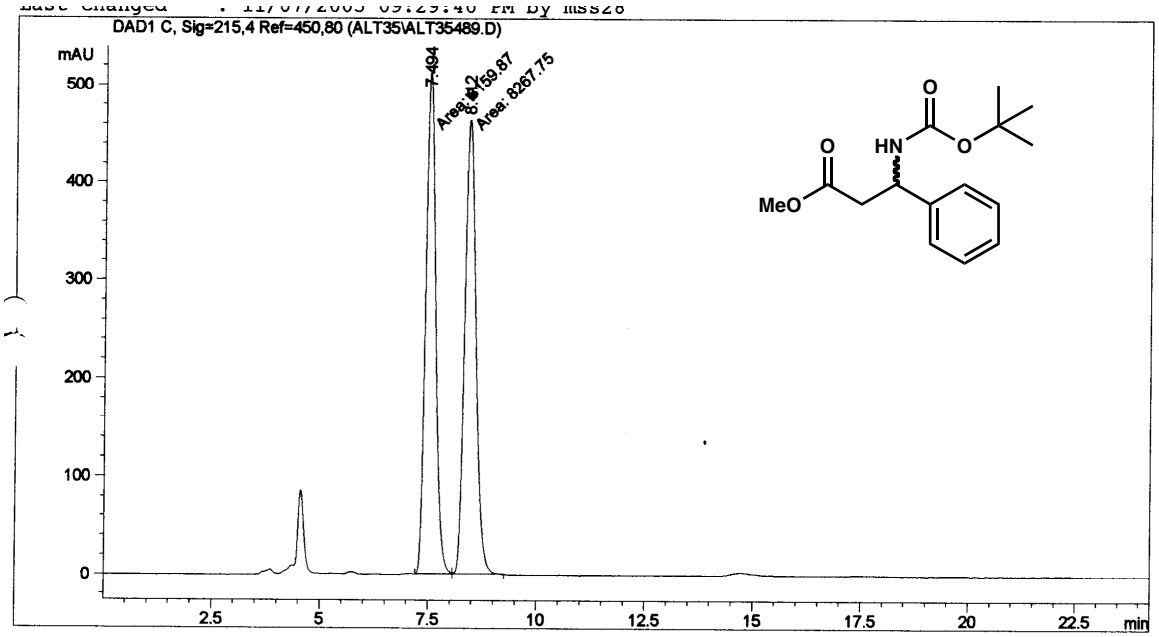


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.995	MF	0.6040	1.11991e4	309.01361	46.4756
2	13.013	FM	0.5182	1022.50702	32.88592	4.2433
3	13.525	FM	0.6362	1177.65735	30.84894	4.8872
4	19.149	MM	0.9821	1.06975e4	181.54449	44.3939

Scheme 5 – 23

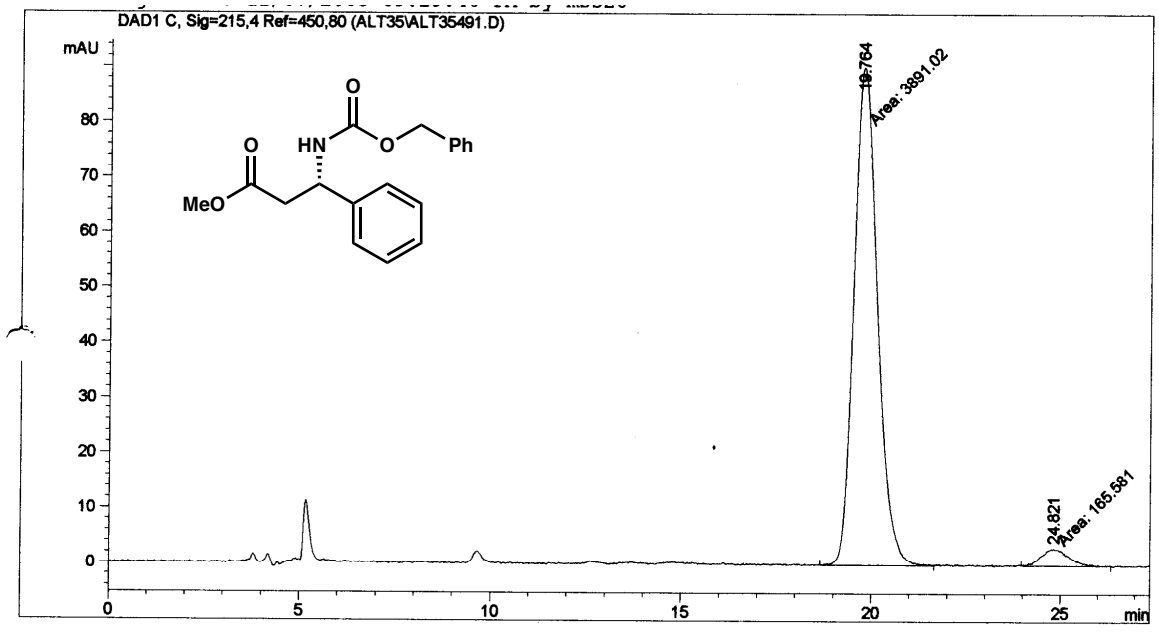


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.095	MF	0.2556	167.57359	10.92638	5.4717
2	9.158	FM	0.3151	2894.95728	153.13329	94.5283

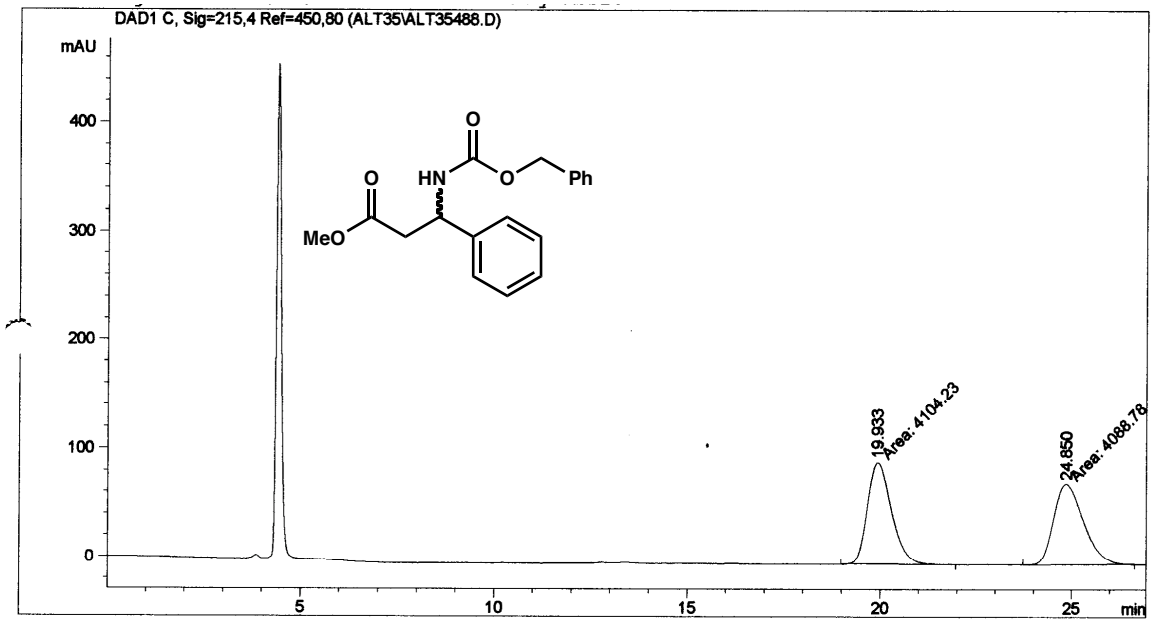


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.494	MF	0.2650	8159.86865	513.13782	49.6717
2	8.412	FM	0.2970	8267.74609	464.03146	50.3283

Scheme 5 - 24



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.764	MM	0.7184	3891.02466	90.27192	95.9182
2	24.821	MM	0.8679	165.58055	3.17968	4.0818



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.933	MM	0.7264	4104.22705	94.16273	50.0943
2	24.850	MM	0.9170	4088.77686	74.31191	49.9057