Catalytic Asymmetric Synthesis of Highly Substituted Pyrrolizidines

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Supporting Information 1 (Experimental Procedures):

Table of Contents

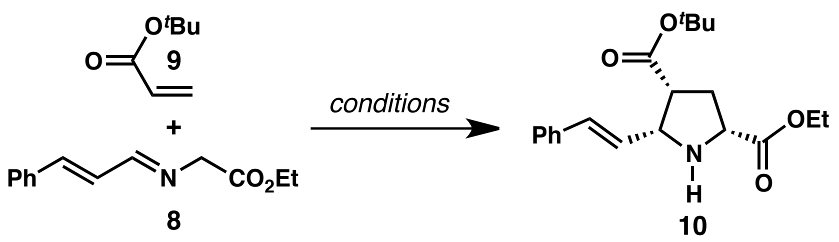
1. Materials and Methods. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Triethylamine (Et_3N) was distilled over calcium hydride prior to use. Unless otherwise stated, chemicals and reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or $KMnO_4$ staining. Flash column chromatography was performed either as described by Still et al.[1] using silica gel (partical size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, $\delta = 7.26$), MeCN-d_2 (^1H, $\delta = 1.94$), or acetone-d_5 (^1H, $\delta = 2.05$), and $CDCl_3$ (^{13}C, $\delta = 77.0$), CD_3CN (^{13}C, $\delta = 118.26$), DMSO-d_6 (^{13}C, $\delta = 39.52$). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. Analytical SFC was performed with a Mettler SFC supercritical CO2 analytical chromatography system with Chiralcel AD-H, OD-H, AS-H, OB-H, and OJ-H columns (4.6 mm x 25 cm) with visualization at 254 nm. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak AD column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with visualization at 254 nm. Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected.

2. General procedure for the synthesis of α-iminoesters. The α-iminoesters were prepared according to the procedure reported by Longmire et al. (Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400–13401). To a suspension of the glycine methyl ester hydrochloride (1.1 equiv) and magnesium sulfate (2.0 equiv) in methylene chloride was added triethylamine (1.1 equiv). This solution was stirred at room temperature for 1 h before the aldehyde (1.0 equiv) was added. After stirred at room temperature overnight, magnesium sulfate was filtered off and washed with methylene chloride. The filtrate was washed with distilled water 5 times and then brine, dried over magnesium sulfate, filtered and concentrated to afford the α-iminoesters. The crude iminoesters could be used directly for the cycloaddition reactions. The reactions reported above were performed on the scale of 1.0–4.0 g of aldehydes at 0.5 M concentration. **NOTE:** Formation of α-iminoester **8** was allowed to proceed for 1.5 h rather than overnight in order to avoid decomposition.

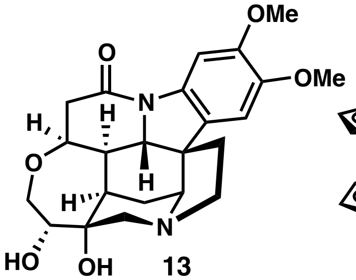
3. General procedure for the double (3+2) cycloaddition reactions. Silver(I) acetate (1.0 equiv) and (*S*)-QUINAP (1.0 equiv) were added to a vial. Tetrahydrofuran was then introduced, and this solution was stirred at room temperature for 1 h to make a stock solution of 0.009 M silver(I)/(*S*)-QUINAP catalyst. Silver(I) acetate/(*S*)-QUINAP catalyst solution (0.03 equiv) followed by the dipolarophile (*t*-Bu Acrylate; 1.5 equiv) and Hünig's base (0.1 equiv) were added to the α-iminoester (1.0 equiv) at -45 ^{o}C in the glovebox. The final concentration of the α-iminoester was 0.3 M. After stirring for 24 hours, the reaction was allowed to warm to room temperature and taken out of the glovebox. Dipolarophile (5 equiv) and then cinnamaldehyde (1 equiv) were added. After stirring for 24 hours, the reaction was quenched with a tetrahydrofuran solution of acetic acid (1.1 equiv) and concentrated directly. The reactions were performed on a scale of 20–80 mg of the iminoester.

4. Optimization of reaction parameters.

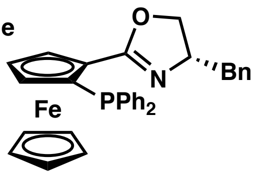
Table S1. Optimization of the catalytic asymmetric (1,3)-dipolar cycloaddition reaction between glycinate imine 9 and *t*-butylacrylate (8).



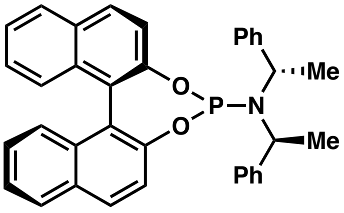
entry	catalyst/ligand/additive	solvent	temp (°C)	yield[e] (%)	ee[f] (%)
1[a]	CuI, **13**, DBU	$CHCl_3$	0 °C	50	96
2[b]	AgOAc, **14**	Et_2O	0 °C	53	–63
3[c]	$AgClO_4$, **15**, DABCO	PhMe	0 °C	59	46
4[d]	AgOAc, **16**, DIPEA	THF	–45 °C	62	**90**
5[d]	AgOAc, **16**, DIPEA	DCM	–45 °C	36	78
6[d]	AgOAc, **16**, DIPEA	$CHCl_3$	–45 °C	5	--
7[d]	AgOAc, **16**, DIPEA	PhMe	–45 °C	60	90
8[d]	AgOAc, **16**, DIPEA	Et_2O	–45 °C	53	90
9[d]	AgOAc, **16**	THF	–45 °C	56	91



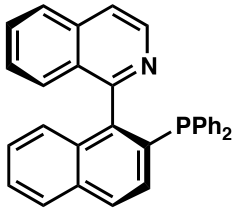
13



14



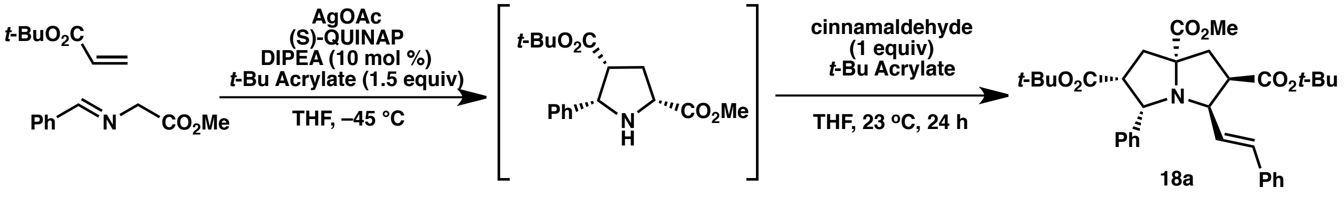
15



16

[a] 10 mol % each CuI, **13**, and DBU, 1.5 equiv *t*-butyl acrylate. [b] 3 mol % AgOAc, 3.3 mol % **14**, 2.0 equiv *t*-butyl acrylate. [c] 5 mol % each $AgClO_4$, **15**, and DABCO, 1.5 equiv *t*-butyl acrylate. [d] 3 mol % each AgOAc and **16**, 10 mol % DIPEA, 1.5 equiv *t*-butyl acrylate. [e] Isolated yield. [f] Determined by HPLC analysis of the corresponding methyl carbamate derivative (**S1**) using chiral stationary phase. Characterization data for pyrrolidine **10** and methyl carbamate **S1** have been reported previously.[2]

Table S2. Optimization of the catalytic, asymmetric double (1,3)-dipolar cycloaddition reaction.



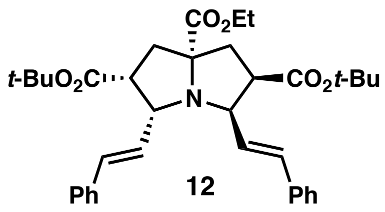
entry	catalyst loading (mol %)	additive	time for first (1,3)-dipolar cycloaddition (h)	equiv *t*-Bu-Acrylate in second (1,3)-dipolar cycloaddition	yield[a] (%)	ee[b] (%)
1	3 mol %	none	24	1.5	74	91
2	3 mol %	none	24	5	90	91
3	1 mol %	none	24	5	64	86
4	1 mol %	mol sieves	24	5	82	88
5	1 mol %	none	48	5	88	90

[a] Isolated yield. [b] Determined by SFC analysis using chiral stationary phase

5. Scale-up procedure for the double (3+2) cycloaddition reactions. 18.8 mg silver (I) acetate (0.113 mmol) and 49.4 mg (*R*)-QUINAP (0.112 mmol) were added to a vial. Tetrahydrofuran (12.5 mL) was then introduced, and this solution was stirred at room temperature for 1 h to make a stock solution of 0.009 M silver(I)/(*R*)-QUINAP catalyst. Silver(I) acetate/(*R*)-QUINAP catalyst solution (10 mL, 0.09 mmol) followed by the 0.66 ml tert-butyl acrylate (4.5 mmol) and 52 µl Hünig's base (0.30 mmol) were added to 532 mg of α-iminoester **17a** (3.00 mmol) at -45 ^{o}C. The final concentration of the α-iminoester was 0.3 M. After stirring for 24 hours, the reaction was allowed to warm to room temperature. 2.2 ml *t*-Bu Acrylate (15 mmol) and then 380 µl cinnamaldehyde (3.0 mmol) were added. After stirring for 24 hours, the reaction was quenched with 2 mL of a tetrahydrofuran solution of acetic acid (10:1 v/v) and concentrated directly. The crude reaction mixture was purified by silica gel column chromatography (5→20% ethyl acetate in hexanes) to obtain 1.46 g pyrrolizidine **18a** in 89% yield and 87% ee.

6. Characterization data.

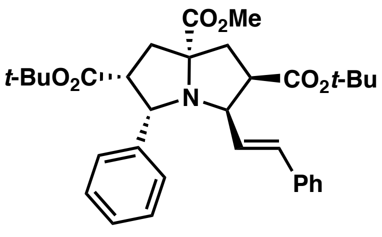
(2*R*,3*R*,5*R*,6*R*)-2,6-di-*tert*-butyl 7a-ethyl 3,5-di((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (12)



12

According to the general procedure pyrrolizidine **12** was obtained as a light yellow foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 73% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ-H, 2.5 mL/min, 4% IPA in CO$_2$, λ = 254 nm): t_R (major) = 5.2 min, t_R (minor) = 6.6 min. $[\alpha]_D^{25}$ = –109.5 (c = 1.01, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.40 – 7.36 (m, 2H), 7.35 – 7.23 (m, 7H), 7.19 – 7.15 (m, 1H), 6.63 (d, *J* = 15.5 Hz, 1H), 6.53 (d, *J* = 15.5 Hz, 1H), 6.20 (dd, *J* = 15.6, 7.7 Hz, 1H), 6.06 (dd, *J* = 15.5, 10.6 Hz, 1H), 4.30 (dd, *J* = 10.6, 7.6 Hz, 1H), 4.27 – 4.16 (m, 3H), 3.45 (ddd, *J* = 13.3, 7.6, 6.0 Hz, 1H), 3.08 (dt, *J* = 10.3, 7.7 Hz, 1H), 2.78 (dd, *J* = 13.5, 10.3 Hz, 1H), 2.49 (dd, *J* = 13.1, 6.0 Hz, 1H), 2.17 (dd, *J* = 13.5, 7.8 Hz, 1H), 2.11 (t, *J* = 13.0 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.30 (s, 9H), 1.28 (s, 9H); ^{13}C NMR (CDCl$_3$, 126 MHz) δ 176.2, 170.5, 170.1, 137.1, 136.4, 136.2, 131.2, 128.6, 128.3, 128.2, 127.9, 127.1, 126.7, 126.4, 125.2, 80.8, 80.8, 75.5, 67.1, 64.4, 61.2, 50.8, 49.6, 37.4, 36.6, 28.1, 28.0, 14.3; FTIR (NaCl, thin film) 2978, 2932, 1727, 1495, 1477, 1449, 1392, 1367, 1257, 1152, 1029, 968, 848, 754 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 588.3320, found 588.3284.

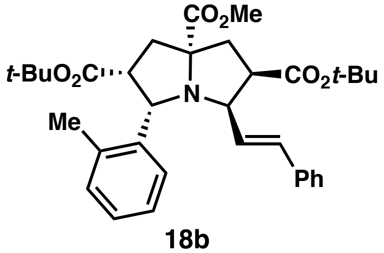
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18a)



18a

According to the general procedure pyrrolizidine **18a** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 90% yield and 91% ee. The enantiomeric excess was determined by chiral SFC analysis (OD, 2.5 mL/min, 10% IPA in CO2, λ = 254 nm): t_R (major) = 6.1 min, t_R (minor) = 7.2 min. $[\alpha]_D^{25}$ = –103.3 (c = 0.74, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.39 (d, *J* = 7.3 Hz, 2H), 7.30 – 7.24 (m, 6H), 7.21-7.10 (m, 2H), 6.30 (d, *J* = 15.6 Hz, 1H), 6.02 (dd, *J* = 15.6, 10.3 Hz, 1H), 4.78 (d, *J* = 8.3 Hz, 1H), 4.19 (dd, *J* = 10.3, 7.7 Hz, 1H), 3.79 (s, 3H), 3.61 (ddd, *J* = 12.1, 7.5, 6.5 Hz, 1H), 3.39 (td, *J* = 7.9, 3.8 Hz, 1H), 2.99 (dd, *J* = 13.2, 3.8 Hz, 1H), 2.37 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.29 (dd, *J* = 19.1, 6.4 Hz, 1H), 2.12 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.26 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (CDCl$_3$, 126 MHz) δ 177.1, 171.0, 170.9, 141.1, 136.4, 135.3, 128.5, 127.9, 127.8, 127.7, 126.7, 126.5, 126.3, 80.7, 80.2, 76.8, 65.2, 65.0, 52.9, 52.2, 51.3, 39.1, 39.0, 28.0, 27.4; FTIR (NaCl, thin film) 2977, 1726, 1493, 1453, 1391, 1367, 1293, 1255, 1204, 1151, 1094, 968, 845, 746 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 548.3007, found 548.3040.

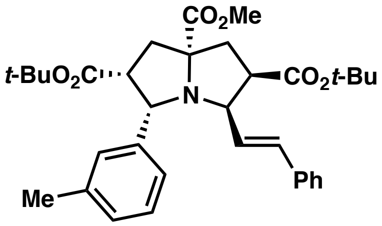
(2*R*,3*R*,5*S*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-((*E*)-styryl)-5-(*o*-tolyl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18b)



18b

According to the general procedure pyrrolizidine **18b** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 91% yield and 89% ee. The enantiomeric excess was determined by chiral SFC analysis (OD, 2.5 mL/min, 7% IPA in CO2, λ = 254 nm): t_R (major) = 10.0 min, t_R (minor) = 11.5 min. $[\alpha]_D^{25}$ = –84.443 (c = 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (d, *J* = 7.7 Hz, 1H), 7.32 – 7.15 (m, 6H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.22 (d, *J* = 15.6 Hz, 1H), 5.99 (dd, *J* = 15.6, 10.4 Hz, 1H), 4.93 (d, *J* = 8.2 Hz, 1H), 4.10 (dd, *J* = 10.2, 7.6 Hz, 1H), 3.82 (s, 3H), 3.65 (ddd, *J* = 13.5, 7.4, 0.8 Hz, 1H), 3.50 (t, *J* = 8.0 Hz, 1H), 3.05 (d, *J* = 13.1 Hz, 1H), 2.40 (dd, *J* = 13.5, 6.0 Hz, 1H), 2.35 (t, *J* = 12.8 Hz, 1H), 2.09 (dd, *J* = 13.1, 7.7 Hz, 1H), 1.28 (s, 9H), 0.90 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.37, 171.20, 170.72, 138.66, 136.50, 135.55, 135.03, 129.21, 128.41, 127.58, 126.78, 126.48, 126.35, 125.89, 80.61, 79.95, 77.25, 77.00, 76.75, 76.22, 64.01, 61.95, 52.14, 51.32, 50.98, 39.80, 39.23, 27.99, 27.47, 27.21, 19.14; FTIR (NaCl, thin film) 2976, 1727, 1479, 1458, 1392, 1367, 1294, 1256, 1199, 1151, 1097, 1034, 967, 844, 749 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 562.3163, found 574.3159.

(2*R*,3*R*,5*S*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-((*E*)-styryl)-5-(*m*-tolyl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18c)

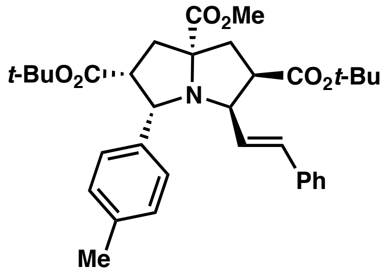


18c

According to the general procedure using 6 mol% AgOAc/QUINAP, pyrrolizidine **18c** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 76% yield and 88% ee. The enantiomeric excess was determined by chiral SFC analysis (OD, 2.5

mL/min, 7% IPA in CO2, λ = 254 nm): t_R (major) = 9.8 min, t_R (minor) = 11.4 min. $[\alpha]_D^{25}$ = -236.413 (c = 0.93, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34 – 7.09 (m, 7H), 6.98 (d, *J* = 7.4 Hz, 2H), 6.35 (d, *J* = 15.6 Hz, 1H), 6.05 (dd, *J* = 15.6, 10.3 Hz, 1H), 4.76 (d, *J* = 8.3 Hz, 1H), 4.22 (dd, *J* = 10.3, 7.7 Hz, 1H), 3.81 (s, 3H), 3.61 (ddd, *J* = 12.2, 7.5, 6.5 Hz, 1H), 3.38 (td, *J* = 7.9, 4.3 Hz, 1H), 3.00 (dd, *J* = 13.3, 4.3 Hz, 1H), 2.39 (dd, *J* = 13.1, 6.4 Hz, 1H), 2.30 (s, 3H), 2.14 (dd, *J* = 13.3, 7.8 Hz, 1H), 1.29 (s, 9H), 0.99 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.1, 171.0, 170.9, 141.0, 137.0, 136.5, 135.3, 128.6, 128.5, 127.8, 127.7, 127.4, 126.5, 126.3, 125.0, 80.7, 80.1, 76.6, 65.2, 65.2, 52.8, 52.2, 51.1, 39.0, 38.9, 28.0, 27.4, 21.5; FTIR (NaCl, thin film) 2978, 2930, 1732, 1606, 1456, 1367, 1256, 1152, 1099, 1038, 969, 846, 740 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 562.3163, found 562.3163.

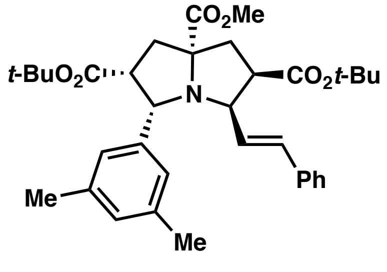
(2*R*,3*R*,5*S*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-((*E*)-styryl)-5-(*p*-tolyl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18d)



18d

According to the general procedure using 6 mol% AgOAc/QUINAP, pyrrolizidine **18d** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 92% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 7% IPA in CO2, λ = 254 nm): t_R (minor) = 10.2 min, t_R (major) = 11.3 min. $[\alpha]_D^{25}$ = -178.7 (c = 0.85, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34 – 7.19 (m, 7H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.35 (d, *J* = 15.6 Hz, 1H), 6.04 (dd, *J* = 15.6, 10.3 Hz, 1H), 4.21 (dd, *J* = 10.2, 7.7 Hz, 1H), 3.81 (d, *J* = 0.7 Hz, 1H), 3.62 (dt, *J* = 13.2, 6.9 Hz, 1H), 3.38 (td, *J* = 8.1, 4.0 Hz, 1H), 3.00 (dd, *J* = 13.3, 4.0 Hz, 1H), 2.38 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.30 (s, 1H), 2.13 (dd, *J* = 13.3, 7.6 Hz, 1H), 1.28 (s, 1H), 1.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.1, 171.0, 170.9, 138.0, 136.5, 136.1, 135.2, 128.4, 128.4, 127.8, 127.7, 126.5, 126.4, 80.7, 80.1, 76.6, 65.1, 64.9, 52.9, 52.2, 51.2, 39.0, 28.0, 27.4, 21.0; FTIR (NaCl, thin film) 2977, 1727, 1512, 1495, 1477, 1457, 1367, 1151, 968, 848, 748 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 562.3163, found 562.3170.

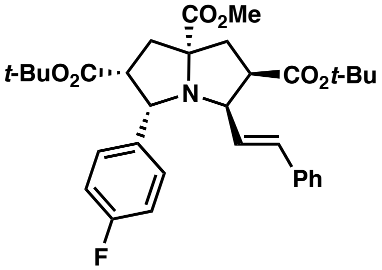
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(3,5-dimethylphenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18e)



18e

According to the general procedure using 6 mol% AgOAc/QUINAP, pyrrolizidine **18e** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 78% yield and 88% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 5% IPA in CO2, λ = 254 nm): t_R (minor) = 9.0 min, t_R (major) = 10.5 min. $[\alpha]_D^{25}$ = -120.032 (c = 0.86, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.33 – 7.22 (m, 6H), 6.97 (s, 1H), 6.80 (s, 1H), 6.38 (d, *J* = 15.6 Hz, 1H), 6.06 (dd, *J* = 15.6, 10.3 Hz, 1H), 4.72 (d, *J* = 8.3 Hz, 1H), 4.22 (dd, *J* = 10.3, 7.7 Hz, 1H), 3.82 (s, 1H), 3.61 (ddd, *J* = 12.3, 7.5, 6.5 Hz, 1H), 3.35 (td, *J* = 7.9, 4.8 Hz, 1H), 2.99 (dd, *J* = 13.3, 4.8 Hz, 1H), 2.39 (dd, *J* = 13.1, 6.4 Hz, 1H), 2.33 – 2.26 (m, 1H), 2.26 (s, 1H), 2.13 (dd, *J* = 13.3, 7.8 Hz, 1H), 1.29 (s, 9H), 1.00 (s, 9H).; ^{13}C NMR (CDCl$_3$, 126 MHz) δ 177.09, 170.91, 170.86, 140.95, 136.89, 136.49, 135.28, 128.44, 128.29, 127.65, 126.53, 126.30, 125.68, 80.68, 80.02, 76.62, 65.34, 65.28, 52.66, 52.16, 51.04, 38.98, 38.69, 28.03, 27.38, 21.35; FTIR (NaCl, thin film) 2977, 1728, 1603, 1456, 1391, 1366, 1152, 968, 847, 747 cm^{-1}; HRMS (MM) calc'd for [M+H]$^+$ 576.3320, found 576.3318.

(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(4-fluorophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18f)

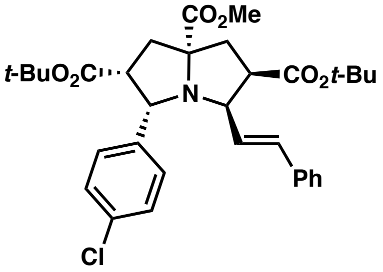


18f

According to the general procedure pyrrolizidine **18f** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 87% yield and 93% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 4% IPA in CO2, λ = 254 nm): t_R (minor) = 7.8 min, t_R (major) = 9.7 min. $[\alpha]_D^{25}$ = -40.596 (c = 0.79, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.41 – 7.36 (m, 2H), 7.30 – 7.26 (m, 2H), 7.24 – 7.20 (m, 3H), 6.93 (t, *J* = 8.8 Hz, 2H), 6.29 (d, *J* = 15.6 Hz, 1H), 6.00 (dd, *J* = 15.6, 10.4 Hz, 1H), 4.76 (d, *J* = 8.2 Hz, 1H), 4.15 (dd, *J* = 10.3, 7.7

Hz, 1H), 3.79 (s, 3H), 3.59 (ddd, *J* = 12.2, 7.5, 6.5 Hz, 1H), 3.36 (td, *J* = 7.8, 3.4 Hz, 1H), 2.36 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.32 – 2.25 (m, 1H), 2.11 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.27 (s, 9H), 0.99 (s, 9H); ^{13}C NMR (CDCl$_3$, 126 MHz) δ 177.0, 170.9, 170.8, 162.9, 160.9, 136.7, 136.7, 136.3, 135.3, 129.5, 129.4, 128.5, 127.8, 126.5, 126.1, 114.6, 114.4, 80.7, 80.3, 76.6, 64.7, 64.4, 53.0, 52.2, 51.3, 39.2, 39.0, 28.0, 27.5; FTIR (NaCl, thin film) 3435, 2978, 2931, 1726, 1603, 1507, 1457, 1392, 1367, 1153, 846, 754 cm^{-1}; HRMS (MM) calc'd for [M+H]$^+$ 566.2912, found 566.2909.

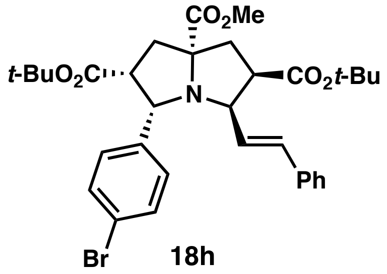
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(4-chlorophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18g)



18g

According to the general procedure pyrrolizidine **18g** was obtained as a yellow oil after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 91% yield and 95% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 2% IPA in CO2, λ = 254 nm): t_R (major) = 6.2 min, t_R (minor) = 8.1 min. $[\alpha]_D^{25}$ = -476.013 (c = 0.98, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.30 – 7.17 (m, 7H), 6.30 (d, *J* = 15.6 Hz, 1H), 6.01 (dd, *J* = 15.6, 10.4 Hz, 1H), 4.77 (d, *J* = 8.2 Hz, 1H), 4.16 (dd, *J* = 10.2, 7.7 Hz, 1H), 3.78 (s, 3H), 3.62 (dt, *J* = 12.3, 6.9 Hz, 1H), 3.38 (td, *J* = 7.9, 2.9 Hz, 1H), 2.99 (dd, *J* = 13.2, 2.7 Hz, 1H), 2.40 – 2.26 (m, 1H), 2.12 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.27 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (CDCl$_3$, 126 MHz) δ 176.8, 170.7, 170.5, 139.5, 136.1, 135.2, 132.2, 129.2, 128.4, 127.7, 127.7, 126.3, 126.0, 80.6, 80.2, 76.5, 64.5, 64.3, 52.9, 52.1, 51.2, 39.2, 38.9, 27.9, 27.3; FTIR (NaCl, thin film) 3431, 2977, 2932, 1727, 1489, 1456, 1292, 1151, 1088, 1014, 847, 750 cm^{-1}; HRMS (MM) calc'd for [M+H]$^+$ 582.2617, found 582.2611

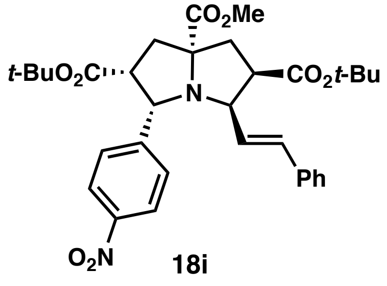
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(4-bromophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18h)



18h

According to the general procedure pyrrolizidine **18h** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 89% yield and 92% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 3% IPA in CO2, λ = 254 nm): t_R (major) = 6.1 min, t_R (minor) = 8.0 min. $[\alpha]_D^{25}$ = -59.159 (c = 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41 – 7.36 (m, 2H), 7.35 – 7.27 (m, 4H), 7.27 – 7.22 (m, 3H), 6.31 (d, *J* = 15.6 Hz, 1H), 6.00 (dd, *J* = 15.6, 10.4 Hz, 1H), 4.75 (d, *J* = 8.2 Hz, 1H), 4.16 (dd, *J* = 10.4, 7.6 Hz, 1H), 3.80 (s, 3H), 3.62 (ddd, *J* = 12.3, 7.4, 6.5 Hz, 1H), 3.38 (td, *J* = 7.8, 3.1 Hz, 1H), 2.99 (dd, *J* = 13.2, 3.1 Hz, 1H), 2.38 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.35 – 2.25 (m, 1H), 2.11 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.28 (s, 9H), 1.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) 177.0, 170.9, 170.7, 140.2, 136.2, 135.4, 130.8, 129.8, 128.5, 127.8, 126.5, 126.1, 120.4, 80.8, 80.4, 76.6, 64.7, 64.5, 53.0, 52.2, 51.3, 39.4, 39.0, 28.0, 27.4; FTIR (NaCl, thin film) 3447, 2978, 2932, 1728, 1586, 1456, 1393, 1368, 1257, 1151, 1011, 845, 739 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 626.2112, found 626.2096.

(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(4-nitrophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18i)

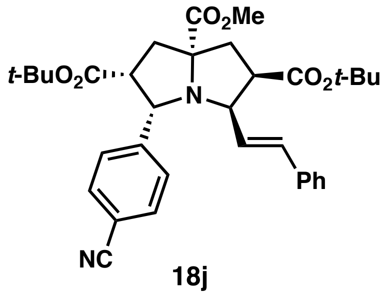


18i

According to the general procedure pyrrolizidine **18i** was obtained as a yellow foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 70% yield and 96% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 2% IPA in CO2, λ = 254 nm): t_R (major) = 3.8 min, t_R (minor) = 5.2 min. $[\alpha]_D^{25}$ = -101.586 (c = 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.31 – 7.19 (m, 5H), 6.27 (d, *J* = 15.6 Hz, 1H), 6.00 (dd, *J* = 15.6, 10.4 Hz, 1H), 4.88 (d, *J* = 8.2 Hz, 1H), 4.16 (dd, *J* = 10.4, 7.6 Hz, 1H), 3.81 (s, 3H), 3.65 (ddd, *J* = 12.2, 7.4, 6.8 Hz, 1H), 3.47 (td, *J* = 7.9, 2.6 Hz, 1H), 3.03 (dd, *J* = 13.2, 2.6 Hz, 1H), 2.38 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.37 – 2.29 (m, 1H), 2.16 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.28 (s, 9H), 0.98 (s, 9H); ^{13}C NMR

($CDCl_3$, 126 MHz) δ 176.7, 170.5, 170.5, 149.2, 146.9, 135.9, 135.7, 128.8, 128.5, 128.0, 126.4, 125.6, 123.0, 80.9, 80.7, 76.7, 64.6, 64.4, 53.1, 52.3, 51.3, 39.6, 39.0, 28.0, 27.4; FTIR (NaCl, thin film) 2978, 1727, 1598, 1522, 1457, 1392, 1367, 1346, 1294, 1249, 1199, 1151, 850, 745 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 593.2857, found 593.2854.

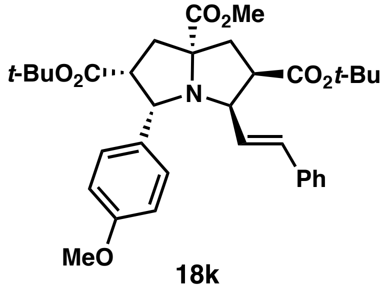
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(4-cyanophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18j)



18j

According to the general procedure pyrrolizidine **18j** was obtained as a yellow foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 80% yield and 96% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 4% IPA in CO2, λ = 254 nm): t_R (major) = 5.7 min, t_R (minor) = 7.1 min. $[\alpha]_D^{25}$ = –57.101 (c = 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 – 7.53 (m, 4H), 7.31 – 7.19 (m, 5H), 6.27 (d, *J* = 15.6 Hz, 1H), 5.99 (dd, *J* = 15.6, 10.4 Hz, 1H), 4.84 (d, *J* = 8.2 Hz, 1H), 4.14 (dt, *J* = 7.1, 5.9 Hz, 1H), 3.79 (s, 3H), 3.67 – 3.57 (m, 1H), 3.44 (td, *J* = 7.9, 2.7 Hz, 1H), 3.01 (dd, *J* = 13.2, 2.6 Hz, 1H), 2.38 (dd, *J* = 13.2, 6.6 Hz, 1H), 2.35 ? 2.28 (m, 1H), 2.14 (dd, *J* = 13.3, 7.8 Hz, 1H), 1.28 (s, 9H), 0.97 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.8, 170.6, 170.6, 147.2, 136.0, 135.7, 131.7, 128.8, 128.6, 128.0, 126.5, 125.8, 119.2, 110.4, 80.9, 80.9, 80.6, 76.8, 64.7, 64.6, 53.0, 52.3, 51.4, 39.6, 39.1, 28.0, 27.5; FTIR (NaCl, thin film) 3453, 2978, 2931, 1732, 1608, 1456, 1393, 1368, 1257, 1151, 844, 738 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 573.2959, found 573.2924.

(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(4-methoxyphenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18k)

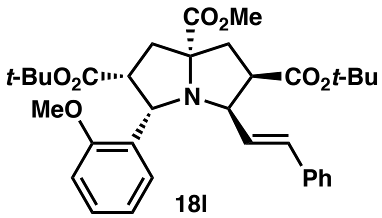


18k

According to the general procedure using 6 mol% AgOAc/QUINAP in 0.1M THF, pyrrolizidine **18k** was obtained as a yellow foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 86% yield and 90% ee.

The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 7% IPA in CO2, λ = 254 nm): t_R (minor) = 9.8 min, t_R (major) = 10.5 min. $[\alpha]_D^{25}$ = -201.710 (c = 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 – 7.20 (m, 7H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.34 (d, *J* = 15.6 Hz, 1H), 6.04 (dd, *J* = 15.6, 10.3 Hz, 1H), 4.75 (d, *J* = 8.3 Hz, 1H), 4.19 (dd, *J* = 10.3, 7.7 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.65 – 3.56 (m, 1H), 3.36 (td, *J* = 7.9, 4.0 Hz, 1H), 2.99 (dd, *J* = 13.3, 4.0 Hz, 1H), 2.38 (dd, *J* = 13.1, 6.4 Hz, 1H), 2.34 – 2.26 (m, 1H), 2.13 (dd, *J* = 13.3, 7.8 Hz, 1H), 1.28 (s, 9H), 1.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.1, 171.0, 170.9, 158.5, 136.4, 135.1, 133.2, 128.9, 128.4, 127.7, 126.5, 126.3, 113.2, 80.6, 80.1, 76.5, 65.0, 64.6, 55.3, 52.9, 52.2, 51.2, 38.9, 38.9, 28.0, 27.5; FTIR (NaCl, thin film) 2977, 1726, 1603, 1511, 1367, 1248, 1151, 1034, 845, 752 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 578.3112, found 578.3119.

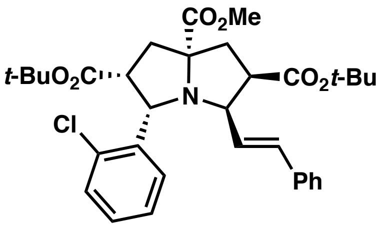
(2*R*,3*R*,5*S*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methoxy 3-((*E*)-styryl)-5-(*o*-tolyl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18l)



18l

According to the general procedure pyrrolizidine **18l** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 72% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (OD, 2.5 mL/min, 15% IPA in CO2, λ = 254 nm): t_R (major) = 4.0 min, t_R (minor) = 4.6 min. $[\alpha]_D^{25}$ = –188.252 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.30 – 7.23 (m, 3H), 7.23 – 7.12 (m, 3H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.23 (d, *J* = 15.6 Hz, 1H), 6.02 (dd, *J* = 15.6, 10.4 Hz, 1H), 5.01 (d, *J* = 7.8 Hz, 1H), 4.14 (dd, *J* = 10.3, 7.6 Hz, 1H), 3.79 (s, 3H), 3.63 (s, 3H), 3.55 (td, *J* = 7.7, 1.5 Hz, 1H), 3.01 (d, *J* = 12.8 Hz, 1H), 2.35 (dd, *J* = 9.4, 4.0 Hz, 2H), 2.10 (dd, *J* = 13.1, 7.7 Hz, 1H), 1.28 (s, 9H), 0.93 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.5, 171.8, 170.7, 157.0, 136.7, 134.8, 129.2, 129.0, 128.3, 127.4, 127.4, 127.0, 126.5, 120.3, 109.3, 80.6, 79.6, 76.2, 64.4, 59.6, 55.0, 52.1, 51.5, 51.3, 39.7, 39.3, 36.6, 28.0, 27.3, 24.6; FTIR (NaCl, thin film) 2977, 2949, 1723, 1600, 1489, 1458, 1437, 1391, 1367, 1294, 1242, 1152, 1106, 1031, 968, 848, 756 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 578.3112, found 578.3137.

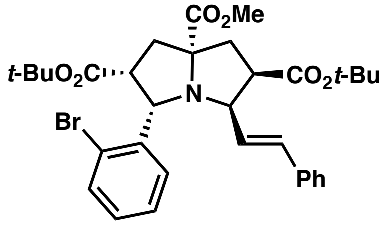
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(2-chlorophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18m)



18m

According to the general procedure pyrrolizidine **18m** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 87% yield and 94% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 2% IPA in CO2, λ = 254 nm): t_R (minor) = 5.3 min, t_R (minor) = 6.2 min. $[\alpha]_D^{25}$ = -76.881 (c = 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.29 – 7.18 (m, 7H), 7.14 (td, *J* = 7.6, 1.7 Hz, 1H), 6.23 (d, *J* = 15.6 Hz, 1H), 5.99 (dd, *J* = 15.6, 10.4 Hz, 1H), 5.11 (d, *J* = 8.1 Hz, 1H), 4.09 (dd, *J* = 10.6, 7.8 Hz, 1H), 3.80 (s, 3H), 3.67 (td, *J* = 7.8, 1.5 Hz, 1H), 3.62 (dt, *J* = 11.8, 7.1 Hz, 1H), 3.04 (d, *J* = 13.0 Hz, 1H), 2.40 (dd, *J* = 13.0, 6.7 Hz, 1H), 2.38 – 2.32 (m, 1H), 2.12 (dd, *J* = 13.2, 7.7 Hz, 1H), 1.29 (s, 9H), 0.94 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) 177.2, 171.2, 170.6, 138.4, 136.5, 135.4, 133.5, 130.5, 128.4, 128.3, 127.9, 127.6, 126.6, 126.5, 126.2, 80.7, 80.0, 76.4, 64.1, 62.3, 52.2, 51.4, 50.8, 39.7, 39.1, 28.0, 27.3; FTIR (NaCl, thin film) 3444, 2978, 1728, 1456, 1393, 1367, 1256, 1205, 1152, 1034, 969, 844, 752 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 582.2617, found 582.2617.

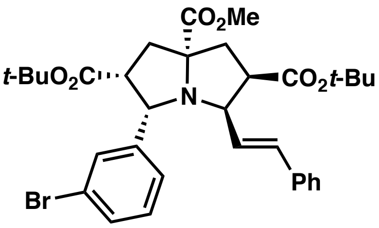
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(2-bromophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18n)



18n

According to the general procedure pyrrolizidine **18n** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 89% yield and 93% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 3% IPA in CO2, λ = 254 nm): t_R (minor) = 4.4 min, t_R (major) = 5.0 min. $[\alpha]_D^{25}$ = -85.978 (c = 0.88, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.09 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.41 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.35 – 7.15 (m, 6H), 7.07 (td, *J* = 7.6, 1.7 Hz, 1H), 6.23 (d, *J* = 15.6 Hz, 1H), 5.98 (dd, *J* = 15.6, 10.4 Hz, 1H), 5.07 (d, *J* = 8.1 Hz, 1H), 4.08 (dd, *J* = 10.3, 7.5 Hz, 1H), 3.81 (s, 3H), 3.70 (td, *J* = 7.9, 1.2 Hz, 1H), 3.61 (dt, *J* = 11.7, 7.2 Hz, 1H), 3.04 (d, *J* = 13.1 Hz, 1H), 2.42 – 2.32 (m, 2H), 2.12 (dd, *J* = 13.2, 7.7 Hz, 1H), 1.29 (s, 9H), 0.94 (s, 9H); ^{13}C NMR (CDCl$_3$, 126 MHz) δ 177.2, 171.2, 170.6, 139.9, 136.5, 135.5, 131.7, 130.9, 128.3, 128.3, 127.6, 127.3, 126.5, 126.2, 123.9, 80.7, 80.0, 76.5, 64.7, 64.0, 52.2, 51.4, 50.7, 39.7, 39.2, 28.0, 27.3; FTIR (NaCl, thin film) 2977, 1727, 1457, 1392, 1367, 1293, 1257, 1203, 1151, 1094, 1022, 968, 843, 751 cm^{-1}; HRMS (MM) calc'd for [M+H]$^+$ 626.2112, found 628.2134.

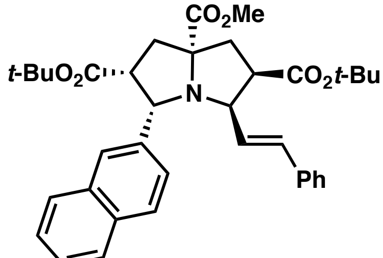
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(3-bromophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18o)



18o

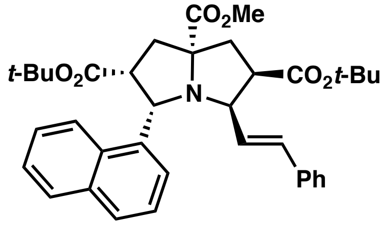
According to the general procedure pyrrolizidine **18o** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 82% yield and 92% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 2% IPA in CO2, λ = 254 nm): *t*$_R$ (minor) = 6.9 min, *t*$_R$ (major) = 8.0 min. $[\alpha]_D^{25}$ = -102.419 (c = 0.67, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.63 (s, 1H), 7.38 – 7.20 (m, 6H), 7.13 (t, *J* = 7.8 Hz, 2H), 6.33 (d, *J* = 15.6 Hz, 1H), 6.01 (dd, *J* = 15.6, 10.4 Hz, 1H), 4.77 (d, *J* = 8.3 Hz, 1H), 4.18 (dd, *J* = 10.3, 7.7 Hz, 1H), 3.82 (s, 3H), 3.61 (ddd, *J* = 12.4, 7.4, 6.6 Hz, 1H), 3.40 (td, *J* = 7.9, 3.3 Hz, 1H), 2.99 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.40 (dd, *J* = 13.1, 6.4 Hz, 1H), 2.31 (t, *J* = 12.8 Hz, 1H), 2.12 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.29 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (CDCl$_3$, 126 MHz) δ 176.9, 170.7, 170.6, 143.8, 136.2, 135.5, 131.0, 129.8, 129.5, 128.5, 127.8, 126.5, 125.9, 122.1, 80.8, 80.5, 76.7, 64.7, 64.5, 53.0, 52.2, 51.2, 39.3, 39.0, 28.0, 27.4; FTIR (NaCl, thin film) 2978, 1728, 1594, 1569, 1456, 1393, 1367, 1293, 1257, 1204, 1151, 969, 845, 746 cm^{-1}; HRMS (MM) calc'd for [M+H]$^+$ 626.2112, found 626.2127.

(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(naphthalen-2-yl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18p)


18p

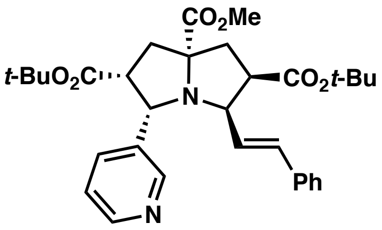
According to the general procedure using 6 mol% AgOAc/QUINAP in 0.1M THF, pyrrolizidine **18p** was obtained as a yellow foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 93% yield and 92% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 7% IPA in CO2, λ = 254 nm): t_R (major) = 6.0 min, t_R (minor) = 9.8 min. $[\alpha]_D^{25}$ = -387.655 (c = 0.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (s, 1H), 7.85 – 7.77 (m, 2H), 7.74 (d, J = 8.5 Hz, 1H), 7.52 (dd, J = 8.5, 1.6 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.30 – 7.19 (m, 4H), 6.29 (d, J = 15.6 Hz, 1H), 6.09 (dd, J = 15.6, 10.3 Hz, 1H), 4.99 (d, J = 8.2 Hz, 1H), 4.27 (dd, J = 10.3, 7.6 Hz, 1H), 3.86 (s, 3H), 3.74 – 3.65 (m, 1H), 3.50 (td, J = 7.8, 3.4 Hz, 1H), 3.08 (dd, J = 13.2, 3.3 Hz, 1H), 2.45 (dd, J = 13.1, 6.4 Hz, 1H), 2.38 (t, J = 12.7 Hz, 1H), 2.19 (dd, J = 13.2, 7.7 Hz, 1H), 1.30 (s, 9H), 0.82 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.11, 170.96, 170.71, 138.60, 136.30, 135.25, 133.30, 132.77, 128.40, 127.91, 127.66, 127.39, 127.18, 126.46, 126.41, 126.25, 125.47, 125.11, 80.68, 80.12, 76.64, 65.26, 64.83, 53.11, 52.19, 51.25, 39.26, 39.05, 27.99, 27.22; FTIR (NaCl, thin film) 2977, 1727, 1457, 1391, 1368, 1256, 1199, 1151, 845, 751 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 598.3163, found 598.3155.

(2*R*,3*S*,5*R*,6*R*)-di-*tert*-butyl 3-(naphthalen-1-yl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6-dicarboxylate (18q)


18q

According to the general procedure using 6 mol% AgOAc/QUINAP, pyrrolizidine **18q** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 84% yield and 93% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 7% IPA in CO2, λ = 254 nm): t_R (minor) = 8.4 min, t_R (major) = 9.8 min. $[\alpha]_D^{25}$ = -188.706 (c = 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.30 (d, J = 7.1 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.83 (dd, J = 8.1, 1.2 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.54 – 7.47 (m, 1H), 7.38 (dddd, J = 22.6, 8.2, 6.8, 1.3 Hz, 2H), 7.20 – 7.13 (m, 3H), 7.01 –6.98 (m, 2H), 6.17 (d, J = 15.6 Hz, 1H), 6.00 (dd, J = 15.6, 10.3 Hz, 1H), 5.56 (d, J = 8.4 Hz, 1H), 4.19 (dd, J = 10.2, 7.5 Hz, 1H), 3.84 (s, 3H), 3.77 (td, J = 8.0, 1.8 Hz, 1H), 3.70 (dt, J = 11.2, 7.4 Hz, 1H), 3.11 (dd, J = 13.0, 1.5 Hz, 1H), 2.45 (dd, J = 9.3, 3.3 Hz, 2H), 2.19 (dd, J = 13.1, 7.7 Hz, 1H), 1.28 (s, 9H), 0.53 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 177.3, 171.1, 170.9, 136.4, 136.3, 135.3, 133.4, 131.7, 128.3, 128.3, 127.5, 127.2, 126.6, 126.4, 125.9, 125.3, 124.8, 123.3, 80.7, 79.6, 76.3, 64.4, 61.5, 52.3, 52.2, 51.5, 40.0, 39.2, 28.0, 26.9; FTIR (NaCl, thin film) 2977, 1727, 1596, 1457, 1391, 1367, 1152, 968, 775, 752 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 598.3163, found 598.3156.

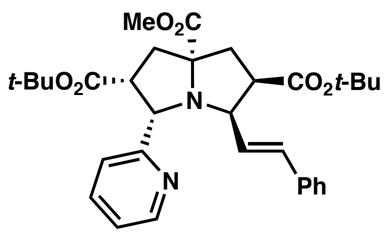
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(pyridin-3-yl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18r)



18r

According to the general procedure pyrrolizidine **18r** was obtained as a yellow foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 90% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 20% IPA in CO2, λ = 254 nm): t_R (major) = 2.7 min, t_R (minor) = 3.7 min. $[\alpha]_D^{25}$ = -218.400 (c = 0.79, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.53 (s, 1H), 8.43 (d, J = 4.7 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.32 – 7.18 (m, 6H), 6.31 (d, J = 15.6 Hz, 1H), 6.01 (dd, J = 15.6, 10.4 Hz, 1H), 4.83 (d, J = 8.3 Hz, 1H), 4.15 (dd, J = 10.2, 7.7 Hz, 1H), 3.80 (s, 3H), 3.59 (dt, J = 12.1, 7.0 Hz, 1H), 3.44 (td, J = 8.0, 3.4 Hz, 1H), 3.01 (dd, J = 13.2, 3.4 Hz, 1H), 2.40 (dd, J = 13.2, 6.5 Hz, 1H), 2.31 (t, J = 12.7 Hz, 1H), 2.15 (dd, J = 13.3, 7.7 Hz, 1H), 1.27 (s, 9H), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.78, 170.62, 149.35, 147.87, 136.89, 136.00, 135.63, 128.50, 127.89, 126.46, 125.69, 123.19, 80.83, 80.61, 76.63, 64.78, 62.65, 52.75, 52.28, 51.26, 39.26, 38.90, 27.98, 27.40; FTIR (NaCl, thin film) 2978, 1730, 1586, 1457, 1420, 1369, 1256, 1152, 1026, 844, 737 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 549.2954, found 549.2954.

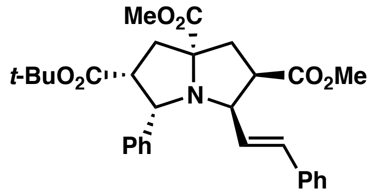
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(pyridin-2-yl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18s)



18s

According to the general procedure pyrrolizidine **18s** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 33% yield and 44% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 20% IPA in CO2, λ = 254 nm): t_R (major) = 2.2 min, t_R (minor) = 3.9 min. $[\alpha]_D^{25}$ = -68.157 (c = 0.92, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, J = 4.1 Hz, 1H), 7.72 (d, J = 7.8 Hz, 2H), 7.67 – 7.55 (m, 2H), 7.26 – 7.19 (m, 2H), 7.08 (dd, J = 6.5, 5.1 Hz, 2H), 6.45 (dd, J = 22.7, 15.6 Hz, 1H), 6.04 (dt, J = 28.1, 14.0 Hz, 1H), 4.83 (d, J = 7.9 Hz, 1H), 4.26 (dt, J = 22.8, 11.4 Hz, 1H), 3.75 (d, J = 8.7 Hz, 2H), 3.68 – 3.59 (m, 1H), 3.51 (td, J = 8.0, 5.5 Hz, 1H), 3.08 (dd, J = 13.3, 5.4 Hz, 1H), 2.38 – 2.35 (m, 1H), 2.34 (d, J = 3.1 Hz, 1H), 2.22 (dt, J = 15.5, 7.8 Hz, 1H), 1.31 – 1.20 (m, 8H), 1.06 (s, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.04, 170.94, 170.47, 161.47, 136.22, 135.97, 128.47, 127.85, 126.66, 125.49, 122.60, 121.63, 80.80, 80.20, 76.64, 66.44, 66.06, 52.27, 52.18, 50.80, 39.08, 38.87, 28.06, 27.54; FTIR (NaCl, thin film) 2976, 1726, 1589, 1457, 1434, 1366, 1256, 1151, 968, 847, 751 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 549.2959, found 549.2908.

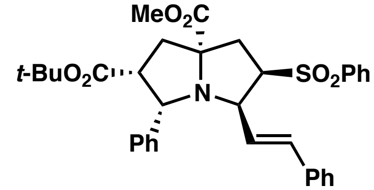
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2-*tert*-butyl 6,7a-dimethyl 3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (19a)



19a

According to the general procedure using 1.1 equivalents of *t*-Bu acrylate in the first (1,3)-dipolar cycloaddition and methyl acrylate as the dipolarophile in the second (1,3)-dipolar cycloaddition, pyrrolizidine **19a** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 92% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 10% IPA in CO2, λ = 254 nm): t_R (major) = 7.6 min, t_R (minor) = 9.4 min. $[\alpha]_D^{25}$ = -96.513 (c = 0.94, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.42 – 7.38 (m, 2H), 7.32 – 7.21 (m, 6H), 7.19 – 7.15 (m, 2H), 6.34 (d, J = 15.6 Hz, 1H), 6.03 (dd, J = 15.6, 10.3 Hz, 1H), 4.83 (d, J = 8.4 Hz, 1H), 4.28 (dd, J = 10.2, 7.8 Hz, 1H), 3.82 (s, 3H), 3.70 (ddd, J = 11.9, 7.7, 6.8 Hz, 1H), 3.56 (s, 3H), 3.44 (td, J = 7.8, 4.5 Hz, 1H), 3.03 (dd, J = 13.3, 4.5 Hz, 1H), 2.45 (dd, J = 13.2, 6.6 Hz, 1H), 2.37 (dd, J = 13.2, 11.9 Hz, 1H), 2.19 (dd, J = 13.3, 7.8 Hz, 1H), 0.98 (s, 9H); ^{13}C NMR (CDCl$_3$, 126 MHz) δ 176.8, 172.4, 170.8, 140.9, 136.4, 135.3, 128.5, 127.9, 127.8, 127.8, 126.8, 126.6, 125.8, 80.3, 76.8, 65.3, 52.6, 52.3, 51.8, 50.5, 39.1, 38.7, 27.4; FTIR (NaCl, thin film) 3450, 2978, 1730, 1493, 1451, 1367, 1152, 970, 844, 747 cm^{-1}; HRMS (MM) calc'd for [M+H]$^+$ 506.2537, found 506.2523.

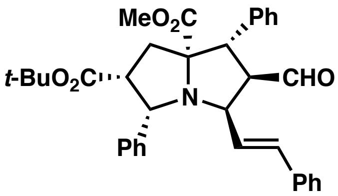
(2*R*,3*S*,5*R*,6*R*,7a*S*)-2-*tert*-butyl 7a-methyl 3-phenyl-6-(phenylsulfonyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,7a-dicarboxylate (19b)



19b

According to the general procedure using 1.1 equivalents of *t*-Bu acrylate in the first (1,3)-dipolar cycloaddition and vinyl sulphone as the dipolarophile in the second (1,3)-dipolar cycloaddition, pyrrolizidine **19b** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 64% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 10% IPA in CO2, λ = 254 nm): t_R (minor) = 3.9 min, t_R (major) = 4.6 min; $[\alpha]_D^{25}$ = -10.465 (c = 0.87, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.77 (dd, J = 8.3, 1.1 Hz, 2H), 7.55 (t, J = 7.5 Hz, 2H), 7.42 – 7.10 (m, 11H), 6.28 (dd, J = 15.6, 10.6 Hz, 1H), 5.96 (d, J = 15.6 Hz, 1H), 4.87 (d, J = 8.6 Hz, 1H), 4.41 – 4.29 (m, 1H), 3.98 (dd, J = 10.5, 7.0 Hz, 1H), 3.80 (s, 3H), 3.43 (ddd, J = 16.7, 10.2, 6.2 Hz, 1H), 3.07 (dd, J = 13.2, 3.8 Hz, 1H), 2.69 (dd, J = 13.0, 6.4 Hz, 1H), 2.56 (t, J = 12.5 Hz, 1H), 2.14 (dd, J = 13.3, 7.8 Hz, 1H), 0.95 (s, 9H); ^{13}C NMR (CDCl$_3$, 126 MHz) δ 175.8, 170.8, 140.4, 138.9, 136.1, 135.6, 133.6, 128.8, 128.4, 128.4, 127.8, 127.8, 126.8, 126.7, 124.0, 80.3, 75.8, 68.0, 64.6, 64.0, 52.4, 52.1, 38.9, 36.9, 27.3, 27.3; FTIR (NaCl, thin film) 2979, 1726, 1446, 1367, 1305, 1248, 1148, 1085, 749, 722 cm^{-1}; HRMS (MM) calc'd for [M+H]$^+$ 588.2414, found 588.2407.

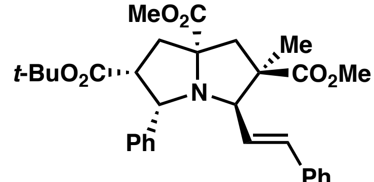
(2*R*,3*S*,5*R*,6*R*,7*S*,7a*S*)-2-*tert*-butyl 7a-methyl 6-formyl-3,7-diphenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,7a-dicarboxylate (19c)



19c

According to the general procedure using 1.1 equivalents of *t*-Bu acrylate in the first (1,3)-dipolar cycloaddition and cinnamaldehyde as the dipolarophile in the second (1,3)-dipolar cycloaddition, pyrrolizidine **19c** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 90% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (OB-H, 2.5 mL/min, 10% IPA in CO2, λ = 254 nm): t_R (minor) = 3.7 min, t_R (major) = 4.9 min; $[\alpha]_D^{25}$ = -39.981 (c = 0.96, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.64 (d, *J* = 1.8 Hz, 1H), 7.37 – 7.11 (m, 14H), 6.44 (d, *J* = 15.5 Hz, 1H), 6.14 (dd, *J* = 15.5, 10.7 Hz, 1H), 4.87 (d, *J* = 7.9 Hz, 1H), 4.79 (dd, *J* = 10.7, 8.1 Hz, 1H), 4.55 (ddd, *J* = 12.0, 8.1, 1.7 Hz, 1H), 3.86 (d, *J* = 12.1 Hz, 1H), 3.47 (td, *J* = 7.9, 4.5 Hz, 1H), 3.30 (s, 3H), 3.04 (dd, *J* = 13.5, 4.6 Hz, 1H), 2.40 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.33 – 1.23 (m, 1H), 1.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 199.9, 174.1, 170.5, 140.4, 136.1, 136.0, 135.9, 128.5, 128.5, 128.1, 127.9, 127.6, 127.4, 126.8, 126.7, 125.8, 81.8, 80.4, 64.6, 63.1, 60.1, 54.2, 52.7, 51.4, 37.3, 27.4; FTIR (NaCl, thin film) 2978, 1728, 1495, 1452, 1391, 1367, 1204, 1152, 1073, 747 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 552.2744, found 552.2712.

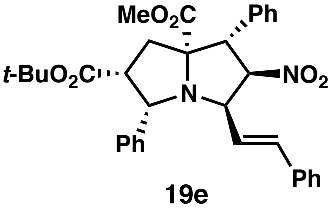
(2*R*,3*R*,5*S*,6*R*,7a*S*)-6-*tert*-butyl 2,7a-dimethyl 2-methyl-5-phenyl-3-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (19d)



19d

According to the general procedure using 1.1 equivalents of *t*-Bu acrylate in the first (1,3)-dipolar cycloaddition and methyl methacrylate as the dipolarophile in the second (1,3)-dipolar cycloaddition, pyrrolizidine **19d** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 91% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (OB-H, 2.5 mL/min, 10% IPA in CO2, λ = 254 nm): t_R (major) = 2.8 min, t_R (minor) = 3.3 min; $[\alpha]_D^{25}$ = -67.966 (c = 0.97, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.45 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.26 – 7.17 (m, 6H), 7.13 – 7.07 (m, 3H), 6.39 (d, *J* = 15.6 Hz, 1H), 5.99 (dd, *J* = 15.6, 9.7 Hz, 1H), 5.02 (d, *J* = 9.0 Hz, 1H), 3.90 (d, *J* = 9.3 Hz, 1H), 3.84 (s, 3H), 3.64 (s, 3H), 3.56 (ddd, *J* = 9.0, 7.8, 6.3 Hz, 1H), 3.02 (dd, *J* = 13.2, 6.3 Hz, 1H), 2.78 (d, *J* = 13.8 Hz, 1H), 2.36 – 2.28 (m, 2H), 1.38 (s, 3H), 0.99 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 176.8, 176.8, 170.9, 142.1, 136.7, 134.6, 128.3, 128.2, 127.7, 127.5, 126.7, 126.4, 125.1, 80.2, 76.9, 75.0, 65.4, 56.1, 56.1, 52.3, 51.9, 50.4, 48.0, 39.0, 27.4, 23.1; FTIR (NaCl, thin film) 2950, 1727, 1493, 1433, 1450, 1367, 1253, 1152, 1121, 969, 746 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 520.2694, found 520.2644.

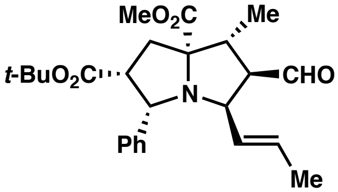
(2*R*,3*S*,5*R*,6*R*,7*R*,7a*S*)-2-*tert*-butyl 7a-methyl 6-nitro-3,7-diphenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,7a-dicarboxylate (19e)



19e

According to the general procedure using 1.1 equivalents of *t*-Bu acrylate in the first (1,3)-dipolar cycloaddition and crotonaldehyde as the dipolarophile in the second (1,3)-dipolar cycloaddition, pyrrolizidine **19e** was obtained as a yellow foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 89% yield and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (OJ, 2.5 mL/min, 10% IPA in CO2, $\lambda = 254$ nm): t_R (minor) = 6.0 min, t_R (major) = 7.4 min; $[\alpha]_D^{25} = -27.059$ (c = 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40 – 7.15 (m, 15H), 6.48 (d, *J* = 15.5 Hz, 1H), 6.22 – 6.11 (m, 1H), 5.05 (d, *J* = 8.1 Hz, 1H), 4.94 (dd, *J* = 10.1, 8.0 Hz, 1H), 4.23 (d, *J* = 11.1 Hz, 1H), 3.59 (td, *J* = 7.9, 4.9 Hz, 1H), 3.38 (s, 3H), 3.12 (dd, *J* = 13.6, 4.9 Hz, 1H), 2.48 (dd, *J* = 13.7, 7.9 Hz, 1H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.2, 170.2, 139.9, 138.2, 135.6, 133.7, 128.8, 128.4, 128.3, 128.3, 127.9, 127.5, 127.1, 127.0, 126.8, 122.0, 92.1, 80.6, 80.5, 65.3, 64.8, 57.2, 51.6, 51.5, 37.1, 27.4; FTIR (NaCl, thin film) 2949, 1730, 1550, 1452, 1205, 1152, 1074, 911, 734 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 569.2646, found 569.2632.

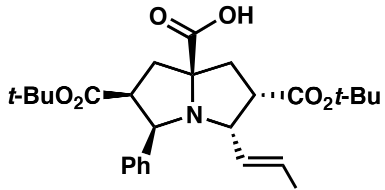
(2*R*,3*S*,5*R*,6*R*,7*R*,7a*S*)-2-*tert*-butyl 7a-methyl 6-formyl-7-methyl-3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,7a-dicarboxylate (19f)



19f

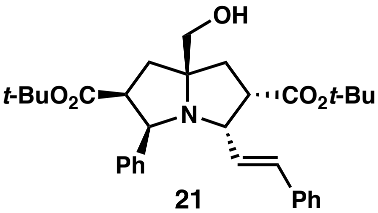
According to the general procedure using 1.1 equivalents of *t*-Bu acrylate in the first (1,3)-dipolar cycloaddition and crotonaldehyde as the dipolarophile in the second (1,3)-dipolar cycloaddition, pyrrolizidine **19f** was obtained as a white foam after silica gel column chromatography (5→20% ethyl acetate in hexanes) in 59% yield (3:1mixture of diastereomers) and 90% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 5% IPA in CO2, λ = 254 nm): t_R (major) = 5.9 min, t_R (minor) = 6.7 min; $[\alpha]_D^{25}$ = -39.981 (c = 0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.56 (d, *J* = 1.6 Hz, 1H), 7.30 – 7.20 (m, 5H), 5.50 (dq, *J* = 14.8, 6.5 Hz, 1H), 5.27 (ddd, *J* = 15.0, 10.9, 1.6 Hz, 1H), 4.70 (d, *J* = 7.9 Hz, 1H), 4.36 (dd, *J* = 10.8, 8.2 Hz, 1H), 3.78 (s, 3H), 3.48 (ddd, *J* = 11.7, 8.2, 1.5 Hz, 1H), 3.33 – 3.26 (m, 1H), 3.00 (dd, *J* = 13.6, 5.3 Hz, 1H), 2.44 (tt, *J* = 13.6, 6.8 Hz, 1H), 2.04 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.61 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 201.2, 175.3, 170.6, 141.0, 132.6, 128.3, 127.8, 127.8, 127.6, 127.6, 127.4, 126.7, 80.3, 80.3, 77.3, 77.0, 76.8, 64.4, 63.3, 62.3, 52.6, 51.7, 43.3, 36.8, 27.5, 17.7, 13.7; FTIR (NaCl, thin film) 2976, 2932, 1732, 1453, 1367, 1367, 974, 745 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 428.2431, found 428.2431.

(2*S*,3*R*,5*S*,6*S*,7a*S*)-2,6-bis(*tert*-butoxycarbonyl)-3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-7a-carboxylic acid (20)



20

20 mg of pyrrolizidine **18a** was dissolved in 0.4 ml THF. 4.4 mg of LiOH was dissolved in 0.4 ml of H_2O and then transferred to the organic solution. The reaction was allowed to stir for 14 h and then quenched with 1 ml of 10% NaH_2PO_4 and extracted with 1 ml DCM 3 times. The organic solution was then dried with $MgSO_4$, filtered, and concentrated. The crude mixture was then purified (5→20% ethyl acetate in hexanes) to afford 14 mg of **21** in 74% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR 7.32 – 7.22 (m, 6H), 7.12 (dd, *J* = 7.6, 1.7 Hz, 4H), 6.32 (d, *J* = 15.5 Hz, 1H), 5.98 (dd, *J* = 15.5, 10.5 Hz, 1H), 4.87 (d, *J* = 7.7 Hz, 1H), 4.29 (dd, *J* = 10.4, 7.8 Hz, 1H), 3.45 (tdd, *J* = 7.6, 6.0, 3.9 Hz, 2H), 2.88 (dd, *J* = 13.9, 2.5 Hz, 1H), 2.74 (dd, *J* = 13.3, 6.5 Hz, 1H), 2.47 – 2.33 (m, 2H), 1.28 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.83, 171.33, 169.92, 138.32, 136.48, 135.82, 128.54, 128.37, 128.18, 127.54, 127.21, 126.56, 123.56, 81.67, 81.41, 78.12, 77.28, 77.02, 76.77, 66.20, 65.71, 53.40, 51.37, 38.80, 38.53, 27.99, 27.42; FTIR (NaCl, thin film) 2977, 2928,1725, 1495, 1454, 1367, 1250, 1151, 1030, 970, 845, 744 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 534.2832, found 534.285.

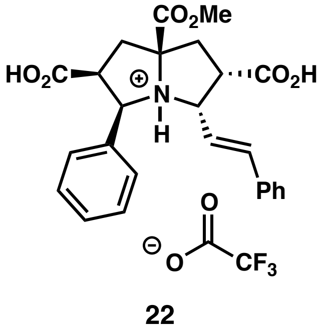


21

(2*R*,3*S*,5*R*,6*R*,7a*R*)-di-*tert*-butyl 7a-(hydroxymethyl)-3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6-dicarboxylate (21)

20 mg of pyrrolizidine **18a** was dissolved in 0.73 ml THF and put to 0 °C. 0.11 ml of 1 M $LiEt_3BH$ in THF was added drop-wise. The reaction was then quenched with 1 ml of saturated aqueous NH_4Cl and extracted with 1 ml DCM 3 times. The organic solution was then dried with $MgSO_4$, filtered, and concentrated. The crude mixture was then purified (5→20% ethyl acetate in hexanes) to afford 14 mg of **21** in 74% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 8.1, 1.0 Hz, 2H), 7.15 – 7.06 (m, 4H), 7.06 – 6.99 (m, 2H), 6.94 – 6.91 (m, 2H), 6.29 (d, *J* = 15.6 Hz, 1H), 5.90 (dd, *J* = 15.6, 9.8 Hz, 1H), 4.89 (d, *J* = 9.4 Hz, 1H), 4.15 – 4.05 (m, 1H), 3.48 (s, 2H), 3.47 – 3.42 (m, 1H), 3.18 (dd, *J* = 17.4, 8.7 Hz, 1H), 2.62 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.17 (dd, *J* = 13.4, 9.1 Hz, 1H), 2.03 (dd, *J* = 13.5, 8.9 Hz, 1H), 1.95 (dd, *J* = 13.4, 8.4 Hz, 1H), 1.22 (s, 9H), 0.90 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.15, 172.26, 141.97, 136.59, 134.14, 128.32, 128.23, 127.92, 127.51, 126.87, 126.31, 126.09, 80.87, 80.41, 77.28, 77.02, 76.77, 75.48, 66.18, 65.77, 65.54, 51.63, 50.12, 38.22, 36.07, 29.72, 28.01, 27.40; FTIR (NaCl, thin film) 2975, 2928,1722, 1493, 1452, 1367, 1249, 1151, 1030, 970, 846, 743 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 520.3012, found 520.3012.

(2*S*,3*R*,5*S*,6*S*,7a*S*)-2,6-dicarboxy-7a-(methoxycarbonyl)-3-phenyl-5-((*E*)-styryl)octahydropyrrolizin-4-ium 2,2,2-trifluoroacetate (22)

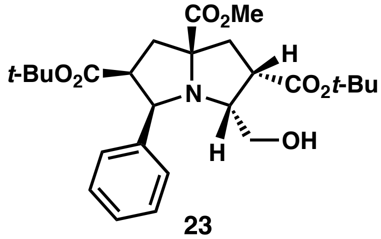


22

To a stirring solution of triester ***ent*-18a** (204 mg, 0.372 mmol) in 2.6 mL of CH_2Cl_2 was added triethylsilane (0.29 mL, 1.8 mmol), followed by 1.0 mL of trifluoroacetic acid. The resulting solution was stirred for 20 h, and subsequently concentrated *in vacuo.* The crude residue was dissolved in 4 mL of Et_2O, and added dropwise to 30 mL of vigorously stirring hexanes, resulting in precipitation of a white solid (the reaction vessel was rinsed twice with 2 mL of Et_2O, and the rinsates added to the hexanes mixture). The solids were isolated by filtration to afford 180 mg (88% yield) of trifluoroacetate salt **22** as a white amorphous solid. $[\alpha]_D^{25} = +171.4°$ (c = 1.04, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.89 (s, 3H), 7.36 –

7.26 (m, 10H), 6.52 (d, J = 15.5 Hz, 1H), 6.23 (dd, J = 15.5, 10.5 Hz, 1H), 5.16 (d, J = 7.4 Hz, 1H), 4.68 (dd, J = 10.5, 7.6 Hz, 1H), 3.84 (s, 3H), 3.67 – 3.60 (m, 1H), 2.97 (dd, J = 13.9, 3.4 Hz, 1H), 2.69 – 2.55 (m, 3H); ^{13}C NMR (CDCl$_3$, 126 MHz) δ 173.8, 173.6, 171.5, 160.7 (q, $J_{C\text{-}F}$ = 36.5 Hz), 140.9, 136.1, 134.8, 129.9, 129.7, 129.6, 129.5, 128.4, 127.9, 120.0, 117.2 (q, $J_{C\text{-}F}$ = 290.8 Hz), 81.1, 69.5, 68.8, 54.5, 52.3, 50.3, 38.8, 38.1; FTIR (NaCl, thin film) 2960, 2530, 1955, 1907, 1732, 1652, 1495, 1454, 1439, 1409, 1318, 1263, 1193, 1141, 976, 797, 750 cm^{-1}; HRMS (MM) calc'd for [M–$C_2F_3O_2$]$^+$ 436.1760, found 436.1779.

(3a*R*,5*R*,6*S*,7a*R*,8a*S*)-7a-(methoxycarbonyl)-1-oxo-5-phenyloctahydro-1*H*-furo[3,4-*b*]pyrrolizine-6-carboxylic acid (23)

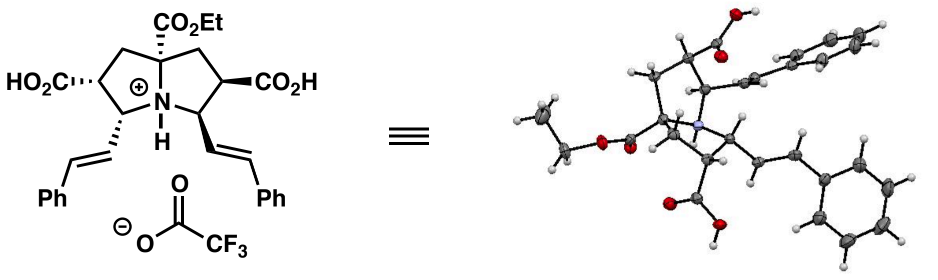


23

A solution of styrene ***ent*-18a** (150 mg, 0.274 mmol) and *p*-toluenesulfonic acid hydrate (261 mg, 1.37 mmol) in 2.8 mL of EtOAc was cooled to –78 °C with stirring. Ozone was bubbled through the solution until it became a pale blue suspension. The suspension was then sparged with oxygen (until the blue color no longer persisted), warmed to 0 °C in an ice bath, and diluted with 2.8 mL of saturated aqueous NaHCO$_3$. Sodium borohydride (104 mg, 2.75 mmol) was added portionwise, and the resulting mixture was stirred vigorously at 0 °C for 1 h. An additional portion of sodium borohydride (104 mg, 2.75 mmol) was added, and vigorous stirring continued at 0 °C for 1 h. A final portion of sodium borohydride (52 mg, 1.37 mmol) was added, and vigorous stirring continued at 0 °C for 1 h. The reaction mixture was then further diluted with saturated aqueous NaHCO$_3$ and extracted with EtOAc (5 x 5 mL) (**NOTE:** effervescence was allowed to subside prior to extraction), and the combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. The resulting residue was subjected to silica gel column chromatography (50:1→10:1 CH$_2$Cl$_2$–Et$_2$O), to afford 83 mg (64% yield) of a white foam. $[\alpha]_D^{25}$ = +346.27 (c = 0.98, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.48 – 7.42 (m, 2H), 7.29 – 7.24 (m, 2H), 7.21 – 7.17 (m, 1H), 4.83 (d, J = 8.9 Hz, 1H), 3.79 (s, 3H), 3.68 – 3.60 (m, 2H), 3.57 – 3.48 (m, 2H), 3.28 (dd, J = 16.7, 8.2 Hz, 1H), 2.95 (dd, J = 13.0, 5.8 Hz, 1H), 2.41 (dd, J = 13.1, 7.9 Hz, 1H), 2.32 – 2.23 (m, 2H), 2.20 (dd, J = 8.7, 5.0 Hz, 1H), 1.49 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (CDCl$_3$, 126 MHz) δ

176.56, 174.21, 170.85, 141.72, 128.11, 127.91, 127.17, 81.90, 80.16, 77.26, 77.00, 76.75, 64.83, 64.01, 60.67, 52.25, 51.25, 49.13, 39.75, 37.40, 27.98, 27.38; FTIR (NaCl, thin film) 3502, 2977, 2929, 1729, 1478, 1456, 1392, 1367, 1303, 1252, 1209, 1152, 1094, 1042, 919, 845, 735 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 476.2643, found 476.2644.

(2*R*,3*R*,5*R*,6*R*)-2,6-dicarboxy-7a-(ethoxycarbonyl)-3,5-di((*E*)-styryl)octahydropyrrolizin-4-ium 2,2,2-trifluoroacetate (S-2)

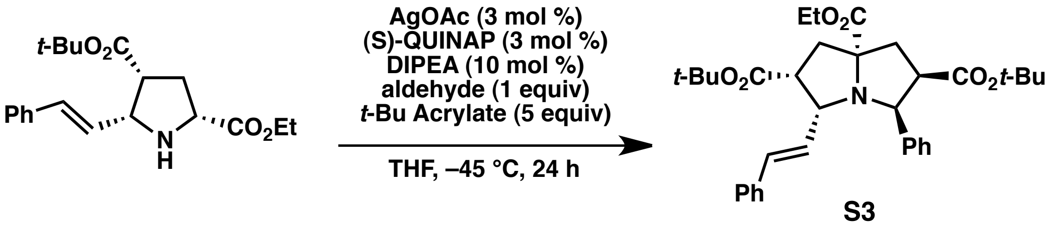


S2

(trifluoroacetate counterion omitted for clarity)

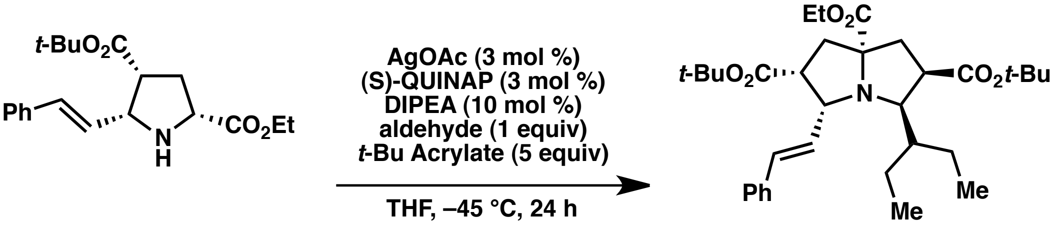
To a stirring solution of triester **12** (racemic, 191 mg, 0.325 mmol) in 2.3 mL of CH_2Cl_2 was added triethylsilane (0.26 mL, 1.6 mmol), followed by 0.93 mL of trifluoroacetic acid. The resulting solution was stirred for 24 h, and subsequently concentrated *in vacuo.* The crude residue was suspended in 3 mL of EtOAc, and added dropwise to 35 mL of vigorously stirring hexanes, resulting in precipitation of a white solid (the reaction vessel was rinsed twice with 2 mL of EtOAc, and the rinsates added to the hexanes mixture). The solids were isolated by filtration to afford 153 mg (80% yield) of trifluoroacetate salt **S-2** as a white amorphous solid. Crystals suitable for X-ray diffraction analysis (XRD) were obtained by vapor diffusion of pentane into a saturated solution of **S-2** in acetone. ^{1}H NMR (acetone-d_6, 500 MHz) δ 9.88 (s, 3H), 7.54 – 7.50 (m, 2H), 7.38 – 7.26 (m, 7H), 7.25 – 7.20 (m, 1H), 6.85 (d, J = 15.5 Hz, 1H), 6.74 (dd, J = 15.7, 1.1 Hz, 1H), 6.50 (dd, J = 15.5, 10.6 Hz, 1H), 6.34 (dd, J = 15.7, 7.6 Hz, 1H), 4.72 (dd, J = 10.6, 7.5 Hz, 1H), 4.63 (td, J = 7.4, 1.3 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.69 (ddd, J = 11.7, 7.6, 6.8 Hz, 1H), 3.57 (dt, J = 9.0, 7.6 Hz, 1H), 2.93 (dd, J = 13.7, 9.0 Hz, 1H), 2.65 – 2.54 (m, 1H), 2.49 (dd, J = 13.7, 7.7 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 173.8 (br), 171.8, 171.2, 158.5 (q, $J_{C\text{-}F}$ = 36.1 Hz), 137.5 (br), 136.4, 135.9, 132.5 (br), 128.7, 128.4, 127.9, 127.1, 126.4, 125.7 (br), 122.6 (br), 115.8 (q, $J_{C\text{-}F}$ = 291.8 Hz), 76.5, 68.0, 64.8, 61.7, 49.3, 48.5, 36.8, 35.4, 14.0; FTIR (NaCl, thin film) 3029, 2528, 1718, 1653, 1452, 1405, 1375, 1263, 1191, 1139, 971, 797, 749, 720 cm^{-1}; HRMS (MM) calc'd for $[M–C_2F_3O_2]^+$ 476.2068, found 476.2068.

(2*R*,3*S*,5*R*,6*R*,7a*S*)-2,6-di-*tert*-butyl 7a-ethyl 3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (S3)



3 mol % catalyst solution in THF was pre-stirred for 30 minutes and then added to 52 mg of pyrrolidine **S2**. 15 µl of benzaldehyde was added followed by 11 µl of *t*-Bu Acrylate and 3 µl of DIPEA. After 24 h the reaction mixture was concentrated and purified by silica gel column chromatography (5→20% ethyl acetate in hexanes) to afford **S3** in in 14% yield. The enantiomeric excess was determined by chiral SFC analysis (OD, 2.5 mL/min, 7% IPA in CO2, λ = 254 nm): t_R (major) = 10.6 min, t_R (minor) = 11.5 min. $[\alpha]_D^{25}$ = –66.858 (c = 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 5H), 7.23 – 7.13 (m, 5H), 6.33 (dd, *J* = 15.7, 0.8 Hz, 1H), 6.07 (dd, *J* = 15.7, 7.1 Hz, 1H), 4.79 (d, *J* = 9.0 Hz, 1H), 4.25 (tdd, *J* = 10.7, 7.1, 3.6 Hz, 2H), 3.84 – 3.73 (m, 1H), 3.69 (t, *J* = 7.2 Hz, 1H), 3.11 (dd, *J* = 14.9, 8.0 Hz, 1H), 2.88 (dd, *J* = 13.4, 6.9 Hz, 1H), 2.51 (dd, *J* = 13.1, 6.8 Hz, 1H), 2.37 (t, *J* = 13.2 Hz, 1H), 2.20 (dd, *J* = 13.4, 8.1 Hz, 1H), 1.33 (dd, *J* = 23.0, 12.8 Hz, 1H), 1.26 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.81, 170.86, 170.59, 138.21, 137.26, 130.50, 129.44, 128.97, 128.32, 128.24, 127.95, 127.00, 126.37, 80.56, 80.38, 76.04, 67.07, 63.22, 61.05, 51.89, 50.88, 39.01, 37.18, 28.07, 27.98, 27.35, 14.35; FTIR (NaCl, thin film) 2977, 2930,1728, 1599, 1494, 1477, 1458, 1367, 1247, 1152, 1096, 1029, 969, 848, 744 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 562.3169, found 562.3148.

(2*R*,3*R*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(pentan-3-yl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (S4)



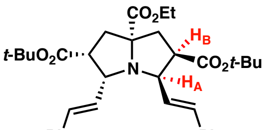
S4

3 mol % catalyst solution in THF was pre-stirred for 30 minutes and then added to 52 mg of pyrrolidine **S2**. 18 µl of 2-ethyl butyraldehyde was added followed by 11 µl of *t*-Bu Acrylate and 3 µl of DIPEA. After 24 h the reaction mixture was concentrated and purified by silica gel column chromatography (5→20% ethyl acetate in hexanes) to afford **S4** in 12% yield and 96% ee. The enantiomeric excess was determined by chiral SFC analysis (AD, 2.5 mL/min, 5% IPA in CO2, λ = 254 nm): t_R (minor) = 3.4 min, t_R (major) = 5.3 min. $[\alpha]_D^{25}$ = –70.072 (c = 0.89, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.35 – 7.26 (m, 2H), 7.23 – 7.17 (m, 2H), 6.74 (d, *J* = 15.6 Hz, 1H), 6.16 (dd, *J* = 15.7, 6.7 Hz, 1H), 4.46 – 4.38 (m, 1H), 4.26 – 4.14 (m, 2H), 3.60 (ddd, *J* = 13.0, 8.8, 6.3 Hz, 1H), 3.35 (dd, *J* = 11.7, 6.7 Hz, 1H), 2.91 (ddd, *J* = 10.3, 6.8, 3.7 Hz, 1H), 2.74 (dd, *J* = 14.3, 10.2 Hz, 1H), 2.66 (t, *J* = 13.0 Hz, 1H), 2.09 (dd, *J* = 12.8, 6.2 Hz, 1H), 1.89 (dd, *J* = 14.3, 3.7 Hz, 1H), 1.54 (s, 9H), 1.38 (s, 9H), 1.32 (t, *J* = 7.1 Hz, 1H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.76 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.57, 174.77, 170.79, 137.62, 131.09, 130.48, 128.37, 126.91, 126.46, 80.95, 80.55, 75.83, 69.39, 60.89, 60.41, 48.34, 47.21, 41.04, 38.19, 35.98, 28.15, 28.15, 21.78, 20.75, 14.31, 10.48, 7.55; FTIR (NaCl, thin film) 2974, 1718, 1559, 1457, 1366, 1247, 1146, 847 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 556.3638, found 556.3625.

7. *Endo* stereochemical assignment for pyrrolizidines in Table 3.

The relative stereochemistry of the pyrrolizidines in Table 3 was assigned using a combination of ^{1}H NOESY and ^{1}H NMR coupling constant data. The relative stereochemistry of compound **12** was confirmed by single crystal X-ray diffraction. For pyrrolizidine **12**, the H_A-H_B *J*-value of 7.6 Hz is diagnostic of the *cis*-relationship between the styrene substituent and the *t*-butyl ester. The related compounds **18a** and **S5** show similar *J* values, between 7.5 and 7.8 Hz, for H_A and H_B. Alternatively, the *J*-values for *trans*-disposed protons, for example H_B and H_C (see compound 19a), were found to be ~11–12 Hz. Based on this coupling constant analysis, and the NOESY data, the relative stereochemistry was assigned as that resulting from an *endo*-selective (1,3)-

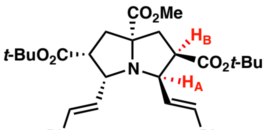
DCA for compounds **19a**–**19f**. The key *J*-values and observed NOESY data are tabulated below. The NOESY spectra are included with the rest of the NMR characterization data in the Supporting Information Part II.



12

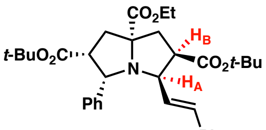
J_{HB}=7.6
J_{HA}=7.6

(confirmed by X-ray diffraction)



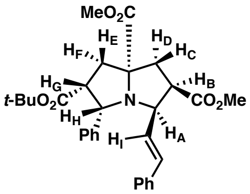
S5

J_{HA}=7.8
J_{HB}=7.5



18a

J_{HA}=7.7
J_{HB}=7.5

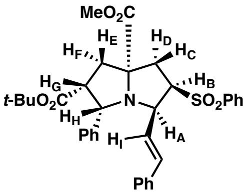


19a

	J (Hz)
H_A	7.8
H_B	7.8
H_B	11.8
H_C	11.8
H_B	6.6
H_D	6.6

NOEs

H_AH_B
H_CH_E
H_EH_G
H_GH_H
H_BH_D
H_IH_H
H_IH_C
no H_IH_B

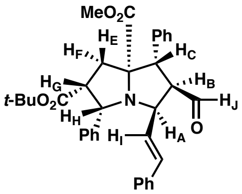


19b

	J (Hz)
H_A	7.0
H_B	6.6
H_B	12.1
H_C	12.0
H_B	6.6
H_D	6.4

NOEs

H_AH_B
H_CH_E
H_EH_G
H_GH_H
H_BH_D
H_IH_H
H_IH_C
no H_IH_B

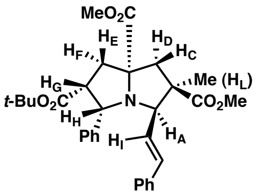


19c

	J (Hz)
H_A	8.1
H_B	8.1
H_B	12.0
H_C	12.0
H_B	1.8
H_D	1.8

NOEs

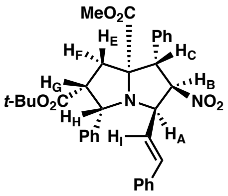
H_AH_B
H_CH_E
H_EH_G
H_GH_H
H_IH_H
H_IH_C
no H_IH_B



19d

NOEs

H_AH_L
H_DH_L
H_EH_C
H_EH_G
H_GH_H
H_IH_H

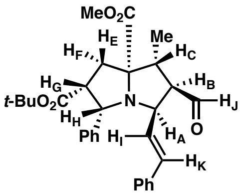


19e

	J (Hz)
H_A	8.0
H_B	8.0
H_B	11.1
H_C	11.1

NOEs

H_AH_B
H_CH_E
H_EH_G
H_GH_H
H_IH_H
H_IH_C
H_HH_C
H_HH_E



19f

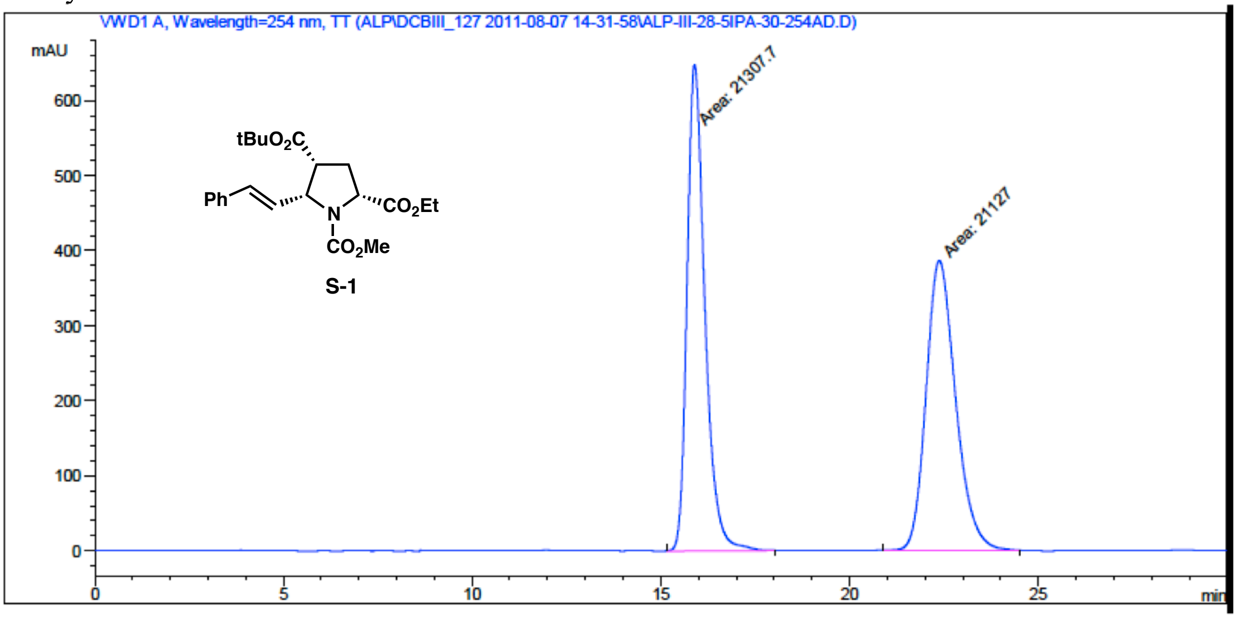
	J (Hz)
H_A	8.2
H_B	8.2
H_B	11.7
H_C	11.8
H_B	1.6
H_J	1.6

NOEs

H_AH_B
H_CH_E
H_EH_G
H_GH_H
H_IH_H
H_KH_C
H_IH_C
no H_IH_B

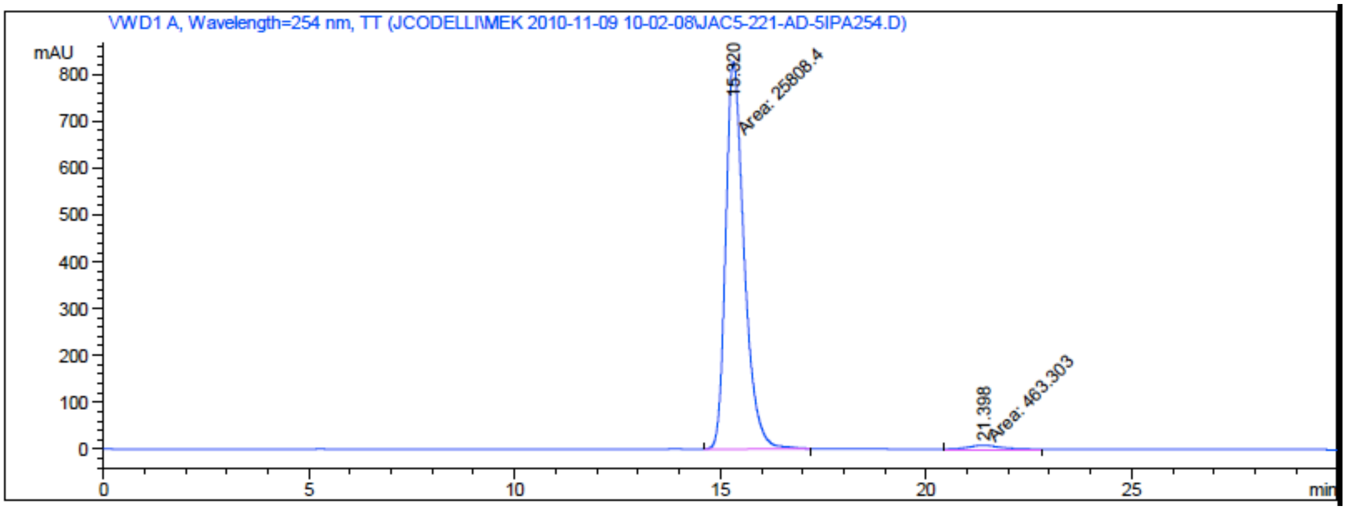
8. SFC/HPLC traces of racemic and enantioenriched products.

Methyl carbamate **S1**: racemic



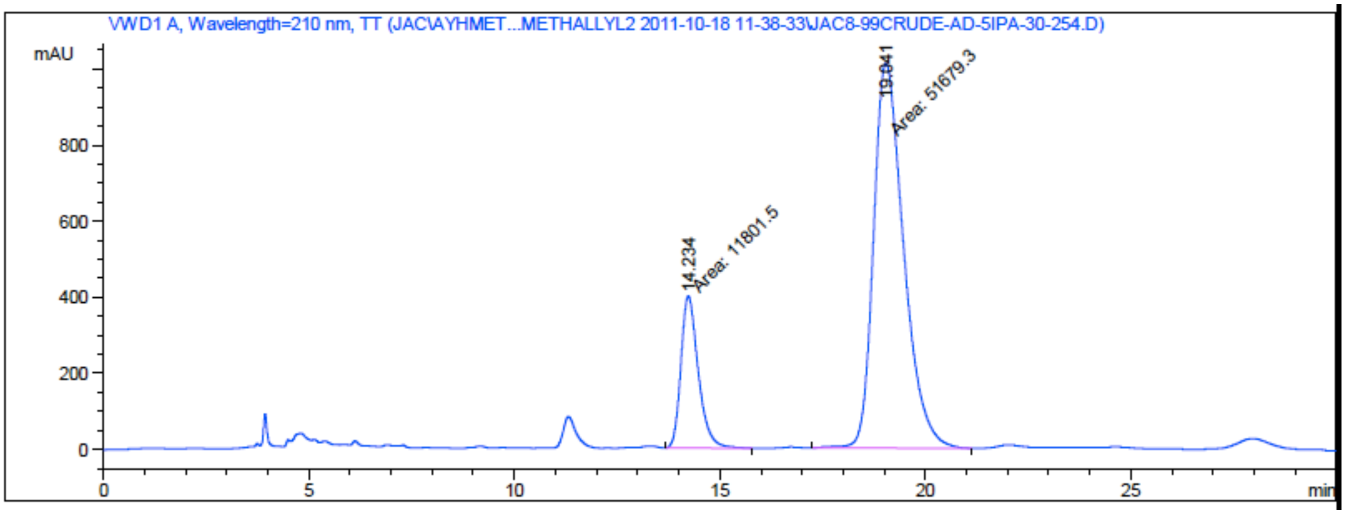
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  15.894 MM     0.5477 2.13077e4  648.35150  50.2129
   2  22.377 MM     0.9097 2.11270e4  387.07867  49.7871
```

Table S1, entry 1: enantioenriched, 96% ee



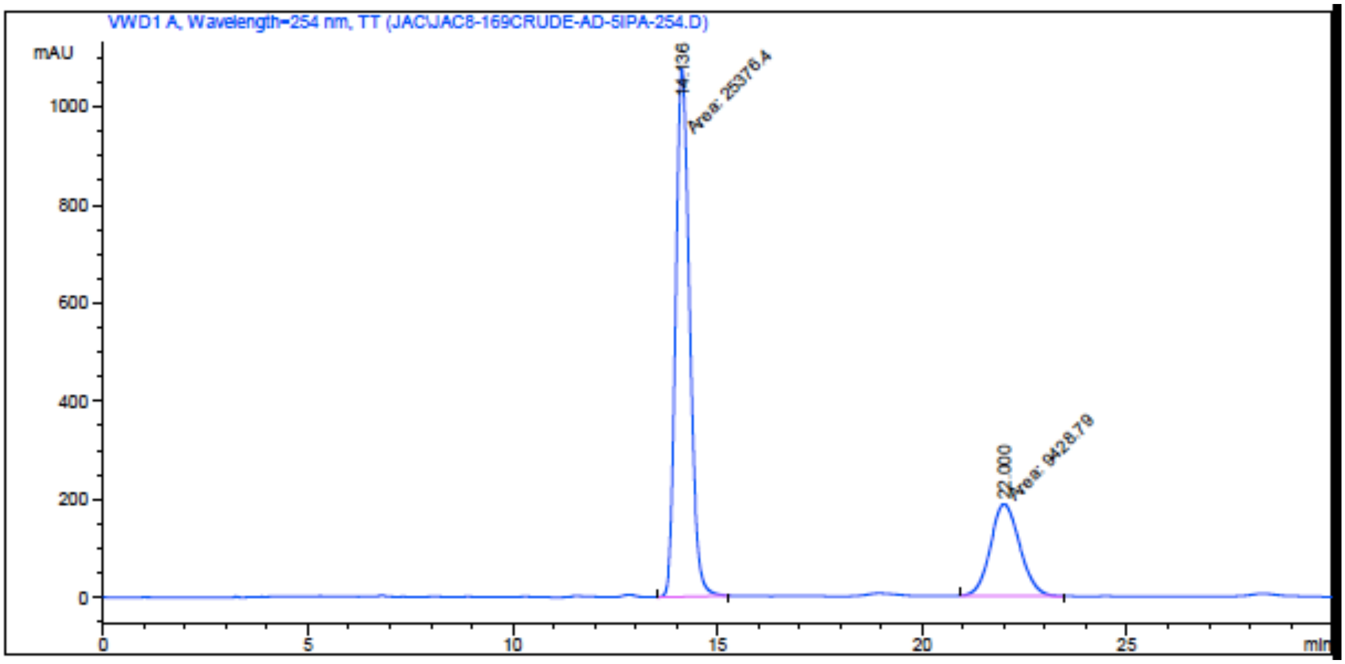
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
  1  15.320 MM    0.5202 2.58084e4   826.91376  98.2365
  2  21.398 MM    0.9279  463.30341    8.32209   1.7635
```

Table S1, entry 2: enantioenriched, 63% ee



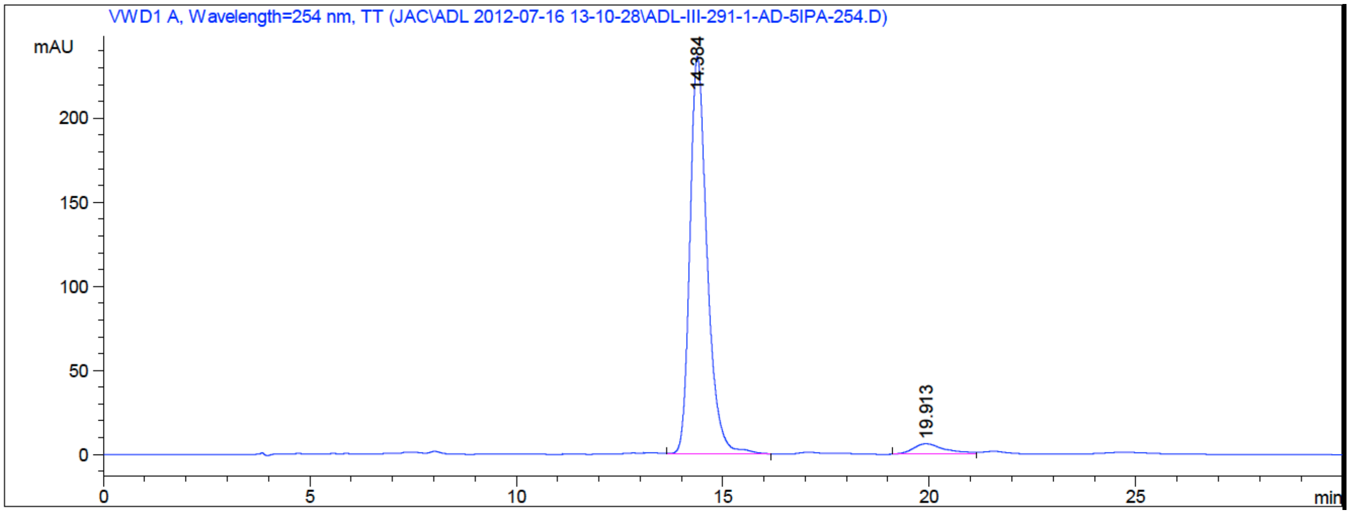
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
  1  14.234 MM    0.4913 1.18015e4  400.33957  18.5907
  2  19.041 MM    0.8507 5.16792e4 1012.46924  81.4093
```

Table S1, entry 3: enantioenriched, 46% ee



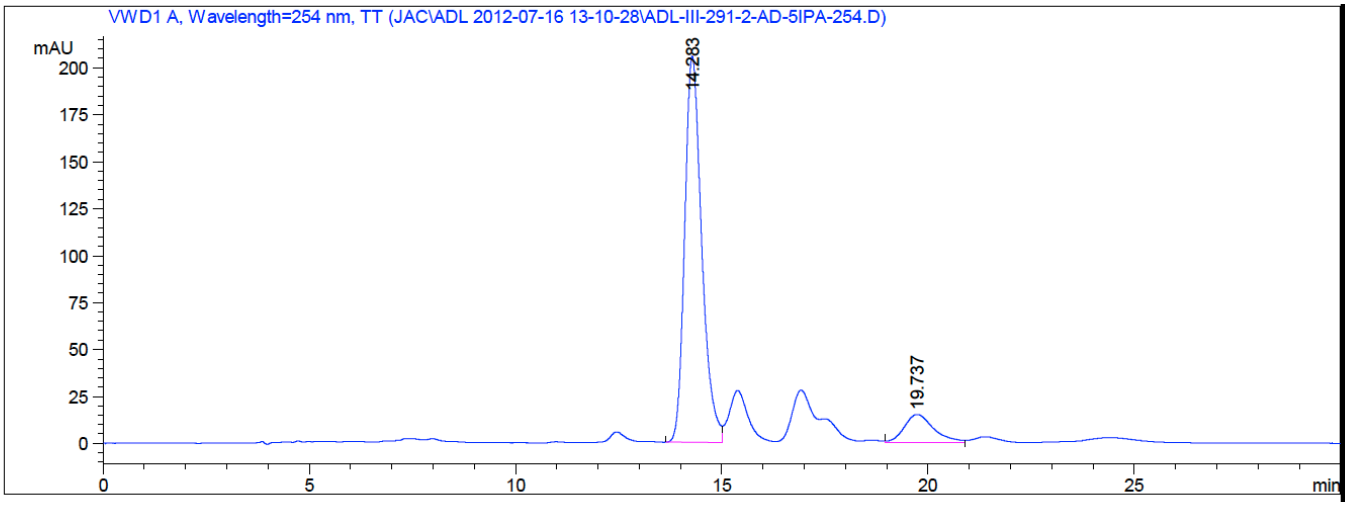
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
  1  14.136 MM    0.3931 2.53764e4 1075.82861  72.9098
  2  22.000 MM    0.8369 9428.79492  187.78340  27.0902
```

Table S1, entry 4: enantrioenriched, 90% ee



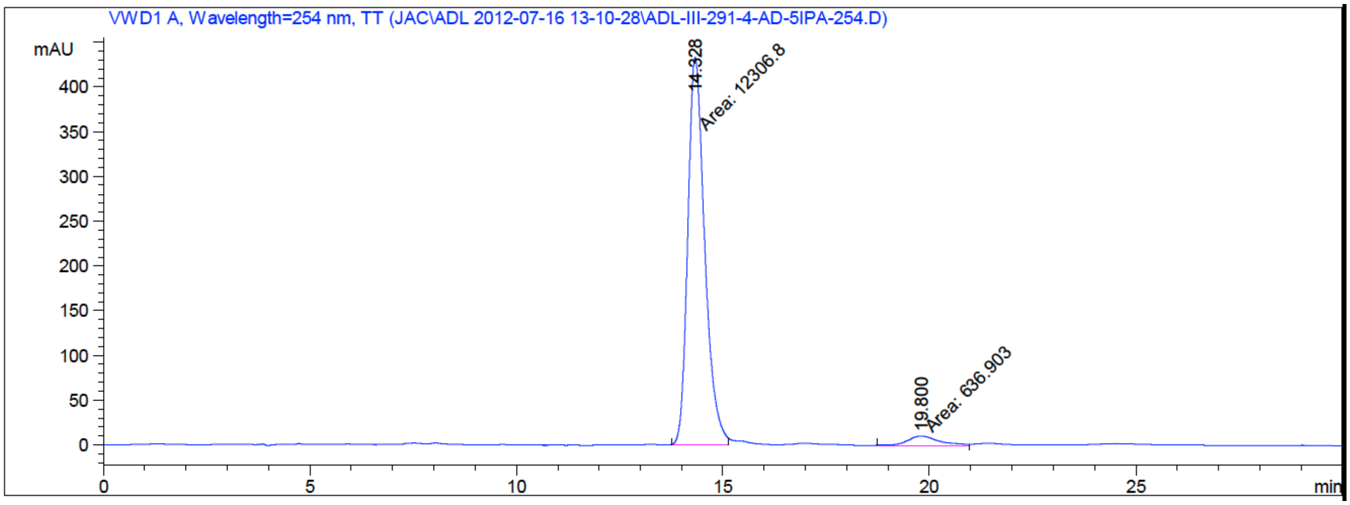
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s    [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
   1  14.384 VB    0.4361 6863.74121  236.53506  95.3206
   2  19.913 BV    0.6398  336.95078    6.23651   4.6794
```

Table S1, entry 5: enantrioenriched, 78% ee



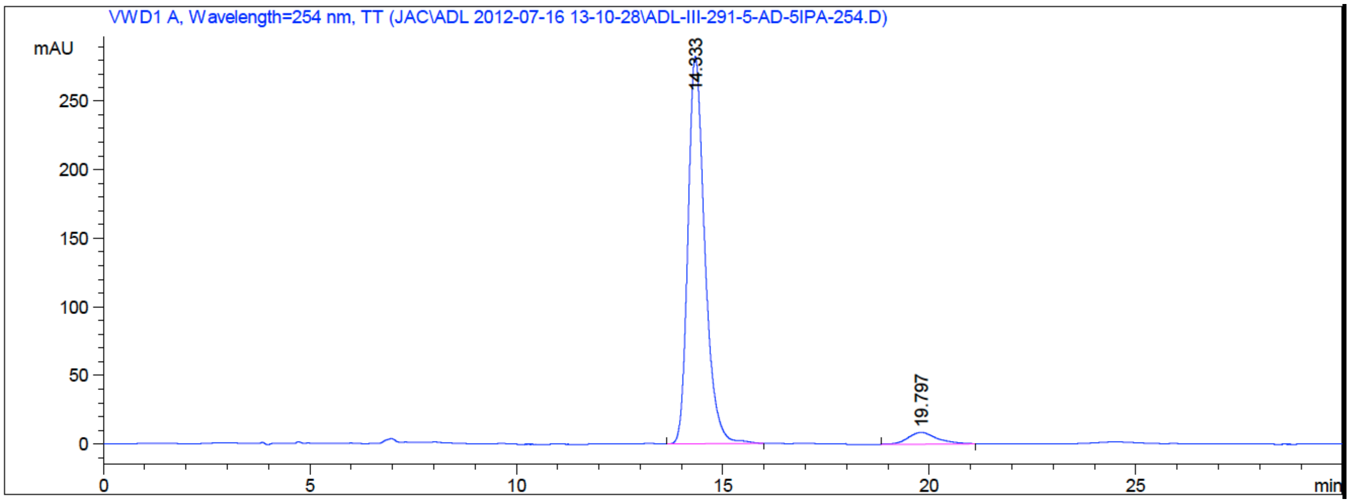
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s    [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
   1  14.283 BV    0.4353 5902.47510  205.65765  88.6961
   2  19.737 VV    0.6069  752.24481   14.98246  11.3039
```

Table S1, entry 7: enantrioenriched, 90% ee



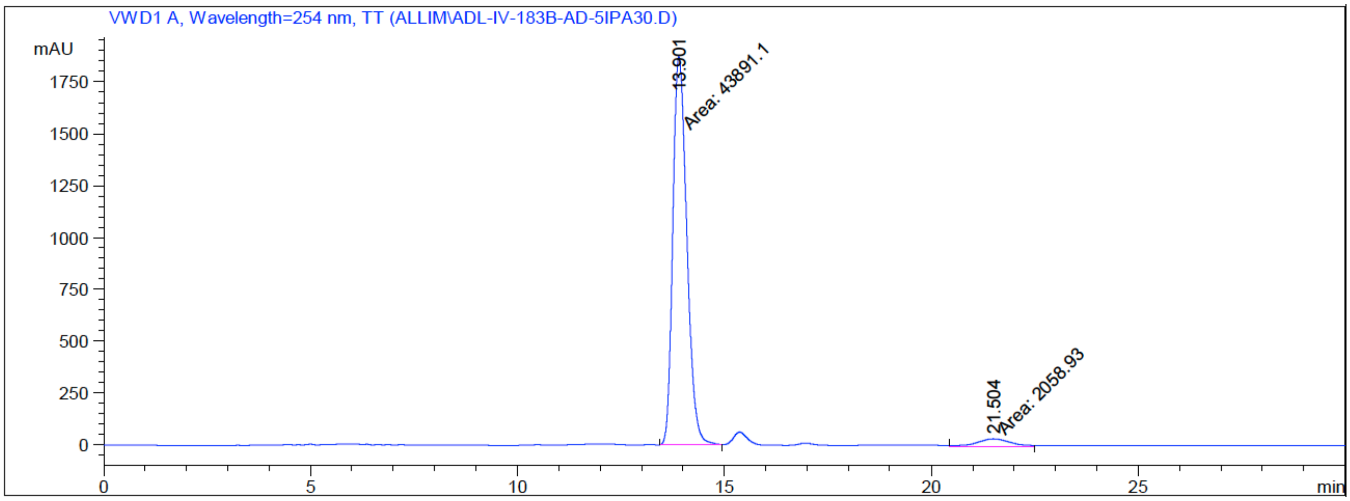
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s    [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1  14.328 MM     0.4745 1.23068e4   432.23904  95.0795
   2  19.800 MM     0.9596  636.90289   11.06230   4.9205
```

Table S1, entry 8: enantrioenriched, 90% ee



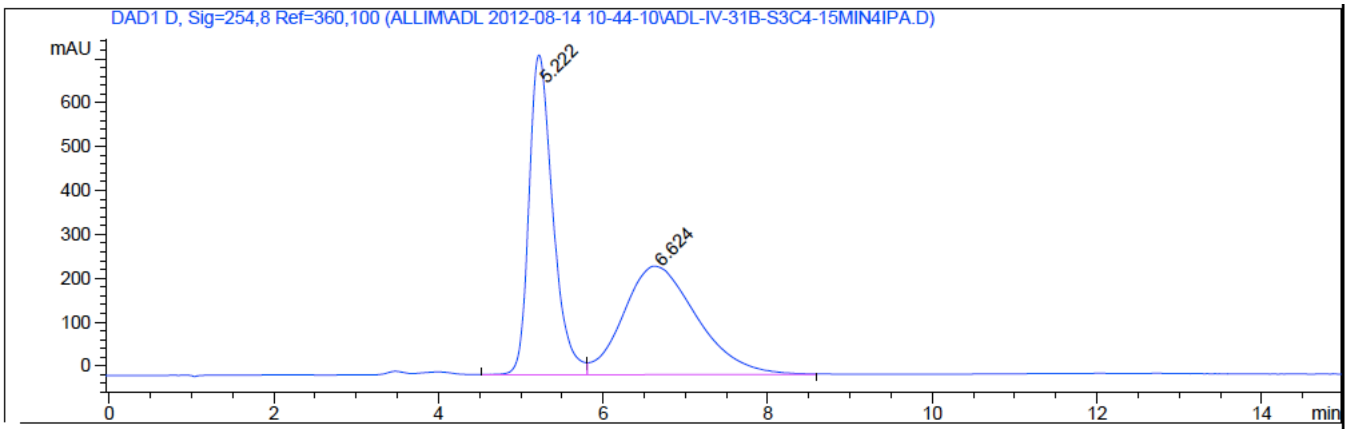
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s    [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1  14.333 VB     0.4292 8036.22461  282.65863  95.1434
   2  19.797 BB     0.5753  410.20886    8.45801   4.8566
```

Table S1, entry 9: enantrioenriched, 91% ee



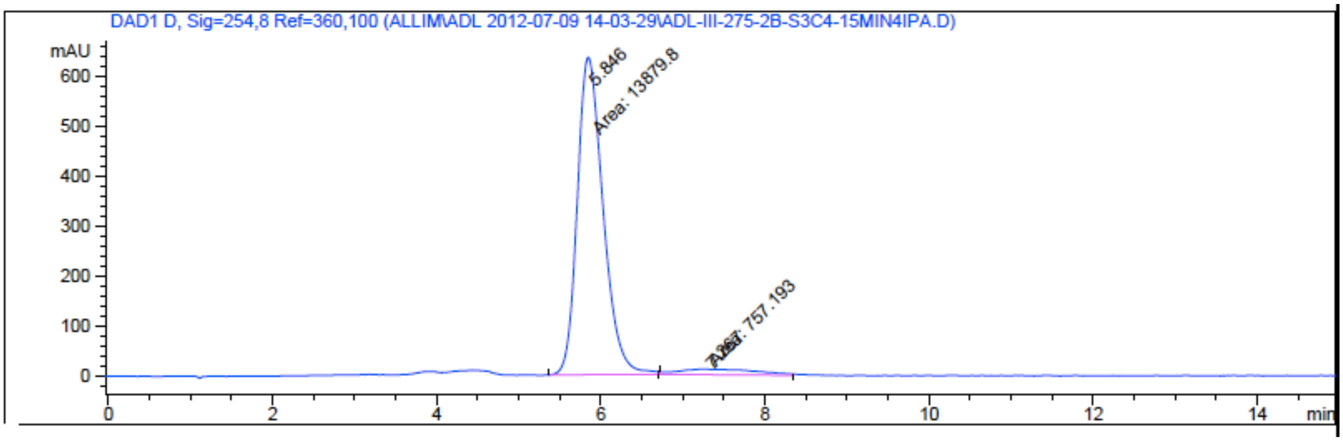
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU    ]      %
----|-------|----|-------|----------|----------|--------|
   1  13.901 MM    0.3918 4.38911e4 1867.15771  95.5192
   2  21.504 MM    0.9339 2058.93115  36.74272   4.4808
```

Pyrrolizidine 12: racemic



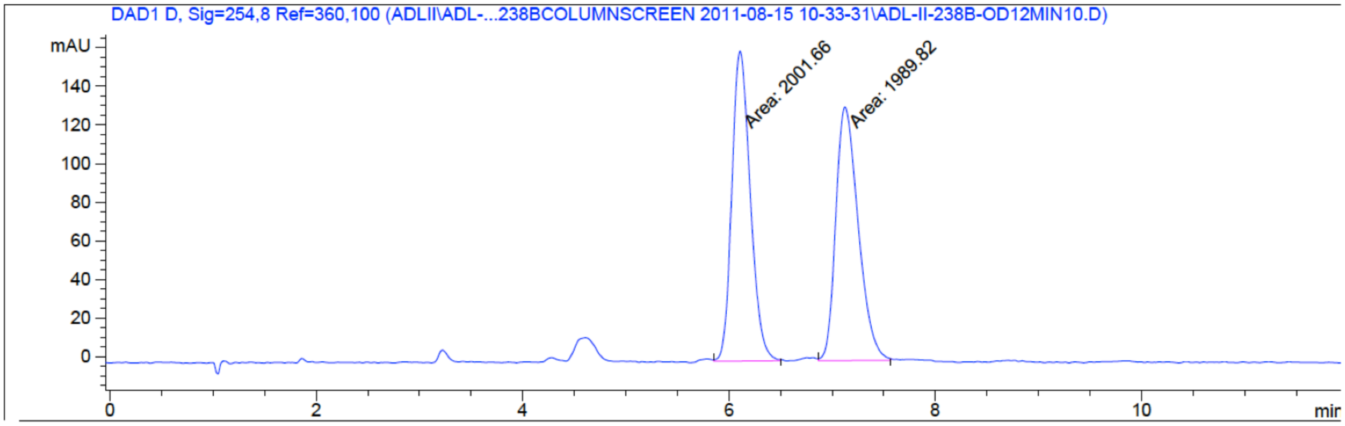
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.222 VV    0.3078 1.47293e4  728.71198  48.9407
   2   6.624 VB    0.9374 1.53668e4  247.16225  51.0593
```

Pyrrolizidine 12: enantioenriched, 90% ee



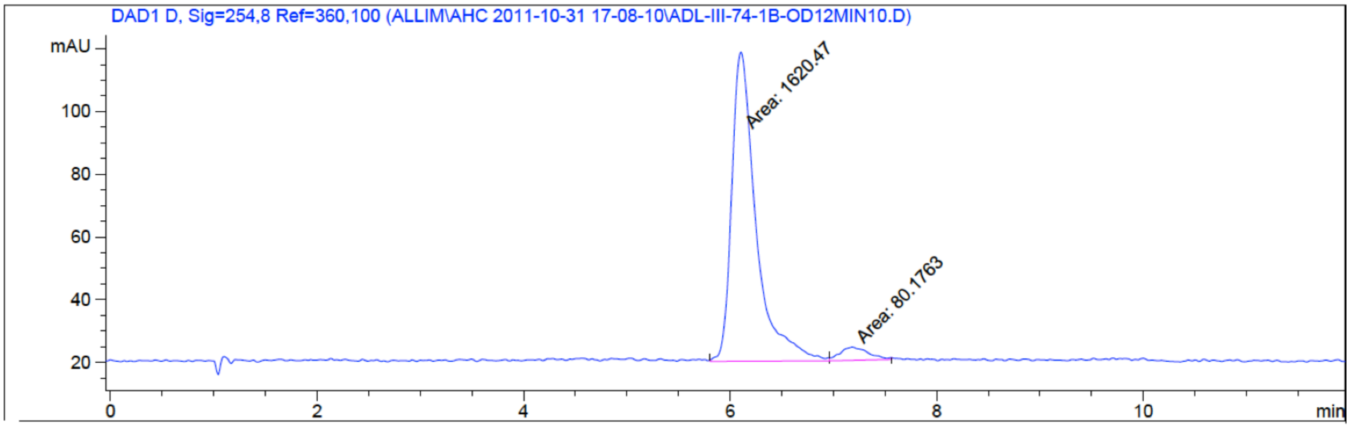
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.846 MM    0.3649 1.38798e4  633.94122  94.8269
   2   7.267 MM    1.1258  757.19305  11.20974   5.1731
```

18a (Table 2, entry 1): racemic



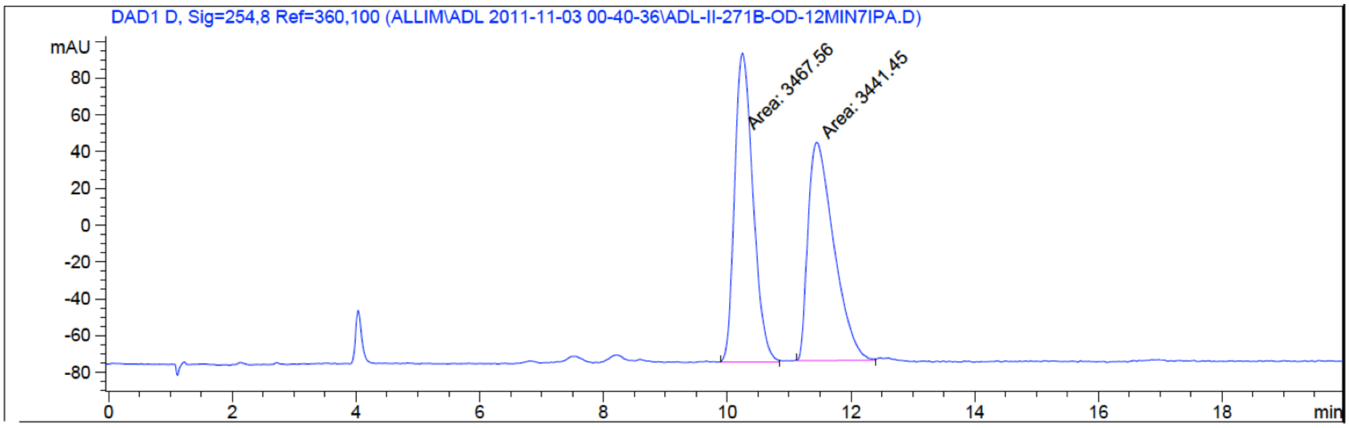
```
Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   6.108 MM    0.2078 2001.65894  160.51328  50.1483
   2   7.126 MM    0.2525 1989.82288  131.33904  49.8517
```

18a (Table 2, entry 1): enantioenriched, 91% ee



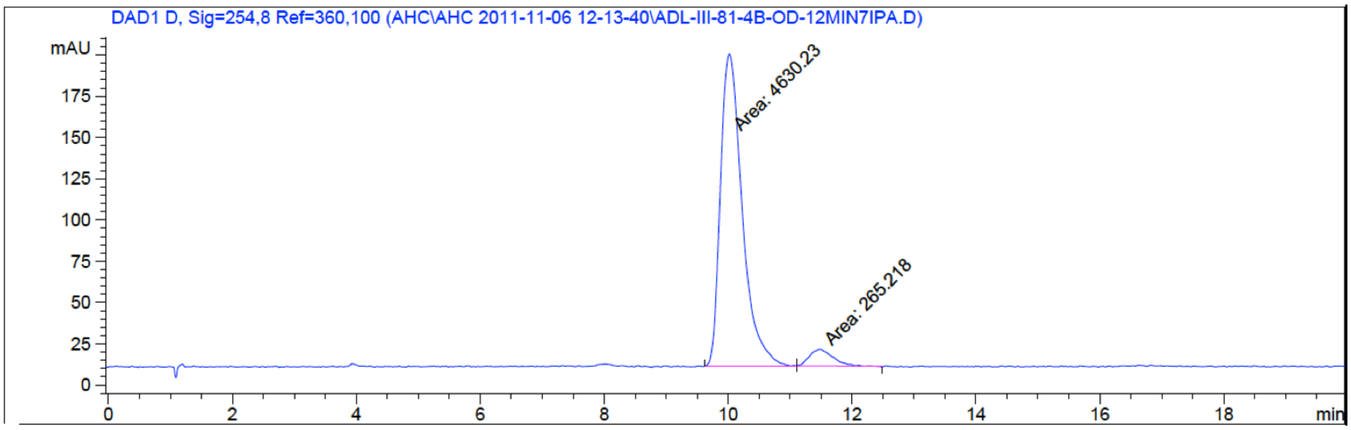
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.105 MM    0.2734 1620.47278   98.79230  95.2855
   2   7.181 MM    0.3144   80.17634    4.25047   4.7145
```

18b (Table 2, entry 2): racemic



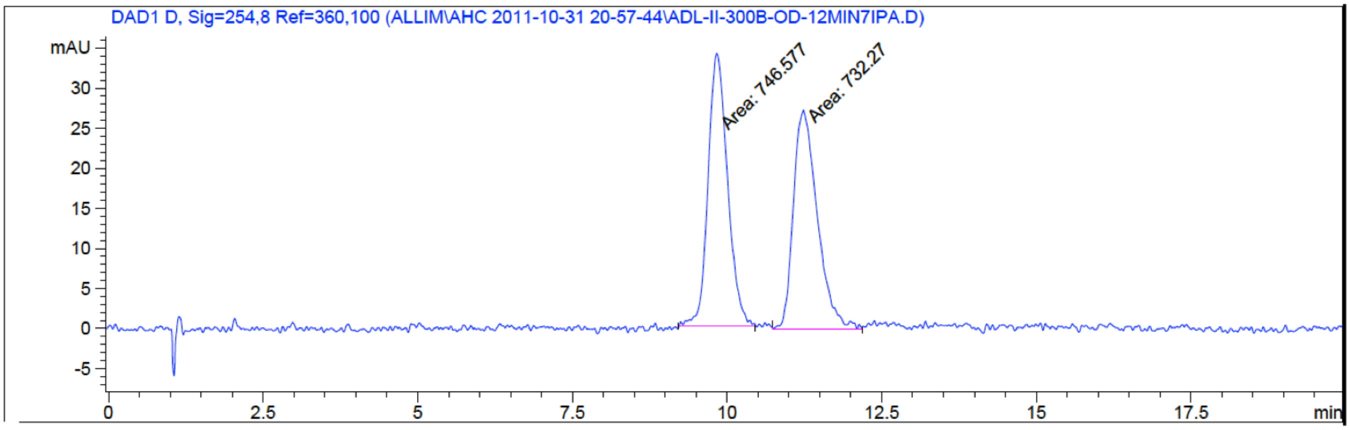
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.248 MM    0.3441 3467.56030  167.93707  50.1890
   2  11.449 MM    0.4829 3441.44751  118.78632  49.8110
```

18b (Table 2, entry 2): enantioenriched, 91% ee



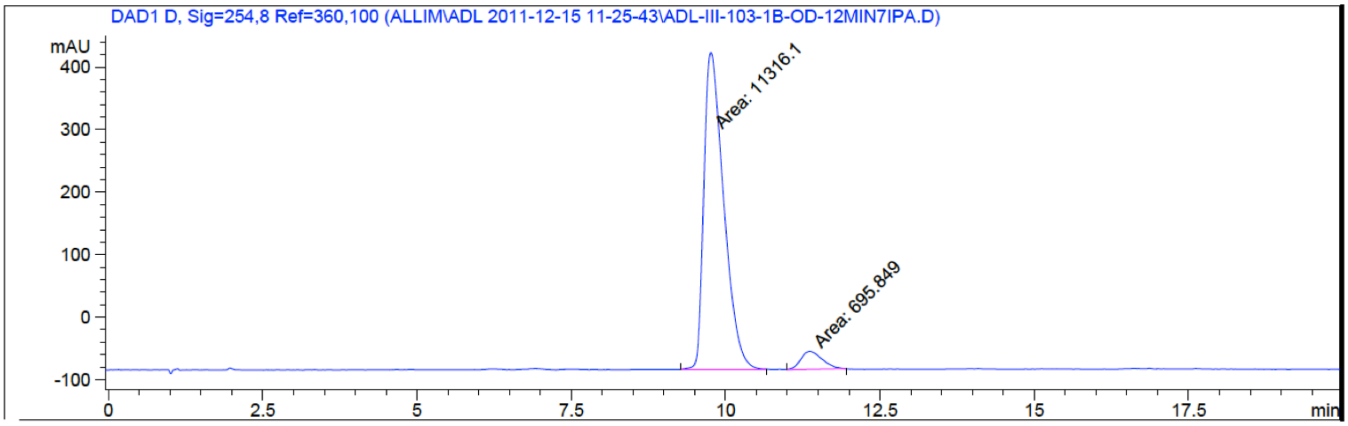
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.021 MM    0.4076 4630.22852  189.33492  94.5824
   2  11.489 MM    0.4401  265.21768   10.04365   5.4176
```

18c (Table 2, entry 3): racemic



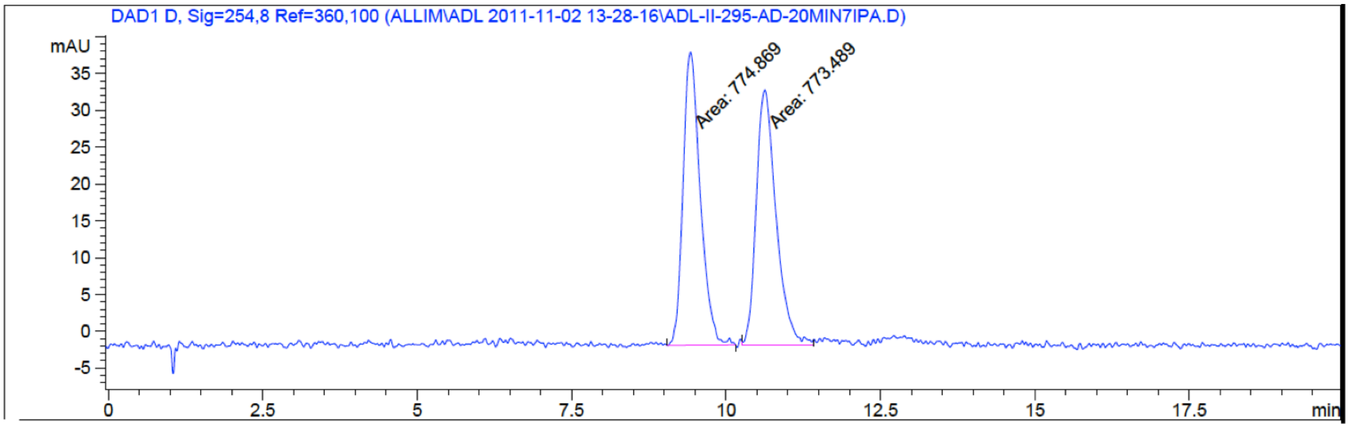
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   9.834 MM    0.3654  746.57739   34.05050  50.4837
   2  11.236 MM    0.4474  732.26959   27.27870  49.5163
```

18c (Table 2, entry 3): enantioenriched, 88% ee



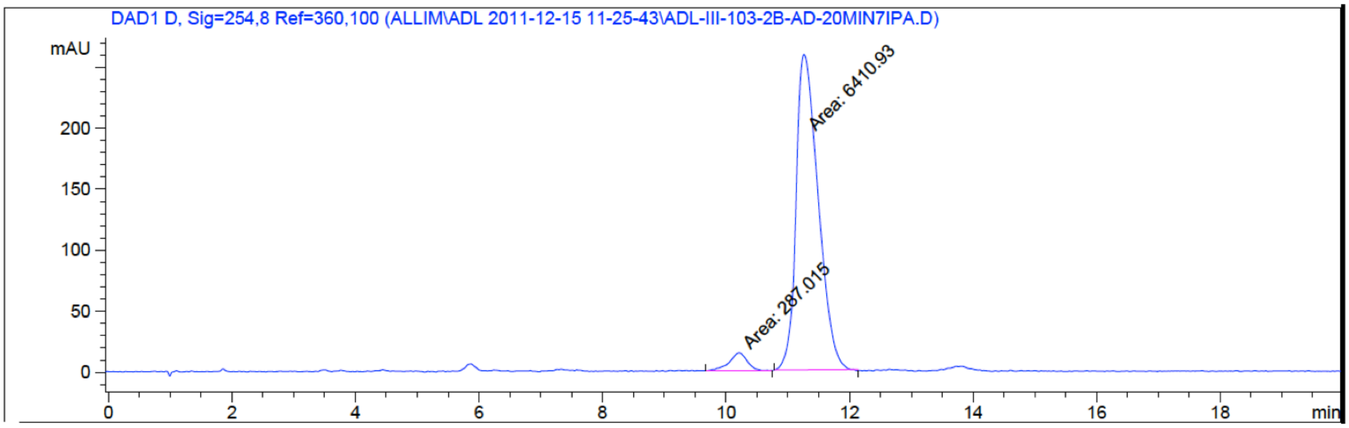
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   9.762 MM    0.3720 1.13161e4   507.00854  94.2070
   2  11.367 MM    0.4038  695.84937   28.72410   5.7930
```

18d (Table 2, entry 4): racemic



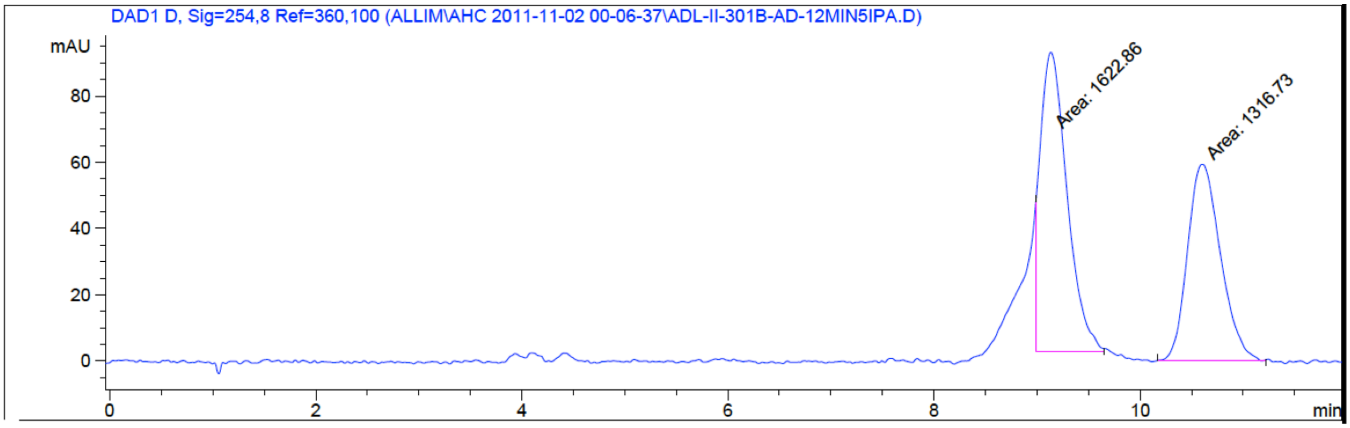
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1    9.424 MM    0.3245  774.86896   39.79745  50.0446
  2   10.628 MM    0.3721  773.48914   34.64676  49.9554
```

18d (Table 2, entry 4): enantioenriched, 92% ee



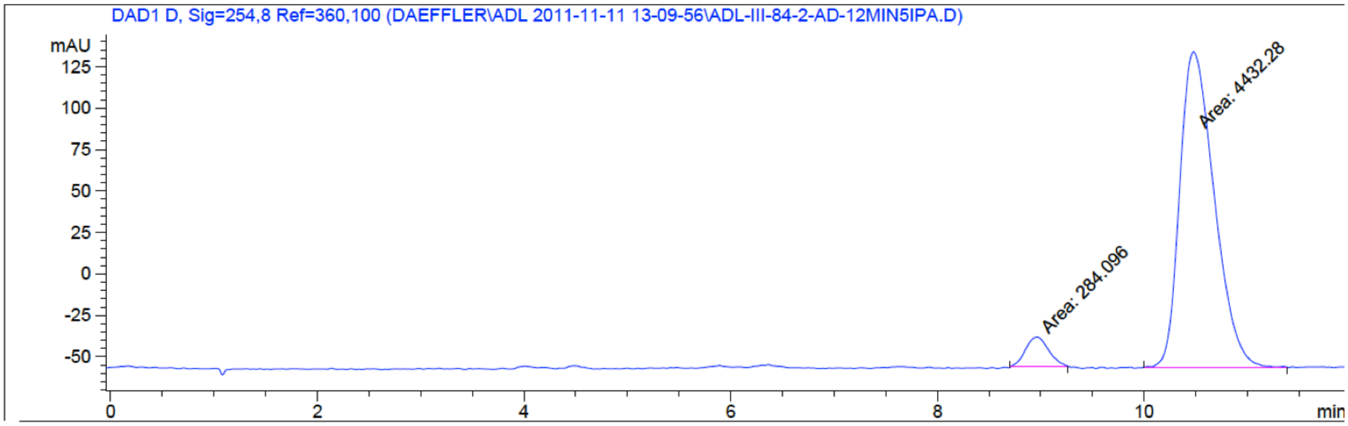
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   10.212 MM    0.3282  287.01508   14.57303   4.2851
  2   11.264 MM    0.4134 6410.92969  258.47113  95.7149
```

18e (Table 2, entry 5): racemic



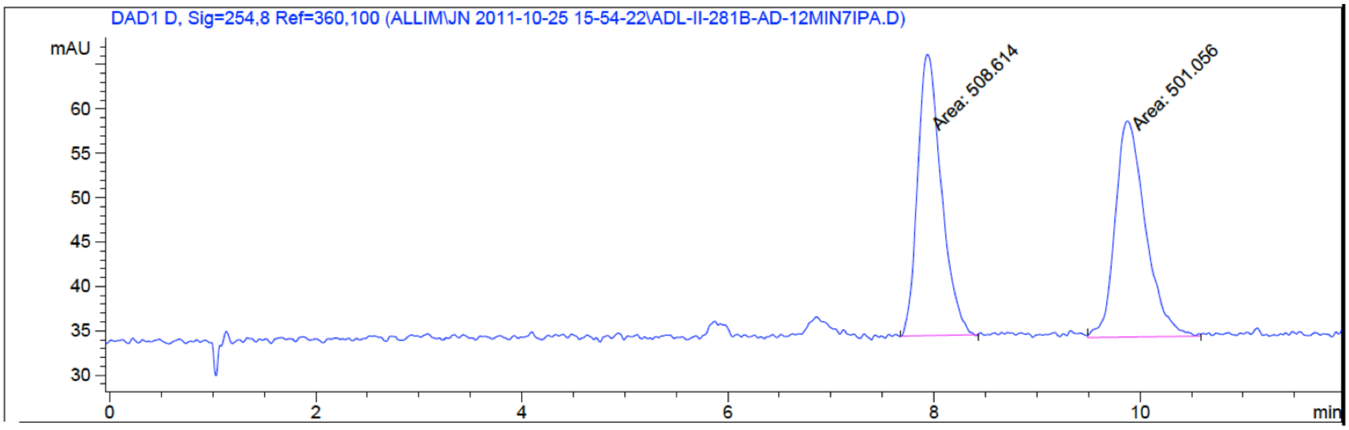
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   9.136 MM    0.2995 1622.86243   90.31247  55.2070
   2  10.604 MM    0.3699 1316.73352   59.32040  44.7930
```

18e (Table 2, entry 5): enantioenriched, 88% ee



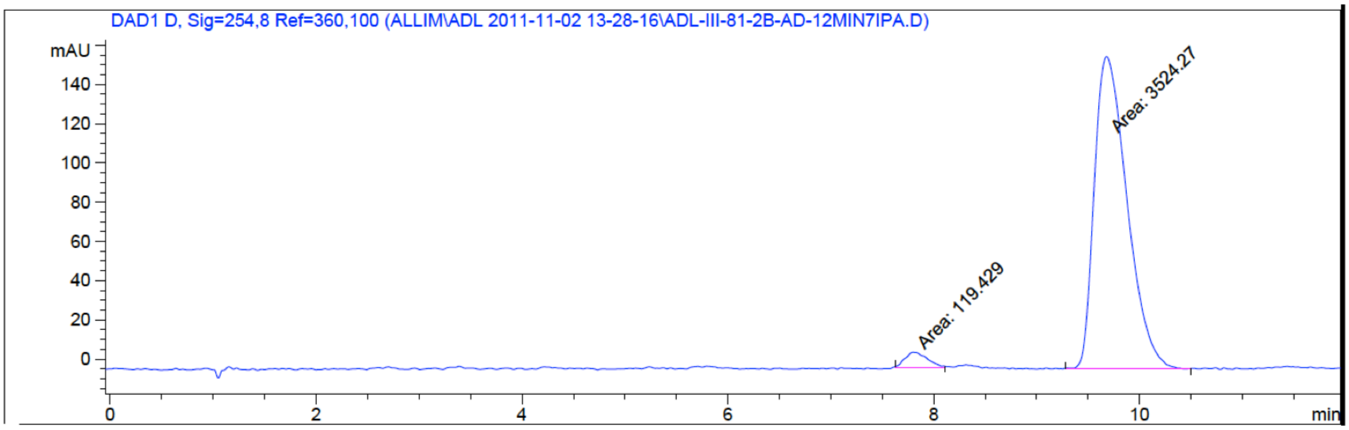
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   8.965 MM    0.2622  284.09586   18.05857   6.0236
   2  10.478 MM    0.3875 4432.28174  190.62163  93.9764
```

18f (Table 2, entry 6): racemic



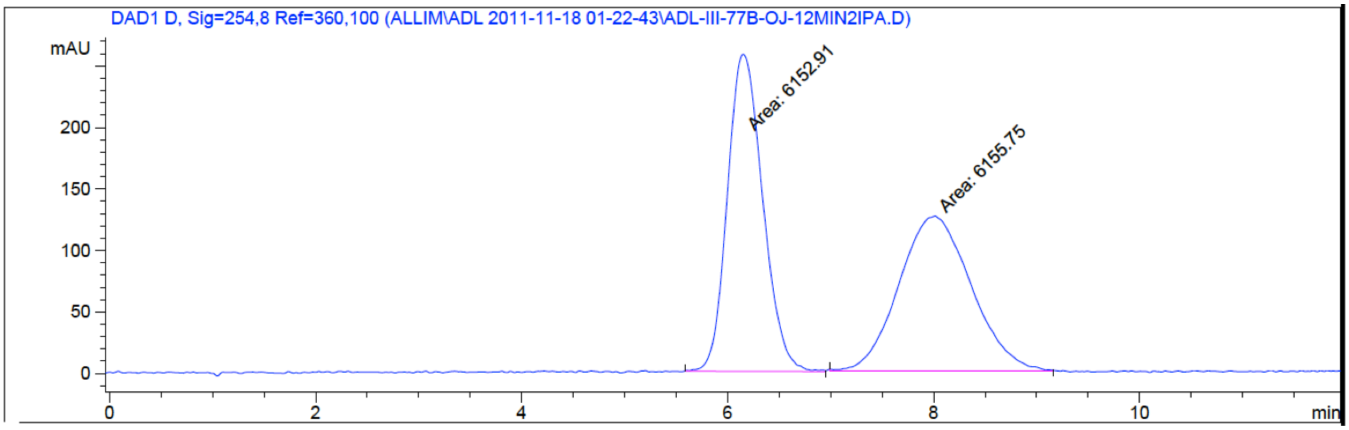
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]         [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.939 MM    0.2672  508.61426   31.72702  50.3743
   2   9.879 MM    0.3428  501.05600   24.35941  49.6257
```

18f (Table 2, entry 6): enantioenriched, 93% ee



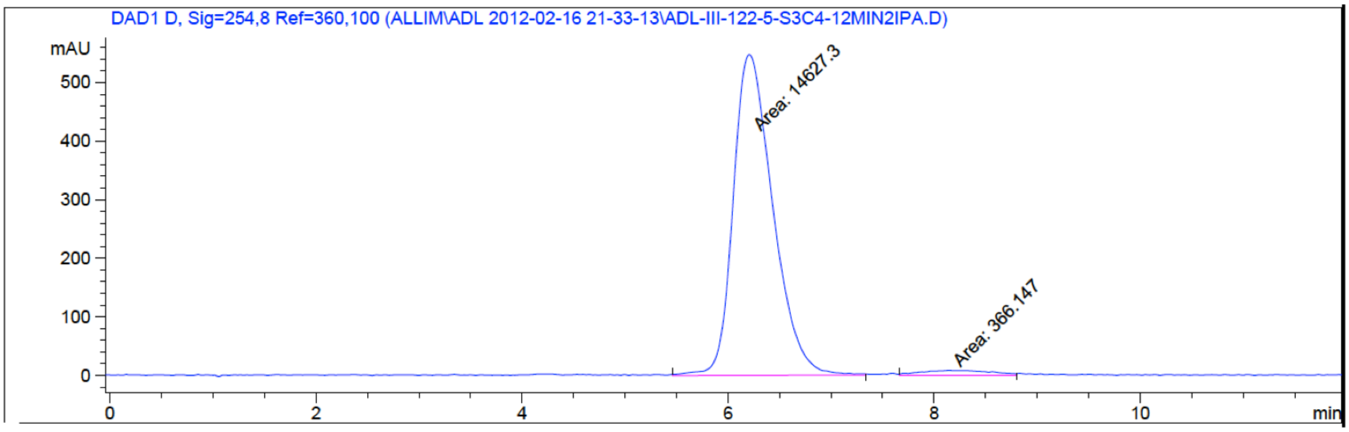
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]         [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.801 MM    0.2545  119.42921    7.82248   3.2777
   2   9.680 MM    0.3688 3524.26855  159.27747  96.7223
```

18g (Table 2, entry 7): racemic



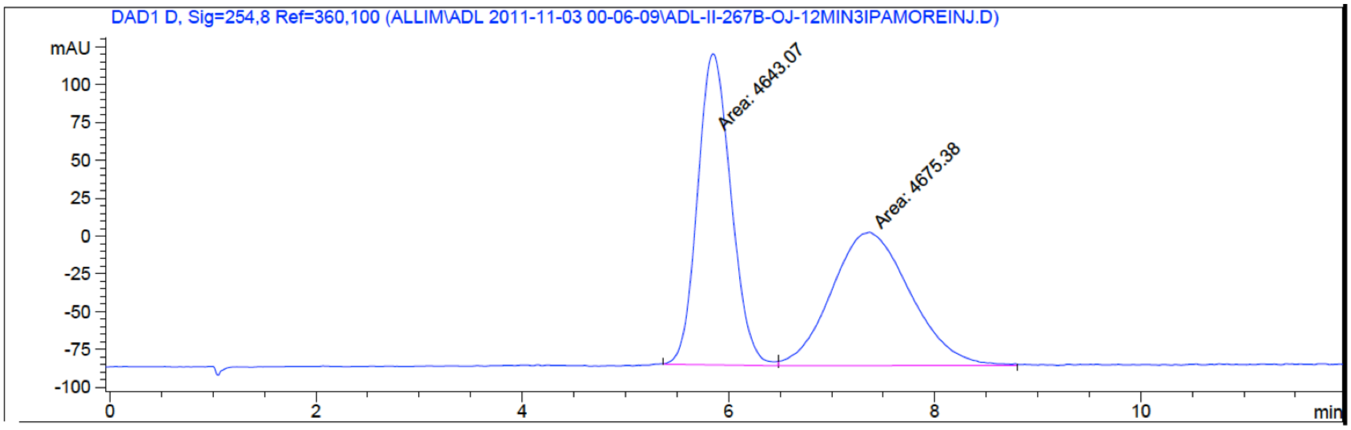
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   6.153 MM    0.3977 6152.91113  257.88422  49.9885
  2   8.012 MM    0.8130 6155.75195  126.18888  50.0115
```

18g (Table 2, entry 7): enantioenriched, 95% ee



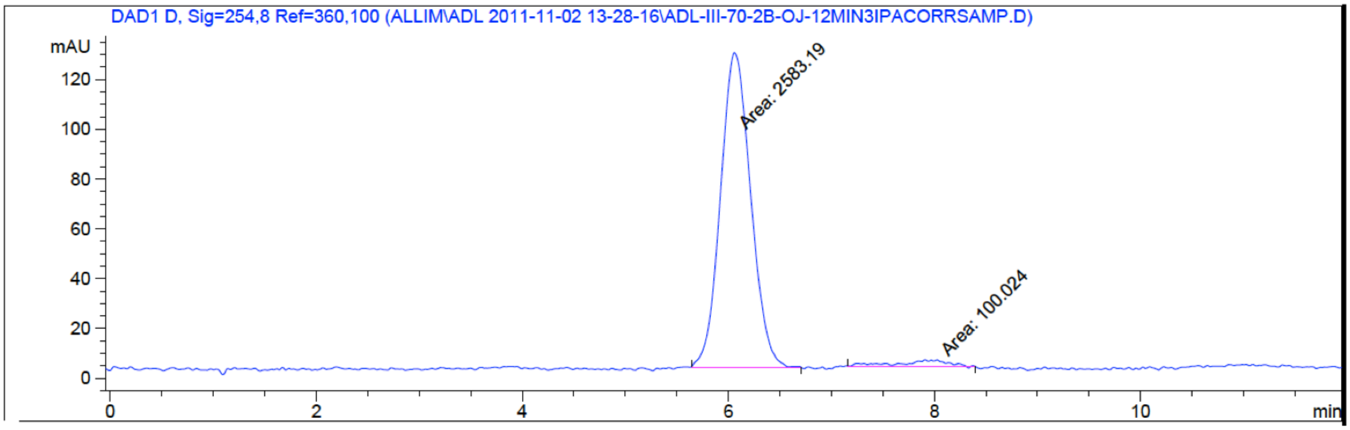
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   6.205 MM    0.4450 1.46273e4   547.89642  97.5580
  2   8.144 MM    0.7646  366.14673    7.98159   2.4420
```

18h (Table 2, entry 8): racemic



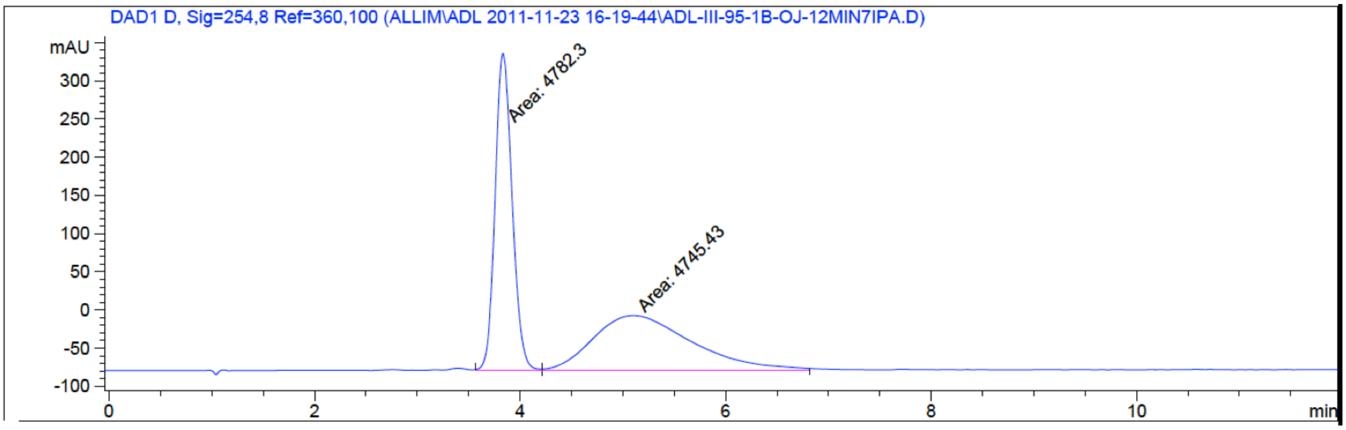
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   5.851 MM    0.3763 4643.07080  205.62646  49.8266
  2   7.368 MM    0.8845 4675.37891   88.09424  50.1734
```

18h (Table 2, entry 8): enantioenriched, 92% ee



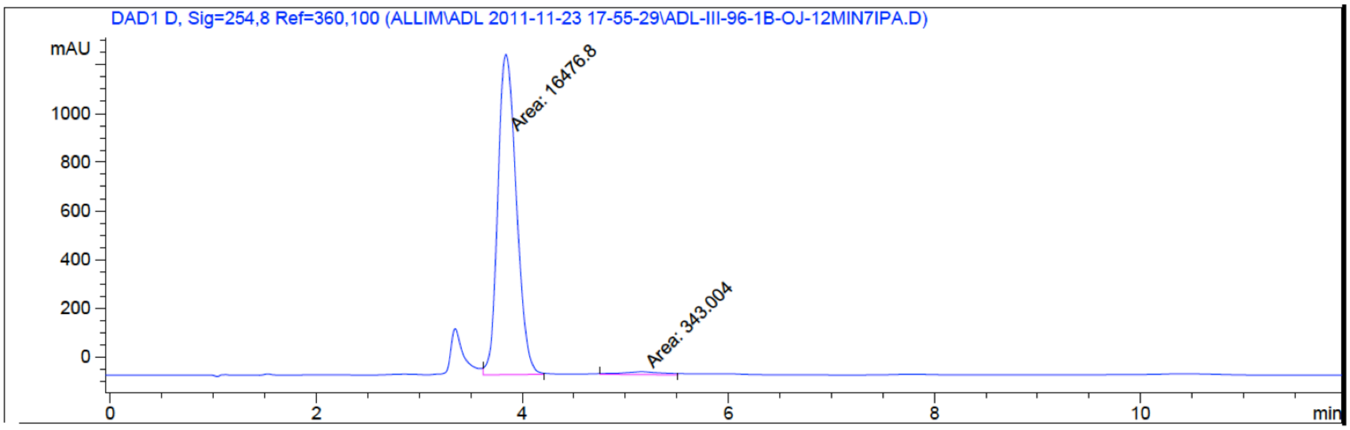
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   6.060 MM    0.3404 2583.18530  126.47279  96.2722
  2   8.025 MM    0.5850  100.02399    2.84972   3.7278
```

18i (Table 2, entry 9): racemic



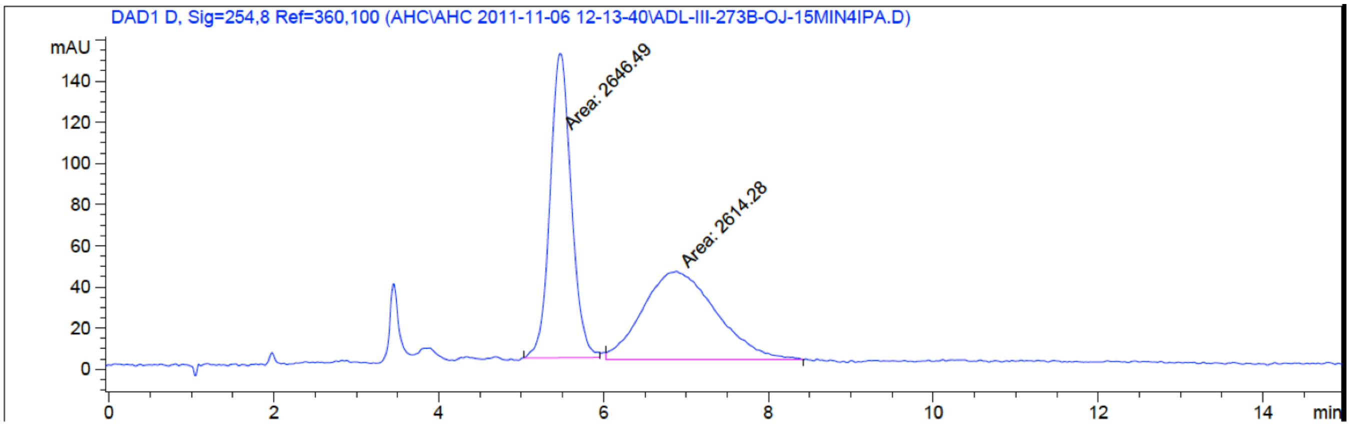
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1    3.834 MM    0.1917 4782.29639  415.74722  50.1935
  2    5.104 MM    1.1066 4745.43164   71.46948  49.8065
```

18i (Table 2, entry 9): enantioenriched, 96% ee



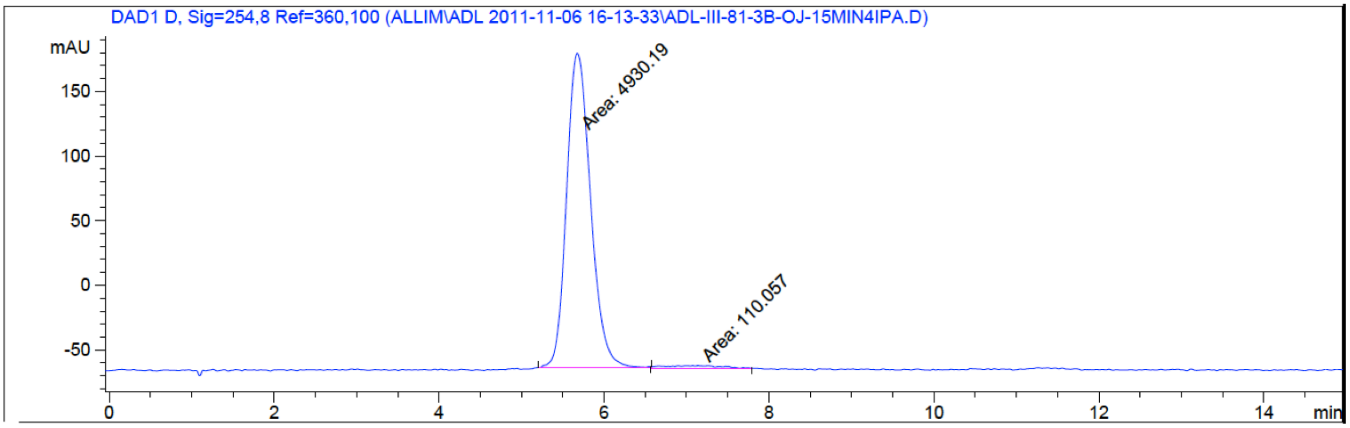
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1    3.840 MM    0.2084 1.64768e4 1317.58875  97.9607
  2    5.158 MM    0.4531  343.00388   12.61787   2.0393
```

18j (Table 2, entry 10): racemic



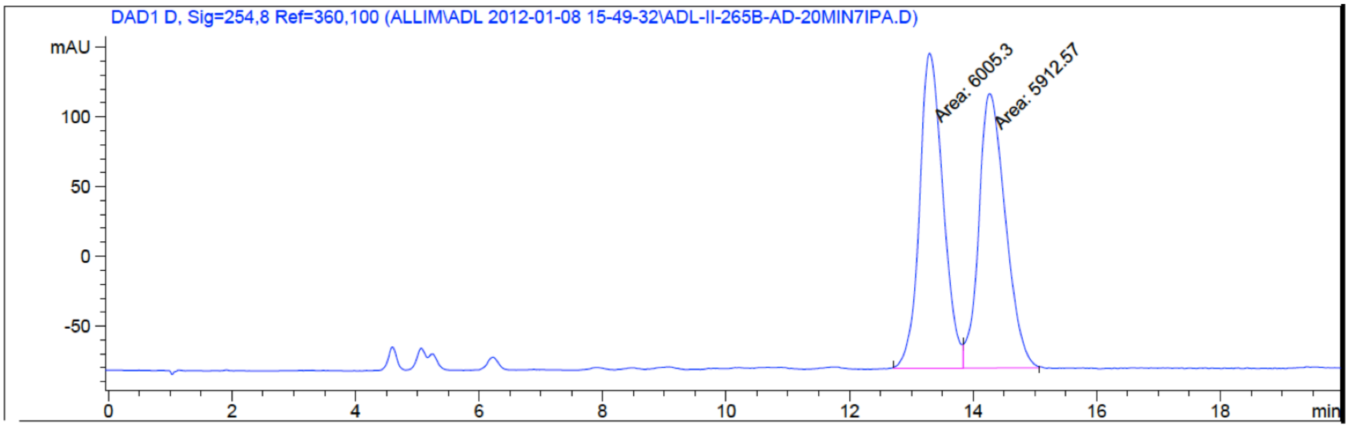
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.472 MM    0.2981 2646.49268  147.98149  50.3062
   2   6.882 MM    1.0248 2614.28003   42.51883  49.6938
```

18j (Table 2, entry 10): enantioenriched, 96% ee



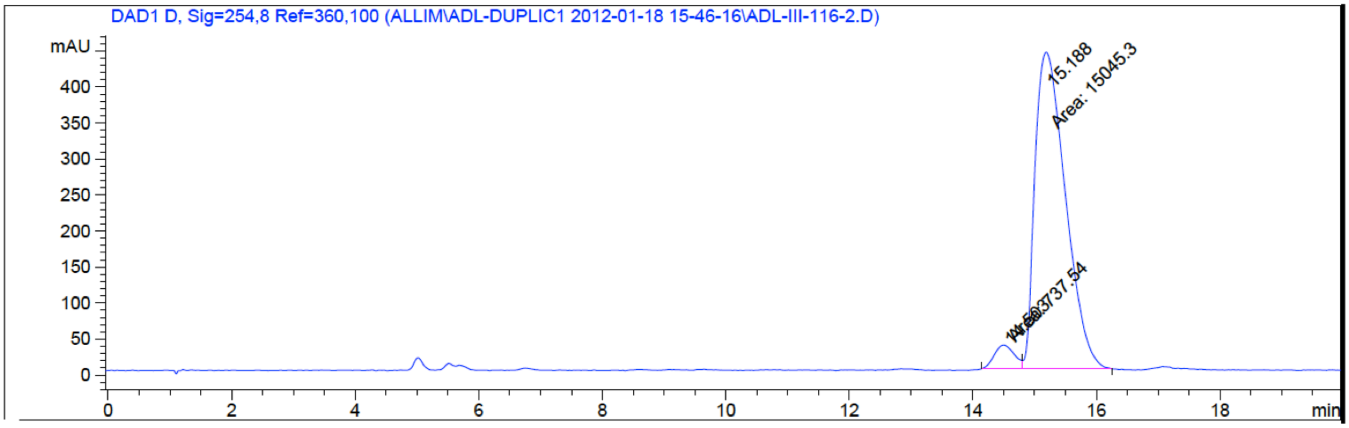
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.677 MM    0.3374 4930.19434  243.51300  97.8164
   2   7.139 MM    0.8023  110.05745    2.28640   2.1836
```

18k (Table 2, entry 11): racemic



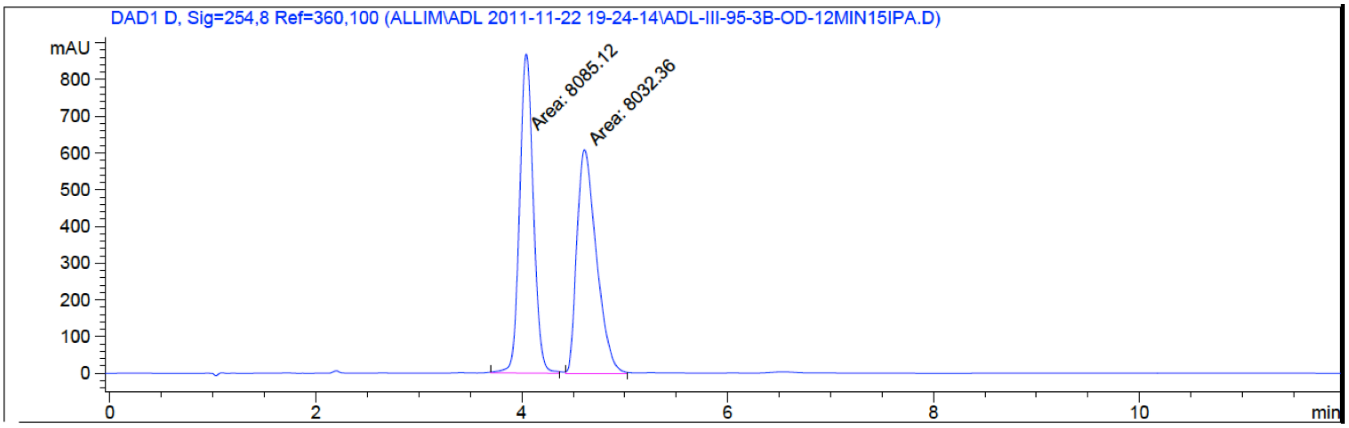
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  13.296 MM    0.4428 6005.30225  226.05704  50.3891
   2  14.269 MM    0.5006 5912.56543  196.85155  49.6109
```

18k (Table 2, entry 11): enantioenriched, 90% ee



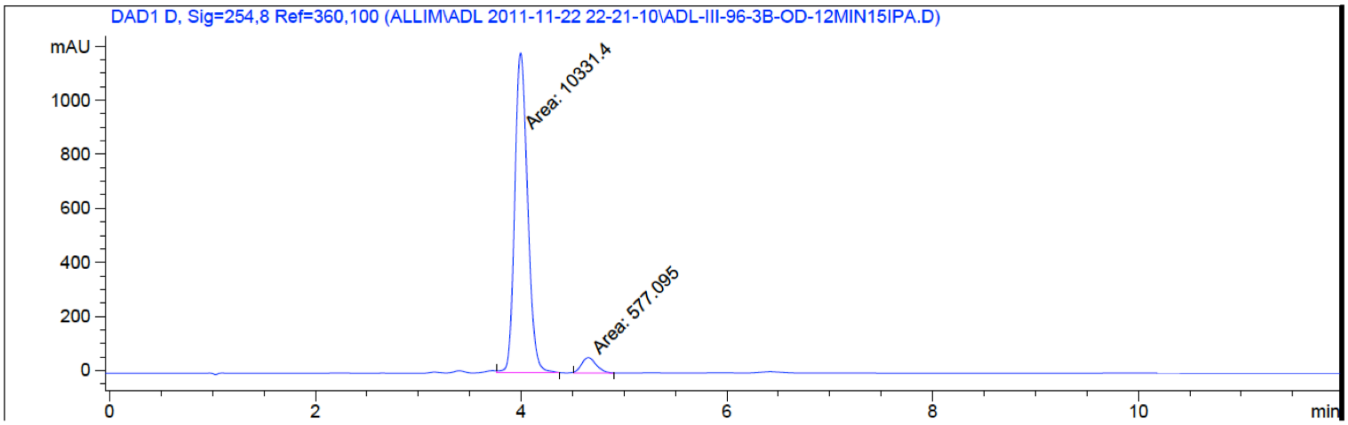
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  14.503 MM    0.3753  737.53986   32.75238   4.6730
   2  15.188 MM    0.5713 1.50453e4   438.93250  95.3270
```

18l (Table 2, entry 12): racemic



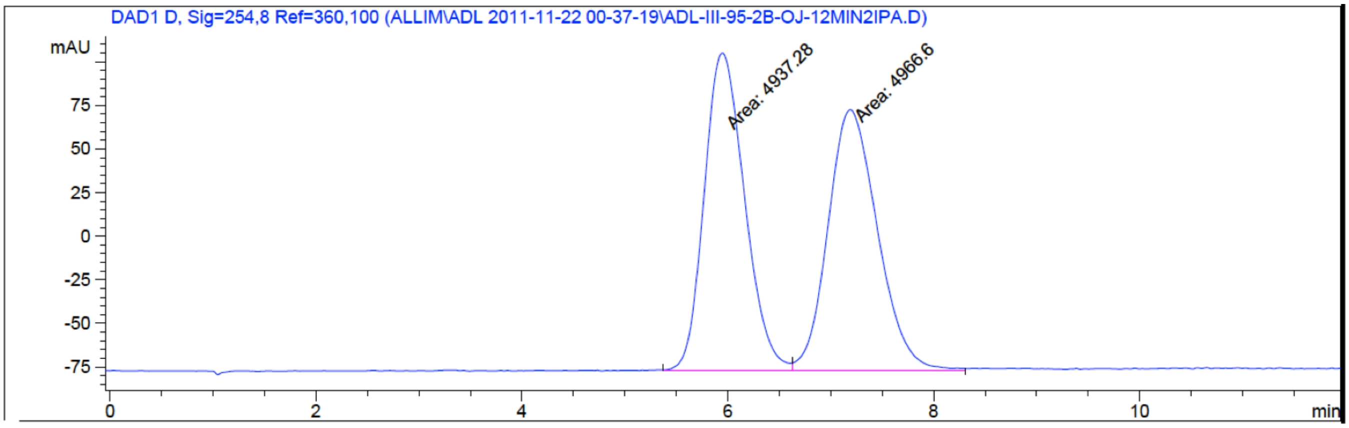
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.043 MM     0.1548 8085.12256  870.35547  50.1637
   2   4.610 MM     0.2194 8032.36475  610.30841  49.8363
```

18l (Table 2, entry 12): enantioenriched, 90% ee



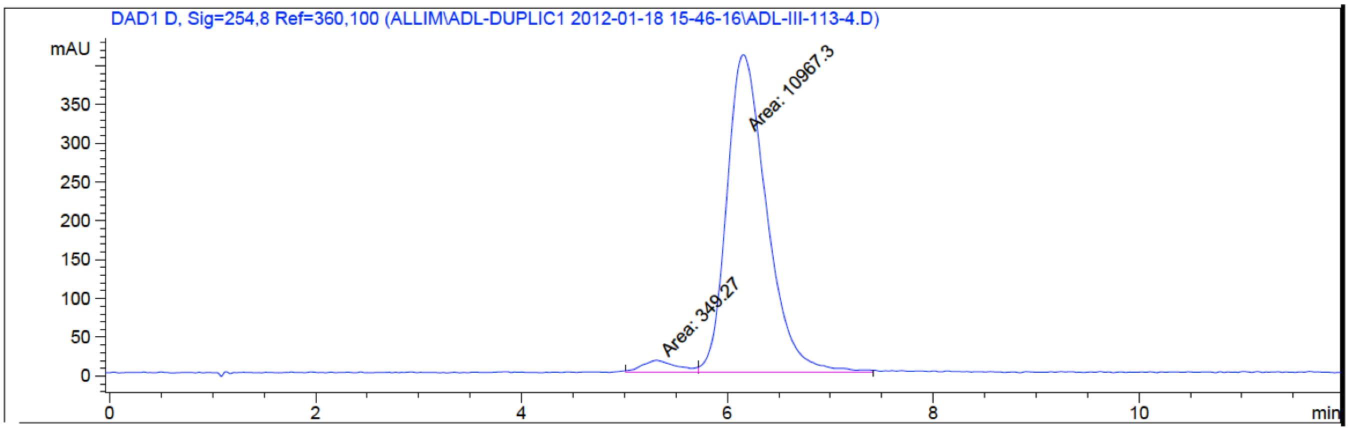
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   3.996 MM     0.1450 1.03314e4 1187.44409  94.7097
   2   4.652 MM     0.1678  577.09467   57.32602   5.2903
```

18m (Table 2, entry 13): racemic



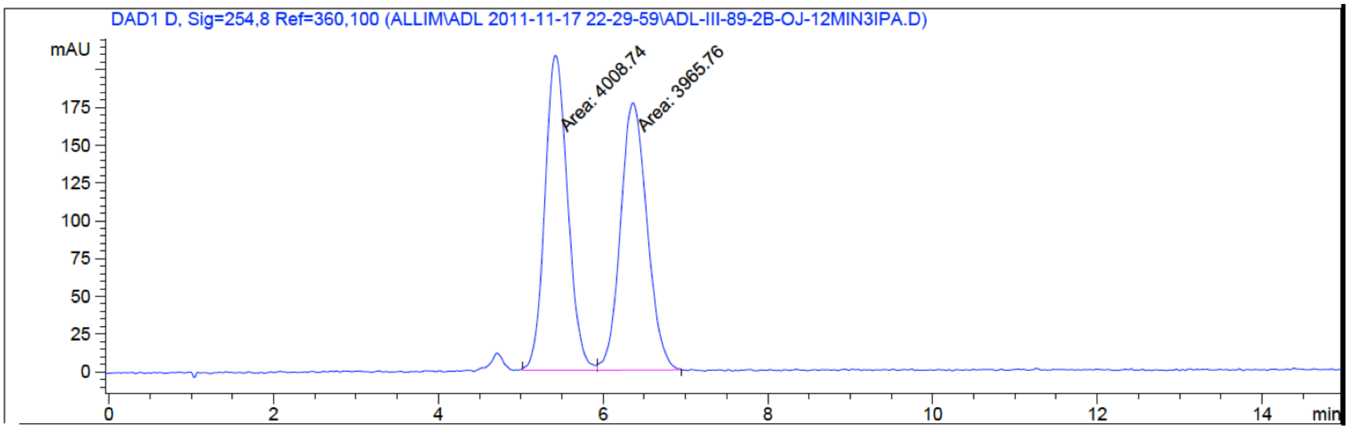
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   5.948 MM    0.4531 4937.27930 181.62985  49.8520
  2   7.191 MM    0.5548 4966.60352 149.20677  50.1480
```

18m (Table 2, entry 13): enantioenriched, 94% ee



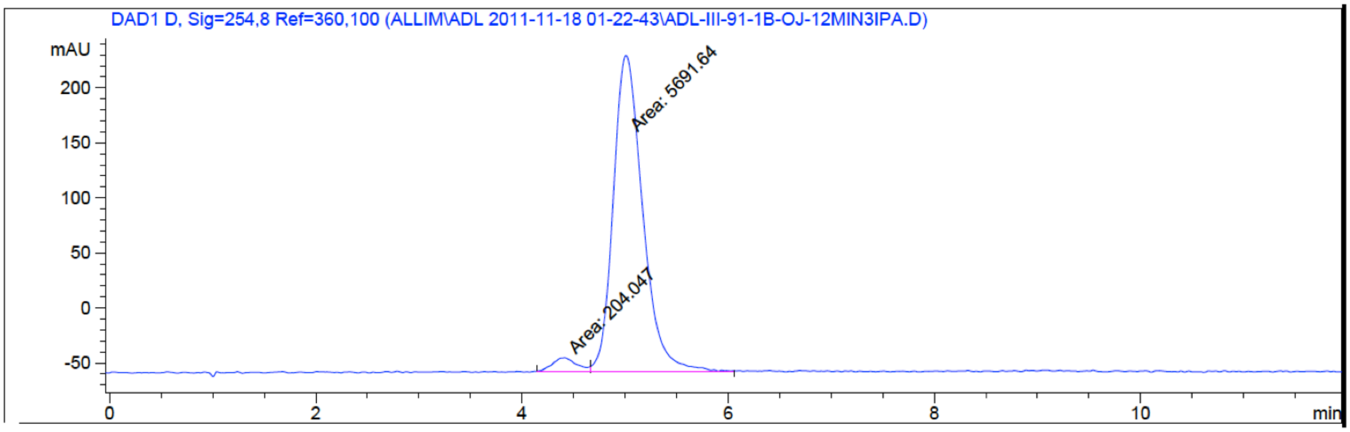
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   5.317 MM    0.3888  349.27008   14.97120   3.0863
  2   6.156 MM    0.4472 1.09673e4   408.74576  96.9137
```

18n (Table 2, entry 14): racemic



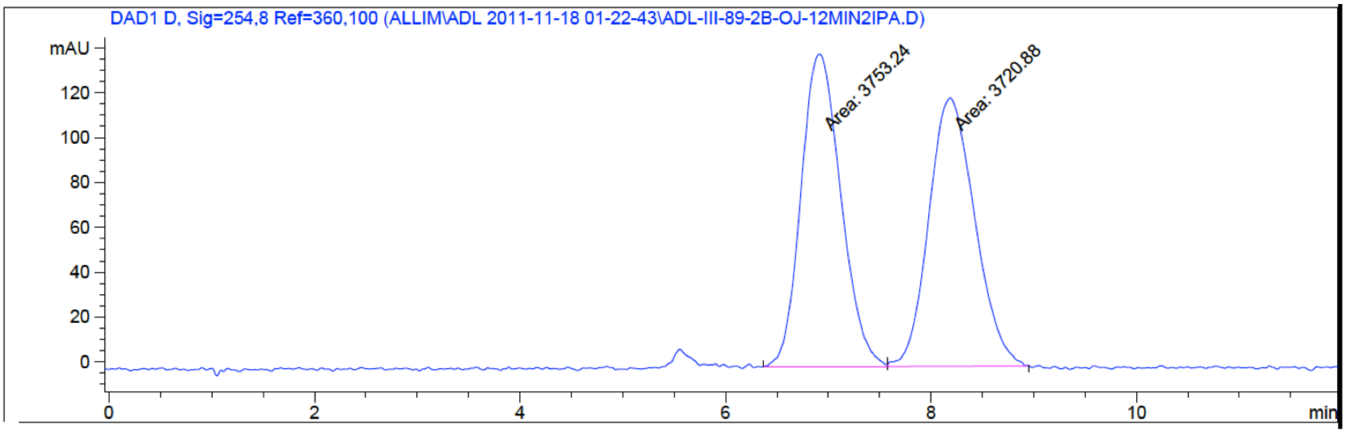
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.422 MM    0.3205 4008.73901  208.46022  50.2695
   2   6.362 MM    0.3737 3965.76196  176.85144  49.7305
```

18n (Table 2, entry 14): enantioenriched, 93% ee



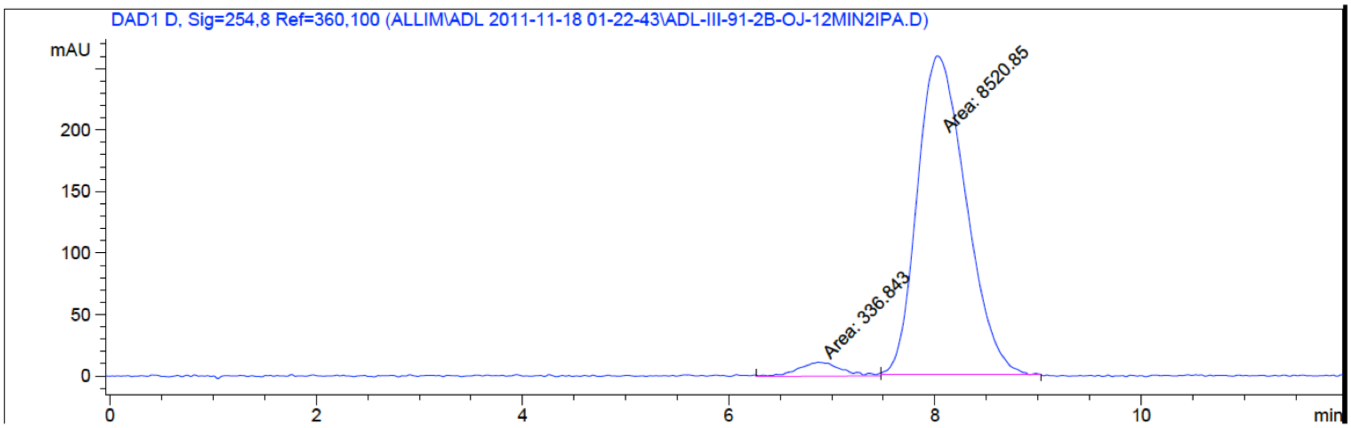
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.412 MM    0.2714  204.04715   12.53074   3.4610
   2   5.009 MM    0.3301 5691.64258  287.34784  96.5390
```

18o (Table 2, entry 15): racemic



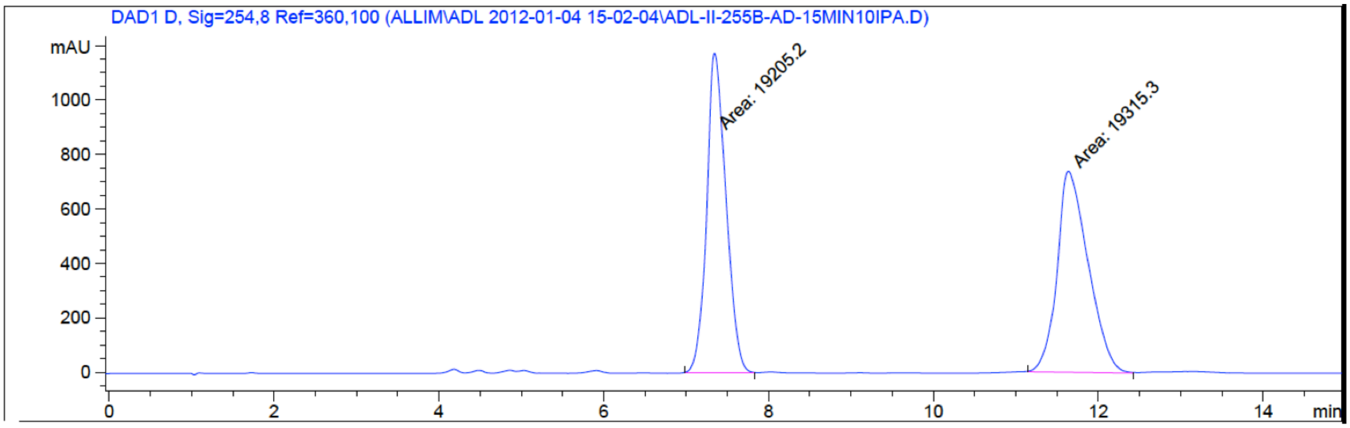
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   6.916 MM    0.4495 3753.23584  139.15379  50.2164
   2   8.186 MM    0.5183 3720.88330  119.64903  49.7836
```

18o (Table 2, entry 15): enantioenriched, 92% ee



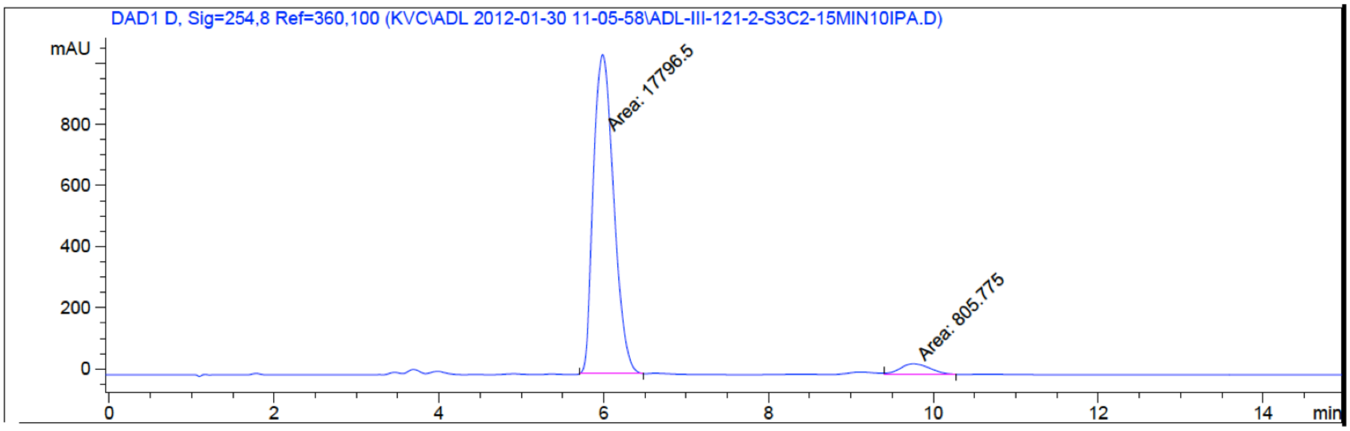
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   6.875 MM    0.4951  336.84314   11.33872   3.8028
   2   8.028 MM    0.5478 8520.84766  259.25595  96.1972
```

18p (Table 2, entry 16): racemic



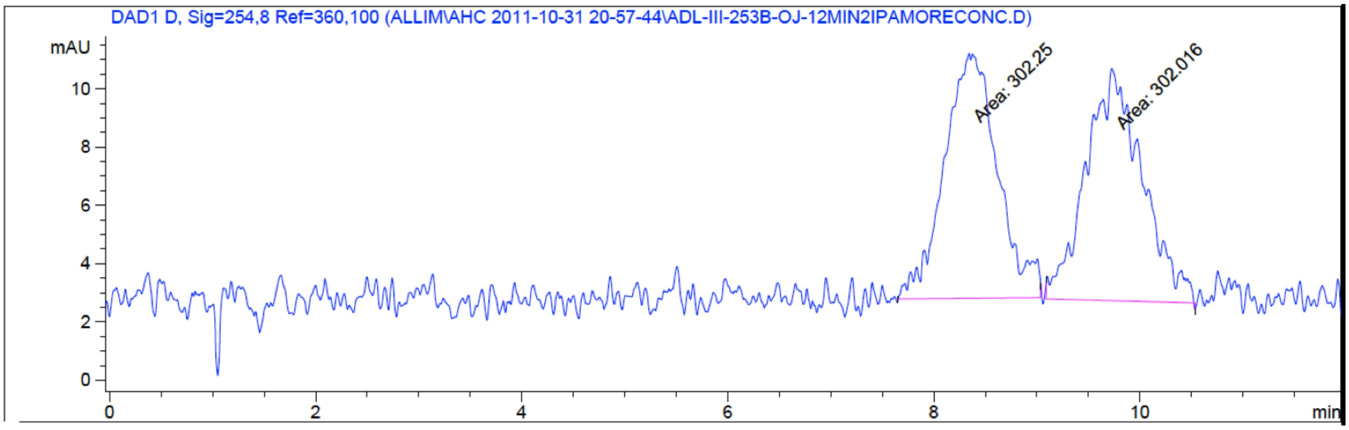
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   7.344 MM    0.2724 1.92052e4 1174.87732 49.8570
  2  11.638 MM    0.4363 1.93153e4  737.87109 50.1430
```

18p (Table 2, entry 16): enantioenriched, 92% ee



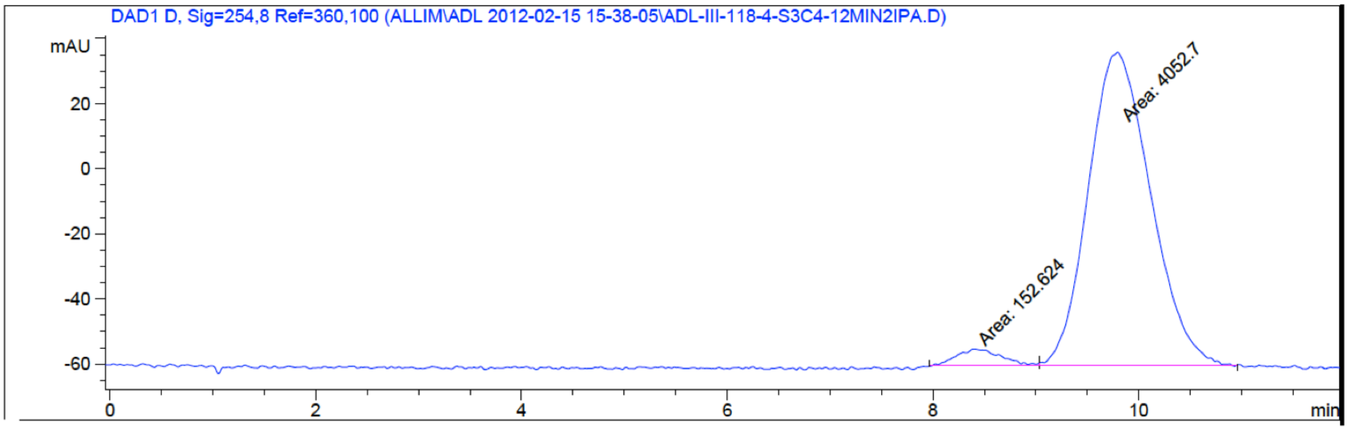
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   5.986 MM    0.2845 1.77965e4 1042.43127 95.6684
  2   9.756 MM    0.4056  805.77496   33.10773  4.3316
```

18q (Table 2, entry 17): racemic



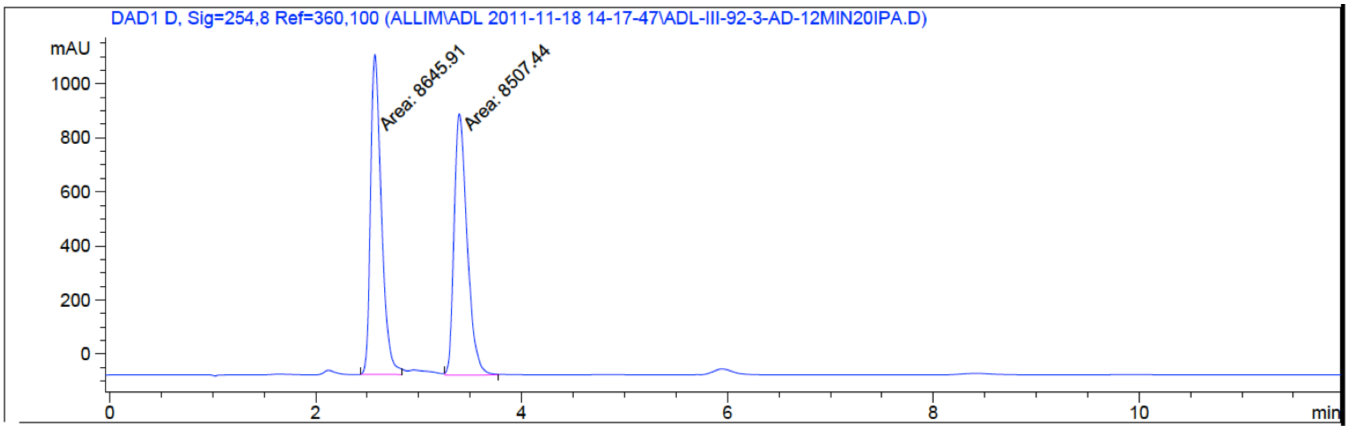
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   8.342 MM    0.5983  302.25012    8.41932  50.0193
   2   9.729 MM    0.6295  302.01633    7.99656  49.9807
```

18q (Table 2, entry 17): enantioenriched, 93% ee



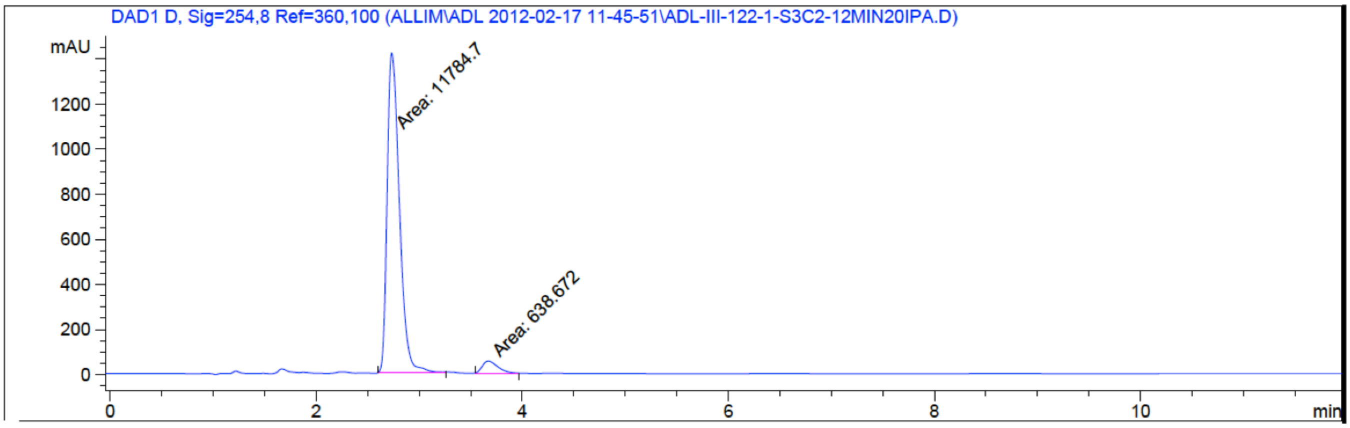
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   8.397 MM    0.5067  152.62421    5.01974   3.6293
   2   9.795 MM    0.7024 4052.70093   96.15991  96.3707
```

18r (Table 2, entry 18): racemic



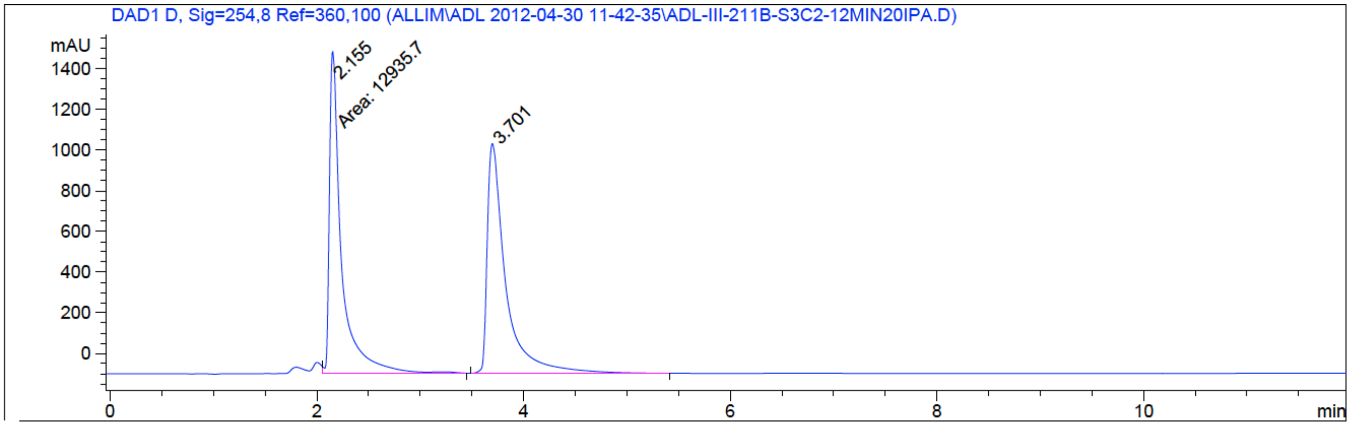
```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1    2.576 MM    0.1212 8645.91406 1189.34485 50.4036
  2    3.396 MM    0.1461 8507.43750  970.72430 49.5964
```

18r (Table 2, entry 18): enantioenriched, 90% ee



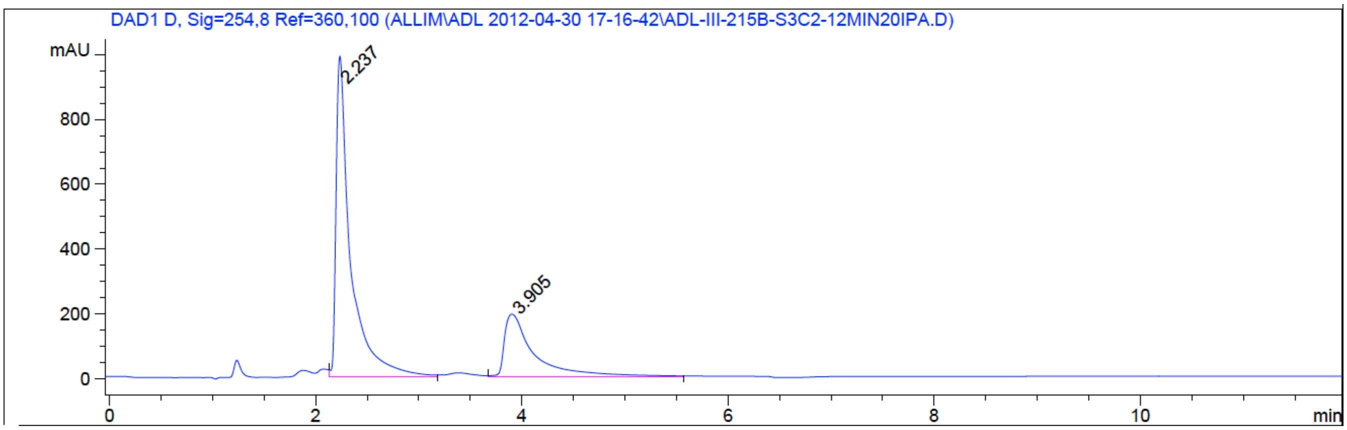
```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1    2.735 MM    0.1378 1.17847e4  1425.19104 94.8591
  2    3.671 MM    0.1867  638.67236   57.00725  5.1409
```

18s (Table 2, entry 19): racemic



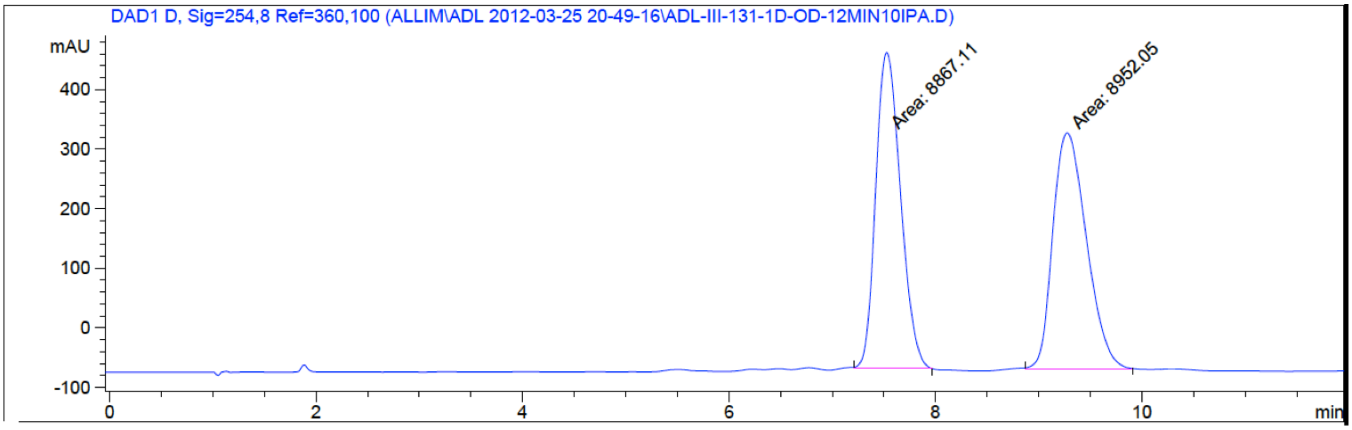
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   2.155 MM    0.1354 1.29357e4 1592.16809  48.0838
  2   3.701 VB    0.1806 1.39667e4 1126.56702  51.9162
```

18s (Table 2, entry 19): enantioenriched, 44% ee



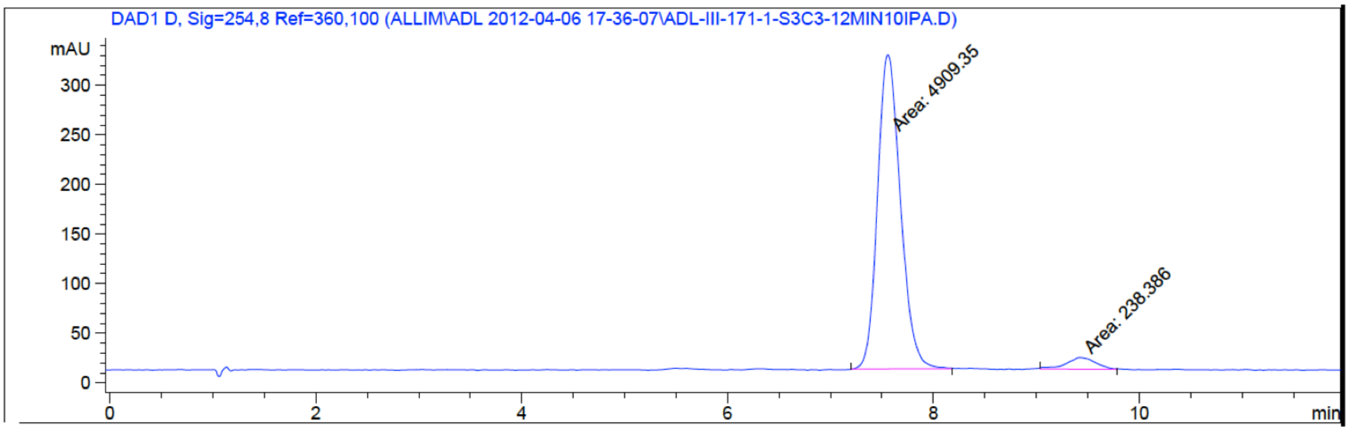
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   2.237 VB    0.1419 9604.80957  983.68304  71.8777
  2   3.905 VB    0.2807 3757.89526  191.67908  28.1223
```

19a (Table 3): racemic



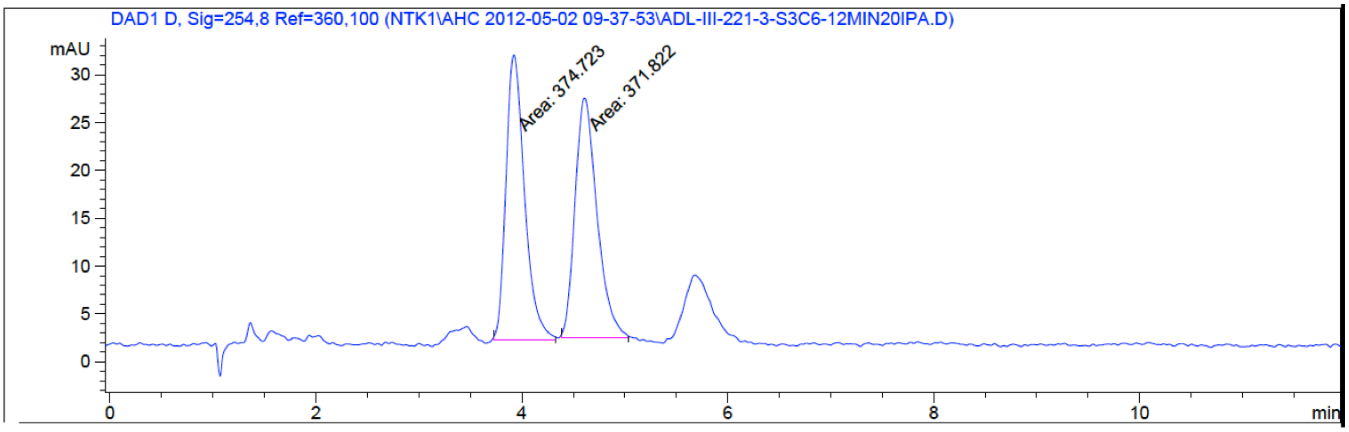
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   7.528 MM    0.2786 8867.11035  530.54260  49.7617
   2   9.276 MM    0.3763 8952.04590  396.47534  50.2383
```

19a (Table 3): enantioenriched, 90% ee



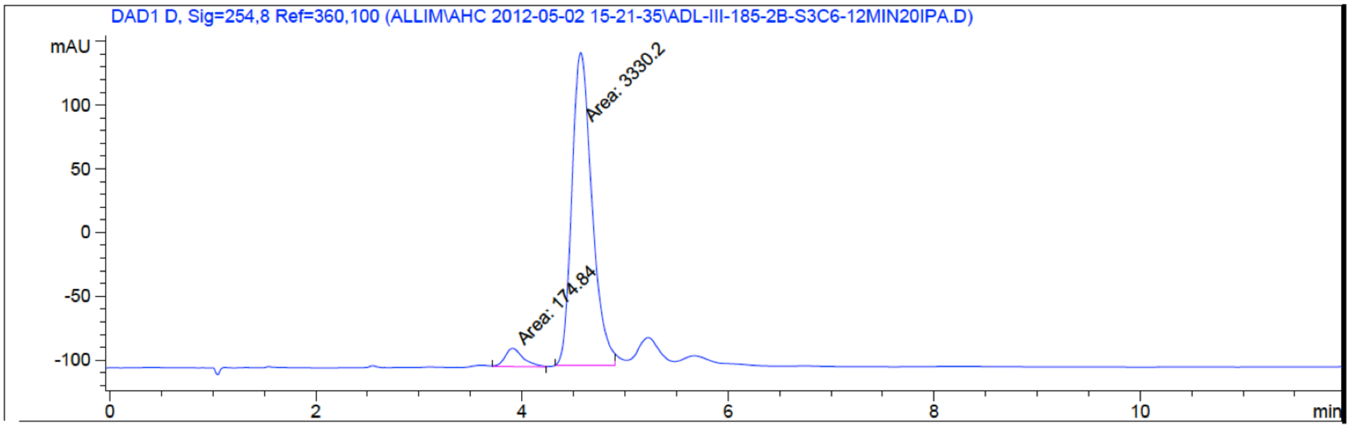
```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   7.558 MM    0.2580 4909.35205  317.09402  95.3691
   2   9.425 MM    0.3346  238.38634   11.87408   4.6309
```

19b (Table 3): racemic



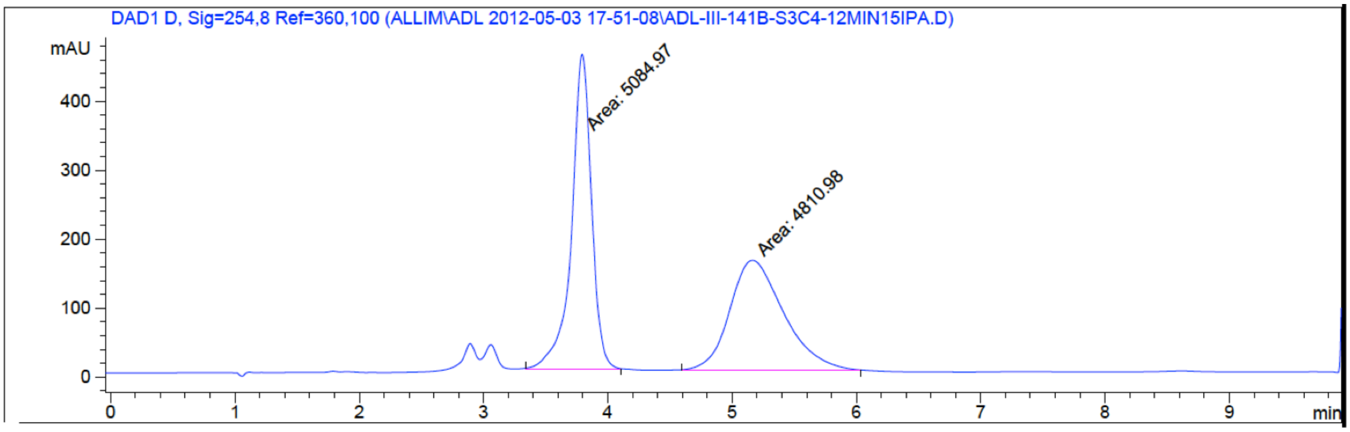
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   3.923 MM    0.2092  374.72302   29.85601  50.1943
  2   4.609 MM    0.2470  371.82239   25.08781  49.8057
```

19b (Table 3): enantioenriched, 90% ee



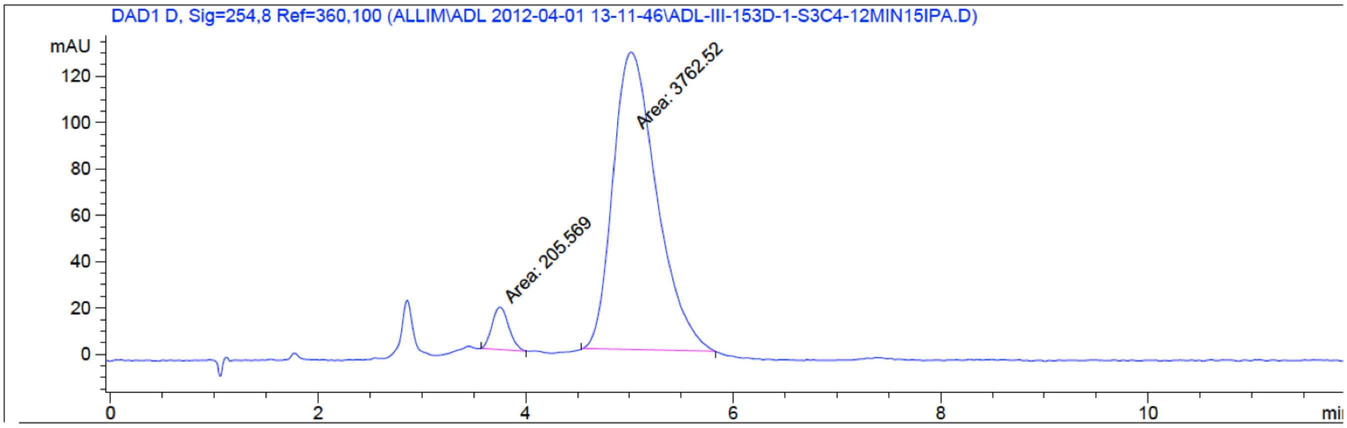
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   3.909 MM    0.2045  174.84013   14.24727   4.9882
  2   4.570 MM    0.2260 3330.20483  245.55070  95.0118
```

19c (Table 3): racemic



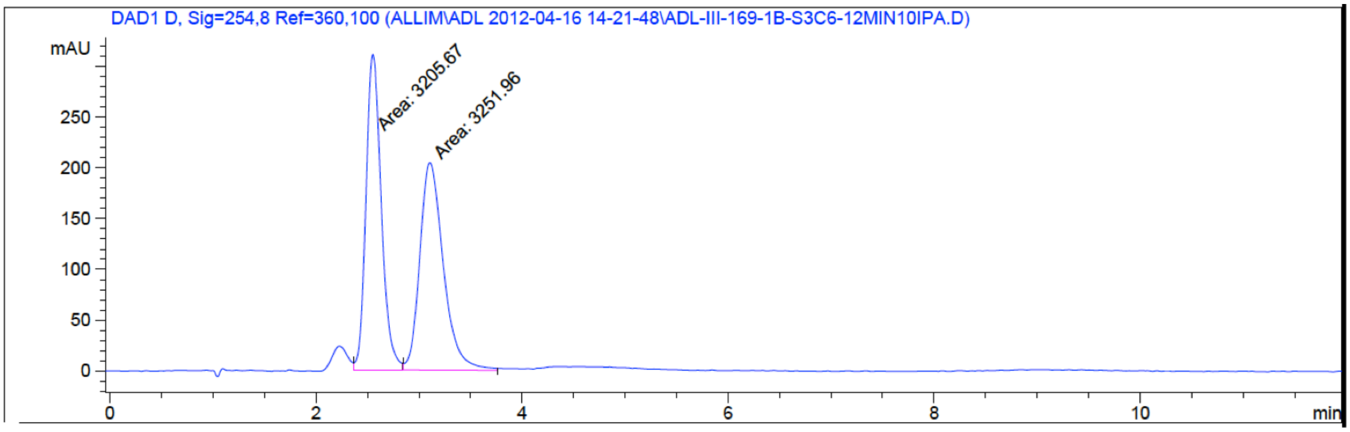
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]         [min]   [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1   3.794 MM    0.1854 5084.96924  457.11218  51.3844
   2   5.165 MM    0.5036 4810.97998  159.20520  48.6156
```

19c (Table 3): enantioenriched, 90% ee



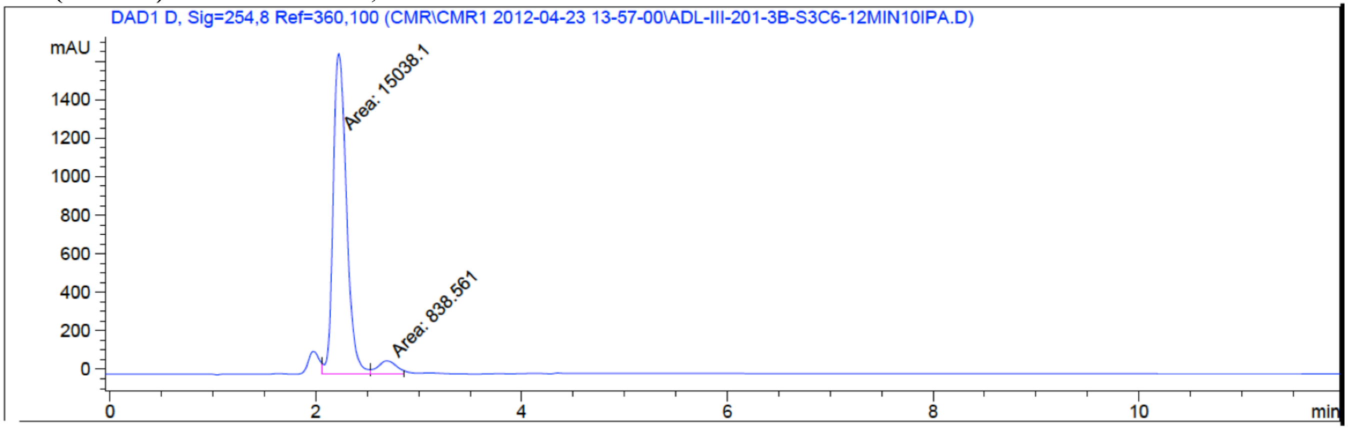
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]         [min]   [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1   3.752 MM    0.1869  205.56940   18.33098   5.1806
   2   5.016 MM    0.4891 3762.51758  128.21497  94.8194
```

19d (Table 3): racemic



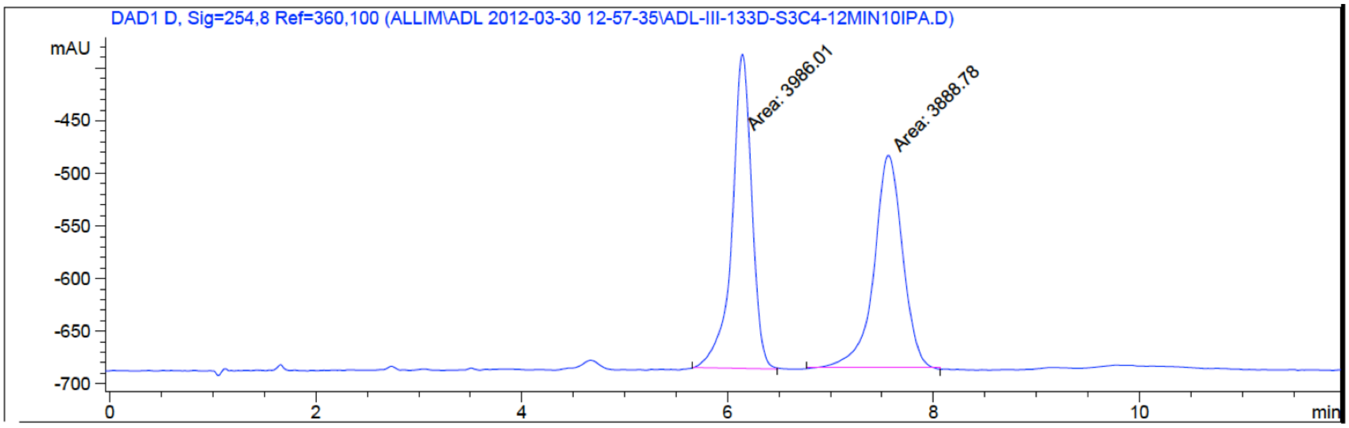
```
Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   2.552 MM    0.1717 3205.67017  311.25909  49.6416
   2   3.106 MM    0.2652 3251.96484  204.37744  50.3584
```

19d (Table 3): enantioenriched, 90% ee



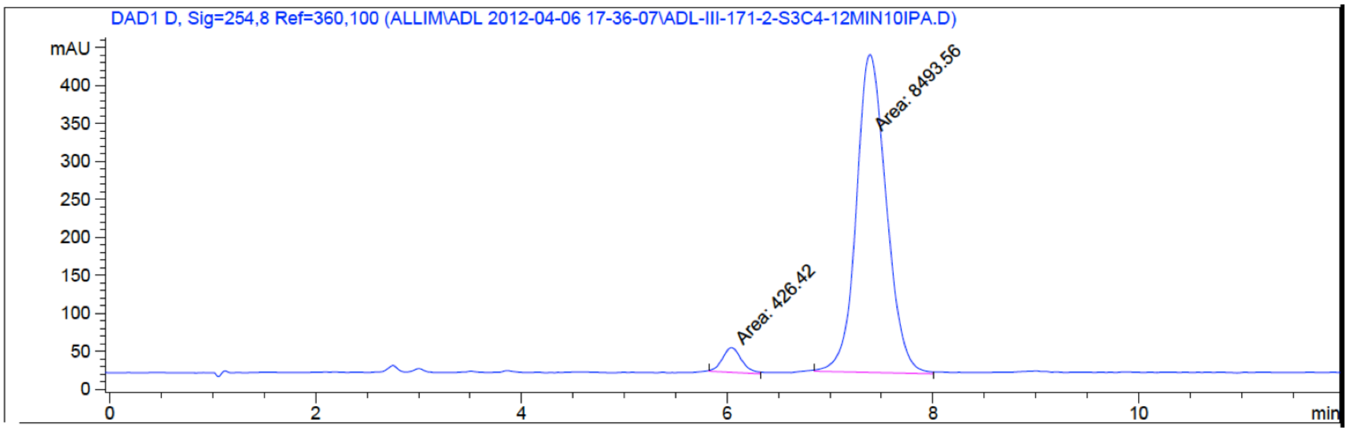
```
Peak RetTime Type  Width      Area       Height      Area
  #   [min]        [min]    [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   2.224 MM    0.1504 1.50381e4 1666.51477  94.7183
   2   2.693 MM    0.2084  838.56067   67.05596   5.2817
```

19e (Table 3): racemic



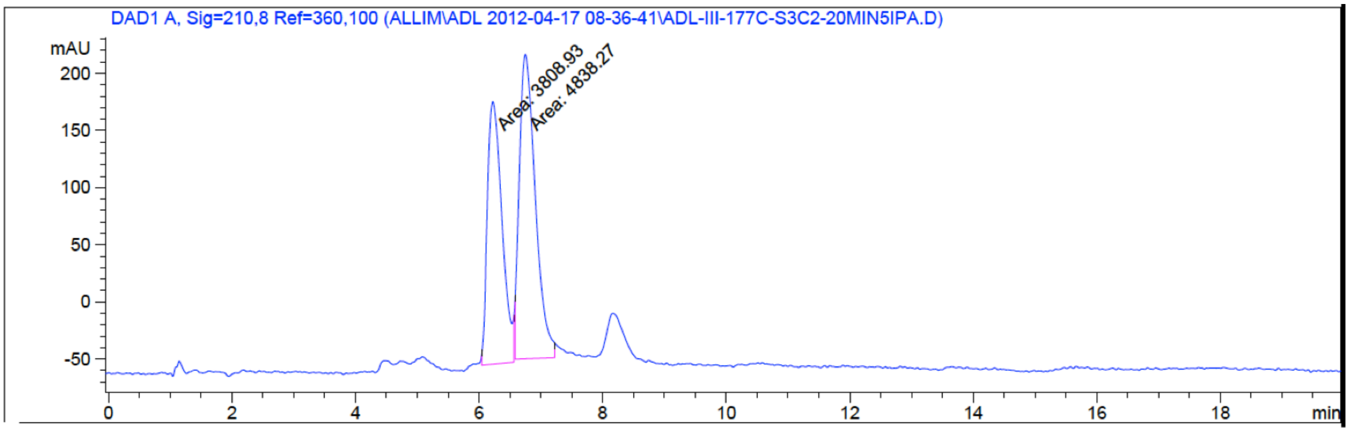
```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1    6.144 MM    0.2222 3986.00659  298.95831  50.6173
  2    7.563 MM    0.3216 3888.78369  201.55779  49.3827
```

19e (Table 3): enantioenriched, 90% ee



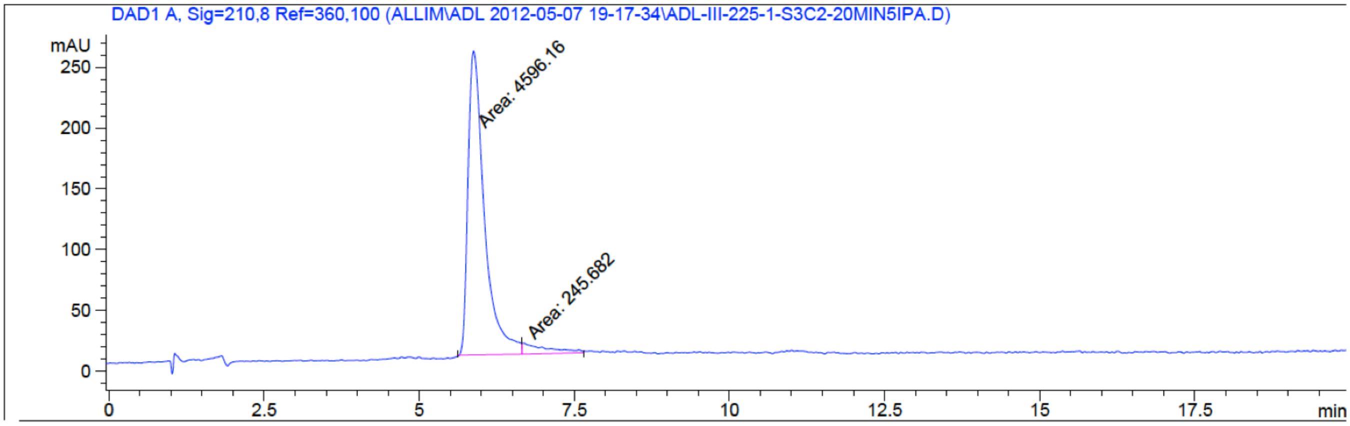
```
Peak RetTime Type  Width     Area       Height     Area
  #   [min]        [min]   [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1    6.042 MM    0.2176  426.42010   32.65453   4.7805
  2    7.388 MM    0.3377 8493.55664  419.18365  95.2195
```

19f (Table 3): racemic



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]         [min]   [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
  1   6.222 MM    0.2762 3808.92651  229.80165  44.0481
  2   6.749 MM    0.3024 4838.27002  266.61557  55.9519
```

19f (Table 3): enantioenriched, 90% ee



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]         [min]   [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
  1   5.878 MM    0.3065 4596.16162  249.90791  94.9258
  2   6.674 MM    0.4528  245.68248    9.04279   5.0742
```

References

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