Catalytic Asymmetric Synthesis of Highly Substituted Pyrrolizidines

Andrew D. Lim, Julian A. Codelli, Sarah E. Reisman*

The Warren and Katharine Schlinger Laboratory of Chemistry and Chemical Engineering

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

reisman@caltech.edu

Supporting Information 1 (Experimental Procedures):

Table of Contents

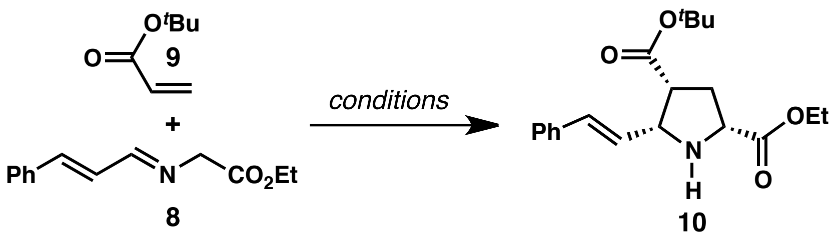
1. Materials and Methods. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina 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. ^{1}H 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 $CHCl_3$ (^{1}H, δ = 7.26), MeCN-d_2 (^{1}H, δ = 1.94), or acetone-d_5 (^{1}H, δ = 2.05), and $CDCl_3$ (^{13}C, δ = 77.0), CD_3CN (^{13}C, δ = 118.26), DMSO-d_6 (^{13}C, δ = 39.52). Data for ^{1}H 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.

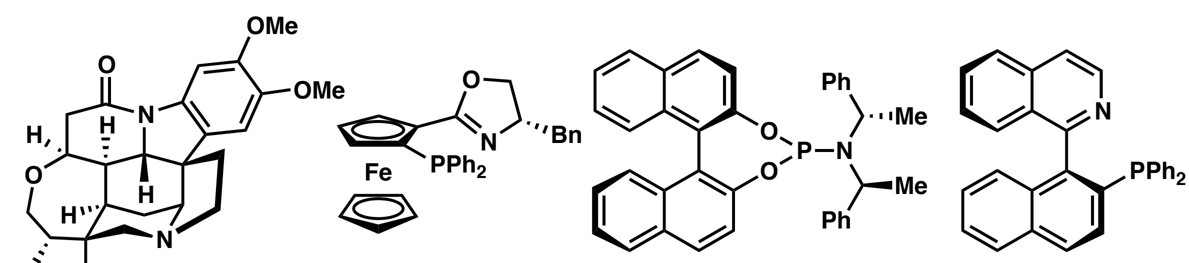
3. General procedure for the double (3+2) cycloaddition reactions. Silver(I) acetate (1.0 equiv) and (*S*)-QUINAP (1.0 equiv) were added to a vial. Tetrahydrofuran was then introduced, and this solution was stirred at room temperature for 1 h to make a stock solution of 0.009 M silver(I)/(*S*)-QUINAP 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).



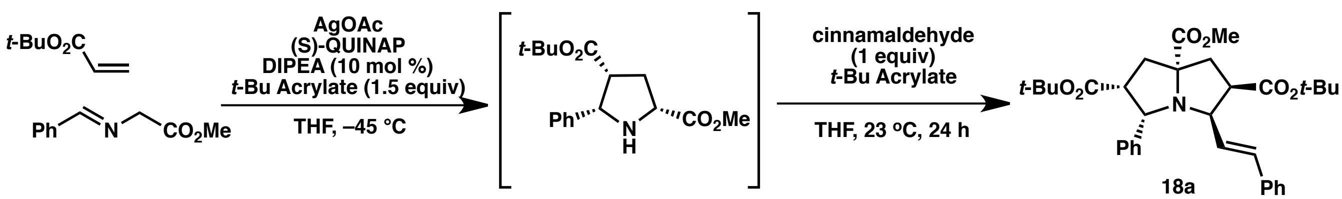
entry	catalyst/ligand/additive	solvent	temp (°C)	yield[e] (%)	ee[f] (%)
1[a]	CuI, **13**, DBU	$CHCl_3$	0 °C	50	96
2[b]	AgOAc, **14**	Et_2O	0 °C	53	–63
3[c]	$AgClO_4$, **15**, DABCO	PhMe	0 °C	59	46
4[d]	AgOAc, **16**, DIPEA	THF	–45 °C	62	**90**
5[d]	AgOAc, **16**, DIPEA	DCM	–45 °C	36	78
6[d]	AgOAc, **16**,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



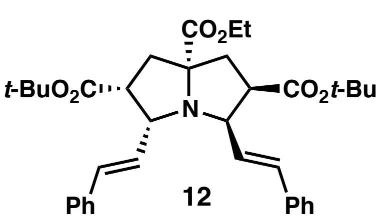
entry	catalyst loading (mol %)	additive	time for first (1,3)-dipolar cycloaddition (h)	equiv *t*-Bu-Acrylate in second (1,3)-dipolar cycloaddition	yield[a] (%)	ee[b] (%)
1	3 mol %	none	24	1.5	74	91
2	3 mol %	none	24	5	90	91
3	1 mol %	none	24	5	64	86
4	1 mol %	mol sieves	24	5	82	88
5	1 mol %	none	48	5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

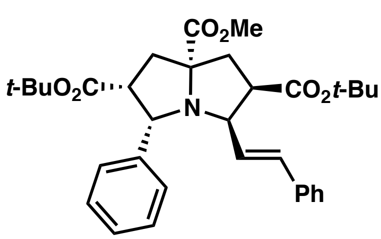
(2*R*,3*R*,5*R*,6*R*)-2,6-di-*tert*-butyl 7a-ethyl 3,5-di((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (12)



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, $CHCl_3$); ^1H 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.

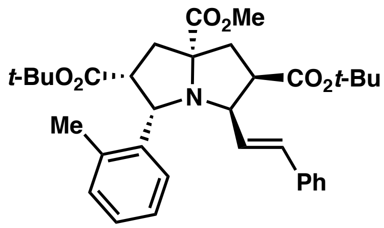
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18a)



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, $CHCl_3$); ^1H 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.

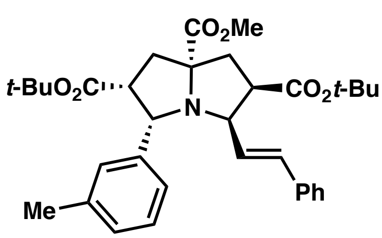
(2*R*,3*R*,5*S*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-((*E*)-styryl)-5-(*o*-tolyl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18b)



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, $CHCl_3$); ^1H 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)

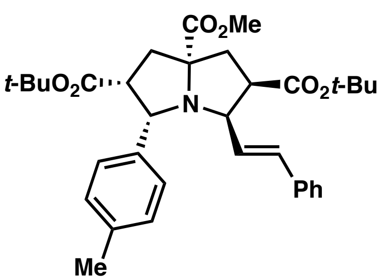


18c

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, $CHCl_3$); ^{1}H 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.

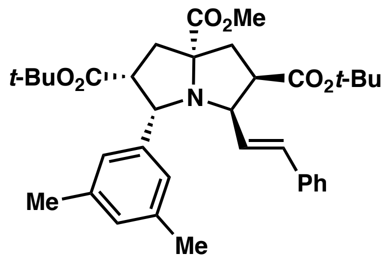
(2*R*,3*R*,5*S*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-((*E*)-styryl)-5-(*p*-tolyl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18d)



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, $CHCl_3$); ^{1}H 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.

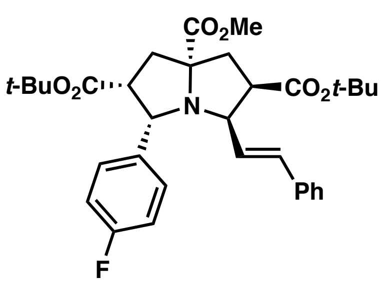
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(3,5-dimethylphenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18e)



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, $CHCl_3$); ^1H 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)

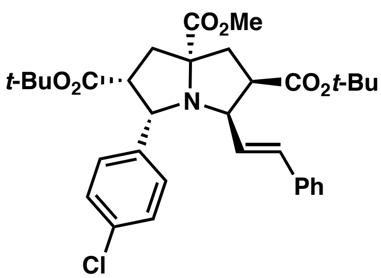


18f

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, $CHCl_3$); ^1H 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.

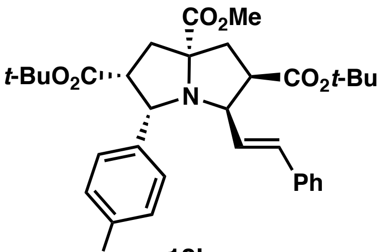
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(4-chlorophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18g)



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

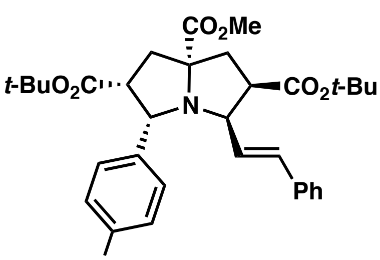
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(4-bromophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18h)



Br 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)

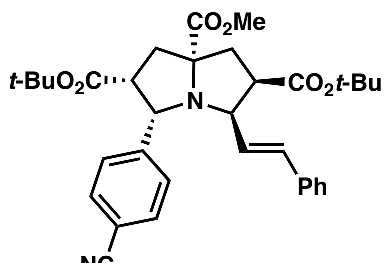


O_2N 18i

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.

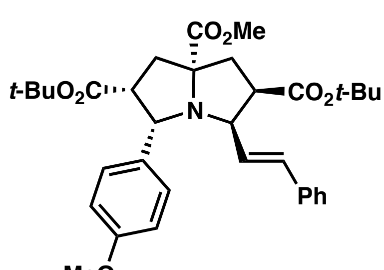
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(4-cyanophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18j)



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)

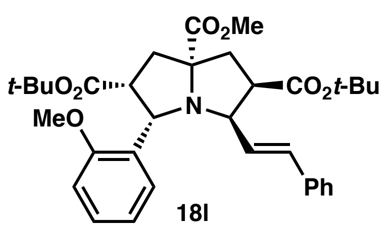


18k

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.

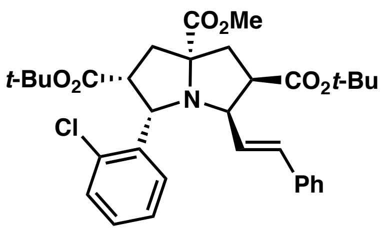
(2*R*,3*R*,5*S*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methoxy 3-((*E*)-styryl)-5-(*o*-tolyl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18l)



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.

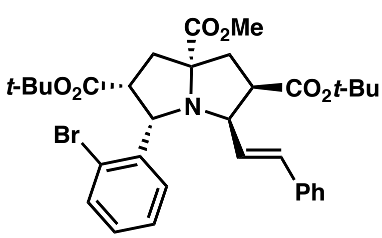
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(2-chlorophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18m)



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.

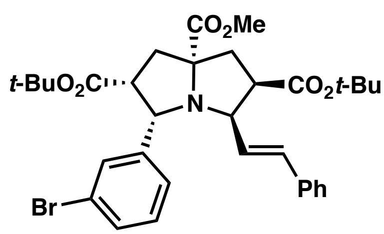
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(2-bromophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18n)



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.

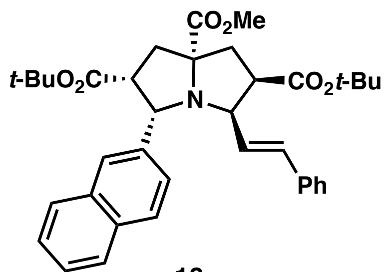
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(3-bromophenyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18o)



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.

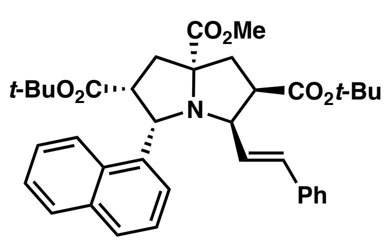
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(naphthalen-2-yl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18p)



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.

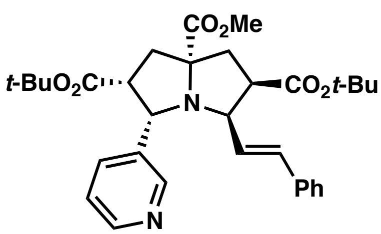
(2*R*,3*S*,5*R*,6*R*)-di-*tert*-butyl 3-(naphthalen-1-yl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6-dicarboxylate (18q)



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.

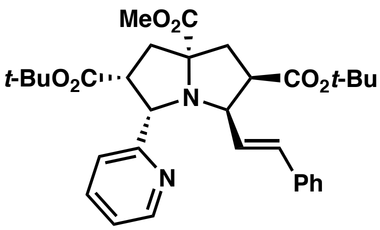
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(pyridin-3-yl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18r)



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$_3$); ^{1}H 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.

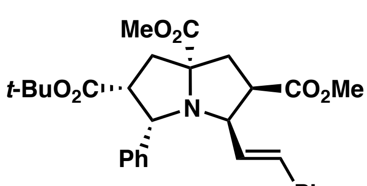
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2,6-di-*tert*-butyl 7a-methyl 3-(pyridin-2-yl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (18s)



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.

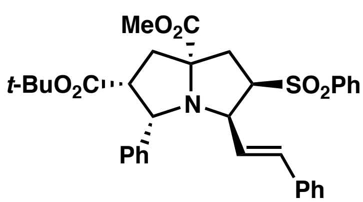
(2*R*,3*S*,5*R*,6*R*,7a*R*)-2-*tert*-butyl 6,7a-dimethyl 3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (19a)



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.

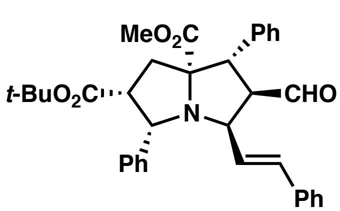
(2*R*,3*S*,5*R*,6*R*,7a*S*)-2-*tert*-butyl 7a-methyl 3-phenyl-6-(phenylsulfonyl)-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,7a-dicarboxylate (19b)



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.

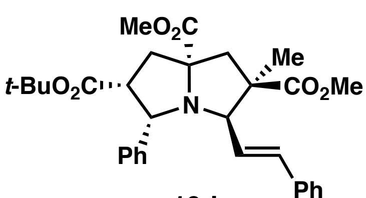
(2*R*,3*S*,5*R*,6*R*,7*S*,7a*S*)-2-*tert*-butyl 7a-methyl 6-formyl-3,7-diphenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,7a-dicarboxylate (19c)



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, $CHCl_3$); ^{1}H 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.

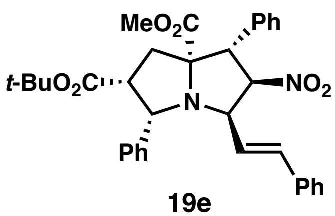
(2*R*,3*R*,5*S*,6*R*,7a*S*)-6-*tert*-butyl 2,7a-dimethyl 2-methyl-5-phenyl-3-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (19d)



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, $CHCl_3$); ^{1}H 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.

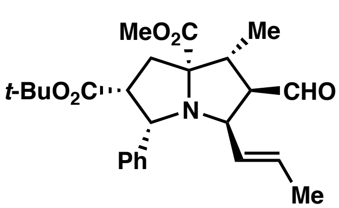
(2*R*,3*S*,5*R*,6*R*,7*R*,7a*S*)-2-*tert*-butyl 7a-methyl 6-nitro-3,7-diphenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,7a-dicarboxylate (19e)



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, λ = 254 nm): t_R (minor) = 6.0 min, t_R (major) = 7.4 min; $[\alpha]_D^{25}$ = -27.059 (c = 0.98, $CHCl_3$); ^{1}H 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.

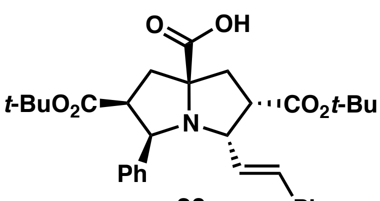
(2*R*,3*S*,5*R*,6*R*,7*R*,7a*S*)-2-*tert*-butyl 7a-methyl 6-formyl-7-methyl-3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,7a-dicarboxylate (19f)



19f

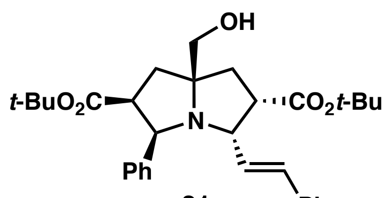
According to the general procedure using 1.1 equivalents of *t*-Bu acrylate in the first (1,3)-dipolar cycloaddition and crotonaldehyde as the dipolarophile in the second (1,3)-dipolar cycloaddition, pyrrolizidine **19f** was obtained as a white foam after silica gel column chromatography (5→20% ethyl 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.

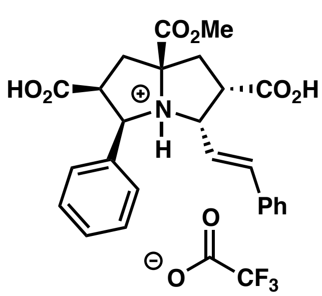


21

(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)

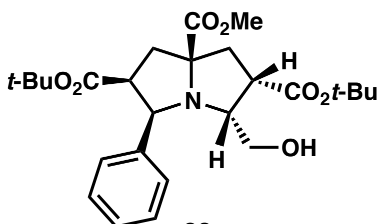


22

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)

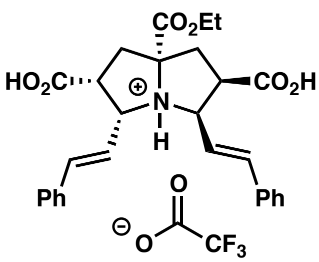


23

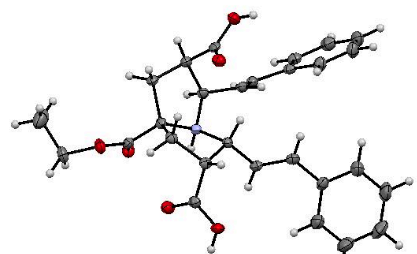
A solution of styrene ***ent*-18a** (150 mg, 0.274 mmol) and *p*-toluenesulfonic acid hydrate (261 mg, 1.37 mmol) in 2.8 mL of EtOAc was cooled to –78 °C with stirring. Ozone was bubbled through the solution until it became a pale blue suspension. The suspension was then sparged with oxygen (until the 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_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was subjected to silica gel column chromatography (50:1→10:1 CH_2Cl_2–Et_2O), 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)



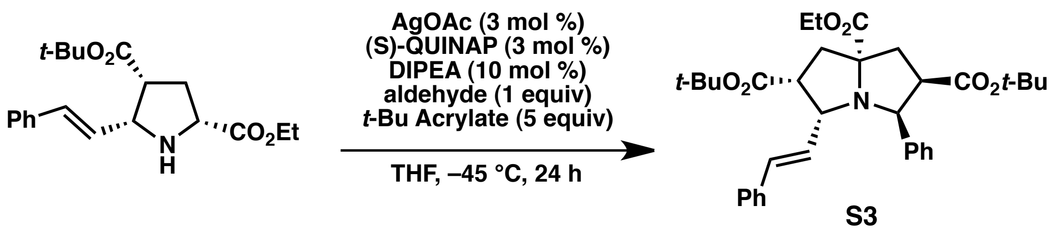
S2



(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. ^1H 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.

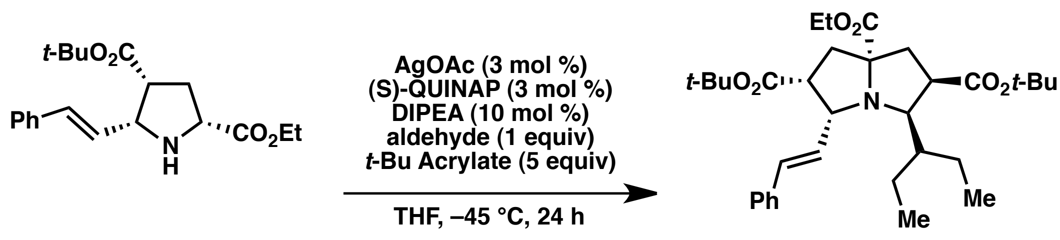
(2*R*,3*S*,5*R*,6*R*,7a*S*)-2,6-di-*tert*-butyl 7a-ethyl 3-phenyl-5-((*E*)-styryl)hexahydro-1*H*-pyrrolizine-2,6,7a-tricarboxylate (S3)



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)

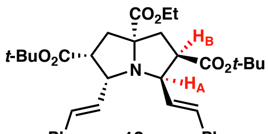


3 mol % catalyst solution in THF was pre-stirred for 30 minutes and then added to 52 mg of pyrrolidine **S2**. 18 µl of 2-ethyl butyraldehyde was added followed by 11 µl of *t*-Bu Acrylate and 3 µl of DIPEA. After 24 h the reaction mixture was concentrated and purified by silica gel column chromatography (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)-

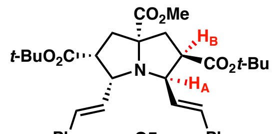
DCA for compounds **19a–19f**. The key *J*-values and observed NOESY data are tabulated below. The NOESY spectra are included with the rest of the NMR characterization data in the Supporting Information Part II.



12

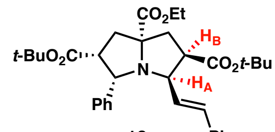
J_{HB}=7.6
J_{HA}=7.6

(confirmed by X-ray diffraction)



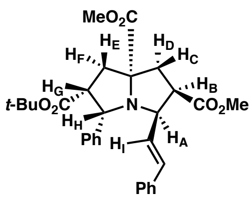
S5

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



18a

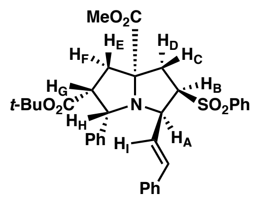
J_{HA}=7.7
J_{HB}=7.5



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

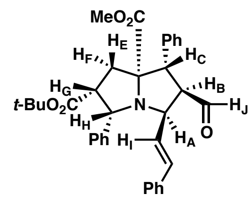
NOEs	
H_AH_B	H_BH_D
H_CH_E	H_IH_H
H_EH_G	H_IH_C
H_GH_H	no H_IH_B



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

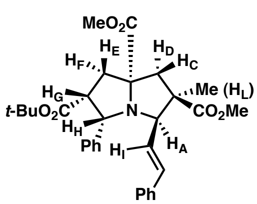
NOEs	
H_AH_B	H_BH_D
H_CH_E	H_IH_H
H_EH_G	H_IH_C
H_GH_H	no H_IH_B



19c

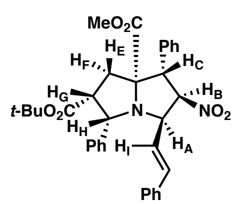
	J (Hz)
H_A	8.1
H_B	8.1
H_B	12.0
H_C	12.0
H_B	1.8
H_D	1.8

NOEs	
H_AH_B	H_IH_H
H_CH_E	H_IH_C
H_EH_G	no H_IH_B
H_GH_H	



19d

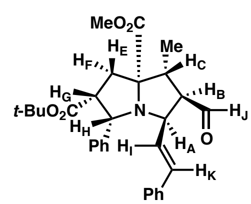
NOEs	
H_AH_L	H_GH_H
H_DH_L	H_IH_H
H_EH_C	
H_EH_G	



19e

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

NOEs	
H_AH_B	H_IH_H
H_CH_E	H_IH_C
H_EH_G	H_HH_C
H_GH_H	H_HH_E



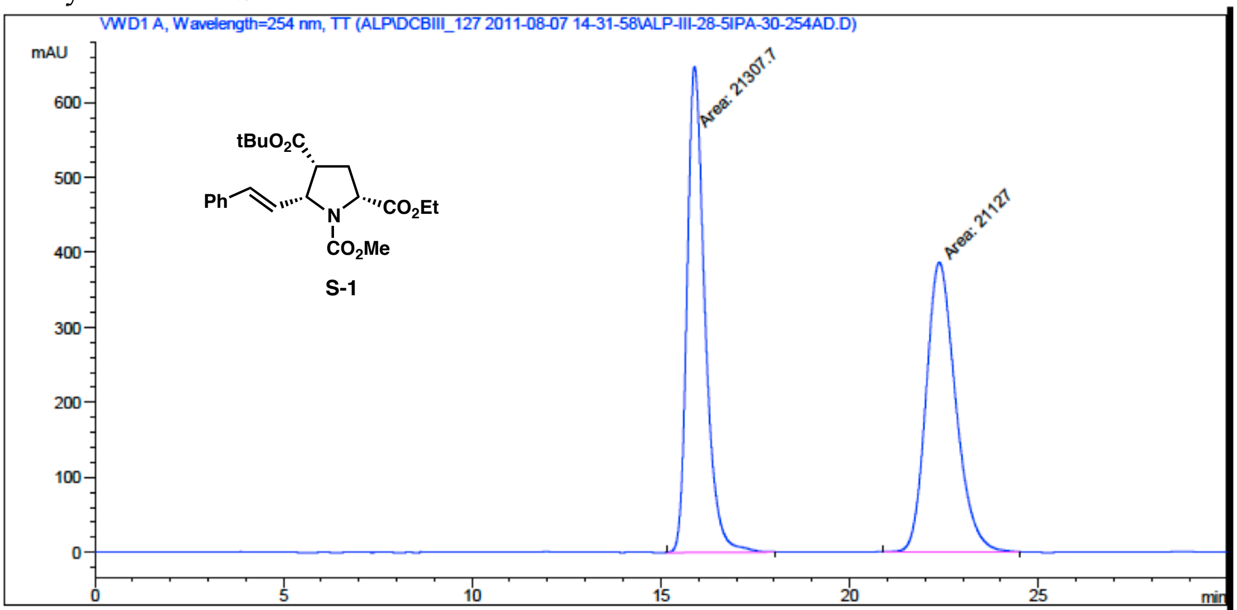
19f

	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_IH_H
H_CH_E	H_KH_C
H_EH_G	H_IH_C
H_GH_H	no H_IH_B

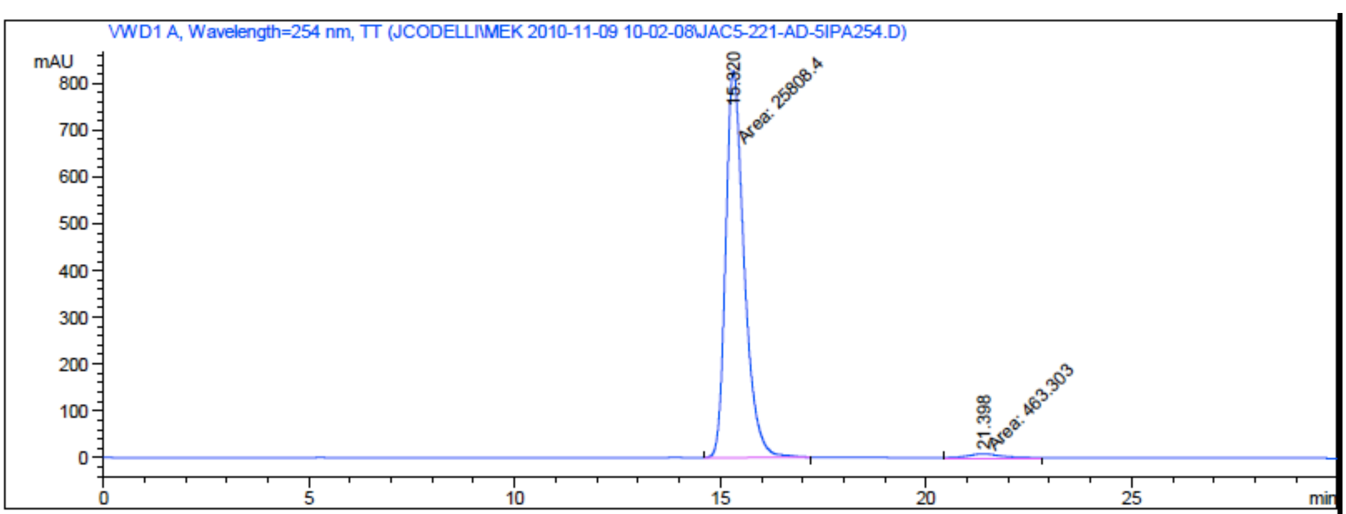
8. SFC/HPLC traces of racemic and enantioenriched products.

Methyl carbamate **S1**: racemic



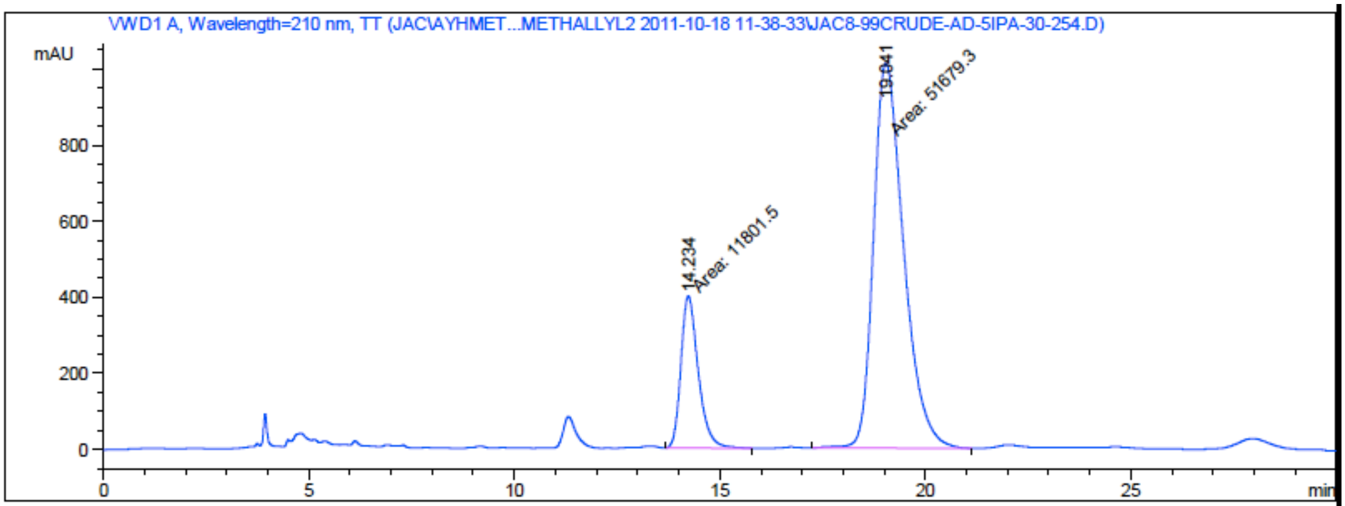
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	15.894	MM	0.5477	2.13077e4	648.35150	50.2129
2	22.377	MM	0.9097	2.11270e4	387.07867	49.7871

Table S1, entry 1: enantioenriched, 96% ee



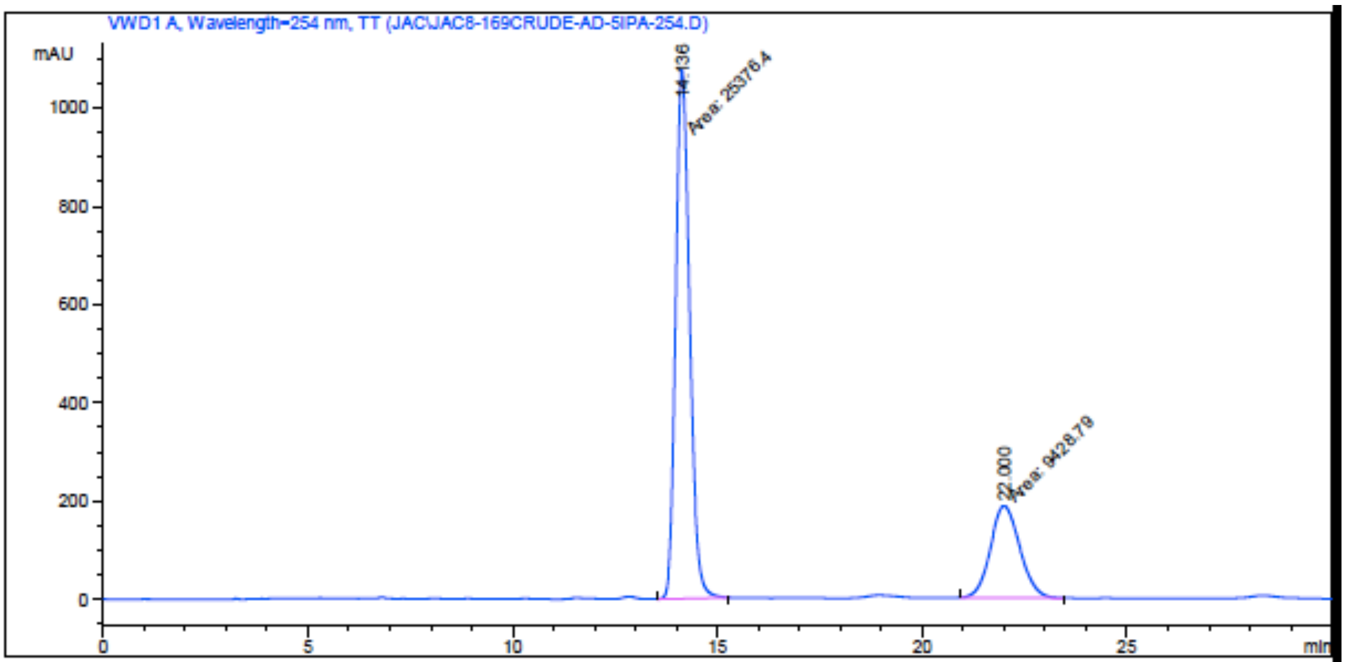
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	15.320	MM	0.5202	2.58084e4	826.91376	98.2365
2	21.398	MM	0.9279	463.30341	8.32209	1.7635

Table S1, entry 2: enantioenriched, 63% ee



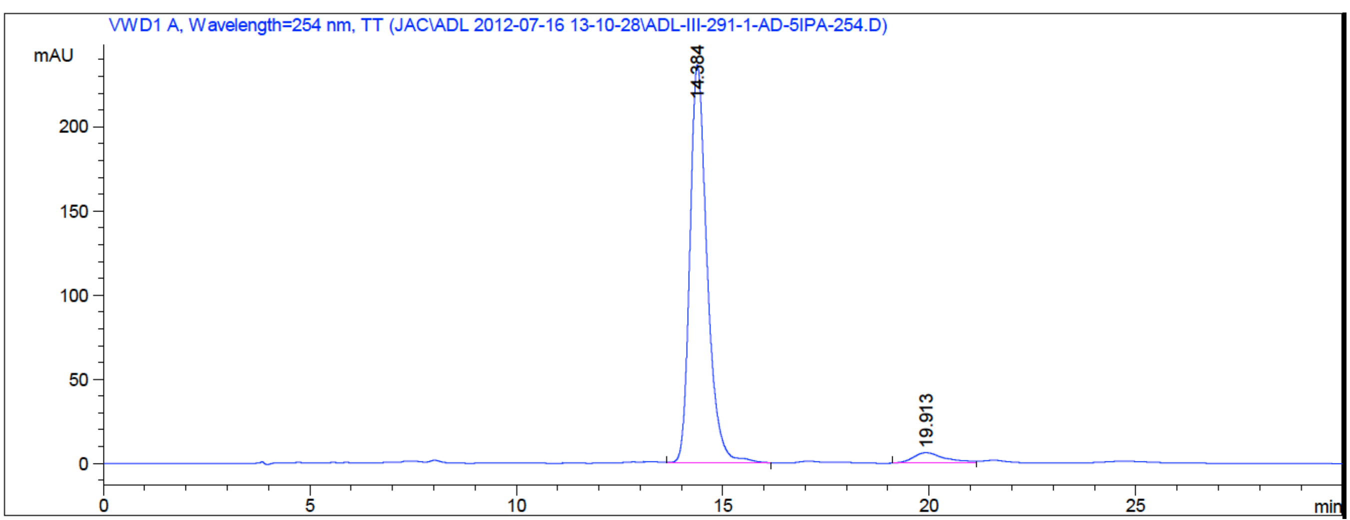
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.234	MM	0.4913	1.18015e4	400.33957	18.5907
2	19.041	MM	0.8507	5.16792e4	1012.46924	81.4093

Table S1, entry 3: enantioenriched, 46% ee



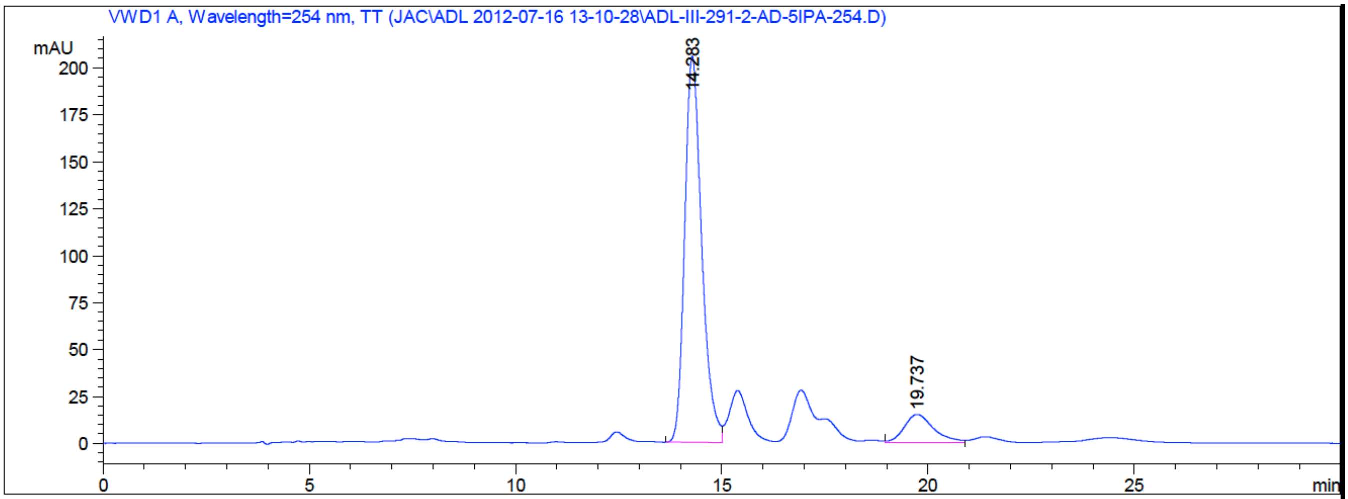
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.136	MM	0.3931	2.53764e4	1075.82861	72.9098
2	22.000	MM	0.8369	9428.79492	187.78340	27.0902

Table S1, entry 4: enantrioenriched, 90% ee



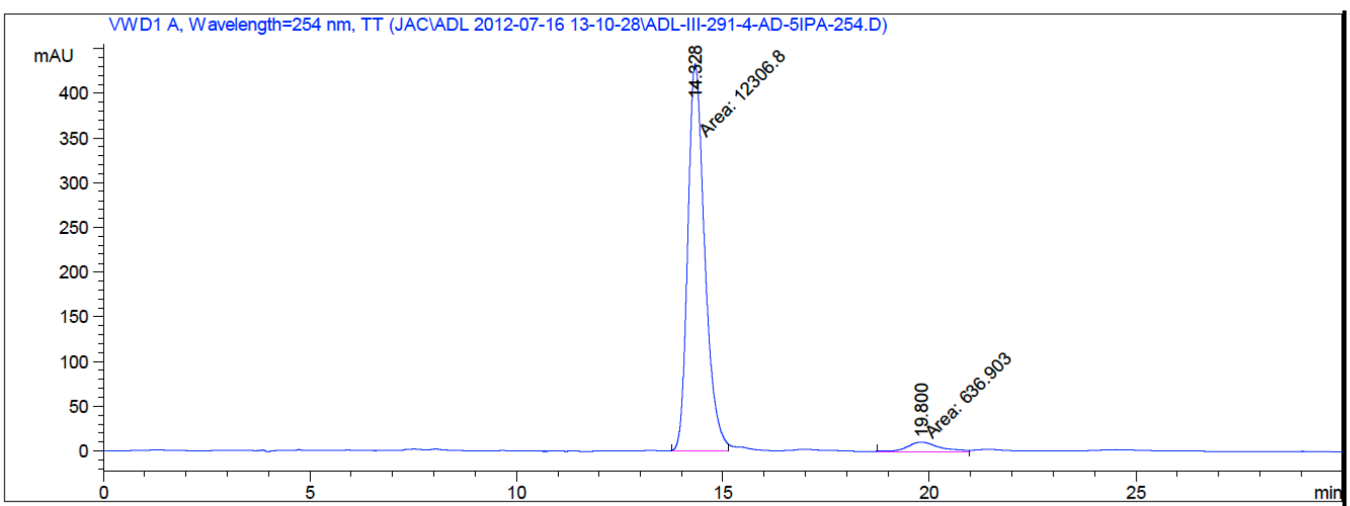
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.384	VB	0.4361	6863.74121	236.53506	95.3206
2	19.913	BV	0.6398	336.95078	6.23651	4.6794

Table S1, entry 5: enantrioenriched, 78% ee



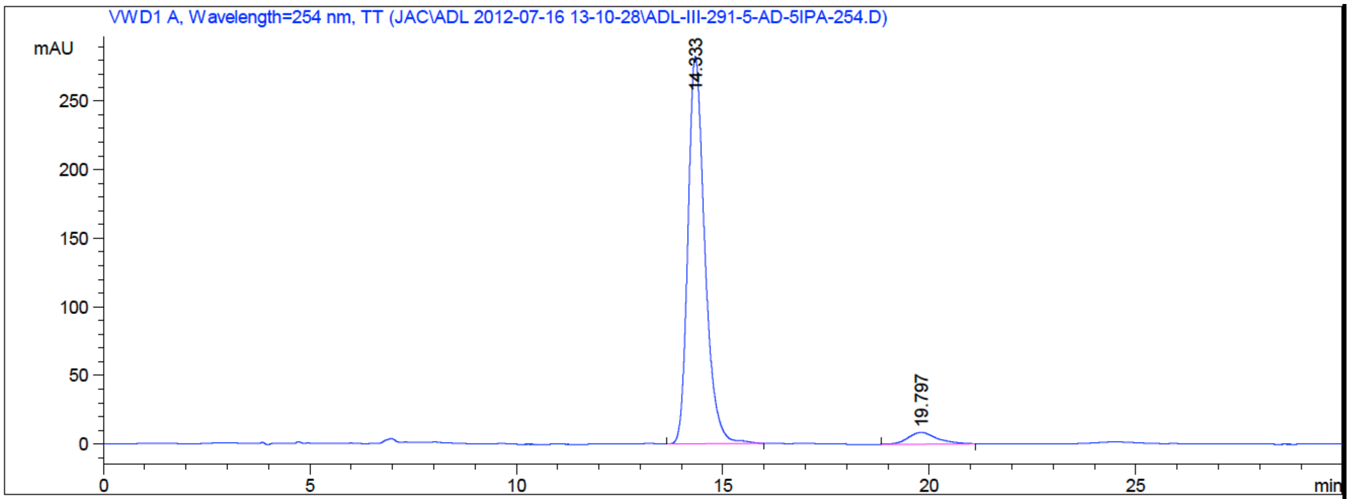
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.283	BV	0.4353	5902.47510	205.65765	88.6961
2	19.737	VV	0.6069	752.24481	14.98246	11.3039

Table S1, entry 7: enantrioenriched, 90% ee



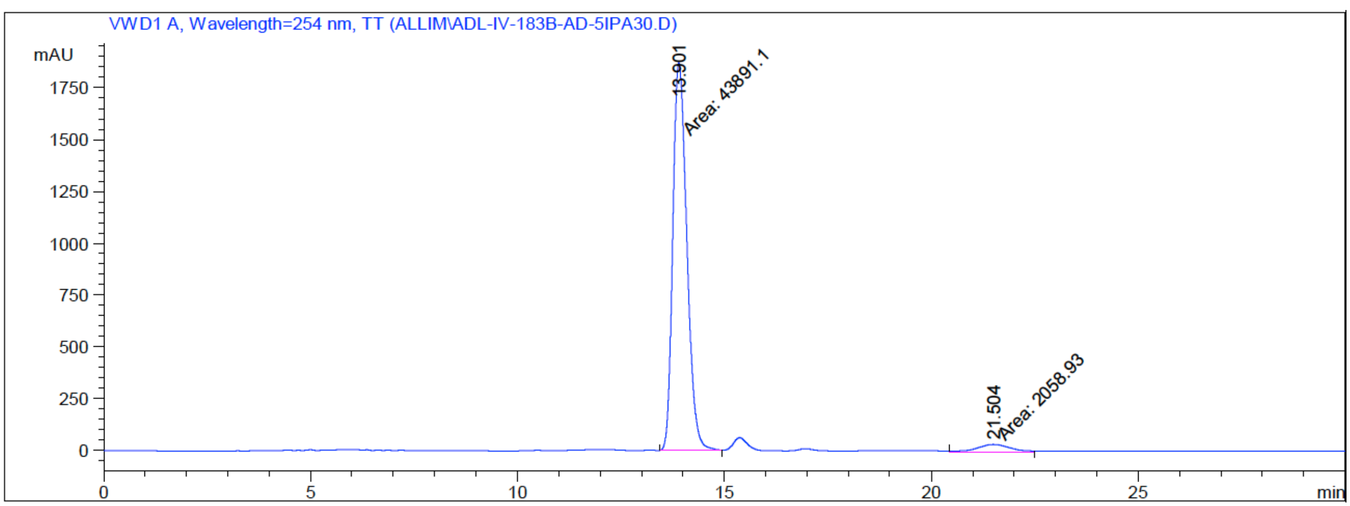
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.328	MM	0.4745	1.23068e4	432.23904	95.0795
2	19.800	MM	0.9596	636.90289	11.06230	4.9205

Table S1, entry 8: enantrioenriched, 90% ee



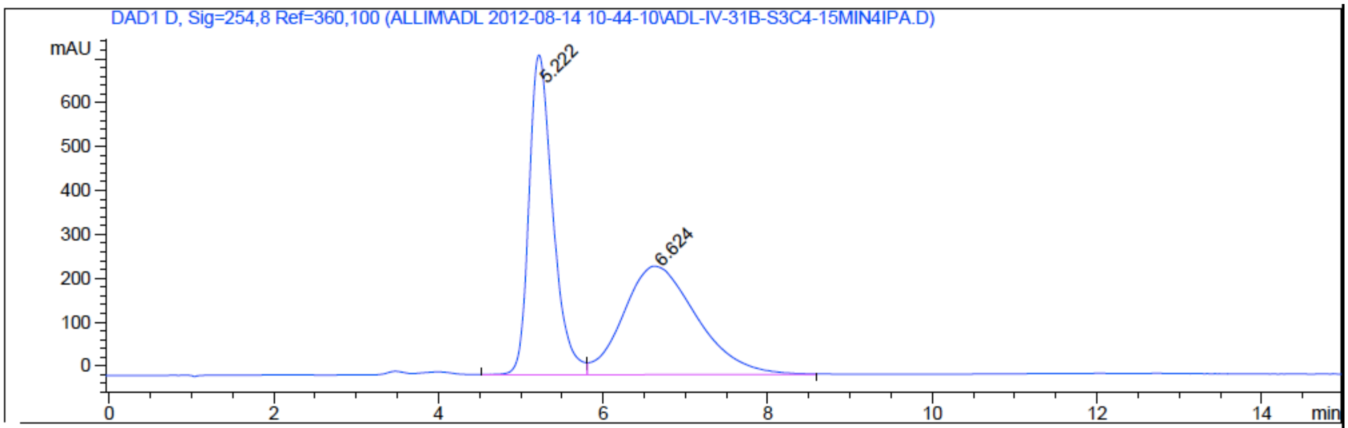
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	14.333	VB	0.4292	8036.22461	282.65863	95.1434
2	19.797	BB	0.5753	410.20886	8.45801	4.8566

Table S1, entry 9: enantrioenriched, 91% ee



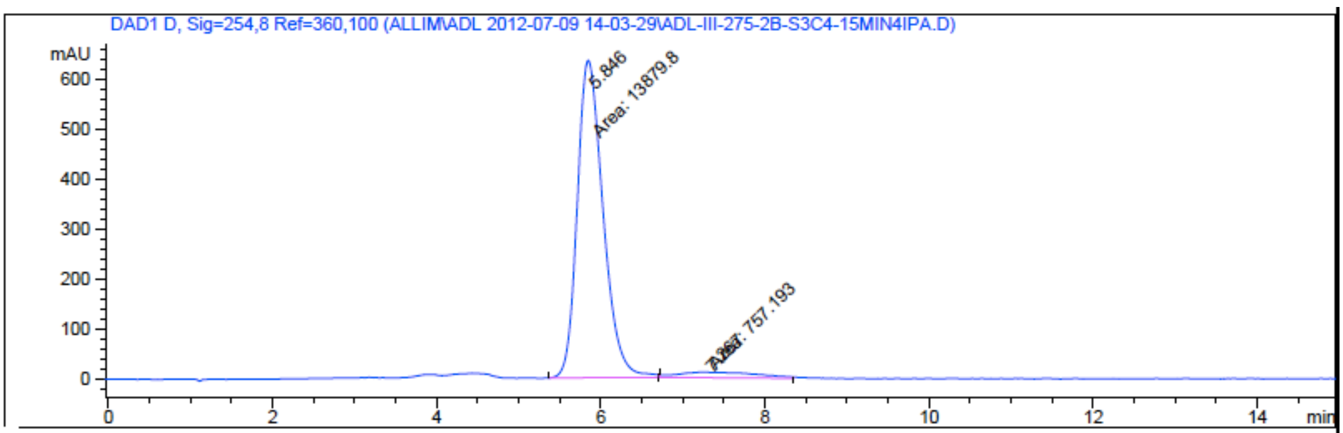
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	13.901	MM	0.3918	4.38911e4	1867.15771	95.5192
2	21.504	MM	0.9339	2058.93115	36.74272	4.4808

Pyrrolizidine 12: racemic



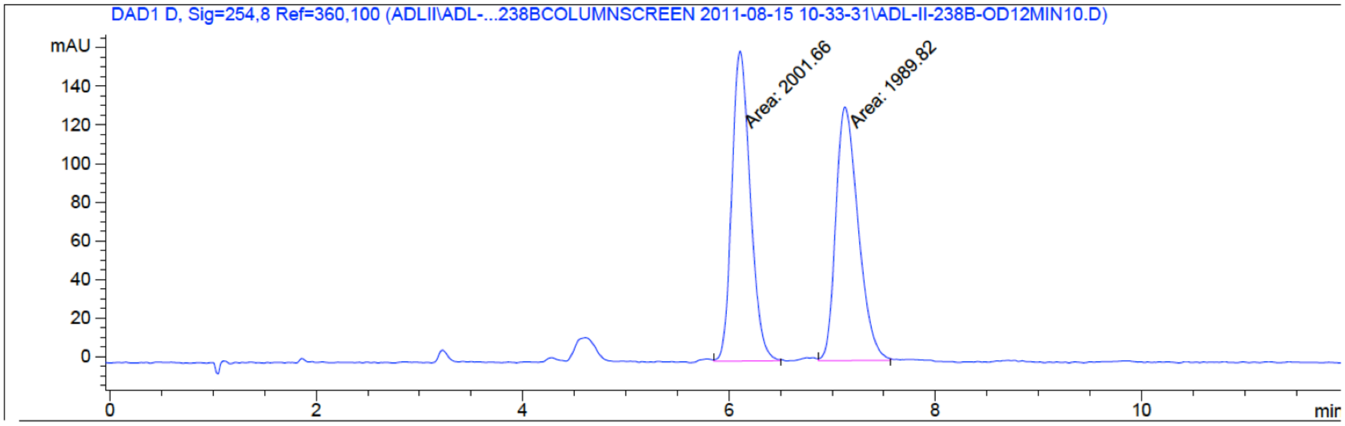
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.222	VV	0.3078	1.47293e4	728.71198	48.9407
2	6.624	VB	0.9374	1.53668e4	247.16225	51.0593

Pyrrolizidine 12: enantioenriched, 90% ee



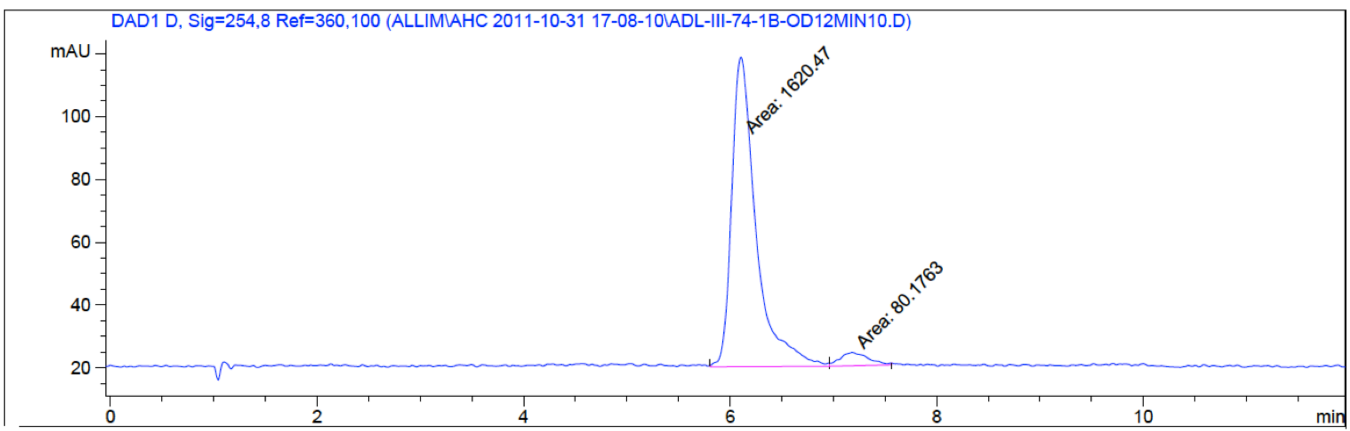
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.846	MM	0.3649	1.38798e4	633.94122	94.8269
2	7.267	MM	1.1258	757.19305	11.20974	5.1731

18a (Table 2, entry 1): racemic



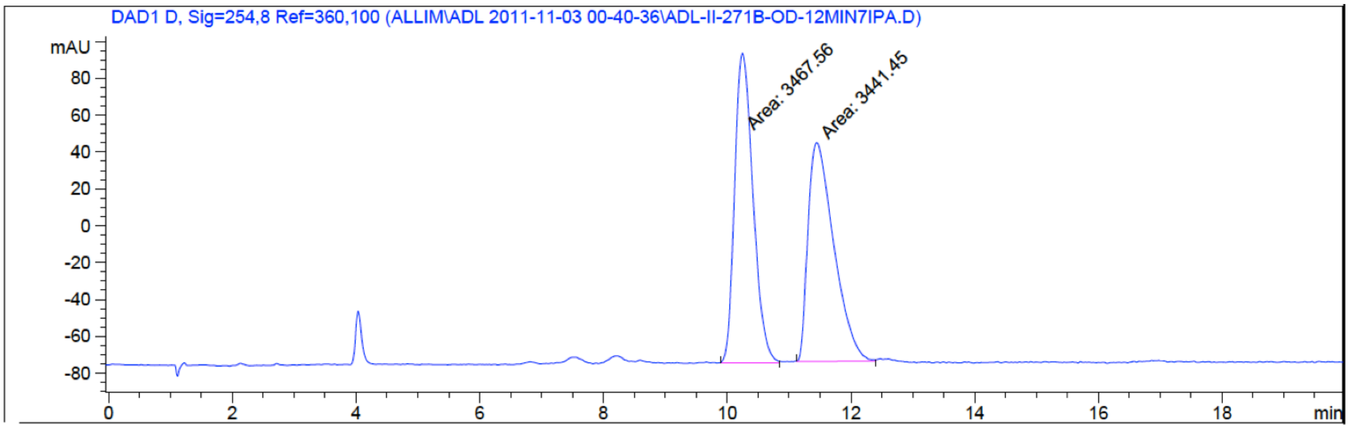
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.108	MM	0.2078	2001.65894	160.51328	50.1483
2	7.126	MM	0.2525	1989.82288	131.33904	49.8517

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



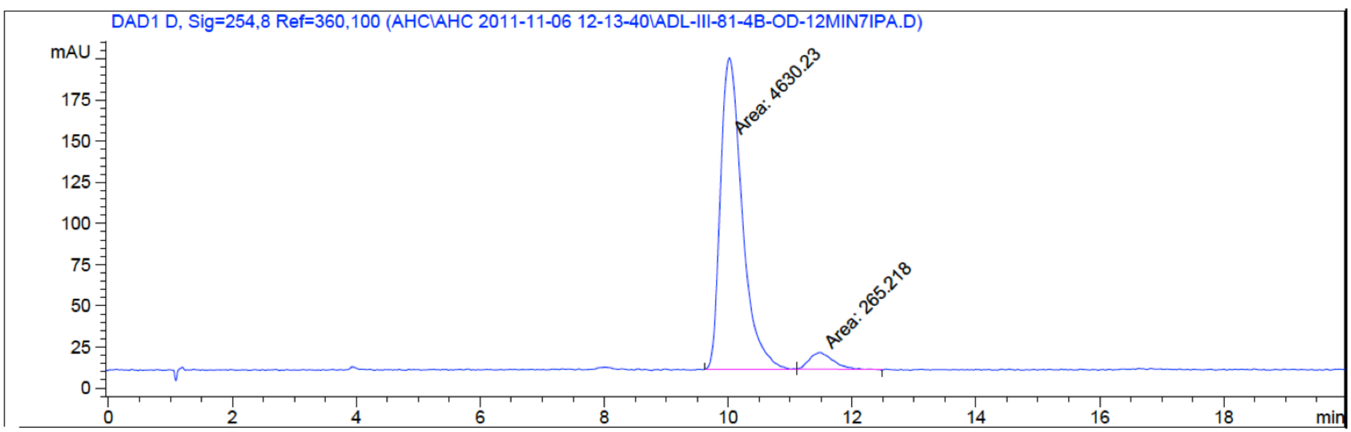
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.105	MM	0.2734	1620.47278	98.79230	95.2855
2	7.181	MM	0.3144	80.17634	4.25047	4.7145

18b (Table 2, entry 2): racemic



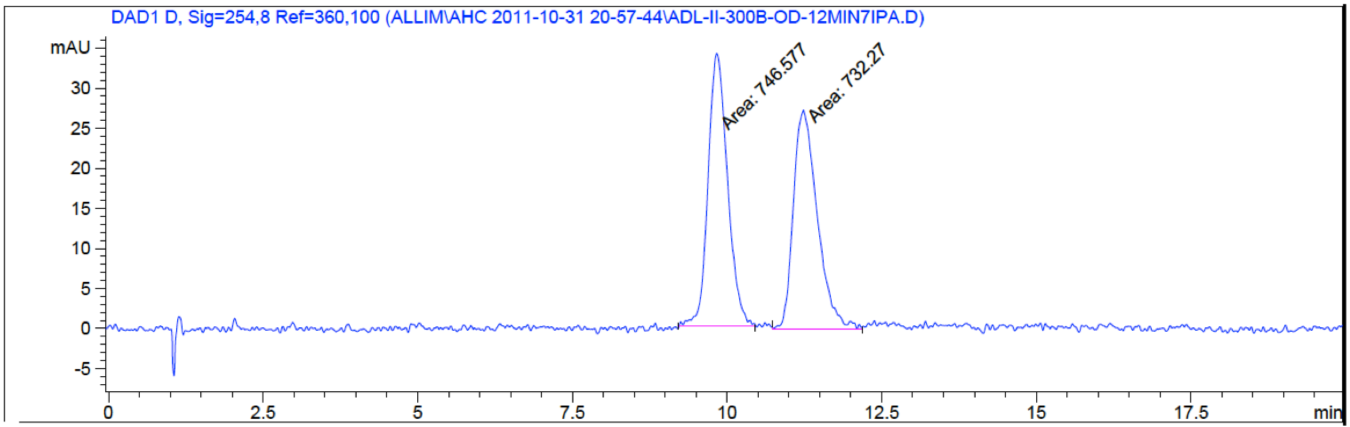
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.248	MM	0.3441	3467.56030	167.93707	50.1890
2	11.449	MM	0.4829	3441.44751	118.78632	49.8110

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



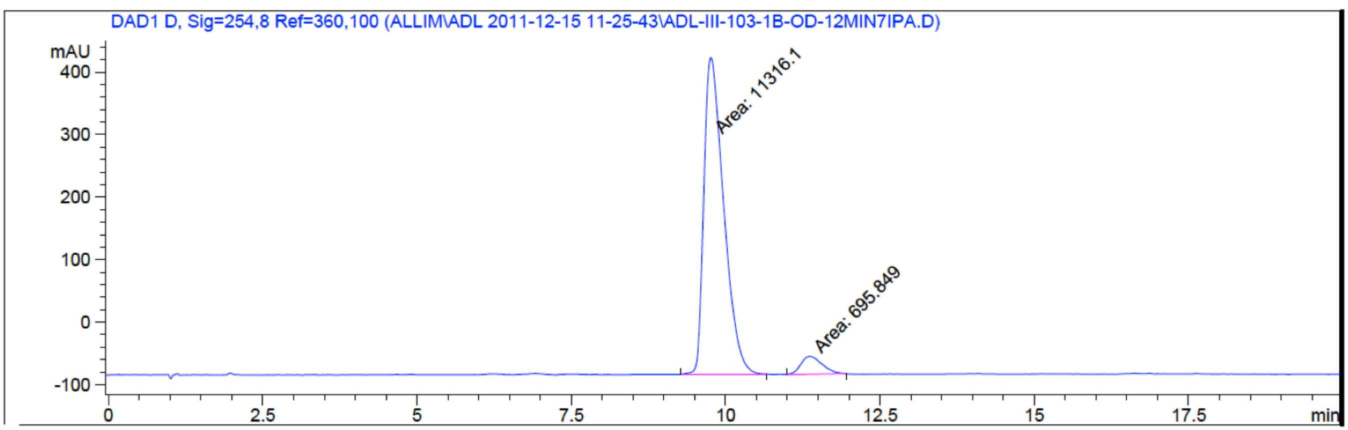
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.021	MM	0.4076	4630.22852	189.33492	94.5824
2	11.489	MM	0.4401	265.21768	10.04365	5.4176

18c (Table 2, entry 3): racemic



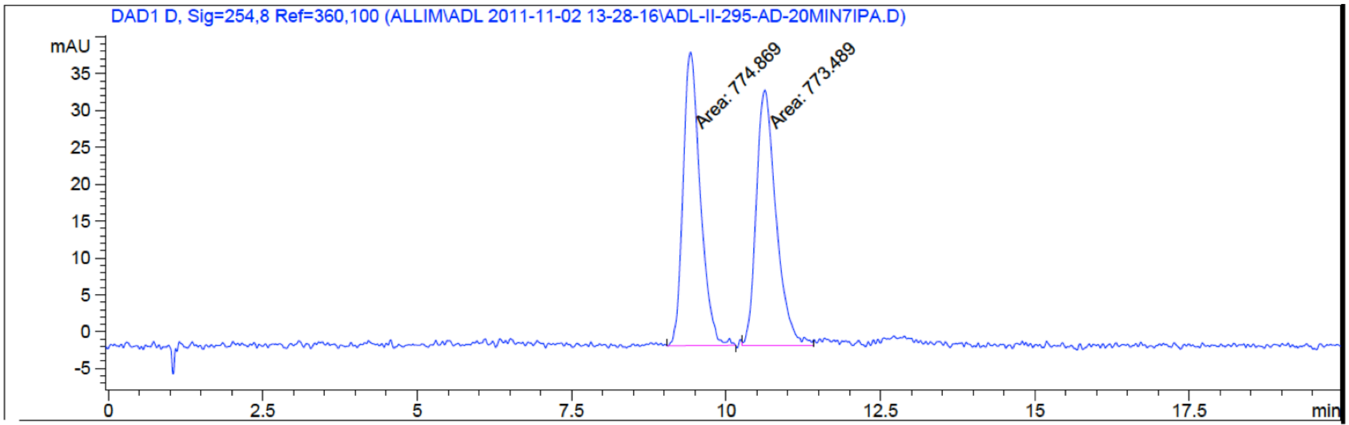
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.834	MM	0.3654	746.57739	34.05050	50.4837
2	11.236	MM	0.4474	732.26959	27.27870	49.5163

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



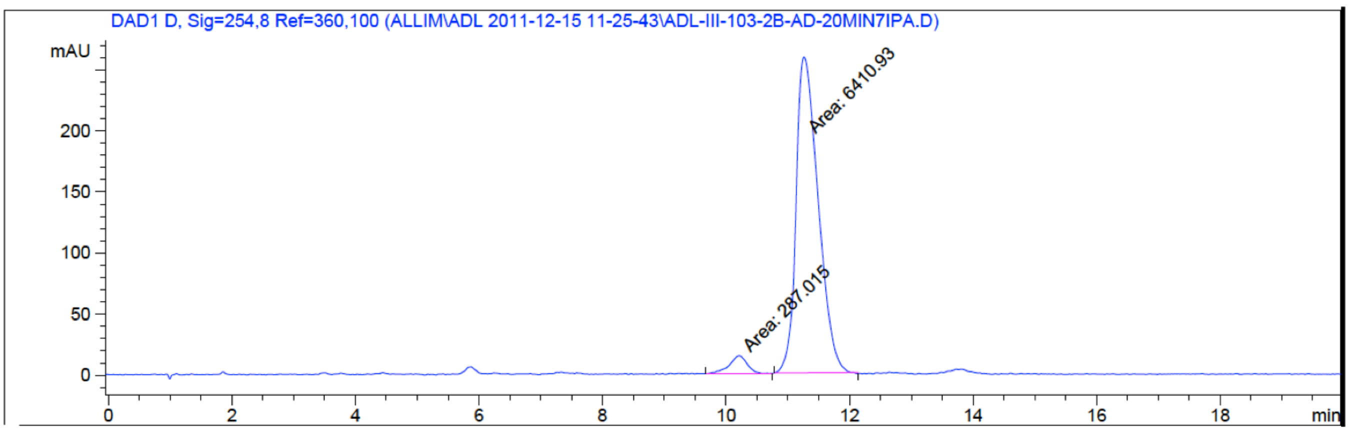
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.762	MM	0.3720	1.13161e4	507.00854	94.2070
2	11.367	MM	0.4038	695.84937	28.72410	5.7930

18d (Table 2, entry 4): racemic



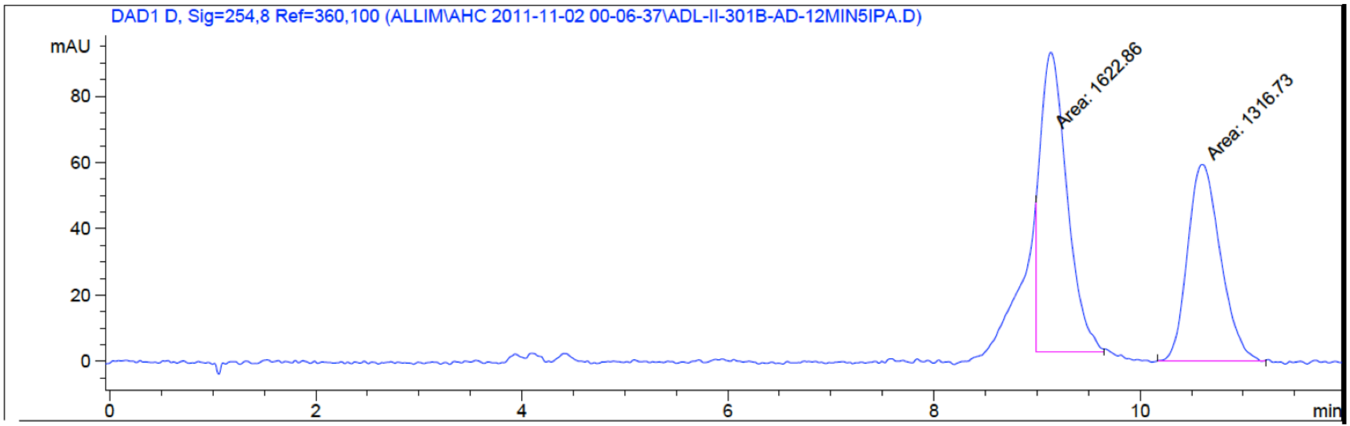
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.424	MM	0.3245	774.86896	39.79745	50.0446
2	10.628	MM	0.3721	773.48914	34.64676	49.9554

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



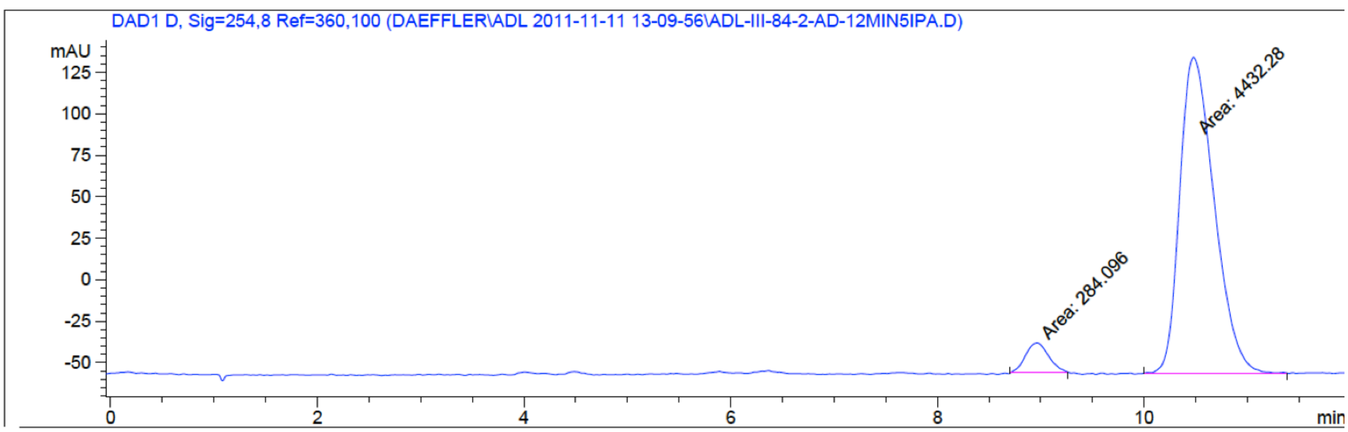
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.212	MM	0.3282	287.01508	14.57303	4.2851
2	11.264	MM	0.4134	6410.92969	258.47113	95.7149

18e (Table 2, entry 5): racemic



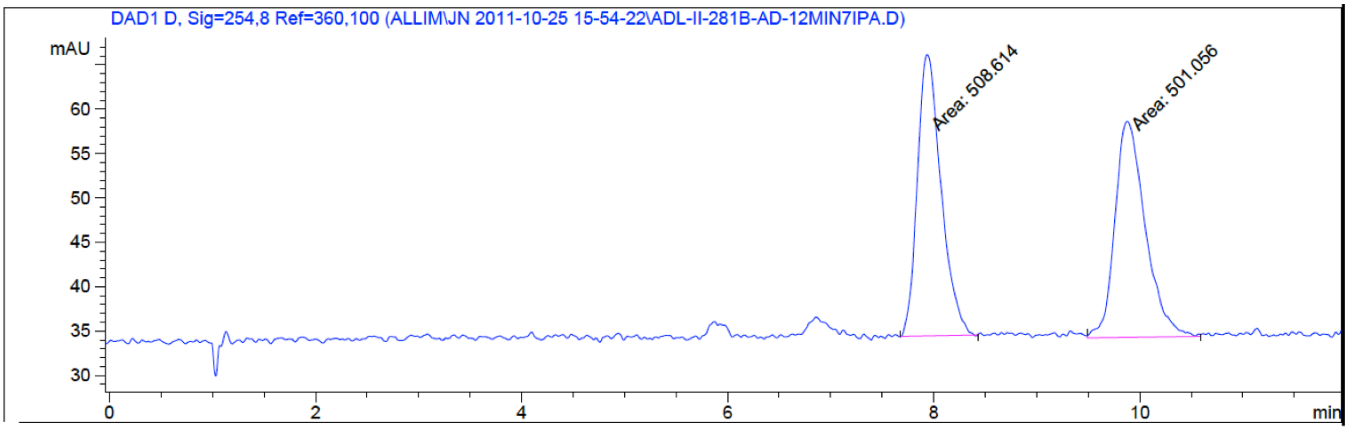
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.136	MM	0.2995	1622.86243	90.31247	55.2070
2	10.604	MM	0.3699	1316.73352	59.32040	44.7930

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



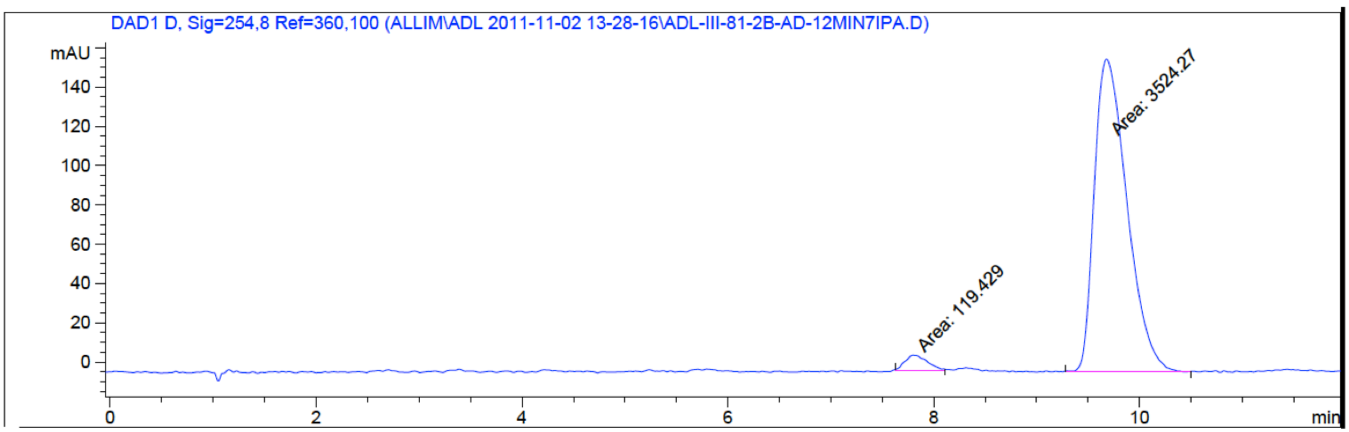
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.965	MM	0.2622	284.09586	18.05857	6.0236
2	10.478	MM	0.3875	4432.28174	190.62163	93.9764

18f (Table 2, entry 6): racemic



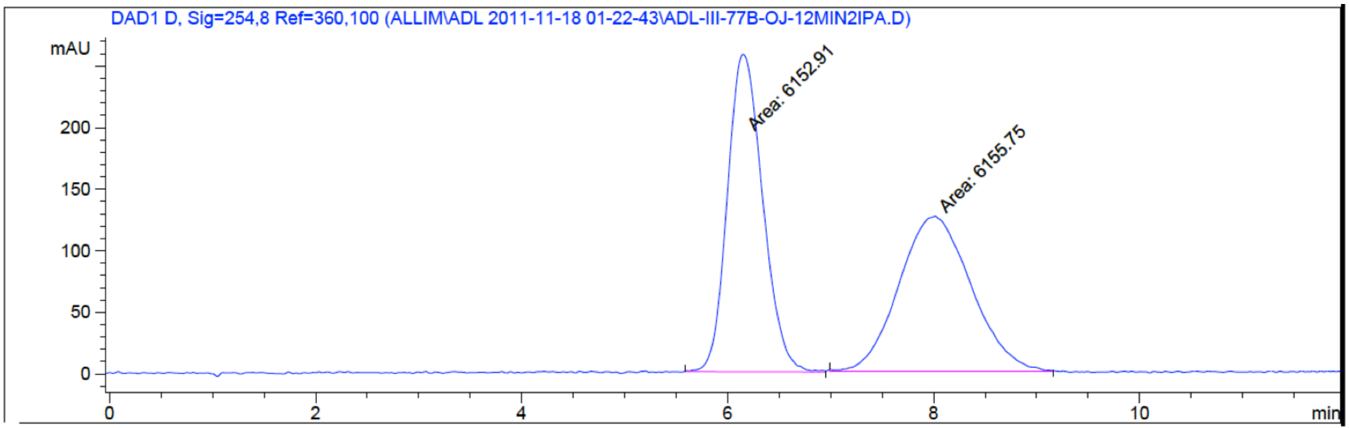
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.939	MM	0.2672	508.61426	31.72702	50.3743
2	9.879	MM	0.3428	501.05600	24.35941	49.6257

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



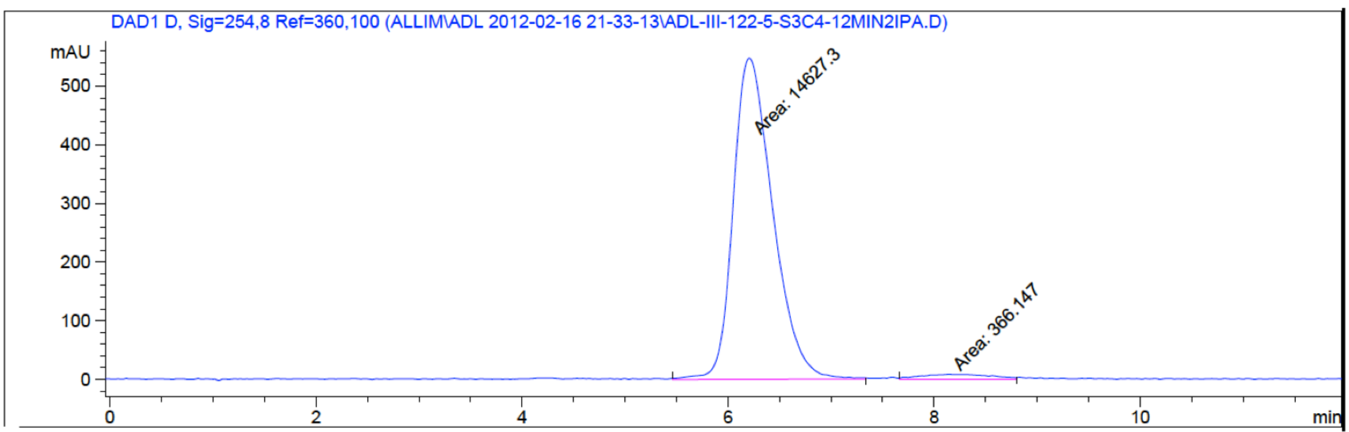
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.801	MM	0.2545	119.42921	7.82248	3.2777
2	9.680	MM	0.3688	3524.26855	159.27747	96.7223

18g (Table 2, entry 7): racemic



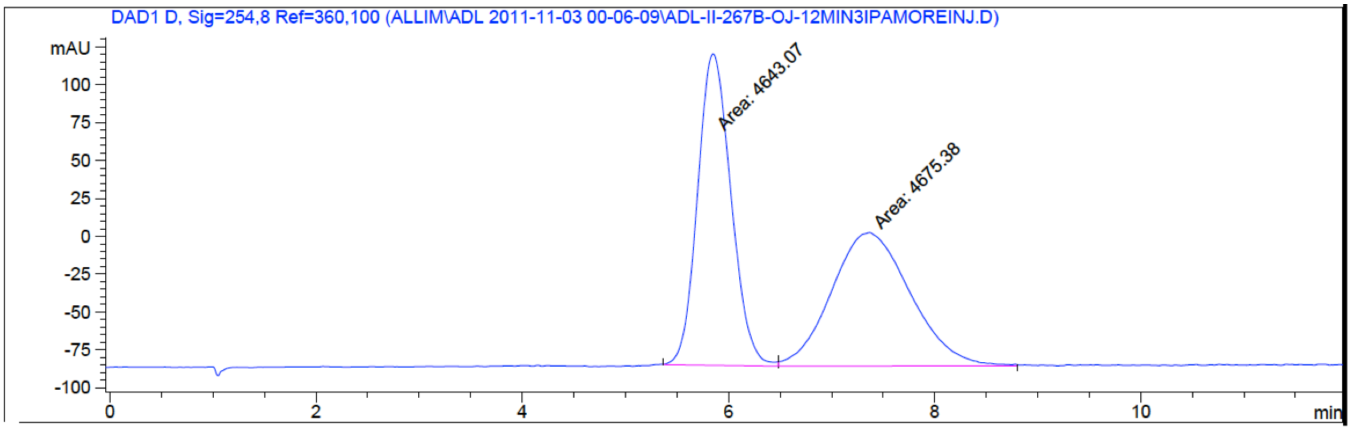
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.153	MM	0.3977	6152.91113	257.88422	49.9885
2	8.012	MM	0.8130	6155.75195	126.18888	50.0115

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



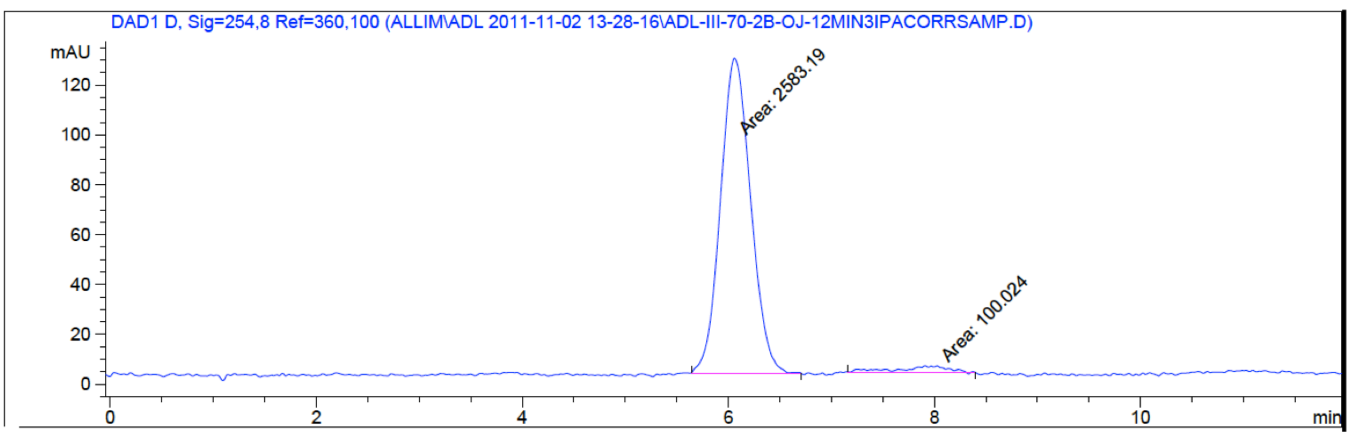
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.205	MM	0.4450	1.46273e4	547.89642	97.5580
2	8.144	MM	0.7646	366.14673	7.98159	2.4420

18h (Table 2, entry 8): racemic



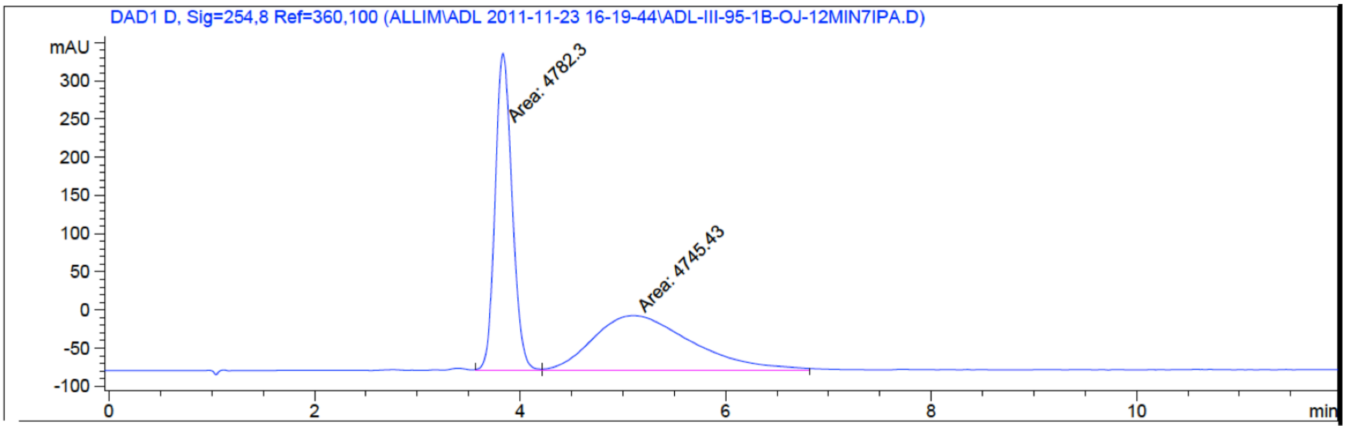
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.851	MM	0.3763	4643.07080	205.62646	49.8266
2	7.368	MM	0.8845	4675.37891	88.09424	50.1734

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



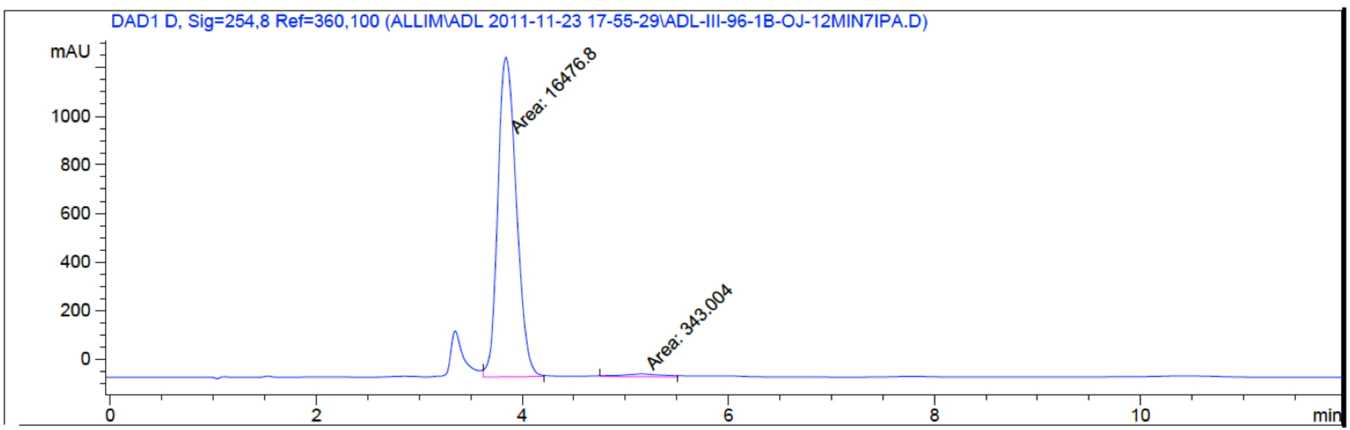
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.060	MM	0.3404	2583.18530	126.47279	96.2722
2	8.025	MM	0.5850	100.02399	2.84972	3.7278

18i (Table 2, entry 9): racemic



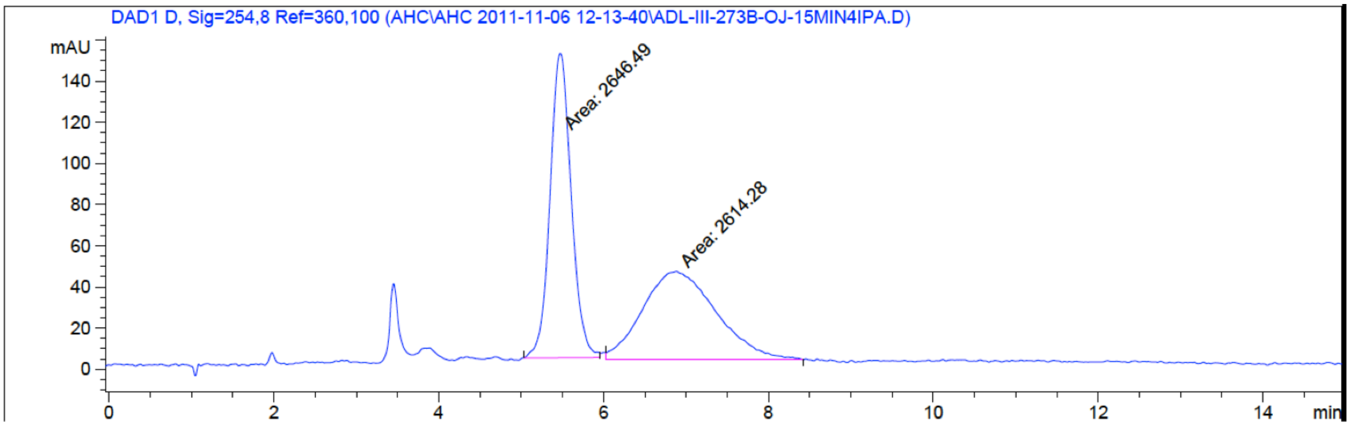
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.834	MM	0.1917	4782.29639	415.74722	50.1935
2	5.104	MM	1.1066	4745.43164	71.46948	49.8065

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



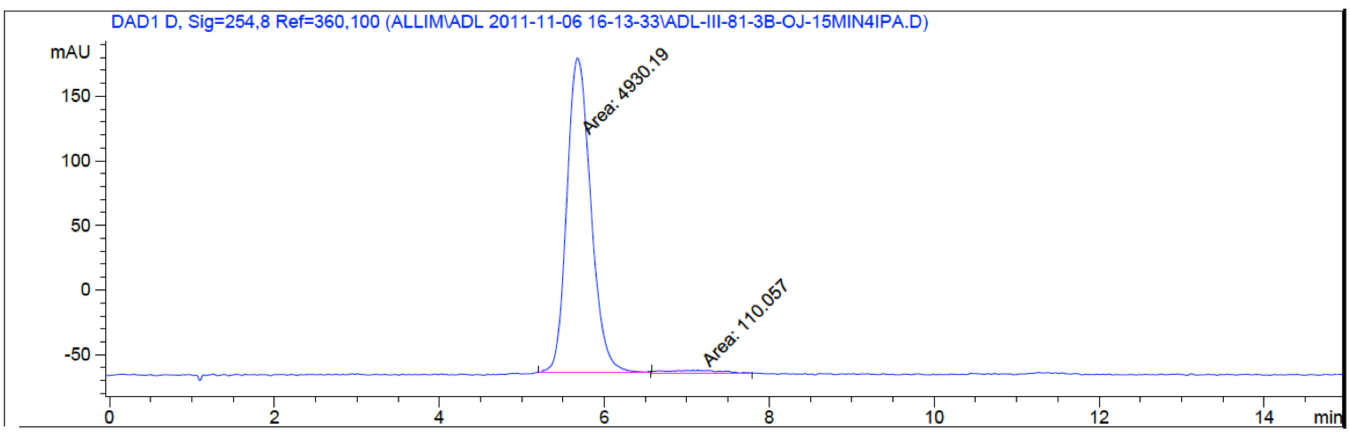
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.840	MM	0.2084	1.64768e4	1317.58875	97.9607
2	5.158	MM	0.4531	343.00388	12.61787	2.0393

18j (Table 2, entry 10): racemic



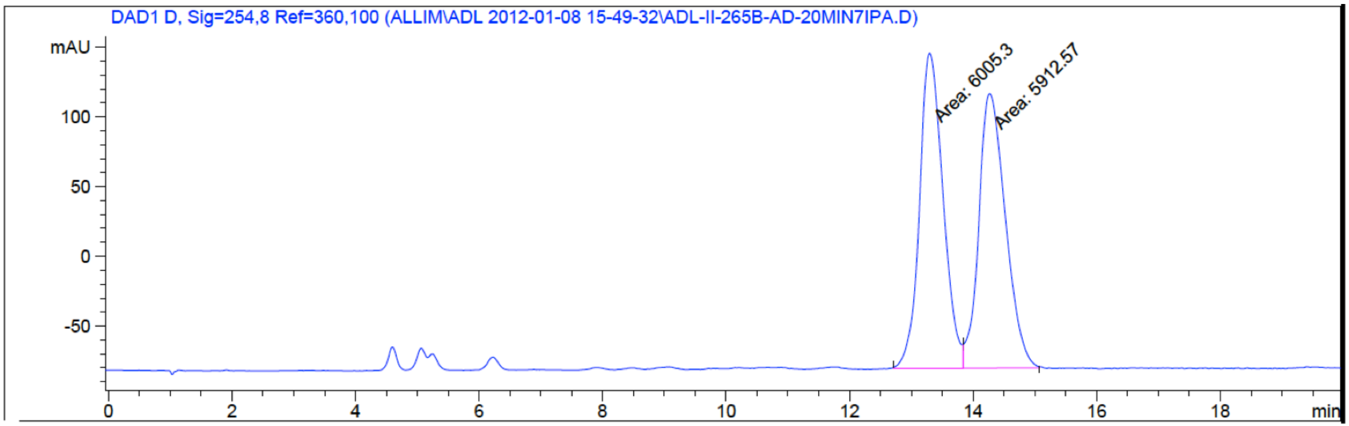
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.472	MM	0.2981	2646.49268	147.98149	50.3062
2	6.882	MM	1.0248	2614.28003	42.51883	49.6938

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



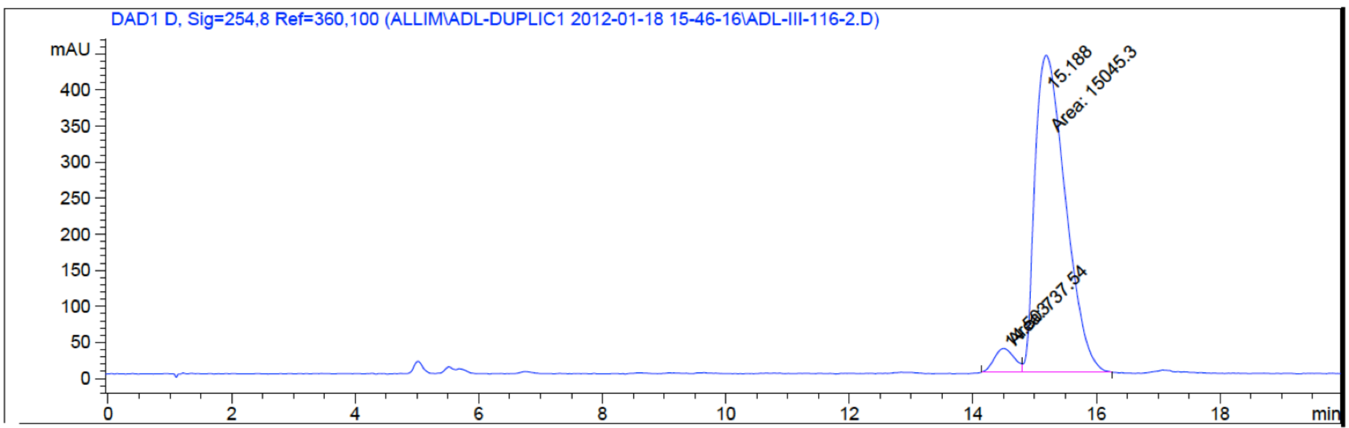
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.677	MM	0.3374	4930.19434	243.51300	97.8164
2	7.139	MM	0.8023	110.05745	2.28640	2.1836

18k (Table 2, entry 11): racemic



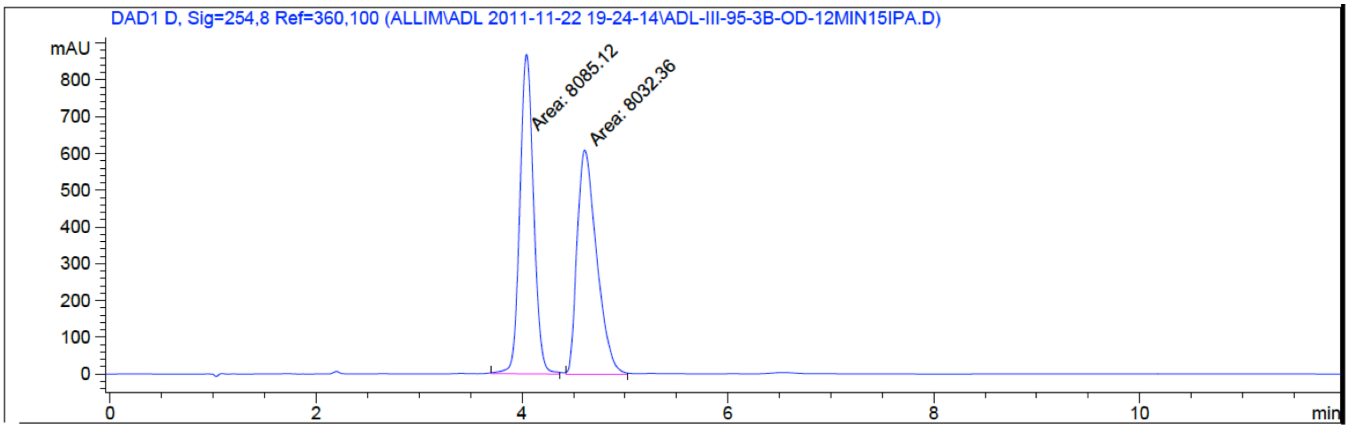
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.296	MM	0.4428	6005.30225	226.05704	50.3891
2	14.269	MM	0.5006	5912.56543	196.85155	49.6109

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



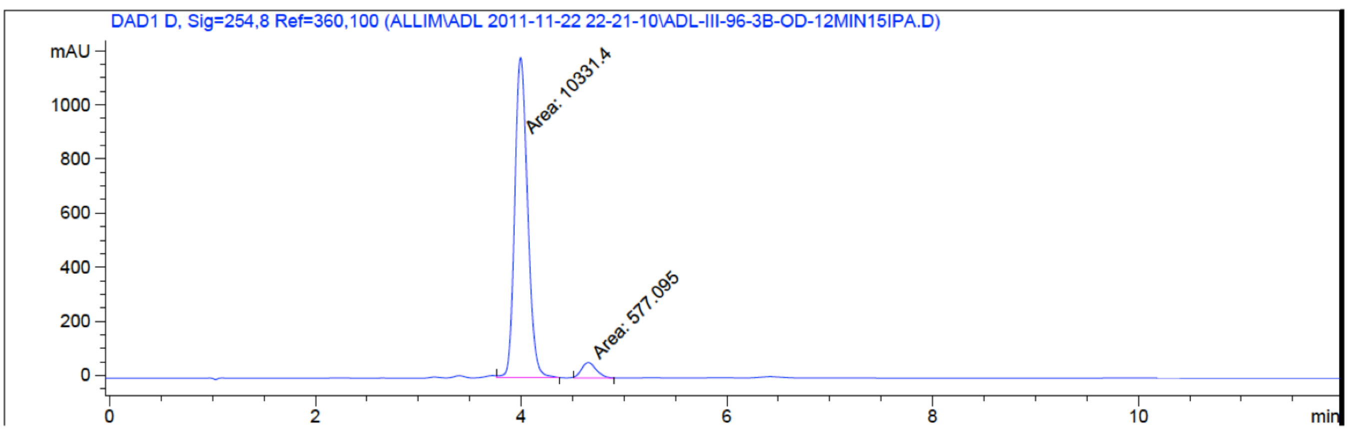
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.503	MM	0.3753	737.53986	32.75238	4.6730
2	15.188	MM	0.5713	1.50453e4	438.93250	95.3270

18l (Table 2, entry 12): racemic



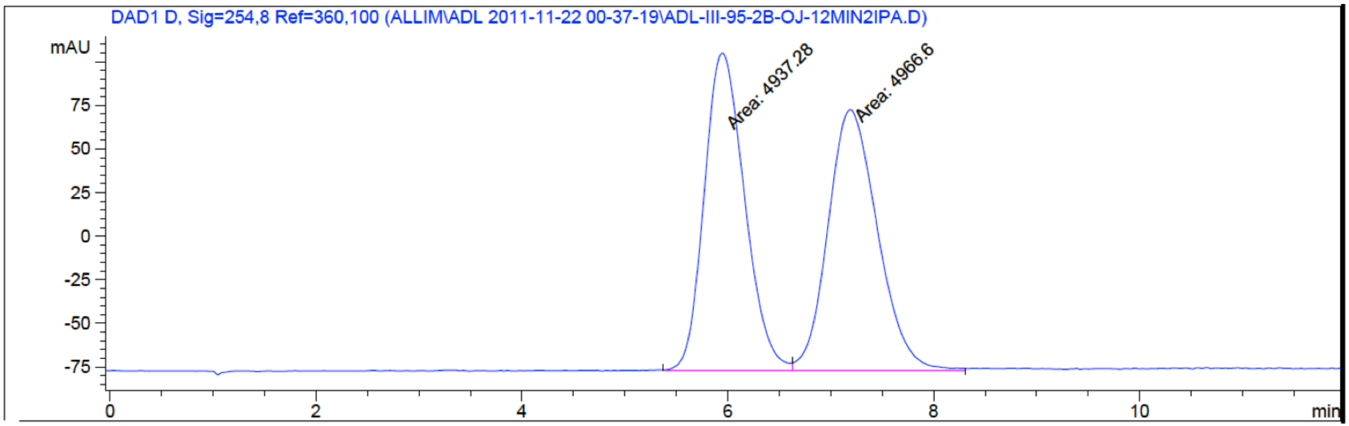
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.043	MM	0.1548	8085.12256	870.35547	50.1637
2	4.610	MM	0.2194	8032.36475	610.30841	49.8363

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



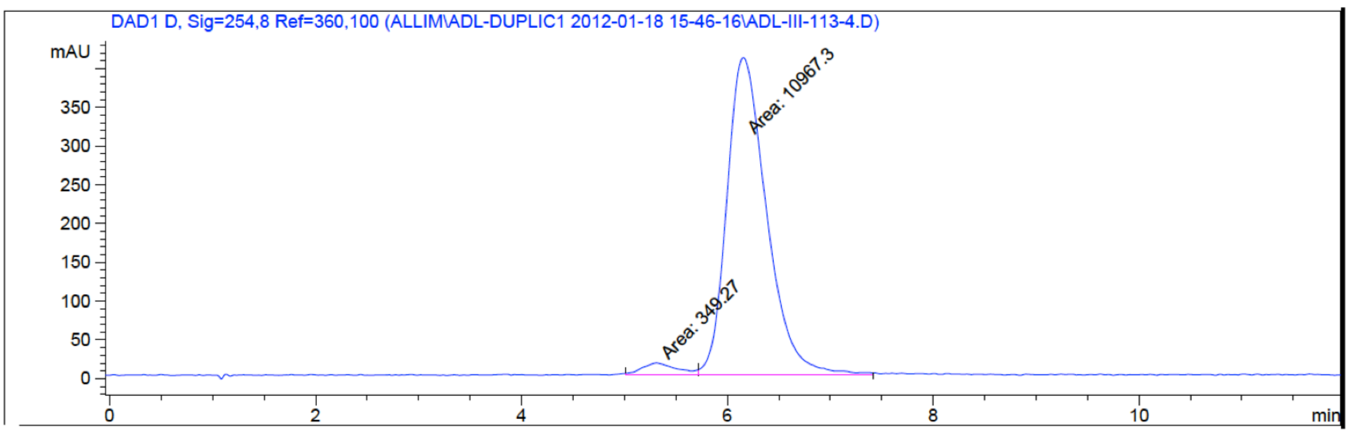
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.996	MM	0.1450	1.03314e4	1187.44409	94.7097
2	4.652	MM	0.1678	577.09467	57.32602	5.2903

18m (Table 2, entry 13): racemic



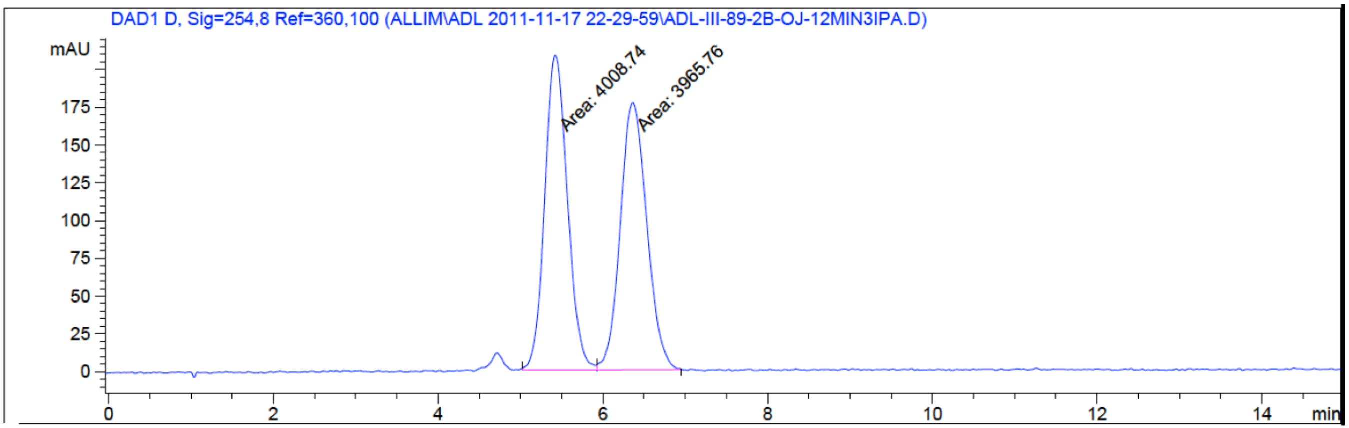
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.948	MM	0.4531	4937.27930	181.62985	49.8520
2	7.191	MM	0.5548	4966.60352	149.20677	50.1480

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



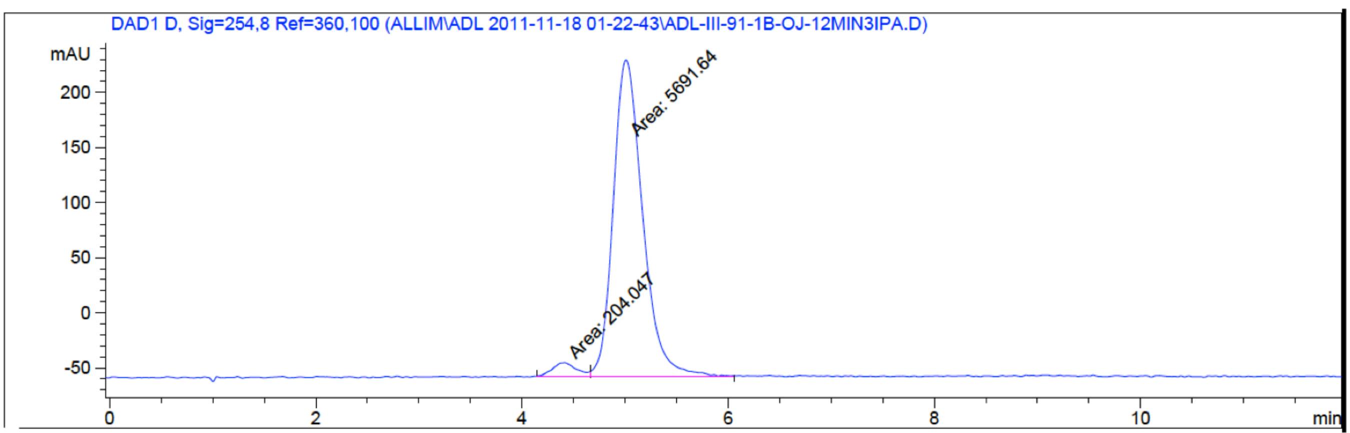
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.317	MM	0.3888	349.27008	14.97120	3.0863
2	6.156	MM	0.4472	1.09673e4	408.74576	96.9137

18n (Table 2, entry 14): racemic



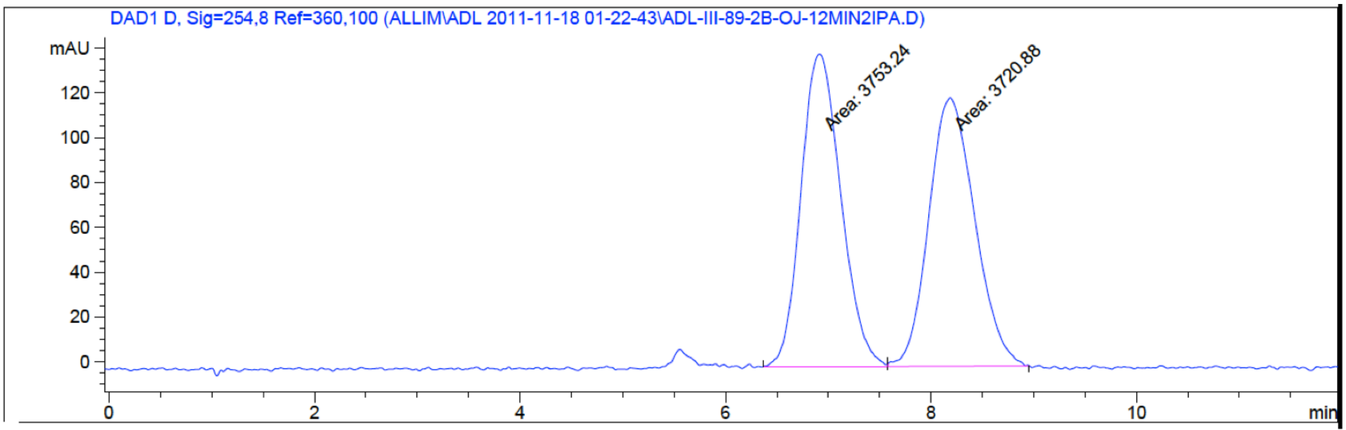
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.422	MM	0.3205	4008.73901	208.46022	50.2695
2	6.362	MM	0.3737	3965.76196	176.85144	49.7305

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



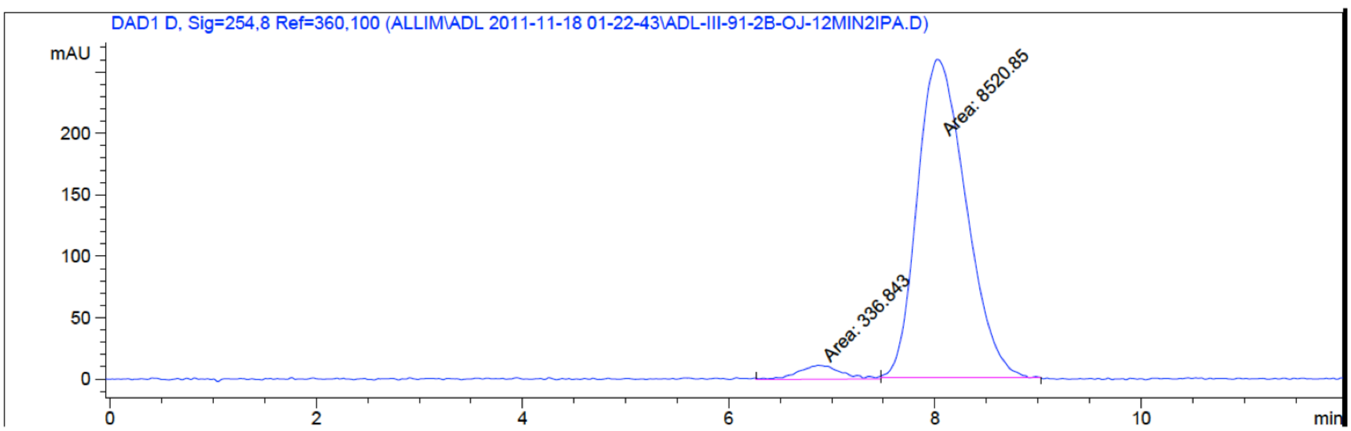
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.412	MM	0.2714	204.04715	12.53074	3.4610
2	5.009	MM	0.3301	5691.64258	287.34784	96.5390

18o (Table 2, entry 15): racemic



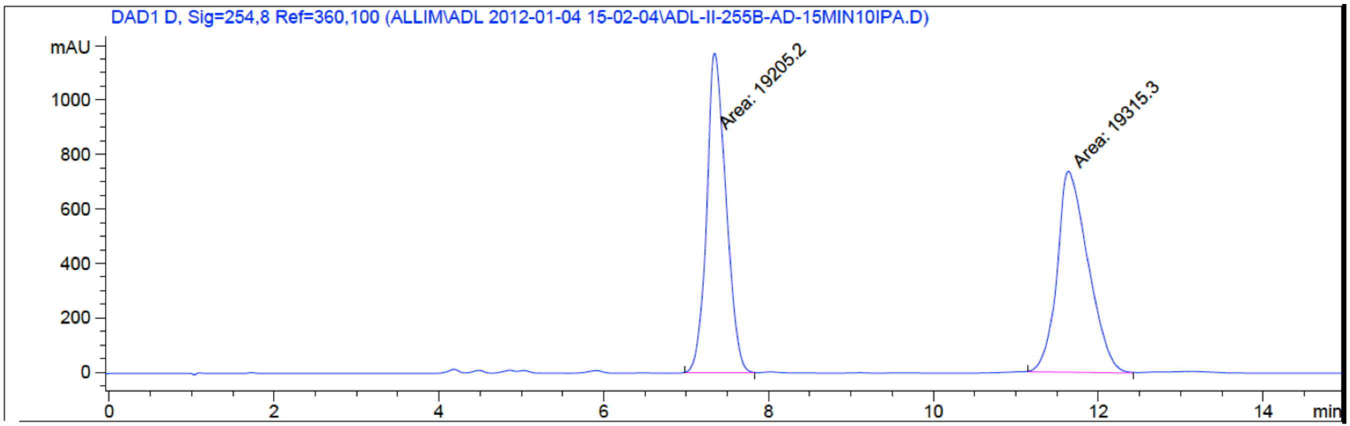
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.916	MM	0.4495	3753.23584	139.15379	50.2164
2	8.186	MM	0.5183	3720.88330	119.64903	49.7836

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



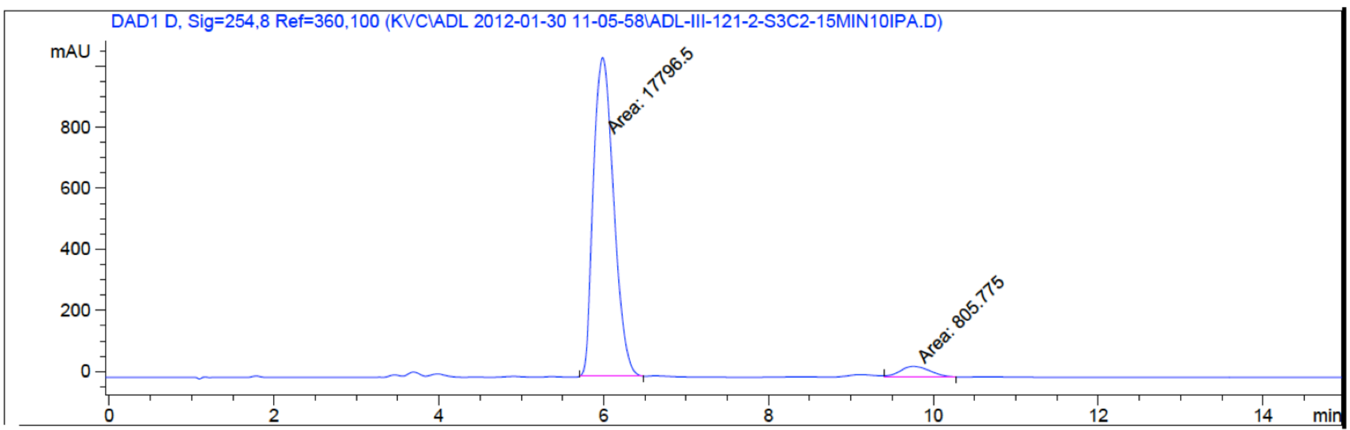
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.875	MM	0.4951	336.84314	11.33872	3.8028
2	8.028	MM	0.5478	8520.84766	259.25595	96.1972

18p (Table 2, entry 16): racemic



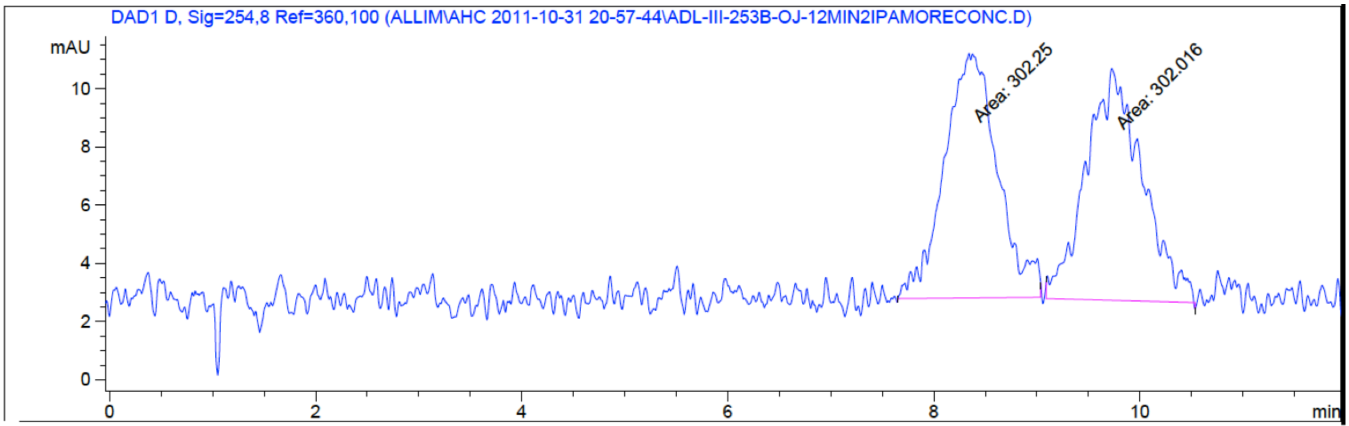
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.344	MM	0.2724	1.92052e4	1174.87732	49.8570
2	11.638	MM	0.4363	1.93153e4	737.87109	50.1430

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



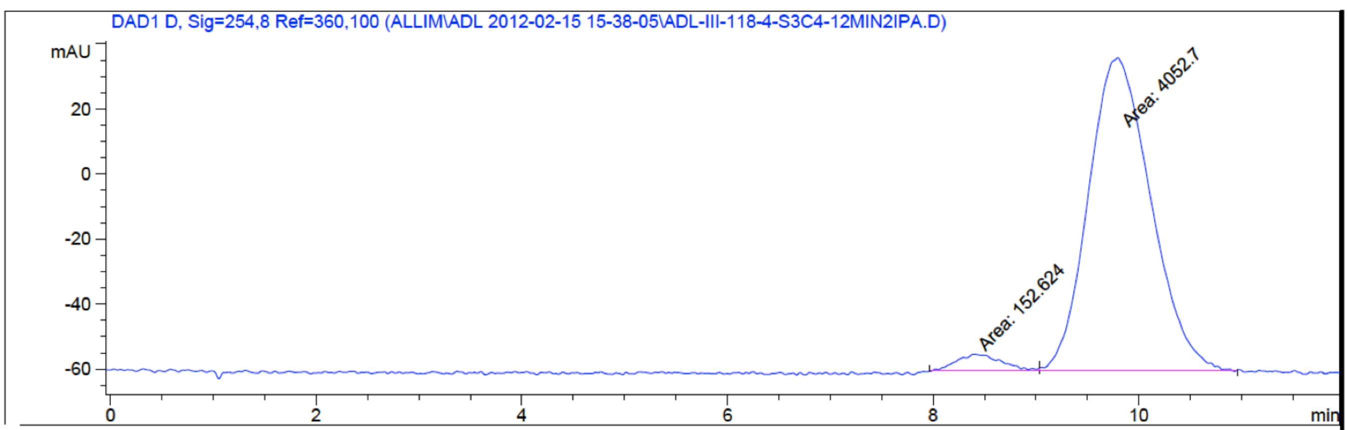
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.986	MM	0.2845	1.77965e4	1042.43127	95.6684
2	9.756	MM	0.4056	805.77496	33.10773	4.3316

18q (Table 2, entry 17): racemic



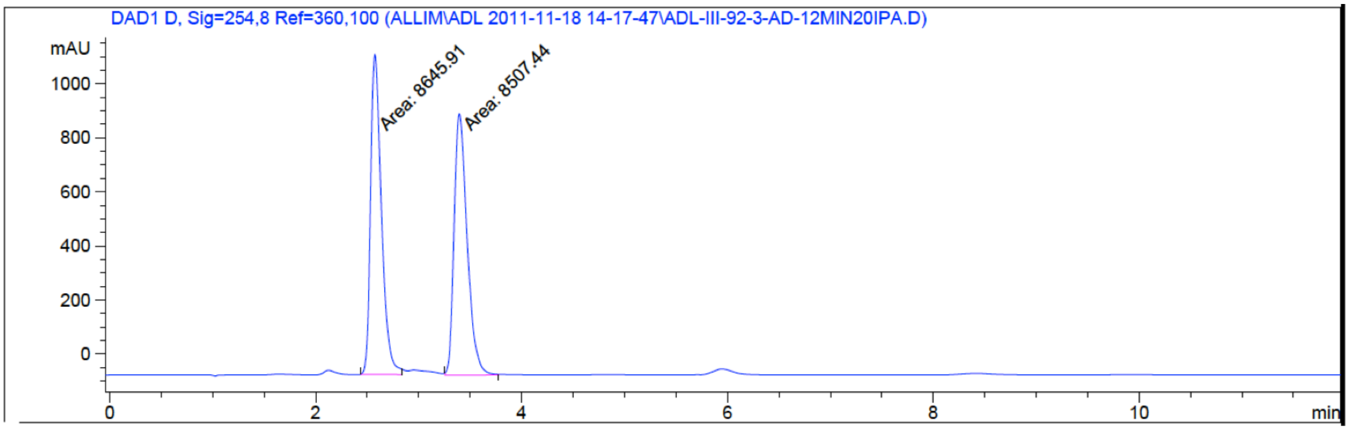
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.342	MM	0.5983	302.25012	8.41932	50.0193
2	9.729	MM	0.6295	302.01633	7.99656	49.9807

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



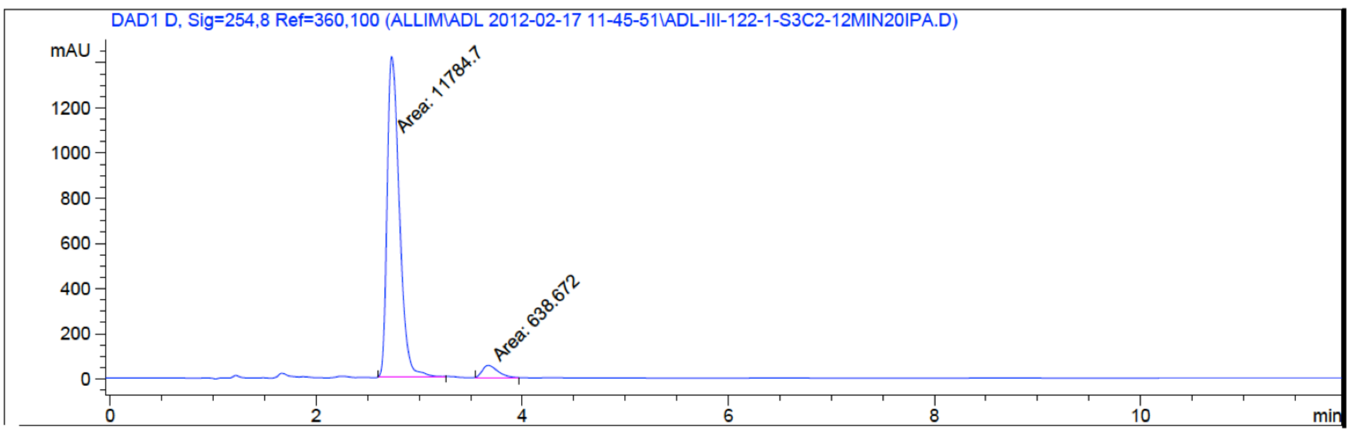
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.397	MM	0.5067	152.62421	5.01974	3.6293
2	9.795	MM	0.7024	4052.70093	96.15991	96.3707

18r (Table 2, entry 18): racemic



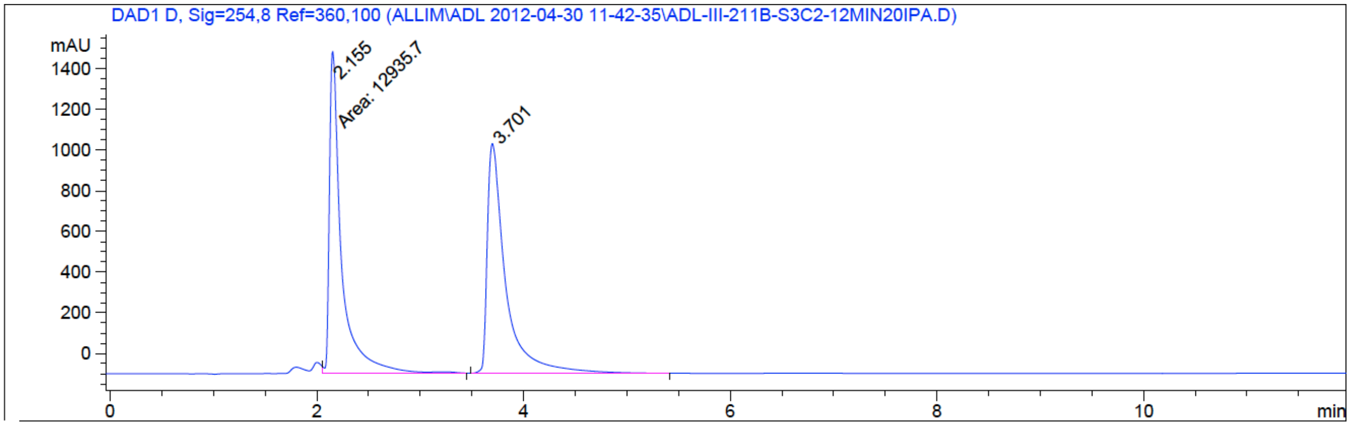
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.576	MM	0.1212	8645.91406	1189.34485	50.4036
2	3.396	MM	0.1461	8507.43750	970.72430	49.5964

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



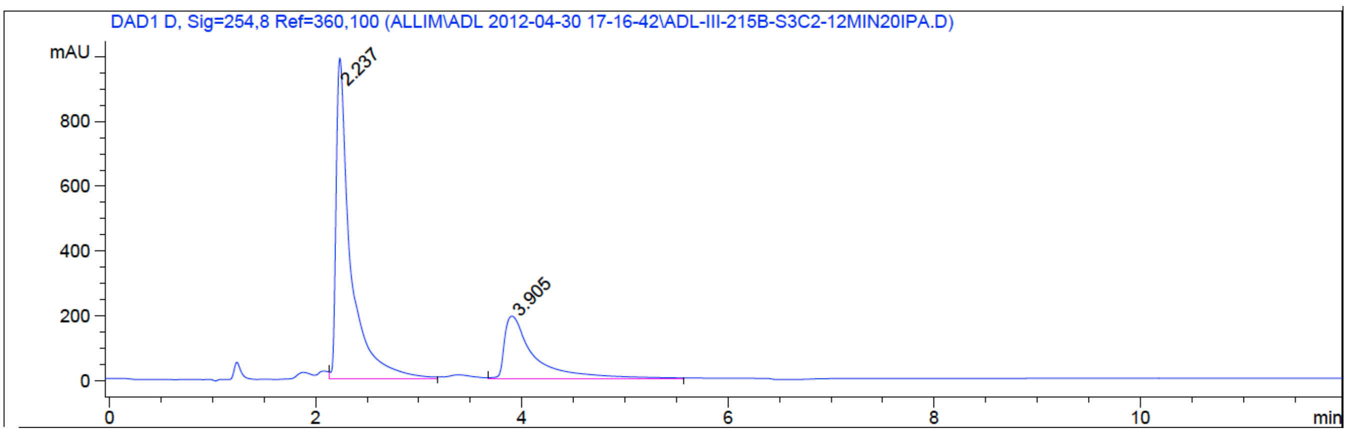
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.735	MM	0.1378	1.17847e4	1425.19104	94.8591
2	3.671	MM	0.1867	638.67236	57.00725	5.1409

18s (Table 2, entry 19): racemic



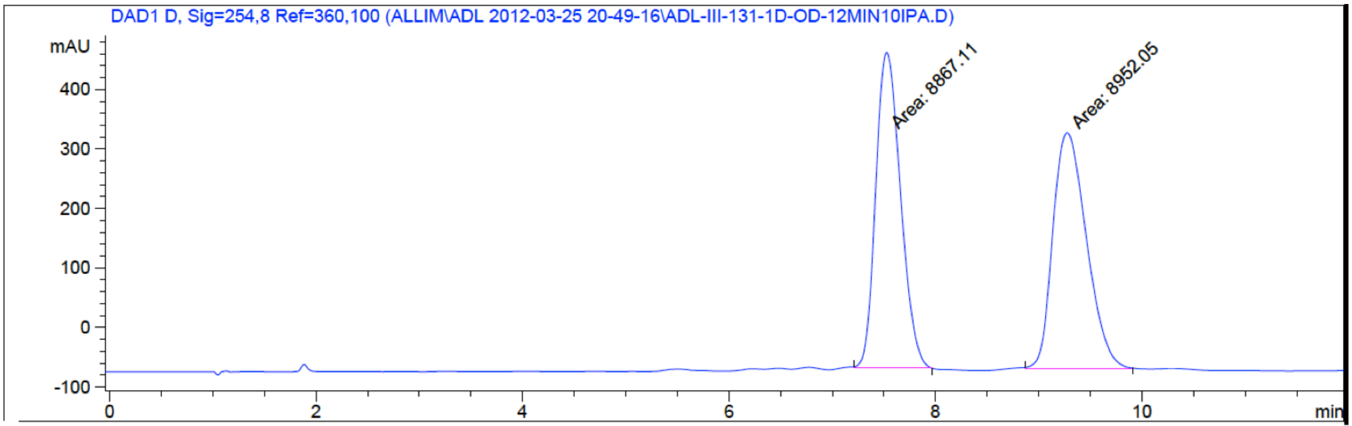
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.155	MM	0.1354	1.29357e4	1592.16809	48.0838
2	3.701	VB	0.1806	1.39667e4	1126.56702	51.9162

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



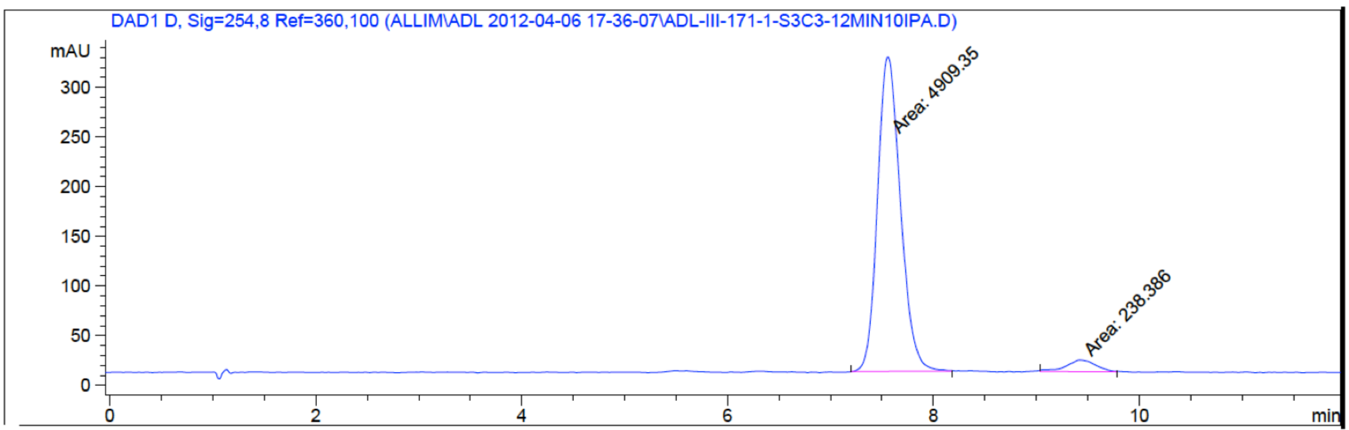
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.237	VB	0.1419	9604.80957	983.68304	71.8777
2	3.905	VB	0.2807	3757.89526	191.67908	28.1223

19a (Table 3): racemic



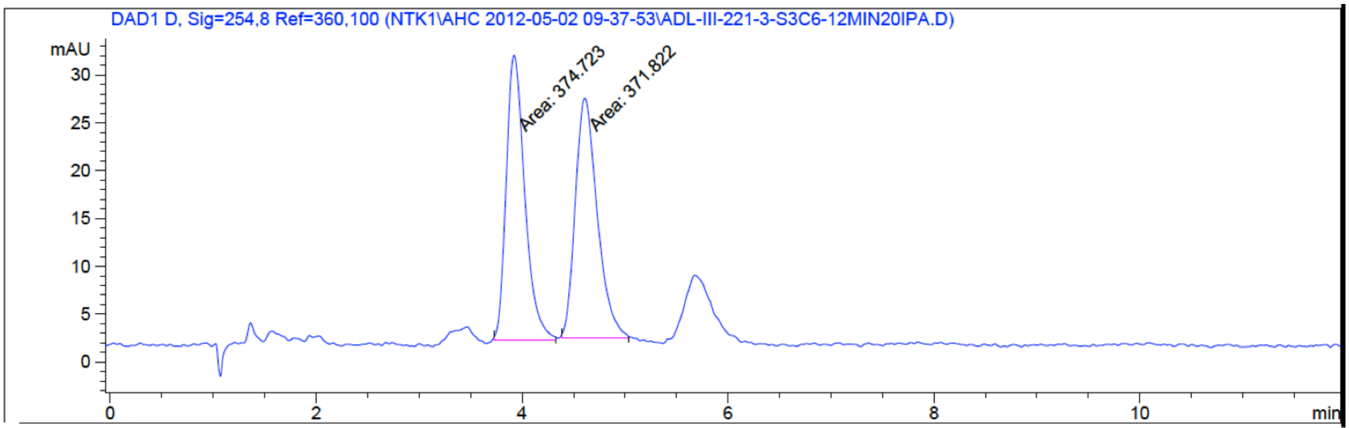
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.528	MM	0.2786	8867.11035	530.54260	49.7617
2	9.276	MM	0.3763	8952.04590	396.47534	50.2383

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



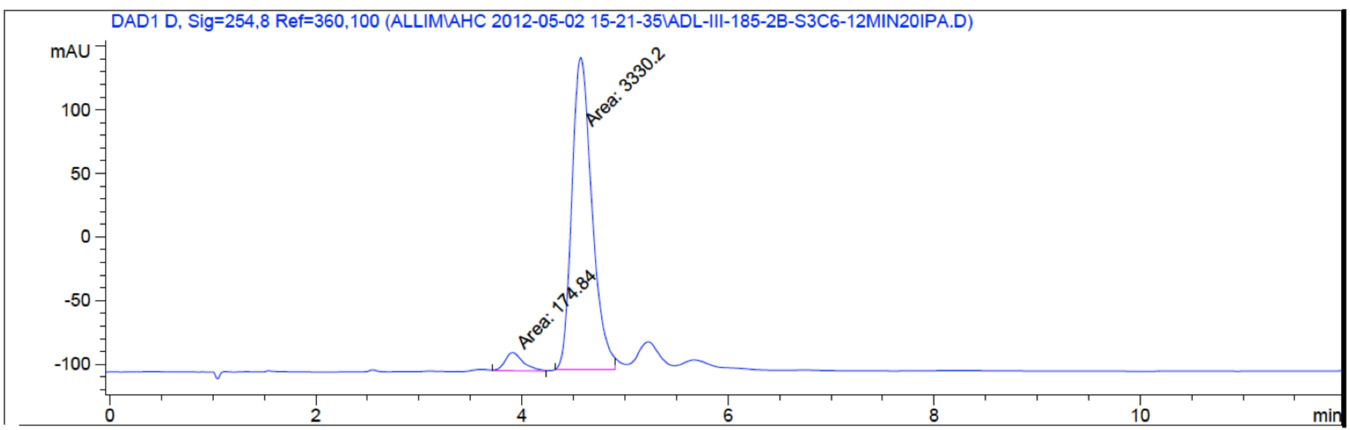
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.558	MM	0.2580	4909.35205	317.09402	95.3691
2	9.425	MM	0.3346	238.38634	11.87408	4.6309

19b (Table 3): racemic



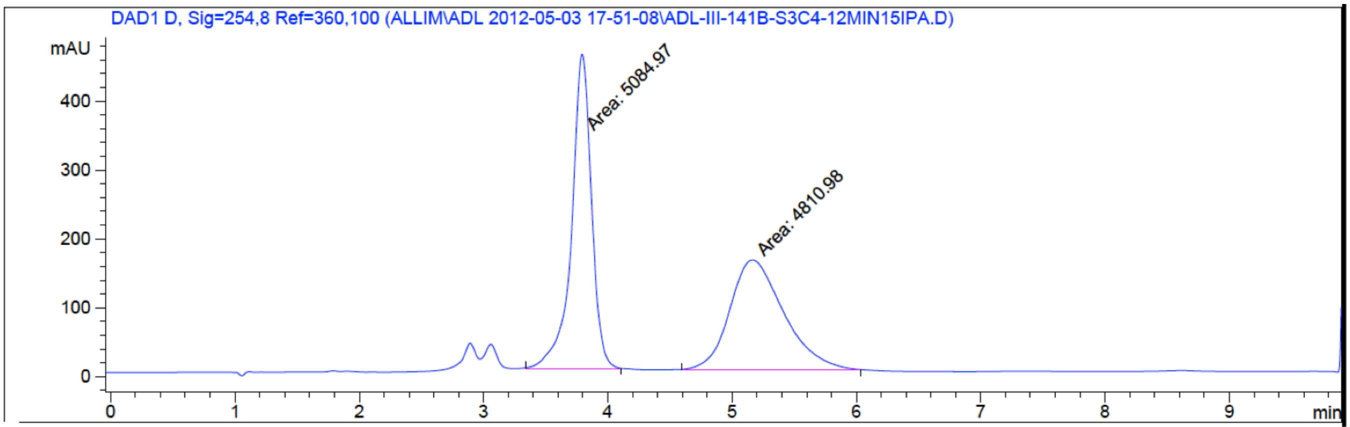
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.923	MM	0.2092	374.72302	29.85601	50.1943
2	4.609	MM	0.2470	371.82239	25.08781	49.8057

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



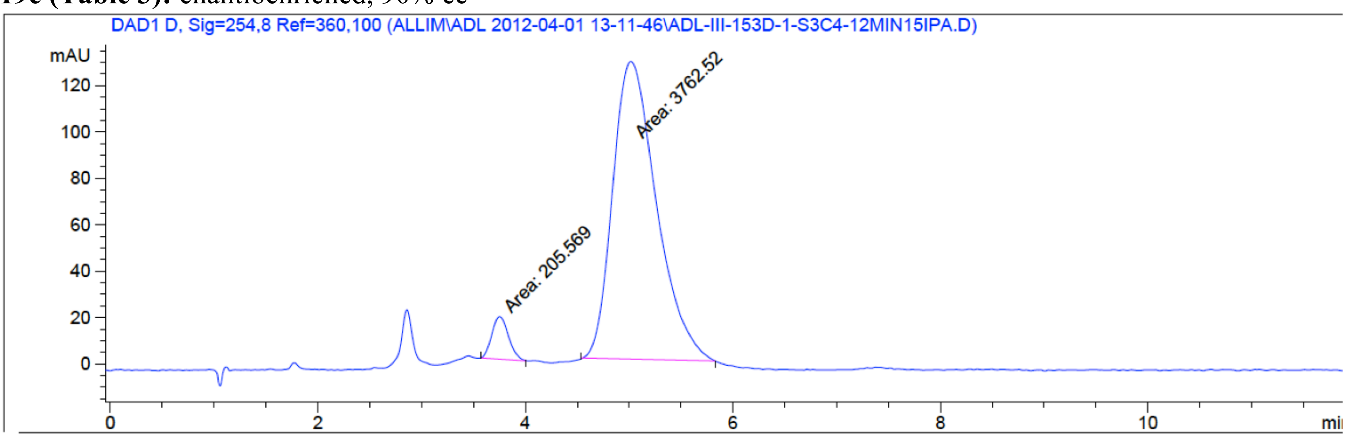
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.909	MM	0.2045	174.84013	14.24727	4.9882
2	4.570	MM	0.2260	3330.20483	245.55070	95.0118

19c (Table 3): racemic



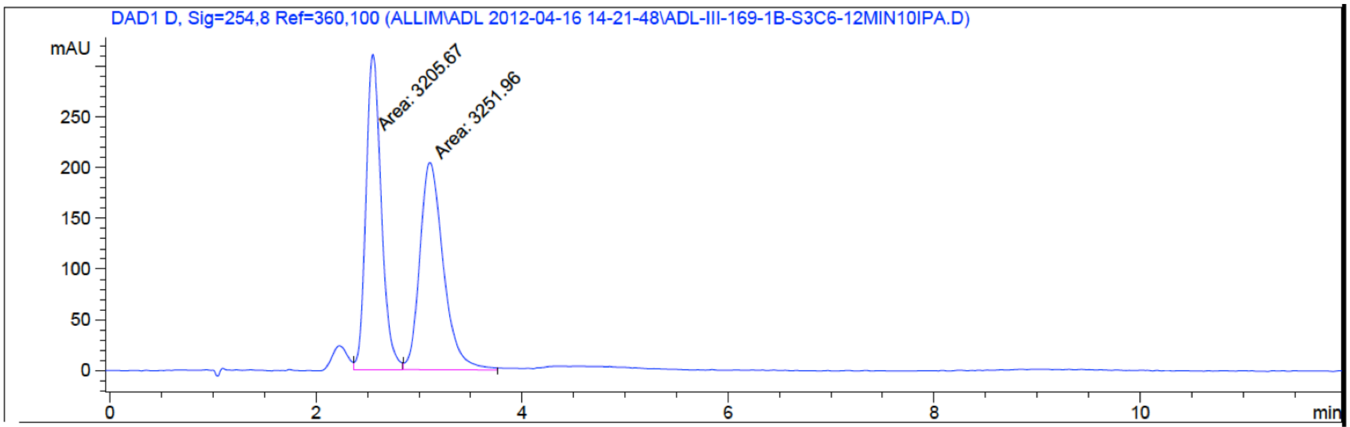
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.794	MM	0.1854	5084.96924	457.11218	51.3844
2	5.165	MM	0.5036	4810.97998	159.20520	48.6156

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



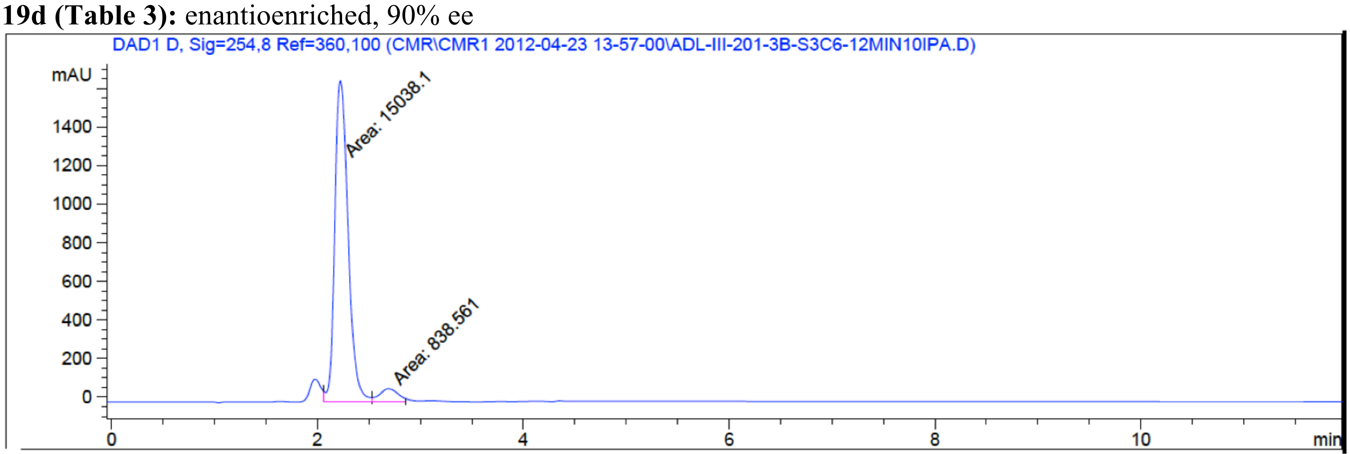
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.752	MM	0.1869	205.56940	18.33098	5.1806
2	5.016	MM	0.4891	3762.51758	128.21497	94.8194

19d (Table 3): racemic



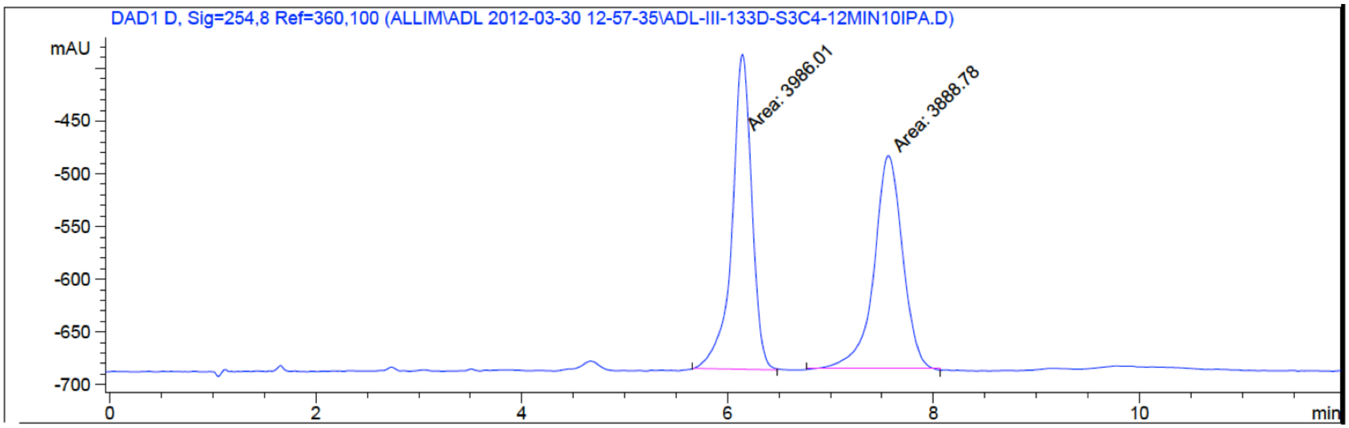
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.552	MM	0.1717	3205.67017	311.25909	49.6416
2	3.106	MM	0.2652	3251.96484	204.37744	50.3584

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



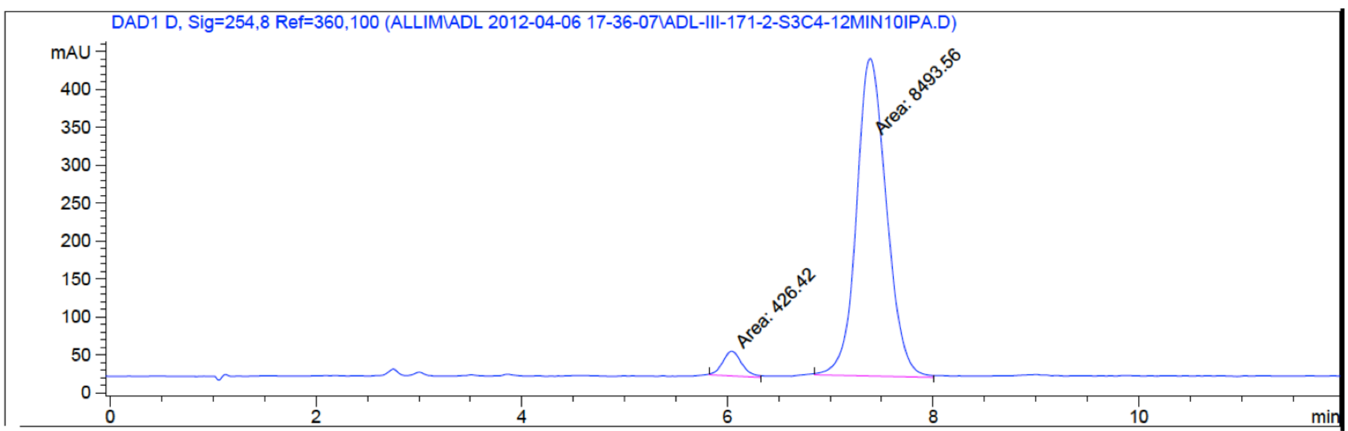
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.224	MM	0.1504	1.50381e4	1666.51477	94.7183
2	2.693	MM	0.2084	838.56067	67.05596	5.2817

19e (Table 3): racemic



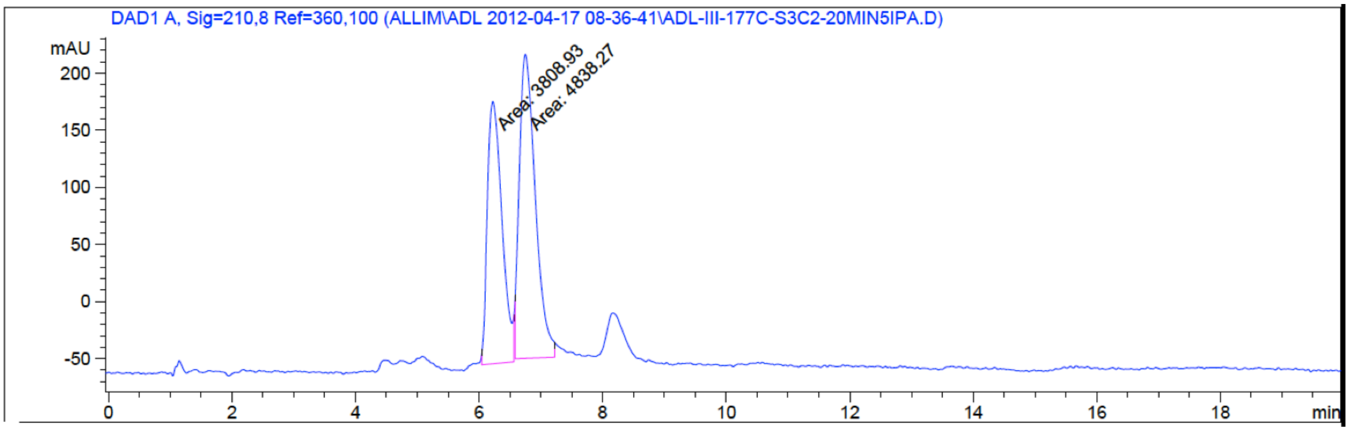
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.144	MM	0.2222	3986.00659	298.95831	50.6173
2	7.563	MM	0.3216	3888.78369	201.55779	49.3827

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



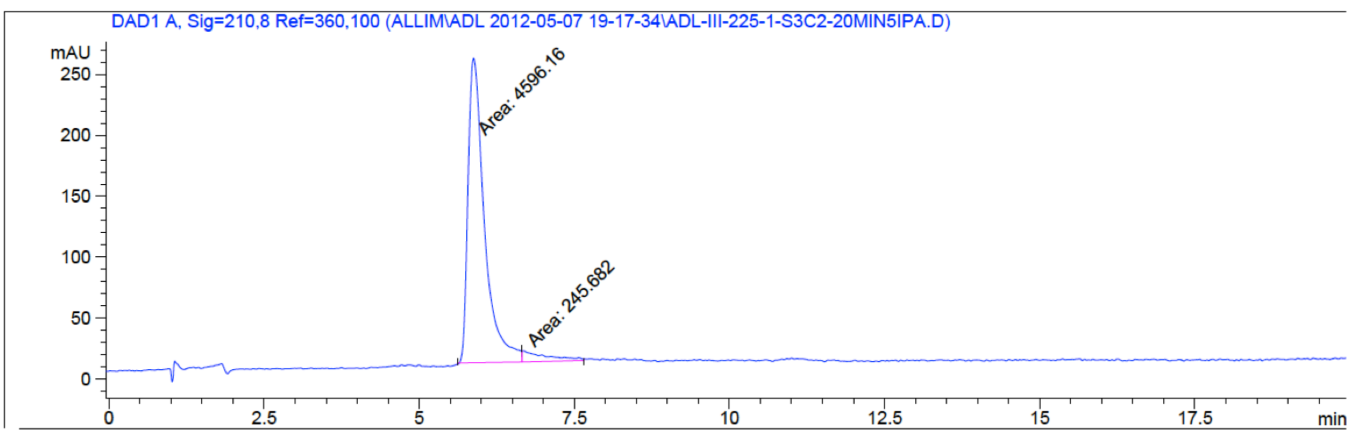
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.042	MM	0.2176	426.42010	32.65453	4.7805
2	7.388	MM	0.3377	8493.55664	419.18365	95.2195

19f (Table 3): racemic



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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 [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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

[1] Still, W. C., Kahn, M. & Mitra, A. Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem*. **43**, 2923-2925 (1978).

[2] Codelli, J. A., Puchlopek, A. L. A. & Reisman, S. E. Enantioselective Total Synthesis of (–)-Acetylaranotin, a Dihydrooxepine Epidithiodiketopiperazine. *J. Am. Chem. Soc.* **134**, 1930-1933 (2012).