Synthesis and Structural Features of α-Fluorocarbonyl Systems

FISHER, CRAIG,AARON

Electronic Supplementary Material (ESI) for Green Chemistry.

Sustainable synthesis of enantiopure fluorolactam derivatives by a selective direct fluorination - amidase strategy

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SI-3.1 Method Name: CSH~2min_For Method Description: Formic Acid Generic Analytical UPLC LC/MS 2 Minute Method

The UPLC analysis was conducted on an Acquity UPLC CSH C18 column (50 mm x 2.1 mm x i.d. 1.7 µm packing diameter) at 40 ^{o}C.

The solvents employed were:
A = 0.1 % v/v solution of Formic Acid in Water.
B = 0.1 % v/v solution of Formic Acid in Acetonitrile.

Time (min)	Flow rate (mL/min)	% A	% B
0	1	97	3
1.5	1	5	95
1.9	1	5	95
2.0	1	97	3

The UV detection was a summed signal from wavelength of 210 nm to 350 nm.

Injection volume : 0.5 µL

MS Conditions
MS : Waters ZQ
Ionisation mode : Alternate-scan Positive and Negative Electrospray
Scan Range : 100 to 1000 AMU
Scan Time : 0.27 seconds
Inter scan Delay : 0.10 seconds

SI-3.2 UPLC Calibration

Standard solutions of 3-fluoro-2-oxopiperidine-3-carboxylic acid **5** (41.2 mmol in MeOH, 5 mL), methyl 3-fluoro-2-oxopiperidine-3-carboxylate **2b,c** (41.2 mmol in MeOH, 5 mL) and 1,4-dimethoxy benzene (20.6 mmol in MeOH, 10 mL) were prepared in triplicate.

These solutions were added to an array of HPLC vials in triplicate (volumes defined in the Table below), which were then analyzed *via* UPLC-MS (Method CSH~2min_For). The acid and ester UV response factors were compared to the analytical standard and the average response factor was plotted against concentration to give a UPLC calibration curve.

Vial	A		B		C		D	E
	(µL)	(µmol)	(µL)	(µmol)	(µL)	(µmol)	(µL)	(µL)
1	250	10.3	250	10.3	500	10.3	0	500
2	175	7.0	175	7.0	500	10.3	150	500
3	125	5.2	125	5.2	500	10.3	250	500
4	75	3.0	75	3.0	500	10.3	350	500
5	50	2.0	50	2.0	500	10.3	450	500
6	25	1.0	25	1.0	500	10.3	450	500

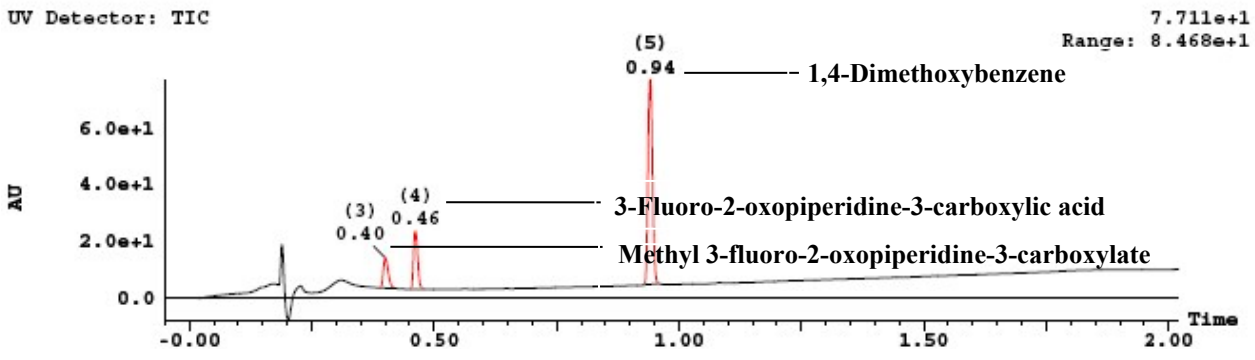
A = 3-Fluoro-2-oxopiperidine-3-carboxylic acid **5** (41.2 mmol in MeOH)

B = Methyl 3-fluoro-2-oxopiperidine-3-carboxylate **2b,c** (41.2 mmol in MeOH)

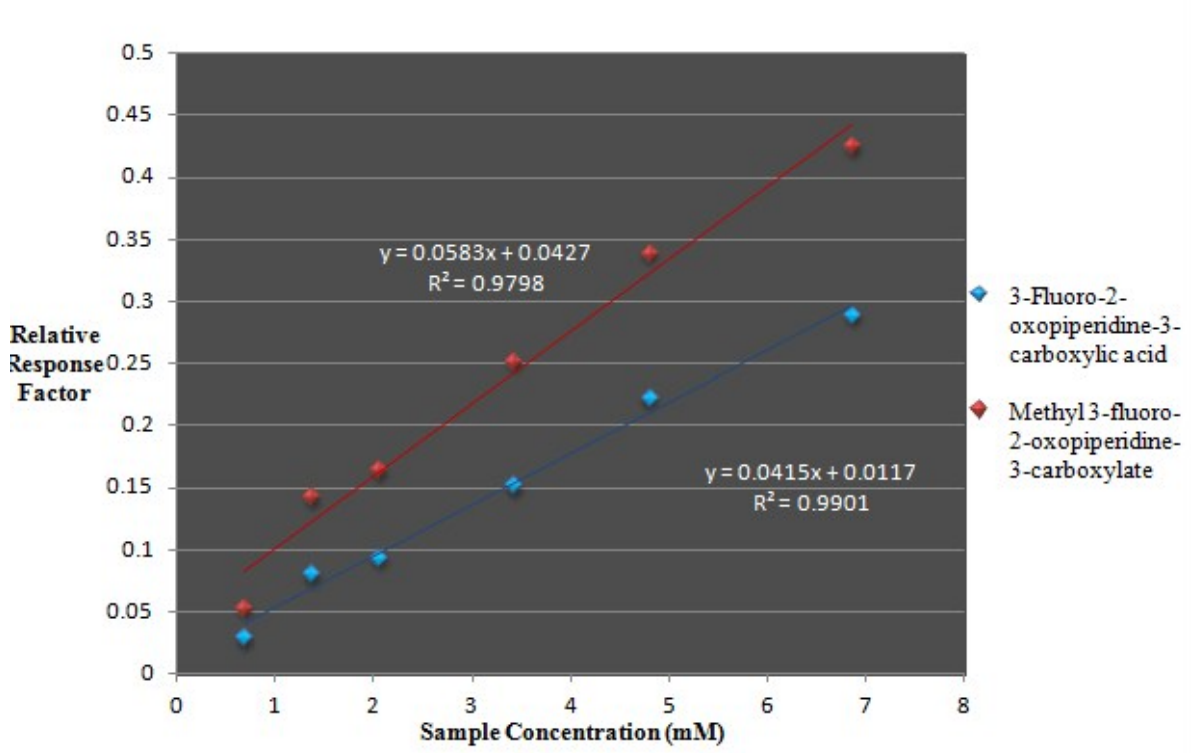
C = 1,4-Dimethoxy benzene (20.6 mmol in MeOH)

D = MeOH

E = 60mM Na_2HPO_4: 60mM KH_2PO_4 Buffer (3:1; pH 7.3, 20 ^oC)



Representative UPLC Trace

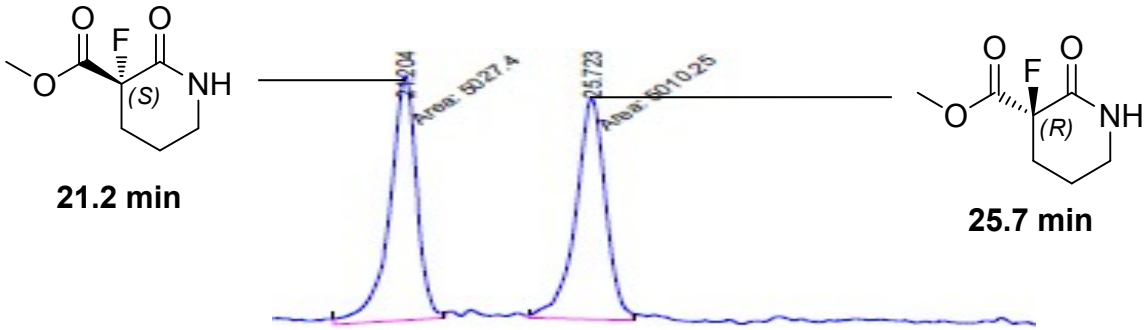


UPLC Calibration

SI-3.3 High Throughput Chiral HPLC Analysis

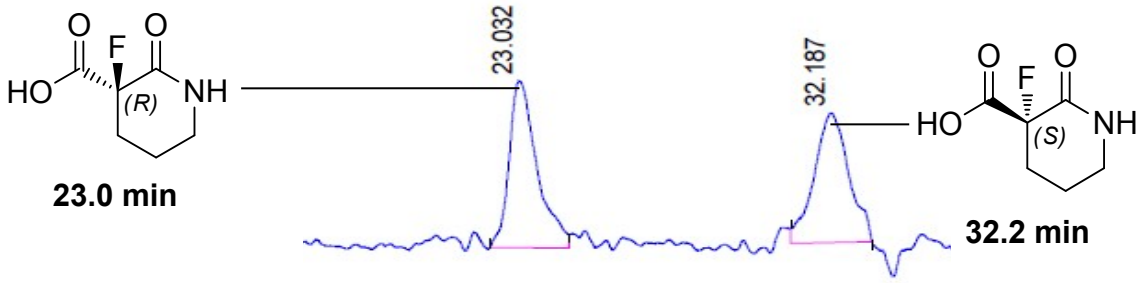
Column Conditions: Diacel Chiralpak IA 4.6 mm x 250 mm; Ethanol:Heptane / 0.1 % TFA (8:92); 1 mL min^{-1}; 215 nm; 25 ^{o}C; 40 min.

2b Standard



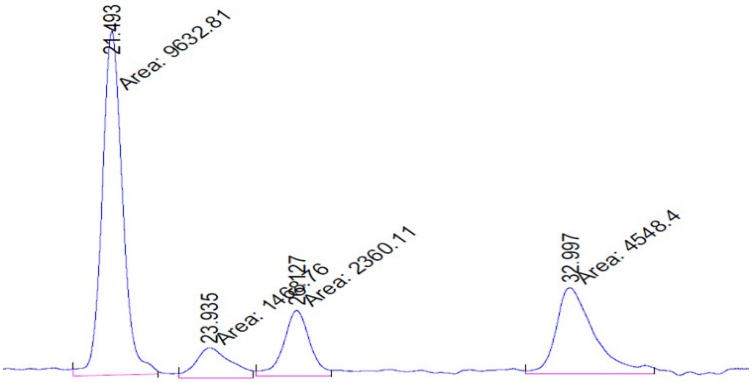
21.2 min **25.7 min**

(±)-5b Standard



23.0 min **32.2 min**

Representative example from high throughput hydrolase screen (JM EST47)



21 min, (*S*)-ester (80 %); 23 min, (*R*)-ester (20 %), [60 % *ee* (*S*)]

23 min, (*S*)-acid (76 %); 32 min, (*R*)-acid (24 %), [52 % *ee* (*R*)]

SI-3.4 Preparative Chiral HPLC

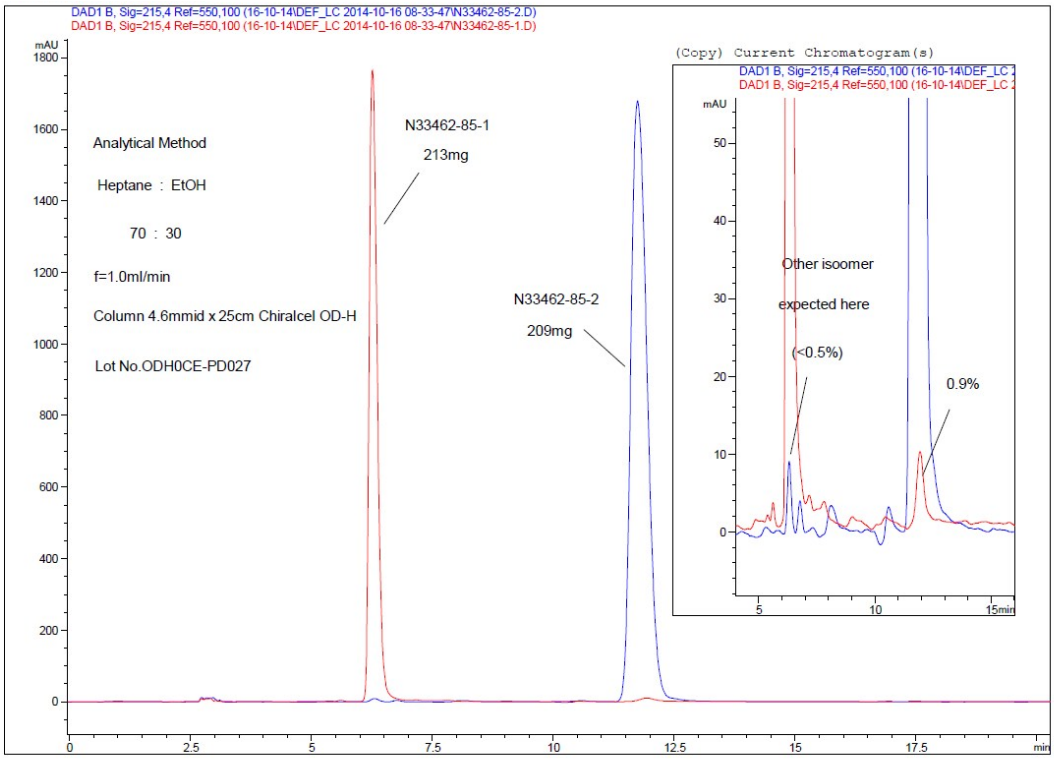
Lactam **2b,c** (540 mg) was dissolved in 10 mL EtOH to give a clear solution and purified by preparative chiral HPLC (3 mL injection volume).

Chiral HPLC Conditions: Column 30 mm x 25 cm Chiralcel OD-H; EtOH:Heptane (3:7), 215 nm, 20 °C.

Fractions from 4.5 – 6 min were collected together and concentrated at RT to give (*S*)-**2b** (213 mg) as a white solid, >99 % *ee*, $[\alpha]_D^{20}$ +14.393° (*c* 1.00, MeCN).

Fractions from 11.0 - 13.0 min were collected together and concentrated at RT to give (*R*)-**2c** (209 mg) as an off-white solid, 98 % *ee*, $[\alpha]_D^{20}$ -14.128° (*c* 1.00, MeCN).

A 50 mg sample of each enantiomer was recrystallised from heptane/methanol and analysed by X-ray crystallography to determine absolute configuration.



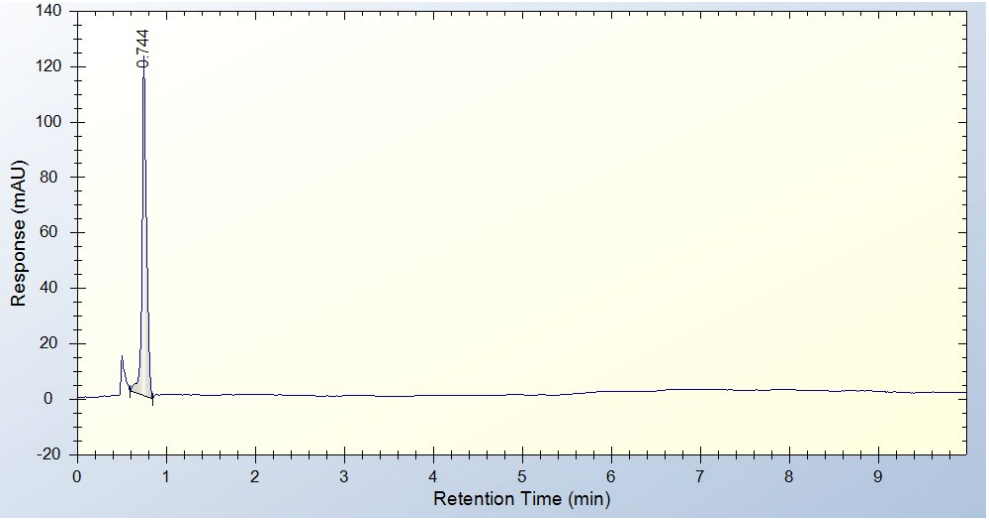
Analytical Chiral HPLC Trace

SI-3.5 Scale-up Chiral HPLC Assay

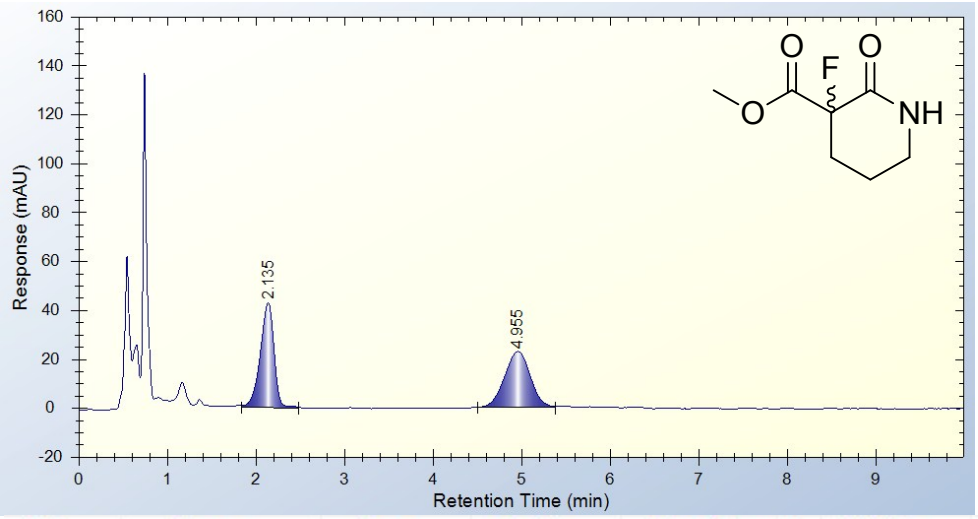
Samples were prepared as a solution in methanol and analysed using the following method.

Column Conditions: Phenomenex Lux 5 μm Cellulose-1 50 x 4.6 mm Column; Ethanol:Heptane (2:8); 2 mL min^{-1}; 215 nm; 25 ^{o}C; 10 min.

Methanol

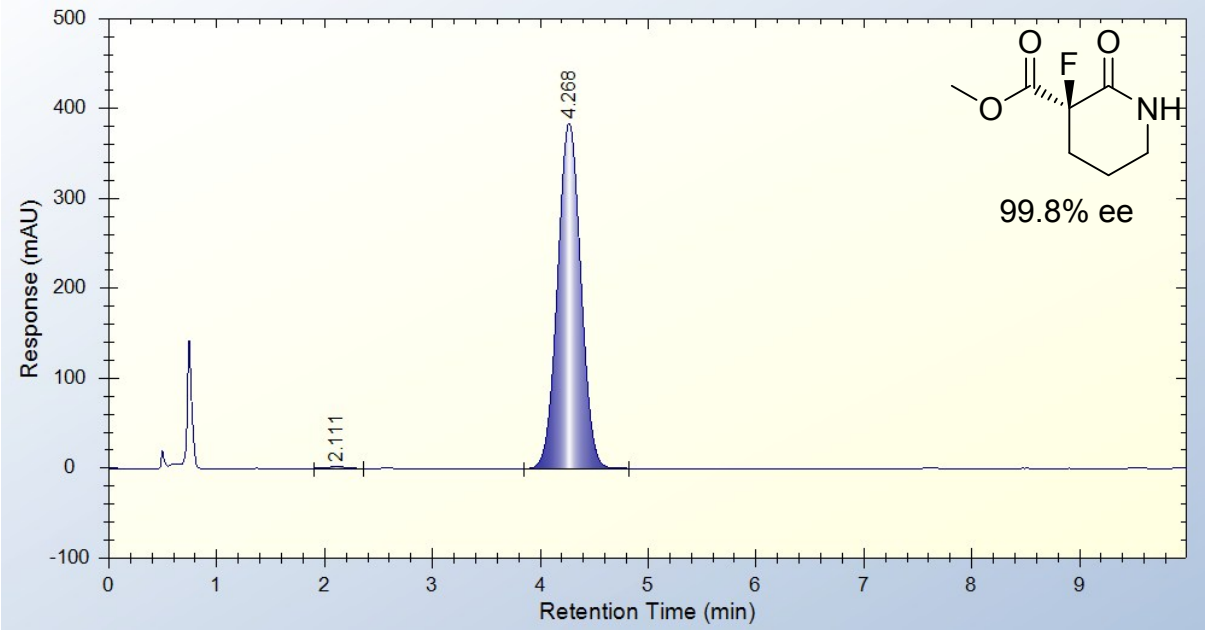


Racemate



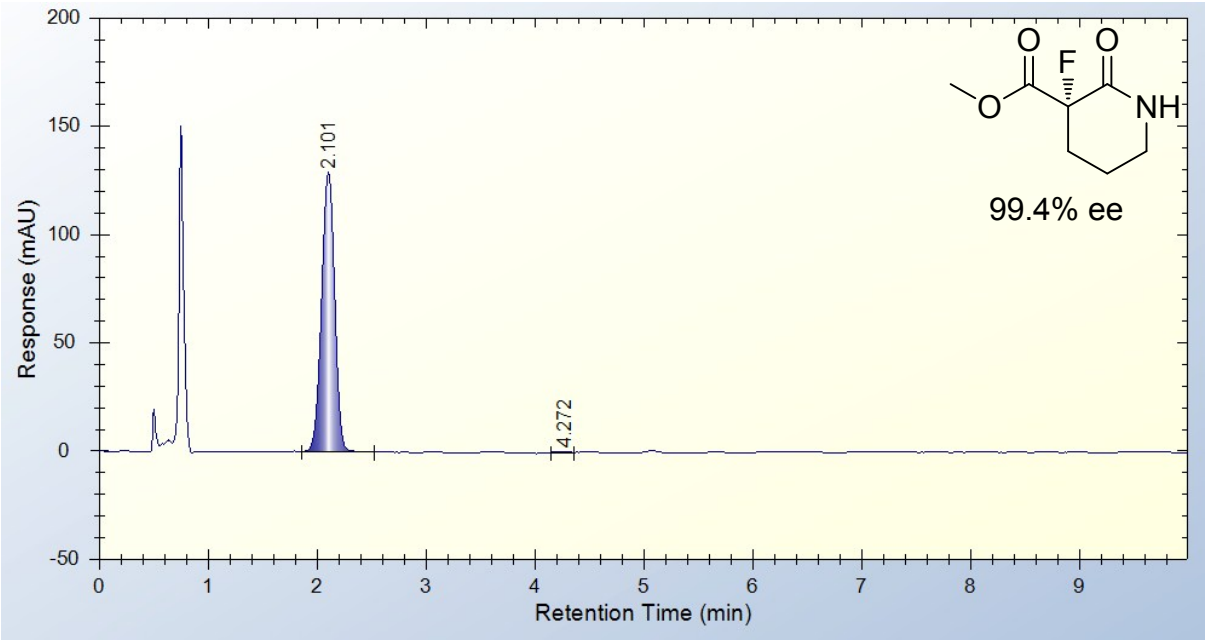
RT	Name	Area	Area %	Named Area %	Height	Width
2.135		463.834	49.871	0.000	42.839	0.180
4.955		466.226	50.129	0.000	22.948	0.339

(*R*)-2c from preparative HPLC



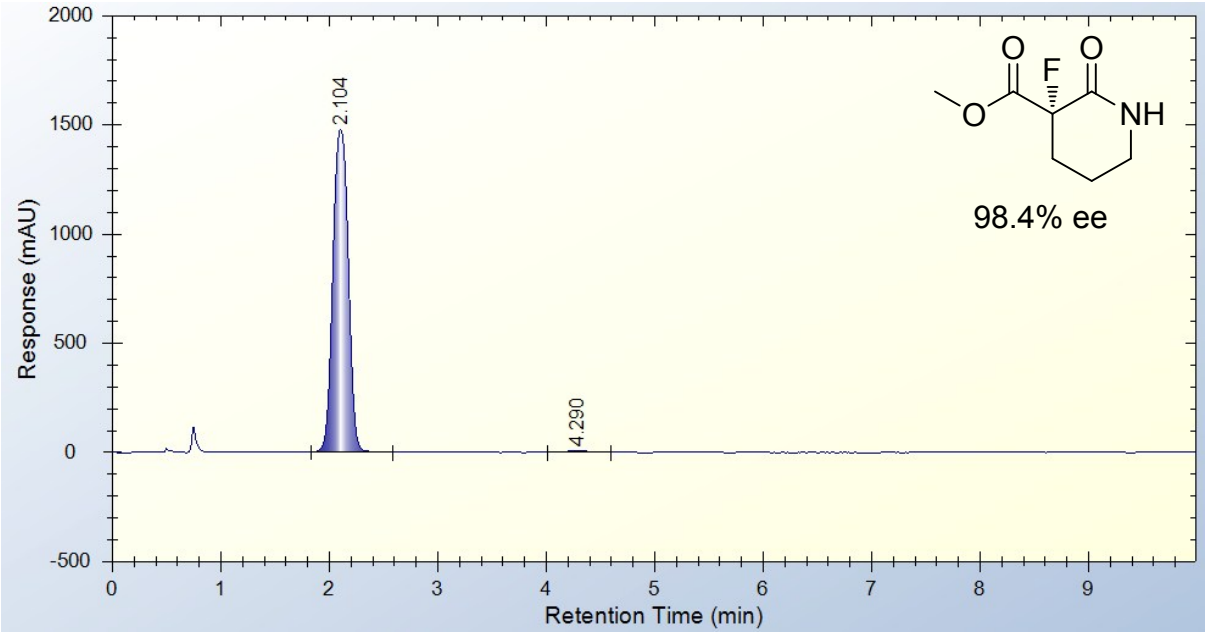
RT	Name	Area	Area %	Named Area %	Height	Width
2.111		33.618	0.581	0.000	2.730	0.205
4.268		5750.471	99.419	0.000	384.613	0.232

(*S*)- 2b from preperative HPLC



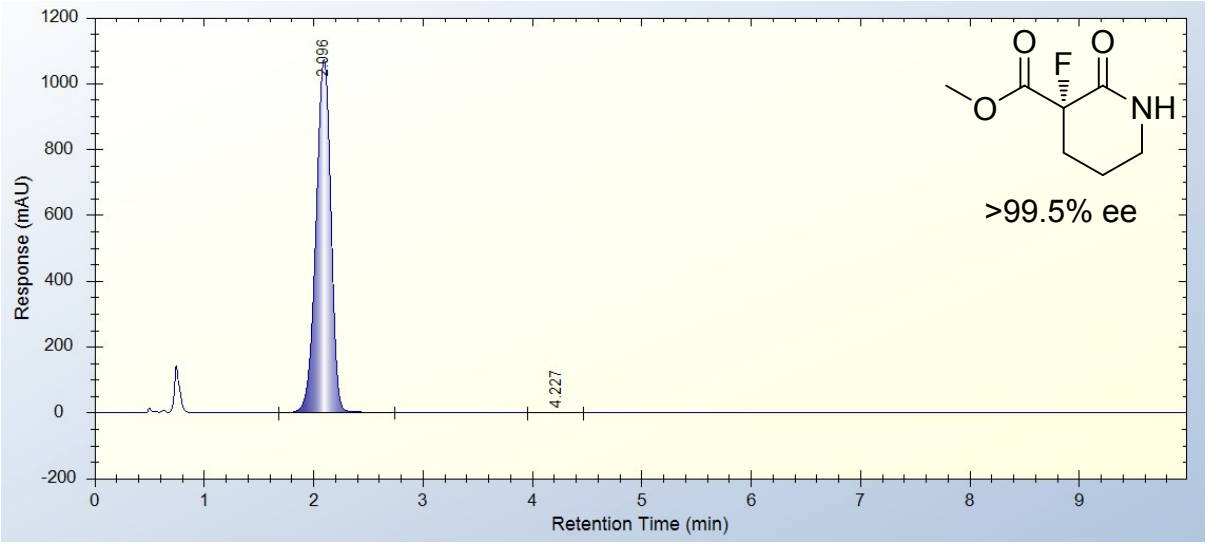
RT	Name	Area	Area %	Named Area %	Height	Width
2.101		1075.169	99.719	0.000	129.045	0.130
4.272		3.031	0.281	0.000	0.349	0.145

Milligram scale hydrolysis



RT	Name	Area	Area %	Named Area %	Height	Width
2.104		14495.644	99.205	0.000	1476.682	0.159
4.290		116.112	0.795	0.000	7.993	0.177

Multi-gram scale hydrolysis



RT	Name	Area	Area %	Named Area %	Height	Width
2.096		10215.472	99.781	0.000	1074.106	0.159
4.227		22.373	0.219	0.000	1.301	0.287