

Supporting Information

Enantioselective dearomatization of alkyl pyridiniums by N-heterocyclic carbene-catalyzed nucleophilic acylation

Graziano Di Carmine,^a Daniele Ragno,^a Olga Bortolini,^a Pier Paolo Giovannini,^a Andrea Mazzanti,^b Alessandro Massi^{a*} and Marco Fogagnolo

^a*Dipartimento di Scienze Chimiche e Farmaceutiche, Università di Ferrara, Via Luigi Borsari, 46, I-44121 Ferrara (Italy)*

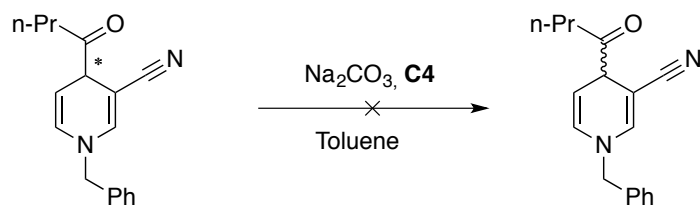
^b*Dipartimento di Chimica Industriale "Toso Montanari", Università di Bologna, V. Risorgimento 4, I-40136 Bologna (Italy)*

alessandro.massi@unife.it

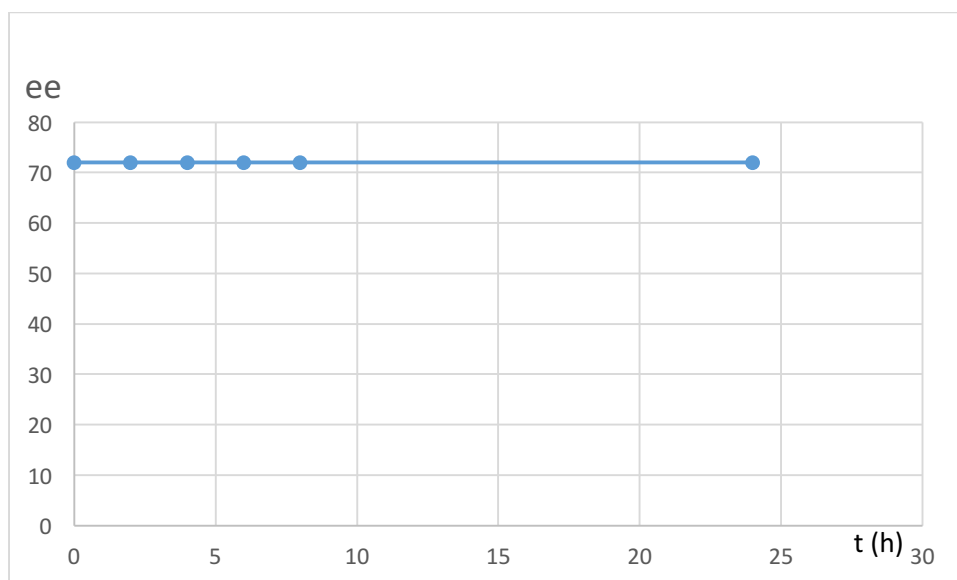
Table of content:

Eventual racemization of 1,4-DHPs 3 : a control experiment	S2
NMR spectra	S3
Chiral HPLC chromatograms	S29
Absolute configuration of compounds 3ba and 3af	S46
Proposed stereochemical model to account for selectivity	S61

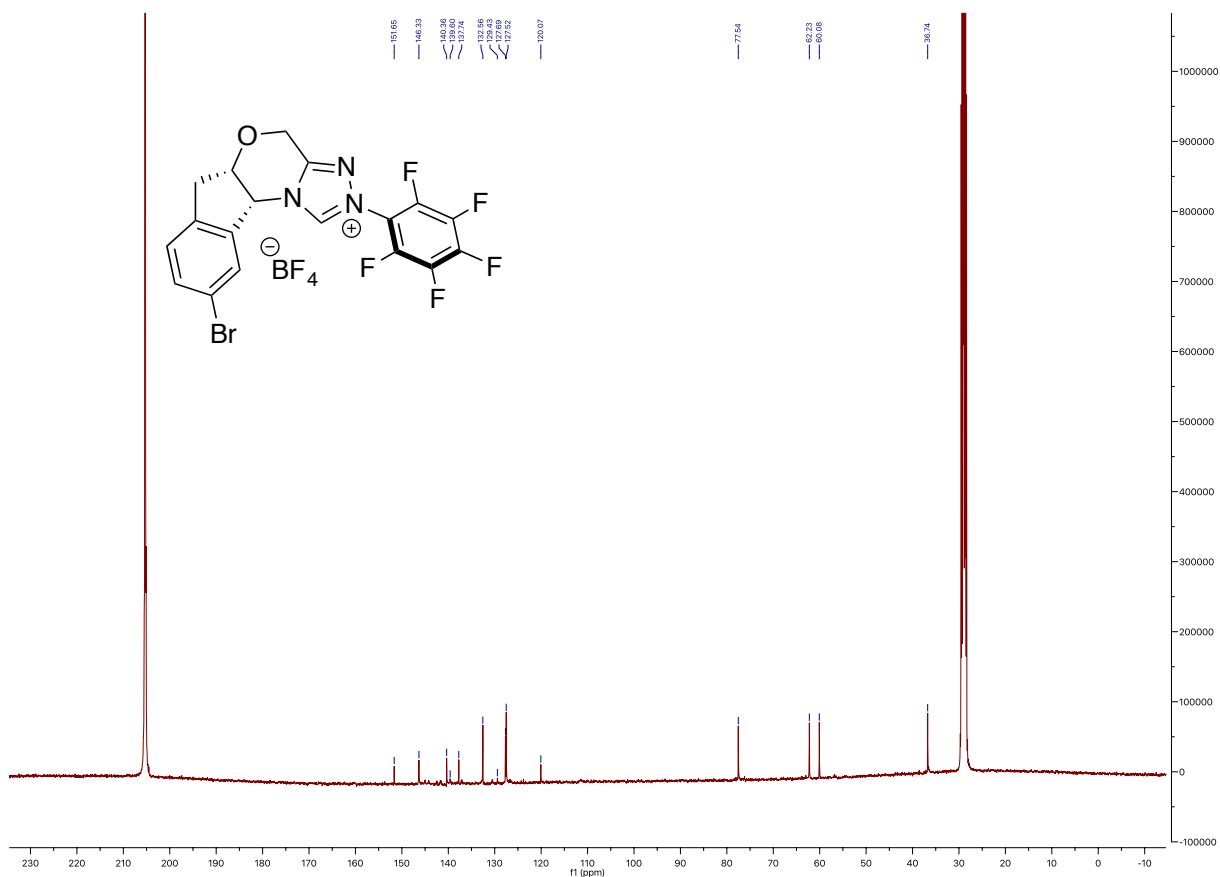
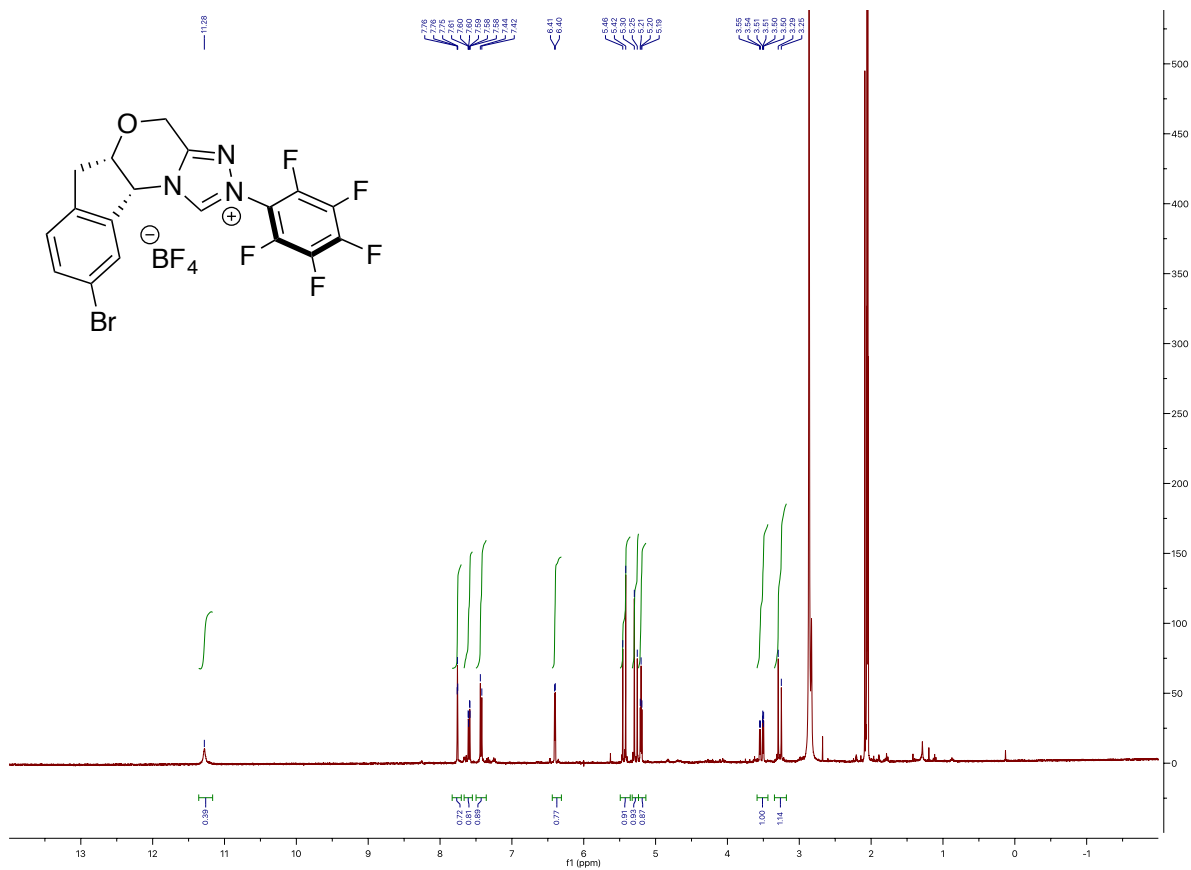
Eventual racemization of 1,4-DHPs 3: a control experiment

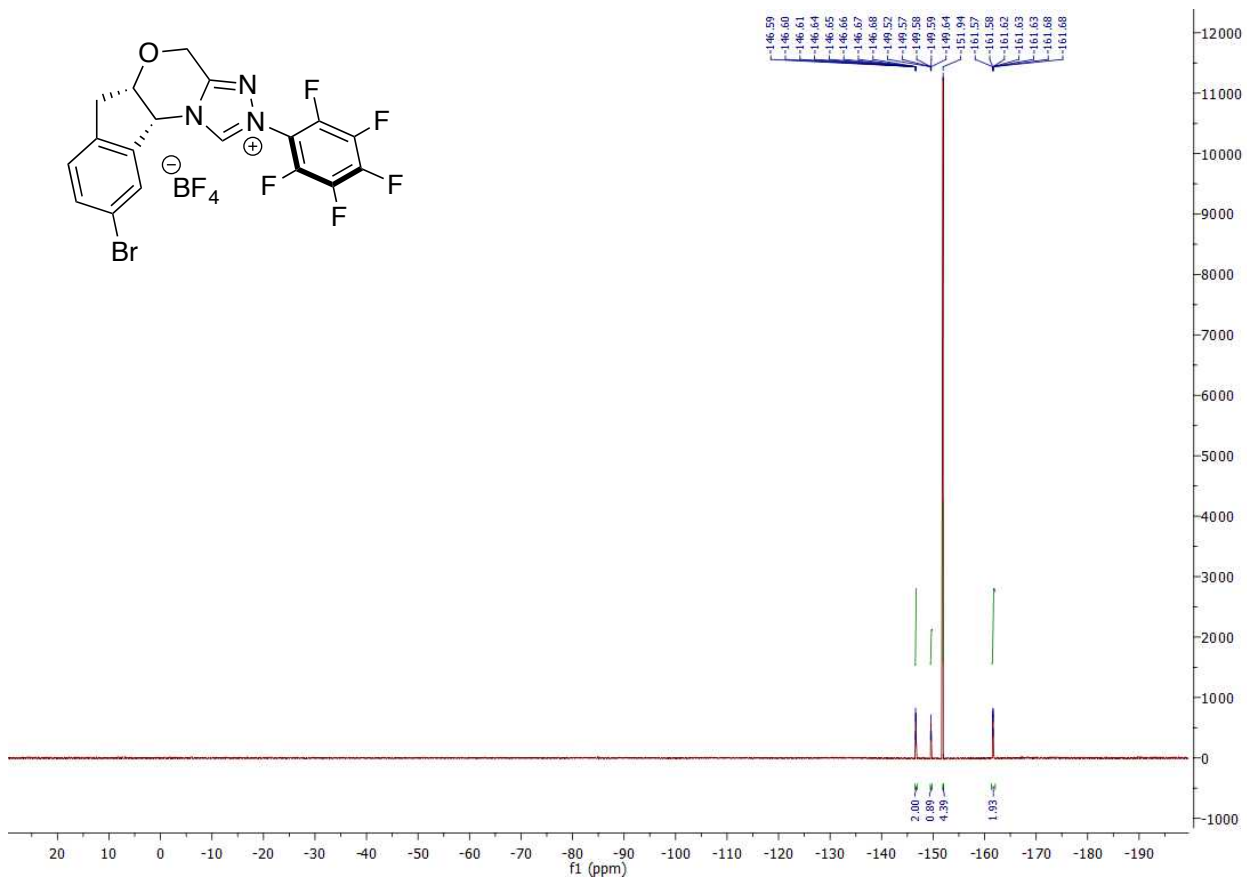


A mixture of DHP **3aa** (0.20 mmol, ee = 70%), pre-catalyst **C4** (0.02 mmol, 0.1 equiv.), anhydrous sodium carbonate (0.22 mmol, 1.1 equiv.), and anhydrous Toluene (1 mL) was vigorously stirred at room temperature under Argon. The eventual racemization was controlled by chiral HPLC analysis of aliquots (50 μL) of the reaction mixture. The results are summarized in the graph below.

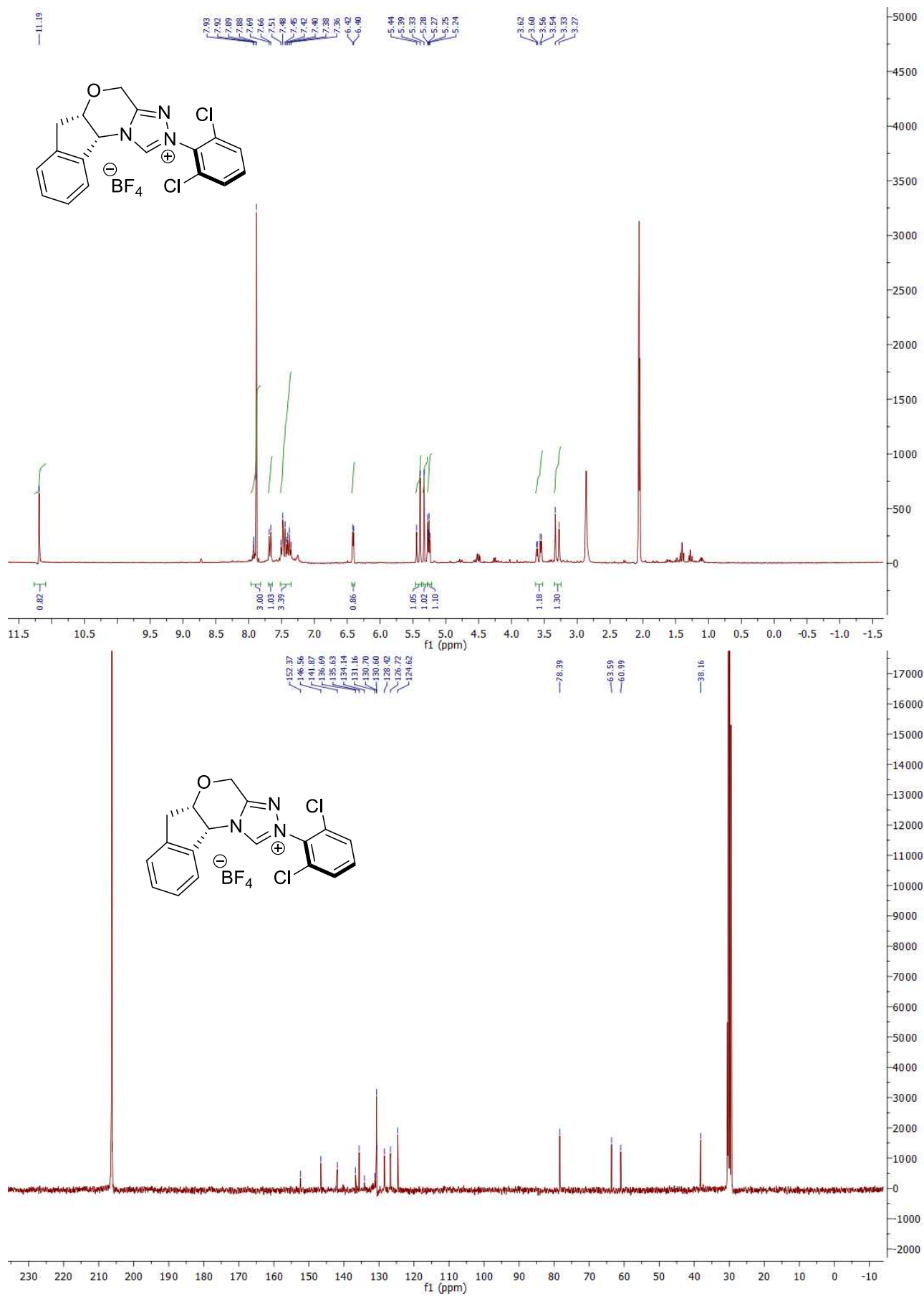


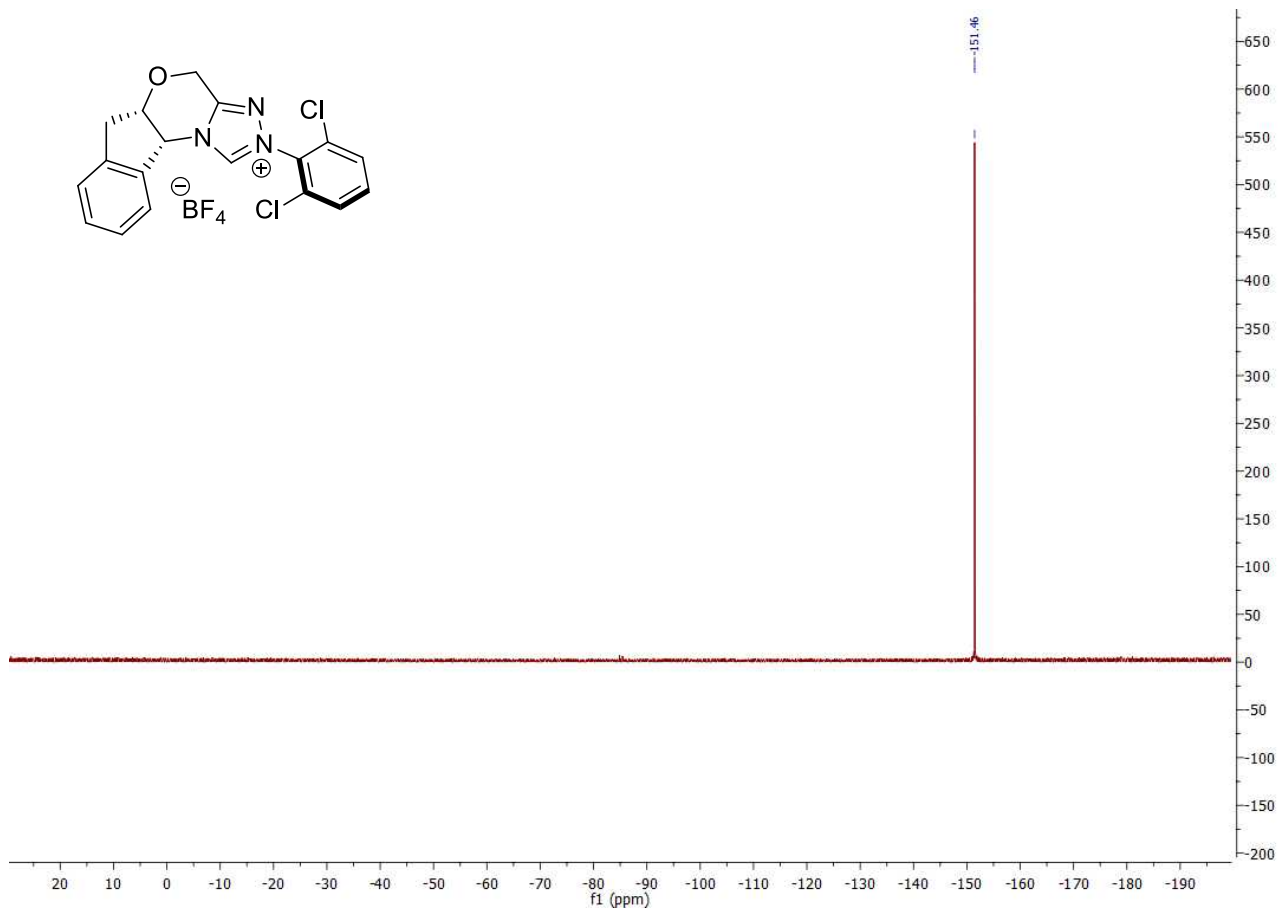
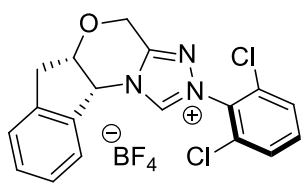
^1H (400 MHz), ^{13}C (101 MHz) and ^{19}F (376 MHz) spectra (acetone- d_6) of C2



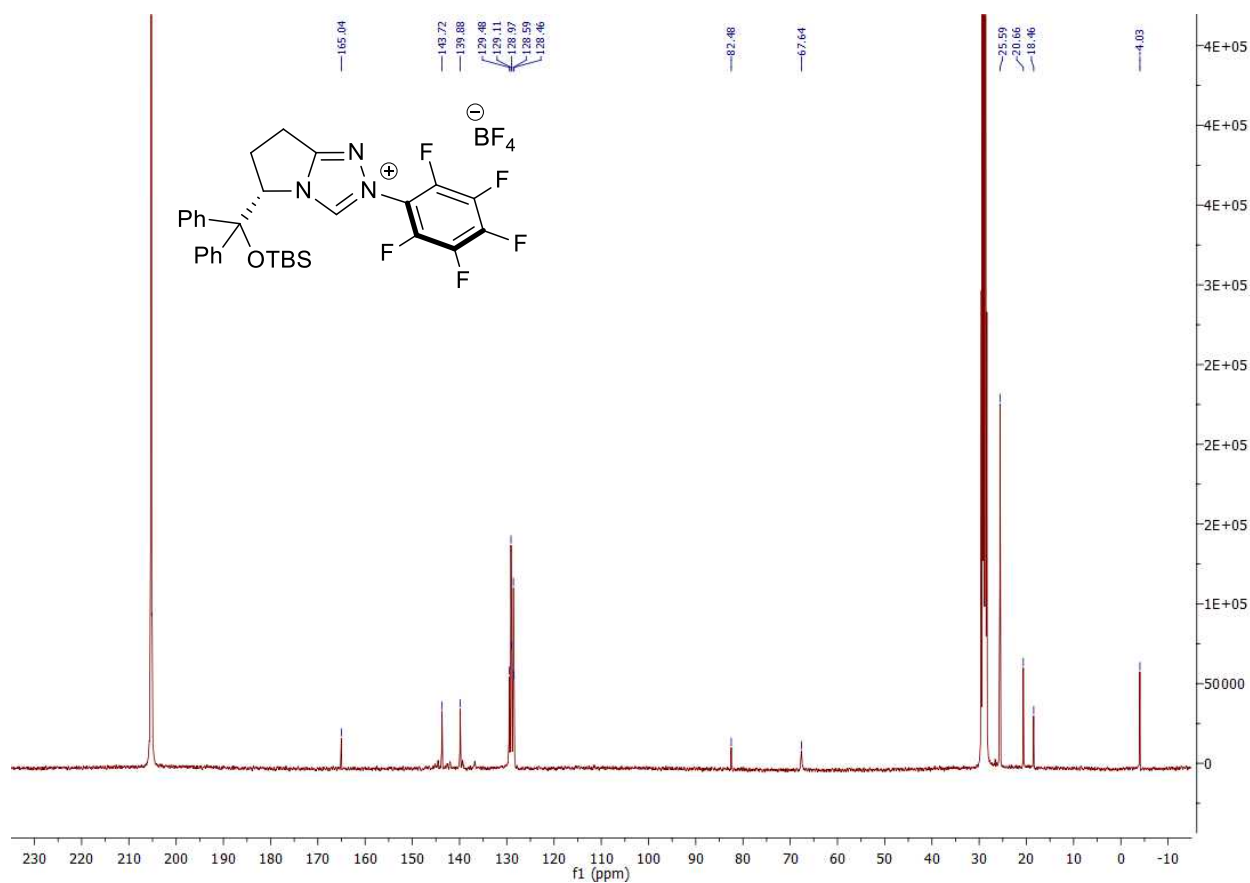
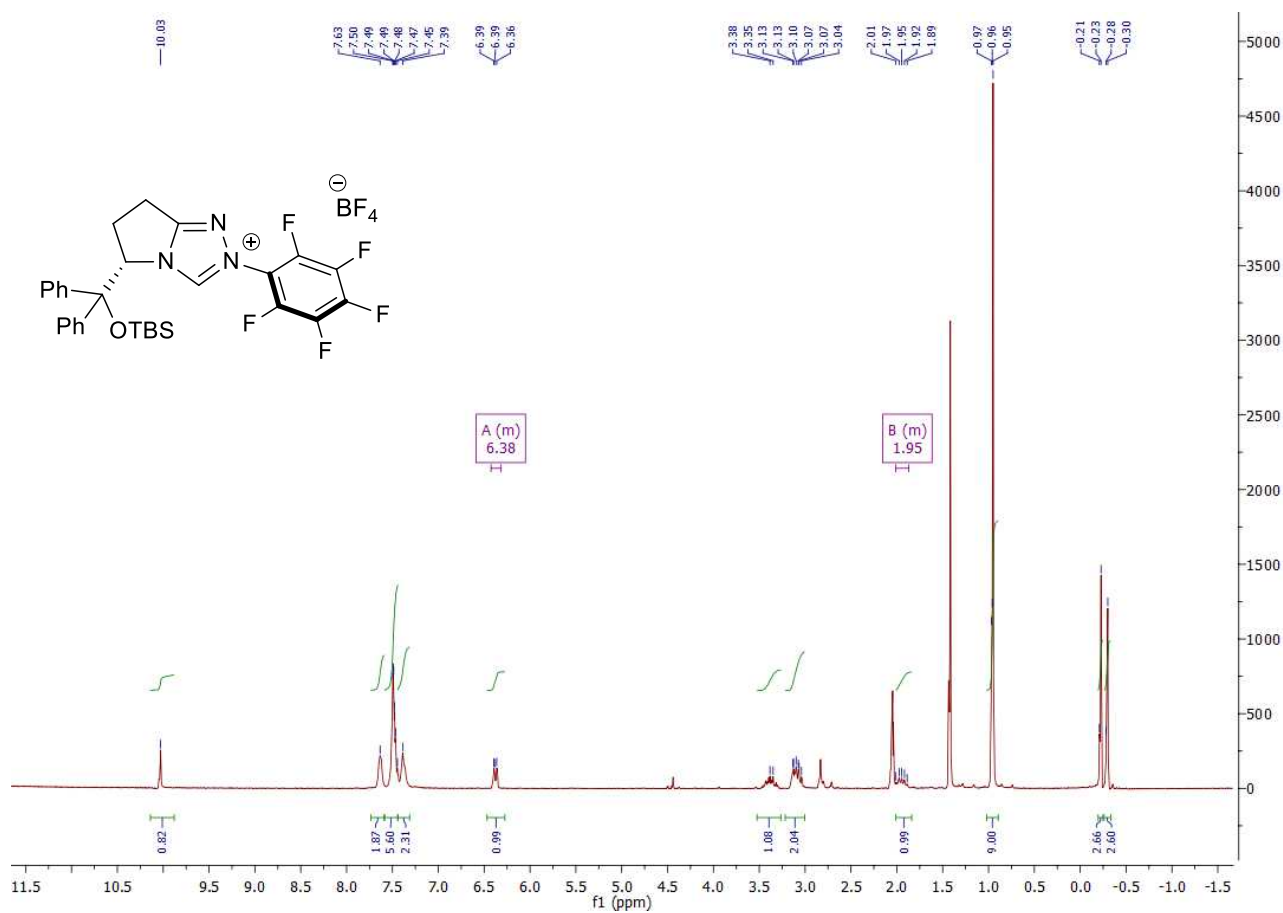


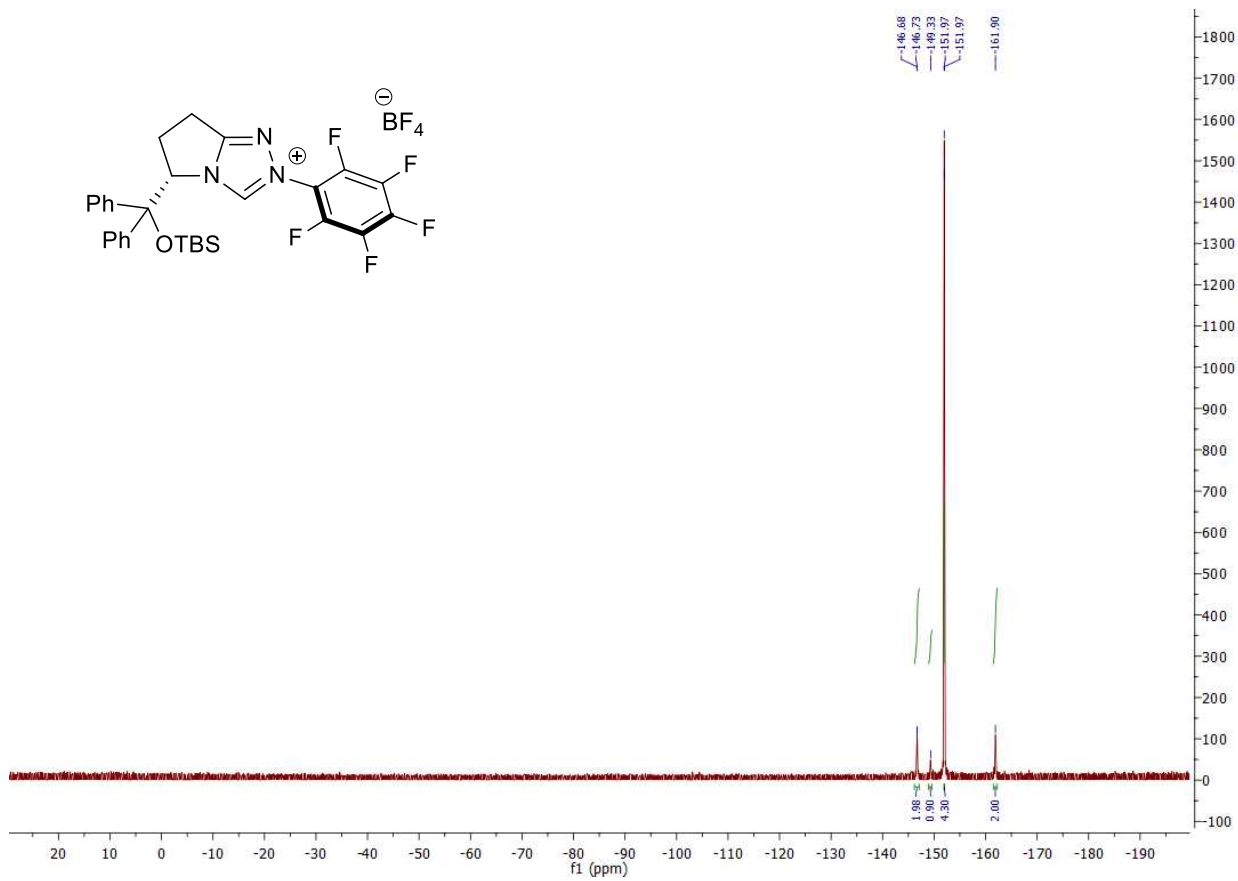
^1H (300 MHz), ^{13}C (101 MHz) and ^{19}F (376 MHz) spectra (acetone- d_6) of C4



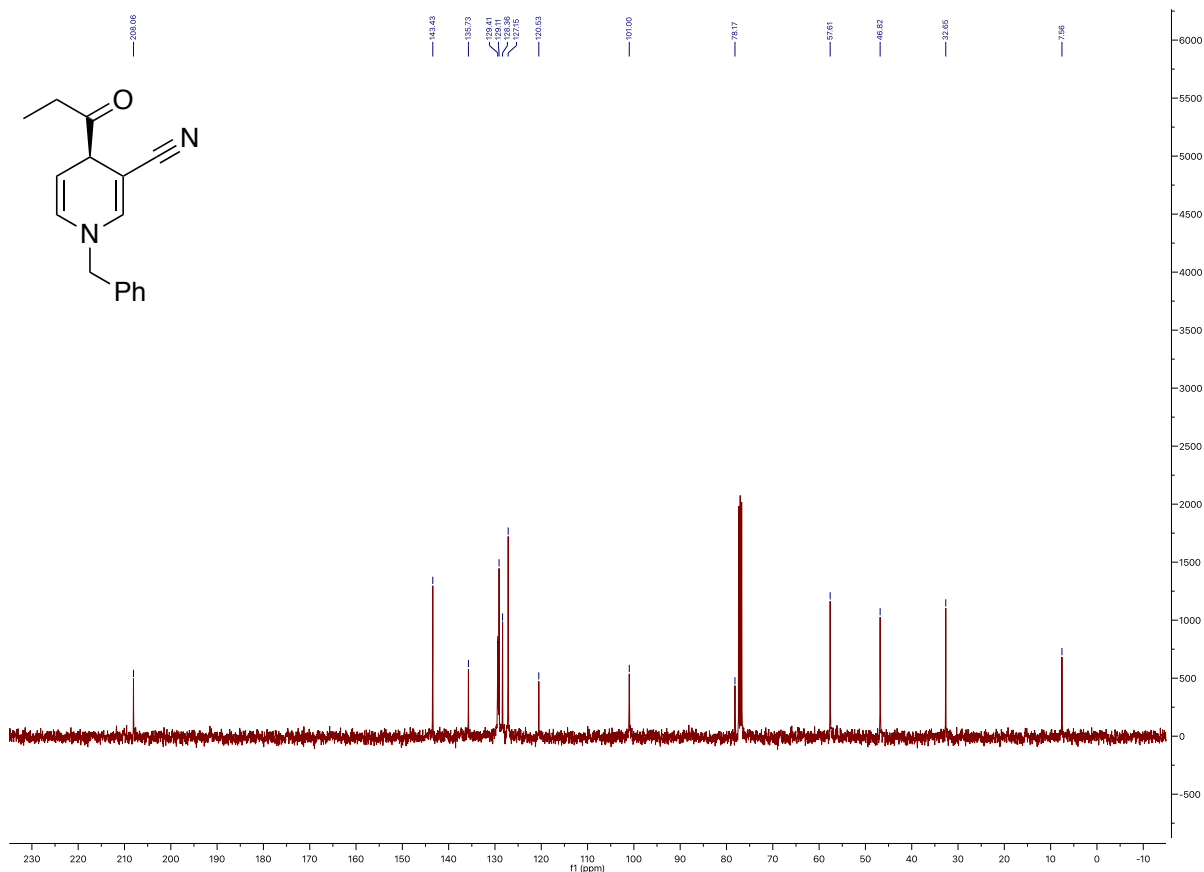
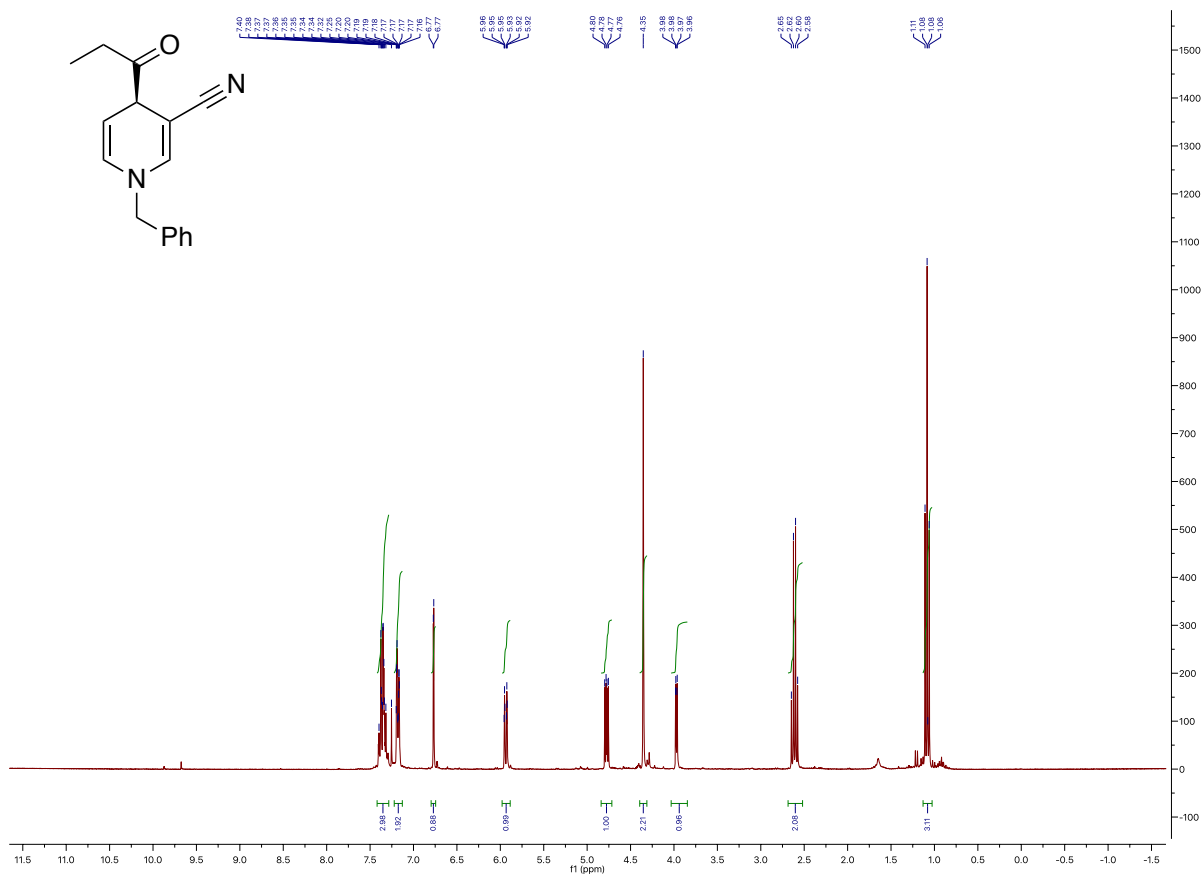


^1H (300 MHz), ^{13}C (101 MHz) and ^{19}F (376 MHz) spectra (acetone- d_6) of C5

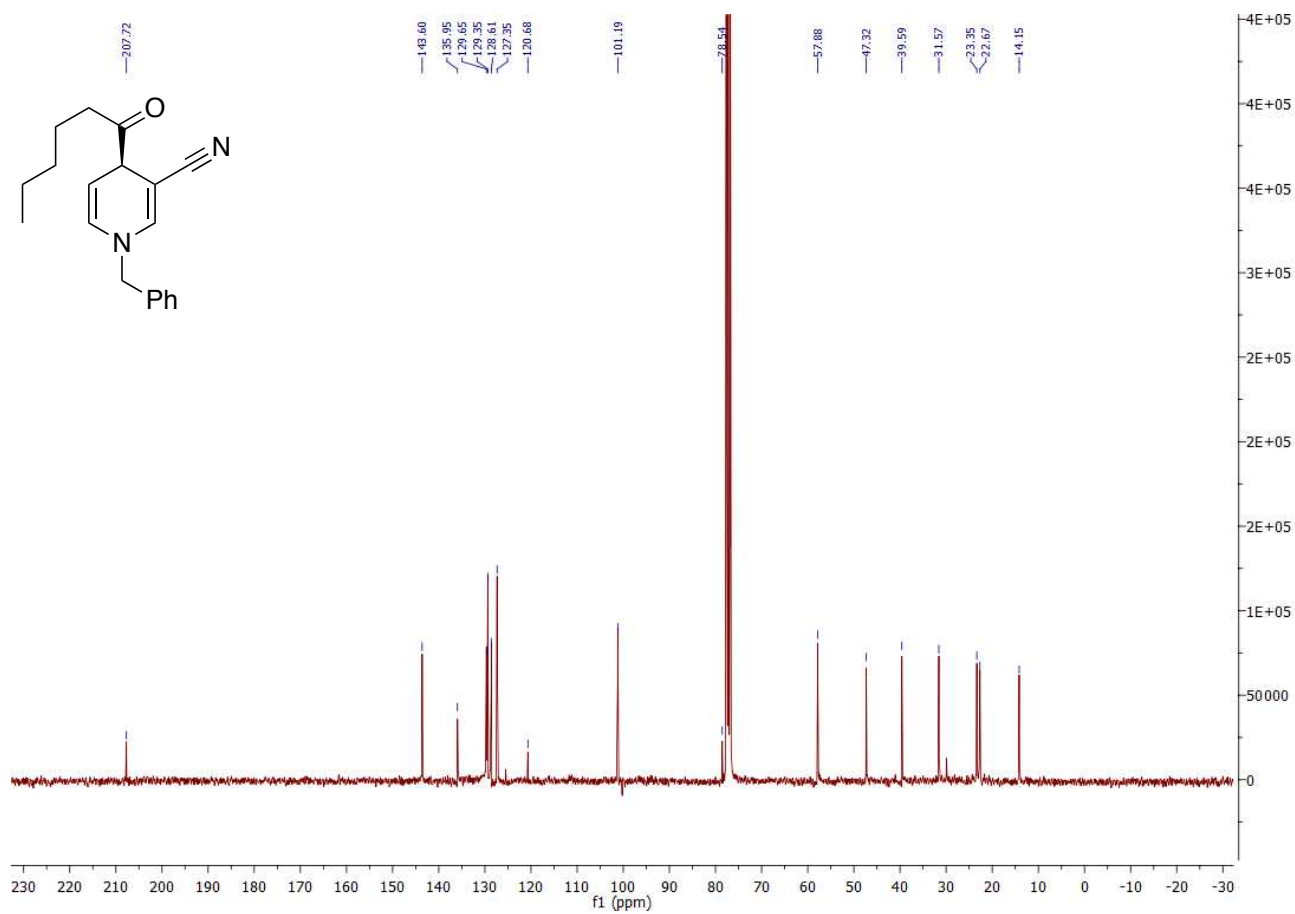
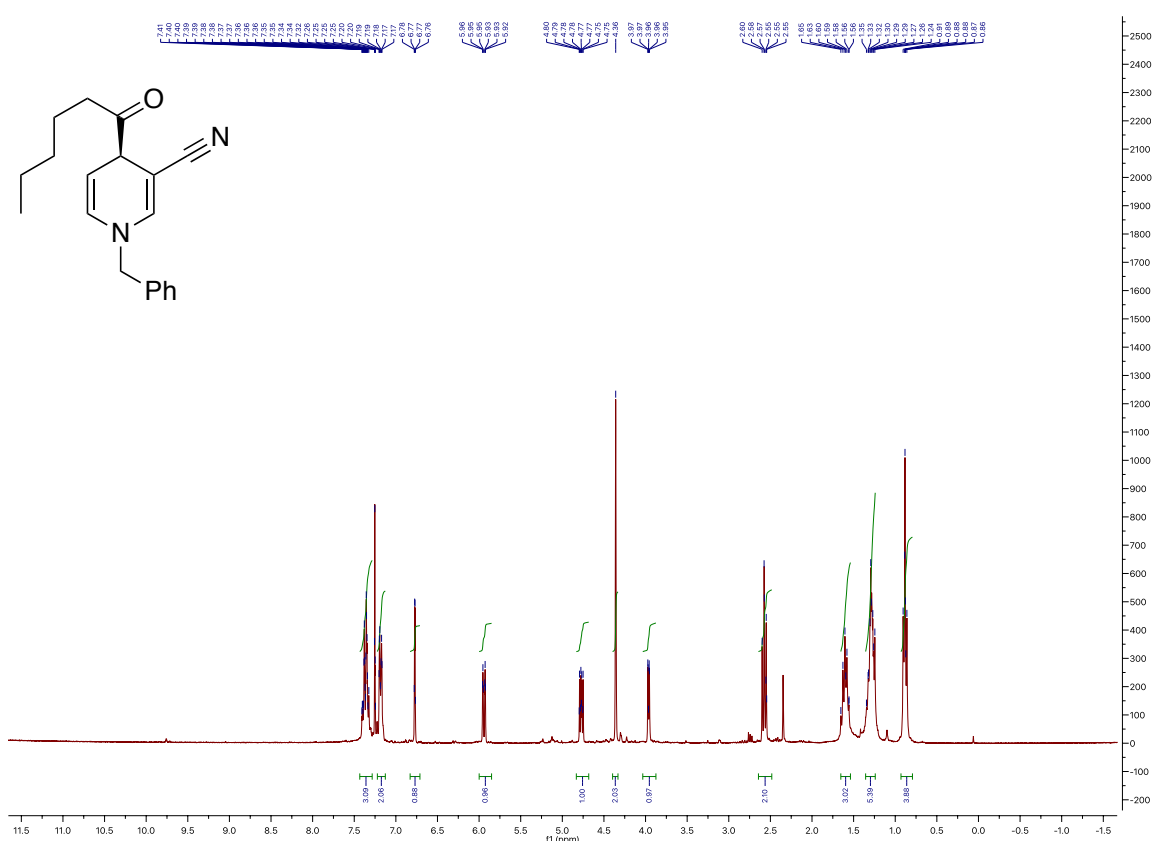




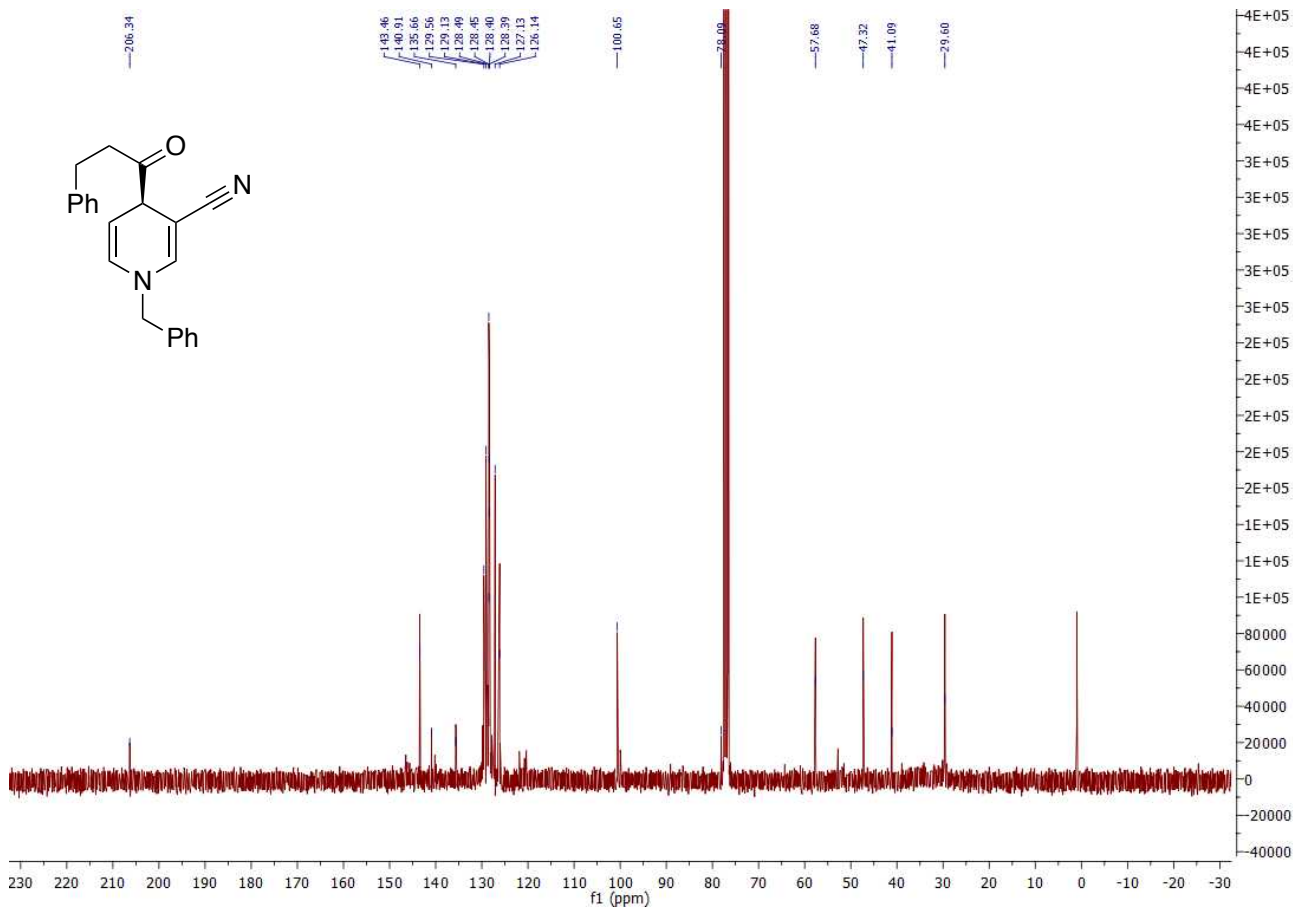
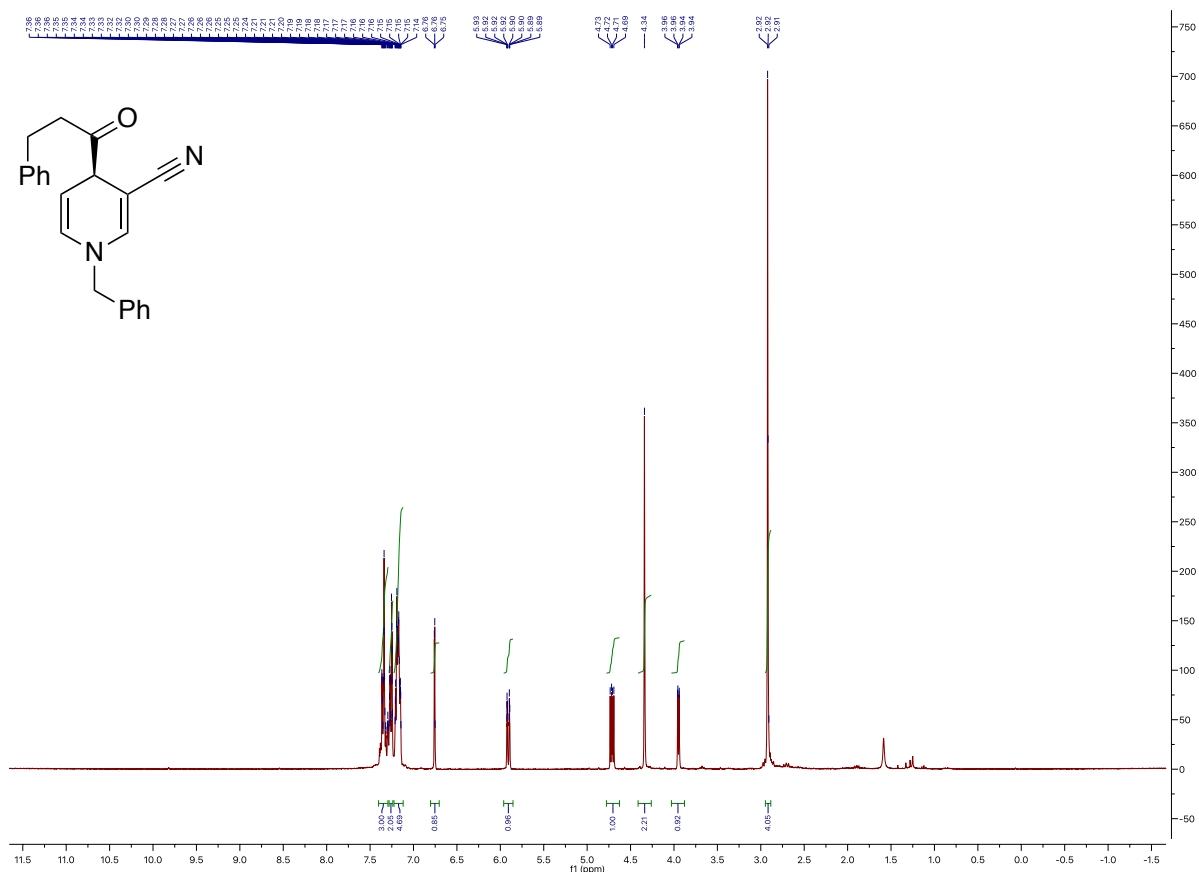
^1H (300 MHz) and ^{13}C (101 MHz) spectra (CDCl_3) of 3ba



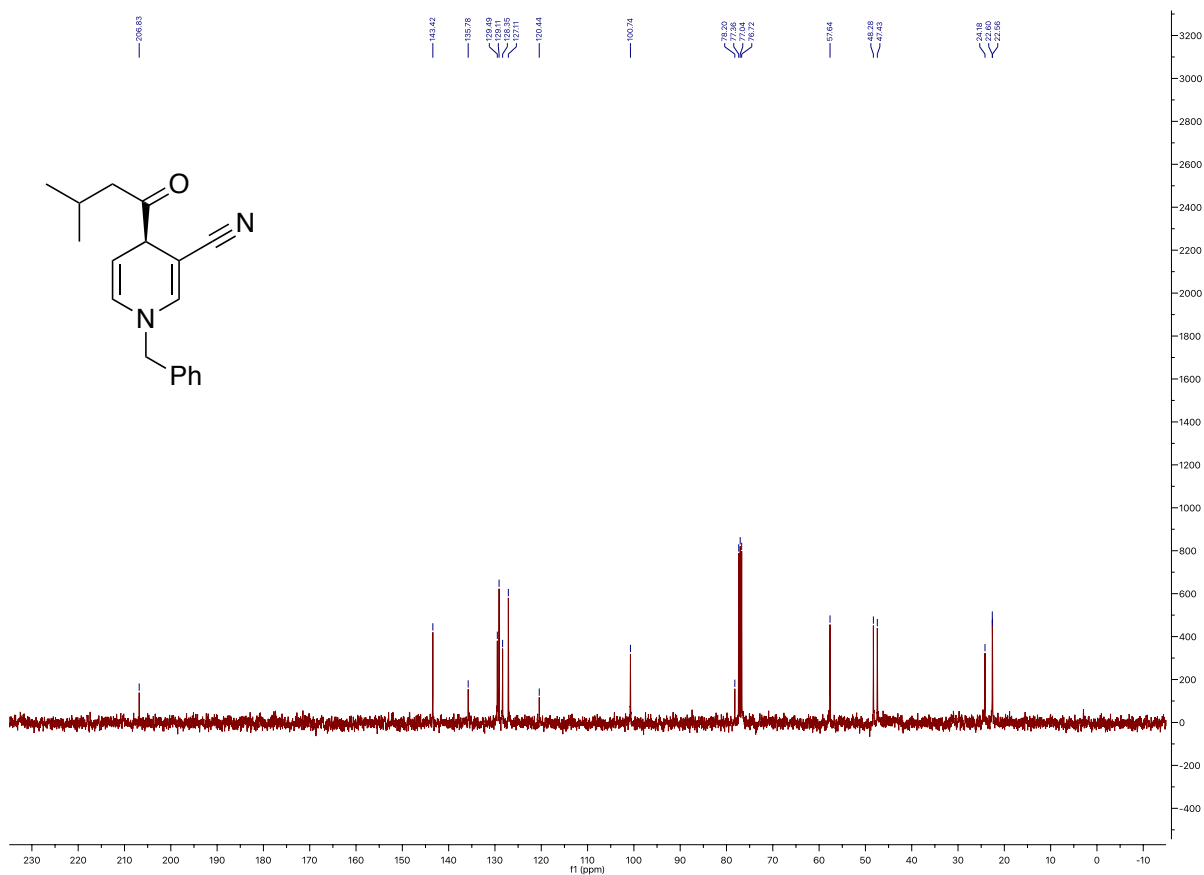
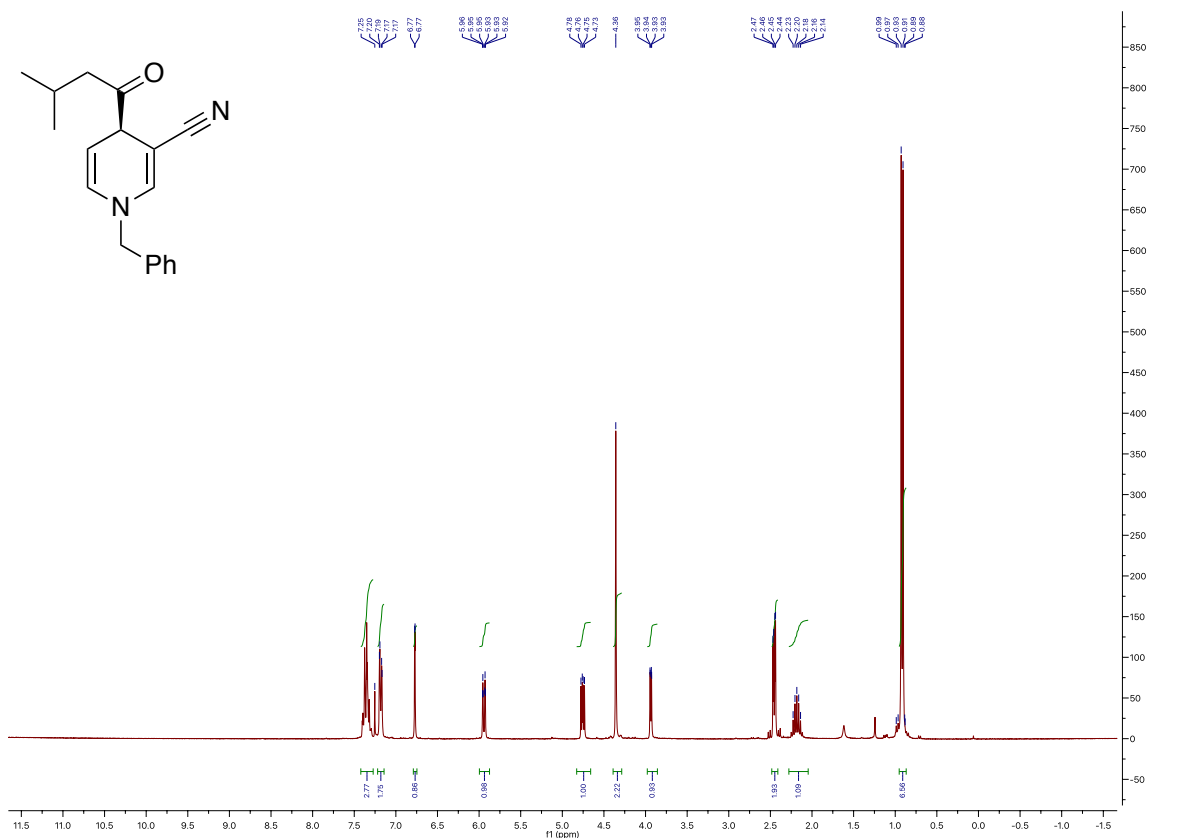
¹H (300 MHz) and ¹³C (76 MHz) spectra (CDCl₃) of 3da



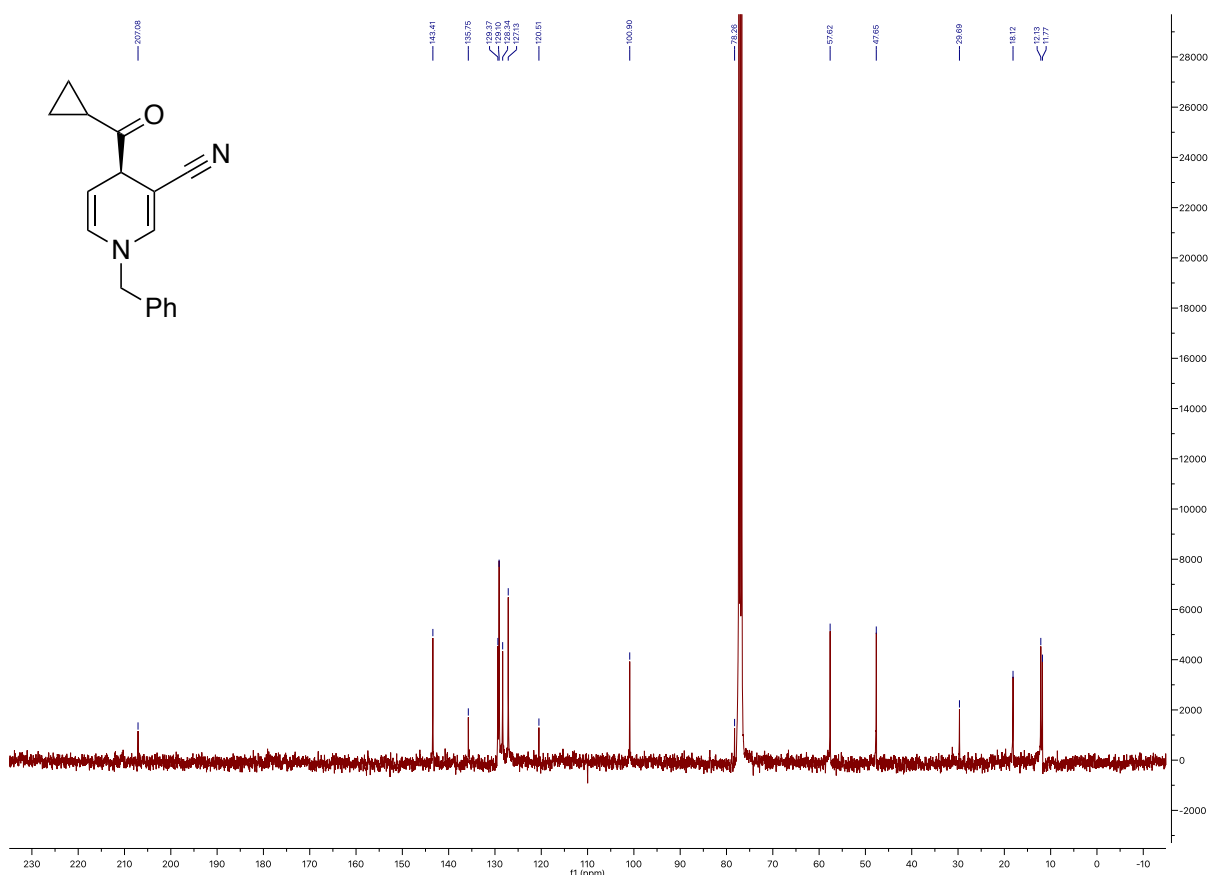
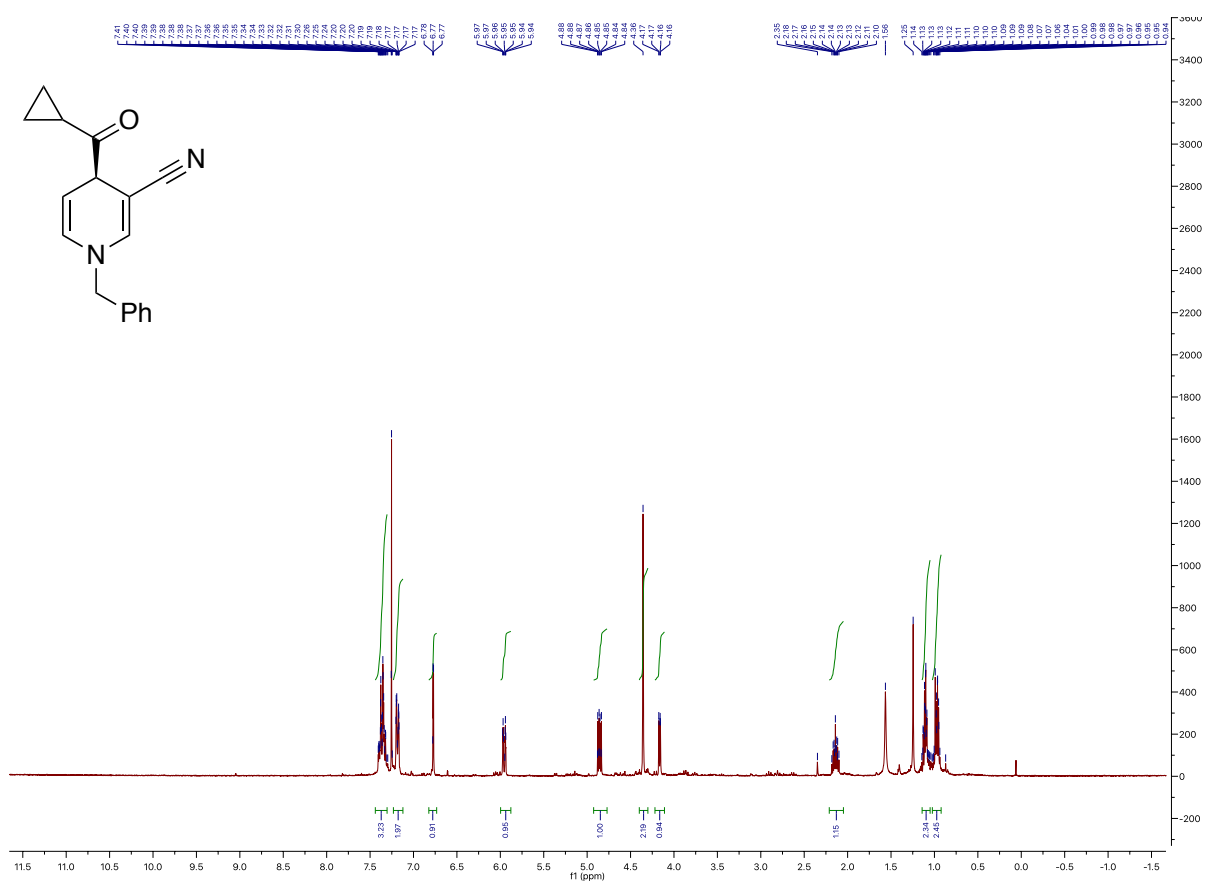
^1H (300 MHz) and ^{13}C (76 MHz) spectra (CDCl_3) of 3ea



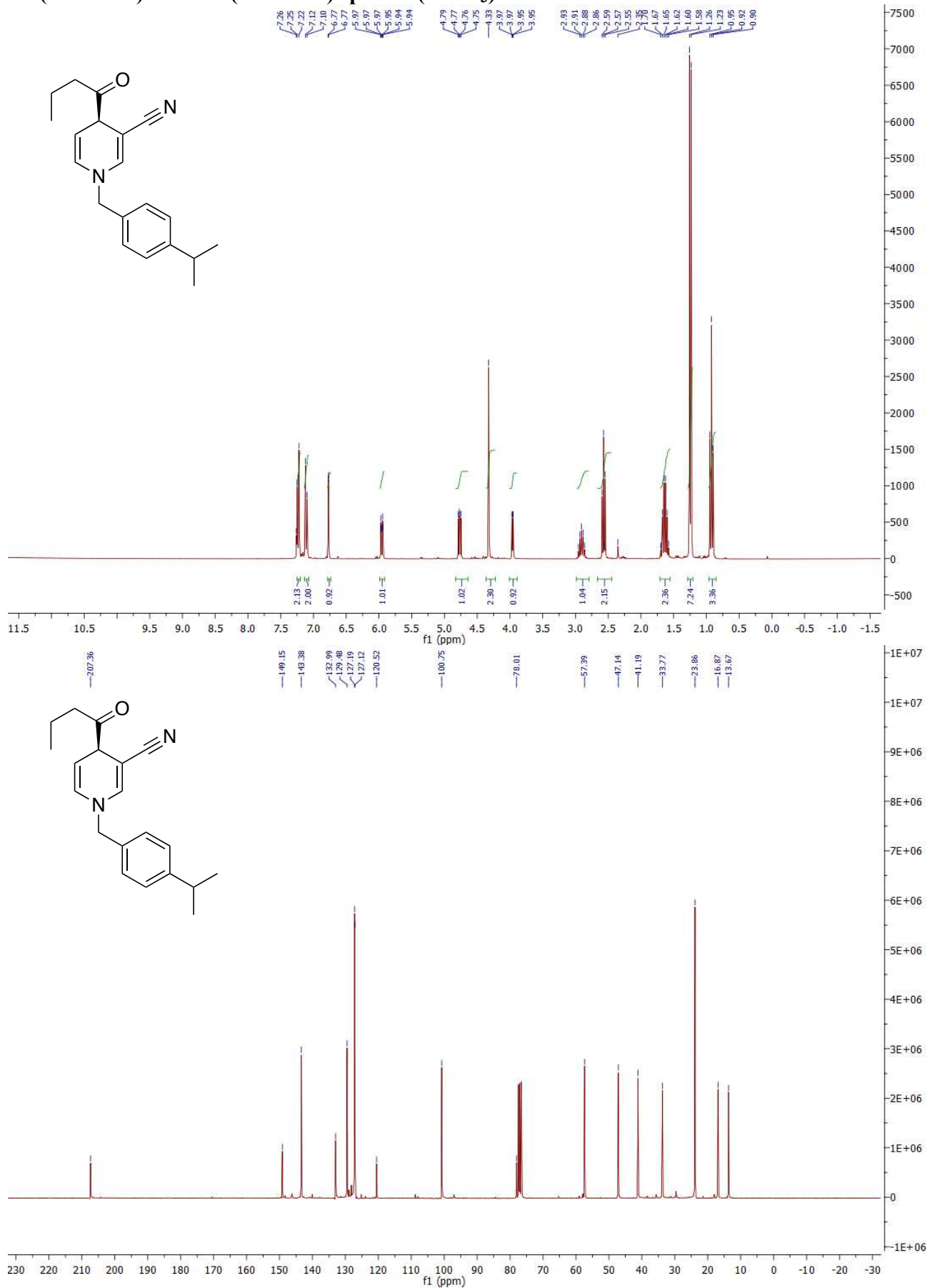
^1H (300 MHz) and ^{13}C (101 MHz) spectra (CDCl_3) of 3fa



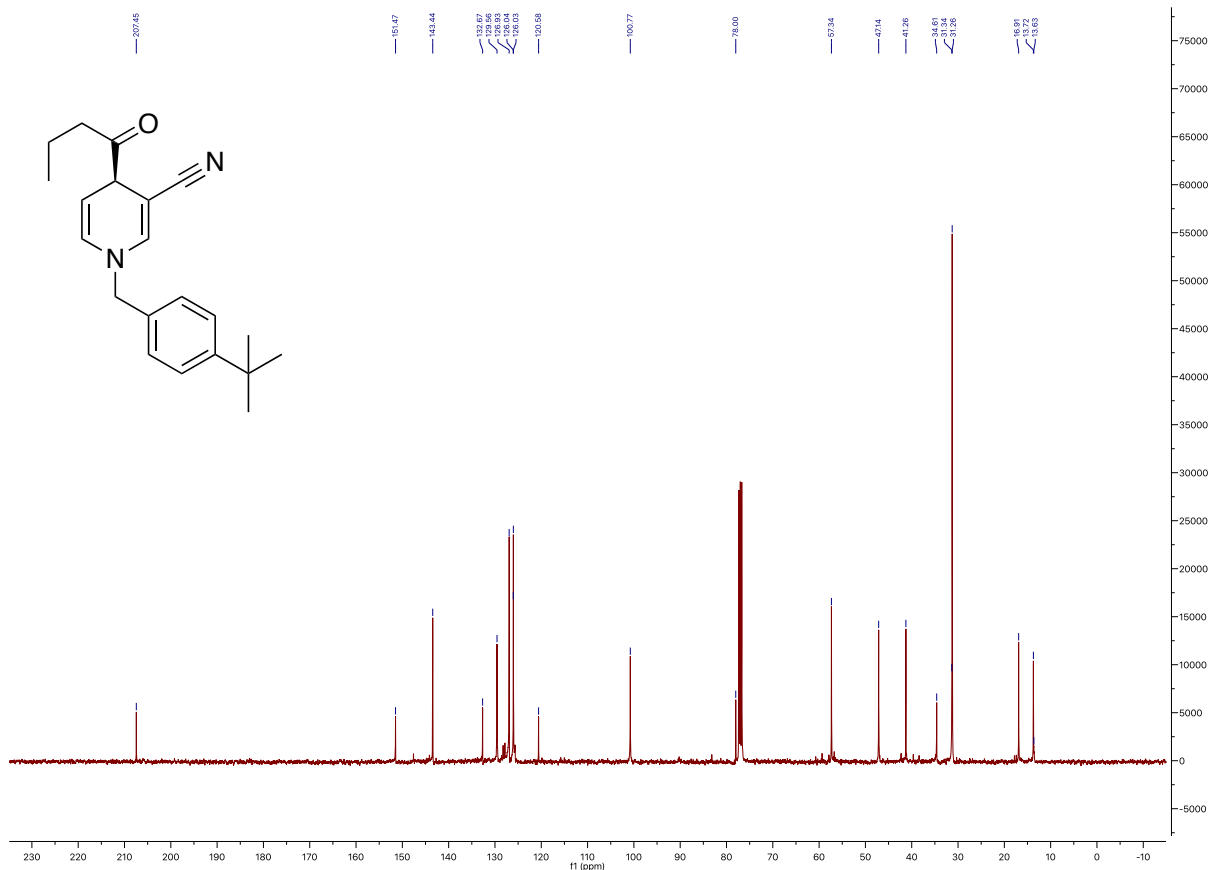
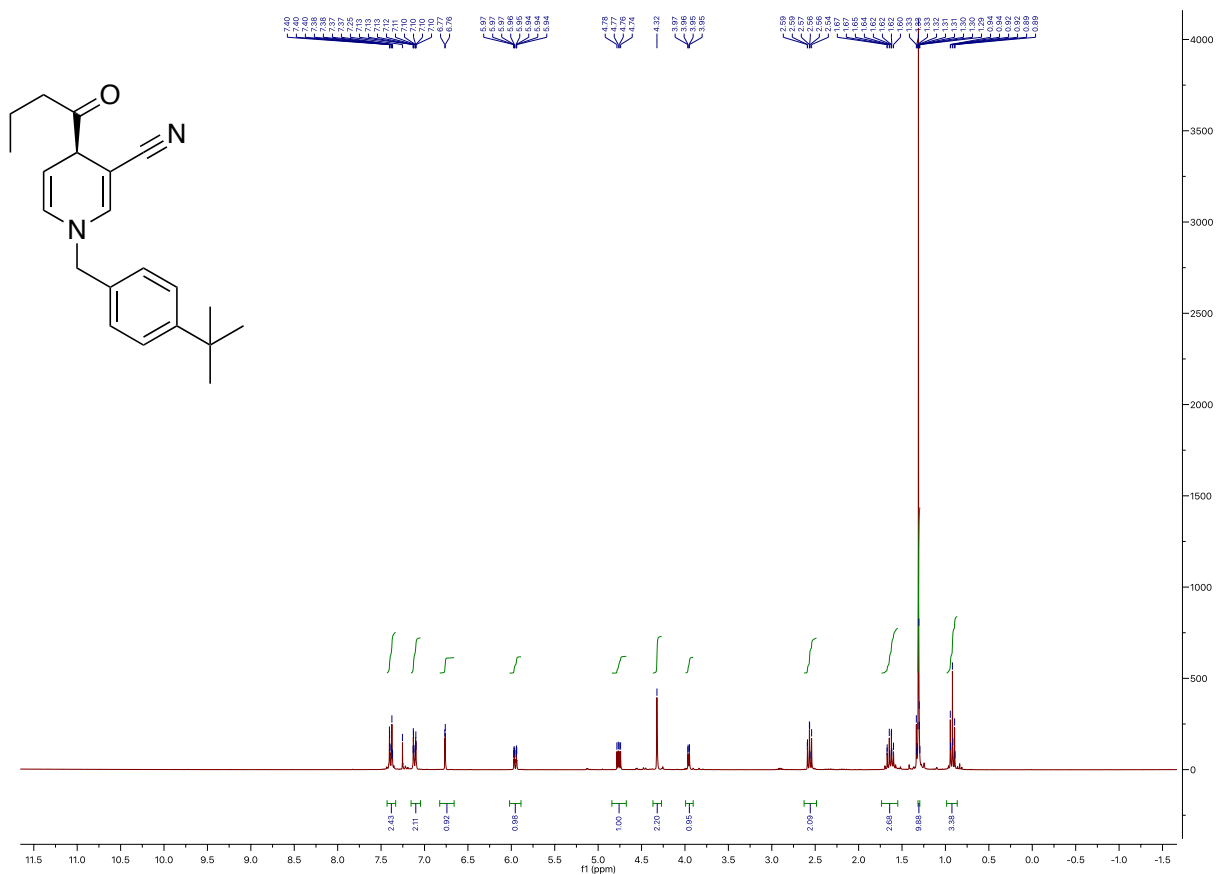
^1H (300 MHz) and ^{13}C (101 MHz) spectra (CDCl_3) of 3ha



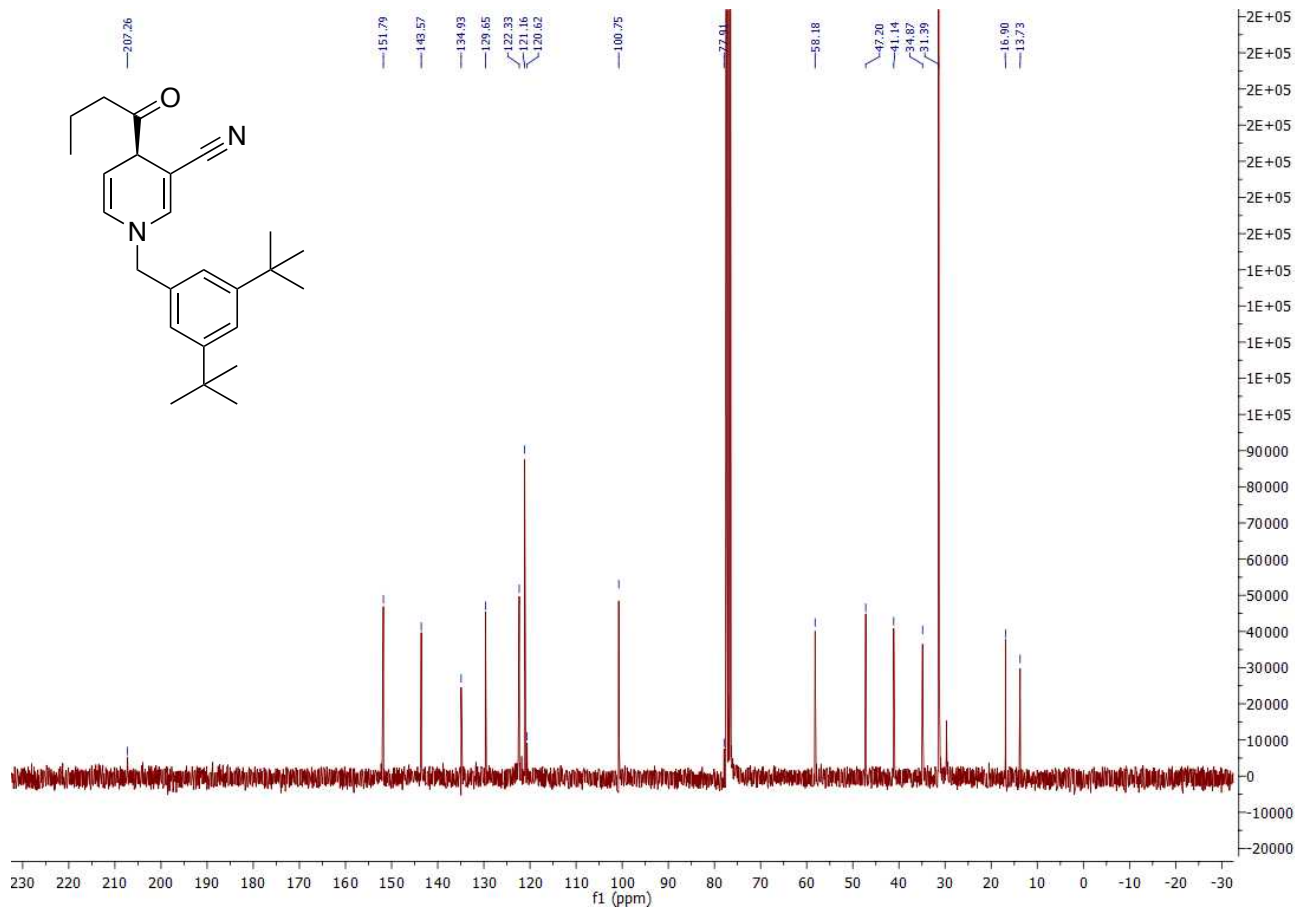
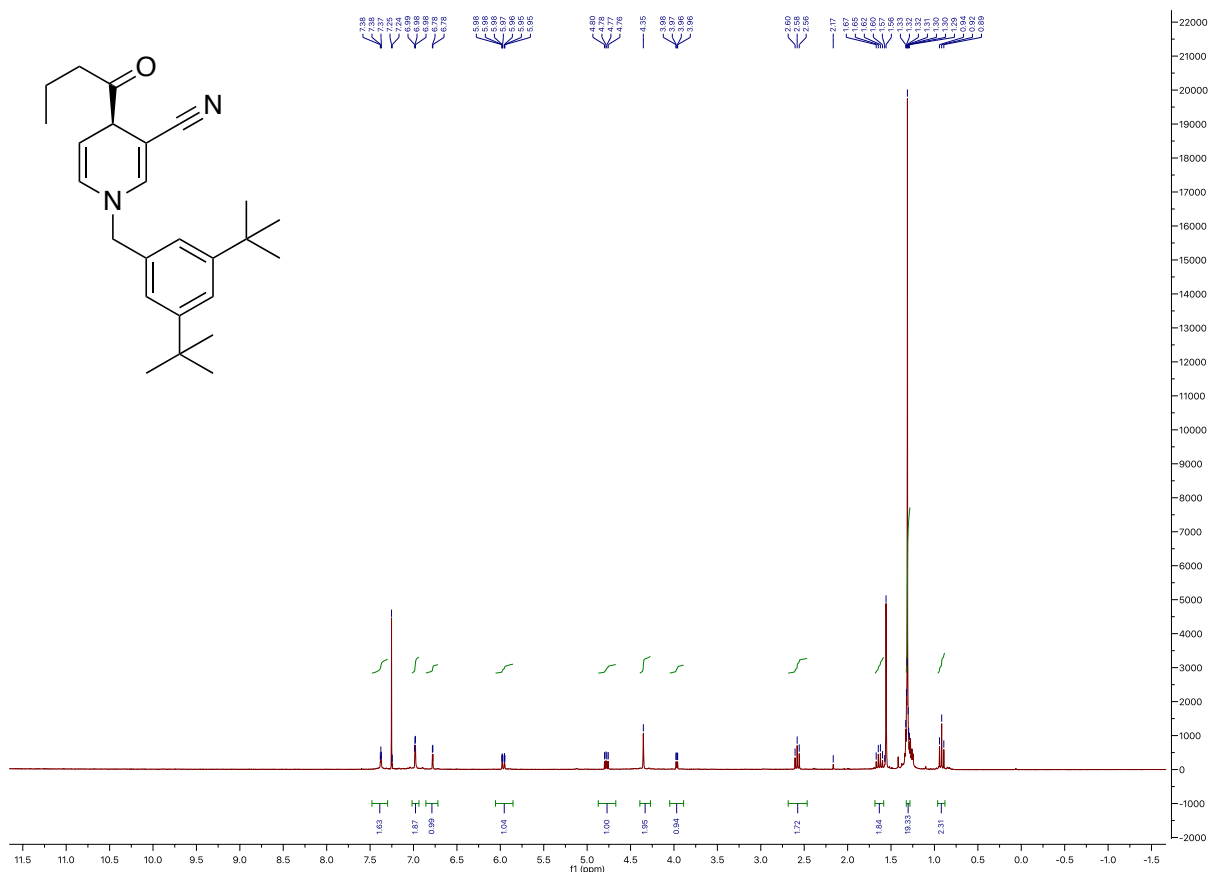
^1H (300 MHz) and ^{13}C (101 MHz) spectra (CDCl_3) of 3ab



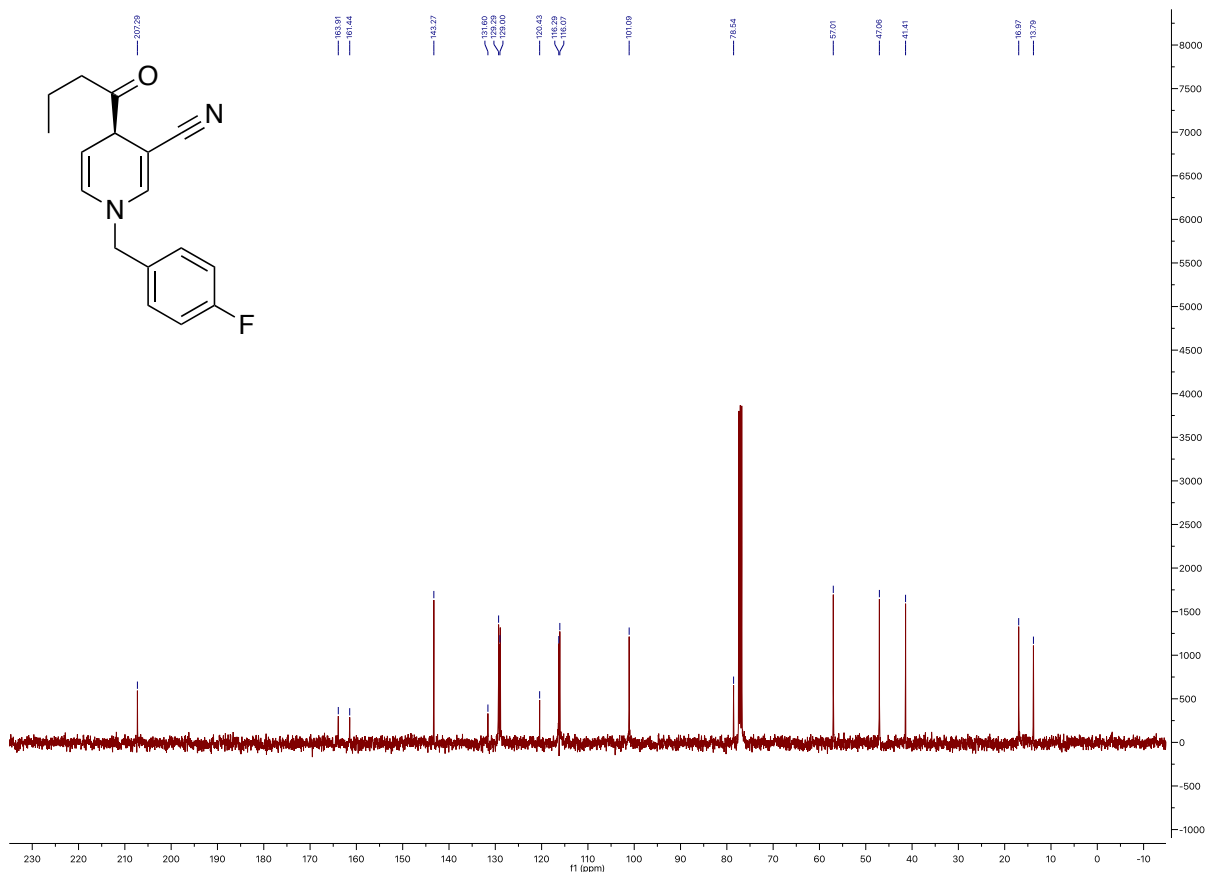
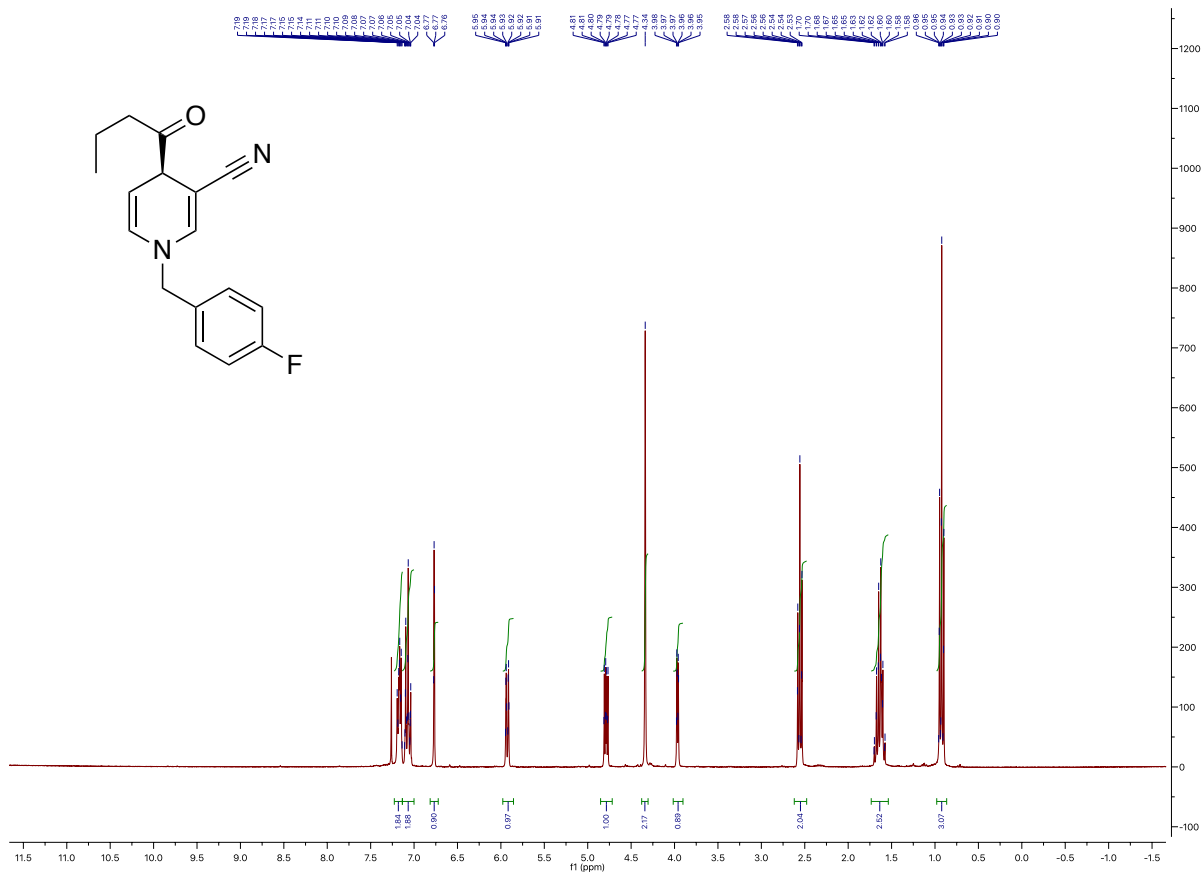
^1H (300 MHz) and ^{13}C (101 MHz) spectra (CDCl_3) of **3ac**

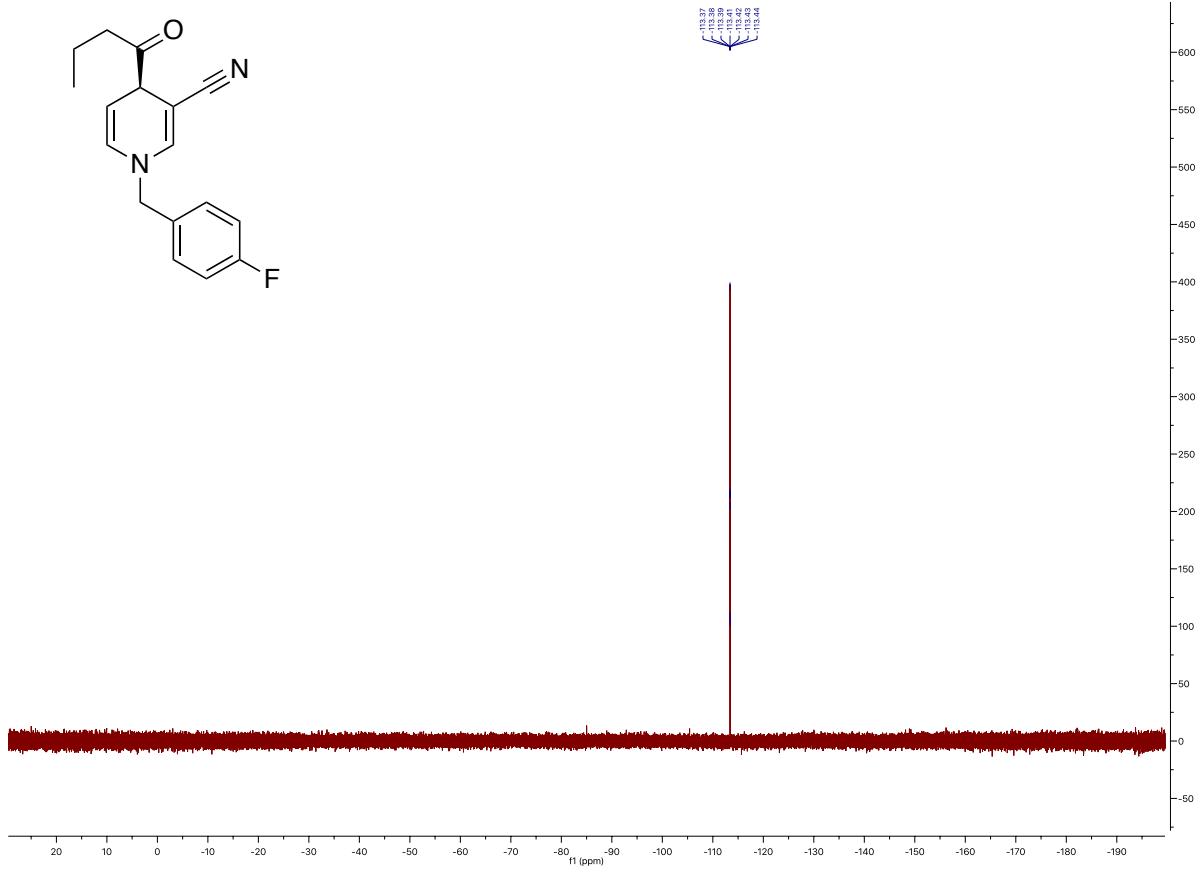


^1H (300 MHz) and ^{13}C (101 MHz) spectra (CDCl_3) of 3ad

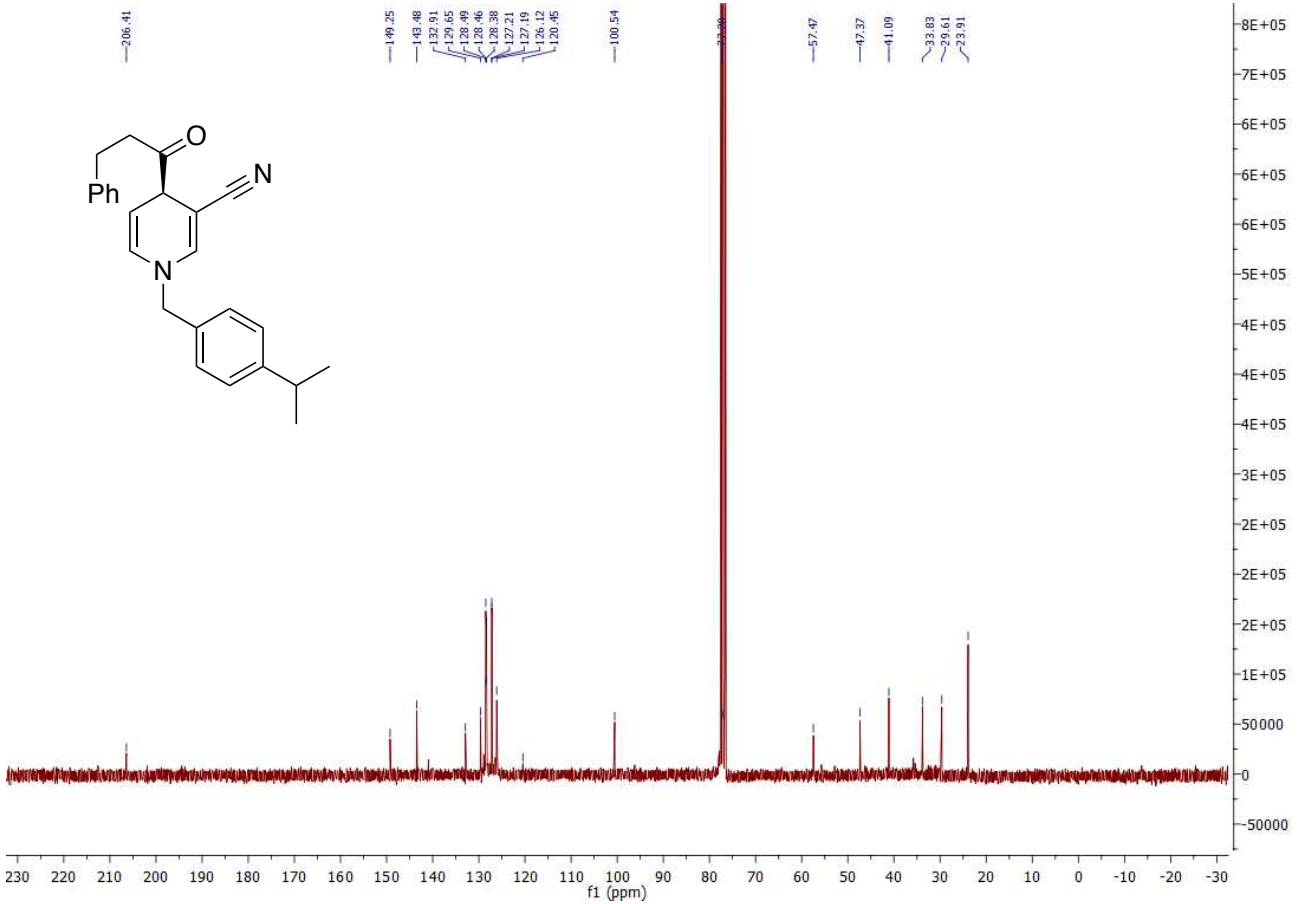
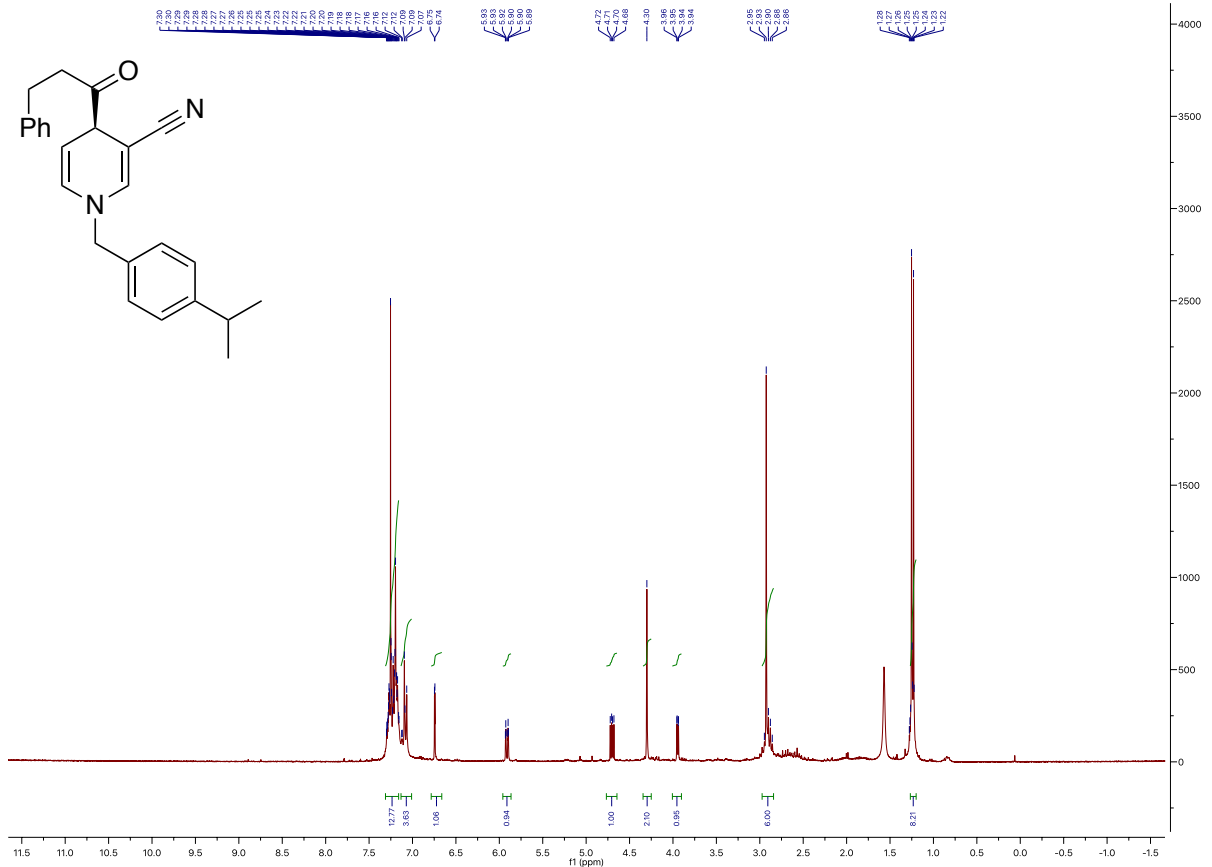


^1H (300 MHz), ^{13}C (101 MHz) and ^{19}F (376 MHz) spectra (CDCl_3) of 3ae

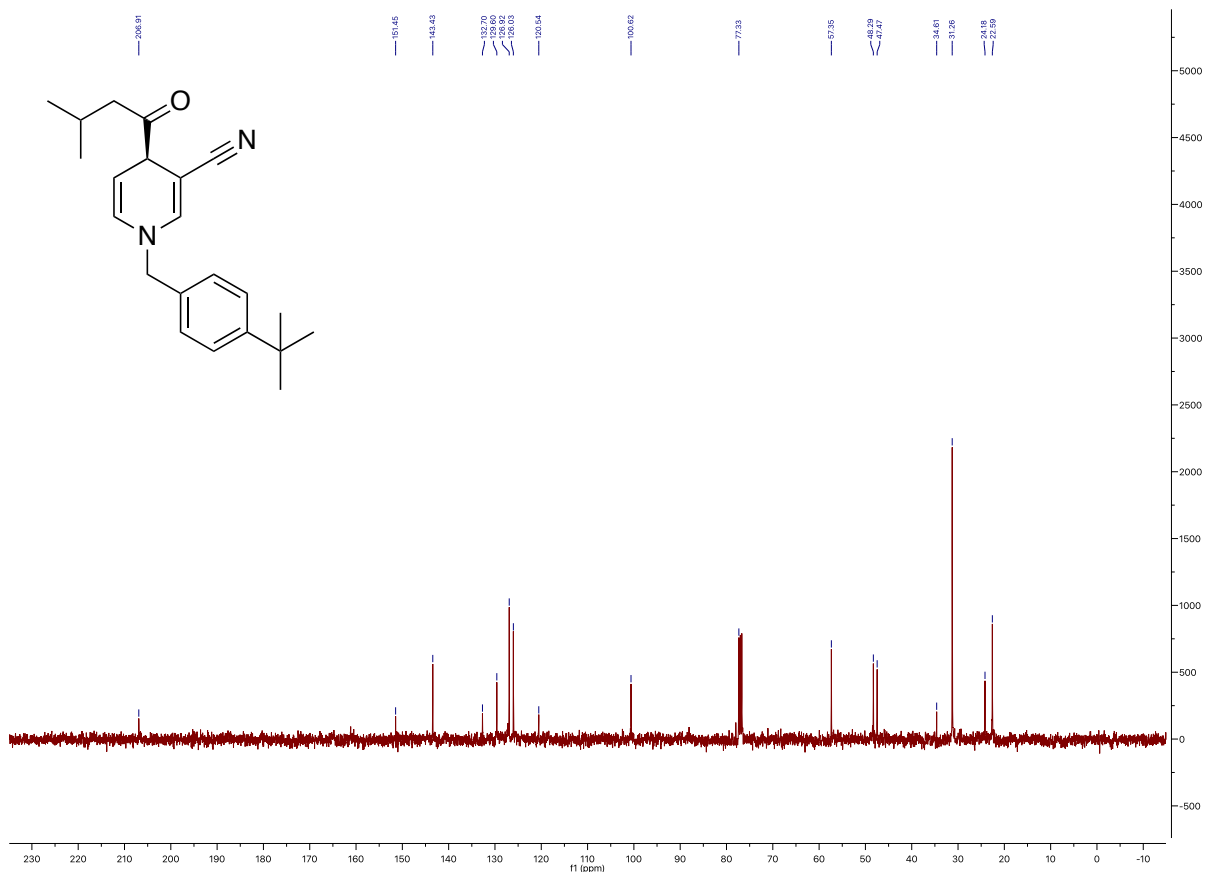
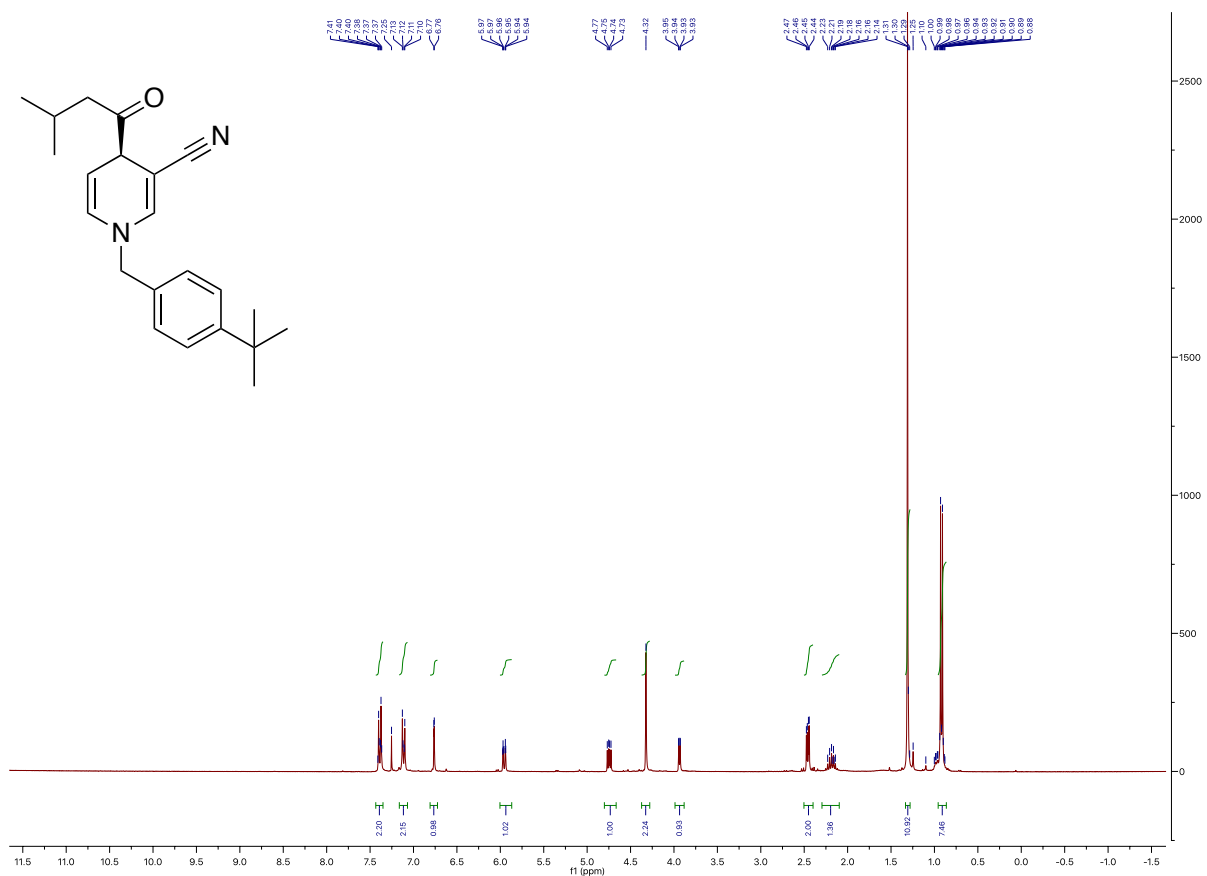




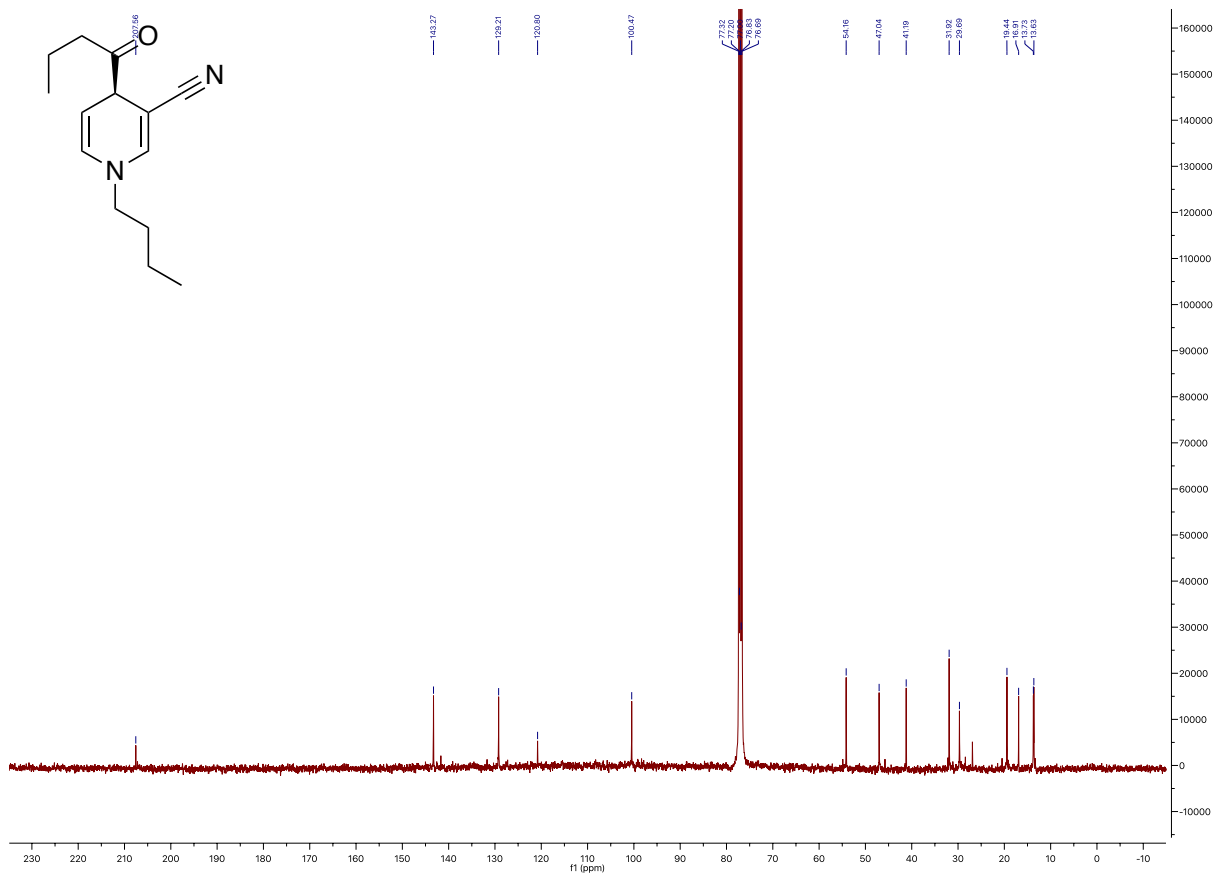
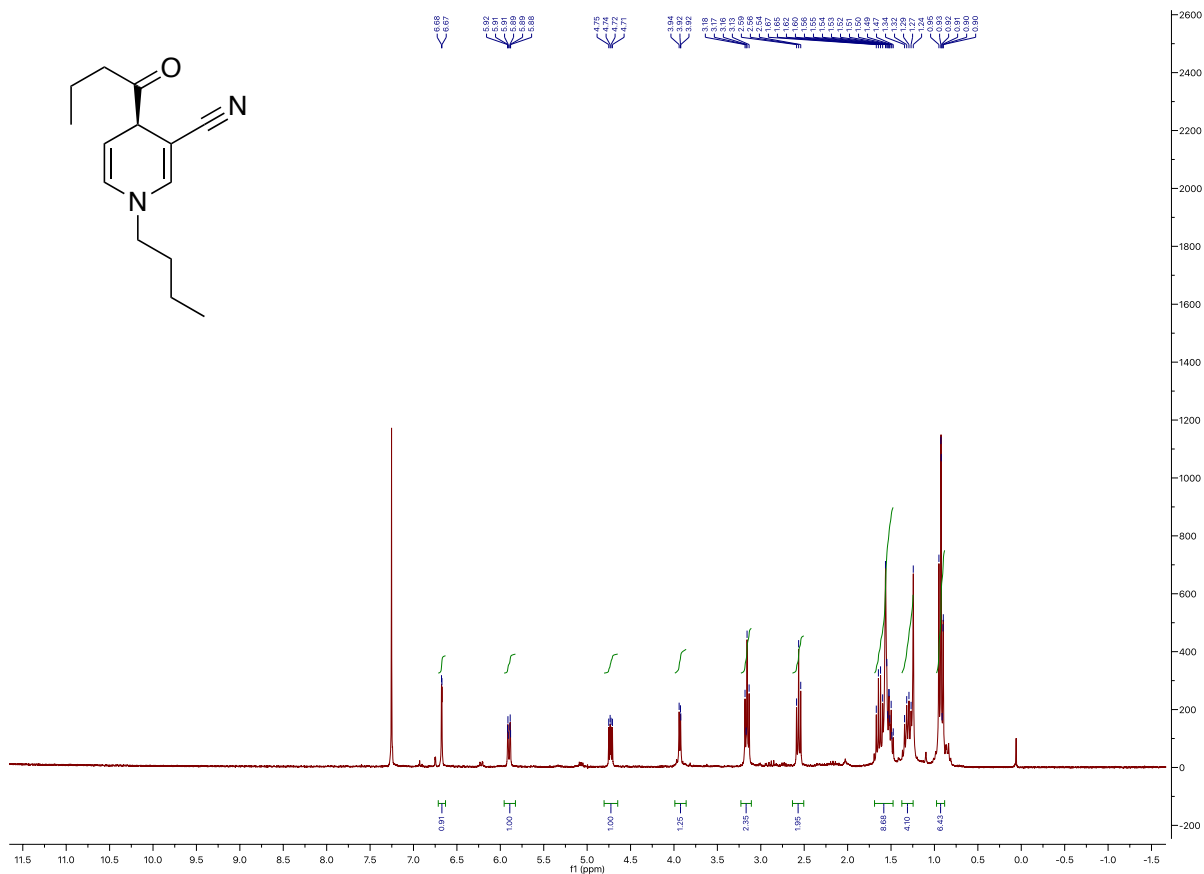
¹H (300 MHz) and ¹³C (101 MHz) spectra (CDCl₃) of 3eb



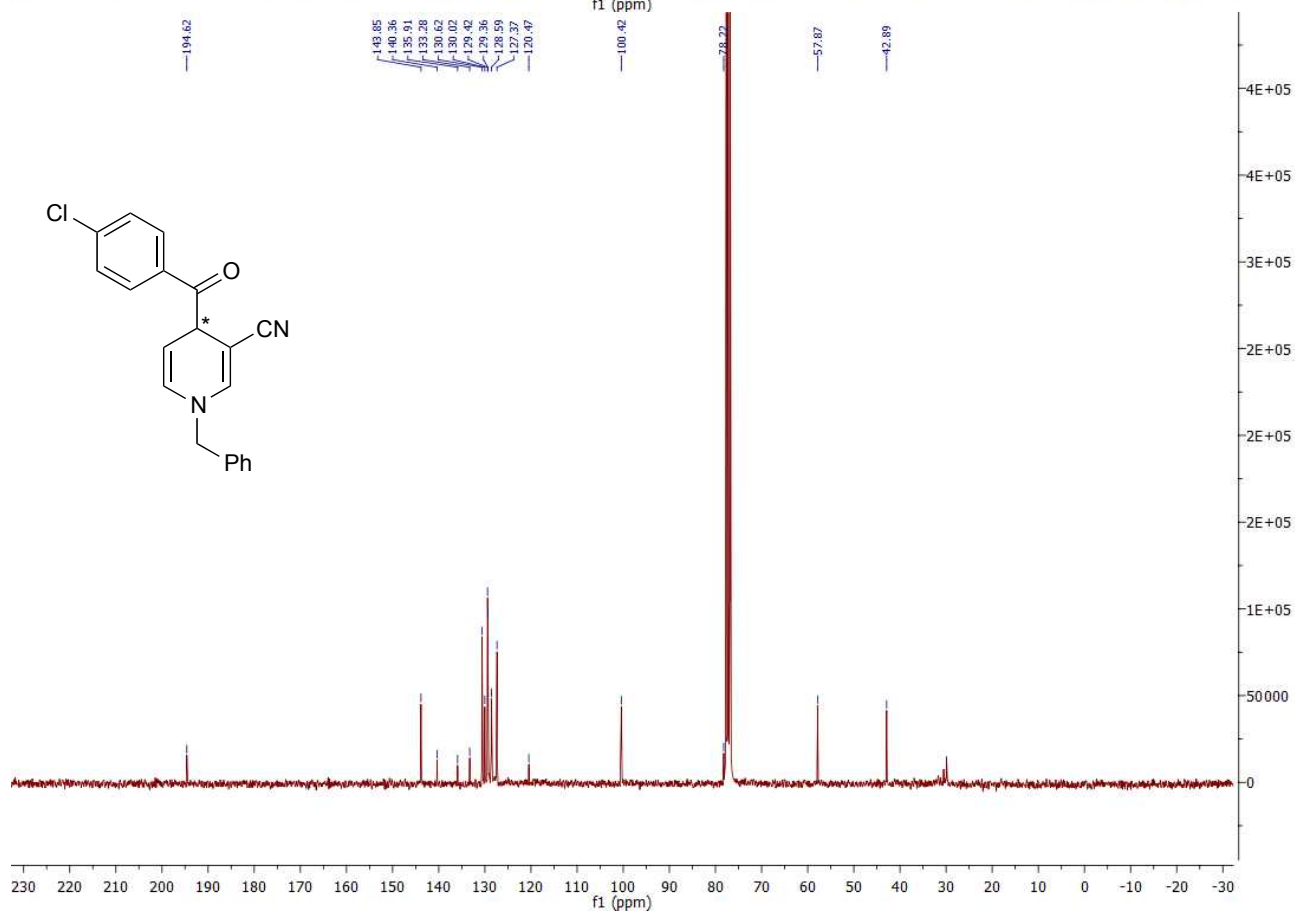
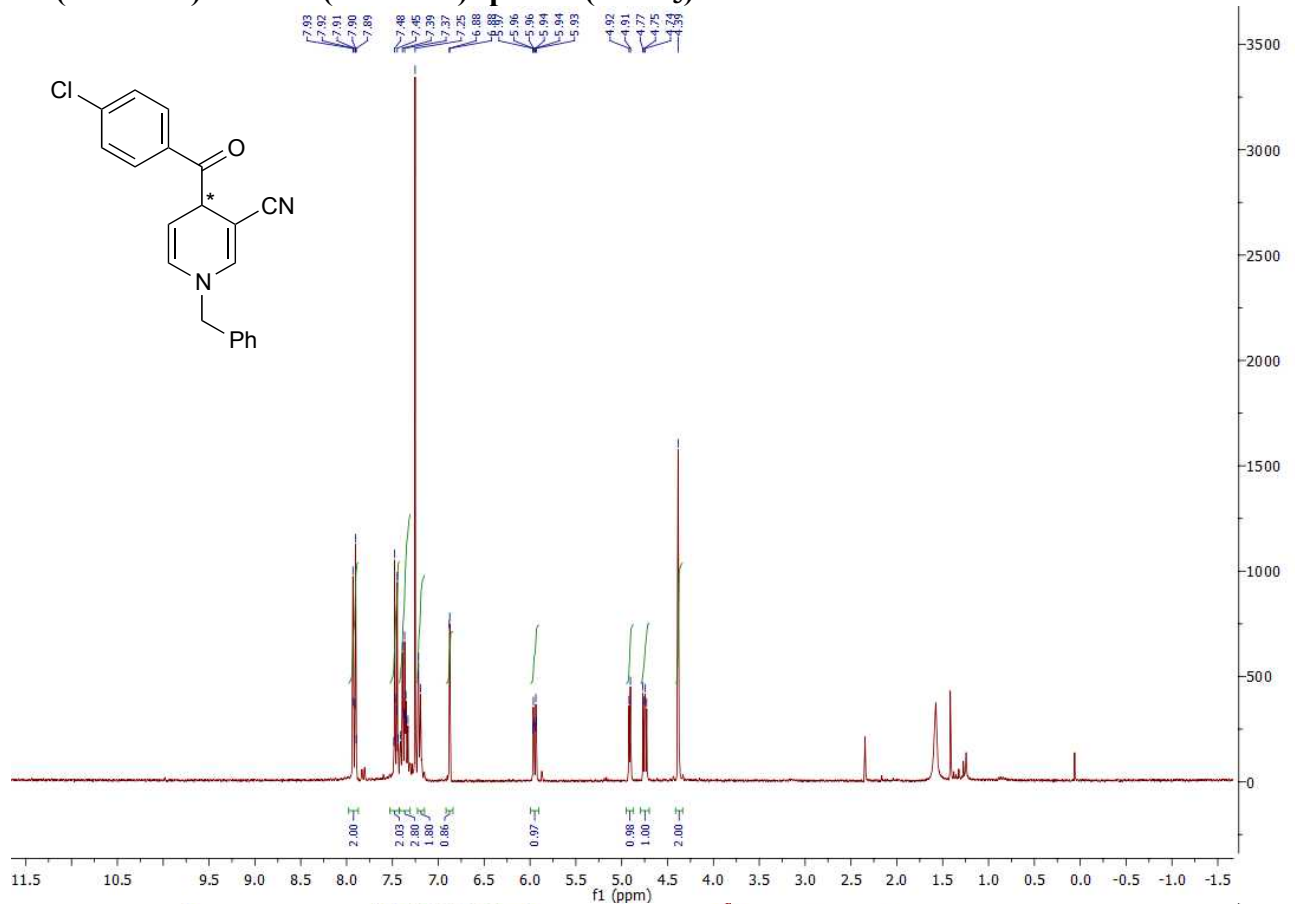
¹H (300 MHz) and ¹³C (101 MHz) spectra (CDCl₃) of 3fc



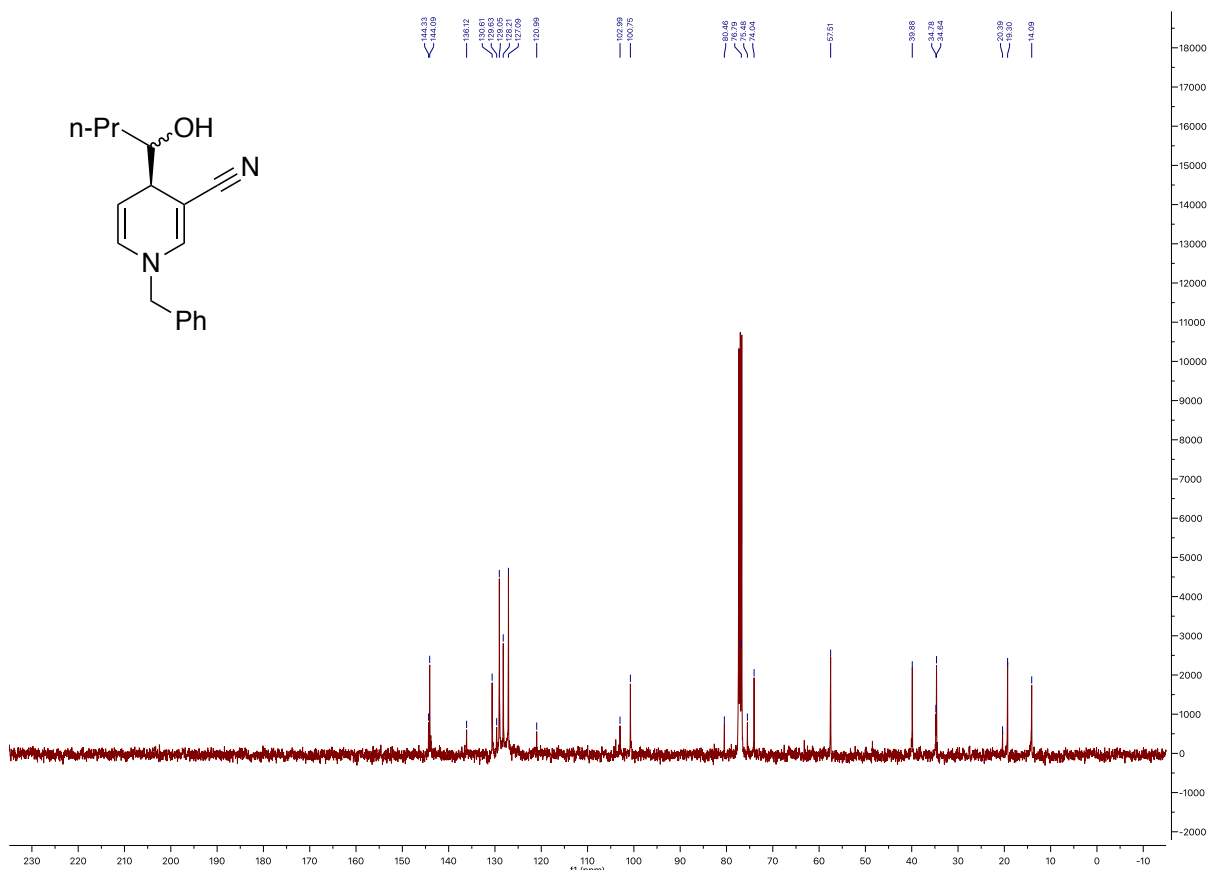
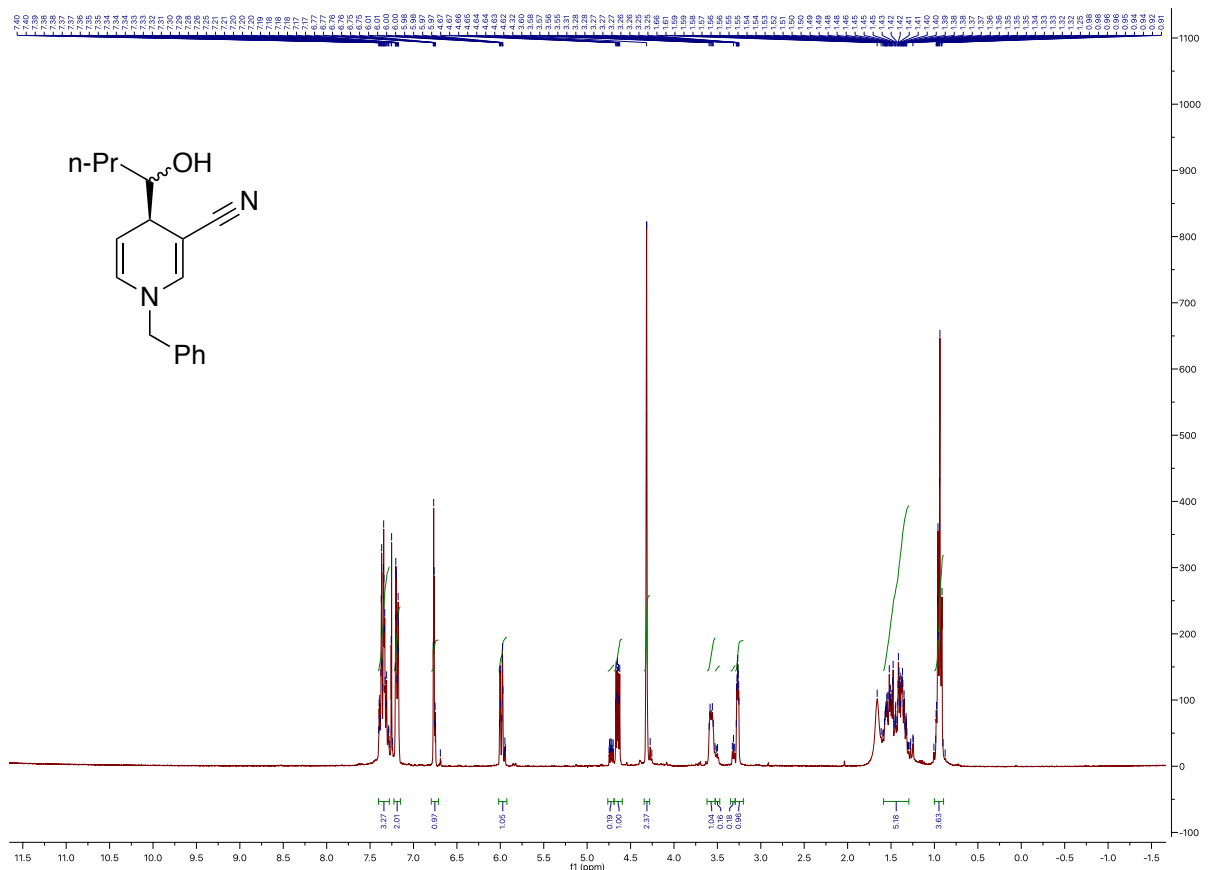
^1H (300 MHz) and ^{13}C (101 MHz) spectra (CDCl_3) of 3af



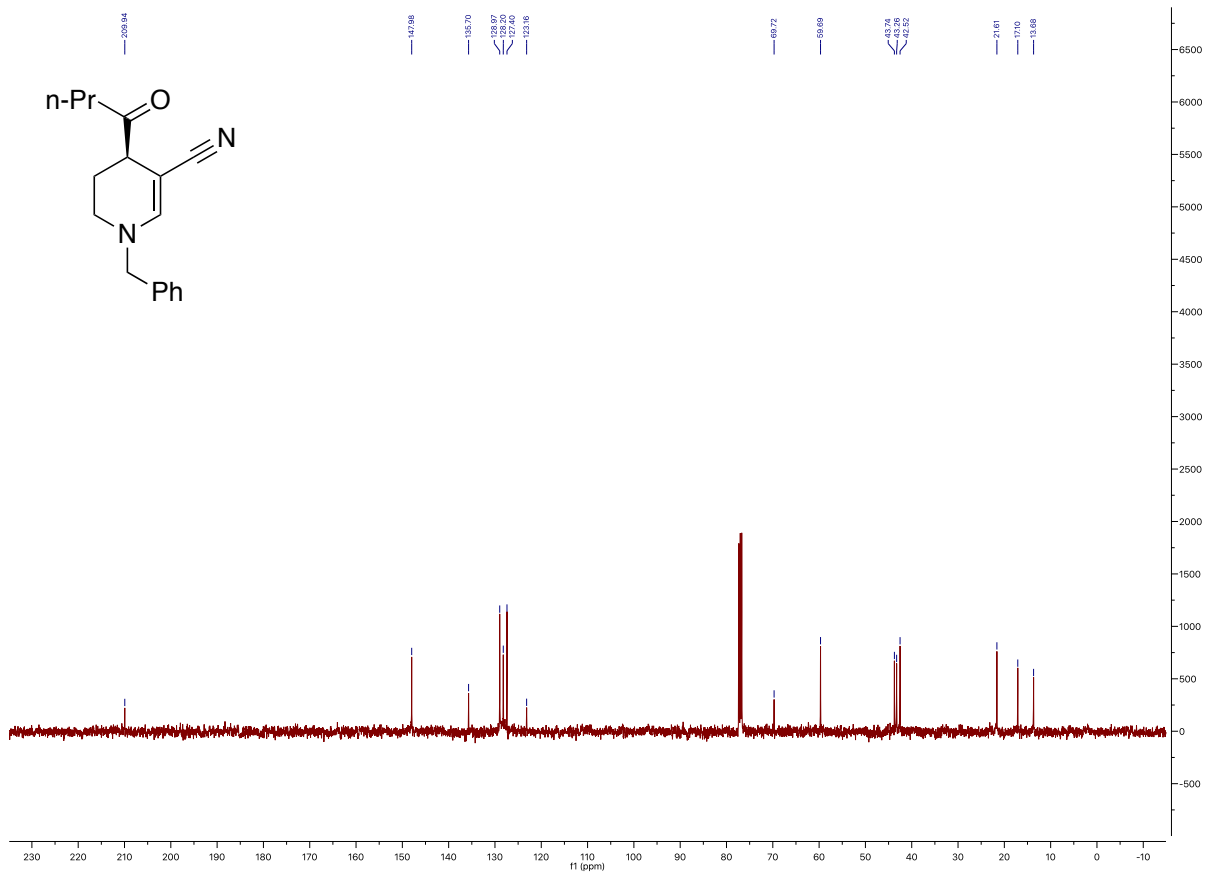
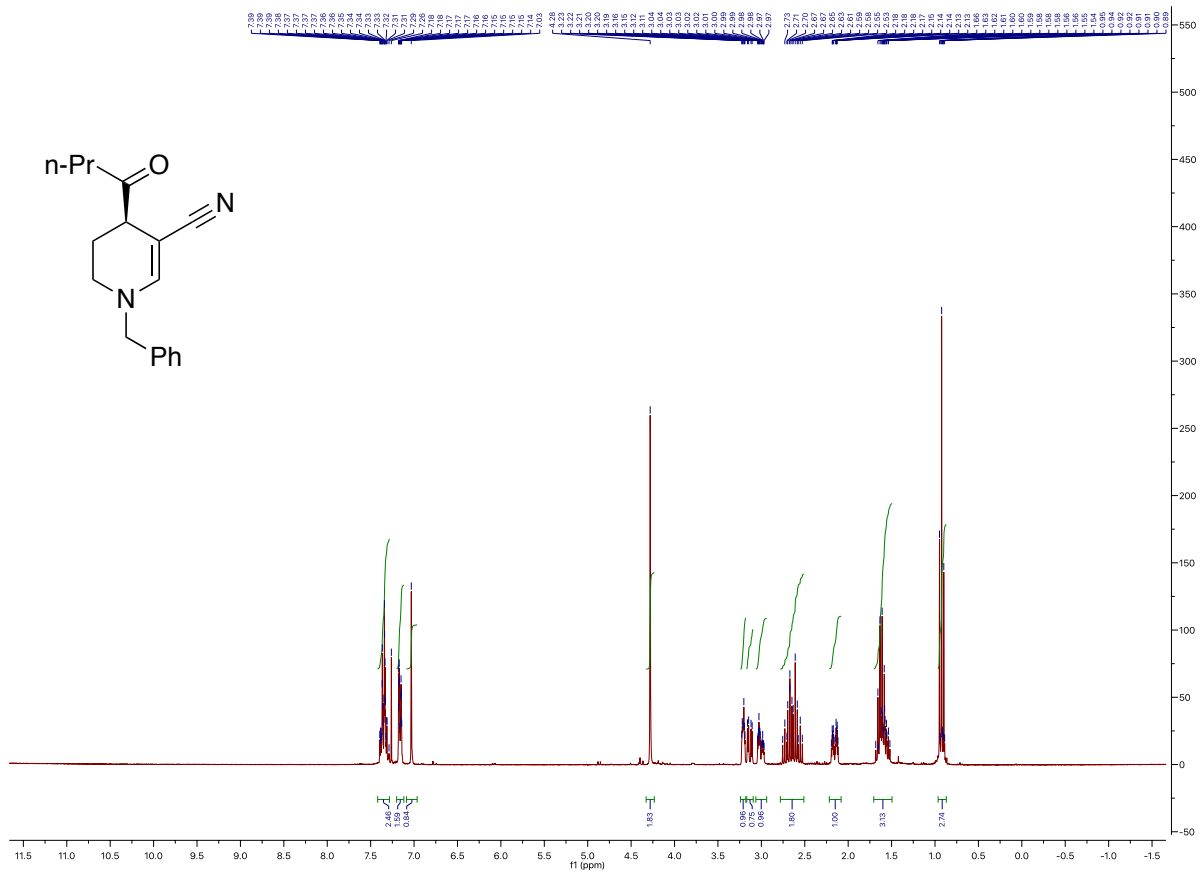
^1H (300 MHz) and ^{13}C (101 MHz) spectra (CDCl_3) of 7a



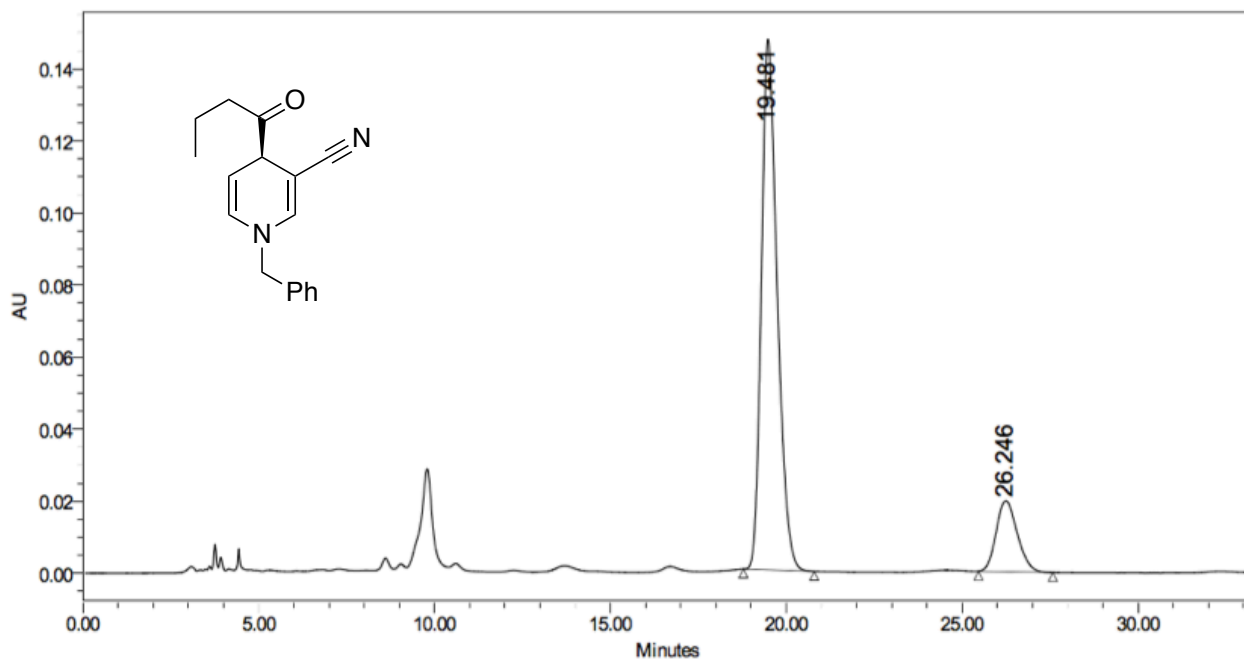
^1H (300 MHz) and ^{13}C (101 MHz) spectra (CDCl_3) of 11aa



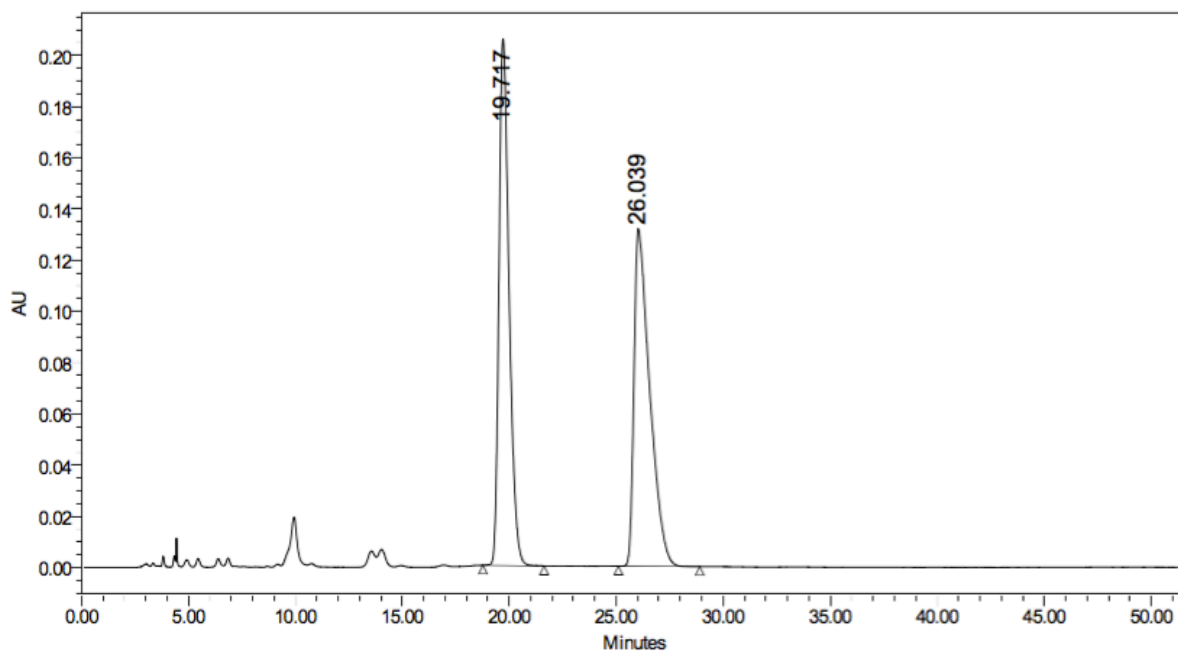
¹H (300 MHz) and ¹³C (101 MHz) spectra (CDCl₃) of 12aa



HPLC chromatograms of 3aa and 3aa-rac

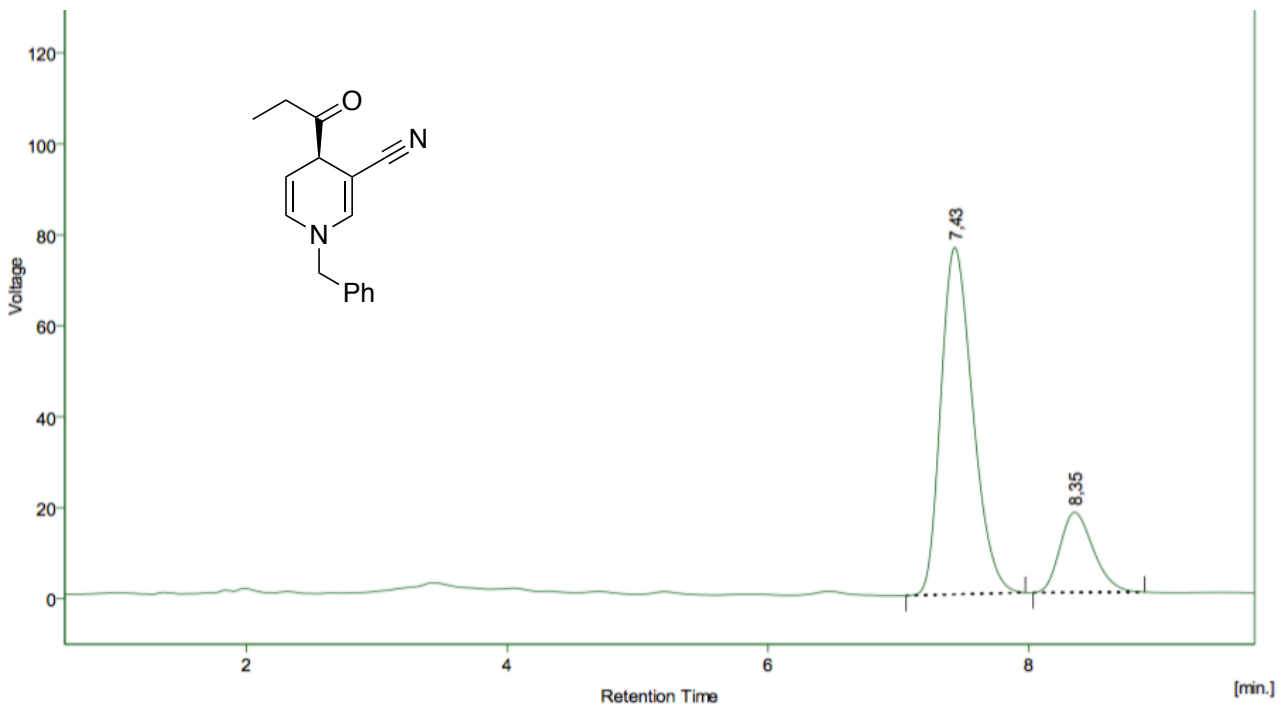


	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	19.481	4600008	84.83	147323	88.24
2	26.246	822902	15.17	19629	11.76

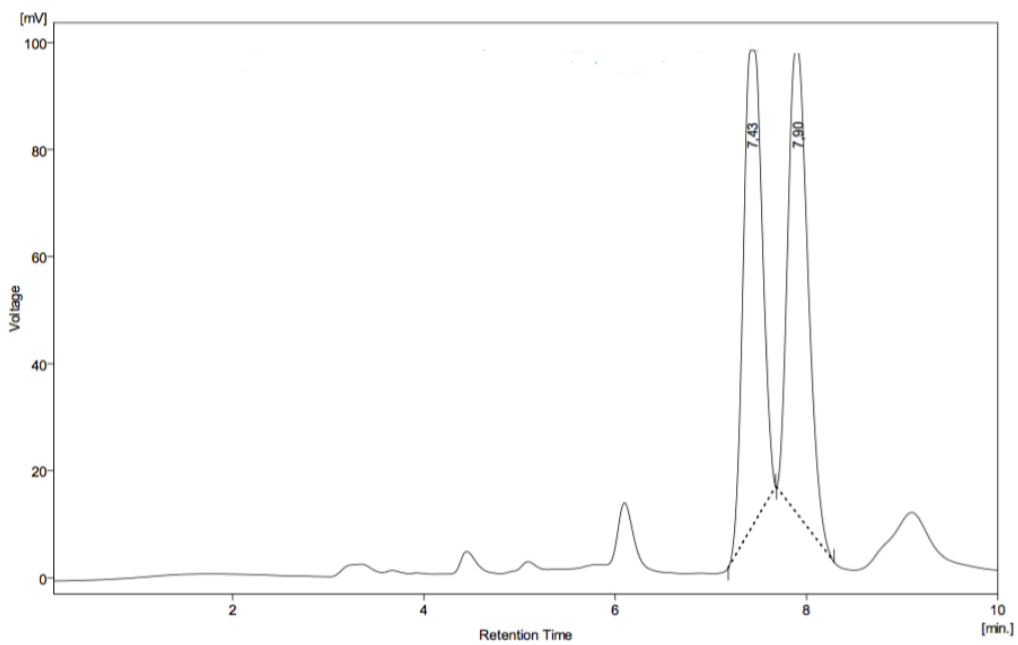


	RT (min)	Peak Type	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	19.717	Unknown	6737307	50.07	205536	60.94	bb	1710	18.777	21.627
2	26.039	Unknown	6718203	49.93	131719	39.06	bb	2280	25.107	28.907

HPLC chromatograms of 3ba and 3ba-rac

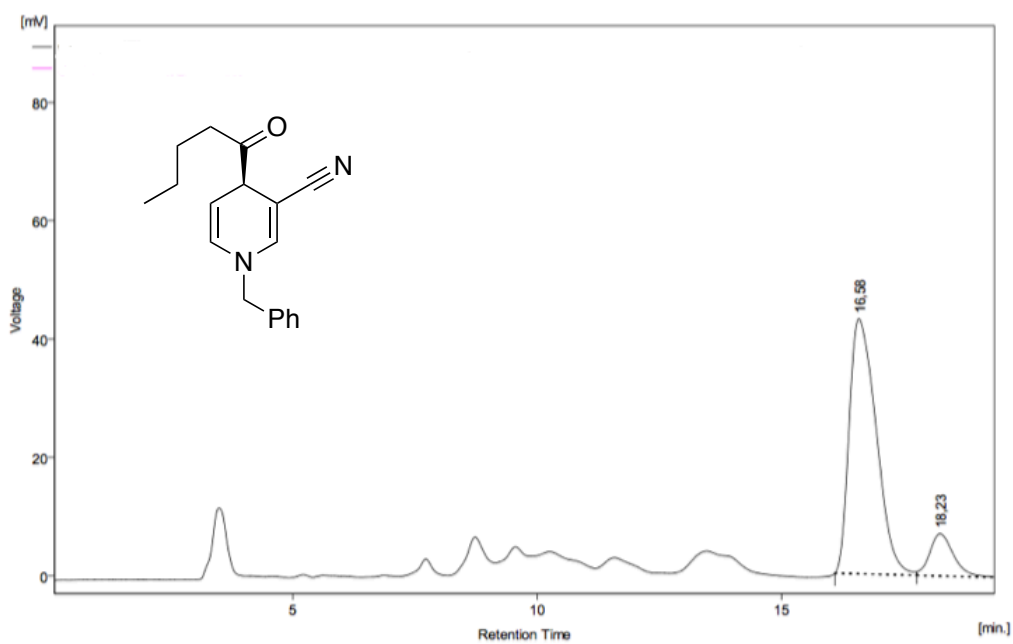


	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	7,430	1294,082	76,268	80,5	81,3	0,27
2	8,350	313,168	17,577	19,5	18,7	0,28
Total		1607,251	93,846	100,0	100,0	

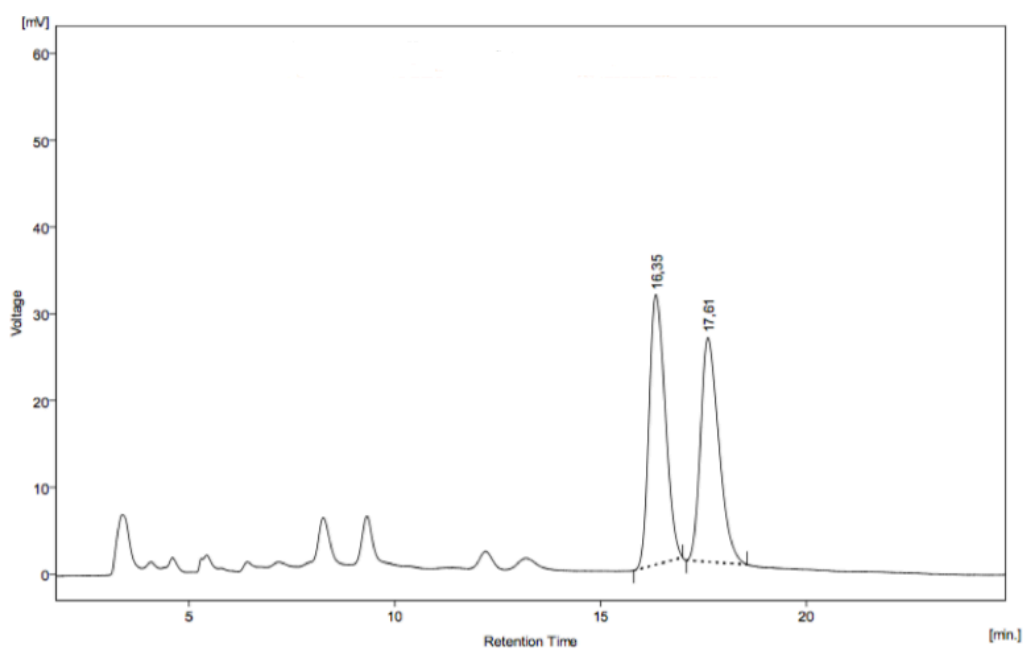


	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	7,427	1225,863	89,197	49,2	50,7	0,23
2	7,900	1263,442	86,572	50,8	49,3	0,23
Total		2489,305	175,769	100,0	100,0	

HPLC chromatograms of 3ca and 3ca-rac

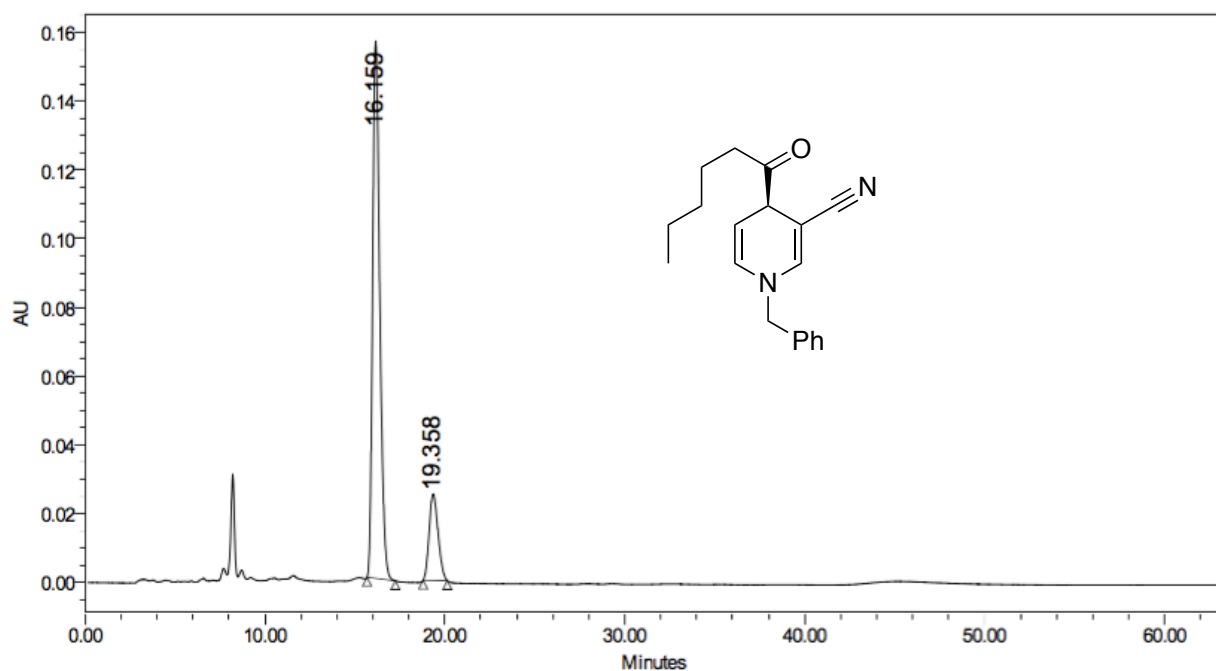


	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	16,580	1652,768	43,121	87,3	85,8	0,62
2	18,233	240,245	7,107	12,7	14,2	0,51
Total		1893,012	50,228	100,0	100,0	

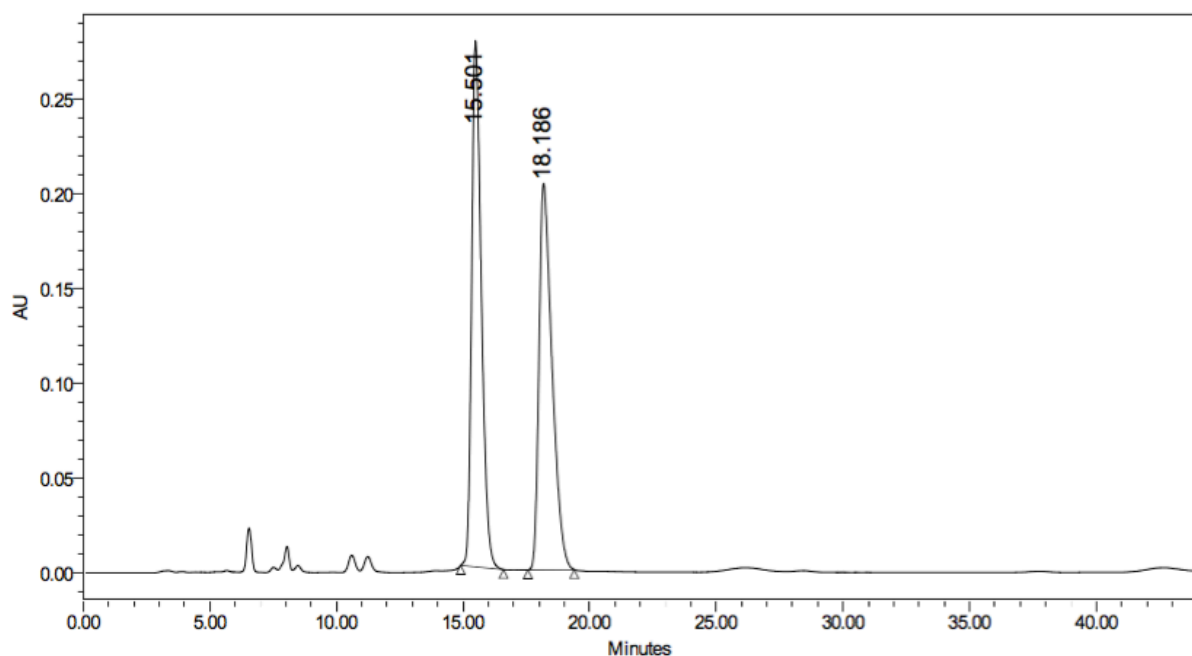


	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	16,350	842,469	31,082	51,2	54,6	0,43
2	17,607	802,192	25,814	48,8	45,4	0,48
Total		1644,660	56,897	100,0	100,0	

HPLC chromatograms of 3da and 3da-rac

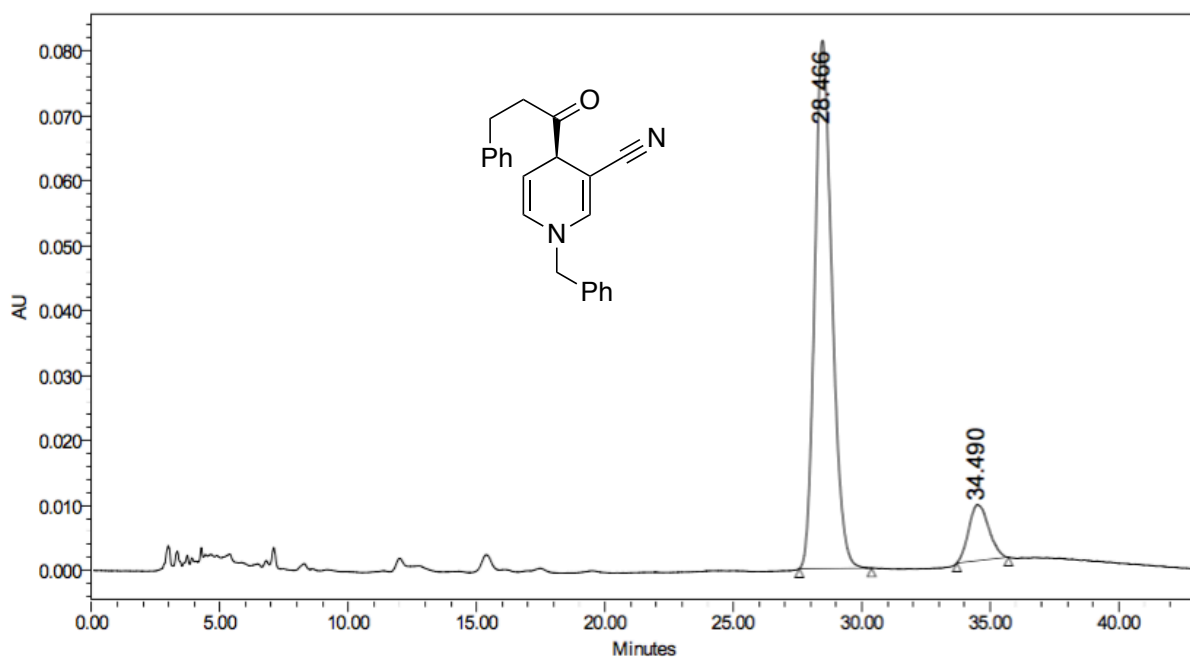


	RT (min)	Peak Type	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	16.159	Unknown	4296652	83.26	156169	86.16	bb	941	15.681	17.250
2	19.358	Unknown	864028	16.74	25091	13.84	bb	804	18.800	20.140

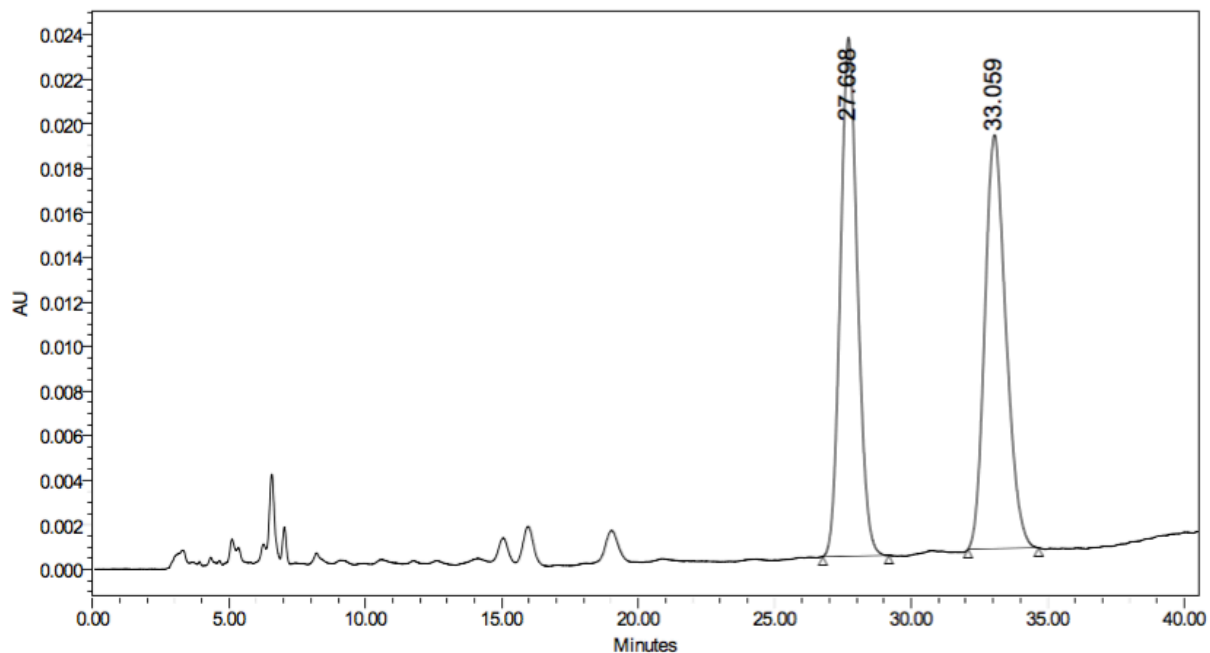


	RT (min)	Peak Type	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	15.501	Unknown	7334612	50.18	277313	57.65	bb	1013	14.916	16.605
2	18.186	Unknown	7281935	49.82	203688	42.35	bb	1097	17.567	19.395

HPLC chromatograms of 3ea and 3ea-rac

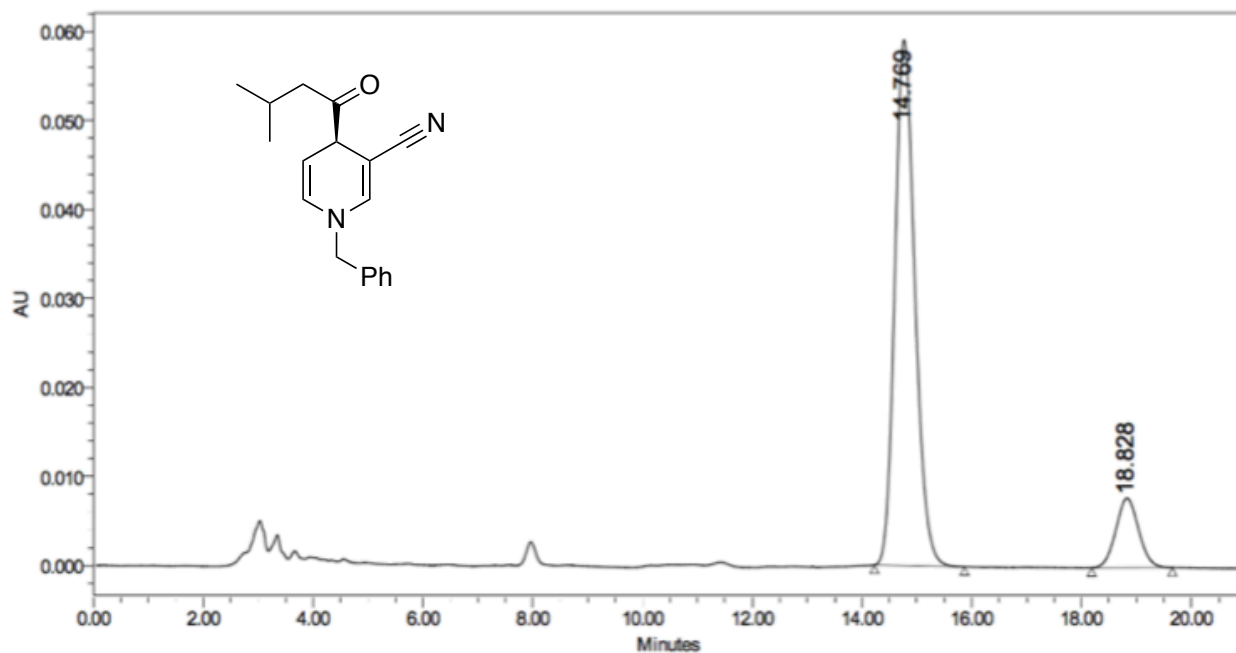


	RT (min)	Peak Type	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	28.466	Unknown	3783362	89.03	81299	90.40	bb	1688	27.565	30.379
2	34.490	Unknown	466246	10.97	8632	9.60	bb	1207	33.700	35.712

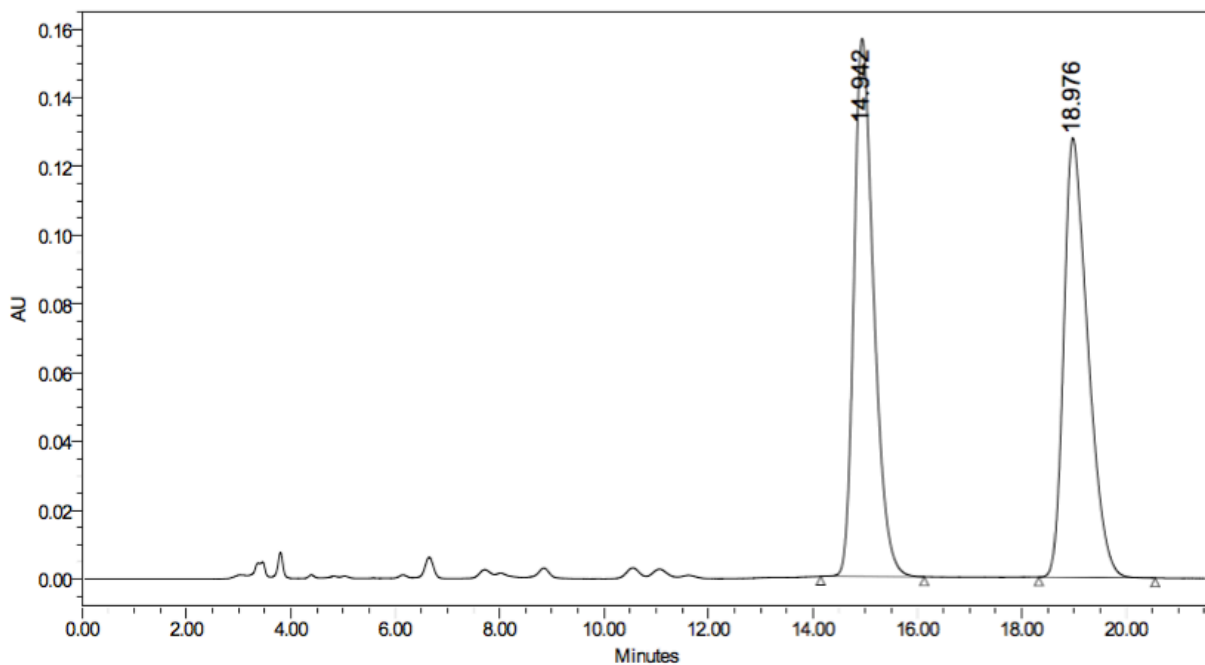


	RT (min)	Peak Type	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	27.698	Unknown	1013303	50.38	23272	55.61	bb	1456	26.755	29.182
2	33.059	Unknown	998081	49.62	18573	44.39	bb	1554	32.083	34.674

HPLC chromatograms of 3fa and 3fa-rac

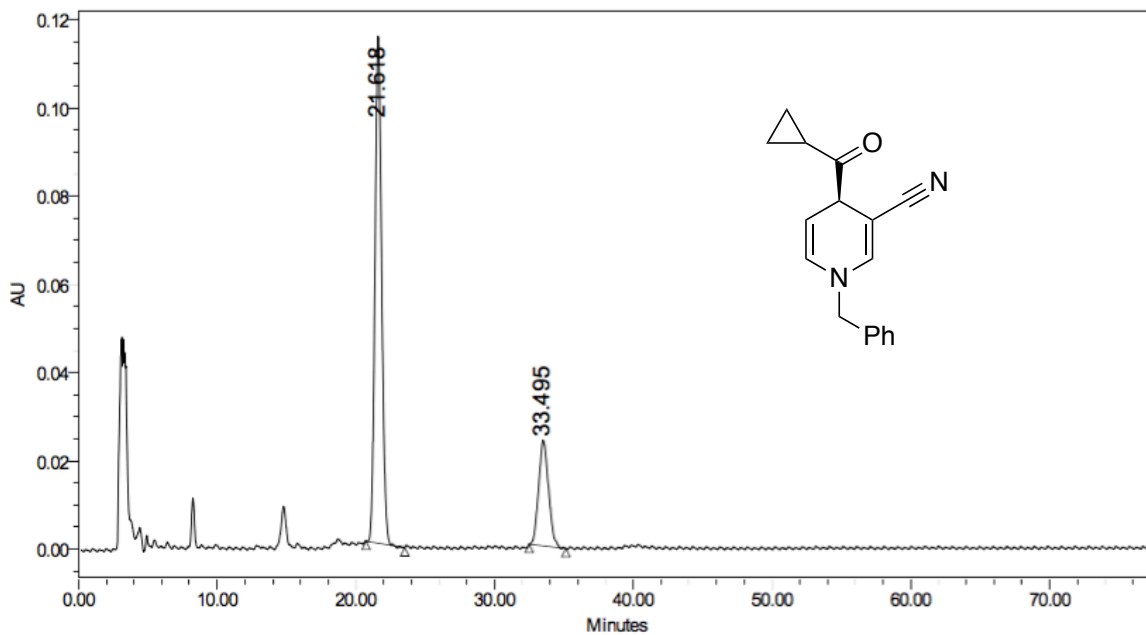


	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	14.769	1492551	86.87	59084	88.31
2	18.828	225551	13.13	7823	11.69

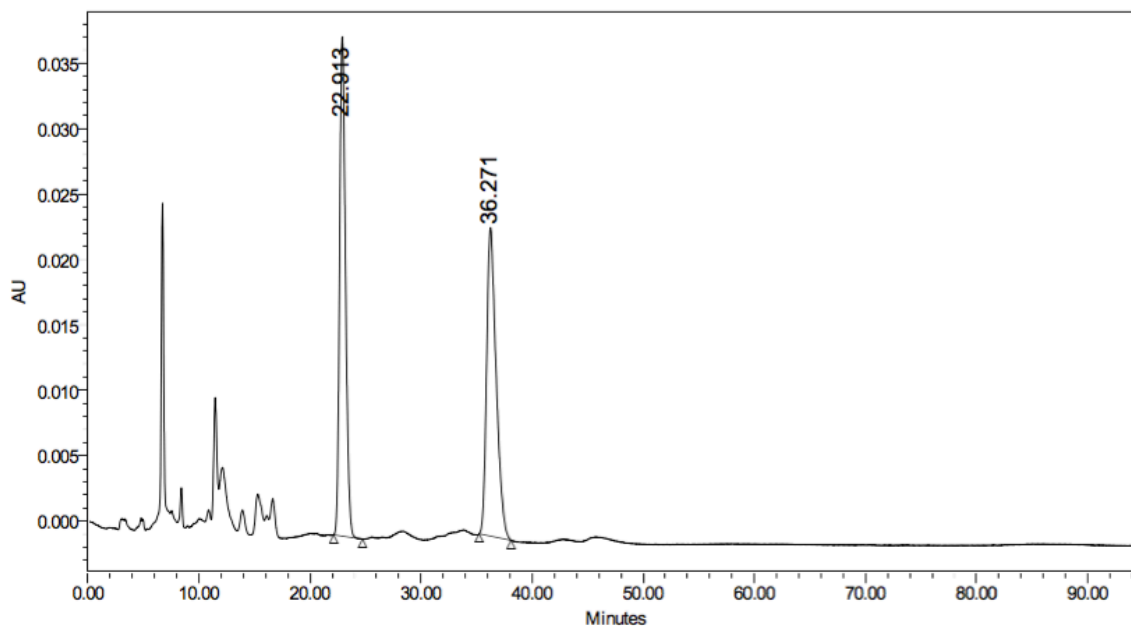


	RT (min)	Peak Type	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	14.942	Unknown	4129350	50.24	156433	55.05	bb	1194	14.144	16.135
2	18.976	Unknown	4089834	49.76	127744	44.95	BB	1334	18.330	20.554

HPLC chromatograms of 3ha and 3ha-rac

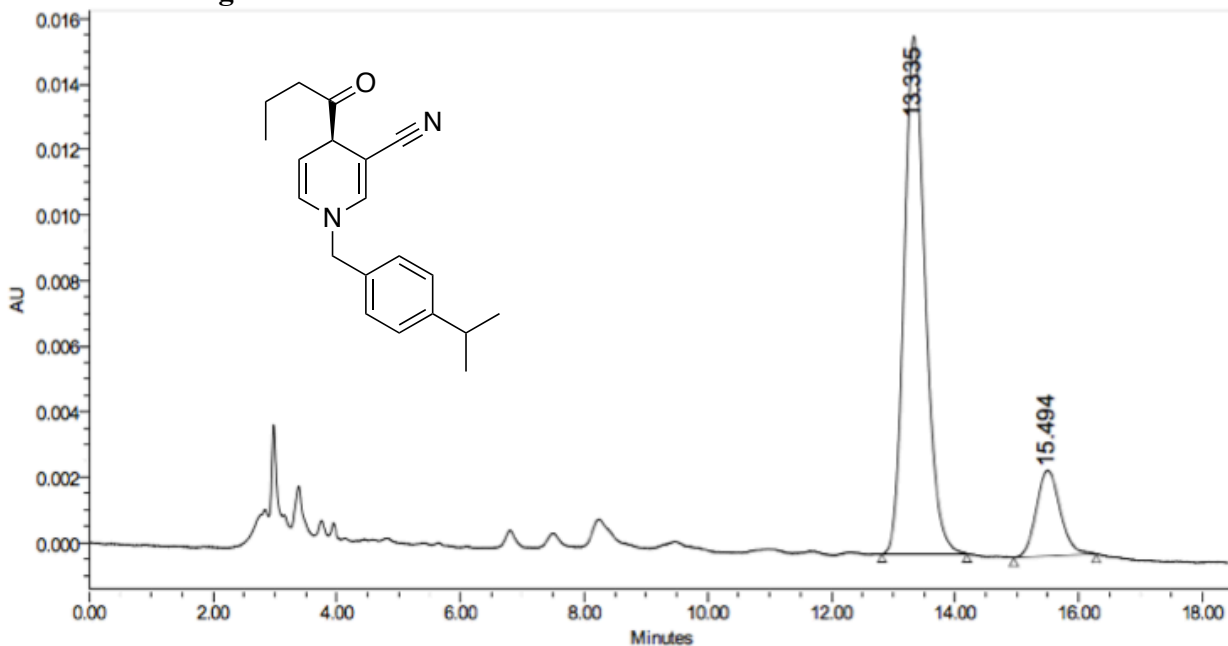


	RT (min)	Peak Type	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	21.618	Unknown	3830718	76.31	114874	82.75	bb	1670	20.742	23.526
2	33.495	Unknown	1189402	23.69	23943	17.25	bb	1586	32.495	35.139

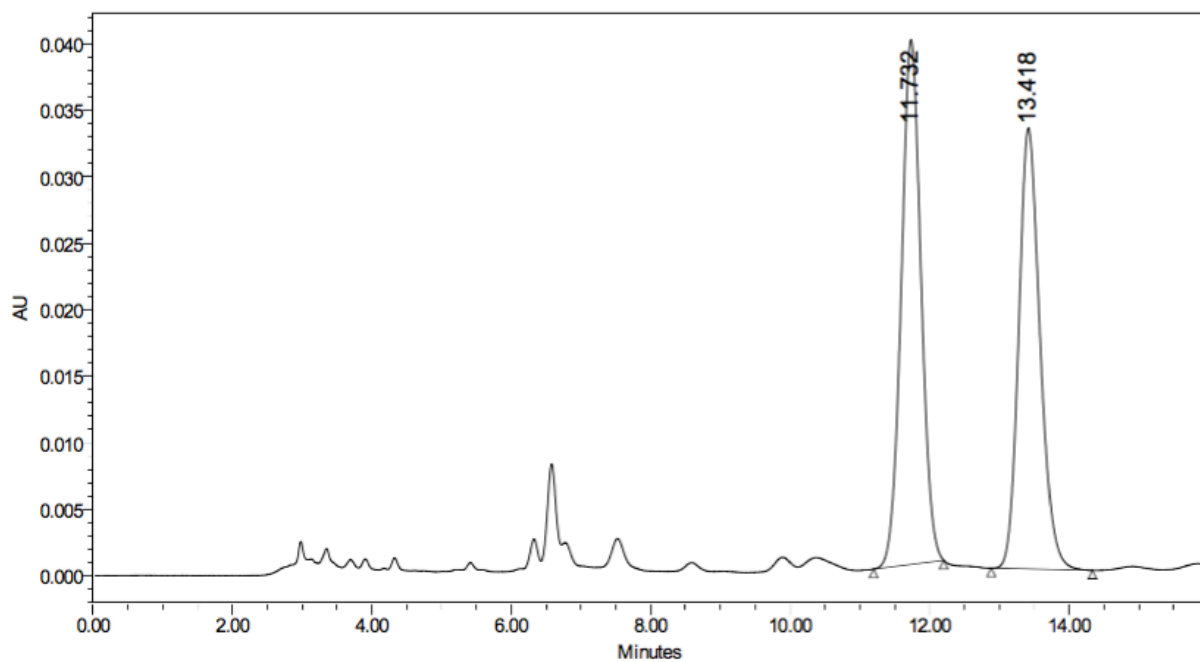


	RT (min)	Peak Type	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	22.913	Unknown	1406827	50.17	38148	61.80	bb	1557	22.141	24.736
2	36.271	Unknown	1397525	49.83	23580	38.20	bb	1714	35.249	38.106

HPLC chromatograms of 3ab and 3ab-rac

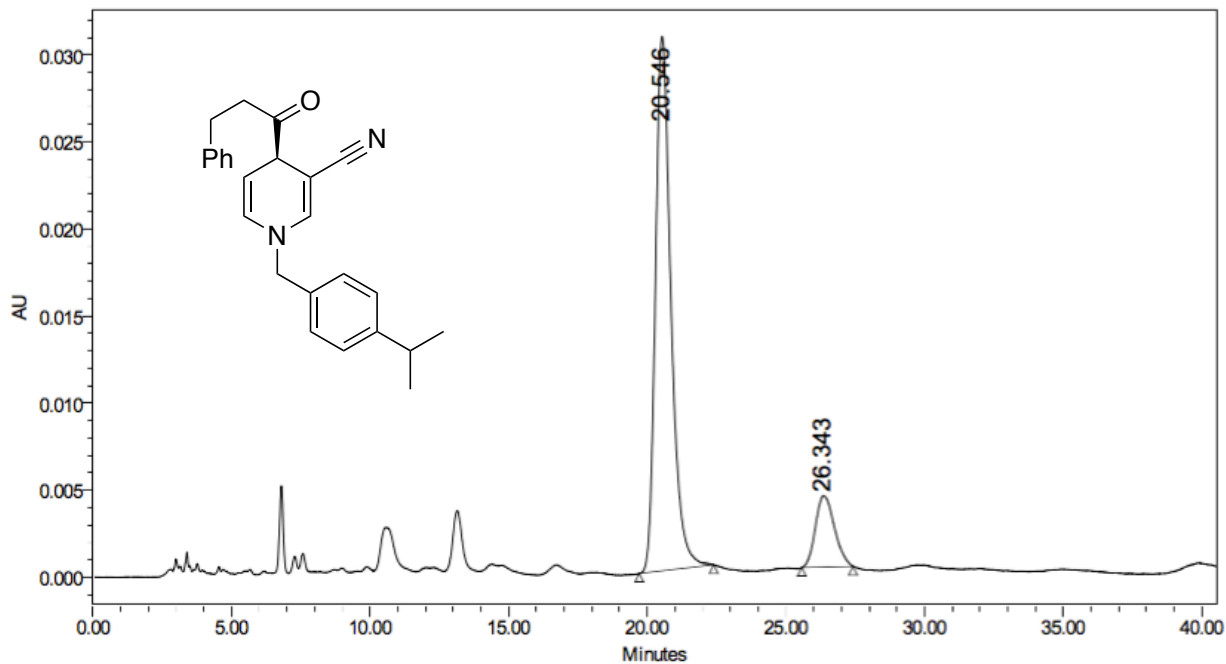


	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	13.335	373174	84.14	15788	85.76
2	15.494	70331	15.86	2621	14.24

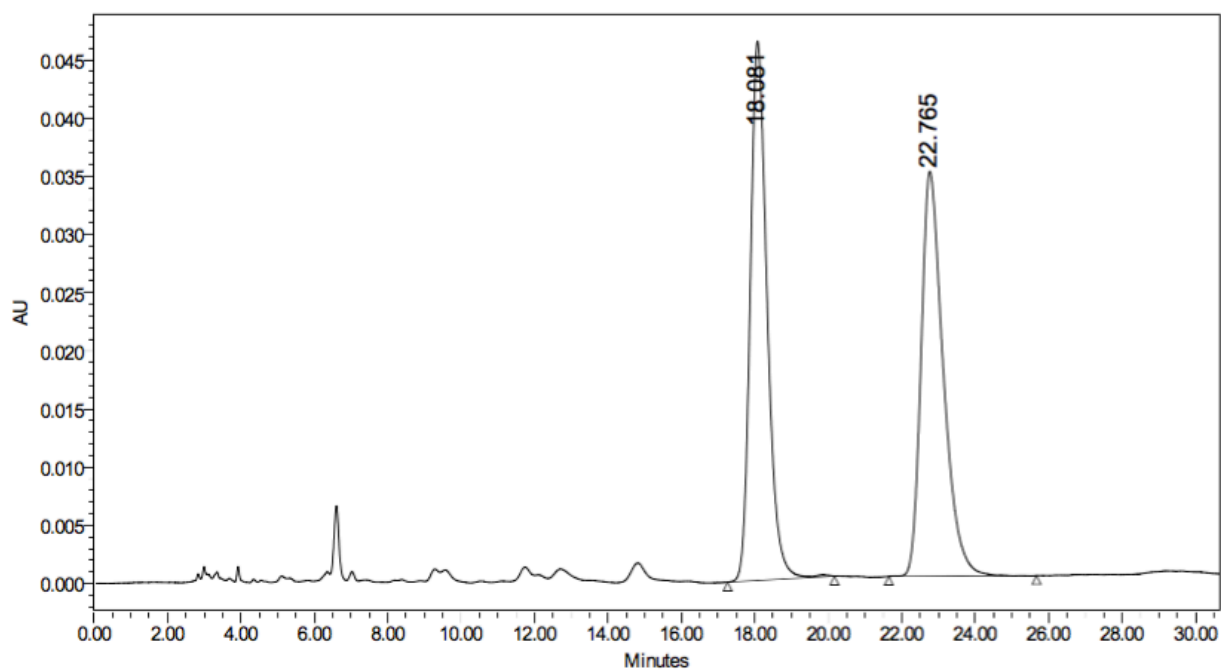


	RT (min)	Peak Type	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	11.732	Unknown	773782	52.43	39439	54.35	bb	602	11.197	12.200
2	13.418	Unknown	701966	47.57	33122	45.65	bb	868	12.884	14.331

HPLC chromatograms of 3eb and 3eb-rac

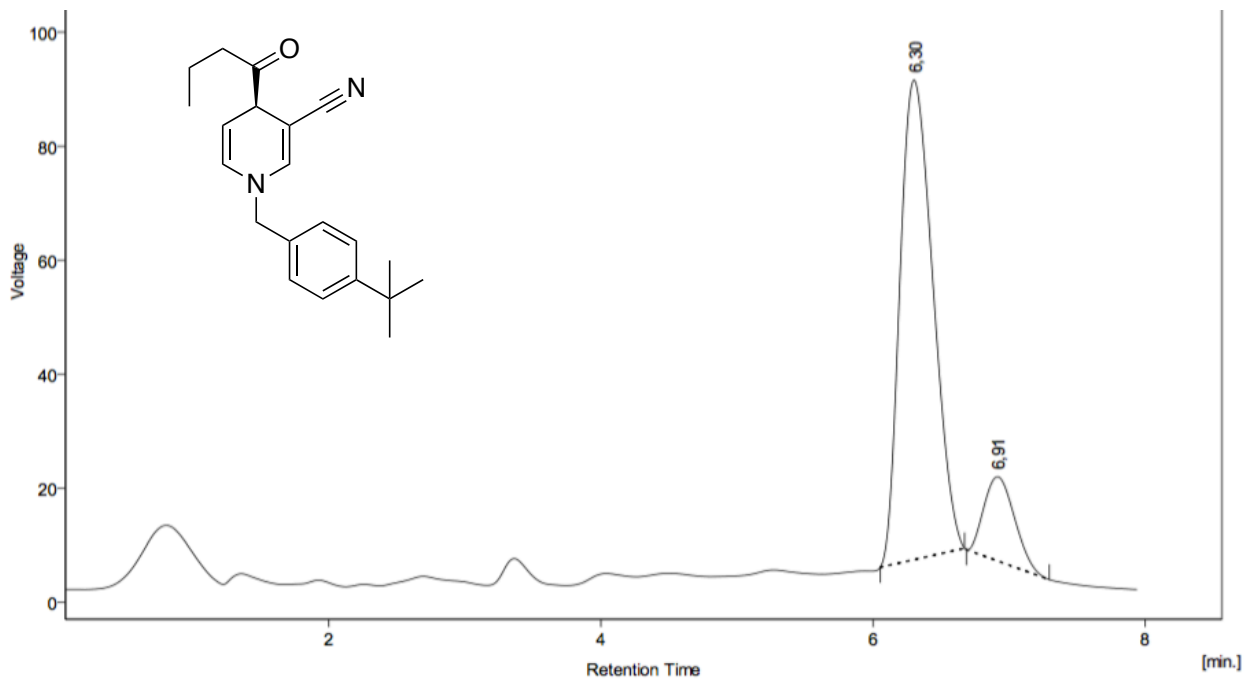


	RT (min)	Peak Type	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	20.546	Unknown	1190841	85.87	30670	88.19	bb	1613	19.715	22.404
2	26.343	Unknown	195895	14.13	4106	11.81	bb	1110	25.568	27.419

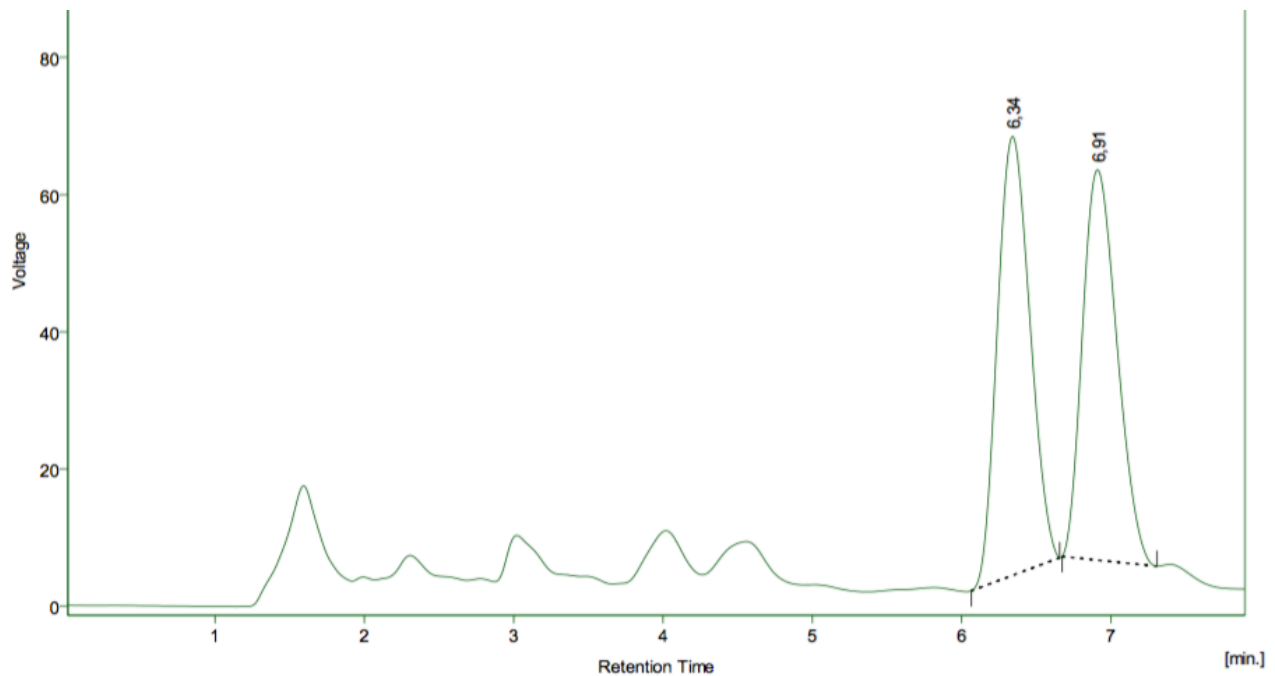


	RT (min)	Peak Type	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	18.081	Unknown	1475497	50.29	46315	57.10	bb	1738	17.267	20.164
2	22.765	Unknown	1458740	49.71	34793	42.90	bb	2416	21.647	25.675

HPLC chromatograms of 3ac and 3ac-rac

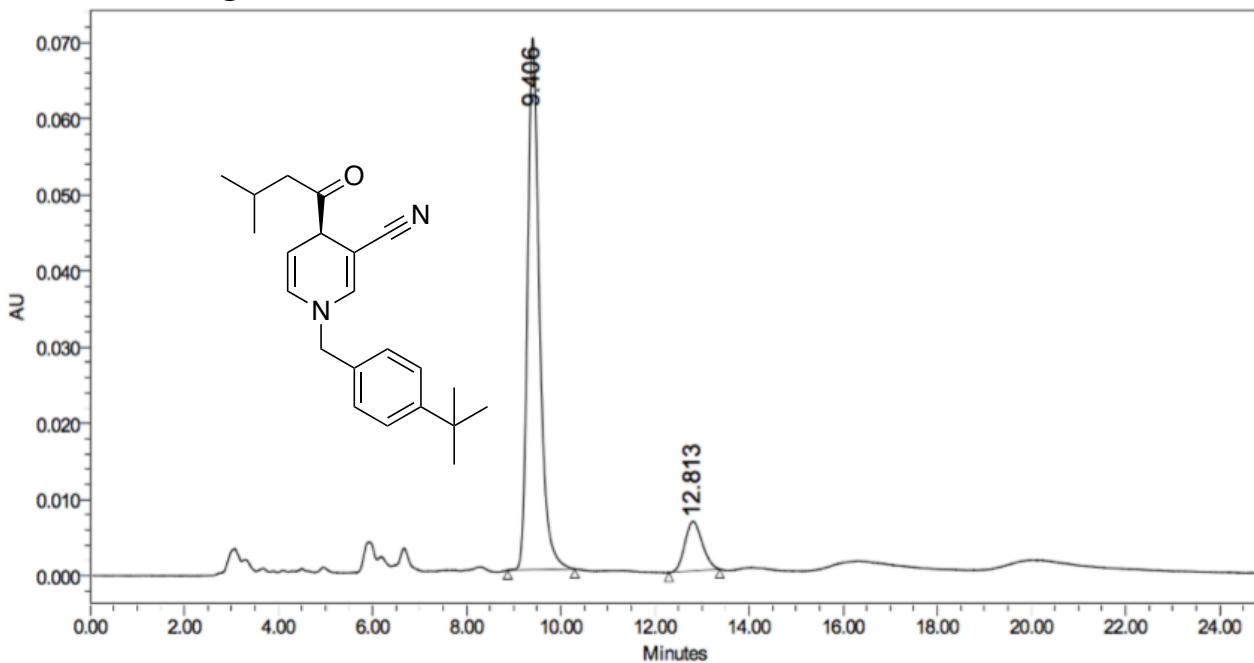


	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	6,303	1412,259	84,095	85,9	85,1	0,27
2	6,913	232,447	14,731	14,1	14,9	0,25
	Total	1644,706	98,825	100,0	100,0	

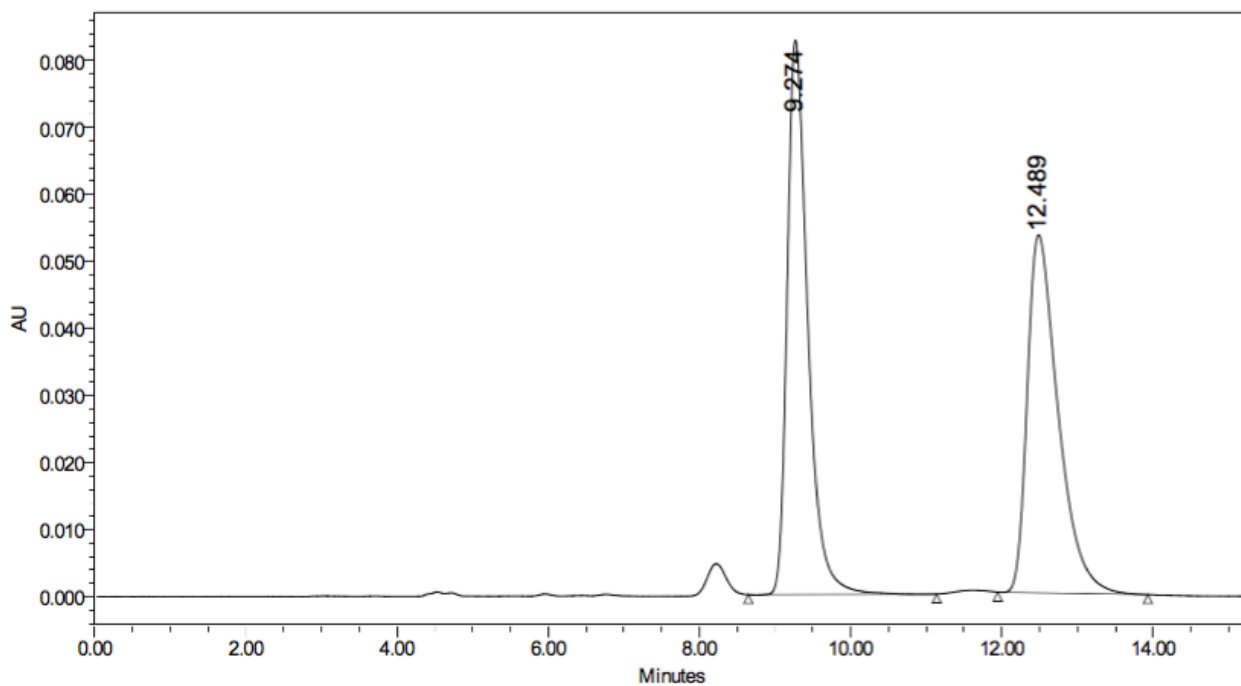


	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	6,340	967,557	64,013	51,5	52,9	0,25
2	6,910	912,741	56,936	48,5	47,1	0,26
	Total	1880,298	120,949	100,0	100,0	

HPLC chromatograms of 3fc and 3fc-rac

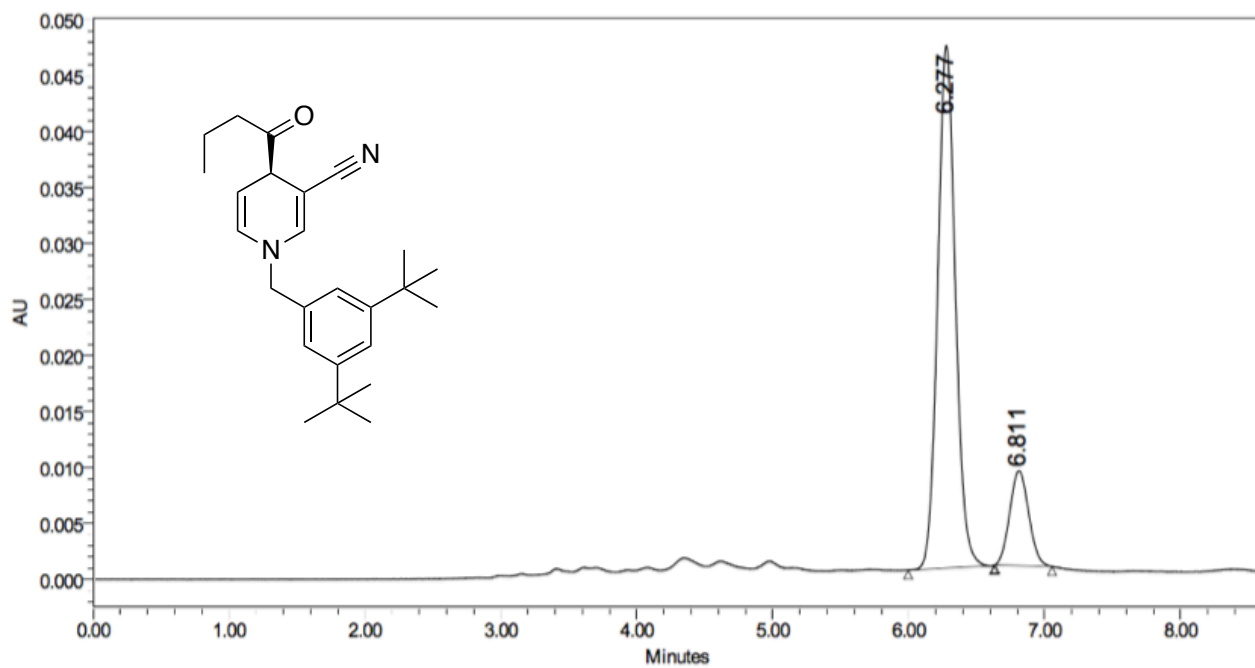


	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	9.406	1226470	87.98	69893	91.46
2	12.813	167633	12.02	6526	8.54

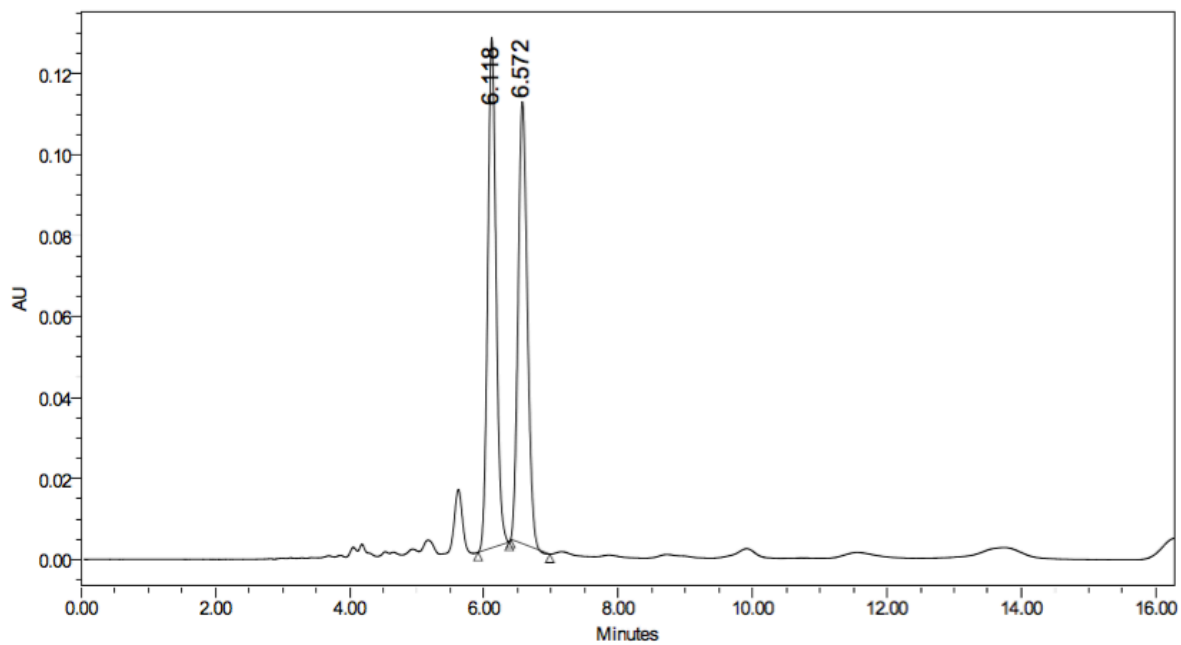


	RT (min)	Peak Type	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	9.274	Unknown	1561698	50.81	82681	60.77	bb	1493	8.651	11.140
2	12.489	Unknown	1512011	49.19	53373	39.23	bb	1189	11.947	13.929

HPLC chromatograms of 3ad and 3ad-rac

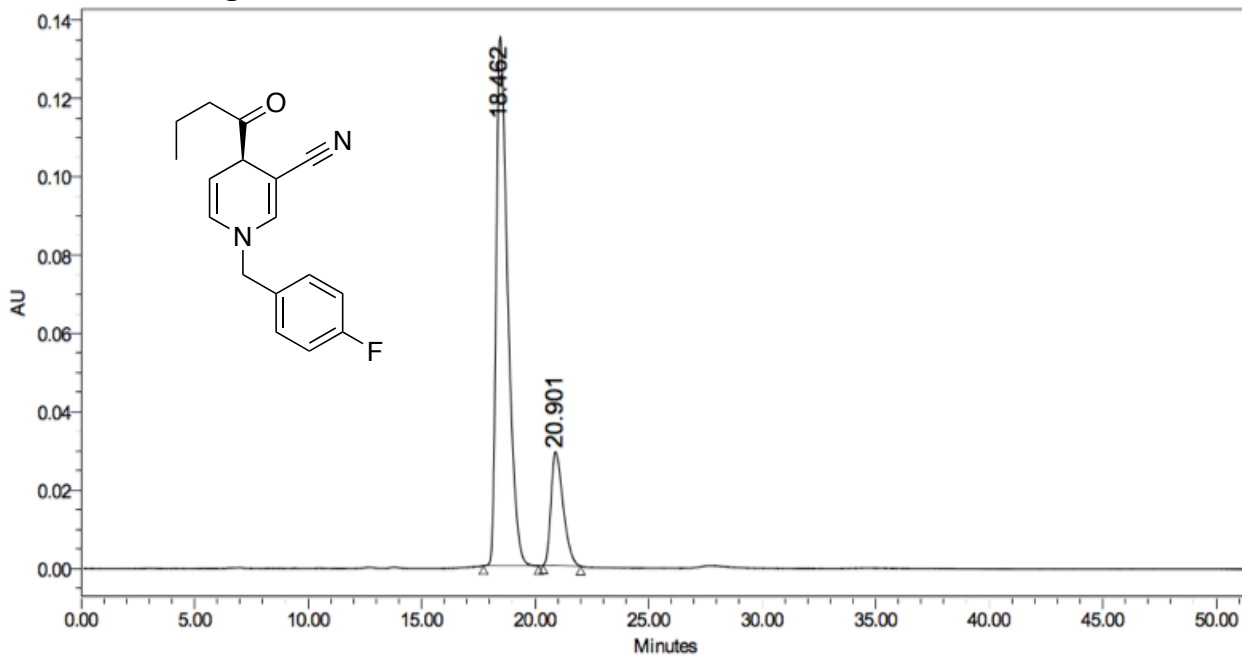


	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	6.277	423042	83.75	46741	84.67
2	6.811	82077	16.25	8465	15.33

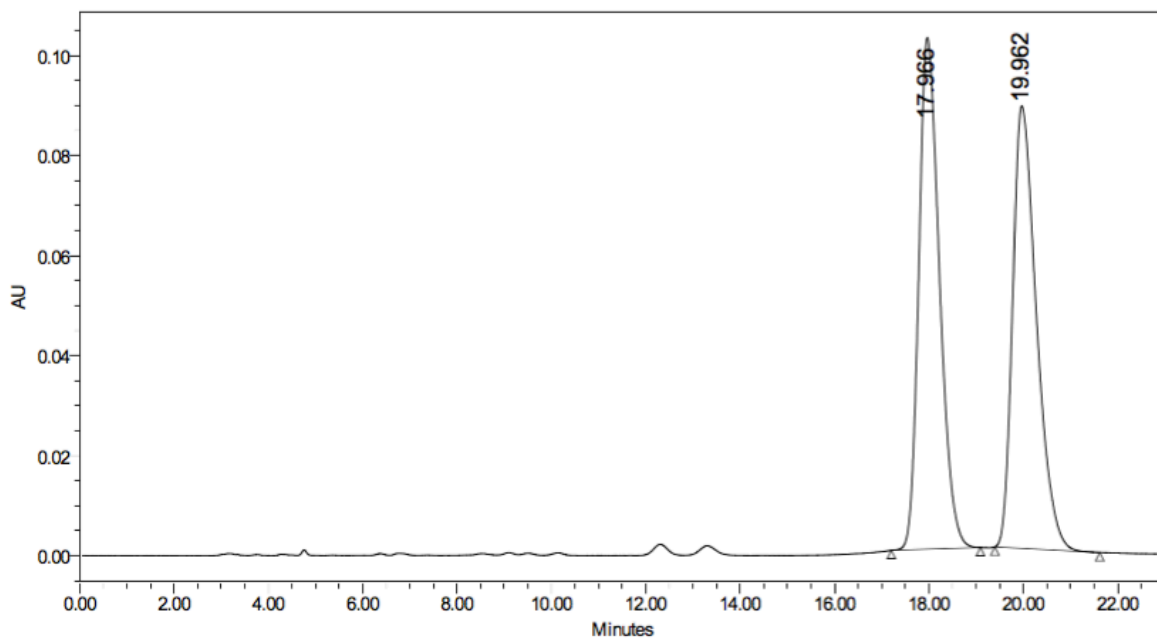


	RT (min)	Peak Type	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	6.118	Unknown	1086600	51.04	126093	53.60	bb	279	5.915	6.380
2	6.572	Unknown	1042244	48.96	109176	46.40	bb	348	6.401	6.981

HPLC chromatograms of 3ae and 3ae-rac

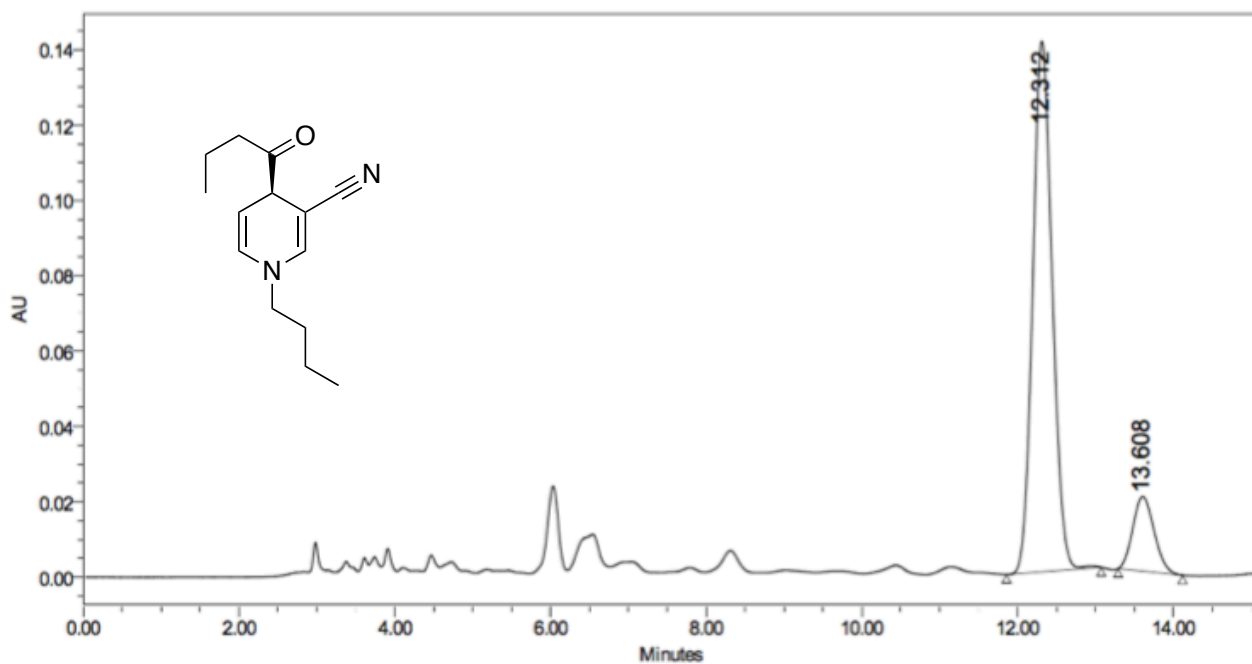


	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	18.462	4740840	81.50	135118	82.33
2	20.901	1076180	18.50	29007	17.67

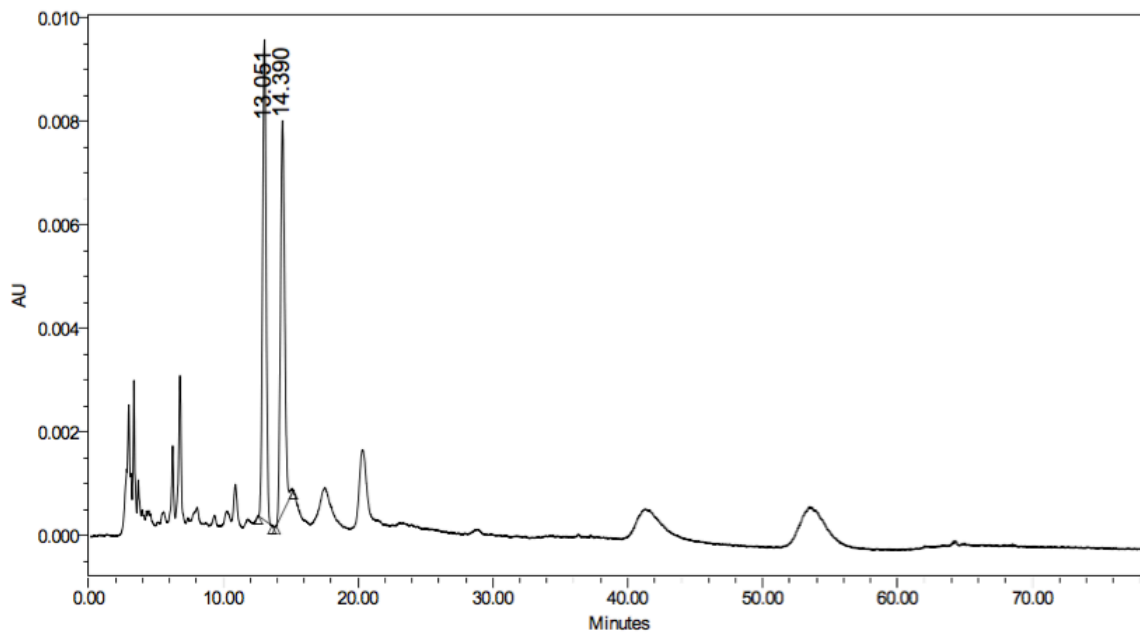


	RT (min)	Peak Type	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	17.966	Unknown	3112468	50.38	102280	53.63	bb	1134	17.203	19.094
2	19.962	Unknown	3065309	49.62	88425	46.37	bb	1331	19.399	21.617

HPLC chromatograms of 3af and 3af-rac

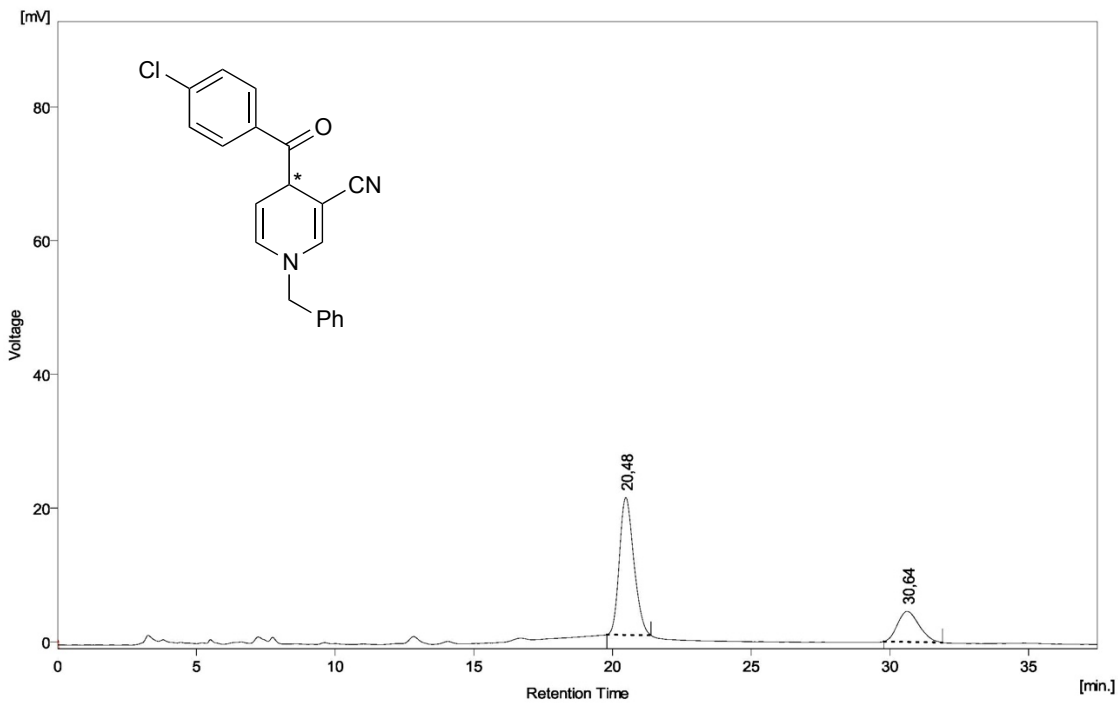


	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	12.312	2431310	86.61	140821	87.68
2	13.608	375894	13.39	19778	12.32

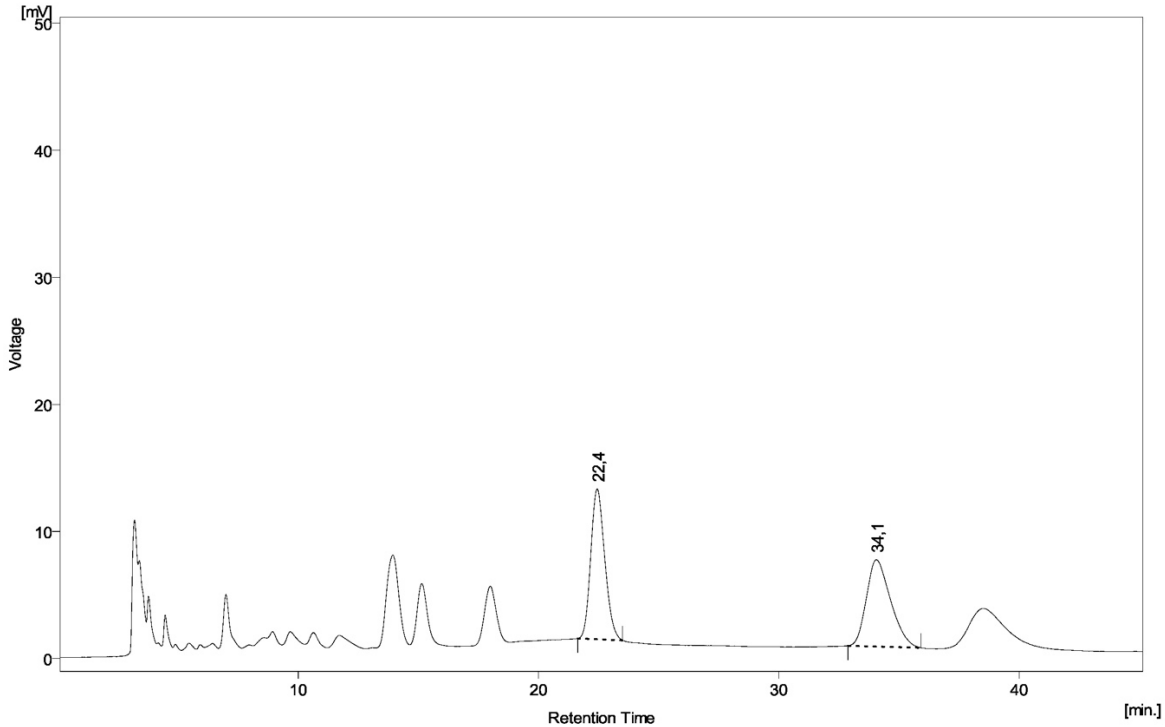


	RT (min)	Peak Type	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height	Integration Type	Points Across Peak	Start Time (min)	End Time (min)
1	13.051	Unknown	170134	50.94	9274	55.04	bb	610	12.611	13.627
2	14.390	Unknown	163851	49.06	7577	44.96	bb	761	13.929	15.198

HPLC chromatograms of 7a and 7a-rac

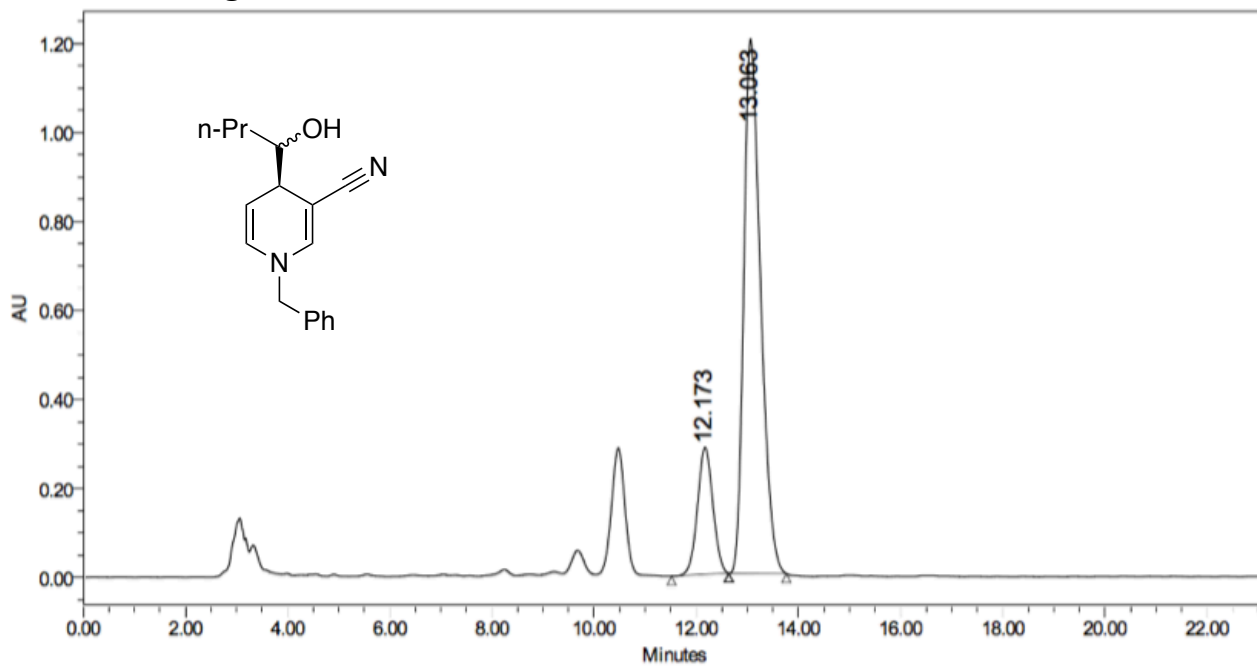


	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	20,483	746,371	20,550	75,1	81,8	0,56
2	30,637	247,832	4,584	24,9	18,2	0,85
Total		994,203	25,134	100,0	100,0	

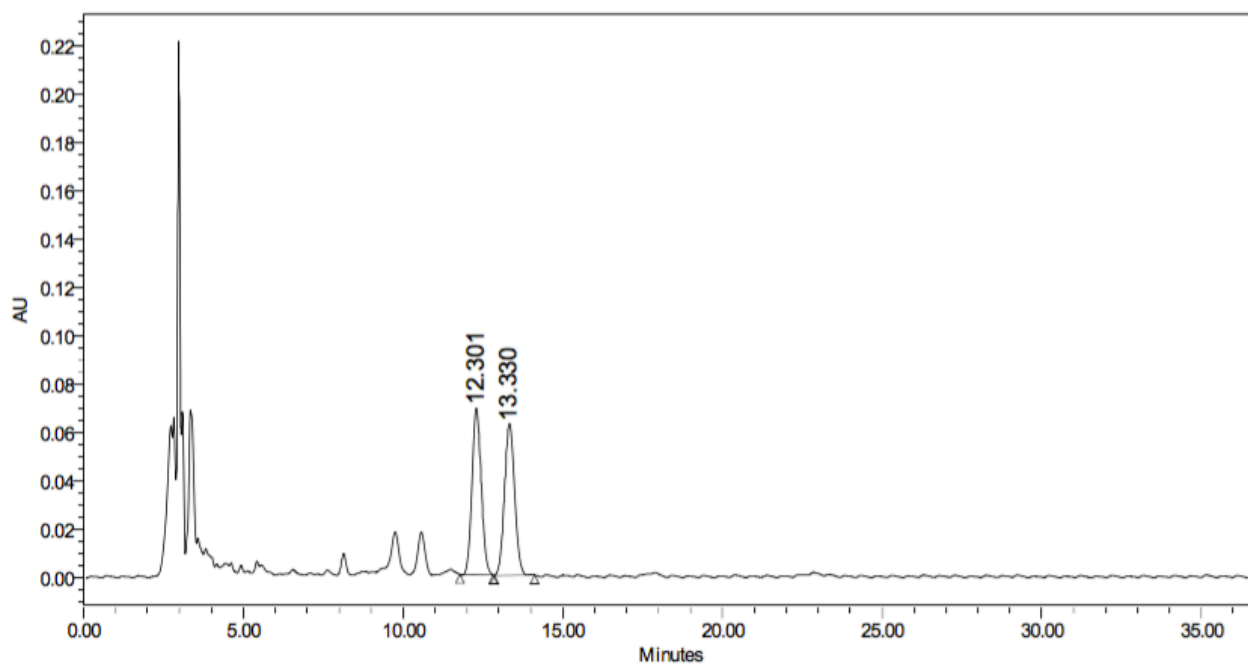


	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	22,443	479,923	11,832	50,1	63,4	0,63
2	34,057	477,110	6,831	49,9	36,6	1,09
Total		957,033	18,662	100,0	100,0	

HPLC chromatograms of 11aa and 11aa-rac

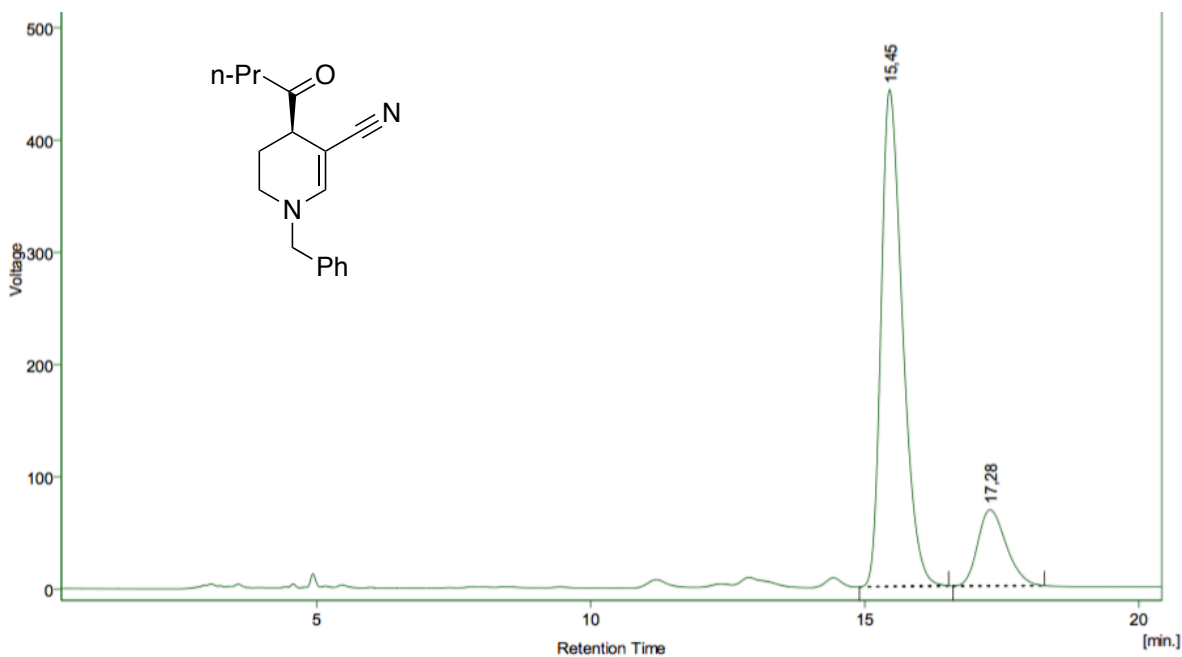


	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	12.173	5976959	17.92	285907	19.22
2	13.063	27382063	82.08	1201872	80.78

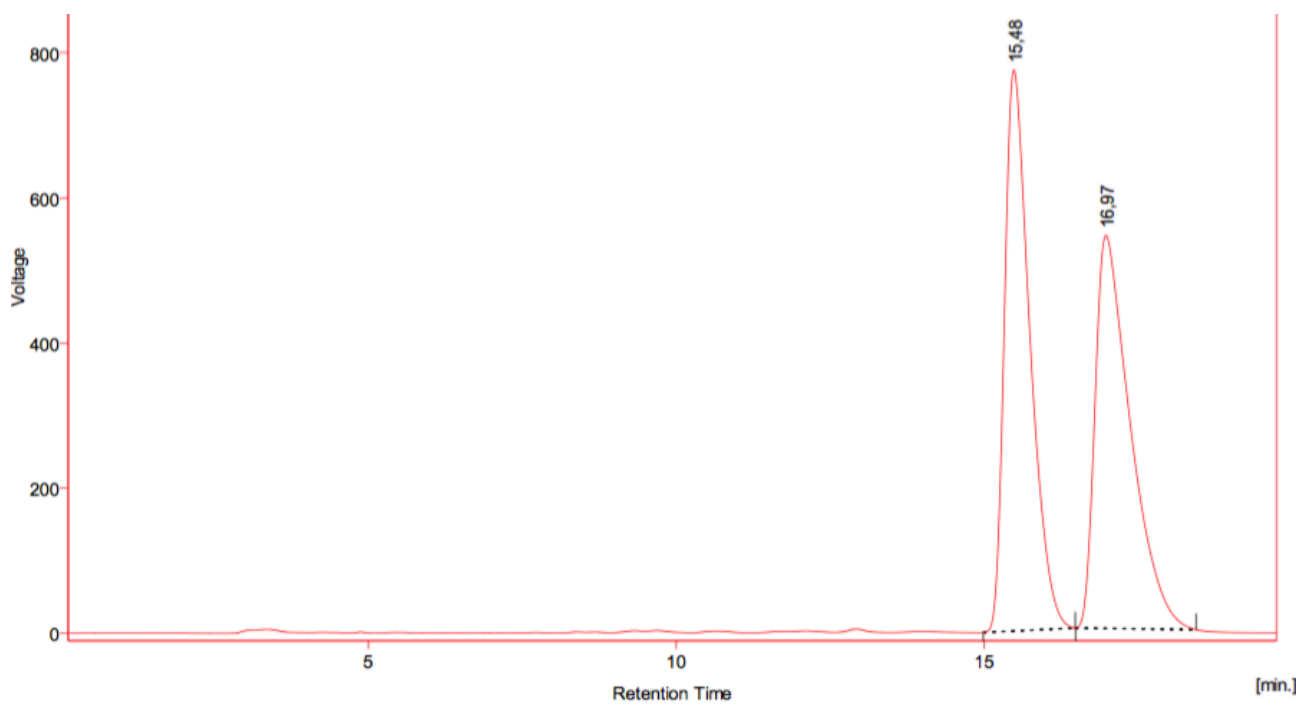


	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	12.301	1376232	50.02	68877	52.35
2	13.330	1375135	49.98	62682	47.65

HPLC chromatograms of 12aa and 12aa-rac



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	15,453	12014,676	442,385	83,0	86,7	0,42
2	17,283	2452,403	67,652	17,0	13,3	0,56
	Total	14467,079	510,037	100,0	100,0	



	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	15,480	22224,835	772,707	50,7	58,8	0,44
2	16,973	21607,268	541,711	49,3	41,2	0,61
	Total	43832,104	1314,418	100,0	100,0	

Absolute configuration of compounds **3ba** and **3af**

All the attempts to obtain good enantiopure crystals of the prepared compounds were not successful. For this reason, the absolute configuration was determined by a combination of conformational analysis and theoretical simulations of chiro-optical spectra. Compounds **3ba** and **3af** were selected as representative compounds.

Conformational analysis.

A full conformational search was performed on a model of **3ba** (**model-3ba**), where the ethyl group was substituted by a methyl, using molecular mechanics (MMFF force field). The best structures enclosed in a 5 kcal/mol energy range were further optimized at the B3LYP/6-31G(d) DFT level of theory. After DFT optimization only four conformations were found in a 2.0 kcal/mol range. Frequency analysis was performed to check whether they corresponded to energy minima (no imaginary frequencies were observed). The four conformations (see Figure S1) are different because of the disposition of the COMe and benzyl moieties. The preferred conformation of the benzyl group is almost perpendicular to the dihydropyridine ring, and the phenyl can be on the same side of the COMe, or on the opposite side. On the other side, the oxygen of the carbonyl group can be oriented outside the ring or inside the ring. The combination of these degrees of freedom justify the four conformations found by conformational search.

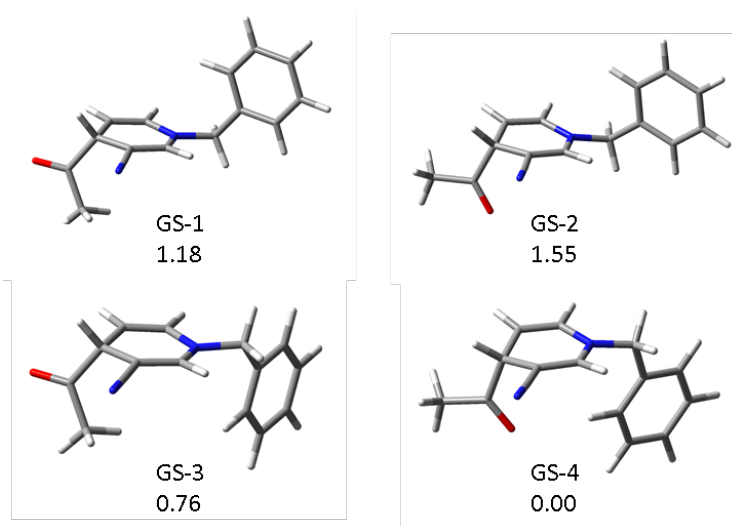


Figure S1. The four most stable conformations of the model of **model-3ba**, optimized with DFT at the B3LYP/6-31g(d) level. The reported relative energies (in kcal/mol) are ZPE-corrected enthalpies.

In the case of compound **3af**, the conformational search was performed on a model where the propyl and N-butyl groups were replaced by two methyls (**model-3af**), to reduce the conformational freedom

of the molecule. This substitution will not invalidate the chiro-optical simulations (see below) because the aliphatic chains are not UV-chromophores. As conceivable, the removal of the phenyl group reduces the number of conformations to the two due to the rotation on the COMe moiety (Figure S2)

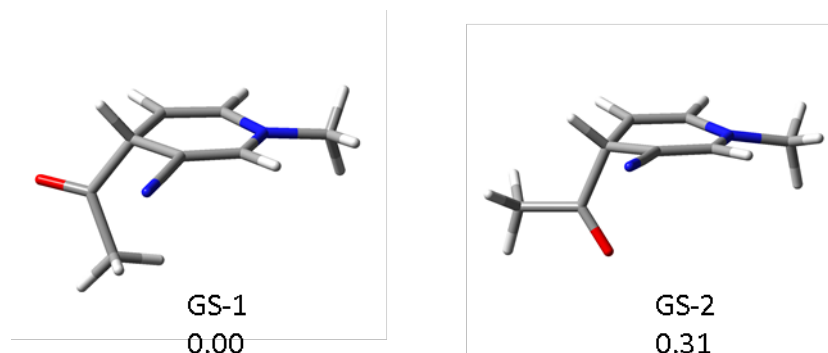


Figure S2. The two most stable conformations of the model of **model-3af**, optimized with DFT at the B3LYP/6-31g(d) level. The reported relative energies (in kcal/mol) are ZPE-corrected enthalpies.

Absolute configuration

The determination of the absolute configuration (AC) of chiral molecules using chiro-optical techniques such as circular dichroism (Electronic CD and Vibrational CD) has become very reliability because of the development of theoretical methods for the prediction of these properties based on DFT (for VCD) and on Time-Dependent DFT (for ECD).¹ In the present case the theoretical calculation of the electronic circular dichroism spectra (ECD) was selected for the absolute configuration assignment. The ECD spectra of compounds **3ba** and **3af** were acquired in HPLC-grade acetonitrile solution (about $1 \cdot 10^{-4}$ M) with a cell path of 0.2 cm in the 190-400 nm region by the sum of 32 scans at 50 nm/min scan rate (Figure S3). The two spectra are very similar, with two negative bands between 375 and 275 nm, a positive one at 250 and a negative at 215 nm. The similarity within the two spectra suggests that the phenyl group is not responsible for any CD band, probably because of conformational averaging.

¹ For reviews see: a) G. Bringmann, T. Bruhn, K. Maksimenka, Y. Hemberger, *Eur. J. Org. Chem.* **2009**, 2717-2727. b) T. D. Crawford, M. C. Tam, M. L. Abrams, *J. Chem. Phys. A* **2007**, *111*, 12057–12068. c) G. Pescitelli, L. Di Bari, N. Berova, *Chem. Soc. Rev.* **2011**, *40*, 4603-4625. For a review on conformational analysis for the absolute configuration determination, see: A. Mazzanti, D. Casarini, *D. WIRES Comput. Mol. Sci.* **2012**, *2*, 613-641

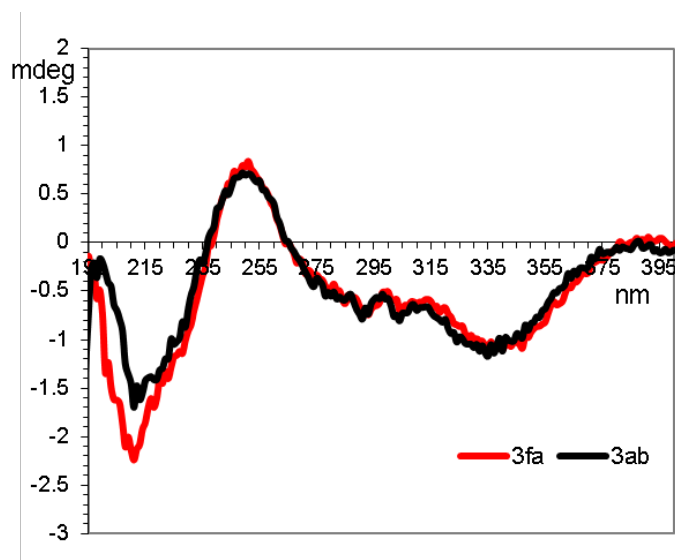


Figure S3. ECD spectrum of the two compounds **3ba** and **3af** in acetonitrile.

The TD-DFT simulations of the ECD spectra were performed using the geometries of the four conformations of **model-3ba** and of the two conformations of the **model-3af**. For data redundancy, calculations were performed with the hybrid functionals BH&HLYP² and M06-2X,³ with ω B97XD that includes empirical dispersion,⁴ and with CAM-B3LYP⁵ that includes long range correction using the Coulomb Attenuating Method. The calculations employed the 6-311++G(2d,p), that is known to yield good performances at a reasonable computational cost.⁶ The rotational strengths were calculated in both length and velocity representation, obtaining similar results (RMS difference < 5%) that ruled out large basis set incompleteness errors (BSSE).⁷

In the case of the **model-3ba** the TD-DFT calculations were run on the *R* absolute configuration and the results are shown in Figure S4. The simulations obtained for the four conformation are rather similar in the low-energy region (from 400 to 230 nm) while they are substantially different below 215 nm. This is probably due to the different conformation of the phenyl group, that is *anti* to the COMe in GS1 and GS2, and *syn* in GS3 and GS4. In this region of the spectrum a large variation of the conformational ratio can therefore produce opposite CD sign of the resulting averaged spectrum.

² In Gaussian 09 the BH&HLYP functional has the form: $0.5 * E_X^{HF} + 0.5 * E_X^{LSDA} + 0.5 * \Delta E_X^{Becke88} + E_C^{LYP}$

³ Y. Zhao and D.G. Truhlar, *Theor. Chem. Acc.* 2008, **120**, 215-241.

⁴ J.-D. Chai and M. Head-Gordon, *Phys. Chem. Chem. Phys.*, 2008, **10**, 6615-6620.

⁵ T. Yanai, D. Tewand, and N.Handy, *Chem. Phys. Lett.* 2004, **393**, 51-57.

⁶ a) M. Meazza, M. E. Light, A. Mazzanti and R. Rios. *Chem. Sci.* **2016**, *7*, 984; b) P. Gunasekaran, S. Perumal, J. Carlos Menéndez, M. Mancinelli, S. Ranieri, A. Mazzanti, *J. Org. Chem.* **2014**, *79*, 11039–11050. c) L. Caruana, M. Fochi, M. Comes Franchini, S. Ranieri, A. Mazzanti, L. Bernardi, *Chem. Commun.* **2014**, *50*, 445-447. d) M. Ambrogio, A. Cioqli, M. Mancinelli, S. Ranieri, A. Mazzanti, *J. Org. Chem.* **2013**, *78*, 3709-3719. e) L. Caruana, M. Fochi, S. Ranieri, A. Mazzanti, L. Bernardi, *Chem. Commun.* **2013**, *49*, 880-882.

⁷ P.J. Stephens, D.M. McCann, F.J. Devlin, J.R. Cheeseman and M.J. Frisch, *J. Am. Chem. Soc.* 2004, **126**, 7514-7521

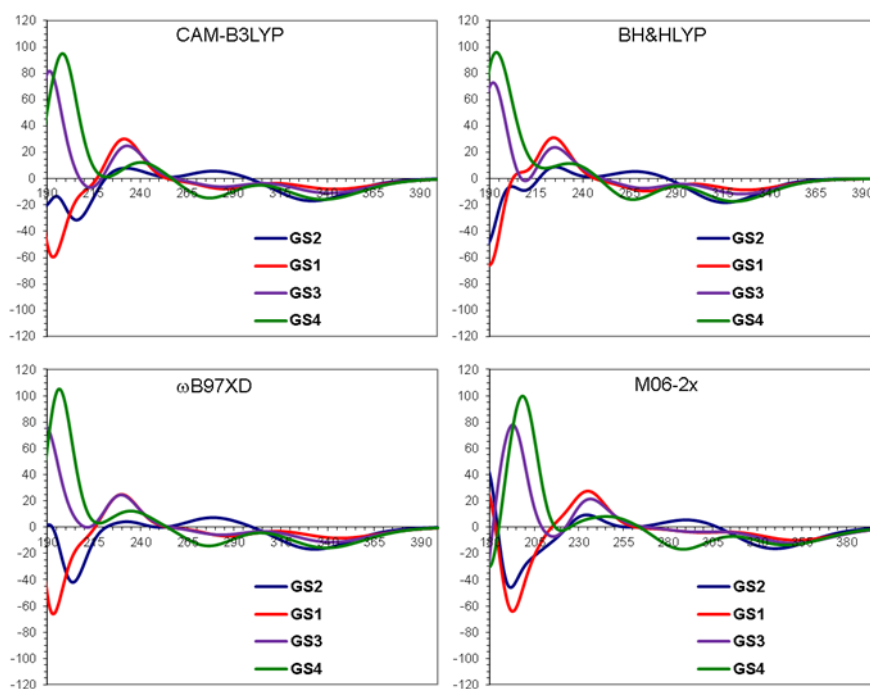


Figure S4. TD-DFT simulated spectra calculated for the four conformations of **model-3ba** assuming the *R* absolute configuration and using CAM-B3LYP, BH&HLYP, M06-2X, ω B97XD and the 6-311++G(2d,p) basis set. Each spectrum was obtained using a 0.25 eV line width at half height and using the first 50 calculated excited states.

However, the lowest energy band at about 335 nm is simulated as negative in all the simulated spectra. A close investigation of the molecular orbitals (MO) involved in this transition revealed that it is mainly due to the HOMO-LUMO transition (>95%), and the two MO are mainly localized on the dihydropyridine system (Figure S5). For this reason, the corresponding transition is not sensitive to the conformation of the benzyl moiety.

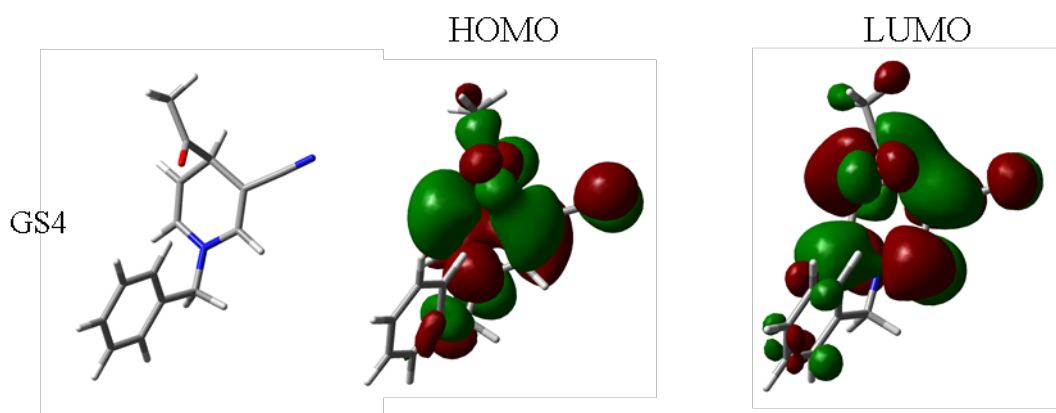


Figure S5. HOMO and LUMO Molecular orbitals calculated for the GS4 conformation of **model-3ba** at the CAM-B3LYP/6-311++g(2d,p) level of theory.

The conformationally weighted spectra were obtained by using the populations obtained from Boltzmann distribution and the relative enthalpies obtained from the DFT-optimization (9:5:19:67 ratio).

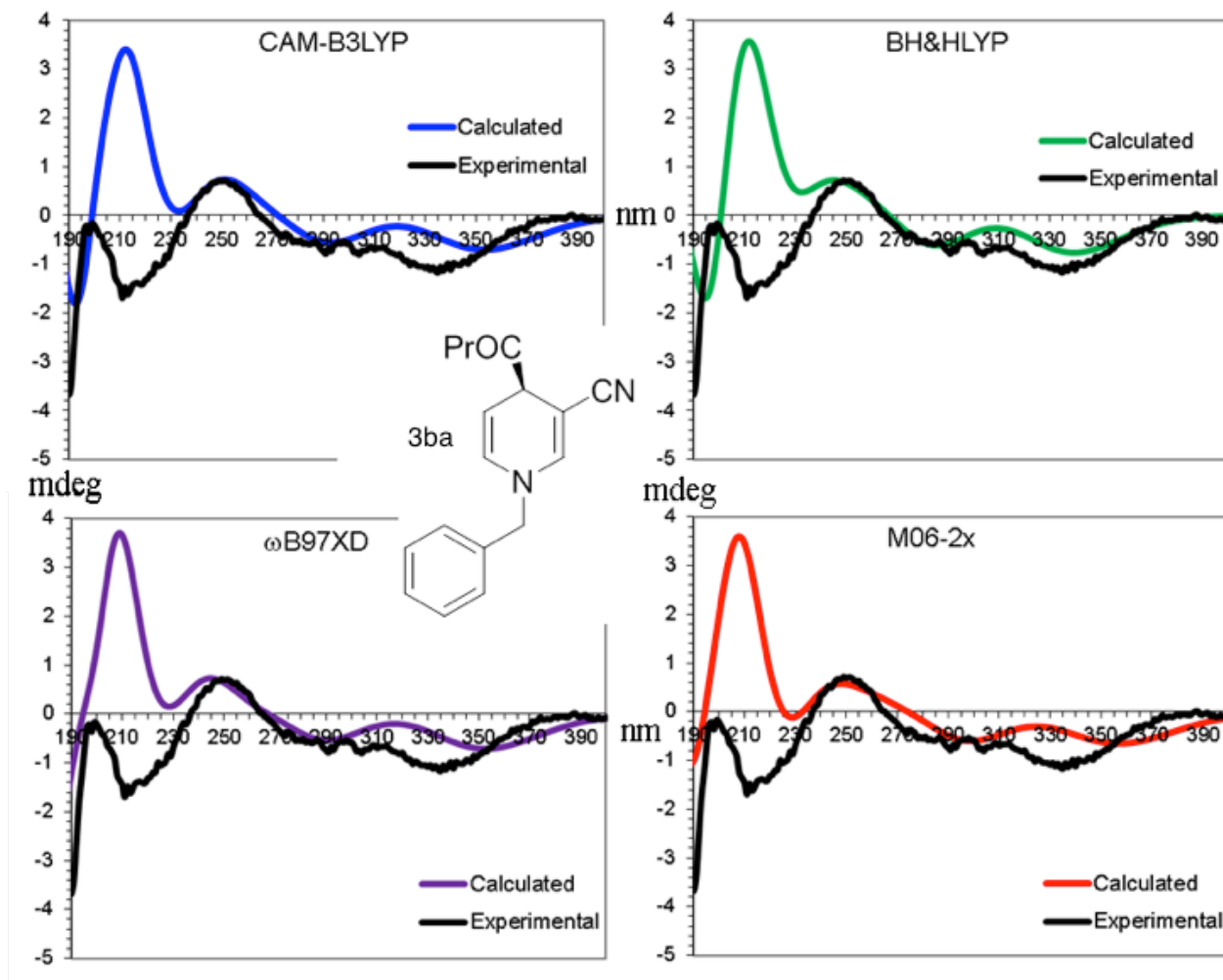


Figure S6. Simulations of the experimental ECD spectrum of **3ba**. For each quadrant, the black line corresponds to the experimental spectrum. The colored lines correspond to the simulations obtained on **model-3ba** (CO-Me instead of CO-Pr) using the populations derived from B3LYP/6-31G(d) optimization and the spectra shown in Figure S4.

The simulated spectra were vertically scaled and red-shifted to get the best match with the experimental spectrum (Figure S6. scaling factors: 0.05, 0.05, 0.05, 0.05; red shift: 15, 13, 10, 18 nm for CAM-B3LYP, ω B97XD, M06-2X and BH&HLYP, respectively). The red-shift was calibrated to match the positive band at 250 nm (Figure S6). In all the cases the simulated spectra for the *R* absolute configuration match very well the experimental spectrum in the low energy region. On the other hand, the high energy branch of the ECD spectrum does not match the experimental one. This part of the simulated spectra corresponds to the phenyl transition and is therefore very sensitive to the orientation

of the phenyl with respect the plane of the dihydropyridine and with respect to the cyano group. However, the experimental outcome derived from Figure S3 is that the phenyl ring does not contribute to the ECD spectrum, so this mismatch in the simulations could be ignored.

To overcome this problem the same theoretical approach was used in the case of **model-3af**, where only two conformations have to be considered and the phenyl ring is not present. Figure S7 shows the simulations obtained with the four theoretical models.

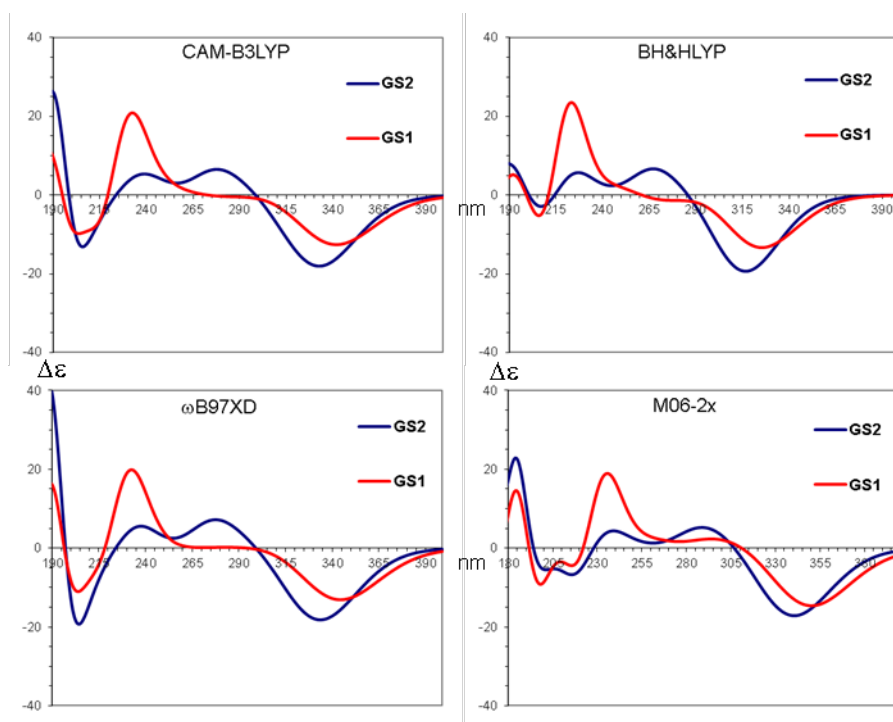


Figure S7. TD-DFT simulated spectra calculated for the four conformations of **model-3ba** assuming the *R* absolute configuration and using CAM-B3LYP, BH&HLYP, M06-2X, ω B97XD and the 6-311++G(2d,p) basis set. Each spectrum was obtained using a 0.25 eV line width at half height and using the first 50 calculated excited states.

As for the previous case, simulations were run on the *R* enantiomer, and the averaged spectra to be compared with the experimental one were obtained using the conformational ratio suggested by calculations (63:37, as from Figure S2). All the four simulations (Figure S8; scaling factors: 0.07, 0.08, 0.08, 0.07; red shift: 10, 12, 10, 18 nm for CAM-B3LYP, ω B97XD, M06-2X and BH&HLYP, respectively). match well the experimental spectrum, particularly in the case of the ω B97XD and CAM-B3LYP theoretical models.

Taken together, the TD-DFT simulations for the two compounds agree in the assignment of the *R* absolute configuration.

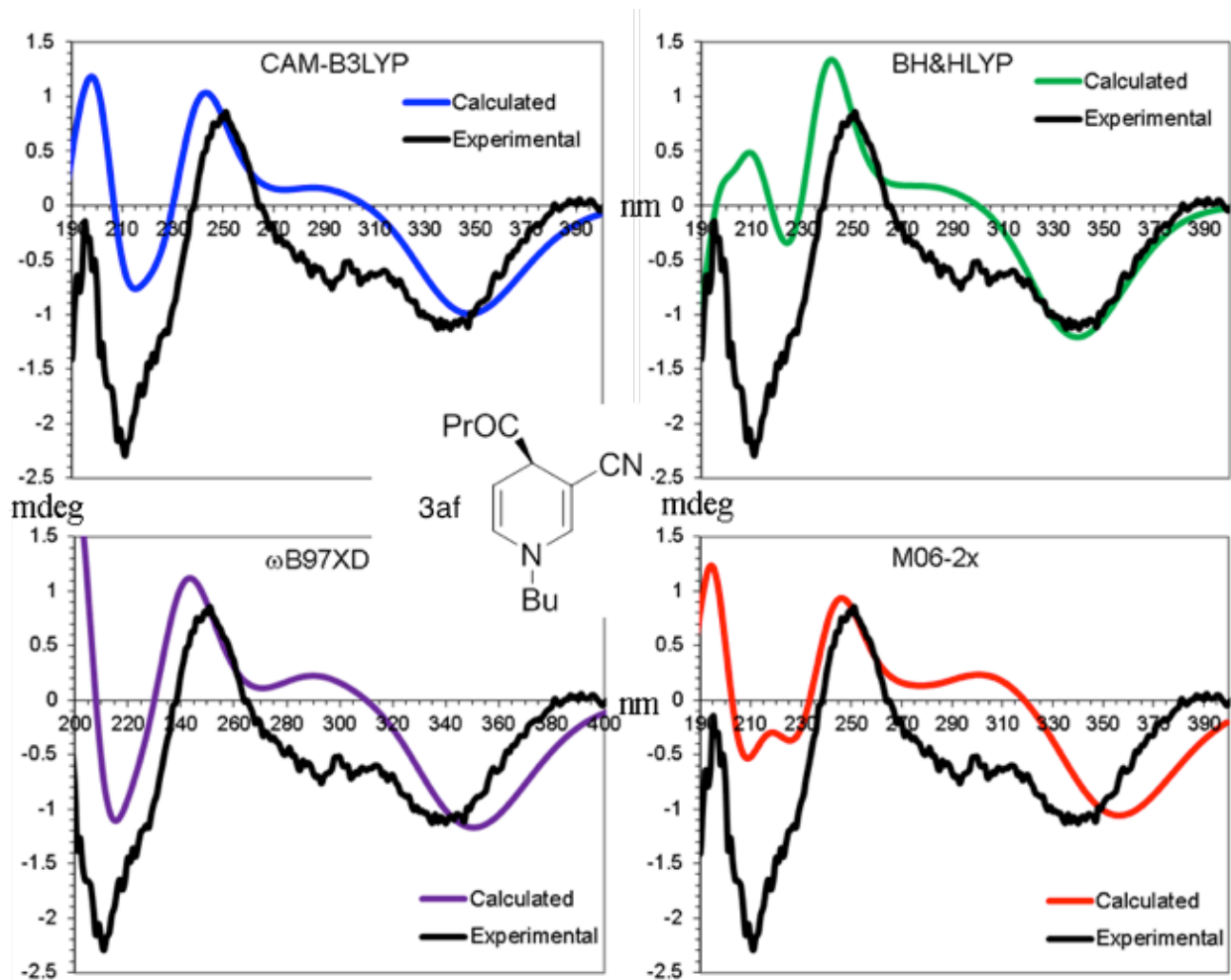


Figure S8. Simulations of the experimental ECD spectrum of **3af**. For each quadrant, the black line corresponds to the experimental spectrum. The colored lines correspond to the simulations obtained on **model-3af** (CO-Me instead of CO-Pr and N-Me instead of N-Bu) using the populations derived from B3LYP/6-31G(d) optimization and the spectra shown in Figure S7.

Model-3ba-conformation GS1

Calculation Type = FREQ
Calculation Method = RB3LYP
Basis Set = 6-31G(d)
Charge = 0
Spin = Singlet
Solvation = None
E(RB3LYP) = -764.70637 Hartree
RMS Gradient Norm = 6.078e-06 Hartree/Bohr
Imaginary Freq = 0
Dipole Moment = 7.6520523 Debye
Polarizability (?) = 164.50833 a.u.
Point Group = C1
Job cpu time: 0 days 17 hours 17 minutes 9.2 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0
Temperature = 298.15 Kelvin
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -764.70637 Hartree
Zero-point Energy Correction = 0.257194 Hartree
Thermal Correction to Energy = 0.273624 Hartree
Thermal Correction to Enthalpy = 0.274569 Hartree
Thermal Correction to Free Energy = 0.208453 Hartree
EE + Zero-point Energy = -764.44917 Hartree
EE + Thermal Energy Correction = -764.43274 Hartree
EE + Thermal Enthalpy Correction = -764.4318 Hartree
EE + Thermal Free Energy Correction = -764.49791 Hartree
E (Thermal) = 171.702 kcal/mol
Heat Capacity (Cv) = 61.217 cal/mol-kelvin
Entropy (S) = 139.152 cal/mol-kelvin

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	7	0	0.126058	-0.800351	0.497045
2	6	0	-0.323612	0.490455	0.401386
3	6	0	-1.501407	0.831678	-0.186690
4	6	0	-2.457832	-0.199726	-0.777653
5	6	0	-1.798367	-1.565616	-0.731868
6	6	0	-0.632984	-1.804450	-0.115966
7	6	0	1.400709	-1.093086	1.157516
8	6	0	2.616280	-0.485725	0.477194
9	6	0	3.584723	0.176590	1.238458
10	6	0	4.727094	0.705284	0.633399
11	6	0	4.906734	0.581861	-0.743976
12	6	0	3.940299	-0.072165	-1.513050
13	6	0	2.803251	-0.603236	-0.906753
14	6	0	-3.840393	-0.317468	-0.075323
15	8	0	-4.779211	-0.760089	-0.706800
16	6	0	-3.947720	0.062497	1.386796
17	6	0	-1.852622	2.208842	-0.261050
18	7	0	-2.181265	3.326079	-0.328672
19	1	0	0.336258	1.247543	0.811407
20	1	0	-2.326138	-2.386669	-1.205044
21	1	0	-0.194355	-2.795806	-0.075019

22	1	0	1.488349	-2.184539	1.191906
23	1	0	1.354682	-0.753390	2.199973
24	1	0	3.445989	0.279988	2.312674
25	1	0	5.469431	1.219379	1.237734
26	1	0	5.791475	0.997028	-1.218598
27	1	0	4.072368	-0.167098	-2.587387
28	1	0	2.051470	-1.103190	-1.512362
29	1	0	-3.152068	-0.411511	1.973004
30	1	0	-3.828872	1.146768	1.503300
31	1	0	-4.925998	-0.236897	1.767620
32	1	0	-2.707374	0.054601	-1.817929

Model-3ba-conformation GS2

Calculation Type = FREQ
 Calculation Method = RB3LYP
 Basis Set = 6-31G(d)
 Charge = 0
 Spin = Singlet
 Solvation = None
 E(RB3LYP) = -764.70571 Hartree
 RMS Gradient Norm = 4.519e-06 Hartree/Bohr
 Imaginary Freq = 0
 Dipole Moment = 6.7294701 Debye
 Polarizability (?) = 165.33367 a.u.
 Point Group = C1
 Job cpu time: 0 days 1 hours 46 minutes 16.2 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0
 Temperature = 298.15 Kelvin
 Pressure = 1 atm
 Frequencies scaled by = 1
 Electronic Energy (EE) = -764.70571 Hartree
 Zero-point Energy Correction = 0.257108 Hartree
 Thermal Correction to Energy = 0.273554 Hartree
 Thermal Correction to Enthalpy = 0.274499 Hartree
 Thermal Correction to Free Energy = 0.209203 Hartree
 EE + Zero-point Energy = -764.4486 Hartree
 EE + Thermal Energy Correction = -764.43215 Hartree
 EE + Thermal Enthalpy Correction = -764.43121 Hartree
 EE + Thermal Free Energy Correction = -764.4965 Hartree
 E (Thermal) = 171.658 kcal/mol
 Heat Capacity (Cv) = 61.245 cal/mol-kelvin
 Entropy (S) = 137.425 cal/mol-kelvin

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	7	0	0.097066	-0.885478	0.156859
2	6	0	-0.265105	0.438308	0.210667
3	6	0	-1.463338	0.894192	-0.233215
4	6	0	-2.565715	-0.047790	-0.696183

5	6	0	-1.961131	-1.411918	-0.970268
6	6	0	-0.756876	-1.770779	-0.500030
7	6	0	1.324237	-1.349898	0.812140
8	6	0	2.579917	-0.620503	0.368864
9	6	0	3.456999	-0.090782	1.320540
10	6	0	4.635165	0.547754	0.925851
11	6	0	4.942262	0.668297	-0.428880
12	6	0	4.067890	0.147429	-1.387121
13	6	0	2.895776	-0.493502	-0.990938
14	6	0	-3.676696	-0.196830	0.381541
15	8	0	-3.452462	0.034883	1.550589
16	6	0	-5.032073	-0.666033	-0.112830
17	6	0	-1.721237	2.293026	-0.239378
18	7	0	-1.969137	3.431938	-0.276629
19	1	0	0.490214	1.115755	0.592726
20	1	0	-2.536498	-2.135838	-1.537876
21	1	0	-0.351432	-2.765514	-0.654377
22	1	0	1.409148	-2.418448	0.585781
23	1	0	1.215202	-1.269009	1.901551
24	1	0	3.217680	-0.177514	2.378209
25	1	0	5.305422	0.956320	1.677092
26	1	0	5.854960	1.169313	-0.739419
27	1	0	4.300345	0.241742	-2.444387
28	1	0	2.215336	-0.890459	-1.740325
29	1	0	-5.675096	-0.910928	0.734794
30	1	0	-5.501011	0.133626	-0.701407
31	1	0	-4.937684	-1.536370	-0.773221
32	1	0	-3.042856	0.337221	-1.610039

Model-3ba-conformation GS3

Calculation Type = FREQ
 Calculation Method = RB3LYP
 Basis Set = 6-31G(d)
 Charge = 0
 Spin = Singlet
 Solvation = None
 E(RB3LYP) = -764.70708 Hartree
 RMS Gradient Norm = 2.937e-06 Hartree/Bohr
 Imaginary Freq = 0
 Dipole Moment = 8.0325913 Debye
 Polarizability (?) = 165.76067 a.u.
 Point Group = C1
 Job cpu time: 0 days 3 hours 20 minutes 32.6 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0
 Temperature = 298.15 Kelvin
 Pressure = 1 atm
 Frequencies scaled by = 1
 Electronic Energy (EE) = -764.70708 Hartree
 Zero-point Energy Correction = 0.257314 Hartree
 Thermal Correction to Energy = 0.273666 Hartree
 Thermal Correction to Enthalpy = 0.27461 Hartree
 Thermal Correction to Free Energy = 0.209706 Hartree
 EE + Zero-point Energy = -764.44977 Hartree
 EE + Thermal Energy Correction = -764.43342 Hartree

EE + Thermal Enthalpy Correction = -764.43247 Hartree
 EE + Thermal Free Energy Correction = -764.49738 Hartree
 E (Thermal) = 171.728 kcal/mol
 Heat Capacity (Cv) = 61.171 cal/mol-kelvin
 Entropy (S) = 136.604 cal/mol-kelvin

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	7	0	0.161932	-0.956635	0.498289
2	6	0	-0.919872	-1.459935	-0.171755
3	6	0	-2.180583	-0.963803	-0.043564
4	6	0	-2.508691	0.226257	0.852600
5	6	0	-1.274621	0.592473	1.655077
6	6	0	-0.067680	0.052252	1.446095
7	6	0	1.481187	-1.589165	0.418660
8	6	0	2.594851	-0.629836	0.037669
9	6	0	2.480383	0.188862	-1.093988
10	6	0	3.518790	1.045097	-1.454814
11	6	0	4.687687	1.092866	-0.689633
12	6	0	4.809753	0.282121	0.438232
13	6	0	3.765483	-0.572147	0.800365
14	6	0	-2.993105	1.507729	0.116156
15	8	0	-3.695804	2.297183	0.714968
16	6	0	-2.513293	1.753128	-1.299313
17	6	0	-3.232441	-1.581680	-0.775143
18	7	0	-4.116321	-2.057048	-1.370127
19	1	0	-0.719292	-2.303977	-0.823458
20	1	0	-1.387772	1.357503	2.415955
21	1	0	0.809132	0.352999	2.008370
22	1	0	1.400801	-2.391449	-0.322828
23	1	0	1.719781	-2.068650	1.377881
24	1	0	1.570953	0.158361	-1.689046
25	1	0	3.417636	1.675584	-2.333989
26	1	0	5.496335	1.761489	-0.971534
27	1	0	5.712895	0.316802	1.041325
28	1	0	3.863212	-1.200335	1.683293
29	1	0	-2.790819	2.763500	-1.605665
30	1	0	-1.427539	1.621079	-1.370913
31	1	0	-2.971454	1.027840	-1.982890
32	1	0	-3.333803	-0.017755	1.536744

Model-3ba-conformation GS4

Filename = D:/CALCOLI/Rufus/rufus-GS4.log

Overview Tab Data Section:

Calculation Type = FREQ

Calculation Method = RB3LYP

Basis Set = 6-31G(d)

Charge = 0

Spin = Singlet

Solvation = None

E(RB3LYP) = -764.70829 Hartree

RMS Gradient Norm = 6.17e-06 Hartree/Bohr

Imaginary Freq = 0

Dipole Moment = 6.00073 Debye
Polarizability (?) = 164.542 a.u.
Point Group = C1
Job cpu time: 0 days 2 hours 58 minutes 26.0 seconds.

Thermo Tab Data Section:
Imaginary Freq = 0
Temperature = 298.15 Kelvin
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -764.70829 Hartree
Zero-point Energy Correction = 0.257419 Hartree
Thermal Correction to Energy = 0.27366 Hartree
Thermal Correction to Enthalpy = 0.274605 Hartree
Thermal Correction to Free Energy = 0.211134 Hartree
EE + Zero-point Energy = -764.45087 Hartree
EE + Thermal Energy Correction = -764.43463 Hartree
EE + Thermal Enthalpy Correction = -764.43368 Hartree
EE + Thermal Free Energy Correction = -764.49716 Hartree
E (Thermal) = 171.725 kcal/mol
Heat Capacity (Cv) = 61.102 cal/mol-kelvin
Entropy (S) = 133.585 cal/mol-kelvin

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	7	0	0.070826	-1.292065	0.648955
2	6	0	-0.878093	-1.545276	-0.307105
3	6	0	-2.111838	-0.978515	-0.287233
4	6	0	-2.462362	0.125519	0.700393
5	6	0	-1.499174	0.055018	1.871198
6	6	0	-0.306461	-0.549616	1.770109
7	6	0	1.454542	-1.723675	0.486586
8	6	0	2.418692	-0.621332	0.068101
9	6	0	1.983451	0.520961	-0.613542
10	6	0	2.906601	1.488592	-1.017020
11	6	0	4.266100	1.325682	-0.748912
12	6	0	4.703840	0.188864	-0.065942
13	6	0	3.783313	-0.775184	0.343275
14	6	0	-2.335753	1.533644	0.053102
15	8	0	-1.508415	1.754752	-0.808020
16	6	0	-3.265687	2.605678	0.582931
17	6	0	-3.088792	-1.378545	-1.238538
18	7	0	-3.923568	-1.681619	-1.994841
19	1	0	-0.599643	-2.265994	-1.068771
20	1	0	-1.765785	0.544241	2.802283
21	1	0	0.417302	-0.549529	2.578610
22	1	0	1.454520	-2.529697	-0.257110
23	1	0	1.793282	-2.173833	1.428651
24	1	0	0.927266	0.671345	-0.819043
25	1	0	2.555684	2.373192	-1.541390
26	1	0	4.980391	2.081433	-1.064319
27	1	0	5.759639	0.056212	0.155219
28	1	0	4.128893	-1.655782	0.882063
29	1	0	-2.980535	3.582567	0.187726
30	1	0	-4.295917	2.377353	0.279300
31	1	0	-3.254413	2.627839	1.679681
32	1	0	-3.494442	0.007542	1.058049

Model-3af-conformation GS1

Calculation Type = FREQ
Calculation Method = RB3LYP
Basis Set = 6-31G(d)
Charge = 0
Spin = Singlet
Solvation = None
E(RB3LYP) = -533.65583 Hartree
RMS Gradient Norm = 7.184e-06 Hartree/Bohr
Imaginary Freq = 0
Dipole Moment = 7.4708 Debye
Polarizability (?) = 105.226 a.u.
Point Group = C1
Job cpu time: 0 days 1 hours 37 minutes 47.1 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0
Temperature = 298.15 Kelvin
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -533.65583 Hartree
Zero-point Energy Correction = 0.175504 Hartree
Thermal Correction to Energy = 0.18775 Hartree
Thermal Correction to Enthalpy = 0.188694 Hartree
Thermal Correction to Free Energy = 0.135004 Hartree
EE + Zero-point Energy = -533.48032 Hartree
EE + Thermal Energy Correction = -533.46808 Hartree
EE + Thermal Enthalpy Correction = -533.46713 Hartree
EE + Thermal Free Energy Correction = -533.52082 Hartree
E (Thermal) = 117.815 kcal/mol
Heat Capacity (Cv) = 43.206 cal/mol-kelvin
Entropy (S) = 113 cal/mol-kelvin

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	7	0	2.104405	-0.113949	0.063392
2	6	0	1.269434	0.968595	0.066284
3	6	0	-0.035801	0.910850	-0.315564
4	6	0	-0.712760	-0.389305	-0.739529
5	6	0	0.330647	-1.488477	-0.810127
6	6	0	1.597992	-1.332631	-0.406839
7	6	0	3.463923	-0.041099	0.576837
8	6	0	-1.865757	-0.884968	0.180151
9	8	0	-2.695069	-1.641668	-0.284251
10	6	0	-1.874901	-0.456904	1.632397
11	6	0	-0.793794	2.114264	-0.330389
12	7	0	-1.449987	3.078953	-0.341006
13	1	0	1.716166	1.907247	0.377049
14	1	0	0.010194	-2.450843	-1.194554
15	1	0	2.323136	-2.138460	-0.450992
16	1	0	3.745943	1.006081	0.705541
17	1	0	4.162961	-0.500293	-0.130711
18	1	0	-2.649158	-1.010041	2.167349
19	1	0	-0.897146	-0.631167	2.096358
20	1	0	-2.077361	0.618504	1.707105
21	1	0	-1.188548	-0.275311	-1.724371
22	1	0	3.559545	-0.549362	1.545193

Model-3af-conformation GS2

Calculation Type = FREQ
Calculation Method = RB3LYP
Basis Set = 6-31G(d)
Charge = 0
Spin = Singlet
Solvation = None
E(RB3LYP) = -533.65527 Hartree
RMS Gradient Norm = 6.695e-06 Hartree/Bohr
Imaginary Freq = 0
Dipole Moment = 6.6545495 Debye
Polarizability (?) = 105.79167 a.u.
Point Group = C1
Job cpu time: 0 days 3 hours 4 minutes 13.0 seconds.

Thermo Tab Data Section:

Imaginary Freq = 0
Temperature = 298.15 Kelvin
Pressure = 1 atm
Frequencies scaled by = 1
Electronic Energy (EE) = -533.65527 Hartree
Zero-point Energy Correction = 0.175527 Hartree
Thermal Correction to Energy = 0.187691 Hartree
Thermal Correction to Enthalpy = 0.188635 Hartree
Thermal Correction to Free Energy = 0.135956 Hartree
EE + Zero-point Energy = -533.47975 Hartree
EE + Thermal Energy Correction = -533.46758 Hartree
EE + Thermal Enthalpy Correction = -533.46664 Hartree
EE + Thermal Free Energy Correction = -533.51932 Hartree
E (Thermal) = 117.778 kcal/mol
Heat Capacity (Cv) = 43.196 cal/mol-kelvin
Entropy (S) = 110.872 cal/mol-kelvin

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	7	0	2.055066	-0.233282	0.024119
2	6	0	1.313345	0.915778	0.119625
3	6	0	0.014329	0.991457	-0.267220
4	6	0	-0.772147	-0.242587	-0.686043
5	6	0	0.204412	-1.353054	-1.024650
6	6	0	1.482309	-1.332045	-0.616598
7	6	0	3.371207	-0.338151	0.635662
8	6	0	-1.716067	-0.732117	0.449122
9	8	0	-1.495111	-0.458918	1.609729
10	6	0	-2.897714	-1.580263	0.018849
11	6	0	-0.648190	2.249155	-0.252675
12	7	0	-1.223530	3.263564	-0.269363
13	1	0	1.842315	1.788568	0.487516
14	1	0	-0.149088	-2.207777	-1.592003
15	1	0	2.167613	-2.149335	-0.817415
16	1	0	3.810731	0.658470	0.726834
17	1	0	4.026736	-0.945380	0.003487
18	1	0	-3.376848	-2.026352	0.892569
19	1	0	-3.625454	-0.948097	-0.507092
20	1	0	-2.591371	-2.366262	-0.681677
21	1	0	-1.397487	-0.020719	-1.563536

22

1

0

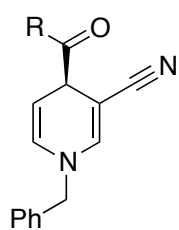
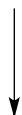
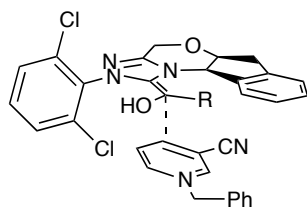
3.324072

-0.792779

1.633760

Proposed stereochemical model to account for selectivity

Transition state leading to the major (R) enantiomer



Transition state leading to the minor (S) enantiomer

