Probing Chemical Space with Alkaloid-Inspired Libraries

Michael C McLeod, Gurpreet Singh, James N Plampin III, Digamber Rane,
Jenna L. Wang, Victor W. Day & Jeffrey Aubé*

Department of Medicinal Chemistry, Delbert M. Shankel Structural Biology Center, University of Kansas, 2034 Becker Drive, Lawrence, Kansas 66045, United States

jaube@ku.edu

Supplementary Information

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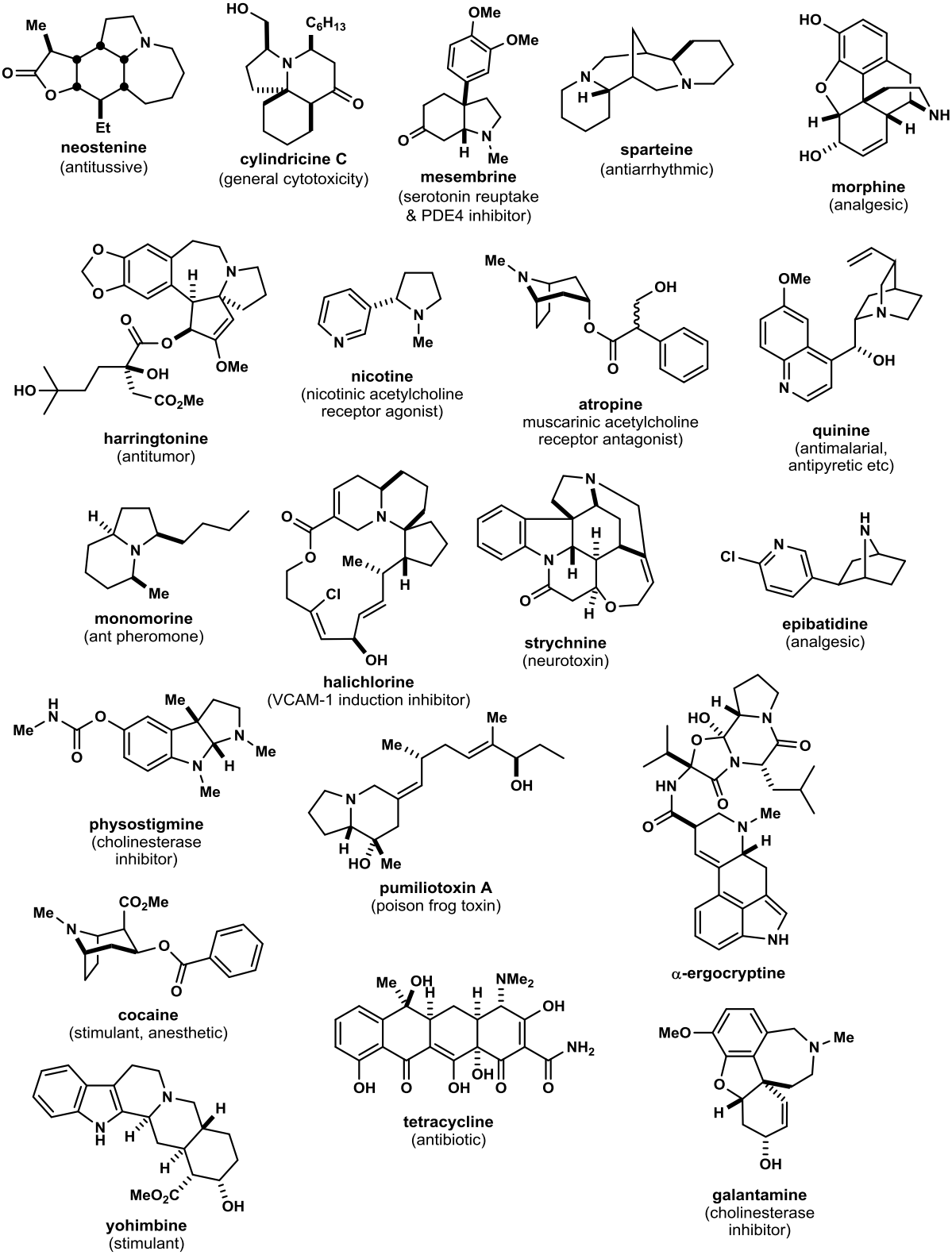
Supplementary Table 1. Comprehensive list of references associated with bioactivity in the *Stemona*, cylindricine/lepadiformine/fasicularin, *Amaryllidaceae* and Lupin families of alkaloids.

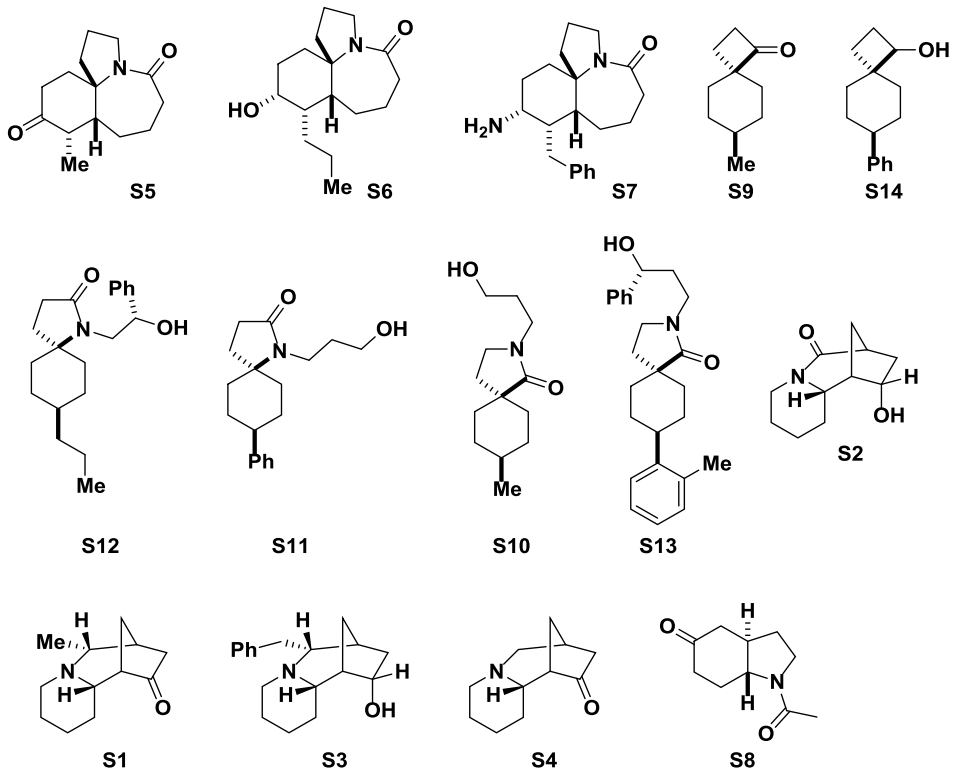
Alkaloid Family	Reviews / original biological activity articles
Stemona alkaloids	• Reviews[1-3] • Antitussive[4-8] • Insecticidal, antifeedant, larvicidal[9-15] • neuromuscular[16] • anthelmintic[17] • AChE inhibition[14,18-20] • Reversal of MDR-cancers[21,22]
cylindricine/lepadiformine/fasicularin	• Review[23] • cytotoxicity[24-27] • cardiovascular actions[28,29]
Amaryllidaceae alkaloids	• Review[30] • serotonin reuptake inhibition[31] • 5-hydroxytryptamine reuptake inhibition[32] • PDE4 inhibition[32,33] • AChE inhibition[34] • antileukemic[35] • cytotoxicity[36]
Lupin alkaloids	• Reviews: cytisine[37,38] sparteine[38] • anti-arrythmic[39] • nicotinic ester agonism[40]/antagonism[38,41] • acetylcholine agonist: (cytisine – many different studies. For examples of early work on bioactivity with *in vivo* studies see [42-44]; for later work with radiolabelled cytisine see [45,46])

Supplementary Table 2. Average bioavalability properties and fraction sp^3 hybridized carbon atoms of scaffolds, library members and reference set compounds.

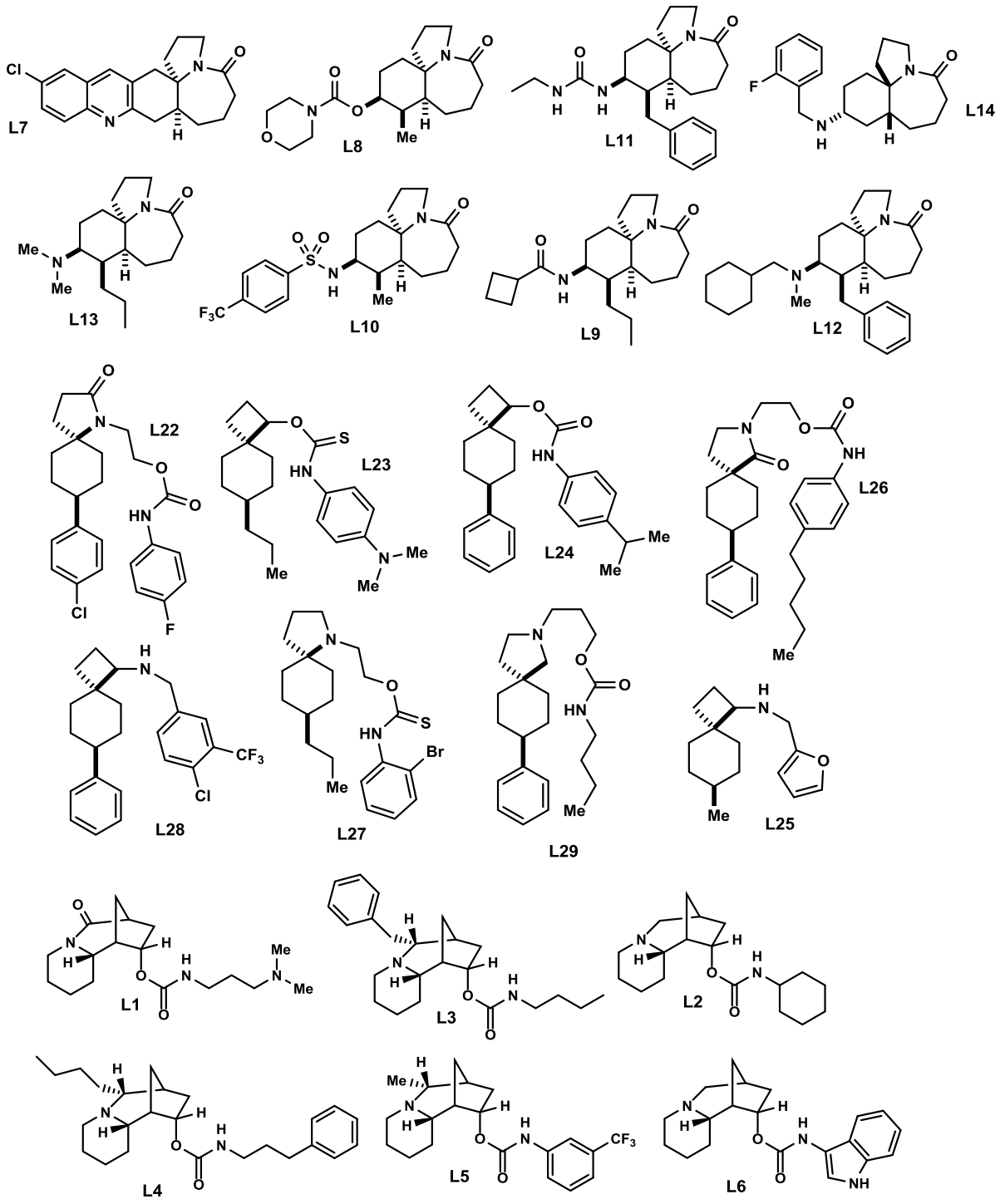
	Drugs	NPs	Commercial	Alk NP	Scaffolds	Sparteine library	Stenine library	Mesembrine library	Cylindricine library	All libraries
m/w	361	629	414	319	243	354	364	311	387	355
XlogP	2.7	1.5	2.4	2.0	2.3	3.7	3.5	2.7	6.1	4.0
HBD	1.5	4.9	1.5	1.3	0.7	1.2	0.6	0.4	1.0	0.8
HBA	5.4	10.8	6.8	4.4	2.5	4.8	4.5	4.3	3.8	4.3
% Pass Lipinski (4/4)	85	42	95	90	100	83	100	100	13	72
% Pass Lipinski (3/4)	98	53	100	100	100	100	100	100	100	100
RotB	6.3	9.7	5.7	2.8	1.7	5.2	3.0	2.0	6.3	4.1
tPSA	69	183	98	54	33	48	47	38	35	42
% Pass Veber	88	33	95	95	100	100	100	100	100	100
Fsp3 C atoms	0.41	0.64	0.23	0.65	0.77	0.73	0.75	0.57	0.58	0.66



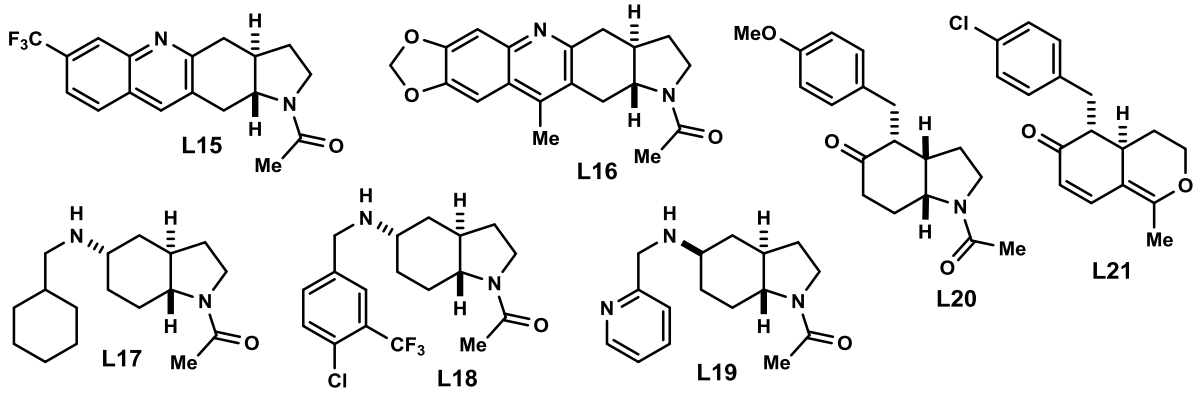
Supplementary Figure 1. Alkaloid natural product reference set for PCA analysis (20 structures).



Supplementary Figure 2. Representative scaffolds used in PCA analysis (14 structures).



Supplementary Figure 3. Representative library compounds used in PCA analysis (29 structures) (continued on next page).



Supplementary Figure 3 (continued). Representative library compounds used in PCA analysis (29 structures).

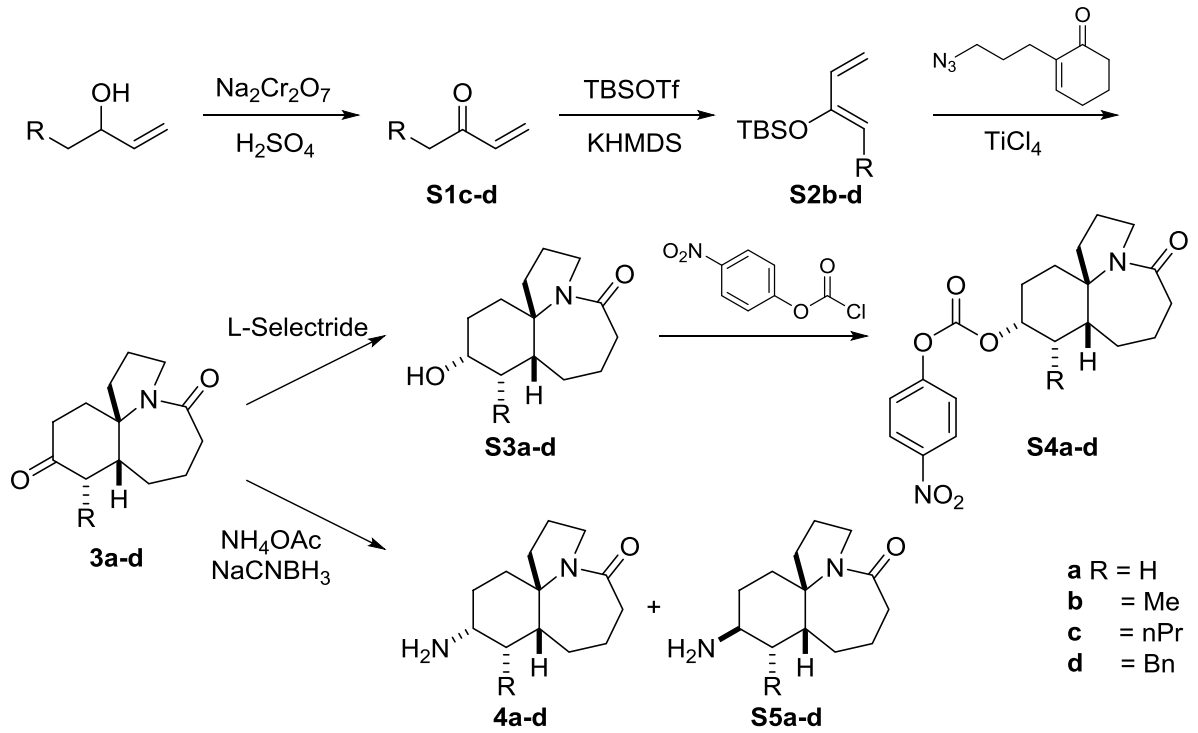
Supplementary Table 3. Composition of reference set of drugs, commercial library compounds and natural products[47] used in PCA.

	Compounds			
Drugs (40 compounds)	Lipitor	Lexapro	Topamax	Coreg
	Nexium	Seroquel	Toprol	Valtrex
	Prevacid	Protonix	Zetia	Adderall
	Flonase	Ambien	Fosamax	Aciphex
	Serevent	Actos	Abilify	Cymbalta
	Singulair	Zoloft	Levaquin	Crestor
	Effexor	Wellbutrin	Lamictal	Diovan
	Plavix	Avandia	Celebrex	Tricor
	Zocor	Risperdal	Benazepril	Concerta
	Norvasc	Zyprexa	Zyrtec	Imitrex
Commercial screening libraries (20 compounds; pubchem compound CIDs)	**ChemBridge:**	5771429	5309975	5308431
	5771374	5309772	5309246	5771496
	5771371	5309762	5309020	
	ChemDiv:	2529482	2474145	2490046
	2474174	1340935	2490068	2529498
	2471337	2490059	1342784	
Natural products (60 compounds)	cephamycin C	mizoribine	coformycin	compactin
	spergualin	SQ26180	arglabin	artemisinin
	forskolin	thienamycin	bestatin	plaunotol
	daptomycin	validamycin	midecamycin A1	rapamycin
	echinocandin B	avermectin B1a	taxol	FK506
	calicheamicin g1	cyclosporin A	pseudomonic acid A	
	lipstatin	geldanamycin	trapoxin B	talaromycin B
	bleomycin	actinonin	vincristine	spongistatin 1
	brefeldin A	discodermolide	colchicines	radicicol
	cytochalasin B	monensin	trichostatin	salicylihalamide A
	epothilone A	calyculin A	fumagillin	brevetoxin B
	apoptolidin	amphotericin B	staurosporine	rifamycin B
	lactacystin	adriamycin	erythromycin A	quinine
	duocarmycin A	ginkgolide B	streptomycin	mycobactin S
	zaragozic acid A			

II. Supplementary Methods

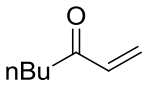
A. Experimental procedures and characterization data for *Stemona* alkaloid-inspired scaffolds.

Supplementary Figure 4. Synthesis of *Stemona* alkaloid-inspired scaffolds



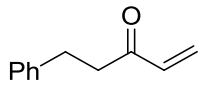
General procedure A: Oxidation of vinylic alcohols

Butylvinylketone, S1c



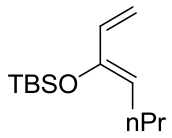
Concentrated H_2SO_4 (48.8 mL, 880 mmol) was added dropwise over 10 min to a solution of sodium dichromate (65.6 g, 220 mL) in water (150 mL) at 0 °C. The resulting bright orange solution was stirred at 0 °C for a further 15 min, then added portionwise to a pre-cooled solution of 3-hydroxyhept-1-ene[48] (45.7 g, 400 mmol) in Et_2O (150 mL) at 0 °C. The biphasic mixture was stirred vigorously at 0 °C for 2 – 4 h. The organic layer was removed, and the aqueous extracted with Et_2O (2 x 100 mL). The combined organics were washed with saturated aq $NaHCO_3$ (100 mL), water (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated to afford a brown oil. The residue was purified by chromatography (silica gel, 9:1 hexanes : ethyl acetate) to afford the title compound (34.8 g, 78%) as a yellow oil. δ_H (400 MHz, $CDCl_3$) 6.38 (1H, dd, *J* 17.6, 10.5), 6.24 (1H, dd, *J* 17.6, 1.3), 5.81 (1H, dd, *J* 10.5, 1.3), 2.58 (2H, t, *J* 7.4), 1.60 (2H, quintet *J* 7.4), 1.34 (2H, sextet, *J* 7.4), 0.91 (3H, t, *J* 7.4); δ_C (100 MHz, $CDCl_3$) 201.2 (C), 136.6 (CH), 127.9 (CH_2), 39.3 (CH_2), 26.1 (CH_2), 22.4 (CH_2), 13.9 (CH_3). The data closely matches that previously reported.[49]

5-Phenylpent-1-en3-one, S1d



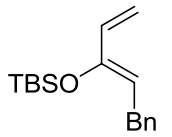
Following general procedure A, reaction of 3-hydroxyl-5-phenylpent-1-ene[50] (83.8 g, 517 mmol) provided the title compound (57.7 g, 70%) as a yellow oil. δ_H (400 MHz, $CDCl_3$) 7.42-7.17 (5H, m), 6.40 (1H, dd, *J* 17.7, 10.5), 6.26 (1H, dd, *J* 17.7, 1.1), 5.87 (1H, dd, *J* 10.5, 1.1), 3.10-2.88 (4H, m); δ_C (100 MHz, $CDCl_3$) 199.8 (C), 141.1 (C), 136.5 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH_2), 126.2 (CH), 41.2 (CH_2), 29.8 (CH_2). The data closely matches that previously reported.[51]

(*Z*)-*tert*-Butyl(hepta-1,3-dien-3-yloxy)dimethylsilane, S2c



In an analogous method to Carreño *et al*.,[52] KHMDS (235 mL, 0.91 M in THF, 214 mmol) was added dropwise over 30 min to a solution of butylvinylketone **S1c** (20.0 g, 178 mmol) and TBSOTf (49.1 mL, 214 mmol) in dry THF (800 mL) at -78 ^oC under argon. After the addition was complete, the reaction mixture was stirred at -78 ^oC for 30 min then at room temperature for 1h, then quenched with sat. aq. $NaHCO_3$ (150 mL) and extracted with Et_2O (3 x 300 mL). The combined organics were washed with brine (200 mL), dried (Na_2SO_4) and concentrated to afford a yellow oil. The residue was purified by chromatography (silica gel, 100% hexanes) to afford the title compound (24.7 g, 61%) as a colourless oil. ν_{max} (film)/cm^{-1} 2958, 1362, 1254; δ_H (500 MHz, $CDCl_3$) 6.16 (1H, dd, *J* 17.2, 10.8), 5.31-5.25 (1H, m), 4.95 (1H, ddd, *J* 10.8, 1.6, 0.6), 4.79 (1H, t, *J* 7.3), 2.10-2.05 (2H, m), 1.41-1.33 (2H, m), 1.00 (9H, s), 0.91 (3H, t, *J* 7.4), 0.11 (6H, s); δ_C (125 MHz, $CDCl_3$) 148.3 (C), 135.7 (CH), 116.0 (CH), 111.8 (CH_2), 28.2 (CH_2), 26.0 (CH_3), 22.8 (CH_2), 18.5 (C), 13.9 (CH_3), −3.7 (CH_3).

(*Z*)-*tert*-Butyldimethyl(5-phenylpenta-1,3-dien-3-yloxy)silane, S2d

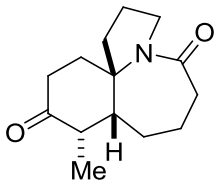


KHMDS (250 mL, 0.91 M in THF, 225 mmol) was added dropwise over 30 min to a solution of enone **S1d** (40.0 g, 250 mmol) and TBSOTf (68.8 mL, 300 mmol) in dry THF (1000 mL) at -78 ^oC under argon. After the addition was complete, the reaction mixture was stirred at -78 ^oC for 1.5 h, then quenched with sat. aq. $NaHCO_3$ (300 mL), warmed to room temperature and extracted with Et_2O (3 x 500 mL). The combined organics were washed with brine (300 mL), dried (Na_2SO_4) and concentrated to afford a yellow oil. The residue was purified by chromatography (silica gel, 100% hexanes) to afford the title compound (47.1 g, 76% w.r.t KHMDS) as a colourless oil. ν_{max} (film)/cm^{-1} 2931, 1359, 1255; δ_H (500 MHz, $CDCl_3$) 7.35-7.21 (5H, m), 6.24 (1H, dd, *J* 17.1, 10.8), 5.41 (1H, dd, *J* 17.1, 1.0), 5.08-5.01 (2H,

m), 3.52 (2H, d, *J* 7.3), 1.07 (9H, s), 0.20 (6H, s); δ_C (125 MHz, $CDCl_3$) 148.9 (C), 141.2 (C), 135.5 (CH), 128.42 (CH), 128.39 (CH), 125.9 (CH), 114.1 (CH), 112.8 (CH_2), 32.3 (CH_2), 26.0 (CH_3), 18.5 (C), −3.5 (CH_3).

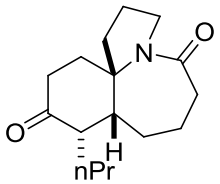
General procedure B: Diels-Alder/Schmidt reaction

(8a*S*,9*R*,12a*R*)-9-Methyloctahydrobenzo[*b*]pyrrolo[1,2-*a*]azepine-5,10(1*H*,6*H*)-dione, 3b



Titanium tetrachloride (1 M in dichloromethane, 100 mmol) was added dropwise to a solution of azide[53] (7.15 g, 40 mmol) and (*Z*)-*tert*-butyldimethyl(penta-1,3-dien-3-yloxy)silane[52] (19.8 g, 100 mmol) in anhydrous dichloromethane (500 mL) at 0 °C under argon. The resulting red/brown solution was stirred at 0 °C for 2 h, then allowed to warm slowly to room temperature overnight. The reaction mixture was quenched with water (100 mL) and stirred at room temperature for 1 h. The organic layer was removed, and the aqueous extracted with dichloromethane (3 x 100 mL). The combined organics were dried (Na_2SO_4) and concentrated to afford a brown oil. The residue was purified by chromatography (silica gel, 95:5 ethyl acetate: methanol) to afford the title compound (5.0 g, 53%) as a cream solid foam. A portion of this was recrystallised from hexanes and ethyl acetate to afford colourless needles. Mp 133-135 °C; ν_{max} (film)/cm^{-1} 2943, 1708, 1611; δ_H (500 MHz, $CDCl_3$) 3.87-3.81 (1H, m), 3.29 (1H, ddd, *J*11.7, 11.7, 7.1), 2.78-2.74 (1H, m), 2.61 (1H, dd, *J* 12.3, 6.4), 2.51 (1H, ddt, *J* 15.0, 6.4, 1.4), 2.37-2.22 (4H, m), 1.97-1.88 (1H, m), 1.88-1.65 (6H, m), 1.39-1.27 (1H, m), 1.08-1.02 (1H, m), 0.88 (3H, d, *J* 6.7); δ_C (125 MHz, $CDCl_3$) 210.3 (C), 173.8 (C), 66.0 (C), 52.1 (CH), 49.2 (CH_2), 47.2 (CH), 40.1 (CH_2), 38.32 (CH_2), 38.25 (CH_2), 28.1 (CH_2), 27.1 (CH_2), 22.8 (CH_2), 20.6 (CH_2), 12.4 (CH_3); *m/z* (ESI+) found $[M+H]^+$ 236.1674. $C_{14}H_{22}NO_2^+$ requires 236.1645.

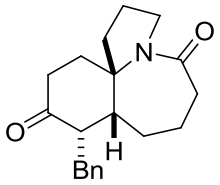
(8a*S*,9*R*,12a*R*)-9-Propyloctahydrobenzo[*b*]pyrrolo[1,2-*a*]azepine-5,10(1*H*,6*H*)-dione, 3c



Following general procedure B, reaction with azide (7.0 g, 39.1 mmol) and diene **S2c** (22.1 g, 97.7 mmol) provided the title compound (4.5 g, 44%) as a colourless solid. A portion this was recrystallised from hexanes and ethyl acetate to afford colourless needles. Mp 86.5 – 88.0 °C; ν_{max} (film)/cm^{-1} 2954, 1707, 1613; δ_H (500 MHz, $CDCl_3$) 3.98 (1H, dd, *J* 11.9, 8.4), 3.43 (1H, ddd, *J* 11.9, 11.9, 7.0), 2.76 (1H, dd, *J* 12.2, 6.2), 2.70-2.61 (2H, m), 2.48-2.37 (4H, m), 2.07-1.99 (1H, m), 1.96-1.72 (7H, m), 1.50-1.40 (1H, m), 1.28-1.11 (4H, m), 0.90 (3H, t, *J* 7.2); δ_C (125 MHz, $CDCl_3$) 210.0 (C), 173.7 (C), 65.9 (C), 52.5 (CH), 50.3 (CH), 49.2 (CH_2), 40.3 (CH_2), 38.8 (CH_2), 38.3 (CH_2), 29.1 (CH_2), 28.4

(CH_2), 27.4 (CH_2), 22.9 (CH_2), 20.6 (CH_2), 20.5 (CH_2), 14.1 (CH_3); *m/z* (ESI+) found $[M+H]^+$ 264.1994. $C_{16}H_{26}NO_2^+$ requires 264.1958.

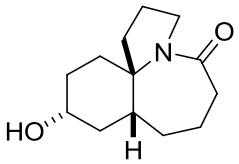
(8a*S*,9*R*,12a*R*)-9-Benzyloctahydrobenzo[*b*]pyrrolo[1,2-*a*]azepine-5,10(1*H*,6*H*)-dione, 3d



Following general procedure B, reaction with azide (12.3 g, 68.6 mmol) and diene **S2d** (47.1 g, 172 mmol) provided the title compound (11.9 g, 56%) as a colourless solid. A portion this was recrystallised from hexanes and ethyl acetate to afford colourless needles. Mp 117-119 ^oC; ν_{max} (film)/cm^{-1} 2945, 1709, 1611; δ_H (500 MHz, $CDCl_3$) 7.29-7.26 (2H, m), 7.22-7.18 (1H, m), 7.14-7.11 (2H, m), 3.95-3.90 (1H, m), 3.37-3.31 (1H, m), 3.15 (1H, dd, *J* 14.3, 6.1), 3.06-3.02 (1H, m), 2.72-2.68 (1H, m), 2.63 (1H, dd, *J* 15.0, 6.6), 2.53-2.38 (5H, m), 2.06-2.01 (1H, m), 1.92-1.74 (6H, m), 1.44-1.35 (1H, m), 1.31-1.22 (1H, m); δ_C (125 MHz, $CDCl_3$) 209.2 (C), 173.6 (C), 139.6 (C), 128.7 (CH), 128.6 (CH), 126.3 (CH), 65.8 (C), 54.6 (CH), 49.3 (CH), 49.2 (CH_2), 40.2 (CH_2), 38.6 (CH_2), 38.3 (CH_2), 32.1 (CH_2), 29.1 (CH_2), 27.3 (CH_2), 22.7 (CH_2), 20.5 (CH_2); *m/z* (ESI+) found $[M+H]^+$ 312.1982. $C_{20}H_{26}NO_2^+$ requires 312.1958.

General procedure D: L-Selectride reduction of ketones

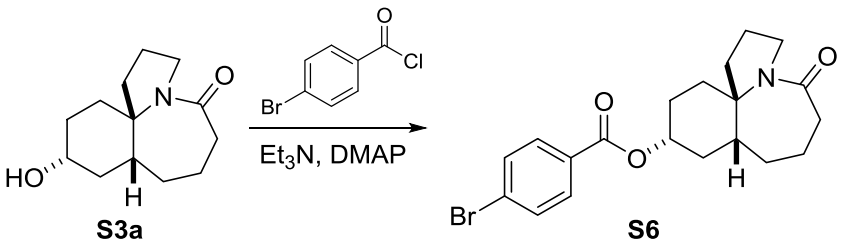
(8a*S*,10*S*,12a*R*)-10-Hydroxydecahydrobenzo[*b*]pyrrolo[1,2-*a*]azepin-5(1*H*)-one, S3a



L-Selectride (1M in tetrahydrofuran, 33.9 mL) was added dropwise to a solution of ketone **3a**[54] (3.0 g, 13.6 mmol) in anhydrous tetrahydrofuran (180 mL) at -78 ^oC under argon. The reaction mixture was stirred at -78 ^oC for 4 h, then allowed to warm slowly to room temperature overnight. The mixture was then cooled to 0 ^oC, quenched carefully with 30% aq. H_2O_2 (15 mL) and 2M NaOH (20 mL), then extracted with dichloromethane (3 x 100 mL). The combined organics were washed with brine (100 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by automated column chromatography (40 g silica column, 0% MeOH in CH_2Cl_2 for 3 min, then 0 to 10% over 10 min, the 10% for 5 min) to afford the title compound (2.73 g, 90%) as a pale yellow oil. A portion was recrystallised from hexanes and ethyl acetate to afford colourless plates. Mp 112.5-114.5 ^oC; ν_{max} (film)/cm^{-1} 3380, 2926, 1592; δ_H (500 MHz, $CDCl_3$) 4.09-4.06 (1H, m), 3.80-3.75 (1H, m), 3.54-3.47 (1H, m), 2.67-2.58 (2H, m), 2.55-2.45 (1H, m), 2.40-2.36 (1H, m), 2.30 (1H, td, *J* 13.1, 5.3), 1.97 (1H, dt, *J* 9.0, 5.0), 1.94-1.69 (9H, m), 1.49-1.37 (2H, m); δ_C (125 MHz, $CDCl_3$) 174.5 (C), 66.4 (C), 65.2 (CH),

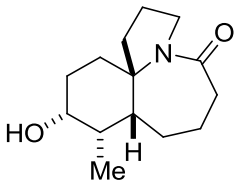
49.0 (CH_2), 43.9 (CH), 39.0 (CH_2), 38.6 (CH_2), 38.4 (CH_2), 34.7 (CH_2), 31.4 (CH_2), 24.3 (CH_2), 23.7 (CH_2), 20.3 (CH_2); *m/z* (ESI+) found $[M+H]^+$ 224.1660. $C_{13}H_{22}NO_2^+$ requires 224.1645.

(8a*S*,10*S*,12a*R*)-5-Oxododecahydrobenzo[*b*]pyrrolo[1,2-*a*]azepin-10-yl 4-bromobenzoate, S6



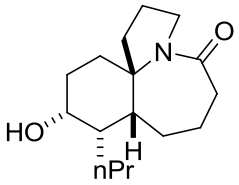
Triethylamine (75 μL, 0.54 mmol) was added to a solution of alcohol **S3a** (100 mg, 0.45 mmol), 4-bromobenzoyl chloride (150 mg, 0.67 mmol) and DMAP (66 mg, 0.54 mmol) in anhydrous CH_2Cl_2 (5 mL) at room temperature under argon. The reaction mixture was stirred for 7.5 h, then water (5 mL) was added. The organic layer was removed and the aqueous extracted with CH_2Cl_2 (2 x 5 mL). The combined organics were dried (Na_2SO_4) and concentrated to afford a yellow oil. The crude product was purified by automated column chromatography (4 g silica column, 0 to 100% EtOAc in hexanes over 15 min) followed by recrystallisation from EtOAc to afford the title compound (130 mg, 71%) as cream plates. Mp 104-107 °C; ν_{max} (film)/cm^{-1} 2928, 1711, 1612; δ_H (500 MHz, $CDCl_3$) 7.90 (2H, d, *J* 8.3), 7.62 (2H, d, *J* 8.3), 5.25 (1H, br s), 3.84-3.78 (1H, m), 3.56-3.47 (1H, m), 2.74-2.66 (1H, m), 2.52-2.35 (3H, m), 2.32-2.23 (1H, m), 2.13 (1H, td, *J* 15.5, 4.4), 2.06-1.94 (3H, m), 1.92-1.70 (6H, m), 1.54-1.44 (2H, m); δ_C (125 MHz, $CDCl_3$) 174.2 (C), 165.2 (C), 131.9 (CH), 131.0 (CH), 129.5 (C), 128.2 (C), 68.8 (CH), 66.0 (C), 49.2 (CH_2), 43.5 (CH), 39.0 (CH_2), 38.6 (CH_2), 35.7 (CH_2), 34.4 (CH_2), 28.5 (CH_2), 24.7 (CH_2), 23.7 (CH_2), 20.3 (CH_2); *m/z* (ESI+) found $[M+H]^+$ 406.1023. $C_{20}H_{25}BrNO_3^+$ requires 406.1012.

(8a*S*,9*R*,10*S*,12a*R*)-10-Hydroxy-9-methyldecahydrobenzo[*b*]pyrrolo[1,2-a]azepin-5(1*H*)-one, S3b



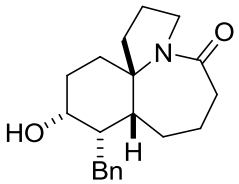
Following general procedure D, reaction with ketone **3b** (2.65 g, 11.3 mmol) and L-Selectride (1.0 M in tetrahydrofuran, 28.2 mL) provided the title compound (2.54 g, 95%) as a pale yellow crystalline solid. Mp 189-191 °C; ν_{max} (film)/cm^{-1} 3389, 2932, 1591; δ_H (500 MHz, $CDCl_3$) 3.85-3.59 (2H, m), 3.41-3.34 (1H, m), 2.62 (1H, ddt, *J* 14.9, 6.9, 1.4), 2.50-2.42 (2H, m), 2.26-2.16 (2H, m), 1.98-1.66 (6H, m), 1.47 (1H, dt, *J* 12.7, 3.1), 1.38-1.24 (2H, m), 1.06 (3H, t, *J* 7.2); δ_C (125 MHz, $CDCl_3$) 173.9 (C), 68.3 (CH), 67.0 (C), 49.0 (CH), 48.1 (CH_2), 37.9 (CH_2), 37.8 (CH_2), 36.9 (CH), 30.5 (CH_2), 27.2 (CH_2), 22.9 (CH_2), 22.7 (CH_2), 19.3 (CH_2), 15.2 (CH_3); *m/z* (ESI+) found $[M+H]^+$ 238.1817. $C_{14}H_{24}NO_2^+$ requires 238.1802.

(8a*S*,9*R*,10*S*,12a*R*)-10-Hydroxy-9-propyldecahydrobenzo[*b*]pyrrolo[1,2-*a*]azepin-5(1*H*)-one, S3c



Following general procedure D, reaction with ketone **3c** (1.16 g, 4.4 mmol) and L-Selectride (1.0 M in tetrahydrofuran, 10.9 mL) provided the title compound (1.11 g, 95%) as a pale yellow crystalline solid. Mp 134-135 °C; ν_{max} (film)/cm^{-1} 3391, 2953, 1593; δ_H (500 MHz, $CDCl_3$) 3.85 – 3.78 (2H, m), 3.43 – 3.36 (1H, m), 2.58 (1H, dd, *J* 15.0, 6.9), 2.48 – 2.40 (2H, m), 2.28 – 2.18 (3H, m), 1.89 – 1.60 (8H, m), 1.53 – 1.22 (7 H, m), 0.90 (3H, t, *J* 7.3); δ_C (125 MHz, $CDCl_3$) 174.9 (C), 68.0 (C), 67.8 (CH), 49.1 (CH_2), 48.0 (CH), 43.0 (CH), 39.0 (CH_2), 38.8 (CH_2), 32.0 (CH_2), 31.7 (CH_2), 28.3 (CH_2), 24.4 (CH_2), 23.8 (CH_2), 20.2 (CH_2), 20.1 (CH_2), 14.3 (CH_3); *m/z* (ESI+) found $[M+H]^+$ 266.2134. $C_{16}H_{28}NO_2^+$ requires 266.2115.

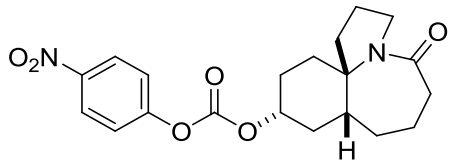
(8a*S*,9*R*,10*S*,12a*R*)-9-Benzyl-10-hydroxydecahydrobenzo[*b*]pyrrolo[1,2-*a*]azepin-5(1*H*)-one, S3d



Following general procedure D, reaction with ketone **3d** (2.50 g, 8.0 mmol) and L-Selectride (1.0 M in tetrahydrofuran, 20.1 mL) provided the title compound (2.29 g, 91%) as a colourless solid foam. A portion of this was recrystallised from ethyl acetate and tetrahydrofuran to afford colourless plates. Mp 169-171 °C; ν_{max} (film)/cm^{-1} 3388, 2926, 1593; δ_H (500 MHz, $CDCl_3$) 7.29-7.26 (2H, m), 7.21-7.17 (3H, m), 3.84-3.74 (2H, m), 3.41-3.34 (1H, m), 2.92 (1H, dd, *J* 13.4, 8.7), 2.67-2.57 (2H, m), 2.50-2.20 (4H, m), 2.07-1.97 (2H, m), 1.86-1.57 (6H, m), 1.53-1.47 (1H, m), 1.37-1.22 (2H, m); δ_C (125 MHz, $CDCl_3$) 174.9 (C), 140.6 (C), 128.9 (CH), 128.5 (CH), 126.1 (CH), 68.0 (C), 66.5 (CH), 49.1 (CH_2), 48.5 (CH), 45.7 (CH), 38.9 (CH_2), 38.8 (CH_2), 36.5 (CH_2), 32.0 (CH_2), 28.7 (CH_2), 24.3 (CH_2), 23.7 (CH_2), 20.2 (CH_2); *m/z* (ESI+) found $[M+H]^+$ 314.2127. $C_{20}H_{28}NO_2^+$ requires 314.2115.

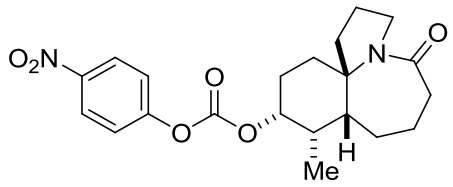
<u>General procedure E: Formation of carbonates</u>

4-Nitrophenyl (8a*S*,10*S*,12a*R*)-5-oxododecahydrobenzo[*b*]pyrrolo[1,2-*a*]azepin-10-yl carbonate, S4a



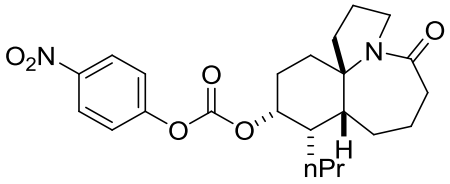
4-Nitrophenylchloroformate (2.88 g, 14.3 mmol) was added in one portion to a solution of alcohol **S3a** (2.13 g, 9.54 mmol) and pyridine (1.54 mL, 19.1 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 ^oC under argon. The resulting suspension was stirred at room temperature for 1.5 h, then diluted with CH_2Cl_2 (200 mL) and washed quickly with 1M HCl (50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated to afford a colourless solid foam. The crude product was purified by automated column chromatography (40 g silica column, 0 to 100% EtOAc in hexanes over 5 min, then 100% EtOAc for 10 min) to afford the title compound (2.81 g, 76%) as a white amorphous solid. Mp 159-160 ^oC; ν_{max} (film)/cm^{-1} 2946, 1760, 1614; δ_H (500 MHz, $CDCl_3$) 8.45-8.18 (2H, m), 7.49-7.32 (2H, m), 5.03-4.86 (1H, m), 3.86-3.78 (1H, m), 3.56-3.49 (1H, m), 2.70 (1H, dd, *J* 15.0, 6.7), 2.48 (1H, t, *J* 13.3), 2.44-2.31 (2H, m), 2.27 (1H, td, *J* 14.1, 3.5), 2.14-2.06 (2H, m), 2.06-1.91 (3H, m), 1.89-1.72 (5H, m), 1.54-1.44 (2H, m); δ_C (125 MHz, $CDCl_3$) 174.3 (C), 155.5 (C), 151.8 (C), 145.4 (C), 125.3 (CH), 121.9 (CH), 74.0 (CH), 65.8 (C), 49.1 (CH_2), 43.3 (CH), 39.0 (CH_2), 38.4 (CH_2), 35.5 (CH_2), 34.0 (CH_2), 28.3 (CH_2), 24.5 (CH_2), 23.6 (CH_2), 20.3 (CH_2); *m/z* (ESI+) found $[M+H]^+$ 389.1727. $C_{20}H_{25}N_2O_6^+$ requires 389.1702.

(8a*S*,9*R*,10*S*,12a*R*)-9-Methyl-5-oxododecahydrobenzo[*b*]pyrrolo[1,2-*a*]azepin-10-yl 4-nitrophenyl carbonate, S4b



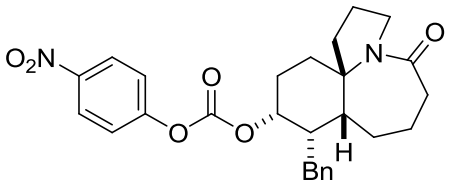
Following general procedure E, reaction of alcohol **S3b** (2.90 g, 12.2 mmol) provided the title compound (2.71 g, 55%) as a cream solid foam. ν_{max} (film)/cm^{-1} 2956, 1759, 1612; δ_H (500 MHz, $CDCl_3$) 8.29-8.26 (2H, m), 7.40-7.37 (2H, m), 4.90 (1H, br s), 3.88-3.83 (1H, m), 3.48-3.41 (1H, m), 2.66 (1H, dd, *J* 15.1, 7.0), 2.48-2.40 (2H, m), 2.24-2.12 (2H, m), 2.08-2.02 (1H, m), 1.99-1.68 (7H, m), 1.55 (1H, ddd, *J* 12.0, 3.7, 3.7), 1.47-1.42 (1H, m), 1.40-1.32 (1H, m), 1.07 (3H, d, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 174.6 (C), 155.6 (C), 152.3 (C), 145.4 (C), 125.3 (CH), 121.9 (CH), 77.9 (CH), 67.2 (C), 49.5 (CH), 49.1 (CH_2), 39.0 (CH_2), 38.8 (CH_2), 37.2 (CH), 28.5 (CH_2), 27.7 (CH_2), 24.0 (CH_2), 23.5 (CH_2), 20.2 (CH_2), 15.9 (CH_3); *m/z* (ESI+) found $[M+H]^+$ 403.1884. $C_{21}H_{27}N_2O_6^+$ requires 403.1864.

4-Nitrophenyl (8a*S*,9*R*,10*S*,12a*R*)-5-oxo-9-propyldodecahydrobenzo[*b*]pyrrolo[1,2-*a*]azepin-10-yl carbonate, S4c



Following general procedure E, reaction of alcohol **S3c** (1.11 g, 4.2 mmol) provided the title compound (1.20 g, 67%) as a colourless solid foam. ν_{max} (film)/cm^{-1} 2947, 1761, 1614; δ_H (500 MHz, $CDCl_3$) 8.35-8.28 (2H, m), 7.45-7.38 (2H, m), 5.01 (1H, br s), 4.14 (1H, d, *J* 7.1), 3.91 (1H, dd, *J* 12.6, 7.2), 3.49 (1H, dd, *J* 7.8, 2.7), 2.76 (1H, dd, *J* 15.1, 6.9), 2.49 (2H, dd 16.2, 10.8), 2.22 (1H, dd, *J* 13.6, 4.7), 2.13-1.80 (10H, m), 1.80-1.67 (3H, m), 1.65 (1H, s), 1.54-1.32 (6H, m), 1.28 (1H, t, *J* 7.1), 0.99-0.91 (3H, m); δ_C (125 MHz, $CDCl_3$) 174.8 (C), 155.6 (C), 152.2 (C), 125.3 (CH), 121.9 (CH), 76.7 (CH), 67.4 (C), 49.3 (CH_2), 47.3 (CH), 42.2 (CH), 39.0 (CH_2), 38.6 (CH_2), 31.5 (CH_2), 28.6 (CH_2), 27.7 (CH_2), 24.4 (CH_2), 23.5 (CH_2), 20.2 (CH_2), 19.9 (CH_2), 14.2 (CH_3); *m/z* (ESI+) found $[M+H]^+$ 431.2202. $C_{23}H_{31}N_2O_6^+$ requires 431.2177.

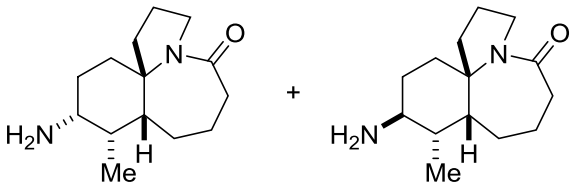
(8a*S*,9*R*,10*S*,12a*R*)-9-Benzyl-5-oxododecahydrobenzo[*b*]pyrrolo[1,2-*a*]azepin-10-yl 4-nitrophenyl carbonate, S4d



Following general procedure E, reaction of alcohol **S3d** (2.19 g, 7.0 mmol) provided the title compound (2.49 g, 74%) as a colourless amorphous solid. Mp 211-213 ^oC; ν_{max} (film)/cm^{-1} 2958, 1760, 1611; δ_H (500 MHz, $CDCl_3$) 8.35-8.32 (2H, m), 7.47-7.43 (2H, m), 7.34-7.31 (2H, m), 7.27-7.22 (1H, m), 7.17-7.13 (2H, m), 4.84 (1H, br s), 3.89-3.84 (1H, m), 3.45-3.39 (1H, m), 2.87 (1H, dd, *J* 13.6, 8.1), 2.73-2.66 (2H, m), 2.51-2.43 (2H, m), 2.34-2.29 (1H, m), 2.23 (1H, ddd, *J* 13.6, 13.6, 4.6), 2.13-2.02 (3H, m), 1.92-1.59 (6H, m), 1.48 (1H, dd, *J* 13.6, 5.1), 1.40-1.31 (1H, m); δ_C (125 MHz, $CDCl_3$) 174.4 (C), 155.6 (C), 152.0 (C), 145.4 (C), 139.1 (C), 128.8 (CH), 128.7 (CH), 126.7 (CH), 125.4 (CH), 121.9 (CH), 76.0 (CH), 67.0 (C), 49.1 (CH_2), 47.6 (CH), 44.9 (CH), 39.0 (CH_2), 38.8 (CH_2), 36.0 (CH_2), 28.3 (CH_2), 28.0 (CH_2), 24.4 (CH_2), 23.4 (CH_2), 20.2 (CH_2); *m/z* (ESI+) found $[M+H]^+$ 479.2169. $C_{27}H_{31}N_2O_6^+$ requires 479.2177.

General procedure F: Reductive amination with ammonium acetate

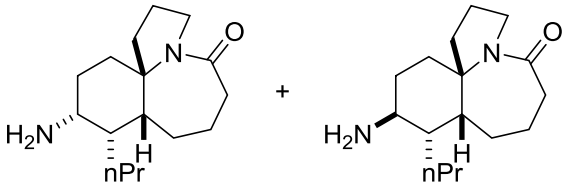
(8a*S*,9*R*,10*S*,12a*R*)-10-Amino-9-methyldecahydrobenzo[*b*]pyrrolo[1,2-*a*]azepin-5(1*H*)-one, 4b and (8a*S*,9*R*,10*R*,12a*R*)-10-amino-9-methyldecahydrobenzo[*b*]pyrrolo[1,2-*a*]azepin-5(1*H*)-one, S5b



4b **S5b**

Ammonium acetate (20.0 g, 260 mmol) was added to a solution of ketone **3b** (6.11 g, 26.0 mmol) in anhydrous methanol (100 mL) under argon. Sodium cyanoborohydride (12.3 g, 195 mmol) was then added, and the resulting yellow solution stirred at room temperature for 7 h. After this time, an additional aliquot of ammonium acetate (20.0 g, 260 mmol) and sodium cyanoborohydride (12.3 g, 195 mmol) was added and the mixture stirred overnight at room temperature, then concentrated under reduced pressure to remove the methanol. The residue was diluted with 2M NaOH until basic, then extracted with dichloromethane (10 x 50 mL). The combined organics were dried (Na_2SO_4) and concentrated to afford a yellow oil (6.7 g). The crude ~2:1 diastereomeric mixture of products was purified by automated column chromatography (2 g batches of crude material on a 130 g C18 column, 10 to 30% acetonitrile in basic water over 5 min, then 30-50% over 15 min, then 100% acetonitrile for 5 min) to afford the (9*R*,10*S*) isomer **4b** (3.66 g, 60%) and the (9*R*,10*R*) isomer **S5b** (1.76 g, 29%) as colourless amorphous solids. **(8a*S*,9*R*,10*S*,12a*R*) isomer 4b:** Mp 106-108 ^{o}C; ν_{max} (film)/cm^{-1} 3374, 2930, 1603; δ_H (500 MHz, $CDCl_3$) 3.82-3.77 (1H, m), 3.45-3.39 (1H, m), 3.06 (1H, t, *J* 3.7), 2.60 (1H, ddt, *J* 15.0, 7.0, 1.4), 2.51-2.42 (2H, m), 2.35 (1H, ddd, *J* 13.5, 13.5, 2.5), 2.22 (1H, td, *J* 13.5, 4.5), 2.02-1.97 (1H, m), 1.95-1.90 (1H, m), 1.89-1.64 (5H, m), 1.60-1.55 (1H, m), 1.46-1.42 (1H, m), 1.33-1.24 (2H, m), 1.01 (3H, d, *J* 7.3); δ_C (125 MHz, $CDCl_3$) 171.8 (C), 68.4 (C), 50.1 (CH), 49.04 (CH_2), 48.96 (CH), 39.0 (CH_2), 38.9 (CH_2), 37.2 (CH), 31.8 (CH_2), 28.9 (CH_2), 24.0 (CH_2), 23.7 (CH_2), 20.2 (CH_2), 16.7 (CH_3); *m/z* (ESI+) found $[M+H]^+$ 237.1984. $C_{14}H_{25}N_2O^+$ requires 237.1961. **(8a*S*,9*R*,10*R*,12a*R*) isomer S5b:** Mp 97-99 ^{o}C; ν_{max} (film)/cm^{-1} 3394, 2941, 1597; δ_H (500 MHz, MeOD) 3.84-3.78 (1H, m), 3.41-3.31 (1H, m), 2.81 (1H, ddd, *J* 11.5, 11.5, 5.4), 2.70-2.66 (1H, m), 2.61-2.53 (2H, m), 2.24 (1H, ddd, *J* 13.5, 13.5, 5.0), 2.01-1.71 (8H, m), 1.61-1.56 (2H, m), 1.52-1.36 (2H, m), 1.04 (3H, d, *J* 6.8); δ_C (125 MHz, MeOD) 176.8 (C), 69.5 (C), 51.8 (CH_2), 50.5 (CH), 50.4 (CH_2), 41.2 (CH_2), 40.3 (CH_2), 39.0 (CH), 32.7 (CH_2), 28.7 (CH_2), 26.7 (CH_2), 24.4 (CH_2), 21.2 (CH_2), 17.5 (CH_3); *m/z* (ESI+) found $[M+H]^+$ 237.1978. $C_{14}H_{25}N_2O^+$ requires 237.1961.

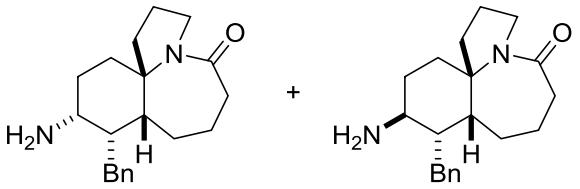
(8a*S*,9*R*,10*S*,12a*R*)-10-Amino-9-propyldecahydrobenzo[*b*]pyrrolo[1,2-*a*]azepin-5(1*H*)-one, 4c and (8a*S*,9*R*,10*R*,12a*R*)-10-amino-9-propyldecahydrobenzo[*b*]pyrrolo[1,2-*a*]azepin-5(1*H*)-one, S5c



4c **S5c**

Following general procedure F, reaction of ketone **3c** (5.50 g, 13.7 mmol) provided the (9*R*,10*S*) isomer **4c** (3.66 g, 66%) and the (9*R*,10*R*) isomer **S5c** (880 mg, 16%) as pale yellow oils. **(8a*S*,9*R*,10*S*,12a*R*) isomer 4c:** ν_{max} (film)/cm^{-1} 3405, 2927, 1603; δ_H (500 MHz, $CDCl_3$) 3.83-3.78 (1H, m), 3.46-3.39 (1H, m), 3.14 (1H, br s), 2.64-2.57 (1H, m), 2.52-2.33 (3H, m), 2.26 (1H, ddd, *J* 13.4, 13.4, 4.4), 1.90-1.48 (9H, m), 1.40-1.22 (6H, m), 0.92 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 174.8 (C), 68.3 (C), 49.1 (CH_2), 48.3 (CH), 47.5 (CH), 42.3 (CH), 39.1 (CH_2), 38.9 (CH_2), 32.5 (CH_2), 31.9 (CH_2), 28.9 (CH_2), 24.5 (CH_2), 23.8 (CH_2), 20.19 (CH_2), 20.15 (CH_2), 14.3 (CH_3); *m/z* (ESI+) found $[M+H]^+$ 265.2309. $C_{16}H_{29}N_2O^+$ requires 265.2274. **(8a*S*,9*R*,10*R*,12a*R*) isomer S5c:** ν_{max} (film)/cm^{-1} 3375, 2935, 1604; δ_H (500 MHz, $CDCl_3$) 3.82-3.77 (1H, m), 3.35-3.28 (1H, m), 2.69 (1H, br s), 2.59-2.48 (2H, m), 2.37 (1H, dd, *J* 13.9, 13.9), 2.04 (1H, ddd, *J* 13.5, 13.5, 4.9), 1.85-1.25 (14H, m), 1.15-1.05 (2H, m), 0.85 (3H, t, *J* 7.0); δ_C (125 MHz, $CDCl_3$) 174.3 (C), 67.4 (C), 49.1 (CH_2), 48.4 (CH), 45.9 (CH), 45.8 (CH), 39.5 (CH_2), 38.7 (CH_2), 33.7 (CH_2), 31.0 (CH_2), 28.1 (CH_2), 25.6 (CH_2), 23.4 (CH_2), 20.3 (CH_2), 19.4 (CH_2), 14.2 (CH_3); *m/z* (ESI+) found $[M+H]^+$ 265.2301. $C_{16}H_{29}N_2O^+$ requires 265.2274.

(8a*S*,9*R*,10*S*,12a*R*)-10-Amino-9-benzyldecahydrobenzo[*b*]pyrrolo[1,2-*a*]azepin-5(1*H*)-one, 4d and (8a*S*,9*R*,10*R*,12a*R*)-10-amino-9-benzyldecahydrobenzo[*b*]pyrrolo[1,2-*a*]azepin-5(1*H*)-one, S5d



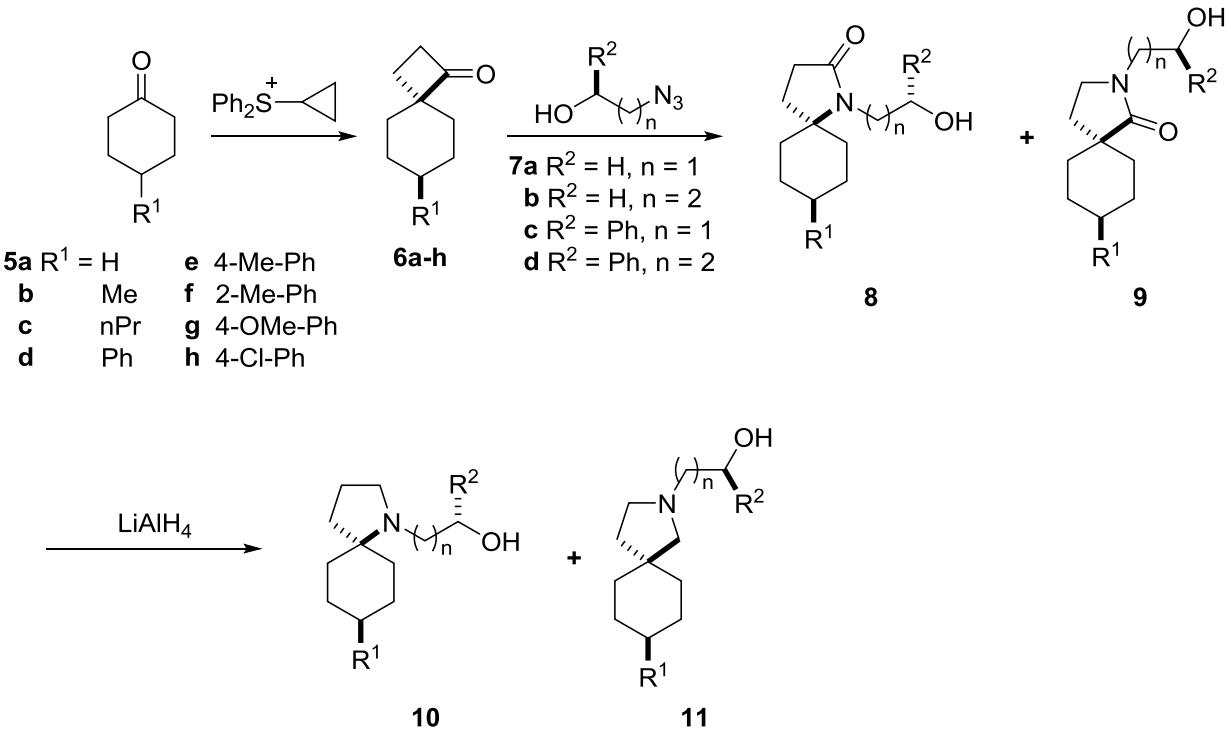
4d **S5d**

Following general procedure F, reaction of ketone **3d** (9.40 g, 30.2 mmol) provided the (9*R*,10*S*) isomer **4d** (6.85 g, 73%) and the (9*R*,10*R*) **S5d** isomer (1.05 g, 11%) as pale yellow oils. The (9*R*,10*R*) isomer solidified to a yellow solid upon standing. **(8a*S*,9*R*,10*S*,12a*R*) isomer 4d:** ν_{max} (film)/cm^{-1} 3376, 2926, 1604; δ_H (500 MHz, $CDCl_3$) 7.32-7.27 (2H, m), 7.23-7.17 (3H, m), 3.84-3.78 (1H, m), 3.39 (1H, ddd, *J* 12.3, 9.7, 7.7), 3.06 (1H, dd, *J* 3.6, 3.6), 2.79 (1H, dd, *J* 13.5, 8.2), 2.71-2.60 (2H, m), 2.53-2.43 (3H, m), 2.28 (1H, ddd, *J* 13.5, 13.5, 3.8), 2.14-2.10 (1H, m), 2.07-2.02 (1H, m), 1.87-1.55 (6H, m), 1.50-1.45 (1H, m), 1.38-1.33 (1H, m), 1.32-1.22 (1H, m); δ_C (125 MHz, $CDCl_3$) 174.4 (C), 140.3 (C), 128.7 (CH), 128.5 (CH), 126.2 (CH), 68.2 (C), 49.1 (CH_2), 48.5 (CH), 46.8 (CH), 45.1 (CH), 39.0 (CH_2), 38.9 (CH_2), 37.0 (CH_2), 32.0 (CH_2), 29.3 (CH_2), 24.4 (CH_2), 23.7 (CH_2), 20.1 (CH_2); *m/z* (ESI+) found $[M+H]^+$ 313.2282. $C_{20}H_{29}N_2O^+$ requires 313.2274. **(8a*S*,9*R*,10*R*,12a*R*) isomer S5d:** Mp 72-74 ^oC; ν_{max} (film)/cm^{-1} 3365, 2939, 1598; δ_H (500 MHz, $CDCl_3$) 7.30 (2H, t, *J* 7.3), 7.21 (1H, t, *J* 7.3), 7.16 (2H, t, *J* 7.3), 3.84-3.76 (1H, m), 3.28-3.23 (1H, m), 3.12 (1H, dd, *J* 13.8, 4.9), 2.94 (1H, ddd, *J* 11.2, 11.2, 5.4), 2.62-2.55 (2H, m), 2.43-2.36 (2H, m), 2.12 (1H, dddd, *J* 13.4, 13.4, 5.0, 1.3), 2.04-1.91 (3H, m), 1.84-1.76 (1H, m), 1.73-1.35 (6H, m), 1.29-1.17 (2H, m); δ_C (125 MHz, $CDCl_3$) 174.1 (C), 139.9 (C), 128.60

(CH), 128.59 (CH), 126.1 (CH), 67.2 (C), 49.1 (CH_2), 48.30 (CH), 48.26 (CH), 45.5 (CH), 39.3 (CH_2), 38.6 (CH_2), 35.3 (CH_2), 34.0 (CH_2), 28.2 (CH_2), 25.8 (CH_2), 23.0 (CH_2), 20.2 (CH_2); *m/z* (ESI+) found $[M+H]^+$ 313.2266. $C_{20}H_{29}N_2O^+$ requires 313.2274.

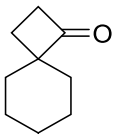
B. Experimental procedures and characterization data for cylindricine-inspired scaffolds.

Supplementary Figure 5. Synthesis of cyclindricine-inspired scaffolds



General procedure G: Synthesis of cyclobutanones **6a-h**

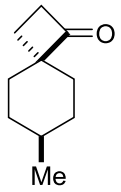
Spiro[3.5]nonan-1-on, 6a



In an analogous method to Guérot *et al*,[55] THF (110 mL) was added to solid potassium bis(trimethylsilyl)amide (7.5 g, 38 mmol) in an oven-dried flask. The solution was cooled to -45 °C and aged for 15 min. Cyclopropyldiphenylsulfonium tetrafluoroborate[56] (13.0 g, 41 mmol) was then added and the solution stirred at -45 °C for 30 min. A solution of cyclohexanone (2.8 mL, 27 mmol) in THF (25 mL) was then added and the solution was allowed to warm to room temperature over 4 h and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 x 50 mL). The combined organics were washed with water, dried ($MgSO_4$) and

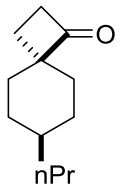
concentrated. The resulting oil was dissolved in anhydrous benzene (100 mL) and to the solution was added lithium tetrafluoroborate (0.10 g, 1.0 mmol). The solution was heated at reflux for 3 h, then cooled to room temperature and concentrated to an oil. The crude product was purified by automated column chromatography (40 g silica column, 0 to 10% EtOAc in hexanes over 30 min) to afford the title compound (2.2 g, 59%) as a colorless oil as a single diastereomer. The 1H and 13C NMR data closely matched that previously reported [57].

(4*S*,7*S*)-7-methylspiro[3.5]nonan-1-one, 6b



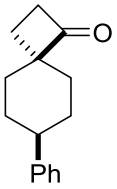
Following general procedure G, reaction with 4-methylcyclohexanone (1.8 mL, 15 mmol) provided the title compound (1.3 g, 62%) as a colorless viscous oil as a single diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92 – 2.85 (m, 2H), 2.00 – 1.89 (m, 2H), 1.70 (t, *J* = 8.5, 8.5 Hz, 2H), 1.59 – 1.48 (m, 2H), 1.46 – 1.36 (m, 2H), 1.35 – 1.24 (m, 3H), 0.88 (d, *J* = 5.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.3, 65.1, 41.3, 33.5, 32.1, 25.2; *m/z* (ESI+) found $[M+H]^+$ 153.1354. $C_{10}H_{17}O^+$ requires 153.1274.

(4*S*,7*S*)-7-propylspiro[3.5]nonan-1-one, 6c



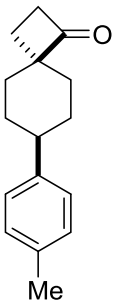
Following general procedure G, reaction with 4-propylcyclohexanone (2.0 mL, 13 mmol) provided the title compound (1.6 g, 74%) as a colorless oil as a single diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 – 2.74 (m, 2H), 1.90 – 1.79 (m, 2H), 1.67 – 1.56 (m, 2H), 1.54 – 1.44 (m, 2H), 1.35 – 1.25 (m, 2H), 1.24 – 1.12 (m, 4H), 1.12 – 1.00 (m, 3H), 0.75 (t, *J* = 7.1, 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.8, 65.0, 40.8, 38.5, 36.2, 32.9, 29.6, 24.7, 20.0, 14.4; *m/z* (ESI+) found $[M+H]^+$ 181.1581. $C_{12}H_{21}O^+$ requires 181.1587.

(4*S*,7*S*)-7-phenylspiro[3.5]nonan-1-one, 6d



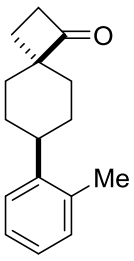
Following general procedure G, reaction with 4-phenylcyclohexanone (3.0 g, 17 mmol) provided the title compound (2.4 g, 70%, 20:1 dr) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.20 (m, 4H), 7.20 – 7.13 (m, 1H), 3.01 – 2.89 (m, 2H), 2.45 (tt, *J* = 12.0, 12.0, 3.6, 3.6 Hz, 1H), 2.17 – 2.04 (m, 2H), 1.99 – 1.83 (m, 2H), 1.82 – 1.71 (m, 4H), 1.58 (td, *J* = 13.3, 13.3, 3.8 Hz, 2H).^{13}C NMR (126 MHz, DMSO) δ 214.9, 146.7, 128.3, 126.5, 125.9, 63.2, 42.4, 40.5, 32.7, 30.7, 24.1; *m/z* (ESI+) found $[M+H]^+$ 215.1430. $C_{15}H_{19}O^+$ requires 215.1430.

(4*S*,7*S*)-7-(*p*-tolyl)spiro[3.5]nonan-1-one, 6e



Following general procedure G, reaction with 4-tolylcyclohexanone[58] (1.9 g, 10 mmol) provided the title compound (1.6 g, 72%, 7:1 dr) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.05 (m, 3H), 2.95 (t, *J* = 8.4, 8.4 Hz, 1H), 2.40 (tt, *J* = 12.0, 12.0, 3.6, 3.6 Hz, 1H), 2.29 (s, 2H), 2.10 (d, *J* = 13.8 Hz, 2H), 1.94 – 1.80 (m, 2H), 1.80 – 1.71 (m, 3H), 1.61 – 1.52 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 135.4, 129.0, 126.8, 64.1, 43.2, 40.8, 33.7, 31.1, 24.7, 20.9; *m/z* (ESI+) found $[M+H]^+$ 229.1577. $C_{16}H_{21}O^+$ requires 229.1587.

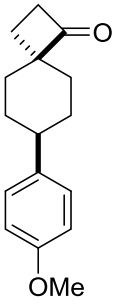
(4s,7s)-7-(*o*-tolyl)spiro[3.5]nonan-1-one, 6f



Following general procedure G, reaction with 4-*o*-tolylcyclohexanone[59] (4.0 g, 20.0 mmol) provided the title compound (3.1 g, 72%) as a colorless solid as a single diastereomer. ^{1}H NMR (400 MHz, CDCl3) δ 7.27 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.16 (td, *J* = 7.5, 1.8 Hz, 1H), 7.12 – 7.03 (m, 2H), 2.96 (t, *J* = 8.4 Hz, 2H), 2.65 (tt, *J* = 12.1, 3.3 Hz, 1H), 2.31 (s, 3H), 2.17 – 2.08 (m, 2H), 1.88 (ddd, *J* = 25.5, 13.3, 3.4

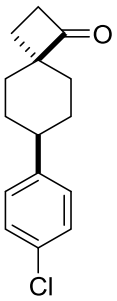
Hz, 2H), 1.78 (t, *J* = 8.4 Hz, 2H), 1.69 (dd, *J* = 13.8, 3.3 Hz, 2H), 1.65 – 1.56 (m, 2H).[13]C NMR (101 MHz, CDCl3) δ 215.3, 144.7, 134.9, 130.1, 126.2, 125.8, 125.7 , 64.2, 40.9, 39.1, 33.9, 30.2, 24.8, 19.4; *m/z* (ESI+) found $[M+H]^+$ 229.1557. $C_{16}H_{21}O^+$ requires 229.1587.

(4*S*,7*S*)-7-(4-methoxyphenyl)spiro[3.5]nonan-1-one, 6g



Following general procedure G, reaction with 4-methoxyphenylcyclohexanone[58] (1.0 g, 4.9 mmol) provided the title compound (0.89 g, 78%) as a colorless solid as a single diastereomer. [1]H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 3.77 (s, 3H), 2.95 (t, *J* = 8.4, 8.4 Hz, 2H), 2.39 (tt, *J* = 11.9, 11.9, 3.6, 3.6 Hz, 1H), 2.09 (d, *J* = 13.7 Hz, 2H), 1.97 – 1.69 (m, 6H), 1.68 – 1.48 (m, 2H). [13]C NMR (101 MHz, $CDCl_3$) δ 215.6, 158.0, 139.3, 127.9, 113.9, 64.3, 55.4, 42.9, 41.0, 33.9, 31.4, 24.9; *m/z* (ESI+) found $[M+H]^+$ 245.1551. $C_{16}H_{21}O_2^+$ requires 245.1536.

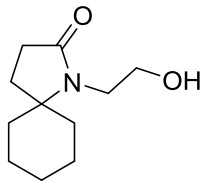
(4*S*,7*S*)-7-(4-chlorophenyl)spiro[3.5]nonan-1-one, 6h



Following general procedure G, reaction with 4-chlorophenylcyclohexanone[60] (1.6 g, 7.7 mmol) provided the title compound (1.2 g, 67%) as a colorless solid. [1]H NMR (500 MHz, DMSO) δ 7.40 – 7.27 (m, 2H), 7.27 – 7.13 (m, 2H), 3.08 – 2.86 (m, 2H), 2.50 – 2.44 (m, 1H), 2.06 (d, *J* = 13.8 Hz, 2H), 1.76 – 1.70 (m, 3H), 1.70 – 1.64 (m, 3H), 1.59 – 1.50 (m, 2H). [13]C NMR (126 MHz, DMSO) δ 214.9, 145.6, 130.4, 128.4, 128.2, 63.1, 41.7, 40.5, 32.6, 30.5, 24.0; *m/z* (ESI+) found $[M+H]^+$ 249.1048. $C_{15}H_{18}ClO^+$ requires 249.1041.

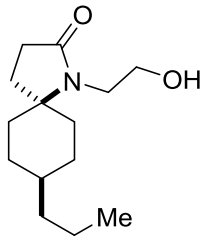
General procedure H: Azido Schmidt reaction with cyclobutanones **6**

1-(2-Hydroxyethyl)-1-azaspiro[4.5]decan-2-one, 8aa



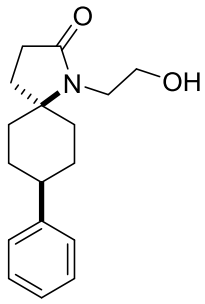
Boron trifluoride etherate (2.3 mL, 27 mmol) was added to a solution of cyclobutanone **6a** (0.75 g, 5.4 mmol) in dichloromethane (40 mL) at -78° C under argon. The mixture was stirred at -78° C for 30 min then a solution of azidoalcohol **7a** (1.4 g, 16 mmol) in dichloromethane (10 mL) was added. The solution was stirred at -78 °C for 3 h then allowed to warm to room temperature and stirred for an additional 12 h. The reaction was then concentrated on a rotary evaporator and the resulting oil was dissolved in 15% aqueous potassium hydroxide solution and stirred for 30 min, then extracted with dichloromethane (x 3). The combined organics were washed with water, dried ($MgSO_4$) and concentrated. The crude product was purified by automated column chromatography (40 g silica column, 0 to 100% EtOAc in hexanes over 30 min) to afford the title compound (0.74 g, 70%) as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (t, *J* = 5.3 Hz, 1H), 3.65 (q, *J* = 5.1 Hz, 2H), 3.34 – 3.20 (m, 2H), 2.33 (t, *J* = 8.1 Hz, 2H), 1.89 (t, *J* = 8.1 Hz, 2H), 1.72 – 1.57 (m, 3H), 1.44 (dd, *J* = 8.9, 3.0 Hz, 4H), 1.33 (ddt, *J* = 16.3, 8.1, 4.3 Hz, 2H), 1.03 (qt, *J* = 12.9, 3.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 64.6, 63.8, 43.0, 35.1, 29.2, 29.1, 25.0, 22.9.

(5*R*,8*S*)-1-(2-Hydroxyethyl)-8-propyl-1-azaspiro[4.5]decan-2-one, 8ca



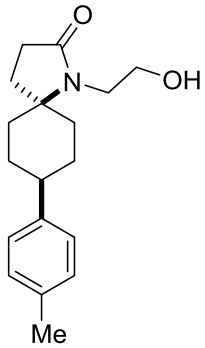
Following general procedure H, reaction with cyclobutanone **6c** (1.2 g, 6.7 mmol) and azidoalcohol **7a** (1.7 g, 20 mmol) provided the title compound (1.1 g, 68%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (t, *J* = 5.0, 5.0 Hz, 1H), 3.58 (q, *J* = 5.2, 5.2, 5.1 Hz, 2H), 3.21 (t, *J* = 5.5, 5.5 Hz, 2H), 2.25 (t, *J* = 8.1, 8.1 Hz, 2H), 1.84 (t, *J* = 8.1, 8.1 Hz, 2H), 1.68 – 1.35 (m, 7H), 1.31 – 1.04 (m, 6H), 0.79 (t, *J* = 7.0, 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 64.6, 62.9, 42.8, 32.4, 30.6, 29.5, 29.2, 29.0, 26.2, 20.8, 14.2; *m/z* (ESI+) found $[M+H]^+$ 240.1966. $C_{14}H_{26}NO_2^+$ requires 240.1955.

(5*S*,8*S*)-1-(2-Hydroxyethyl)-8-phenyl-1-azaspiro[4.5]decan-2-one, 8da



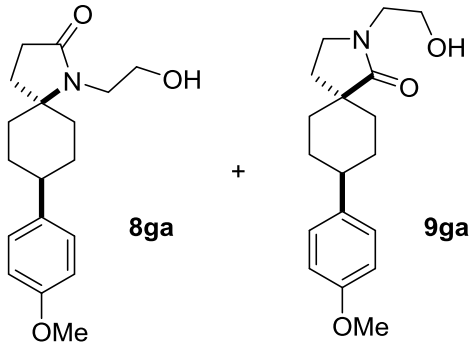
Following general procedure H, reaction with cyclobutanone **6d** (1.5 g, 7.0 mmol) and azidoalcohol **7a** (1.7 g, 21 mmol) provided the title compound (1.7 g, 87%) as a colorless oil. ^{1}H NMR (500 MHz, DMSO) δ 7.43 – 7.31 (m, 4H), 7.20 (td, *J* = 7.3, 0.4 Hz, 1H), 4.69 (br s, 1H), 3.28 (t, *J* = 6.9 Hz, 2H), 2.99 – 2.90 (m, 3H), 2.25 – 2.11 (m, 4H), 1.95 – 1.85 (m, 4H), 1.63 (td, *J* = 13.0, 3.6 Hz, 2H), 1.37 – 1.29 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 174.1, 143.4, 128.4, 127.2, 125.6, 62.6, 59.1, 41.9, 34.9, 30.7, 29.6, 28.7, 26.3; *m/z* (ESI+) found $[M+H]^+$ 274.1806. $C_{17}H_{24}NO_2^+$ requires 274.1798.

(5*S*,8*S*)-1-(2-Hydroxyethyl)-8-(p-tolyl)-1-azaspiro[4.5]decan-2-one, 8ea



Following general procedure H, reaction with cyclobutanone **6e** (800 mg, 3.5 mmol) and azidoalcohol **7a** (900 mg, 10.5 mmol) provided the title compound (860 mg, 85%) as a colorless oil. ^{1}H NMR (500 MHz, DMSO) δ 7.28 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 4.68 (br s, 1H), 3.28 (d, *J* = 7.1 Hz, 2H), 2.91 (t, *J* = 7.2 Hz, 3H), 2.28 (s, 3H), 2.21 (t, *J* = 7.9 Hz, 2H), 2.18 – 2.09 (m, 2H), 1.98 – 1.77 (m, 3H), 1.67 – 1.54 (m, 2H), 1.31 (d, *J* = 13.2 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 174.0, 140.1, 134.4, 129.0, 127.1, 62.7, 59.1, 41.8, 34.4, 30.5, 29.5, 28.7, 26.2, 20.5; *m/z* (ESI+) found $[M+H]^+$ 288.1968. $C_{18}H_{26}NO_2^+$ requires 288.1955.

(5*S*,8*S*)-1-(2-Hydroxyethyl)-8-(4-methoxyphenyl)-1-azaspiro[4.5]decan-2-one, 8ga and (5*S*,8*S*)-2-(2-Hydroxyethyl)-8-(4-methoxyphenyl)-2-azaspiro[4.5]decan-1-one, 9ga



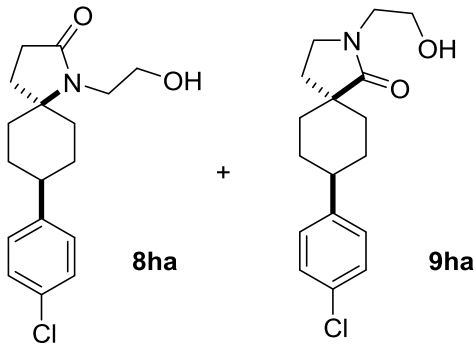
8ga **9ga**

Following general procedure H, reaction with cyclobutanone **6g** (1.0 g, 4.1 mmol) and azidoalcohol **7a** (1.1 g, 12.3 mmol) provided the title compounds **8ga** (930 mg, 75%) and **9ga** (120 mg, 10%) as colorless oils.

8ga: ^{1}H NMR (500 MHz, DMSO) δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.93 – 6.88 (m, 2H), 4.69 (t, *J* = 5.7 Hz, 1H), 3.74 (s, 3H), 3.30-3.26 (m, 2H), 2.97 – 2.85 (m, 3H), 2.21 (t, *J* = 7.9 Hz, 2H), 2.16 – 2.05 (m, 2H), 1.97 – 1.81 (m, 4H), 1.62 (td, *J* = 12.9, 12.9, 3.5 Hz, 2H), 1.30 (d, *J* = 13.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 174.0, 157.0, 134.9, 128.1, 113.6, 62.6, 59.0, 54.9, 41.8, 34.0, 30.4, 29.5, 28.7, 26.3; *m/z* (ESI+) found $[M+H]^+$ 304.1885. $C_{18}H_{26}NO_3^+$ requires 304.1913.

9ga: ^{1}H NMR (500 MHz, DMSO) δ 7.30 (d, *J* = 8.3 Hz, 2H), 6.92 – 6.86 (m, 2H), 4.69 (s, 1H), 3.78 – 3.66 (m, 3H), 3.31 – 3.25 (m, 3H), 2.99 – 2.85 (m, 3H), 2.21 (t, *J* = 7.9 Hz, 2H), 2.12 (dd, *J* = 14.1, 2.6 Hz, 2H), 1.97 – 1.81 (m, 3H), 1.62 (td, *J* = 12.9, 3.5 Hz, 2H), 1.30 (d, *J* = 13.2 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 174.0, 157.1, 134.9, 128.2, 113.7, 62.7, 59.1, 54.9, 41.8, 34.0, 30.5, 29.5, 28.7, 26.4; *m/z* (ESI+) found $[M+H]^+$ 304.1910. $C_{18}H_{26}NO_3^+$ requires 304.1913.

(5*S*,8*S*)-8-(4-Chlorophenyl)-1-(2-hydroxyethyl)-1-azaspiro[4.5]decan-2-one, 8ha and (5*S*,8*S*)-8-(4-chlorophenyl)-2-(2-hydroxyethyl)-2-azaspiro[4.5]decan-1-one, 9ha



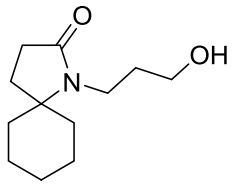
8ha **9ha**

Following general procedure H, reaction with cyclobutanone **6h** (500 mg, 2.0 mmol) and azidoalcohol **7a** (500 mg, 6.0 mmol) provided the title compounds **8ha** (450 mg, 72%) and **9ha** (40 mg, 7%) as colorless oils.

8ha: ^{1}H NMR (500 MHz, DMSO) δ 7.49 – 7.31 (m, 4H), 4.67 (t, *J* = 5.8 Hz, 1H), 3.31 – 3.24 (m, 2H), 3.00 – 2.85 (m, 3H), 2.22 (t, *J* = 7.9 Hz, 2H), 2.13 (d, *J* = 11.6 Hz, 2H), 1.98 – 1.82 (m, 4H), 1.68 – 1.51 (m, 2H), 1.32 (d, *J* = 13.3 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 174.1, 142.3, 130.2, 129.3, 128.2, 62.6, 59.1, 41.9, 34.4, 30.5, 29.5, 28.7, 26.1; *m/z* (ESI+) found $[M+H]^+$ 308.1402. $C_{17}H_{23}ClNO_2^+$ requires 308.1409.

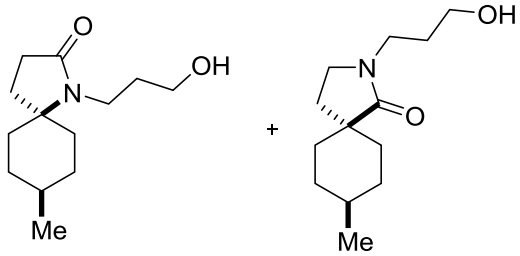
9ha: ^{1}H NMR (500 MHz, DMSO) δ 7.38 – 7.31 (m, 2H), 7.29 – 7.21 (m, 2H), 4.70 (t, *J* = 5.2 Hz, 1H), 3.47 (dd, *J* = 10.8, 5.6 Hz, 2H), 3.35 (d, *J* = 4.7 Hz, 2H), 3.21 (t, *J* = 5.9 Hz, 2H), 2.54 (dd, *J* = 7.9, 3.6 Hz, 1H), 2.16 (qd, *J* = 12.7, 3.5 Hz, 2H), 1.84 (d, *J* = 13.8 Hz, 2H), 1.76 (t, *J* = 6.8 Hz, 2H), 1.64 – 1.51 (m, 2H), 1.41 (td, *J* = 13.2, 3.8 Hz, 2H); ^{13}C NMR (126 MHz, DMSO) δ 177.6, 146.1, 130.2, 128.6, 128.2, 58.6, 44.6, 43.9, 41.7, 41.1, 34.6, 33.7, 28.9; *m/z* (ESI+) found $[M+H]^+$ 308.1420. $C_{17}H_{23}ClNO_2^+$ requires 308.1417.

1-(3-hydroxypropyl)-1-azaspiro[4.5]decan-2-one, 8ab



Following general procedure H, reaction with cyclobutanone **6a** (500 mg, 2.0 mmol) and azidoalcohol **7b** (1.8 g, 17.4 mmol) provided the title compound (430 mg, 35%) as a colorless oil. ^{1}H NMR (500 MHz, DMSO) δ 4.70 (t, *J* = 5.7 Hz, 1H), 3.43 – 3.33 (m, 3H), 3.10 (t, *J* = 7.2 Hz, 2H), 2.18 (t, *J* = 8.0 Hz, 2H), 1.81 (t, *J* = 8.0 Hz, 2H), 1.68 – 1.60 (m, 2H), 1.56 (dd, *J* = 11.7, 5.2 Hz, 2H), 1.51 (dd, *J* = 13.0, 3.9 Hz, 2H), 1.42 – 1.26 (m, 4H), 1.15 – 1.01 (m, 1H). ^{13}C NMR (126 MHz, DMSO) δ 174.0, 63.0, 59.5, 41.4, 40.7, 34.5, 28.7, 28.4, 24.5, 22.6; *m/z* (ESI+) found $[M+H]^+$ 212.1650. $C_{12}H_{22}NO_2^+$ requires 212.1642.

(5*S*,8*S*)-1-(3-Hydroxypropyl)-8-methyl-1-azaspiro[4.5]decan-2-one, 8bb and (5*S*,8*S*)-2-(3-hydroxypropyl)-8-methyl-2-azaspiro[4.5]decan-1-one, 9bb



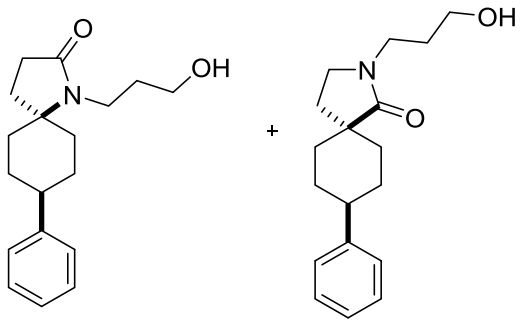
8bb **9bb**

Following general procedure H, reaction with cyclobutanone **6b** (750 mg, 4.9 mmol) and azidoalcohol **7b** (1.5 g, 15 mmol) provided the title compounds **8bb** (440 mg, 40%) and **9bb** (500 mg, 45%) as colorless oils.

8bb: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 – 3.42 (m, 2H), 3.38 – 3.25 (m, 2H), 2.33 (t, *J* = 7.9 Hz, 2H), 1.87 (dd, *J* = 9.9, 6.1 Hz, 3H), 1.78 (td, *J* = 13.2, 3.9 Hz, 2H), 1.69 – 1.53 (m, 5H), 1.51 – 1.39 (m, 2H), 1.19 (d, *J* = 12.9 Hz, 2H), 0.95 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 65.1, 58.2, 35.2, 33.2, 29.21, 29.20, 29.1, 28.3, 25.6, 17.0; *m/z* (ESI+) found $[M+H]^+$ 226.1778. $C_{13}H_{24}NO_2^+$ requires 226.1798.

9bb: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 1H), 3.43 (t, *J* = 5.5 Hz, 2H), 3.40 – 3.29 (m, 2H), 3.21 (t, *J* = 6.9 Hz, 2H), 1.92 – 1.74 (m, 4H), 1.67 – 1.58 (m, 2H), 1.58 – 1.40 (m, 6H), 1.32 – 1.14 (m, 2H), 0.91 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 58.0, 44.3, 38.5, 33.3, 32.0, 30.0, 29.4, 29.3, 20.3; *m/z* (ESI+) found $[M+H]^+$ 226.1776. $C_{13}H_{24}NO_2^+$ requires 226.1798.

(5*S*,8*S*)-1-(3-hydroxypropyl)-8-phenyl-1-azaspiro[4.5]decan-2-one, 8db and (5*S*,8*S*)-2-(3-hydroxypropyl)-8-phenyl-2-azaspiro[4.5]decan-1-one, 9db



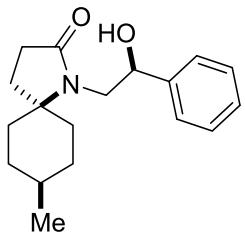
8db **9db**

Following general procedure H, reaction with cyclobutanone **6d** (1.5 g, 7.0 mmol) and azidoalcohol **7b** (2.1 g, 21 mmol) provided the title compounds **8db** (840 mg, 42%) and **9db** (800 mg, 40%) as colorless oils.

8db: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 4.4 Hz, 4H), 7.19 – 7.12 (m, 1H), 4.25 (s, 1H), 3.42 (t, *J* = 5.7 Hz, 2H), 3.23 – 3.11 (m, 2H), 3.03 – 2.90 (m, 1H), 2.36 (dd, *J* = 8.4, 7.4 Hz, 2H), 2.19 (dtd, *J* = 12.0, 4.1, 3.5, 1.7 Hz, 2H), 1.95 (t, *J* = 7.9 Hz, 2H), 1.93 – 1.81 (m, 2H), 1.74 (td, *J* = 12.9, 3.7 Hz, 2H), 1.55 – 1.39 (m, 2H), 1.32 (dt, *J* = 13.4, 3.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 143.0, 128.5, 127.2, 125.9, 64.6, 58.1, 35.4, 35.3, 33.0, 31.0, 30.3, 29.2, 26.8.

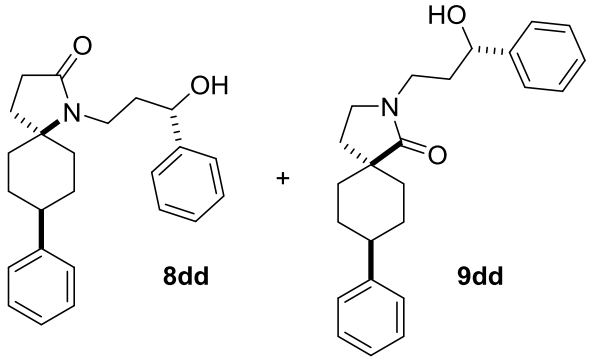
9db: ^{1}H NMR (500 MHz, DMSO) δ 7.31 – 7.26 (m, 2H), 7.25 – 7.19 (m, 2H), 7.19 – 7.13 (m, 1H), 4.45 (br s, 1H), 3.43 – 3.36 (m, 2H), 3.27 (t, *J* = 6.8 Hz, 2H), 3.20 (t, *J* = 7.1 Hz, 2H), 2.58 – 2.51 (m, 1H), 2.25 – 2.12 (m, 2H), 1.82 (d, *J* = 13.8 Hz, 2H), 1.77 (t, *J* = 6.8 Hz, 2H), 1.63 – 1.53 (m, 3H), 1.42 (td, *J* = 13.3, 3.8 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 177.5, 147.1, 128.3, 126.7, 125.8, 58.4, 43.1, 42.4, 41.3, 39.0, 34.6, 33.9, 30.1, 29.0; *m/z* (ESI+) found $[M+H]^+$ 288.1936. $C_{18}H_{26}NO_2^+$ requires 288.1955.

(5*S*,8*R*)-1-((*S*)-2-Hydroxy-2-phenylethyl)-8-methyl-1-azaspiro[4.5]decan-2-one, 8bc



Following general procedure H, reaction with cyclobutanone **6b** (500 mg, 3.3 mmol) and azidoalcohol **7c** (1.6 g, 9.9 mmol) provided the title compound (520 mg, 55%) as a colorless oil. ^{1}H NMR (500 MHz, DMSO) δ 7.37 – 7.30 (m, 4H), 7.26 – 7.20 (m, 1H), 5.49 (d, *J* = 4.5 Hz, 1H), 4.88 (dt, *J* = 7.3, 4.9 Hz, 1H), 3.26 – 3.10 (m, 2H), 2.22 (t, *J* = 8.1 Hz, 2H), 1.89 – 1.66 (m, 4H), 1.64 – 1.51 (m, 2H), 1.51 – 1.42 (m, 1H), 1.38 (d, *J* = 13.3 Hz, 1H), 1.33 – 1.23 (m, 1H), 1.18 (dd, *J* = 13.0, 2.4 Hz, 1H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.80 (dd, *J* = 12.4, 2.5 Hz, 1H).; ^{13}C NMR (126 MHz, DMSO) δ 175.1, 143.9, 127.9, 127.0, 126.0, 70.7, 63.4, 48.4, 28.8, 28.6, 28.4, 28.1, 27.9, 27.9, 25.2, 16.9; *m/z* (ESI+) found $[M+H]^+$ 288.1973. $C_{18}H_{26}NO_2^+$ requires 288.1958.

(5*S*,8*R*)-1-((*S*)-3-Hydroxy-3-phenylpropyl)-8-phenyl-1-azaspiro[4.5]decan-2-one, 8dd and (5*S*,8*R*)-2-((*S*)-3-hydroxy-3-phenylpropyl)-8-phenyl-2-azaspiro[4.5]decan-1-one, 9dd

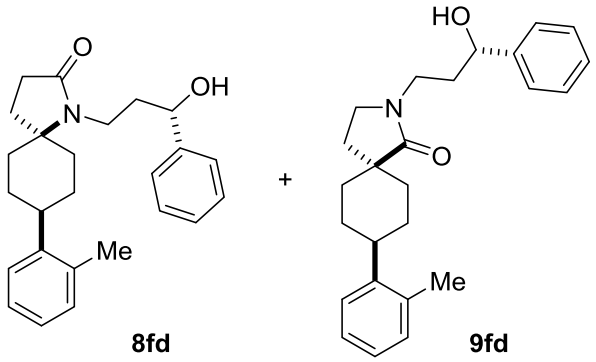


Following general procedure H, reaction with cyclobutanone **6d** (500 mg, 2.3 mmol) and azidoalcohol **7d** (1.2 g, 6.6 mmol) provided the title compounds **8dd** (340 mg, 40%) and **9dd** (340 mg, 40%) as colorless oils.

8dd: ^{1}H NMR (500 MHz, DMSO) δ 7.32 (d, *J* = 4.4 Hz, 4H), 7.29 – 7.22 (m, 4H), 7.22 – 7.17 (m, 2H), 5.26 (d, *J* = 4.3 Hz, 1H), 4.52 – 4.38 (m, 1H), 3.10 – 2.95 (m, 2H), 2.94 – 2.85 (m, 1H), 2.26 – 2.17 (m, 2H), 2.08 (d, *J* = 11.3 Hz, 2H), 1.97 – 1.82 (m, 4H), 1.76 – 1.59 (m, 4H), 1.38 – 1.28 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 173.8, 145.4, 143.7 (u)), 128.3, 128.0, 127.2, 126.7, 125.6, 125.6, 70.3, 62.8, 39.2, 36.7, 35.6, 31.3, 30.9, 30.3, 28.8, 26.6, 26.6; *m/z* (ESI+) found $[M+H]^+$ 364.2286. $C_{24}H_{30}NO_2^+$ requires 364.2285.

9dd: ^{1}H NMR (500 MHz, DMSO) δ 7.29 (m, 10H), 5.32 (s, 1H), 4.55 (s, 1H), 3.40, 3.26 (s, 4H), 2.51 (s, 1H), 2.21 (d, *J* = 11.0 Hz, 2H), 1.77 (m, 6H), 1.58 (d, *J* = 7.9 Hz, 2H), 1.41 (d, *J* = 10.8 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 177.5, 147.1, 145.9, 128.2, 128.0, 126.7, 126.7, 125.7, 125.7, 70.3, 43.1, 42.5, 41.3, 39.2, 36.8, 34.6, 33.9, 29.0; *m/z* (ESI+) found $[M+H]^+$ 364.2286. $C_{24}H_{30}NO_2^+$ requires 364.2271.

(5*S*,8*R*)-1-((*S*)-3-Hydroxy-3-phenylpropyl)-8-(o-tolyl)-1-azaspiro[4.5]decan-2-one, 8fd and (5*S*,8*R*)-2-((*S*)-3-hydroxy-3-phenylpropyl)-8-(o-tolyl)-2-azaspiro[4.5]decan-1-one, 9fd



8fd **9fd**

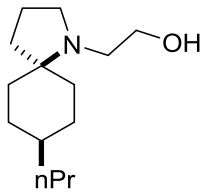
Following general procedure H, reaction with cyclobutanone **6f** (500 g, 2.2 mmol) and azidoalcohol **7b** (1.2 g, 6.6 mmol) provided the title compounds **8fd** (310 mg, 38%) and **9fd** (330 mg, 40%) as colorless oils.

8fd: ^{1}H NMR (500 MHz, DMSO) δ 7.35 – 7.27 (m, 4H), 7.26 – 7.19 (m, 2H), 7.18 – 7.12 (m, 2H), 7.11 – 7.07 (m, 1H), 5.36 (d, *J* = 4.2 Hz, 1H), 4.64 – 4.48 (m, 1H), 3.44 – 3.36 (m, 1H), 3.34 – 3.26 (m, 1H), 3.03 – 2.88 (m, 1H), 2.28 (s, 3H), 2.26 – 2.20 (m, 2H), 1.96 – 1.70 (m, 10H), 1.62 – 1.45 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 173.9, 145.6, 144.2, 135.2, 130.3, 128.0, 126.7, 126.0, 125.8, 125.6, 70.4, 61.7, 40.4, 39.3, 38.0, 34.4, 33.9, 33.7, 32.7, 28.9, 27.3, 27.2, 19.2; *m/z* (ESI+) found $[M+H]^+$ 378.2438. $C_{25}H_{32}NO_2^+$ requires 378.2428.

9fd: ^{1}H NMR (500 MHz, DMSO) δ 7.39 – 7.35 (m, 2H), 7.35 – 7.29 (m, 2H), 7.26 – 7.19 (m, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 7.0 Hz, 1H), 7.04 (td, *J* = 7.4, 1.2 Hz, 1H), 5.33 (d, *J* = 4.4 Hz, 1H), 4.63 – 4.46 (m, 1H), 3.29 (t, *J* = 7.4 Hz, 2H), 3.25 (t, *J* = 6.8 Hz, 2H), 2.75 – 2.63 (m, 1H), 2.29 (s, 3H), 2.27 – 2.14 (m, 2H), 1.89 – 1.82 (m, 2H), 1.82 – 1.75 (m, 2H), 1.75 – 1.68 (m, 2H), 1.54 – 1.38 (m, 4H); ^{13}C NMR (126 MHz, DMSO) δ 177.5, 145.9, 145.3, 134.6, 130.0, 128.0, 126.7, 126.0, 125.7, 125.4, 70.3, 43.1, 41.1, 39.1, 38.7, 36.8, 35.0, 34.6, 34.5, 28.4, 19.0; *m/z* (ESI+) found $[M+H]^+$ 378.2449. $C_{25}H_{32}NO_2^+$ requires 378.2428.

General procedure I: Lactam reduction

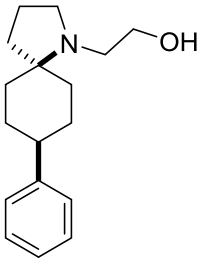
2-((5*R,8*S**)-8-propyl-1-azaspiro[4.5]decan-1-yl)ethanol, 10ca**



Lithium aluminum hydride (1M solution in diethyl ether, 2.5 mL, 2.5 mmol) was added to a solution of lactam **8ca** (0.14 g, 0.56 mmol) in anhydrous THF (2.0 mL) under argon. The reaction was heated

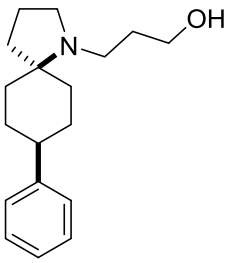
at reflux for 8 h, then cooled to 0° C and quenched by slow addition of sodium sulfate decahydrate (excess). The reaction was allowed to warm to rt and filtered through Celite® to remove the salts. The filtrate was concentrated, dissolved in ethyl acetate (50 mL), and washed with brine (3x50 mL). The combined organics were dried (Na_2SO_4) and concentrated to afford the title compound (0.10 g, 78%) as a colorless solid, which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 – 3.60 (m, 4H), 3.56 (t, *J* = 5.4 Hz, 2H), 2.86 – 2.76 (m, 1H), 2.65 (t, *J* = 5.4 Hz, 1H), 1.73 (dd, *J* = 4.1, 2.5 Hz, 3H), 1.70 – 1.58 (m, 5H), 1.58 – 1.47 (m, 4H), 1.27 (ddd, *J* = 7.0, 4.4, 2.7 Hz, 3H), 1.09 (s, 1H), 0.96 – 0.82 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 62.4, 62.3, 58.8, 50.0, 49.7, 34.1, 33.0, 31.9, 29.9, 27.6, 27.0, 21.0, 14.3; *m/z* (ESI+) found $[M+H]^+$ 226.2220. $C_{14}H_{28}NO^+$ requires 226.2165.

2-((5*R*,8*S*)-8- Phenyl -1-azaspiro[4.5]decan-1-yl)ethanol, 10da



Following general procedure I, reaction with lactam **8da** (2.2 g, 8.1 mmol) provided the title compound (1.4 g, 65%) as an oil.^{1}H NMR (500 MHz, DMSO) δ 7.39 – 7.26 (m, 4H), 7.17 (ddt, *J* = 8.5, 6.4, 1.8 Hz, 1H), 4.28 (s, 1H), 3.39 – 3.35 (m, 2H), 2.88 – 2.78 (m, 1H), 2.74 (t, *J* = 7.0 Hz, 2H), 2.35 (t, *J* = 6.8 Hz, 2H), 2.13 – 1.99 (m, 2H), 1.81 – 1.65 (m, 4H), 1.65 – 1.59 (m, 2H), 1.59 – 1.49 (m, 2H), 1.29 – 1.12 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 144.7, 128.2, 127.0, 125.4, 62.9, 60.7, 50.6, 50.5, 37.7, 35.2, 29.4, 28.0, 20.8; *m/z* (ESI+) found $[M+H]^+$ 260.1989. $C_{17}H_{26}NO^+$ requires 260.1976.

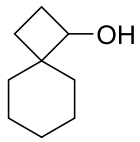
(5*S*,8*S*)-1-(3-Hydroxypropyl)-8-phenyl-1-azaspiro[4.5]decan-2-one , 10db



Following general procedure I, reaction with lactam **8db** (1.0 g, 3.5 mmol) provided the title compound (620 mg, 65%) as an oil.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dt, *J* = 12.9, 7.5 Hz, 4H), 7.16 – 7.08 (m, 1H), 3.83 – 3.67 (m, 2H), 2.88 – 2.82 (m, 2H), 2.79 (q, *J* = 5.4 Hz, 1H), 2.61 – 2.48 (m, 2H), 2.02 (ddd, *J* = 12.2, 6.5, 2.9 Hz, 2H), 1.79 – 1.56 (m, 10H), 1.22 (ddd, *J* = 17.7, 7.8, 4.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1, 128.3, 127.3, 125.6, 65.2, 64.0, 50.0, 49.3, 38.8, 35.5, 29.8, 28.5, 20.8.

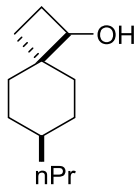
General procedure J: Cyclobutanone reduction

Spiro[3.5]nonan-1-ol, S9a



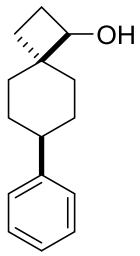
Sodium borohydride (2.5 g, 66 mmol) was added to a solution of cyclobutanone **6a** (3.6 g, 26 mmol) in THF (120 mL), followed by dropwise addition of methanol (12 ml). The solution was stirred at room temperature for 8 h. The reaction was quenched by the slow addition of acetone at 0° C. Water was then added and the solution extracted dichloromethane (x3). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified by automated column chromatography (40 g silica column, 0 to 30% EtOAc in hexanes over 30 min) to afford the title compound (3.5 g, 95%) as a colorless oil. The NMR data closely matched that previously reported[61].

(1*R*,4*R*,7*S*)-7-Propylspiro[3.5]nonan-1-ol, S9c



Following general procedure J, reaction with ketone **6c** (1.8 g, 10 mmol) provided the title compound (1.7 g, 94%) as a colorless oil.^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (t, *J* = 7.4 Hz, 1H), 2.24 – 2.09 (m, 1H), 2.01 – 1.92 (m, 1H), 1.70 (dddd, *J* = 11.7, 10.4, 9.0, 7.2 Hz, 1H), 1.62 – 1.46 (m, 3H), 1.45 – 1.38 (m, 1H), 1.32 – 1.09 (m, 9H), 1.09 – 0.95 (m, 1H), 0.82 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 74.9, 45.2, 38.5, 37.9, 36.1, 30.3, 30.1, 29.3, 27.3, 26.6, 20.2, 14.4 (dn).

(1*R*,4*S*,7*S*)-7-Phenylspiro[3.5]nonan-1-ol, S9d

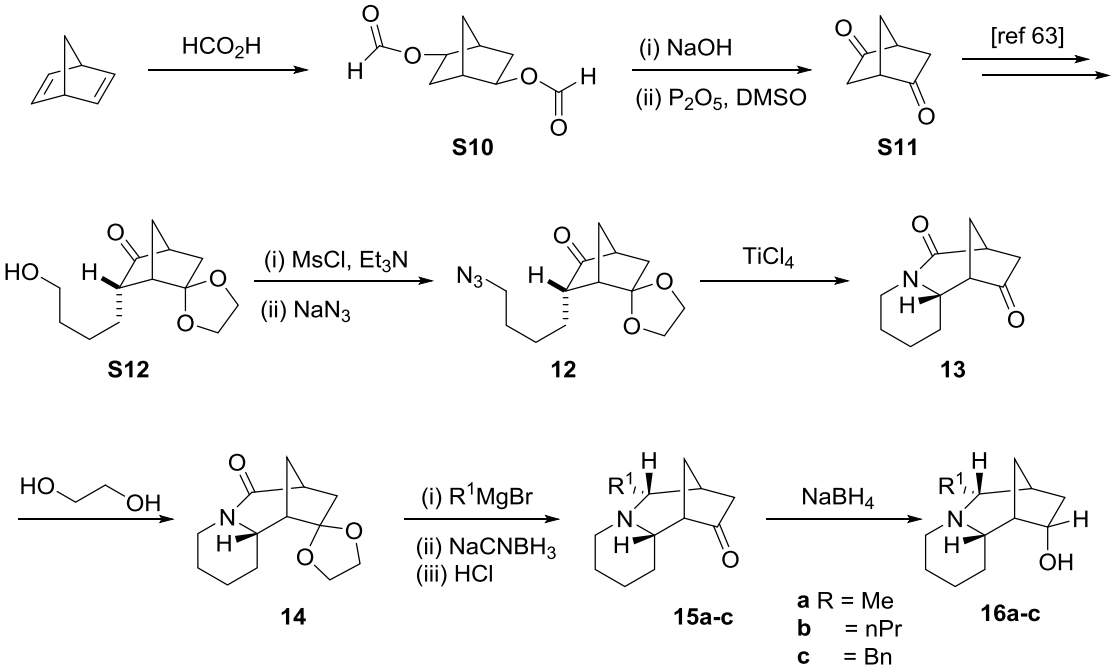


Following general procedure J, reaction with ketone **6d** (5.4 g, 25 mmol) provided the title compound (5.3 g, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.19 (m, 5H), 4.10 (t, *J* = 7.3 Hz, 1H), 2.53 (qd, *J* = 9.7, 8.5, 3.2 Hz, 1H), 2.40 – 2.24 (m, 2H), 1.88 – 1.77 (m, 5H), 1.75 – 1.63 (m,

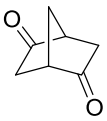
1H), 1.62 – 1.50 (m, 2H), 1.49 – 1.30 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5, 128.3, 126.9, 125.9, 75.0, 44.6, 43.7, 39.1, 31.9, 31.9, 30.7, 27.5, 26.9.

C. Experimental procedures and characterization data for sparteine-inspired scaffolds.

Supplementary Figure 6. Synthesis of sparteine-inspired scaffolds



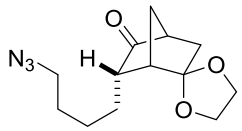
Bicyclo[2.2.1]heptane-2,5-dione, S11



In a 1L round bottom flask, 2, 5-norbornadiene (100 g, 1.08 mol) and 97% formic acid (600 mL) was added under an argon atmosphere. The reaction was refluxed at 120 °C for 24h then the formic acid was distilled off and the diformate **S10** was obtained by vacuum distillation (120-130 ºC at 10 mmHg) as a clear liquid. The crude diformate (198.7 g, 1.07 mol) was placed in a 3L round bottom flask and dissolved in THF (1.5 l). The solution was cooled to 0 °C and a solution of NaOH (424 g) in water (600 mL) was added via a dropping funnel over 30 min. The reaction mixture was stirred at room temperature for 10 h then extracted with ethyl acetate. The aqueous layer was saturated with sodium chloride then extracted again with ethyl acetate. The combined organics were dried ($MgSO_4$) and concentrated to obtain the crude diol (100 g) as a colorless solid. The diol was vacuum dried for 4h and transferred to a three-neck 4L round bottom flask fitted with a mechanical stirrer. Anhydrous dimethylsulfoxide (225 mL) was added and the mixture was stirred till the solution became

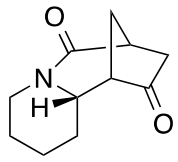
completely clear. The solution was diluted with dichloromethane (800 mL) and phosphorous pentoxide (450 g, 1.58 mol) was added. The reaction mixture was stirred vigorously for 1h at rt then cooled to 0 ºC and triethylamine (661 mL, 4.75 mol) was added dropwise over 1 h. After the addition was complete, the reaction was stirred at 0 ºC for 1 h, then quenched with 10% aqueous HCl (800 mL) and extracted with dichloromethane (4 x 600 mL). The combined organics were dried ($MgSO_4$) and concentrated. The crude product was purified chromatography (silica gel, 70:30 hexanes: ethyl acetate) to obtain the title compound (80 g, 60%) as a colorless oil. δ_H (400 MHz, $CDCl_3$) 2.98 – 2.77 (m, 2H), 2.36 – 2.14 (m, 2H), 2.11 – 1.80 (m, 4H); δ_C (100 MHz, $CDCl_3$) 212.3, 48.5, 38.8, 36.2. The spectral data was consistent with that previously reported.[62]

(1*S*,4*S*,6*S*)-6-(4-azidobutyl)spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolan]-5-one, 12



Methanesulfonyl chloride (4.83 mL, 62.4 mmol) was added dropwise to a solution of (1*S*,4*S*,6*S*)-6-(4-hydroxybutyl)spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolan]-5-one (**S12**)[63] (10 g, 41.6 mmol) in dichloromethane (200 mL) at 0 °C under argon. Triethylamine (8.68 mL, 62.4 mmol) was then added dropwise and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated to afford the crude mesylate product. The product was dried over high vacuum for 30 min and the residue was dissolved in DMF (100 mL). Sodium azide (9.42 g, 14.5 mmol) was added to the solution and the mixture was heated at 50 ºC for 7 h, then diluted with water and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated. The crude product was purified by chromatography (90:10 hexanes/ethyl acetate) to afford the title compound (10.1 g, 92%) as a colorless liquid. δ_H (400 MHz, $CDCl_3$) 4.15 – 3.57 (m, 2H), 3.27 (t, *J* = 6.8 Hz, 2H), 2.56 (dd, *J* = 38.1, 3.6 Hz, 2H), 2.23 – 1.97 (m, 3H), 1.92 – 1.26 (m, 8H); δ_C (100 MHz, $CDCl_3$) 217.7, 115.0, 65.4, 63.5, 52.7, 51.2, 49.2, 45.9, 39.1, 36.5, 28.8, 26.7, 25.7. The spectral data was consistent with that previously reported.[63]

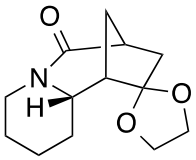
(7*S*,10*S*,10a*S*)-octahydro-7,10-methanopyrido[1,2-*a*]azepine-6,9-dione, 13



$TiCl_4$ (20.7 mL, 188.5 mmol) was added dropwise by syringe to a solution of azide **12** (10.0 g, 37.7 mmol) in dichloromethane (350 mL) at 0 °C under argon. The resulting yellow precipitate was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched with water and extracted with dichloromethane. The combined organics were dried (Na_2SO_4) and concentrated to afford an oil. The crude product was purified by chromatography (silica gel, 100% EtOAc) to afford

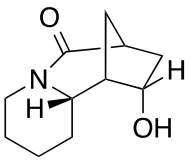
the title compound (4.5 g, 62%) as a colorless solid. δ_H (400 MHz, $CDCl_3$) 4.53 (ddt, *J* = 13.4, 4.1, 2.0 Hz, 1H), 3.30 (ddd, *J* = 11.8, 4.2, 2.6 Hz, 1H), 3.05 (dt, *J* = 5.4, 1.9 Hz, 1H), 2.47 (dt, *J* = 5.7, 3.4 Hz, 1H), 2.41 – 2.24 (m, 3H), 2.18 – 2.02 (m, 2H), 1.85 – 1.51 (m, 3H), 1.40 – 1.10 (m, 3H); δ_C (100 MHz, $CDCl_3$) 214.7, 171.7, 59.2, 50.5, 43.7, 41.8, 41.0, 30.6, 30.6, 25.0, 24.2. The spectral data was consistent with that previously reported.[63]

(7*S*,10*S*,10a*S*)-hexahydro-1*H*-spiro[7,10-methanopyrido[1,2-*a*]azepine-9,2'-[1,3]dioxolan]-6(2*H*)-one, 14



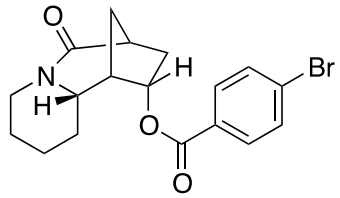
Chlorotrimethylsilane (13.1 mL, 103 mmol) was added dropwise to a solution of lactam **13** (5.0 g, 25.9 mmol) in dry ethylene glycol (80 mL) at room temperature under argon. The reaction mixture was stirred for 6 h at room temperature then water (50 mL) was added and the mixture extracted with diethyl ether (3 x 50 mL). The combined organics were dried (Na_2SO_4) and concentrated. The crude product was purified by chromatography (silica gel, 70:30 ethyl acetate/hexanes) to afford the title compound (4.29 g, 70%) as a colorless solid. Mp 90-91 °C; ν_{max} (film)/cm^{-1} 2940, 1638; δ_H (400 MHz, $CDCl_3$) 4.52 (1H, ddt, *J* 13.3, 4.2, 2.0), 4.04–3.69 (4H, m), 3.19 (1H, dt, *J* 12.3, 2.9), 2.69 (1H, ddd, *J* 7.3, 4.5, 1.6), 2.36 (1H, td, *J* 13.0, 3.2), 2.27–1.98 (5H, m), 1.87–1.73 (2H, m), 1.70–1.58 (1H, m), 1.58–1.46 (1H, m), 1.42–1.16 (2H, m); δ_C (100 MHz, $CDCl_3$) 174.3, 117.1, 65.2, 63.3, 61.2, 46.0, 42.2, 42.0, 41.2, 32.5, 29.8, 25.3, 25.0; *m/z* (ESI+) found $[M+H]^+$ 238.143. $C_{13}H_{20}NO_3^+$ requires 238.1438.

(7*S*,9*S*,10*S*,10a*S*)-9-hydroxyoctahydro-7,10-methanopyrido[1,2-*a*]azepin-6(2*H*)-one, S13



Sodium borohydride (196 mg, 5.18 mmol) was added to a solution of lactam **13** (500 mg, 2.58 mmol) in methanol (25 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h, then quenched with 10% aqueous NaOH and extracted with ethyl acetate. The combined organics were dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography (silica gel, 100% ethyl acetate) to afford the title compound (444 mg, 88%) as a colorless solid as a single diastereomer. Mp 110-111 °C; ν_{max} (film)/cm^{-1} 1623, 2931, 3355 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.60 – 4.38 (m, 2H), 3.32 (d, *J* = 12.4 Hz, 1H), 3.12 (s, 1H), 2.67 – 2.51 (m, 1H), 2.48 – 2.19 (m, 4H), 1.80 (dd, *J* = 12.8, 1.6 Hz, 1H), 1.75 – 1.53 (m, 5H), 1.43 – 1.10 (m, 2H); δ_C (100 MHz, $CDCl_3$) 175.1, 75.3, 62.7, 43.1, 42.2, 42.1, 38.3, 31.8, 30.6, 25.5, 25.2; *m/z* (ESI+) found $[M+H]^+$ 196.1330. $C_{11}H_{18}NO_2^+$ requires 196.1332.

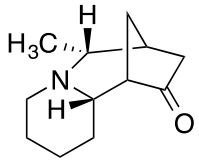
(7*S*,9*S*,10*S*,10a*S*)-6-oxodecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl 4-bromobenzoate, S14



To a solution of alcohol **S13** (50 mg, 0.25 mmol) in dichloromethane (3 mL) was added triethylamine (0.071 mL, 0.51 mmol) and *N*,*N*-dimethylaminopyridine (2 mg). *p*-Bromobenzoyl chloride (84 mg, 0.38 mmol) was then added and the reaction mixture stirred at room temperature for 8 h. The solvent was evaporated and the crude reaction mixture was purified by chromatography (silica gel, 60:40 ethyl acetate/hexanes) to obtain the title compound (89 mg, 92%) as a colorless solid. Mp 130-132 °C; ν_{max} (film)/cm^{-1} 1647, 1716, 2938; δ_H (400 MHz, $CDCl_3$) 7.93 – 7.76 (m, 2H), 7.67 – 7.50 (m, 2H), 5.50 – 5.37 (m, 1H), 4.66 – 4.52 (m, 1H), 3.36 (ddd, *J* = 12.3, 7.5, 4.7 Hz, 1H), 2.83 – 2.70 (m, 2H), 2.56 (m,1H), 2.41 (td, *J* = 13.0, 3.1 Hz, 1H), 2.00 – 1.80 (m, 4H), 1.81 – 1.53 (m, 3H), 1.45 – 1.13 (m, 2H); δ_C (100 MHz, $CDCl_3$) 174.2, 165.9, 132.0, 131.2, 128.9, 128.5, 77.1, 62.2, 42.2, 41.6, 41.5, 35.2, 31.8, 30.5, 25.6, 25.3; *m/z* (ESI+) found $[M+H]^+$ 378.0695. $C_{18}H_{21}BrNO_3^+$ requires 378.0699.

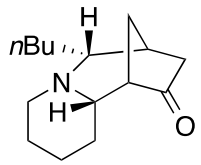
General procedure K: Grignard addition to lactam; reduction of aminal

(6*R*,7*S*,10*S*,10a*S*)-6-methyloctahydro-7,10-methanopyrido[1,2-*a*]azepin-9(6*H*)-one, 15a



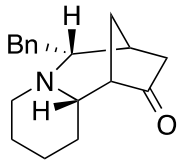
MeMgCl (2.8 mL, 8.4 mmol, 3M in THF) was added dropwise to a stirring solution of lactam **13** (500 mg, 2.1 mmol) in dry THF (20 mL). The mixture was heated at 60 °C for 3 h, then cooled to 0 °C and $NaBH_3CN$ (792 mg, 12.6 mmol) added followed by glacial acetic acid (1.0 mL). The reaction mixture was stirred for 1 h at room temperature then quenched with 10% aqueous NaOH (10 mL) and extracted with ethyl acetate (3 x 50mL). The combined organics were dried ($MgSO_4$) and concentrated. The residue was dissolved in conc. HCl (2 mL) and acetone (20 mL) and refluxed for 2 h. The reaction mixture was cooled to 0 °C and basified to pH >10 by addition of 10 % aqueous NaOH and extracted with ethyl acetate. The combined organics were dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography (silica gel, 1:4:0.5 ethyl acetate/hexanes/NH_4OH) to afford the title compound (354 mg, 87%) as a colorless oil as a single diastereomer. ν_{max} (film)/cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.05 (m, 1H), 2.43 (m, 1H), 2.33 – 2.22 (m, 2H), 2.14 (m,1H), 2.06 – 1.91 (m, 3H), 1.86 – 1.77 (m, 1H), 1.75 – 1.61 (m, 3H), 1.61 – 1.10 (m, 5H), 1.06 (d, *J* = 6.3 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 218.6, 67.5, 61.1, 52.2, 51.2, 40.5, 39.8, 37.3, 30.3, 25.9, 24.6, 19.0; *m/z* (ESI+) found $[M+H]^+$ 194.1530. $C_{12}H_{20}NO^+$ requires 194.1539.

(6*R*,7*S*,10*S*,10a*S*)-6-butyloctahydro-7,10-methanopyrido[1,2-*a*]azepin-9(6*H*)-one, 15b



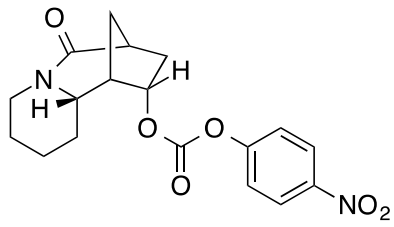
Following general procedure K, reaction of lactam **13** (500 mg, 2.1 mmoL) and *n*-butylmagnesium chloride (2M in THF, 4.2 ml, 8.4 mmol) provided the title compound (400 mg, 88%) as a colorless oil. ν_{max} (film)/cm^{-1} 2933, 1741; δ_H (400 MHz, $CDCl_3$) 3.08 (d, *J* = 11.2 Hz, 1H), 2.42 (s, 1H), 2.27 – 2.03 (m, 3H), 2.01 – 1.84 (m, 3H), 1.71 (dd, *J* = 11.0, 3.6 Hz, 1H), 1.67 – 1.55 (m, 3H), 1.55 – 1.02 (m, 10H), 0.83 (dd, *J* = 10.0, 4.0 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 218.1, 67.5, 66.4, 52.1, 51.1, 39.8, 36.8, 36.6, 31.3, 30.4, 29.6, 25.8, 24.5, 23.1, 14.1; *m/z* (ESI+) found $[M+H]^+$ 236.2004. $C_{15}H_{26}NO^+$ requires 236.2009.

(6*R*,7*S*,10*S*,10a*S*)-6-benzyloctahydro-7,10-methanopyrido[1,2-*a*]azepin-9(6*H*)-one, 15c



Following general procedure K, reaction of lactam **13** (500 mg, 2.1 mmoL) and benzylmagnesium chloride (2M in THF, 4.2 ml, 8.4 mmol) provided the title compound (429 mg, 87%) as a colorless liquid. ν_{max} (film)/cm^{-1} 1740, 2935 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.30 (dd, *J* = 10.1, 4.5 Hz, 2H), 7.21 (dd, *J* = 8.4, 6.3 Hz, 1H), 7.17 – 7.08 (m, 2H), 3.34 (d, *J* = 11.2 Hz, 1H), 3.20 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.58 (ddd, *J* = 9.9, 4.1, 1.4 Hz, 1H), 2.41-2.36 (m, 2H), 2.27 – 2.14 (m, 2H), 2.07 – 1.78 (m, 4H), 1.78 – 1.38 (m, 6H), 1.35 – 1.14 (m, 1H); δ_C (100 MHz, $CDCl_3$) 217.7, 139.8, 129.4, 128.5, 126.1, 67.7, 67.5, 52.1, 51.3, 39.5, 37.6, 36.6, 35.2, 30.4, 25.9, 24.5; *m/z* (ESI+) found $[M+H]^+$ 270.1855. $C_{18}H_{24}NO^+$ requires 270.1852.

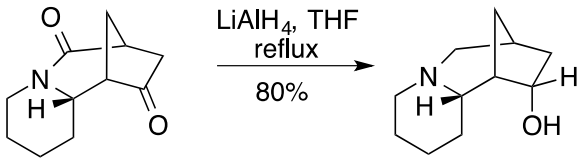
4-Nitrophenyl ((7*S*,9*S*,10*S*,10a*S*)-6-oxodecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl) carbonate, 39



4-nitorphenyl chloroformate (1.86 g, 9.2 mmol) was added to a solution of alcohol **S13** (1.5 g, 7.68 mmol) and pyridine (0.92 mL, 11.5 mmol) in anhydrous THF (40 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the crude residue was purified by chromatography (silica gel, 7:3 EtOAc/hexane) to afford the

title compound (2.62 g, 95%) as a colorless solid. ν_{max} (film)/cm^{-1} 1740, 2935 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.32 – 8.24 (m, 2H), 7.42 – 7.30 (m, 2H), 5.26 (dt, *J* = 10.9, 5.6 Hz, 1H), 4.67 – 4.49 (m, 1H), 3.47 – 3.34 (m, 1H), 2.81 – 2.70 (m, 2H), 2.57 (ddd, *J* = 14.4, 10.6, 7.8 Hz, 1H), 2.44 (td, *J* = 13.1, 3.1 Hz, 1H), 2.10 – 1.62 (m, 7H), 1.51 – 1.20 (m, 2H); δ_C (100 MHz, $CDCl_3$) 173.8, 155.5, 152.3, 145.6, 125.5, 122.0, 81.2, 62.2, 42.3, 41.6, 41.4, 35.1, 31.6, 30.3, 25.6, 25.2. *m/z* (ESI+) found $[M+H]^+$ 361.1392. $C_{18}H_{21}N_2O_6^+$ requires 361.1394.

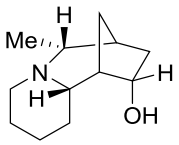
(7*S*,9*S*,10*S*,10a*S*)-decahydro-7,10-methanopyrido[1,2-*a*]azepin-9-ol, 41



Lithium aluminum hydride (784 mg, 20.71 mmol) was added to a solution of lactam **13** (2.0 g, 10.3 mmol) in methanol (quantity) at 0 °C. The reaction mixture was refluxed for 4 h, then cooled, quenched with 10% aqueous NaOH and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated to afford the crude amino alcohol, which was purified by flash column chromatography (silica gel, 1:5:0.5 EtOAc/hexane/aq.NH_3) to obtain the title product (1.5g, 80%) as a colorless oil. ν_{max} (film)/cm^{-1} 3394, 2932; δ_H (400 MHz, $CDCl_3$) 4.20 (s, 1H), 4.15 – 4.05 (m, 1H), 2.64 – 2.46 (m, 2H), 2.09 – 1.94 (m, 2H), 1.94 – 1.78 (m, 3H), 1.78 – 1.63 (m, 2H), 1.49 (t, *J* = 15.2 Hz, 1H), 1.45 – 1.12 (m, 6H), 1.02 – 0.85 (m, 1H); δ_C (100 MHz, $CDCl_3$) 74.5, 68.0, 62.6, 55.5, 42.3, 41.8, 38.8, 34.7, 30.6, 25.4, 24.3.

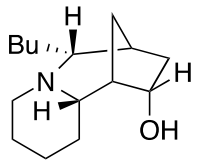
General procedure L: Reduction of ketones **15a-c**

(6*R*,7*S*,9*S*,10*S*,10a*S*)-6-methyldecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-ol, 16a



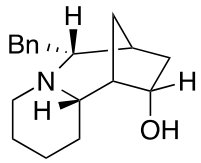
Sodium borohydride (978 mg, 25.85 mmol) was added to a solution of amine **15a** (2.0 g, 10.3 mmol) in methanol (40 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h, then quenched with 10% aqueous NaOH and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated to afford the crude amino-alcohols. Purification by chromatography (silica gel, 1:4:0.5 EtOAc/Hexane/aq.NH_3) provided the title compound (1.59 g, 79%) as a colorless oil. ν_{max} (film)/cm^{-1} 3392, 2932; δ_H (400 MHz, $CDCl_3$) 4.28 (m, 2H), 3.14 (m, 1H), 2.19 (qd, *J* = 6.3, 1.5 Hz, 1H), 2.13 – 1.93 (m, 3H), 1.92 – 1.85 (m, 1H), 1.84 – 1.75 (m, 1H), 1.73 – 1.30 (m, 9H), 1.03 (d, *J* = 6.3 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 74.4, 68.6, 63.3, 51.9, 43.2, 42.5, 39.9, 37.8, 31.7, 26.2, 25.1, 18.6.

(6*R*,7*S*,9*S*,10*S*,10a*S*)-6-butyldecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-ol, 16b



Following general procedure L, reaction of ketone **15b** (2.0 g, 8.42 mmol) provided the title compound (1.6 g, 80%) as a colorless oil. ν_{max} (film)/cm^{-1} 3393, 2944; δ_H (400 MHz, $CDCl_3$) 4.64 – 3.97 (m, 2H), 3.23 (d, *J* = 11.3 Hz, 1H), 2.22 – 1.79 (m, 6H), 1.79 – 0.97 (m, 15H), 0.88 (t, *J* = 7.1 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 74.4, 69.1, 68.7, 52.0, 43.3, 39.7, 38.7, 38.1, 32.0, 31.2, 29.9, 26.3, 25.1, 23.2, 14.2.

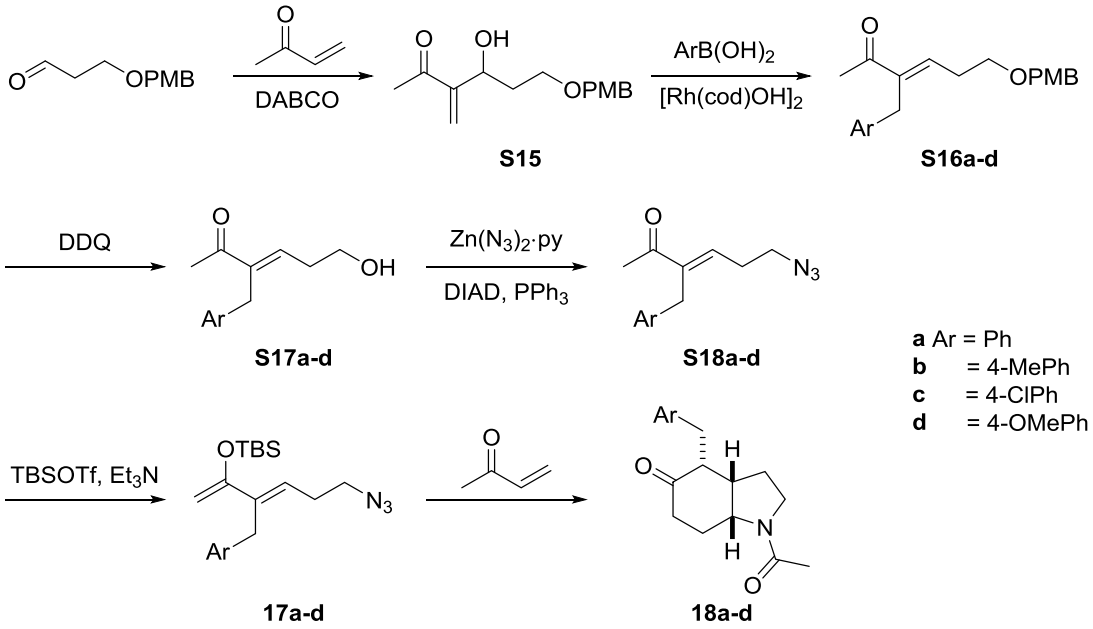
(6*R*,7*S*,9*S*,10*S*,10a*S*)-6-benzyldecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-ol, 16c



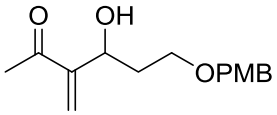
Following general procedure L, reaction of ketone **15c** (1.8 g, 6.68 mmol) provided the title compound (1.57 g, 87%) as a colorless oil. ν_{max} (film)/cm^{-1} 3394, 2930; δ_H (400 MHz, $CDCl_3$) 7.34 – 7.25 (m, 2H), 7.25 – 7.18 (m, 1H), 7.18 – 7.12 (m, 2H), 4.60 – 4.19 (m, 2H), 3.47 (m, 1H), 3.21 (dd, *J* = 13.2, 3.5 Hz, 1H), 2.57 – 2.32 (m, 2H), 2.28 – 1.90 (m, 4H), 1.89 – 1.61 (m, 5H), 1.61 – 1.38 (m, 4H), 1.37 – 1.11 (m, 1H); δ_C (100 MHz, $CDCl_3$) 140.3, 129.4, 128.4, 125.9, 74.2, 70.0, 69.2, 52.2, 43.3, 39.4, 37.7, 37.3, 37.2, 31.9, 26.2, 25.0.

D. Experimental procedures and characterization data for mesembrine-inspired scaffolds.

Supplementary Figure 7. Synthesis of *Stemona* alkaloid-inspired scaffolds



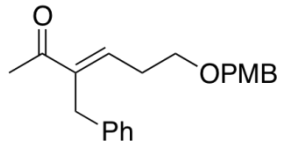
4-Hydroxy-6-((4-methoxybenzyl)oxy)-3-methylenehexan-2-one, S15



DABCO (4.63 g, 38.3 mmol) was added to a solution of 3-(4-methoxybenzyloxy)-propan-1-al[64] in 2-octanol (40 ml) at room temperature, followed by methyl vinyl ketone (12.7 ml, 153 mmol). The reaction mixture was stirred at room temperature for 16 h, then the reaction mixture was directly loaded onto a silica gel column and eluted with 60:40 hexanes:ethyl acetate to afford the title compound (21.5 g, 64%) as a viscous oil. ν_{max} (film)/cm^{-1} 3463, 2862, 1736, 1671, 1612, 1512, 1243; δ_H (400 MHz, $CDCl_3$) 7.29 – 7.21 (m, 2H), 6.92 – 6.83 (m, 2H), 6.14 (s, 2H), 4.70 (dt, *J* = 7.8, 3.9 Hz, 1H), 4.51 – 4.38 (m, 2H), 3.81 (s, 3H), 3.75 – 3.57 (m, 3H), 2.34 (s, 3H), 2.03 – 1.92 (m, 1H), 1.84 – 1.71 (m, 1H); δ_C (100 MHz, $CDCl_3$) 200.0, 159.5, 150.3, 130.0, 129.5, 125.9, 114.0, 73.2, 70.1, 68.8, 55.4, 36.0, 26.5; *m/z* (ESI+) found $[M+H]^+$ 265.1458. $C_{15}H_{21}O_4^+$: requires 265.1440.

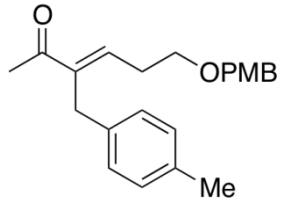
General procedure M: Synthesis of enones *via* Rh(I) catalyzed 1,4-addition

(*E*)-3-Benzyl-6-((4-methoxybenzyl)oxy)hex-3-en-2-one, S16a



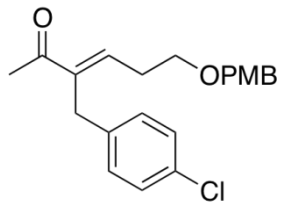
This enone was synthesized using a modified procedure previously reported by Gendrineau and co-workers.[65] Phenyl boronic acid (0.97 g, 8 mmol) was added to a solution of hydroxyketone **S15** (1.05 g, 4.0 mmol) in methanol (5 ml) in a sealed tube. $[Rh(cod)OH]_2$ (18.2 mg, 0.04 mmol) was then added and the mixture heated at 100 ºC for 2 h. The reaction mixture was then cooled transferred to a round bottom flask and the solvent evaporated under reduced to pressure to obtain the crude product. The crude product was purified by chromatography (silica gel, 80:20 hexane/ethyl acetate) to afford the title compound (1.10 g, 86%, *E:Z* >95: 5) as a colorless viscous oil. ν_{max} (film)/cm^{-1} 2928, 2833, 1660, 1611, 1510, 1243; δ_H (400 MHz, $CDCl_3$) 7.28 – 7.18 (m, 4H), 7.16 – 7.10 (m, 3H), 6.91 – 6.86 (m, 2H), 6.82 (t, *J* = 7.0 Hz, 1H), 4.44 (s, 2H), 3.81 (s, 3H), 3.68 (s, 2H), 3.54 (t, *J* = 6.4 Hz, 2H), 2.61 (q, *J* = 6.5 Hz, 2H), 2.32 (s, 3H); δ_C (100 MHz, $CDCl_3$) 199.2, 159.4, 142.2, 141.8, 139.9, 130.3, 129.5, 128.5, 128.4, 126.0, 114.0, 72.8, 68.3, 55.4, 31.3, 30.2, 26.0; *m/z* (ESI+) found $[M+H]^+$ 325.1795. $C_{21}H_{25}O_3^+$: requires 325.1804.

(*E*)-6-((4-methoxybenzyl)oxy)-3-(4-methylbenzyl)hex-3-en-2-one, S16b



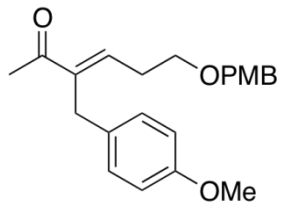
Following general procedure M, reaction of hydroxyketone **S15** (6.0 g, 22.7 mmol) with 4-methylphenyl boronic acid (6.22 g, 45.5 mmol) provided the title compound (6.5 g, 85%, *E:Z* >95:05) as a colorless viscous oil. ν_{max} (film)/cm^{-1} 2925, 2830, 1657, 1610, 1513, 1240; δ_H (400 MHz, $CDCl_3$) 7.27 – 7.23 (m, 2H), 7.02 (s, 4H), 6.91 – 6.86 (m, 2H), 6.79 (t, *J* = 7.0 Hz, 1H), 4.45 (s, 2H), 3.81 (s, 3H), 3.64 (s, 2H), 3.55 (t, *J* = 6.4 Hz, 2H), 2.61 (q, *J* = 6.5 Hz, 2H), 2.29 (d, *J* = 10.5 Hz, 6H); δ_C (100 MHz, $CDCl_3$) 199.1, 159.3, 142.2, 141.3, 136.6, 135.3, 130.2, 129.3, 129.0, 128.2, 113.8, 72.7, 68.2, 55.3, 30.6, 30.0, 25.9, 21.1; *m/z* (ESI+) found $[M+H]^+$ 339.1982. $C_{22}H_{27}O_3^+$: $^+$ requires 339.1960.

(*E*)-3-(4-chlorobenzyl)-6-((4-methoxybenzyl)oxy)hex-3-en-2-one, S16c



Following general procedure M, reaction of hydroxyketone **S15** (1.0 g, 3.78 mmol) with 4-chlorophenyl boronic acid (1.2 g, 7.57 mmol) provided the title compound (0.97 g, 67%, *E:Z* = >95:05) as a colorless viscous oil. ν_{max} (film)/cm^{-1} 2858, 2857, 1655, 1612, 1511, 1490, 1245; δ_H (400 MHz, $CDCl_3$) 7.29 – 7.20 (m, 2H), 7.19 – 7.13 (m, 2H), 7.09 – 7.03 (m, 2H), 6.91 – 6.86 (m, 2H), 6.81 (t, *J* = 7.0 Hz, 1H), 4.45 (s, 2H), 3.81 (s, 3H), 3.62 (s, 2H), 3.55 (t, *J* = 6.3 Hz, 2H), 2.58 (q, *J* = 6.5 Hz, 2H), 2.31 (s, 3H); δ_C (100 MHz, $CDCl_3$) 199.0, 159.4, 142.2, 141.8, 138.4, 131.7, 130.2, 129.8, 129.5, 128.5, 114.0, 72.9, 68.2, 55.4, 30.7, 30.2, 25.9; *m/z* (ESI+) found $[M+H]^+$ 359.1430. $C_{21}H_{24}ClO_3^+$: requires 359.1414.

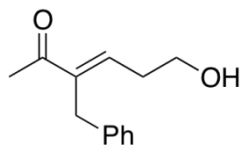
(*E*)-3-(4-methoxybenzyl)-6-((4-methoxybenzyl)oxy)hex-3-en-2-one, S16d



Following general procedure M, reaction of 4 hydroxyketone **S15** (2.0 g, 7.57 mmol) with 4-methoxyphenyl boronic acid (2.3 g, 15.2 mmol) provided the title compound (1.7 g, 63%, *E:Z* >95:05) as a colorless viscous oil. ν_{max} (film)/cm^{-1} 2933, 2836, 1665, 1611, 1509, 1245; δ_H (400 MHz, $CDCl_3$) 7.28 – 7.22 (m, 2H), 7.08 – 7.03 (m, 2H), 6.89 (dt, *J* = 9.5, 2.9 Hz, 2H), 6.82 – 6.72 (m, 3H), 4.45 (s, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 3.61 (s, 2H), 3.55 (t, *J* = 6.4 Hz, 2H), 2.61 (q, *J* = 6.6 Hz, 2H), 2.30 (s, 3H); δ_C (100 MHz, $CDCl_3$) 199.2, 159.4, 157.9, 142.5, 141.3, 131.9, 130.3, 129.4, 129.3, 113.9, 113.9, 72.8, 68.3, 55.4, 55.3, 30.4, 30.1, 26.0; *m/z* (ESI+) found $[M+H]^+$ 355.1935. $C_{22}H_{27}O_4^+$: requires 355.1909.

<u>General procedure N: Synthesis of hydroxy enones **S17**</u>

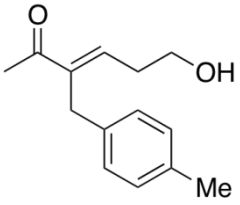
(*E*)-3-benzyl-6-hydroxyhex-3-en-2-one, S17a



DDQ (19.81 g, 87.29 mmol) was added to a solution of enone **S16a** (23.6 g, 72.74 mmol) in dichloromethane (720 ml) and water (37 ml) at room temperature. The initial green reaction mixture was stirred at room temperature for 16 h. A color change to red-orange was observed within 30 min.

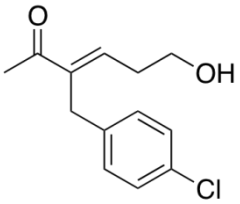
The reaction mixture was then carefully quenched with saturated aqueous $NaHCO_3$ and filtered through a celite plug with dichloromethane washings (250 ml). The combined organics were washed with water (2 x 150 ml), dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography (silica gel, 80:20 hexane:ethyl acetate) to afford the title compound (12.3 g, 83%) as a viscous oil. ν_{max} (film)/cm^{-1} 3416, 2924, 1716, 1660, 1494, 1453; δ_H (400 MHz, $CDCl_3$) 7.27 – 7.20 (m, 2H), 7.15 (dd, *J* = 7.6, 6.1 Hz, 3H), 6.85 (t, *J* = 7.1 Hz, 1H), 3.82 – 3.64 (m, 4H), 2.59 (q, *J* = 6.4 Hz, 2H), 2.34 (s, 3H); δ_C (100 MHz, $CDCl_3$) 199.2, 142.7, 141.1, 139.8, 128.5, 128.3, 126.0, 61.4, 32.8, 31.3, 25.9; *m/z* (ESI+) found $[M+H]^+$ 205.1230. $C_{13}H_{17}O_2^+$: requires 205.1229.

(*E*)-6-hydroxy-3-(4-methylbenzyl)hex-3-en-2-one, S17b



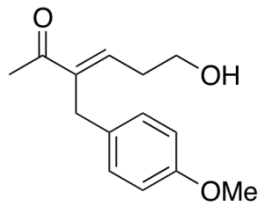
Following general procedure N, reaction of enone **S16b** (5.9 g, 17.54 mmol) provided the title compound (3.5 g, 91%) as a viscous oil. ν_{max} (film)/cm^{-1} 3425, 2924, 1718, 1662, 1513; δ_H (400 MHz, $CDCl_3$) 7.10 – 6.97 (m, 4H), 6.83 (t, *J* = 7.1 Hz, 1H), 3.76 (q, *J* = 6.1 Hz, 2H), 3.66 (s, 2H), 2.58 (q, *J* = 6.5 Hz, 2H), 2.36 – 2.23 (m, 6H); δ_C (100 MHz, $CDCl_3$) 199.3, 142.8, 141.0, 136.7, 135.5, 129.2, 128.2, 61.4, 32.7, 30.8, 25.9, 21.1; *m/z* (ESI+) found $[M+H]^+$ 219.1370. $C_{14}H_{19}O_2^+$: requires 219.1385.

(*E*)-6-hydroxy-3-(4-chlorobenzyl)hex-3-en-2-one, S17c



Following general procedure N, reaction of enone **S16c** (6.95 g, 19.4 mmol) provided the title compound (4.0 g, 86%) as a viscous oil. ν_{max} (film)/cm^{-1} 3432, 2938, 1719, 1664, 1490; δ_H (400 MHz, $CDCl_3$) 7.23 – 7.14 (m, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 6.85 (t, *J* = 7.1 Hz, 1H), 3.77 (q, *J* = 5.7 Hz, 2H), 3.65 (s, 2H), 2.56 (q, *J* = 6.5 Hz, 2H), 2.33 (s, 3H), 1.79 (s, 1H); δ_C (100 MHz, $CDCl_3$) 199.1, 142.3, 141.6, 138.3, 131.7, 129.7, 128.5, 61.3, 32.7, 30.7, 25.9; *m/z* (ESI+) found $[M+H]^+$ 239.0825. $C_{13}H_{16}ClO_2^+$: requires 239.0839.

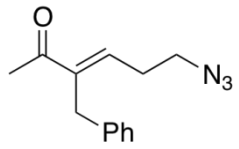
(*E*)-6-hydroxy-3-(4-methoxybenzyl)hex-3-en-2-one, S17d



Following general procedure N, reaction of enone **S16d** (5.0 g, 14.3 mmol) provided the title compound (2.87 g, 86%) as a viscous oil. ν_{max} (film)/cm^{-1} 3421, 2935, 2836, 1660, 1509; δ_H (400 MHz, $CDCl_3$) 7.09 – 7.03 (m, 2H), 6.85 – 6.74 (m, 3H), 3.79 – 3.74 (m, 5H), 3.63 (s, 2H), 2.59 (q, *J* = 6.5 Hz, 2H), 2.32 (s, 3H); δ_C (100 MHz, $CDCl_3$) 199.3, 157.9, 143.0, 140.8, 131.8, 129.3, 113.9, 61.5, 55.3, 32.8, 30.4, 26.0; *m/z* (ESI+) found $[M+H]^+$ 235.1330. $C_{14}H_{19}O_3^+$: requires 235.1334.

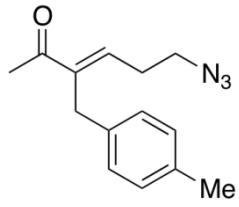
General procedure O: Synthesis of azido enones

(*E*)-6-azido-3-benzylhex-3-en-2-one, S18a



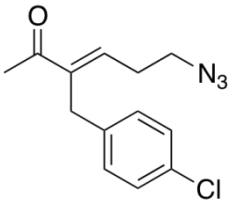
In a flame dried round bottom flask flushed with argon, $Zn(N_3)_2$.Pyr (36.0 g, 118 mmol) and triphenyl phosphine (30.7 g, 118 mmol) were weighed. A solution of alcohol **S17a** (12.0 g, 58.8 mmol) in anhydrous toluene (150 ml) was added. The flask was to -78 ºC, then diisopropyl azodicarboxylate (22.6 ml, 118 mmol) was added to dropwise and the reaction mixture warmed to room temperature and stirred for 16 h. On completion the reaction mixture was filtered through a celite plug and the toluene removed under reduced pressure. The crude reaction mixture was diluted with ethyl acetate (150 ml) and washed with water (2 x 100 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography (silica gel, 90:10 hexane:ethyl acetate) to afford the title compound (8.35 g, 62%) as pale yellow viscous oil. ν_{max} (film)/cm^{-1} 3028, 2925, 2100, 1709, 1664, 1494; δ_H (400 MHz, $CDCl_3$) 7.29 – 7.22 (m, 2H), 7.19 – 7.10 (m, 3H), 6.74 (t, *J* = 7.1 Hz, 1H), 3.71 (s, 2H), 3.39 (t, *J* = 6.7 Hz, 2H), 2.59 (q, *J* = 6.8 Hz, 2H), 2.35 (s, 3H); δ_C (100 MHz, $CDCl_3$) 198.8, 143.0, 139.6, 139.4, 128.5, 128.2, 126.1, 50.1, 31.2, 29.0, 25.9; *m/z* (ESI+) found $[2M+H]^+$ 459.2500. $C_{26}H_{31}N_6O_2^+$: requires 459.2508.

***(E)*-6-azido-3-(4-methylbenzyl)hex-3-en-2-one, S18b**



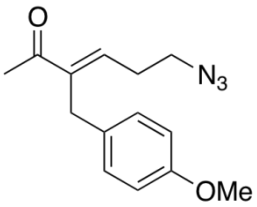
Following general procedure O, reaction of alcohol **S17b** (3.4 g, 15.6 mmol) provided the title compound (2.65 g, 70%) as a viscous oil. ν_{max} (film)/cm^{-1} 2928, 2092, 1695, 1671, 1513; δ_H (400 MHz, $CDCl_3$) 7.04 (q, *J* = 8.1 Hz, 4H), 6.71 (t, *J* = 7.1 Hz, 1H), 3.67 (s, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 2.59 (q, *J* = 6.8 Hz, 2H), 2.39 – 2.24 (m, 6H); δ_C (^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 143.3, 139.4, 136.4, 135.7, 129.3, 128.2, 50.3, 30.9, 29.2, 26.0, 21.1; *m/z* (ESI+) found $[2M+H]^+$ 487.2831. $C_{28}H_{35}N_6O_2^+$: requires 487.2821.

***(E)*-6-azido-3-(4-chlorobenzyl)hex-3-en-2-one, S18c**



Following general procedure O, reaction of alcohol **S17c** (4.0 g, 16.75 mmol) provided the title compound (2.69 g, 61%) as a viscous oil. ν_{max} (film)/cm^{-1} 2929, 2102, 1701, 1665, 1490; δ_H (400 MHz, $CDCl_3$) 7.24 – 7.19 (m, 2H), 7.09 – 7.03 (m, 2H), 6.74 (t, *J* = 7.1 Hz, 1H), 3.66 (s, 2H), 3.42 (t, *J* = 6.7 Hz, 2H), 2.58 (q, *J* = 6.8 Hz, 2H), 2.34 (s, 3H); δ_C (100 MHz, $CDCl_3$) 198.7, 142.8, 140.1, 138.0, 132.0, 129.7, 128.7, 50.2, 30.7, 29.2, 25.9; *m/z* (ESI+) found $[M+H]^+$ 264.0910. $C_{13}H_{15}ClN_3O^+$: requires 264.0904.

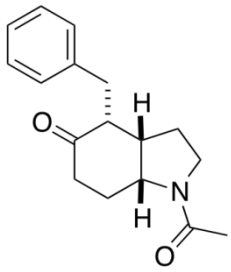
(*E*)-6-azido-3-(4-methoxybenzyl)hex-3-en-2-one, S18d



Following general procedure O, reaction of alcohol **S17d** (2.87 g, 12.24 mmol) provided the title compound (1.95 g, 65%) as a viscous oil. ν_{max} (film)/cm^{-1} 2932, 2836, 2100, 1709, 1664, 1609, 1509; δ_H (400 MHz, $CDCl_3$) 7.07 – 7.02 (m, 2H), 6.82 – 6.76 (m, 2H), 6.70 (t, *J* = 7.1 Hz, 1H), 3.76 (s, 3H), 3.64 (s, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 2.59 (q, *J* = 6.8 Hz, 2H), 2.33 (s, 3H); δ_C (100 MHz, $CDCl_3$) 199.0, 158.0, 143.5, 139.3, 131.5, 129.3, 114.0, 55.4, 50.3, 30.5, 29.1, 26.0; *m/z* (ESI+) found $[M+H]^+$ 260.1385. $C_{14}H_{18}N_3O_2^+$: requires 260.1399.

General procedure P: Diels Alder/ Schmidt reaction with silyloxy dienes derived from α-benzyl enones

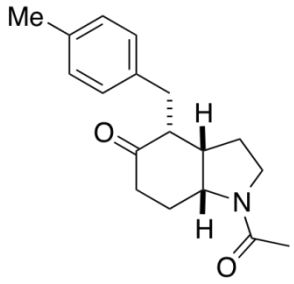
(3a*S*,4*R*,7a*R*)-1-acetyl-4-benzyloctahydro-5*H*-indol-5-one, 18a



Triethylamine (1.83 ml, 13.1 mmol) was added to a solution of enone **S18a** (1.50 g, 6.55 mmol) in anhydrous diethyl ether (15 ml) at 0 ºC under argon. TBSOTf (2.26 ml, 9.82 mmol) was then added dropwise to afford a white turbid solution. The reaction mixture was stirred for 30 min at 0 ºC, then quenched with saturated aqueous $NaHCO_3$ (50 ml). The mixture was extracted with diethyl ether (50 ml), dried ($MgSO_4$) and concentrated to afford the corresponding silyloxydiene **17a** (2.31 g) which was used without any purification.

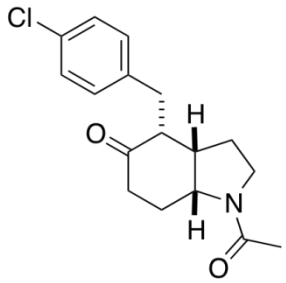
The crude silyloxydiene was transferred to a flame-dried argon-flushed flask and dissolved in anhydrous dichloromethane (15 ml). Methyl vinyl ketone (0.37 ml, 4.51 mmol) was added and the reaction mixture cooled to -78 ºC. Boron trifluoride diethyl etherate (0.86 ml, 6.76 mmol) was then added and the reaction mixture stirred at -78 °C for 4 h then warmed to room temperature. A further aliquot of boron trifluoride diethyl etherate (1.14 ml, 9.02 mmol) was then added and the reaction mixture stirred at room temperature for an additional 16 h. The reaction mixture was diluted with dichloromethane (100 ml) and quenched with saturated aqueous $NaHCO_3$ (100 ml). The organic layer was washed with saturated aqueous NH_4Cl (50 ml), water (50 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated. The crude product was purified by automated column chromatography (4 g silica column, 0 to 100% EtOAc in hexanes, then 90:10 dichloromethane:methanol) to afford the title compound (672 mg, 55%, *endo*:*exo* = 4:1) as yellow viscous oil. ν_{max} (film)/cm^{-1} 2935, 1710, 1635, 1420; δ_H (400 MHz, $CDCl_3$, major diastereomer) 7.31 – 7.14 (m, 5H), 3.63 – 3.51 (m, 2H), 3.43 (td, *J* = 10.7, 6.1 Hz, 1H), 3.29 – 3.13 (m, 2H), 2.67 (m, 2H), 2.55 – 2.38 (m, 2H), 2.02 (s, 3H), 1.96 – 1.74 (m, 2H), 1.59 – 1.36 (m, 2H); δ_C (100 MHz, $CDCl_3$, major diastereomer) 209.7, 171.0, 140.3, 129.2, 128.5, 126.3, 62.3, 55.4, 50.6, 49.4, 39.5, 33.6, 29.3, 29.1, 23.2; *m/z* (ESI+) found $[M+H]^+$ 272.1545. $C_{17}H_{22}NO_2^+$: requires 272.1651.

(3a*S*,4*R*,7a*R*)-1-acetyl-4-(4-methylbenzyl)octahydro-5*H*-indol-5-one, 18b



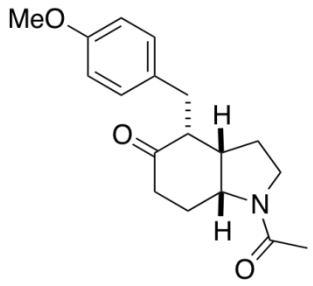
Following general procedure P, reaction of enone **S18b** (4.20 g, 17.3 mmol) provided the title compound (1.68 g, 53%, *endo*:*exo* = 4:1) as a yellow viscous oil. ν_{max} (film)/cm^{-1} 2937, 1711, 1630, 1414; δ_H (400 MHz, $CDCl_3$, major diastereomer) 7.12 – 7.02 (m, 4H), 3.58 – 3.45 (m, 1H), 3.40 – 3.27 (m, 1H), 3.20 (dt, *J* = 14.3, 5.0 Hz, 1H), 3.12 – 2.96 (m, 1H), 2.73 – 2.52 (m, 2H), 2.51 – 2.19 (m, 6H), 2.14 – 1.92 (m, 5H), 1.91 – 1.64 (m, 2H); δ_C (100 MHz, $CDCl_3$, major diastereomer) 211.5, 169.3, 136.2, 129.3, 128.9, 128.5, 54.9, 50.5, 46.5, 42.5, 37.7, 32.2, 27.0, 25.8, 22.3, 21.0; *m/z* (ESI+) found $[M+H]^+$ 286.1825. $C_{18}H_{24}NO_2^+$: requires 286.1807.

(3a*S*,4*R*,7a*R*)-1-acetyl-4-(4-chlorobenzyl)octahydro-5*H*-indol-5-one, 18c



Following general procedure P, reaction of enone **S18c** (5.60 g, 21.2 mmol) provided the title compound (2.72 g, 64%, *endo*:*exo* = 3:1) as a yellow viscous oil. ν_{max} (film)/cm^{-1} 2947, 1711, 1631,1492, 1414; δ_H (400 MHz, $CDCl_3$, major diastereomer) 7.24 (d, *J* = 7.7 Hz, 2H), 7.11 (d, *J* = 7.7 Hz, 2H), 3.53-3.50 (m, 1H), 3.35 (m, 2H), 3.25 – 3.16 (m, 2H), 3.09 (dd, *J* = 13.4, 6.0 Hz, 1H), 3.01 (dt, *J* = 8.6, 6.0 Hz, 1H), 2.74 – 2.53 (m, 2H), 2.51 – 2.20 (m, 2H), 2.12 – 1.96 (m, 3H), 1.96 – 1.57 (m, 2H); δ_C (100 MHz, $CDCl_3$, major diastereomer) 211.1, 169.4, 137.9, 130.5, 130.2, 128.8, 54.9, 50.5, 46.5, 43.0, 37.8, 32.3, 27.2, 25.9, 22.4; *m/z* (ESI+) found $[M+H]^+$ 306.1277. $C_{17}H_{21}ClNO_2^+$: requires 306.1216.

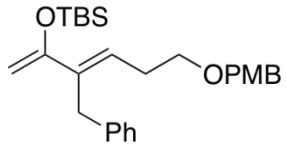
(3a*S*,4*R*,7a*R*)-1-acetyl-4-(4-methoxybenzyl)octahydro-5*H*-indol-5-one, 18d



Following general procedure P, reaction of enone **S18d** (3.20 g, 12.3 mmol) provided the title compound (1.50 g, 60%, *endo*:*exo* = 4:1) as a yellow viscous oil. ν_{max} (film)/cm^{-1} 2944, 1710, 1629, 1511, 1244; δ_H (400 MHz, $CDCl_3$, major diastereomer) 7.08 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 3.76 (s, 3H), 3.60 – 3.44 (m, 2H), 3.41 – 3.25 (m, 1H), 3.17 (dt, *J* = 14.4, 4.8 Hz, 1H), 3.10 – 2.93 (m, 1H), 2.73 – 2.51 (m, 2H), 2.51 – 2.17 (m, 4H), 2.15 – 1.92 (m, 3H), 1.90 – 1.53 (m, 2H); δ_C (100 MHz, $CDCl_3$, major diastereomer) 211.6, 169.3, 158.2, 130.1, 129.7, 114.1, 114.0, 55.3, 54.9, 50.7, 46.5, 42.7, 37.8, 31.8, 27.2, 25.9; *m/z* (ESI+) found $[M+H]^+$ 302.1768. $C_{18}H_{24}NO_3^+$: requires 302.1756.

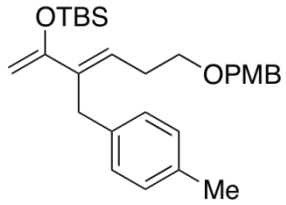
General procedure Q. Synthesis of silyloxydiene

(*E*)-((3-benzyl-6-((4-methoxybenzyl)oxy)hexa-1,3-dien-2-yl)oxy)(*tert*-butyl)dimethylsilane, 22a



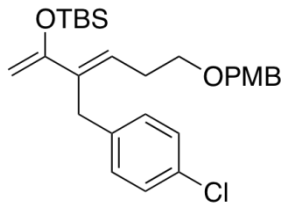
Triethylamine (0.43 ml, 3.08 mmol) was added to a solution of enone **S16a** (500 mg, 1.54 mmol) in anhydrous diethyl ether (5 ml) at 0 ºC under argon. TBSOTf (0.53 ml, 2.31 mmol) was then added dropwise. The reaction mixture was stirred for 20 min at 0 °C then diluted with ether, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography (basic alumina, 96:4 hexanes:ethyl acetate) to afford the title compound (603 mg, 89%) as a colorless viscous oil. ν_{max} (film)/cm^{-1} 2930, 2856, 1600, 1512, 1246; δ_H (400 MHz, $CDCl_3$) 7.28 – 7.19 (m, 4H), 7.19 – 7.11 (m, 3H), 6.89 – 6.83 (m, 2H), 6.29 (t, *J* = 7.3 Hz, 1H), 4.42 (s, 2H), 4.39 – 4.22 (m, 2H), 3.80 (s, 3H), 3.61 (s, 2H), 3.50 (t, *J* = 6.8 Hz, 2H), 2.47 (q, *J* = 7.0 Hz, 2H), 0.96 (s, 9H), 0.17 – 0.09 (ms, 6H); δ_C (100 MHz, $CDCl_3$) 159.2, 156.4, 140.1, 135.4, 130.7, 129.4, 128.4, 128.0, 127.1, 125.9, 113.9, 93.1, 72.8, 69.6, 55.4, 33.5, 29.4, 26.1, 18.5, -4.5; *m/z* (ESI+) found $[M+H]^+$ 439.2650. $C_{27}H_{39}O_3Si^+$: requires 439.2668.

(*E*)-*tert*-butyl((6-((4-methoxybenzyl)oxy)-3-(4-methylbenzyl)hexa-1,3-dien-2-yl)oxy)dimethylsilane, 22b



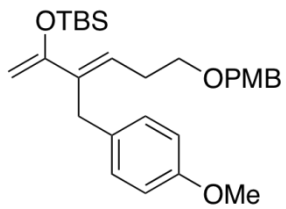
Following general procedure Q, reaction of enone **S16b** (0.79 g, 2.02 mmol) provided the title compound (800 mg, 86%) as a colorless viscous oil. ν_{max} (film)/cm^{-1} 2929, 2856, 1612,1512, 1246; δ_H (400 MHz, $CDCl_3$) 7.15 – 7.08 (m, 2H), 6.95 – 6.88 (m, 4H), 6.74 (dd, *J* = 6.7, 2.1 Hz, 2H), 6.15 (t, *J* = 7.3 Hz, 1H), 4.29 (s, 2H), 4.25 – 4.08 (m, 2H), 3.67 (s, 3H), 3.44 (s, 2H), 3.37 (t, *J* = 6.8 Hz, 2H), 2.34 (q, *J* = 7.0 Hz, 2H), 2.16 (s, 3H), 0.83 (s, 9H), 0.02 – -0.03 (s, 6H); δ_C (100 MHz, $CDCl_3$) 159.2, 156.4, 137.0, 135.5, 135.3, 130.7, 129.4, 129.1, 127.8, 127.0, 113.9, 93.0, 72.8, 69.6, 55.4, 33.0, 29.3, 26.1, 21.1, 18.5, -4.5; *m/z* (ESI+) found $[M+H]^+$ 453.2842. $C_{28}H_{41}SiO_3^+$: requires 453.2825.

(*E*)-*tert*-butyl((3-(4-chlorobenzyl)-6-((4-methoxybenzyl)oxy)hexa-1,3-dien-2-yl)oxy)dimethylsilane, 22c



Following general procedure Q, reaction of enone **S16c** (321 mg, 0.89 mmol) provided the title compound (380 mg, 90%) as a colorless viscous oil. ν_{max} (film)/cm^{-1} 2930, 2856, 1612, 1595, 1512, 1247; δ_H (400 MHz, $CDCl_3$) 7.29 – 7.22 (m, 2H), 7.21 – 7.15 (m, 2H), 7.13 – 7.06 (m, 2H), 6.87 (dd, *J* = 6.6, 2.0 Hz, 2H), 6.29 (t, *J* = 7.3 Hz, 1H), 4.42 (s, 2H), 4.32 – 4.21 (m, 2H), 3.81 (s, 3H), 3.56 (s, 2H), 3.54 – 3.44 (m, 2H), 2.45 (q, *J* = 6.9 Hz, 2H), 0.96 (s, 9H), 0.18 (s, 6H); δ_C (100 MHz, $CDCl_3$) 159.3, 156.2, 138.6, 135.1, 129.5, 129.4, 128.5, 127.6, 113.9, 93.0, 72.9, 69.5, 65.8, 55.4, 32.8, 29.4, 26.0, 17.2, 14.3, -4.5; HRMS calcd. for $C_{27}H_{38}ClO_3Si^+$: 473.2279 Found: 473.2277.

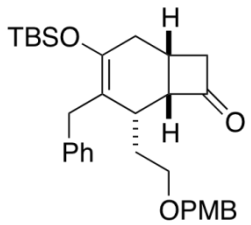
(*E*)-*tert*-butyl((3-(4-methoxybenzyl)-6-((4-methoxybenzyl)oxy)hexa-1,3-dien-2-yl)oxy)dimethylsilane, 22d



Following general procedure Q, reaction of enone **S16d** (356 mg, 1.0 mmol) provided the title compound (450 mg, 96%) as a colorless viscous oil. ν_{max} (film)/cm^{-1} 2931, 2856, 1611, 1510, 1243; δ_H (400 MHz, $CDCl_3$) 7.28 – 7.22 (t, *J* = 2.4 Hz, 2H), 7.11 – 7.05 (d, *J* = 8.7 Hz, 2H), 6.90 – 6.84 (m, 2H), 6.79 – 6.75 (m, 2H), 6.30 – 6.23 (t, *J* = 7.3 Hz, 1H), 4.45 – 4.41 (s, 2H), 4.38 – 4.22 (m, 2H), 3.83 – 3.74 (d, *J* = 15.9 Hz, 6H), 3.58 – 3.44 (m, 4H), 2.52 – 2.43 (q, *J* = 7.0 Hz, 2H), 1.01 – 0.93 (s, 9H), 0.15 – 0.11 (m, 6H); δ_C (100 MHz, $CDCl_3$) 159.2, 157.8, 156.4, 135.8, 132.1, 130.7, 129.4, 128.9, 126.9, 113.9, 113.8, 93.0, 72.8, 66.0, 55.4, 55.4, 32.6, 29.3, 26.1, 18.4, -5.6; *m/z* (ESI+) found $[M+H]^+$ 469.2754. $C_{28}H_{41}SiO_4^+$: requires 469.2774.

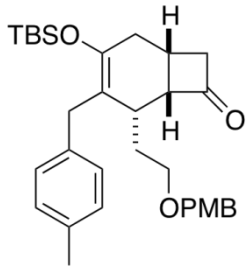
General procedure R: Diels Alder reaction of cyclobutenone with silyloxydienes

(1*R*,5*S*,6*S*)-4-benzyl-3-((*tert*-butyldimethylsilyl)oxy)-5-(2-((4-methoxybenzyl)oxy)ethyl)bicyclo[4.2.0]oct-3-en-7-one, 23a



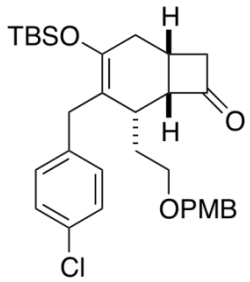
Diisopropylamine (0.53 ml, 2.97 mol) was added dropwise to a solution of 3-bromocyclobutan-1-one[66] (400 mg, 2.70 mmol) in anhydrous acetonitile (1 ml) at 0 ºC under argon. The solution was stirred at 0 ºC for 1 h when ^{1}H NMR analysis of an aliquot showed complete consumption of bromobutanone and formation of cyclobut-2-en-1-one. To this flask was added a solution of silyloxydiene **22a** (400 mg, 0.92 mmol) in acetonitrile (1 ml) followed by $ZnCl_2$ (1.35 ml, 1.0 M solution in Et_2O). The reaction mixture was then heated at 45 ºC for 24 h, then another equivalent of cyclobut-2-en-1-one (0.92 mmol) (prepared separately as described above) was added. The reaction mixture was heated at 45 °C for an additional 24h, then cooled to room temperature and diluted with diethyl ether. The organic layer was washed with saturated aqueous $NaHCO_3$ (50 ml) and water (2 x 50 ml), dried ($MgSO_4$) and concentrated. The crude product was purified by chromatography (basic alumina, 95:5 hexane:ethyl acetate) to afford the title compound (350 mg, 75%) as a colorless viscous oil. ν_{max} (film)/cm^{-1} 2925, 2860, 1710, 1651, 1613, 1507, 1246; δ_H (400 MHz, $CDCl_3$) 7.25 – 7.20 (m, 2H), 7.19 – 7.08 (m, 5H), 6.88 – 6.82 (m, 2H), 4.31 – 4.22 (m, 2H), 3.92 – 3.84 (d, *J* = 15.4 Hz, 1H), 3.83 – 3.77 (s, 3H), 3.53 – 3.39 (m, 3H), 3.23 – 3.08 (m, 2H), 2.82 – 2.71 (m, 1H), 2.66 – 2.51 (m, 3H), 2.34 – 2.23 (m, 1H), 1.91 – 1.83 (m, 2H), 0.90 – 0.87 (s, 9H),0.14 (s, 3H), 0.09 (s, 3H); δ_C (100 MHz, $CDCl_3$) 212.2, 159.2, 145.5, 141.2, 130.7, 129.4, 128.4, 128.3, 125.6, 116.8, 113.8, 72.1, 67.9, 60.6, 55.4, 51.8, 33.7, 33.5, 32.7, 29.1, 25.9, 23.4, 18.2, -3.4, -3.3. *m/z* (ESI+) found $[M+H]^+$ 507.2925 $C_{31}H_{43}O_4Si^+$: requires 507.2931.

(1*R*,5*S*,6*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-(2-((4-methoxybenzyl)oxy)ethyl)-4-(4-methylbenzyl)bicyclo[4.2.0]oct-3-en-7-one, 23b



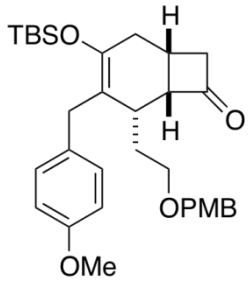
Following general procedure R, reaction of silyloxydiene **22b** (300 mg, 0.66 mmol) provided the title compound (252 mg, 72%) as a colorless viscous oil. ν_{max} (film)/cm^{-1} 2930, 2857, 1713, 1650, 1612, 1511, 1246; δ_H (400 MHz, $CDCl_3$) 7.18 – 7.13 (m, 2H), 7.05 – 6.96 (q, *J* = 8.0 Hz, 4H), 6.87 – 6.81 (m, 2H), 4.35 – 4.19 (m, 2H), 3.83 – 3.75 (s, 4H), 3.51 – 3.38 (m, 3H), 3.17 – 3.05 (ddd, *J* = 17.9, 8.8, 3.9 Hz, 2H), 2.81 – 2.68 (m, 1H), 2.66 – 2.49 (m, 3H), 2.34 – 2.26 (s, 4H), 1.94 – 1.80 (q, *J* = 7.5, 6.9 Hz, 2H), 0.88 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); δ_C (100 MHz, $CDCl_3$) 212.3, 159.2, 145.3, 138.0, 135.0, 130.8, 129.4, 129.0, 128.3, 117.1, 113.8, 72.1, 68.0, 60.7, 55.4, 51.8, 33.7, 33.5, 32.3, 29.1, 25.9, 23.4, 21.2, 18.2, -3.3, -3.4; *m/z* (ESI+) found $[M+H]^+$ 521.3093. $C_{32}H_{45}O_4Si^+$: requires 521.3087.

(1*R*,5*S*,6*S*)-3-((*tert*-butyldimethylsilyl)oxy)-4-(4-methoxybenzyl)-5-(2-((4-chlorobenzyl)oxy)ethyl)bicyclo[4.2.0]oct-3-en-7-one, 23c



Following general procedure R, reaction of silyloxydiene **22c** (205mg, 1.39 mmol) provided the title compound (265 mg, 68%) as a colorless viscous oil. ν_{max} (film)/cm^{-1} 2930, 2856, 1773, 1650, 1612, 1512, 1246; δ_H (400 MHz, $CDCl_3$) 7.23 – 7.12 (m, 4H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.89 – 6.82 (m, 2H), 4.38 – 4.23 (m, 2H), 3.80 (s, 4H), 3.53 – 3.39 (m, 3H), 3.21 – 3.06 (m, 2H), 2.82 – 2.70 (m, 1H), 2.66 – 2.48 (m, 3H), 2.27 (dd, *J* = 15.5, 3.3 Hz, 1H), 1.92 – 1.73 (m, 2H), 0.87 (s, 9H), 0.21 – 0.06 (m, 6H); δ_C (125 MHz, $CDCl_3$) 212.3, 159.2, 145.8, 139.7, 131.3, 130.6, 129.7, 129.4, 128.4, 116.3, 113.8, 72.3, 67.8, 60.6, 55.4, 51.8, 33.6, 33.5, 32.0, 29.1, 25.8, 23.3, 18.2, -3.3, -3.2; *m/z* (ESI+) found $[M+H]^+$ 541.2556. $C_{31}H_{42}ClO_4Si^+$: requires 541.2541.

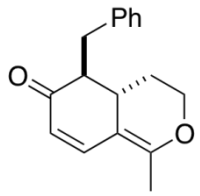
(1*R*,5*S*,6*S*)-3-((*tert*-butyldimethylsilyl)oxy)-4-(4-methoxybenzyl)-5-(2-((4-methoxybenzyl)oxy)ethyl)bicyclo[4.2.0]oct-3-en-7-one, 23d



Following general procedure R, reaction of silyloxydiene **22d** (164mg, 1.11 mmol) provided the title compound (164mg, 55%) as a colorless viscous oil. ν_{max} (film)/cm^{-1} 2931, 2856, 1773, 1650, 1611, 1508; δ_H (400 MHz, $CDCl_3$) 7.19 – 7.14 (m, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.87 – 6.82 (m, 2H), 6.80 – 6.74 (m, 2H), 4.36 – 4.21 (m, 2H), 3.78 (d, *J* = 14.1 Hz, 7H), 3.57 – 3.37 (m, 4H), 3.18 – 3.04 (m, 2H), 2.74 (dt, *J* = 15.3, 5.8 Hz, 1H), 2.66 – 2.47 (m, 3H), 2.26 (dd, *J* = 15.5, 3.6 Hz, 1H), 1.86 (q, *J* = 6.5 Hz, 2H), 0.89 (s, 9H), 0.18 – 0.04 (m, 6H); δ_C (125 MHz, $CDCl_3$) 212.4, 159.2, 157.7, 145.2, 133.1, 130.7, 129.4, 129.3, 117.2, 113.8, 113.7, 72.2, 68.0, 60.6, 55.4, 55.3, 51.8, 33.7, 33.5, 31.8, 29.1, 25.9, 23.4, 18.2, -3.3, -3.4; *m/z* (ESI+) found $[M+H]^+$ 537.3040. $C_{32}H_{46}O_5Si^+$: requires 537.3036.

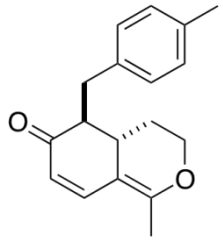
General procedure S: synthesis of tetrahydroisochromenones

(4a*S*,5*S*)-5-benzyl-1-methyl-3,4,4a,5-tetrahydro-6*H*-isochromen-6-one, 24a



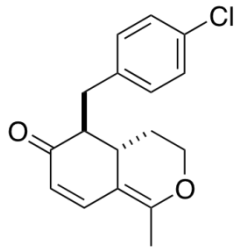
Trifluoromethane sulfonic acid (17.7µl, 0.2 mmol) was added to a solution of silyl enol ether **23a** (51.0 mg, 0.2 mmol) in dichloromethane (1 ml) at room temperature. The reaction mixture was stirred at room temperature for 2 h then loaded directly onto a silica gel column and eluted with 80:20 hexanes:ethyl acetate to afford the title compound (34.0 mg, 67%) as an colorless oil. ν_{max} (film)/cm^{-1} 2926, 1658, 1612, 1495, 1278; δ_H (400 MHz, $CDCl_3$) 7.25 – 7.21 (m, 6H), 5.79 (d, *J* = 9.8 Hz, 1H), 4.27 (ddd, *J* = 10.9, 3.9, 2.3 Hz, 1H), 3.98 – 3.65 (m, 1H), 3.32 – 3.06 (m, 2H), 2.53 (dt, *J* = 12.3, 6.8 Hz, 1H), 2.46 – 2.38 (m, 1H), 2.19 (ddt, *J* = 13.6, 4.7, 2.0 Hz, 1H), 1.97 (d, *J* = 1.5 Hz, 3H), 1.67 (tdd, *J* = 12.9, 11.2, 3.9 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 199.0, 157.7, 143.9, 140.4, 129.5, 128.4, 126.0, 121.6, 108.3, 66.4, 52.4, 34.9, 31.6, 29.2, 17.0; *m/z* (ESI+) found $[M+H]^+$ 255.1365. $C_{17}H_{19}O_2^+$: requires 255.1385.

(4a*S*,5*S*)-1-methyl-5-(4-methylbenzyl)-3,4,4a,5-tetrahydro-6*H*-isochromen-6-one, 24b



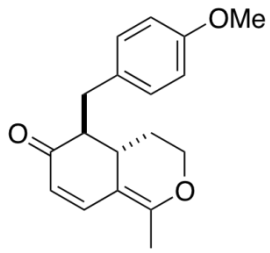
Following general procedure S, reaction of silyl enol ether **23b** (53.6 mg, 0.2 mmol) provided the title compound (35.0 mg, 65%) as a colorless viscous oil. ν_{max} (film)/cm^{-1} 2927, 1656, 1610, 1510, 1243; δ_H (500 MHz, $CDCl_3$) 7.24 (d, *J* = 9.8 Hz, 1H), 7.13 – 7.08 (m, 2H), 7.07 – 7.01 (m, 2H), 5.79 (d, *J* = 9.8 Hz, 1H), 4.27 (ddd, *J* = 10.9, 3.9, 2.3 Hz, 1H), 3.87 – 3.73 (m, 1H), 3.22 (dd, *J* = 14.6, 3.8 Hz, 1H), 3.06 (dd, *J* = 14.6, 5.4 Hz, 1H), 2.58 – 2.48 (m, 1H), 2.38 (ddd, *J* = 13.7, 5.3, 3.9 Hz, 1H), 2.29 (s, 3H), 2.20 (ddt, *J* = 13.5, 4.6, 1.9 Hz, 1H), 1.97 (d, *J* = 1.5 Hz, 3H), 1.73 – 1.61 (m, 1H); δ_C (125 MHz, $CDCl_3$) 199.0, 157.5, 143.7, 137.0, 135.3, 129.3, 128.92, 121.5, 108.2, 66.3, 52.21, 34.6, 30.9, 29.1, 21.0, 16.9; *m/z* (ESI+) found $[M+H]^+$ 269.1551. $C_{18}H_{21}O_2^+$: requires 269.1542.

(4a*S*,5*S*)-1-methyl-5-(4-chlorobenzyl)-3,4,4a,5-tetrahydro-6*H*-isochromen-6-one, 24c



Following general procedure S, reaction of silyl enol ether **23c** (57.6 mg, 0.2 mmol) provided the title compound (32.0 mg, 55%) as a colorless viscous oil. ν_{max} (film)/cm^{-1} 2927, 1661, 1608, 1491, 1279; δ_H (400 MHz, $CDCl_3$) 7.30 – 7.23 (m, 1H), 7.22 – 7.13 (m, 4H), 5.78 (d, *J* = 9.8 Hz, 1H), 4.28 (ddd, *J* = 11.0, 3.9, 2.3 Hz, 1H), 3.90 – 3.69 (m, 1H), 3.28 – 3.17 (m, 1H), 3.10 – 3.00 (m, 1H), 2.50 (dt, *J* = 12.2, 6.6 Hz, 1H), 2.43 – 2.32 (m, 1H), 2.16 (ddt, *J* = 13.4, 4.6, 1.9 Hz, 1H), 1.98 (d, *J* = 1.5 Hz, 3H), 1.69 (tdd, *J* = 12.9, 11.2, 3.9 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 198.8, 158.0, 144.0, 138.8, 131.8, 130.9, 128.5, 121.5, 108.1, 66.3, 52.3, 34.7, 30.9, 29.2, 17.0; HRMS calcd. for $C_{17}H_{18}ClO_2^+$: 289.0995 Found: 289.1005. *m/z* (ESI+) found $[M+H]^+$ 289.1005. $C_{17}H_{18}ClO_2^+$: requires 289.0995.

(4a*S*,5*S*)-1-methyl-5-(4-methoxybenzyl)-3,4,4a,5-tetrahydro-6*H*-isochromen-6-one, 24d



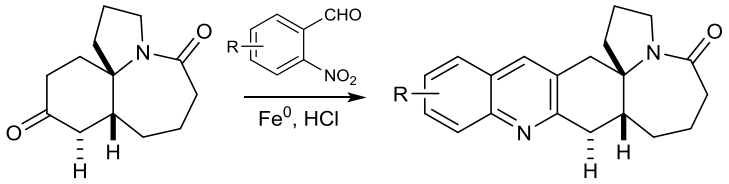
Following general procedure S, reaction of silyl enol ether **23d** (43.0 mg, 0.15 mmol) provided the title compound (23.5 mg, 55%) as a colorless viscous oil. ν_{max} (film)/cm^{-1} 2926, 1659, 1610, 1510, 1247; δ_H (400 MHz, $CDCl_3$) 7.28 – 7.21 (m, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.82 – 6.75 (m, 2H), 5.78 (d, *J* = 9.8 Hz, 1H), 4.27 (ddd, *J* = 10.9, 3.9, 2.3 Hz, 1H), 3.88 – 3.70 (m, 4H), 3.24 (dd, *J* = 14.6, 3.7 Hz, 1H), 3.00 (dd, *J* = 14.6, 5.4 Hz, 1H), 2.60 – 2.47 (m, 1H), 2.36 (ddd, *J* = 13.6, 5.4, 3.7 Hz, 1H), 2.20 (ddd, *J* = 11.5, 5.3, 2.6 Hz, 1H), 2.03 – 1.93 (m, 3H), 1.68 (tdd, *J* = 13.0, 11.3, 3.9 Hz, 1H); δ_C (100 MHz, $CDCl_3$) 199.2, 157.9, 157.7, 143.9, 132.1, 130.5, 121.7, 113.7, 108.3, 66.4, 55.3, 52.4, 34.5, 30.5, 29.2, 17.0; *m/z* (ESI+) found $[M+H]^+$ 285.1475. $C_{18}H_{21}O_3^+$: requires 285.1491.

III. Supplementary Methods: Experimental procedures for library synthesis, tabulated results and characterization data for representative library compounds.

A. *Stemona* alkaloid-inspired libraries.

General procedures for library preparation and tabulated results.

Quinolines 25:



3a **25**{1-6}

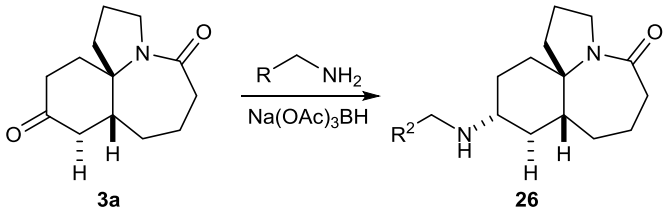
Nitrobenzaldehyde:

{*1*} R = H {*4*} R = 3-OMe
{*2*} R = 5-Cl {*5*} R = 4,5-(-OCH_2O-)
{*3*} R = 6-Cl {*6*} 1-nitro-2-naphthaldehyde

Fe^0 powder (90 mg, 1.6 mmol) was added to a solution of the appropriate nitrobenzaldehyde (0.41 mmol) in ethanol (2 mL) in a microwave vial, followed by 0.1 M HCl (210 µL). The vial was sealed, then heated in an oil bath at 85 °C until complete by TLC (~2 h). The mixture was cooled to rt, then a solution of ketone scaffold **3a** (70 mg, 0.32 mmol) in EtOH (1 mL) added, followed by powdered KOH (22 mg, 0.38 mmol). The mixture was heated at 85 °C until complete by TLC (~3 h), then cooled to rt, passed through a celite plug and eluted with dichloromethane, and concentrated under reduced pressure. The residues were subjected to mass-directed preparative HPLC purification to afford pure quinolines **25**.

Compound	Calculated mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
25{*1*}c	307.1805	307.1816	21.3	21.7	94.6
25{*2*}	341.1415	341.1433	21	26.8	98.9
25{*3*}	341.1415	341.1430	14.8	13.6	100
25{4}	337.1911	337.1928	28.9	26.9	100
25{*5*}	351.1703	351.1725	15.2	13.6	90
25{*6*}	357.1962	357.1997	30.2	26.5	100

Amines 26 (from scaffold 3a)



3a **26**

Amine:

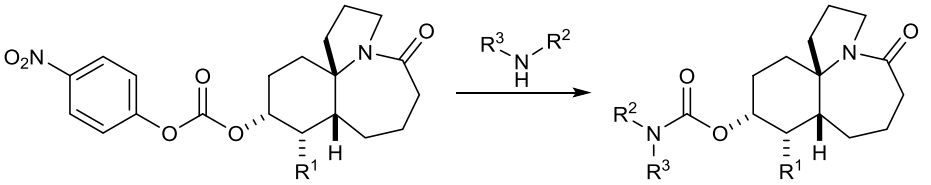
{*1*} R = phenyl
{*2*} R = 2-trifluoromethylphenyl
{*3*} R = 2-methylphenyl
{*4*} R = 2-methoxyphenyl
{*5*} R = 2-fluorophenyl
{*6*} R = 2-chlorophenyl
{*7*} R = 3-iodophenyl
{*8*} R = 3-methylphenyl
{*9*} R = 3-chlorophenyl
{*10*} R = 3-fluorophenyl
{*11*} R = 3-methoxyphenyl
{*12*} R = 4-bromophenyl
{*13*} R = 4-chlorophenyl
{*14*} R = 4-methoxyphenyl
{*15*} R = 4-fluorophenyl
{*16*} R = 4-methylphenyl
{*17*} R = 3,4-dichlorophenyl
{*18*} R = 3,4-dimethoxyphenyl
{*19*} R = 2,4-difluorophenyl
{*20*} R = 4-chloro-3-trifluoro-methylphenyl
{*21*} R = furfuryl
{*22*} R = 5-methylfurfuryl
{*23*} R = thiophen-2-ylmethyl
{*24*} R = pyridin-3-ylmethyl
{*25*} R = pyridin-4-ylethyl

Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the ketone scaffold **3a** (80 mg, 0.36 mmol) in anhydrous THF (2 mL) was added. The appropriate amine (0.54 mmol) was added, followed by acetic acid (21 µL, 0.36 mmol). The reactions were shaken at 500 rpm at rt for 1 h, then sodium triacetoxyborohydride (150 mg, 0.72 mmol) added. The reactions were shaken for a further 13 h, then quenched by addition of 2M NaOH (0.5 mL) and shaken for an additional 10 min. Dichloromethane (2 mL) was added to each tube and the reactions passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure amines **26**.

Compound	Calculated mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
26{1}	313.2275	313.2288	21.8	19.4	95.0
26{2}	381.2148	381.2162	27.3	19.9	98.2
26{3}	327.2431	327.2442	30.5	26.0	100.0
26{4}	343.2380	343.2400	36.3	29.5	100.0
26{5}	331.2180	331.2196	36.8	31.0	100.0
26{6}	347.1885	347.1923	14.4	11.6	100.0
26{7}	439.1241	439.1272	38.8	24.6	100.0
26{8}	327.2431	327.2431	33.5	28.5	100.0
26{9}	347.1885	347.1910	19.8	15.9	97.2
26{10}	331.2180	331.2192	33.3	28.0	90.8
26{11}	343.2380	343.2400	33.7	27.4	100.0
26{12}	391.1380	391.1413	31.6	22.5	100.0
26{13}	347.1885	347.1912	31.0	24.9	100.0
26{14}	343.2380	343.2402	18.5	15.0	100.0
26{15}	331.2180	331.2206	38.3	32.2	100.0
26{16}	327.2431	327.2442	29.1	24.8	100.0
26{17}	381.1495	381.1513	25.1	18.3	96.9
26{18}	373.2486	373.2499	42.4	31.6	100.0
26{19}	349.2086	349.2113	39.0	31.1	100.0
26{20}	415.1759	415.1785	39.0	26.2	100.0

26{21}	303.2067	303.2074	26.9	24.7	100.0
26{22}	317.2224	317.2253	35.3	31.0	100.0
26{23}	319.1839	319.1860	22.8	19.9	100.0
26{24}	314.2227	314.2231	31.2	27.7	100.0
26{25}	328.2384	328.2416	26.9	22.8	100.0

Carbamates 27:



S4a R^1 = H
b = Me
c = nPr
d = Bn

27a-d

Amine:

{*1*} R^2 = benzyl, R^3 = H
{*2*} R^2 = 2-chlorobenzyl, R^3 = H
{*3*} R^2 = 3-trifluoromethylbenzyl, R^3 = H
{*4*} R^2 = 3-chlorobenzyl, R^3 = H
{*5*} R^2 = 4-methylbenzyl, R^3 = H
{*6*} R^2 = 4-chlorobenzyl, R^3 = H
{*7*} R^2 = 4-methoxybenzyl, R^3 = H
{*8*} R^2 = 4-trifluoromethylbenzyl, R^3 = H
{*9*} R^2 = 3,4-dichlorobenzyl, R^3 = H
{*10*} R^2 = 3,4-dimethoxybenzyl, R^3 = H
{*11*} R^2 = furfuryl, R^3 = H
{*12*} R^2 = 5-methylfurfuryl, R^3 = H
{*13*} R^2 = thiophen-2-ylmethyl, R^3 = H
{*14*} R^2 = pyridin-3-ylmethyl, R^3 = H
{*15*} R^2 = phenethyl, R^3 = H
{*16*} R^2 = 2-(1*H*-indol-3-yl)ethyl, R^3 = H
{*17*} R^2 = n-butyl, R^3 = H
{*18*} R^2 = 3-pentyl, R^3 = H
{*19*} R^2 = R^3 = ethyl
{*20*} R^2 = R^3 = morpholinyl
{*21*} R^2 = R^3 = 4-phenylpiperazinyl
{*22*} R^2 = R^3 = pyrrolidinyl
{*23*} R^2 = cyclohexyl, R^3 = H
{*24*} R^2 = cyclobutyl, R^3 = H

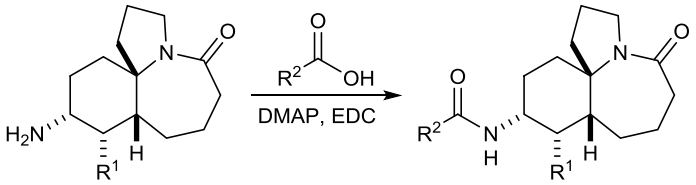
Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the carbonate scaffold **S4a-d** (80 mg) in anhydrous dichloromethane (1.5 mL) was added, followed by the appropriate amine (1.5 equiv). The reactions were shaken at 500 rpm at rt for 48 h, then water (2 mL) added. The reactions were passed through Isolute® hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure carbamates **27**.

Compound	Calculated Mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
27a{1}	357.2173	357.2189	35.9	48.0	100.0
27a{2}	391.1783	391.1788	52.0	63.5	100.0
27a{3}	425.2047	425.2080	54.0	60.6	98.1
27a{4}	391.1783	391.1790	55.0	67.1	98.7
27a{5}	371.2329	371.2357	48.1	61.9	100.0
27a{6}	391.1783	391.1814	49.2	60.0	100.0
27a{7}	387.2279	387.2265	40.1	49.4	100.0
27a{8}	425.2047	425.2043	49.6	55.7	100.0
27a{9}	425.1393	425.1452	48.8	54.8	100.0
27a{10}	417.2384	417.2370	45.0	51.5	100.0
27a{11}	347.1966	347.1975	45.0	61.9	100.0
27a{12}	361.2122	361.2134	28.9	38.2	98.4
27a{13}	363.1737	363.1761	33.7	44.3	100.0

27a{14}	358.2125	358.2135	35.9	47.9	100.0
27a{15}	371.2329	371.2330	56.8	73.1	100.0
27a{16}	410.2438	410.2466	51.0	59.3	98.8
27a{17}	323.2329	323.2342	34.2	50.5	97.5
27a{18}	337.2486	337.2507	38.3	54.2	100.0
27a{19}	323.2329	323.2369	33.3	49.2	90.2
27a{20}	337.2122	337.2154	35.7	50.6	92.9
27a{21}	412.2595	412.2629	35.6	41.2	100.0
27a{22}	321.2173	321.2209	36.1	53.7	95.9
27a{23}	349.2486	349.2506	30.9	42.3	99.0
27a{24}	321.2173	321.2176	31.0	46.1	100.0
27b{1}	371.2329	371.2336	47.5	61.1	100.0
27b{2}	405.1940	405.1938	49.5	58.3	100.0
27b{3}	439.2203	439.2181	45.0	48.9	100.0
27b{4}	405.1940	405.1926	42.3	49.8	100.0
27b{5}	385.2486	385.2510	36.8	45.6	100.0
27b{6}	405.1940	405.1922	29.6	34.9	100.0
27b{7}	401.2435	401.2449	26.3	31.3	98.9
27b{8}	439.2203	439.2206	23.6	25.6	100.0
27b{9}	439.1550	439.1497	38.5	41.8	100.0
27b{10}	431.2541	431.2542	24.9	27.6	100.0
27b{11}	361.2122	361.2135	23.0	30.4	100.0
27b{12}	375.2279	375.2288	35.1	44.7	100.0
27b{13}	377.1894	377.1879	19.1	24.2	98.9
27b{14}	372.2282	372.2301	18.2	23.3	97.9
27b{15}	385.2486	385.2502	32.7	40.5	100.0
27b{16}	424.2595	424.2609	33.4	37.6	100.0
27b{17}	337.2486	337.2522	21.9	31.0	100.0
27b{18}	351.2642	351.2660	26.3	35.8	95.1
27b{19}	337.2486	337.2507	30.4	43.1	92.6
27b{20}	351.2279	351.2295	27.7	37.7	100.0
27b{21}	426.2751	426.2762	31.0	34.7	98.9
27b{22}	335.2329	335.2358	11.7	16.7	92.3
27b{23}	363.2642	363.2659	29.0	38.1	93.9
27b{24}	335.2329	335.2349	26.7	38.0	93.3
27c{1}	399.2642	399.2655	32.4	42.8	100.0
27c{2}	433.2253	433.2271	36.0	43.8	100.0
27c{3}	467.2516	467.2537	34.8	39.3	100.0
27c{4}	433.2253	433.2284	65.6	79.9	100.0
27c{5}	413.2799	413.2822	50.9	65.0	100.0
27c{6}	433.2253	433.2261	29.3	35.7	100.0
27c{7}	429.2748	429.2772	32.7	40.2	100.0
27c{8}	467.2516	467.2519	67.6	76.3	99.0
27c{9}	467.1863	467.1869	35.7	40.3	100.0
27c{10}	459.2854	459.2870	67.8	77.9	97.0
27c{11}	389.2435	389.2434	25.7	34.8	100.0
27c{12}	403.2592	403.2605	57.0	74.6	96.9
27c{13}	405.2207	405.2212	54.9	71.5	100.0
27c{14}	400.2595	400.2621	27.3	36.0	100.0
27c{15}	413.2799	413.2838	31.4	40.1	100.0
27c{16}	452.2908	452.2921	56.0	65.3	100.0
27c{17}	365.2799	365.2807	26.4	38.1	100.0
27c{18}	379.2955	379.2984	29.7	41.3	100.0
27c{19}	365.2799	365.2804	53.3	77.0	89.8
27c{20}	379.2592	379.2579	30.9	43.0	100.0
27c{21}	454.3064	454.3093	40.7	47.3	100.0
27c{22}	363.2642	363.2656	22.5	32.7	100.0
27c{23}	391.2955	391.2966	29.9	40.3	100.0
27c{24}	363.2642	363.2649	48.7	70.8	91.6
27d{1}	447.2642	447.2655	44.0	58.0	100.0
27d{2}	481.2253	481.2273	54.9	67.2	100.0

27d{3}	515.2516	515.2521	53.7	61.4	99.0
27d{4}	481.2253	481.2276	57.6	70.6	98.7
27d{5}	461.2799	461.2777	52.5	67.1	100.0
27d{6}	481.2253	481.2258	43.9	53.8	100.0
27d{7}	477.2748	477.2761	43.8	54.1	100.0
27d{8}	515.2516	515.2517	62.0	70.9	96.9
27d{9}	515.1863	515.1882	61.6	70.5	98.6
27d{10}	507.2854	507.2867	42.5	49.4	100.0
27d{11}	437.2435	437.2456	42.5	57.3	100.0
27d{12}	451.2592	451.2602	49.6	64.8	100.0
27d{13}	453.2207	453.2205	45.3	58.9	100.0
27d{14}	448.2595	448.2596	43.0	56.6	100.0
27d{15}	461.2799	461.2807	51.4	65.7	100.0
27d{16}	500.2908	500.2932	58.1	68.5	100.0
27d{17}	413.2799	413.2802	38.6	55.1	100.0
27d{18}	427.2955	427.2931	50.8	70.1	100.0
27d{19}	413.2799	413.2779	12.7	18.1	96.7
27d{20}	427.2592	427.2596	7.9	10.9	86.1
27d{21}	502.3064	502.3063	52.8	62.0	100.0
27d{22}	411.2642	411.2644	36.1	51.8	98.6
27d{23}	439.2955	439.2951	49.4	66.3	100.0
27d{24}	411.2642	411.2674	57.3	82.2	97.3

General procedure for the preparation of amides 28



4b R^1 = Me
c = nPr
d = Bn

28b-d

Carboxylic acid:

{*1*} R^2 = phenyl
{*2*} R^2 = 4-chlorophenyl
{*3*} R^2 = 4-methoxyphenyl
{*4*} R^2 = 4-methylphenyl
{*5*} R^2 = 4-trifluoromethylphenyl
{*6*} R^2 = 4-dimethylaminophenyl
{*7*} R^2 = 3-chlorophenyl
{*8*} R^2 = 3-dimethylaminophenyl
{*9*} R^2 = 3-methylphenyl
{*10*} R^2 = 3-trifluoromethylphenyl
{*11*} R^2 = 3,4-dichlorophenyl
{*12*} R^2 = 4-chloro-3-trifluoro-methylphenyl
{*13*} R^2 = n-butyl
{*14*} R^2 = n-hexyl
{*15*} R^2 = buten-4-yl
{*16*} R^2 = cyclobutyl
{*17*} R^2 = cyclohexyl
{*18*} R^2 = (tetrahydrofuran-3-yl)methyl
{*19*} R^2 = cinnamoyl
{*20*} R^2 = propyn-1-yl
{*21*} R^2 = 3-phenylpropyn-1-yl
{*22*} R^2 = (thiophen-3-yl)methyl
{*23*} R^2 = nicotinyl
{*24*} R^2 = diphenylmethyl

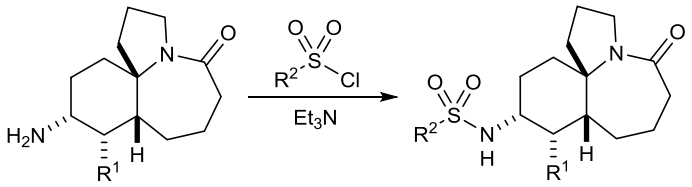
Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the amine scaffold **4b-d** (60 mg) in anhydrous dichloromethane (1.5 mL) was added, followed by the appropriate acid (1.2 equiv), EDC (1.2 equiv) and DMAP (1.2 equiv). The reactions were shaken at 500 rpm at rt for 18 h, then water (2 mL) added. The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were

evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure amides **28**.

Compound	Calculated Mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
28b{1}	341.2224	341.2244	60.3	70.9	93.6
28b{2}	375.1834	375.1847	13.7	14.6	97.4
28b{3}	371.2329	371.2342	122.3	132.1	100.0
28b{5}	409.2098	409.2084	52.8	51.7	100.0
28b{7}	375.1834	375.1864	5.6	6.0	75.4
28b{8}	384.2646	384.2683	50.6	52.8	95.3
28b{9}	355.2380	355.2399	46.7	52.7	98.0
28b{10}	409.2098	409.2082	50.7	49.7	98.9
28b{11}	409.1444	N/A	0.0	0.0	N/A
28b{12}	443.1708	443.1706	59.1	53.5	98.6
28b{13}	321.2537	321.2545	47.7	59.6	100.0
28b{14}	363.3006	363.3026	41.6	45.9	100.0
28b{15}	319.2380	319.2414	36.9	46.4	100.0
28b{16}	319.2380	319.2412	22.3	28.0	100.0
28b{17}	347.2693	347.2701	33.1	38.2	100.0
28b{18}	335.2329	335.2358	25.2	30.2	97.7
28b{19}	367.2380	367.2369	41.4	45.2	100.0
28b{20}	303.2067	303.2083	17.1	22.6	100.0
28b{21}	365.2224	365.2231	25.4	27.9	100.0
28b{22}	361.1944	361.1955	46.4	51.5	100.0
28b{23}	342.2176	342.2206	67.2	78.8	80.4
28b{24}	431.2693	431.2725	25.3	23.5	100.0
28c{1}	369.2537	369.2551	4.6	5.4	89.9
28c{2}	403.2147	403.2168	29.3	31.7	100.0
28c{3}	399.2642	399.2638	23.0	25.1	100.0
28c{4}	383.2693	383.2684	18.3	20.8	100.0
28c{5}	437.2411	437.2430	13.5	13.5	96.7
28c{6}	412.2959	412.2959	9.9	10.5	100.0
28c{7}	403.2147	403.2162	31.8	34.4	100.0
28c{8}	412.2959	412.2958	28.1	29.7	98.5
28c{9}	383.2693	383.2683	15.1	17.2	100.0
28c{10}	437.2411	437.2407	32.2	32.1	100.0
28c{11}	437.1757	437.1804	23.5	23.4	100.0
28c{12}	471.2021	471.2030	37.5	34.7	94.5
28c{13}	349.2850	349.2879	35.9	44.8	98.0
28c{14}	391.3319	391.3318	40.1	44.7	96.8
28c{15}	347.2693	347.2717	31.1	39.1	94.3
28c{16}	347.2693	347.2722	10.9	13.7	100.0
28c{17}	375.3006	375.3038	23.5	27.3	100.0
28c{18}	363.2642	363.2666	30.8	37.0	100.0
28c{19}	395.2693	395.2696	37.7	41.6	100.0
28c{20}	331.2380	331.2421	9.6	12.6	96.2
28c{21}	393.2537	393.2510	7.8	8.6	95.9
28c{22}	389.2257	389.2268	13.7	15.3	71.2
28c{23}	370.2489	370.2507	20.9	24.6	100.0
28c{24}	459.3006	459.3026	55.6	52.7	100.0
28d{1}	417.2537	417.2537	36.2	41.4	98.8
28d{2}	451.2147	451.2148	32.5	34.4	98.3
28d{3}	447.2642	447.2645	39.1	41.7	97.6
28d{4}	431.2693	431.2708	48.9	54.1	100.0
28d{5}	485.2411	485.2403	44.7	44.0	95.4
28d{6}	460.2959	460.2948	73.5	76.2	96.6
28d{7}	451.2147	451.2142	45.8	48.4	99.0
28d{8}	460.2959	460.2949	63.5	65.8	95.3

28d{9}	431.2693	431.2669	44.9	49.7	97.1
28d{10}	485.2411	485.2445	57.3	56.3	98.8
28d{11}	485.1757	485.1770	34.3	33.7	98.3
28d{12}	519.2021	519.2014	55.0	50.5	96.6
28d{13}	397.2850	397.2853	54.6	65.6	98.3
28d{14}	439.3319	439.3316	55.9	60.7	97.7
28d{15}	395.2693	395.2673	54.0	65.2	93.4
28d{16}	395.2693	395.2696	34.0	41.1	98.0
28d{17}	423.3006	423.3005	21.3	24.0	91.6
28d{18}	411.2642	411.2638	45.9	53.3	100.0
28d{19}	443.2693	443.2688	77.0	82.9	93.2
28d{20}	379.2380	379.2379	26.4	33.2	100.0
28d{21}	441.2537	441.2520	33.5	36.2	100.0
28d{22}	437.2257	437.2256	42.8	46.7	100.0
28d{23}	418.2489	418.2500	40.4	46.1	100.0
28d{24}	507.3006	507.2996	74.6	70.2	100.0

General procedure for the preparation of sulfonamides 29



4b R^1 = Me
c = nPr
d = Bn

29b-d

Sulfonyl chloride:

{*1*} R^2 = phenyl
{*2*} R^2 = 2-nitrophenyl
{*3*} R^2 = 2-methylphenyl
{*4*} R^2 = 3-nitrophenyl
{*5*} R^2 = 3-methylphenyl
{*6*} R^2 = 4-methylphenyl
{*7*} R^2 = 4-fluorophenyl
{*8*} R^2 = 4-chlorophenyl
{*9*} R^2 = 4-cyanophenyl
{*10*} R^2 = 4-methoxyphenyl
{*11*} R^2 = 4-nitrophenyl
{*12*} R^2 = 4-trifluoromethylphenyl
{*13*} R^2 = 4-acetamidophenyl
{*14*} R^2 = 4-n-butylphenyl
{*15*} R^2 = 4-biphenyl
{*16*} R^2 = 4-bromophenyl
{*17*} R^2 = 2,4-dinitrophenyl
{*18*} R^2 = 3,5-dichlorophenyl
{19} R^2 = mesityl
{*20*} R^2 = naphth-2-yl
{*21*} R^2 = thiophen-2-yl
{*22*} R^2 = *N*-methylimidazol-4-yl
{*23*} R^2 = benzyl
{*24*} R^2 = cyclohexyl

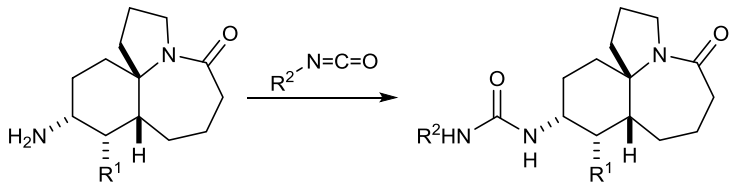
Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the amine scaffold **4b-d** (70 mg) in anhydrous dichloromethane (2 mL) was added, followed by the appropriate sulfonyl chloride (1.5 equiv) and Et_3N (1.5 equiv). The reactions were shaken at 500 rpm at rt for 18 h, then water (2 mL) added. The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure sulfonamides **29**.

Compound	Calculated Mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
29b{1}	377.1894	377.1899	48.5	43.0	100.0
29b{2}	422.1744	422.1725	69.6	55.1	100.0
29b{3}	391.2050	391.2053	77.2	65.9	100.0

29b{4}	422.1744	422.1753	38.2	30.2	100.0
29b{5}	391.2050	391.2075	60.1	51.3	97.5
29b{6}	391.2050	391.2055	0.8	0.7	81.3
29b{7}	395.1799	395.1820	66.8	56.5	100.0
29b{8}	411.1504	411.1505	59.5	48.4	100.0
29b{9}	402.1846	402.1849	60.7	50.4	98.6
29b{10}	407.1999	N/A	0.0	0.0	N/A
29b{11}	422.1744	422.1731	70.3	55.6	96.5
29b{12}	445.1767	445.1782	67.9	51.0	98.5
29b{13}	434.2108	434.2116	3.9	3.0	96.3
29b{14}	433.2520	433.2509	66.4	51.2	100.0
29b{15}	453.2207	453.2216	58.5	43.1	100.0
29b{16}	455.0999	455.1032	81.9	60.1	98.6
29b{17}	467.1595	467.1598	23.6	16.9	100.0
29b{18}	445.1114	445.1129	67.2	50.4	100.0
29b{19}	419.2363	419.2376	36.7	29.3	100.0
29b{20}	427.2050	427.2044	79.5	62.2	100.0
29b{21}	383.1458	383.1481	60.6	52.9	95.7
29b{22}	381.1955	381.1958	15.0	13.2	96.7
29b{23}	391.2050	391.2068	47.2	40.3	100.0
29b{24}	383.2363	383.2385	1.0	0.9	22.1
29c{1}	405.2207	405.2200	42.9	40.8	100.0
29c{2}	450.2057	450.2058	29.2	25.0	100.0
29c{3}	419.2363	419.2366	53.4	49.1	100.0
29c{4}	450.2057	450.2047	45.8	39.2	100.0
29c{5}	419.2363	419.2371	51.5	47.4	100.0
29c{6}	419.2363	419.2378	24.5	22.5	96.8
29c{7}	423.2112	423.2110	46.9	42.7	100.0
29c{8}	439.1817	439.1808	44.0	38.6	100.0
29c{9}	430.2159	430.2155	42.9	38.4	98.2
29c{10}	435.2312	435.2318	53.1	47.0	98.7
29c{11}	450.2057	450.2061	31.4	26.9	100.0
29c{12}	473.2080	473.2077	26.9	21.9	96.2
29c{13}	462.2421	462.2435	60.8	50.7	100.0
29c{14}	461.2833	461.2835	58.3	48.7	98.4
29c{15}	481.2520	481.2521	52.2	41.8	100.0
29c{16}	483.1312	483.1317	60.9	48.6	98.9
29c{17}	495.1908	495.1903	51.9	40.4	96.7
29c{18}	473.1427	473.1418	65.9	53.7	100.0
29c{19}	447.2676	447.2681	10.3	8.9	100.0
29c{20}	455.2363	455.2365	48.5	41.1	100.0
29c{21}	411.1771	411.1767	59.1	55.4	96.7
29c{22}	409.2268	409.2289	9.7	9.1	91.1
29c{23}	419.2363	419.2382	38.5	35.4	100.0
29c{24}	411.2676	411.2697	0.0	0.0	15.3
29d{1}	453.2207	453.2194	52.4	55.2	100.0
29d{3}	467.2363	467.2354	35.2	36.0	100.0
29d{4}	498.2057	498.2050	64.6	61.9	100.0
29d{5}	467.2363	467.2362	56.8	58.0	97.9
29d{6}	467.2363	467.2352	64.1	65.5	100.0
29d{7}	471.2112	471.2092	59.3	60.1	100.0
29d{8}	487.1817	487.1806	78.1	76.5	100.0
29d{9}	478.2159	478.2154	54.8	54.7	98.6
29d{10}	483.2312	483.2308	61.0	60.2	98.7
29d{11}	498.2057	498.2062	51.5	49.3	100.0
29d{12}	521.2080	521.2081	70.7	64.7	100.0
29d{13}	510.2421	510.2429	24.6	23.0	98.5
29d{14}	509.2833	509.2836	63.0	59.0	100.0
29d{15}	529.2520	509.2836	62.3	56.2	100.0
29d{16}	531.1312	531.1308	83.9	75.4	100.0
29d{17}	543.1908	543.1914	35.7	31.4	97.1

29d{18}	521.1427	521.1418	78.0	71.4	100.0
29d{19}	495.2676	495.2667	38.9	37.5	100.0
29d{20}	503.2363	503.2385	14.0	13.3	96.1
29d{21}	459.1771	459.1761	45.9	47.7	97.7
29d{22}	457.2268	457.2260	56.5	59.0	100.0
29d{23}	467.2363	467.2374	48.1	49.1	99.0
29d{24}	459.2676	459.2682	0.6	0.6	8.3

Ureas 30:



4b R^1 = Me
c = nPr
d = Bn

Sulfonyl chloride:

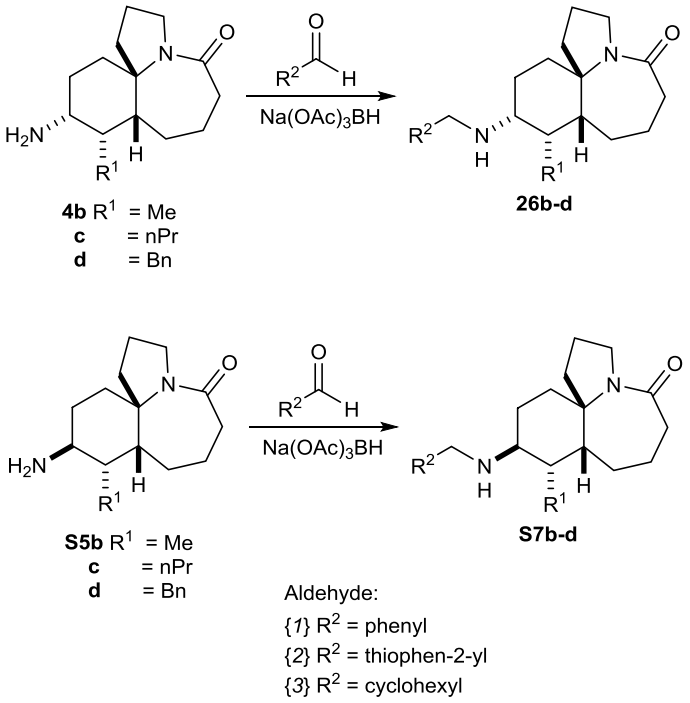
{*1*} R^2 = phenyl
{*2*} R^2 = 2-methylphenyl
{*3*} R^2 = 2-chlorophenyl
{*4*} R^2 = 2-methoxyphenyl
{*5*} R^2 = 2-trifluoromethylphenyl
{*6*} R^2 = 3-methoxyphenyl
{*7*} R^2 = 3-trifluoromethylphenyl
{*8*} R^2 = 3-cyanophenyl
{*9*} R^2 = 4-methylphenyl
{*10*} R^2 = 4-chlorophenyl
{*11*} R^2 = 4-methoxyphenyl
{*12*} R^2 = 4-trofluoromethylphenyl
{*13*} R^2 = 4-cyanophenyl
{*14*} R^2 = 4-fluorophenyl
{*15*} R^2 = 4-isopropylphenyl
{*16*} R^2 = 3,4-(methylene-dioxy)phenyl
{*17*} R^2 = 3,5-dichlorophenyl
{18} R^2 = benzyl
{*19*} R^2 = furfuryl
{*20*} R^2 = $(CH_2)_3CO_2Et$
{*21*} R^2 = ethyl
{*22*} R^2 = n-butyl

Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the amine scaffold **4b-d** (60 mg) in anhydrous toluene (2 mL) was added, followed by the appropriate isocyanate (1.5 equiv). The reactions were shaken at 500 rpm at rt for 18 h, then evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure ureas **30**.

Compound	Cal. Mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
30b{1}	356.2333	356.2344	89.9	84.4	100.0
30b{2}	370.2489	370.2501	59.9	54.1	92.6
30b{3}	390.1943	390.1954	8.6	7.4	66.5
30b{4}	386.2438	386.2447	31.4	27.2	76.1
30b{5}	424.2207	424.2213	30.0	23.6	63.8
30b{6}	386.2438	386.2448	77.5	67.1	98.8
30b{7}	424.2207	424.2223	68.8	54.2	94.2
30b{8}	381.2285	381.2299	26.6	23.3	97.9
30b{9}	370.2489	370.2492	91.6	82.7	81.3
30b{10}	390.1943	390.1949	51.3	43.9	79.2
30b{11}	386.2438	386.2451	60.0	51.9	86.3
30b{12}	424.2207	424.2223	82.2	64.7	99.0
30b{13}	381.2285	381.2291	25.0	21.9	99.0
30b{14}	374.2239	374.2271	70.8	63.2	100.0
30b{15}	398.2802	398.2814	106.0	88.9	99.0
30b{16}	400.2231	400.2246	83.3	69.6	100.0

30b{17}	424.1553	424.1563	16.4	12.9	86.1
30b{18}	370.2489	370.2498	16.3	14.7	92.9
30b{19}	360.2282	360.2297	75.9	70.4	79.2
30b{20}	394.2701	394.2721	103.0	87.3	98.7
30b{21}	308.2333	308.2346	27.8	30.2	97.0
30b{22}	336.2646	336.2660	45.5	45.2	97.5
30c{1}	384.2646	384.2647	24.8	24.9	92.5
30c{2}	398.2802	398.2794	25.6	24.8	100.0
30c{3}	418.2256	418.2276	16.0	14.7	100.0
30c{4}	414.2751	414.2776	29.7	27.6	100.0
30c{5}	452.2520	452.2524	10.1	8.6	76.2
30c{6}	414.2751	414.2784	7.1	6.6	83.8
30c{7}	452.2520	452.2522	31.2	26.6	95.3
30c{8}	409.2598	409.2625	20.3	19.1	88.9
30c{9}	398.2802	398.2783	22.1	21.4	67.0
30c{10}	418.2256	418.2296	29.1	26.8	100.0
30c{11}	414.2751	414.2773	29.8	27.7	86.5
30c{12}	452.2520	452.2521	32.7	27.9	100.0
30c{13}	409.2598	409.2621	21.6	20.3	93.6
30c{14}	402.2552	402.2558	30.9	29.6	72.3
30c{15}	426.3115	426.3122	14.0	12.7	99.0
30c{16}	428.2544	428.2579	7.1	6.4	0.9
30c{17}	452.1866	452.1900	22.0	18.8	96.8
30c{18}	398.2802	398.2800	23.0	22.3	14.0
30c{19}	388.2595	388.2631	26.8	26.6	100.0
30c{20}	422.3014	422.3027	18.0	16.4	94.0
30c{21}	336.2646	336.2686	14.7	16.9	87.2
30c{22}	364.2959	364.2971	32.8	34.7	100.0
30d{1}	432.2646	432.2662	23.7	26.2	98.5
30d{2}	446.2802	446.2825	57.8	61.8	87.2
30d{3}	466.2256	466.2288	23.0	23.5	96.8
30d{4}	462.2751	462.2765	60.5	62.5	79.1
30d{5}	500.2520	500.2492	28.6	27.3	94.3
30d{6}	462.2751	462.2749	50.4	52.0	95.3
30d{7}	500.2520	500.2531	47.0	44.8	96.7
30d{8}	457.2598	457.2616	34.4	35.9	100.0
30d{9}	446.2802	446.2808	19.4	20.7	95.3
30d{10}	466.2256	466.2277	27.6	28.3	100.0
30d{11}	462.2751	462.2757	38.0	39.2	100.0
30d{12}	500.2520	500.2528	54.6	52.1	98.1
30d{13}	457.2598	457.2627	59.8	62.4	86.5
30d{14}	450.2552	450.2566	46.9	49.7	98.4
30d{15}	474.3115	474.3122	40.2	40.4	100.0
30d{16}	476.2544	476.2544	40.8	40.9	90.5
30d{17}	500.1866	-	0.0	0.0	-
30d{18}	446.2802	446.2841	37.8	40.4	73.9
30d{19}	436.2595	436.2616	51.2	56.0	100.0
30d{20}	470.3014	470.3048	62.1	63.0	97.3
30d{21}	384.2646	384.2675	54.0	67.1	100.0
30d{22}	412.2959	412.2988	51.4	59.5	98.7

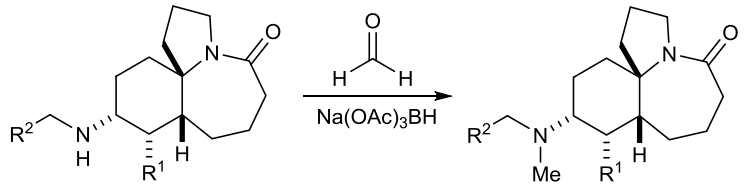
Amines 26 and S7b-d from scaffolds 4b-d and S5b-d:



The appropriate aldehyde (1.2 equiv) was added to a solution of amine scaffold **4b-d** or **S5b-d** (200 mg) in anhydrous dichloromethane (6 mL) at rt under argon. Acetic acid (1 equiv) was then added, and the mixture stirred at rt for 1 h. Sodium triacetoxyborohydride (2 equiv) was added, and the mixture stirred at rt for 18 h, then quenched with 2M NaOH (3 mL) and extracted with dichloromethane (3 x 5 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by Combiflash® automated column chromatography (12 g silica column, 0% MeOH in CH_2Cl_2 for 3 min, then 0 to 5% over 10 min) to afford pure amines **26** or **S7b-d**.

Compound	Calculated mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
26b{*1*}	327.2431	327.2487	430	80.0	95.4
26b{*2*}	333.1995	333.2039	360	66.0	100.0
26b{*3*}	333.2901	333.2922	325	59.0	93.2
26c{*1*}	355.2744	355.2302	198	73.0	98.9
26c{*2*}	361.2308	361.2319	213	78.0	91.6
26c{*3*}	361.3214	361.3221	213	78.0	92.1
26d{*1*}	403.2744	403.2726	145	56.0	98.3
26d{*2*}	409.2308	409.2328	230	88.0	0.0
26d{*3*}	409.3214	409.3232	170	65.0	94.7
S7b{*1*}	327.2431	327.2454	88.8	32.0	79.7
S7b{*2*}	333.1995	333.2016	47.9	17.0	81.0
S7b{*3*}	333.2901	333.2908	77.5	27.4	85.2
S7c{*1*}	355.2744	355.2742	130	48.0	96.4
S7c{*2*}	361.2308	361.2318	143	52.0	97.7
S7c{*3*}	361.3214	361.3214	170	62.0	91.8
S7d{*1*}	403.2744	403.2743	147	57.0	95.2
S7d{*2*}	409.2308	409.2300	152	58.0	94.8
S7d{*3*}	409.3214	409.3233	90	34.0	96.6

General procedure for the preparation of amines 32



26b R^1 = Me
c = nPr
d = Bn

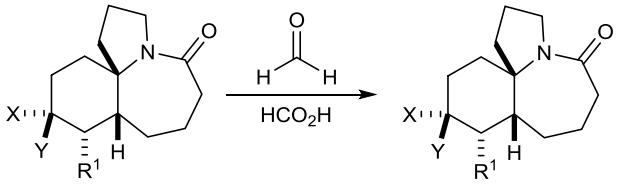
32b-d

{*1*} R^2 = phenyl
{*2*} R^2 = thiophen-2-yl
{*3*} R^2 = cyclohexyl

A solution of amine **26b-d** (150 mg) in dichloromethane (3 mL) was placed in a 2 dram screw cap vial. Formaldehyde (37% aq solution, 3 equiv) was added, followed by acetic acid (1 equiv) and sodium triacetoxyborohydride (3 equiv). The reaction mixture was stirred at rt for 18 h, then quenched with 2M NaOH and passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure amines **32**.

Compound	Calculated mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
32b{*1*}	341.2588	341.2610	97.4	136.3	93.9
32b{*2*}	347.2152	347.2141	41.5	57.1	100.0
32b{*3*}	347.3057	347.3072	74.9	103.0	94.0
32c{*1*}	369.2901	369.2906	76.2	98.5	92.9
32c{*2*}	375.2465	375.2458	79.9	101.7	93.7
32c{*3*}	375.3370	375.3416	80.6	102.5	90.5
32d{*1*}	417.2901	417.2896	97.5	73.2	95.6
32d{*2*}	423.2465	423.2450	86.8	46.7	93.2
32d{*3*}	423.3370	423.3343	181.8	97.8	90.1

Amines 31b-d and S8b-d:



4b-d X = NH_2, Y = H
S5b-d X = H, Y = NH_2

31b-d X = NMe_2, Y = H
S8b-d X = H, Y = NMe_2

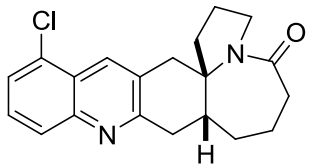
b R^1 = Me
c = nPr
d = Bn

Amine scaffold **4b-d** or **S5b-d** (150 mg) was dissolved in formic acid (900 µL) and formaldehyde (37% aq solution, 1.4 mL). The reaction mixture was heated at 95 ^{o}C for 18 h, then cooled to rt and concentrated under reduced pressure. The residue was made basic with 2M NaOH (2 mL) then extracted with dichloromethane (5 x 3 mL). The combined organics were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subjected to mass-directed preparative HPLC purification to afford pure amines **31** or **S8b-d**.

Compound	Calculated mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
31b	265.2275	265.2284	32	28.8	100.0
31c	293.2588	293.2600	55.1	33.1	100.0
31d	341.2588	341.2588	49.2	30.1	98.3
S8b	265.2275	265.2301	65.3	39.2	97.7
S8c	293.2588	293.2592	187.6	112.6	95.5
S8d	341.2588	341.2607	60.4	37.0	100.0

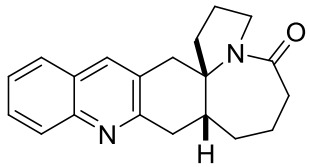
Characterization data for representative library compounds

Quinoline **25**{*3*}



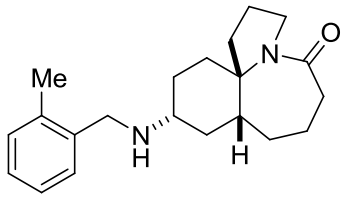
δ_H (500 MHz, $CDCl_3$) 8.26 (1H, s), 7.92-7.87 (1H, m), 7.58-7.53 (2H, m), 4.04-3.99 (1H, m), 3.58-3.43 (3H, m), 3.10-3.03 (2H, m), 2.75-2.69 (1H, m), 2.62-2.53 (1H, m), 2.13-1.96 (3H, m), 1.92-1.80 (4H, m), 1.72-1.59 (2H, m); δ_C (125 MHz, $CDCl_3$) 173.5, 157.2, 147.7, 133.0, 130.6, 128.9, 128.8, 127.6, 126.1, 125.0, 63.8, 49.3, 43.3, 41.00, 40.97, 38.3, 34.3, 33.3, 23.1, 20.3; *m/z* (ESI+) found $[M+H]^+$ 341.1430. $C_{20}H_{22}ClN_2O^+$ requires 341.1415.

Quinoline **25**{*1*}



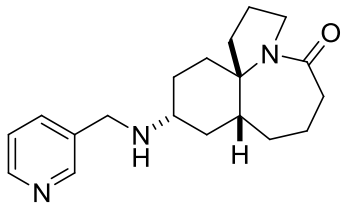
δ_H (500 MHz, $CDCl_3$) 7.98 (1H, d, *J* 8.5), 7.86 (1H, s), 7.74 (1H, d, *J* 8.1), 7.68-7.64 (1H, m), 7.50-7.46 (1H, m), 4.04-3.99 (1H, m), 3.54-3.43 (3H, m), 3.08 (1H, dd, *J* 17.8, 2.0), 2.99 (1H, d, *J* 16.5), 2.75-2.69 (1H, m), 2.61-2.55 (1H, m), 2.12-1.60 (9H, m); δ_C (125 MHz, $CDCl_3$) 173.6, 156.2, 147.1, 136.2, 129.3, 128.3, 127.6, 127.0, 126.9, 126.1, 63.9, 49.3, 43.4, 41.1, 40.6, 38.3, 34.2, 33.3, 23.1, 20.3; *m/z* (ESI+) found $[M+H]^+$ 307.1816. $C_{20}H_{23}N_2O^+$ requires 307.1805.

Amine **26**{*3*}



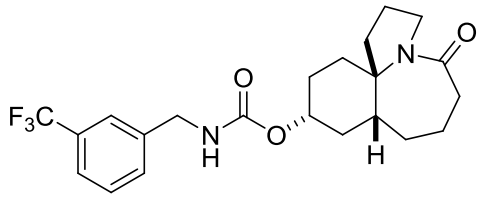
δ_H (500 MHz, $CDCl_3$) 7.28-7.25 (1H, m), 7.19-7.16 (3H, m), 3.75-3.67 (3H, m), 3.52-3.45 (1H, m), 2.95-2.91 (1H, m), 2.62-2.45 (3H, m), 2.40-2.35 (1H, m), 2.36 (3H, s), 2.23 (1H, ddd, *J* 13.3, 13.3, 4.9), 1.92-1.63 (10H, m), 1.53-1.44 (1H, m), 1.36 (1H, ddd, *J* 13.3, 4.2, 2.5); δ_C (125 MHz, $CDCl_3$) 173.8, 138.6, 136.4, 130.3, 128.6, 127.1, 126.0, 66.6, 51.8, 50.2, 48.7, 43.0, 39.7, 37.2, 35.2, 32.4, 28.4, 25.8, 22.3, 20.4, 19.0; *m/z* (ESI+) found $[M+H]^+$ 327.2442. $C_{21}H_{30}N_2O^+$ requires 327.2431.

Amine **26**{*24*}



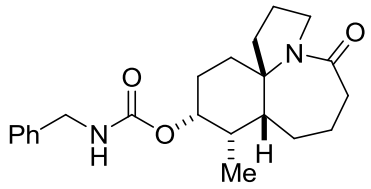
δ_H (500 MHz, $CDCl_3$) 8.54 (1H, d, *J* 1.7), 8.48 (1H, dd, *J* 4.8, 1.7), 7.64-7.62 (1H, m), 7.24 (1H, ddd, *J* 7.8, 4.8, 0.7), 3.78-3.66 (3H, m), 3.49-3.43 (1H, m), 2.90-2.85 (1H, m), 2.58-2.44 (3H, m), 2.36-2.31 (1H, m), 2.19 (1H, ddd, *J* 13.4, 13.4, 4.7), 1.86-1.58 (10H, m), 1.52-1.42 (1H, m), 1.34 (1H, ddd, *J* 13.4, 4.2, 2.2); δ_C (125 MHz, $CDCl_3$) 173.7, 149.6, 148.5, 136.0, 135.7, 123.4, 66.4, 51.2, 49.3, 48.7, 43.0, 39.7, 37.1, 34.8, 32.2, 28.5, 25.6, 22.2, 20.4; *m/z* (ESI+) found $[M+H]^+$ 314.2231. $C_{19}H_{28}N_3O^+$ requires 314.2227.

Carbamate **27a**{*3*}



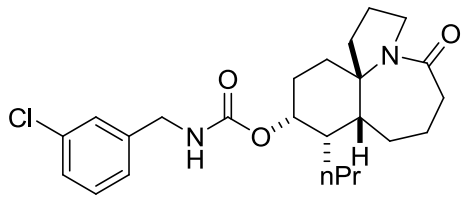
δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 4:1 mixture of rotamers was observed. Major rotamer: 7.52-7.40 (4H, m), 5.52 (1H, s), 4.90 (1H, br s), 4.41 (1H, d, *J* 6.2), 4.38 (1H, d, *J* 6.2), 3.74-3.68 (1H, m), 3.47-3.40 (1H, m), 2.59-2.53 (1H, m), 2.44-2.23 (3H, m), 2.14-2.08 (1H, m), 1.97-1.92 (1H, m), 1.89-1.53 (9H, m), 1.45-1.33 (2H, m). Minor rotamer (characteristic signals): 5.52 (1H, s), 4.44 (1H, d, *J* 6.2), 4.35 (1H, d, *J* 6.2); δ_C (125 MHz, $CDCl_3$) Major rotamer: 174.1, 155.9, 139.8, 130.75, 130.77 (q, *J* 32.0), 129.0, 124.1 (d, *J* 3.5), 124.0 (d, *J* 3.5), 123.9 (q, *J* 270), 68.4, 66.0, 48.9, 44.3, 43.4, 38.8, 38.4, 35.6, 34.0, 28.5, 24.6, 23.5, 20.1; *m/z* (ESI+) found $[M+H]^+$ 425.2080. $C_{22}H_{28}F_3N_2O_3^+$ requires 425.2047.

Carbamate **27b**{*1*}



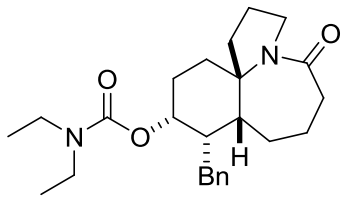
δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 7:3 mixture of rotamers was observed. Major rotamer: 7.33-7.19 (5H, m), 5.50 (1H, br s), 4.85 (1H, br s), 4.45-4.23 (2H, m), 3.83-3.71 (1H, m), 3.43-3.29 (1H, m), 2.62-2.53 (1H, m), 2.46-2.32 (2H, m), 2.11-2.00 (2H, m), 1.95-1.12 (11H, m), 0.96 (3H, d, *J* 6.9). Minor rotamer (characteristic signals): 5.39 (1H, br s), 4.79 (1H, br, s), 0.87 (3H, d, *J* 5.7); δ_C (125 MHz, $CDCl_3$) Major rotamer: 174.6, 156.4, 138.6, 128.7, 127.7, 127.5, 71.7, 67.6, 49.8, 49.1, 45.1, 38.9, 38.8, 37.1, 29.0, 27.8, 24.2, 23.6, 20.2, 15.9; *m/z* (ESI+) found $[M+H]^+$ 371.2336. $C_{22}H_{31}N_2O_3^+$ requires 371.2329.

Carbamate **27c**{*4*}



δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 7:3 mixture of rotamers was observed. Major rotamer: 7.28-7.09 (4H, m), 5.36 (1H, br s), 4.95 (1H, br s), 4.40-4.25 (2H, m), 3.85-3.74 (1H, m), 3.44-3.30 (1H, m), 2.63-2.58 (1H, m), 2.48-2.37 (2H, m), 2.14-1.50 (11H, m), 1.45-1.11 (6H, m), 0.91-0.80 (3H, m). Minor rotamer (characteristic signals): 5.63 (1H, br s), 4.88 (1H, br, s); δ_C (125 MHz, $CDCl_3$) Major rotamer: 174.5, 156.3, 140.8, 134.5, 129.9, 127.58, 127.55, 125.6, 70.7, 67.5, 49.1, 47.7, 44.4, 42.2, 38.9, 38.8, 31.7, 29.0, 27.9, 24.6, 23.7, 20.2, 19.9, 14.2; *m/z* (ESI+) found $[M+H]^+$ 433.2284. $C_{24}H_{34}ClN_2O_3^+$ requires 433.2252.

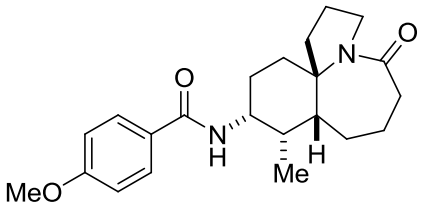
Carbamate **27d**{*19*}



δ_H (500 MHz, $CDCl_3$) 7.30-7.26 (2H, m), 7.22-7.18 (1H, m), 7.11-7.08 (2H, m), 4.85 (1H, br s), 3.86-3.79 (1H, m), 3.42-3.27 (5H, m), 2.78 (1H, dd, *J* 13.6, 7.6), 2.68-2.57 (2H, m), 2.47-2.38 (2H, m), 2.24-2.06 (4H, m), 1.97-1.91 (1H, m), 1.88-1.48 (6H, m), 1.42-1.30 (2H, m), 1.25-1.14 (6H, m); δ_C (125 MHz, $CDCl_3$) 174.3, 155.4, 139.7, 128.8, 128.6, 126.3, 70.2, 67.5, 49.1, 47.4, 45.0, 42.0, 41.4, 39.0, 38.9,

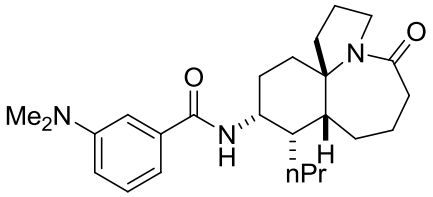
36.3, 28.8, 28.0, 24.6, 23.6, 20.2, 14.4, 13.7; *m/z* (ESI+) found $[M+H]^+$ 413.2779. $C_{25}H_{37}N_2O_3^+$ requires 413.2799.

Amide **28b**{*3*}



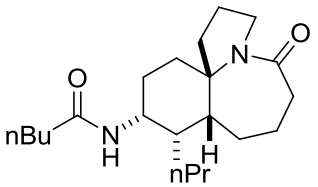
δ_H (500 MHz, $CDCl_3$) 7.69-7.66 (2H, m), 6.93-6.89 (2H, m), 6.25 (1H, d, *J* 8.5), 4.30-4.25 (1H, m), 3.82 (3H, s), 3.83-3.78 (1H, m), 3.46-3.39 (1H, m), 2.71-2.65 (1H, m), 2.44 (1H, dd, *J* 18.0, 18.0), 2.31-2.25 (2H, m), 2.21-2.15 (1H, m), 2.06-1.49 (9H, m), 1.45-1.35 (2H, m), 1.00 (3H, d, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 174.0, 166.7, 162.2, 128.5, 127.1, 113.9, 67.7, 55.5, 50.7, 49.2, 46.8, 39.1, 38.9, 36.7, 29.0, 28.9, 24.4, 23.8, 20.1, 16.5; *m/z* (ESI+) found $[M+H]^+$ 371.2342. $C_{22}H_{31}N_2O_3^+$ requires 371.2329.

Amide **28c**{*8*}



δ_H (500 MHz, $CDCl_3$) 7.26 (1H, t, *J* 8.2), 7.17 (1H, dd, *J* 2.4, 1.7), 6.86 (1H, br d, *J* 8.2), 6.82 (1H, dd, *J* 8.2, 2.4), 6.31 (1H, d, *J* 8.5), 4.35-4.30 (1H, m), 3.85-3.79 (1H, m), 3.47-3.41 (1H, m), 2.97 (6H, s), 2.72-2.65 (1H, m), 2.61-2.57 (1H, m), 2.45-2.37 (1H, m), 2.18-1.86 (7H, m), 1.82-1.58 (4H, m), 1.48-1.24 (6H, m), 0.86 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 173.9, 167.8, 150.8, 135.8, 129.3, 115.1, 113.2, 111.3, 67.7, 49.3, 48.6, 45.6, 41.6, 41.0, 40.4, 39.1, 39.0, 32.4, 29.14, 29.08, 24.8, 23.9, 20.09, 20.05, 14.2; *m/z* (ESI+) found $[M+H]^+$ 412.2958. $C_{25}H_{38}N_3O_2^+$ requires 412.2959.

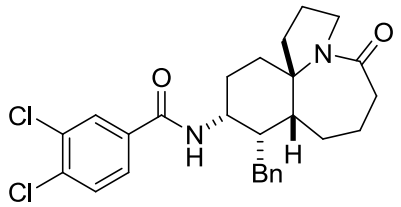
Amide **28c**{*13*}



δ_H (500 MHz, $CDCl_3$) 6.03 (1H, d, *J* 8.9), 4.04-3.98 (1H, m), 3.68-3.62 (1H, m), 3.30-3.23 (1H, m), 2.50-2.29 (3H, m), 2.04 (2H, td, *J* 7.9, 1.9), 1.94 (1H, ddd, *J* 13.7, 13.7, 4.5), 1.85-1.70 (4H, m), 1.66-1.38 (8H, m), 1.29-1.02 (8H, m), 0.77 (3H, t, *J* 7.4), 0.72 (3H, t, *J* 7.5); δ_C (125 MHz, $CDCl_3$) 174.0, 172.6,

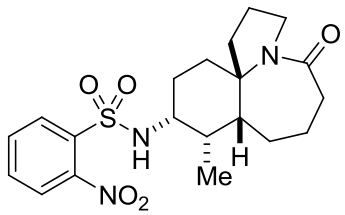
67.6, 49.0, 48.3, 44.6, 41.6, 38.77, 38.76, 36.6, 32.2, 29.2, 28.2, 27.9, 24.8, 23.7, 22.3, 20.0, 19.9, 14.1, 13.8; *m/z* (ESI+) found $[M+H]^+$ 349.2879. $C_{21}H_{36}N_2O_2^+$ requires 349.2850.

Amide **28d**{*11*}



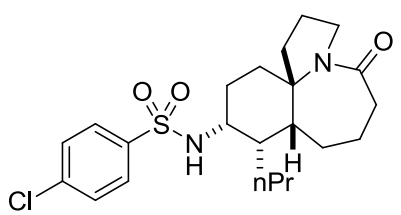
δ_H (500 MHz, $CDCl_3$) 7.88 (1H, br s), 7.59-7.55 (2H, m), 7.73-7.26 (2H, m), 7.23-7.19 (1H, m), 7.12-7.09 (2H, m), 6.39 (1H, d, *J* 8.5), 4.40-4.35 (1H, m), 3.81 (1H, dd, *J* 10.5, 10.5), 3.40-3.33 (1H, m), 2.84 (1H, dd, *J* 13.9, 6.6), 2.72-2.66 (1H, m), 2.63-2.54 (2H, m), 2.46-2.38 (2H, m), 2.34-2.29 (1H, m), 2.10-1.89 (3H, m), 1.80-1.61 (4H, m), 1.56-1.47 (3H, m), 1.38-1.28 (1H, m); δ_C (125 MHz, $CDCl_3$) 173.7, 164.9, 139.0, 136.2, 134.6, 133.4, 130.8, 129.3, 128.7, 128.6, 126.5, 125.7, 67.4, 49.3, 47.6, 46.4, 44.3, 39.1, 38.9, 36.4, 29.2, 29.1, 24.7, 23.6, 19.9; *m/z* (ESI+) found $[M+H]^+$ 485.1770. $C_{27}H_{31}Cl_2N_2O_2^+$ requires 485.1757.

Sulfonamide **29b**{*2*}



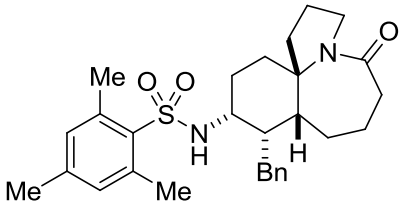
Mp 227-229 ^oC; ν_{max} (film)/cm^{-1} 2942, 1591, 1539; δ_H (500 MHz, $CDCl_3$) 8.12-8.08 (1H, m), 7.91-7.86 (1H, m), 7.78-7.73 (2H, m), 5.55 (1H, d, *J* 7.0), 3.85-3.79 (1H, m), 3.50-3.41 (2H, m), 2.71 (1H, dd, *J* 15.3, 6.7), 2.49-2.40 (2H, m), 2.21-2.01 (3H, m), 1.98-1.90 (1H, m), 1.86-1.32 (9H, m), 0.84 (3H, d, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 174.2 (C), 147.9 (C), 133.9 (C), 133.7 (CH), 132.9 (CH), 130.8 (CH), 125.6 (CH), 67.2 (C), 53.2 (CH), 50.3 (CH), 49.2 (CH_2), 39.1 (CH_2), 39.0 (CH_2), 36.8 (CH), 30.0 (CH_2), 28.6 (CH_2), 23.9 (CH_2), 23.6 (CH_2), 20.0 (CH_2), 16.3 (CH_3); *m/z* (ESI+) found $[M+H]^+$ 422.1765. $C_{20}H_{28}N_3O_5S^+$ requires 422.1744.

Sulfonamide **29c**{*8*}



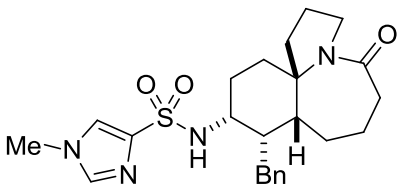
Mp 207-208 °C; δ_H (500 MHz, $CDCl_3$) 7.87-7.83 (2H, m), 7.52-7.49 (2H, m), 5.29 (1H, d, *J* 7.1), 3.81-3.76 (1H, m), 3.44-3.37 (1H, m), 3.27-3.23 (1H, m), 2.59 (1H, dd, *J* 15.2, 6.7), 2.41-2.31 (2H, m), 2.07-2.00 (1H, m), 1.92-1.87 (1H, m), 1.84-1.79 (1H, m), 1.76-1.56 (7H, m), 1.53-1.48 (1H, m), 1.38-0.94 (6H, m), 0.78 (3H, t, *J* 7.1); δ_C (125 MHz, $CDCl_3$) 172.5 (C), 137.4 (C), 136.5 (C), 127.5 (CH), 126.8 (CH), 65.2 (C), 48.7 (CH), 47.2 (CH_2), 46.3 (CH), 40.2 (CH), 37.1 (CH_2), 36.8 (CH_2), 30.3 (CH_2), 27.3 (CH_2), 26.5 (CH_2), 22.4 (CH_2), 21.6 (CH_2), 18.1 (CH_2), 18.0 (CH_2), 12.1 (CH_3); *m/z* (ESI+) found $[M+H]^+$ 439.1808. $C_{22}H_{32}ClN_2O_3S^+$ requires 439.1817.

Sulfonamide **29d**{*19*}



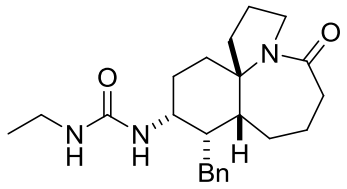
δ_H (500 MHz, $CDCl_3$) 7.26-7.21 (2H, m), 7.20-7.16 (1H, m), 6.98-6.95 (4H, m), 4.92 (1H, d, *J* 7.9), 3.77-3.72 (1H, m), 3.43-3.38 (1H, m), 3.36-3.29 (1H, m), 2.67 (6H, s), 2.67-2.62 (1H, m), 2.58-2.52 (1H, m), 2.44-2.35 (3H, m), 2.29 (3H, s), 2.23-2.18 (1H, m), 2.14-2.09 (1H, m), 2.01 (1H, ddd, *J* 13.5, 13.5, 5.1), 1.89-1.55 (6H, m), 1.46-1.33 (3H, m), 1.26-1.18 (1H, m); δ_C (125 MHz, $CDCl_3$) 174.0, 142.5, 139.1, 139.0, 134.1, 132.1, 128.6, 128.5, 126.3, 67.2, 51.1, 49.1, 46.9, 44.2, 38.90, 38.85, 35.9, 29.3, 28.6, 24.3, 23.4, 23.2, 21.0, 19.9; *m/z* (ESI+) found $[M+H]^+$ 495.2667. $C_{29}H_{38}N_2O_3S^+$ requires 495.2676.

Sulfonamide **29d**{*22*}



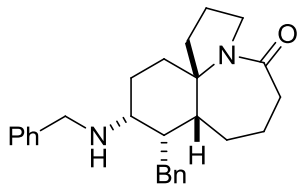
δ_H (500 MHz, $CDCl_3$)7.49 (1H, d, *J* 1.2), 7.46 (1H, d, *J* 1.2), 7.26-7.22 (2H, m), 7.18-7.14 (1H, m), 7.11-7.08 (2H, m), 5.57 (1H, d, *J* 7.5), 3.74-3.70 (1H, m), 3.70 (3H, s), 3.52-3.47 (1H, m), 3.30-3.23 (1H, m), 2.78 (1H, dd, *J* 14.4, 10.2), 2.68 (1H, dd, *J* 14.4, 5.1), 2.57-2.52 (1H, m), 2.42-2.35 (2H, m), 2.23-2.18 (1H, m), 2.14-2.06 (2H, m), 1.85-1.51 (6H, m), 1.42-1.35 (1H, m), 1.32-1.27 (2H, m), 1.21-1.10 (1H, m); δ_C (125 MHz, $CDCl_3$) 174.3, 140.2, 139.6, 139.1, 128.7, 128.5, 126.1, 124.4, 67.3, 51.6, 49.0, 46.3, 44.1, 38.8, 38.6, 35.9, 34.0, 29.2, 27.9, 24.5, 23.4, 19.9; *m/z* (ESI+) found $[M+H]^+$ 457.2260. $C_{24}H_{33}N_4O_3S^+$ requires 457.2268.

Urea **30d**{*21*}



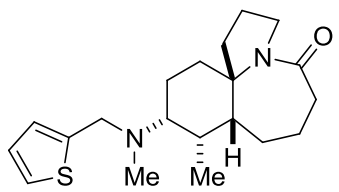
δ_H (500 MHz, $CDCl_3$) 7.28-7.25 (2H, m), 7.20-7.17 (1H, m), 7.14-7.12 (2H, m), 5.43 (1H, d, *J* 8.5), 5.34 (1H, t, *J* 5.0), 4.03-4.01 (1H, m), 3.79-3.75 (1H, m), 3.37-3.31 (1H, m), 3.20 (2H, qd, *J* 7.2, 5.0), 2.85 (1H, dd, *J* 14.0, 6.1), 2.62-2.51 (3H, m), 2.37 (1H, dd, *J* 13.8, 13.8), 2.27-2.22 (1H, m), 2.15-2.09 (1H, m), 2.02 (1H, ddd, *J* 13.4, 13.4, 4.1), 1.94-1.86 (1H, m), 1.80-1.63 (5H, m), 1.53-1.47 (1H, m), 1.40-1.37 (2H, m), 1.27-1.19 (1H, m), 1.09 (3H, t, *J* 7.2); δ_C (125 MHz, $CDCl_3$) 174.2, 158.5, 139.9, 128.7, 128.5, 126.1, 68.0, 49.2, 47.1, 46.2, 44.6, 38.9, 38.8, 36.3, 35.0, 30.2, 28.3, 24.9, 23.6, 20.0, 15.6; *m/z* (ESI+) found $[M+H]^+$ 384.2675. $C_{23}H_{34}N_3O_2^+$ requires 384.2646.

Amine **26d**{*1*}



ν_{max} (film)/cm^{-1} 2931, 2868, 1608; δ_H (500 MHz, $CDCl_3$) 7.40-7.36 (4H, m), 7.32-7.27 (3H, m), 7.23-7.19 (1H, m), 7.12-7.10 (2H, m), 3.86-3.79 (2H, m), 3.50 (1H, d, *J* 13.1), 3.40 (1H, ddd, *J* 12.3, 9.7, 7.7), 2.74 (1H, dd, *J* 13.5, 8.2), 2.69-2.62 (3H, m), 2.56-2.34 (3H, m), 2.26-2.20 (2H, m), 2.01-1.96 (1H, m), 1.92-1.82 (2H, m), 1.75-1.52 (4H, m), 1.49-1.45 (1H, m), 1.36-1.24 (2H, m); δ_C (125 MHz, $CDCl_3$) 174.7 (C), 141.0 (C), 140.3 (C), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 127.0 (CH), 126.2 (CH), 68.3 (C), 54.0 (CH), 53.1 $(CH)_2$, 49.1 $(CH)_2$, 48.5 (CH), 45.8 (CH), 39.1 $(CH)_2$, 39.0 $(CH)_2$, 36.7 $(CH)_2$, 29.2 $(CH)_2$, 27.0 $(CH)_2$, 24.7 $(CH)_2$, 23.5 $(CH)_2$, 20.2 $(CH)_2$; *m/z* (ESI+) found $[M+H]^+$ 403.2726. $C_{27}H_{35}N_2O^+$ requires 403.2744.

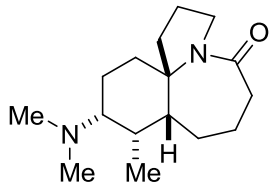
Amine **32b**{*2*}



δ_H (500 MHz, $CDCl_3$) 7.18 (1H, dd, *J* 5.1, 1.2), 6.91 (1H, dd, *J* 5.1, 3.4), 6.86 (1H, dd, *J* 3.4, 1.2), 3.84-3.78 (2H, m), 3.74 (1H, d, *J* 14.3), 3.45-3.38 (1H, m), 2.64-2.59 (2H, m), 2.52-2.38 (2H, m), 2.23 (3H, s), 2.19-2.14 (2H, m), 2.08-1.96 (3H, m), 1.92-1.85 (1H, m), 1.76-1.64 (4H, m), 1.50-1.31 (3H, m), 1.19 (3H, d, *J* 7.3); δ_C (125 MHz, $CDCl_3$) 174.7, 144.6, 126.2, 124.9, 124.4, 67.9, 59.8, 57.3, 51.4, 49.0, 41.0,

39.8, 39.7, 38.9, 27.9, 27.2, 25.3, 23.6, 20.3, 18.3; *m/z* (ESI+) found $[M+H]^+$ 347.2141. $C_{20}H_{31}N_2OS^+$ requires 347.2152.

Amine **31b**

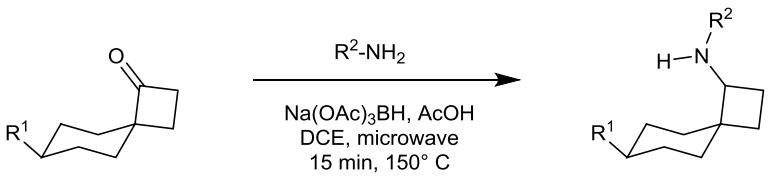


δ_H (500 MHz, $CDCl_3$) 3.80-3.74 (1H, m), 3.44-3.38 (1H, m), 2.59-2.54 (1H, m), 2.48-2.40 (2H, m), 2.24 (6H, s), 2.24-2.14 (2H, m), 2.04-1.94 (4H, m), 1.85-1.79 (1H, m), 1.74-1.58 (4H, m), 1.50-1.44 (1H, m), 1.38-1.30 (2H, m), 1.12 (3H, d, *J* 7.4); δ_C (125 MHz, $CDCl_3$) 174.6, 67.9, 62.6, 50.9, 48.9, 45.7, 40.2, 39.6, 38.5, 27.4, 26.9, 25.7, 23.3, 20.4, 18.6; *m/z* (ESI+) found $[M+H]^+$ 265.2284. $C_{16}H_{29}N_2O^+$ requires 265.2274.

B. Cylindricine-inspired libraries

General procedures for library preparation and tabulated results.

Amines 33



6a, b, d **33a, b, d**

a R^1 = H
b = Me
c = Ph

Amines:

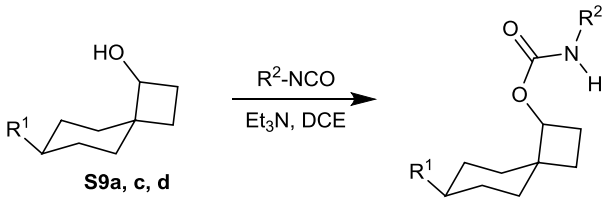
{*1*} R^2= 4-Methylbenzyl
{*2*} R^2= 3,4-Dichlorobenzyl
{*3*} R^2= 2-Methoxybenzyl
{*4*} R^2= 2-Chlorobenzyl
{*5*} R^2= 3-Chlorobenzyl
{*6*} R^2= 3-Fluorobenzyl
{*7*} R^2= 3-(Trifluoromethyl)-4-Chlorobenzyl
{*8*} R^2= 3,4-Dimethoxybenzyl
{*9*} R^2= 2-(Trifluoromethyl)benzyl
{*10*} R^2= 5-Methylfurfuryl
{*11*} R^2= (*S*)-(*alpha*)-Methylbenzyl
{*12*} R^2= 4-(Trifluoromethyl)benzyl
{*13*} R^2= 3-Methylbenzyl
{*14*} R^2= 4-Fluorobenzyl
{*15*} R^2= 4-Ethylpyridine
{*16*} R^2= 3-Methylpyridine
{*17*} R^2= 2-Phenethyl
{*18*} R^2= 3-Fluorobenzyl
{*19*} R^2= 4-Chlorobenzyl
{*20*} R^2= 3-Methoxybenzyl
{*21*} R^2= 3-(Trifluoromethyl)benzyl
{*22*} R^2= 4-Bromobenzyl
{*23*} R^2= Furfuryl
{*24*} R^2= Benzyl
{*25*} R^2= 4-Methoxybenzyl
{*26*} R^2= 2-Methylthiophene
{*27*} R^2= 4-Chlorobenzyl
{*28*} R^2= 2-Methylbenzyl
{*29*} R^2= 2, 4-Difluorobenzyl
{*30*} R^2= 3-Iodobenzyl
{*31*} R^2= 3,5-Dichlorobenzyl
{*32*} R^2= Phenyl

A solution of spiro[3.5]nonan-1-one **6** (90 mg) in DCE (1.5 mL) was added to an oven dried 5 mL microwave reaction vessel. To the solution was added acetic acid (2 equiv.), sodium triacetoxyborohydride (2.25 equiv.), and the appropriate amine (2.25 mmol}. The reaction was conducted utilizing a Biotage® Initiator microwave synthesizer equipped with Robot Eight® platform. Reactions were irradiated at 150° for 15 min. Upon completion, the reaction was cooled to room temperature and quenched with saturated aqueous sodium bicarbonate. The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure amines **33**.

Compound	Cal. Mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
33a{*1*}	244.206	244.2074	37.9	43	94.3
33a{2}	298.1124	298.1131	32	30	93.9
33a{3}	260.2009	260.202	20	21	93
33a{4}	264.1514	264.1527	41.5	44	94.9
33a{6}	248.1809	248.1818	18.2	20	93

33a{8}	290.2115	290.2115	47.1	45	96.2
33a{9}	298.1777	298.1796	31.5	29	91.9
33a{10}	234.1853	234.1857	32.4	38	99.5
33a{11}	244.206	244.2063	21.8	25	97.5
33a{12}	298.1777	298.1789	25.1	23	88.3
33a{13}	244.206	244.2072	29.6	34	86.9
33a{14}	248.1809	248.181	45.7	51	41.2
33a{16}	231.1856	231.1859	18.9	23	78.1
33a{19}	264.1514	264.152	8.1	8	88.9
33a{20}	260.2009	260.2012	34.8	37	89.3
33a{21}	298.1777	298.1797	62.3	58	94.8
33a{26}	236.1468	236.1475	21.9	26	75.9
33a{28}	244.206	244.2074	10.9	12	88.2
33a{29}	332.1388	332.14	22.4	19	93.8
33b{2}	312.128	312.1284	51.8	42	81.7
33b{3}	274.2165	274.2168	43.2	40	82.8
33b{4}	278.167	278.1673	37.2	34	82.3
33b{5}	278.167	278.1679	47.3	43	94.2
33b{8}	304.2271	304.2279	57.3	48	88.4
33b{9}	312.1933	312.1941	37.4	30	87.3
33b{10}	248.2009	248.2006	4.5	5	55.9
33b{11}	258.2216	258.2222	33	33	95
33b{12}	312.1933	312.1942	76.7	62	94.8
33b{13}	258.2216	258.2224	55.8	55	93.7
33b{14}	262.1965	262.1974	48.9	47	87.8
33b{16}	245.2012	245.2023	70.5	73	90.3
33b{23}	234.1852	234.1842	0.8	1	56.7
33b{24}	244.206	244.2066	20.9	22	89.5
33b{25}	274.2165	274.2177	73.1	68	94.7
33d{1}	320.2373	320.2393	22.3	35	77.5
33d{3}	336.2322	336.2347	32.2	48	90
33d{4}	340.1827	340.1813	44.9	66	72.7
33d{5}	340.1827	340.1835	50.3	74	53
33d{6}	324.2122	324.2149	26.2	40	93.8
33d{7}	408.1701	408.1729	61.3	75	94.6
33d{8}	366.2428	366.2454	49.3	67	98.4
33d{9}	374.209	366.2454	93.1	124	55.1
33d{10}	310.2166	310.208	49.9	80	96.5
33d{12}	374.209	374.2096	53.6	72	36.6
33d{13}	320.2373	320.2396	28.6	45	81.8
33d{16}	307.2169	307.2085	11.7	19	61.9
33d{19}	340.1827	340.1841	15.6	23	87.4
33d{20}	336.2322	336.2346	25.8	38	87.8
33d{22}	384.1322	384.1329	28.4	37	79.8
33d{23}	296.2009	296.2029	19.5	33	89.8
33d{26}	312.1781	312.1801	20.4	33	95.4
33d{28}	320.2373	320.2397	32	50	91.4
33d{31}	374.1437	374.1448	31.3	42	94.6

Carbamates 34



S9a, c, d

a R^1 = H
c = nPr
d = Ph

34a, c, d

Isocyanate:

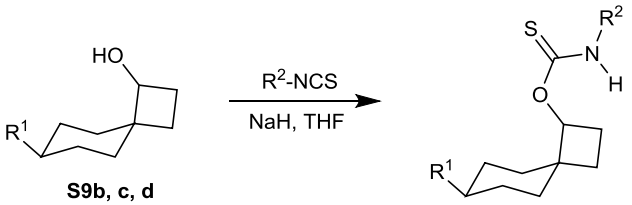
{*1*} R^2= 4-Chlorophenyl
{*2*} R^2= 4-Bromophenyl
{*3*} R^2= 4-Flurorphenyl
{*4*} R^2= 2-Chlorophenyl
{*5*} R^2= 2-Methoxyphenyl
{*6*} R^2= 4-Methylphenyl
{*7*} R^2= 2-Fluorophenyl
{*8*} R^2= 4-(Trifluoromethyl)phenyl
{*9*} R^2= 2-Methylphenyl
{*10*} R^2= 3-Chlorophenyl
{*11*} R^2= Phenyl
{*12*} R^2= 2-(Trifluoromethyl)phenyl
{*13*} R^2= 3,5-dimethylphenyl
{*14*} R^2= ^{t}Butyl
{*15*} R^2= 4-Chlorobenzyl
{*16*} R^2= 3,4-methylenedioxy phenyl
{*17*} R^2= 4-Cyanophenyl
{*18*} R^2= 3-(Trifluoromethyl)phenyl
{*19*} R^2= *n*Butyl
{*20*} R^2= 4-Pentylphenyl
{*21*} R^2= Ethyl butyrate
{*22*} R^2= 3-Fluorophenyl
{*23*} R^2= 4-Ethylphenethyl
{*24*} R^2= 3-Phenylpropyl
{*25*} R^2= 2,6-dimethoxyphenyl
{*26*} R^2= Furfuryl
{*27*} R^2= Benzyl
{*28*} R^2= 2,4-dichloropheny
{*29*} R^2= 3,5-difluorophenyl
{*30*} R^2= 4-Isopropylphenyl

Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the alcohol scaffold **S9** (75 mg) in anhydrous tetrahydrofuran (1.2 mL) was added, followed by the appropriate isocyanate (2 equiv) and Et_3N (2.5 equiv). The reactions were shaken at 500 rpm at rt for 18 h, then water (2 mL) and dichloromethane (3 mL) added. The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure carbamates **34**.

Compound	Cal. Mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
34a{1}	292.1110	292.1093	65	74	92.8
34a{2}	336.0604	336.0582	57.4	57	93.9
34a{3}	276.1405	276.1372	62.8	76	100
34a{5}	290.1751	290.1757	41.2	47	100
34a{6}	274.1802	274.1814	71.9	87	99
34a{8}	326.1373	326.1333	90.6	93	100
34a{9}	274.1802	274.1811	68.4	83	98.8
34a{10}	292.1110	292.1064	75	86	100
34a{11}	258.1499	258.1472	57	74	100
34a{14}	328.2282	328.2237	107	109	68.6
34a{15}	276.1405	276.1357	76.8	93	100
34a{16}	302.1398	304.1562	90	100	95.8
34a{18}	326.1373	326.1316	72.3	74	98.7
34a{23}	316.2271	316.2306	19.4	20	85
34a{37}	288.1958	288.1984	78.4	91	100
34c{3}	318.1875	318.1852	47.2	49	100
34c{5}	330.2074	330.2013	42.2	43	100

34c{6}	314.2125	314.2066	32.3	34	100
34c{7}	318.1875	318.1829	8.7	9	100
34c{9}	314.2125	314.2058	35.3	37	100
34c{10}	334.1579	334.1513	44	44	100
34c{13}	328.2282	328.2257	18.7	19	100
34c{16}	344.1867	344.1818	25.7	25	100
34c{18}	368.1843	368.1804	68.4	62	100
34c{25}	360.2180	360.2131	10.5	10	100
34c{26}	320.1689	320.1690	23.9	25	100
34c{30}	342.2438	342.1933	9	9	100
34d{1}	306.1266	306.1212	57.1	62	95.1
34d{2}	412.0917	431.1362	119	96	95.5
34d{3}	352.1718	352.1686	82	78	100
34d{4}	359.1765	359.1739	69.3	64	100
34d{5}	368.1423	368.1425	31.3	28	91.5
34d{7}	352.1718	352.1712	35.3	33	100
34d{8}	402.1686	402.1642	90.2	75	100
34d{9}	350.2115	350.2129	70.7	67	100
34d{10}	368.1423	368.1389	83.5	76	100
34d{12}	402.1686	402.1624	83.3	69	100
34d{15}	384.1725	384.1755	99.1	86	100
34d{16}	380.1857	380.1871	62	113	96.4
34d{17}	359.1765	378.2201	89.4	83	100
34d{18}	402.1686	402.1681	91.4	76	100
34d{19}	316.2271	316.2291	29.9	32	100
34d{20}	406.2741	406.2773	111.3	91	84.3
34d{21}	374.2326	374.2346	60.8	54	98
34d{22}	352.1718	352.1731	77.3	73	100
34d{23}	392.2584	392.2593	19.1	16	93.8
34d{25}	394.2024	394.1989	42.6	36	99
34d{26}	338.1761	338.1732	69.3	68	100
34d{27}	348.1969	348.1926	51.4	49	100
34d{28}	402.1033	402.0957	57.6	48	95.3
34d{29}	370.1624	370.1594	76.7	69	100
34d{30}	376.2282	376.2230	44.7	40	100
34d{35}	402.1033	402.0996	88	73	100

Thiocarbamates



S9b, c, d

b R^1 = Me
c = nPr
d = Ph

S19b, c, d

Isothiocyanates:

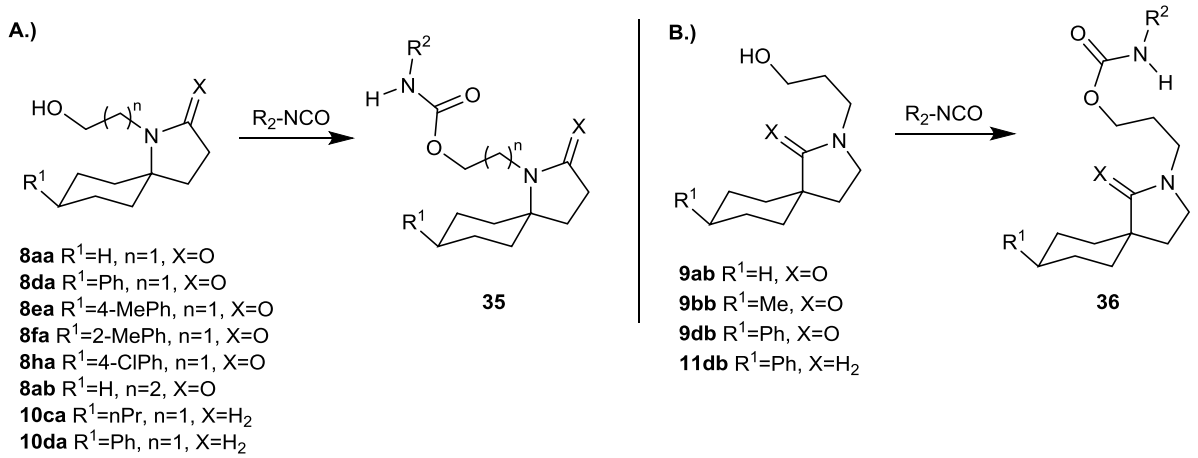
{*1*} R^2= Phenyl
{*2*} R^2= 3-Iodophenyl
{*3*} R^2= 3-Fluorobenzyl
{*4*} R^2= 4-Chlorobenzyl
{*5*} R^2= 2-Fluorobenzyl
{*6*} R^2= 4-Chlorophenyl
{*7*} R^2= Adamantyl
{*8*} R^2= 3-Chlorophenyl
{*9*} R^2= 4-Iodophenyl
{*10*} R^2= 2-Iodophenyl
{*11*} R^2= 4-Bromophenyl
{*12*} R^2= 3-Methylbenzyl
{*13*} R^2= 2-Methylbenzyl
{*14*} R^2= 4-Dimethylaminophenyl
{*15*} R^2= 4-Methoxybenzyl
{*16*} R^2= 4-Chlorophenethyl
{*17*} R^2= 3-Methoxybenzyl
{*18*} R^2= Cyclohexanemethyl
{*19*} R^2= 2-(Trifluoromethyl)phenyl
{*20*} R^2= 3-(Trifluoromethyl)phenyl
{*21*} R^2= *t*-Butyl
{*22*} R^2= Methyl
{*23*} R^2= 2-Methoxyphenyl
{*24*} R^2= 3-Chlorobenzyl
{*25*} R^2= 3-Bromophenyl
{*26*} R^2= 2-Chlorophenyl
{*27*} R^2= 2-Bromophenyl
{*28*} R^2= Furfuryl
{*29*} R^2= 2-Fluorobenzyl

Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the alcohol scaffold **S9** (75 mg) in anhydrous tetrahydrofuran (1.2 mL) was added, followed by sodium hydride (60% in oil, 2 equiv.) and the reactions shaken at 500 rpm for 1 h at room temperature. The appropriate isothiocyanate (2.5 equiv) was then added and the reactions shaken at 500 rpm at room temperature for 18 h, then water (2 mL) and dichloromethane (3 mL) added. The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure thiocarbamates.

Compound	Cal. Mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
S19b{1}	316.1740	316.1748	18.8	20	100
S19b{2}	442.0706	442.0708	72.9	55	92.9
S19b{3}	348.1802	348.1783	78.4	75	100
S19b{4}	364.1507	364.1507	33	35	99.1
S19b{6}	350.1363	350.1416	53.3	51	98.1
S19b{9}	442.0706	442.0711	92.4	70	98.2
S19b{11}	396.0991	396.0827	110.9	93	98.5
S19b{14}	361.2308	361.2310	86.8	80	94.4
S19b{16}	378.1663	378.1662	34.3	30	96.8
S19b{17}	360.2002	360.2003	60.8	56	99.4
S19b{19}	384.1614	384.1615	67	58	100
S19b{20}	384.1614	384.1617	67.6	59	100
S19b{23}	346.1846	346.1850	74.6	72	99.4

S19b{24}	350.1350	350.1349	84.3	80	97.8
S19b{26}	350.1350	350.1348	73.9	70	97.4
S19b{27}	396.0991	396.0817	87.4	74	95.7
S19b{28}	320.1653	320.1690	23.9	25	100
S19c{1}	350.1583	350.1521	61.1	58	100
S19c{4}	398.1350	398.1356	76.4	64	96.6
S19c{6}	384.1194	384.1162	101.8	88	100
S19c{8}	384.1194	384.1139	97.5	85	100
S19c{9}	476.0550	476.0533	114.5	80	100
S19c{10}	476.0550	476.0496	77.8	54	91
S19c{11}	428.0688	428.0660	113.5	88	100
S19c{12}	378.1896	378.1870	61.1	54	100
S19c{13}	378.1896	378.1869	68.3	60	100
S19c{14}	393.2005	393.1968	92.5	78	98.8
S19c{15}	394.1845	394.1822	74.4	73	100
S19c{17}	394.1845	394.1785	78	66	100
S19c{18}	370.2209	370.2187	69	72	100
S19c{19}	418.1457	418.1417	70.7	56	100
S19c{20}	418.1457	418.1411	91.9	73	89.3
S19c{23}	380.1689	380.1637	71.5	63	100
S19c{24}	398.1350	398.1300	89.3	75	97.1
S19c{25}	428.0688	428.0662	55.4	43	98.7
S19d{3}	382.1646	382.1640	106.5	93	100
S19d{4}	398.1350	398.1338	114.2	96	100
S19d{5}	382.1646	382.1639	94.1	95	85
S19d{14}	350.1583	350.1530	77.2	73	100

Carbamates 35 & 36



8aa R^1=H, n=1, X=O
8da R^1=Ph, n=1, X=O
8ea R^1=4-MePh, n=1, X=O
8fa R^1=2-MePh, n=1, X=O
8ha R^1=4-ClPh, n=1, X=O
8ab R^1=H, n=2, X=O
10ca R^1=nPr, n=1, X=H_2
10da R^1=Ph, n=1, X=H_2

9ab R^1=H, X=O
9bb R^1=Me, X=O
9db R^1=Ph, X=O
11db R^1=Ph, X=H_2

Isocyanates:

{*2*} R^2= 4-Bromophenyl
{*3*} R^2= 4-Fluorophenyl
{*5*} R^2= 2-Methoxyphenyl
{*6*} R^2= 4-Methylphenyl
{*9*} R^2= 2-Methylphenyl
{*10*} R^2= 3-Chlorophenyl
{*11*} R^2= Phenyl
{*12*} R^2= 2-(CF_3)phenyl
{*14*} R^2= *t*Butyl
{*15*} R^2= 4-Chlorobenzyl
{*16*} R^2= 3,4-Methylenedioxy phenyl
{*18*} R^2= 3-(CF_3)phenyl
{*19*} R^2= *n*Butyl
{*20*} R^2= 4-Pentylphenyl
{*21*} R^2= Ethyl 4-isocyanatobutyrate
{*22*} R^2= 3-Fluorophenyl
{*23*} R^2= 4-Ethylphenethyl
{*25*} R^2= 2,6-dimethoxyphenyl
{*27*} R^2= Benzyl
{*31*} R^2= 3-Cyanophenyl
{*32*} R^2= 3,4-Dimethylphenyl
{*33*} R^2= Ethyl
{*34*} R^2= 4-Methoxyphenyl
{*35*} R^2= 3,5-dichlorophenyl

Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the alcohol scaffold **8**, **9**, **10** or **11** (75 mg) in anhydrous tetrahydrofuran (1.2 mL) was added, followed by the appropriate isocyanate (2.5 equiv) and Et_3N (2.5 equiv). The reactions were shaken at 500 rpm at rt for 12 h, then water (2 mL) and dichloromethane (3 mL) added. The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure carbamates **35** or **36**.

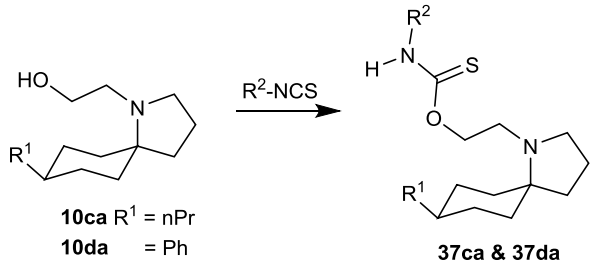
Results for carbamates 35:

R^1	n	X	R^2-N=C=O	Cal. Mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
H	1	O	{3}	335.1766	335.1775	62.8	62	78.4
H	1	O	{27}	331.2016	331.2020	54.2	55	96.3
Ph	1	O	{2}	471.1278	471.1280	10.6	7	97.5
Ph	1	O	{3}	411.2079	411.2079	40.8	33	100
Ph	1	O	{11}	393.2173	393.2184	48.1	41	100
Ph	1	O	{12}	461.2047	461.2048	72.4	52	100
Ph	1	O	{15}	441.1940	441.1954	62.6	47	100
Ph	1	O	{20}	463.2955	463.2962	72.6	52	98.5
Ph	1	O	{27}	407.2329	407.2334	36	29	100
Ph	1	O	{31}	418.2125	418.2122	44.3	35	100
4-Me-Ph	1	O	{2}	485.1435	485.1433	40.8	28	100
4-Me-Ph	1	O	{3}	425.2235	425.2271	44.3	35	100
4-Me-Ph	1	O	{31}	432.2282	432.2281	36	28	100
2-Me-Ph	1	O	{2}	485.1435	485.1438	48.1	33	100
2-Me-Ph	1	O	{3}	425.2235	425.2245	42.9	34	100
2-Me-Ph	1	O	{31}	432.2282	432.2301	46.9	36	100
4-Cl-Ph	1	O	{2}	427.1783	427.1767	92.6	72	100
4-Cl-Ph	1	O	{3}	445.1689	445.1688	19.2	14	100
4-Cl-Ph	1	O	{11}	475.2203	475.2203	12.6	9	100
4-Cl-Ph	1	O	{27}	308.1412	308.1400	32.9	36	100
4-Cl-Ph	1	O	{31}	452.1736	452.1724	13.4	10	100
4-Cl-Ph	1	O	{33}	379.1783	379.1771	31.8	28	100
H	2	O	{3}	349.1922	349.1911	51	49	88.3
H	2	O	{27}	345.2173	345.2166	32.5	31	100
nPr	1	H_2	{2}	423.1641	423.1665	54.8	43	94.4
nPr	1	H_2	{3}	363.2442	363.2459	49.2	45	100
nPr	1	H_2	{5}	375.2642	375.2664	17.1	15	100
nPr	1	H_2	{9}	359.2693	359.2737	44.4	41	100
nPr	1	H_2	{10}	379.2147	379.2171	63.8	56	100
nPr	1	H_2	{11}	345.2536	345.2582	50.2	48	100
nPr	1	H_2	{27}	359.2693	359.2723	48.7	45	97.5
nPr	1	H_2	{36}	375.2642	375.2639	35.7	32	100
Ph	1	H_2	{2}	457.1485	457.1491	32.7	24	100
Ph	1	H_2	{3}	397.2286	397.2327	32.7	27	100
Ph	1	H_2	{5}	409.2485	409.2548	29.1	24	100
Ph	1	H_2	{9}	393.2536	393.2570	23.6	20	100
Ph	1	H_2	{10}	413.1990	413.2032	28.4	23	100
Ph	1	H_2	{11}	379.2380	379.2429	22.5	20	100
Ph	1	H_2	{22}	397.2286	397.2330	19.4	16	100
Ph	1	H_2	{25}	439.2591	439.2663	19.5	15	100
Ph	1	H_2	{35}	447.1600	447.1634	22.7	17	98.9
Ph	1	H_2	{36}	409.2485	409.2499	39.9	32	100

Results for carbamates 36:

R^1	n	X	R^2-N=C=O	Cal. Mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
H	2	O	{2}	409.1122	409.0811	64.6	53	97.2
H	2	O	{3}	349.1922	349.1912	73.2	70	16.1
H	2	O	{19}	311.2329	311.2306	35.8	38	74.5
H	2	O	{31}	356.1969	356.1710	68.2	64	99.4
Me	2	O	{5}	375.2279	375.2251	62.9	56	99.4
Me	2	O	{15}	393.1940	393.1906	76.8	65	100
Me	2	O	{16}	389.2071	389.2039	68.8	59	100
Me	2	O	{18}	413.2047	413.2022	53.1	43	100
Me	2	O	{21}	383.2541	383.2523	67.6	59	70.3
Me	2	O	{22}	363.2079	363.2050	74.3	68	97
Me	2	O	{23}	401.2799	401.2781	61.3	51	96.3
Ph	2	O	{8}	475.2203	475.2180	68.1	48	100
Ph	2	O	{19}	387.2642	387.2617	24.3	21	100
Ph	2	O	{21}	445.2697	445.2678	57.5	43	100
Ph	2	O	{23}	463.2955	463.2936	23.2	17	100
Ph	2	H_2	{3}	411.2443	411.2440	115.4	94	100
Ph	2	H_2	{19}	373.2850	373.2849	101.7	91	99.1

Thiocarbamates 37



10ca R^1 = nPr
10da = Ph

37ca & 37da

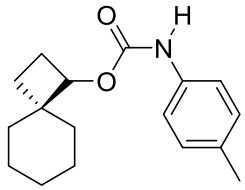
Isothiocyanate:
{*1*} R^2= Phenyl
{*6*} R^2= 4-Chlorophenyl
{*8*} R^2= 3-Chlorophenyl
{*11*} R^2= 4-Bromophenyl
{*12*} R^2= 3-Methylbenzyl
{*14*} R^2= 4-Dimethylaminophenyl
{*19*} R^2= 2-(Trifluoromethyl)phenyl
{*23*} R^2= 2-Methoxyphenyl
{*26*} R^2= 2-Chlorophenyl
{*27*} R^2= 2-Bromophenyl

Each reaction tube of a 24-position Bohdan Miniblock XT was flushed with argon, then a solution of the alcohol scaffold **8**, or **10** (75 mg) in anhydrous tetrahydrofuran (1.2 mL) was added, followed by sodium hydride (60% in oil, 2 equiv.) and the reactions shaken at 500 rpm for 1 h at room temperature. The appropriate isothiocyanate (2 equiv) was then added and the reactions were shaken at 500 rpm at room temperature for 12 h, then water (2 mL) and dichloromethane (3 mL) added. The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure carbamates **37**.

Compound	Cal. Mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
37ca{1}	361.2308	361.2334	61.8	57	100
37ca{8}	395.1918	395.1958	55.5	47	91.3
37ca{12}	389.2621	389.2677	30.7	26	100
37ca{23}	391.2413	391.2449	44.8	38	100
37ca{26}	395.1918	395.1939	54.3	46	95.5
37ca{27}	439.1413	439.1447	40.7	31	98.5
37da{1}	395.2151	395.2214	18.1	15	100
37da{6}	429.1762	429.1815	42.7	33	12.7
37da{8}	429.1762	429.1774	25.5	20	100
37da{11}	473.1256	473.1281	43	30	100
37da{12}	423.2464	423.2523	23.3	18	100
37da{14}	438.2573	438.26.10	22.1	17	65.1
37da{19}	463.2025	463.2084	21.3	15	100
37da{23}	425.2257	425.2251	19.9	16	100
37da{26}	429.1762	429.1796	20.7	16	100
37da{27}	473.1256	473.1265	22.7	16	100

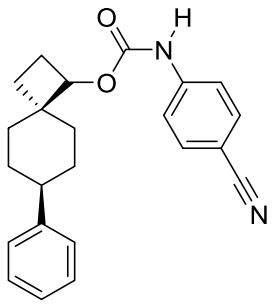
Characterization data for representative library compounds

Carbamate **34a**{6}



^{1}H NMR (500 MHz, DMSO) δ 9.48 (s, 1H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 4.67 (t, *J* = 7.9 Hz, 1H), 2.28 – 2.14 (m, 4H), 2.06 – 1.84 (m, 1H), 1.71 – 1.60 (m, 2H), 1.60 – 1.51 (m, 2H), 1.51 – 1.42 (m, 3H), 1.40 (d, *J* = 12.8 Hz, 1H), 1.37 – 1.29 (m, 2H), 1.26 – 1.08 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 153.2, 136.7, 131.1, 129.1, 118.1, 74.5, 45.4, 40.4, 37.4, 29.7, 25.7, 24.7, 23.8, 22.5, 21.7, 20.3; *m/z* (ESI+) found $[M+H]^+$ 274.1814. $C_{17}H_{24}NO_2^+$ requires 274.1798.

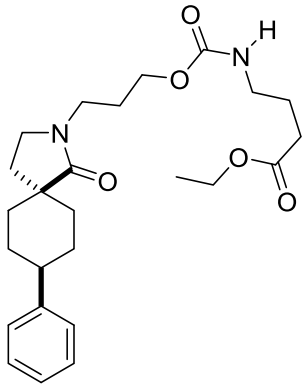
Carbamate **34d**{17}



^{1}H NMR (500 MHz, DMSO) δ 10.14 (s, 1H), 7.96 (s, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.16 – 6.98 (m, 5H), 5.01 (t, *J* = 7.7 Hz, 1H), 2.48 – 2.38 (m, 1H), 2.35 – 2.20 (m,

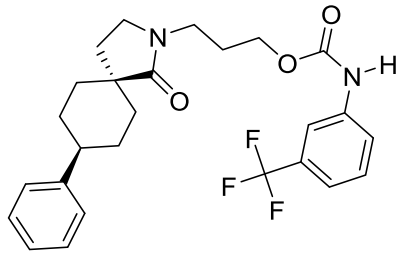
2H), 2.12 – 1.98 (m, 1H), 1.87 – 1.77 (m, 1H), 1.77 – 1.62 (m, 2H), 1.60 – 1.48 (m, 3H), 1.48 – 1.32 (m, 3H). ^{13}C NMR (126 MHz, DMSO) δ 153.0, 147.2, 140.1, 130.3, 128.0, 126.5, 126.0, 125.7, 118.7, 111.6, 74.5, 44.3, 42.4, 37.6, 31.8, 31.3, 29.7, 26.7, 23.8; *m/z* (ESI+) found $[M+H]^+$ 378.2201. $C_{23}H_{25}N_2O_2^+$ requires 361.1907.

Carbamate **36db**{21}



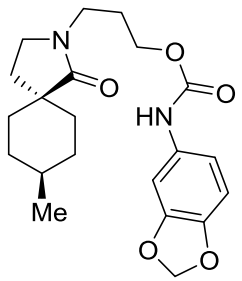
^{1}H NMR (500 MHz, DMSO) δ 7.30 – 7.25 (m, 2H), 7.25 – 7.19 (m, 2H), 7.19 – 7.12 (m, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.90 (t, *J* = 6.5 Hz, 2H), 3.27 (t, *J* = 6.8 Hz, 2H), 3.22 (t, *J* = 7.0 Hz, 2H), 2.98 (dd, *J* = 12.8, 6.6 Hz, 2H), 2.54-2.51 (m, 1H), 2.27 (t, *J* = 7.4 Hz, 2H), 2.18 (qd, *J* = 12.6, 3.4 Hz, 2H), 1.83 (d, *J* = 13.7 Hz, 2H), 1.77 (dd, *J* = 12.4, 5.6 Hz, 2H), 1.72 (dd, *J* = 13.6, 6.8 Hz, 2H), 1.67 – 1.60 (m, 2H), 1.60 – 1.53 (m, 2H), 1.41 (td, *J* = 13.2, 3.8 Hz, 2H), 1.16 (dd, *J* = 9.5, 4.8 Hz, 3H); ^{13}C NMR (126 MHz, DMSO) δ 177.5, 172.6, 156.2, 147.2, 128.3, 126.7, 125.8, 61.5, 59.8, 42.9, 42.4, 41.3, 38.7, 34.5, 33.9, 30.8, 29.0, 26.7, 24.8, 14.1; *m/z* (ESI+) found $[M+H]^+$ 445.2678. $C_{25}H_{37}N_2O_5^+$ requires 445.2694.

Carbamate **36db**{18}



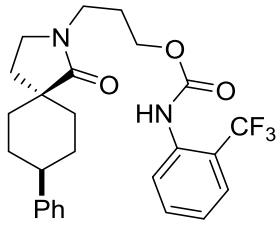
^{1}H NMR (500 MHz, DMSO) δ 9.05 (s, 1H), 7.74 – 7.69 (m, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.31 – 7.25 (m, 2H), 7.25 – 7.20 (m, 2H), 7.19 – 7.12 (m, 1H), 4.02 (t, *J* = 6.5 Hz, 2H), 3.31 – 3.20 (m, 4H), 2.54-2.51 (m, 1H) 2.29 – 2.13 (m, 2H), 1.90 – 1.81 (m, 2H), 1.81 – 1.73 (m, 4H), 1.64 – 1.52 (m, 2H), 1.48 – 1.34 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 177.6, 154.8, 147.2, 135.6, 133.1, 130.0, 128.3, 126.8, 126.6, 126.3 (q, *J* = 5 Hz), 125.8, 125.1 (q, *J* = 29 Hz), 123.6 (q, *J* = 272 Hz), 62.3, 42.9, 42.4, 41.3, 38.5, 34.6, 33.9, 29.0, 26.4; *m/z* (ESI+) found $[M+H]^+$ 475.2180. $C_{26}H_{30}F_3N_2O_3^+$ requires 475.2200.

Carbamate **36bb**{16}



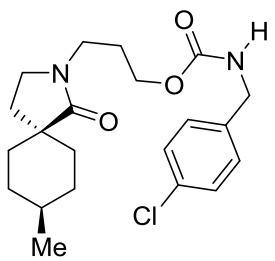
^{1}H NMR (500 MHz, DMSO) δ 9.51 (s, 1H), 7.12 (s, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 5.95 (s, 2H), 4.00 (t, *J* = 6.5 Hz, 2H), 3.30 – 3.18 (m, 4H), 1.83 – 1.73 (m, 4H), 1.73 – 1.66 (m, 2H), 1.56 – 1.48 (m, 3H), 1.48 – 1.39 (m, 2H), 1.25 – 1.14 (m, 2H), 0.90 (d, *J* = 5.7 Hz, 3H).; ^{13}C NMR (126 MHz, DMSO) δ 177.8, 153.6, 147.2, 142.3, 133.6, 110.9, 108.1, 100.9, 100.5, 61.9, 43.0, 42.4, 38.7, 32.6, 31.1, 29.5, 29.0, 26.5, 20.3; *m/z* (ESI+) found $[M+H]^+$ 389.2039. $C_{21}H_{29}N_2O_5^+$ requires 389.2068.

Carbamate **36db**{12}



^{1}H NMR (500 MHz, DMSO) δ 9.07 (s, 1H), 7.75 – 7.70 (m, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.27 (ddd, *J* = 15.1, 8.0, 4.1 Hz, 4H), 7.20 – 7.14 (m, 1H), 4.02 (t, *J* = 6.5 Hz, 2H), 3.28 (dd, *J* = 12.0, 6.7 Hz, 4H), 2.53-2.48 (m, 1H), 1.96 (t, *J* = 6.9 Hz, 2H), 1.80 (p, *J* = 6.7 Hz, 2H), 1.73 (d, *J* = 10.9 Hz, 2H), 1.69 – 1.57 (m, 2H), 1.52 (dt, *J* = 27.3, 8.8 Hz, 4H); ^{13}C NMR (126 MHz, DMSO) δ 177.9, 154.8, 147.0, 135.6, 133.1, 130.0, 128.3, 126.7, 126.6, 126.3 (q, *J* = 5 Hz), 125.9, 125.1 (q, *J* = 29 Hz), 123.6 (q, *J* = 272 Hz), 62.4, 44.0, 43.2, 42.9, 38.8, 32.3, 29.6, 28.6, 26.5; *m/z* (ESI+) found $[M+H]^+$ 475.2180. $C_{26}H_{30}F_3N_2O_3^+$ requires 475.2203.

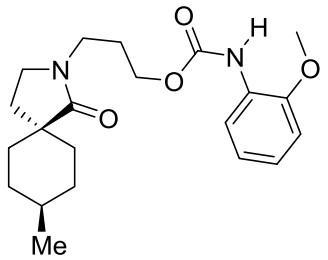
Carbamate **36bb**{15}



^{1}H NMR (500 MHz, DMSO) δ 7.71 (t, *J* = 6.1 Hz, 1H), 7.44 – 7.33 (m, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 4.16 (d, *J* = 6.2 Hz, 2H), 3.91 (t, *J* = 6.5 Hz, 2H), 3.23 (d, *J* = 7.3 Hz, 2H), 3.20 (d, *J* = 7.3 Hz, 2H), 1.85 – 1.62 (m, 6H), 1.59 – 1.49 (m, 3H), 1.49 – 1.37 (m, 2H), 1.27 – 1.09 (m, 2H), 0.90 (d, *J* = 5.8 Hz, 3H); ^{13}C

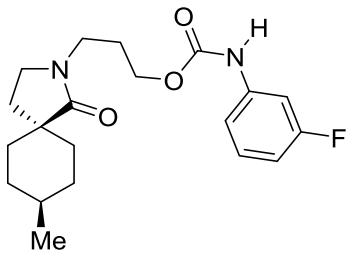
NMR (126 MHz, DMSO) δ 177.7, 156.5, 138.9, 131.3, 128.9, 128.2, 61.8, 43.1, 42.9, 42.4, 38.7, 32.6, 31.2, 29.5, 29.0, 26.6, 20.4; *m/z* (ESI+) found $[M+H]^+$ 393.1866. $C_{21}H_{30}ClN_2O_3^+$ requires 393.1936.

Carbamate **36bb**{5}



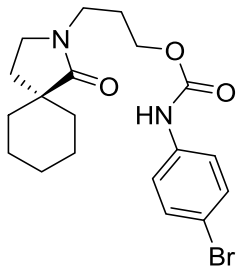
^{1}H NMR (500 MHz, DMSO) δ 8.31 (s, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.09 – 6.98 (m, 2H), 6.94 – 6.86 (m, 1H), 4.01 (t, *J* = 6.5 Hz, 2H), 3.80 (s, 3H), 3.30 – 3.18 (m, 4H), 1.82 – 1.74 (m, 4H), 1.74 – 1.66 (m, 2H), 1.58 – 1.48 (m, 3H), 1.48 – 1.40 (m, 2H), 1.27 – 1.12 (m, 2H), 0.90 (d, *J* = 5.8 Hz, 3H); ^{13}C NMR (126 MHz, DMSO) δ 177.7, 153.7, 150.0, 127.0, 124.2, 121.5, 120.3, 111.2, 62.2, 55.6, 42.9, 42.4, 38.7, 32.6, 31.2, 29.5, 29.0, 26.4, 20.3; *m/z* (ESI+) found $[M+H]^+$ 375.2251. $C_{21}H_{31}N_2O_4^+$ requires 375.2275.

Carbamate **36bb**{22}



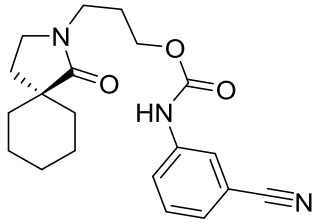
^{1}H NMR (500 MHz, DMSO) δ 9.88 (s, 1H), 7.38 (d, *J* = 11.8 Hz, 1H), 7.34 – 7.26 (m, 1H), 7.26 – 7.18 (m, 1H), 6.87 – 6.71 (m, 1H), 4.04 (t, *J* = 6.5, 6.5 Hz, 2H), 3.25 (td, *J* = 6.9, 6.9, 2.9 Hz, 4H), 1.87 – 1.74 (m, 4H), 1.73 – 1.64 (m, 2H), 1.59 – 1.48 (m, 3H), 1.48 – 1.36 (m, 2H), 1.29 – 1.15 (m, 2H), 0.89 (d, *J* = 5.8 Hz, 3H).; ^{13}C NMR (126 MHz, DMSO) δ 177.7, 162.3 (d, *J* = 239 Hz), 153.3, 141.1 (d, *J* = 11 Hz), 130.d (d, *J* = 10 Hz), 113.9, 108.7 (d, *J* = 21 Hz), 104.8 (d, *J* = 26 Hz), 62.2, 42.9, 42.3, 38.6, 32.6, 31.1, 29.4, 28.9, 26.3, 20.3; *m/z* (ESI+) found $[M+H]^+$ 363.2050. $C_{20}H_{28}FN_2O_3^+$ requires 363.2075.

Carbamate **36ab**{2}



^{1}H NMR (500 MHz, DMSO) δ 9.80 (s, 1H), 7.49 – 7.35 (m, 4H), 4.02 (t, *J* = 6.5 Hz, 2H), 3.26 (q, *J* = 6.8 Hz, 4H), 1.84 (dd, *J* = 12.2, 5.3 Hz, 2H), 1.79 (dd, *J* = 13.6, 6.8 Hz, 2H), 1.66 – 1.52 (m, 3H), 1.48 – 1.38 (m, 2H), 1.36 – 1.23 (m, 4H), 1.23 – 1.10 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 177.9, 153.4, 138.6, 131.5, 120.0, 113.8, 62.1, 44.2, 43.1, 38.8, 32.1, 29.0, 26.3, 25.2, 21.8; *m/z* (ESI+) found $[M+H]^+$ 409.0811. $C_{19}H_{26}BrN_2O_3^+$ requires 409.1118.

Carbamate **36ab**{31}

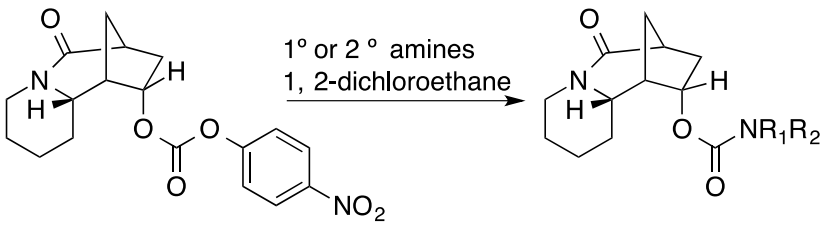


^{1}H NMR (500 MHz, DMSO) δ 10.05 (s, 1H), 7.88 (s, 1H), 7.76 – 7.67 (m, 1H), 7.49 (t, *J* = 7.9, 7.9 Hz, 1H), 7.44 (dt, *J* = 7.6, 1.3, 1.3 Hz, 1H), 4.05 (t, *J* = 6.5, 6.5 Hz, 2H), 3.32 – 3.21 (m, 4H), 1.91 – 1.74 (m, 4H), 1.67 – 1.52 (m, 3H), 1.49 – 1.36 (m, 2H), 1.37 – 1.23 (m, 4H), 1.23 – 1.09 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 177.9, 153.4, 140.1, 130.2, 125.8, 122.7, 120.5, 118.7, 111.5, 62.4, 44.2, 43.0, 38.7, 32.1, 29.0, 26.2, 25.2, 21.8; *m/z* (ESI+) found $[M+H]^+$ 356.1710. $C_{20}H_{26}N_3O_3^+$ requires 356.1965.

C. Sparteine-inspired libraries

General procedures for library preparation and tabulated results.

Carbamates 40



Amine:

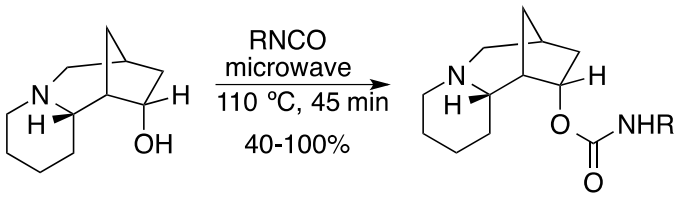
{1} 4-fluorobenzyl	{13} 2-hydroxyethyl
{2} 4-methoxybenzyl	{14} 3-*N*,*N*-dimethylaminopropyl
{3} morpholine	{15} pyridin-3-yl-methyl
{4} n-butyl	{16} 2-(1*H*-indol-3-yl)ethan-1-amine
{5} cyclohexyl	{17} piperidine
{6} benzyl	{18} 4-phenyl piperidine
{7} 4-bromobenzyl	{19} 1-methyl-piperazine
{8} 4-methylbenzyl	{20} 1-pheny-piperazinel
{9} 3, 5-dimethoxybenzyl	{21} 1-(phenylsulfonyl)piperazine
{10} methyl	{22} phenyl(piperazine-1-yl)methanone
{11} n-propyl	{23} 1-(piperazin-1-yl)ethan-1-one
{12} isopropyl	{24} piperazin-1-yl(thiophen-3-yl)methanone

To each reaction tube of a 24-position Bohdan MiniBlock XT was added a solution of carbonate **39** (70 mg, 0.19 mmol) in 1, 2-dichloroethane (2 mL), followed by the appropriate amine (1.26 mmol). The reactions were shaken at 450 rpm for 4 h at 50 °C, then 20% aqueous HCl (3 mL) was added to each tube. The reactions were shaken for 15 additional minutes then passed through hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure carbamates **40**.

Compound	Cal. mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
40{1}	347.1766	347.1798	48.5	73.7	100.0
40{2}	359.1966	359.2099	54.2	79.6	100.0
40{3}	309.1809	309.2050	51.2	87.4	100.0
40{4}	295.2016	295.2288	44.8	80.1	100.0
40{5}	321.2173	321.2421	43.0	70.7	100.0
40{6}	329.1860	329.1831	48.7	78.1	100.0
40{7}	407.0965	407.0986	27.9	36.2	99.4
40{8}	343.2016	343.1972	31.0	47.7	98.8
40{9}	389.2071	389.2049	48.2	65.3	96.1
40{10}	253.1547	253.1495	28.1	58.7	100.0
40{11}	281.1860	281.1848	45.6	85.7	99.5
40{12}	281.1860	281.1858	40.0	75.1	93.0
40{13}	283.1653	283.1595	29.1	54.3	99.4
40{14}	324.2282	324.2248	50.5	82.2	99.2
40{15}	330.1812	330.1796	49.3	78.8	100.0
40{16}	382.2125	382.2110	20.1	27.8	98.4
40{17}	307.2016	307.1973	35.0	60.2	99.0

40{18}	383.2329	383.2296	39.5	54.4	98.4
40{19}	322.2125	322.2086	38.1	62.4	100.0
40{20}	384.2282	384.2287	36.1	49.6	95.5
40{21}	448.1901	448.1935	69.4	81.7	96.3
40{22}	412.2231	412.2260	77.3	98.9	91.5
40{23}	350.2075	350.2017	35.7	53.8	98.5
40{24}	418.1795	418.1779	36.3	45.8	84.5

Carbamates 42



Isocyanate:

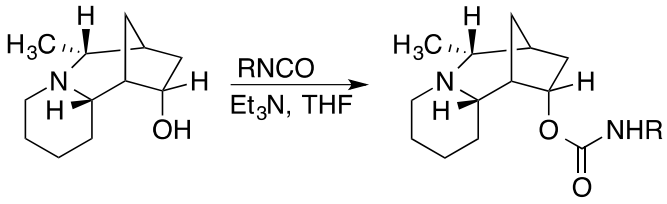
{1} 3,5-dimethylphenyl
{2} 3,4-dimethylphenyl
{3} 4-methoxybenzyl
{4} 2-thiophen
{5} 4-fluorophenyl
{6} 2-indolyl
{7} 3-phenylpropyl
{8} 3-cyanophenyl
{9} ethyl-4-butanoate
{10} 4-methylphenyl
{11} 4-trifluoromethyl phenyl
{12} 2-trifluoromethyl phenyl
{13) 2-methoxy phenyl
{14} 3-methyl phenyl
{15} 4-bromo phenyl
{16} 3-bromo phenyl
{17} 4-cyanophenyl
{18} 4-(*N*,*N*-dimethylamino)phenyl
{19} benzyl
{20} 2-(4'-ethylphenyl)ethyl
{21} cyclohexyl
{22} *n*-butyl
{23} *tert*-butyl
{24} 4-*n*-pentylphenyl

To each pyrex glass vial placed on a 24 position block was added a solution of alcohol **41** (40 mg, 0.22 mmol) in acetonitrile (1 mL), followed by the appropriate isocyanate (0.66 mmol). The vials were irradiated in a microwave at 110 °C for 1 h and then the contents of each vial were transferred to a phase separator fitted on a 24 position Mini Block. Dichloromethane (3 mL) and saturated aqueous sodium bicarbonate solution (3 mL) were added to each tube. The reactions were shaken for 15 minutes, then passed through hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure carbamates **42**.

Compound	Cal. Mass	Found mass	Recovered	Yield(%)	Purity(%)
42{1}	329.2224	329.2217	28.7	39.7	87.5
42{2}	329.2224	329.2185	59.1	81.8	99.0
42{3}	345.2173	345.2169	57.9	76.5	91.2
42{4}	307.1475	307.1428	58.4	86.7	97.3
42{5}	319.1817	319.1777	10.6	15.1	99.9
42{6}	340.2020	340.1991	62.0	83.1	41.7
42{7}	343.2380	343.2325	59.8	79.4	98.1
42{8}	326.1863	326.1801	70.1	97.9	100.0
42{9}	339.2279	339.2277	39.7	53.4	95.5
42{10}	315.2067	315.2030	53.1	76.8	95.8
42{11}	369.1785	369.1769	74.2	91.6	90.4

42{12}	369.1785	369.1769	29.0	35.8	90.1
42{13}	331.2016	331.1999	57.8	69.5	99.6
42{14}	315.2067	315.2012	50.2	72.6	98.5
42{15}	379.1016	379.0995	57.2	68.8	99.2
42{16}	379.1016	379.1003	29.0	34.9	99.4
42{17}	326.1863	326.1805	70.9	99.1	98.2
42{18}	344.2333	344.2319	47.0	62.2	29.8
42{19}	315.2067	315.2043	58.6	84.8	97.4
42{20}	357.2537	357.2539	49.2	62.8	91.9
42{21}	307.2380	307.2286	40.7	60.4	92.4
42{22}	281.2224	281.2201	54.8	88.9	100.0
42{23}	281.2224			0.0	
42{24}	371.2693	371.2697	13.5	16.6	82.7
42{25}	319.1817	319.1796	55.0	78.6	96.8

Carbamates 43a



Isocyanate:

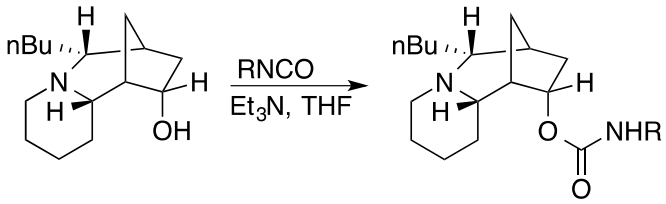
{1} ethyl-4-butanoate	{13} 3-chlorophenyl
{2} 4-chloro benzyl	{14} 4-chloro phenyl
{3} 3-phenyl propyl	{15} 2-trifluoromethyl phenyl
{4} 2-(4'-ethylphenyl)-ethyl	{16} 3,4-(methylenedioxy) phenyl
{5} 4-methyl phenyl	{17} 3-trifluoromethyl phenyl
{6} 4-cyano phenyl	{18} 4-trifluoromethyl phenyl
{7} 3,5-dimethyl phenyl	{19} tert-butyl
{8} 2-methoxy phenyl	{20} benzyl
{9} 3-fluoro phenyl	{21} 4-bromo phenyl
{10} 4-fluoro phenyl	{22} 3-cyano phenyl
{11} 4-n-pentyl phenyl	{23} 4-methoxy benzyl
{12} 2-chloro phenyl	{24} 2-indolyl

To each reaction tube of a 24-position Bohdan MiniBlock XT was added a solution of alcohol **16a** (37 mg, 0.19 mmol) in THF (2 mL), followed by the appropriate isocyanate (0.57 mmol). The reactions were shaken at 450 rpm for 7 h at 50 °C. Saturated aqueous $NaHCO_3$ (2 mL) and dichloromethane (4 mL) were added to each tube and the reactions shaken for 15 min then passed through Isolute hydrophobic phase separator tubes, which allowed the organic solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure carbamates **43a**.

Compound	**Cal. Mass**	**Found mass**	**Recovered**	**Yield(%)**	**Purity(%)**
43a{1}	353.2435	353.2427	32.0	47.8	96.6
43a{2}	363.1834	363.1796	38.6	56.1	99.6
43a{3}	357.2537	357.2525	41.7	61.6	97.6
43a{4}	371.2693	371.2697	39.3	55.9	95.1
43a{5}	329.2224	329.2212	30.9	49.6	98.4

43a{6}	340.2020	340.1962	40.0	62.1	99.8
43a{7}	343.2380	343.2353	29.0	44.6	85.5
43a{8}	345.2173	345.2177	39.2	59.9	98.4
43a{9}	333.1973	333.1945	36.9	58.5	99.7
43a{10}	333.1973	333.1987	36.0	57.0	99.3
43a{11}	385.2850	385.2857	28.9	39.6	57.3
43a{12}	349.1678	349.1665	30.4	46.0	57.5
43a{13}	349.1678	349.1696	29.9	45.2	99.8
43a{14}	349.1678	349.1679	11.5	17.4	87.1
43a{15}	383.1941	383.1960	37.0	51.0	91.6
43a{16}	359.1966	359.1944	41.7	61.3	97.1
43a{17}	383.1941	383.1945	41.2	56.7	98.6
43a{19}	383.1941	383.1940	42.9	59.1	98.7
43a{20}	295.2380	295.2371	1.0	1.8	0.0
43a{21}	329.2224	329.2180	24.5	39.3	98.6
43a{22}	393.1172	393.1173	25.0	33.6	90.2
43a{23}	340.2020	340.2041	28.0	43.4	99.8
43a{24}	359.2329	359.2320	3.0	4.4	82.0
43a{25}	354.2176	354.2171	10.0	14.9	62.0

Carbamates 43b



Isocyanate:

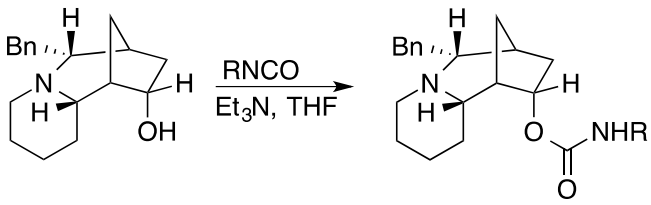
{1} *n*-butyl
{2} ethyl-4-butanoate
{3} phenyl
{4} 4-chloro benzyl
{5} 3-phenyl propyl
{6} 2-(4'-ethylphenyl) ethyl
{7} 2-methyl phenyl
{8} 4-methyl phenyl
{9} 4-cyano phenyl
{10} 3,5-dimethyl phenyl
{11} 2-methoxy phenyl
{12} {13} 3-fluoro phenyl
{13} 4-fluoro phenyl
{14} 3-bromo phenyl
{15) 2-chloro phenyl
{16} 3-chlorophenyl
{17} 4-chloro phenyl
{18} 2-trifluromethyl phenyl
{19} 3,4-(methylenedioxy) phenyl
{20} 3-trifluoromethyl phenyl
{21} 4-trifluoromethyl phenyl
{22} benzyl
{23} 4-bromo phenyl
{24} 3-cyanophenyl

Following the procedure as described for the synthesis of carbamates **43a**, reaction of alcohol **16b** (45 mg, 0.19 mmol) with the corresponding isocyanate (0.57 mmol) in a 24 well Bohdan MiniBlock XT provided a library of carbamates **43b**.

Compound	Calc. mass	Found mass	Recovered	Yield(%)	Purity(%)
43b{1}	337.2850	337.2855	13.6	21.3	67.5
43b{2}	395.2905	395.2900	22.8	30.4	67.2
43b{3}	357.2537	357.2531	18.0	26.6	95.1
43b{4}	405.2304	405.2306	14.8	19.3	93.0
43b{5}	399.3006	399.2991	35.8	47.3	93.3
43b{6}	413.3163	413.3166	16.0	20.4	91.0
43b{7}	371.2693	371.2677	36.8	52.3	95.2

43b{8}	371.2693	371.2698	29.4	41.8	92.8
43b{9}	382.2489	382.2456	36.0	49.7	98.4
43b{10}	385.2850	385.2813	34.2	46.8	97.9
43b{11}	387.2642	387.2618	31.4	42.8	96.3
43b{12}	375.2443	375.2466	35.6	50.1	94.0
43b{13}	375.2443	375.2449	33.8	47.5	94.2
43b{14}	435.1642	435.1610	44.3	53.7	66.7
43b{15}	391.2147	391.2154	31.4	42.4	84.7
43b{16}	391.2147	391.2128	35.8	48.3	92.6
43b{17}	391.2147	391.2126	6.0	8.1	95.4
43b{18}	425.2411	425.2404	25.6	31.8	87.4
43b{19}	401.2435	401.2365	43.7	57.5	99.3
43b{20}	425.2411	425.2383	31.0	38.5	92.7
43b{21}	425.2411	425.2416	30.0	37.2	91.3
43b{22}	371.2693	371.2669	28.2	40.1	100.0
43b{23}	435.1642	435.1621	28.6	34.7	93.3
43b{24}	382.2489	382.2455	37.1	51.2	98.3

Carbamates 43c



Isocyanate:

{1} *n*-butyl
{2} *tert*-butyl
{3} ethyl-4-butanoate
{4} 2-methyl phenyl
{5} 4-methyl phenyl
{6} 4-cyano phenyl
{7} 3-cyano phenyl
{8} phenyl
{9} benzyl
{10} 3-phenyl propyl
{11} 2-(4'-ethylphenyl) ethyl
{12} 2-methoxy phenyl
{13} 3-fluoro phenyl
{14} 4-fluoro phenyl
{15} 3-bromo phenyl
{16) 2-chloro phenyl
{17} 3-chlorophenyl
{18} 4-chloro phenyl
{19} 4-bromo phenyl
{20} 3,4-(methylenedioxy) phenyl
{21} 3-trifluoromethyl phenyl
{22} 4-trifluoromethyl phenyl
{23} 3,5-dimethyl phenyl
{24} 2-indolyl

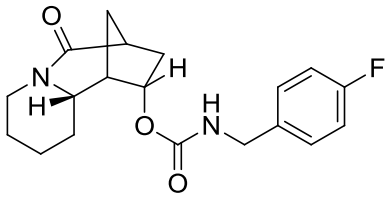
Following the procedure as described for the synthesis of carbamates **43a**, reaction of alcohol **16c** (51 mg, 0.19 mmol) with the appropriate isocyanate (0.57 mmol) in a 24 well Bohdan MiniBlock XT provided a library of carbamates **43c**.

Compound	Cal. Mass	Found mass	Recovered	Yield(%)	Purity(%)
43c{1}	371.2693	371.2707	3.7	5.3	16.0
43c{2}	371.2693	371.2663	0.6	0.9	48.0
43c{3}	429.2748	429.2738	28.0	34.4	98.4
43c{4}	405.2537	405.2476	45.5	59.2	99.6
43c{5}	405.2537	405.2544	48.4	63.0	97.2
43c{6}	416.2333	416.2268	23.4	29.7	99.9
43c{7}	416.2333	416.2168	41.7	52.9	100.0
43c{8}	391.2380	391.2295	38.7	52.2	99.8
43c{9}	405.2537	405.2414	35.3	46.0	76.2
43c{10}	433.2850	433.2820	32.0	39.0	97.1
43c{11}	447.3006	447.3018	19.7	23.2	97.3

43c{12}	421.2486	421.2505	34.6	43.3	98.8
43c{13}	409.2286	409.2243	38.7	49.9	99.9
43c{14}	409.2286	409.2215	40.2	51.8	99.9
43c{15}	469.1485	469.1494	43.4	48.8	84.4
43c{16}	425.1991	425.1863	36.5	45.3	98.6
43c{17}	425.1991	425.1902	42.9	53.2	98.3
43c{18}	425.1991	425.1937	11.9	14.8	86.2
43c{19}	469.1485	469.1480	25.7	28.9	99.9
43c{20}	435.2279	435.2251	40.0	48.5	100.0
43c{21}	459.2254	459.2178	36.4	41.8	100.0
43c{22}	459.2254	459.2260	32.7	37.6	100.0
43c{23}	419.2693	419.2686	31.5	39.6	100.0
43c{24}	430.2489	430.2450	6.0	7.4	44.0

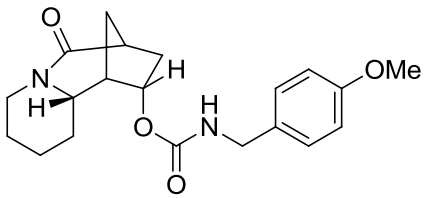
<u>Characterization data for representative library compounds</u>

Carbamate **40**{*1*}



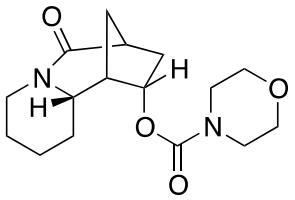
ν_{max} (film)/cm^{-1} 1634, 1709, 2943 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.11 (m, 2H), 7.10 – 6.88 (m, 2H), 5.35 – 5.00 (m, 2H), 4.62 – 4.44 (m, 1H), 4.36 – 4.27 (m, 2H), 3.40 – 3.25 (m, 1H), 2.75 – 2.60 (m, 2H), 2.52 – 2.25 (m, 2H), 2.00 – 1.50 (m, 7H), 1.45 – 1.03 (m, 2H); δ_C (100 MHz, $CDCl_3$) 174.3, 163.4, 160.9, 156.1, 134.3, 129.3, 129.2, 115.6, 115.4, 62.2, 44.3, 42.0, 41.4, 35.0, 30.2, 25.5, 25.2; *m/z* (ESI+) found $[M+H]^+$ 347.1762. $C_{19}H_{24}FN_2O_3^+$ requires 347.1765.

Carbamate **40**{*2*}



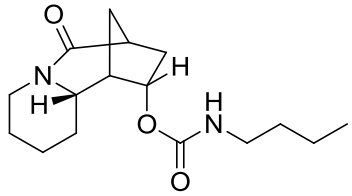
ν_{max} (film)/cm^{-1} 1634, 1710, 2941 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37 – 7.04 (m, 2H), 6.95 – 6.65 (m, 2H), 5.33 – 4.93 (m, 2H), 4.62 – 4.44 (m, 1H), 4.39 – 4.18 (m, 2H), 3.76 (s, 3H), 3.40 – 3.25 (m, 1H), 2.77 – 2.52 (m, 2H), 2.52 – 2.22 (m, 2H), 2.02 – 1.47 (m, 7H), 1.44 – 1.04 (m, 2H); δ_C (100 MHz, $CDCl_3$) 174.3, 159.0, 156.0, 130.6, 128.9, 114.0, 76.7, 62.1, 55.3, 44.5, 42.0, 41.4, 41.3, 35.0, 31.4, 30.1, 25.5, 25.1; *m/z* (ESI+) found $[M+H]^+$ 359.4450. $C_{20}H_{27}N_2O_4^+$ requires 359.4455.

Carbamate **40**{*3*}



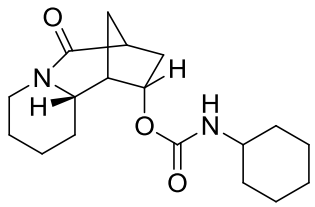
ν_{max} (film)/cm^{-1} 1636, 1697, 2943 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.17 (dt, *J* = 11.1, 5.8 Hz, 1H), 4.74 – 4.35 (m, 1H), 4.00 – 3.10 (m, 9H), 2.74 – 2.59 (m, 2H), 2.50 – 2.28 (m, 2H), 1.89 – 1.53 (m, 7H), 1.39 – 1.15 (m, 2H); δ_C (100 MHz, $CDCl_3$) 174.2, 154.8, 76.7, 66.5, 62.0, 44.3, 43.9, 41.9, 41.4, 41.2, 35.0, 30.2, 25.4, 25.3; *m/z* (ESI+) found $[M+H]^+$ 309.1805. $C_{16}H_{25}N_2O_4^+$ requires 309.1809.

Carbamate **40**{*4*}



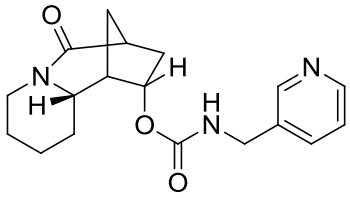
ν_{max} (film)/cm^{-1} 1635, 1711, 2938 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.24 – 4.76 (m, 2H), 4.54 – 4.44 (m, 1H), 3.35 – 3.20 (m, 1H), 3.11 – 2.98 (m, 2H), 2.46 – 2.20 (m, 4H), 1.95 – 1.50 (m, 7H), 1.47 – 1.06 (m, 6H), 0.83 (t, *J* = 7.3 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 174.3, 156.0, 76.3, 62.1, 41.9, 41.3, 41.2, 40.6, 34.9, 31.9, 31.4, 29.9, 25.4, 25.1, 19.7, 13.6; *m/z* (ESI+) found $[M+H]^+$ 295.2018. $C_{16}H_{27}N_2O_3^+$ requires 295.2016.

Carbamate **40**{*5*}



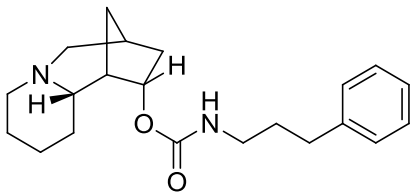
ν_{max} (film)/cm^{-1} 1635, 1710, 2936 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.37 – 4.95 (m, 1H), 4.80 – 4.36 (m, 2H), 3.60 – 3.20 (m, 2H), 2.75 – 2.25 (m, 4H), 2.20 – 1.45 (m, 12H), 1.45 – 1.00 (m, 7H). δ_C (100 MHz, $CDCl_3$) 174.3, 155.2, 76.3, 62.1, 49.8, 42.0, 41.4, 41.3, 34.9, 33.5, 33.2, 31.4, 30.0, 25.5, 25.4, 25.2, 24.8, 24.7; *m/z* (ESI+) found $[M+H]^+$ 321.2170. $C_{18}H_{29}N_2O_3^+$ requires 321.2173.

Carbamate **40**{*15*}



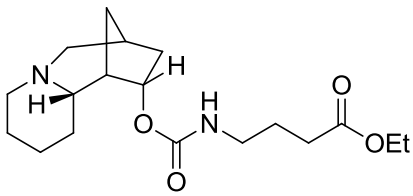
ν_{max} (film)/cm^{-1} 1635, 1712, 2940, 3261 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.60 – 8.25 (m, 2H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.07 (m, 1H), 6.11 (t, *J* = 5.8 Hz, 1H), 5.14 (dt, *J* = 10.8, 5.5 Hz, 1H), 4.57 – 4.25 (m, 3H), 3.35 – 3.15 (m, 1H), 2.36 – 2.29 (m, 4H), 1.93 – 1.36 (m, 7H), 1.30 – 0.90 (m, 2H); δ_C (100 MHz, $CDCl_3$) 174.3, 156.2, 148.9, 148.6, 135.4, 134.4, 123.5, 76.7, 62.1, 42.4, 42.0, 41.4, 41.2, 35.1, 31.4, 30.0, 25.4, 25.1; *m/z* (ESI+) found $[M+H]^+$ 330.1810. $C_{18}H_{24}N_3O_3^+$ requires 330.1812.

Carbamate **42**{*7*}



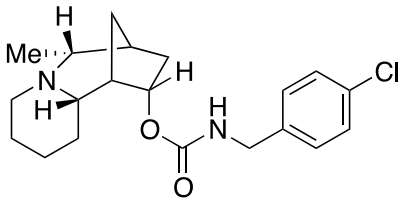
ν_{max} (film)/cm^{-1} 1695, 2934 cm^{-1} ; δ_H (400 MHz, $CDCl_3$) 7.40 – 7.03 (m, 5H), 5.25 – 4.75 (m, 2H), 3.43 – 2.90 (m, 3H), 2.90 – 2.70 (m, 2H), 2.70 – 2.30 (m, 4H), 2.25 – 1.25 (m, 13H), 1.30 – 1.10 (m, 1H); δ_C (100 MHz, $CDCl_3$) 156.8, 141.5, 128.4, 128.3, 125.9, 67.9, 63.2, 56.6, 42.4, 40.8, 40.4, 37.5, 34.1, 33.9, 33.0, 31.6, 30.6, 25.5, 25.3; *m/z* (ESI+) found $[M+H]^+$ 343.2375. $C_{21}H_{31}N_2O_2^+$ requires 343.2380.

Carbamate **40**{*9*}



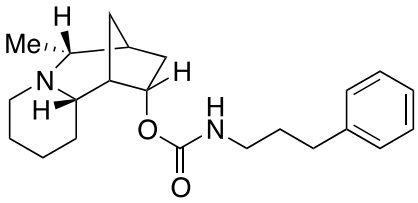
ν_{max} (film)/cm^{-1} 1715, 2934 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.21 – 4.90 (m, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.50 – 2.80 (m, 4H), 2.80 – 2.60 (m, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.22 – 1.44 (m, 13H), 1.44 – 1.29 (m, 2H), 1.21 (t, *J* = 8 Hz, 3H), 1.21 – 0.99 (m, 1H); δ_C (100 MHz, $CDCl_3$) 173.2, 156.8, 76.7, 67.8, 63.1, 60.4, 56.6, 42.3, 40.9, 40.2, 37.4, 34.0, 33.9, 31.4, 30.6, 25.5, 25.2, 14.1; *m/z* (ESI+) found $[M+H]^+$ 339.2270. $C_{18}H_{31}N_2O_4^+$ requires 339.2278.

Carbamate **43a**{*2*}



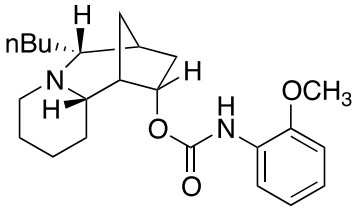
ν_{max} (film)/cm^{-1} 1704, 2935 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.28 (dd, *J* = 4.7, 3.6 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 5.35 (br s, 1H), 5.10 (dt, *J* = 10.8, 5.4 Hz, 1H), 4.38 (dd, *J* = 15.2, 6.4 Hz, 1H), 4.28 (dd, *J* = 15.2, 5.9 Hz, 1H), 3.30 – 3.10 (m, 1H), 2.15 – 1.92 (m, 4H), 1.89 – 1.42 (m, 9H), 1.37 (d, *J* = 12.4 Hz, 1H), 1.27 – 1.08 (m, 1H), 1.03 (d, *J* = 8.0 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 156.8, 137.3, 133.0, 128.8, 128.6, 68.3, 63.7, 52.7, 44.3, 43.1, 41.0, 40.9, 37.7, 31.2, 29.9, 25.9, 25.7, 18.3; *m/z* (ESI+) found $[M+H]^+$ 368.1830. $C_{20}H_{28}ClN_2O_2^+$ requires 363.1834.

Carbamate **43a**{*3*}



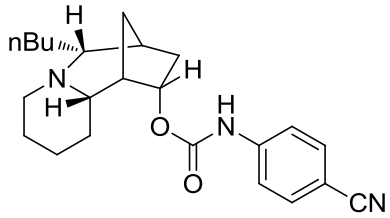
ν_{max} (film)/cm^{-1} 1697, 2931 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.42 – 7.24 (m, 2H), 7.19 (dd, *J* = 10.2, 4.5 Hz, 3H), 5.10 (dt, *J* = 10.8, 5.4 Hz, 1H), 4.96 (br s, 1H), 3.34 – 3.08 (m, 3H), 2.79 – 2.49 (m, 4H), 2.14 – 1.98 (m, 4H), 1.93 – 1.33 (m, 10H), 1.25 – 1.05 (m, 1H); 1.05 (d, *J* = 8.0 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 156.8, 141.5, 128.4, 128.3, 125.9, 68.4, 63.7, 52.8, 43.1, 41.0, 40.9, 40.4, 37.7, 33.0, 31.6, 31.2, 29.9, 26.0, 25.8, 18.3; *m/z* (ESI+) found $[M+H]^+$ 357.2531. $C_{22}H_{33}N_2O_2^+$ requires 357.2537.

Carbamate **43b**{*11*}



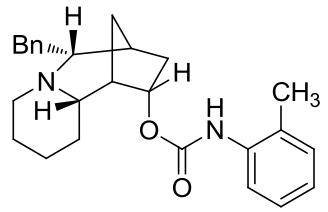
ν_{max} (film)/cm^{-1} 1602, 1723, 2935 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.12 (dd, *J* = 7.6, 2.1 Hz, 1H), 7.39 (br s, 1H), 7.05 – 6.89 (m, 2H), 6.87 – 6.76 (m, 1H), 5.18 (dt, *J* = 10.9, 5.6 Hz, 1H), 3.83 (s, 3H), 3.40 – 3.25 (m, 1H), 2.21 (m, 1H), 2.13 – 1.95 (m, 3H), 1.96 – 1.00 (m, 17H), 0.89 (t, *J* = 7.1 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 153.7, 147.6, 127.9, 122.4, 121.0, 118.1, 109.9, 77.5, 69.4, 68.9, 55.5, 52.9, 43.1, 37.3, 37.1, 31.4, 30.7, 29.8, 29.6, 26.1, 25.8, 23.0, 14.0; *m/z* (ESI+) found $[M+H]^+$ 287.2635. $C_{23}H_{35}N_2O_3^+$ requires 387.2642.

Carbamate **43b**{*9*}



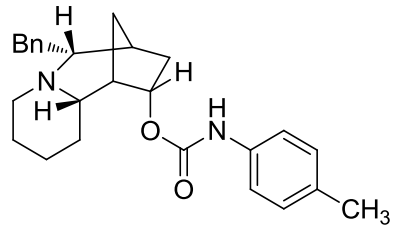
ν_{max} (film)/cm^{-1} 1596, 1727, 2222, 2931 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.65 – 7.37 (m, 5H), 5.15 (dt, *J* = 11.0, 5.5 Hz, 1H), 3.28 (d, *J* = 11.2 Hz, 1H), 2.20 – 2.15 (m, 1H), 2.11 – 1.95 (m, 3H), 1.89 (d, *J* = 6.7 Hz, 1H), 1.85 – 1.34 (m, 11H), 1.34 – 1.05 (m, 6H), 0.86 (t, *J* = 7.1 Hz, 3H); δ_C (100 MHz, $CDCl_3$) 153.26, 142.6, 133.2, 119.0, 118.2, 105.7, 78.1, 69.2, 68.6, 52.7, 43.0, 40.9, 37.1, 31.5, 30.7, 30.1, 29.5, 26.0, 25.7, 23.0, 14.0. *m/z* (ESI+) found $[M+H]^+$ 382.2486. $C_{23}H_{32}N_3O_2^+$ requires 382.2489.

Carbamate **43c**{*4*}



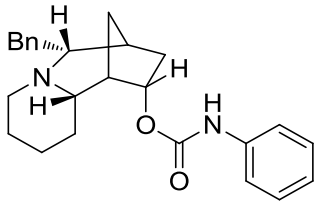
ν_{max} (film)/cm^{-1} 1720, 2935 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.77 (s, 1H), 7.29 (dd, *J* = 8.1, 6.6 Hz, 2H), 7.25 – 7.10 (m, 5H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.63 (s, 1H), 5.17 (dt, *J* = 10.9, 5.6 Hz, 1H), 3.60 – 3.40 (d, *J* = 10.3 Hz, 1H), 3.20 (dd, *J* = 13.3, 2.7 Hz, 1H), 2.50 – 1.20 (m, 19H); δ_C (100 MHz, $CDCl_3$) 153.8, 140.2, 136.0, 130.4, 129.5, 128.3, 126.7, 125.9, 124.2, 70.6, 68.7, 52.9, 43.1, 41.0, 37.2, 37.1, 35.8, 31.4, 29.7, 26.1, 25.7, 17.9; *m/z* (ESI+) found $[M+H]^+$ 405.2528. $C_{26}H_{33}N_2O_2^+$ requires 405.2537.

Carbamate **43c**{*5*}



ν_{max} (film)/cm^{-1} 1718, 2935 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.25 (m, 4H), 7.25-7.21 (m, 1H), 7.18 – 7.06 (m, 4H), 6.85 (s, 1H), 5.19 (dt, *J* = 10.9, 5.5 Hz, 1H), 3.57 (d, *J* = 11.1 Hz, 1H), 3.21 (dd, *J* = 13.3, 2.9 Hz, 1H), 2.63 (s, 3H), 2.40 – 2.35 (m, 1H), 2.25 – 1.60 (m, 12H), 1.60 – 1.40 (m, 1H), 1.37 (dd, *J* = 11.6, 2.3 Hz, 1H), 1.31 – 1.12 (m, 1H); δ_C (100 MHz, $CDCl_3$) 153.8, 140.21, 135.59, 132.79, 129.5, 128.3, 125.9, 120.0, 118.6, 70.6, 68.9, 53.0, 43.2, 41.0, 37.3, 37.2, 35.8, 31.5, 29.9, 26.1, 25.8, 20.7; *m/z* (ESI+) found $[M+H]^+$ 405.2544. $C_{26}H_{33}N_2O_2^+$ requires 405.2537.

Carbamate **43c**{*8*}

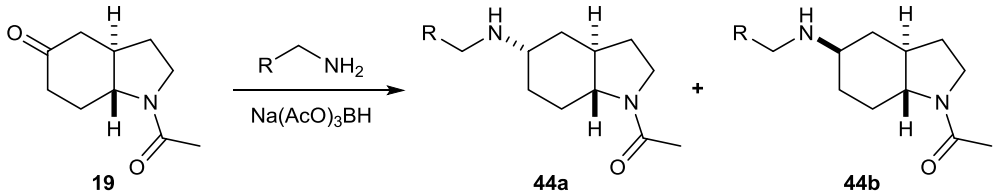


ν_{max} (film)/cm^{-1} 1600, 1702, 2933 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.45 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.39 – 7.26 (m, 4H), 7.22 (dd, *J* = 8.4, 6.3 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.12 – 7.04 (m, 1H), 6.88 (s, 1H), 5.32 – 5.08 (m, 1H), 3.59 – 3.56 (m, 1H), 3.22 (dd, *J* = 13.3, 3.0 Hz, 1H), 2.41 (dd, *J* = 13.2, 10.1 Hz, 1H), 2.36 – 2.24 (m, 1H), 2.25 – 2.06 (m, 3H), 2.06 – 1.56 (m, 8H), 1.52 – 1.45 (m, 1H), 1.37 (dd, *J* = 11.6, 2.4 Hz, 1H), 1.24 (m, 1H): δ_C (100 MHz, $CDCl_3$) 153.6, 140.1, 138.1, 129.5, 129.0, 128.3, 125.9, 123.2, 118.5, 70.6, 68.9, 53.0, 43.2, 41.0, 37.3, 37.2, 35.8, 31.6, 29.9, 26.1, 25.7; *m/z* (ESI+) found $[M+H]^+$ 391.2387. $C_{25}H_{31}N_2O_2^+$ requires 391.2380.

D. Mesembrine-inspired libraries.

General procedures for library preparation and tabulated results.

Amines 44:



19 **44a** **44b**

Amine:

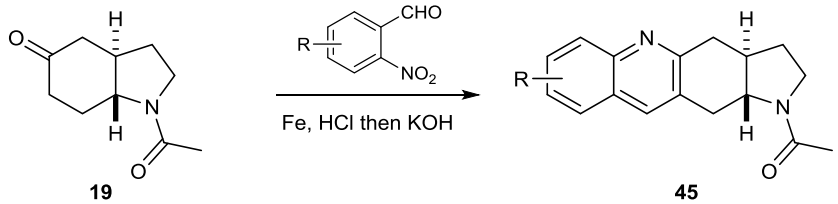
{1} R = phenyl	{13} R = 4-methylphenyl
{2} R = 2-chlorophenyl	{14} R = 2-methoxyphenyl
{3} R = 3-chlorophenyl	{15} R = 3-methoxyphenyl
{4} R = 4-chlorophenyl	{16} R = 3,4-dimethoxyphenyl
{5} R = 2-fluorophenyl	{17} R = 4-hydroxyphenyl
{6} R = 3-fluorophenyl	{18} R = 4-chloro-3-trifluoromethylphenyl
{7} R = 4-fluorophenyl	{19} R = 2-thienyl
{8} R = 4-bromophenyl	{20} R = 2-furyl
{9} R = 3,4-dichlorophenyl	{21} R = 3-methylfuryl
{10} R = 2-trifluoromethylphenyl	{22} R = 2-pyridyl
{11} R = 2-methylphenyl	{23} R = 2-(2-pyridyl)methyl
{12} R = 3-methylphenyl	{24} R = cyclohexyl

A solution of ketone scaffold **19** (50 mg, 0.27 mmol) in anhydrous THF (2 mL) was added to a 4-dram vial flushed with argon. The appropriate amine (0.54 mmol) was added, followed by acetic acid (21 µL, 0.36 mmol). The reaction was stirred at room temperature for 1 h, then sodium triacetoxyborohydride (150 mg, 0.72 mmol) added. The reactions were shaken for a further 13 h, then quenched by addition of 2M NaOH (0.5 mL) and shaken for an additional 10 min. Dichloromethane (2 mL) was added to each tube and the reactions passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The aqueous layers were extracted with dichloromethane (2 x 2 mL). The combined organics were

evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure amines **44a** and **44b**.

Product	Calculated mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
44a{*1*}	273.1967	273.1966	15.5	20	100
44a{*2*}	307.1577	307.1600	30.0	35	100
44a{*3*}	307.1577	307.1602	30.5	35	100
44a{*4*}	307.1577	307.1589	2.0	02	99
44a{*5*}	291.1873	277.1695	5.6	07	83
44a{*6*}	291.1873	291.1875	7.6	10	100
44a{*7*}	291.1873	291.1879	5.2	07	100
44a{*8*}	351.1072	351.1096	26.1	27	100
44a{*9*}	341.1187	341.1198	33.2	35	100
44a{*10*}	341.1841	341.1850	30.9	33	100
44a{*11*}	287.2123	287.2129	24.1	35	100
44a{*12*}	287.2123	287.2156	26.1	33	100
44a{*13*}	287.2123	287.2120	3.1	04	100
44a{*14*}	303.2073	303.2083	13.4	16	98
44a{*15*}	303.2073	303.2075	25.3	32	100
44a{*16*}	333.2178	333.2188	28.6	31	100
44a{*17*}	289.1916	289.1940	2.7	04	100
44a{*18*}	375.1451	375.1464	31.1	30	98
44a{*19*}	279.1531	279.1556	22.3	29	100
44a{*20*}	263.1760	263.1783	16.8	23	100
44a{*21*}	277.1916	277.1955	23.7	31	100
44a{*22*}	274.1919	274.1931	20.8	28	100
44a{*23*}	288.2076	288.2100	18.1	23	86
44a{*24*}	265.2280	265.2302	9.9	13	94
44b{*1*}	273.1967	273.1983	7.0	09	100
44b{*2*}	307.1577	307.1599	12.8	15	100
44b{*3*}	307.1577	307.1586	14.3	17	100
44b{*5*}	291.1873	277.1680	2.7	03	97
44b{*8*}	351.1072	351.1075	14.5	15	100
44b{*11*}	287.2123	287.2148	10.4	13	100
44b{*12*}	287.2123	287.2134	10.2	13	100
44b{*15*}	303.2073	303.2091	9.6	12	100
44b{*18*}	375.1451	375.1466	19.6	19	100
44b{*19*}	279.1531	279.1551	10.2	13	100
44b{*20*}	263.1760	263.1783	10.2	10	86
44b{*21*}	277.1916	277.1950	10.1	13	100
44b{*22*}	274.1919	274.1939	8.7	12	84

Quinolines 45 from 2-nitrobenzaldehydes



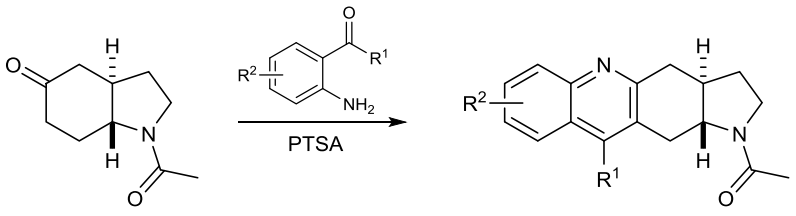
Nitrobenzaldehyde:

{1} R = H
{2} R = 5-Cl
{3} R = 3-OMe
{4} R = 4-CF_3
{5} R = 5-OH
{6} R = 6-Cl
{7} 1-nitro-2-naphthaldehyde

Fe^0 powder (90 mg, 1.6 mmol) was added to a solution of the appropriate 2-nitrobenzaldehyde (0.41 mmol) in ethanol (2 mL) in a microwave vial, followed by 0.1 M HCl (210 µL). The vial was sealed, then heated in an oil bath at 85 °C until complete by TLC (~2 h). The mixture was cooled to room temperature, then a solution of ketone scaffold **19** (50 mg, 0.27 mmol) in EtOH (1 mL) added, followed by powdered KOH (22 mg, 0.38 mmol). The mixture was heated at 85 °C until complete by TLC (~3 h), then cooled to room temperature, passed through a celite plug, eluting with dichloromethane, and concentrated under reduced pressure. The residues were subjected to mass-directed preparative HPLC purification to afford pure quinolines **45**.

Product	Calculated mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
45{*1*}	267.1497	267.1496	27.1	51	93
45{*2*}	301.1108	301.1130	30.0	46	100
45{*3*}	297.1603	297.1613	36.5	60	92
45{*4*}	335.1371	335.1383	39.0	58	100
45{*5*}	283.1447	283.1438	41.0	73	100
45{*6*}	301.1108	301.1117	39.4	66	100
45{*7*}	317.1654	317.1667	9.7	15	88

Quinolines 45 from 2-aminoacetophenones and 2-aminobenzophenones



Acetophenone/benzophenone:

{8} R^1 = Me, R_2 = H
{9} R^1 = Me, R_2 = 4,5-OMe
{10} R^1 = Me, R_2 = 4,5-OCH_2O-
{11} R^1 = Ph, R_2 = 5-Cl
{12} R^1 = Ph, R_2 = 5-NO_2

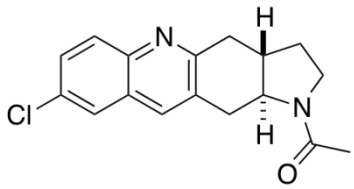
Ketone scaffold **19** (50 mg, 0.27 mmol) was placed in a 2-dram vial containing a magnetic stir bar. The appropriate 2-amino benzophenone or 2-amino acetophenone (0.30 mmol) was then added, followed by *p*-toluenesulphonic acid (0.27 mmol). The vial was sealed shut and heated at 100 °C in

an oil bath for 12 h, then cooled to room temperature, diluted with dichloromethane (2 ml) and quenched with 0.1M NaOH (5 ml). The reactions were passed through Isolute hydrophobic phase separator tubes, which allowed the halogenated solvent layer to pass through. The combined organics were evaporated in a Genevac EZ-2 Plus parallel evaporator and subjected to mass-directed preparative HPLC purification to afford pure quinolines **45**.

Product	Calculated mass	Found mass	Recovered weight (mg)	Yield (%)	Purity (%)
45{*8*}	281.1654	281.1662	28.7	45	100
45{*9*}	341.1865	341.1891	13.0	10	100
45{*10*}	325.1552	325.1565	42.8	60	86
45{*11*}	377.1421	377.1414	49.6	60	100
45{*12*}	388.1661	388.1677	35.2	41	100

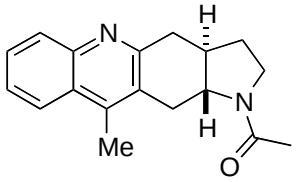
Characterization data for representative library compounds

Quinoline **45**{*2*}



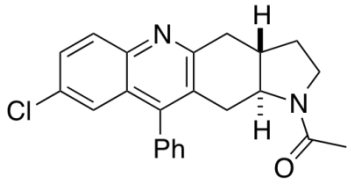
δ_H (400 MHz, $CDCl_3$) At ambient temperature, a 5:1 mixture of rotamers was observed. Major rotamer: 7.96 – 7.80 (m, 2H), 7.72 (d, *J* = 2.3 Hz, 1H), 7.56 (dd, *J* = 9.0, 2.3 Hz, 1H), 4.25 (dd, *J* = 16.2, 4.7 Hz, 1H), 3.77 – 3.38 (m, 4H), 3.04 – 2.77 (m, 2H), 2.32 – 2.16 (m, 2H), 2.12 (s, 3H), 1.83 – 1.71 (m, 1H). Minor rotamer (characteristic signals): 4.02 (dd, *J* = 11.9, 8.1 Hz, 1H), 3.08 – 2.97 (m, 1H), 2.13 (s, 3H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.9, 157.9, 145.2, 136.1, 131.8, 130.4, 130.1, 127.7, 125.9, 60.3, 49.1, 42.9, 38.3, 35.6, 30.3, 23.4; *m/z* (ESI+) found $[M+H]^+$ 301.1130. $C_{17}H_{18}ClN_2O^+$: requires 301.1108.

Quinoline **45**{*8*}



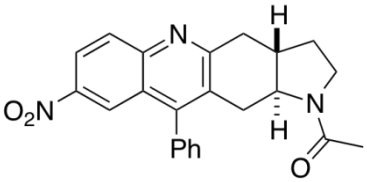
δ_H (400 MHz, $CDCl_3$) At ambient temperature, a 5:1 mixture of rotamers was observed. Major rotamer: 7.98 (dd, *J* = 18.3, 8.3 Hz, 2H), 7.74 – 7.57 (m, 1H), 7.49 (m, 1H), 4.29 (dd, *J* = 16.3, 5.0 Hz, 1H), 3.83 – 3.33 (m, 4H), 3.01 (dd, *J* = 16.8, 12.7 Hz, 1H), 2.68 – 2.60 (m, 4H), 2.35 – 2.09 (m, 5H), 1.75 (dd, *J* = 11.6, 8.6 Hz, 1H). Minor rotamer (characteristic signals): 4.18 – 4.05 (m, 1H), 2.89 (d, *J* = 16.4 Hz, 1H), 2.17 (s, 3H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 171.0, 156.9, 146.2, 143.4, 129.1, 128.7, 127.4, 126.8, 125.8, 123.6, 61.0, 49.3, 42.3, 38.9, 33.7, 30.3, 23.5, 14.3; *m/z* (ESI+) found $[M+H]^+$ 281.1662. $C_{18}H_{21}N_2O^+$: requires 281.1654.

Quinoline **45**{*11*}



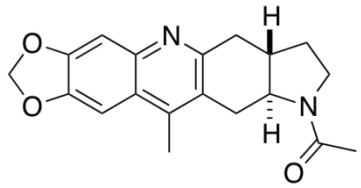
δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 5:1 mixture of rotamers was observed. Major rotamer: 7.97 – 7.92 (m, 1H), 7.58 – 7.51 (m, 2H), 7.49 – 7.44 (m, 2H), 7.29 – 7.24 (m, 2H), 7.16 – 7.09 (m, 1H), 3.89 – 3.77 (dd, *J* = 16.8, 4.8 Hz, 1H), 3.74 – 3.63 (m, 1H), 3.62 – 3.41 (m, 2H), 3.14 – 2.99 (m, 1H), 2.50 – 2.39 (dd, *J* = 16.8, 11.4 Hz, 1H), 2.29 – 2.12 (m, 2H), 2.07 – 1.94 (s, 3H), 1.80 – 1.67 (m, 2H). Minor rotamer (characteristic signals): 4.04 (dd, *J* = 11.8, 8.0 Hz, 1H), 3.28 – 3.20 (m, 1H), 2.70 – 2.62 (m, 1H), 1.85 (s, 3H), 1.67 – 1.58 (m, 1H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.7, 157.8, 148.0, 144.9, 136.0, 131.7, 130.2, 129.8, 129.3, 129.0, 128.8, 128.5, 128.0, 127.4, 124.9, 60.8, 49.2, 42.5, 39.0, 34.4, 30.3, 23.4; *m/z* (ESI+) found $[M+H]^+$ 377.1414. $C_{23}H_{22}ClN_2O^+$: requires 377.1421.

Quinoline **45**{*12*}



δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 3.5:1 mixture of rotamers was observed. Major rotamer: 8.38 (dd, *J* = 9.2, 2.5 Hz, 1H), 8.29 (d, *J* = 2.5 Hz, 1H), 8.11 (d, *J* = 9.2 Hz, 1H), 7.59 (tt, *J* = 7.4, 3.4 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.31 – 7.27 (m, 1H), 7.19 – 7.14 (m, 1H), 3.89 (dd, *J* = 16.9, 4.7 Hz, 1H), 3.75 – 3.67 (m, 1H), 3.58 (dt, *J* = 17.2, 4.8 Hz, 2H), 3.48 (td, *J* = 11.1, 4.7 Hz, 1H), 3.11 (dd, *J* = 17.3, 12.8 Hz, 1H), 2.49 (dd, *J* = 16.9, 11.4 Hz, 1H), 2.30 – 2.17 (m, 2H), 2.03 (s, 3H), 1.82 – 1.70 (m, 1H). Minor rotamer (characteristic signals): 3.35 – 3.25 (m, 1H), 2.72 (dd, *J* = 16.1, 11.4 Hz, 1H), 2.43 – 2.30 (m, 1H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.8, 161.8, 150.7, 148.5, 145.3, 135.0, 130.4, 129.5, 129.4, 129.2, 129.1, 129.0, 128.8, 125.8, 123.3, 122.4, 60.6, 49.2, 42.3, 39.3, 34.5, 30.3, 23.4; *m/z* (ESI+) found $[M+H]^+$ 388.1677. $C_{23}H_{22}N_3O_3^+$: requires 388.1661.

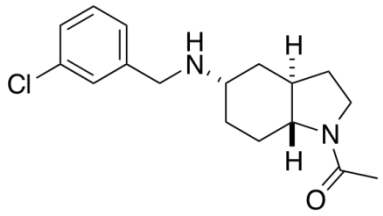
Quinoline **45**{*10*}



δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 2:1 mixture of rotamers was observed. Major rotamer: 7.54 – 7.35 (m, 2H), 6.28 – 6.25 (m, 1H), 6.09 (s, 1H), 4.40 (dd, *J* = 16.0, 5.0 Hz, 1H), 3.99 –

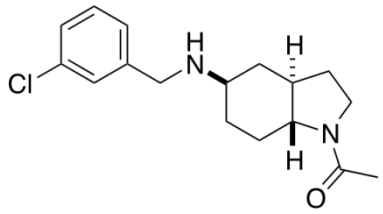
3.88 (m, 1H), 3.80 (td, *J* = 10.7, 10.2, 6.1 Hz, 1H), 3.68 (tq, *J* = 11.5, 6.4, 5.6 Hz, 1H), 3.57 – 3.46 (m, 1H), 3.21 – 3.06 (m, 1H), 2.84 – 2.73 (m, 1H), 2.73 – 2.61 (m, 4H), 2.49 – 2.38 (m, 1H), 2.37 – 2.25 (m, 3H), 1.99 – 1.85 (m, 1H). Minor rotamer (characteristic signals): 4.30 – 4.26 (m, 1H), 3.64 – 3.59 (m, 1H), 3.02 – 2.97 (m, 1H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.9, 154.4, 149.9, 147.6, 125.7, 123.5, 109.1, 105.4, 101.6, 99.3, 96.8, 61.0, 49.3, 42.4, 38.5, 33.4, 30.3, 23.5, 14.7; *m/z* (ESI+) found $[M+H]^+$ 325.1565. $C_{19}H_{21}N_2O_3^+$: requires 325.1552.

Amine **44a**{*3*}



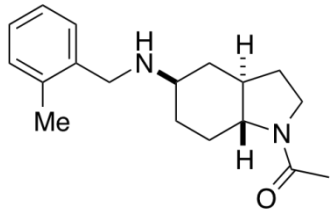
δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 2.6:1 mixture of rotamers was observed. Major rotamer: 7.32 (s, 1H), 7.27 – 7.17 (m, 3H), 3.86 – 3.76 (m, 2H), 3.52 (dd, *J* = 9.7, 8.4 Hz, 1H), 3.42 (td, *J* = 10.5, 6.4 Hz, 1H), 3.05 – 2.90 (m, 2H), 2.70 – 2.54 (m, 1H), 2.26 – 2.13 (m, 1H), 2.12 – 1.97 (m, 4H), 1.94 – 1.80 (m, 2H), 1.67 – 1.36 (m, 2H), 1.36 – 1.04 (m, 2H). Minor rotamer (characteristic signals): 3.79 – 3.65 (m, 1H), 3.16 (td, *J* = 11.7, 6.3 Hz, 1H), 2.27 (dq, *J* = 11.8, 3.3 Hz, 1H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.8, 142.8, 134.3, 129.8, 128.2, 127.2, 126.2, 64.0, 56.3, 50.8, 49.1, 44.9, 36.3, 32.2, 29.7, 29.4, 23.4; *m/z* (ESI+) found $[M+H]^+$ 307.1586. $C_{17}H_{24}ClN_2O^+$: requires 307.1577.

Amine **44b**{*3*}



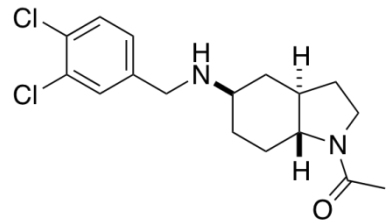
δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 3:1 mixture of rotamers was observed. Major rotamer: 7.32 (s, 1H), 7.25 – 7.16 (m, 3H), 3.78 – 3.66 (m, 2H), 3.53 – 3.34 (m, 2H), 3.01 – 2.85 (m, 2H), 2.82 – 2.71 (m, 1H), 2.12 – 1.70 (m, 7H), 1.61 – 1.29 (m, 4H). Minor rotamer (characteristic signals): 3.83 (dd, *J* = 11.8, 8.1 Hz, 1H), 3.30 (td, *J* = 11.6, 6.3 Hz, 1H), 2.07 (s, 3H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.8, 143.2, 134.3, 129.7, 128.1, 127.1, 126.2, 64.4, 51.8, 51.3, 48.6, 39.7, 34.2, 30.0, 29.6, 26.3, 23.5; *m/z* (ESI+) found $[M+H]^+$ 307.1602. $C_{17}H_{24}ClN_2O^+$: requires 307.1577.

Amine **44b**{*11*}



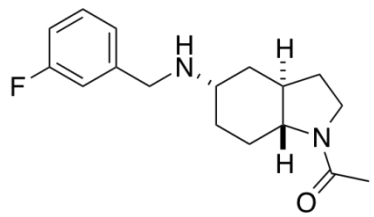
δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 2.5:1 mixture of rotamer was observed. Major rotamer: 7.27 (d, *J* = 1.9 Hz, 1H), 7.20 – 7.12 (m, 3H), 3.79 (s, 2H), 3.58 – 3.38 (m, 2H), 3.05 – 2.89 (m, 2H), 2.73 – 2.60 (m, 1H), 2.40 – 2.31 (m, 3H), 2.16 – 1.98 (m, 3H), 1.93 – 1.83 (m, 1H), 1.68 – 1.07 (m, 7H). Minor rotamer (characteristic signals): 3.91 – 3.82 (m, 1H), 3.31 (td, *J* = 11.6, 6.3 Hz, 1H), 2.42 (ddd, *J* = 11.2, 7.4, 4.0 Hz, 1H), 2.07 (s, 3H); δ_C (125 MHz, $CDCl_3$) 170.8, 138.6, 136.3, 130.4, 128.4, 127.1, 126.1, 64.2, 57.0, 49.3, 49.1, 45.0, 36.4, 32.4, 29.7, 29.5, 23.5, 19.1; *m/z* (ESI+) found $[M+H]^+$ 287.2148. $C_{18}H_{27}N_2O^+$: requires 287.2123.

Amine **44b**{*9*}



δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 2.7:1 mixture of rotamer was observed. Major rotamer: 7.45 (d, *J* = 1.7 Hz, 1H), 7.42 – 7.34 (m, 1H), 7.17 (dd, *J* = 8.2, 1.8 Hz, 1H), 3.79 – 3.63 (m, 2H), 3.57 – 3.36 (m, 2H), 3.07 – 2.87 (m, 2H), 2.87 – 2.71 (m, 1H), 2.15 – 1.68 (m, 7H), 1.63 – 1.20 (m, 4H). Minor rotamer (characteristic signals): 3.82 (dd, *J* = 11.8, 8.2 Hz, 1H), 3.32 – 3.26 (m, 1H), 2.06 (s, 3H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.8, 141.5, 132.4, 130.4, 130.0, 127.5, 127.4, 64.4, 51.9, 50.7, 48.6, 39.8, 34.2, 30.0, 29.6, 26.4, 23.5; *m/z* (ESI+) found $[M+H]^+$ 341.1198. $C_{17}H_{23}Cl_2N_2O^+$: requires 341.1187.

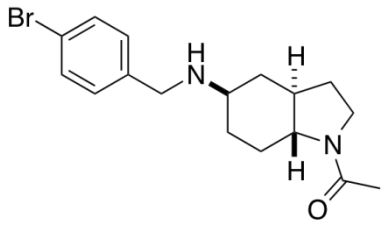
Amine **44a**{*6*}



δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 2.3:1 mixture of rotamer was observed. Major rotamer: 7.30 – 7.23 (m, 1H), 7.12 – 7.03 (m, 2H), 6.92 (td, *J* = 8.4, 2.4 Hz, 1H), 3.81 – 3.70 (m, 2H), 3.52 – 3.36 (m, 2H), 3.04 – 2.88 (m, 2H), 2.82 – 2.73 (m, 1H), 2.14 – 1.71 (m, 7H), 1.62 – 1.28 (m, 4H). Minor rotamer (characteristic signals): 3.87 – 3.78 (m, 1H), 3.32 – 3.23 (m, 1H), 2.06 (s, 3H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.8, 163.1 (d, $^1J_{cf}$ = 245 Hz), 143.7, 129.9 (d, $^3J_{cf}$ = 9 Hz), 123.6 (d, $^4J_{cf}$ =

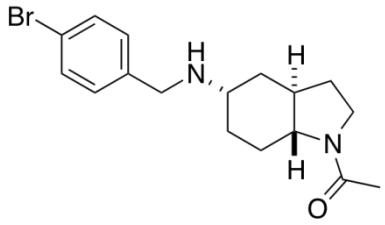
3 Hz), 114.9 (d, $^2J_{cf}$ = 21 Hz), 113.8 (d, $^2J_{cf}$ = 21 Hz), 64.5, 51.8, 51.2, 48.6, 39.8, 34.2, 30.0, 29.6, 26.3, 23.5; *m/z* (ESI+) found $[M+H]^+$ 291.1879. $C_{17}H_{24}FN_2O^+$: requires 291.1873.

Amine **44b**{*8*}



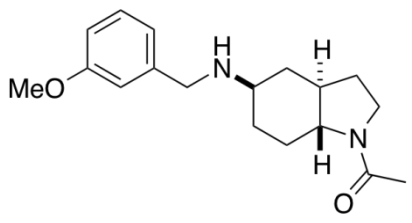
δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 2.5:1 mixture of rotamer was observed. Major rotamer: 7.48 – 7.40 (m, 2H), 7.19 (m, 2H), 3.84 – 3.73 (m, 2H), 3.59 – 3.49 (m, 1H), 3.42 (td, *J* = 10.4, 6.4 Hz, 1H), 3.04 – 2.92 (m, 2H), 2.69 – 2.53 (m, 1H), 2.26 – 2.13 (m, 1H), 2.13 – 1.97 (m, 4H), 1.95 – 1.81 (m, 1H), 1.66 – 1.04 (m, 5H). Minor rotamer (characteristic signals): 3.89 – 3.79 (m, 1H), 3.28 (td, *J* = 11.7, 6.3 Hz, 1H), 2.46 – 2.36 (m, 1H), 2.05 (s, 3H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.8, 139.8, 131.6, 129.8, 120.8, 64.1, 56.3, 50.8, 49.1, 45.0, 36.3, 32.3, 29.7, 29.5, 23.5; *m/z* (ESI+) found $[M+H]^+$ 351.1075. $C_{17}H_{24}BrN_2O^+$: requires 351.1072.

Amine **44a**{*8*}



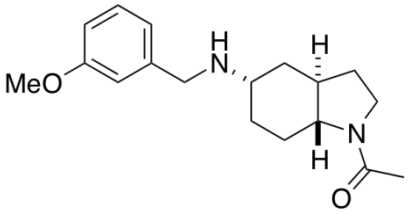
δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 2.5:1 mixture of rotamer was observed. Major rotamer: 7.45 – 7.39 (m, 2H), 7.18 (m, 2H), 3.75 – 3.66 (m, 2H), 3.50 – 3.44 (m, 1H), 3.43 – 3.35 (m, 1H), 3.01 – 2.86 (m, 2H), 2.80 – 2.72 (m, 1H), 2.11 – 1.98 (m, 4H), 1.98 – 1.67 (m, 3H), 1.60 – 1.27 (m, 4H). Minor rotamer (characteristic signals): 3.86 – 3.75 (m, 1H), 3.35 – 3.27 (m, 1H), 2.25 – 2.13 (m, 2H), 2.05 (s, 3H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.8, 140.1, 131.5, 129.8, 120.6, 64.5, 51.8, 51.1, 48.6, 39.8, 34.2, 30.0, 29.6, 26.3, 23.5; *m/z* (ESI+) found $[M+H]^+$ 351.1096. $C_{17}H_{24}BrN_2O^+$: requires 351.1072.

Amine **44b**{*15*}



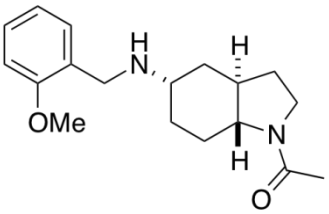
δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 2.5:1 mixture of rotamer was observed. Major rotamer: 7.26 – 7.19 (m, 1H), 6.92 – 6.85 (m, 2H), 6.82 – 6.76 (m, 1H), 3.86 – 3.73 (m, 5H), 3.56 – 3.48 (m, 1H), 3.41 (td, *J* = 10.5, 6.4 Hz, 1H), 3.03 – 2.91 (m, 2H), 2.70 – 2.57 (m, 1H), 2.28 – 2.14 (m, 1H), 2.12 – 1.96 (m, 4H), 1.91 – 1.80 (m, 1H), 1.74 – 1.36 (m, 3H), 1.35 – 1.04 (m, 2H). Minor rotamer (characteristic signals): 3.29 (td, *J* = 11.7, 6.3 Hz, 1H), 2.46 – 2.37 (m, 1H), 2.06 (s, 2H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.8, 159.9, 142.3, 129.6, 120.4, 113.7, 112.5, 64.1, 56.3, 55.3, 51.4, 49.1, 45.0, 36.3, 32.3, 29.7, 29.5, 23.5; *m/z* (ESI+) found $[M+H]^+$ 303.2091. $C_{18}H_{27}N_2O_2^+$: requires 303.2073.

Amine **44a**{*15*}



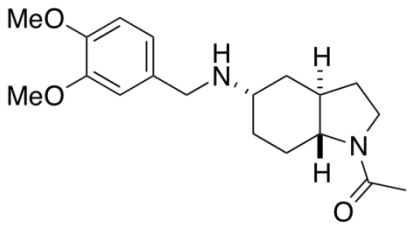
δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 2.5:1 mixture of rotamer was observed. Major rotamer: 7.25 – 7.20 (m, 1H), 6.91 – 6.85 (m, 2H), 6.80 – 6.74 (m, 1H), 3.79 (s, 3H), 3.73 (s, 2H), 3.50 – 3.33 (m, 2H), 3.04 – 2.85 (m, 2H), 2.80 – 2.70 (m, 1H), 2.14 – 1.71 (m, 6H), 1.59 – 1.25 (m, 5H). Minor rotamer (characteristic signals): 3.27 (td, *J* = 11.6, 6.3 Hz, 1H), 2.05 (s, 3H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.8, 159.8, 142.7, 129.4, 120.4, 113.8, 112.1, 64.5, 55.3, 51.7, 51.6, 48.6, 39.8, 34.2, 30.0, 29.6, 26.4, 23.5; *m/z* (ESI+) found $[M+H]^+$ 303.2075. $C_{18}H_{27}N_2O_2^+$: requires 303.2073.

Amine **44a**{*14*}



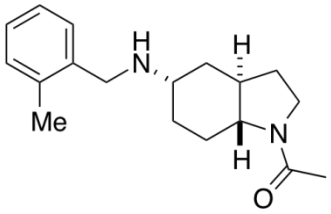
δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 2.3:1 mixture of rotamer was observed. Major rotamer: 7.25 – 7.19 (m, 1H), 6.94 – 6.81 (m, 3H), 3.89 – 3.79 (s, 3H), 3.75 (s, 2H), 3.52 – 3.33 (m, 2H), 2.98 – 2.86 (m, 2H), 2.80 – 2.70 (m, 1H), 2.14 – 1.94 (m, 5H), 1.93 – 1.70 (m, 2H), 1.59 – 1.27 (m, 4H). Minor rotamer (characteristic signals): 3.27 (td, *J* = 11.6, 6.2 Hz, 1H), 2.20 (ddd, *J* = 15.0, 10.0, 3.2 Hz, 2H), 2.05 (s, 3H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.7, 157.7, 129.9, 128.2, 120.5, 110.4, 64.5, 55.4, 51.2, 48.7, 47.1, 39.9, 34.2, 30.1, 29.6, 26.6, 23.6; *m/z* (ESI+) found $[M+H]^+$ 303.2083. $C_{18}H_{27}N_2O_2^+$: requires 303.2073.

Amine **44a**{*16*}



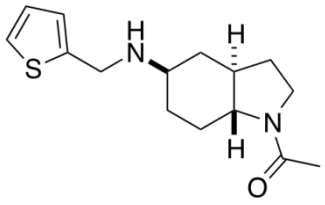
δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 2.6:1 mixture of rotamer was observed. Major rotamer: 6.88 – 6.77 (m, 3H), 3.86 (m, 6H), 3.72 – 3.63 (m, 2H), 3.51 – 3.32 (m, 2H), 3.02 – 2.86 (m, 2H), 2.82 – 2.70 (m, 1H), 2.11 – 1.69 (m, 7H), 1.58 – 1.26 (m, 4H). Minor rotamer (characteristic signals): 3.26 (td, *J* = 11.7, 6.3 Hz, 1H), 2.25 – 2.13 (m, 2H), 2.04 (s, 3H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.8, 149.0, 148.0, 133.6, 120.1, 111.4, 111.1, 64.5, 56.1, 56.0, 51.7, 51.6, 48.6, 39.8, 34.3, 30.0, 29.5, 26.4, 23.5; *m/z* (ESI+) found $[M+H]^+$ 333.2188. $C_{19}H_{29}N_2O_3^+$: requires 333.2178.

Amine **44a**{*11*}



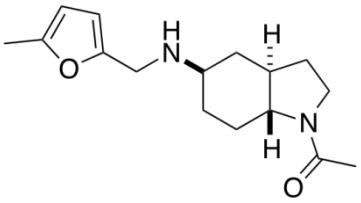
δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 2.3:1 mixture of rotamer was observed. Major rotamer: 7.31 – 7.26 (m, 1H), 7.19 – 7.11 (m, 3H), 3.77 – 3.66 (m, 2H), 3.53 – 3.32 (m, 2H), 3.09 – 2.99 (m, 1H), 2.97 – 2.87 (m, 1H), 2.82 – 2.73 (m, 1H), 2.36 (s, 3H), 2.16 – 1.72 (m, 7H), 1.64 – 1.31 (m, 4H). Minor rotamer (characteristic signals): 3.82 (dd, *J* = 11.9, 8.2 Hz, 1H), 3.27 (td, *J* = 11.7, 6.3 Hz, 1H), 2.07 (s, 3H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.8, 138.9, 136.6, 130.4, 128.7, 127.1, 126.0, 64.6, 52.6, 50.0, 48.7, 39.9, 34.6, 30.0, 29.7, 26.5, 23.6, 19.1; *m/z* (ESI+) found $[M+H]^+$ 287.2129. $C_{18}H_{27}N_2O^+$: requires 287.2123.

Amine **44b**{*19*}



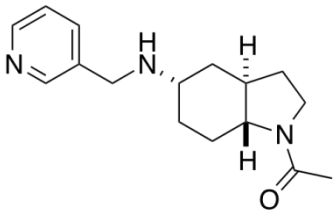
δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 2.5:1 mixture of rotamer was observed. Major rotamer: 7.23 – 7.17 (m, 1H), 6.98 – 6.87 (m, 2H), 4.02 (s, 2H), 3.59 – 3.35 (m, 2H), 3.06 – 2.89 (m, 2H), 2.76 – 2.56 (m, 1H), 2.27 – 1.94 (m, 4H), 1.93 – 1.80 (m, 1H), 1.68 – 1.00 (m, 6H). Minor rotamer (characteristic signals): 3.84 (dd, *J* = 11.8, 8.2 Hz, 1H), 3.29 (td, *J* = 11.7, 6.3 Hz, 1H), 2.45 – 2.37 (m, 1H), 2.05 (s, 3H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.8, 144.5, 126.8, 124.8, 124.4, 64.1, 55.9, 49.1, 45.9, 45.0, 36.2, 32.2, 29.7, 29.5, 23.5; *m/z* (ESI+) found $[M+H]^+$ 279.1556. $C_{15}H_{23}N_2OS^+$: requires 279.1531.

Amine **44b**{*21*}



δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 2.6:1 mixture of rotamer was observed. Major rotamer: 6.02 (s, 1H), 5.86 (s, 1H), 3.74 (s, 2H), 3.57 – 3.48 (m, 1H), 3.41 (td, *J* = 10.5, 6.4 Hz, 1H), 3.03 – 2.89 (m, 2H), 2.71 – 2.49 (m, 1H), 2.26 (s, 3H), 2.11 – 1.95 (m, 4H), 1.94 – 1.77 (m, 2H), 1.77 – 1.04 (m, 6H). Minor rotamer (characteristic signals): 3.84 (dd, *J* = 11.9, 8.2 Hz, 1H), 3.29 (td, *J* = 11.7, 6.3 Hz, 1H), 2.45 – 2.36 (m, 1H), 2.05 (s, 3H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.8, 152.1, 151.6, 107.7, 106.0, 64.1, 55.9, 49.1, 44.9, 43.9, 36.0, 32.0, 29.7, 29.4, 23.5, 13.7; *m/z* (ESI+) found $[M+H]^+$ 277.1955. $C_{16}H_{25}N_2O_2^+$: requires 277.1916.

Amine **44a**{*23*}



δ_H (500 MHz, $CDCl_3$) At ambient temperature, a 3:1 mixture of rotamer was observed. Major rotamer: 8.53 (s, 1H), 8.50 – 8.39 (m, 1H), 7.74 – 7.57 (m, 1H), 7.26 – 7.17 (m, 1H), 3.81 – 3.69 (m, 2H), 3.53 – 3.32 (m, 2H), 3.04 – 2.83 (m, 2H), 2.80 – 2.68 (m, 1H), 2.12 – 1.67 (m, 7H), 1.59 – 1.28 (m, 4H). Minor rotamer (characteristic signals): 3.25 (td, *J* = 11.6, 6.3 Hz, 1H), 2.03 (s, 3H); δ_C (125 MHz, $CDCl_3$) Major rotamer: 170.8, 149.6, 148.4, 136.3, 135.8, 123.4, 64.4, 51.9, 49.1, 48.6, 39.7, 34.1, 29.9, 29.5, 26.3, 23.5; *m/z* (ESI+) found $[M+H]^+$ 274.1931. $C_{16}H_{24}N_3O^+$: requires 274.1919.

IV. Supplementary Note: Cheminformatic analysis

Principal Component Analysis

The plots shown in **Fig 6a-c** were generated from principal component analysis (PCA) of a total of 183 compounds:

- Tan's established reference set consisting of 40 small molecule drugs, 20 drug-like compounds from commercial vendors (ChemBridge and Chem Div) and 60 diverse natural products (**Suppl. Table 3**),[47]
- 20 alkaloid natural products (**Suppl. Fig. 1**),
- 14 representative scaffolds (**Suppl. Fig. 2**),
- 29 representative library members (**Suppl. Fig. 3**).

The 20 structural and physiochemical properties (**Supplementary Table 4**) introduced by Tan[47] were determined by SYBYL[67], free online cheminformatic tools (VCC Lab[6869]), ChemDraw and manual inspection. For a discussion on the relevance of the 20 selected parameters, see Tan's earlier paper.[47] This property data for all the compounds was assembled in a Microsoft Excel spreadsheet (*Supplementary Dataset 1 PCA.xls*). The mean average value for each parameter was calculated for each compound series (**Supplementary Table 5**). This hypothetical average structure for each series was also included in the PCA analysis.

Supplementary Table 4. Parameters employed in PCA.

Parameter	Description	Method of Determination
MW	molecular weight	SYBYL
N	number of nitrogen atoms	SYBYL
O	number of oxygen atoms	SYBYL
XLogP	calc n-octanol/water partition coefficient	http://www.vcclab.org
HBD	number of hydrogen bond donors	SYBYL
HBA	number of hydrogen bond acceptors	SYBYL
RotB	number of rotatable bonds	SYBYL
tPSA	topological polar surface area	SYBYL
nStereo	number of stereocenters	SYBYL
R	number of R stereocentres	ChemDraw Show Stereochemistry
S	number of S stereocentres	ChemDraw Show Stereochemistry
nStMW	*R* – *S*	Microsoft Excel
RSdelta	*nStereo* / *MW* (stereochemical density)	Microsoft Excel
Rings	number of rings	Manual inspection
RngAr	number of aromatic rings	Manual inspection
RngSys	number of ring systems	Manual inspection
RngLg	number of atoms in largest ring outline	Manual inspection
RRSys	*Rings* / *RngSys* (ring complexity)	Microsoft Excel
ALOGPs	calc n-octanol/water partition coefficient (alt)	http://www.vcclab.org
ALOGpS	calc aqueous solubility	http://www.vcclab.org

Supplementary Table 5. Average parameters by compound series.

	Drugs	NPs	Commercial	Alkaloid NPs	Scaffolds	Libraries
m/w	361	629	414	319	243	355
N	2.2	2.6	4.5	1.7	0.9	1.9
O	2.9	9.7	3.3	2.8	1.6	1.8
XlogP	2.7	1.5	2.4	2.0	2.3	4.0
HBD	1.5	4.9	1.5	1.3	0.7	0.8
HBA	5.4	10.8	6.8	4.4	2.5	4.3
RotB	6.3	9.7	5.7	2.8	1.7	4.1
tPSA	69	183	98	54	33	42
ALOGPs	2.8	2.1	3.0	2.3	2.4	4.0
ALOGpS	-3.9	-3.8	-3.9	-2.7	-2.5	-4.5
nStereo	1.4	9.1	0.5	4.0	3.1	3.3
R	0.6	4.1	0.3	1.7	1.6	1.6
S	0.8	5.0	0.3	2.3	1.6	1.6
nStMW*	3.7	13.9	1.1	12.7	13.5	9.4
RSdelta	-0.2	-0.9	0.0	-0.6	0.0	0.0
Rings	2.9	3.8	3.7	3.9	3.0	3.8
RngAr	2.1	1.0	2.9	0.9	0.5	1.1
RngSys	2.1	2.0	3.1	1.4	1.5	2.0
RngLg	8.4	15.8	7.9	13.4	10.9	11.9
RRSys	1.4	2.3	1.2	3.2	2.2	2.1

*nStMW x 1000

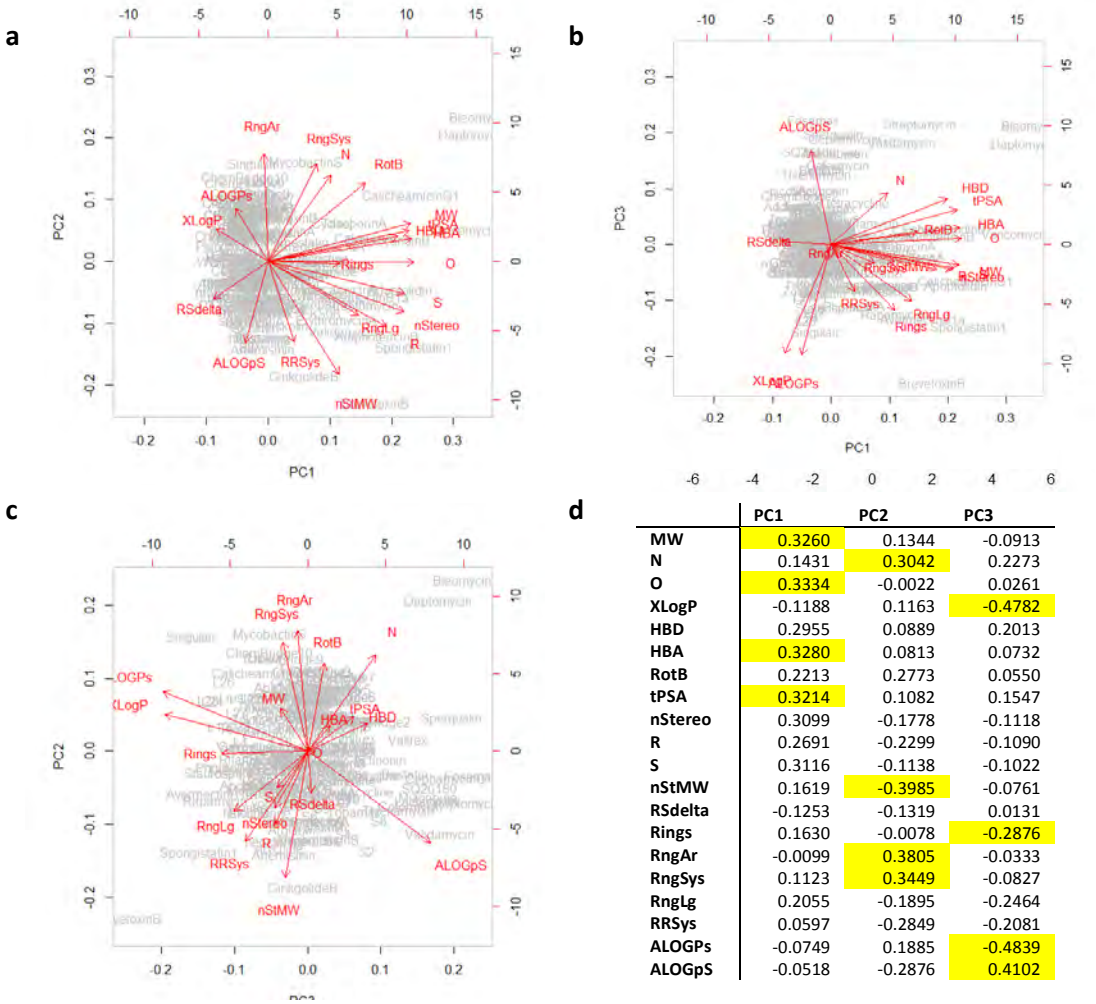
Principal component analysis was then carried out using the procedure outlined by Tan.[47] This resulted in the construction of 3 plots of PC1 v PC2, PC1 v PC3 and PC2 v PC3 (**Supplementary Fig. 1a-c**). Summary information from R (the open source statistical computing package[70] used for the PCA analysis) is shown below in **Supplementary Table 6**.

Supplementary Table 6. Standard deviation and proportion of variance for each component in PCA plot (R Summary).

	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10
Standard deviation	2.871	1.856	1.747	1.384	1.094	0.844	0.575	0.568	0.468	0.374
Proportion of Variance	0.412	0.172	0.153	0.096	0.060	0.036	0.017	0.016	0.011	0.007
Cumulative Proportion	0.412	0.584	0.737	0.833	0.893	0.928	0.945	0.961	0.972	0.979

This data shows that of the 20-dimensional dataset, >90% of the variance is accounted for within the first 6 principal components (PC1 – PC6). In order to simplify the interpretation of this data, the first 3 principal components (accounting for ~74% of the variation) were used to generate the PCA plots shown in **Fig. 6a-c**.

The R program was used to plot the weightings of the original 20 parameters for each of the three 2-dimensional PCA plots (**Supplementary Fig. 8**). The parameters that have the greatest influence on PC1 are MW, O, HBA and tPSA, which move compounds to the right for plots PC1 v PC2 and PC1 v PC3. The descriptors with the largest loading on PC2 are N, RingAr and RingSys, which shift compounds up in plots PC1 v PC2 and PC2 v PC3, as well as nStMW, which shifts compounds down in these plots. Finally, PC3 is affected to the greatest degree by XLogP, Rings and ALOGPs, shifting compounds in a negative direction along the PC3 axis in plots PC1 v PC3 and PC2 v PC3, in addition to ALOGpS, which shifts compounds in a positive direction in these plots.



	PC1	PC2	PC3
MW	0.3260	0.1344	-0.0913
N	0.1431	0.3042	0.2273
O	0.3334	-0.0022	0.0261
XLogP	-0.1188	0.1163	-0.4782
HBD	0.2955	0.0889	0.2013
HBA	0.3280	0.0813	0.0732
RotB	0.2213	0.2773	0.0550
tPSA	0.3214	0.1082	0.1547
nStereo	0.3099	-0.1778	-0.1118
R	0.2691	-0.2299	-0.1090
S	0.3116	-0.1138	-0.1022
nStMW	0.1619	-0.3985	-0.0761
RSdelta	-0.1253	-0.1319	0.0131
Rings	0.1630	-0.0078	-0.2876
RngAr	-0.0099	0.3805	-0.0333
RngSys	0.1123	0.3449	-0.0827
RngLg	0.2055	-0.1895	-0.2464
RRSys	0.0597	-0.2849	-0.2081
ALOGPs	-0.0749	0.1885	-0.4839
ALOGpS	-0.0518	-0.2876	0.4102

Supplementary Figure 8. Biplots and component loadings for PCA of alkaloid-inspired scaffolds and libraries, and reference sets. The biplots for (**a**) PC1 v PC2. (**b**) PC1 v PC3. (**c**) PC2 v PC3. (**d**) Component loadings of each of the 20 structural and physiochemical descriptors for the first 3 principal components (PC1 – PC3). The four descriptors with the highest weightings are highlighted for each principal component.

Principal Moment of Inertia Analysis

Principal moment of inertia analysis was carried out by calculation of the lowest energy conformation of each representative scaffold and library compound, and each compound from the above reference set. The conformation calculation was performed using the MOE molecular modelling software package[7172] in a similar manner to that reported by Tan[73], with the only difference being the selection of parameters employed for conformation generation:

- maxConfs: 1000

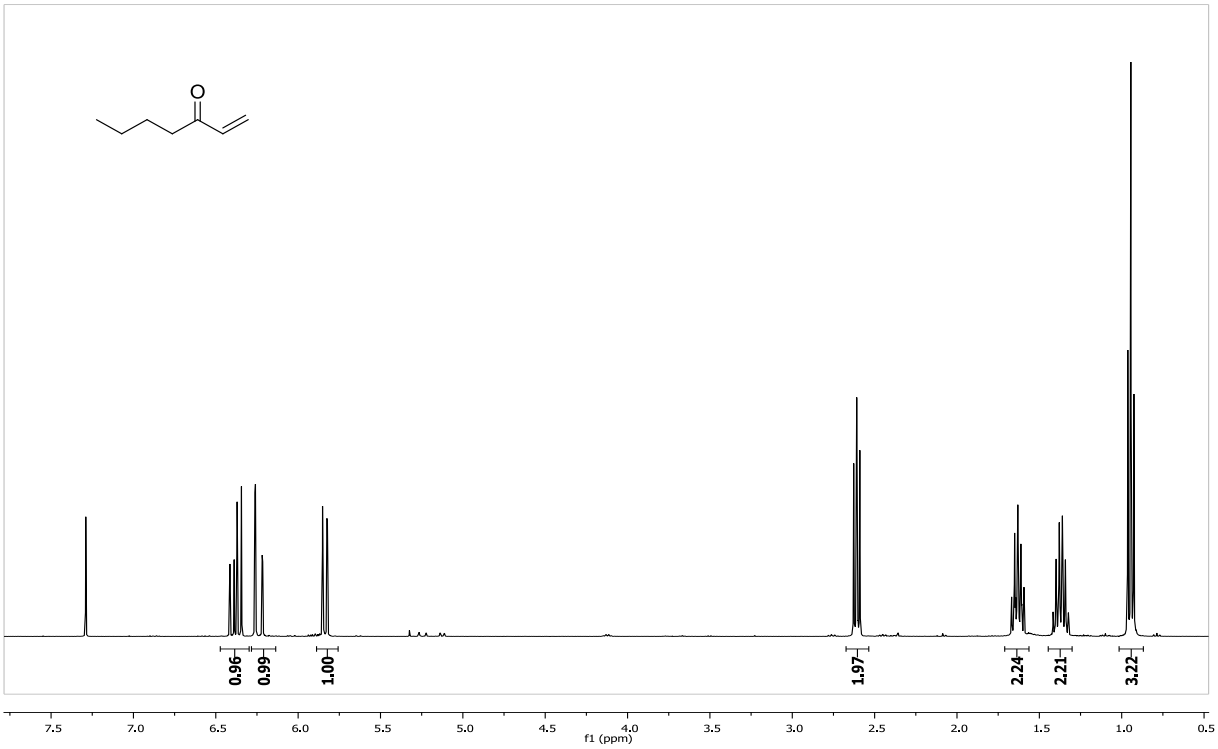
- RMSD: ≤0.15
- Failure limit: 100
- Energy cutoff: 7 kcal/mol
- Iteration limit: 1000
- MM iteration limit: 500

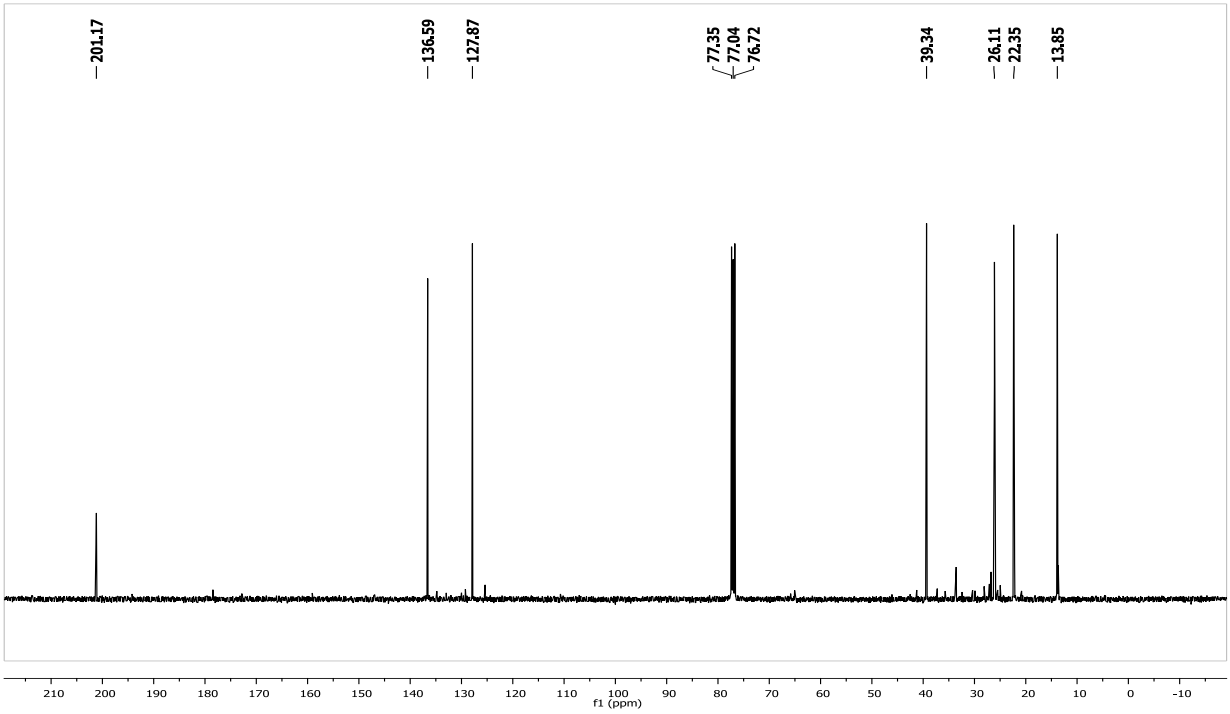
Once the lowest energy conformer was calculated, the three principal moments of inertia (Ixx, Iyy, Izz) and normalized principal moments of inertia, npr1 (Ixx/Izz) and npr2 (Iyy/Izz) were determined using MOE. These PMI ratios were calculated for our representative scaffolds and library members, in addition to the reference sets[47] of alkaloids, drugs, commercial drug-like library compounds and natural products. The ratios were plotted on a triangular graph where the vertices (0,1), (0.5,0.5) and (1,1) represent a perfect rod, disc and sphere, respectively (**Fig. 6d**).[74]

V. Supplementary Note: 1H and 13C NMR spectra for intermediates, scaffolds and representative library compounds

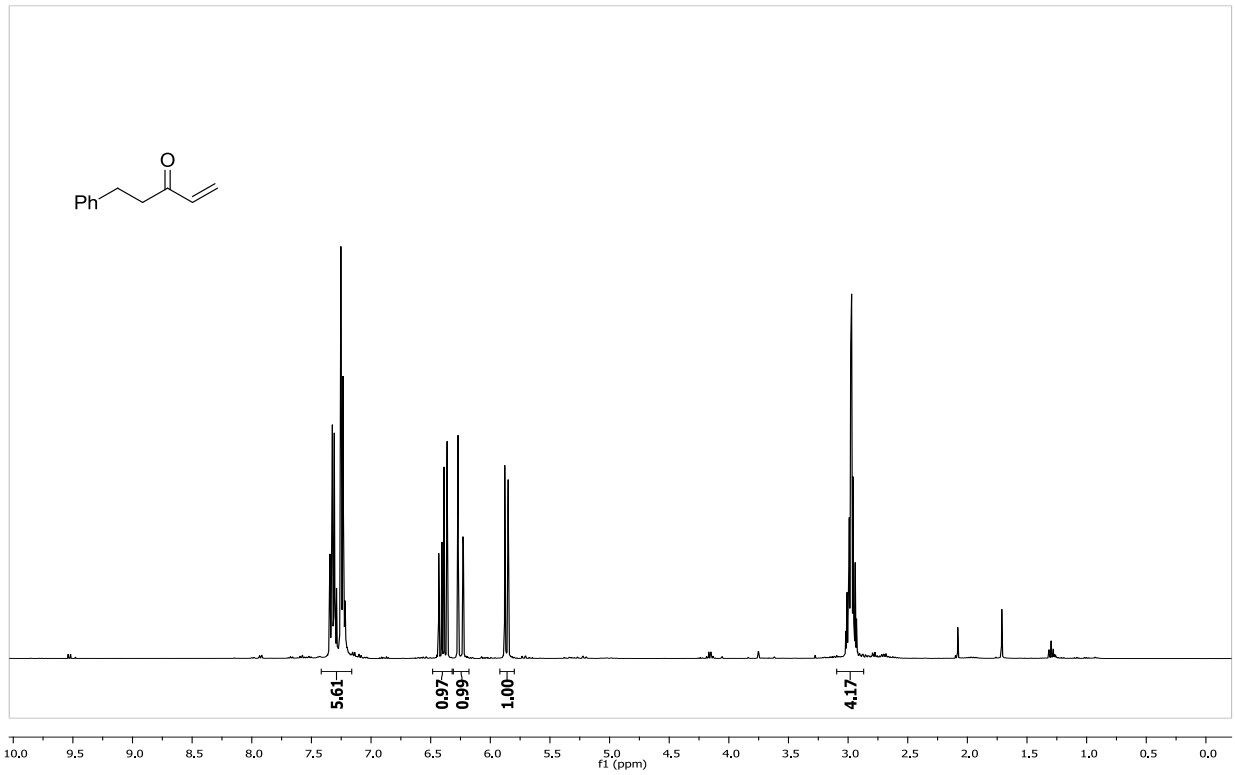
Stemona alkaloid-inspired series

S1c





S1d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Ph
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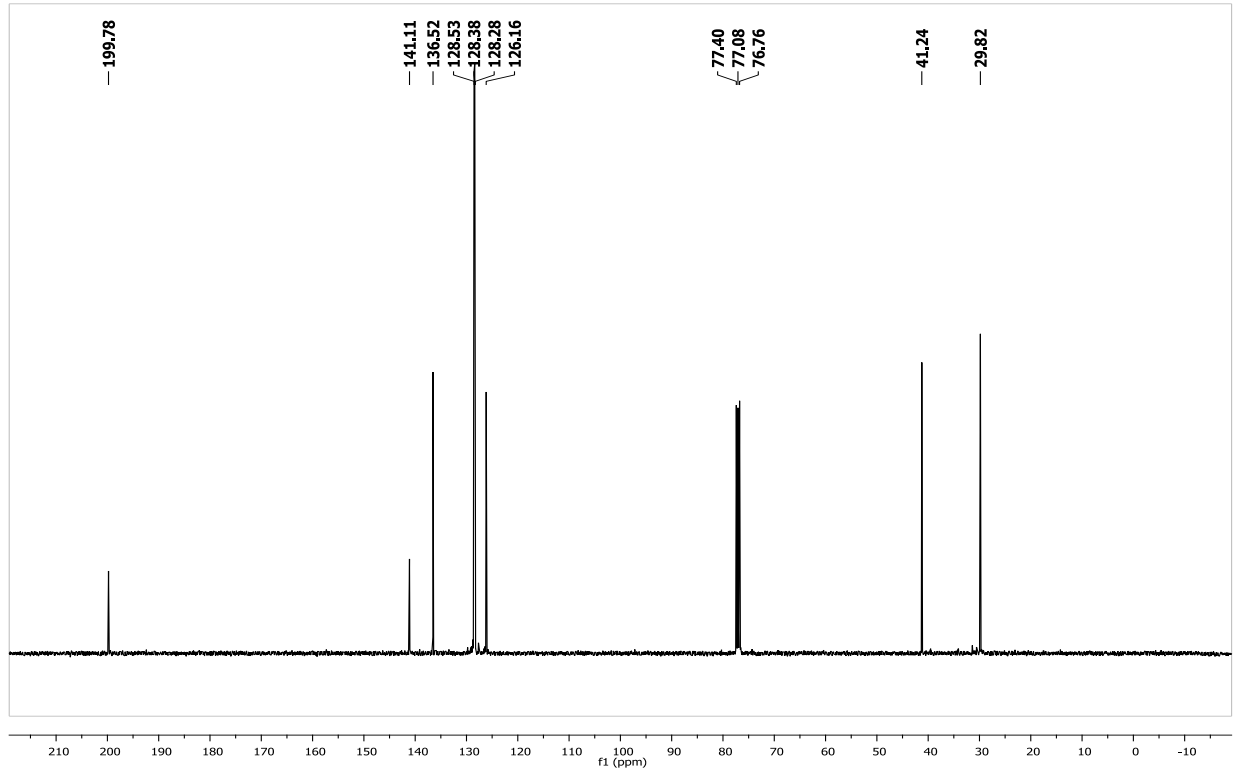
1.00
4.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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128.53
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128.28
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76.76
41.24
29.82
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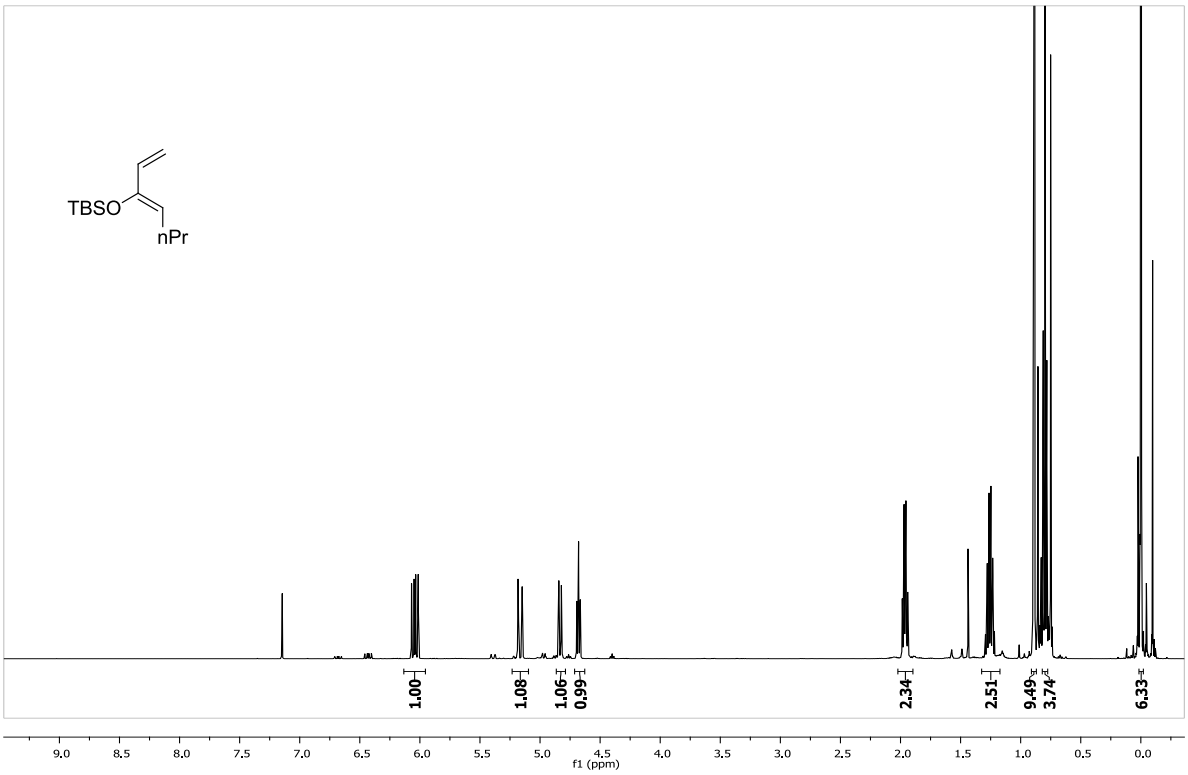
f1 (ppm)

S2c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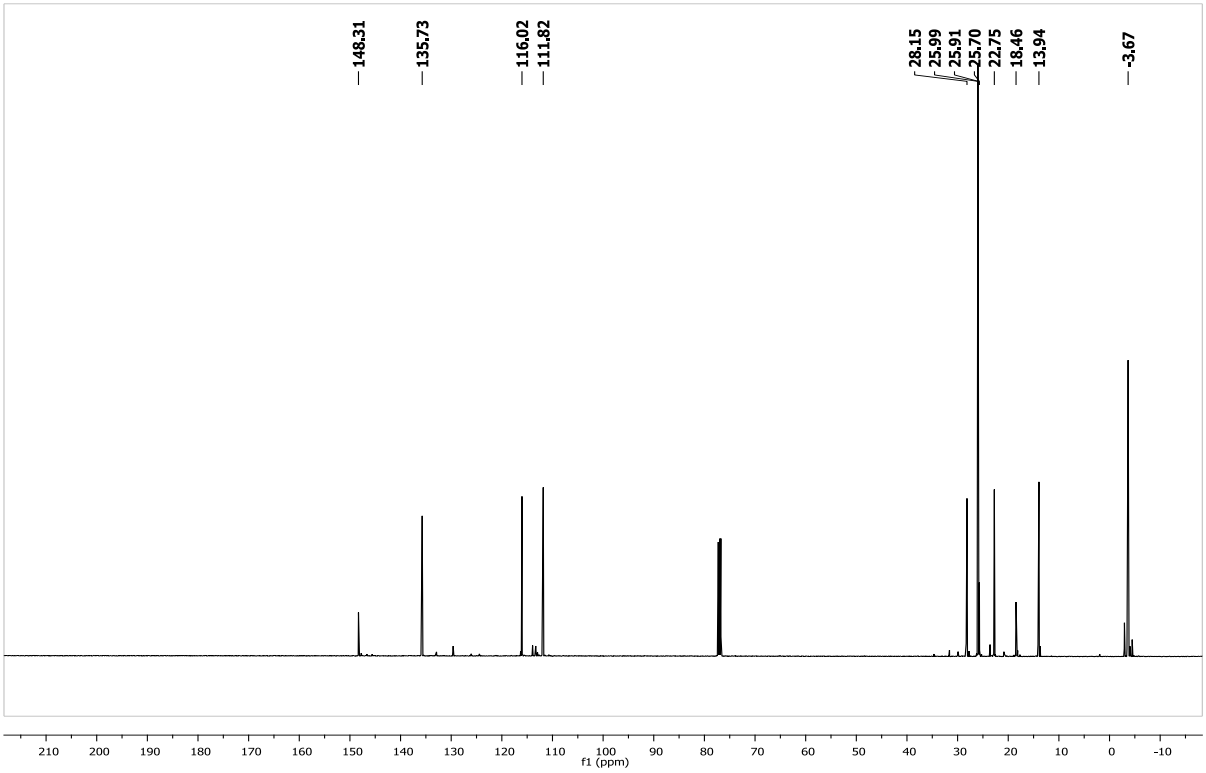
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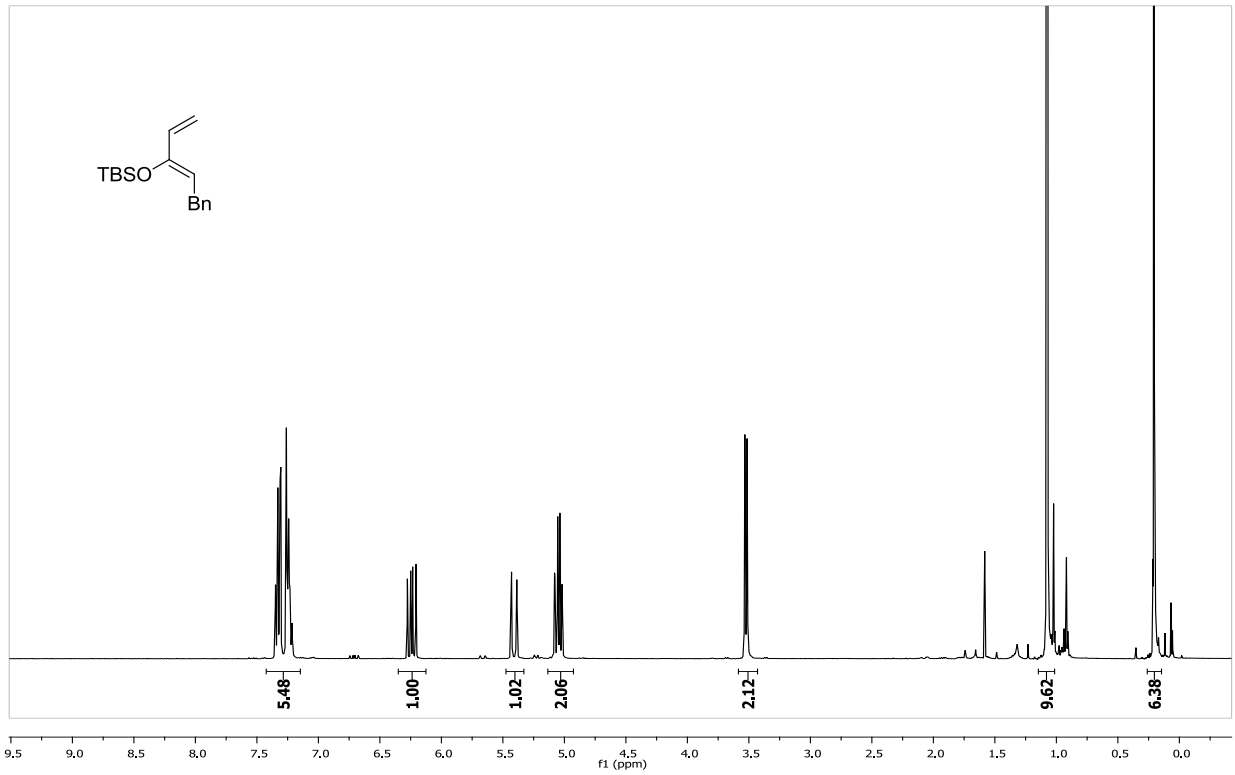
S2d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6.38
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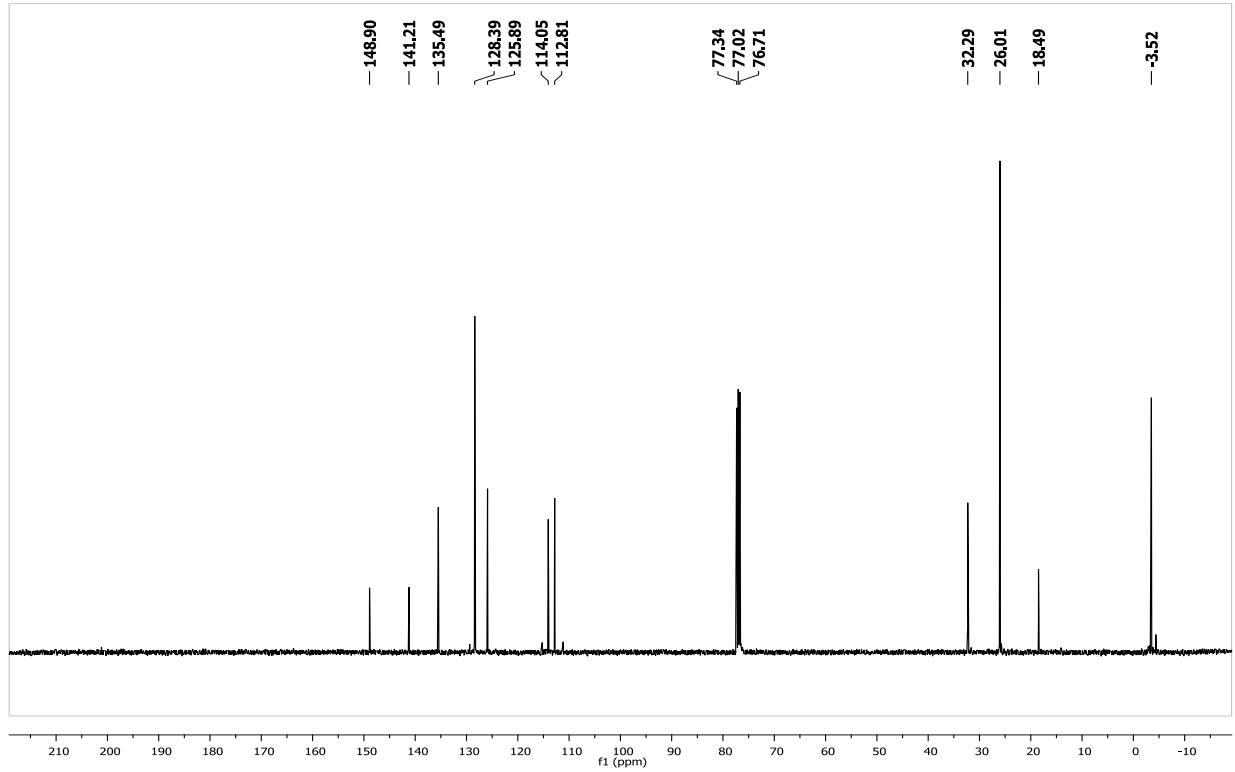
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26.01
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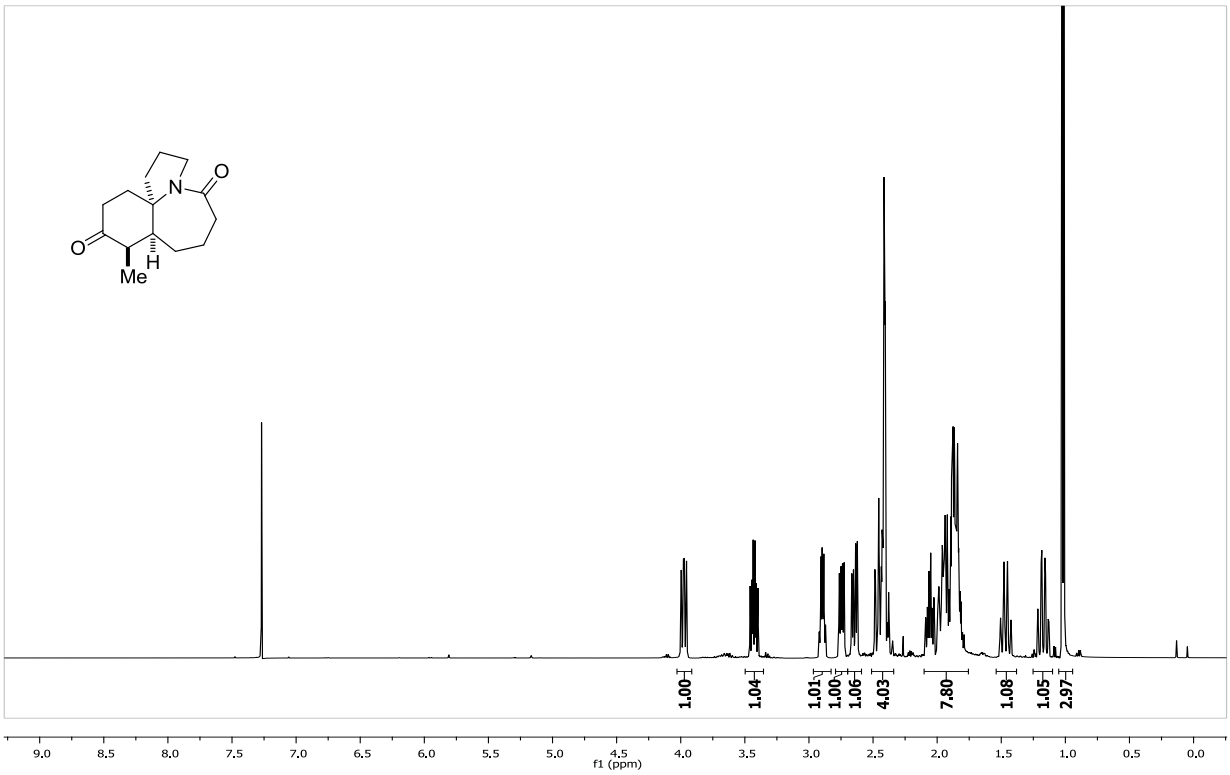
f1 (ppm)

3b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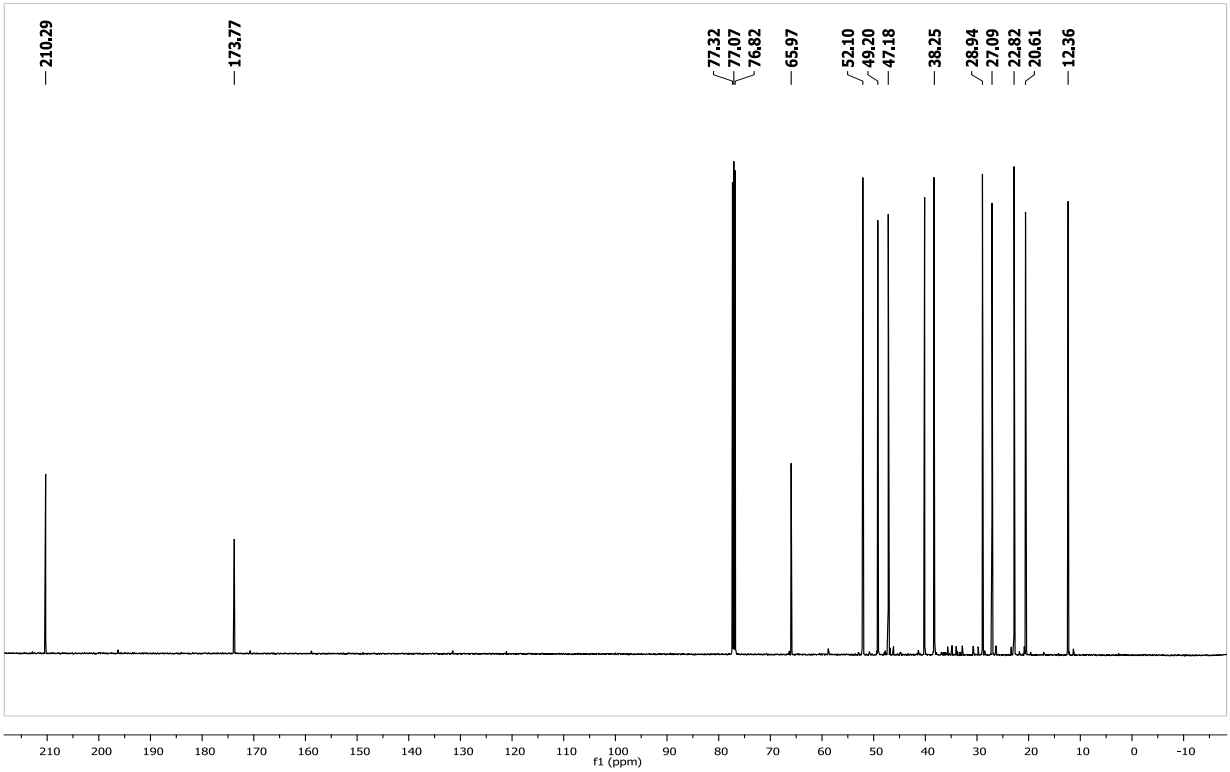
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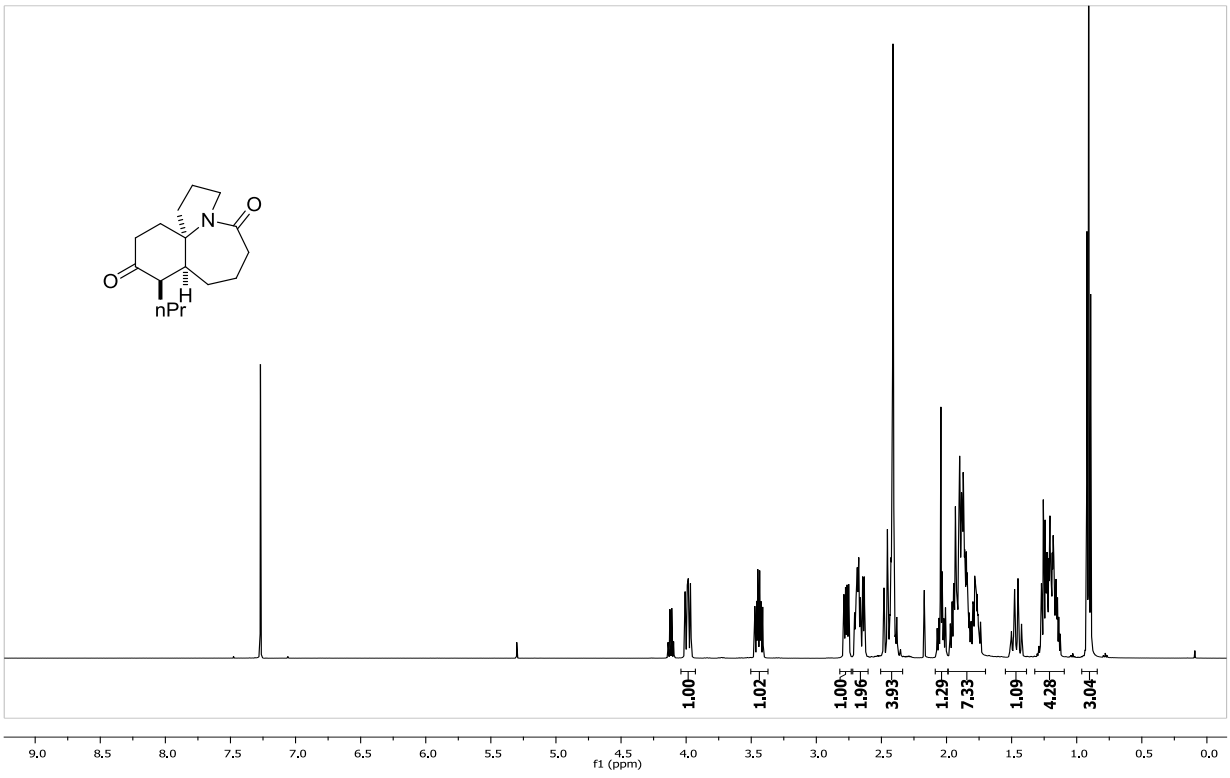
f1 (ppm)

3c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H
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
3.0
2.5
2.0
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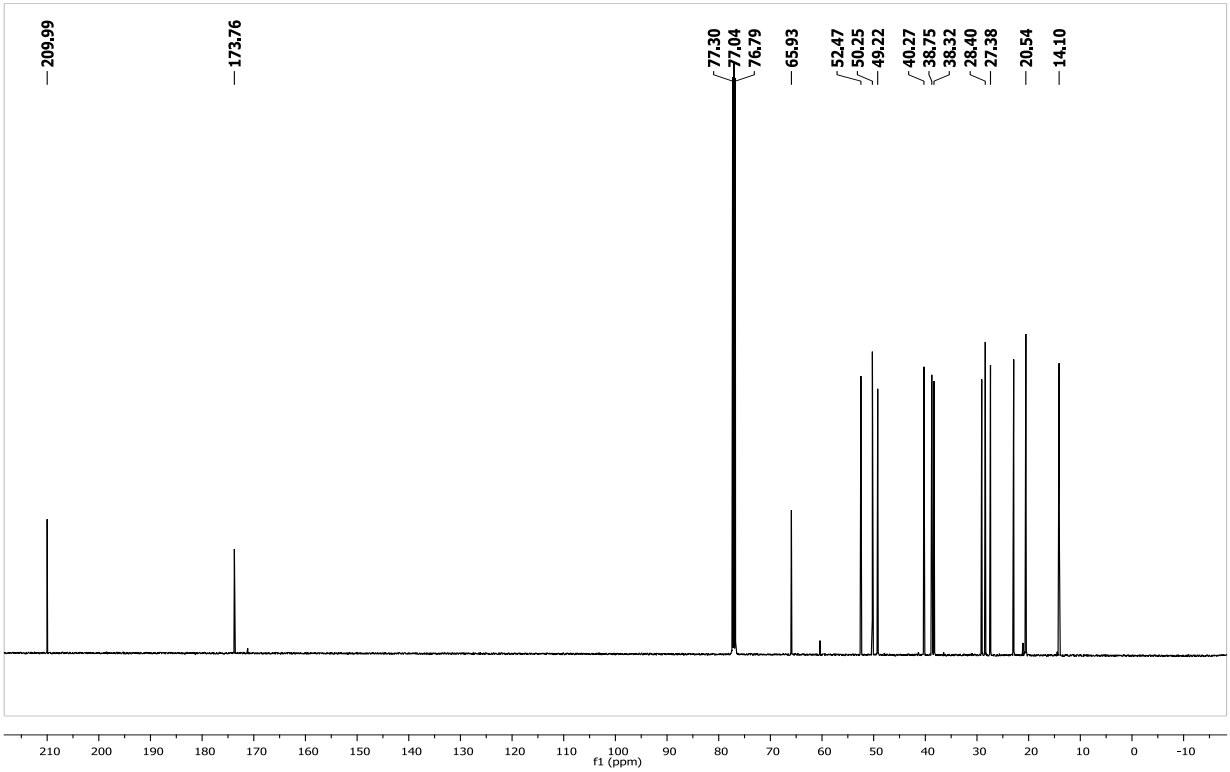
1.0
0.5
0.0
f1 (ppm)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65.93
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40.27
38.75
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20.54
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200
190
180
170
160
150
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90
80
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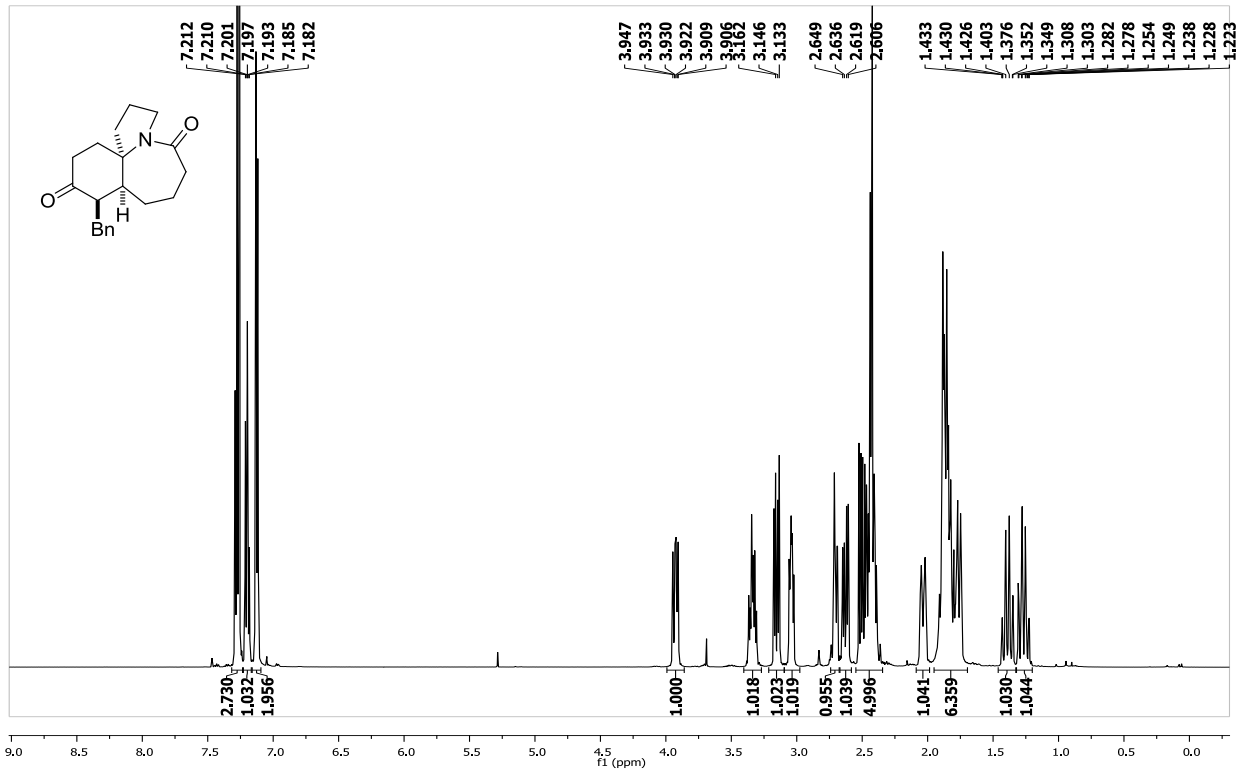
60
50
40
30
20
10
0
-10
f1 (ppm)

3d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0.955
1.039
4.996
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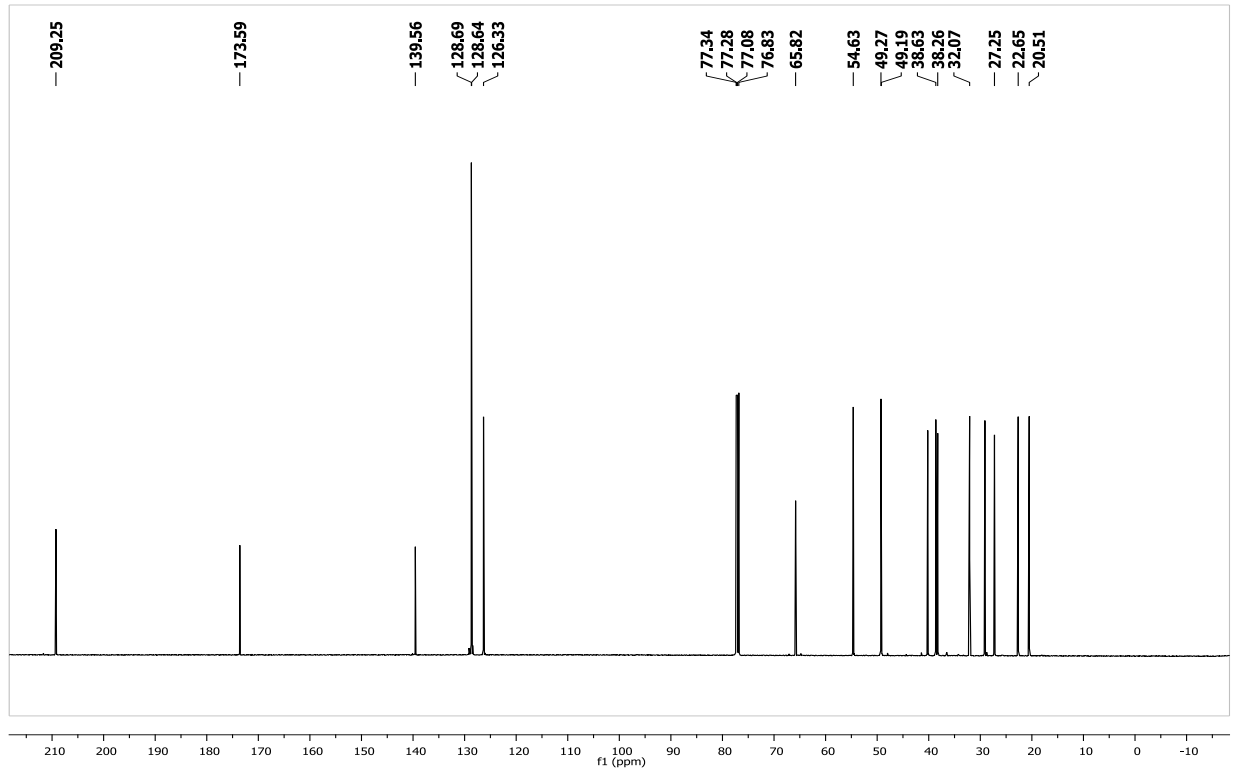
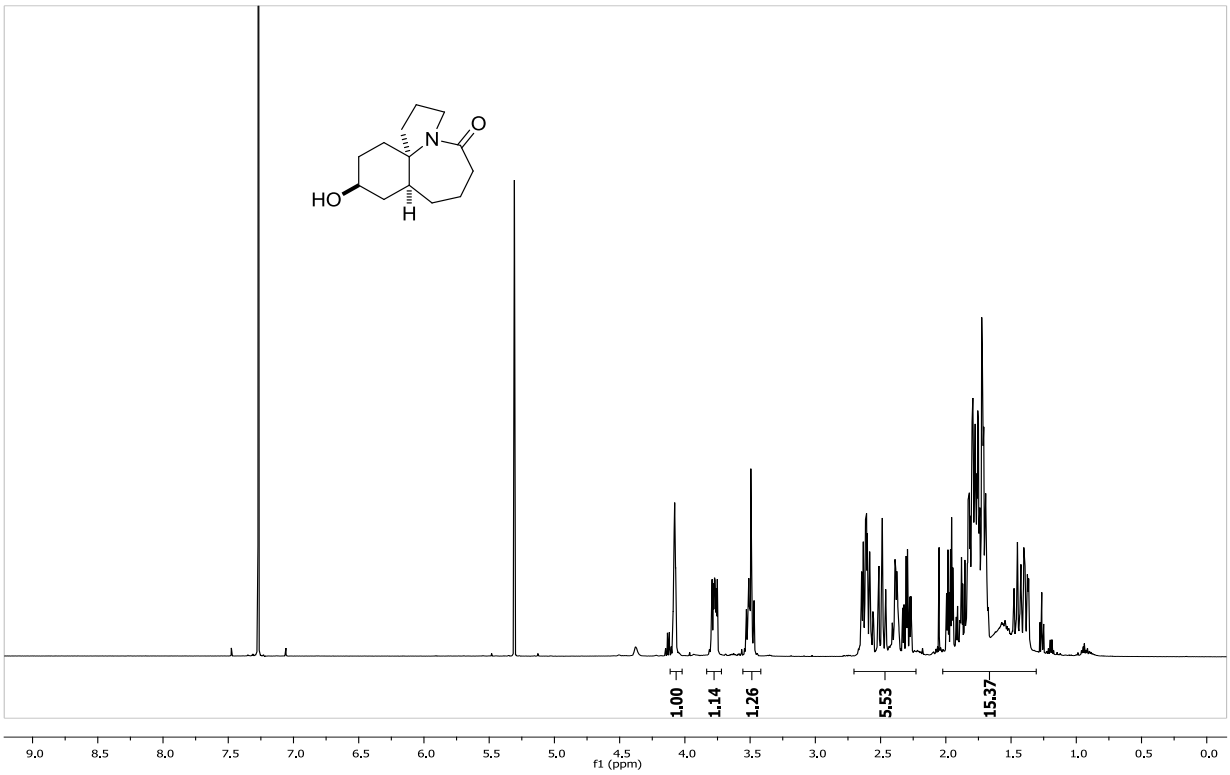
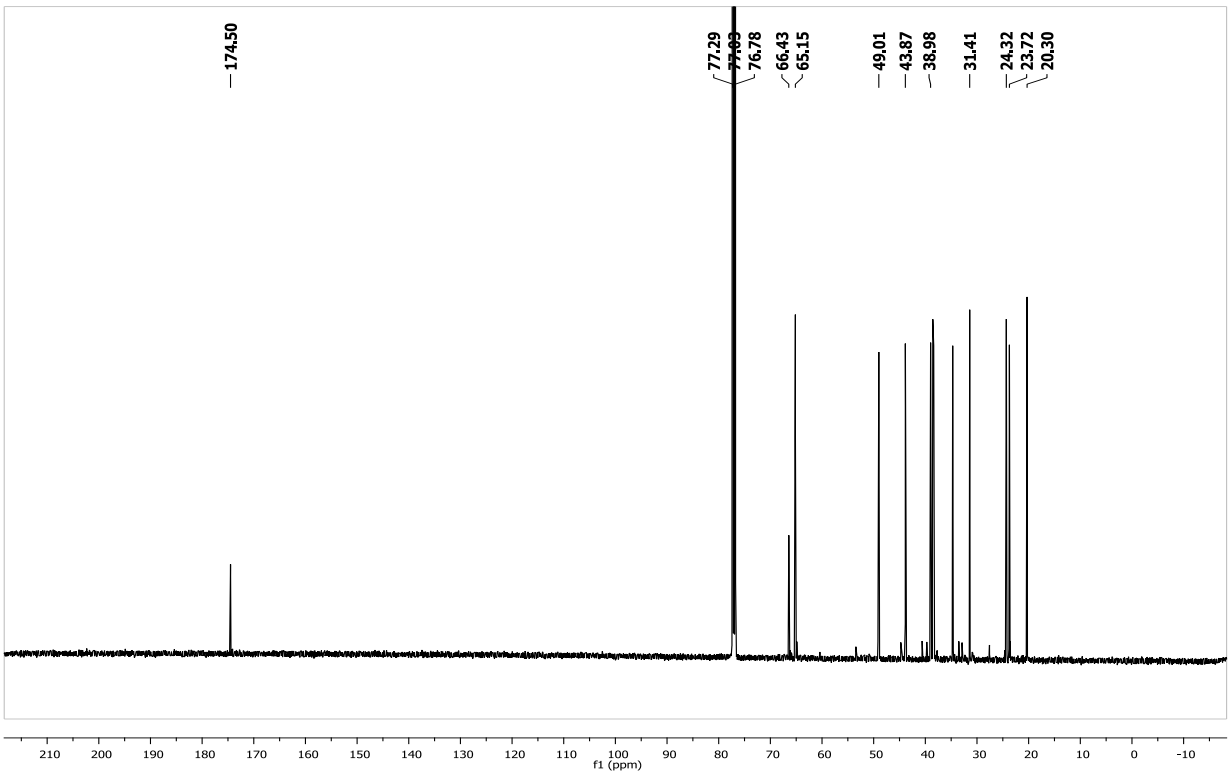
6.359
1.030
1.044
f1 (ppm)

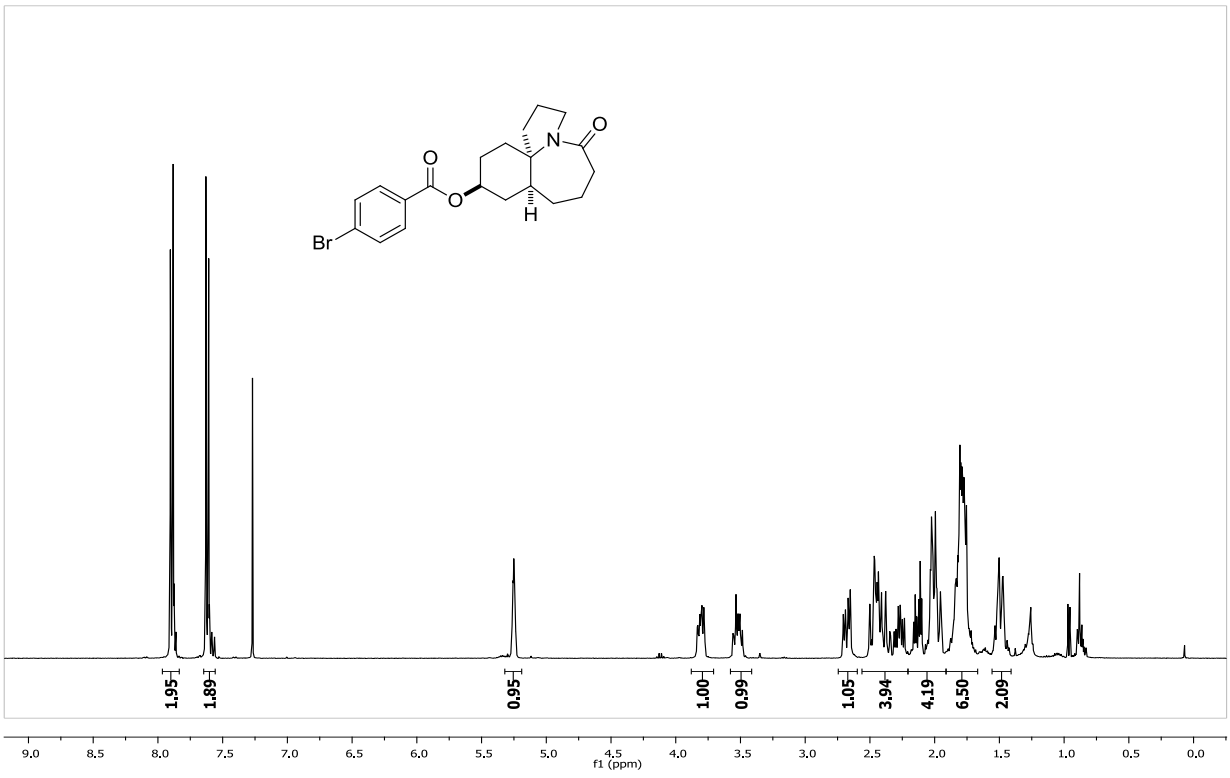

209.25
173.59
139.56
128.69
128.64
126.33
77.34
77.28
77.08
76.83
65.82
54.63
49.27
49.19
38.63
38.26
32.07
27.25
22.65
20.51
f1 (ppm)

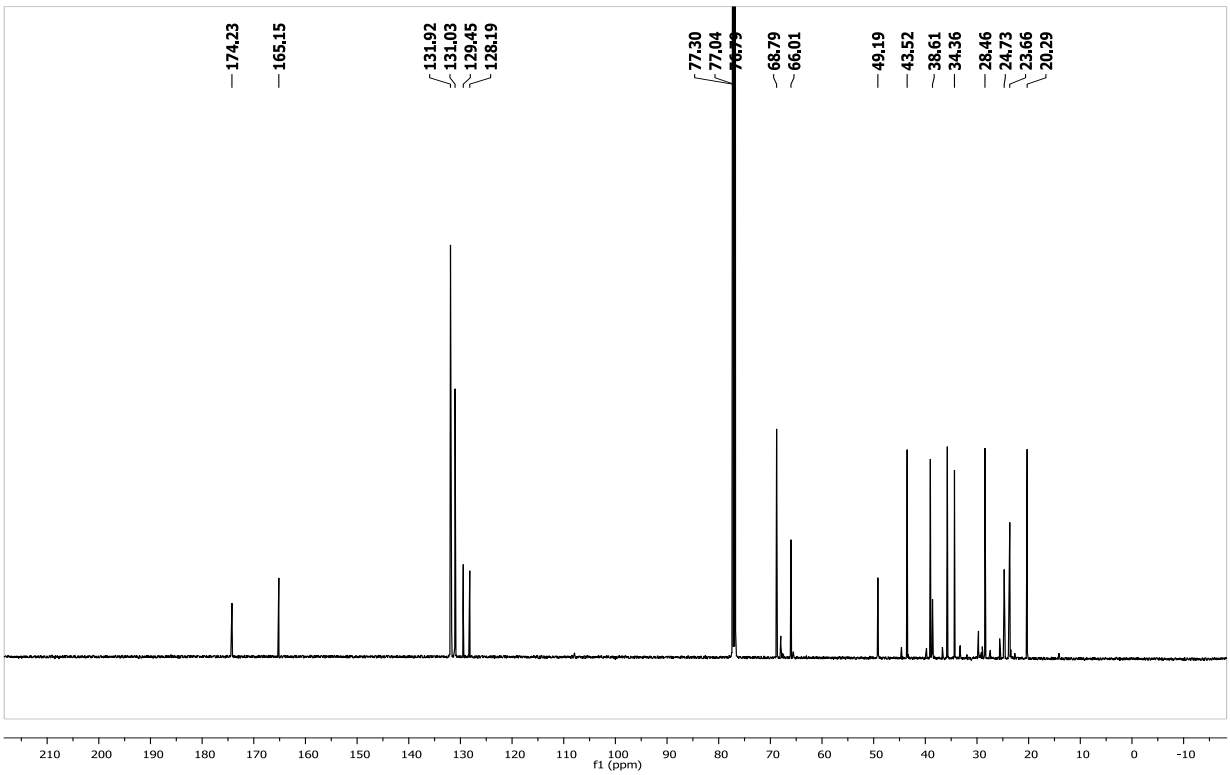
S3a


HO
N
O
H
1.00
1.14
1.26
5.53
15.37
f1 (ppm)

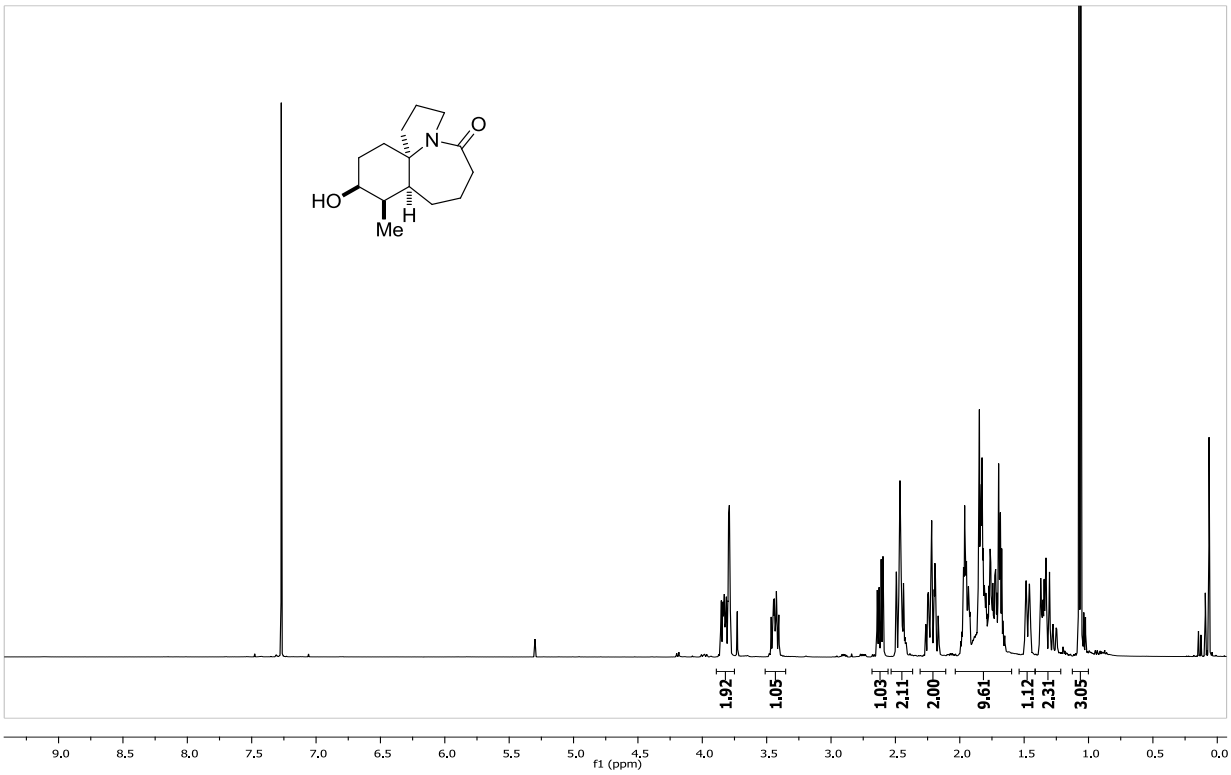

174.50
77.29
77.03
76.78
66.43
65.15
49.01
43.87
38.98
31.41
24.32
23.72
20.30
f1 (ppm)

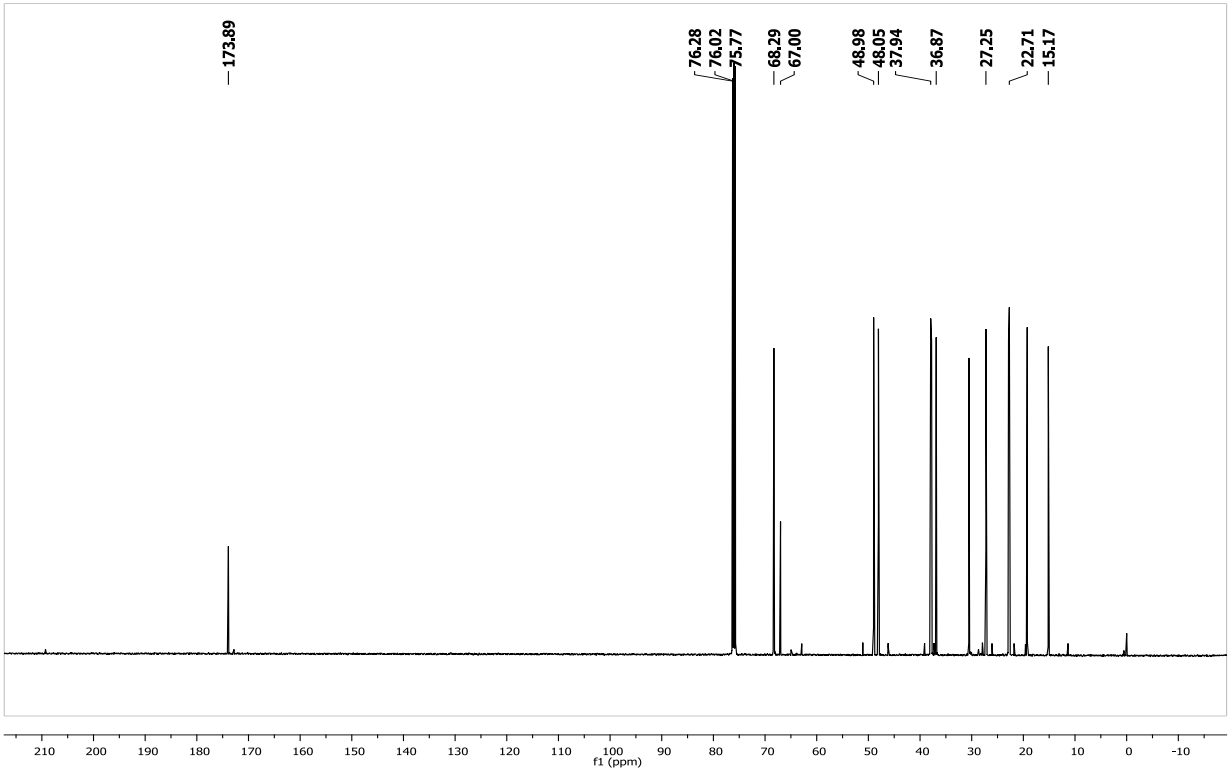
S6


Br
O
O
N
O
H
1.95
1.89
0.95
1.00
0.99
1.05
3.94
4.19
6.50
2.09
f1 (ppm)

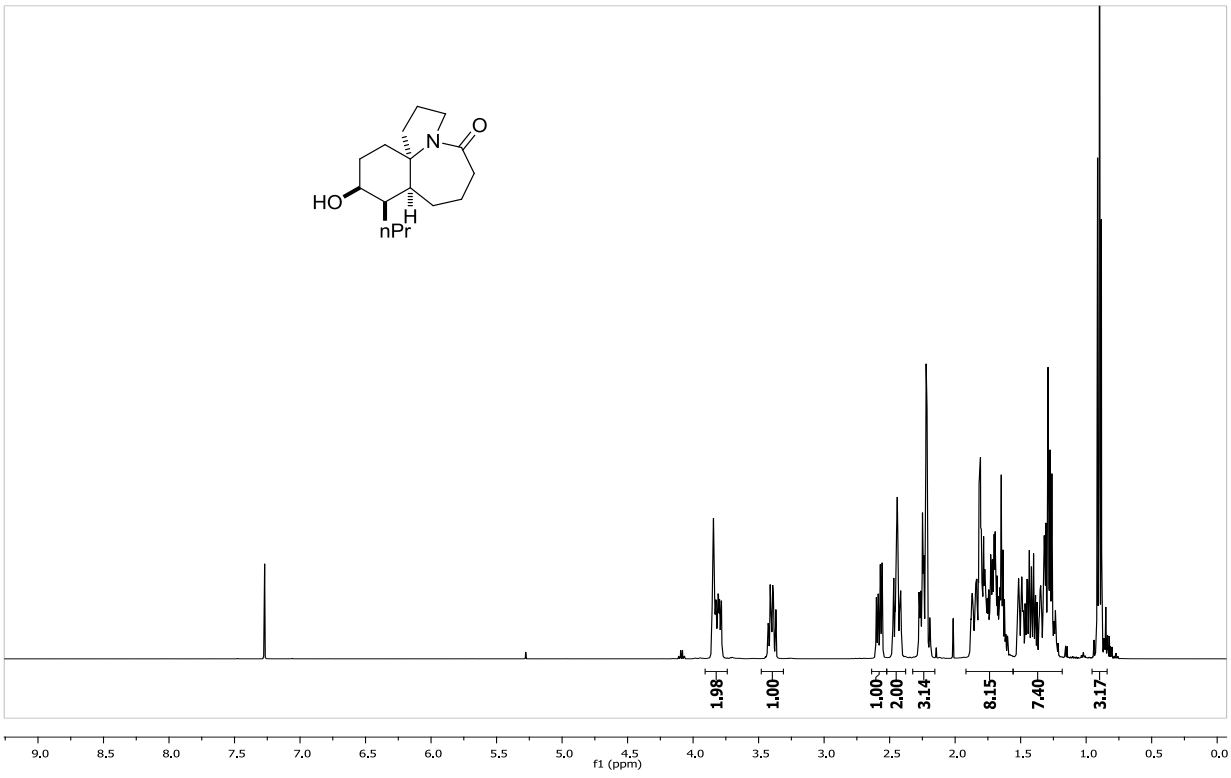

174.23
165.15
131.92
131.03
129.45
128.19
77.30
77.04
76.79
68.79
66.01
49.19
43.52
38.61
34.36
28.46
24.73
23.66
20.29
f1 (ppm)

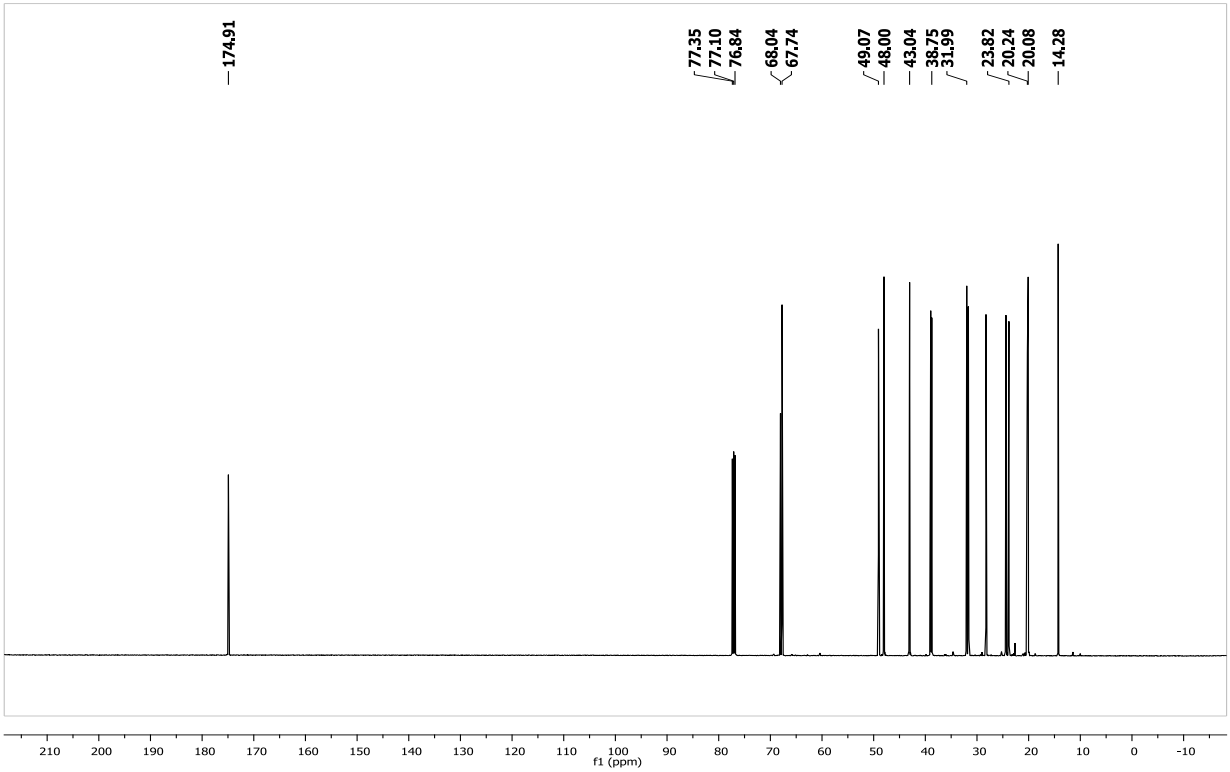
S3b


HO
Me
H
N
O
1.92
1.05
1.03
2.11
2.00
9.61
1.12
2.31
3.05
f1 (ppm)

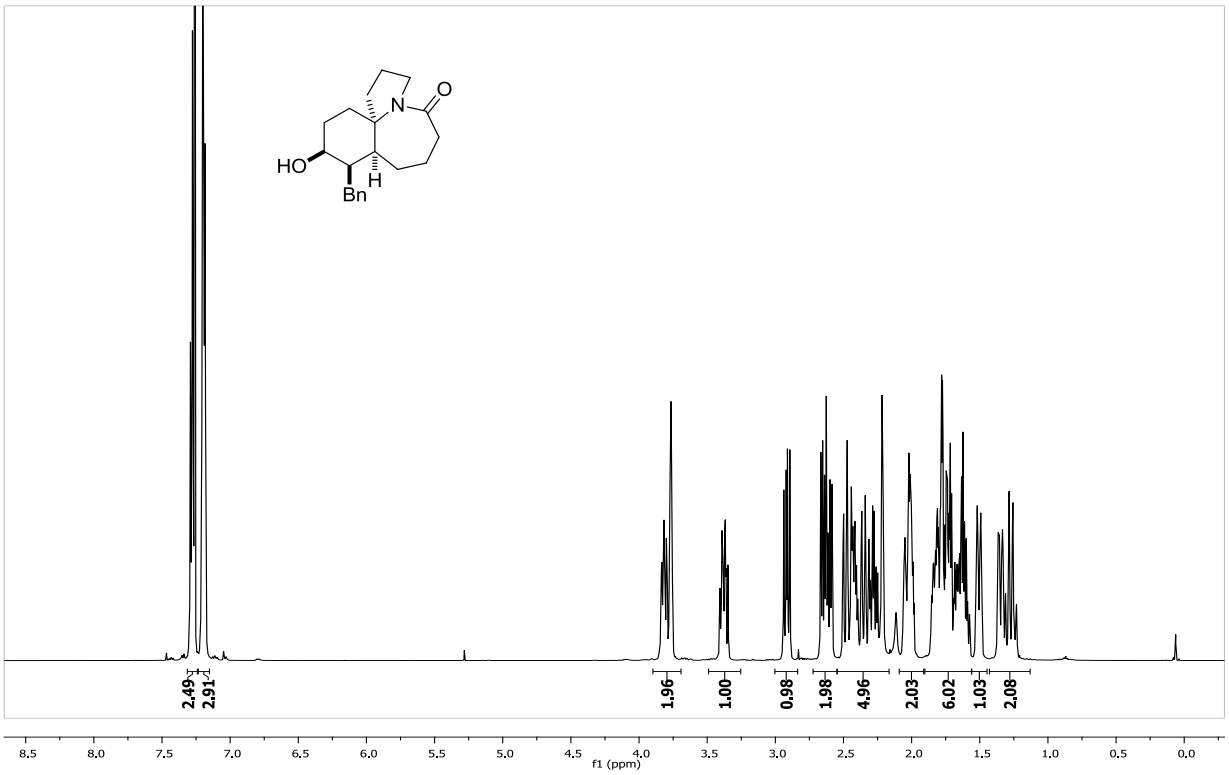

173.89
76.28
76.02
75.77
68.29
67.00
48.98
48.05
37.94
36.87
27.25
22.71
15.17
f1 (ppm)

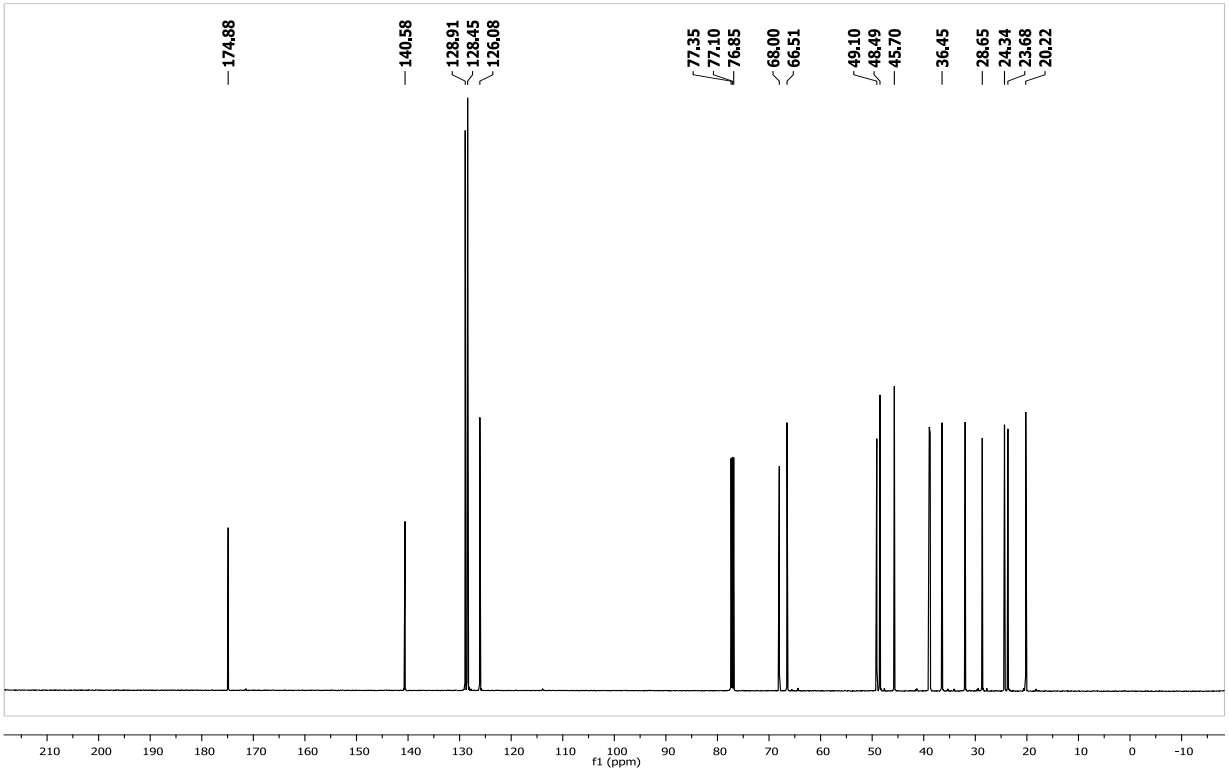
S3c


HO
nPr
H
N
O
1.98
1.00
1.00
2.00
3.14
8.15
7.40
3.17
f1 (ppm)

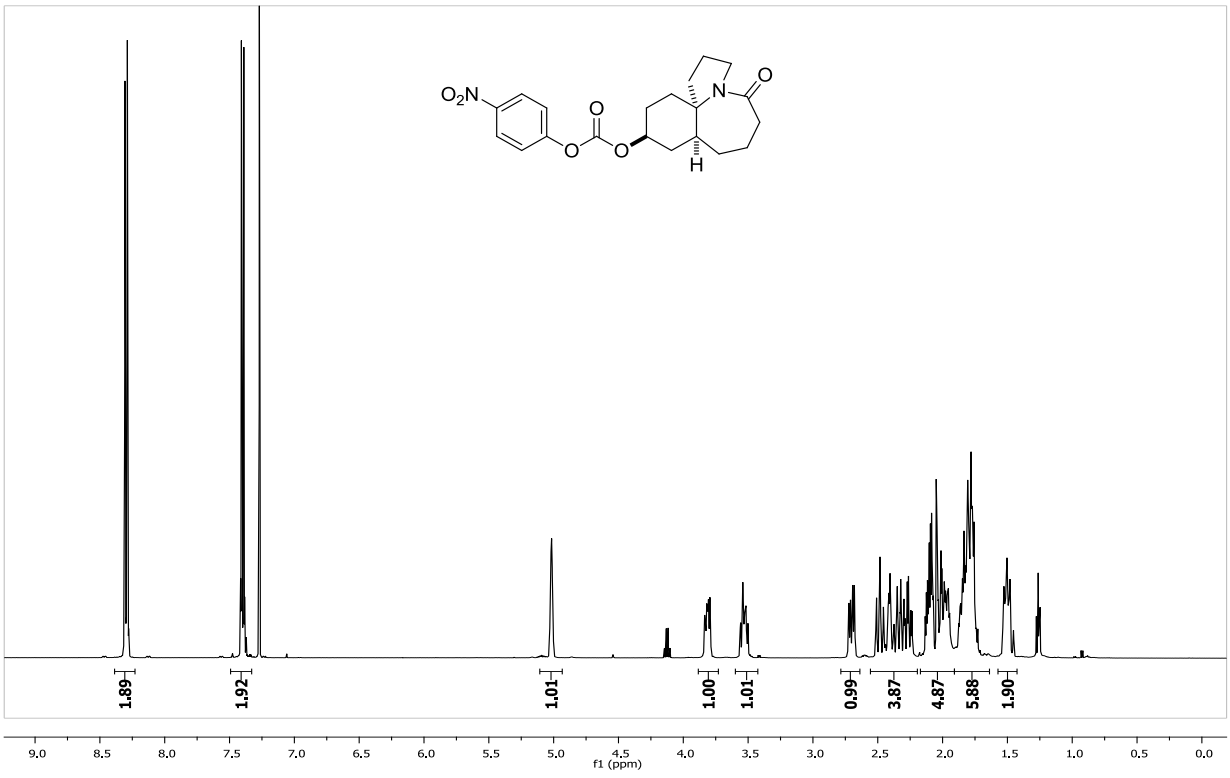

174.91
77.35
77.10
76.84
68.04
67.74
49.07
48.00
43.04
38.75
31.99
23.82
20.24
20.08
14.28
f1 (ppm)

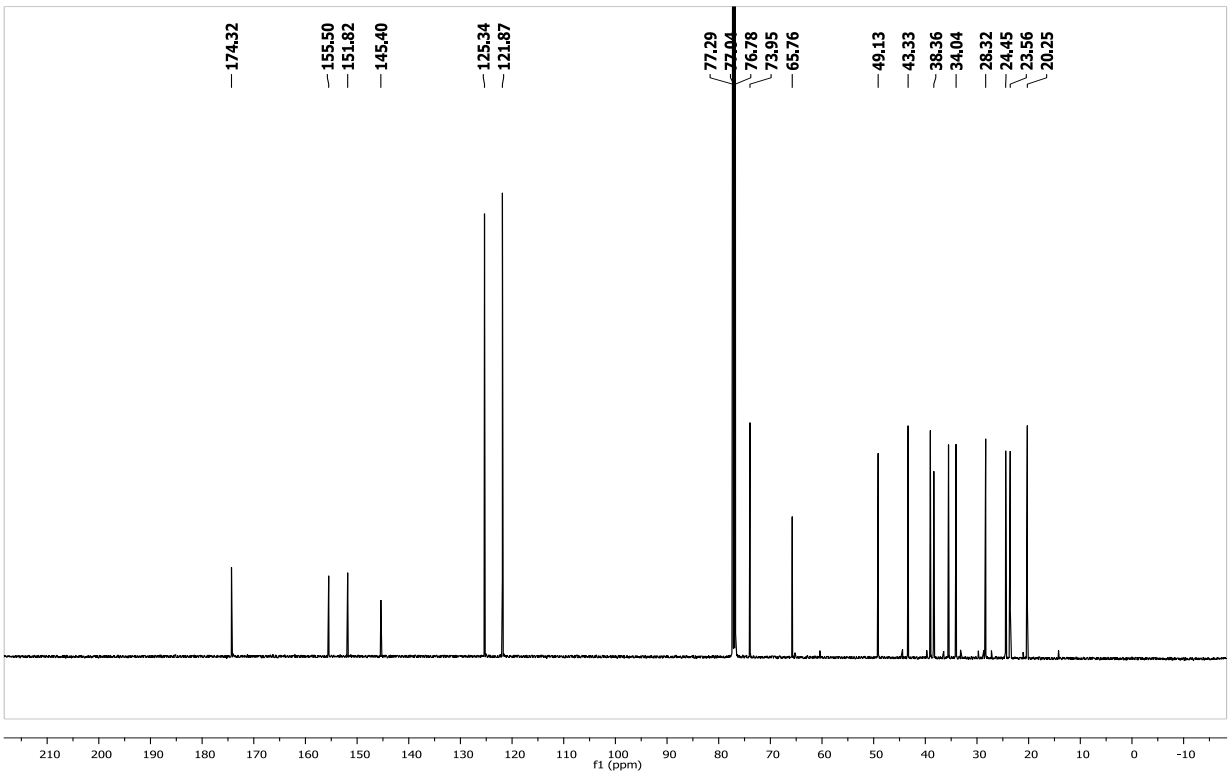
S3d


HO
N
O
H
Bn
2.49
2.91
1.96
1.00
0.98
1.98
4.96
2.03
6.02
1.03
2.08
f1 (ppm)

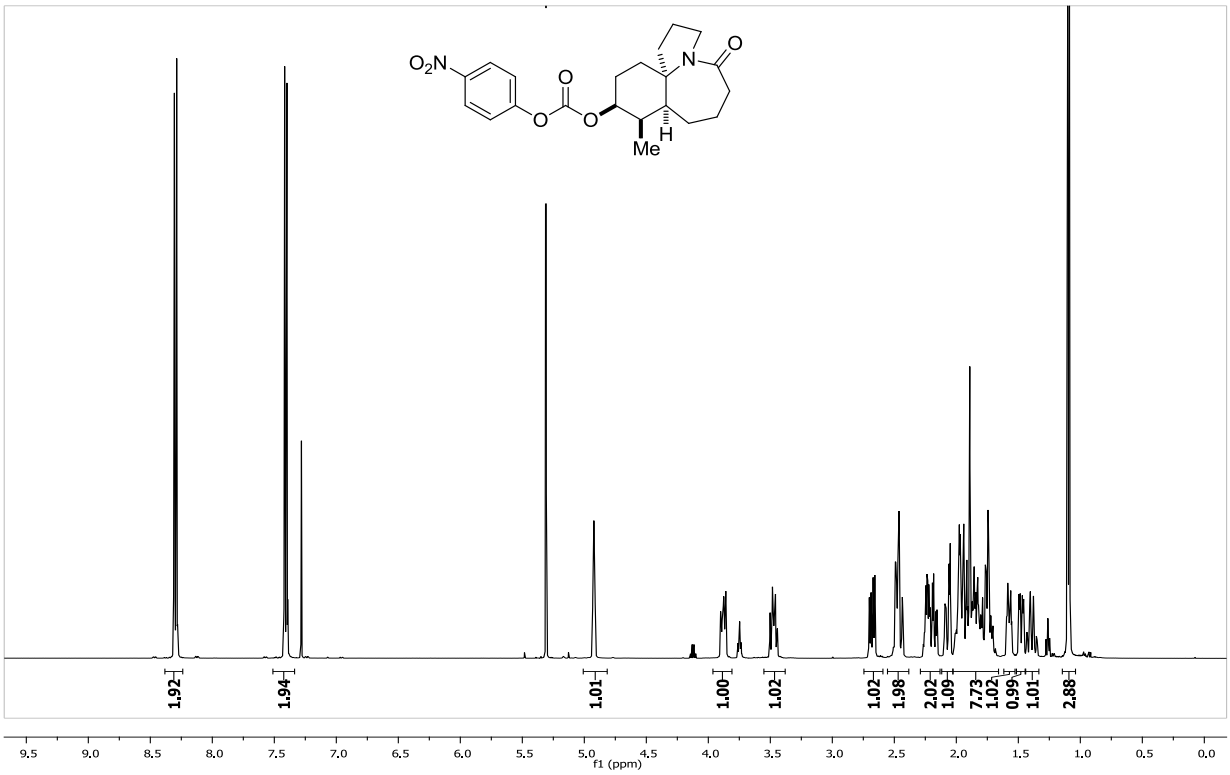

174.88
140.58
128.91
128.45
126.08
77.35
77.10
76.85
68.00
66.51
49.10
48.49
45.70
36.45
28.65
24.34
23.68
20.22
f1 (ppm)

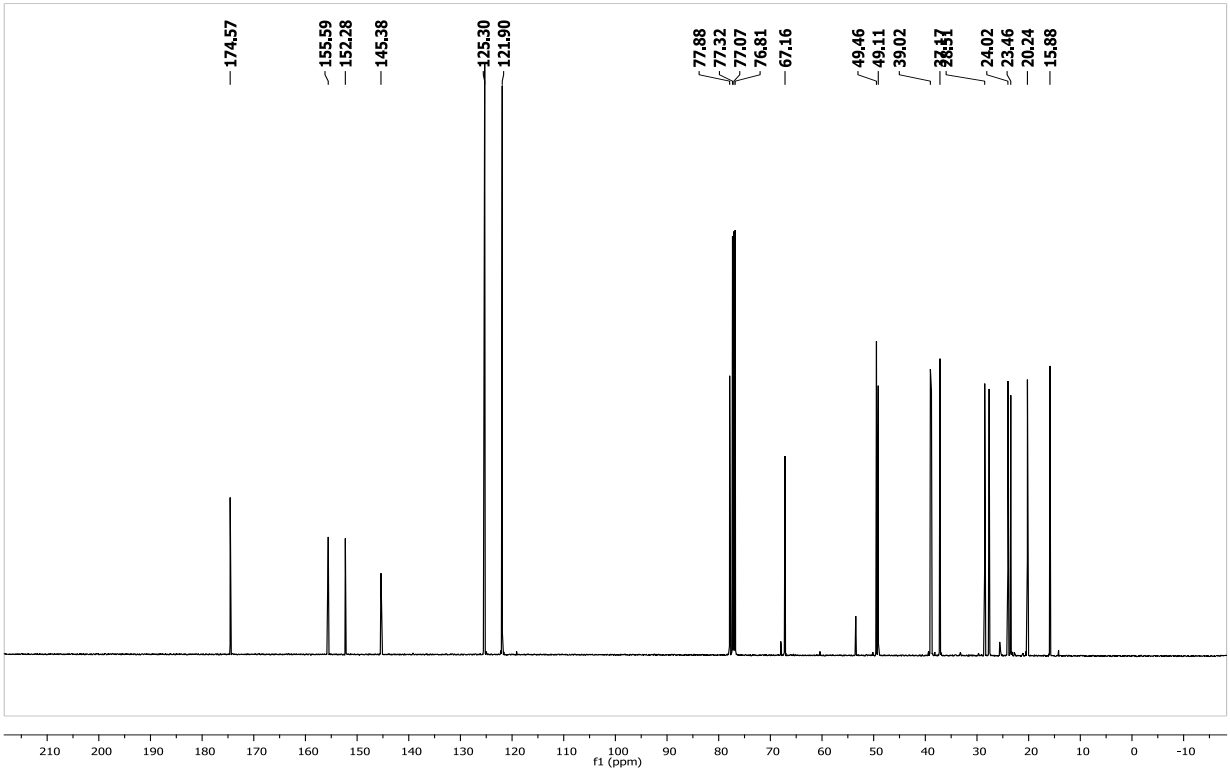
S4a


O2N
O
O
O
N
O
H
1.89
1.92
1.01
1.00
1.01
0.99
3.87
4.87
5.88
1.90
f1 (ppm)

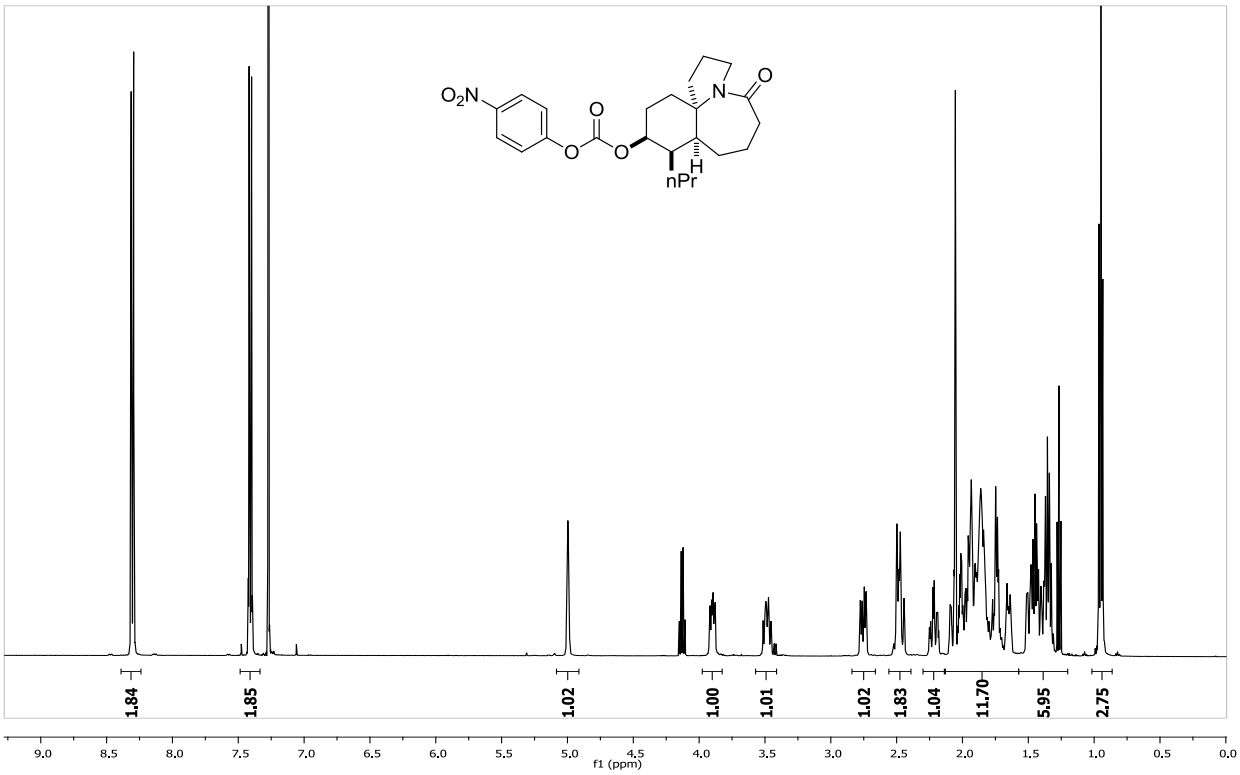

174.32
155.50
151.82
145.40
125.34
121.87
77.29
77.04
76.78
73.95
65.76
49.13
43.33
38.36
34.04
28.32
24.45
23.56
20.25
f1 (ppm)

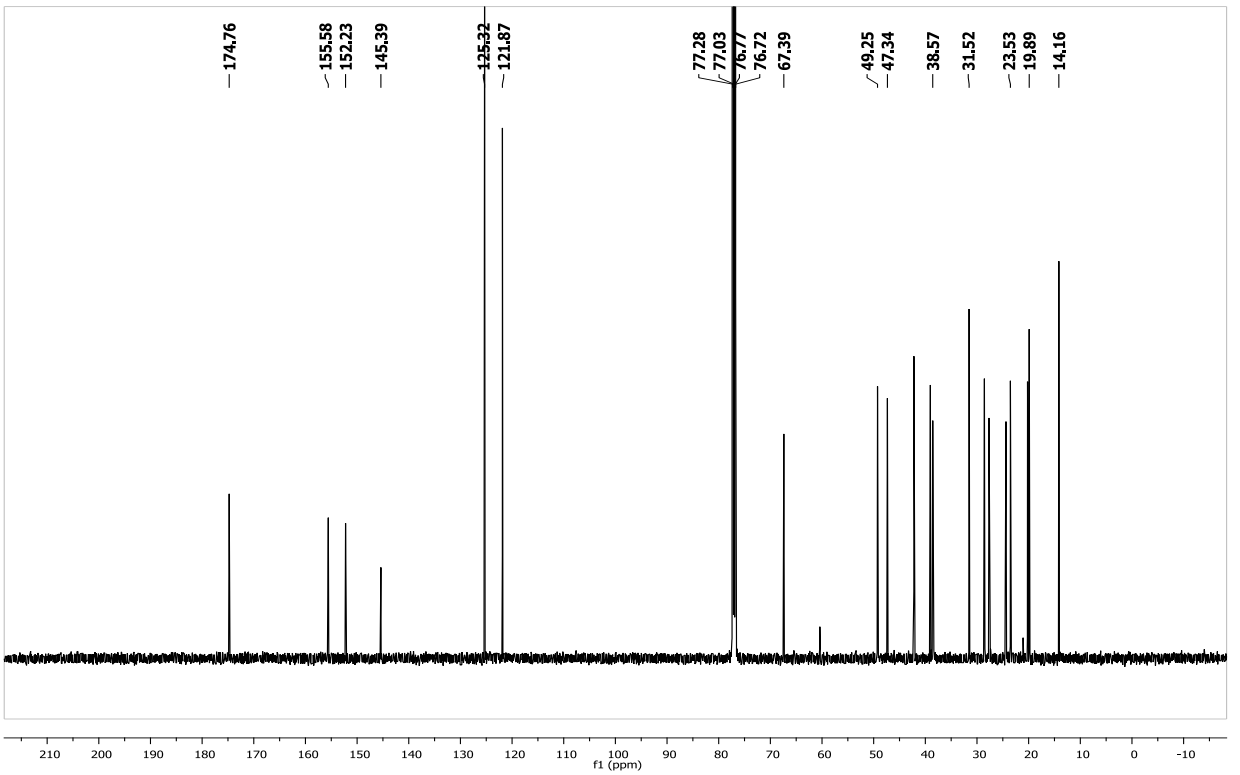
S4b


O2N
O
O
O
N
O
H
Me
1.92
1.94
1.01
1.00
1.02
1.02
1.98
2.02
1.09
7.73
1.02
0.99
1.01
2.88
f1 (ppm)

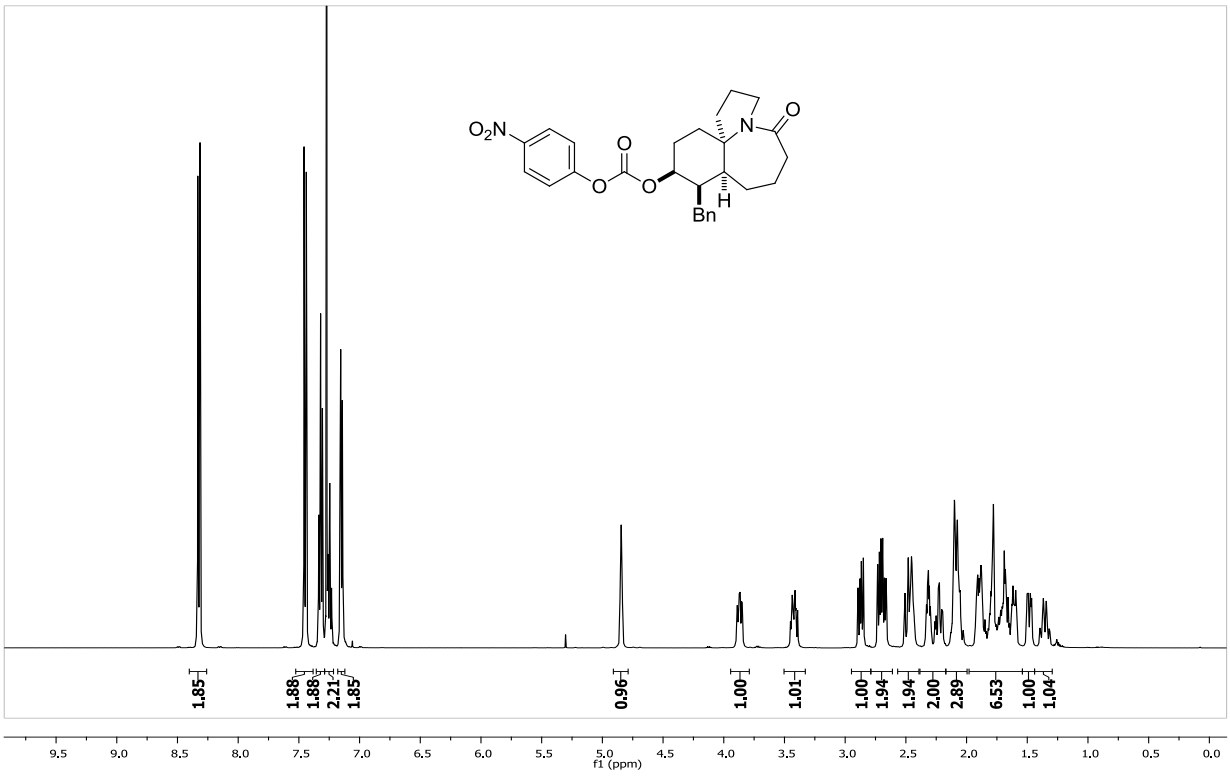

174.57
155.59
152.28
145.38
125.30
121.90
77.88
77.32
77.07
76.81
67.16
49.46
49.11
39.02
24.02
23.46
20.24
15.88
f1 (ppm)

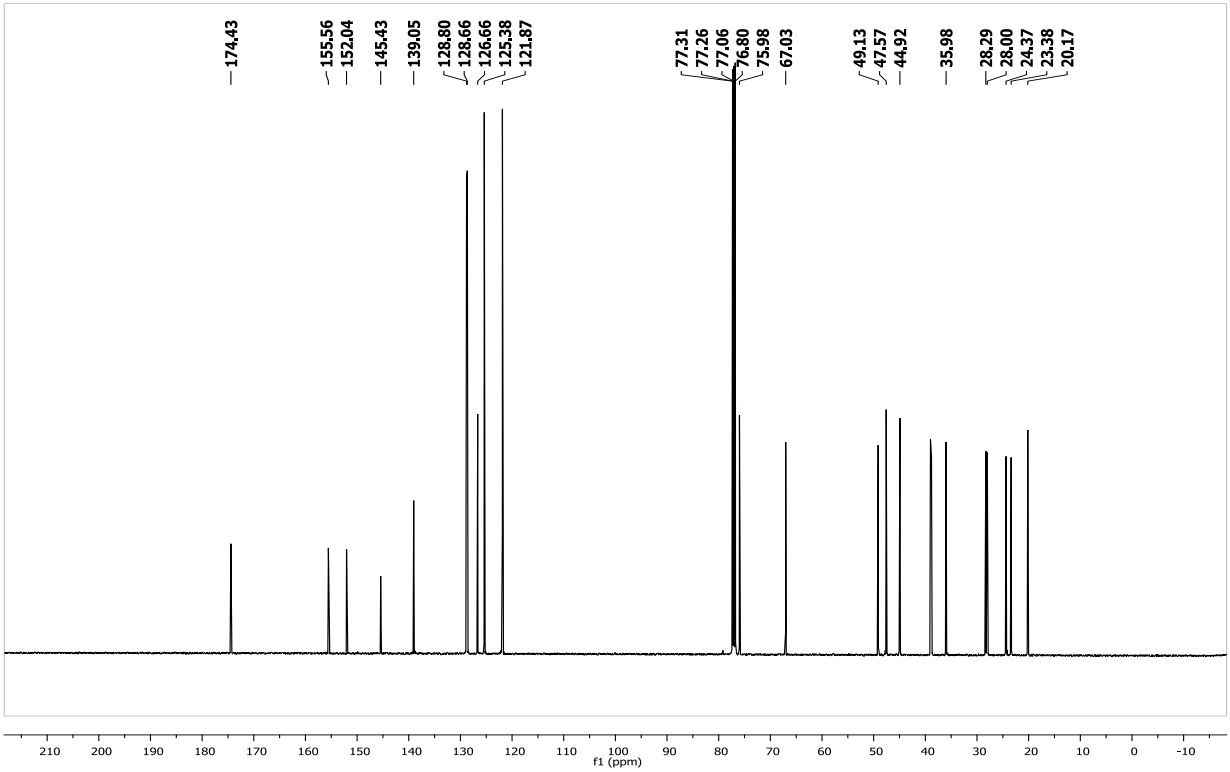
S4c


O2N
O
O
O
N
O
H
nPr
1.84
1.85
1.02
1.00
1.01
1.02
1.83
1.04
11.70
5.95
2.75
f1 (ppm)

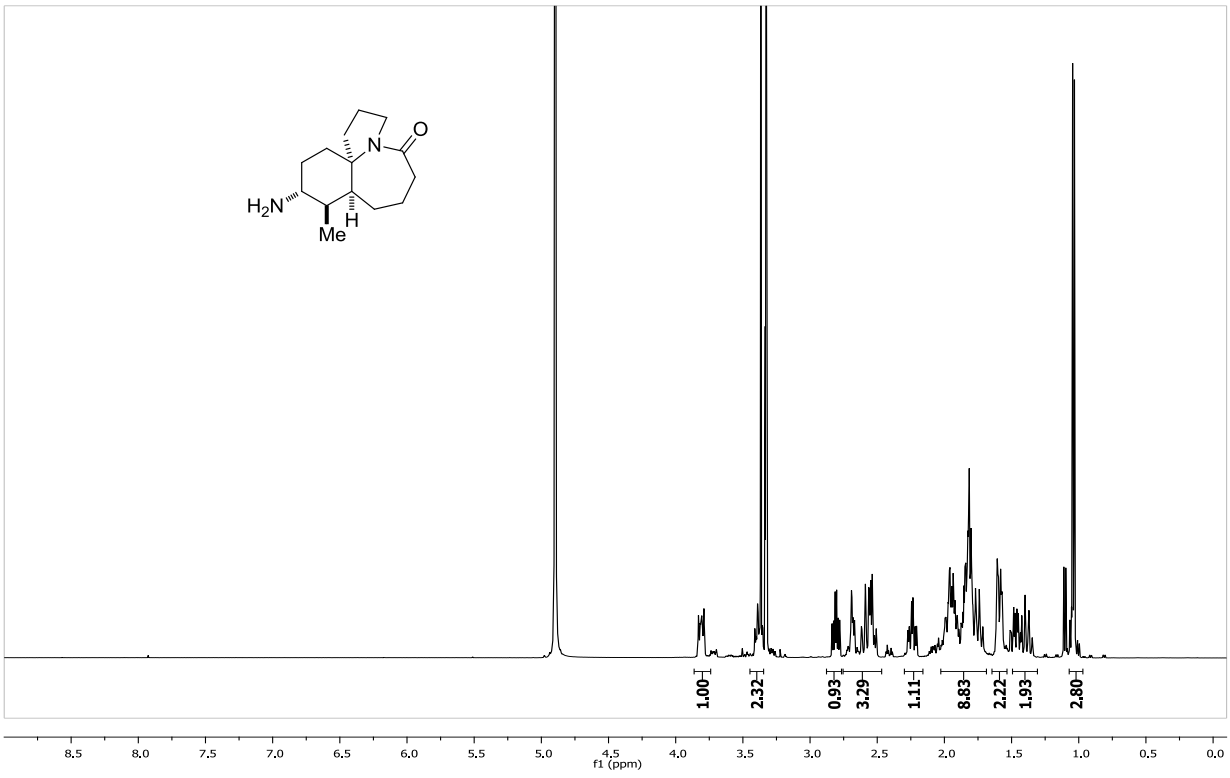

174.76
155.58
152.23
145.39
125.32
121.87
77.28
77.03
76.77
76.72
67.39
49.25
47.34
38.57
31.52
23.53
19.89
14.16
f1 (ppm)

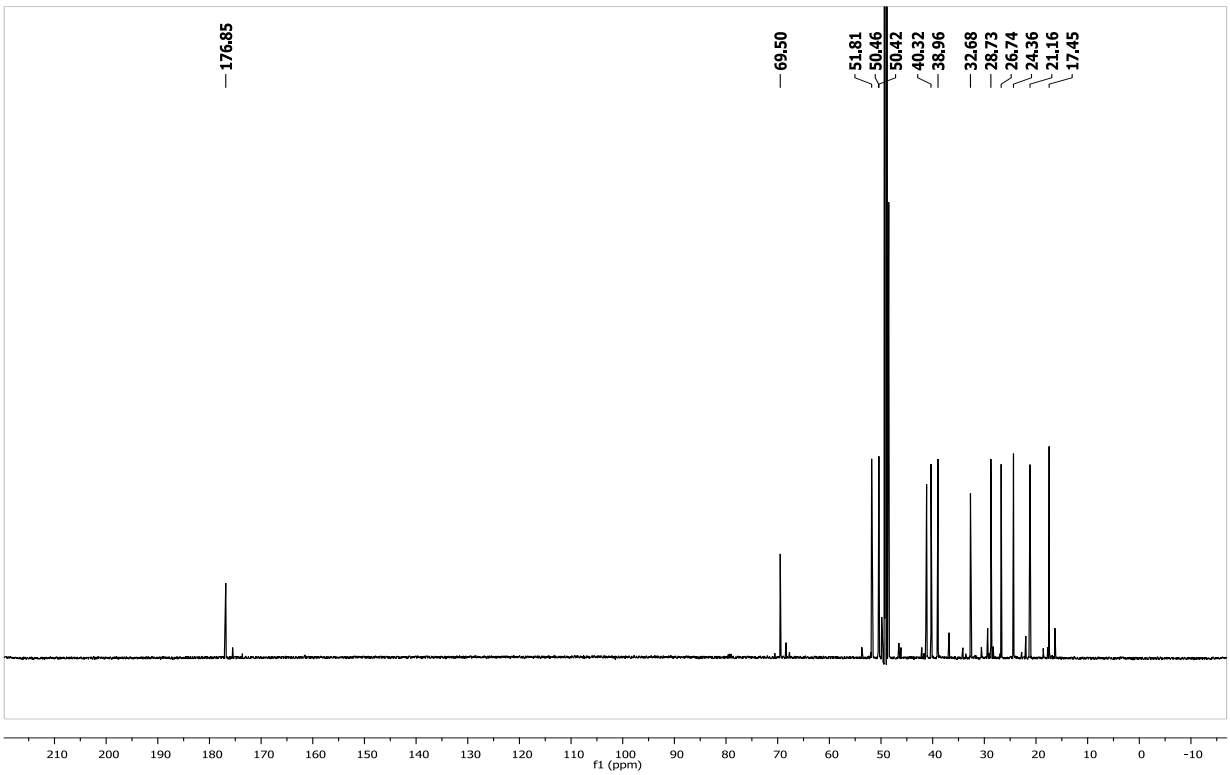
S4d


O2N
O
O
O
N
O
H
Bn
1.85
1.88
1.88
2.21
1.85
0.96
1.00
1.01
1.00
1.94
1.94
2.00
2.89
6.53
1.00
1.04
f1 (ppm)

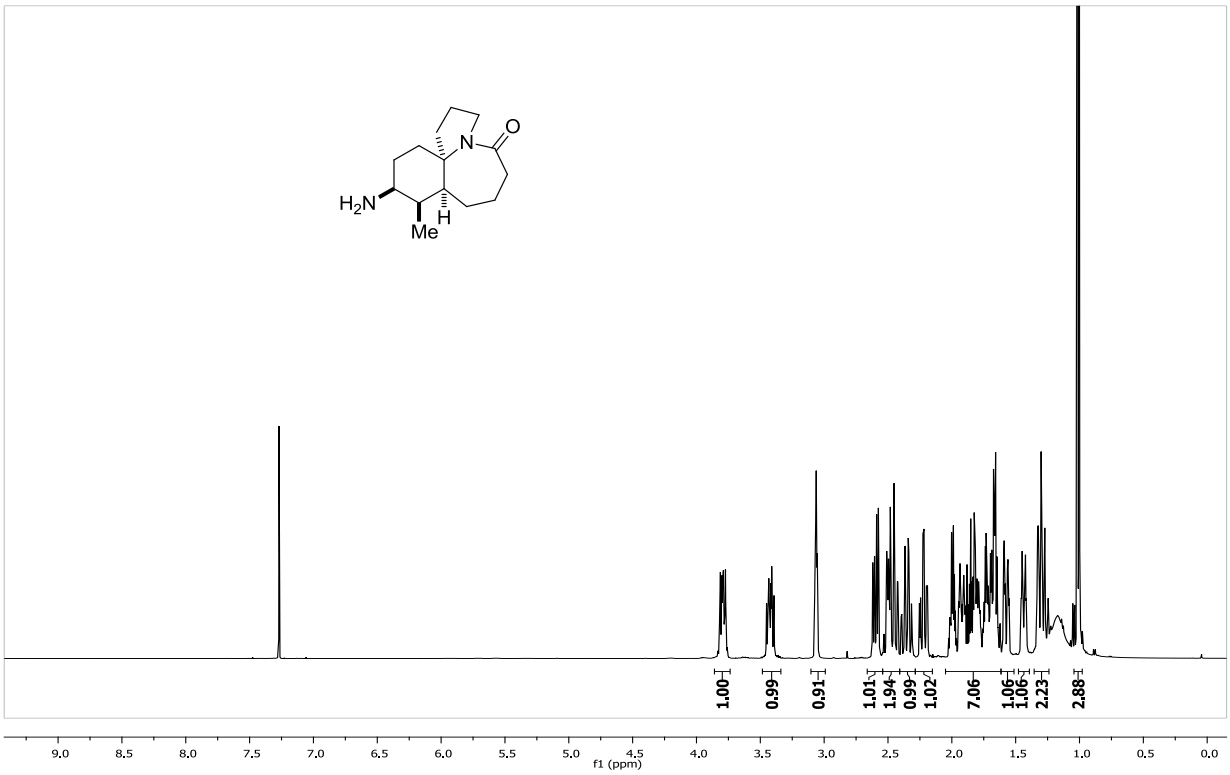

174.43
155.56
152.04
145.43
139.05
128.80
128.66
126.66
125.38
121.87
77.31
77.26
77.06
76.80
75.98
67.03
49.13
47.57
44.92
35.98
28.29
28.00
24.37
23.38
20.17
f1 (ppm)

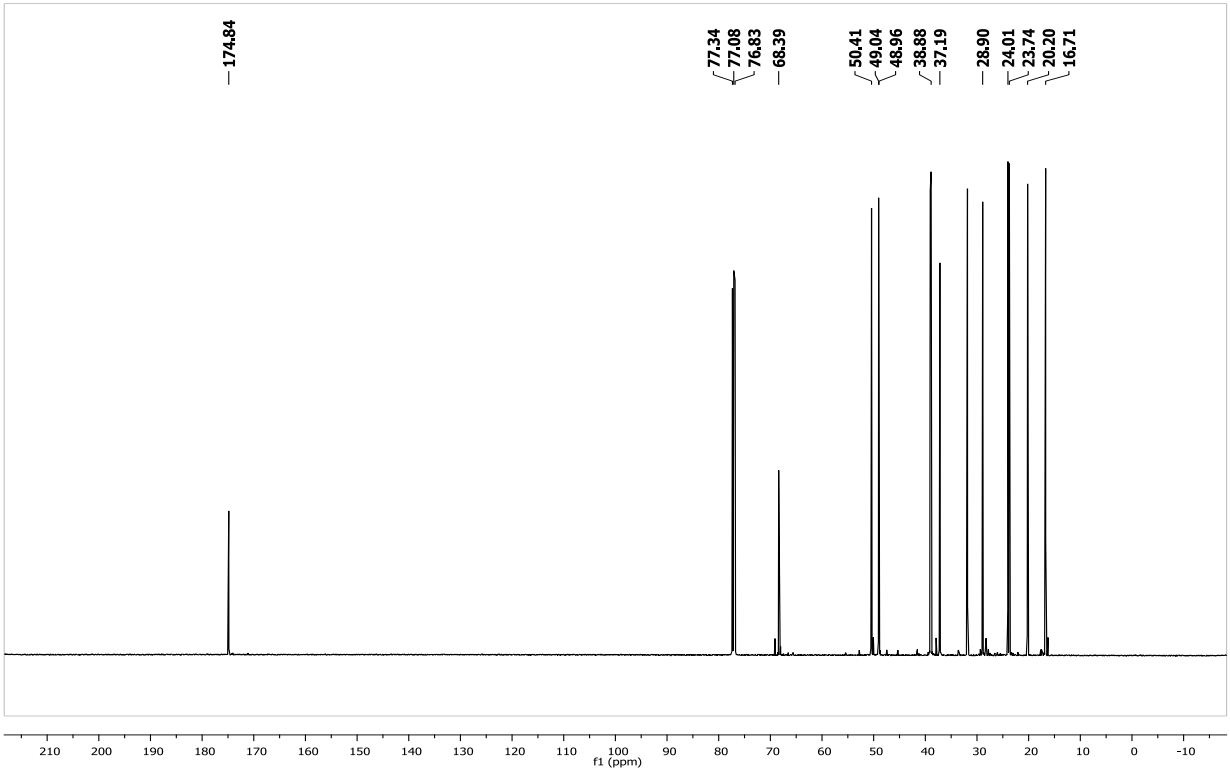
S5b


O
N
H2N
H
Me
1.00
2.32
0.93
3.29
1.11
8.83
2.22
1.93
2.80
f1 (ppm)

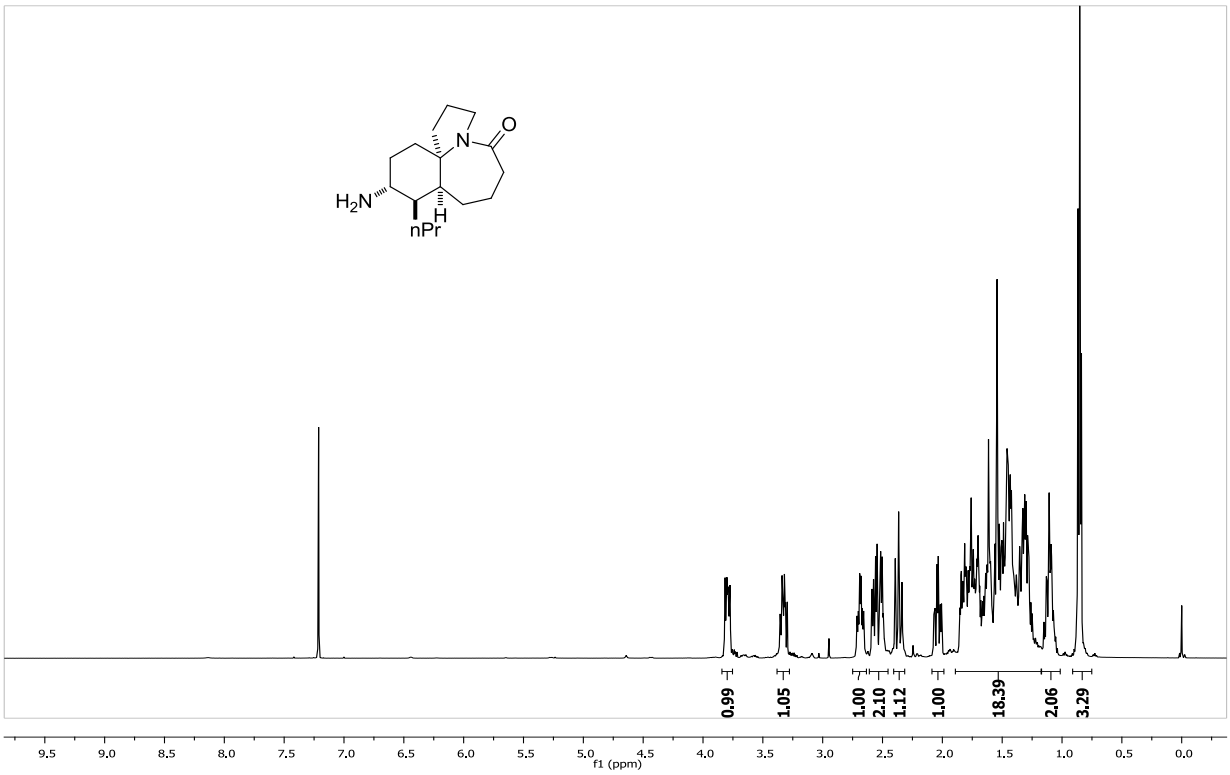

176.85
69.50
51.81
50.46
50.42
40.32
38.96
32.68
28.73
26.74
24.36
21.16
17.45
f1 (ppm)

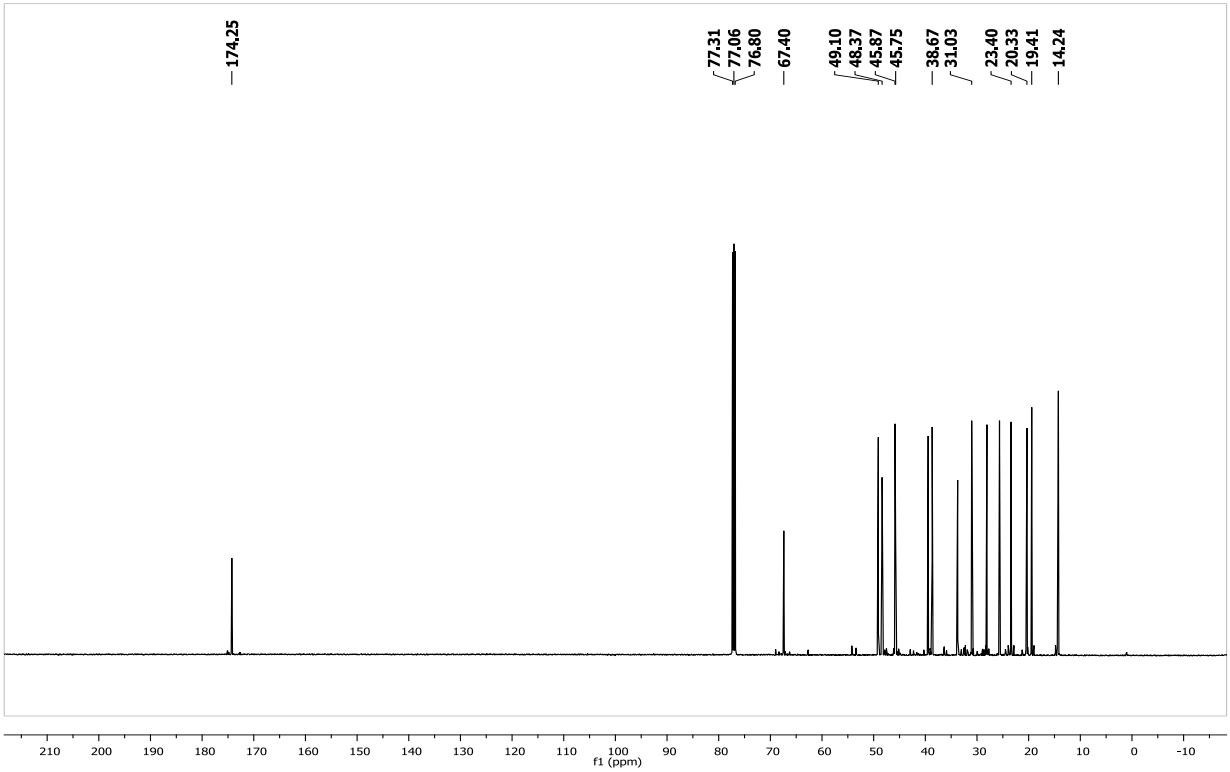
4b


O
N
H2N
H
Me
1.00
0.99
0.91
1.01
1.94
0.99
1.02
7.06
1.06
1.06
2.23
2.88
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

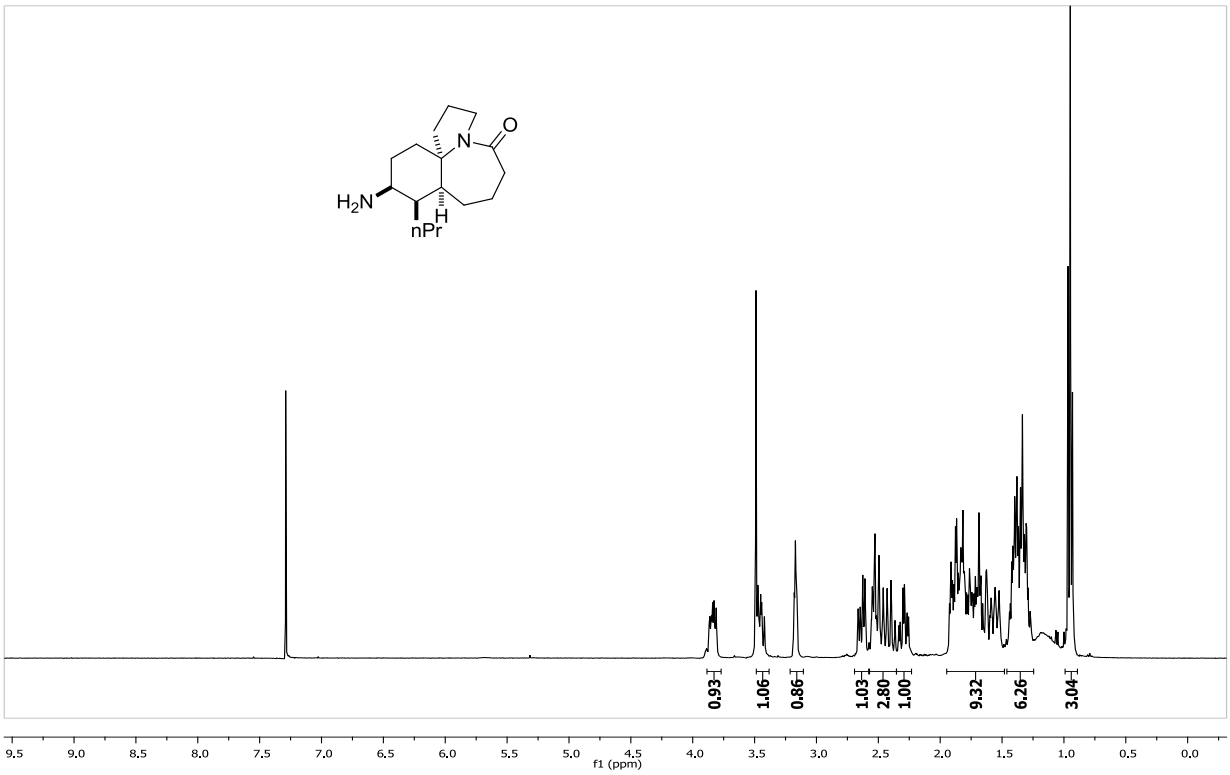

174.84
77.34
77.08
76.83
68.39
50.41
49.04
48.96
38.88
37.19
28.90
24.01
23.74
20.20
16.71
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

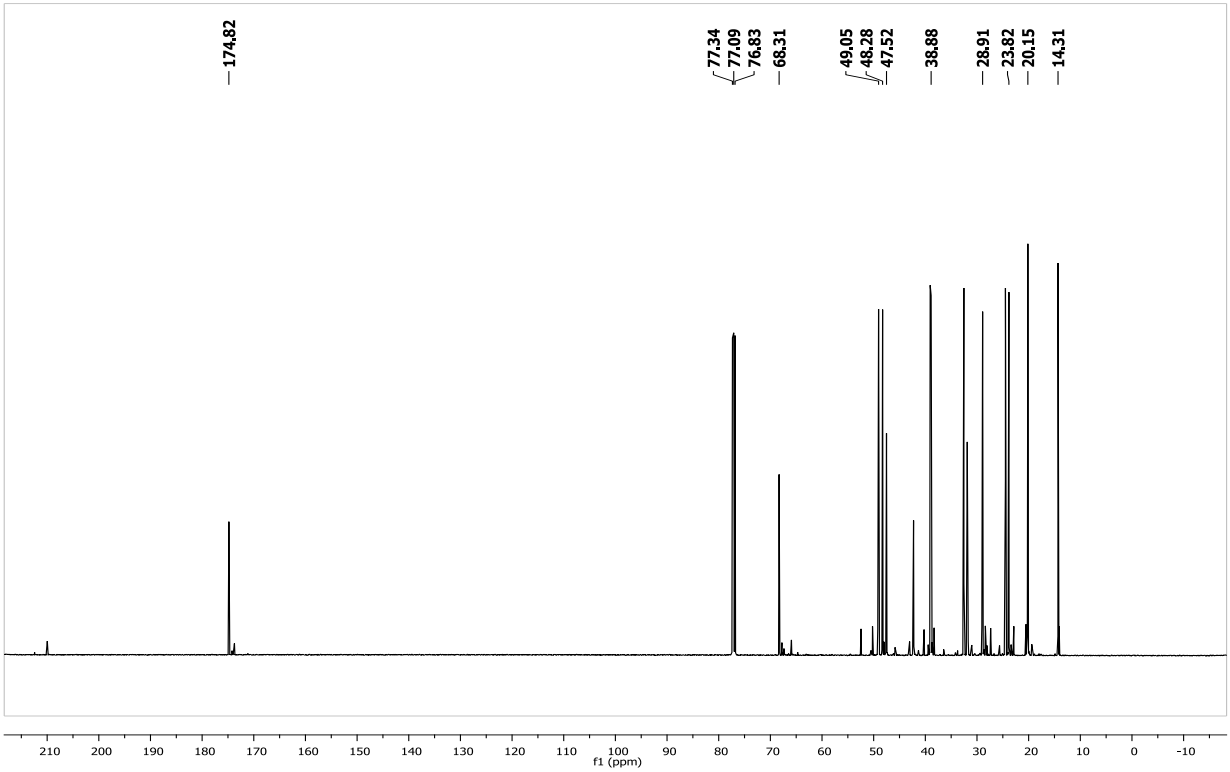
S5c


O
N
H2N
H
nPr
0.99
1.05
1.00
2.10
1.12
1.00
18.39
2.06
3.29
f1 (ppm)

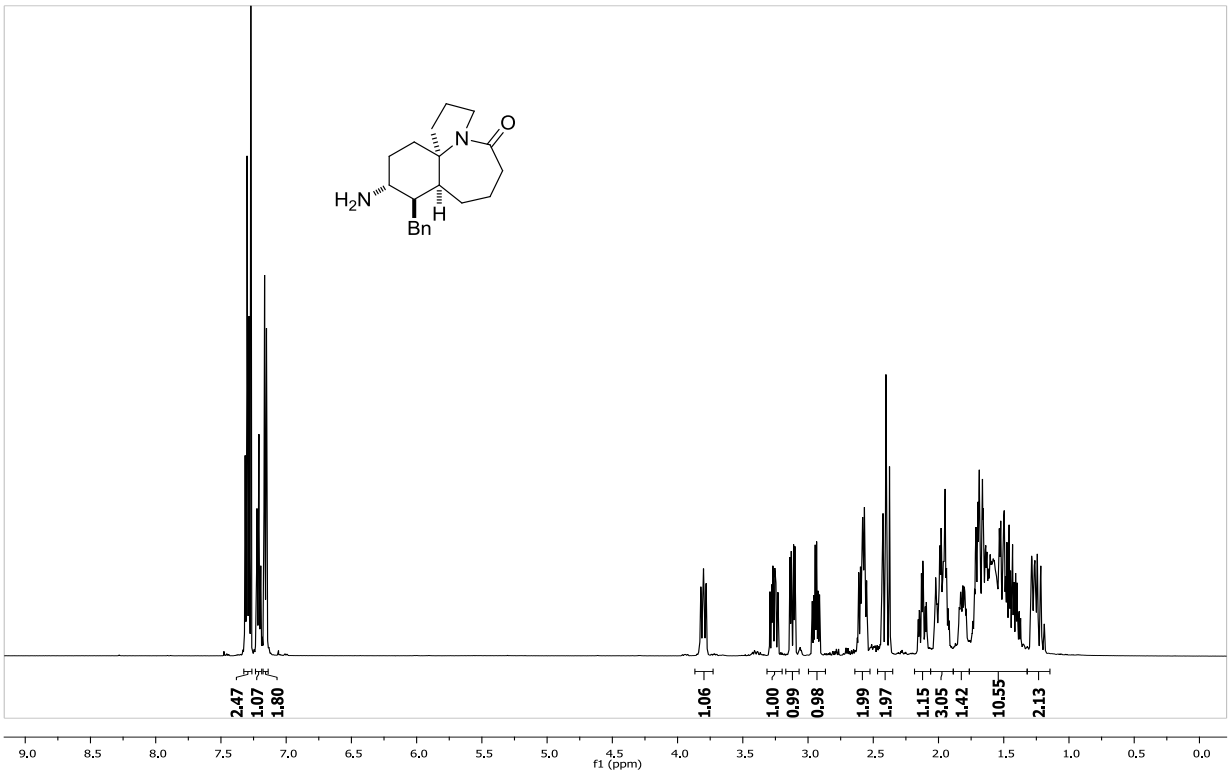

174.25
77.31
77.06
76.80
67.40
49.10
48.37
45.87
45.75
38.67
31.03
23.40
20.33
19.41
14.24
f1 (ppm)

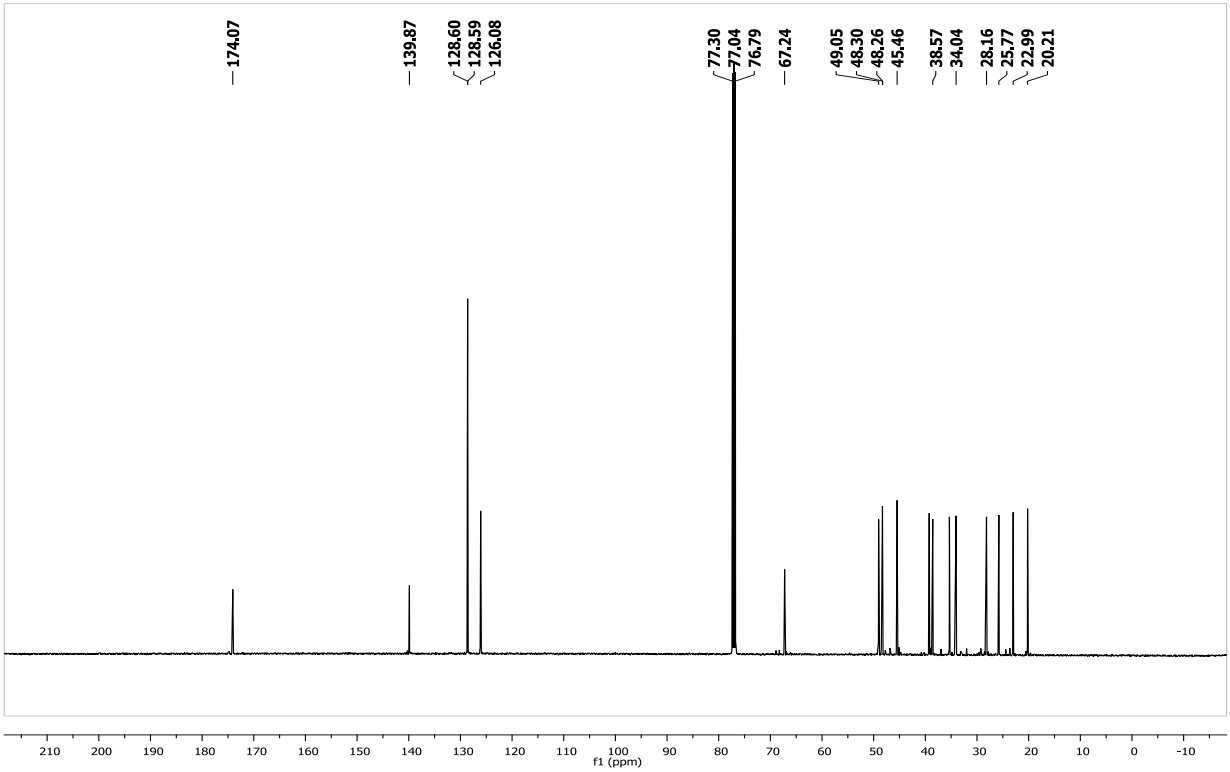
4c


O
N
H2N
H
nPr
0.93
1.06
0.86
1.03
2.80
1.00
9.32
6.26
3.04
f1 (ppm)

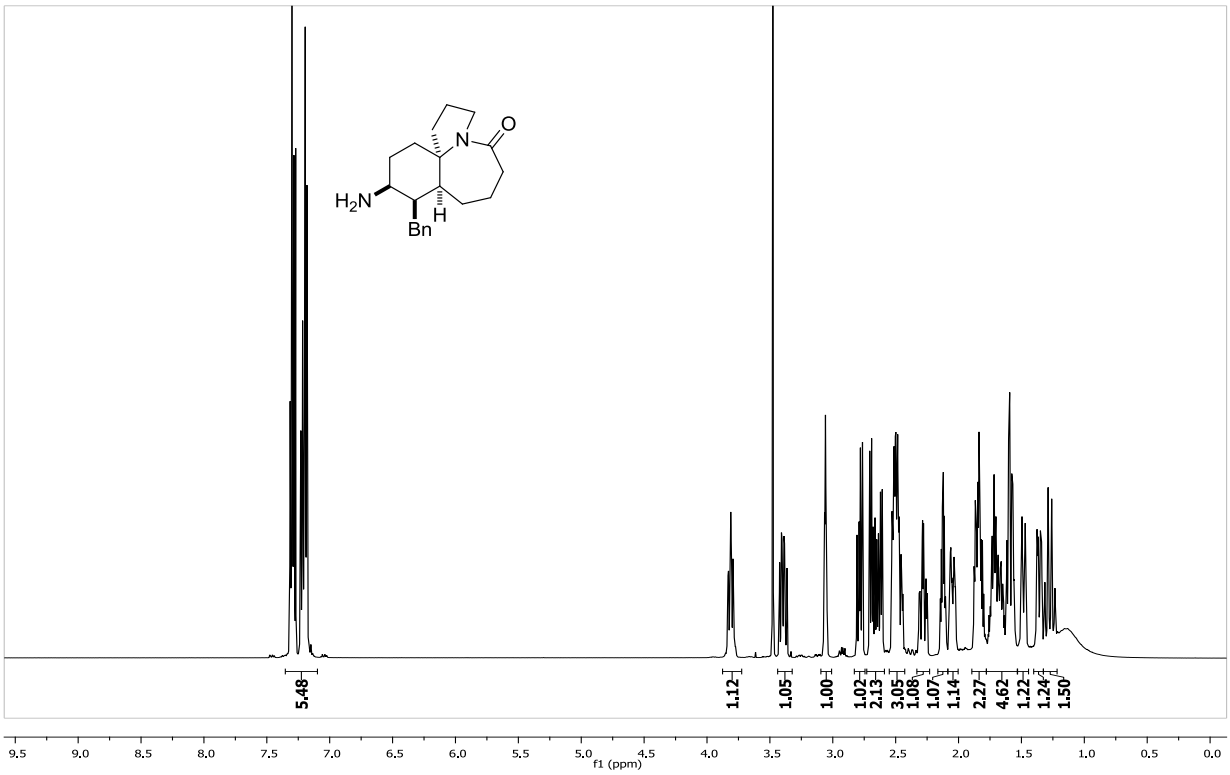

174.82
77.34
77.09
76.83
68.31
49.05
48.28
47.52
38.88
28.91
23.82
20.15
14.31
f1 (ppm)

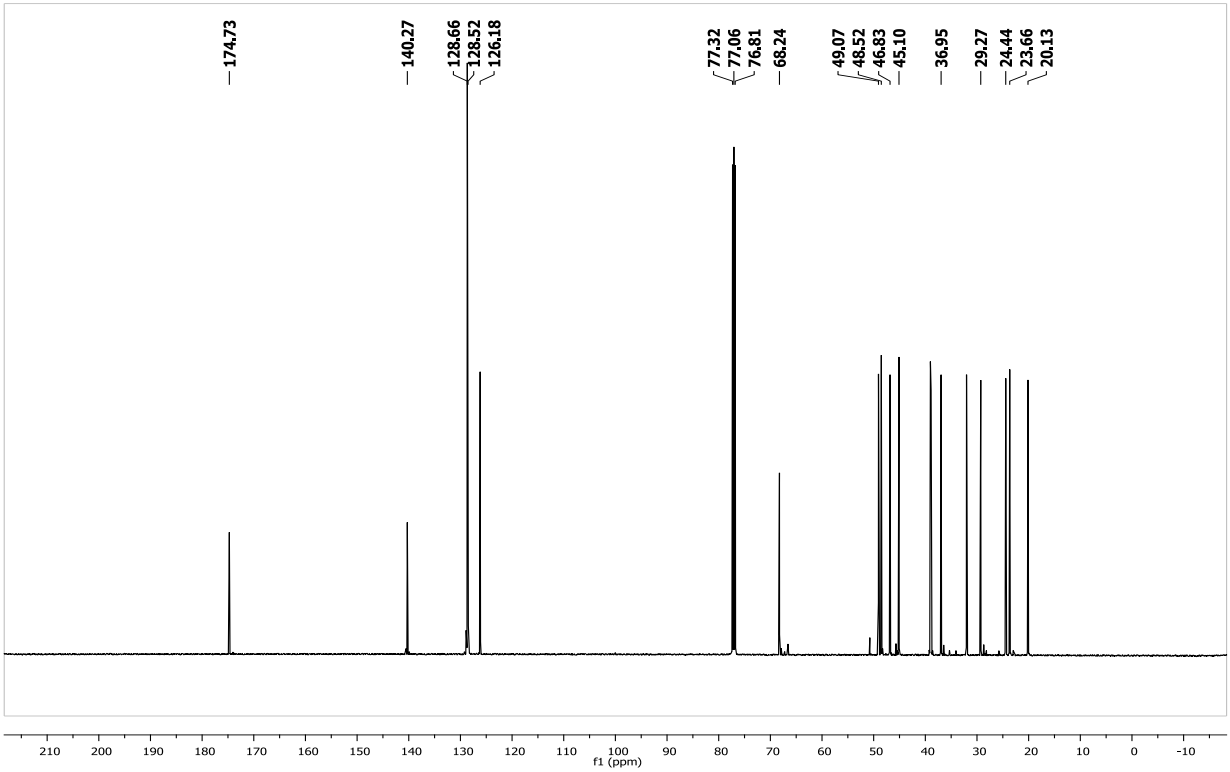
S5d


O
N
H2N
H
Bn
2.47
1.07
1.80
1.06
1.00
0.99
0.98
1.99
1.97
1.15
3.05
1.42
10.55
2.13
f1 (ppm)

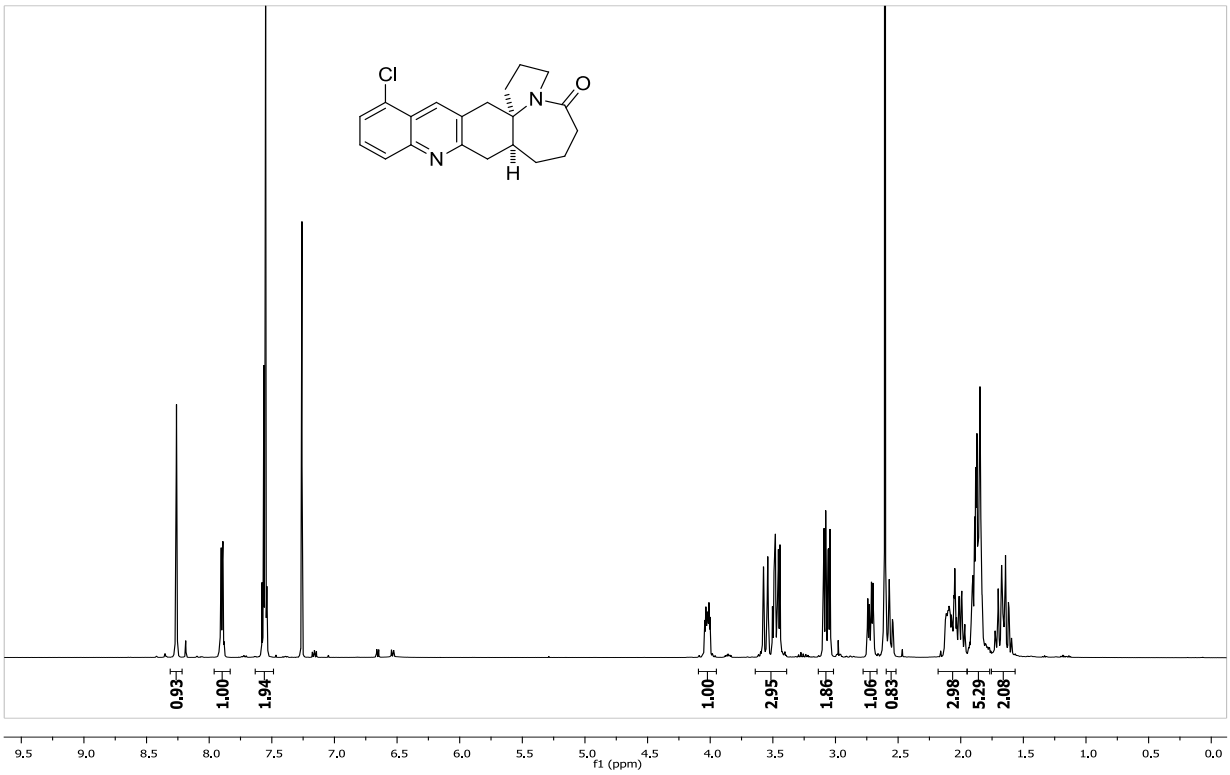

174.07
139.87
128.60
128.59
126.08
77.30
77.04
76.79
67.24
49.05
48.30
48.26
45.46
38.57
34.04
28.16
25.77
22.99
20.21
f1 (ppm)

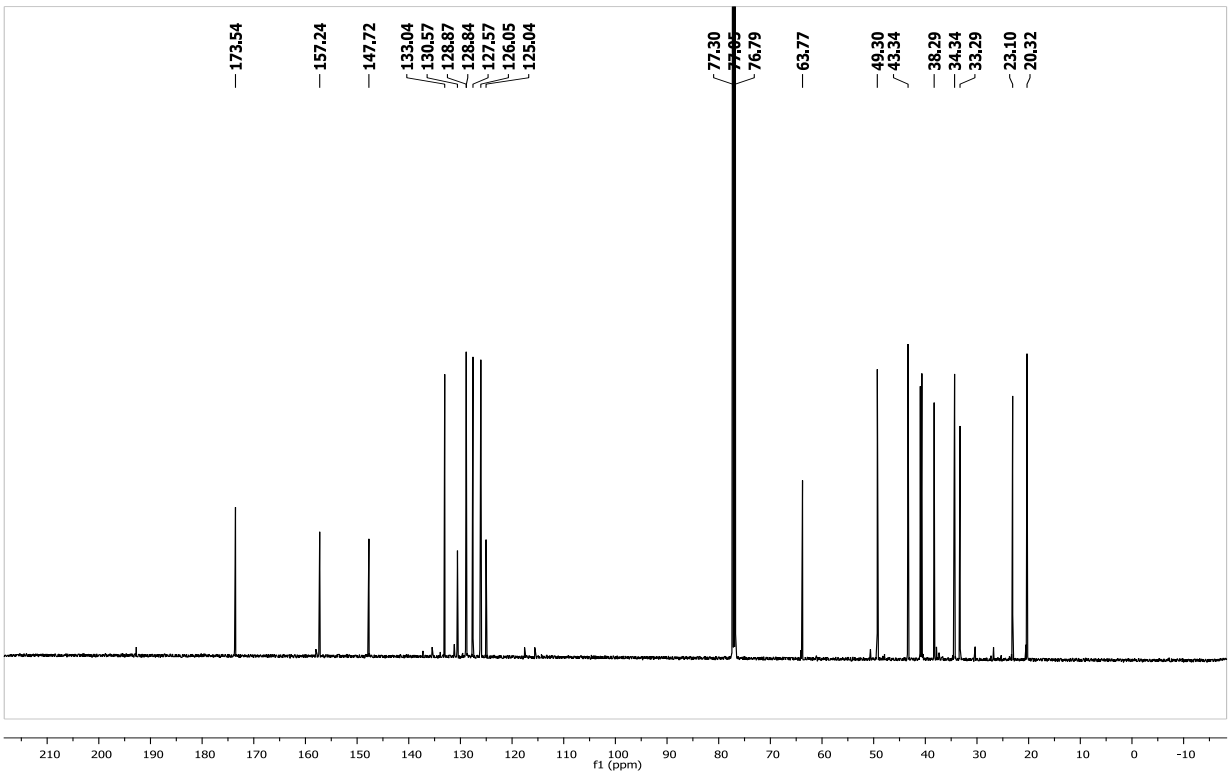
4d


H2N
Bn
H
N
O
5.48
1.12
1.05
1.00
1.02
2.13
3.05
1.08
1.07
1.14
2.27
4.62
1.22
1.24
1.50
f1 (ppm)

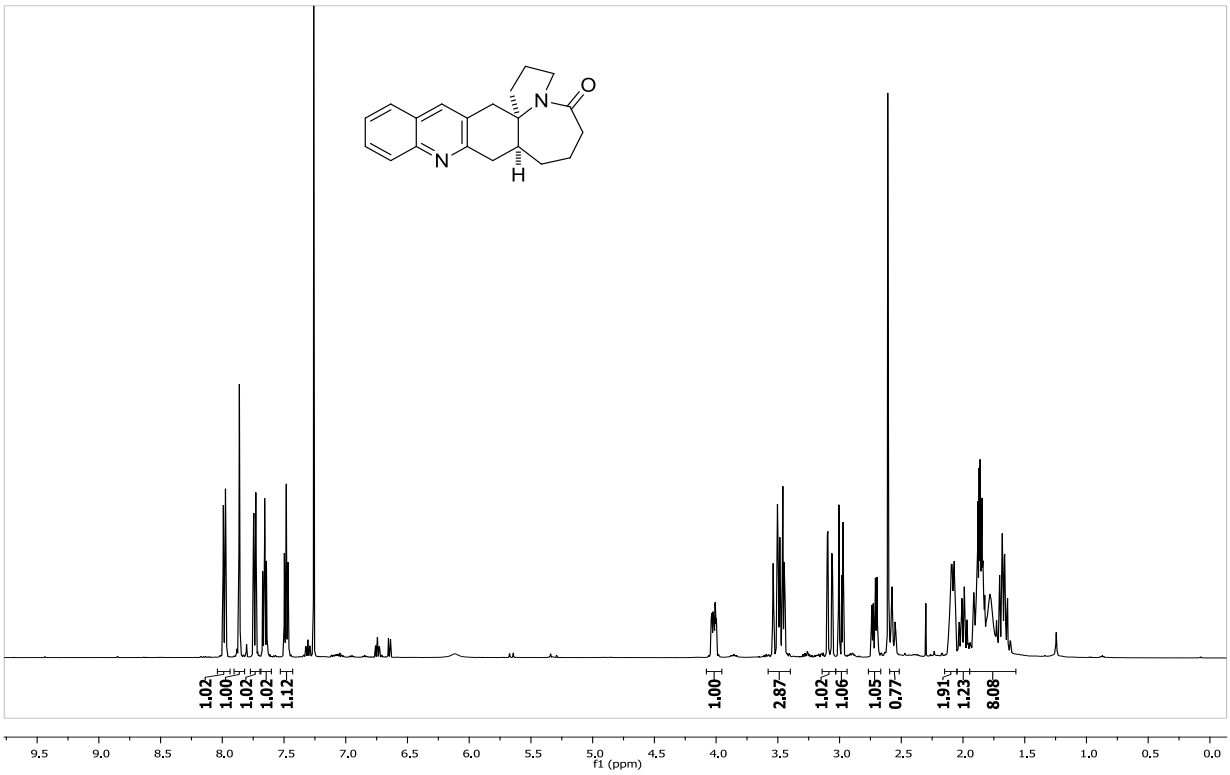

174.73
140.27
128.66
128.52
126.18
77.32
77.06
76.81
68.24
49.07
48.52
46.83
45.10
36.95
29.27
24.44
23.66
20.13
f1 (ppm)

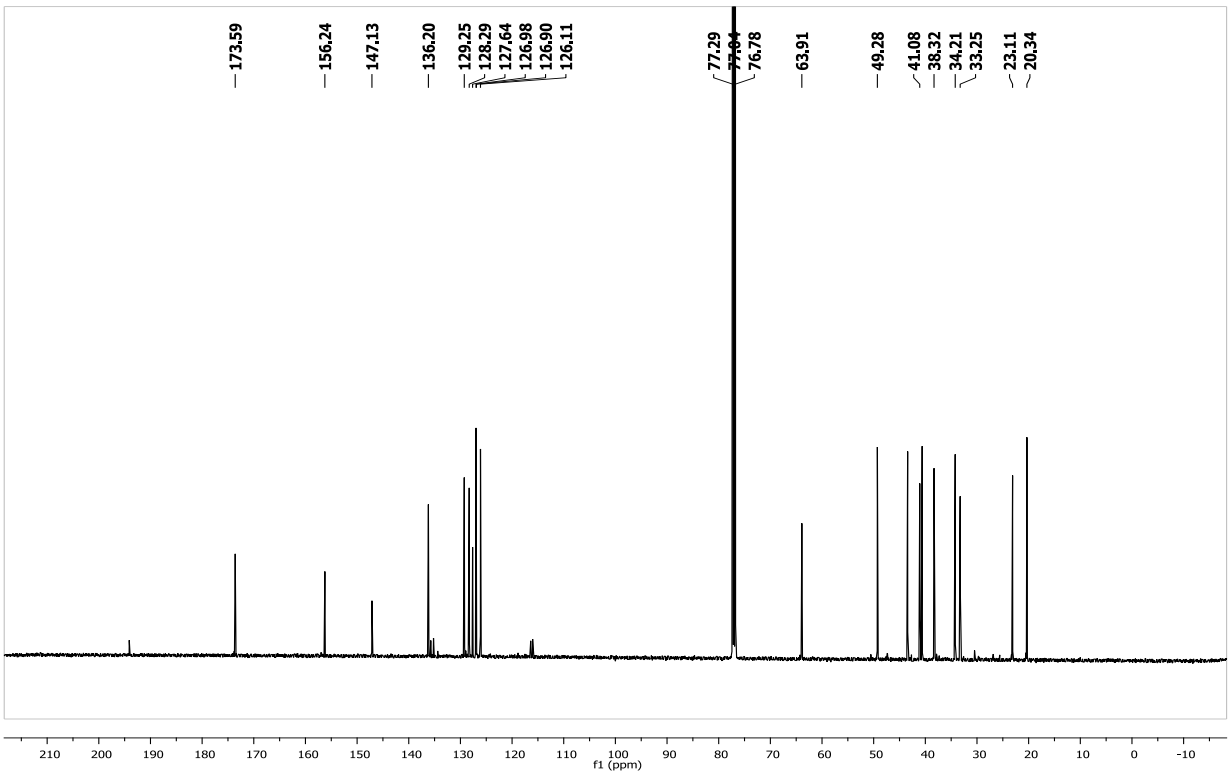
25{*3*}


Cl
N
O
N
H
0.93
1.00
1.94
1.00
2.95
1.86
1.06
0.83
2.98
5.29
2.08
f1 (ppm)

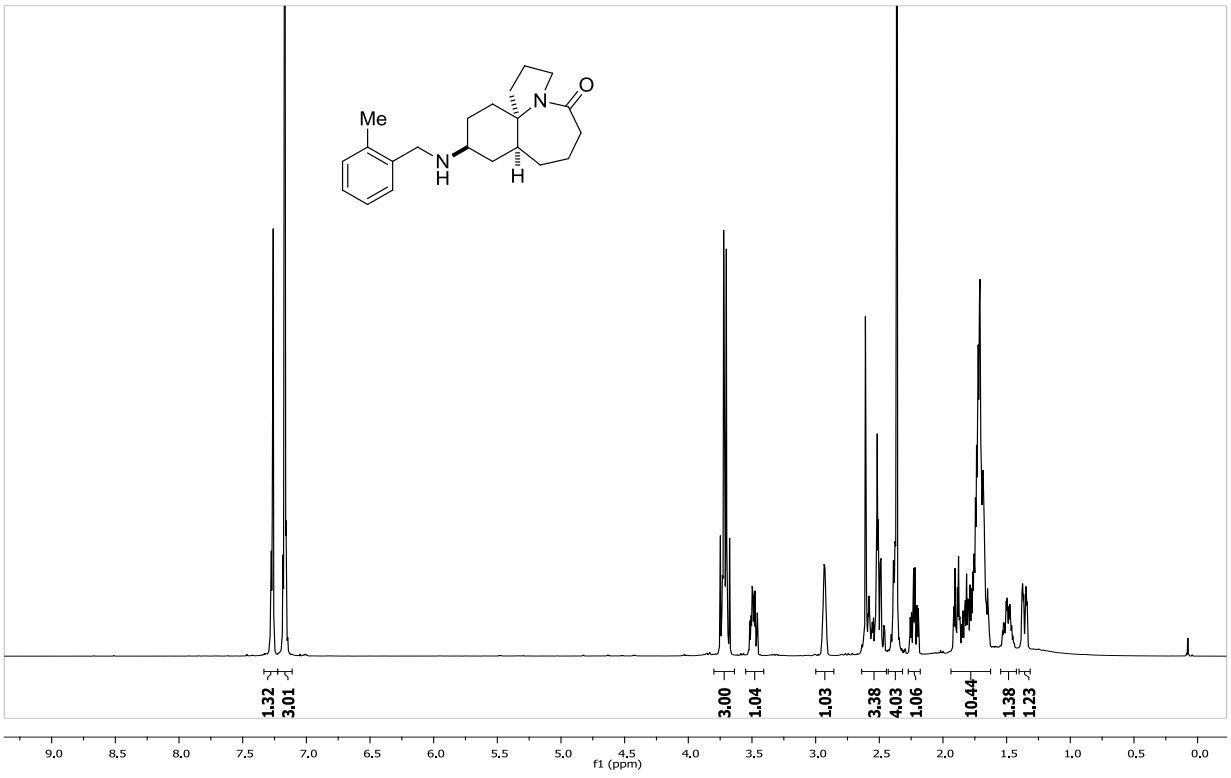

173.54
157.24
147.72
133.04
130.57
128.87
128.84
127.57
126.05
125.04
77.30
77.05
76.79
63.77
49.30
43.34
38.29
34.34
33.29
23.10
20.32
f1 (ppm)

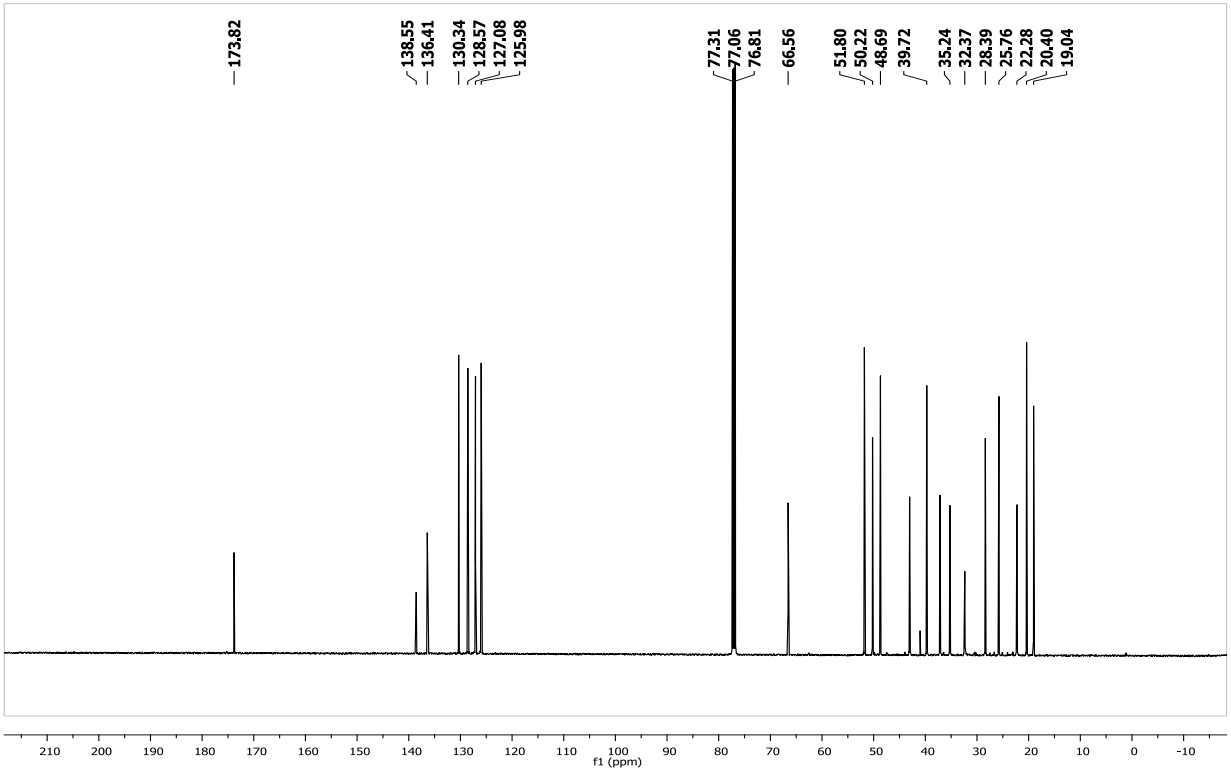
25{*1*}


O
N
N
H
1.02
1.00
1.02
1.02
1.12
1.00
2.87
1.02
1.06
1.05
0.77
1.91
1.23
8.08
f1 (ppm)

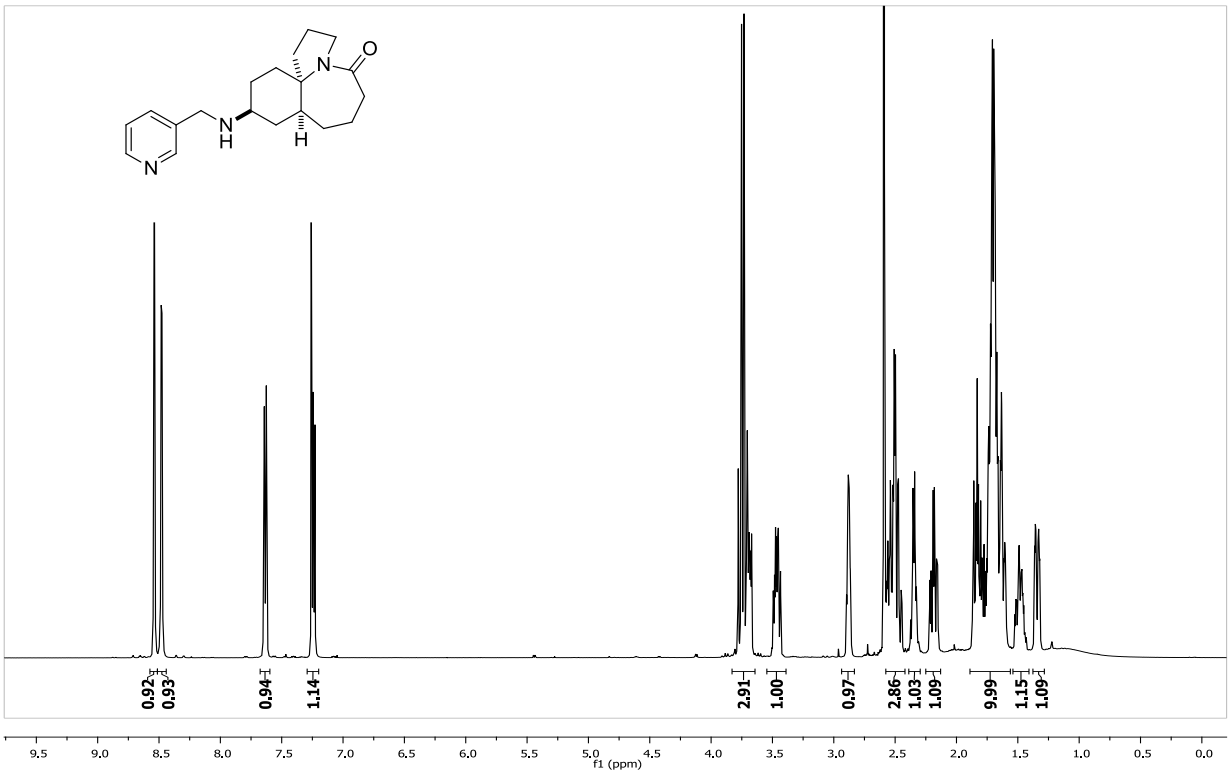

173.59
156.24
147.13
136.20
129.25
128.29
127.64
126.98
126.90
126.11
77.29
77.04
76.78
63.91
49.28
41.08
38.32
34.21
33.25
23.11
20.34
f1 (ppm)

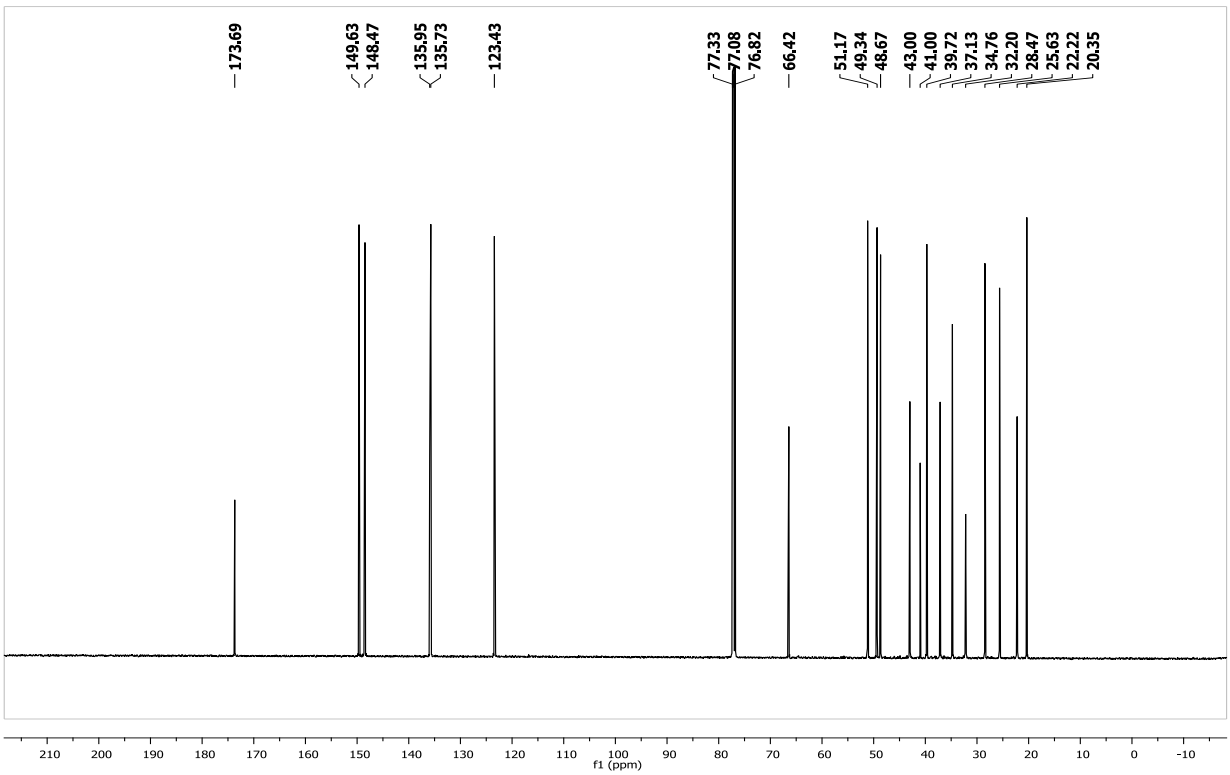
26{*3*}


Me
N
H
O
N
H
1.32
3.01
3.00
1.04
1.03
3.38
4.03
1.06
10.44
1.38
1.23
f1 (ppm)

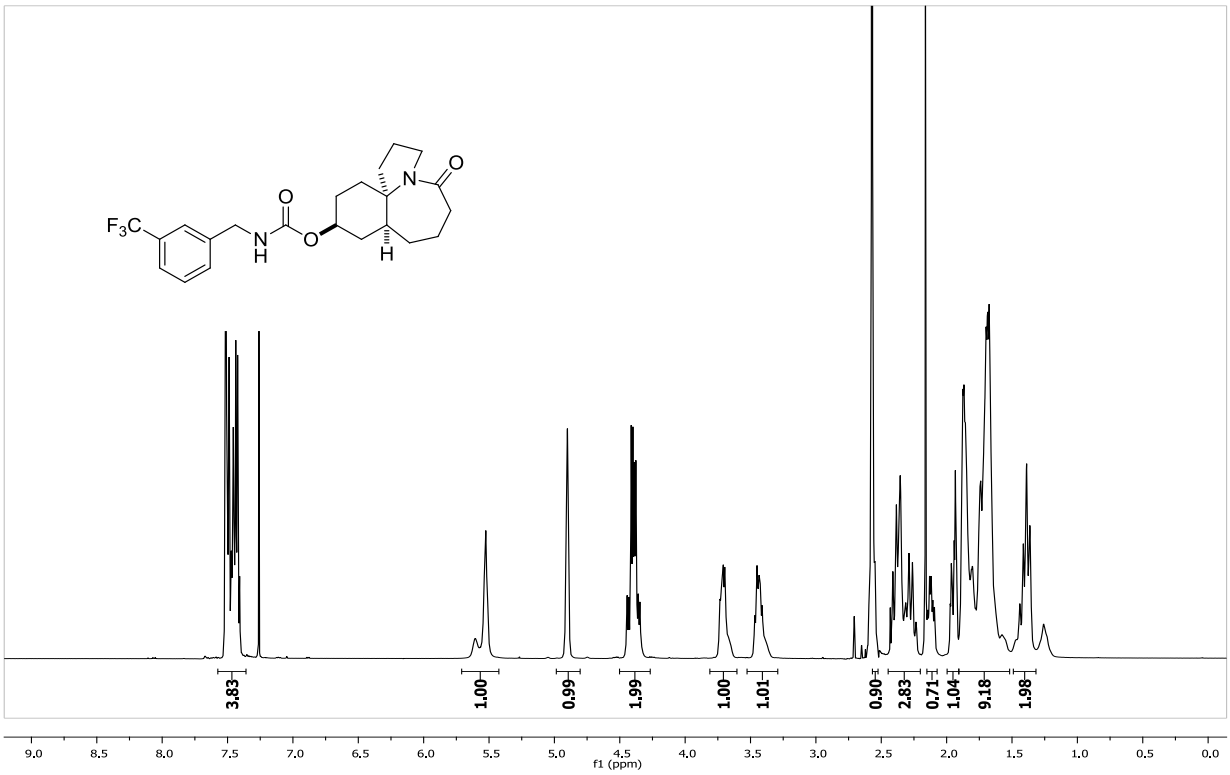

173.82
138.55
136.41
130.34
128.57
127.08
125.98
77.31
77.06
76.81
66.56
51.80
50.22
48.69
39.72
35.24
32.37
28.39
25.76
22.28
20.40
19.04
f1 (ppm)

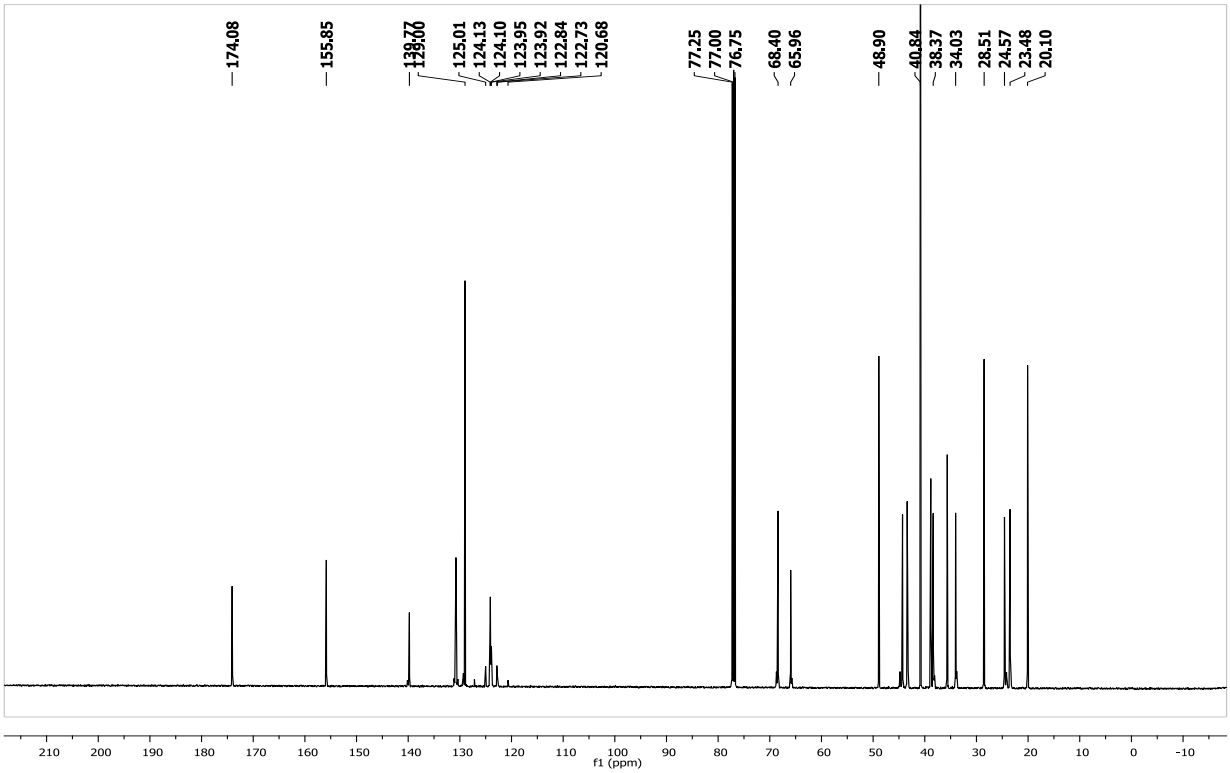
26{*24*}


O
N
N
H
H
N
0.92
0.93
0.94
1.14
2.91
1.00
0.97
2.86
1.03
1.09
9.99
1.15
1.09
f1 (ppm)

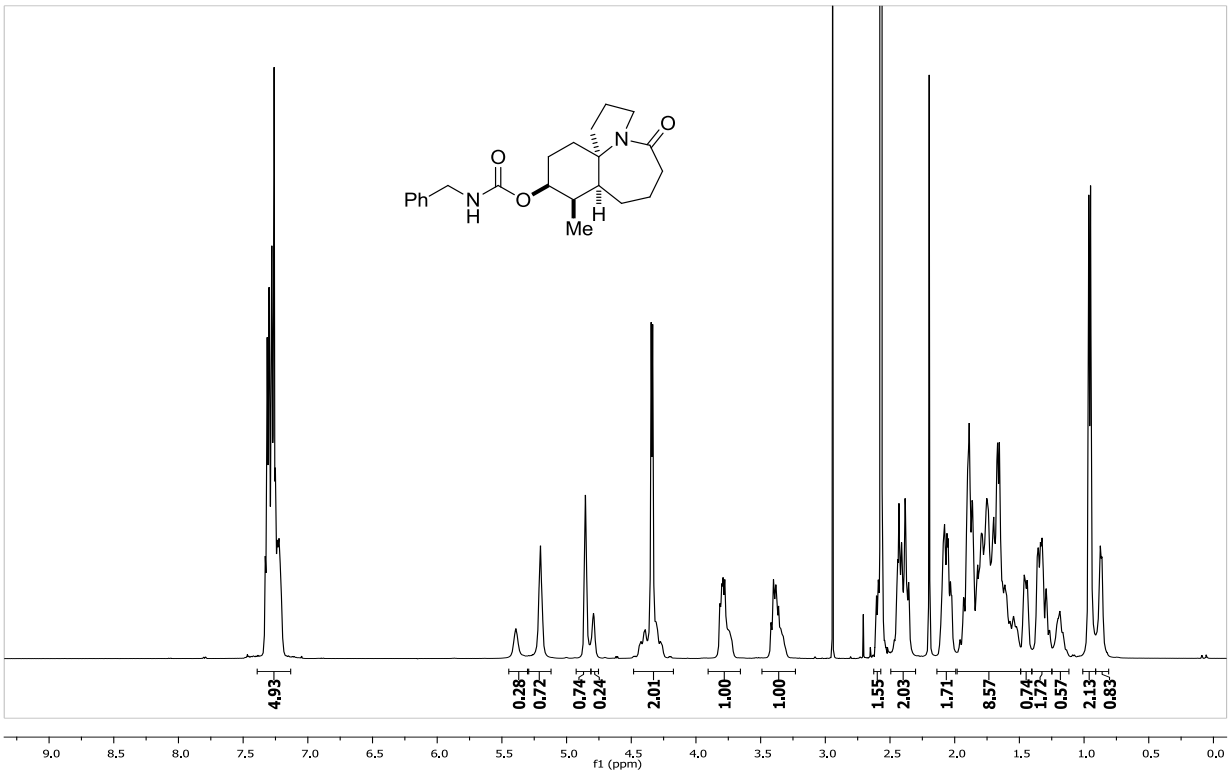

173.69
149.63
148.47
135.95
135.73
123.43
77.33
77.08
76.82
66.42
51.17
49.34
48.67
43.00
41.00
39.72
37.13
34.76
32.20
28.47
25.63
22.22
20.35
f1 (ppm)

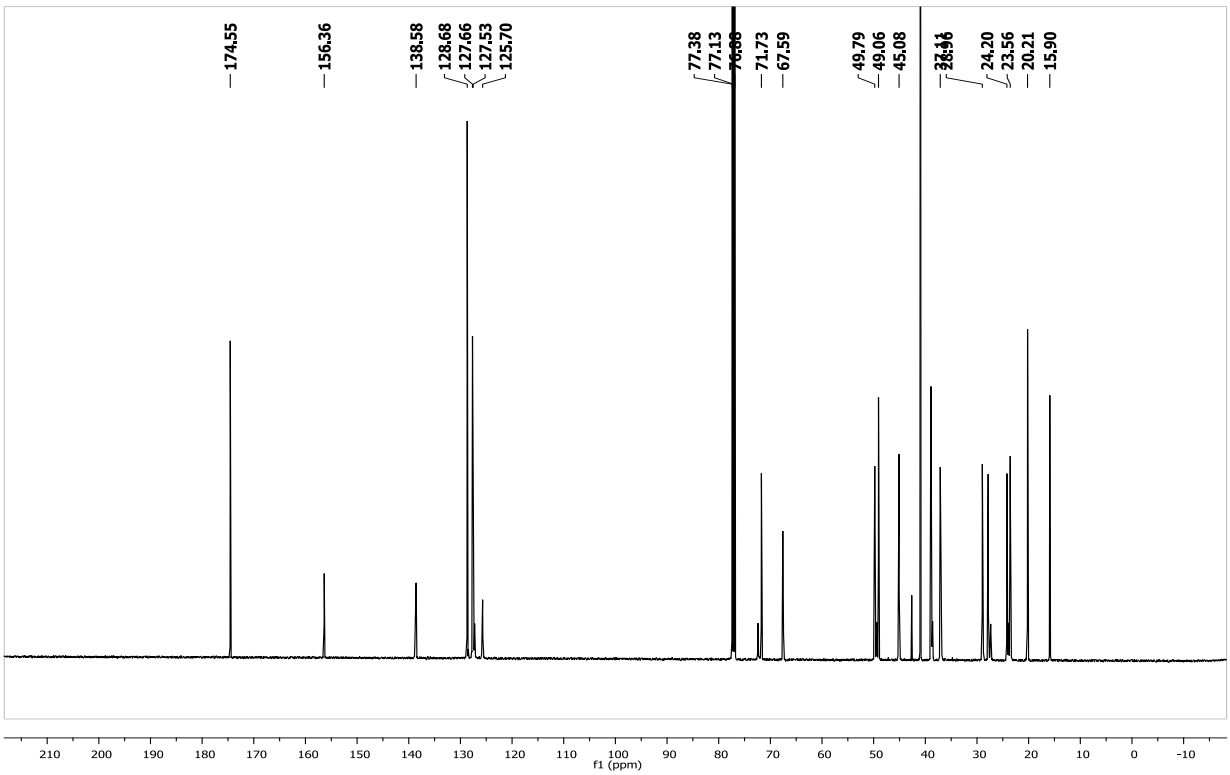
27a{*3*}


F3C
N
H
O
O
N
O
H
3.83
1.00
0.99
1.99
1.00
1.01
0.90
2.83
0.71
1.04
9.18
1.98
f1 (ppm)

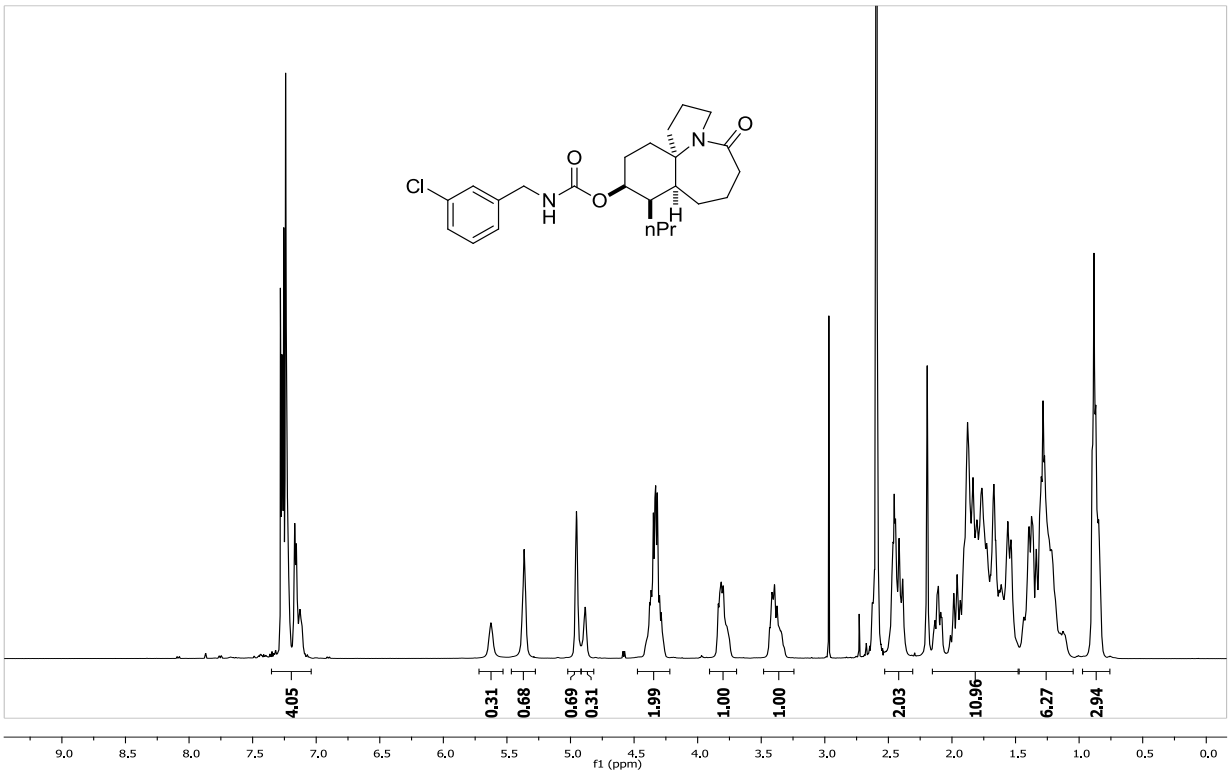

174.08
155.85
138.77
129.00
125.01
124.13
124.10
123.95
123.92
122.84
122.73
120.68
77.25
77.00
76.75
68.40
65.96
48.90
40.84
38.37
34.03
28.51
24.57
23.48
20.10
f1 (ppm)

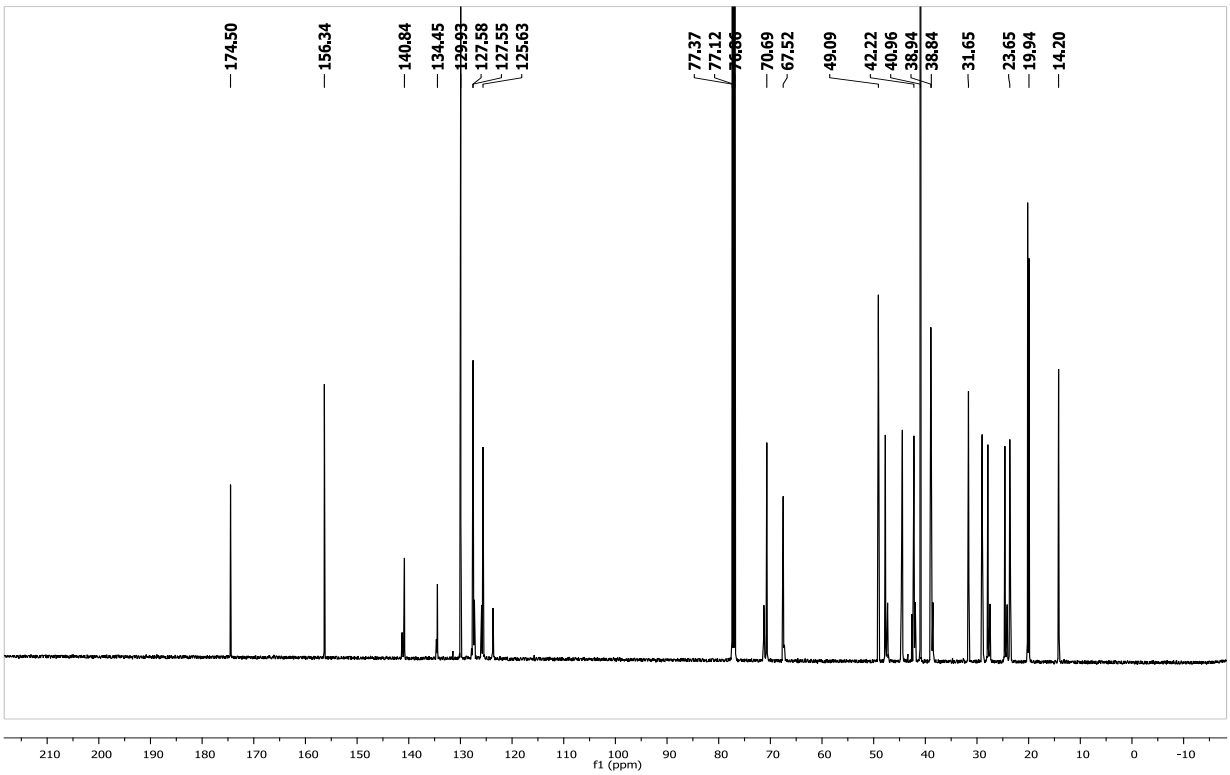
27b{*1*}


Ph
N
H
O
O
O
N
O
H
Me
4.93
0.28
0.72
0.74
0.24
2.01
1.00
1.00
1.55
2.03
1.71
8.57
0.74
1.72
0.57
2.13
0.83
f1 (ppm)

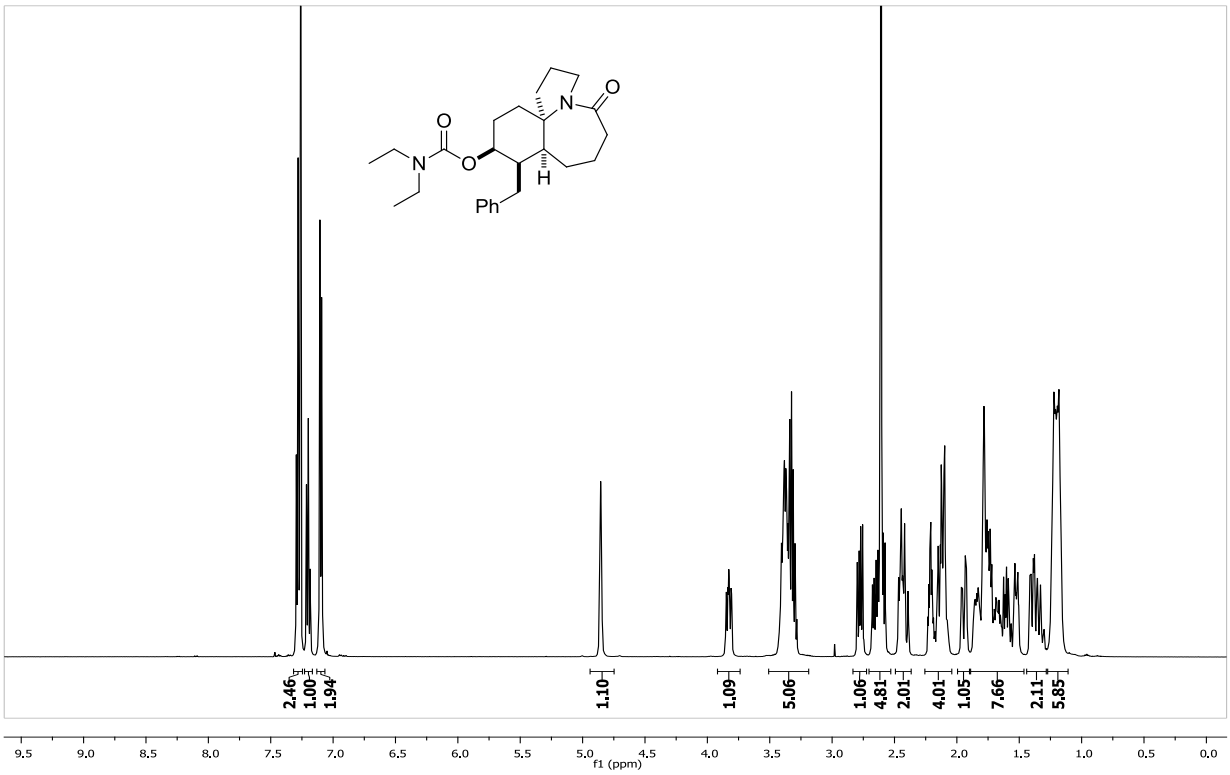

174.55
156.36
138.58
128.68
127.66
127.53
125.70
77.38
77.13
76.88
71.73
67.59
49.79
49.06
45.08
24.20
23.56
20.21
15.90
f1 (ppm)

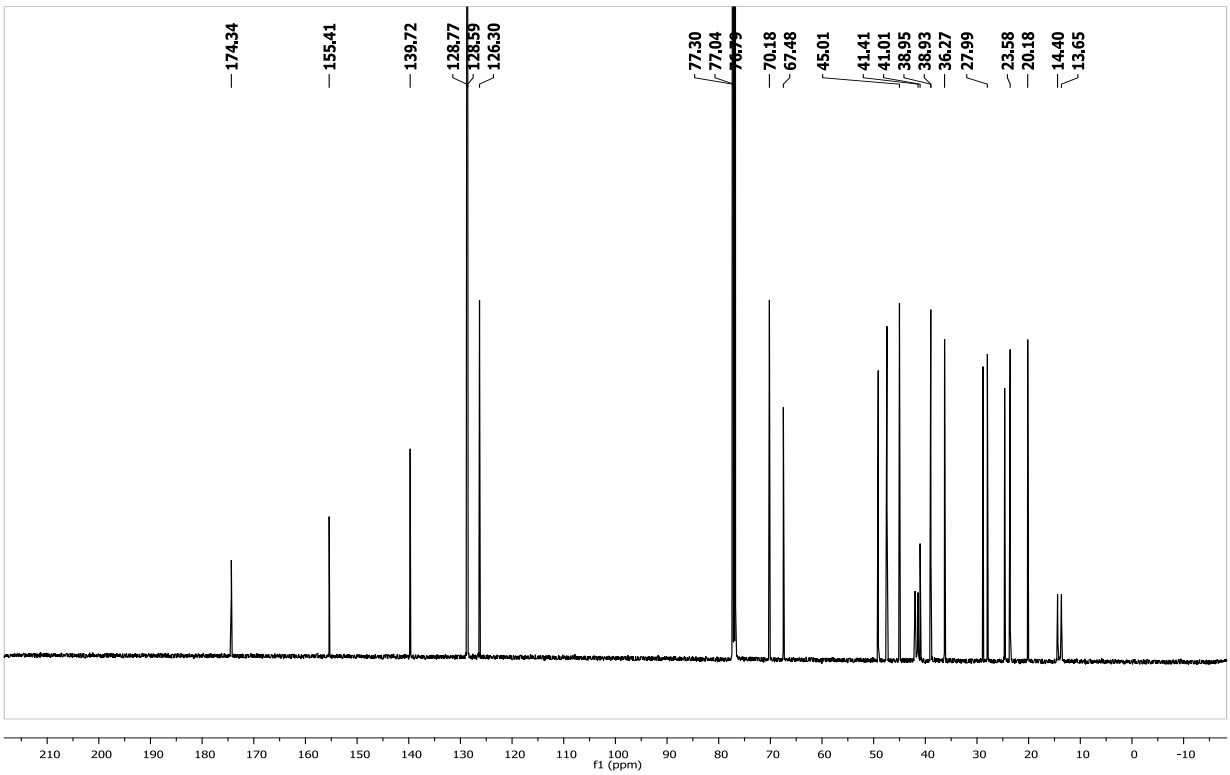
27c{*4*}


Cl
N
H
O
O
O
N
O
H
nPr
4.05
0.31
0.68
0.69
0.31
1.99
1.00
1.00
2.03
10.96
6.27
2.94
f1 (ppm)

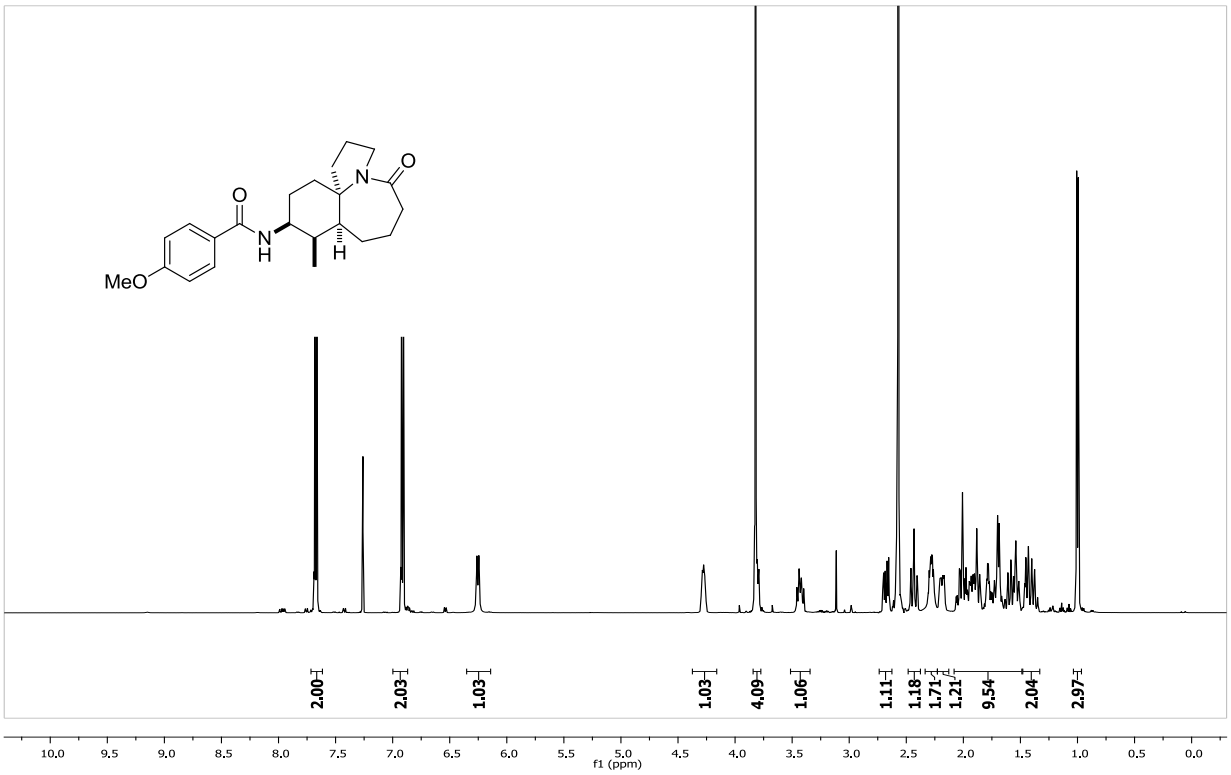

174.50
156.34
140.84
134.45
129.93
127.58
127.55
125.63
77.37
77.12
76.86
70.69
67.52
49.09
42.22
40.96
38.94
38.84
31.65
23.65
19.94
14.20
f1 (ppm)

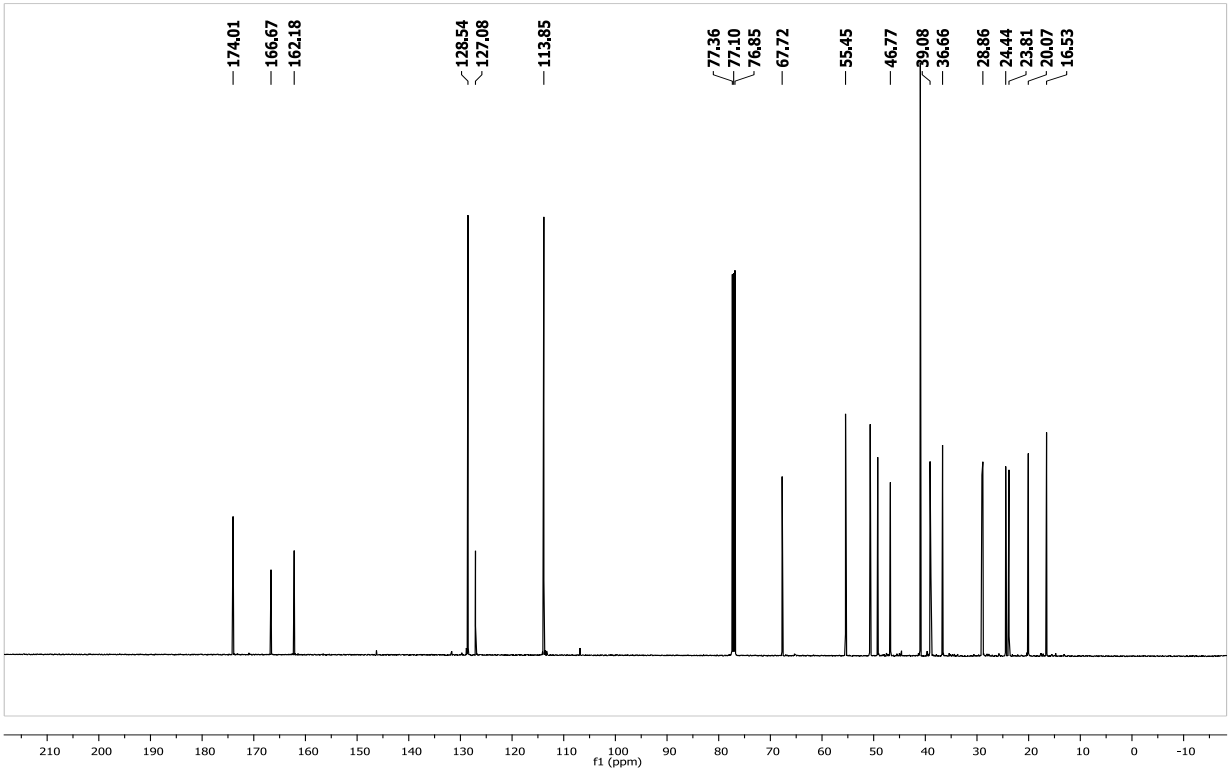
27d{*19*}


O
N
O
O
N
H
Ph
2.46
1.00
1.94
1.10
1.09
5.06
1.06
4.81
2.01
4.01
1.05
7.66
2.11
5.85
f1 (ppm)

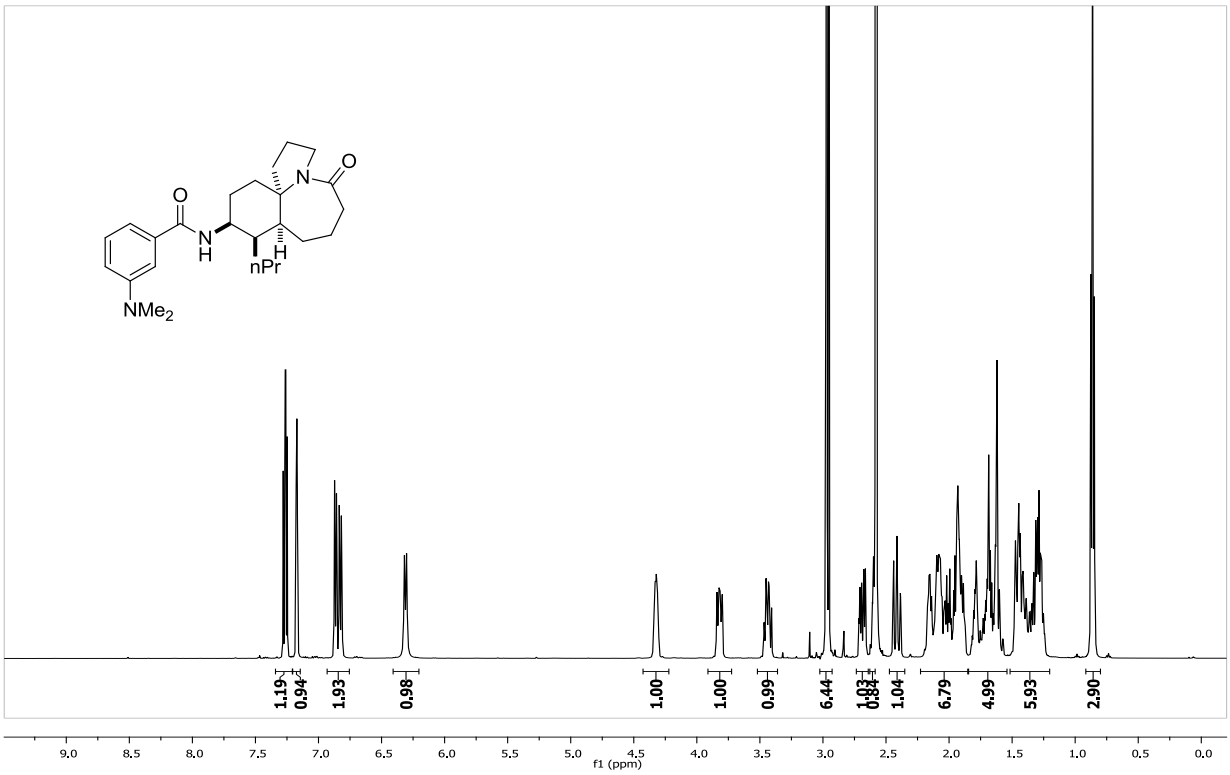

174.34
155.41
139.72
128.77
128.59
126.30
77.30
77.04
76.79
70.18
67.48
45.01
41.41
41.01
38.95
38.93
36.27
27.99
23.58
20.18
14.40
13.65
f1 (ppm)

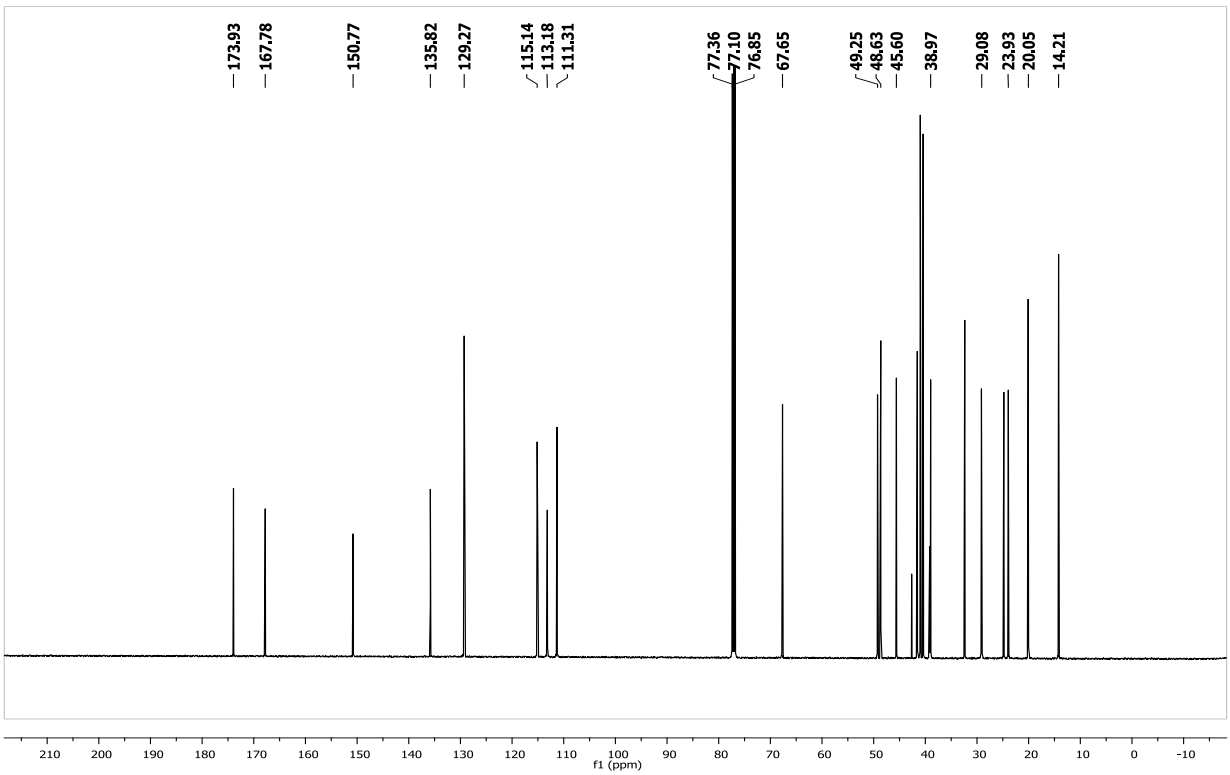
28b{*3*}


MeO
O
N
H
O
N
H
2.00
2.03
1.03
1.03
4.09
1.06
1.11
1.18
1.71
1.21
9.54
2.04
2.97
f1 (ppm)

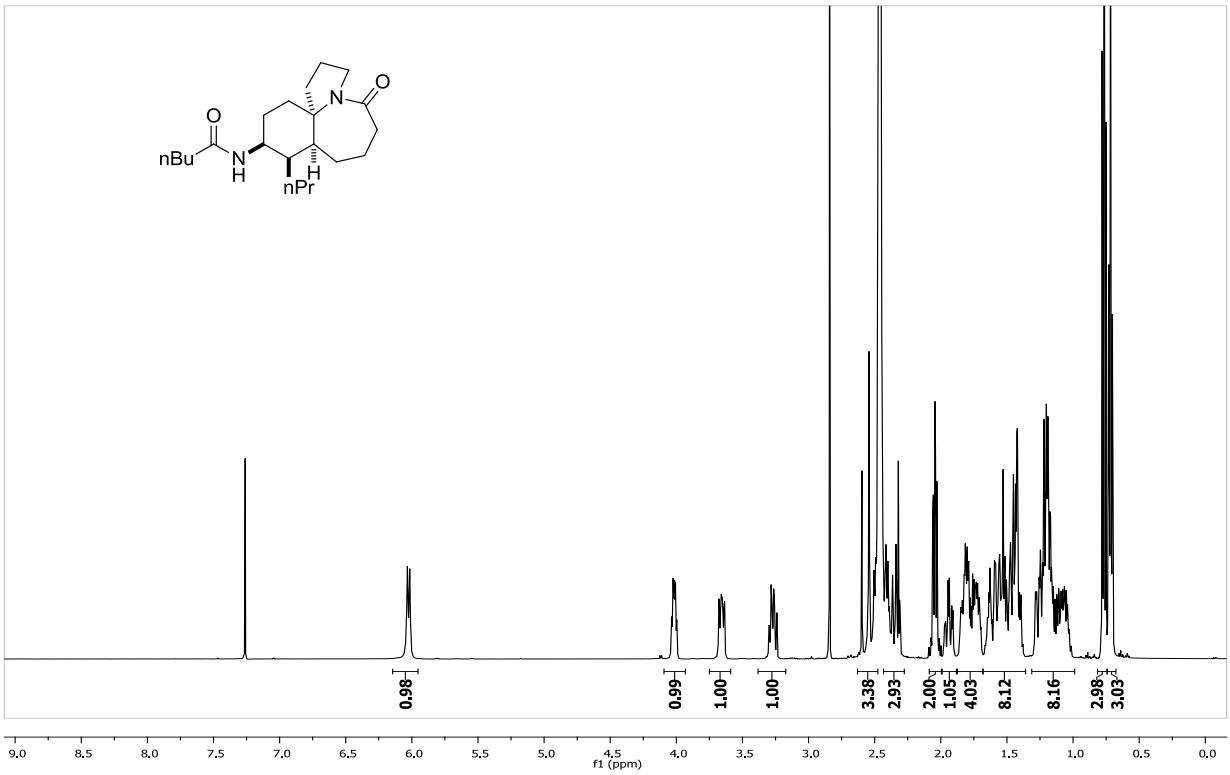

174.01
166.67
162.18
128.54
127.08
113.85
77.36
77.10
76.85
67.72
55.45
46.77
39.08
36.66
28.86
24.44
23.81
20.07
16.53
f1 (ppm)

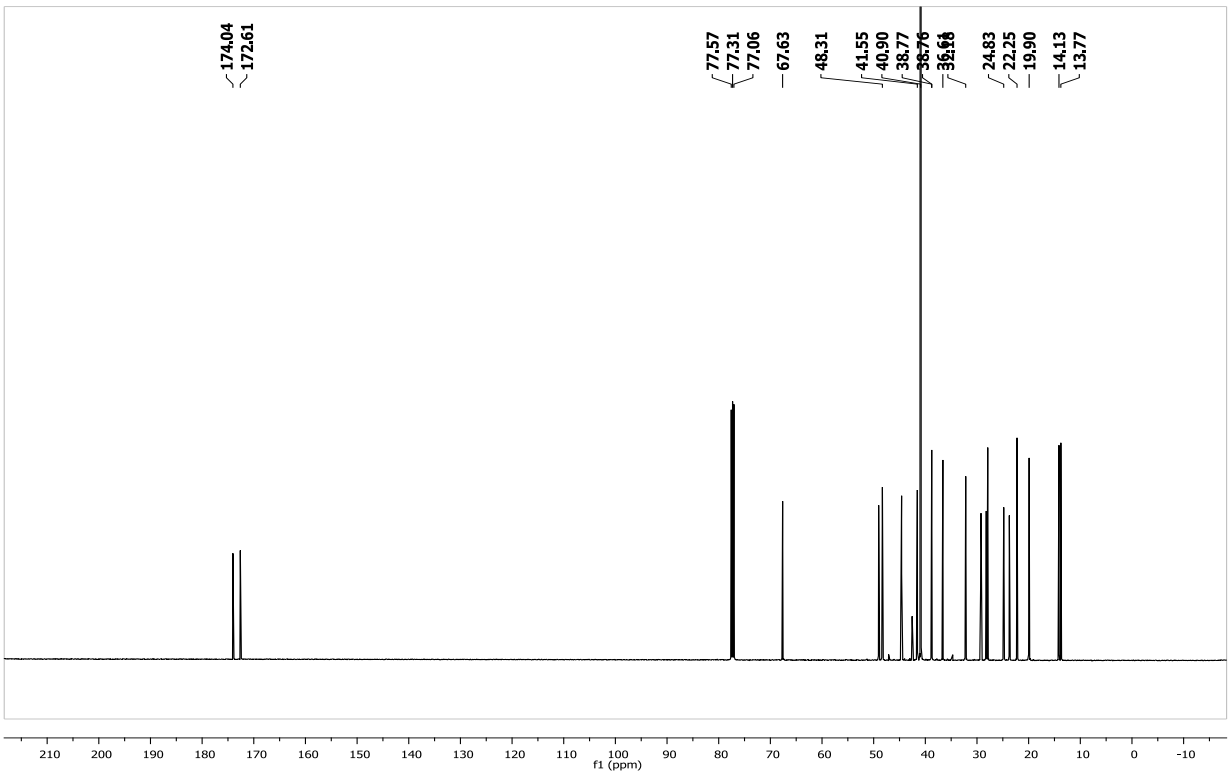
28c{*8*}


O
N
H
O
N
H
nPr
NMe2
1.19
0.94
1.93
0.98
1.00
1.00
0.99
6.44
1.03
0.82
1.04
6.79
4.99
5.93
2.90
f1 (ppm)

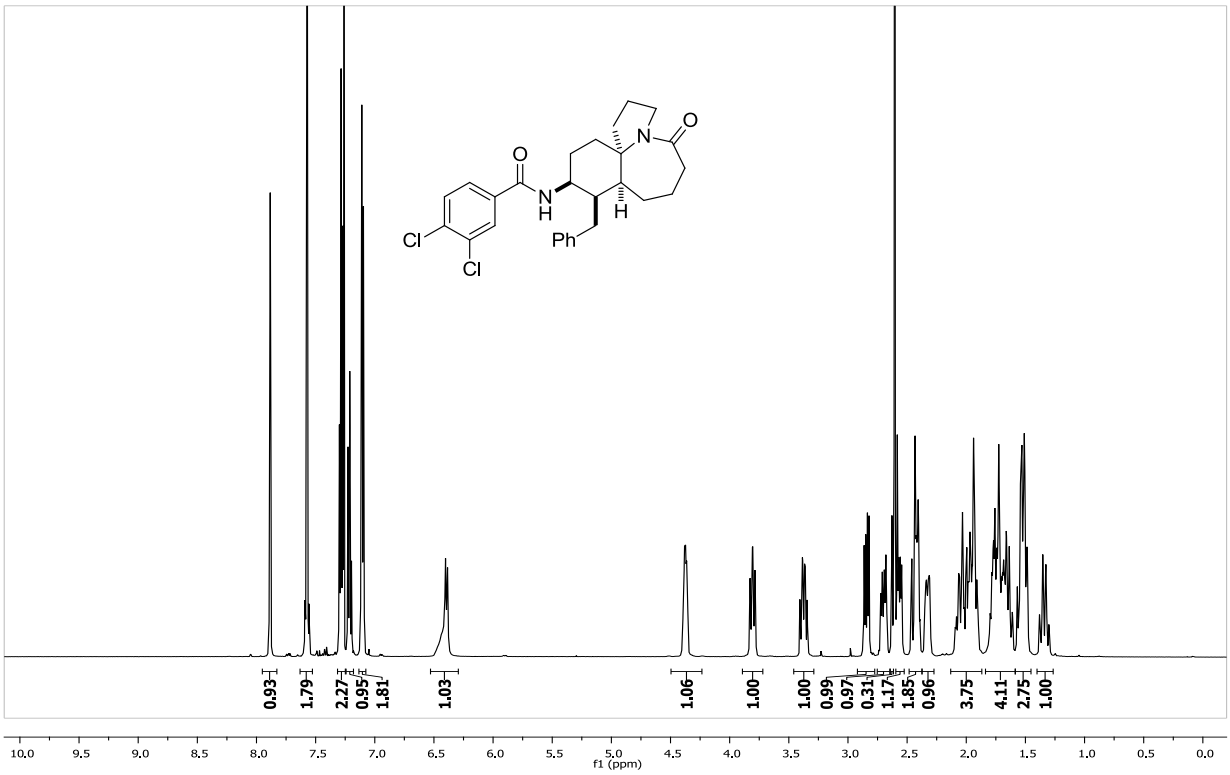

173.93
167.78
150.77
135.82
129.27
115.14
113.18
111.31
77.36
77.10
76.85
67.65
49.25
48.63
45.60
38.97
29.08
23.93
20.05
14.21
f1 (ppm)

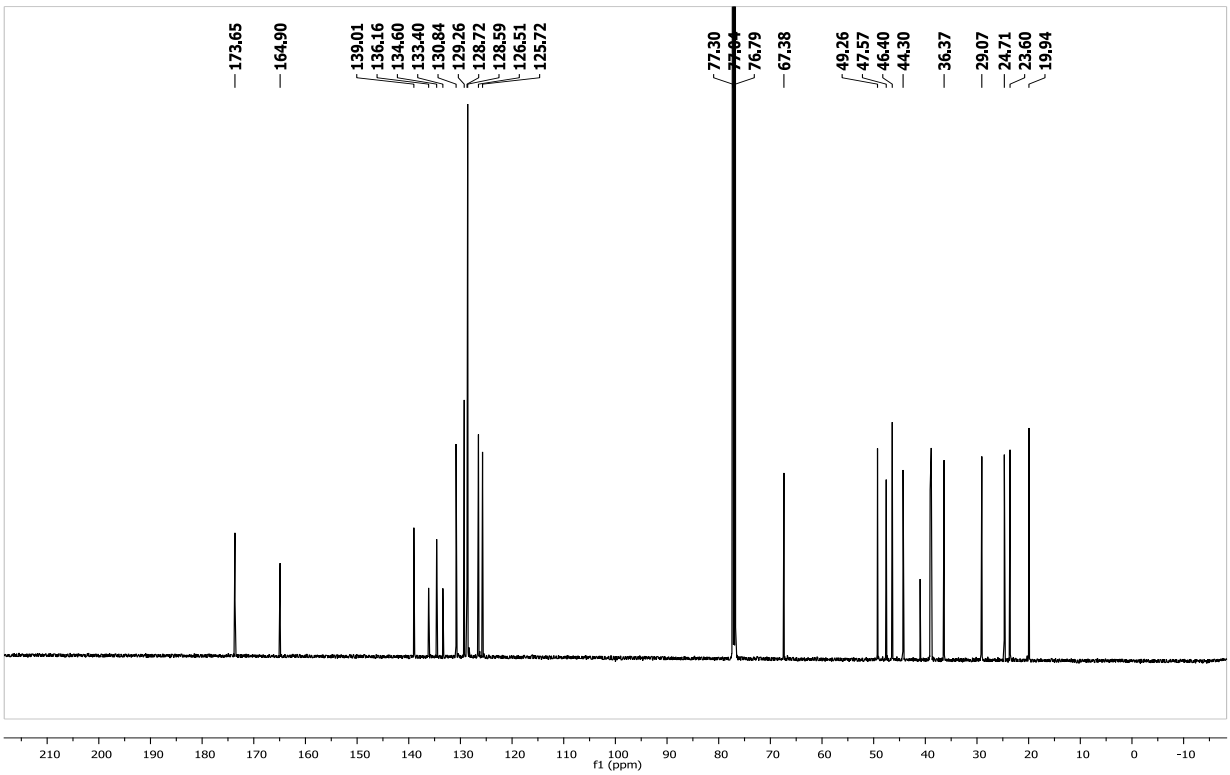
28c{*13*}


nBu
N
H
O
nPr
H
N
O
0.98
0.99
1.00
1.00
3.38
2.93
2.00
1.05
4.03
8.12
8.16
2.98
3.03
f1 (ppm)

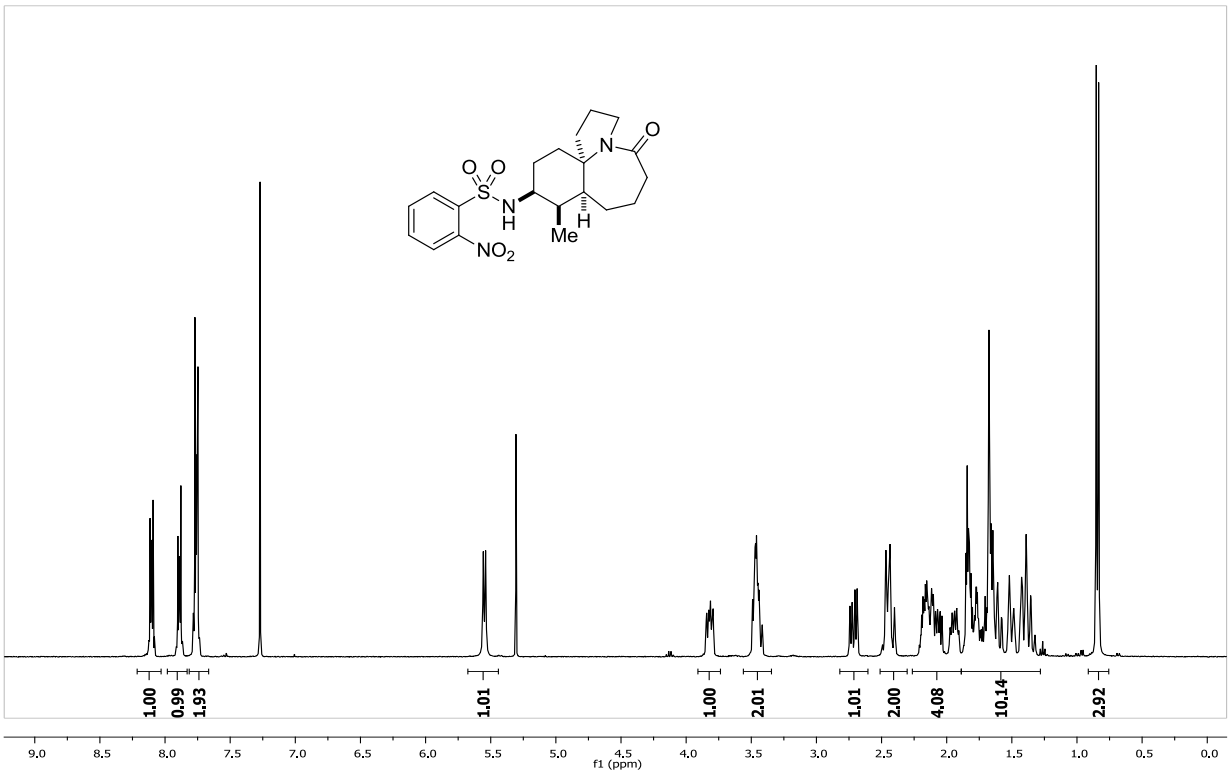

174.04
172.61
77.57
77.31
77.06
67.63
48.31
41.55
40.90
38.77
38.76
24.83
22.25
19.90
14.13
13.77
f1 (ppm)

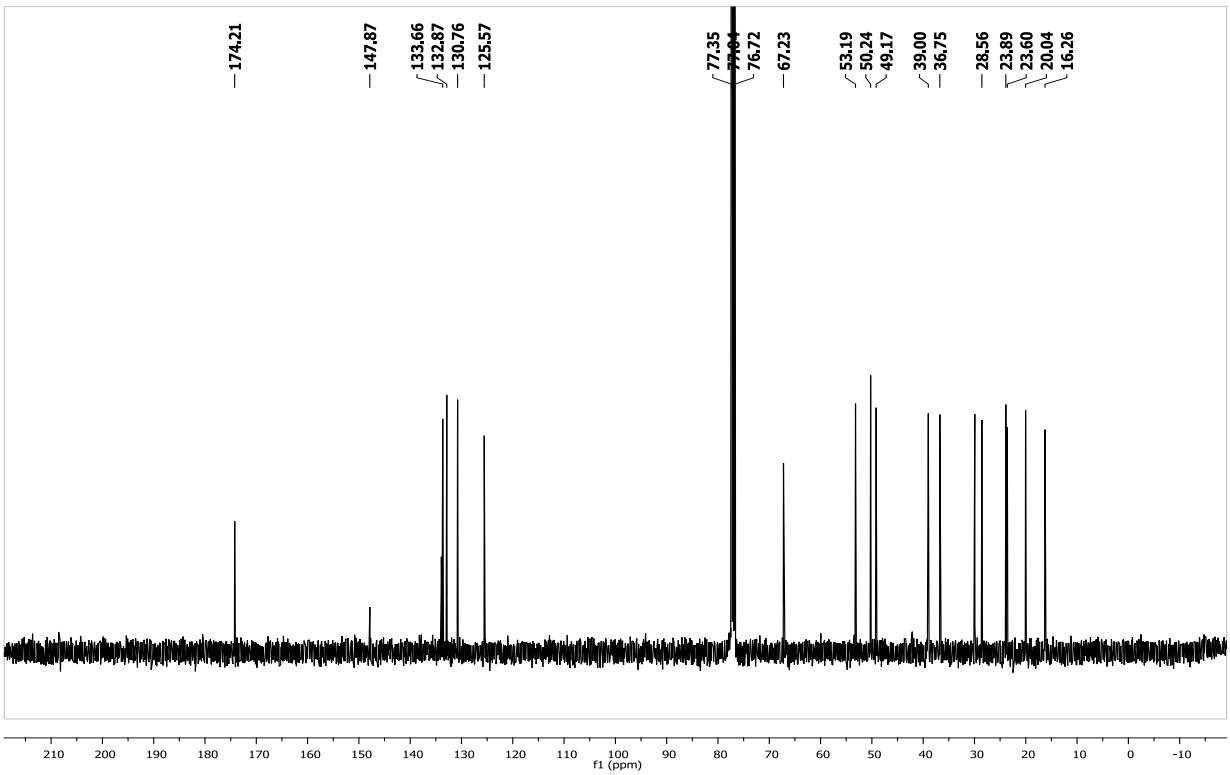
28d{*11*}


O
N
H
Cl
Cl
N
O
H
Ph
0.93
1.79
2.27
0.95
1.81
1.03
1.06
1.00
1.00
0.99
0.97
0.31
1.17
1.85
0.96
3.75
4.11
2.75
1.00
f1 (ppm)

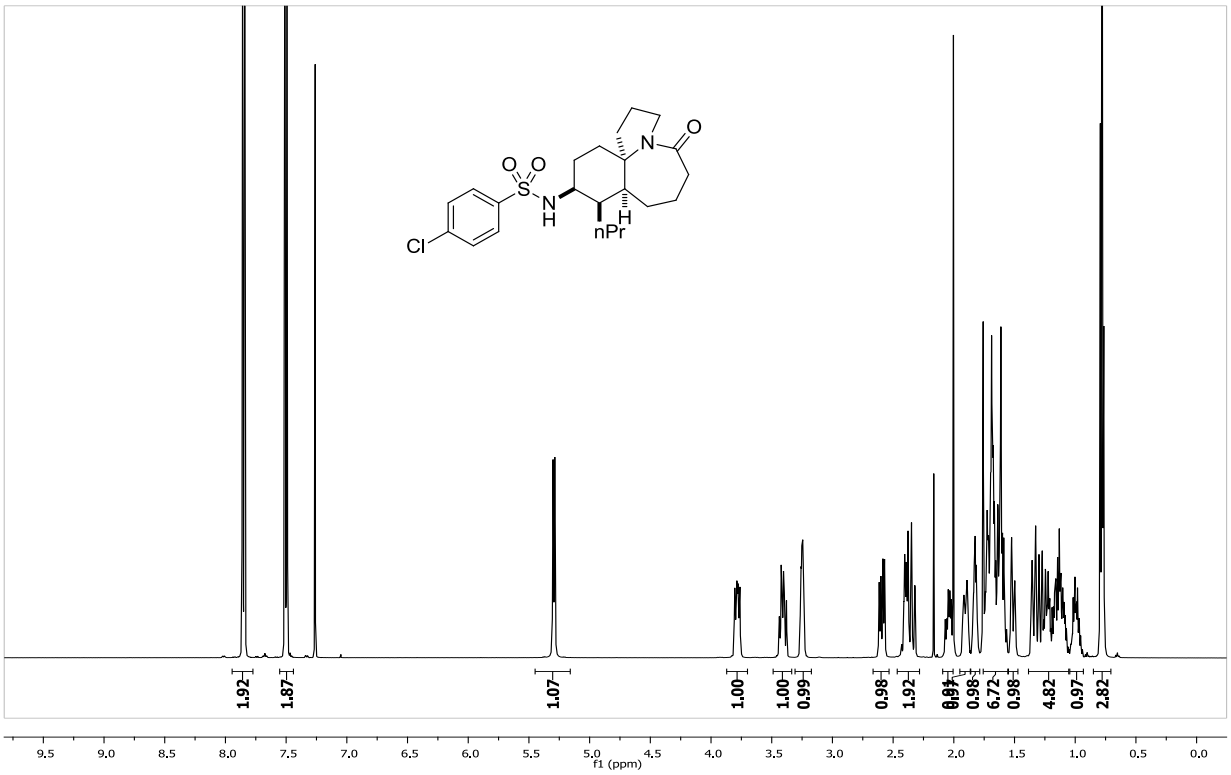

173.65
164.90
139.01
136.16
134.60
133.40
130.84
129.26
128.72
128.59
126.51
125.72
77.30
77.04
76.79
67.38
49.26
47.57
46.40
44.30
36.37
29.07
24.71
23.60
19.94
f1 (ppm)

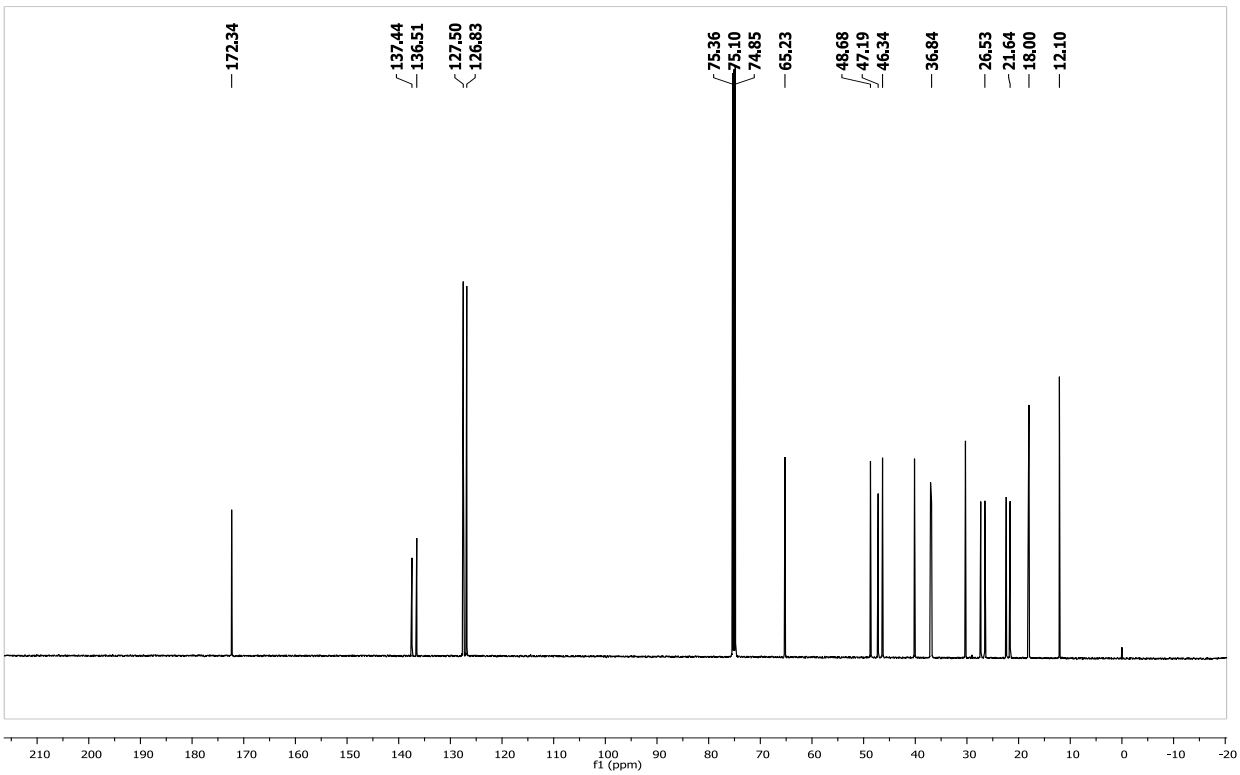
29b{*2*}


O
N
O
O
S
N
H
H
Me
NO2
1.00
0.99
1.93
1.01
1.00
2.01
1.01
2.00
4.08
10.14
2.92
f1 (ppm)

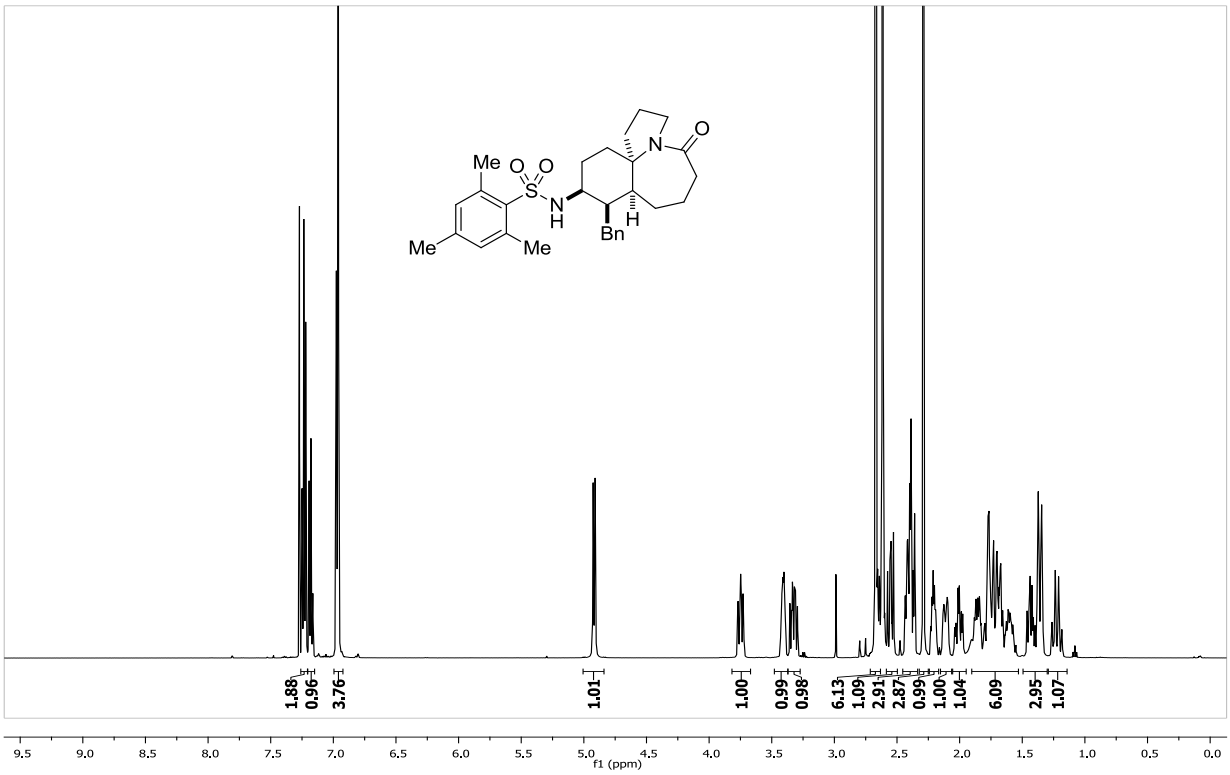

174.21
147.87
133.66
132.87
130.76
125.57
77.35
77.04
76.72
67.23
53.19
50.24
49.17
39.00
36.75
28.56
23.89
23.60
20.04
16.26
f1 (ppm)

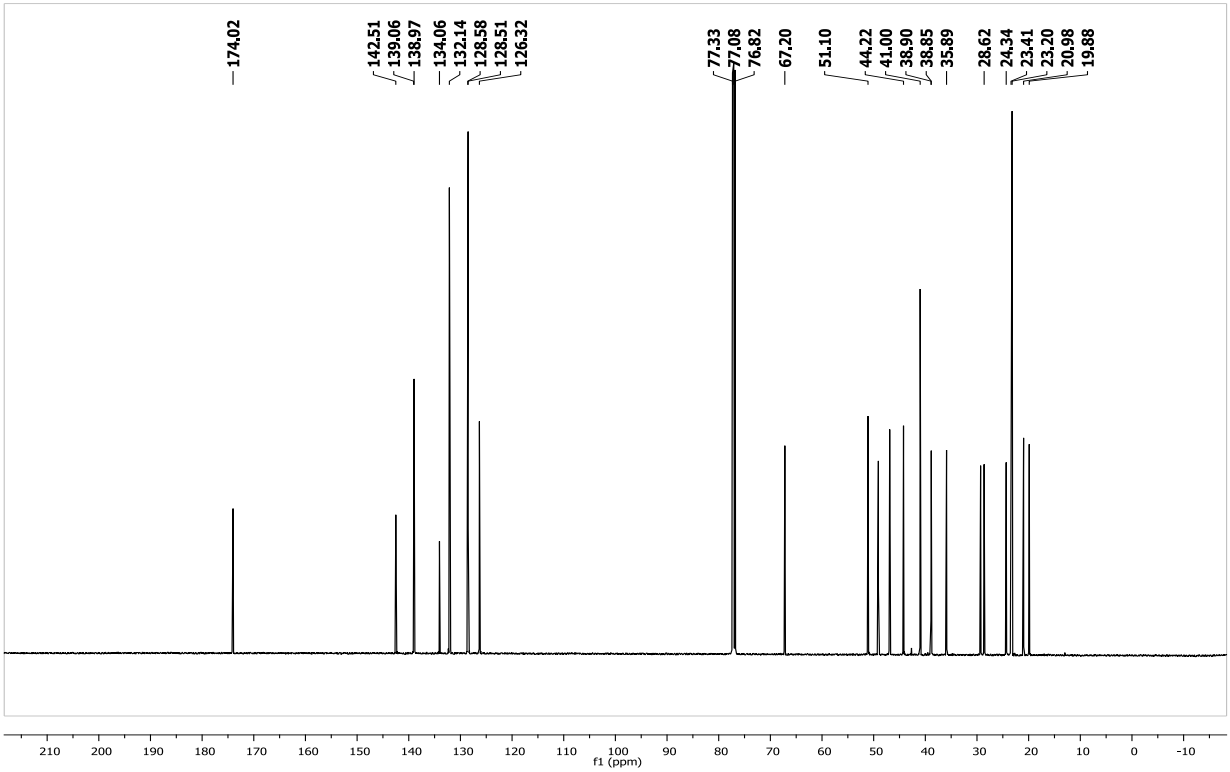
29c{*8*}


O
O
S
N
H
Cl
N
O
nPr
H
1.92
1.87
1.07
1.00
1.00
0.99
0.98
1.92
0.98
6.72
0.98
4.82
0.97
2.82
f1 (ppm)

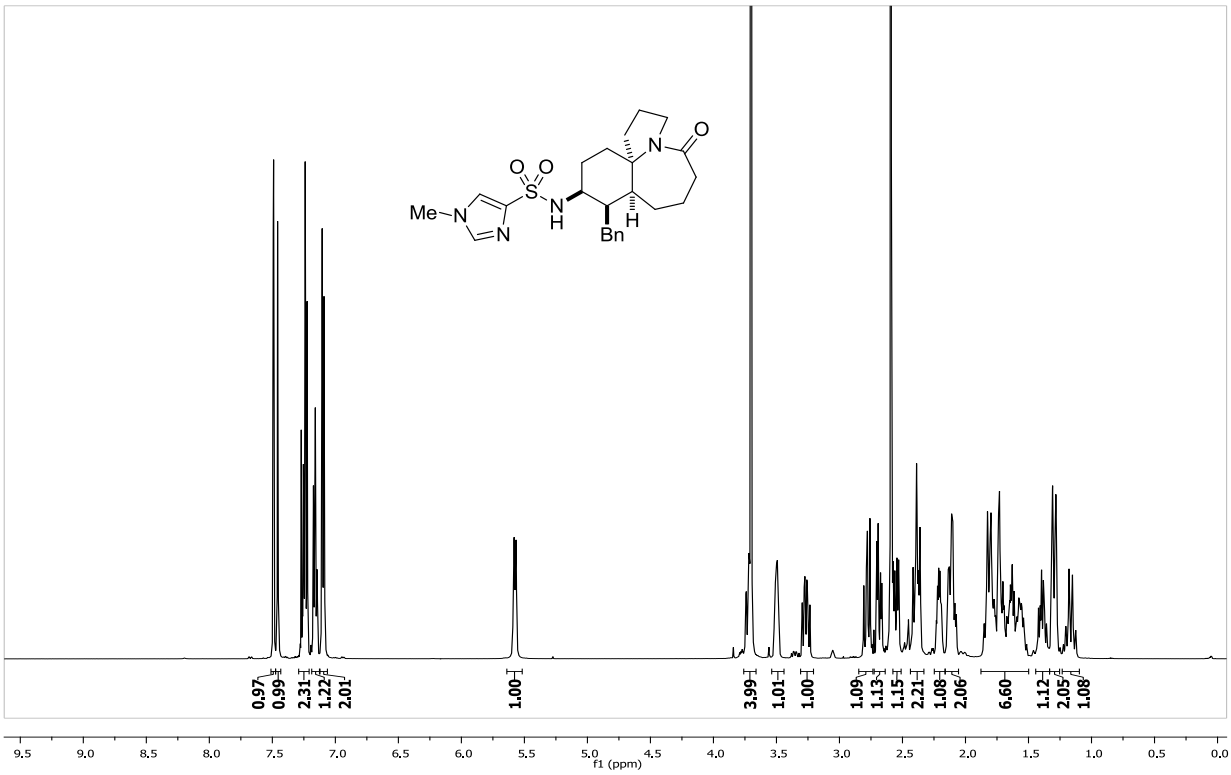

172.34
137.44
136.51
127.50
126.83
75.36
75.10
74.85
65.23
48.68
47.19
46.34
36.84
26.53
21.64
18.00
12.10
f1 (ppm)

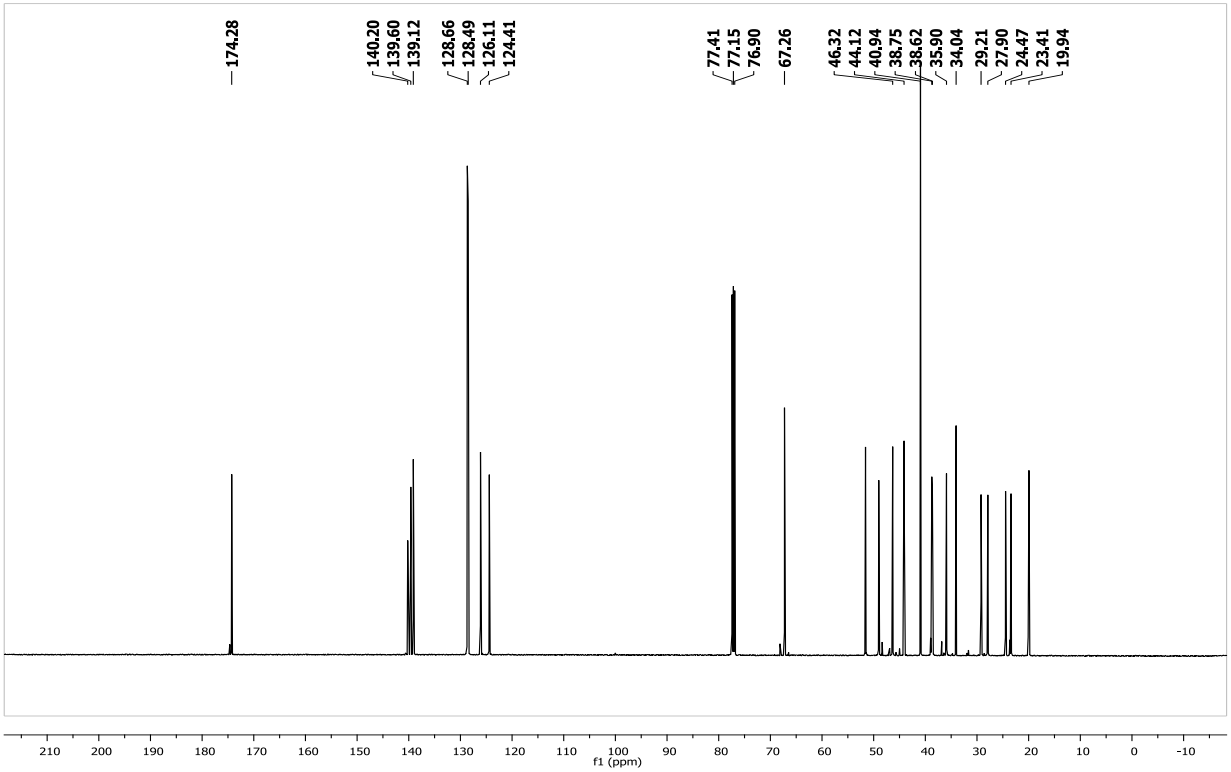
29d{*19*}


Me
O
O
S
N
H
Bn
H
N
O
Me
Me
1.88
0.96
3.76
1.01
1.00
0.99
0.98
6.13
1.09
2.91
2.87
0.99
1.00
1.04
6.09
2.95
1.07
f1 (ppm)

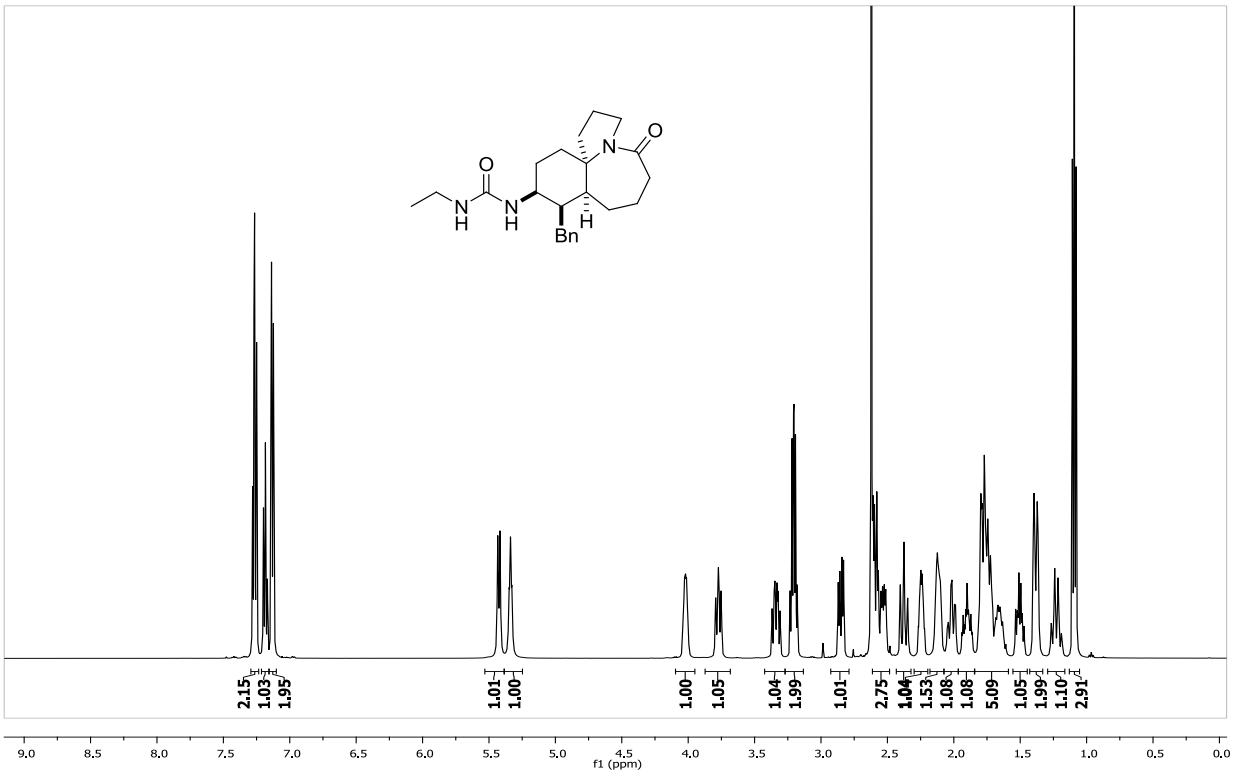

174.02
142.51
139.06
138.97
134.06
132.14
128.58
128.51
126.32
77.33
77.08
76.82
67.20
51.10
44.22
41.00
38.90
38.85
35.89
28.62
24.34
23.41
23.20
20.98
19.88
f1 (ppm)

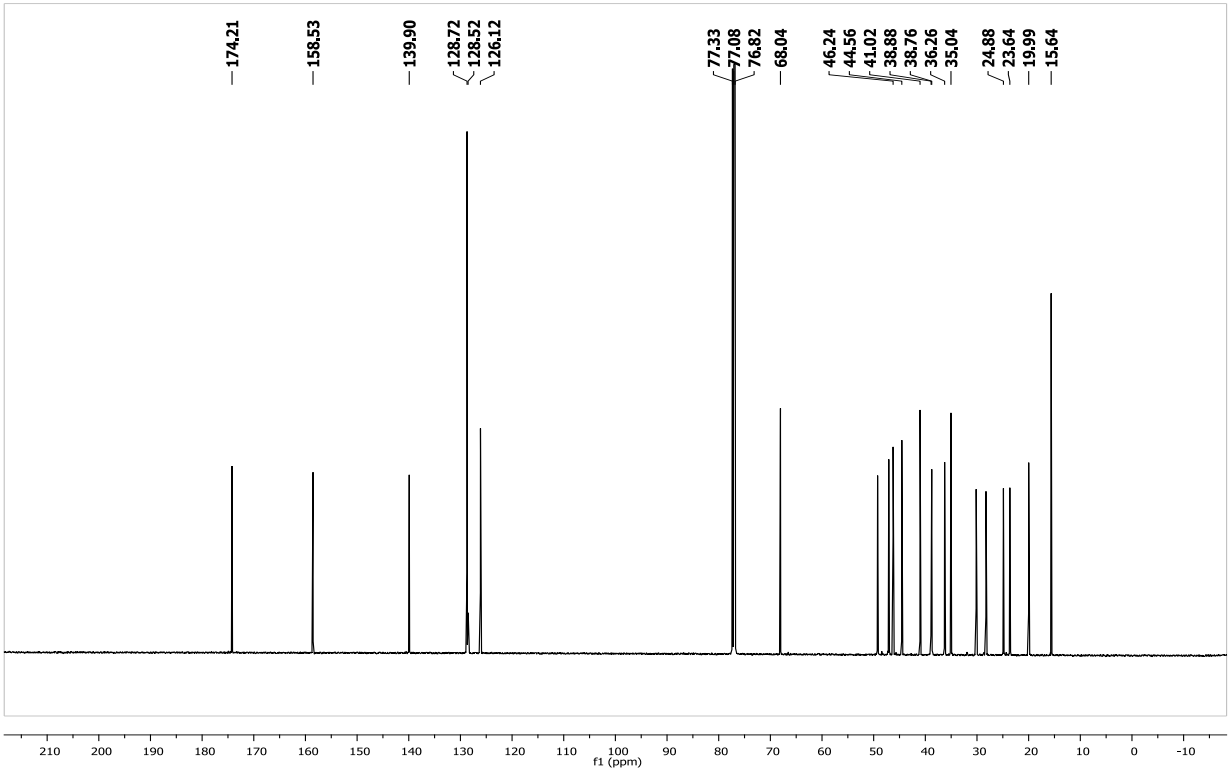
29d{*22*}


Me
N
N
O
O
S
N
H
N
O
H
Bn
0.97
0.99
2.31
1.22
2.01
1.00
3.99
1.01
1.00
1.09
1.13
1.15
2.21
1.08
2.06
6.60
1.12
2.05
1.08
f1 (ppm)

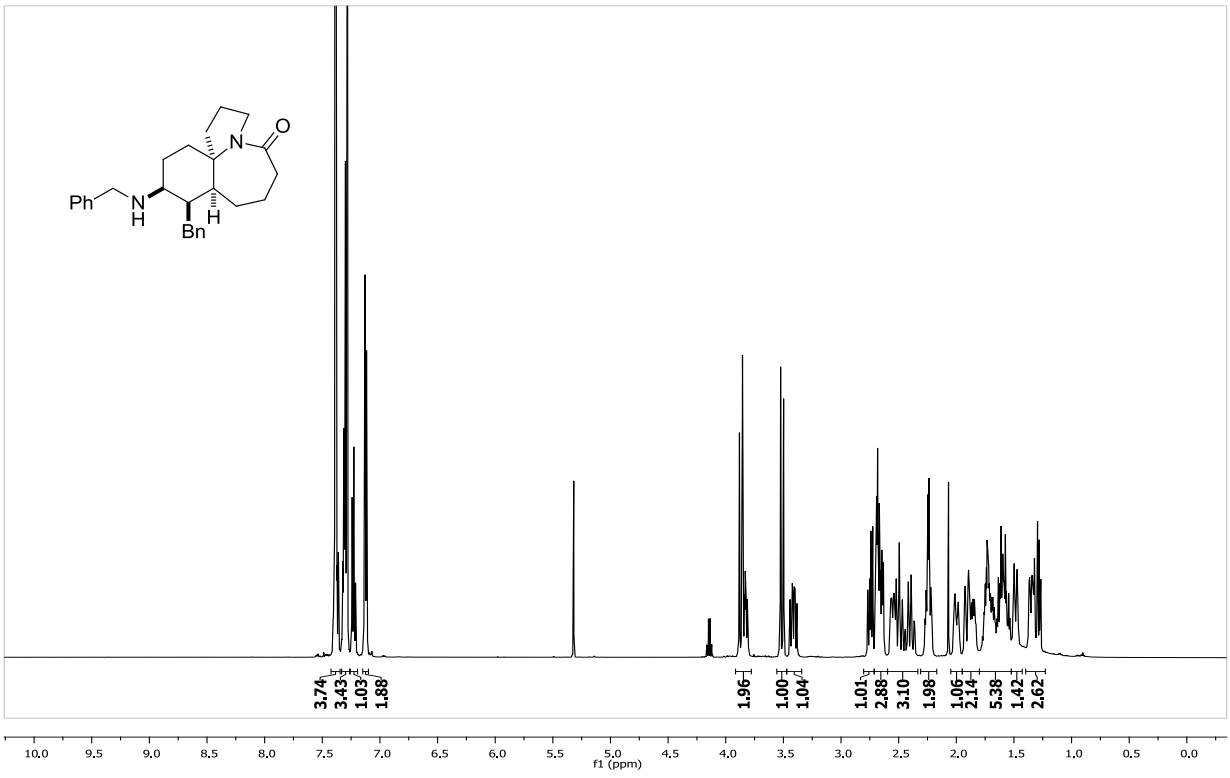

174.28
140.20
139.60
139.12
128.66
128.49
126.11
124.41
77.41
77.15
76.90
67.26
46.32
44.12
40.94
38.75
38.62
35.90
34.04
29.21
27.90
24.47
23.41
19.94
f1 (ppm)

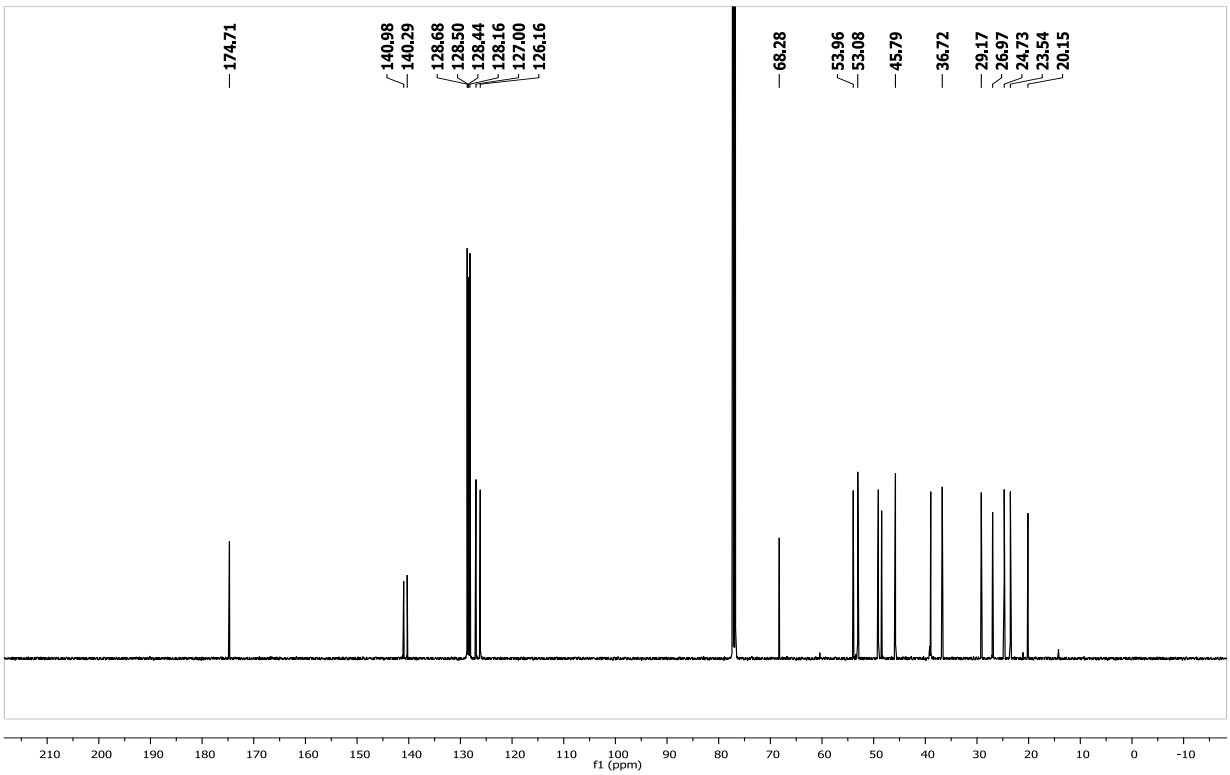
30d{*21*}


O
N
H
O
N
H
N
O
H
Bn
2.15
1.03
1.95
1.01
1.00
1.00
1.05
1.04
1.99
1.01
2.75
1.04
1.53
1.08
1.08
5.09
1.05
1.99
1.10
2.91
f1 (ppm)

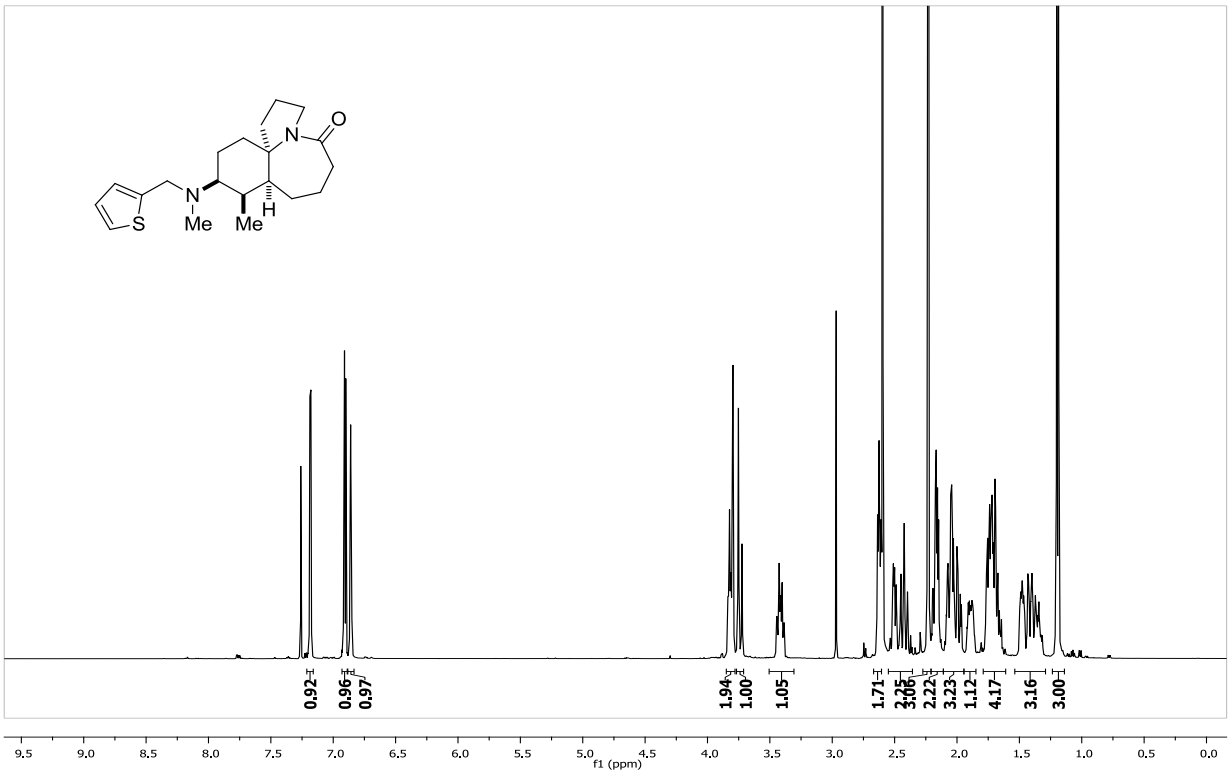

174.21
158.53
139.90
128.72
128.52
126.12
77.33
77.08
76.82
68.04
46.24
44.56
41.02
38.88
38.76
36.26
35.04
24.88
23.64
19.99
15.64
f1 (ppm)

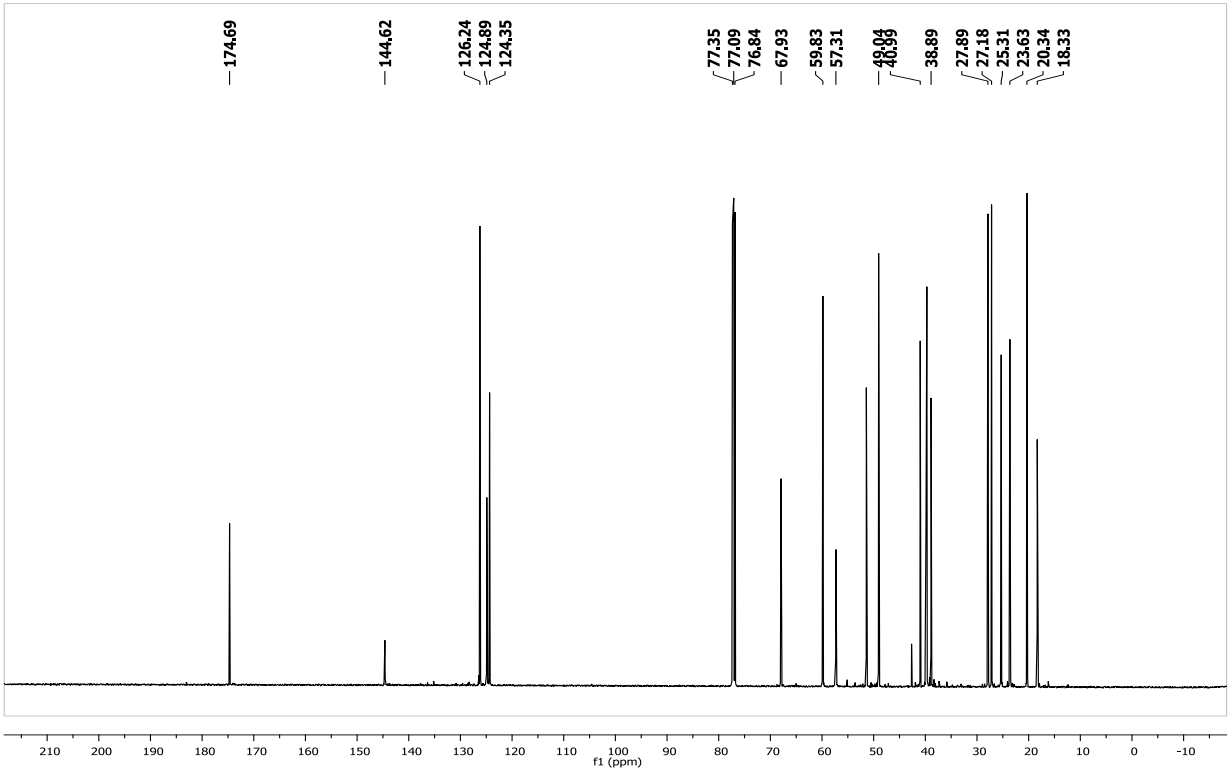
26d{*1*}


Ph
N
H
Bn
H
N
O
3.74
3.43
1.03
1.88
1.96
1.00
1.04
1.01
2.88
3.10
1.98
1.06
2.14
5.38
1.42
2.62
f1 (ppm)

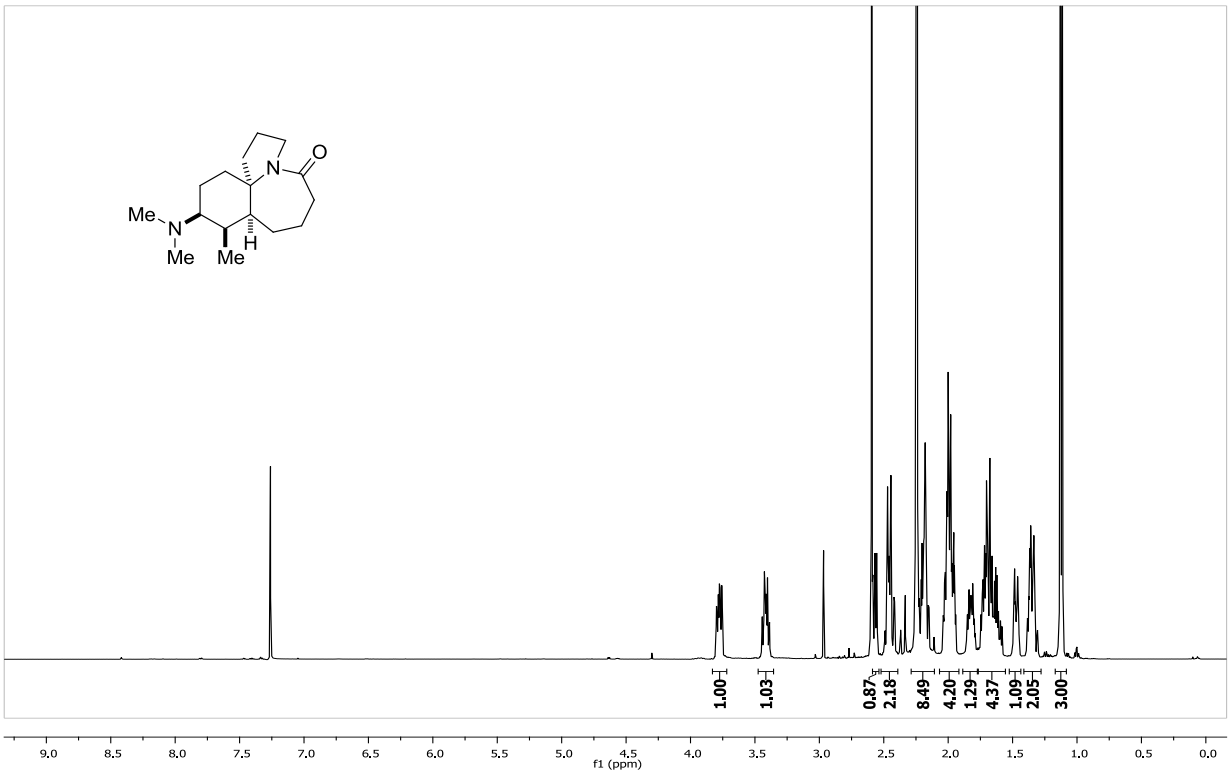

174.71
140.98
140.29
128.68
128.50
128.44
128.16
127.00
126.16
68.28
53.96
53.08
45.79
36.72
29.17
26.97
24.73
23.54
20.15
f1 (ppm)

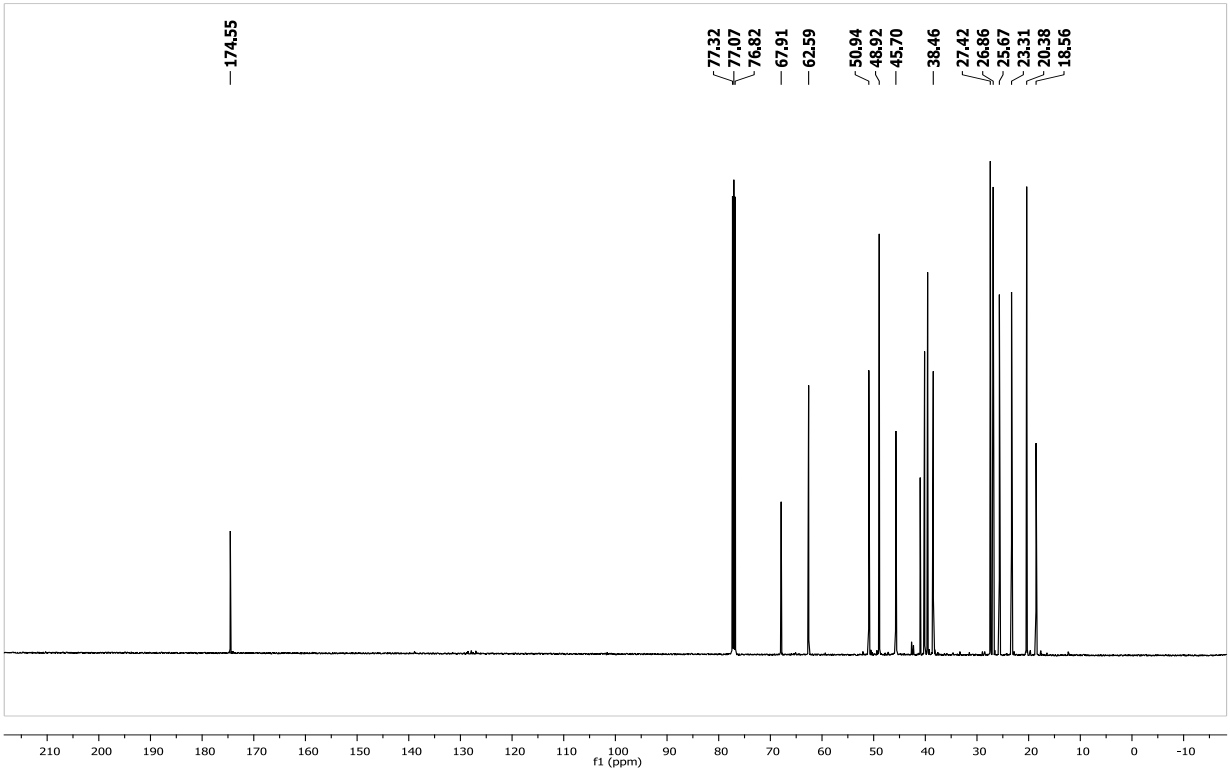
32b{*2*}


N
O
N
Me
Me
H
S
0.92
0.96
0.97
1.94
1.00
1.05
1.71
2.25
3.06
2.22
3.23
1.12
4.17
3.16
3.00
f1 (ppm)


174.69
144.62
126.24
124.89
124.35
77.35
77.09
76.84
67.93
59.83
57.31
49.04
40.99
38.89
27.89
27.18
25.31
23.63
20.34
18.33
f1 (ppm)

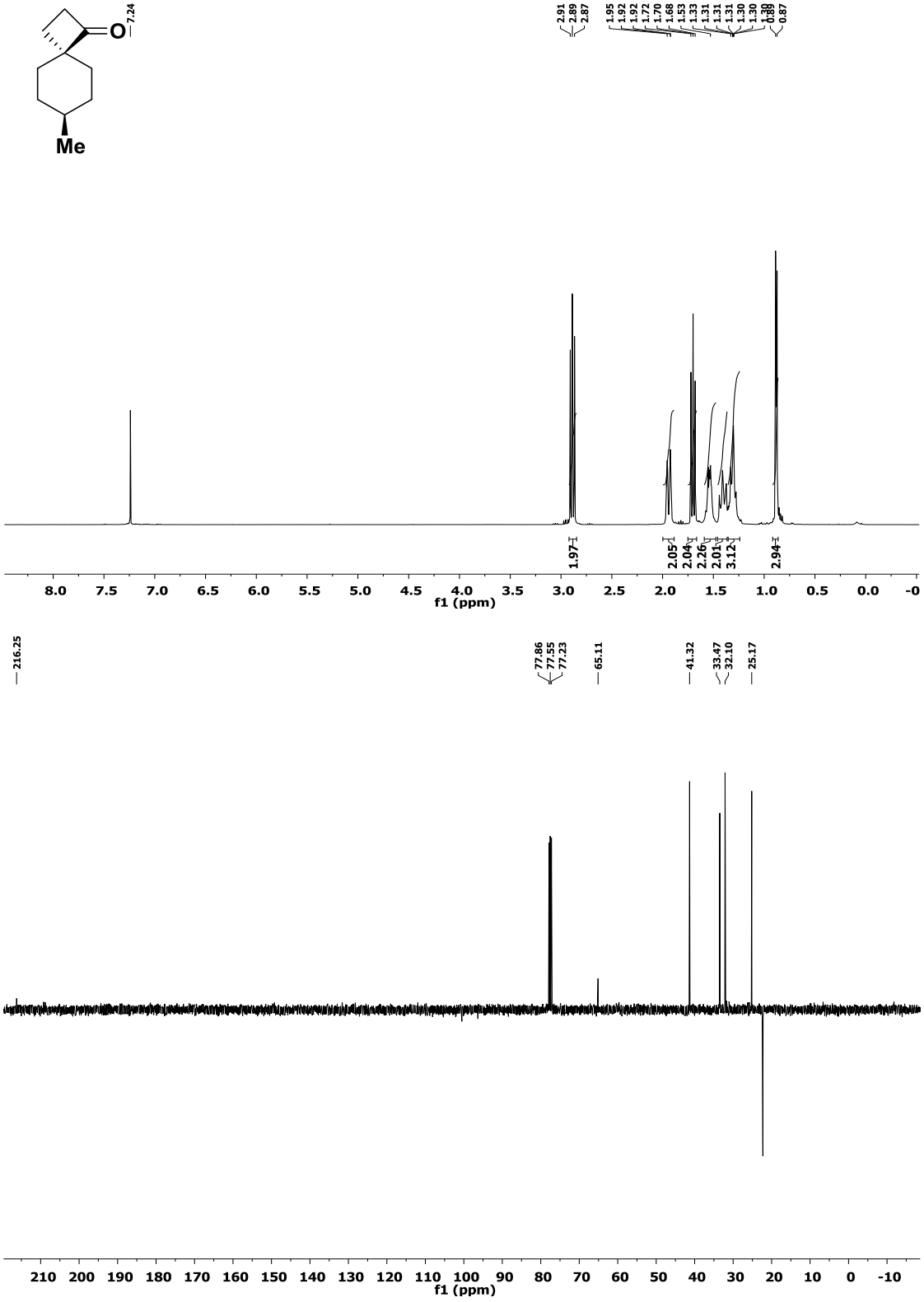
31b


Me
N
Me
Me
H
O
N
1.00
1.03
0.87
2.18
8.49
4.20
1.29
4.37
1.09
2.05
3.00
f1 (ppm)

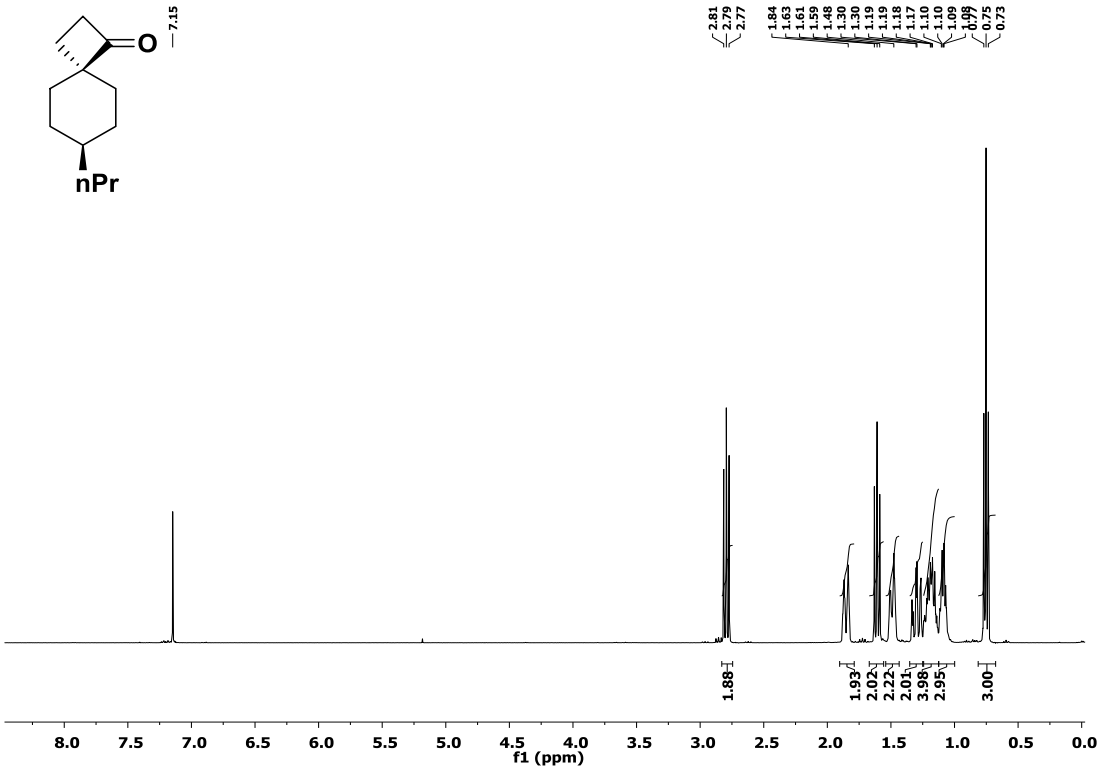

174.55
77.32
77.07
76.82
67.91
62.59
50.94
48.92
45.70
38.46
27.42
26.86
25.67
23.31
20.38
18.56
f1 (ppm)

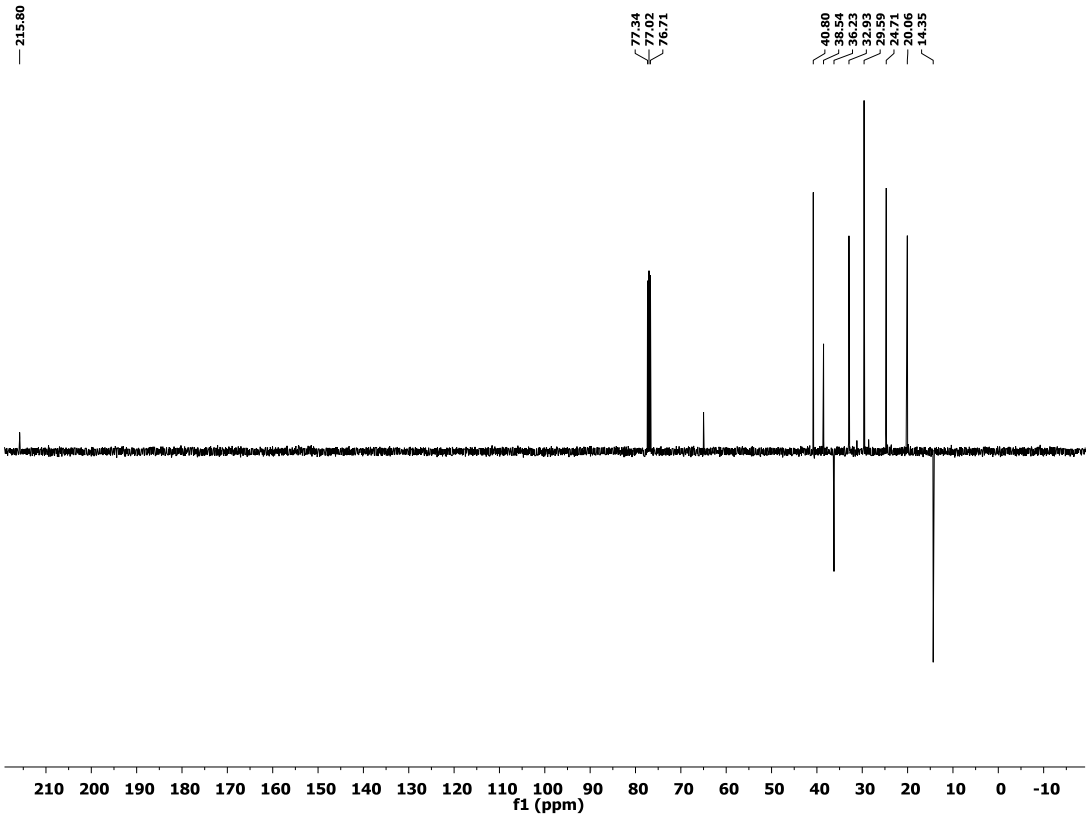
Cylindricine-inspired series

Ketone **6b**

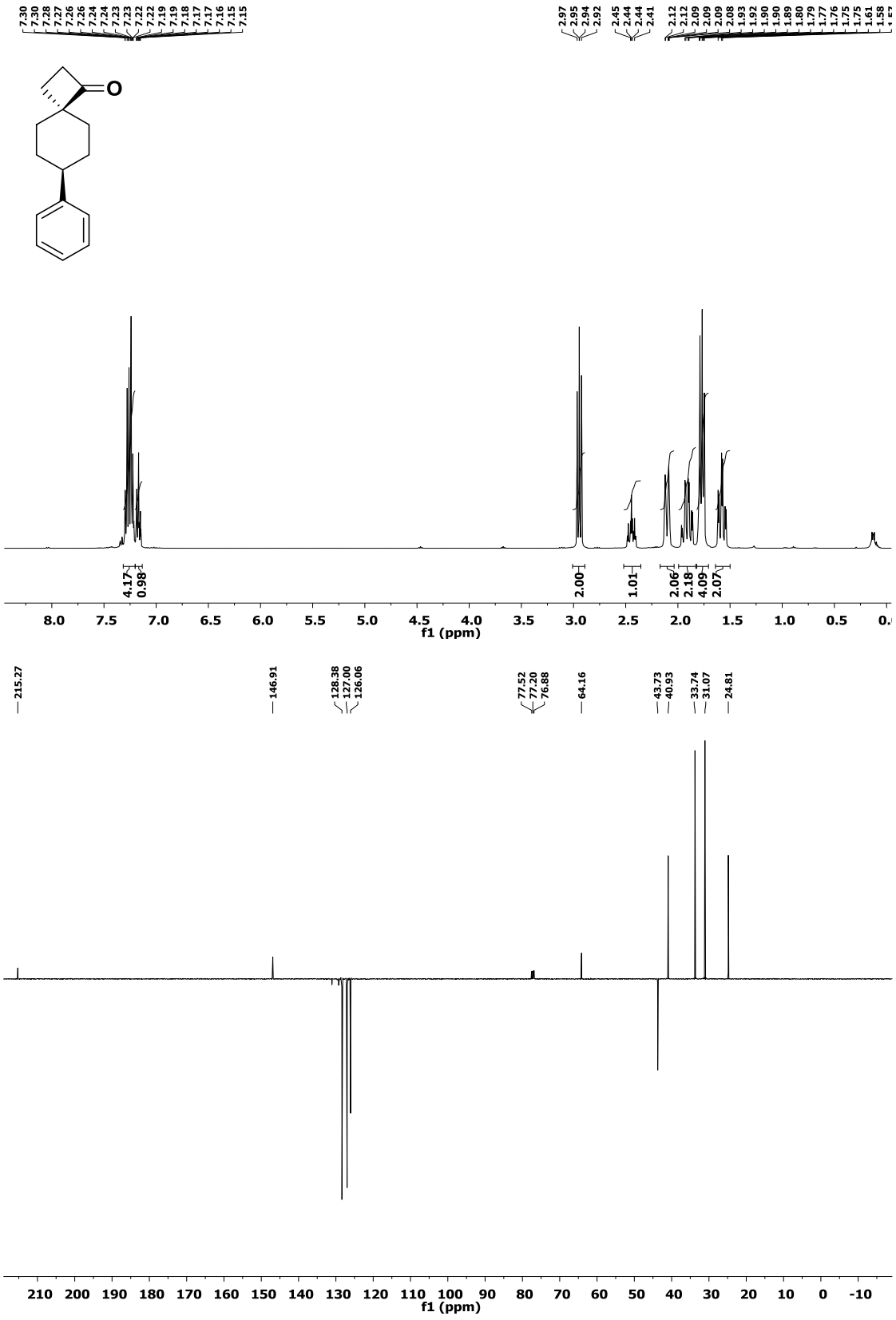


Ketone **6c**

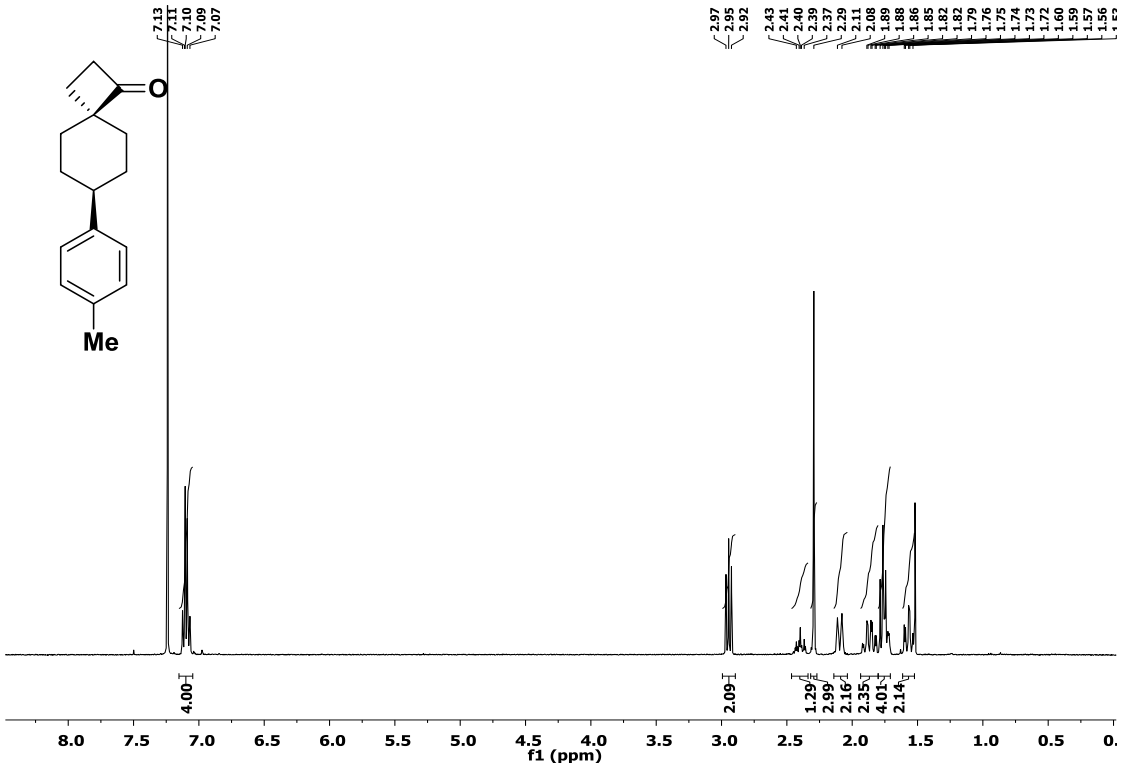

O
nPr
7.15
2.81
2.79
2.77
1.84
1.63
1.61
1.59
1.48
1.30
1.19
1.18
1.17
1.10
1.09
1.08
0.77
0.75
0.73
1.88
1.93
2.02
2.22
2.01
3.98
2.95
3.00
f1 (ppm)

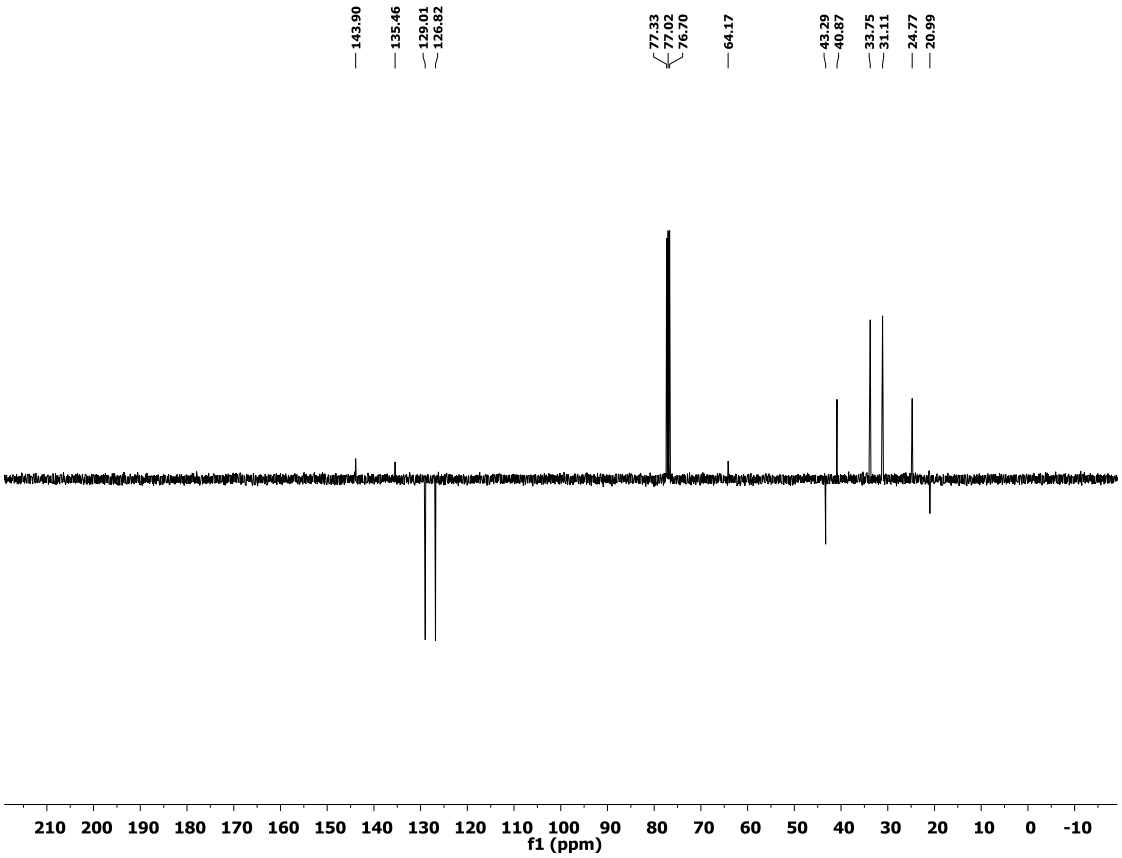

215.80
77.34
77.02
76.71
40.80
38.54
36.23
32.93
29.59
24.71
20.06
14.35
f1 (ppm)

Ketone **6d**

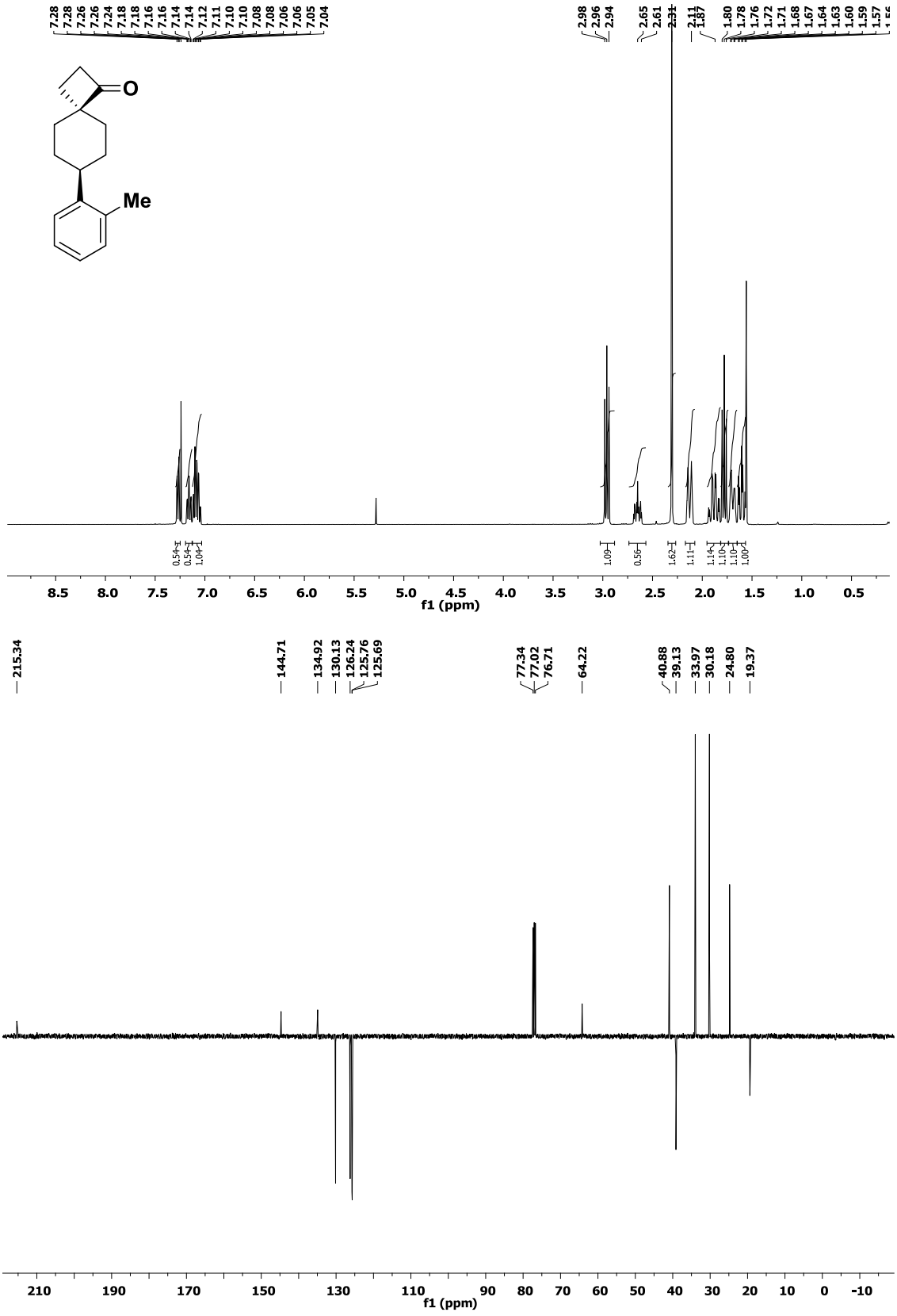

7.30 7.30 7.28 7.27 7.26 7.26 7.24 7.24 7.23 7.22 7.22 7.19 7.19 7.18 7.17 7.17 7.16 7.15 7.15
2.97 2.95 2.94 2.92 2.45 2.44 2.44 2.41 2.12 2.12 2.05 2.09 2.09 2.08 1.93 1.92 1.90 1.90 1.89 1.80 1.79 1.77 1.76 1.75 1.75 1.61 1.58
O
4.17 0.98 2.00 1.01 2.06 2.18 4.09 2.07
f1 (ppm)
215.27 146.91 128.38 127.00 126.06 77.52 77.20 76.88 64.16 43.73 40.93 33.74 31.07 24.81
f1 (ppm)

Ketone **6e**

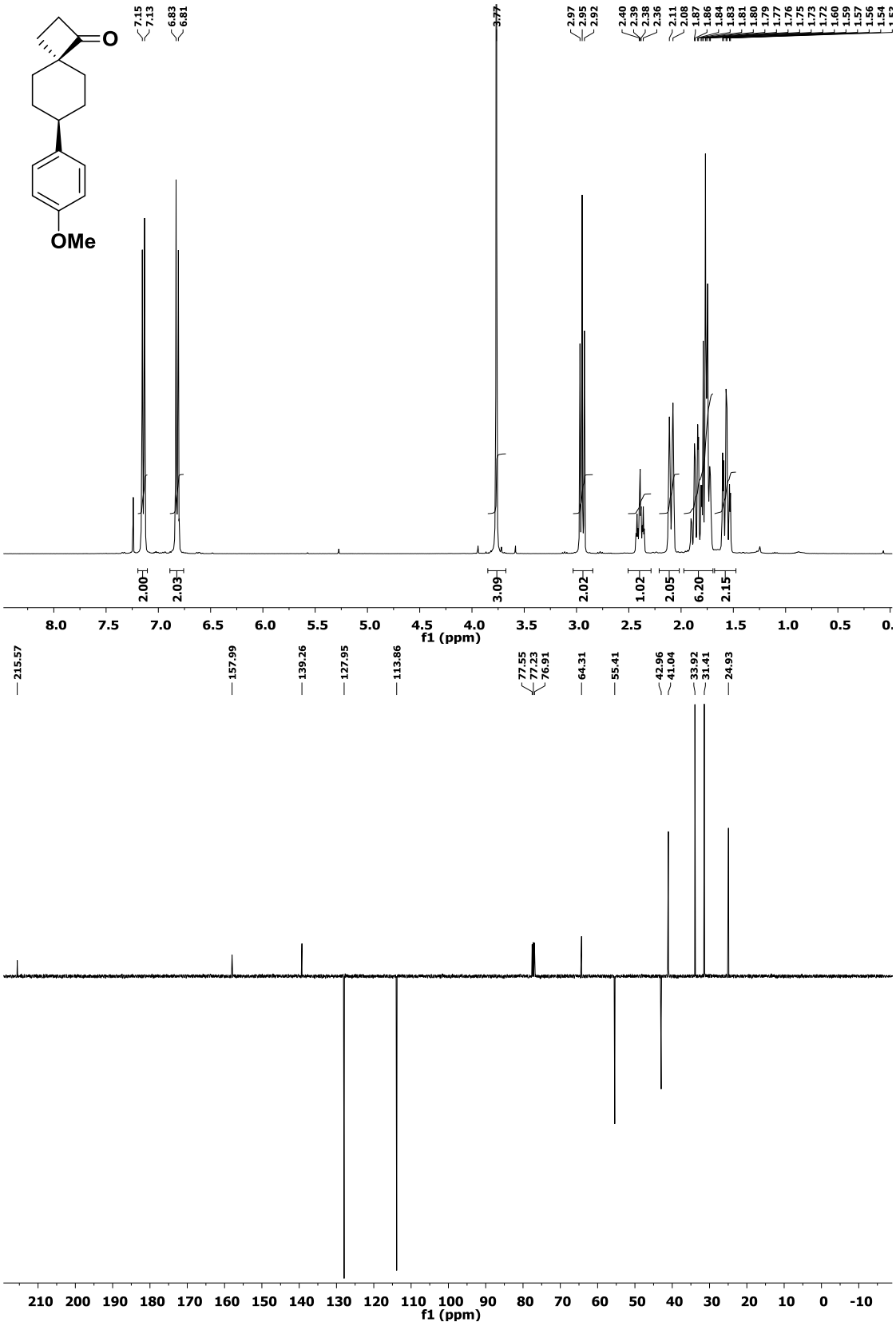

O
Me
7.13
7.11
7.10
7.09
7.07
2.97
2.95
2.92
2.43
2.41
2.40
2.39
2.37
2.29
2.11
2.08
1.89
1.88
1.86
1.85
1.82
1.79
1.76
1.75
1.74
1.73
1.72
1.60
1.59
1.57
1.56
4.00
2.09
1.29
2.99
2.16
2.35
4.01
2.14
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


143.90
135.46
129.01
126.82
77.33
77.02
76.70
64.17
43.29
40.87
33.75
31.11
24.77
20.99
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

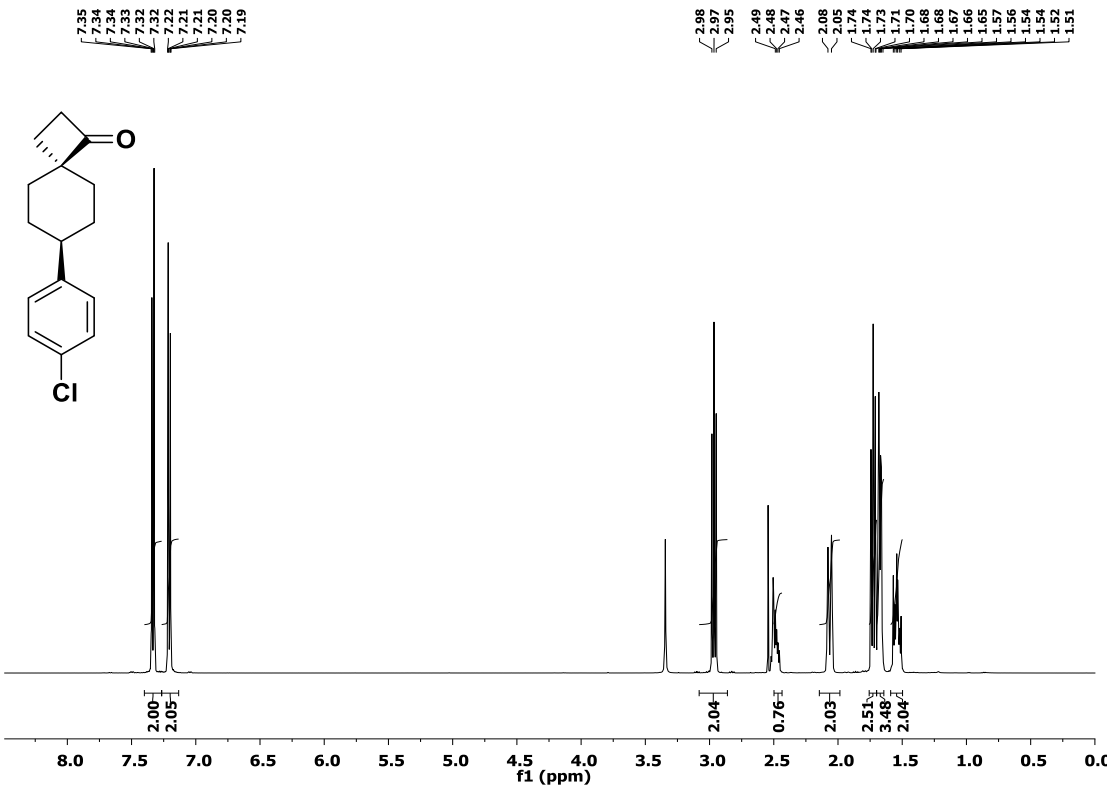
Ketone **6f**

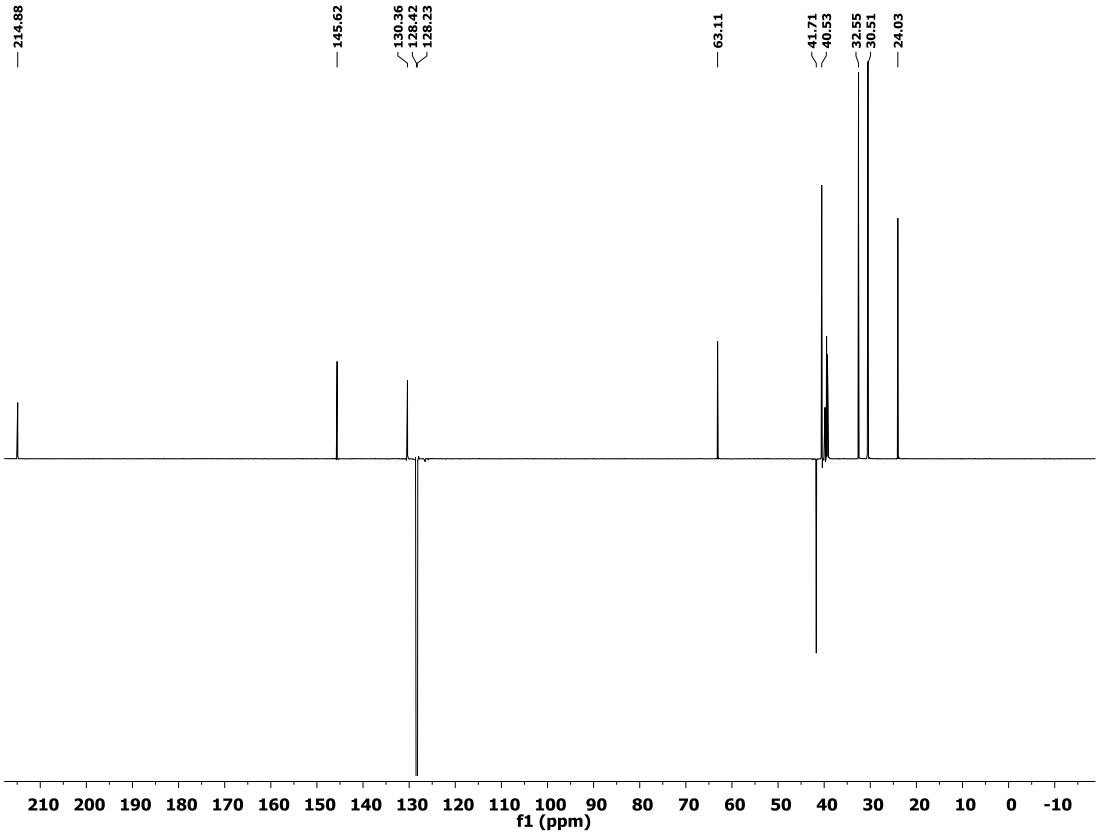


Ketone **6g**

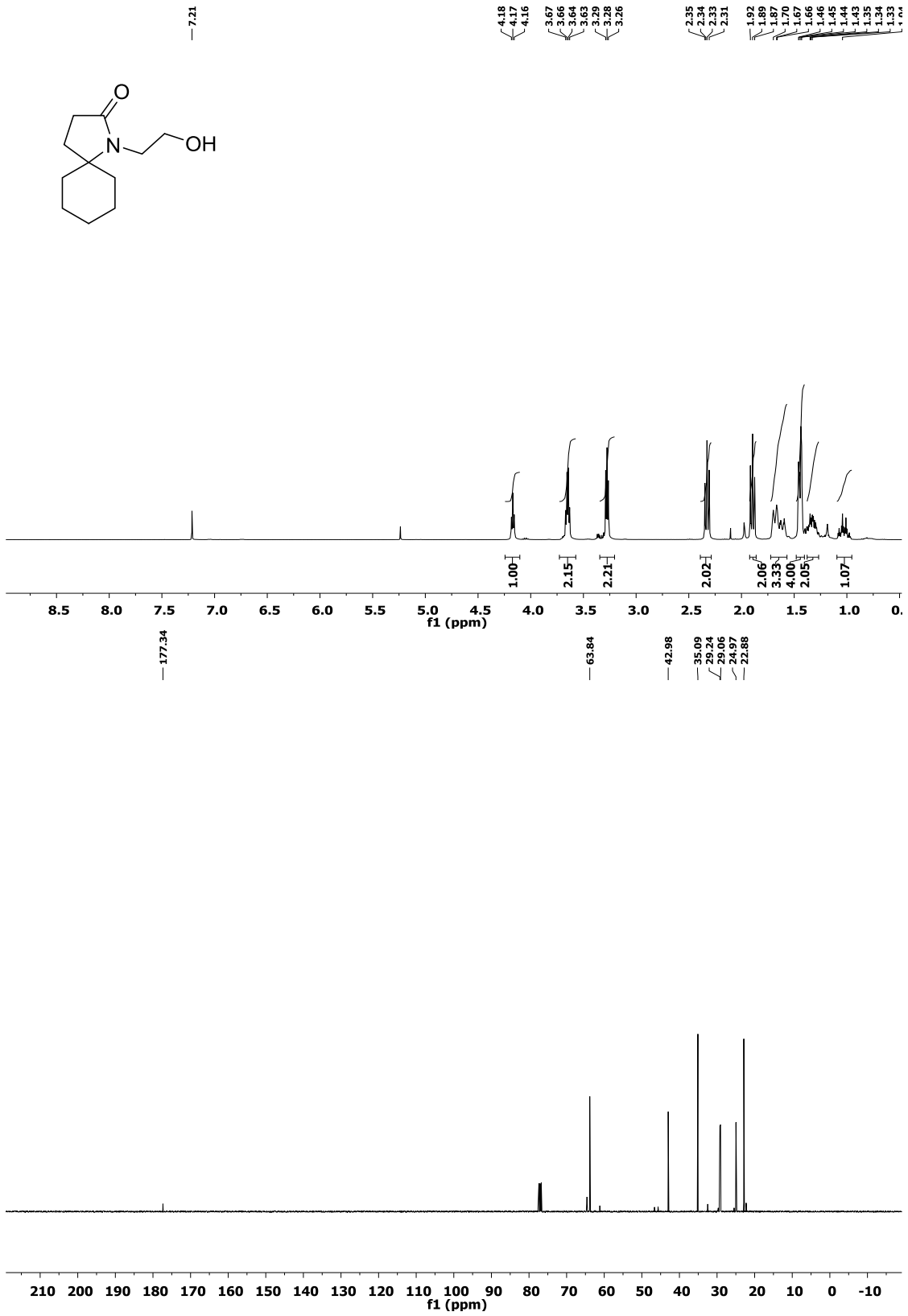

O
OMe
7.15
7.13
6.83
6.81
3.77
2.97
2.95
2.92
2.40
2.39
2.38
2.36
2.11
2.08
2.00
2.03
3.09
2.02
1.02
2.05
6.20
2.15
f1 (ppm)
215.57
157.99
139.26
127.95
113.86
77.55
77.23
76.91
64.31
55.41
42.96
41.04
33.92
31.41
24.93
f1 (ppm)

Ketone **6h**

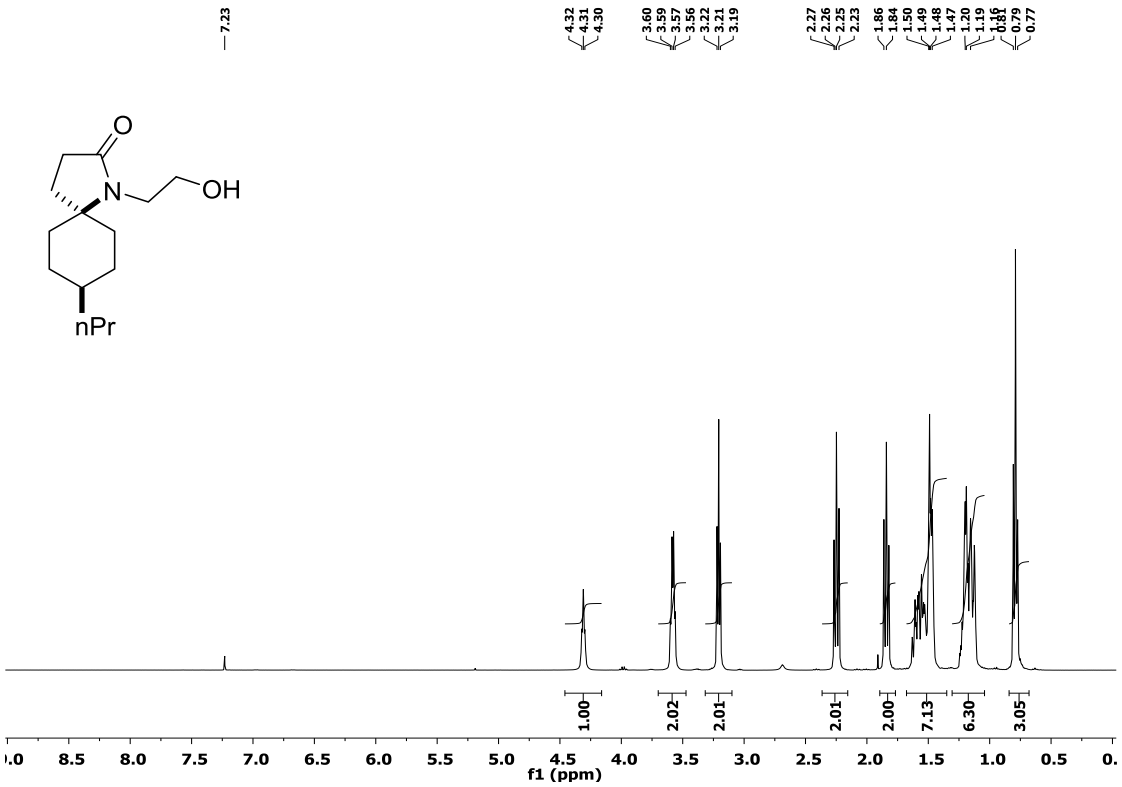

7.35
7.34
7.34
7.33
7.32
7.32
7.22
7.21
7.21
7.20
7.20
7.19
2.98
2.97
2.95
2.49
2.48
2.47
2.46
2.08
2.05
1.74
1.74
1.73
1.71
1.70
1.68
1.68
1.67
1.66
1.65
1.57
1.56
1.54
1.54
1.52
1.51
O
Cl
2.00
2.05
2.04
0.76
2.03
2.51
3.48
2.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

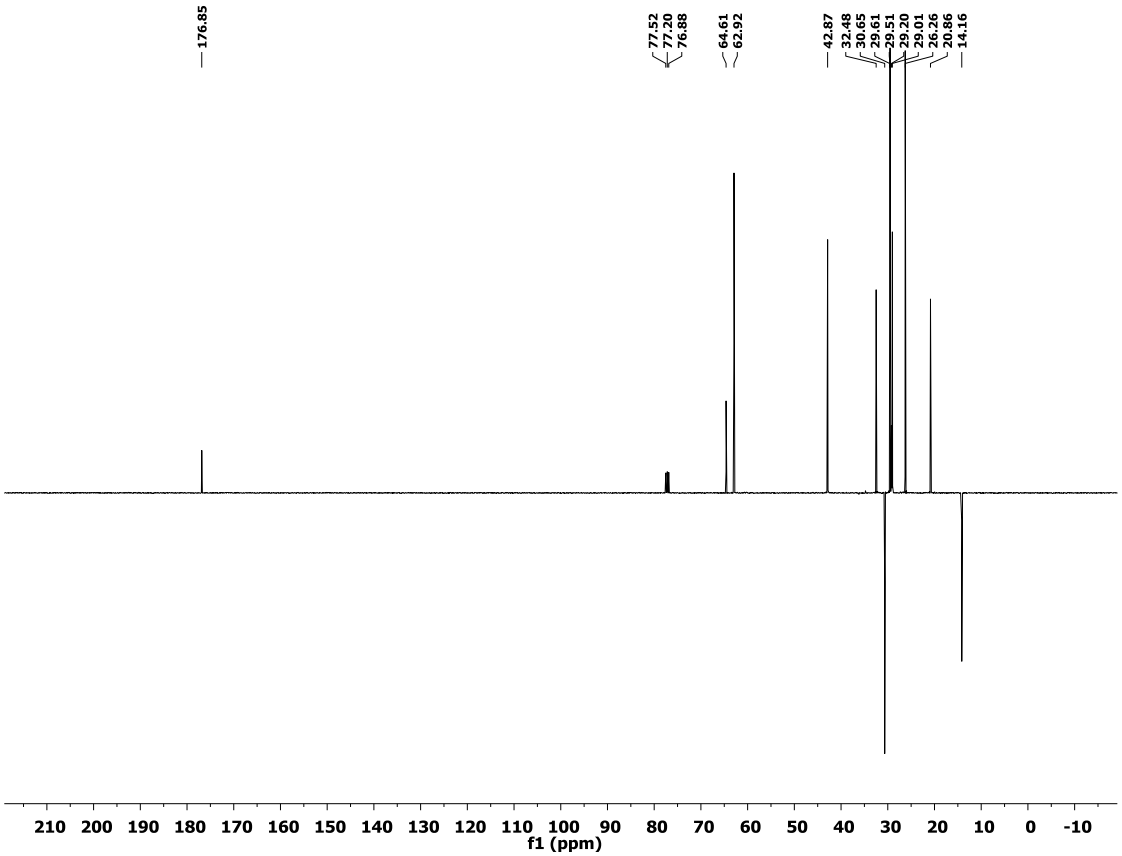

214.88
145.62
130.36
128.42
128.23
63.11
41.71
40.53
32.55
30.51
24.03
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Lactam **8aa**

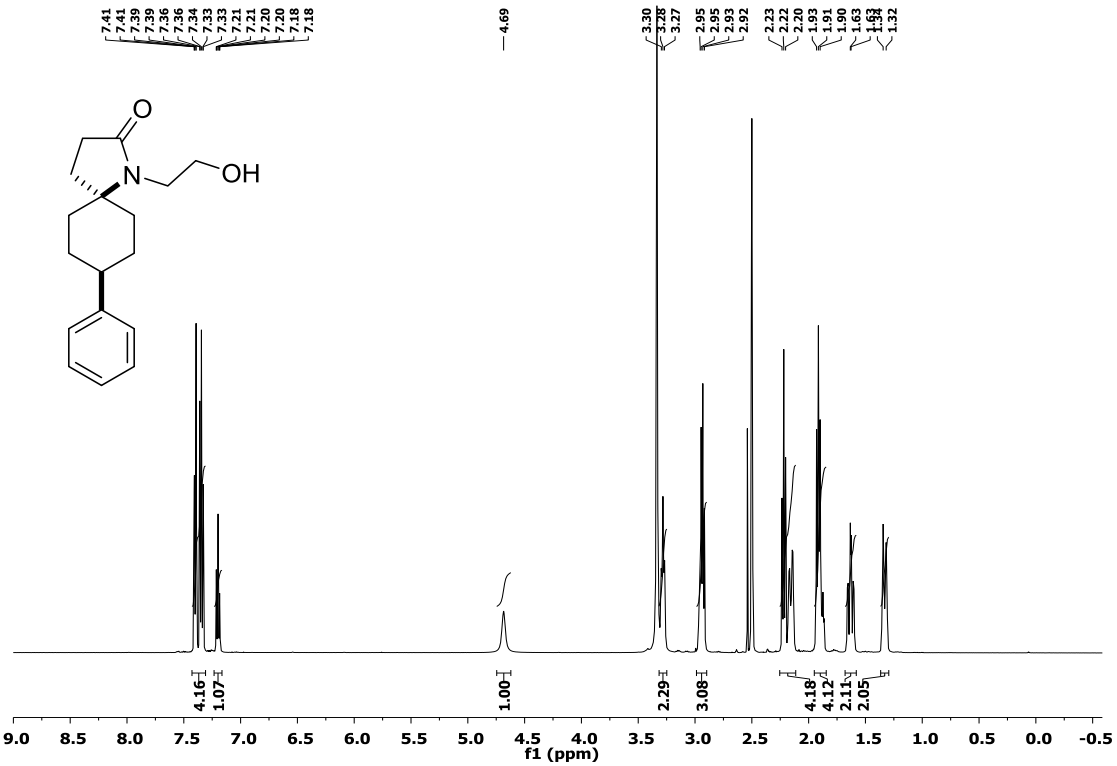

7.21
4.18
4.17
4.16
3.67
3.66
3.64
3.63
3.29
3.28
3.26
2.35
2.34
2.33
2.31
1.92
1.89
1.87
1.70
1.67
1.66
1.46
1.45
1.44
1.43
1.35
1.34
1.33
O
N
OH
1.00
2.15
2.21
2.02
2.06
3.33
4.00
2.05
1.07
f1 (ppm)
177.34
63.84
42.98
35.09
29.24
29.06
24.97
22.88
f1 (ppm)

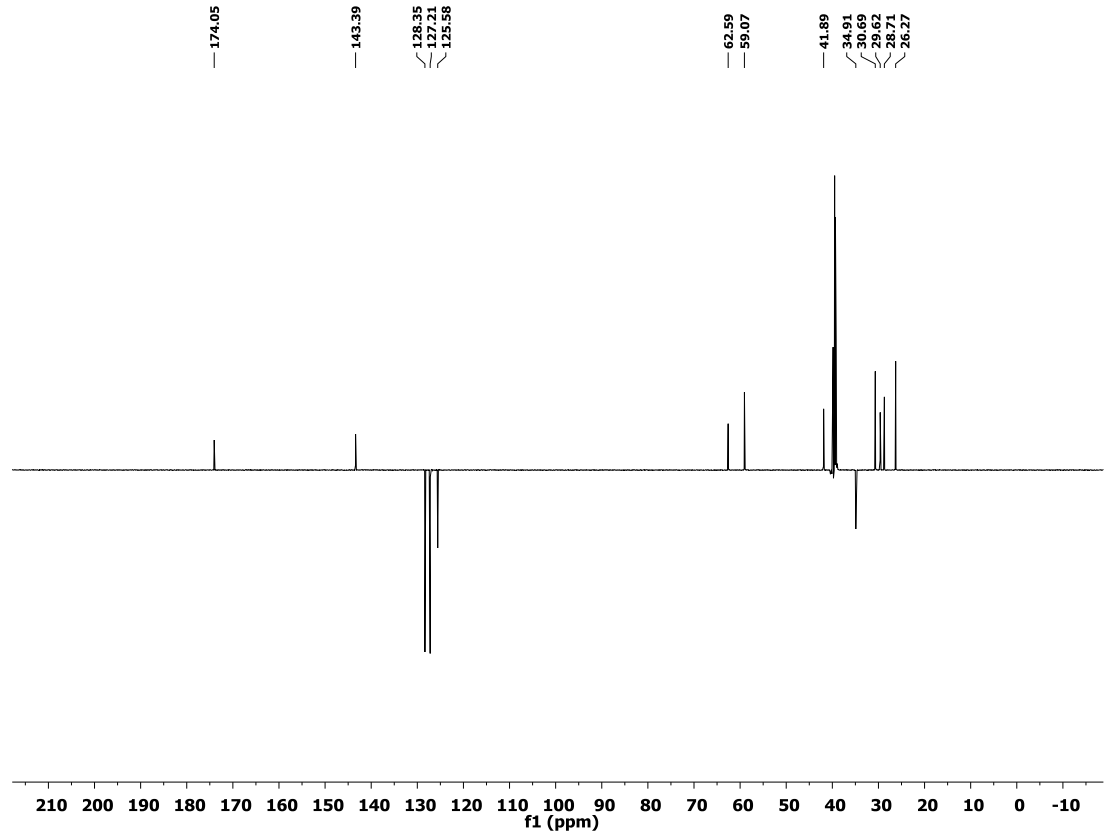
Lactam **8ca**


7.23
4.32
4.31
4.30
3.60
3.59
3.57
3.56
3.22
3.21
3.19
2.27
2.26
2.25
2.23
1.86
1.84
1.50
1.49
1.48
1.47
1.20
1.19
1.16
0.81
0.79
0.77
O
N
OH
nPr
1.00
2.02
2.01
2.01
2.00
7.13
6.30
3.05
f1 (ppm)

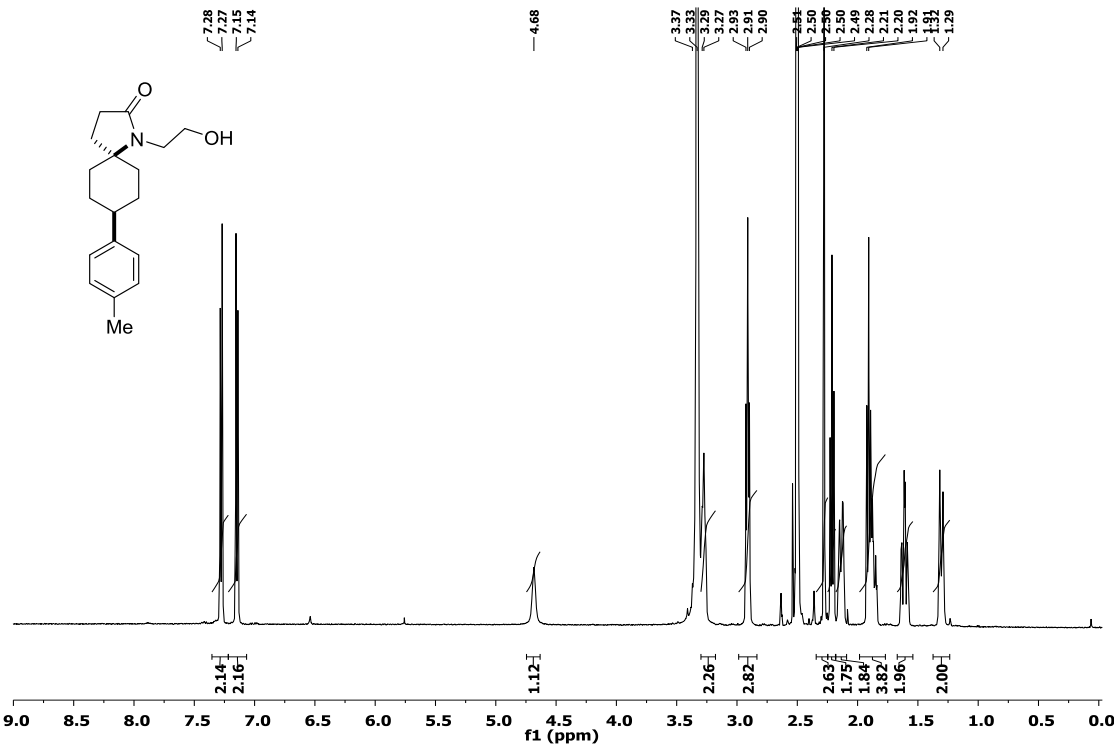

176.85
77.52
77.20
76.88
64.61
62.92
42.87
32.48
30.65
29.61
29.51
29.20
29.01
26.26
20.86
14.16
f1 (ppm)

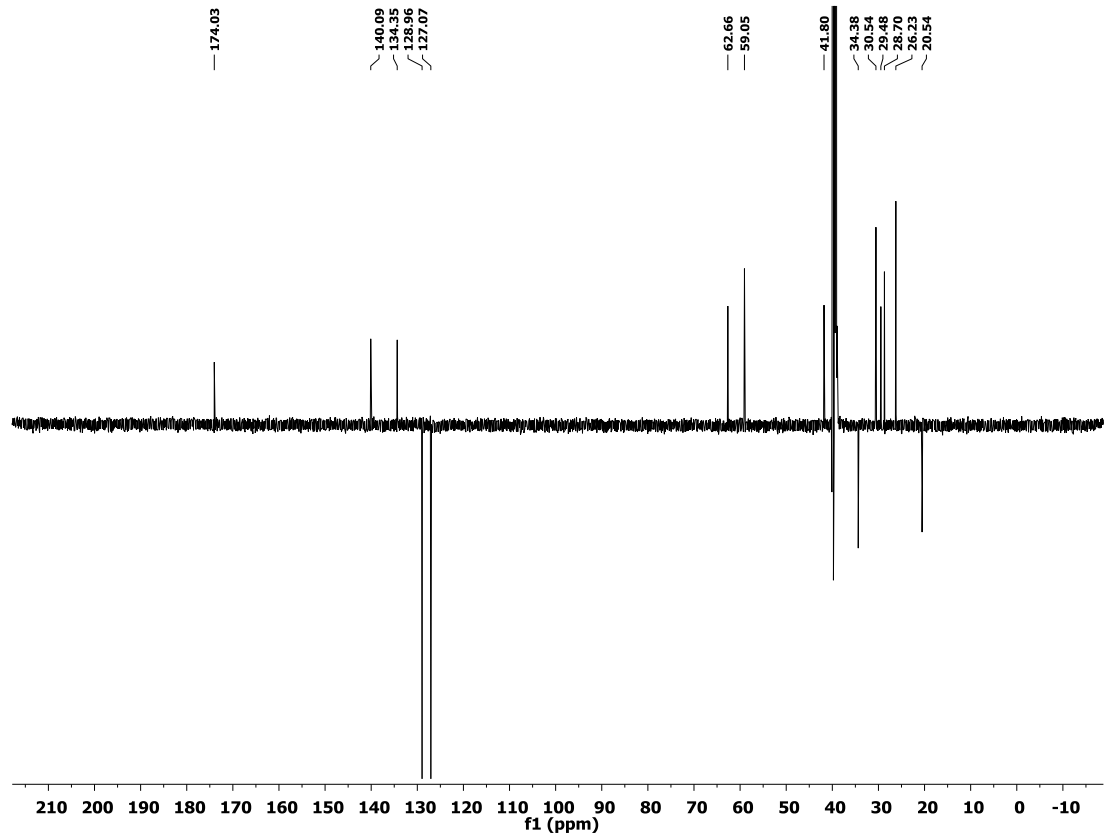
Lactam **8da**


7.41
7.41
7.39
7.39
7.36
7.36
7.34
7.33
7.33
7.21
7.21
7.20
7.20
7.18
7.18
4.69
3.30
3.28
3.27
2.95
2.95
2.93
2.92
2.23
2.22
2.20
1.93
1.91
1.90
1.63
1.32
O
N
OH
4.16
1.07
1.00
2.29
3.08
4.18
4.12
2.11
2.05
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

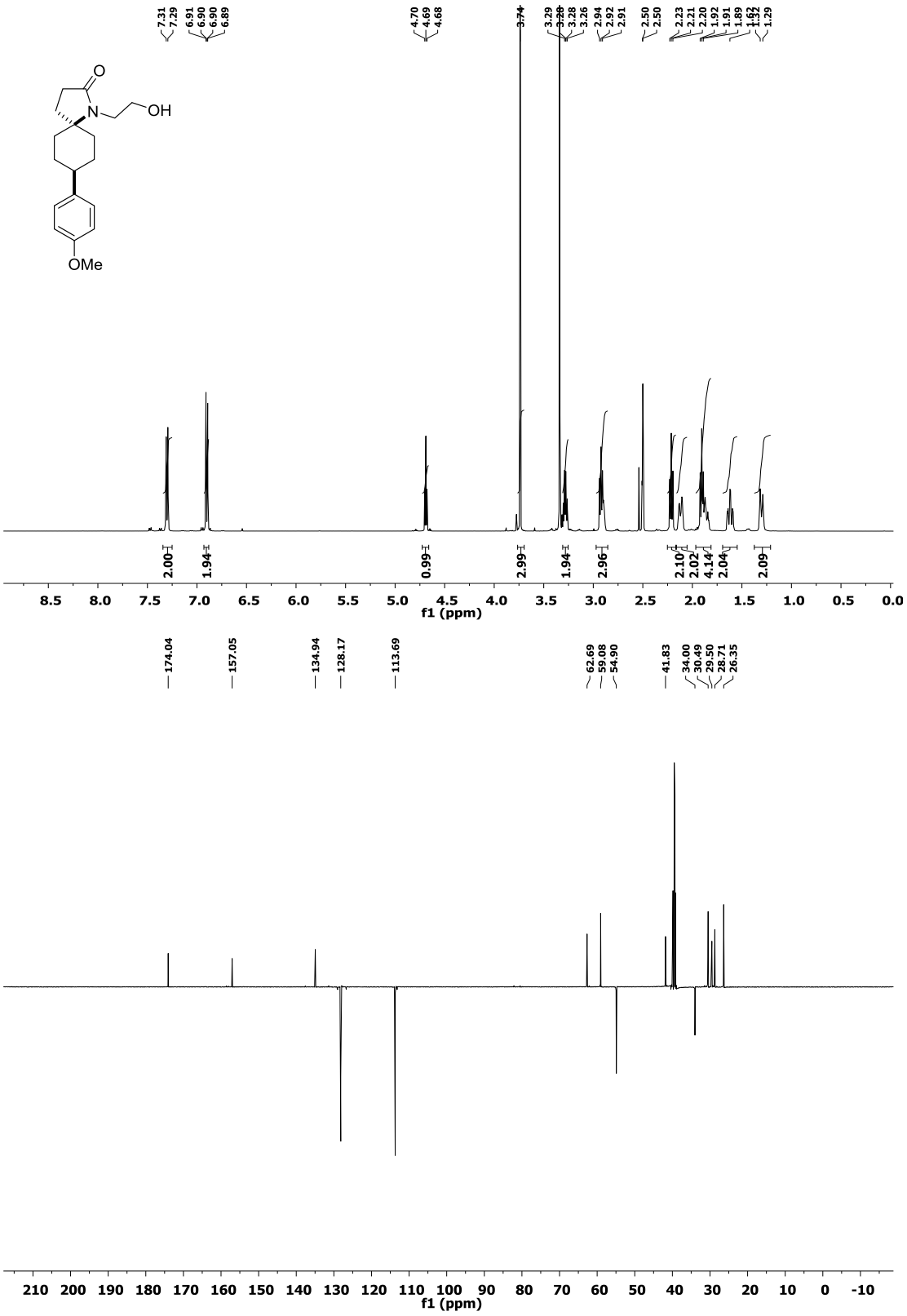

174.05
143.39
128.35
127.21
125.58
62.59
59.07
41.89
34.91
30.69
29.62
28.71
26.27
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Lactam **8ea**

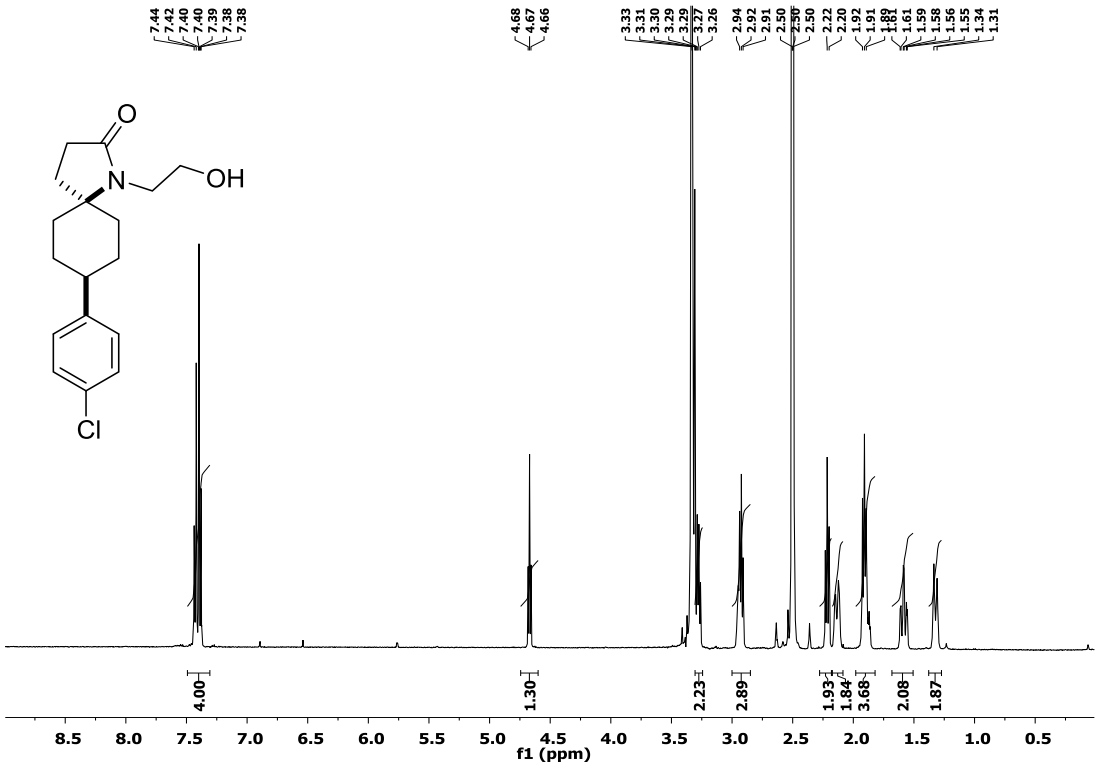

7.28
7.27
7.15
7.14
4.68
3.37
3.33
3.29
3.27
2.93
2.91
2.90
2.51
2.50
2.50
2.49
2.28
2.21
2.20
1.92
1.31
1.29
O
N
OH
Me
2.14
2.16
1.12
2.26
2.82
2.63
1.75
1.84
3.82
1.96
2.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

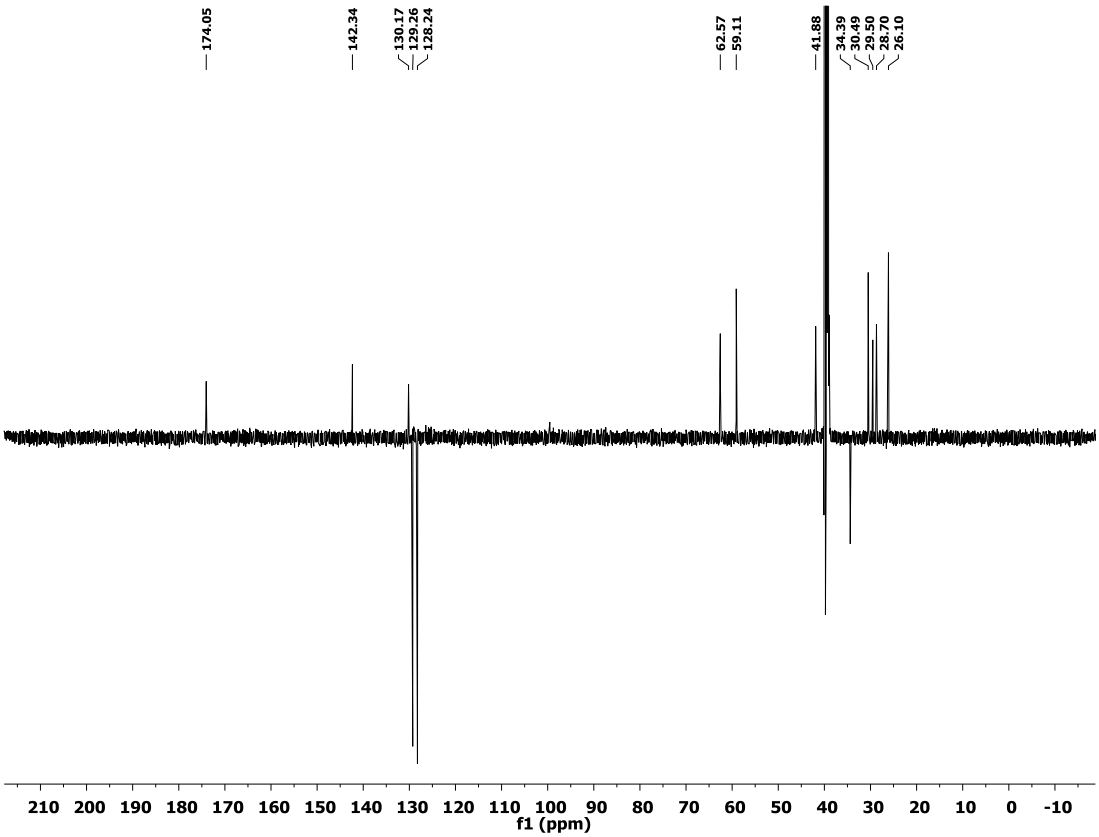

174.03
140.09
134.35
128.96
127.07
62.66
59.05
41.80
34.38
30.54
29.48
28.70
26.23
20.54
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Lactam **8ga**

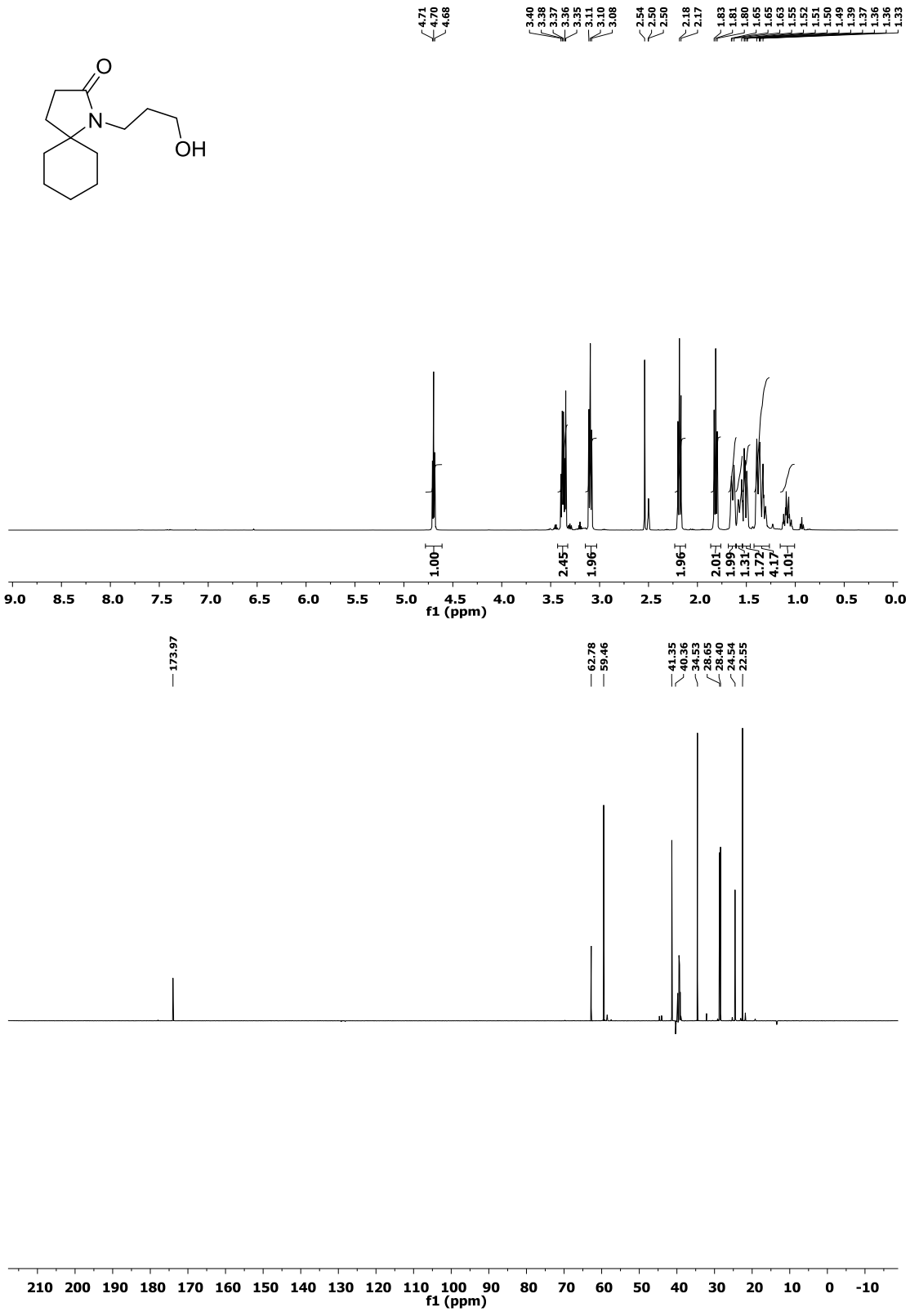

O
N
OH
OMe
7.31
7.29
6.91
6.90
6.90
6.89
4.70
4.69
4.68
3.74
3.29
3.28
3.28
3.26
2.94
2.92
2.91
2.50
2.50
2.23
2.21
2.20
1.92
1.91
1.89
1.32
1.29
2.00
1.94
0.99
2.99
1.94
2.96
2.10
2.02
4.14
2.04
2.09
f1 (ppm)
174.04
157.05
134.94
128.17
113.69
62.69
59.08
54.90
41.83
34.00
30.49
29.50
28.71
26.35
f1 (ppm)

Lactam **8ha**

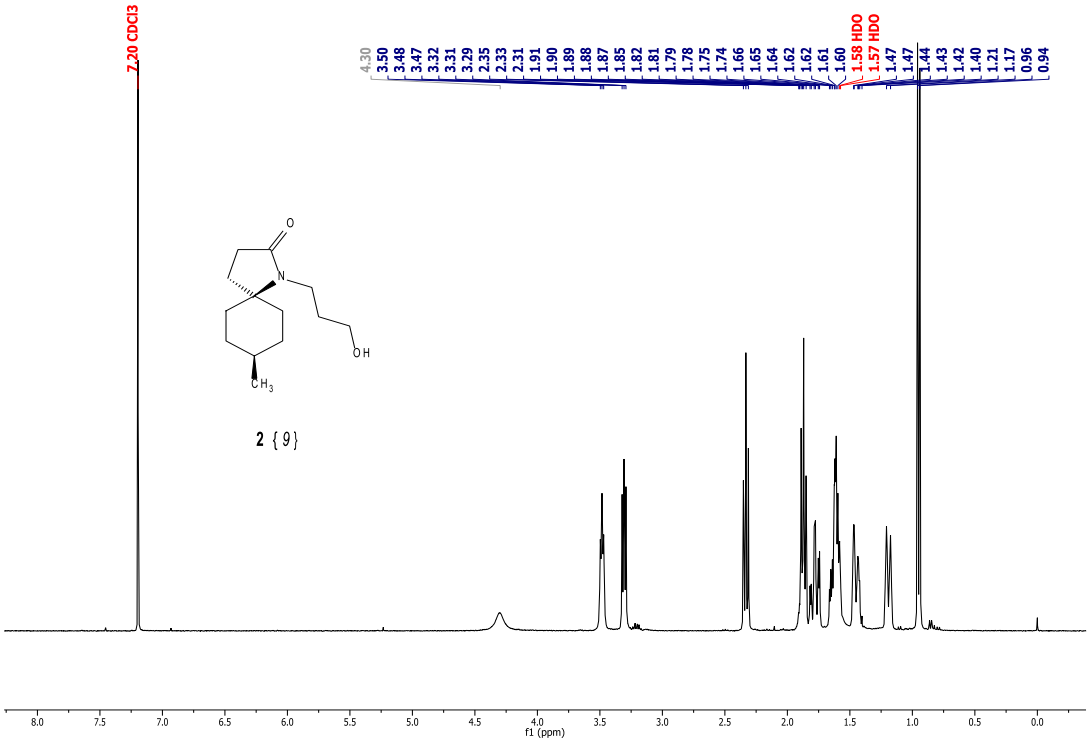

7.44
7.42
7.40
7.40
7.39
7.38
7.38
4.68
4.67
4.66
3.33
3.31
3.30
3.29
3.29
3.27
3.26
2.94
2.92
2.91
2.50
2.50
2.50
2.22
2.20
1.92
1.91
1.89
1.81
1.61
1.59
1.58
1.56
1.55
1.34
1.31
O
N
OH
Cl
4.00
1.30
2.23
2.89
1.93
1.84
3.68
2.08
1.87
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

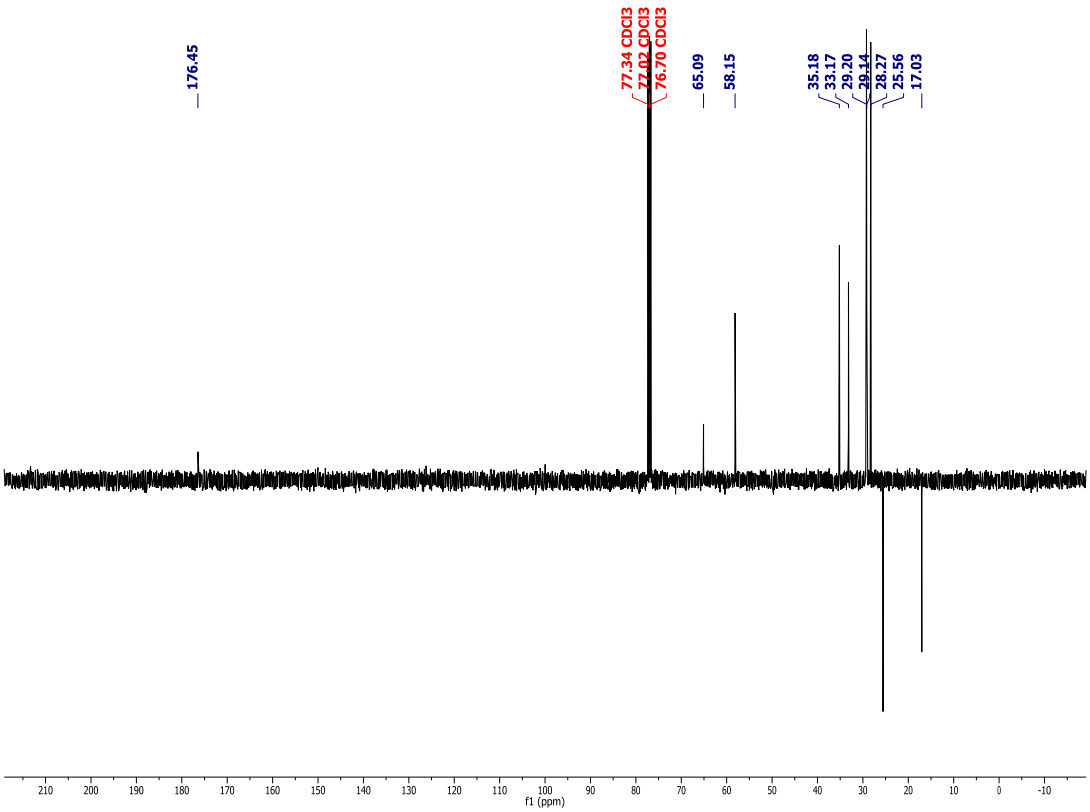

174.05
142.34
130.17
129.26
128.24
62.57
59.11
41.88
34.39
30.49
29.50
28.70
26.10
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Lactam **8ab**

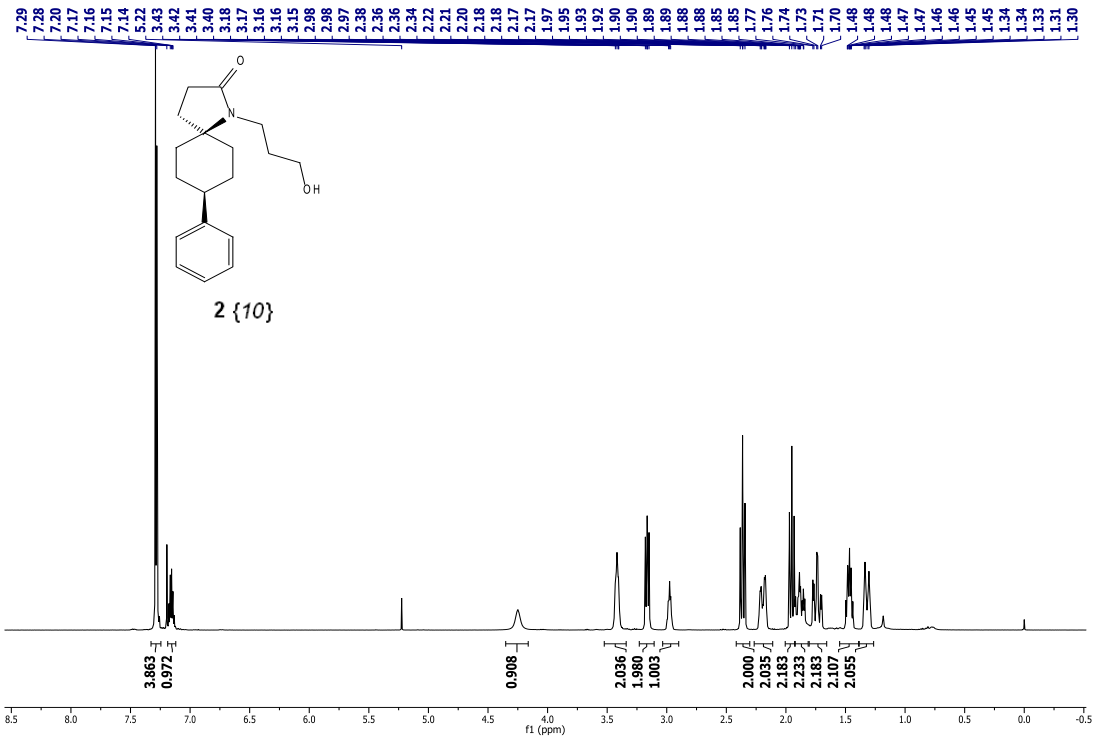

4.71
4.70
4.68
3.40
3.38
3.37
3.36
3.35
3.11
3.10
3.08
2.54
2.50
2.50
2.18
2.17
1.83
1.81
1.80
1.65
1.65
1.63
1.55
1.52
1.51
1.50
1.49
1.39
1.37
1.36
1.36
1.33
O
N
OH
1.00
2.45
1.96
1.96
2.01
1.99
1.31
1.72
4.17
1.01
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
173.97
62.78
59.46
41.35
40.36
34.53
28.65
28.40
24.54
22.55
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

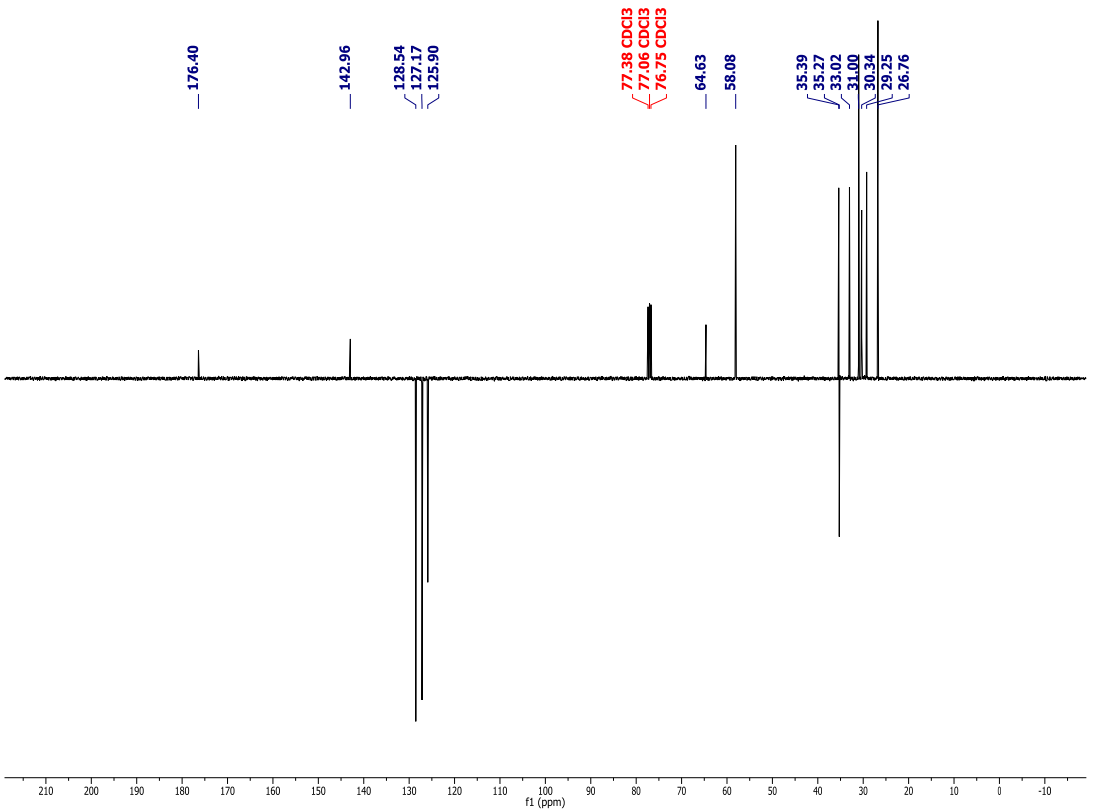
Lactam **8bb**


7.20 CDCl3
4.30
3.50
3.48
3.47
3.32
3.31
3.29
2.35
2.33
2.31
1.91
1.90
1.89
1.88
1.87
1.85
1.82
1.81
1.79
1.78
1.75
1.74
1.66
1.65
1.64
1.62
1.62
1.61
1.60
1.58 HDO
1.57 HDO
1.47
1.47
1.44
1.43
1.42
1.40
1.21
1.17
0.96
0.94
O
N
OH
CH3
2 {9}
f1 (ppm)

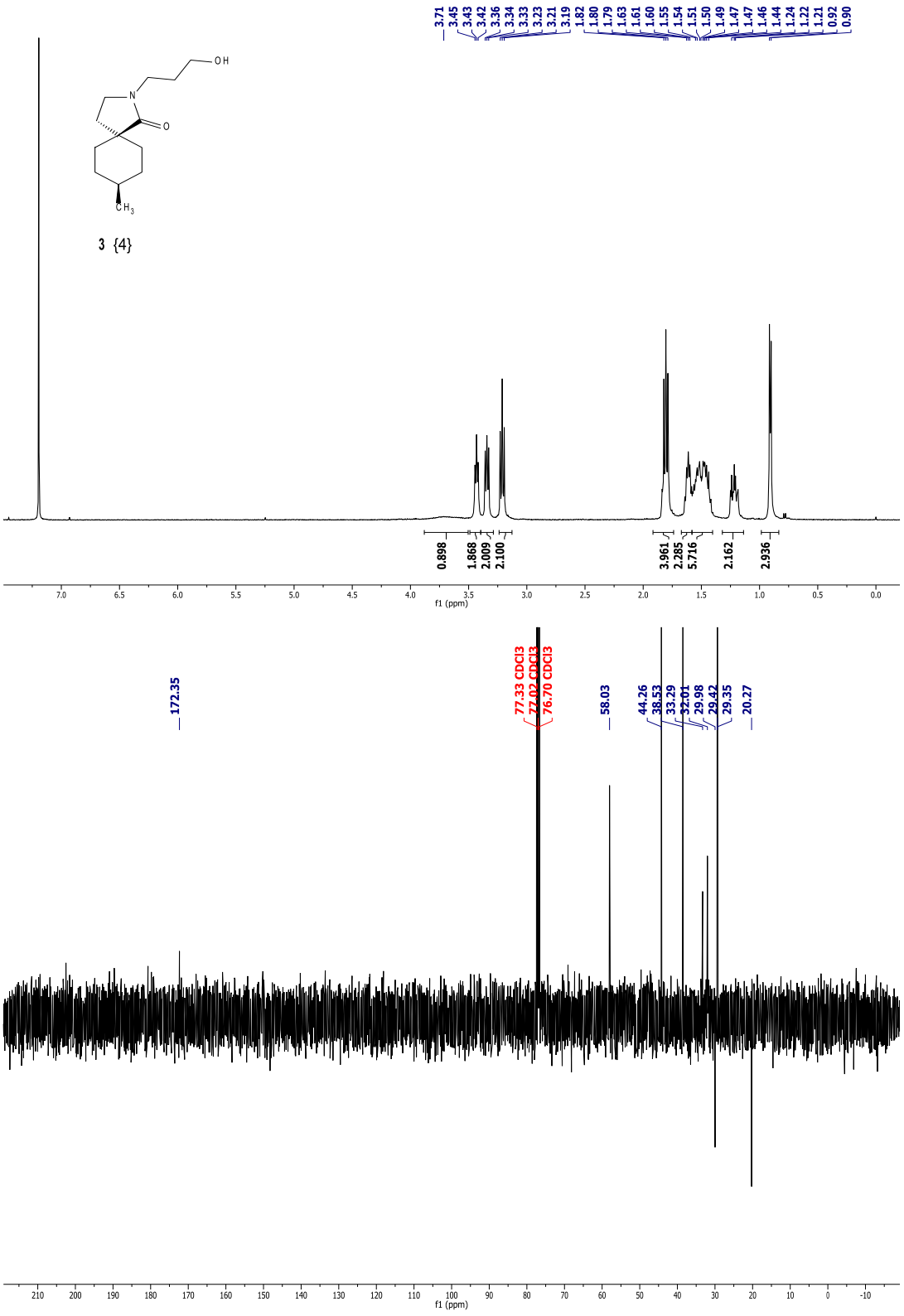

176.45
77.34 CDCl3
77.02 CDCl3
76.70 CDCl3
65.09
58.15
35.18
33.17
29.20
29.14
28.27
25.56
17.03
f1 (ppm)

Lactam **8db**

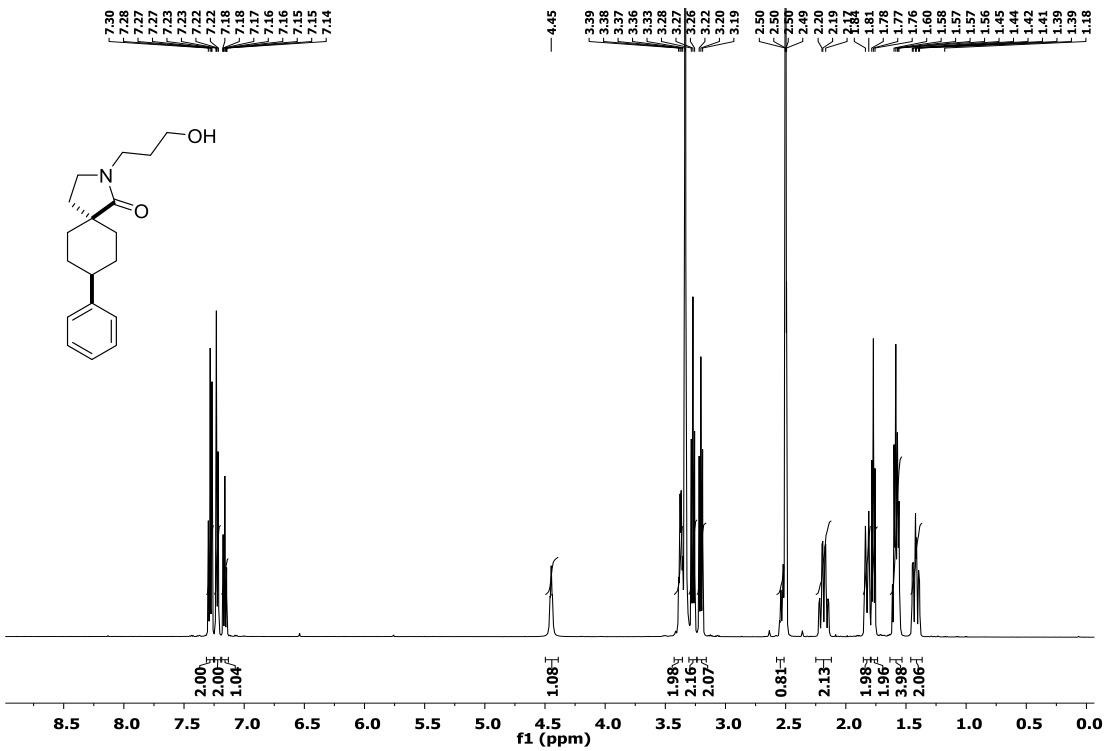

7.29 7.28 7.20 7.17 7.16 7.15 7.14 5.22 3.43 3.42 3.41 3.40 3.18 3.17 3.16 3.16 3.15 2.98 2.98 2.97 2.38 2.36 2.36 2.34 2.22 2.21 2.20 2.18 2.18 2.17 2.17 1.97 1.95 1.93 1.92 1.90 1.90 1.89 1.89 1.88 1.88 1.85 1.85 1.77 1.76 1.74 1.73 1.71 1.70 1.48 1.48 1.48 1.47 1.47 1.46 1.45 1.45 1.34 1.34 1.33 1.31 1.30
O
N
OH
2 {10}
3.863
0.972
0.908
2.036
1.980
1.003
2.000
2.035
2.183
2.233
2.183
2.107
2.055
f1 (ppm)

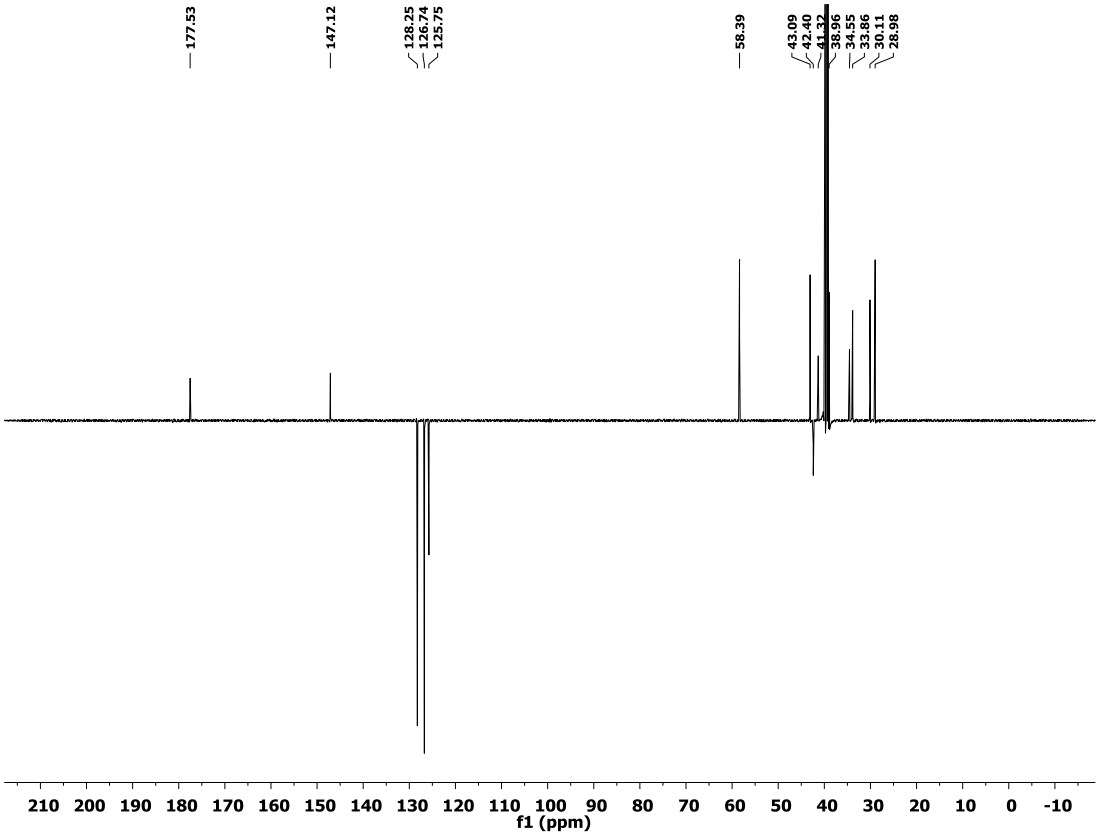

176.40
142.96
128.54
127.17
125.90
77.38 CDCl3
77.06 CDCl3
76.75 CDCl3
64.63
58.08
35.39
35.27
33.02
31.00
30.34
29.25
26.76
f1 (ppm)

Lactam **9bb**

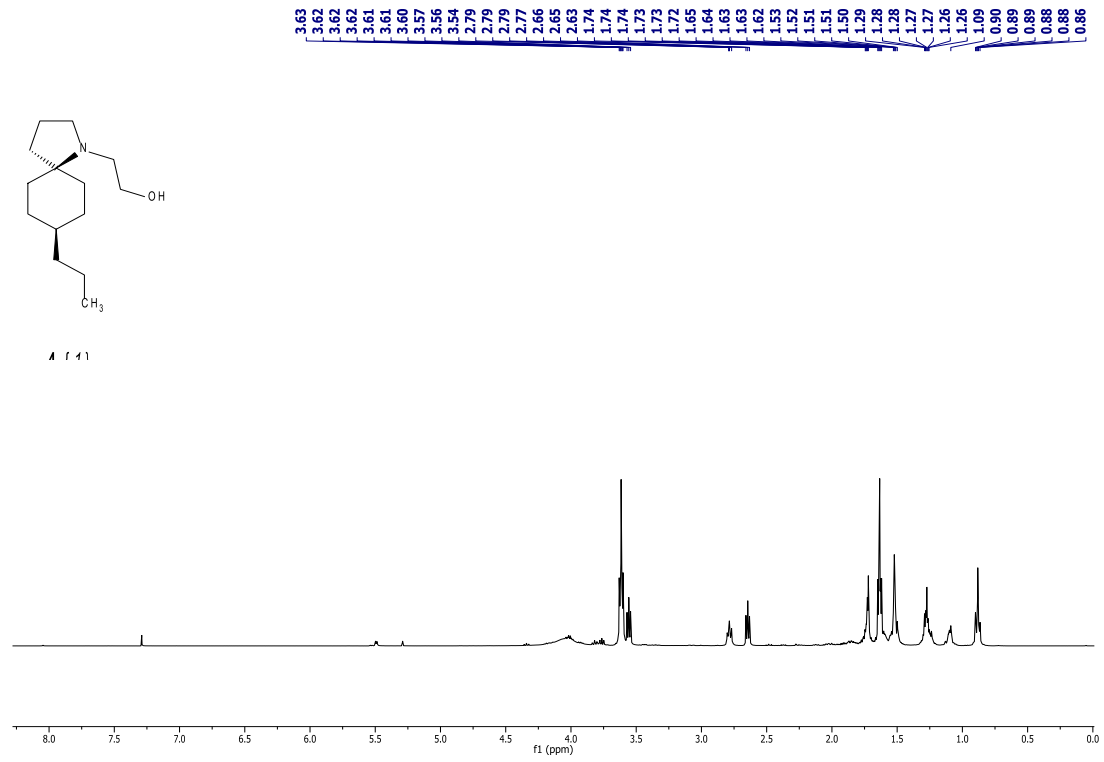

3.71
3.45
3.43
3.42
3.36
3.34
3.33
3.23
3.21
3.19
1.82
1.80
1.79
1.63
1.61
1.60
1.55
1.54
1.51
1.50
1.49
1.47
1.47
1.46
1.44
1.24
1.22
1.21
0.92
0.90
OH
N
O
CH3
3 {4}
0.898
1.868
2.009
2.100
3.961
2.285
5.716
2.162
2.936
f1 (ppm)
172.35
77.33 CDCl3
77.02 CDCl3
76.70 CDCl3
58.03
44.26
38.53
33.29
32.01
29.98
29.42
29.35
20.27
f1 (ppm)

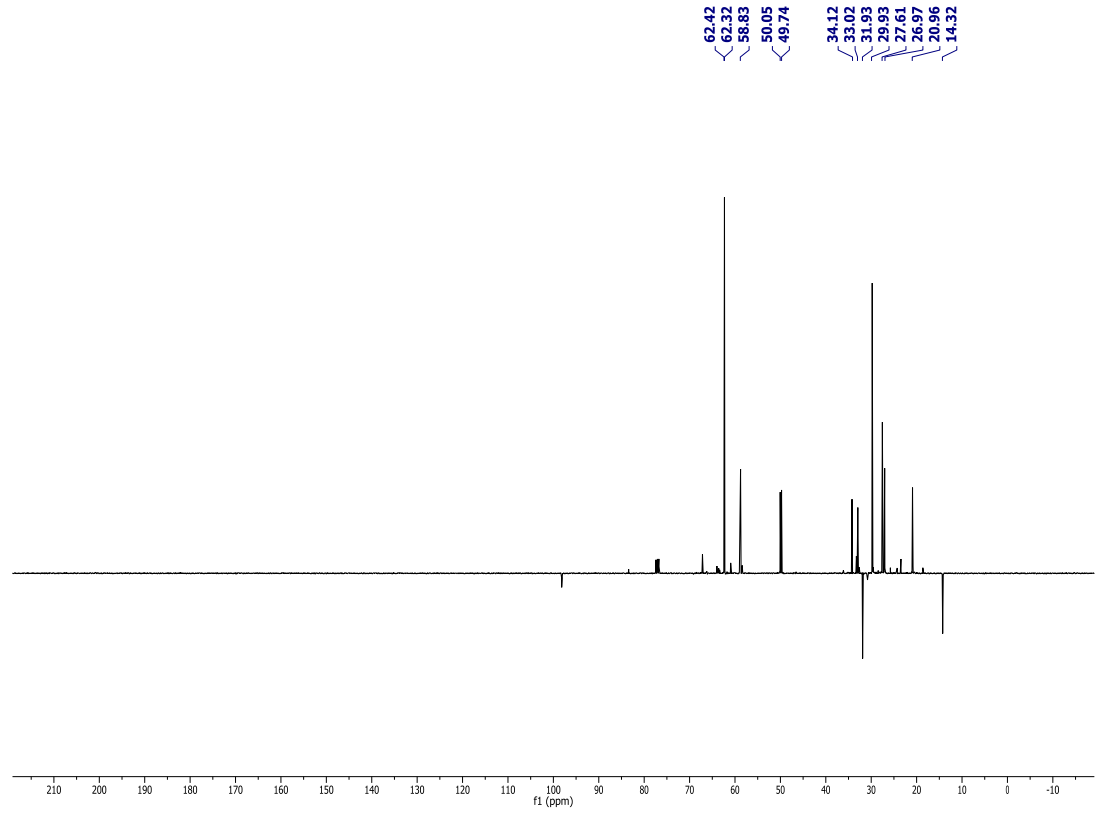
Lactam **9db**



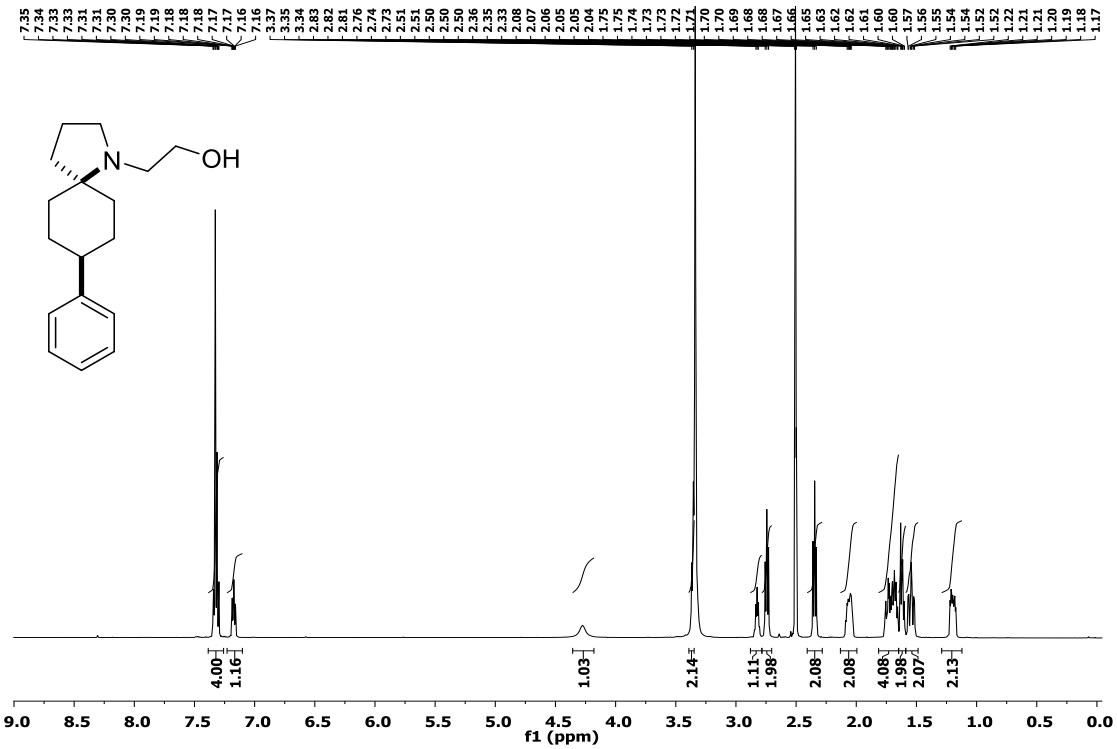


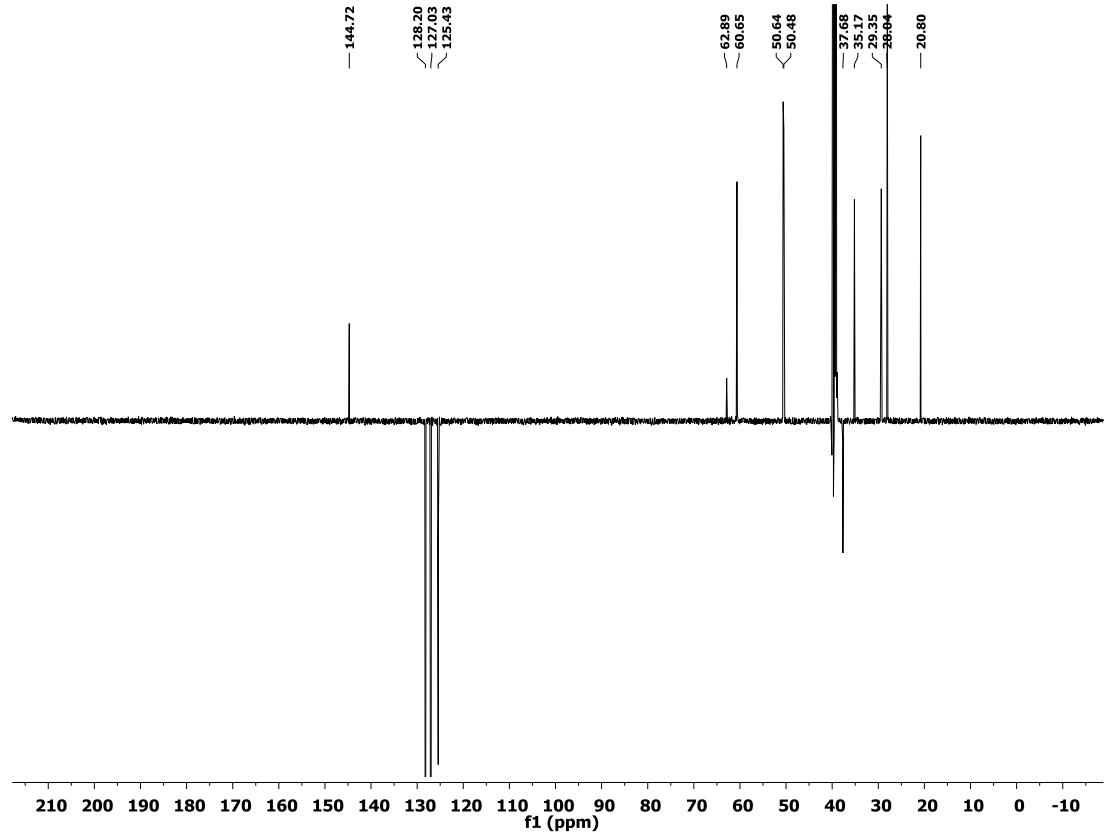
Amine **10ca**


3.63
3.62
3.62
3.62
3.61
3.61
3.60
3.57
3.56
3.54
2.79
2.79
2.79
2.77
2.66
2.65
2.63
1.74
1.74
1.74
1.73
1.73
1.72
1.65
1.64
1.63
1.63
1.62
1.53
1.52
1.51
1.51
1.50
1.29
1.28
1.28
1.27
1.27
1.26
1.26
1.09
0.90
0.89
0.89
0.88
0.88
0.86
N
OH
CH3
f1 (ppm)

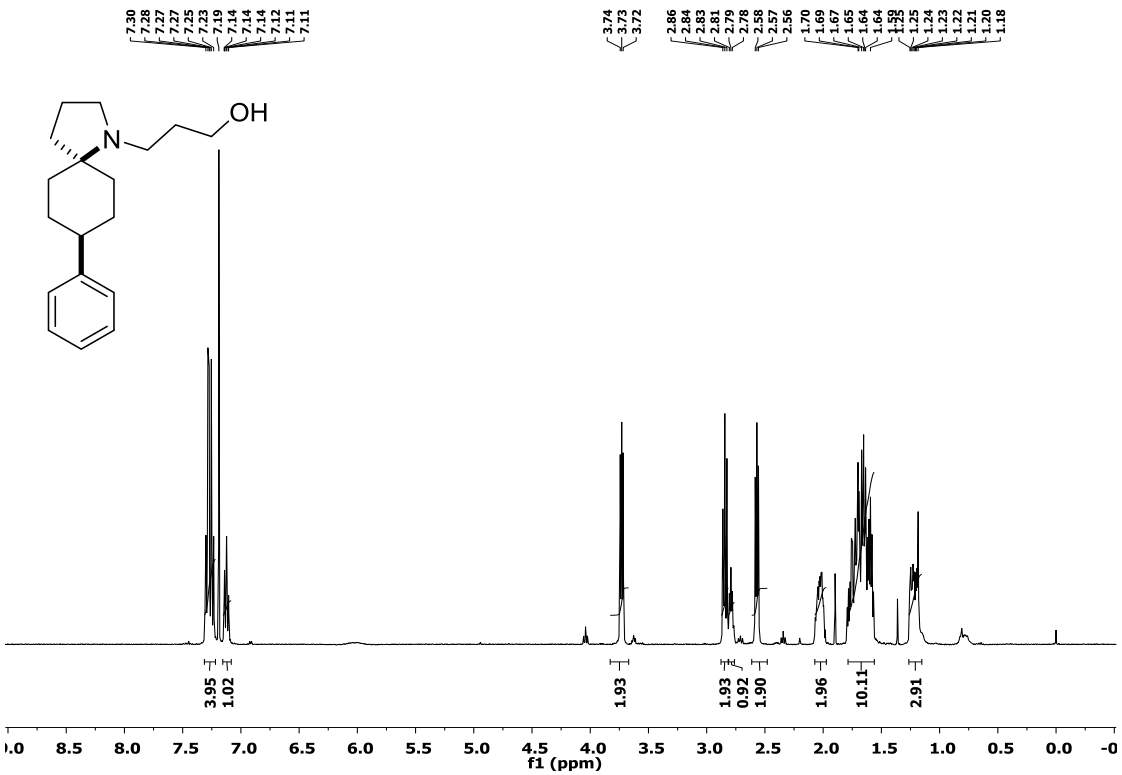

62.42
62.32
58.83
50.05
49.74
34.12
33.02
31.93
29.93
27.61
26.97
20.96
14.32
f1 (ppm)

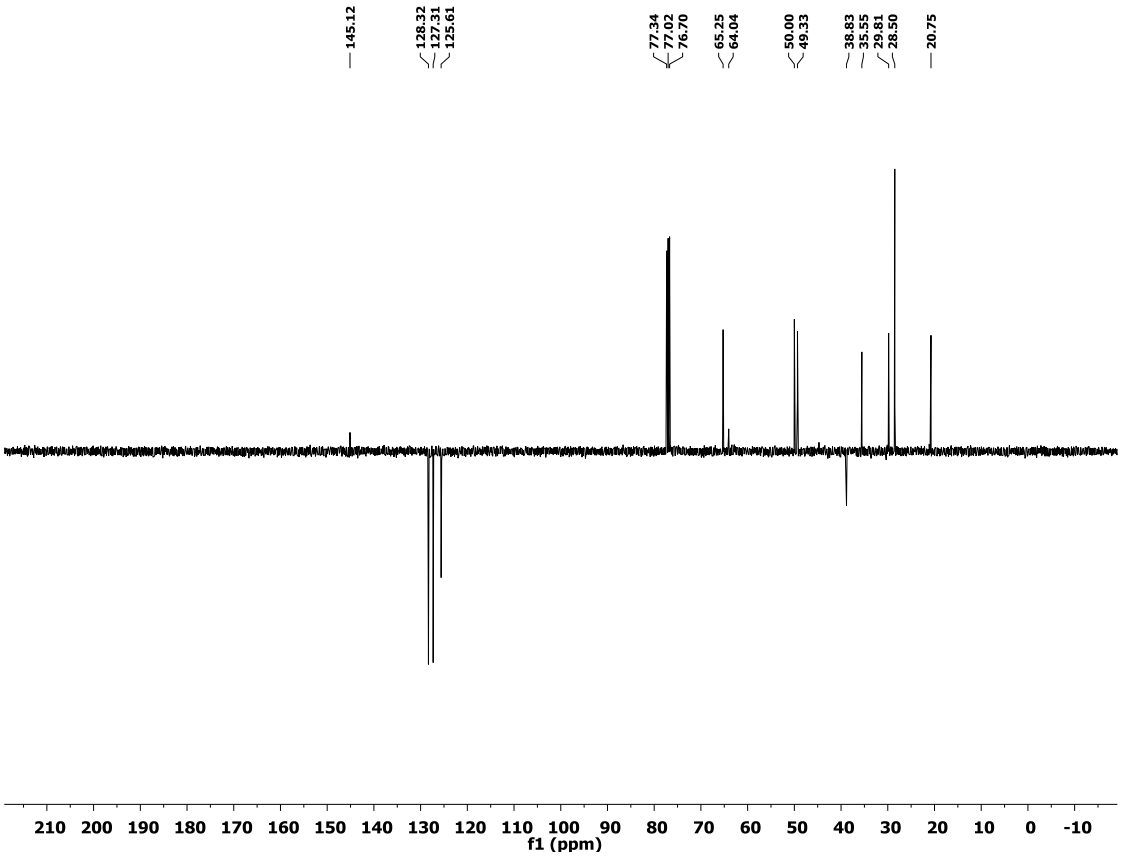
Amine **10da**


N
OH
4.00
1.16
1.03
2.14
1.11
1.98
2.08
2.08
4.08
1.98
2.07
2.13
f1 (ppm)

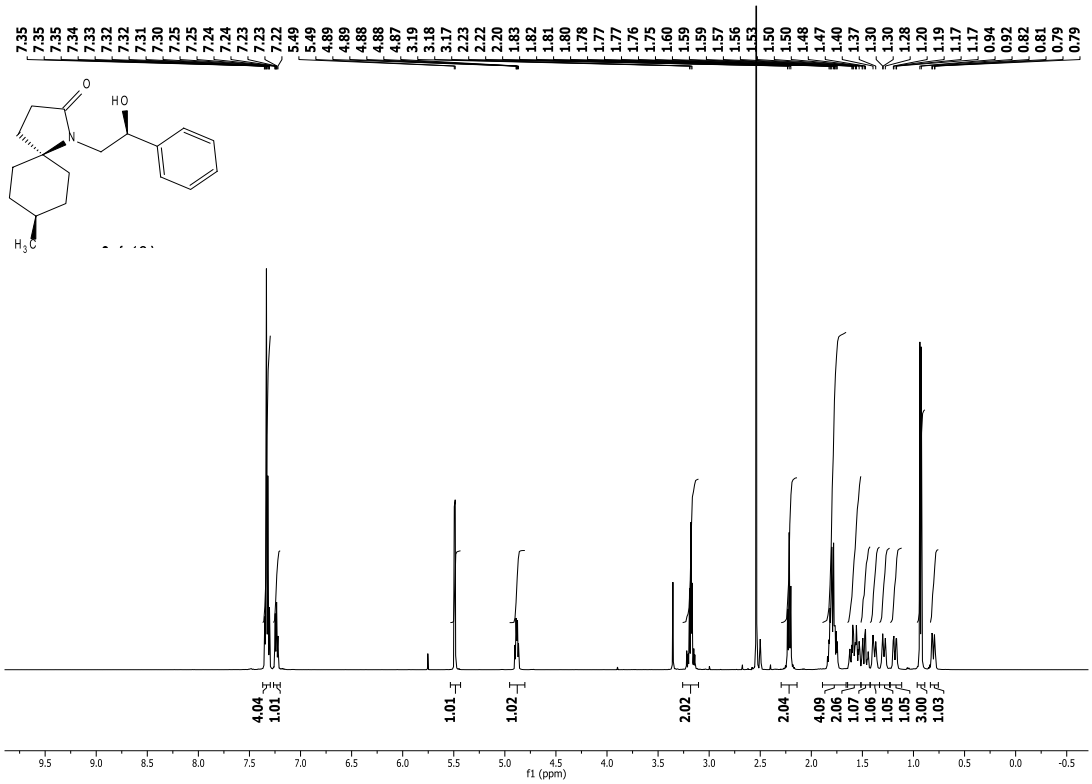

144.72
128.20
127.03
125.43
62.89
60.65
50.64
50.48
37.68
35.17
29.35
28.04
20.80
f1 (ppm)

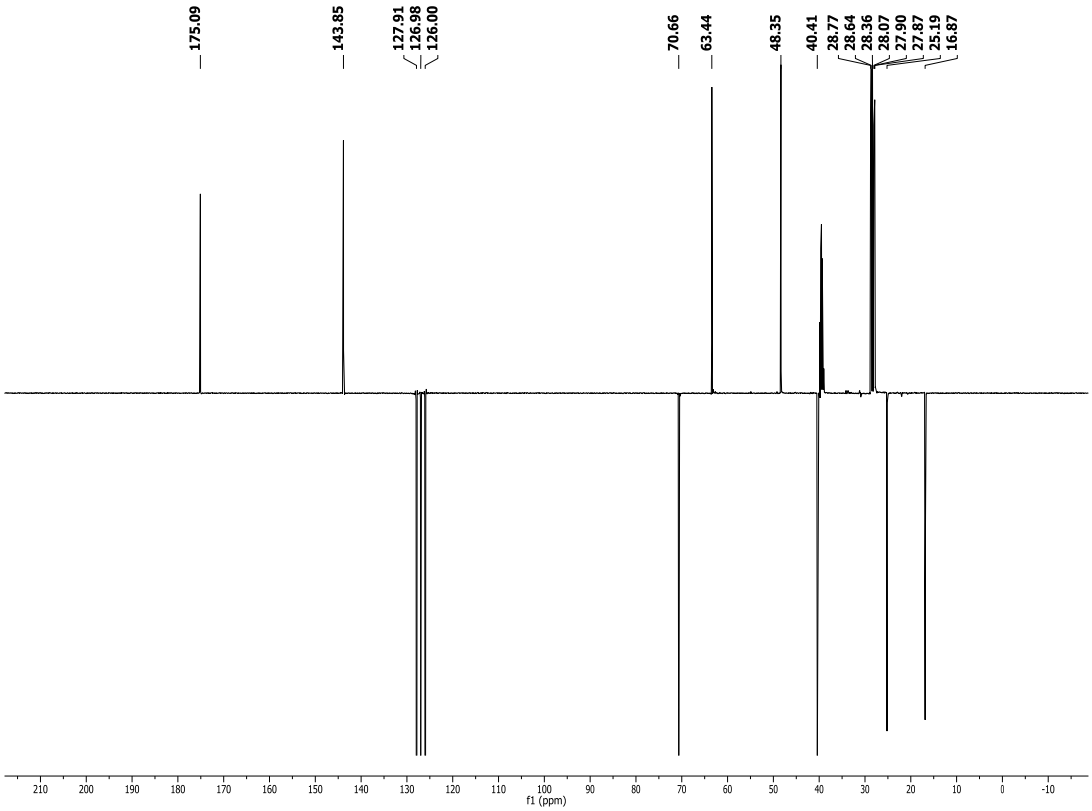
Amine **10db**


7.30
7.28
7.27
7.27
7.25
7.23
7.19
7.14
7.14
7.14
7.12
7.11
7.11
3.74
3.73
3.72
2.86
2.84
2.83
2.81
2.79
2.78
2.58
2.57
2.56
1.70
1.69
1.67
1.65
1.64
1.64
1.25
1.24
1.23
1.22
1.21
1.20
1.18
OH
N
3.95
1.02
1.93
1.93
0.92
1.90
1.96
10.11
2.91
f1 (ppm)

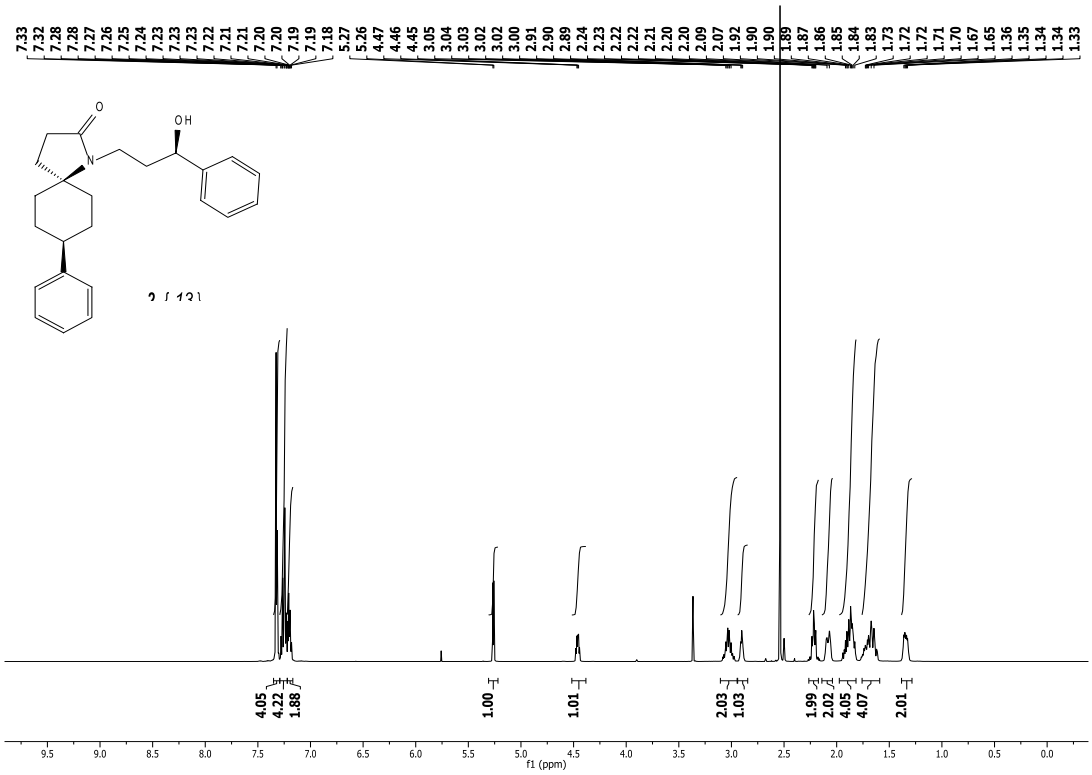

145.12
128.32
127.31
125.61
77.34
77.02
76.70
65.25
64.04
50.00
49.33
38.83
35.55
29.81
28.50
20.75
f1 (ppm)

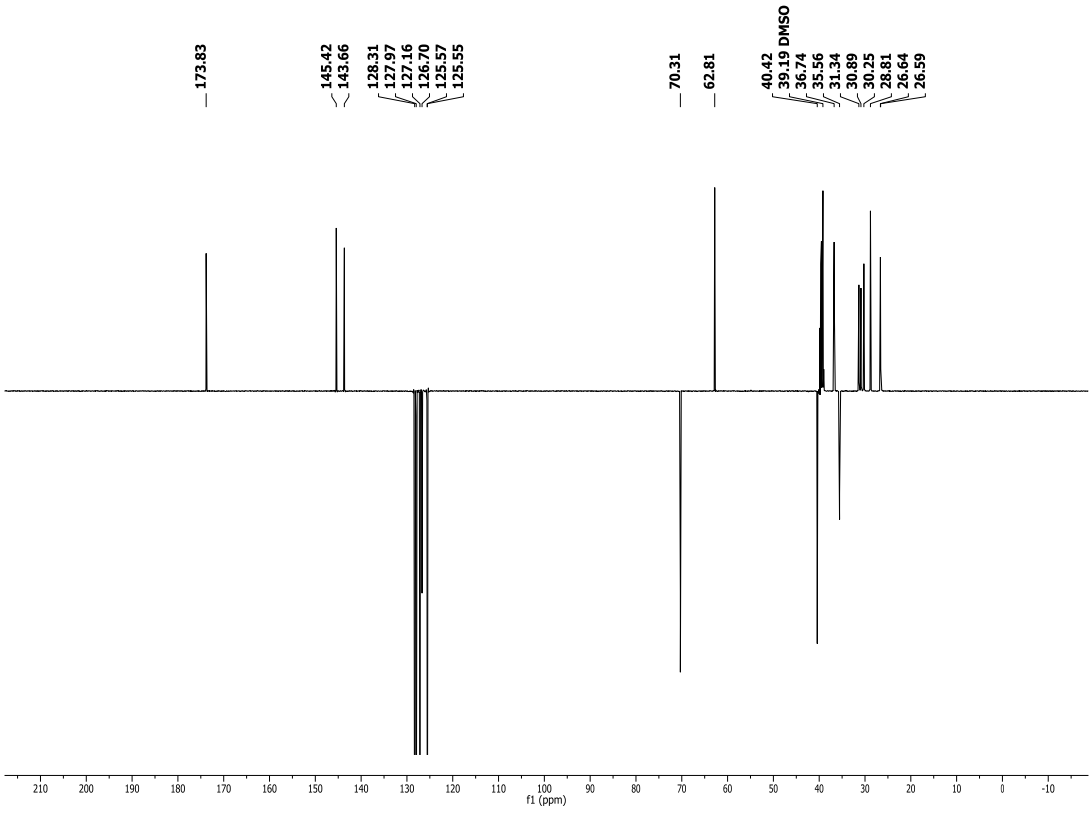
Lactam **8bc**


7.35 7.35 7.35 7.34 7.33 7.32 7.32 7.31 7.30 7.25 7.25 7.24 7.24 7.23 7.23 7.22 5.49 5.49 4.89 4.89 4.88 4.88 4.87 3.19 3.18 3.17 2.23 2.22 2.20 1.83 1.82 1.81 1.80 1.78 1.77 1.77 1.76 1.75 1.60 1.59 1.59 1.57 1.56 1.53 1.50 1.50 1.48 1.47 1.40 1.37 1.30 1.30 1.28 1.20 1.19 1.17 1.17 0.94 0.92 0.82 0.81 0.79 0.79
O
HO
N
H3C
4.04 1.01 1.01 1.02 2.02 2.04 4.09 2.06 1.07 1.06 1.05 1.05 3.00 1.03
f1 (ppm)

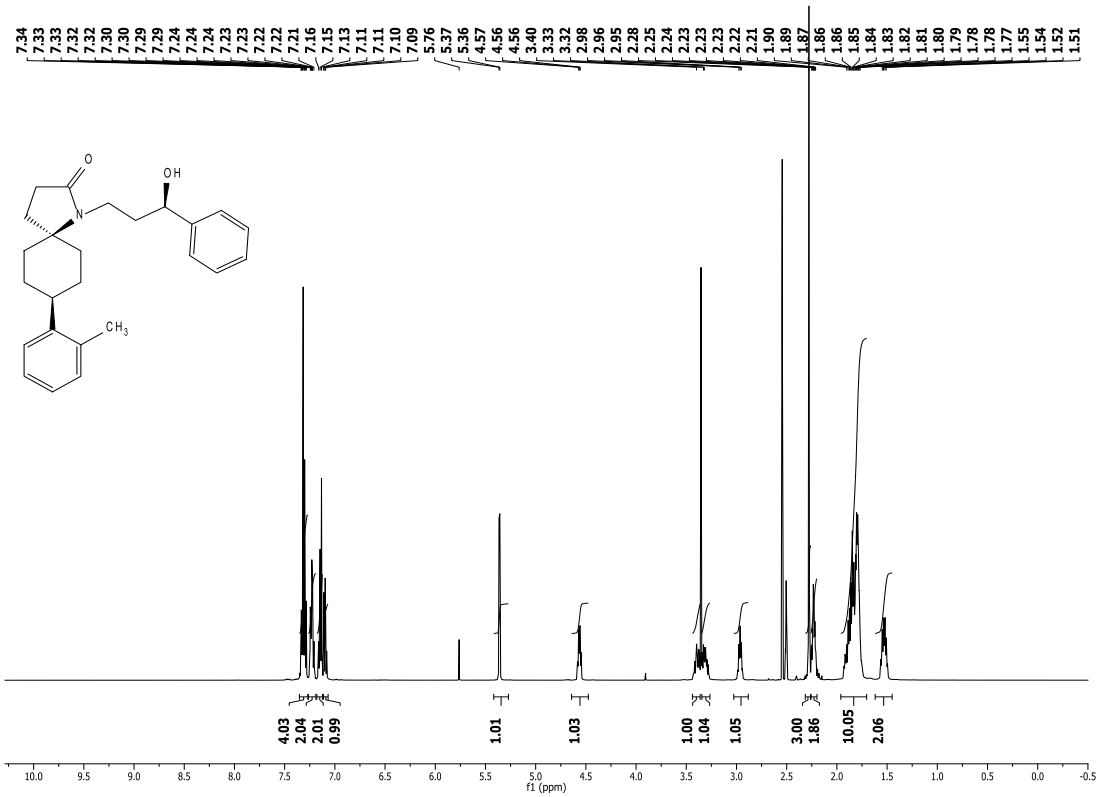

175.09
143.85
127.91
126.98
126.00
70.66
63.44
48.35
40.41
28.77
28.64
28.36
28.07
27.90
27.87
25.19
16.87
f1 (ppm)

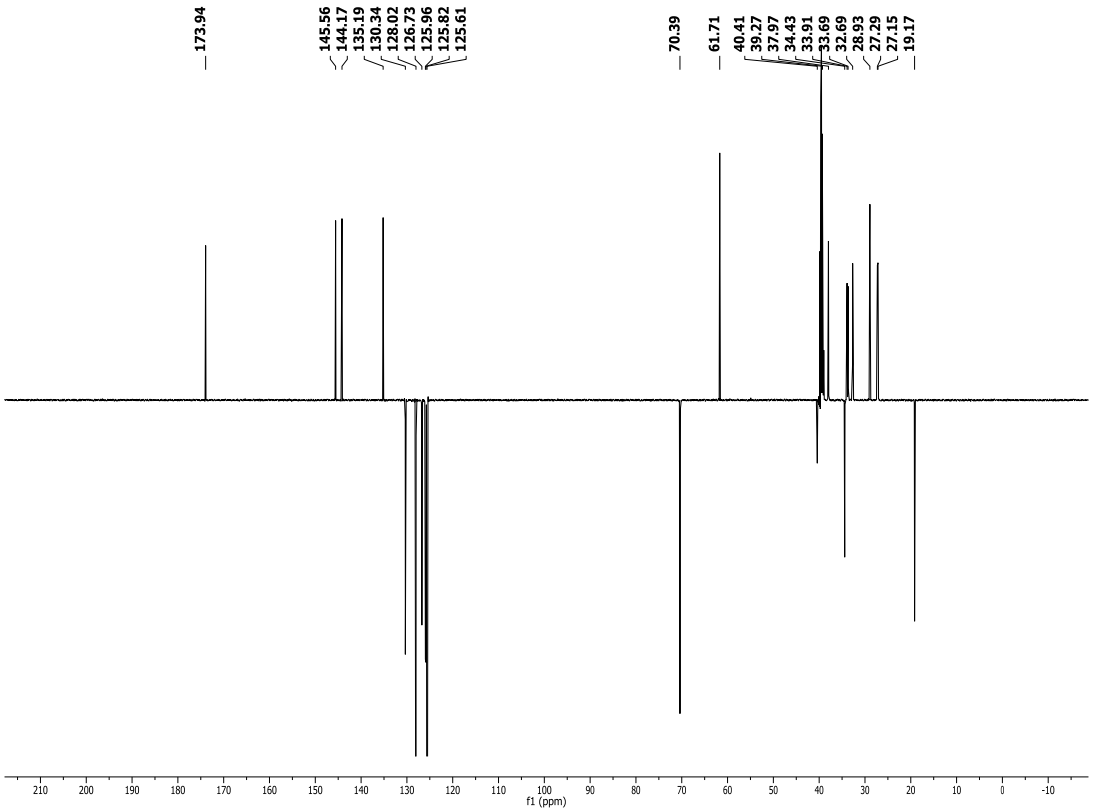
Lactam **8dd**


7.33 7.32 7.28 7.28 7.27 7.26 7.25 7.24 7.23 7.23 7.23 7.22 7.21 7.21 7.20 7.20 7.19 7.19 7.18 5.27 5.26 4.47 4.46 4.45 3.05 3.04 3.03 3.02 3.02 3.00 2.91 2.90 2.89 2.24 2.23 2.22 2.22 2.21 2.20 2.20 2.09 2.07 1.92 1.90 1.90 1.89 1.87 1.86 1.85 1.84 1.83 1.73 1.72 1.71 1.70 1.67 1.65 1.36 1.35 1.34 1.34 1.33
O
OH
N
4.05 4.22 1.88 1.00 1.01 2.03 1.03 1.99 2.02 4.05 4.07 2.01
f1 (ppm)

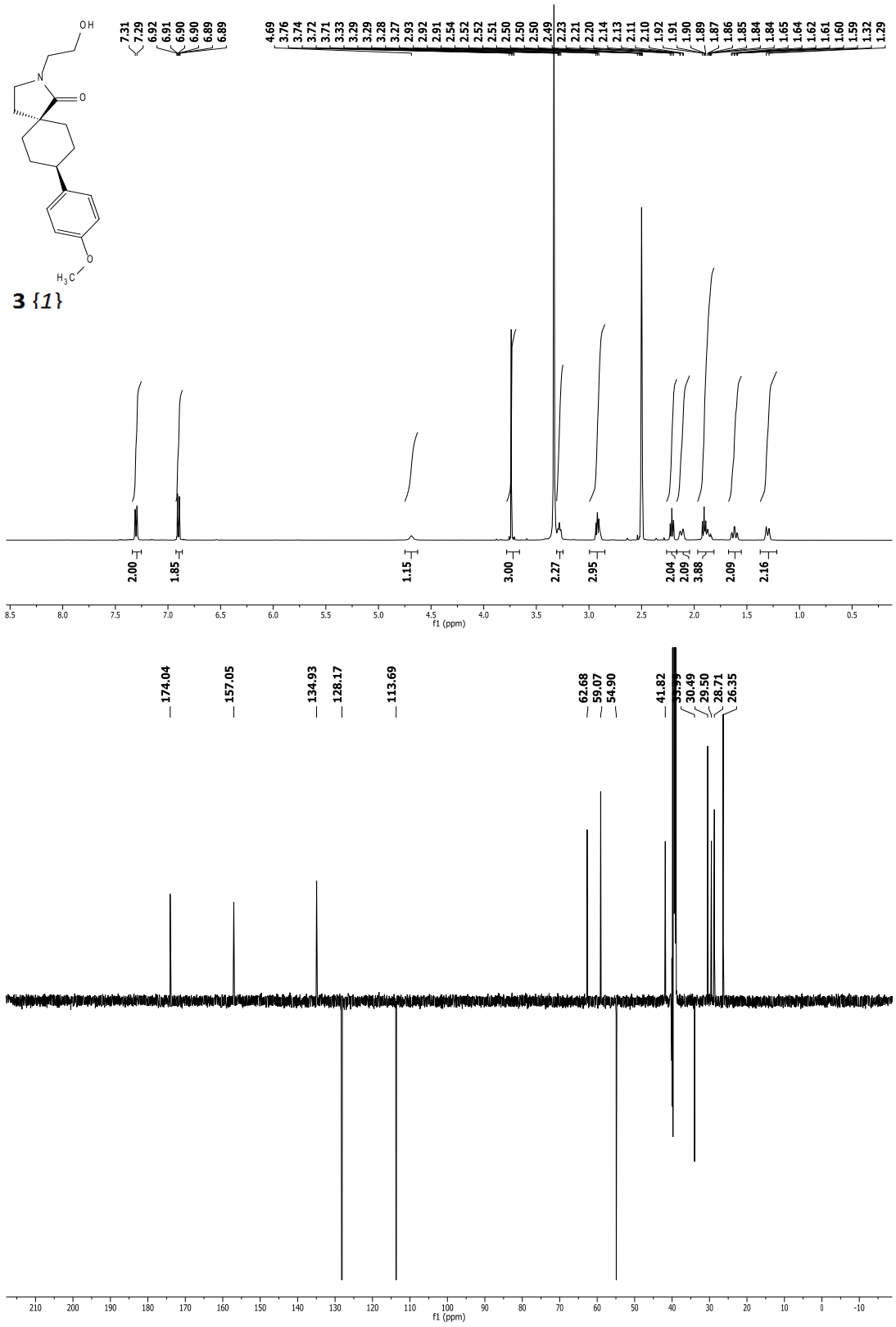

173.83
145.42 143.66 128.31 127.97 127.16 126.70 125.57 125.55
70.31 62.81
40.42 39.19 DMSO 36.74 35.56 31.34 30.89 30.25 28.81 26.64 26.59
f1 (ppm)

Lactam **8fd**

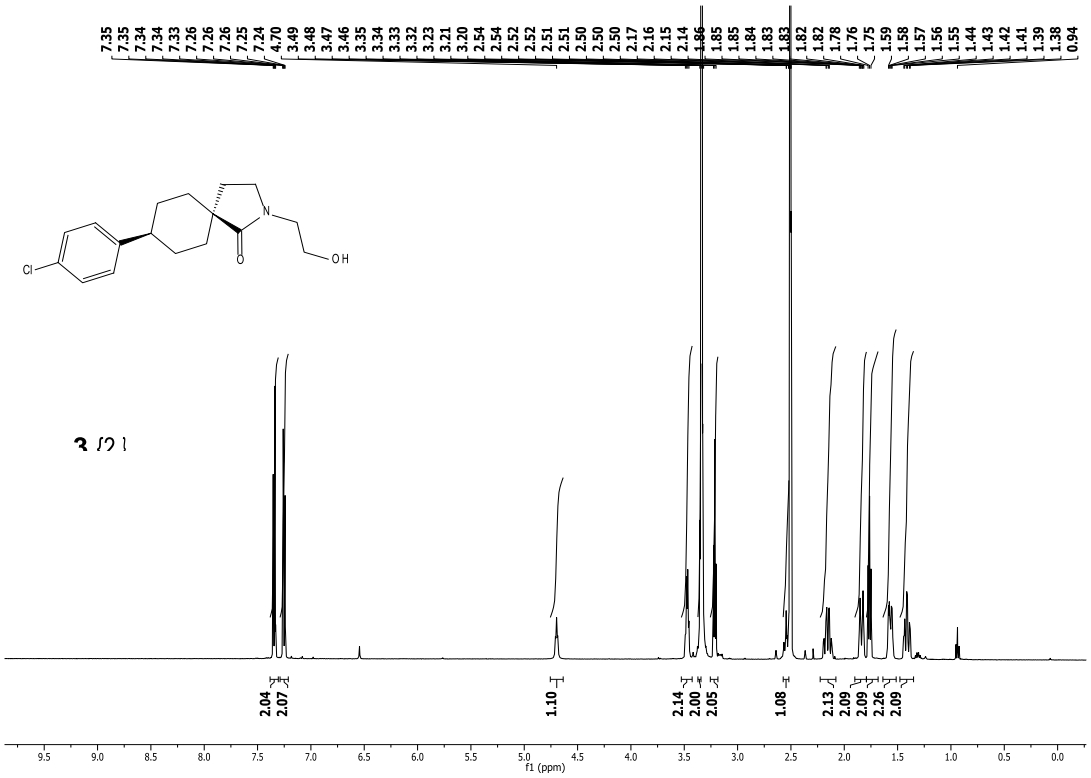

7.34 7.33 7.33 7.32 7.32 7.30 7.30 7.29 7.29 7.24 7.24 7.24 7.23 7.23 7.22 7.22 7.21 7.16 7.15 7.13 7.11 7.11 7.10 7.09 5.76 5.37 5.36 4.57 4.56 4.56 3.40 3.33 3.32 2.98 2.96 2.95 2.28 2.25 2.24 2.23 2.23 2.23 2.22 2.21 1.90 1.89 1.87 1.86 1.86 1.85 1.84 1.83 1.82 1.81 1.80 1.79 1.78 1.78 1.77 1.55 1.54 1.52 1.51
O
OH
N
CH3
4.03 2.04 2.01 0.99 1.01 1.03 1.00 1.04 1.05 3.00 1.86 10.05 2.06
f1 (ppm)

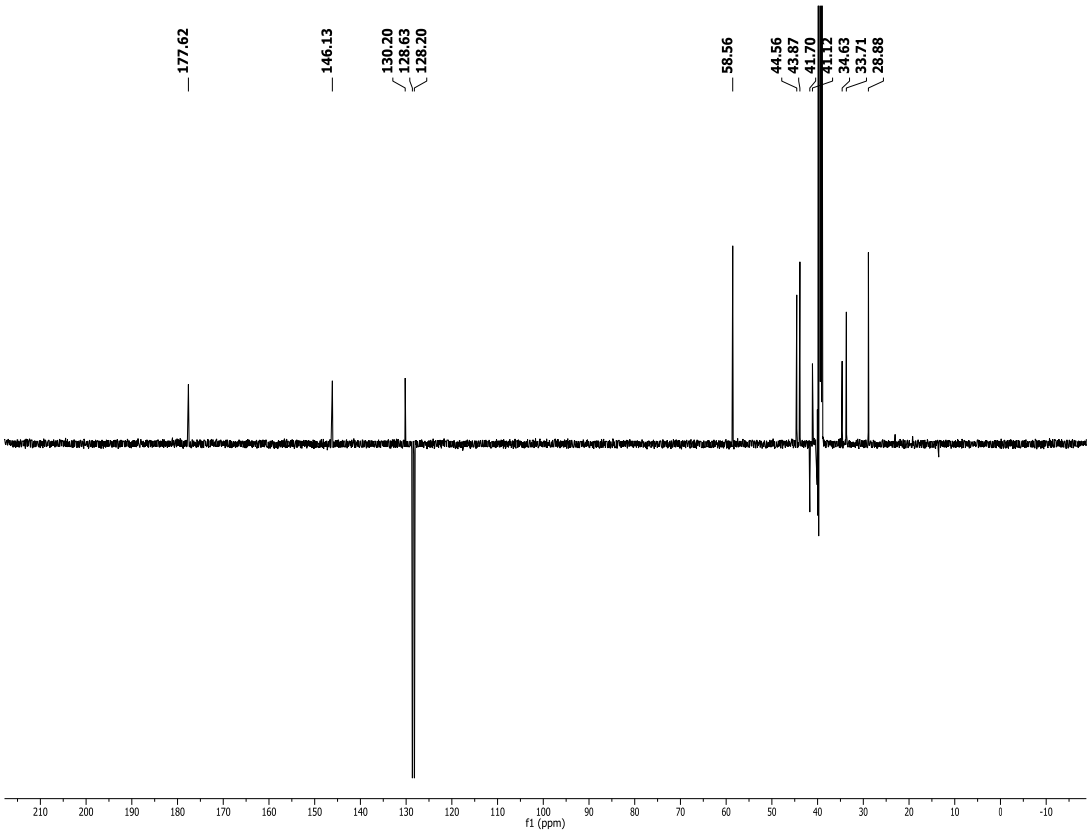

173.94
145.56 144.17 135.19 130.34 128.02 126.73 125.96 125.82 125.61
70.39
61.71
40.41 39.27 37.97 34.43 33.91 33.69 32.69 28.93 27.29 27.15 19.17
f1 (ppm)

Lactam **9ga**

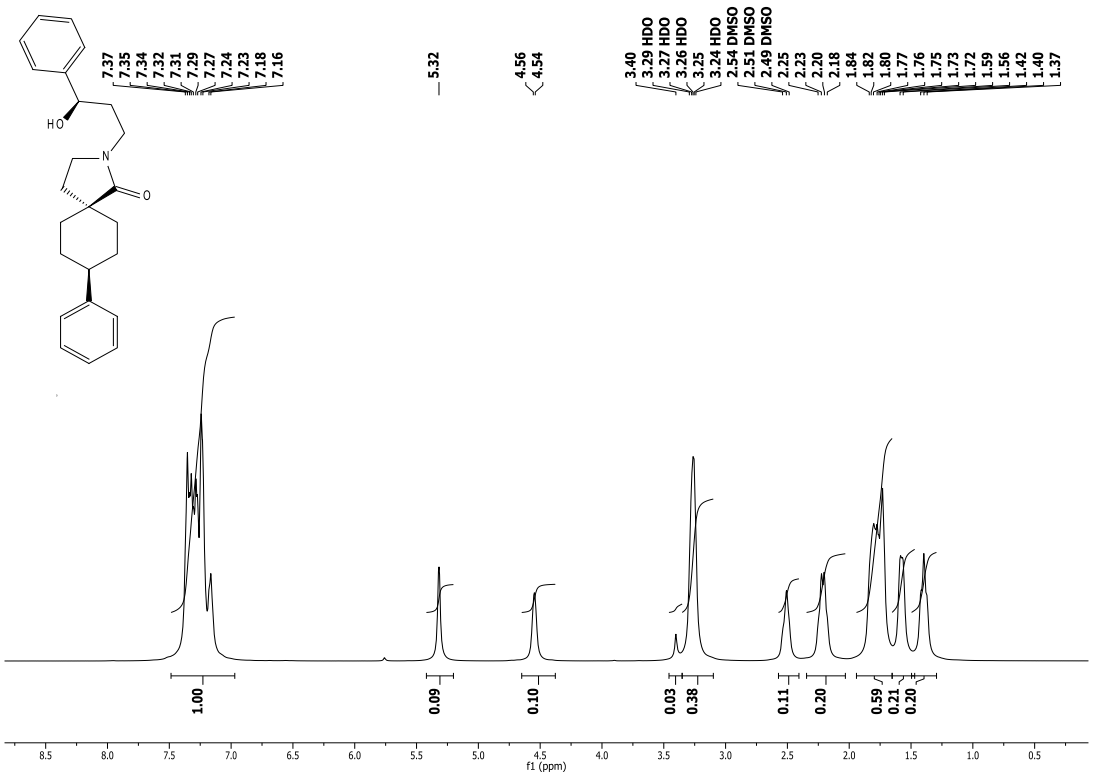

7.31
7.29
6.92
6.91
6.90
6.90
6.89
6.89
4.69
3.76
3.74
3.72
3.71
3.33
3.29
3.29
3.28
3.27
2.93
2.92
2.91
2.54
2.52
2.52
2.51
2.50
2.50
2.50
2.49
2.23
2.21
2.20
2.14
2.13
2.11
2.10
1.92
1.91
1.90
1.89
1.87
1.86
1.85
1.84
1.84
1.65
1.64
1.62
1.61
1.60
1.59
1.32
1.29
OH
N
O
O
H3C
3 {1}
2.00
1.85
1.15
3.00
2.27
2.95
2.04
2.09
3.88
2.09
2.16
f1 (ppm)
174.04
157.05
134.93
128.17
113.69
62.68
59.07
54.90
41.82
30.49
29.50
28.71
26.35
f1 (ppm)

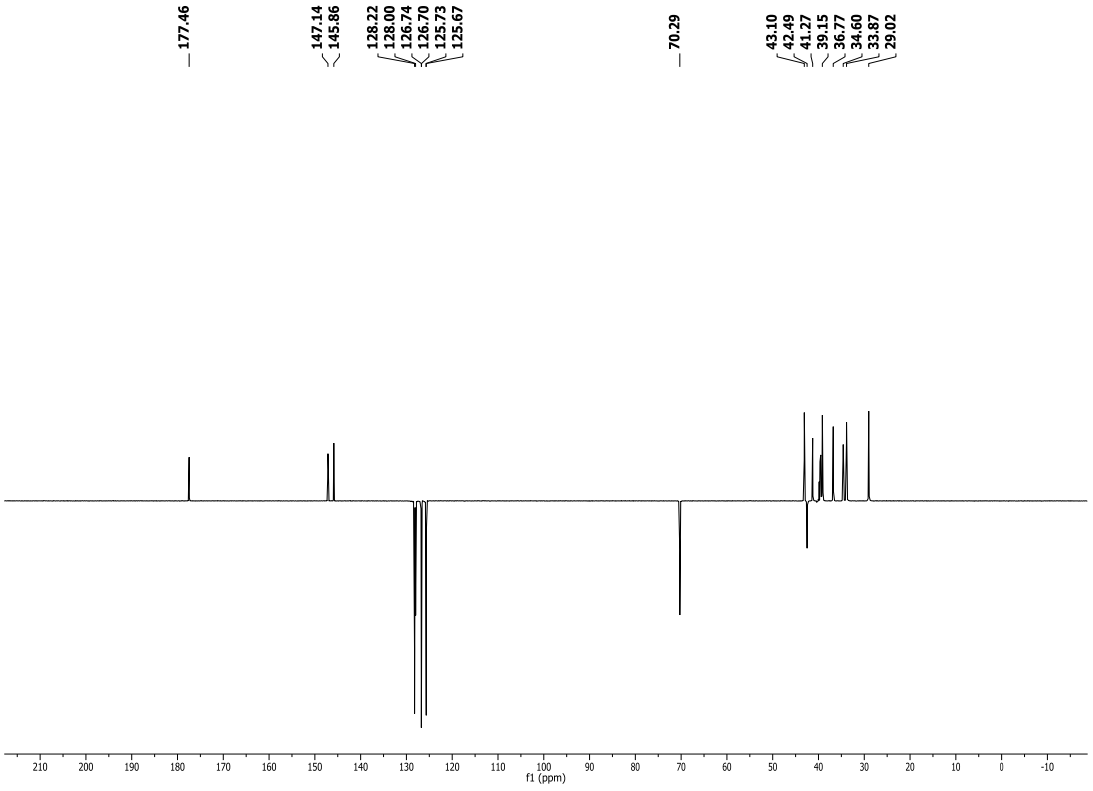
Lactam **9ha**


7.35 7.35 7.34 7.34 7.33 7.26 7.26 7.26 7.25 7.24 4.70 3.49 3.48 3.47 3.46 3.35 3.34 3.33 3.32 3.23 3.21 3.20 2.54 2.54 2.52 2.52 2.51 2.51 2.50 2.50 2.50 2.17 2.16 2.15 2.14 1.86 1.85 1.85 1.84 1.83 1.83 1.82 1.82 1.78 1.76 1.75 1.59 1.58 1.57 1.56 1.55 1.44 1.43 1.42 1.41 1.39 1.38 0.94
N
O
OH
Cl
2.04 2.07 1.10 2.14 2.00 2.05 1.08 2.13 2.09 2.09 2.26 2.09
f1 (ppm)

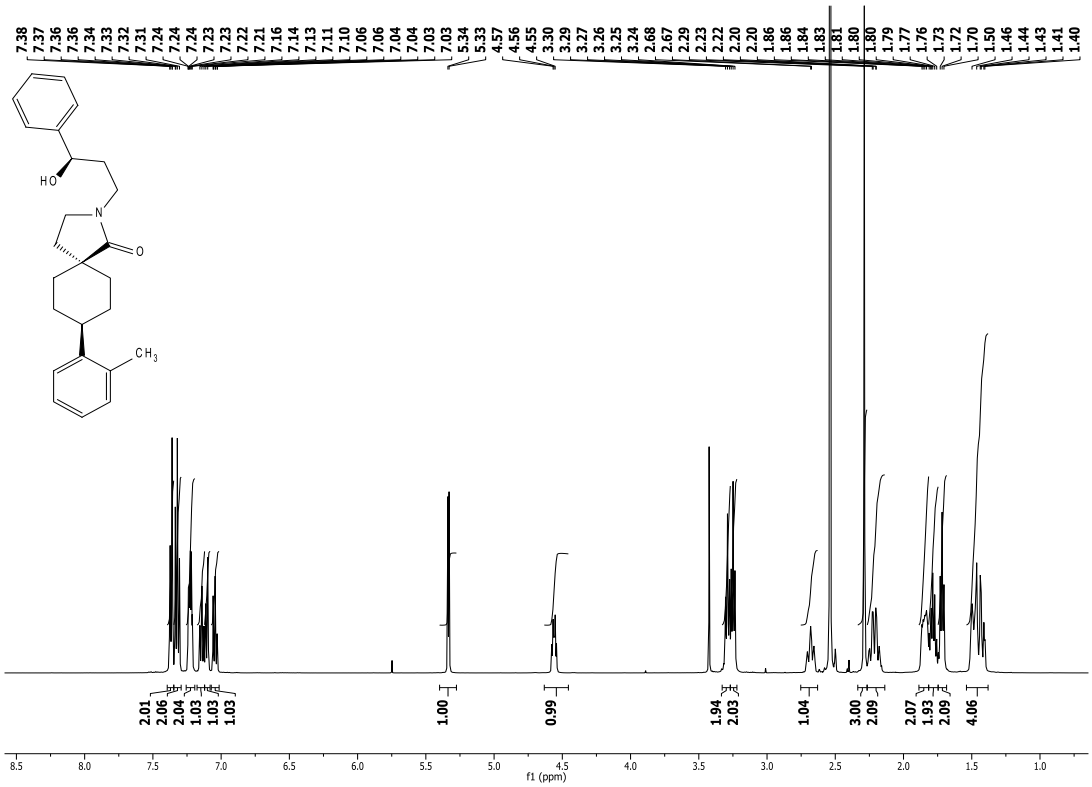

177.62 146.13 130.20 128.63 128.20 58.56 44.56 43.87 41.70 41.12 34.63 33.71 28.88
f1 (ppm)

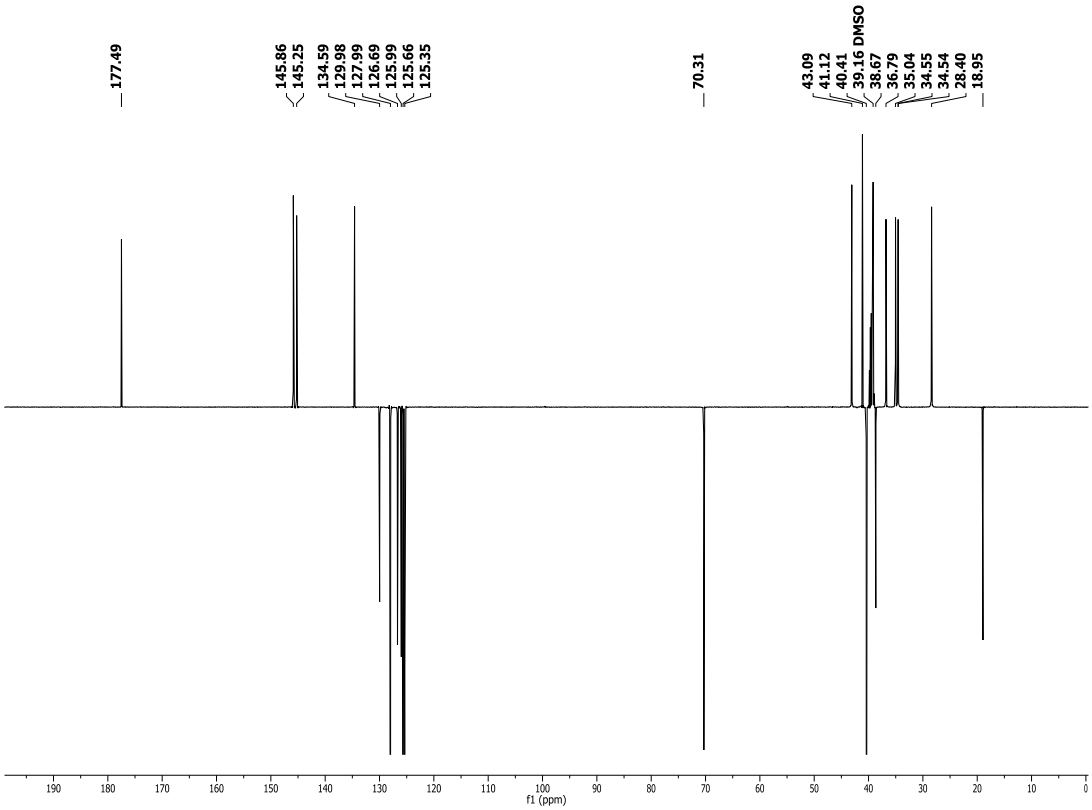
Lactam **9dd**


7.37
7.35
7.34
7.32
7.31
7.29
7.27
7.24
7.23
7.18
7.16
5.32
4.56
4.54
3.40
3.29 HDO
3.27 HDO
3.26 HDO
3.25
3.24 HDO
2.54 DMSO
2.51 DMSO
2.49 DMSO
2.25
2.23
2.20
2.18
1.84
1.82
1.80
1.77
1.76
1.75
1.73
1.72
1.59
1.56
1.42
1.40
1.37
HO
N
O
1.00
0.09
0.10
0.03
0.38
0.11
0.20
0.59
0.21
0.20
f1 (ppm)

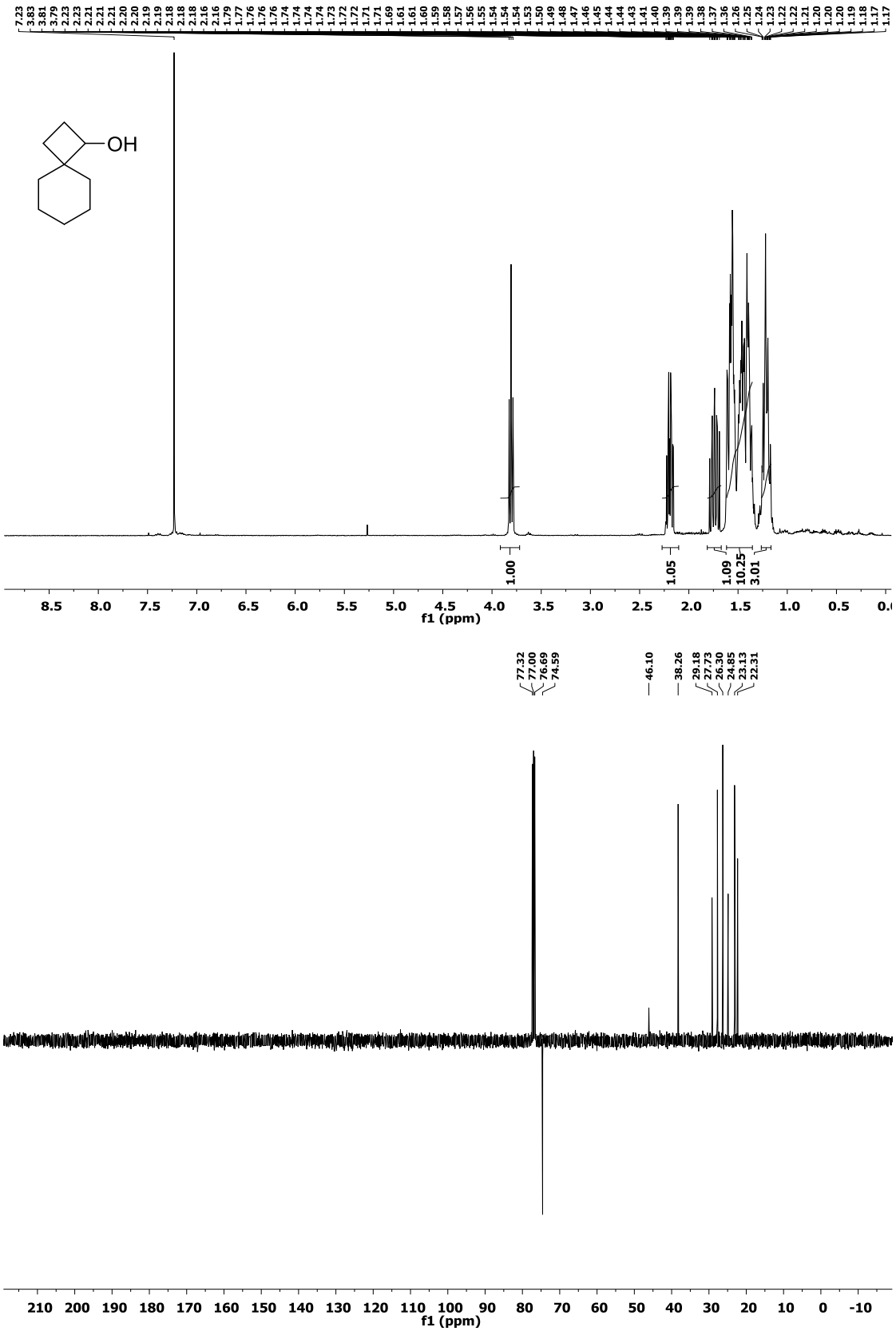

177.46
147.14
145.86
128.22
128.00
126.74
126.70
125.73
125.67
70.29
43.10
42.49
41.27
39.15
36.77
34.60
33.87
29.02
f1 (ppm)

Lactam **9fd**

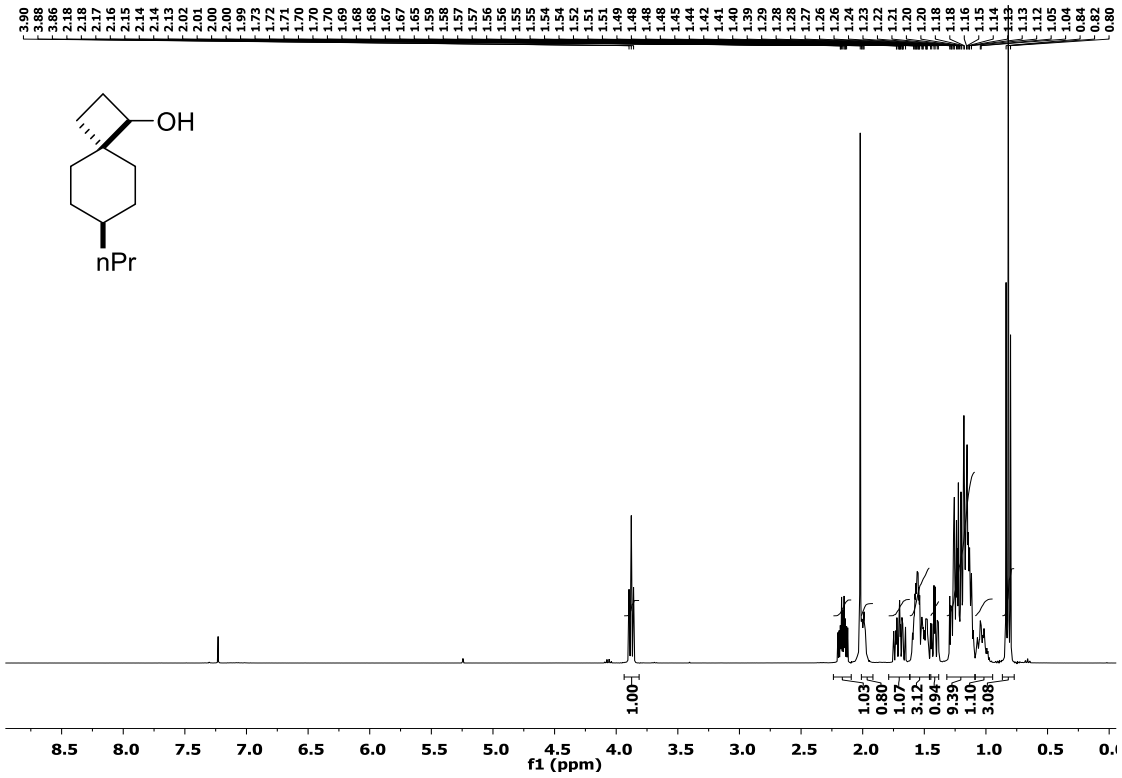

7.38 7.37 7.36 7.36 7.34 7.33 7.32 7.31 7.24 7.24 7.24 7.23 7.23 7.22 7.21 7.16 7.14 7.13 7.11 7.10 7.06 7.06 7.04 7.04 7.03 7.03 5.34 5.33 4.57 4.56 4.55 3.30 3.29 3.27 3.26 3.25 3.24 2.68 2.67 2.29 2.23 2.22 2.20 2.20 1.86 1.86 1.84 1.83 1.81 1.80 1.80 1.79 1.77 1.76 1.73 1.72 1.70 1.50 1.46 1.44 1.43 1.41 1.40
HO
N
O
CH3
2.01 2.06 2.04 1.03 1.03 1.03 1.00 0.99 1.94 2.03 1.04 3.00 2.09 2.07 1.93 2.09 4.06
f1 (ppm)

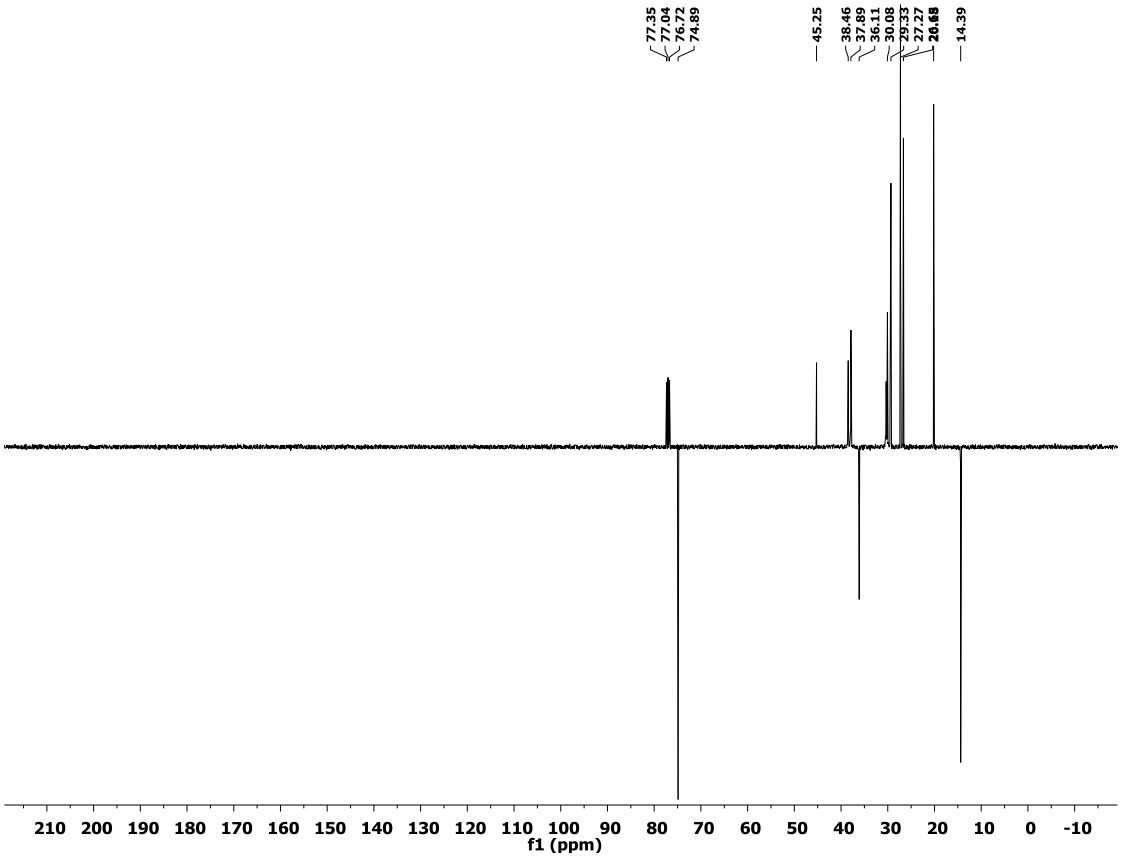

177.49
145.86 145.25 134.59 129.98 127.99 126.69 125.99 125.66 125.35
70.31
43.09 41.12 40.41 39.16 DMSO 38.67 36.79 35.04 34.55 34.54 28.40 18.95
f1 (ppm)

Alcohol **S9a**

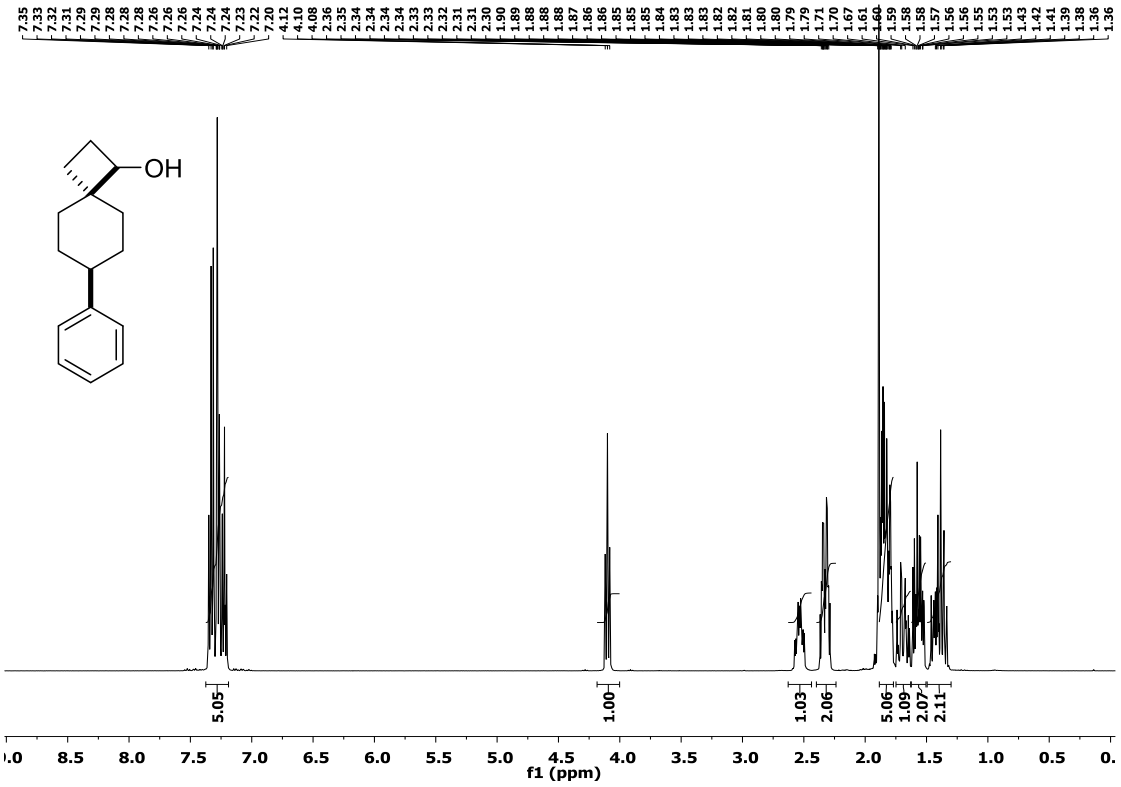

OH
1.00
1.05
1.09
10.25
3.01
f1 (ppm)
77.32
77.00
76.69
74.59
46.10
38.26
29.18
27.73
26.30
24.85
23.13
22.31
f1 (ppm)

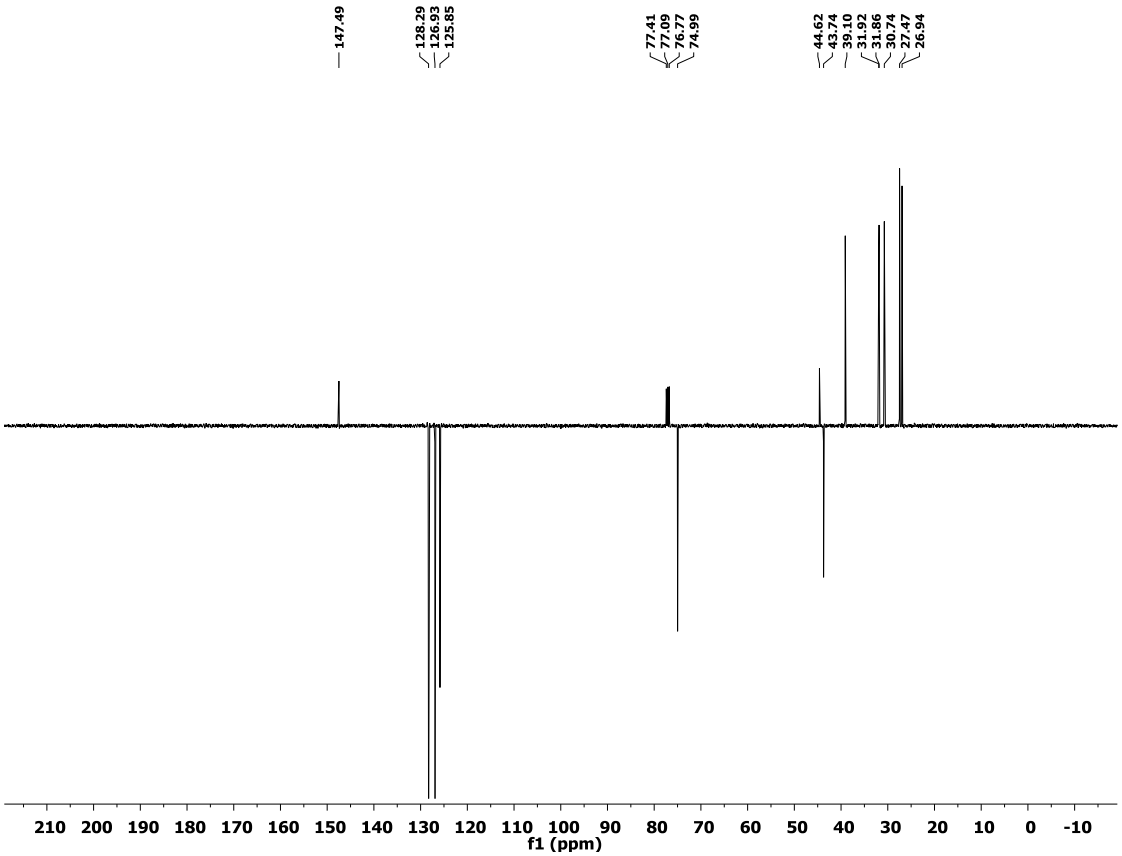
Alcohol **S9c**


OH
nPr
1.00
1.03
0.80
1.07
3.12
0.94
9.39
1.10
3.08
f1 (ppm)

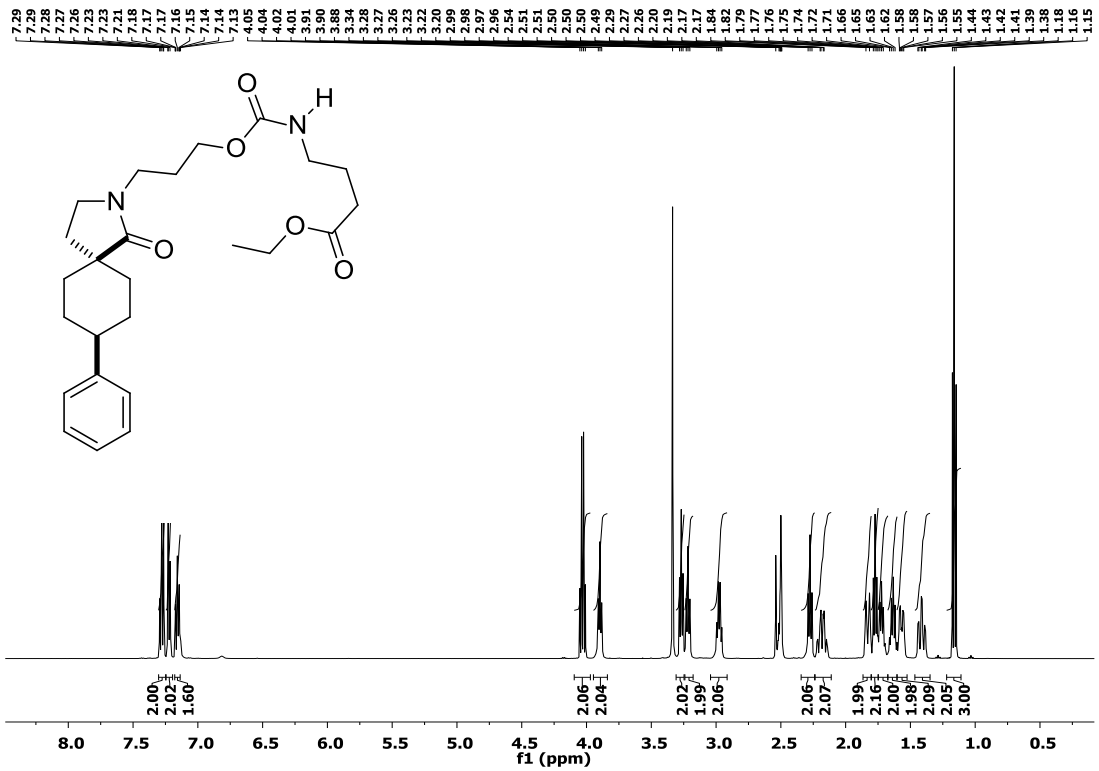

77.35
77.04
76.72
74.89
45.25
38.46
37.89
36.11
30.08
29.33
27.27
14.39
f1 (ppm)

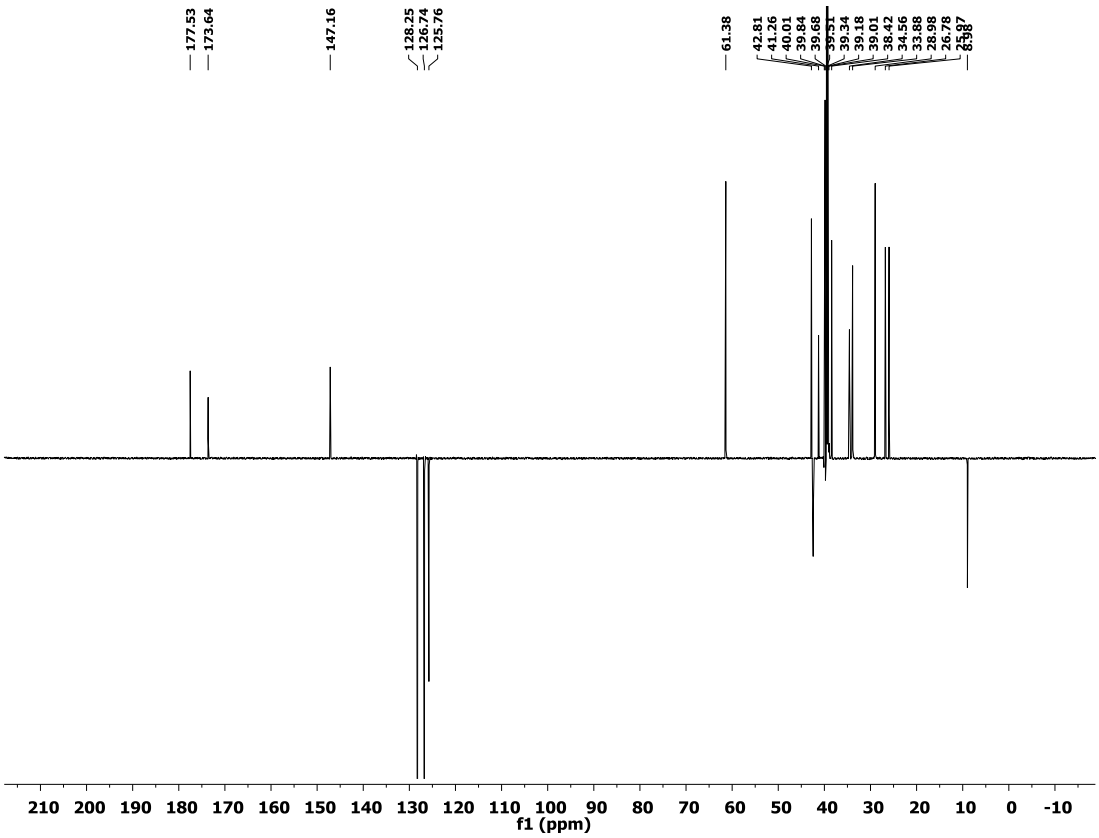
Alcohol **S9d**



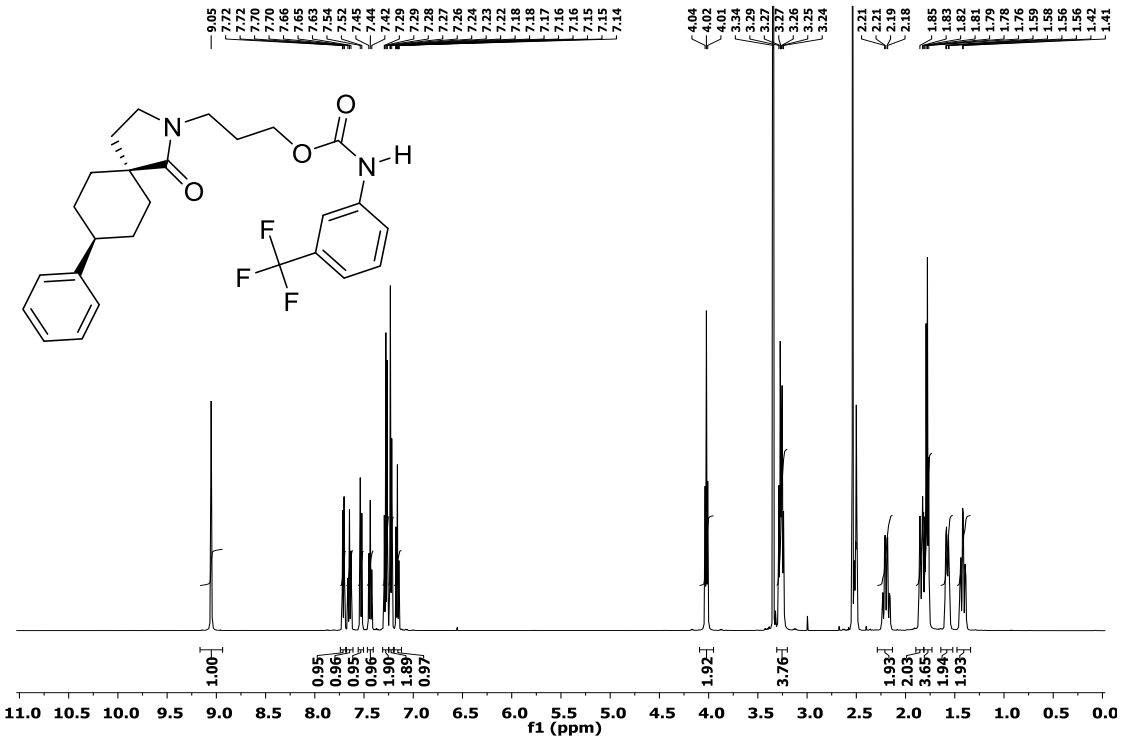


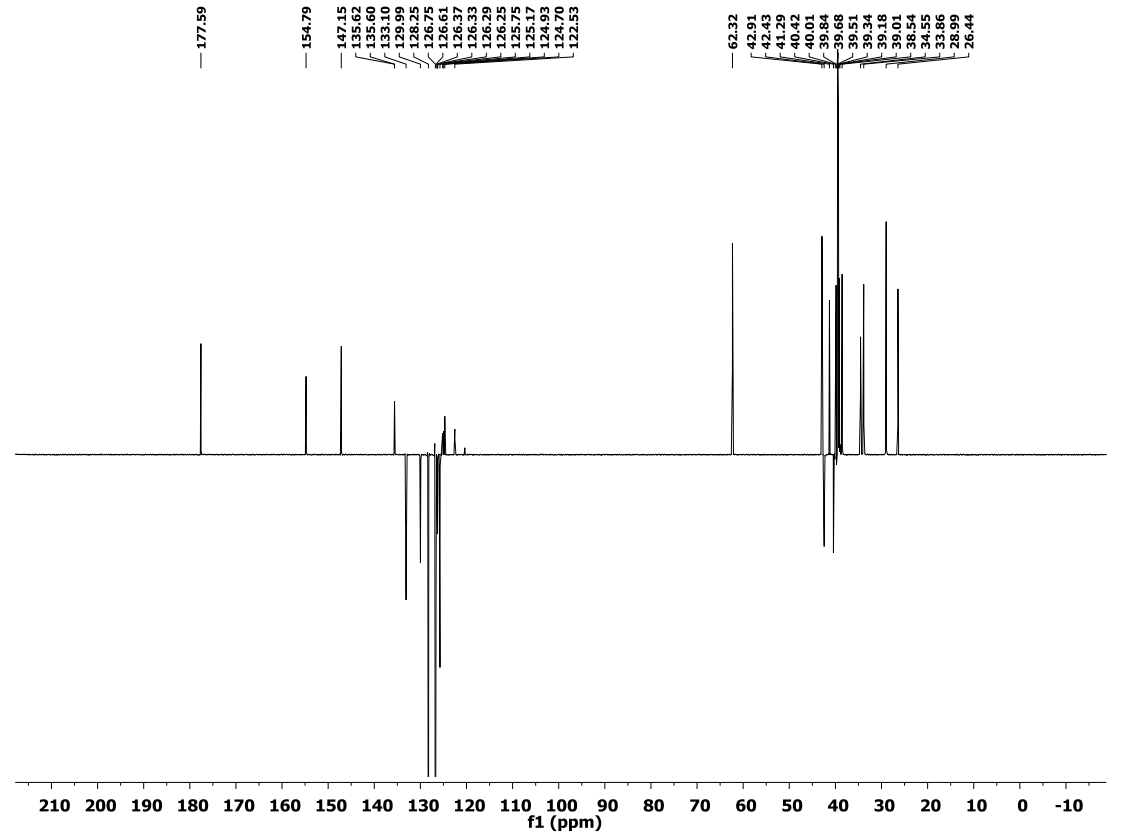
Carbamate **36db**{21}



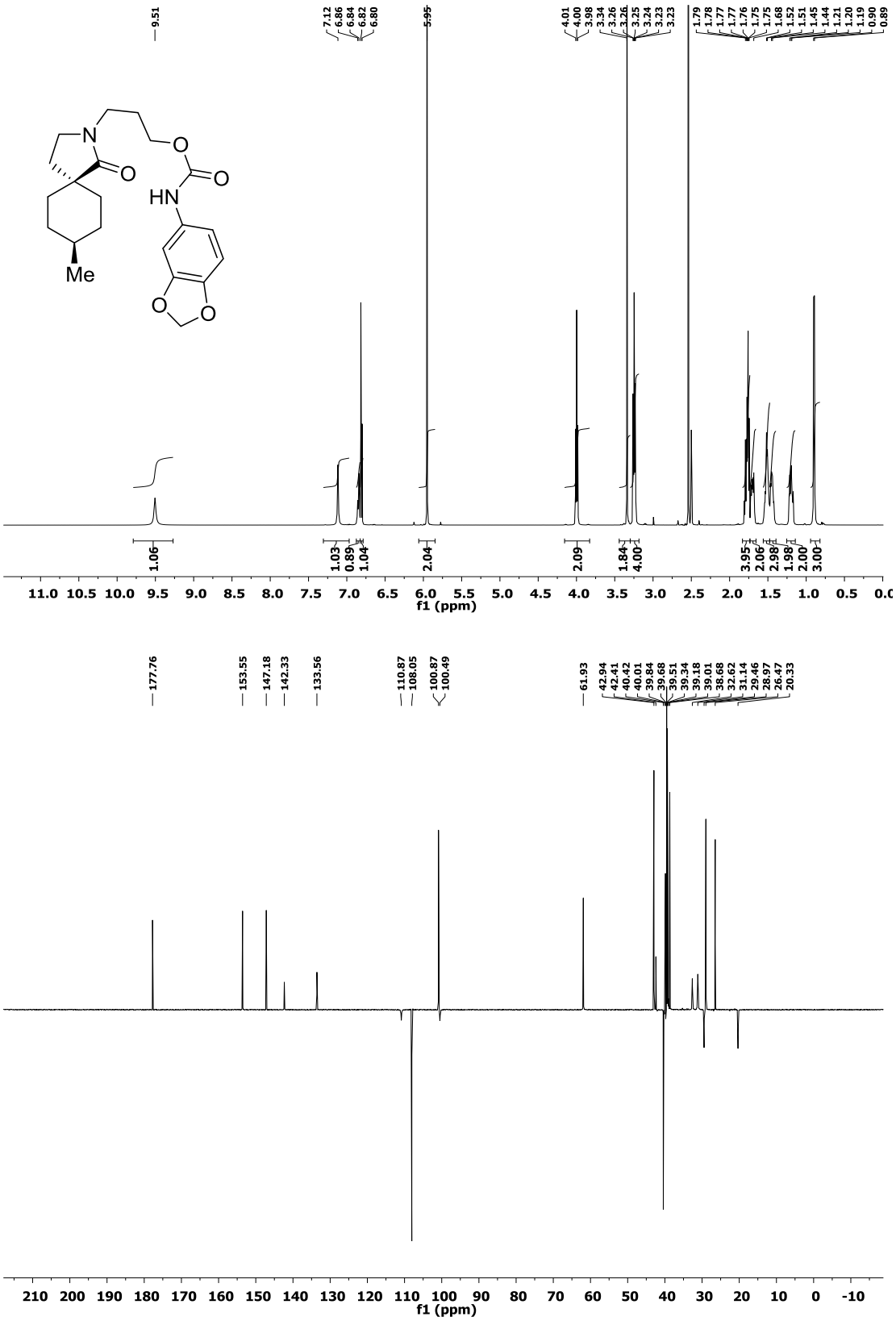


Carbamate **36db**{18}

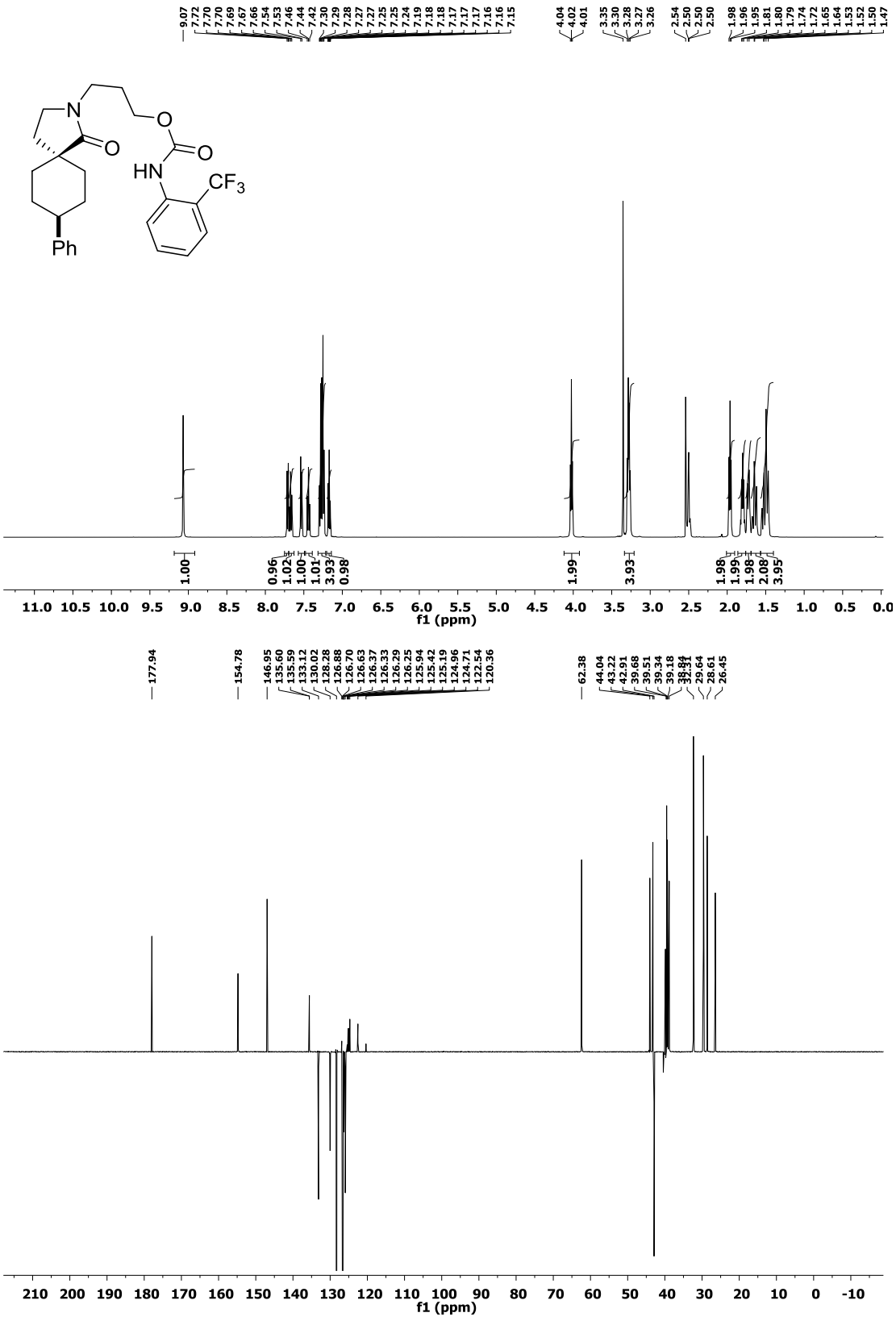




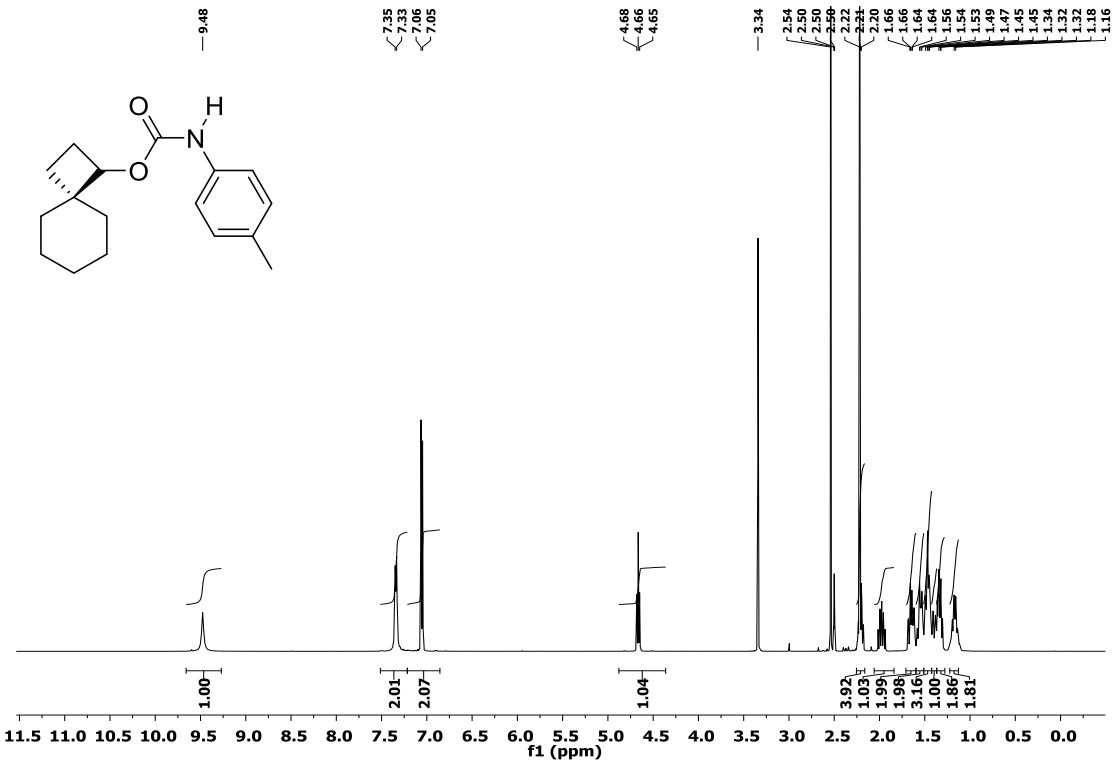
Carbamate **36bb**{16}

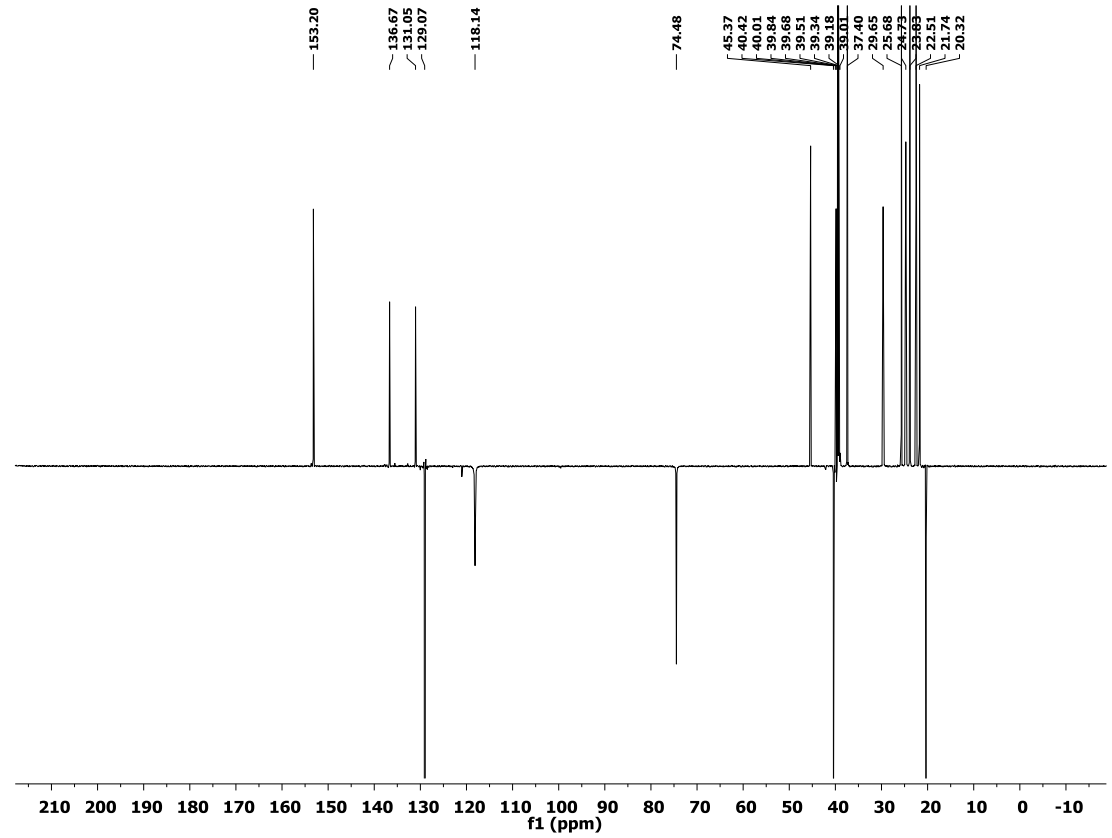


Carbamate **36db**{12}

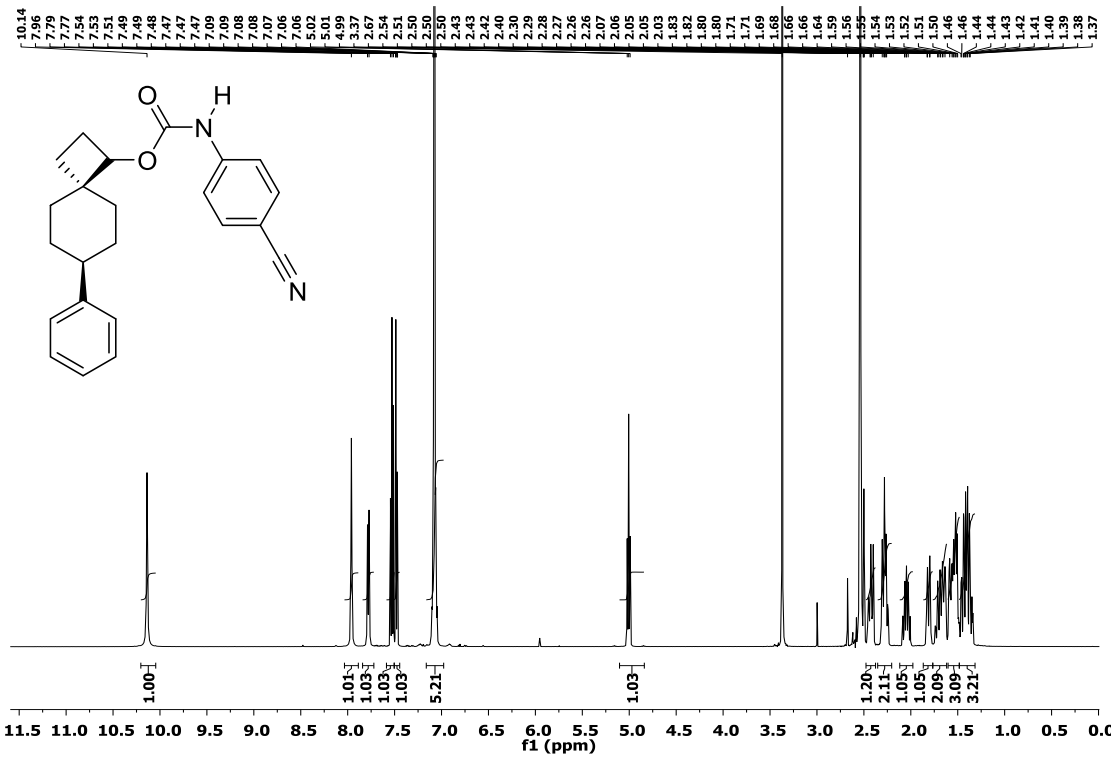


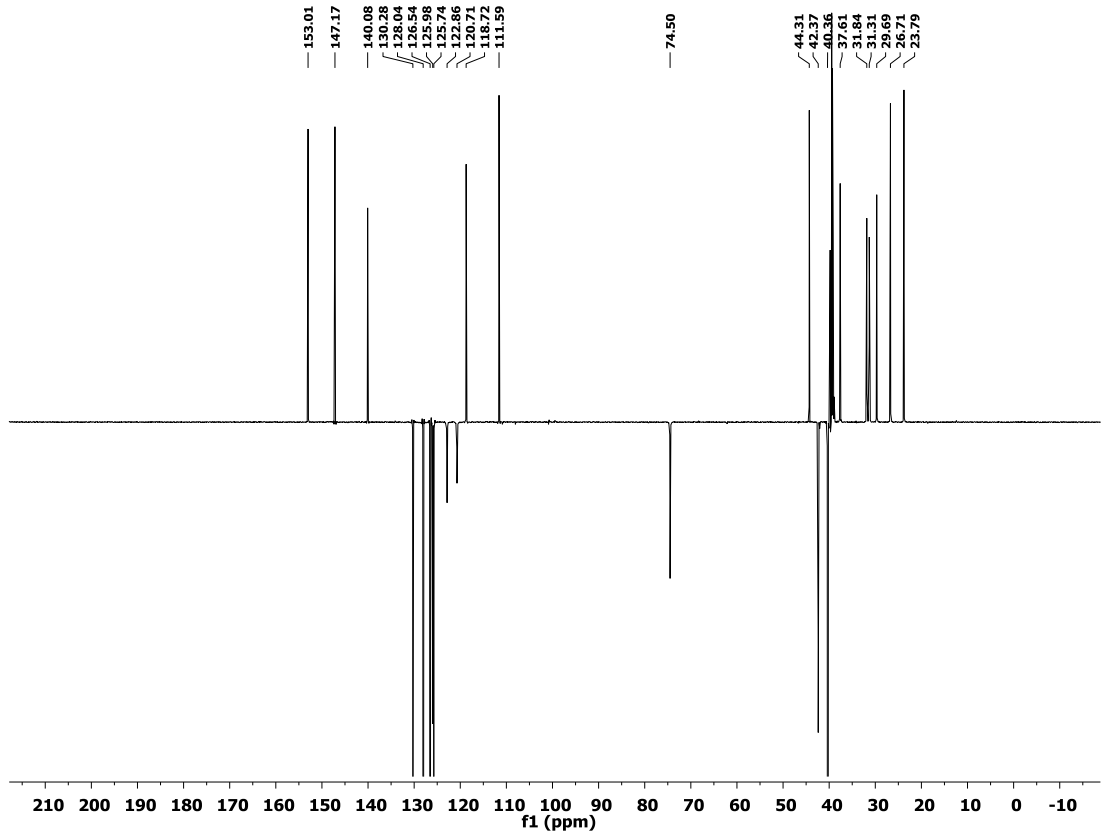
Carbamate **34a**{6}



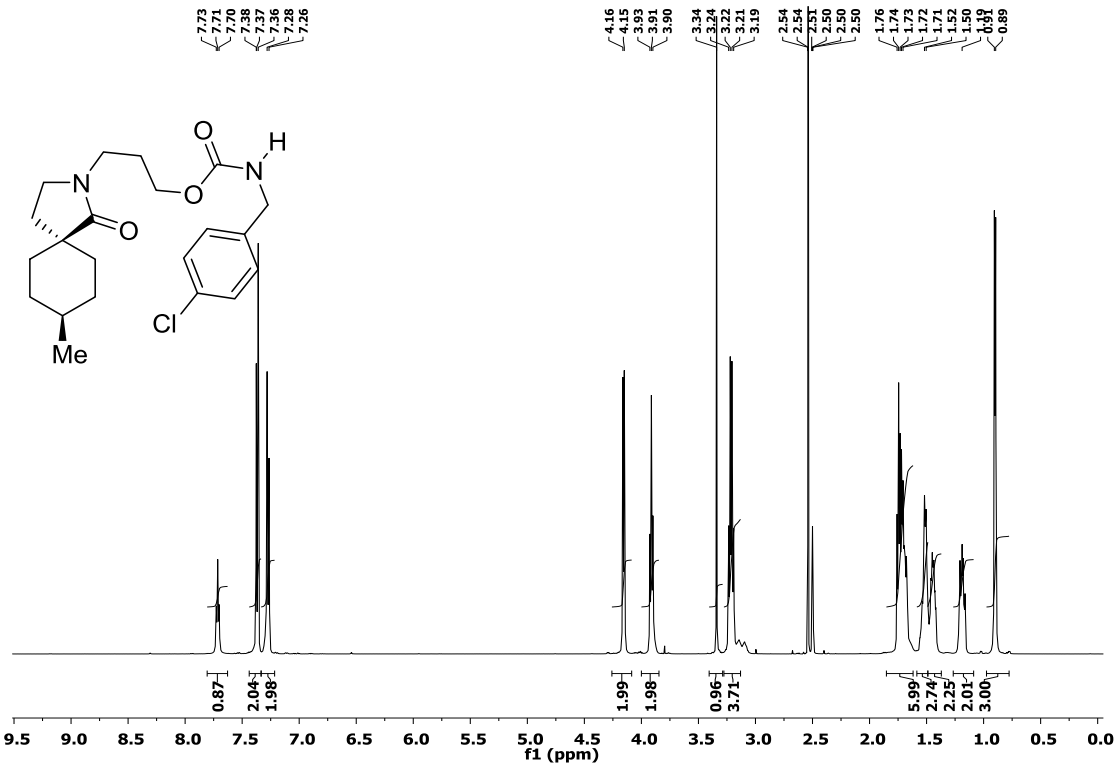


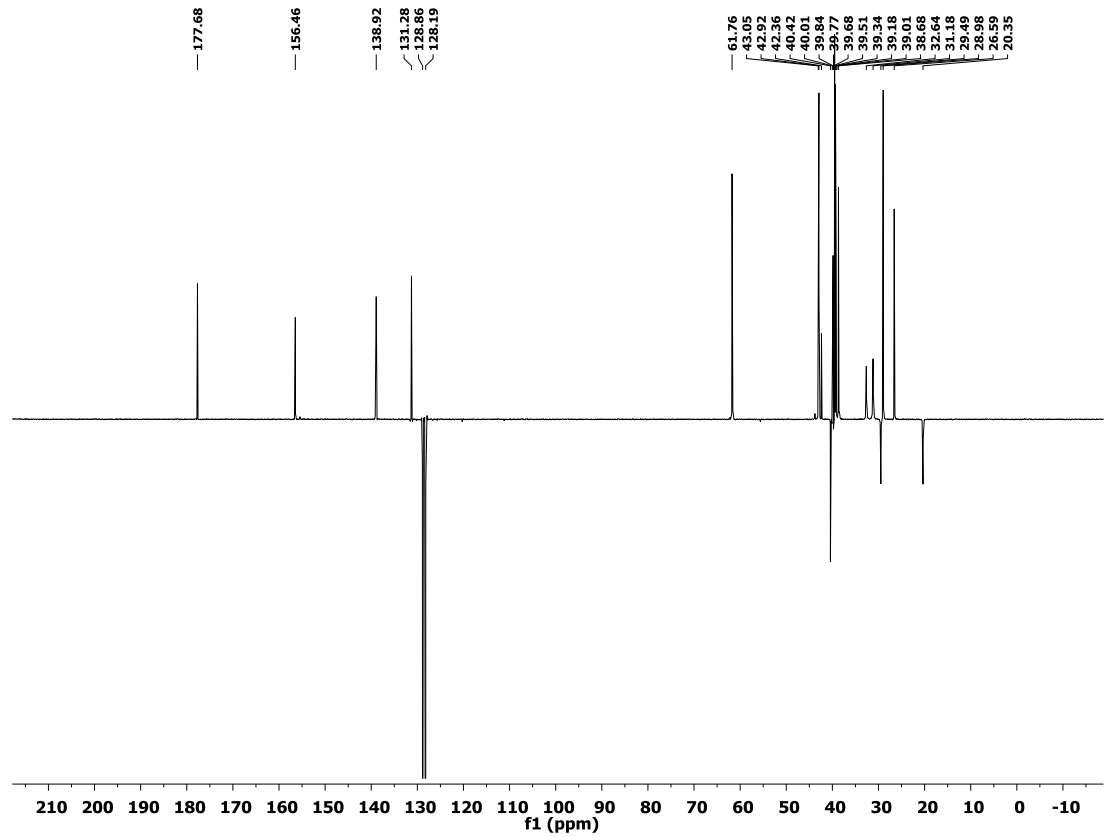
Carbamate **34d**{17}



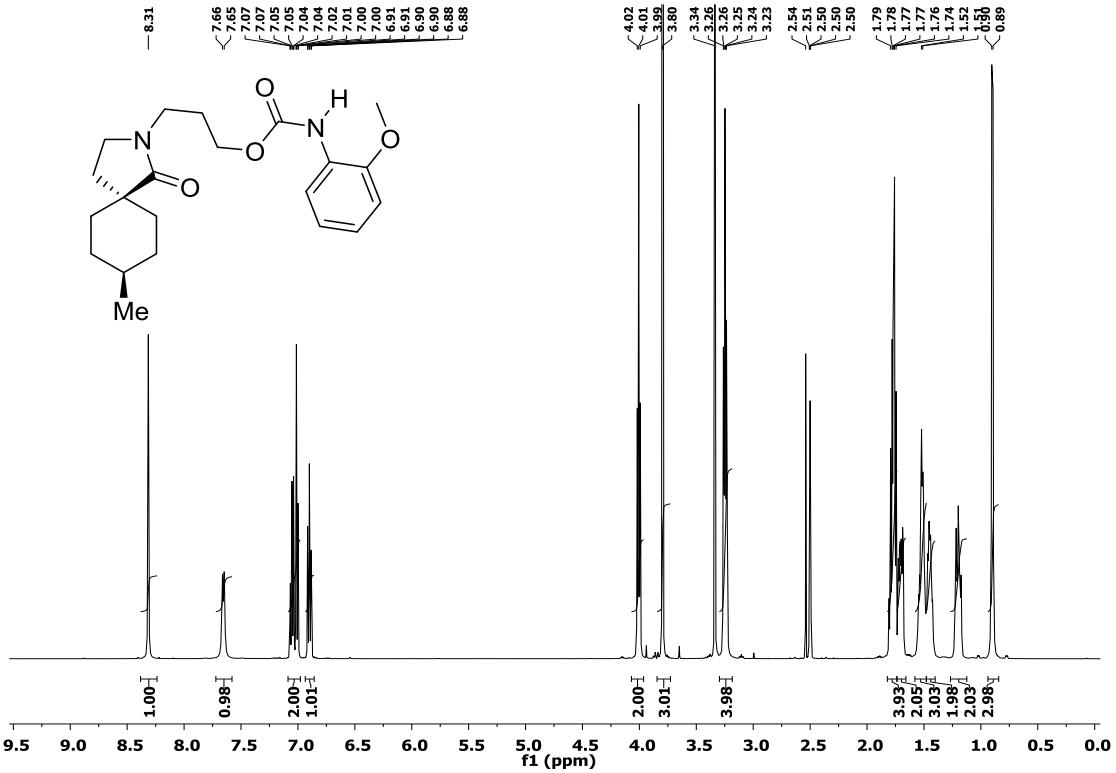


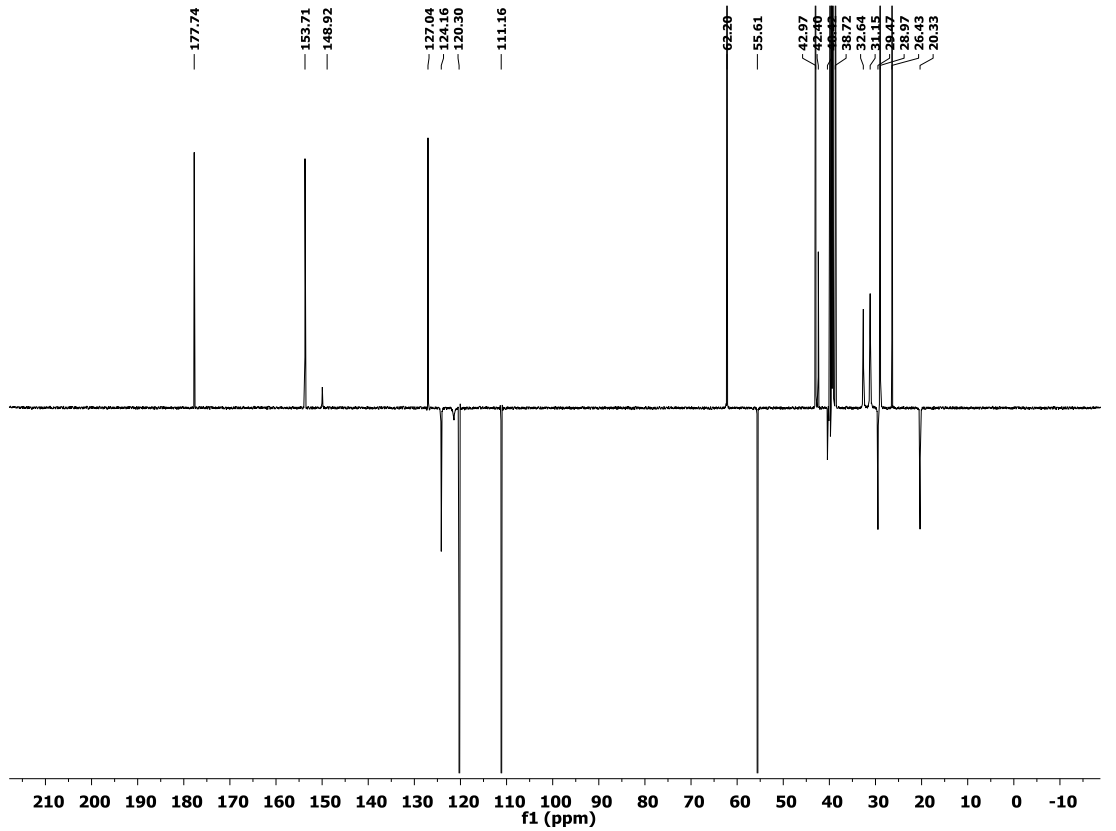
Carbamate **36bb**{15}



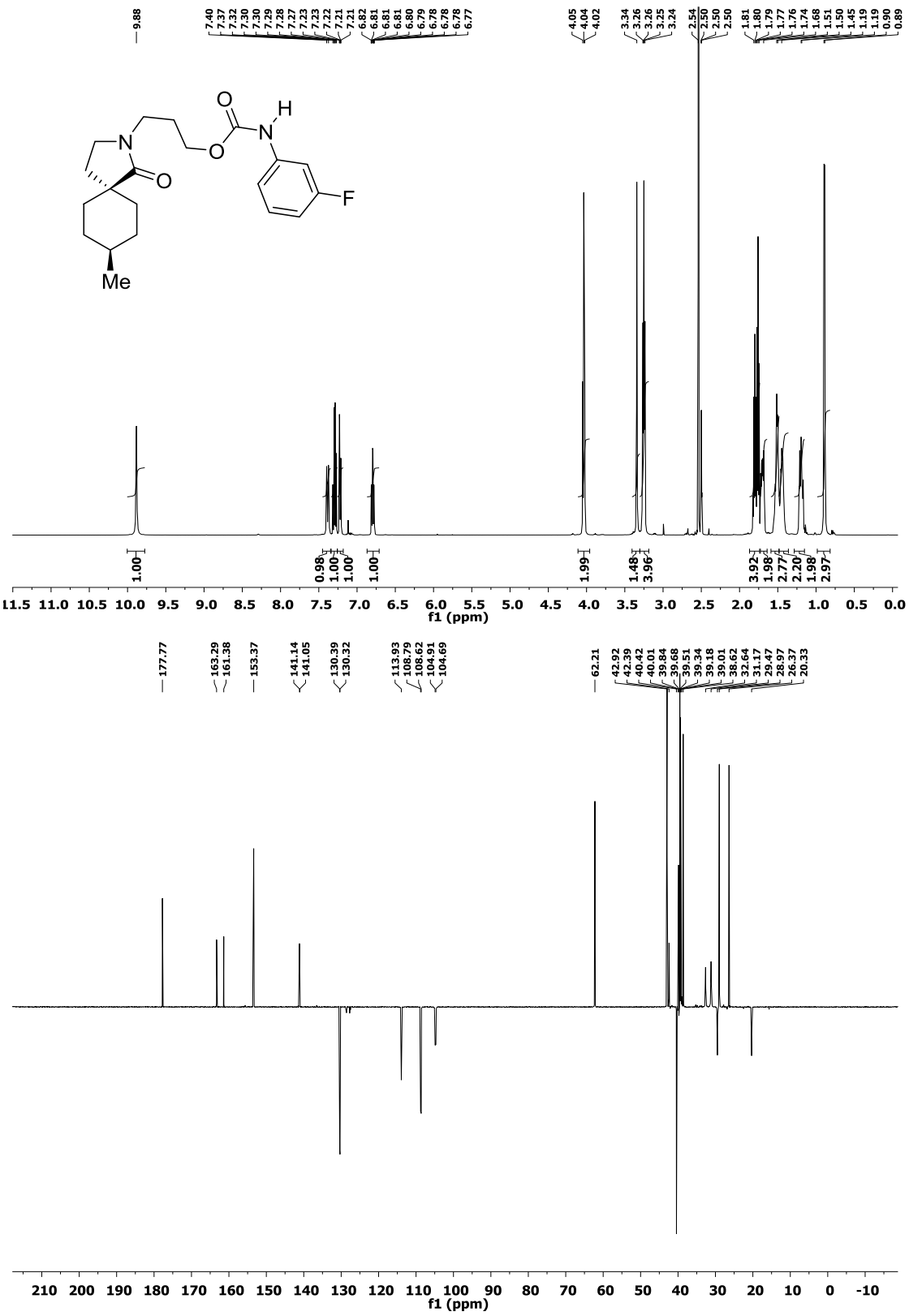


Carbamate **36bb**{5}

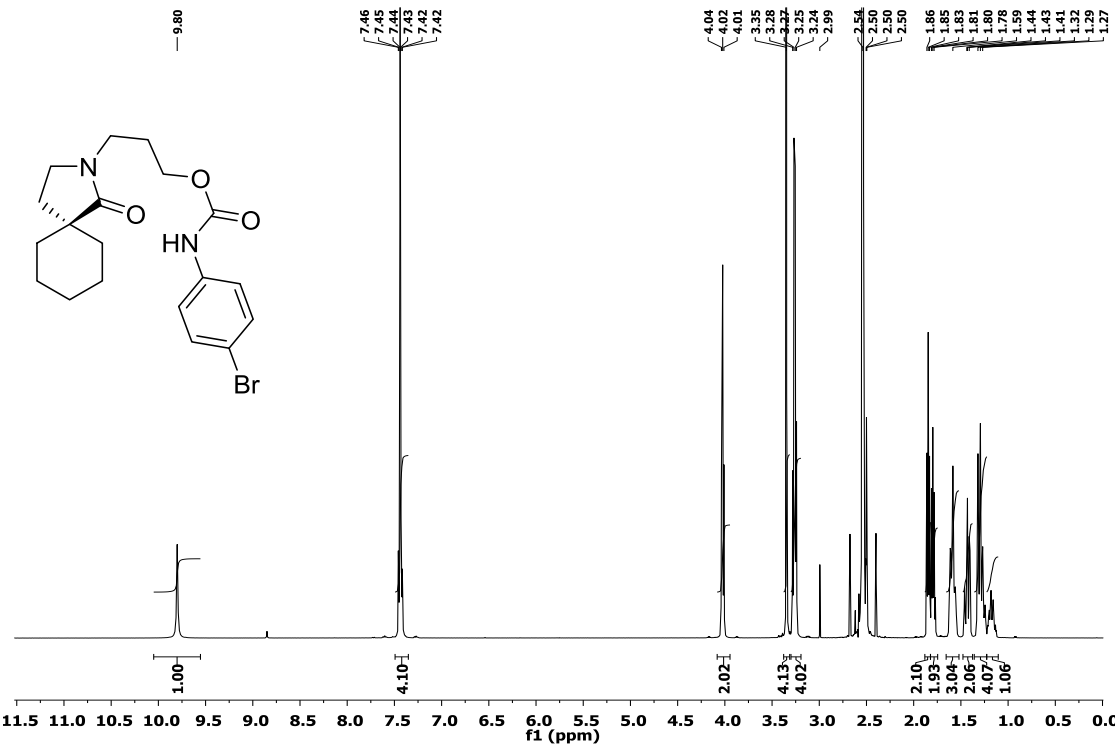


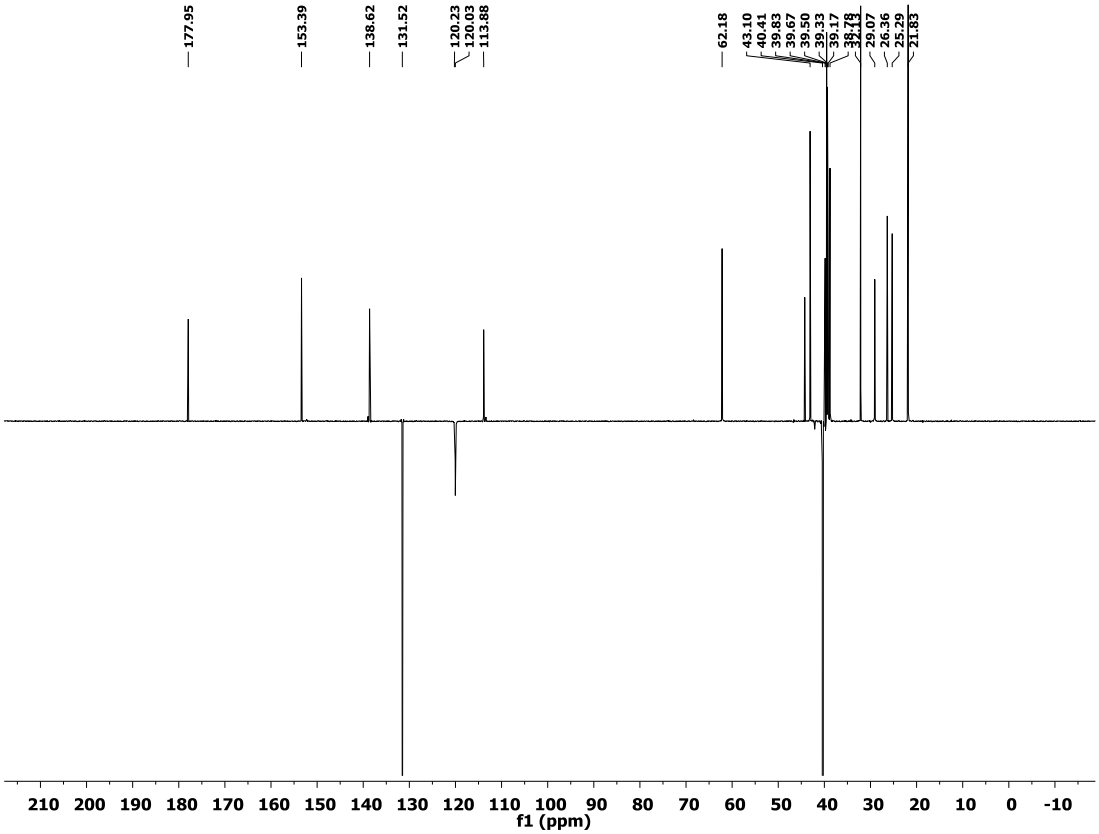


Carbamate **36bb**{22}

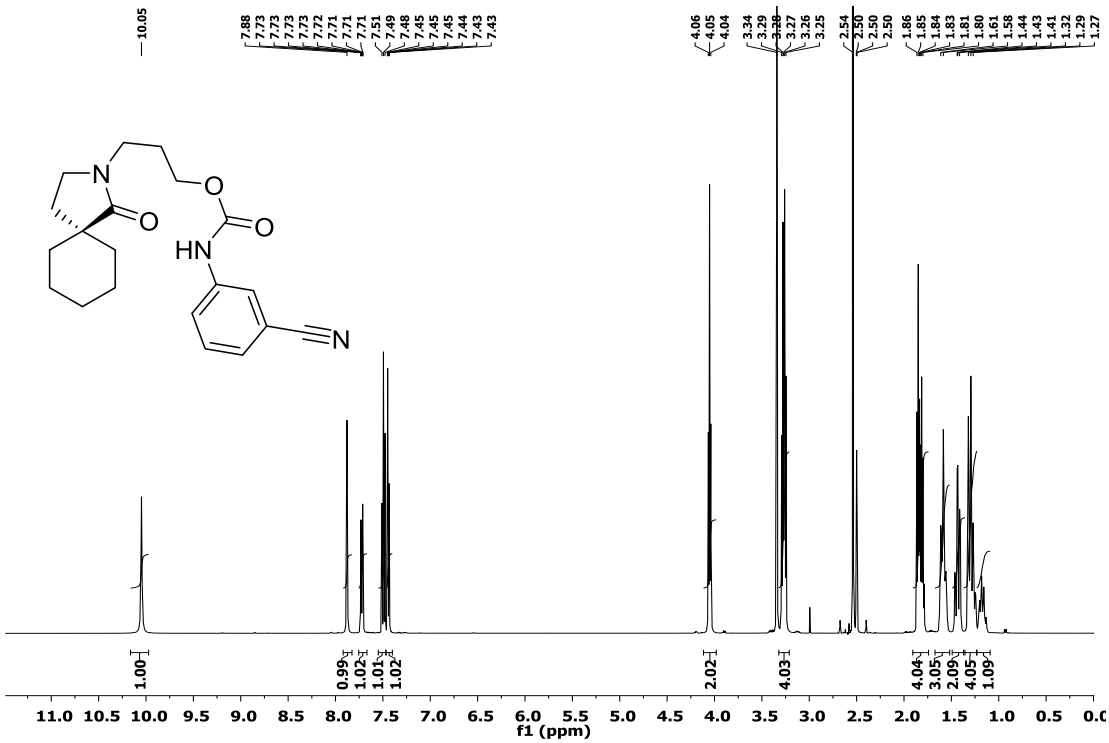


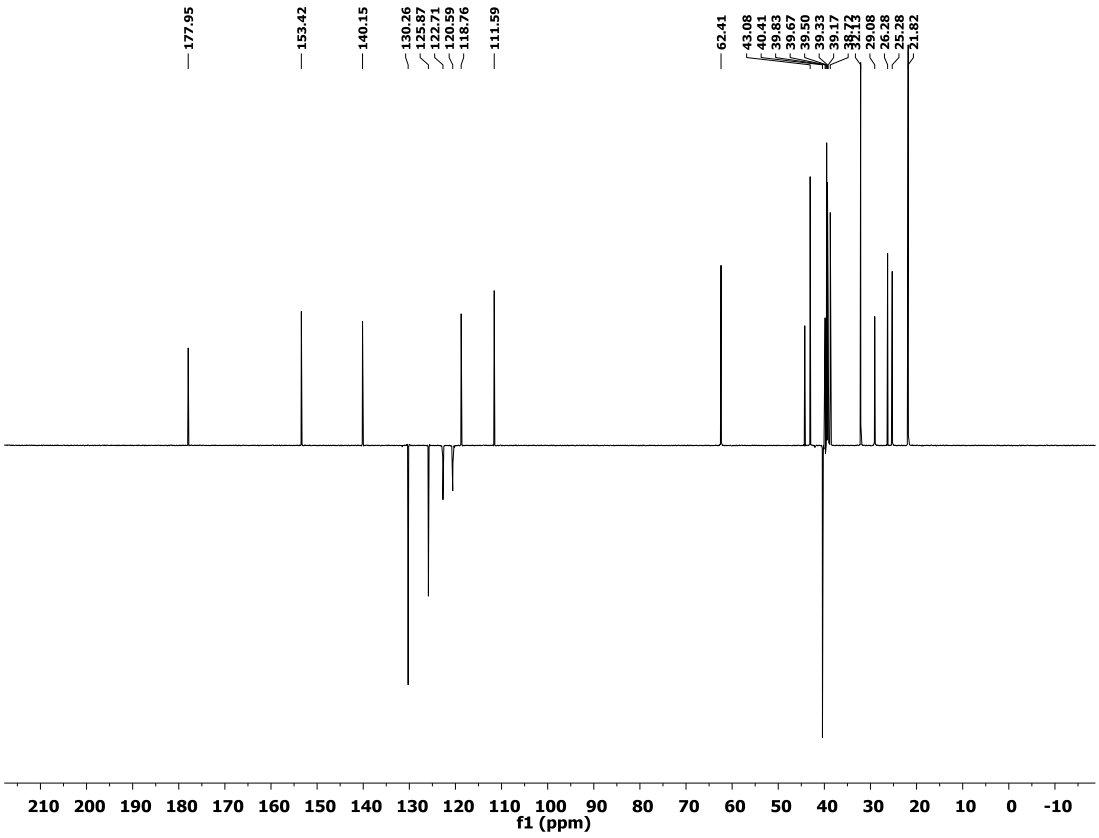
Carbamate **36ab**{2}





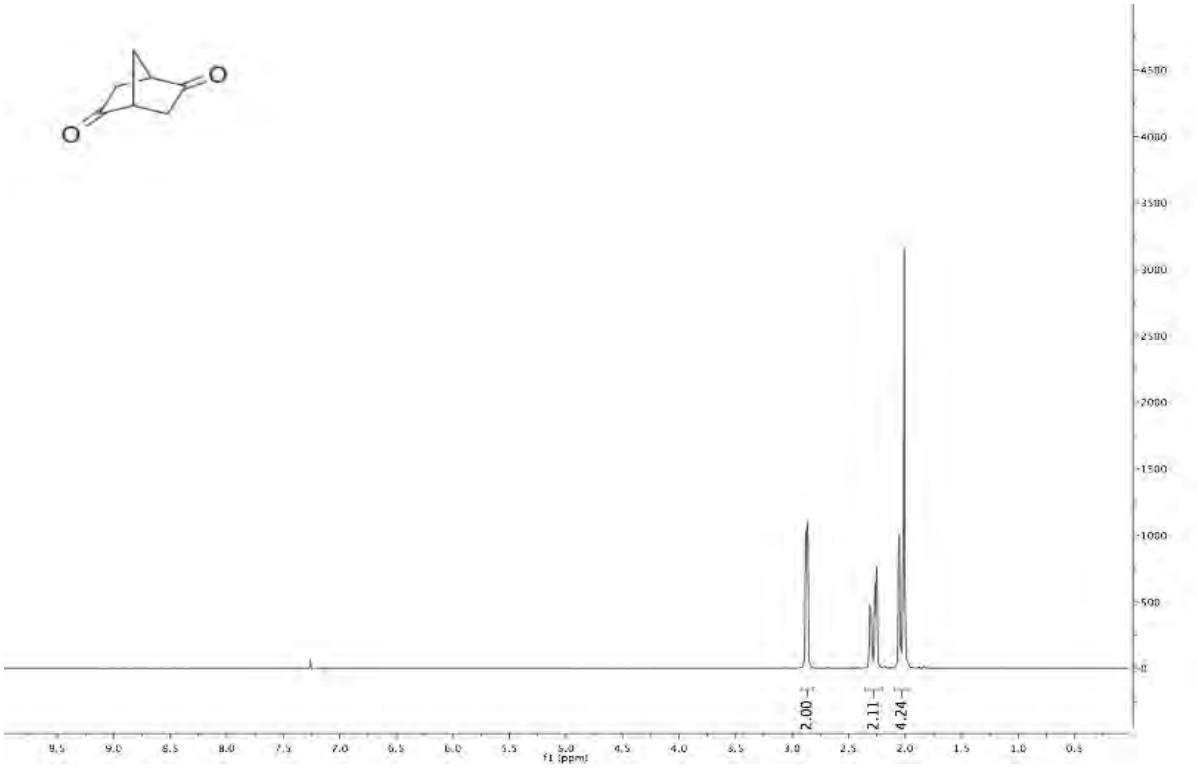
Carbamate **36ab**{31}

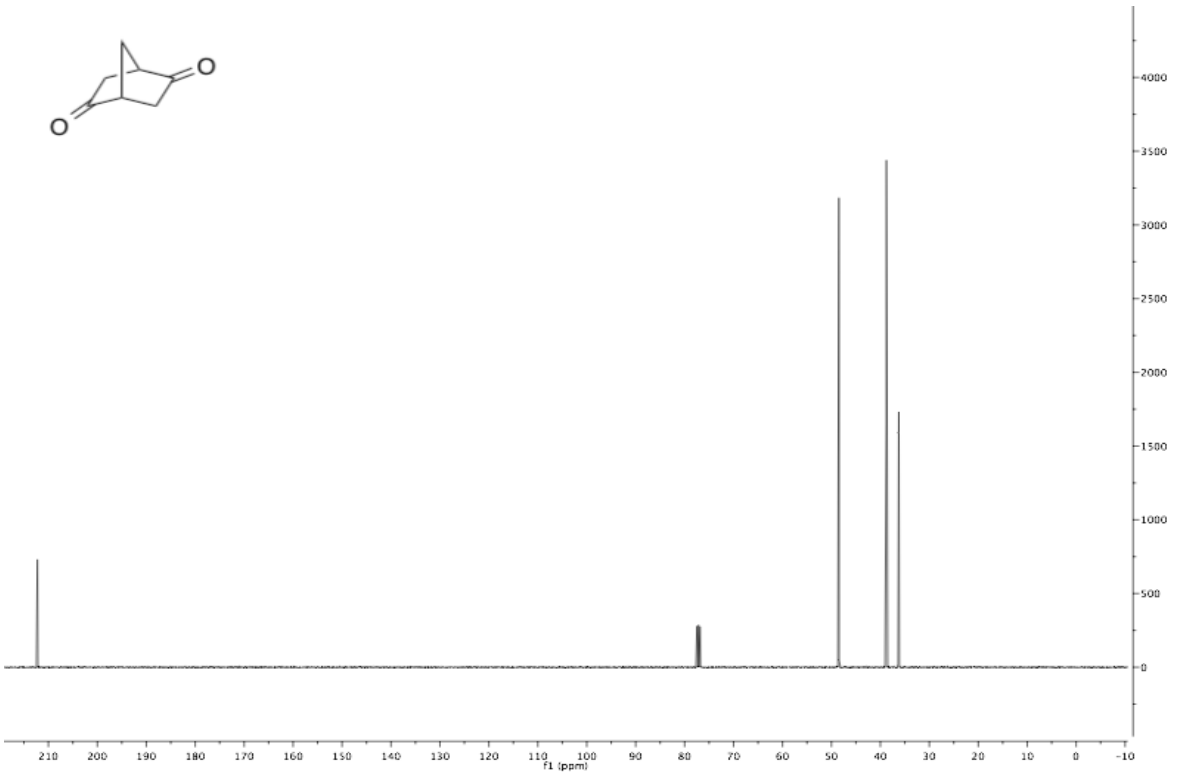




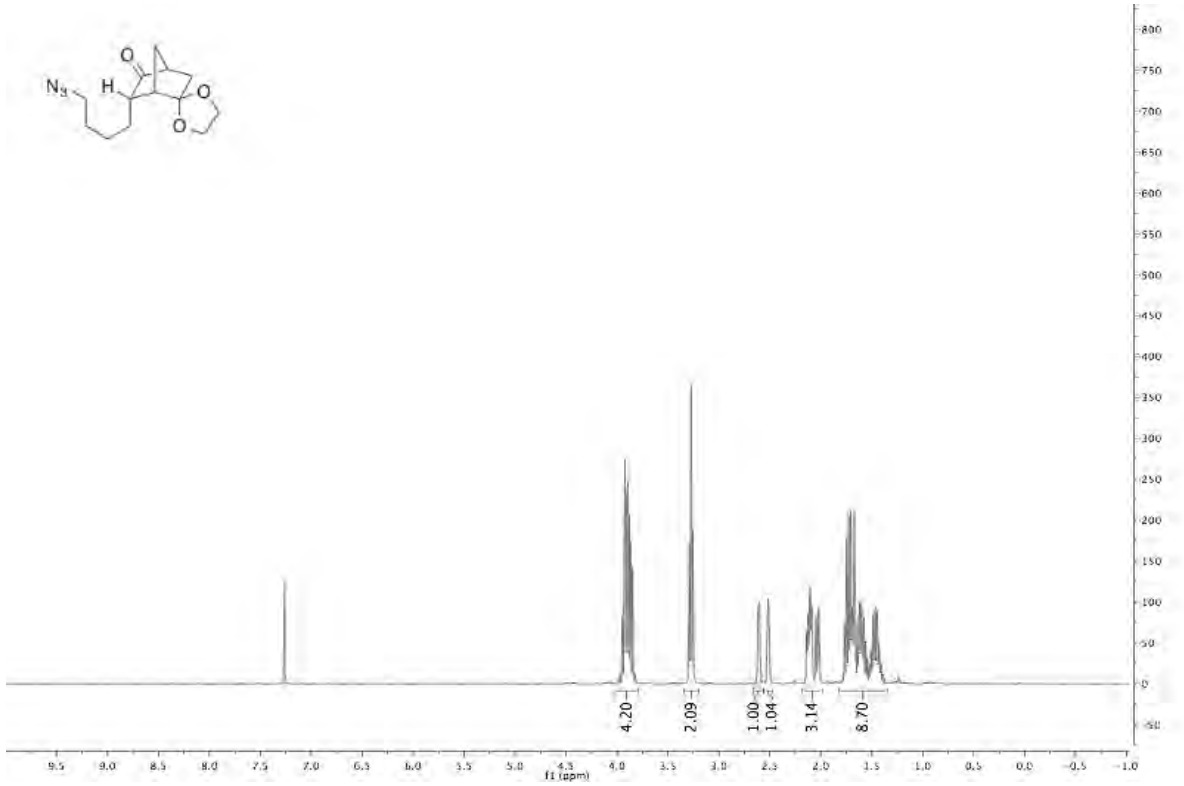
Sparteine-inspired series

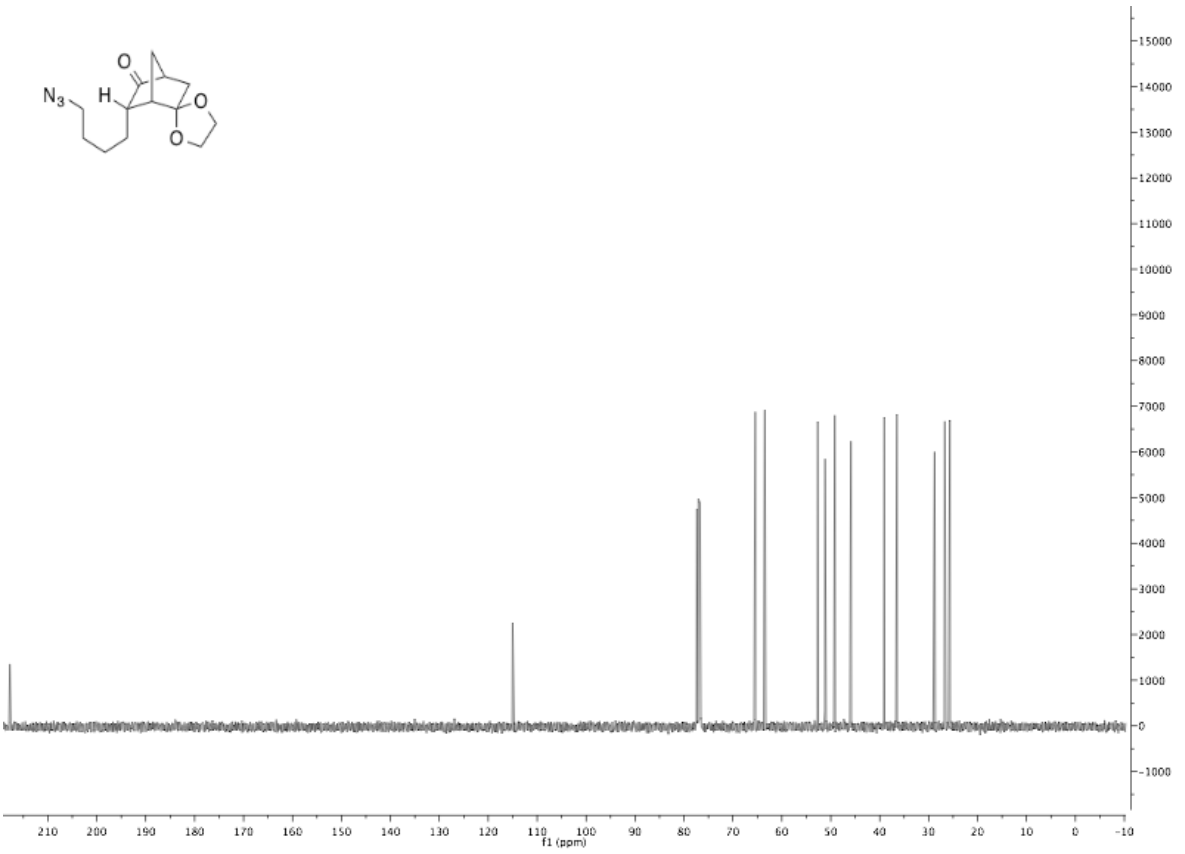
S11





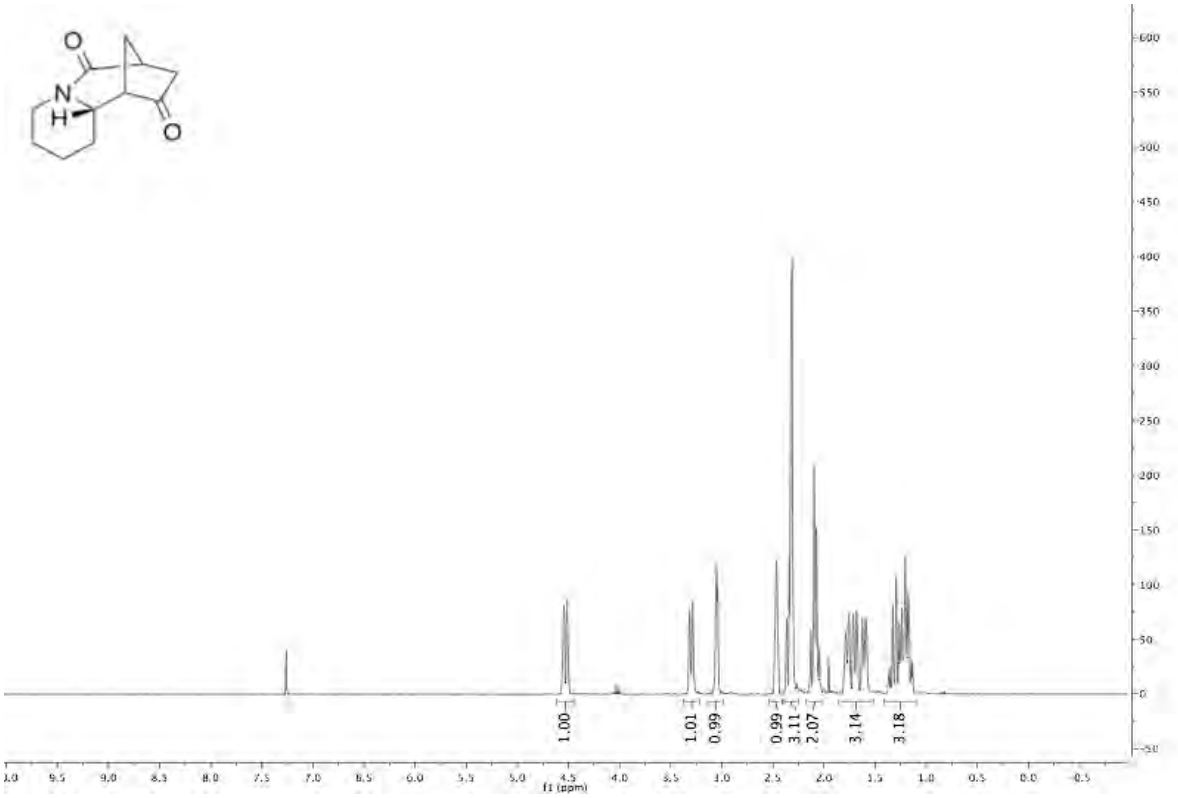
12

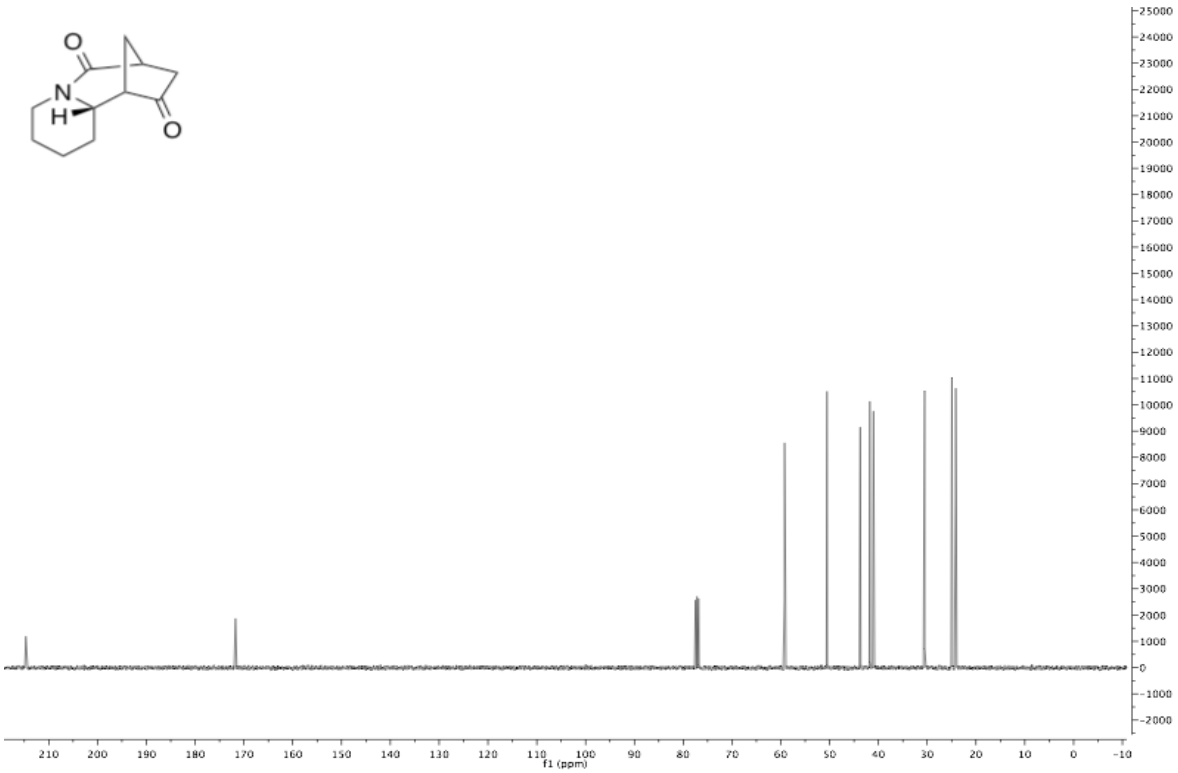




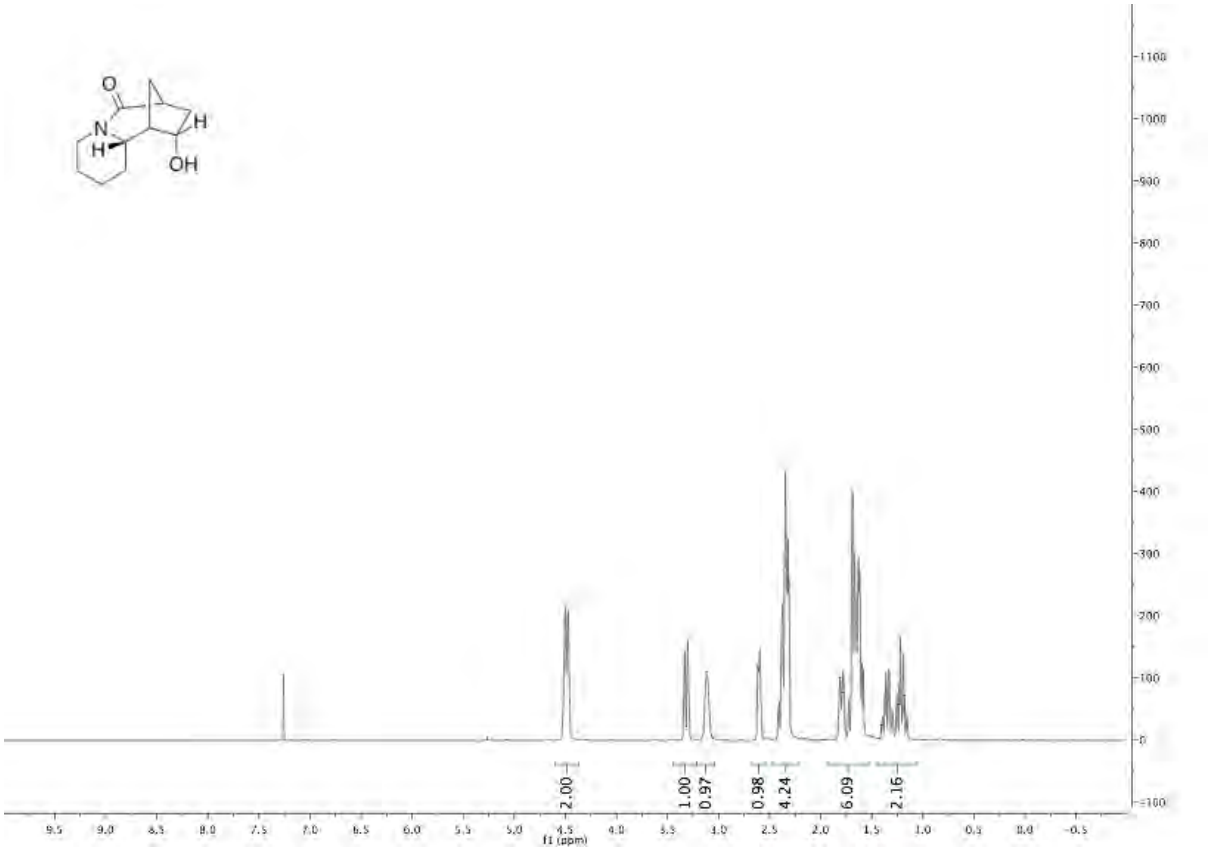
`

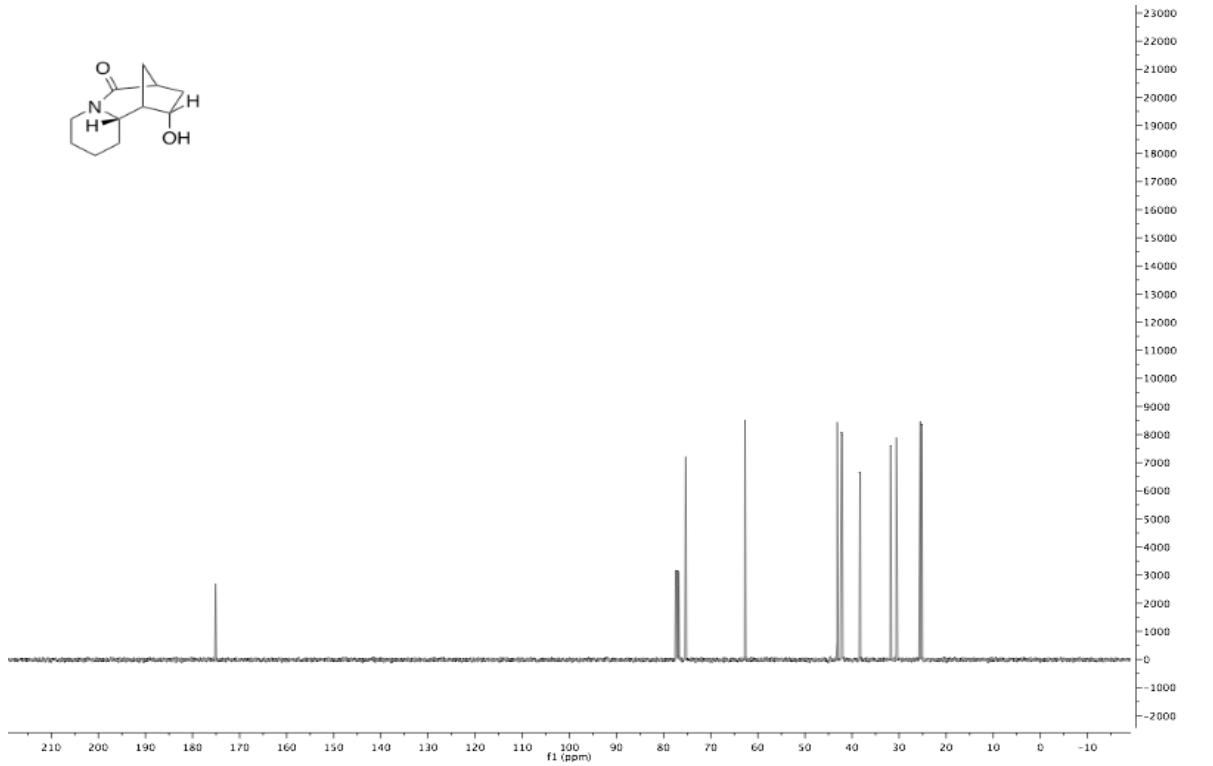
13



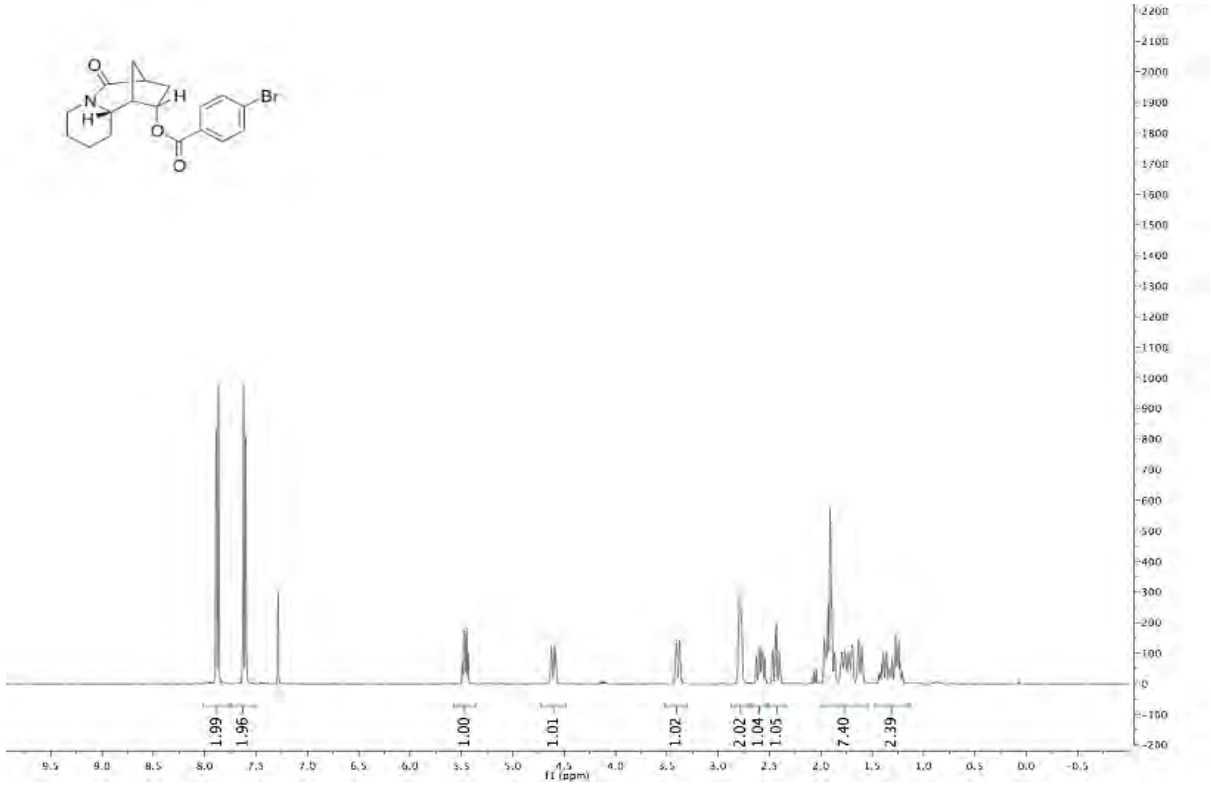


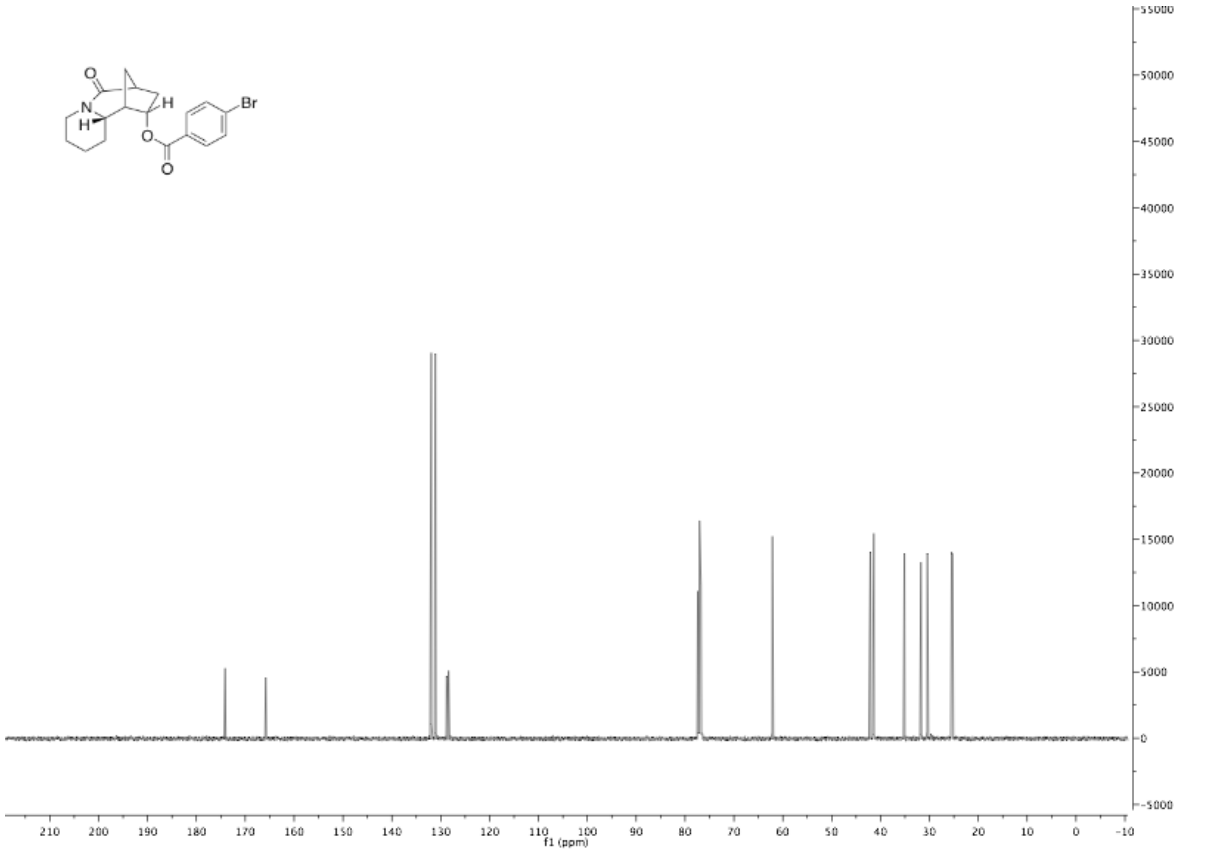
S13



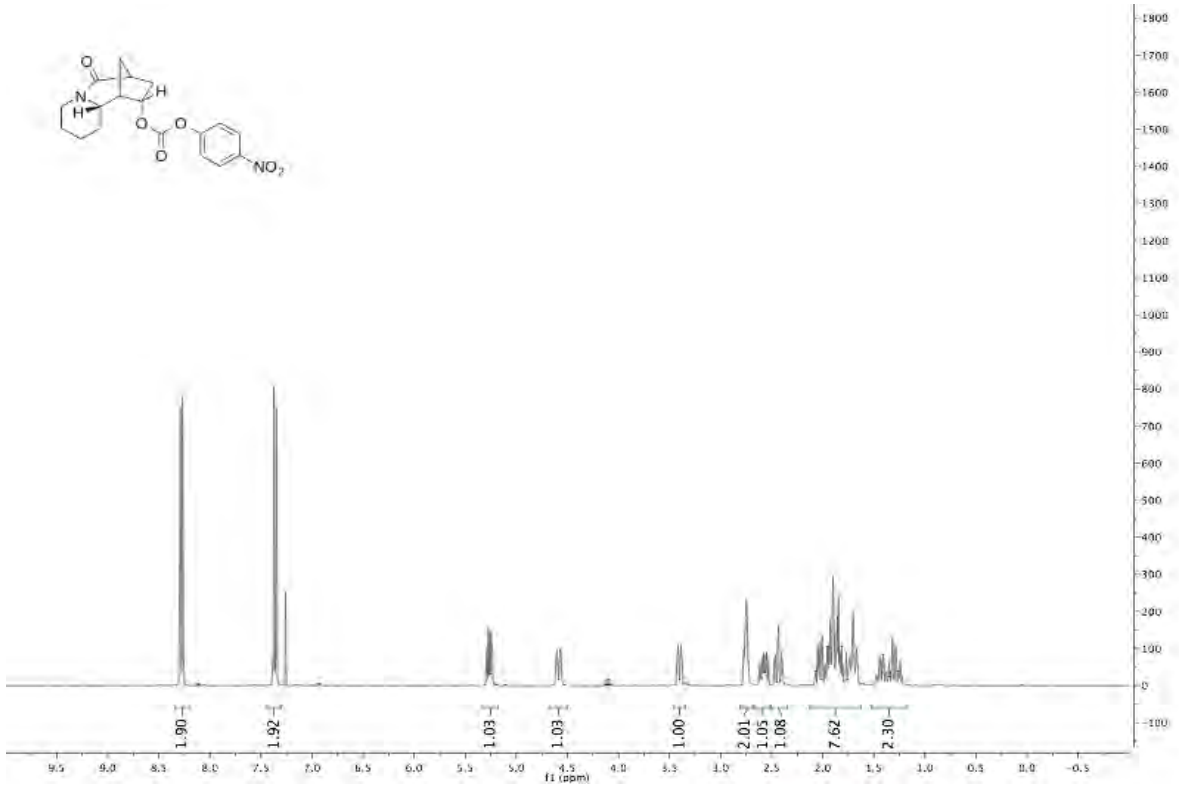


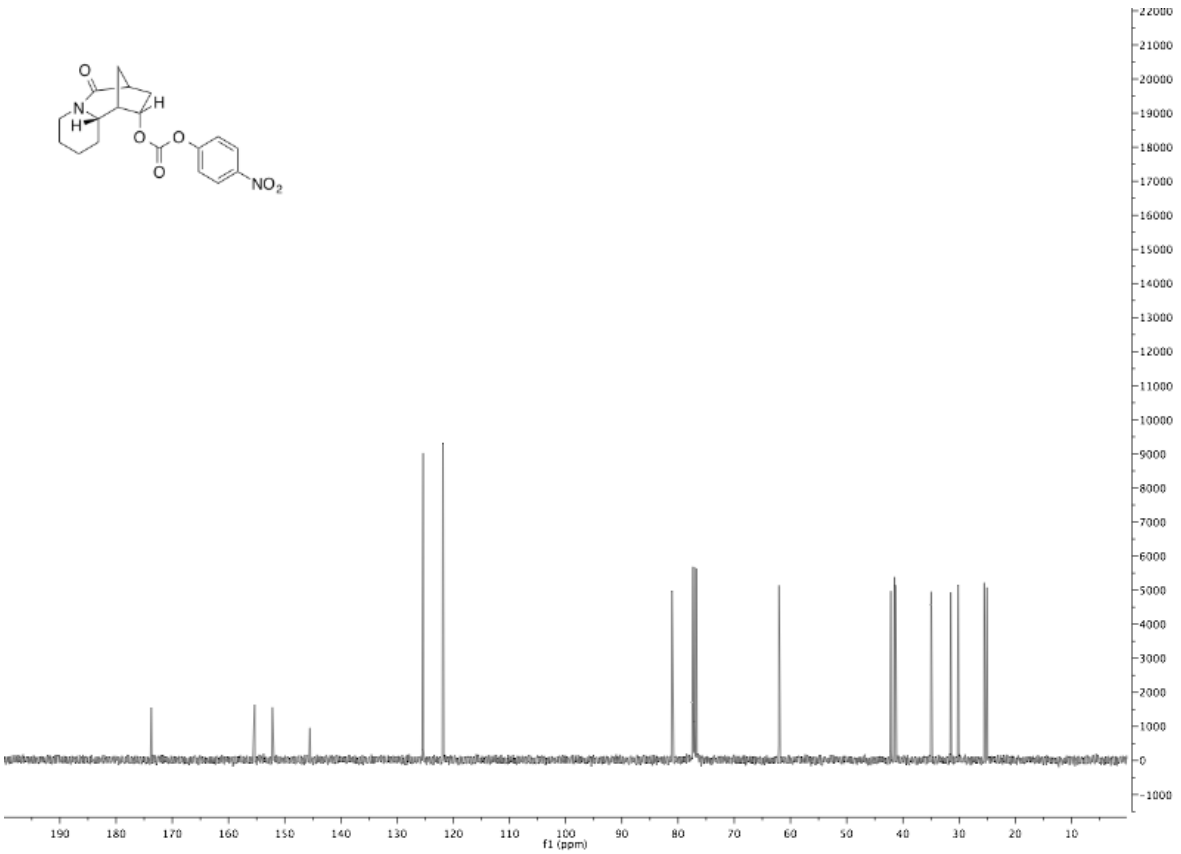
S14


O
N
H
H
O
O
Br
1.99
1.96
1.00
1.01
1.02
2.02
1.04
1.05
7.40
2.39
f1 (ppm)

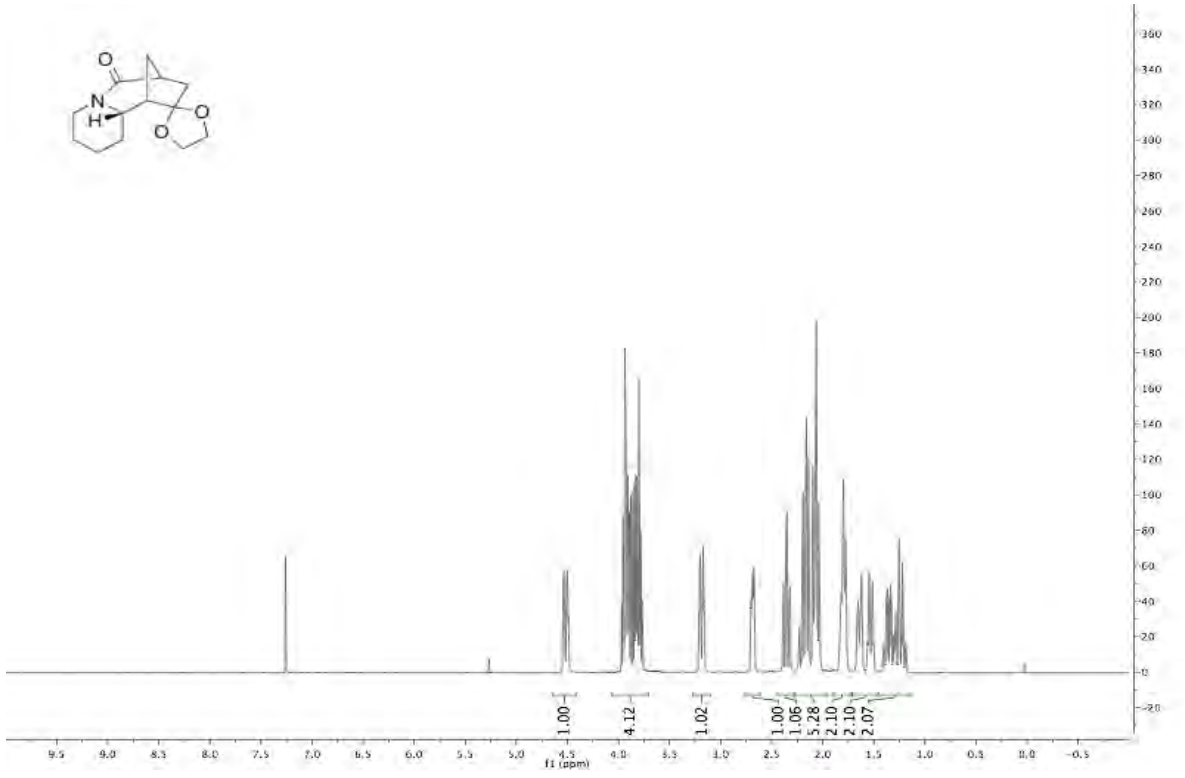

O
N
H
H
O
O
Br
f1 (ppm)

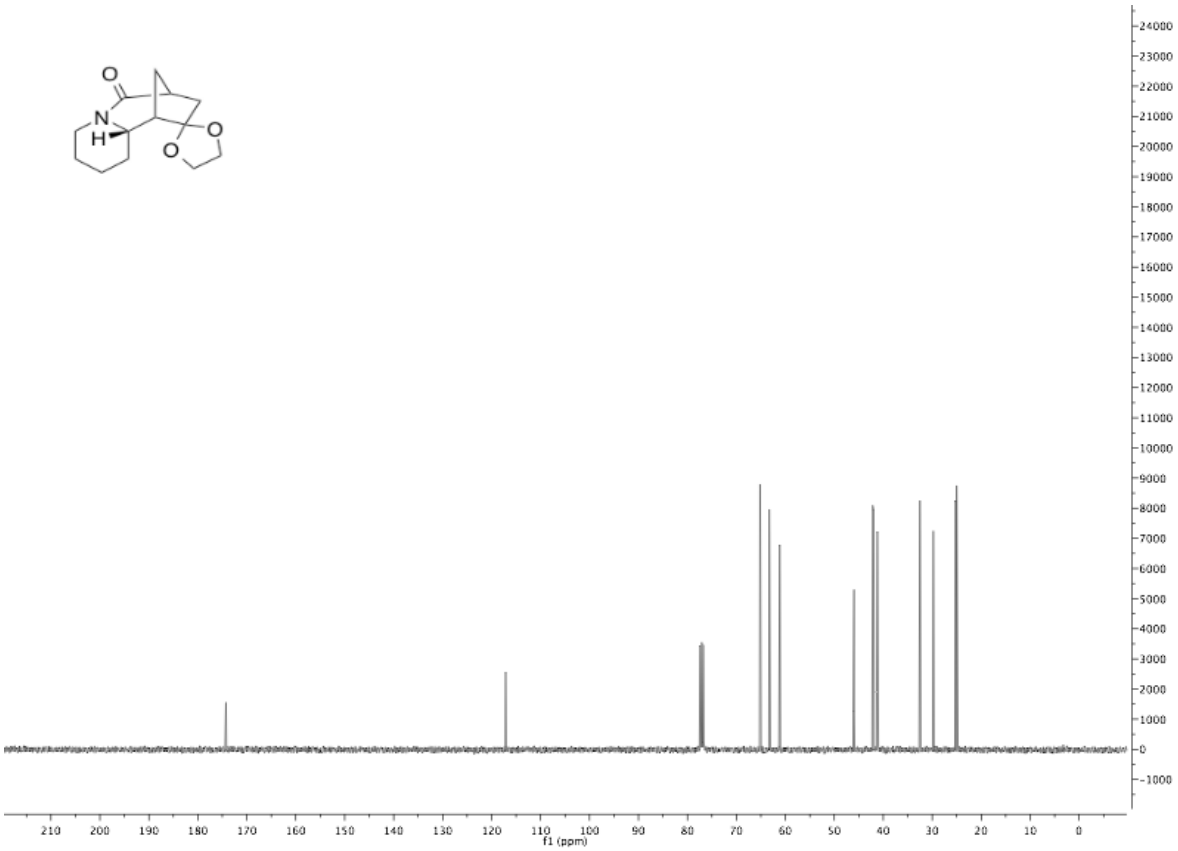
39



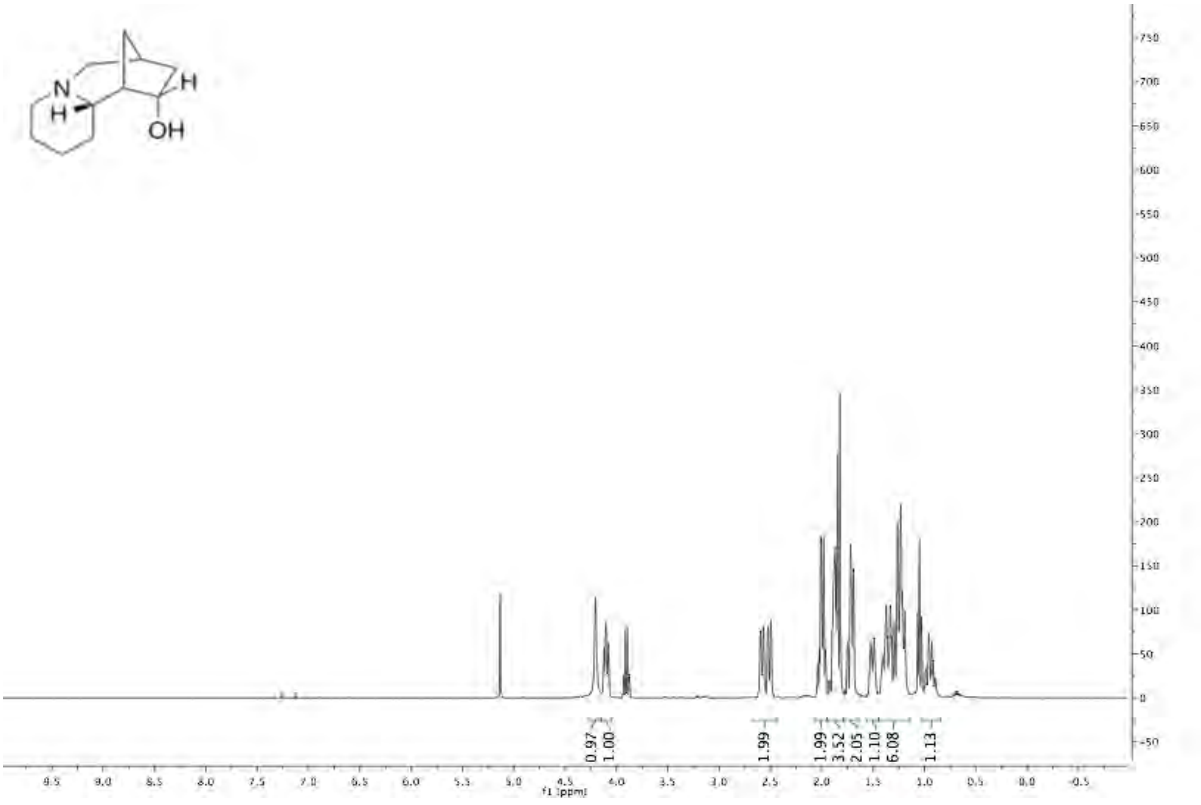


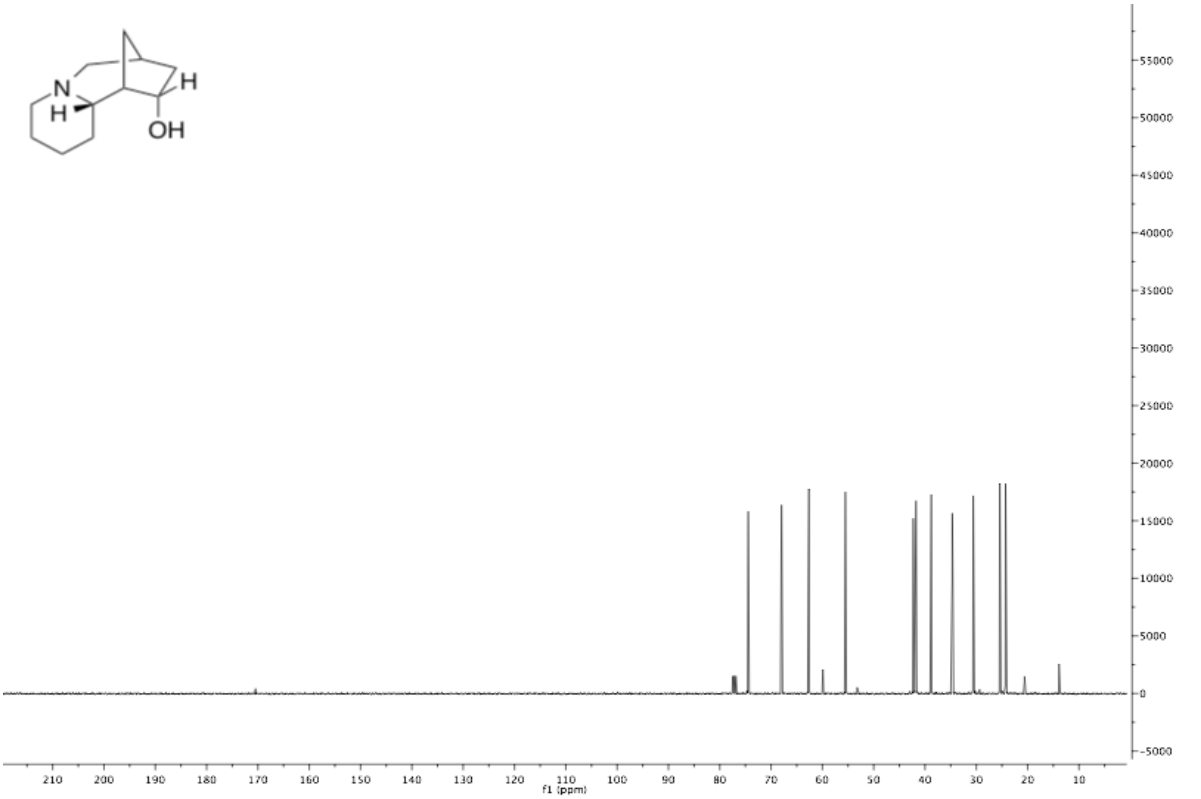
14



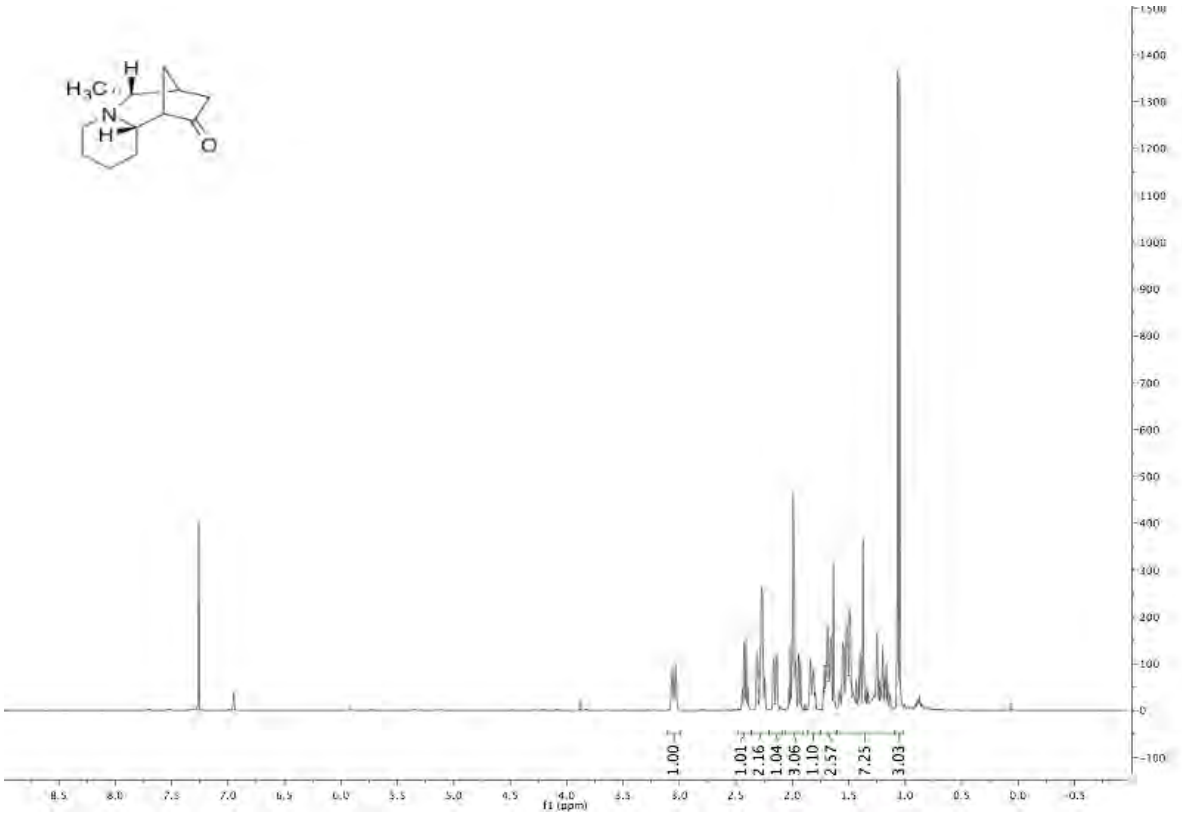


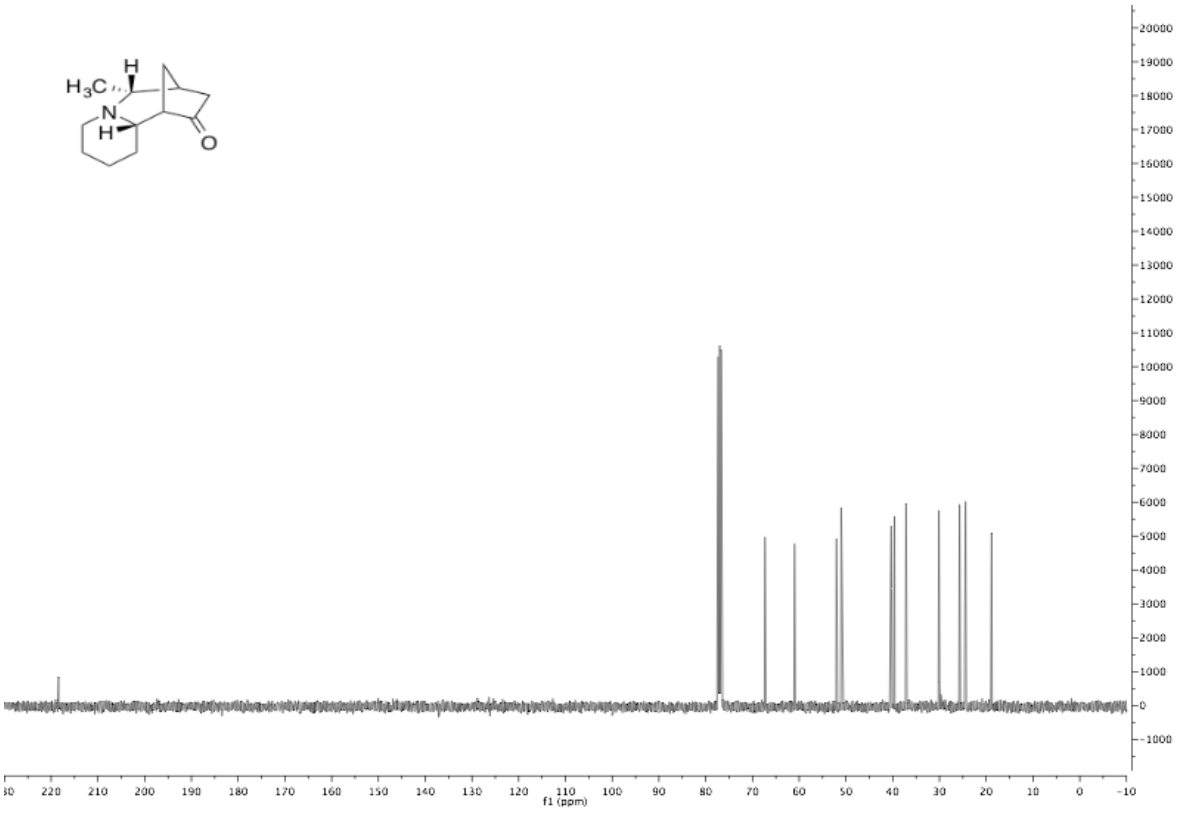
41



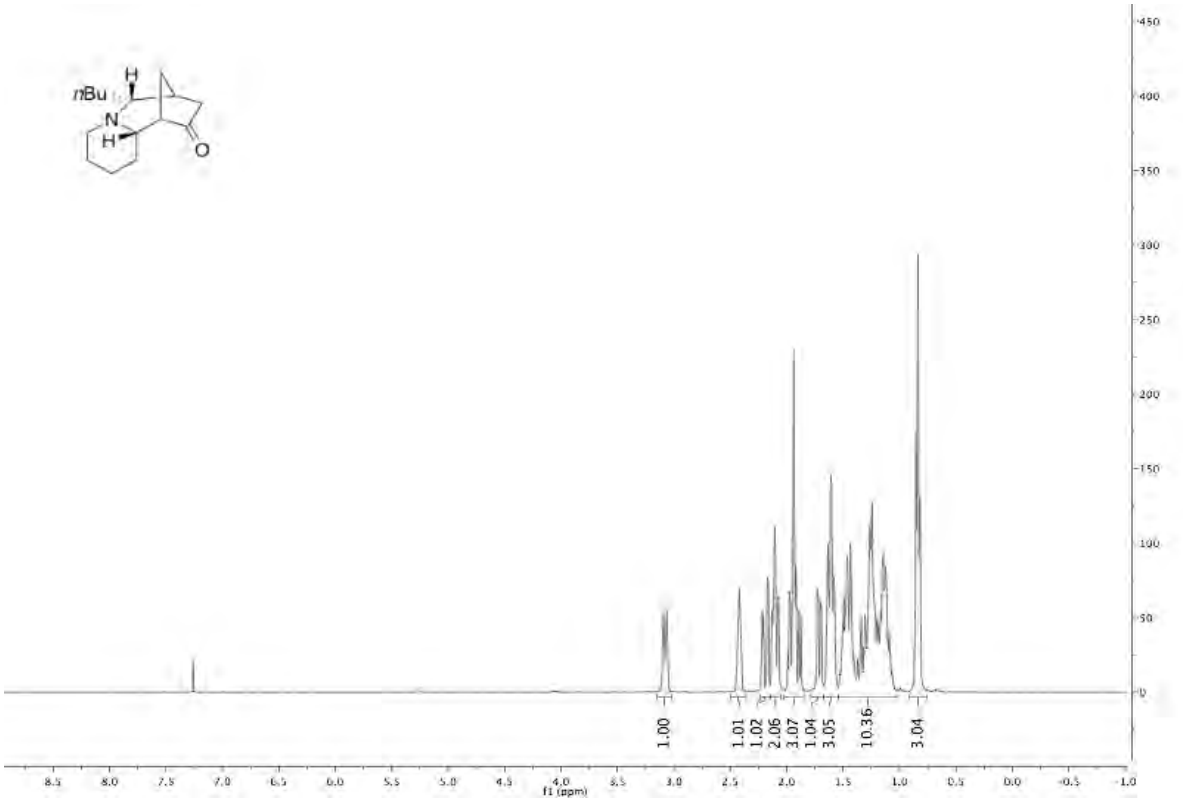


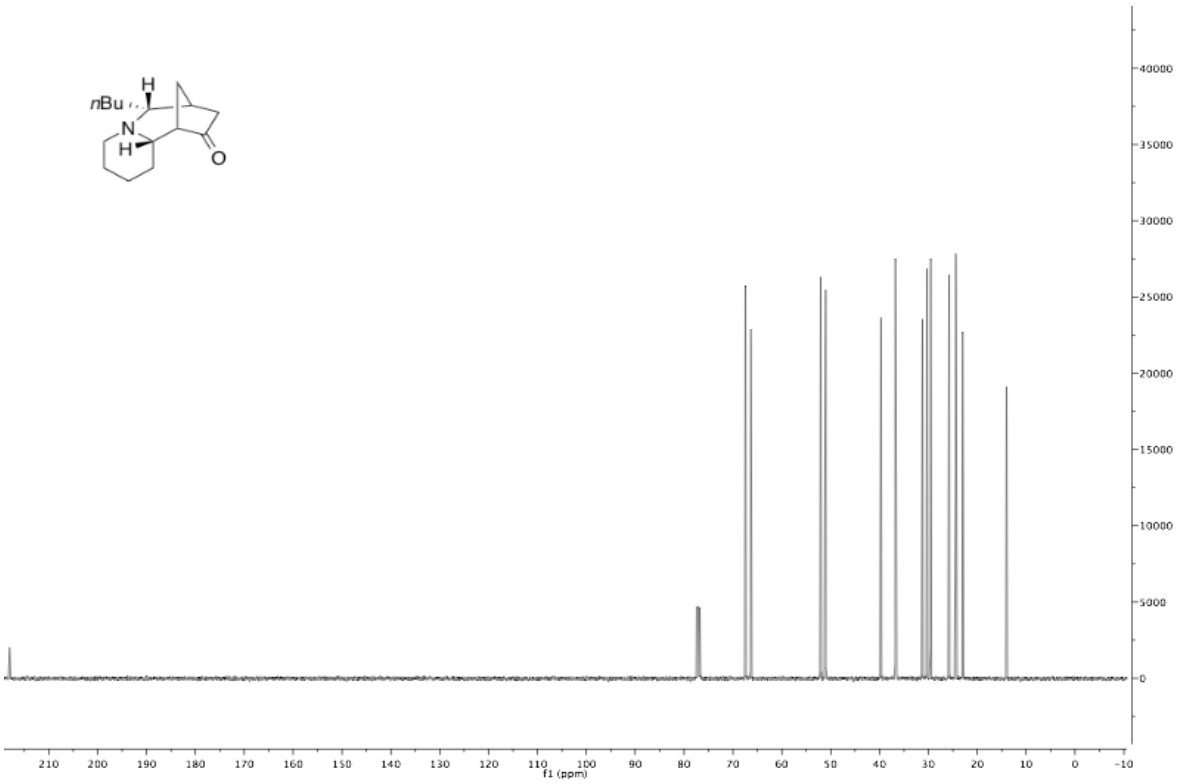
15a


H
H3C
N
H
O
1.00
1.01
2.16
1.04
3.06
1.10
2.57
7.25
3.03
f1 (ppm)

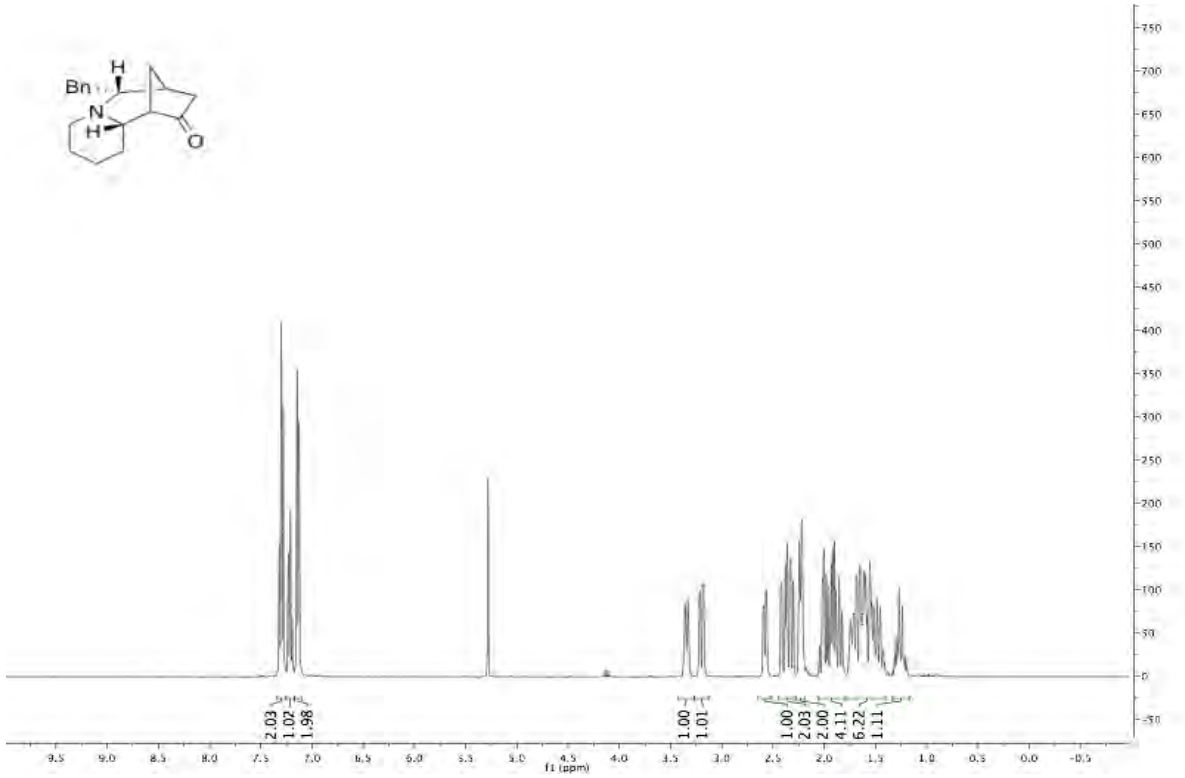

H
H3C
N
H
O
f1 (ppm)

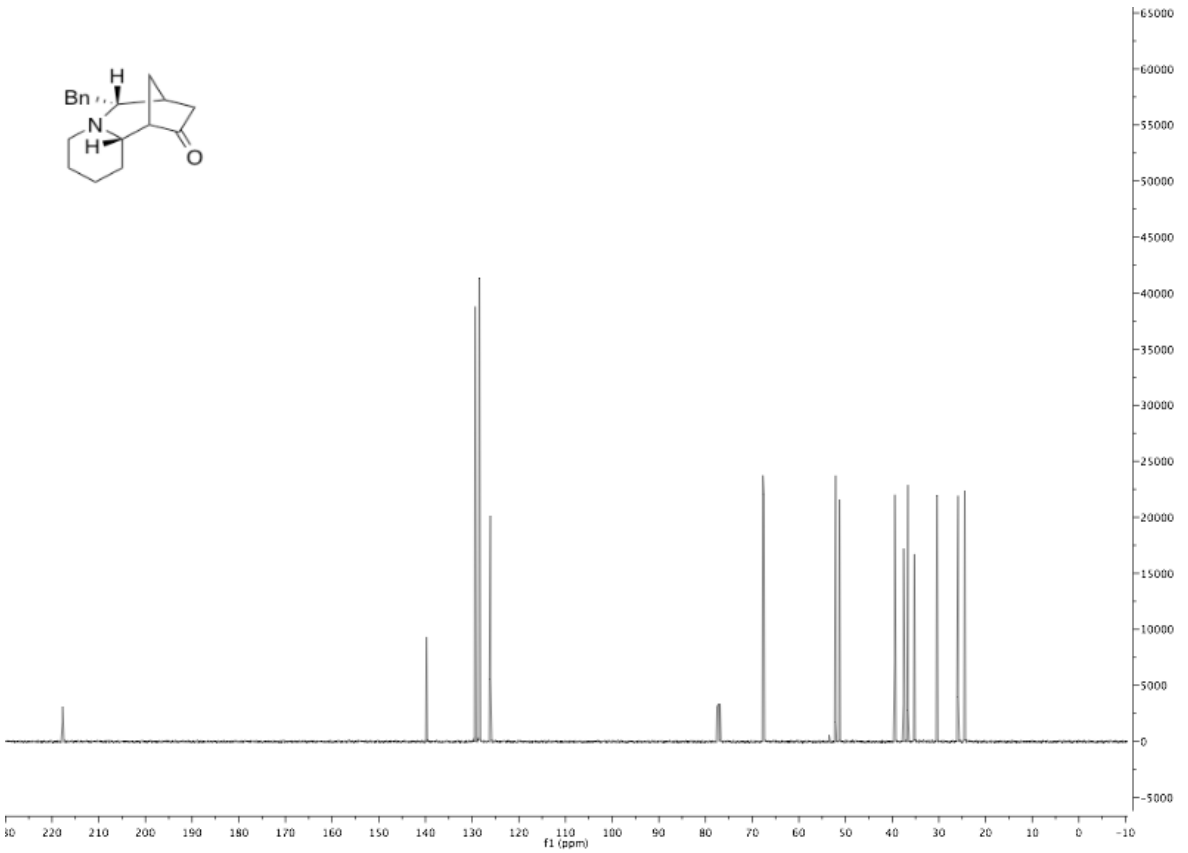
15b


nBu
H
N
H
O
1.00
1.01
1.02
2.06
3.07
1.04
3.05
10.36
3.04
f1 (ppm)

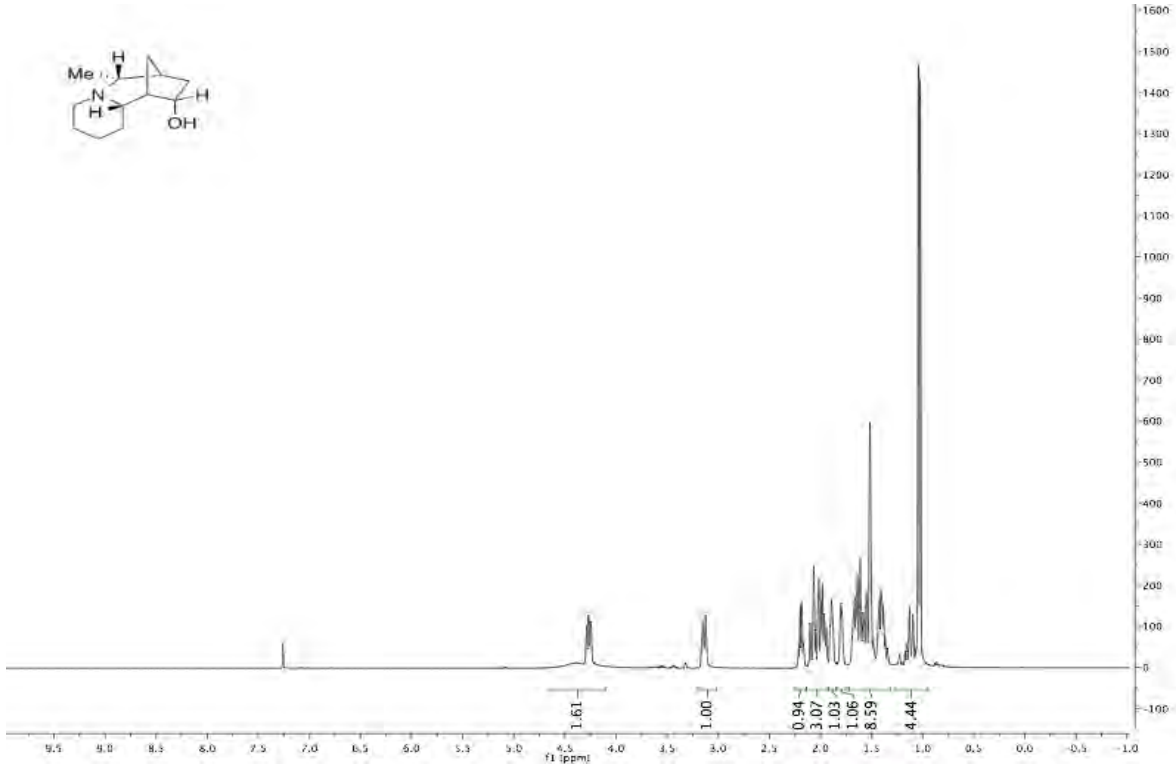

nBu
H
N
H
O
f1 (ppm)

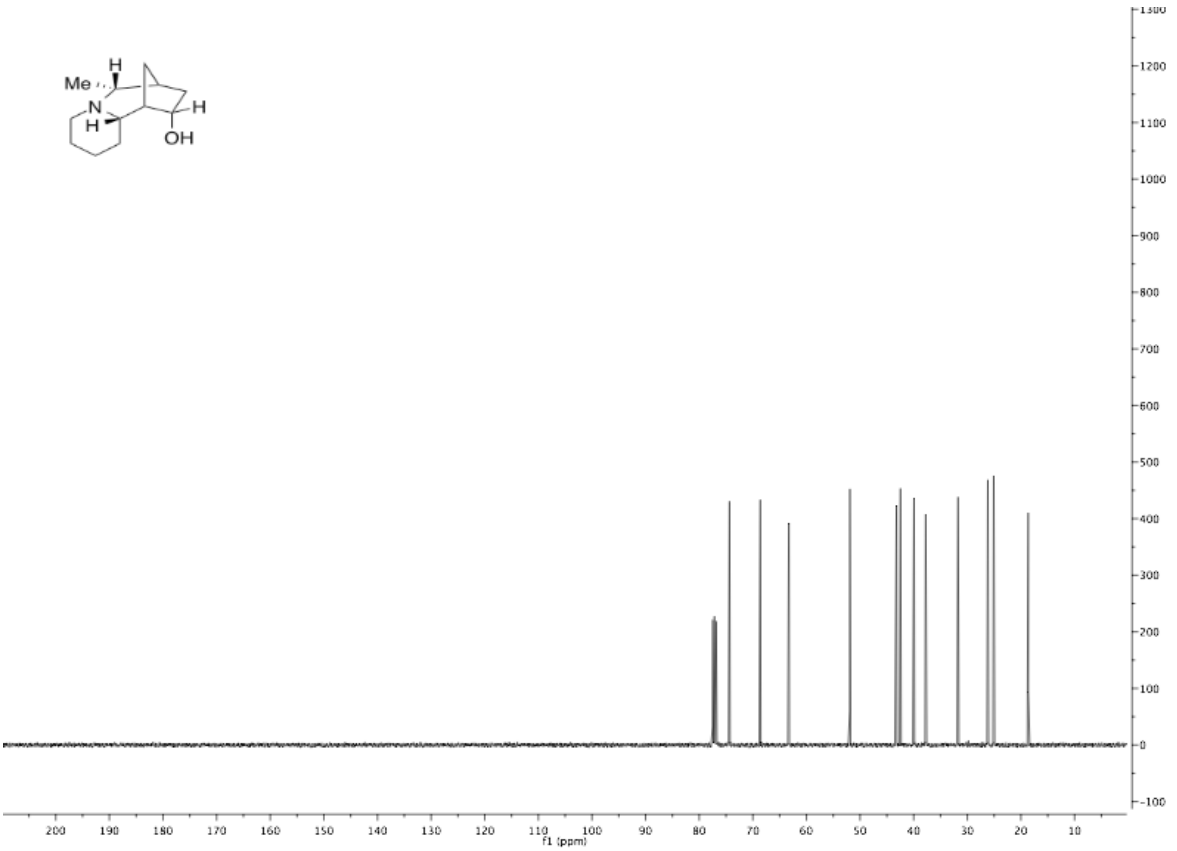
15c


Bn
H
N
H
O
2.03
1.02
1.98
1.00
1.01
1.00
2.03
2.00
4.11
6.22
1.11
f1 (ppm)

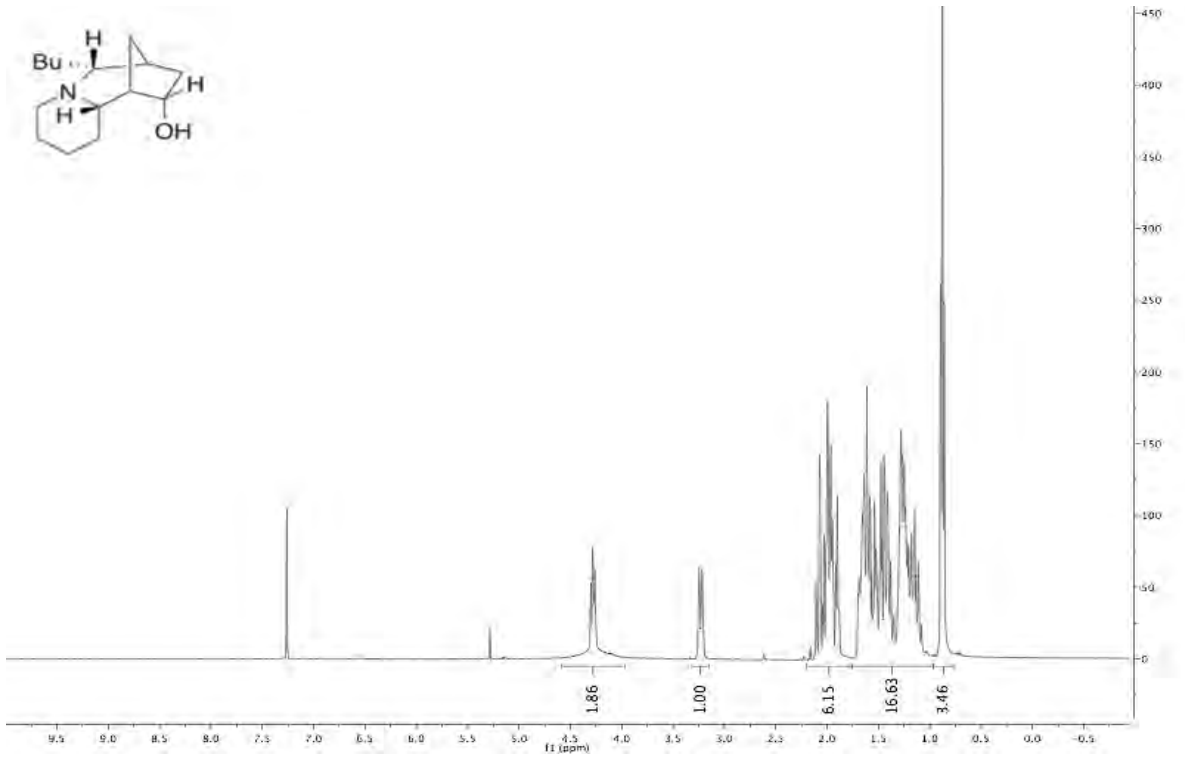

Bn
H
N
H
O
f1 (ppm)

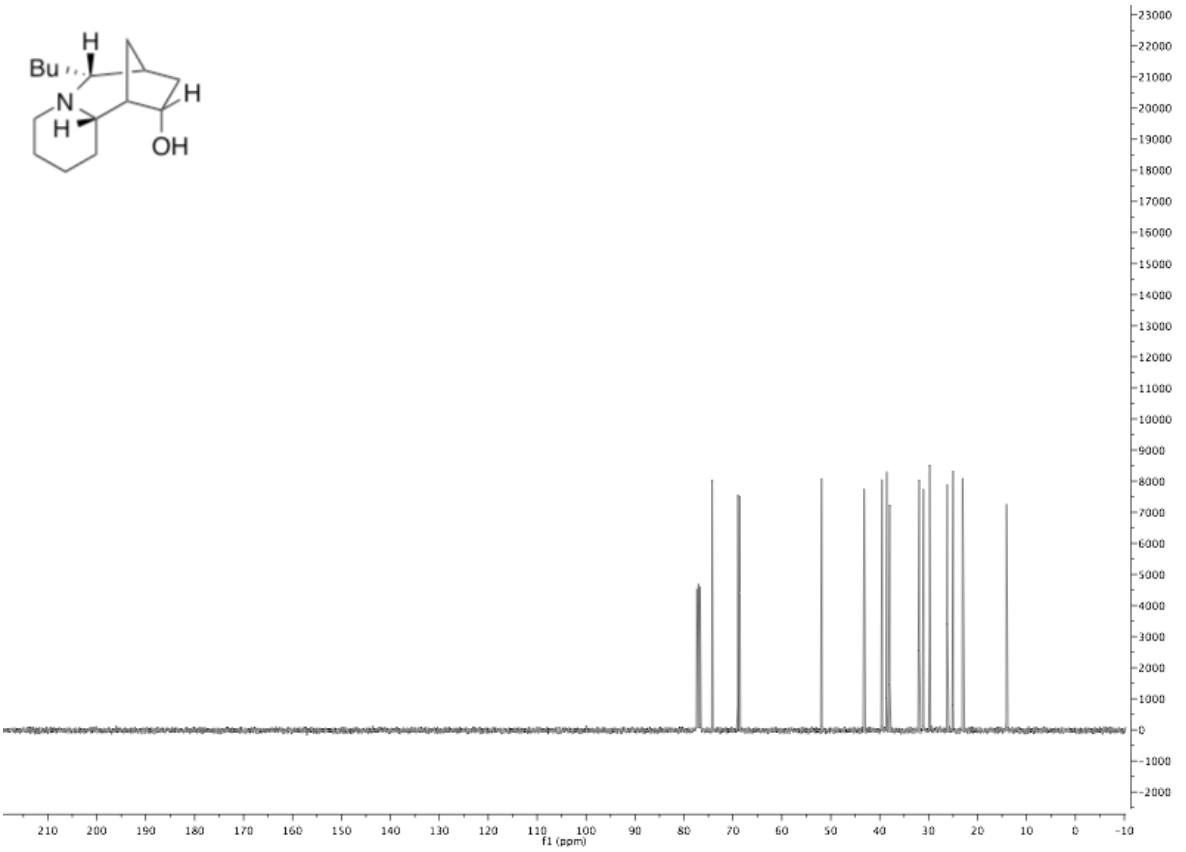
16a


Me
H
N
H
H
OH
1.61
1.00
0.94
3.07
1.03
1.06
8.59
4.44
f1 (ppm)

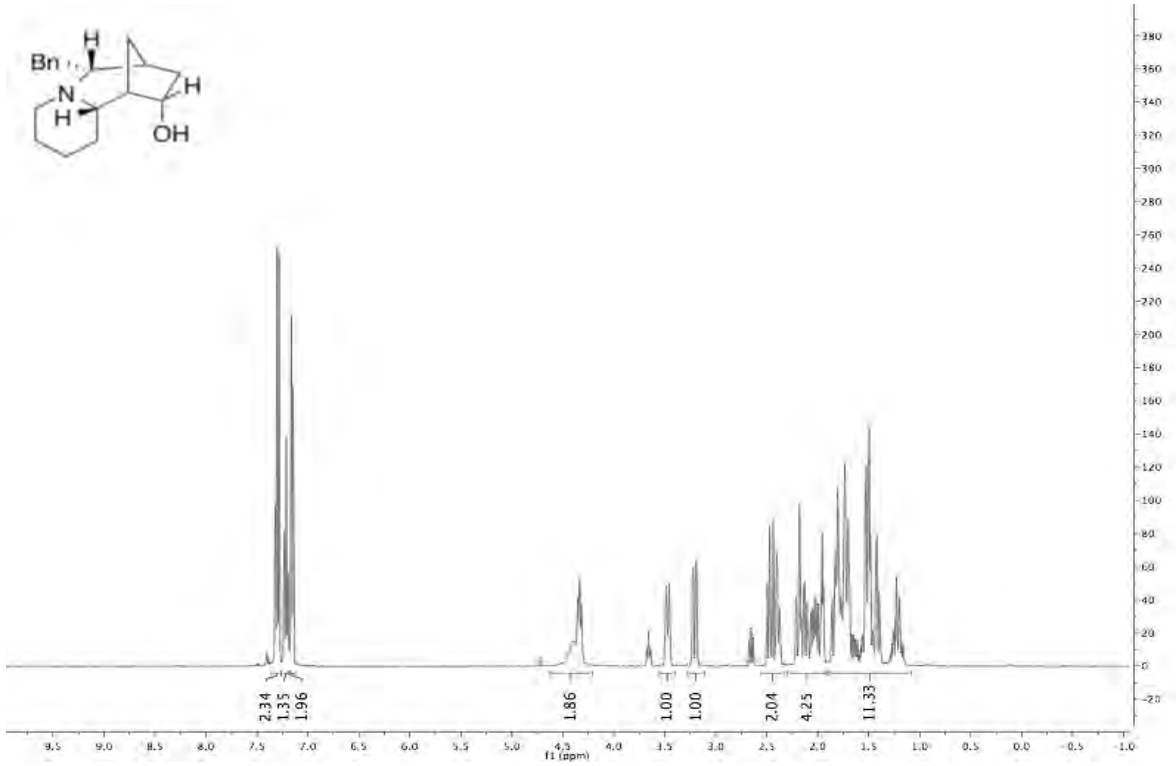

Me
H
N
H
H
OH
f1 (ppm)

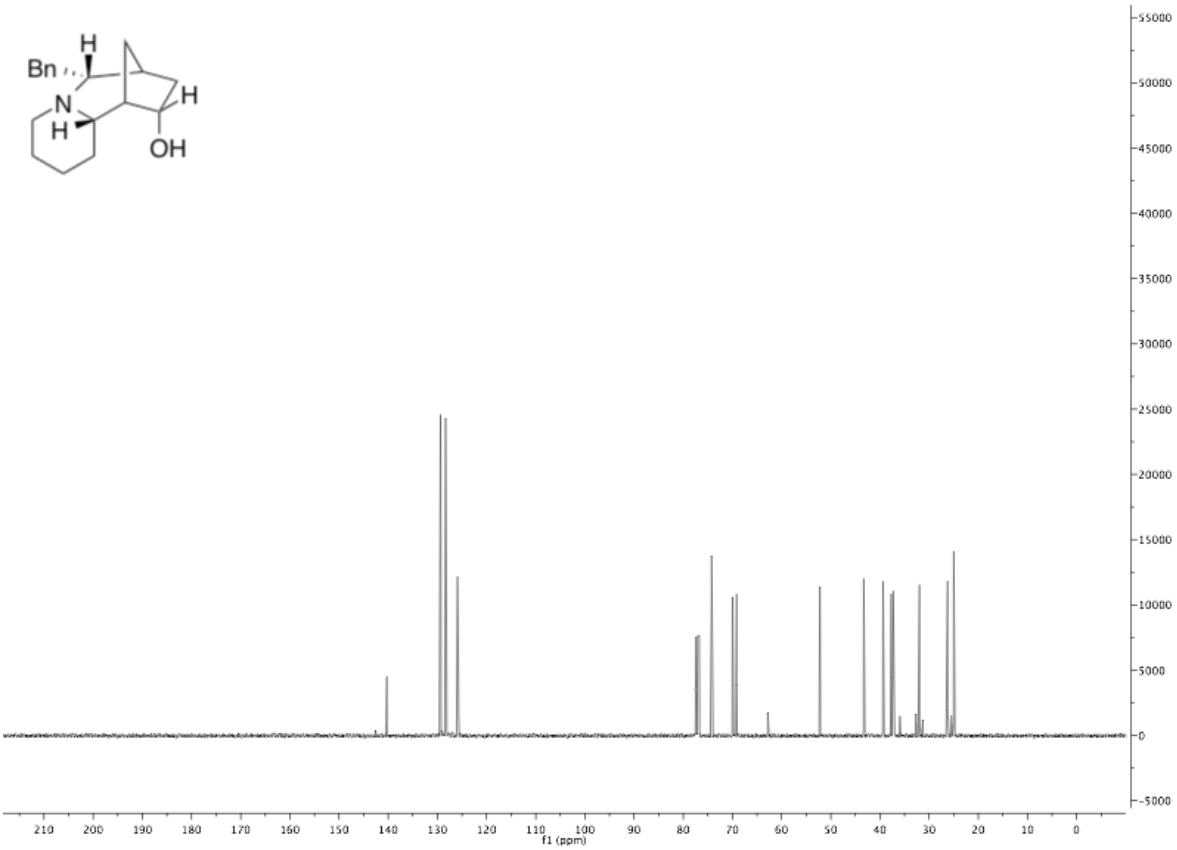
16b



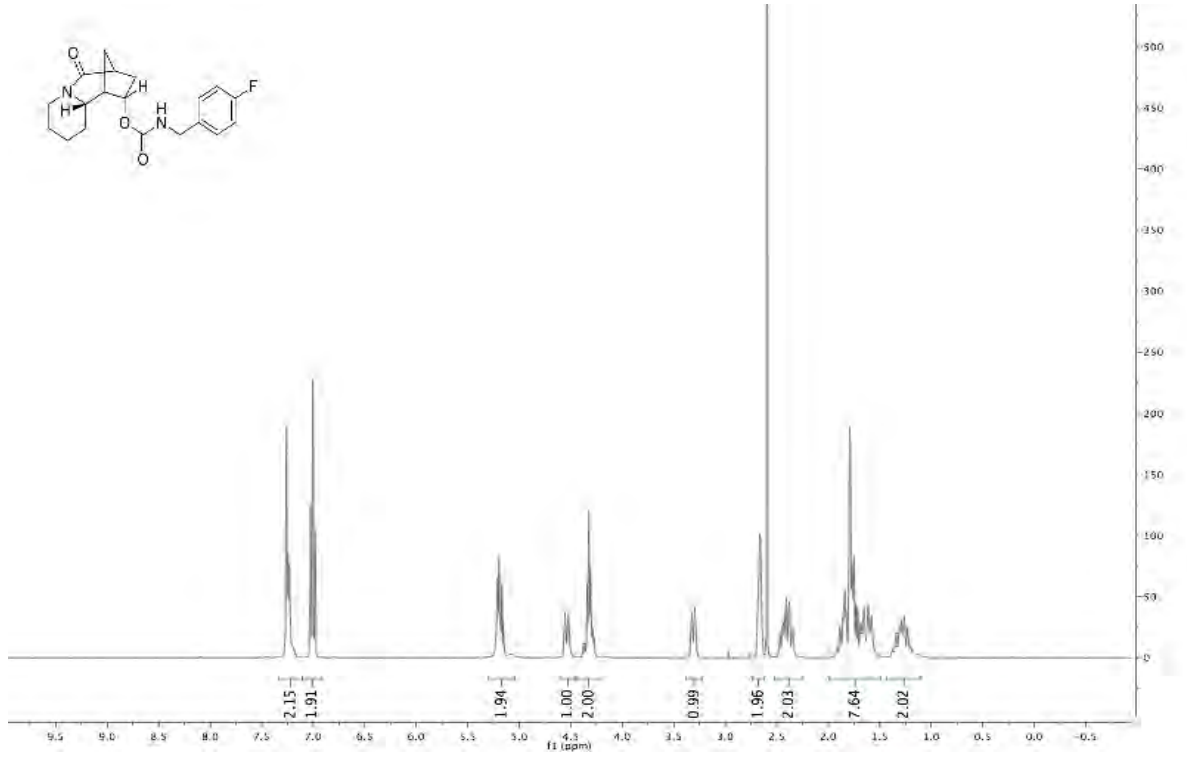


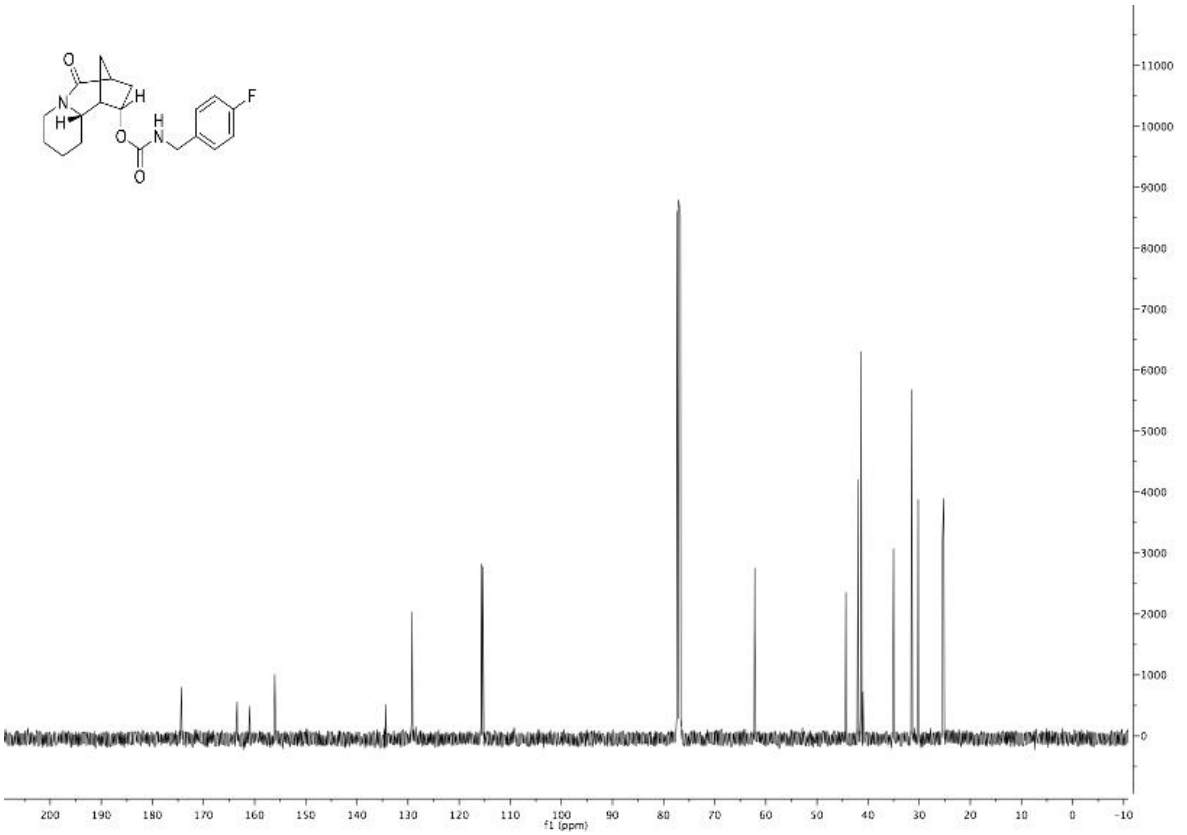
16c


Bn
N
H
H
H
OH
2.34
1.35
1.96
1.86
1.00
1.00
2.04
4.25
11.33
f1 (ppm)

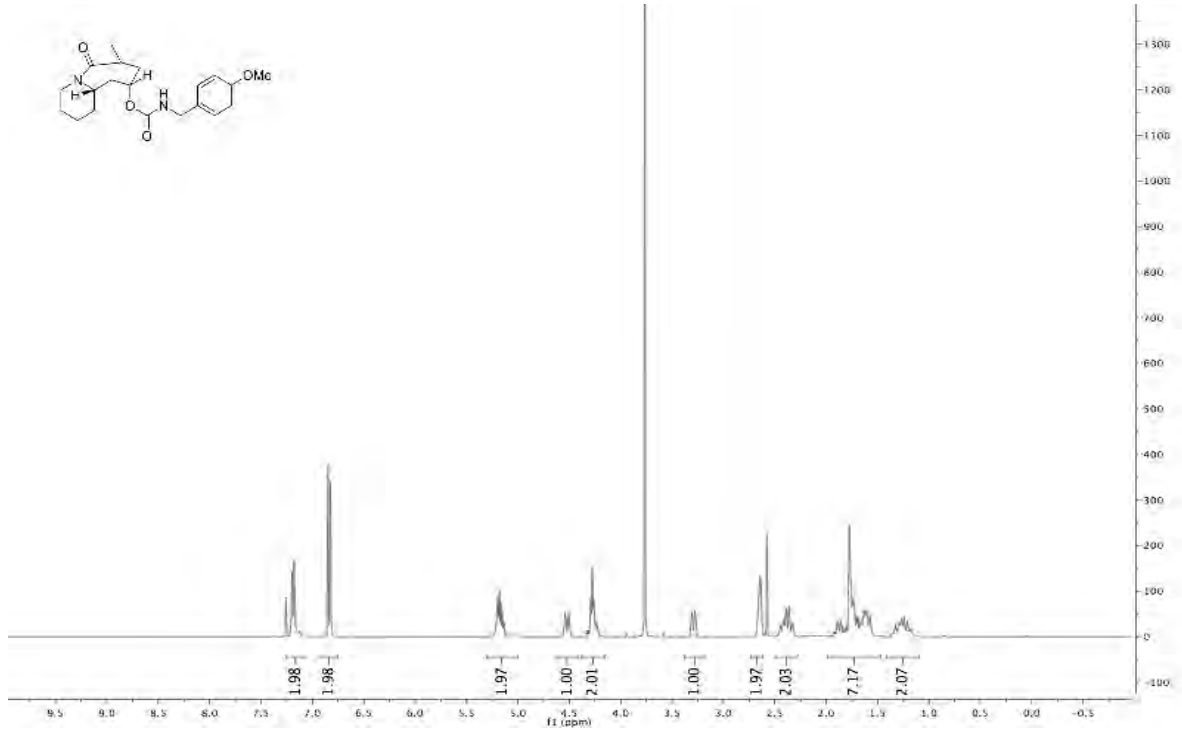

Bn
N
H
H
H
OH
f1 (ppm)

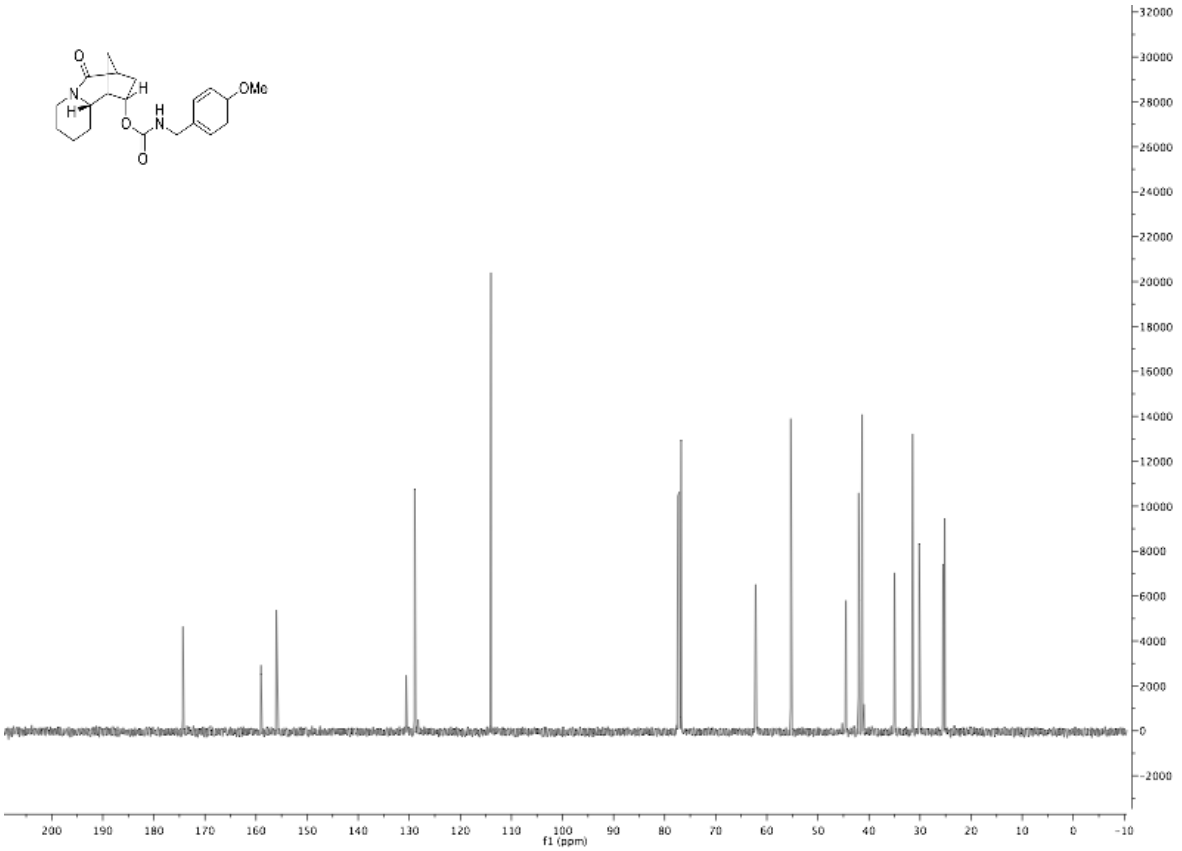
40{*1*}



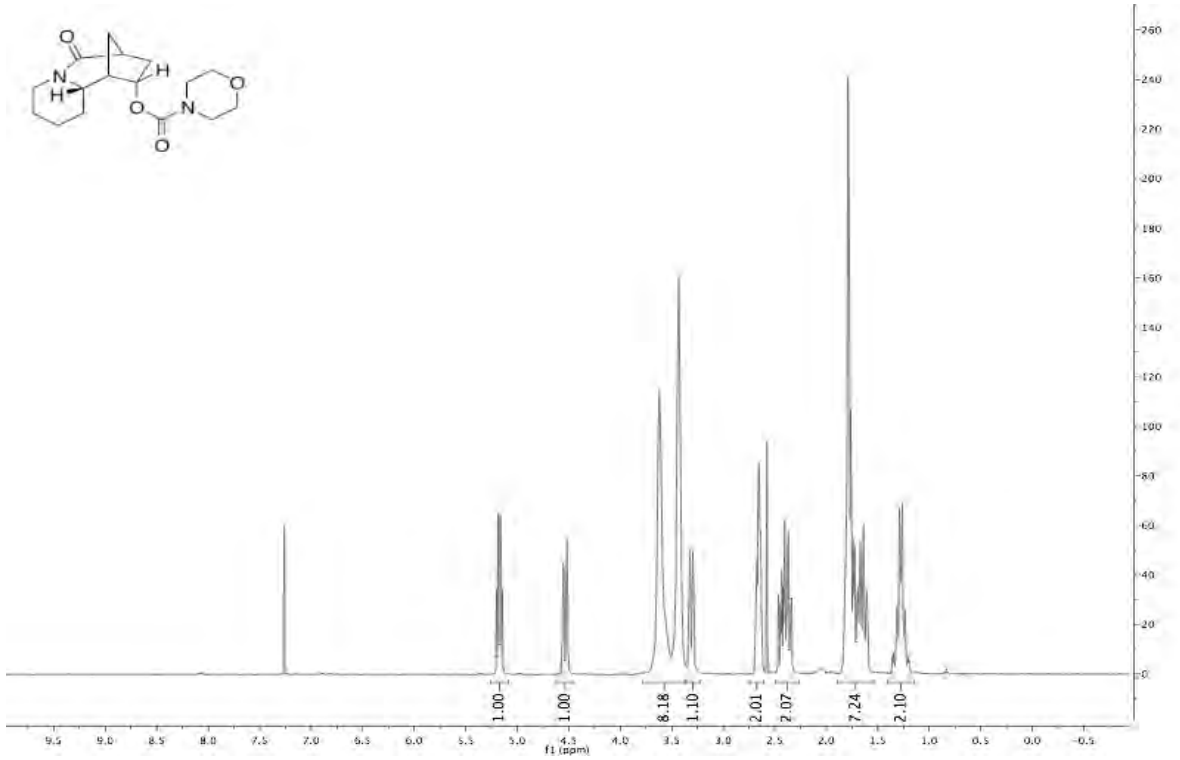


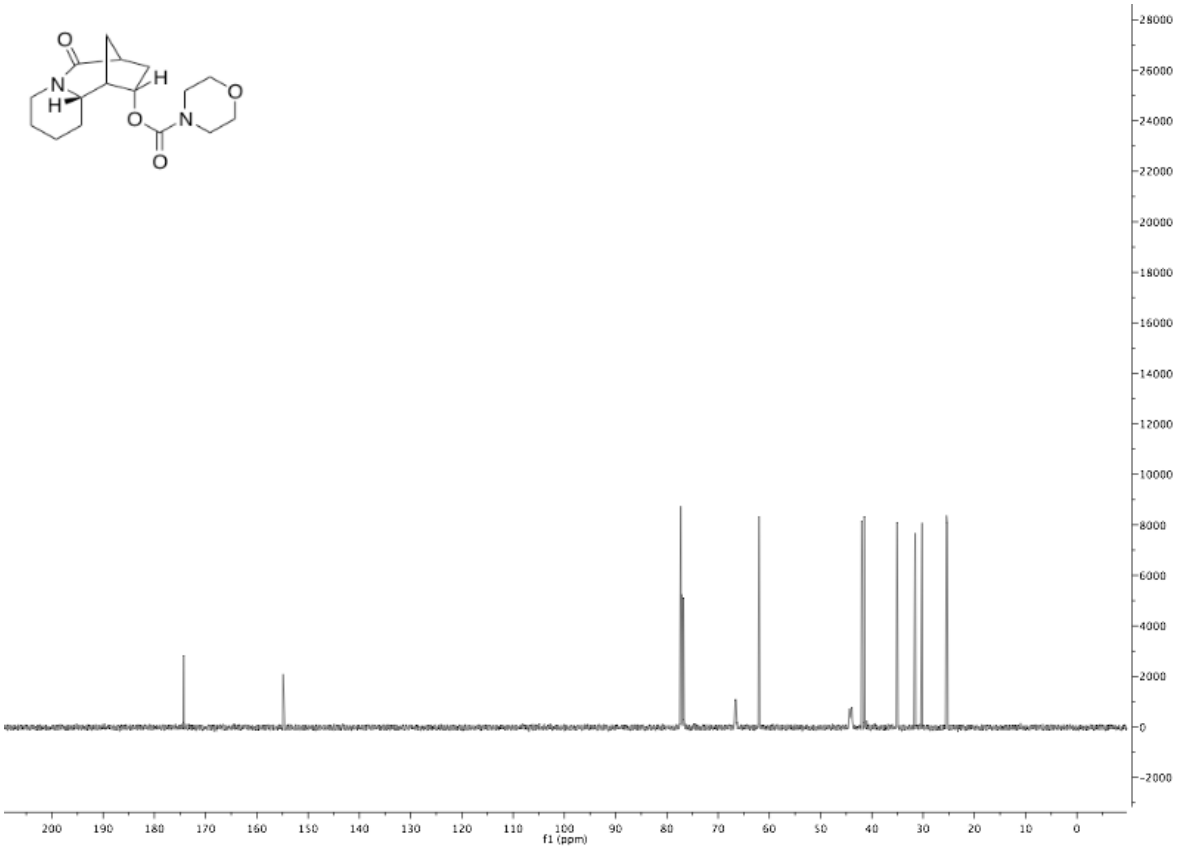
40{*2*}



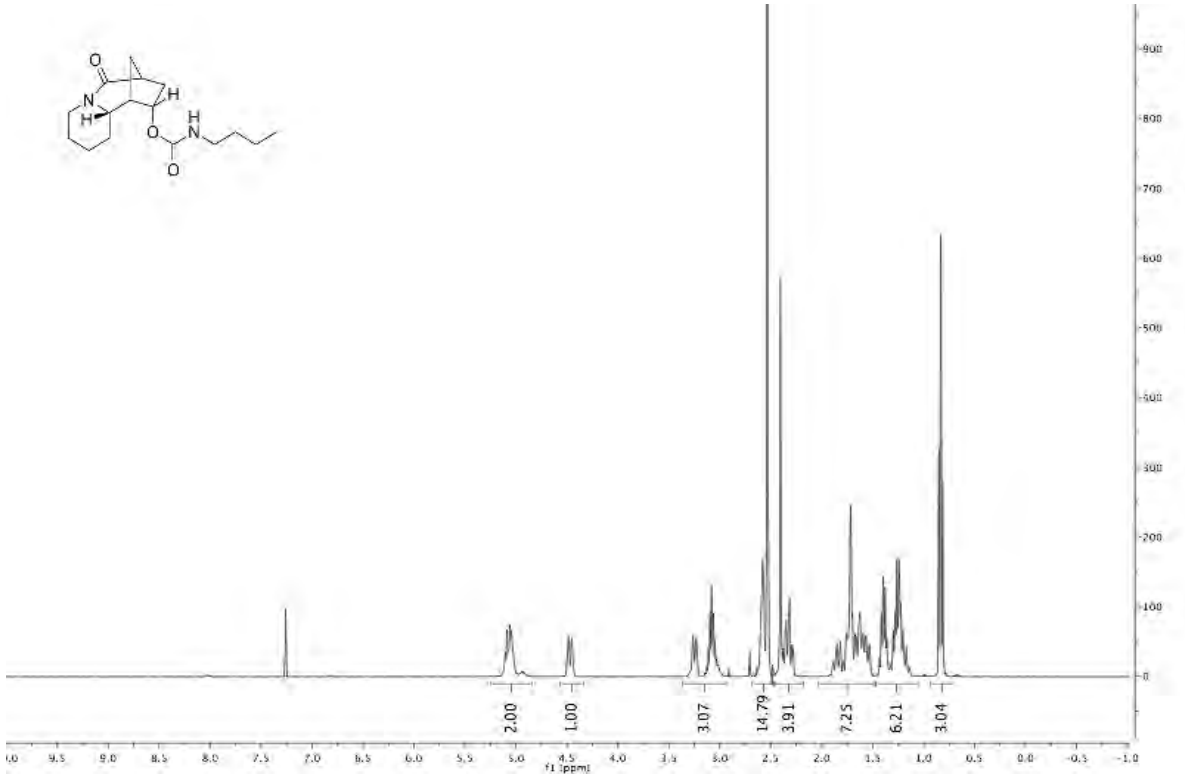


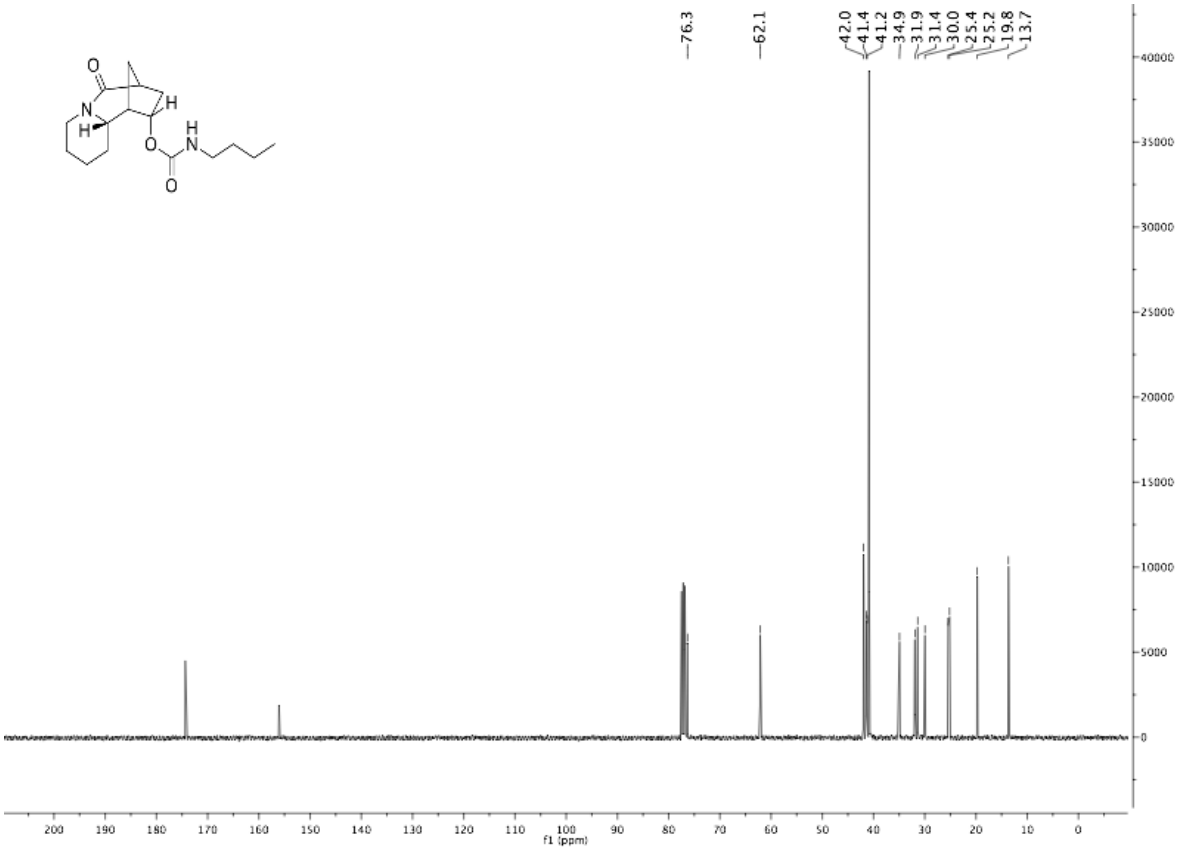
40{*3*}



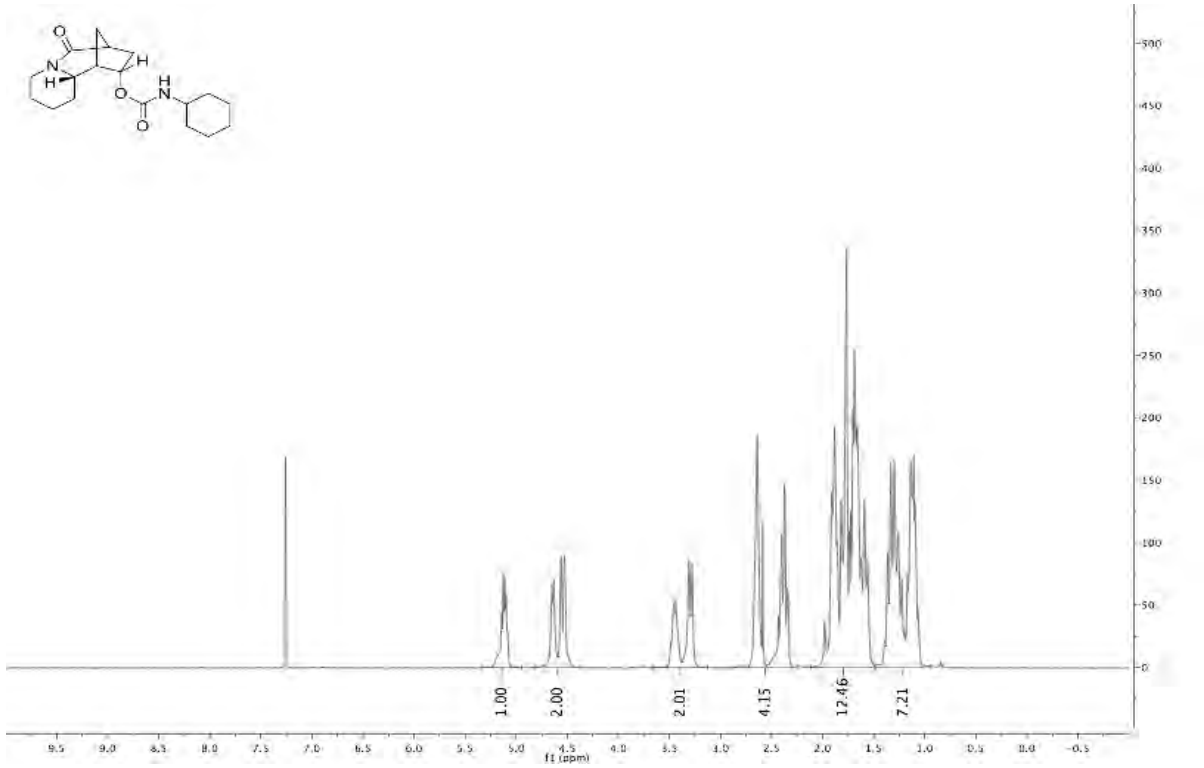


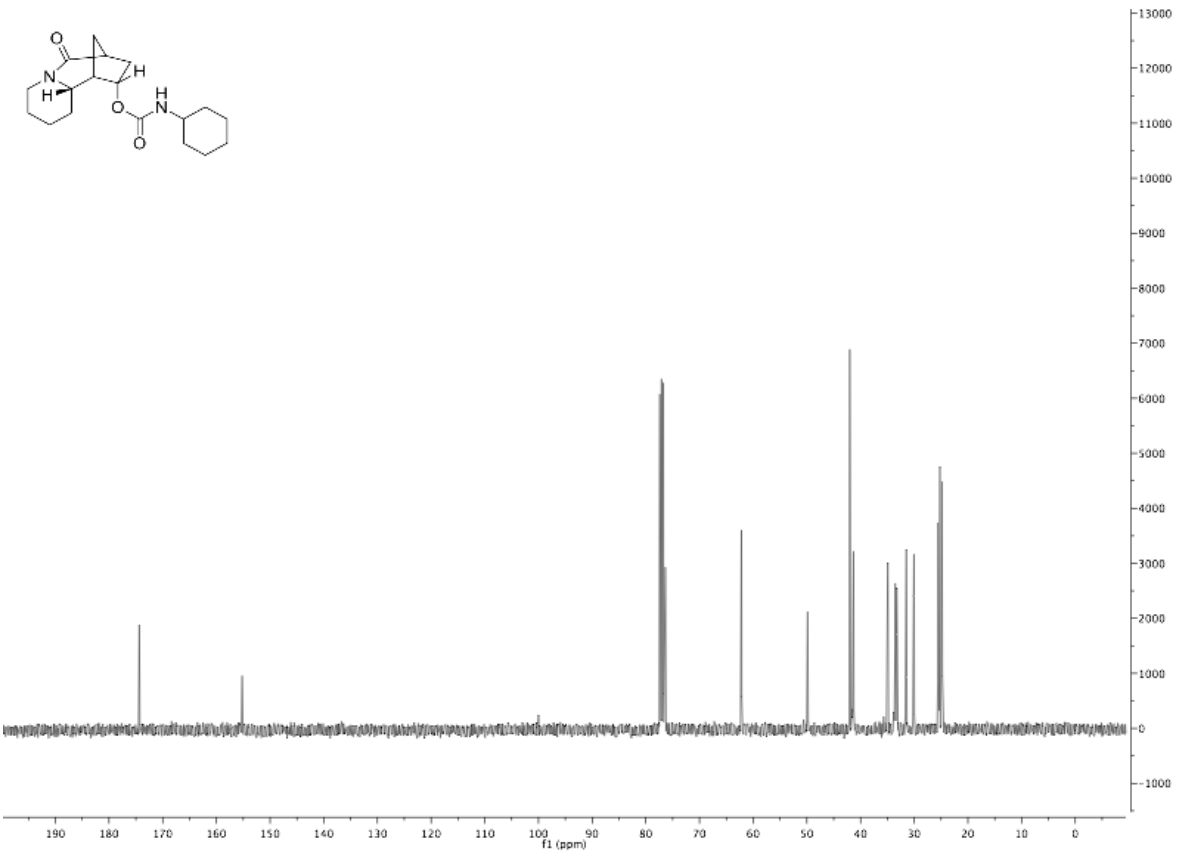
40{*4*}


2.00
1.00
3.07
14.79
3.91
7.25
6.21
3.04
f1 (ppm)

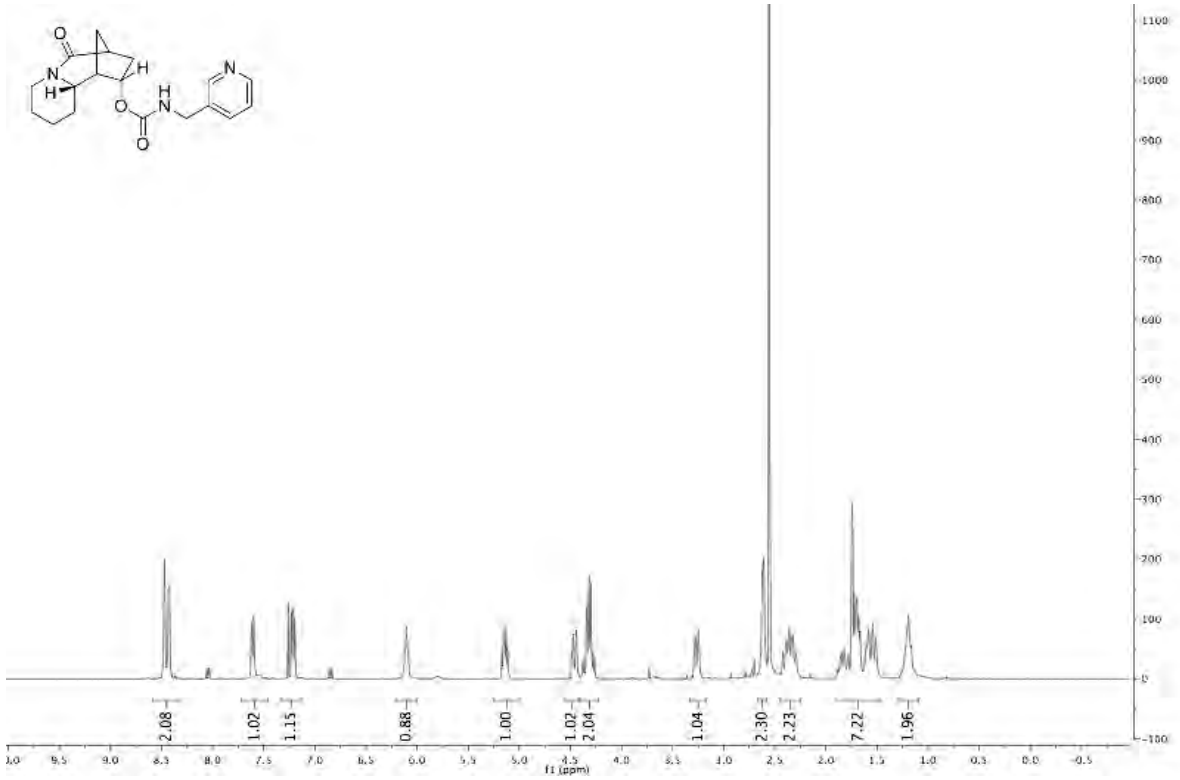

76.3
62.1
42.0
41.4
41.2
34.9
31.9
31.4
30.0
25.4
25.2
19.8
13.7
f1 (ppm)

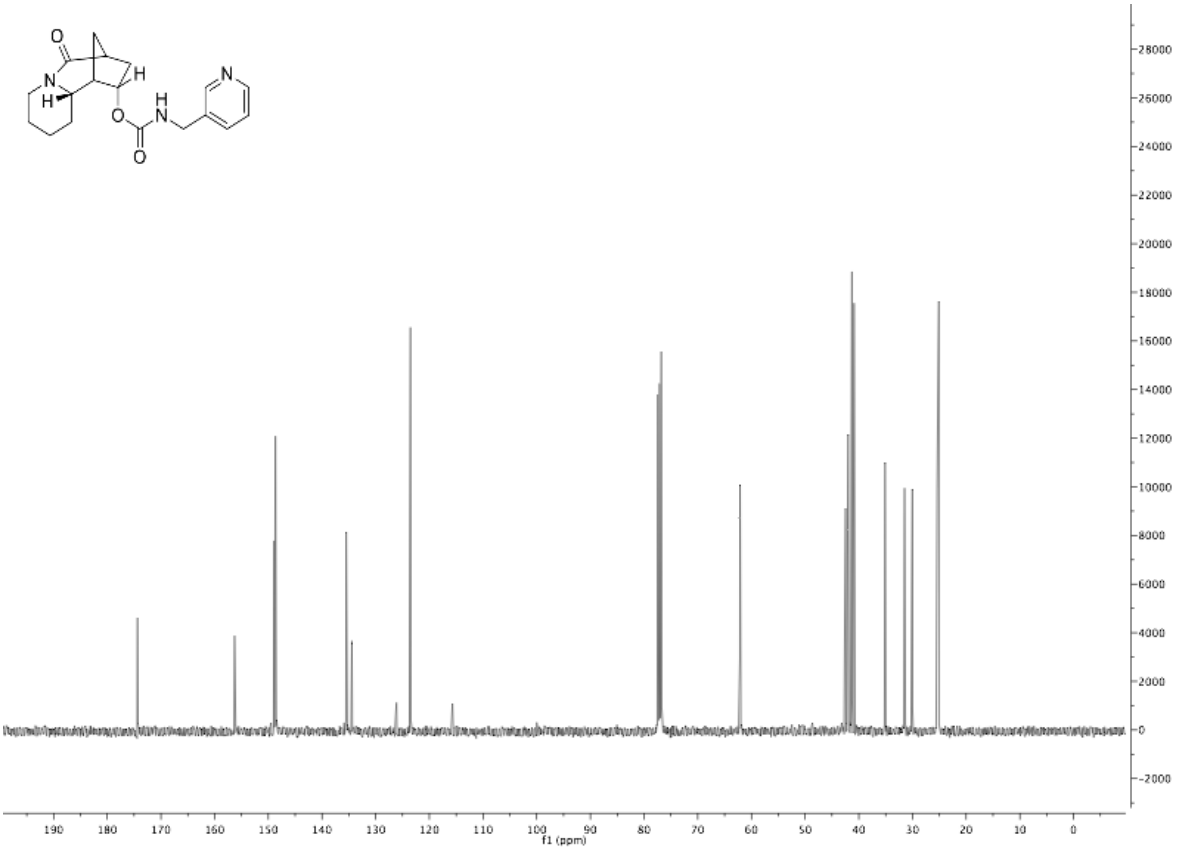
40{*5*}



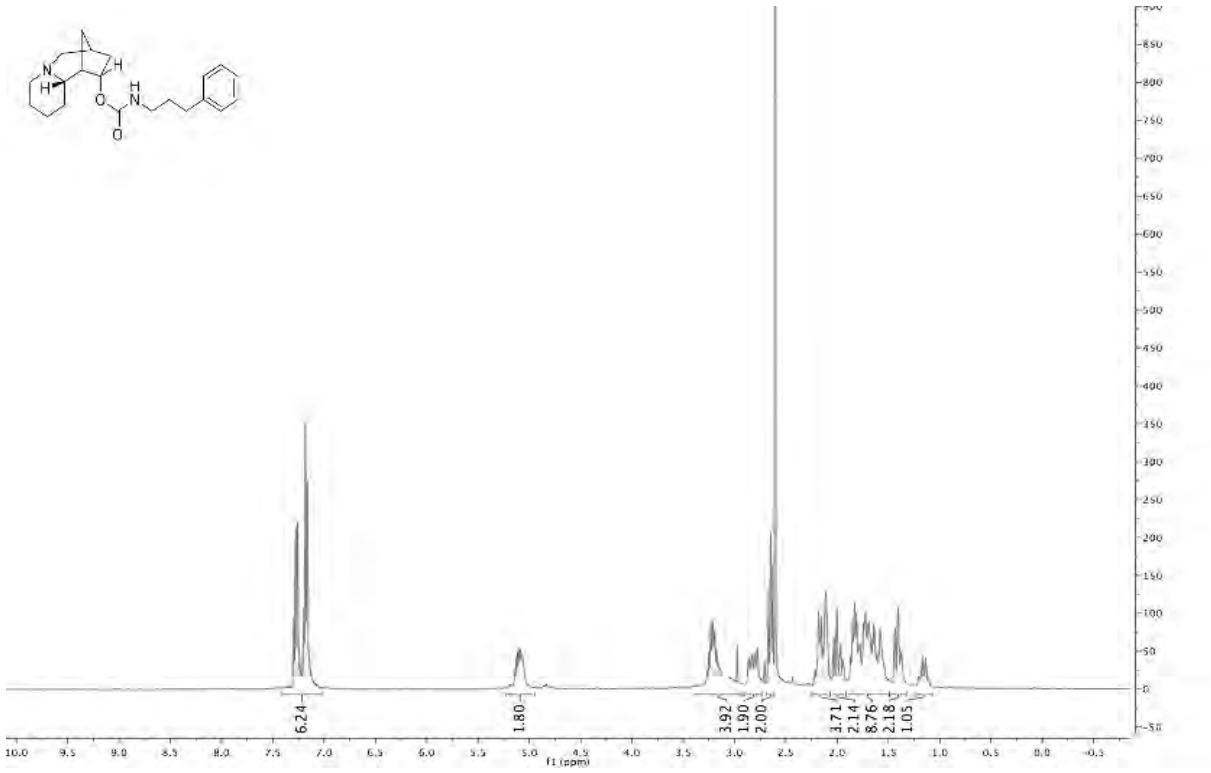


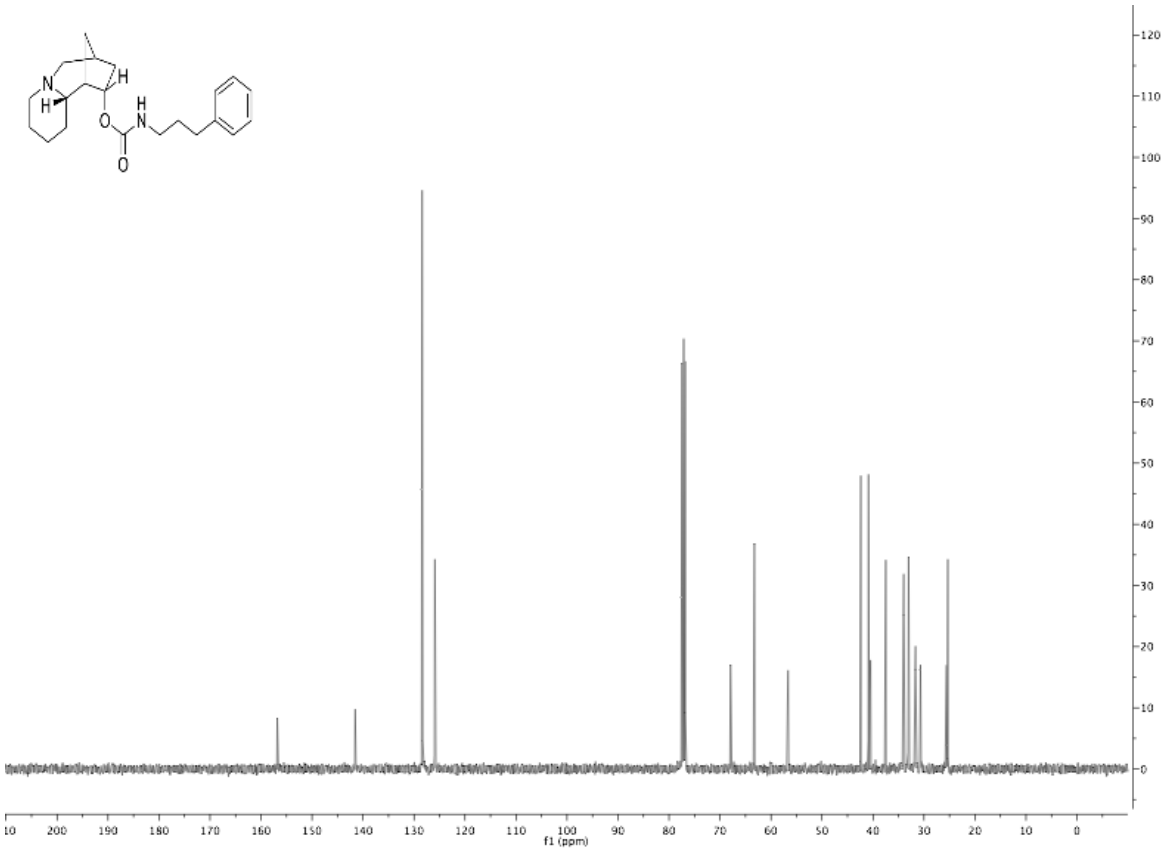
40{*15*}



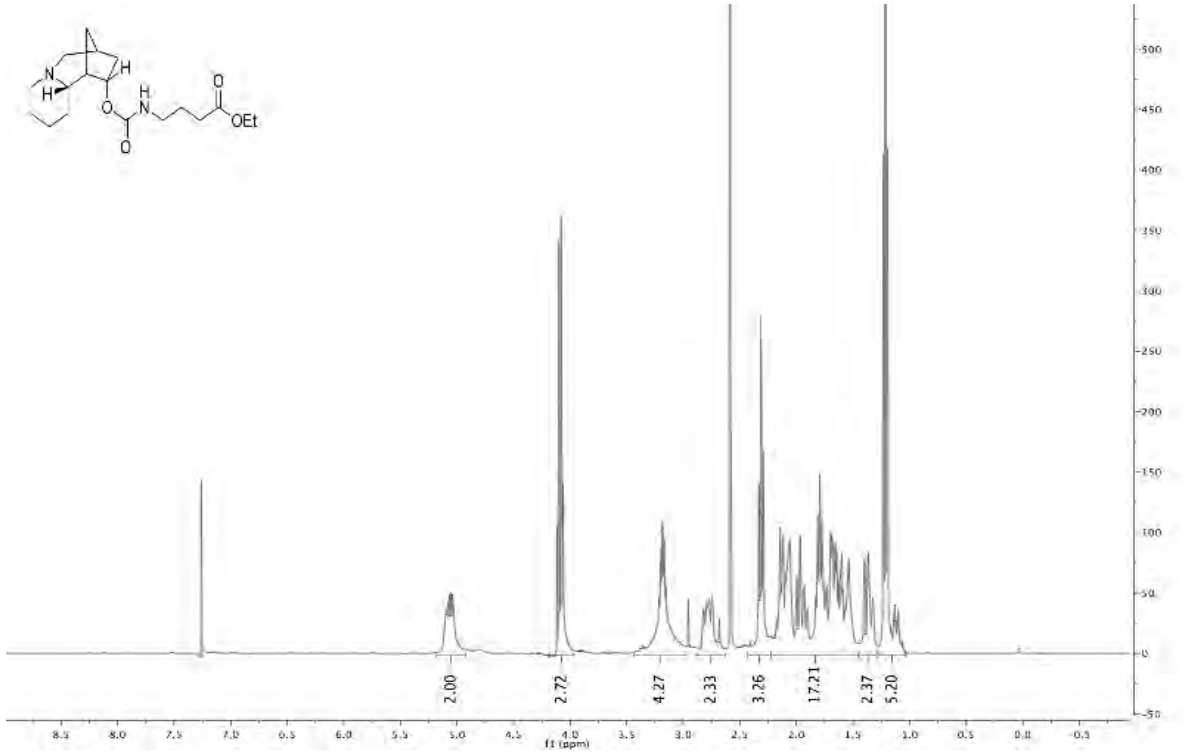


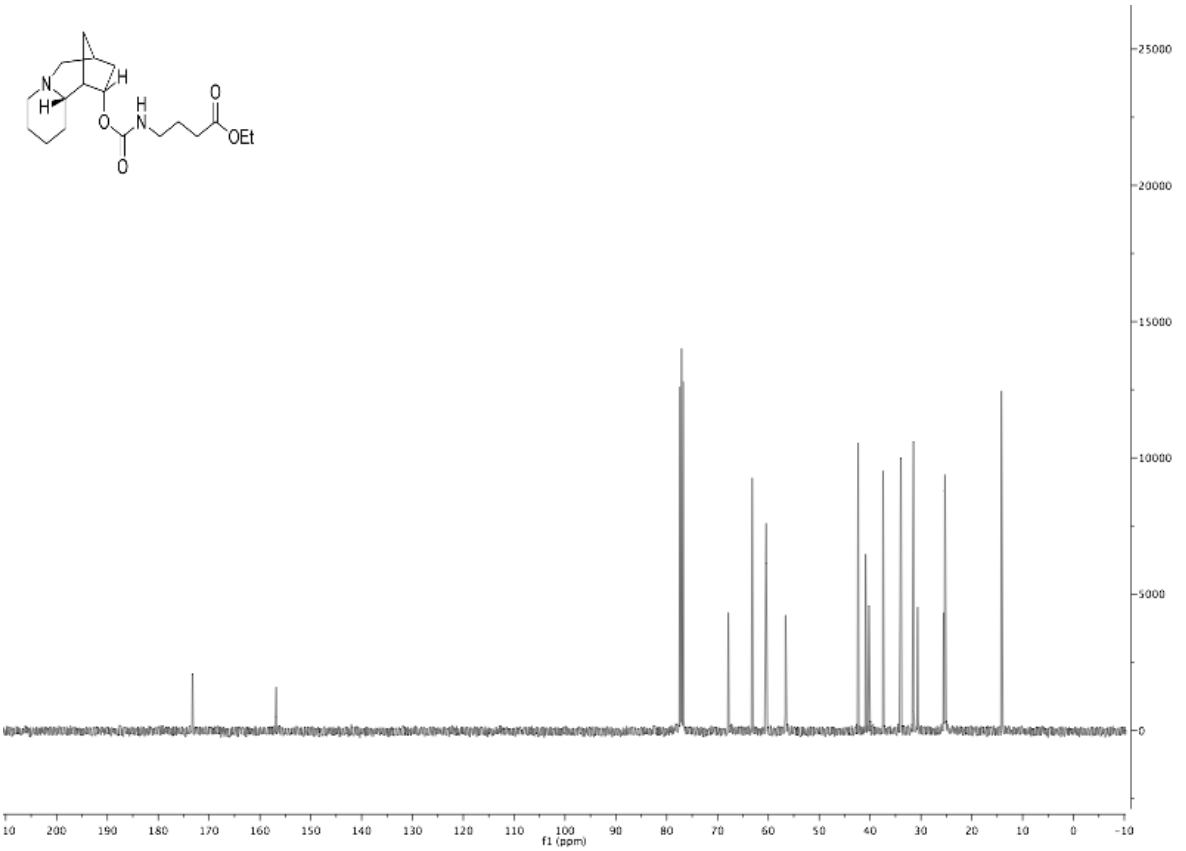
42{*7*}



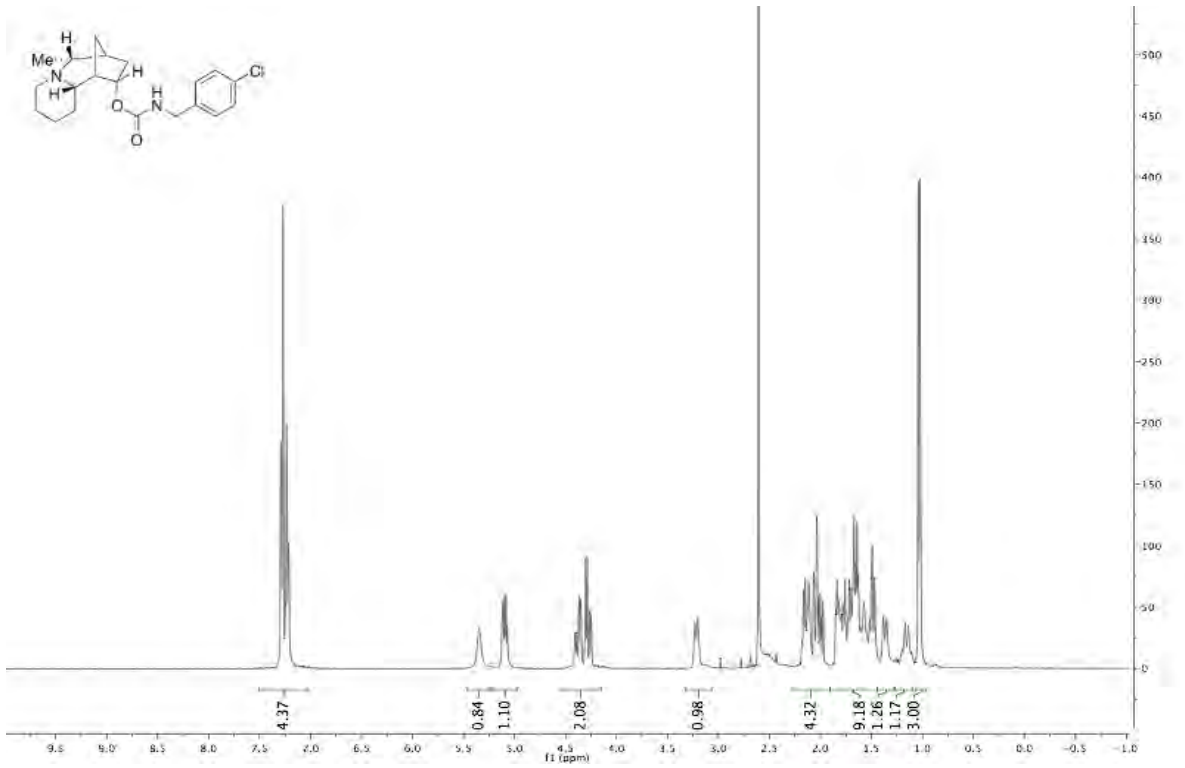


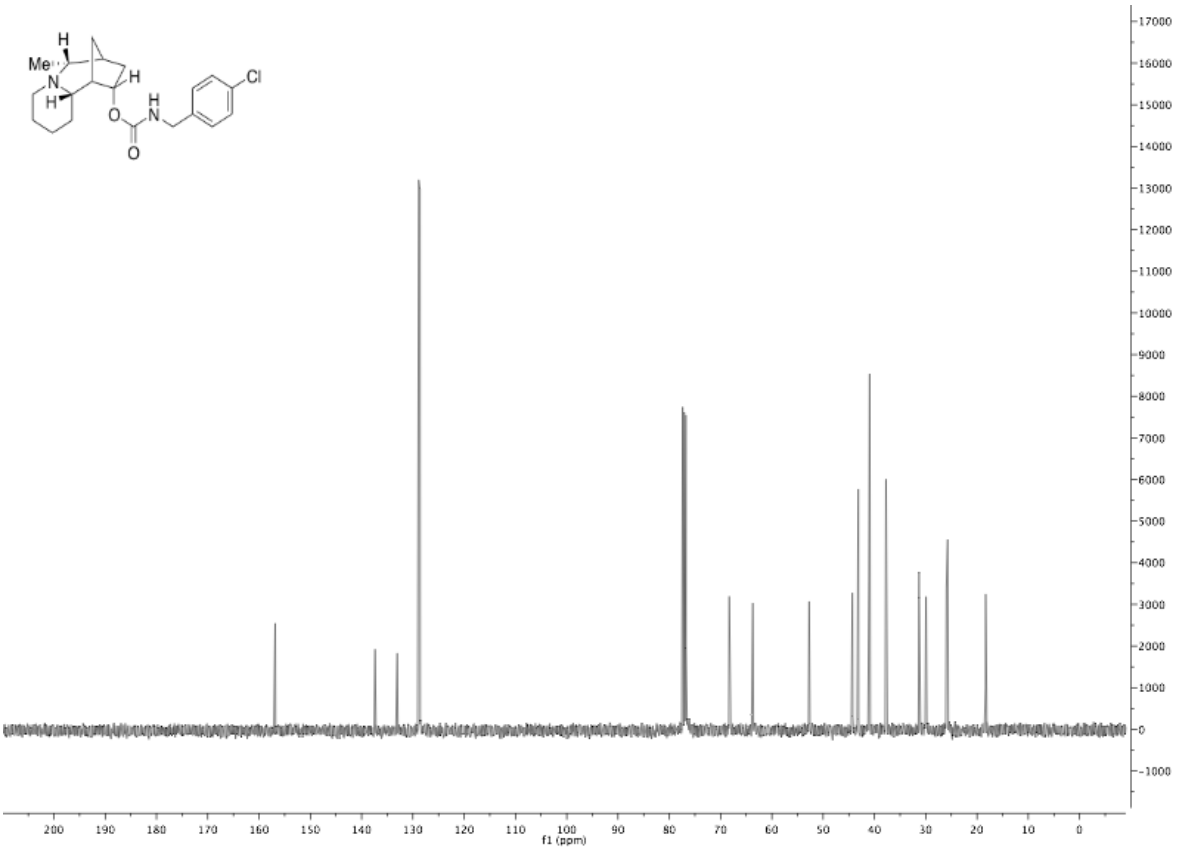
42{*9*}



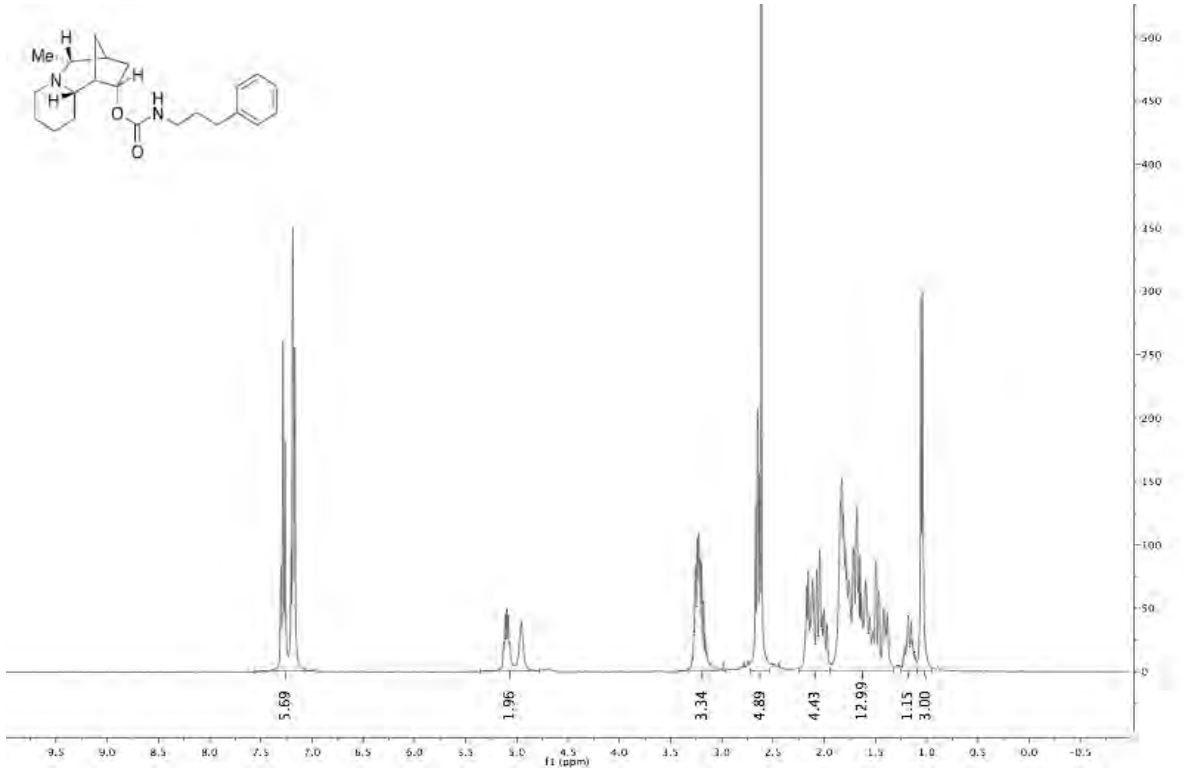


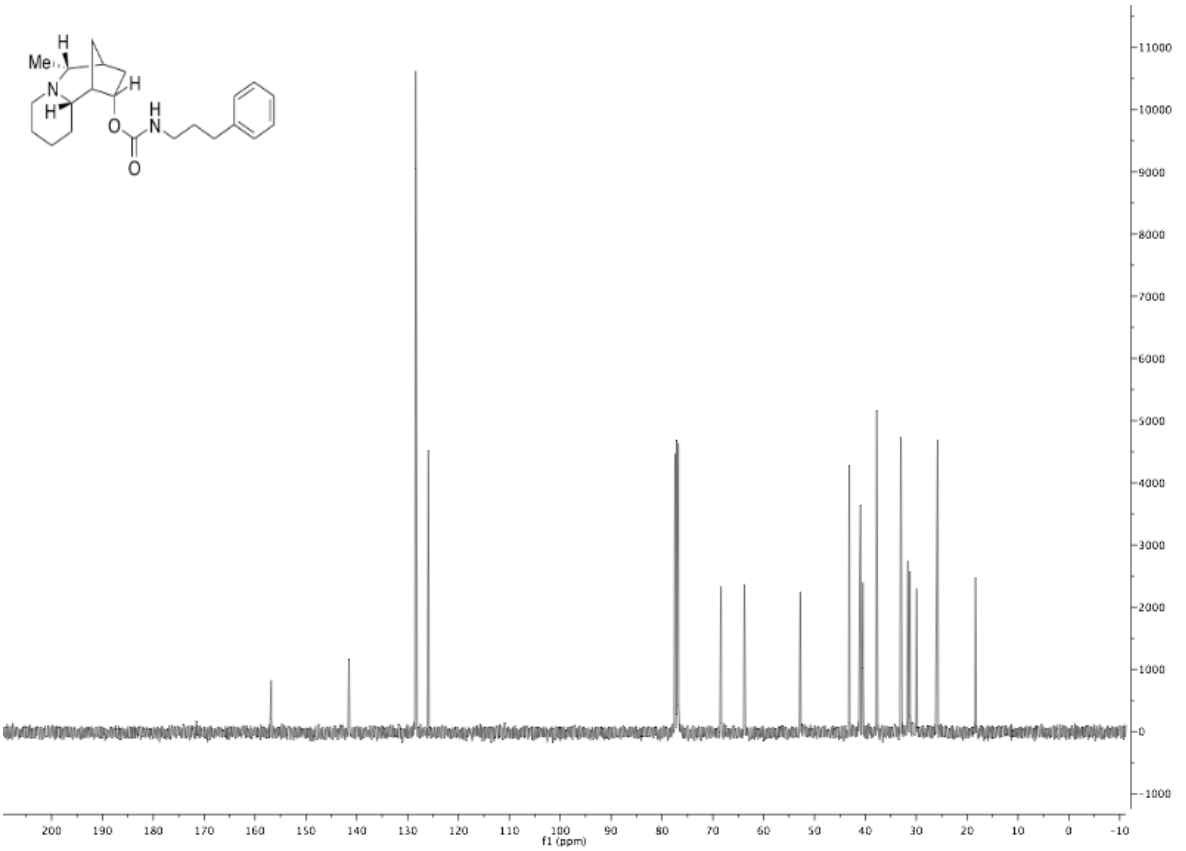
43a{*2*}


Me
H
N
H
H
O
O
H
N
Cl
4.37
0.84
1.10
2.08
0.98
4.32
9.18
1.26
1.17
3.00
f1 (ppm)

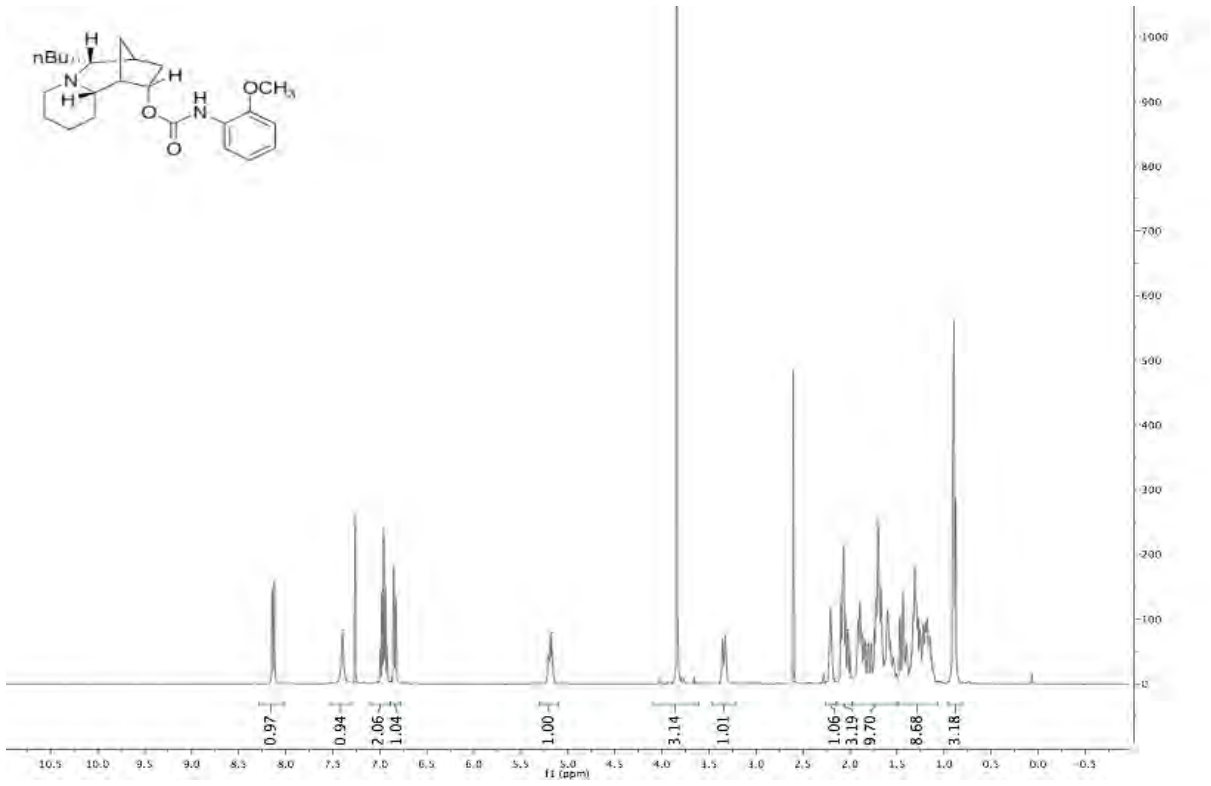

Me
H
N
H
H
O
O
H
N
Cl
f1 (ppm)

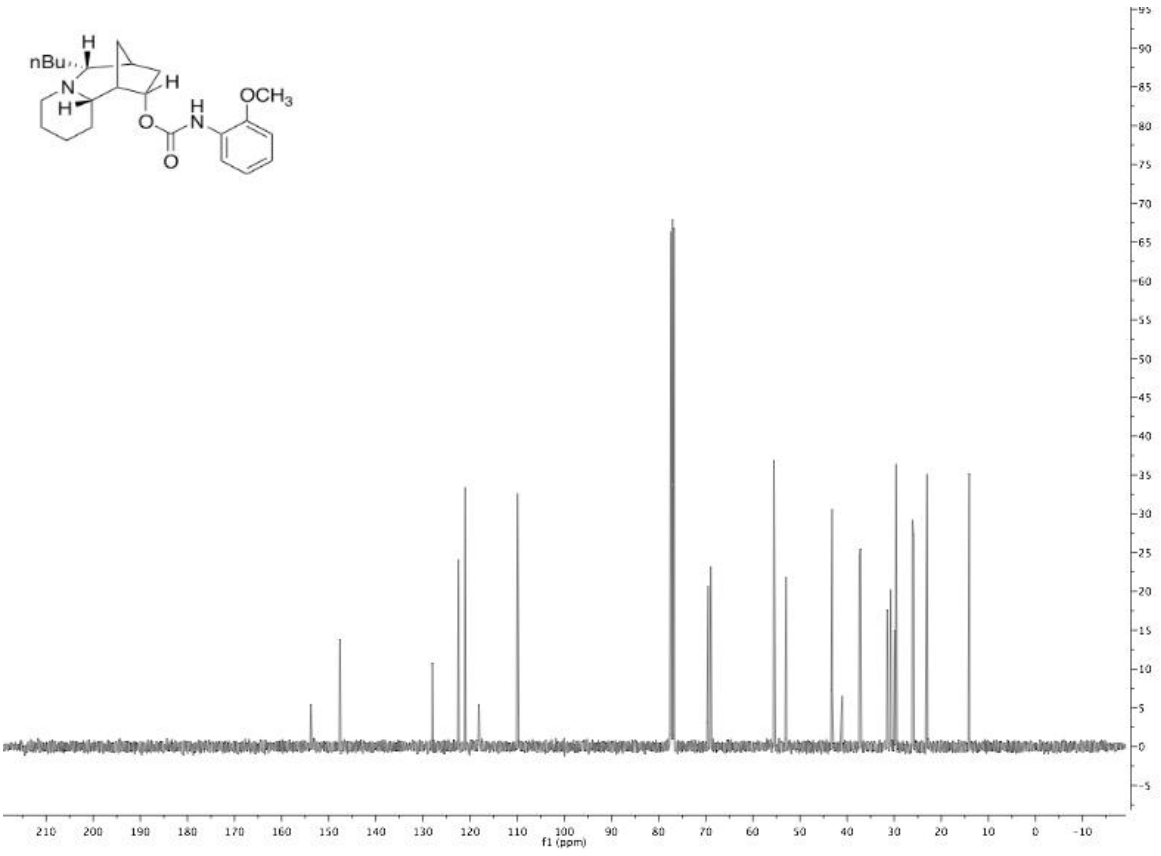
43a{*3*}


Me
H
N
H
H
O
H
N
O
5.69
1.96
3.34
4.89
4.43
12.99
1.15
3.00
f1 (ppm)

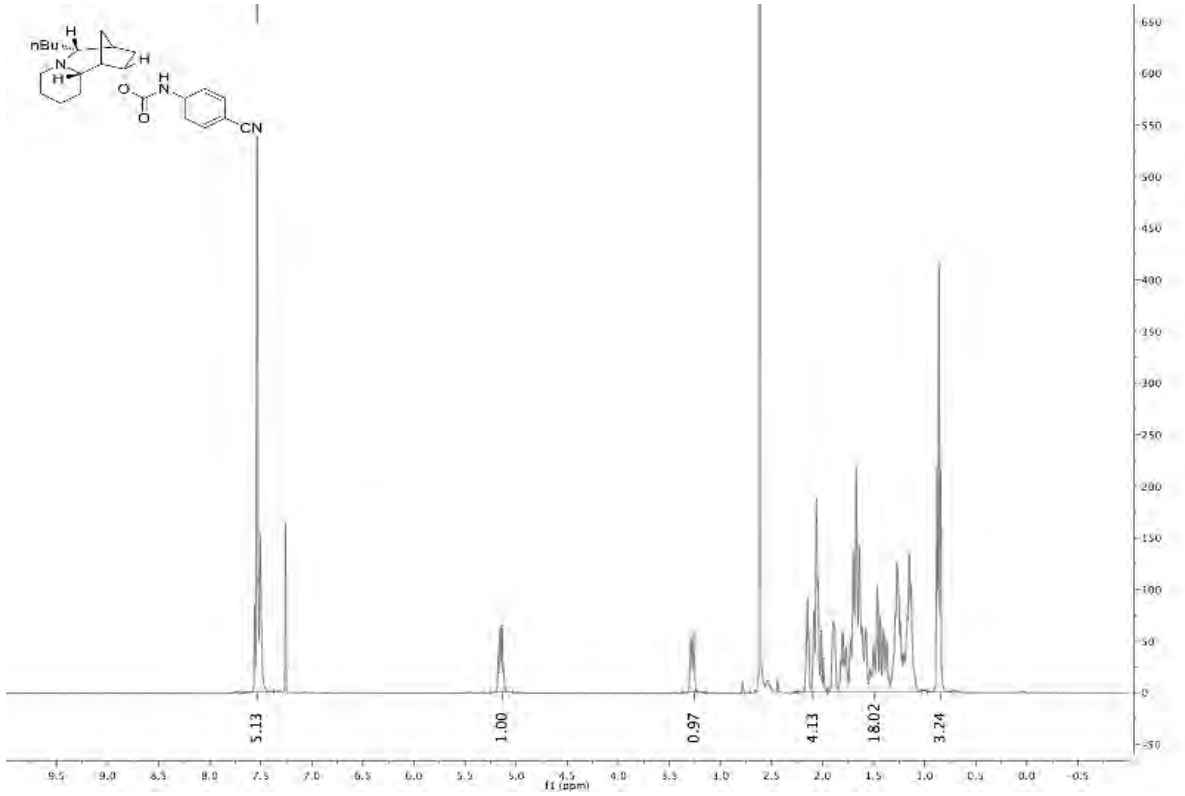

Me
H
N
H
H
O
H
N
O
f1 (ppm)

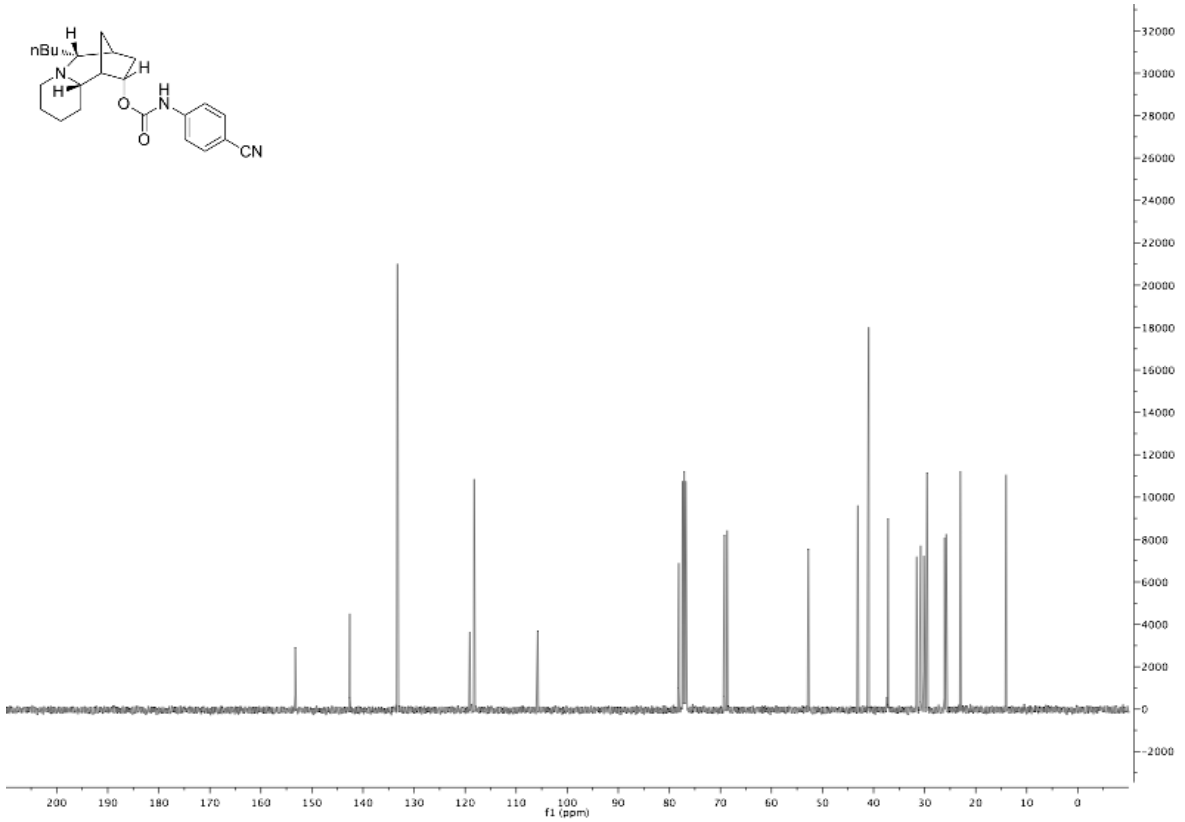
43b{*11*}


nBu
H
N
H
H
O
O
H
N
OCH3
0.97
0.94
2.06
1.04
1.00
3.14
1.01
1.06
3.19
9.70
8.68
3.18
f1 (ppm)

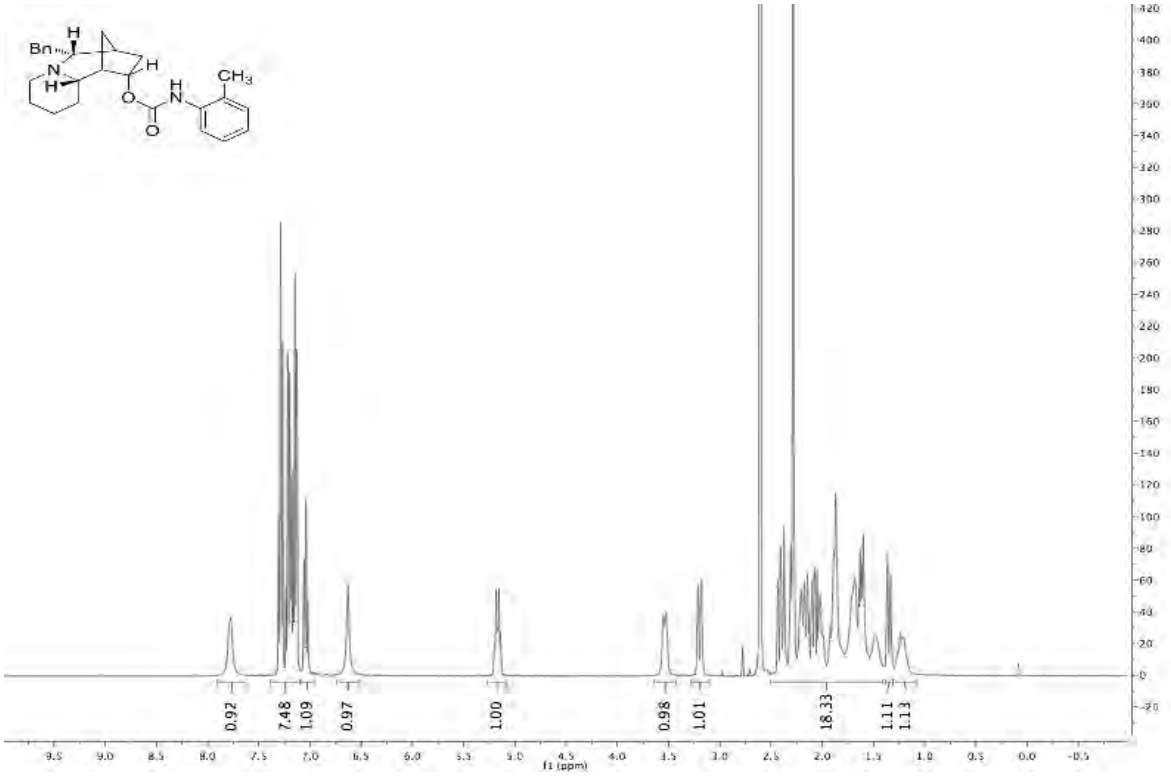

nBu
H
N
H
H
O
O
H
N
OCH3
f1 (ppm)

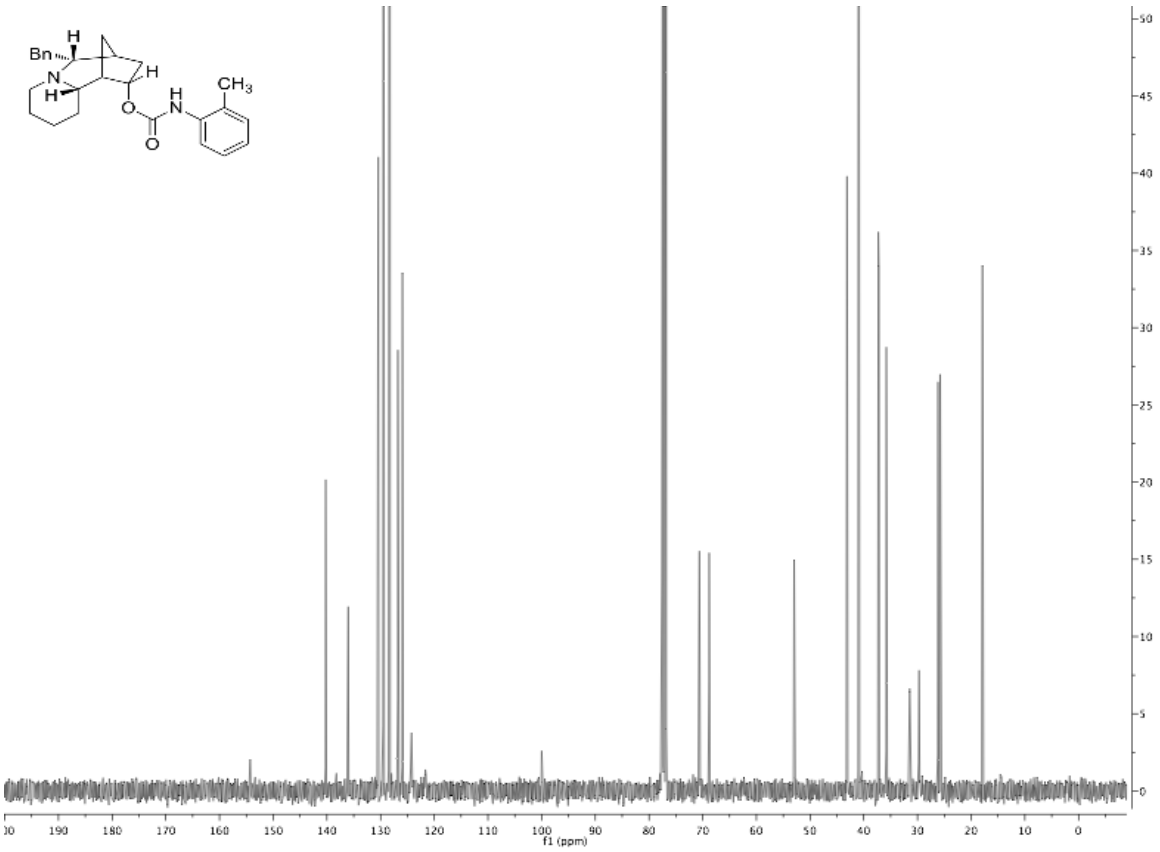
43b{*9*}


nBu
H
N
H
O
O
H
N
CN
5.13
1.00
0.97
4.13
18.02
3.24
f1 (ppm)

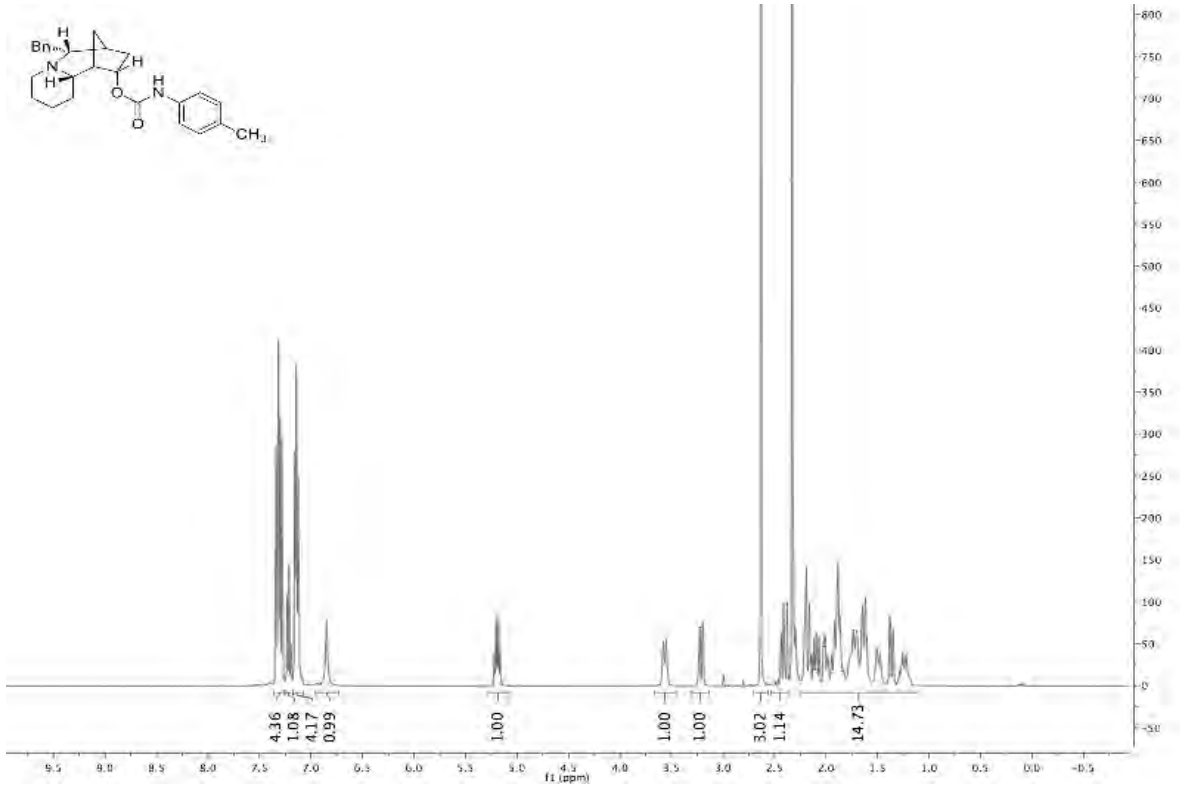

nBu
H
N
H
O
O
H
N
CN
f1 (ppm)

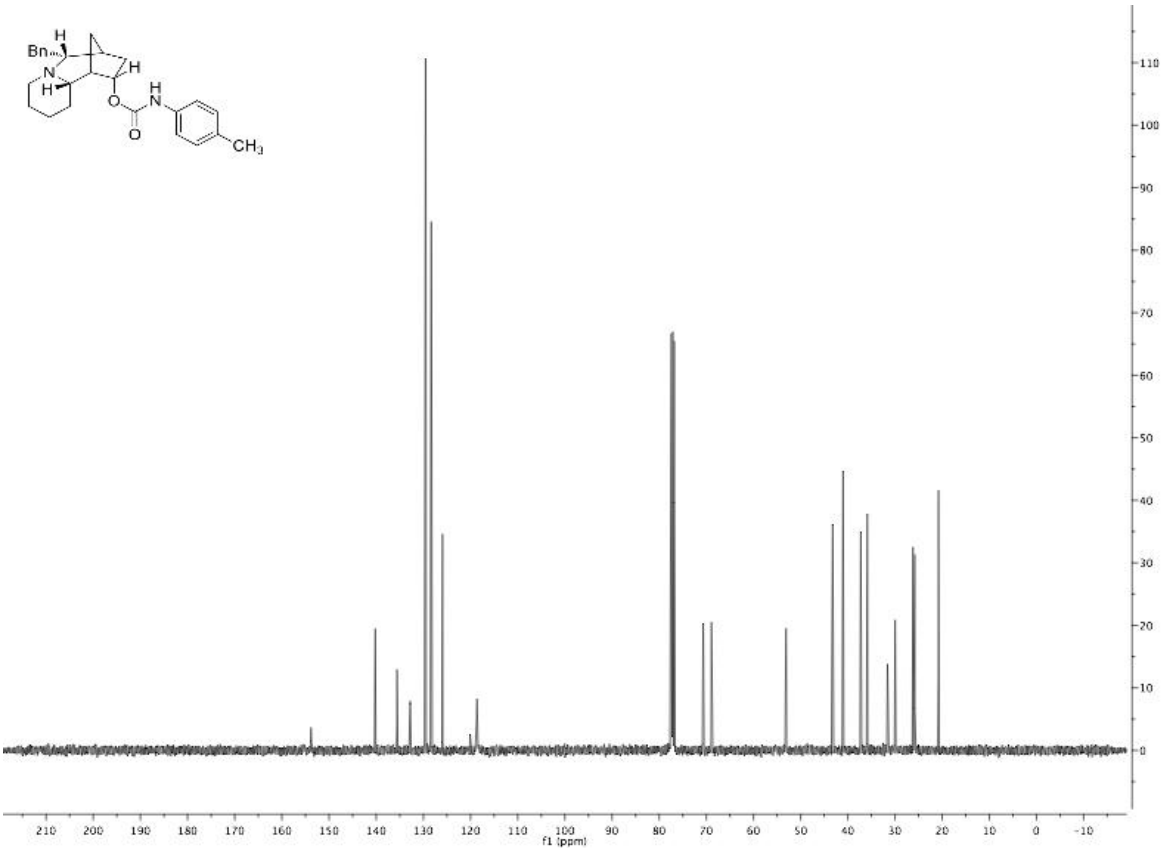
43c{*4*}


Bn
N
H
H
O
N
H
O
CH3
0.92
7.48
1.09
0.97
1.00
0.98
1.01
18.33
1.11
1.13
f1 (ppm)

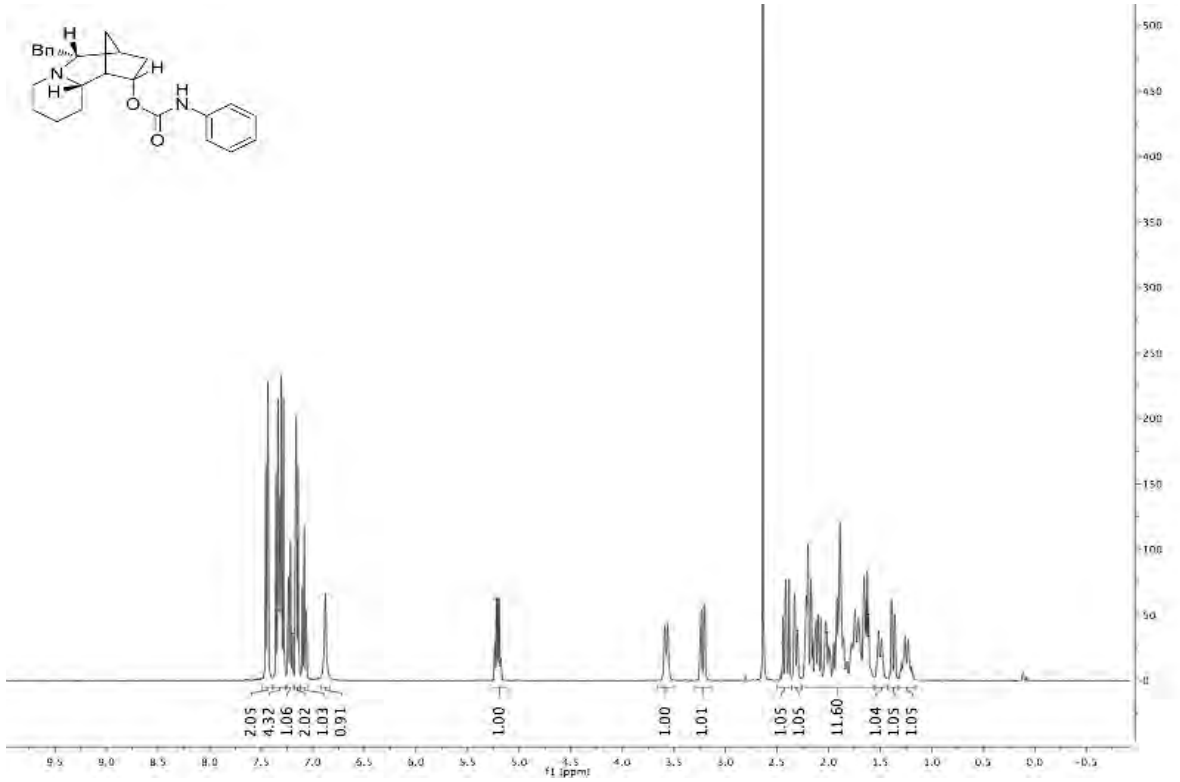

Bn
N
H
H
O
N
H
O
CH3
f1 (ppm)

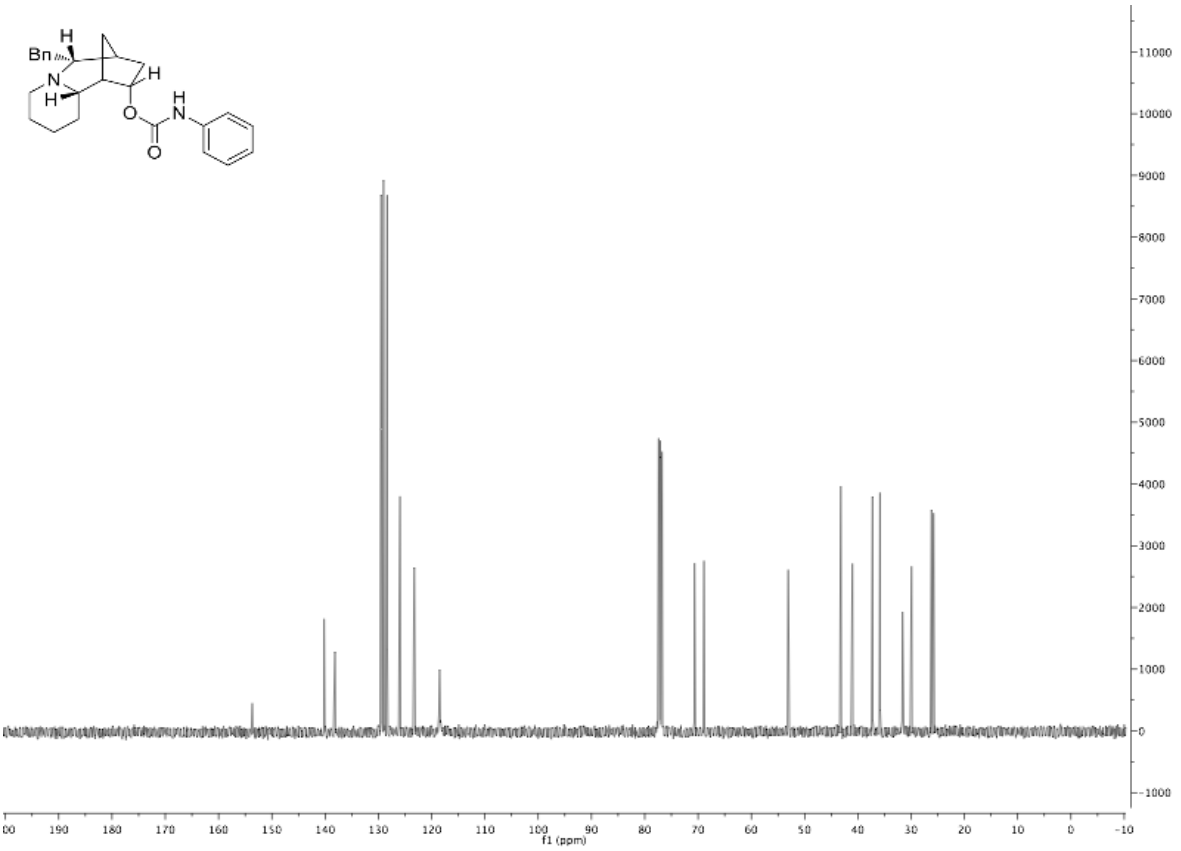
43c{*5*}





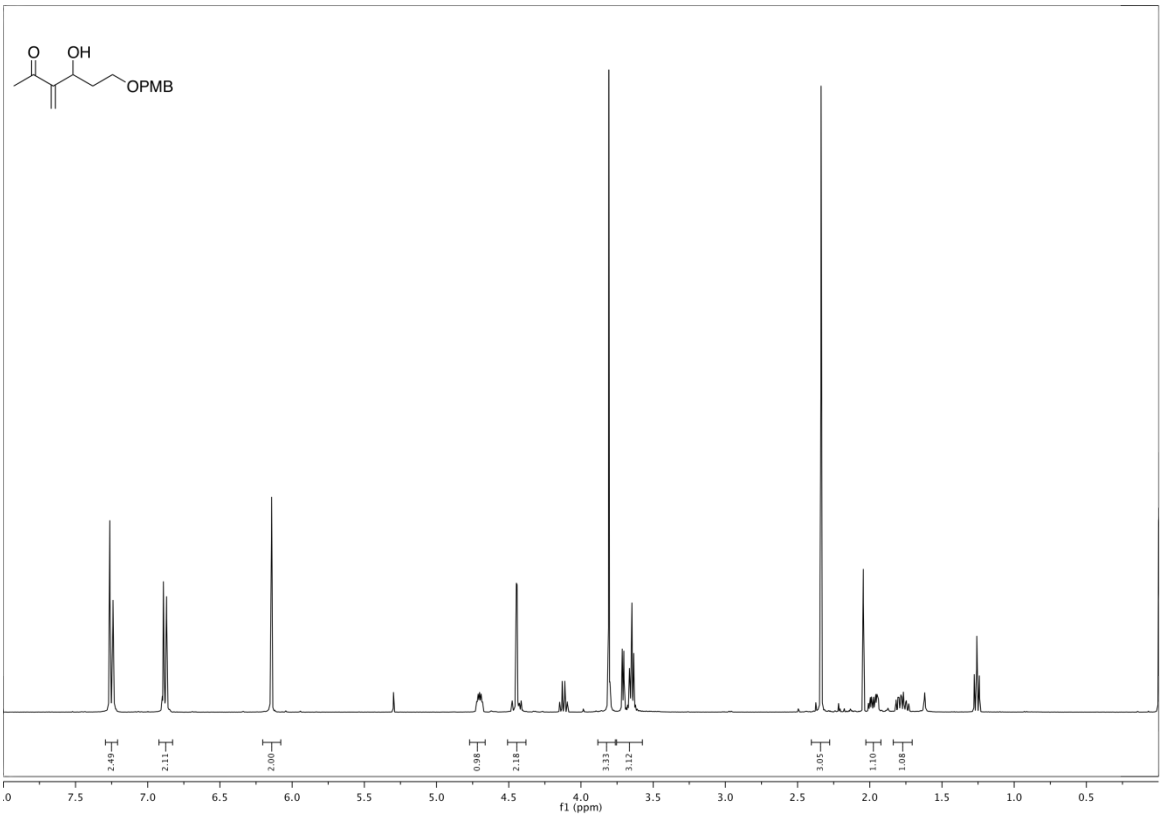
43c{*8*}

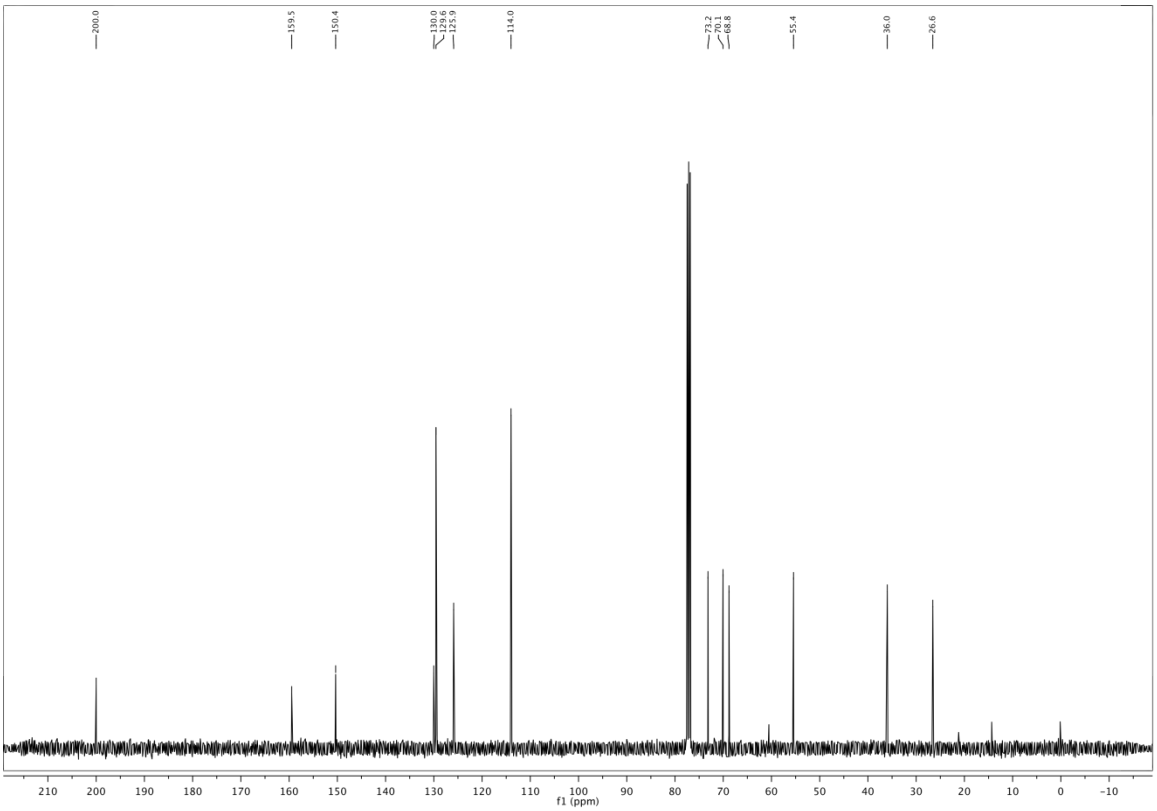

2.05
4.32
1.06
2.02
1.03
0.91
1.00
1.00
1.01
1.05
1.05
11.60
1.04
1.05
1.05
f1 (ppm)


f1 (ppm)

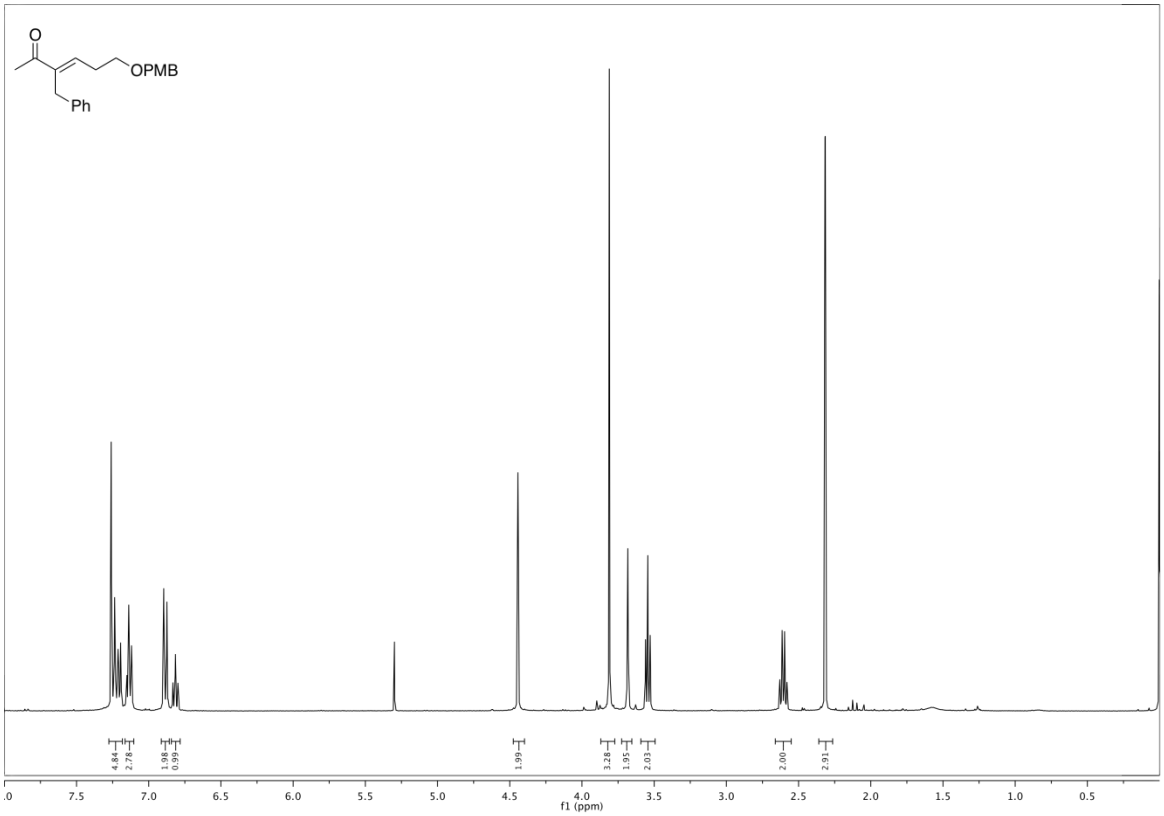
Mesembrine-inspired series:

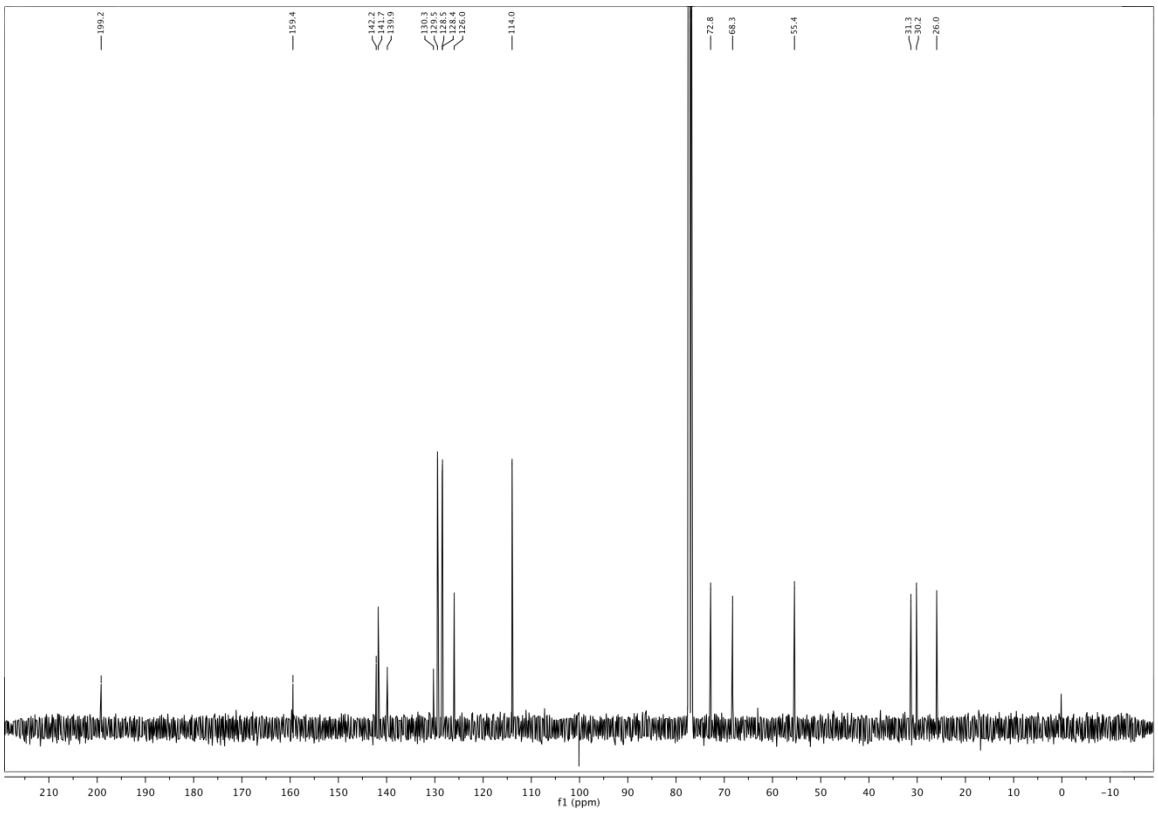
Hydroxyketone **S15**



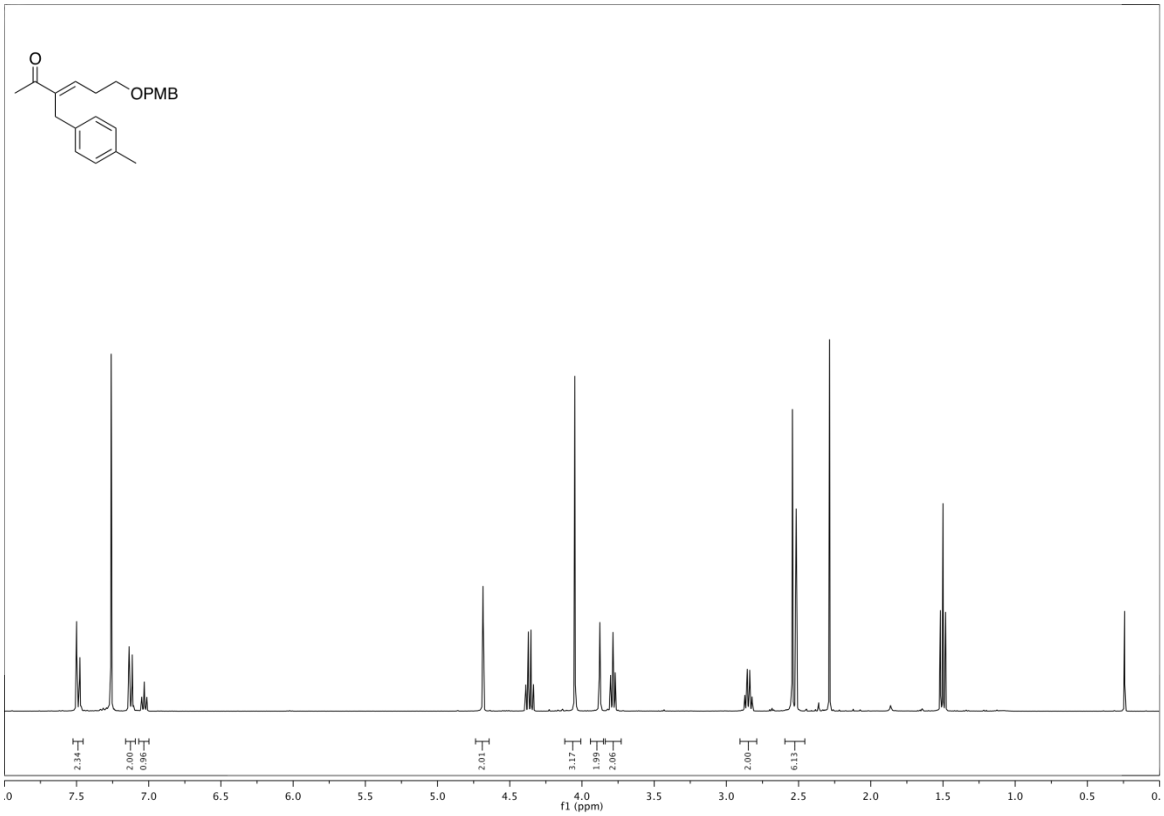


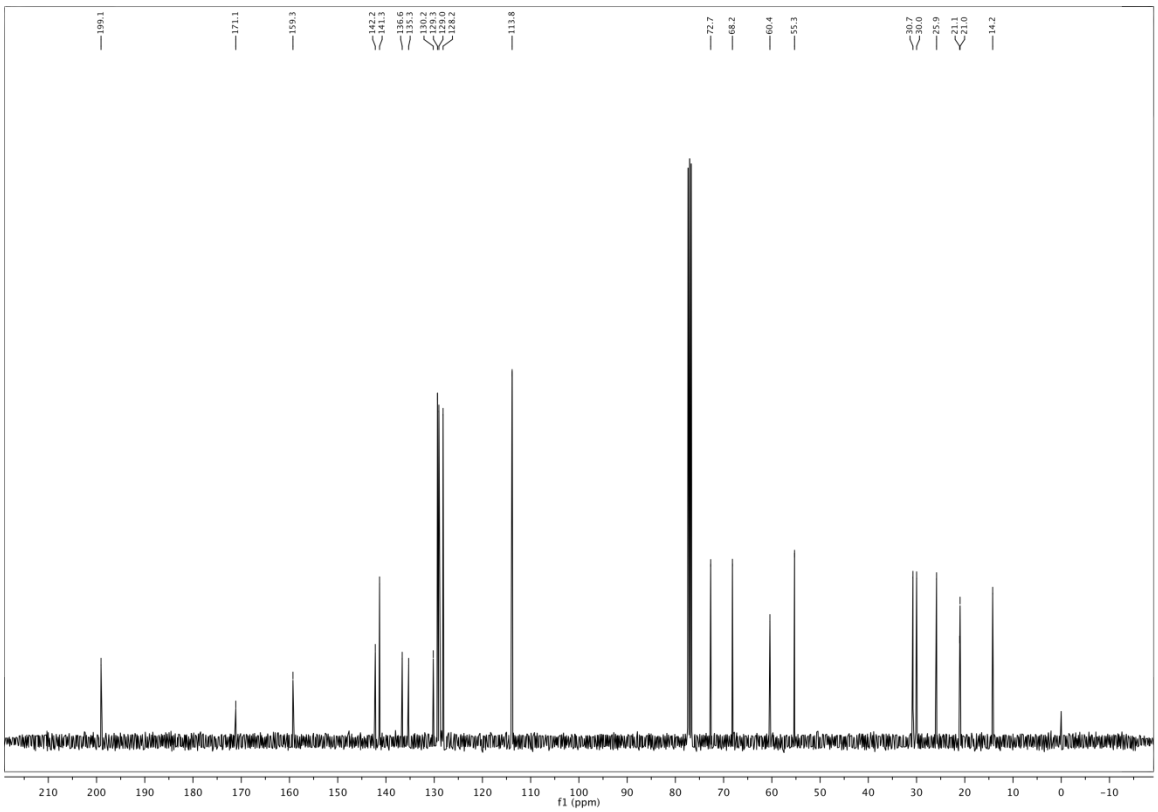
Enone **S16a**


O
OPMB
Ph
4.84
2.78
1.98
0.99
1.99
3.28
1.95
2.03
2.00
2.91
f1 (ppm)

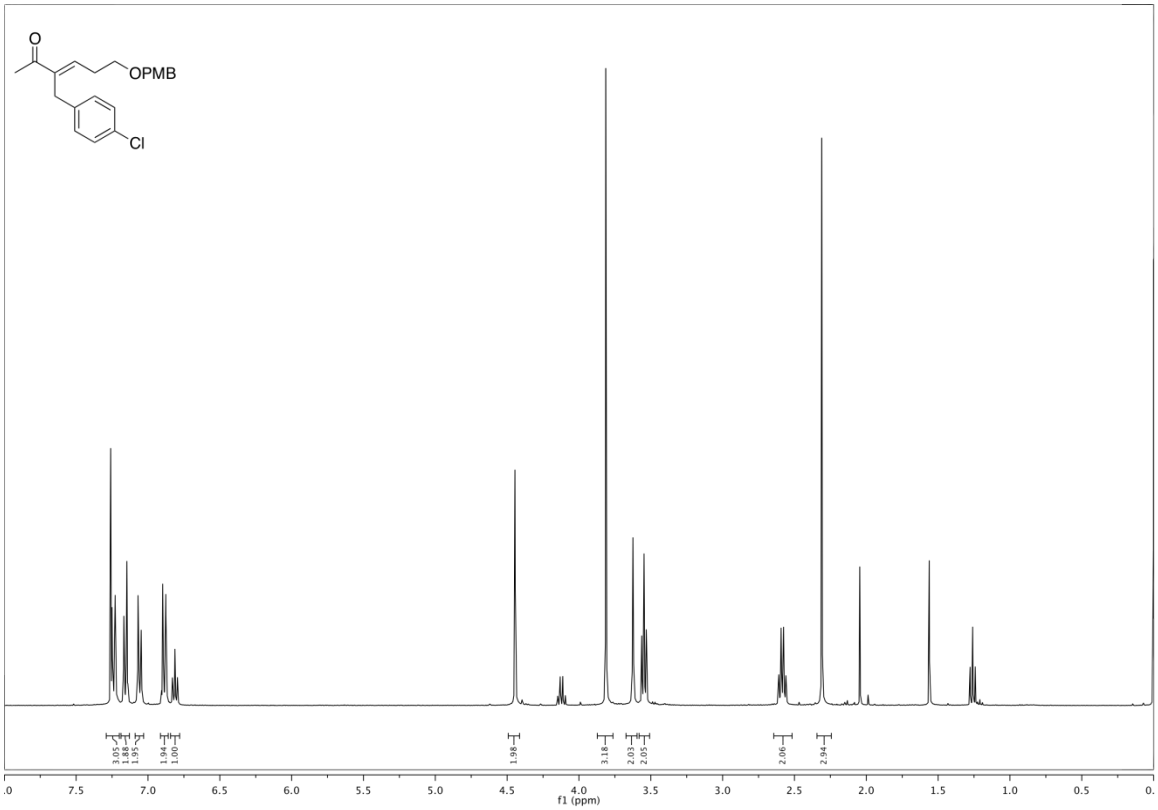

199.2
159.4
142.2
141.7
139.9
130.3
129.5
128.5
128.4
126.0
114.0
72.8
68.3
55.4
31.3
30.2
26.0
f1 (ppm)

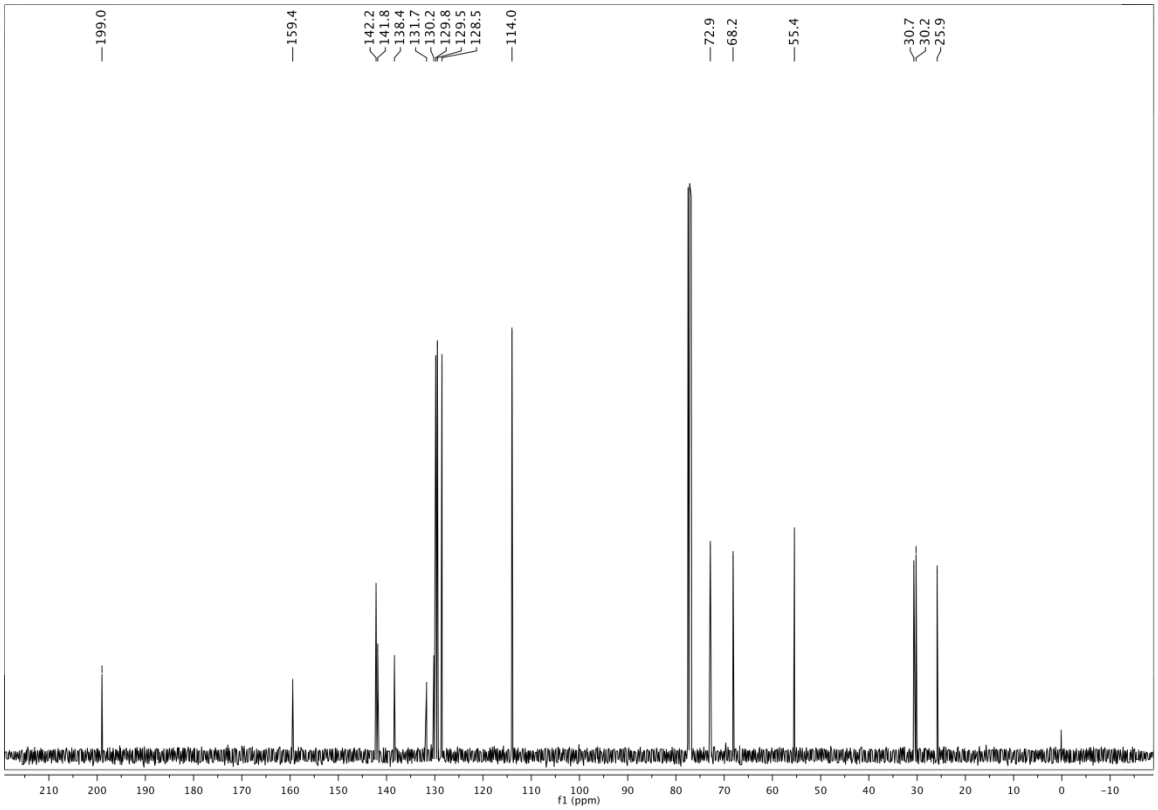
Enone **S16b**


O
OPMB
2.34
2.00
0.96
2.01
3.17
1.99
2.06
2.00
6.13
f1 (ppm)

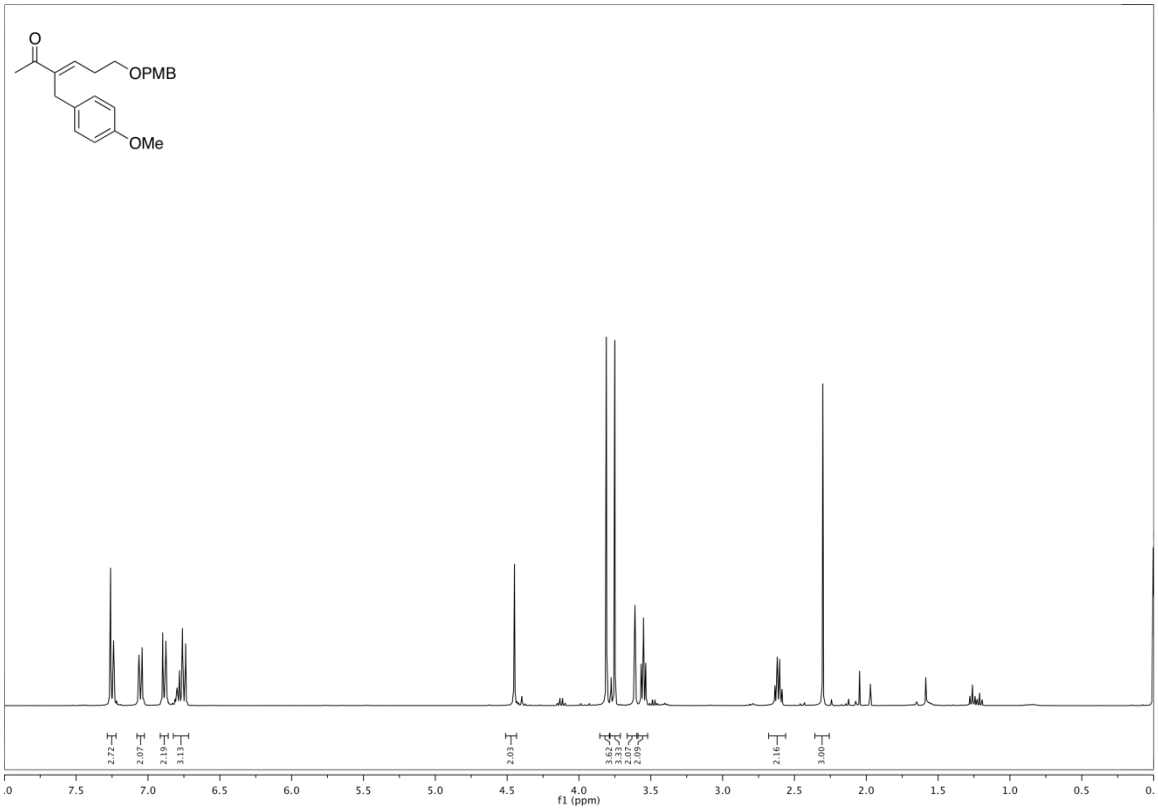

199.1
171.1
159.3
142.2
141.3
136.6
135.3
130.2
129.3
129.0
128.2
113.8
72.7
68.2
60.4
55.3
30.7
30.0
25.9
21.1
21.0
14.2
f1 (ppm)

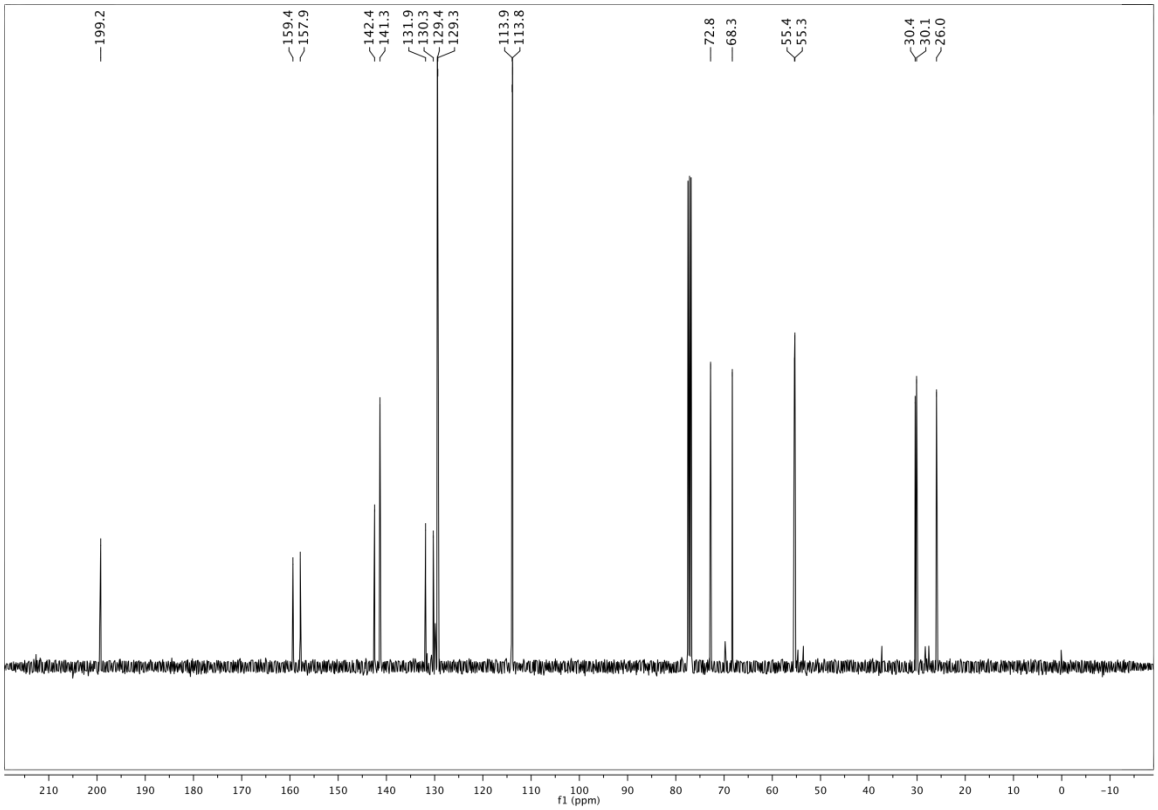
Enone **S16c**


O
OPMB
Cl
3.05
1.88
1.95
1.94
1.00
1.98
3.18
2.03
2.05
2.06
2.94
f1 (ppm)

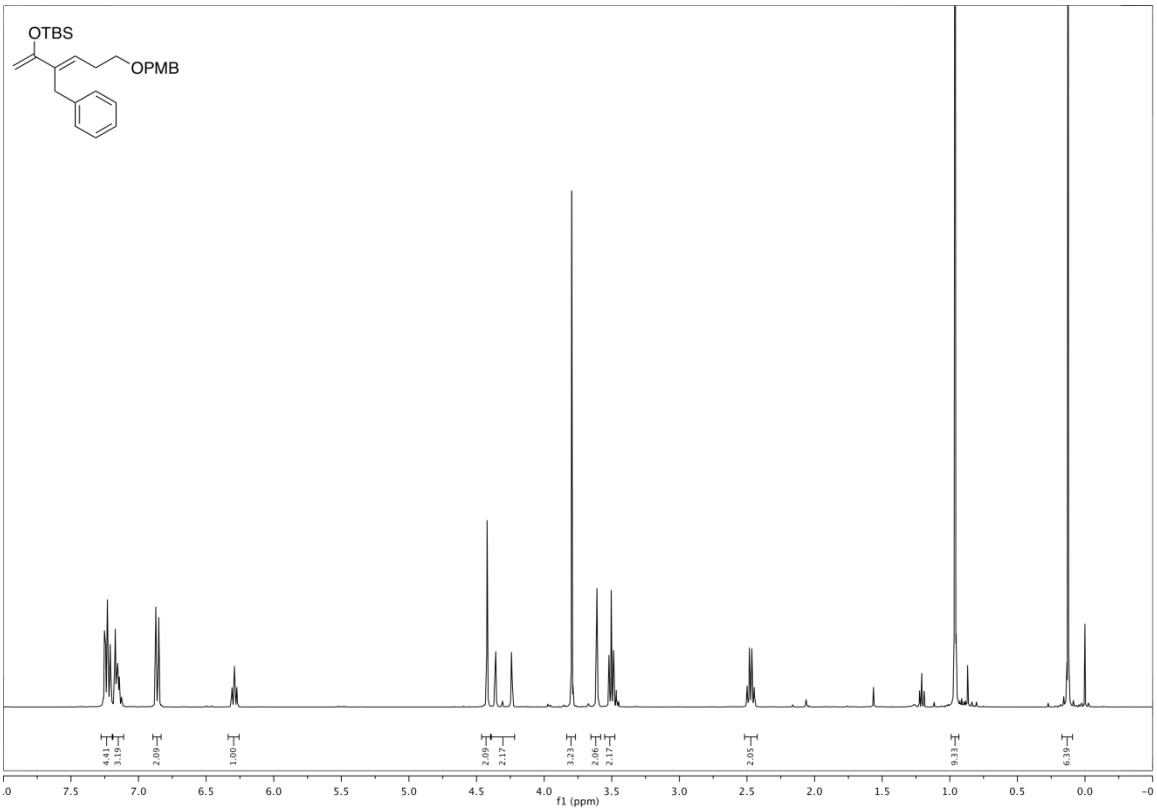

199.0
159.4
142.2
141.8
138.4
131.7
130.2
129.8
129.5
128.5
114.0
72.9
68.2
55.4
30.7
30.2
25.9
f1 (ppm)

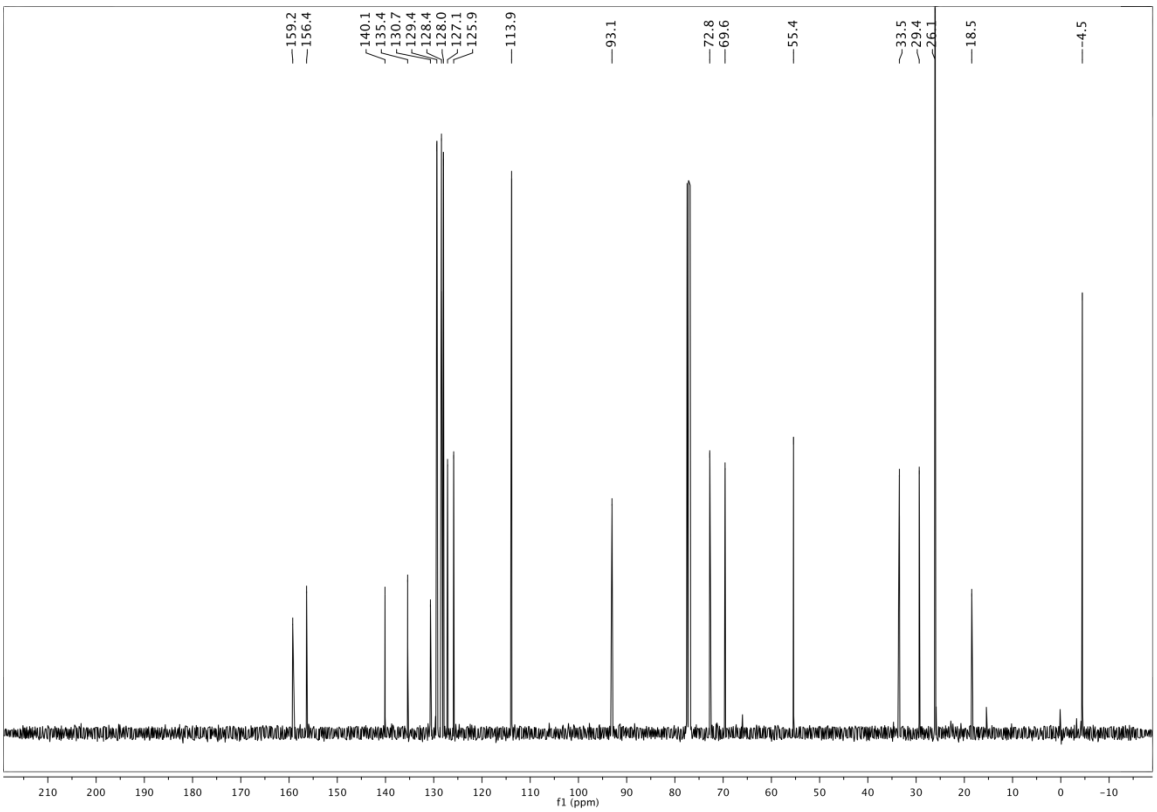
Enone **S16d**


O
OPMB
OMe
2.72
2.07
2.19
3.13
2.03
3.82
3.24
2.07
2.09
2.16
3.00
f1 (ppm)

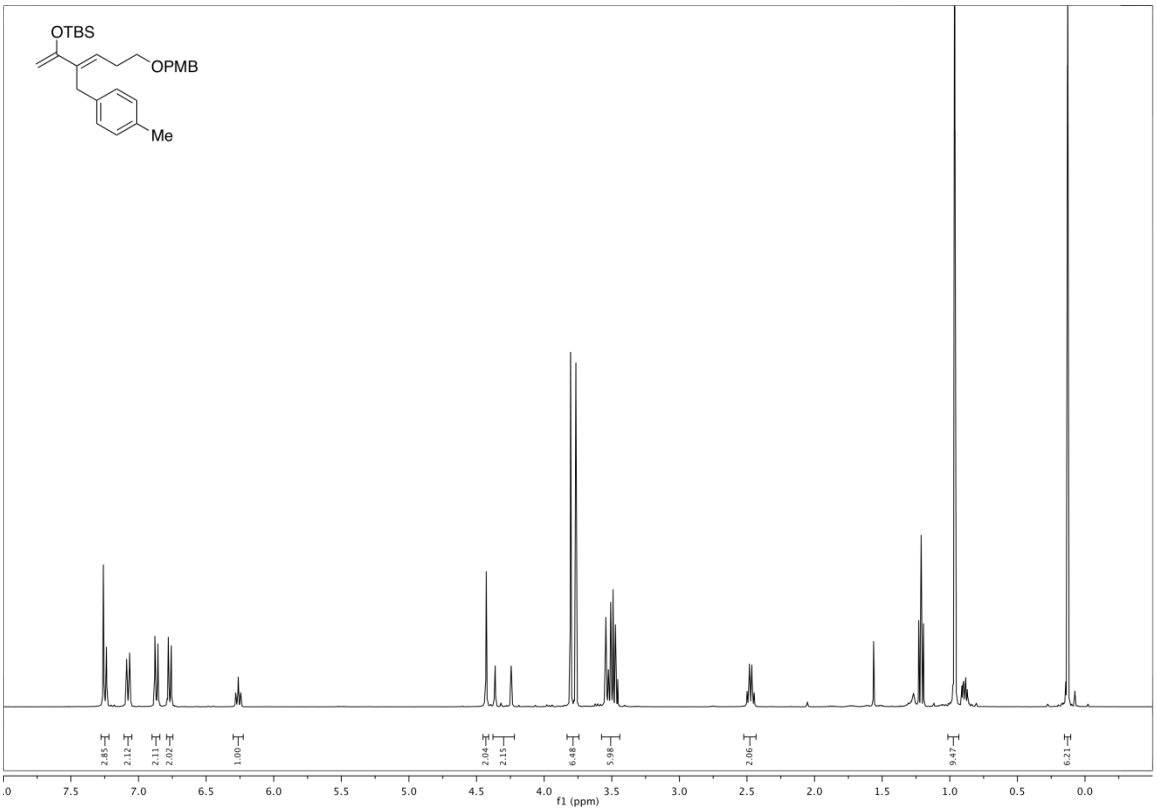

199.2
159.4
157.9
142.4
141.3
131.9
130.3
129.4
129.3
113.9
113.8
72.8
68.3
55.4
55.3
30.4
30.1
26.0
f1 (ppm)

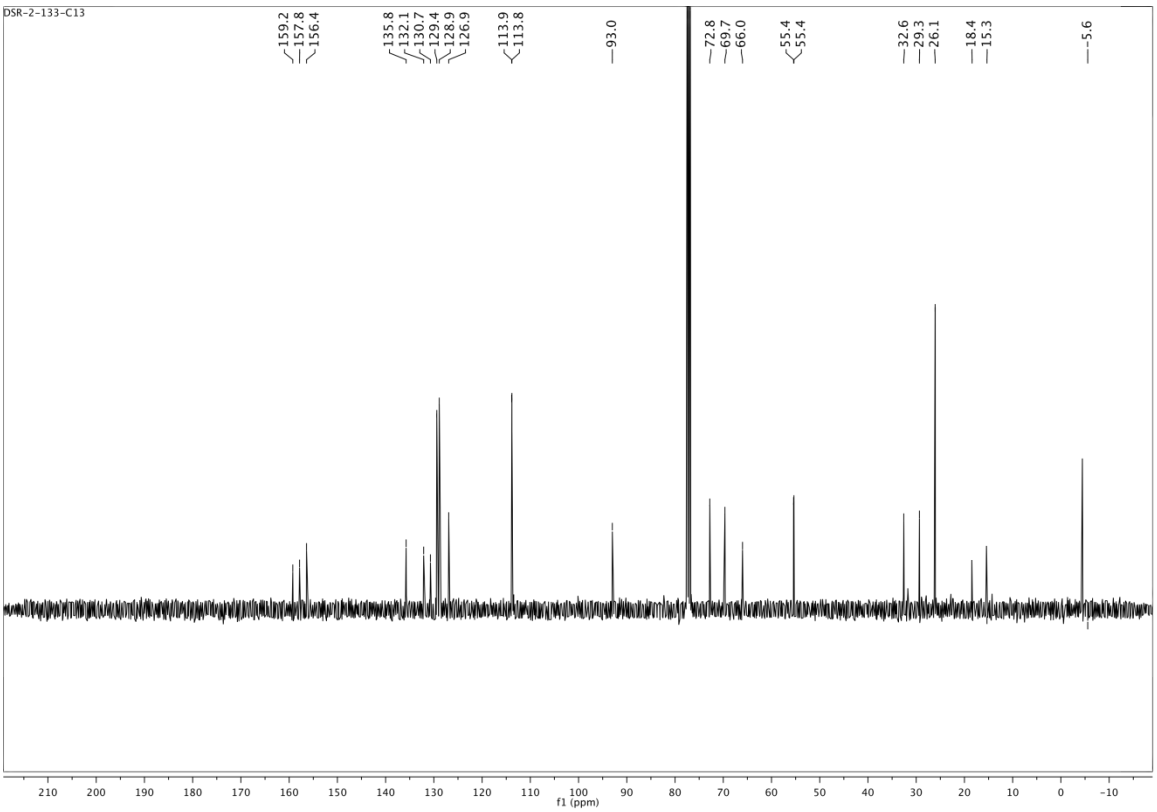
Silyloxydiene **22a**



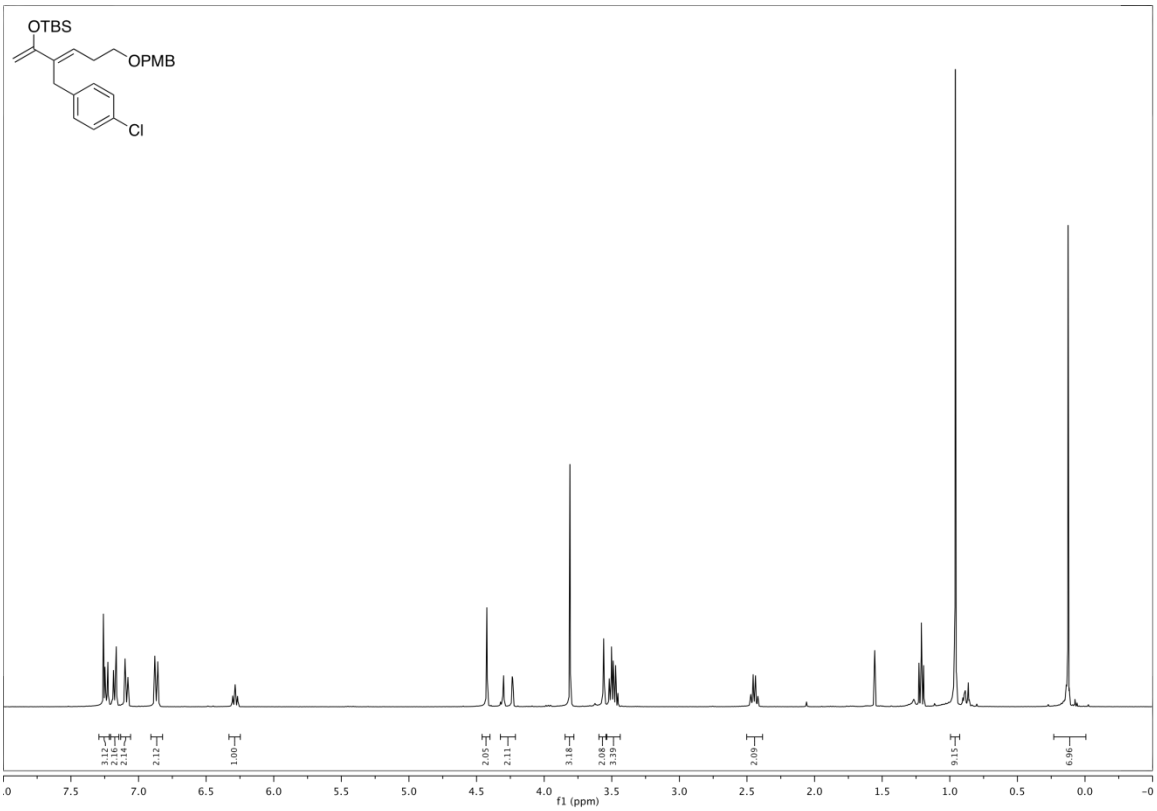


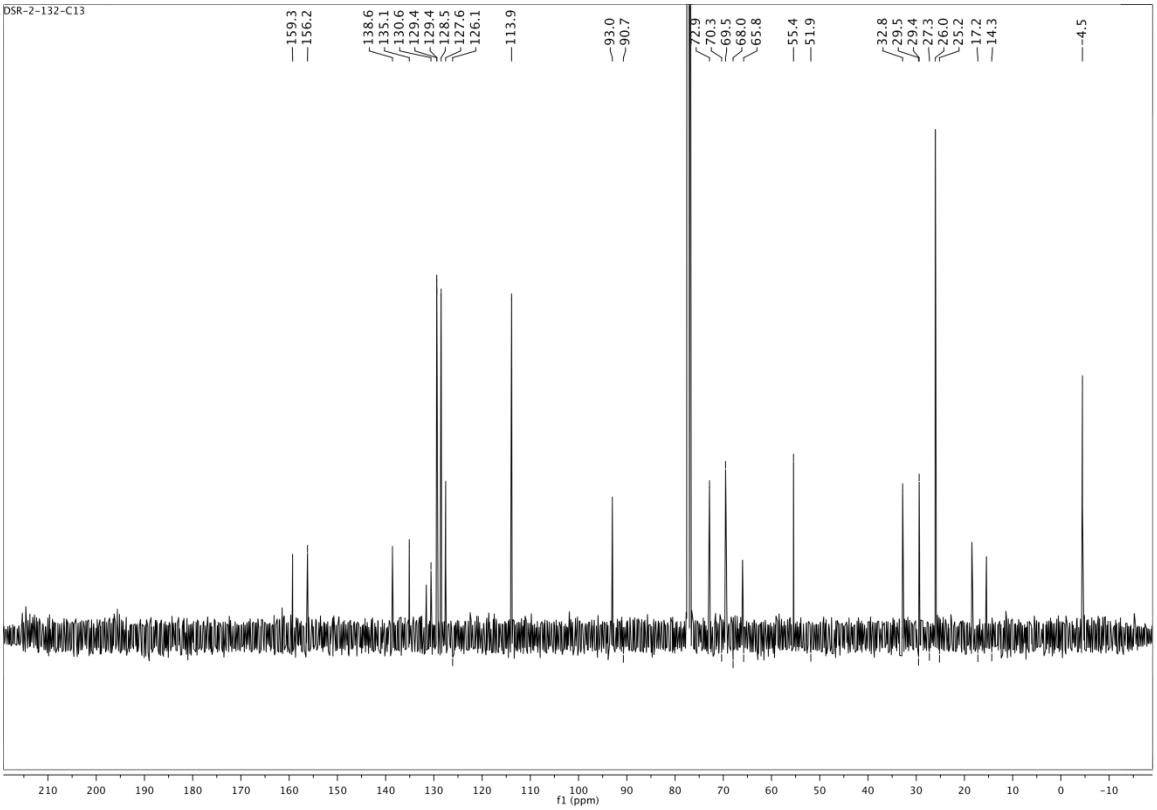
Silyloxydiene **22b**



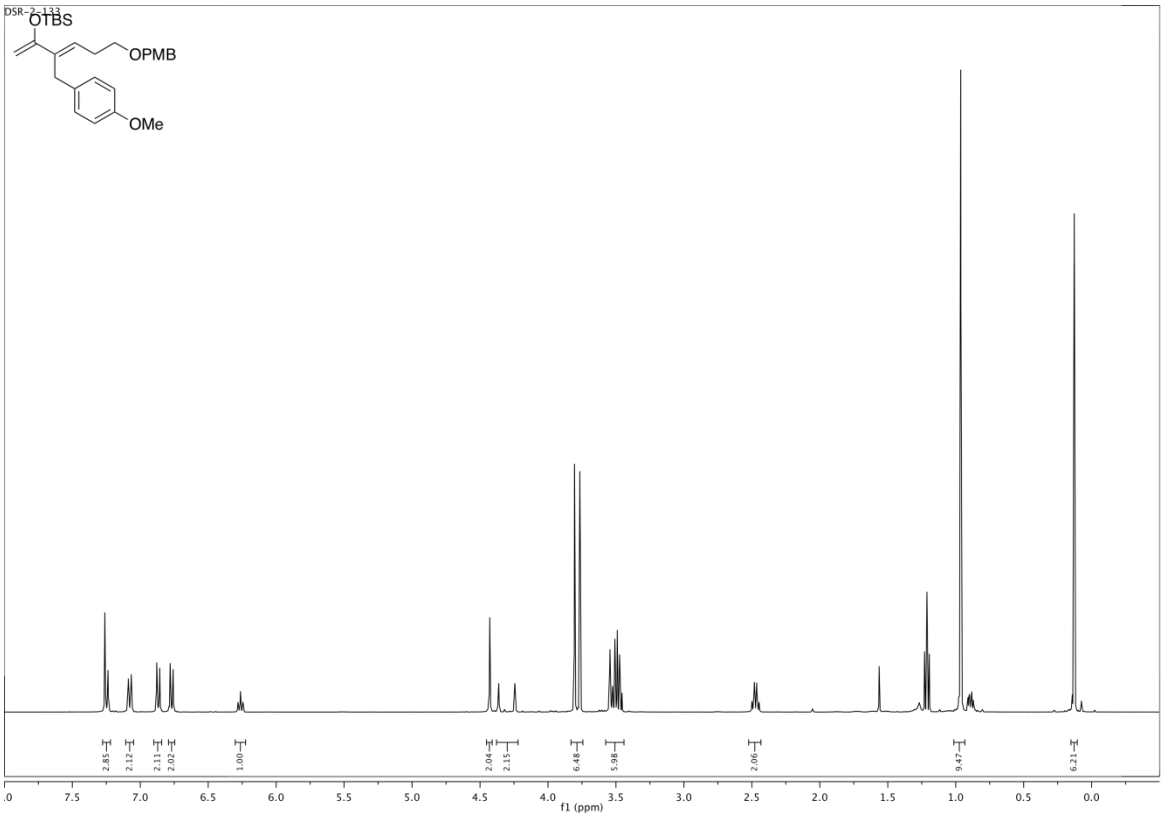


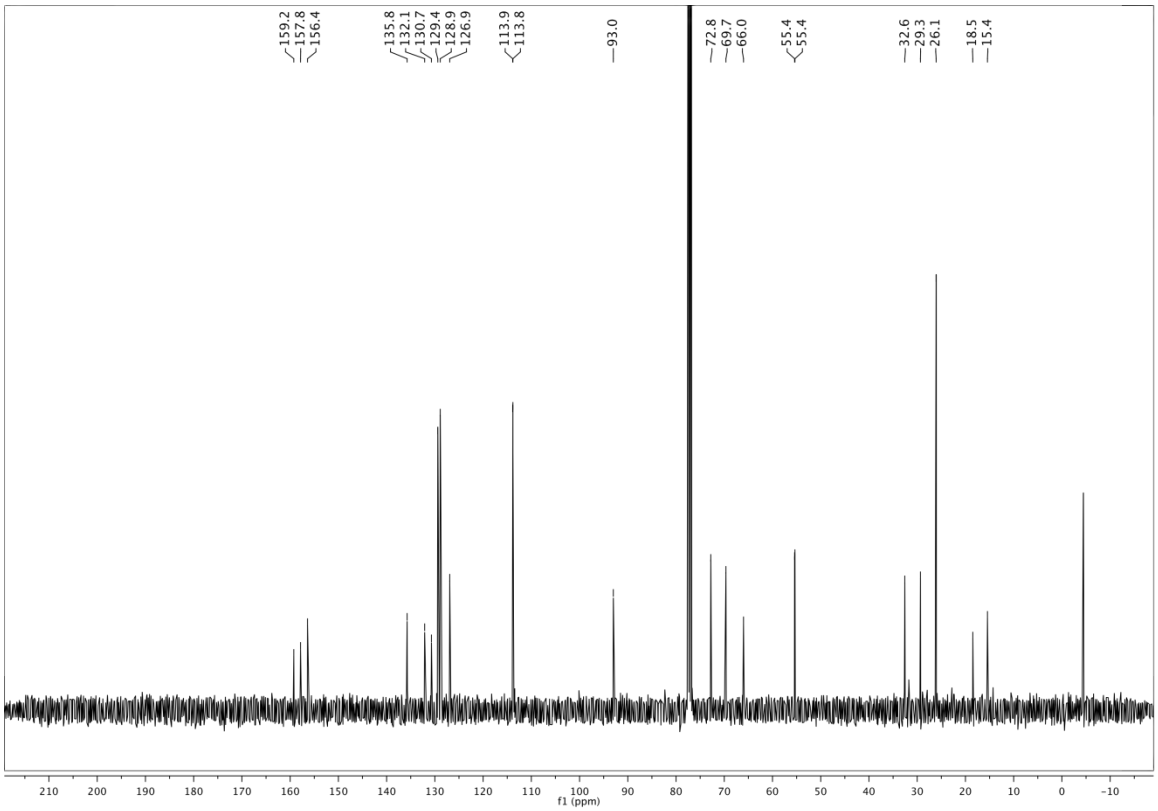
Silyloxydiene **22c**



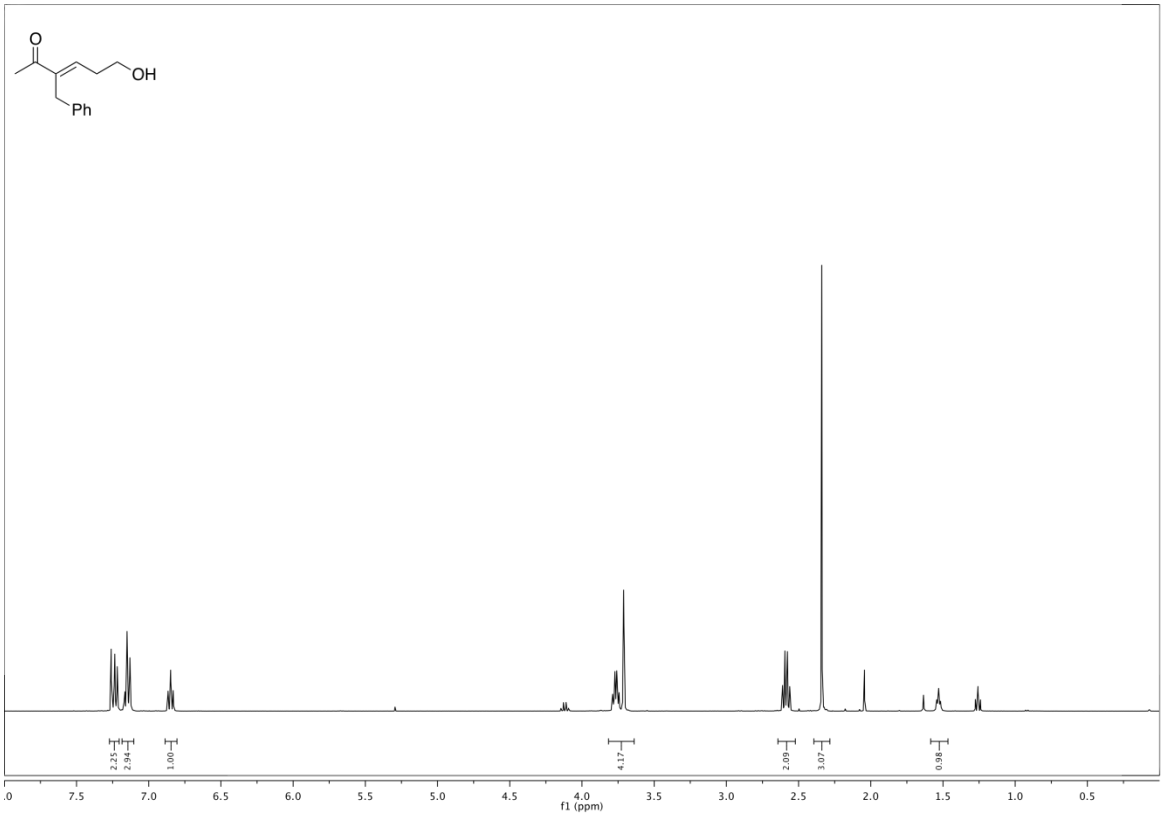


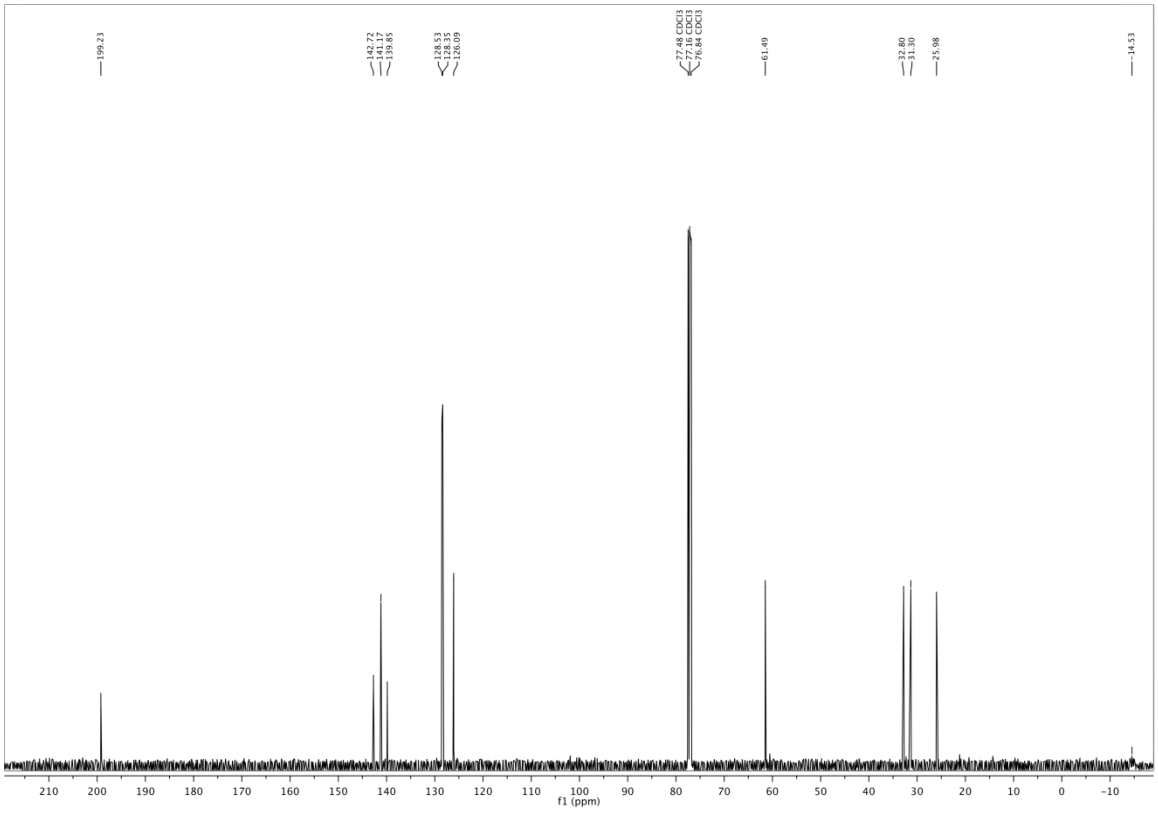
Silyloxydiene **22d**



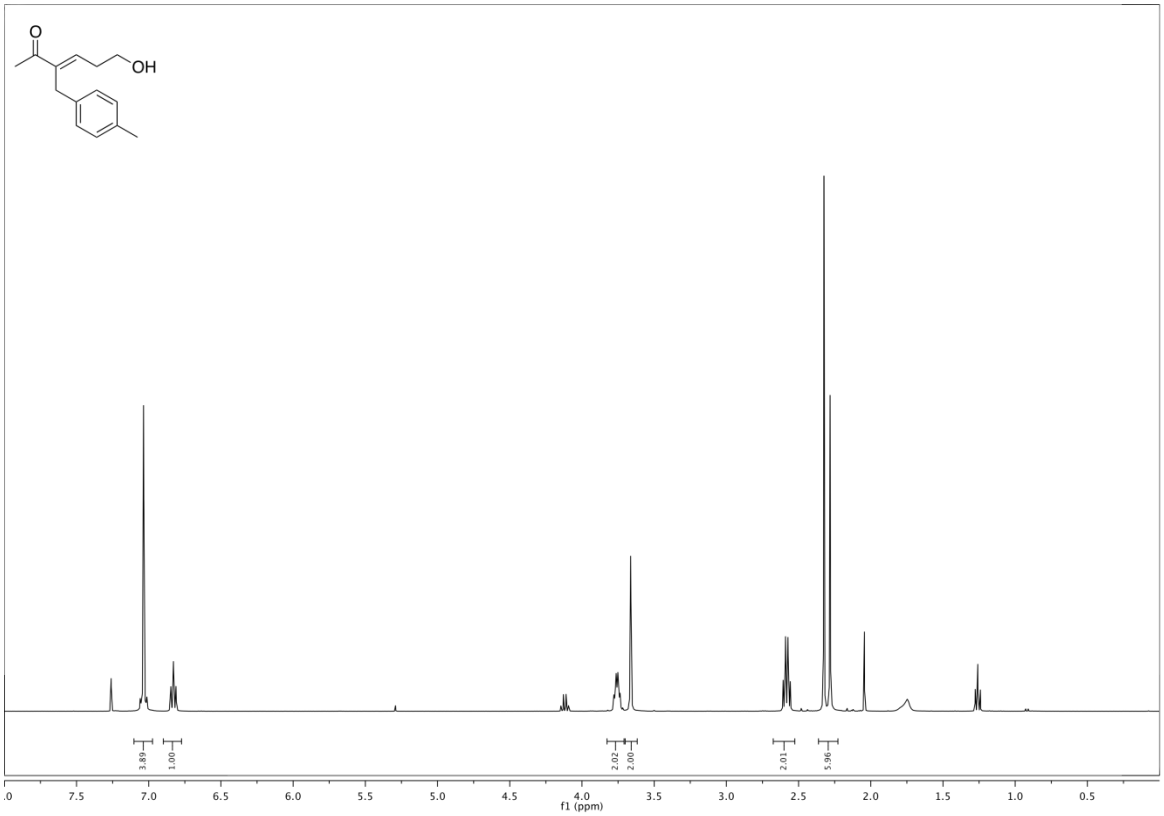


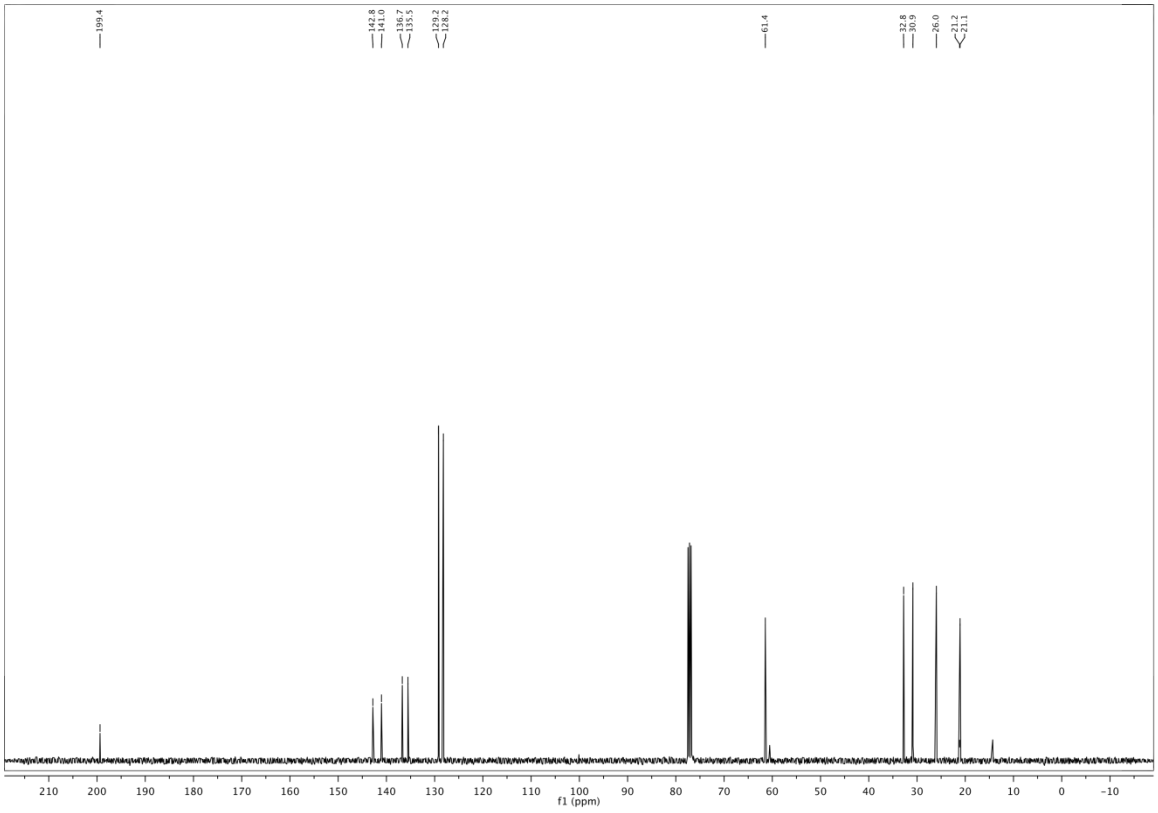
Hydroxy enone **S17a**



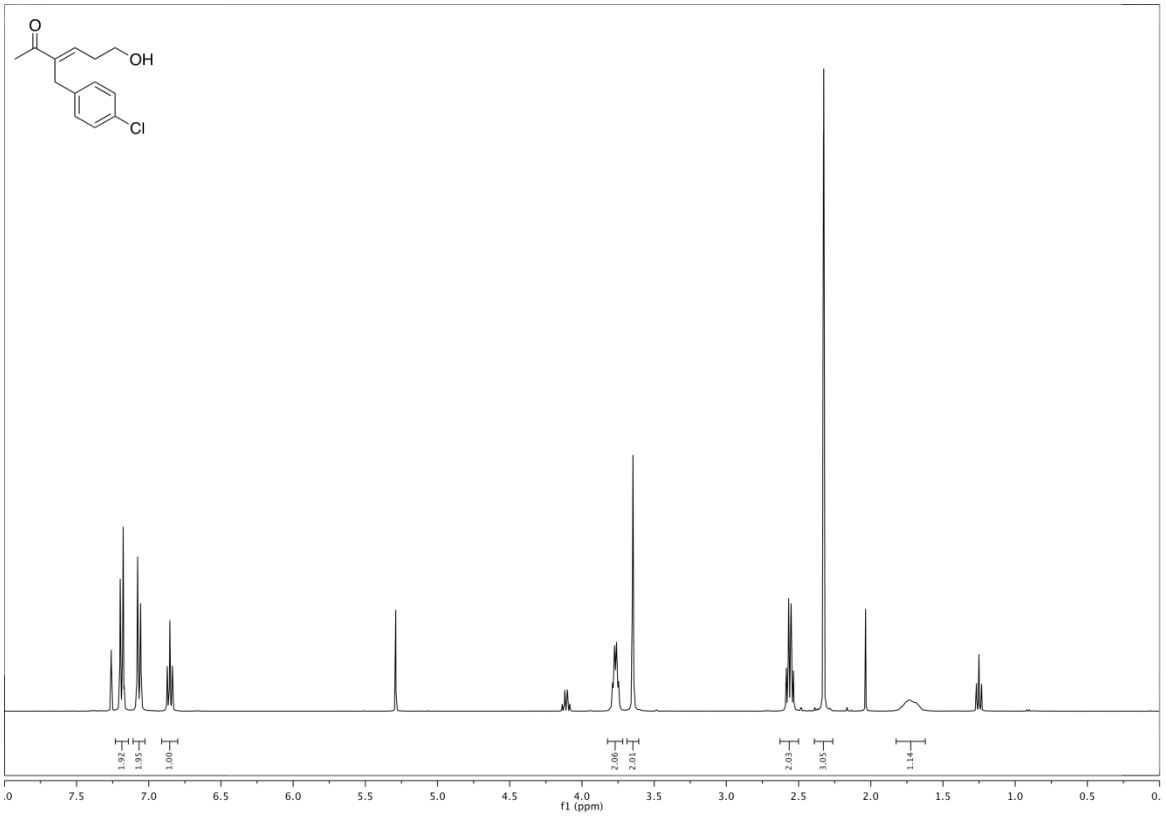


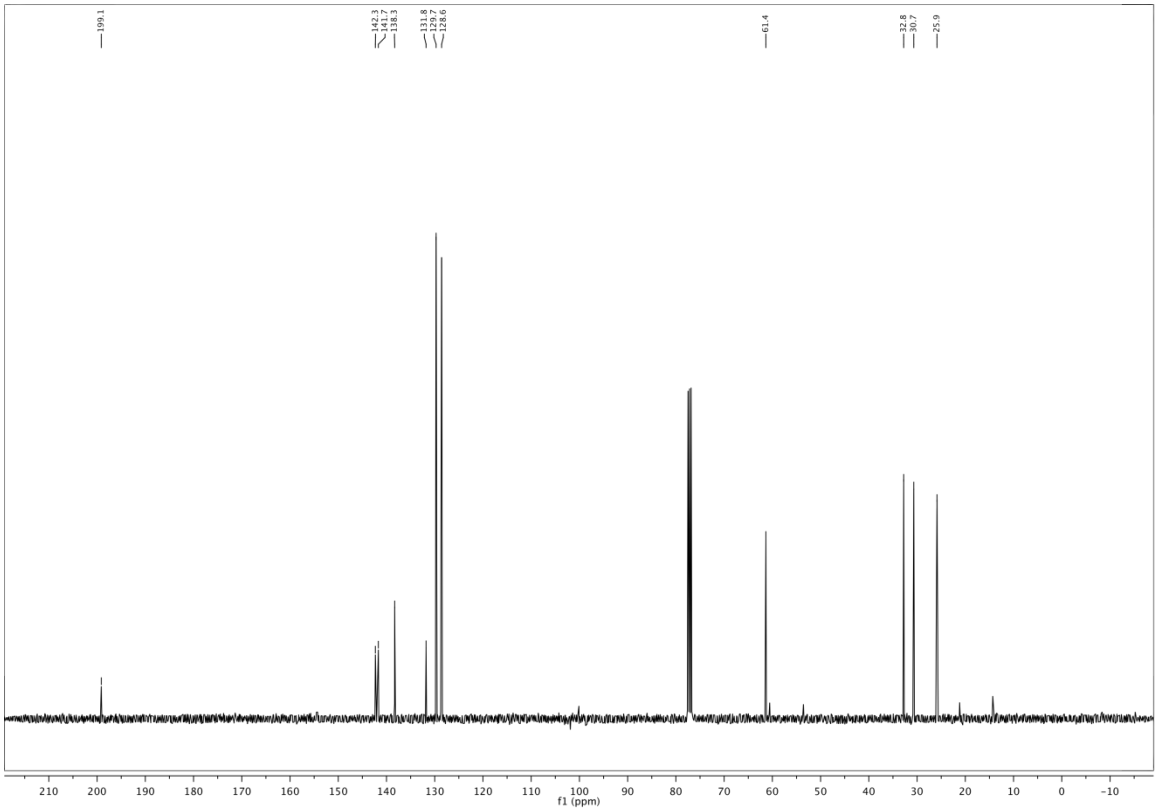
Hydroxy enone **S17b**



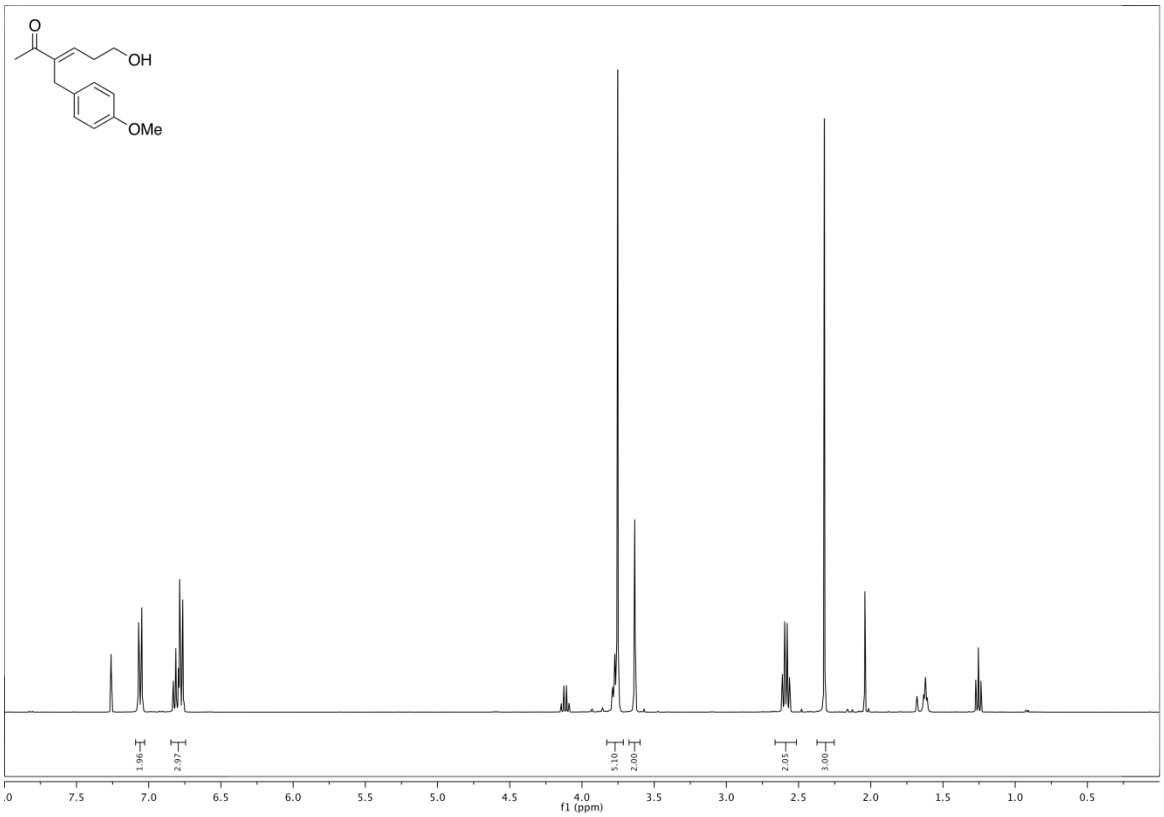


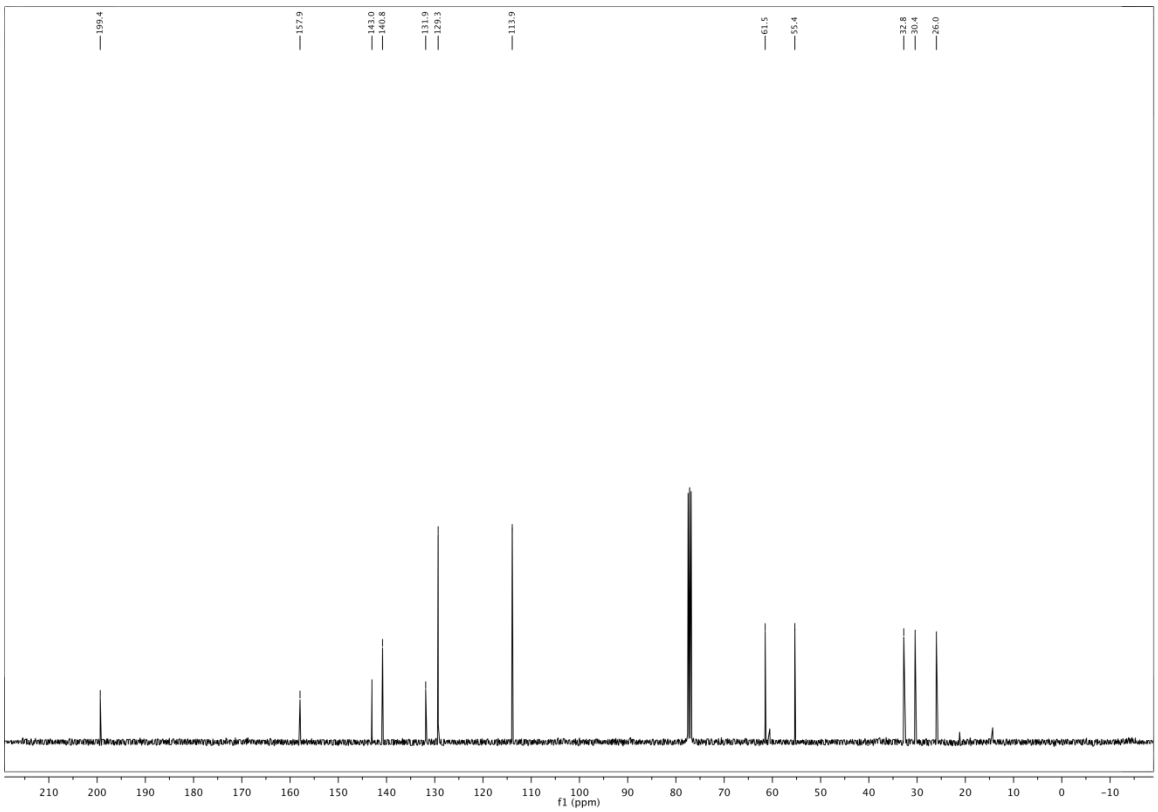
Hydroxy enone **S17c**



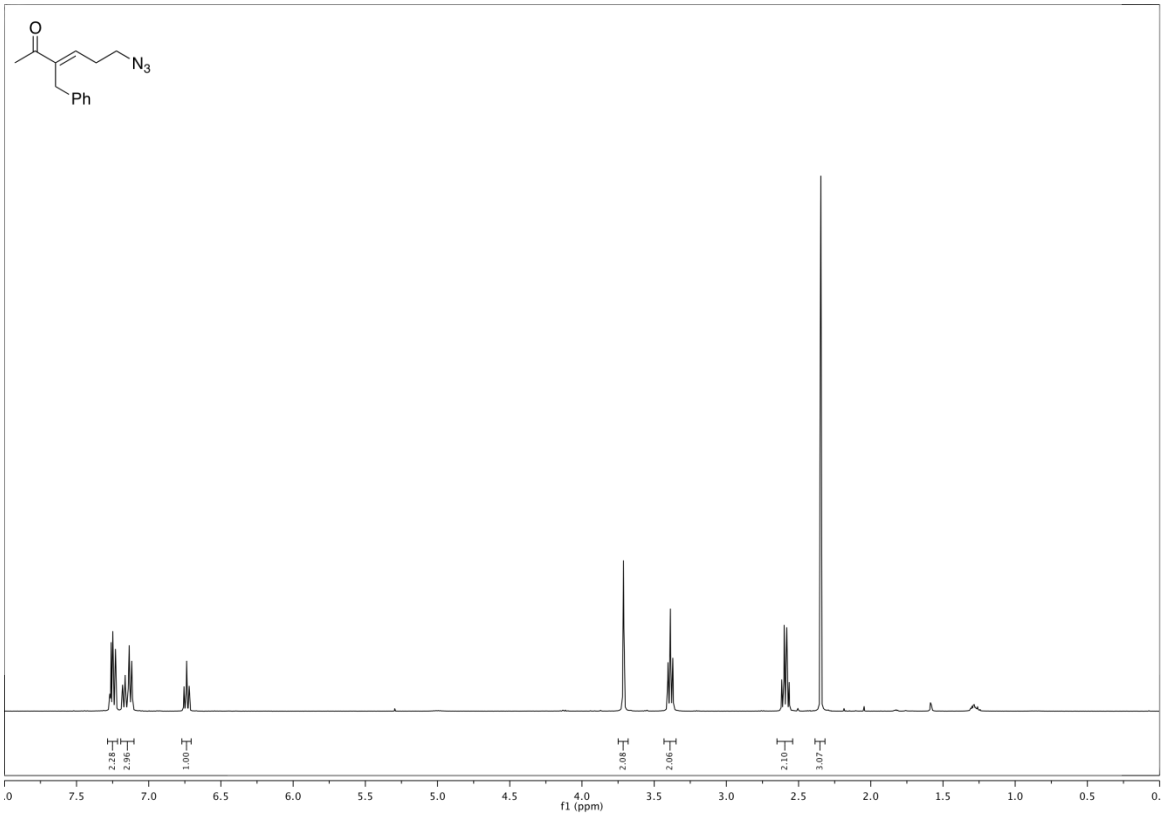


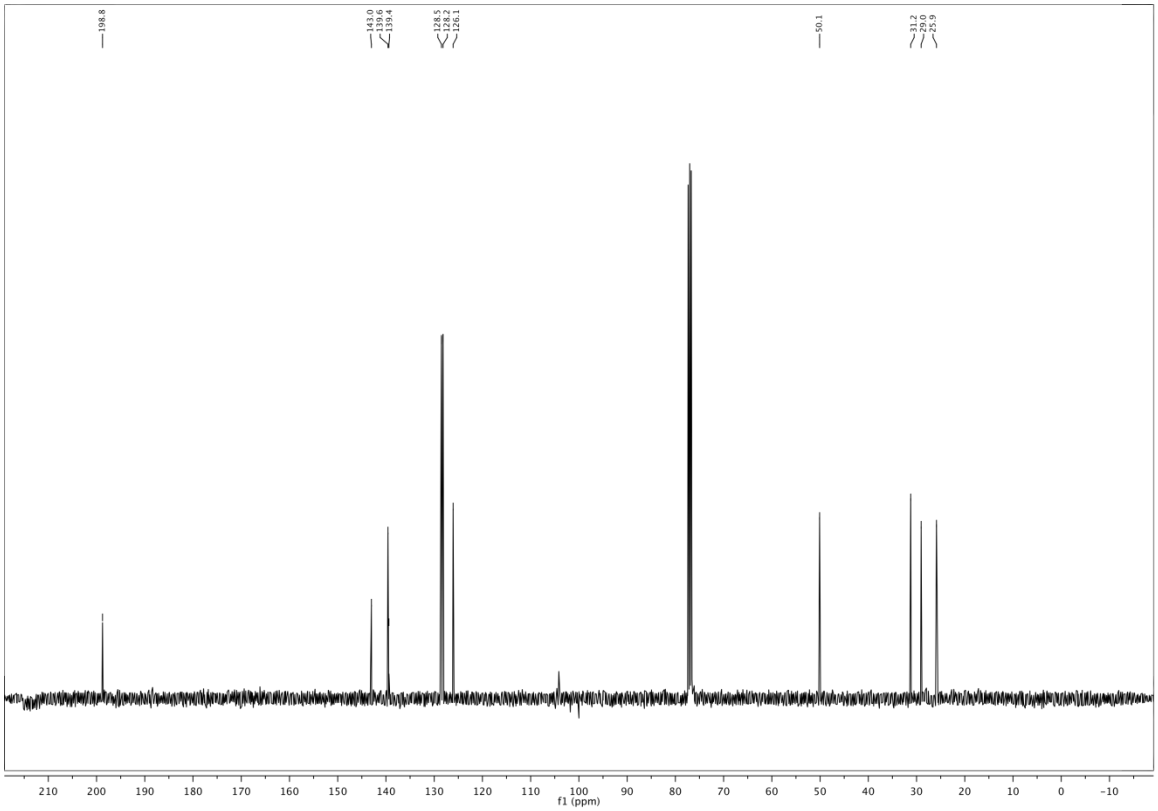
Hydroxy enone **S17d**



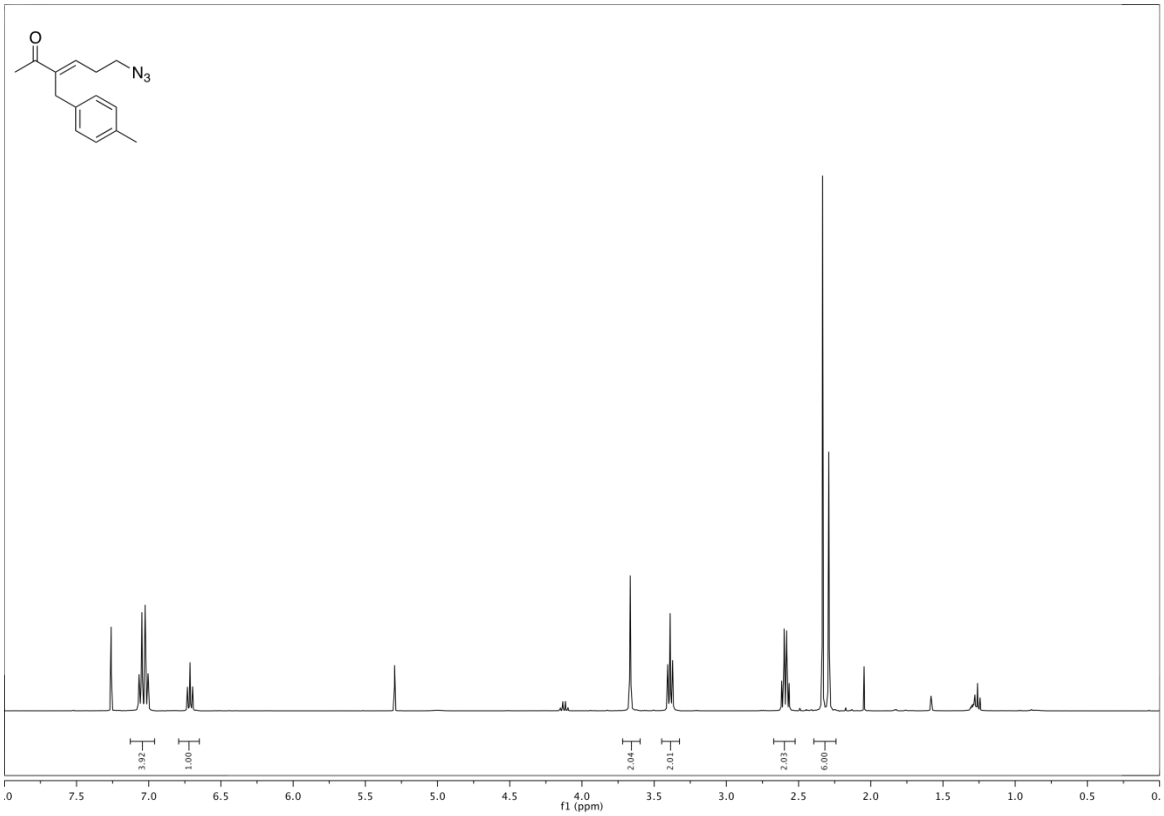


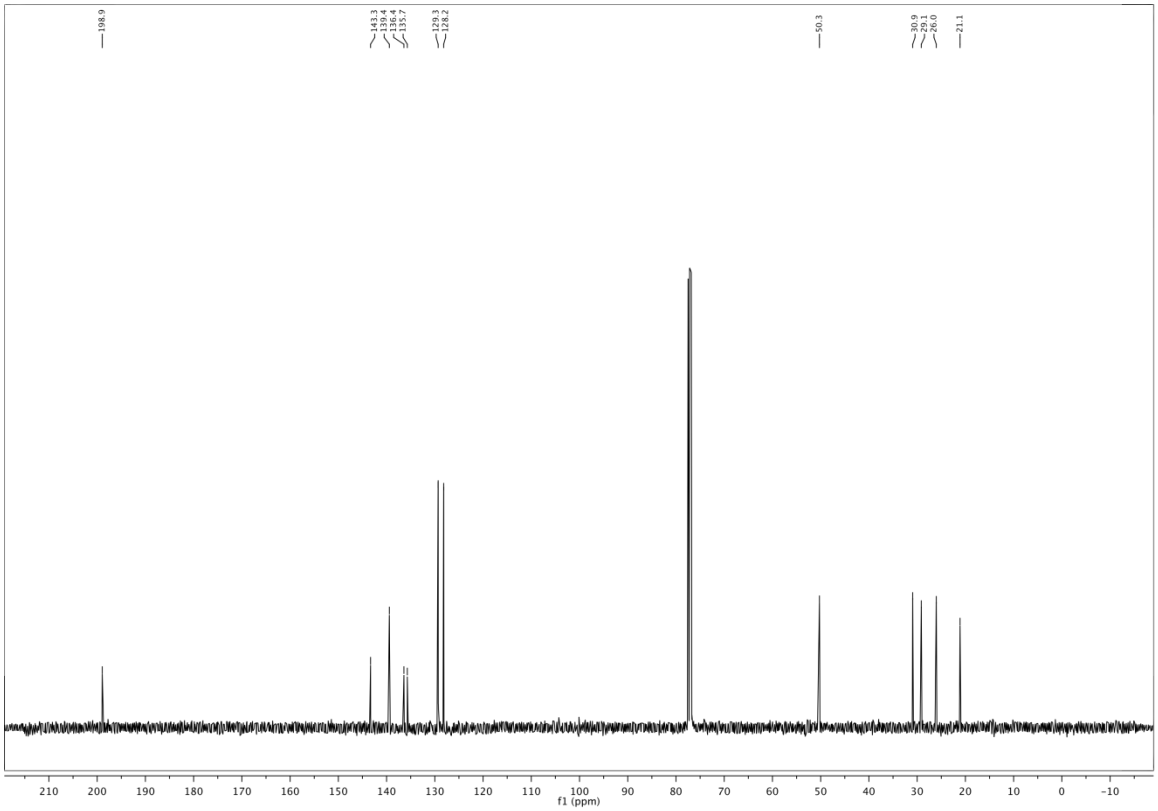
Azidoketone **S18a**



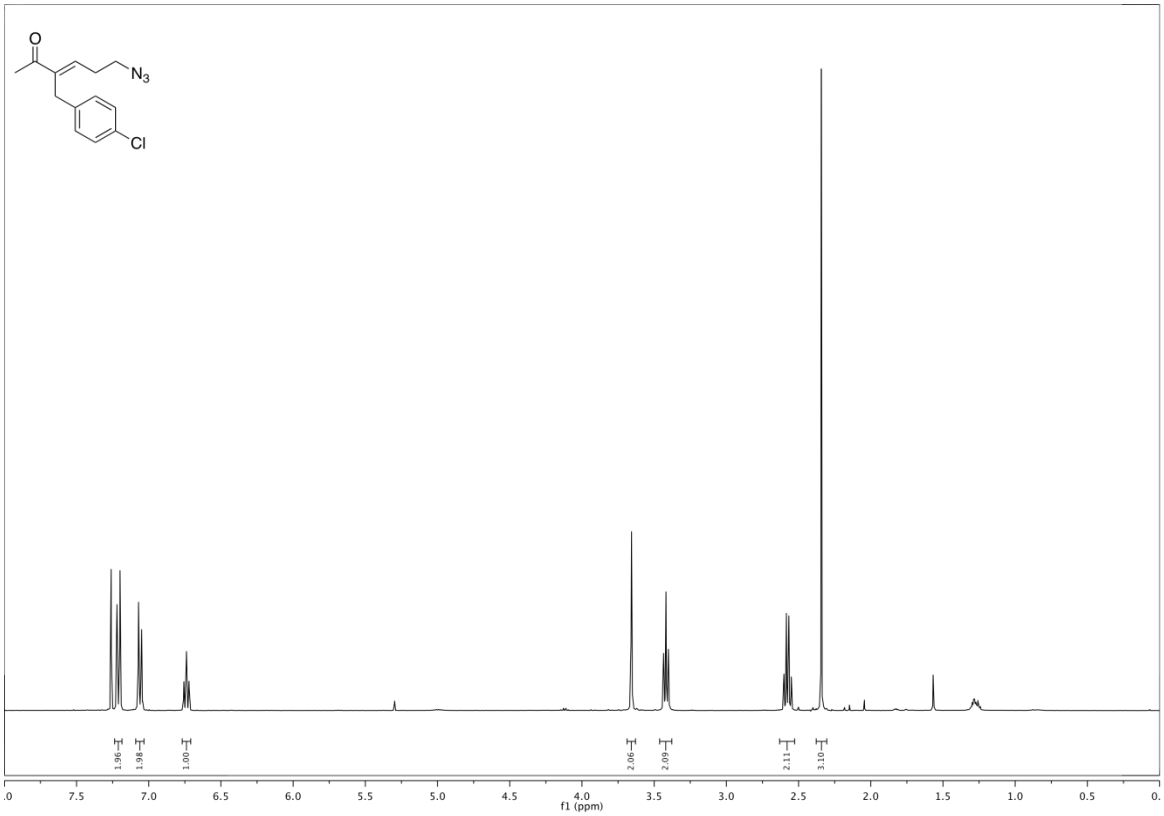


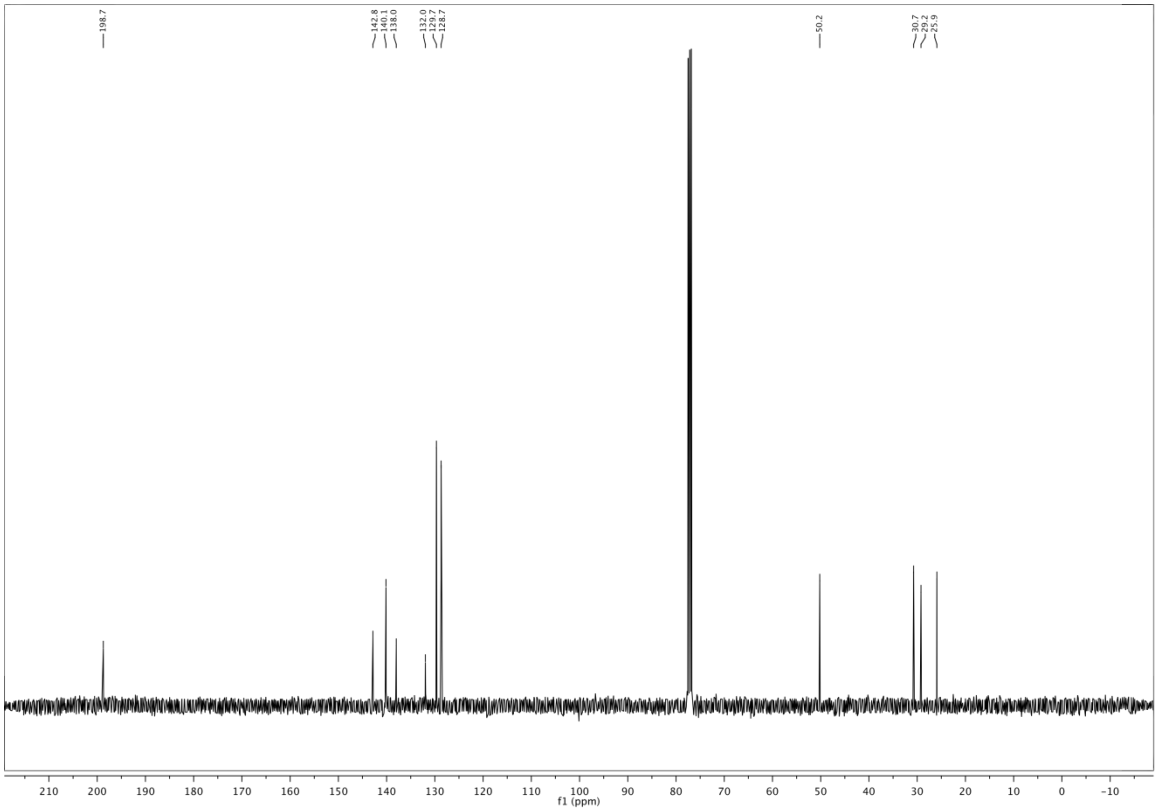
Azidoketone **S18b**



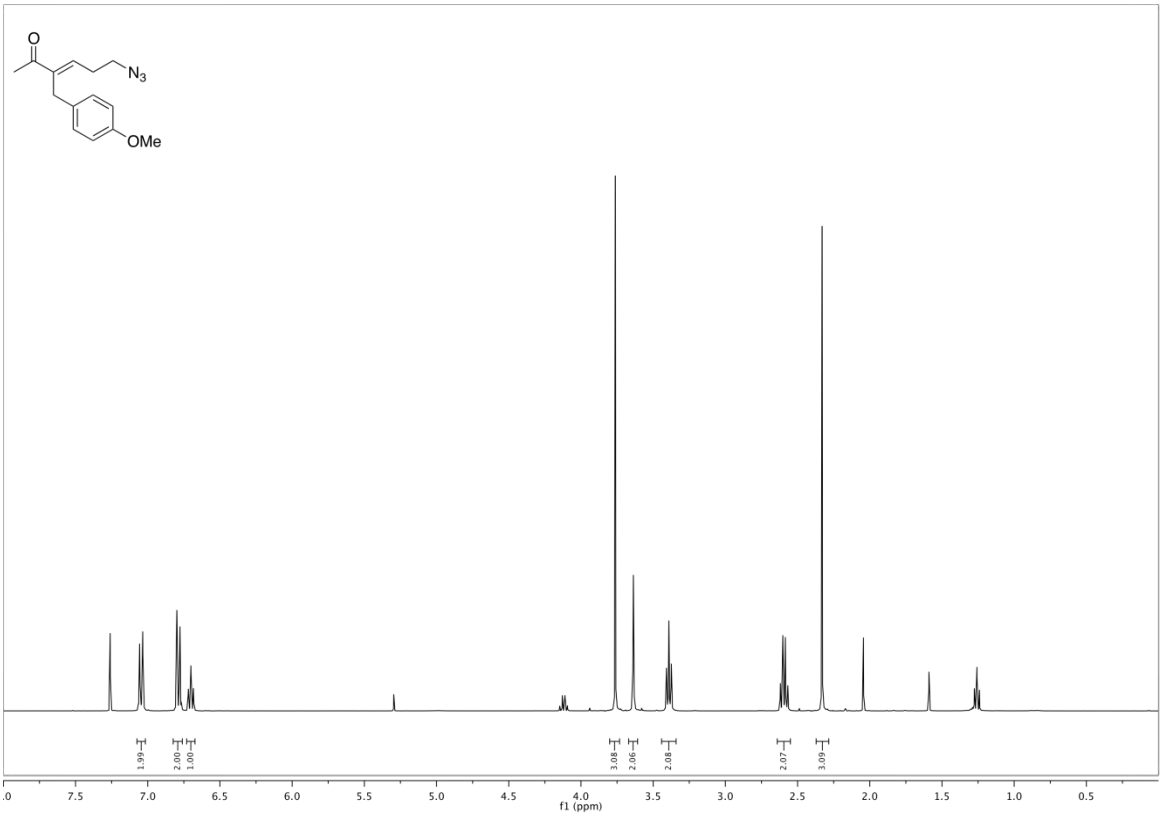


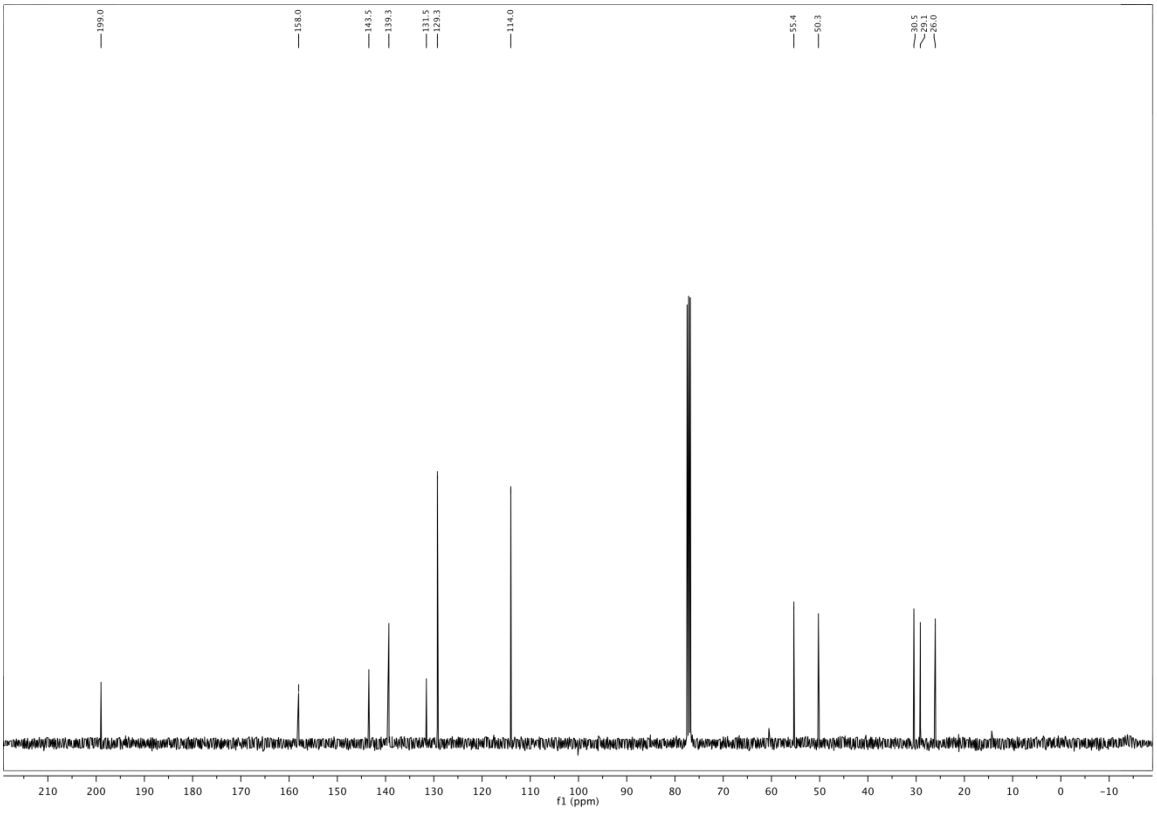
Azidoketone **S18c**



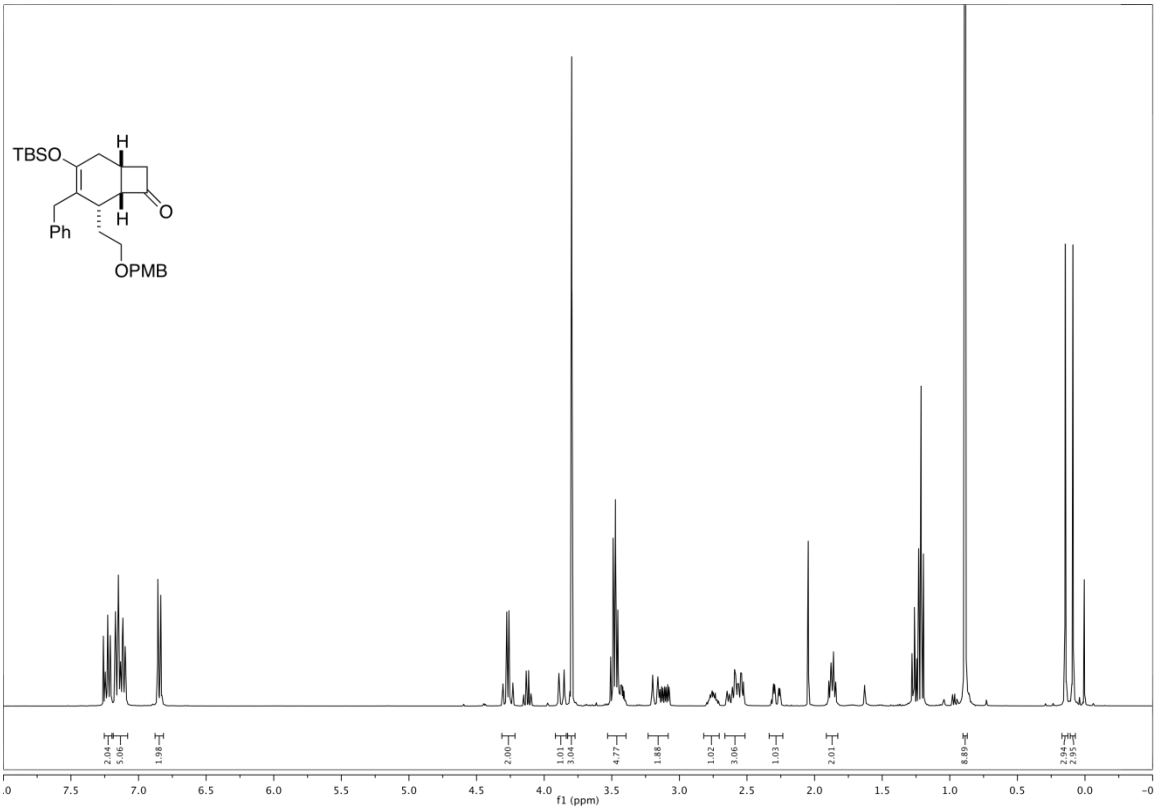


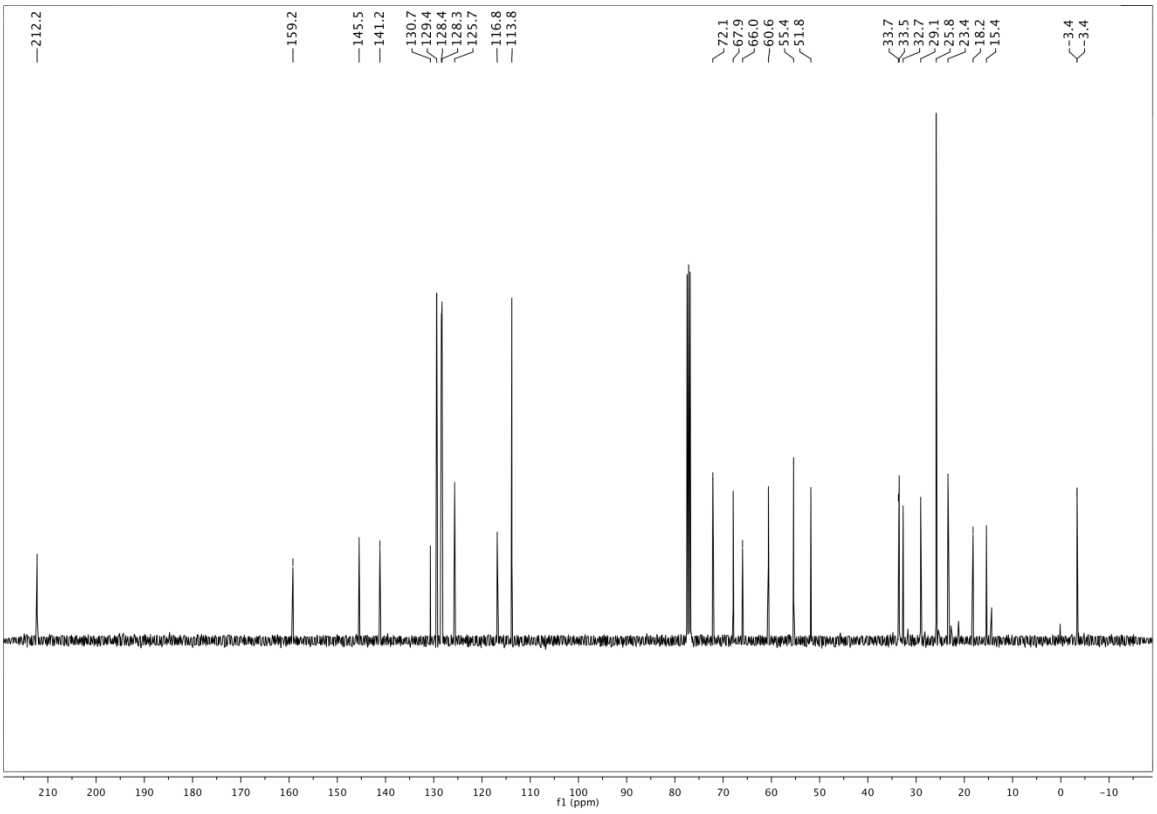
Azidoketone **S18d**



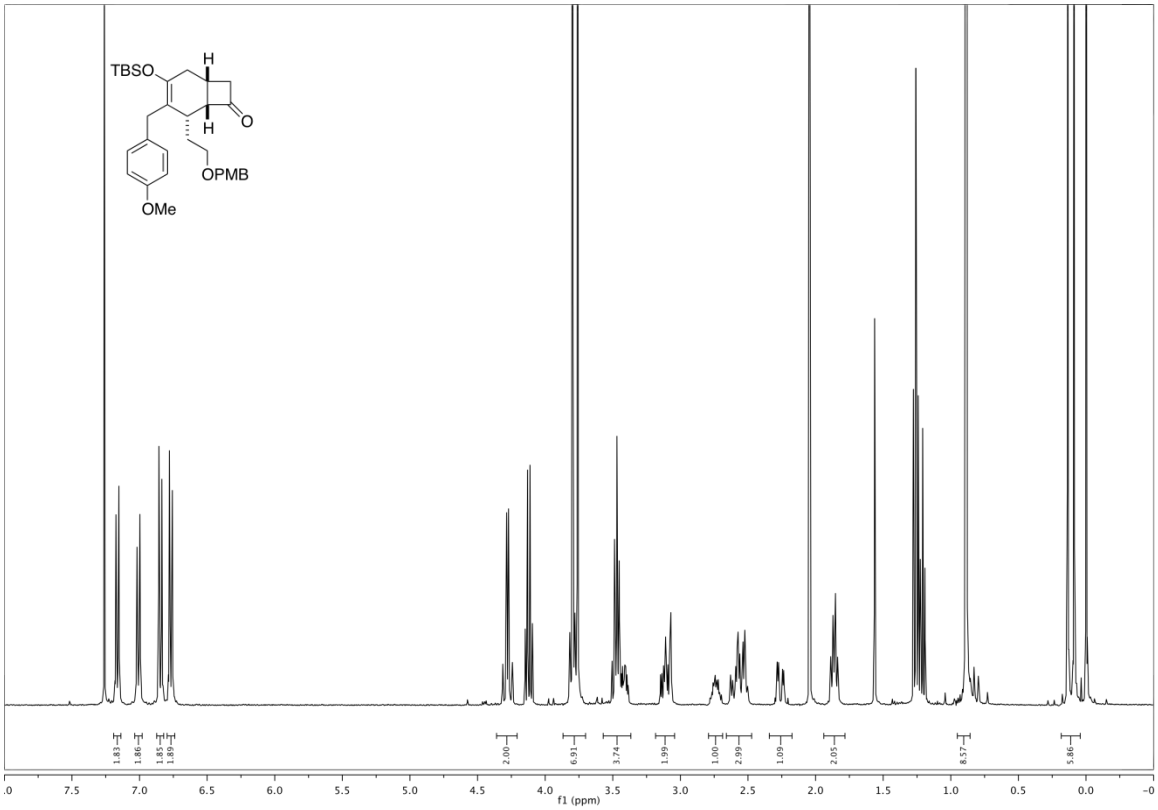


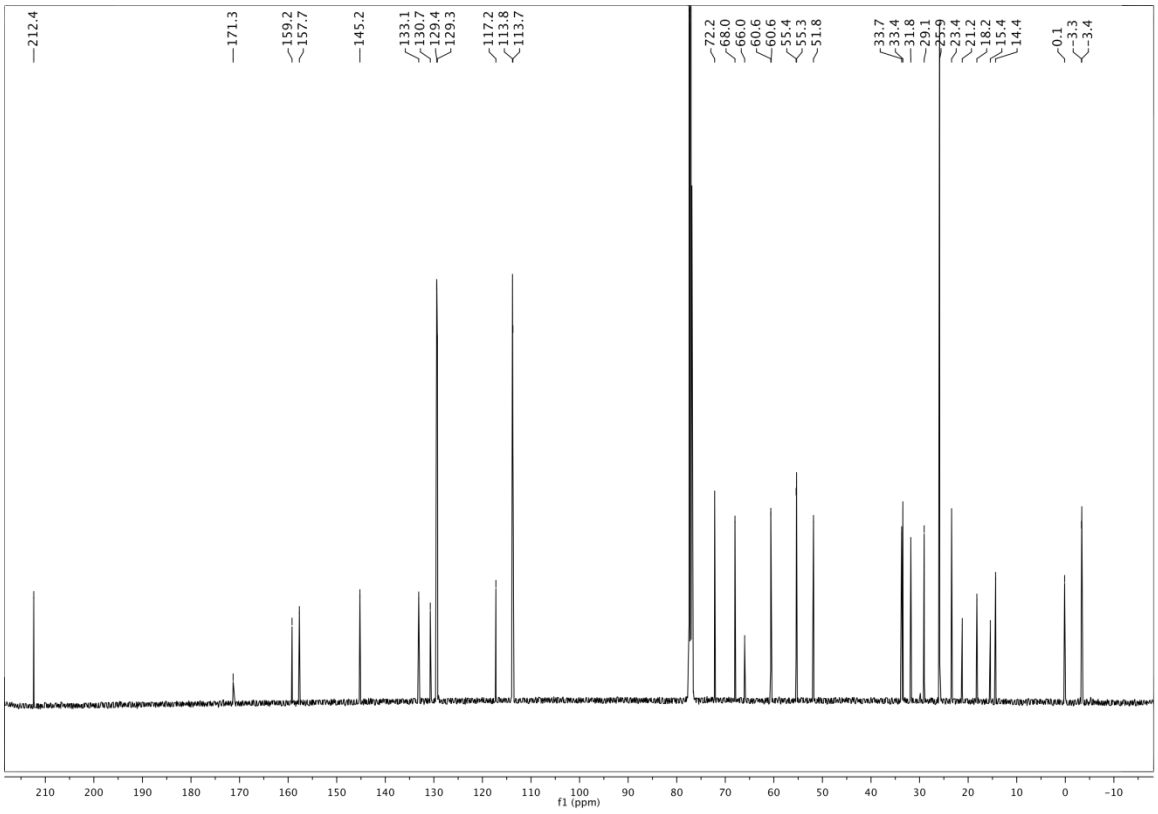
Silyl enol ether **23a**



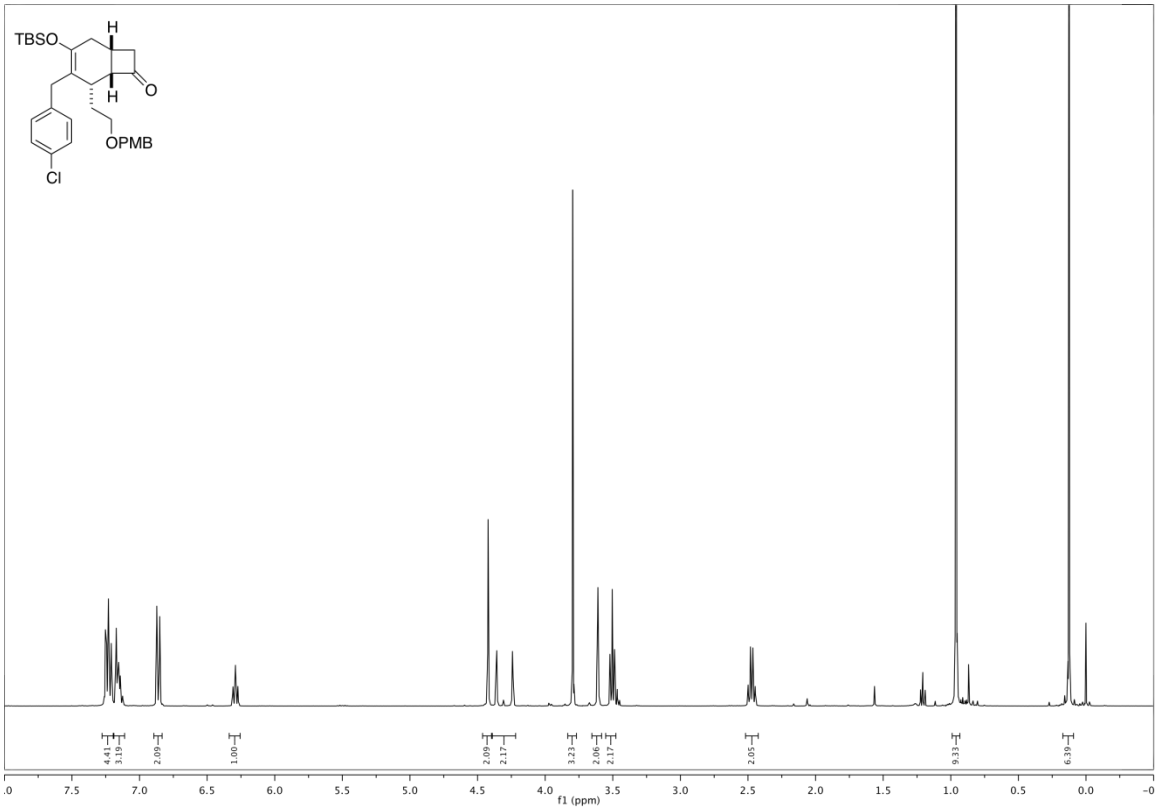


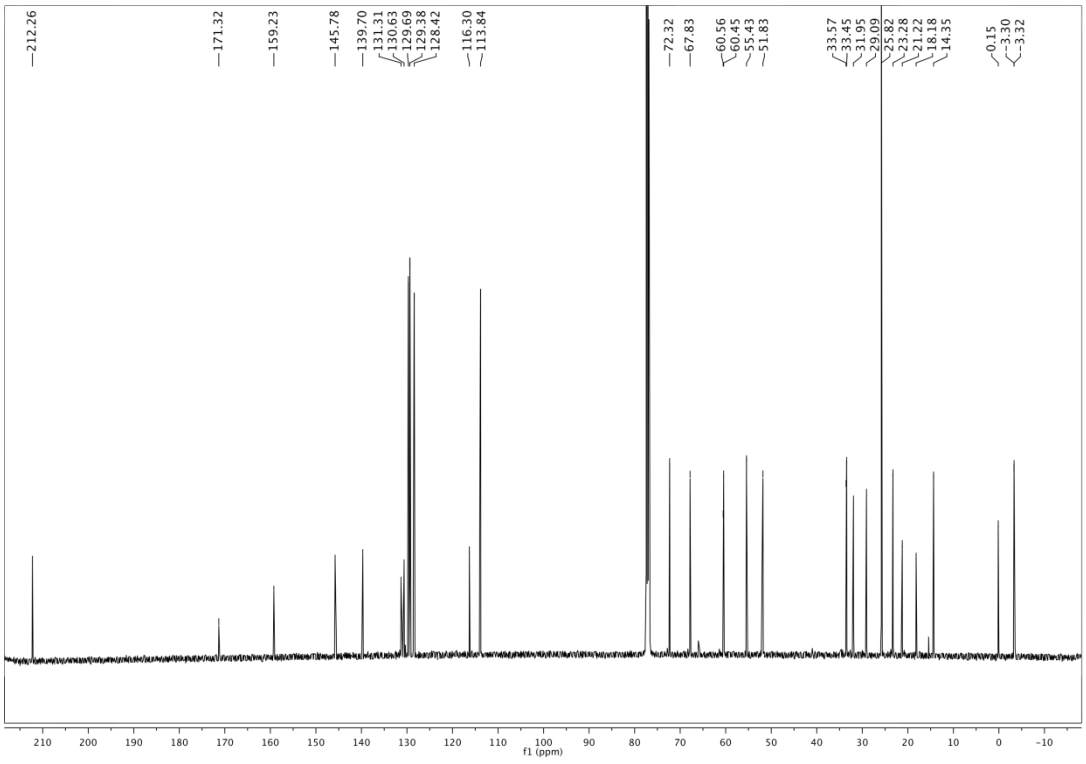
Silyl enol ether **23d**



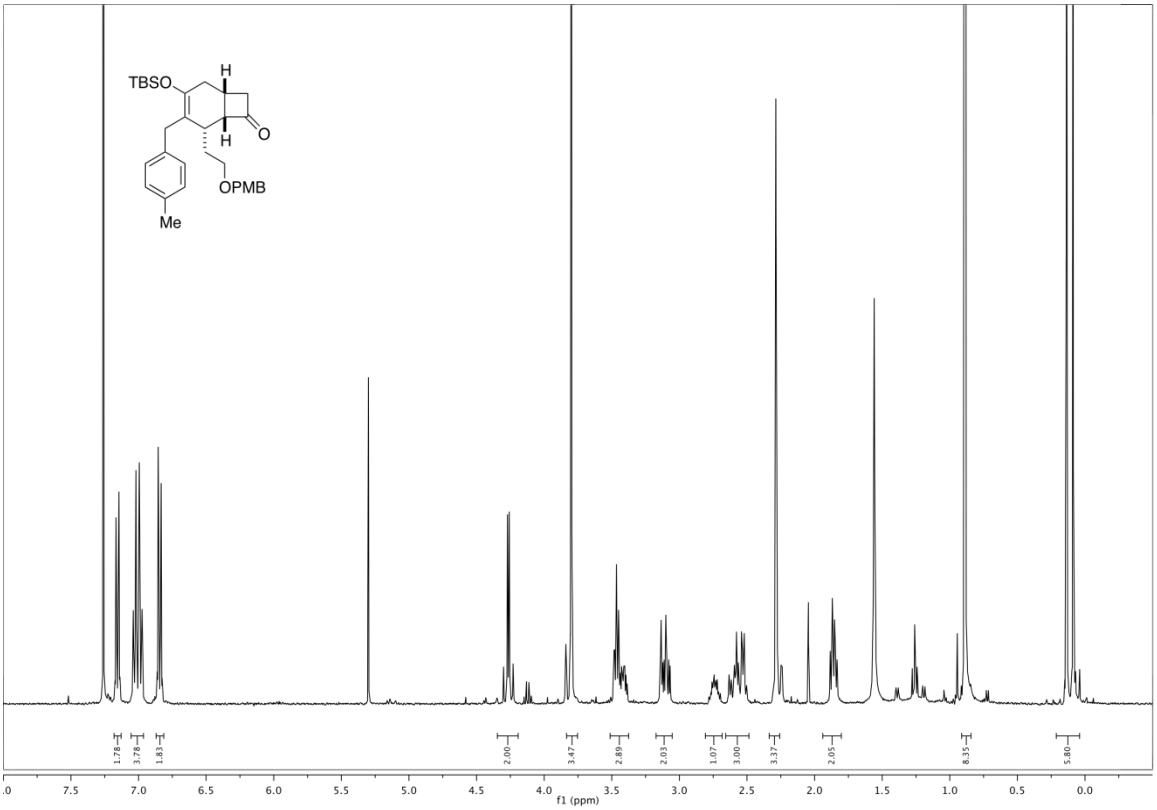


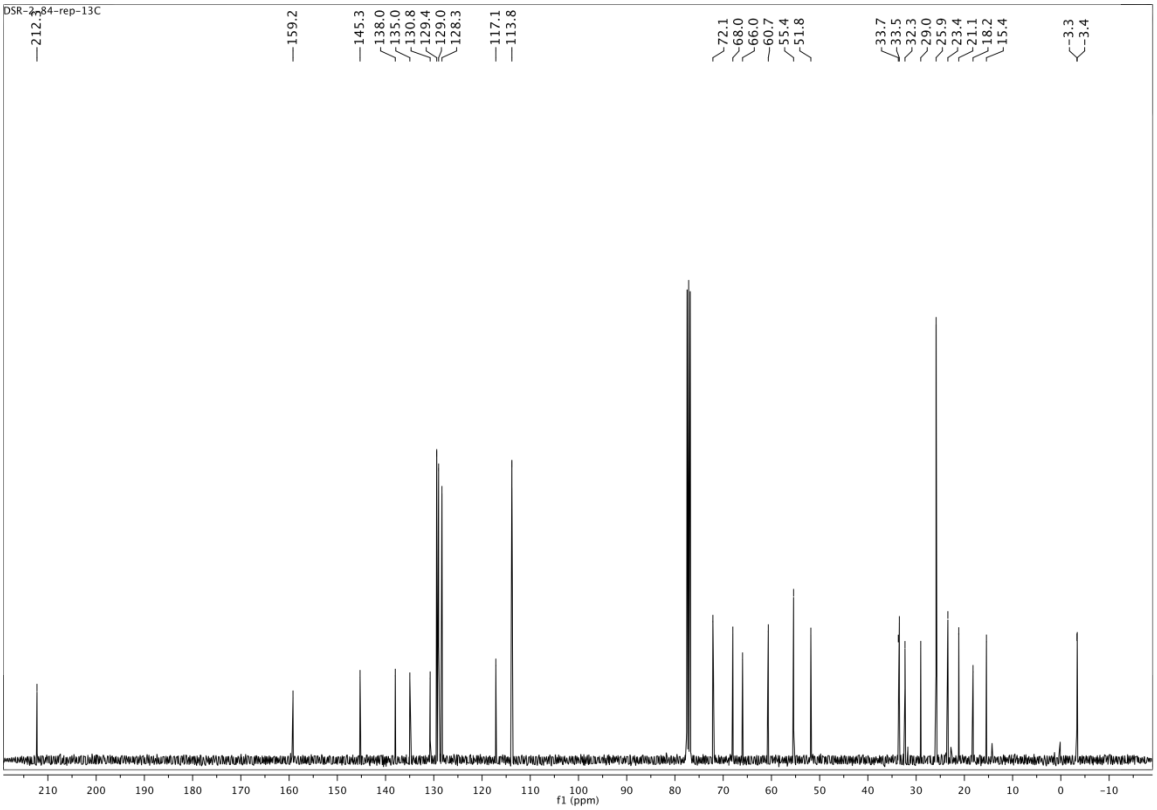
Silyl enol ether **23c**



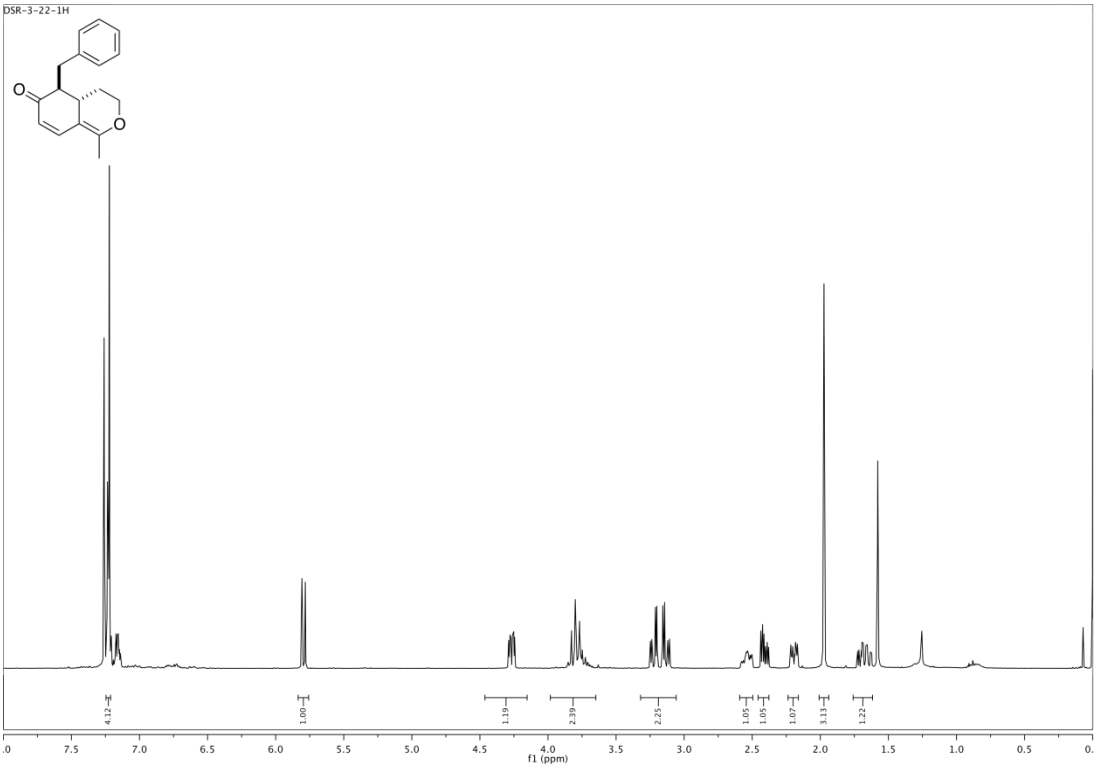


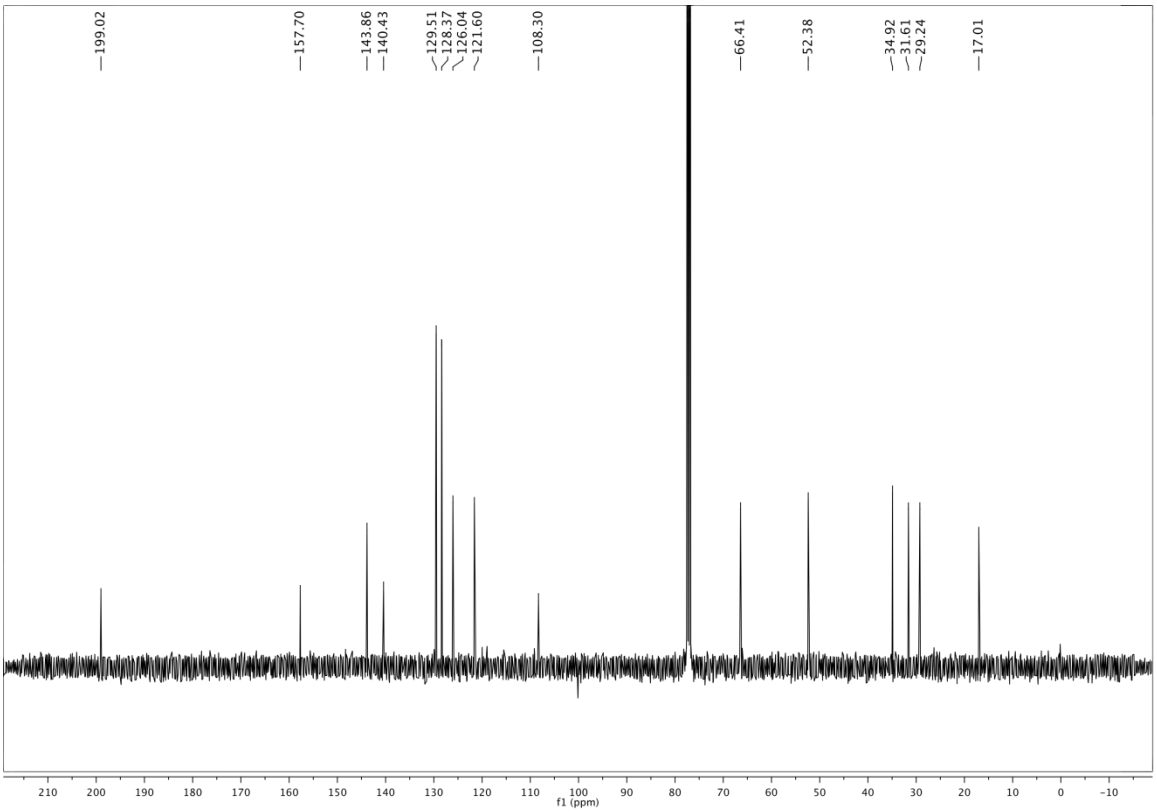
Silyl enol ether **23b**



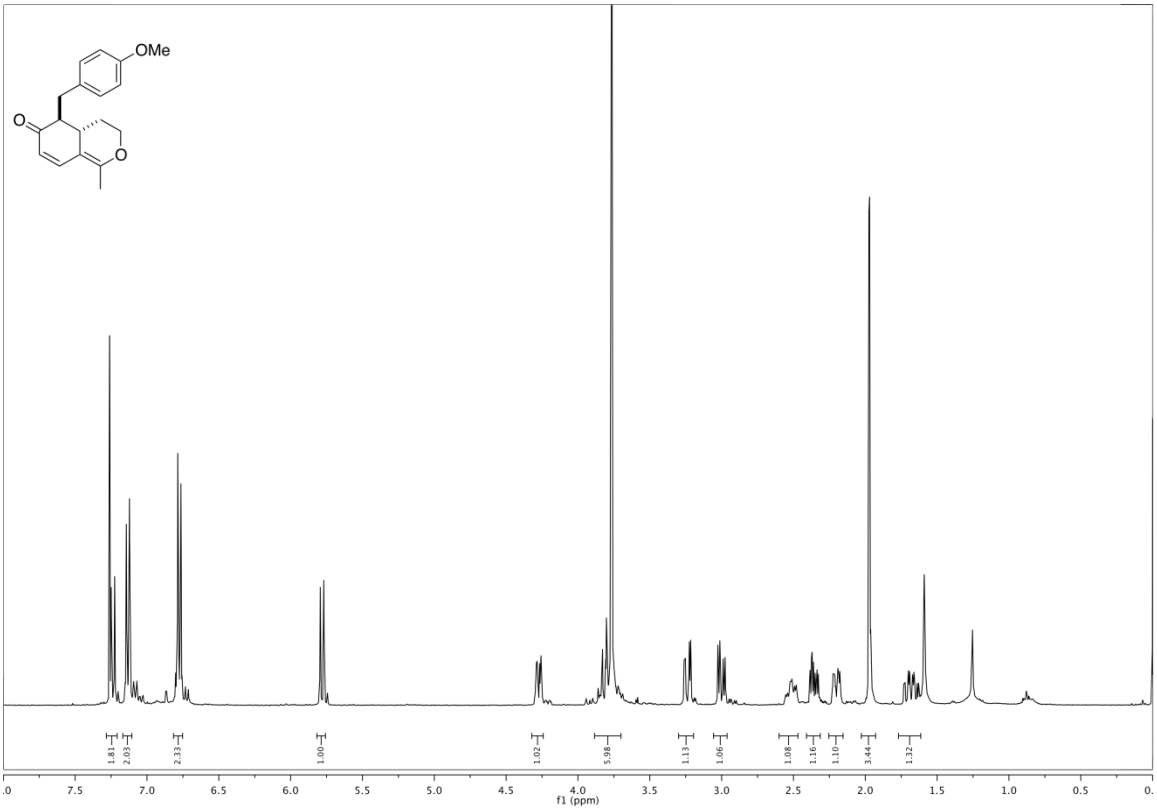


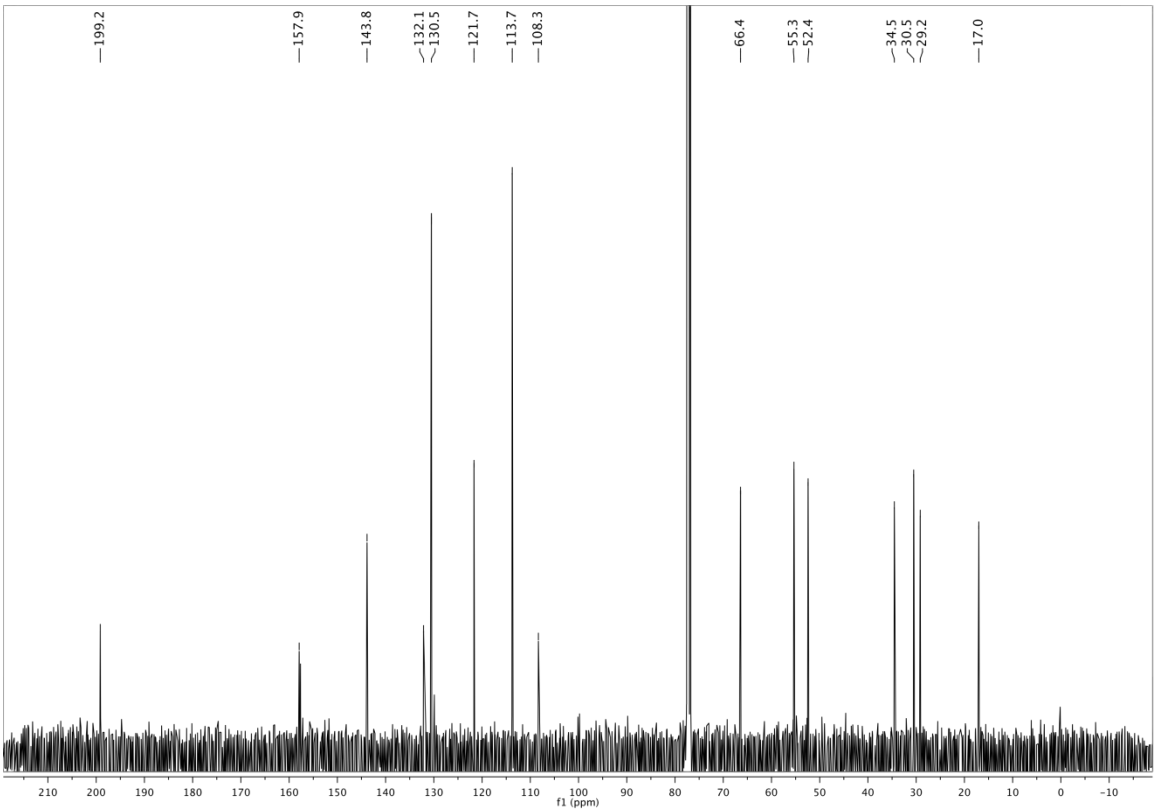
Tetrahydroisochromenone **24a**



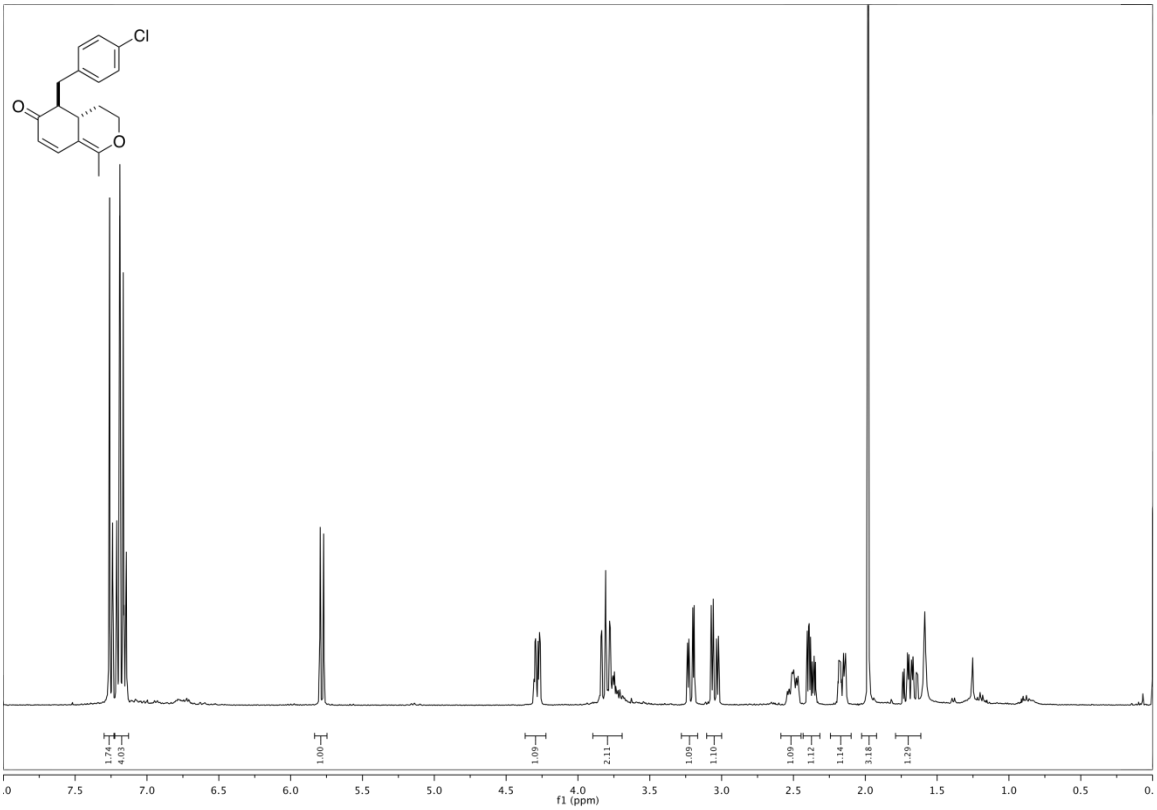


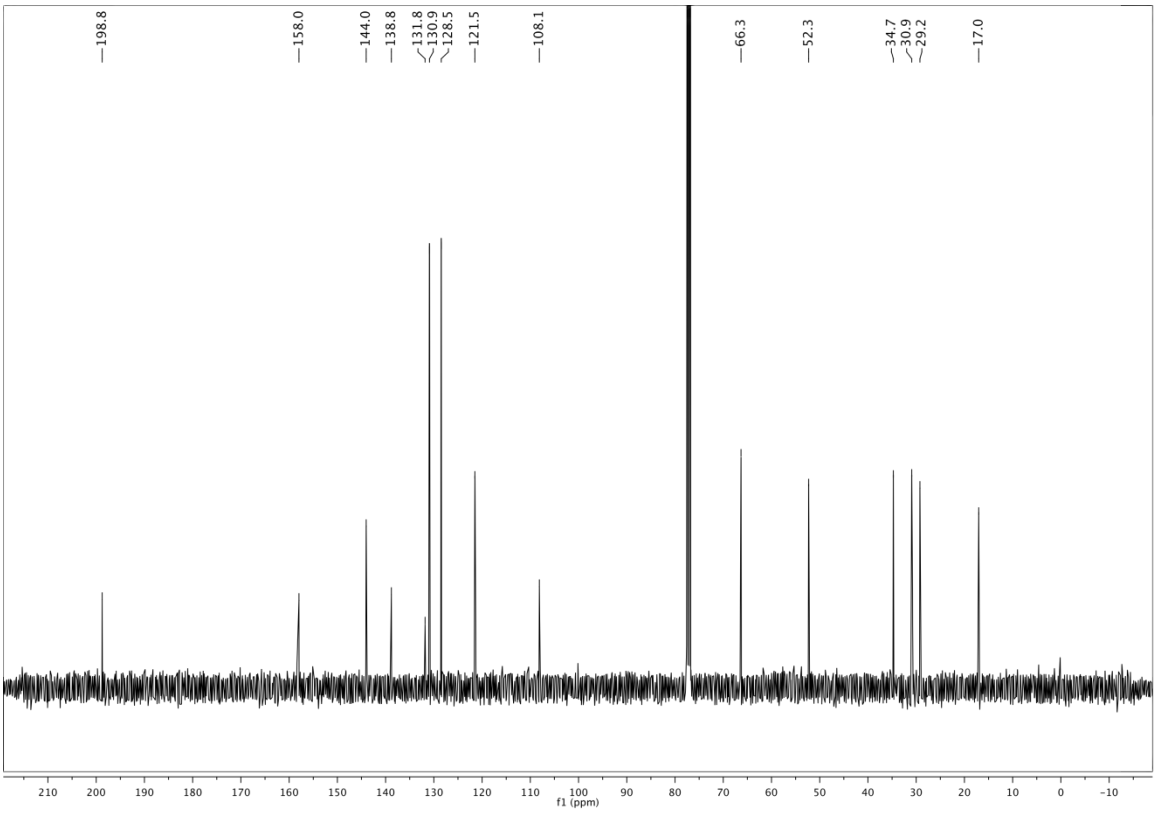
Tetrahydroisochromenone **24d**



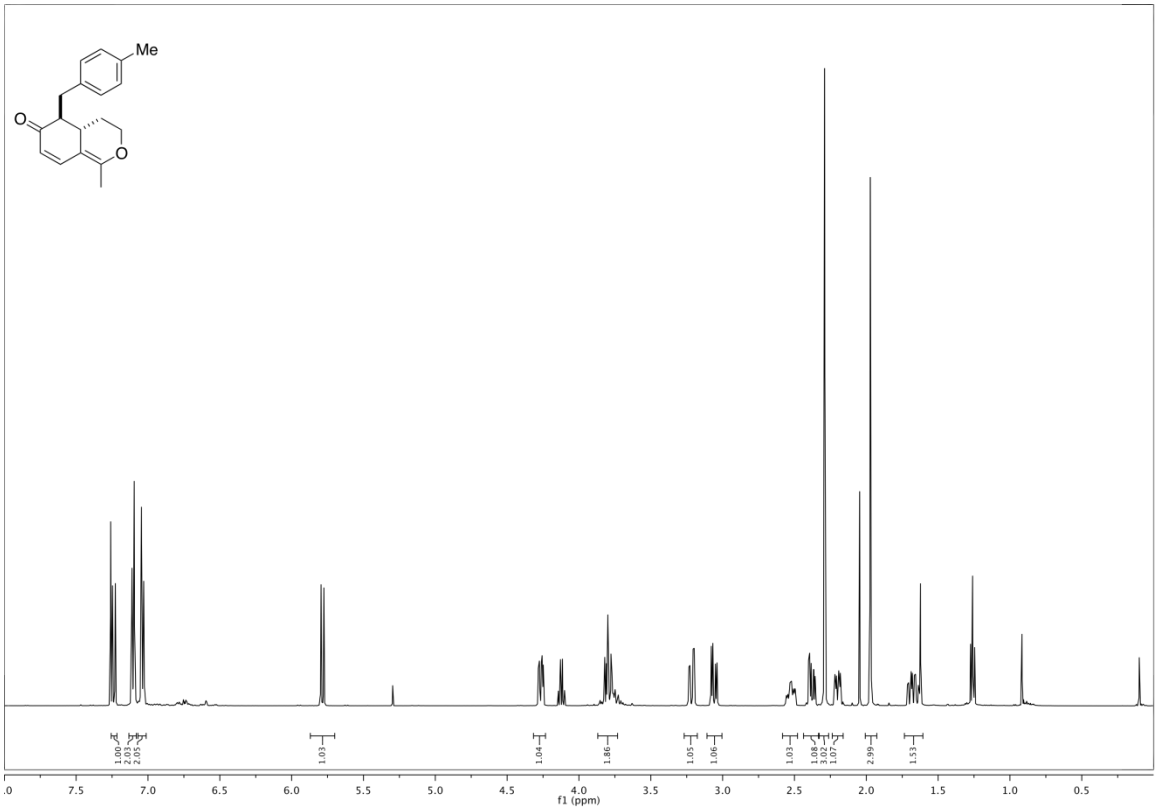


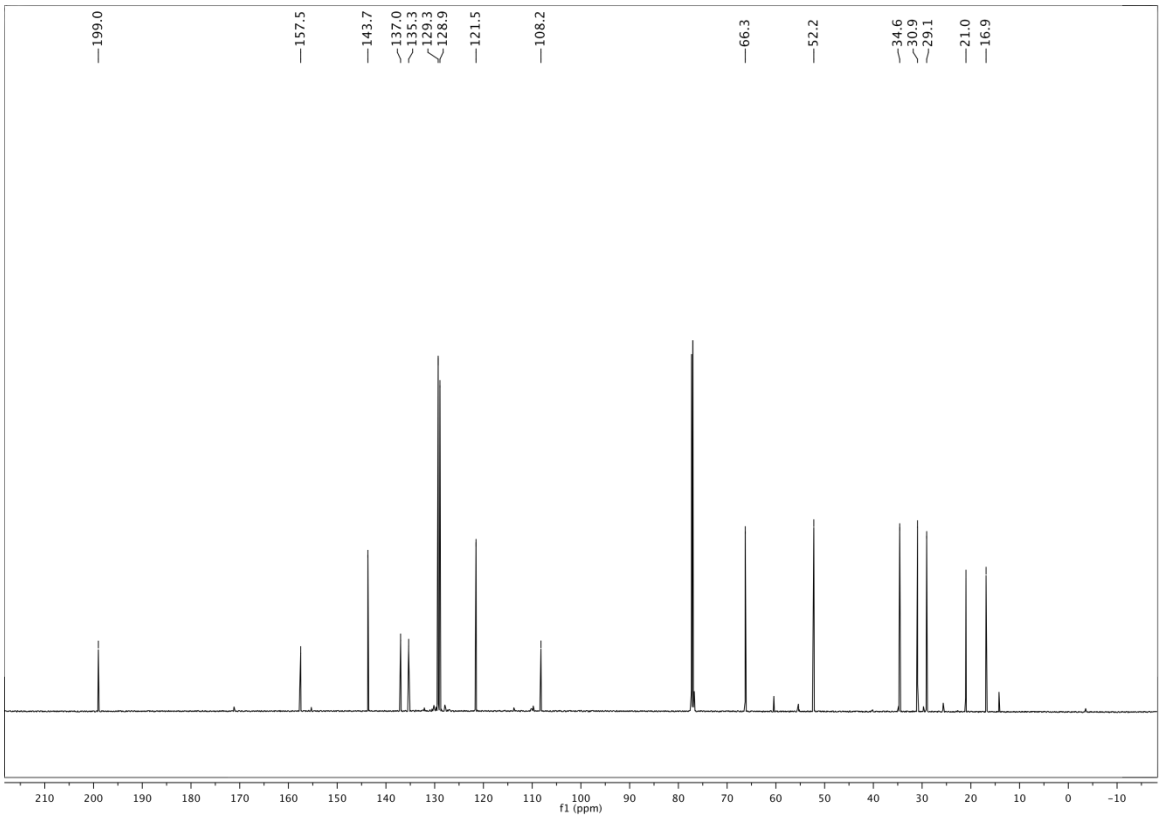
Tetrahydroisochromenone **24c**



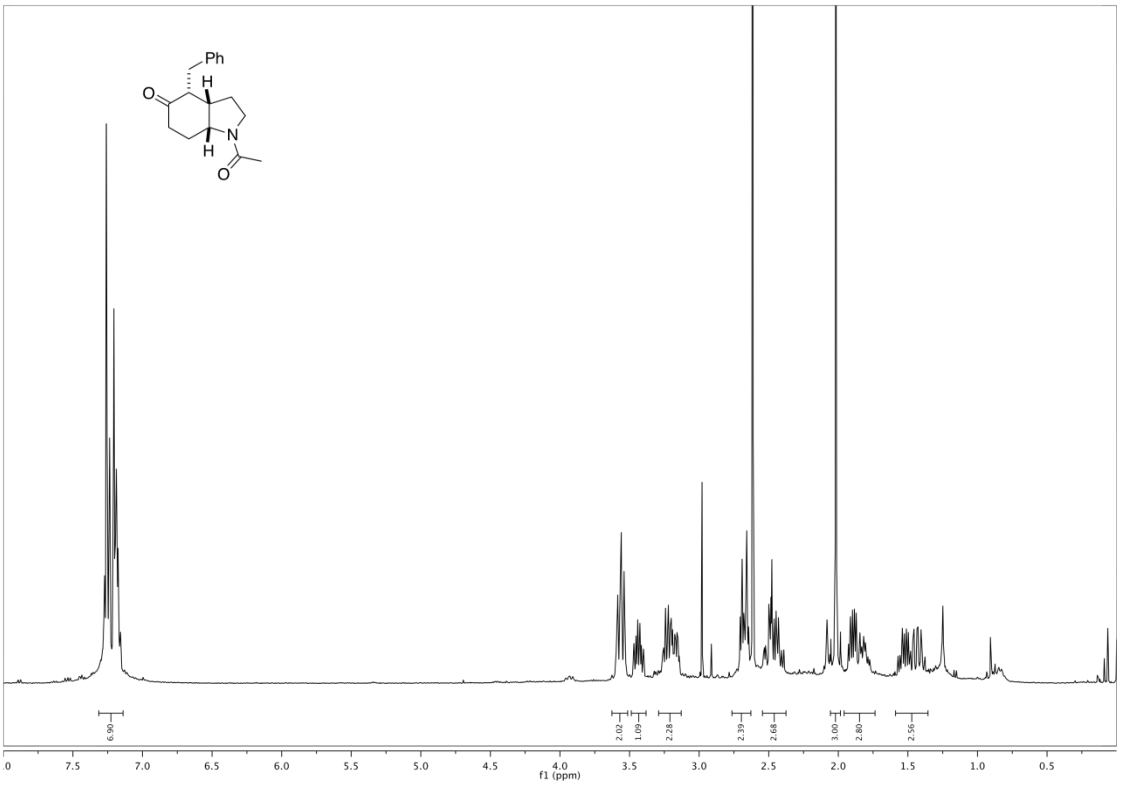


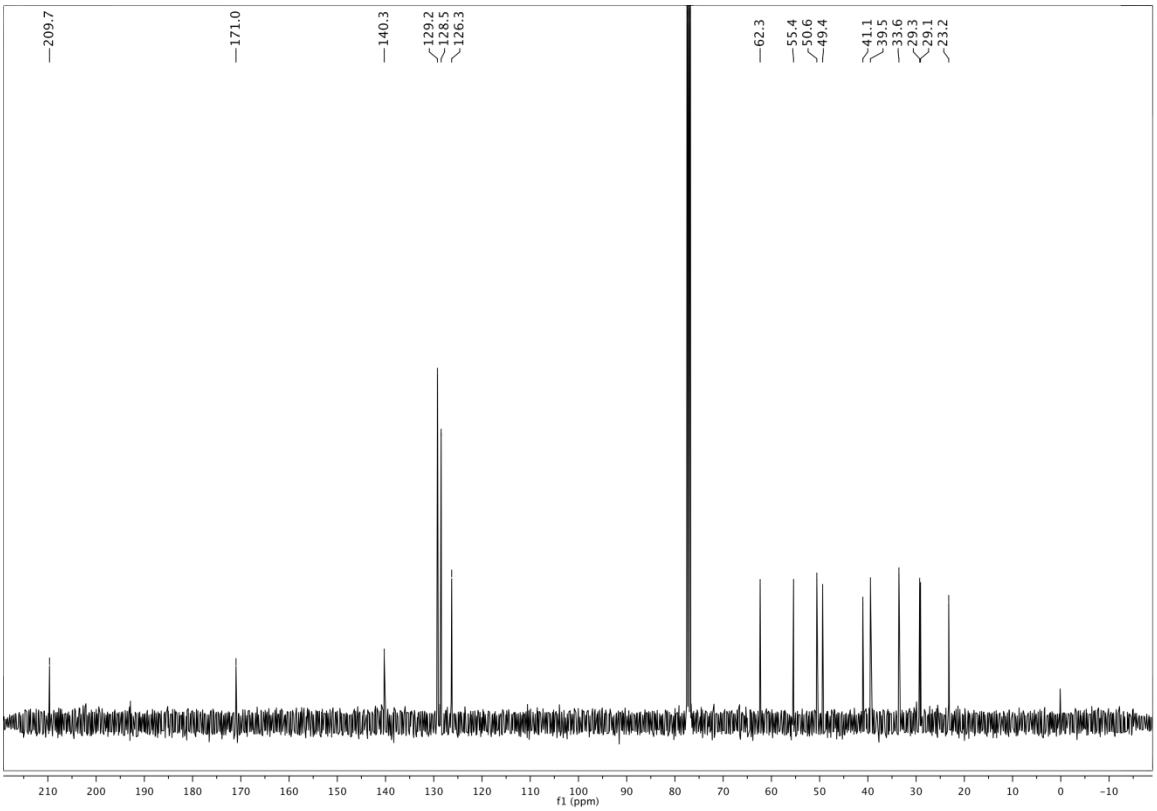
Tetrahydroisochromenone **24b**



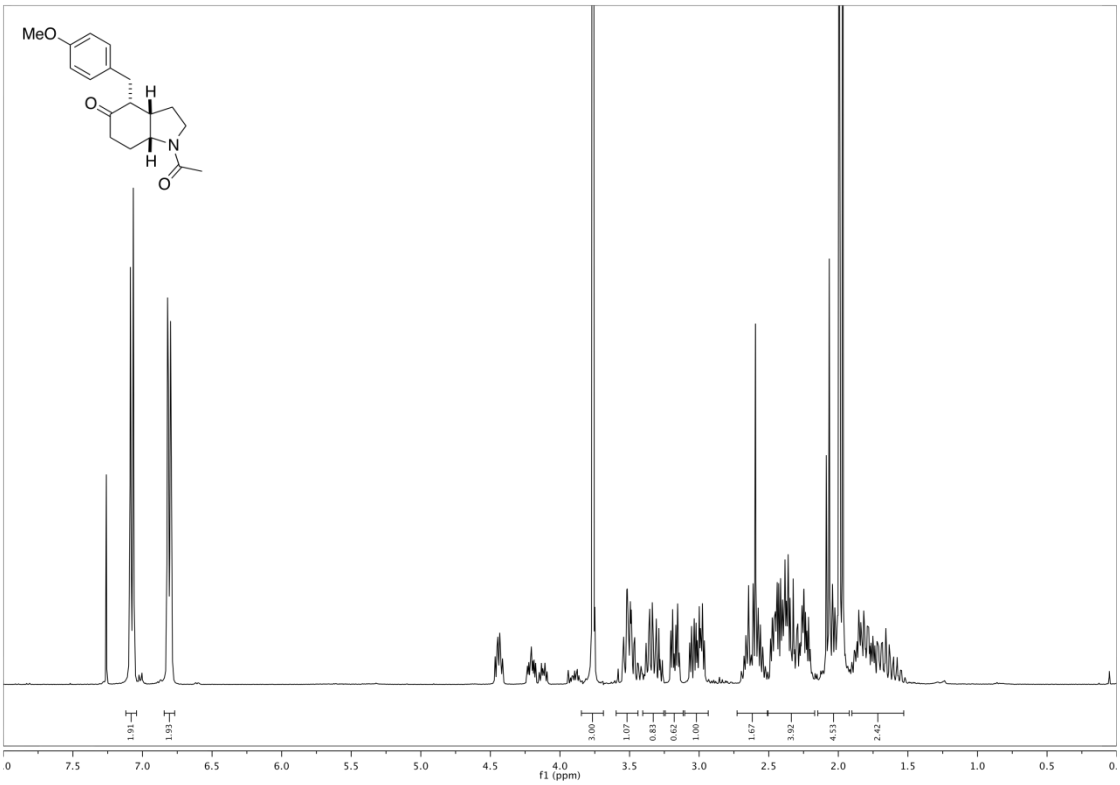


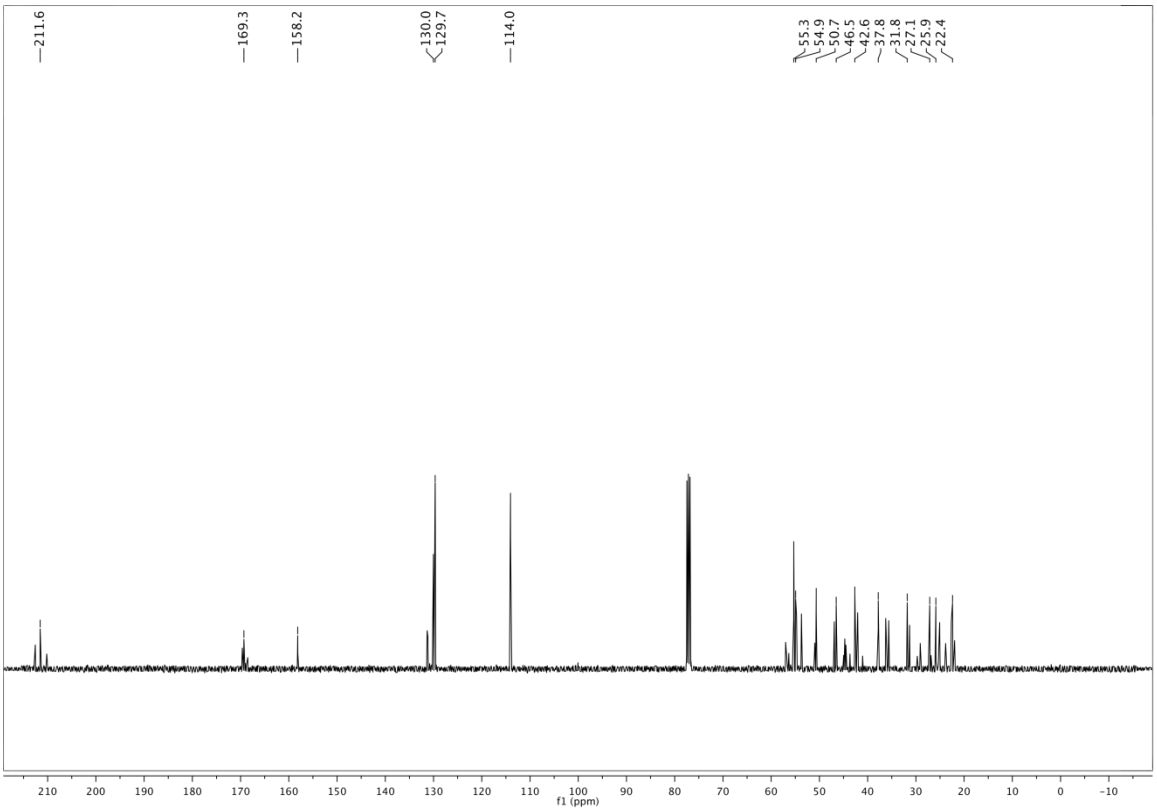
Amide **18a**


Ph
H
O
N
H
O
6.90
2.02
1.09
2.28
2.39
2.68
3.00
2.80
2.56
f1 (ppm)

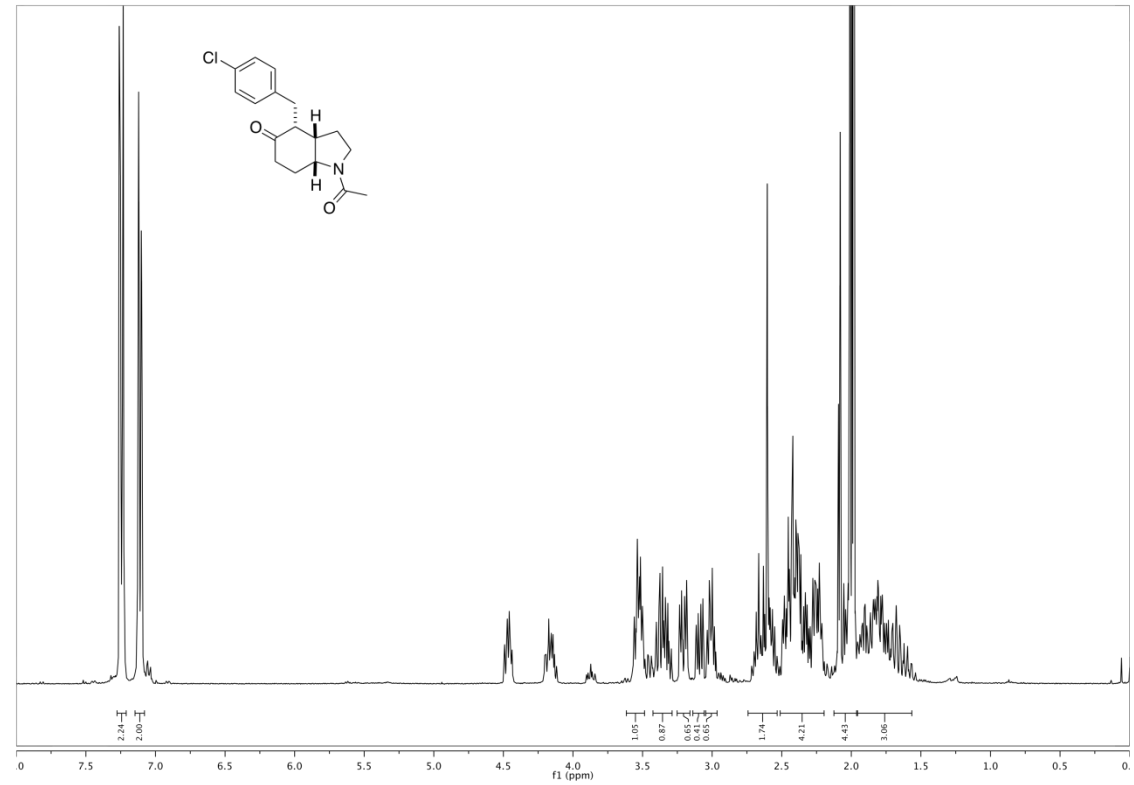

209.7
171.0
140.3
129.2
128.5
126.3
62.3
55.4
50.6
49.4
41.1
39.5
33.6
29.3
29.1
23.2
f1 (ppm)

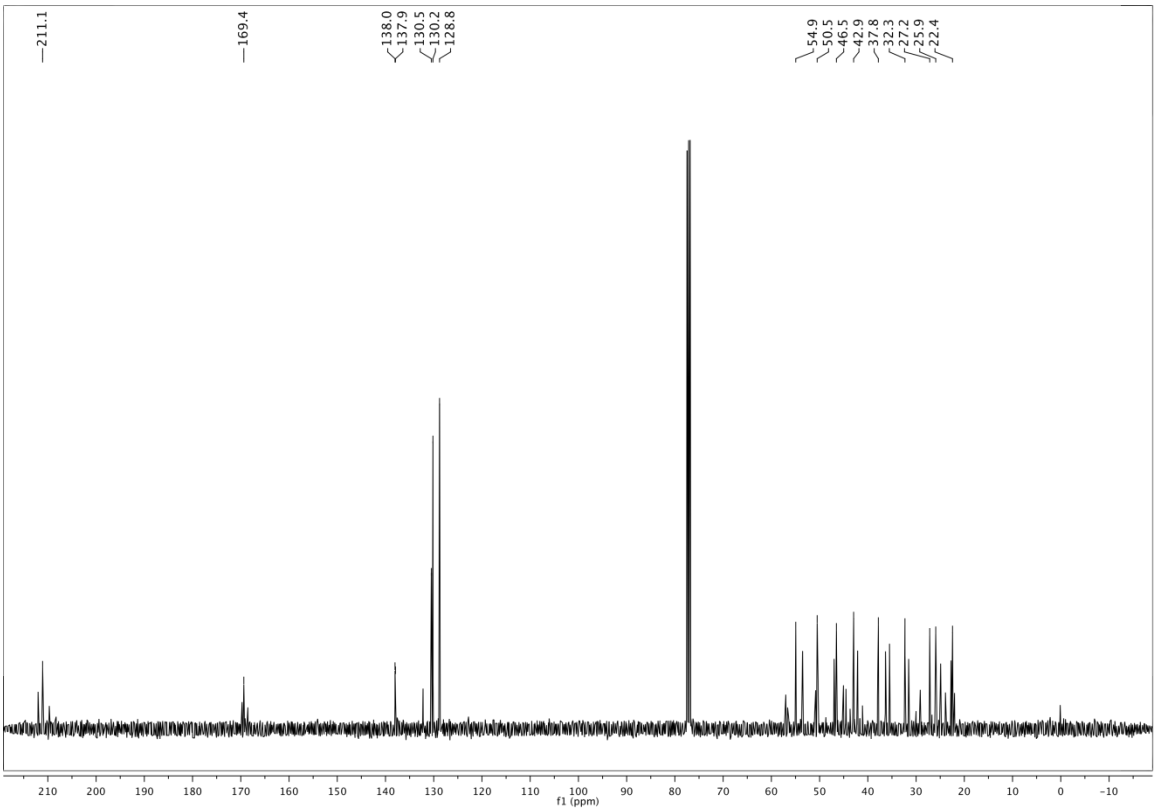
Amide **18d**


MeO
O
H
N
H
O
1.91
1.93
3.00
1.07
0.83
0.62
1.00
1.67
3.92
4.53
2.42
f1 (ppm)

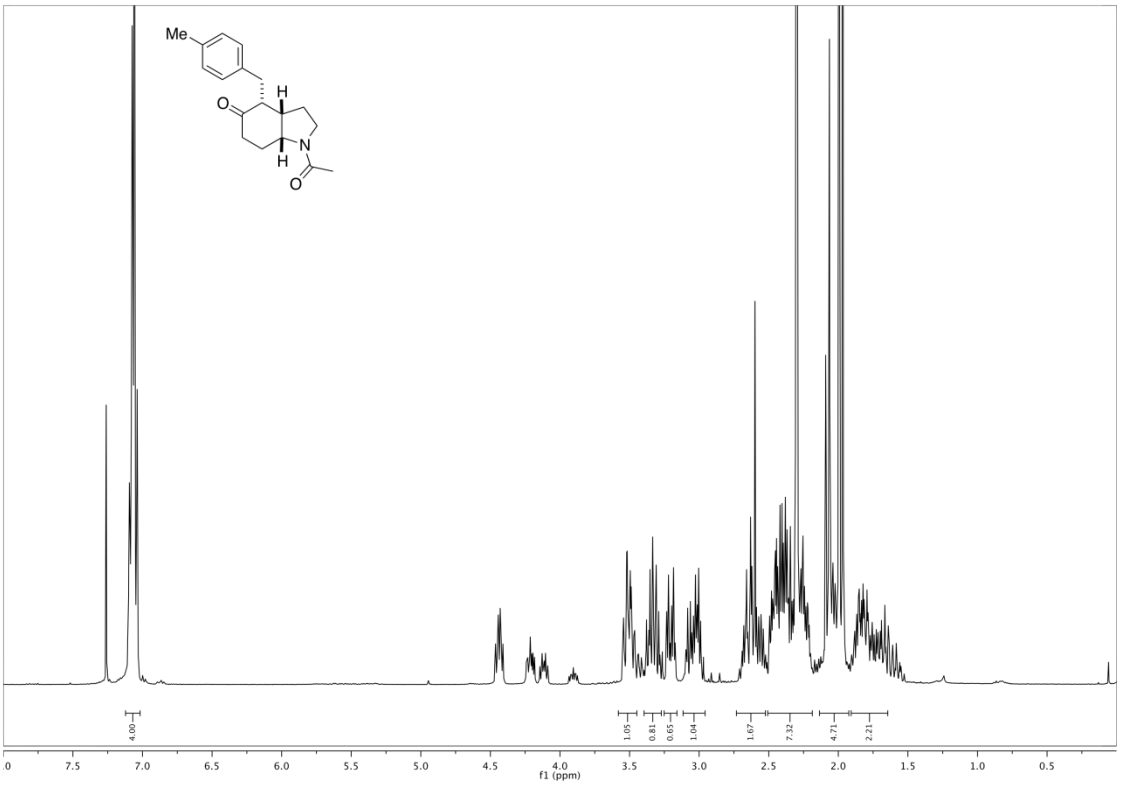

211.6
169.3
158.2
130.0
129.7
114.0
55.3
54.9
50.7
46.5
42.6
37.8
31.8
27.1
25.9
22.4
f1 (ppm)

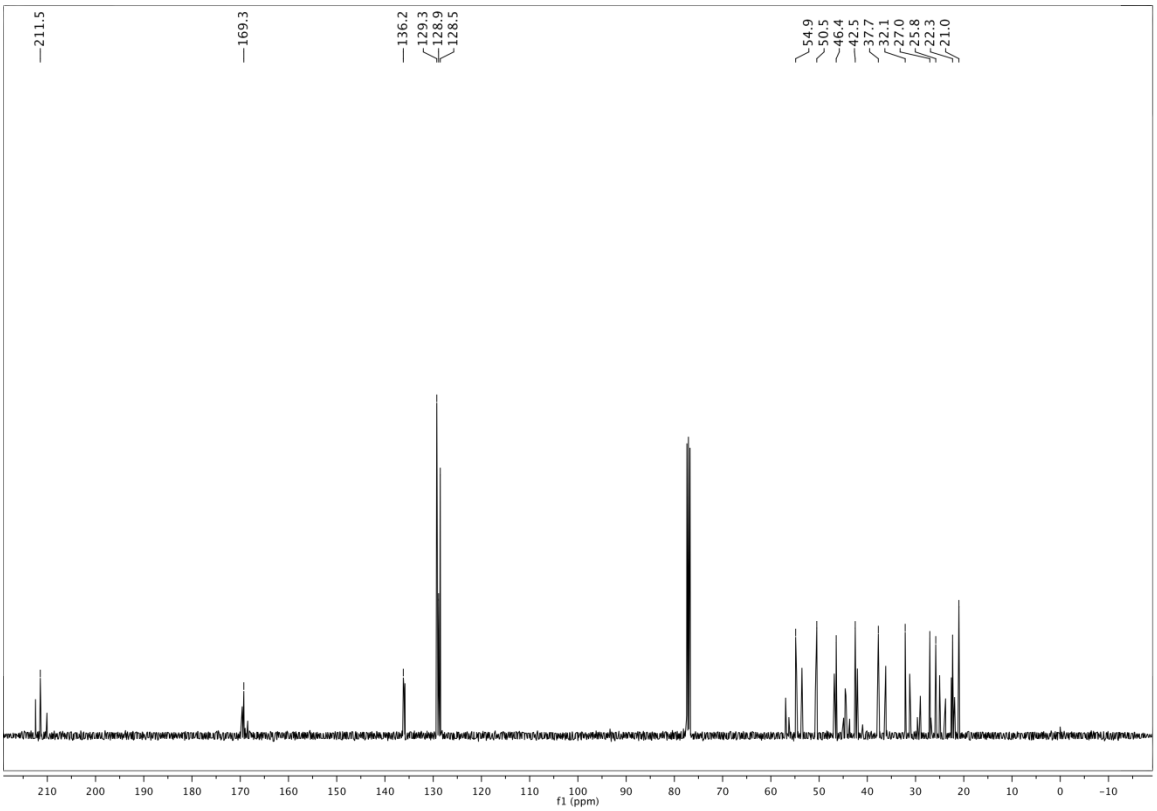
Amide **18c**


Cl
O
H
N
H
O
2.24
2.00
1.05
0.87
0.65
0.41
0.65
1.74
4.21
4.43
3.06
f1 (ppm)

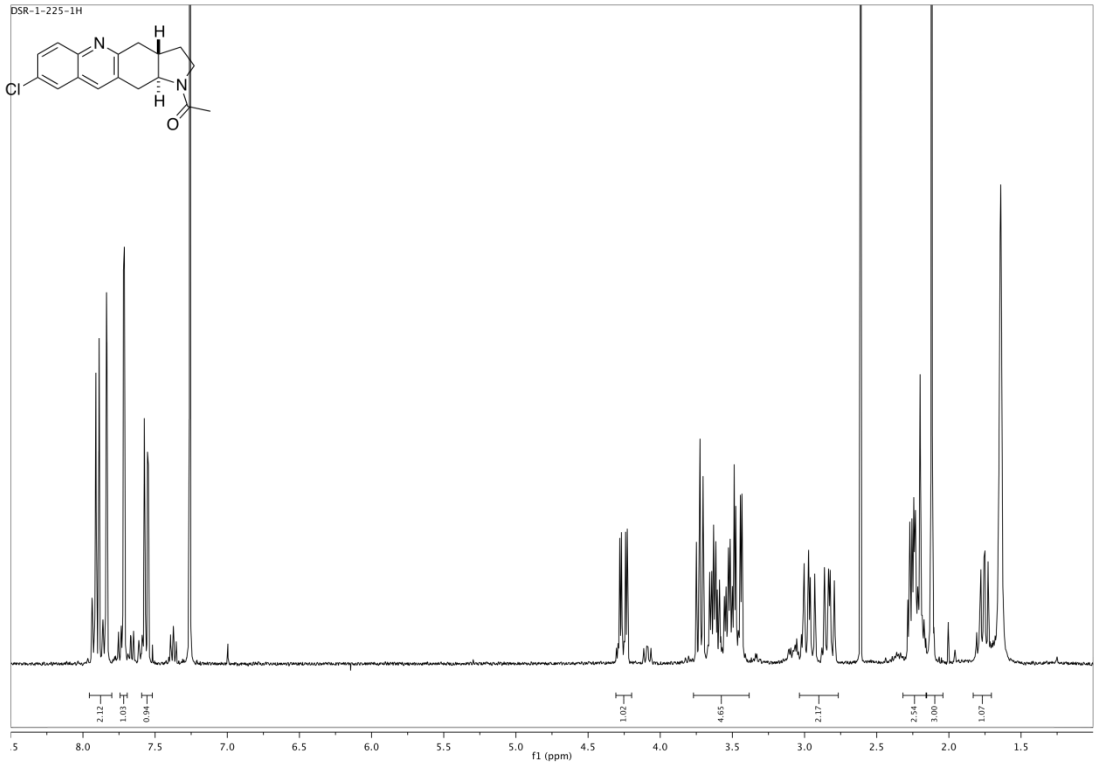

211.1
169.4
138.0
137.9
130.5
130.2
128.8
54.9
50.5
46.5
42.9
37.8
32.3
27.2
25.9
22.4
f1 (ppm)

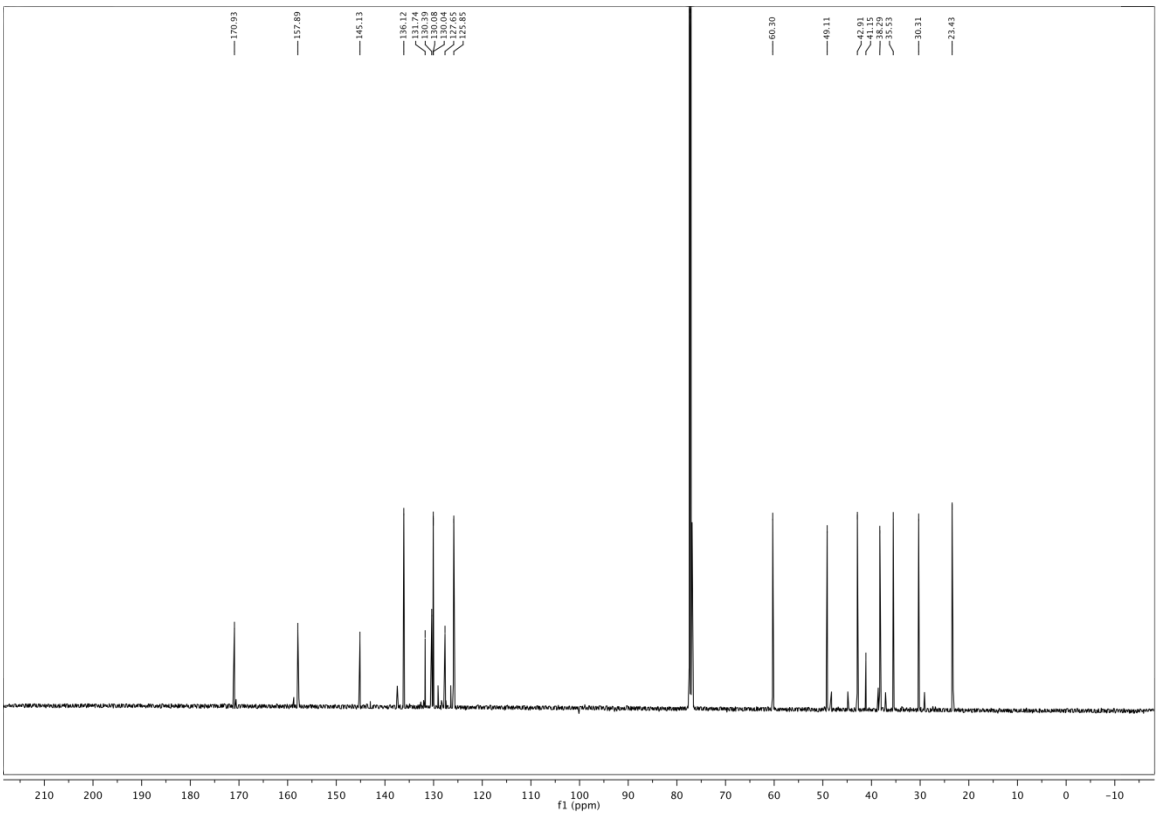
Amide **18b**


Me
H
O
N
H
O
4.00
1.05
0.81
0.65
1.04
1.67
7.32
4.71
2.21
f1 (ppm)

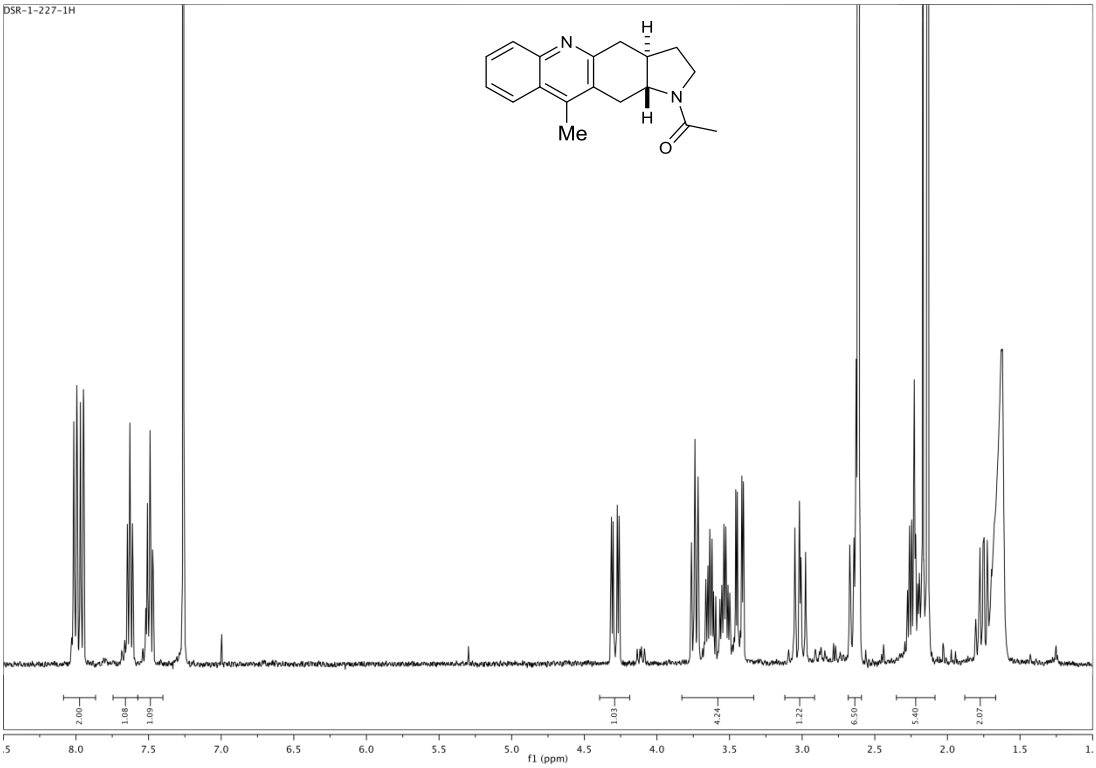

211.5
169.3
136.2
129.3
128.9
128.5
54.9
50.5
46.4
42.5
37.7
32.1
27.0
25.8
22.3
21.0
f1 (ppm)

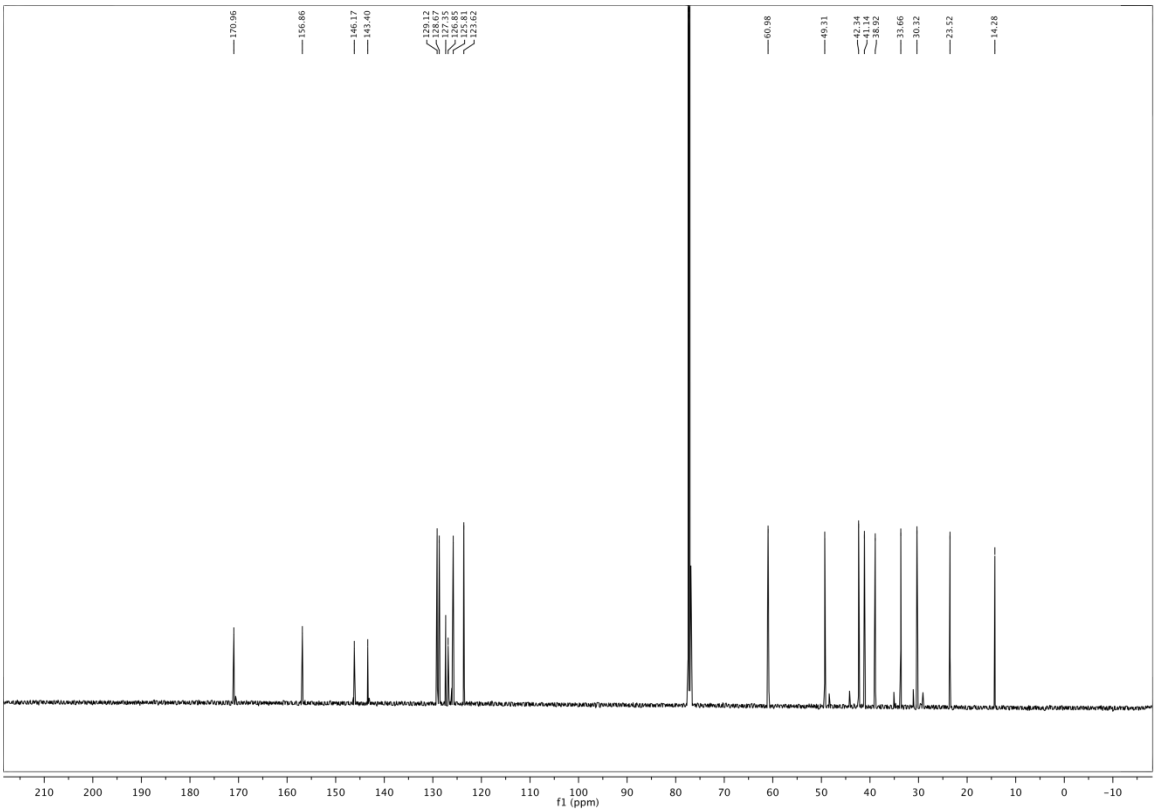
Quinoline **45**{*2*}



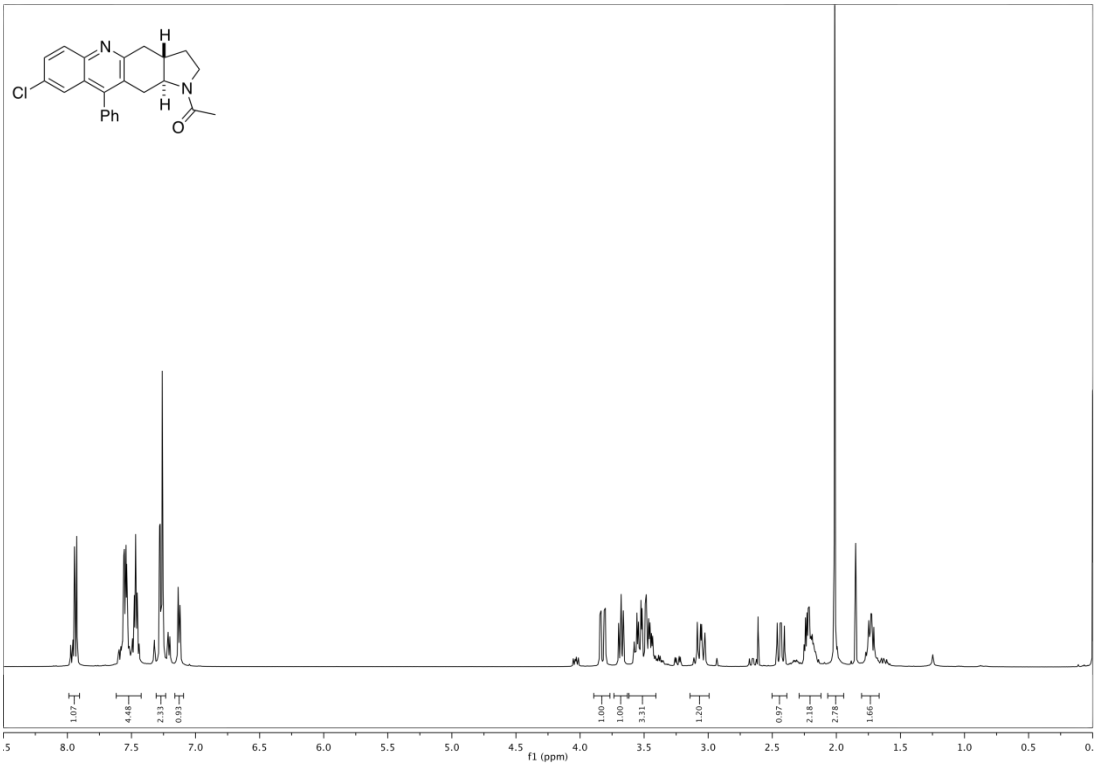


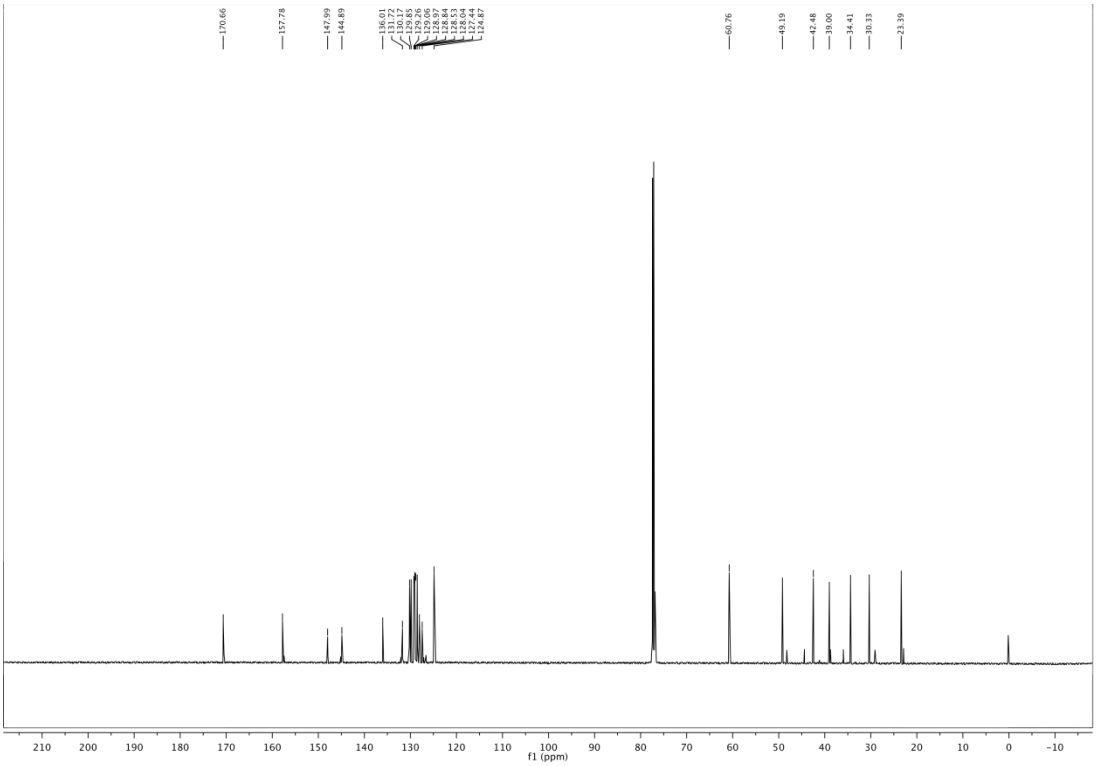
Quinoline **45**{*8*}



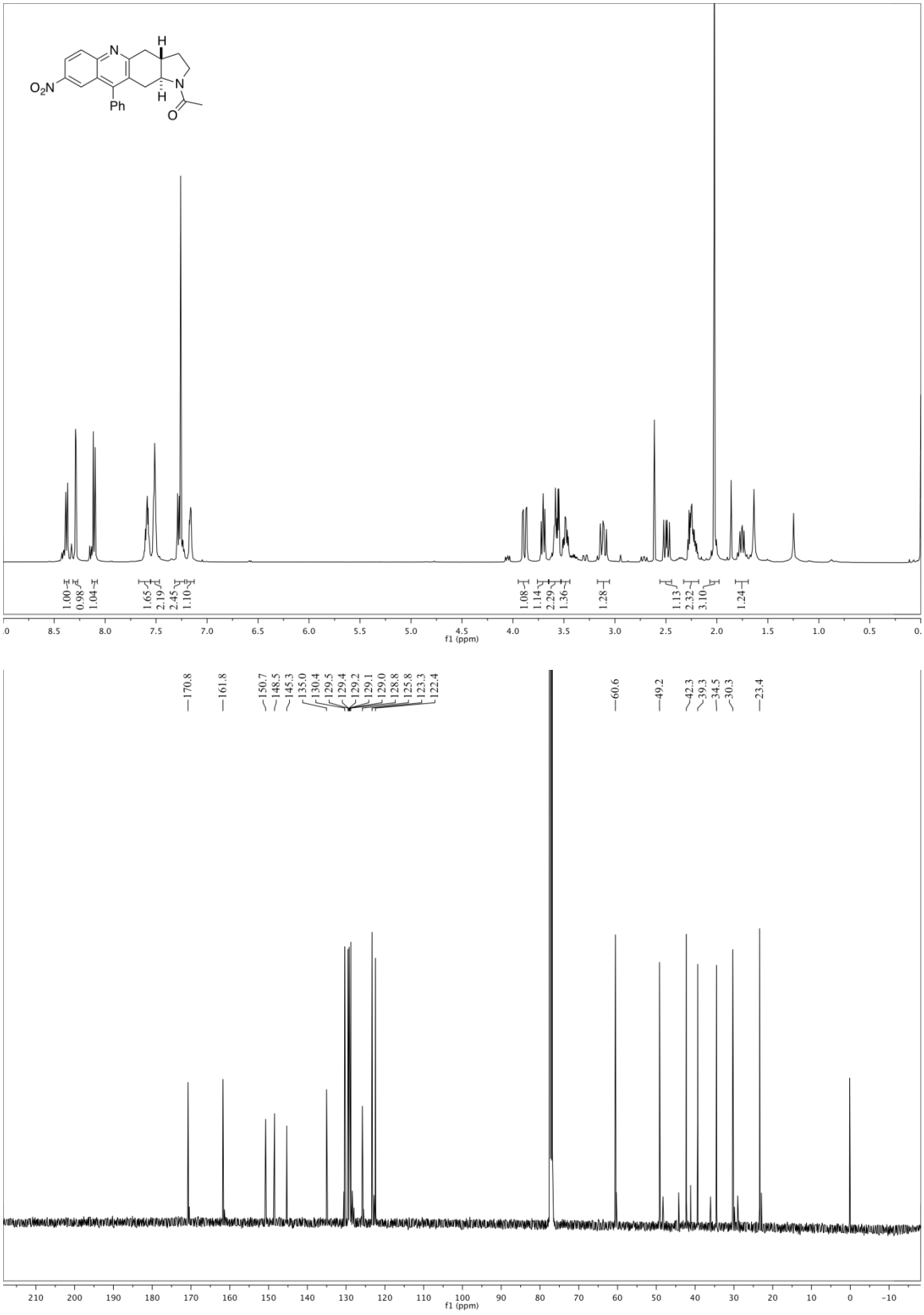


Quinoline **45**{*11*}

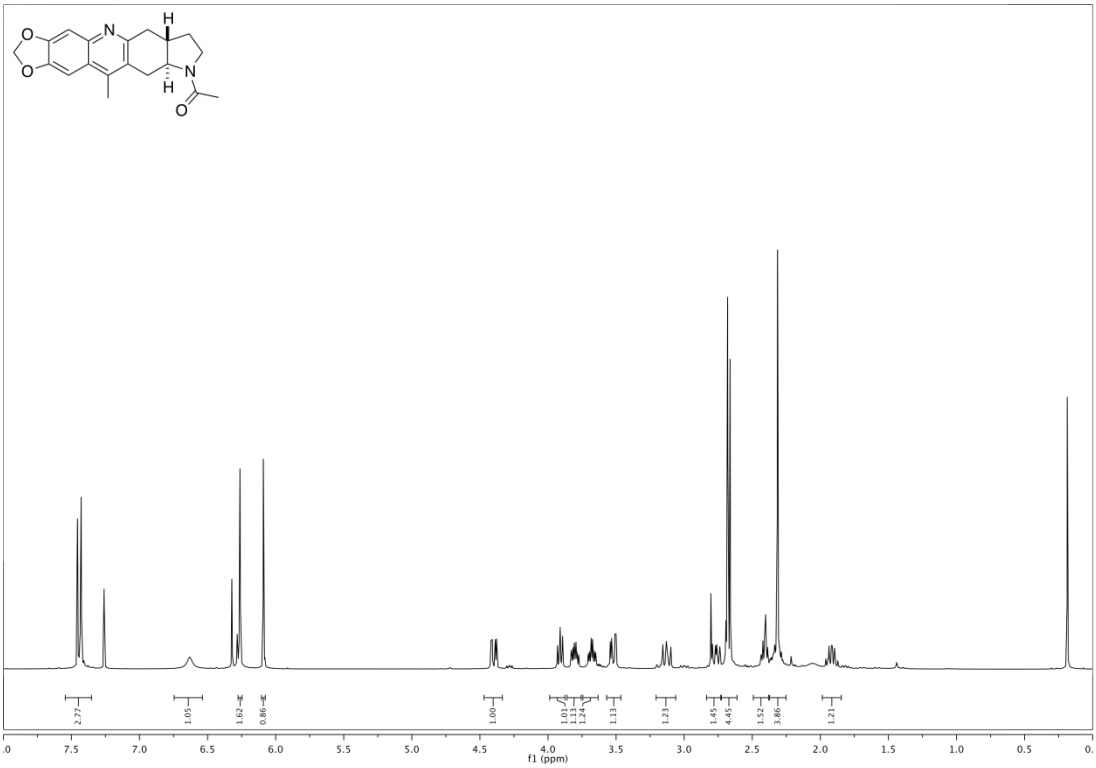


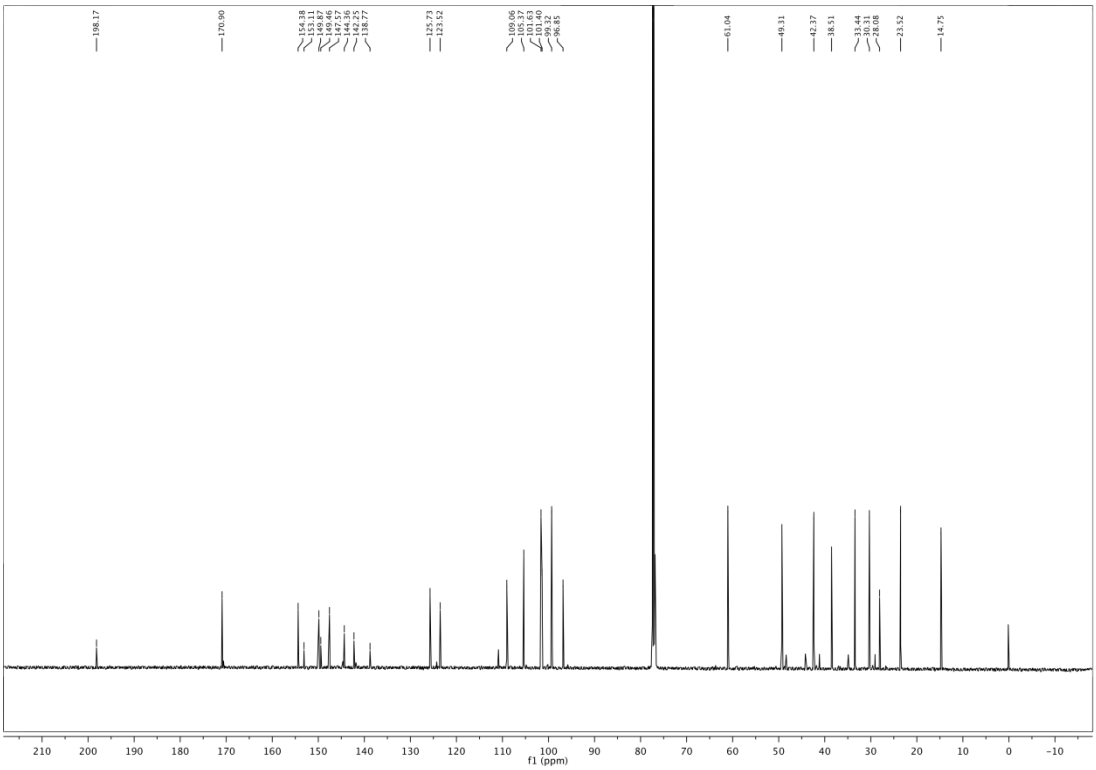


Quinoline **45**{*12*}

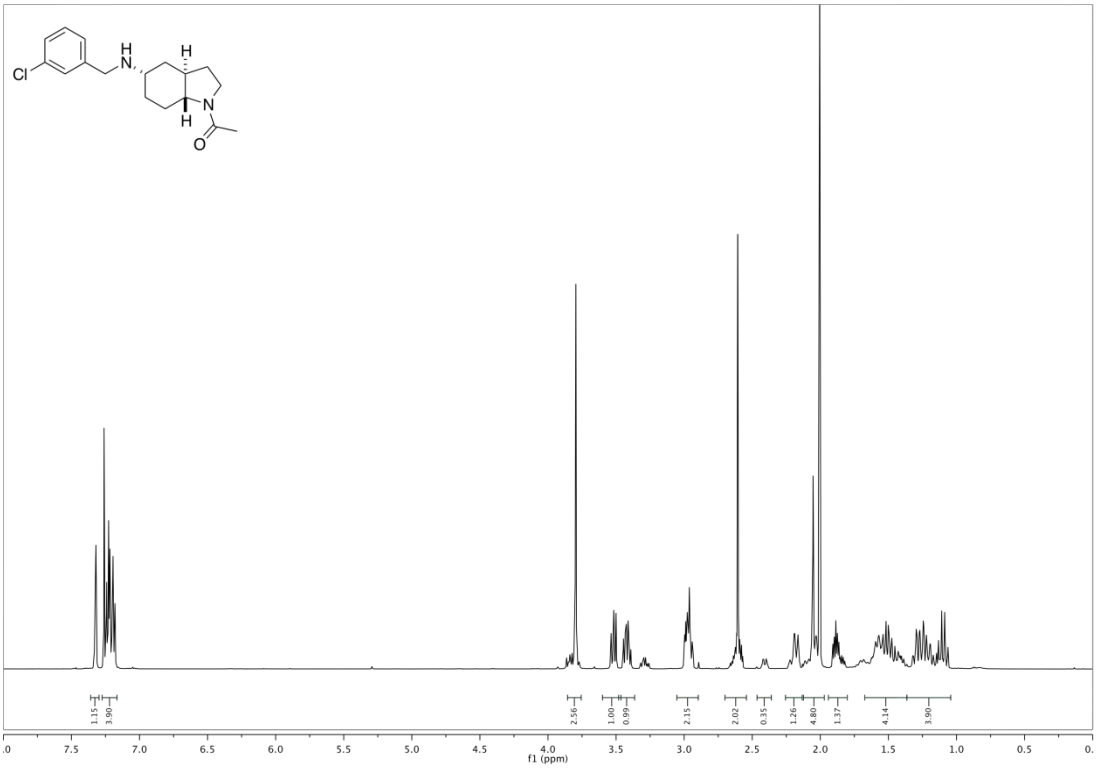


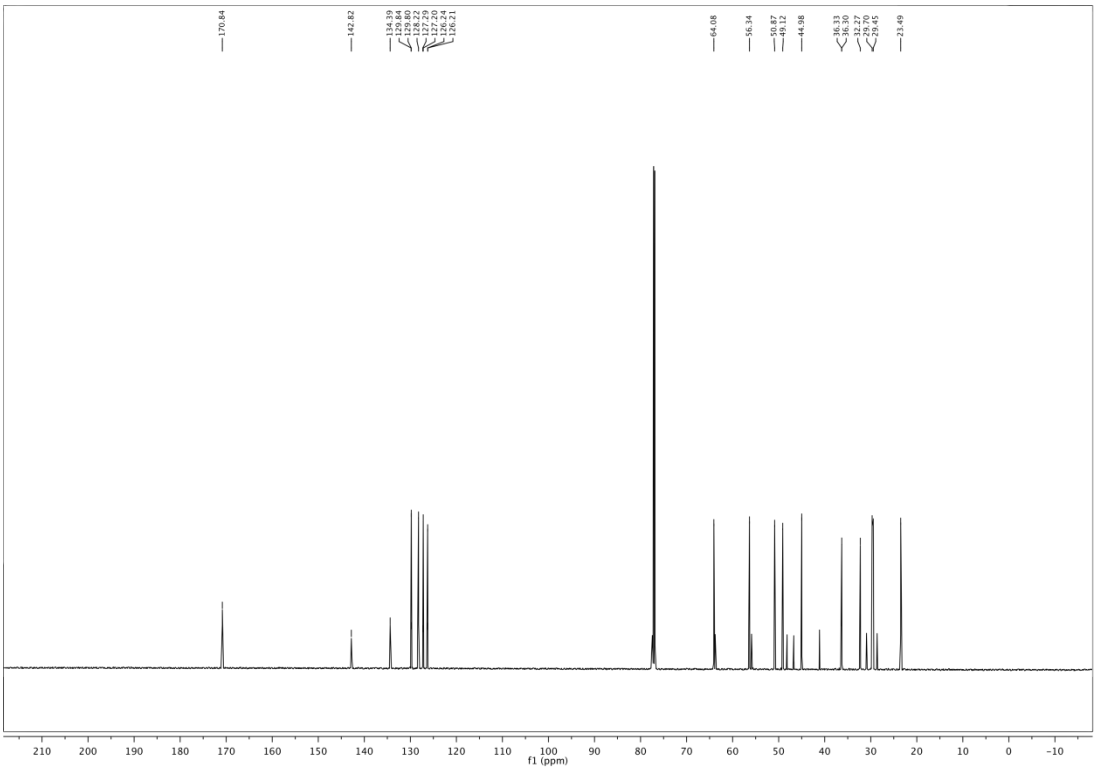
Quinoline **45**{*10*}



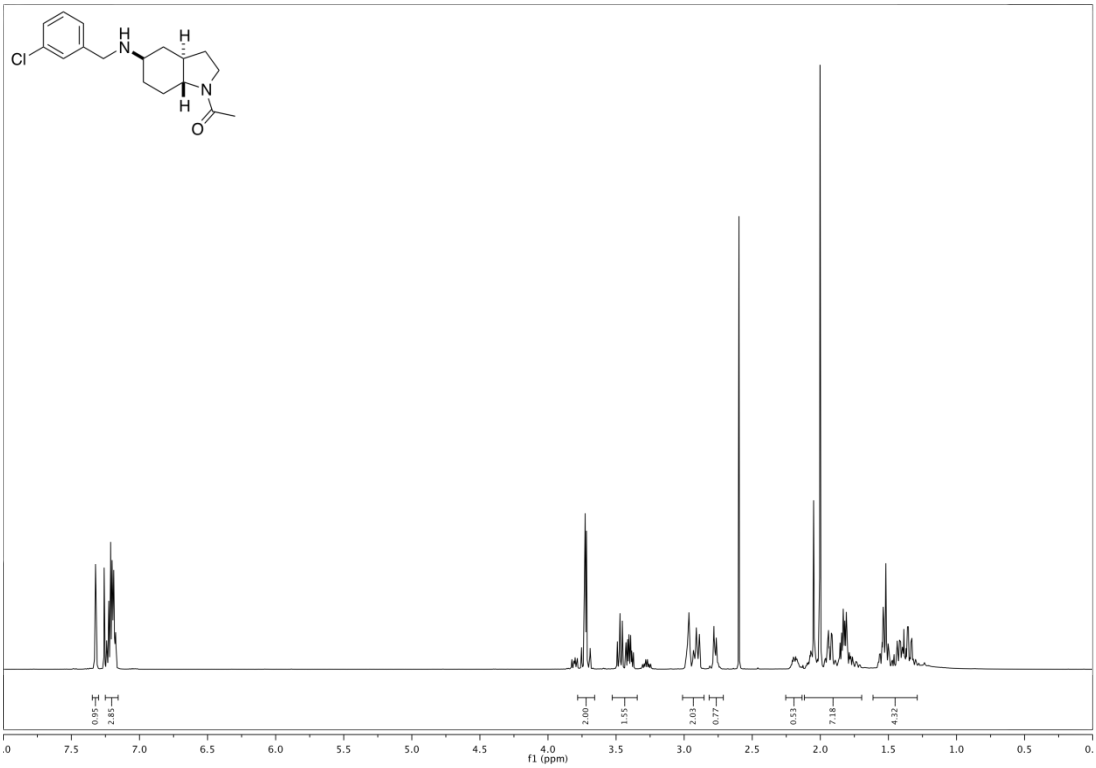


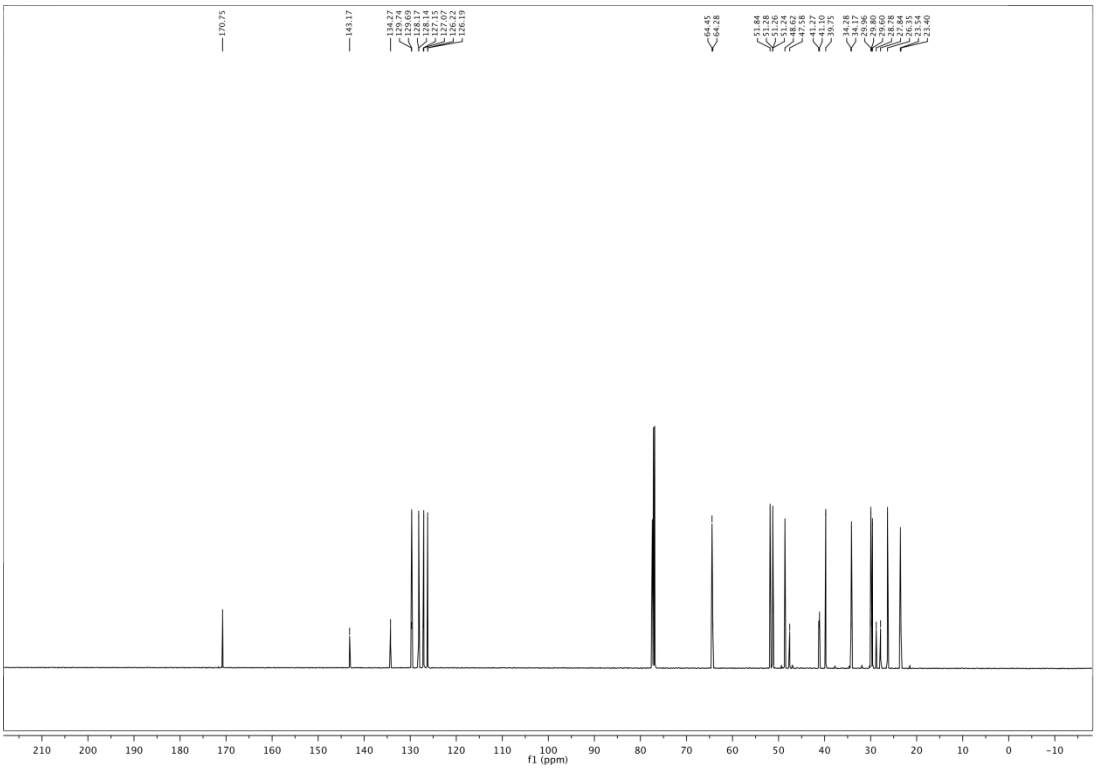
Amine **44a**{*3*}


Cl
H
N
H
N
H
O
1.15
3.90
2.56
1.00
0.99
2.15
2.02
0.35
1.26
4.80
1.37
4.14
3.90
f1 (ppm)

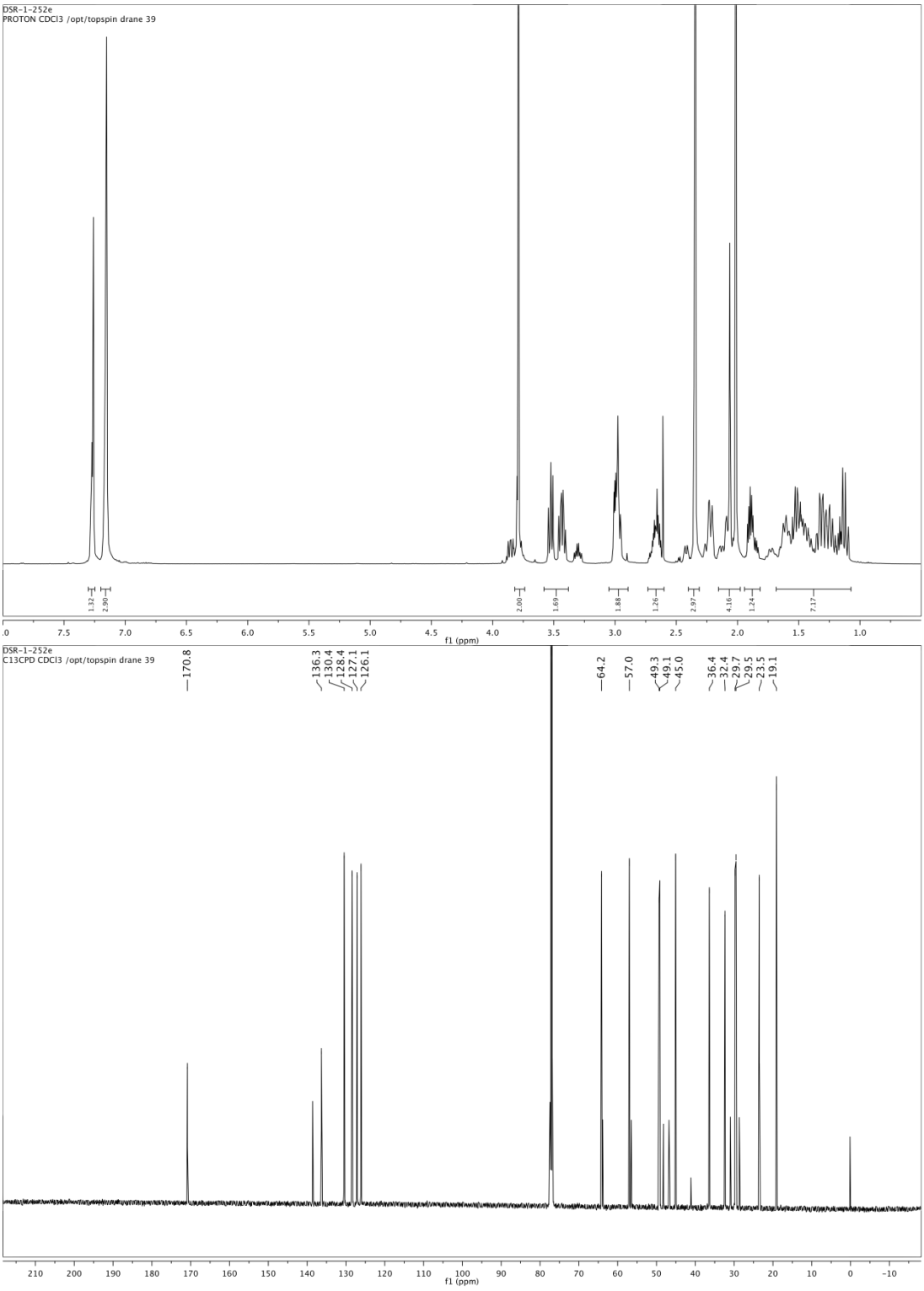

170.64
142.82
134.39
129.84
128.60
128.22
127.29
127.20
126.24
126.21
64.08
56.34
50.87
49.12
44.98
36.33
36.30
31.27
29.70
29.45
23.49
f1 (ppm)

Amine **44b**{*3*}

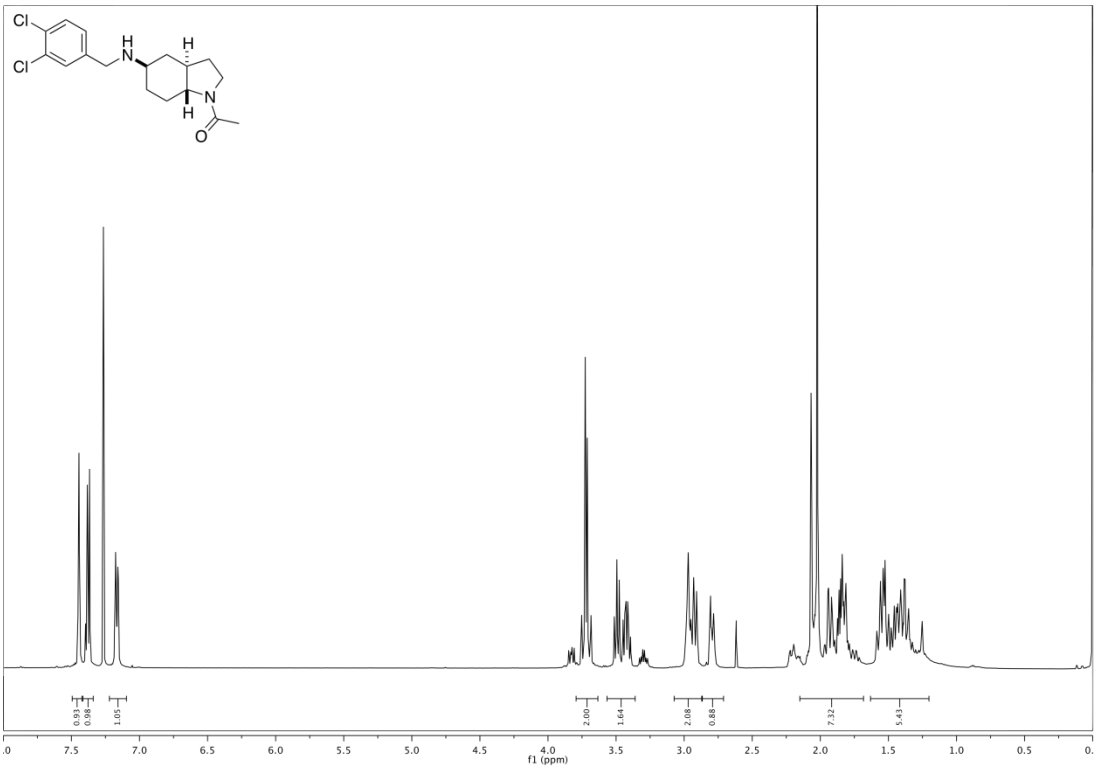

Cl
H
N
H
N
H
O
0.95
2.85
2.00
1.55
2.03
0.77
0.53
7.18
4.32
f1 (ppm)

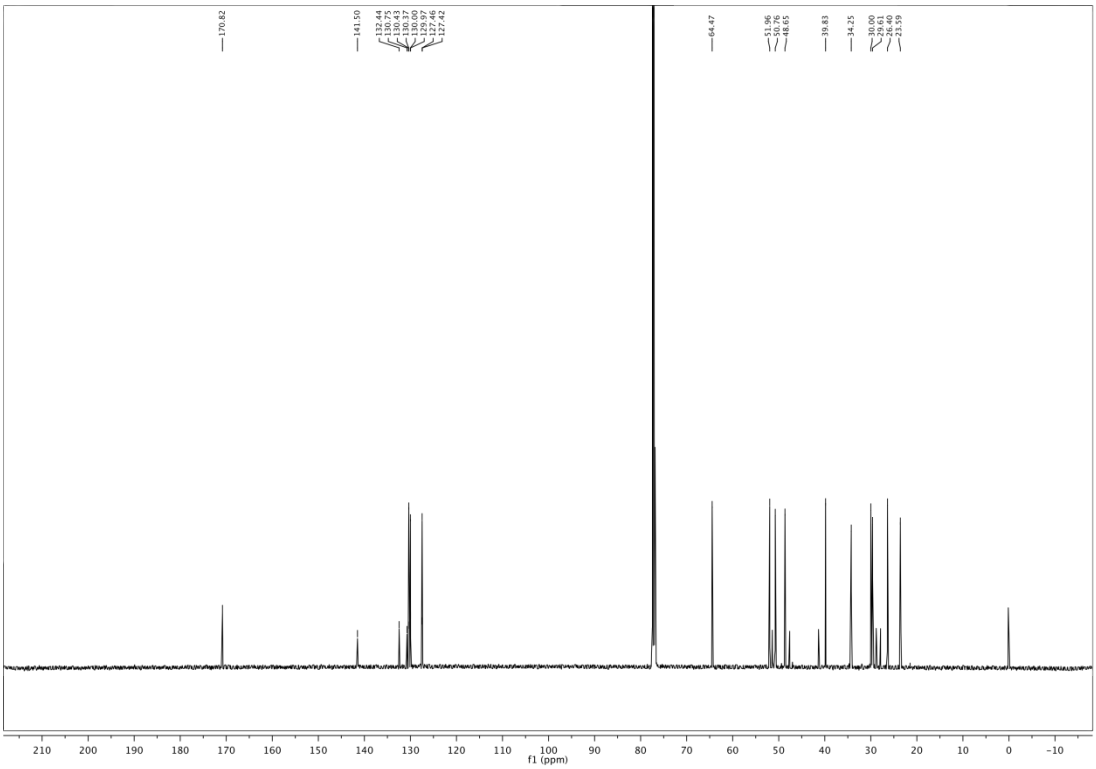

170.75
143.17
134.27
129.74
129.60
128.17
128.14
127.15
127.07
126.23
126.10
64.45
64.28
51.84
51.28
51.26
51.24
48.62
47.56
47.37
41.10
39.75
34.28
34.17
29.96
29.80
29.60
28.78
27.84
26.51
23.54
23.40
f1 (ppm)

Amine **44b**{*11*}

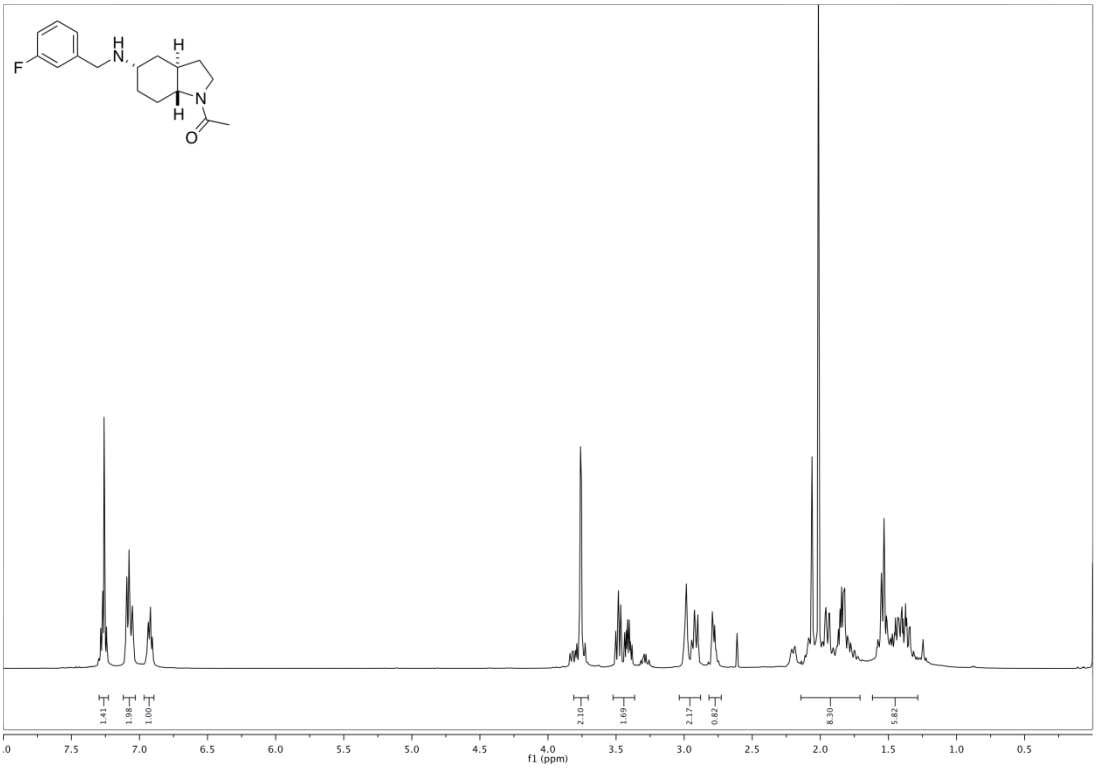

DSR-1-252e
PROTON CDCl3 /opt/topspin drane 39
1.32
2.90
2.00
1.69
1.88
1.26
2.97
4.16
1.24
7.17
f1 (ppm)
DSR-1-252e
C13CPD CDCl3 /opt/topspin drane 39
170.8
136.3
130.4
128.4
127.1
126.1
64.2
57.0
49.3
49.1
45.0
36.4
32.4
29.7
29.5
23.5
19.1
f1 (ppm)

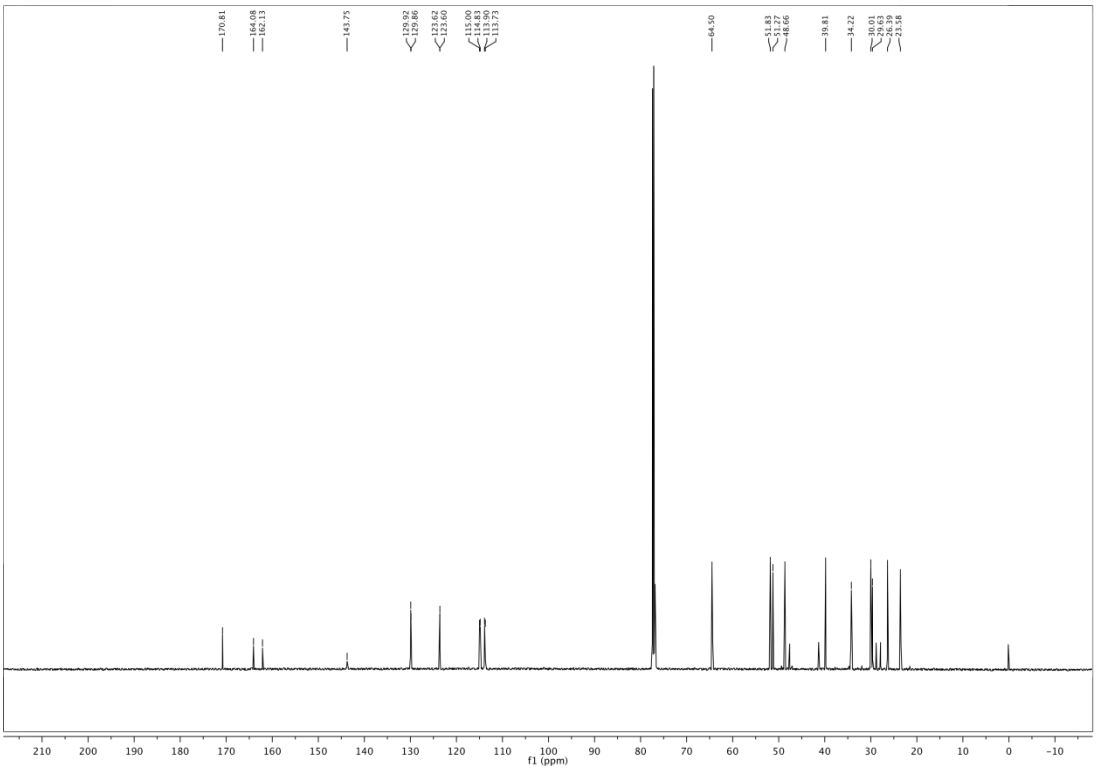
Amine **44b**{*9*}


Cl
Cl
H
N
H
N
H
O
0.93
0.98
1.05
2.00
1.64
2.08
0.88
7.32
5.43
f1 (ppm)

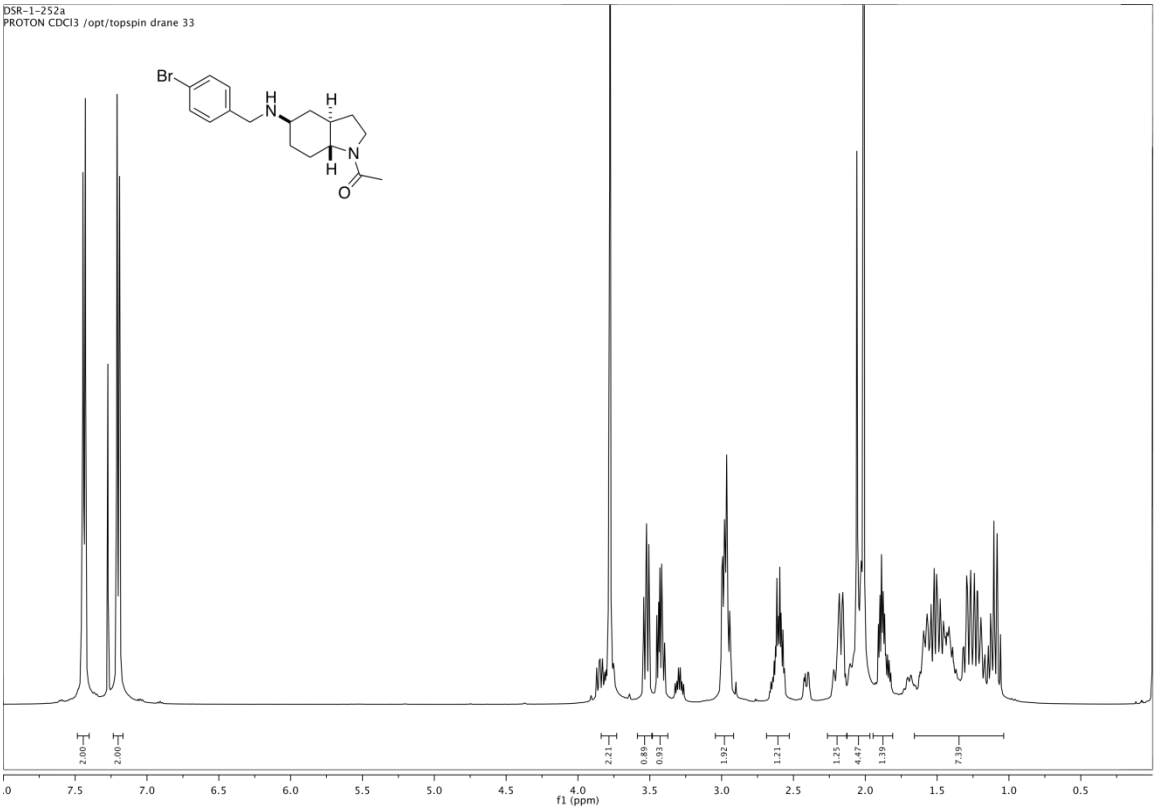

170.82
141.50
132.44
130.75
130.43
130.32
130.00
129.57
127.46
127.42
64.47
51.96
50.76
48.65
39.83
34.25
30.00
29.61
26.40
23.59
f1 (ppm)

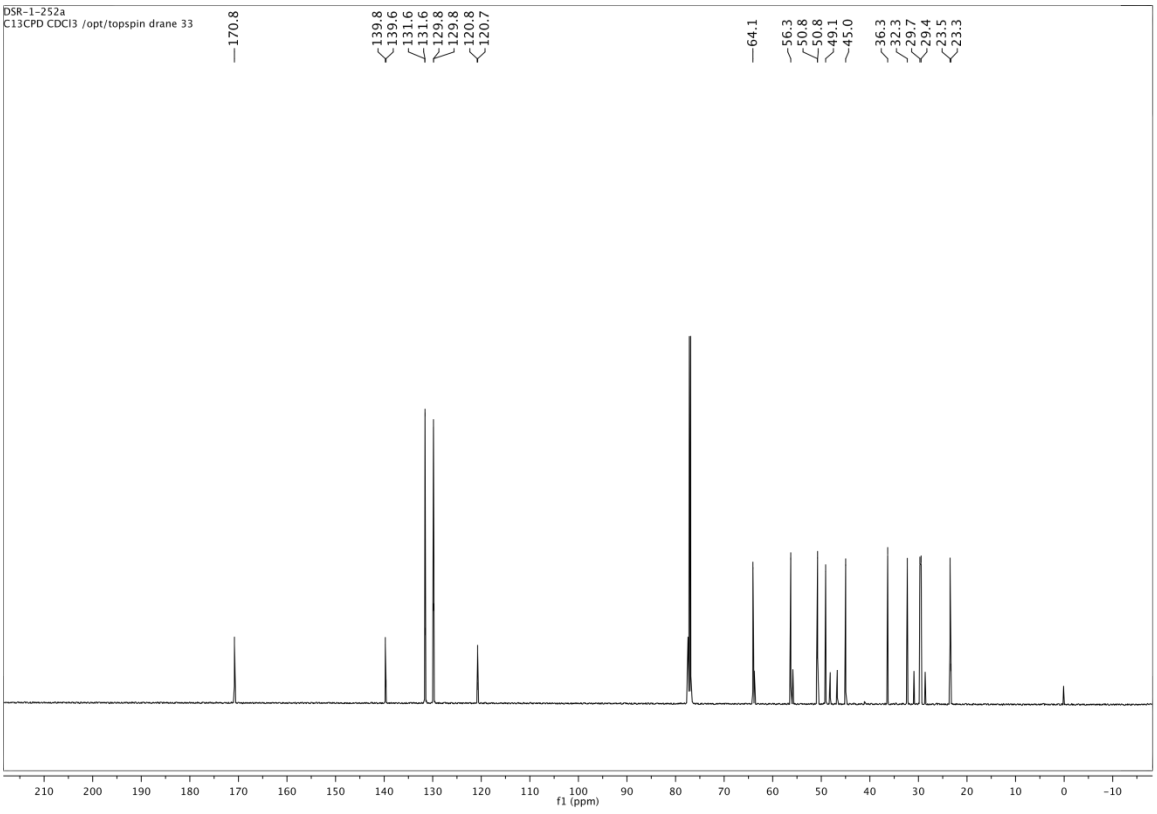
Amine **44a**{*6*}


F
H
N
H
N
H
O
1.41
1.98
1.00
2.10
1.69
2.17
0.82
8.30
5.82
f1 (ppm)

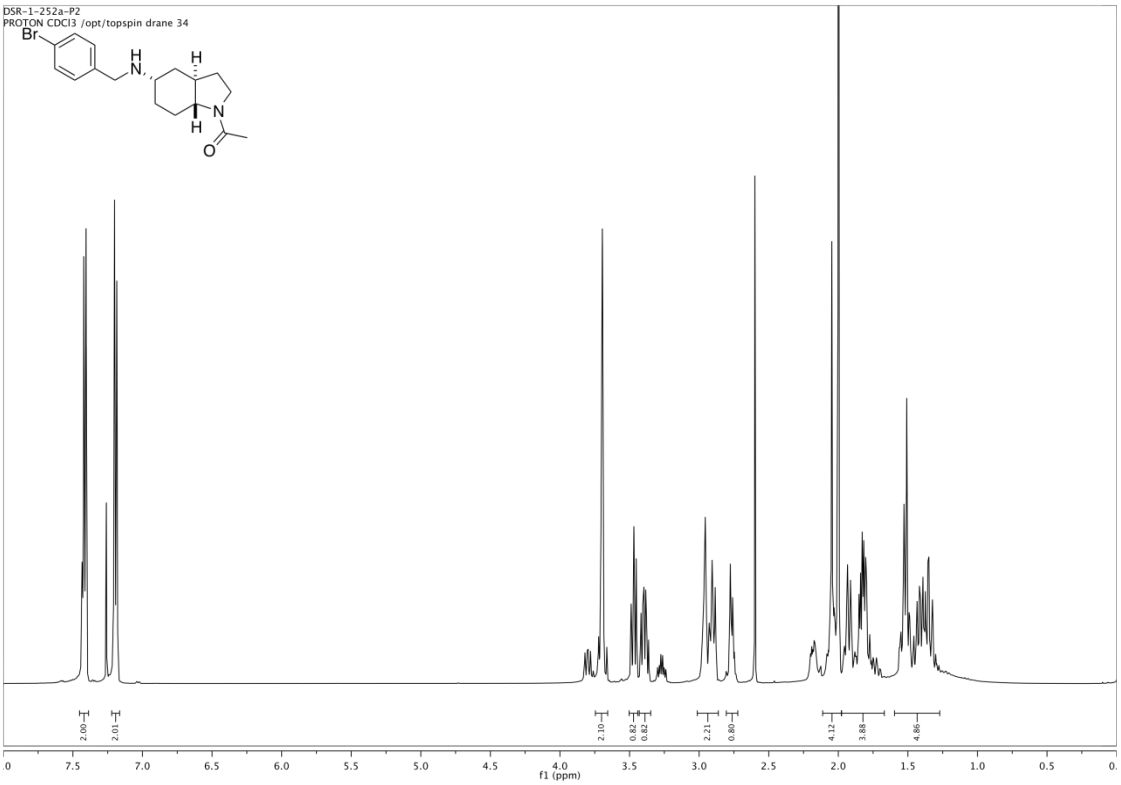

170.61
164.08
162.13
143.75
129.92
129.86
123.62
123.60
115.00
114.85
113.90
113.73
64.50
51.83
51.27
48.66
39.81
34.22
30.01
29.63
26.39
25.98
f1 (ppm)

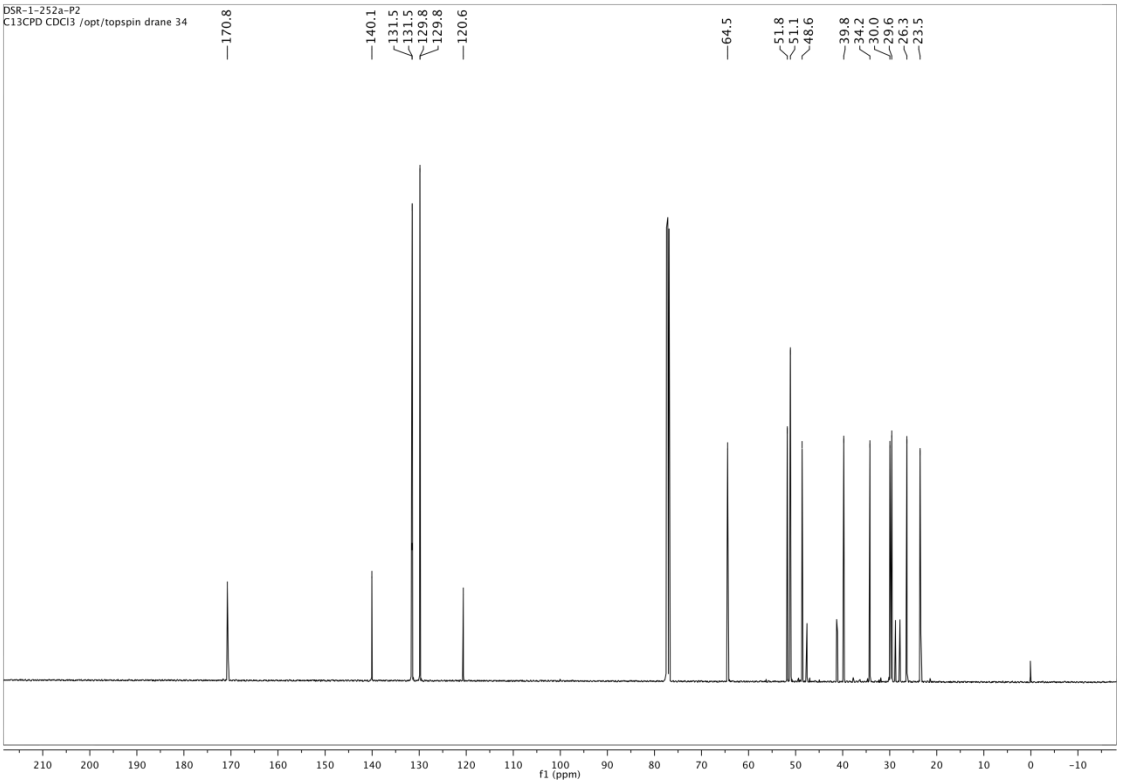
Amine **44b**{*8*}


DSR-1-252a
PROTON CDCl3 /opt/topspin drane 33
Br
H
N
H
N
H
O
2.00
2.00
2.21
0.89
0.93
1.92
1.21
1.25
4.47
1.39
7.39
f1 (ppm)

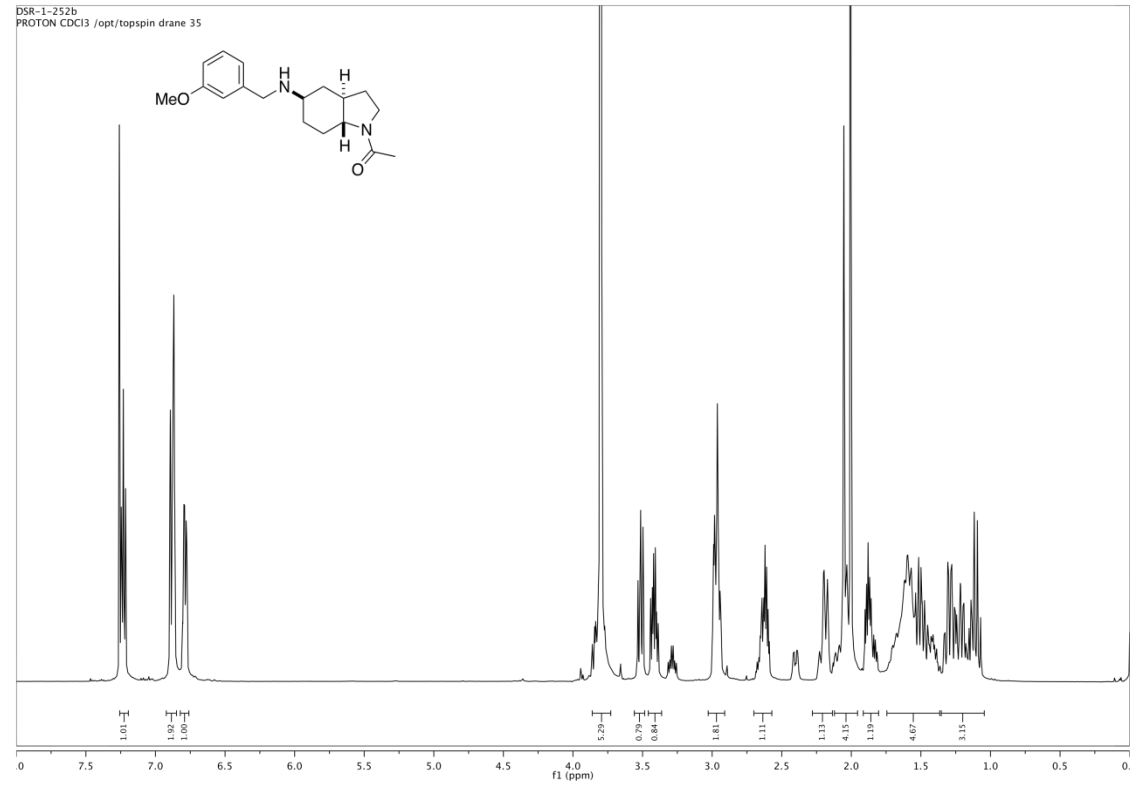

DSR-1-252a
C13CPD CDCl3 /opt/topspin drane 33
170.8
139.8
139.6
131.6
131.6
129.8
129.8
120.8
120.7
64.1
56.3
50.8
50.8
49.1
45.0
36.3
32.3
29.7
29.4
23.5
23.3
f1 (ppm)

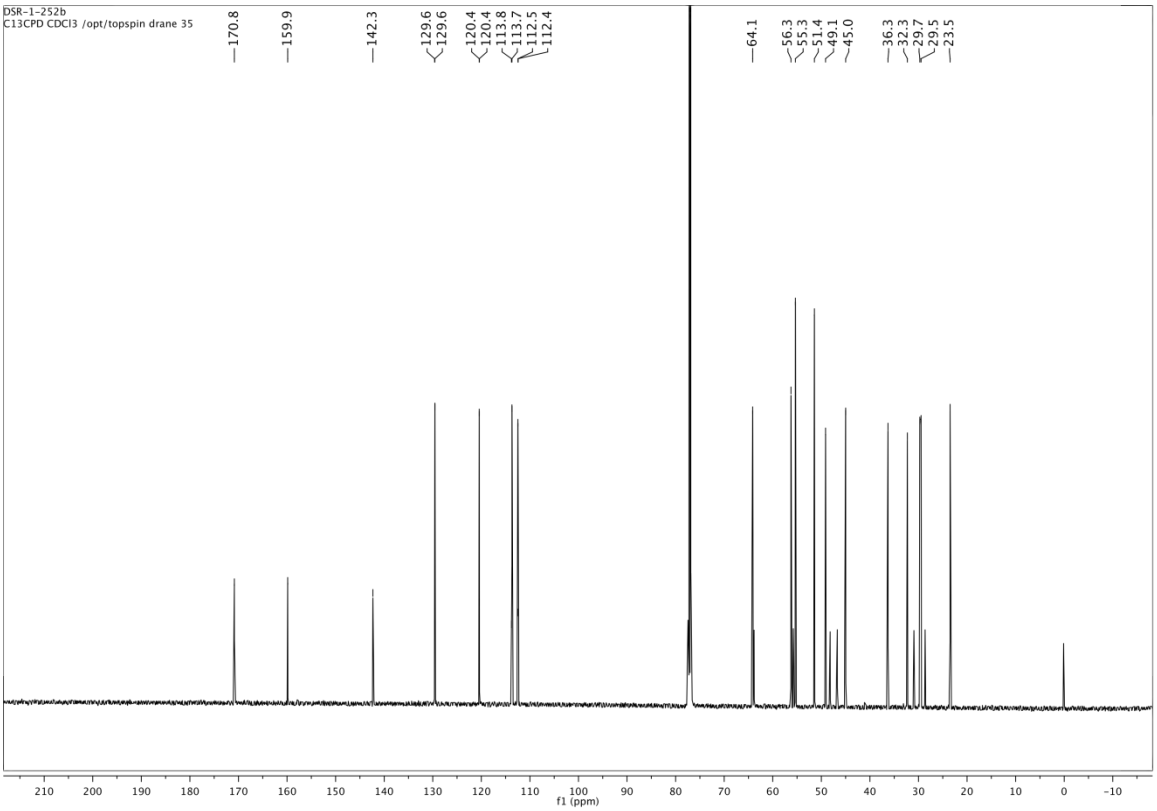
Amine **44a**{*8*}


DSR-1-252a-P2
PROTON CDCl3 /opt/topspin drane 34
Br
H
N
H
N
H
O
2.00
2.01
2.10
0.82
0.82
2.21
0.89
4.12
3.88
4.86
f1 (ppm)

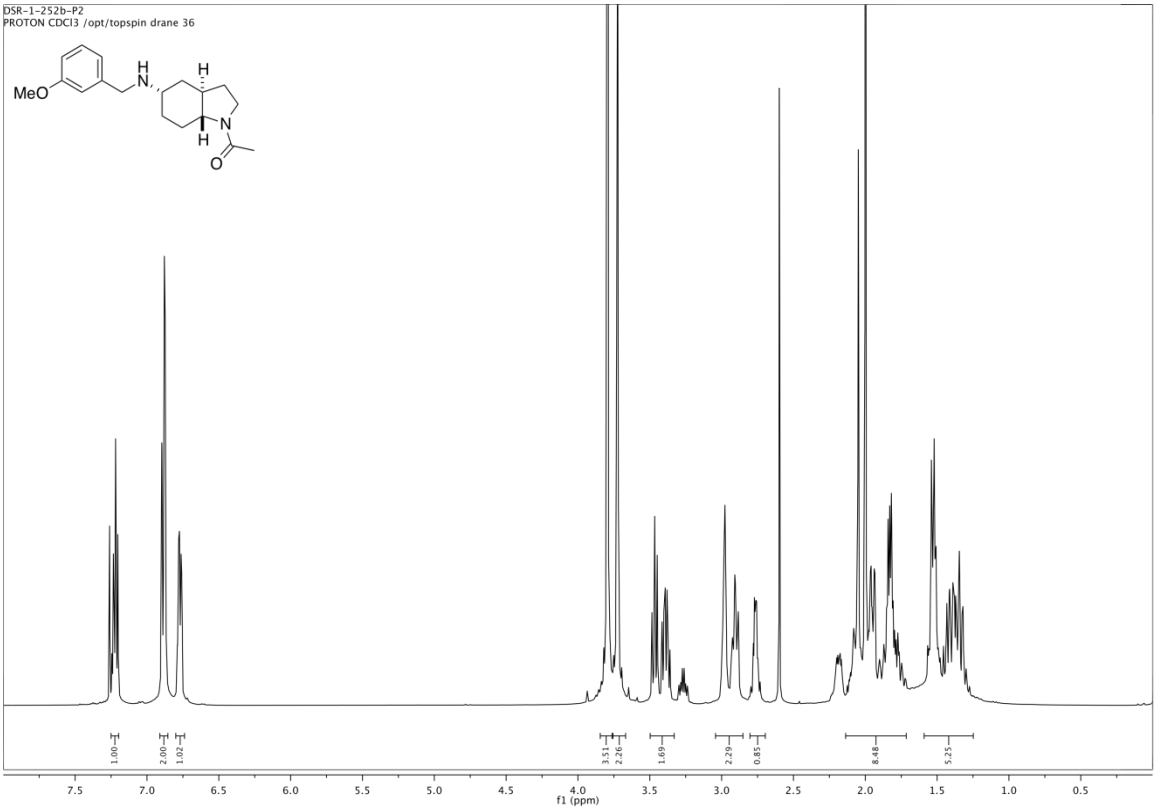

DSR-1-252a-P2
C13CPD CDCl3 /opt/topspin drane 34
170.8
140.1
131.5
131.5
129.8
129.8
120.6
64.5
51.8
51.1
48.6
39.8
34.2
30.0
29.6
26.3
23.5
f1 (ppm)

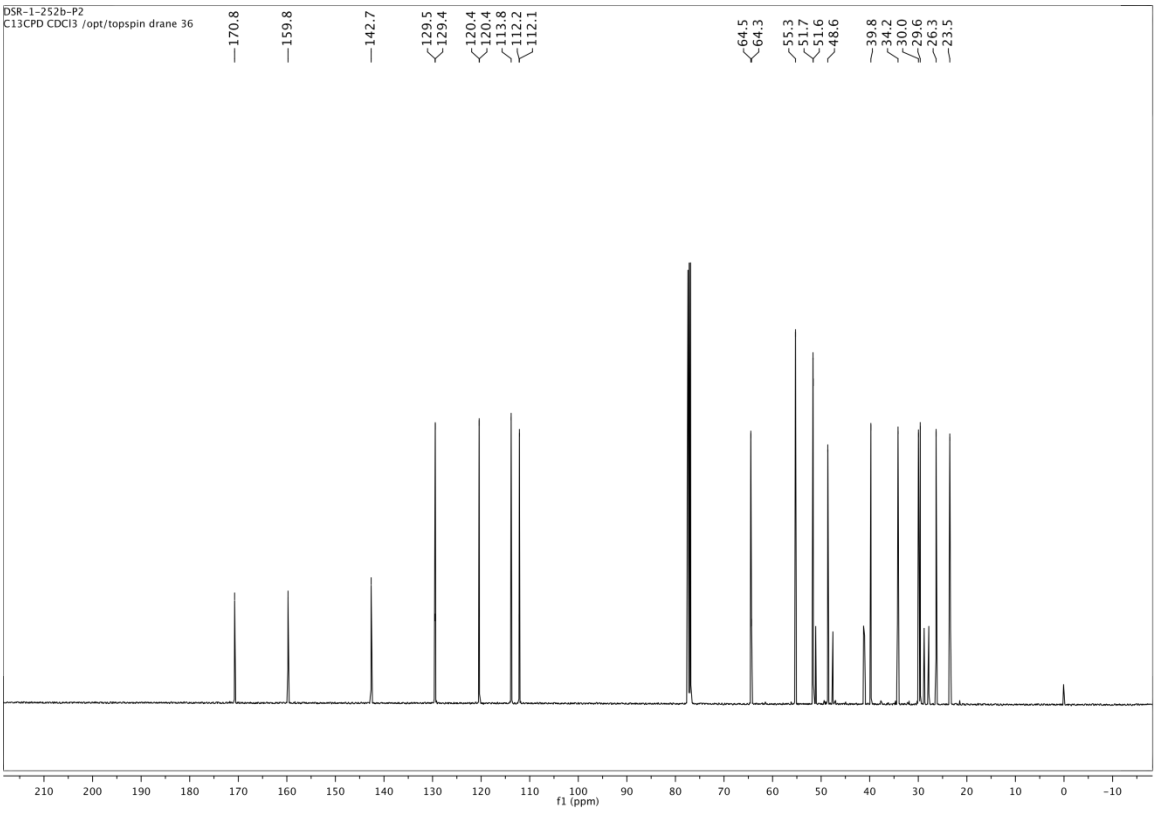
Amine **44b**{*15*}


DSR-1-252b
PROTON CDCl3 /opt/topspin drane 35
MeO
H
N
H
N
H
O
1.01
1.92
1.00
5.29
0.79
0.84
1.81
1.11
1.13
4.15
1.19
4.67
3.15
f1 (ppm)

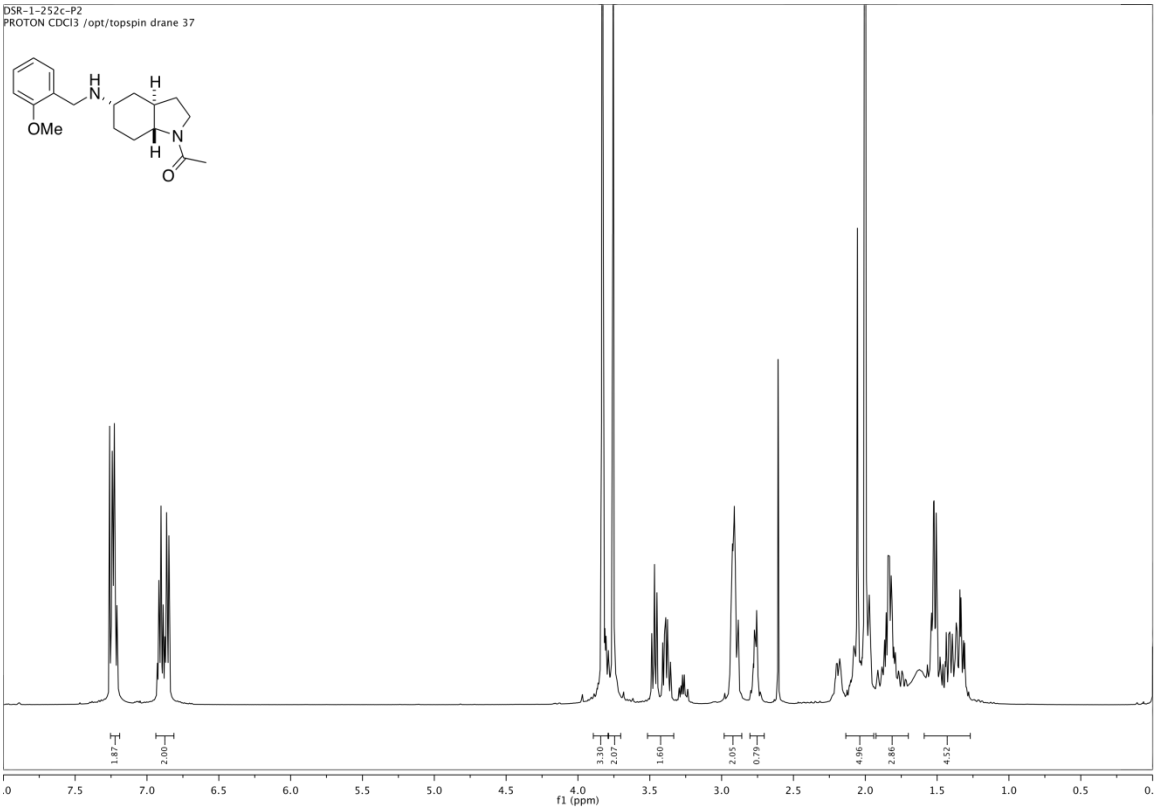

DSR-1-252b
C13CPD CDCl3 /opt/topspin drane 35
170.8
159.9
142.3
129.6
129.6
120.4
120.4
113.8
113.7
112.5
112.4
64.1
56.3
55.3
51.4
49.1
45.0
36.3
32.3
29.7
29.5
23.5
f1 (ppm)

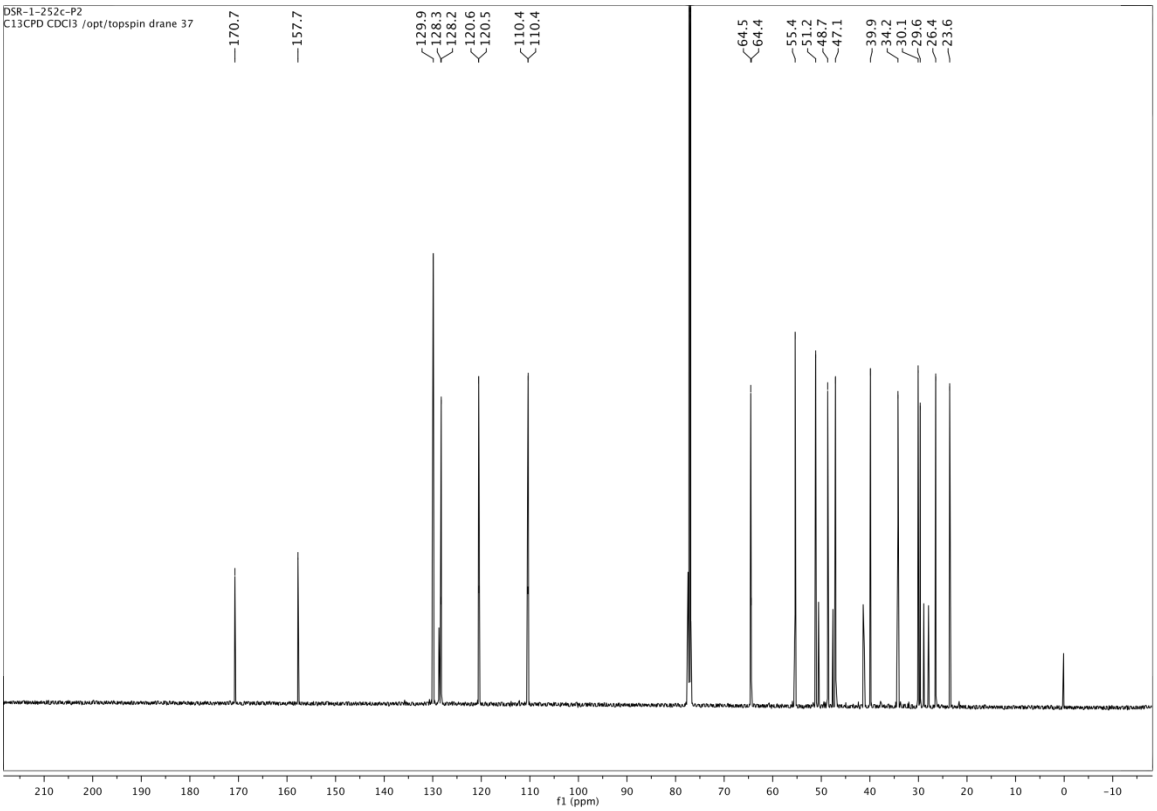
Amine **44a**{*15*}


DSR-1-252b-P2
PROTON CDCl3 /opt/topspin drane 36
MeO
H
N
H
N
H
O
1.00
2.00
1.02
3.51
2.26
1.69
2.29
0.85
8.48
5.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

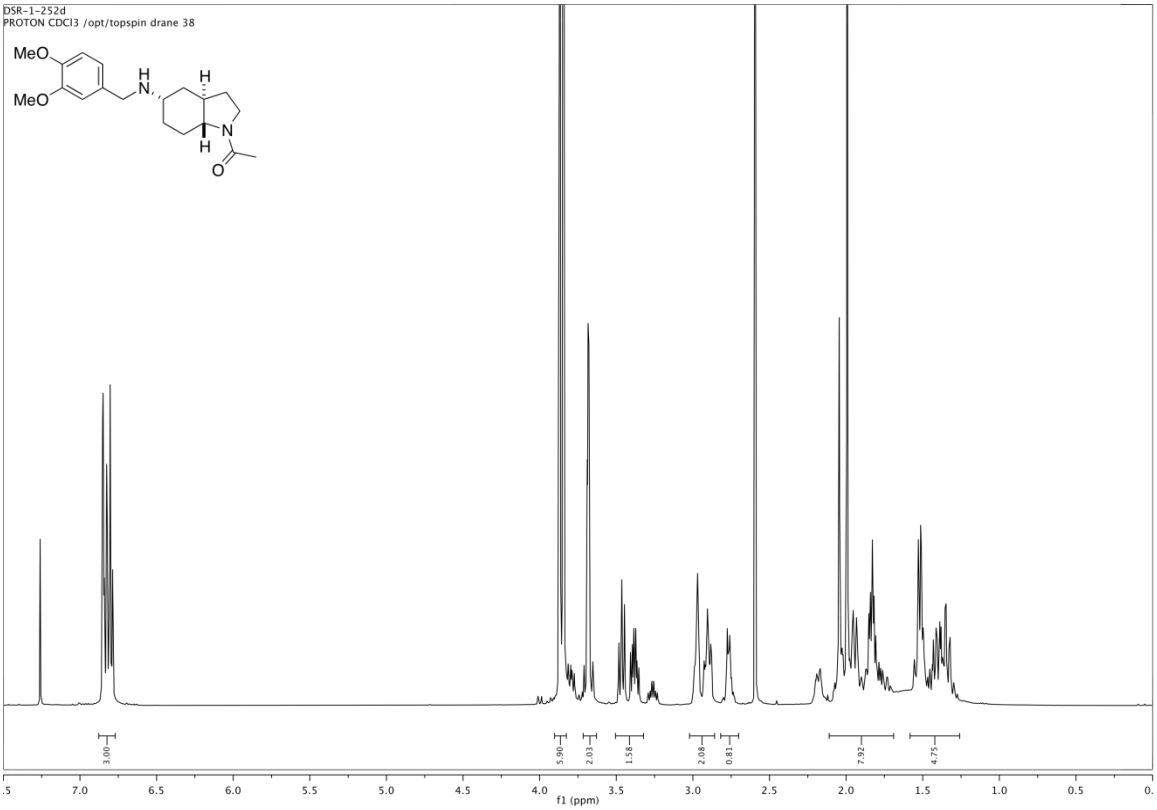

DSR-1-252b-P2
C13CPD CDCl3 /opt/topspin drane 36
170.8
159.8
142.7
129.5
129.4
120.4
120.4
113.8
112.2
112.1
64.5
64.3
55.3
51.7
51.6
48.6
39.8
34.2
30.0
29.6
26.3
23.5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

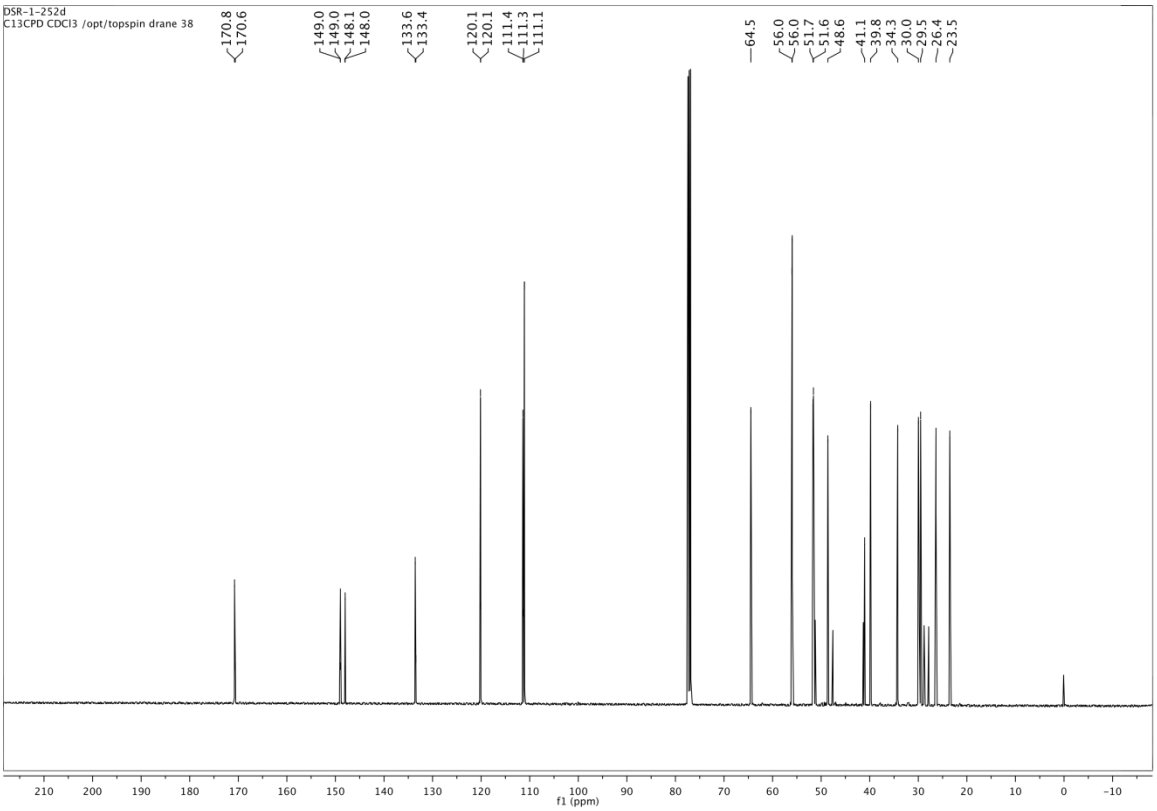
Amine **44a**{*14*}


DSR-1-252c-P2
PROTON CDCl3 /opt/topspin drane 37
OMe
H
N
H
N
H
O
1.87
2.00
3.30
2.07
1.60
2.05
0.79
4.96
2.86
4.52
f1 (ppm)

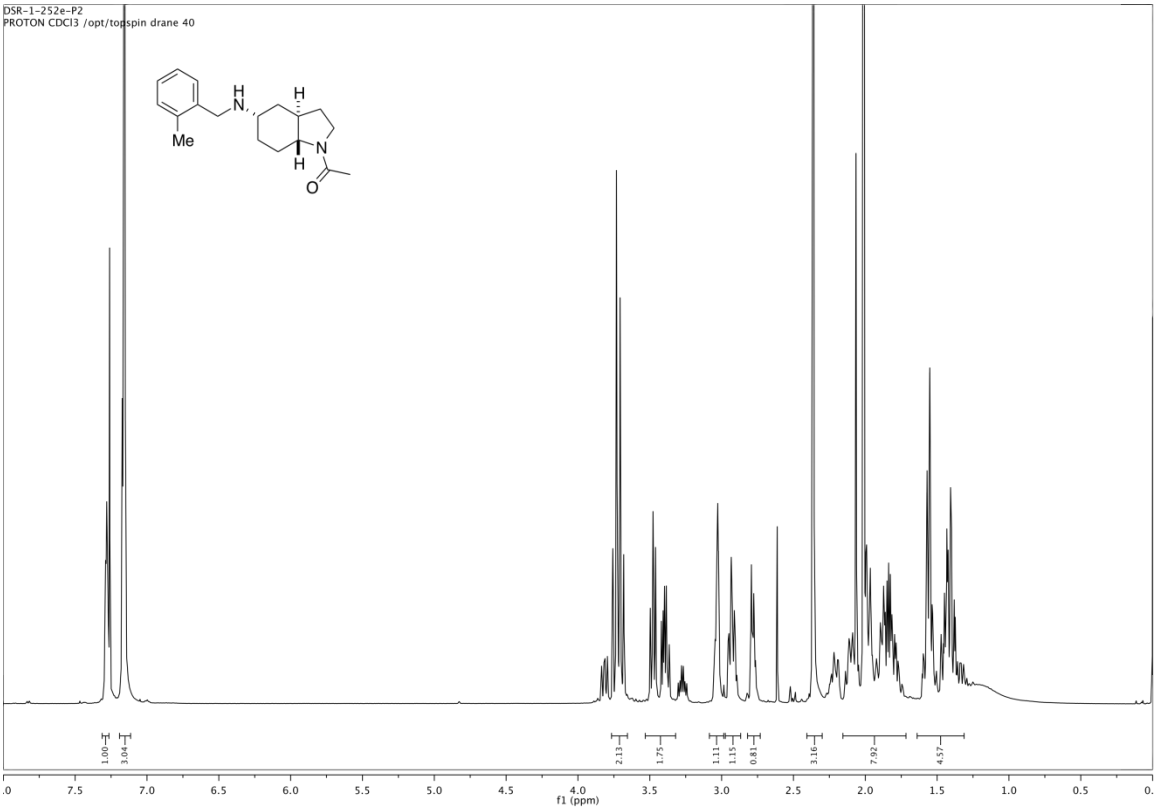

DSR-1-252c-P2
C13CPD CDCl3 /opt/topspin drane 37
170.7
157.7
129.9
128.3
128.2
120.6
120.5
110.4
110.4
64.5
64.4
55.4
51.2
48.7
47.1
39.9
34.2
30.1
29.6
26.4
23.6
f1 (ppm)

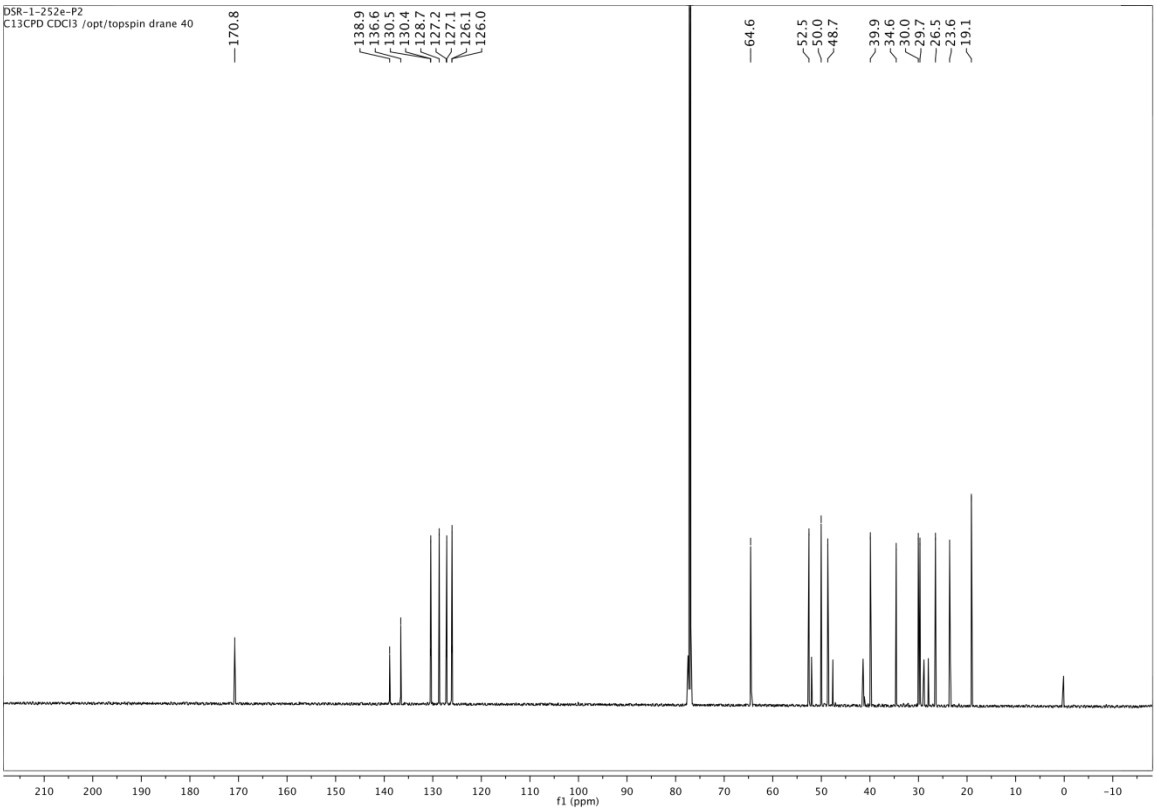
Amine **44a**{*16*}


DSR-1-252d
PROTON CDCl3 /opt/topspin drane 38
MeO
MeO
H
N
H
N
H
O
3.00
5.90
2.03
1.58
2.08
0.81
7.92
4.75
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

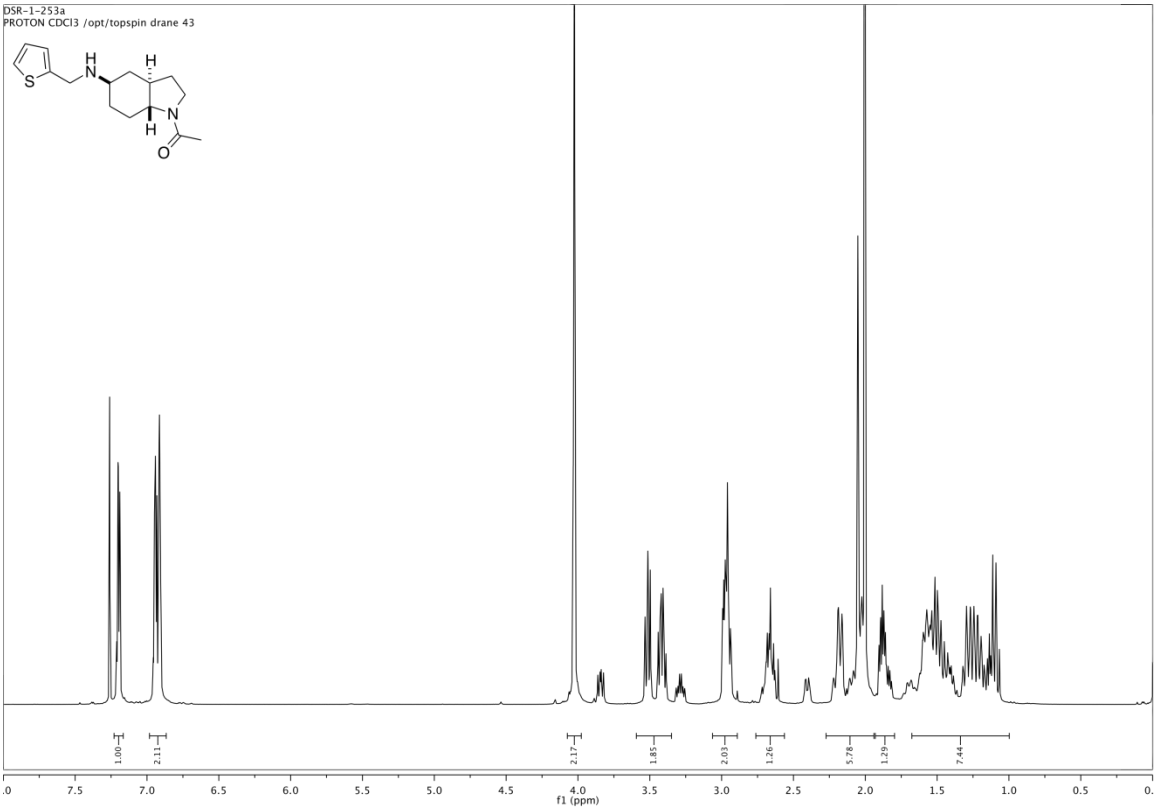

DSR-1-252d
C13CPD CDCl3 /opt/topspin drane 38
170.8
170.6
149.0
149.0
148.1
148.0
133.6
133.4
120.1
120.1
111.4
111.3
111.1
64.5
56.0
56.0
51.7
51.6
48.6
41.1
39.8
34.3
30.0
29.5
26.4
23.5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

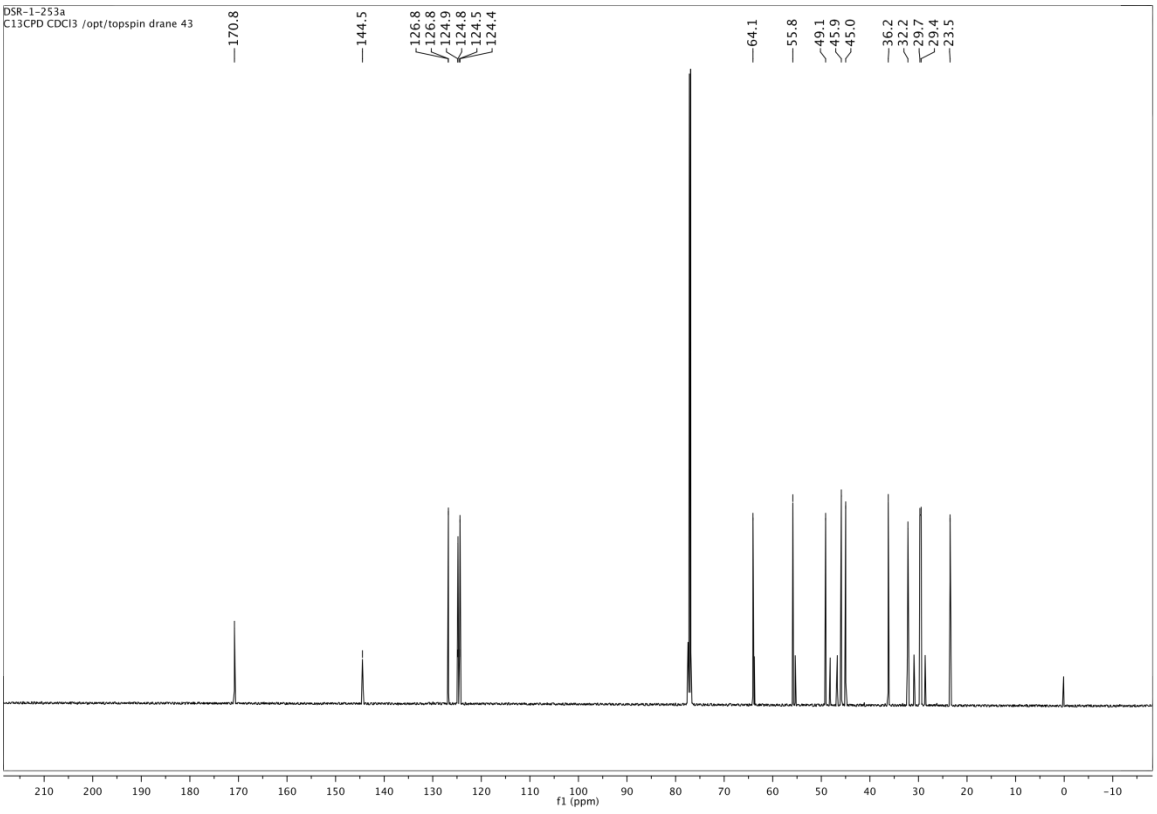
Amine **44a**{*11*}


DSR-1-252e-P2
PROTON CDCl3 /opt/topspin drane 40
Me
H
N
H
N
H
O
1.00
3.04
2.13
1.75
1.11
1.15
0.81
3.16
7.92
4.57
f1 (ppm)

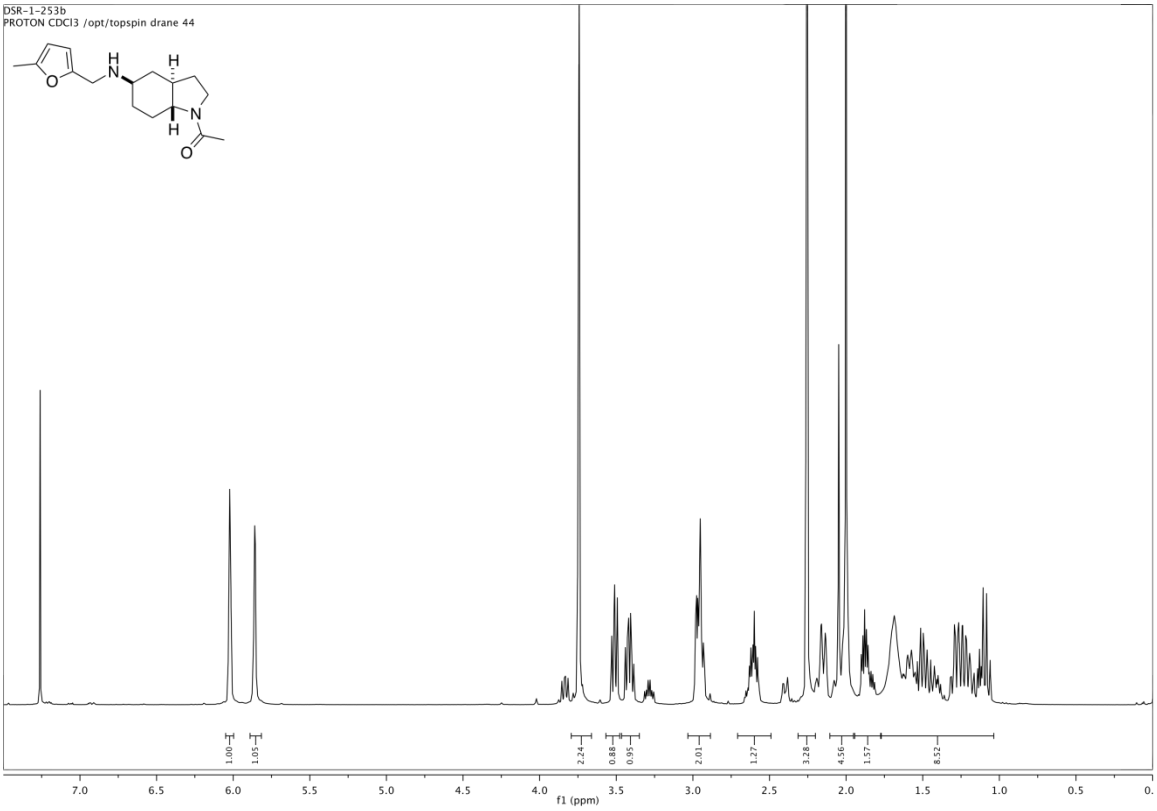

DSR-1-252e-P2
C13CPD CDCl3 /opt/topspin drane 40
170.8
138.9
136.6
130.5
130.4
128.7
127.2
127.1
126.1
126.0
64.6
52.5
50.0
48.7
39.9
34.6
30.0
29.7
26.5
23.6
19.1
f1 (ppm)

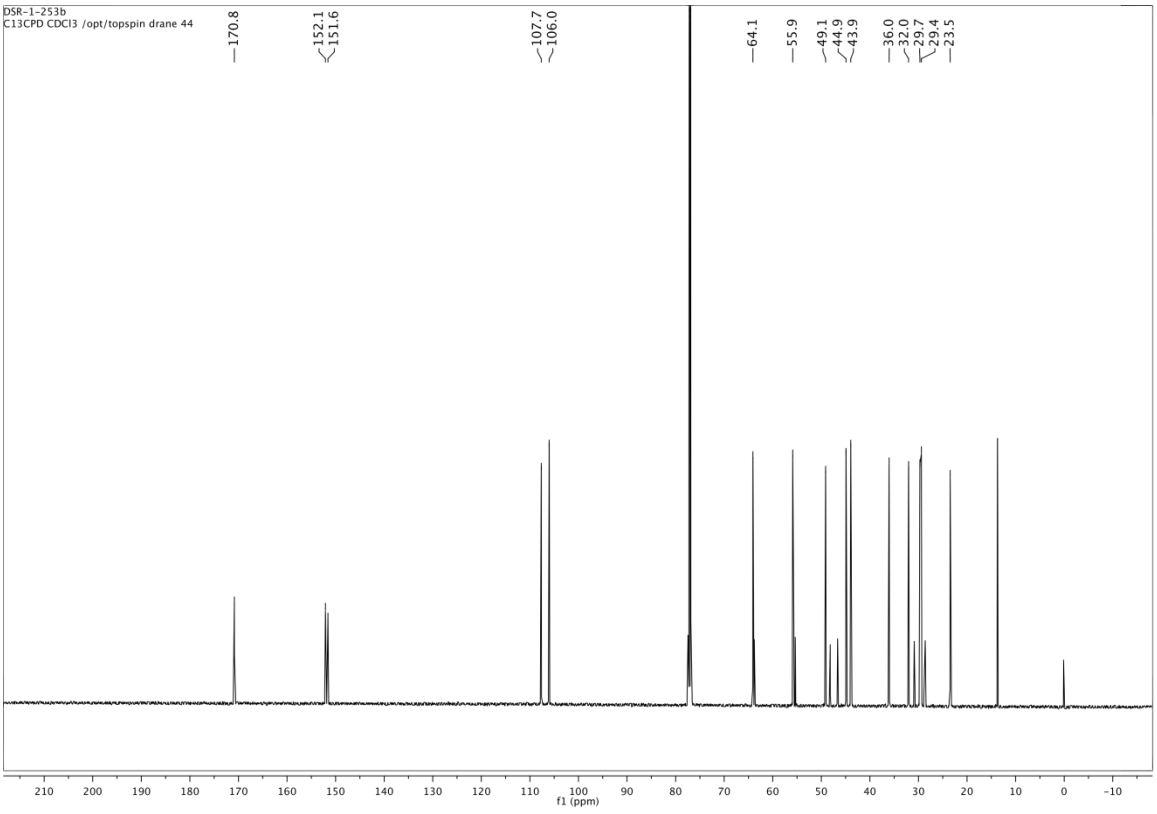
Amine **44b**{*19*}


DSR-1-253a
PROTON CDCl3 /opt/topspin drane 43
1.00
2.11
2.17
1.85
2.03
1.26
5.78
1.29
7.44
f1 (ppm)

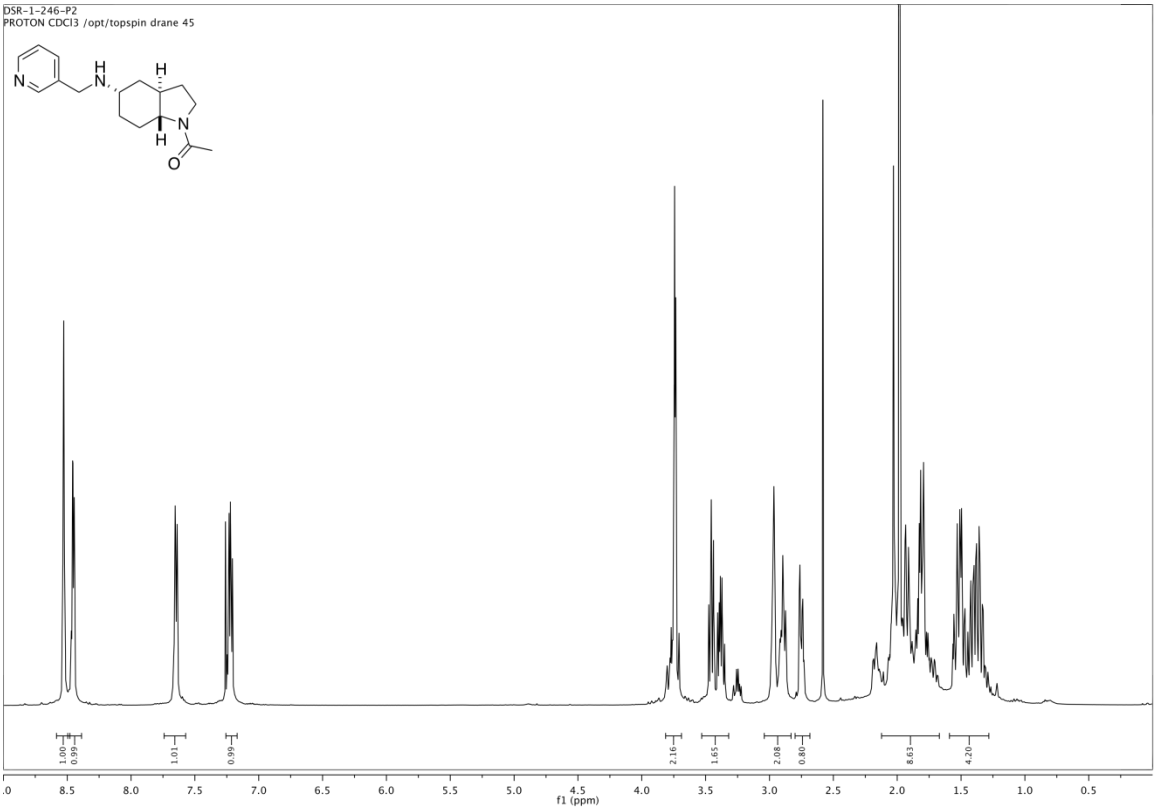

DSR-1-253a
C13CPD CDCl3 /opt/topspin drane 43
170.8
144.5
126.8
126.8
124.9
124.8
124.5
124.4
64.1
55.8
49.1
45.9
45.0
36.2
32.2
29.7
29.4
23.5
f1 (ppm)

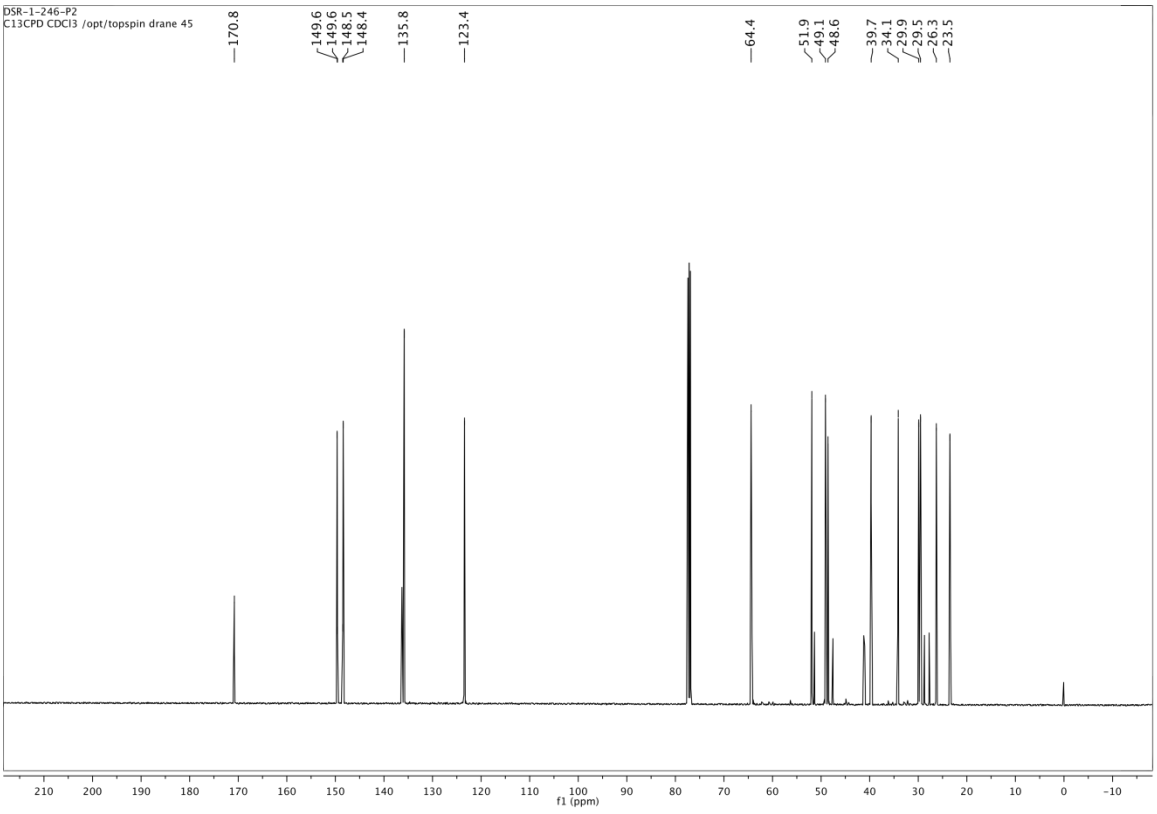
Amine **44b**{*21*}


DSR-1-253b
PROTON CDCl3 /opt/topspin drane 44
1.00
1.05
2.24
0.88
0.95
2.01
1.27
3.28
4.56
1.57
8.52
f1 (ppm)


DSR-1-253b
C13CPD CDCl3 /opt/topspin drane 44
170.8
152.1
151.6
107.7
106.0
64.1
55.9
49.1
44.9
43.9
36.0
32.0
29.7
29.4
23.5
f1 (ppm)

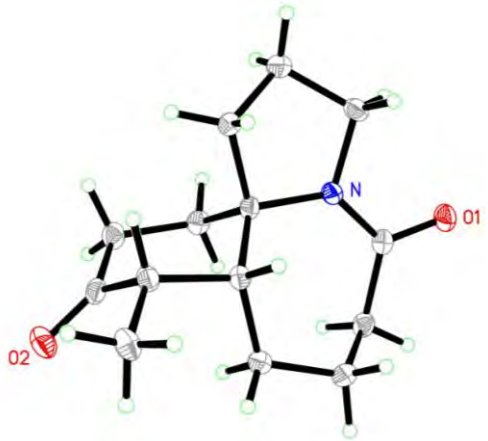
Amine **44a**{*23*}

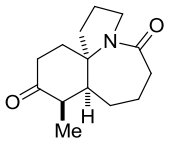

DSR-1-246-P2
PROTON CDCl3 /opt/topspin drane 45
f1 (ppm)


DSR-1-246-P2
C13CPD CDCl3 /opt/topspin drane 45
170.8
149.6
149.6
148.5
148.4
135.8
123.4
64.4
51.9
49.1
48.6
39.7
34.1
29.9
29.5
26.3
23.5
f1 (ppm)

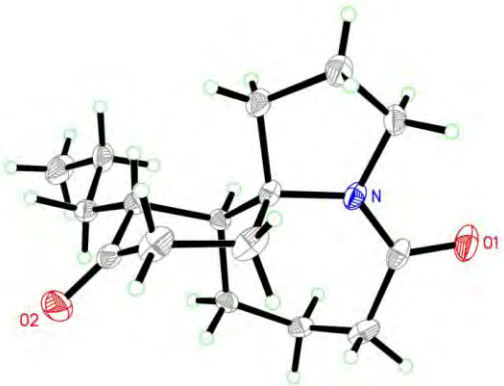
VI. Supplementary Note: X-ray crystallography data.

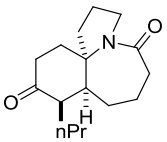
Structure of **3b** (Deposition number: CCDC 945414):



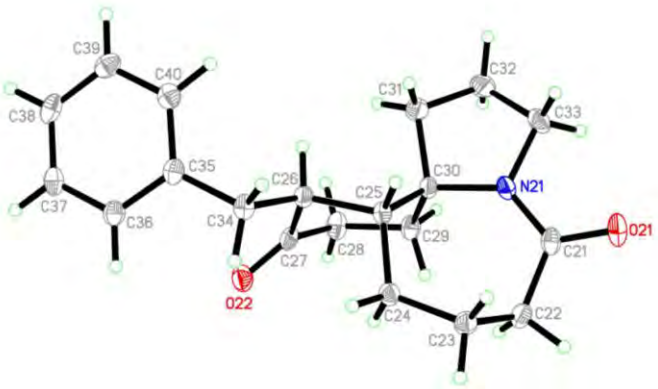


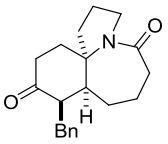
Structure of **3c** (Deposition number: CCDC 945415):



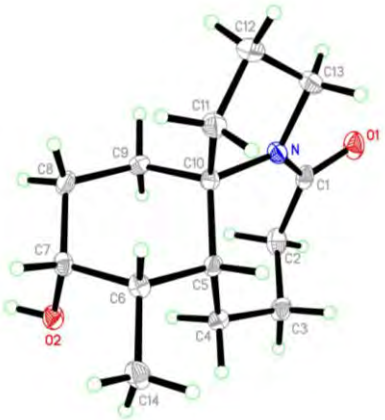


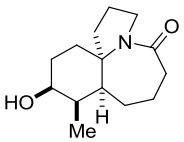
Structure of **3d** (Deposition number: CCDC 945419):



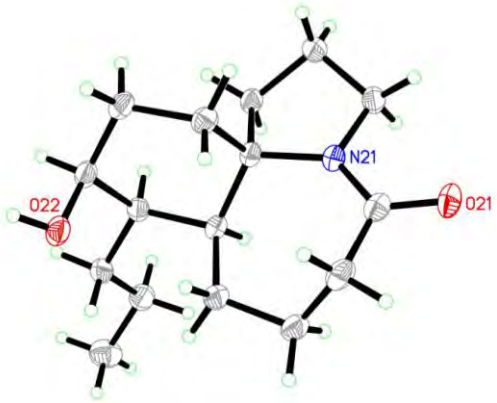


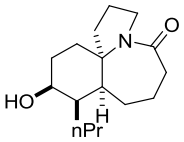
Structure of **S3b** (Deposition number: CCDC 945416):



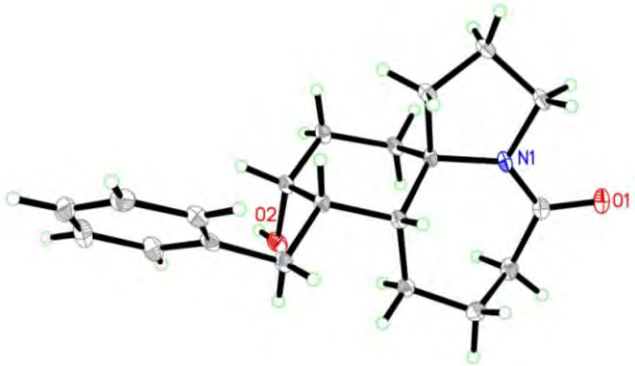


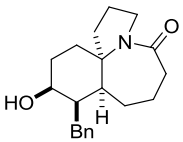
Structure of **S3c** (Deposition number: CCDC 945417):



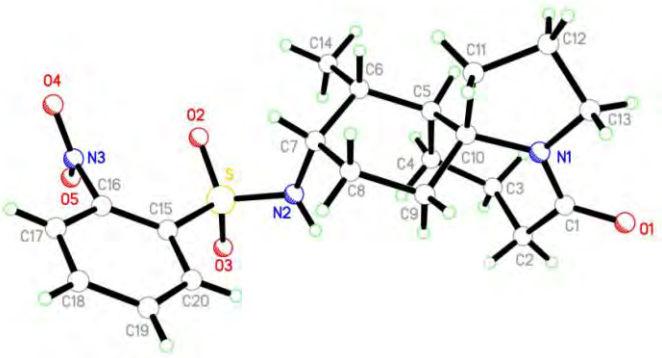


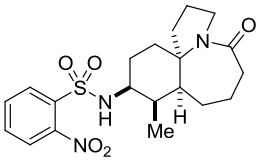
Structure of **S3d** (Deposition number: CCDC 945421):



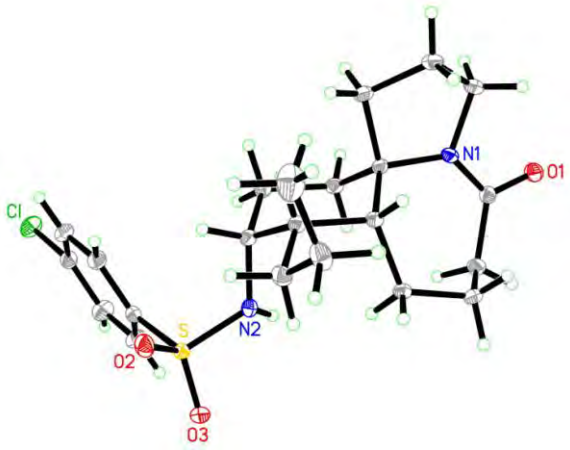


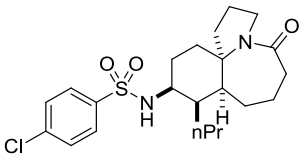
Structure of **29d**{*2*} (Deposition number: CCDC 945418):



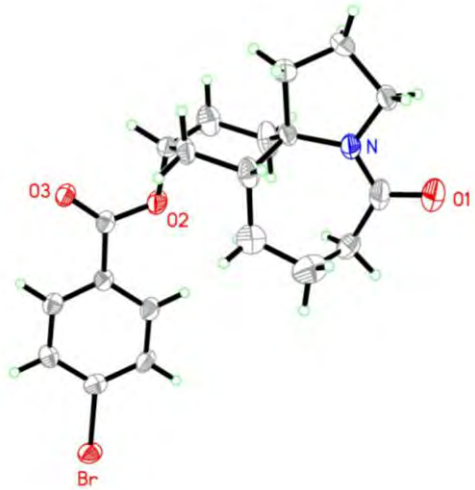


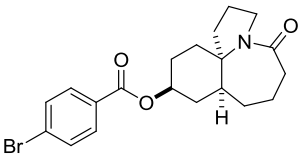
Structure of **29c**{*8*} (Deposition number: CCDC 945420):



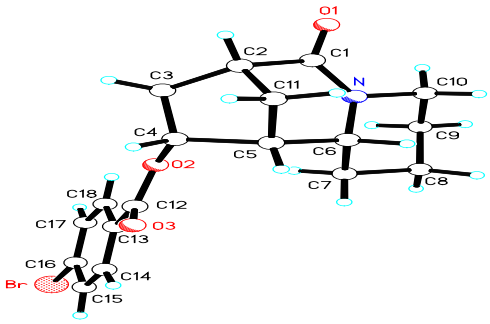


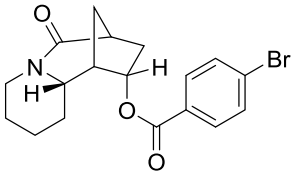
Structure of **S6** (Deposition number: CCDC 945413):



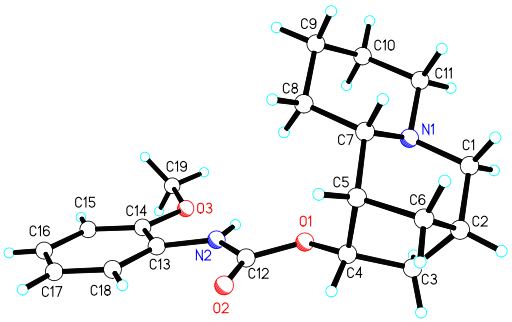


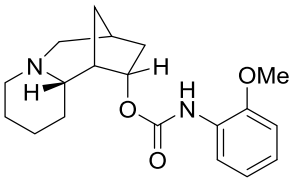
Structure of **S14** (Deposition number: CCDC 946099):



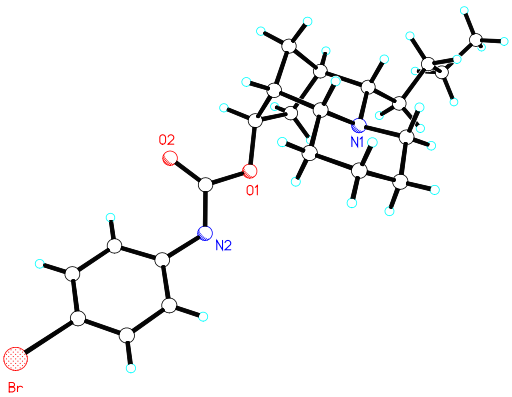


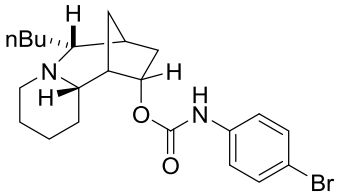
Structure of **42**{*13*} (Deposition number: CCDC 946100):





Structure of **43b**{*23*} (Deposition number: CCDC 946101):





Level A & B alerts encountered during IUCR's CheckCIF routine:

Compound name	CCDC reference	A/B level alerts
3b	945414	PLAT029_ALERT_3_B _diffrn_measured_fraction_theta_full Low 0.952
3c	945415	PLAT222_ALERT_3_B Large Non-Solvent H Uiso(max)/Uiso(min) .. 8.6 Ratio
3d	945419	PLAT029_ALERT_3_B _diffrn_measured_fraction_theta_full Low 0.952
S3b	945416	None
S3c	945417	PLAT089_ALERT_3_B Poor Data / Parameter Ratio (Zmax < 18) 5.13
S3d	945421	PLAT029_ALERT_3_B _diffrn_measured_fraction_theta_full Low ..... 0.950 PLAT031_ALERT_4_B Refined Extinction Parameter within Range ..... 1.000 Sigma
S6	945413	PLAT410_ALERT_2_B Short Intra H...H Contact H9B .. H11D .. 1.89 Ang. PLAT431_ALERT_2_B Short Inter HL..A Contact Br .. O3 . 3.06 Ang.
29d{*2*}	945418	PLAT029_ALERT_3_B _diffrn_measured_fraction_theta_full Low 0.953
29c{*8*}	945420	None
S14	946099	PLAT431_ALERT_2_B Short Inter HL..A Contact Br .. O1 . 3.03 Ang.
42{*13*}	946100	None
43b{*23*}	946101	None

Justification for alerts:

- The checkCIF B-alerts for the crystal structures reported in this manuscript are principally due to the fact that Cu radiation, instead of the more traditional Mo radiation, was used to collect the diffraction data or that hydrogen atom parameters were actually refined instead of being fixed at idealized values. Most of the crystals (10 of 12) used in the present studies were too small to use with the in-house instrument that uses a Mo sealed-tube x-ray source. Since it is physically difficult to get close to full coverage at high diffraction angles with Cu radiation on a CCD diffractometer, four of the twelve structures (Compounds **3b**, **3d**, **S3d** and **29d**{*2*}; CCDC reference numbers 945414, 945419, 945421, and 945418) have PLAT029_ALERT_3_B_diffrn_measured_fraction _theta_full_Low alerts because their coverage was between 95% and 96% at a resolution of 0.844 Å. The alert B "threshold" value is 96% at this resolution.

- The PLAT222_ALERT_3_B Large Non-Solvent H Uiso(max)/Uiso(min) alert for Compound **3c** (CCDC reference # 945415) is due to the fact that hydrogen atom thermal parameters were actually refined instead of being fixed at a multiplier of the nonhydrogen atom to which it is covalently bonded. The ability to actually refine hydrogen atom parameters to reasonable values is an indication of high quality data. Some of the hydrogen isotropic thermal parameters refined to low (but positive) values.

- The PLAT089_ALERT_3_B Poor Data/Parameter Ratio alert for compound **S3c** (CCDC reference # 945417) is due to the facts that Cu radiation was used, hydrogen atom parameters were actually refined instead of being fixed at idealized values and the crystal utilized a noncentrosymmetric space group.

- The PLAT431_ALERT_2B Short Inter HL..A Contact Br..O alerts for Compounds **S6** and **S14** (CCDC Reference Nos. 945413 and 946099) are due to checkCIF's choice of van der Waals radii for Br and O. A contact of 3.03- 3.06 Å is not unreasonable.

- The PLATT410ALERT_2_B Short Intra H…H Contact for Compound **S6** (CCDC Reference # 945413) alert is caused by disorder.

- The PLAT031_ALERT_4_B Refined Extinction Parameter with Range…1.000 Sigma for compound **S3d** (CCDC Reference 945421) just informs you that the s.u. of the extinction parameter is the nearly the same as its value.

VII. Supplementary References:

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