Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Synthesis and pharmacological characterization of new tetrahydrofuran based compounds as conformationally constrained histamine receptor ligands

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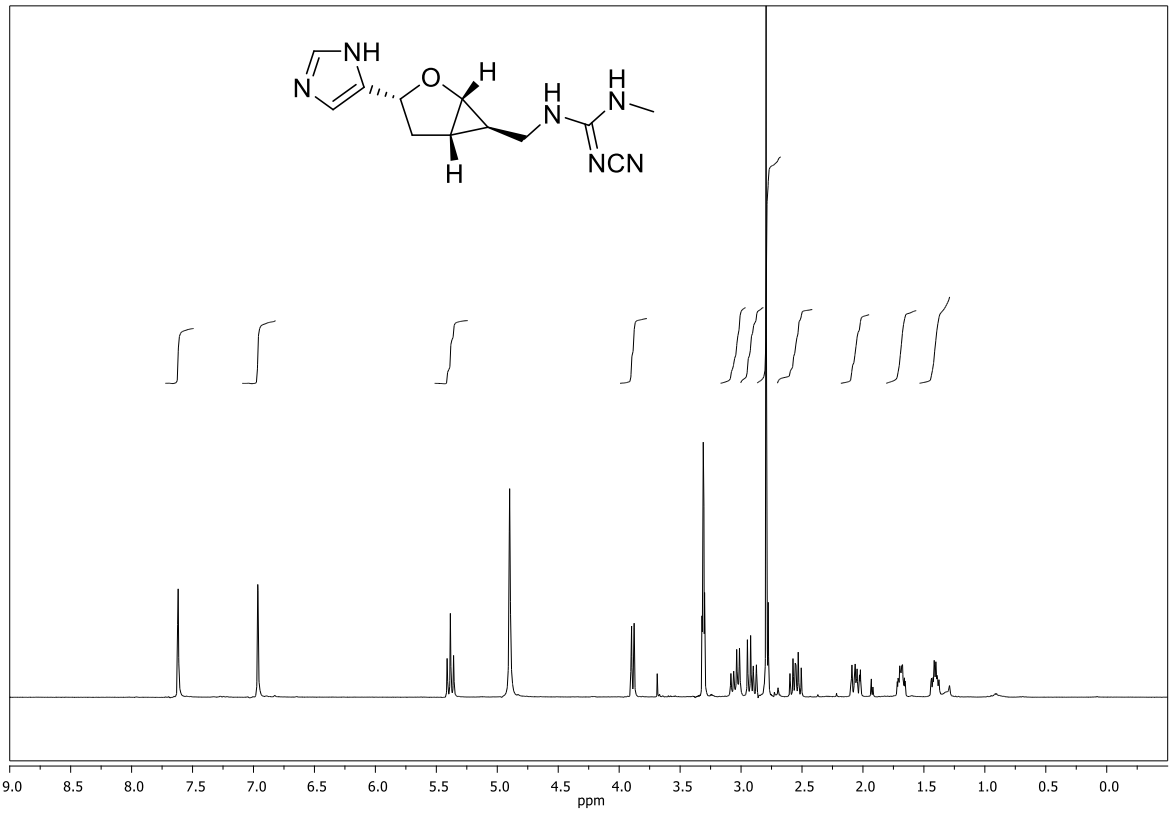
Supporting Information

Table of Content

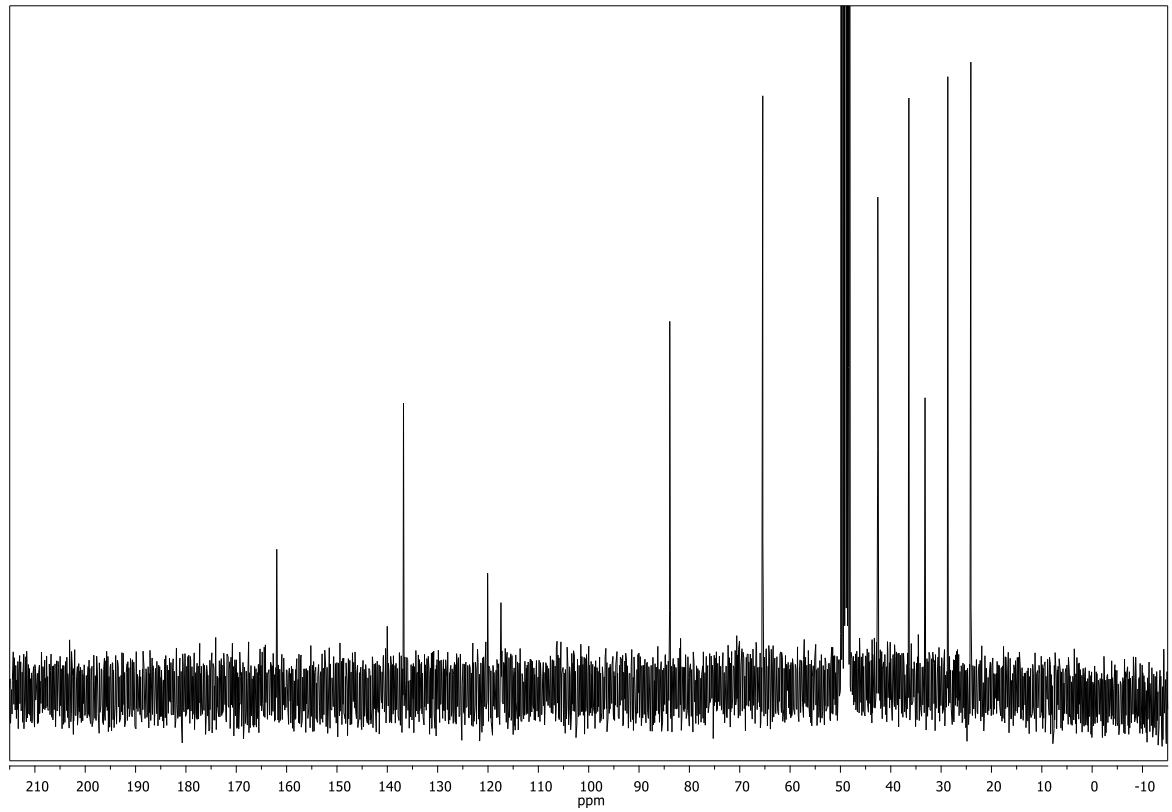
1. NMR Spectra

1-(((1*S*,3*R*,5*S*,6*R*)-3-(1*H*-imidazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)-2-cyano-3-methylguanidine (6a)

^{1}H-NMR (300 MHz, MeOD)

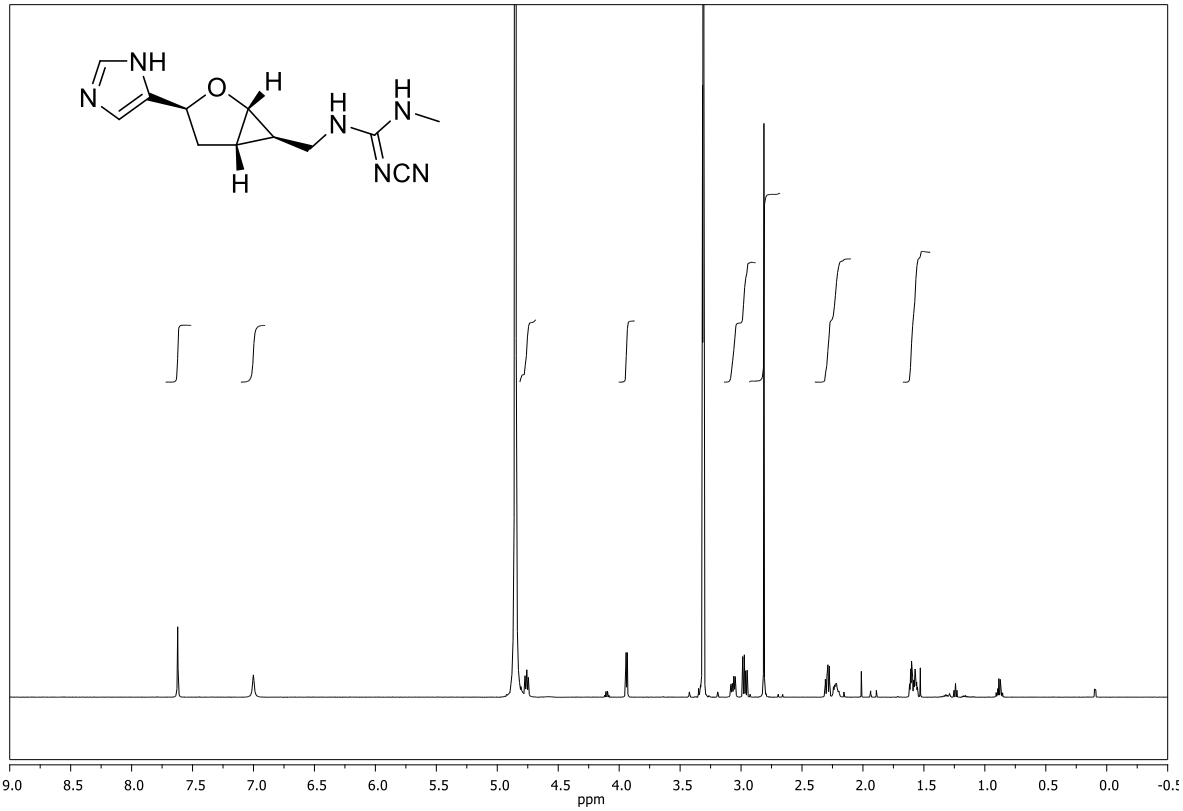


^{13}C-NMR (75 MHz, MeOD)

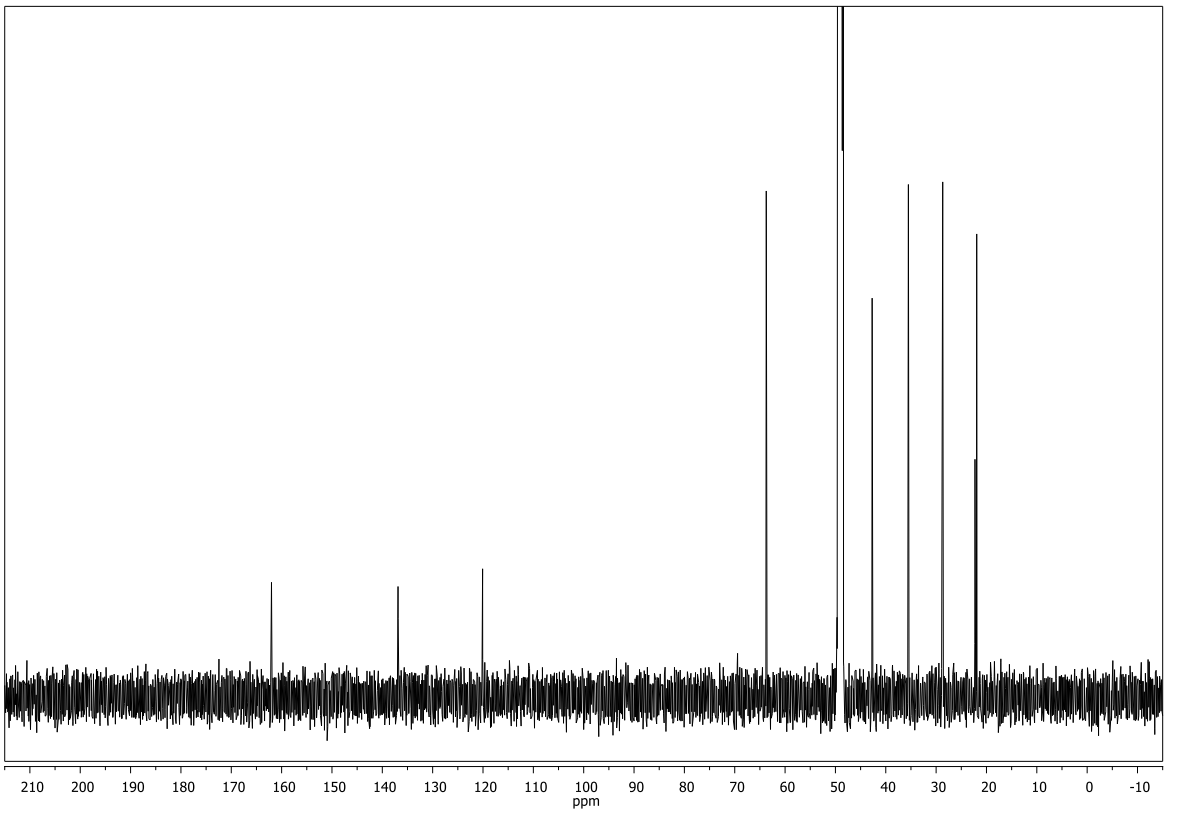


1-(((1*S*,3*S*,5*S*,6*R*)-3-(1*H*-imidazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)-2-cyano-3-methylguanidine (6b)

^{1}H-NMR (600 MHz, MeOD)

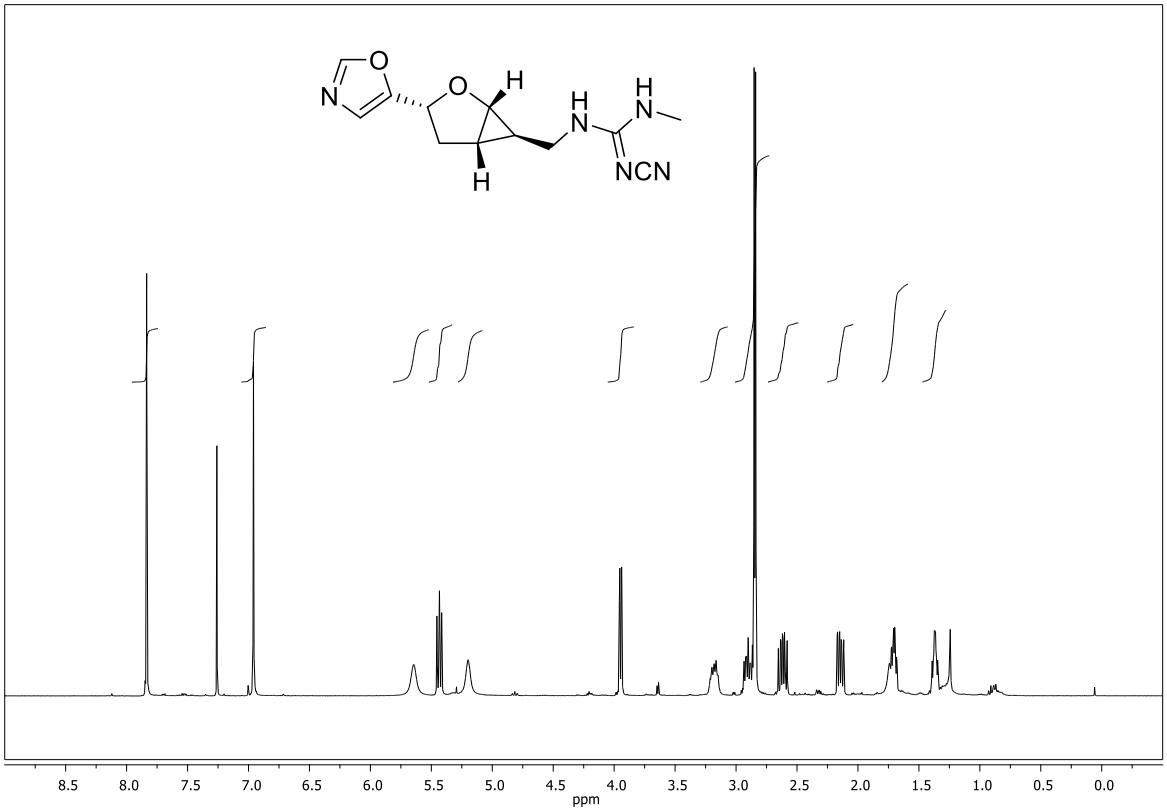


^{13}C-NMR (150 MHz, MeOD)

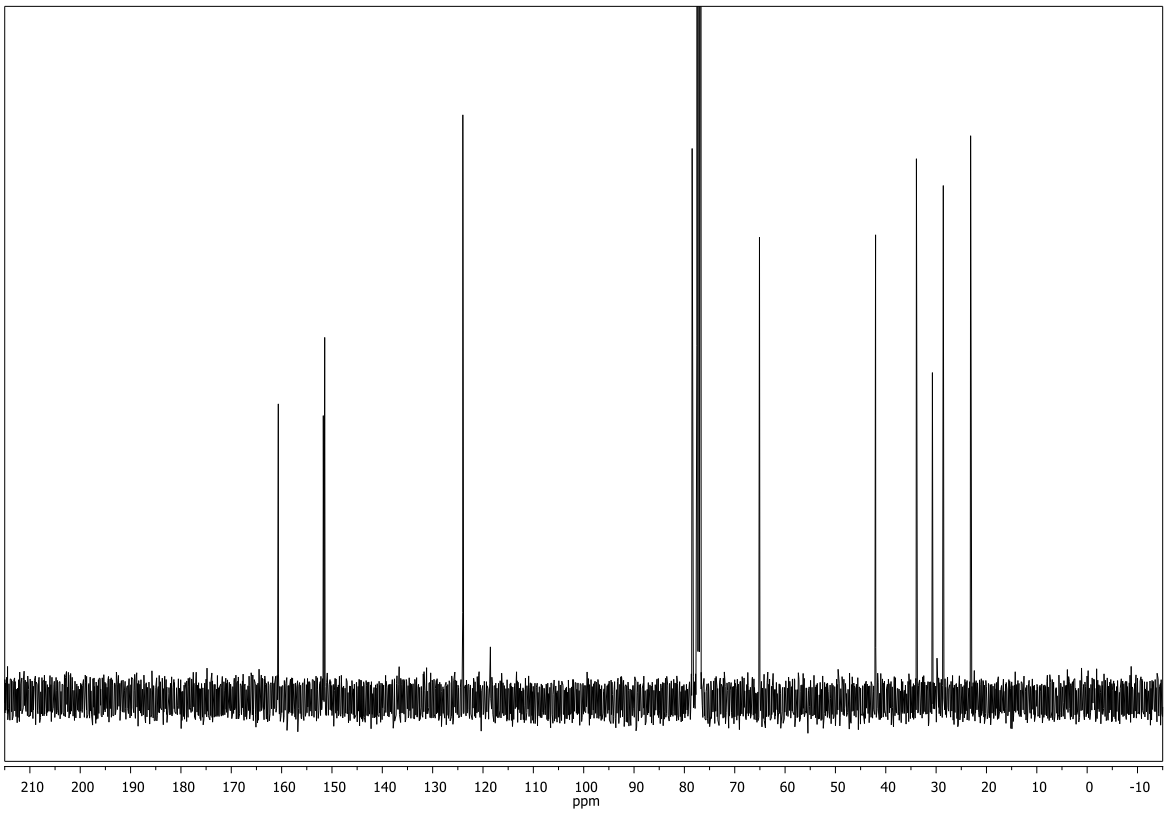


2-cyano-1-methyl-3-(((1*S*,3*R*,5*S*,6*R*)-3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl) guanidine (7a)

^{1}H-NMR (400 MHz, $CDCl_3$)

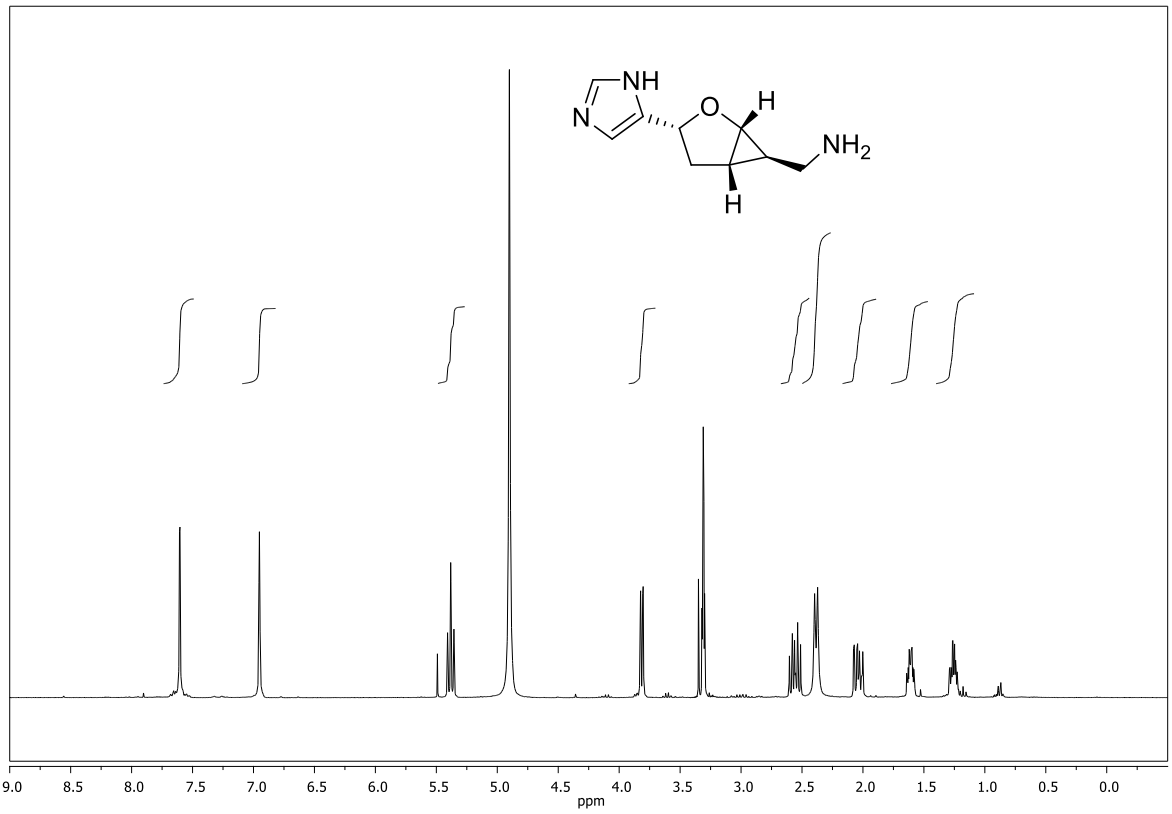


^{13}C-NMR (100 MHz, $CDCl_3$)

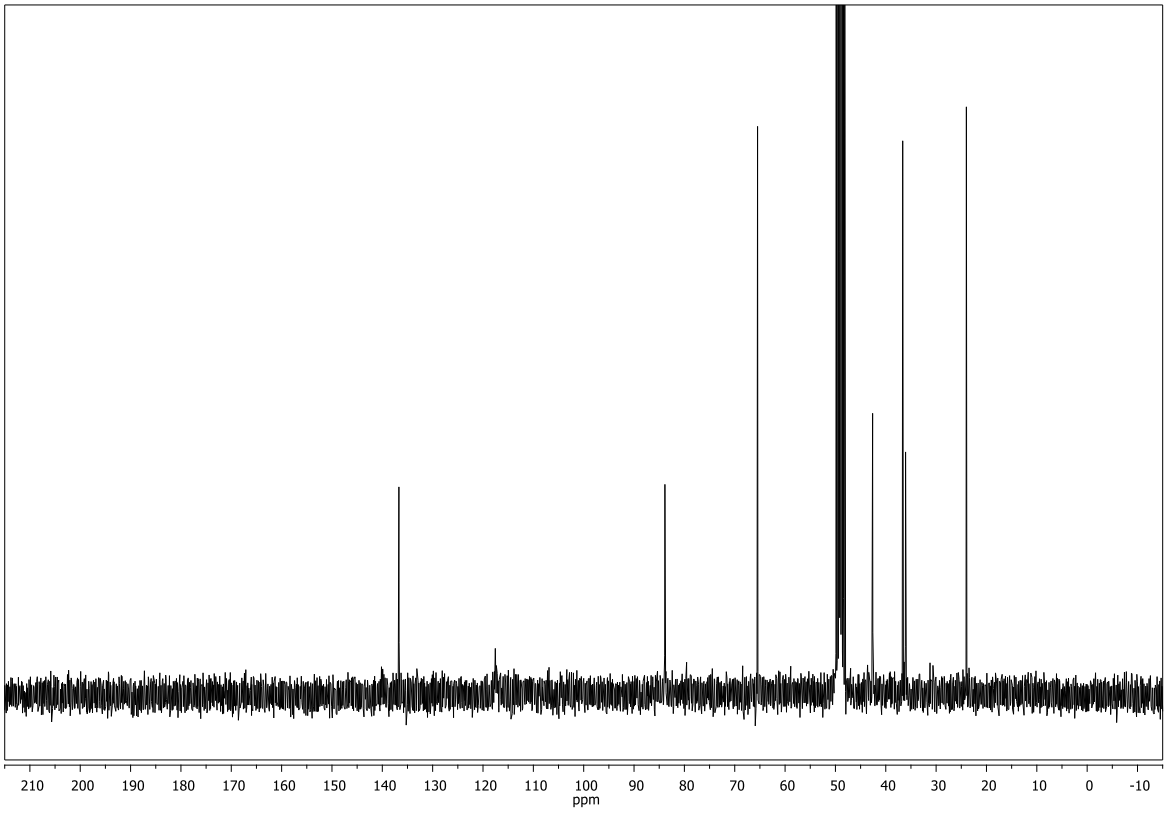


((1*S*,3*R*,5*S*,6*R*)-3-(1*H*-imidazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methanamine (8a)

^{1}H-NMR (300 MHz, MeOD)

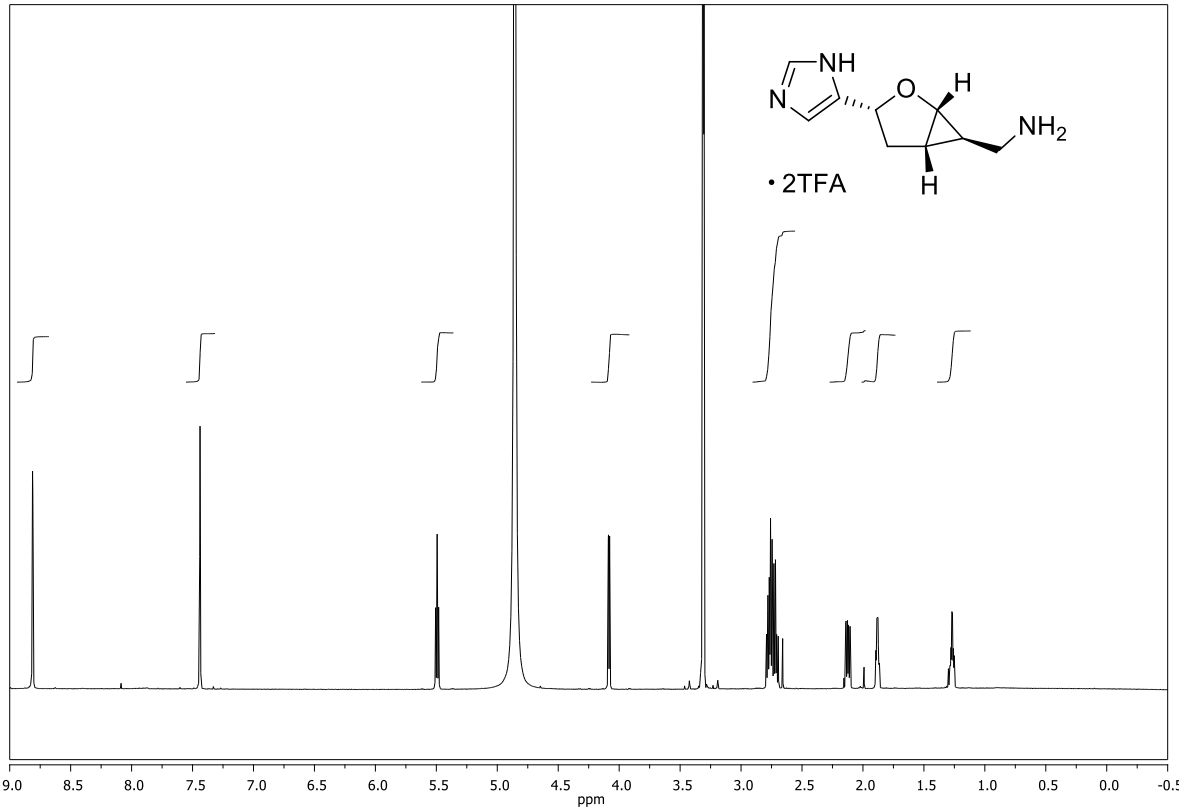


^{13}C-NMR (75 MHz, MeOD)

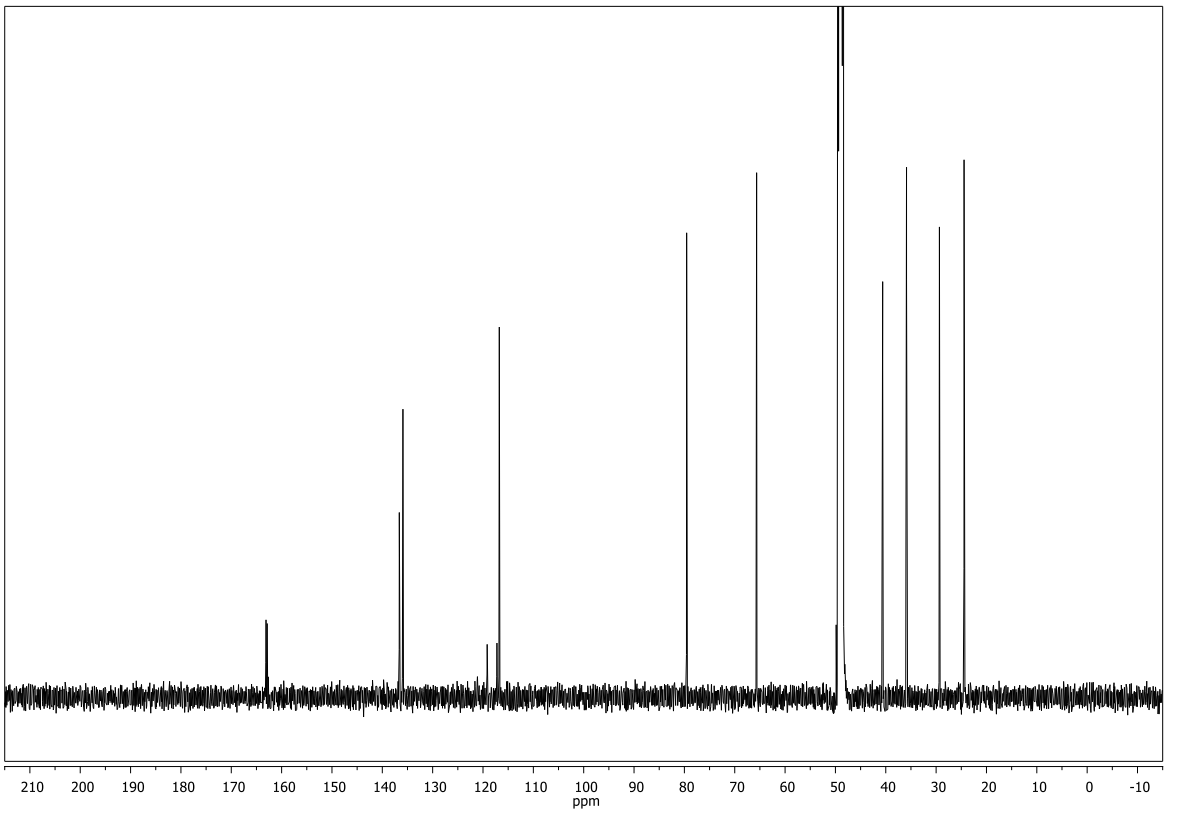


((1*S*,3*R*,5*S*,6*R*)-3-(1*H*-imidazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methanamine • 2TFA (8a•2TFA)

^{1}H-NMR (600 MHz, MeOD)

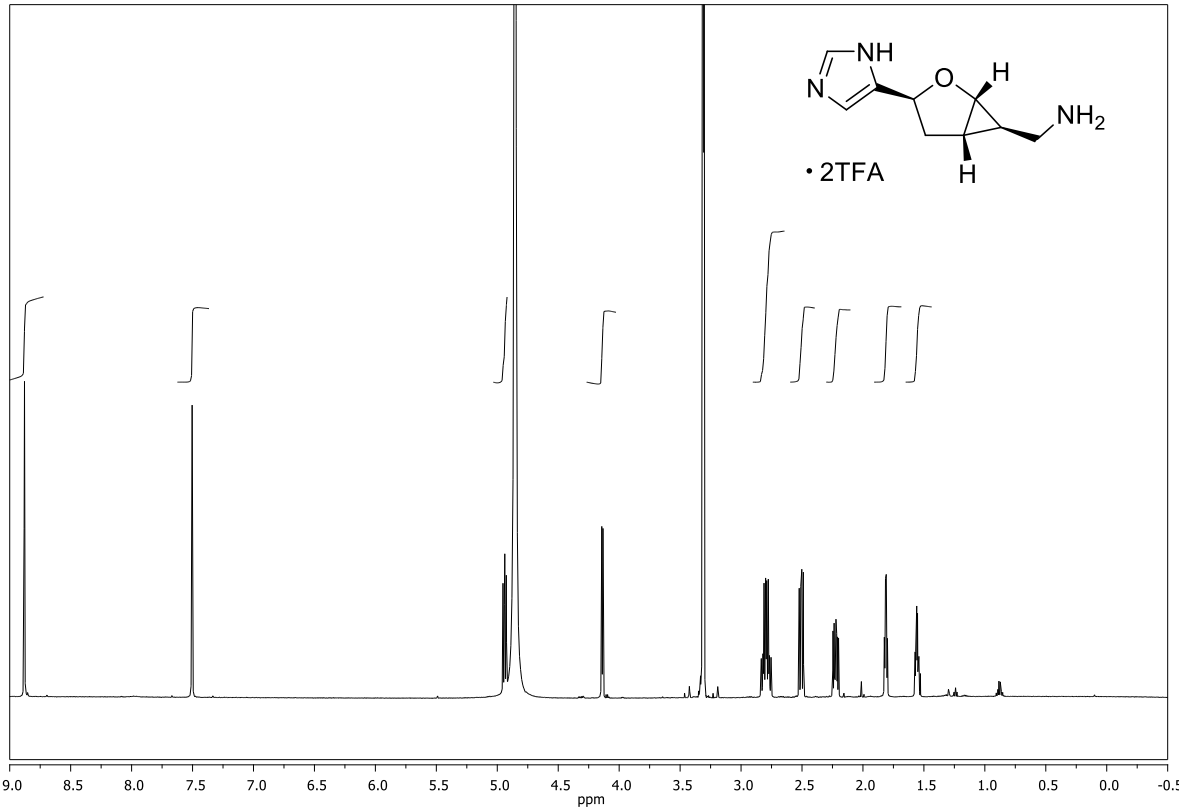


^{13}C-NMR (150 MHz, MeOD)

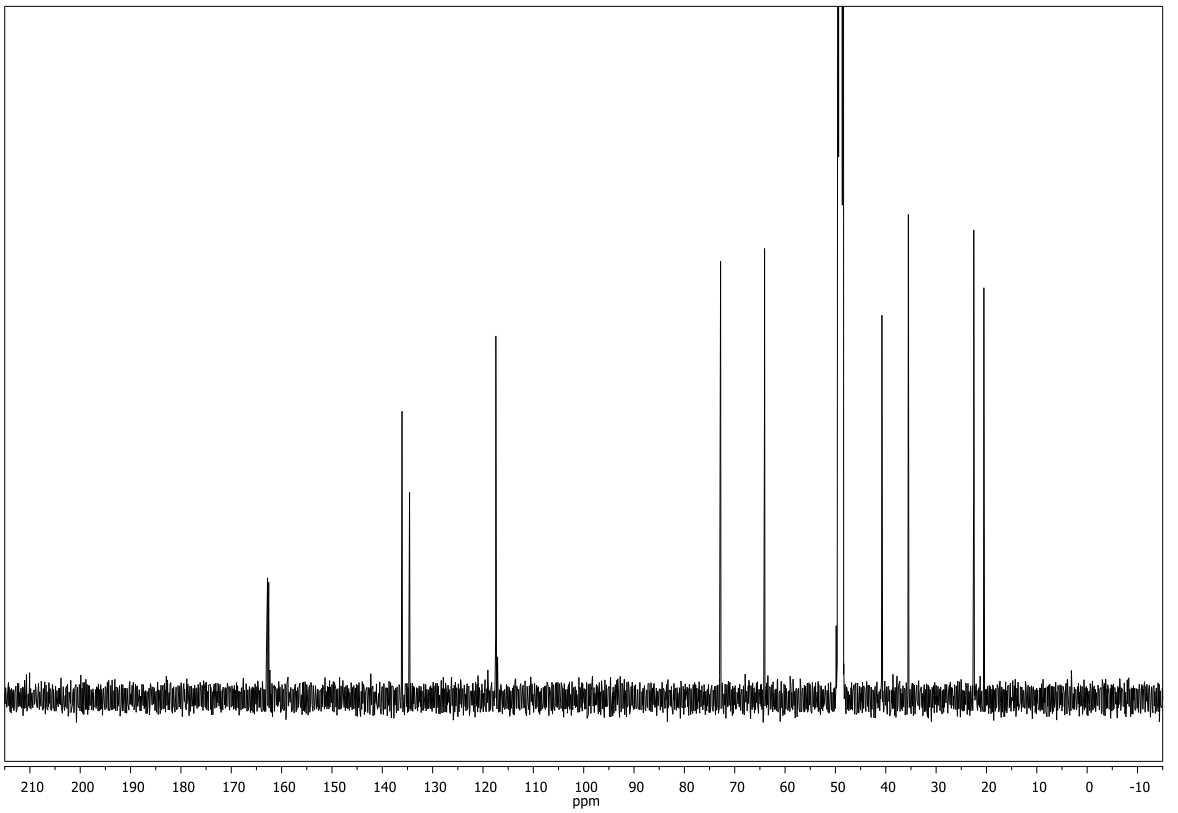


((1*S*,3*S*,5*S*,6*R*)-3-(1*H*-imidazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methanamine • 2TFA 8b•2TFA)

^{1}H-NMR (600 MHz, MeOD)

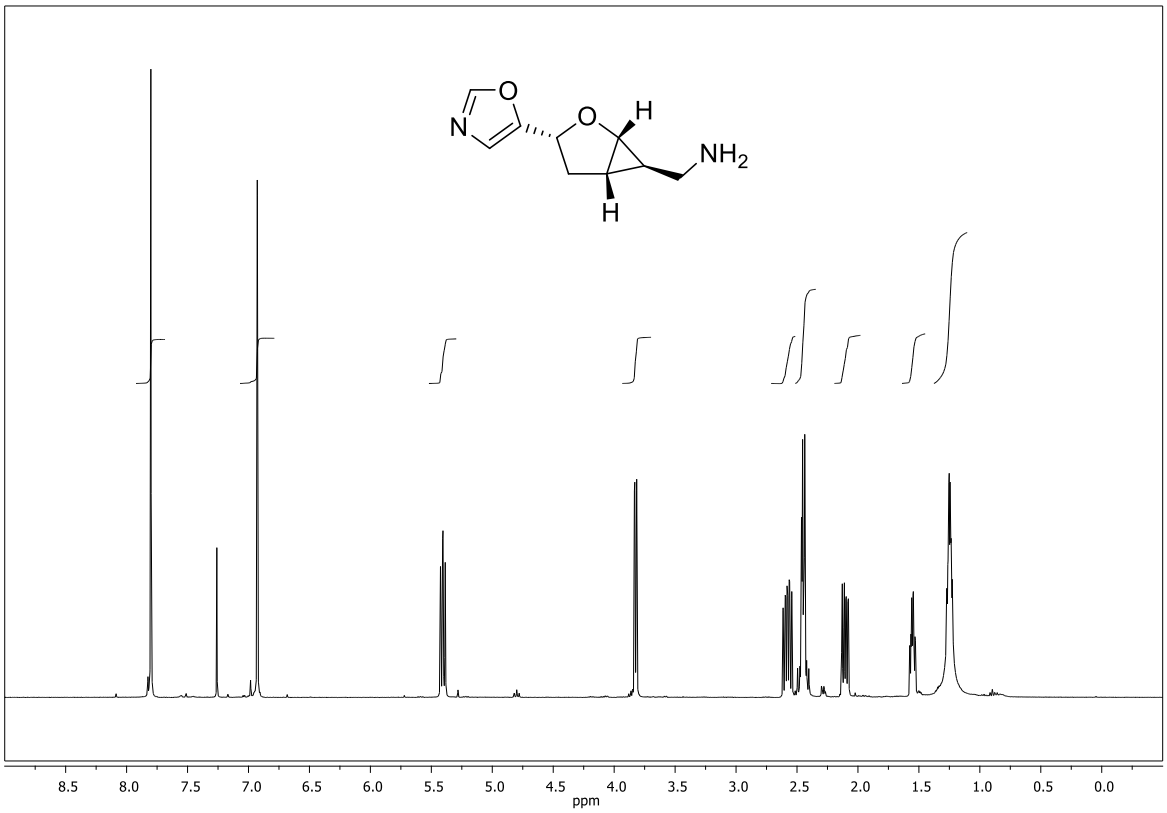


^{13}C-NMR (150 MHz, MeOD)

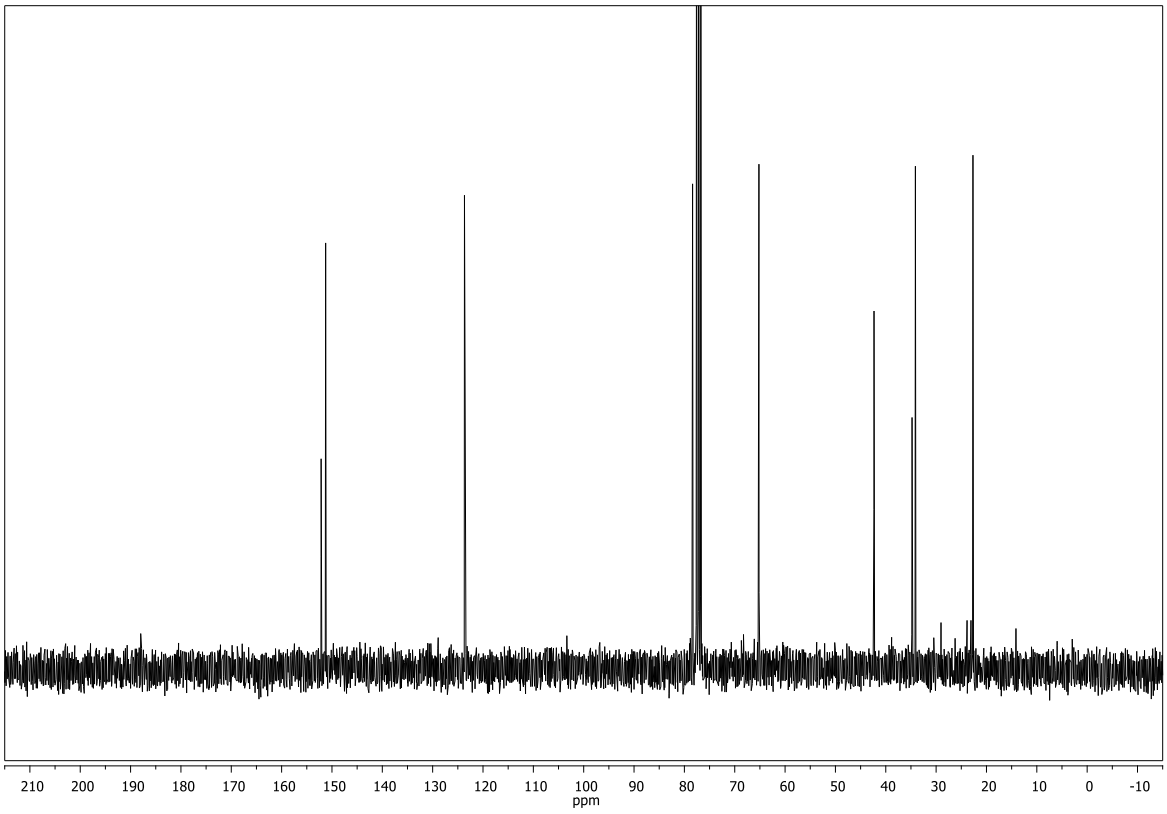


((1*S*,3*R*,5*S*,6*R*)-3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methanamine (9a)

^{1}H-NMR (400 MHz, $CDCl_3$)

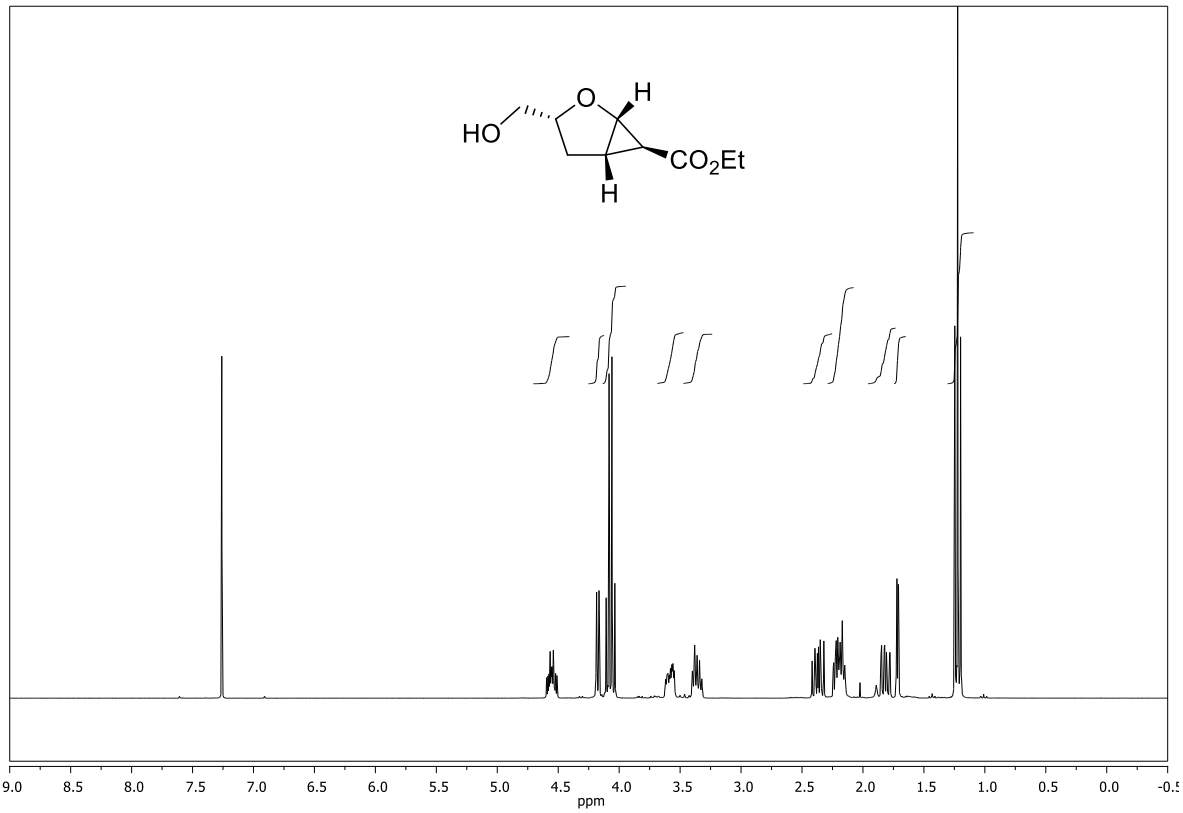


^{13}C-NMR (75 MHz, $CDCl_3$)

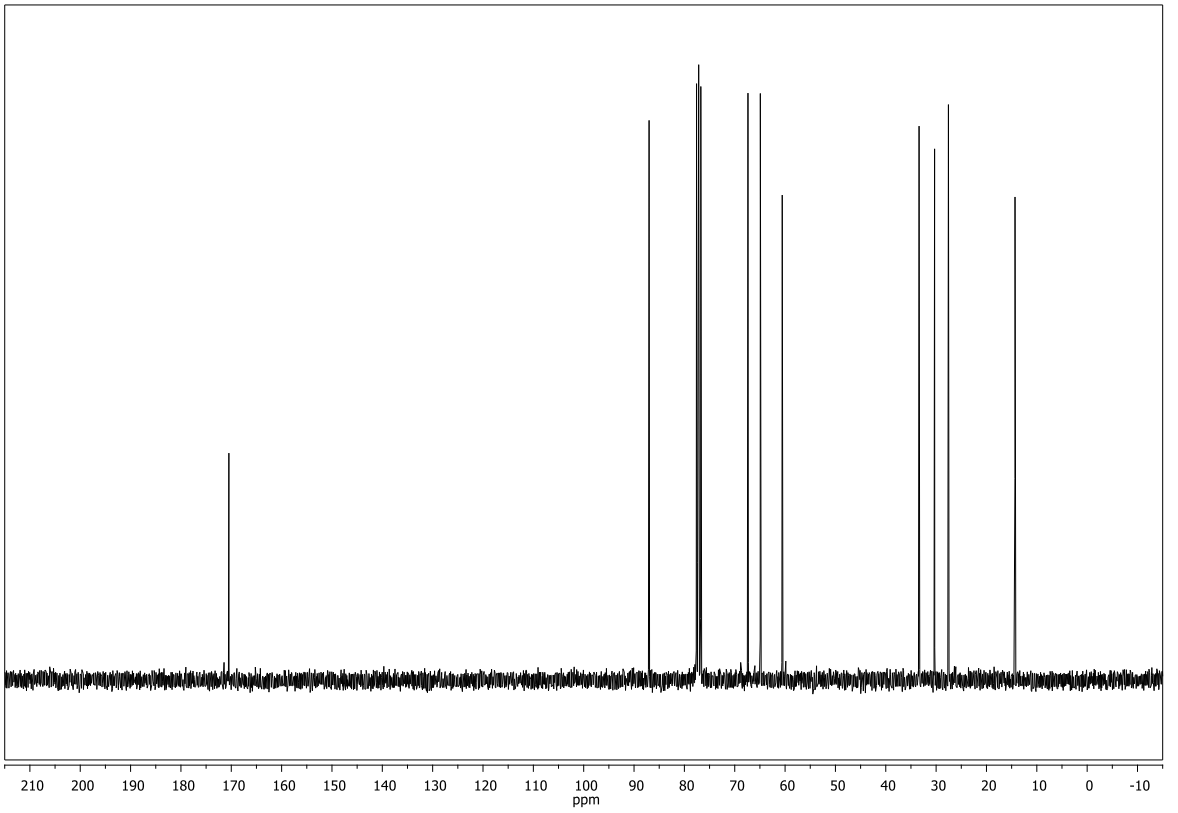


(1*S*,3*R*,5*S*,6*S*)-ethyl 3-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (14)

^{1}H-NMR (300 MHz, $CDCl_3$)

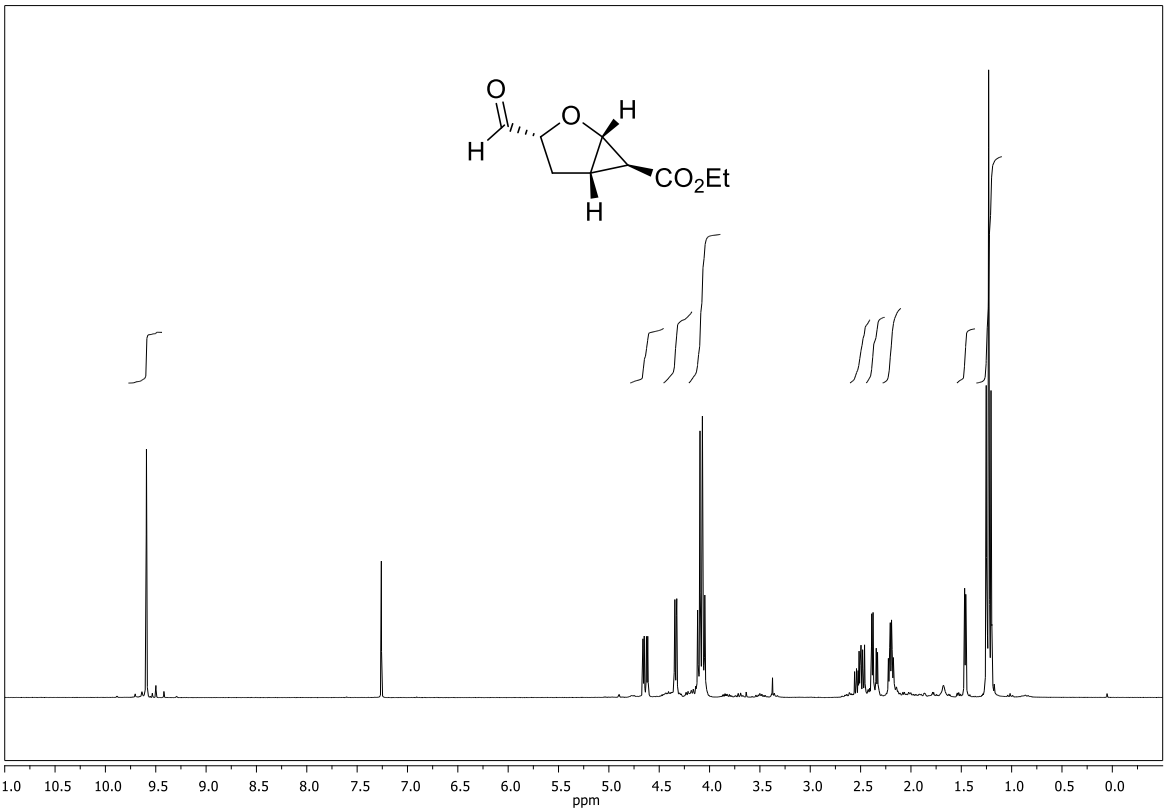


^{13}C-NMR (75 MHz, $CDCl_3$)

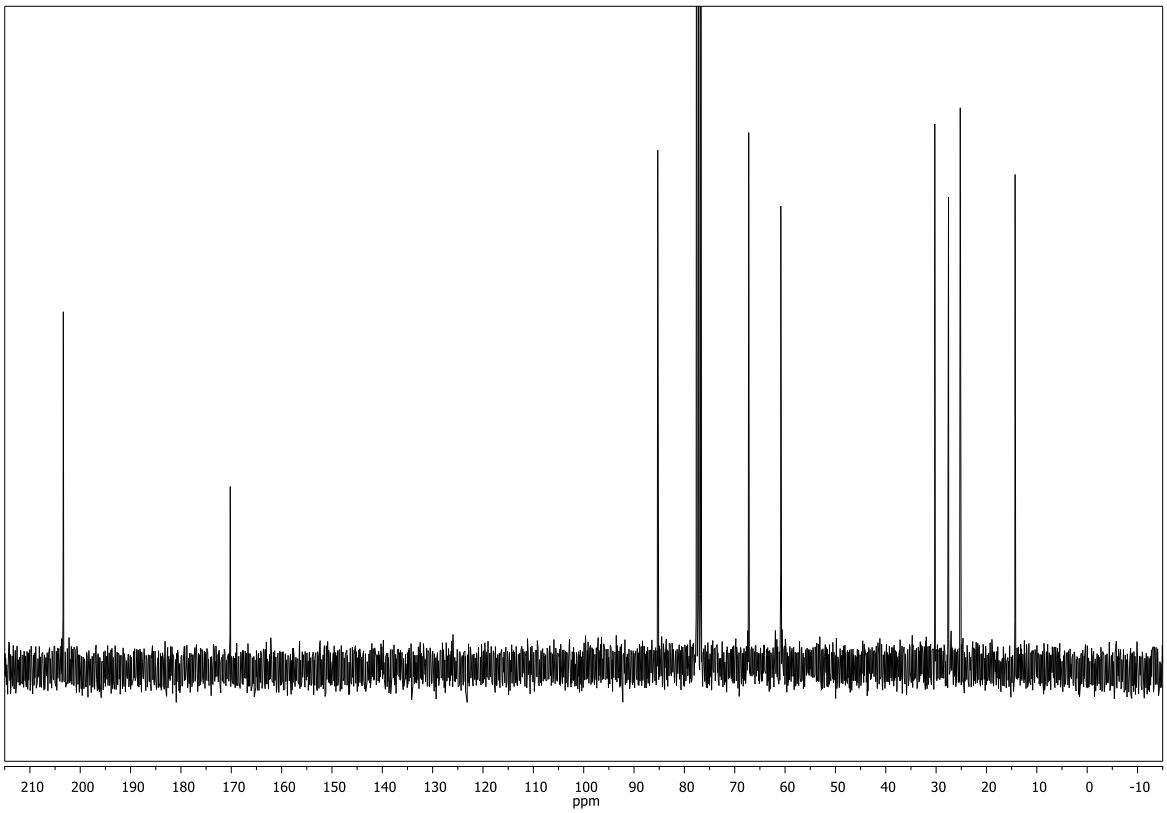


(1*S*,3*R*,5*S*,6*S*)-ethyl 3-formyl-2-oxabicyclo[3.1.0]hexane-6-carboxylate (15)

^{1}H-NMR (300 MHz, $CDCl_3$)

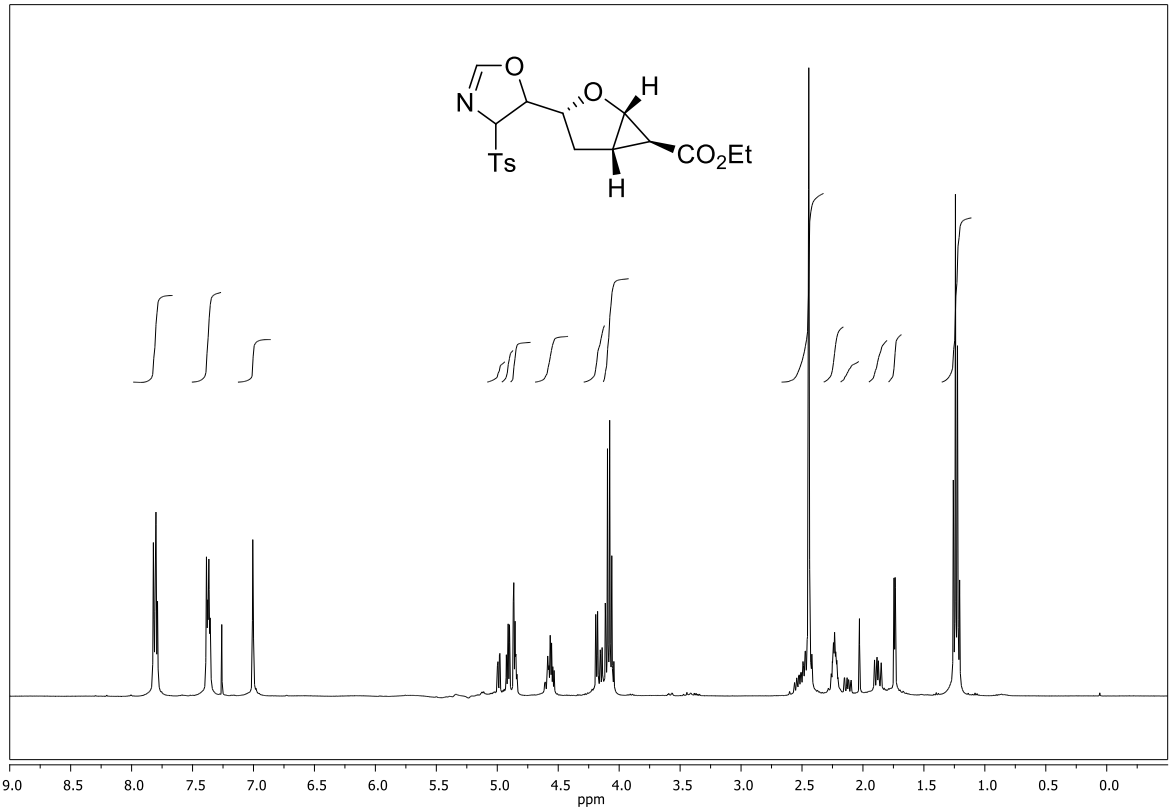


^{13}C-NMR (75 MHz, $CDCl_3$)

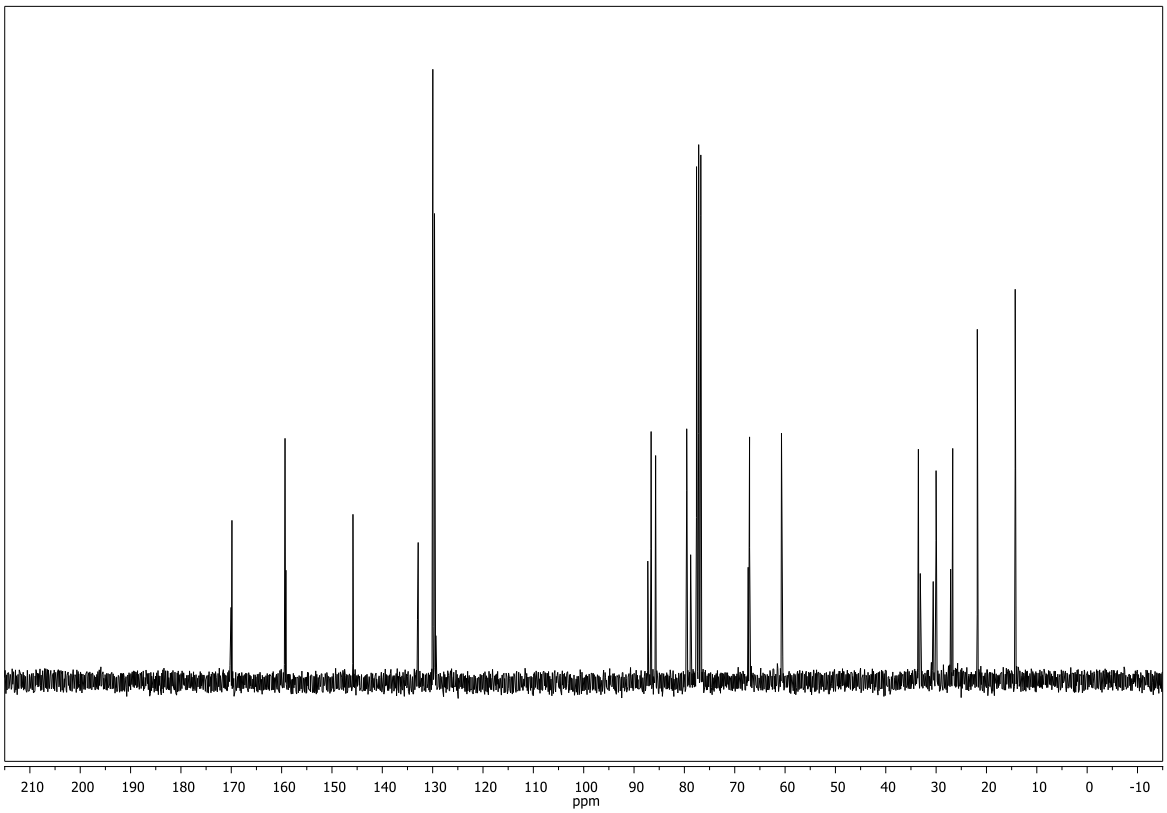


(1*S*,3*R*,5*S*,6*S*)-ethyl 3-(4-tosyl-4,5-dihydrooxazol-5-yl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (16)

^{1}H-NMR (400 MHz, $CDCl_3$)

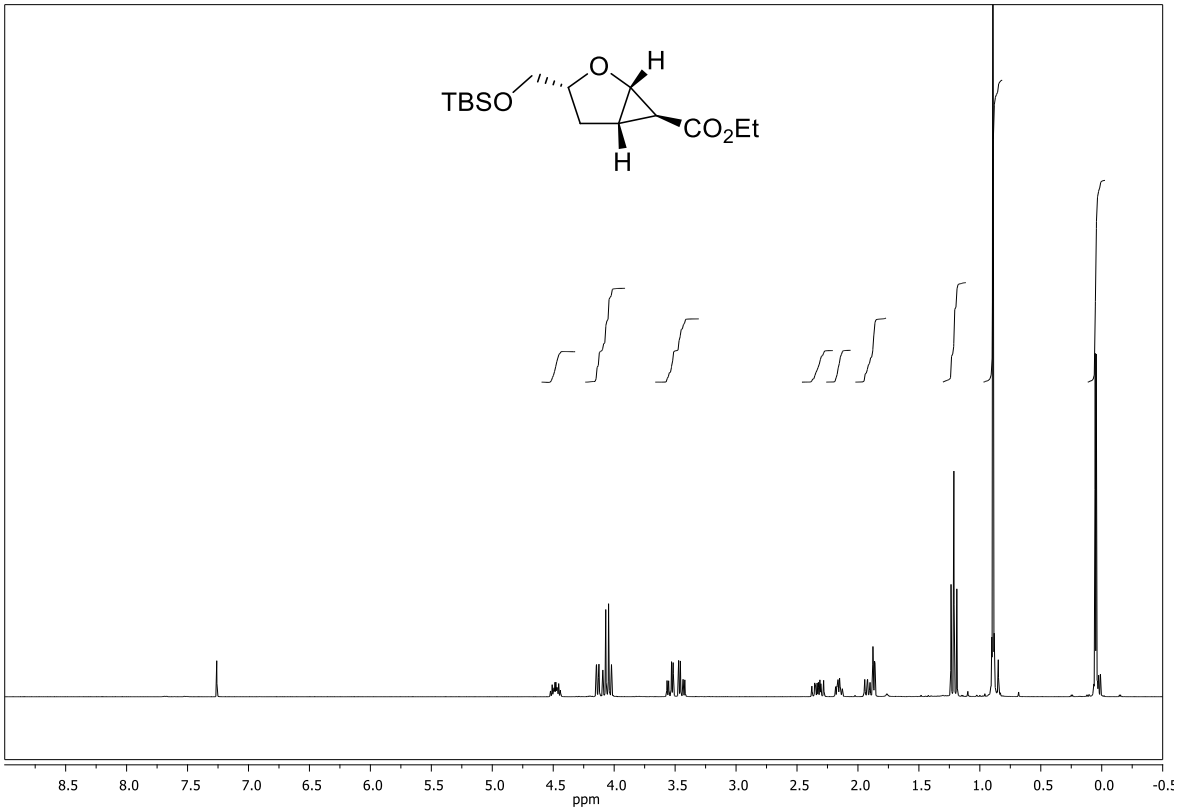


^{13}C-NMR (75 MHz, $CDCl_3$)

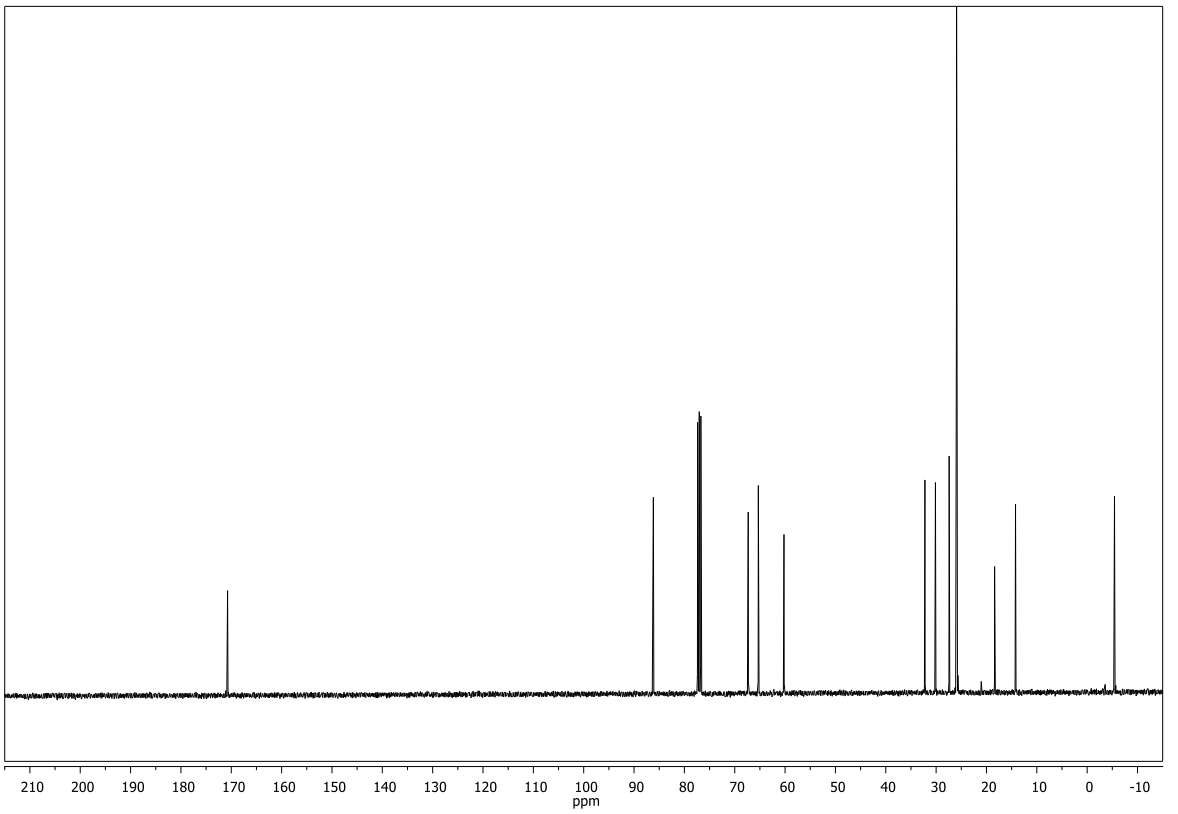


(1*S*,3*R*,5*S*,6*S*)-ethyl 3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (18)

^{1}H-NMR (300 MHz, $CDCl_3$)

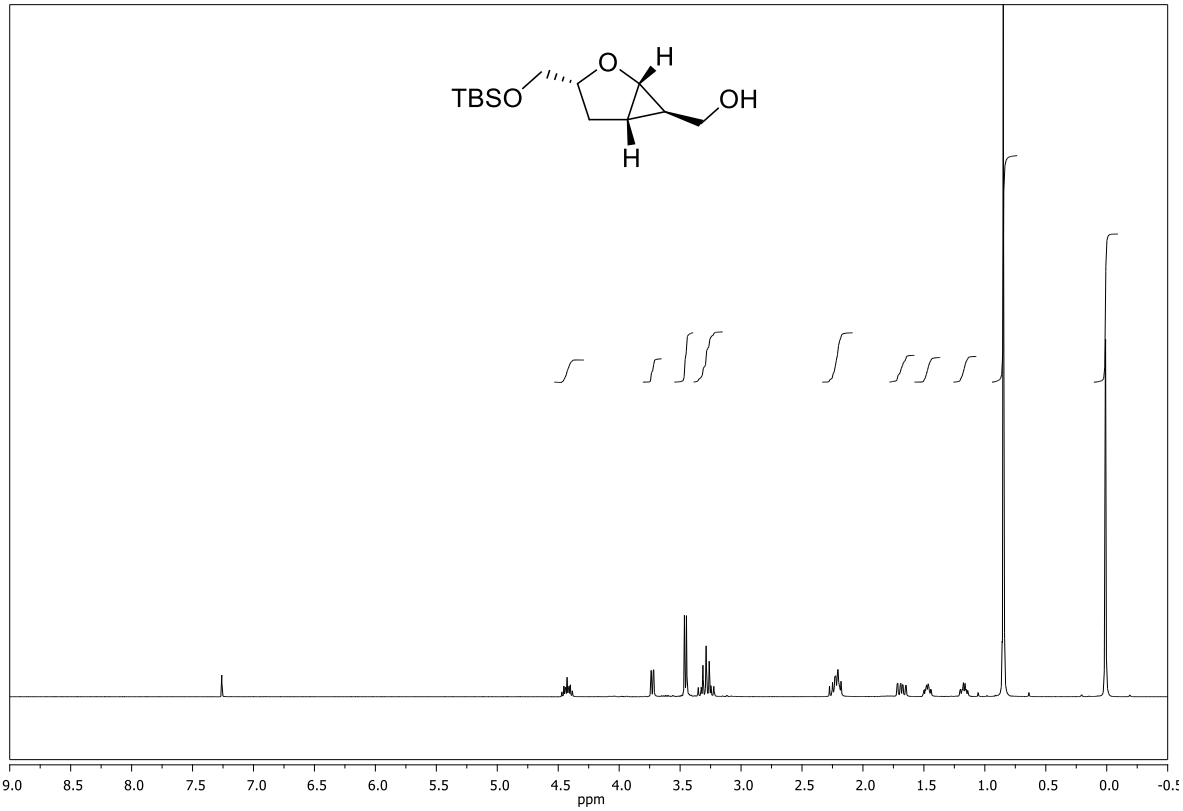


^{13}C-NMR (100 MHz, $CDCl_3$)

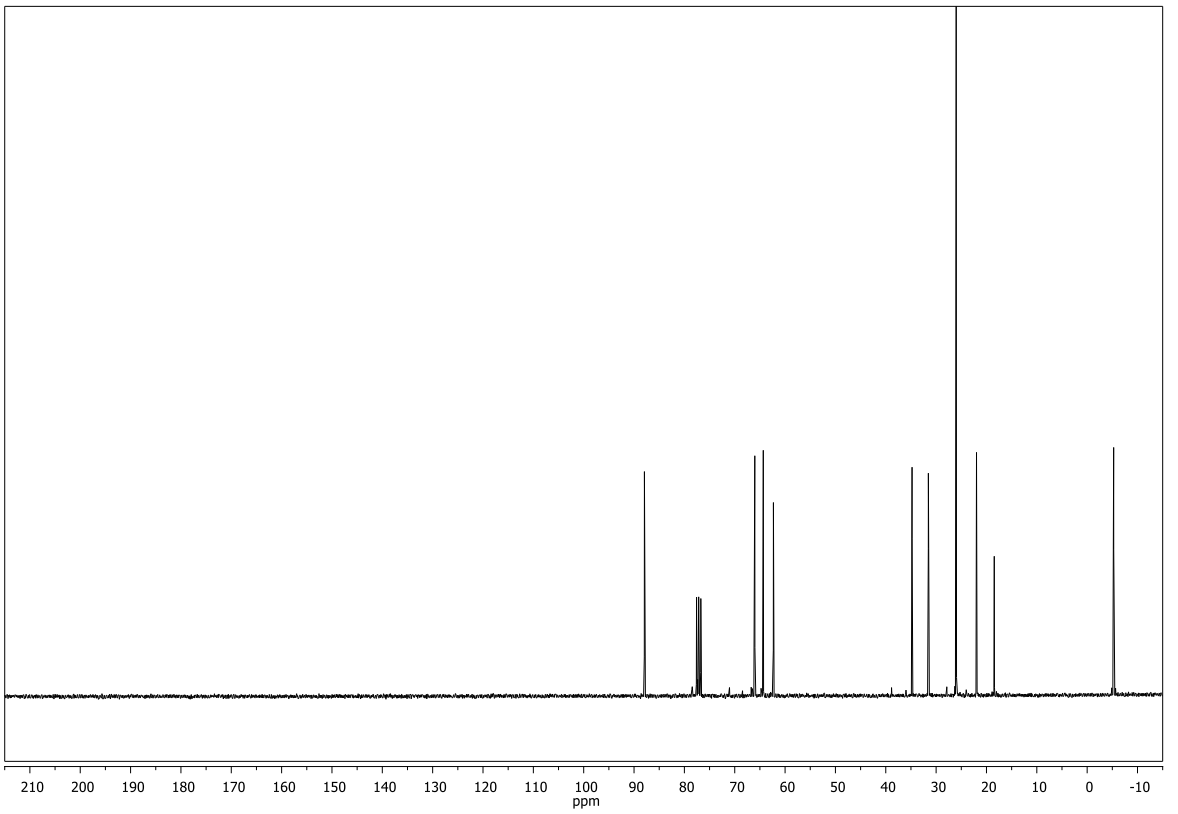


((1*S*,3*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexan-6-yl)-methanol (19)

^{1}H-NMR (300 MHz, $CDCl_3$)

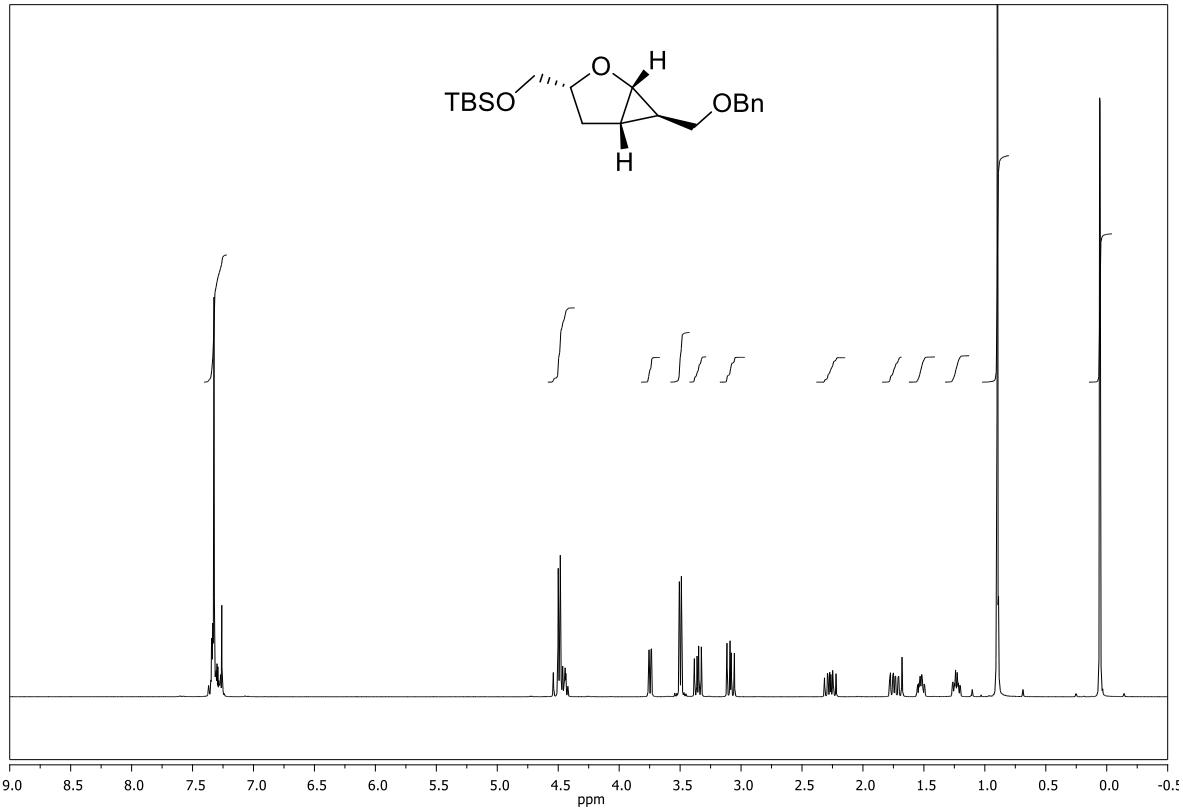


^{13}C-NMR (75 MHz, $CDCl_3$)

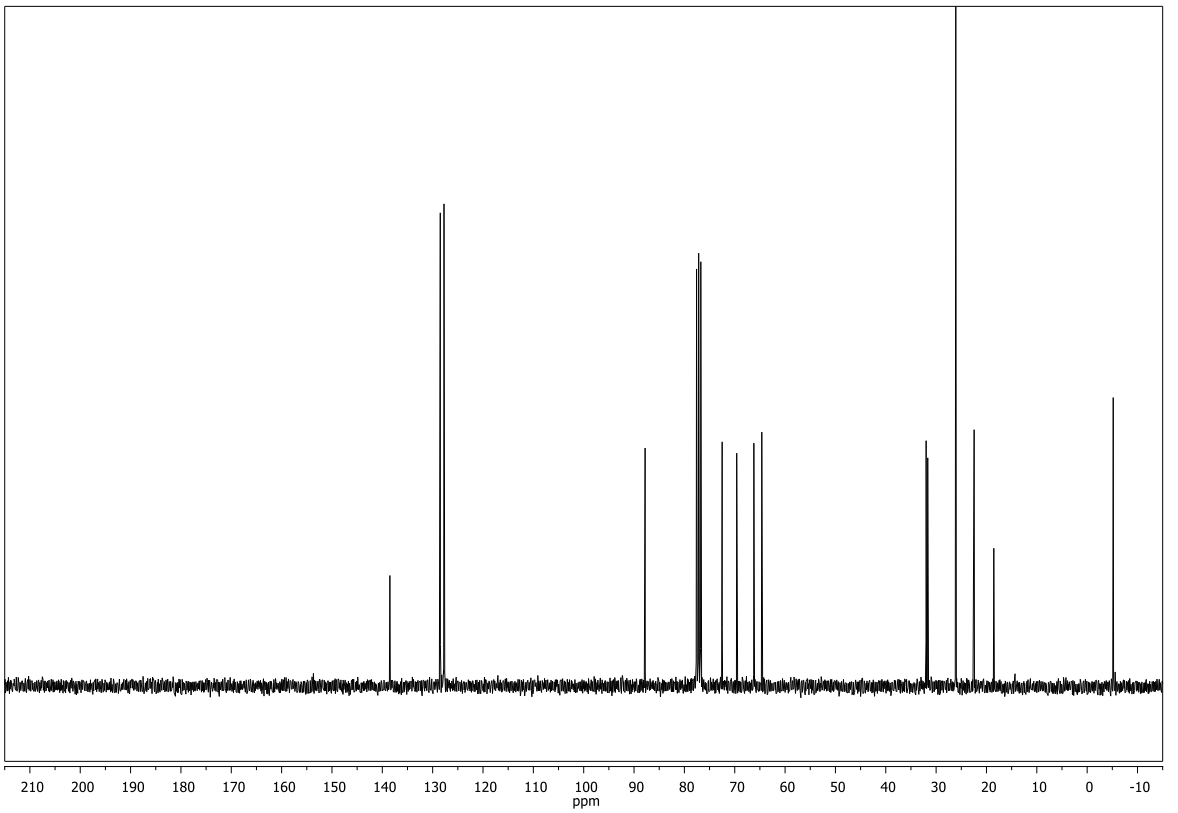


(((1*S*,3*R*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)methoxy)(*tert*-butyl)-dimethylsilane (20)

^{1}H-NMR (300 MHz, $CDCl_3$)

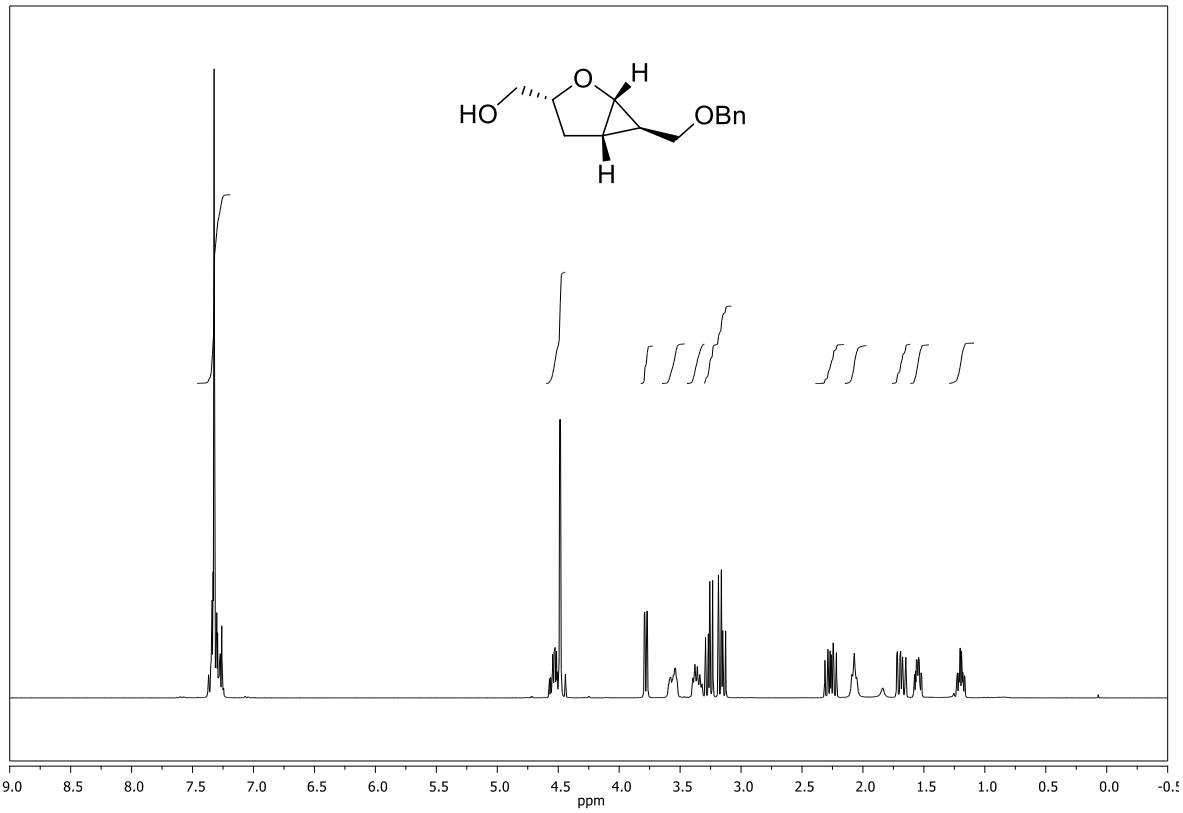


^{13}C-NMR (75 MHz, $CDCl_3$)

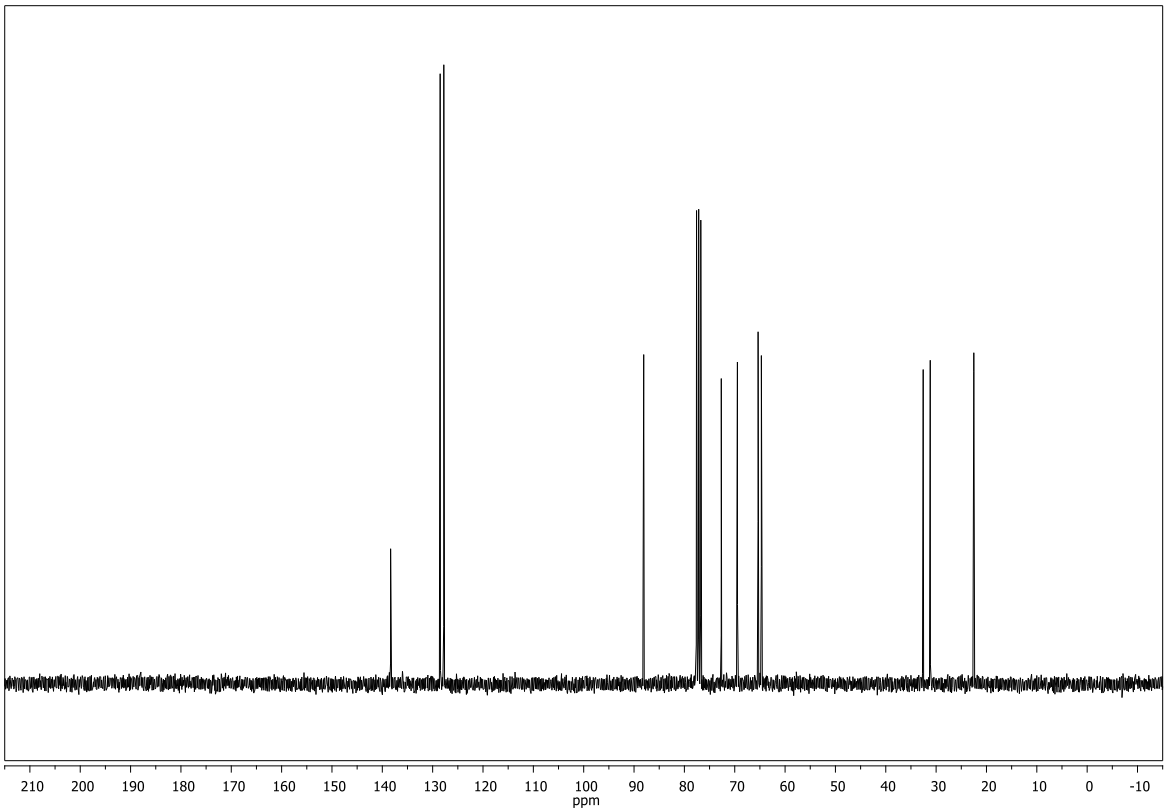


(1*S*,3*R*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)methanol (21)

^{1}H-NMR (300 MHz, $CDCl_3$)

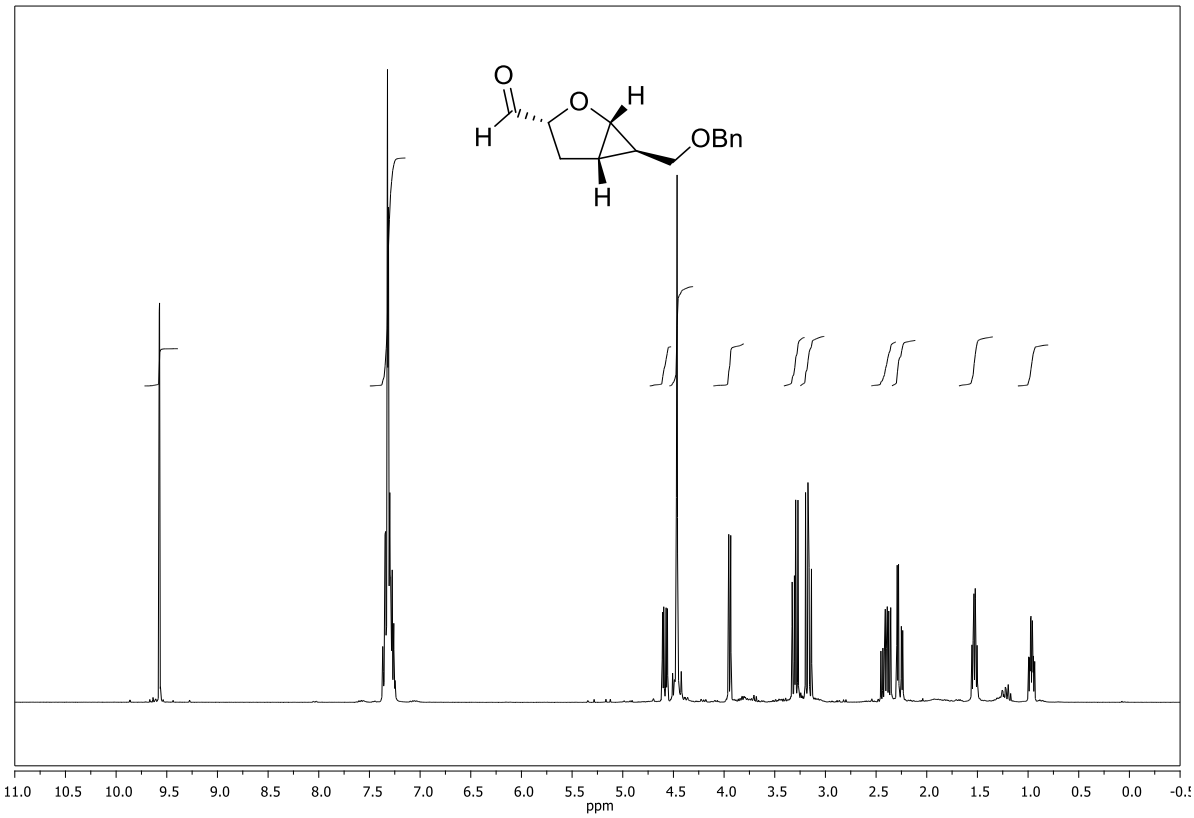


^{13}C-NMR (75 MHz, $CDCl_3$)

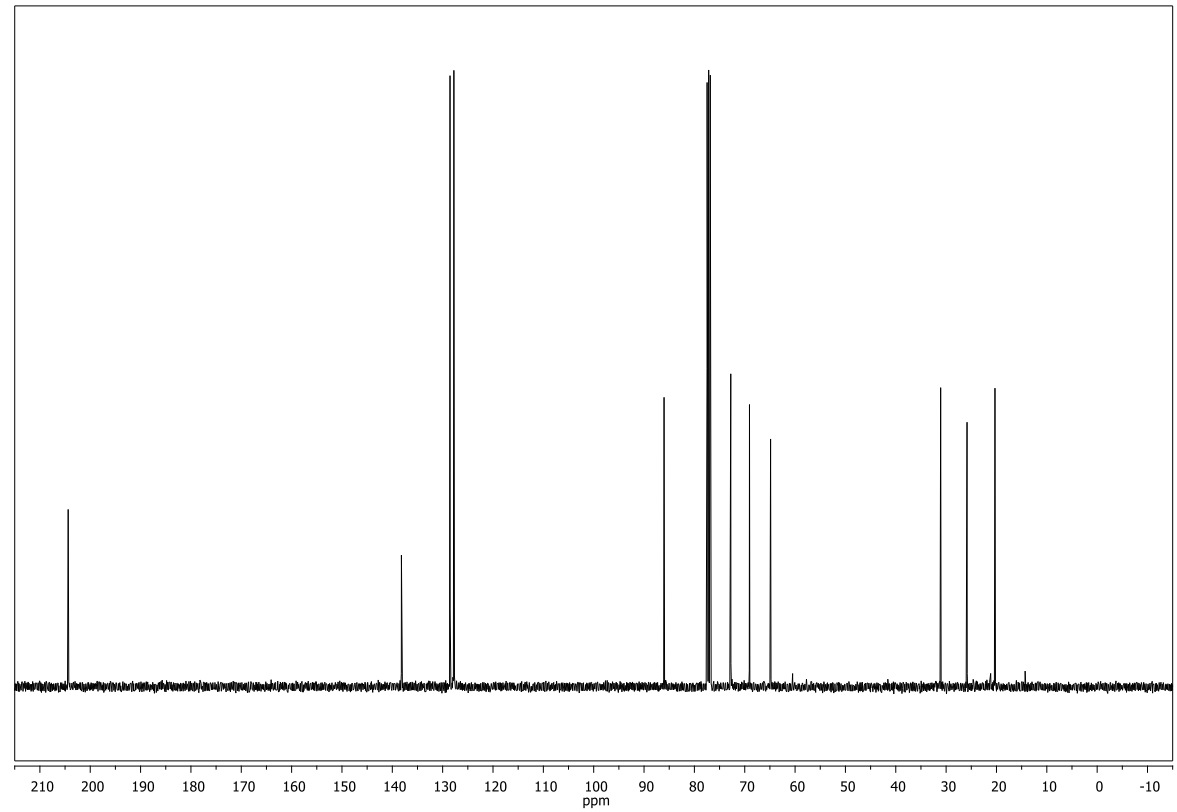


(1*S*,3*R*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexane-3-carbaldehyde (22)

^{1}H-NMR (300 MHz, $CDCl_3$)

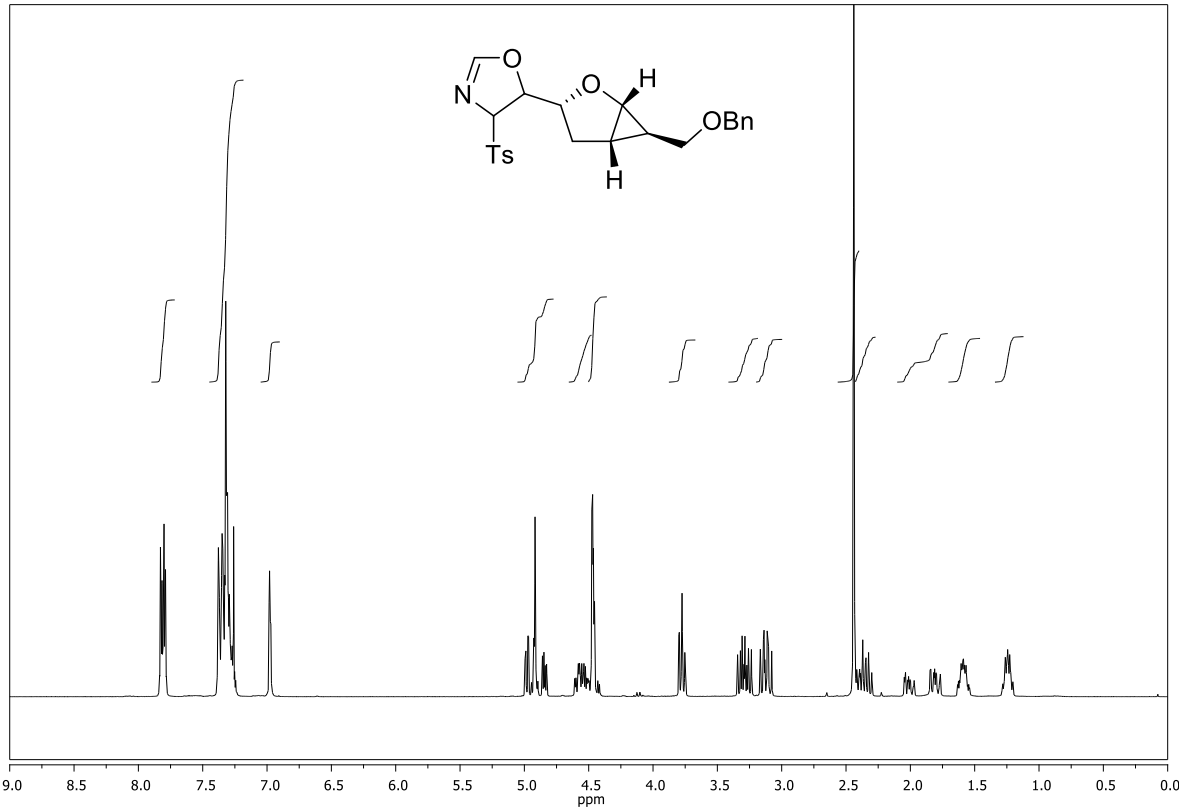


^{13}C-NMR (100 MHz, $CDCl_3$)

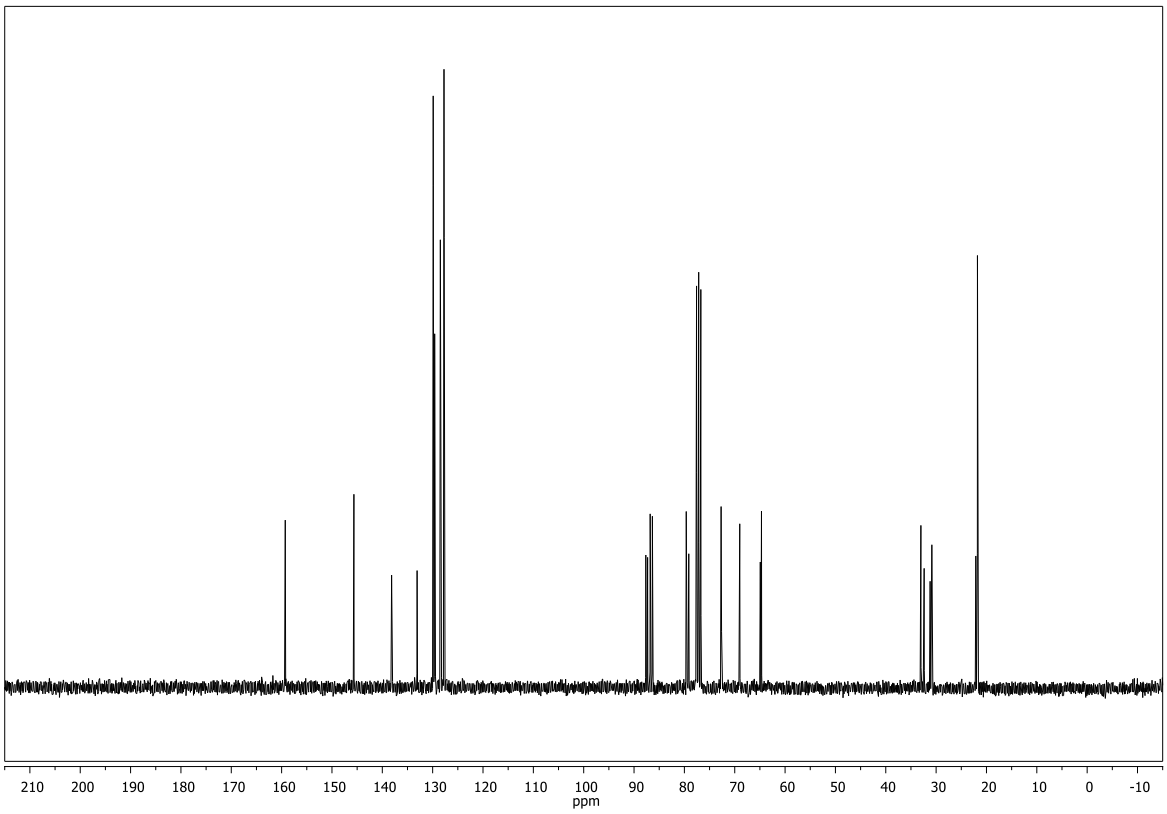


5-((1*S*,3*R*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-4-tosyl-4,5-dihydrooxazole (23)

^{1}H-NMR (300 MHz, $CDCl_3$)

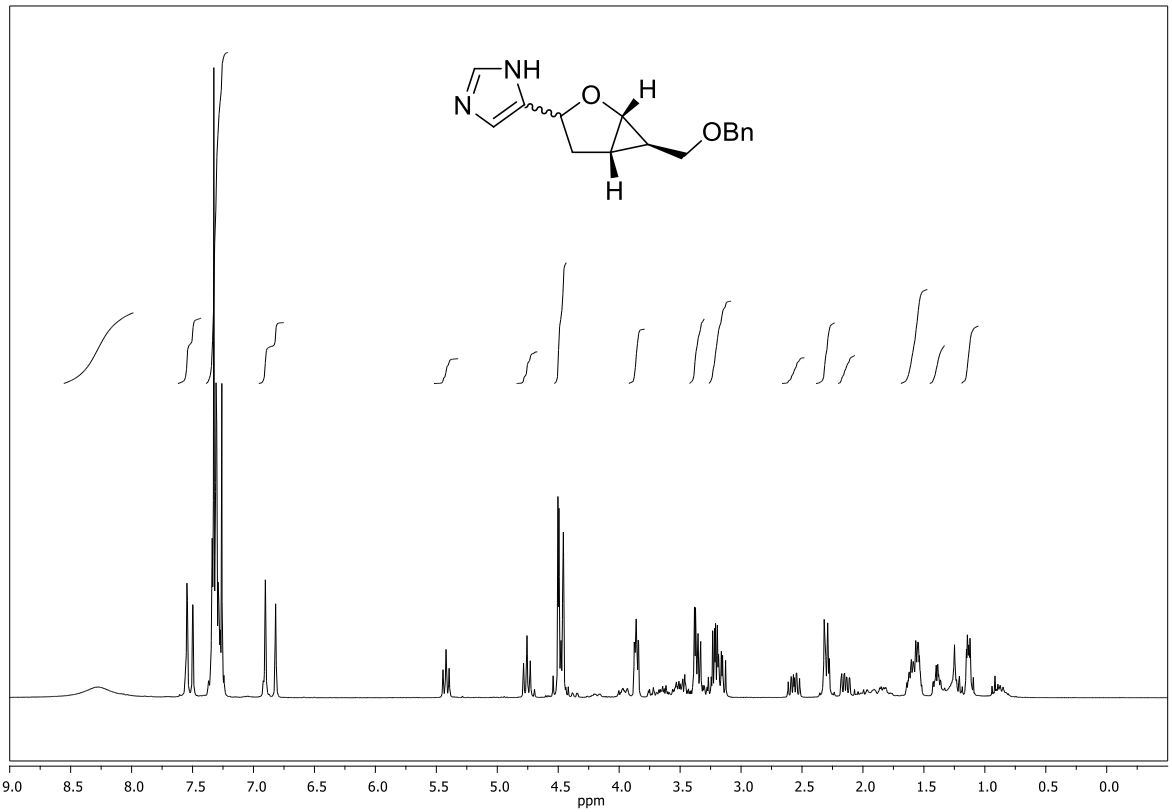


^{13}C-NMR (75 MHz, $CDCl_3$)

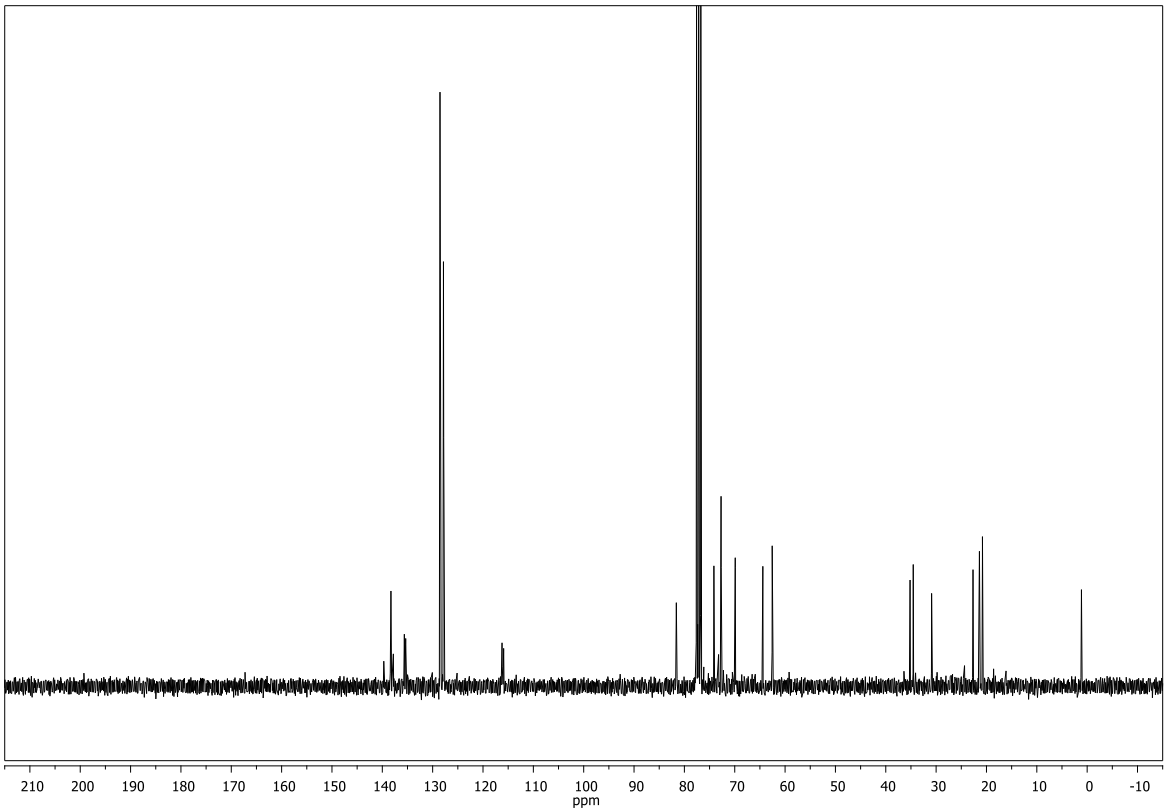


5-((1*S*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole (24ab)

^{1}H-NMR (300 MHz, $CDCl_3$)

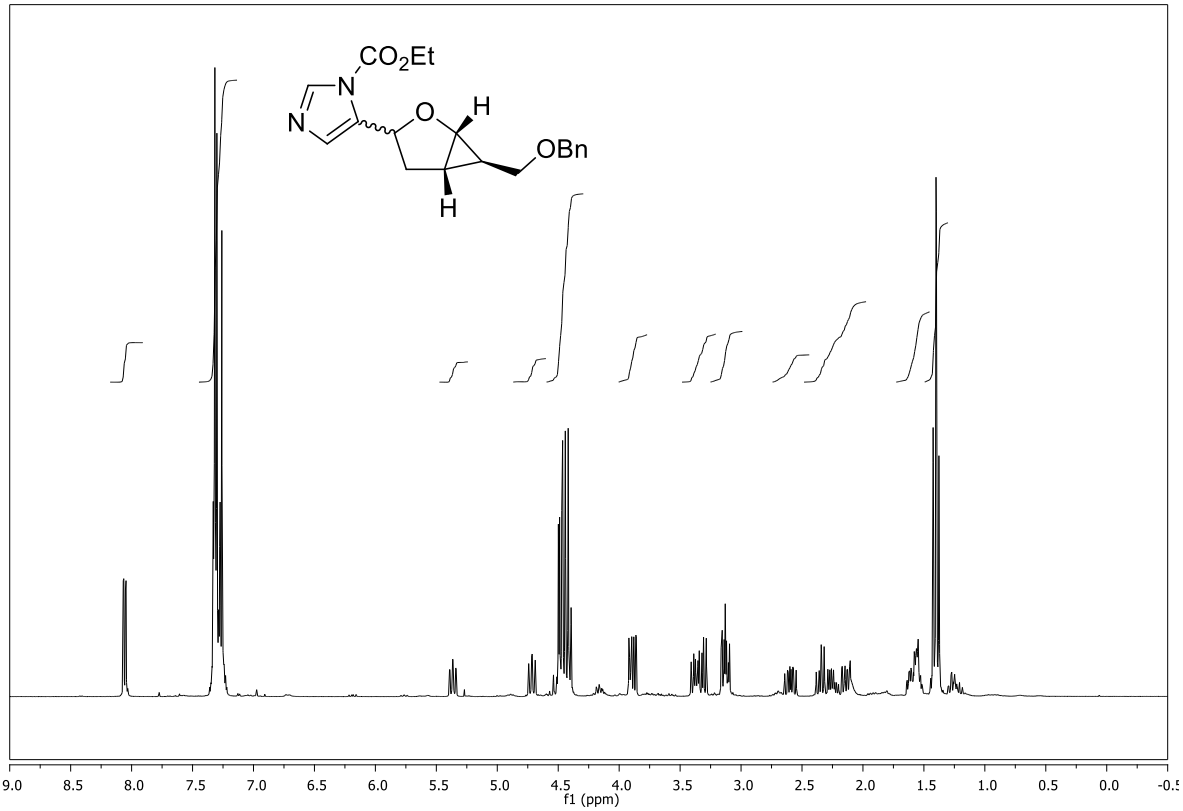


^{13}C-NMR (75 MHz, $CDCl_3$)

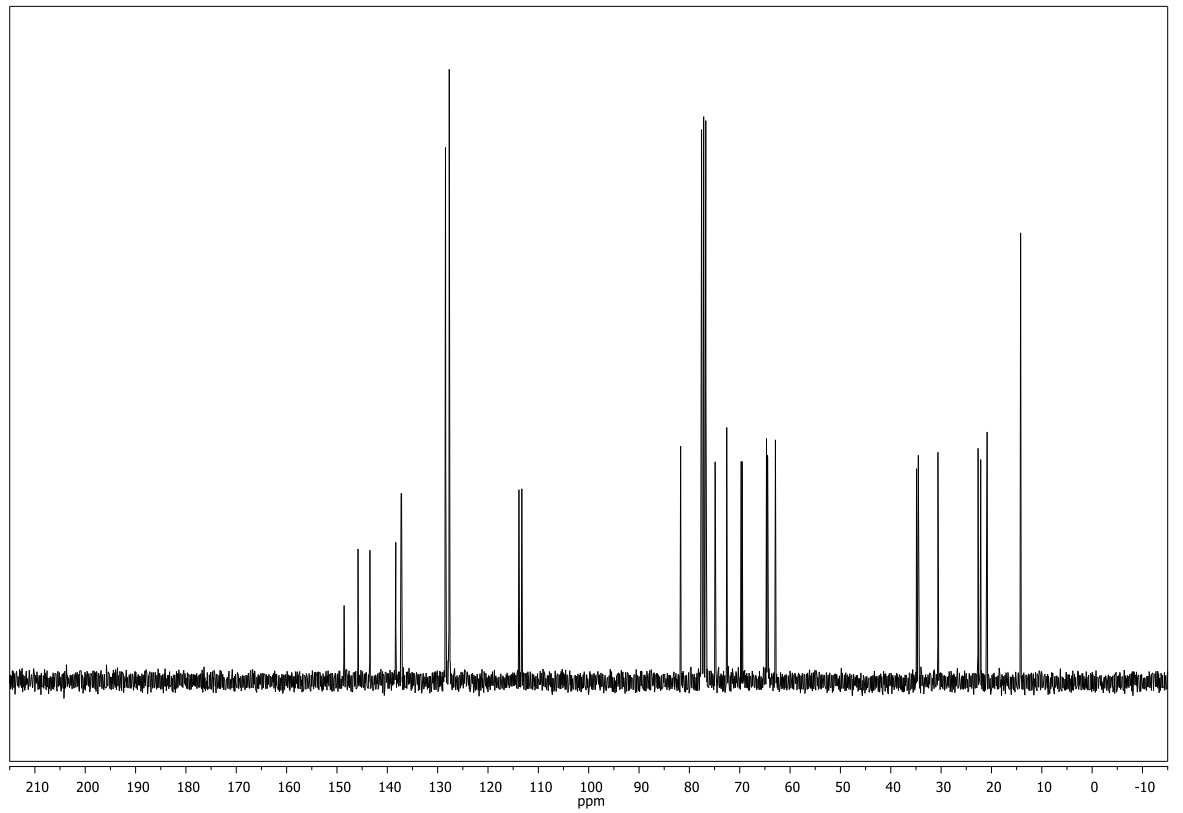


ethyl 5-((1*S*,5*S*,6*R*)-6-(benzyloxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (25ab)

^{1}H-NMR (300 MHz, $CDCl_3$)

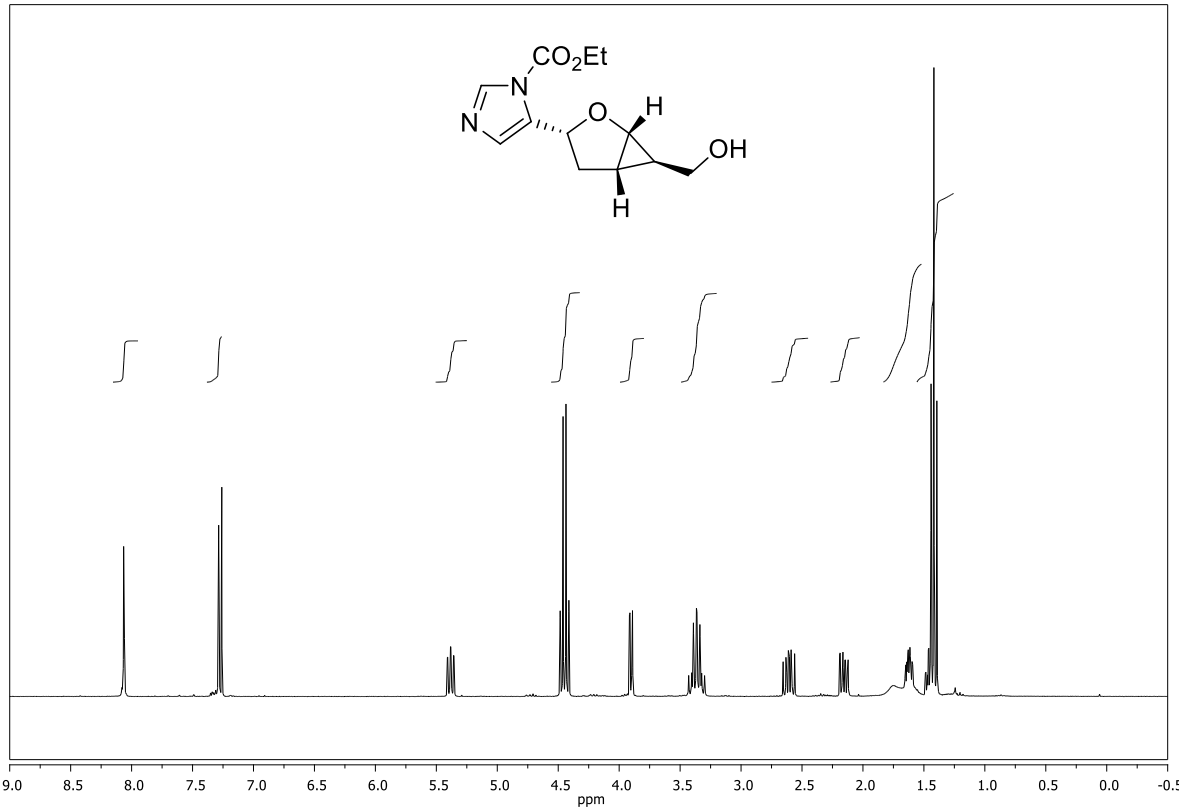


^{13}C-NMR (75 MHz, $CDCl_3$)

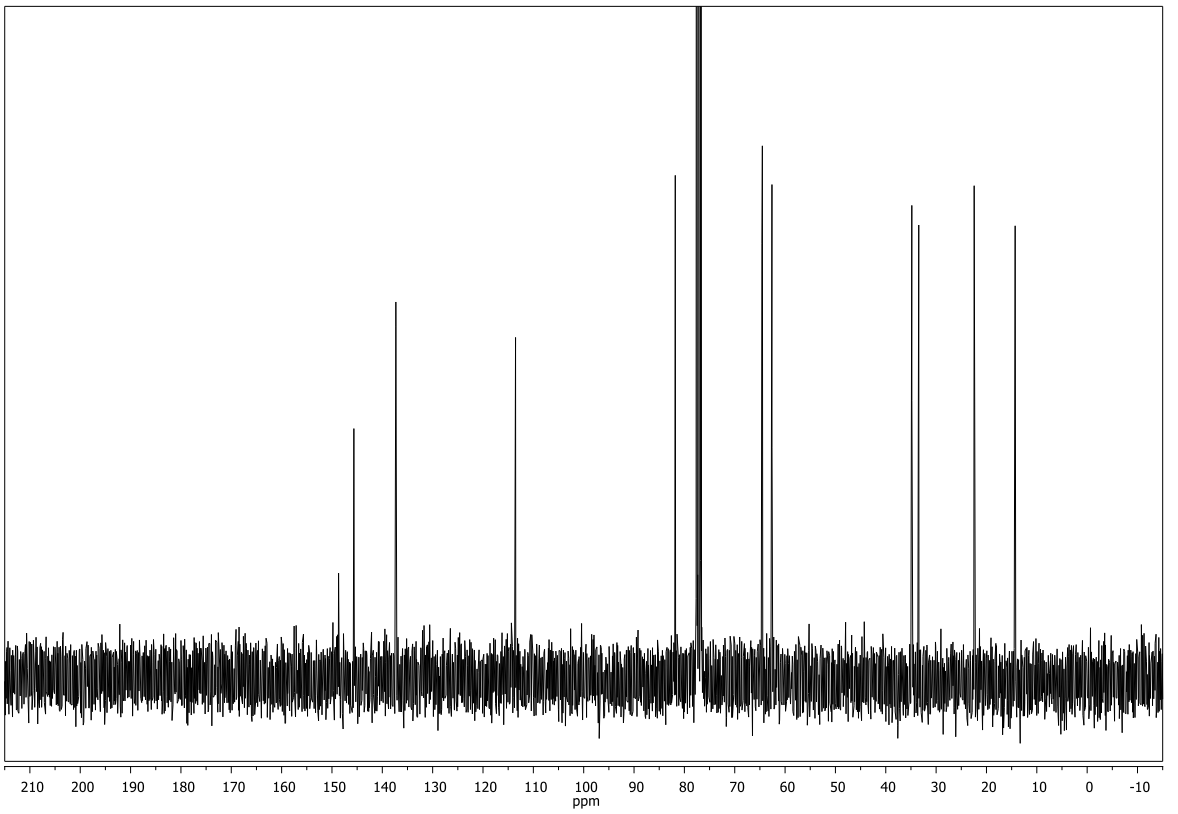


ethyl 5-((1*S*,3*R*,5*S*,6*R*)-6-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (26a)

^{1}H-NMR (300 MHz, $CDCl_3$)

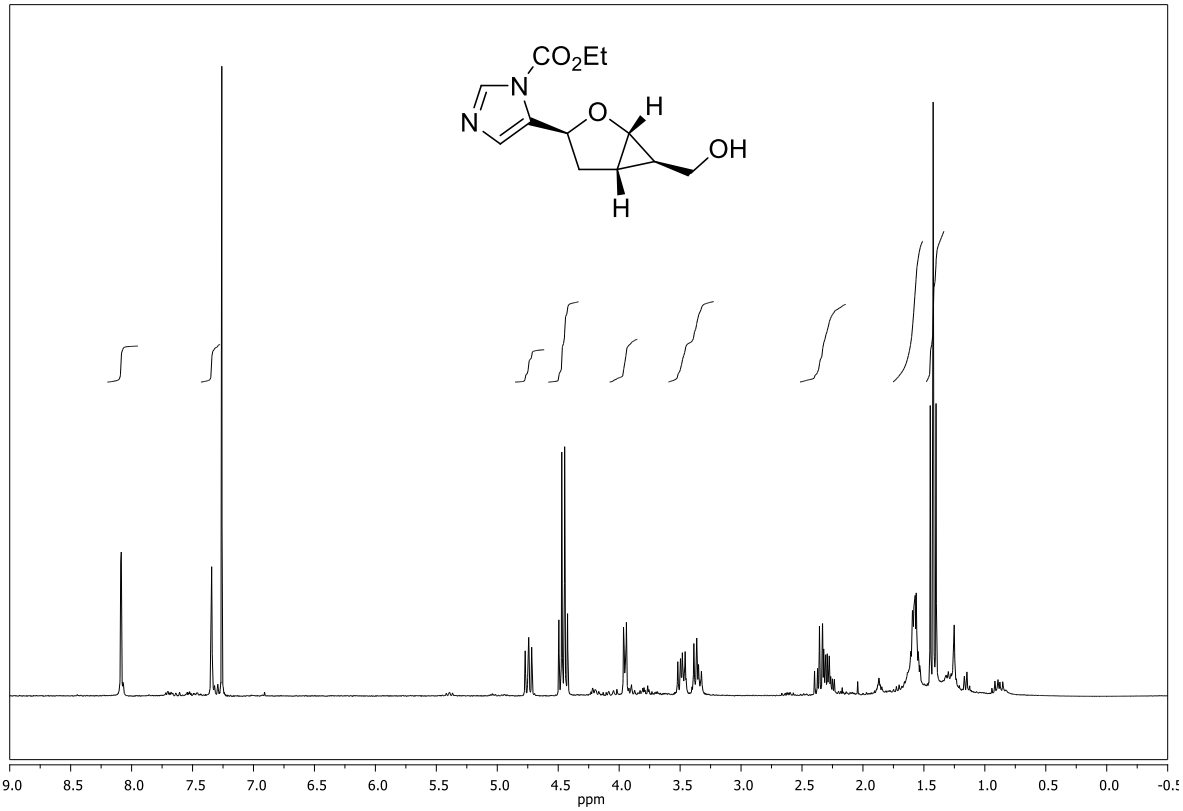


^{13}C-NMR (75 MHz, $CDCl_3$)

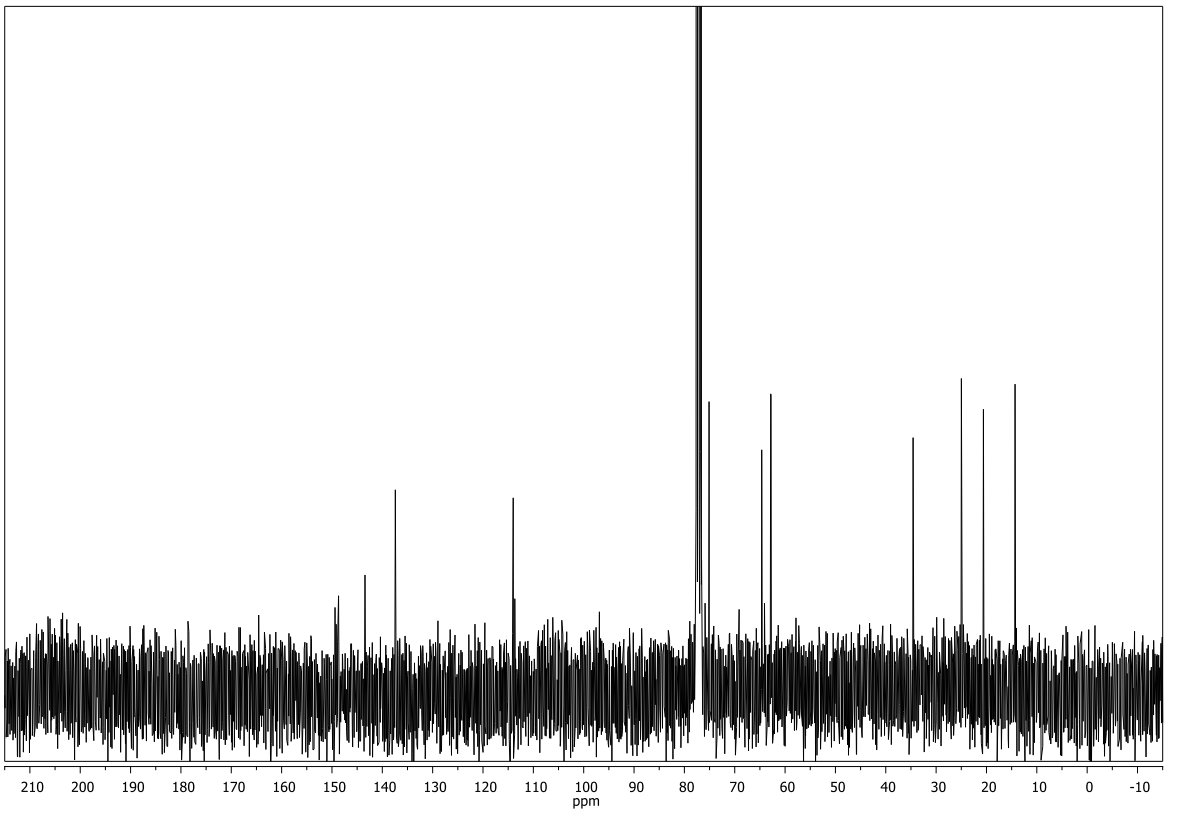


ethyl 5-((1*S*,3*S*,5*S*,6*R*)-6-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (26b)

^{1}H-NMR (300 MHz, $CDCl_3$)

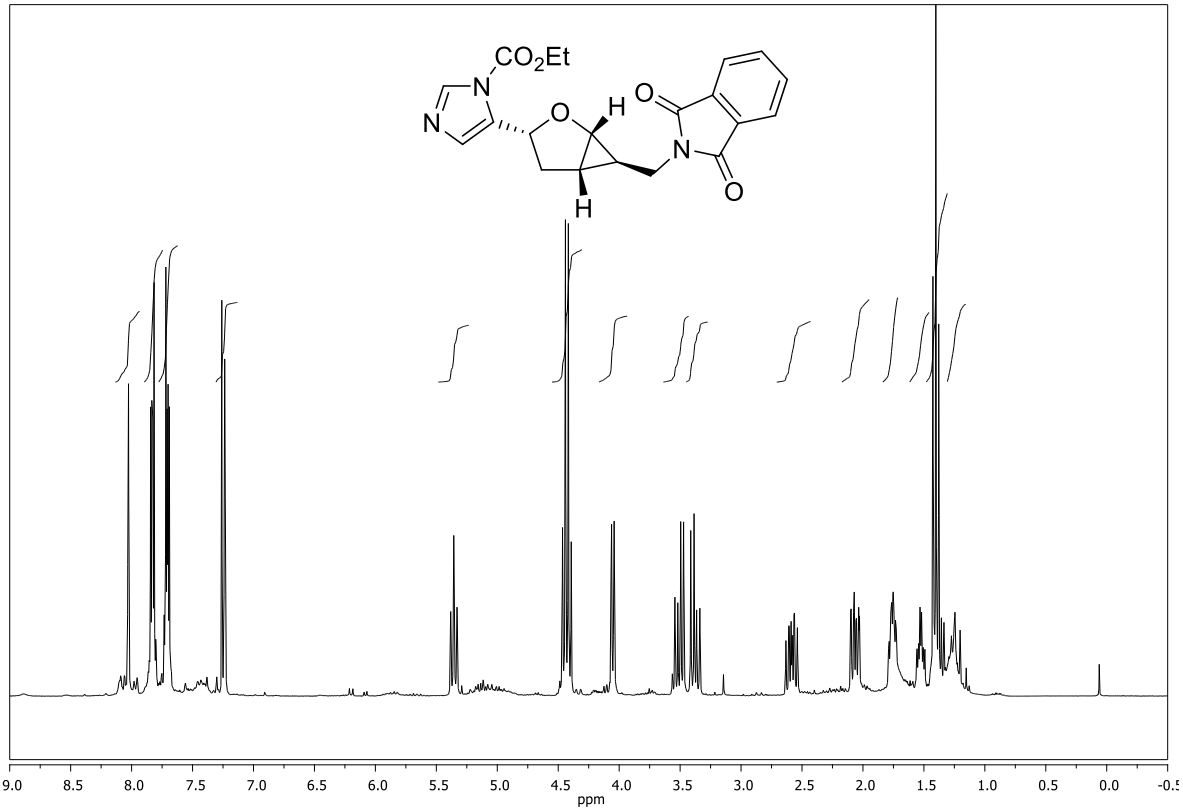


^{13}C-NMR (75 MHz, $CDCl_3$)

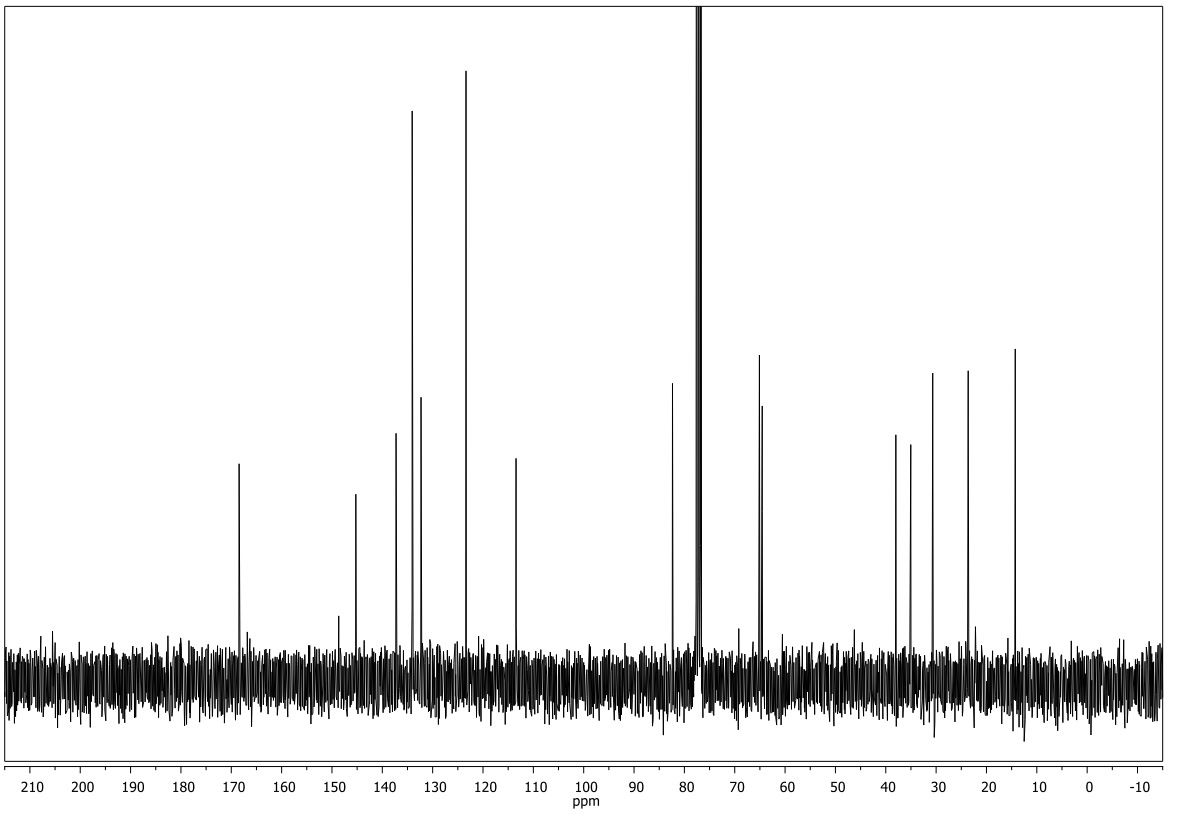


ethyl 5-((1*S*,3*R*,5*S*,6*R*)-6-((1,3-dioxoisoindolin-2-yl)methyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (27a)

^{1}H-NMR (300 MHz, $CDCl_3$)

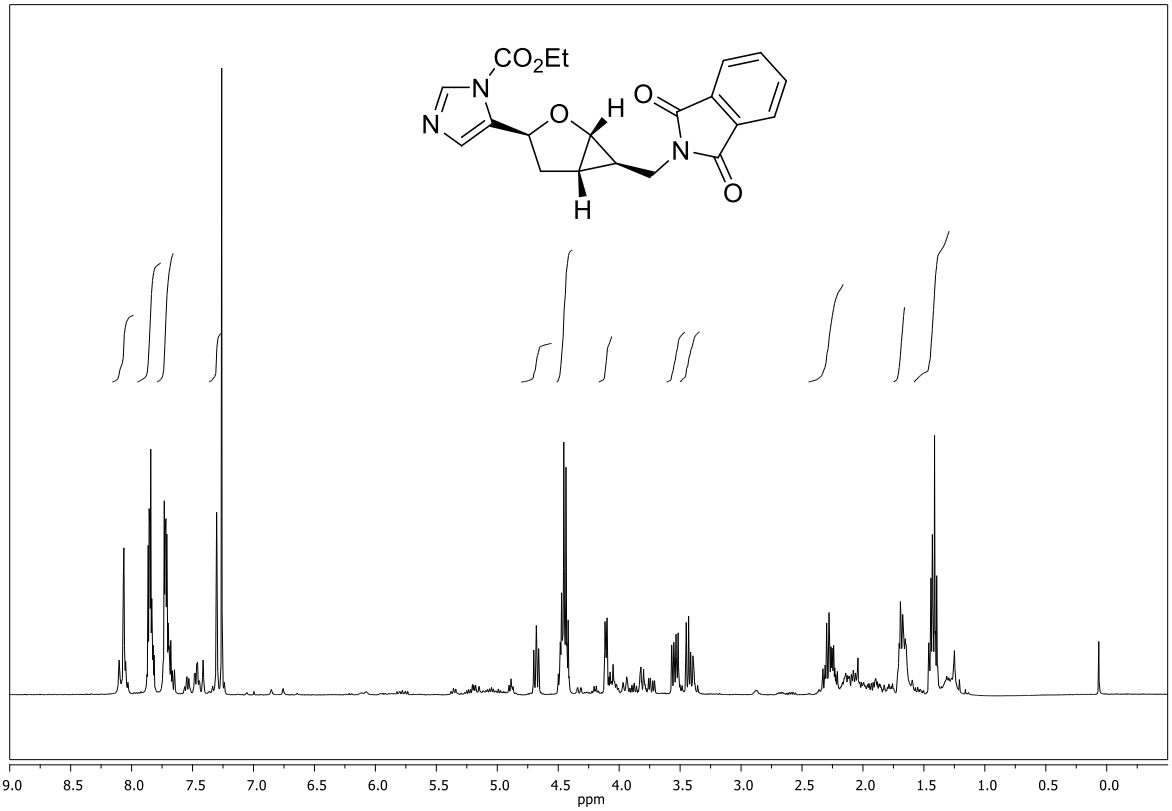


^{13}C-NMR (75 MHz, $CDCl_3$)

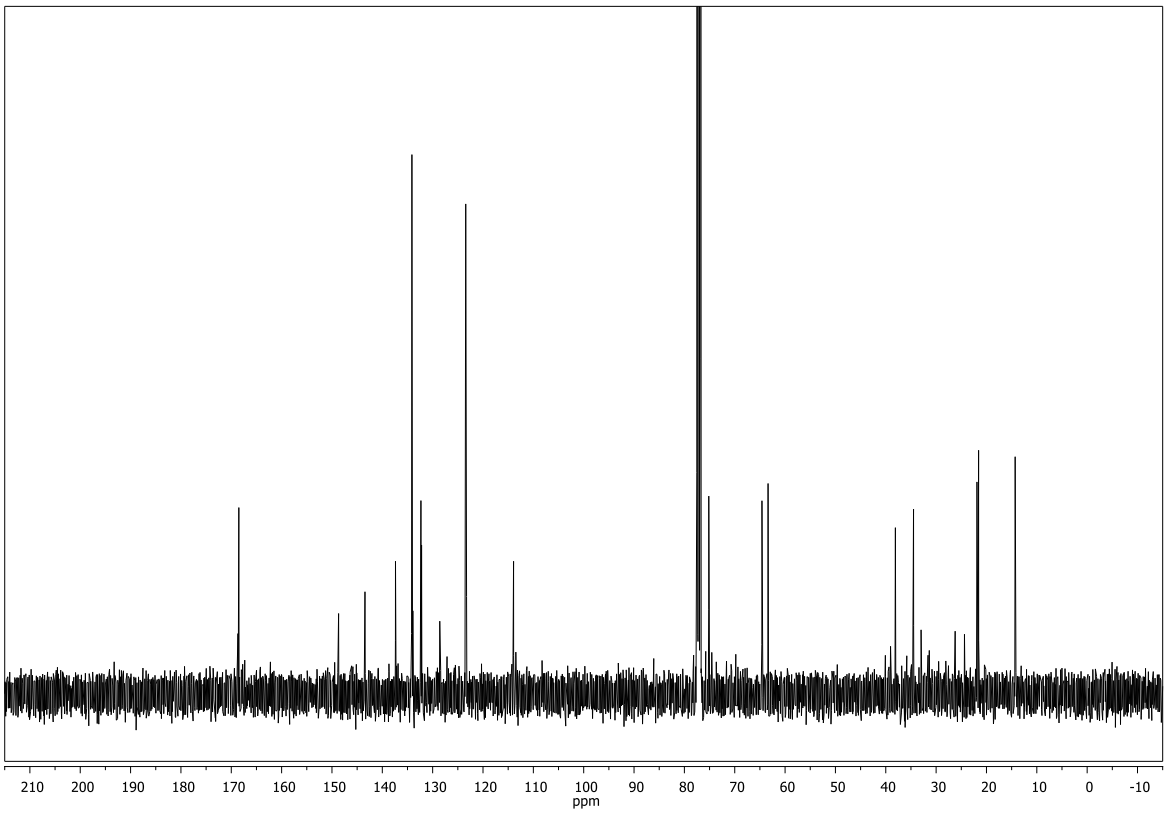


ethyl 5-((1*S*,3*S*,5*S*,6*R*)-6-((1,3-dioxoisoindolin-2-yl)methyl)-2-oxabicyclo[3.1.0]hexan-3-yl)-1*H*-imidazole-1-carboxylate (27b)

^{1}H-NMR (400 MHz, $CDCl_3$)

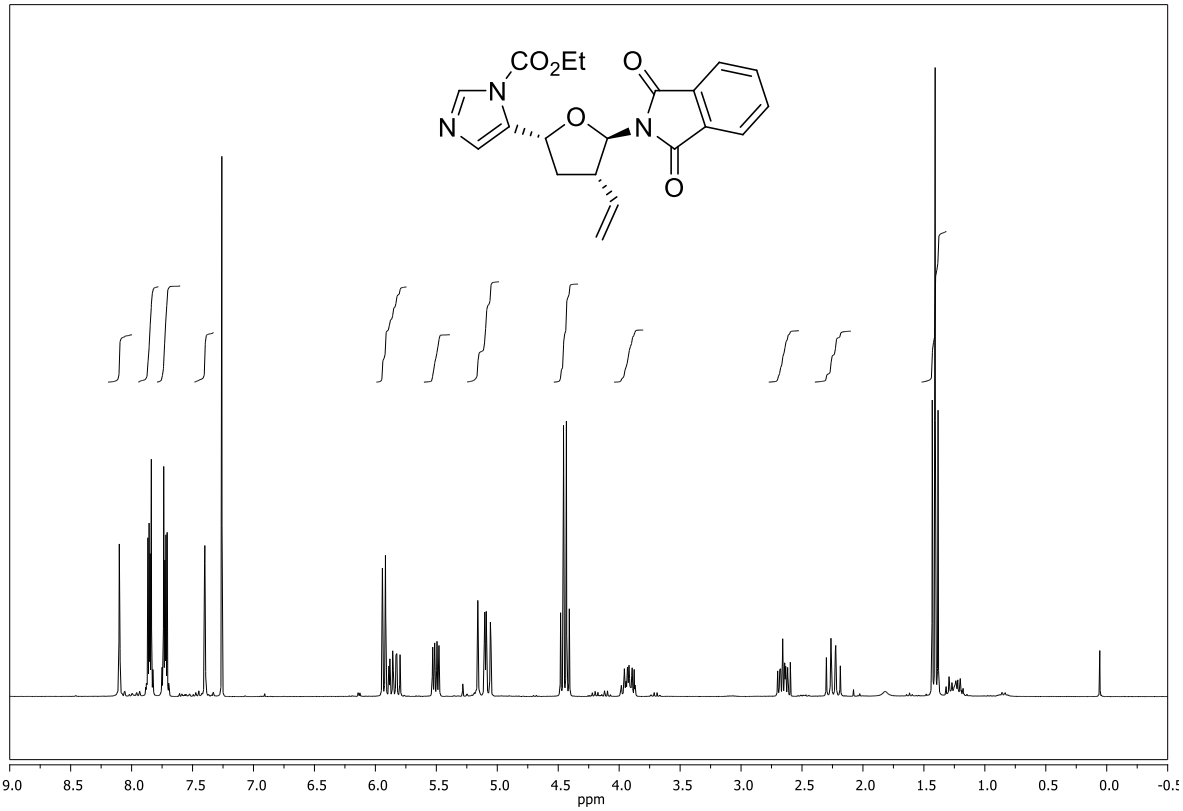


^{13}C-NMR (100 MHz, $CDCl_3$)

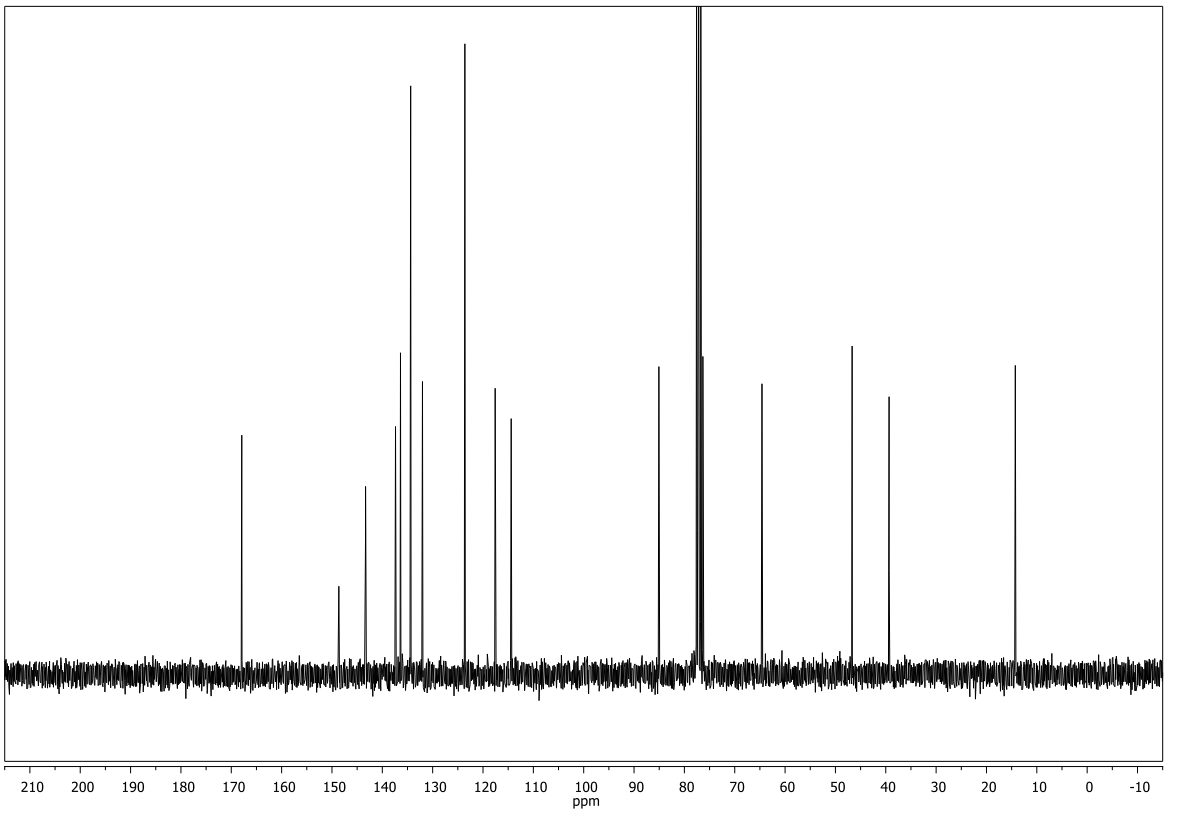


ethyl 5-((2*R*,4*S*,5*R*)-5-(1,3-dioxoisoindolin-2-yl)-4-vinyltetrahydrofuran-2-yl)-1*H*-imidazole-1-carboxylate (28a)

^{1}H-NMR (300 MHz, $CDCl_3$)

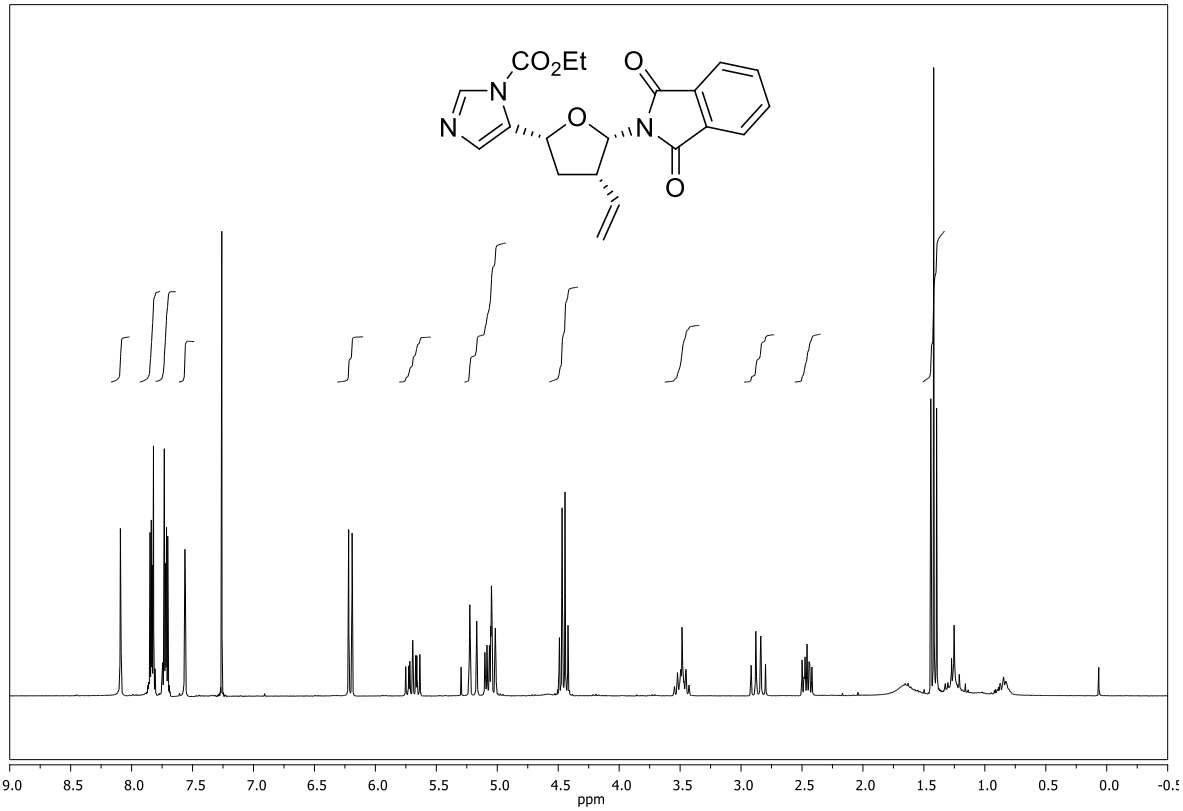


^{13}C-NMR (75 MHz, $CDCl_3$)

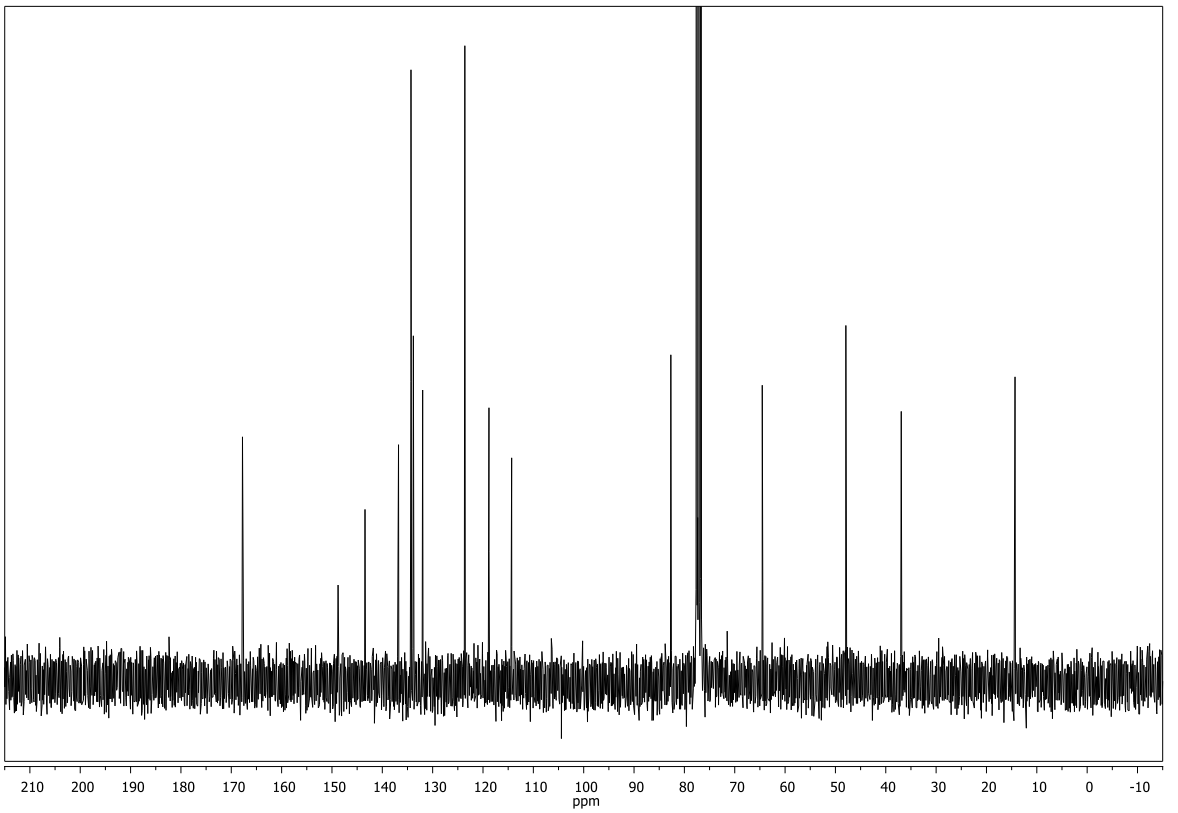


ethyl 5-((2*R*,4*S*,5*S*)-5-(1,3-dioxoisoindolin-2-yl)-4-vinyltetrahydrofuran-2-yl)-1*H*-imidazole-1-carboxylate (28b)

^{1}H-NMR (300 MHz, $CDCl_3$)

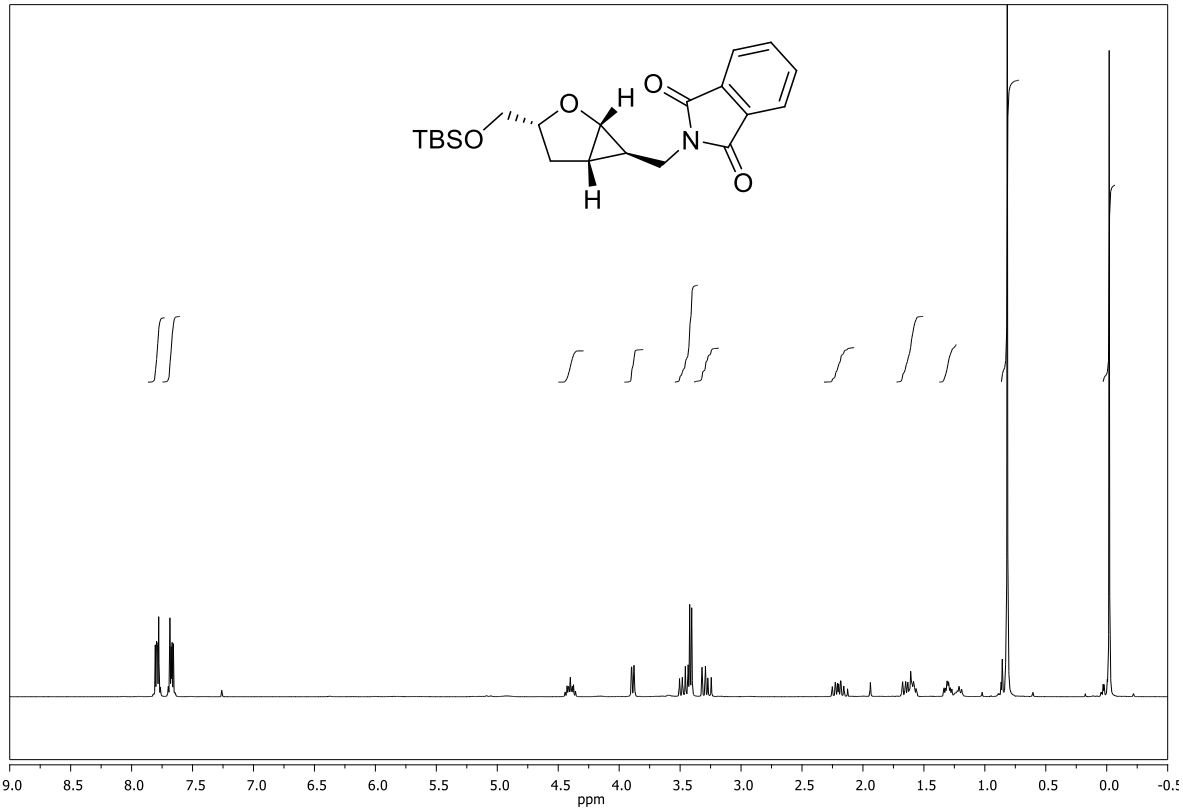


^{13}C-NMR (75 MHz, $CDCl_3$)

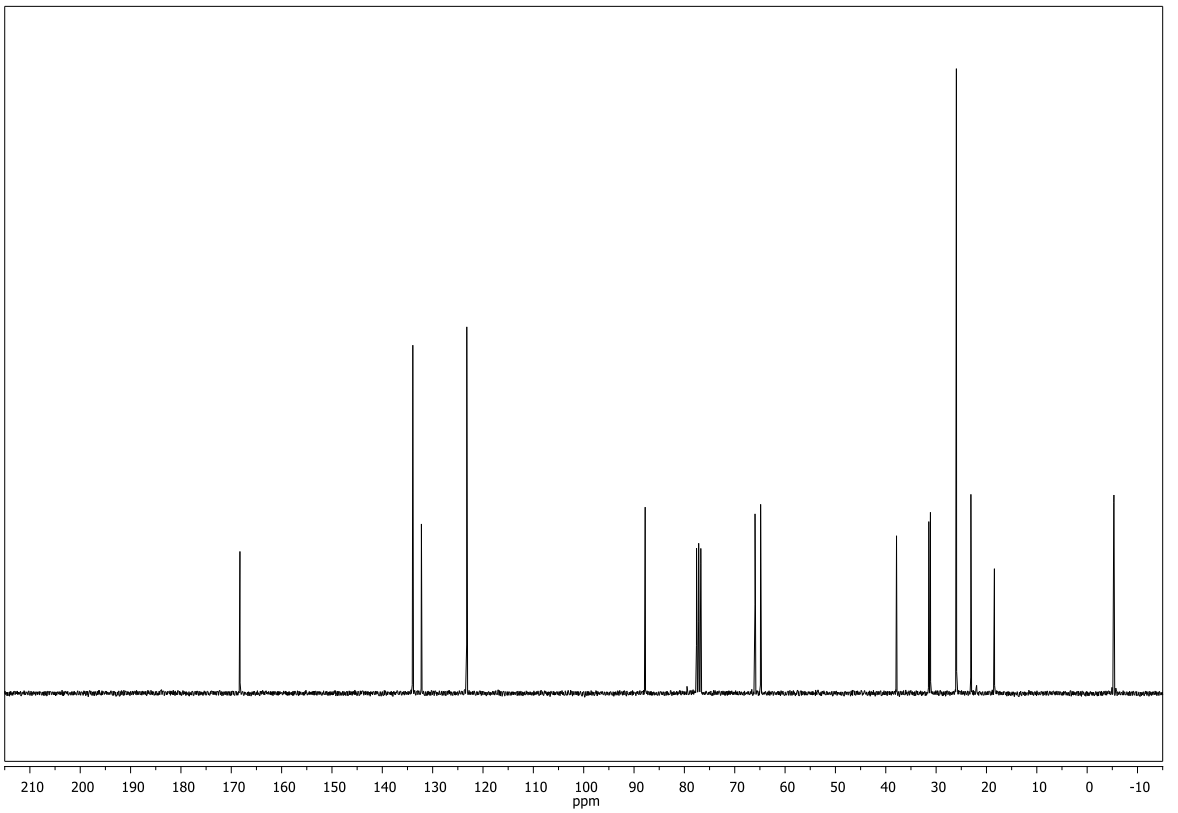


2-(((1*S*,3*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)isoindoline-1,3-dione (30)

^{1}H-NMR (300 MHz, $CDCl_3$)

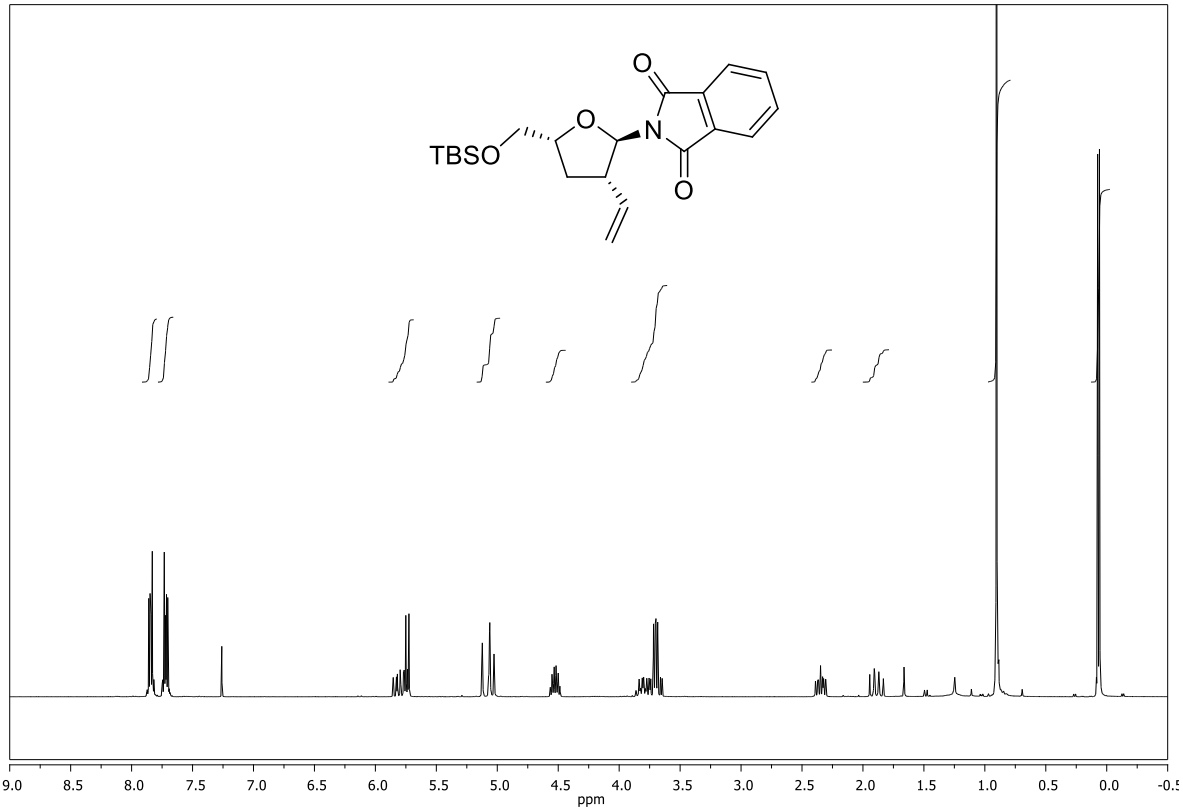


^{13}C-NMR (75 MHz, $CDCl_3$)

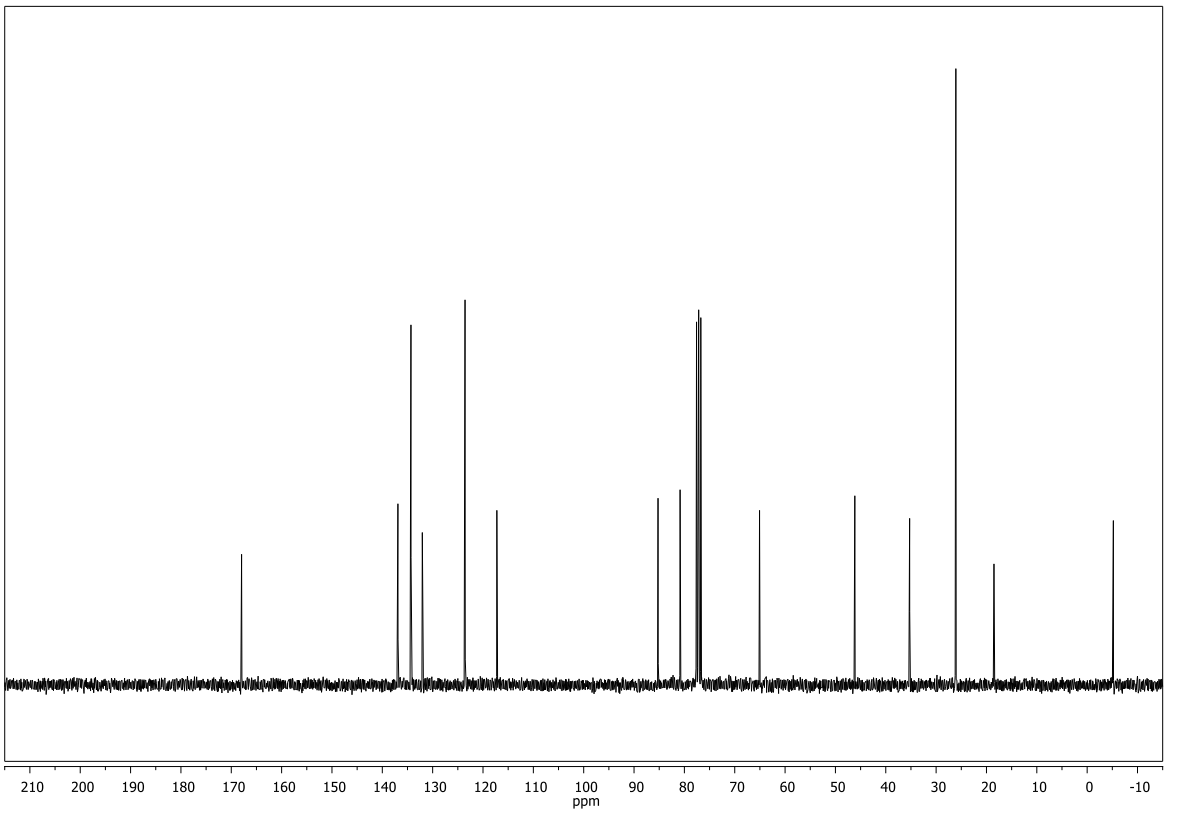


2-((2*R*,3*S*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-3-vinyltetrahydrofuran-2-yl)-isoindoline-1,3-dione (31a)

^{1}H-NMR (300 MHz, $CDCl_3$)

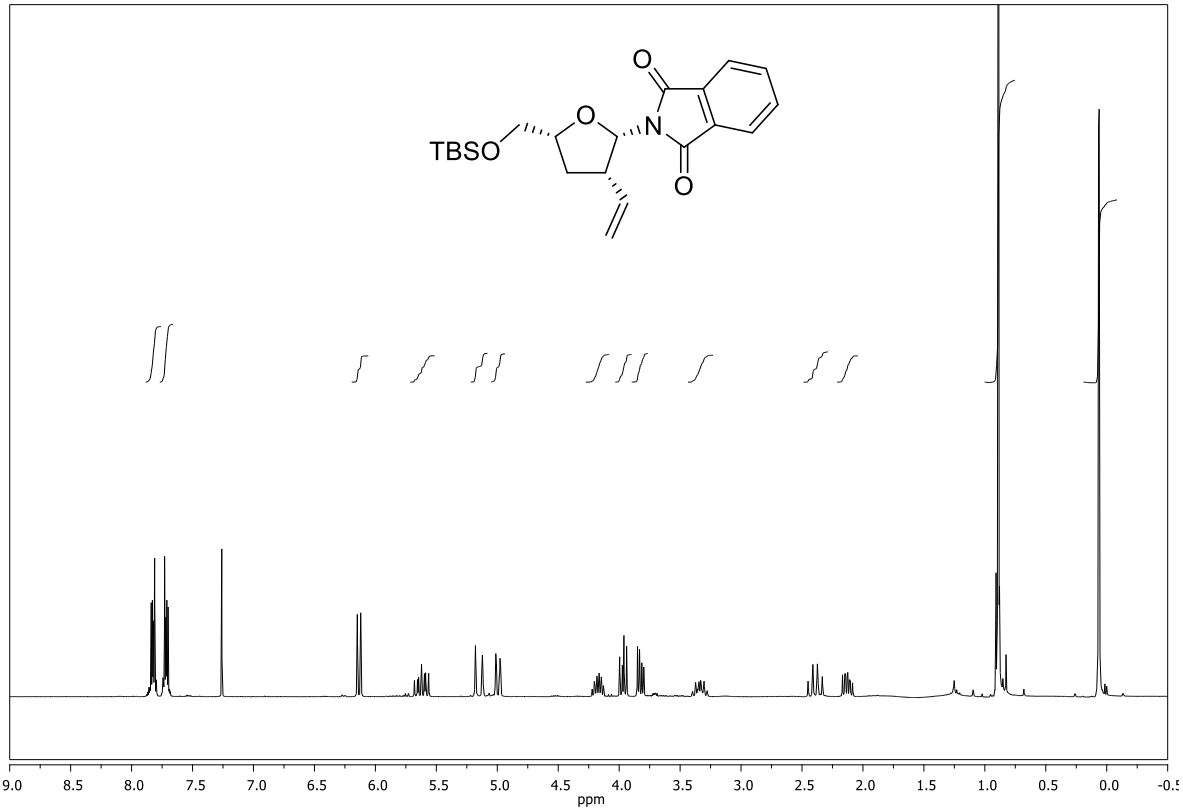


^{13}C-NMR (75 MHz, $CDCl_3$)

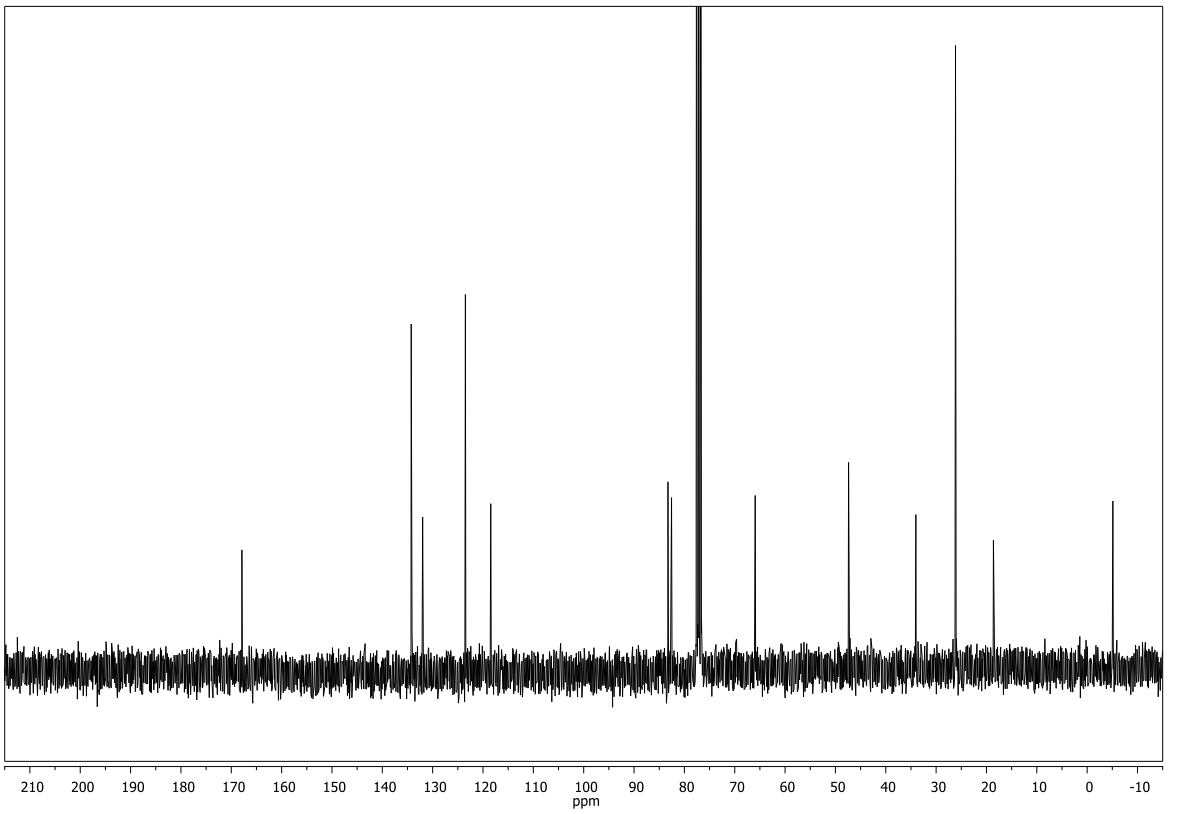


2-((2*S*,3*S*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-3-vinyltetrahydrofuran-2-yl)-isoindoline-1,3-dione (31b)

^{1}H-NMR (300 MHz, $CDCl_3$)

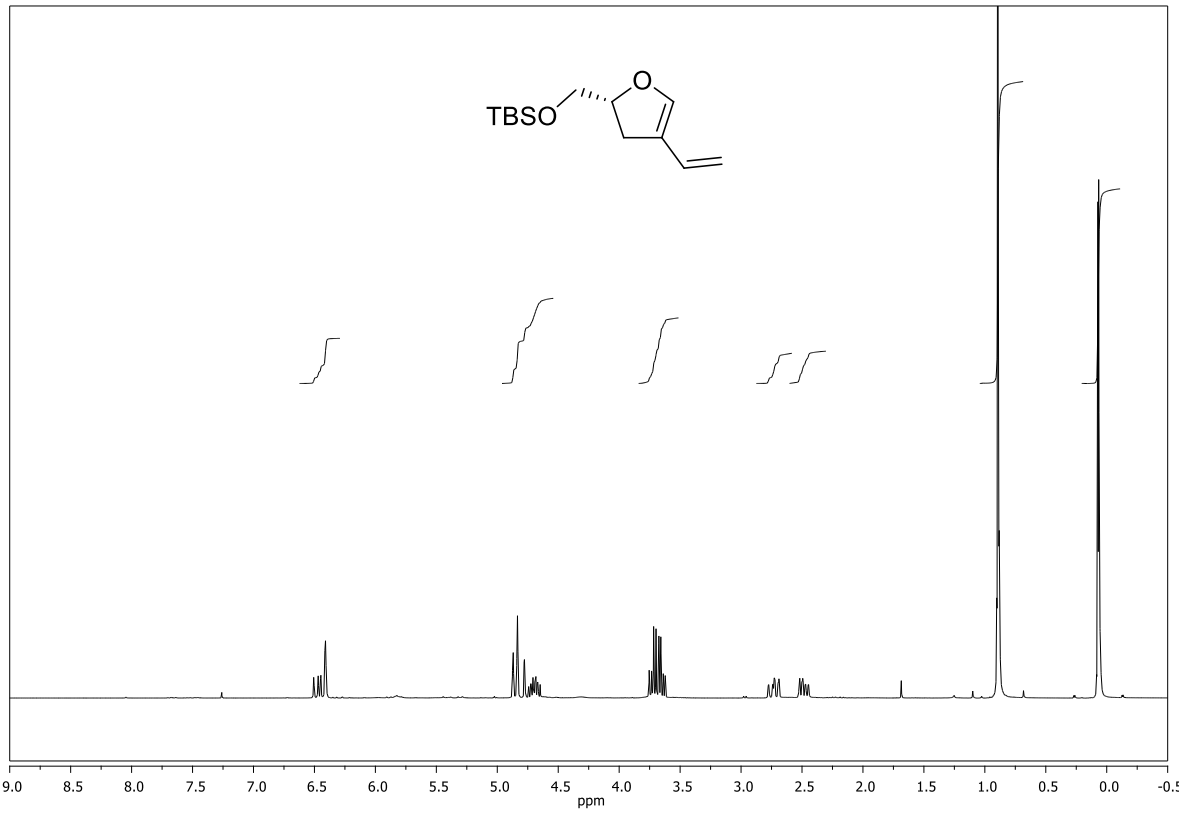


^{13}C-NMR (75 MHz, $CDCl_3$)

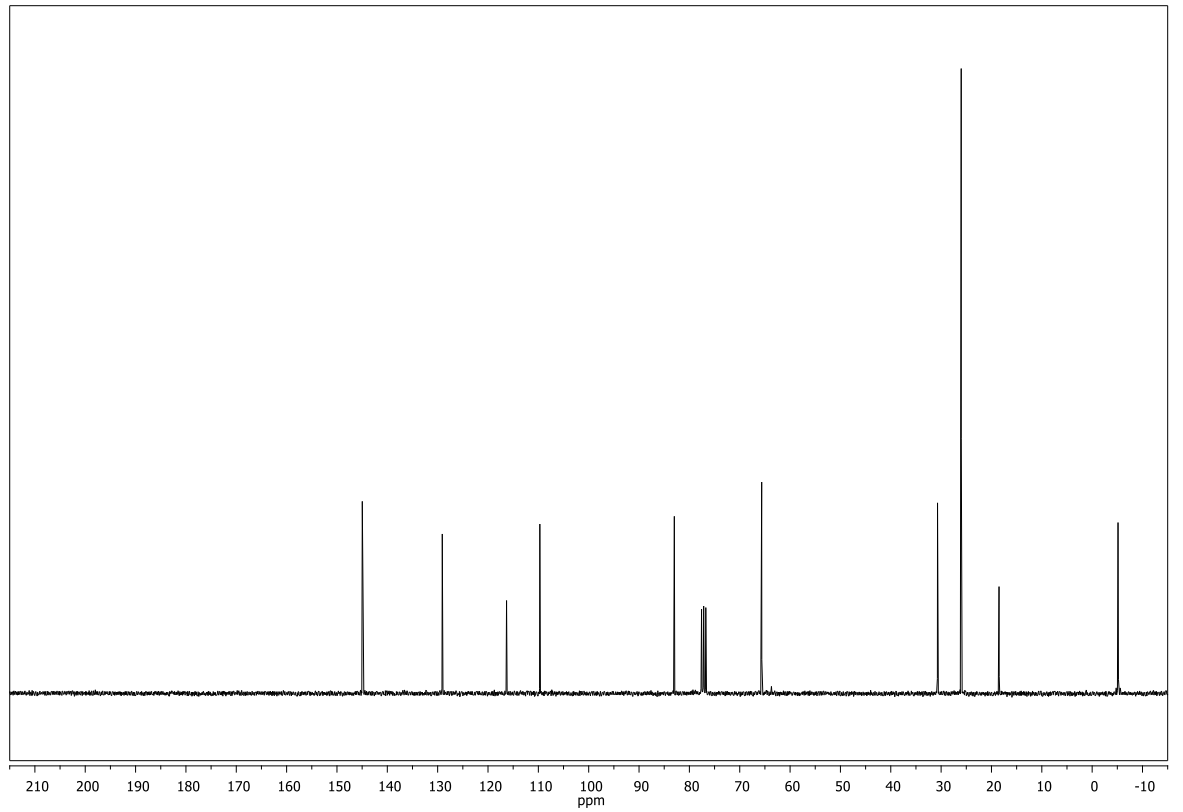


(*R*)-*tert*-butyldimethyl((4-vinyl-2,3-dihydrofuran-2-yl)methoxy)silane (32)

^{1}H-NMR (300 MHz, $CDCl_3$)

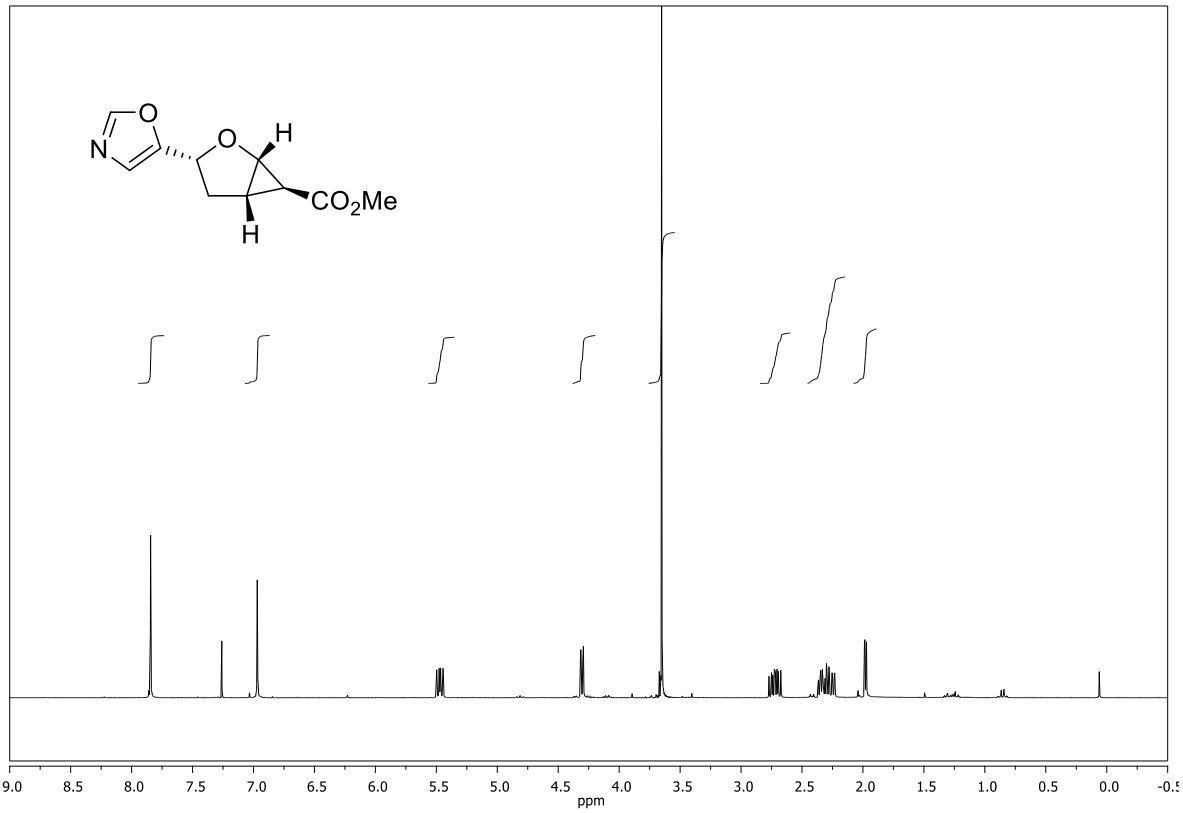


^{13}C-NMR (75 MHz, $CDCl_3$)

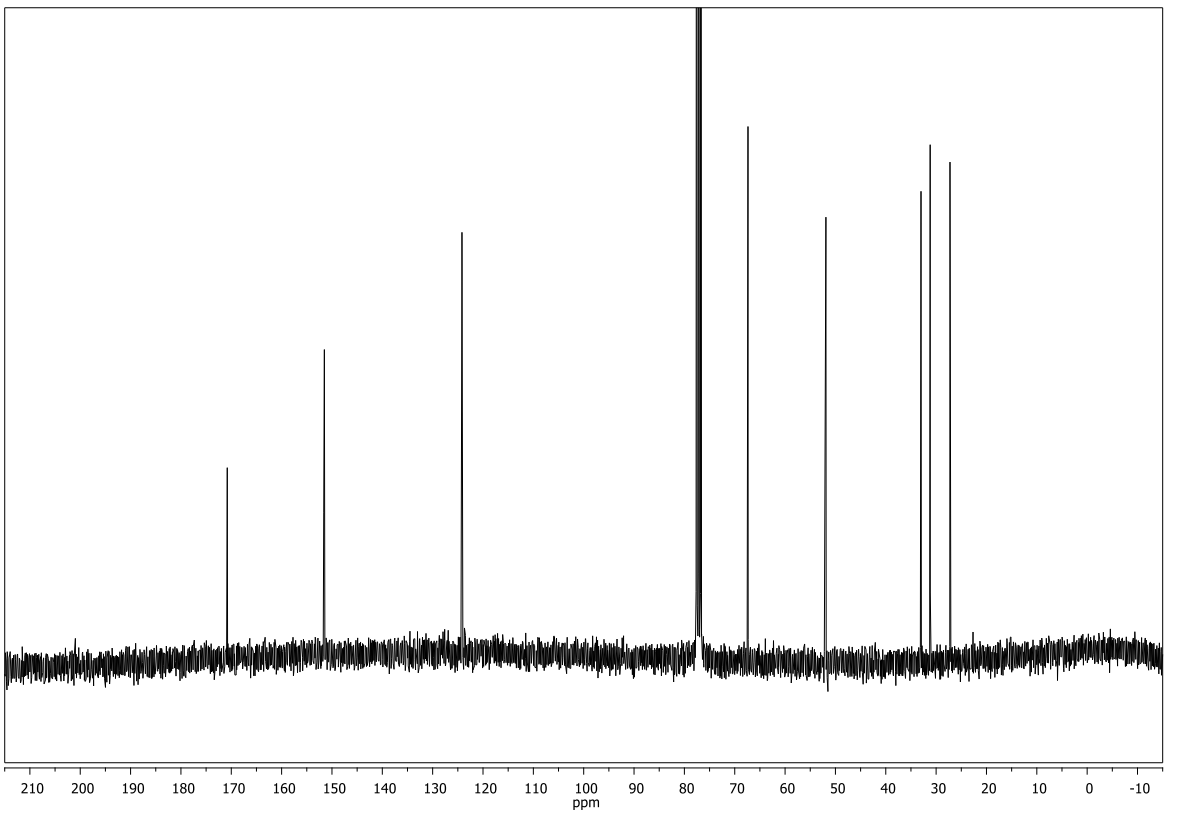


(1*S*,3*R*,5*S*,6*S*)-methyl 3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (33)

^{1}H-NMR (300 MHz, $CDCl_3$)

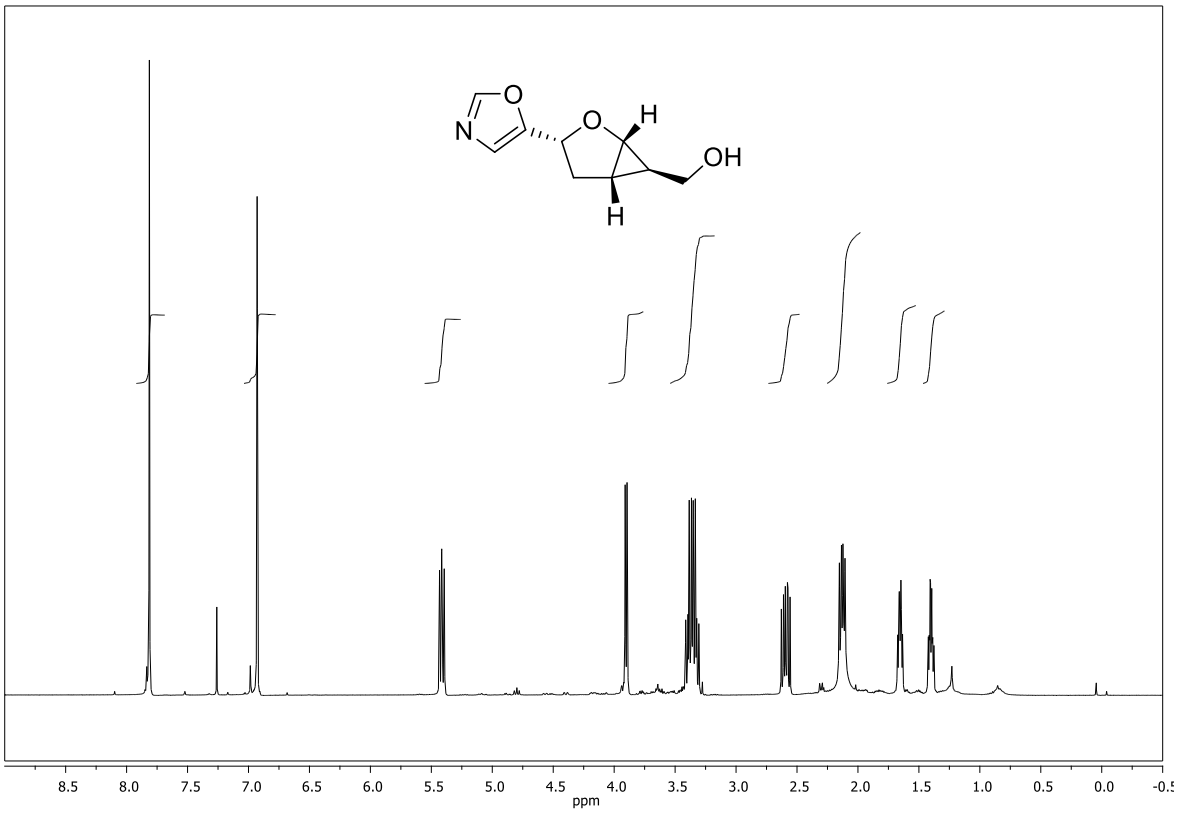


^{13}C-NMR (75 MHz, $CDCl_3$)

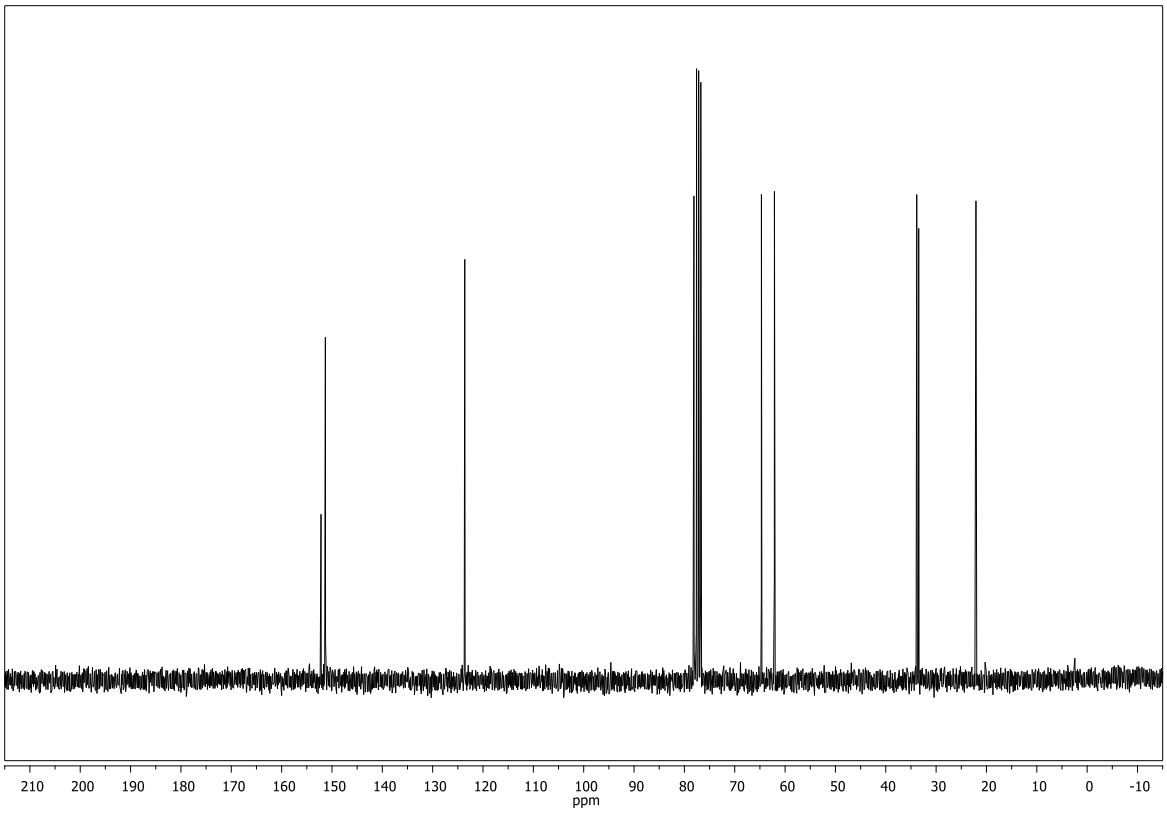


((1*S*,3*R*,5*S*,6*R*)-3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methanol (34)

^{1}H-NMR (400 MHz, $CDCl_3$)

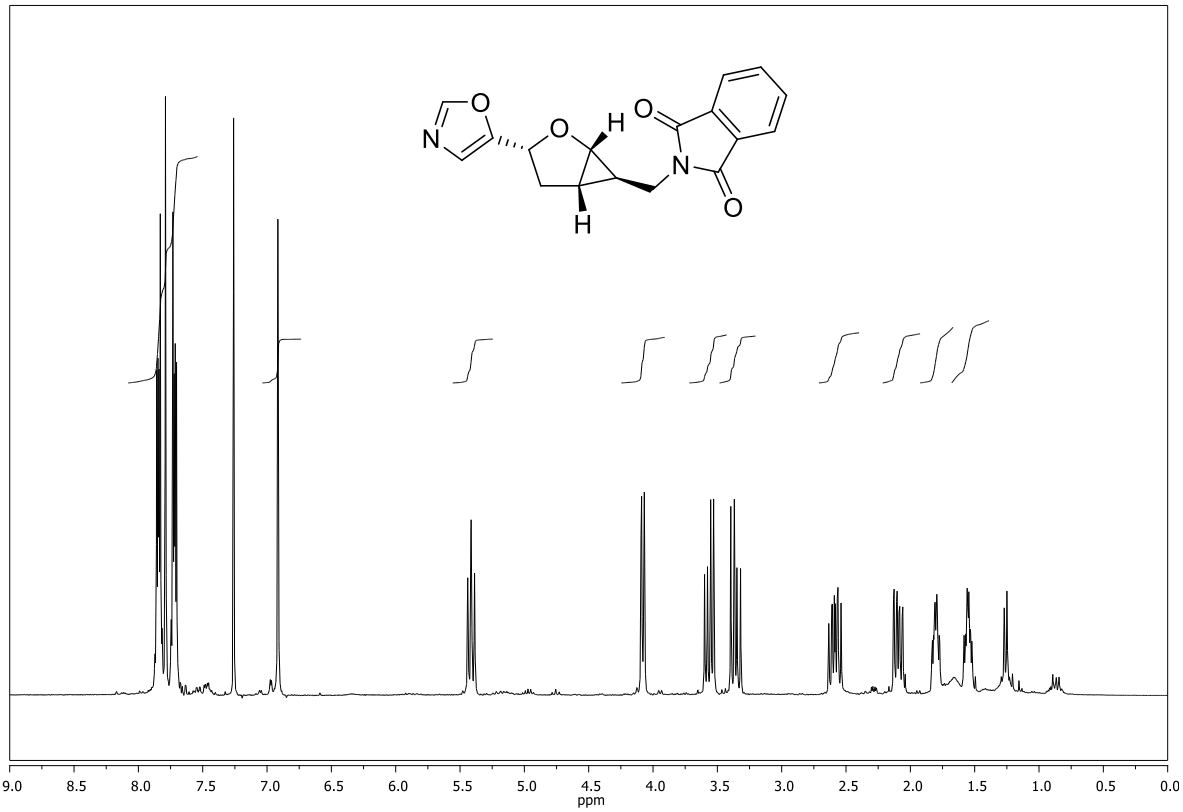


^{13}C-NMR (75 MHz, $CDCl_3$)

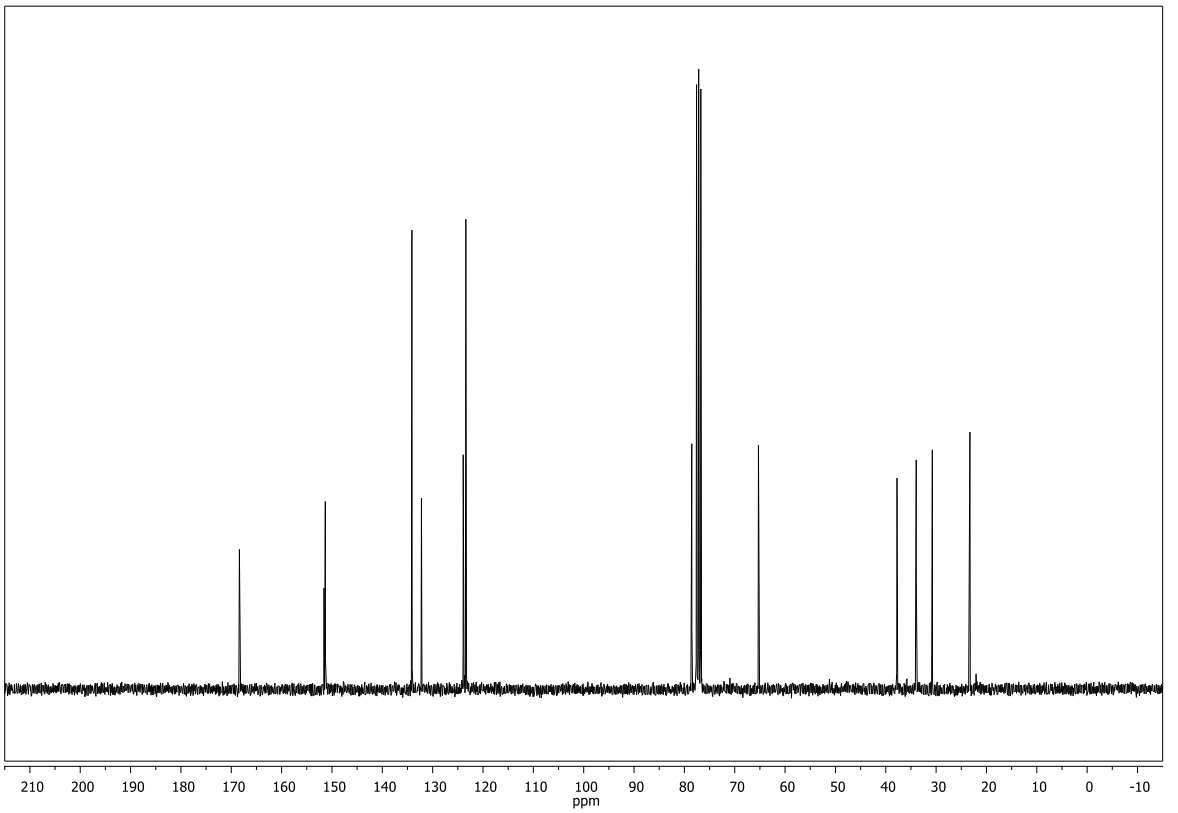


2-(((1*S*,3*R*,5*S*,6*R*)-3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)isoindoline-1,3-dione (35)

^{1}H-NMR (300 MHz, $CDCl_3$)

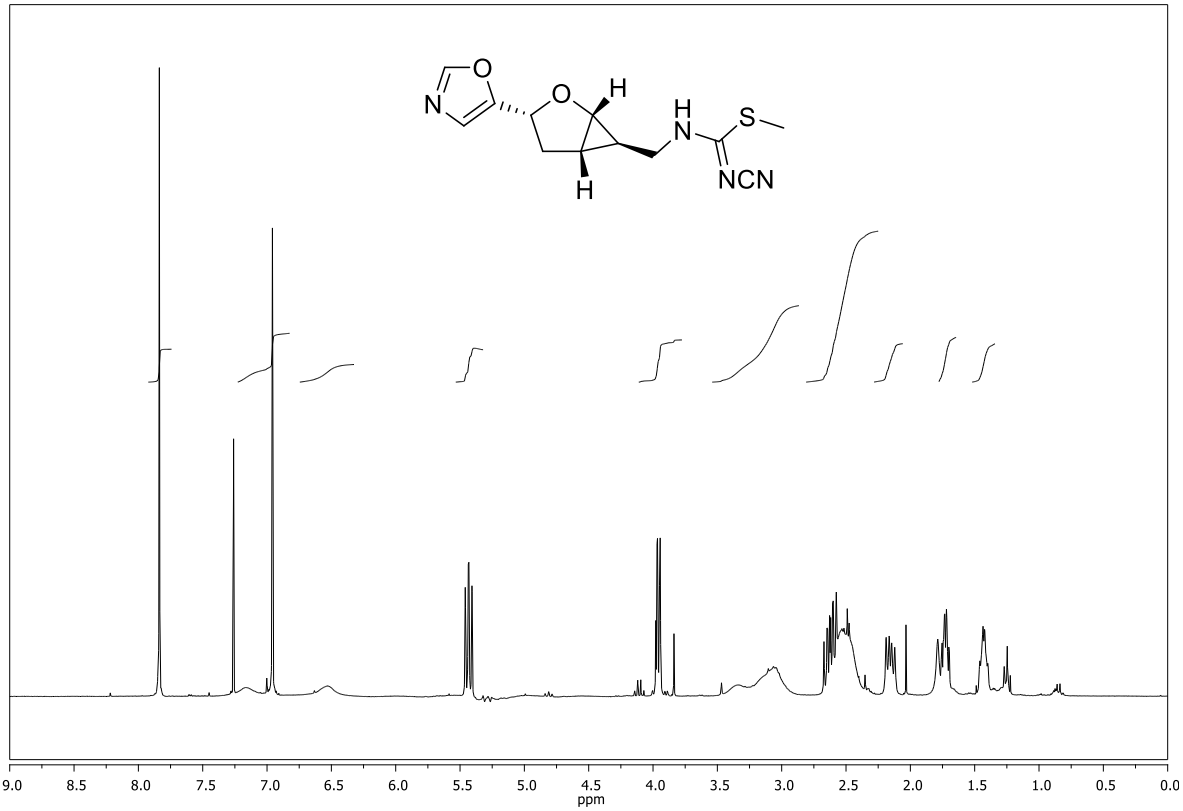


^{13}C-NMR (75 MHz, $CDCl_3$)

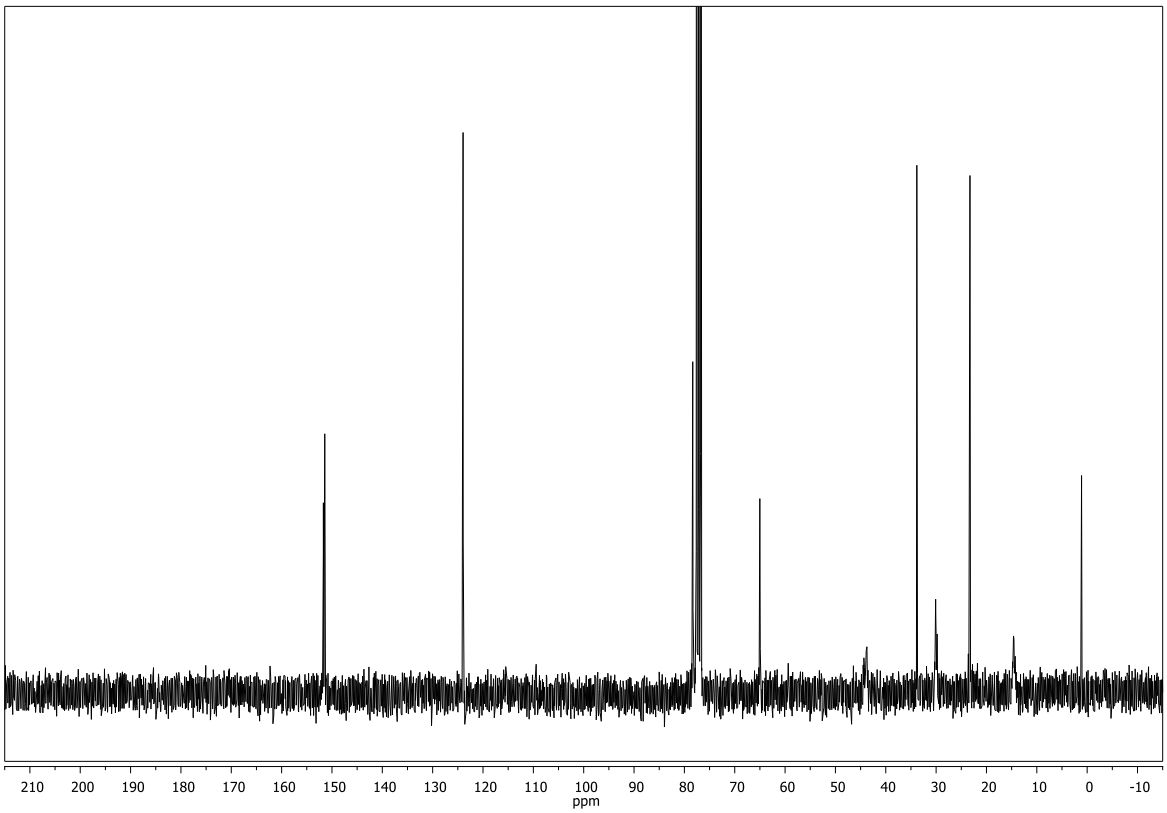


methyl *N*'-cyano-*N*-(((1*S*,3*R*,5*S*,6*R*)-3-(oxazol-5-yl)-2-oxabicyclo[3.1.0]hexan-6-yl)methyl)carbamimidothioate (36)

^{1}H-NMR (300 MHz, $CDCl_3$)



^{13}C-NMR (75 MHz, $CDCl_3$)



2. HPLC purity data

Table 1. HPLC purity data of the synthesized target compounds.[a]

no.	t_R (min)	k'	purity (%)	no.	t_R (min)	k'	purity (%)
6a[b]	4.20 8.34	0.80 2.58	> 99	**6c**[b]	4.20 8.35	0.80 2.58	> 99
6b[b]	4.22 8.26	0.81 2.55	> 99	**6d**[b]	4.22 8.29	0.81 2.56	> 99
7a[b]	4.27 11.38	0.83 3.88	> 99	**7b**[b]	4.16 11.33	0.79 3.86	95
8a	3.30	0.42	98	**8c**	3.31	0.42	94
8b	3.29	0.41	> 99	**8d**	3.30	0.42	> 99
9a	4.34	0.86	93	**9b**	4.23	0.82	91

[a] Eurosphere-100 C18, 250 × 4.0 mm, 5 µm; Knauer, Berlin, Germany; t_0 = 2.33 min; gradient mode: MeCN (0.1% TFA)/water (0.1% TFA): 0 min: 10/90, 20 min: 90/10, 30 min: 90/10; [b] two t_R values due two partial protonation of the cyanoguanidines.