

Access to α -Substituted Amino Acid Derivatives via 1,3-Dipolar Cycloaddition of α -Amino Ester Derived Nitrones

Thanh Binh Nguyen, Alice Beauseigneur, Arnaud Martel, Robert Dhal* Mathieu Laurent and Gilles Dujardin*

Sections Include:

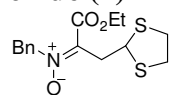
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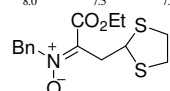
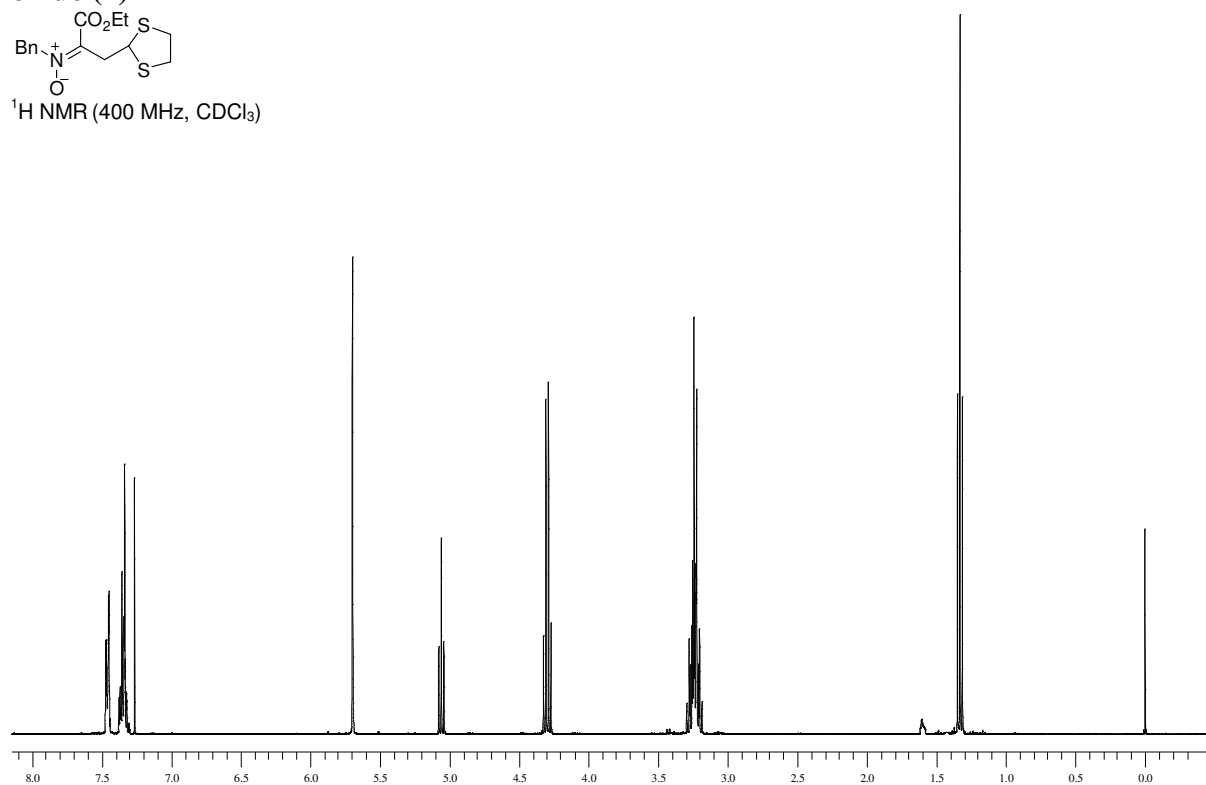
General Information and Methods

All reactions were conducted in oven- or flame-dried glassware. NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as the standard. Flash column chromatography was carried out using Silicagel (230-400 mesh). All reactions were monitored by TLC with UV 254 silica gel-coated plates. The organic solvents used were dried by standard methods when necessary.

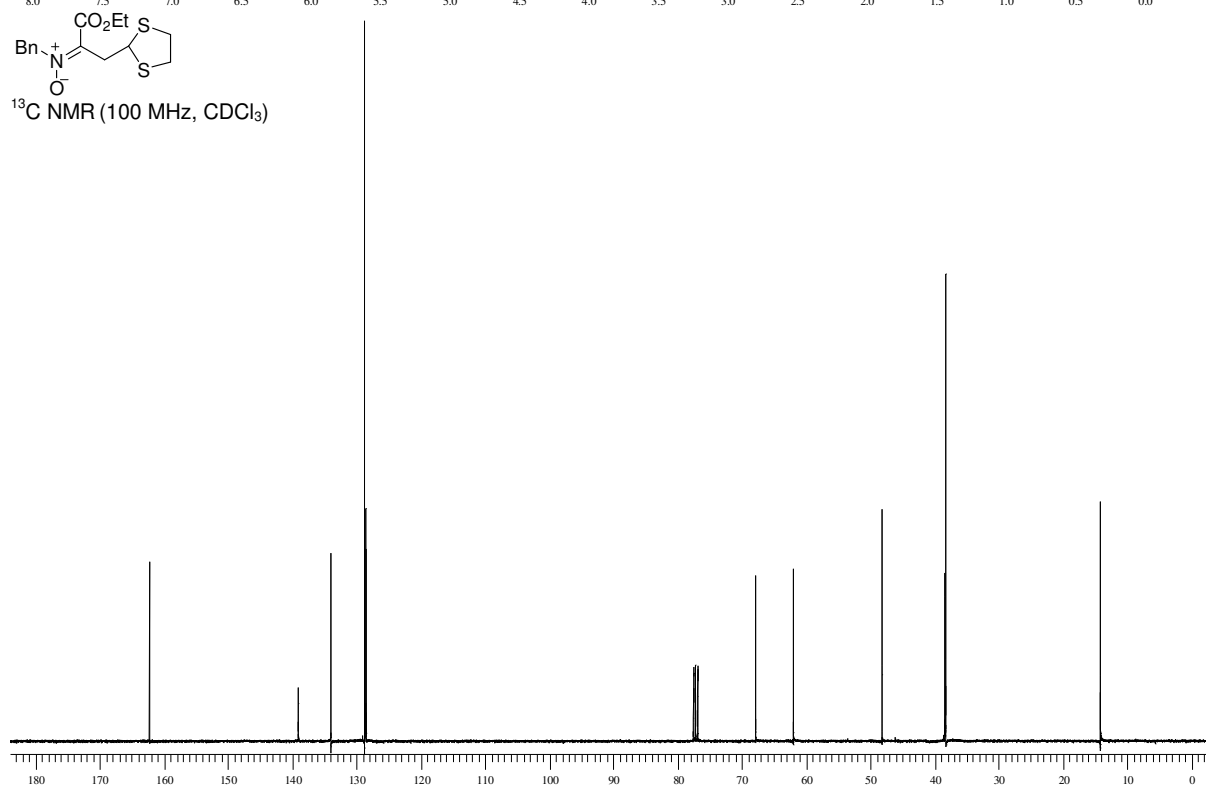
(*E*)-*N*-(3-(1,3-dithiolan-2-yl)-1-ethoxy-1-oxopropan-2-ylidene)(phenyl)methanamine oxide (4)



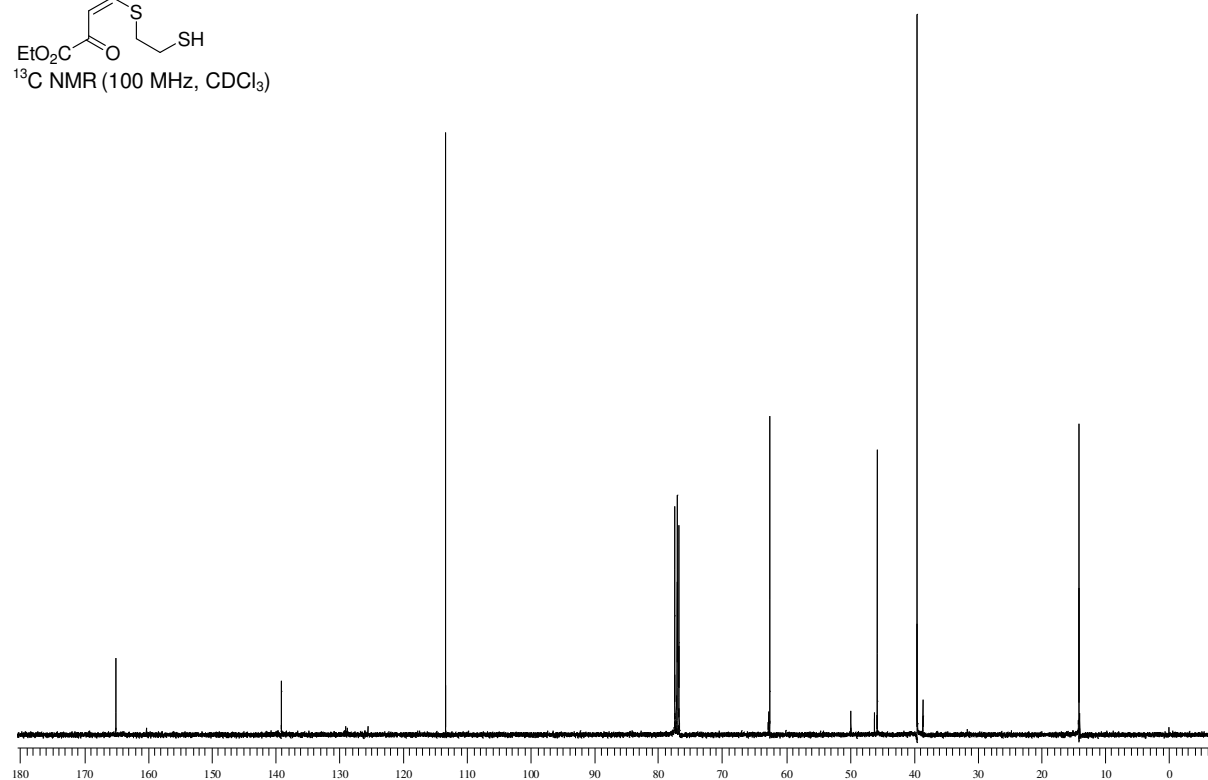
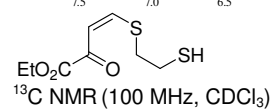
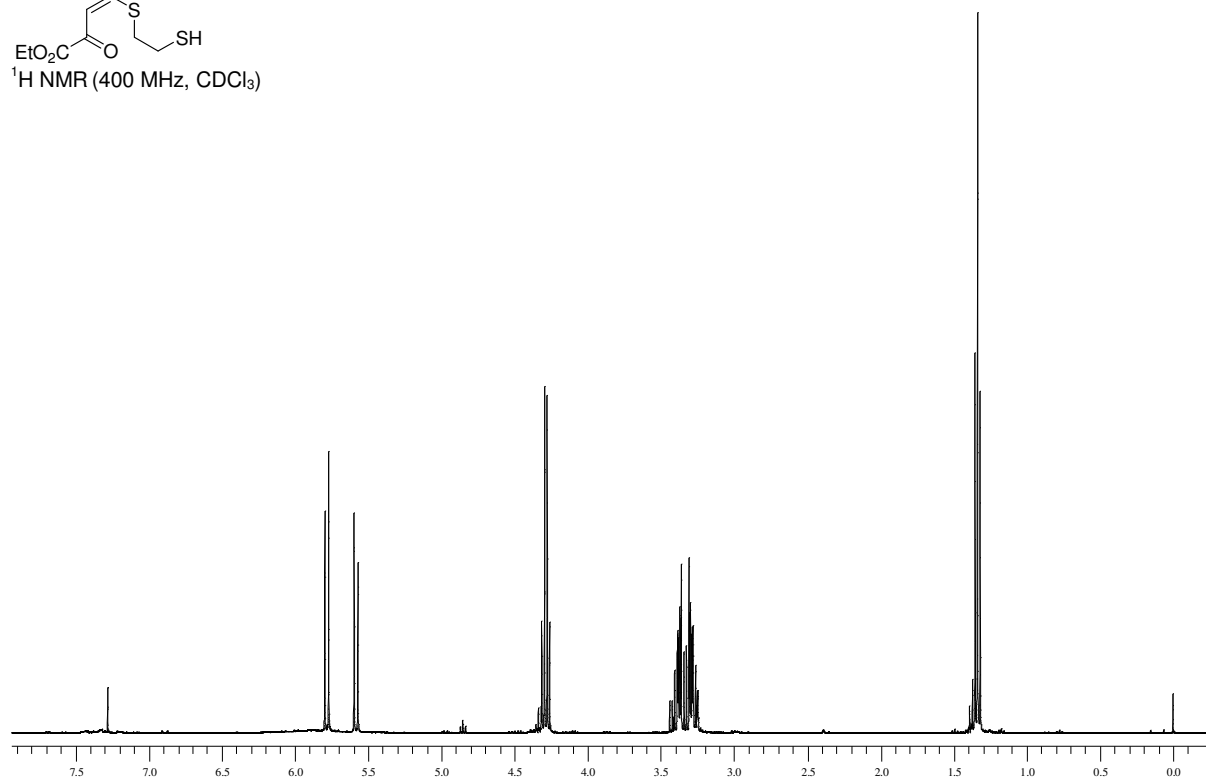
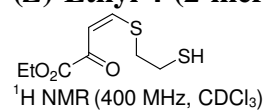
^1H NMR (400 MHz, CDCl_3)



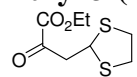
^{13}C NMR (100 MHz, CDCl_3)



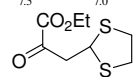
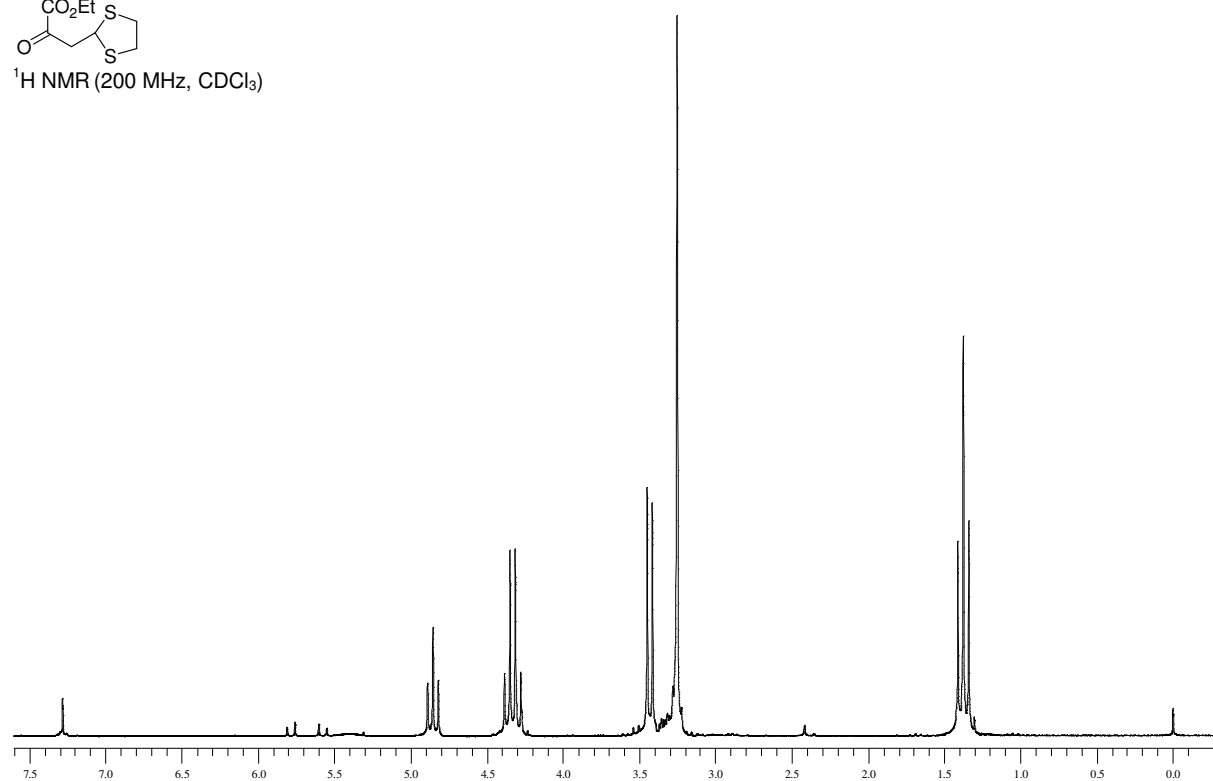
(Z)-Ethyl 4-(2-mercaptoethylthio)-2-oxobut-3-enoate (5')



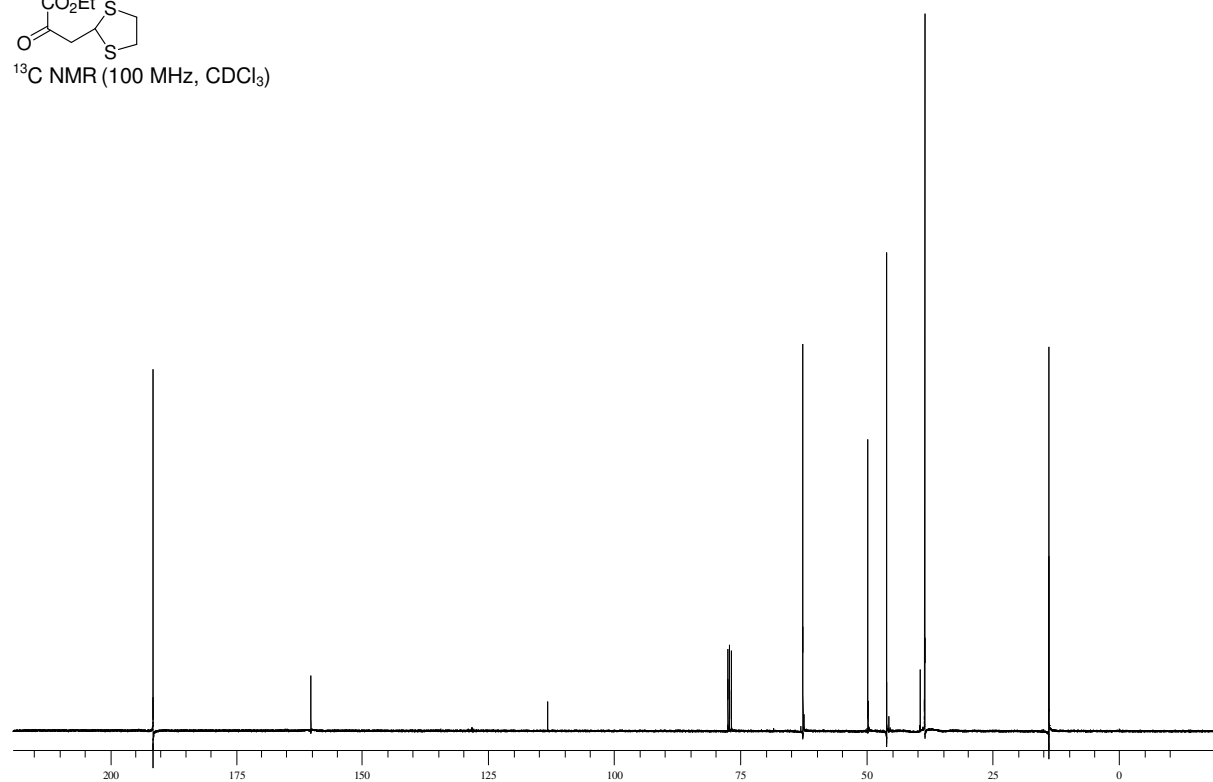
Ethyl 3-(1,3-dithiolan-2-yl)-2-oxopropanoate (5)



^1H NMR (200 MHz, CDCl_3)

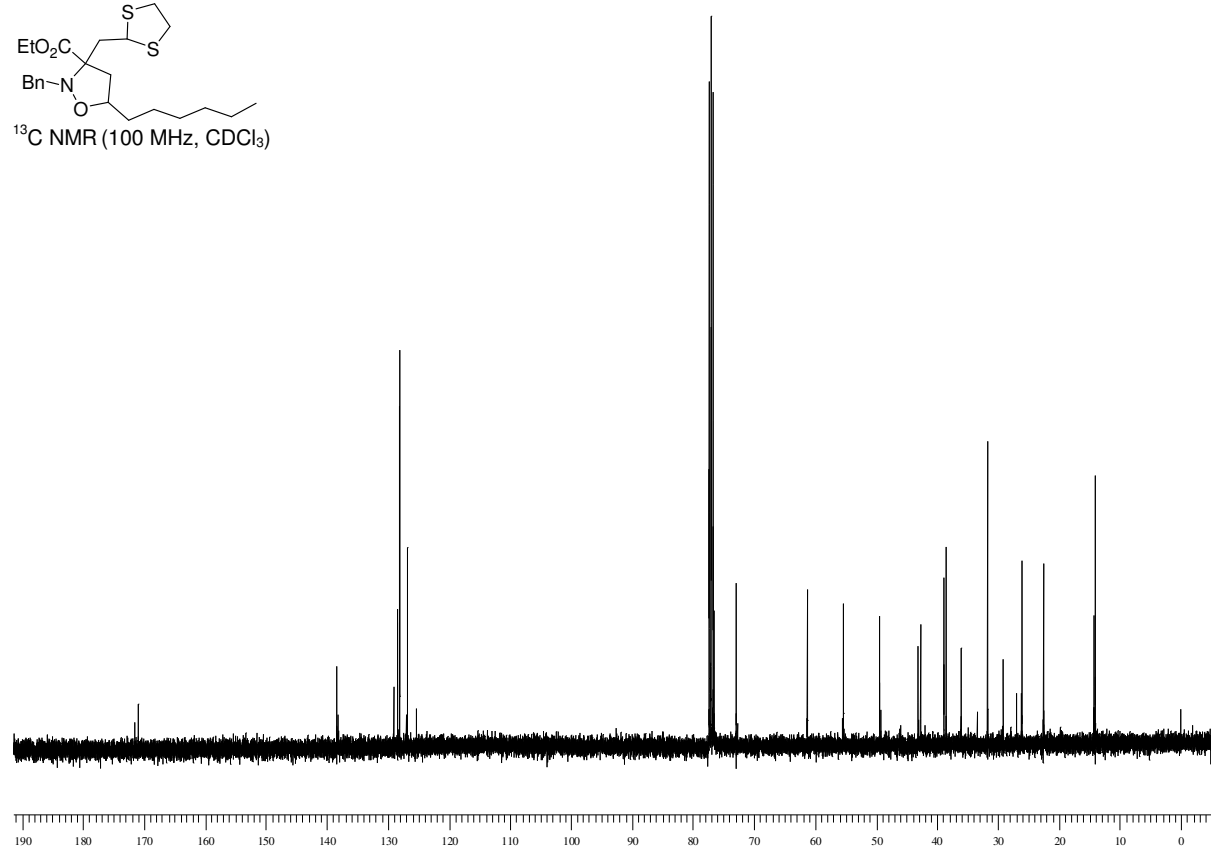
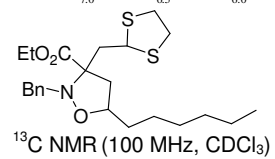
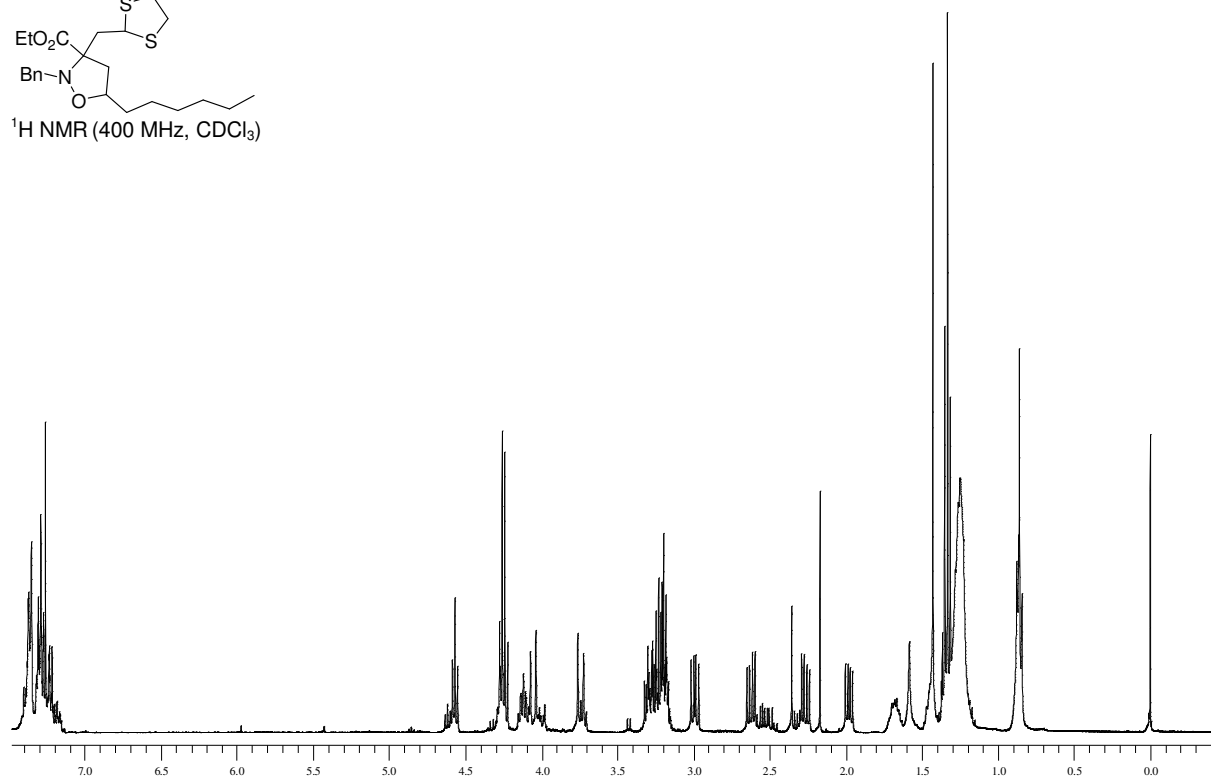
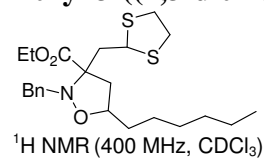


^{13}C NMR (100 MHz, CDCl_3)

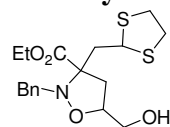


Adducts of nitron 4 and alkenes 7a-i

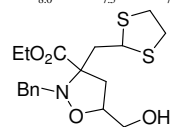
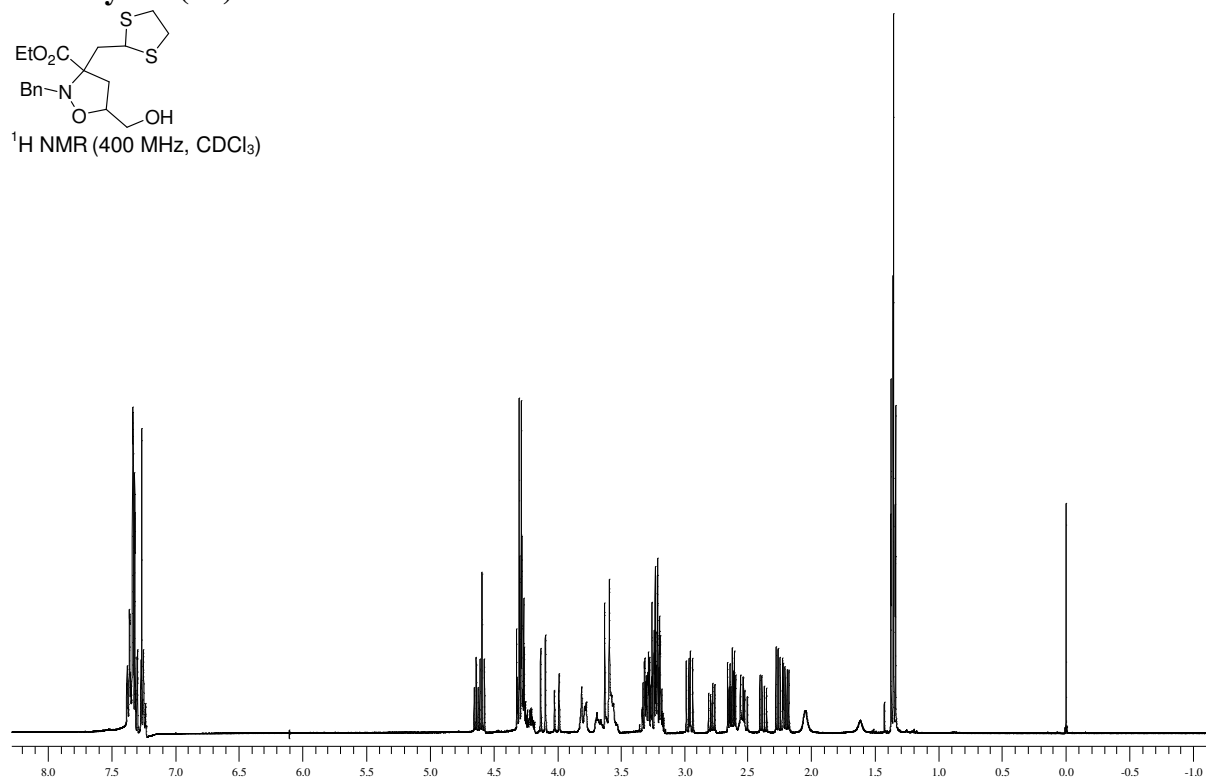
Ethyl 3-((1,3-dithiolan-2-yl)methyl)-2-benzyl-5-hexylisoxazolidine-3-carboxylate (8a)



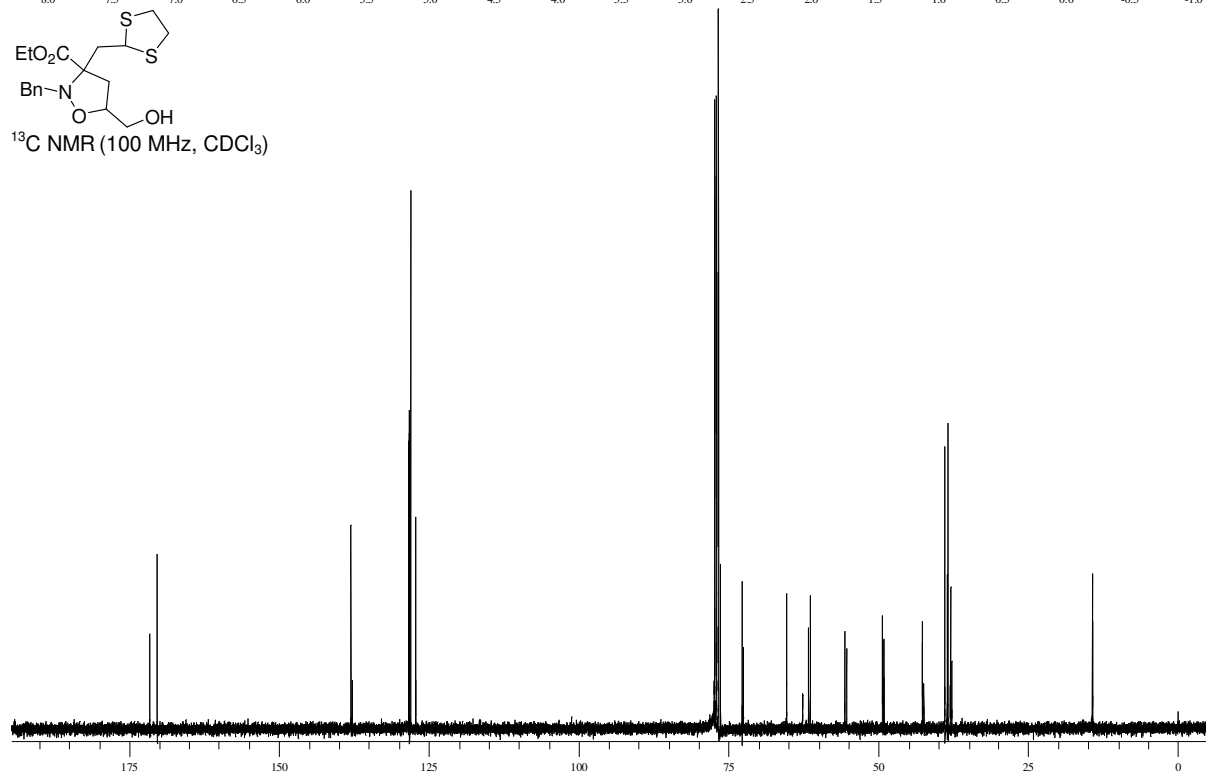
Ethyl 3-((1,3-dithiolan-2-yl)methyl)-2-benzyl-5-(hydroxymethyl)isoxazolidine-3-carboxylate (8b)



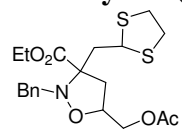
^1H NMR (400 MHz, CDCl_3)



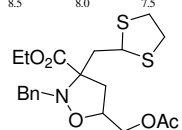
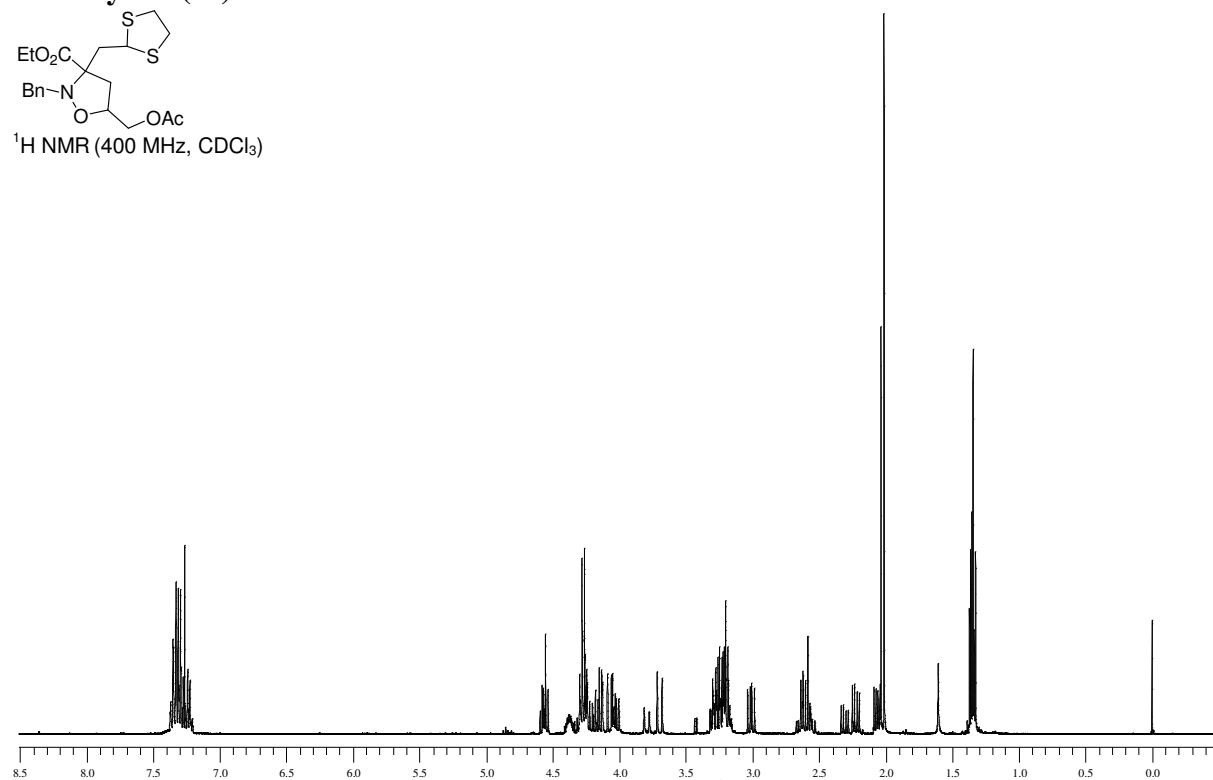
^{13}C NMR (100 MHz, CDCl_3)



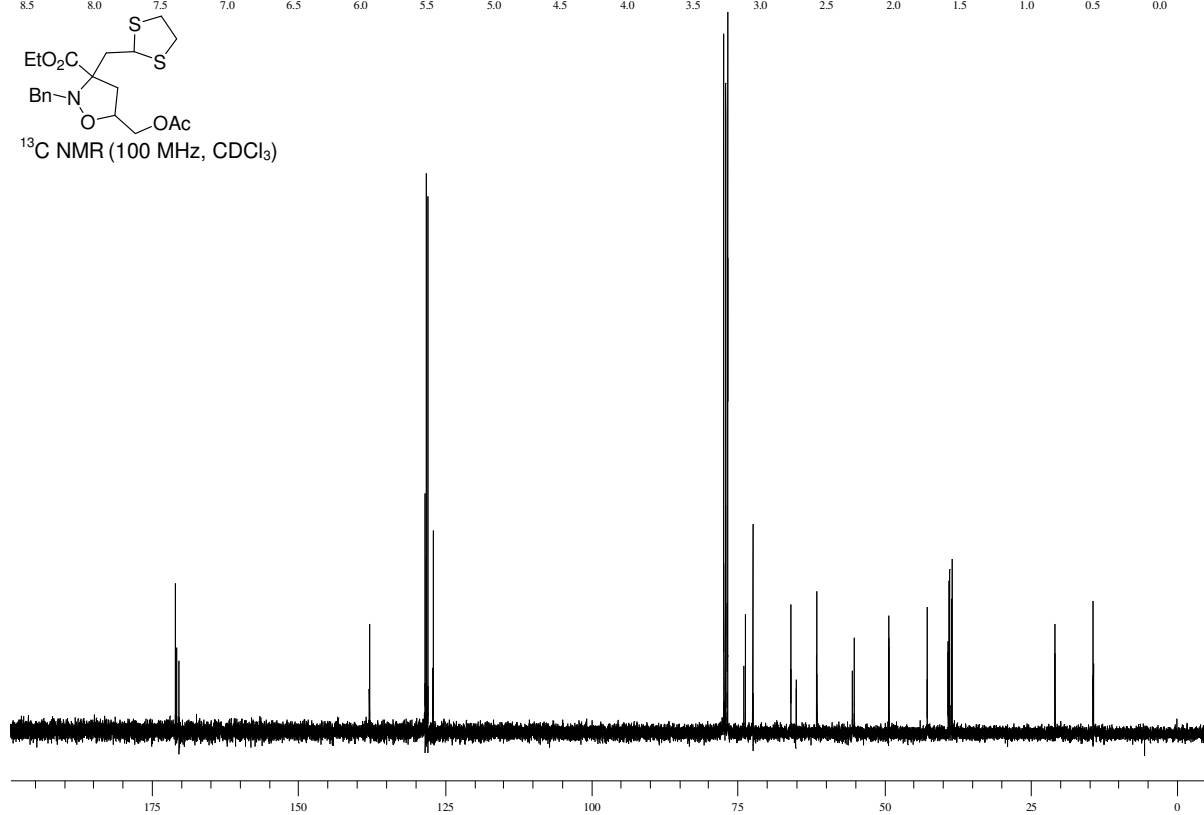
Ethyl 3-((1,3-dithiolan-2-yl)methyl)-5-(acetoxymethyl)-2-benzylisoxazolidine-3-carboxylate (8c)



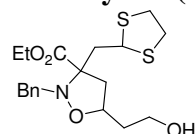
^1H NMR (400 MHz, CDCl_3)



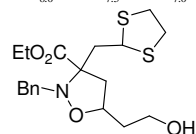
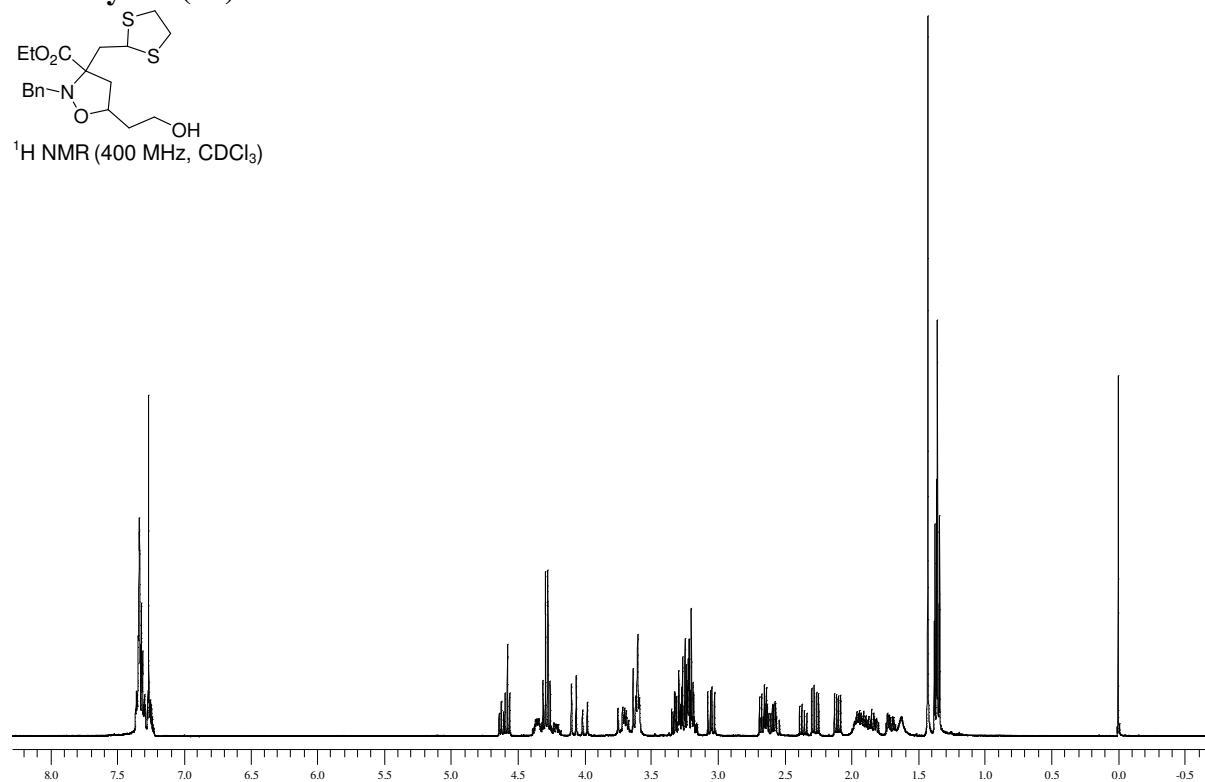
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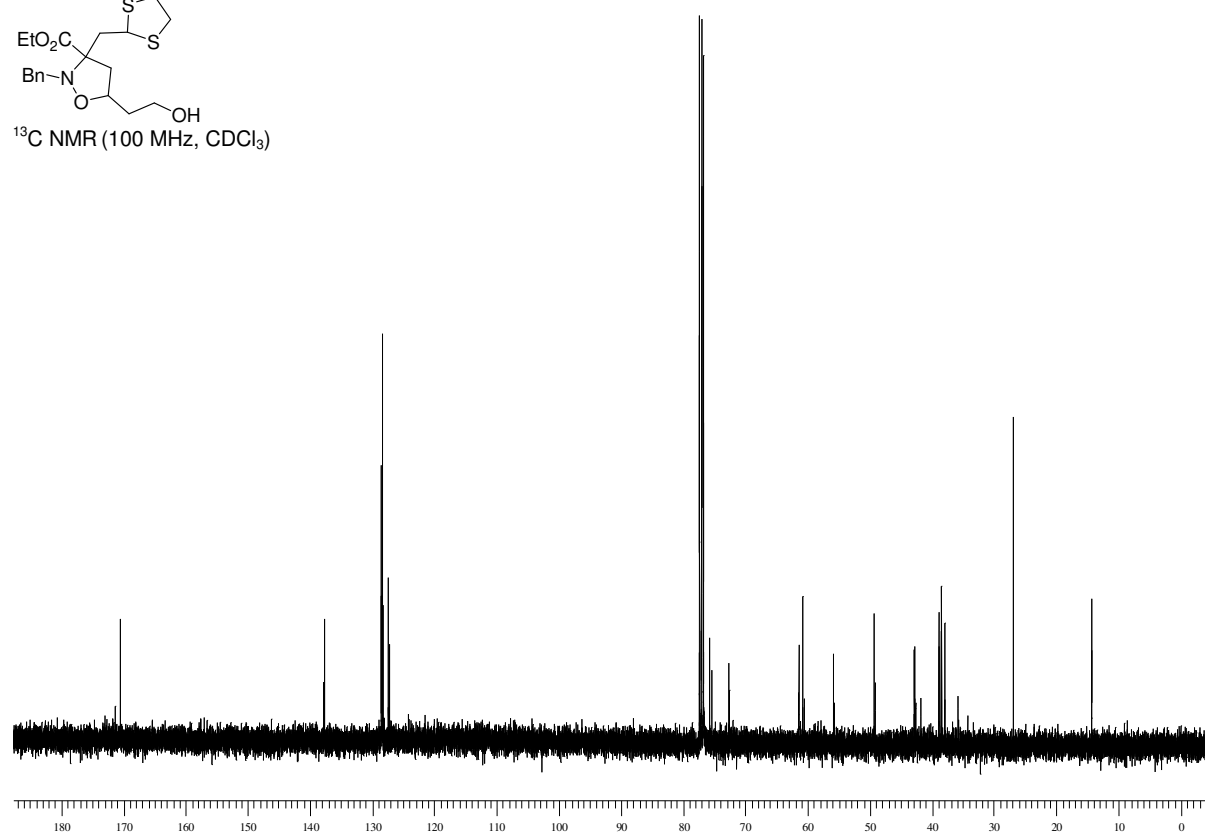
Ethyl 3-((1,3-dithiolan-2-yl)methyl)-2-benzyl-5-(2-hydroxyethyl)isoxazolidine-3-carboxylate (8d)



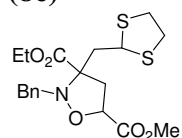
^1H NMR (400 MHz, CDCl_3)



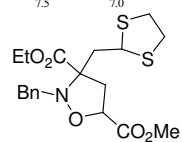
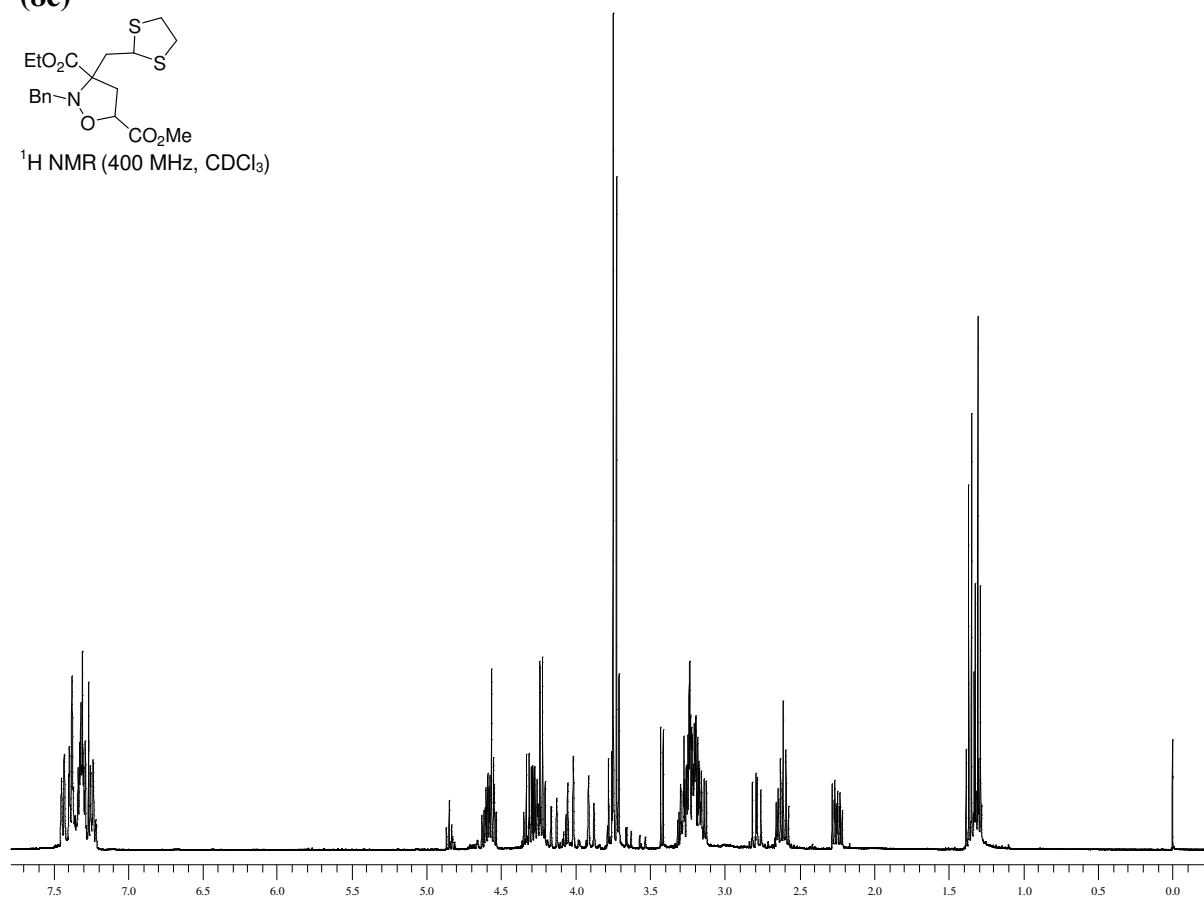
^{13}C NMR (100 MHz, CDCl_3)



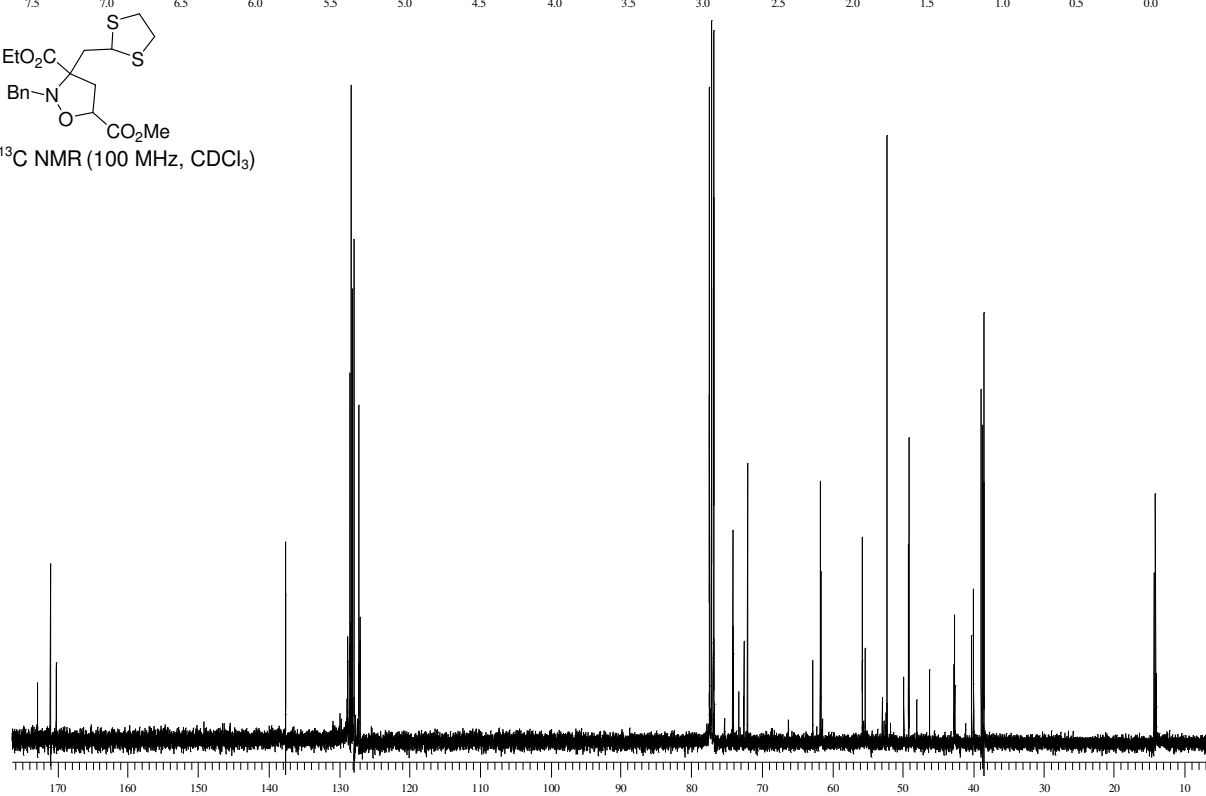
3-Ethyl 5-methyl 3-((1,3-dithiolan-2-yl)methyl)-2-benzylisoxazolidine-3,5-dicarboxylate (8e)



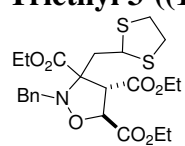
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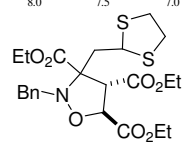
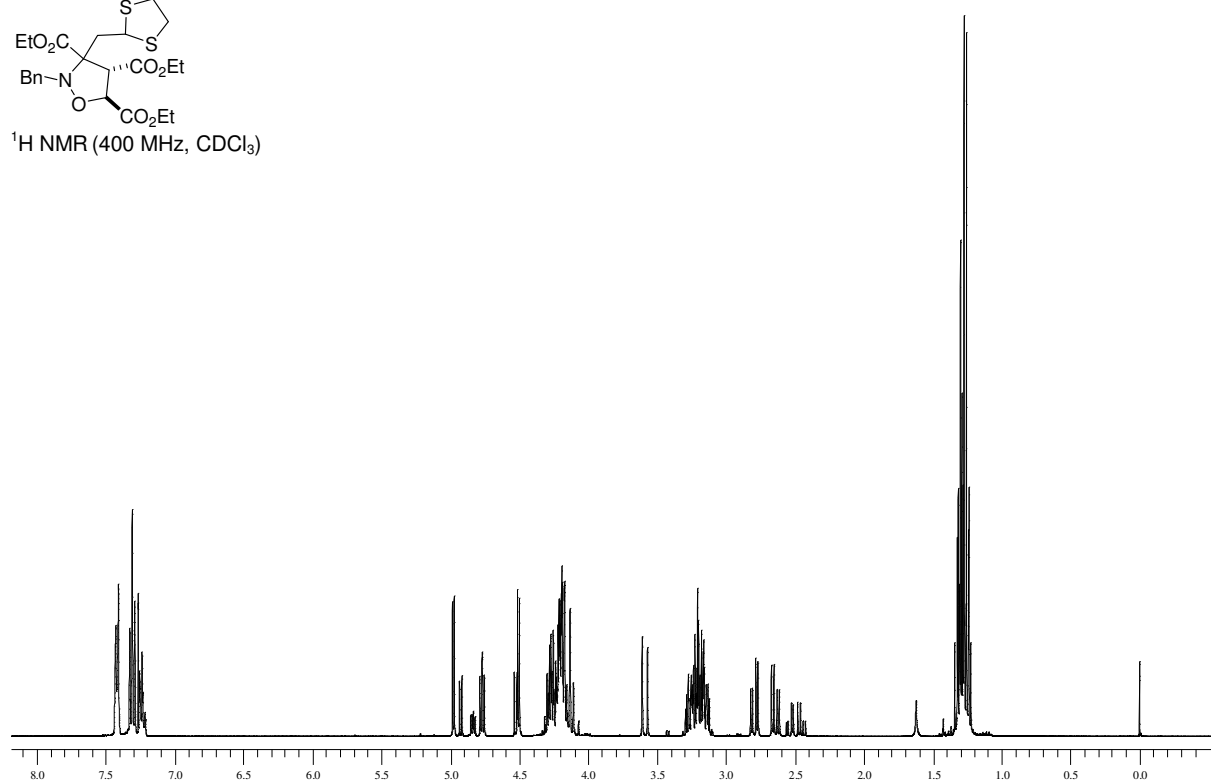
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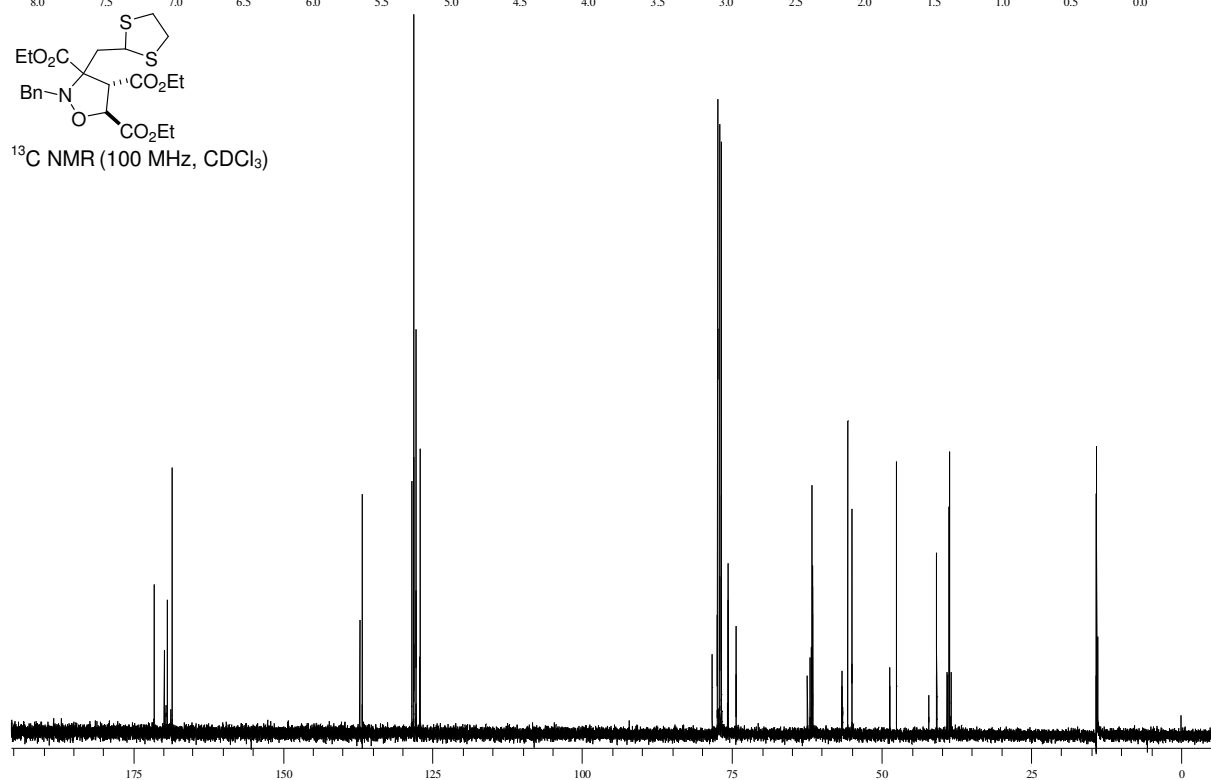
Triethyl 3-((1,3-dithiolan-2-yl)methyl)-2-benzylisoxazolidine-3,4,5-tricarboxylate (8f)



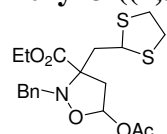
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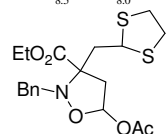
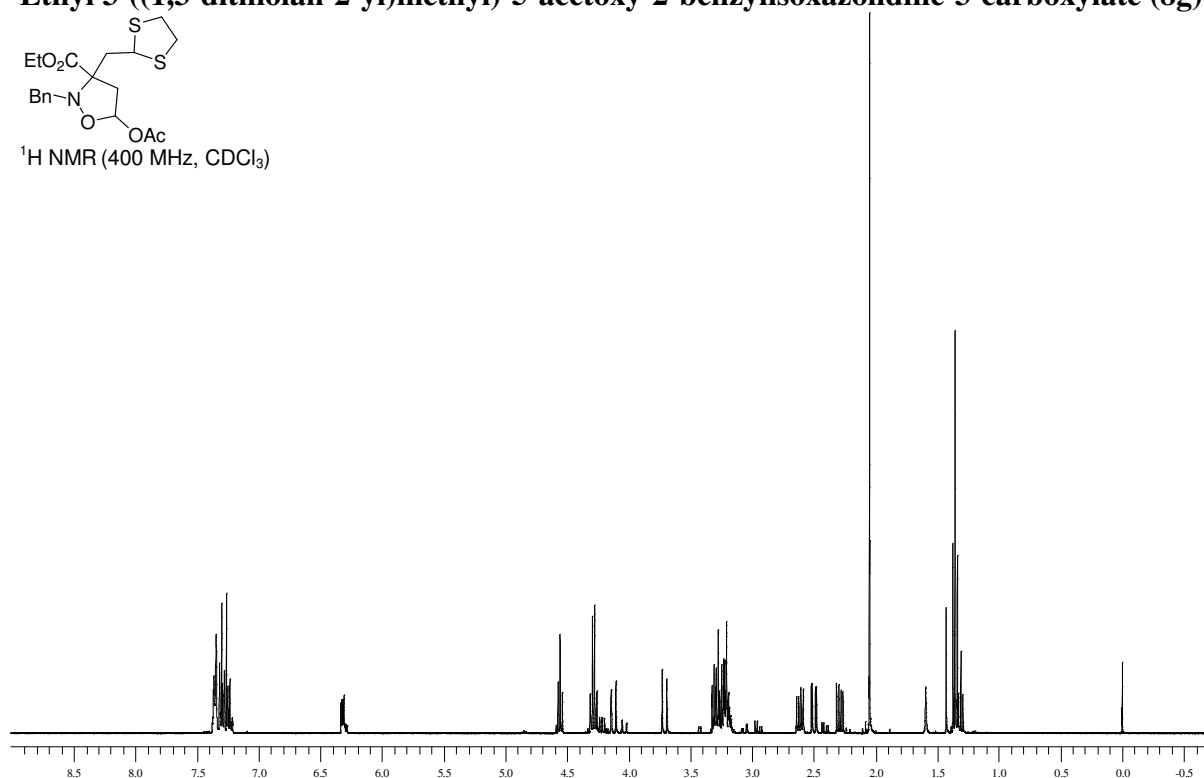
^{13}C NMR (100 MHz, CDCl_3)



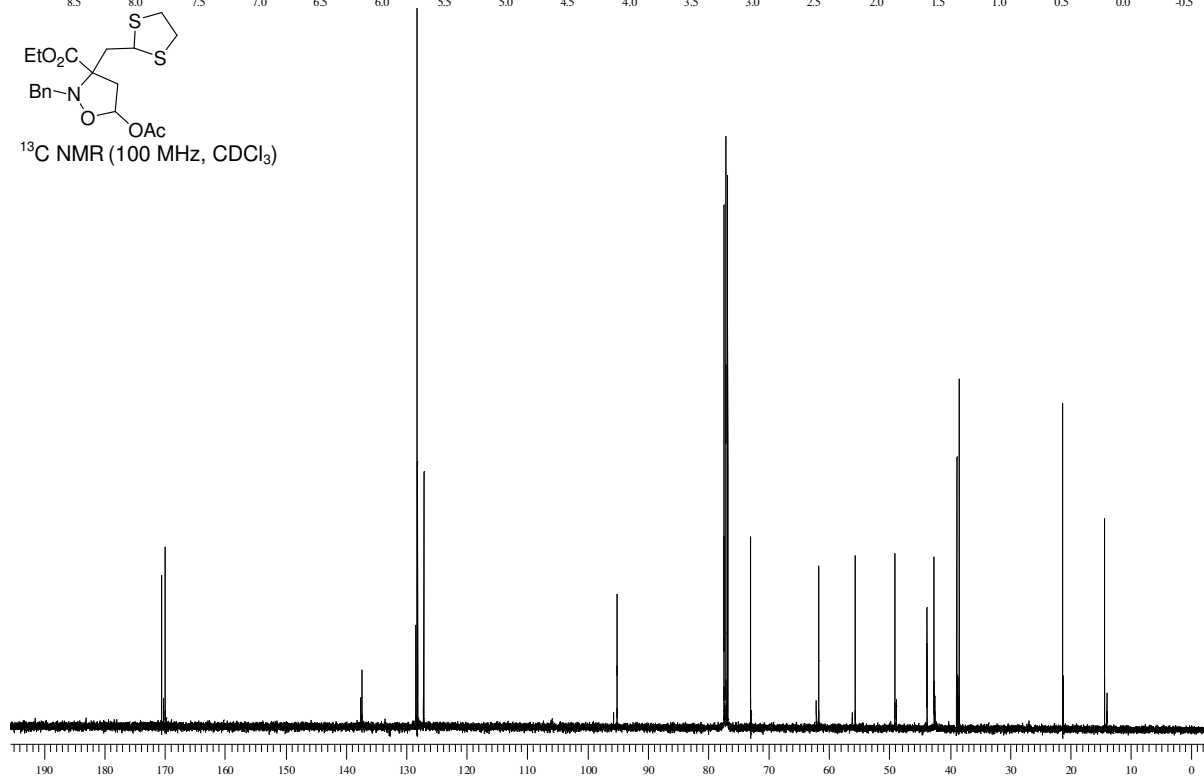
Ethyl 3-((1,3-dithiolan-2-yl)methyl)-5-acetoxy-2-benzylisoxazolidine-3-carboxylate (8g)



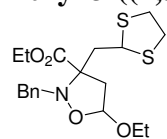
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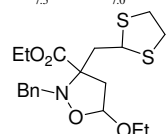
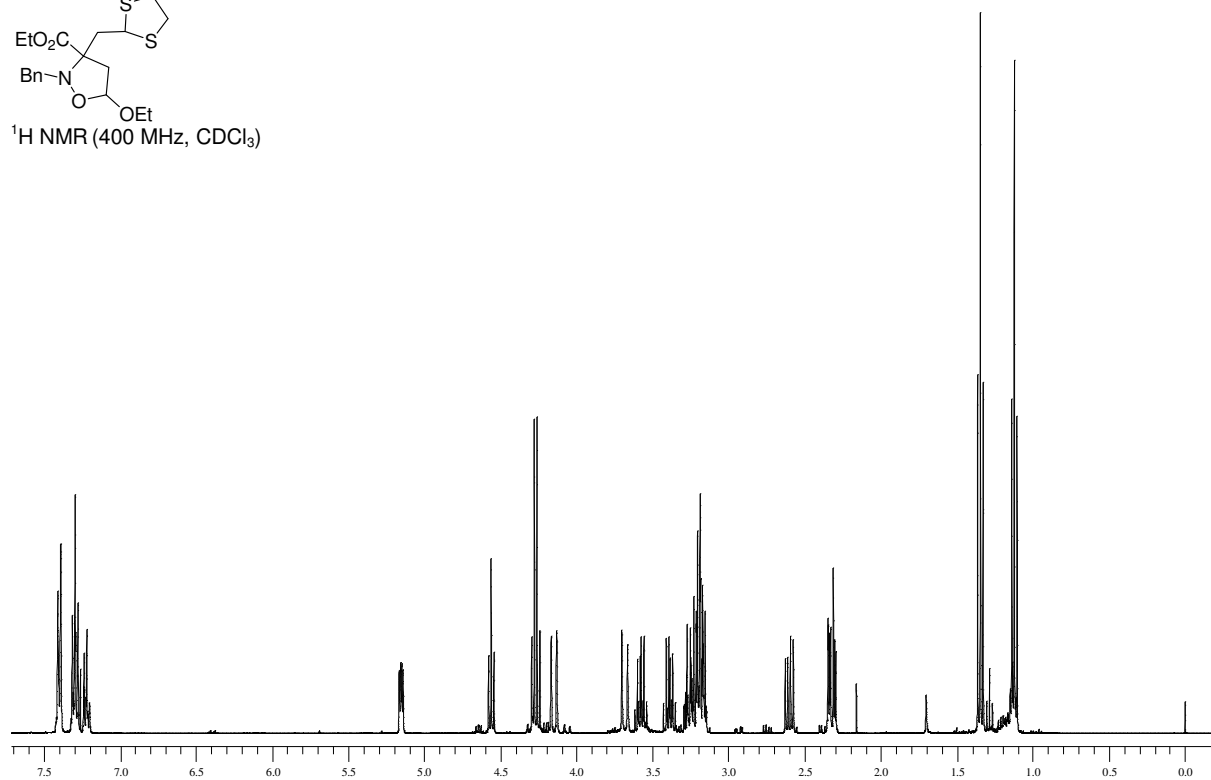
^{13}C NMR (100 MHz, CDCl_3)



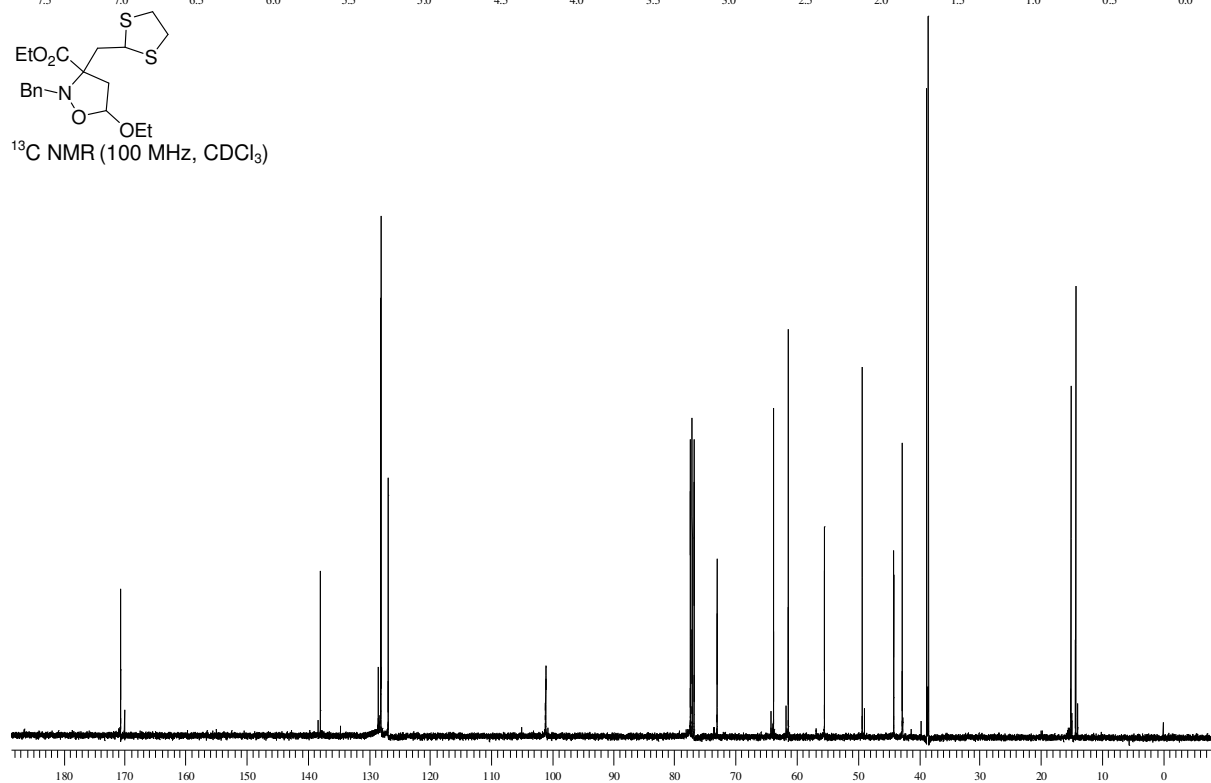
Ethyl 3-((1,3-dithiolan-2-yl)methyl)-5-acetoxy-2-benzylisoxazolidine-3-carboxylate (8h)



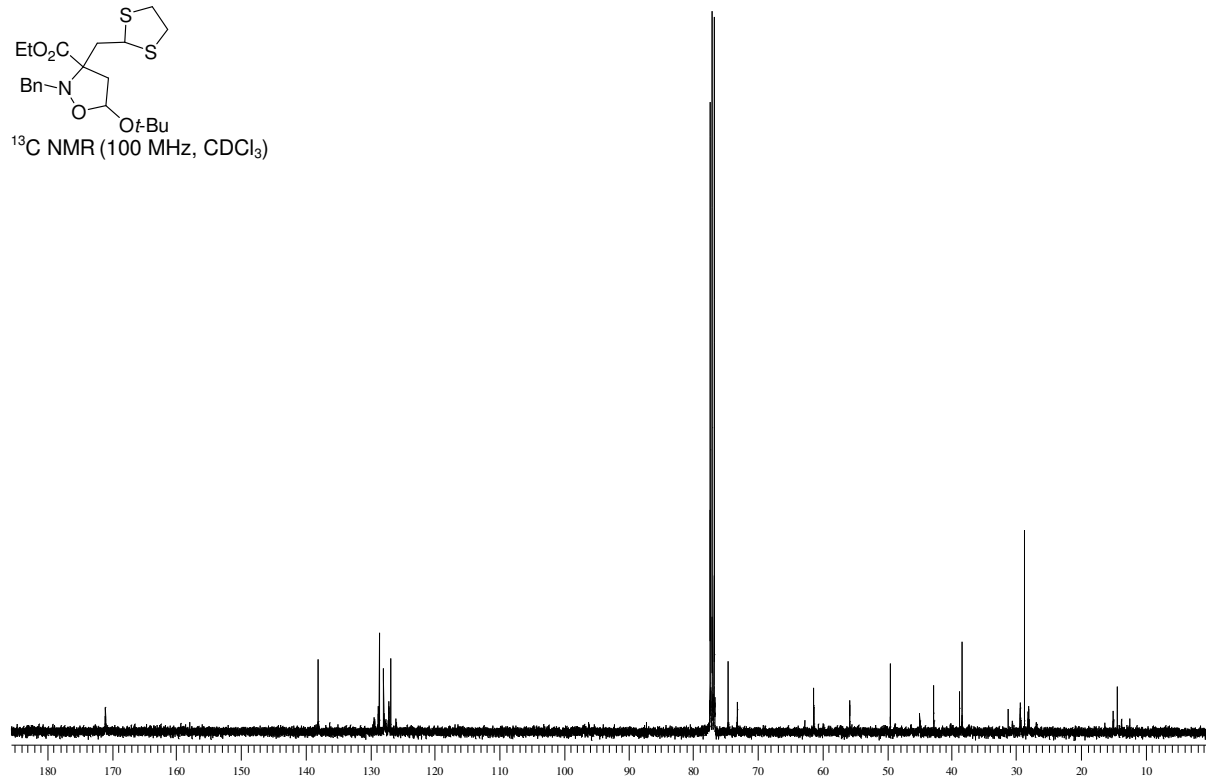
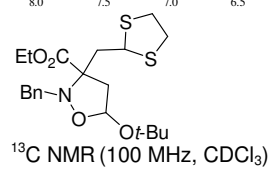
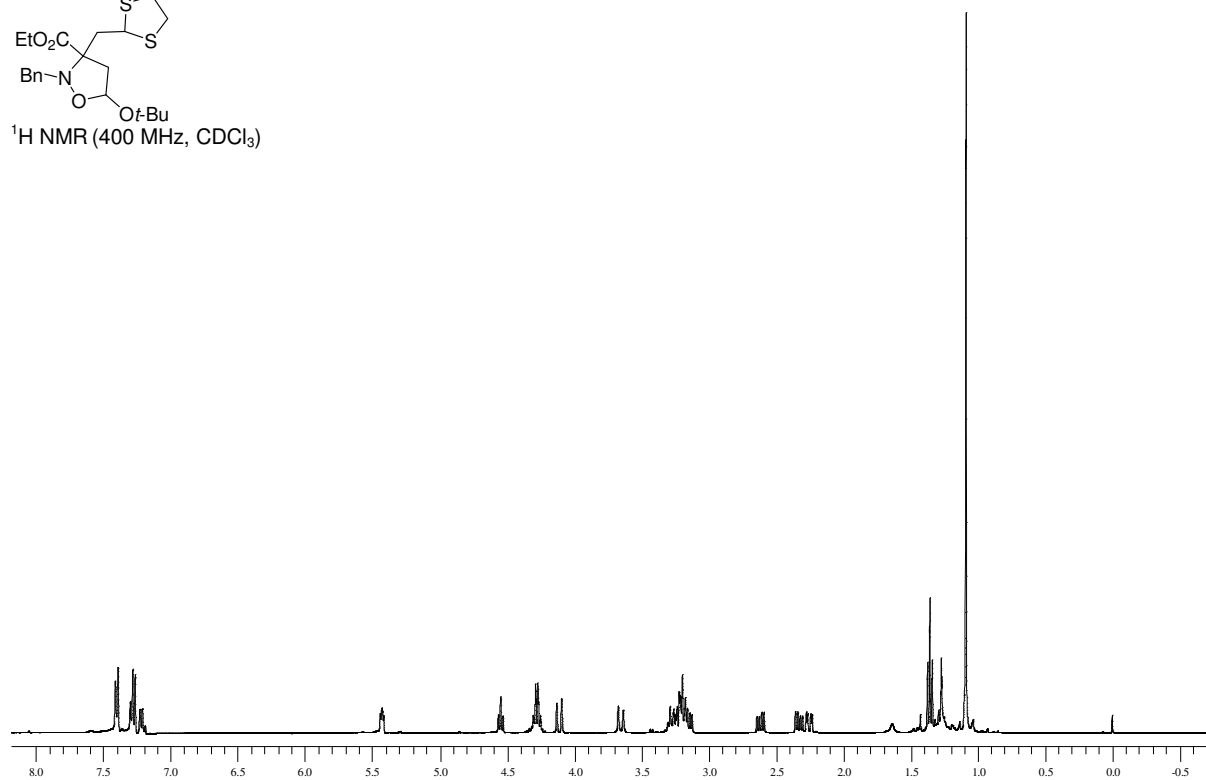
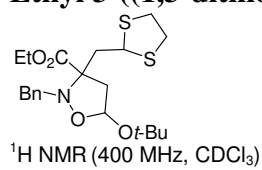
^1H NMR (400 MHz, CDCl_3)



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

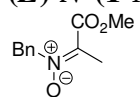


Ethyl 3-((1,3-dithiolan-2-yl)methyl)-2-benzyl-5-ethoxyisoxazolidine-3-carboxylate (8i)

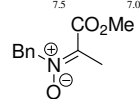
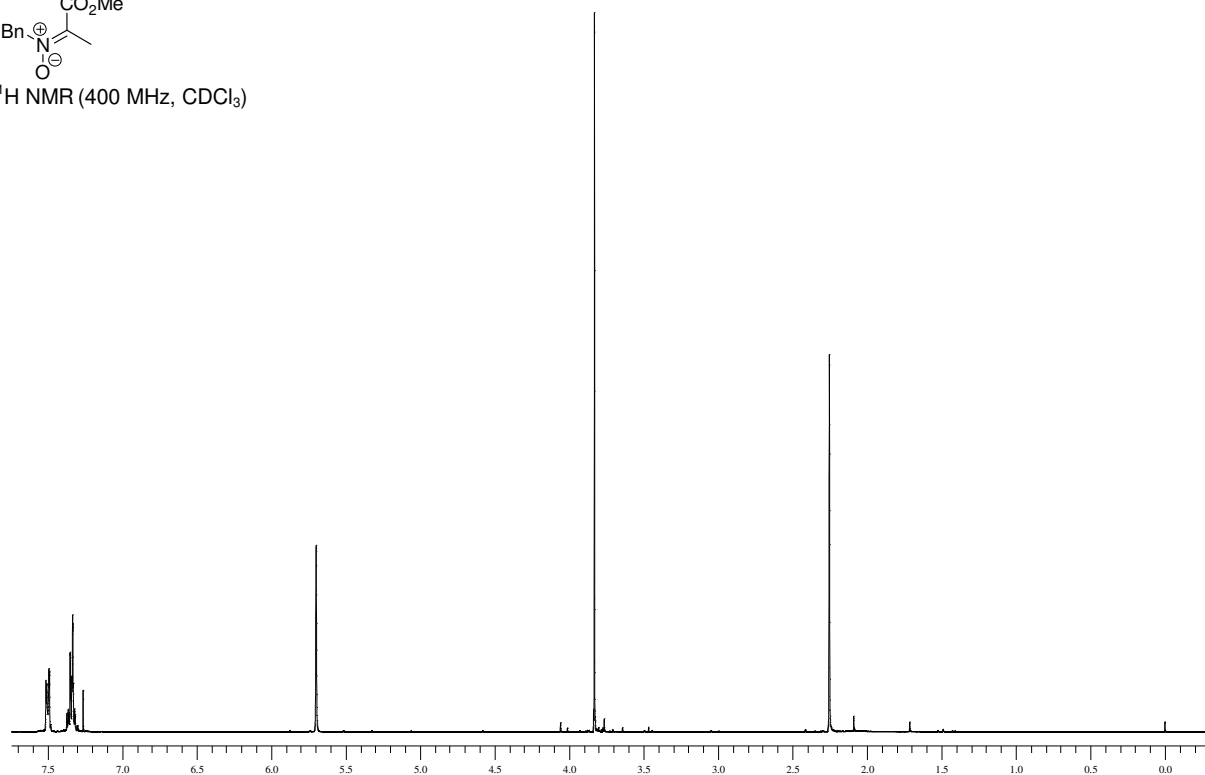


Nitrones 9a-d

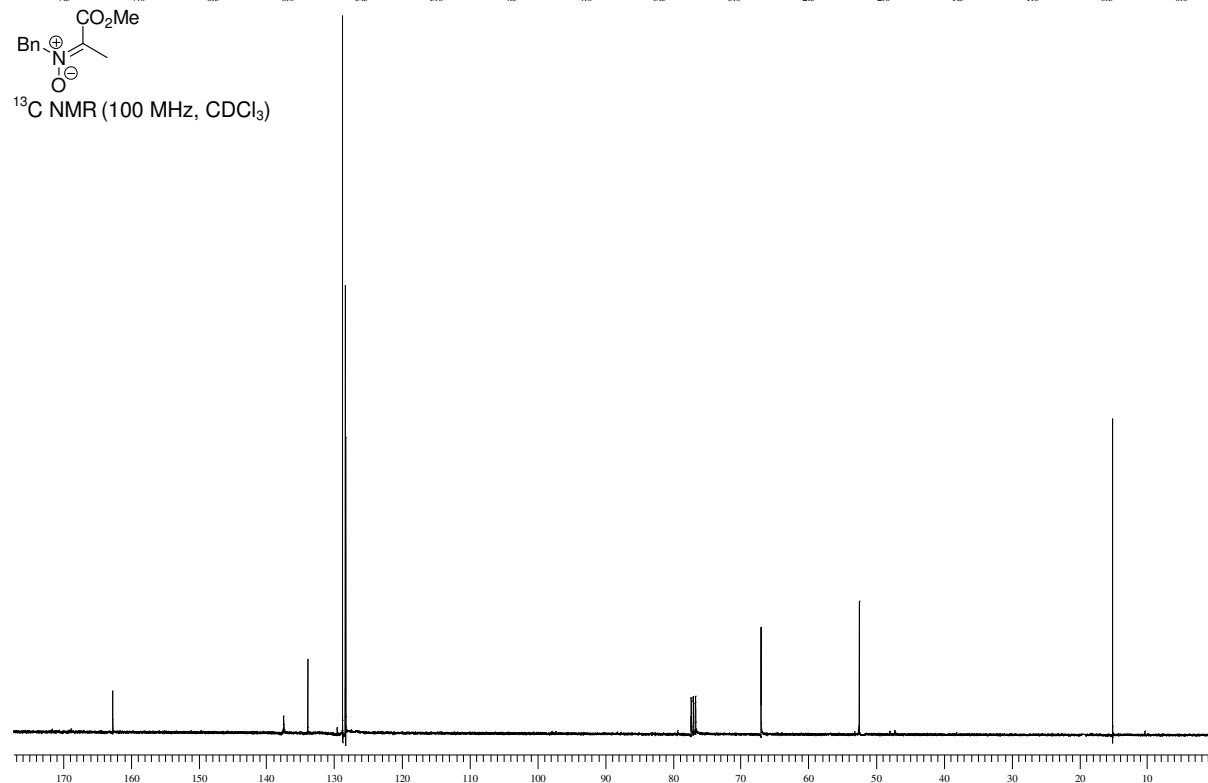
(*E*)-*N*-(1-Methoxy-1-oxopropan-2-ylidene)(phenyl)methanamine oxide (9a)



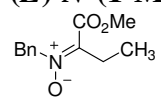
^1H NMR (400 MHz, CDCl_3)



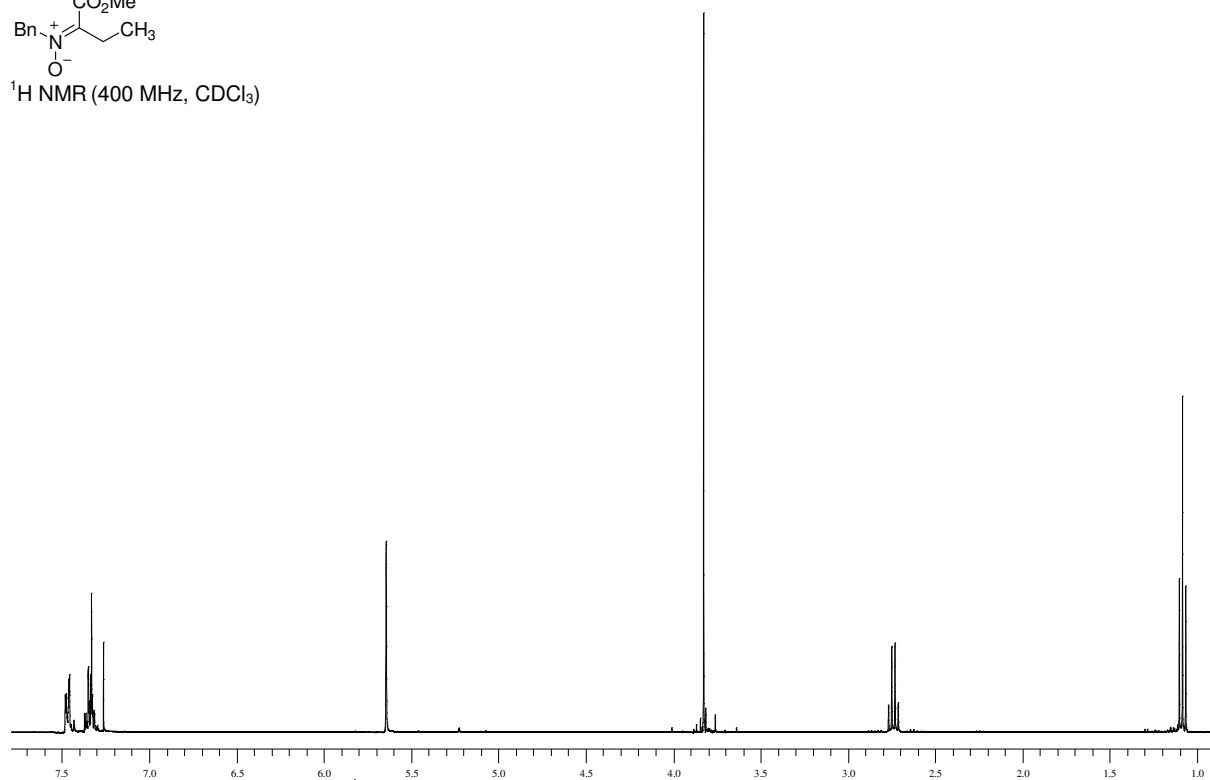
^{13}C NMR (100 MHz, CDCl_3)



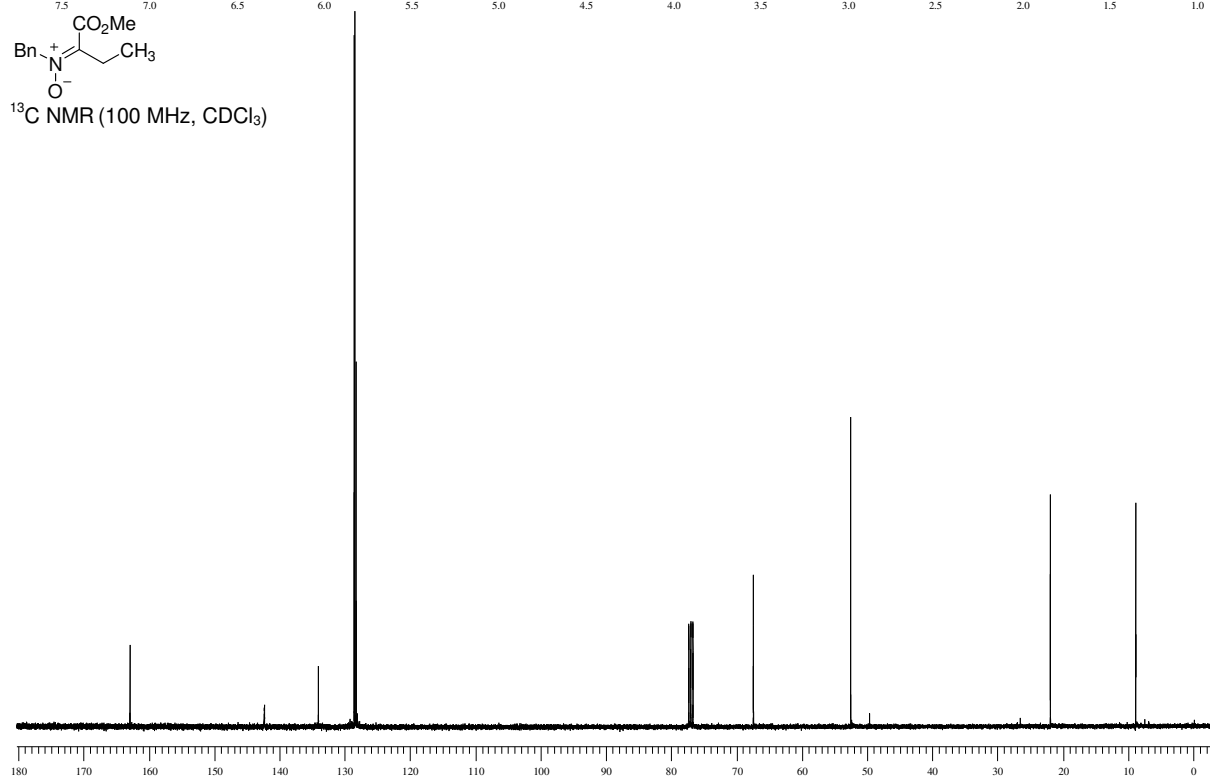
(E)-N-(1-Methoxy-1-oxobutan-2-ylidene)(phenyl)methanamine oxide (9b)



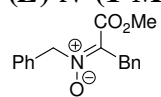
¹H NMR (400 MHz, CDCl₃)



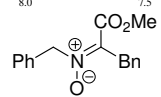
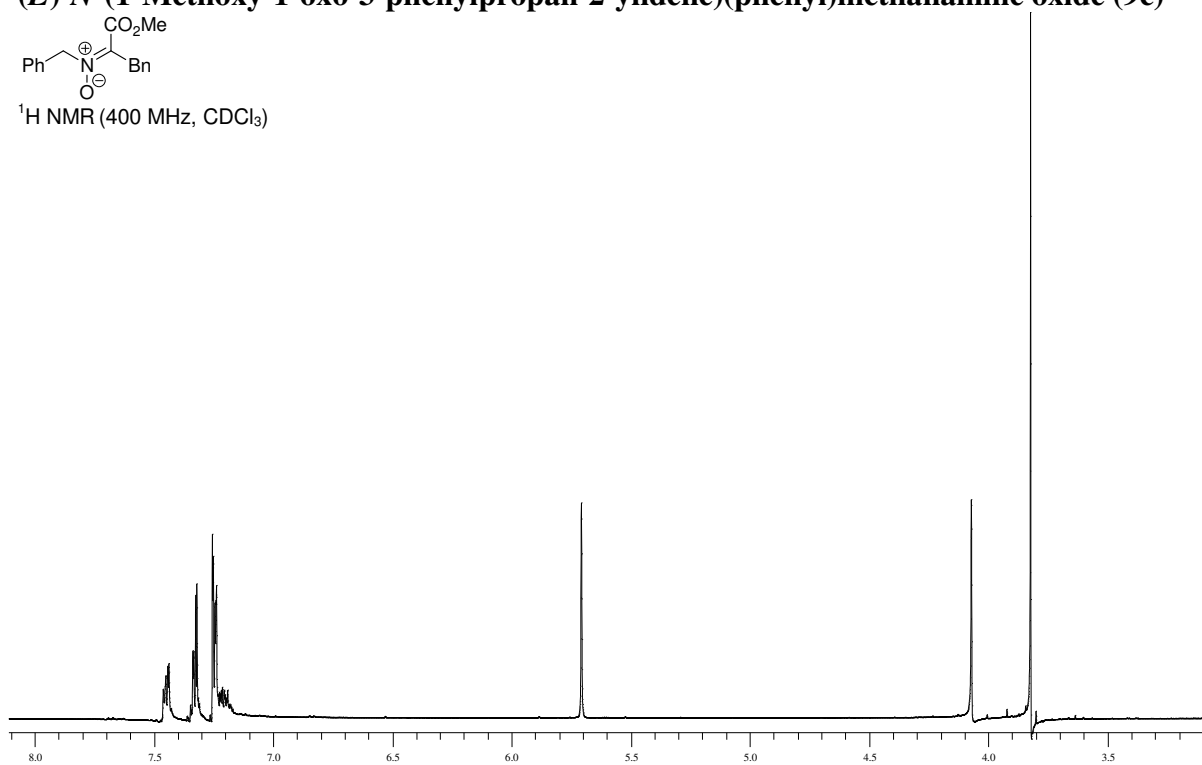
¹³C NMR (100 MHz, CDCl₃)



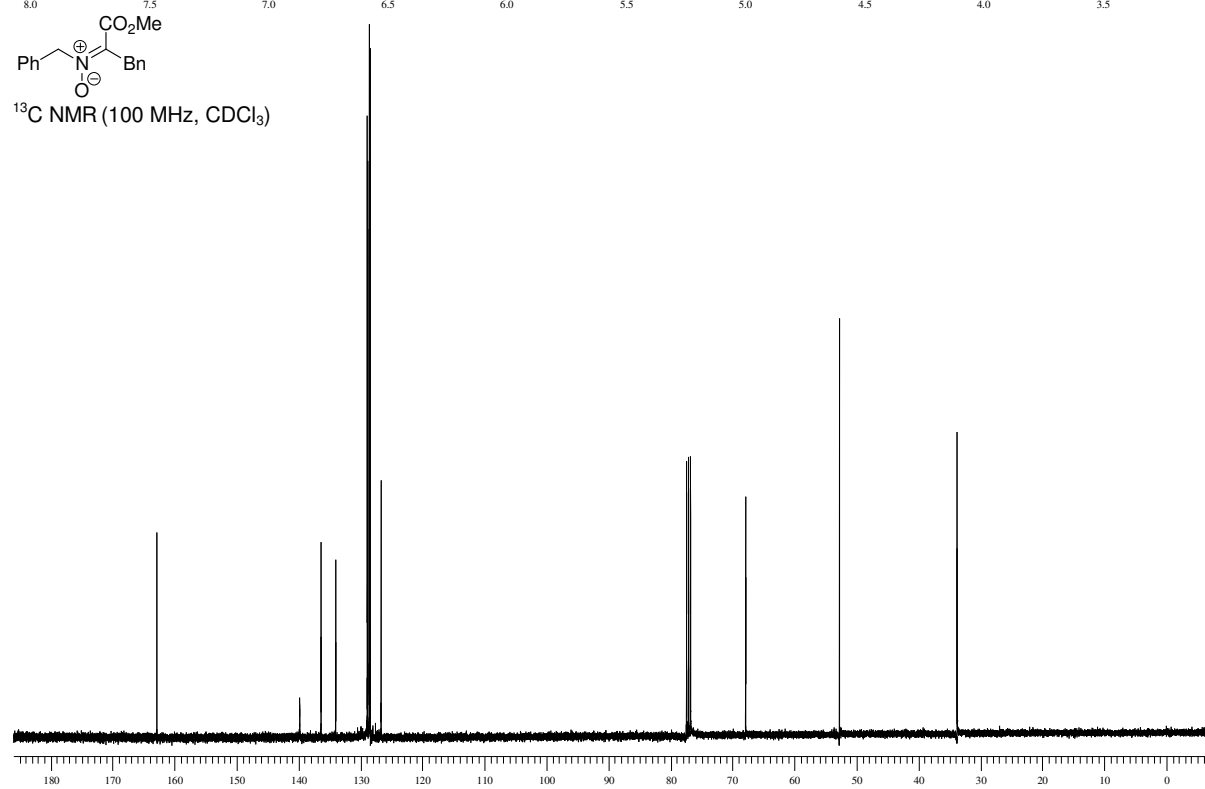
(E)-N-(1-Methoxy-1-oxo-3-phenylpropan-2-ylidene)(phenyl)methanamine oxide (9c)



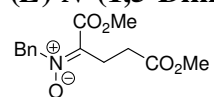
^1H NMR (400 MHz, CDCl_3)



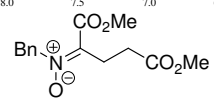
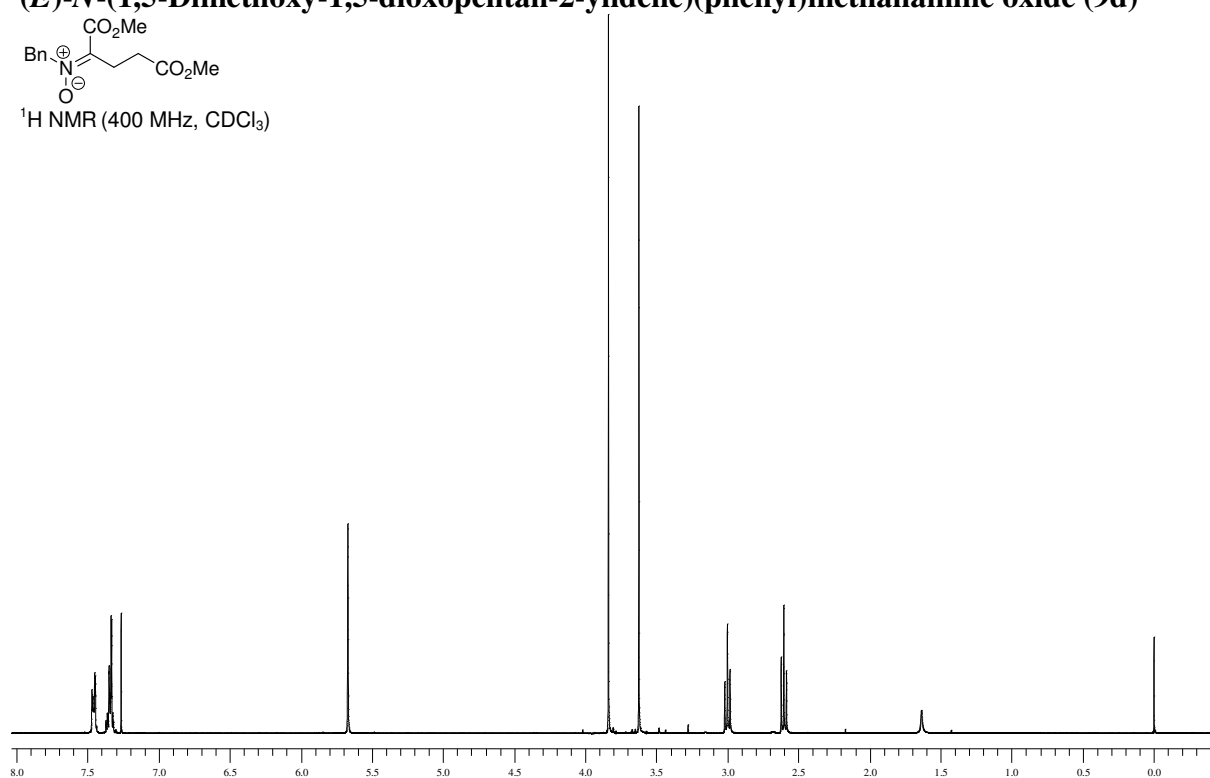
^{13}C NMR (100 MHz, CDCl_3)



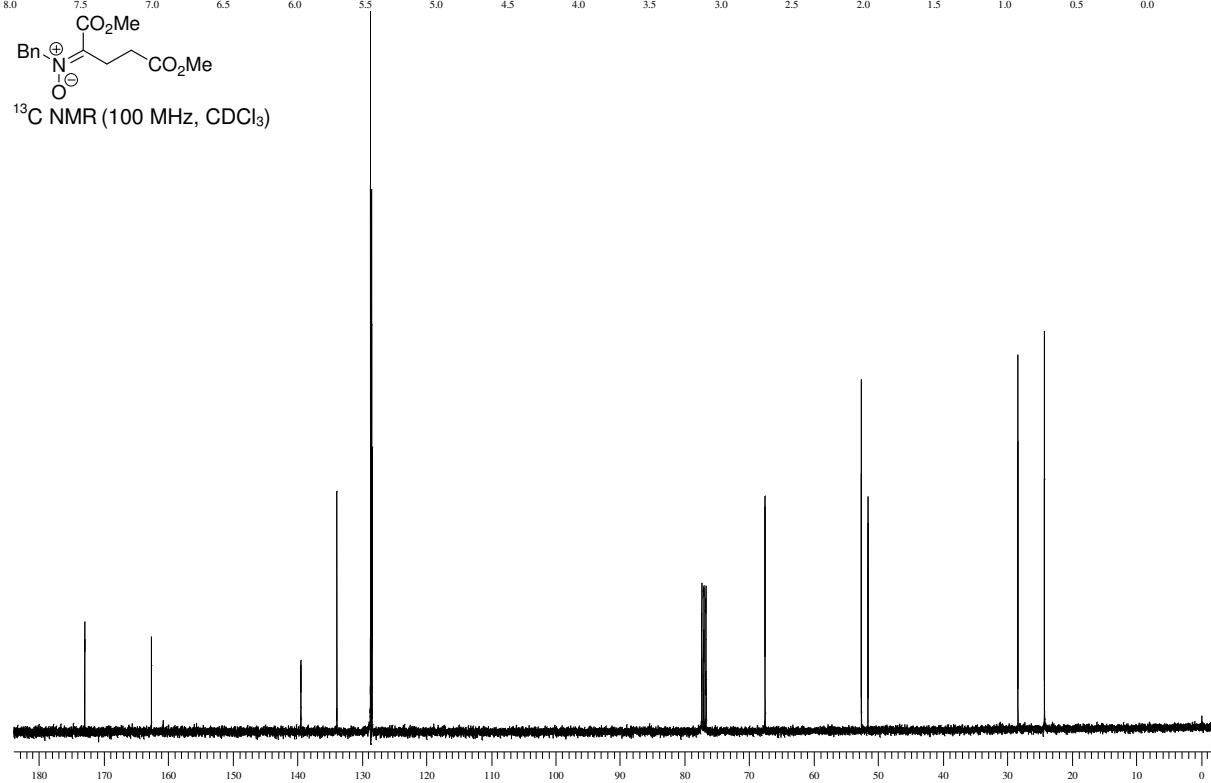
(E)-N-(1,5-Dimethoxy-1,5-dioxopentan-2-ylidene)(phenyl)methanamine oxide (9d)



^1H NMR (400 MHz, CDCl_3)

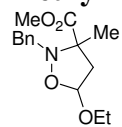


^{13}C NMR (100 MHz, CDCl_3)

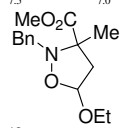
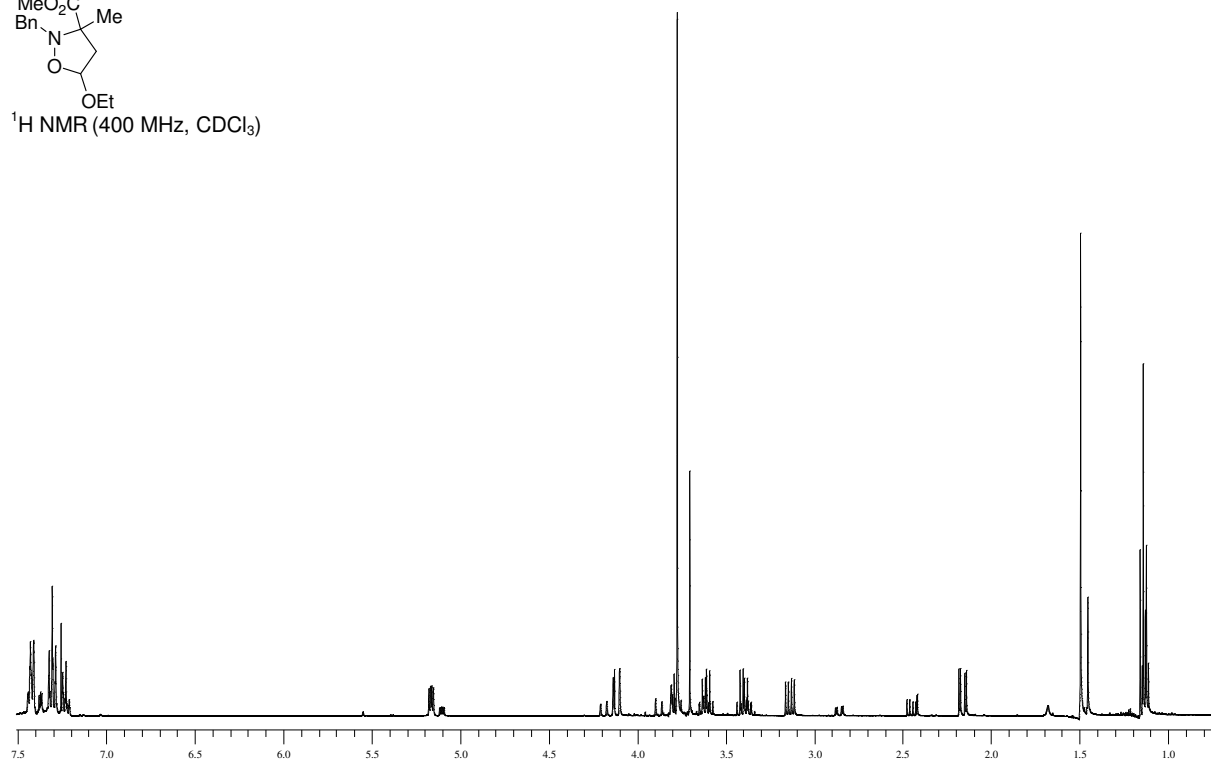


Adducts 10a-e

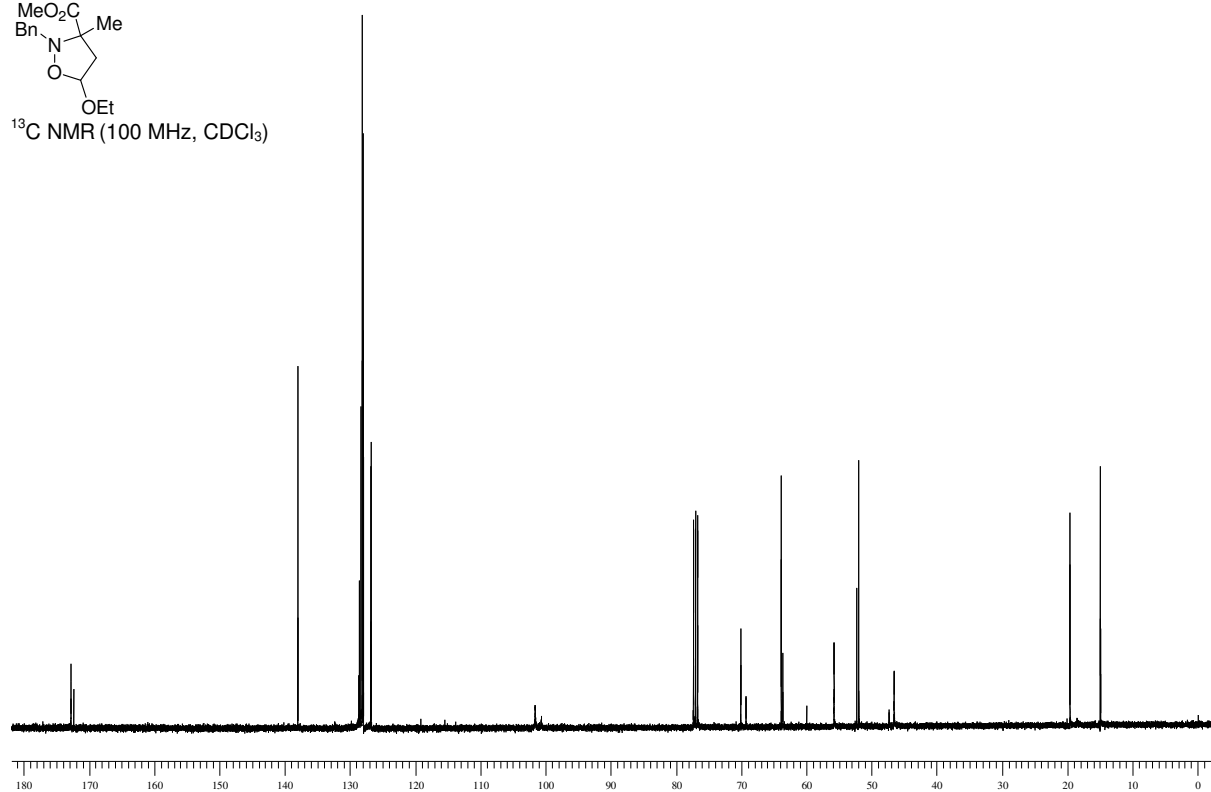
Methyl 2-benzyl-5-ethoxy-3-methylisoxazolidine-3-carboxylate (10a)



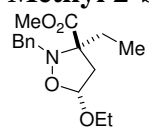
^1H NMR (400 MHz, CDCl_3)



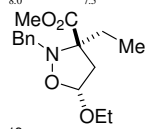
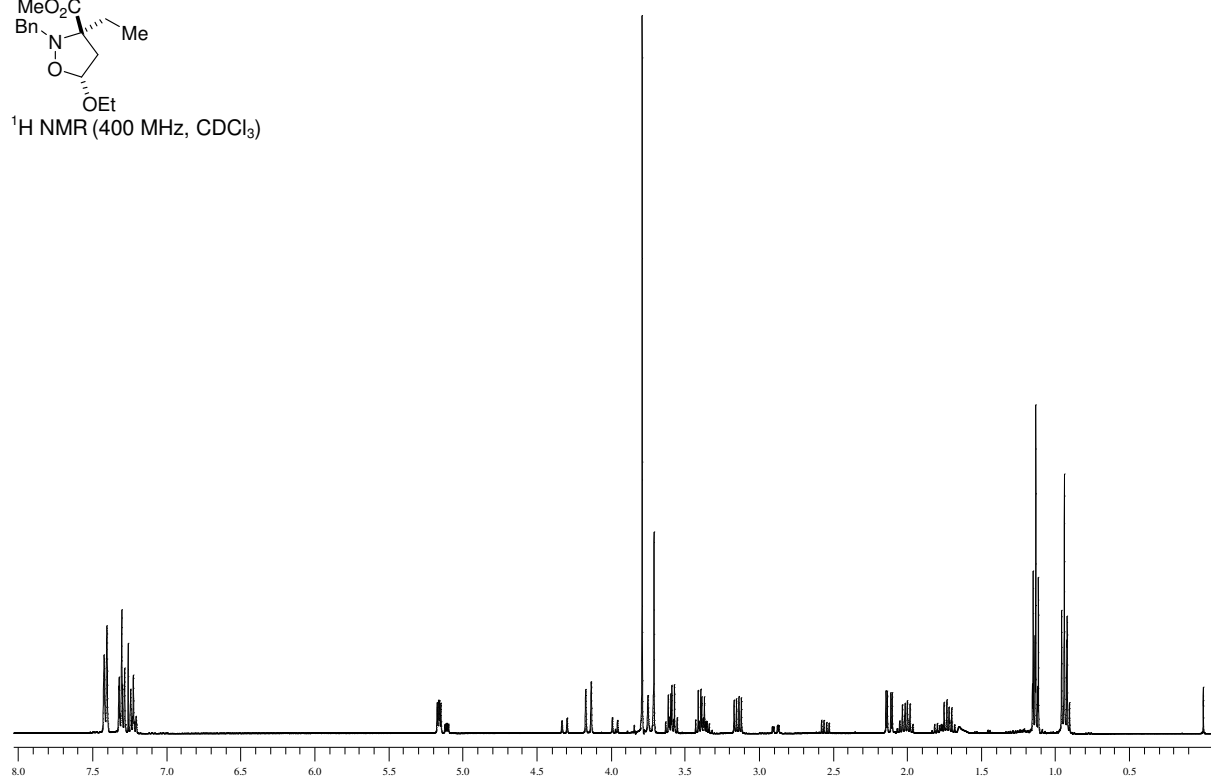
^{13}C NMR (100 MHz, CDCl_3)



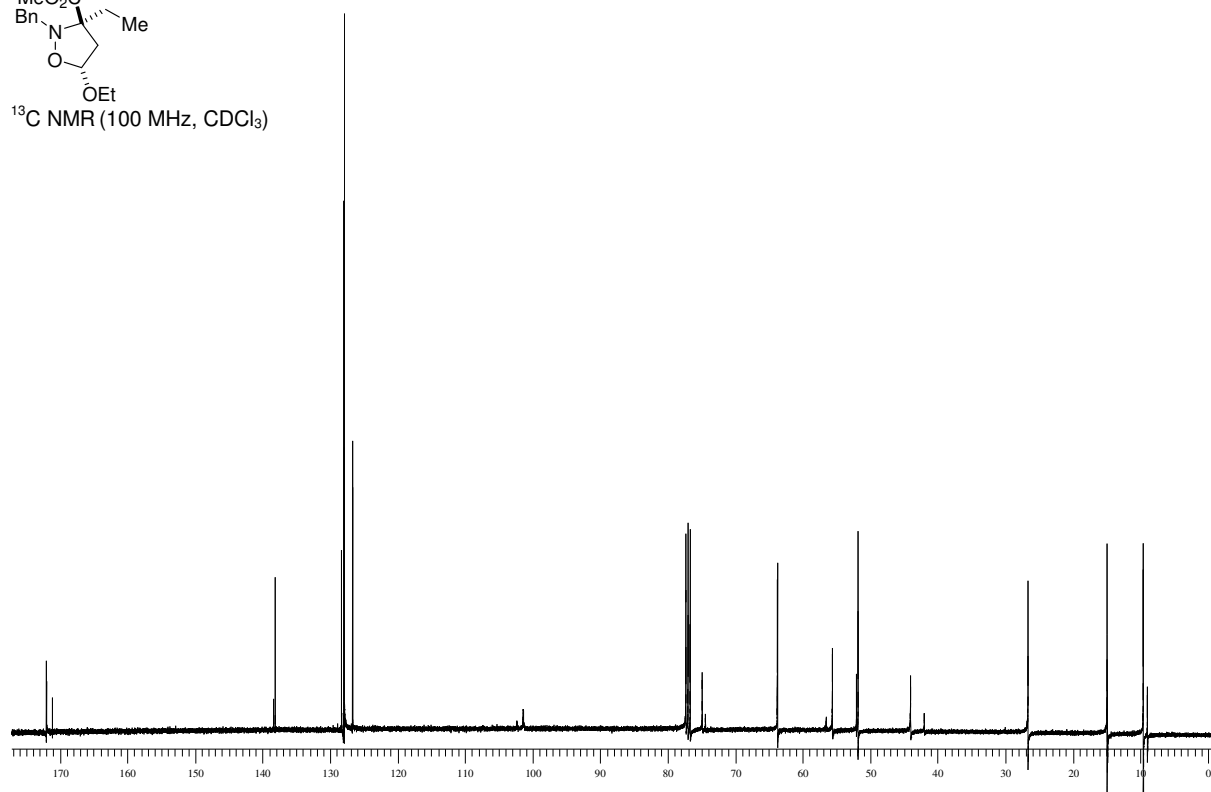
Methyl 2-benzyl-5-ethoxy-3-ethylisoxazolidine-3-carboxylate (10b)



^1H NMR (400 MHz, CDCl_3)

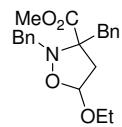


^{13}C NMR (100 MHz, CDCl_3)



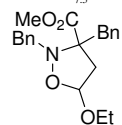
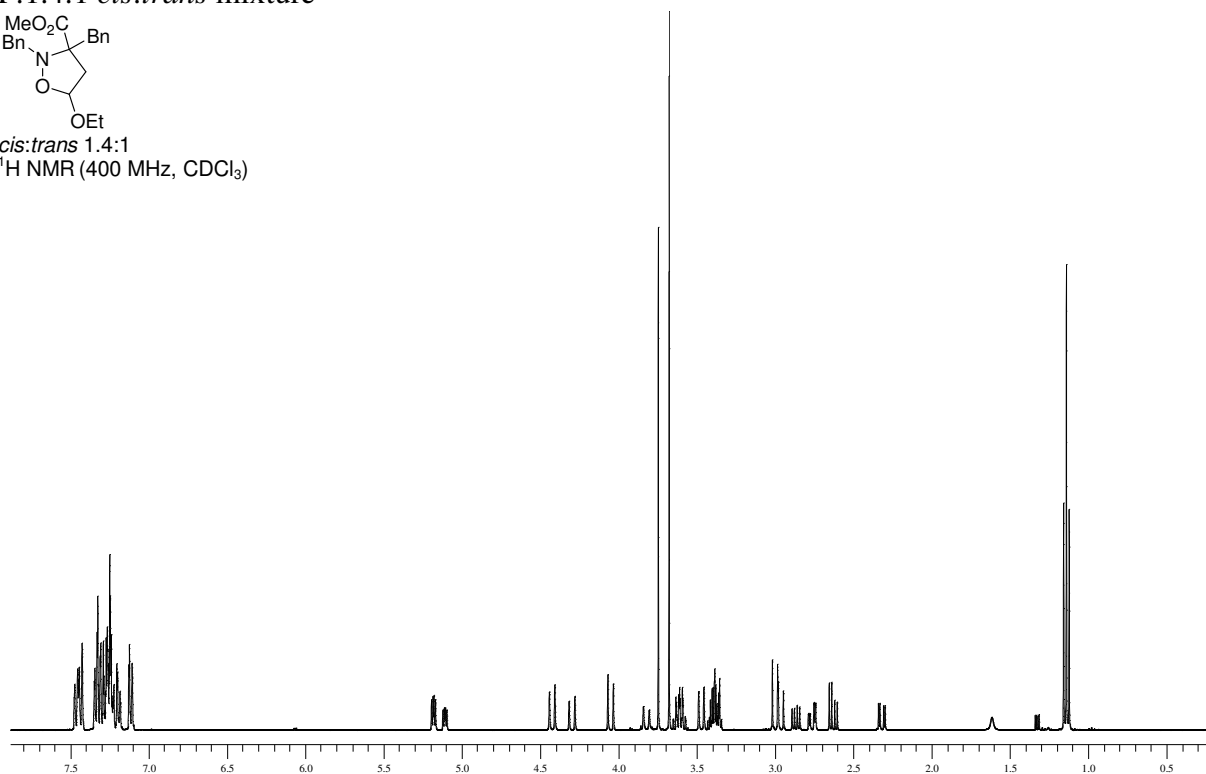
Methyl 2,3-dibenzyl-5-ethoxyisoxazolidine-3-carboxylate (10c)

F: 1.4:1 *cis:trans* mixture



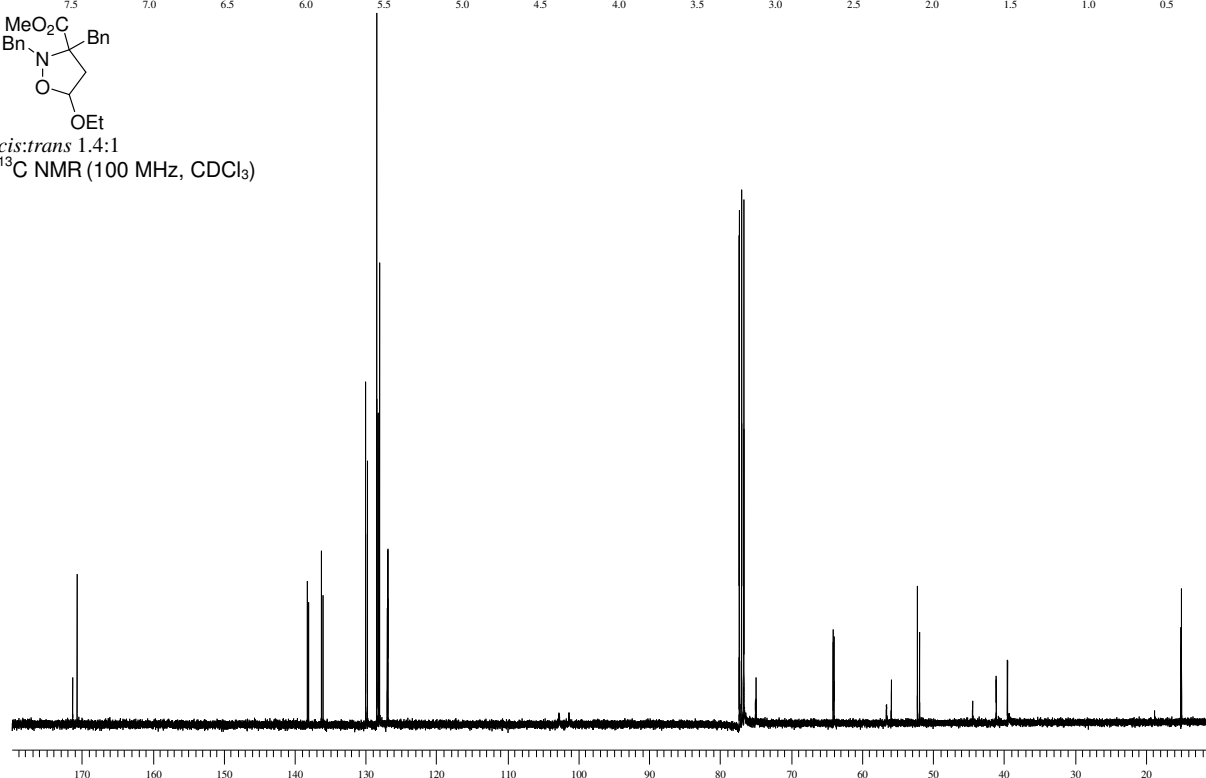
cis:trans 1.4:1

¹H NMR (400 MHz, CDCl₃)

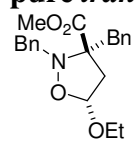


cis:trans 1.4:1

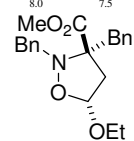
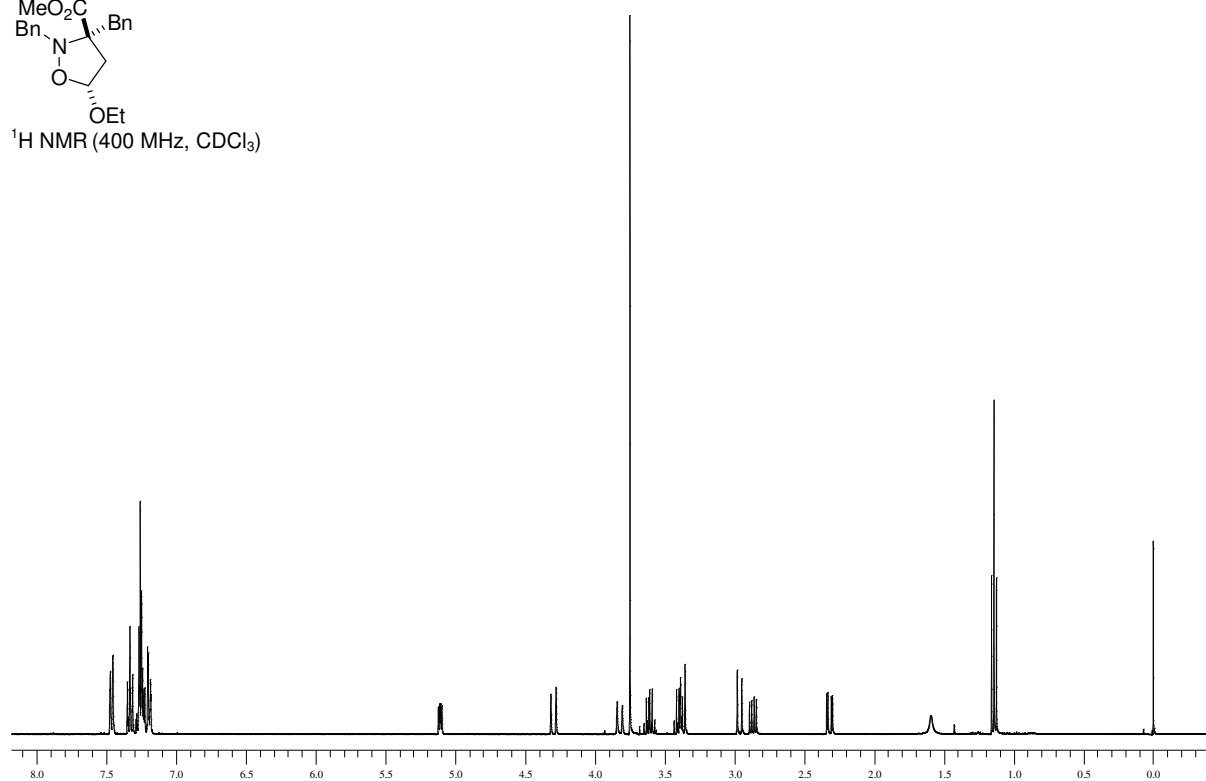
¹³C NMR (100 MHz, CDCl₃)



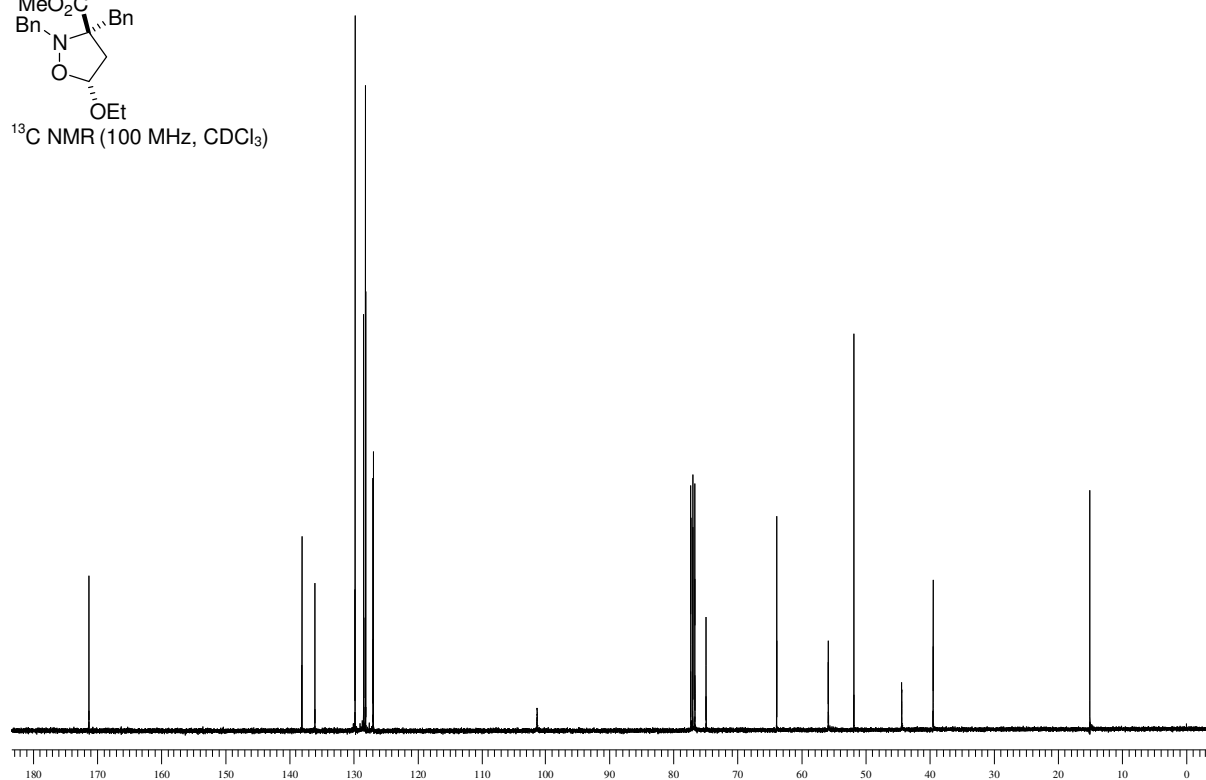
pure *trans*-10c



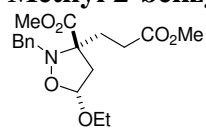
¹H NMR (400 MHz, CDCl₃)



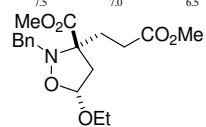
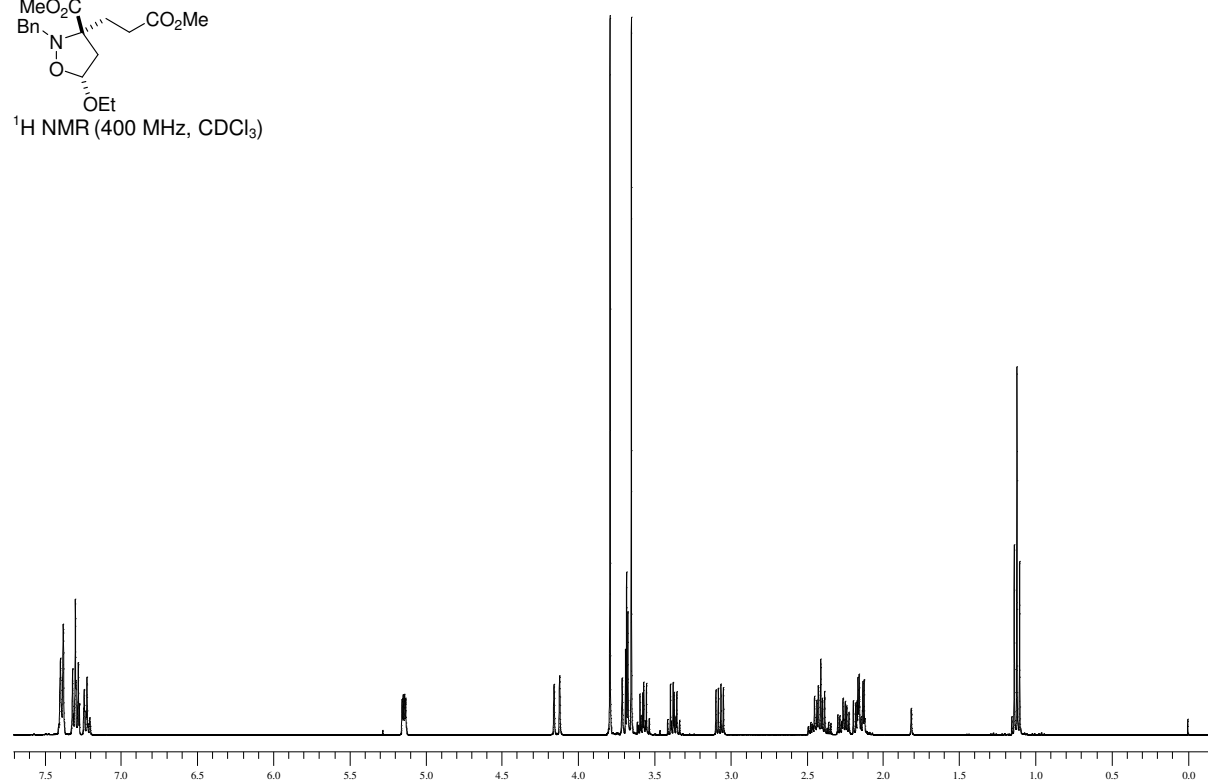
¹³C NMR (100 MHz, CDCl₃)



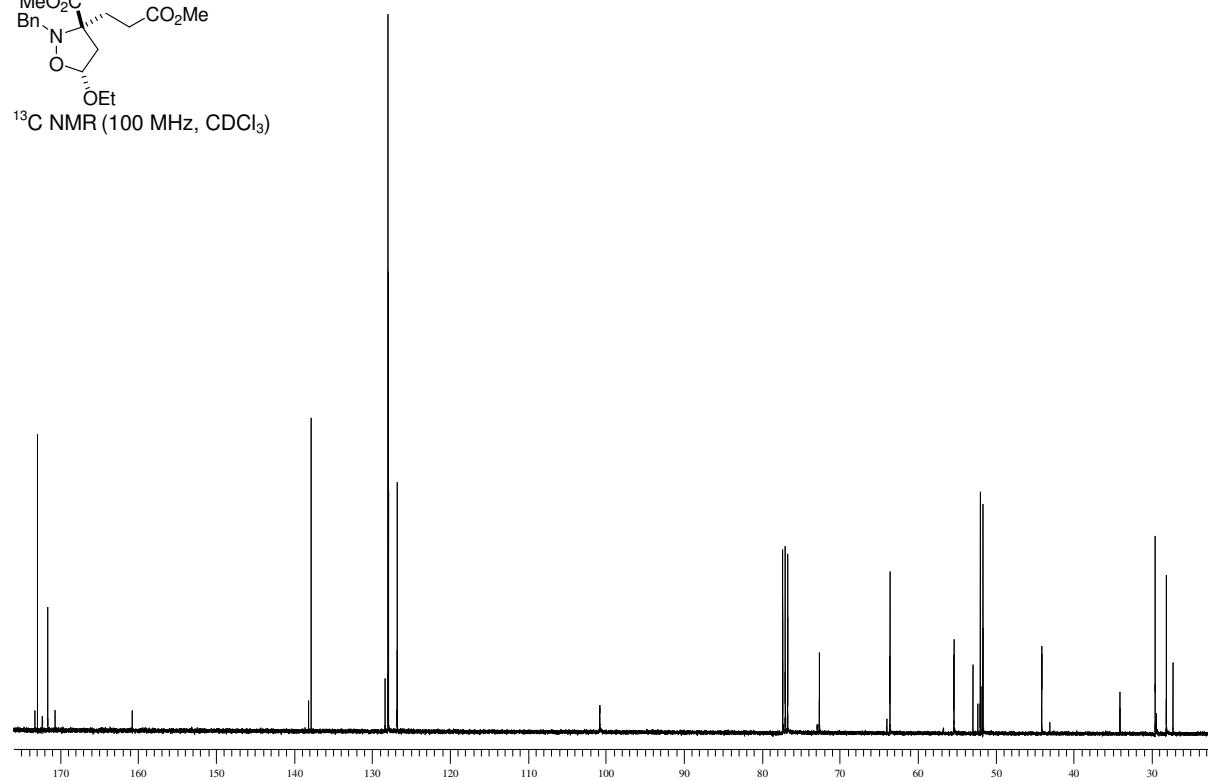
Methyl 2-benzyl-5-ethoxy-3-(3-methoxy-3-oxopropyl)isoxazolidine-3-carboxylate (10d)



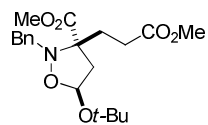
^1H NMR (400 MHz, CDCl_3)



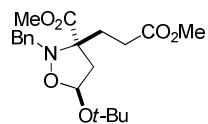
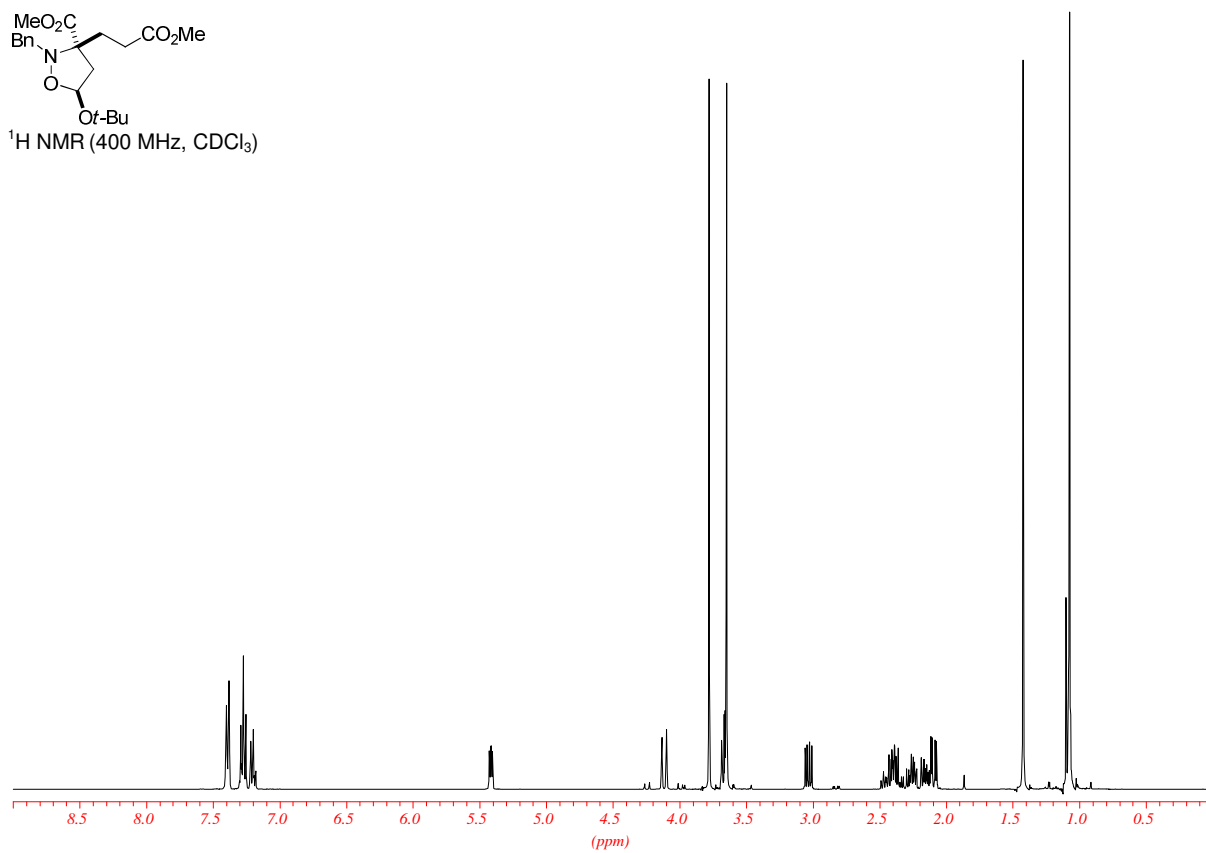
^{13}C NMR (100 MHz, CDCl_3)



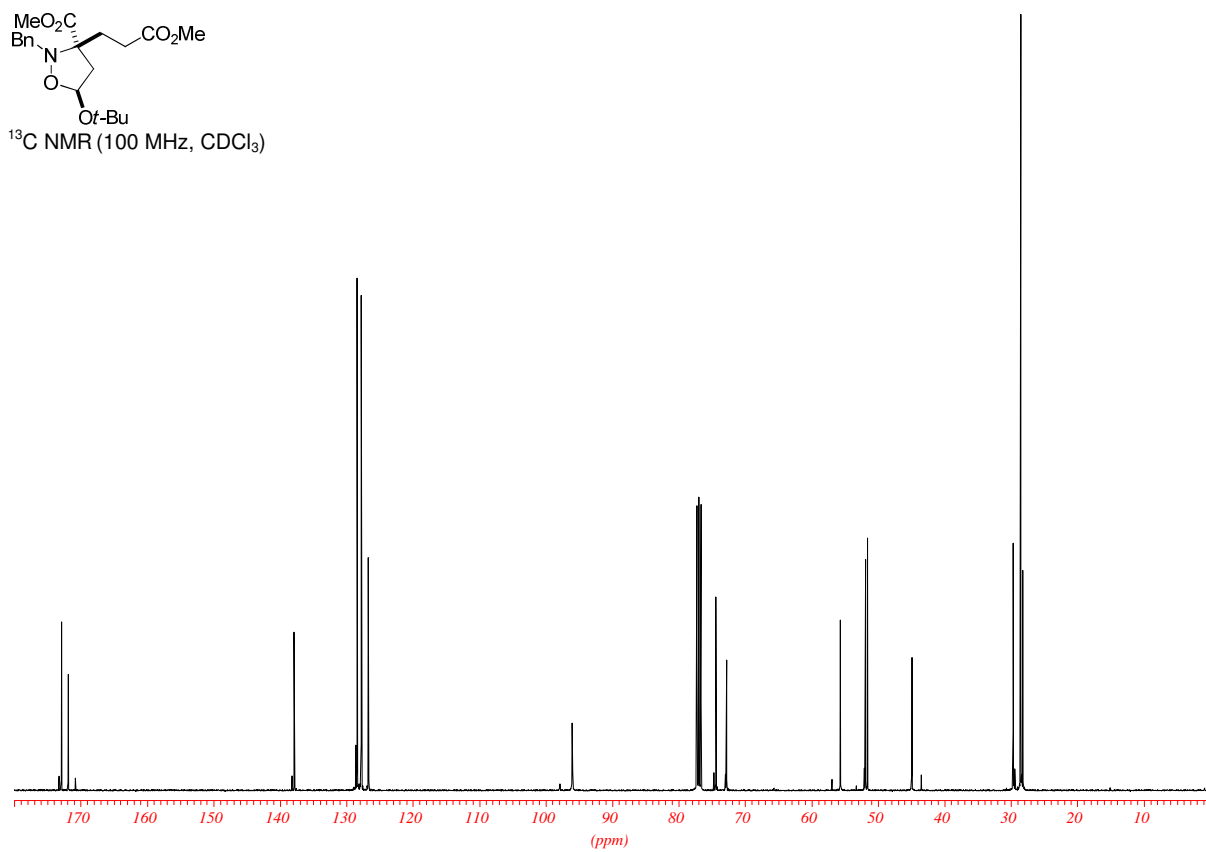
Methyl 2-benzyl-5-tert-butoxy-3-(3-methoxy-3-oxopropyl)isoxazolidine-3-carboxylate (10e)



^1H NMR (400 MHz, CDCl_3)

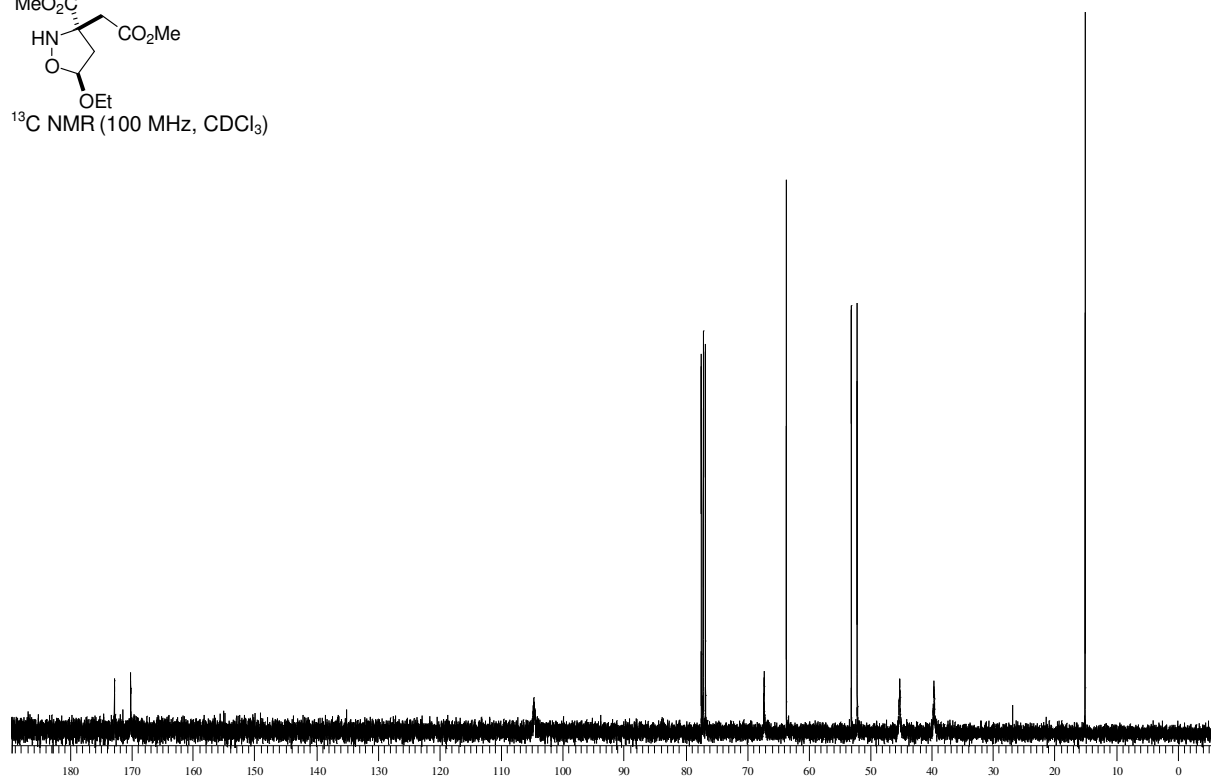
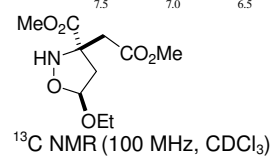
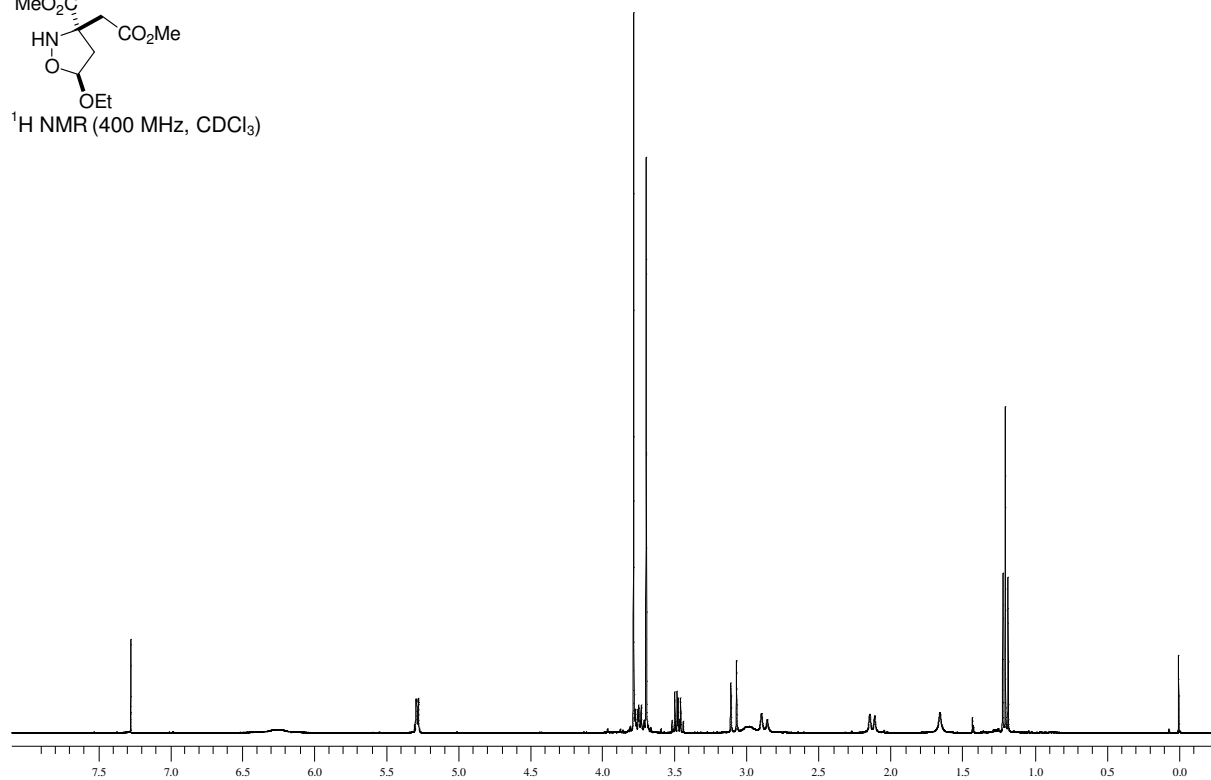
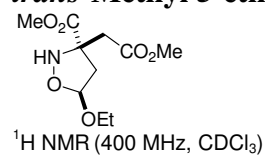


^{13}C NMR (100 MHz, CDCl_3)

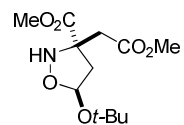


Debenzylated adducts 11a-d

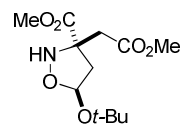
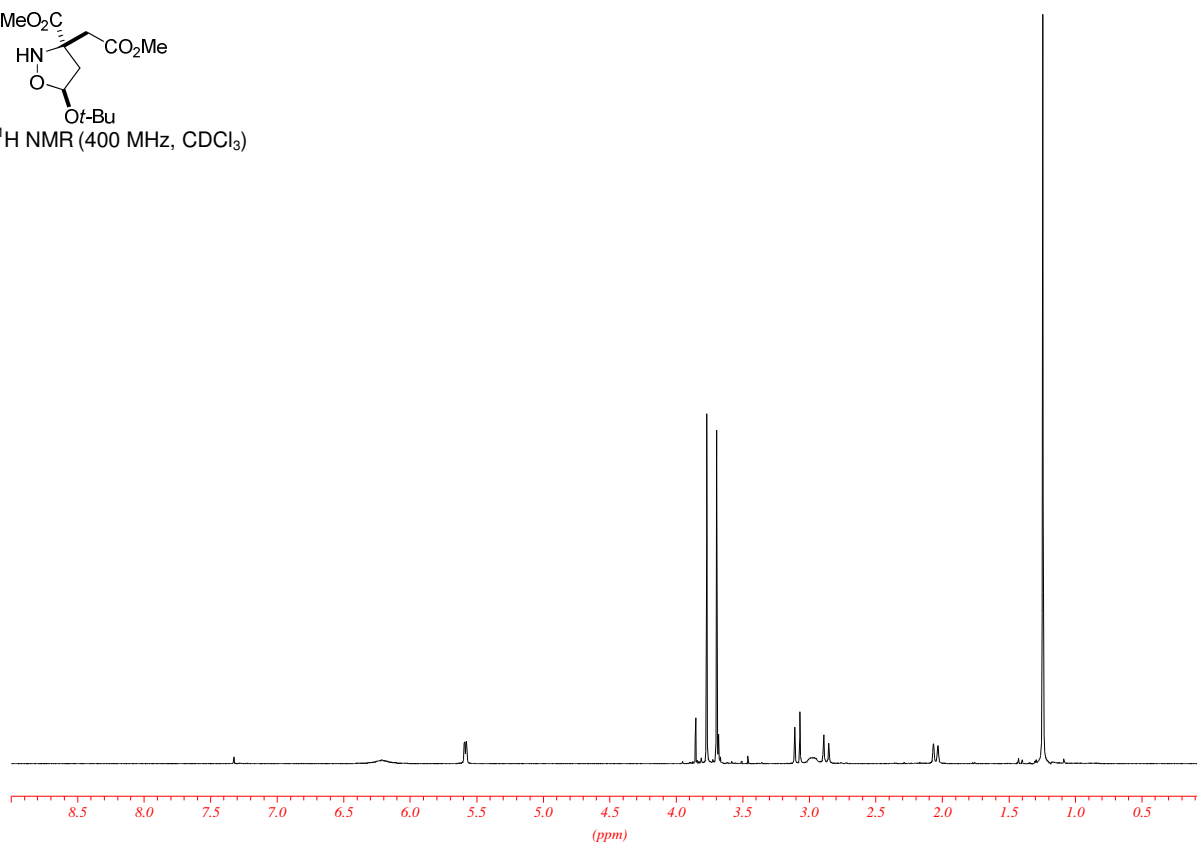
trans-Methyl 5-ethoxy-3-(2-methoxy-2-oxoethyl)isoxazolidine-3-carboxylate (11a)



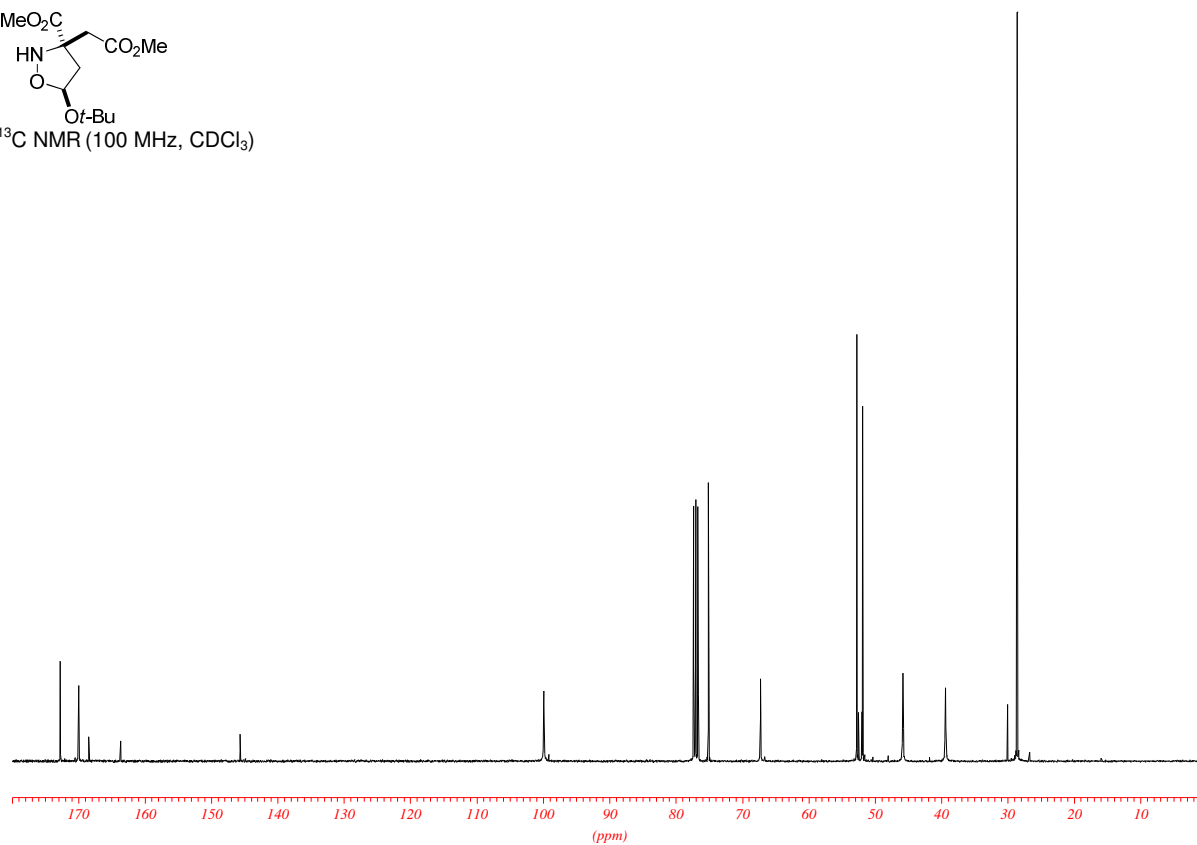
***trans*-Methyl 5-*tert*-butoxy-3-(2-methoxy-2-oxoethyl)isoxazolidine-3-carboxylate (11b)**



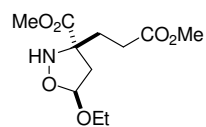
^1H NMR (400 MHz, CDCl_3)



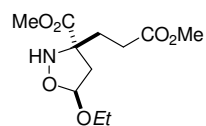
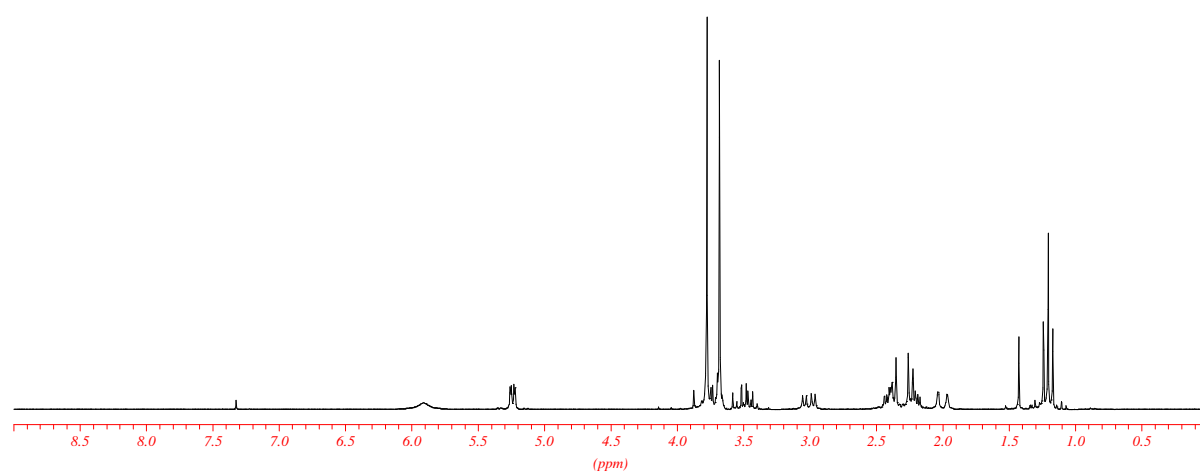
^{13}C NMR (100 MHz, CDCl_3)



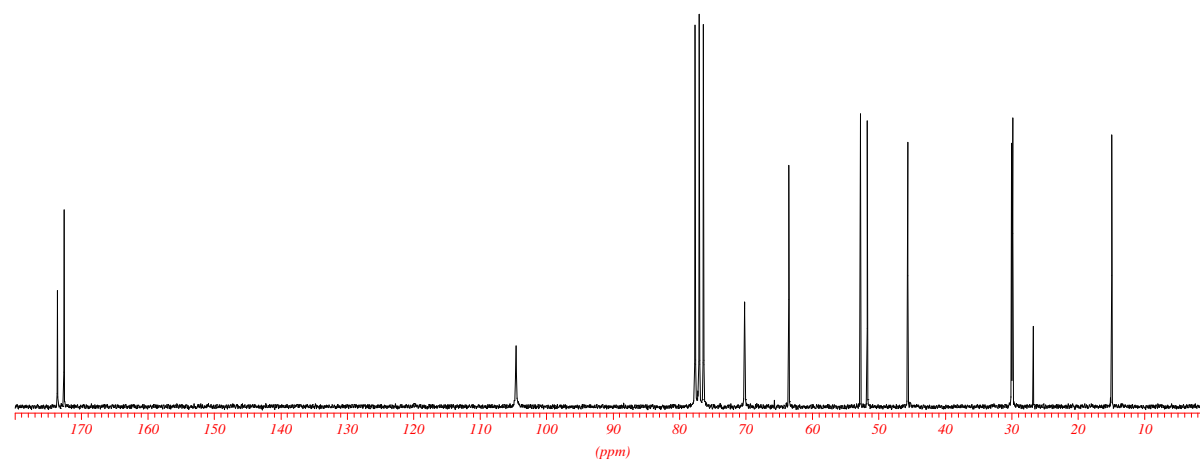
***trans*-methyl 5-ethoxy-3-(3-methoxy-3-oxopropyl)isoxazolidine-3-carboxylate (11c)**



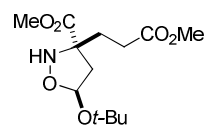
^1H NMR (400 MHz, CDCl_3)



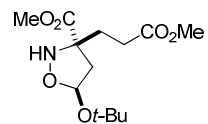
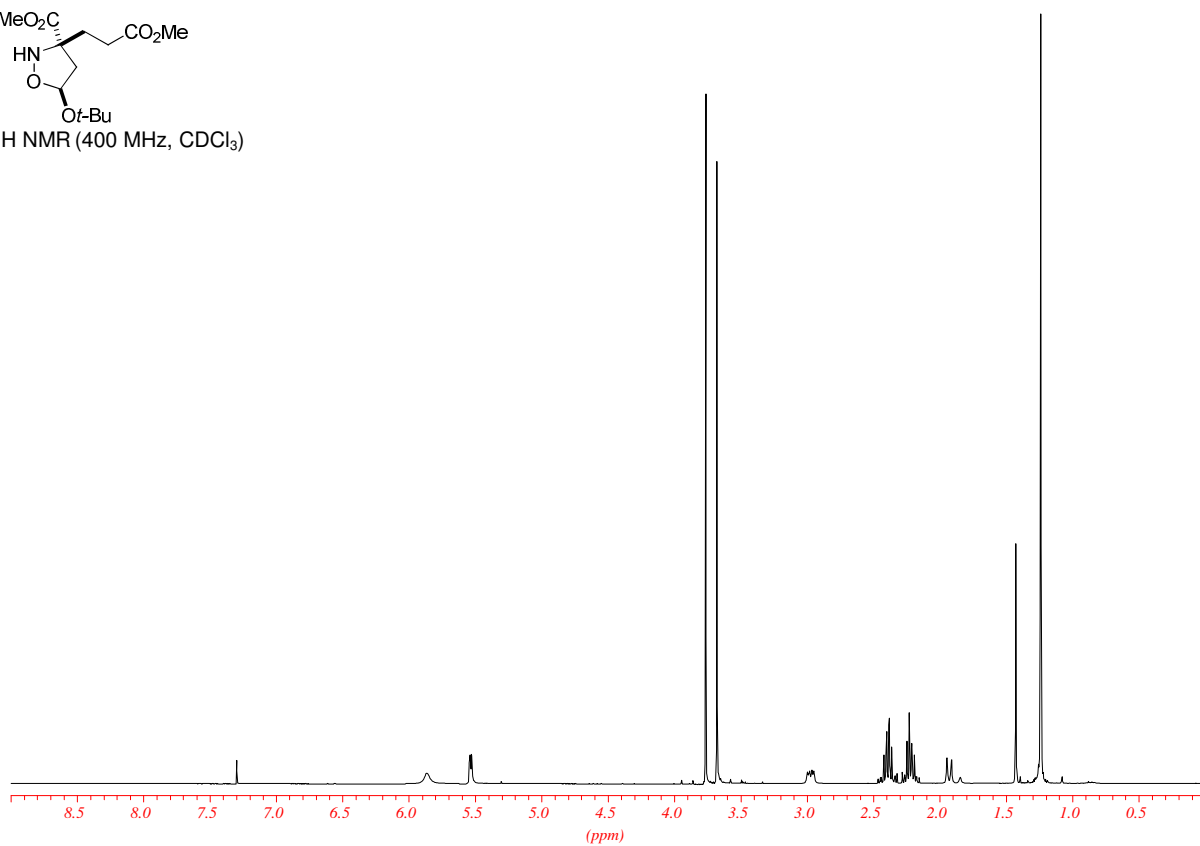
^{13}C NMR (100 MHz, CDCl_3)



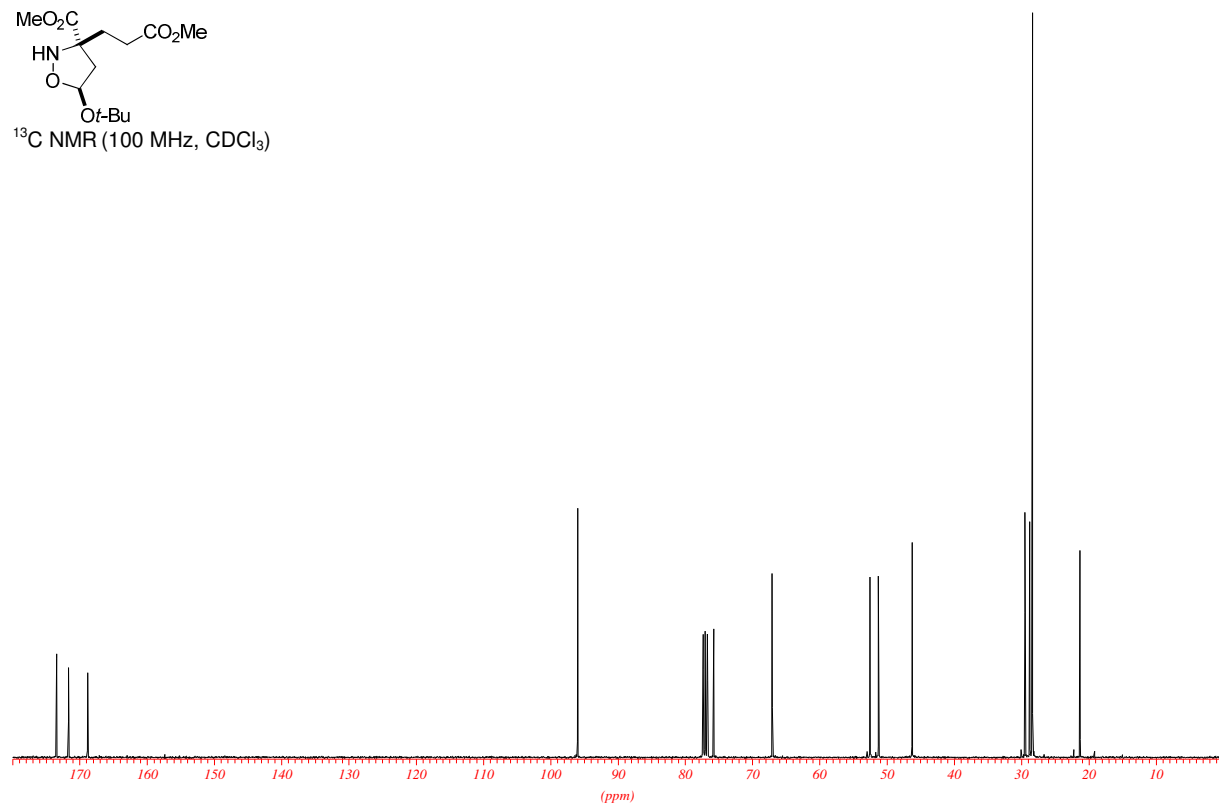
***trans*-methyl 5-*tert*-butoxy-3-(3-methoxy-3-oxopropyl)isoxazolidine-3-carboxylate (11d)**



¹H NMR (400 MHz, CDCl₃)



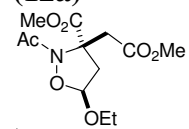
¹³C NMR (100 MHz, CDCl₃)



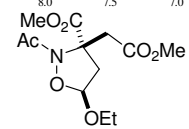
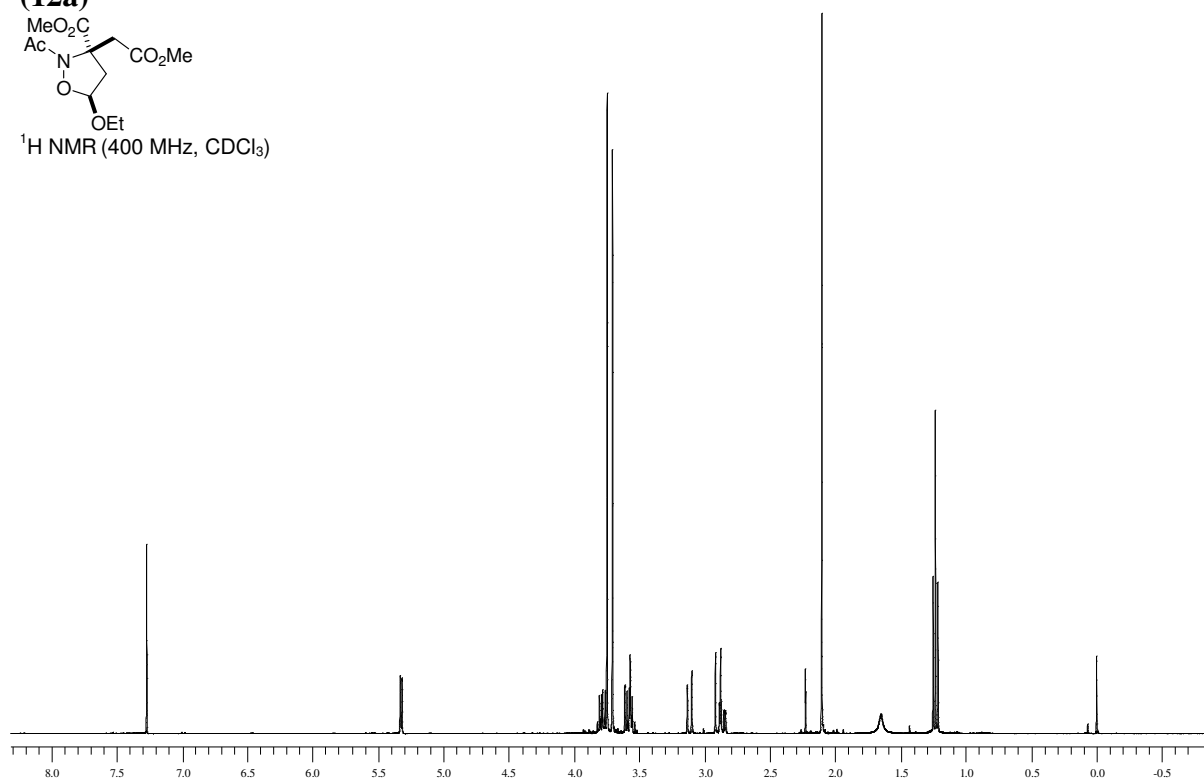
N-Acetylated adducts 12a-d

***trans*-Methyl 2-acetyl-5-ethoxy-3-(2-methoxy-2-oxoethyl)isoxazolidine-3-carboxylate**

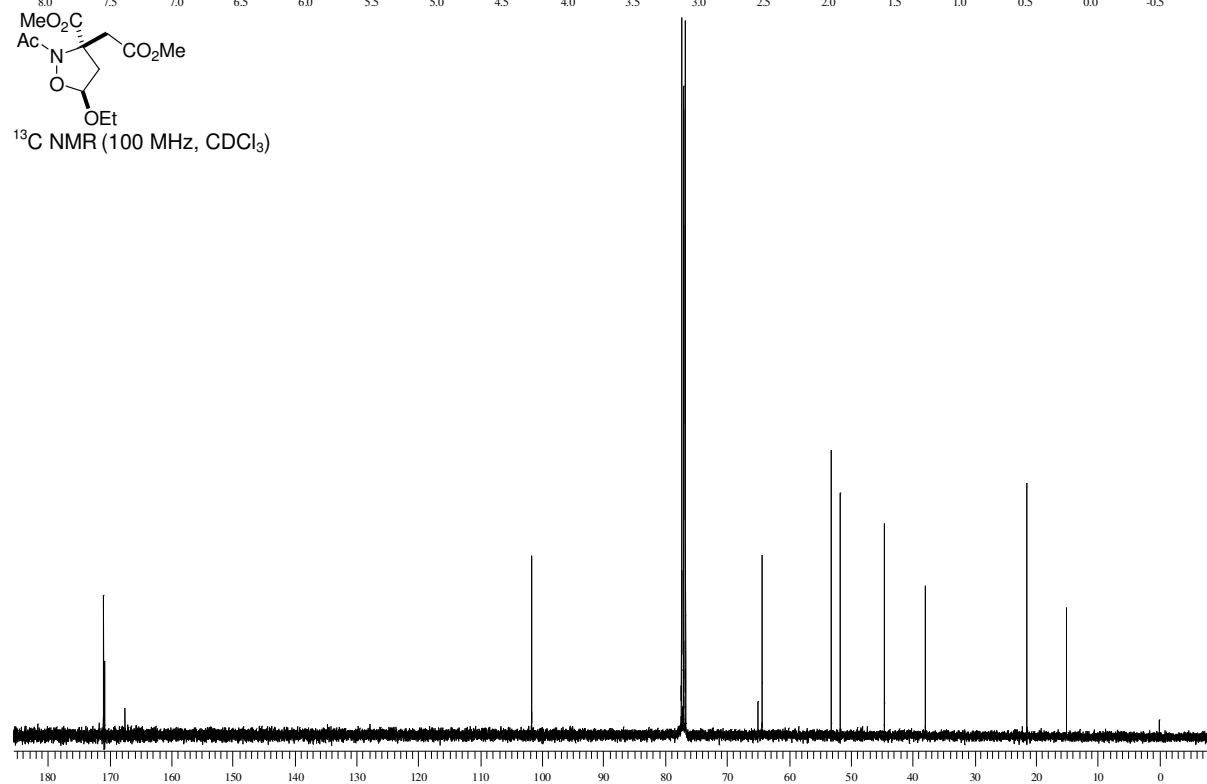
(12a)



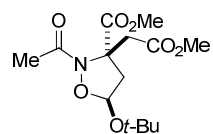
^1H NMR (400 MHz, CDCl_3)



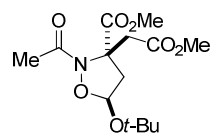
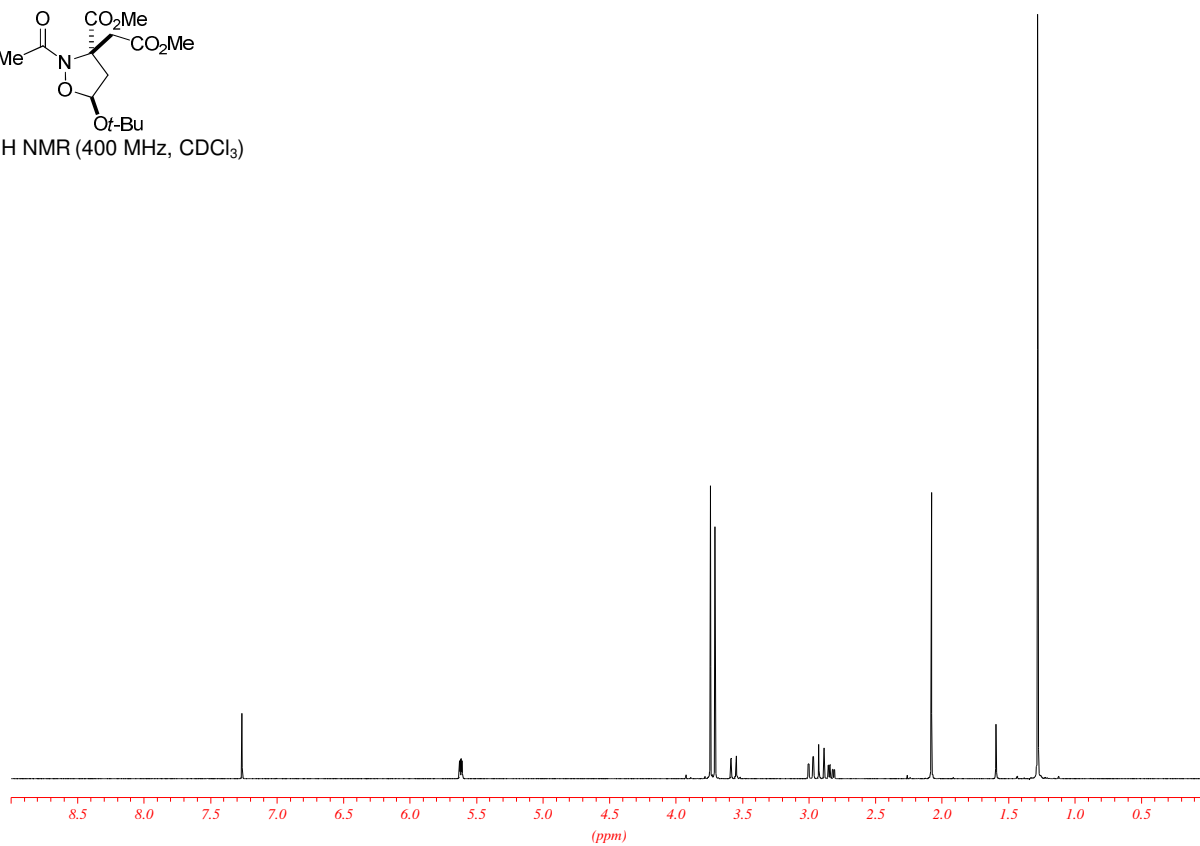
^{13}C NMR (100 MHz, CDCl_3)



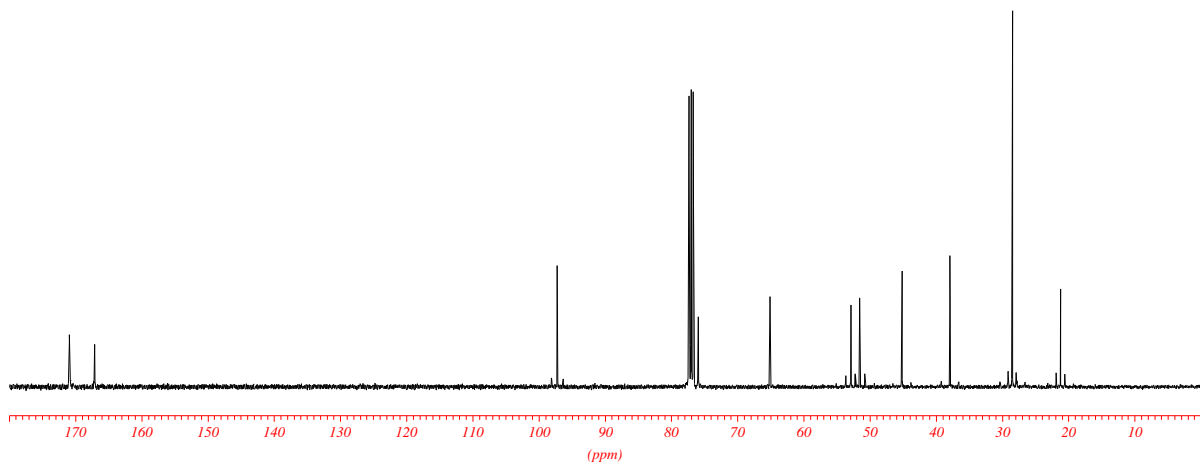
***trans*-Methyl 2-acetyl-5-tert-butoxy-3-(2-methoxy-2-oxoethyl)isoxazolidine-3-carboxylate (12b)**



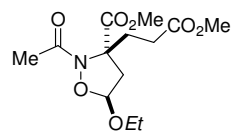
^1H NMR (400 MHz, CDCl_3)



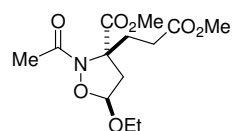
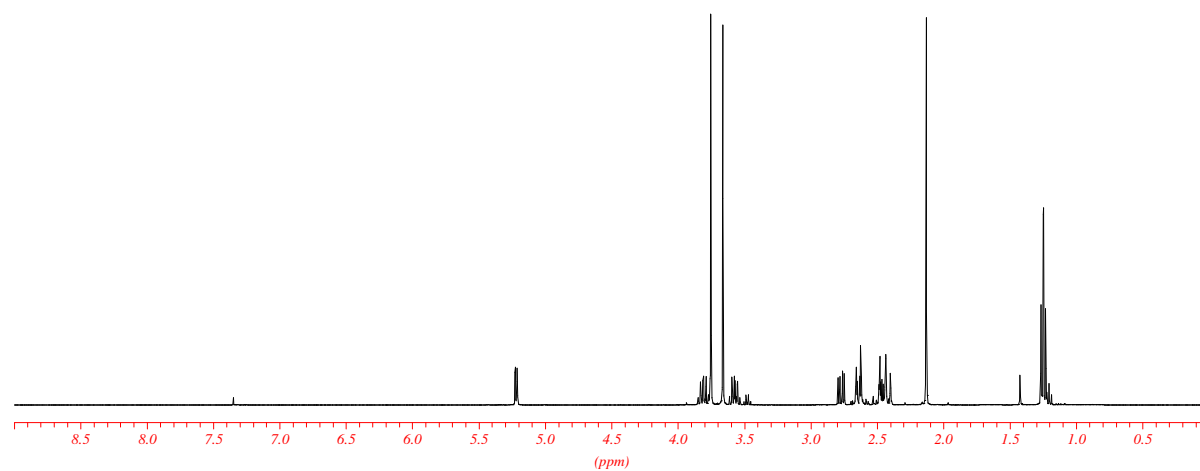
^{13}C NMR (100 MHz, CDCl_3)



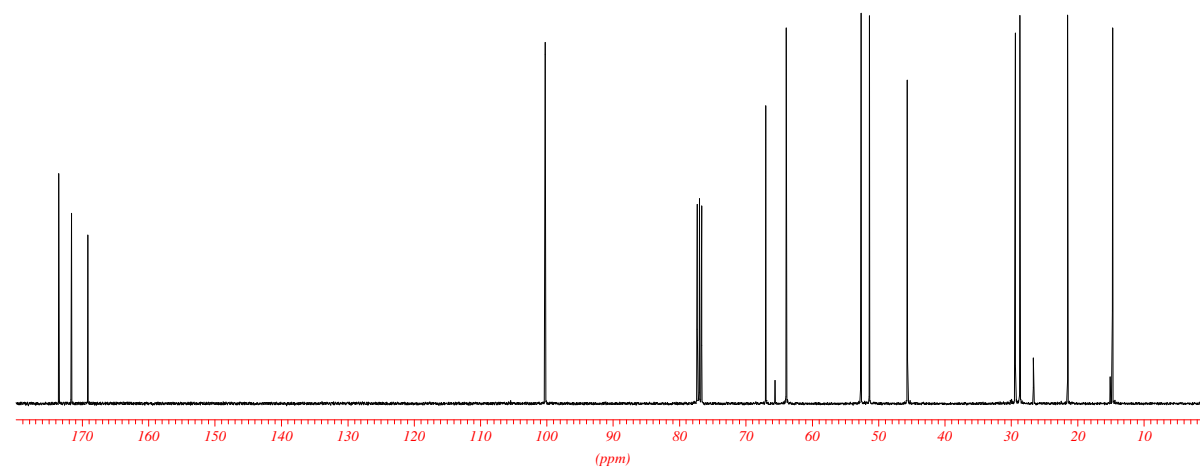
***trans*-Methyl 2-acetyl-5-ethoxy-3-(3-methoxy-3-oxopropyl)isoxazolidine-3-carboxylate (12c)**



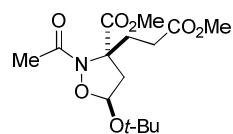
^1H NMR (400 MHz, CDCl_3)



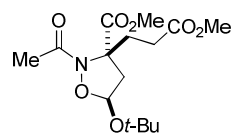
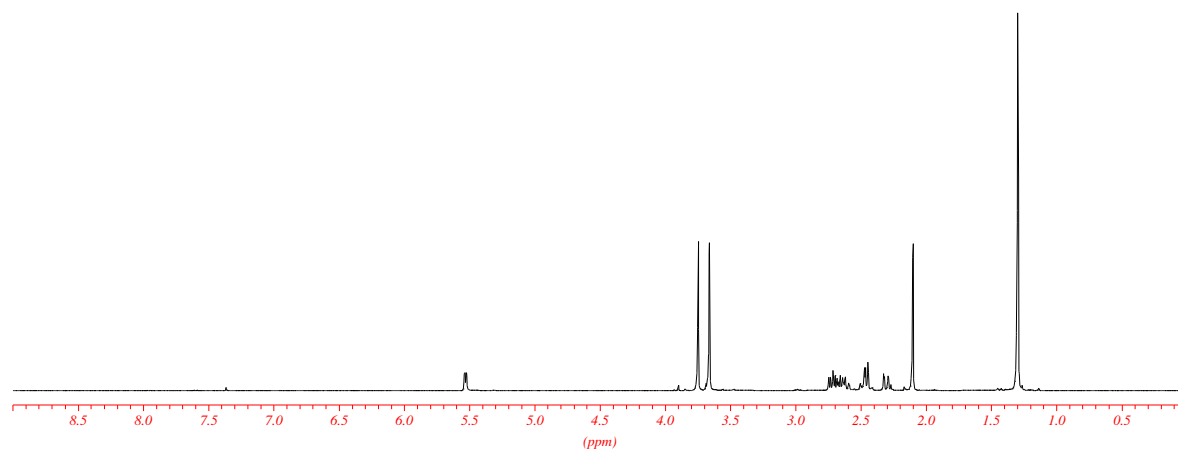
^{13}C NMR (100 MHz, CDCl_3)



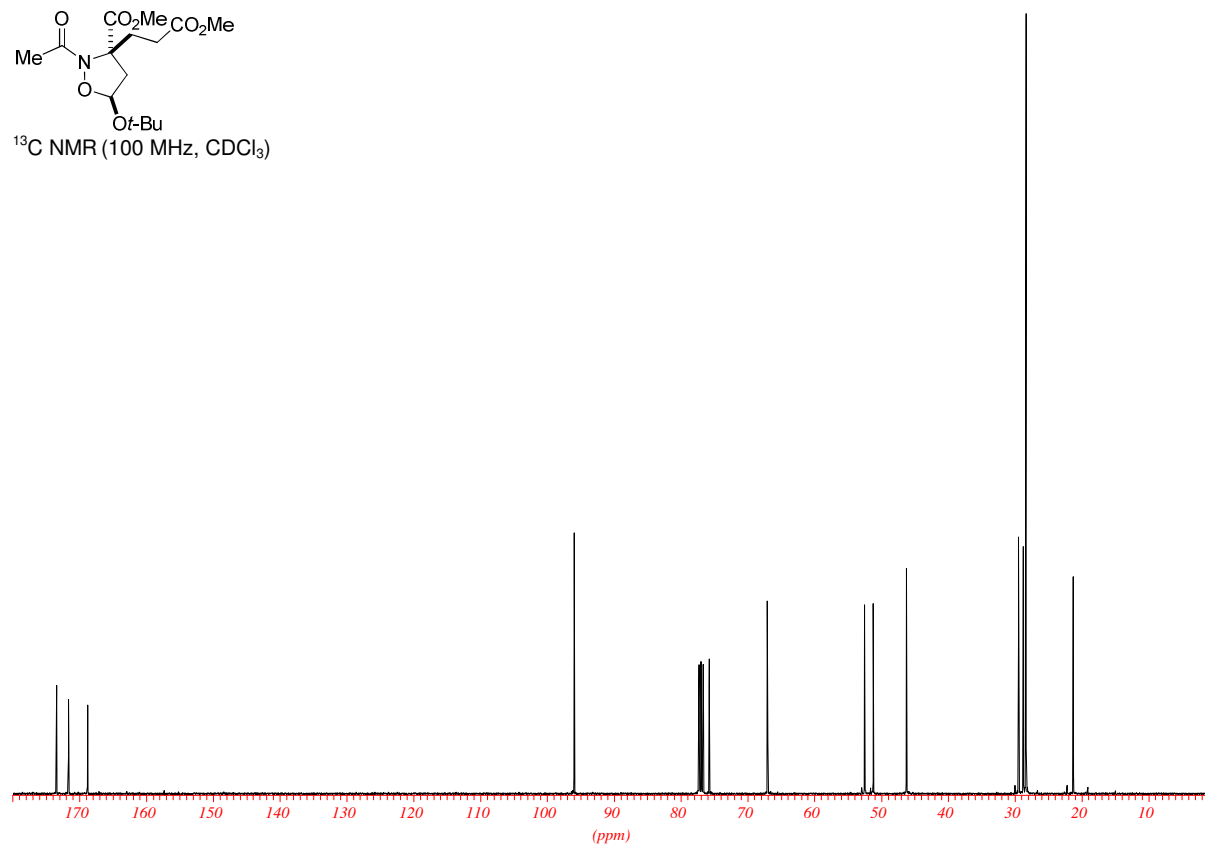
***trans*-Methyl 2-acetyl-5-tert-butoxy-3-(3-methoxy-3-oxopropyl)isoxazolidine-3-carboxylate (12d)**



^1H NMR (400 MHz, CDCl_3)

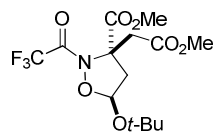


^{13}C NMR (100 MHz, CDCl_3)

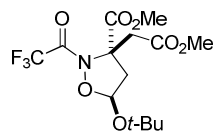
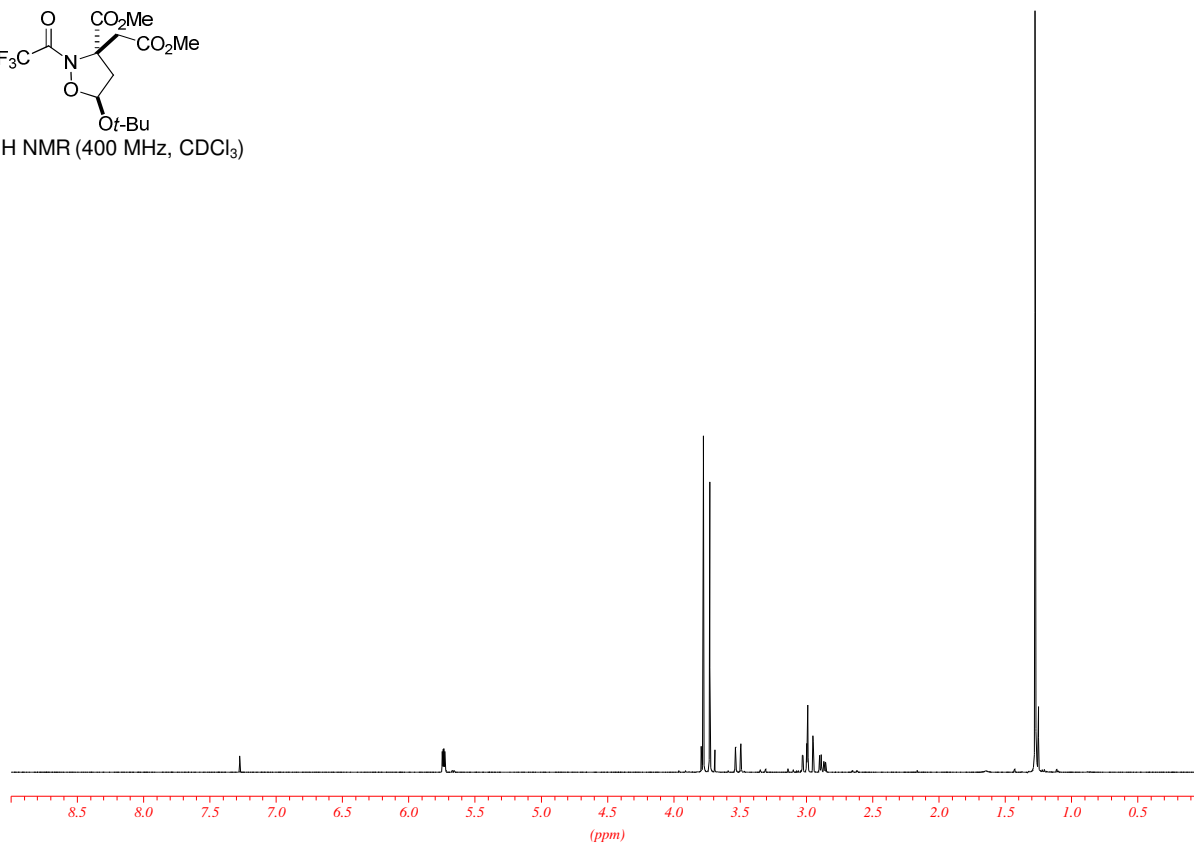


N-Trifluoroacetylated adducts 13a-b

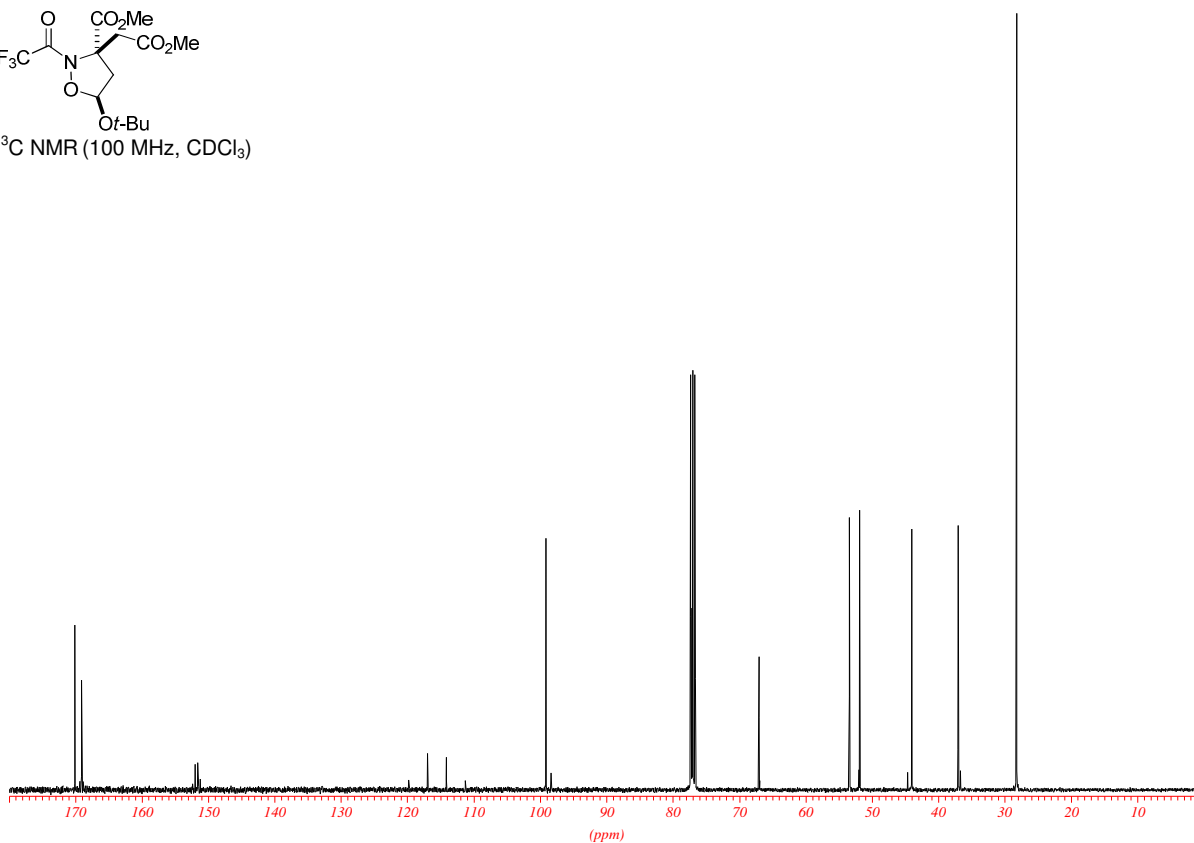
***trans*-Methyl 5-tert-butoxy-3-(2-methoxy-2-oxoethyl)-2-(2,2,2-trifluoroacetyl)isoxazolidine-3-carboxylate (13a)**



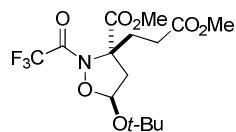
^1H NMR (400 MHz, CDCl_3)



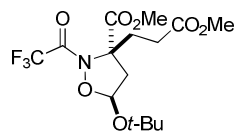
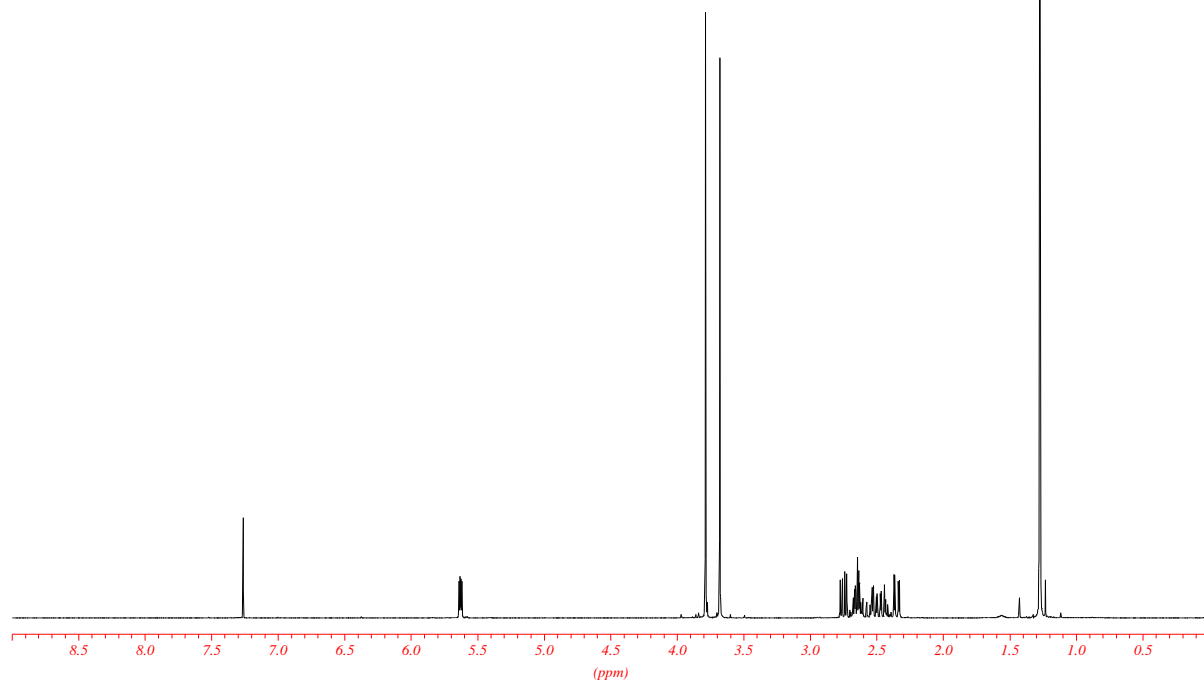
^{13}C NMR (100 MHz, CDCl_3)



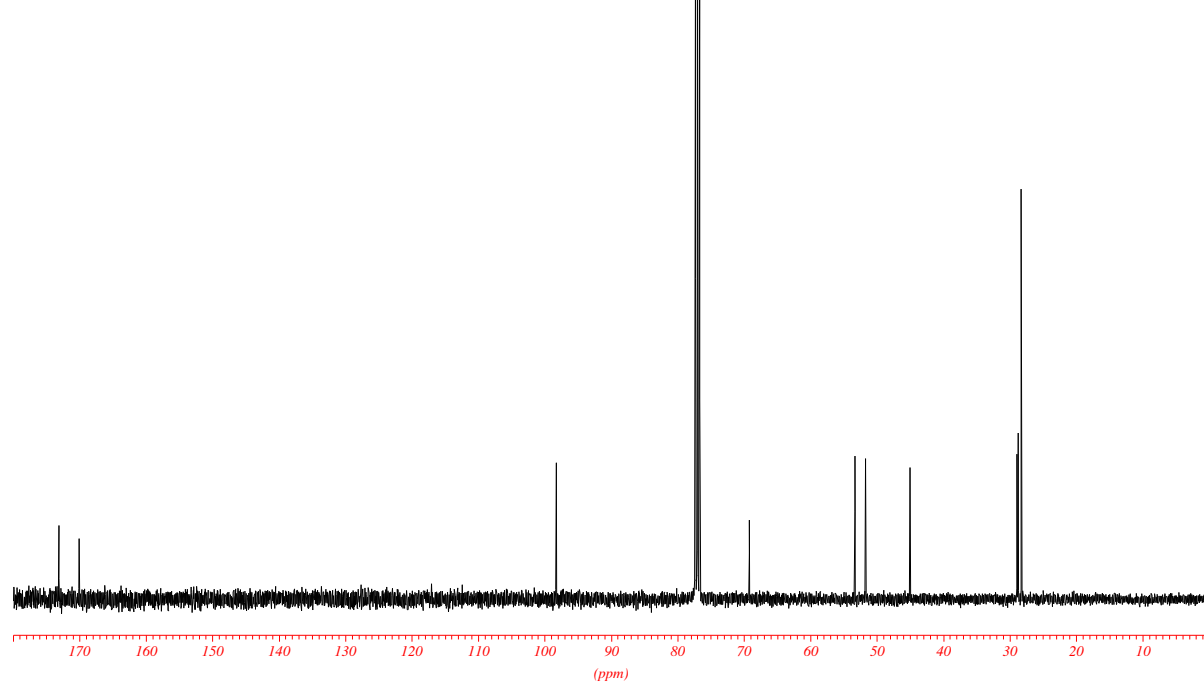
***trans*-Methyl 5-*tert*-butoxy-3-(3-methoxy-3-oxopropyl)-2-(2,2,2-trifluoroacetyl)isoxazolidine-3-carboxylate (13b)**



^1H NMR (400 MHz, CDCl_3)

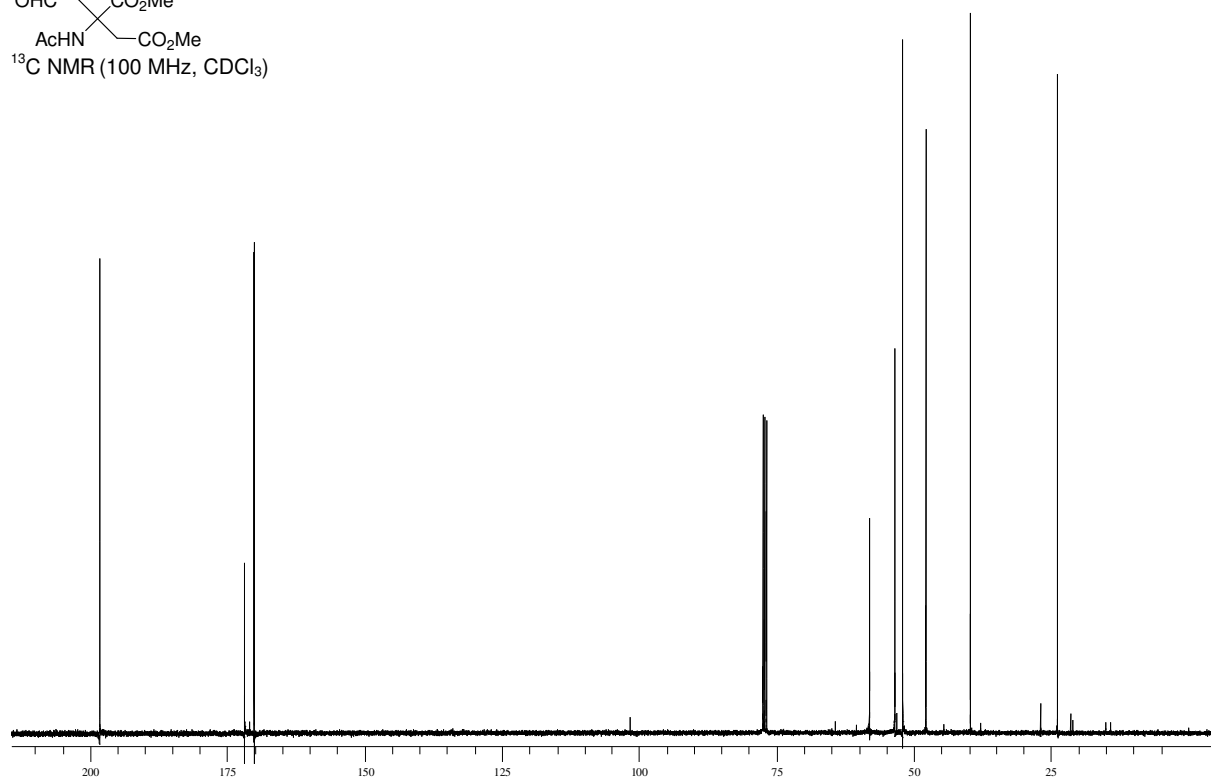
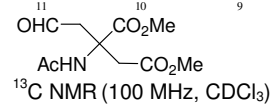
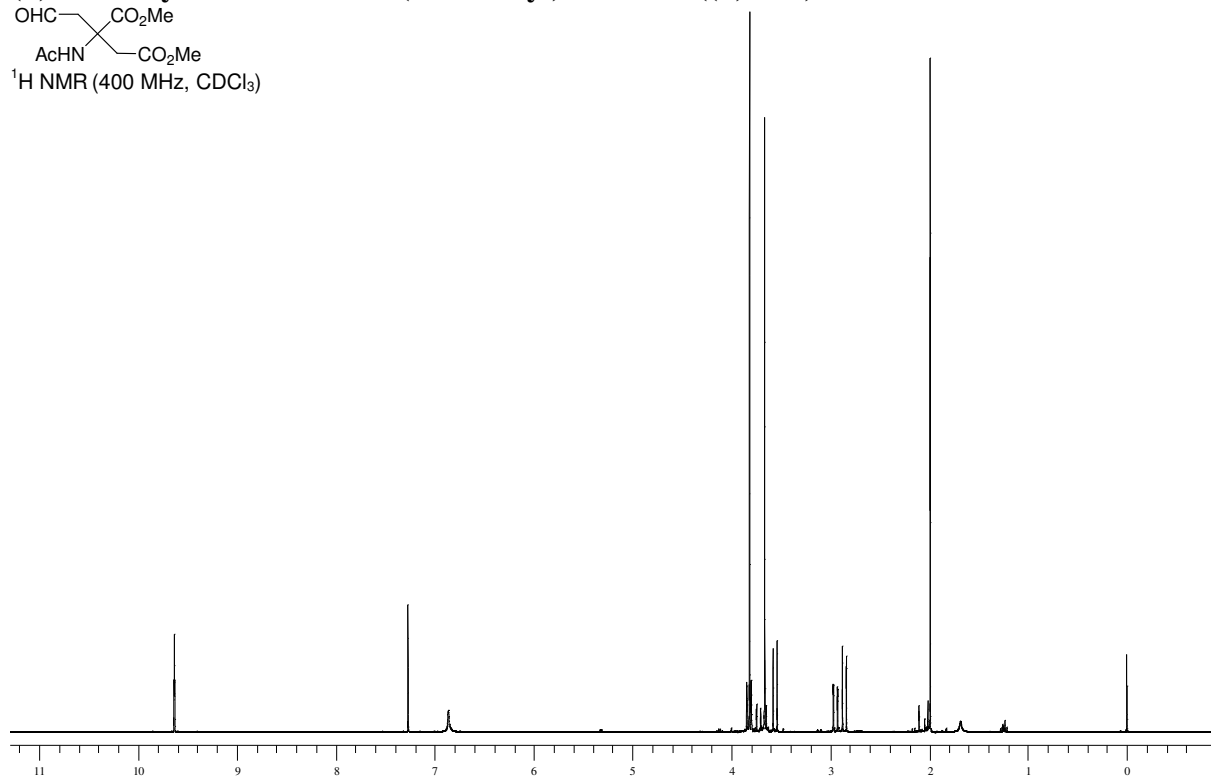
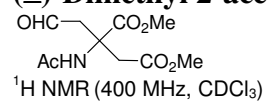


^{13}C NMR (100 MHz, CDCl_3)

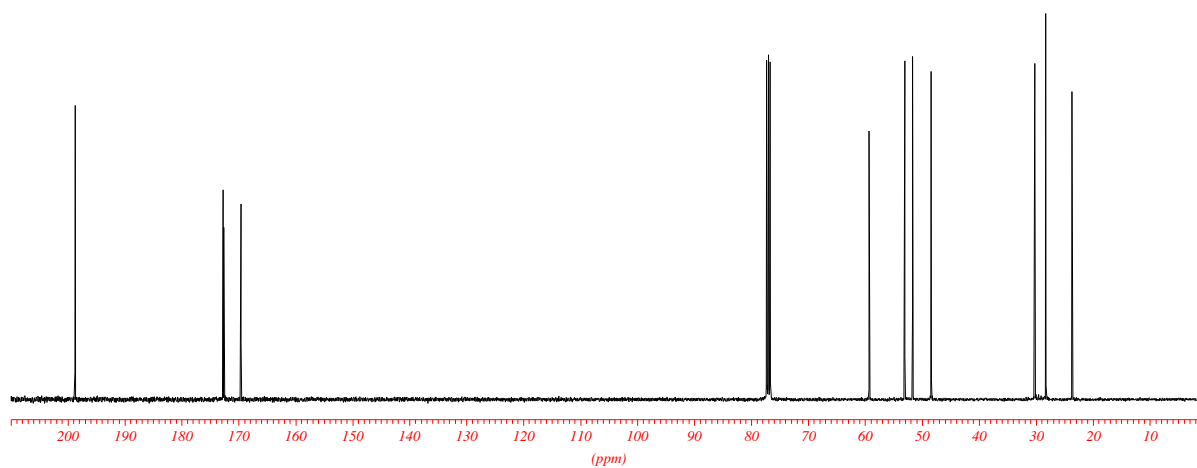
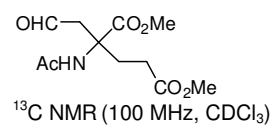
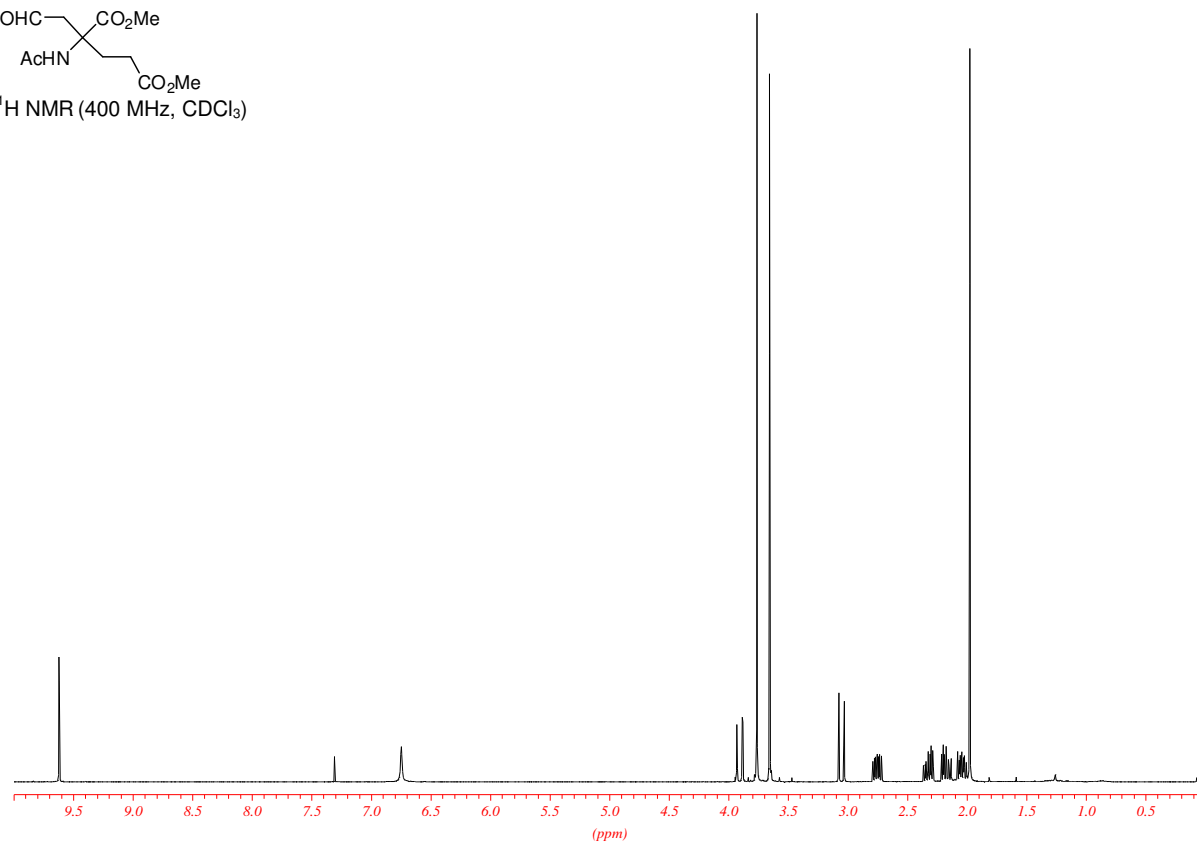
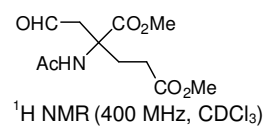


Aldehydes 14a-b

(±)-Dimethyl 2-acetamido-2-(2-oxoethyl)succinate ((±)-14a)

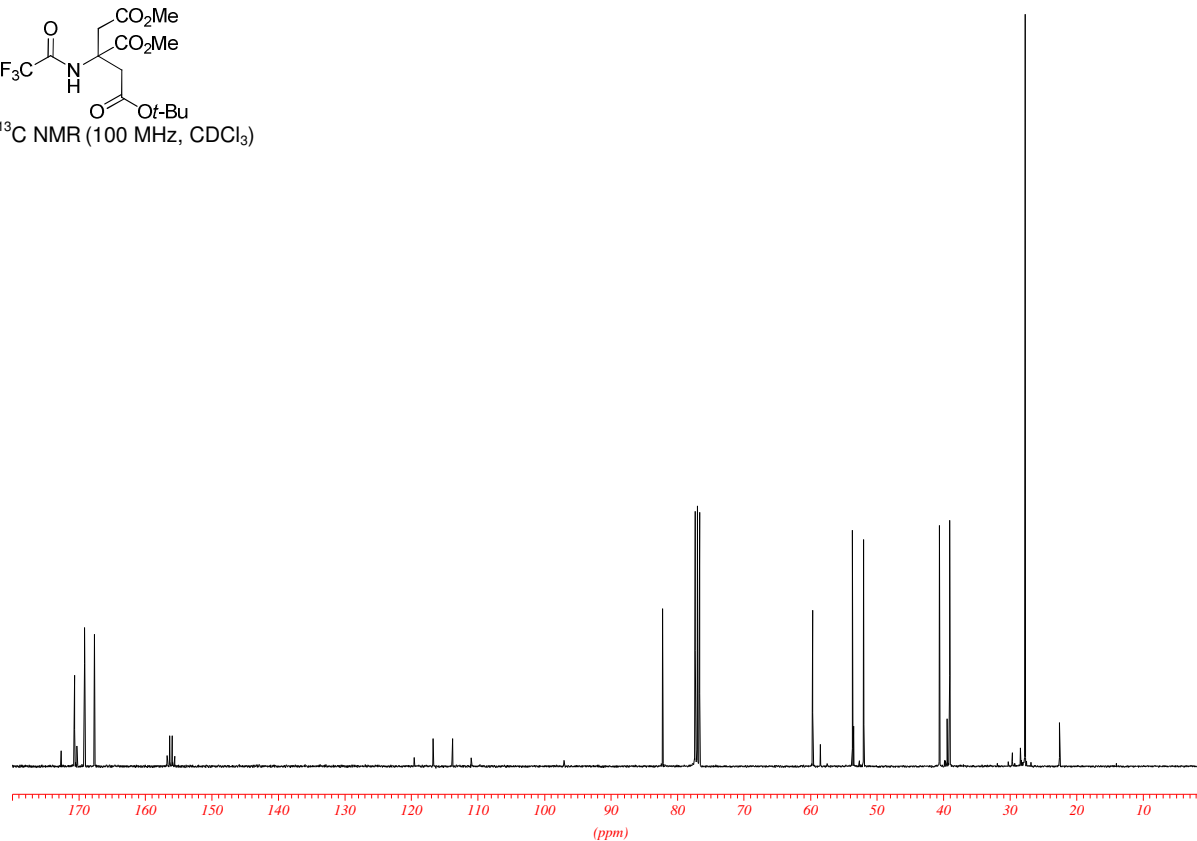
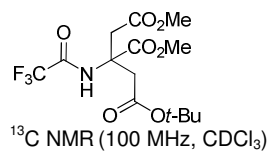
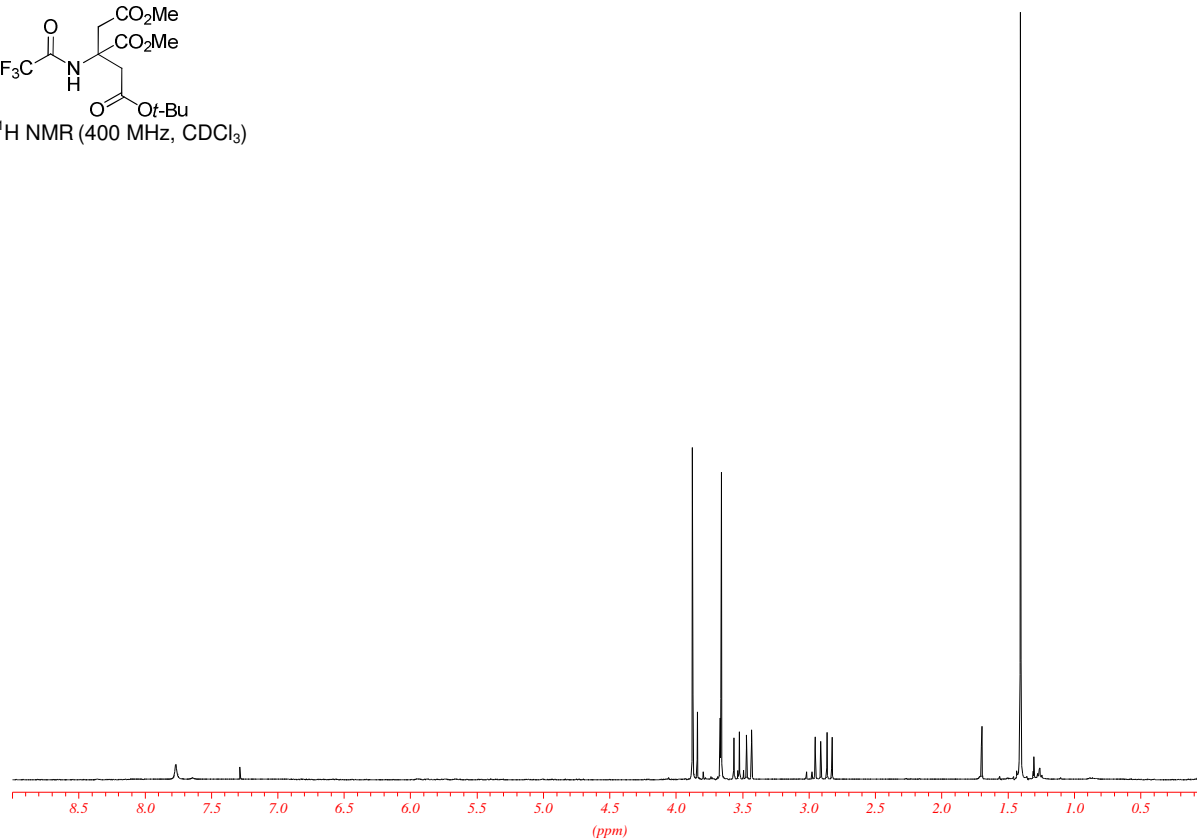
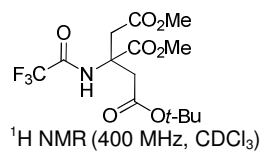


Dimethyl 2-acetamido-2-(2-oxoethyl)pentanedioate 14b



Tert-Butyl esters 15a-b

1-*tert*-butyl 2,3-dimethyl 2-(2,2,2-trifluoroacetamido)propane-1,2,3-tricarboxylate 15a



1-*tert*-butyl 2,4-dimethyl 2-(2,2,2-trifluoroacetamido)butane-1,2,4-tricarboxylate 15b

