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The preparation of substituted azetidines and larger-ring, nitrogen-containing saturated heterocycles is enabled through efficient and selective intermolecular sp<sup>3</sup>-C–H amination of alkyl bromide derivatives. A range of substrates is demonstrated to undergo C–H amination and subsequent sulfamate alkylation in good to excellent yield. N-Phenoxysulfonyl-protected products can be unmasked under neutral or mild basic conditions to yield the corresponding cyclic 2° amines. The preparative convenience of this protocol is demonstrated through gram-scale and telescoped multi-step procedures. Application of this technology is highlighted in a nine step total synthesis of an unusual azetidine-containing natural product, penaresidin B.

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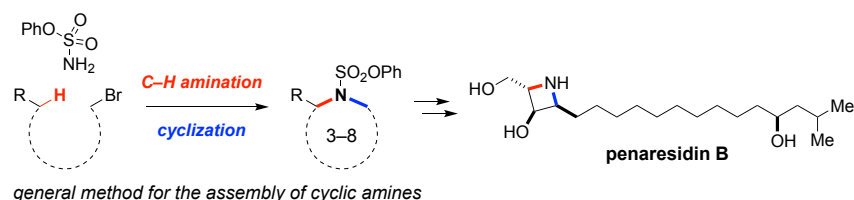
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# Intermolecular $sp^3$ -C–H Amination for the Synthesis of Saturated Azacycles

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Supporting Information Placeholder

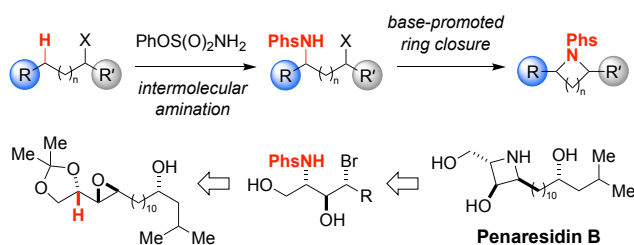


**ABSTRACT:** The preparation of substituted azetidines and larger-ring, nitrogen-containing saturated heterocycles is enabled through efficient and selective intermolecular  $sp^3$ -C–H amination of alkyl bromide derivatives. A range of substrates is demonstrated to undergo C–H amination and subsequent sulfamate alkylation in good to excellent yield. *N*-Phenoxysulfonyl-protected products can be unmasked under neutral or mild basic conditions to yield the corresponding cyclic 2° amines. The preparative convenience of this protocol is demonstrated through gram-scale and telescoped multi-step procedures. Application of this technology is highlighted in a nine step total synthesis of an unusual azetidine-containing natural product, penaresidin B.

Saturated azacycles are ubiquitous structural elements in natural products.<sup>1</sup> Cyclic amines also appear in designed molecules owing to the unique and disparate physicochemical and topological properties of such heterocycles.<sup>2,3</sup> Pyrrolidine and piperidine derivatives can be accessed through numerous means, which rely on both conventional and modern C–N bond forming methods including C–H oxidation.<sup>4–6</sup> We have been interested in developing a general protocol for assembling substituted azacycles of differing ring size, with a specific focus on azetidine structures. The value of such amines is considerable in synthesis, pharmacology, and medicine.<sup>7–10</sup> Herein, we present a method for the preparation of small ( $n = 3–5$ ) and medium ( $n = 6–8$ ) ring-sized azacycles that capitalizes on selective, intermolecular  $sp^3$ -C–H amination of brominated hydrocarbon substrates (Scheme 1). The efficient functionalization of substrates in which the desired site of C–H oxidation is proximal to an electron-withdrawing halogen group underscores recent advances in Rh-catalyzed amination.<sup>11–18</sup>

Typical methods for *de novo* azetidine synthesis include  $S_N2$  displacement reactions of mono- and dihalopropanes with alkyl amines,<sup>6,7,19</sup> aziridine ring expansion,<sup>6,7,20,21</sup> thermal and photochemical [2+2] cycloadditions,<sup>6,7,22,23</sup> and Pd-catalyzed C–N cross coupling.<sup>6,7,24,25</sup> Our approach for constructing azetidine derivatives involves selective, intermolecular C–H amination of bromoalkanes to introduce the requisite nitrogen center followed by ring closure. Accordingly, the scope of this method is potentially quite broad and extends beyond 4-membered ring synthesis. As Rh-catalyzed C–H amination is

stereospecific, access to optically active cyclic amines is also possible.<sup>26</sup>



Exploratory studies to develop a process for azetidine synthesis were conducted with 1-bromo-3-phenylpropane **1a** (Table 1). The proximity of the electronegative Br-group in **1a** to the benzylic site deactivates this position towards oxidation. Consequently, a number of reported C–H amination protocols fail to engage this substrate; others furnish small amounts of the desired product in combination with unidentifiable species (see Supporting Information Table S2 for relevant comparisons). Using a recently disclosed amination protocol developed in our lab,<sup>27</sup> intermolecular C–H amination of **1a** with phenyl sulfamate (PhsNH<sub>2</sub>) proceeds in 64% yield to furnish **2a** (23% RSM). The intermediate bromoalkyl sulfamate ester efficiently cyclizes upon treatment with base to provide the corresponding azetidine **3a** (see Supporting Information Table S1 for optimization). Through the application of this two-step

sequence, **3a** is obtained in 62% overall yield (Table 1, entry 1). The effectiveness of the amination reaction, which affords largely product and recovered starting material, allows the cyclization reaction to be telescoped in a single-flask procedure. Following this protocol, pure azetidine **3a** can be isolated in 49% (Table S1; see Scheme 2 for more details).

**Table 1.** Cyclic amine synthesis through C–H amination.

$\text{Ph-CH}_2\text{-(CH}_2\text{)}_n\text{-X} \xrightarrow[1.5 \text{ equiv PhI(OPiv)}_2, \text{ Al}_2\text{O}_3, \text{ } t\text{-BuCN, 6h}]{1 \text{ mol \% [Rh}_2(\text{esp})_2, 1.2 \text{ equiv PhOSO}_2\text{NH}_2} \text{Ph-CH(NHPhs)-(CH}_2\text{)}_n\text{-X} \xrightarrow[\text{DMF, 2h}]{\text{K}_2\text{CO}_3} \text{Ph-CH}_2\text{-(CH}_2\text{)}_n\text{-N(Phs)-CH}_2\text{Ph}$				
<b>1</b>	<b>C–H Aminated Product<sup>a</sup></b>	<b>Cyclized Product<sup>b</sup></b>		
	X = Br <b>2a-1</b>	64% (23)		97%
	OMs <b>2a-2</b>	38% (56)		
<b>2</b>		<b>2b</b> 40% (15)		— <sup>c</sup>
<b>3</b>		<b>2c</b> 42% (45)		97%
<b>4</b>		<b>2d</b> 52% (40)		98%
<b>5</b>	X = Br <b>2e-1</b>	65% (22)		98%
	OMs <b>2e-2</b>	42% (47)		
<b>6</b>		<b>2f</b> 74% (17)		22% <sup>d</sup>

<sup>a</sup>Reactions performed with 0.3 mmol starting material and 0.3 mL *t*-BuCN for 6 h; values in parentheses represent percent recovered starting material. <sup>b</sup>Cyclization performed with 0.1 mmol C–H aminated product in 1 mL DMF for 2 h. <sup>c</sup>The product aziridine is unstable to the reaction conditions; complete conversion of starting material is observed by <sup>1</sup>H NMR. <sup>d</sup>Reaction conducted for 10 h at ambient temperature. Phs = PhOS(O)<sub>2</sub>–; DMF = *N,N*-dimethylformamide.

To examine the generality of the amination method for assembling cyclic amines of varying ring size, a systematic analysis of reaction performance with phenyl-substituted bromoalkanes was conducted. Azacycles from 3–8 in size can be fashioned through our two-step sequence. For the most part, C–H amination yields improve as the distance between the Br-substituent and the benzylic center is increased; nonetheless, even phenethylbromide **2a** can be oxidized in 40% yield to generate sulfamate **2b** (Table 1, entry 2). The cyclization event is consistently high yielding with the one exception involving azocane **3f** (entry 6). As a final note, reactions performed with alkyl mesylate substrates show diminished product yields stemming from the inefficiency of the amination reaction (entries 1 and 5). Somewhat surprisingly, this finding holds even for 6-phenylhexyl mesylate (entry 5), thus leaving open an explanation for the suboptimal performance of the amination reaction with mesylate-derived starting materials.

**Table 2.** Optimized protocol for cyclic amine assembly.

Entry	C–H Aminated Product <sup>a</sup>	Cyclized Product <sup>b</sup>
<b>1</b>	<b>2g<sup>c</sup></b> 60% (28)	<b>3g</b> 92%
<b>2</b>	<b>2h</b> 43% (37)	<b>3h</b> 78%
<b>3</b>	<b>2i</b> 71% (15)	<b>3i</b> 95%
<b>4</b>	<b>2j<sup>d</sup></b> 69% (21)	<b>3j</b> 98%
<b>5</b>	<b>2k<sup>e</sup></b> 61%	<b>3k</b> 83%
<b>6</b>	<b>2l<sup>f</sup></b> 37% (57)	<b>3l</b> 95%
<b>7</b>	<b>2m<sup>g</sup></b> 53% (31)	<b>3m<sup>g</sup></b> 93%
<b>8</b>	<b>2n<sup>h</sup></b> 42% (38)	<b>3n</b> 91%
<b>9</b>	<b>2o<sup>g</sup></b> 47% (10)	<b>3o<sup>g</sup></b> 62%
<b>10</b>	<b>2p<sup>e</sup></b> 63%	<b>3p</b> 78%
<b>11</b>	<b>2q</b> 64% (22)	<b>3q</b> 86%

<sup>a</sup>Reactions performed with 0.3 mmol starting material and 0.3 mL *t*-BuCN for 6 h; values in parentheses represent percent recovered starting material. <sup>b</sup>Cyclization performed with 0.1 mmol C–H aminated product in 1 mL DMF for 2 h. <sup>c</sup>Product isolated as a 1:1.8 mix of diastereomers; cyclization was conducted on pure *syn*-diastereomer. <sup>d</sup>Product isolated as a 1:1.1 mix of diastereomers. <sup>e</sup>Recovered starting material was not obtained due to the high volatility of this compound. <sup>f</sup>Product isolated as a 1:1 mix of diastereomers. <sup>g</sup>Product decomposition occurs on silica gel. <sup>h</sup>Amination gives a >10:1 mix of isomeric products; ring closure was conducted on a pure sample of the isomer shown.

To further explore the scope of our azacycle assembly method and to demonstrate its utility for fine chemical synthesis, substituted 1° and 2° alkyl bromide derivatives were subjected to the optimized protocol (Table 2). C–H amination generally proceeds in yields ranging from 37–71%; subsequent ring closure is efficient and affords the desired azacycle products. In several cases, Phs-protected cyclic amines are obtained in high purity following aqueous work-up without recourse to silica gel chromatography (entries 1, 4, 5).

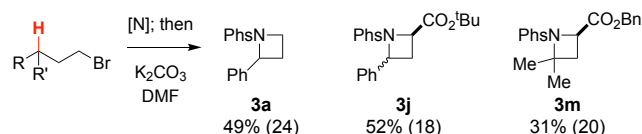
Substrates bearing benzylic (Table 2, entries 1–4), tertiary (Table 2, entries 5–7, 11), and protected carbinol C–H bonds (Table 2, entries 8–10) are successfully converted into the corresponding azetidines. The mild conditions for cyclization

are tolerant of base-sensitive functional groups including pinacolborane (entry 2), *N*-Boc indole (entry 3), and esters (entries 4, 7). Subjecting 1,3-dioxane and dioxolane-derived substrates (entries 8–10) to the two-step sequence affords unusual *N,O*-acetal azetidines, which are amenable to further modification.<sup>28,29</sup> As highlighted previously (see Table 1), cyclic amines of different ring size are accessible using our amination/cyclization technology. Entry 10 is notable in this regard, as the glycerol-based substrate undergoes site-selective oxidation and ring-closure with K<sub>2</sub>CO<sub>3</sub> to furnish an isolable, spirocyclic aziridine *N,O*-acetal.

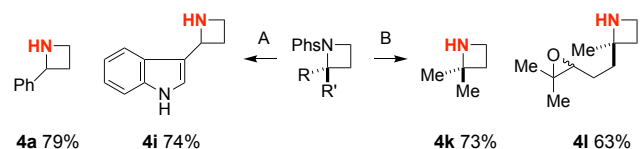
It is possible to conduct sequential C–H amination/cyclization in a single flask with only a small diminution in overall reaction performance (Scheme 2). This modified protocol is convenient when isolation of the C–H amination product is capricious, as is sometimes the case for *N,O*-acetal and other derivatives.

Phenoxysulfonyl (Phs) is a convenient and chromatographically stable *N*-protecting group, which can be readily removed to liberate the amine product (Scheme 3). Heating a Phs-amine starting material in aqueous CH<sub>3</sub>CN or aqueous pyridine cleaves the Phs-group; both conditions afford the desired amine in high purity following reversed-phase chromatography (HPLC) or trituration of the oxalate salt.<sup>30</sup>

To demonstrate the synthetic utility of our method for complex chemical synthesis, an unusual, azetidine-derived lipid penaresidin B was identified as a natural product target (Scheme 4).<sup>31</sup> Penaresidin B consists of a densely functionalized azetidine core with three contiguous stereocenters and a distally hydroxylated alkane side chain. Several total syntheses of penaresidin B<sup>32–34</sup> and related congeners<sup>35–41</sup> have been described, all relying on early-stage nitrogen incorporation using starting materials such as Garner's aldehyde<sup>42</sup> and/or multi-step functional group interconversions to construct the azetidine core. The shortest of the reported syntheses of penaresidin B is 17 linear steps.<sup>34</sup> Accordingly, application of our C–H amination/cyclization method should streamline access to this natural product.



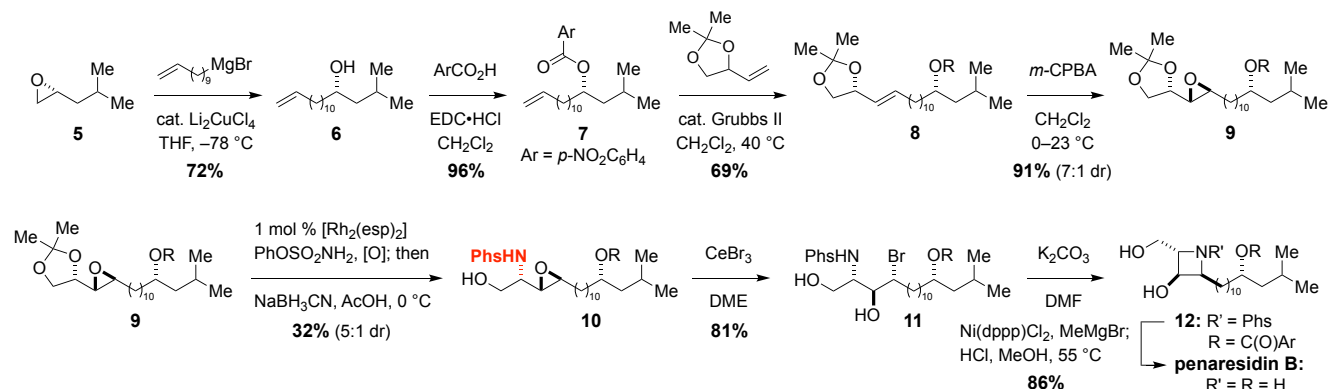
**Scheme 2.** Single-flask procedure for azetidine construction. Values in parentheses represent percent recovered starting material.



**Scheme 3.** Facile Phs-deprotection affords N–H azetidines. *Method A:* H<sub>2</sub>O/CH<sub>3</sub>CN, 90 °C; product isolated as the CF<sub>3</sub>CO<sub>2</sub>H salt following HPLC purification. *Method B:* H<sub>2</sub>O/pyridine; oxalate salt of the product isolated by trituration.

Our route to penaresidin B capitalizes on the performance of dioxolane substrates for C–H amination. Beginning from enantiopure oxirane **5**,<sup>43</sup> organocuprate addition to the less-hindered terminus yielded alcohol **6**. Protection of the alcohol group as the *p*-nitrobenzoyl ester was intended to deactivate the carbinol C–H bond and the proximal 3° site towards C–H amination. Grubbs' cross-metathesis of **7** with commercially available (*R*)-2,2-dimethyl-4-vinyl-1,3-dioxolane afforded olefin **8**, which was subsequently epoxidized to give **9** as a ~7:1 mixture of diastereomeric products.

Generation of the desired sulfamate ester **10** from **9** necessitated the development of a single-flask protocol for sequential amination/reduction owing to problems with isolation of the intermediate *N,O*-acetal. Subjecting **9** to standard amination conditions followed by NaBH<sub>3</sub>CN furnished aminoalcohol **10** as a ~5:1 mixture favoring the desired stereoisomer. This result is striking given the large number of disparate C–H bonds in **9** and the adjacent functional groups flanking the desired site of oxidation. We anticipate that this amination/reduction protocol will prove useful for the assembly of structurally related amino-polyol motifs.



**Scheme 4.** Asymmetric synthesis of penaresidin B.

To complete the synthesis of penaresidin B, epoxide **10** was converted to bromohydrin **11** under the action of CeBr<sub>3</sub>. Bromide displacement of **10** occurred regioselectively at C4 (penaresidin B numbering) to give **11** as the only detectable prod-

uct.<sup>44,45</sup> Finally, ring closure of the azetidine followed by sulfamate and nitrobenzoate deprotection yielded the desired target. Removal of the Phs-protecting group in **12** proved more challenging than with less functionalized azetidines (see Scheme 3).<sup>46</sup> Successful deprotection, however, was ultimately achieved by adapting a procedure for cross-coupling of cyclic



sulfamate esters.<sup>47</sup> Under nickel catalysis with MeMgBr, displacement of the phenyl ring afforded the sulfated azetidine; subsequent treatment with methanolic HCl furnished the natural product. All told, the enantioselective synthesis of penaresidin B proceeds in 9 steps from commercial starting materials, a substantial decrease in the overall step count compared to previous syntheses.

We have described reaction technology for the generation of structurally diverse small and medium-sized cyclic 2° amines. This process capitalizes on site-selective, intermolecular C–H amination to first introduce the obligatory nitrogen center as a sulfamate ester. Efficient C–H oxidation is viable across a range of functionalized propyl- and longer chain alkylbromide starting materials, substrates that have not been previously documented for amination reactions. We expect this work to advance the utility of C–H amination for the preparation of complex chemicals.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and characterization data (PDF)

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### Author Contributions

<sup>‡</sup>These authors contributed equally to this work.

### Notes

The authors declare no competing financial interest.

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  - (46) Acidic hydrolysis conditions using 1:1 6.0 N aqueous HCl/MeCN (90 °C, 24 h) provided the natural product in approximately 40% yield, but some decomposition was also observed. The other reported deprotection methods (H<sub>2</sub>O, Pyridine or H<sub>2</sub>O, MeCN) resulted in similar unsatisfactory performance.
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Azetidine MS Final Draft 082619.pdf (554.07 KiB)

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## Supporting Information for:

### Intermolecular $\text{sp}^3\text{-C-H}$ Amination for the Synthesis of Saturated Azacycles

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#### General Information

All reagents were obtained commercially unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated under reduced pressure (~15 Torr) by rotary evaporation. Solvents were purified by passage under 12 psi N<sub>2</sub> through activated alumina columns. Chromatography was performed on Silicycle Silia-P Silica Gel (40-63  $\mu\text{m}$ ). Thin layer chromatography was performed on EMD Chemicals Silica Gel 60 F254 plates (250  $\mu\text{m}$ ). Visualization of the developed chromatogram was accomplished by fluorescence quenching or by staining with ethanolic ninhydrin, aqueous potassium permanganate (KMnO<sub>4</sub>), aqueous ceric ammonium molybdate (CAM), or ethanolic anisaldehyde.

Nuclear magnetic resonance (NMR) spectra were acquired on either a Varian Inova-600 operating at 600 and 151 MHz, a Varian Inova-500 operating at 500 and 126 MHz or a Varian Mercury-400 operating at 400 and 101 MHz for <sup>1</sup>H and <sup>13</sup>C, respectively, and are referenced internally according to residual solvent signals. Data for <sup>1</sup>H NMR are recorded as follows: chemical shift ( $\delta$ , ppm), multiplicity (s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; m, multiplet), coupling constant (Hz), integration. Data for <sup>13</sup>C NMR are reported in terms of chemical shift ( $\delta$ , ppm). Infrared spectra were recorded on either a Thermo-Nicolet IR100 spectrometer or a Thermo-Nicolet IR300 spectrometer as thin films using NaCl salt plates and are reported in frequency of absorption. High-resolution mass spectra (ESI/TOF) were obtained using a Waters LCP Premier XE instrument.

### Optimization of cyclization conditions

**Table S1.** Influence of reaction conditions on sulfamate N-alkylation

Ph-CH2-CH2-CH2-NHPhs + Br (2a-1)  $\xrightarrow[\text{temperature, 2 h}]{\text{base, solvent}}$  Ph-CH2-CH2-CH2-N(Phs)1 (3a)

Entry <sup>a</sup>	Cyclization Conditions	% Yield <sup>b</sup>
1	NaO <sup>t</sup> Bu (1.1 equiv), Et <sub>2</sub> O	60
2	NaO <sup>t</sup> Bu (2.0 equiv), <i>t</i> -BuOMe	35
3	NaO <sup>t</sup> Bu (2.0 equiv), <i>t</i> -BuCN	80
4	NaO <sup>t</sup> Bu (2.0 equiv), <i>t</i> -BuCN, 55 °C	60
5	K <sub>2</sub> CO <sub>3</sub> (2.0 equiv), DMF	>95
6	K <sub>2</sub> CO <sub>3</sub> (1.5 equiv), DMF	>95
7	Single-flask C–H amination (5.0 equiv K <sub>2</sub> CO <sub>3</sub> , DMF)	50 <sup>c</sup>

<sup>a</sup>Cyclization performed with 0.1 mmol substrate in 1.0 mL of solvent for 2 h. <sup>b</sup>Yields determined by <sup>1</sup>H NMR with 4-nitrotoluene as an external standard. <sup>c</sup>1-Bromo-3-phenylpropane was used as the substrate for this reaction; ~20% of this material was recovered.

### Comparison with reported C–H amination protocols

1-Bromo-3-phenylpropane was oxidized following reported protocols for intermolecular sp<sup>3</sup>-C–H amination. Under these conditions, < 5% of the desired C–H amination product was detected by <sup>1</sup>H NMR. Using a Mn-based catalyst, starting material was recovered with imperfect mass balance; employing a Ag catalyst afforded little to no product, but mass recovery was nearly quantitative.

**Table S2.** Comparison of intermolecular C–H amination methods for oxidation of 1-bromo-3-phenyl propane

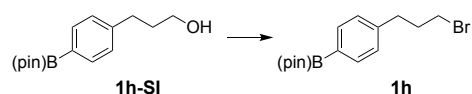
Ph-CH2-CH2-CH2-Br  $\xrightarrow{\text{conditions}}$  Ph-CH2-CH2-CH2-NHPhs + Br (2a-1)

Conditions <sup>a</sup>	Amination % Yield	% Recovered SM	Reference
10 mol % Mn(CIPc)Cl <sup>b</sup>	< 5	55	Clark, <i>et al.</i> <sup>1</sup>
10 mol % AgSbF <sub>6</sub>			
2.0 equiv PhI=NTces			
5 Å MS, C <sub>6</sub> H <sub>6</sub>			
10 mol % AgOTf	< 5	95	Dolan, <i>et al.</i> <sup>2</sup>
12 mol % tpa <sup>c</sup>			
1.0 equiv DfsNH <sub>2</sub>			
1.2 equiv PhI=O			
4 Å MS, CH <sub>2</sub> Cl <sub>2</sub>			

<sup>a</sup>Reactions performed using 1.0 equiv of 1-bromo-3-phenylpropane. <sup>b</sup>CIPc = Cl<sub>16</sub>phthalocyanine. <sup>c</sup>tpa = tris(2-pyridylmethyl)amine.

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## Experimental procedures and characterization data for select starting materials appearing in Table 2



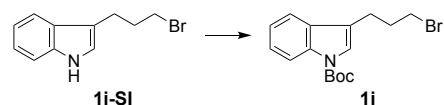
**2-(4-(3-Bromopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1h):** Alcohol **1h-SI** (262 mg, 1.0 mmol)<sup>3</sup> and CBr<sub>4</sub> (696 mg, 2.1 mmol, 2.1 equiv) were dissolved in 2.0 mL of CH<sub>2</sub>Cl<sub>2</sub>. The solution was cooled to 0 °C and Ph<sub>3</sub>P (656 mg, 2.5 mmol, 2.5 equiv) was added in a single bolus. After 10 min, the reaction mixture was diluted with 25 mL of hexanes and filtered over a small pad of Celite through a sintered glass funnel. The flask and filter cake were rinsed with 10 mL of 1:1 hexanes/CH<sub>2</sub>Cl<sub>2</sub>. The filtrate was concentrated under reduced pressure to a viscous oil, which was re-dissolved in ~3 mL of CH<sub>2</sub>Cl<sub>2</sub> and 10 mL of hexanes were added. The suspension was filtered through a small pad of Celite, the flask and filter cake were rinsed with 15 mL of hexanes, and the combined filtrates were concentrated under reduced pressure to a dark yellow oil. Purification of this material by chromatography on silica gel (gradient elution: 10→15% EtOAc in hexanes) yielded the desired product **1h** (136 mg, 42%) as a yellow oil.

R<sub>f</sub>: 0.51 (15% EtOAc/hexanes)

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*): δ 7.78–7.71 (m, 2H), 7.25–7.19 (m, 2H), 3.38 (td, *J* = 6.6, 0.5 Hz, 2H), 2.79 (t, *J* = 7.4 Hz, 2H), 2.23–2.11 (m, 2H), 1.34 (s, 12H) ppm

<sup>13</sup>C NMR (101 MHz, Chloroform-*d*): δ 144.1, 135.2, 128.2, 113.7, 83.8, 34.3, 34.1, 33.2, 25.0 ppm

IR: ν 2977, 2927, 2854, 1612, 1517, 1447, 1398, 1362, 1320, 1271, 1213, 1144, 1090, 1021, 962 cm<sup>-1</sup>



**tert-Butyl-3-(3-bromopropyl)-1H-indole-1-carboxylate (1i):** Indole **1i-SI** (238 mg, 1.0 mmol)<sup>4</sup> was dissolved in 5.0 mL of CH<sub>2</sub>Cl<sub>2</sub> and to this solution were added sequentially 4-dimethylaminopyridine (25 mg, 0.2 mmol, 0.2 equiv) and di-*tert*-butyl dicarbonate (331 mg, 1.5 mmol, 1.5 equiv). The reaction was stirred 2 h, following which time the reaction mixture was transferred to a separatory funnel with 25 mL of CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with 1 x 10 mL of H<sub>2</sub>O and 1 x 10 mL of saturated aqueous NaCl, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to a brown oil. Purification of this material by chromatography on silica gel (10% Et<sub>2</sub>O in hexanes) furnished the product **1i** (308 mg, 90%) as a brown oil.

R<sub>f</sub>: 0.48 (10% Et<sub>2</sub>O in hexanes)

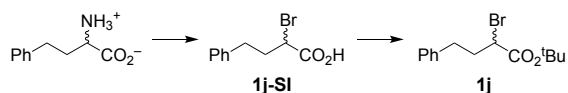
<sup>1</sup>H NMR (400 MHz, Chloroform-*d*): δ 8.10 (dd, *J* = 18.2, 8.1 Hz, 1H), 7.59–7.48 (m, 1H), 7.40 (s, 1H), 7.32 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.23 (dd, *J* = 7.3, 1.1 Hz, 1H), 3.47 (t, *J* = 6.5 Hz, 2H), 2.87 (td, *J* = 7.3, 1.0 Hz, 2H), 2.35–2.19 (m, 2H), 1.67 (s, 9H) ppm

<sup>13</sup>C NMR (101 MHz, Chloroform-*d*): δ 124.5, 123.0, 122.5, 119.3, 119.0, 115.5, 33.5, 32.3, 29.9, 28.4, 23.4 ppm

IR: ν 2925, 2854, 1711, 1612, 1517, 1458, 1396, 1361, 1320, 1271, 1144, 1089, 1021, 962 cm<sup>-1</sup>

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**2-Bromo-4-phenylbutanoic acid (1j-SI):** A 250 mL 2-neck flask was charged with homophenylalanine (2.19 g, 12.2 mmol), NaBr (4.33 g, 42.7 mmol, 3.5 equiv), and 40 mL of H<sub>2</sub>O, and the mixture was cooled to 0 °C. The flask was fitted with a gas outlet adapter attached to a bubbler that was immersed in a 1.0 N aqueous NaOH solution. To the vigorously stirred solution was added 2.5 mL of concentrated H<sub>2</sub>SO<sub>4</sub> followed by 2.5 mL of an aqueous solution of 40 wt % NaNO<sub>2</sub> (15.25 mmol, 1.25 equiv) at a rate such that no gas evolution was observed. The mixture was stirred at 0 °C for 45 min, then warmed to room temperature and stirred for 6 h. Following this time, the solution was transferred to a separatory funnel and extracted with 3 x 25 mL of EtOAc. The combined organic fractions were washed with 1 x 25 mL of saturated aqueous NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to a yellow oil. This material was determined to be sufficiently pure by <sup>1</sup>H NMR for use in the subsequent reaction (1.50 g, 51%).

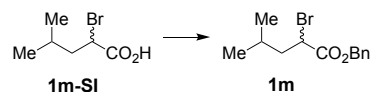
**tert-Butyl-2-bromo-4-phenylbutanoate (1j):** Bromide **1ej-SI** (1.49 g, 6.13 mmol) was dissolved in 25 mL of <sup>t</sup>BuOAc and the solution was cooled to 0 °C. An aqueous solution of 70 wt % HClO<sub>4</sub> (80 μL, 0.557 mmol, 0.1 equiv) was added dropwise. The reaction was warmed to room temperature, stirred for 12 h, and then quenched by the slow addition of 30 mL of saturated aqueous NaHCO<sub>3</sub>. The mixture was transferred to a separatory funnel and extracted with 3 x 15 mL of EtOAc. The organic fractions were washed with 1 x 15 mL of saturated aqueous NaHCO<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel (100% hexanes) furnished ester **1j** (952 mg, 52%) as a pale yellow oil.

R<sub>f</sub>: 0.41 (100% hexanes)

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*): δ 7.31 (t, *J* = 7.8 Hz, 2H), 7.25–7.16 (m, 3H), 4.08 (dd, *J* = 8.1, 6.5 Hz, 1H), 2.87–2.62 (m, 2H), 2.42–2.15 (m, 2H), 1.49 (s, 9H) ppm

<sup>13</sup>C NMR (101 MHz, Chloroform-*d*): δ 168.8, 140.2, 128.71, 128.67, 126.5, 82.5, 47.2, 36.5, 33.4, 27.9 ppm

IR: ν 2980, 2930, 1729, 1488, 1457, 1295, 1252, 1068, 1041, 1025, 980 cm<sup>-1</sup>



**Benzyl 2-bromo-4-methylpentanoate (1m):** Benzyl ester **1m** was prepared from acid **1m-SI**<sup>5</sup> following the procedure of Karoyan, *et al.*<sup>6</sup>

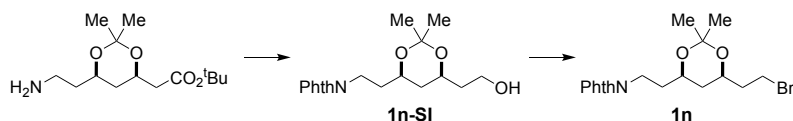
R<sub>f</sub>: 0.28 (2% EtOAc in hexanes)

<sup>1</sup>H NMR (400 MHz, Chloroform-*d*): δ 7.23–6.95 (m, 5H), 5.00 (s, 2H), 4.26 (dd, *J* = 8.2, 7.3 Hz, 1H), 2.04 (dt, *J* = 14.7, 7.4 Hz, 1H), 1.65 (ddd, *J* = 14.1, 8.3, 5.3 Hz, 1H), 0.86 (t, *J* = 5.3 Hz, 1H), 0.65 (dd, *J* = 16.4, 6.6 Hz, 6H) ppm

<sup>13</sup>C NMR (101 MHz, Benzene-*d*<sub>6</sub>): δ 169.5, 135.8, 128.7, 128.5, 128.5, 128.3, 128.1, 127.8, 67.4, 44.8, 43.4, 24.7, 21.3 ppm

IR: ν 2959, 2871, 1745, 1456, 1369, 1325, 1277, 1191, 1149, 1125, 1074, 1003 cm<sup>-1</sup>

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**2-((4R,6S)-6-(2-Hydroxyethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethylisoindoline-1,3-dione (1n-SI):** *tert*-Butyl 2-((4R,6R)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (1.09 g, 4.0 mmol) in 12.0 mL of Et<sub>2</sub>O was added dropwise via syringe to an ice-cold suspension of LiAlH<sub>4</sub> (167 mg, 4.4 mmol, 1.1 equiv) in 12.0 mL of Et<sub>2</sub>O. Transfer of the starting material was made quantitative with an addition of 2.0 mL of Et<sub>2</sub>O. The mixture was warmed to ambient temperature and stirred for 4 h. Following this time, the gray suspension was cooled to 0 °C and the reaction was quenched by the slow, successive addition of 0.2 mL of H<sub>2</sub>O, 0.2 mL of 15% aqueous NaOH, and 0.6 mL of H<sub>2</sub>O. After stirring vigorously for 30 min, the white suspension was filtered through a small pad of Celite. The flask and filter cake were rinsed with ~10 mL of Et<sub>2</sub>O. The combined filtrates were dried over K<sub>2</sub>CO<sub>3</sub>, filtered and concentrated under reduced pressure to a brown oil. The impure product was dissolved in 15 mL of toluene and filtered through a small plug of silica gel, eluting with ~5 mL of toluene, filtered through silica. To this solution was added phthalic anhydride (1.18 g, 8.0 mmol, 2.0 equiv). The mixture was stirred at reflux in a flask equipped with a Dean-Stark trap for 3 h, and then concentrated under reduced pressure to a yellow oil (1.04 g, 78%). The product **1n-SI** was determined to be sufficiently pure by <sup>1</sup>H NMR for use in the subsequent step.

**2-((4R,6R)-6-(2-Bromoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethylisoindoline-1,3-dione (1n):** Alcohol **1n-SI** (666 mg, 2.0 mmol) was dissolved in 5.0 mL of CH<sub>2</sub>Cl<sub>2</sub>, the solution cooled to 0 °C, and Et<sub>3</sub>N (556 μL, 4.0 mmol, 2.0 equiv) was added followed by MeSO<sub>2</sub>Cl (186 μL, 2.4 mmol, 1.2 equiv). The reaction was warmed to ambient temperature and stirred for 2 h, following which time the reaction was quenched by addition of 5.0 mL of H<sub>2</sub>O. The solution was transferred to a separatory funnel and extracted with 3 x 5 mL of CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were combined and washed sequentially with 1 x 5 mL of H<sub>2</sub>O and 1 x 10 mL of saturated aqueous NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The oily residue was re-dissolved in 2.3 mL of anhydrous acetone to which LiBr (537 mg, 6.2 mmol, 3.1 equiv) was then added. The mixture was stirred at 55 °C for 2 h. The reaction was cooled to ambient temperature and filtered through a small pad of Celite. The flask and filter cake were rinsed with ~5 mL of acetone, and the combined filtrates were concentrated under reduced pressure. The brown oil was transferred to a separatory funnel with 5.0 mL of H<sub>2</sub>O and 5.0 mL of Et<sub>2</sub>O. The organic phase was collected and the aqueous layer was extracted with 3 x 5 mL of Et<sub>2</sub>O. The combined ethereal fractions were washed with brine 1 x 5 mL of saturated aqueous NaCl, dried over MgSO<sub>4</sub>, and concentrated under reduced pressure to a brown oil. Purification of this material by chromatography on silica gel (15% EtOAc in hexanes) afforded bromide **1n** (523 mg, 66%) as a light yellow oil.

**R<sub>f</sub>:** 0.34 (15% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** δ 7.86–7.77 (m, 2H), 7.74–7.64 (m, 2H), 4.19 (ddt, *J* = 13.5, 9.1, 4.4 Hz, 1H), 3.91 (ddt, *J* = 11.6, 9.1, 2.8 Hz, 1H), 3.79 (td, *J* = 6.5, 3.1 Hz, 2H), 2.38 (dd, *J* = 15.1, 7.0 Hz, 1H), 2.25 (dd, *J* = 15.1, 6.2 Hz, 1H), 1.94–1.81 (m, 1H), 1.81–1.66 (m, 1H), 1.51 (dt, *J* = 12.3, 2.4 Hz, 1H), 1.35 (s, 3H), 1.20–1.16 (m, 1H), 1.11 (s, 3H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** δ 170.3, 168.6, 133.9, 132.4, 123.2, 98.8, 80.7, 67.3, 66.1, 42.8, 36.5, 34.7, 29.9, 28.2 ppm

**IR:** ν 3090, 2978, 2929, 2853, 1770, 1701, 1662, 1630, 1491, 1465, 1485, 1399, 1252, 1151, 1090, 1070, 1026, 1009, 959 cm<sup>-1</sup>

## General procedures for substrate amination and cyclization for Table 1 and Table 2

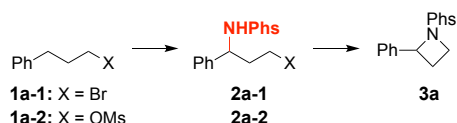
**Note:** All reactions performed under air using commercial *t*-BuCN (Acros Organics) as received.  $[\text{Rh}_2(\text{esp})_2]$  and  $\text{PhI}(\text{O}_2\text{C}^t\text{Bu})_2$  were prepared as described by Fiori, *et al*<sup>7</sup> or purchased from commercial vendors (Aldrich).  $\text{Al}_2\text{O}_3$  is unactivated, neutral, Brockman Grade I, from J.T. Baker.

### General procedure:

**C–H Amination:** To a 1-dram reaction vial equipped with a stir bar was added substrate followed by  $[\text{Rh}_2(\text{esp})_2]$  (1.0 mol%),  $\text{PhOSO}_2\text{NH}_2$  (1.3 equiv),  $\text{Al}_2\text{O}_3$  (4.0 equiv), and *t*-BuCN (the initial concentration of substrate should be set at 1.0 M). The mixture was stirred for 10 min until the solution is a vivid blue color. A single portion of  $\text{PhI}(\text{O}^t\text{Bu})_2$  (1.5 equiv.) was added and the solution immediately turned brick-red. The reaction vial was capped and the suspension was stirred for 6h, following which time the reaction was diluted with 3 mL  $\text{CH}_2\text{Cl}_2$  and filtered through a small pad of Celite. The flask and filter cake were rinsed with 5 mL  $\text{CH}_2\text{Cl}_2$  and the combined filtrates were concentrated under reduced pressure. The isolated material was redissolved in 3 mL of  $\text{CH}_2\text{Cl}_2$  and to this solution was added Celite (200–400 mg Celite/mmol starting material). The slurry was evaporated under reduced pressure to a powder, which was loaded onto a chromatography column pre-packed with silica gel and solvent (conditions given below). Purification was performed by chromatography on silica gel. In select cases, products with trace Rh-contaminant were obtained following chromatography; decolorization was accomplished using the methods described in Chiappini, *et al*.<sup>8</sup>

**Cyclization:** The purified C–H amination product was dissolved in DMF at a concentration of 0.1 M. Anhydrous  $\text{K}_2\text{CO}_3$  (1.5 equiv) was added and the mixture was stirred until thin-layer chromatography indicated the complete consumption of starting material. The reaction was transferred to a separatory funnel with 10 mL of EtOAc and washed with 10 mL of  $\text{H}_2\text{O}$  and 3 x 10 mL of saturated aqueous NaCl. The organic layer was dried over  $\text{MgSO}_4$  or  $\text{Na}_2\text{SO}_4$ , filtered, concentrated under reduced pressure. Purification was performed by chromatography on silica gel (conditions given below).

### Characterization of C–H amination and cyclization products from Table 1



**Phenyl (3-bromo-1-phenylpropyl)sulfamate (2a-1):** Prepared according to the general C–H amination procedure using **1a-1** (60 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (15% EtOAc in hexanes) afforded **2a-1** (71 mg, 64%) as an off-white oily solid along with 23% recovered starting material.

**R<sub>f</sub>:** 0.29 (15% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):**  $\delta$  7.43–7.34 (m, 3H), 7.35–7.17 (m, 5H), 7.01–6.95 (m, 2H), 5.46 (d,  $J$  = 8.0 Hz, 1H), 4.78 (q,  $J$  = 7.5 Hz, 1H), 3.38 (dt,  $J$  = 10.3, 6.2 Hz, 1H), 3.16 (ddd,  $J$  = 10.4, 7.8, 6.0 Hz, 1H), 2.60–2.40 (m, 1H), 2.29 (ddt,  $J$  = 14.0, 7.6, 6.1 Hz, 1H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):**  $\delta$  150.1, 139.2, 129.8, 129.3, 128.8, 127.0, 126.9, 121.8, 58.2, 39.8, 29.0 ppm

**IR:**  $\nu$  3295, 2923, 1587, 1487, 1456, 1368, 1257, 1194, 1171, 1148, 1055, 969  $\text{cm}^{-1}$

- Williams-Fiori, K. Rhodium-catalyzed carbon-hydrogen amination: Mechanistic insights and application to new reaction development. Ph.D. Dissertation, Stanford University, **2007**.
- Chiappini, N. D.; Mack, J. B. C.; Du Bois, J. Intermolecular  $\text{C}(\text{sp}^3)\text{--H}$  Amination of Complex Molecules. *Angew. Chem. Int. Ed.* **2018**, 57, 4956–4959.

**Phenyl (3-((methylsulfonyl)oxy)-1-phenylpropyl)sulfamate (2a-2):** Prepared according to the general C–H amination procedure using **1a-2**<sup>9</sup> (64 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (gradient elution: 10%→40% EtOAc in hexanes) afforded **2a-2** (44 mg, 38%) as a tan solid along with 56% recovered starting material.

**R<sub>f</sub>:** 0.05 (25% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** δ 7.45–7.33 (m, 3H), 7.33–7.13 (m, 5H), 6.93–6.87 (m, 2H), 5.53 (d, *J* = 8.4 Hz, 1H), 4.74 (td, *J* = 8.3, 6.4 Hz, 1H), 4.30 (ddd, *J* = 10.3, 7.3, 4.8 Hz, 1H), 4.17 (ddd, *J* = 10.3, 6.5, 5.1 Hz, 1H), 2.98 (s, 3H), 2.44–2.26 (m, 1H), 2.26–2.13 (m, 1H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** δ 150.0, 139.3, 129.8, 129.3, 128.8, 127.0, 126.8, 121.7, 66.5, 56.3, 37.4, 36.4 ppm

**IR:** ν 3266, 3031, 2939, 1587, 1353, 1195, 1173, 974, 927 cm<sup>−1</sup>

**Phenyl 2-phenylazetidine-1-sulfonate (3a):** Prepared according to the general cyclization procedure using **2a-1** (37 mg, 0.1 mmol) or **2a-2** (38 mg, 0.1 mmol). Purification of this material by chromatography on silica gel (gradient elution: 10%→25% EtOAc in hexanes) yielded the azetidine product **3a** (from **2a-1**: 28 mg, 97%; from **2a-2**: 28 mg, 96%) as a viscous brown oil.

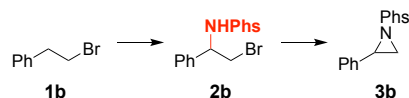
**R<sub>f</sub>:** 0.50 (25% EtOAc in hexanes)

**<sup>1</sup>H NMR (600 MHz, Chloroform-*d*):** δ 7.35 (dt, *J* = 11.9, 6.6 Hz, 3H), 7.30–7.16 (m, 5H), 6.97 (dd, *J* = 7.7, 1.5 Hz, 2H), 5.25 (d, *J* = 7.9 Hz, 1H), 4.76 (q, *J* = 7.5 Hz, 1H), 3.36 (dt, *J* = 10.1, 6.2 Hz, 1H), 3.15 (ddd, *J* = 10.2, 7.8, 6.1 Hz, 1H), 2.47 (dq, *J* = 14.2, 7.0 Hz, 1H), 2.36–2.16 (m, 1H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** δ 150.2, 139.9, 129.8, 128.7, 128.5, 126.8, 126.5, 121.8, 67.5, 49.2, 25.6 ppm

**IR:** ν 2912, 2849, 1586, 1486, 1373, 1194, 1172, 1148, 1087, 1021 cm<sup>−1</sup>

**HRMS (ESI<sup>+</sup>):** calculated for C<sub>15</sub>H<sub>15</sub>NO<sub>3</sub>S[H]<sup>+</sup> 290.0845, found 290.0842



**Phenyl (2-bromo-1-phenylethyl)sulfamate (2b):** Prepared according to the general C–H amination procedure using **1b** (56 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (gradient elution: 100% hexanes→10% EtOAc in hexanes) afforded **2b** (43 mg, 40%) as a brown solid along with 15% recovered starting material.

**R<sub>f</sub>:** 0.15 (10% EtOAc in hexanes)

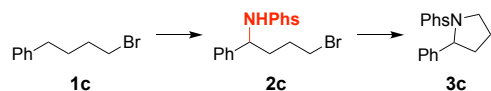
**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** δ 7.44–7.35 (m, 3H), 7.35–7.20 (m, 5H), 7.10 (dd, *J* = 7.5, 1.7 Hz, 2H), 5.48 (d, *J* = 7.3 Hz, 1H), 4.91 (dt, *J* = 7.3, 5.8 Hz, 1H), 3.79–3.67 (m, 2H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** δ 150.0, 137.4, 129.8, 129.1, 129.0, 127.1, 126.9, 121.8, 59.0, 36.5 ppm

**IR:** ν 3288, 3063, 2919, 2850, 1419, 1363, 1147 cm<sup>−1</sup>

9. Albrecht, S.; Defoin, A.; Tarnus, C. Simple Preparation of *O*-Substituted Hydroxylamines from Alcohols. *Synthesis* **2006**, 10, 1635–1638.

**Phenyl 2-phenylaziridine-1-sulfonate (3b):** Prepared according to the general cyclization procedure using **2b** (36 mg, 0.1 mmol). The product aziridine is unstable and decomposes under the reaction conditions. Preparation of an authentic sample of this material using a previously reported method confirmed this result.<sup>10</sup> NMR analysis of the isolated material following work-up indicated complete consumption of starting material.



**Phenyl (4-bromo-1-phenylbutyl)sulfamate (2c):** Prepared according to the general C–H amination procedure using **1c** (64 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (gradient elution: 100% hexanes→10% EtOAc in hexanes) afforded **2c** (48 mg, 42%) as a pale yellow oil along with 45% recovered starting material.

**R<sub>f</sub>:** 0.19 (10% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** δ 7.43–7.15 (m, 8H), 6.99–6.83 (m, 2H), 5.15 (d, *J* = 7.9 Hz, 1H), 4.55 (q, *J* = 7.4 Hz, 1H), 3.38 (t, *J* = 6.2 Hz, 2H), 2.20–1.68 (m, 4H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** δ 150.1, 140.2, 129.7, 129.2, 128.5, 126.9, 126.8, 121.8, 59.1, 35.7, 33.0, 29.1 ppm

**IR:** ν 3297, 3064, 2959, 1587, 1432, 1365, 1194, 1149 cm<sup>-1</sup>

**Phenyl 2-phenylpyrrolidine-1-sulfonate (3c):** Prepared according to the general cyclization procedure using **2c** (38 mg, 0.1 mmol). Purification of this material by chromatography on silica gel (gradient elution: 10%→25% EtOAc in hexanes) yielded the pyrrolidine product **3c** (29 mg, 97%) as an off-white solid.

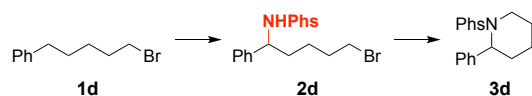
**R<sub>f</sub>:** 0.19 (15% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** δ 7.43–7.20 (m, 10H), 5.00 (dd, *J* = 8.0, 3.9 Hz, 1H), 3.88–3.67 (m, 2H), 2.41 (dq, *J* = 11.9, 7.7 Hz, 1H), 2.12–1.88 (m, 3H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** δ 150.4, 142.1, 129.8, 128.6, 127.5, 126.7, 126.1, 121.8, 64.9, 50.7, 36.0, 24.4 ppm

**IR:** ν 2958, 2919, 1653, 1636, 1558, 1540, 1487, 1456, 1373, 1194, 1168, 1147, 1069, 1011, 854, 749, 690, 620 cm<sup>-1</sup>

**HRMS (ESI<sup>+</sup>):** calculated for C<sub>16</sub>H<sub>17</sub>NO<sub>3</sub>S[Na]<sup>+</sup> 326.0827, found 326.0821



**Phenyl (5-bromo-1-phenylpentyl)sulfamate (2d):** Prepared according to the general C–H amination procedure using **1d** (68 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (gradient elution: 100% hexanes→10% EtOAc in hexanes) afforded **2d** (62 mg, 52%) as a colorless oil along with 40% recovered starting material.

**R<sub>f</sub>:** 0.14 (10% EtOAc in hexanes)

**<sup>1</sup>H NMR (500 MHz, Chloroform-*d*):** δ 7.45–7.17 (m, 8H), 7.09–6.88 (m, 2H), 4.93 (d, *J* = 7.7 Hz, 1H), 4.53 (q, *J* = 7.5 Hz, 1H), 3.35 (td, *J* = 6.7, 3.2 Hz, 2H), 1.98 (dddd, *J* = 15.8, 12.4, 6.9, 5.3 Hz, 1H), 1.84 (tdd, *J* = 12.6, 8.5, 4.8 Hz, 3H), 1.50 (dddd, *J* = 15.5, 10.4, 7.4, 5.6 Hz, 1H), 1.36 (dtt, *J* = 10.7, 7.8, 5.5 Hz, 1H) ppm

10. Subbarayan, V.; Jin, L.-M.; Cui, X.; Zhang, X. P. Room temperature activation of aryloxysulfonyl azides by [Co(II)(TPP)] for selective radical aziridination of alkenes via metalloradical catalysis. *Tetrahedron Lett.* **2015**, *56*, 3431–3434.

**$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*):**  $\delta$  150.1, 140.4, 129.7, 129.1, 128.4, 126.9, 126.8, 121.8, 59.7, 36.3, 33.3, 32.2, 24.7 ppm

**IR:**  $\nu$  3299, 2933, 1587, 1364, 1194, 1149  $\text{cm}^{-1}$

**Phenyl 2-phenylpiperidine-1-sulfonate (3d):** Prepared according to the general cyclization procedure using **2d** (40 mg, 0.1 mmol). Purification of this material by chromatography on silica gel (gradient elution: 10%→25% EtOAc in hexanes) yielded the piperidine product **3d** (31 mg, 98%) as an off-white solid.

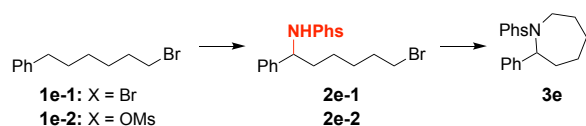
**R<sub>f</sub>:** 0.31 (15% EtOAc in hexanes)

**$^1\text{H}$  NMR (600 MHz, Chloroform-*d*):**  $\delta$  7.41–7.32 (m, 6H), 7.32–7.28 (m, 2H), 7.29–7.21 (m, 2H), 5.26 (dd,  $J$  = 9.5, 3.6 Hz, 1H), 3.87 (dt,  $J$  = 14.7, 2.9 Hz, 1H), 3.12 (td,  $J$  = 13.4, 2.6 Hz, 1H), 2.39–2.21 (m, 1H), 2.04 (tdd,  $J$  = 15.2, 5.7, 2.5 Hz, 1H), 1.83–1.61 (m, 2H), 1.61–1.42 (m, 2H) ppm

**$^{13}\text{C}$  NMR (151 MHz, Chloroform-*d*):**  $\delta$  150.7, 138.2, 129.8, 128.9, 127.3, 127.1, 126.7, 121.8, 57.2, 43.5, 27.3, 24.4, 19.0 ppm

**IR:**  $\nu$  2923, 2850, 1653, 1585, 1558, 1486, 1456, 1372, 1275, 1260, 1199, 1173, 1147, 1100, 1056  $\text{cm}^{-1}$ .

**HRMS (ESI<sup>+</sup>):** calculated for  $\text{C}_{17}\text{H}_{19}\text{NO}_3\text{S}[\text{Na}]^+$  340.0983, found 340.0986



**Phenyl (6-bromo-1-phenylhexyl)sulfamate (2e-1):** Prepared according to the general C–H amination procedure using **1e-1** (72 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (gradient elution: 100% hexanes→15% EtOAc in hexanes) afforded **2e-1** (80 mg, 65%) as a colorless oil along with 22% recovered starting material.

**R<sub>f</sub>:** 0.16 (15% EtOAc in hexanes)

**$^1\text{H}$  NMR (500 MHz, Chloroform-*d*):**  $\delta$  7.43–7.29 (m, 5H), 7.24–7.13 (m, 3H), 6.97–6.91 (m, 2H), 4.90 (d,  $J$  = 7.6 Hz, 1H), 4.53 (q,  $J$  = 7.4 Hz, 1H), 3.36 (td,  $J$  = 6.7, 0.9 Hz, 2H), 2.01–1.87 (m, 1H), 1.87–1.75 (m, 3H), 1.66–1.51 (m, 2H), 1.45 (p,  $J$  = 8.4, 7.6 Hz, 2H), 1.39–1.30 (m, 2H) ppm

**$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*):**  $\delta$  150.1, 140.6, 129.7, 129.0, 128.3, 126.8, 126.8, 121.7, 59.7, 37.1, 33.8, 32.6, 27.8, 25.2 ppm

**IR:**  $\nu$  3299, 2935, 1587, 1487, 1365, 1195, 1171  $\text{cm}^{-1}$

**Phenyl (6-((methylsulfonyl)oxy)-1-phenylhexyl)sulfamate (2e-2):** Prepared according to the general C–H amination procedure using **1e-2**<sup>11</sup> (77 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (gradient elution: 10%→40% EtOAc in hexanes) afforded **2e-2** (54 mg, 42%) as a pale yellow oil along with 47% recovered starting material.

**R<sub>f</sub>:** 0.05 (25% EtOAc in hexanes)

**$^1\text{H}$  NMR (400 MHz, Chloroform-*d*):**  $\delta$  7.42–7.12 (m, 8H), 6.95–6.88 (m, 2H), 5.27 (d,  $J$  = 7.8 Hz, 1H), 4.50 (q,  $J$  = 7.5 Hz, 1H), 4.17 (t,  $J$  = 6.4 Hz, 2H), 2.96 (d,  $J$  = 2.2 Hz, 3H), 2.00–1.53 (m, 4H), 1.46–1.12 (m, 4H) ppm

11. Gapinski, D. M.; Mallett, B. E.; Froelich, L. L.; Jackson, W. T. Benzophenone dicarboxylic acid antagonists of leukotriene B<sub>4</sub>. 2. Structure-activity relationships of the lipophilic side chain. *J. Med. Chem.* **1990**, *33*, 2807–2813.



**$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*):**  $\delta$  150.1, 140.7, 129.7, 129.0, 128.3, 126.8, 126.8, 121.7, 70.0, 59.7, 37.4, 37.0, 28.9, 25.4, 25.1 ppm

**IR:**  $\nu$  3290, 2940, 1587, 1351, 1195, 1173, 1150  $\text{cm}^{-1}$

**Phenyl 2-phenylazepane-1-sulfonate (3e):** Prepared according to the general cyclization procedure using **2e-1** (41 mg, 0.1 mmol) or **2e-2** (43 mg, 0.1 mmol). Purification of this material by chromatography on silica (15% EtOAc in hexanes) yielded the azepane product **3e** (from **2e-1**: 32 mg, 98%; from **2e-2**: 22 mg, 68%) as a white solid.

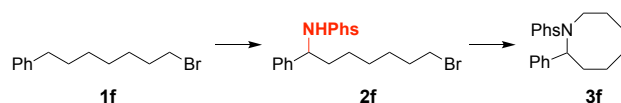
**R<sub>f</sub>:** 0.32 (15% EtOAc in hexanes)

**$^1\text{H}$  NMR (600 MHz, Chloroform-*d*):**  $\delta$  7.35–7.28 (m, 4H), 7.29–7.20 (m, 3H), 7.14 (t,  $J$  = 7.4 Hz, 1H), 6.97–6.89 (m, 2H), 5.01 (dd,  $J$  = 11.8, 6.0 Hz, 1H), 3.91 (dt,  $J$  = 15.0, 3.1 Hz, 1H), 3.48–3.25 (m, 1H), 2.32 (ddd,  $J$  = 14.8, 8.4, 6.2 Hz, 1H), 1.99–1.60 (m, 7H) ppm

**$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*):**  $\delta$  150.5, 142.0, 129.6, 128.7, 127.6, 126.6, 126.4, 121.7, 63.1, 46.6, 36.7, 29.54, 29.52, 25.5 ppm

**IR:**  $\nu$  2950, 2923, 2850, 1653, 1576, 1559, 1457, 1374, 1272, 1190, 1146, 1022  $\text{cm}^{-1}$

**HRMS (ESI<sup>+</sup>):** calculated for  $\text{C}_{18}\text{H}_{21}\text{NO}_3\text{S}[\text{Na}]^+$  354.1140, found 354.1142



**Phenyl (7-bromo-1-phenylheptyl)sulfamate (2f):** Prepared according to the general C–H amination procedure using **1f** (68 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (gradient elution: 100% hexanes→10% EtOAc in hexanes) afforded **2f** (95 mg, 74%) as a colorless oil along with 17% recovered starting material.

**R<sub>f</sub>:** 0.13 (10% EtOAc in hexanes)

**$^1\text{H}$  NMR (400 MHz, Chloroform-*d*):**  $\delta$  7.43–7.12 (m, 8H), 6.98–6.87 (m, 2H), 5.07 (d,  $J$  = 7.7 Hz, 1H), 4.52 (q,  $J$  = 7.5 Hz, 1H), 3.37 (t,  $J$  = 6.8 Hz, 2H), 1.93 (dddd,  $J$  = 11.9, 10.2, 7.6, 4.1 Hz, 1H), 1.85–1.71 (m, 3H), 1.47–1.10 (m, 6H) ppm

**$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*):**  $\delta$  150.1, 140.7, 129.7, 129.0, 128.3, 126.8, 126.8, 121.8, 59.8, 37.1, 34.0, 32.7, 28.4, 28.0, 25.9 ppm

**IR:**  $\nu$  3295, 2939, 1584, 1482, 1364, 1195, 1173  $\text{cm}^{-1}$

**Phenyl 2-phenylazocane-1-sulfonate (3f):** Prepared according to the general cyclization procedure using **2f** (43 mg, 0.1 mmol). Purification of this material by chromatography on silica gel (gradient elution: 10%→25% EtOAc in hexanes) yielded the azocane product **3f** (8 mg, 22%) as opaque film.

**R<sub>f</sub>:** 0.54 (25% EtOAc in hexanes)

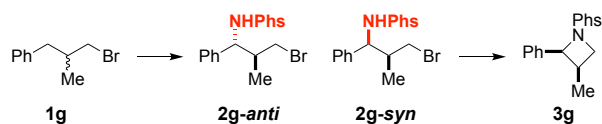
**$^1\text{H}$  NMR (400 MHz, Chloroform-*d*):**  $\delta$  7.46–7.29 (m, 8H), 6.87–6.81 (m, 2H), 5.04 (dd,  $J$  = 12.3, 3.8 Hz, 1H), 3.64 (dt,  $J$  = 15.3, 4.0 Hz, 1H), 3.44 (ddd,  $J$  = 15.2, 11.2, 3.7 Hz, 1H), 2.35–2.17 (m, 1H), 2.13–1.88 (m, 6H), 1.87–1.75 (m, 3H) ppm

**$^{13}\text{C}$  NMR (126 MHz, Chloroform-*d*):**  $\delta$  149.9, 144.9, 129.4, 128.5, 127.8, 127.4, 126.2, 121.5, 63.2, 45.2, 37.1, 30.8, 30.2, 29.4, 22.7 ppm

**IR:**  $\nu$  2961, 2922, 2850, 1735, 1653, 1565, 1540, 1457, 1376, 1260, 1199, 1154, 1074, 1024  $\text{cm}^{-1}$

**HRMS (ESI<sup>+</sup>):** calculated for C<sub>19</sub>H<sub>23</sub>NO<sub>3</sub>S[Na]<sup>+</sup> 368.1296, found 368.1291

### Characterization of C–H amination and cyclization products from Table 2



**Phenyl (3-bromo-2-methyl-1-phenylpropyl)sulfamate (2g):** Prepared according to the general C–H amination procedure using **1g** (64 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (15% EtOAc in hexanes) afforded two diastereomeric C–H aminated products **2g** (44 mg, 39%, *anti*-diastereomer; 25 mg, 21%, *syn*-diastereomer) as brown oily solids along with 28% recovered starting material. Less than 3% of the product derived from tertiary C–H amination was obtained.

**R<sub>f</sub>:** 0.26 (*anti*) and 0.21 (*syn*) (15% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** (*syn*) δ 7.48–7.31 (m, 4H), 7.25–7.16 (m, 4H), 6.90–6.80 (m, 2H), 5.29 (d, *J* = 8.8 Hz, 1H), 4.61 (t, *J* = 8.4 Hz, 1H), 3.52 (dd, *J* = 10.3, 4.9 Hz, 1H), 3.43 (dd, *J* = 10.3, 6.1 Hz, 1H), 2.33 (dt, *J* = 13.2, 6.5 Hz, 1H), 0.93 (d, *J* = 6.8 Hz, 3H) ppm

(*anti*) δ 7.46–7.27 (m, 5H), 7.24–7.14 (m, 3H), 6.89–6.79 (m, 2H), 5.21 (d, *J* = 9.3 Hz, 1H), 4.65 (dd, *J* = 9.3, 7.7 Hz, 1H), 3.37 (dd, *J* = 10.3, 4.7 Hz, 1H), 3.06 (dd, *J* = 10.3, 5.2 Hz, 1H), 2.32–2.20 (m, 1H), 1.21 (d, *J* = 6.7 Hz, 3H) ppm; further purification of the product was not possible due to co-elution with an unidentified product (5:1 ratio).

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** (*syn*) δ 151.0, 138.3, 129.6, 129.0, 128.5, 127.2, 126.8, 121.6, 62.1, 40.9, 29.8, 15.9 ppm

(*anti*) δ 154.1, 140.8, 129.7, 129.2, 128.5, 127.0, 126.8, 121.7, 62.2, 37.5, 29.9, 15.5 ppm

**IR:** (*syn*) ν 3424, 2962, 2920, 2851, 1647, 1586, 1487, 1450, 1372, 1198, 1172, 1121, 1020 cm<sup>-1</sup>

***cis*-Phenyl 3-methyl-2-phenylazetidinium-1-sulfonate (3g):** Prepared according to the general cyclization procedure using the *syn*-diastereomer **2g** (38 mg, 0.1 mmol). The azetidinium product **3g** (28 mg, 92%) was obtained following work-up as a viscous brown gel. This material was determined to be pure by <sup>1</sup>H NMR without recourse to chromatography.

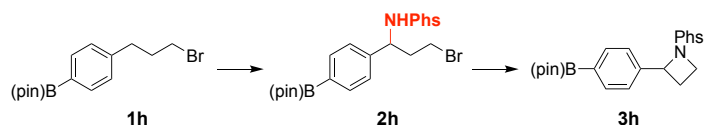
**R<sub>f</sub>:** 0.11 (15% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** δ 7.43–7.28 (m, 8H), 7.24–7.17 (m, 2H), 4.96 (d, *J* = 7.3 Hz, 1H), 4.08 (t, *J* = 7.8 Hz, 1H), 3.89 (t, *J* = 7.7 Hz, 1H), 2.65 (p, *J* = 7.3 Hz, 1H), 1.31 (dd, *J* = 6.9, 0.9 Hz, 3H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** δ 150.3, 140.0, 129.8, 128.8, 128.5, 126.9, 126.4, 121.8, 56.3, 35.1, 29.9, 18.0 ppm

**IR:** ν 2961, 2922, 2850, 1647, 1587, 1487, 1454, 1375, 1197, 1173, 1149, 1127, 1022 cm<sup>-1</sup>

**HRMS (ESI<sup>+</sup>):** calculated for C<sub>16</sub>H<sub>17</sub>NO<sub>3</sub>S[H]<sup>+</sup> 304.1002, found 304.1000



**Phenyl 3-(3-bromo-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)sulfamate (2h):** Prepared according to the general C–H amination procedure using **1h** (98 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (gradient elution: 15%→25% EtOAc in hexanes) afforded **2h** (64 mg, 43%) as an off-white solid along with 37% recovered starting material.

**R<sub>f</sub>:** 0.39 (25% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** δ 7.87–7.79 (m, 2H), 7.35–7.16 (m, 5H), 7.05–6.96 (m, 2H), 5.18 (d, *J* = 7.8 Hz, 1H), 4.80 (q, *J* = 7.5 Hz, 1H), 3.43–3.27 (m, 1H), 3.15 (ddd, *J* = 10.4, 7.9, 6.1 Hz, 1H), 2.51 (dq, *J* = 14.1, 7.0 Hz, 1H), 2.31 (ddt, *J* = 14.0, 12.1, 6.7 Hz, 1H), 1.35 (s, 12H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** δ 150.0, 142.0, 135.8, 135.6, 129.8, 127.0, 126.1, 121.8, 84.2, 58.2, 39.7, 29.9, 25.02, 25.00 ppm

**IR:** ν 3325, 2980, 2925, 2851, 1618, 1520, 1451, 1392, 1365, 1312, 1252, 1215, 1198, 1152, 1085, 970 cm<sup>-1</sup>

**Phenyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)azetidine-1-sulfonate (3h):** Prepared according to the general cyclization procedure using **2h** (46 mg, 0.1 mmol). Purification of this material by chromatography on silica gel (25% EtOAc in hexanes) yielded the azetidine product **3h** (32 mg, 78%) as a light yellow gel.

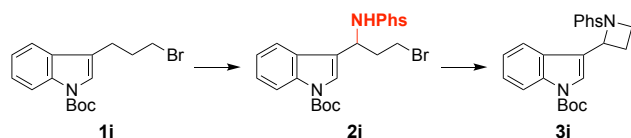
**R<sub>f</sub>:** 0.28 (25% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** δ 7.84–7.76 (m, 2H), 7.45–7.24 (m, 5H), 7.24–7.18 (m, 2H), 5.49 (t, *J* = 8.4 Hz, 1H), 4.31 (q, *J* = 8.6 Hz, 1H), 3.98 (ddd, *J* = 9.0, 7.7, 4.0 Hz, 1H), 2.68 (dtd, *J* = 11.1, 9.0, 4.0 Hz, 1H), 2.35 (dq, *J* = 11.2, 8.6 Hz, 1H), 1.34 (s, 12H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** δ 150.3, 142.9, 135.3, 129.8, 126.9, 125.7, 121.8, 84.0, 67.4, 49.3, 25.6, 25.0 ppm

**IR:** ν 2912, 2849, 1618, 1520, 1489, 1457, 1361, 1260, 1197, 1145, 1090, 1022 cm<sup>-1</sup>

**HRMS (ESI<sup>+</sup>):** calculated for C<sub>21</sub>H<sub>26</sub>BNO<sub>5</sub>S[H]<sup>+</sup> 416.1698, found 416.1696



***tert*-Butyl 3-(3-bromo-1-((phenoxy)sulfonyl)amino)propyl)-1H-indole-1-carboxylate (2i):** Prepared according to the general C–H amination procedure using **1i** (102 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (gradient elution: 10%→15% EtOAc in hexanes) afforded **2i** (108 mg, 71%) as a light brown oil along with 15% recovered starting material.

**R<sub>f</sub>:** 0.22 (10% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** δ 8.17 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.56 (s, 1H), 7.37 (ddt, *J* = 8.4, 7.2, 2.1 Hz, 1H), 7.31–7.14 (m, 4H), 7.10–7.01 (m, 2H), 5.38 (d, *J* = 7.5 Hz, 1H), 5.10 (q, *J* = 7.3 Hz, 1H), 3.47 (dt, *J* = 10.3, 6.2 Hz, 1H), 3.28 (ddd, *J* = 10.4, 7.6, 6.0 Hz, 1H), 2.72–2.41 (m, 2H), 1.69 (s, 9H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** δ 150.0, 129.7, 127.8, 126.9, 125.3, 124.0, 123.2, 122.1, 121.6, 119.3, 118.4, 115.8, 84.5, 51.3, 38.3, 29.2, 28.3 ppm

**IR:** ν 3440, 2921, 1737, 1644, 1454, 1369, 1255, 1152 cm<sup>-1</sup>

**tert-Butyl 3-(1-(phenoxysulfonyl)azetidin-2-yl)-1H-indole-1-carboxylate (3i):** Prepared according to the general cyclization procedure using **2i** (49 mg, 0.1 mmol). Purification of this material by chromatography on silica gel (15% EtOAc in hexanes) yielded the azetidine product **3i** (41 mg, 95%) as a viscous yellow oil.

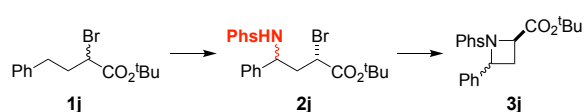
**R<sub>f</sub>:** 0.26 (15% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** δ 8.17 (d, *J* = 8.4 Hz, 1H), 7.66 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.63 (s, 1H), 7.39–7.32 (m, 2H), 7.33–7.11 (m, 6H), 5.70 (t, *J* = 8.4 Hz, 1H), 4.36 (q, *J* = 8.7 Hz, 1H), 4.08 (td, *J* = 8.2, 4.8 Hz, 1H), 2.76–2.57 (m, 2H), 1.67 (s, 9H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** δ 150.2, 129.7, 129.5, 128.1, 126.8, 124.9, 124.3, 122.8, 121.7, 119.51, 119.46, 115.7, 84.1, 61.2, 49.5, 28.3, 24.0 ppm

**IR:** ν 3289, 3070, 2960, 1702, 1589, 1487, 1428, 1380, 1302, 1257, 1199, 1173, 1151, 1119, 1069, 998 cm<sup>-1</sup>

**HRMS (ESI<sup>+</sup>):** calculated for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>S[NH<sub>4</sub>]<sup>+</sup> 446.1744, found 446.1751



**tert-Butyl 2-bromo-4-((phenoxysulfonyl)amino)-4-phenylbutanoate (2j):** Prepared according to the general C–H amination procedure using **1j** (90 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (10% EtOAc in hexanes) afforded **2j** (97 mg, 69%) as a pale yellow oil along with 21% recovered starting material. The product was isolated as a mixture of two diastereomers in approximately 1.1:1 ratio, as estimated by <sup>1</sup>H NMR integration of the C–H signals at 4.22 ppm (integration 1.00) and 3.93 ppm (integration 0.88).

**R<sub>f</sub>:** 0.38 (10% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*, mixture of diastereomers):** δ 7.45–7.25 (m, 6H), 7.24–7.16 (m, 2H), 6.93 (ddd, *J* = 29.5, 8.3, 1.5 Hz, 2H), 5.46 (dd, *J* = 18.6, 8.3 Hz, 1H), 4.83–4.72 (m, 1H), 4.07 (dt, *J* = 116.5, 7.3 Hz, 1H), 2.79–2.26 (m, 2H), 1.48 (dd, *J* = 14.5, 0.8 Hz, 9H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*, mixture of diastereomers):** δ 168.9, 168.3, 150.0, 139.7, 138.9, 129.8, 129.7, 129.4, 129.3, 128.9, 128.8, 127.0, 126.9, 126.8, 126.7, 121.8, 121.7, 83.3, 83.2, 57.9, 57.9, 43.3, 43.3, 42.1, 41.7, 27.8, 27.2 ppm

**IR:** ν 3286, 2979, 2925, 1730, 1487, 1457, 1369, 1294, 1259, 1195, 1067, 1024, 972 cm<sup>-1</sup>

**tert-Butyl 1-(phenoxysulfonyl)-4-phenylazetidine-2-carboxylate (3j):** Prepared according to the general cyclization procedure using **2j** (47 mg, 0.1 mmol, 1.1:1 mixture of diastereomers). The azetidine product **3j** (38 mg, 98%) was obtained following work-up as a viscous yellow gel (inseparable 1.1:1 mixture of diastereomers). This material was determined to be pure by <sup>1</sup>H NMR without recourse to chromatography.

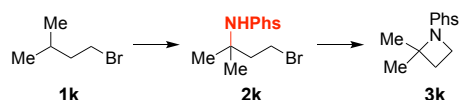
**R<sub>f</sub>:** 0.18 (10% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*, mixture of diastereomers):** δ 7.48–7.27 (m, 12H), 7.26 (s, 1H), 7.25–7.17 (m, 4H), 6.94 (dd, *J* = 7.8, 1.7 Hz, 1H), 5.68 (t, *J* = 8.0 Hz, 1H), 5.31 (t, *J* = 8.2 Hz, 1H), 4.81 (t, *J* = 8.5 Hz, 1H), 4.52 (dd, *J* = 8.9, 3.8 Hz, 1H), 2.92 (dt, *J* = 11.5, 9.1 Hz, 1H), 2.66 (dt, *J* = 11.4, 8.3 Hz, 1H), 2.56 (ddd, *J* = 11.7, 8.5, 3.8 Hz, 1H), 2.41 (dt, *J* = 11.4, 7.8 Hz, 1H), 1.57 (d, *J* = 0.9 Hz, 8H), 1.50 (d, *J* = 0.9 Hz, 9H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*, mixture of diastereomers):** δ 169.7, 168.7, 150.1, 139.2, 138.4, 129.6, 129.6, 129.1, 128.8, 128.7, 128.7, 127.6, 127.1, 126.9, 126.7, 121.9, 121.7, 83.2, 82.8, 77.5, 77.2, 76.8, 67.7, 64.7, 63.7, 59.8, 29.8, 29.7, 29.3, 28.1, 28.0 ppm

**IR:** 3430, 2961, 2910, 2852, 1732, 1644, 1488, 1382, 1256, 1150, 1067, 1022, 970 cm<sup>-1</sup>

**HRMS (ESI<sup>+</sup>):** calculated for C<sub>20</sub>H<sub>23</sub>NO<sub>5</sub>S[Na]<sup>+</sup> 412.1189, found 412.1184



**Phenyl (4-bromo-2-methylbutan-2-yl)sulfamate (2k):** Prepared according to the general C–H amination procedure using **1k** (45 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (15% EtOAc in hexanes) afforded **2k** (59 mg, 61%) as a yellow oil. Recovered starting material was not obtained due to its volatility.

**R<sub>f</sub>:** 0.32 (15% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** δ 7.44–7.37 (m, 2H), 7.33–7.27 (m, 3H), 4.92 (s, 1H), 3.42 (ddd, *J* = 9.5, 7.6, 1.5 Hz, 2H), 2.27 (td, *J* = 8.2, 1.4 Hz, 2H), 1.43 (d, *J* = 1.7 Hz, 6H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** δ 150.4, 129.9, 127.0, 121.7, 58.3, 45.1, 27.6, 27.1 ppm

**IR:** ν 3350, 3010, 2980, 2850, 1413, 1380, 1365, 1320, 1258, 1230, 1165 cm<sup>-1</sup>

**Phenyl 2,2-dimethylazetidine-1-sulfonate (3k):** Prepared according to the cyclization procedure using **2k** (32 mg, 0.1 mmol). The azetidine product **3k** (20 mg, 83%) was obtained following work-up as a viscous yellow oil. This material was determined to be pure by <sup>1</sup>H NMR without recourse to chromatography.

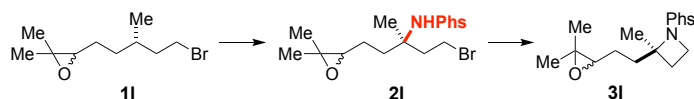
**R<sub>f</sub>:** 0.56 (25% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** δ 7.43–7.36 (m, 2H), 7.34–7.25 (m, 3H), 4.04–3.98 (m, 2H), 2.22–2.08 (m, 2H), 1.55 (s, 6H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** δ 150.5, 129.7, 126.6, 121.9, 72.5, 46.6, 31.3, 27.3 ppm

**IR:** ν 3012, 2981, 2852, 1412, 1380, 1365, 1320, 1258, 1230, 1165, 1021 cm<sup>-1</sup>

**HRMS (ESI<sup>+</sup>):** calculated for C<sub>11</sub>H<sub>15</sub>NO<sub>3</sub>S[H]<sup>+</sup> 242.0845, found 242.0842



**Phenyl ((3*R*)-1-bromo-5-(3,3-dimethyloxiran-2-yl)-3-methylpentan-3-yl)sulfamate (2l):** Prepared according to the general C–H amination procedure using **1l**<sup>12</sup> as a 1:1 mixture of diastereomers (71 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (50% EtOAc in hexanes) afforded **2l** (45 mg, 37%) as a brown oil along with 57% recovered starting material. The product was isolated as a ~1:1 mixture of diastereomers, as estimated by <sup>1</sup>H NMR integration of the N–H signals at 5.37 ppm (integration 0.96) and 5.42 ppm (integration 1.00).

**R<sub>f</sub>:** 0.31 (50% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*, mixture of diastereomers):** δ 7.39 (ddd, *J* = 9.1, 7.1, 2.2 Hz, 2H), 7.30 (ddd, *J* = 8.4, 4.9, 1.9 Hz, 3H), 5.30 (d, *J* = 54.1 Hz, 1H), 3.53–3.33 (m, 2H), 2.72 (td, *J* = 7.4, 4.5 Hz, 1H), 2.45–2.15 (m, 2H), 1.94–1.61 (m, 3H), 1.44 (d, *J* = 9.4 Hz, 3H), 1.31 (d, *J* = 3.1 Hz, 3H), 1.27 (s, 3H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*, mixture of diastereomers):** δ 150.4, 129.8, 126.8, 121.9, 74.7, 64.0, 58.6, 46.8, 37.3, 29.0, 28.2, 25.0, 23.8, 18.8 ppm

**IR:** ν 3305, 2972, 2924, 1487, 1451, 1359, 1180, 1150, 1091 cm<sup>-1</sup>

**Phenyl (2*R*)-2-(2-(3,3-dimethyloxiran-2-yl)ethyl)-2-methylazetidine-1-sulfonate (3l):** Prepared according to the general cyclization procedure using **2l** (41 mg, 0.1 mmol, 1:1 mixture of diastereomers). The azetidine product **3l**

12. Sakauchi, H.; Higashi, E.; Shimizu, Y.; Kojima, M.; Asamitsu, Y.; Kuwahara, S.; Izumi, M.; Kiyota, H. Synthesis of the spiroacetal fragments of spirofungins A and B, antibiotics isolated from *Streptomyces violaceusniger* Tü 4113. *Heterocyclic Comm.* **2015**, *21*, 337–343.

(31 mg, 95%) was obtained following work-up as a viscous yellow gel (inseparable 1:1 mixture of diastereomers). This material was determined to be pure by  $^1\text{H}$  NMR without recourse to chromatography.

**R<sub>f</sub>**: 0.18 (50% EtOAc in hexanes)

**$^1\text{H}$  NMR (400 MHz, Chloroform-*d*, mixture of diastereomers)**:  $\delta$  7.43–7.34 (m, 2H), 7.33–7.25 (m, 3H), 4.08 (dt,  $J$  = 9.4, 7.4 Hz, 1H), 3.90 (dddd,  $J$  = 18.6, 9.2, 7.6, 5.2 Hz, 1H), 2.73–2.63 (m, 1H), 2.33–2.19 (m, 1H), 2.10–1.93 (m, 2H), 1.93–1.80 (m, 1H), 1.59 (d,  $J$  = 8.2 Hz, 4H), 1.56–1.45 (m, 1H), 1.30 (s, 4H), 1.25 (d,  $J$  = 2.5 Hz, 4H) ppm

**$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*, mixture of diastereomers)**:  $\delta$  150.3, 129.7, 126.7, 121.8, 74.6, 63.9, 58.5, 46.7, 37.2, 28.9, 28.1, 24.9, 23.7, 18.7 ppm

**IR**: 2962, 2925, 2854, 1602, 1588, 1488, 1455, 1367, 1260, 1096, 1024, 862, 799  $\text{cm}^{-1}$

**HRMS (ESI<sup>+</sup>)**: calculated for  $\text{C}_{16}\text{H}_{23}\text{BNO}_4\text{S}[\text{H}]^+$  326.1421, found 326.1418



**Benzyl 2-bromo-4-methyl-4-((phenoxysulfonyl)amino)pentanoate (2m)**: Prepared according to the general C–H amination procedure using **1m** (86 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (15% EtOAc in hexanes) afforded **2m** (60 mg, 53%) as a brown oil along with 31% recovered starting material. Further attempts to purify the product resulted in decomposition.

**R<sub>f</sub>**: 0.37 (15% EtOAc in hexanes)

**$^1\text{H}$  NMR (400 MHz, Benzene-*d*<sub>6</sub>)**:  $\delta$  7.38–7.24 (m, 3H), 7.11–6.91 (m, 6H), 6.86 (td,  $J$  = 10.9, 4.6 Hz, 1H), 4.99 (d,  $J$  = 3.5 Hz, 2H), 4.52 (s, 1H), 4.34 (dd,  $J$  = 9.4, 3.9 Hz, 1H), 2.66 (dd,  $J$  = 15.0, 9.4 Hz, 1H), 2.04 (dd,  $J$  = 15.0, 4.0 Hz, 1H), 0.98 (s, 3H), 0.93 (s, 3H) ppm

**$^{13}\text{C}$  NMR (101 MHz, Benzene-*d*<sub>6</sub>)**:  $\delta$  185.3, 135.4, 129.9, 128.8, 128.8, 128.7, 126.7, 122.2, 122.1, 68.1, 57.4, 46.8, 40.4, 27.5, 26.7 ppm

**IR**:  $\nu$  3286, 2980, 2920, 2847, 1644, 1742, 1451, 1262, 1199, 1095, 1072, 1023, 980  $\text{cm}^{-1}$

**Benzyl 4,4-dimethyl-1-(phenoxysulfonyl)azetidine-2-carboxylate (3m)**: Prepared according to the general cyclization procedure using **2m** (46 mg, 0.1 mmol). The azetidine product **3m** (20 mg, 93%) was obtained following work-up as a tan oily solid. This material was determined to be pure by  $^1\text{H}$  NMR without recourse to chromatography. Further attempts to purify the product resulted in decomposition.

**R<sub>f</sub>**: 0.51 (25% EtOAc in hexanes)

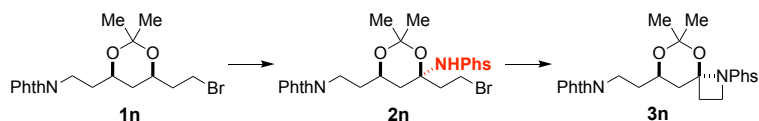
**$^1\text{H}$  NMR (400 MHz, Benzene-*d*<sub>6</sub>)**:  $\delta$  7.46 (d,  $J$  = 8.0 Hz, 2H), 7.11–6.93 (m, 6H), 6.85 (t,  $J$  = 7.4 Hz, 2H), 5.08–4.90 (m, 2H), 4.69 (dd,  $J$  = 9.2, 7.3 Hz, 1H), 1.82 (dd,  $J$  = 10.8, 7.3 Hz, 1H), 1.50 (dd,  $J$  = 10.8, 9.2 Hz, 1H), 1.28 (s, 3H), 1.13 (s, 3H) ppm

**$^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)**:  $\delta$  169.8, 169.5, 135.8, 128.7, 128.6, 128.57, 128.52, 124.0, 122.9, 72.5, 67.4, 67.1, 39.7, 26.4 ppm

**IR**:  $\nu$  3022, 2990, 1744, 1643, 1410, 1260, 1096, 1022, 985  $\text{cm}^{-1}$

**HRMS (ESI<sup>+</sup>)**: calculated for  $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{S}[\text{H}]^+$  376.1213, found 376.1215





**Phenyl ((4R,6S)-4-(2-bromoethyl)-6-(2-(1,3-dioxoisindolin-2-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)sulfamate (2n):** Prepared according to the general C–H amination procedure using **1n** (119 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (30% EtOAc in hexanes) afforded **2n** (86 mg, 42%) as a clear gel-like solid along with 38% recovered starting material. Further attempts to purify the product resulted in decomposition.

**R<sub>f</sub>:** 0.17 (15% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):**  $\delta$  7.79 (dd,  $J$  = 5.5, 3.1 Hz, 2H), 7.69 (dd,  $J$  = 5.5, 3.1 Hz, 2H), 7.40–7.25 (m, 3H), 7.18–7.10 (m, 2H), 5.15 (s, 1H), 3.98 (t,  $J$  = 8.5 Hz, 1H), 3.88 (dd,  $J$  = 8.0, 4.5 Hz, 2H), 3.16 (s, 1H), 2.85 (dd,  $J$  = 14.6, 3.2 Hz, 1H), 2.52 (dd,  $J$  = 14.6, 8.8 Hz, 1H), 1.92 (dtt,  $J$  = 17.8, 9.6, 4.7 Hz, 1H), 1.83–1.61 (m, 3H), 1.44 (d,  $J$  = 2.5 Hz, 3H), 1.36–1.29 (m, 1H), 1.25 (d,  $J$  = 1.5 Hz, 3H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):**  $\delta$  169.1, 151.5, 134.2, 132.0, 130.0, 127.6, 123.6, 122.0, 101.7, 81.8, 66.3, 49.4, 40.3, 36.4, 35.4, 34.5, 28.2, 28.1 ppm

**IR:**  $\nu$  3269, 3086, 2979, 2926, 2850, 1770, 1708, 1661, 1631, 1488, 1467, 1483, 1396, 1370, 1256, 1172, 1149, 1088, 1071, 1024, 1007, 959 cm<sup>-1</sup>

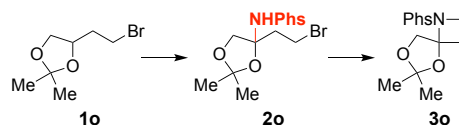
**Phenyl (4S,8S)-8-(2-(1,3-dioxoisindolin-2-yl)ethyl)-6,6-dimethyl-5,7-dioxa-1-azaspiro[3.5]nonane-1-sulfonate (3n):** Prepared according to the general cyclization procedure using **2n** (57 mg, 0.1 mmol). The azetidine product **3n** (44 mg, 91%) was obtained following work-up as a clear off-white solid. This material was determined to be pure by <sup>1</sup>H NMR without recourse to chromatography. Further attempts to purify the product resulted in decomposition.

**R<sub>f</sub>:** 0.28 (50% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Benzene-*d*<sub>6</sub>):**  $\delta$  7.74 (dd,  $J$  = 5.4, 3.1 Hz, 2H), 7.64 (dd,  $J$  = 5.4, 3.0 Hz, 2H), 7.51–7.30 (m, 2H), 7.03–6.84 (m, 3H), 3.98–3.92 (m, 1H), 3.72–3.60 (m, 3H), 3.34 (d,  $J$  = 4.2 Hz, 1H), 2.92–2.82 (m, 1H), 2.33 (dd,  $J$  = 16.9, 9.0 Hz, 1H), 2.16–2.02 (m, 1H), 1.67–1.50 (m, 2H), 1.29–1.17 (m, 7H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):**  $\delta$  169.1, 151.5, 134.2, 132.0, 130.0, 127.6, 123.6, 122.0, 101.7, 81.8, 66.3, 49.4, 40.3, 36.4, 35.4, 34.5, 28.2, 28.1 ppm

**IR:**  $\nu$  2962, 2925, 2854, 1712, 1701, 1551, 1446, 1411, 1260, 1094, 1028 cm<sup>-1</sup>



**Phenyl (4-(2-bromoethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)sulfamate (2o):** Prepared according to the general C–H amination procedure using **1o**<sup>13</sup> (63 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (15% EtOAc in hexanes) afforded **2o** (54 mg, 47%) as a brown oil along with 10% recovered starting material (note: the product slowly decomposes on silica gel). This product was isolated as a 2:1 mixture with what is presumably an elimination product; the latter was not identified due to the instability of this material on silica gel.

**R<sub>f</sub>:** 0.22 (15% EtOAc in hexanes)

13. Garvey, D.; Letts, L.; Earl, R.; Ezawa, M.; Fang, X.; Gaston, R.; Khanapure, S.; Lin, C.-E.; Ranatunge, R.; Stevenson, C.; Wey, S.-J. Nitric oxide enhancing diuretic compounds, compositions and methods of use. US20060189603 A1, February 24, 2006.

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):**  $\delta$  7.44–7.27 (m, 5H), 5.66 (s, 1H), 4.39 (d,  $J$  = 9.9 Hz, 1H), 3.96 (d,  $J$  = 10.0 Hz, 1H), 3.54–3.36 (m, 2H), 2.81–2.66 (m, 1H), 2.54 (ddd,  $J$  = 14.7, 8.6, 7.4 Hz, 1H), 1.52 (s, 3H), 1.39 (s, 3H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):**  $\delta$  150.1, 129.9, 127.3, 122.1, 112.1, 93.4, 78.3, 40.3, 26.8, 25.9 ppm

**IR:**  $\nu$  3283, 2918, 1586, 1371, 1194, 1171, 1149, 1070, 1022, 917  $\text{cm}^{-1}$

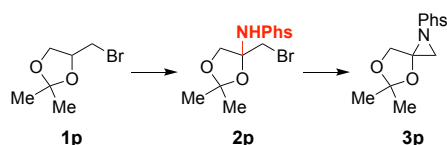
**Phenyl 6,6-dimethyl-5,7-dioxa-1-azaspiro[3.4]octane-1-sulfonate (3o):** Prepared according to the general cyclization procedure using **2o** (19 mg, 0.05 mmol). Purification of this material on preparative TLC (16 cm x 11 cm, 5% EtOAc in hexanes) afforded **3o** (12 mg, 75%) as a viscous colorless oil.

**R<sub>f</sub>:** 0.13 (5% EtOAc in hexanes)

**<sup>1</sup>H NMR (500 MHz, Chloroform-*d*):**  $\delta$  7.46 – 7.30 (m, 5H), 7.29 (s, 1H), 5.85 (d,  $J$  = 4.5 Hz, 1H), 4.82 (t,  $J$  = 4.4 Hz, 1H), 3.71 (dd,  $J$  = 9.9, 7.9 Hz, 1H), 3.54 (ddd,  $J$  = 11.5, 9.9, 5.2 Hz, 1H), 2.17–2.05 (m, 1H), 1.97 (dddd,  $J$  = 13.3, 12.0, 7.9, 4.4 Hz, 1H), 1.50 (s, 3H), 1.36 (s, 3H) ppm

**<sup>13</sup>C NMR (126 MHz, Chloroform-*d*):**  $\delta$  150.14, 129.66, 126.86, 121.99, 112.41, 92.15, 80.19, 77.27, 77.01, 76.76, 46.83, 31.23, 26.59, 25.67 ppm

**IR:**  $\nu$  2952, 2921, 2861, 1462, 1410, 1372, 1265, 1104, 1099, 1032, 985  $\text{cm}^{-1}$



**Phenyl (4-(bromomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)sulfamate (2p):** Prepared according to the general C–H amination procedure using **1p** (59 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (17% Et<sub>2</sub>O in pentane) afforded **2p** (69 mg, 46%) as a clear gel-like solid (note: the product slowly decomposes on silica gel). Recovered starting material was not obtained due to its volatility.

**R<sub>f</sub>:** 0.32 (17% Et<sub>2</sub>O in pentane)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):**  $\delta$  7.43–7.37 (m, 4H), 7.35–7.28 (m, 1H), 5.46 (s, 1H), 4.50 (d,  $J$  = 10.0 Hz, 1H), 4.15 (d,  $J$  = 10.0 Hz, 1H), 3.84 (d,  $J$  = 11.1 Hz, 1H), 3.70 (d,  $J$  = 11.1 Hz, 1H), 1.54 (s, 4H), 1.46 (s, 4H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):**  $\delta$  150.1, 129.9, 127.4, 122.3, 113.4, 91.7, 71.4, 35.6, 26.6, 26.3 ppm

**IR:**  $\nu$  3282, 2975, 2919, 1587, 1488, 1374, 1171, 1148, 1071, 965  $\text{cm}^{-1}$

**Phenyl 5,5-dimethyl-4,6-dioxa-1-azaspiro[2.4]heptane-1-sulfonate (3p):** Prepared according to the general cyclization procedure using **2p** (37 mg, 0.1 mmol). The aziridine product **3p** (27 mg, 78%) was obtained following work as a colorless oil. This material was determined to be pure by <sup>1</sup>H NMR without recourse to chromatography. Further attempts to purify the product resulted in decomposition.

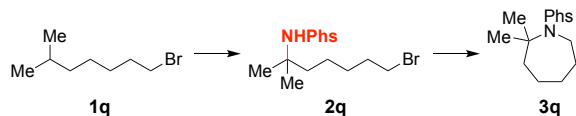
**R<sub>f</sub>:** 0.29 (50% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Benzene-*d*<sub>6</sub>):**  $\delta$  7.01–6.74 (m, 4H), 4.22 (d,  $J$  = 10.3 Hz, 1H), 4.06 (d,  $J$  = 10.4 Hz, 1H), 3.82 (dd,  $J$  = 13.7, 6.7 Hz, 1H), 3.64 (dd,  $J$  = 13.7, 6.5 Hz, 1H), 1.32 (s, 3H), 1.16 (s, 3H) ppm

**<sup>13</sup>C NMR (101 MHz, Benzene-*d*<sub>6</sub>):**  $\delta$  150.7, 130.0, 127.0, 122.4, 112.4, 107.1, 72.1, 47.2, 30.2, 26.9 ppm

**IR:**  $\nu$  2962, 2925, 2854, 1457, 1411, 1376, 1260, 1094, 1026  $\text{cm}^{-1}$

**HRMS (ESI<sup>+</sup>):** calculated for C<sub>12</sub>H<sub>15</sub>NO<sub>5</sub>S[H]<sup>+</sup> 286.0744, found 286.0741



**Phenyl (7-bromo-2-methylheptan-2-yl)sulfamate (2q):** Prepared according to the general cyclization procedure using **1q** (58 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (15% EtOAc in hexanes) afforded **2q** (70 mg, 64%) as a colorless oil along with 22% recovered starting material.

**R<sub>f</sub>:** 0.39 (15% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):**  $\delta$  7.43–7.35 (m, 2H), 7.34–7.27 (m, 3H), 4.66 (s, 1H), 3.39 (t,  $J$  = 6.7 Hz, 2H), 1.85 (p,  $J$  = 6.9 Hz, 2H), 1.68–1.59 (m, 2H), 1.49–1.22 (m, 10H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):**  $\delta$  150.5, 129.9, 129.9, 129.8, 126.9, 126.8, 121.8, 121.6, 121.6, 58.2, 42.3, 33.9, 32.7, 28.4, 27.4, 23.2 ppm

**IR:**  $\nu$  3298, 2925, 2866, 1580, 1487, 1456, 1427, 1388, 1357, 1260, 1243, 1195, 1171, 1149, 1070, 1016, 910 cm<sup>-1</sup>

**Phenyl 2,2-dimethylazepane-1-sulfonate (3q):** Prepared according to the general cyclization procedure using **2q** (36 mg, 0.1 mmol) **2i**. Purification of this material by chromatography on silica gel (15% EtOAc in hexanes) yielded the azepane product **3q** (24 mg, 86%) as a colorless gel.

**R<sub>f</sub>:** 0.55 (15% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):**  $\delta$  7.41–7.34 (m, 2H), 7.34–7.18 (m, 3H), 3.62–3.49 (m, 2H), 1.82–1.63 (m, 6H), 1.54 (s, 6H), 1.47–1.33 (m, 2H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):**  $\delta$  150.6, 129.8, 129.7, 126.4, 122.0, 121.9, 121.9, 62.3, 47.2, 45.1, 30.0, 28.7, 27.8, 23.1 ppm

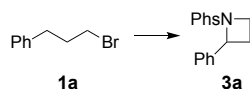
**IR:**  $\nu$  2951, 2922, 2850, 1558, 1456, 1394, 1386, 1373, 1274, 1260, 1192, 1170, 1149, 1091, 1025, 948 cm<sup>-1</sup>

**HRMS (ESI<sup>+</sup>):** calculated for C<sub>14</sub>H<sub>21</sub>NO<sub>3</sub>S[H]<sup>+</sup> 284.1315, found 284.1311

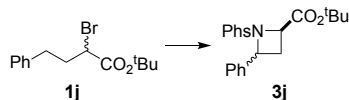
### Telescoped (Single-flask) Procedures

#### General Protocol: Single-flask Amination & Cyclization

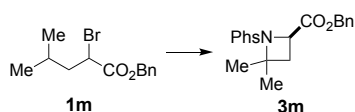
The C–H amination reaction was performed as described in the general procedure (pg S6). Following the 6 h reaction time, the reaction mixture was diluted with DMF to a substrate concentration of 0.1 M. Solid K<sub>2</sub>CO<sub>3</sub> (5 equiv) was added and the mixture was stirred for 2 h. The reaction work-up is as follows: the solution was transferred to a separatory funnel with 10 mL of EtOAc and washed with 10 mL of H<sub>2</sub>O then 3 x 10 mL of saturated aqueous NaCl. The organic layer was collected, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The isolated material was redissolved in 3 mL of CH<sub>2</sub>Cl<sub>2</sub> and to this solution was added Celite (200–400 mg Celite/mmol starting material). The slurry was evaporated under reduced pressure to a powder, which was loaded onto a chromatography column pre-packed with silica gel and solvent (conditions given below). Purification was performed by chromatography on silica gel.



**Phenyl 2-phenylazetidine-1-sulfonate (3a):** Prepared according to the above protocol using **1a** (60 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (25% EtOAc in hexanes) yielded the azetidine product **3a** (42 mg, 49%) as a viscous brown oil along with 11% of the C–H amination product **2a** and 24% recovered starting material.

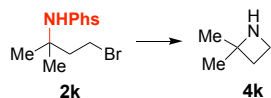


**tert-Butyl 1-(phenoxysulfonyl)-4-phenylazetidine-2-carboxylate (3j):** Prepared according to the above protocol using **1j** (90 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (gradient elution: 10%→20% EtOAc in hexanes) yielded a mixture of the two isomers **3j-trans** and **3j-cis** (61 mg, 52%, 1.1:1 mixture of diastereomers) along with 5% of the C–H amination product **2j** and 18% recovered starting material.



**Benzyl 4,4-dimethyl-1-(phenoxysulfonyl)azetidine-2-carboxylate (3m):** Prepared according to the above protocol using **1m** (86 mg, 0.3 mmol). Purification of this material by chromatography on silica gel (25% EtOAc in hexanes) yielded the azetidine product **3m** (35 mg, 31%) as a light brown oily solid along with 9% of the C–H amination product **2m** and 20% recovered starting material.

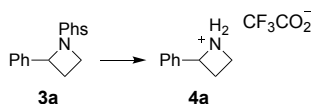
#### Single-Flask Cyclization & Deprotection



**2,2-Dimethylazetidine (4k):** Phenyl (4-bromo-2-methylbutan-2-yl)sulfamate **2k** (64 mg, 0.2 mmol) was dissolved in 1.0 mL DMF. Solid  $K_2CO_3$  (42 mg, 0.3 mmol, 1.5 equiv) was added and the contents were stirred for 2 h. Following this time, 0.8 mL of  $H_2O$  was added to the reaction mixture. The flask was sealed and placed in an oil bath at 90 °C. The solution was stirred at this temperature for 48 h. The reaction mixture was cooled to room temperature, diluted with 3 mL of acetone, and concentrated under reduced pressure to a yellow gel. This material was dissolved in 15 mL of MeOH and to this solution was added oxalic acid (18 mg, 0.2 mmol). The mixture was stirred for 10 min then concentrated under reduced pressure to a yellow solid. This material was triturated with  $Et_2O$  (10–25 mL) to furnish the product **4k** (21 mg, 61%) as the oxalate salt as a pale off-white solid. Prior to spectroscopic analysis, the oxalate salt was dissolved in 2 mL of MeOH to which  $K_2CO_3$  (42 mg, 0.3 mmol, 1.5 equiv) was added. The solution was evaporated under reduced pressure to obtain **4k** as the free base.

#### General procedures and characterization for deprotection of phenylsulfonate azetidines

**Method A:** Azetidine (0.1 mmol) was dissolved in 0.5 mL of MeCN and 0.4 mL of  $H_2O$ . The flask was sealed and placed in an oil bath at 90 °C. The mixture was stirred for for 48 h, following which time the solution was cooled to room temperature, diluted with ~3 mL of acetone, and concentrated under reduced pressure to an oily residue. Isolation of the pure azetidinium trifluoroacetate salt was accomplished using reversed-phase HPLC (conditions given below).

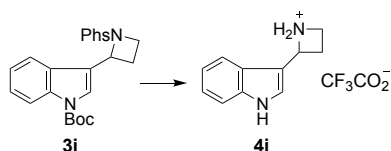


**2-Phenylazetidine (4a):** Prepared following Method A. Purified by reverse phase HPLC (Shimadzu C18, 10  $\mu m$ , 21.2 x 250 nm column, eluting with a gradient flow over 60 min of 15%→100% MeCN in 0.1% aqueous  $CF_3CO_2H$ , 254 nm UV detection). At a flow rate of 12 mL/min, the desired compound had a retention time of 21.37 min and was isolated following concentration under reduced pressure as a pale off-white solid (19 mg, 79%).

**<sup>1</sup>H NMR (400 MHz, Benzene-*d*<sub>6</sub>, CF<sub>3</sub>CO<sub>2</sub>H salt):** δ 8.38 (s, 2H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.12 (t, *J* = 7.5 Hz, 2H), 7.03 (t, *J* = 7.4 Hz, 1H), 4.23–4.13 (m, 1H), 4.00 (dt, *J* = 10.8, 5.3 Hz, 1H), 3.70 (dt, *J* = 12.2, 6.3 Hz, 1H), 2.43–2.28 (m, 1H), 2.08–1.92 (m, 1H) ppm

**<sup>13</sup>C NMR (101 MHz, Benzene-*d*<sub>6</sub>, CF<sub>3</sub>CO<sub>2</sub>H salt):** δ 133.8, 132.3, 131.9, 126.0, 59.4, 39.7, 31.8 ppm

**IR:** ν 3390, 3058, 2963, 1642, 1589, 1482, 1370, 1321, 1258, 1195, 1164, 1148, 1047, 998 cm<sup>-1</sup>



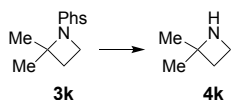
**3-(Azetidin-2-yl)-1H-indole (4i):** Prepared following Method A. Purified by reversed-phase HPLC (Shimadzu C18, 10 μm, 21.2 x 250 nm column, eluting with a gradient flow over 60 min of 15%→100% MeCN in 0.1% aqueous CF<sub>3</sub>CO<sub>2</sub>H, 254 nm UV detection). At a flow rate of 12 mL/min, the desired compound had a retention time of 32.65 min and was isolated following concentration under reduced pressure as pale white crystals (20 mg, 74%).

**<sup>1</sup>H NMR (400 MHz, Benzene-*d*<sub>6</sub>, CF<sub>3</sub>CO<sub>2</sub>H salt):** δ 9.30 (s, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 1.5 Hz, 1H), 6.98–6.82 (m, 1H), 6.82–6.66 (m, 1H), 6.66–6.50 (m, 1H), 5.76 (d, *J* = 7.8 Hz, 1H), 2.90 (t, *J* = 6.3 Hz, 2H), 2.03–1.63 (m, 2H) ppm

**<sup>13</sup>C NMR (101 MHz, Benzene-*d*<sub>6</sub>, CF<sub>3</sub>CO<sub>2</sub>H salt):** δ 134.8, 131.8, 131.2, 129.7, 127.3, 124.1, 121.1, 113.6, 57.1, 47.3, 31.7 ppm

**IR:** ν 3389, 3062, 2961, 1708, 1590, 1485, 1450, 1381, 1322, 1260, 1228, 1190, 1182, 1154, 1072, 1048, 990 cm<sup>-1</sup>

*Method B:* A 0.15 M solution of azetidine in a 10:1 pyridine/H<sub>2</sub>O mixture was stirred for 24 h. Following this time, all volatiles were removed under reduced pressure in a ~40 °C water bath to give a viscous oil. This material was re-dissolved in 15 mL of MeOH and oxalic acid (0.5 equiv) was added. The mixture was stirred for 10 min then concentrated under reduced pressure to a yellow solid. This material was triturated with 3 x 3 mL of Et<sub>2</sub>O to furnish the desired product as the oxalate salt.

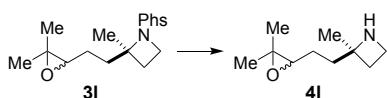


**2,2-Dimethylazetidine (4k):** Prepared following Method B. Reaction performed using 374 mg of azetidine **3k** (1.55 mmol). Product obtained as the oxalate salt as an off-white solid (198 mg, 73%). Prior to spectroscopic analysis, the oxalate salt was dissolved in 5 mL of MeOH to which K<sub>2</sub>CO<sub>3</sub> (321 mg, 2.32 mmol, 1.5 equiv) was added. The solution was evaporated under reduced pressure to obtain **4k** as the free base.

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** δ 4.21 (t, *J* = 6.4 Hz, 2H), 3.31 (s, 1H), 1.99 (t, *J* = 6.5 Hz, 2H), 1.39 (s, 6H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** 59.9, 42.3, 36.3, 29.9 ppm

**IR:** ν 3402, 3051, 2962, 2958, 1252, 1157, 1043, 1012, 994 cm<sup>-1</sup>



**(2R)-2-(2-(3,3-Dimethyloxiran-2-yl)ethyl)-2-methylazetidine (4l):** Prepared following Method B. Reaction performed using 33 mg of azetidine **3l** (0.1 mmol). Product obtained as the oxalate salt as an off-white solid (21

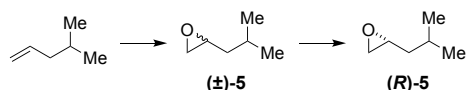
mg, 63%). Prior to spectroscopic analysis, the oxalate salt was dissolved in 1 mL of MeOH to which K<sub>2</sub>CO<sub>3</sub> (21 mg, 0.15 mmol, 1.5 equiv) was added. The solution was evaporated under reduced pressure to obtain **4l** as the free base.

**<sup>1</sup>H NMR (400 MHz, Benzene-*d*<sub>6</sub>):** δ 3.63–3.53 (m, 1H), 3.42–3.29 (m, 1H), 2.35–2.24 (m, 1H), 1.83–1.33 (m, 4H), 1.25 (d, *J* = 2.9 Hz, 3H), 1.18–1.06 (m, 1H), 1.02 (d, *J* = 6.6 Hz, 6H), 0.86 (s, 1H), 0.83–0.70 (m, 1H) ppm

**<sup>13</sup>C NMR (101 MHz, Benzene-*d*<sub>6</sub>):** δ 71.3, 65.2, 63.4, 43.2, 39.3, 33.2, 31.7, 25.5, 21.5 ppm

**IR:** ν 3391, 2960, 2922, 2850, 1369, 1255, 1098, 1025 cm<sup>-1</sup>

#### Procedures and characterization of intermediates in the total synthesis of penaresidin B (Scheme 4)



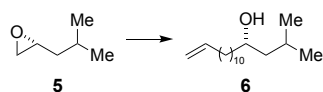
**(*R*)-2-Isobutyloxirane (5):** *meta*-Chloroperbenzoic acid (27.4 g, 158.8 mmol, 1.3 equiv) was dissolved in 300 mL of CH<sub>2</sub>Cl<sub>2</sub> and the solution was cooled to 0 °C. Neat 4-methyl-1-pentene (15.0 mL, 118.8 mmol) was added dropwise via syringe, the reaction mixture was warmed to room temperature and stirred for 10 h. Following this time, the mixture was filtered through a pad of Celite, and the flask and filter cake were rinsed with ~25 mL of CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrates were transferred to a separatory funnel and washed with 2 x 50 mL of 10% aqueous NaOH and 2 x 30 mL of saturated aqueous NaCl. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure (note: given the volatility of the product, the bath temperature of the rotovap was kept at ~4 °C) (*±*)-2-Isobutyloxirane (**(±)-5**) was obtained as a clear oil contaminated with ~5% CH<sub>2</sub>Cl<sub>2</sub>. This material was determined to be sufficiently pure by <sup>1</sup>H NMR for use in the subsequent reaction.

Pure (*R*)-2-isobutyloxirane was obtained following the method of Schaus, et al.<sup>14</sup> A 50 mL round-bottom flask was charged with (*R,R*)-*N,N'*-bis(3,5-*di-tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (359 mg, 0.59 mmol, 0.5 mol %) and 2-isobutyloxirane (**(±)-5**) (11.9 g, 118.8 mmol) to which glacial acetic acid (140 μL, 2.38 mmol, 2 mol %) and 1.2 mL of THF were then added. The dark red mixture was cooled to 0 °C and 1.2 mL of H<sub>2</sub>O was added (65.3 mmol, 0.55 equiv). The reaction flask was removed from the ice bath and the solution was stirred for 16 h. The flask was then fitted with a short-path distillation head and epoxide **5** was isolated as a colorless liquid (4.76 g, 80%) by distillation at 0.25 Torr into a receiving flask cooled to –78 °C. The %ee of this material was determined to be >99% by chiral GC using pre-established literature conditions:<sup>15</sup> CSP-GC on a 25 m β-cyclodex colum I.D. 0.25 mm, film 0.25 μm, T<sub>inj</sub>=250 °C T<sub>det</sub>=300 °C, carrier He 1 mL/min, 45 °C x 30 min then 5 °C/min up to 200 °C; t<sub>s</sub> 18.1 min, t<sub>R</sub> 19.3 min. The optical rotation of the neat epoxide was measured to be [α]<sub>D</sub><sup>20</sup> = +19.68, indicative of the (*R*) enantiomer based on comparison to literature values ([α]<sub>D</sub><sup>20</sup> = +20.47, neat).<sup>16</sup>

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** δ 2.92 (dddd, *J* = 6.6, 5.3, 4.0, 2.8 Hz, 1H), 2.75 (ddd, *J* = 5.1, 4.0, 0.6 Hz, 1H), 2.43 (dd, *J* = 5.1, 2.7 Hz, 1H), 1.82 (ddq, *J* = 13.2, 7.5, 6.6 Hz, 1H), 1.49–1.30 (m, 2H), 0.97 (dd, *J* = 6.7, 3.4 Hz, 6H) ppm

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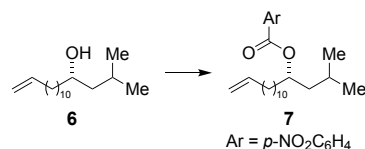
**(S)-2-Methylhexadec-15-en-4-ol (6):** To an oven-dried flask charged with  $\text{CuCl}_2$  (270 mg, 2.0 mmol, 0.1 equiv) and  $\text{LiCl}$  (170 mg, 4.0 mmol, 0.2 equiv) were added successively 20 mL of THF and (*R*)-2-isobutyloxirane **5** (2.0 g, 20 mmol). In a separate oven-dried flask, the Grignard reagent was prepared as follows: Mg turnings (583 mg, 24.0 mmol, 1.2 equiv) were suspended in 2.0 mL of  $\text{Et}_2\text{O}$  and the mixture was cooled to 0 °C. A single drop of 1,2-dibromoethane was then added and gas evolution ensued. A solution of 11-bromo-1-undecene (5.3 mL, 24.0 mmol, 1.2 equiv) in 20 mL of  $\text{Et}_2\text{O}$  was added dropwise via syringe. The flask was removed from the ice bath and the mixture was stirred for 1 h. Following this time, the solution of Grignard reagent was added dropwise via syringe to the mixture of epoxide and  $\text{Li}_2\text{CuCl}_4$ . The reaction was stirred for 16 h, then cooled to 0 °C and quenched by the addition of 30 mL of saturated aqueous  $\text{NH}_4\text{Cl}$ . The mixture was transferred to a separatory funnel and the organic fraction was collected. The aqueous layer was extracted with 3 x 25 mL of  $\text{Et}_2\text{O}$ . The combined organic extracts were washed with 1 x 30 mL of saturated aqueous  $\text{NaCl}$ , dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (15%  $\text{EtOAc}$  in hexanes) furnished the desired product **6** as a light yellow oil (3.66 g, 72%).

**R<sub>f</sub>:** 0.37 (15%  $\text{EtOAc}$  in hexanes)

**$^1\text{H}$  NMR (400 MHz,  $\text{CHloroform-d}$ ):**  $\delta$  5.81 (ddt,  $J$  = 17.0, 10.2, 6.7 Hz, 1H), 5.08–4.85 (m, 2H), 3.66 (tt,  $J$  = 8.5, 4.0 Hz, 1H), 2.12–1.94 (m, 2H), 1.87–1.69 (m, 1H), 1.47–1.16 (m, 20H), 0.91 (dd,  $J$  = 6.6, 5.1 Hz, 6H) ppm

**$^{13}\text{C}$  NMR (101 MHz,  $\text{CHloroform-d}$ ):**  $\delta$  139.4, 114.2, 70.1, 47.0, 38.2, 34.0, 29.9, 29.8, 29.7, 29.6, 29.3, 29.1, 25.8, 24.8, 23.7, 22.2 ppm

**IR:**  $\nu$  3347, 3077, 2925, 2854, 1641, 1466, 1383, 1366, 1141, 1064, 992  $\text{cm}^{-1}$



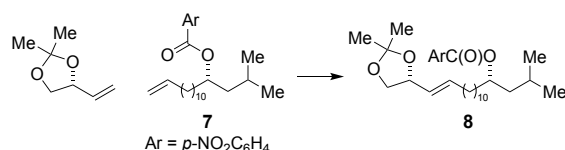
**(S)-2-Methylhexadec-15-en-4-yl 4-nitrobenzoate (7):** Alkene **6** (763 mg, 3.0 mmol) was dissolved in 25 mL of  $\text{CH}_2\text{Cl}_2$  and *p*-nitrobenzoic acid (752 mg, 4.5 mmol, 1.5 equiv) was added. The solution was cooled to 0 °C prior to the sequential addition of  $\text{EDC} \cdot \text{HCl}$  (863 mg, 4.5 mmol, 1.5 equiv) and DMAP (550 mg, 4.5 mmol, 1.5 equiv). The reaction mixture was warmed to ambient temperature and stirred for 16 h. Following this time, the reaction was quenched by the addition of 5 mL of saturated aqueous  $\text{NaCl}$ . The solution was transferred to a separatory funnel with ~10 mL of  $\text{H}_2\text{O}$  and extracted with 3 x 20 mL of  $\text{CH}_2\text{Cl}_2$ . The organic fractions were combined and washed with 1 x 10 mL of saturated aqueous  $\text{NaHCO}_3$  and 1 x 10 mL of saturated aqueous  $\text{NaCl}$ , dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (gradient elution 5%  $\rightarrow$  10%  $\text{EtOAc}$  in hexanes) furnished the desired product **7** as a light yellow oil (1.16 g, 96%).

**R<sub>f</sub>:** 0.50 (10%  $\text{EtOAc}$  in hexanes)

**$^1\text{H}$  NMR (400 MHz,  $\text{CHloroform-d}$ ):**  $\delta$  8.32–8.26 (m, 2H), 8.23–8.17 (m, 2H), 5.80 (ddt,  $J$  = 16.9, 10.2, 6.7 Hz, 1H), 5.29–5.20 (m, 1H), 4.98 (dq,  $J$  = 17.1, 1.7 Hz, 1H), 4.92 (ddt,  $J$  = 10.2, 2.3, 1.3 Hz, 1H), 2.07–1.97 (m, 2H), 1.74–1.60 (m, 4H), 1.50–1.18 (m, 17H), 0.94 (d,  $J$  = 6.4 Hz, 6H) ppm

**$^{13}\text{C}$  NMR (101 MHz,  $\text{CHloroform-d}$ ):**  $\delta$  164.6, 150.5, 139.4, 136.3, 130.8, 123.6, 114.2, 75.1, 43.5, 34.9, 33.9, 29.7, 29.7, 29.6, 29.6, 29.3, 29.1, 25.4, 24.9, 23.3, 22.4 ppm

**IR:**  $\nu$  3082, 2922, 2857, 1714, 1644, 1582, 1470, 1410, 1381, 1372, 1241, 1217, 1141, 1064, 1042, 980  $\text{cm}^{-1}$



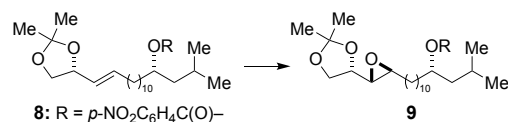
**(*S,E*)-16-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-methylhexadec-15-en-4-yl 4-nitrobenzoate (**8**):** To an oven-dried flask containing alkene **7** (404 mg, 1.0 mmol) and (*R*)-2,2-dimethyl-4-vinyl-1,3-dioxolane (769 mg, 6.0 mmol, 6.0 equiv obtained following the procedure of Howes, et al.<sup>17</sup>) was added 100 mL of CH<sub>2</sub>Cl<sub>2</sub> followed by Grubbs 2<sup>nd</sup> generation catalyst (42 mg, 0.05 mmol, 5 mol %). The mixture was stirred at 40 °C for 8 h, following which time the solution was concentrated under reduced pressure to a brown-red oil. Purification of this material by chromatography on silica gel (gradient elution: 5%→10% EtOAc in hexanes) furnished the desired product **8** as a light yellow oil (385 mg, 69%).

**R<sub>f</sub>:** 0.54 (10% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Chloroform-*d*):** δ 8.31–8.25 (m, 2H), 8.24–8.16 (m, 2H), 5.77 (dt, *J* = 15.3, 6.7 Hz, 1H), 5.41 (ddt, *J* = 15.3, 8.0, 1.5 Hz, 1H), 5.25 (tt, *J* = 6.5, 4.7 Hz, 1H), 4.45 (td, *J* = 7.9, 6.0 Hz, 1H), 4.05 (dd, *J* = 8.1, 6.1 Hz, 1H), 3.63–3.40 (m, 2H), 2.10–1.93 (m, 2H), 1.78–1.56 (m, 4H), 1.51–1.13 (m, 23H), 0.93 (d, *J* = 6.4 Hz, 6H) ppm

**<sup>13</sup>C NMR (101 MHz, Chloroform-*d*):** δ 164.5, 150.5, 136.3, 130.8, 127.2, 123.6, 109.1, 77.6, 75.0, 69.6, 43.4, 34.9, 32.4, 29.7, 29.64, 29.62, 29.56, 29.3, 29.0, 26.9, 26.1, 25.4, 24.9, 23.3, 22.4 ppm

**IR:** ν 3078, 2925, 2852, 1715, 1650, 1578, 1465, 1385, 1242, 1212, 1145, 1064, 1041, 998, 984 cm<sup>-1</sup>



**(4*S*,15*S*,16*R*)-16-(2,2-Dimethyl-1,3-dioxolan-4-yl)-15,16-dihydroxy-2-methylhexadecan-4-yl 4-nitrobenzoate (**9**):** Alkene **8** (321 mg, 0.58 mmol) was dissolved in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> and the solution was cooled to 0 °C. *meta*-Chloroperbenzoic acid (198 mg, 1.15 mmol, 2.0 equiv) was added portionwise. The reaction was warmed to room temperature and stirred for 2 h. Following this time, a second bolus of *meta*-chloroperbenzoic acid (198 mg, 1.15 mmol, 2.0 equiv) was added. The reaction was stirred for an additional 16 h. The mixture was transferred to a separatory funnel with 15 mL of CH<sub>2</sub>Cl<sub>2</sub> and 10 mL of saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. The organic phase was collected and washed with 2 x 15 mL of 10% aqueous NaOH and 2 x 15 mL of saturated aqueous NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to a dark yellow oil. Purification of this material by chromatography on silica gel (10% EtOAc in hexanes) gave the desired product as a light yellow oil (300 mg, 91%, 6.8:1 mixture of diastereomers). The stereochemical outcome of the epoxidation reaction was inferred based on comparison of relevant <sup>1</sup>H NMR signals and coupling constants to those reported in the literature for similar structures.<sup>18</sup>

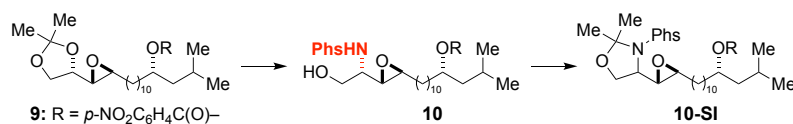
**R<sub>f</sub>:** 0.18 (10% EtOAc in hexanes)

**<sup>1</sup>H NMR (600 MHz, Chloroform-*d*, mixture of diastereomers):** δ 8.29 (d, *J* = 8.8 Hz, 2H), 8.20 (d, *J* = 8.8 Hz, 2H), 5.26 (ddt, *J* = 9.2, 7.0, 4.7 Hz, 1H), 4.09 (dd, *J* = 8.2, 6.1 Hz, 1H), 3.95–3.83 (m, 2H), 2.83 (ddd, *J* = 6.8, 5.0, 2.1 Hz, 1H), 2.77 (dd, *J* = 5.9, 2.3 Hz, 1H), 1.68 (ddt, *J* = 24.3, 11.1, 5.5 Hz, 4H), 1.62–1.22 (m, 32H), 0.94 (d, *J* = 6.4 Hz, 6H) ppm

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**<sup>13</sup>C NMR (126 MHz, Chloroform-*d*, mixture of diastereomers):**  $\delta$  164.6, 150.5, 136.3, 130.8, 123.6, 113.7, 109.1, 78.0, 77.5, 77.2, 77.0, 76.8, 75.1, 73.5, 73.0, 72.1, 70.8, 66.3, 66.1, 43.5, 34.9, 33.8, 29.71, 29.67, 29.65, 29.63, 29.59, 26.8, 26.5, 25.8, 25.4, 24.9, 23.3, 22.4 ppm



**(*S*)-14-((2*S*,3*S*)-3-((*S*)-2-Hydroxy-1-((phenoxy)sulfonyl)ethyl)oxiran-2-yl)-2-methyltetradecan-4-yl 4-nitrobenzoate (**10**):** Epoxide **9** (200 mg, 0.35 mmol) was dissolved in 0.4 mL of *t*-BuCN and 40  $\mu$ L of CH<sub>2</sub>Cl<sub>2</sub> (note: the latter solvent was added to ensure solubility of the starting material). To this solution were added sequentially [Rh<sub>2</sub>(esp)<sub>2</sub>] (2.7 mg, 4  $\mu$ mol, 1 mol %), PhOSO<sub>2</sub>NH<sub>2</sub> (79 mg, 0.35 mmol, 1.3 equiv), and Al<sub>2</sub>O<sub>3</sub> (142 mg, 1.4 mmol, 4.0 equiv). The deep blue-colored suspension was stirred for ~15 min prior to the addition of PhI(O<sup>*t*</sup>Bu)<sub>2</sub> (213 mg, 0.53 mmol, 1.5 equiv). The reaction immediately turned dark brown upon addition of oxidant. After stirring for 6 h, the reaction mixture was filtered through a short plug of silica gel, eluting with 15 mL of CH<sub>2</sub>Cl<sub>2</sub>. The filtrate was concentrated under reduced pressure to a dark brown oil, which was immediately dissolved in 1.0 mL of MeOH. After cooling this solution to 0 °C, glacial acetic acid (44  $\mu$ L, 0.77 mmol, 2.2 equiv) and NaBH<sub>3</sub>CN (48 mg, 0.77 mmol, 2.2 equiv) were added sequentially. The reaction mixture was stirred at 0 °C for 1.5 h. A second portion of acetic acid (22  $\mu$ L, 0.39 mmol, 1.1 equiv) and NaBH<sub>3</sub>CN (24 mg, 0.39 mmol, 1.1 equiv) were added and the contents were stirred for an additional 1.5 h at 0 °C. Following this time, the mixture was transferred to a separatory funnel with 5 mL of CH<sub>2</sub>Cl<sub>2</sub> and 5 mL of H<sub>2</sub>O. The organic phase was collected and washed with 3 x 5 mL of H<sub>2</sub>O and 1 x 5 mL of saturated aqueous NaCl. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to a brown oil. Purification of this material by chromatography on silica gel (gradient elution: 15%→25% EtOAc in hexanes) yielded the desired aminoalcohol product **10** (77 mg, 32% over two steps) as a yellow oil. <sup>1</sup>H NMR analysis of this material showed a poorly resolved spectrum with line-broadened signals.

Aminoalcohol **10** was converted to the corresponding N,O-acetal in order to determine the relative stereochemical outcome of the C–H amination/hydride reduction sequence. Accordingly, **10** (7 mg, 0.01 mmol) was dissolved in dimethoxypropane (86  $\mu$ L, 0.7 mmol, 70 equiv) to which *p*-TsOH (0.2 mg, 0.8  $\mu$ mol, 0.08 equiv) as a solution in 100  $\mu$ L of benzene was added. The mixture was stirred at 45 °C for 4 h, following which time the solution was transferred to a separatory funnel with 2 mL of CH<sub>2</sub>Cl<sub>2</sub> and 2 mL of saturated aqueous Na<sub>2</sub>CO<sub>3</sub>. The organic phase was collected and the aqueous layer was extracted with 2 x 1 mL of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were washed with 1 x 2 mL of saturated aqueous NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure to a yellow oil. Purification of this material by chromatography on silica gel (10% EtOAc in hexanes, *R*<sub>f</sub> 0.26) afforded pure **10-SI** as a pale yellow oil (6 mg, 85%). The stereochemistry of this product is tentatively assigned based on comparison of <sup>1</sup>H NMR spectra with analogous reported structures.<sup>19,20</sup>

***R*<sub>f</sub> (for **10**):** 0.54 (25% EtOAc in hexanes)

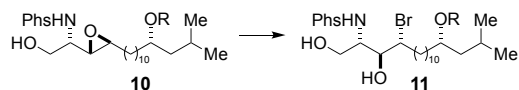
**<sup>1</sup>H NMR (for **10-SI**, 400 MHz, Methanol-*d*<sub>4</sub>):**  $\delta$  8.34 (d, *J* = 8.6 Hz, 2H), 8.30–8.15 (m, 2H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.38–7.25 (m, 3H), 5.36–5.19 (m, 1H), 4.17 (t, *J* = 4.2 Hz, 1H), 4.10 (dd, *J* = 9.6, 6.2 Hz, 1H), 3.92 (dd, *J* = 9.4, 1.6 Hz, 1H), 3.04 (dd, *J* = 4.3, 2.2 Hz, 1H), 3.00–2.89 (m, 1H), 1.78–1.55 (m, 11H), 1.54–1.20 (m, 18H), 0.95 (d, *J* = 6.4 Hz, 6H) ppm

**<sup>13</sup>C NMR (for **10-SI**, 126 MHz, Methanol-*d*<sub>4</sub>):**  $\delta$  165.9, 152.1, 151.7, 137.2, 131.7, 130.9, 128.0, 124.7, 123.0, 99.9, 75.8, 65.7, 61.2, 58.9, 57.0, 44.6, 35.8, 32.6, 30.6, 30.5, 30.42, 30.38, 28.3, 27.0, 26.4, 26.0, 24.3, 23.6, 22.5 ppm

**IR (for **10-SI**):**  $\nu$  2925, 2854, 1718, 1684, 1653, 1647, 1559, 1527, 1488, 1373, 1274, 1193, 1146, 1101 cm<sup>–1</sup>

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20. Koviach, J. L.; Chappell, M. D.; Halcomb, R. L. Design and Synthesis of Conformationally Constrained Glycosylated Amino Acids. *J. Org. Chem.* **2001**, *66*, 2318–2326.

**HRMS (for 10-SI, ESI<sup>+</sup>):** calculated for C<sub>35</sub>H<sub>50</sub>N<sub>2</sub>O<sub>9</sub>S[Na]<sup>+</sup> 697.3135, found 697.3129



**(4*S*,15*R*,16*S*,17*S*)-15-Bromo-16,18-dihydroxy-2-methyl-17-((phenoxysulfonyl)amino)octadecan-4-yl 4-nitrobenzoate (11):** Sulfamate **10** (112 mg, 0.17 mmol) was dissolved in 4.0 mL of 1,2-dimethoxyethane (DME) to which anhydrous CeBr<sub>3</sub> (126 mg, 0.33 mmol, 2.0 equiv) was added in a single portion. The reaction mixture was stirred at 65 °C for 8 h, following which time a second portion of CeBr<sub>3</sub> (126 mg, 0.33 mmol, 2.0 equiv) was added. The reaction was stirred at 65 °C for an additional 8 h. The turbid solution was transferred to a separatory funnel with 10 mL of CH<sub>2</sub>Cl<sub>2</sub> and 5 mL of H<sub>2</sub>O. The organic layer was collected and washed with 3 x 7 mL of saturated aqueous NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to a light brown oil. Purification of this material by chromatography on silica gel (gradient elution: 10%→25% EtOAc in hexanes) furnished the desired product **11** as a light yellow oil (117 mg, 81%). Regio- and stereochemistry of this product is inferred based on conversion to the natural product.

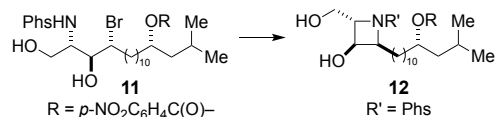
**R<sub>f</sub>:** 0.54 (25% EtOAc in hexanes)

**<sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>):** δ 8.41–8.30 (m, 2H), 8.28–8.17 (m, 2H), 7.49–7.19 (m, 5H), 5.28 (dq, *J* = 12.0, 5.8, 5.2 Hz, 1H), 4.29 (ddd, *J* = 10.6, 5.3, 2.2 Hz, 1H), 3.99 (t, *J* = 5.7 Hz, 1H), 3.89–3.74 (m, 3H), 1.79–1.60 (m, 6H), 1.47 (ddd, *J* = 13.1, 8.0, 4.0 Hz, 1H), 1.41–1.18 (m, 16H), 0.95 (d, *J* = 6.3 Hz, 6H) ppm

**<sup>13</sup>C NMR (126 MHz, Methanol-*d*<sub>4</sub>):** δ 165.9, 152.0, 137.2, 131.7, 130.8, 130.7, 127.6, 124.7, 123.0, 83.7, 75.8, 61.6, 59.7, 59.1, 44.6, 35.8, 33.5, 30.9, 30.65, 30.58, 30.5, 30.4, 30.0, 28.7, 26.4, 26.0, 23.6, 22.5 ppm

**IR:** ν 3424, 2923, 2856, 1719, 1644, 1532, 1448, 1275, 1202, 1129, 1110, 1024, 977 cm<sup>-1</sup>

**HRMS (ESI<sup>+</sup>):** calculated for C<sub>32</sub>H<sub>47</sub>N<sub>2</sub>O<sub>9</sub>SBr[Na]<sup>+</sup> 737.2083, found 737.2078 (<sup>79</sup>Br) and 739.2103 (<sup>81</sup>Br)



**(5*S*)-14-((2*S*,3*R*,4*S*)-3-Hydroxy-4-(hydroxymethyl)-1-(phenoxysulfonyl)azetidin-2-yl)-2-methyltetradecan-4-yl 4-nitrobenzoate (12):** Alkyl bromide **11** (72 mg, 0.1 mmol) was dissolved in 1.0 mL of DMF and to this solution was added K<sub>2</sub>CO<sub>3</sub> (21 mg, 0.15 mmol, 1.5 equiv). The reaction mixture was stirred at for 2 h, then transferred to a separatory funnel with 10 mL of EtOAc and 10 mL of H<sub>2</sub>O. The organic layer was collected and washed with 3 x 10 mL of H<sub>2</sub>O and 1 x 10 mL of saturated aqueous NaCl, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure to a colorless oil. Purification of this material by chromatography on silica gel (gradient elution: 25%→50% EtOAc in hexanes) yielded the desired product **12** as a pale yellow oil (45 mg, 71%).

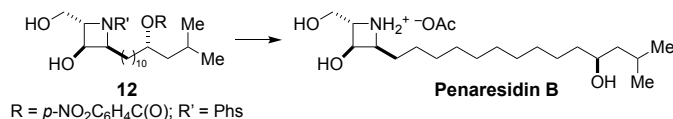
**R<sub>f</sub>:** 0.46 (50% EtOAc in hexanes)

**<sup>1</sup>H NMR (600 MHz, Methanol-*d*<sub>4</sub>):** δ 8.35–8.27 (m, 2H), 8.20 (d, *J* = 8.8 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.26 (dd, *J* = 13.5, 7.5 Hz, 3H), 5.25 (tt, *J* = 8.8, 4.8 Hz, 1H), 4.49 (dd, *J* = 6.8, 4.4 Hz, 1H), 4.33–4.24 (m, 1H), 4.11 (q, *J* = 4.2 Hz, 1H), 3.87 (dd, *J* = 12.3, 4.6 Hz, 1H), 3.76 (dd, *J* = 12.3, 3.1 Hz, 1H), 2.05–1.90 (m, 1H), 1.88–1.78 (m, 1H), 1.67 (ddq, *J* = 20.8, 13.8, 6.8, 6.2 Hz, 4H), 1.44 (ddd, *J* = 13.1, 8.3, 4.1 Hz, 1H), 1.41–1.10 (m, 18H), 0.92 (d, *J* = 6.5 Hz, 6H) ppm

**<sup>13</sup>C NMR (126 MHz, Methanol-*d*<sub>4</sub>):** δ 164.7, 151.2, 150.3, 136.0, 130.6, 129.6, 126.5, 123.6, 121.9, 74.6, 74.4, 70.4, 64.7, 59.8, 53.6, 43.4, 34.6, 29.5, 29.4, 29.33, 29.27, 26.9, 25.5, 25.2, 24.8, 22.4, 21.3 ppm

**IR:** ν 3410, 2925, 2854, 1719, 1654, 1624, 1608, 1560, 1527, 1488, 1466, 1458, 1374, 1275, 1191, 1139, 1116, 1102, 1015 cm<sup>-1</sup>

**HRMS (ESI<sup>+</sup>):** calculated for C<sub>32</sub>H<sub>46</sub>N<sub>2</sub>O<sub>9</sub>S[Na]<sup>+</sup> 657.2822, found 657.2824



**(2*S*,3*R*,4*S*)-2-((*S*)-11-Hydroxy-13-methyltetradecyl)-4-(hydroxymethyl)azetidin-3-ol (Penaresidin B):** Azetidine **12** (6 mg, 0.01 mmol) and Ni(dppp)Cl<sub>2</sub> (0.3 mg, 0.5 μmol, 0.05 equiv) were transferred to an oven-dried 1 mL vial, which was stoppered with a rubber septum, evacuated and refilled with nitrogen three times. The vial was charged with 200 μL of benzene followed by 30 μL of an ethereal solution of MeMgBr (3.0 M solution in Et<sub>2</sub>O, 0.07 mmol, 7 equiv). The vessel was placed in an oil bath at 55 °C and the contents were stirred for 15 h. The mixture was then cooled to ambient temperature and the reaction was quenched by the addition of 100 μL of MeOH. All volatiles were removed under reduced pressure to give a brown-colored residue, which was re-dissolved in 40 μL of 3.0 M anhydrous methanolic HCl solution (note: this solution was prepared from acetyl chloride and MeOH). The flask was sealed and the contents were stirred at 55 °C for 6 h. Following this time, the solution was cooled to ambient temperature and the reaction was quenched by the addition of 100 μL of saturated aqueous NaHCO<sub>3</sub>. All volatiles were removed under reduced pressure to give a light yellow film. Purification of this material by chromatography on silica gel (5:1:0.1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH/30% aqueous NH<sub>4</sub>OH) afforded the desired product as a clear oil. The acetate salt of penaresidin B was obtained by re-dissolving the free-base in 0.5 mL of MeOH to which 10 μL of glacial acetic acid was added. Concentration of this solution under reduced pressure yielded **penaresidin B•AcOH** as a pale yellow oil (4 mg, 86%).

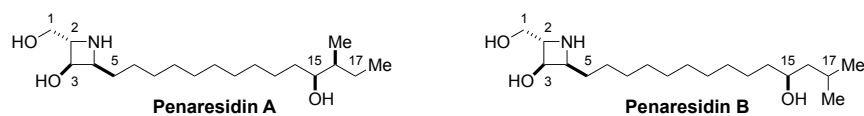
*Note:* this product can also be obtained, albeit in lowered yield (40%), by stirring azetidine **12** in a 1:1 6.0 N aqueous HCl/MeCN solution (0.05 M in substrate) at 90 °C for 24 h. Following concentration of this solution, the product is purified as indicated above.

**R<sub>f</sub>:** 0.18 (5:1:0.1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH/30% aq. NH<sub>4</sub>OH, visualized with ninhydrin stain)

**<sup>1</sup>H NMR (600 MHz, Methanol-*d*<sub>4</sub>, AcOH salt):** δ 4.52 (dd, *J* = 6.8, 4.5 Hz, 1H), 4.36–4.28 (m, 1H), 4.17–4.10 (m, 1H), 3.90 (dd, *J* = 12.3, 4.6 Hz, 1H), 3.79 (dd, *J* = 12.2, 3.2 Hz, 1H), 3.63–3.54 (m, 1H), 1.99–1.80 (m, 6H), 1.49–1.22 (m, 19H), 1.22–1.16 (m, 1H), 0.91 (t, *J* = 6.6, 5.2 Hz, 6H) ppm (Note: the azetidine C–H signals will shift based on sample concentration and choice of counterion)

**<sup>13</sup>C NMR (126 MHz, Methanol-*d*<sub>4</sub>, AcOH salt):** δ 179.0, 70.4, 70.0, 66.4, 65.2, 59.6, 47.9, 39.1, 30.9, 30.8, 30.7, 30.6, 30.5, 30.4, 27.7, 26.8, 26.3, 25.7, 23.2, 22.4 ppm

**IR:** ν 3310, 2928, 2850, 1569, 1410, 1374, 1124, 1042, 1018, 928 cm<sup>-1</sup>.

**Table S3.** Comparison of  $^1\text{H}$  and  $^{13}\text{C}$  NMR signals for penaresidin B.

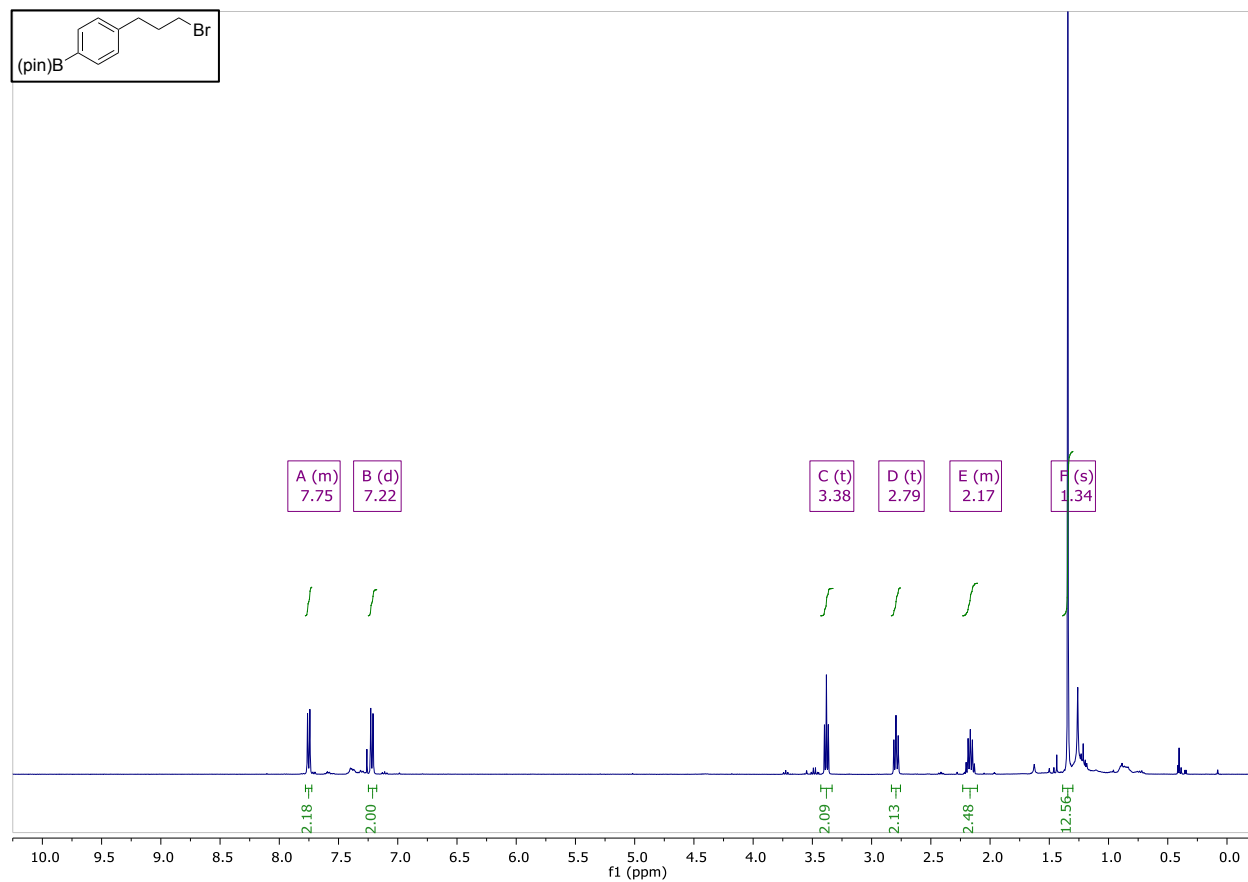
Carbon Number	Subba Reddy, <i>et al.</i> <sup>21</sup>	Fujiwara, <i>et al.</i> <sup>22</sup>	This work
	Penaresidin A•AcOH ( $^1\text{H}$ NMR, 500 MHz, $\text{CD}_3\text{OD}$ )	Penaresidin B•AcOH ( $^1\text{H}$ NMR, 400 MHz, $\text{CD}_3\text{OD}$ )	Penaresidin B•AcOH ( $^1\text{H}$ NMR, 600 MHz, $\text{CD}_3\text{OD}$ )
<b>1</b>	3.85–3.80 (m, 2H)	3.85 (br dd, $J = 12.8, 4.6$ Hz, 1H) 3.82 (br dd, $J = 12.8, 3.7$ Hz, 1H)	3.90 (dd, $J = 12.3, 4.6$ Hz, 1H) 3.79 (dd, $J = 12.2, 3.2$ Hz, 1H)
<b>2</b>	4.21–4.15 (m, 1H)	4.24 (br q, $J = 7.8$ Hz, 1H)	4.36–4.28 (m, 1H)
<b>3</b>	4.53–4.49 (m, 1H)	4.52 (br dd, $J = 6.9, 5.0$ Hz, 1H)	4.52 (dd, $J = 6.8, 4.5$ Hz, 1H)
<b>4</b>	4.07–4.02 (m, 1H)	4.08 (br q, $J = 4.1$ Hz, 1H)	4.17–4.10 (m, 1H)
<b>5</b>	1.96–1.79 (m, 2H)	1.94–1.72 (m, 3H) 1.44–1.28 (m, 19H)	1.99–1.80 (m, 6H) 1.49–1.22 (m, 19H)
<b>6–14</b>	1.43–1.22 (m, 19H)	1.44–1.28 (m, 19H)	1.49–1.22 (m, 19H)
<b>15</b>	3.45–3.41 (m, 1H)	3.61–3.55 (m, 1H)	3.63–3.54 (m, 1H)
<b>16</b>	1.53–1.44 (m, 1H)	1.94–1.72 (m, 3H))	1.99–1.80 (m, 6H)
<b>17</b>	1.20–1.14 (m, 1H) 1.43–1.22 (m, 19H)	1.18 (ddd, $J = 13.7, 8.7, 4.1$ Hz, 1H)	1.22–1.16 (m, 1H)
<b>16/17-Me</b>	0.91 (t, $J = 7.3$ Hz, 3H)	0.91 (d, $J = 6.9$ Hz, 3H)	0.91 (t, $J = 6.6, 5.2$ Hz, 6H)
<b>17-Me</b>	0.86 (t, $J = 6.3$ Hz, 3H)	0.90 (d, $J = 6.9$ Hz, 3H)	0.91 (t, $J = 6.6, 5.2$ Hz, 6H)
<b>AcOH</b>	1.90 (s, 3H)	1.91 (s, 3H)	1.99–1.80 (m, 6H)

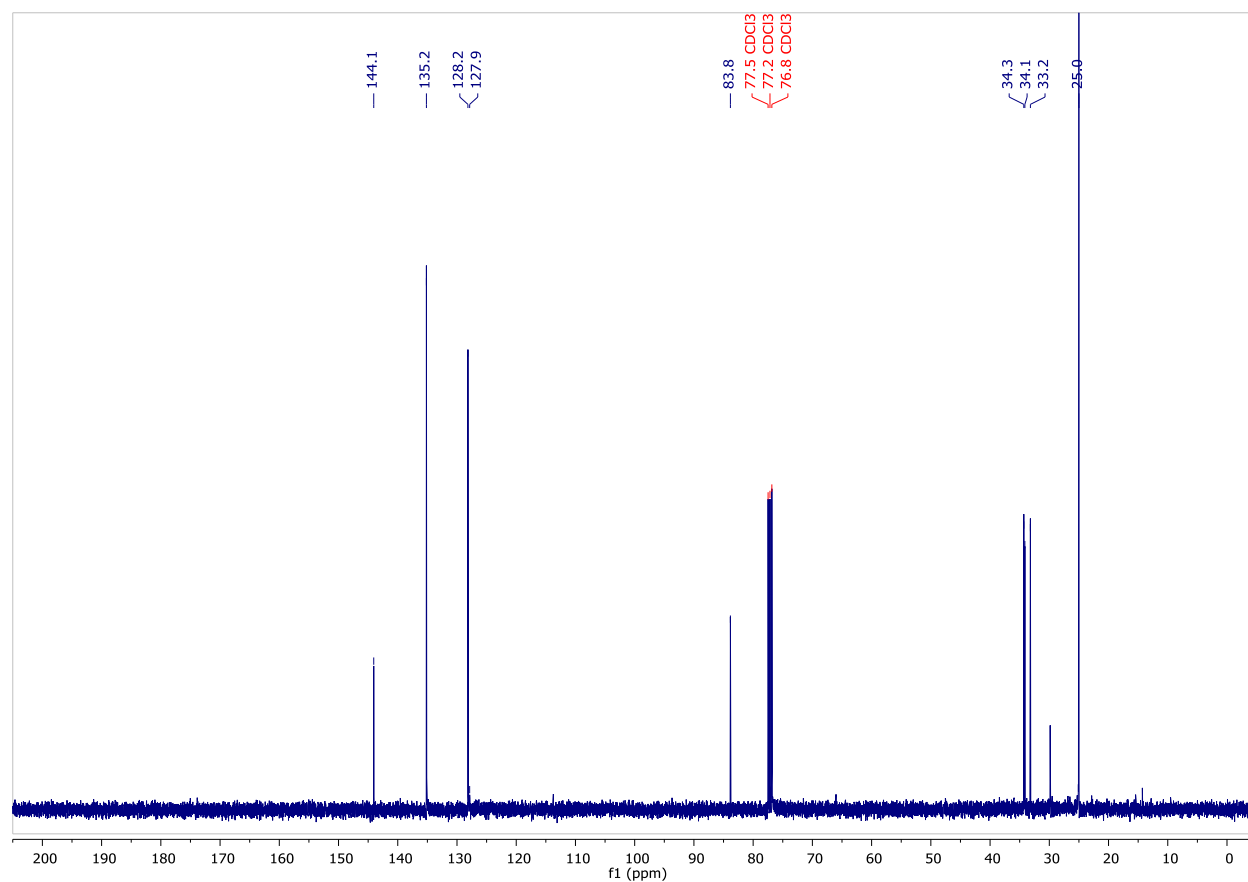
Carbon Number	Subba Reddy, <i>et al.</i>	Fujiwara, <i>et al.</i>	This work
	Penaresidin A•AcOH ( $^{13}\text{C}$ NMR, 126 MHz, $\text{CD}_3\text{OD}$ )	Penaresidin B•AcOH ( $^{13}\text{C}$ NMR, 101 MHz, $\text{CD}_3\text{OD}$ )	Penaresidin B•AcOH ( $^{13}\text{C}$ NMR, 151 MHz, $\text{CD}_3\text{OD}$ )
<b>1</b>	65.1	65.2	65.2
<b>2</b>	66.6	66.4	66.4
<b>3</b>	69.8	69.9	70.0
<b>4</b>	60.0	59.6	59.6
<b>5</b>	30.9	30.85	30.9
<b>6</b>	30.8	30.75	30.8
<b>7</b>	30.75	30.69	30.7
<b>8</b>	30.7	30.63	30.6
<b>9</b>	30.6	30.5	30.5
<b>10</b>	30.5	30.4	30.4
<b>11</b>	27.9	27.7	27.7
<b>12</b>	27.5	26.8	26.8
<b>13</b>	27.1	26.2	26.3
<b>14</b>	35.4	39.1	39.1
<b>15</b>	75.5	70.4	70.4
<b>16</b>	41.5	47.2	47.9
<b>17</b>	26.2	25.7	25.7
<b>16/17-Me</b>	13.9	23.2	23.2
<b>17-Me</b>	12.3	22.4	22.4
<b>AcOH</b>	178.3	179.0	179.0

21. Subba Reddy, B. V.; Kishore, C.; Srinivas Reddy, A. Stereoselective total synthesis of penaresidin A starting from D-galactal. *Tetrahedron Lett.* **2014**, *55*, 49–51.
22. Fujiwara, T.; Hashimoto, K.; Umeda, M.; Murayama, S.; Ohno, Y.; Liu, B.; Nambu, H.; Yakura, T. Divergent total synthesis of penaresidin B and its straight side chain analogue. *Tetrahedron* **2018**, *74*, 4578–4591.

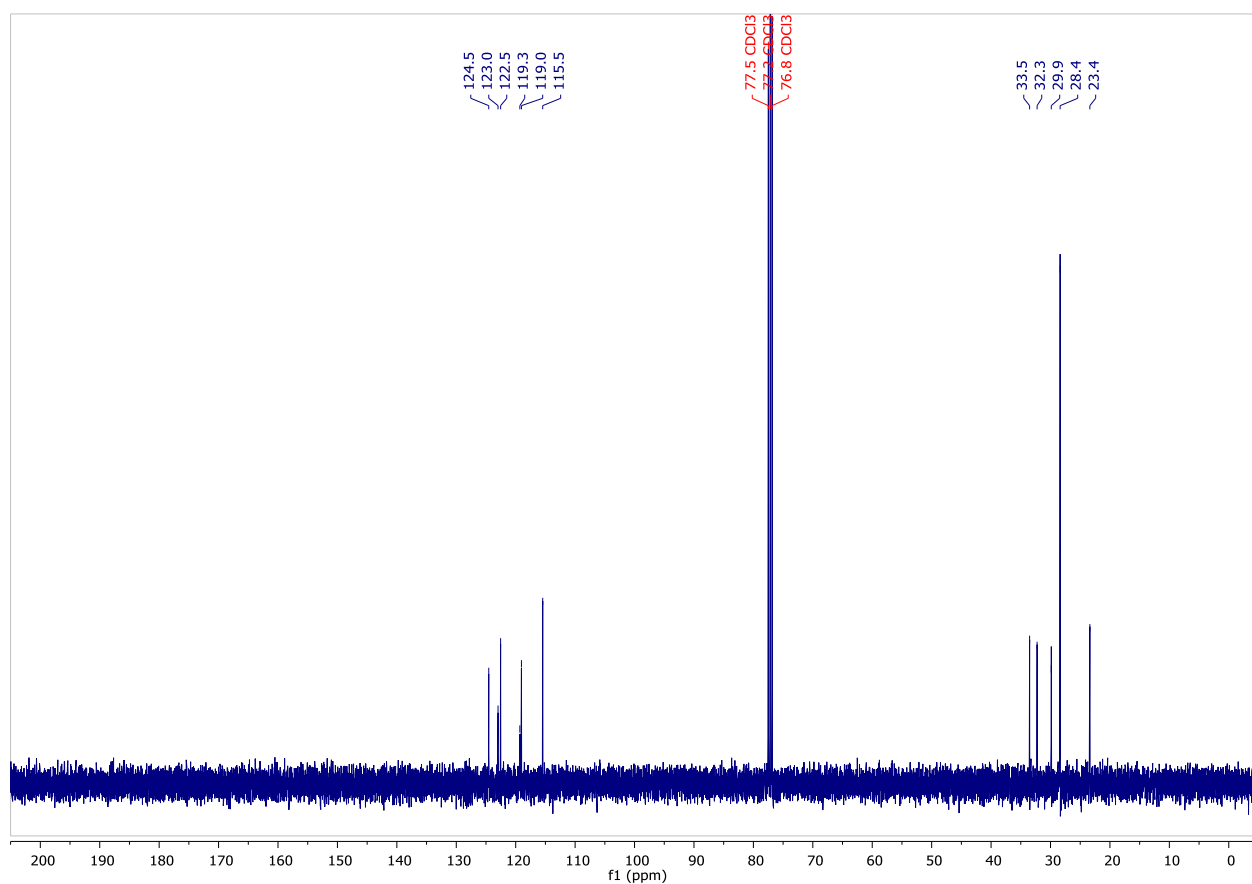
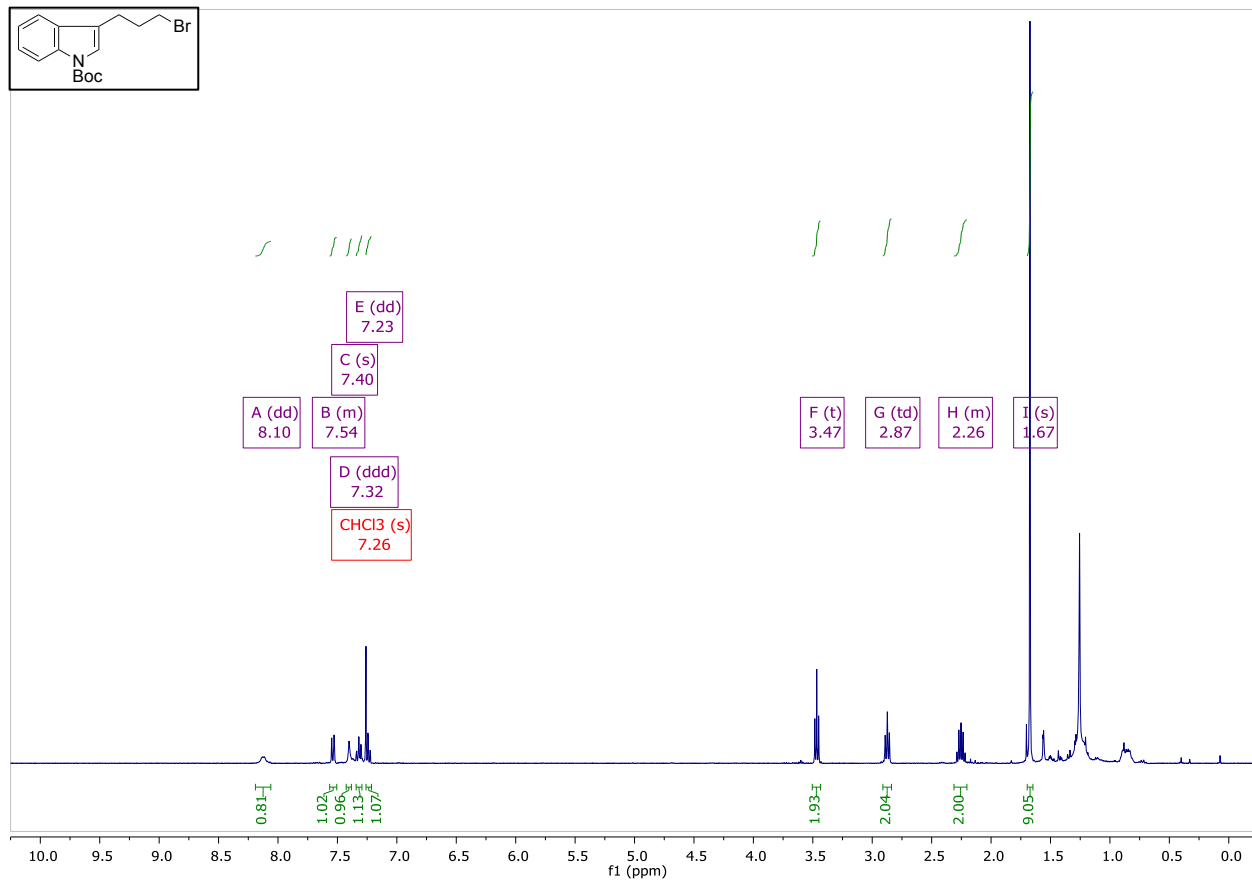
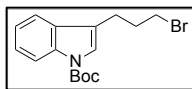
# <sup>1</sup>H and <sup>13</sup>C NMR Spectra of New Compounds



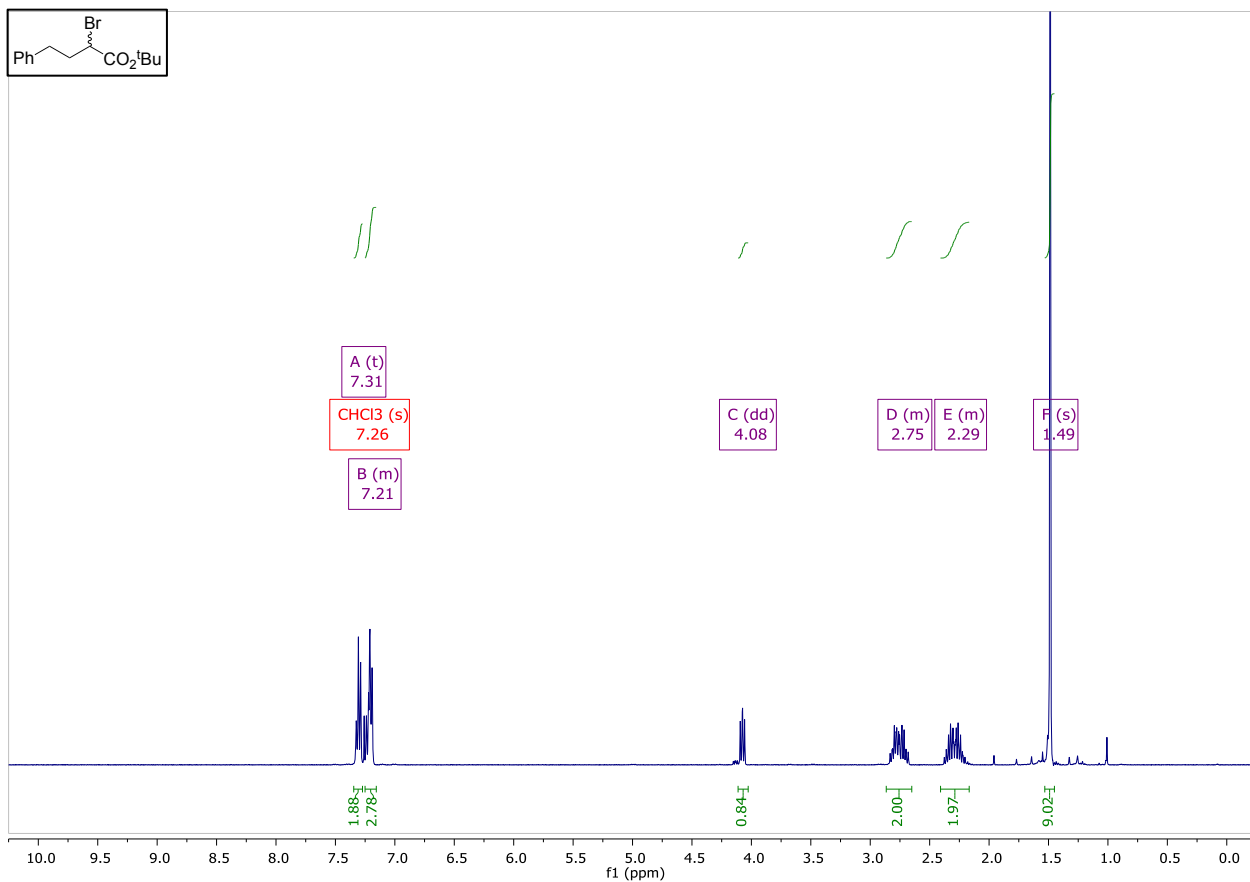
1h: <sup>1</sup>H NMR (400 MHz, Chloroform-d)



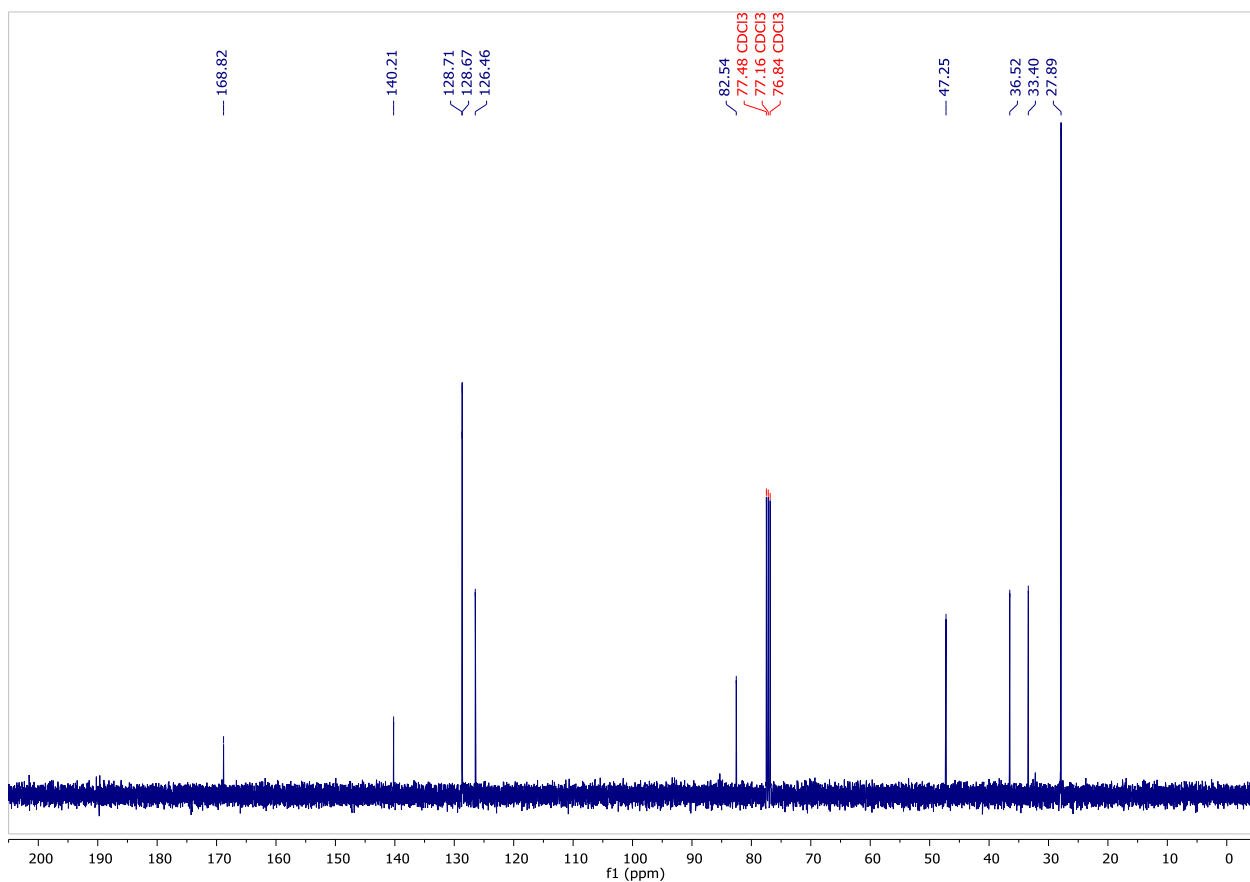
1h: <sup>13</sup>C NMR (101 MHz, Chloroform-d)



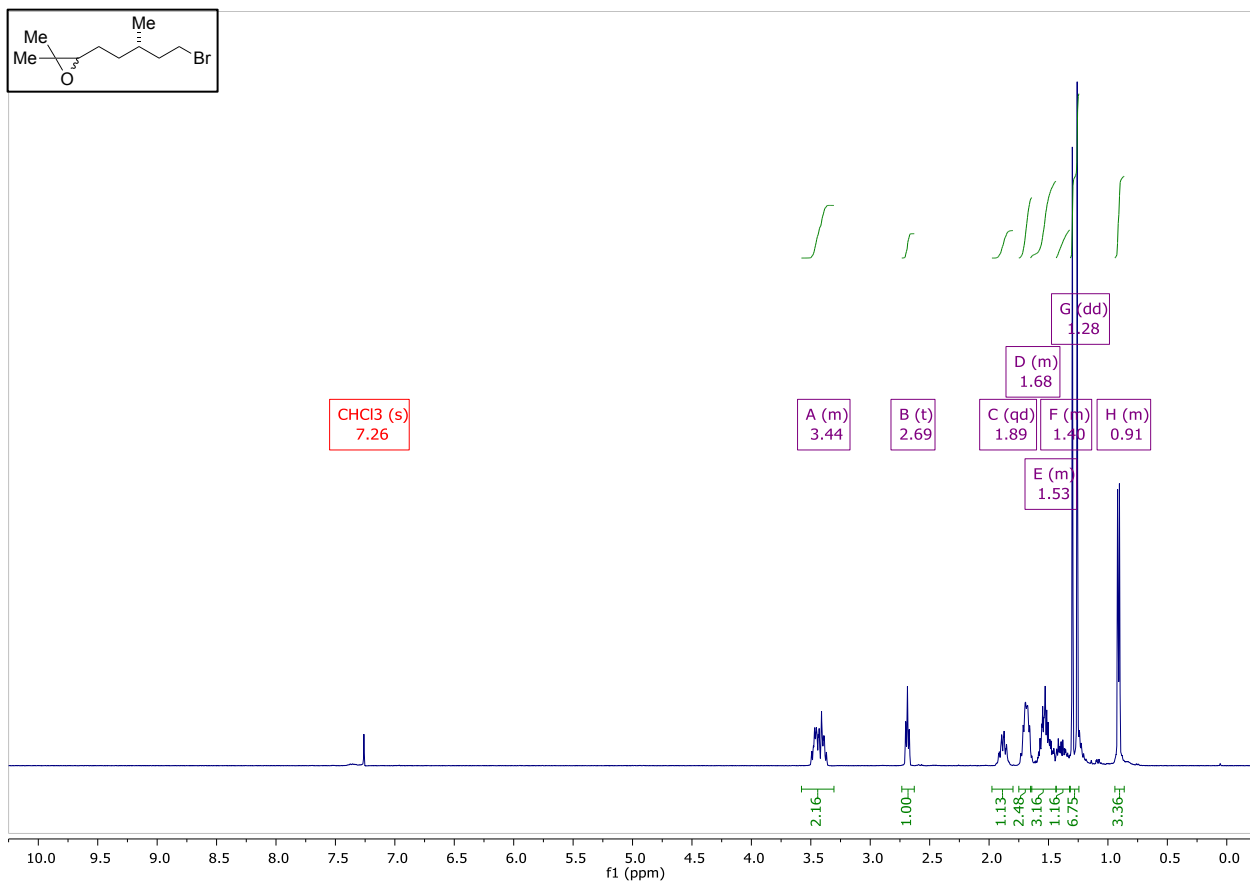




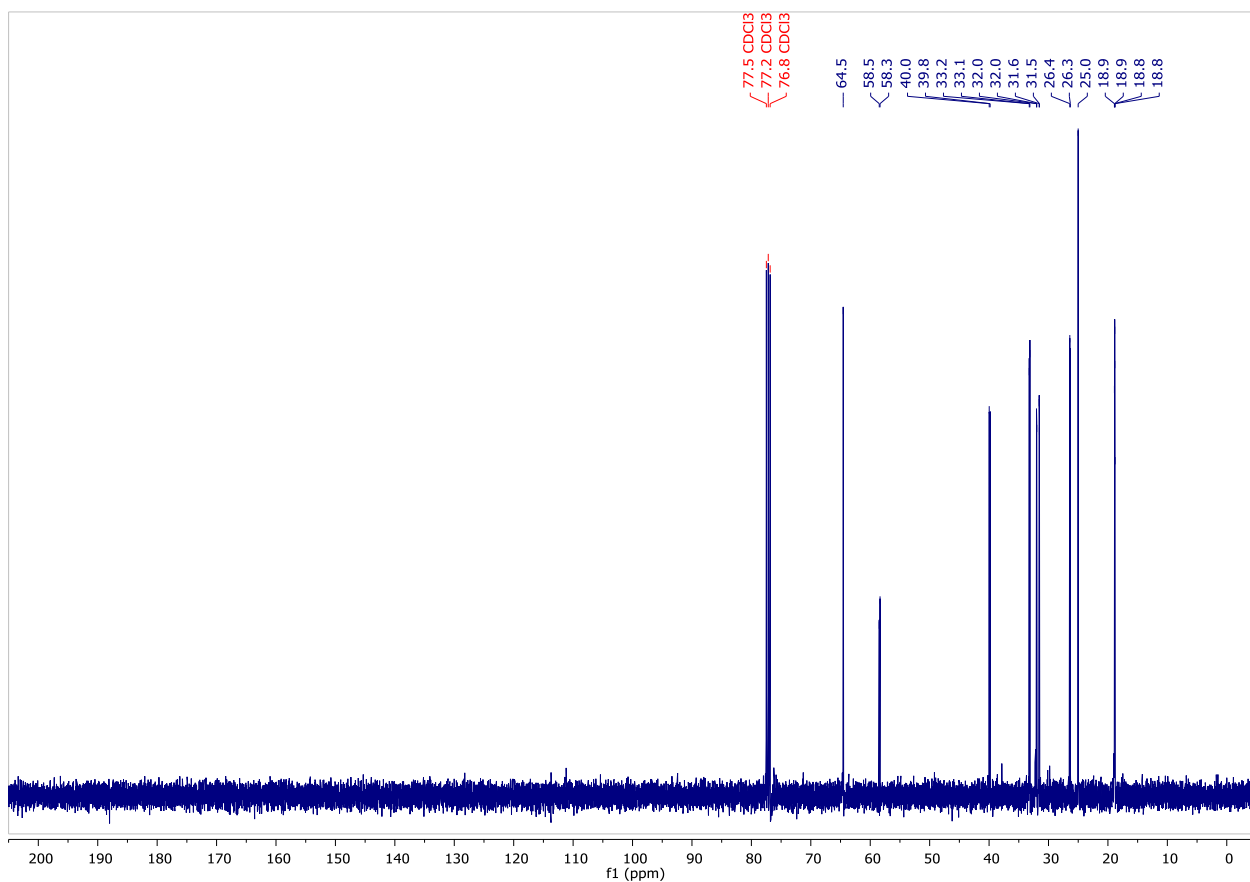
**1j: <sup>1</sup>H NMR (400 MHz, Chloroform-d)**



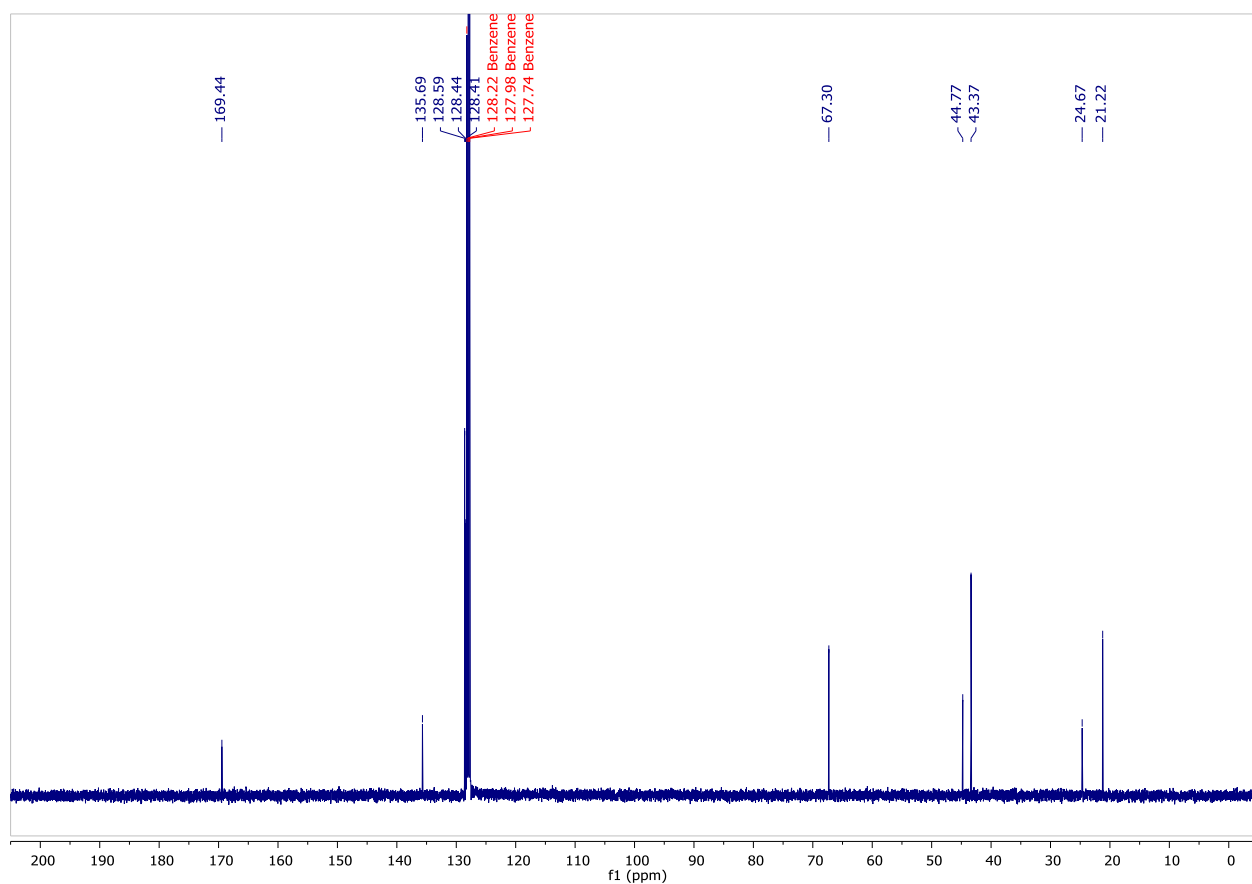
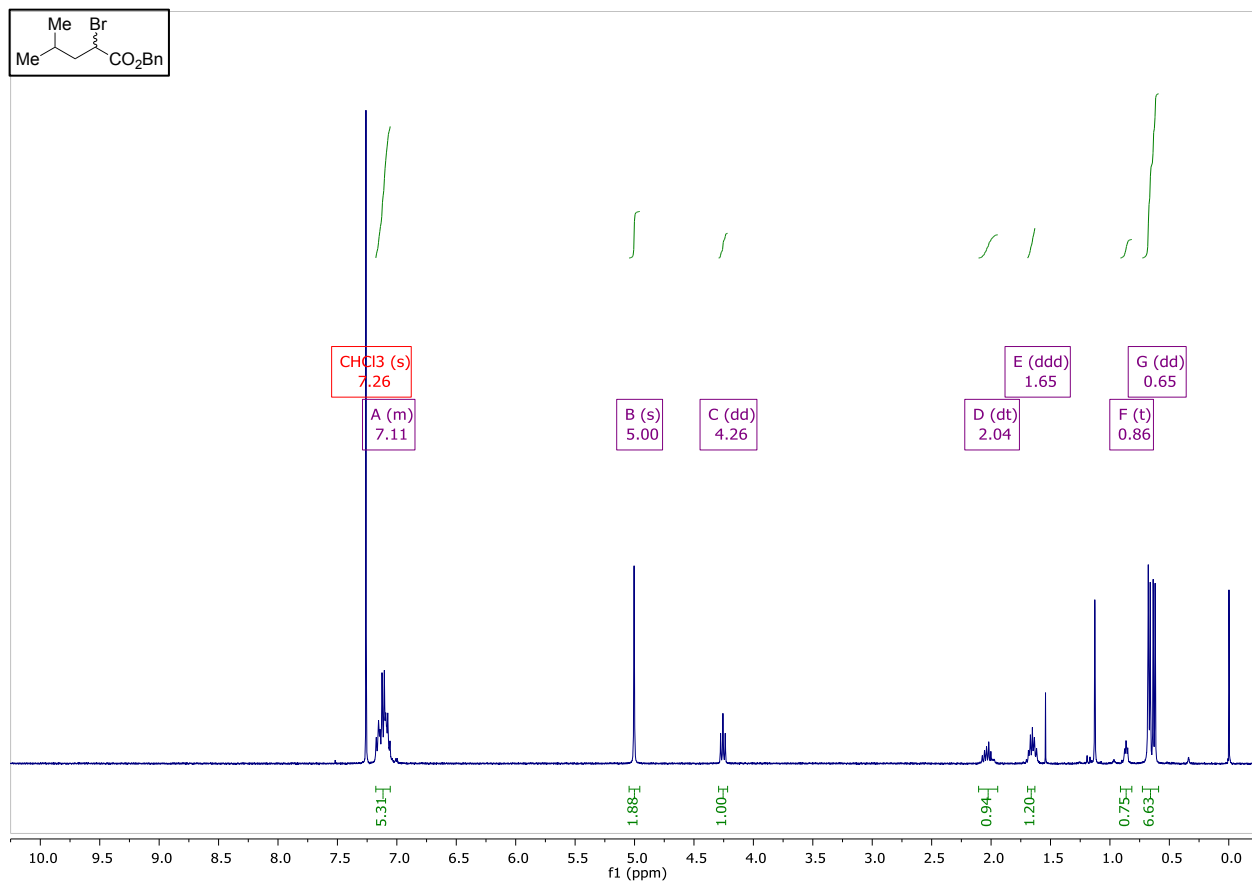
**1j: <sup>13</sup>C NMR (101 MHz, Chloroform-d)**

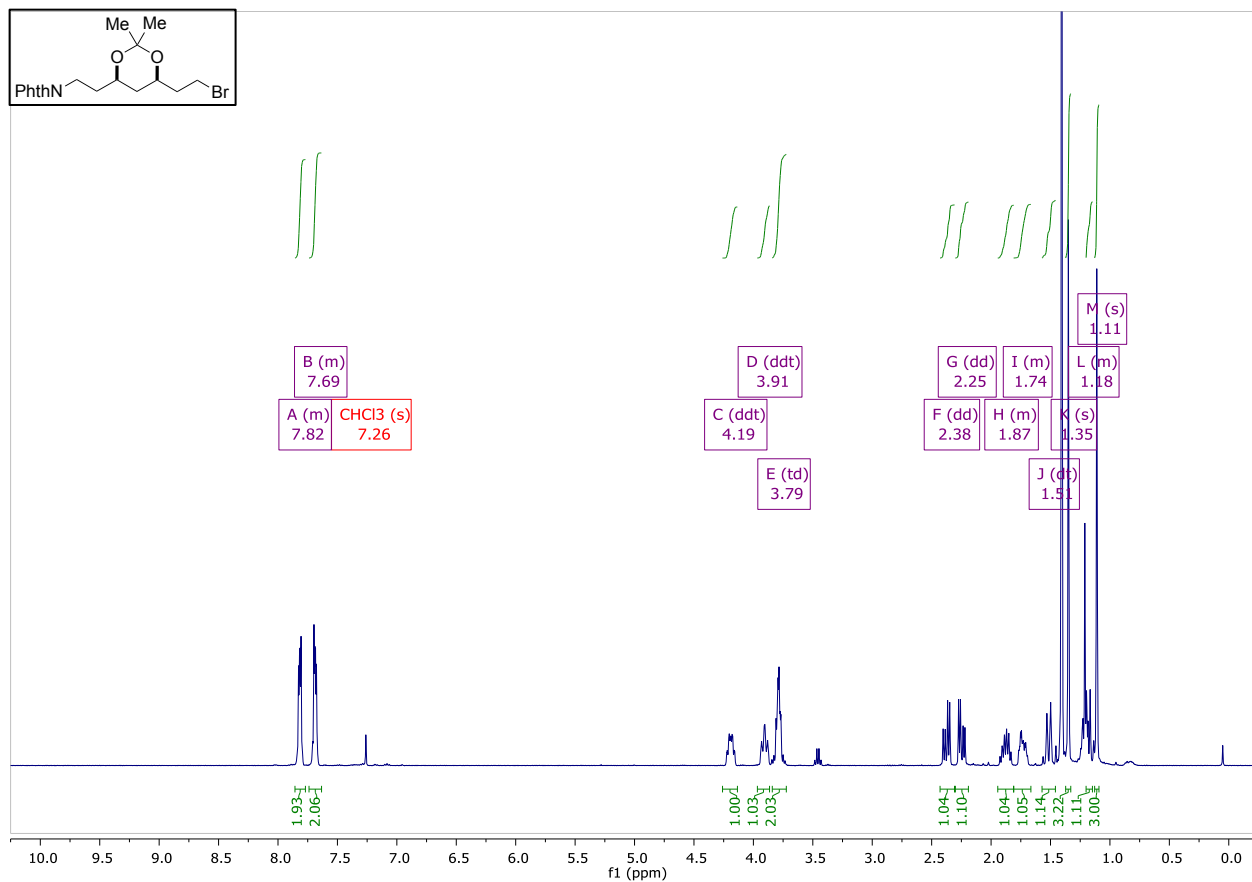


1l: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)

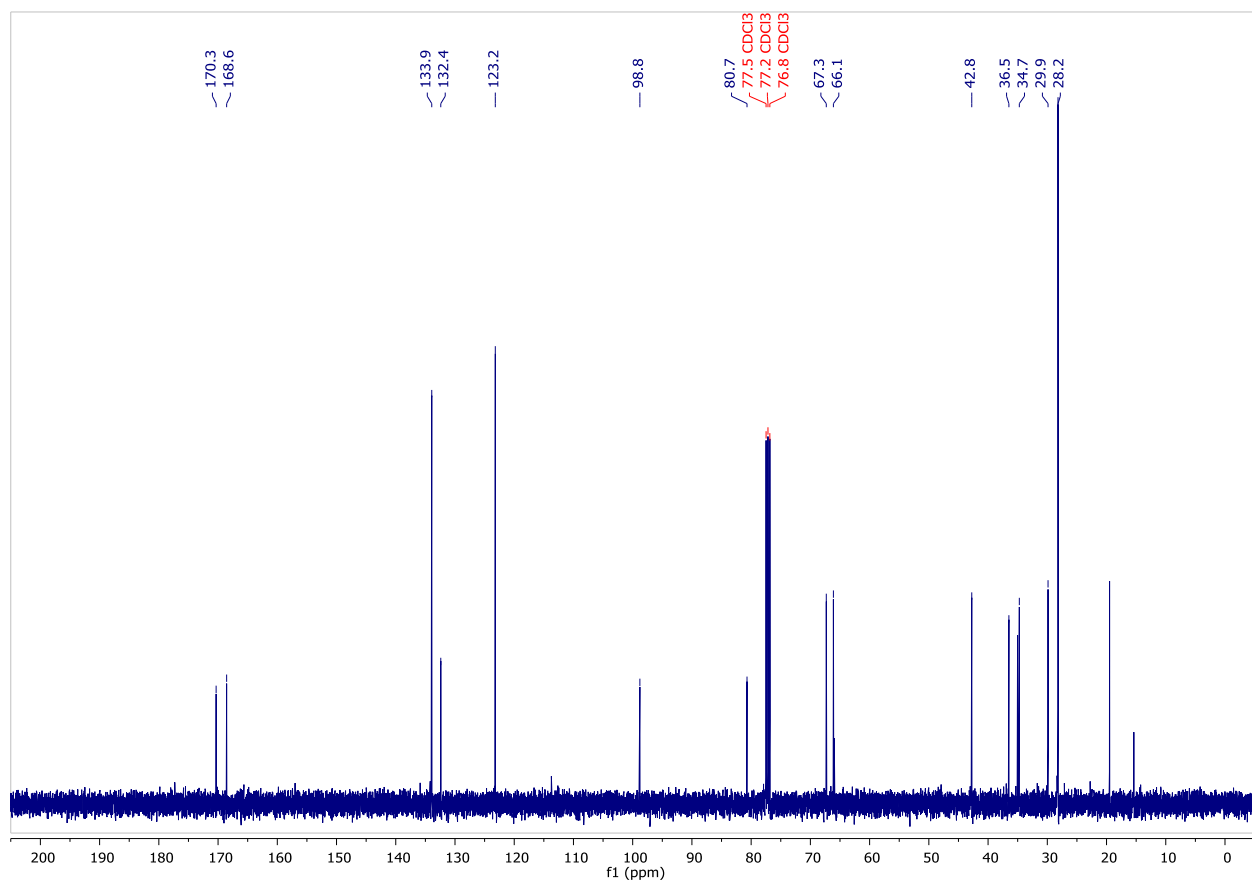


1l: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)

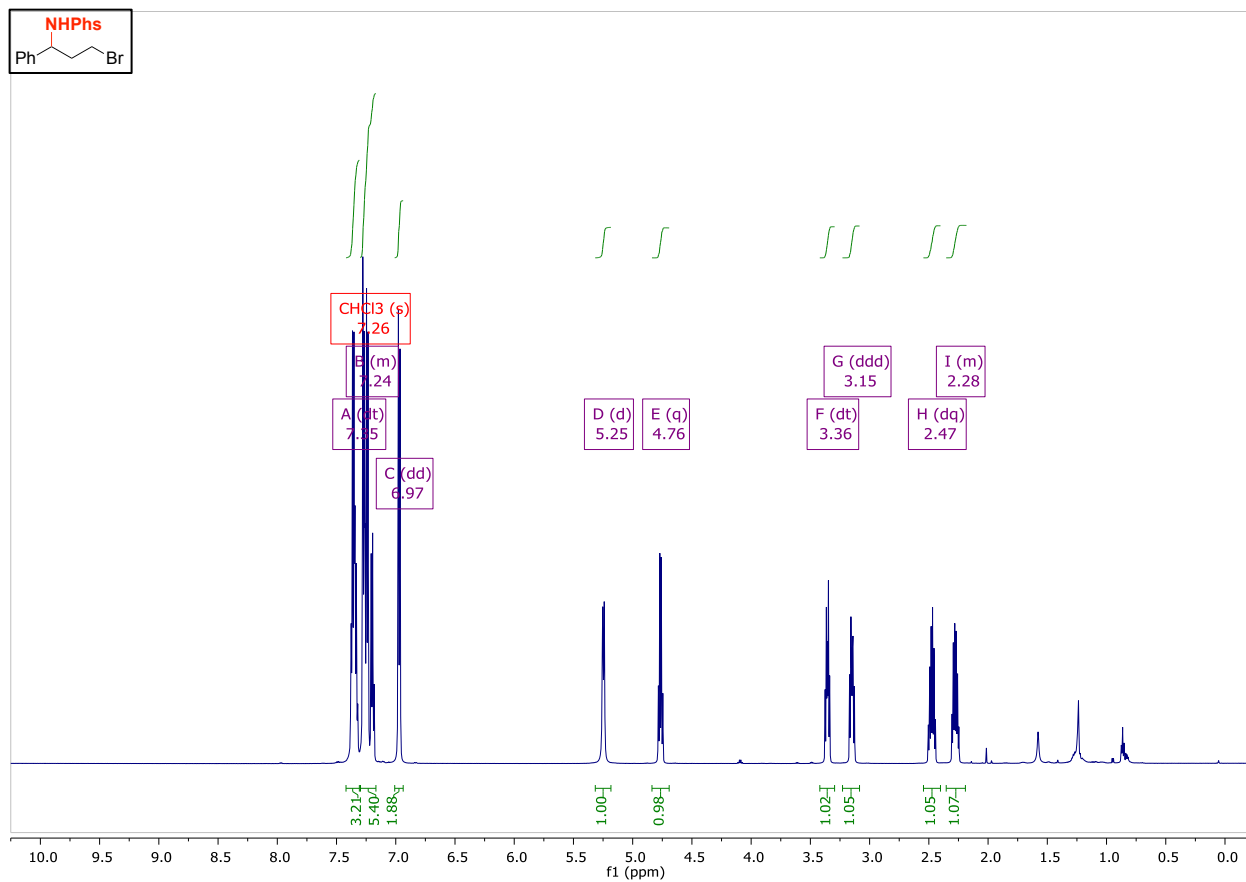




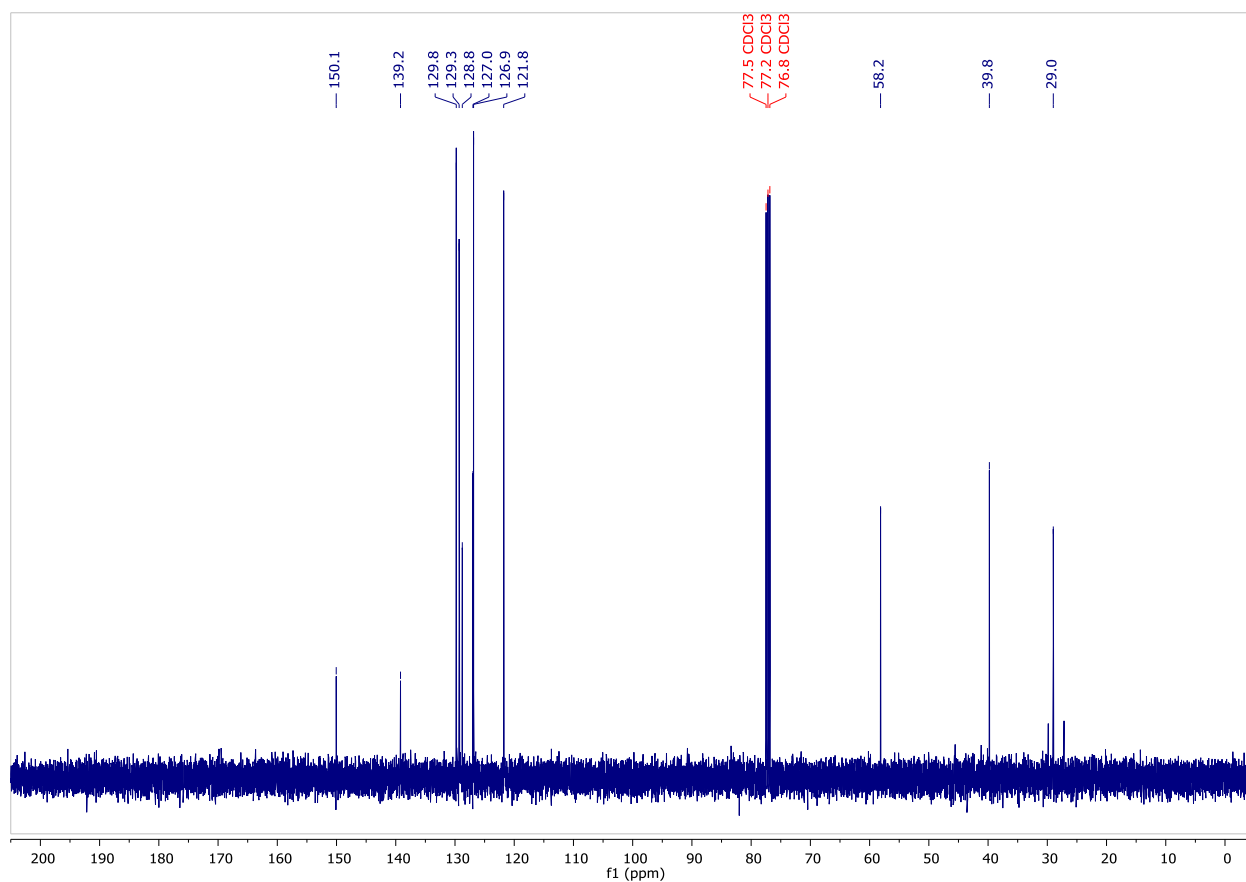
**1n: <sup>1</sup>H NMR (400 MHz, Chloroform-d)**



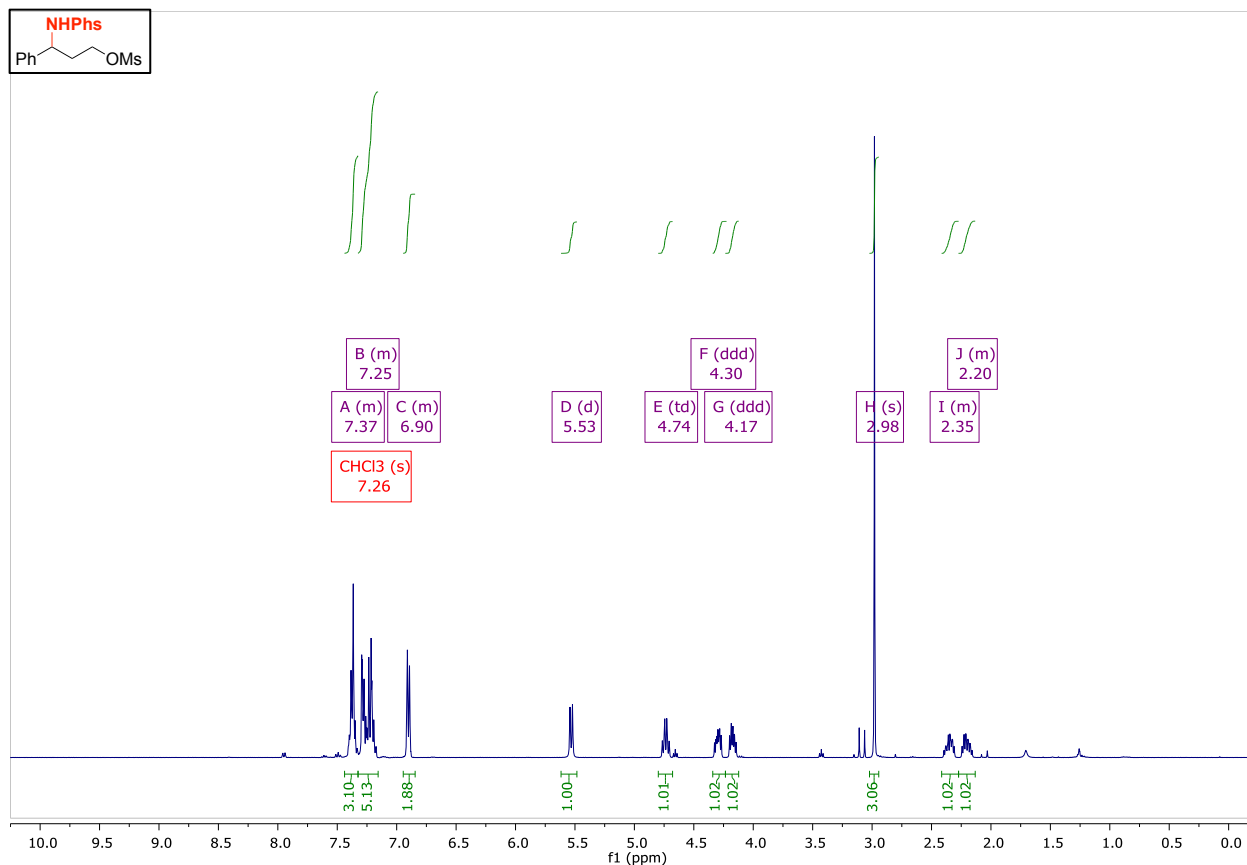
**1n: <sup>13</sup>C NMR (101 MHz, Chloroform-d)**



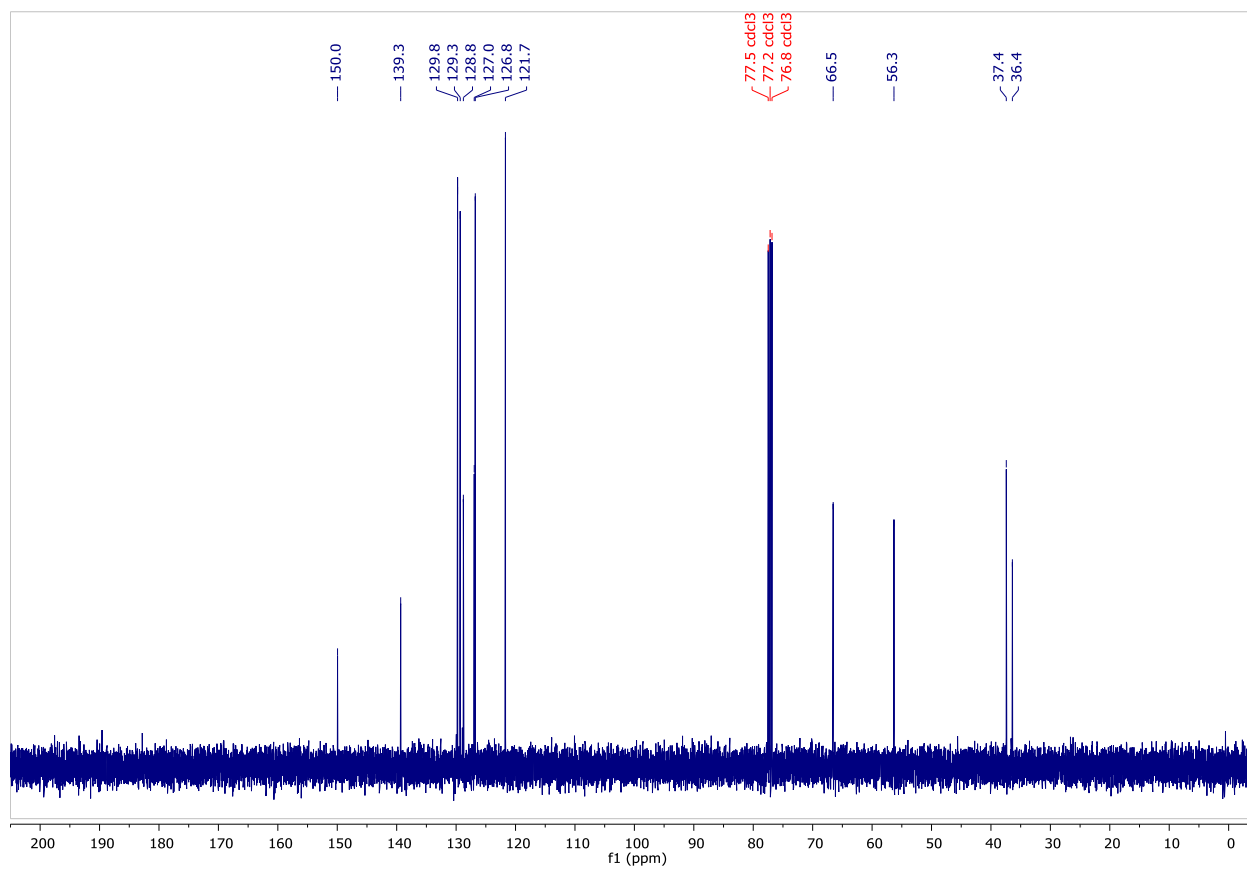
**2a-1: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)**



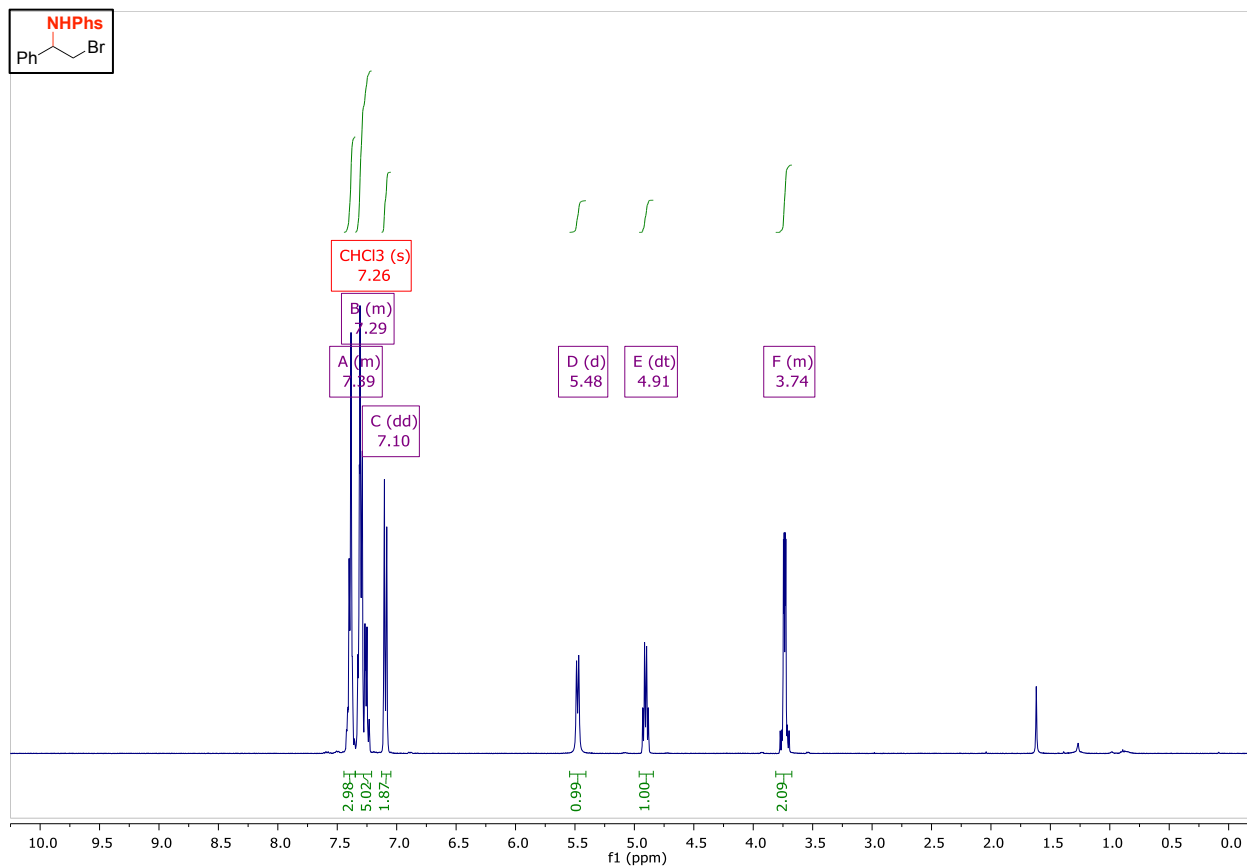
**2a-1: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)**



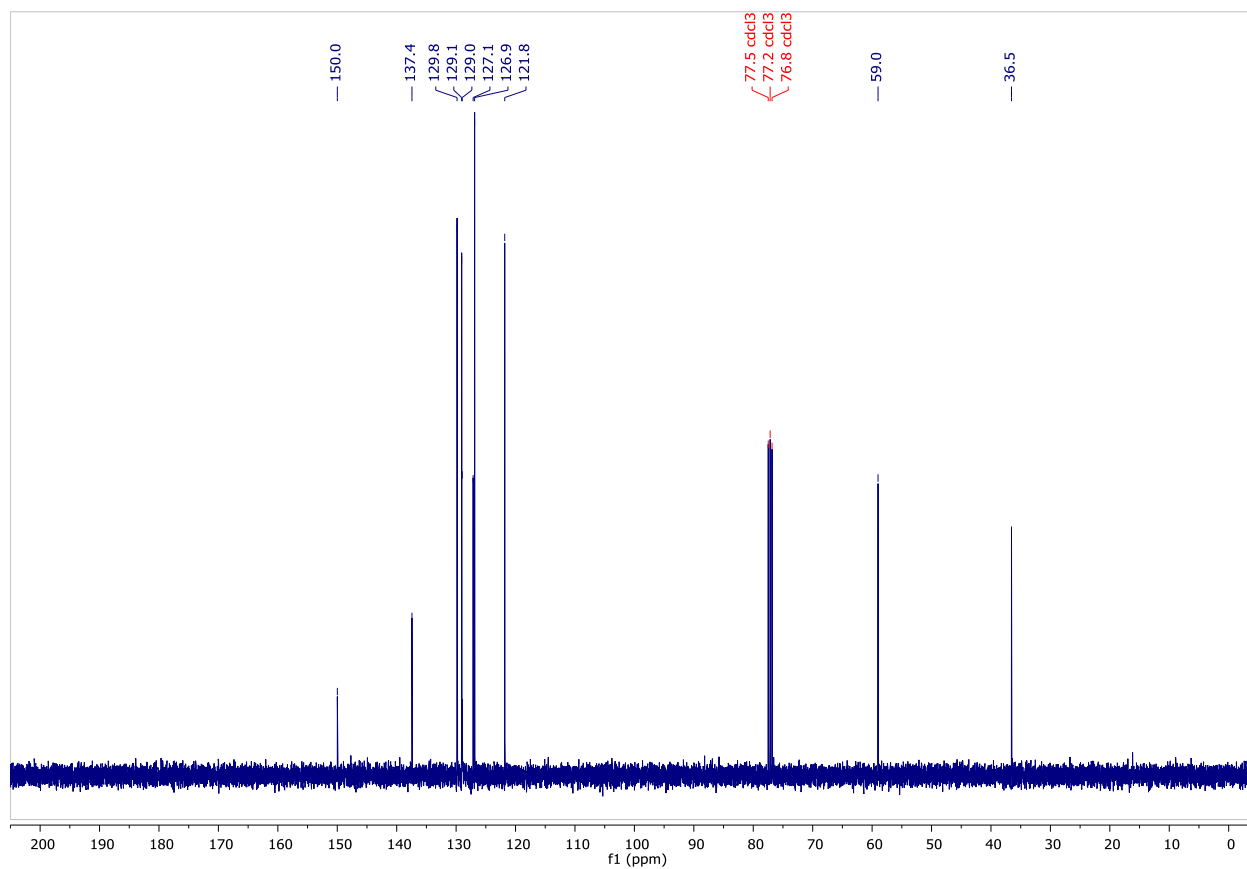
**2a-2:  $^1\text{H}$  NMR (400 MHz, Chloroform- $d$ )**



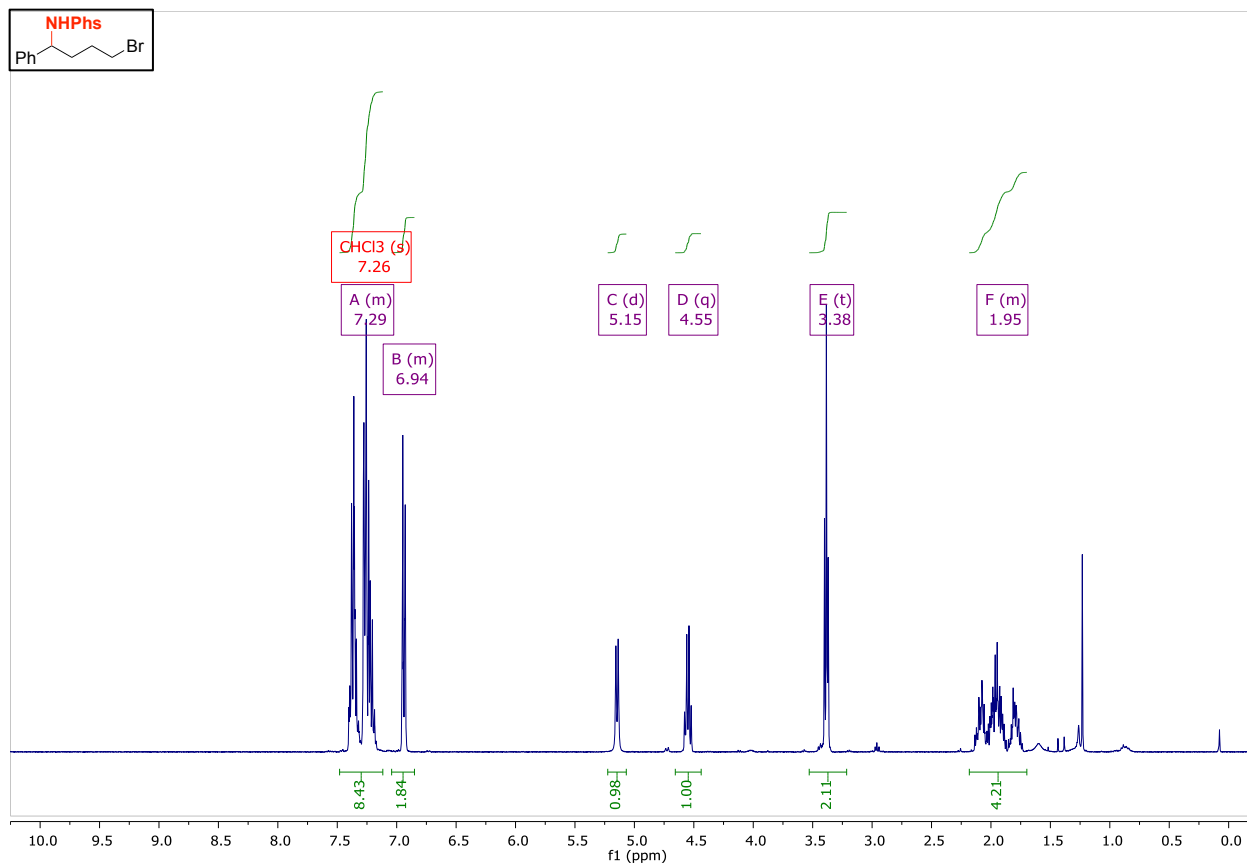
**2a-2:  $^{13}\text{C}$  NMR (101 MHz, Chloroform- $d$ )**



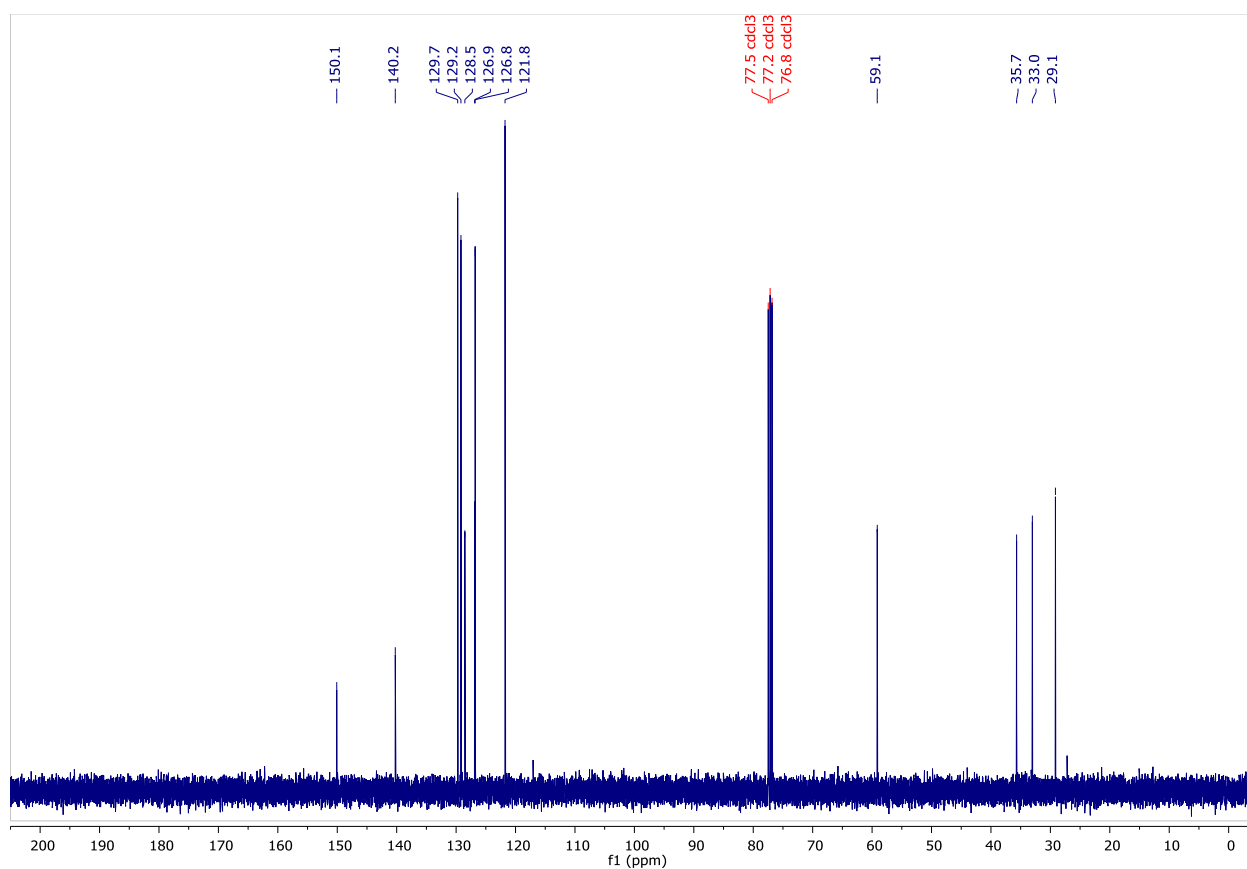
**2b: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)**



**2b: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)**

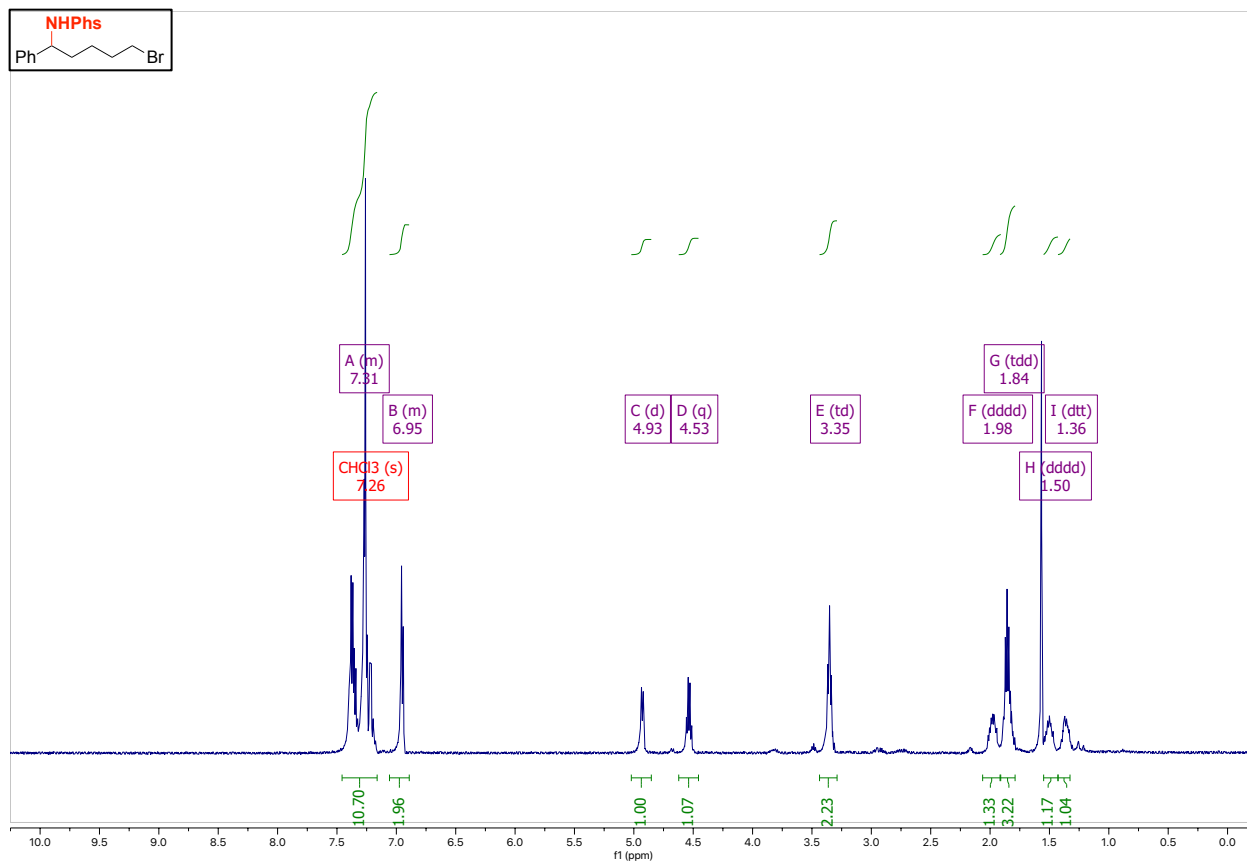


**2c: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)**

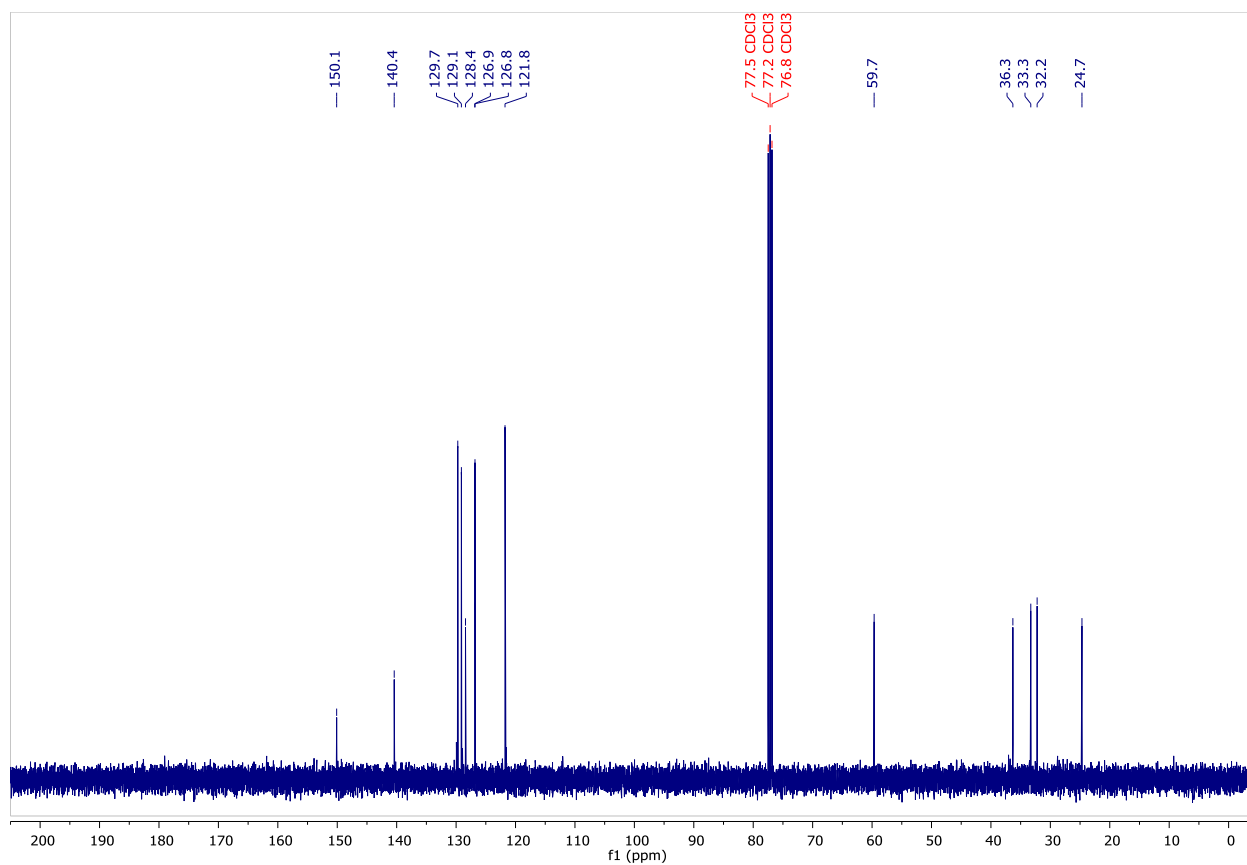


**2c: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)**

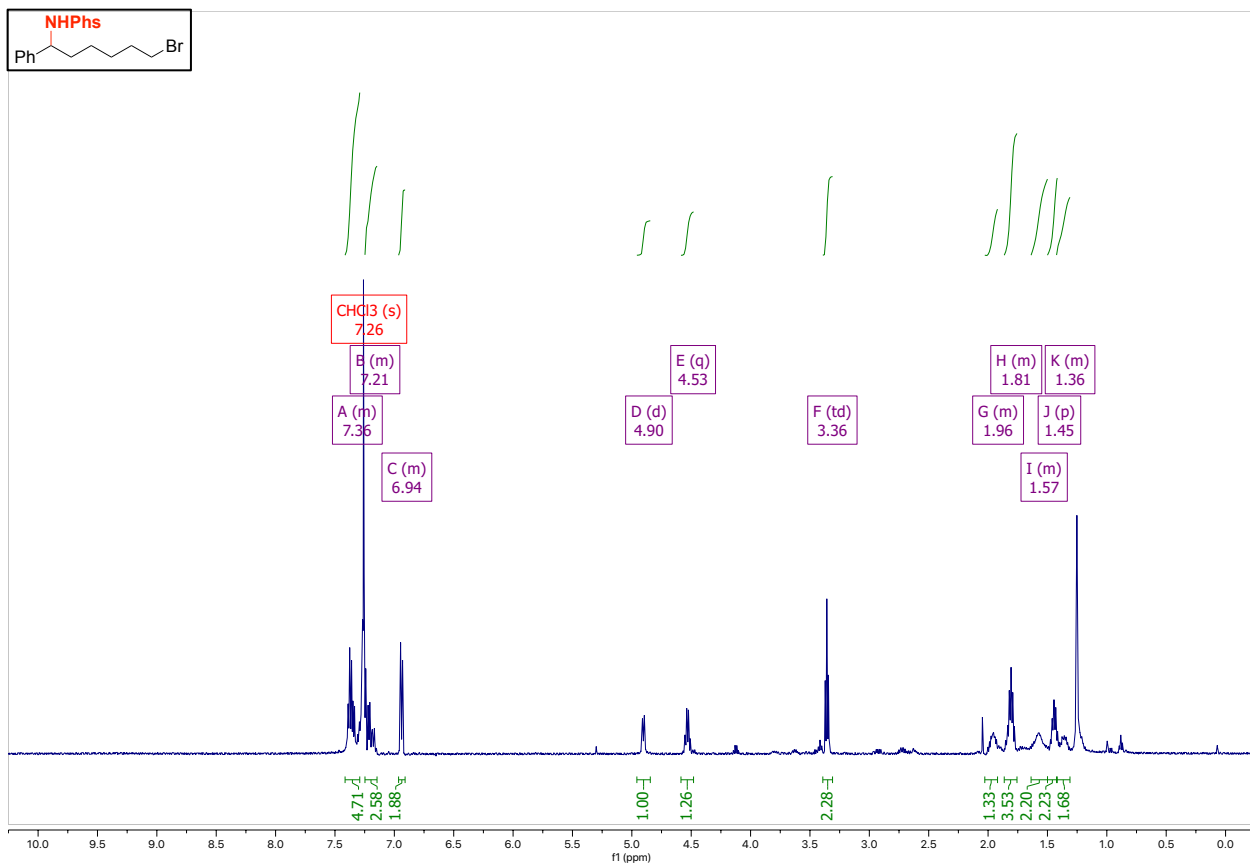




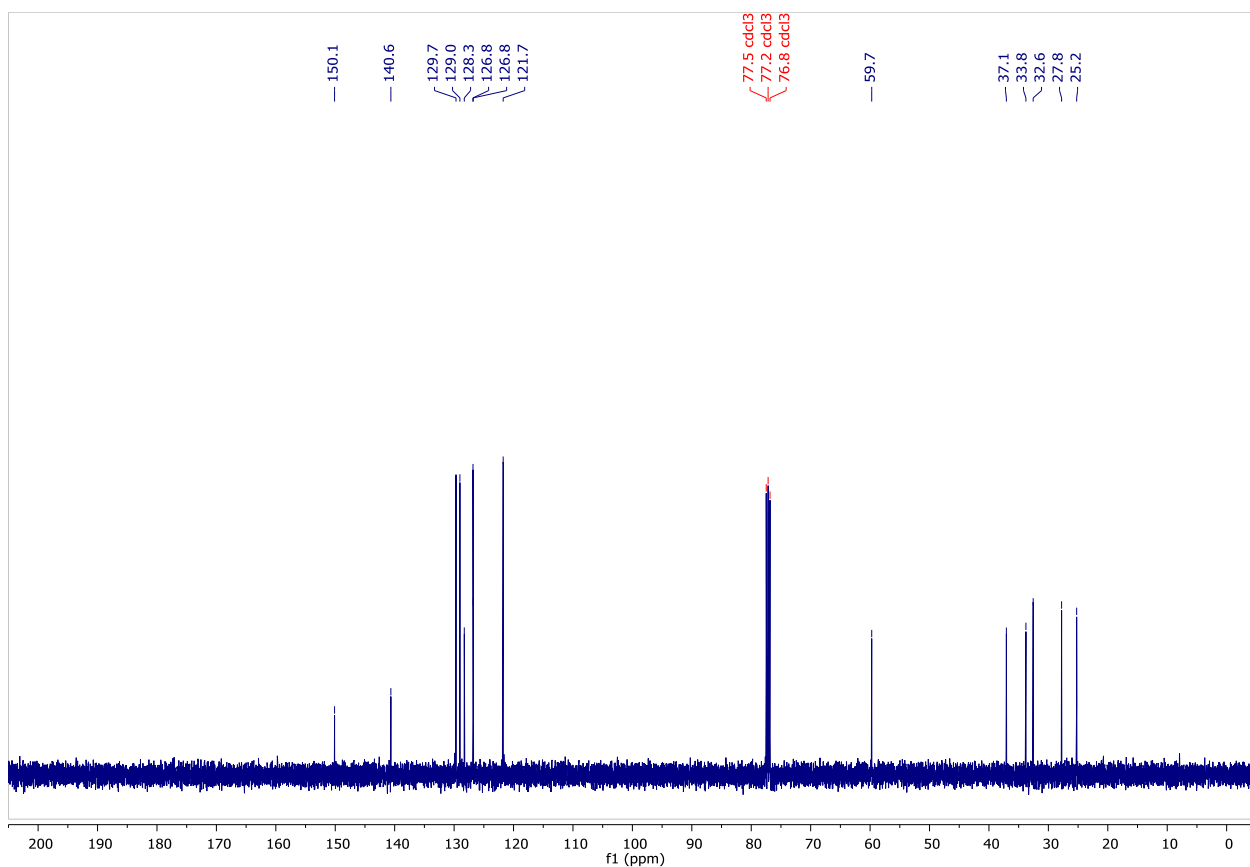
**2d: <sup>1</sup>H NMR (500 MHz, Chloroform-*d*)**



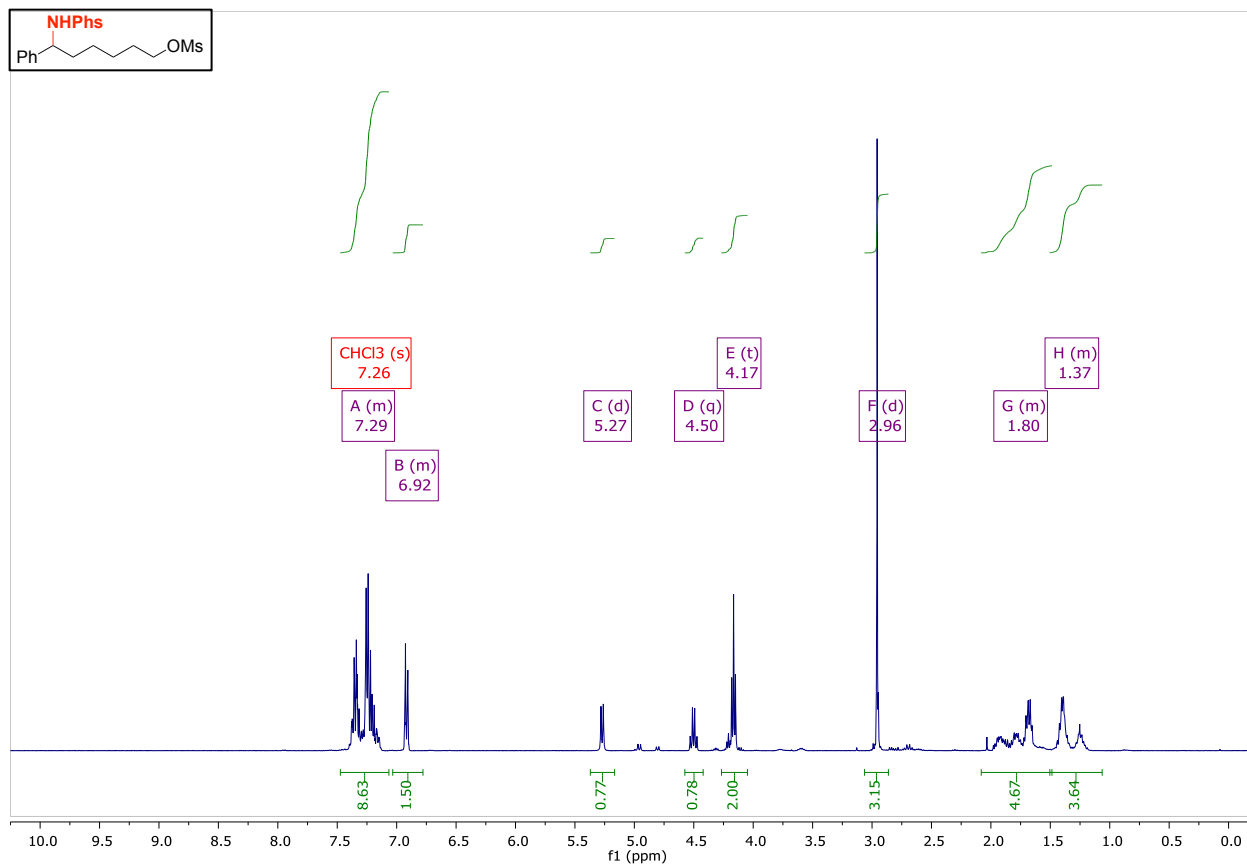
**2d: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)**



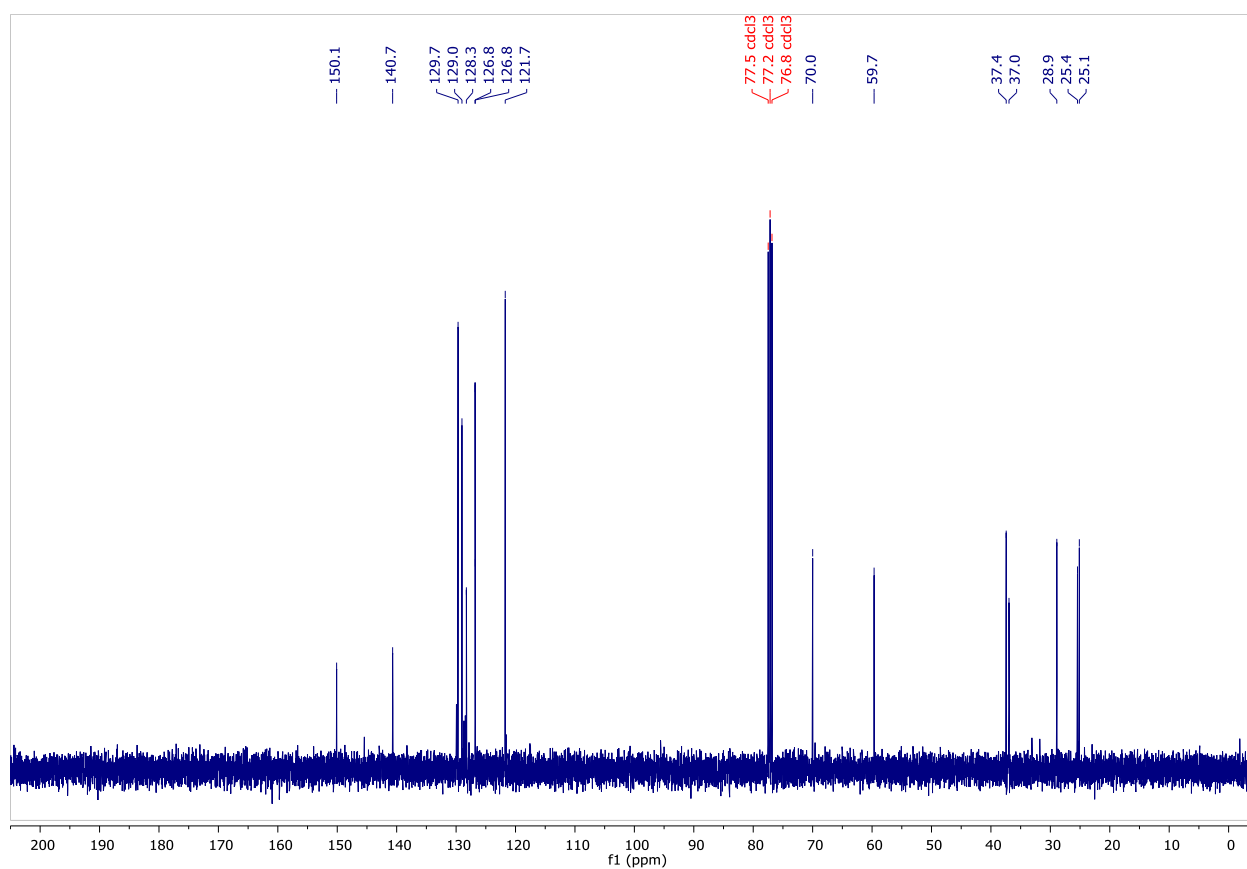
**2e-1: <sup>1</sup>H NMR (500 MHz, Chloroform-*d*)**



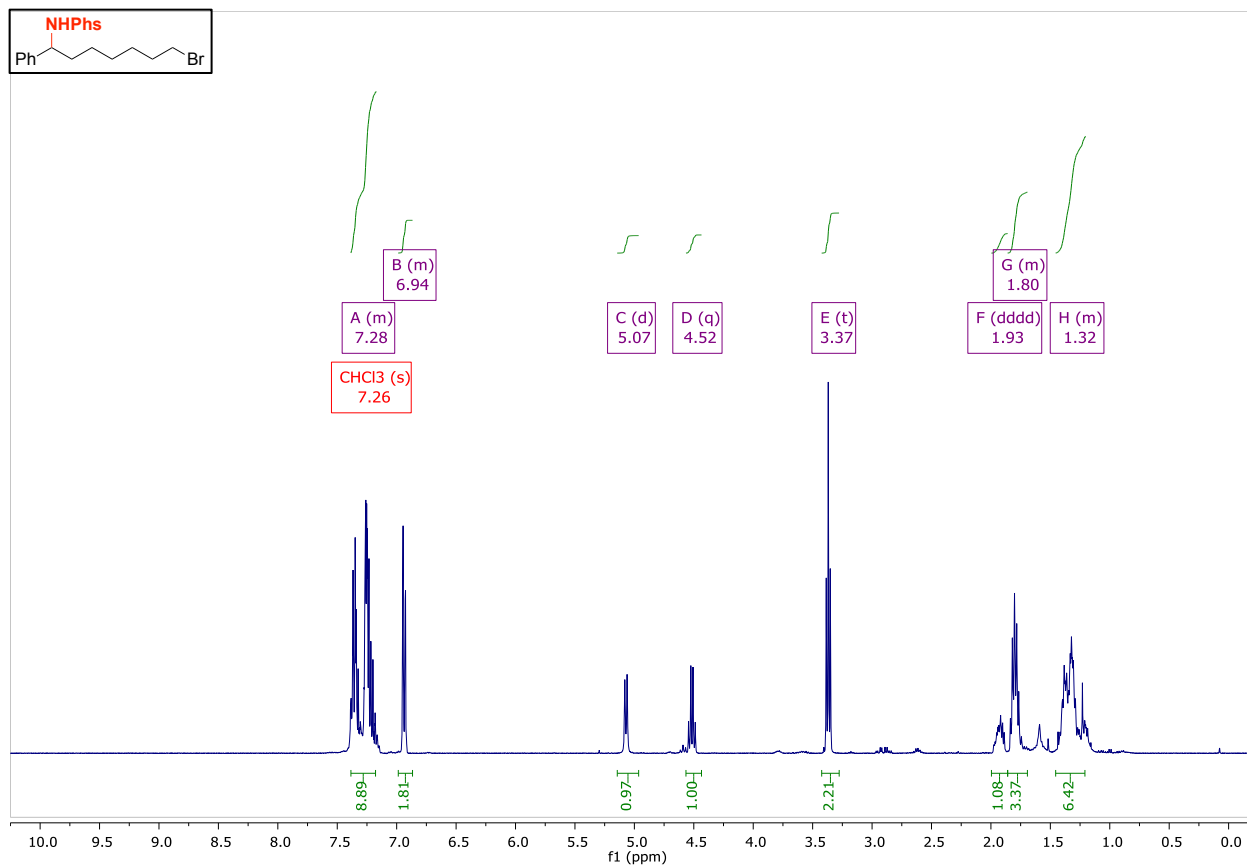
**2e-1: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)**



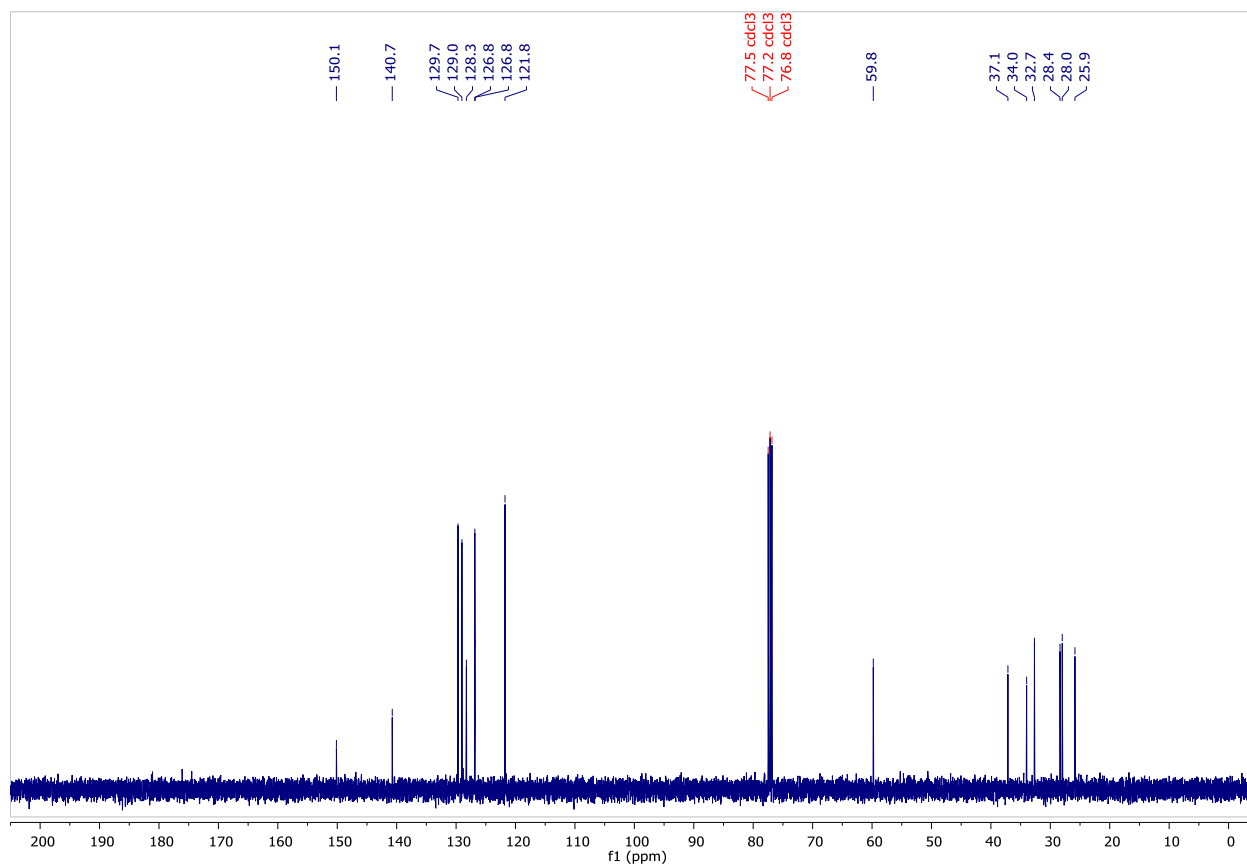
**2e-2: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)**



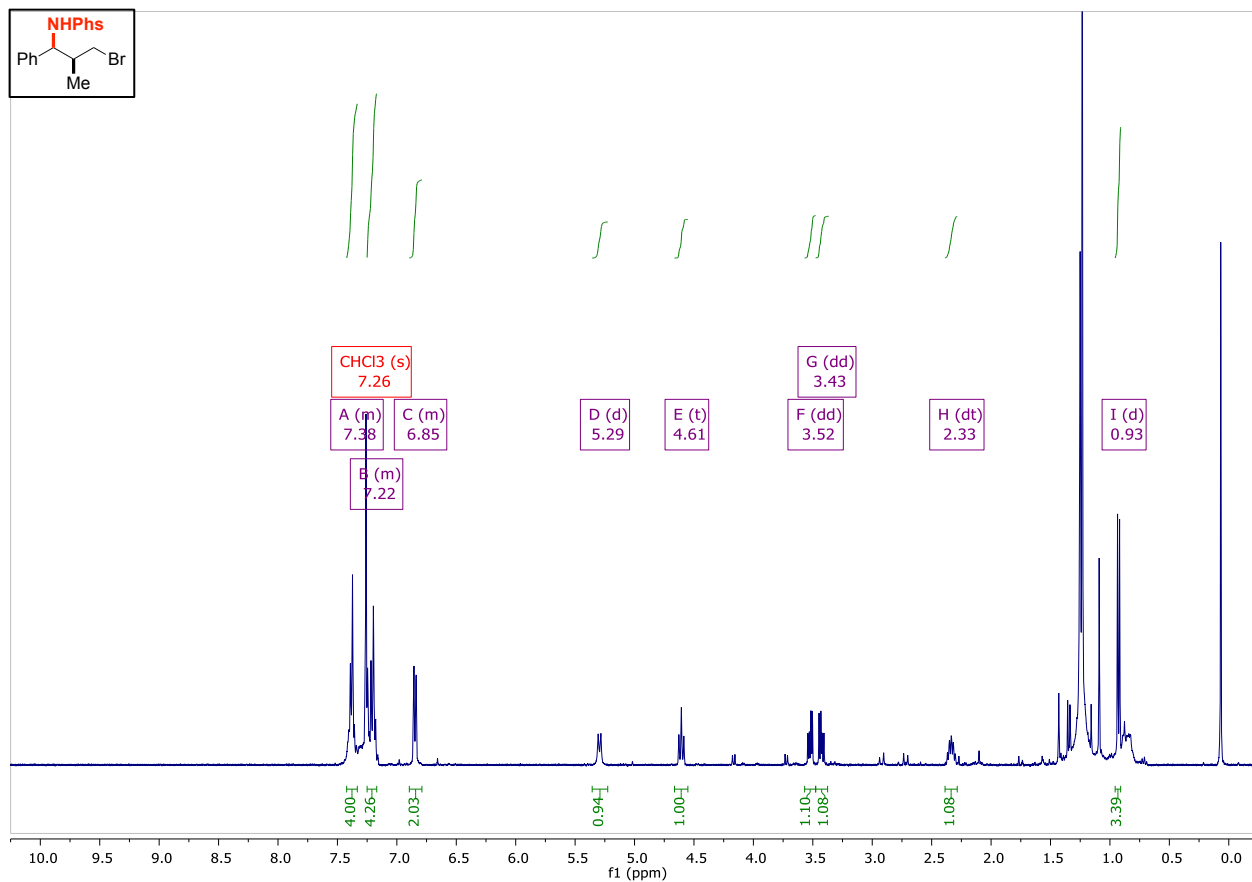
**2e-2: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)**



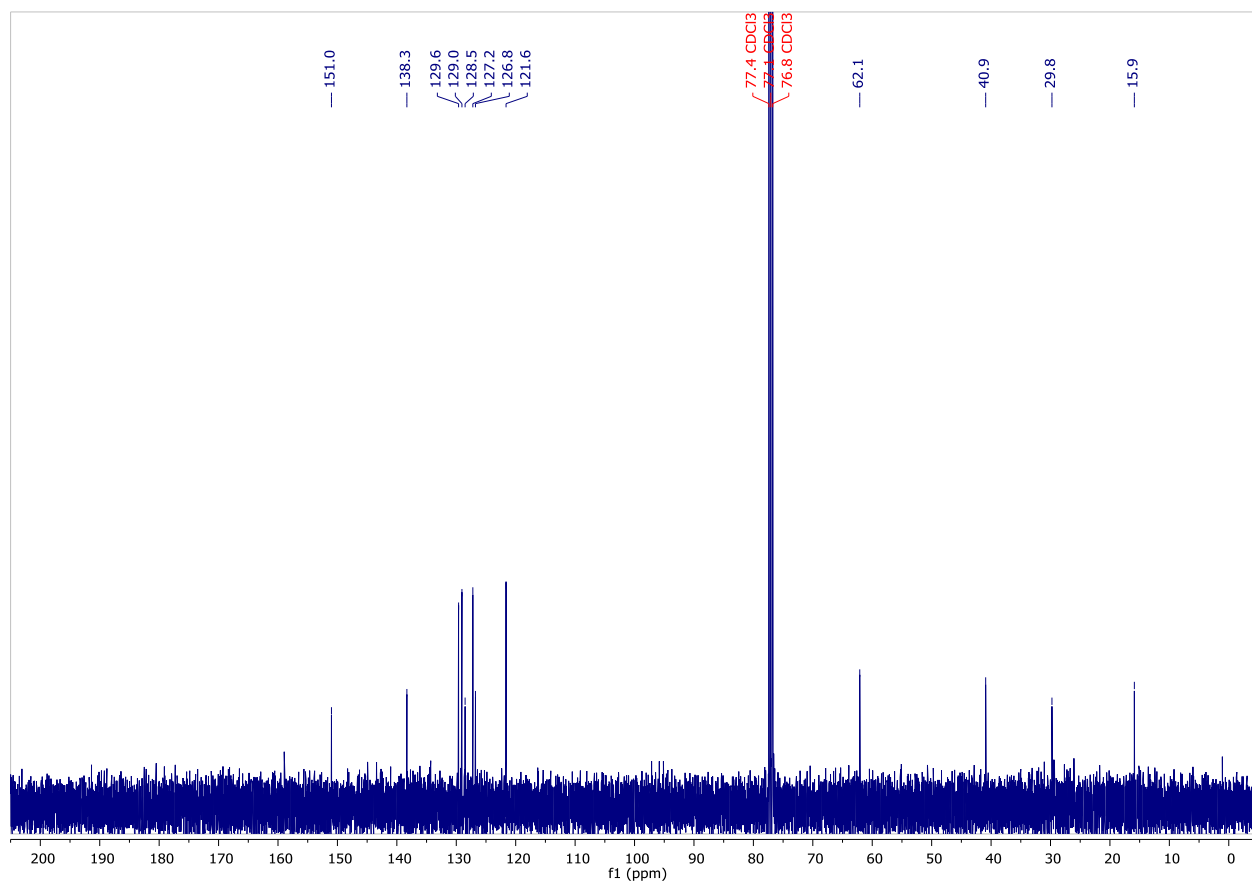
**2f: <sup>1</sup>H NMR (400 MHz, Chloroform-d)**



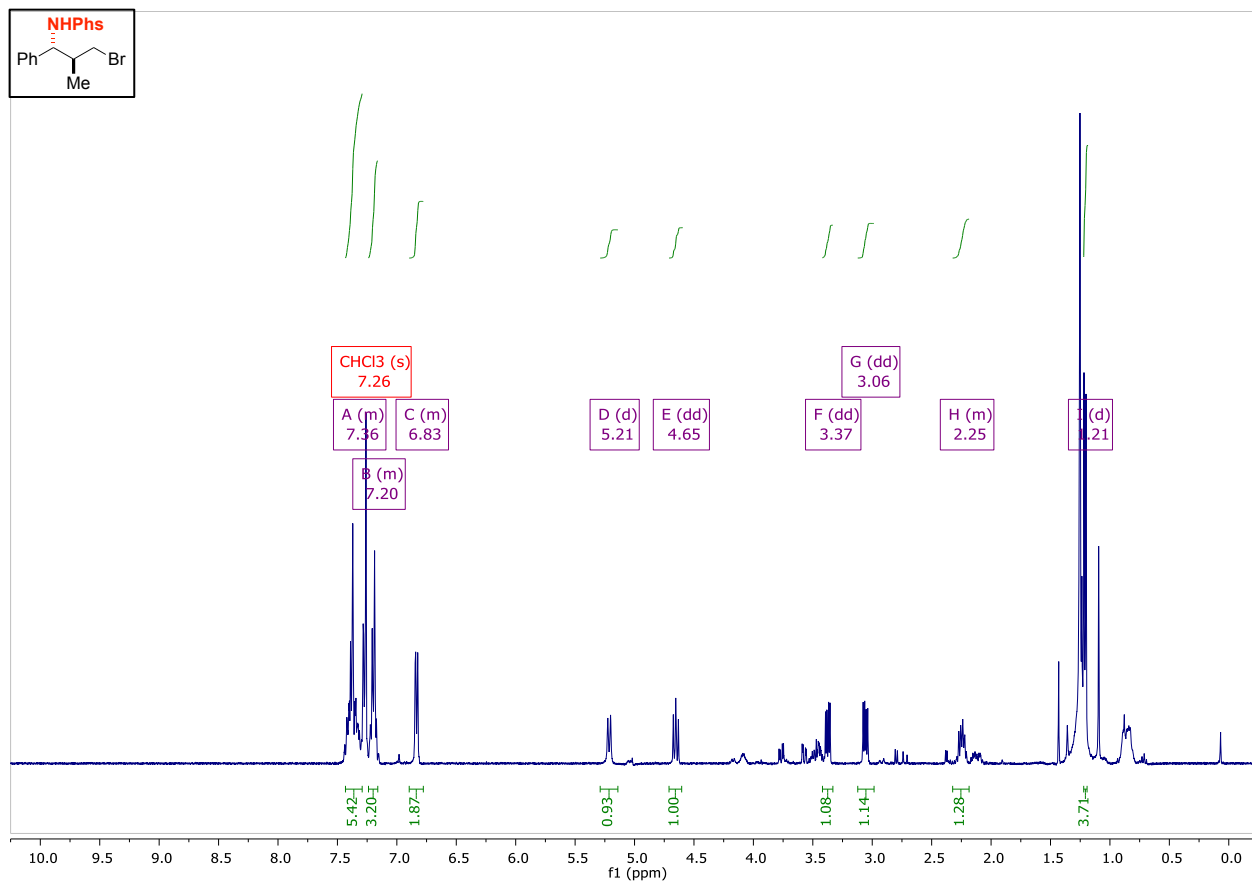
**2f: <sup>13</sup>C NMR (101 MHz, Chloroform-d)**



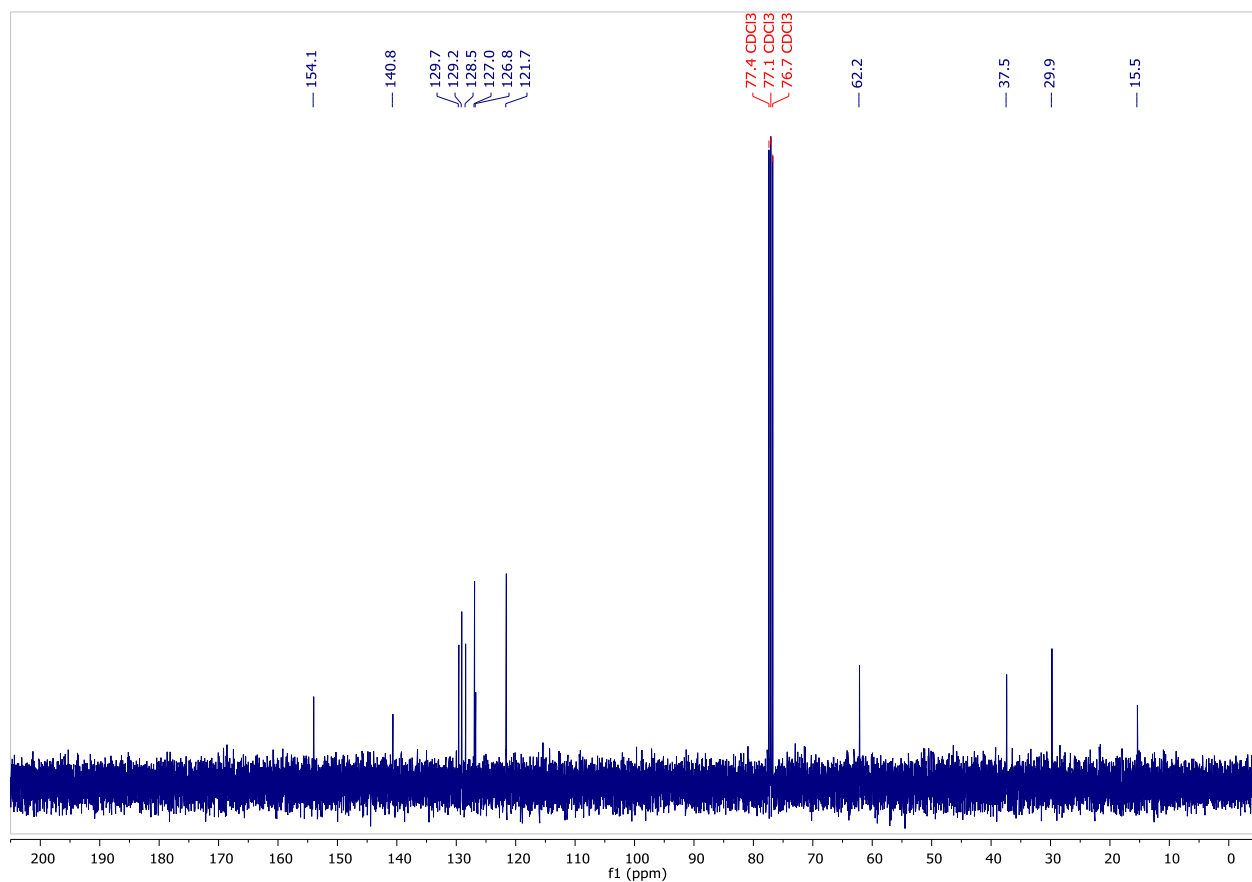
**2g-syn: <sup>1</sup>H NMR (400 MHz, Chloroform-d)**



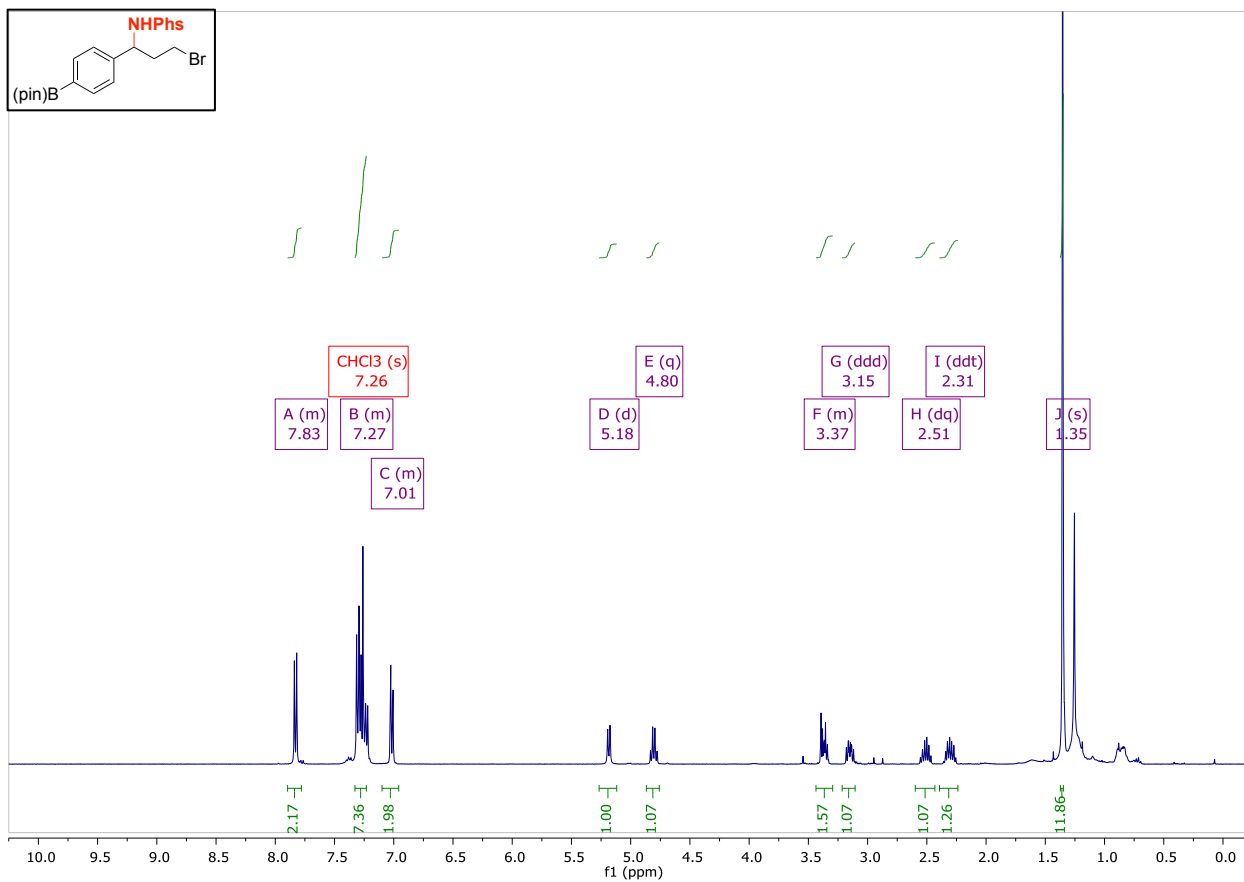
**2g-syn: <sup>13</sup>C NMR (101 MHz, Chloroform-d)**



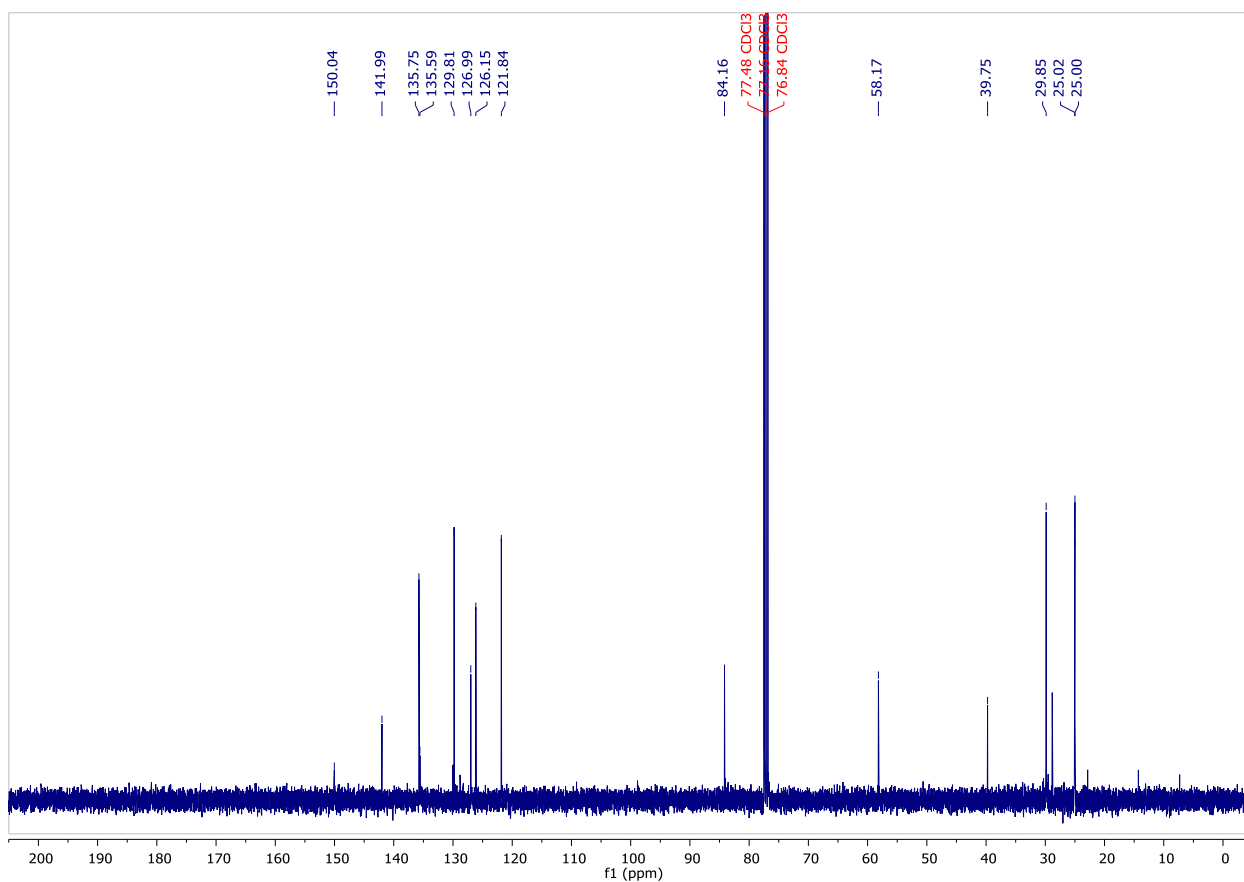
**2g-anti: <sup>1</sup>H NMR (400 MHz, Chloroform-d)**



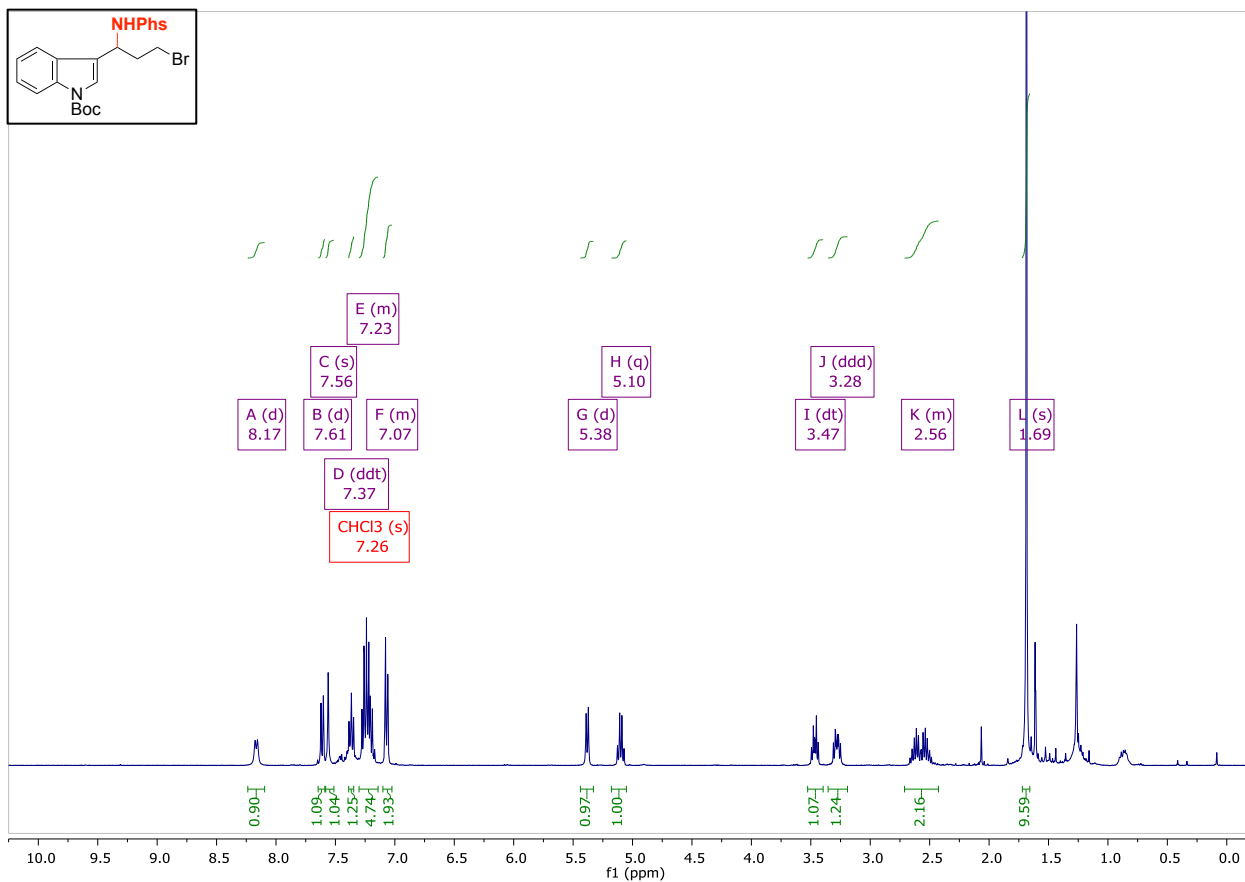
**2g-anti: <sup>13</sup>C NMR (101 MHz, Chloroform-d)**



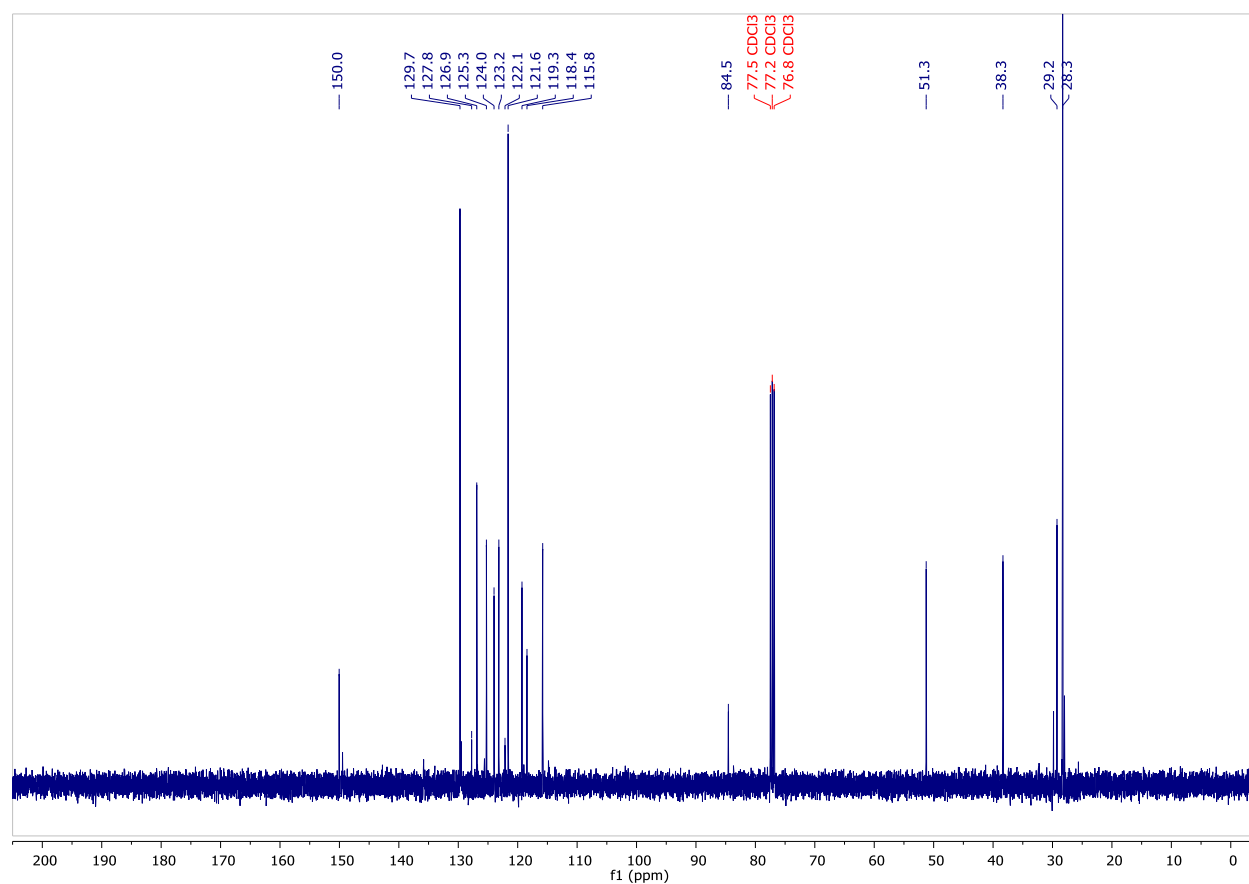
2h:  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)



2h:  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)

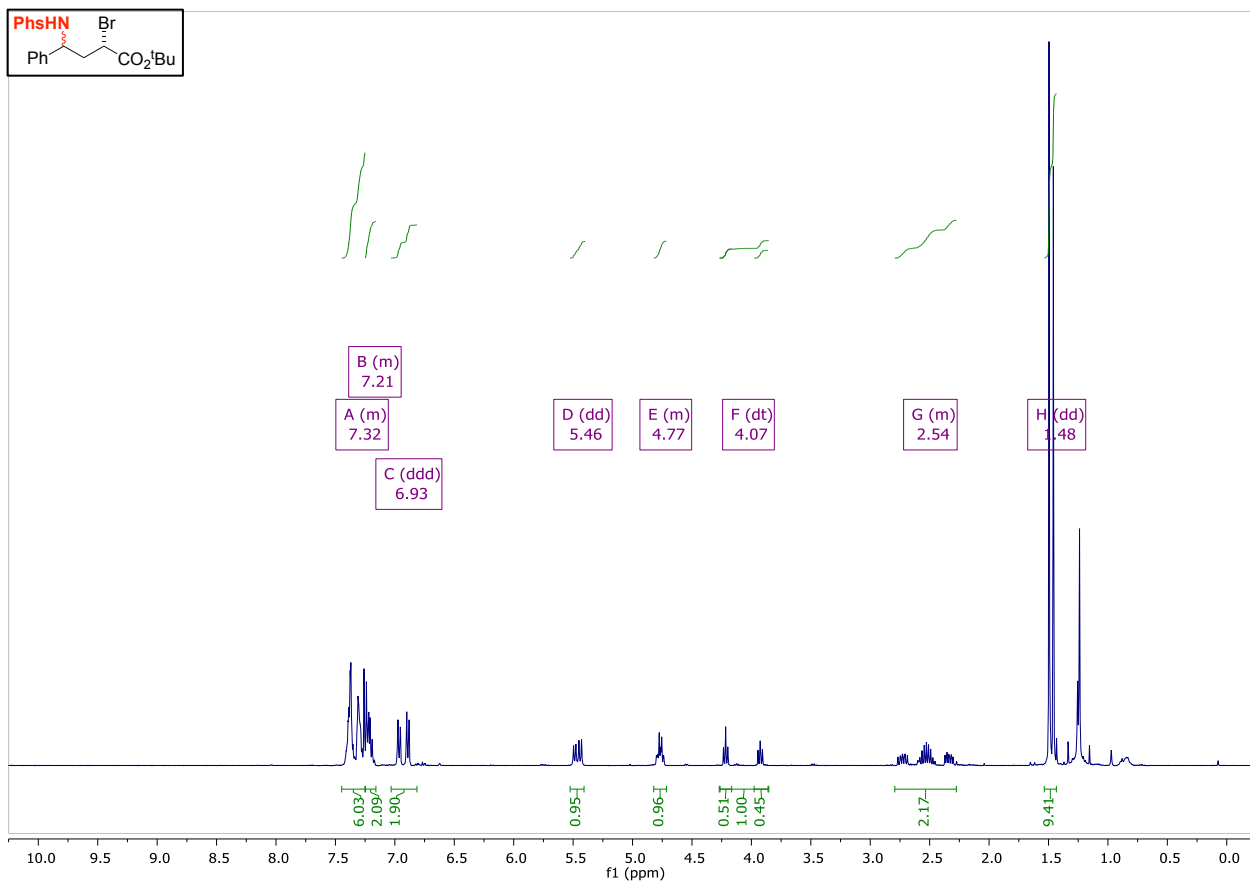


**2i: <sup>1</sup>H NMR (400 MHz, Chloroform-d)**

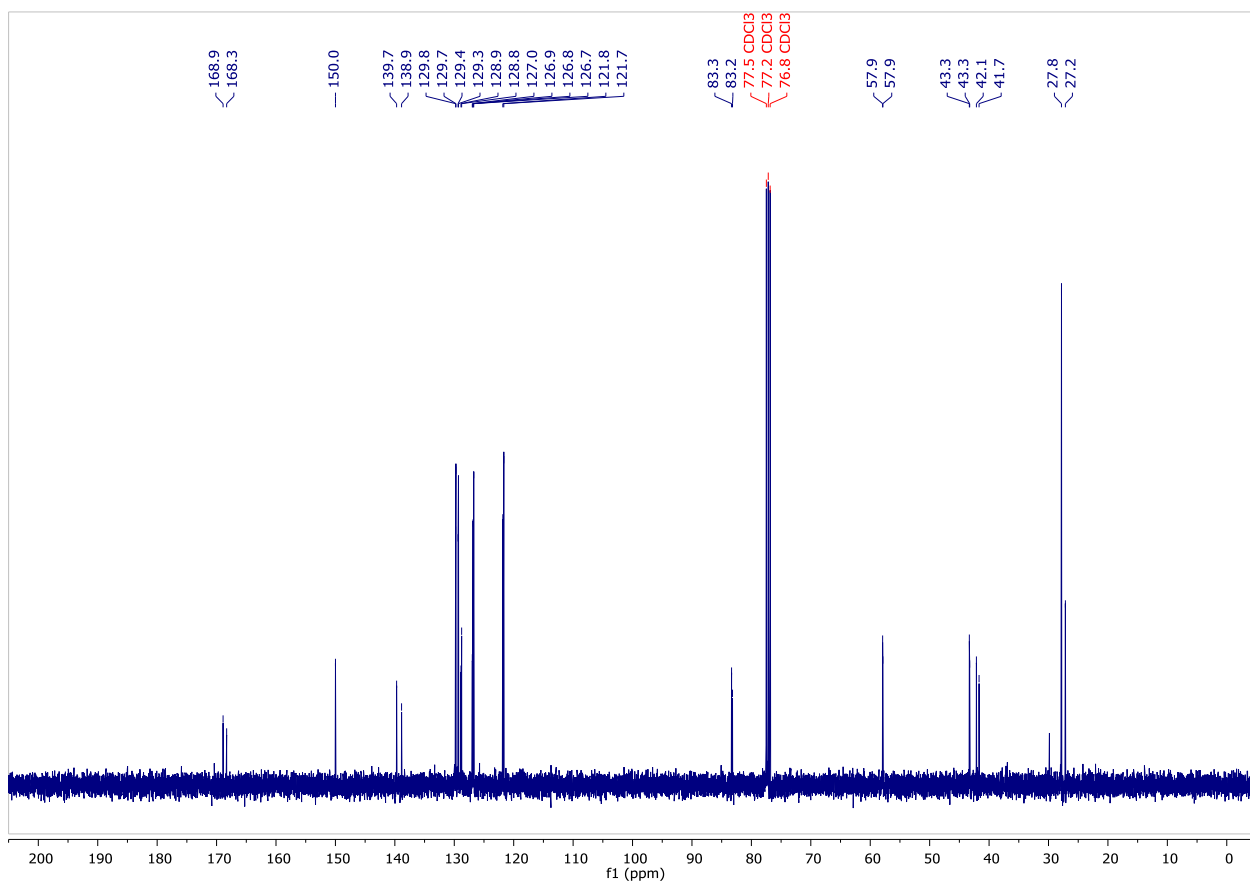


**2i: <sup>13</sup>C NMR (101 MHz, Chloroform-d)**

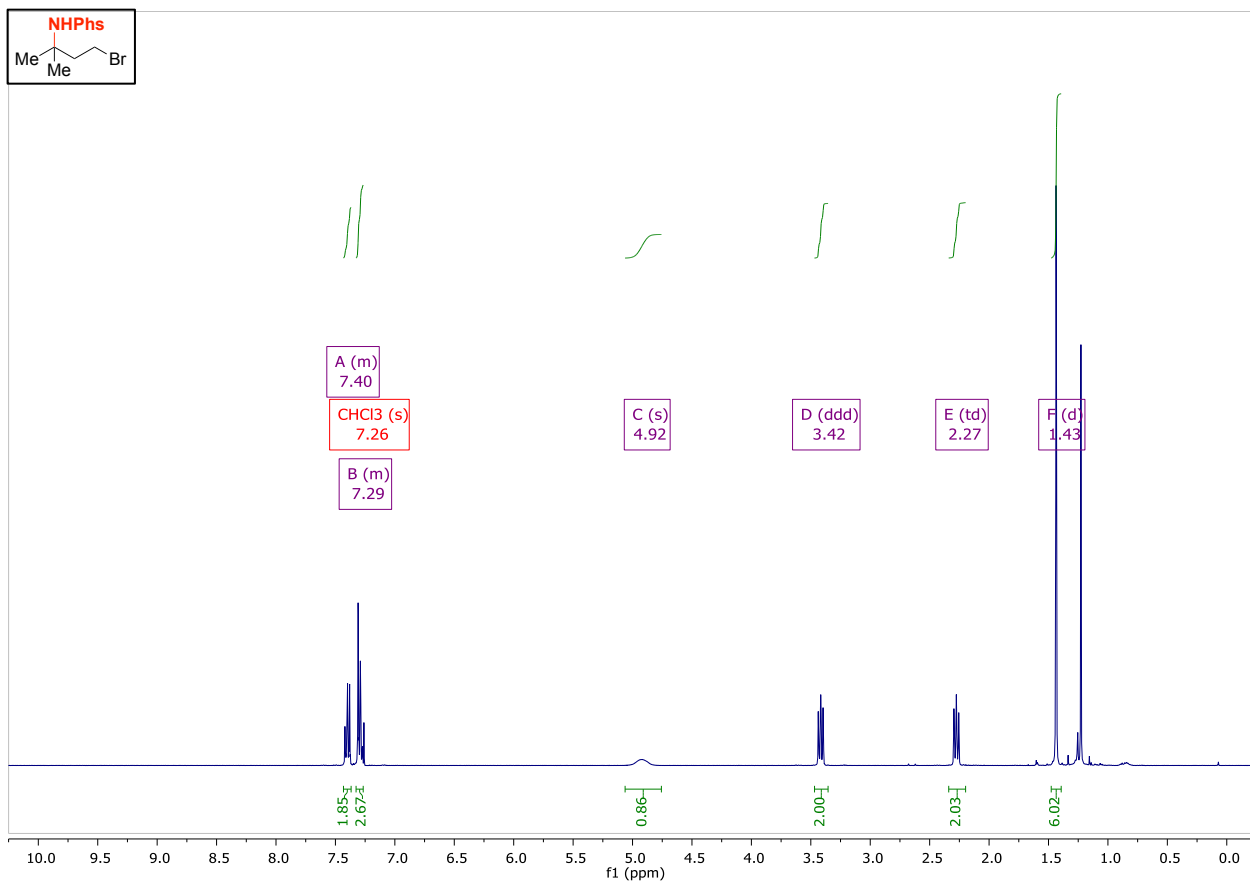




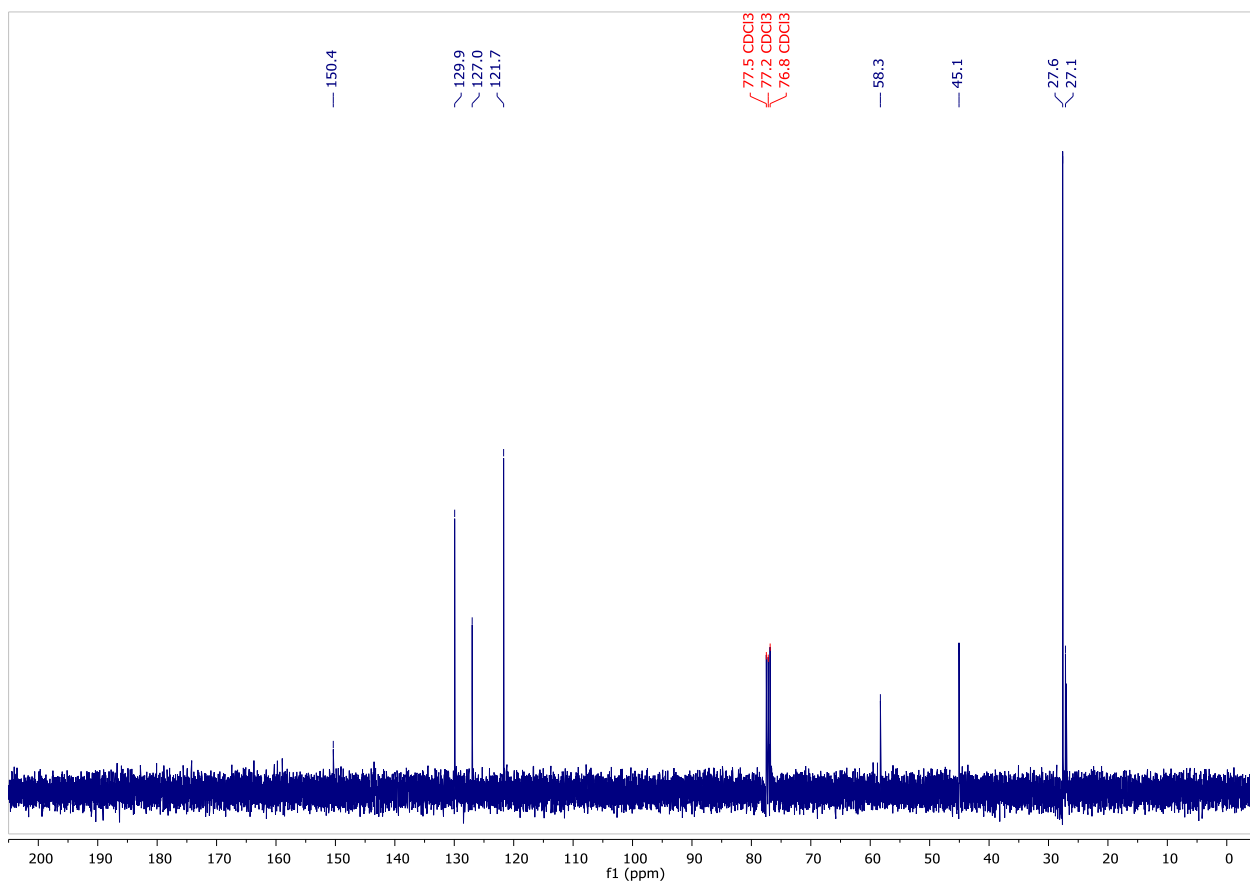
**2j (mixture of diastereomers):  $^1\text{H}$  NMR (400 MHz, Chloroform-*d*)**



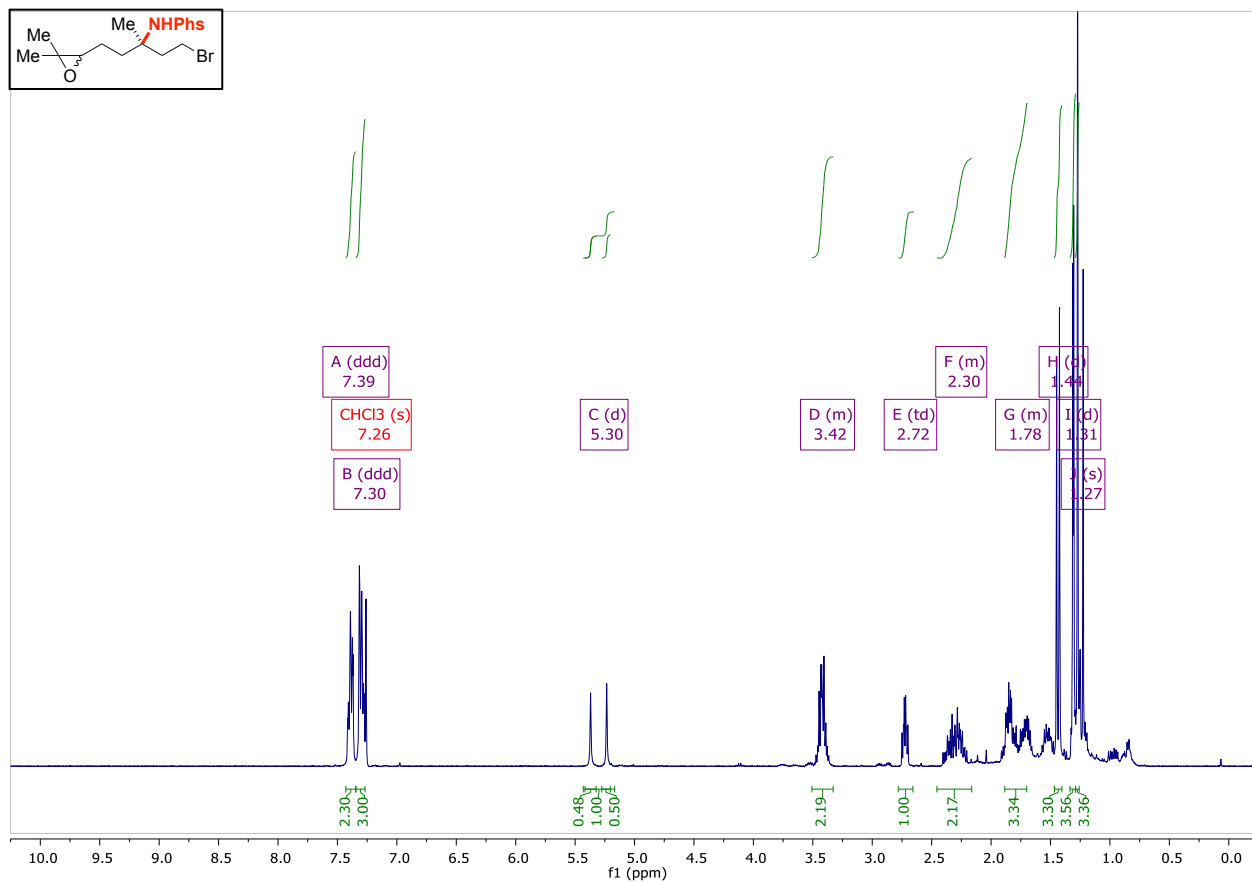
**2j (mixture of diastereomers):  $^{13}\text{C}$  NMR (101 MHz, Chloroform-*d*)**



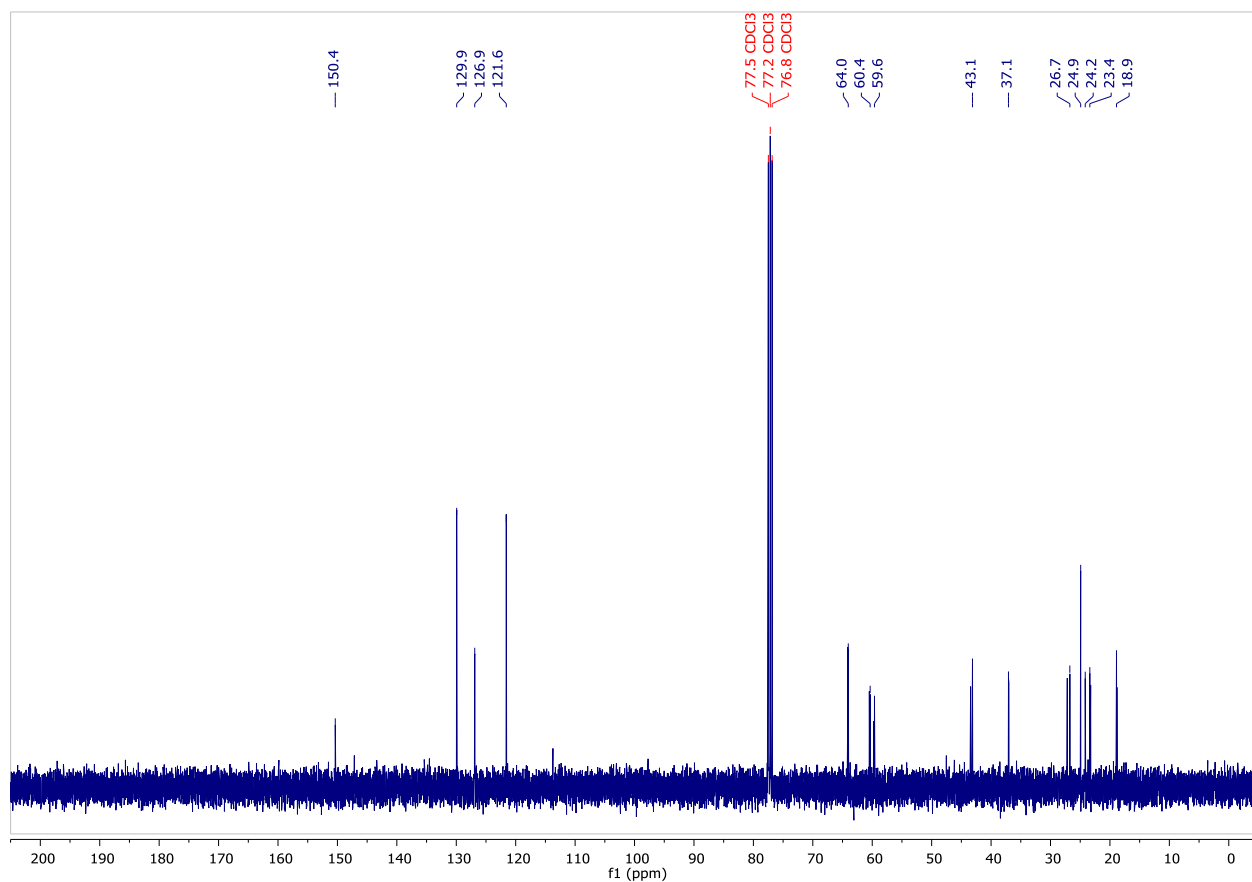
**2k: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)**



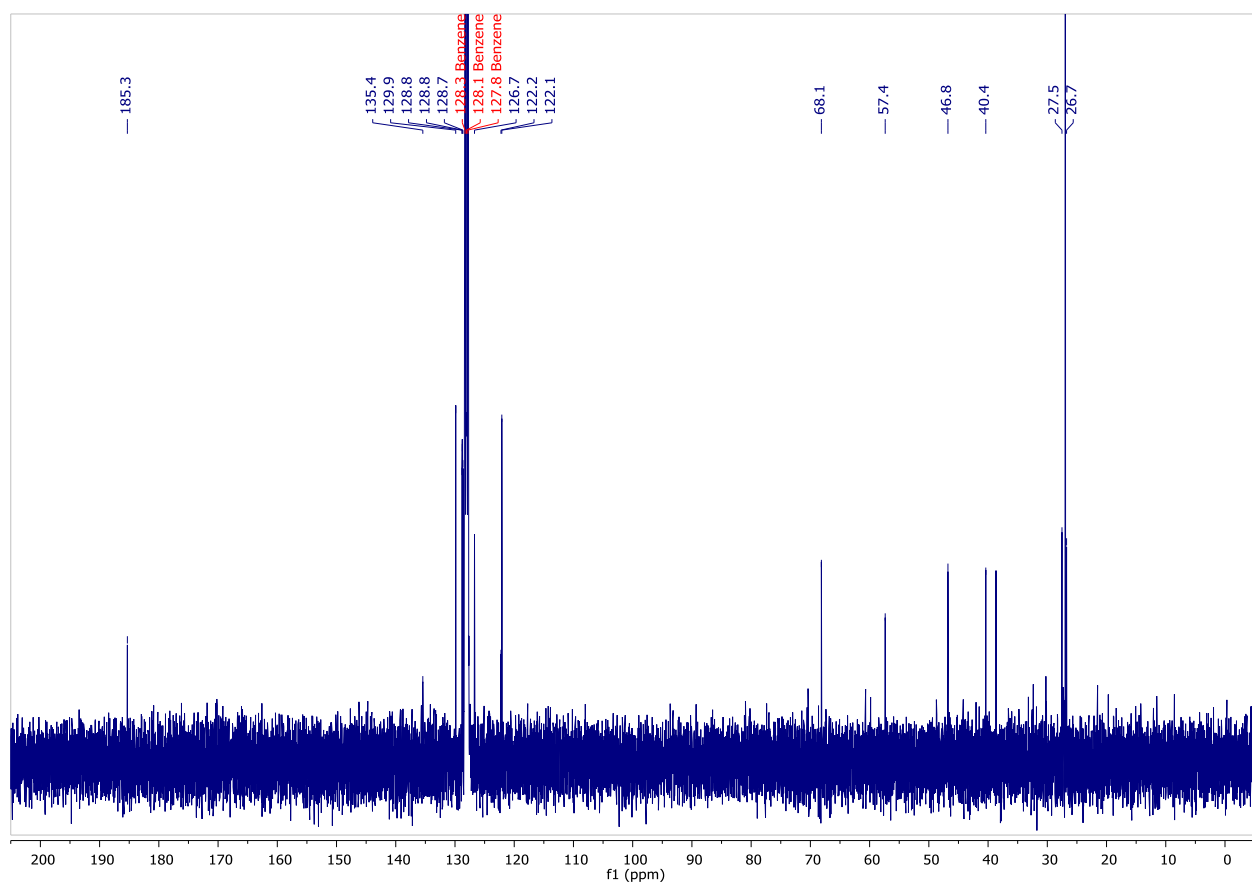
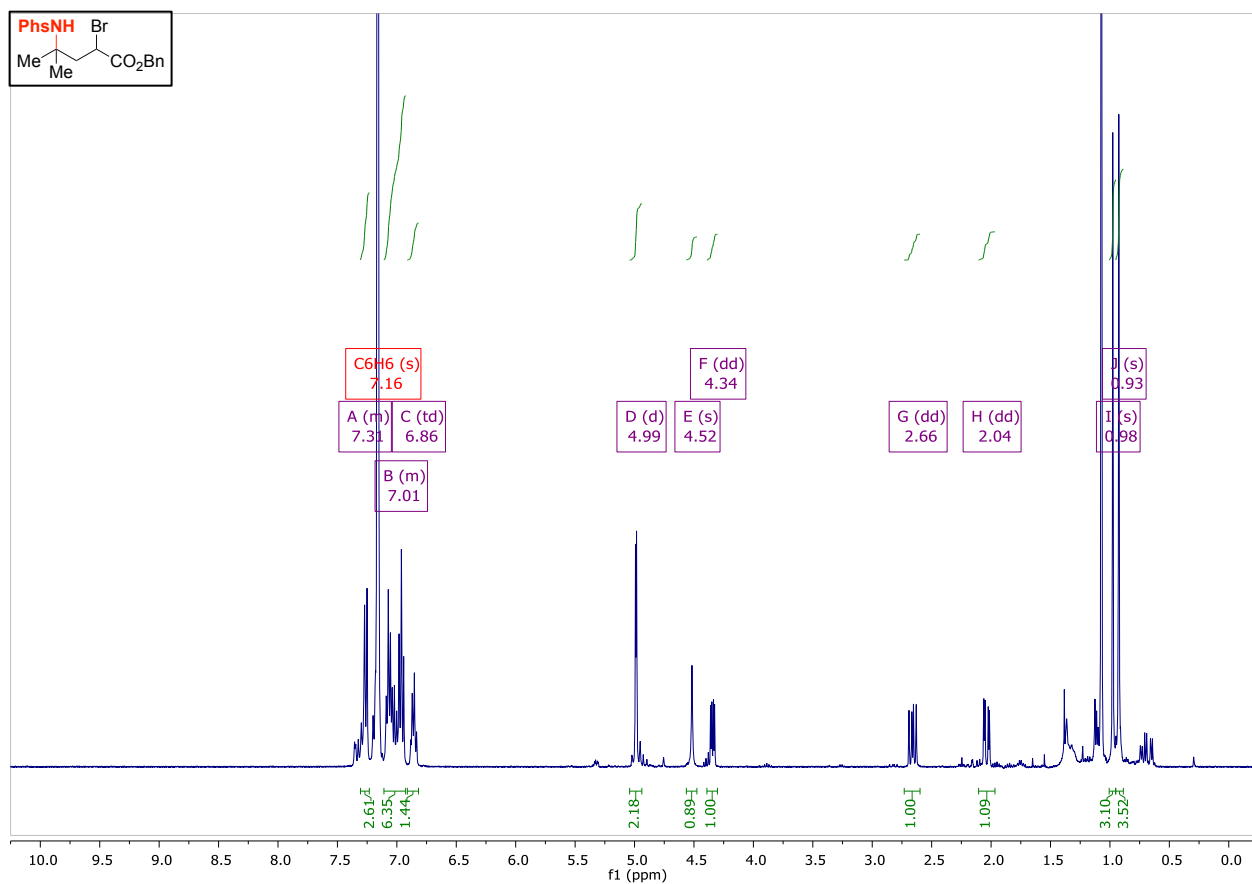
**2k: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)**

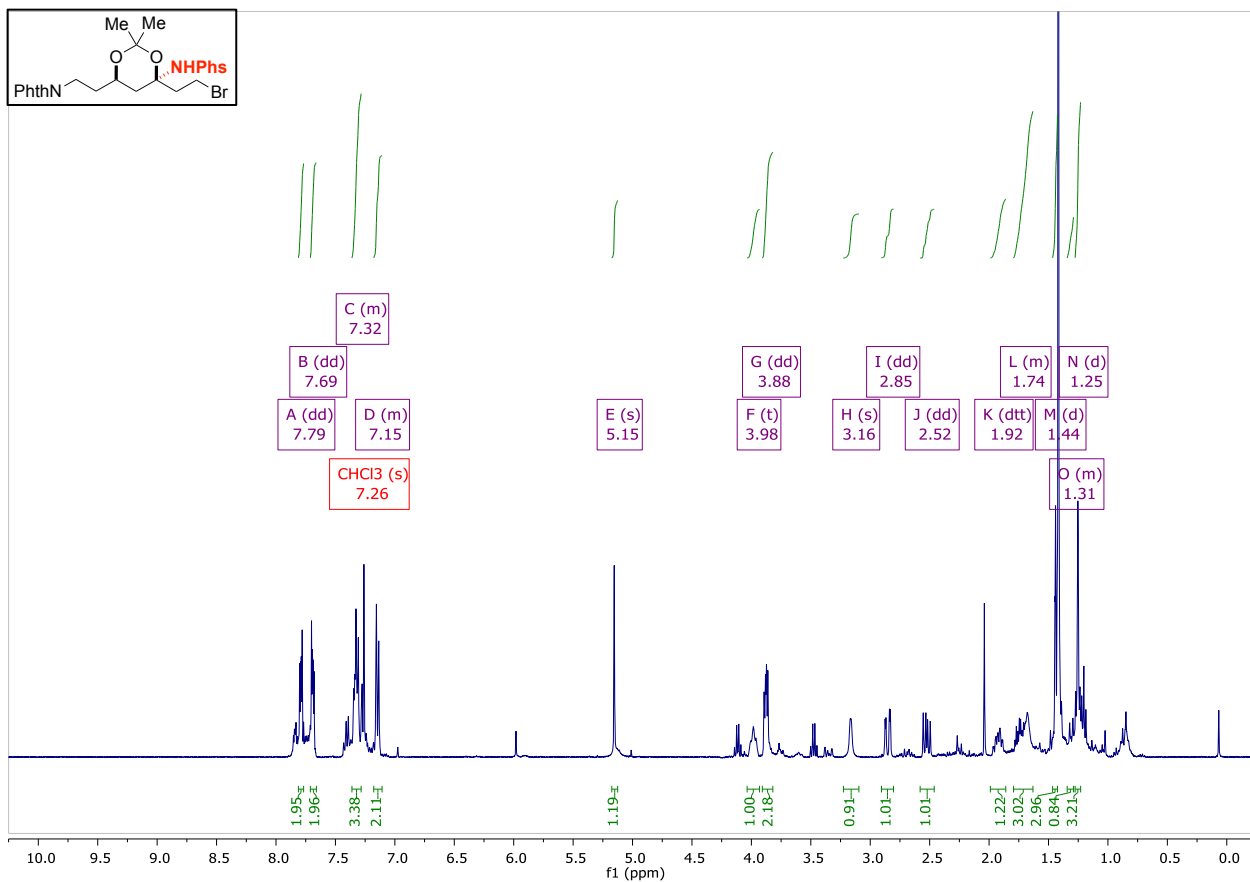


**2I (mixture of diastereomers): <sup>1</sup>H NMR (400 MHz, Chloroform-d)**

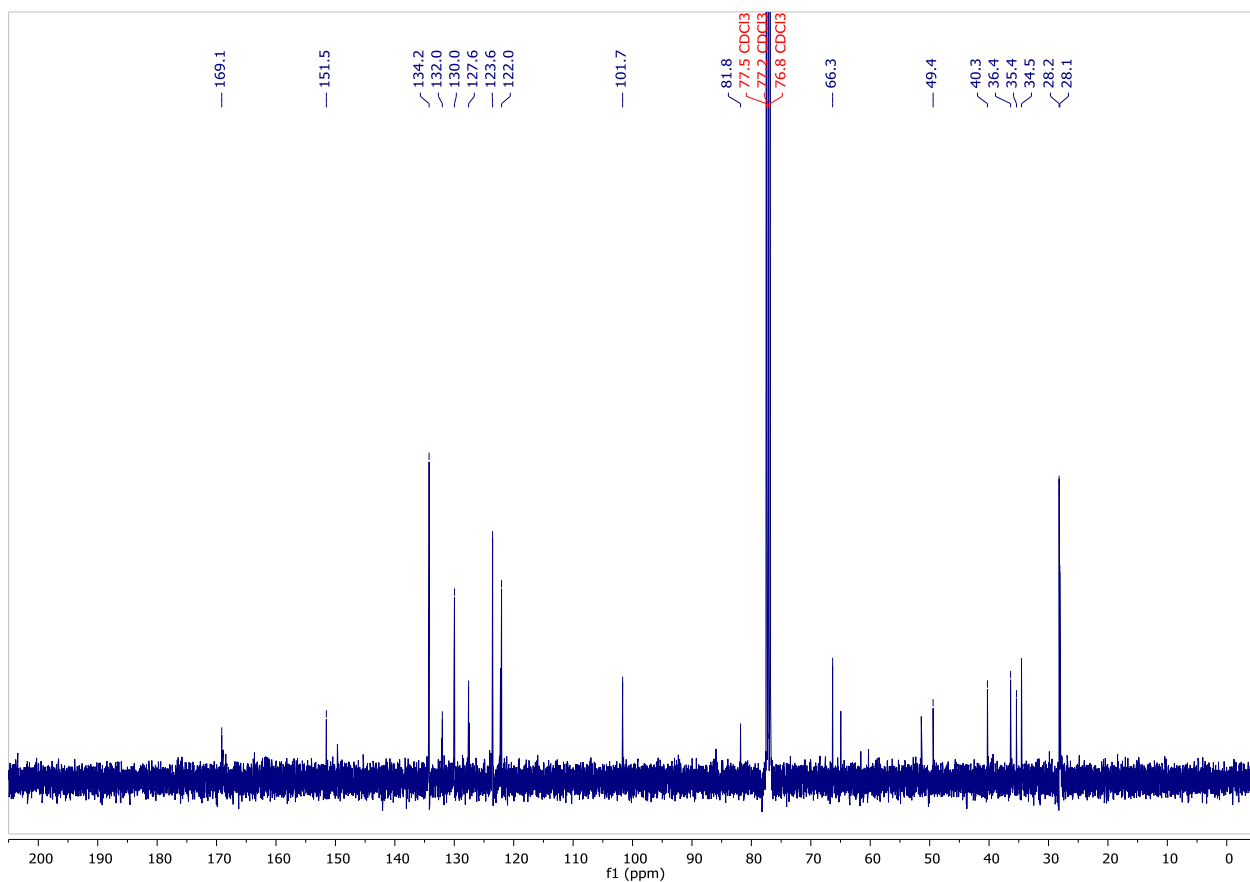


**2I (mixture of diastereomers): <sup>13</sup>C NMR (101 MHz, Chloroform-d)**

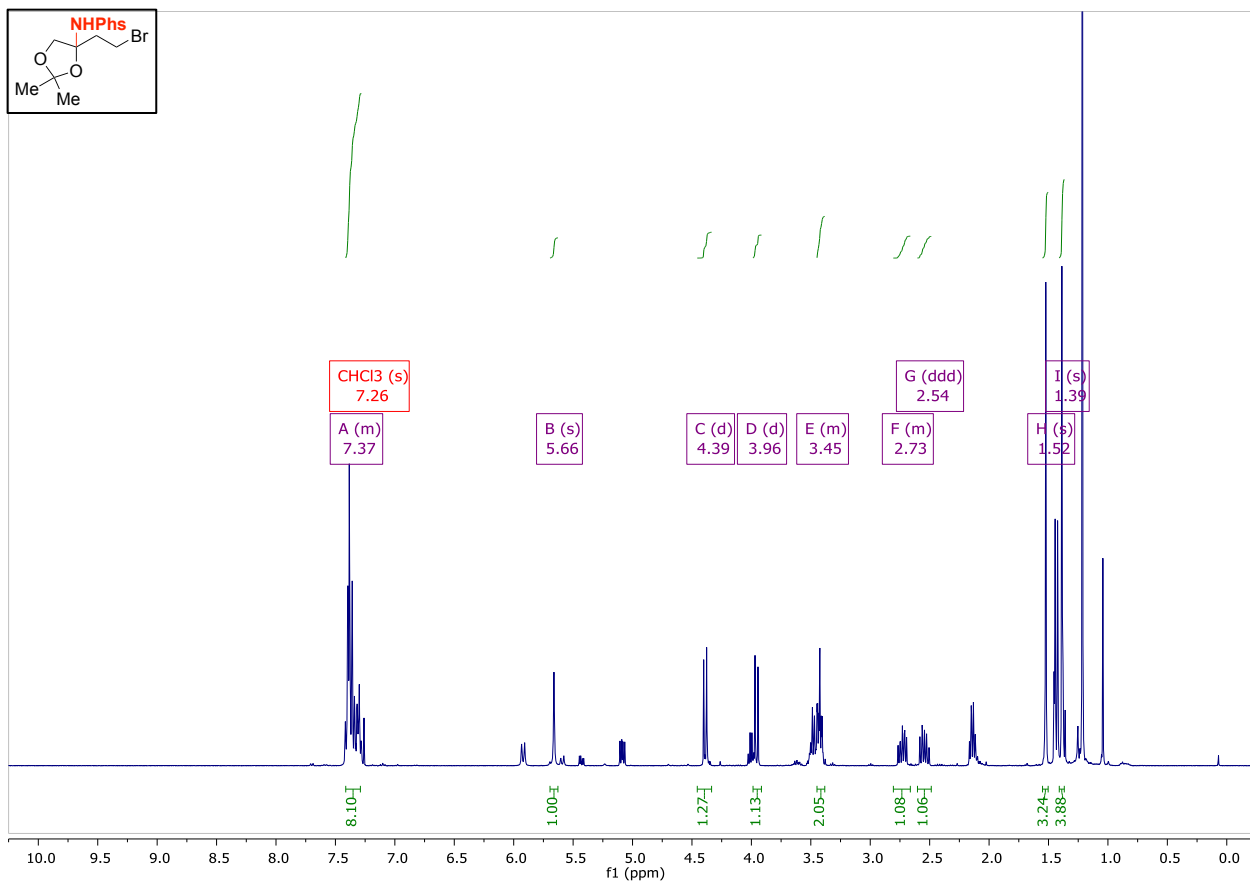




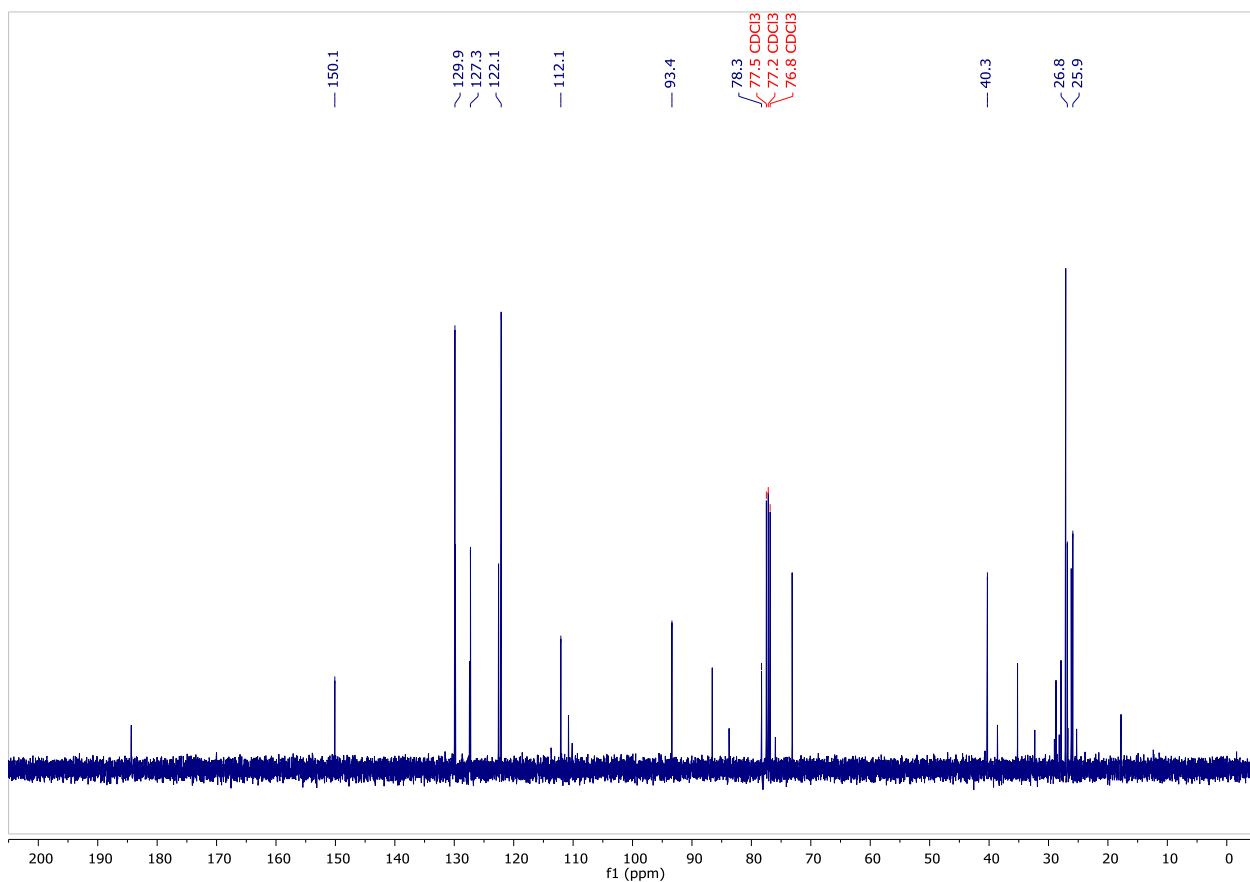
2n: <sup>1</sup>H NMR (400 MHz, Chloroform-d)



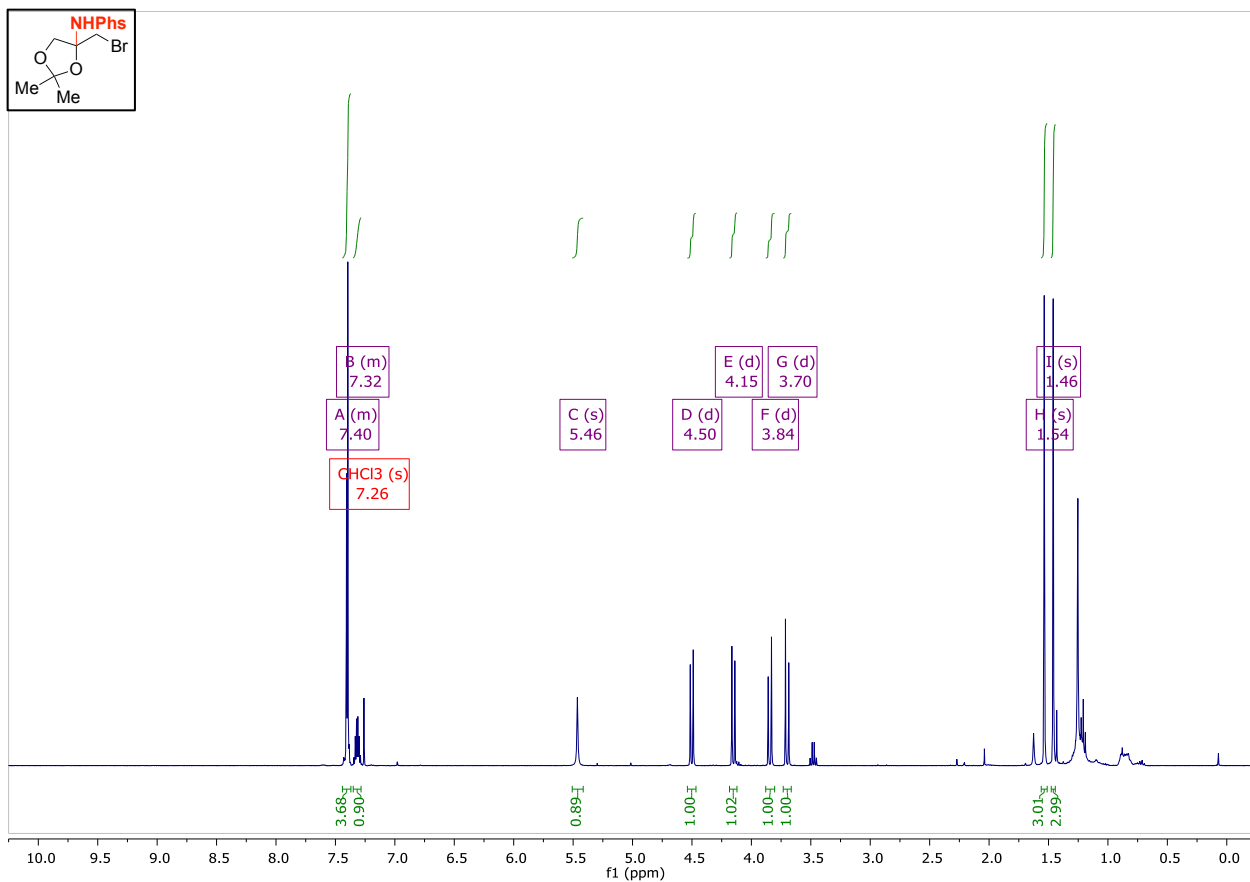
2n: <sup>13</sup>C NMR (101 MHz, Chloroform-d)



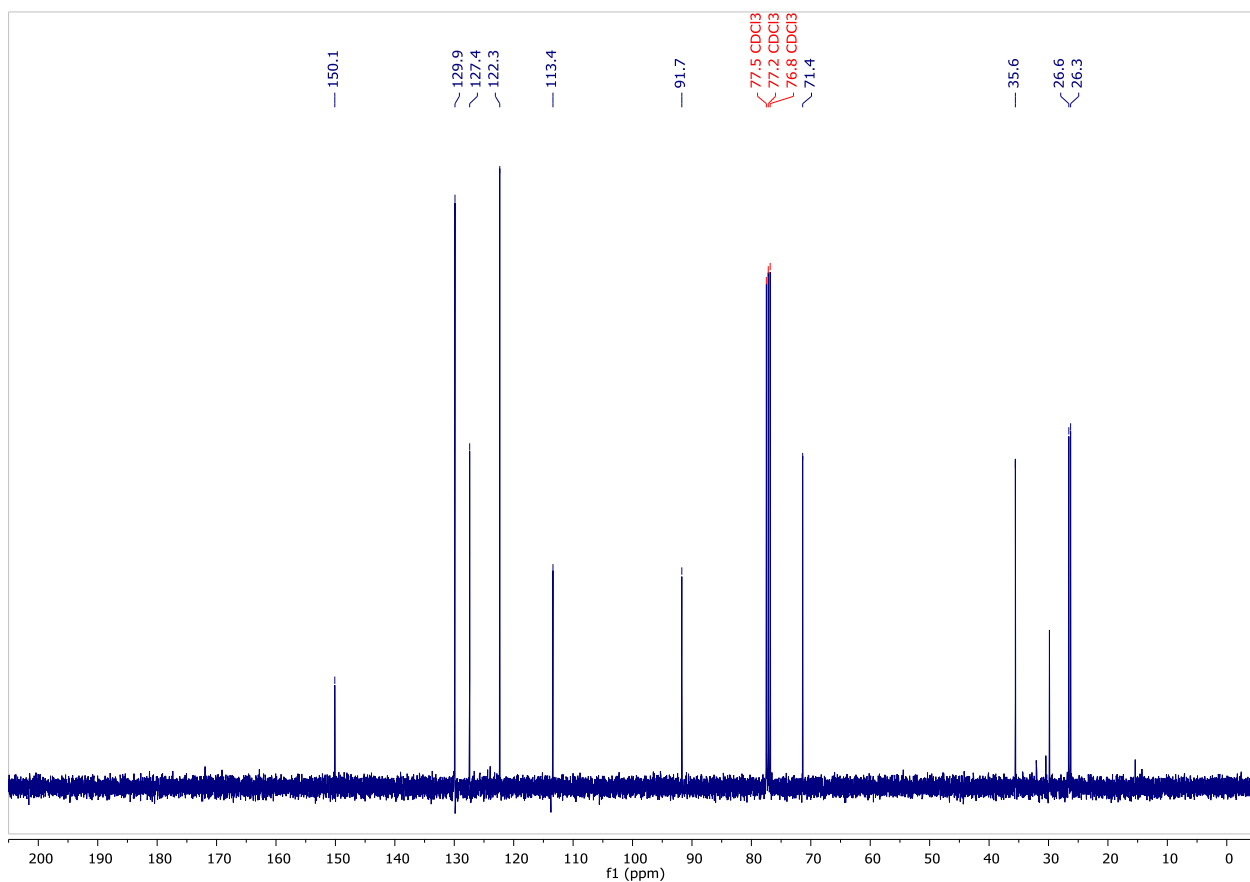
**2o: <sup>1</sup>H NMR (400 MHz, Chloroform-d)**



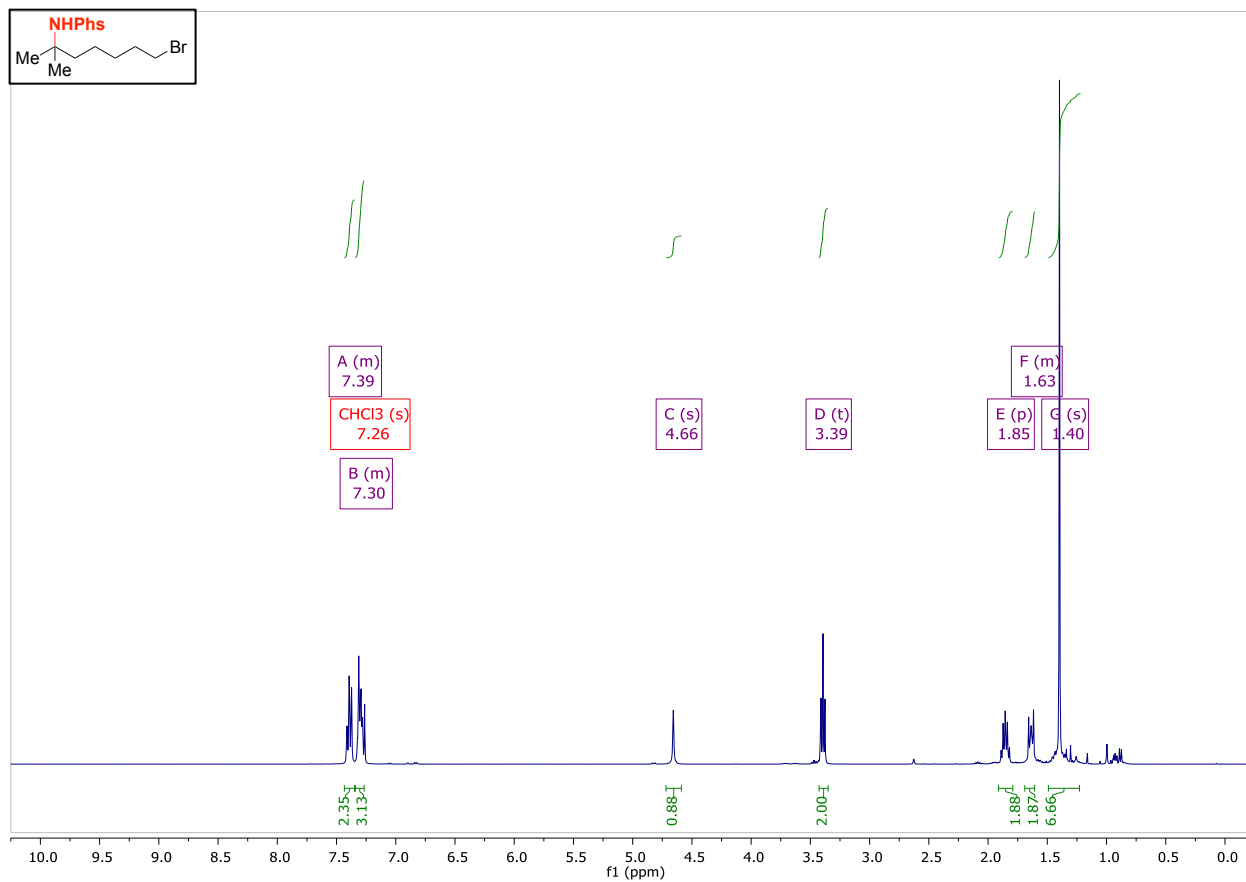
**2o: <sup>13</sup>C NMR (101 MHz, Chloroform-d)**



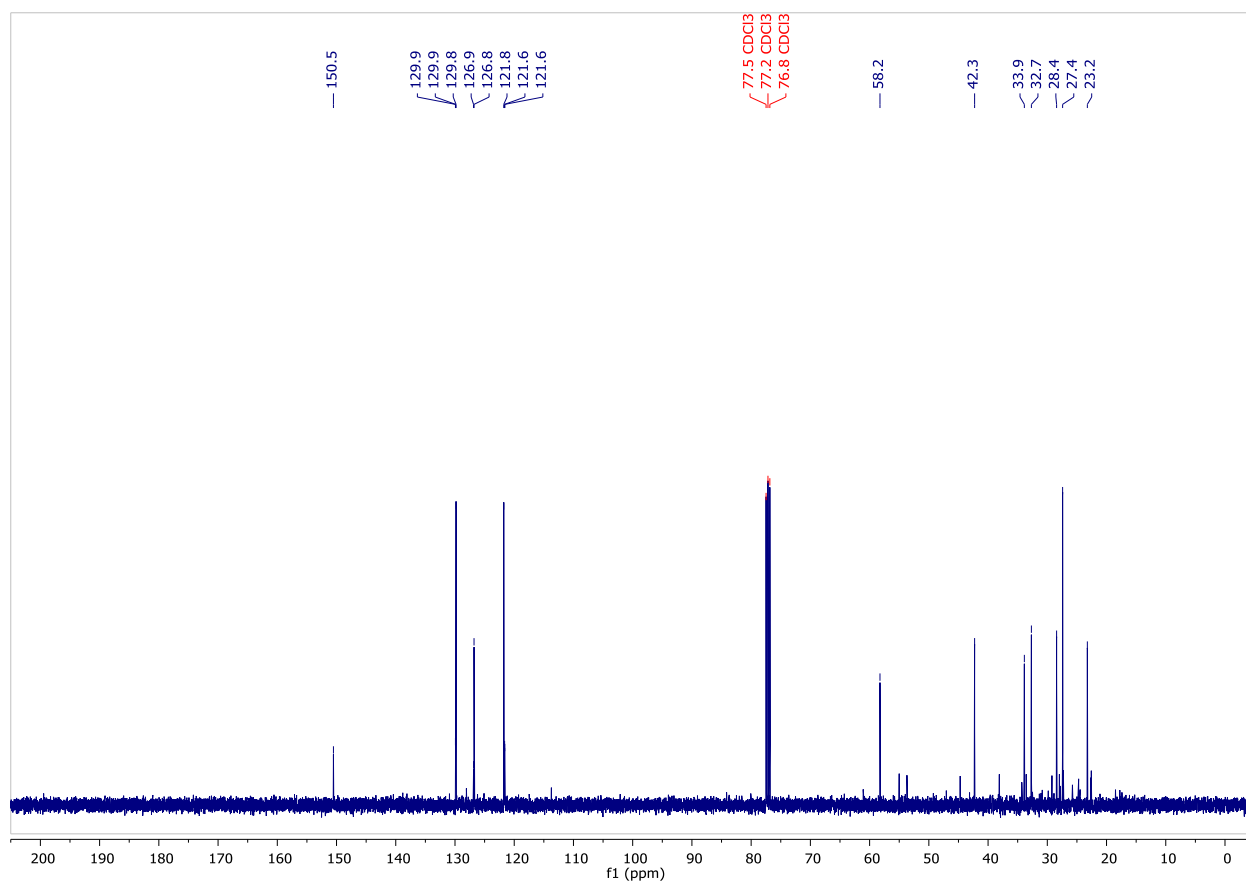
**2p: <sup>1</sup>H NMR (400 MHz, Chloroform-d)**



**2p: <sup>13</sup>C NMR (101 MHz, Chloroform-d)**

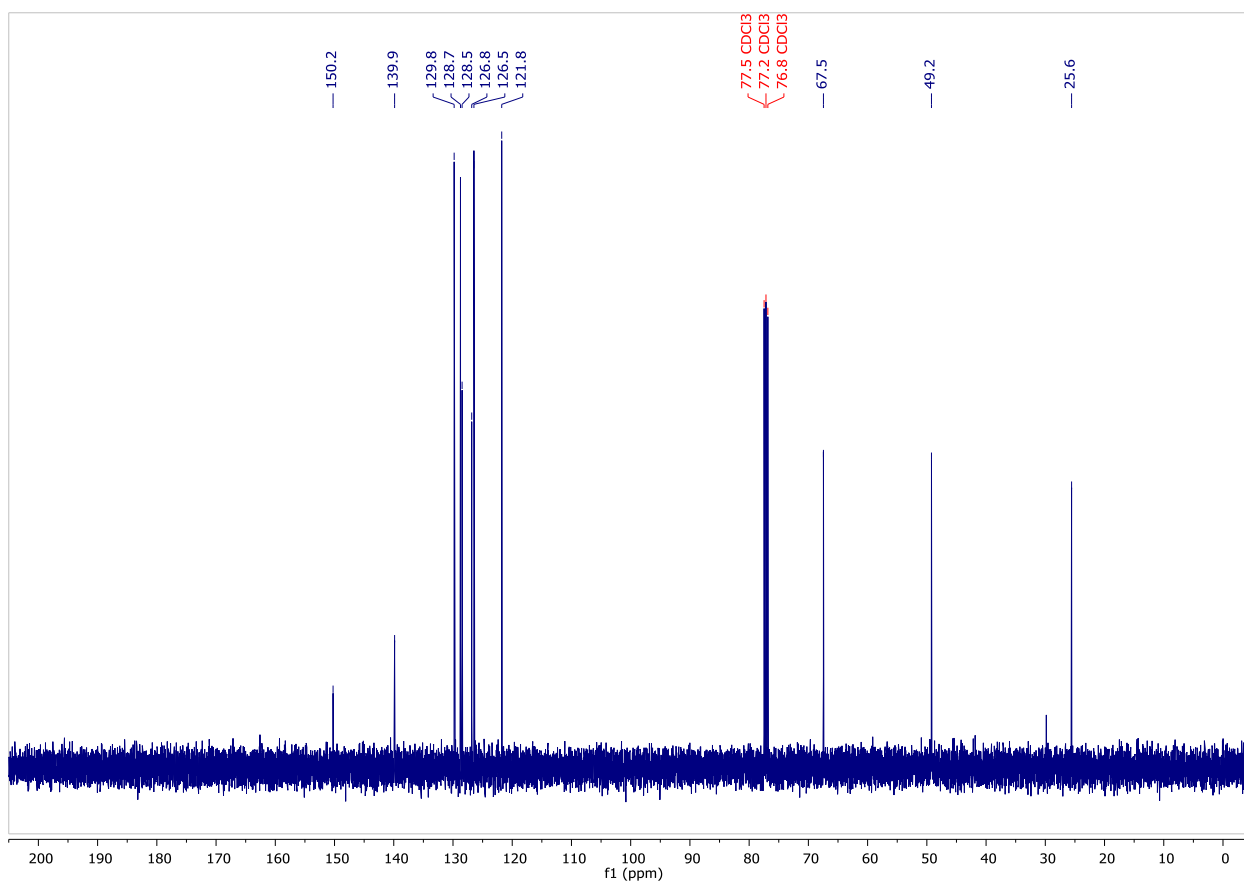
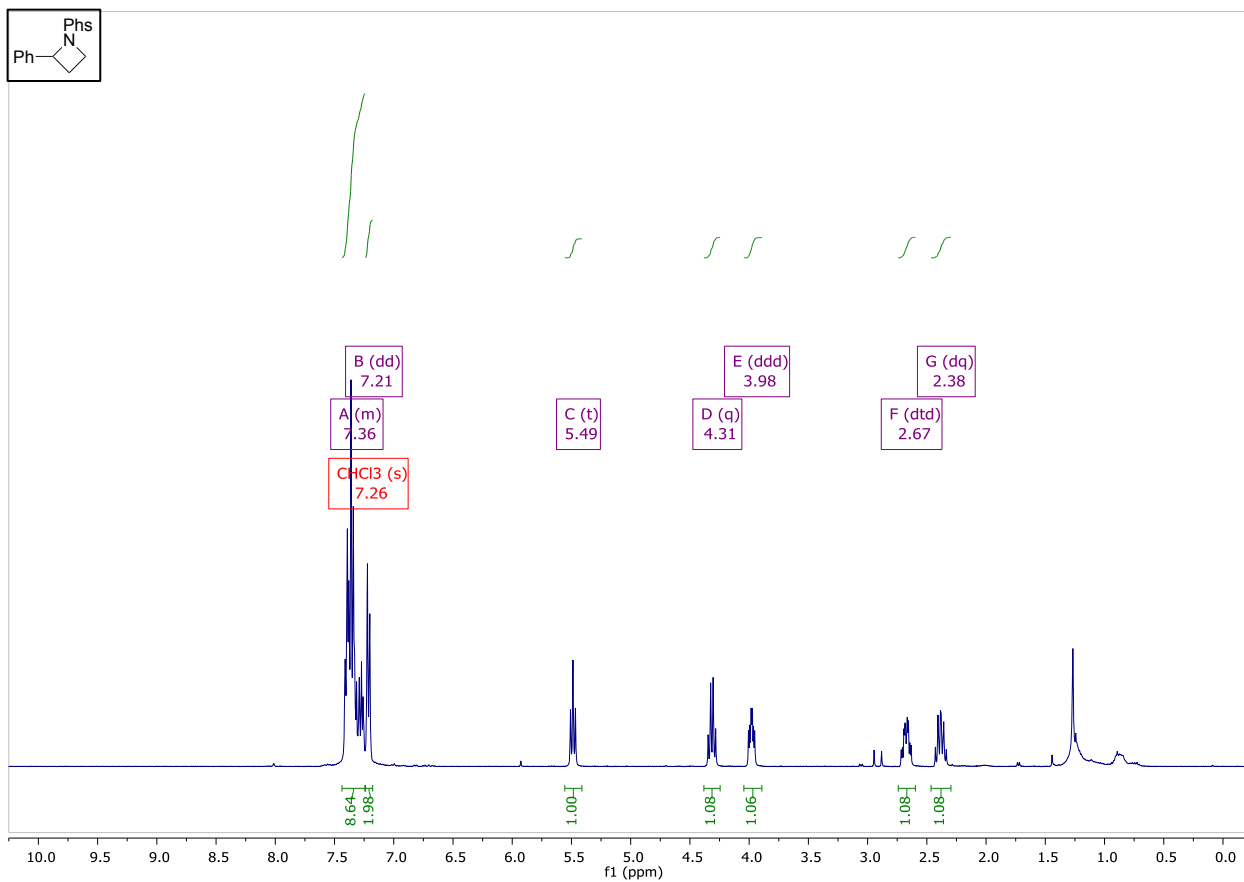


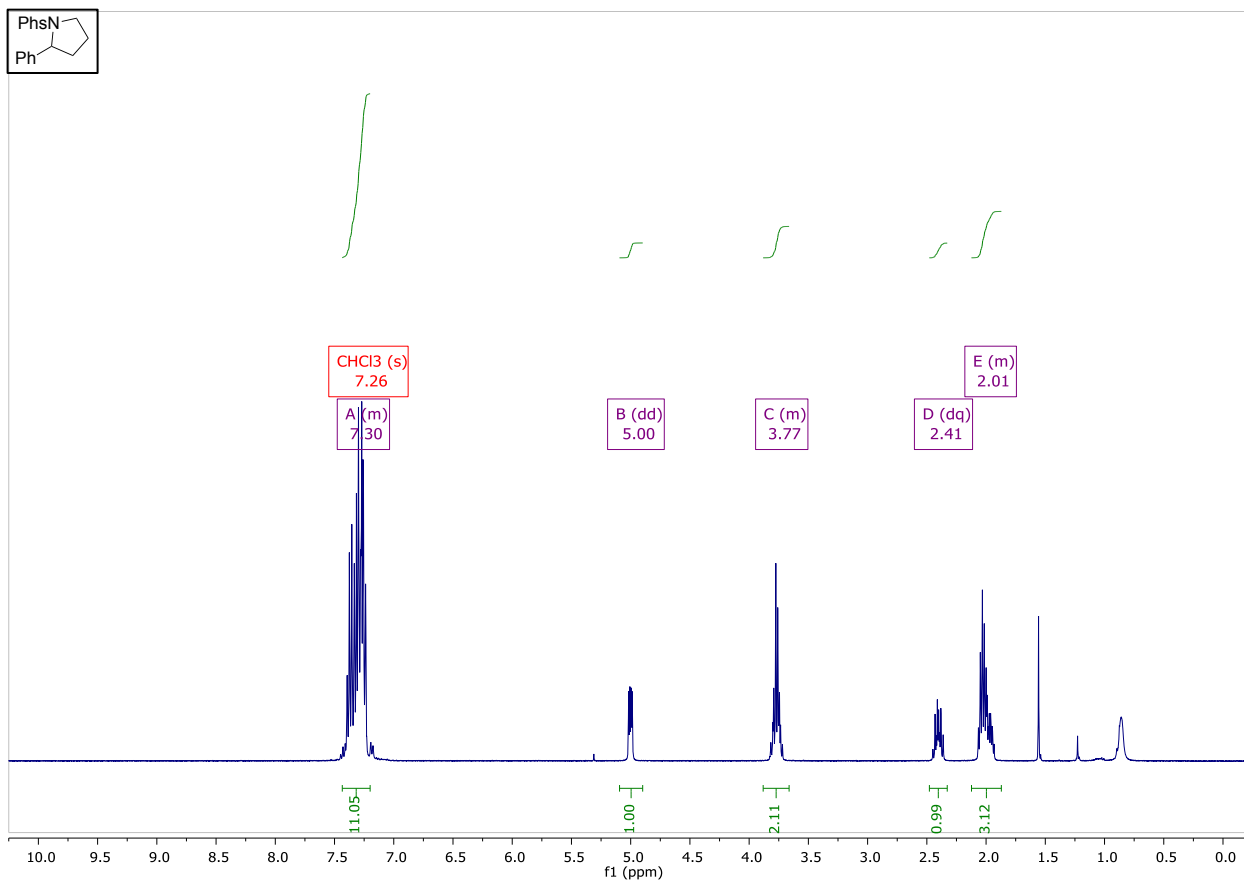
**2q: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)**



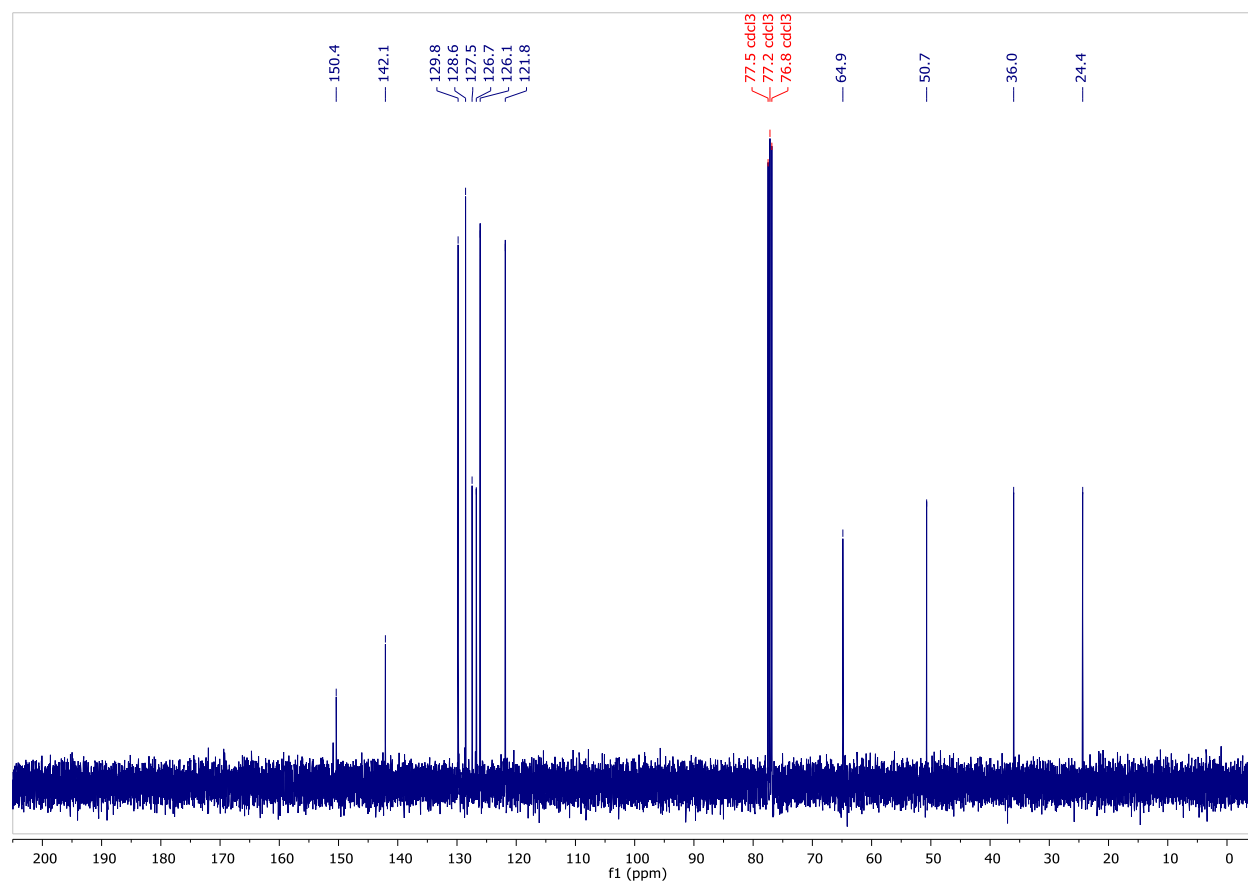
**2q: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)**



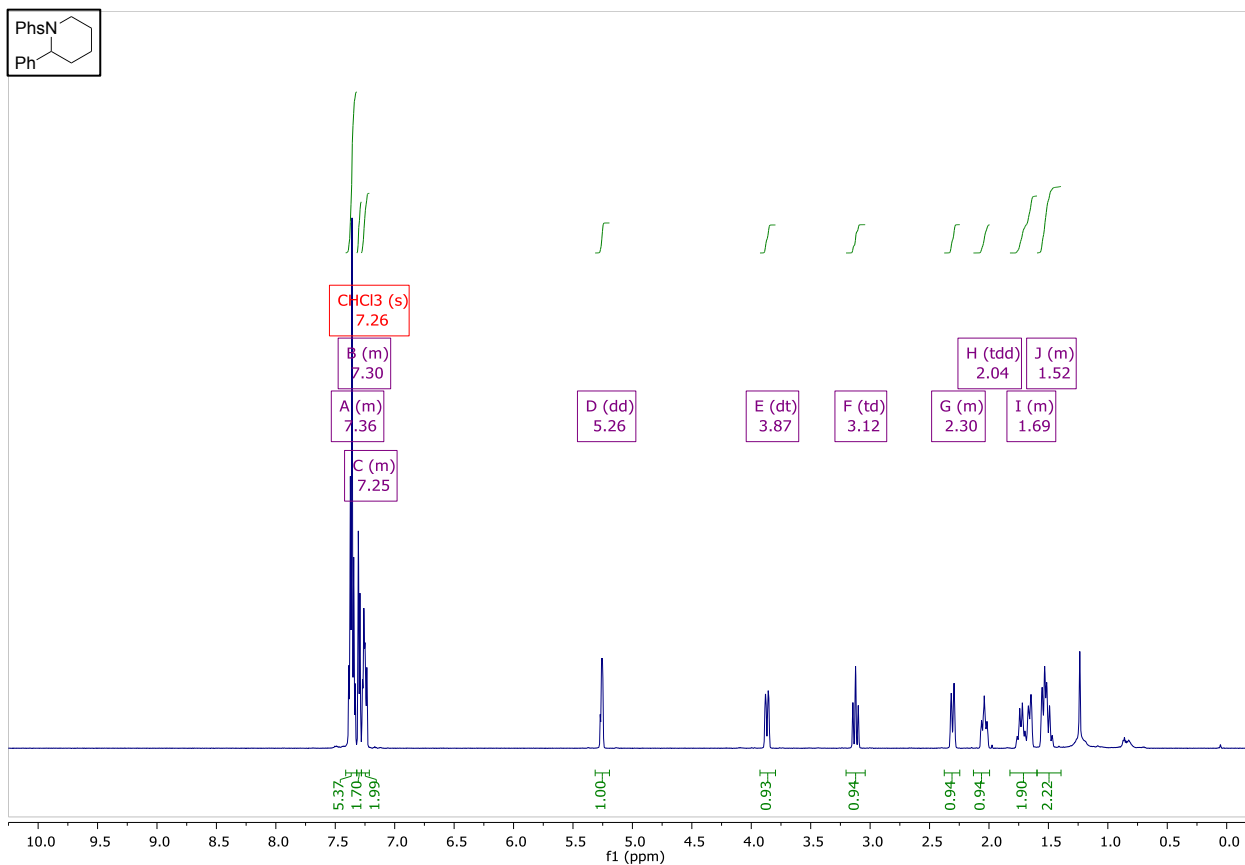




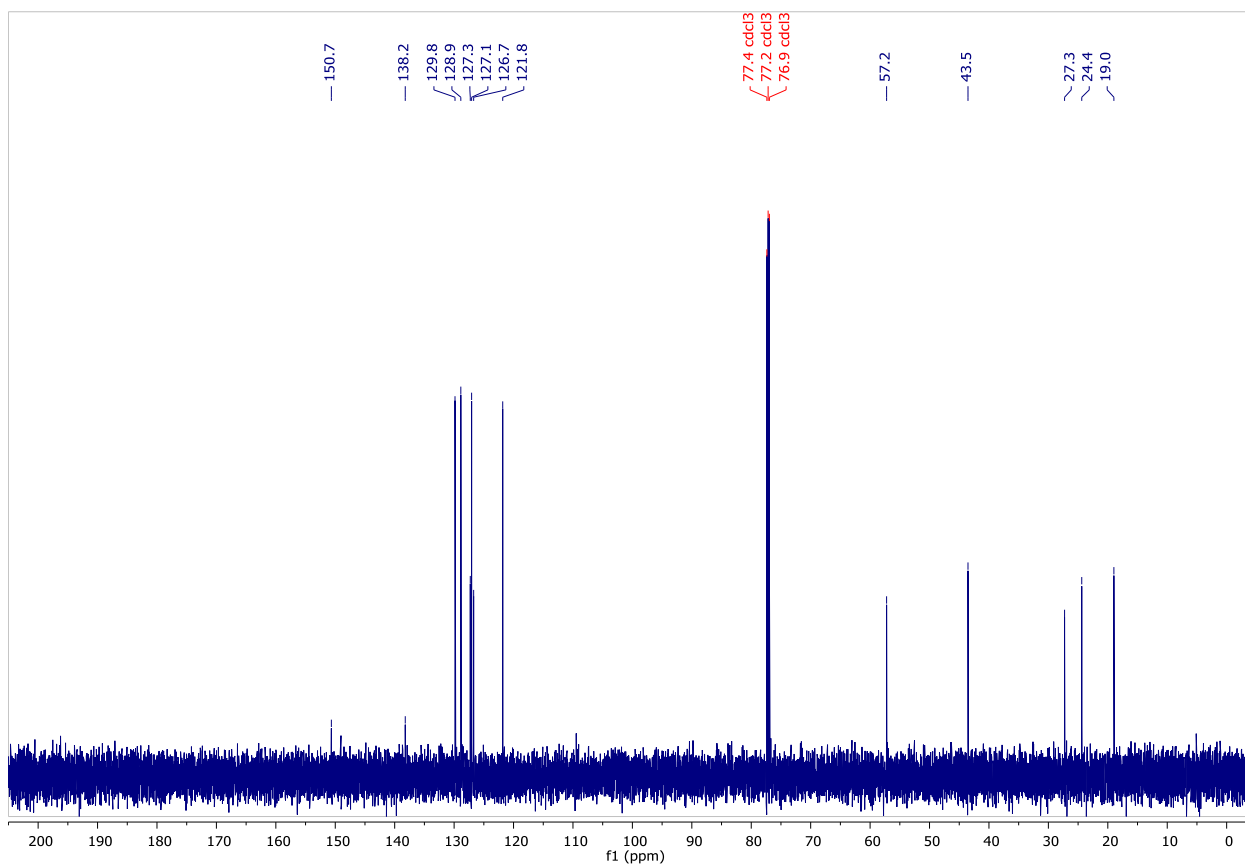
**3c: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)**



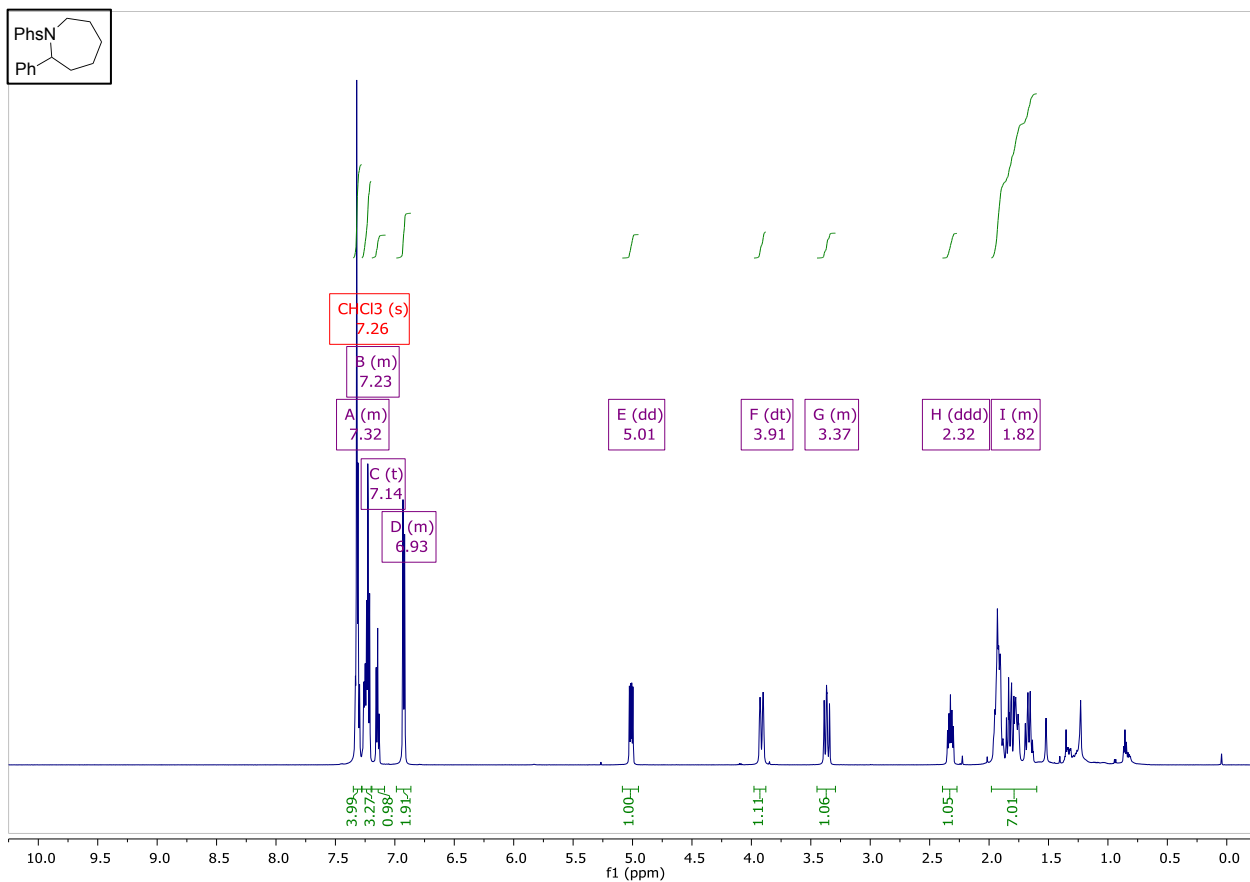
**3c: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)**



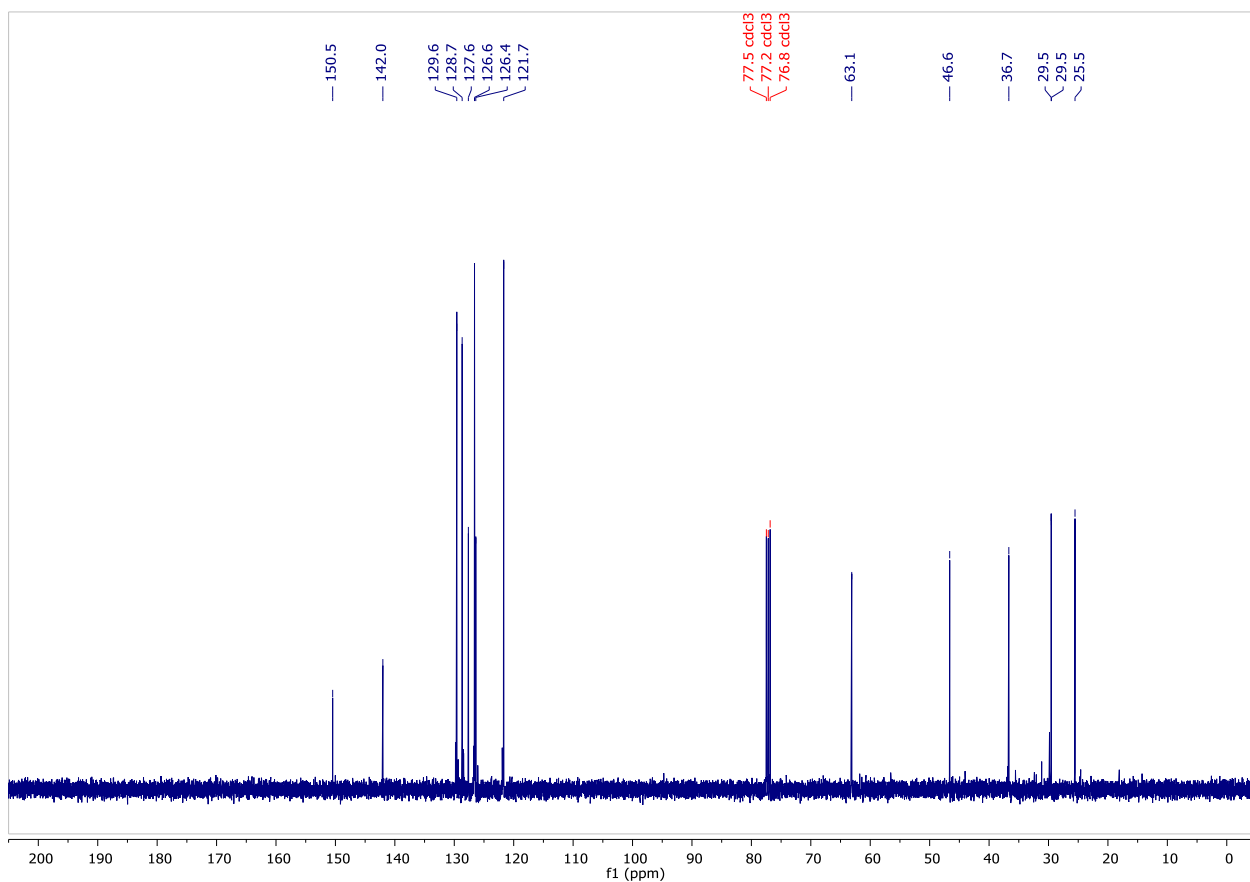
**3d:  $^1\text{H}$  NMR (600 MHz, Chloroform-*d*)**



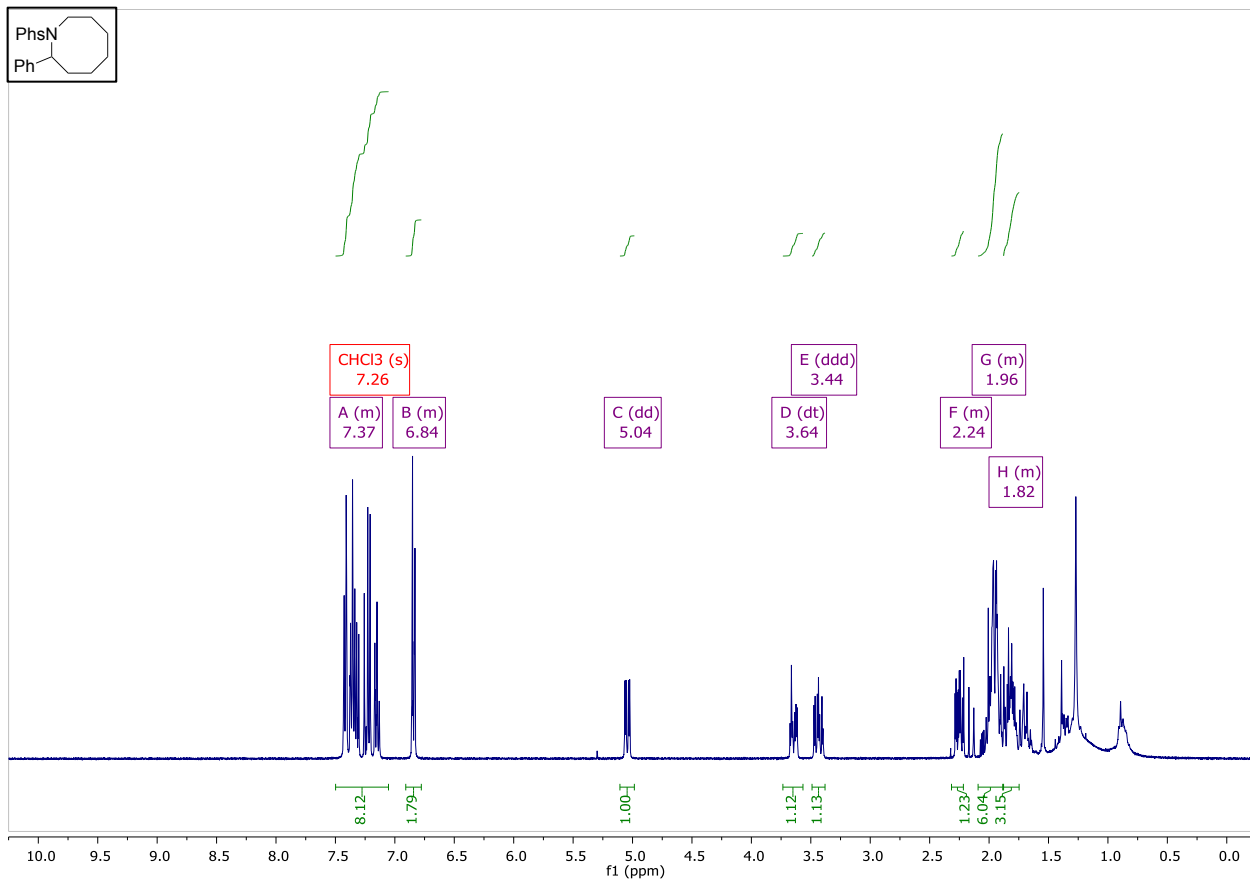
**3d:  $^{13}\text{C}$  NMR (151 MHz, Chloroform-*d*)**



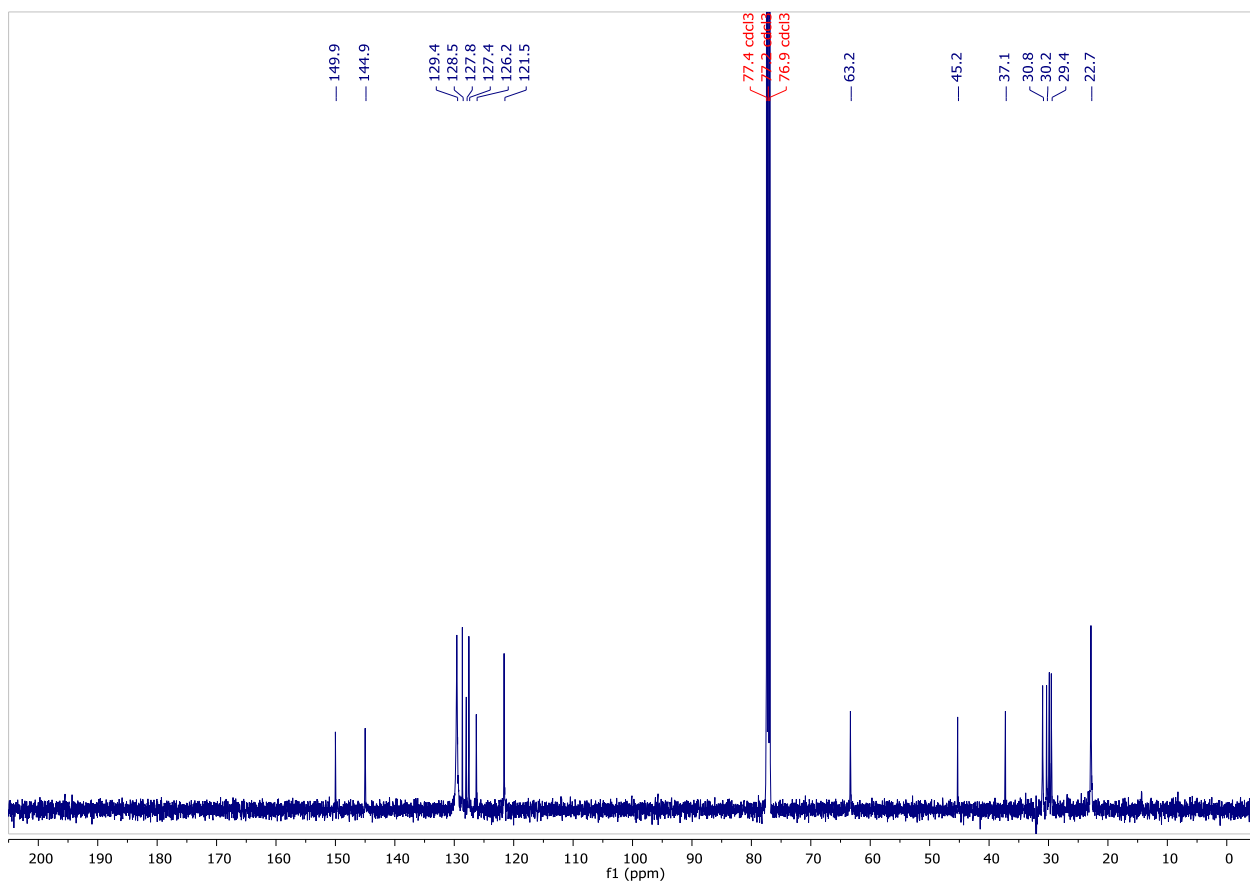
**3e: <sup>1</sup>H NMR (600 MHz, Chloroform-d)**



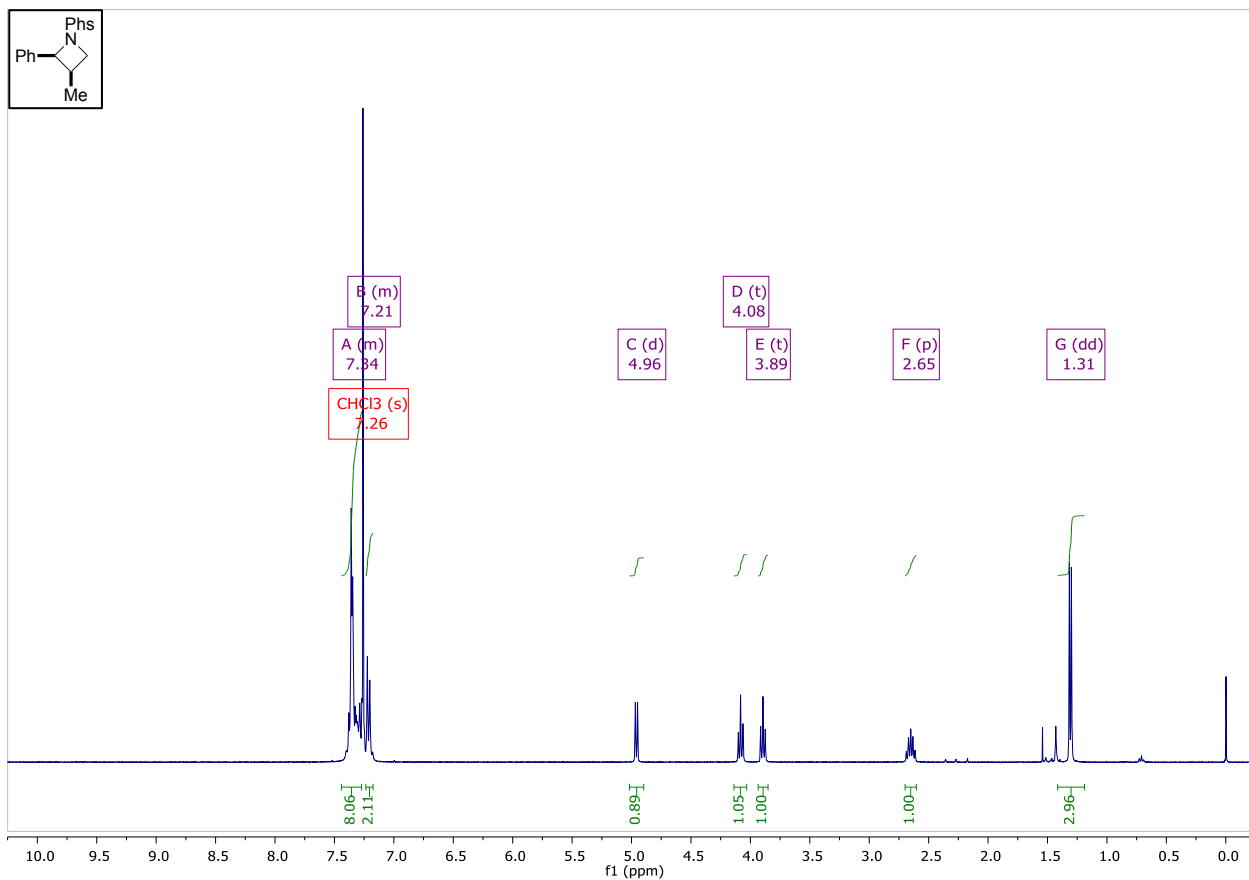
**3e: <sup>13</sup>C NMR (101 MHz, Chloroform-d)**



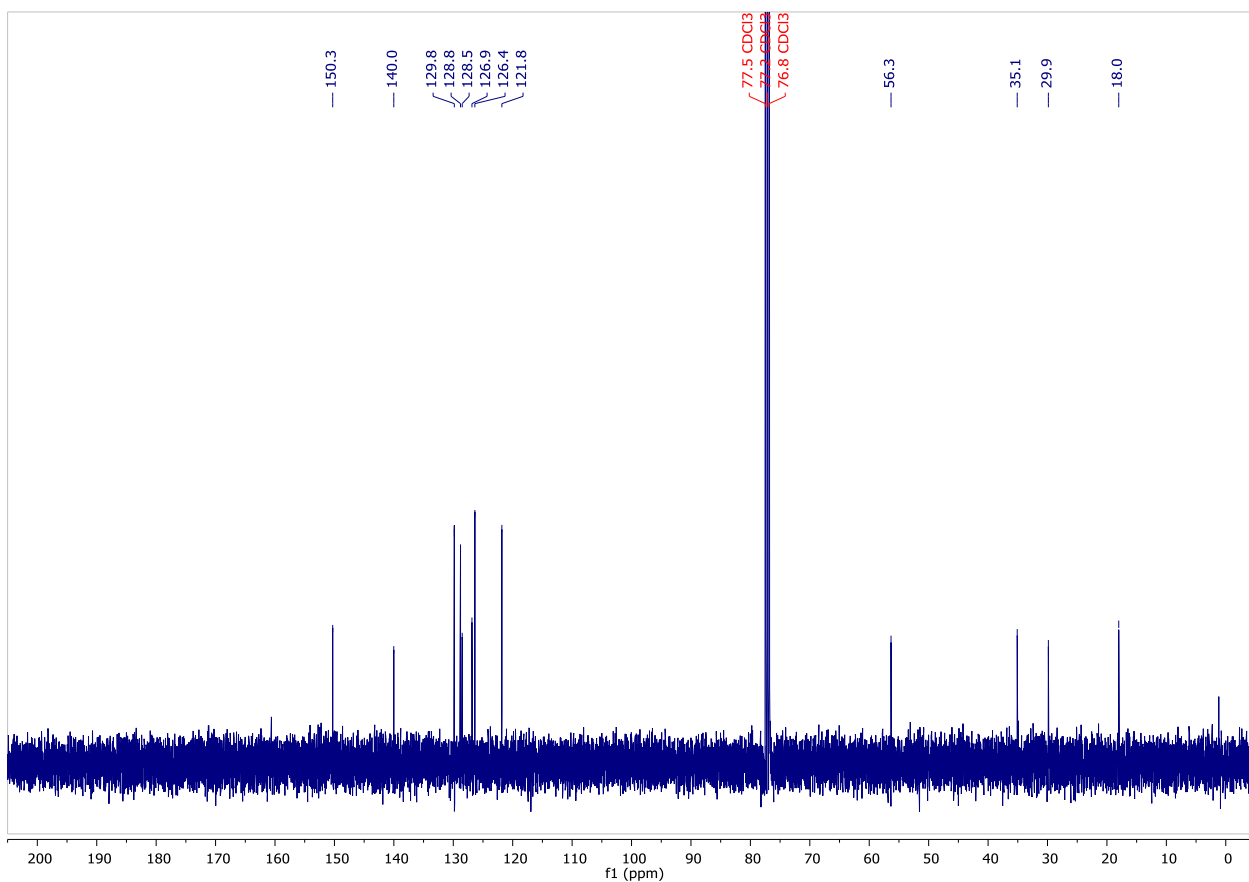
**3f: <sup>1</sup>H NMR (400 MHz, Chloroform-d)**



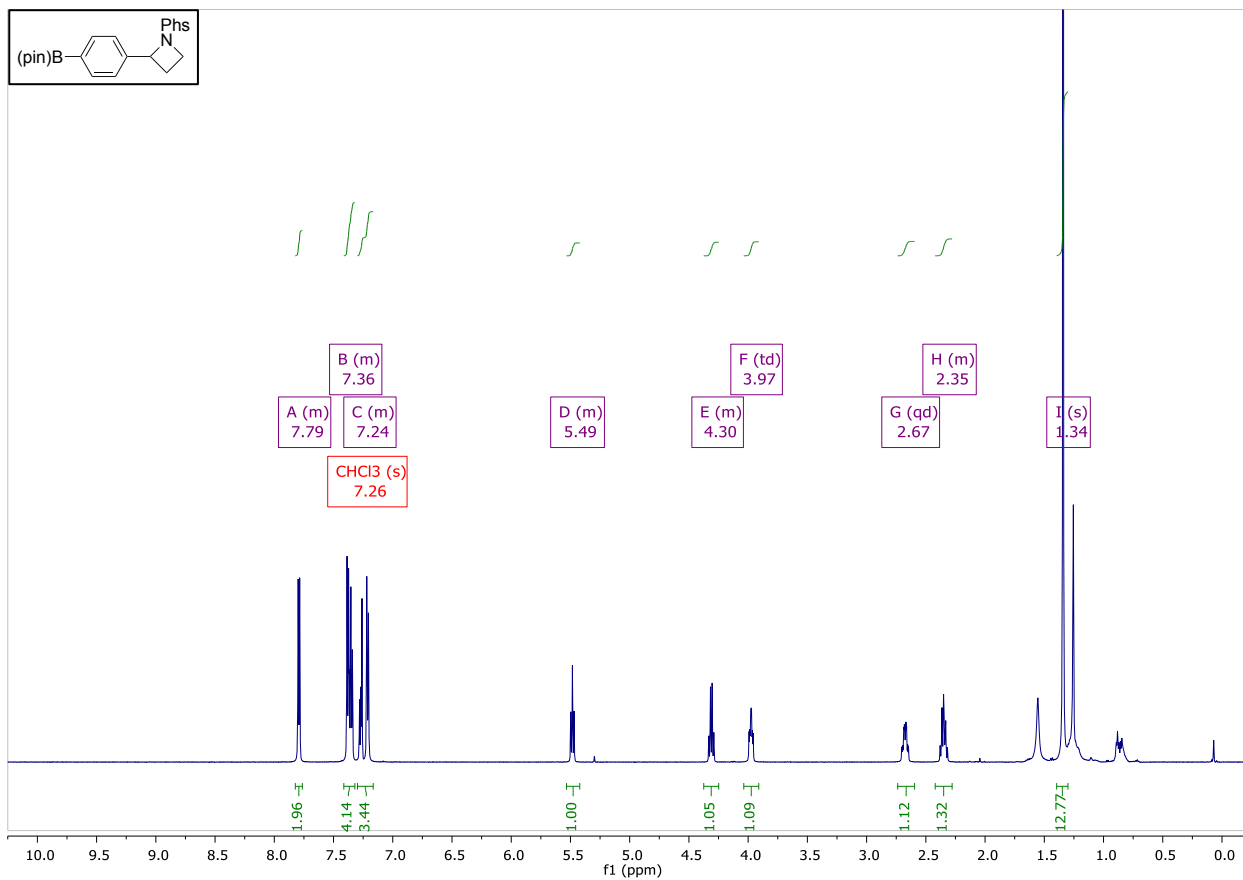
**3f: <sup>13</sup>C NMR (126 MHz, Chloroform-d)**



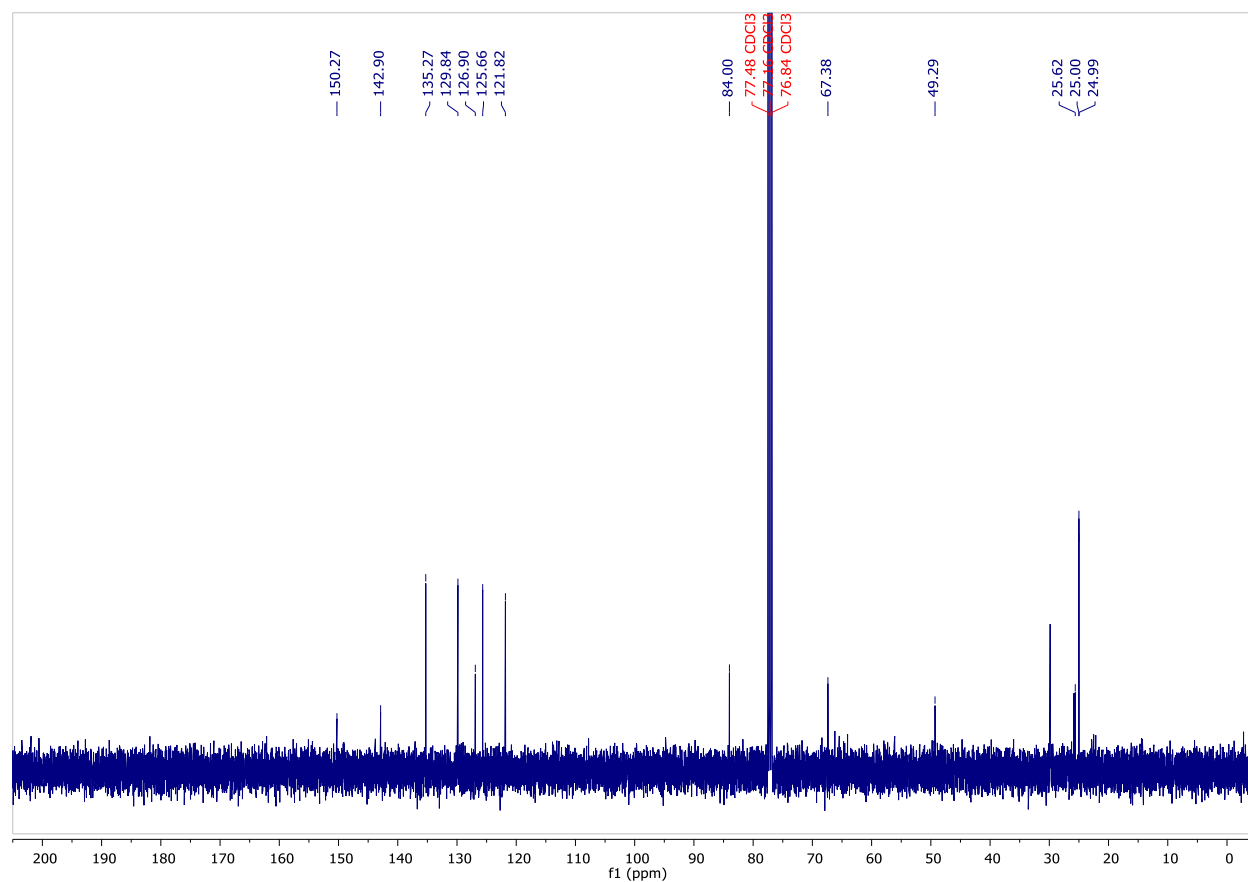
**3g: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)**



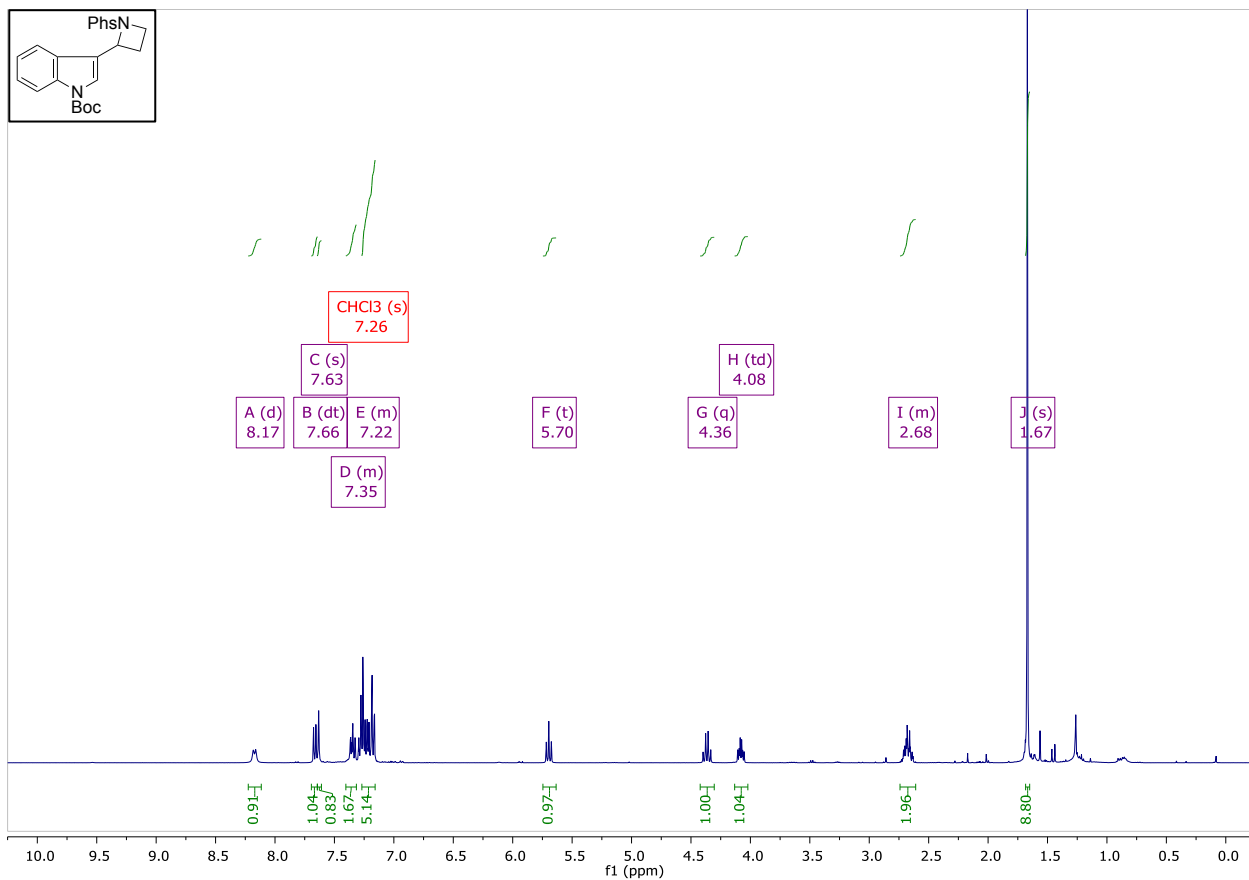
**3g: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)**



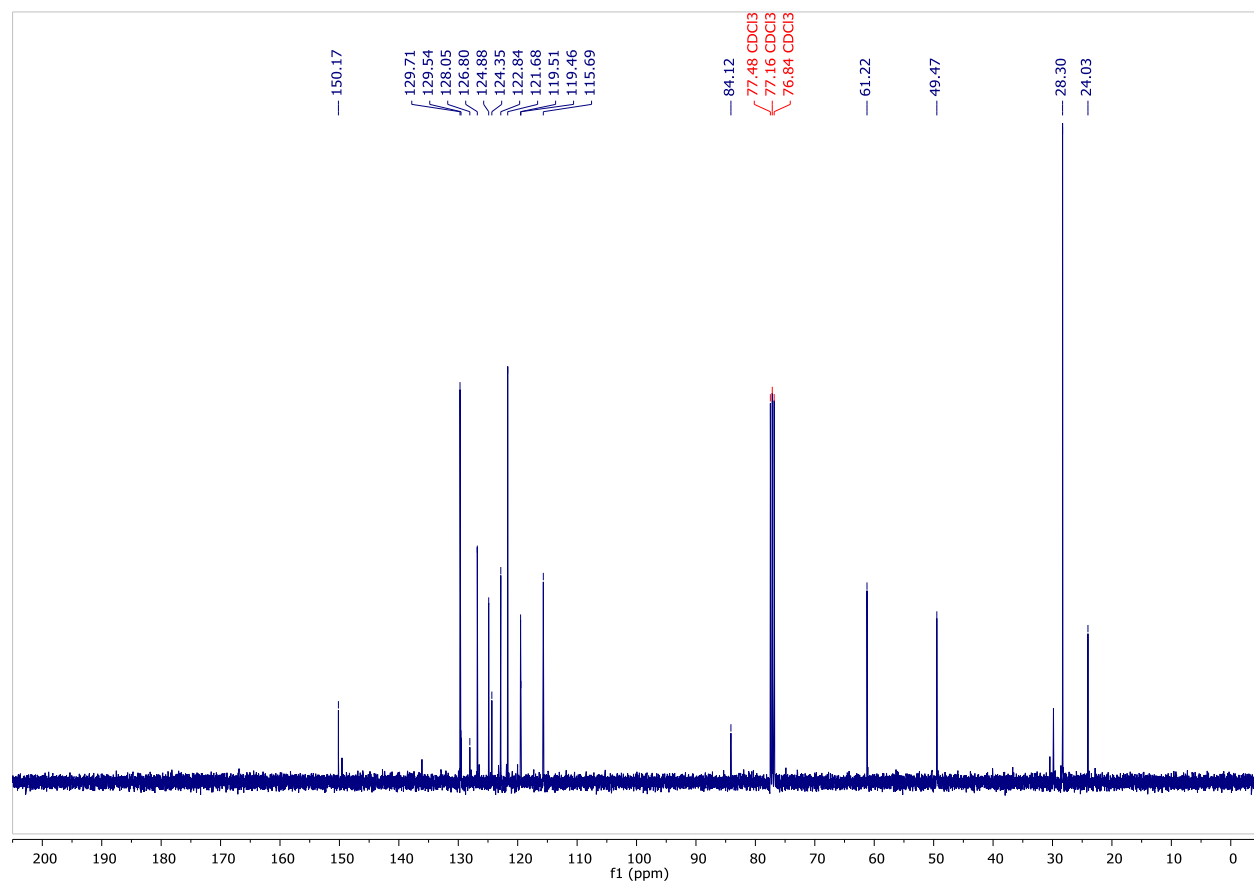
3h: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)



3h: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)

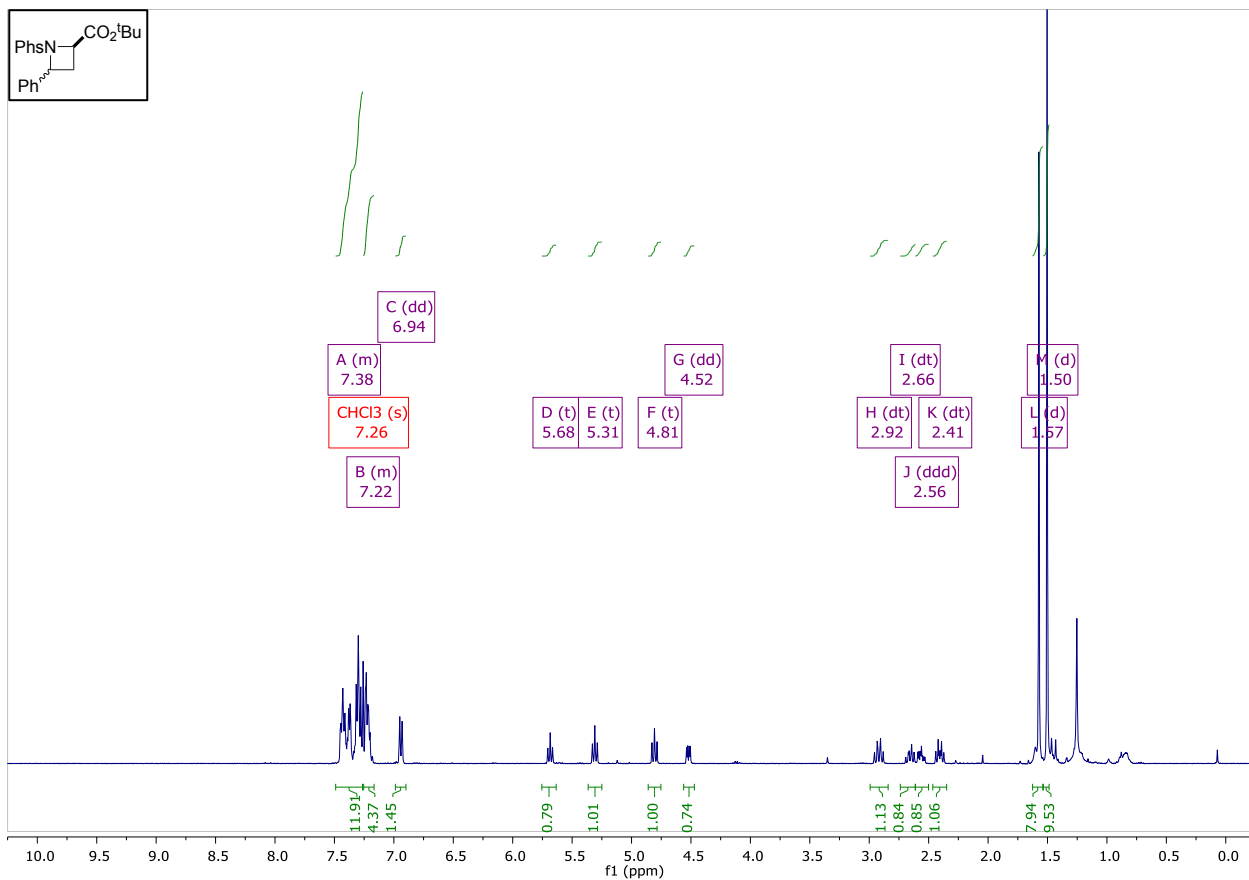


**3i: <sup>1</sup>H NMR (400 MHz, Chloroform-d)**

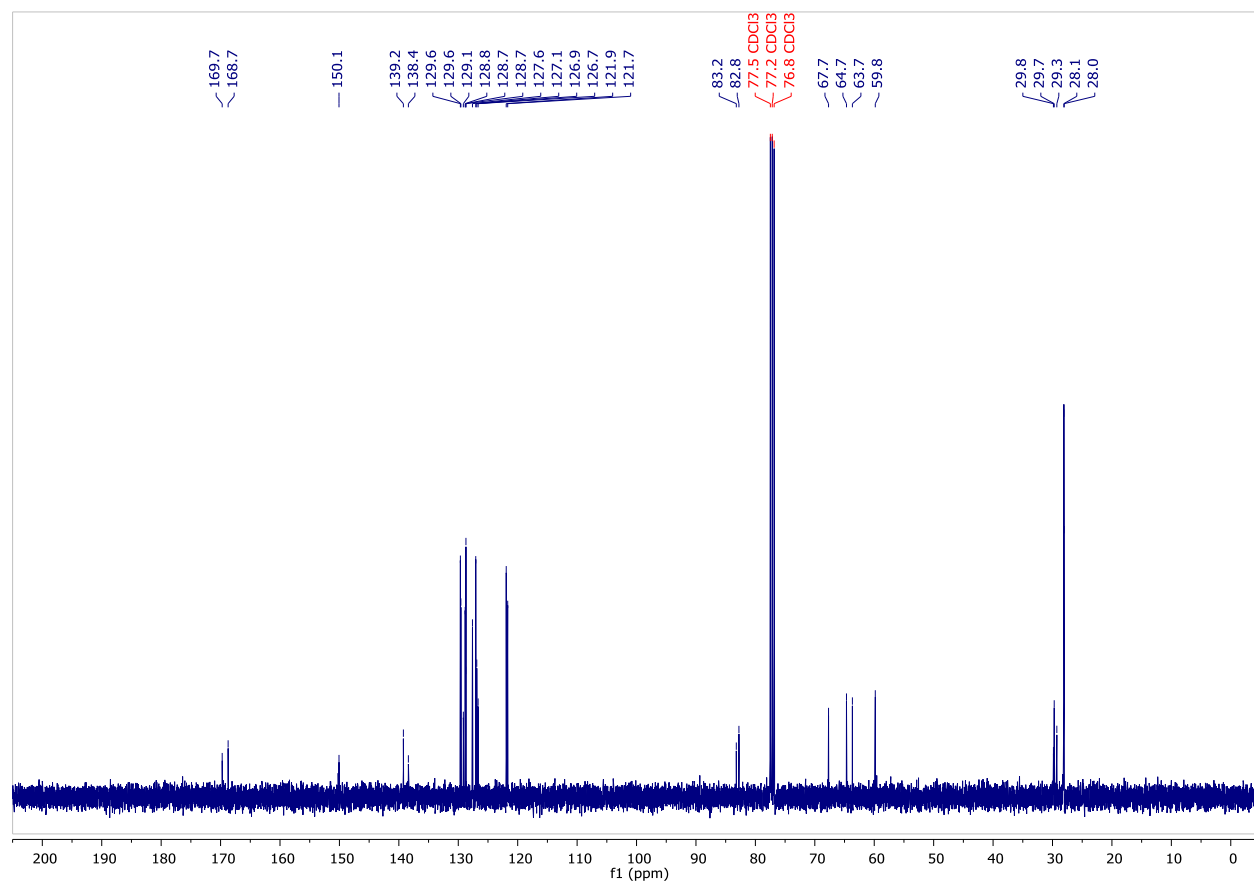


**3i: <sup>13</sup>C NMR (101 MHz, Chloroform-d)**

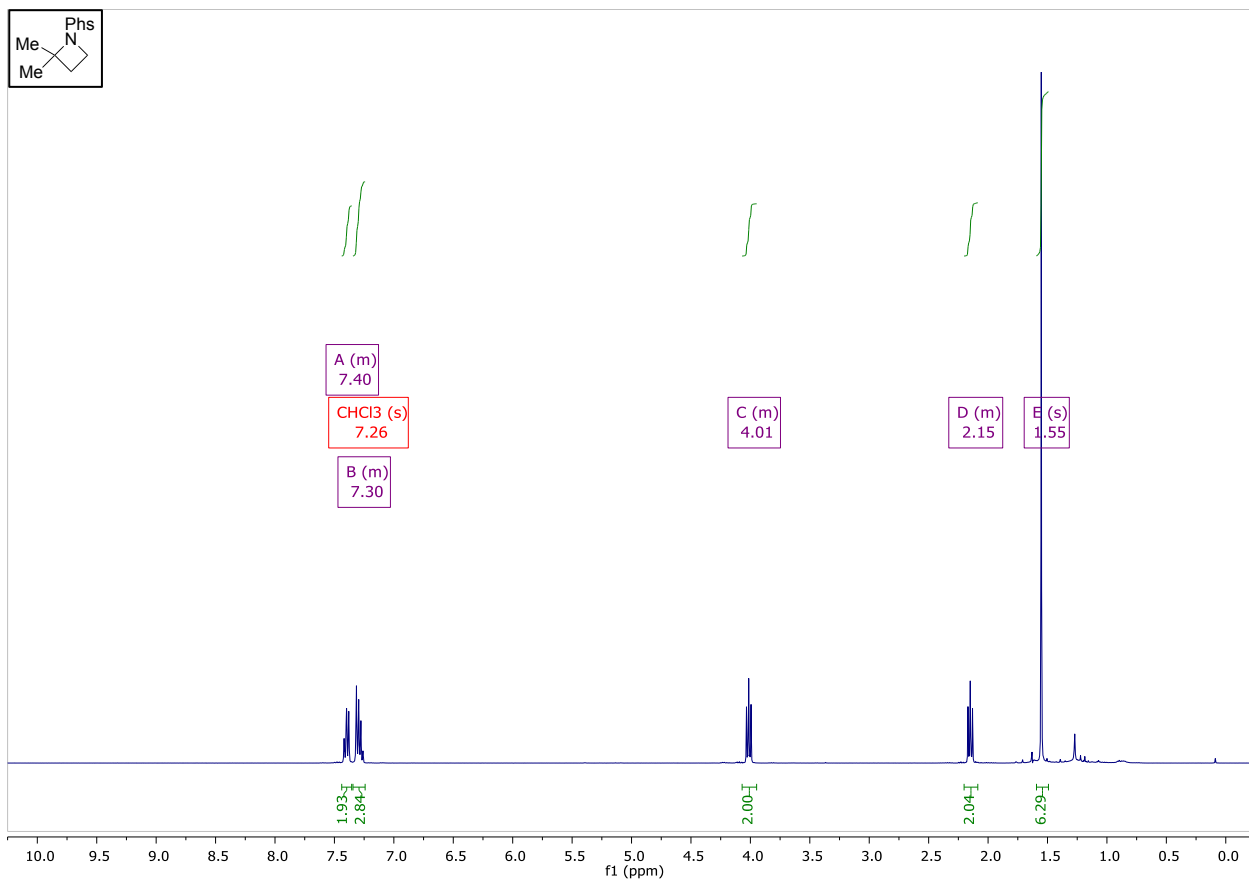




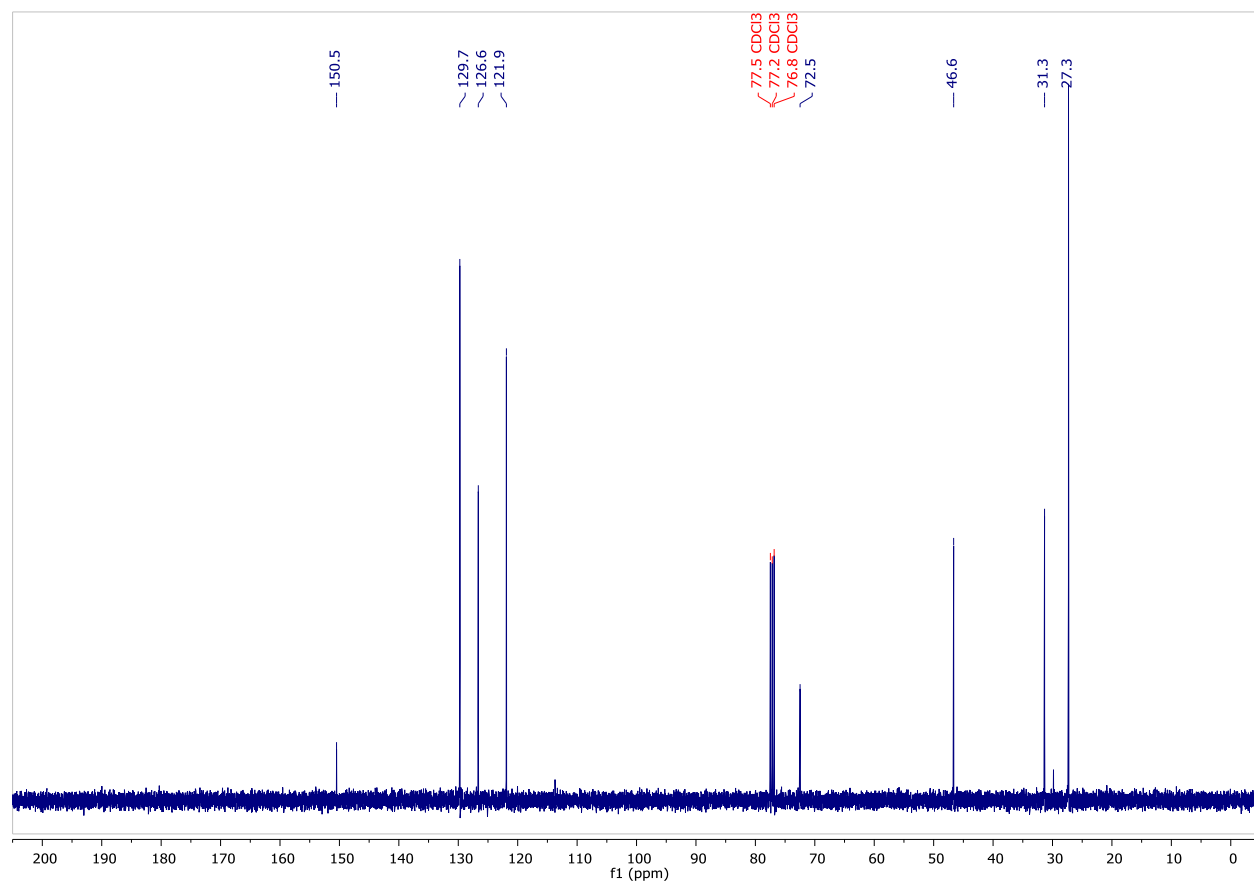
**3j (mixture of diastereomers): <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)**



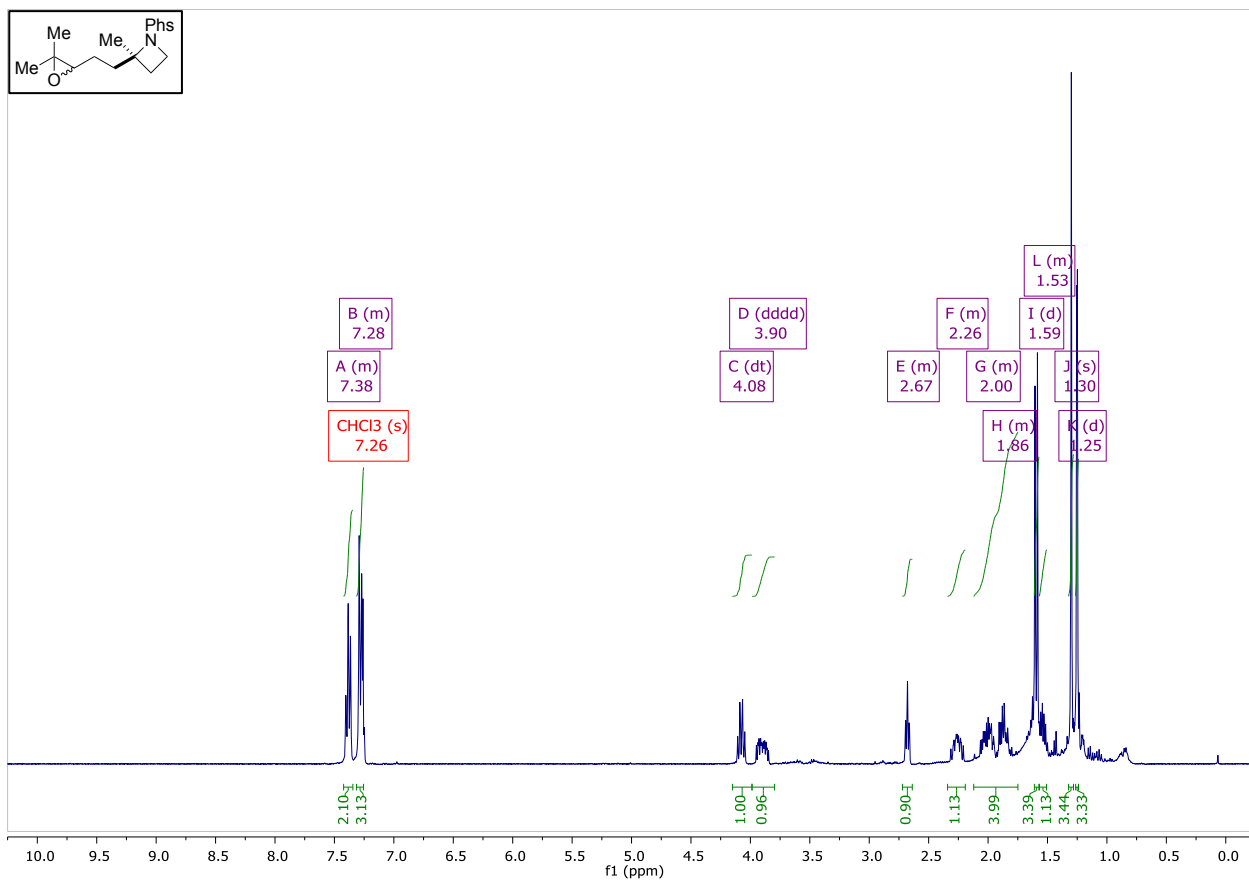
**3j (mixture of diastereomers): <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)**



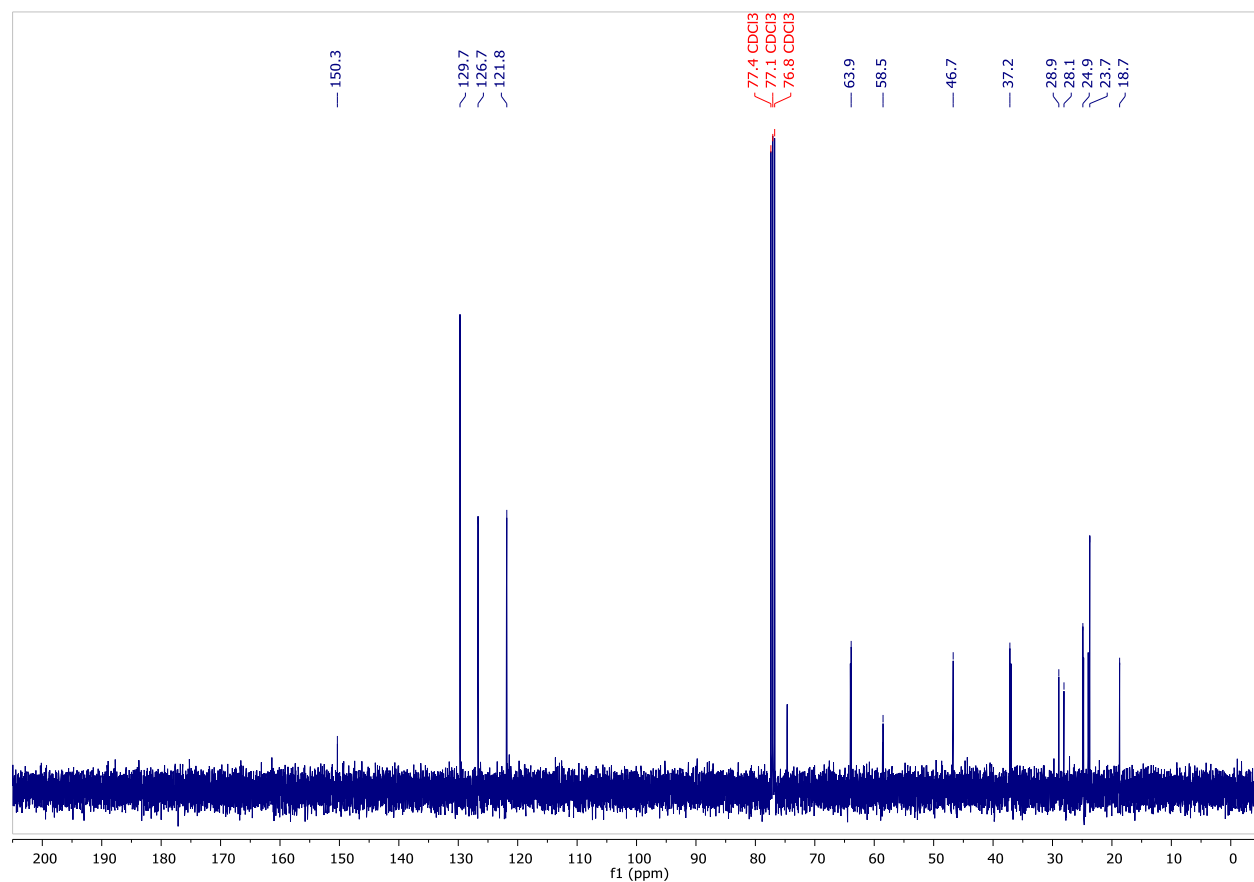
**3k: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)**



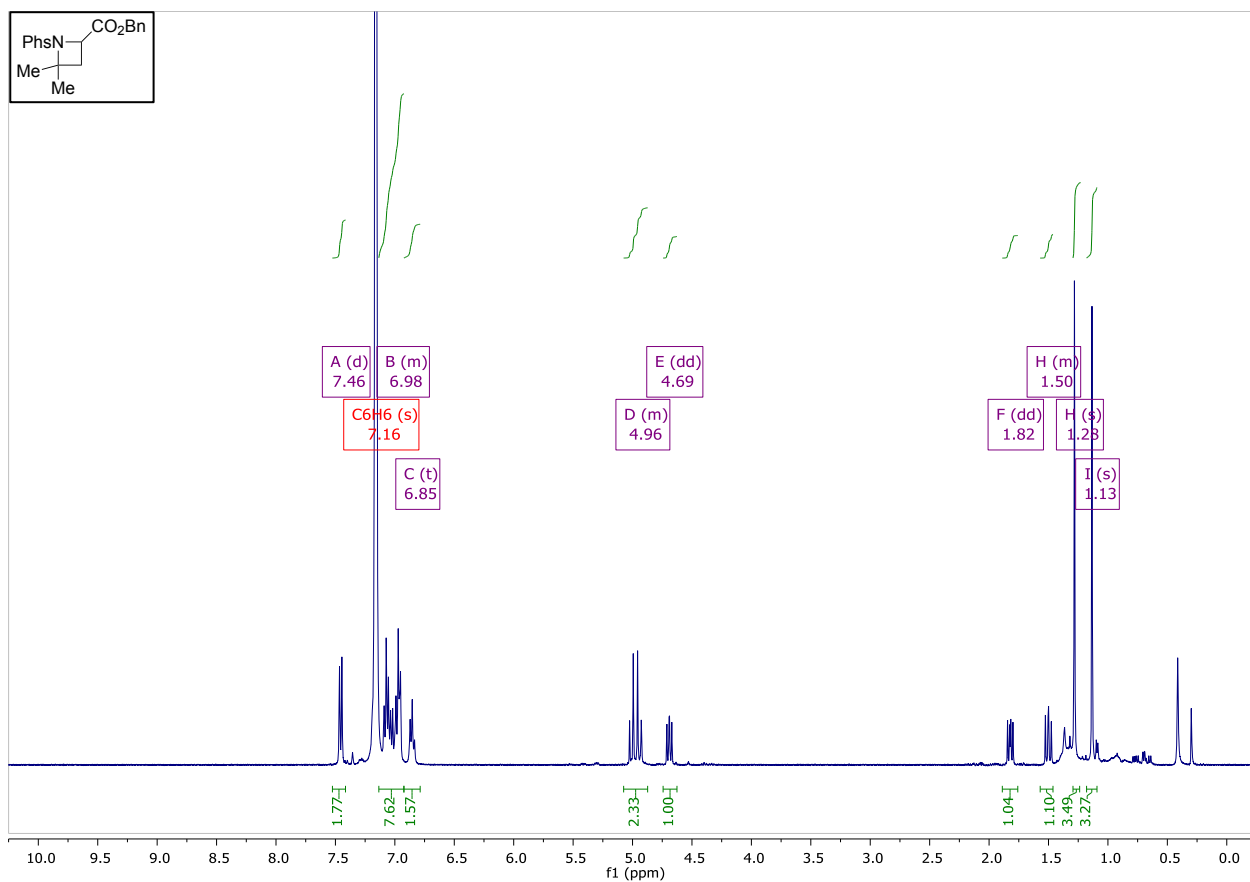
**3k: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)**



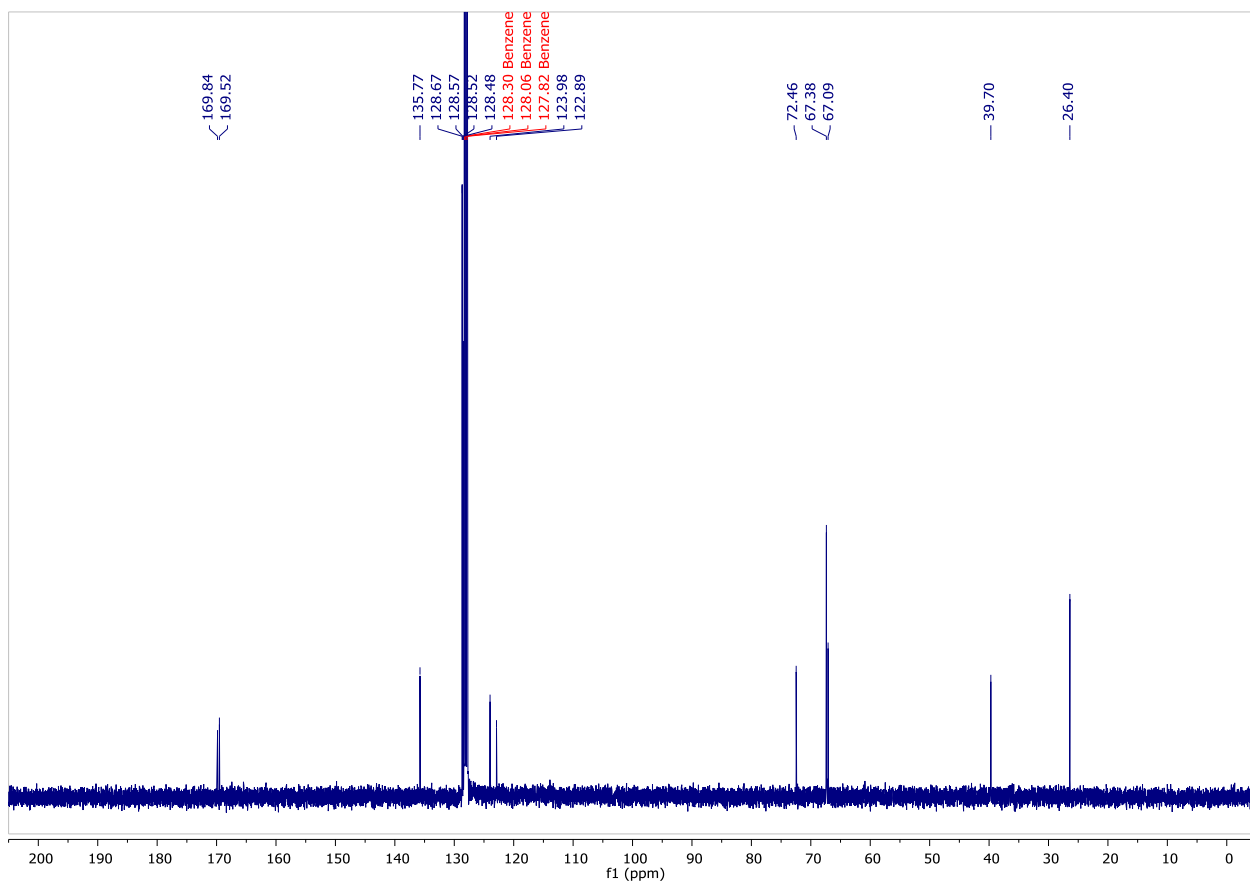
**3l: <sup>1</sup>H NMR (400 MHz, Chloroform-d)**



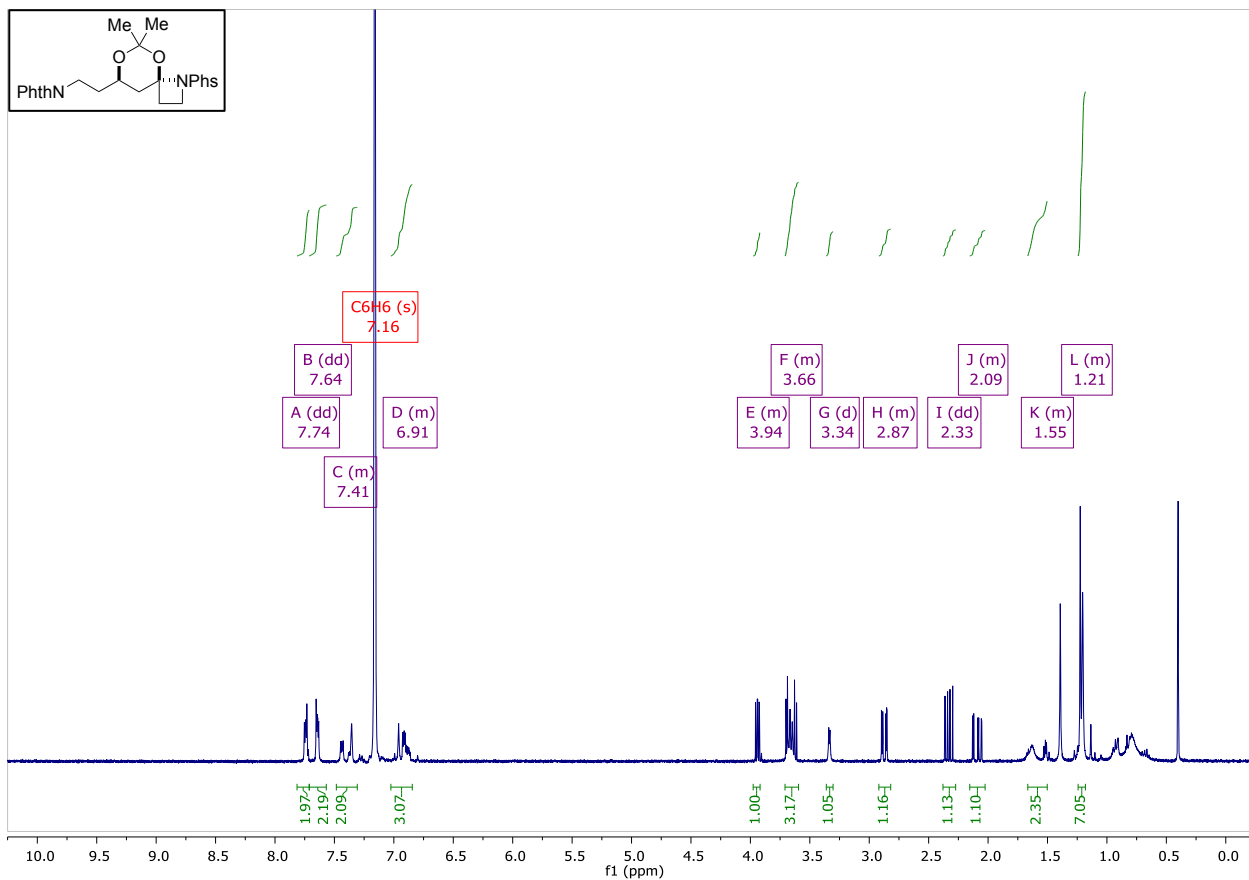
**3l: <sup>13</sup>C NMR (101 MHz, Chloroform-d)**



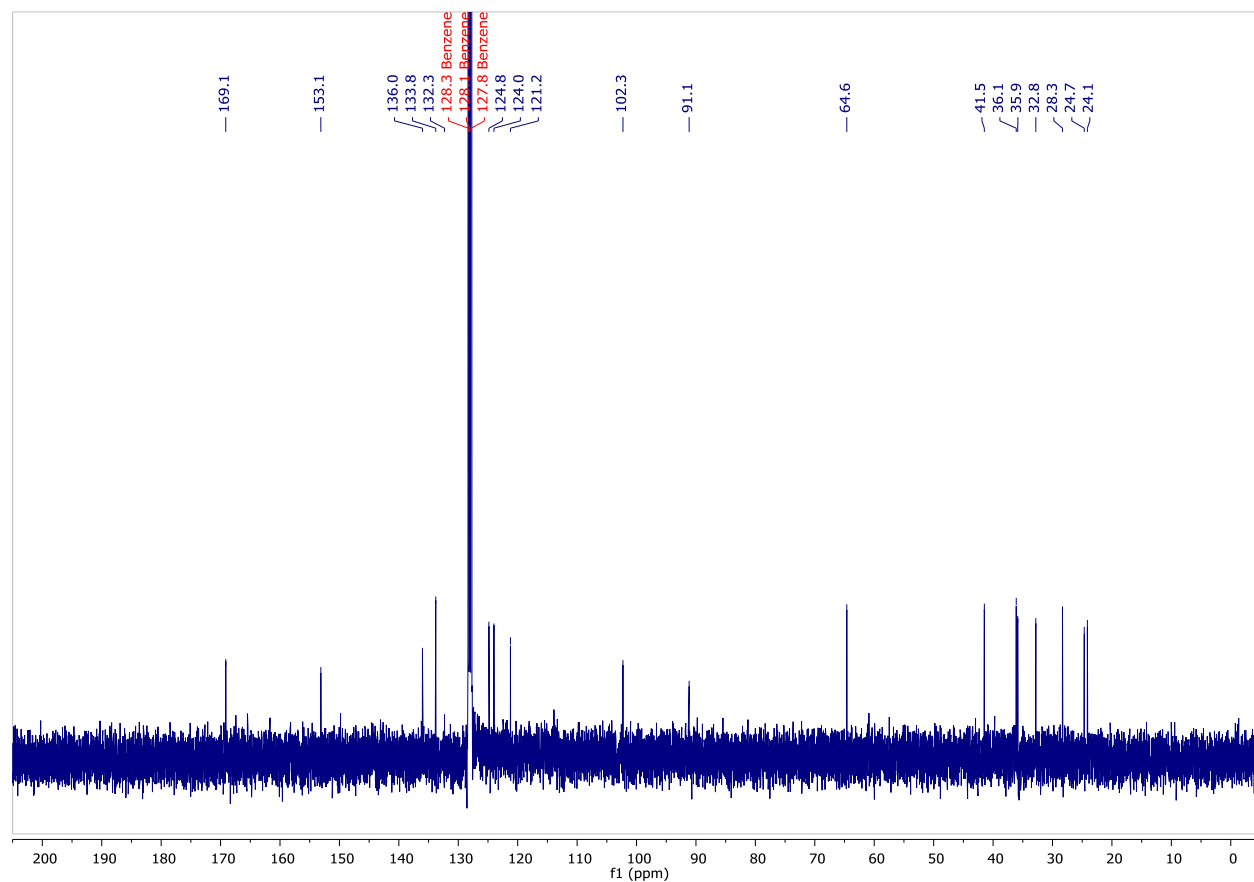
**3m: <sup>1</sup>H NMR (400 MHz, Benzene-*d*<sub>6</sub>)**



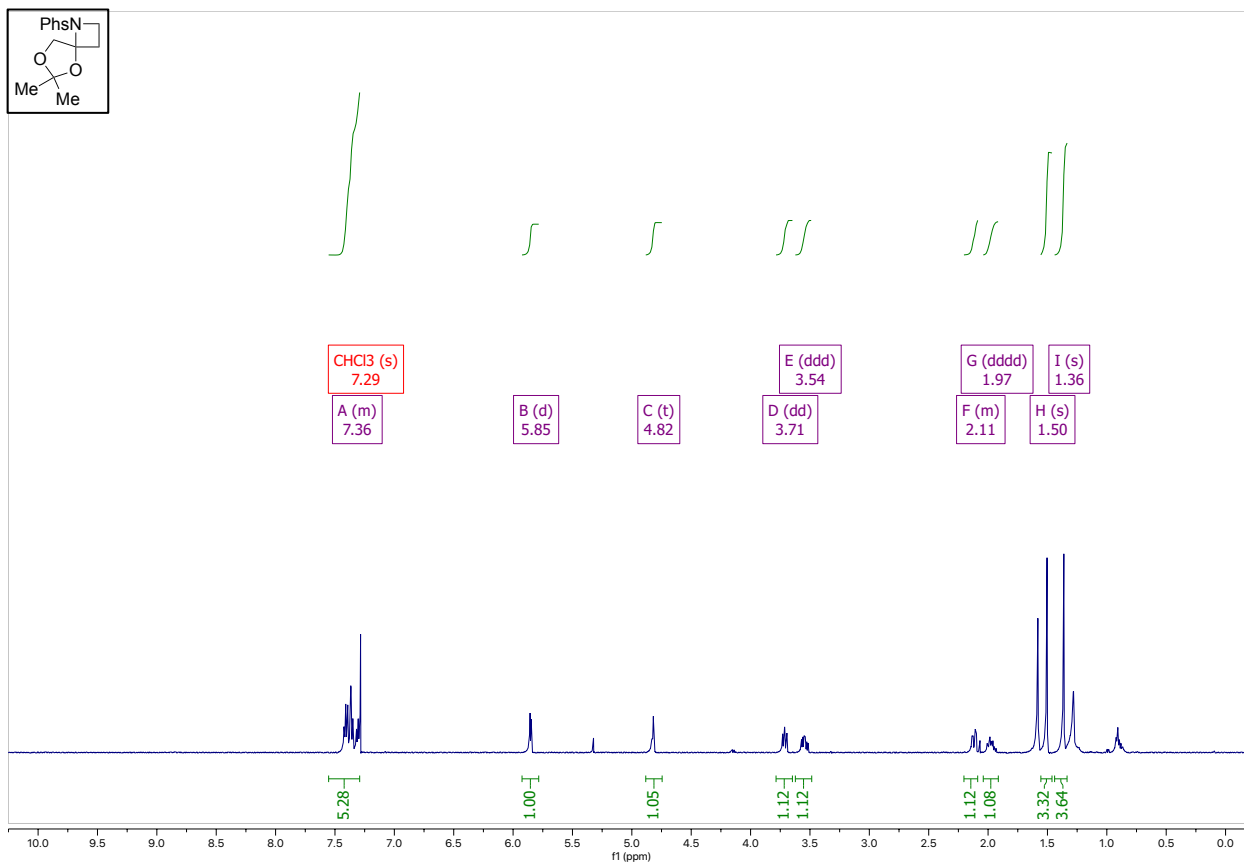
**3m: <sup>13</sup>C NMR (101 MHz, Benzene-*d*<sub>6</sub>)**



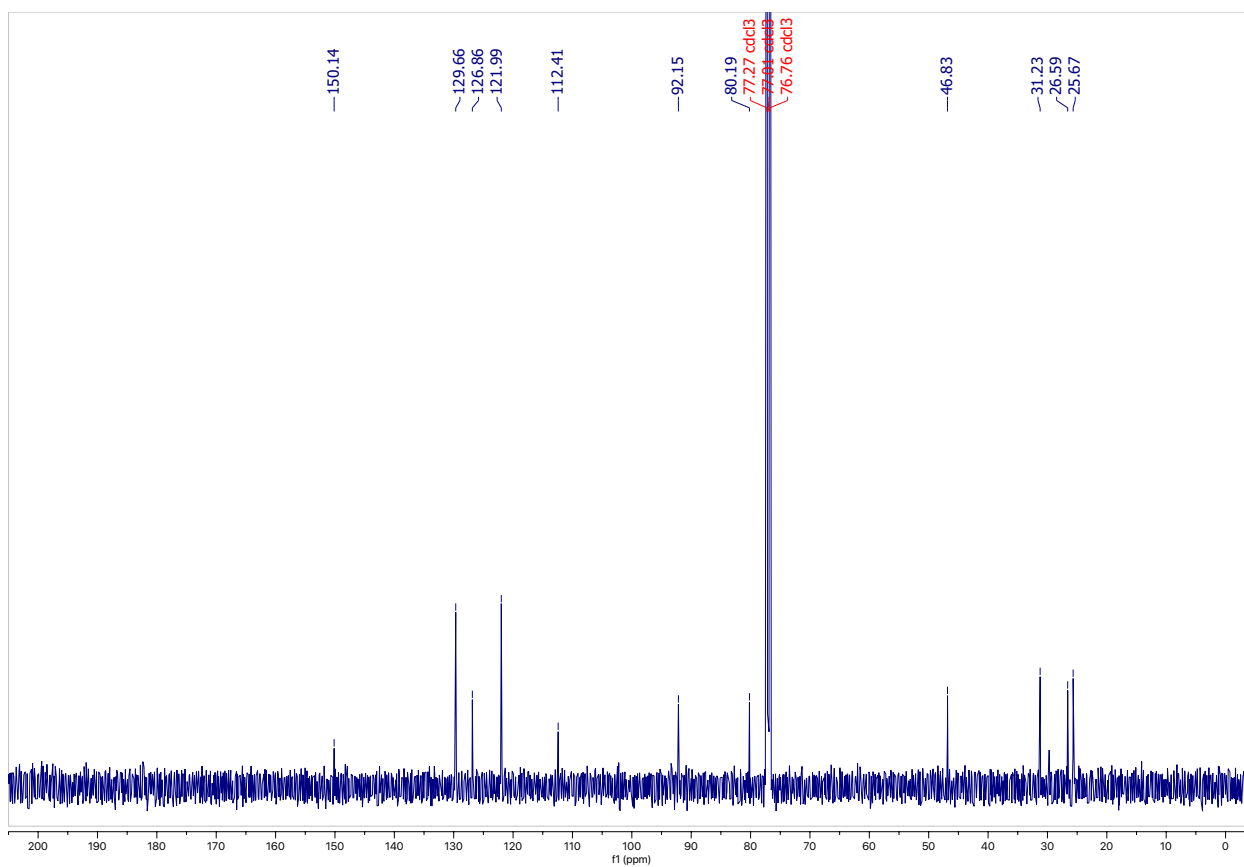
**3n: <sup>1</sup>H NMR (400 MHz, Benzene-*d*<sub>6</sub>)**



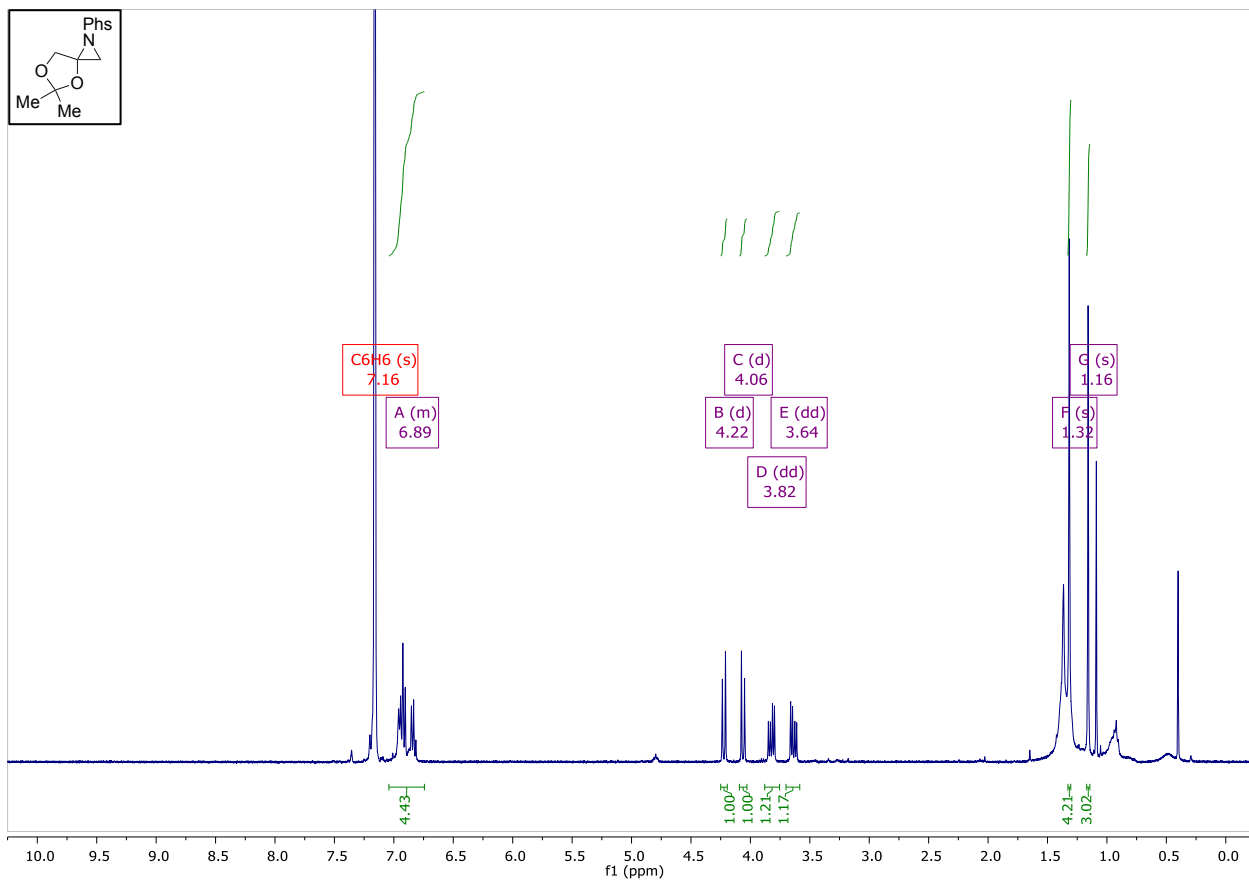
**3n: <sup>13</sup>C NMR (101 MHz, Benzene-*d*<sub>6</sub>)**



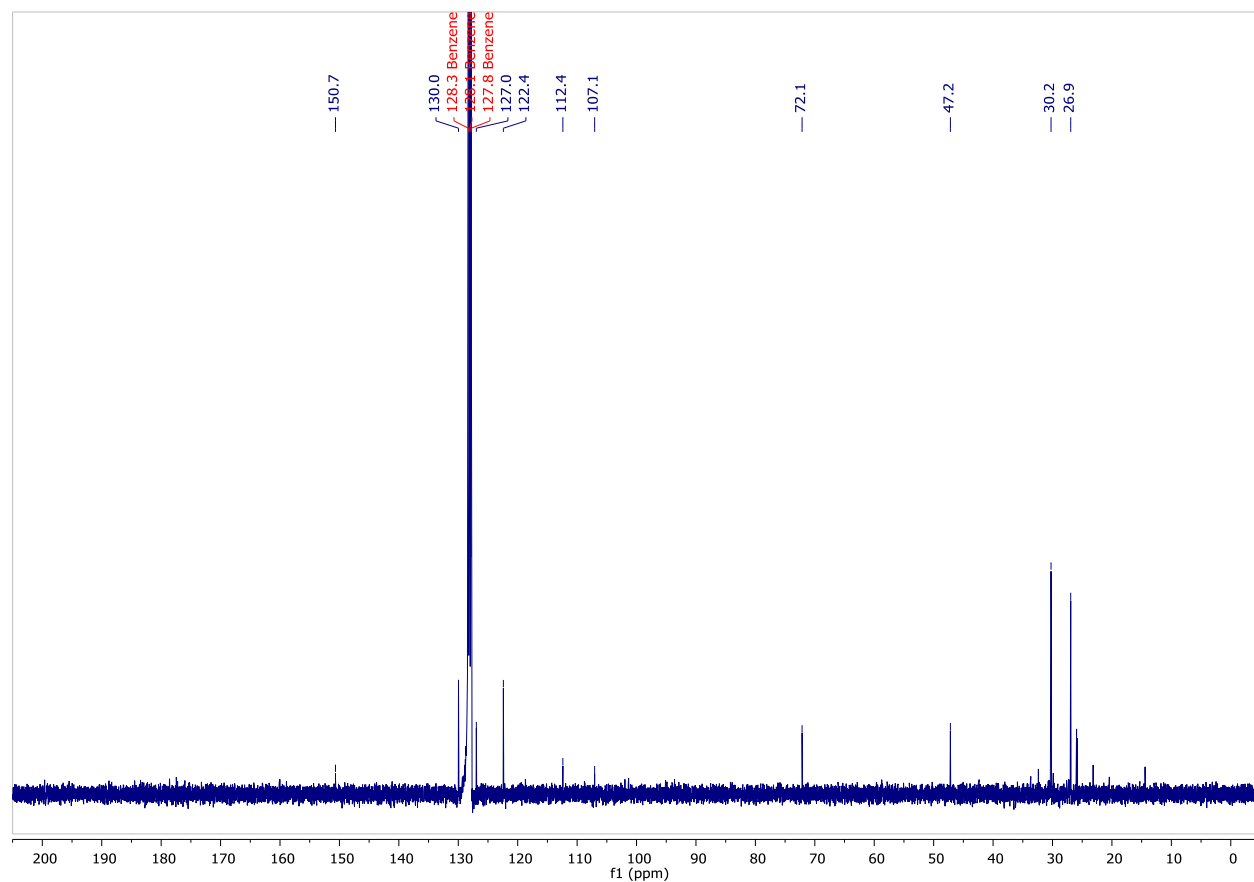
**3o: <sup>1</sup>H NMR (500 MHz, Chloroform-d)**



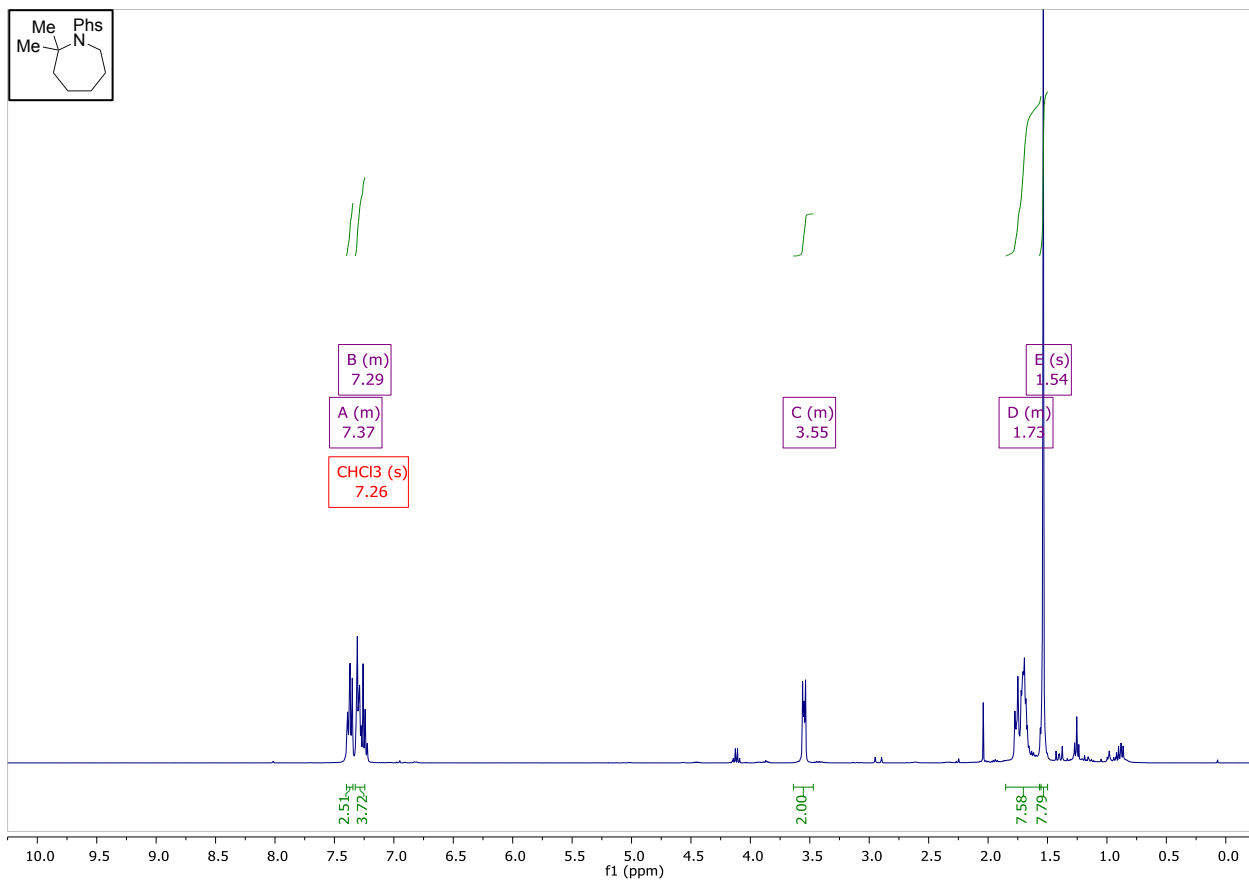
**3o: <sup>13</sup>C NMR (126 MHz, Chloroform-d)**



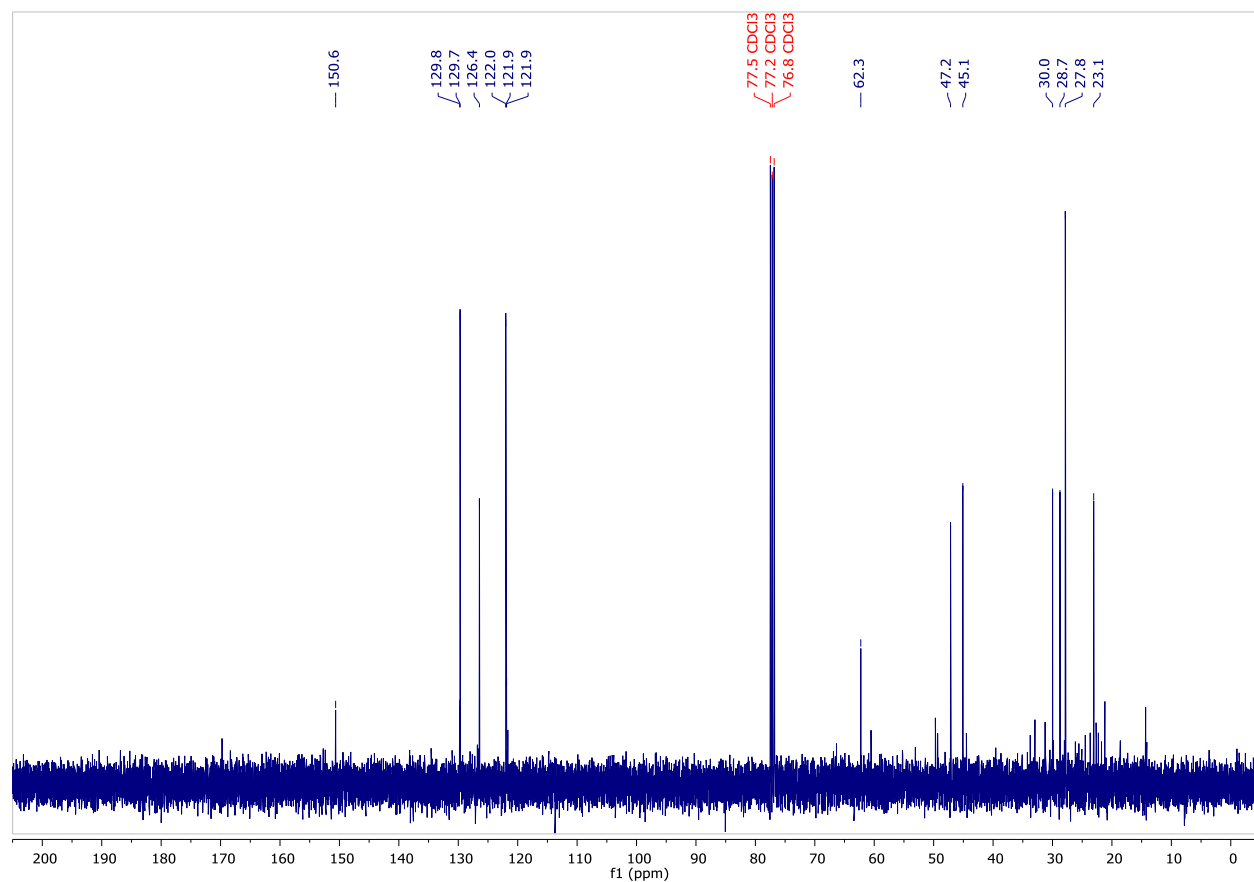
**3p: <sup>1</sup>H NMR (400 MHz, Benzene-*d*<sub>6</sub>)**



**3p: <sup>13</sup>C NMR (101 MHz, Benzene-*d*<sub>6</sub>)**

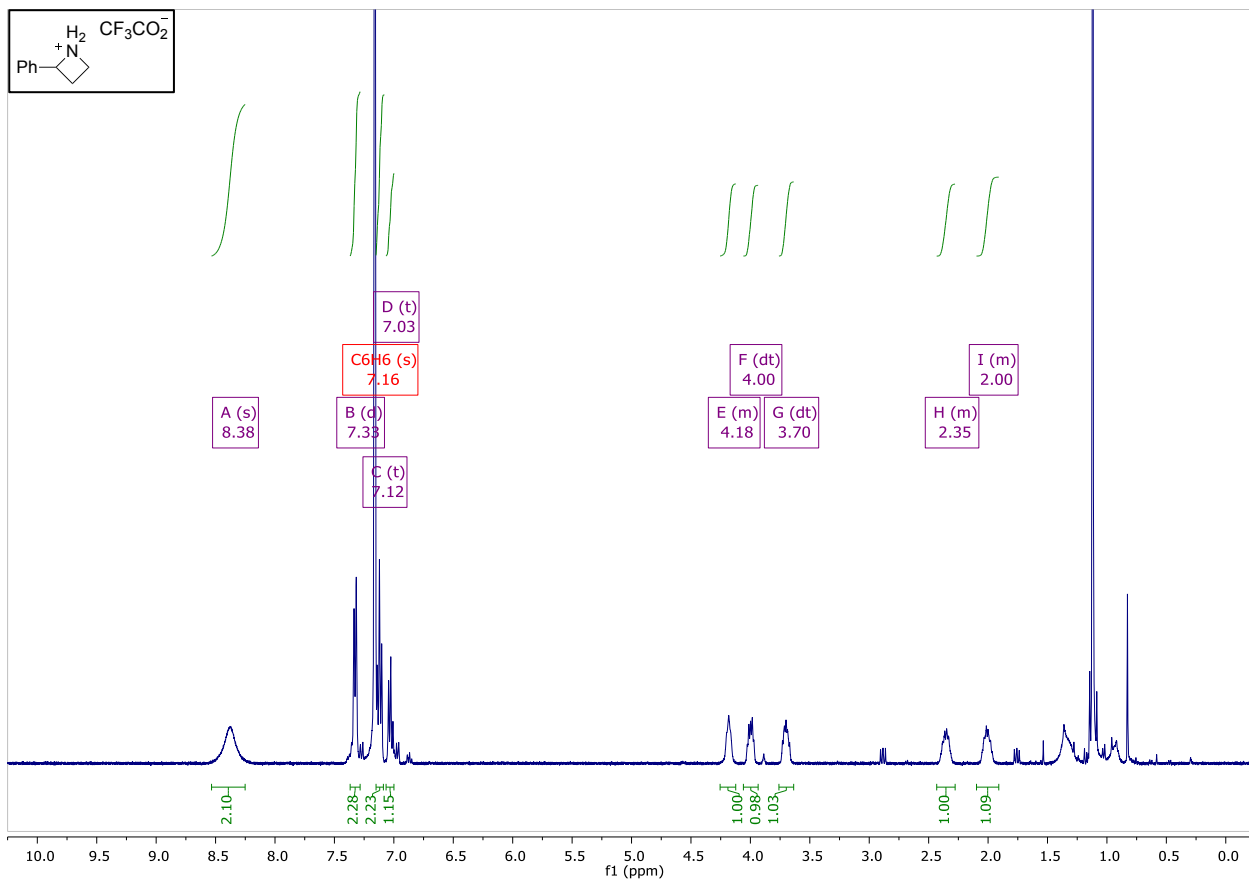


**3q: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)**

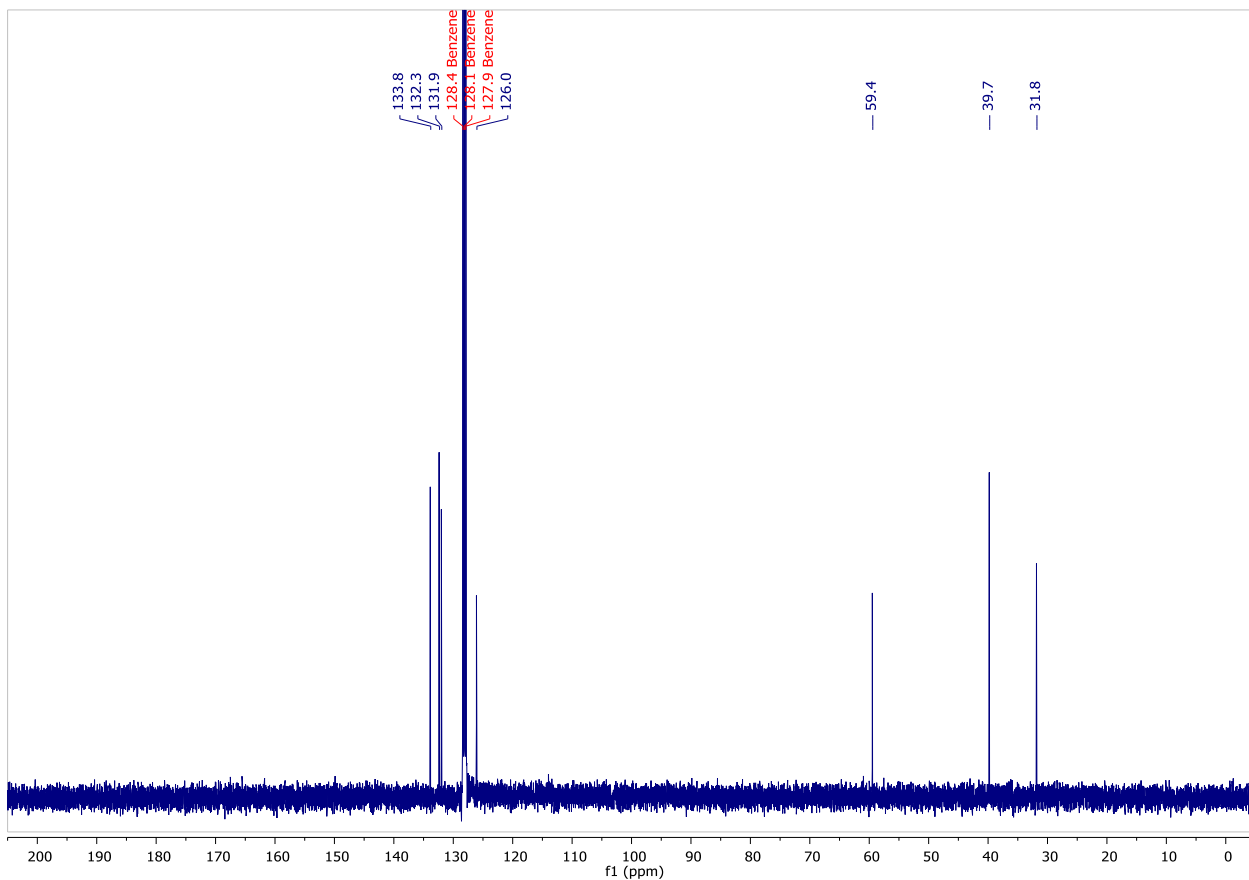


**3q: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)**

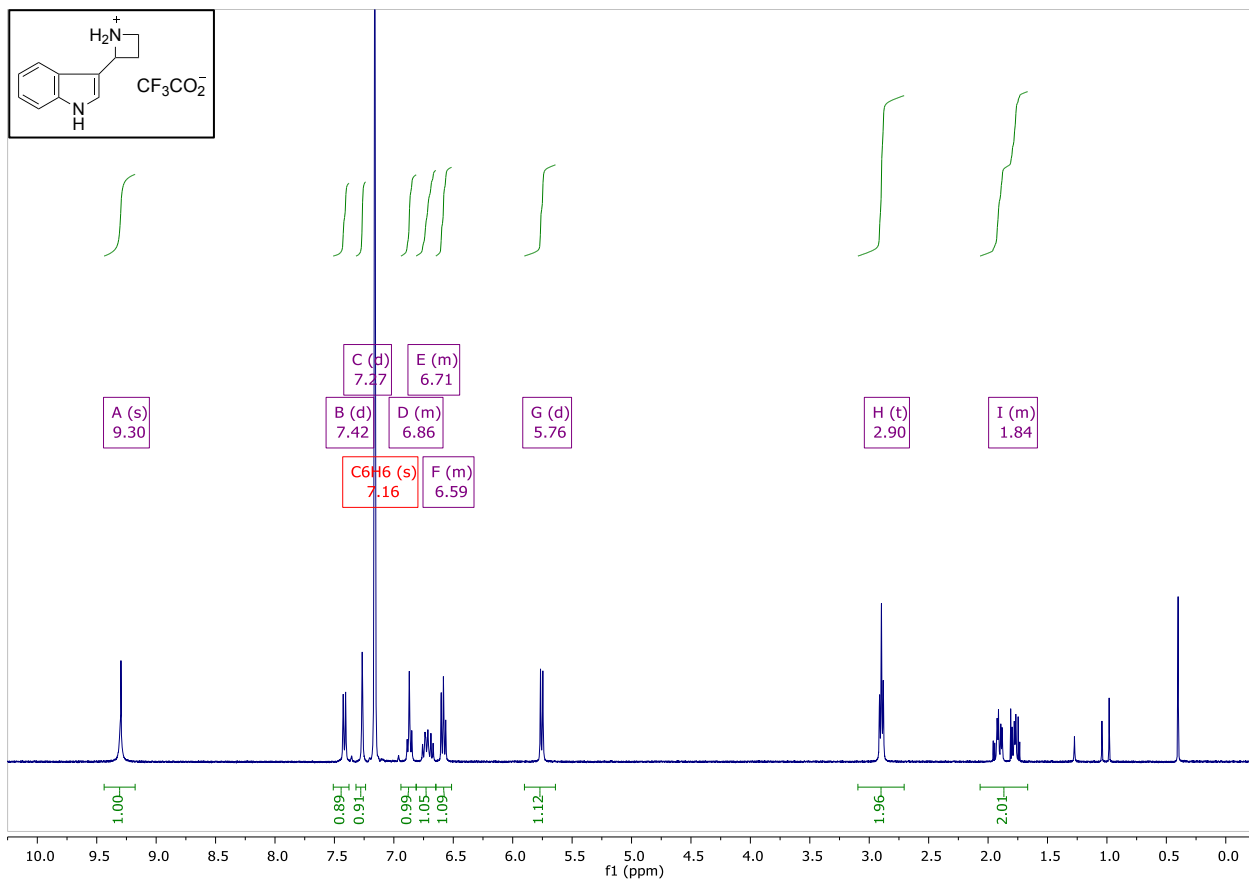




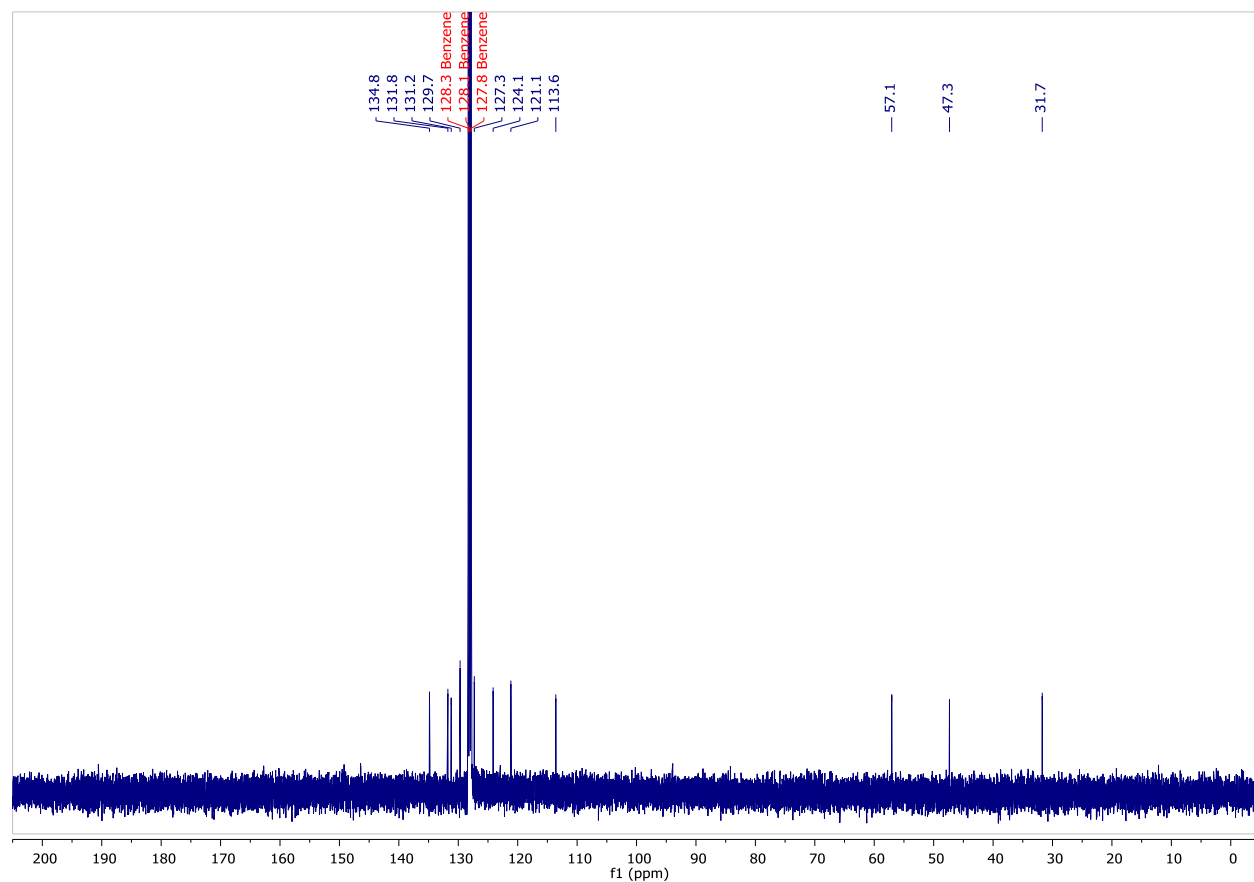
**4a:  $^1\text{H}$  NMR (400 MHz, Benzene- $d_6$ ) ( $\text{CF}_3\text{CO}_2\text{H}$  Salt)**



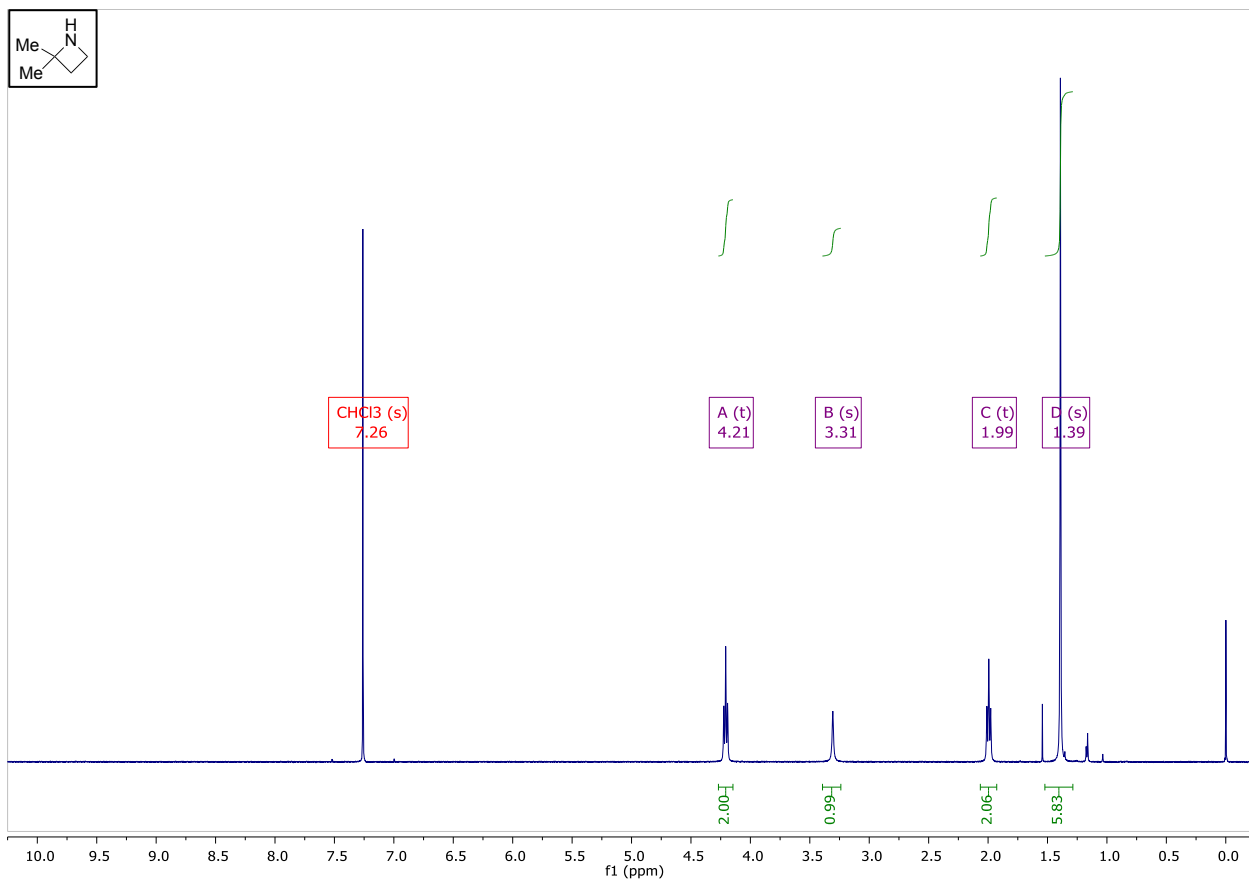
**4a:  $^{13}\text{C}$  NMR (101 MHz, Benzene- $d_6$ ) ( $\text{CF}_3\text{CO}_2\text{H}$  Salt)**



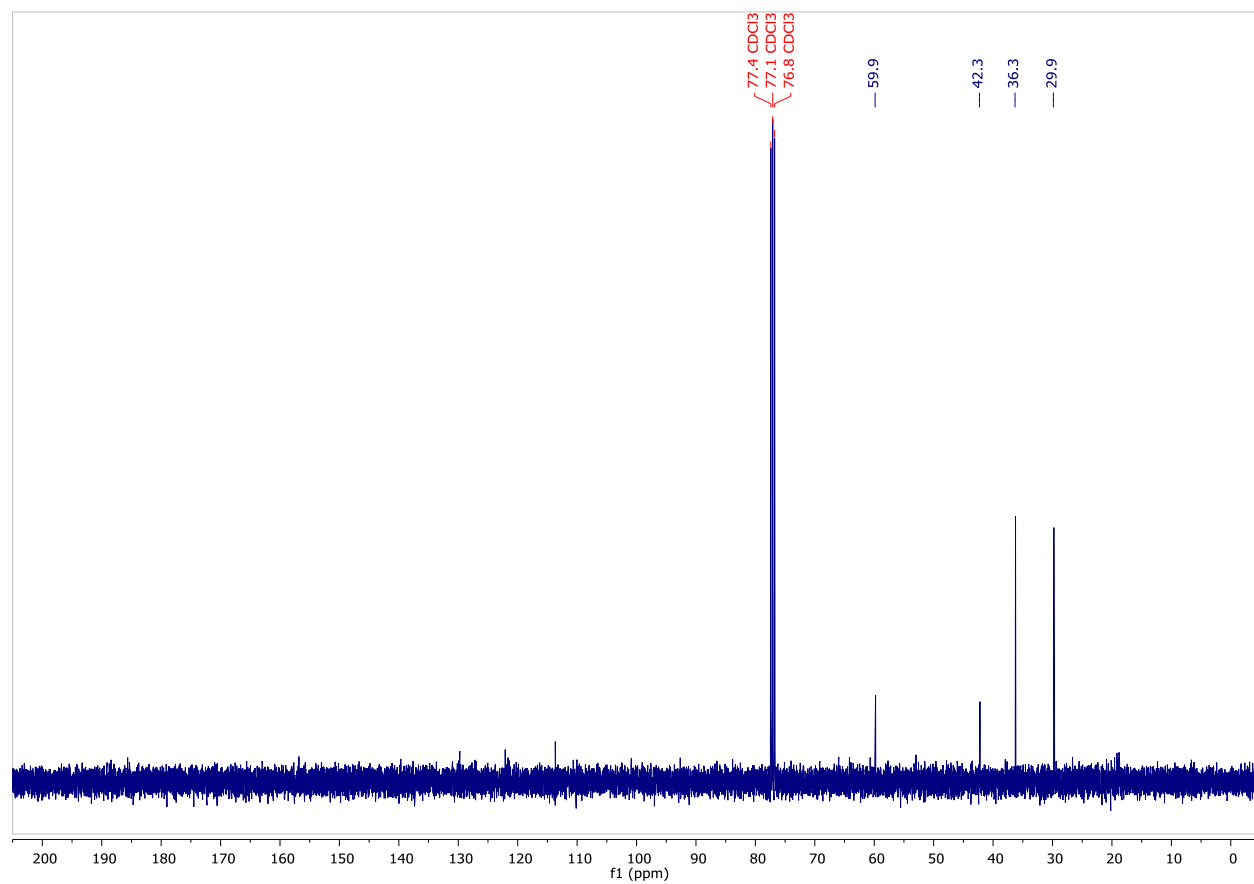
**4i: <sup>1</sup>H NMR (400 MHz, Benzene-*d*<sub>6</sub>) (CF<sub>3</sub>CO<sub>2</sub>H Salt)**



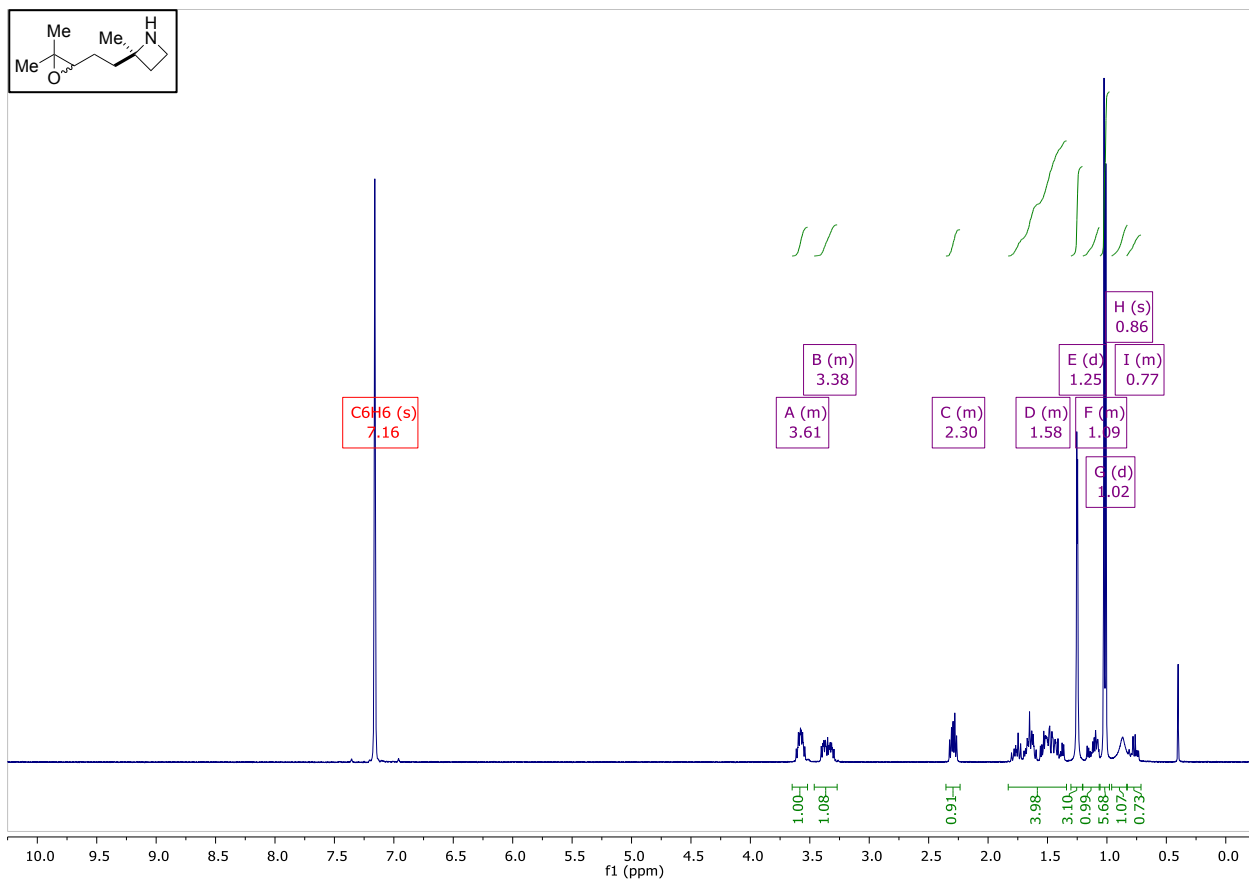
**4i: <sup>13</sup>C NMR (101 MHz, Benzene-*d*<sub>6</sub>) (CF<sub>3</sub>CO<sub>2</sub>H Salt)**



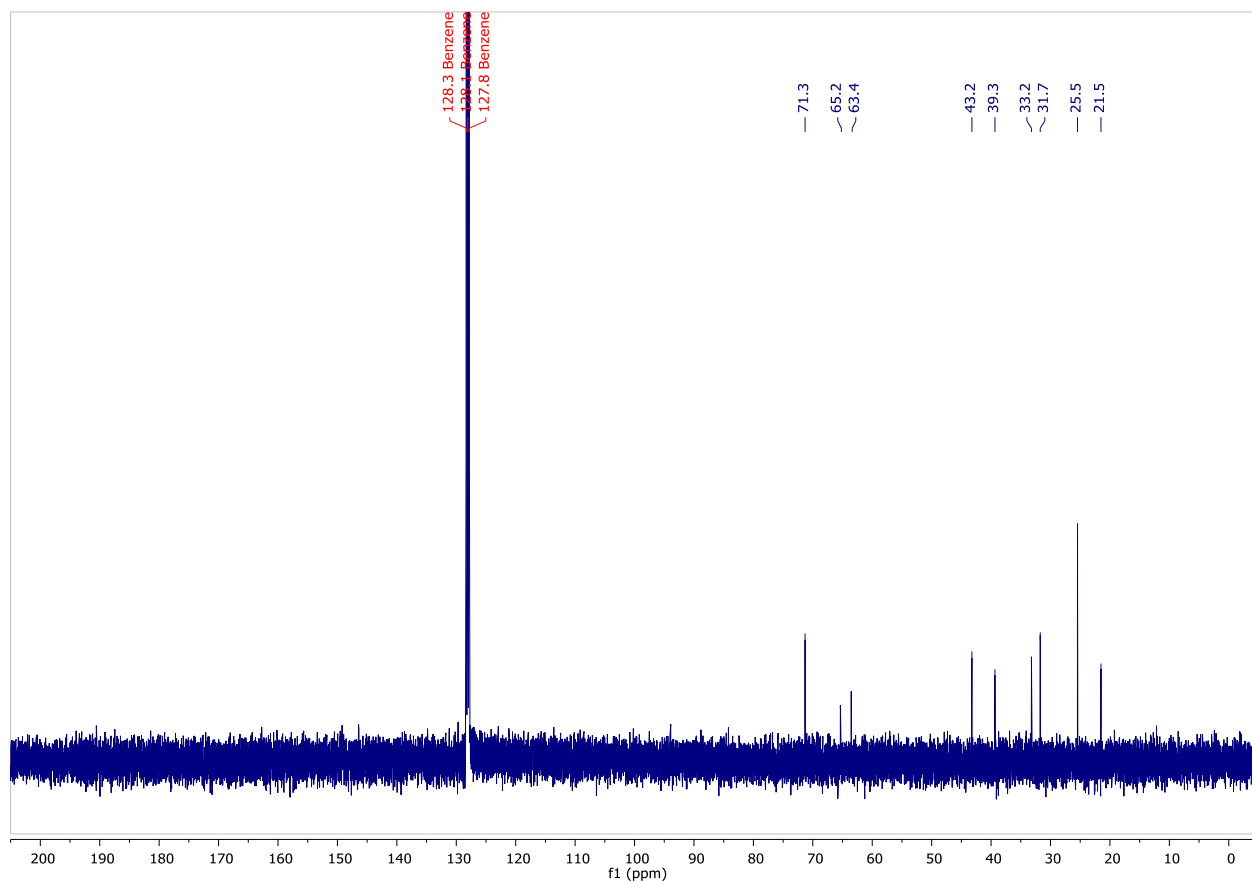
**4k: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)**



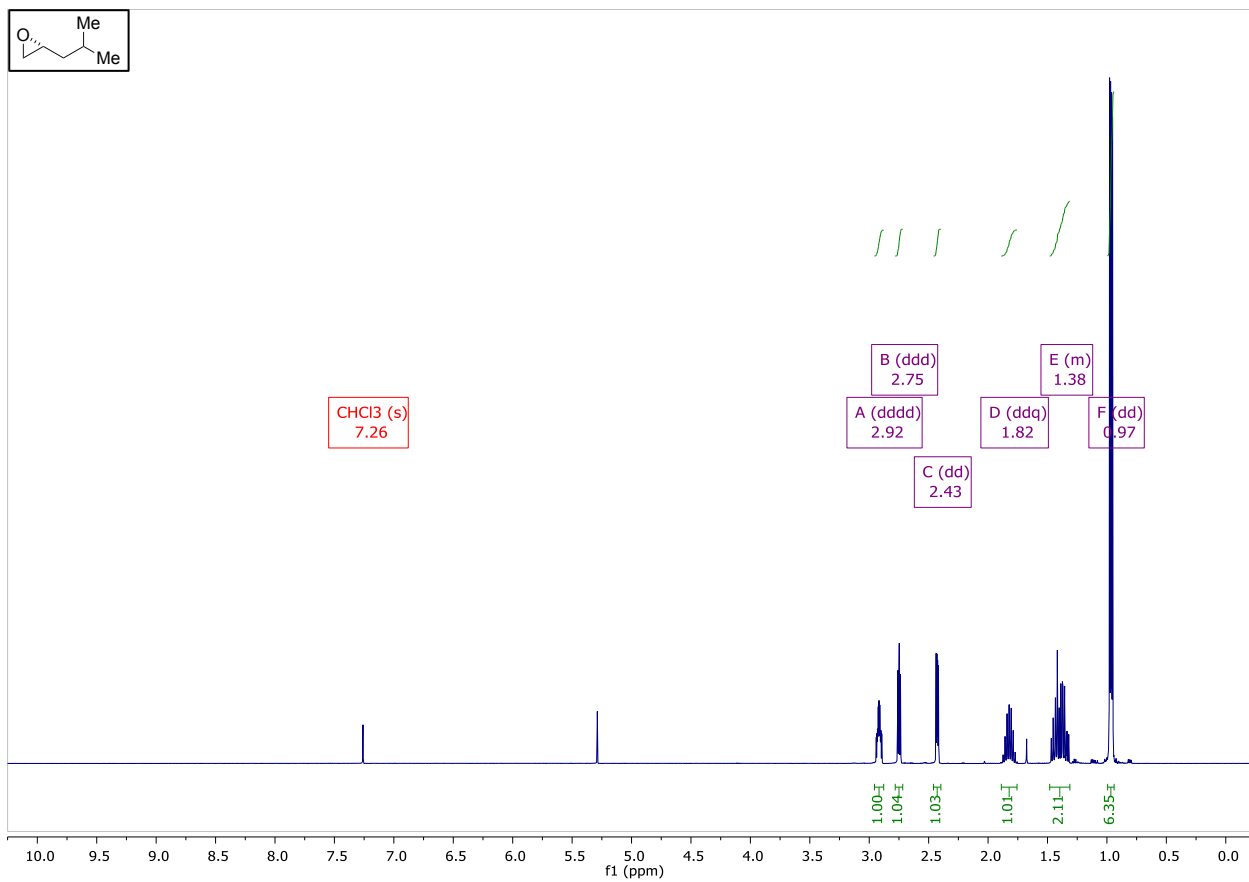
**4k: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)**



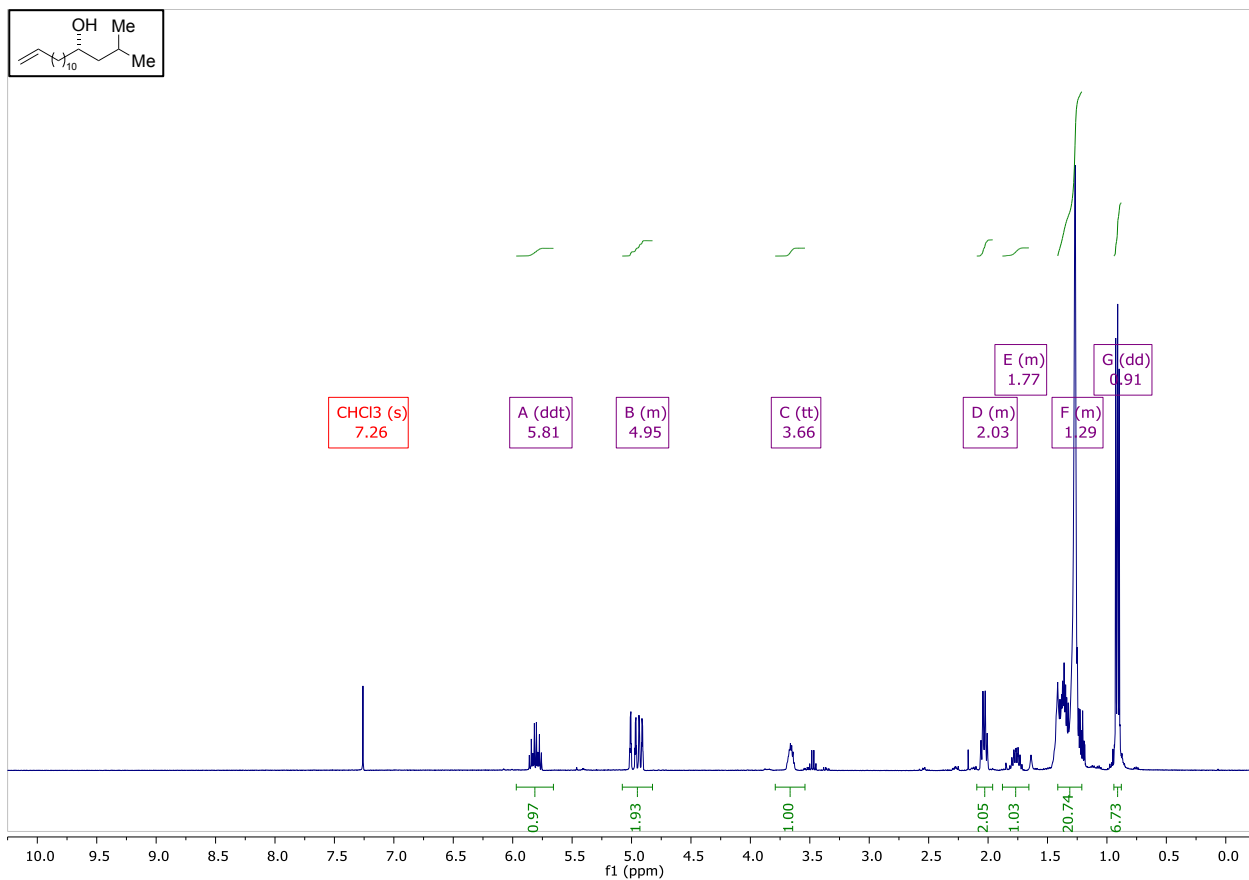
**4l: <sup>1</sup>H NMR (400 MHz, Benzene-*d*<sub>6</sub>)**



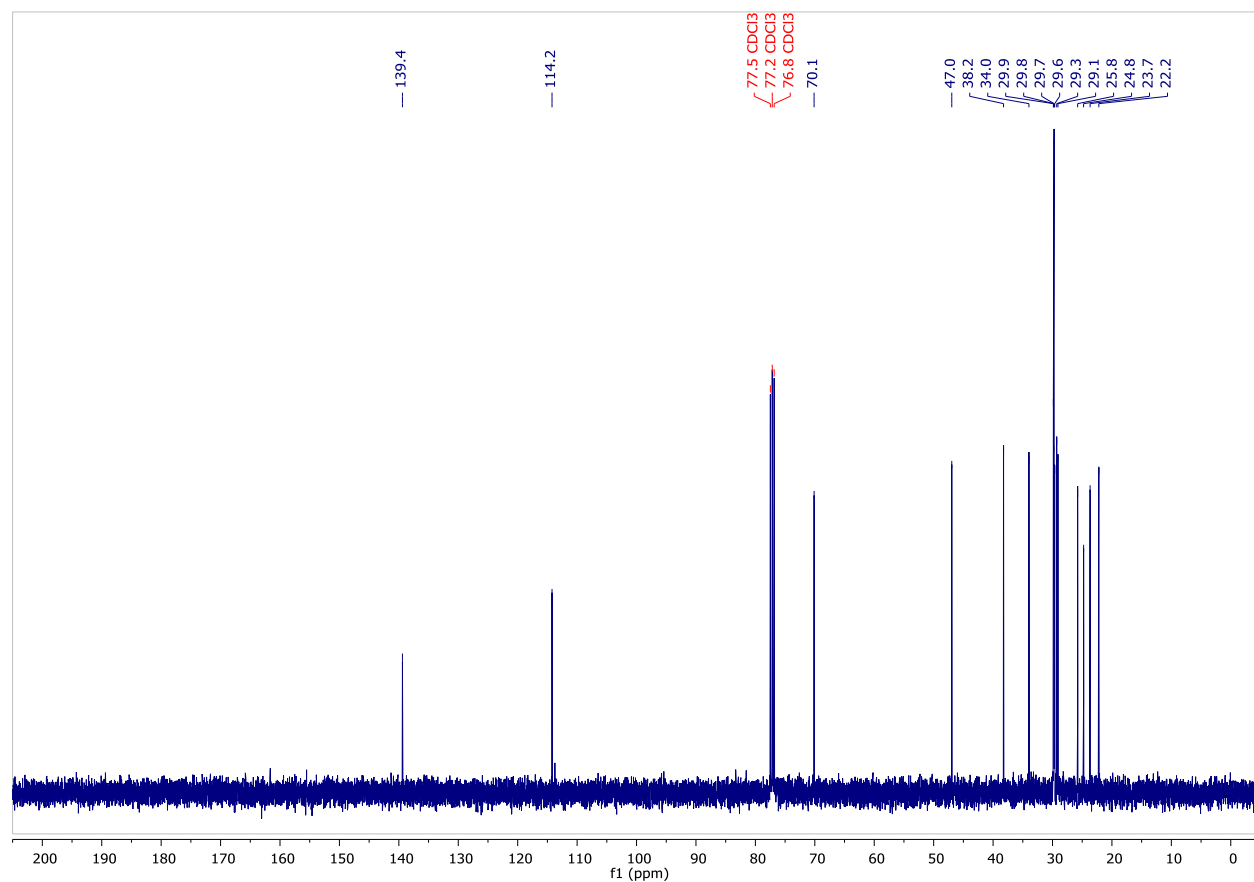
**4l: <sup>13</sup>C NMR (101 MHz, Benzene-*d*<sub>6</sub>)**



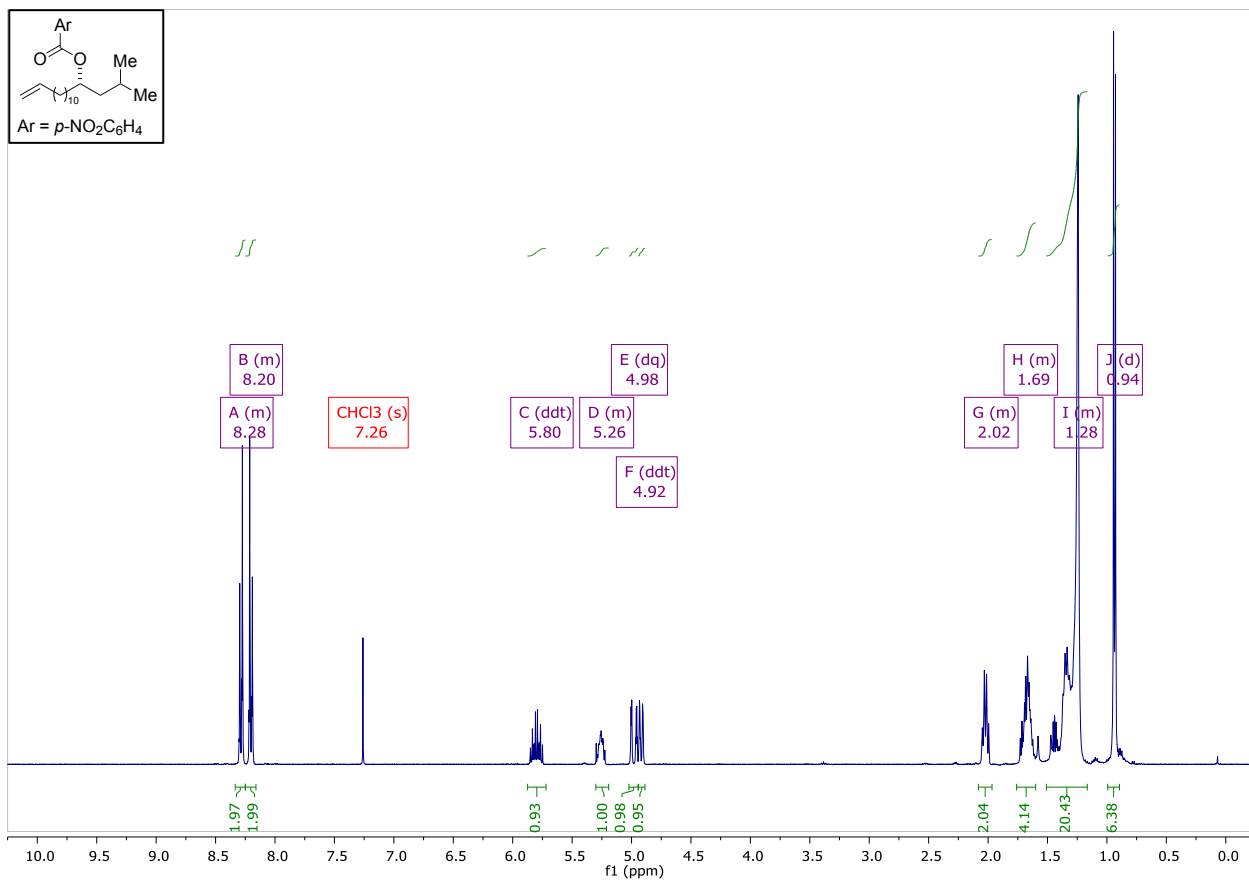
5: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)



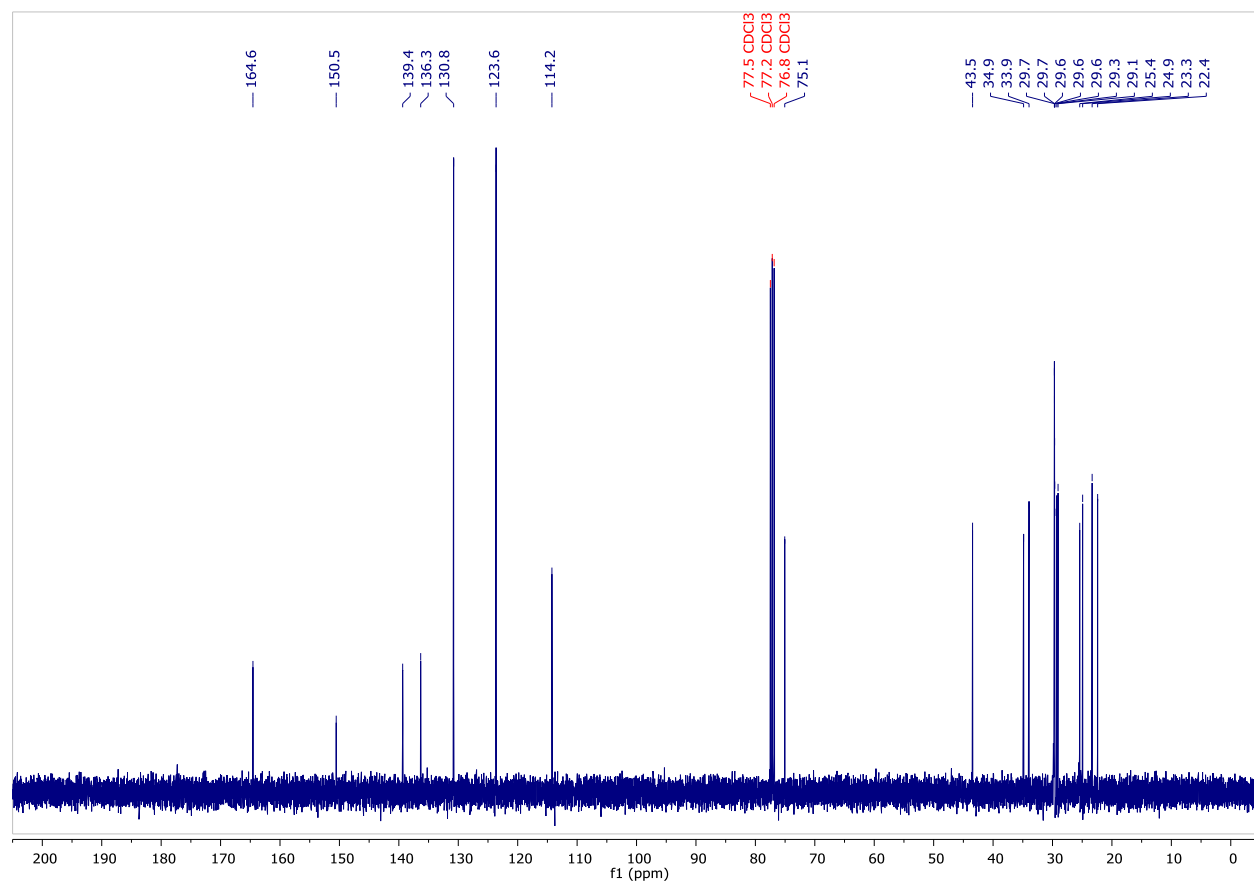
6: <sup>1</sup>H NMR (400 MHz, Chloroform-d)



6: <sup>13</sup>C NMR (101 MHz, Chloroform-d)



7: <sup>1</sup>H NMR (400 MHz, Chloroform-*d*)



7: <sup>13</sup>C NMR (101 MHz, Chloroform-*d*)

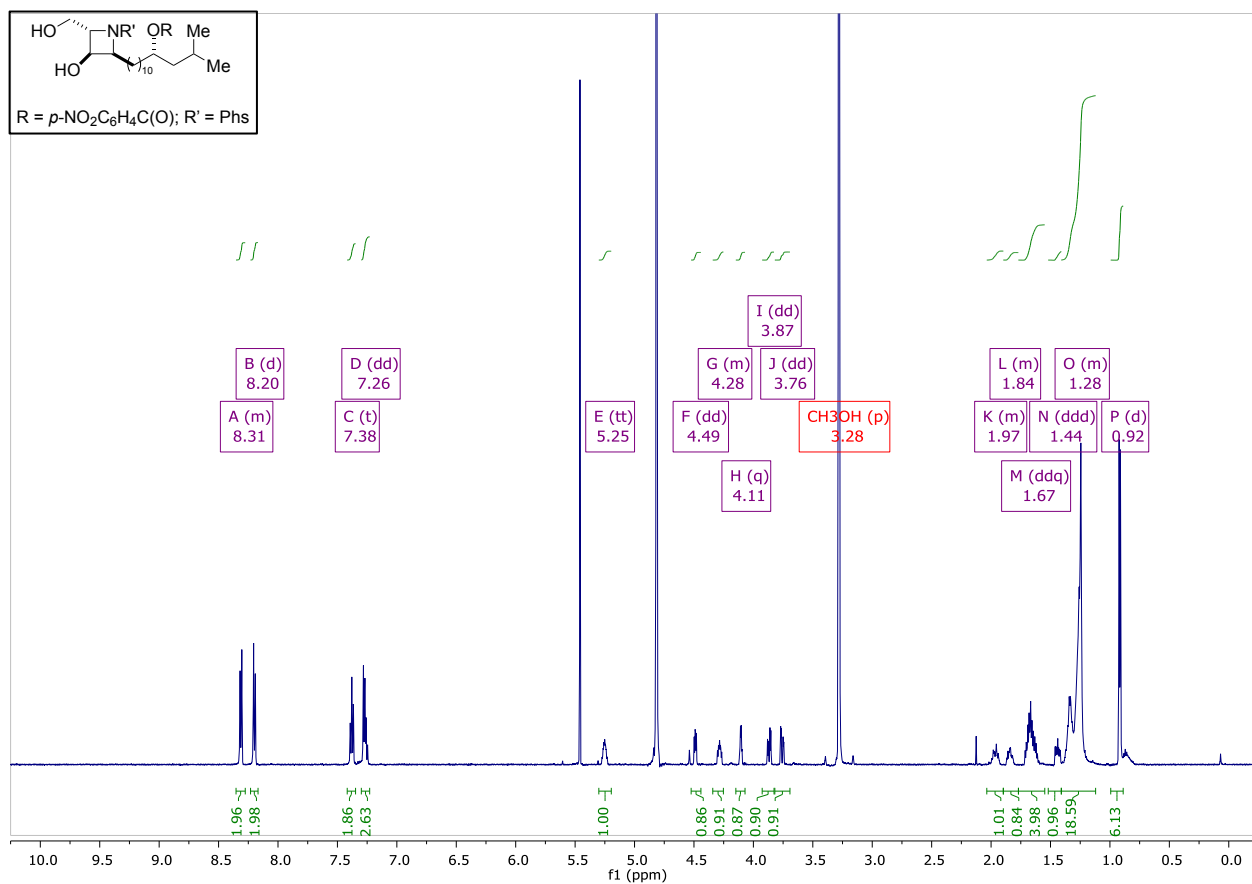




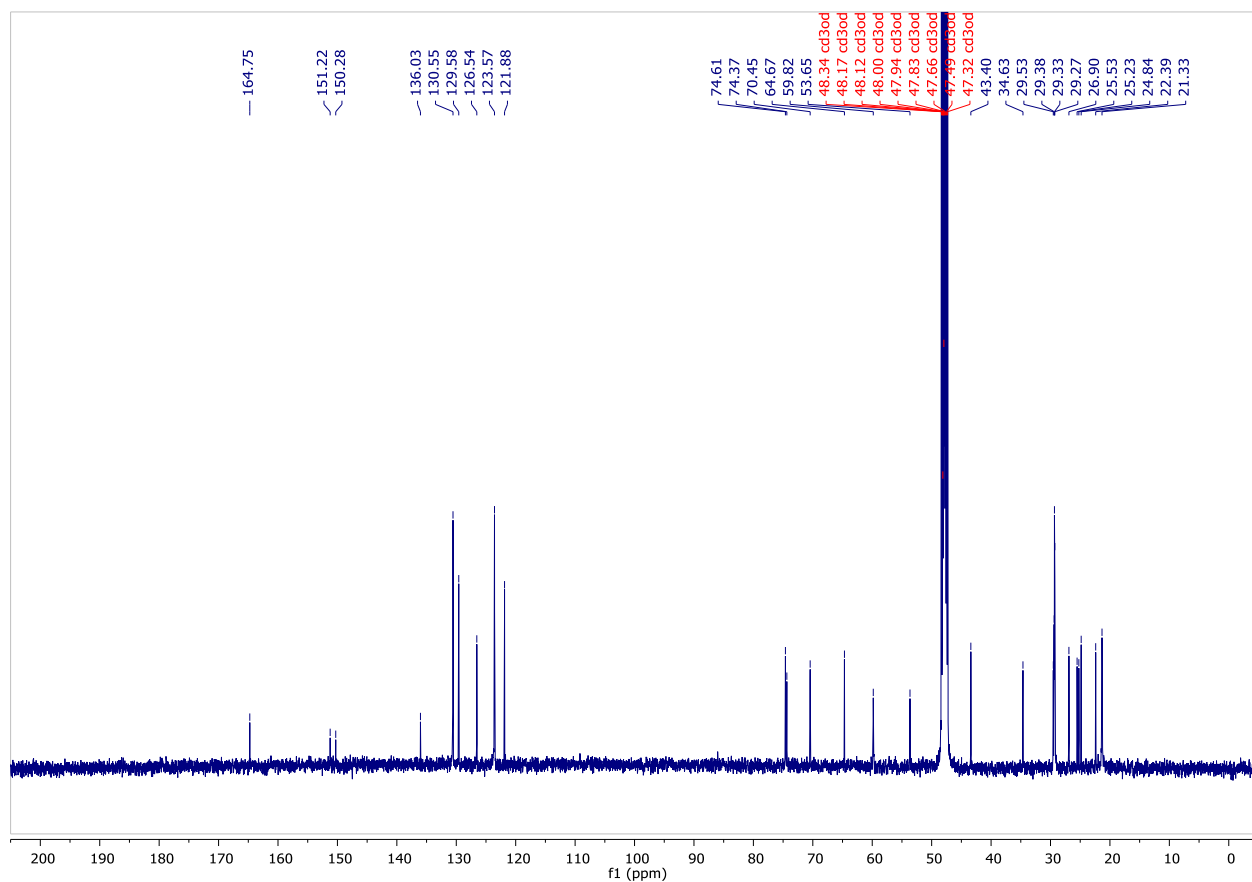




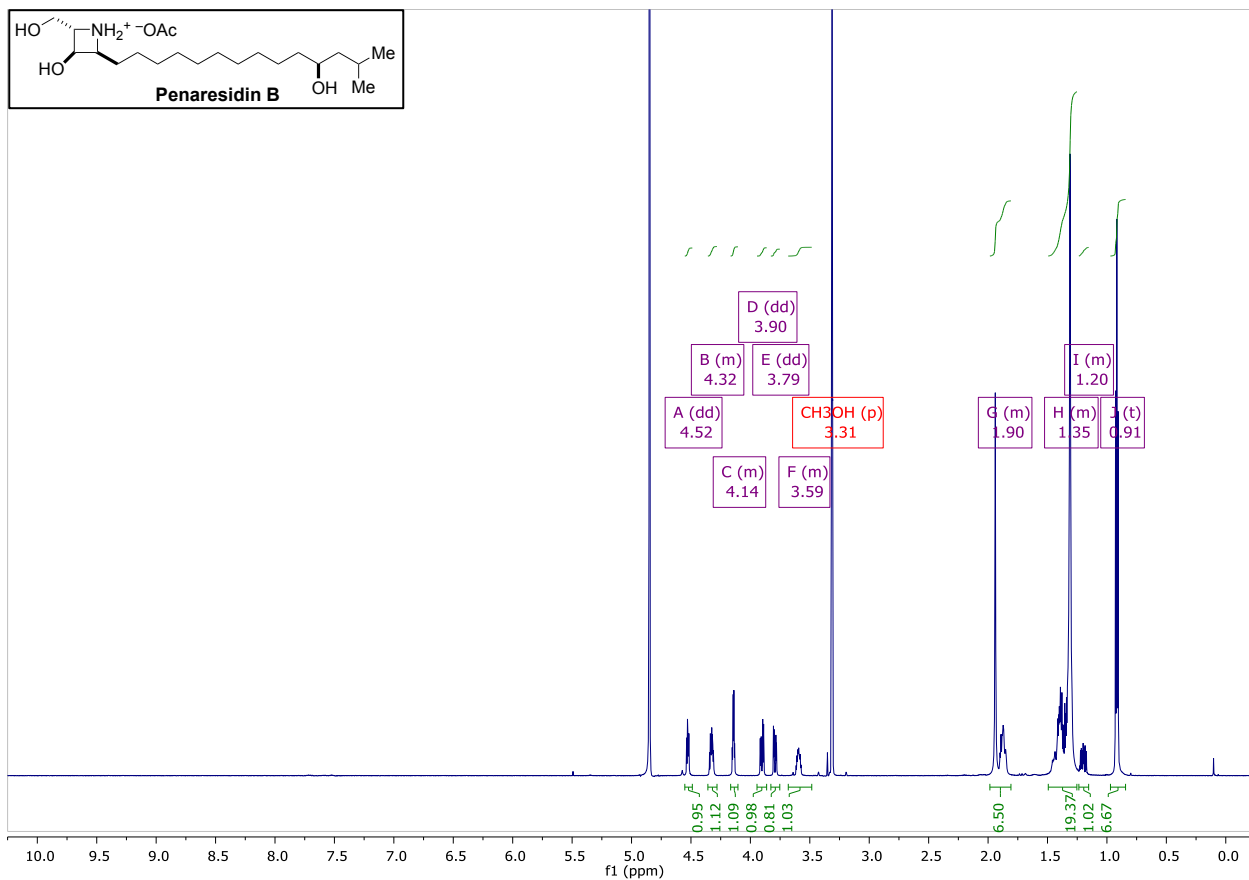




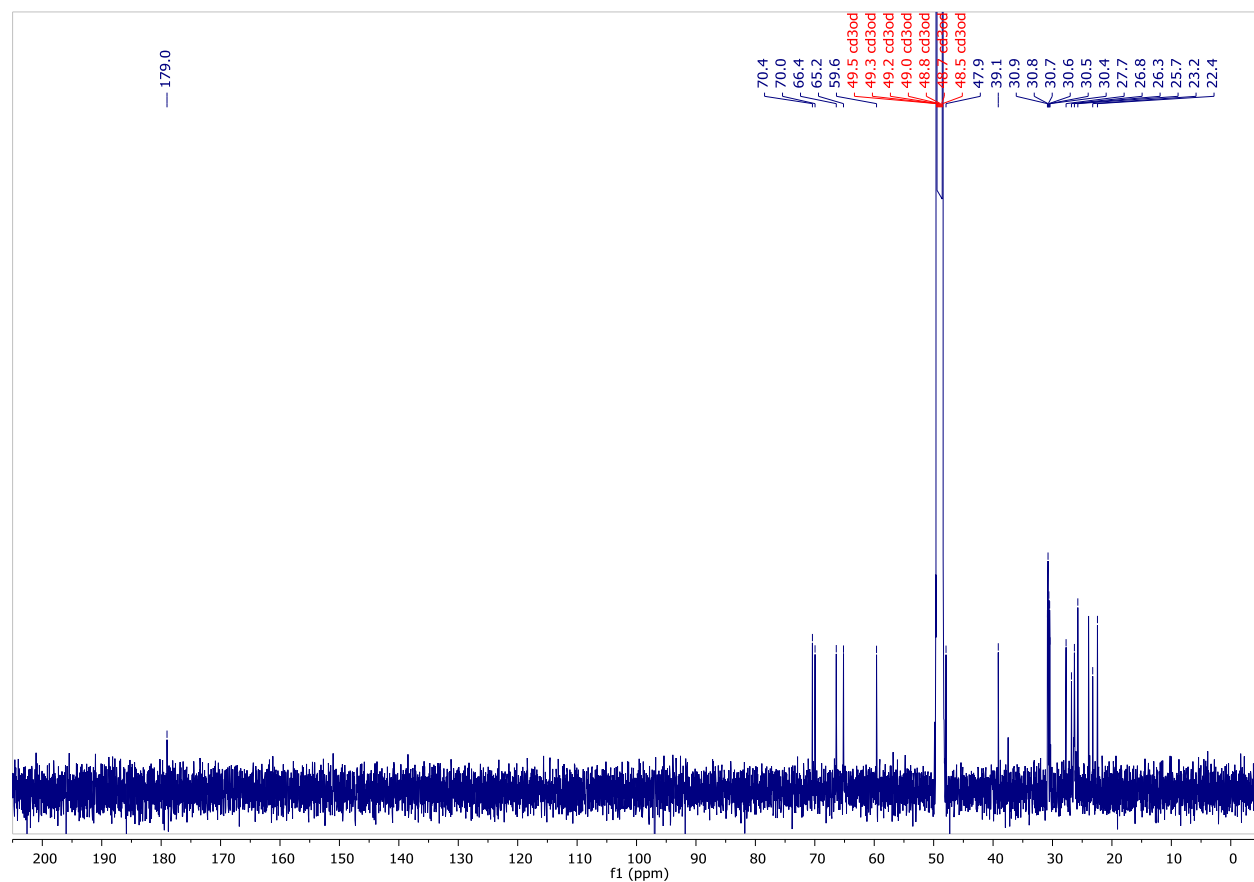
12:  $^1\text{H}$  NMR (600 MHz, Methanol- $d_4$ )



12:  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ )



**Penaresidin B:  $^1\text{H}$  NMR (600 MHz, Methanol- $d_4$ ) (AcOH salt)**



**Penaresidin B:  $^{13}\text{C}$  NMR (126 MHz, Methanol- $d_4$ ) (AcOH salt)**

Supporting Information - azetidine final draft 082619.pdf (14.56 MiB)

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