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Base-mediated formation of N-hydroxy- and N-alkoxyindoles, synthesis of dilemmaones A and B, and novel efforts in indole methodology and total synthesis

Katharine Elizabeth Lambson

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Base-mediated formation of *N*-hydroxy- and *N*-alkoxyindoles, synthesis of dilemmaones A and B, and novel efforts in indole methodology and total synthesis

Katharine Elizabeth Lambson

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In partial fulfillment of the requirements for the degree of

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in

Chemistry

Björn C.G. Söderberg, Ph.D., Chair

Patrick Callery, Ph.D.

Harry O. Finklea, Ph.D.

Jessica Hoover, Ph.D.

Brian Popp, Ph.D.

Department of Chemistry

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Abstract

Base-mediated formation of *N*-hydroxy- and *N*-alkoxyindoles, synthesis of dilemmaones A and B, and novel efforts in indole methodology and total synthesis

Katharine E. Lambson

A novel and facile base-mediated formation of *N*-hydroxy- and *N*-alkoxyindoles from 2-(2-nitrophenyl)butenoates has been developed. Either potassium *tert*-butoxide in *tert*-butanol or sodium *tert*-pentoxide in toluene, with or without the subsequent addition of an electrophile, can be used to afford an array of *N*-oxyindoles. The first total syntheses of dilemmaones A and B has been accomplished, utilizing Kosugi-Migita-Stille couplings and a reductive cyclization of an epoxide precursor with hydrogen gas in the presence of either palladium on carbon or platinum oxide as the key steps. Progress toward the total synthesis of dilemmaone C using similar methodology has been made. Additional methodological work, including screening of a regioselective Mizoroki-Heck reaction to form *o*-nitrostyrenes has been performed. Work toward the synthesis of the marinoquinolines has been studied, wherein the key step in precursor synthesis is a one-pot condensation and cyclization to form the quinoline core.

In memory of my sister,

Camryn Gohmann;

Dedicated to my husband,

Jeremy Lambson

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Gohmann, and brother Chris in Minnesota. To Dale, Dave, and Jo Lambson in Utah. To my sister, Camryn: the memory of you has kept me going when things were hardest.

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Chapter 1—Base-catalyzed cyclization to form *N*-alkoxy and *N*-hydroxyindoles

I.   Introduction

     N-hydroxy- and *N*-alkoxyindoles have received an increased amount of attention over the last decades for several reasons. Both classes of compounds are present in an array of biologically active natural and synthetic products.[1] Examples of structurally diverse natural compounds that contain either an *N*-hydroxy- or *N*-alkoxyindole core include the cytotoxic compound stephacidin B (**1**),[2] tetrahydro-*β*-carboline derivative **2**,[3] and (*R*)-paniculidine B (**3**)[4] (Figure 1). Additionally, synthetic *N*-hydroxyindoles such as **4** can act as powerful inhibitors of human lactate dehydrogenase isoform A (LDH-A).[5] Further, derivatives of indole-3-carbinol such as *N*-alkoxyindole **5** (Figure 1), have been shown to enhance the I3C-induced G1 cell cycle arrest of human breast cancer cells.[6] *N*-hydroxy-and *N*-alkoxyindoles have additionally found widespread use as synthetic intermediates, particularly toward the production of previously difficult-to-access precursors to indole alkaloids.[7]
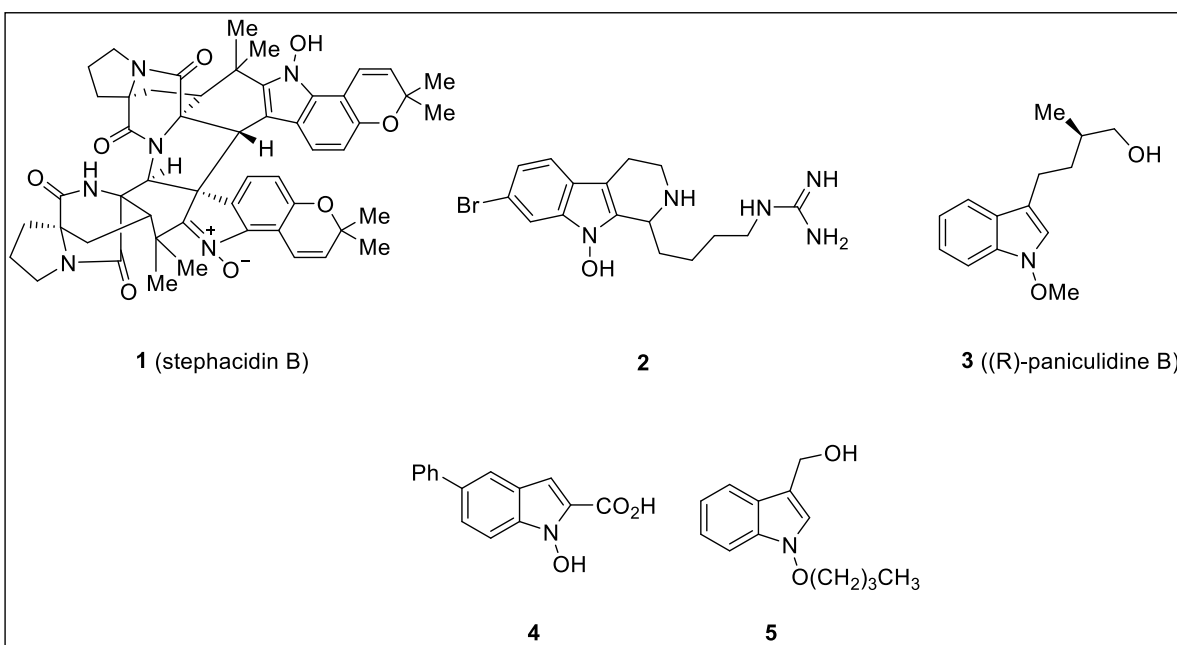
Figure 1. Structures of bioactive natural products **1**-**3** and synthetic compounds **4** and **5**.

There are a number of reported synthetic routes to *N*-hydroxyindoles. Some examples of how these compounds can be formed are by the oxidations of indoles[8] and indolines,[9] reductive cyclizations of 2-(2-nitrophenyl)-aldehydes and -ketones,[10] Batcho-Leimgruber type indole synthesis,[11] annulation of nitrosoarenes with alkynes[12] and rhodium-catalyzed cyclization of arylnitrones[13] (Scheme 1). *N*-alkoxyindoles have only been obtained by alkylation of the corresponding *N*-hydroxyindole derivatives in the presence of a base.[14, 15]
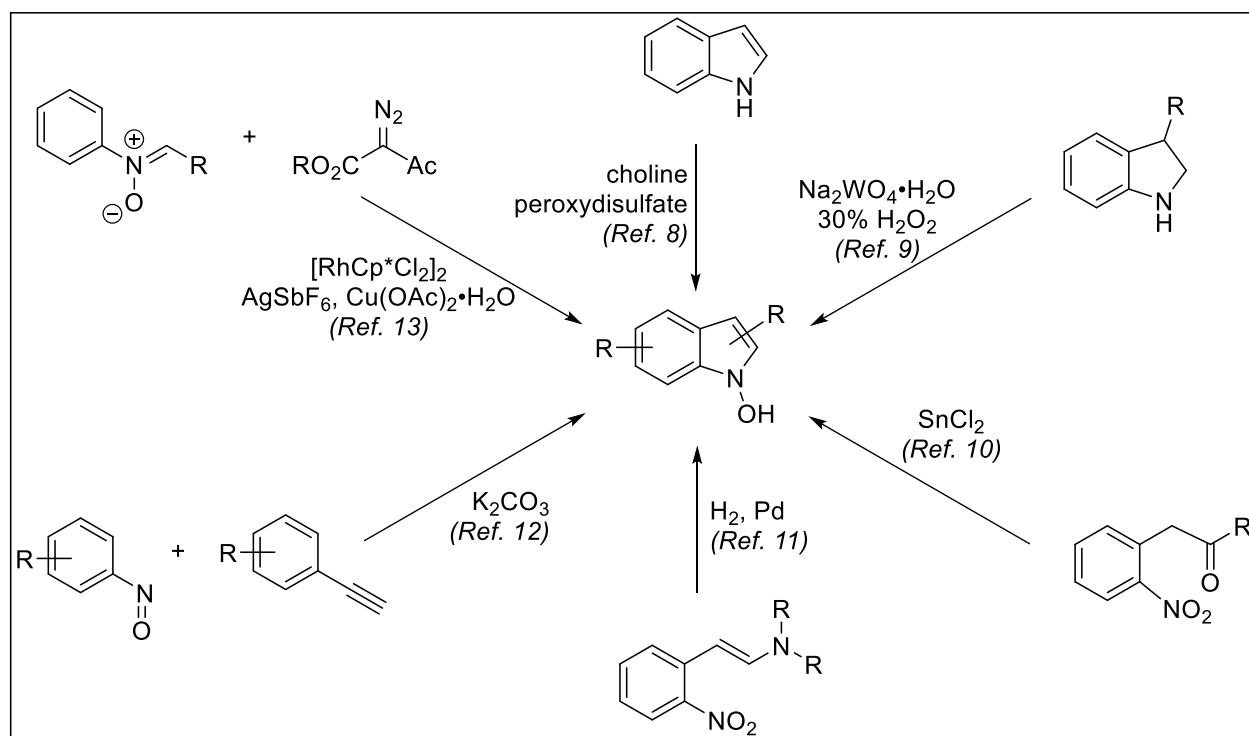
Scheme 1. Previously reported transformations to *N*-hydroxyindoles.

Of particular note to this research is the report by Wróbel and Mąkosza of three examples of the conversion of *tert*-butyl 2-(2-nitroaryl)butanoates to *N*-hydroxyindole derivatives in the presence of a strong base.[16] One example illustrated in Scheme 2 showcases the treatment of *tert*-butyl 2-(5-chloro-2-nitrophenyl)butanoate with sodium

hydroxide in a mixed solvent system to afford *tert*-butyl 5-chloro-*N*-hydroxyindole-3-carboxylate in moderate yield.
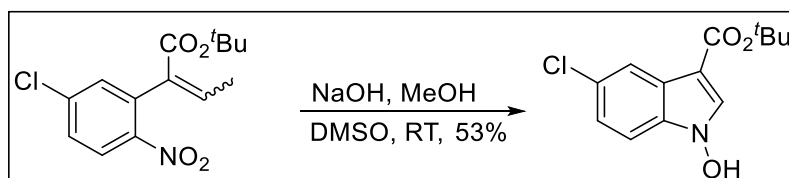
Scheme 2. Cyclization of a *tert*-butyl 2-(5-chloro-2-nitrophenyl)butanoate.

Previously reported in our lab by Dr. Sergei Banini is an example of a related cyclization using ethyl 2-(5-methoxy-2-nitrophenyl)butenoate (**6**).[17] The substrate was deprotonated with potassium *tert*-butoxide followed by addition of methyl iodide with the intent to trap reactive intermediates (Scheme 3). Interestingly, he isolated only *N*-methoxyindole **8** without a trace of other alkylation products. It is noteworthy to mention that treatment of the corresponding nitrile, **7**, under the same reaction conditions only yielded quinoline *N*-oxide **9** (Scheme 3).
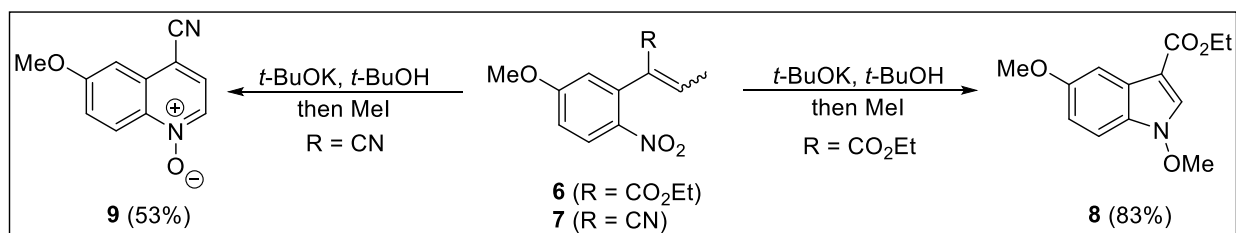
Scheme 3. Cyclization of **6** to *N*-methoxyindole **8** or of **7** to quinoline *N*-oxide **9**.

In addition to the example of the formation of *N*-methoxyindole **8** seen in Scheme 3, Dr. Nurul Ansari of the Söderberg lab recently described a related cyclization of 2-nitroimine derivatives to yield *N*-methoxybenzimidazoles (Scheme 4).[18] Based on the observation that 2-(2-nitroaryl)butenoates esters can be transformed into *N*-alkoxyindoles, we sought to expand on this transformation. Herein is described the scope and limitations of the direct and facile base-mediated synthesis of *N*-hydroxy- and *N*-alkoxyindoles.
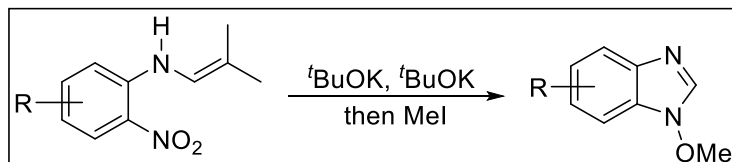
Scheme 4. Formation of *N*-methoxybenzimidazoles from 2-nitro-*N*-(2-methyl-1-propen-1-yl)benzenamines.

II.   Results and Discussion

The discovery of a base-mediated formation of *N*-methoxyindoles was initially observed by Dr. Banini during his attempts to probe the effects of nitrile versus ester functionalized cyclization precursors. The conditions shown in Scheme 3 were originally selected in his efforts to understand the preference of nitrile-substituted precursors for cyclization to quinolines, while ester-substituted precursors favored cyclization to *N*-alkoxyindoles. With the formation of *N*-methoxyindole **8** observed under basic, non-catalytic conditions, we sought to probe the versatility of this type of transformation. Using precursor **6** as a model substrate, two additional 2-(2-nitroaryl)butenoates were prepared. Ethyl ester **10** was synthesized as shown in Scheme 5 according to literature reports, and the corresponding methyl ester **11** was prepared according to a previously reported methodology.[19]
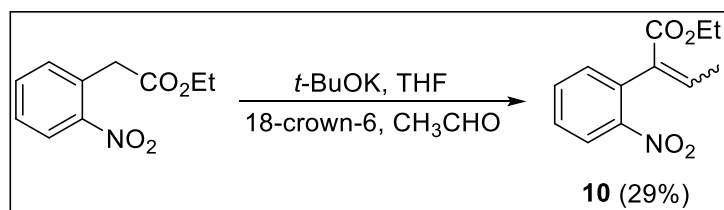
Scheme 5. Synthesis of compound **10**.

Dr. Banini pioneered the work outlined in Table 1. He found that, utilizing the same conditions as described in Scheme 3 for the cyclization of ester-derivatives, precursors **10**

and **11** also reacted to form *N*-alkoxyindoles. Precursor **10** underwent one-pot cyclization and alkylation with methyl iodide to form *N*-methoxyindole **12** in good yield (Table 1, entry 1). Methyl ester precursor **11** reacted to form methyl *N*-methoxy-3-indolecarboxylate (**15**) in 74% yield (Table 1, entry 4). Notably, compound **15** is a naturally-occurring antifungal metabolite produced by Wasabi (*Wasabia japonica*) in response to plant infection.[20] This alkaloid has also been isolated from the wild crucifer *Arabidopsis thaliana*.[21] The preparation of **11** and subsequent transformation to **15** illustrates a novel and efficient method for the preparation of this natural product.[22] For both precursors **10** and **11**, electrophiles other than methyl iodide could be used. *N*-benzyloxyindole **13** and *N*-allyloxyindole **14** (Table 1, entries 2-3) were obtained in good yields from reactions with benzyl bromide and allyl bromide, respectively.

Table 1. Formation of *N*-alkoxyindoles using potassium *tert*-butoxide.
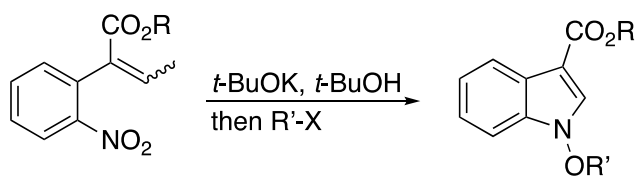
Entry	2-(2-nitrophenyl)butanoate	R'-X	N-alkoxyindole[a,b]
1	**10** (R = Et)	Me-I	**12** (R = Et, R' = Me, 84%)
2	**10** (R = Et)	Bn-Br	**13** (R = Et, R' = Bn, 78%)
3	**11** (R = Me)	Allyl-Br	**14** (R = Me, R' = $CH_2CH=CH_2$, 91%)
4	**11** (R = Me)	Me-I	**15** (R = Me, R' = Me, 74%)

[a] General conditions for the preparation of *N*-alkoxyindoles: 11 equiv. of *t*-BuOK, then 1.5 equiv. of alkylhalide. See experimental section for full details.
[b] Yield of pure product isolated after chromatography.
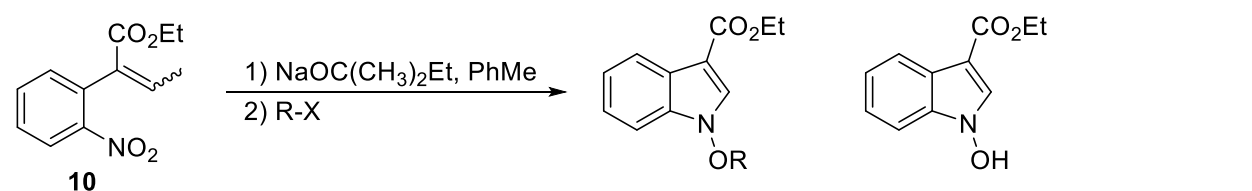
Despite the promising data reported in Table 1, the results lacked reproducibility and the values given in the Table are the best yields observed from several attempts by Dr. Banini and myself.

In an effort to develop a more consistent means of producing *N*-alkoxyindoles, we explored an alternate hindered base. Sodium *tert*-pentoxide was selected due to its commercial availability in solution and solubility in a variety of organic solvents. Treatment of **11** with sodium *tert*-pentoxide in toluene, in place of potassium *tert*-butoxide in *tert*-butanol, followed by addition of methyl iodide under the reaction conditions described in Table 2 (entry 1) did not yield the expected *N*-methoxyindole **12**. Rather, the corresponding *N*-hydroxyindole **19** was obtained as the only observed product. In an effort to encourage the formation of **12**, the amount of base was sequentially decreased. It was found that under all conditions using greater than 2 equivalents of base, the only isolated product was *N*-hydroxyindole **19** (Table 2, entries 2-3). Indeed, even when the amount of base was decreased further, **19** remained the major product, and *N*-methoxyindole **12** was isolated in only 5% yield as an inseparable mixture with 32% unreacted starting material **10** (Table 2, entry 4). To confirm that this type of cyclization does not require the presence of an alkyl halide such as MeI to proceed, **10** was reacted with 2.3 equivalents of base without the addition of methyl iodide (Table 2, entry 5). As expected, *N*-hydroxyindole **19** was isolated as the sole product, albeit in slightly lower isolated yield. The reason for this observation is unknown.

Further examination of similar alkyl halides (Table 2, entries 6-7) illustrated consistent results, in that **19** was isolated as the sole product, while the corresponding *N*-alkoxyindoles (**13** or **16**) were not observed. This formation of *N*-hydroxyindoles is most

similar to the work done by Wróbel and Mąkosza, and yields are comparable across the two studies.[16] It is worth noting that, using the reaction conditions reported in Table 2, quinoline *N*-oxides were never observed. Despite alkyl halides being unsuitable reagents for the preparation of *N*-alkoxyindoles under these reaction conditions, three alternate electrophiles, acetic anhydride, tosyl chloride, and dimethylsulfate (DMS), were screened (Table 2, entries 8-10). In these three cases, the reactions all proceeded smoothly to produce *N*-oxygenated indoles **17**, **18**, and **12**.

Table 2 Optimization of the formation of *N*-hydroxy- and *N*-alkoxyindoles from **10**.[a,b]

Entry	Equiv. base	R-X (3 equiv.)	*N*-Alkoxyindole	*N*-Hydroxyindole
1	11	MeI		**19** (52%)
2	5	MeI		**19** (51%)
3	2.3	MeI		**19** (52%)
4	1.1	MeI	**12** (5%)[c]	**19** (23%)
5	2.3	-		**19** (42%)
6	2.3	1-bromohexane	**16** (-)	**19** (47%)
7	2.3	BnBr	**13** (-)	**19** (18%)
8	2.3	Ac₂O	**17** (48%)	
9	2.3	TsCl	**18** (44%)	
10	2.3	DMS[d]	**12** (54%)	

[a] See experimental section for details. The methodology for entries 1-4 differs only in the equiv. of base used.
[b] Yields are of pure product isolated after chromatography, unless otherwise noted.
[c] Inseparable mixture of starting material (32%) and **12** (5%) as determined by ¹H-NMR.
[d] DMS = dimethyl sulfate.

With a consistent means of forming both *N*-hydroxy- and *N*-alkoxyindoles thus developed, we turned our attention to the tolerance of the reaction conditions to an expanded array of substrates. First, we chose to examine the effect of a longer alkyl chain to

determine if groups larger than formaldehyde would be eliminated over the course of the cyclization (see Scheme 10 for a mechanistic explanation). Our initial approach to forming longer chain 2-(2-nitroaryl)alkenoates involved a concurrent Wittig/iodination reaction followed by a Kosugi-Migita-Stille coupling (Scheme 6).
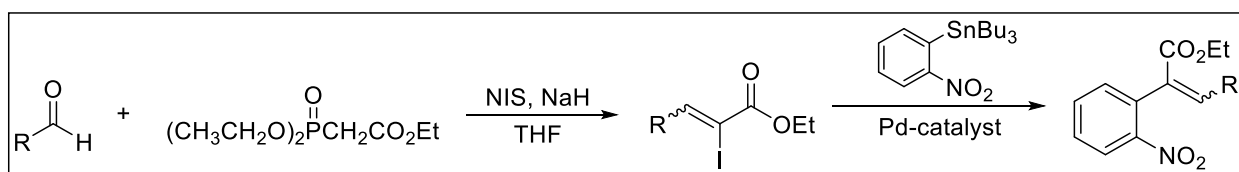
Scheme 6. Proposed route to 2-(2-nitroaryl)alkenoates.

With this in mind, we endeavored to synthesize a variety of ethyl 2-iodo-2-alkenoates using a one-pot reaction involving a Wittig reaction[23] and olefin iodination.[24] The compounds made using this methodology are outlined in Table 3.

Of the aldehydes screened using this methodology, it was found that the unbranched varieties readily condensed to their corresponding alkenoates in good to excellent yields (Table 3, entries 1-4). Although branched aldehydes such as cyclohexanecarboxaldehyde and 2-phenylpropionaldehyde (Table 3, entries 5 and 6, respectively) condensed to afford the desired products, the yields dropped considerably, presumably due to greater steric hindrance around the site of condensation. All compounds made using this method (**20-25**) were obtained as inseparable mixtures of E/Z stereoisomers. Additionally, these compounds display significant instability in deuterated solvents. It was observed that, upon dissolution in chloroform-*d* for NMR analysis, the solutions (all starting as pale yellow to orange in color) turned pink over the course of time ranging from seconds to 30 minutes. Based upon ^{1}H NMR analysis, it is surmised that, in solution with chloroform-*d*, compounds **20-25** degrade to their respective dehalogenated derivatives. It is worth mentioning that, although two

ketones (acetone and acetophenone) were screened in place of aldehydes (not illustrated in Table 3), no condensation was observed for either reaction.

Table 3. Formation of ethyl-2-iodo-2-alkenoate

Entry	Aldehyde	Ethyl 2-iodo-2-alkenoate[a,b]
1	R = Et	**20** [R = Et, 96%]
2	R = $(CH_2)_2CH_3$	**21** [R = $(CH_2)_2CH_3$, 83%]
3	R = $(CH_2)_4CH_3$	**22** [R = $(CH_2)_4CH_3$, 92%]
4	R = $(CH_2)_5CH_3$	**23** [R = $(CH_2)_5CH_3$, 61%]
5	R = Cyclohexyl	**24** [R = Cyclohexyl, 55%]
6	R = $CH(CH_3)(Ph)$	**25** [R = $CH(CH_3)(Ph)$, 28%]

[a] General conditions for the preparation of iodoalkenoates: 1.25 equiv. *N*-iodosuccinimide (NIS), 3.5 equiv. NaH, 1.0 equiv. triethylphosphonoacetate, then 1.0 equiv. aldehyde. See experimental section for full details.
[b] Yield of pure product isolated after chromatography.

With compounds **20-25** in hand, Kosugi-Migita-Stille couplings of each compound with tributyl(2-nitrophenyl)stannane were attempted. Unfortunately, in no case was clean coupling observed. Rather, results ranged from recovery or decomposition of starting material to trace amounts of product contaminated with unknown impurities being obtained. Thus, a different means of access to 2-(2-nitroaryl)alkenoates was sought.

We next attempted to form these alkenoates in a similar fashion as for the production of compound **10**. However, upon reaction of either methyl 2-nitrophenylacetate or ethyl 2-nitrophenylacetate with any aldehyde of longer chain length than acetaldehyde, no reaction was observed. Therefore, we envisioned a third route, this time from 2-nitrobenzaldehyde. Known α-ketoester **26** was able to be prepared from 2-nitrobenzaldehyde in 4 steps as reported by Chorev *et al.*[25] Compound **27** was selected as a representative 2-(2-nitroaryl)alkenoate for cyclization, and was successfully prepared by a Wittig reaction of **26**,

albeit in low isolated yield (Scheme 7). Interestingly, compound **10** was not formed under similar reaction conditions between **26** and ethyltriphenylphosphonium iodide.
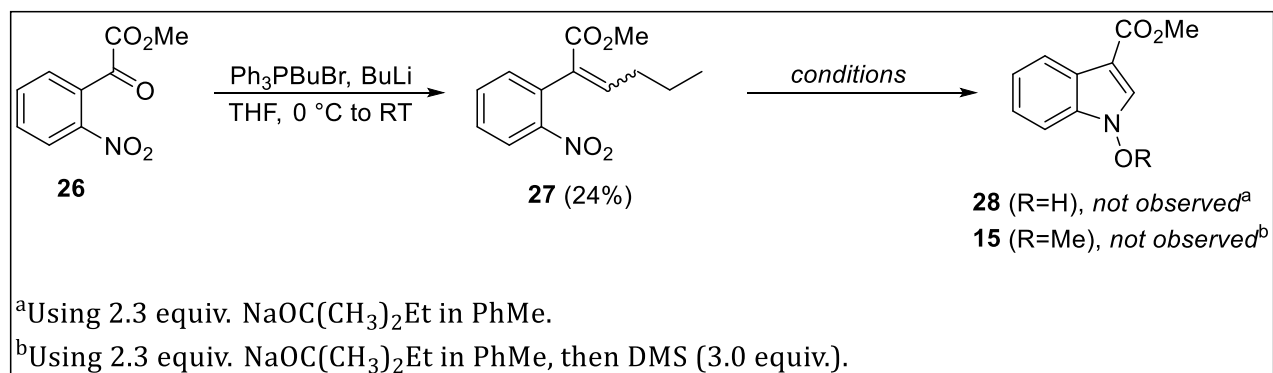
Scheme 7. Formation of and attempted cyclizations of precursor **21**.

With **27** in hand, cyclizations to *N*-hydroxyindole **28** and *N*-methoxyindole **15** under optimized conditions were attempted. In both cases, no desired product was observed, nor was the starting material recovered. Instead, it appears that decomposition occurs over the course of the reaction. Based on several additional failed attempts to cyclize **27** under a variety of conditions, it was determined that precursors with carbon chains beyond the butenoate derivatives were unsuitable substrates for this class of cyclization.
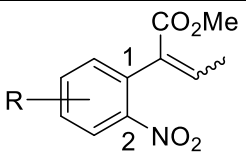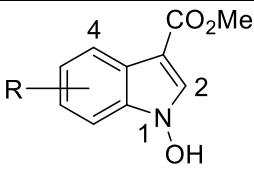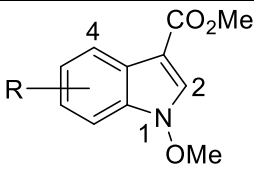
The steric and electronic effects of substitution on the aryl ring of the cyclization precursor were examined next. Six additional methyl 2-(2-nitroaryl)butenoate derivatives (Table 3, compounds **29-34**) were synthesized via a Kosugi-Migita-Stille cross coupling of substituted 2-nitro-1-bromophenyls with methyl 2-(tributyltin)-2-butenoate.[26] All coupling products were isolated in low to moderate yield as a mixture of E/Z stereoisomers (Scheme 8).
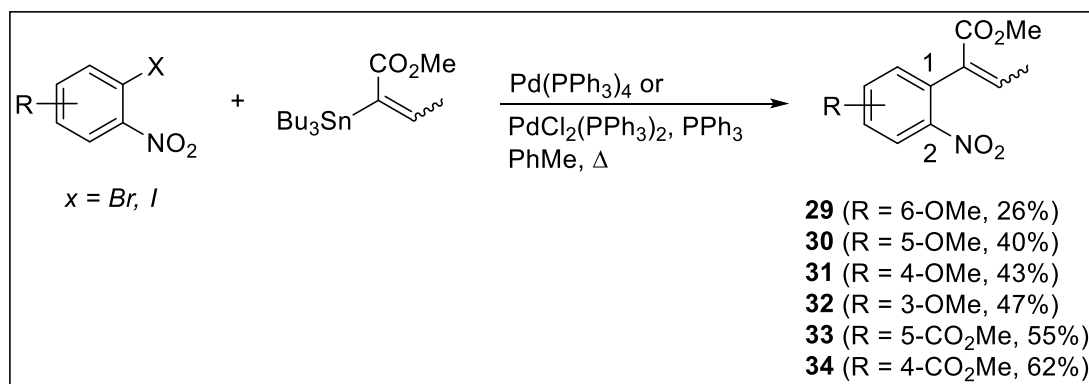
Scheme 8. Kosugi-Migita-Stille coupling to give **29-34**.

Once compounds **29-34** were isolated, each was subjected to optimized cyclization conditions in an attempt to isolate both the *N*-hydroxy- and *N*-methoxyindole derivatives. It was found that the reaction was highly sensitive to the position of substitution on the benzene ring. The derivatives substituted with a methoxy group in the 4- and 5-position (**30-31**) yielded their respective *N*-hydroxy- and *N*-methoxyindoles in fair to moderate yields (Table 4 entries 2A-3B). However, the corresponding 3- and 6-methoxy substituted analogs yielded neither *N*-hydroxy- nor *N*-methoxyindole products, and no starting material was recovered in either case (entries 1A-B and 4A-B). Although it appears that cyclization does not tolerate steric encumbrance at the latter positions, we currently are unsure of the reasons for that limitation. Ester-substituted butenoates (**33** and **34**) also successfully cyclized to form either the corresponding *N*-hydroxy- or *N*-methoxyindole in low to moderate yields (Table 4, entries 5A-6B). While the desired *N*-methoxyindoles were obtained, in three of the examples seen in Table 4 (entries 3-B and 5B-6B), pure samples could not be isolated, indicating that direct cyclization to *N*-alkoxyindoles by this method is not an ideal approach to these products. However, compounds **38** and **40** could be readily produced in excellent isolated yields by the alkylation of the corresponding *N*-hydroxyindoles with methyl iodide in the presence of potassium carbonate (Scheme 9).

Table 4. Formation of *N*-hydroxyindoles and *N*-methoxyindoles from aryl-substituted precursors.

Entry	Precursor	N-hydroxyindole[a]	N-methoxyindole[b]
1-A	**29** (R = 6-OMe)	not observed	
1-B	**29** (R = 6-OMe)		not observed
2-A	**30** (R = 5-OMe)	**35** (R = 5-OMe, 36%)	
2-B	**30** (R = 5-OMe)		**36** (R = 5-OMe, 60%)
3-A	**31** (R = 4-OMe)	**37** (R = 6-OMe, 42%)	
3-B	**31** (R = 4-OMe)		**38** (R = 6-OMe, 46%)[c]
4-A	**32** (R = 3-OMe)	not observed	
4-B	**32** (R = 3-OMe)		not observed
5-A	**33** (R = 5-CO$_2$Me)	**39** (R = 5-CO$_2$Me, 29%)	
5-B	**33** (R = 5-CO$_2$Me)		**40** (R = 5-CO$_2$Me, 27%)[d]
6-A	**34** (R = 4-CO$_2$Me)	**41** (R = 6-CO$_2$Me, 25%)	
6-B	**34** (R = 4-CO$_2$Me)		**42** (R = 6-CO$_2$Me, 45%)[e]

[a] Conditions use for all 1-6-A entries: 2.3 Equiv. sodium *tert*-pentoxide. See experimental section for details. Yields are reported as pure isolated compounds after chromatography unless otherwise noted.

[b] Conditions use for all 1-6-B entries: 2.3 Equiv. sodium tert-pentoxide, then 3 equiv. dimethyl sulfate. See experimental section for details. Yields are reported as pure isolated compounds after chromatography unless otherwise noted.

[c] Product was isolated with an inseparable impurity. Compound **38** was confirmed by methylation of **37** as described in Scheme 4.

[d] Product was isolated with an inseparable impurity. Compound **40** was confirmed by methylation of **39** as described in Scheme 4.

[e] Isolated as an inseparable mixture, 14.3:1 ratio of product to starting material. Yield and ratio determined by ^{1}H NMR.

Scheme 9. Formation of *N*-methoxyindoles **38/40** from *N*-hydroxyindoles **37/39**.

The base-mediated transformation reported to afford *N*-hydroxy- and *N*-alkoxyindoles can be mechanistically rationalized as illustrated in Scheme 10, and is supported by a number of related observations described in the literature.[15a, 17, 27, 28] First, the deprotonation of **43** will afford **44** as one of several possible resonance forms. 1,7-electrocyclization of **44** would give rise to **45**, which can subsequently undergo ring-opening to furnish nitroso-intermediate **46**. 1,5-electrocyclization of **46** is plausible based upon literature precedence, and would afford intermediate **47**. It is then theorized that the loss of formaldehyde from **47** would drive the formation of **48**. Compound **48** should then readily undergo aromatization to **49**. Depending on reaction conditions, **49** could either be protonated during acidic work-up to yield *N*-hydroxyindole **50**, or react with an added electrophile to afford *N*-alkoxyindole **51**.

Based upon the mechanism outlined, while the major products formed from the two pathways are proposed to be either the *N*-hydroxy- or *N*-alkoxyindole, in both cases formaldehyde should also be lost in the conversion of **47** to **48**. For all data entries reported in this chapter, formaldehyde was never observed, presumably due to evaporation during the removal of solvents.

Scheme 10. Proposed mechanism for the formation of *N*-hydroxy- and *N*-alkoxyindoles.

III. Conclusion

N-hydroxy- and *N*-alkoxyindoles can be prepared from a base-mediated cyclization of 2-(2-nitroaryl)-2-butenoate methyl or ethyl esters. *N*-hydroxyindoles are formed from a one-step reaction using sodium *tert*-pentoxide, and *N*-alkoxyindoles are formed in a two-step, one pot reaction using sodium *tert*-pentoxide followed by addition of an electrophile. Cyclization and alkylation using potassium *tert*-butoxide in *tert*-butanol can be accomplished, but the yields from these reactions are highly variable. Additionally, while it has been shown that cyclization conditions are suitable for an array of 2-(2-nitroaryl)-2-butenoates with steric and electronic variety on either the phenyl ring or added electrophile, alkenoates chains longer than the showcased butenoate are not tolerated. This chemistry illustrates a novel method for the production of both *N*-hydroxy- and *N*-alkoxyindoles.

Chapter 2—Total syntheses of dilemmaones A and B and progress toward the

synthesis of dilemmaone C

I.   Introduction

In 1997, a variety of specimens were collected off the coast of Cape Town, South Africa in order to explore the biomedical potential of South African marine invertebrates. A bioassay-directed fractionation of the crude extract from a mixed collection of sponges led to the determination of a sphingolipid as the active metabolite. Subsequent ^{1}H NMR and ^{13}C NMR investigations of the inactive fractions led to the structural elucidation of dilemmaones A (**52**), B (**53**), and C (**54**) (Figure 2).[29] These indole alkaloids obtained their unique familial name based upon the confusion surrounding their sponge source. However, a process of elimination suggested that one of the sponges in the mixed collection, *Ectyonanchora flabellata*, was the source of the dilemmaones.
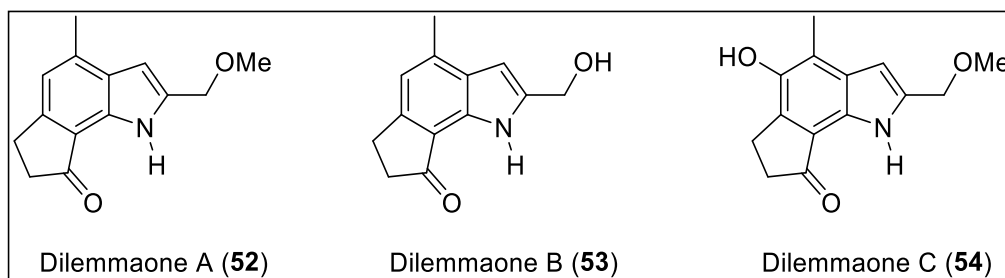
Figure 2. Structures of the dilemmaones.

The relatively simple structures of dilemmaones A-C are unusual. To the best of our knowledge, no other 2-hydroxymethylene- or 2-methoxymethylene-substituted indoles have been isolated and fully characterized to date. In addition to the unique C2-substituent, only a few other examples of 6,7-annulated indole natural products have been reported in the literature. These include the trikentrins, a family of compounds displaying antibacterial

activity that were first isolated by Capon *et al* from the marine sponge *Trikentrion flabelliforme.*[30] Members of this family of compounds include cis-trikentrin A (**55**), trans-trikentrin A (**56**), cis-trikentrin B (**57**), and trans-trikentrin B (**58**) (Figure 3), along with several other compounds.

cis-trikentrin A (**55**) *trans*-trikentrin A (**56**) *cis*-trikentrin B (**57**) *trans*-trikentrin B (**58**)
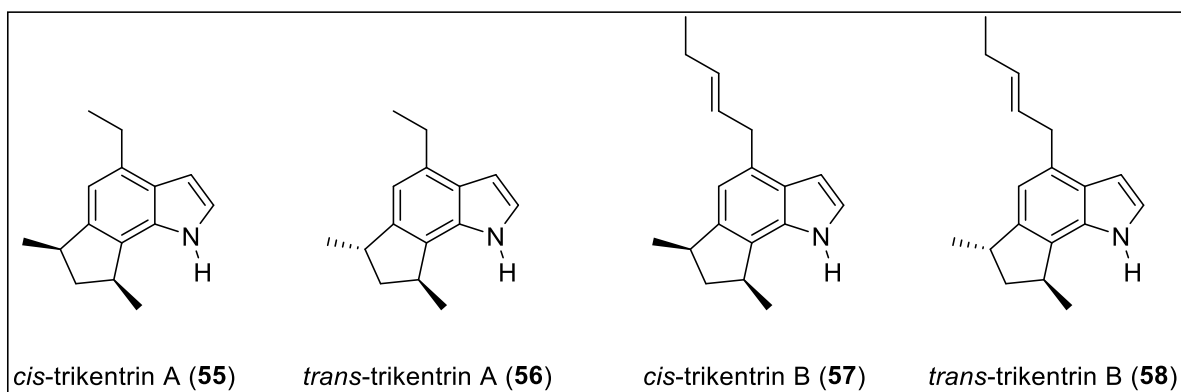
Figure 3. Structures of four trikentrins.

Subsequent to the isolation of the trikentrins, the related trikendiol,[31] trikentramine,[32] and trikentramides[33] have all been isolated from sponges belonging to the genus *Trikentrion*. The structurally similar herbindoles were isolated from *Axinella sp.*, an Australian sponge, by Scheuer *et al.*[34] Herbindole A (**59**), herbindole B (**60**), and herbindole C (**61**) possess both cytotoxic and antifeedant properties (Figure 4).

herbindole A (**59**) herbindole B (**60**) herbindole C (**61**)
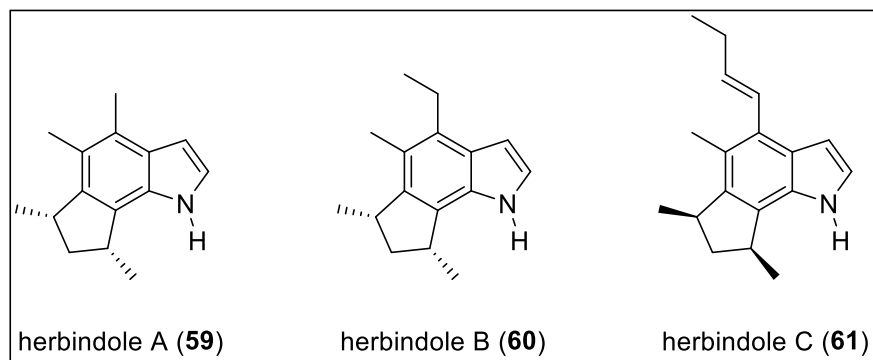
Figure 4. Structures of the herbindoles.

Two related compounds, monomargine (**62**) and monomarginine (**63**), are cytotoxic lactams isolated from *Monocarpia marginalis* (Figure 5).[35] These tetracyclic compounds possess the 6,7-annulated indanone-like framework characterized by the dilemmaones.

monomargine (**62**)   monomarginine (**63**)
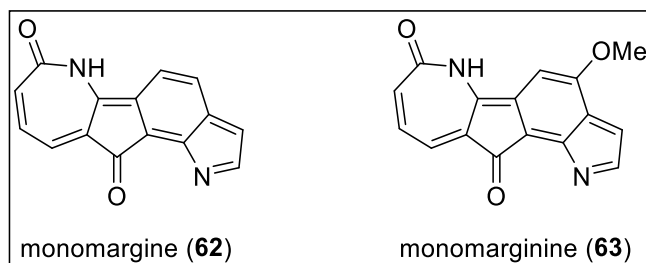
Figure 5. Structures of monomargine and monomarginine.

The uncommon structural framework and interesting biological profiles of the trikentrins and herbindoles have made them attractive targets for total synthesis. The challenges associated with the construction of these complex systems are reflected in the many distinct approaches that have been reported for their racemic and enantioselective total syntheses. Between 2005-2007, Kerr *et al* reported the racemic syntheses of herbindole A (**59**), herbindole B (**60**), *cis*-trikentrin A (**55**), and *cis*-trikentrin B (**57**) utilizing a Diels-Alder reaction of quinoid imines.[36,37] Previous to those reports, Kanematsu *et al* reported the enantioselective synthesis of *cis*-trikentrin B (**57**) which featured an intramolecular Diels-Alder reaction of an allenic dienamide and stereoselective cleavage of a bicyclic system.[38] To date, there has been no reported synthesis for any member of the dilemmaone family, despite their skeletal resemblance to the trikentrins and herbindoles. Hence, we envisioned a route to the dilemmaones showcasing a Watanabe-Cenini-Söderberg cyclization[39] as the key, terminal step. Herein we report the first total syntheses of dilemmaones A and B and progress toward the synthesis of dilemmaone C.

II.   Results and Discussion

Retrosynthetically, dilemmaone B (**53**) can be constructed from the palladium-catalyzed *N*-heterocyclization via Watanabe-Cenini-Söderberg cyclization conditions of *o*-nitrostyrene **64**. Compound **64** can arise from the Kosugi-Migita-Stille cross-coupling between vinyl stannane **65** and an arylhalide (**66**). Arylindanone **66** could be fashioned through the manipulation of commercially-available 2,3-dihydro-5-methylinden-1-one (**67**).
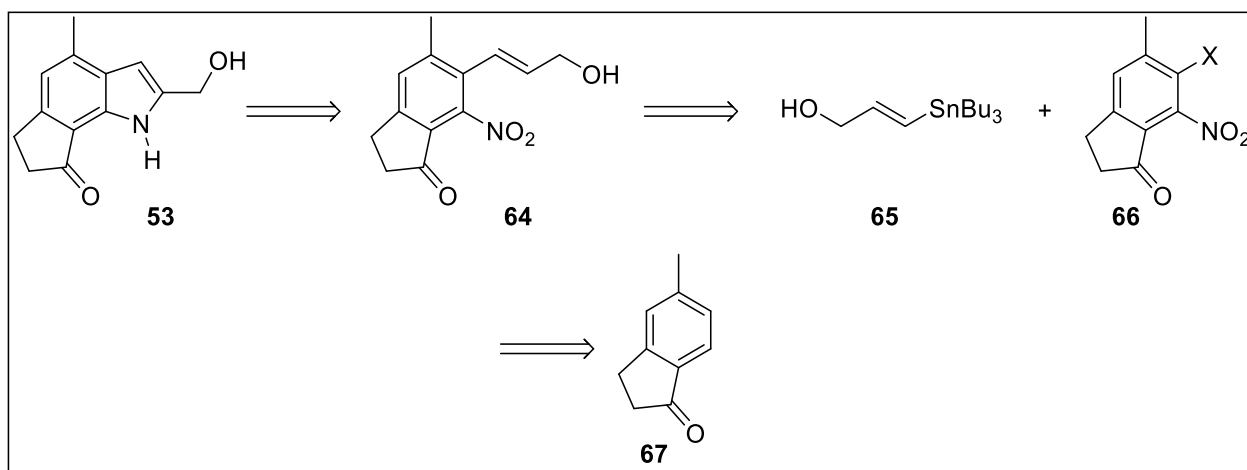
Scheme 11. Retrosynthetic route to dilemmaone B.

a. *Synthesis of Dilemmaone B*

Initial work toward dilemmaone B was pioneered by Dr. Christopher Dacko of the Söderberg lab. 6-Amino-2,3-dihydro-5-methylinden-1-one (**68**) was prepared in two steps from commercially available 2,3-dihydro-5-methylinden-1-one (**67**) as reported by Pinna *et al*[40] (Scheme 12). As described in Scheme 12, Dr. Dacko originally reported the first syntheses of compounds **69**, **70**, and **71**. Optimization work for some of these reactions was done by a number of the undergraduates who worked with me.
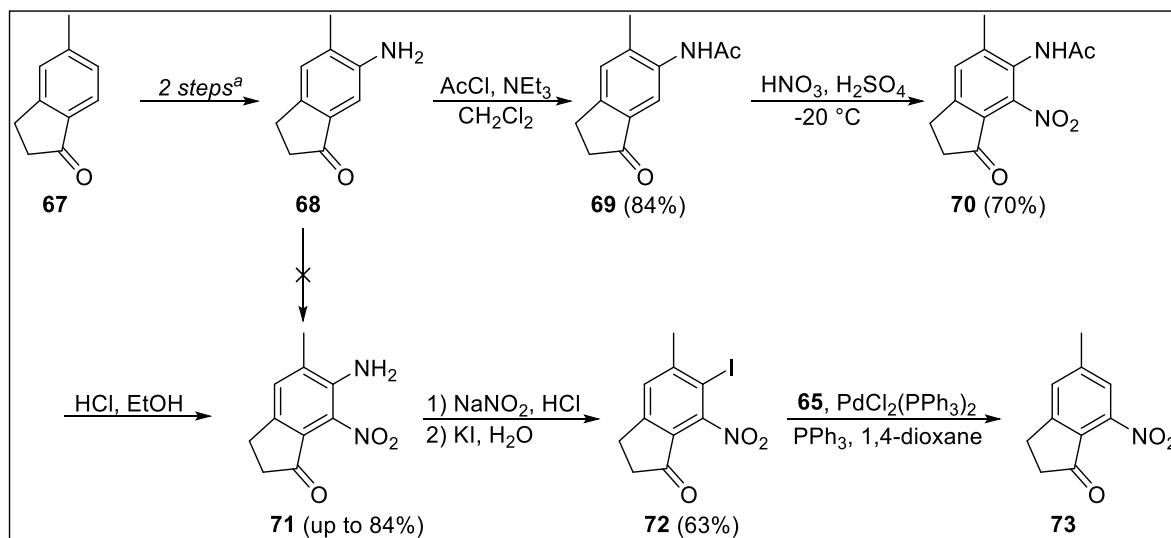
Scheme 12. Initial synthetic approach to dilemmaone B.

In order to install the nitro group present on C7 of the *N*-heterocyclization precursor **64**, a direct nitration of **68** to intermediate **71** was attempted by Dr. Dacko. Lemaire *et al* have reported a one-step nitration of several anilines using 2,3,5,6-tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dienone (**74**)[41] as a nitronium ion source.[42] Utilizing Lemaire's reaction conditions, aniline **68** was seemingly converted to nitroaniline **71**. Dr. Dacko confirmed that electrophilic aromatic substitution had taken place by the presence of only one aromatic proton by ^{1}H NMR. However, upon HRMS analysis, no molecular ion or protonated molecular ion was observed for presumed **71**. Instead, the HRMS spectrum surprisingly displayed two peaks of equal intensity at m/z = 240 and 242, indicating the presence of a bromine atom. Thus, Dr. Dacko determined that aniline **68** was not nitrated, but rather brominated by **74** to give bromoindanone **75** in 59% isolated yield (Scheme 13). Iranpoor and Firouzabadi have also reported the nitration of aromatic amines using a AgNO₃/Br₂, PPh₃ reagent system.[43] Interestingly, Dr. Dacko's exposure of aniline **68** to these conditions also produced

the undesired bromoindanone **75** as the sole reaction product in comparable yield to that seen when using Lemaire's conditions.
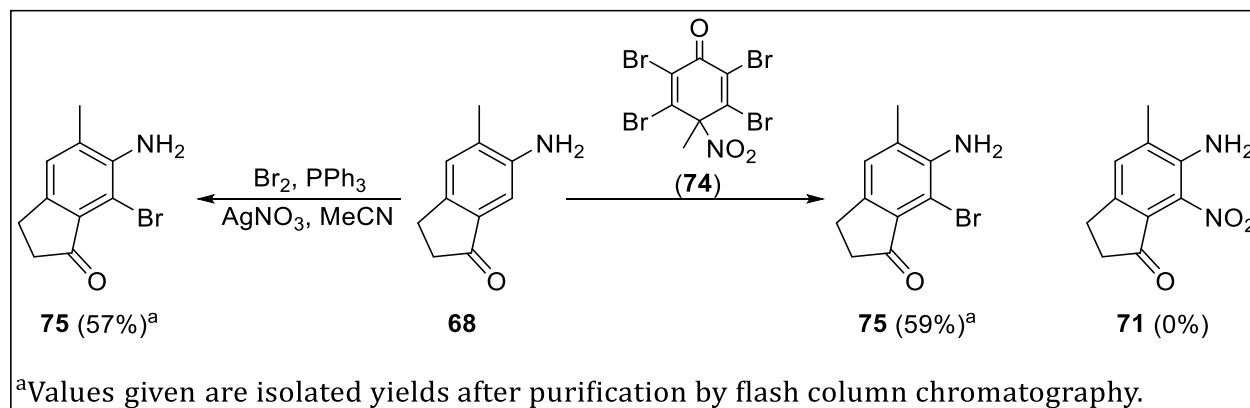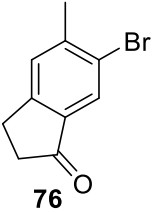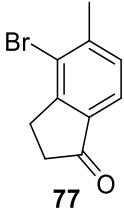
Scheme 13. Unexpected bromination of aniline **68** as observed by Dr. Dacko.

After the failure of these direct aniline nitration methods, a more traditional route to *o*-nitroaniline **71** was envisioned, involving sequential protection, nitration, and deprotection protocol. Aniline **68** was first reacted with acetyl chloride in the presence of triethylamine to afford acetanilide **69** in good yield (Scheme 12). Nitration of **69** initially proved to be problematic. However, after optimization of the reaction conditions, it was discovered that the most effective and concise procedure was through the use of fuming HNO$_3$ and concentrated H$_2$SO$_4$ at a reaction temperature of -20 °C for 90 min. Using these conditions, nitroindanone **70** was furnished in 70% yield. Subsequent deprotection of **70** to *o*-nitroaniline **71** was attempted using a procedure reported by Pouli *et al.*[44] While these conditions did afford nitroaniline **71**, yields were inconsistent, with results ranging from 5-84% isolated yields. It is hypothesized that the wide range of yields are due to the sensitivity of the free amine present on **71** to fluctuations in pH during both work-up and chromatography. Conversion of **71** to the corresponding halides also proved challenging. One pot diazotization and iodination of aromatic amine **71** furnished iodoindanone **72** in

moderately good yield, but we were unable to prepare the corresponding bromoindanone from **71** using several variations of similar methodology. Next, Kosugi-Migita-Stille cross-coupling of iodoindanone **72** with (*E*)-3-(tributylstannyl)-2-propen-1-ol (**65**) was attempted. Under all screened sets of conditions, however, the only observed products were dehalogenated nitroindanone **73** or apparent decomposition of **72**. Additionally, a Sonogashira coupling reaction between **72** and 3-(*tert*-butyldimethylsiloxy)-1-propyne was attempted (not pictured), in an attempt to afford cyclization precursor **64** via a sequential coupling and reduction route. However, those reaction conditions also afforded deiodinated nitroindanone **73**. As iodoindanone **72** was not a good candidate for the access of cyclization precursor **64**, a different approach was envisioned.

The second iteration of the synthesis of dilemmaone B sought to install an aromatic halogen prior to nitration, thus avoiding the more circuitous route involving a protection/deprotection protocol. To that end, various conditions were screened in an attempt to access the desired bromoindanone **76** (Table 5). One pot diazotization and bromination of aniline **68** proceeded to afford the desired bromoindanone **76** in 75% yield (Table 5, entry 1). In an effort to directly convert commercially available 2,3-dihydro-5-methylinden-1-one (**67**) to compound **76**, thus effectively eliminating the two-step process to afford **68** (Scheme 12), bromination with $Br_2/AlCl_3$ (Table 5, entry 2) was attempted, however, only the undesired isomer (**77**) was observed. However, when **67** was subjected to conditions based upon those previously reported in our laboratory by Dr. Matthew Cummings,[45] both the desired bromoindanone (**76**) and its regioisomer (**77**) were obtained in 32% and 41% isolated yields, respectively (Table 5, entry 3).

Table 5. Alternate synthetic access to intermediate **76**.[a,b]

Entry	Starting Material	Reagents	Yield **76** (%)	Yield **77** (%)
			76	**77**
1	**68**	HBr, NaNO$_2$, CuBr	75	
2	**67**	Br$_2$, AlCl$_3$		12
3	**67**	NBS[b], H$_2$SO$_4$	32	41

[a]Values given are isolated yields. Compounds **76** and **77** are separable by flash column chromatography.

[b]NBS = *N*-bromosuccinimide.

With **76** in hand, nitration using fuming HNO$_3$ and concentrated H$_2$SO$_4$ was attempted (Scheme 14). As expected, two isomers were obtained, the desired nitroindanone **79** as the major product (64% isolated yield) and regioisomer **78** as the minor product (17% isolated yield). This protocol has allowed for the formation of arylindanone **79** in two steps from a commercially-available substrate rather than the originally-proposed six steps. Nitroindanone **79** was then subjected to Kosugi-Migita-Stille cross-coupling with (E)-3-(tributylstannyl)-2-propen-1-ol (**65**). Upon optimization, we were gratified to find that cyclization precursor **64** could be obtained cleanly in 55% yield. Compound **64** was then subjected to Watanabe-Cenini-Söderberg reductive cyclization conditions. Despite our confidence in conversion of **64** to dilemmaone B (**53**) as expected, disappointingly, the reaction proved to be unsuccessful. Rather, unreacted starting material (**64**) was recovered in all screened sets of conditions for Watanabe-Cenini-Söderberg cyclization.
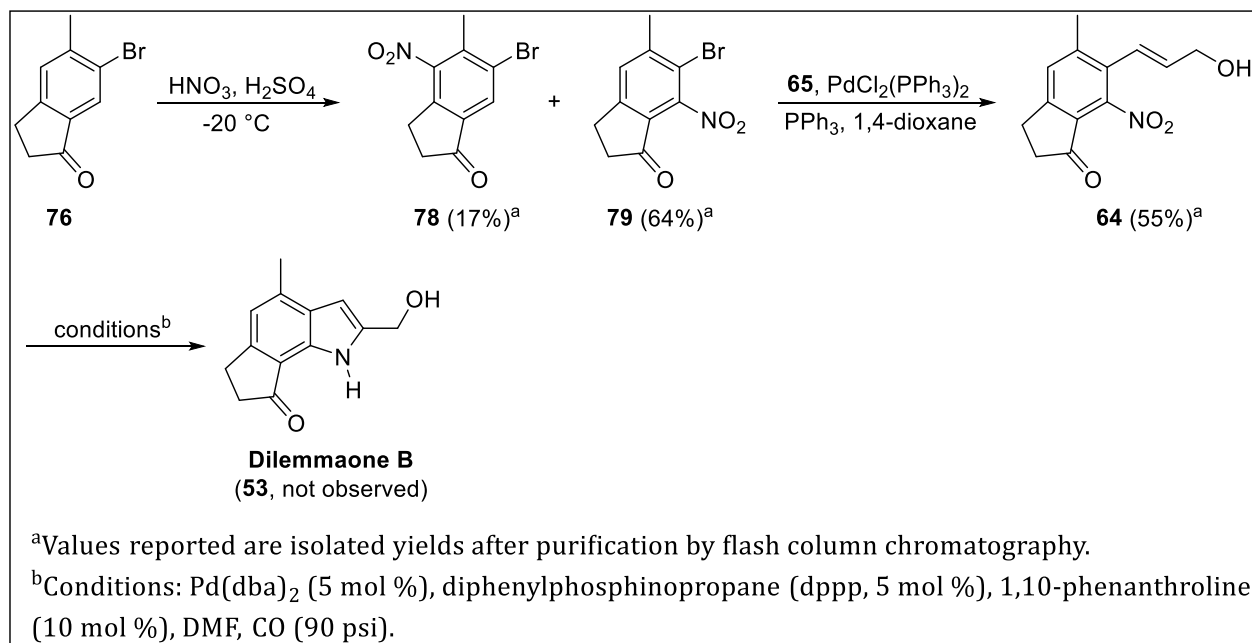
Scheme 14. Second synthetic approach to dilemmaone B.

Theorizing that the electronics of either the indanone ring or free alcohol might be affecting the cyclization, compound **79** was first converted to *o*-nitrostyrene derivative **81** via Kosugi-Migita-Stille cross-coupling with (E)-tributyl(3-methoxy-1-propenyl)stannane (**80**) (Scheme 15). **81** was then subjected to acidic reaction conditions with trimethyl orthoformate in an effort to synthesize diemethylacetal derivative **82**. However, whereas **82** was not observed, the corresponding methoxyindene (**83**) was obtained in low yield in addition to 11% isolated starting material (**81**). Despite this unexpected result, we surmised that **83** was sufficiently altered in its electronics from compound **64**, and thus derivative **83** was subjected to reductive cyclization conditions. Upon examination of the resultant crude ^{1}H NMR, no indole product (predicted compound **84**) was observed. Rather, chemical shifts indicated that **83** had instead reverted to indanone **81**.
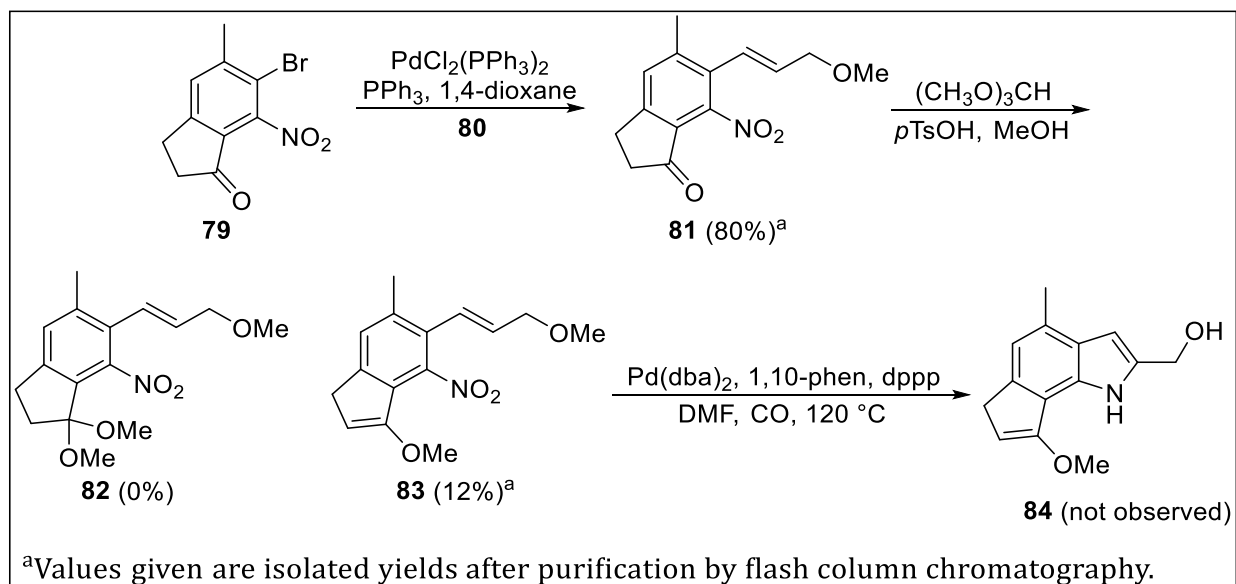
Scheme 15. Synthesis of derivative **83**.

Based upon these results, it was determined that it was unlikely that the electronics of the system were affecting the attempted cyclization. This discovery was not particularly surprising, as compounds containing unprotected carbonyls such as esters of variety **85**[46] and precursors to complex compounds such as cimitrypazepine (**86**) that contain free alcohols[47] have cyclized utilizing Watanabe-Cenini-Soderberg conditions without issue in our hands (Figure 6).
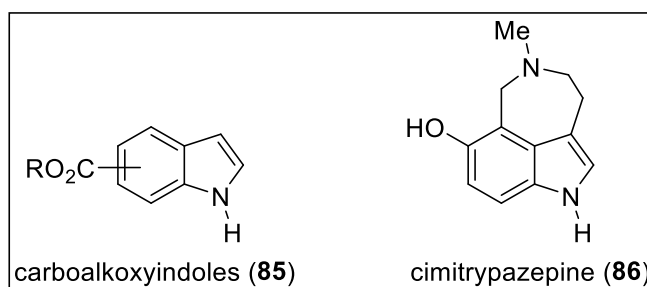
Figure 6. Two compounds made from reductive cyclizations in the Söderberg lab.

In an effort to effect cyclization by different but related means, both *o*-nitrostyrene derivatives that had been synthesized (**64** and **81**) were subjected to an array of other

reductive cyclizations. In addition to the originally-attempted Watanabe-Cenini-Söderberg cyclization conditions, TiCl₃-promoted reductive cyclization,[48] diborane-mediated deoxygenation,[49] and a modified Cadogan-Sundberg cyclization[50] were screened in the attempt to convert either **64** or **81** directly to dilemmaone B. In all cases, cyclization to the desired natural product was never observed. Instead starting material (**64** or **81**) was recovered. Upon further examination, we were intrigued to find that sterically-encumbered *o*-nitrostyrenes of the type shown in Scheme 16 (non-hydrogen groups on adjacent carbons to both the nitro and styrene substituents) have not been reported to proceed for any of the aforementioned reductive cyclizations. This discovery highlights a universal limitation for reductive *N*-heterocyclizations of *o*-nitrostyrenes. Despite not being able to use the desired Watanabe-Cenini-Söderberg cyclization conditions toward the dilemmaones, we garnered greater understanding of a reaction that has been widely used in the Söderberg lab since Dr. James Shriver's original report in 1997.[46]
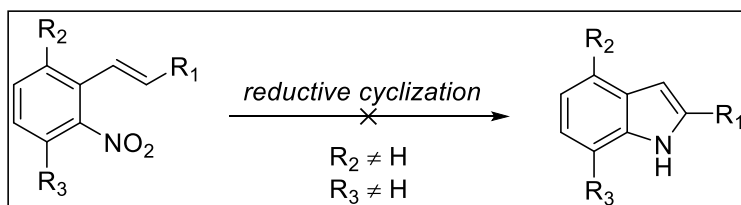
Scheme 16. Sterically encumbered *o*-nitrostyrenes unable to proceed by reductive cyclization.

Due to the steric encumbrance of the dilemmaone core being unavoidable, and the proposed use of our late-stage cyclization of *o*-nitrostyrene **64** having thus been ruled out as a direct means of access to dilemmaone B, an alternate pathway was envisioned.

Compound **64** was transformed into epoxide **89** using 4 equivalents of *meta*-chloroperbenzoic acid (*m*-CPBA). It was anticipated that treatment of **89** with Pd/C and H$_2$ could result in not only reduction of the nitro group to the corresponding amine, but also a subsequent epoxide ring-opening and elimination to afford the desired product, dilemmaone B (**53**). Upon a literature search, to the best of our knowledge, this type of transformation has only been reported once, and with very limited scope, demonstrated in the example transformation shown in Scheme 17.[51]
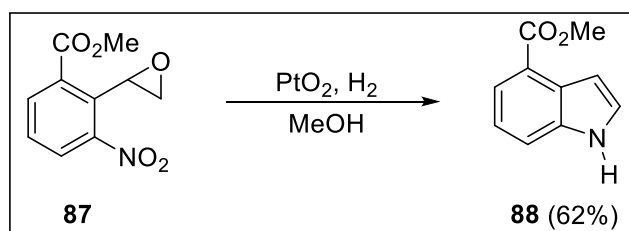
Scheme 17. The catalytic reduction of **87** reported by Watanabe *et al*.

Our first attempt of subjecting **34** to conditions similar to Watanabe's did afford an indole, however, upon detailed investigation, the ^{1}H NMR chemical shifts were similar but not in agreement with the shifts reported by Faulkner *et al* for their structural elucidation of dilemmaone B. The structure of the isolated product (**90**) was determined to be the *N*-hydroxy analog of dilemmaone B (Scheme 18), which presumably arises from incomplete reduction of the nitro group of **89**. Additionally, 46% of unreacted starting epoxide **89** was isolated.

Encouraged by this result, we examined this one-pot reductive cyclization for its viability toward the synthesis of dilemmaone B. As our first attempt had yielded 27% of the *N*-hydroxy derivative (**90**) and had not proceeded to completion, we next attempted to run the reaction at elevated temperature (50 °C, Table 6, entry 2).
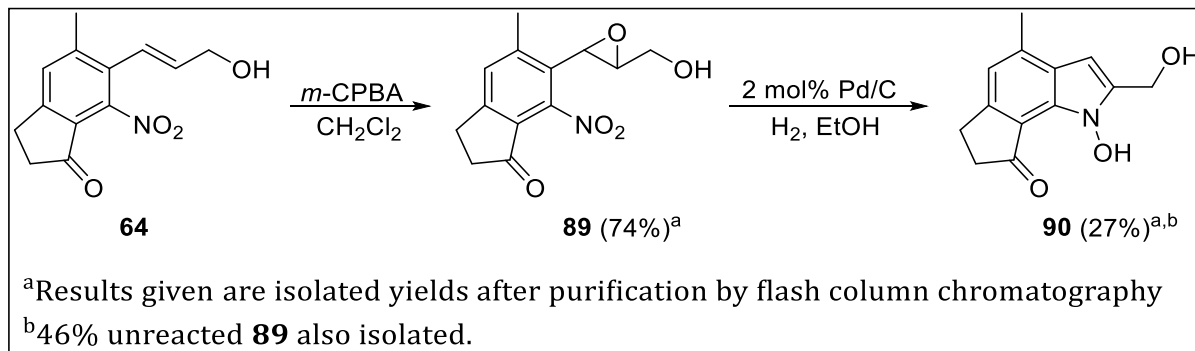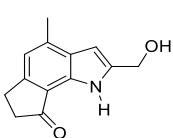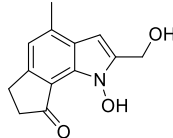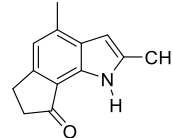
Scheme 18. Synthesis of derivative **90** via sequential epoxidation-reductive cyclization.

In this case, the reaction proceeded to completion, but the only observed product was *N*-hydroxyindole **90**. We next increased the catalyst loading to 5 mol % Pd/C. Upon work-up and purification, a new product was observed, however, it was found that over-reduction had occurred, yielding 2,4-dimethylindole derivative **91** as the sole product (Table 6, entry 3). Theorizing that the *N*-hydroxyindole (**90**) could be further reduced to the desired indole at higher catalyst loading, **90** was subjected to reductive conditions with 5 mol % Pd/C. The progress of this reaction was carefully monitored by TLC. After 2 h, we were excited to observe that starting material **90** had been completely converted to dilemmaone B (**53**) in 27% yield, and no over-reduction to **91** was isolated (Table 6, entry 4). In an effort to obtain dilemmaone B directly from the epoxide precursor, we chose to screen the reducing agent originally used by Watanabe *et al*. Upon subjecting **89** to reduction with 2 mol % PtO_2 at 50 °C, and again carefully monitoring the reaction progress by TLC, we were gratified to find that dilemmaone B was indeed obtained in 48% isolated yield after 3 h, and neither *N*-hydroxyindole **90** nor 2,5-dimethylindole **91** were observed (Table 6, entry 5). It is worth noting that, while the identities of *N*-hydroxyindole **90** and dilemmaone B (**53**) can be confirmed and differentiated via ^{1}H NMR analysis in $CDCl_3$, solubility of both compounds in $CDCl_3$ is minimal. Because of this, splitting patterns in that solvent are unclear. However,

27

both **90** and **53** are readily solubilized in DMSO-d_6. Interestingly, in contrast to their ^{1}H NMR spectral data in CDCl$_3$, chemical shifts in DMSO-d_6 are nearly identical, necessitating structural confirmation by ^{1}H-^{15}N gHSQC analysis (see Chapter 4 and appendix for details). Notably, Faulkner *et al* did not report all resonances for ^{13}C NMR analysis of dilemmaone B, and thus did not provide detailed characterization (HMBC and NOESY) as they had for dilemmaone A. Therefore, full NMR analysis was performed for dilemmaone B in DMSO-d_6, and all data for this compound can be found in Chapter 4 (experimental section) and the appendix.

Table 6. Cyclizations to dilemmaone B.[a]

Entry	SM	Catalyst	Time	Yield **53** (%)	Yield **90** (%)	Yield **91** (%)
1[b]	**89**	2 mol % Pd/C	16 h		27[c]	
2	**89**	2 mol % Pd/C	16 h		37	
3	**89**	5 mol % Pd/C	16 h			16
4	**90**	5 mol % Pd/C	2 h	27		
5	**89**	2 mol % PtO$_2$	3 h	48		

[a]All reactions were run in EtOH under 40 psi H$_2$ at 50 °C unless otherwise noted. Yields reported are isolated yields after chromatography. See experimental section for details.
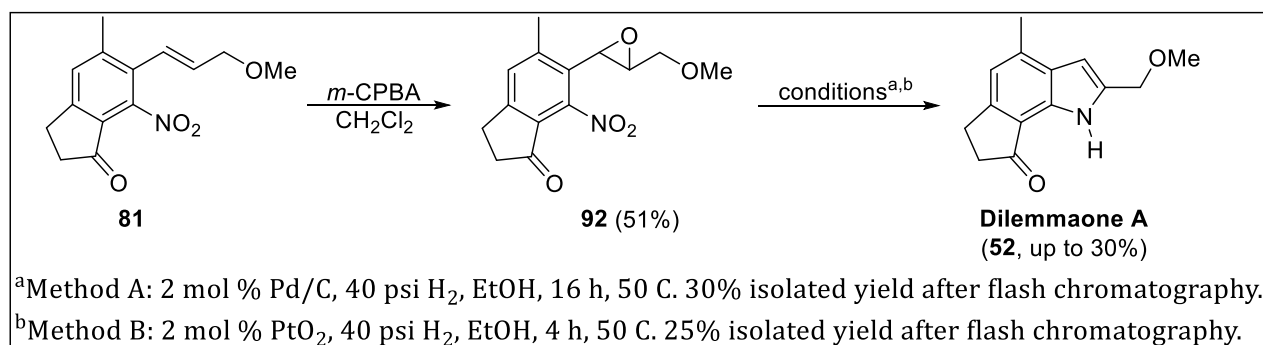
[b]Reaction run at ambient temperature.

[c]Also isolated was 46% unreacted starting material **89**.

b. *Synthesis of Dilemmaone A*

With the dilemmaone B successfully synthesized, we turned our attention to the synthesis of dilemmaone A (**52**), which differs in structure from dilemmaone B only at the

C2 position (dilemmaone A possesses a 2-methoxymethyl whereas dilemmaone B has a 2-hydroxymethyl substituent). With Kosugi-Migita-Stille coupling adduct **81** in hand (Scheme 19), epoxidation proceeded smoothly to furnish compound **92** as expected in 51% yield. Cyclization precursor **92** was then subjected to reductive conditions using both Pd/C and PtO$_2$.

^{a}Method A: 2 mol % Pd/C, 40 psi H$_2$, EtOH, 16 h, 50 C. 30% isolated yield after flash chromatography.
^{b}Method B: 2 mol % PtO$_2$, 40 psi H$_2$, EtOH, 4 h, 50 C. 25% isolated yield after flash chromatography.

Scheme 19. Synthesis of dilemmaone A.

While we expected to observe similar results for the reduction of **82** when utilizing 2 mol % Pd/C, as for the conversion of **89** to **90** (synthesis of dilemmaone B), interestingly, both screened sets of conditions afforded clean conversion of epoxide **92** to dilemmaone A (**52**). While 2 mol % Pd/C consistently led to the production of *N*-hydroxyindole **90** while attempting to form dilemmaone B, the same conditions fully reduced precursor **92** to dilemmaone A, and its corresponding *N*-hydroxyindole was never observed. While the use of PtO$_2$ worked cleanly toward the production of both dilemmaones A and B, it seems that the use of Pd/C is marginally more effective for the reduction of epoxide **92**. Notably, dilemmaone A (**52**) is readily soluble in CDCl$_3$, and ^{1}H NMR chemical shifts match the data reported by Faulkner *et al.* A complete analysis of this natural product can be found in the experimental section and appendix.

Progress Toward the Synthesis of Dilemmaone C

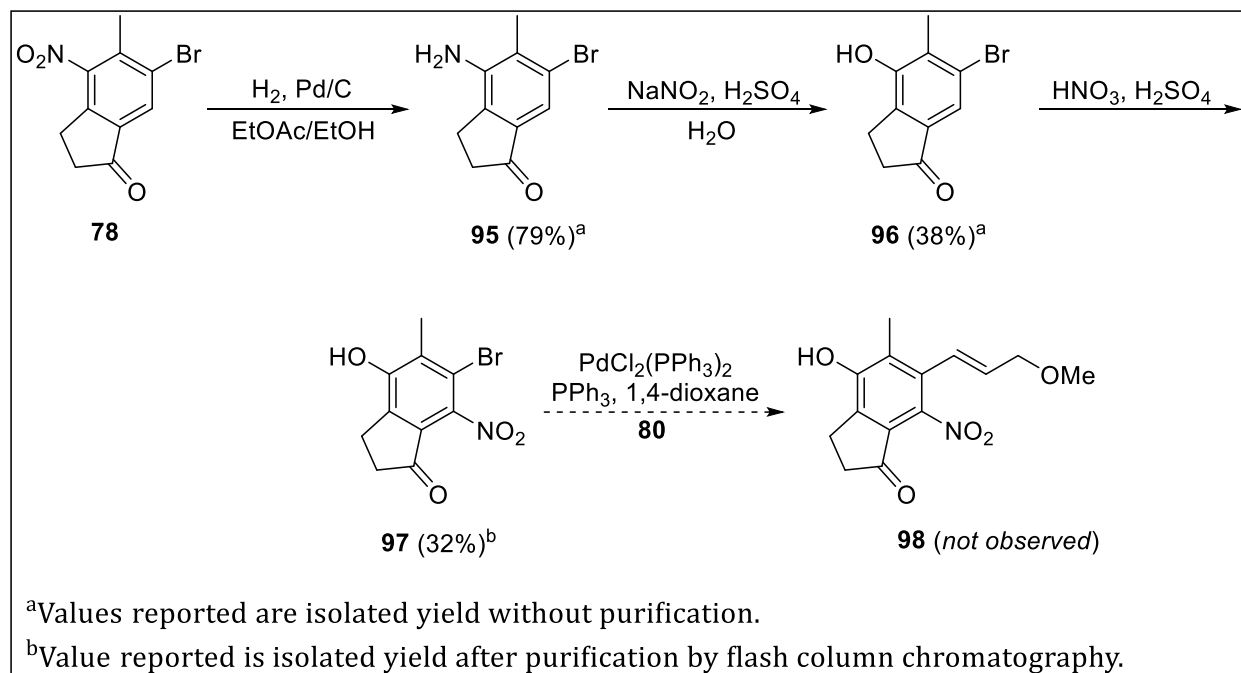With the successful synthesis of dilemmaones A and B accomplished, we turned our attention to the synthesis of dilemmaone C. Structurally, the core of dilemmaone C is nearly identical to that of dilemmaone A, however, dilemmaone C is the only member of the family of compounds that possesses aromatic substitution at C5. Retrosynthetically, we envisioned that dilemmaone C could be prepared from compound **93** (Scheme 20), which in turn could arise from Kotsugi-Migita-Stille coupling of **94** with **80**. This divergent approach was selected, as **78** is one of the two isomers formed in the nitration reaction of **76**, thus allowing for the utilization of both isomers across the syntheses of the dilemmaones.
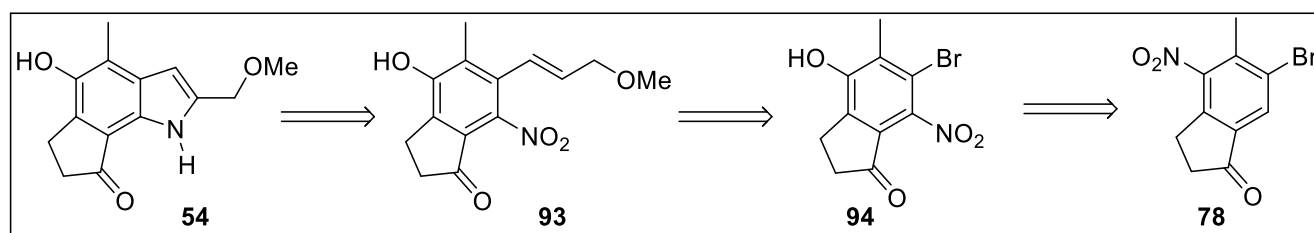
Scheme 20. Retrosynthesis of dilemmaone C.

With this approach in mind, compound **78** was subjected to reductive conditions and aniline derivative **95** was obtained in 79% yield (Scheme 21). Subsequently, sequential diazotization and hydrolysis of compound **95** was performed, and after optimization of the work-up, phenol **96** was obtained in 38% yield. Nitration of **96** was also successful in affording **97**, albeit in low yield. Further, this transformation has proven to be inconsistent in its results, and studies toward a reliable method of nitration are ongoing. With the coupling partner in hand, Kotsugi-Migita-Stille coupling was attempted on compound **97** with **80** under the same conditions used in the synthesis of dilemmaone A. Upon analysis of the crude ^{1}H NMR, it appeared that coupling had taken place, as characteristic peaks between

5-7 ppm were observed. However, when purification was attempted, no product was isolated, presumably due to the small (under 10 mg) scale on which the reaction had been run.

Scheme 21. Attempted synthesis of compound **98**.

It is believed that, pending successful synthesis of *o*-nitrostyrene **98**, dilemmaone C could be synthesized in the same manner as for dilemmaone A (Scheme 22).
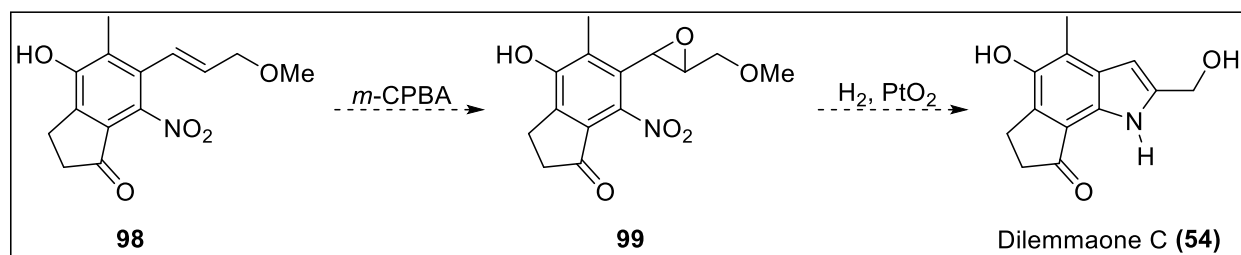
Scheme 22. Proposed future steps toward dilemmaone C.

Compound **98** should undergo epoxidation to form **99**, which should subsequently undergo one-pot reduction and cyclization to form the desired indole. These proposed steps are the same as for dilemmaones A and B, thus, it is hypothesized that dilemmaone C can be accessed with relative ease.

III.   Conclusion

The first total syntheses of the naturally occurring tricyclic indole alkaloids, dilemmaones A and B, has been successfully accomplished. These compounds can be efficiently prepared from 2,3-dihydro-5-methylinden-1-one (**67**), with both syntheses featuring a Kosugi-Migita-Stille coupling and an interesting one-pot reductive cyclization using H_2 and either a Pd/C or PtO_2. As the scope of this reductive cyclization using either Pd/C or PtO_2 has not yet been widely explored, studies are ongoing in our laboratory to determine its versatility. Dilemmaone B (**53**) was synthesized in 5 steps (overall yield = 4.0%). From common intermediate 6-Bromo-2,3-dihydro-5-methyl-7-nitroinden-1-one (**79**), dilemmaone A (**52**) was then synthesized in 3 additional steps (overall yield = 12.2%). Work toward the synthesis of dilemmaone C (**54**), the most highly-substituted member of this family of compounds, has begun, and the initial promising results suggest that future efforts could lead to its production using a related approach.

Chapter 3—Additional methodological and synthetic work toward indole derivatives

In addition to the projects discussed in chapters 1 and 2, I have worked on a number of additional side-projects. The first of these was a methodology screening for an efficient means of access to *o*-nitrostyrenes that could be subsequently subjected to Watanabe-Cenini-Söderberg cyclization reactions. The second involved efforts toward the synthesis of the naturally occurring marinoquinolines, and was pioneered by two undergraduate students under my supervision. The third was a collaborative effort with the West Virginia University Division of Forestry and Natural Resources, wherein an exploration of an azide-alkyne cycloaddition using lignocellulosic materials as a scaffold for copper nanoparticle catalysis was performed (not discussed in this report).

I.   **Access of substituted *o*-nitrostyrene derivatives via regioselective Mizoroki-Heck reactions**

a. **Introduction**

One of the major reactions that has been used over the last two decades by the Söderberg lab is the Watanabe-Cenini-Söderberg cyclization.[39] This reaction, as illustrated in previous chapters, involves the palladium-catalyzed reductive cyclization of *o*-nitrostyrene derivatives to afford indoles. The production of these cyclization precursors can be accomplished via a vast range of methodologies, including Wittig reactions,[52] Suzuki[53] and Stille[54] cross-couplings, and others. An additional reaction that has been widely applied to the synthesis of *o*-nitrostyrenes and related compounds is the Heck reaction.[55] Traditionally, this reaction involves the reaction of an unsaturated halide or triflate with an alkene in the presence of a palladium catalyst and base to afford an array of substituted alkenes. Despite

its versatility, the Heck reaction is often limited by preference for coordination with the terminal olefinic carbon. While exploring the literature during work on my original research proposal, I happened upon a modified Mizoroki-Heck reaction reported by Qin *et al*, wherein the opposite substitution preference was observed. As illustrated in Scheme 23, when aryl triflate **100** was reacted with 3-buten-1-ol (**101**) under modified Heck conditions, there was high selectivity for the formation of geminal alkene **102** over its corresponding vicinal isomer, **103**.
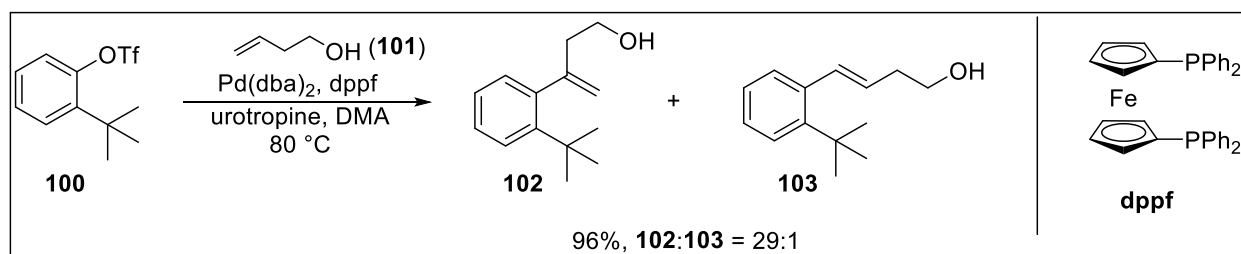
Scheme 23. Modified Mizoroki-Heck reaction as reported by Qin *et al*.

This reactivity was intriguing, as we surmised that it could be applied sequentially, preceding a Watanabe-Cenini-Söderberg reaction, to afford indoles with substitution at C3. Although there are numerous methods for the production of 3-substituted indoles, this would allow for the pre-installation of a substituent at C3 and late-stage cyclization to afford the indole. This is in contrast to many of the current methodologies, which rely on substitution at the C3 position of an existing indole.[57] This approach additionally could contribute to the synthetic field, as there are numerous naturally-occurring compounds that exhibit C3-substitution of an indole core. For example, the structurally diverse tryptamines are a class of monoamine alkaloids an array of neurological and psychedelic effects. Tryptamine (**104**) has been synthesized via the Abramovitch-Shapiro tryptamine synthesis

(Scheme 24), which is one such example of desired C3-substitution being introduced after the indole core has been created.[58]
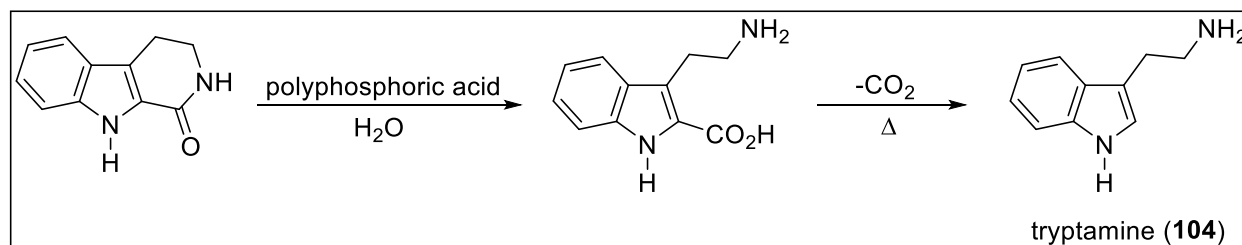
Scheme 24. Abramovitch-Shapiro tryptamine synthesis.

In an effort to probe the versatility of this modified and regioselective Mizoroki-Heck reaction, we endeavored to screen its applicability toward the production of *o*-nitrostyrenes, particularly those with pre-installed C3 substitution. Here, we report the initial findings of this study.

b. **Results and Discussion**

To initiate our screening of the regioselective Mizoroki-Heck conditions applied to nitroaryl triflates, we selected a simple nitroaryltriflate precursor (2-nitrophenyl trifluoromethanesulfonate, **105**) and subjected it to the reaction conditions reported by Qin *et al*.
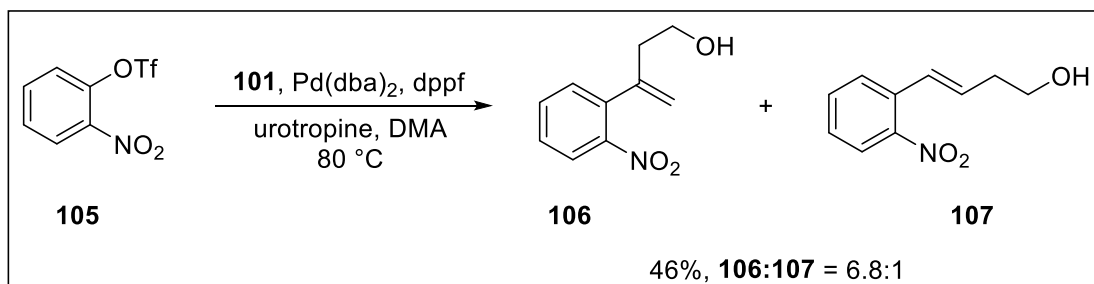

Scheme 25. Reaction of **105** under modified Mizoroki-Heck conditions.

We were gratified to find that the desired regioisomer, **106**, was formed as the major isomer in an inseparable mixture with Heck product, **107**, in a 6.8:1 ratio and 46% yield (Scheme 25). Despite attempting this reaction under a variety of conditions, including different solvents, altered catalyst loading, and elevated temperatures, the yields and regioselectivity remained comparable or depressed from the originally observed values as shown in Scheme 25. Interestingly, when the reaction was run under the same conditions, but with the temperature increased to 105 °C, the yield and selectivity remained almost identical (47% and 6.3:1, respectively), an additional product, *o*-nitrophenol, was also isolated in 11% yield. This suggests that the reaction can be prone to de-triflation under certain conditions, such as elevated temperature. Although the results that we obtained were not as promising as reported in the literature examples, we were nevertheless encouraged by these preliminary findings. Additionally, upon further perusal of Qin's results, it was discovered that each triflate/alkene combination appeared to be specifically tailored to one of several ferrocene-based ligands. We chose to screen our reactions with only 1,1'-bis(diphenylphosphino)ferrocene (dppf), which could be a contributing factor to our moderately lower yields.

With our initial findings proving to be a promising lead, we subsequently subjected a number of other aryltriflates to the same conditions. We first sought to confirm the preference of the reaction for coupling at the triflate-carbon. To that end, we subjected two substrates previously made in our lab by Dr. Ansari[59] to the Mizoroki-Heck conditions at 105 °C (Scheme 26). The elevated temperature was found to be necessary with our selected set of reagents in order to avoid recovery of only starting materials. While we did observe the formation of the desired geminal alkenes from both substrates **108** and **109**, the yields were

very poor (7% of **110** and 7% of **112**, respectively). Additionally, for substrate **109**, as for

the reaction of **105** with 3-buten-1-ol at elevated temperature, we observed the formation

of the corresponding phenol (**113**) in 52% yield.
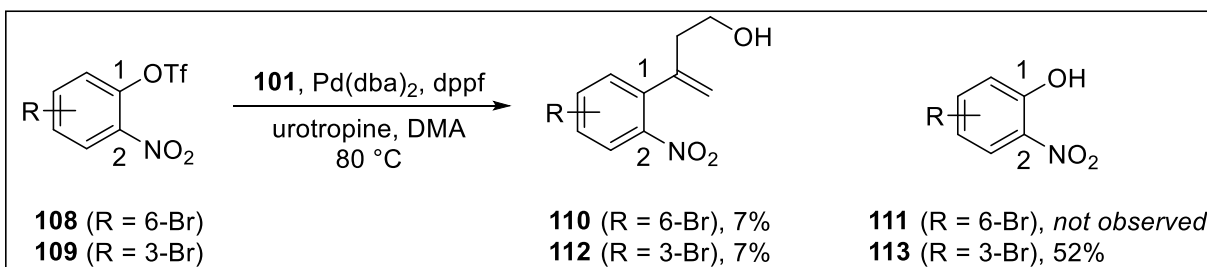
Scheme 26. Reaction of bromonitroaryl triflates under Mizoroki-Heck conditions.

While the initial results for these substrates were poor, nevertheless, we were encouraged

to find that coupling still proceeded, presumably with higher affinity for reaction with the

aryl-triflate carbon.

An additional set of compounds that we attempted Mizoroki-Heck coupling on were

precursors to two natural products, the tetracyclic indole alkaloids ht-13-A (**114**) and ht-13-

B (**115**) (Figure 7).
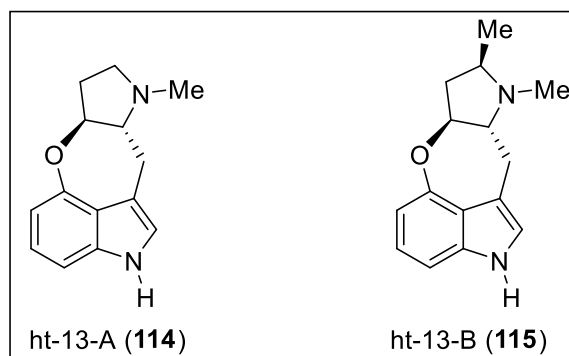
Figure 7. Structures of indole alkaloids **114** and **115**.

The screened precursors, **116** and **118** (Scheme 27) were originally made by Dr. Jeremiah

Hubbard in his efforts to synthesize ht-13-A and ht-13-B. Although the route that these

precursors were made for ultimately proved unsuccessful, and an alternate pathway led to the production of the natural compounds,[60,61] it was hypothesized that if intramolecular coupling using Mizoroki-Heck conditions were successful, it could alleviate some of the difficulties faced by Drs. Hubbard and Zhang, and allow for a more efficient means of access to these compounds and others of similar molecular structure.
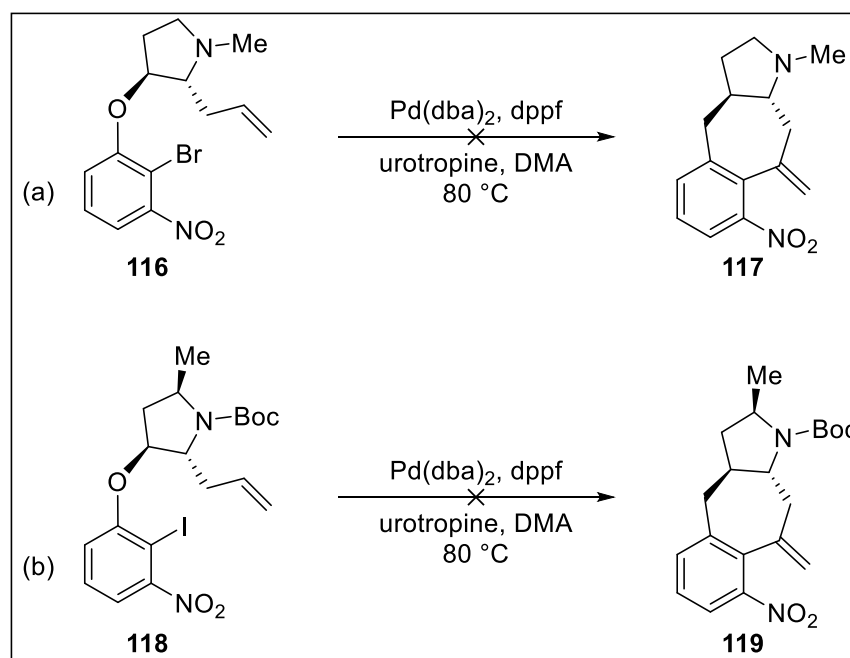

Scheme 27. Attempted Mizoroki-Heck couplings of **116** and **118**.

Upon subjecting **116** and **118** to coupling conditions, it was found that neither of the attempted intramolecular Mizoroki-Heck reactions successfully formed **117** or **119**, respectively. Rather, examination of the crude ^{1}H NMR spectra indicated that no reaction had taken place, and only shifts for the starting materials were observed. Despite these reactions not progressing forward as desired, it did serve to reinforce that this methodology appears to be highly selective for reaction with aryl triflates, whereas aryl halides seem to be unreactive.

Finally, three additional cyclization precursors were made utilizing this methodology. First, known 2-aryl-1-octene **120** was synthesized as reported by Qin *et al* (Scheme 28).[56] Although **120** was successfully made when utilizing the same reaction conditions as reported, in our hands, the reaction yielded only 37% of the desired compound, whereas a yield of 83% was reported in the literature. Although we are unsure of the reasons for this disparity, it may be that unknown variances in conditions from their reports to ours could be a contributing factor to the overall poor to moderate yields seen for all substrates we have screened using this chemistry.
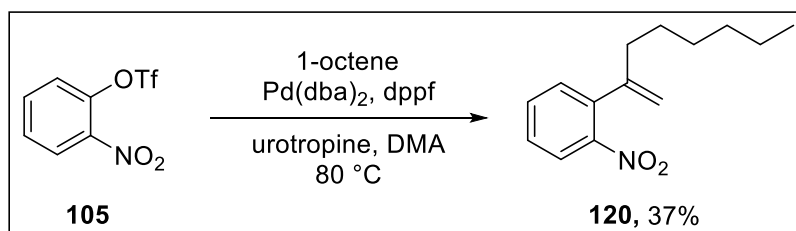
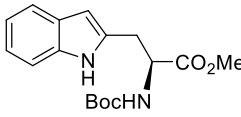**Scheme 28**. Synthesis of *o*-nitrostyrene derivative **120**.
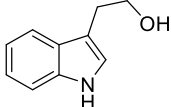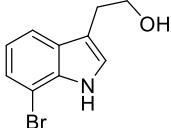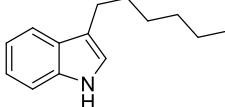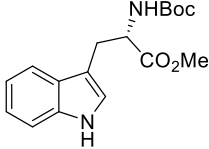
The second and third cyclization precursors were made in the reaction of nitroaryl triflate **105** with coupling partner **121** to screen for the potential of access to tryptophan derivatives (Scheme 29).

[a]Isolated as an inseparable mixture with 19% unreacted **105**.
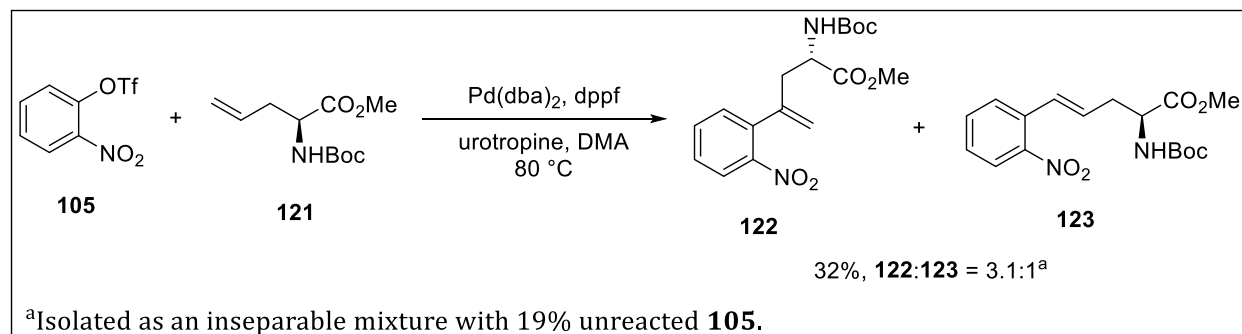
Scheme 29. Reaction of **105** with amino acid derivative **121**.

Upon subjection to coupling conditions, we observed an inseparable mixture of desired compound **122** and its regioisomer **123** (32%, 3.1:1 mixture of **122**:**123**) and 19% unreacted starting material. The yields and regioselectivity for this inseparable mixture of the three compounds were determined by ^{1}H NMR.

Table 7. Formation of indoles from *o*-nitrostyrenes made using Mizoroki-Heck reactions.

Entry	Substrate	Conditions[a]	Product	Yield[b]
1	**106**	Method A		**124**, 74%
2	**112**	Method A		**125**, 0%
3	**120**	Method B		**126**, 37%[c]
4	**122, 123**[d]	Method C		**127**, 22%
				128, 10%

[a]Method A: Pd(OAc)$_2$, PPh$_3$, MeOH/DMF, CO (90 psi), 60 °C, 24 h; Method B: Pd(OAc)$_2$, PPh$_3$, CH$_3$CN, CO (90 psi), 100 °C, 24 h; Method C: Pd(dba)$_2$, dppp, 1,10-phen., DMF, CO (90 psi), 120 °C, 48 h. See experimental section for details.

[b]Values reported are isolated yields after purification by chromatography.

[c]Also isolated was 13% unreacted **120**.

[d]Inseparable mixture of **122** and **123** as reported in Scheme 29 was subjected to the reaction.

With an assortment of *o*-nitrostyrene derivatives formed as described above, each was subjected to Watanabe-Cenini-Söderberg cyclization conditions. The results for these reactions are illustrated in Table 7. Compounds **106** and **120** cyclized as expected, affording their respective indole derivatives (**124** and **126**) in moderate to good yields (Table 7, entries 1 and 3). Interestingly, indole **125** was not observed (Table 7, entry 2). It is possible that this reaction could be promoted using altered Watanabe-Cenini-Söderberg conditions, although only the listed conditions were screened in this preliminary investigation. Finally, when the mixed sample of **122** and **123** was subjected to reductive cyclization conditions (Table 7, entry 4), we were gratified to find that both expected cyclization products (**127** and **128**) were isolated. In particular, this illustrates a promising method of forming tryptophan derivatives such as **127** in an expedient fashion.

c. **Conclusion**

Preliminary work on the applicability of modified Mizoroki-Heck chemistry has been performed, and initial results suggest that while this is a possible method for the production of indoles with pre-installed C3 substitution, further optimization is needed. This is particularly needed for the first, Mizoroki-Heck coupling, reaction in the sequence, as yields for the resultant *o*-nitrostyrenes were consistently observed in the poor-to-moderate range. It is believed that further screening of reaction conditions, particularly focused on the ligand used, could enhance the yields and regioselectivity of these reactions. A number of indoles were also synthesized using this two-step pathway. This is highlighted by the production of tryptophan derivative, **127**, and suggests that this methodology may hold promise as a

means of producing other tryptophan derivatives, which are valuable synthetic building blocks.

II.   Progress toward the syntheses of the marinoquinolines

a.   Introduction

In 2011, six compounds were isolated from a marine gliding bacteria, *Ohtaekwangia kribbensis* (strain PWU 25) off the coast of Korea.[62] Upon analysis, it was found that one of these compounds was marinoquinoline A (**129**), which has previously been isolated from a marine bacterium, *Rapidithrix thanilandica*,[63] and was determined to act as an acetylcholine esterase inhibitor.[64] Along with marinoquinoline A, five novel additional compounds were isolated from *O. kribbensis*: marinoquinolines B-F (**130**-**134**), whose structures were elucidated using a series of 1D and 2D NMR techniques (Figure 8).

129, marinoquinoline A   **130**, marinoquinoline B   **131**, marinoquinoline C

132, marinoquinoline D   **133**, marinoquinoline E   **134**, marinoquinoline F
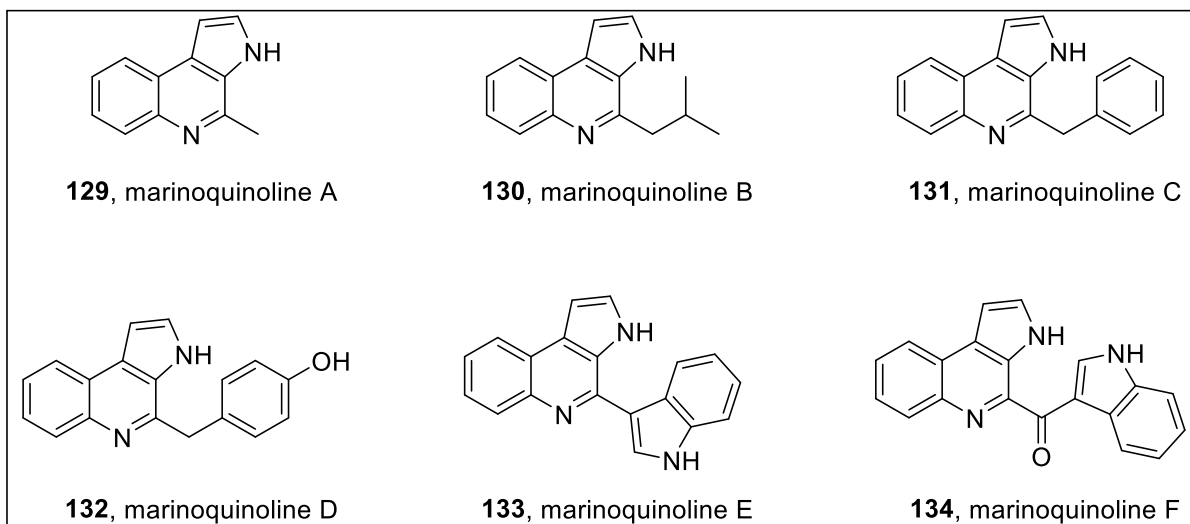
Figure 8. Structures of marinoquinolines A-F.

Although the marinoquinolines have only weak activity against a panel of bacteria and fungi and modest antiprotozoal activity, they are nevertheless structurally interesting and further studies of them and potential structural analogs merit examination. This is

highlighted by the variety of methods used to synthesize various members of the marinoquinoline family. These approaches have used key steps such as a Bronstad-acid-mediated arene-ynamide cyclization,[65] a palladium-catalyzed cyclization of imines,[66] a palladium-catalyzed Ullmann cross-coupling,[67] and an interesting divergent synthetic approach.[68] The first concise syntheses of marinoquinolines A-C was accomplished using a Morgen-Walls reaction to assemble the quinoline ring by Yao *et al* in 2012.[69]

We hypothesized that the marinoquinoles could be synthesized using a Henry reaction and modified Watanabe-Cenini-Söderberg cyclizations as the key steps in a novel and concise approach. This work was largely performed by two of the summer undergraduate students who worked under my supervision in the Söderberg lab. Herein are presented preliminary results toward the syntheses of these interesting tricyclic alkaloids.

b. **Results and Discussion**

In an attempt to ascertain proof-of-concept, we first endeavored to create the non-substituted marinoquinoline core, **135**. Retrosynthetically, we envisioned that **135** could be formed from the cyclization of nitrostyrene **136**, which could in turn be constructed from the Henry reaction of **137**. Aldehyde **137** could be obtained from **138**, which could be cyclized using a palladium-catalyzed *N*-heterocyclization as reported by Dr. Banini[17] from **139**. Compound **139** could be obtained by the condensation of commercially available 2-nitrophenylacetonitrile (**140**). With these transformations thus proposed, we set out to make the marinoquinoline core (**135**), and pending its success, to synthesize the marinoquinolines utilizing similar protocol.
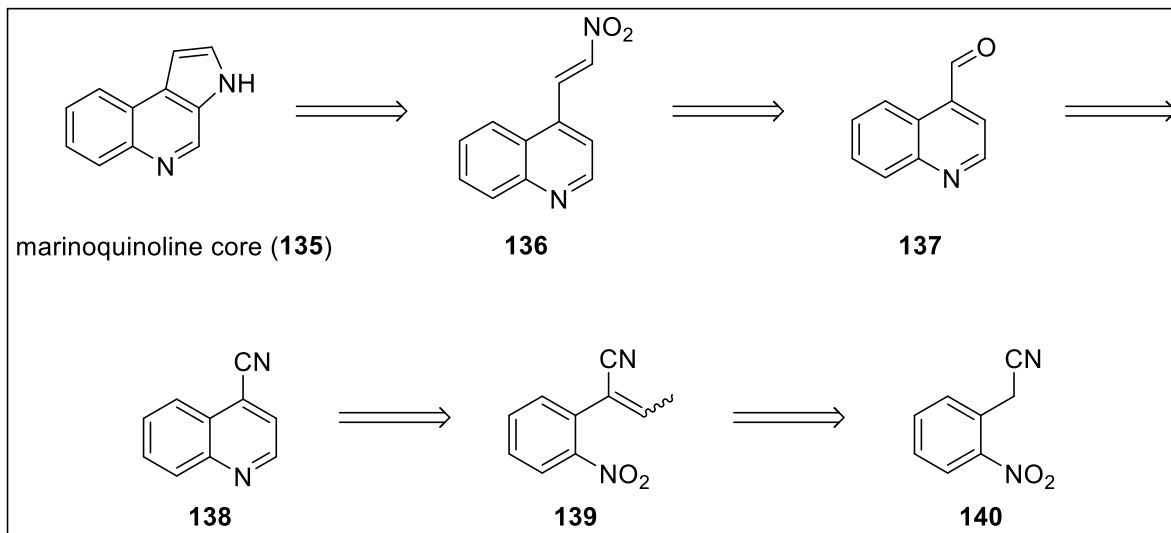
Scheme 30. Retrosynthesis of the marinoquinoline core.

We first sought to accomplish the condensation of 2-nitrophenylacetonitrile (**140**) with acetaldehyde in the hopes of obtaining compound **139**. Upon reaction utilizing similar conditions as for the construction of cyclization precursor **10** (Chapter 1), we were initially discouraged, as there was no evidence of the expected olefinic quartet in the ^{1}H NMR spectrum. However, upon further investigation, we found that instead of the reaction ceasing at the production of **139**, spontaneous cyclization had occurred to afford 4-quinolinecarbonitrile-*N*-oxide (**141**) in 47% yield (Scheme 31).
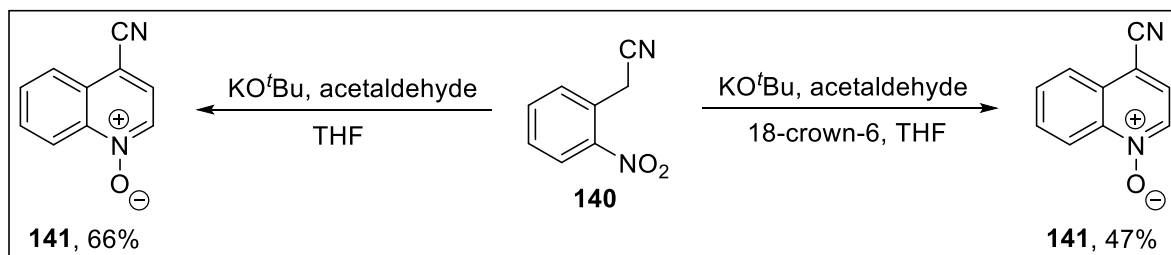
Scheme 31. Unexpected formation of *N*-oxide **141**.

Despite this unexpected product and its modest yield, we were encouraged by the result, as this set of conditions negated the need for a two-step condensation and sequential

cyclization pathway as originally envisioned. Additionally, when compared to the related condensations that have been performed (as described in Chapter 1), the yields here are higher for the equivalent of a two-step process than for the single condensation. We then queried whether this reaction required the addition of 18-crown-6 in order to occur. Thus, we screened the reaction of compound **140** as before, changing the conditions only by omitting the addition of the crown ether. Compound **141** was gratifyingly once again obtained, interestingly, in elevated yield (66%, Scheme 31).

Encouraged by these results, we next attempted to form the three quinolinecarbonitrile-*N*-oxides that could act as precursors to marinoquinolines A-C using similar methodology (Scheme 32).

Aldehyde R-groups:
to **142**, R = *n*-Pr
to **143**, R = (CH₂)₂CH(CH₃)₂
to **144**, R = (CH₂)₂Ph

142 (R = Me, *not observed*)
143 (R = *i*Pr, *not observed*)
144 (R = Bn, *not observed*)

ᵃAttempted these reactions both with and without 18-crown-6.
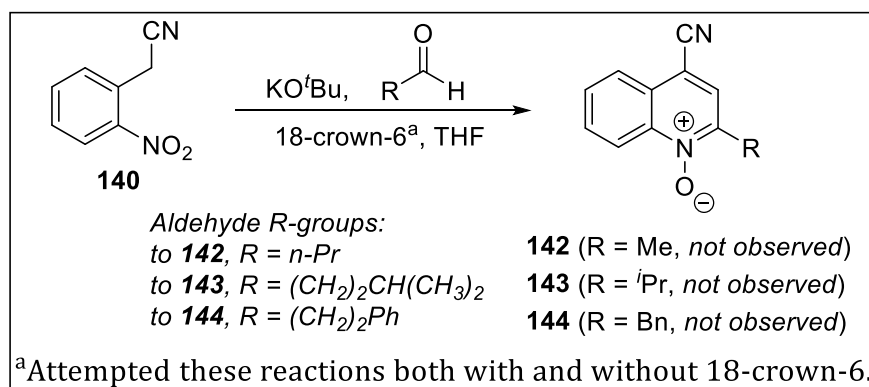
Scheme 32. Attempted formation of compounds **142**, **143**, and **144**.

Unfortunately, when substituting any aldehyde for acetaldehyde, none of the cyclization products (**142**-**144**) were observed, nor were condensation products that are derivatives of **139** (seen in Scheme 30). Instead, in all cases, whether the reaction was run with or without 18-crown-6, degradation of the starting material appeared to have occurred. Although obtaining quinolinecarbonitrile-*N*-oxides **142**-**144** via this reaction would have been a facile and direct method, it was noted that these negative results were consistent with what was

observed when attempting to form 2-(2-nitroaryl)alkenoates via similar means (Chapter 1), in that any aldehyde of longer chain length than formaldehyde or acetaldehyde would not undergo condensation.

Despite the lack of success in forming substituted quinolinecarbonitrile-*N*-oxides directly from 2-nitrophenylacetonitrile, we hypothesized that they could instead be produced from the subjection of unsubstituted quinolinecarbonitrile-*N*-oxide **141** to reaction with Grignard reagents. Further, we expected that when exposed to the reaction conditions necessary to facilitate substitution, the *N*-oxide would reduce to the quinoline. Thus, compound **141** was screened for reactivity with three Grignard reagents in the attempt to form the corresponding 2-substituted quinoline derivatives (Scheme 33).
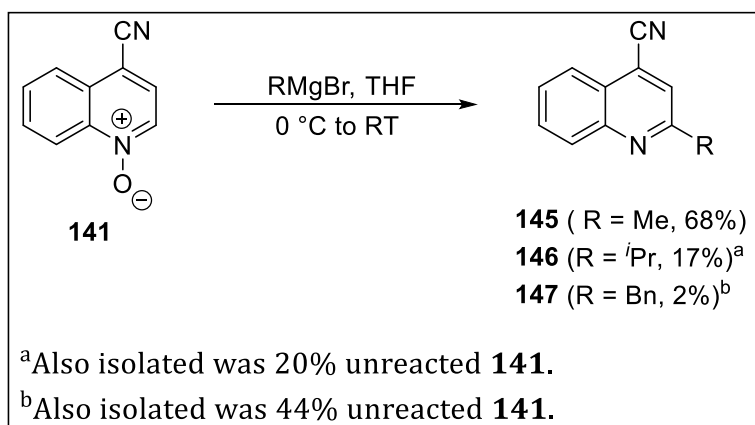
Scheme 33. Reaction of **141** with Grignard reagents to form **145-147**.

After screening a variety of methods of reaction, it was found that either using commercially-purchased and anhydrous Grignard reagents or formation of Grignard reagents *in situ* followed by their direct addition to **141** afforded compounds **145-147** in a wide range of yields. Methyl-substituted quinoline **145** was obtained in good yield, however, compounds **146** and **147** were formed in 17% and 2% yields, respectively, and in both cases unreacted

starting material was obtained in significant quantities (20% and 44% recovered, respectively).

With compounds **145-147** in hand, we next attempted to convert the cyano-group to an aldehyde in preparation for the subsequent Henry reaction. However, when compound **145** was subjected to reaction with diisobutylaluminum hydride (DIBAL-H), reduction to the corresponding aldehyde was never observed under any screened conditions (Scheme 34). Instead, in all cases, starting material (**145**) was recovered.
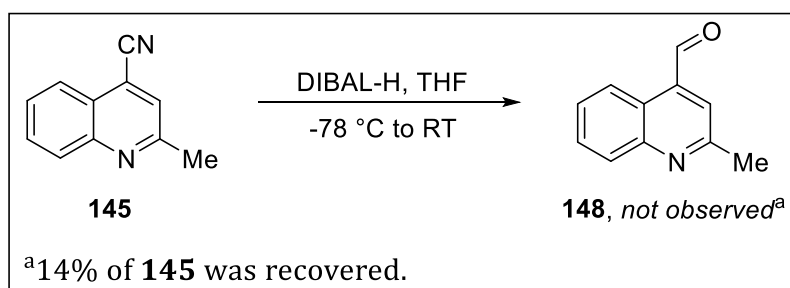
Scheme 34. Attempted reduction of **145**.

We next attempted to access aldehyde **148** by an alternate pathway. By subjecting compound **145** to hydrolysis conditions with H_2SO_4 and H_2O, we hoped to obtain the corresponding carboxylic acid, which we theorized could be subsequently reduced to obtain **148**. However, upon analysis of the presumed acid, while most of the observed ^1H NMR peaks were in agreement with literature values, not all matched.[70] Additionally, our experimental melting point was not in agreement with the literature value of 244 °C. Due to these inconclusive data, as well as difficulties encountered while attempting to produce aldehyde **148**, additional work is needed in order to further the research toward the production of the marinoquinolines.

c. **Conclusion**

Initial progress has been made toward the syntheses of marinoquinolines A-C. This work has showcased an unexpected one-pot condensation/cyclization of 2-nitrophenylacetonitrile to form quinolinecarbonitrile-*N*-oxide that can be accomplished with or without the use of a crown ether. Although 2-substituted quinolinecarbonitrile-*N*-oxides cannot be formed by this one-pot methodology, the respective 2-alkylquinolinecarbonitriles can be formed from the reaction of quinolinecarbonitrile-*N*-oxide with a Grignard reagent in poor to good yields. Thus far, the reduction of the cyano-group to the corresponding aldehyde has proven to be difficult. Future work may necessitate the Henry reaction of an aldehyde prior to installation of substitution at the 2-position in order to avoid these unprecedentedly difficult reductions if an alternate means of access to the aldehydes cannot be accomplished. Upon successful Henry reactions to the nitrostyrenes of variety **136**, it is believed that a palladium-catalyzed reductive *N*-heterocyclization will be successful in affording the marinoquinolines.

Chapter 4—Experimental Methods

I.   General Procedures

All NMR spectra were recorded in either CDCl$_3$ or DMSO-d_6 at 400 MHz (^{1}H-NMR) and 100 MHz (^{13}C-NMR) or 600 MHz(^{1}H-NMR) and 150 MHz (^{13}C-NMR) at ambient temperatures unless otherwise stated. The chemical shifts are expressed in δ values relative to SiMe$_4$ (0.0 ppm, ^{1}H and ^{13}C) or CDCl$_3$ (77.0 ppm, ^{13}C) internal standards. The multiplicity of each resonance observed in the ^{1}H NMR spectra are reported as, s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. HRMS data were obtained via electrospray ionization (ESI) with an ion trap mass analyzer. Solvents (tetrahydrofuran, dichloromethane, and toluene) were purified and dried prior to use via two consecutive columns composed of activated alumina and Q5 catalyst on a Glass Contours solvent purification system. Anhydrous *N,N*-dimethylformamide and anhydrous *N,N*-dimethylacetamide were used as received. Hexanes, ethyl acetate, and 1,4-dioxane were distilled from calcium hydride. Chemicals prepared according to literature procedures have been referenced the first time used. All other reagents were obtained from commercial sources and used as received. Reactions were performed under a nitrogen atmosphere in oven-dried glassware unless otherwise noted. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure unless otherwise stated. Melting points (uncorrected) were recorded from pure products obtained by chromatography.

II.   Experimental
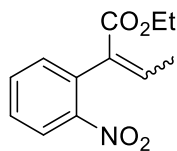
 Ethyl 2-(2-nitrophenyl)-2-butenoate (10). Ethyl 2-(2-nitrophenyl)acetate (740 mg, 3.60 mmol) and 18-crown-6 (240 mg, 0.90 mmol) were combined in a round-bottomed flask and the system was purged with N_2. THF (9 mL) was added and the solution was cooled to -78 °C. A suspension of t-BuOK (440 mg, 3.90 mmol) in THF (6 mL) was added dropwise via syringe and solution immediately turned deep blue. Acetaldehyde (1.0 mL, 17.9 mmol) was added in one portion via syringe, and the resulting solution was stirred at -78 °C for 30 min, then warmed to ambient temperature and stirred for 16 h. The reaction was quenched by slow addition of saturated aqueous NH_4Cl and extracted with EtOAc (3 x 15 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The resulting residue was purified by chromatography (hexane/EtOAc 9:1 then 7:3) to afford **10** (246 mg, 1.05 mmol, 29%) as a yellow oil as a mixture of stereoisomers (major/minor = 33.3:1 by ^{1}H NMR). Analytical data from the 33.3:1 mixture of stereoisomers: ^{1}H NMR (major isomer) δ 8.14 (dd, J=8.2, 1.2 Hz, 1H), 7.65 (td, J=7.5, 1.3 Hz, 1H), 7.56-7.49 (m, 1H), 7.27 (dd, J = 7.6, 1.4 Hz, 1H), 7.22 (q, J = 7.2 Hz, 1H), 4.15 (m, 2H), 1.73 (d, J = 7.2 Hz, 2H), 1.20 (t, J = 7.1 Hz, 3H); ^{1}H NMR (minor isomer, partial data) δ 8.06 (dd, J = 8.1, 1.2 Hz, 1H), 7.34 (dd, J = 7.6, 1.4 Hz, 1H), 6.41 (q, J = 7.3 Hz, 1H), 2.30 (d, J = 7.3 Hz, 3H); ^{13}C NMR (major isomer) δ 165.5, 148.7, 139.6, 133.3, 132.8, 132.6, 131.1, 129.0, 124.9, 61.2, 15.6, 14.2; ^{13}C NMR (minor isomer, partial data) δ 142.8, 133.6, 132.7, 128.7, 124.5, 60.7, 16.3, 14.1; IR (ATR) 2982, 1709, 1523, 1345, 1267, 1241, 1188, 1047, 1035 cm^{-1}; HRMS (ESI) calculated for $C_{12}H_{14}NO_4$ (M+H^{+}) 236.0917; found, 236.0930.
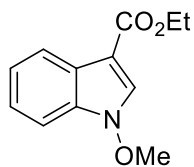
Ethyl 1-methoxyindole-3-carboxylate (12). *Method A:* A solution of **10** (181 mg, 0.77 mmol) in *t*-BuOH (2 mL) was added slowly to a pre-formed solution of *t*-BuOK (1.01 g, 8.16 mmol) in *t*-BuOH (3 mL) under a nitrogen atmosphere. The mixture was cooled in an ice bath for 10 min. MeI (170 µL, 1.10 mmol) was added drop-wise over a period of 2 min. The solution was allowed to warm to ambient temperature and stirred for 3 h. The reaction was quenched with a solution of saturated NH_4Cl (aqueous, 10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic phases were washed with H_2O (3 x 10 mL) and dried ($MgSO_4$). Solvents were removed under reduced pressure to obtain **12** (141 mg, 0.65 mmol, 84%) without further purification as a pale yellow oil.

Method B: Compound **10** (128 mg, 0.54 mmol) was added to a round-bottomed flask, and the system was purged with nitrogen gas. Anhydrous PhMe (6 mL) was added via syringe, and the solution was cooled to 0 °C. Sodium *tert*-pentoxide (40% solution in PhMe, 380 ⸮L, 1.24 mmol) was added drop wise, and the solution immediately turned purple then red. The solution was stirred at 0 °C for 10 min and dimethyl sulfate (150 ⸮L, 1.62 mmol) was added via syringe. Solution was warmed to ambient temperature and stirred for 3 h. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by chromatography (hexane/EtOAc, 7:3) to afford **12** (64 mg, 0.29 mmol, 54%) as a pale yellow oil. ^{1}H NMR δ 8.18 (d, *J*=7.8 Hz, 1H), 7.96 (s, 1H), 7.45 (dd, *J*=7.8, 1.2 Hz, 1H), 7.32-7.27 (m, 2H), 4.38 (q, *J*=7.2 Hz, 2H), 4.13 (s, 3H), 1.41 (t, *J*=7.2 Hz, 3H); ^{13}C NMR δ 164.6, 132.0, 128.3, 123.4, 122.8,

122.3, 121.8, 108.5, 103.7, 66.6, 59.8, 14.5; IR (ATR) 3118, 2906, 2831, 1686, 1514, 1224, 1023, 772 cm^{-1}; HRMS (ESI) calculated for $C_{12}H_{14}NO_3$ (M+H$^+$) 220.0968; found, 220.0968.
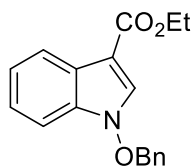
Ethyl 1-benzyloxyindole-3-carboxylate (13). Treatment of **10** (169 mg, 0.72 mmol) in *t*-BuOH (3 mL) with *t*-BuOK (1.01 g, 8.16 mmol) in *t*-BuOH (3 mL) followed by the addition of benzyl bromide (180 μL, 1.08 mmol), as described for **12** (ambient temperature, 3 h), gave after work up but without chromatographic purification **13** (166 mg, 0.56 mmol, 78%) as a pale yellow oil. ^{1}H NMR δ 8.17 (dt, *J*=7.8, 1.2 Hz, 1H), 7.71 (s, 1H), 7.40-7.24 (m, 8H), 5.21 (s, 2H), 4.35 (q, *J*=7.2 Hz, 2H), 1.39 (t, *J*=7.2 Hz, 3H); ^{13}C NMR δ 164.6, 133.8, 132.5, 129.6, 129.5, 129.4, 128.8, 123.3, 122.7, 122.3, 121.7, 108.8, 103.4, 81.0, 59.8, 14.5; IR (ATR) 3123, 2947, 1698, 1521, 1204, 1082, 740 cm^{-1}; HRMS (ESI) calculated for $C_{18}H_{18}NO_3$ (M+H$^+$) 296.1287; found, 296.1289.
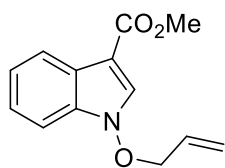
Methyl 1-(2-propen-1-yloxy)indole-3-carboxylate (14). Treatment of **11**[19] (94 mg, 0.43 mmol) in *t*-BuOH (2 mL) with *t*-BuOK (600 mg, 4.90 mmol) in *t*-BuOH (3 mL) followed by 3-bromo-1-propene (110 μL, 0.65 mmol), as described for **12** (ambient temperature, 3 h), gave after chromatography (hexanes/EtOAc, 9:1), **14** (91 mg, 0.39 mmol, 91%) as a pale yellow oil. ^{1}H NMR δ 8.16 (d, *J*=7.8 Hz, 1H), 7.92 (s, 1H), 7.46 (d, *J*=8.1 Hz, 1H), 7.31 (dd, *J*=7.5, 1.2 Hz, 1H), 7.27 (dt, *J*=8.0, 1.2 Hz, 1H), 6.10 (ddt, *J*=17.0, 10.2, 6.6 Hz, 1H), 5.37 (dd, *J*=10.2, 0.9 Hz, 1H), 5.33 (dq, *J*=17.1, 1.2 Hz, 1H), 4.74 (dt, *J*=7.2, 1.2 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR δ 165.0, 132.6, 130.7, 129.5, 123.3, 122.8, 122.4, 121.7, 108.9, 103.1, 79.7, 51.1;

IR (ATR) 3126, 2981, 2940, 1693, 1520, 1200, 1081, 1030, 740 cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{14}NO_3$ (M+H$^+$) 232.0968; found, 232.0968.
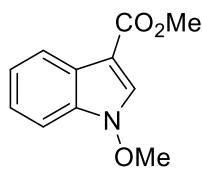
Methyl 1-methoxyindole-3-carboxylate (15). Treatment of **11** (176 mg, 0.80 mmol) in *t*-BuOH (3 mL) with *t*-BuOK (1.01 g, 8.16 mmol) in *t*-BuOH (3 mL) followed by addition of MeI (200 μL, 1.20 mmol), as described for **12** (ambient temperature, 3 h), gave after work up but without chromatographic purification **1** (121 mg, 0.59 mmol, 74%) as a pale yellow oil. ^{1}H NMR δ 8.18 (dt, *J*=7.8, 1.2 Hz, 1H), 7.96 (s, 1H), 7.46 (dt, *J*=7.8, 1.2 Hz, 1H), 7.33-7.26 (m, 2H), 4.14 (s, 3H), 3.91 (s, 3H); ^{13}C NMR δ 165.0, 132.0, 128.3, 123.4, 122.8, 122.4, 121.8, 108.6, 103.4, 66.6, 51.1.
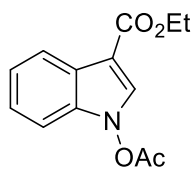
Ethyl 1-acetoxyindole-3-carboxylate (17). Compound **10** (106 mg, 0.45 mmol) was added to a round-bottomed flask, and the system was purged with N$_2$. Anhydrous PhMe (5 mL) was added via syringe, and the solution and cooled to 0 °C. Sodium *tert*-pentoxide (40% solution in PhMe, 310 μL, 1.04 mmol) was added drop wise, and the solution immediately turned purple then red. This solution stirred at 0 °C for 10 min and acetic anhydride (130 μL, 1.35 mmol) was added via syringe. Solution was warmed to ambient temperature and stirred for 3 h. The resultant mixture was quenched by addition of saturated aqueous ammonium chloride and extracted with EtOAc (3x10 mL). The combined organics were dried (MgSO$_4$) and the solvent was removed under reduced pressure. The resulting residue was purified by chromatography (hexane/EtOAc 7:3) to afford **17** (53 mg,

0.21 mmol, 48%) as an orange oil. ^{1}H NMR δ 8.23-8.17 (m, 1H), 7.83 (s, 1H), 7.32-7.28 (m, 2H), 7.23-7.20 (m, 1H), 4.38 (q, J = 7.1 Hz, 2H), 2,43 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 168.0, 164.6, 133.4, 129.9, 124.1, 122.9, 122.8, 122.0, 108.4, 105.3, 60.2, 18.1, 14.7; IR (ATR) 3130, 2967, 1809, 1691, 1525, 1206, 1164 cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{14}NO_4$ (M+H$^+$) 248.0917; found, 248.09294.
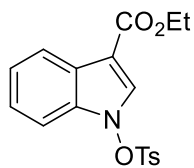
Ethyl 1-tosyloxyindole-3-carboxylate (18). Treatment of **10** (91 mg, 0.39 mmol) in PhMe (5 mL) with sodium *tert*-pentoxide (40% solution in PhMe, 270 µL, 0.90 mmol) followed by *p*-toulenesulfonyl chloride (223 mg, 1.17 mmol) as described for **17** (ambient temperature, 3 h) gave after chromatography (hexane/EtOAc 7:3) **18** (62 mg, 0.17 mmol, 44%) as an oil which solidified upon standing to an orange solid. mp = 87-90 °C; ^{1}H NMR δ 8.11 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.67 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.21 (t, J = 7.6 Hz, 1H), 7.12 (t, J = 7.7 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 2.45 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 164.2, 147.8, 134.1, 130.7, 130.6, 129.7, 129.6, 124.3, 123.2, 122.5, 121.7, 109.3, 106.5, 60.4, 22.0, 14.6; IR (ATR) 2926, 1707, 1526, 1389, 1192, 1075 cm^{-1}; HRMS (ESI) calculated for $C_{18}H_{18}NO_5S$ (M+H$^+$) 360.0900; found, 360.0913.
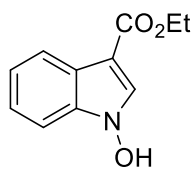
Ethyl 1-hydroxyindole-3-carboxylate (19).[10c] Compound **10** (120 mg, 0.51 mmol) was added to a round-bottomed flask, and the system was purged with N_2. Anhydrous PhMe (6 mL) was added via syringe, and the solution and cooled to 0 °C. Sodium *tert*-pentoxide (40% solution in PhMe, 350 µL, 1.17 mmol) was added dropwise, and the solution

immediately turned purple. The mixture was allowed to warm to ambient temperature and stirred for 3 h. The resultant mixture was quenched by addition of saturated aqueous ammonium chloride and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (MgSO$_4$) and the solvent was removed under reduced pressure. The resulting residue was purified by chromatography (hexane/EtOAc 1:1) to afford **19** (44 mg, 0.22 mmol, 42%) as an orange oil. ^{1}H NMR δ 9.47 (s, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.64 (s, 1H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 1.32 (t, *J* = 7.1, 3H); ^{13}C NMR δ 167.0, 134.0, 130.8, 123.4, 122.6, 122.5, 121.2, 109.4, 102.0.
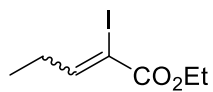
Ethyl 2-iodo-2-pentenoate (20). N-iodosuccinimide (NIS, 1.18 g, 5.24 mmol) and NaH (60% dispersion in mineral oil, 590 mg, 14.7 mmol) were suspended in tetrahydrofuran (THF, 15 mL). Triethylphosphonoacetate (830 µL, 4.19 mmol) was added dropwise, and solution stirred at ambient temperature for 1 h. Propionaldehyde (300 µL, 4.19 mmol) was added dropwise via syringe, and the solution stirred at ambient temperature for an additional 1 h. The reaction was quenched by slow addition of saturated aqueous NH$_4$Cl and extracted with ethyl acetate (3 x 15 mL). The combined organics were washed sequentially with saturated aqueous NaHSO$_3$ (15 mL) and H$_2$O (15 mL), dried over MgSO$_4$, and the solvent was removed under reduced pressure. The resulting residue was purified by chromatography over a short plug of silica (hexane/EtOAc 1:1) to afford **20** (1.02 g, 4.03 mmol, 96%) as a pale yellow oil, mixture of stereoisomers (major:minor = 2.6:1 by ^{1}H NMR). Analytical data from the 2.6:1 mixture of stereoisomers: ^{1}H NMR (400 MHz, chloroform-*d*, major isomer) δ 7.19 (t, *J* = 7.0 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.32 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.3 Hz, 3H); ^{1}H NMR (400 MHz, chloroform-*d*, minor isomer, partial data)

δ 6.89 (t, J = 7.6 Hz, 1H), 4.19 (m, 2H), 2.47 (m, 2H); ^{13}C NMR (101 MHz, chloroform-d, major isomer) δ 162.9, 154.3, 94.6, 62.5, 30.5, 14.4, 11.8; ^{13}C NMR (101 MHz, chloroform-d, minor isomer) δ 163.8, 157.3, 84.2, 62.1, 29.6, 13.1, 12.1.
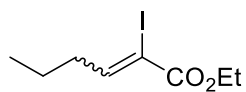
Ethyl 2-iodo-2-hexenoate (21). *n*-Butyraldehyde (500 μL, 5.57 mmol) was reacted with triethylphosphonoacetate (1.10 mL, 5.57 mmol), NIS (1.57 g, 6.96 mmol), and NaH (60% dispersion in mineral oil, 780 mg, 19.5 mmol) in THF (20 mL) as described for **20**. After purification over a short plug of silica gel (hexanes:EtOAc 1:1), **21** (1.24 g, 4.64 mmol, 83%) was obtained as a pale yellow oil, mixture of stereoisomers (major:minor = 2.1:1 by ^{1}H NMR). Analytical data from the 2.1:1 mixture of stereoisomers: ^{1}H NMR (400 MHz, chloroform-d, major isomer) δ 7.20 (t, J = 7.0 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 2.29 (q, J = 7.3 Hz, 2H), 1.59-1.52 (m, 2H), 1.33 (t, J = 7.2 Hz, 3H), 0.99 (t, J = 7.4 Hz, 3H); ^{1}H NMR (400 MHz, chloroform-d, minor isomer, partial data) δ 6.89 (t, J = 7.8 Hz, 1H), 4.22-4.15 (m, 2H), 2.43 (q, J = 7.6 Hz, 2H), 1.47 (m, 2H); ^{13}C NMR (101 MHz, chloroform-d, major isomer) δ 171.0, 152.9, 95.2, 60.2, 38.8, 29.6, 20.8, 14.1; ^{13}C NMR (101 MHz, chloroform-d, minor isomer) δ 166.2, 155.7, 84.5, 60.0, 35.2, 29.3, 20.9, 13.7.
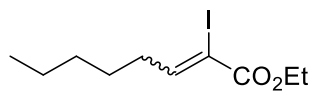
Ethyl 2-iodo-2-octenoate (22). Hexanal (500 μL, 4.08 mmol) was reacted with triethylphosphonoacetate (810 μL, 4.08 mmol), NIS (1.15 g, 5.10 mmol), and NaH (60% dispersion in mineral oil, 570 mg, 14.3 mmol) in THF (15 mL) as described for **20**. After purification over a short plug of silica gel (hexanes:EtOAc 1:1), **22** (1.12 g, 3.77 mmol, 92%) was obtained as a pale yellow oil, mixture of stereoisomers (major:minor = 3.6:1 by ^{1}H NMR). Analytical data from the 3.6:1 mixture of stereoisomers: ^{1}H NMR (400 MHz,

chloroform-*d*, major isomer) δ 7.20 (t, *J* = 7.0 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 2.36-2.27 (m, 2H), 1.35-1.25 (m, 9H), 0.92-0.87 (m, 3H); ^{1}H NMR (400 MHz, chloroform-*d*, minor isomer, partial data) δ 6.90 (t, *J* = 7.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.45 (q, *J* = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, chloroform-*d*, major isomer) δ 162.8, 153.2, 95.1, 62.5, 36.9, 31.3, 29.6, 27.1, 22.4, 13.9; ^{13}C NMR (101 MHz, chloroform-*d*, minor isomer, partial data) δ 163.8, 149.4, 84.4, 62.0, 31.2, 29.3, 27.0, 22.3, 14.1; IR (ATR) 2955, 2925, 1717, 1464, 1367, 1242, 1175, 1038 cm^{-1}; HRMS (ESI) calculated for $C_{10}H_{18}IO_2$ (M+H$^+$) 297.03; found, 297.0346.
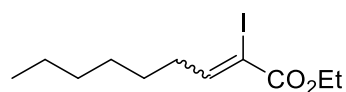
 Ethyl 2-iodo-2-nonenoate (23). Heptanal (500 μL, 3.55 mmol) was reacted with triethylphosphonoacetate (700 μL, 3.55 mmol), NIS (1.00 g, 4.44 mmol), and NaH (60% dispersion in mineral oil, 500 mg, 12.4 mmol) in THF (15 mL) as described for **20**. After purification over a short plug of silica gel (hexanes:EtOAc 1:1), **23** (670 mg, 2.16 mmol, 61%) was obtained as a pale yellow oil, mixture of stereoisomers (major:minor = 6.3:1 by ^{1}H NMR). Analytical data from the 6.3:1 mixture of stereoisomers: ^{1}H NMR (400 MHz, chloroform-*d*, major isomer) δ 7.20 (t, *J* = 7.0 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 2.31 (q, *J* = 7.2 Hz, 2H), 1.35-1.31 (m, 11H), 0.90-0.88 (m, 3H); ^{1}H NMR (400 MHz, chloroform-*d*, minor isomer, partial data) δ 6.90 (t, *J* = 7.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.45 (q, *J* = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, chloroform-*d*, major isomer) δ 163.0, 153.3, 95.1, 62.6, 37.1, 31.6, 29.7, 29.0, 27.4, 22.5, 14.1; ^{13}C NMR (101 MHz, chloroform-*d*, minor isomer, partial data) δ 156.2, 93.4, 62.1, 28.8, 22.7, 14.2.
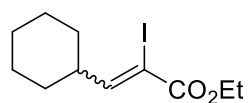
 Ethyl 3-cyclohexyl-2-iodopropenoate (24). Cyclohexanecarboxaldehyde (500 μL, 4.13 mmol) was reacted with

triethylphosphonoacetate (820 μL, 4.13 mmol), NIS (1.16 g, 5.16 mmol), and NaH (60% dispersion in mineral oil, 580 mg, 14.5 mmol) in THF (15 mL) as described for **20**. After purification over a short plug of silica gel (hexanes:EtOAc 1:1), **24** (705 mg, 2.29 mmol, 55%) was obtained as a pale yellow oil, mixture of stereoisomers (major:minor = 4.5:1 by ^{1}H NMR). Analytical data from the 4.5:1 mixture of stereoisomers: ^{1}H NMR (400 MHz, chloroform-*d*, major isomer) δ 6.98 (d, *J* = 9.0 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.49-2.37 (m, 1H), 1.77-1.73 (m, 5H), 1.36-1.30 (m, 8H); ^{1}H NMR (400 MHz, chloroform-*d*, minor isomer, partial data) δ 6.71 (d, *J* = 10.0 Hz, 1H), 2.91-2.78 (m, 1H); ^{13}C NMR (101 MHz, chloroform-*d*, major isomer) δ 163.1, 157.1, 92.7, 62.6, 45.9, 32.1, 30.5, 25.3, 14.2; ^{13}C NMR (101 MHz, chloroform-*d*, minor isomer, partial data) δ 160.5, 62.1, 31.9, 29.7, 25.7, 14.1.
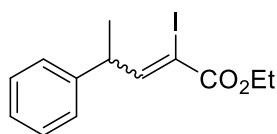
Ethyl 2-iodo-4-phenylpentenoate (25). 2-Phenylpropionaldehyde (500 μL, 3.74 mmol) was reacted with triethylphosphonoacetate (740 μL, 3.74 mmol), NIS (1.05 g, 4.68 mmol), and NaH (60% dispersion in mineral oil, 520 mg, 13.1 mmol) in THF (15 mL) as described for **20**. After purification over a short plug of silica gel (hexanes:EtOAc 1:1), **25** (348 mg, 1.06 mmol, 28%) was obtained as a yellow oil, mixture of stereoisomers (major:minor = 2.1:1 by ^{1}H NMR).Analytical data from the 4.8:1 mixture of stereoisomers: ^{1}H NMR (400 MHz, chloroform-*d*, major isomer) δ 7.33-7.30 (m, 3H), 7.24-7.18 (m, 2H), 7.11 (dd, *J* = 15.7, 6.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.62 (m, 1H), 1.44 (t, *J* = 7.0 Hz, 3H), 1.28 (d, *J* = 7.1 Hz, 3H); ^{1}H NMR (400 MHz, chloroform-*d*, minor isomer, partial data) δ 6.91 (d, *J* = 10.4 Hz, 1H), 3.76-3.71 (m, 1H); ^{13}C NMR (101 MHz, chloroform-*d*, major isomer) δ 201.1, 166.8, 152.6, 143.3, 129.1, 128.7, 127.3, 126.7, 120.1, 60.3, 42.0, 20.2, 14.2; ^{13}C NMR (101

MHz, chloroform-*d*, minor isomer) δ 202.1, 163.0, 155.8, 142.4, 128.8, 127.2, 127.0, 62.8, 46.9, 19.5, 14.6; IR (ATR) 3027, 2976, 1715, 1493, 1452, 1367, 1264, 1173, 1028, 759 cm^{-1}; HRMS (ESI) calculated for $C_{10}H_{18}IO_2$ (M+H$^+$) 337.07; found, 337.1796.
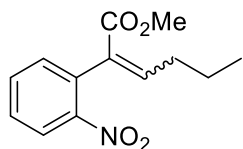
Methyl 2-(2-nitrophenyl)-2-hexenoate (27). Under an nitrogen atmosphere, butyltriphenylphosphonium bromide (350 mg, 0.87 mmol) was dissolved in THF (3 mL) and the solution was cooled to 0 °C. BuLi (2.5 M, 350 μL, 0.87 mmol) was added drop wise via syringe and the resultant orange solution was stirred at 0 °C for 1 h. Compound **26** (150 mg, 0.72 mmol) dissolved in THF (2 mL) was added via syringe, and solution was warmed to ambient temperature and stirred for 17 h. The reaction mixture was quenched by addition of H_2O and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (MgSO$_4$) and solvent was removed under reduced pressure. The resultant residue was purified by chromatography (hexane/EtOAc 9:1) to afford **27** (43 mg, 0.17 mmol, 24%) as a pale yellow oil as a mixture of stereoisomers (major/minor = 11.6:1 by ^1H NMR). Analytical data from the 11.6:1 mixture of stereoisomers: ^1H NMR (major isomer) δ 8.14 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.64 (td, *J* = 7.5, 1.3 Hz, 1H), 7.55-7.48 (m, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 1H), 3.70 (s, 3H), 2.04-1.89 (m, 2H), 1.45 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H); ^1H NMR (minor isomer, partial data) δ 6.27 (t, *J* = 7.6 Hz, 1H), 2.82-2.72 (m, 2H); ^{13}C NMR (major isomer) δ 166.2, 148.7, 145.0, 133.4, 132.7, 131.4, 129.0, 124.9, 52.3, 31.8, 22.0, 13.9.
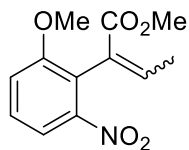
Methyl 2-(6-methoxy-2-nitrophenyl)-2-butenoate (29). Under an nitrogen atmosphere, methyl 2-(tributyltin)-2-butenoate[26] (232 mg, 0.59 mmol) in PhMe (2 mL) was added via syringe to a solution of 2-bromo-1-methoxy-3-nitrobenzene (125 mg, 0.54 mmol), $Pd(PPh_3)_4$ (62 mg, 0.054 mmol) in PhMe (3 mL). The solution was heated to reflux for 16 h, then cooled to ambient temperature, quenched with H_2O, and extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (3 x 10 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The resulting residue was purified by chromatography (hexane/EtOAc 9:1 then 7:3) to afford **29** (35 mg, 0.14 mmol, 26%) as an orange oil as a mixture of stereoisomers (major/minor = 2.3:1 by ^1H NMR). Analytical data from the 2.3:1 mixture of stereoisomers: ^1H NMR (major isomer) δ 7.63 (d, J = 8.2 Hz, 1H), 7.46 (t, J = 8.4 Hz, 1H), 7.20 (dd, J = 14.2 7.6 Hz, 2H), 3.84 (s, 3H), 3.71 (s, 3H), 1.58 (d, J = 7.2 Hz, 3H); ^1H NMR (minor isomer, partial data) δ 7.39 (t, J = 8.2 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.15 (q, J = 7.3 Hz, 1H), 3.83 (s, 3H), 2.23 (d, J = 7.3 Hz, 3H); ^{13}C NMR (major isomer) δ 166.3, 157.8, 150.0, 141.5, 129.6, 126.8, 119.9, 116.3, 115.4, 56.6, 52.2, 15.6; ^{13}C NMR (minor isomer) δ 166.1, 158.2, 150.2, 143.6, 129.0, 125.6, 123.9, 115.9, 115.0, 57.2, 51.8, 16.3; IR (ATR) 2951, 1718, 1527, 1355, 1266, 1200, 1053; HRMS (ESI) calculated for $C_{12}H_{14}NO_5$ (M+H$^+$) 252.0866; found, 252.0878.
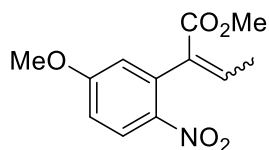
Methyl 2-(5-methoxy-2-nitrophenyl)-2-butenoate (30). Treatment of 1-bromo-5-methoxy-2-nitrobenzene (270 mg, 1.17 mmol) in PhMe (6 mL) with $Pd(PPh_3)_4$ (140 mg, 0.12 mmol) and methyl 2-(tributyltin)-2-butenoate (500 mg, 1.29 mmol), as

described for **29** (reflux, 16 h), gave after chromatography (hexane/EtOAc 9:1 then 7:3) **30**

(117 mg, 0.47 mmol, 40%) as an orange oil as a mixture of stereoisomers (major/minor =

15.9:1 by ^{1}H NMR). Analytical data from the 15.9:1 mixture of stereoisomers: ^{1}H NMR (major

isomer) δ 8.22 (d, J = 9.1 Hz, 1H), 7.17 (q, J = 7.2 Hz, 1H), 6.97 (dd, J = 9.2, 2.8 Hz, 1H), 6.70

(d, J = 2.8 Hz, 1H), 3.90 (s, 3H), 3.69 (s, 3H), 1.72 (d, J = 7.2 Hz, 3H); ^{1}H NMR (minor isomer,

partial data) δ 8.14 (d, J = 9.1 Hz, 1H), 6.92 (dd, J = 9.1, 2.8 Hz, 1H), 6.78 (d, J = 2.8 Hz, 1H),

6.35 (q, J = 7.3 Hz, 1H), 3.65 (s, 3H), 2.30-2.27 (m, 3H); ^{13}C NMR (major isomer) δ 166.0,

163.3, 141.5, 139.0, 133.8, 132.9, 127.6, 117.8, 113.4, 56.1, 52.2, 15.5; ^{13}C NMR (minor

isomer, partial data) δ 165.5, 163.6, 142.1, 138.2, 135.3, 132.8, 127.3, 117.9, 113.2, 51.6, 16.1;

IR (ATR) 2950, 1713, 1576, 1509, 1336, 1233, 1041 cm^{-1}; HRMS (ESI) calculated for

$C_{12}H_{14}NO_5$ (M+H$^+$) 252.0866; found, 252.0879.
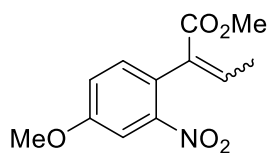
Methyl 2-(4-methoxy-2-nitrophenyl)-2-butenoate (31). Treatment

of 1-bromo-4-methoxy-2-nitrobenzene (126 mg, 0.55 mmol) in PhMe (5 mL) with Pd(PPh$_3$)$_4$

(64 mg, 0.06 mmol), and methyl 2-(tributyltin)-2-butenoate (234 mg, 0.60 mmol), as

described for **29** (reflux, 16 h), gave after chromatography (hexane/EtOAc 9:1 then 7:3) **31**

(59 mg, 0.24 mmol, 43%) as an orange oil, mixture of stereoisomers (major/minor = 11.7:1

by ^{1}H NMR). Analytical data from the 11.7:1 mixture of stereoisomers: ^{1}H NMR (major

isomer) δ 7.66 (s, 1H), 7.21-7.12 (m, 3H), 3.91 (s, 3H), 3.69 (s, 3H), 1.71 (d, J = 7.1 Hz, 3H); ^{1}H

NMR (minor isomer, partial data) δ 7.58 (s, 1H), 6.38-6.29 (m, 1H), 3.89 (s, 3H), 3.65 (s, 3H),

2.27 (d, J = 7.8 Hz, 3H); ^{13}C NMR (major isomer) δ 166.4, 159.7, 149.1, 139.8, 133.5, 132.0,

123.0, 120.0, 109.5, 56.1, 52.3, 15.7; ^{13}C NMR (minor isomer) δ 165.9, 159.5, 148.3, 142.4,

135.6, 131.7, 121.5, 120.2, 109.4, 56.2, 51.7, 16.3; IR (ATR) 2951, 1720, 1530, 1351, 1235, 1032 cm^{-1}; HRMS (ESI) calculated for C$_{12}$H$_{14}$NO$_5$ (M+H$^+$) 252.0866; found, 252.0878.
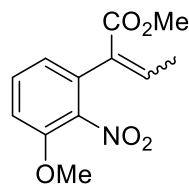
Methyl 2-(3-methoxy-2-nitrophenyl)-2-butenoate (32). Treatment of 1-bromo-3-methoxy-2-nitrobenzene (148 mg, 0.64 mmol) in PhMe (5 mL) with Pd(PPh$_3$)$_4$ (74 mg, 0.06 mmol), and methyl 2-(tributyltin)-2-butenoate (500 mg, 1.29 mmol), as described for **29** (reflux, 48 h), gave after chromatography (hexane/EtOAc 7:3 then 1:1) **32** (76 mg, 0.30 mmol, 47%) as an orange oil, mixture of stereoisomers (major:minor = 6.0/1 by ^{1}H NMR). Analytical data from the 6.0:1 mixture of stereoisomers: ^{1}H NMR (major isomer) δ 7.45 (t, J = 8.1 Hz, 1H), 7.26 (q, J = 7.2 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.79 (d, J = 7.7 Hz, 1H), 3.93 (s, 3H), 3.71 (s, 3H), 1.69 (d, J = 7.2 Hz); ^{1}H NMR (minor isomer) δ 7.40 (t, J = 8.1 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 6.38 (q, J = 7.3 Hz, 1H), 3.91 (s, 3H), 3.70 (s, 3H), 2.19 (d, J = 7.3 Hz, 3H); ^{13}C NMR (major isomer) δ 165.9, 151.2, 144.1, 133.8, 131.3, 130.0, 129.6, 122.7, 112.3, 56.6, 52.4, 15.8; ^{13}C NMR (minor isomer, partial data) δ 151.1, 145.1, 131.1, 129.1, 122.8, 112.0, 56.6, 51.9, 16.4; IR (ATR) 2951, 1718, 1578, 1530, 1434, 1369, 1263, 1224, 1038 cm^{-1}; HRMS (ESI) calculated for C$_{12}$H$_{14}$NO$_5$ (M+H$^+$) 252.0866; found, 252.0878.
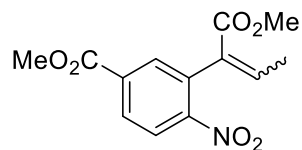
Methyl 2-(5-carbomethoxy-2-nitrophenyl)-2-butenoate (33). Under a nitrogen atmosphere, methyl 2-(tributyltin)-2-butenoate (500 mg, 1.29 mmol) in PhMe (4 mL) was added via syringe to a solution of 3-bromo-4-nitrobenzoic acid methyl

ester (303 mg, 1.17 mmol), PdCl$_2$(PPh$_3$)$_2$ (16 mg, 0.02 mmol), PPh$_3$ (12 mg, 0.05 mmol) in PhMe (8 mL). The solution was heated to reflux for 24 h, then cooled to ambient temperature, quenched with H$_2$O, and extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (3 x 10 mL), dried (MgSO$_4$), and the solvent was removed under reduced pressure. The resulting residue was purified by chromatography (hexane/EtOAc 9:1 then 7:3 gradient) to afford **33** (180 mg, 0.65 mmol, 55%) as a pale orange oil, mixture of stereoisomers (major/minor = 5.5:1 by ^{1}H NMR). Analytical data from the 5.5:1 mixture of stereoisomers: ^{1}H NMR (major isomer) δ 8.17 (s, 2H), 7.94 (s, 1H), 7.28 (q, J = 7.3 Hz, 1H), 3.97 (s, 3H), 3.70 (s, 3H), 1.74 (d, J = 7.3 Hz, 3H); ^{1}H NMR (minor isomer, partial data) δ 8.01 (s, 1H), 6.48 (q, J = 7.6 Hz, 1H), 3.66 (s, 3H), 2.32 (d, J = 7.3 Hz, 3H); ^{13}C NMR (major isomer) δ 165.7, 165.2, 151.2, 144.4, 141.1, 134.3, 134.1, 131.3, 130.2, 125.1, 53.1, 52.4, 15.8; ^{13}C NMR (minor isomer, partial data) δ 141.9, 134.5, 133.9, 131.2, 129.9, 124.7, 52.2, 51.8, 16.5; IR (ATR) 2954, 1726, 1529, 1437, 1347, 1283, 1250, 1116 cm^{-1}; HRMS (ESI) calculated for C$_{13}$H$_{14}$NO$_6$ (M+H$^+$) 280.0972; found, 280.0828.
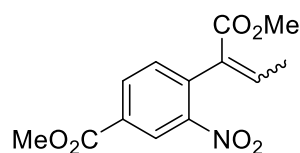
Methyl 2-(4-carbomethoxy-2-nitrophenyl)-2-butenoate (34). Treatment of 4-bromo-3-nitrobenzoic acid methyl ester (97 mg, 0.38 mmol) in PhMe (5 mL) with Pd(PPh$_3$)$_4$ (43 mg, 0.04 mmol), and methyl 2-(tributyltin)-2-butenoate (160 mg, 0.41 mmol) as described for **29** (reflux, 24 h) gave after chromatography (hexane/EtOAc 7:3 to 1:1 gradient) **34** (65 mg, 0.23 mmol, 62%) as a yellow oil, mixture of stereoisomers (major/minor = 10.9:1 by ^{1}H NMR). Analytical data from the 10.9:1 mixture of stereoisomers: ^{1}H NMR (DMSO-d_6) (major isomer) δ 8.58 (s, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.61

(d, J = 7.9 Hz, 1H), 7.21 (q, J = 7.2 Hz, 1H), 3.94 (s, 3H), 3.62 (s, 3H), 1.71 (d, J = 7.2 Hz, 3H); [1]H

NMR (DMSO-d_6) (minor isomer) δ 8.49 (s, 1H), 8.27 (d, J = 7.4 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H),

6.66 (q, J = 7.4 Hz, 1H), 3.56 (s, 3H), 2.24 (d, J = 7.3 Hz, 3H); ^{13}C NMR (DMSO-d_6) (major

isomer) δ 164.8, 164.3, 148.2, 141.4, 134.3, 133.8, 133.7, 130.7, 130.5, 125.1, 52.9, 52.1, 15.5;

^{13}C NMR (DMSO-d_6) (minor isomer, partial data) δ 149.6, 132.2, 123.9; IR (ATR) 2954, 1726,

1534, 1436, 1350, 1280, 1198, 1114 cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{14}NO_6$ (M+H$^+$)

280.0972; found, 280.0829.
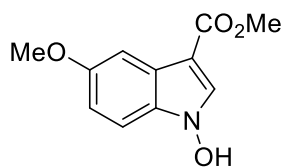
Methyl 1-hydroxy-5-methoxyindole-3-carboxylate (35). Treatment

of **30** (89 mg, 0.36 mmol) in PhMe (5 mL) with sodium *tert*-pentoxide (40% solution in PhMe,

250 μL, 0.83 mmol), as described for **19** (ambient temperature, 3 h), gave after

chromatography (hexane/EtOAc 7:3) **35** (28 mg, 0.13 mmol, 36%) as an orange oil. ^{1}H NMR

(DMSO-d_6) δ 10.90 (s, br, 1H), 6.95 (s, 1H), 6.34 (d, J = 2.3 Hz, 1H), 6.26 (d, J = 8.9 Hz, 1H),

5.78 (dd, J = 8.9, 2.4 Hz, 1H), 2.65 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 164.6, 155.6,

130.4, 128.8, 123.3, 113.2, 110.6, 102.0, 100.1, 55.5, 50.9; IR (ATR) 3213, 2951, 1657,

1435,1367, 1264, 1209, 1088, 1012 cm^{-1}; HRMS (ESI) calculated for $C_{11}H_{12}NO_4$ (M+H$^+$)

222.0761; found, 222.0771.
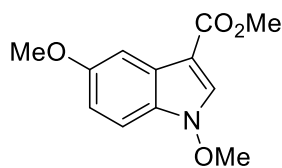
Methyl 1,5-dimethoxyindole-3-carboxylate (36). Treatment of **30**

(28 mg, 0.11 mmol) in PhMe (5 mL) with sodium *tert*-pentoxide (40% solution in PhMe, 28

μL, 0.25 mmol) followed by dimethyl sulfate (32 μL, 0.34 mmol), as described for **12**

(ambient temperature, 3 h) gave after chromatography (hexane/EtOAc 7:3) **36** (16 mg, 0.07 mmol, 60%) as an orange oil. ^{1}H NMR δ 7.89 (s, 1H), 7.65 (d, *J* = 2.4 Hz, 1H), 7.35 (d, *J* = 8.9 Hz, 1H), 6.96 (dd, *J* = 8.9, 2.4 Hz, 1H), 4.13 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H); ^{13}C NMR δ 165.3, 156.5, 128.3, 127.2, 123.9, 114.4, 109.7, 103.0, 102.8, 66.9, 56.0, 51.2; IR (ATR) 2942, 1699, 1518, 1456, 1369, 1262, 1201, 1086, 1016; HRMS (ESI) calculated for $C_{12}H_{14}NO_4$ (M+H$^+$) 236.0917; found, 236.0929.
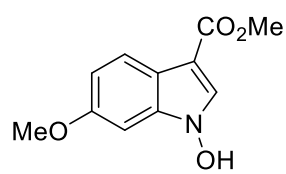
Methyl 1-hydroxy-6-methoxyindole-3-carboxylate (37). Treatment of **31** (44 mg, 0.18 mmol) in PhMe (3 mL) with sodium *tert*-pentoxide (40% solution in PhMe, 121 μL, 0.41 mmol), as described for **19** (ambient temperature, 3 h), gave after chromatography (hexane/EtOAc 1:1) **37** (16 mg, 0.07 mmol, 42%) as an orange solid. mp = 137-140 °C; ^{1}H NMR δ 9.13 (s, br, 1H), 7.81 (d, *J* = 8.7 Hz, 1H), 7.59 (s, 1H), 6.94-6.76 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (CDCl$_3$, DMSO-*d$_6$*) δ 163.7, 155.6, 133.3, 128.0, 120.6, 115.5, 111.1, 100.2, 90.5, 54.2, 49.6; IR (ATR) 3118, 1651, 1503, 1435, 1233, 1082 cm^{-1}; HRMS (ESI) calculated for $C_{11}H_{12}NO_4$ (M+H$^+$) 222.0761; found, 222.0772.
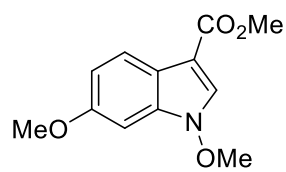
Methyl 1,6-dimethoxyindole-3-carboxylate (38). Treatment of **31** (56 mg, 0.22 mmol) in PhMe (3 mL) with sodium *tert*-pentoxide (40% solution in PhMe, 154 μL, 0.51 mmol) followed by dimethyl sulfate (63 μL, 0.66 mmol), as described for **12** (ambient temperature, 3 h), gave after chromatography (hexane/EtOAc 7:3) **38** as an inseparable mixture with an unknown impurity. ***Alternative synthesis of 38.*** To a solution

of **37** (16 mg, 0.07 mmol) in acetone (3 mL) was added K_2CO_3 (19 mg, 0.14 mmol). The resulting suspension was stirred at ambient temperature for 10 min., then MeI (6 μL, 0.10 mmol) was added and solution stirred for an additional 4 h at ambient temperature. Water was added to the reaction mixture followed by extraction with EtOAc (3 x 10mL). The combined organic phases were dried ($MgSO_4$) and solvent was removed under reduced pressure. The resulting residue was purified by chromatography (hexane/EtOAc 7:3) to afford pure **38** (16 mg, 0.07 mmol, 94%) as a pale yellow oil that solidified upon standing. mp = 69-70 °C; ^{1}H NMR δ 8.02 (dd, *J* = 8.7, 0.6 Hz, 1H), 7.86 (s, 1H), 6.94-6.89 (m, 2H), 4.13 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H); ^{13}C NMR δ 165.2, 157.6, 133.0, 127.4, 122.8, 117.0, 112.7, 103.7, 91.7, 66.6, 55.8, 51.3; IR (ATR) 2945, 1699, 1521, 1440, 1230, 1078, 1016; HRMS (ESI) calculated for $C_{12}H_{14}NO_4$ ($M+H^+$) 236.0917; found, 236.0928.
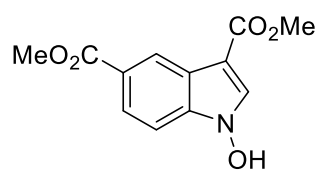
Methyl 5-carbomethoxy-1-hydroxyindole-3-carboxylate (39). Treatment of **33** (115 mg, 0.41 mmol) in PhMe (5 mL) with sodium *tert*-pentoxide (40% solution in PhMe, 285 μL, 0.94 mmol), as described for **19** (ambient temperature, 3 h), gave after chromatography (hexane/EtOAc 1:1) **39** (30 mg, 0.12 mmol, 29%) as a pale orange solid. mp = 148-150 °C; ^{1}H NMR δ 11.34 (s br, 1H), 8.86 (s, 1H), 8.01-7.95 (m, 2H), 7.54 (d, *J* = 8.7 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (CDCl$_3$, DMSO-*d$_6$*) δ 167.4, 164.4, 135.6, 131.4, 123.7, 123.6, 123.3, 121.5, 108.6, 102.8, 51.5, 50.7; IR (ATR) 3390, 2953, 1704, 1281, 992, 763 cm^{-1}; HRMS (ESI) calculated for $C_{12}H_{12}NO_5$ ($M+H^+$) 250.0710; found, 250.1198.
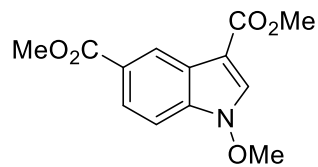
Methyl 5-carbomethoxy-1-methoxyindole-3-carboxylate (40). Treatment of **33** (65 mg, 0.23 mmol) in PhMe (5 mL) with sodium *tert*-pentoxide (40% solution in PhMe, 160 μL, 0.53 mmol) followed by dimethyl sulfate (66 μL, 0.69 mmol) as described for **12** (ambient temperature, 3 h) gave after chromatography (hexane/EtOAc 7:3) **40** as an inseparable mixture with an unknown impurity. *Alternative synthesis of 40.* To a solution of **39** (11 mg, 0.04 mmol) in acetone (3 mL) was added K_2CO_3 (12 mg, 0.09 mmol). The resulting suspension was stirred at ambient temperature for 10 min., then MeI (4 μL, 0.07 mmol) was added and the solution stirred for an additional 4 h at ambient temperature. The resultant mixture was quenched with H_2O and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$) and solvent was removed under reduced pressure. The residue was purified by chromatography (hexane/EtOAc 7:3) to afford pure **40** (11 mg, 0.04 mmol, 93%) as a pale yellow oil that solidified upon standing. mp = 128-130 °C; ^{1}H NMR δ 8.89 (dd, *J* = 1.5, 0.6 Hz, 1H), 8.05-8.02 (m, 2H), 7.50 (dd, *J* = 8.7, 0.6 Hz, 1H), 4.17 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H); ^{13}C NMR δ 167.8, 164.7, 134.4, 130.0, 125.0, 124.8, 124.7, 122.2, 108.6, 105.1, 67.1, 52.3, 51.6; IR (ATR) 2949, 1708, 1434, 1367, 1277, 1202, 1081, 1023 cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{14}NO_5$ (M+H^{+}) 264.0866; found, 264.0880.
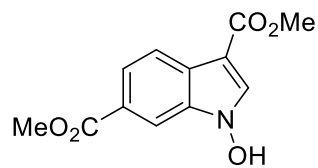
Methyl 6-carbomethoxy-1-hydroxyindole-3-carboxylate (41). Treatment of **34** (110 mg, 0.40 mmol) in PhMe (5 mL) with sodium *tert*-pentoxide (40% solution in PhMe, 277 μL, 0.92 mmol) as described for **19** (ambient temperature, 3 h) gave

after chromatography (hexane/EtOAc 1:1) **41** (24 mg, 0.10 mmol, 25%) as a pale orange solid. mp = 156-157 °C; ^{1}H NMR (DMSO-d_6) δ 12.31 (s, br, 1H), 8.40 (s, 1H), 8.11-8.08 (m, 2H), 7.82 (d, *J* = 8.3 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.5, 163.8, 133.5, 132.9, 125.6, 123.9, 122.2, 120.6, 111.2, 101.3, 52.1, 51.0; IR (ATR) 3394, 1697, 1256, 1211, 1023, 993, 762 cm^{-1}; HRMS (ESI) calculated for $C_{12}H_{12}NO_5$ (M+H$^+$) 250.0710; found, 250.1198.
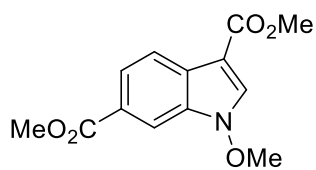
Methyl 6-carbomethoxy-1-methoxyindole-3-carboxylate (42). Treatment of **34** (41 mg, 0.15 mmol) in PhMe (3 mL) with sodium *tert*-pentoxide (40% solution in PhMe, 101 μL, 0.35 mmol) followed by dimethyl sulfate (42 μL, 0.45 mmol) as described for **12** (ambient temperature, 3 h) gave after chromatography (hexane/EtOAc 7:3) a 14.3:1 inseparable mixture of **42/34** (11.7:1 by ^{1}H NMR) (17 mg, 0.07 mmol, 44%, calculated from spectrum) as an orange oil. ^{1}H NMR δ 8.23-8.19 (m, 2H), 8.09 (s, 1H), 7.96 (dd, *J* = 8.4, 1.5 Hz, 1H), 4.20 (s, 3H), 3.97 (s, 3H), 3.93 (s, 3H); ^{13}C NMR δ 167.5, 164.7, 131.7, 131.1, 126.3, 125.6, 123.5, 121.7, 11.2, 104.1, 67.4, 52.4, 51.5; IR (ATR) 2950, 1707, 1437, 1381, 1254, 1206, 1070, 776 cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{14}NO_5$ (M+H$^+$) 264.0866; found, 264.0880.
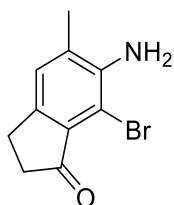
6-Amino-7-bromo-2,3-dihydro-5-methylinden-1-one (75). 2,3,5,6-Tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dienone **74** (2.13 g, 4.55 mmol) was added to a stirred solution of **68** (733 mg, 4.55 mmol) in AcOH (5 mL). The resulting solution was

stirred for 4 hours at ambient temperature and then poured into a 10% NaHCO₃ (aq) solution (15 mL). The suspension was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organics were washed with H_2O (2 x 30 mL), dried (MgSO₄), filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes:EtOAc 8:2) to afford **75** (640 mg, 2.66 mmol, 59%) as a brown solid. mp=177-179 °C; ^{1}H NMR (600 MHz, CDCl₃) δ 2.30 (s, 3H), 2.67-2.72 (m, 2H), 2.93-2.97 (m, 2H), 4.26 (br s, 2H), 7.11 (s, 1H); ^{13}C NMR (151 MHz, CDCl₃) δ 19.2, 23.8, 37.4, 103.6, 126.7, 131.2, 132.5, 142.4, 147.4, 204.2; IR (ATR) 871, 1318, 1469, 1621, 1688, 3352, 3378 cm^{-1}; HRMS (ESI) calculated for $C_{10}H_{11}BrNO$ (M+H^{+}) 240.0024, found 240.0018.
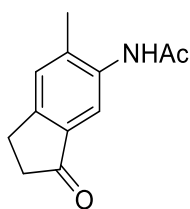
N-(2,3-Dihydro-5-methyl-1-oxo-1H-inden-6-yl)acetamide (69). To a stirring solution of **68** (4.62 g, 28.7 mmol) in 100 mL of CH_2Cl_2 was added NEt₃ (3.19 g, 31.5 mmol) at ambient temperature and the solution was allowed to stir for 15 min. Acetyl chloride (2.70 g, 34.4 mmol) was then added dropwise and the reaction mixture was stirred for 22 h at ambient temperature. The crude mixture was washed with water (2 x 100 mL) and brine (1 x 100 mL), dried (MgSO₄), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc) to give **69** (4.86 g, 23.9 mmol, 84%) as a tan solid. mp = 221-223 °C; ^{1}H NMR (600 MHz, CDCl₃) δ 2.21 (s, 3H), 2.34 (s, 3H), 2.66-2.68 (m, 2H), 3.05-3.07 (m, 2H), 7.14 (br s, 1H), 7.31 (s, 1H), 7.95 (s, 1H); ^{13}C NMR (151 MHz, CDCl₃) δ 18.9, 24.0, 25.3, 36.6, 119.2, 128.4, 135.2, 136.0, 138.8, 152.4, 168.5, 206.0; IR (ATR) 864, 1527, 1656, 1691, 3310 cm^{-1}; HRMS (ESI) calculated for $C_{12}H_{14}NO_2$ (M+H^{+}) 204.1019, found 204.1019.
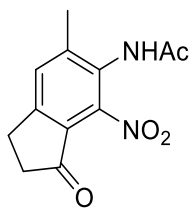
N-(2,3-Dihydro-5-methyl-7-nitro-1-oxo-1H-inden-6-yl)acetamide (70).
Fuming nitric acid (10 mL) was stirred at -20 °C for 5 min, then 25 drops of concentrated H$_2$SO$_4$ was added and the resulting mixture was stirred at -20 °C for 20 min. This mixture was added dropwise to **69** (1.0 g, 4.92 mmol), cooled to -20 °C, and stirred at the same temperature for 1.5 h before quenching with 20 mL of H$_2$O and then 20 mL of a saturated NH$_4$Cl solution (aq). The aqueous mixture was extracted with EtOAc (3 x 50 mL) and washed with H$_2$O (3 x 50 mL). The organic phase was dried (MgSO$_4$), filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (EtOAc) to afford **70** (860 mg, 3.46 mmol, 70%) as a dark yellow solid. mp = 225-227 °C; ^{1}H NMR δ 2.18 (s, 3H), 2.39 (s, 3H), 2.77-2.79 (m, 2H), 3.14-3.16 (m, 2H), 7.31 (br s, 1H), 7.53 (s, 1H); ^{13}C NMR δ 19.5, 23.2, 25.3, 36.8, 126.1, 126.7, 130.7, 142.4, 146.3, 154.6, 168.9, 200.4; IR (ATR) 782, 1536, 1673, 1718, 3347 cm^{-1}; HRMS (ESI) calculated for C$_{12}$H$_{13}$N$_2$O$_4$ (M+H$^+$) 249.0870, found 249.0871.
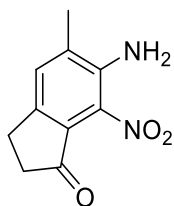
6-Amino-2,3-dihydro-5-methyl-7-nitroinden-1-one (71). A solution of **70** (140 mg, 0.56 mmol) in EtOH (15 mL) was refluxed with 5 M HCl (aqueous, 10 mL) for 18 h. The organic phase was removed in vacuo and the resulting aqueous solution was made alkaline (pH 8-9) with a NaOH solution (aq). This solution was then extracted with CH$_2$Cl$_2$ (3 x 20 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo. The resulting residue was

purified by flash chromatography (hexanes:EtOAc 1:1) to afford **71** (98 mg, 0.48 mmol, 84%) as a bright yellow solid. mp = 229-231 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 2.32 (s, 3H), 2.72-2.74 (m, 2H), 2.97-2.99 (m, 2H), 5.10 (br s, 2H), 7.31 (s, 1H); ^{13}C NMR (151 MHz, CDCl$_3$) δ 18.6, 24.6, 37.1, 129.0, 131.2, 133.6, 139.7, 145.7, 200.6 (1 resonance not found); IR (ATR) 887, 1313, 1518, 1634, 1689, 3362, 3460 cm^{-1}; HRMS (ESI) calculated for C$_{10}$H$_{11}$N$_2$O$_3$ (M+H$^+$) 207.0764, found 207.0764.
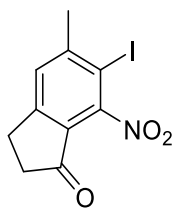
2,3-Dihydro-6-iodo-5-methyl-7-nitroinden-1-one (72). To a stirred solution of **71** (21 mg, 0.10 mmol) in concentrated HCl (1 mL) and ice at 0 °C, a solution of sodium nitrite (8 mg, 0.11 mmol) in H$_2$O (1 mL) was added dropwise. The mixture was stirred at 0 °C for 30 min before adding it dropwise to a stirred solution of KI (50 mg, 0.30 mmol) in H$_2$O (1 mL) at ambient temperature. The mixture remained stirring for 16 hours at ambient temperature and was then extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic extracts were washed with 10% NaOH (aq.) (1 x 20 mL), 5% NaHCO$_3$ (aq.) (1 x 20 mL), and H$_2$O (1 x 20 mL) before being dried (MgSO$_4$), filtered, and concentrated in vacuo. The resulting dark yellow residue was purified by flash chromatography (hexanes: EtOAc, 9:1 then 8:2) to afford **72** (20 mg, 0.063 mmol, 63%) as an off-white solid. mp = 173-175 °C; ^{1}H NMR δ 2.60 (s, 3H), 2.73-2.75 (m, 2H), 2.98-3.00 (m, 2H), 7.28 (s, 1H); ^{13}C NMR δ 24.5, 31.1, 36.9, 107.4, 125.8, 131.8, 136.3, 150.5, 156.8, 201.9; IR (ATR) 871, 1149, 1432, 1694, 2923 cm^{-1}; HRMS (ESI) calculated for C$_{10}$H$_9$INO$_3$ (M+H$^+$) 317.9627 (peak not found experimentally).
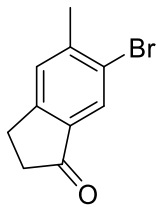
 6-Bromo-2,3-dihydro-5-methylinden-1-one (76).

Method 1 (Table 5, entry 1): A solution of **68** (100 mg, 0.62 mmol) in HBr (48%, 500 μL), H_2O (1 mL), and 1,4-dioxane (500 μL) was heated to reflux for 20 min. The resulting solution was cooled to ambient temperature, then placed in an ice bath. A solution of $NaNO_2$ (40 mg, 0.62 mmol) in H_2O (1 mL) was added dropwise, and the resulting orange solution stirred at 0 °C for 20 min. This solution was added dropwise to a solution of CuBr (100 mg, 0.68 mmol) in HBr (48%, 500 μL) and H_2O (1 mL) at 0 °C, during which time the evolution of gas was observed. The dark red-brown solution was warmed to ambient temperature and stirred for 16 h. The solution was quenched by slow addition of saturated $NaHCO_3$ (aq) and extracted with EtOAc (3 x 10 mL). The combined organics were washed with H_2O (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes:EtOAc 8:2) to afford **76** (104 mg, 0.46 mmol, 75%) as an orange solid.

Method 2 (Table 5, entry 3): **67** (2.0 g, 13.7 mmol) was added to stirring conc. H_2SO_4 (15 mL) at ambient temperature. *N*-bromosuccinimide (NBS, 3.05 g, 17.1 mmol) was added in portions, and the resulting orange solution stirred at ambient temperature for 3 h. The reaction was quenched by addition of ice chips and the solution was extracted with EtOAc (3 x 15 mL). The combined organics were washed with saturated $NaHCO_3$ (aq, 15 mL) and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes: EtOAc, 9:1 to 7:3 gradient) to afford **76** (973 mg, 4.33 mmol, 32%) as an orange solid, and **77** (1.26 g, 5.61 mmol, 41%) as a pale orange solid.

Analytical data for **76**: mp = 114-116 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.92 (s, 1H), 7.36 (s, 1H), 3.07-3.04 (m, 2H), 2.71-2.68 (m, 2H), 2.48 (s, 3H); ^{13}C NMR (151 MHz, CDCl$_3$) δ 205.1, 154.0, 144.9, 136.7, 128.6, 127.4, 124.4, 36.5, 25.3, 23.9; IR (ATR) 1702, 1597, 1432, 1379, 1171, 884 cm^{-1}; HRMS (ESI) calculated for C$_{10}$H$_{10}$BrO (M+H$^+$) 224.9915, found 224.9918.
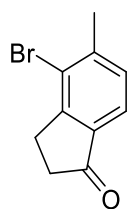
 4-Bromo-2,3-dihydro-5-methylinden-1-one (77).

Method 1 (Table 5, entry 2): **67** (500 mg, 3.42 mmol) in CH$_2$Cl$_2$ (4 mL) was added dropwise over 30 min to a suspension of AlCl$_3$ (910 mg, 6.84 mmol) in CH$_2$Cl$_2$ (4 mL). To this solution was added Br$_2$ (190 μL, 3.76 mmol) in CH$_2$Cl$_2$ (4 mL) dropwise. The resulting dark red-orange solution was heated to 50 C and stirred for 22 h. The solution was cooled to ambient temperature and quenched by slow addition of H$_2$O (5 mL). The organics were washed with H$_2$O (10 mL) and brine (10 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes:EtOAc 9:1) to afford **77** (92 mg, 0.41 mmol, 12%) as a pale orange solid.

Method 2 (Table 5, entry 3): **67** (2.0 g, 13.7 mmol) was added to stirring conc. H$_2$SO$_4$ (15 mL) at ambient temperature. N-bromosuccinimide (NBS, 3.05 g, 17.1 mmol) was added in portions, and the resulting orange solution stirred at ambient temperature for 3 h. The reaction was quenched by addition of ice chips and the solution was extracted with EtOAc (3 x 15 mL). The combined organics were washed with saturated NaHCO$_3$ (aq, 15 mL) and brine (15 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes: EtOAc, 9:1 to 7:3 gradient) to afford **76** (973 mg, 4.33 mmol, 32%) as an orange solid, and **77** (1.26 g, 5.61 mmol, 41%) as a pale orange solid.

Analytical data for **77**: mp = 65-68 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.61 (d, J = 7.7 Hz, 1H), 7.27 (d, J = 9.7 Hz, 1H), 3.09-3.05 (m, 2H), 2.75-2.72 (m, 2H), 2.51 (s, 3H); ^{13}C NMR (151 MHz, CDCl$_3$) δ 205.8, 155.4, 145.1, 136.8, 130.2, 124.1, 122.0, 36.4, 27.5, 23.1; IR (ATR) 1702, 1595, 1258, 1116, 1038, 808 cm^{-1}; HRMS (ESI) calculated for C$_{10}$H$_{10}$BrO (M+H$^+$) 224.9915, found 224.9917.
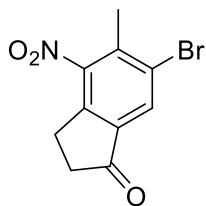
6-Bromo-2,3-dihydro-5-methyl-4-nitroinden-1-one (78). 76 (1.52 g, 6.77 mmol) was reacted with fuming HNO$_3$ (15 mL) and conc. H$_2$SO$_4$ (40 drops) as described for **70** (-20 °C, 90 min). After chromatography (hexanes:EtOAc 7:3 then EtOAc), **78** (317 mg, 1.18 mmol, 17%, off-white solid) and **79** (1.15 g, 4.30 mmol, 64%, orange solid) were obtained. Analytical data for **78**: mp = 145 °C (sublimation); ^{1}H NMR (600 MHz, chloroform-d) δ 8.11 (s, 1H), 3.20-3.16 (m, 2H), 2.80-2.76 (m, 2H), 2.56 (s, 3H); ^{13}C NMR (151 MHz, chloroform-d) δ 202.6, 147.0, 145.8, 137.8, 137.3, 130.2, 126.2, 35.9, 23.9, 19.6; IR (ATR) 3069, 1712, 1527, 1356, 1241, 1199, 1161 cm^{-1}; HRMS (ESI) calculated for C$_{10}$H$_9$BrNO$_3$ (M+H$^+$) 271.97, found 271.9748.
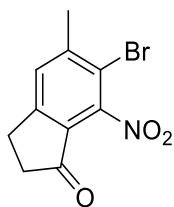
**6-Bromo-2,3-dihydro-5-methyl-7-nitroinden-1-one (79). 76** (1.52 g, 6.77 mmol) was reacted with fuming HNO$_3$ (15 mL) and conc. H$_2$SO$_4$ (40 drops) as described for **70** (-20 °C, 90 min). After chromatography (hexanes:EtOAc 7:3 then EtOAc), **78** (317 mg, 1.18 mmol, 17%, off-white solid) and **79** (1.15 g, 4.30 mmol, 64%, orange solid) were

obtained. Analytical data for **79**: mp = 137-138 °C; ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.51 (s, 1H), 3.14-3.11 (m, 2H), 2.80-2.78 (m, 2H), 2.57 (s, 3H); ^{13}C NMR (151 MHz, chloroform-*d*) δ 199.7, 154.7, 147.0, 145.4, 129.7, 126.3, 114.1, 36.3, 25.0, 23.9; IR (ATR) 2928, 1704, 1599, 1538, 1431, 1375, 1309, 1165, 887, 801 cm^{-1}; HRMS (ESI) calculated for $C_{10}H_9BrNO_3$ (M+H$^+$) 271.97, found 271.9745.
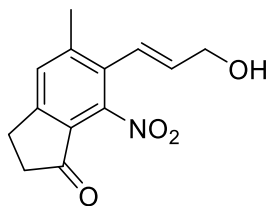
6-(3-hydroxy-1-propenyl)-2,3-dihydro-5-methyl-7-nitroinden-1-one (64). To an oven-dried flask equipped with a cold water condenser were added **79** (688 mg, 2.56 mmol), PdCl$_2$(PPh$_3$)$_2$ (36 mg, 0.05 mmol), and PPh$_3$ (27 mg, 0.10 mmol), and the system was purged with N$_2$. 1,4-dioxane (anhydrous, 15 mL) was added via syringe, and the solution was stirred at ambient temperature. (E)-3-(tributylstannyl)-2-propen-1-ol (**65**, 1.15 g, 3.33 mmol) in 1,4-dioxane (anhydrous, 5 mL) was added via syringe and the solution was heated to 110 °C for 120 h. The resulting reaction mixture was cooled to ambient temperature and quenched with H$_2$O (20 mL). Solution was extracted with EtOAc (3 x 30 mL). The combined organics were washed with brine (3 x 30 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes:EtOAc 2:8) to afford **64** (345 mg, 1.40 mmol, 55%) as a pale yellow oil. ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.43 (s, 1H), 6.51 (d, *J* = 16.2 Hz, 1H), 6.06 (dt, *J* = 16.2, 4.6 Hz, 1H), 4.30 (dd, *J* = 4.6, 1.9 Hz, 2H), 3.15-3.11 (m, 2H), 2.76-2.72 (m, 2H), 2.42 (s, 3H), 2.18 (s, br, 1H); ^{13}C NMR (151 MHz, chloroform-*d*) δ 201.2, 154.8, 146.4, 144.0, 137.3, 129.3, 128.1, 125.1, 120.5, 62.7, 36.5, 25.2, 21.3; IR (ATR) 3409, 2924, 1710, 1614, 1536, 1381, 1314, 1124, 1022 cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{14}NO_4$ (M+H$^+$) 248.09, found 248.0928.
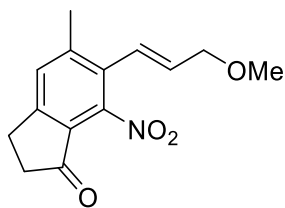
6-(3-methoxy-1-propenyl)-2,3-dihydro-5-methyl-7-nitroinden-1-one (81). To an oven-dried flask equipped with a cold water condenser were added **79** (601 mg, 2.23 mmol), PdCl$_2$(PPh$_3$)$_2$ (32 mg, 0.05 mmol), and PPh$_3$ (24 mg, 0.09 mmol), and the system was purged with N$_2$. 1,4-dioxane (anhydrous, 15 mL) was added via syringe, and the solution was stirred at ambient temperature. (E)-tributyl(3-methoxy-1-propenyl)stannane (**80**, 1.05 g, 2.90 mmol) in 1,4-dioxane (anhydrous, 7 mL) was added via syringe and the solution was heated to 110 °C for 120 h. The resulting reaction mixture was cooled to ambient temperature and quenched with H$_2$O (20 mL). Solution was extracted with EtOAc (3 x 30 mL). The combined organics were washed with brine (3 x 30 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes:EtOAc 1:1) to afford **81** (467 mg, 1.79 mmol, 80%) as an orange solid. mp = 109-113 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.43 (s, 1H), 6.49 (d, *J* = 16.2 Hz, 1H), 5.99 (dt, *J* = 16.2, 5.0 Hz, 1H), 4.05 (dd, *J* = 5.0, 1.8 Hz, 2H), 3.39 (s, 3H), 3.16-3.10 (m, 2H), 2.78-2.73 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (151 MHz, chloroform-*d*) δ 200.9, 154.8, 146.2, 134.9, 131.9, 129.3, 128.2, 125.2, 122.0, 72.2, 58.3, 36.5, 25.2, 21.4; IR (ATR) 2929, 1716, 1615, 1539, 1441, 1382, 1315, 1186, 1120 cm^{-1}; HRMS (ESI) calculated for C$_{14}$H$_{16}$NO$_4$ (M+H$^+$) 262.1074, found 262.1084.
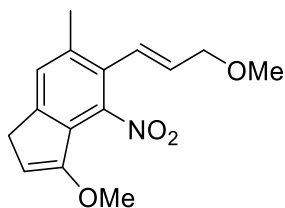
3-methoxy-5-(3-methoxy-1-propenyl)-6-methyl-4-nitroindene

(83). 81 (101 mg, 0.39 mmol) was dissolved in MeOH (3 mL), and *p*-toluenesulfonic acid (3 mg, 0.02 mmol) was added, followed by trimethyl orthoformate (84 μL, 0.77 mmol). The resulting solution was stirred at ambient temperature for 16 h before being diluted with EtOAc (5 mL) and quenched with a solution of NaOH (1M, 5 mL). This solution was extracted with EtOAc (3 x 10 mL), and the combined organics were dried (MgSO$_4$), filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes:EtOAc 7:3 to 1:1 gradient) to afford **83** (13 mg, 0.05 mmol, 12%) as a viscous yellow oil and unreacted **81** (11 mg, 0.04 mmol, 11%). Analytical data for **83**: ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.30 (s, 1H), 6.53 (d, *J* = 16.3 Hz, 1H), 5.94 (dt, *J* = 16.2, 5.4 Hz, 1H), 5.35 (t, *J* = 2.4 Hz, 1H), 4.07-4.05 (m, 2H), 3.79 (s, 3H), 3.38 (s, 3H), 3.30 (d, *J* = 2.3 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (151 MHz, chloroform-*d*) δ 156.2, 143.8, 135.0, 133.3, 128.0, 126.9, 126.8, 126.5, 124.2, 100.0, 72.6, 58.0, 57.3, 33.6, 20.6; IR (ATR) 2927, 1712, 1613, 1533, 1379, 1116 cm^{-1}; HRMS (ESI) calculated for C$_{13}$H$_{14}$NO$_4$ (M+H$^+$) 276.12, found 276.1232.
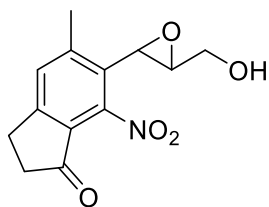
6-(1,2-epoxy-3-hydroxypropyl)-2,3-dihydro-5-methyl-7-

nitroinden-1-one (89). 64 (340 mg, 1.40 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL), and solution was cooled to 0 °C. 3-chloroperoxybenzoic acid (*m*-CPBA, 70-75%/wt, 1.38 g, 5.60 mmol) was added in portions. The resulting suspension was warmed to ambient

temperature and stirred for 16 h. The reaction mixture was quenched by slow addition of saturated Na_2SO_3 (aq, 10 mL) and diluted with CH_2Cl_2 (5 mL), then washed with saturated $NaHCO_3$ (aq, 10 mL) and brine (10 mL). The organics were dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (EtOAc) to afford **89** (268 mg, 1.02 mmol, 74%) as a colorless oil. ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.46 (s, 1H), 4.07 (d, *J* = 2.3 Hz, 1H), 3.99 (dd, *J* = 13.0, 2.6 Hz, 1H), 3.82 (dd, *J* = 13.0, 3.1 Hz, 1H), 3.15-3.12 (m, 3H), 2.75-2.72 (m, 2H), 2.55 (s, 3H), 2.36 (s, br, 1H); ^{13}C NMR (151 MHz, chloroform-*d*) δ; IR (ATR) 3419, 2927, 1713, 1618, 1541, 1372, 1309, 1121, 903 cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{14}NO_5$ (M+H^{+}) 264.0866, found 264.0876.
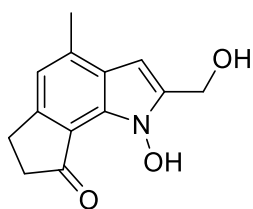
6,7-dihydro-2-(hydroxymethyl)-4-methylcyclopent[*g*]-(*N*-hydroxy)indol-8(1*H*)-one (90). Method from Table 6, entry 2: To a thick-walled pressure tube was added **89** (84 mg, 0.32 mmol) and Pd/C (10% Pd, 7 mg, 0.006 mmol). Absolute EtOH (3 mL) was added, and the resulting suspension was charged with 40 psi H_2. The reaction mixture was heated to 50 °C and stirred for 12 h. The solution was cooled to ambient temperature and filtered over Celite, rinsing with hot EtOH, and the filtrate was concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes:EtOAc 1:1) to afford **90** (27 mg, 0.12 mmol, 37%) as a yellow solid. mp = 164-166 °C; ^{1}H NMR (400 MHz, DMSO-*d6*/chloroform-*d*) δ 11.69 (s, br, 1H), 6.87 (s, 1H), 6.39 (s, 1H), 4.98 (t, *J* = 5.8 Hz, 1H), 4.73 (d, *J* = 5.6 Hz, 2H), 3.26-3.22 (m, 2H), 2.77-2.73 (m, 2H), 2.55 (s, 3H); ^{1}H NMR (400 MHz, chloroform-*d*) δ 12.17 (s, 1H), 6.88 (s, 1H), 6.39 (s, 1H), 4.86 (d, *J* = 6.6 Hz, 2H), 3.31-3.27 (m, 2H), 2.84-2.79 (m, 2H), 2.57 (s, 3H), 2.23 (t, *J* = 6.6 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-

d₆/chloroform-*d*) δ 206.8, 153.0, 140.4, 135.3, 125.6, 121.1, 118.4, 116.6, 95.2, 54.3, 35.5, 26.9, 18.7; IR (ATR) 3350, 2925, 1614, 1367, 1299, 1158, 1076, 1006 cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{14}NO_3$ (M+H$^+$) 232.0968, found 232.0978.
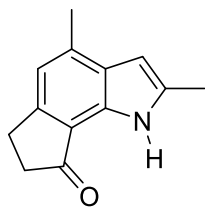
6,7-dihydro-2,4-dimethylcyclopent[*g*]indol-8(1*H*)-one (91). Method from Table 6, entry 3: To a thick-walled pressure tube was added **89** (58 mg, 0.22 mmol) and Pd/C (10% Pd, 12 mg, 0.011 mmol). Absolute EtOH (3 mL) was added, and the resulting suspension was charged with 40 psi H₂. The reaction mixture was heated to 50 °C and stirred for 16 h. The solution was cooled to ambient temperature and filtered over Celite, rinsing with hot EtOH, and the filtrate was concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes:EtOAc 1:1) to afford **91** as a pale-orange viscous oil. ¹H NMR (400 MHz, chloroform-*d*) δ 9.19 (s, br, 1H), 6.93 (s, 1H), 6.27 (s, 1H), 3.23-3.16 (m, 2H), 2.74-2.68 (m, 2H), 2.58 (s, 3H), 2.48 (s, 3H); ¹³C NMR (101 MHz, DMSO-*d₆*/chloroform-*d*) δ 206.7, 151.4, 138.7, 135.0, 130.3, 128.1, 119.2, 117.7, 99.0, 36.5, 26.6, 19.7, 13.6; IR (ATR) 3327, 2921, 1678, 1633, 1554, 1298 cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{14}NO$ (M+H$^+$) 200.1075, found 200.1070.
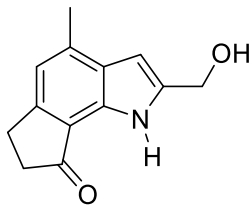
Dilemmaone B (53).

Method A (Table 6, entry 4): **90** (17 mg, 0.074 mmol) was reacted with Pd/C (10% Pd, 4 mg, 0.004 mmol) and EtOH (3mL) under 40 psi H_2 as described for **91** (50 °C, 2 h) to afford after purification (hexanes:EtOAc 2:8) **53** (4 mg, 0.02 mmol, 27%) as an off-white solid.

Method B (Table 6, entry 5): To a thick-walled pressure tube was added **89** (126 mg, 0.48 mmol) and PtO_2 (3 mg, 0.010 mmol). Absolute EtOH (3 mL) was added, and the resulting suspension was charged with 40 psi H_2. The reaction mixture was heated to 50 °C and stirred for 3 h. The solution was cooled to ambient temperature and filtered over Celite, rinsing with hot EtOH, and the filtrate was concentrated in vacuo. The resulting residue was purified by flash chromatography (hexanes:EtOAc 2:8) to afford **53** (49 mg, 0.23 mmol, 48%) as an off-white solid.

Analytical data for **53**: mp = 188-190 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.70, 6.97, 6.49, 4.87, 3.21, 2.73, 2.60, 2.04 (multiplicity not reported as solubility in chloroform-*d* is poor— full analysis was done in DMSO-*d6*); ^{1}H NMR (600 MHz, DMSO-*d6*) δ 11.30 (s, br, 1H), 6.94 (s, 1H), 6.43 (s, 1H), 5.07 (t, *J* = 6.1 Hz, 1H), 4.61 (d, *J* = 6.1 Hz, 2H), 3.15-3.11 (m, 2H), 2.65-2.60 (m, 2H), 2.53 (s, 3H); ^{13}C NMR (151 MHz, DMSO-*d6*) δ 204.7, 151.4, 140.7, 138.1, 129.4, 127.3, 119.3, 117.2, 98.1, 56.6, 35.9, 26.0, 19.2; IR (ATR) 3376, 2851, 1634., 1556, 1439, 1299, 1233, 1125, 1025 cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{14}NO_2$ (M+H^{+}) 216.1019, found 216.1028.
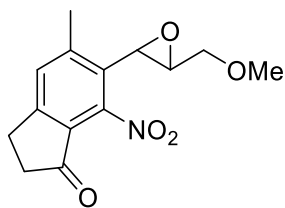
6-(1,2-epoxy-3-methoxypropyl)-2,3-dihydro-5-methyl-7-nitroinden-1-one (92). 81 (220 mg, 0.84 mmol) was reacted with *m*-CPBA (70-75%/wt, 830 mg, 3.36 mmol) in CH_2Cl_2 (5mL) as described for **89** to afford after purification (hexanes:EtOAc 2:8) **92** (119 mg, 0.43 mmol, 51%) as a colorless oil. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.46 (s, 1H), 3.95 (d, *J* = 1.8 Hz, 1H), 3.77(dd, *J* = 11.7, 2.8 Hz, 1H), 3.54 (dd, *J* = 11.7, 4.8 Hz, 1H), 3.42 (s, 3H), 3.18-3.10 (m, 3H), 2.77-2.70 (m, 2H), 2.56 (s, 3H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 216.0, 200.5, 186.8, 155.9, 147.2, 130.0, 126.0, 125.2, 71.2, 59.4, 57.7, 51.4, 36.5, 25.2, 20.2; IR (ATR) 2929, 1714, 1618, 1541, 1449, 1371, 1309, 1110, 907 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{16}NO_5$ (M+H$^+$) 278.1028, found 278.1025.
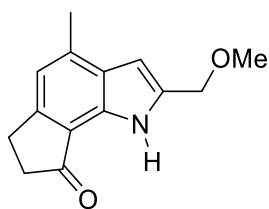
Dilemmaone A (52).

Method A (Scheme 19): **92** (88 mg, 0.32 mmol) was reacted with Pd/C (10% Pd, 7 mg, 0.006 mmol) and EtOH (3mL) under 40 psi H_2 as described for **90** (50 °C, 16 h) to afford after purification (hexanes:EtOAc 1:1) **52** (22 mg, 0.10 mmol, 30%) as an off-white solid.

Method B (Scheme 19): **92** (119 mg, 0.43 mmol) was reacted with PtO_2 (2 mg, 0.009 mmol) and EtOH (3mL) under 40 psi H_2 as described for **53** (50 °C, 4 h) to afford after purification (hexanes:EtOAc 1:1) **52** (25 mg, 0.11 mmol, 25%) as an off-white solid.

mp = 151-154 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.52 (s, br, 1H), 6.95 (s, 1H), 6.49 (d, *J* = 2.2 Hz, 1H), 4.61 (s, 2H), 3.37 (s, 3H), 3.22-3.17 (m, 2H), 2.73-2.69 (m, 2H), 2.59 (s, 3H).; ^{1}H NMR

(600 MHz, DMSO-d_6) δ 11.59 (s, br, 1H), 6.95 (s, 1H), 6.52 (d, J = 1.8 Hz, 1H), 4.54 (s, 2H), 3.28 (s, 3H), 3.14-3.11 (m, 2H), 2.64-2.61 (m, 2H), 2.54 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 204.6, 152.0, 138.3, 136.2, 129.5, 127.3, 119.5, 117.3, 100.4, 66.4, 57.2, 35.9, 26.0, 19.2; IR (ATR) 3339, 2920, 1657, 1560, 1294, 1128 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{16}NO_2$ (M+H$^+$) 230.1181, found 230.1174.
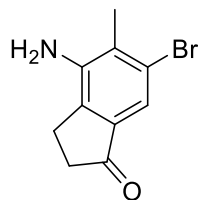
4-Amino-6-bromo-2,3-dihydro-5-methylinden-1-one (95). **78** (440 mg, 1.63 mmol) was combined in a thick-walled glass pressure tube with Pd/C (10% Pd, 35 mg, 0.03 mmol) and absolute EtOH (6 mL). The resulting suspension was charged with 40 psi H_2 and the system was heated to 50 °C and stirred for 21 h. The reaction mixture was cooled to ambient temperature and filtered over Celite, rinsing with hot EtOH. The combined filtrates were concentrated in vacuo, and without further purification **95** (391 mg, 1.29 mmol, 79%) was obtained as a tan solid. mp = 183-192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.01 (s, 1H), 5.56 (br, s, 2H), 2.78 (m, 2H), 2.64-2.60 (m, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 205.6, 145.4, 139.1, 136.1, 124.5, 123.6, 112.8, 35.9, 23.1, 17.6; IR (ATR) 3346, 2910, 1693, 1632, 1587, 1429, 1294, 1094 cm^{-1}; HRMS (ESI, negative mode) calculated for $C_{10}H_9BrNO$ (M-H$^+$) 239.9853, found 239.9847.
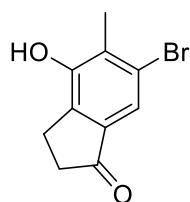
6-Bromo-2,3-dihydro-4-hydroxy-5-methylinden-1-one (96). **95** (481 mg, 2.01 mmol) was suspended in H_2O (7 mL), and concentrated H_2SO_4 was added dropwise until

dissolution of the solid (approx.. 8 mL). This solution was heated to 45 °C and stirred for 30 min. The solution was removed from heat and allowed to cool to ambient temperature before being placed in an ice bath. A solution of $NaNO_2$ (420 mg, 6.04 mmol) in H_2O (3 mL) was added dropwise, and the resulting solution stirred at 0 °C for 10 min before being heated to reflux and stirred for 16 h. The resulting mixture was cooled to ambient temperature and then added slowly in portions to a flask of ice water. Upon addition, a dark precipitate was immediately formed. The suspension was filtered rinsing with cold H_2O, and the solid was dried in vacuo to afford **96** (185 mg, 0.77 mmol, 38%) as a brown solid without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 7.31 (s, 1H), 2.96-2.92 (m, 2H), 2.65-2.62 (m, 2H), 2.33 (s, 3H).
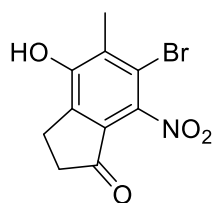
6-Bromo-2,3-dihydro-4-hydroxy-5-methyl-7-nitroinden-1-one (97). **96** (88 mg, 0.36 mmol) was reacted with fuming HNO_3 (2 mL) and conc. H_2SO_4 (5 drops) as described for **70** (-20 °C, 90 min). After chromatography (hexanes:EtOAc 1:1), **97** (33 mg, 0.12 mmol, 32%) was obtained as an orange solid. ^{1}H NMR (400 MHz, chloroform-d) δ 2.92-2.87 (m, 2H), 2.84-2.79 (m, 2H), 1.68 (s, 3H).
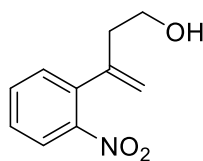
3-(2-nitrophenyl)-3-buten-1-ol (106). To a round-bottomed flask equipped with cold-water condenser was added Pd(dba)$_2$ (11 mg, 0.02 mmol), dppf (21 mg, 0.04 mmol), and urotropine (104 mg, 0.74 mmol), and the system was purged with N_2. DMA (3 mL) was added via syringe, and the solution was heated to 105 °C. A mixture of 3-buten-

1-ol (63 μL, 0.74 mmol) and **105** (100 mg, 0.37 mmol) in DMA (2 mL) was added via syringe, and the solution stirred at 105 °C for 72 h. The resulting mixture was cooled to ambient temperature and quenched with H_2O then extracted with EtOAc (3 x 10 mL). The combined organics were washed with saturated $NaHCO_3$ (aq., 10 mL) and brine (10 mL), dried ($MgSO_4$), and solvents were removed in vacuo. The resulting residue was purified by flash chromatography (hexanes:EtOAc 7:3 to 2:8) to afford **106** (34 mg, 0.18 mmol, 47%) as an orange oil as a mixture of stereoisomers (**106/107** = 6.3:1 by ^{1}H NMR), and 2-nitrophenol (6 mg, 0.04 mmol, 11%). Analytical data for the 6.3:1 mixture (data provided for compound **106**): ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.86 (d, *J* = 8.2 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 5.30 (s, 1H), 5.08 (s, 1H), 3.72 (t, *J* = 5.8 Hz, 2H), 2.70 (t, *J* = 6.0 Hz, 2H), 1.84 (br s, 1H).
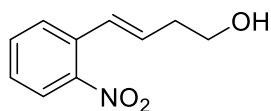
4-(2-nitrophenyl)-3-buten-1-ol (107). *Method used to obtain **107** as the major isomer:* To a round-bottomed flask equipped with cold-water condenser was added **105** (500 mg, 1.85 mmol), Pd(OAc)$_2$ (20 mg, 0.09 mmol) and PPh$_3$ (50 mg, 0.19 mmol), and the system was purged with N_2. NEt$_3$ (9.25 mL) was added via syringe, followed by 3-buten-1-ol (320 μL, 3.7 mmol) via syringe. The solution was heated to 80 °C and stirred for 18 h. The resulting reaction mixture was cooled to ambient temperature and quenched with H_2O then extracted with EtOAc (3 x 10 mL). The combined organics were washed with saturated $NaHCO_3$ (aq., 10 mL) and brine (10 mL), dried ($MgSO_4$), and solvents were removed in vacuo. The resulting residue was purified by flash chromatography (hexanes:EtOAc 7:3 to 1:1) to afford **107** (22 mg, 0.11 mmol, 6%) as an orange oil as a mixture of stereoisomers (major/minor = 3.6:1 by ^{1}H NMR). Analytical data for the 3.6:1

mixture: ^{1}H NMR (400 MHz, chloroform-*d*, major isomer) δ 7.90 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.56 (dtd, *J* = 15.6, 8.1, 1.4 Hz, 2H), 7.41-7.33 (m, 2H), 6.95 (d, *J* = 15.7 Hz, 1H), 6.23 (dt, *J* = 15.7, 7.1 Hz, 1H), 3.81 (t, *J* = 6.2 Hz, 2H), 2.55 (qd, *J* = 6.3, 1.4 Hz, 2H); ^{1}H NMR (400 MHz, chloroform-*d*, minor isomer, partial data) δ 7.85 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.43 (td, *J* = 7.8, 1.5 Hz, 2H), 6.86 (d, *J* = 11.5 Hz, 1H).
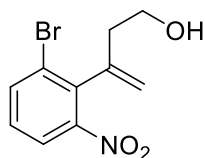
3-(2-bromo-6-nitrophenyl)-3-buten-1-ol (110). **108** (520 mg, 1.49 mmol) was reacted with 3-buten-1-ol (256 μL, 2.98 mmol), Pd(dba)$_2$ (43 mg, 0.08 mmol), dppf (83 mg, 0.15 mmol), and urotropine (417 mg, 2.98 mmol) in DMA (7 mL) as described for **106** (105 °C, 72 h) to afford after purification by flash chromatography (hexanes:EtOAc 7:3) **110** (27 mg, 0.10 mmol, 7%) as an orange oil. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.31 (t, *J* = 8.1 Hz, 1H), 5.41 (s, 1H), 5.07 (s, 1H), 3.89 (t, *J* = 6.2 Hz, 2H), 2.88-2.67 (m, 2H).
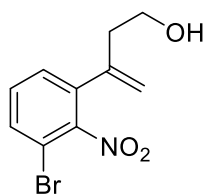
3-(3-bromo-2-nitrophenyl)-3-buten-1-ol (112). **109** (231 mg, 0.66 mmol) was reacted with 3-buten-1-ol (113 μL, 1.32 mmol), Pd(dba)$_2$ (19 mg, 0.04 mmol), dppf (37 mg, 0.07 mmol), and urotropine (185 mg, 1.32 mmol) in DMA (5 mL) as described for **106** (105 °C, 72 h) to afford after purification by flash chromatography (hexanes:EtOAc 7:3) **112** (12 mg, 0.04 mmol, 7%) as an orange oil as a mixture of isomers (1:11 by ^{1}H NMR) and 3-bromo-2-nitrophenol (**113**, 75 mg, 0.34 mmol, 52%). Analytical data for the 1:11

mixture (data provided for compound **112**): ^{1}H NMR (400 MHz, chloroform-*d*, partial data) δ 5.33 (s, 1H), 5.19 (s, 1H), 3.69 (t, *J* = 6.0 Hz, 2H), 2.69-2.63 (m, 2H).
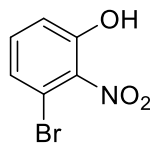
3-bromo-2-nitrophenol (113). **109** (231 mg, 0.66 mmol) was reacted with 3-buten-1-ol (113 µL, 1.32 mmol), Pd(dba)$_2$ (19 mg, 0.04 mmol), dppf (37 mg, 0.07 mmol), and urotropine (185 mg, 1.32 mmol) in DMA (5 mL) as described for **106** (105 °C, 72 h) to afford after purification by flash chromatography (hexanes:EtOAc 7:3) **112** (12 mg, 0.04 mmol, 7%) as an orange oil as a mixture of isomers (1:11 by ^{1}H NMR) and **113** (75 mg, 0.34 mmol, 52%). Analytical data for **113**: ^{1}H NMR (400 MHz, chloroform-*d*) δ 9.38 (br, s, 1H), 7.33-7.28 (m, 2H), 7.15-7.08 (m, 1H).
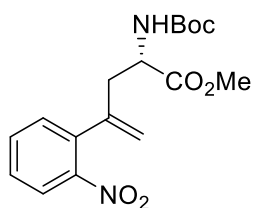
(*S*)-methyl-2-(*tert*-butylcarbonylamino)-4-(2-nitrophenyl)pent-4-enoate (122). 105 (100 mg, 0.37 mmol) was reacted with **121** (170 mg, 0.74 mmol), Pd(dba)$_2$ (21 mg, 0.04 mmol), dppf (25 mg, 0.04 mmol), and urotropine (104 mg, 0.74 mmol) in DMA (5 mL) as described for **106** (105 °C, 72 h) to afford after purification by flash chromatography (hexanes:EtOAc 7:3) an orange oil as a mixture of compounds (1.5:1 **122** and **123** (32%) : **105** (19%) by ^{1}H NMR). Analytical data for the mixture of stereoisomers (data provided for compound **122**): ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.18 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.50-7.44 (m, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 5.28 (s, 1H), 5.14 (s, 1H), 4.35 (d, *J* = 10.4 Hz, 1H), 3.58 (s, 3H), 3.01-2.90 (m, 1H), 2.77 (dd, *J* = 15.5, 7.9 Hz, 2H), 1.41 (s, 9H).
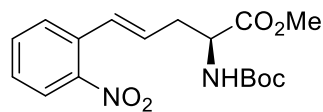
(*S*)-methyl-2-(*tert*-butylcarbonylamino)-5-(2-nitrophenyl)pent-4-enoate (123). **105** (100 mg, 0.37 mmol) was reacted with **121** (170 mg, 0.74 mmol), Pd(dba)$_2$ (21 mg, 0.04 mmol), dppf (25 mg, 0.04 mmol), and urotropine (104 mg, 0.74 mmol) in DMA (5 mL) as described for **106** (105 °C, 72 h) to afford after purification by flash chromatography (hexanes:EtOAc 7:3) an orange oil as a mixture of compounds (1.5:1 **122** and **123** (32%) : **105** (19%) by ^{1}H NMR). Analytical data for the mixture of stereoisomers (data provided for compound **123**): ^{1}H NMR (400 MHz, chloroform-*d*, partial data) δ 6.96-6.77 (m, 1H), 6.14-6.01 (m, 1H), 4.58-4.44 (m, 1H), 3.78 (s, 3H), 2.71-2.58 (m, 1H), 1.43 (s, 9H).
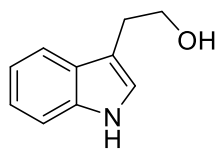
3-ethanol-1*H*-indole (124). To a thick-walled pressure tube equipped with stir bar was added **106** (50 mg, 0.26 mmol), Pd(OAc)$_2$ (5 mg, 0.02 mmol), and PPh$_3$ (20 mg, 0.06 mmol). A 2:1 mixture of MeOH:DMF (2 mL) was added, and the system was charged with 90 psi CO. The solution was heated to 60 °C and stirred vigorously for 24 h. The resulting solution was cooled to ambient temperature and extracted with EtOAc (3 x 5 mL). The combined organics were washed with H$_2$O (2 x 5 mL), dried (MgSO$_4$), and solvents were removed in vacuo. The resultant residue was purified via flash chromatography (hexanes:EtOAc 1:1) to afford **124** (31 mg, 0.19 mmol, 74%) as an off-white solid. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.11 (br s, 1H), 7.63-7.58 (m, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.22-7.17 (m, 1H), 7.12 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 1H), 7.01 (d, *J* = 2.3 Hz, 1H), 3.88 (t, *J* = 6.4 Hz, 2H), 3.05-2.97 (m, 2H), 1.71 (br s, 1H).
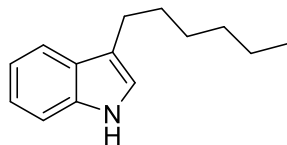
3-hexyl-1*H***-indole (126)**. **120** (49 mg, 0.21 mmol) was reacted with Pd(OAc)$_2$ (5 mg, 0.02 mmol), and PPh$_3$ (22 mg, 0.08 mmol) in CH$_3$CN (3 mL) under 90 psi CO as described for **124** (100 °C, 24 h) to afford after purification by flash chromatography (hexanes:EtOAc 9:1) **126** (16 mg, 0.08 mmol, 37%) and unreacted starting material (**120**, 6 mg, 0.03 mmol, 13%). Analytical data for **126**: ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.87 (s, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.96 (s, 1H), 2.75 (t, *J* = 7.6 Hz, 2H), 1.71 (m, *J* = 7.6 Hz, 2H), 1.45-1.28 (m, 6H), 0.90 (m, 3H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 136.3, 131.6, 127.6, 121.8, 120.9, 119.0, 117.2, 111.0, 31.8, 30.1, 29.3, 25.1, 22.7, 14.1.
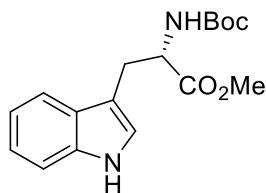
***N-tert*-butoxycarbonyl-tryptophan methyl ester (127)**. The mixture of **122** with **123,** with **105** (80 mg, ~0.23 mmol) was reacted with Pd(dba)$_2$ (8 mg, 0.013 mmol), dppp (5 mg, 0.013 mmol), 1,10-phenanthroline (5 mg, 0.03 mmol) in DMF (3 mL) under 90 psi CO as described for **124** (120 °C, 48 h) to afford after purification by flash chromatography (hexanes:EtOAc 7:3) two isolated compounds: **127** (16 mg, 0.05 mmol, 22%) and **128** (7 mg, 0.02 mmol, 10%). Analytical data for **127**: ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.16 (s, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.02-6.98 (m, 1H), 5.09 (d, *J* = 7.8 Hz, 1H), 4.65 (d, *J* = 7.8 Hz, 1H), 3.68 (s, 3H), 3.29 (s, 2H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 172.8, 155.2, 136.0, 129.6, 122.7, 122.2, 119.6, 118.7, 111.1, 110.2, 79.8, 54.1, 52.2, 28.3, 27.9.

α-[[1,1-dimethylethoxy)carbonyl]amino]-1*H*-indole-2-**propanoic acid methyl ester (128)**. The mixture of **122** with **123,** with **105** (80 mg, ~0.23 mmol) was reacted with Pd(dba)$_2$ (8 mg, 0.013 mmol), dppp (5 mg, 0.013 mmol), 1,10-phenanthroline (5 mg, 0.03 mmol) in DMF (3 mL) under 90 psi CO as described for **124** (120 °C, 48 h) to afford after purification by flash chromatography (hexanes:EtOAc 7:3) two isolated compounds: **127** (16 mg, 0.05 mmol, 22%) and **128** (7 mg, 0.02 mmol, 10%). Analytical data for **128**: ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.31 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.1 Hz, 2H), 6.28 (s, 1H), 5.13 (d, *J* = 8.5 Hz, 1H), 4.66 (s, 1H), 3.76 (s, 3H), 3.29 (d, *J* = 4.1 Hz, 2H), 1.43 (s, 9H).

1-oxide-4-quinolinecarbonitrile (141).
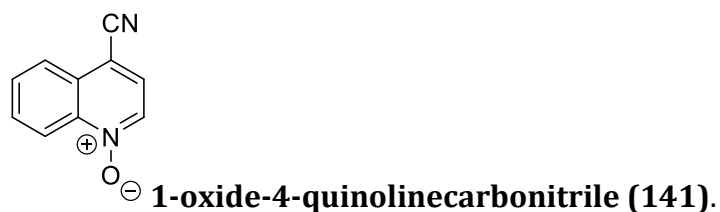
Method A: A round-bottomed flask was charged with **140** (111 mg, 0.62 mmol) and 18-crown-6 (49 mg, 0.19 mmol), and the system was purged with N$_2$. THF (5 mL) was added via syringe, and the solution was cooled to -78 °C. A suspension of KO^{t}Bu (179 mg, 1.60 mmol) in THF (1 mL) was added slowly via syringe, followed by dropwise addition of acetaldehyde (346 μL, 6.17 mmol) via syringe. The resulting solution was stirred at -78 °C for 2 h. The reaction mixture was allowed to warm to ambient temperature and was quenched by slow addition of a saturated solution of NH$_4$Cl (aq) and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organics were washed with brine (10 mL), dried (MgSO$_4$), and solvents were

removed in vacuo. The resulting residue was purified by flash chromatography (EtOAc) to afford **141** (55 mg, 0.32 mmol, 47%) as a brown solid.

Method B: A round-bottomed flask was charged with **140** (1.01 g, 6.17 mmol) and the system was purged with N_2. THF (43 mL) was added via syringe, and the solution was cooled to -78 °C. A suspension of KO^{t}Bu (2.07 g, 18.5 mmol) in THF (8.6 mL) was added slowly via syringe, followed by dropwise addition of acetaldehyde (3.46 mL, 61.7 mmol) via syringe. The resulting solution was stirred at -78 °C for 2 h. The reaction mixture was allowed to warm to ambient temperature and was quenched by slow addition of a saturated solution of NH_4Cl (aq) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were washed with brine (30 mL), dried ($MgSO_4$), and solvents were removed in vacuo. The resulting residue was purified by flash chromatography (EtOAc) to afford **141** (698 mg, 4.10 mmol, 66%) as a brown solid.

Analytical data for **141**: ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.74 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.50 (d, *J* = 6.4 Hz, 1H), 8.23 (dd, *J* = 7.0, 2.6 Hz, 1H), 7.92-7.82 (m, 2H), 7.67 (d, *J* = 6.4 Hz, 1H).
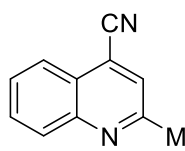
2-methyl-4-quinolinecarbonitrile (145). A round-bottomed flask was charged with **141** (36 mg, 0.21 mmol) and the system was purged with N_2. THF (2 mL) was added via syringe, and the resulting solution was cooled to -30 °C. Methylmagnesium bromide (3.0M solution in THF, 71 μL, 0.21 mmol) was added via syringe, and the reaction mixture was stirred at -30 °C for 1 h. The solution was allowed to warm to ambient temperature and stirred for an additional 1 h, during which time the reaction mixture darkened in color. Upon completion, the reaction was quenched with H_2O and extracted with

EtOAc (3 x 10 mL). The combined organics were dried (MgSO$_4$) and solvents were removed in vacuo. The resulting residue was purified by flash chromatography (hexanes:EtOAc 1:1 to EtOAc) to afford **145** (24 mg, 0.14 mmol, 68%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.75 (d, *J* = 8.7 Hz,1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.86 (t, *J* = 7.9 Hz, 1H), 7.83-7.75 (m, 1H), 7.72 (s, 1H), 2.70 (s, 3H).
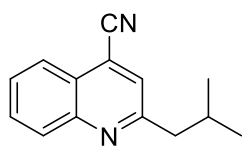
 2-(2-methylpropyl)-4-quinolinecarbonitrile (146). A 2-necked round-bottomed flask equipped with a cold-water condenser and addition funnel was charged with Mg (243 mg, 10.13 mmol) and I$_2$ (crystals) and the system was purged with N$_2$. The flask was heated until a purple vapor was visible. A solution of 1-bromo-2-methylpropane (1.0 mL, 9.21 mmol) in THF (14 mL) was added via the addition funnel and the resulting solution was stirred at ambient temperature for 2 h to afford a solution of the desired Grignard reagent. A round-bottomed flask was charged with **141** (86 mg, 0.59 mmol) and the system was purged with N$_2$. THF (4 mL) was added via syringe, and the solution was cooled to -30 °C. An aliquot of the Grignard solution (820 L, 9.0 mmol) was added via syringe, and the resulting solution was stirred at -30 °C for 1 h. The solution was allowed to warm to ambient temperature and stirred for an additional 1 h, during which time the reaction mixture darkened in color. Upon completion, the reaction was quenched with H$_2$O and extracted with EtOAc (3 x 10 mL). The combined organics were dried (MgSO$_4$) and solvents were removed in vacuo. The resulting residue was purified by flash chromatography (hexanes:EtOAc 7:3 then EtOAc) to afford **146** (21 mg, 0.10 mmol, 17%) and recovered **141** (21 mg, 0.12 mmol, 20%).
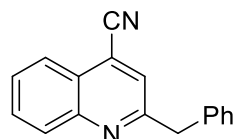
 2-benzyl-4-quinolinecarbonitrile (147). **141** (200 mg, 1.18 mmol) was reacted with benzylmagnesium bromide (288 μL, 1.18 mmol) in THF (8 mL) as described for **145** (-30 °C, 1 h, then ambient temperature, 1 h) to afford after purification by flash chromatography (hexanes:EtOAc 7:3 then EtOAc) **147** (6 mg, 0.02 mmol, 2%) and recovered **141** (87 mg, 0.45 mmol, 44%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.78 (d, *J* = 8.7 Hz, 1H), 8.22 (dd, *J* = 8.2, 4.1 Hz, 1H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.90-7.83 (m, 1H), 7.83-7.76 (m, 1H), 7.39 (d, *J* = 5.7 Hz, 3H), 7.31 (d, *J* = 6.9 Hz, 2H), 4.41 (s, 2H).

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Appendix

Figure 9: Ethyl 2-(2-nitrophenyl)-2-butenoate (**10**)—^{1}H NMR
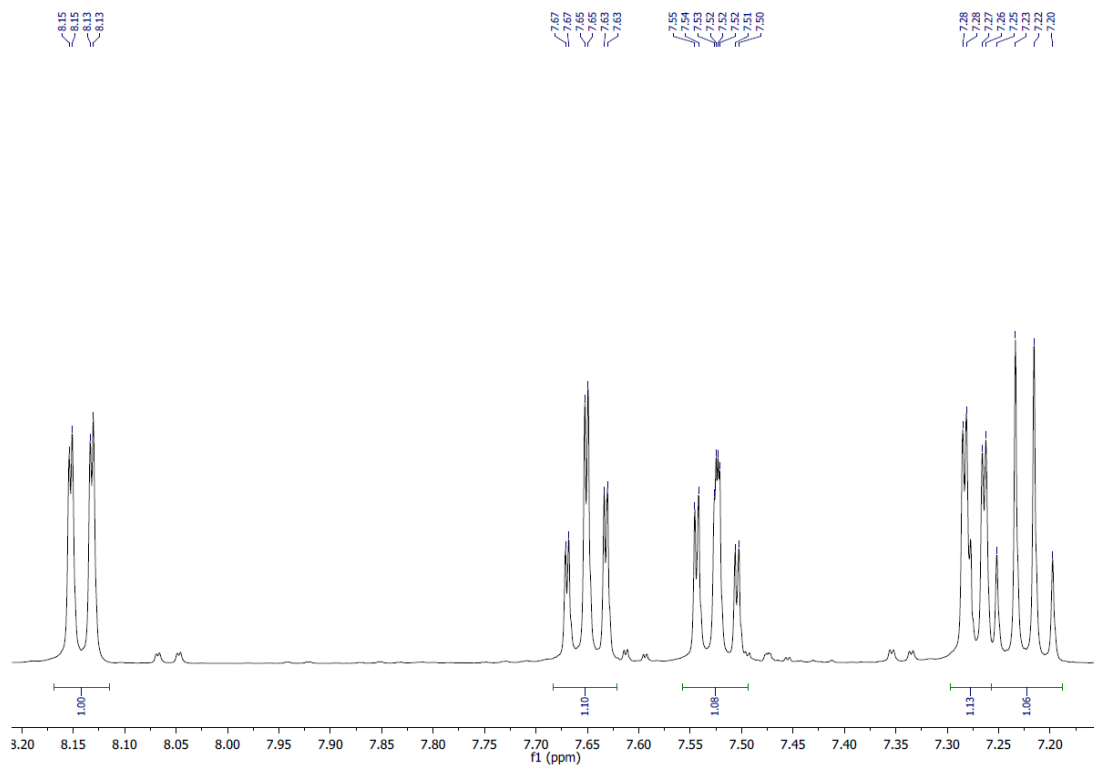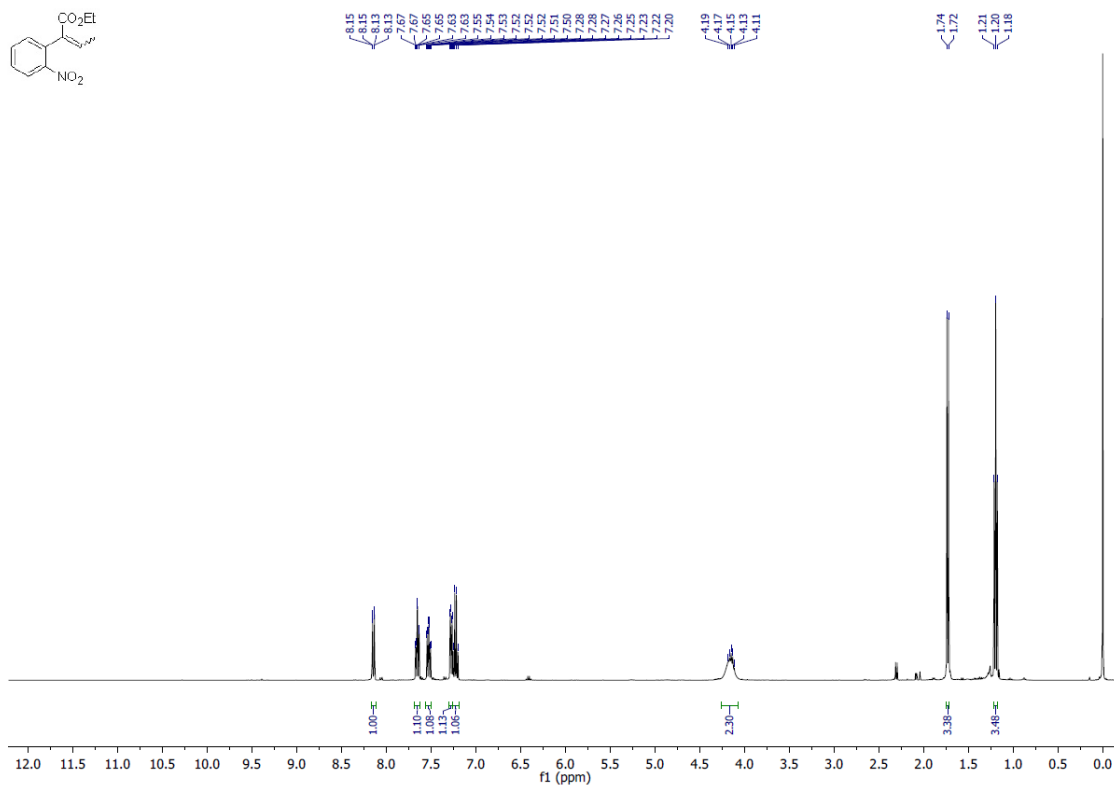
Figure 10: Ethyl 2-(2-nitrophenyl)-2-butenoate (**10**)—¹³C NMR
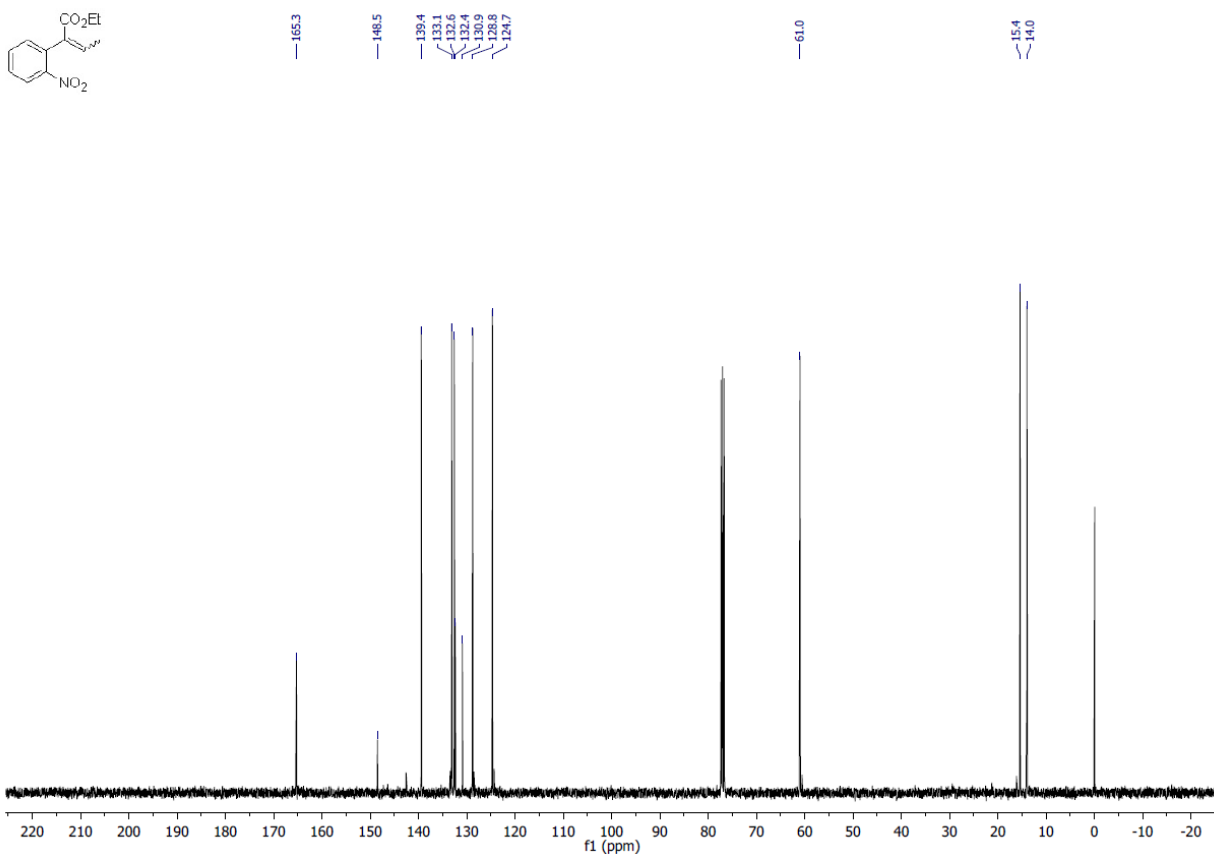
Figure 11: Ethyl 1-methoxyindole-3-carboxylate (**12**)—^{1}H NMR
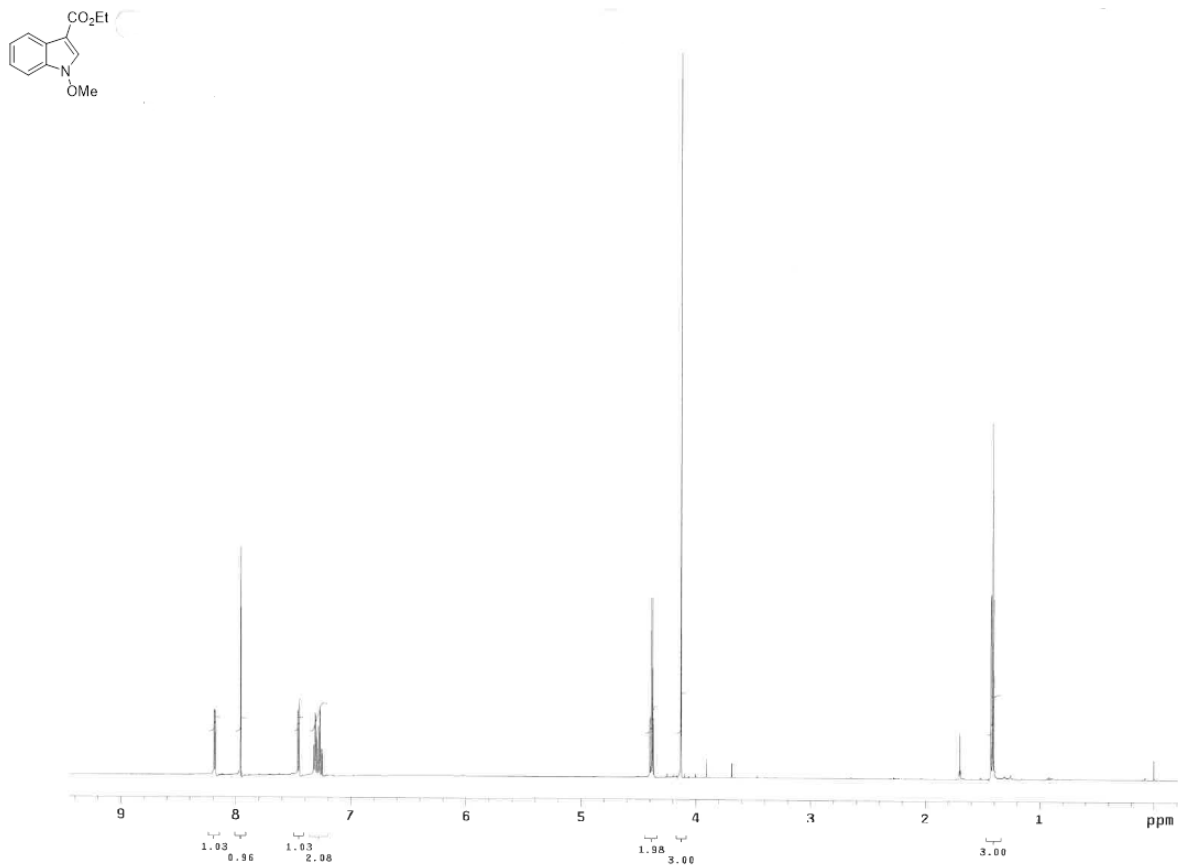
Figure 12: Ethyl 1-methoxyindole-3-carboxylate (**12**)—^{13}C NMR
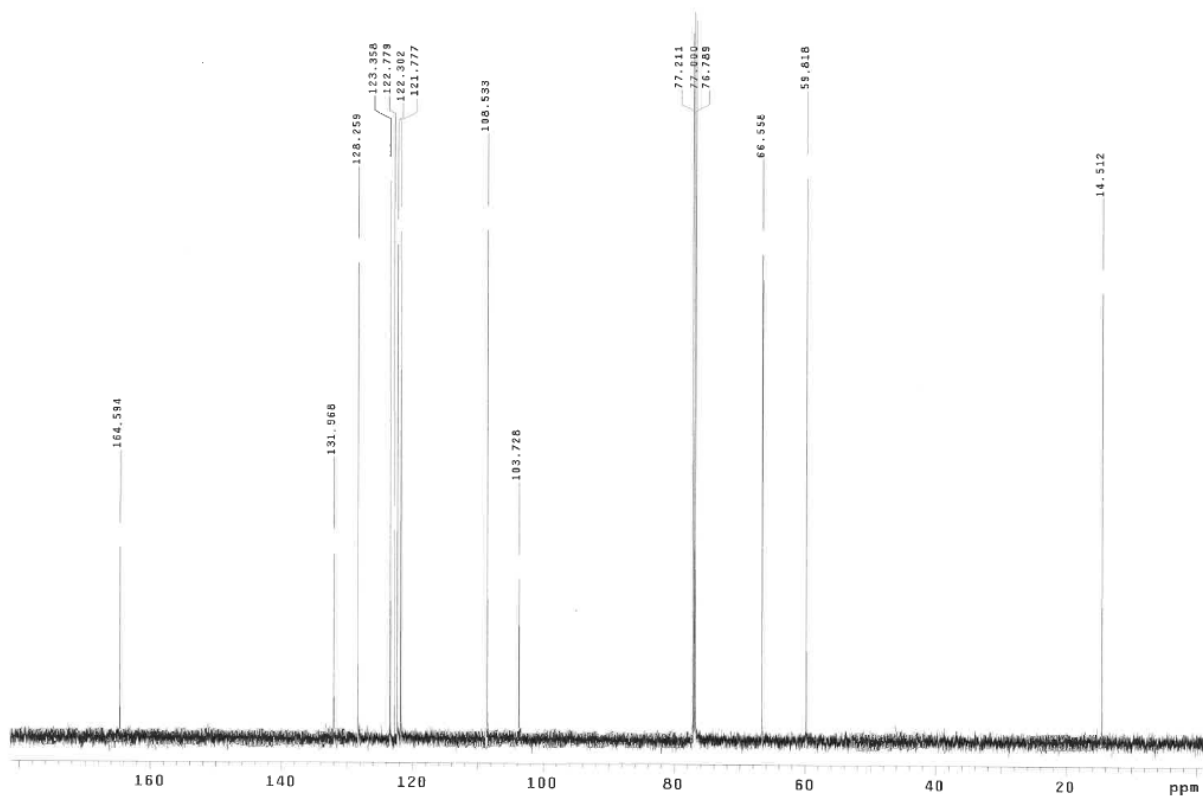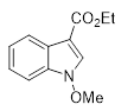
Figure 13: Ethyl 1-benzyloxyindole-3-carboxylate (**13**)—^{1}H NMR
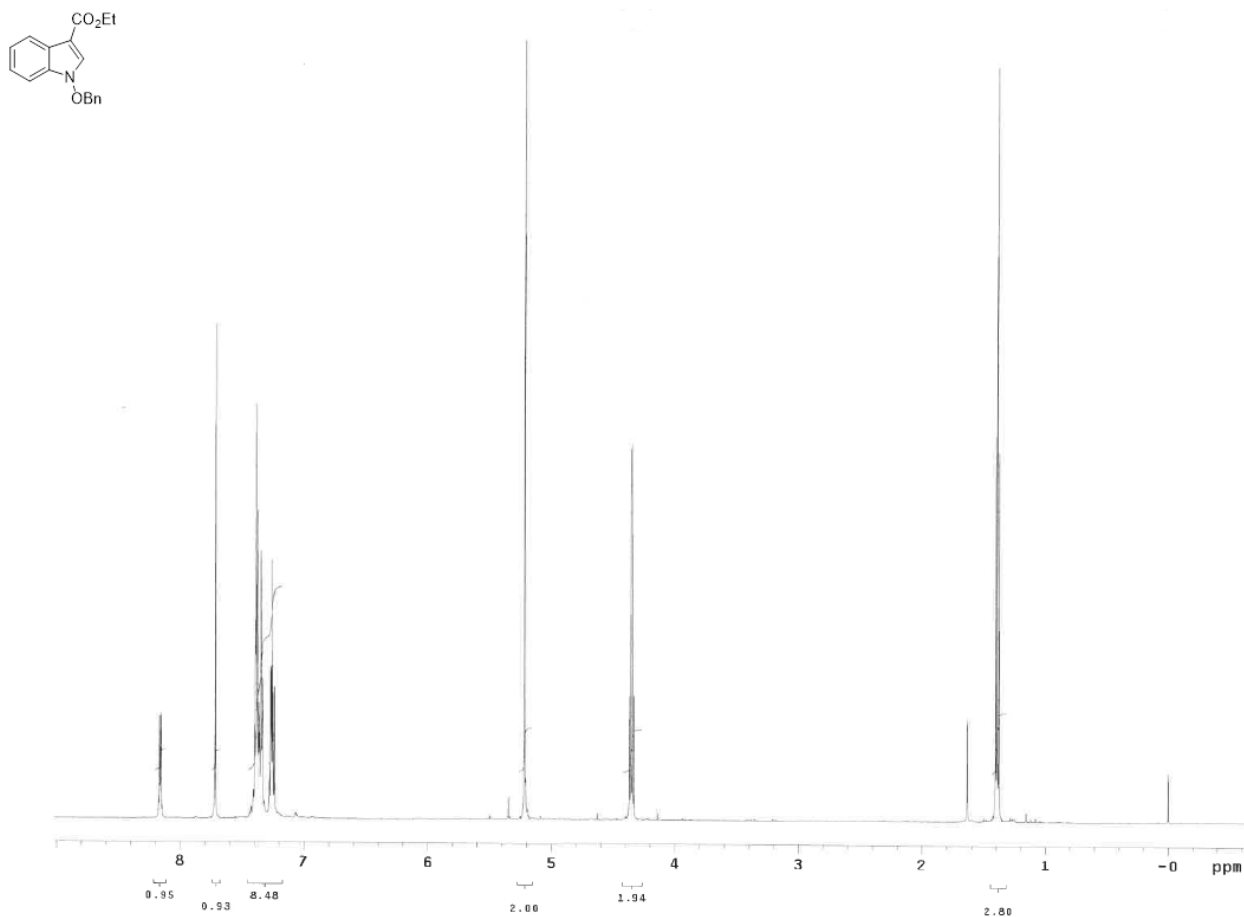
Figure 14: Ethyl 1-benzyloxyindole-3-carboxylate (**13**)—^{13}C NMR
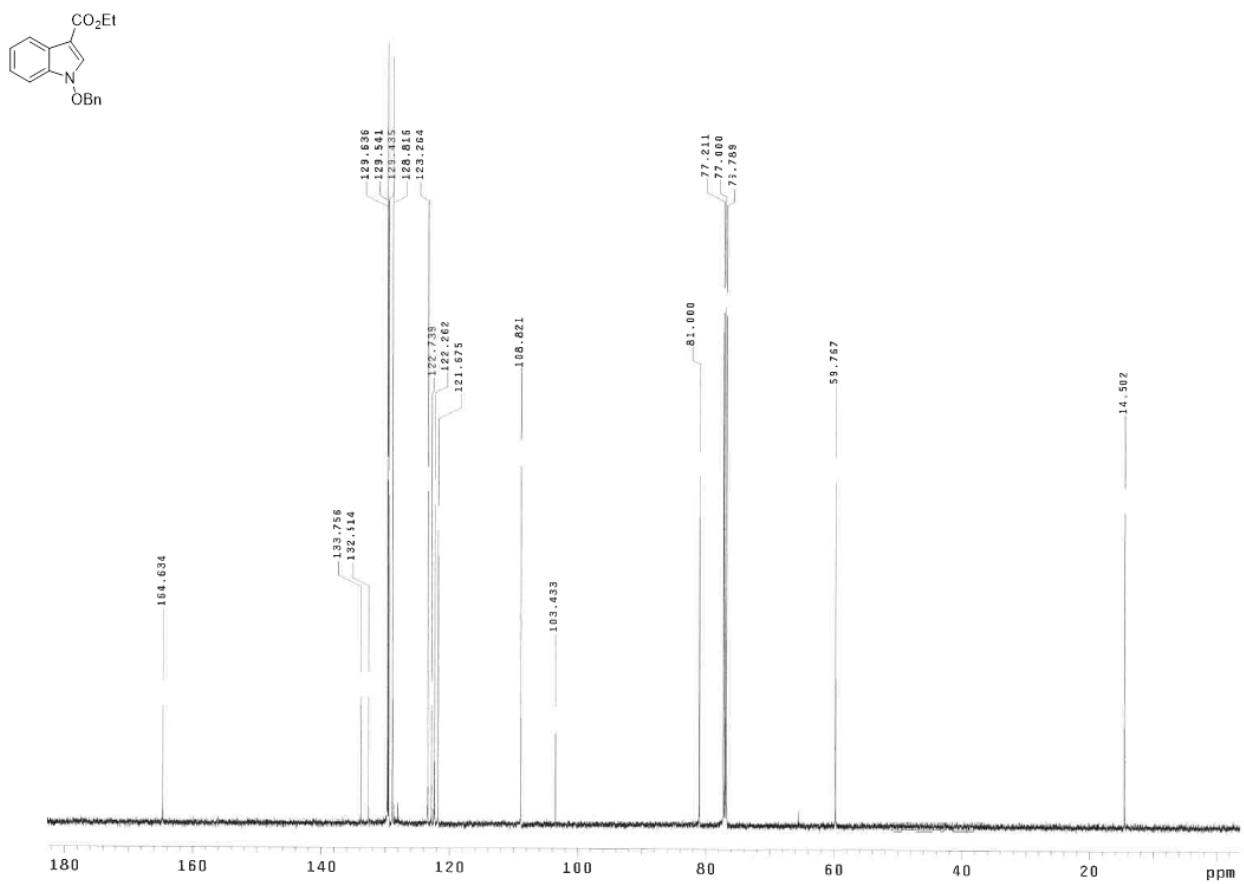
Figure 15: Methyl 1-(2-propen-1-yloxy)indole-3-carboxylate (**14**)—^{1}H NMR
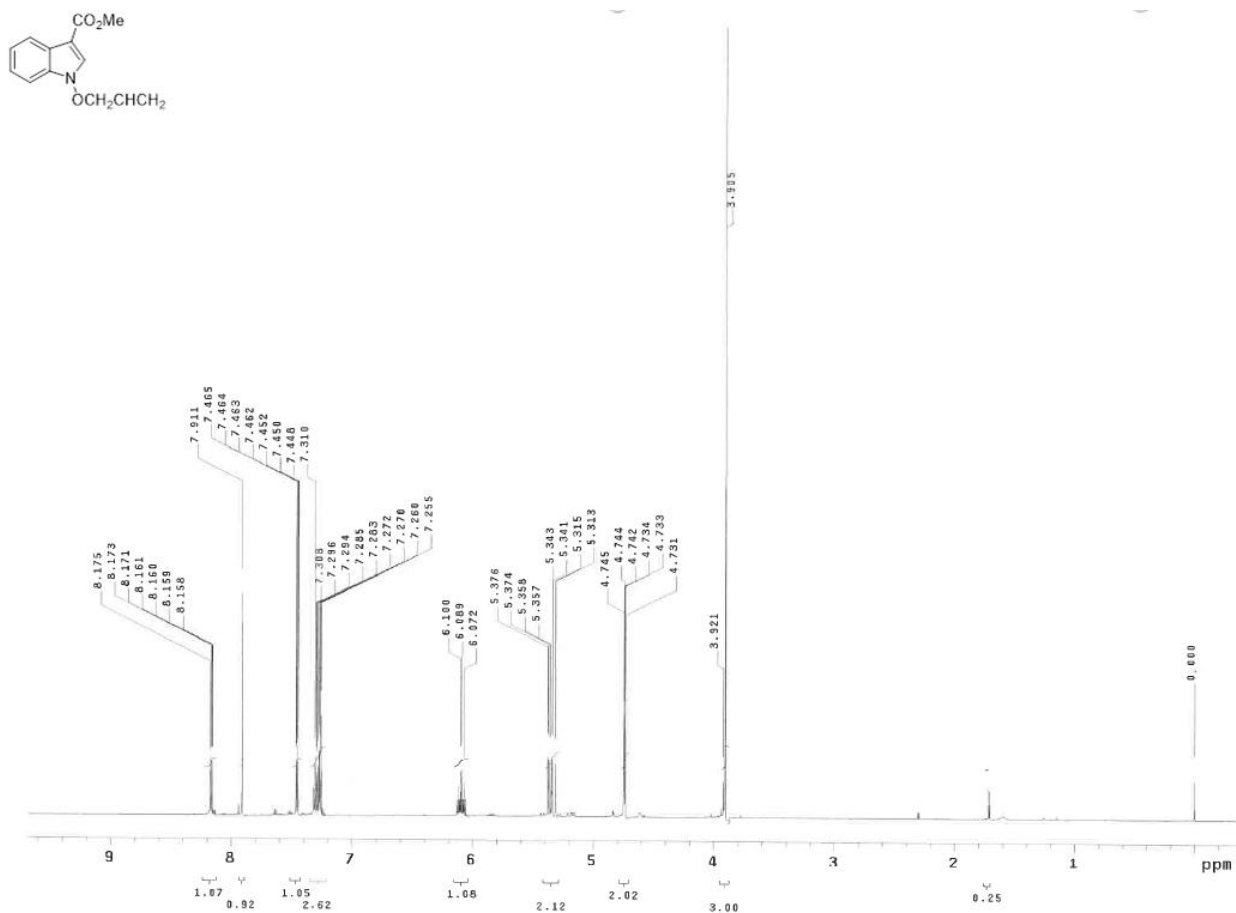
Figure 16: Methyl 1-(2-propen-1-yloxy)indole-3-carboxylate (**14**)—^{13}C NMR
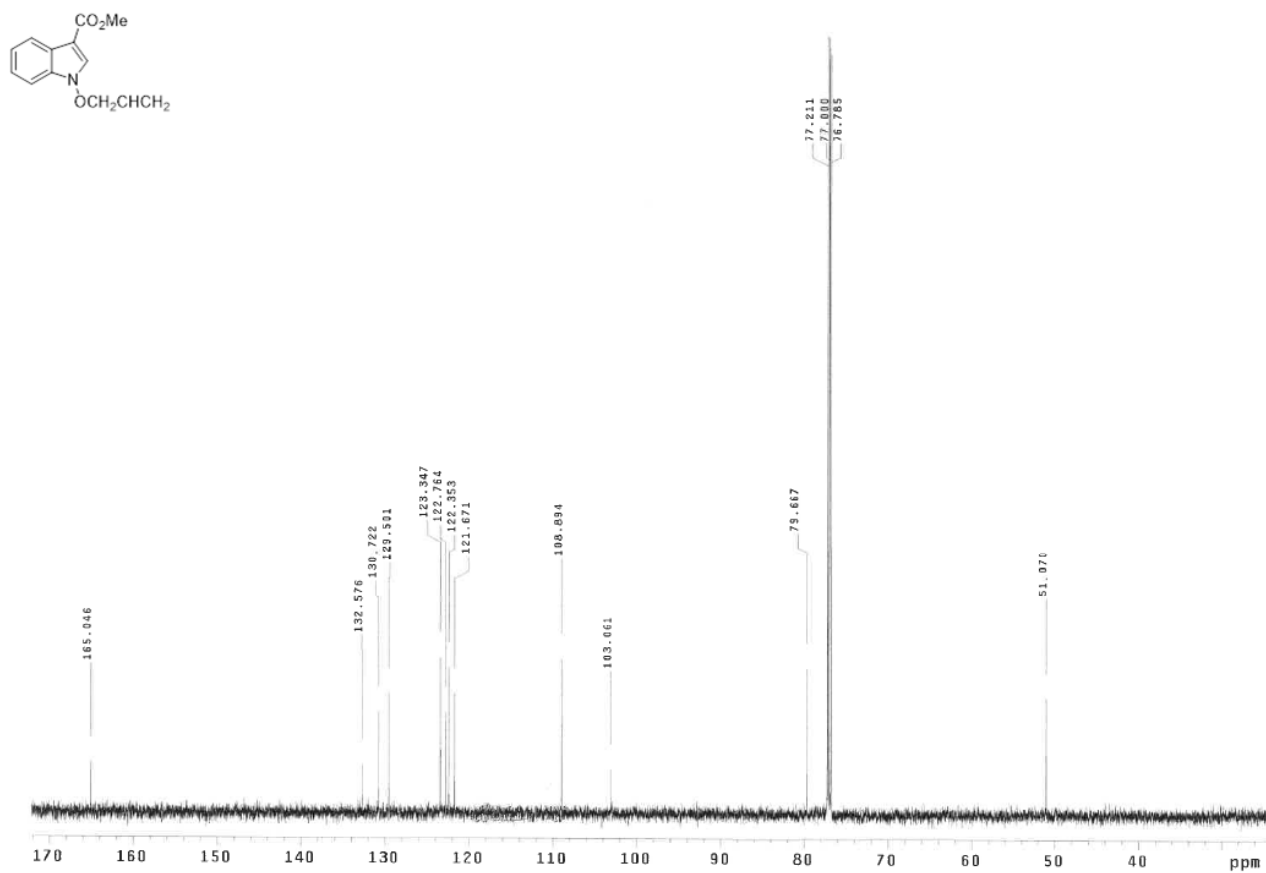
Figure 17: Methyl 1-methoxyindole-3-carboxylate (**15**)—^{1}H NMR
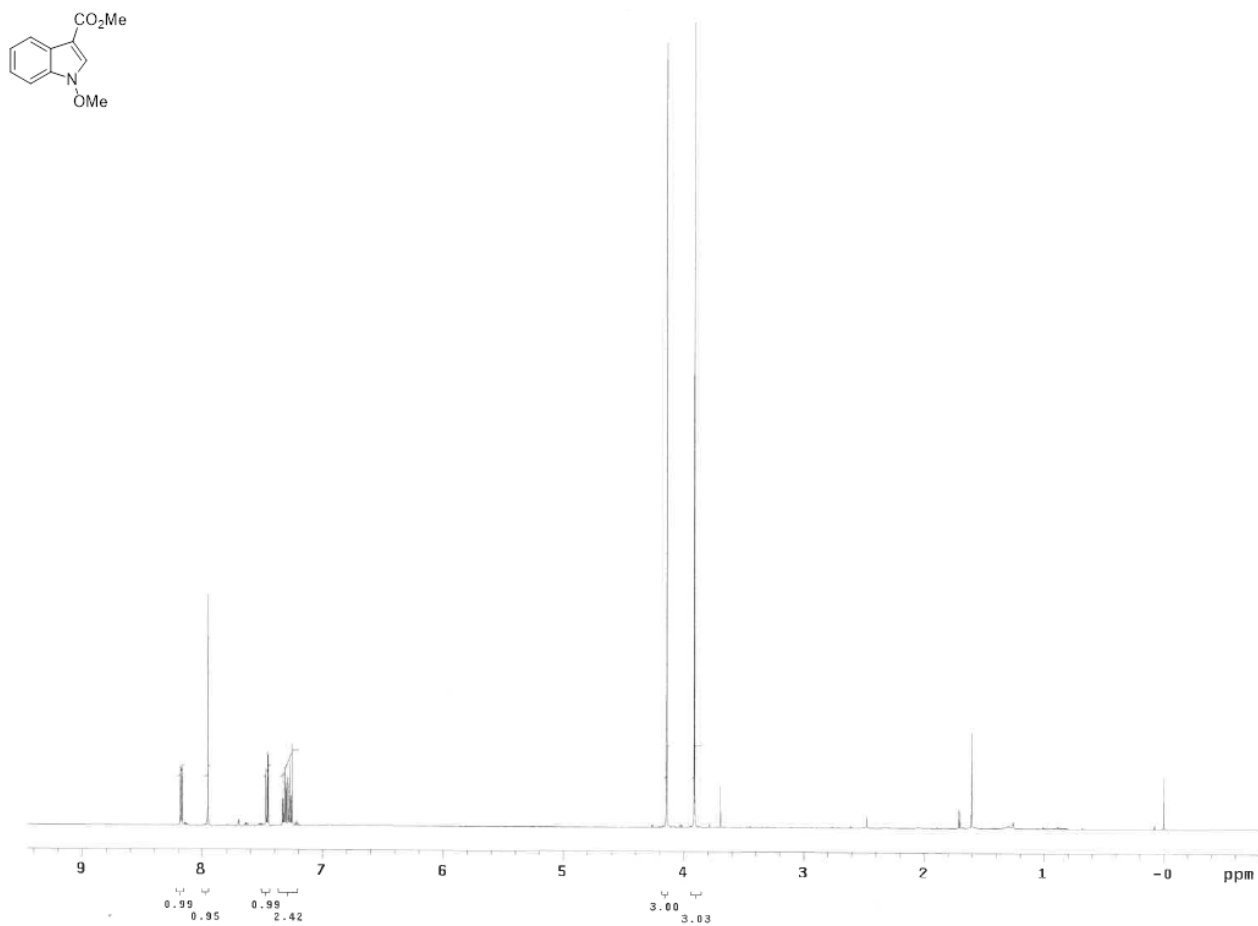
Figure 18: Methyl 1-methoxyindole-3-carboxylate (**15**)—^{13}C NMR

Figure 19: Ethyl 1-acetoxyindole-3-carboxylate (**17**)—^{1}H NMR
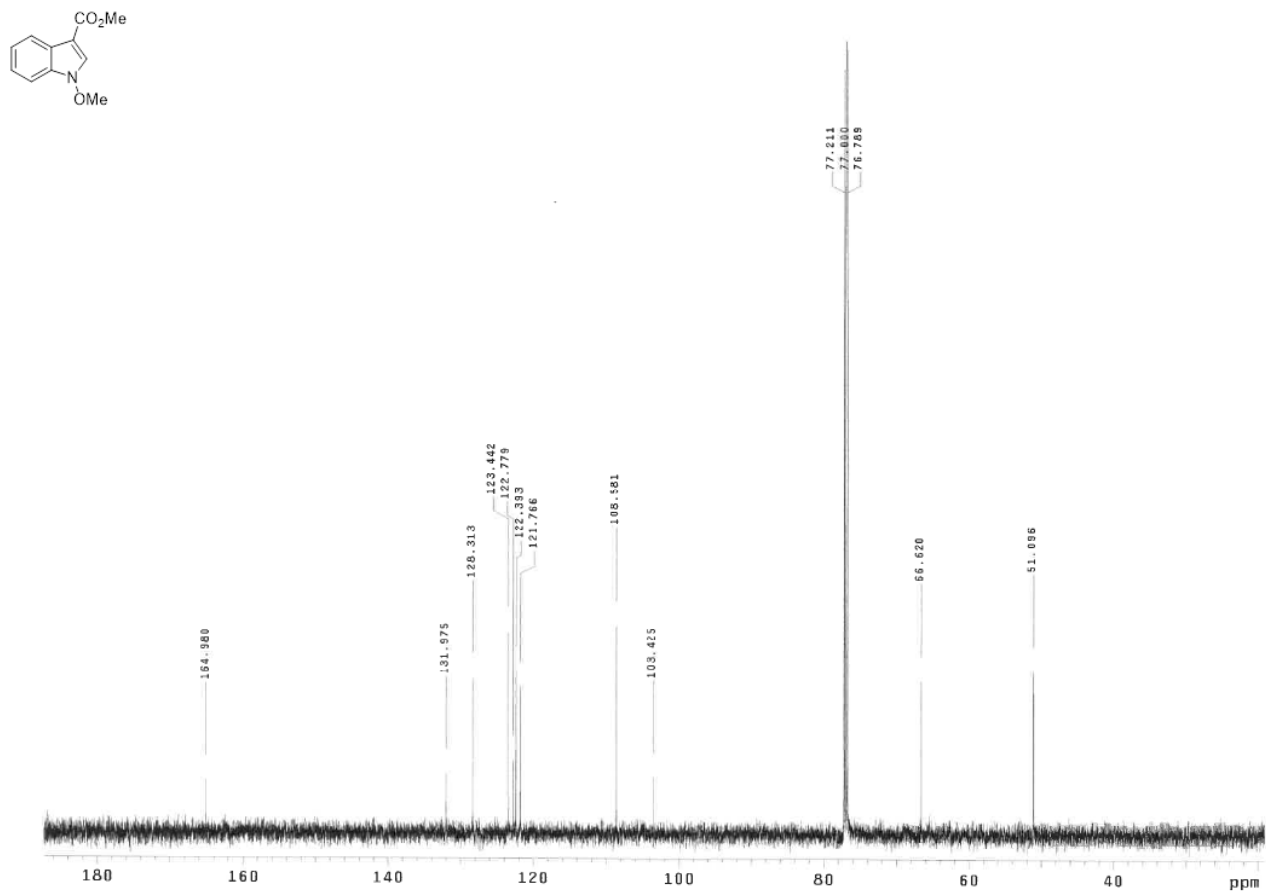
Figure 20: Ethyl 1-acetoxyindole-3-carboxylate (**17**)—¹³C NMR
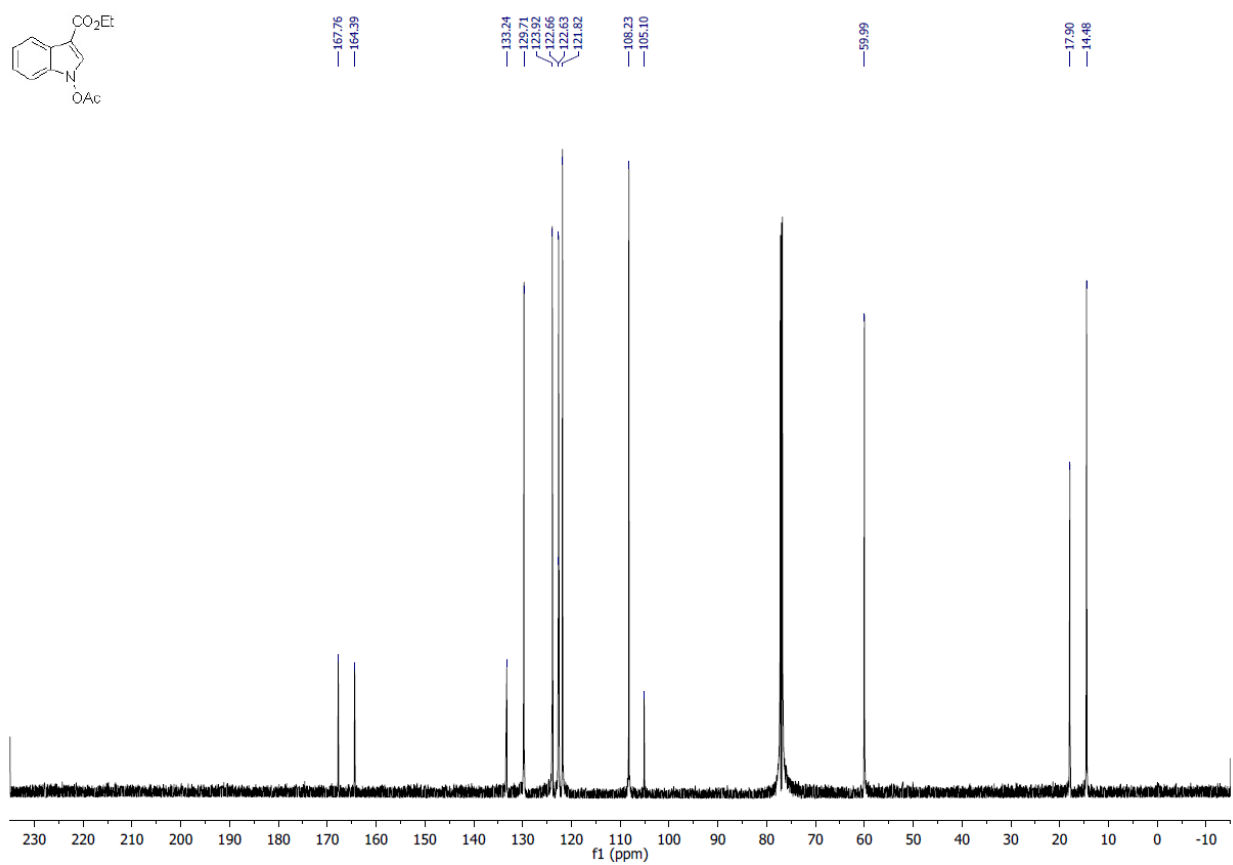
Figure 22: Ethyl 1-tosyloxyindole-3-carboxylate (**18**)—^{13}C NMR
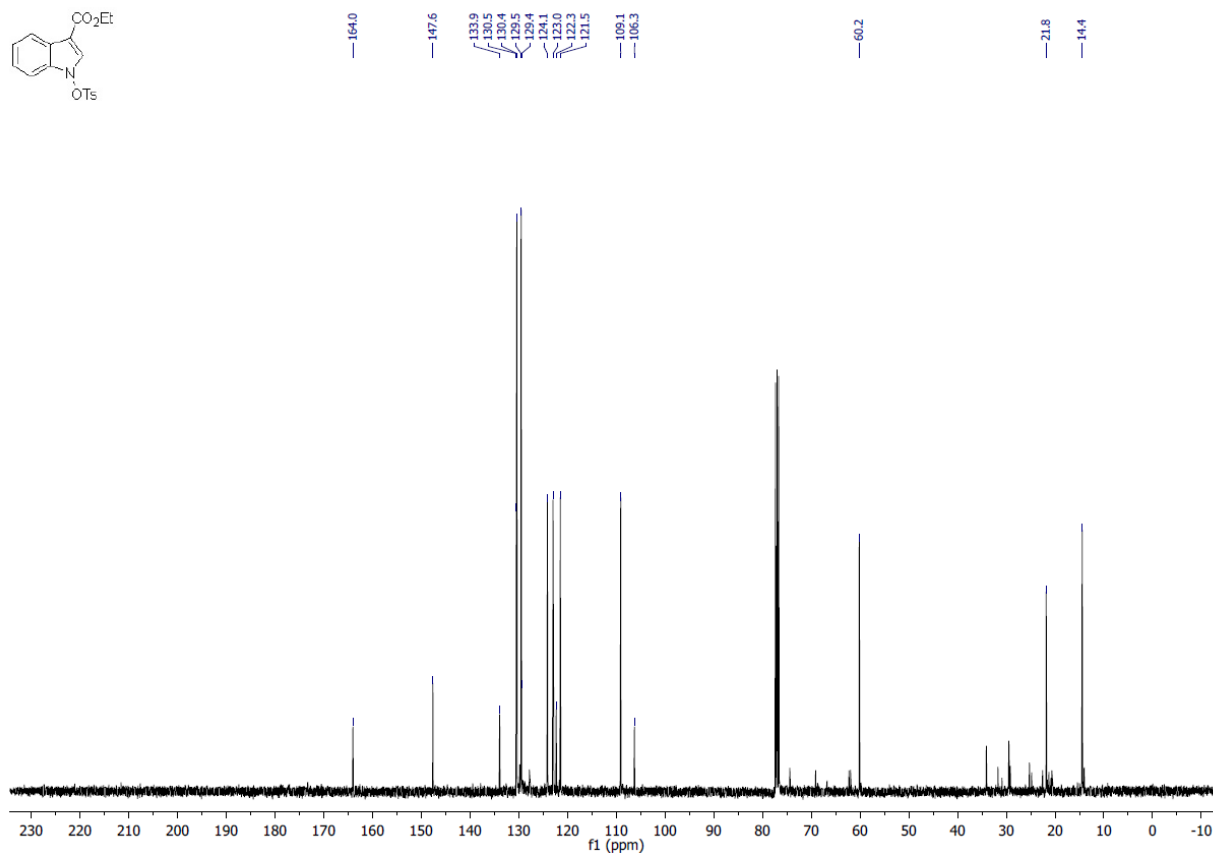
Figure 23: Ethyl 1-hydroxyindole-3-carboxylate (**19**)—¹H NMR
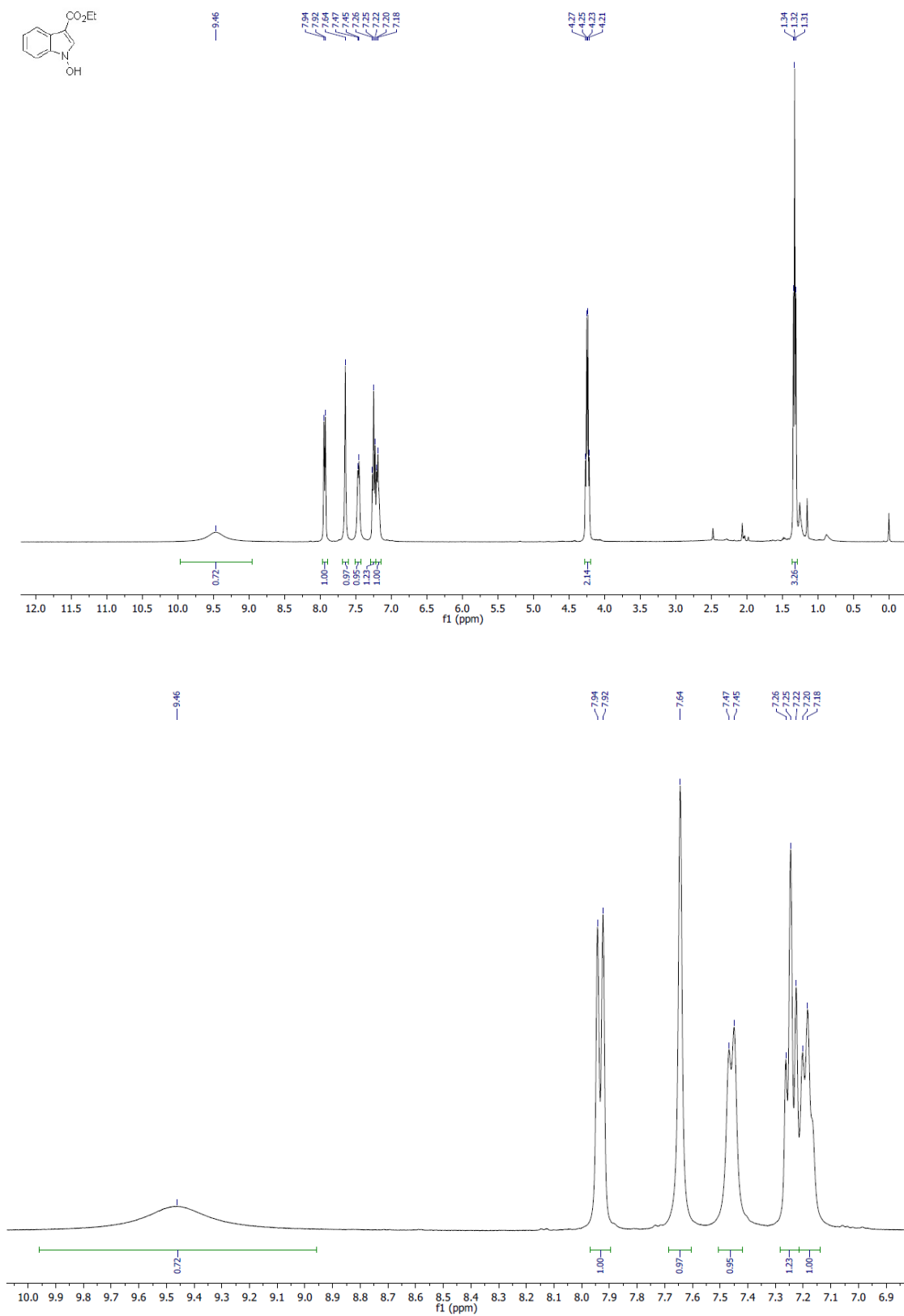
Figure 24: Ethyl 1-hydroxyindole-3-carboxylate (**19**)—^{13}C NMR
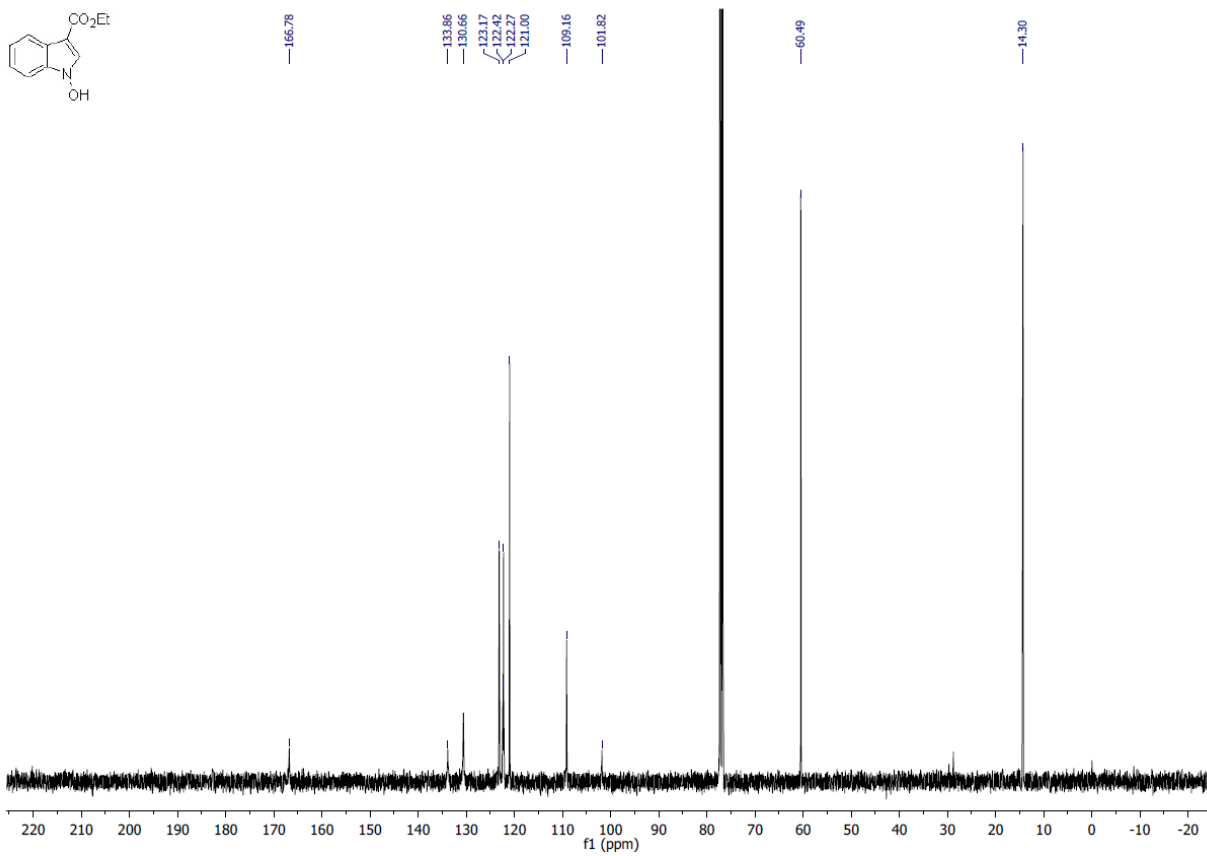
Figure 25: Ethyl 2-iodo-2-pentenoate (**20**)—^{1}H NMR
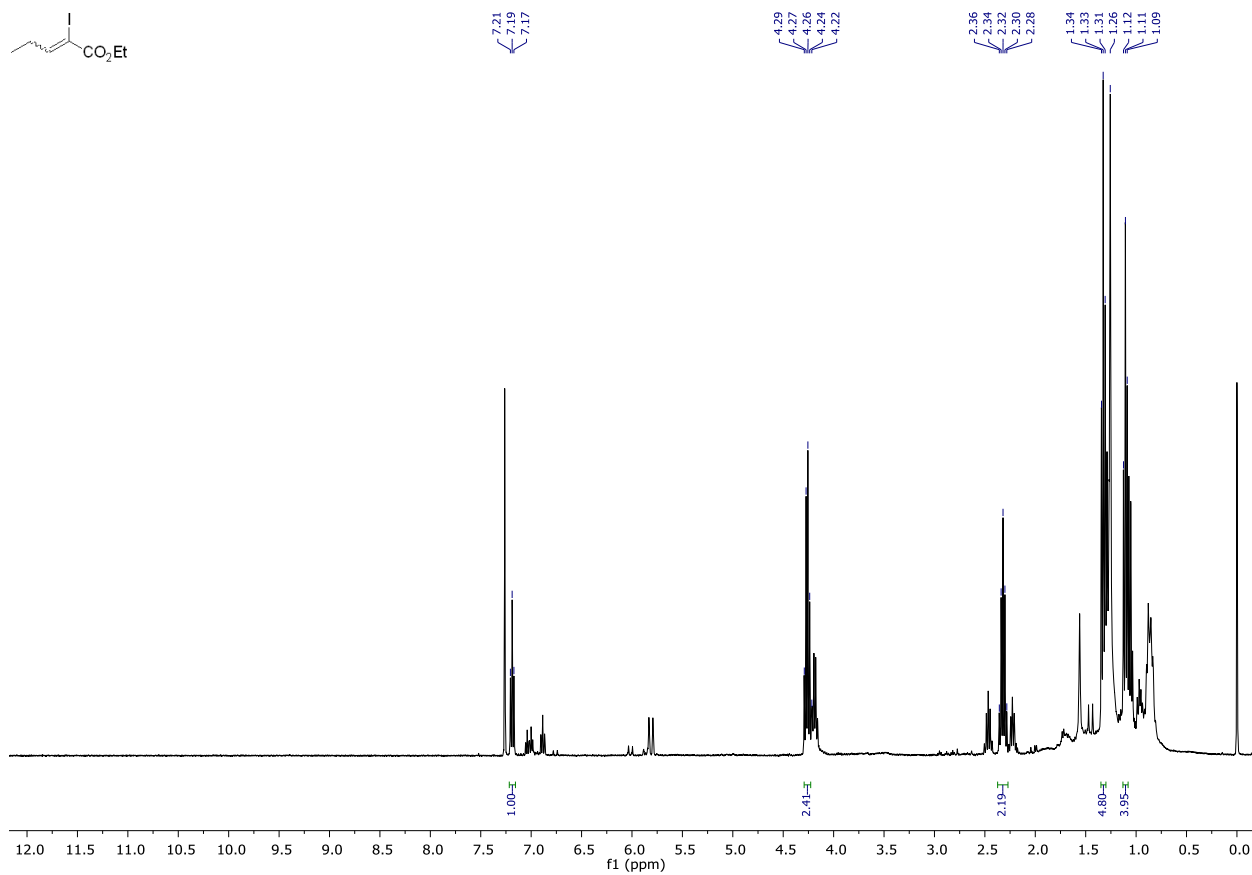
Figure 26: Ethyl 2-iodo-2-pentenoate (**20**)—^{13}C NMR
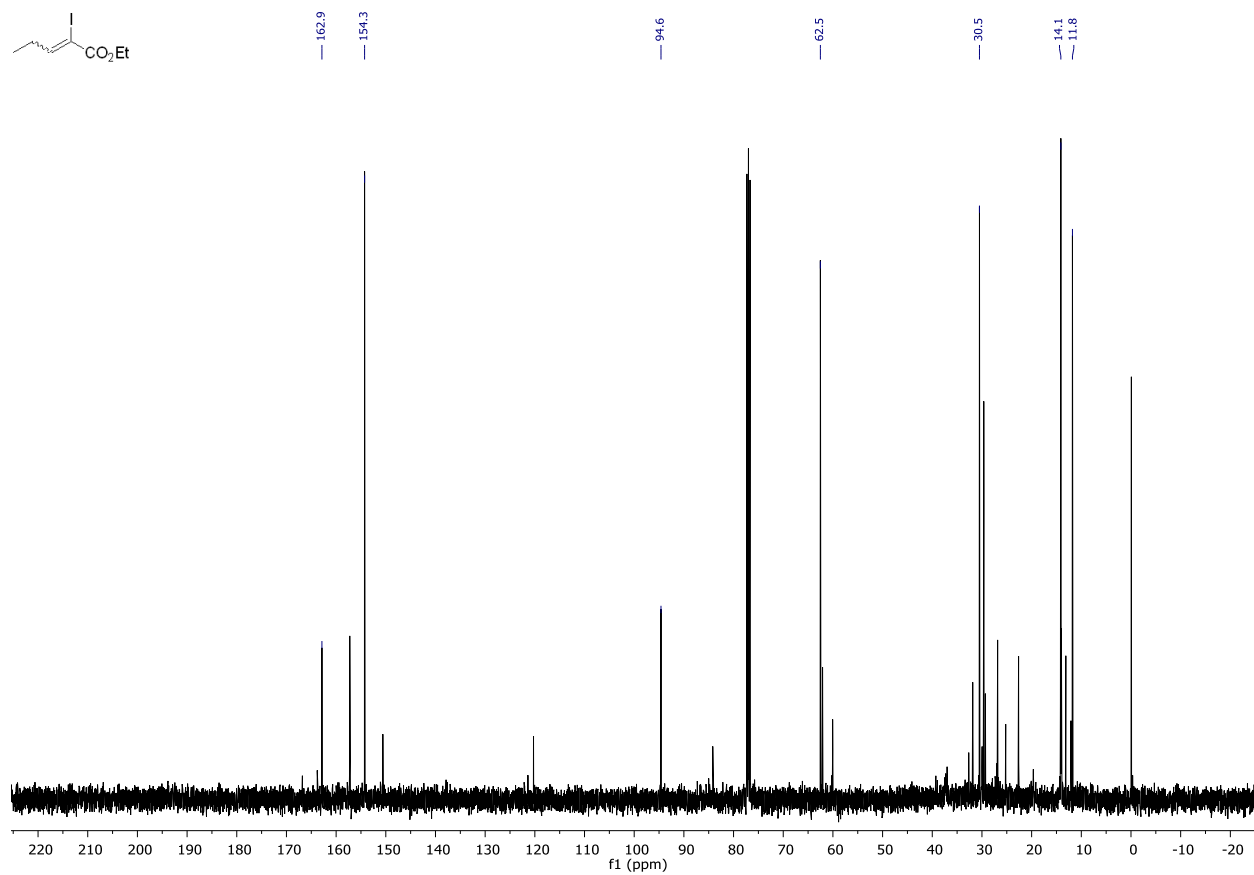
Figure 27: Ethyl 2-iodo-2-hexenoate (**21**)—^{1}H NMR
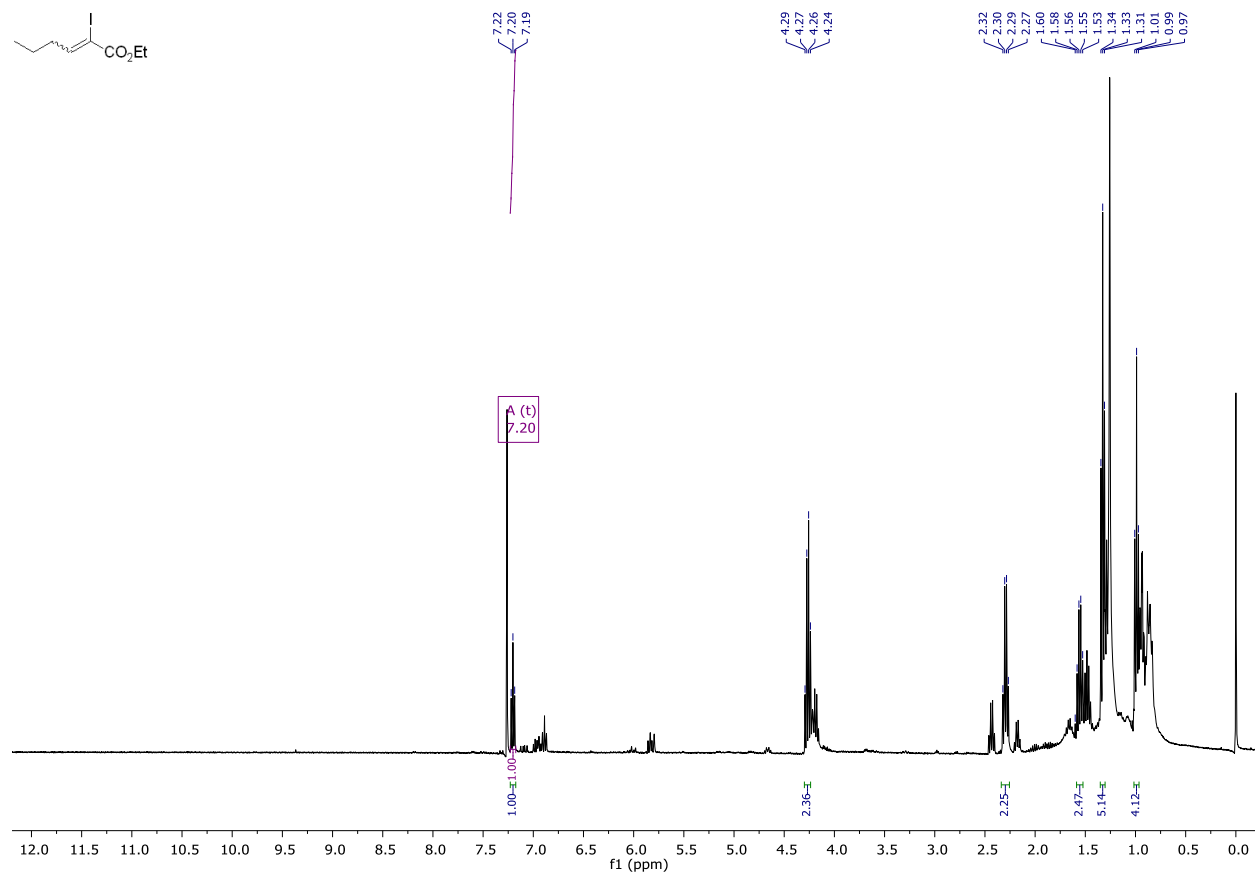
Figure 28: Ethyl 2-iodo-2-hexenoate (**21**)—^{13}C NMR
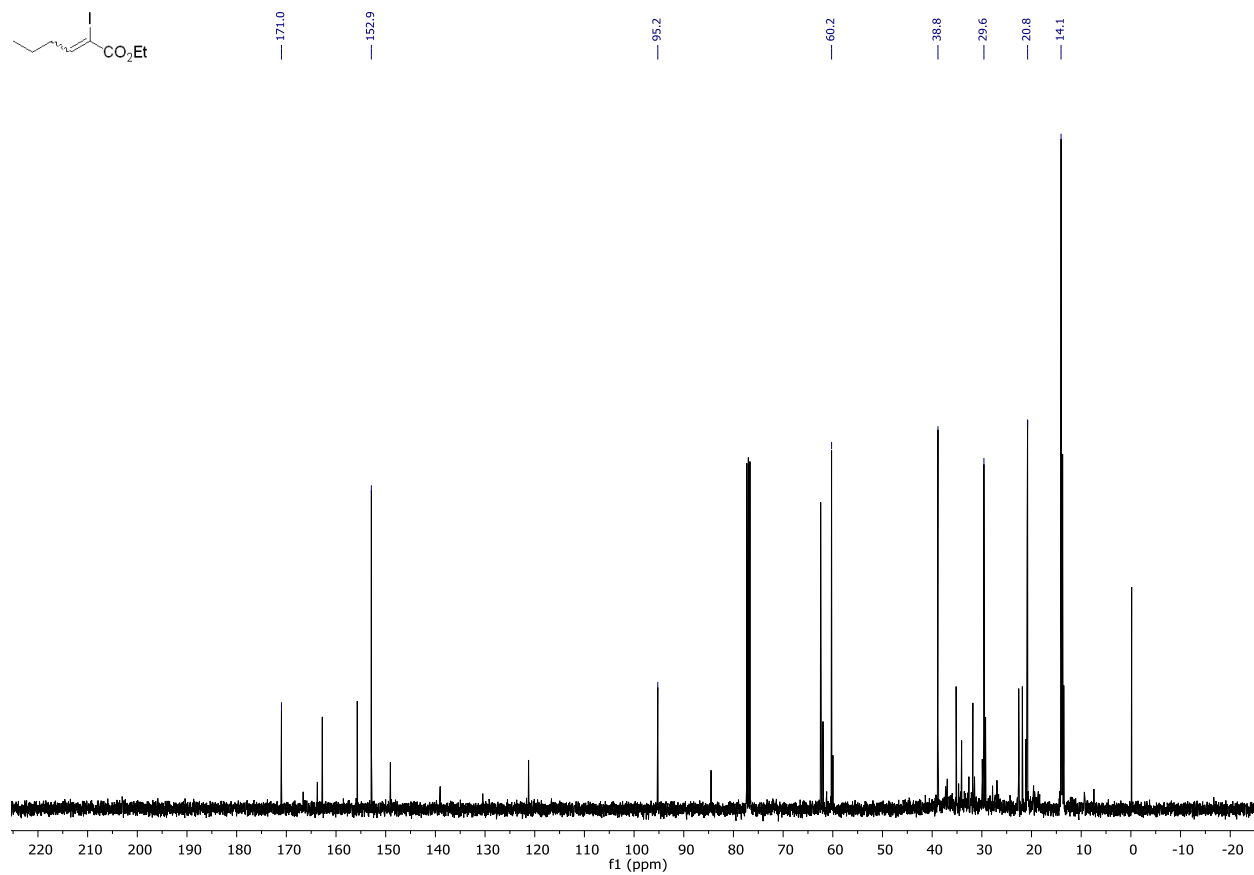
Figure 29: Ethyl 2-iodo-2-octenoate (**22**)—^{1}H NMR
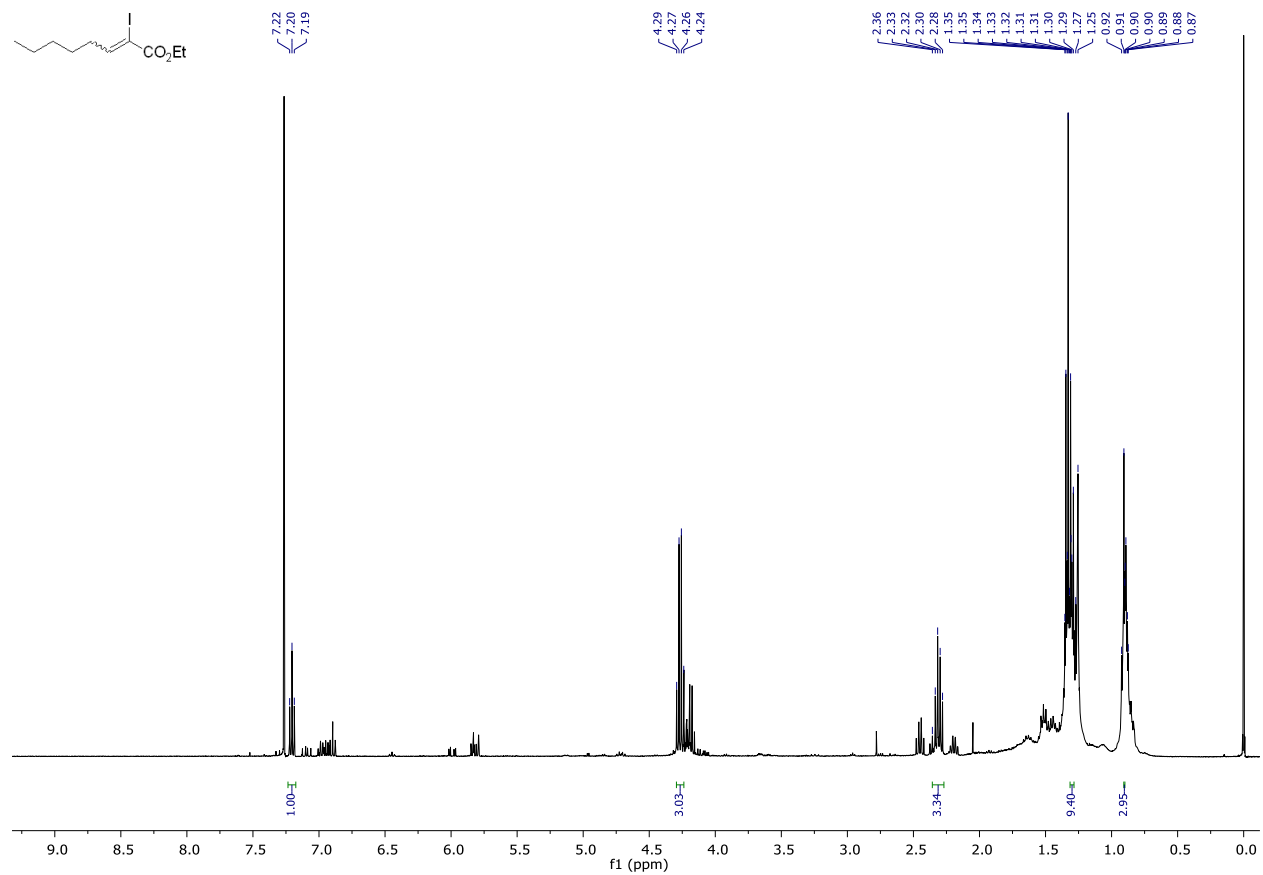
Figure 30: Ethyl 2-iodo-2-octenoate (**22**)—^{13}C NMR
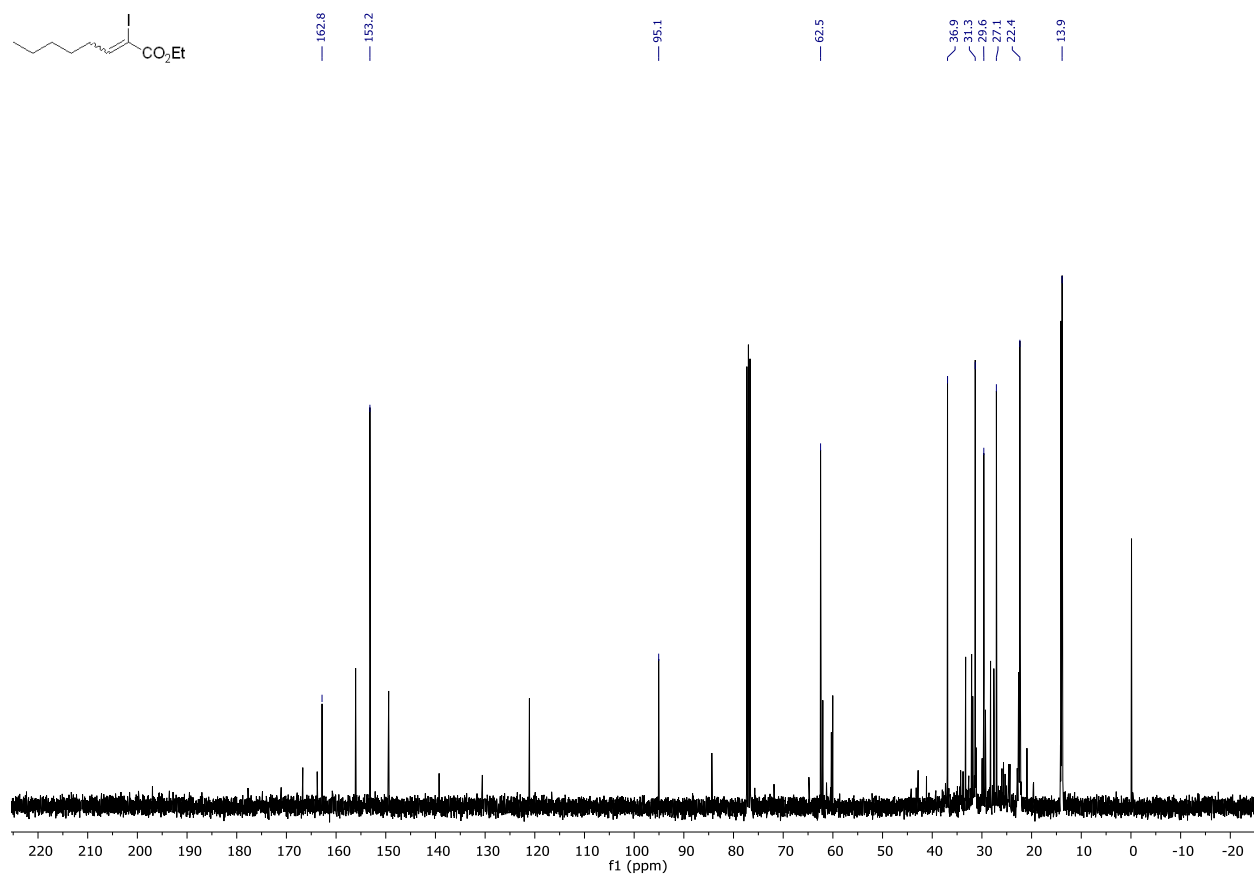
Figure 31: Ethyl 2-iodo-2-nonenoate (**23**)—^{1}H NMR
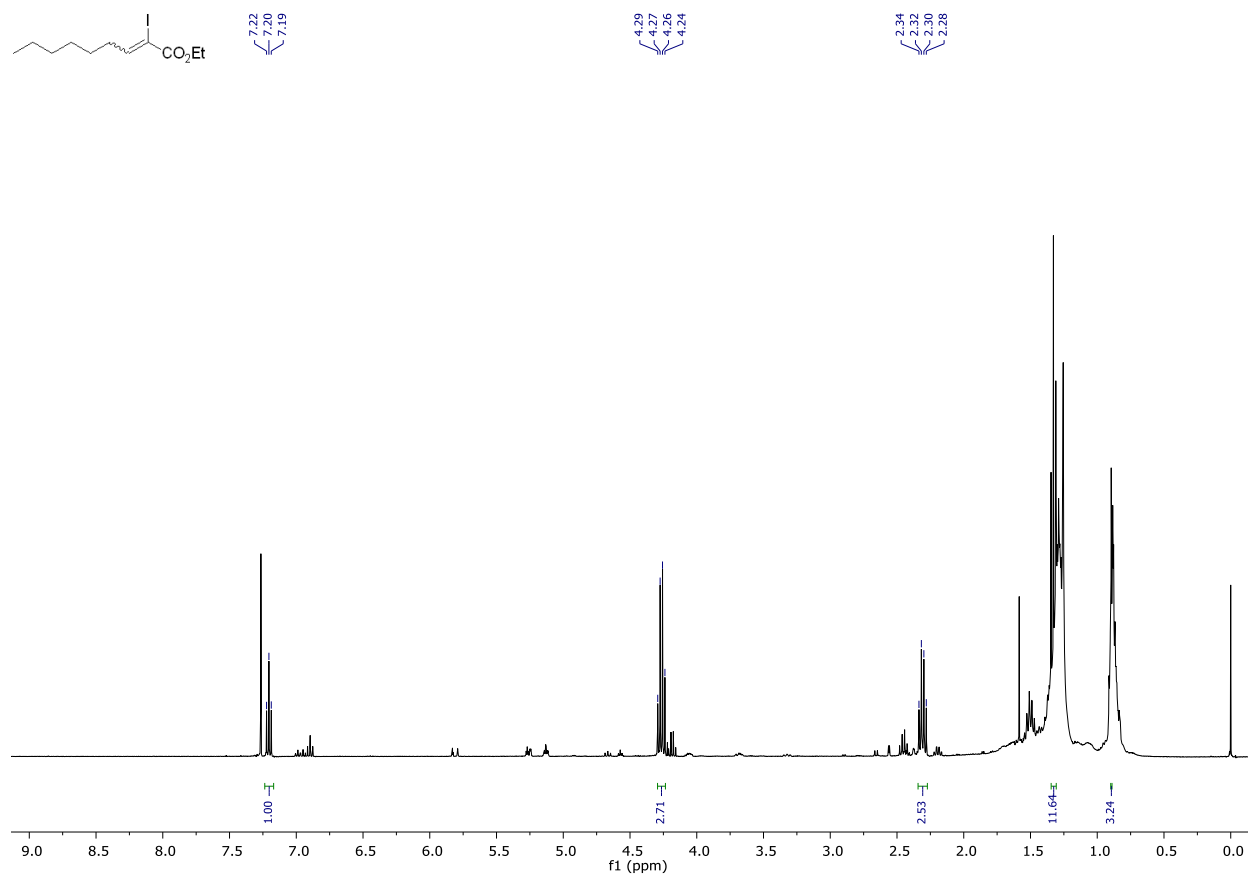
Figure 32: Ethyl 2-iodo-2-nonenoate (**23**)—^{13}C NMR
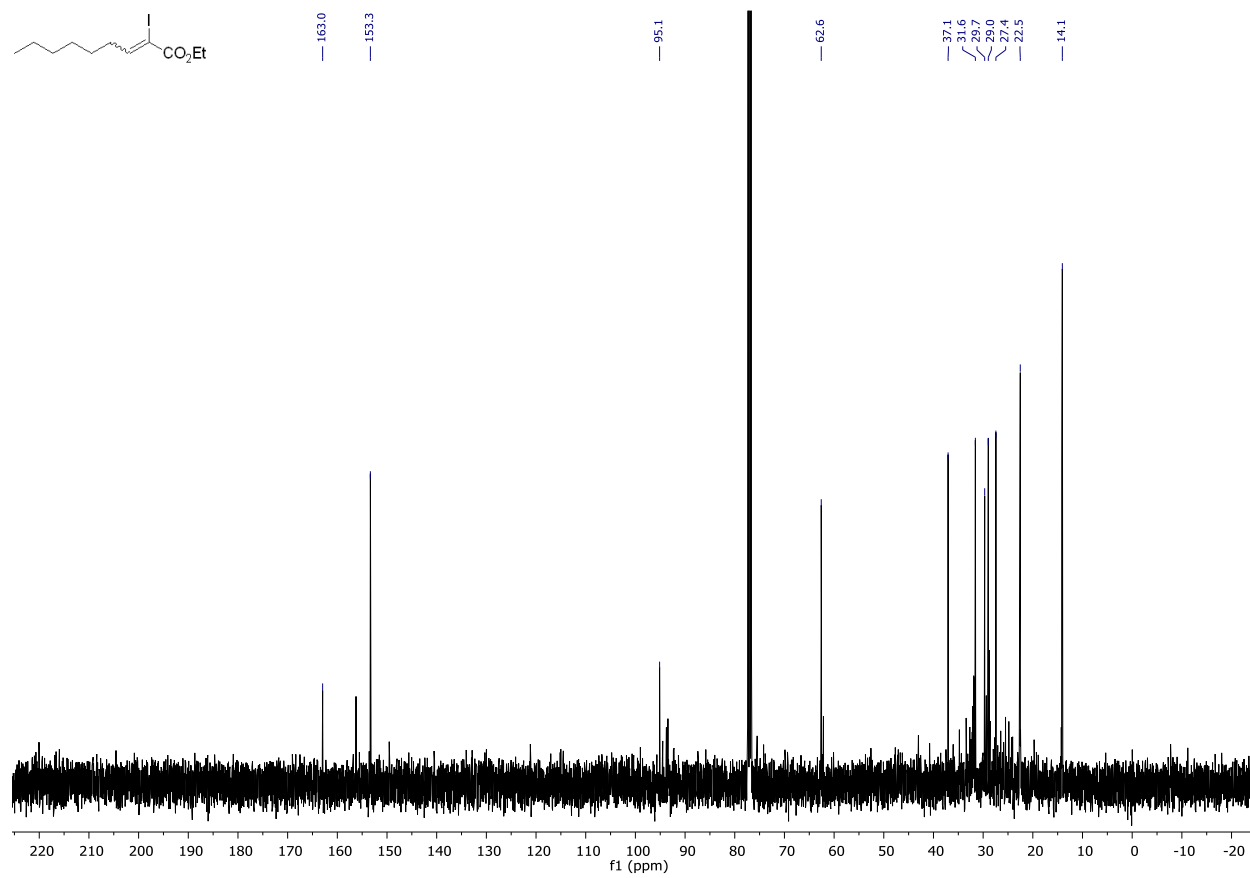
Figure 33: Ethyl 3-cyclohexyl-2-iodopropenoate (**24**)—¹H NMR
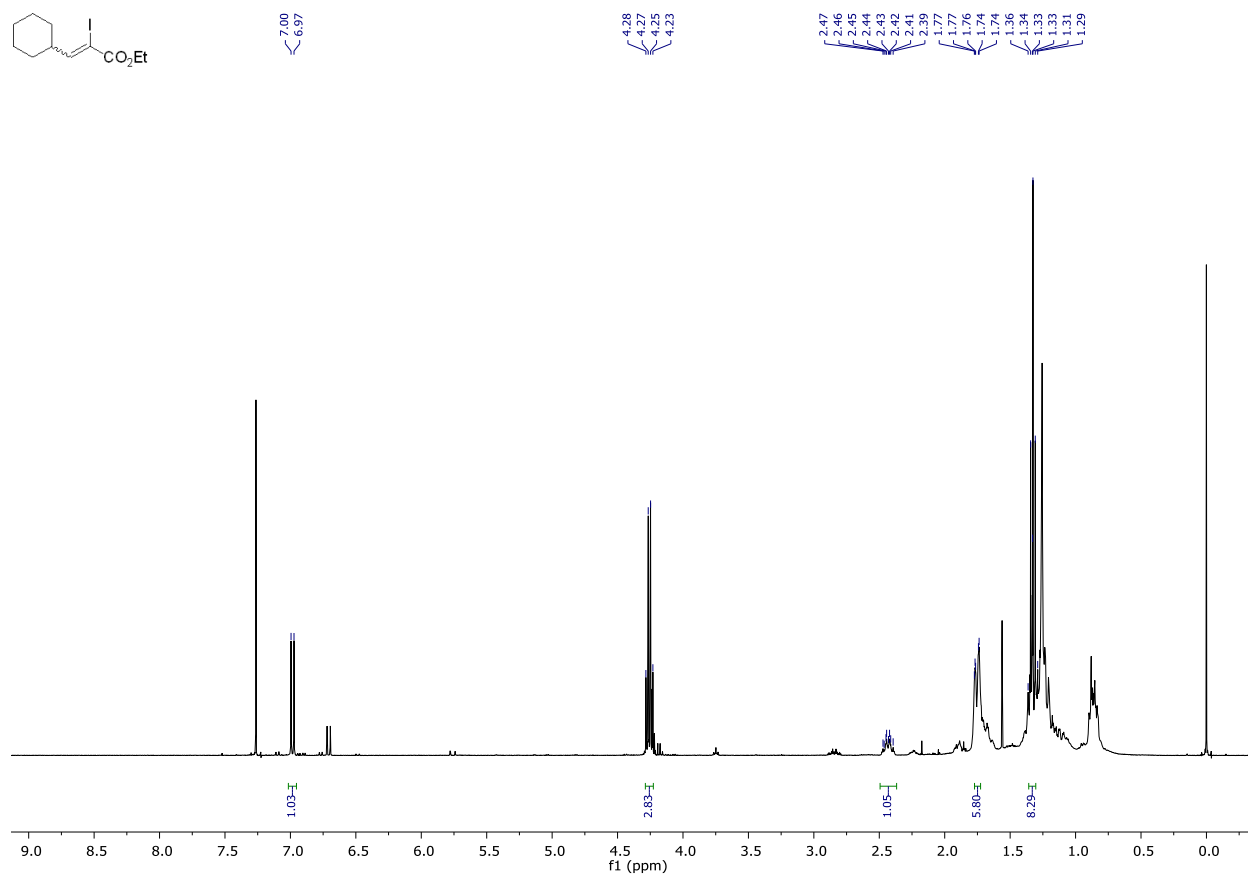
Figure 34: Ethyl 3-cyclohexyl-2-iodopropenoate (**24**)—^{13}C NMR
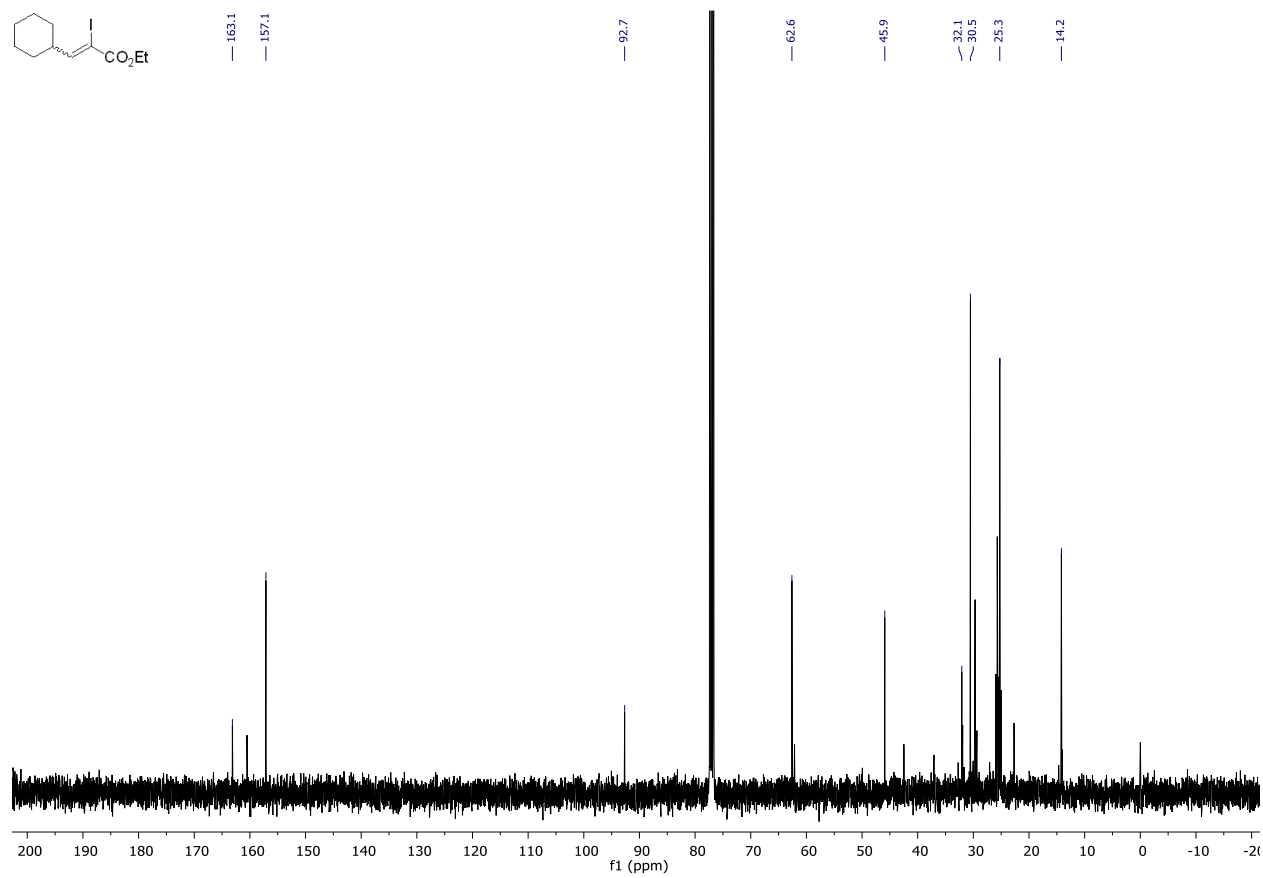
Figure 35: Ethyl 2-iodo-4-phenylpentenoate (**25**)—^{1}H NMR
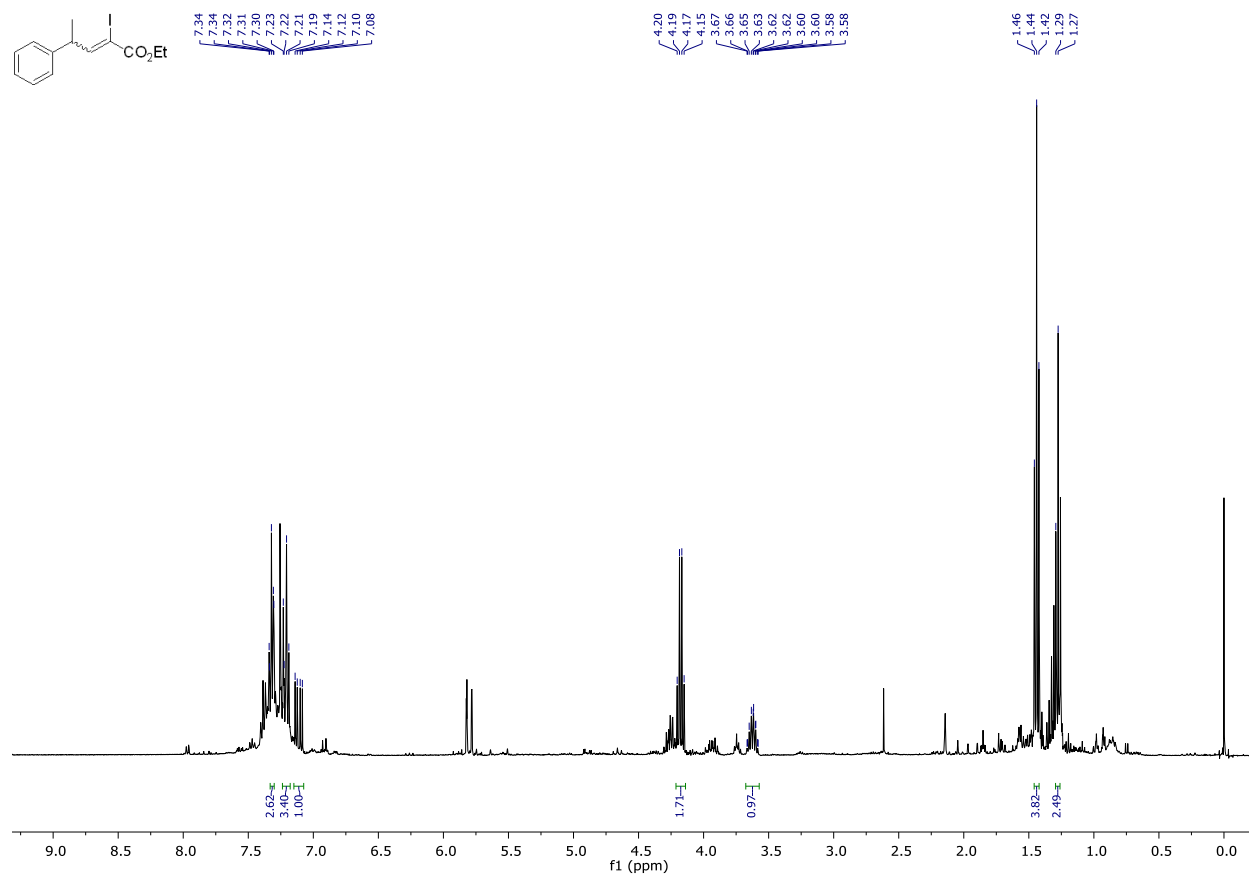
Figure 36: Ethyl 2-iodo-4-phenylpentenoate (**25**)—^{13}C NMR
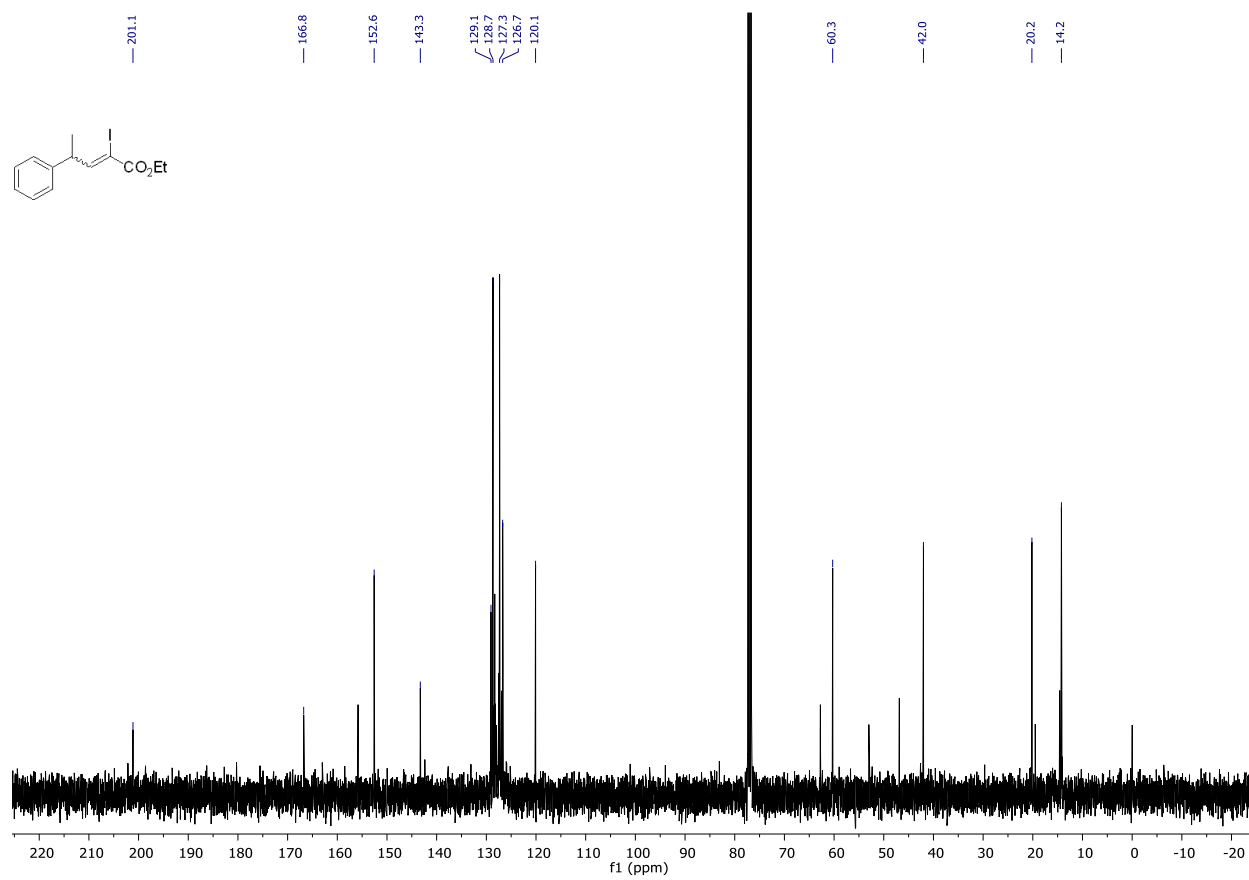
Figure 37: Methyl 2-(2-nitrophenyl)-2-hexenoate (**27**)—^{1}H NMR
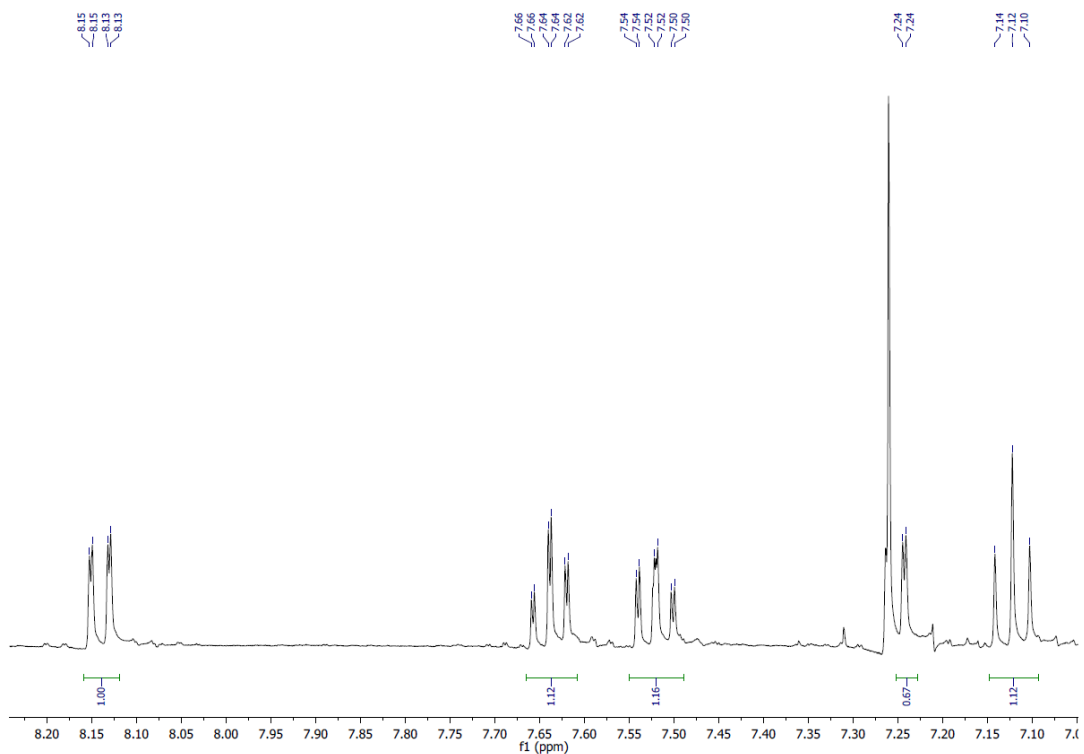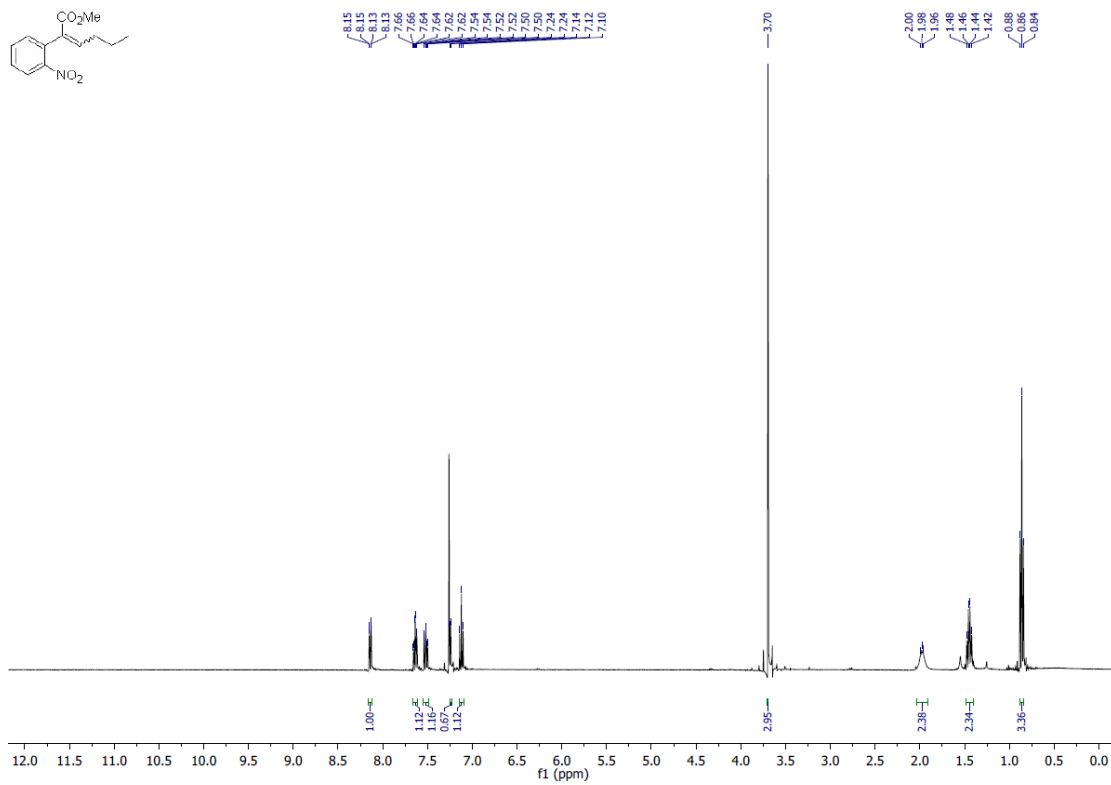
Figure 38: Methyl 2-(2-nitrophenyl)-2-hexenoate (**27**)—^{13}C NMR
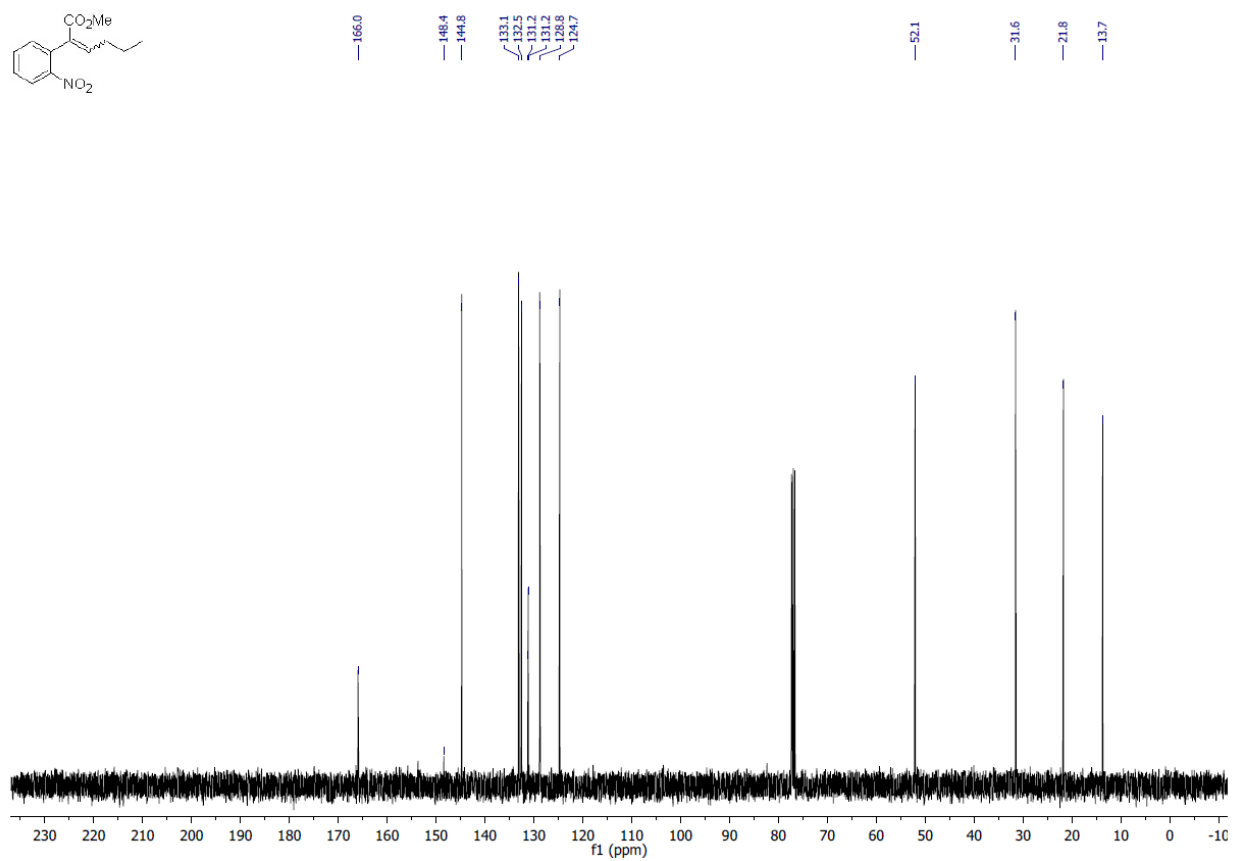
Figure 39: Methyl 2-(6-methoxy-2-nitrophenyl)-2-butenoate (**29**)—^{1}H NMR
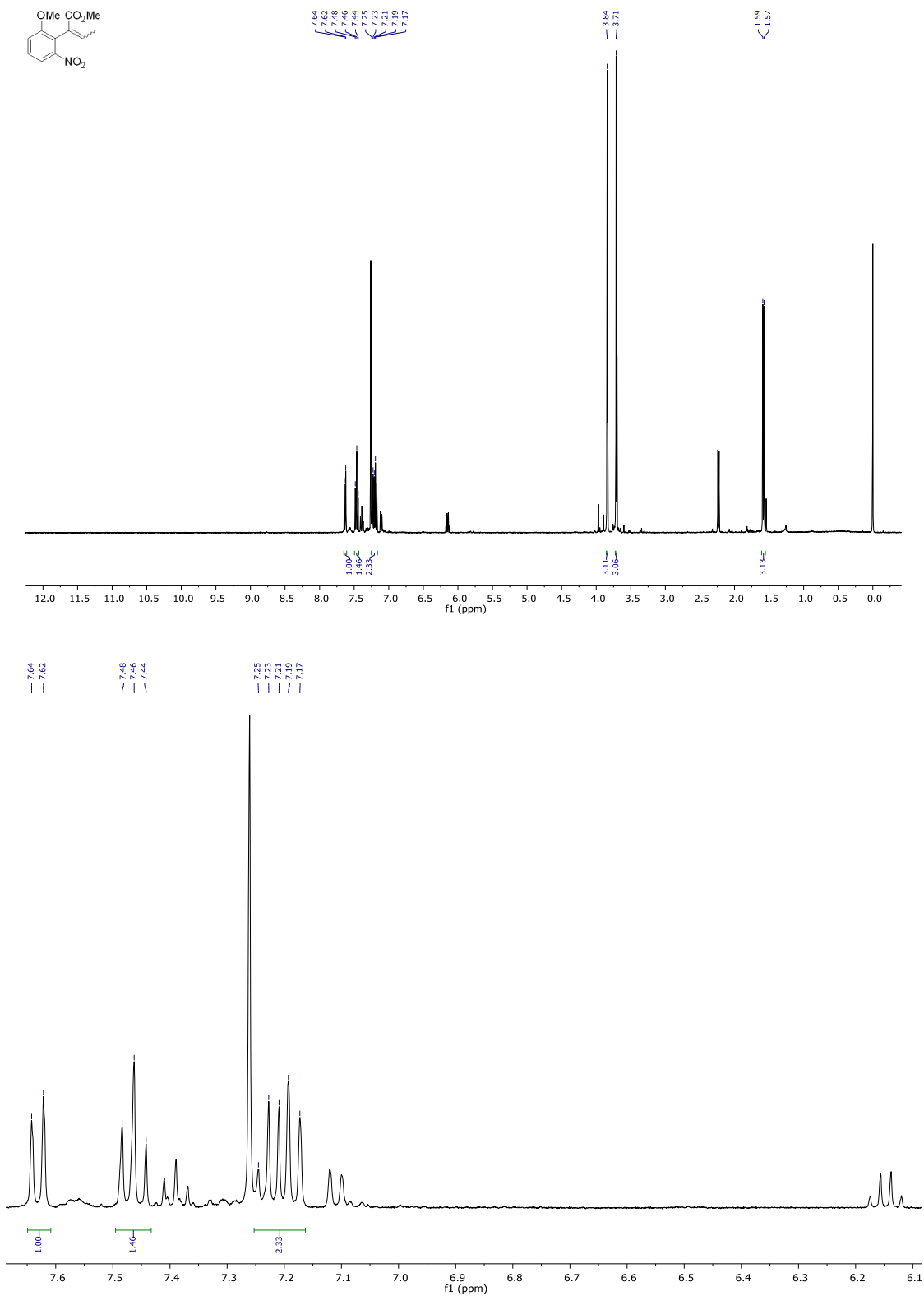
Figure 40: Methyl 2-(6-methoxy-2-nitrophenyl)-2-butenoate (**29**)—^{13}C NMR
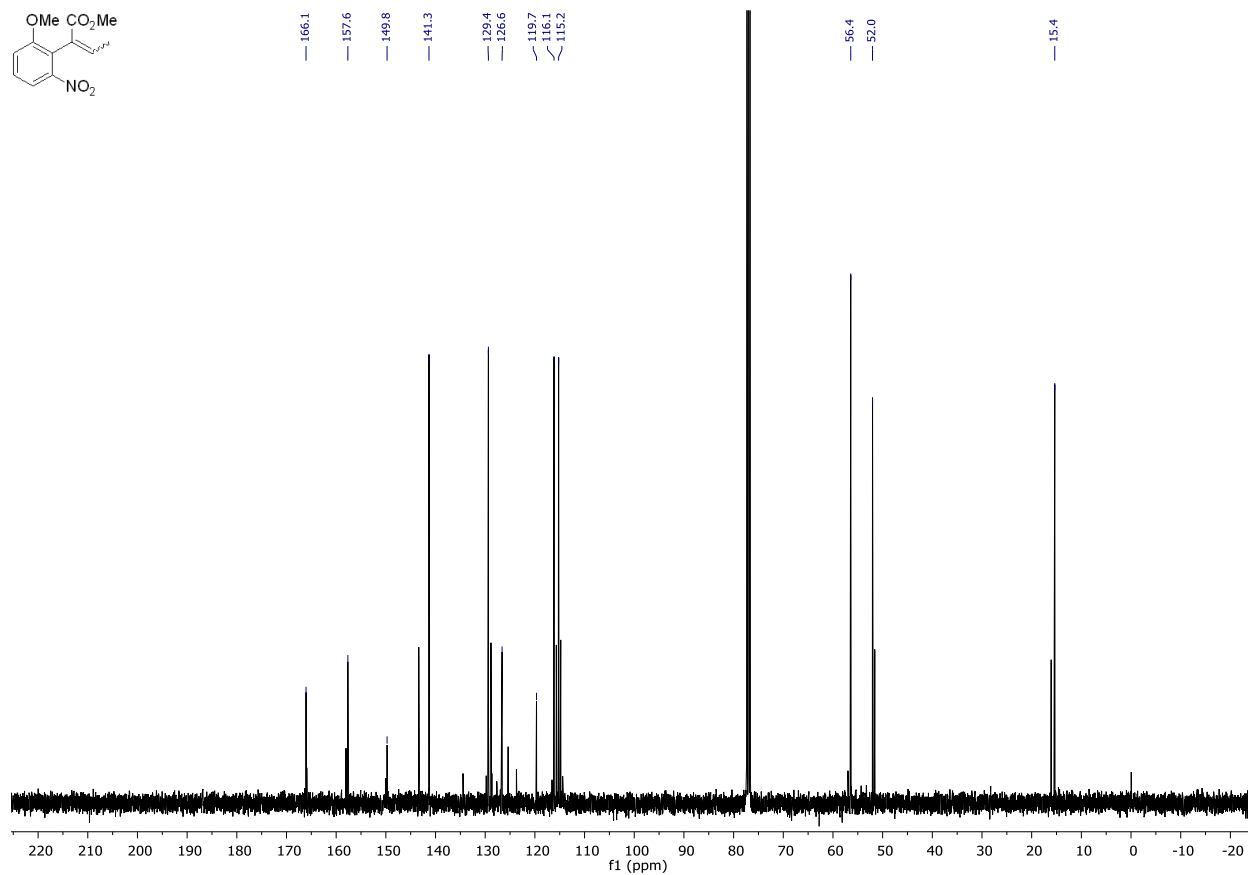
Figure 41: Methyl 2-(5-methoxy-2-nitrophenyl)-2-butenoate (**30**)—¹H NMR
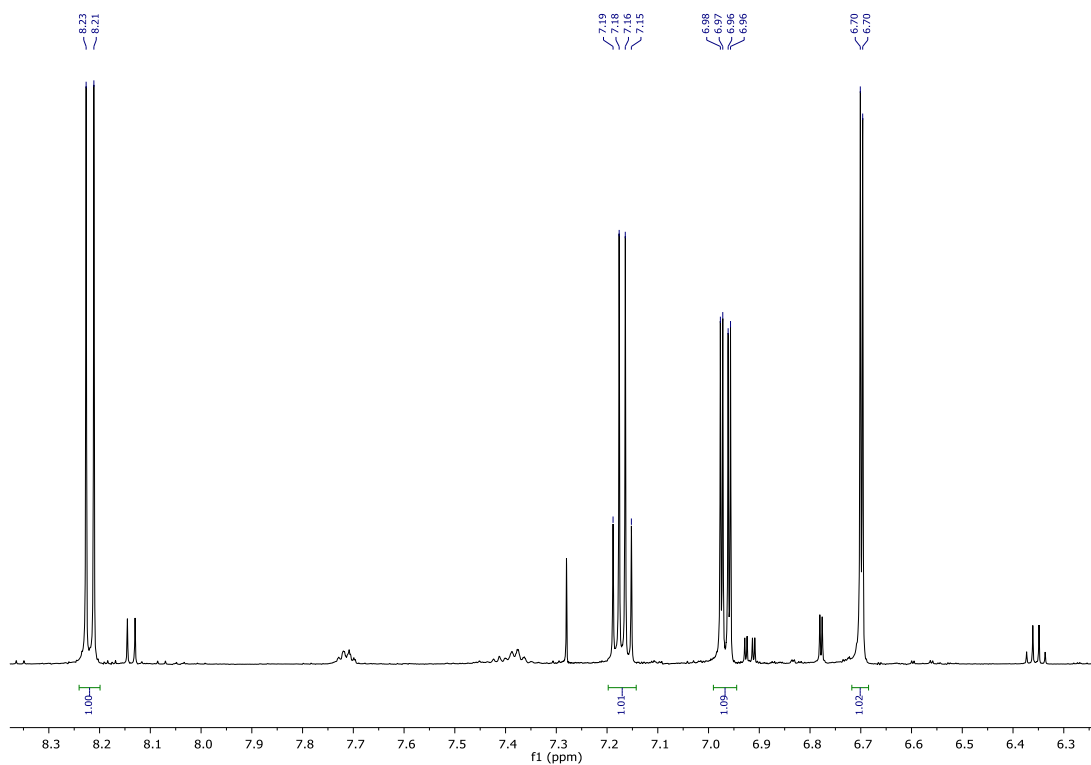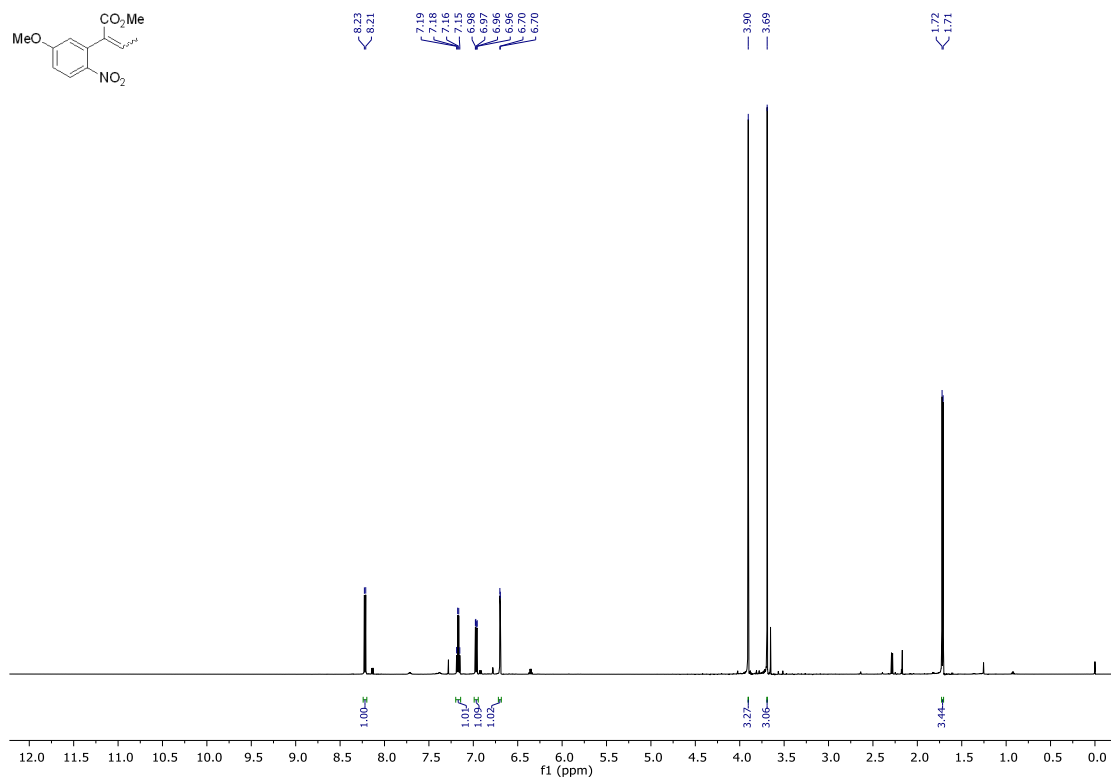
Figure 42: Methyl 2-(5-methoxy-2-nitrophenyl)-2-butenoate (**30**)—^{13}C NMR
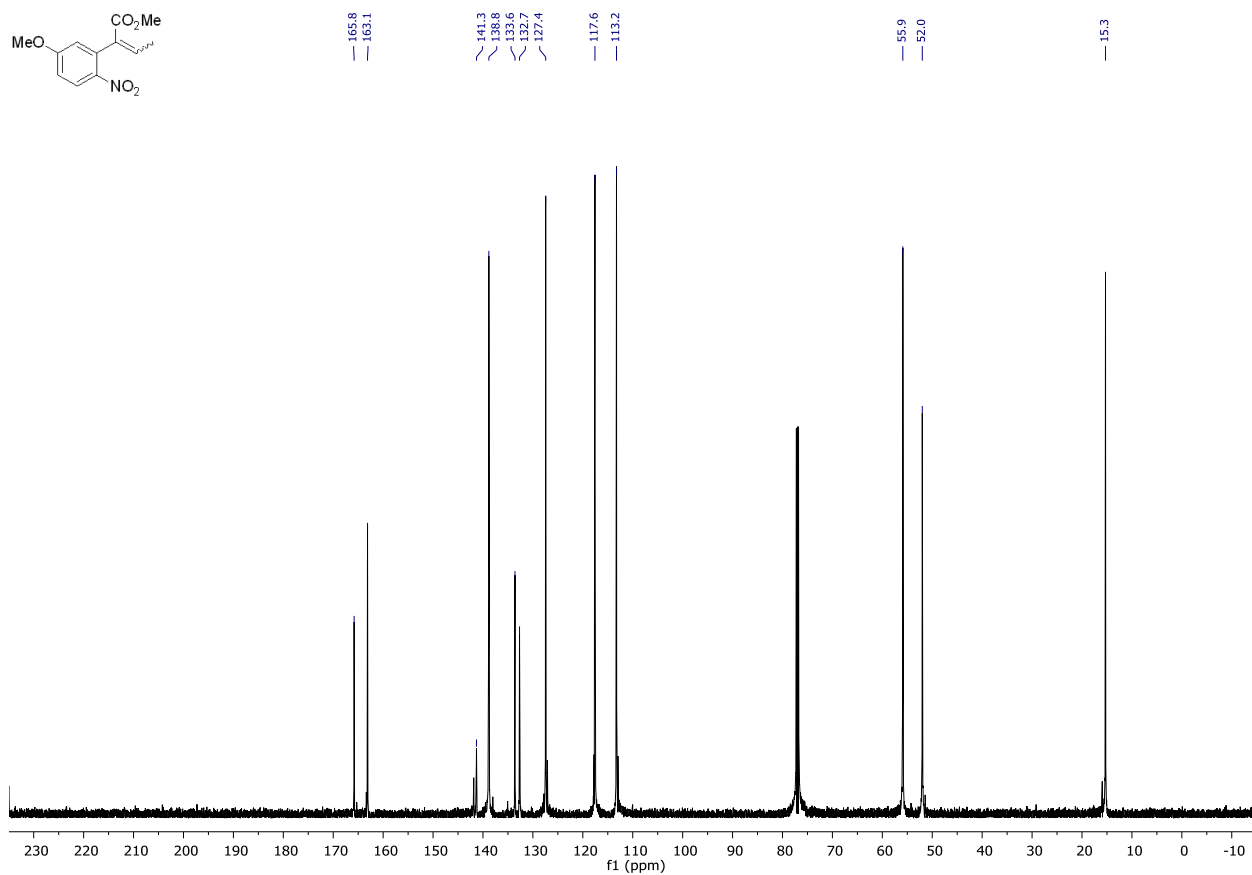
Figure 43: Methyl 2-(4-methoxy-2-nitrophenyl)-2-butenoate (**31**)—^{1}H NMR
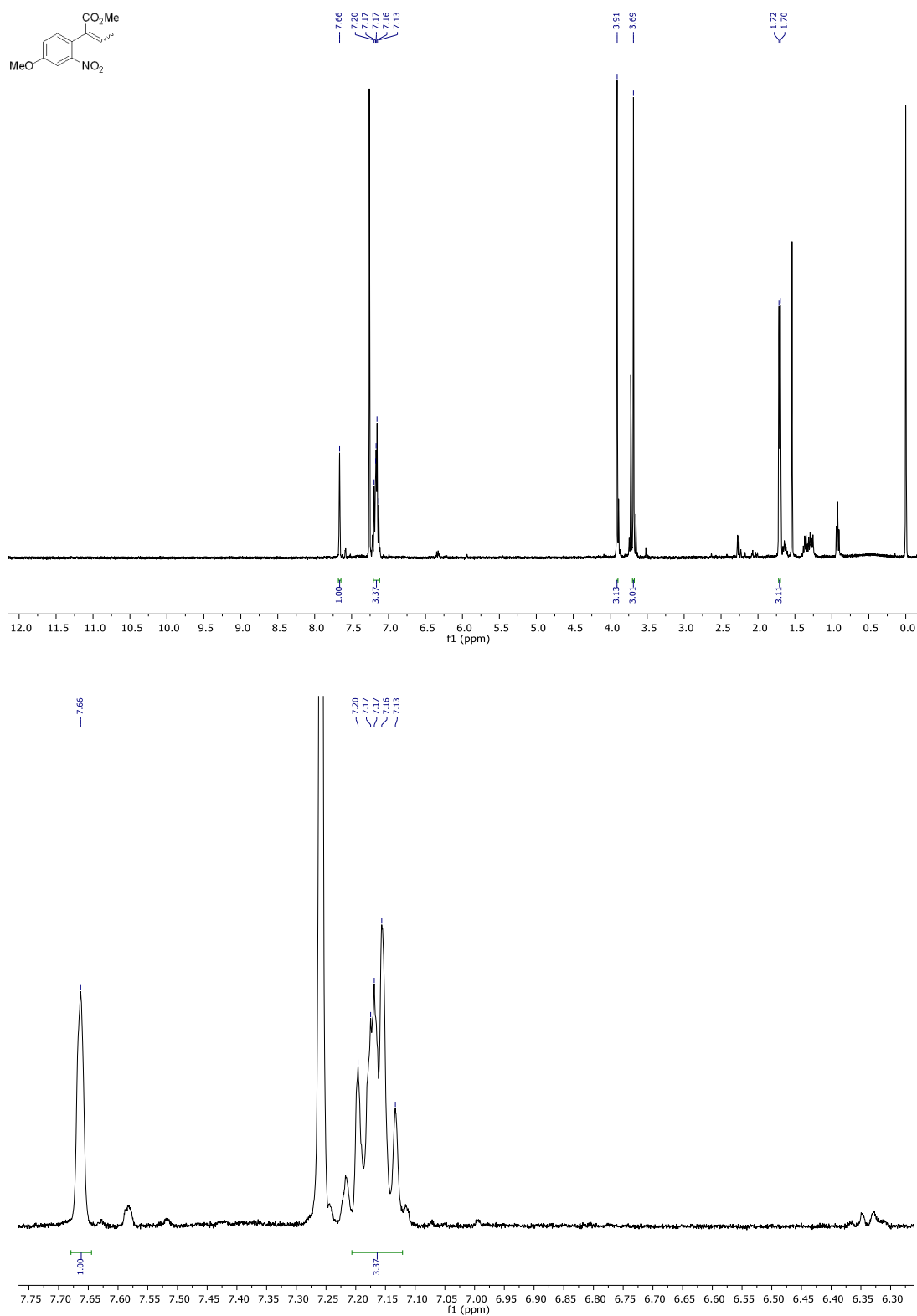
Figure 44: Methyl 2-(4-methoxy-2-nitrophenyl)-2-butenoate (**31**)—¹³C NMR
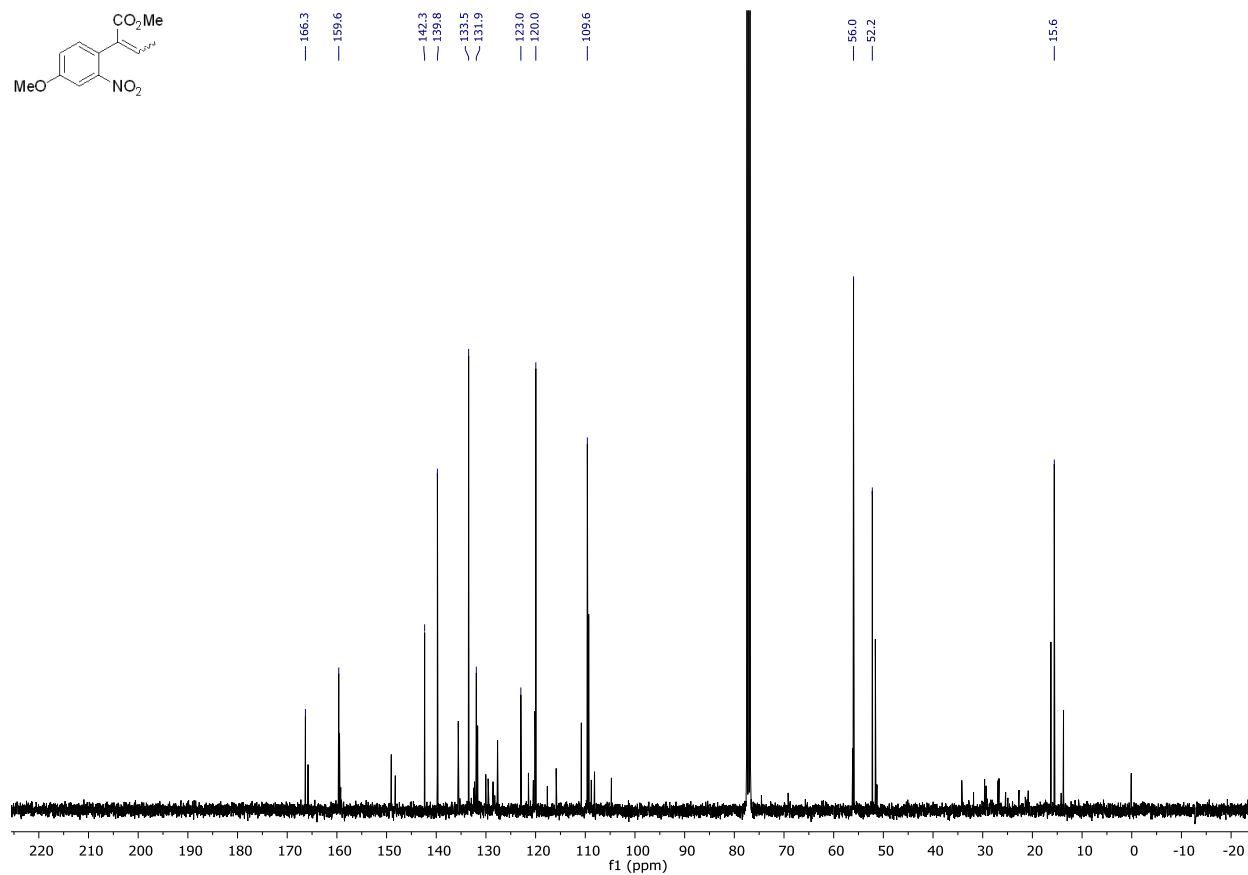
Figure 45: Methyl 2-(3-methoxy-2-nitrophenyl)-2-butenoate (**32**)—^{1}H NMR
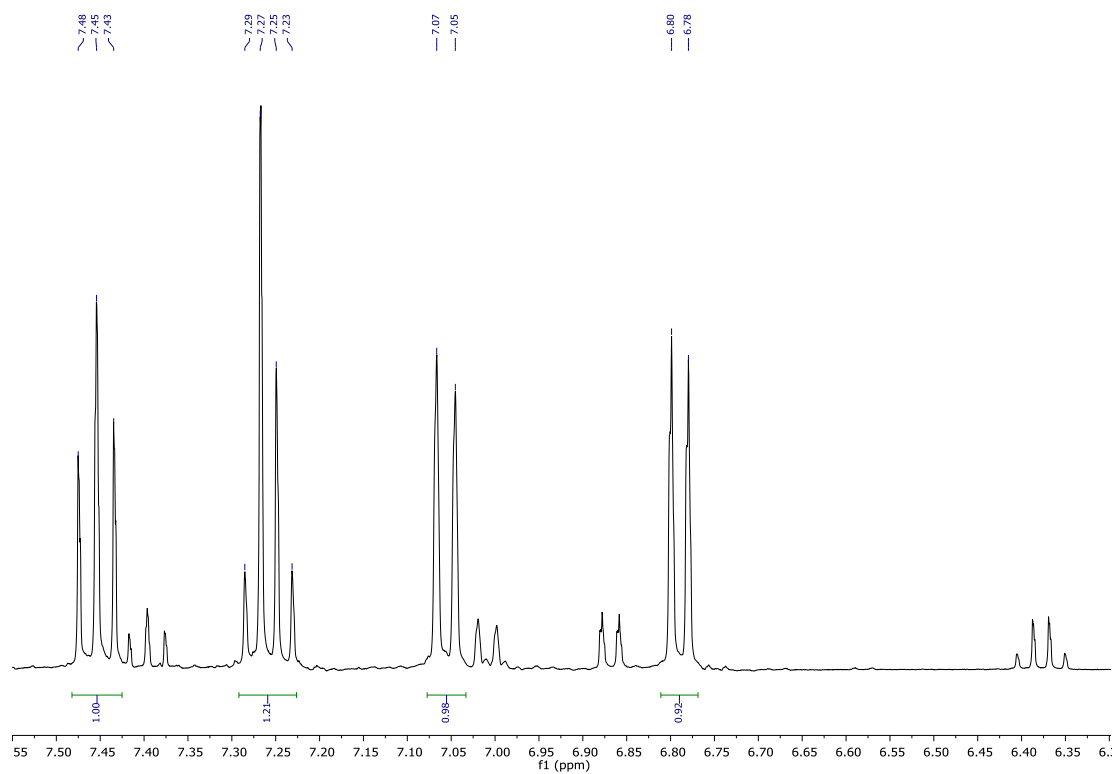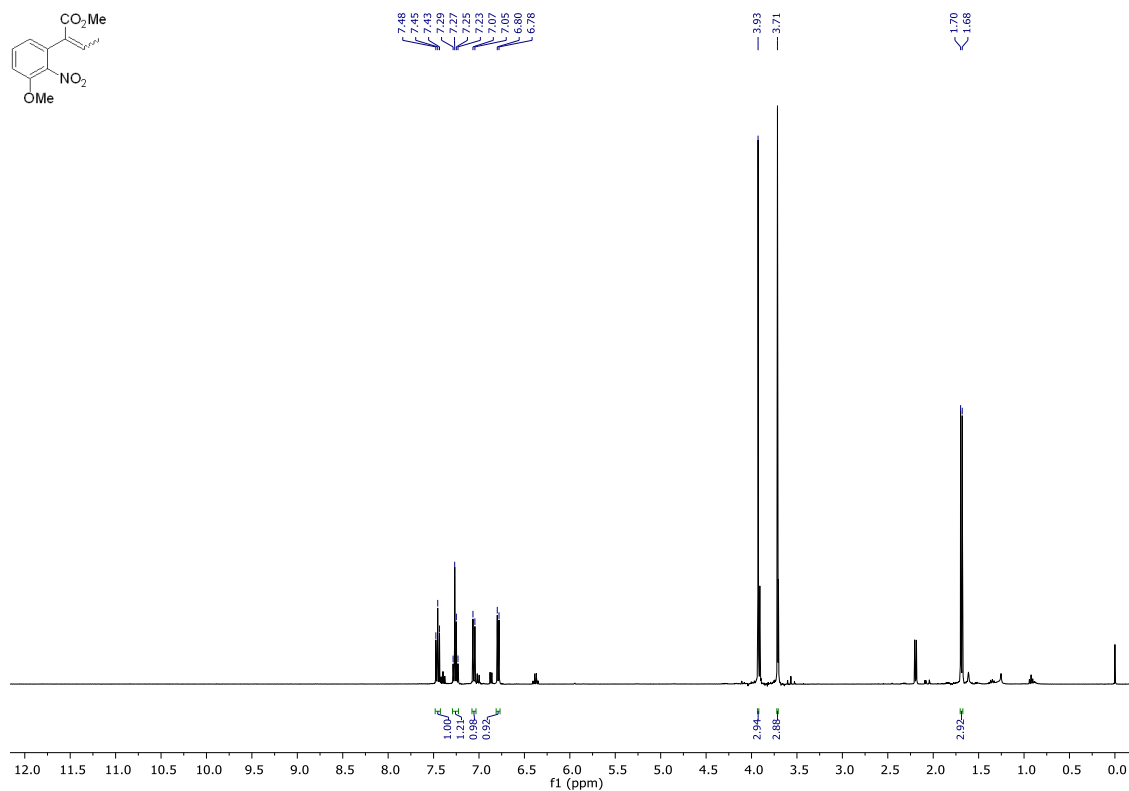
Figure 46: Methyl 2-(3-methoxy-2-nitrophenyl)-2-butenoate (**32**)—¹³C NMR
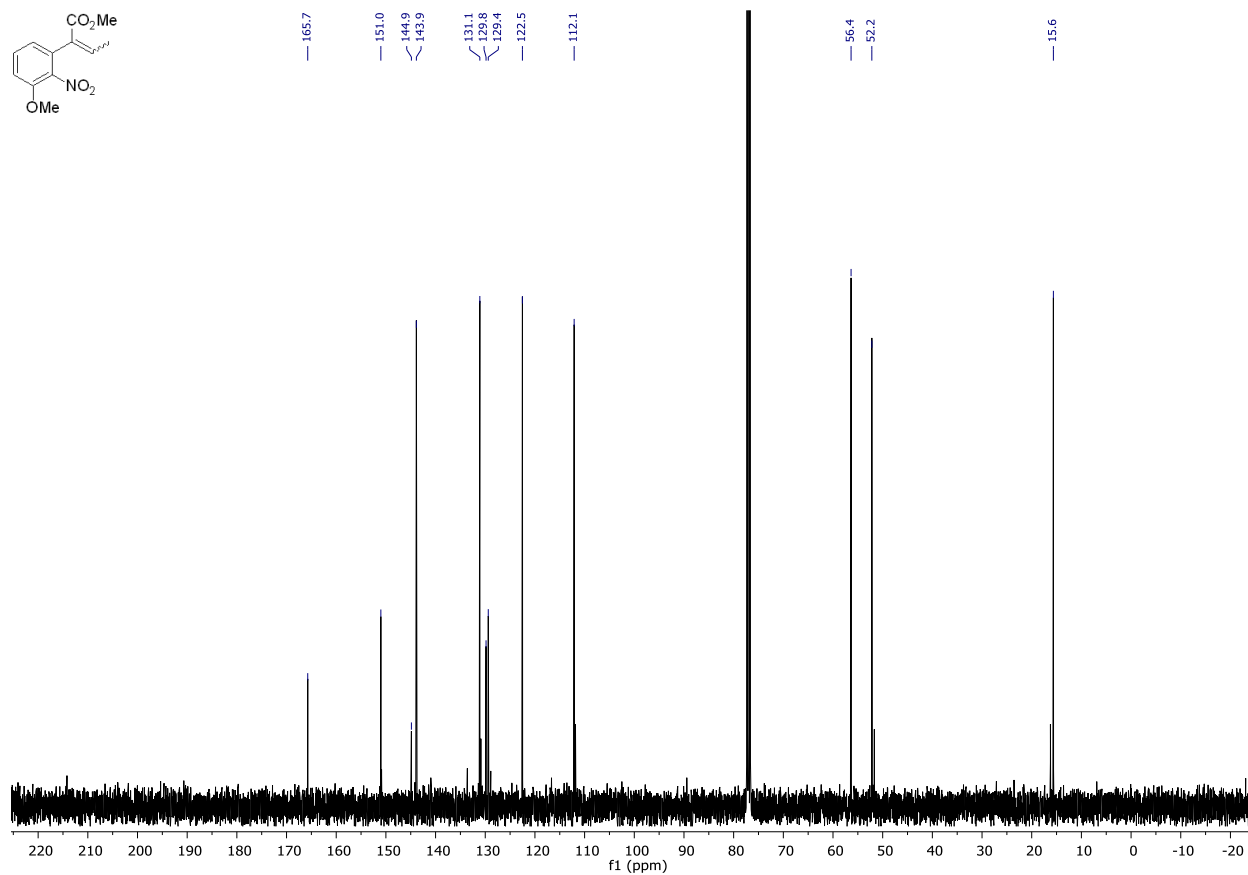
Figure 47: Methyl 2-(5-carbomethoxy-2-nitrophenyl)-2-butenoate (**33**)—^{1}H NMR
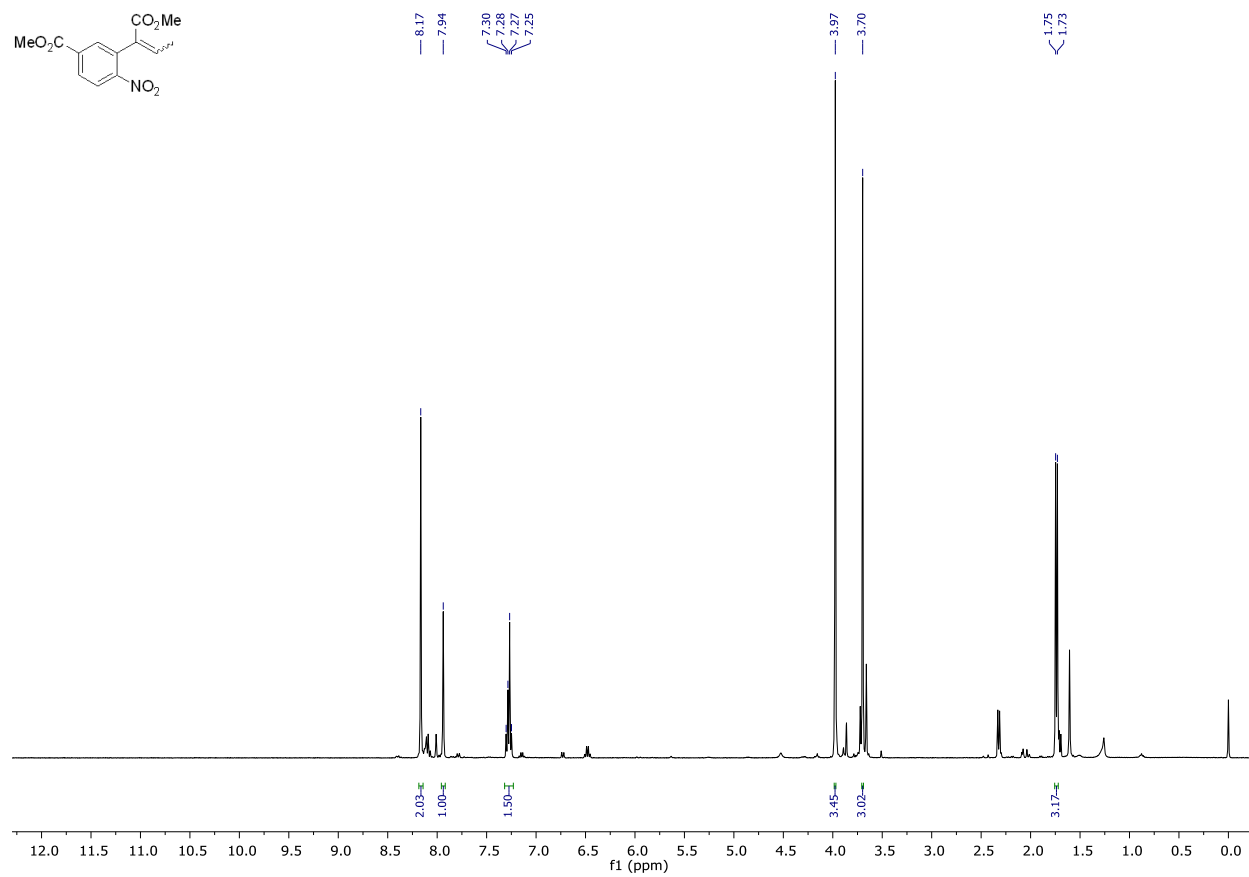
Figure 48: Methyl 2-(5-carbomethoxy-2-nitrophenyl)-2-butenoate (**33**)—^{13}C NMR
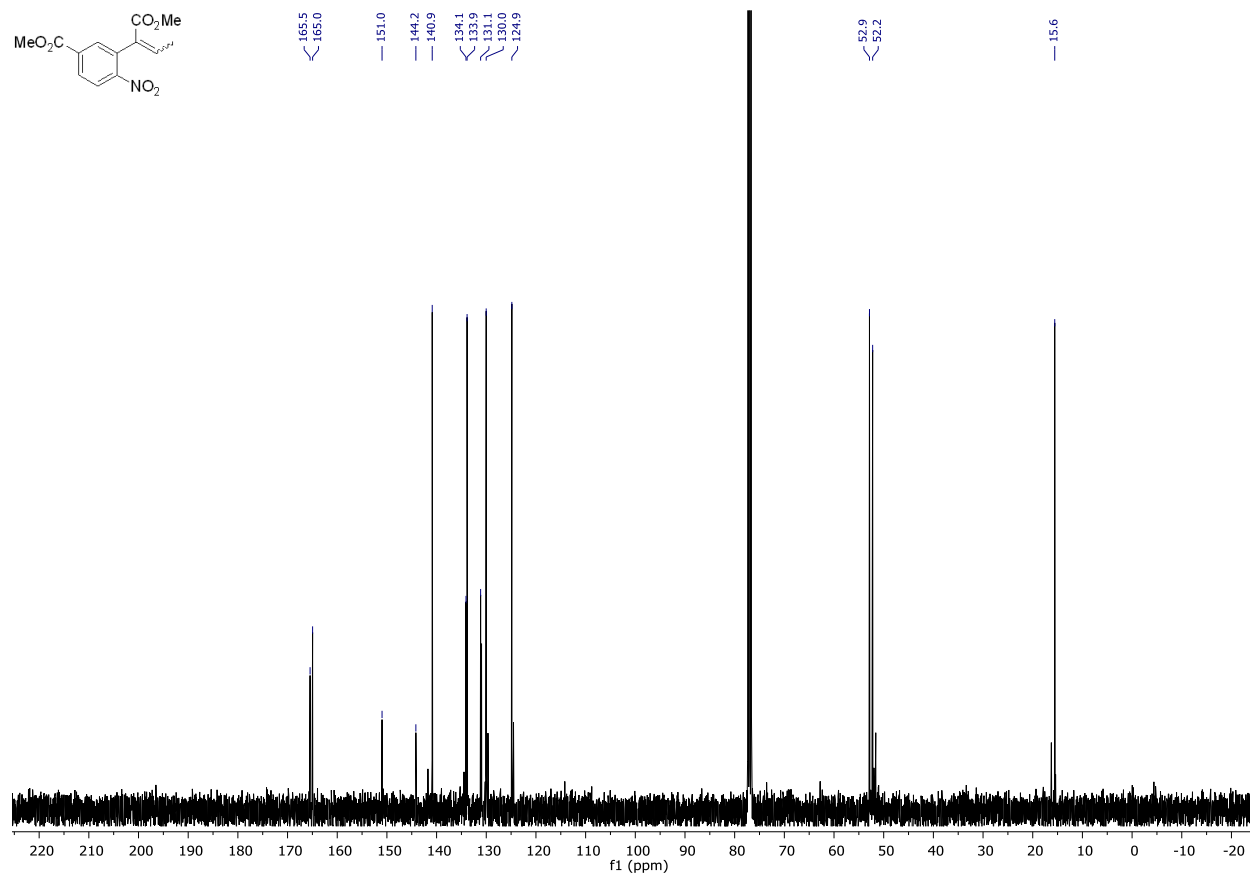
Figure 49: Methyl 2-(4-carbomethoxy-2-nitrophenyl)-2-butenoate (**34**)—¹H NMR
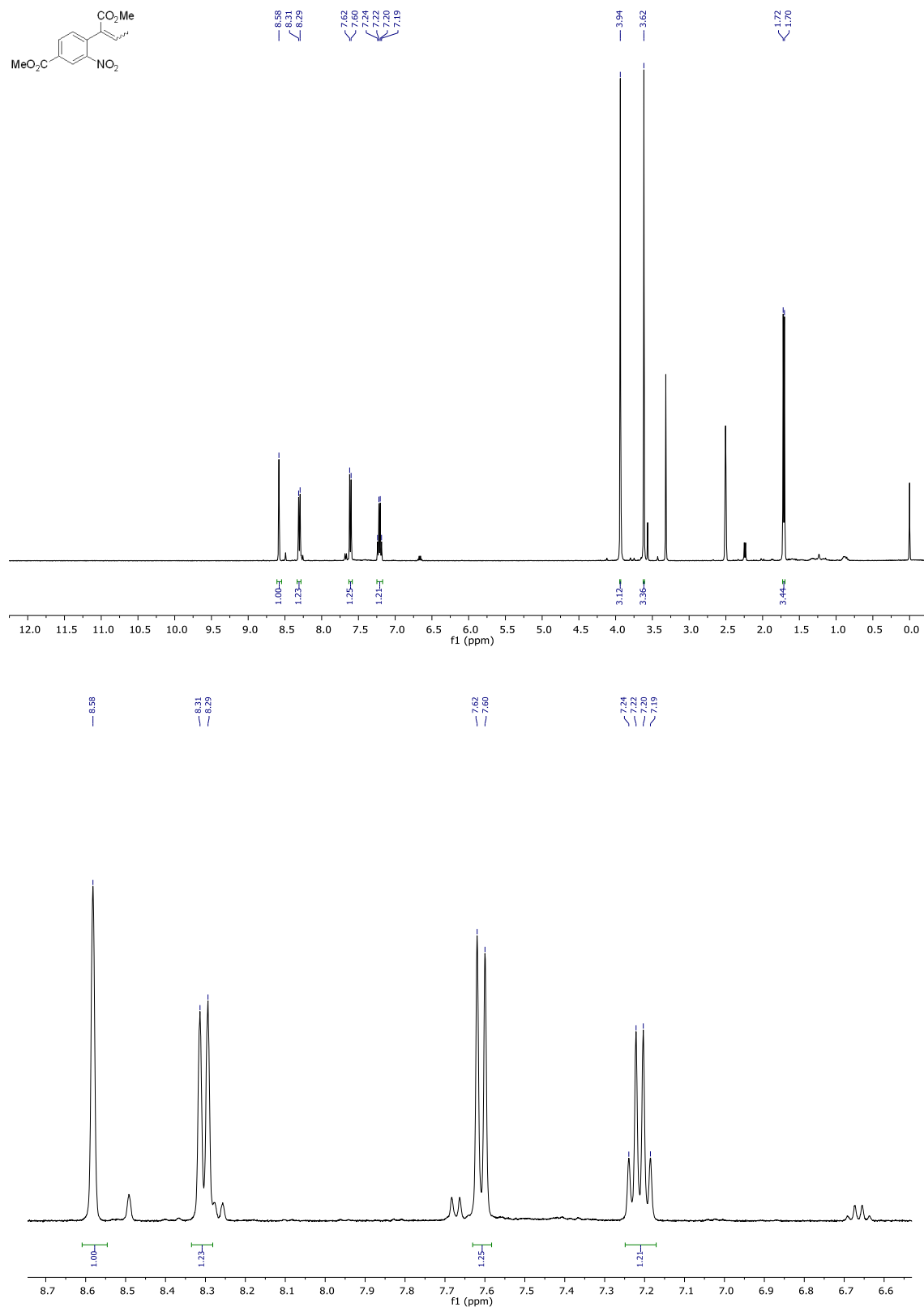
Figure 50: Methyl 2-(4-carbomethoxy-2-nitrophenyl)-2-butenoate (**34**)—¹³C NMR
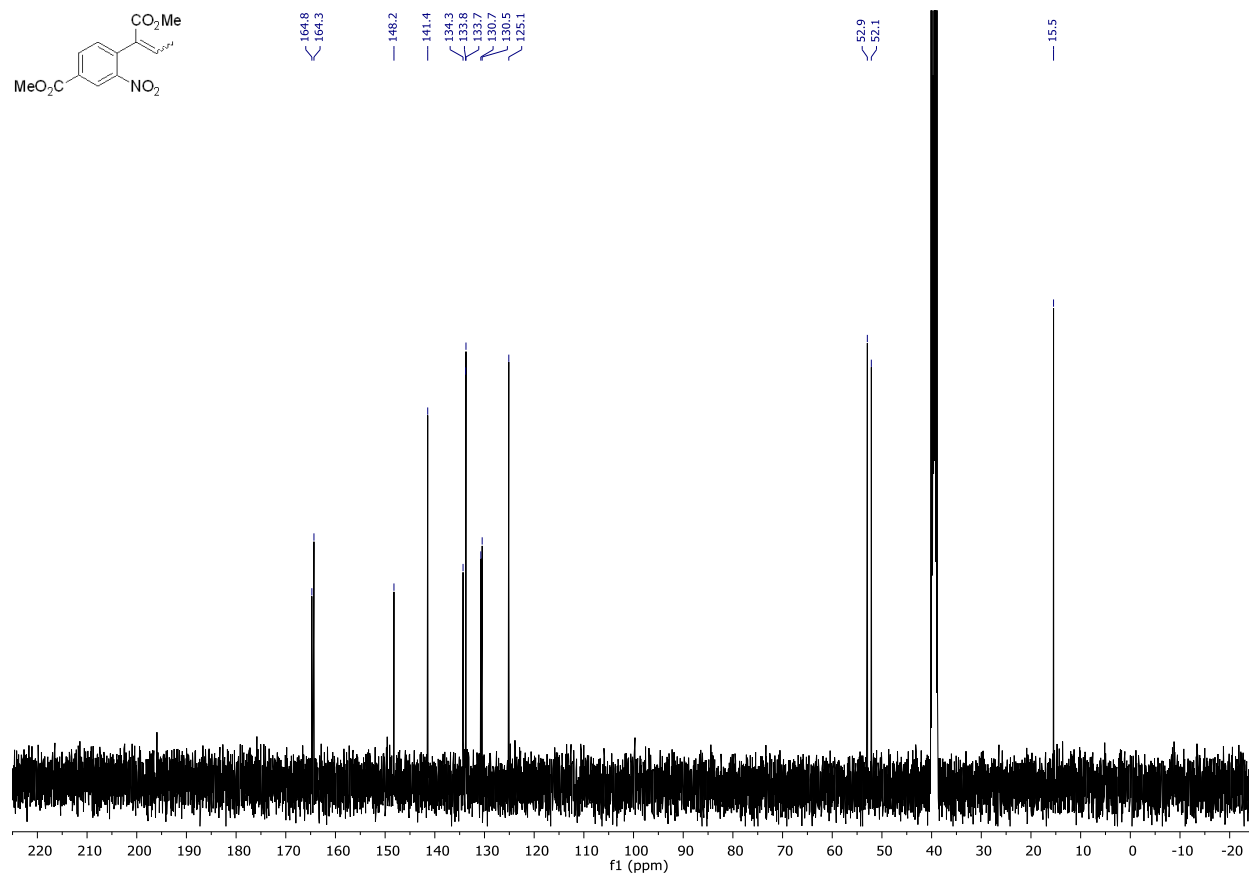
Figure 51: Methyl 1-hydroxy-5-methoxyindole-3-carboxylate (**35**)—¹H NMR
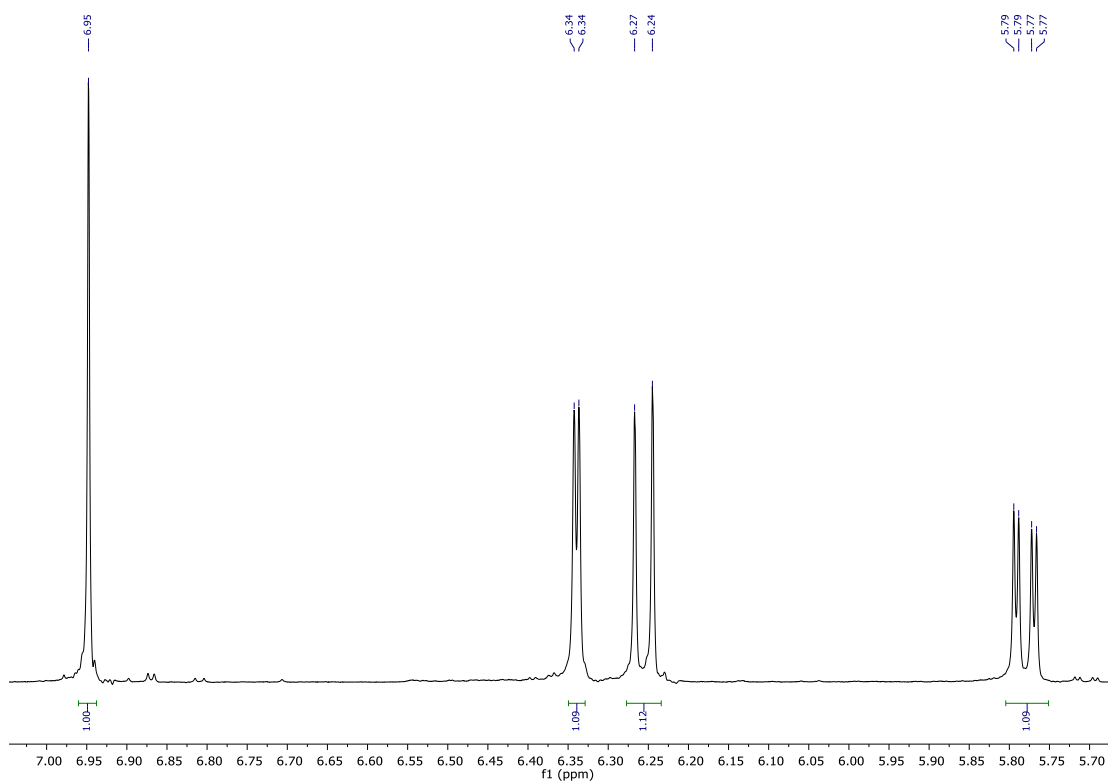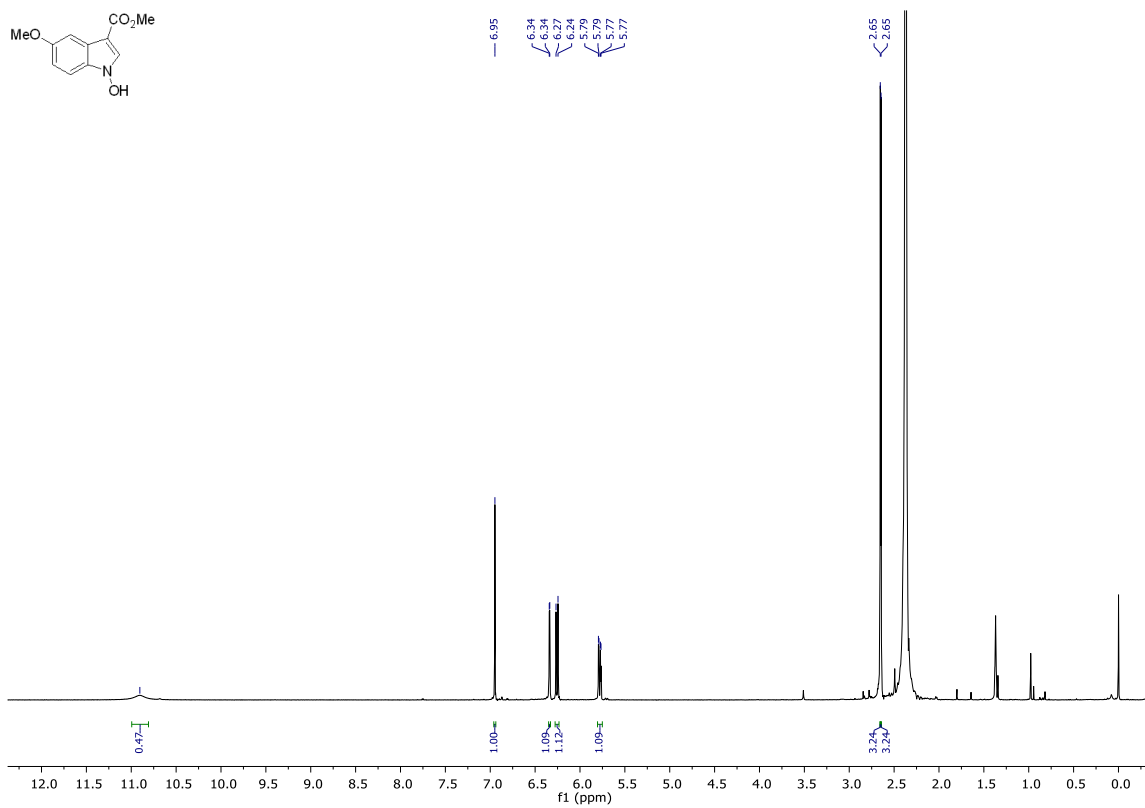
Figure 52: Methyl 1-hydroxy-5-methoxyindole-3-carboxylate (**35**)—^{13}C NMR
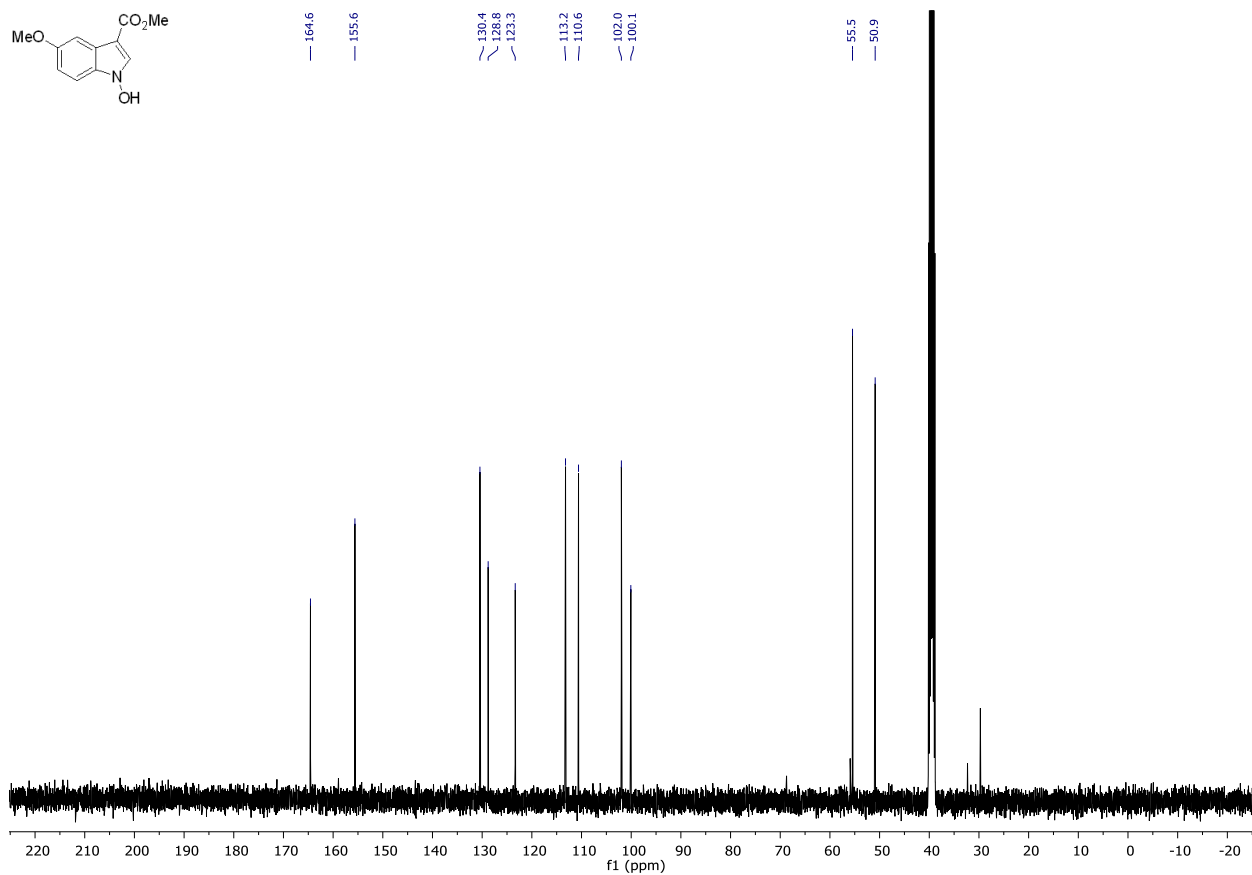
Figure 53: Methyl 1,5-dimethoxyindole-3-carboxylate (**36**)—¹H NMR
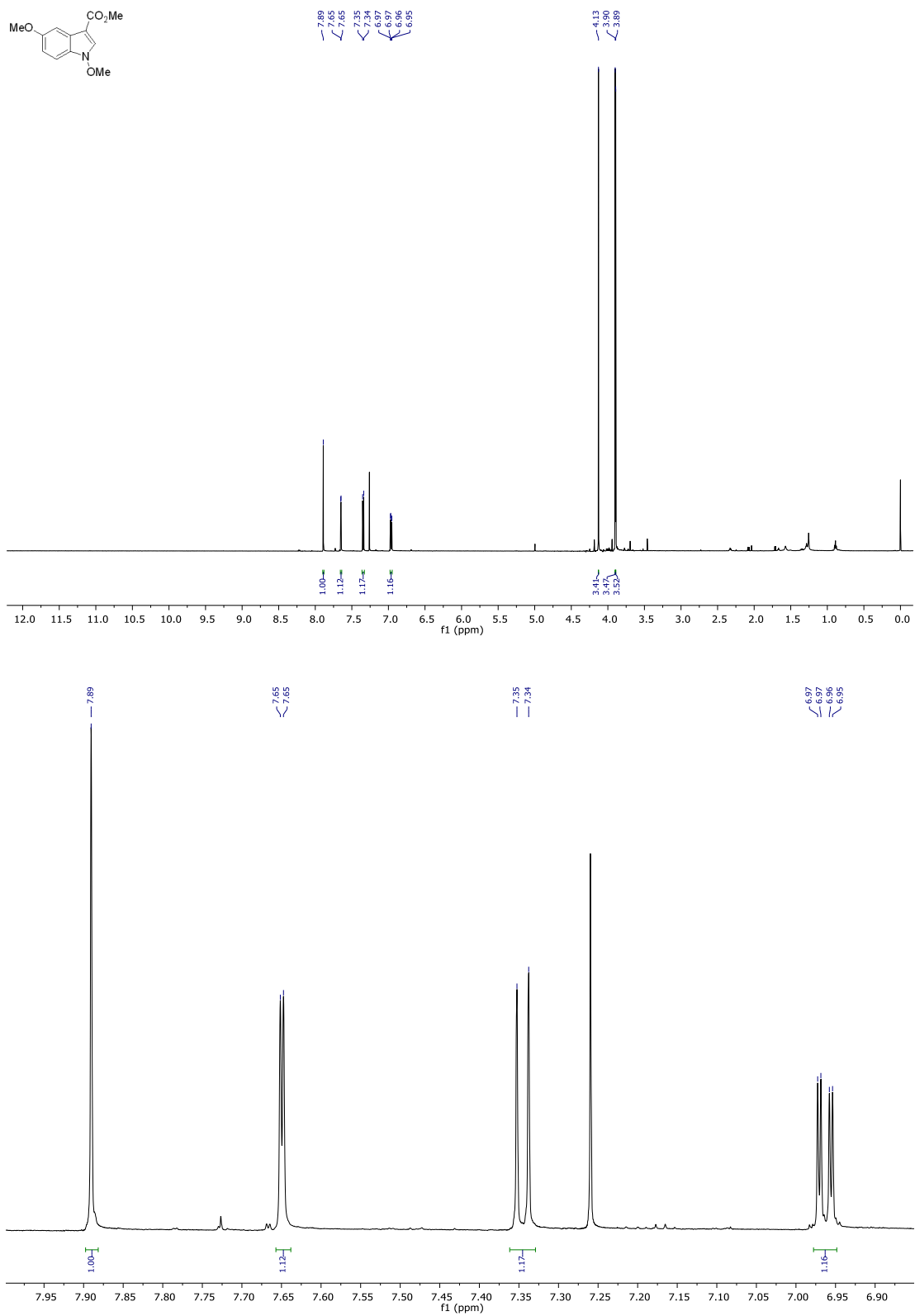
Figure 54: Methyl 1,5-dimethoxyindole-3-carboxylate (**36**)—^{13}C NMR
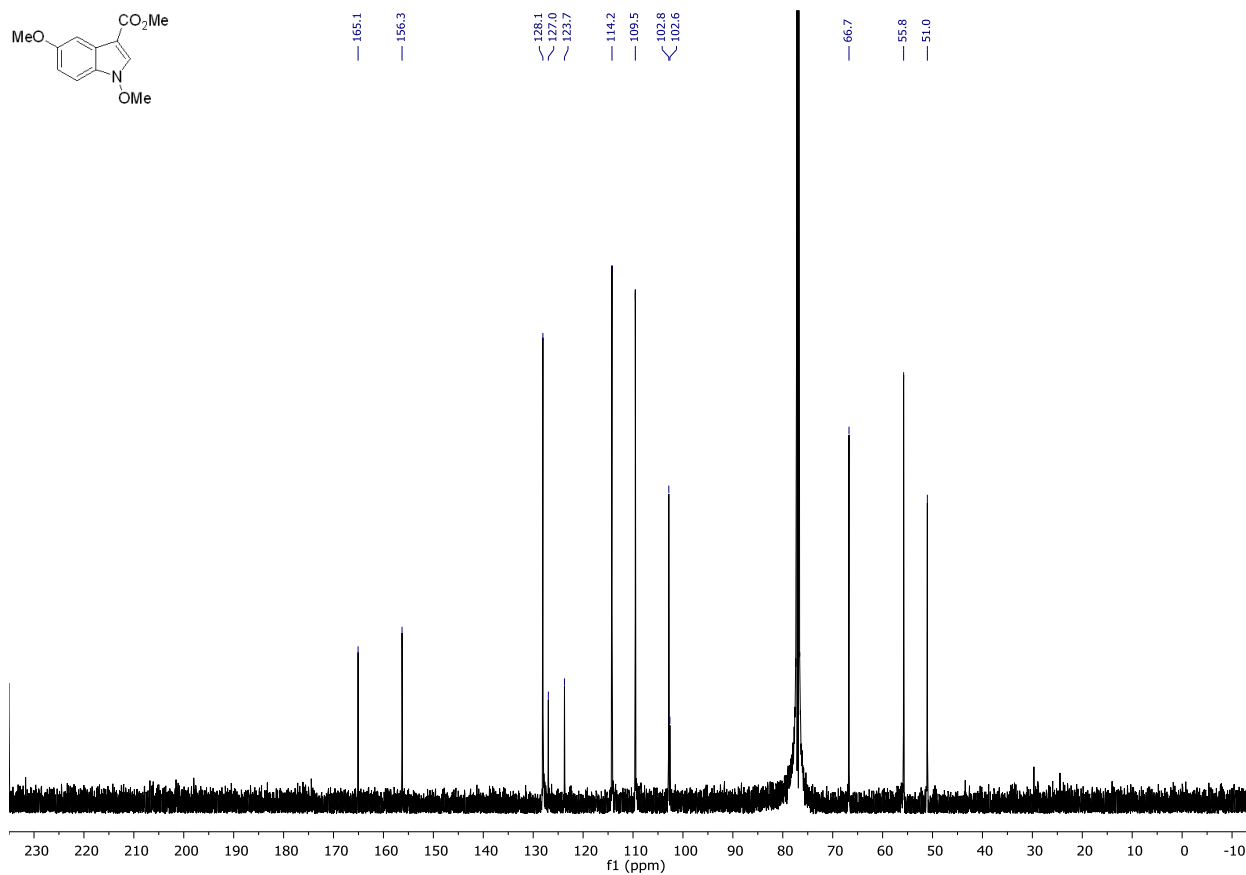
Figure 55: Methyl 1-hydroxy-6-methoxyindole-3-carboxylate (**37**)—^{1}H NMR
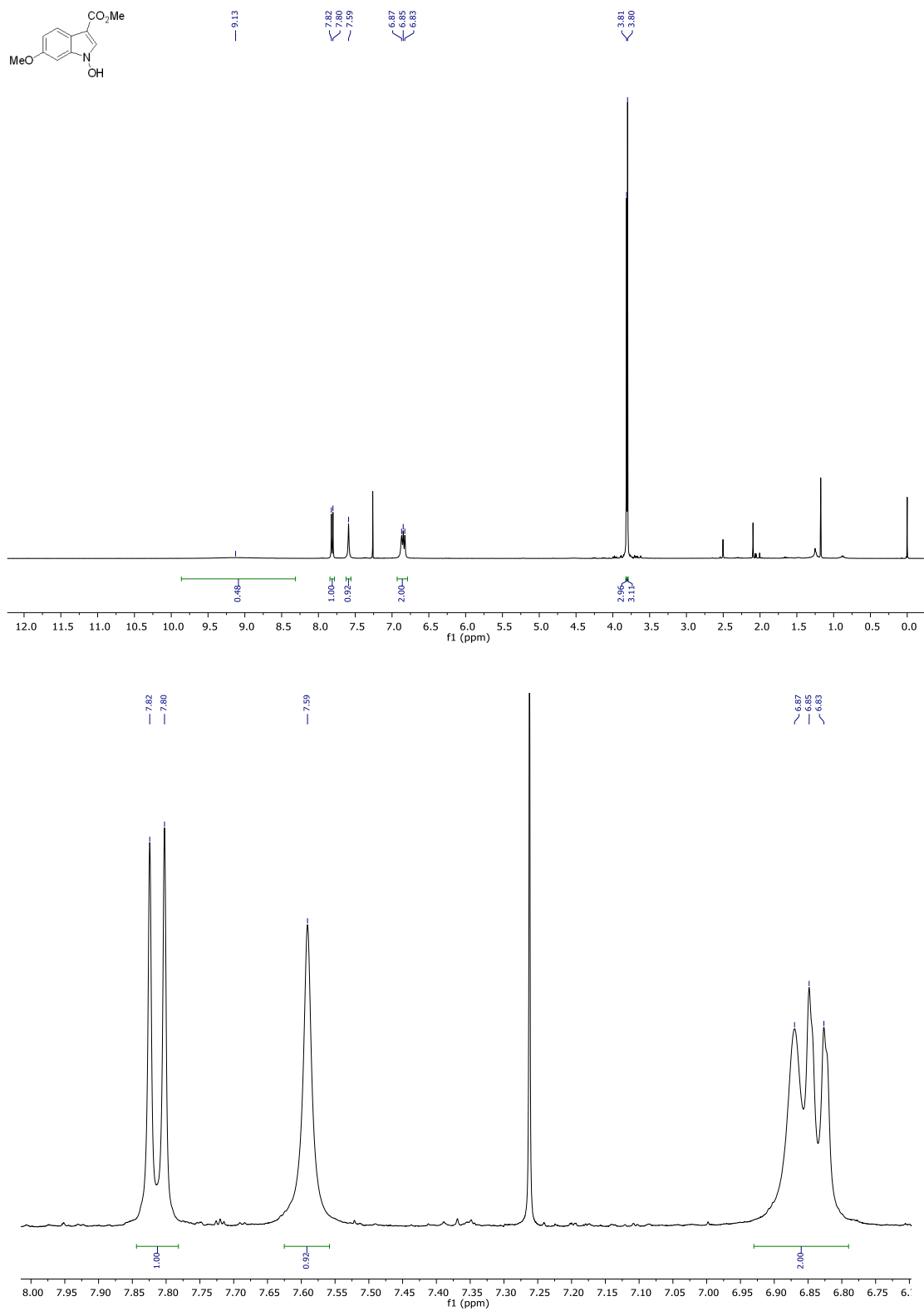
Figure 56: Methyl 1-hydroxy-6-methoxyindole-3-carboxylate (**37**)—^{13}C NMR
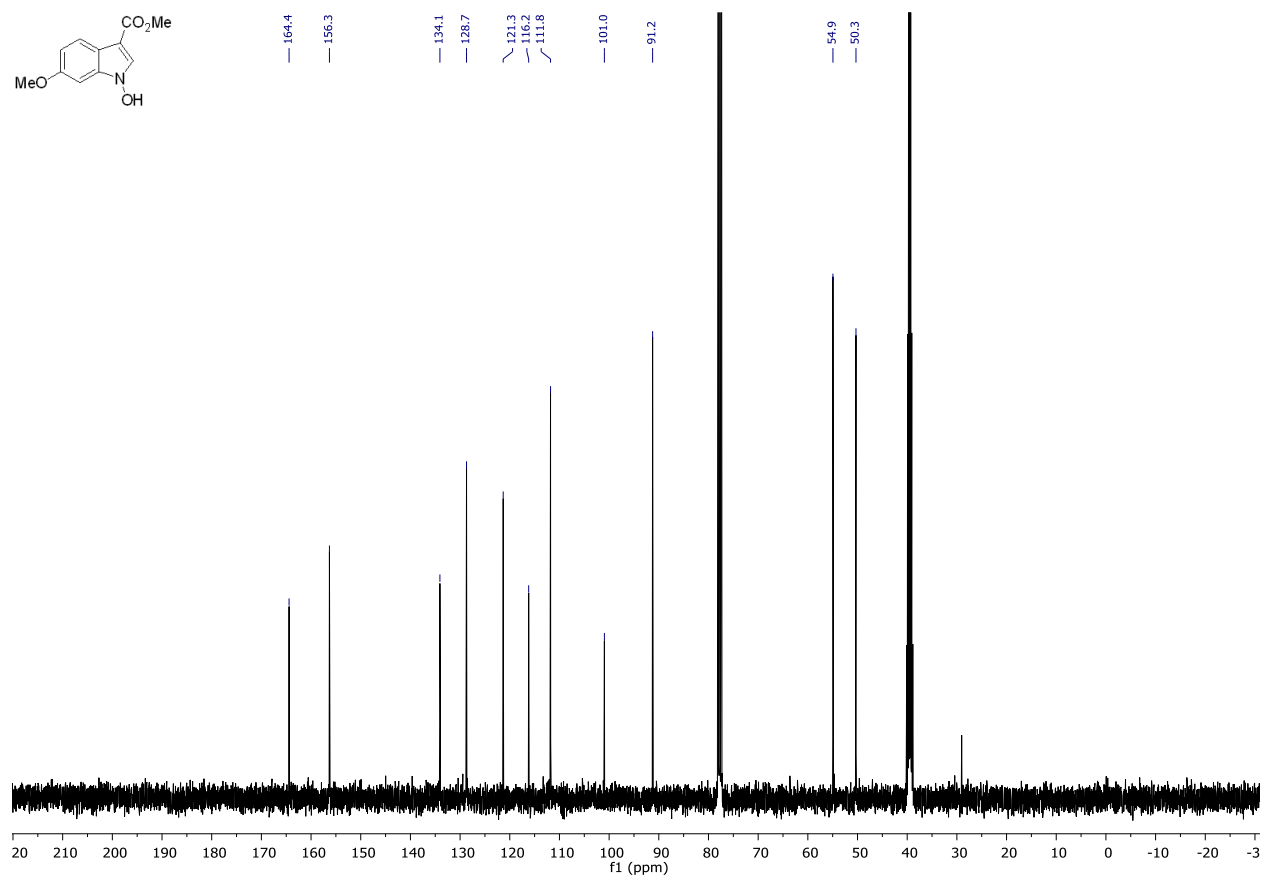
Figure 57: Methyl 1,6-dimethoxyindole-3-carboxylate (**38**)—¹H NMR
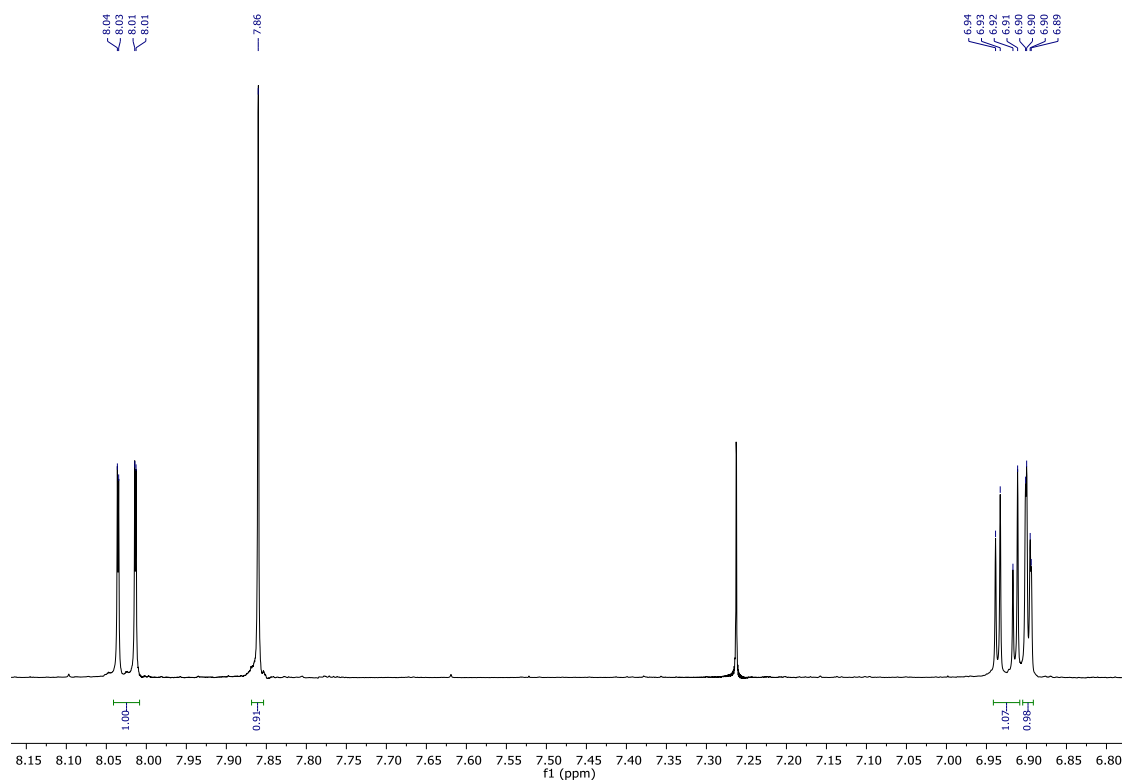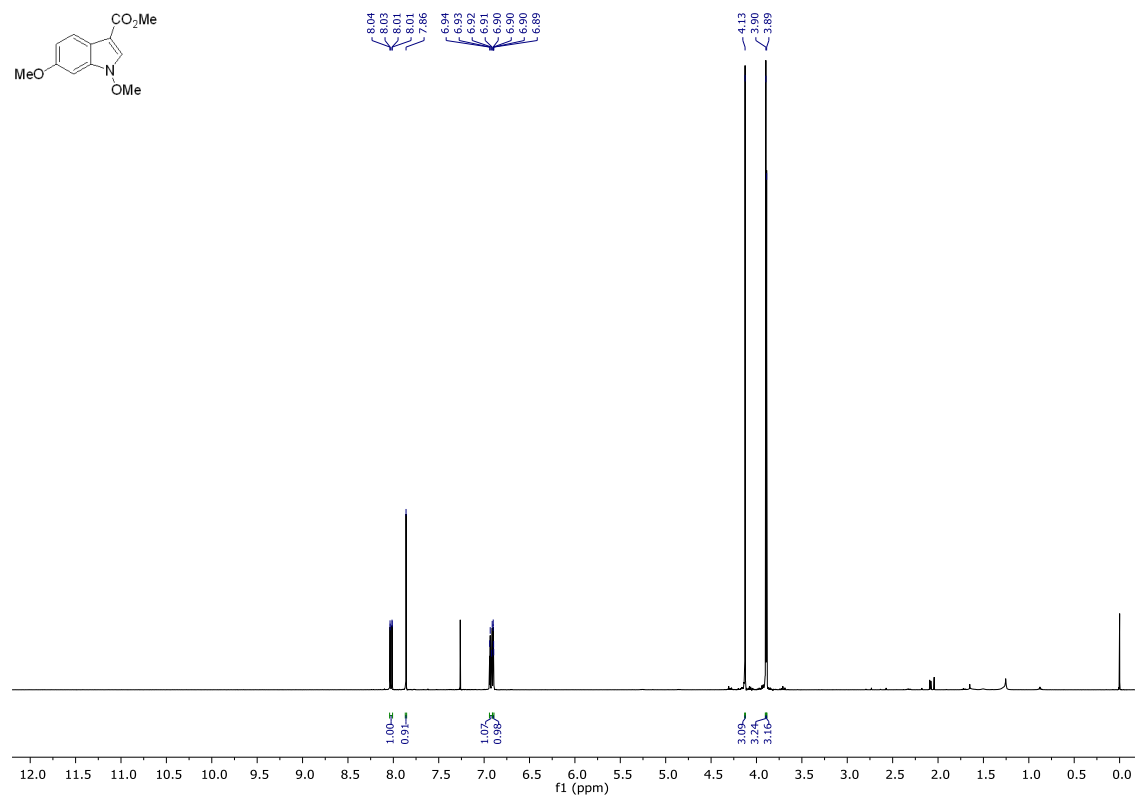
Figure 58: Methyl 1,6-dimethoxyindole-3-carboxylate (**38**)—^{13}C NMR
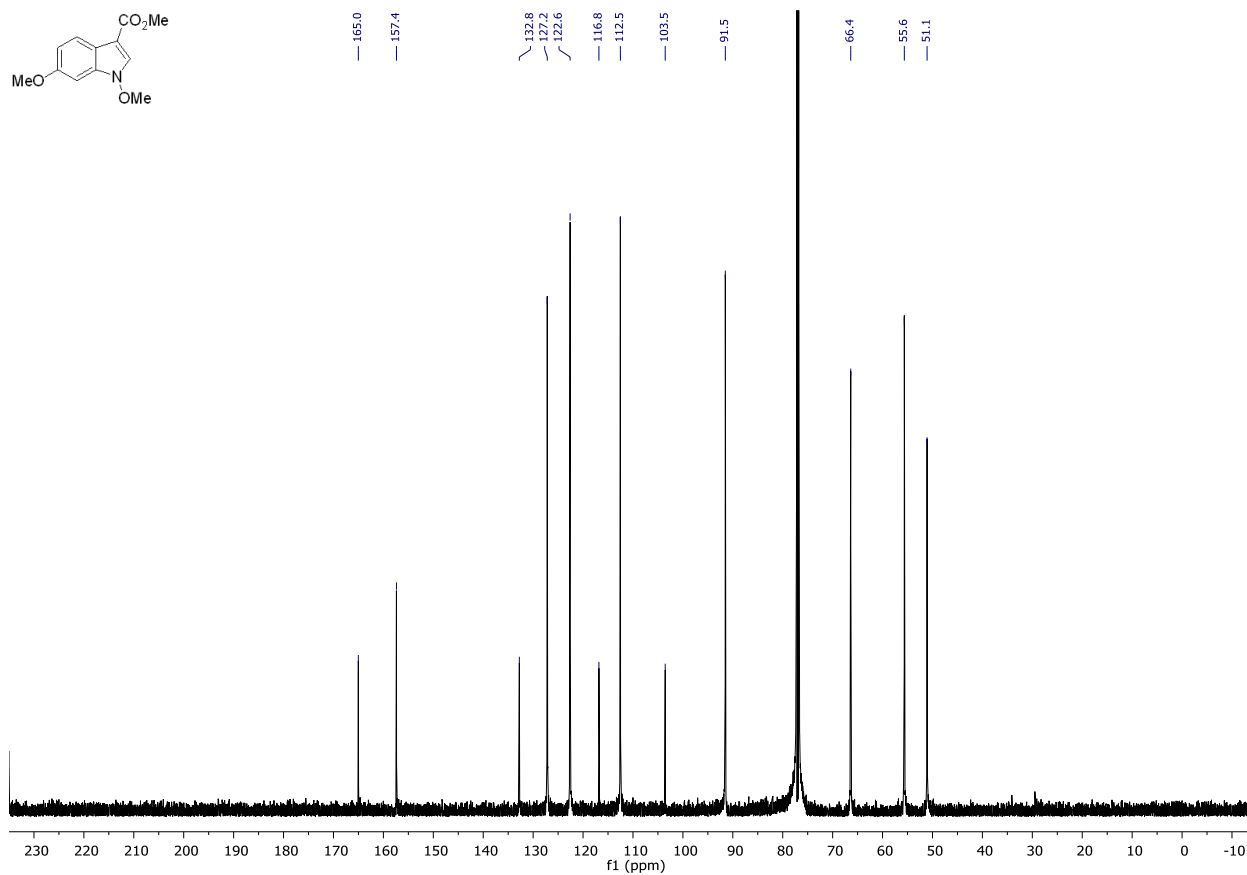
Figure 59: Methyl 5-carbomethoxy-1-hydroxyindole-3-carboxylate (**39**)—^{1}H NMR
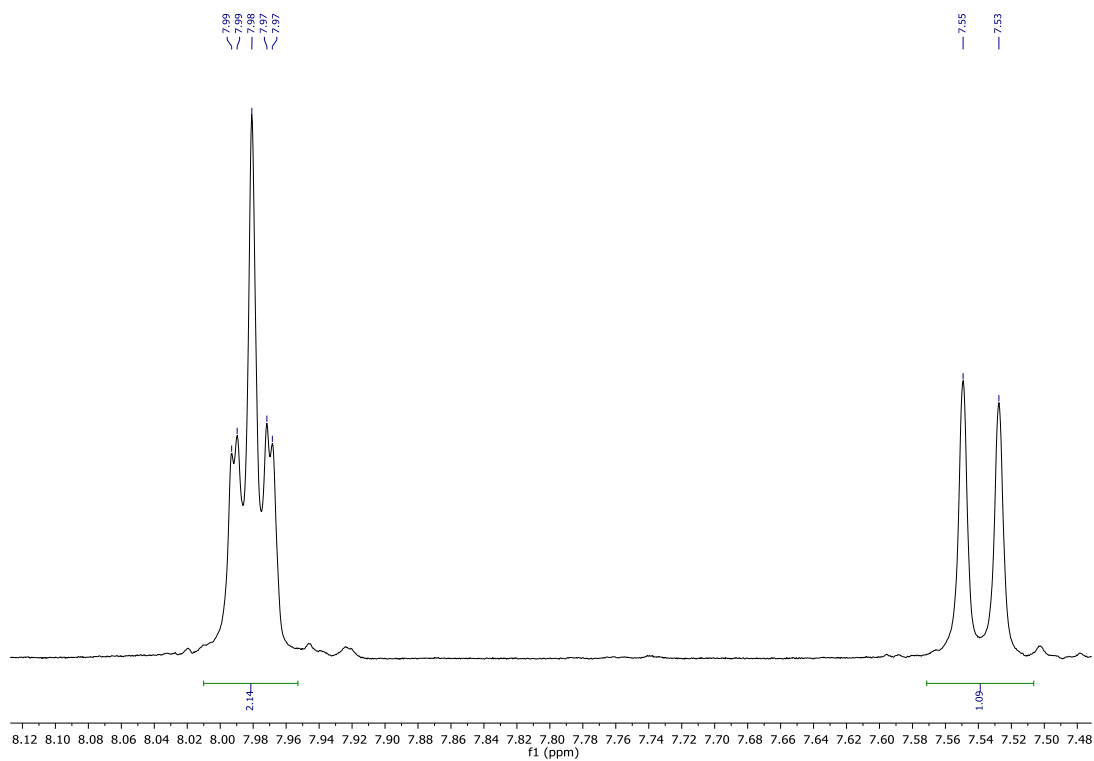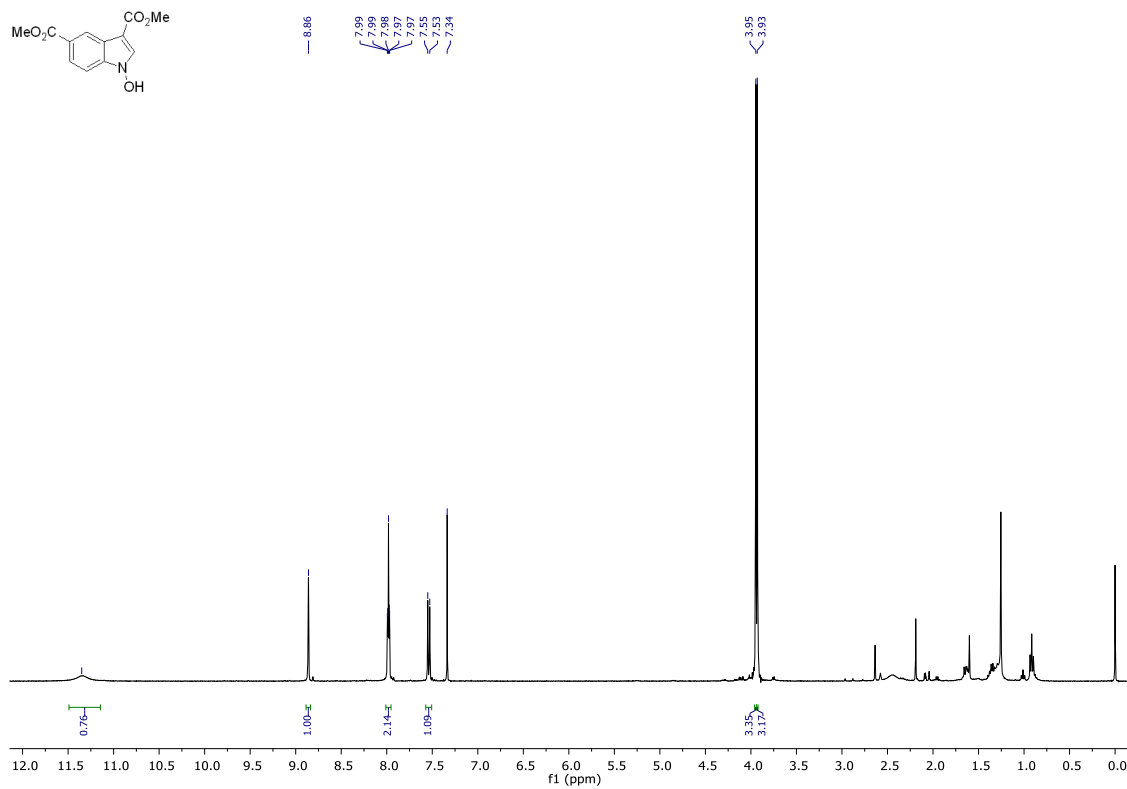
Figure 60: Methyl 5-carbomethoxy-1-hydroxyindole-3-carboxylate (**39**)—^{13}C NMR
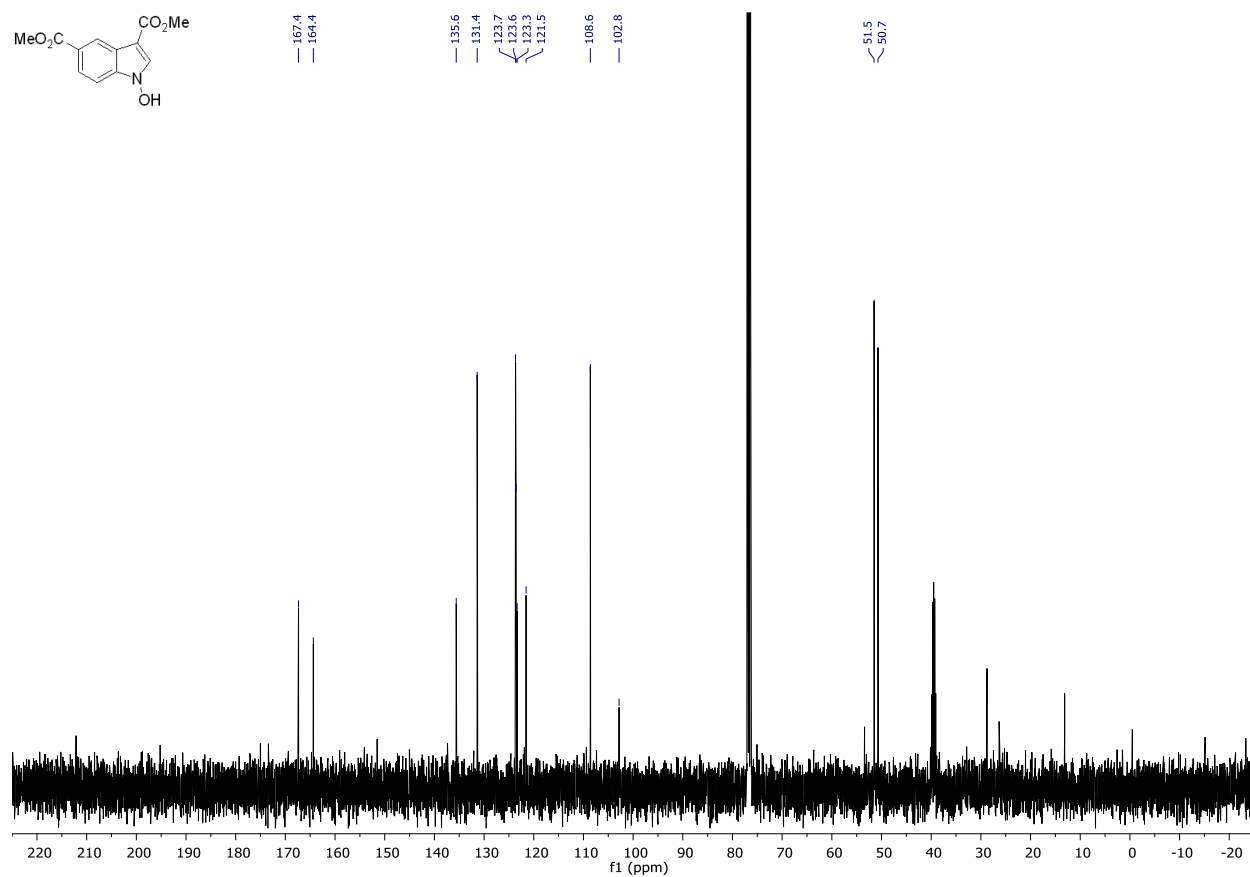
Figure 61: Methyl 5-carbomethoxy-1-methoxyindole-3-carboxylate (**40**)—¹H NMR
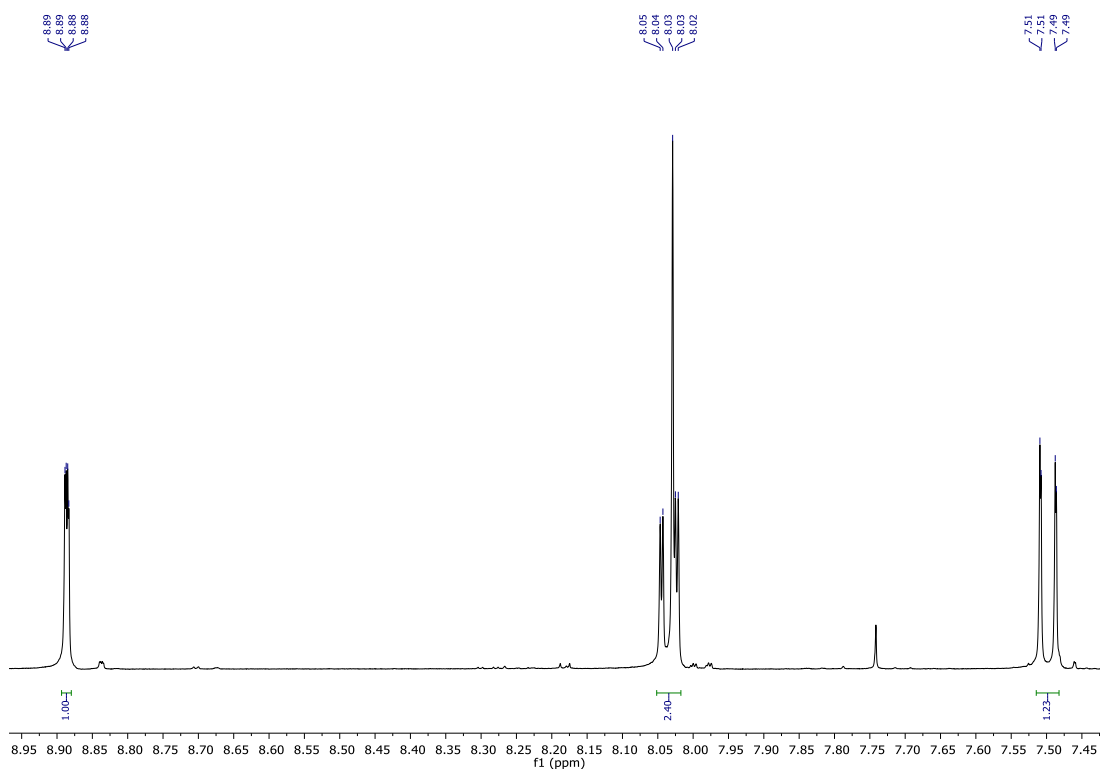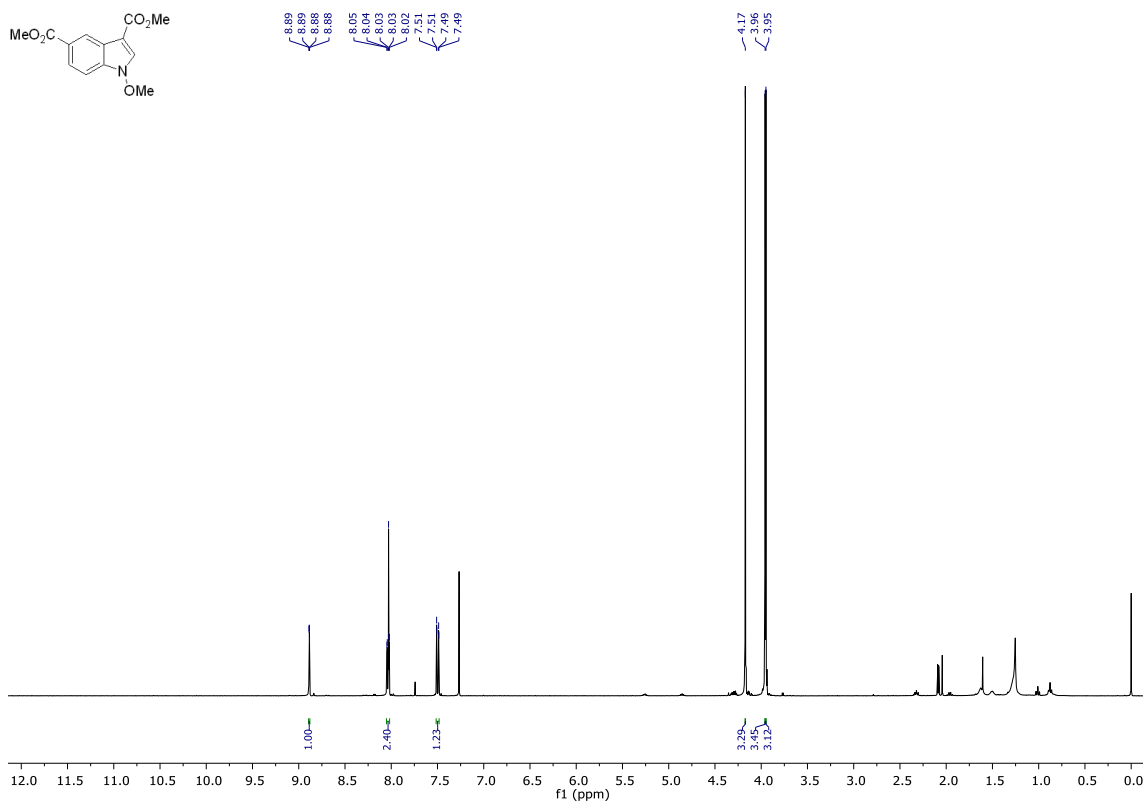
Figure 62: Methyl 5-carbomethoxy-1-methoxyindole-3-carboxylate (**40**)—¹³C NMR
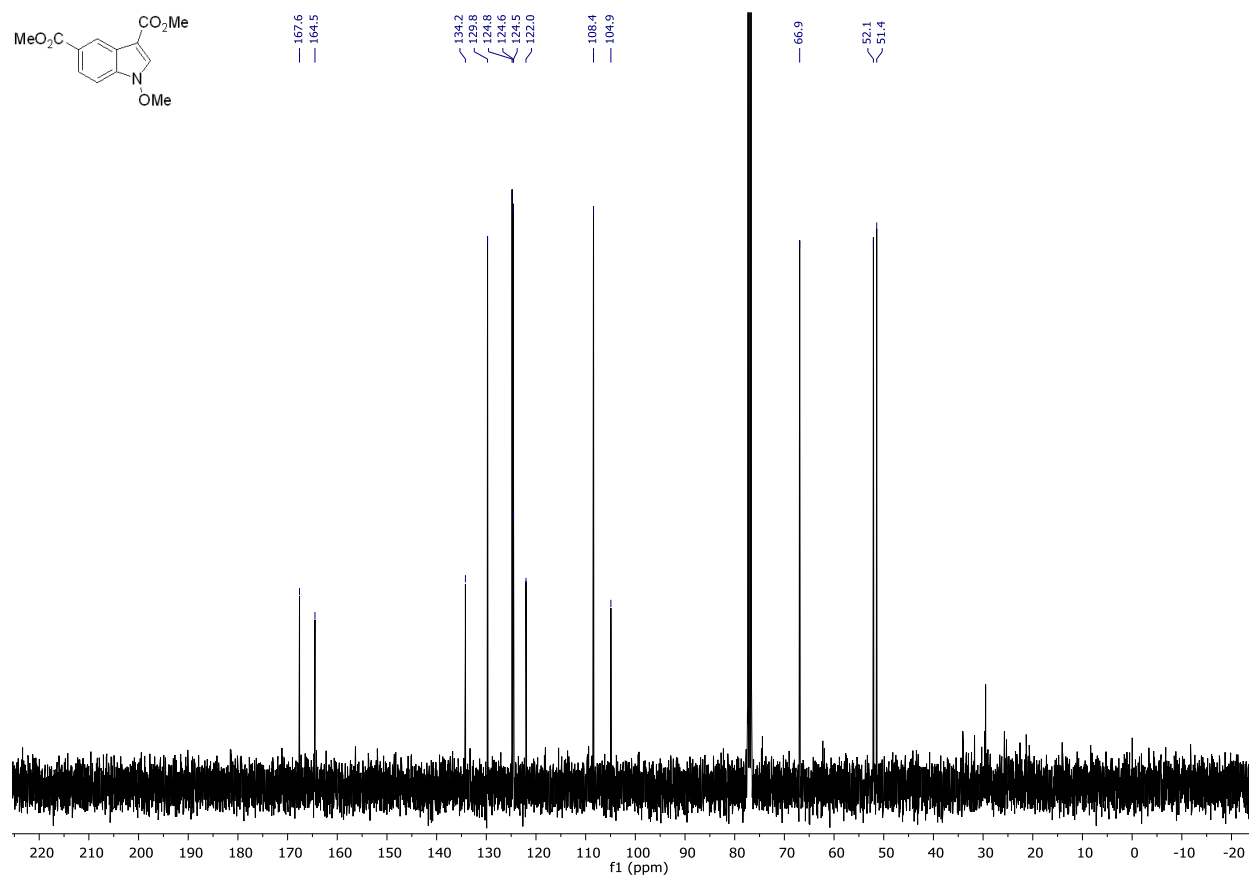
Figure 63: Methyl 6-carbomethoxy-1-hydroxyindole-3-carboxylate (**41**)—^{1}H NMR
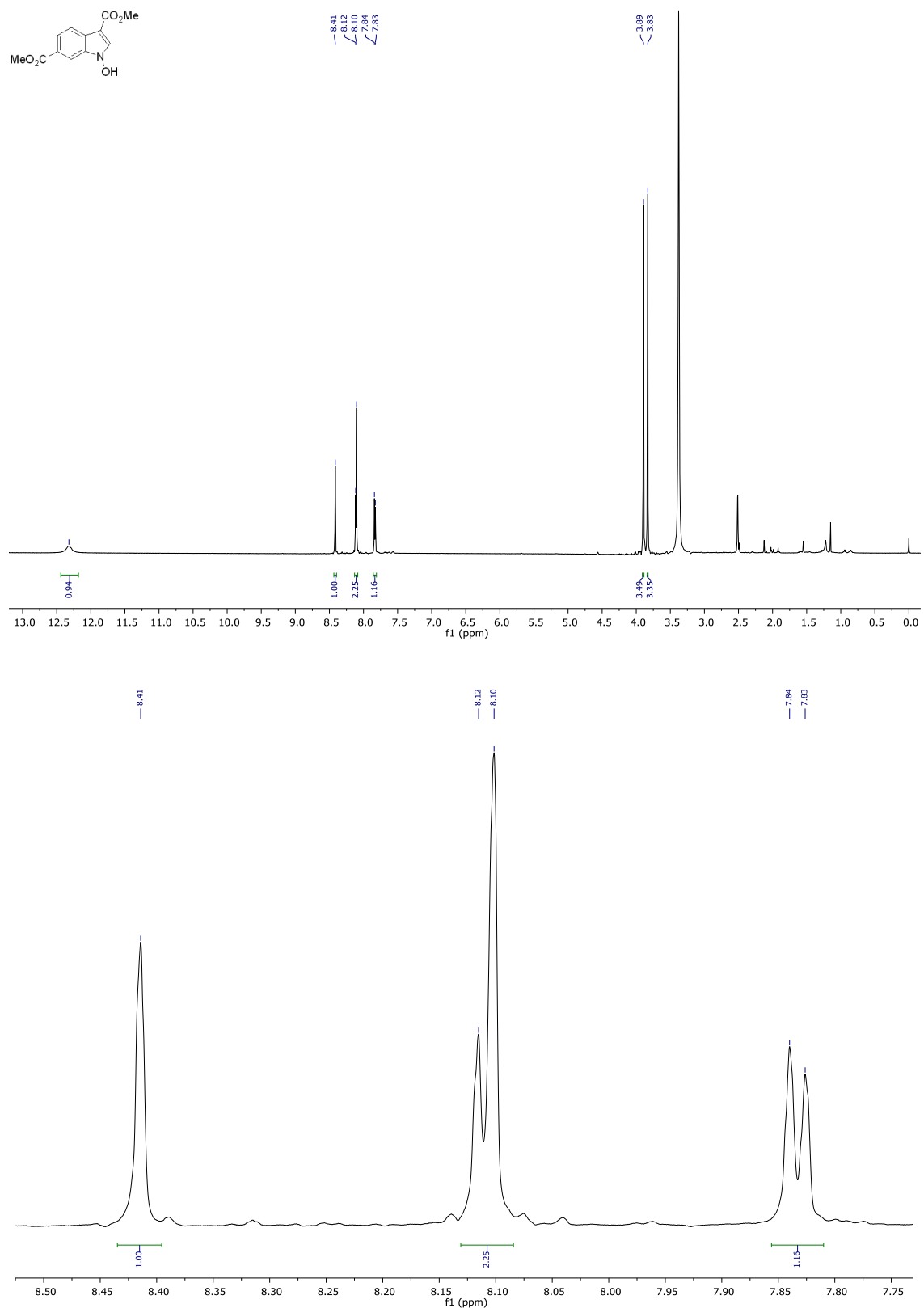
Figure 64: Methyl 6-carbomethoxy-1-hydroxyindole-3-carboxylate (**41**)—^{13}C NMR
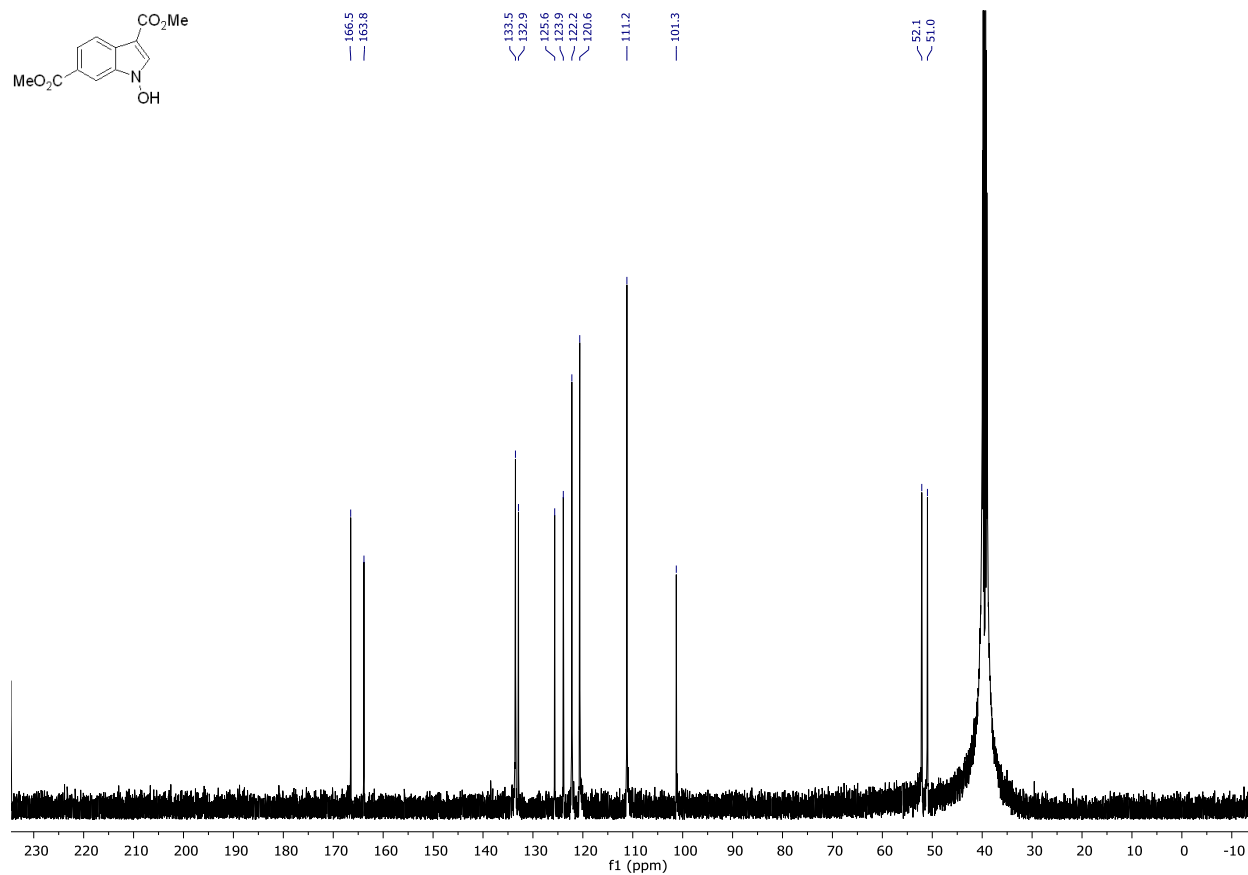
Figure 65: Methyl 6-carbomethoxy-1-methoxyindole-3-carboxylate (**42**)—¹H NMR
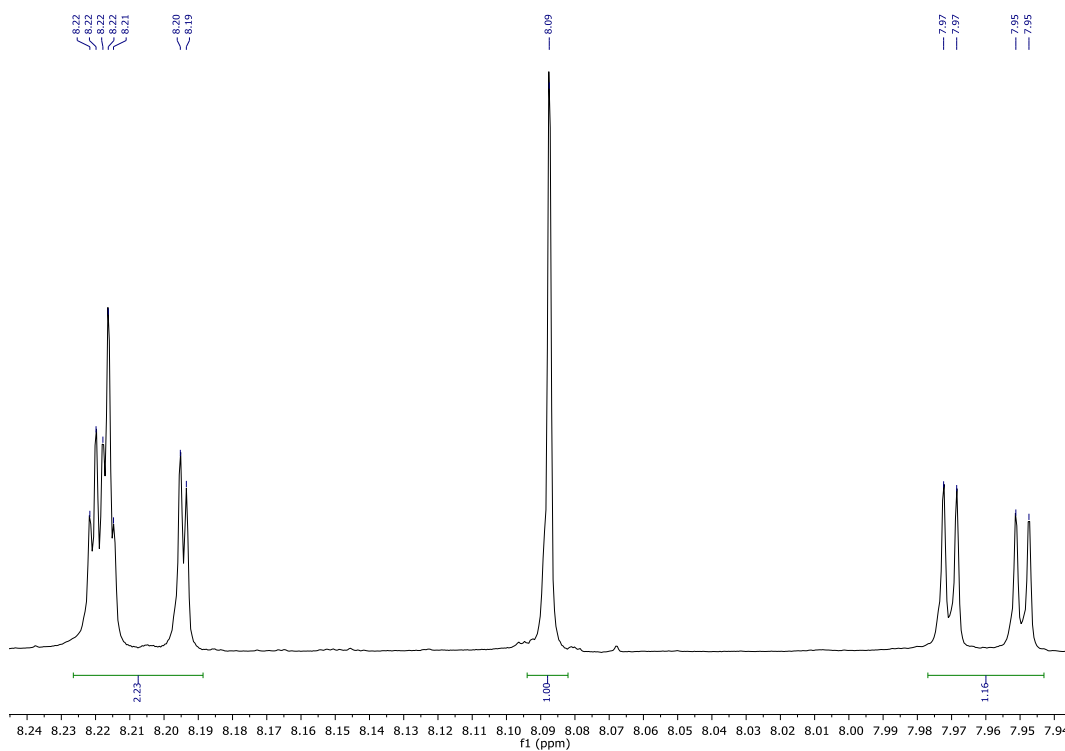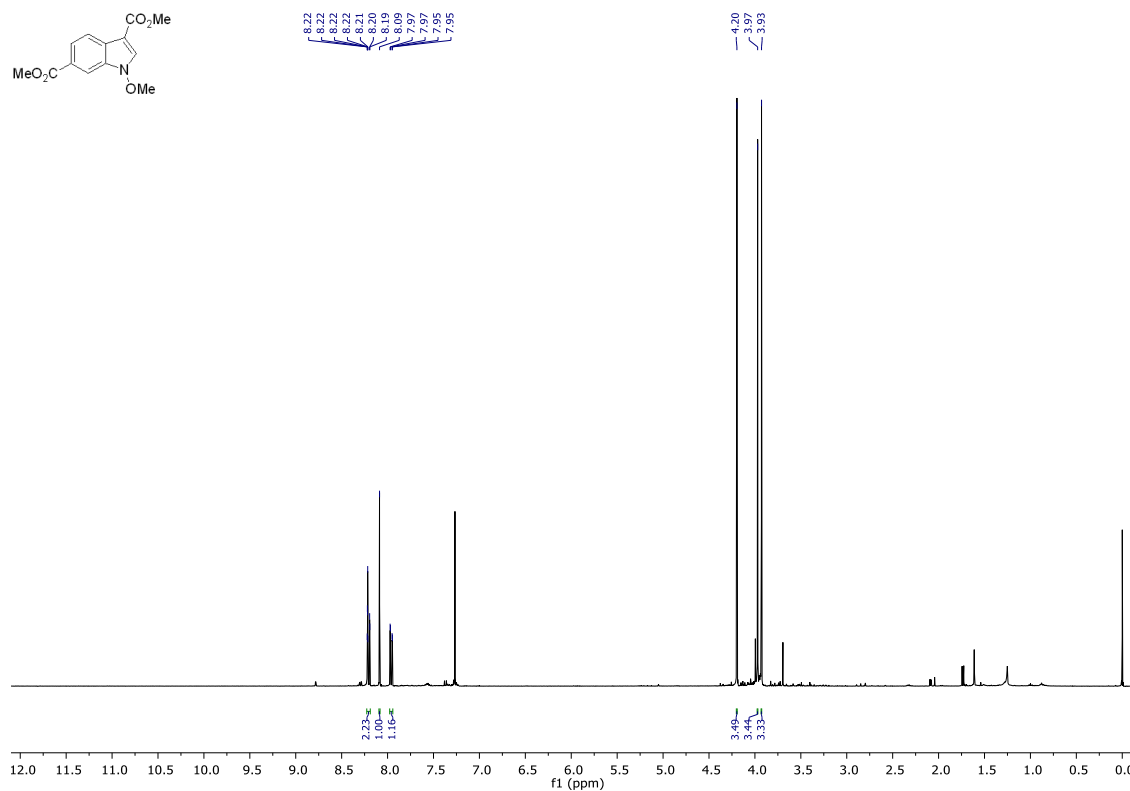
Figure 66: Methyl 6-carbomethoxy-1-methoxyindole-3-carboxylate (**42**)—^{13}C NMR
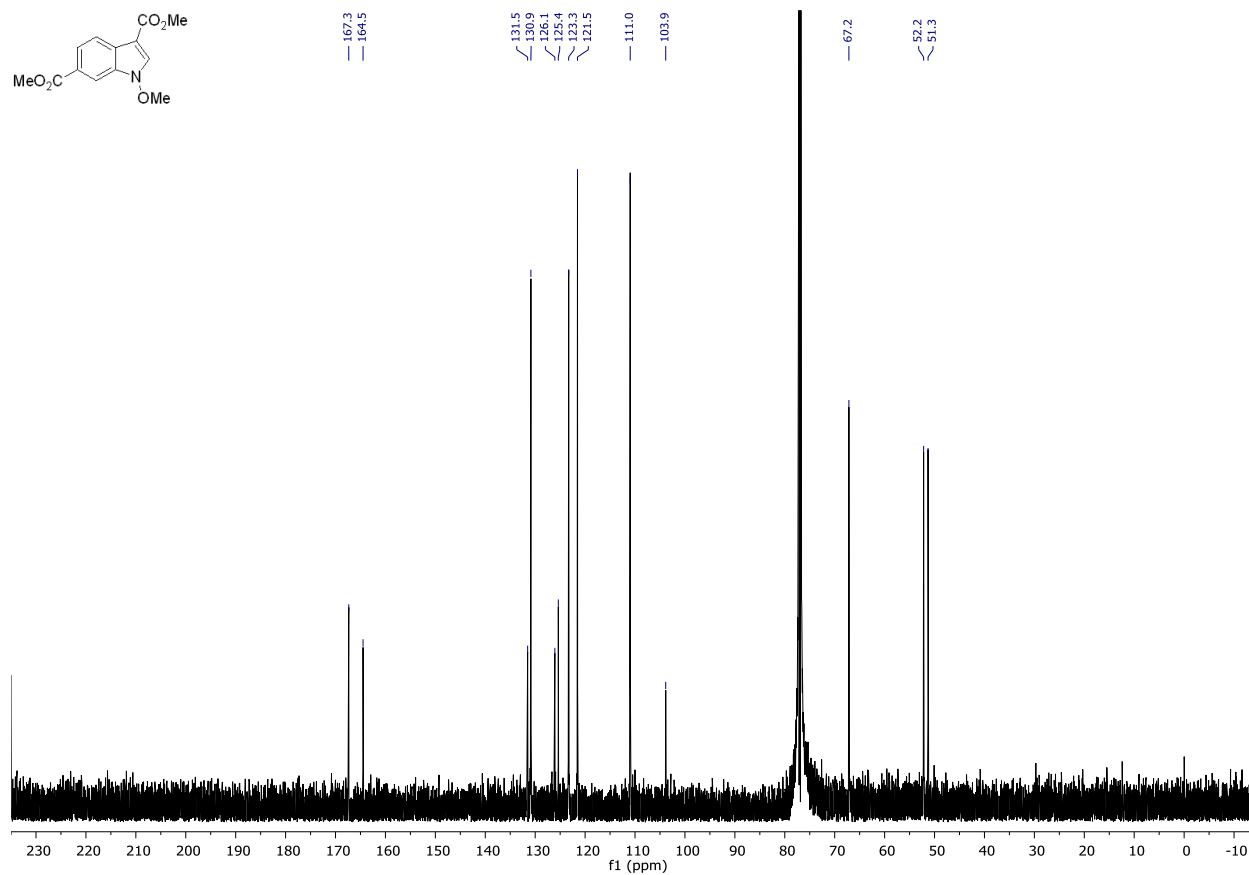
Figure 67: 6-Amino-7-bromo-2,3-dihydro-5-methylinden-1-one (**75**)—¹H NMR
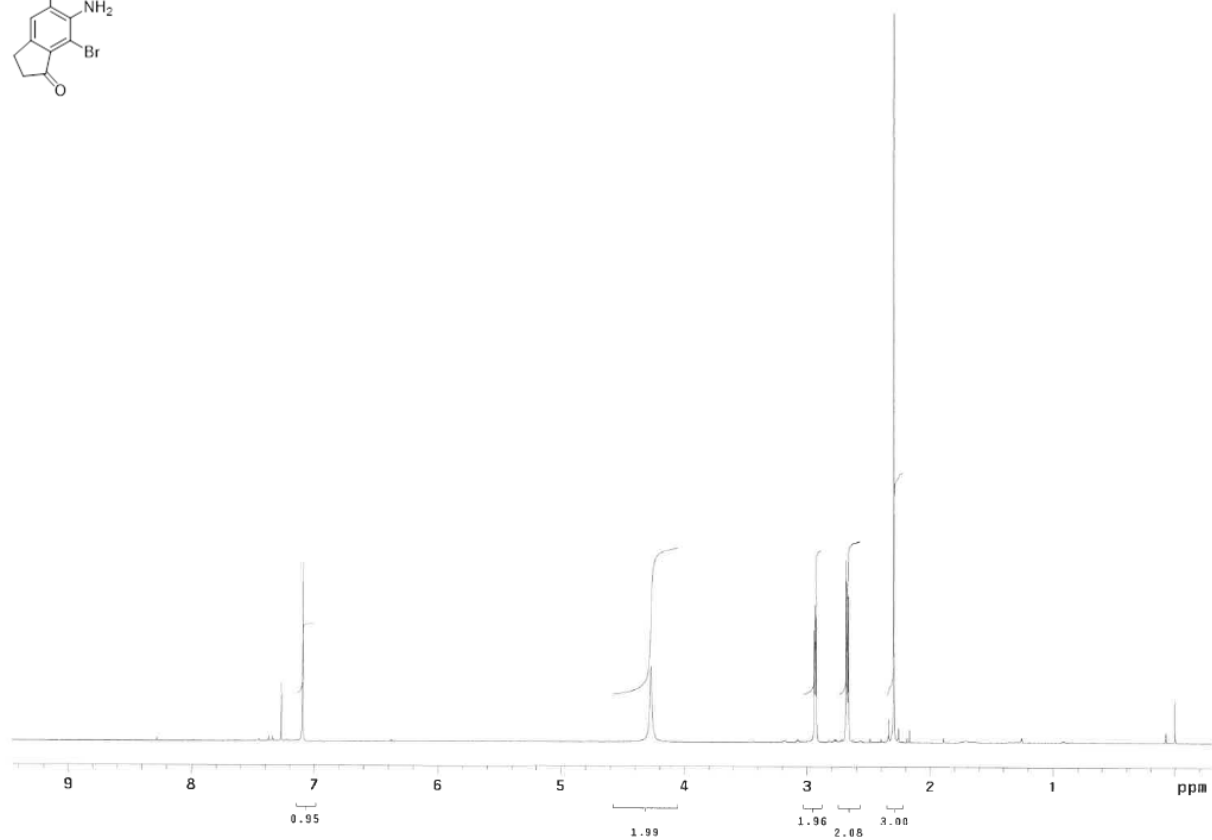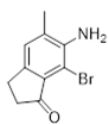
Figure 68: 6-Amino-7-bromo-2,3-dihydro-5-methylinden-1-one (**75**)—^{13}C NMR
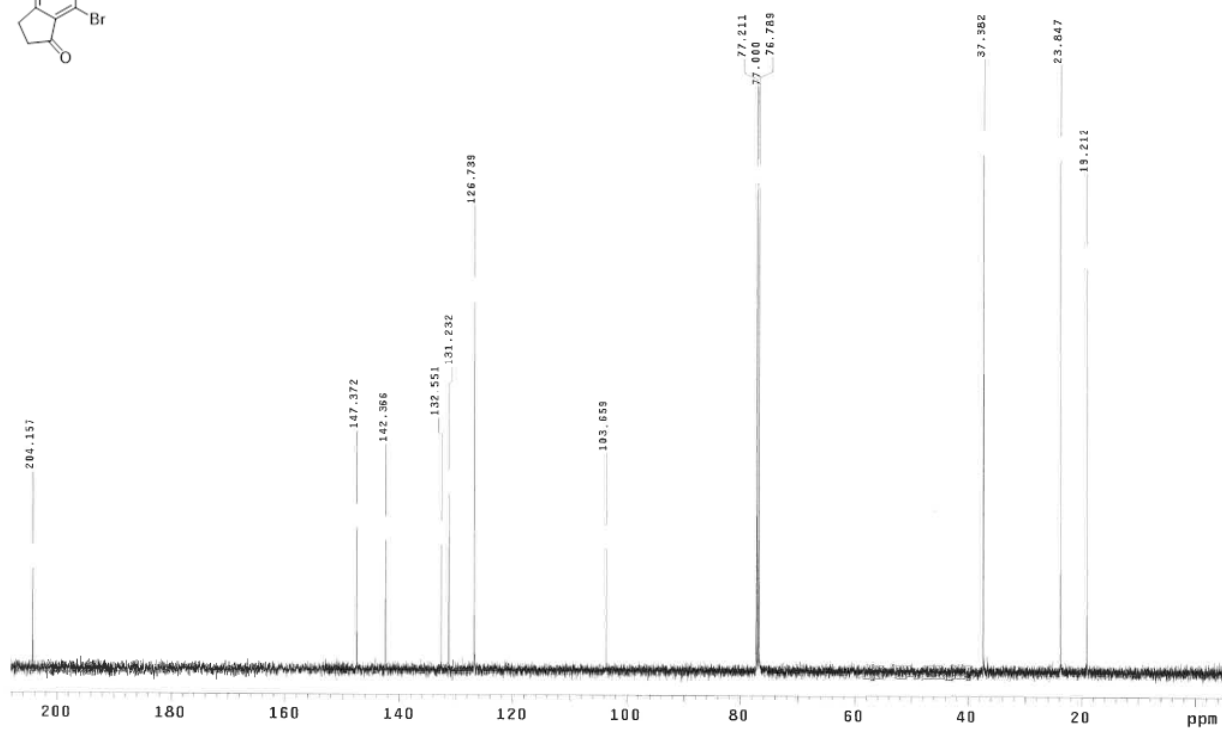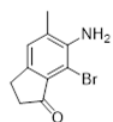
Figure 69: *N*-(2,3-Dihydro-5-methyl-1-oxo-1H-inden-6-yl)acetamide (**69**)—¹H NMR
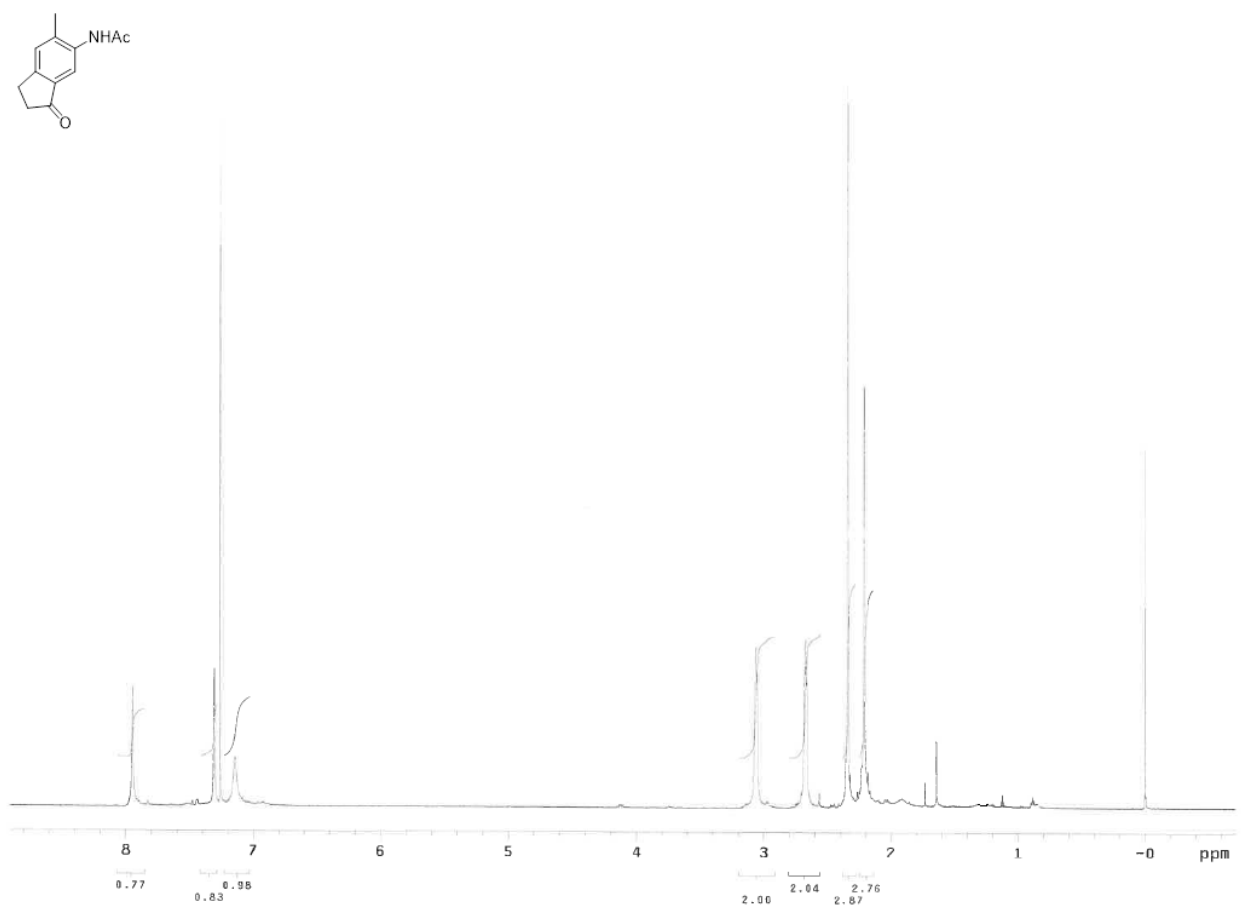
Figure 70: *N*-(2,3-Dihydro-5-methyl-1-oxo-1H-inden-6-yl)acetamide (**69**)—^{13}C NMR
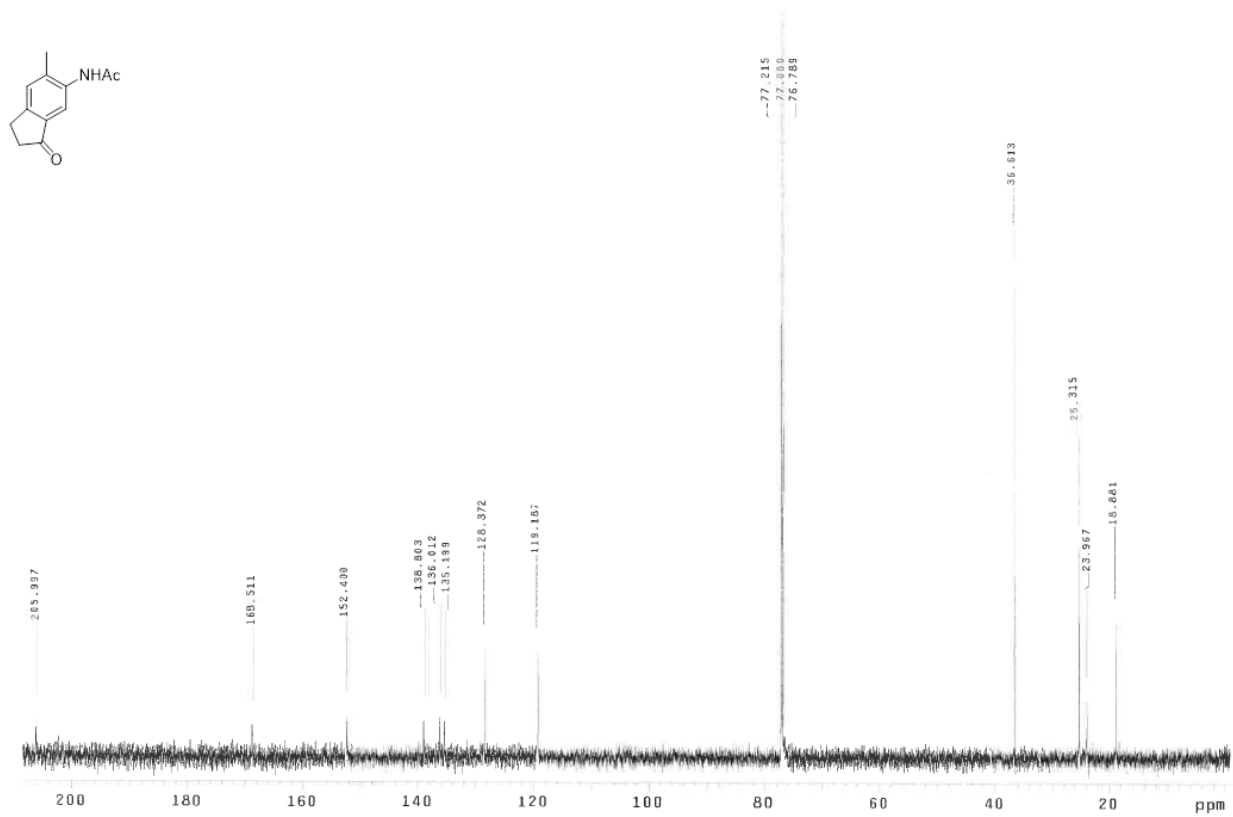
Figure 71: *N*-(2,3-Dihydro-5-methyl-7-nitro-1-oxo-1H-inden-6-yl)acetamide (**70**)—¹H NMR
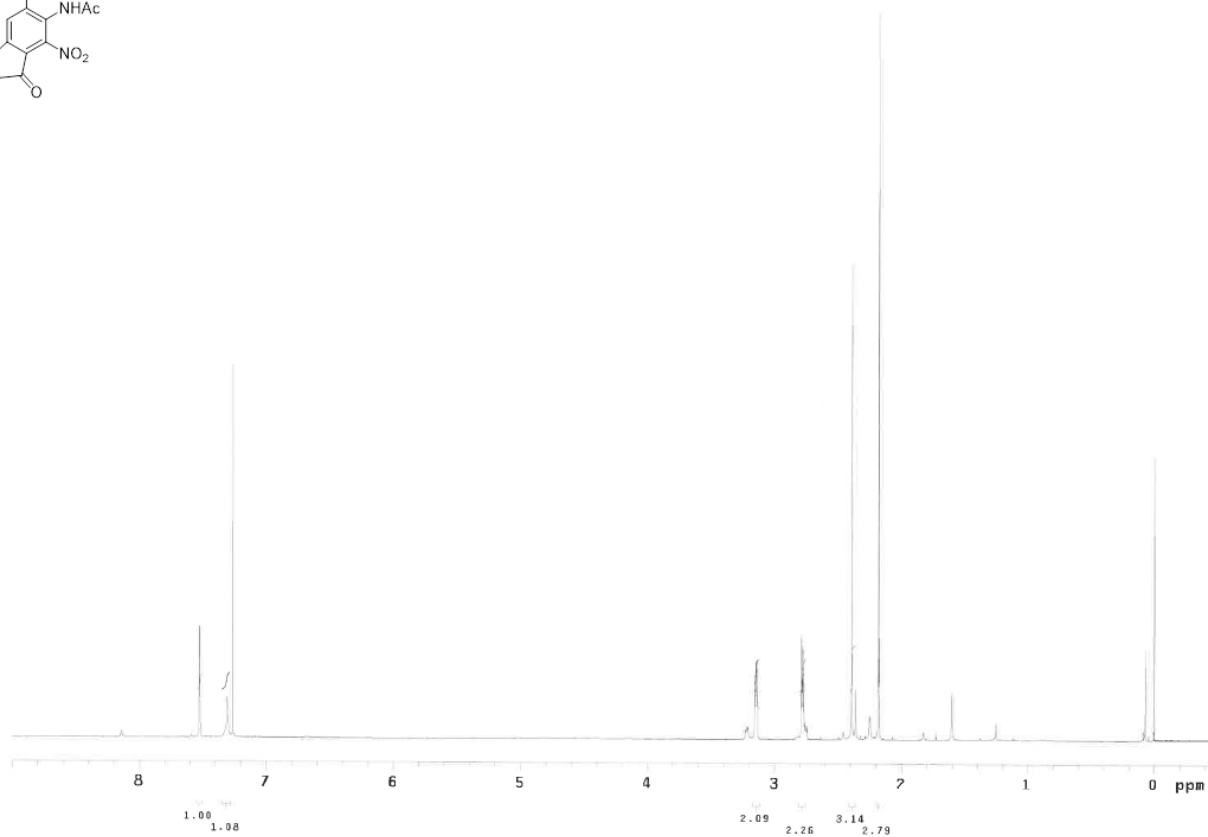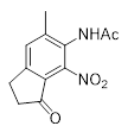
Figure 72: *N*-(2,3-Dihydro-5-methyl-7-nitro-1-oxo-1H-inden-6-yl)acetamide (**70**)—^{13}C NMR
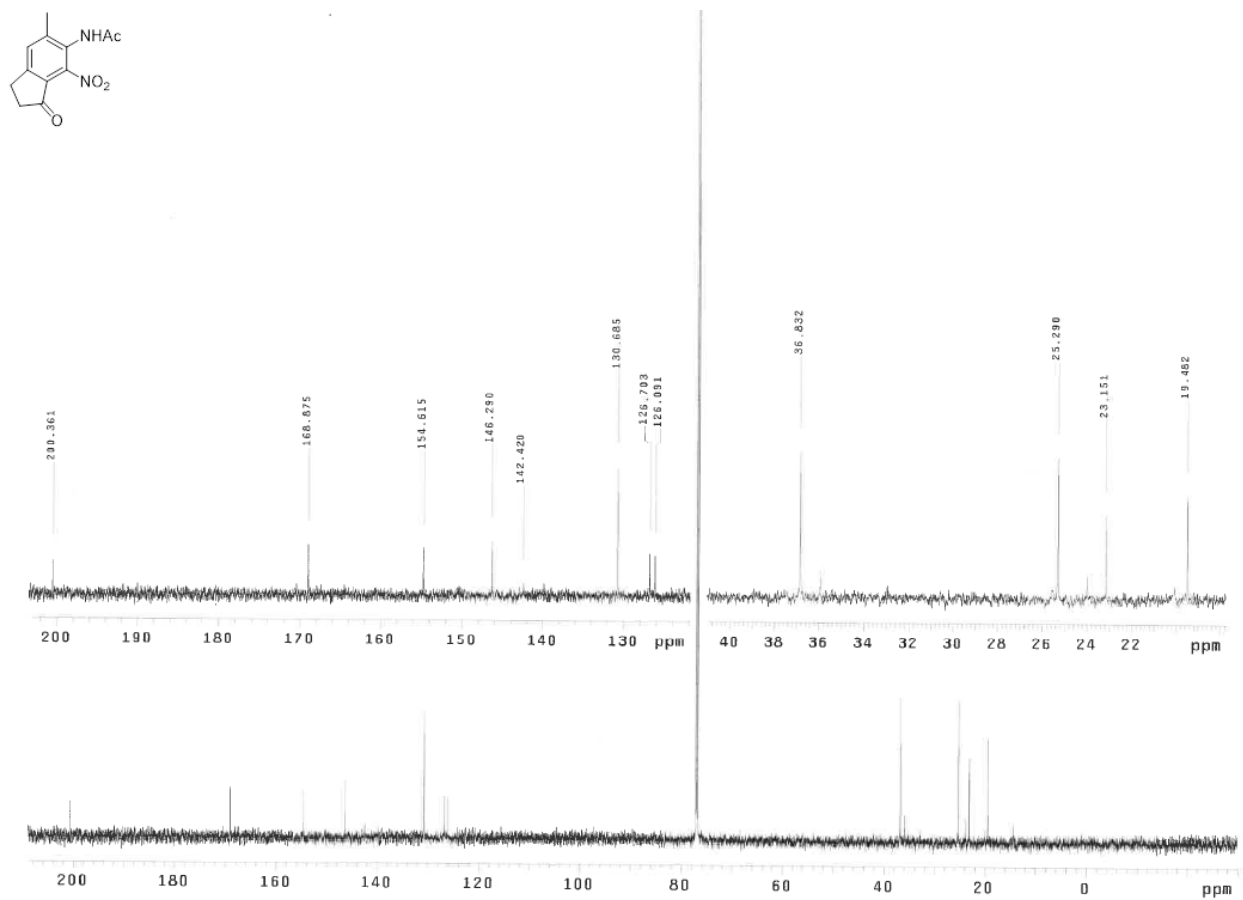
Figure 73: 6-Amino-2,3-dihydro-5-methyl-7-nitroinden-1-one (**71**)—¹H NMR
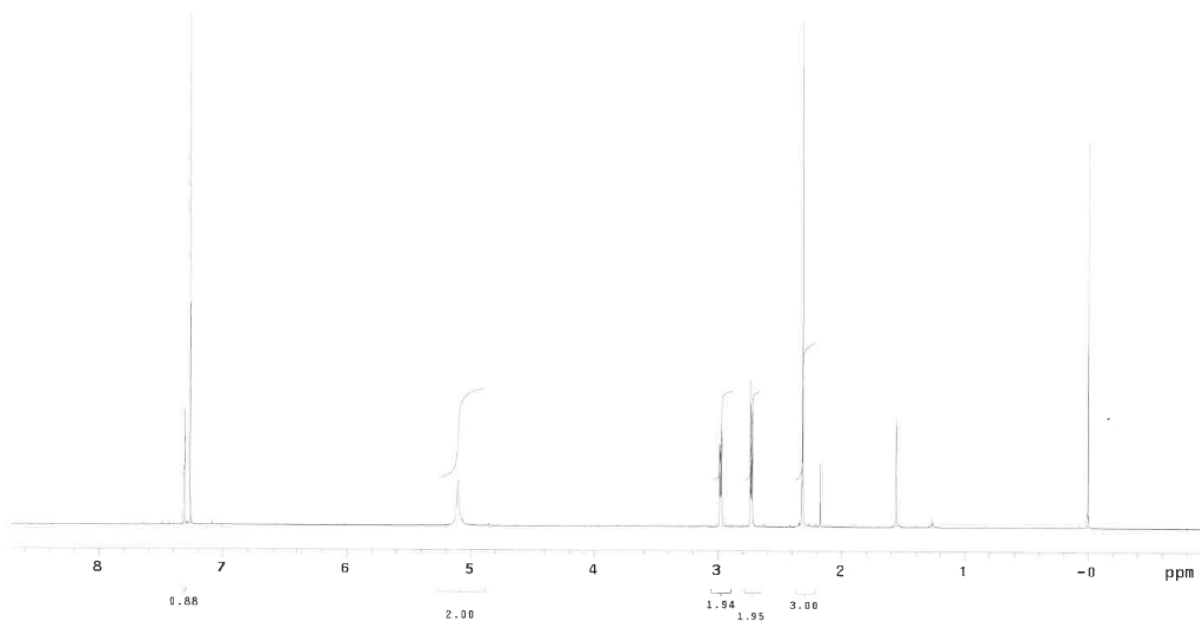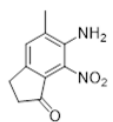
Figure 74: 6-Amino-2,3-dihydro-5-methyl-7-nitroinden-1-one (**71**)—^{13}C NMR
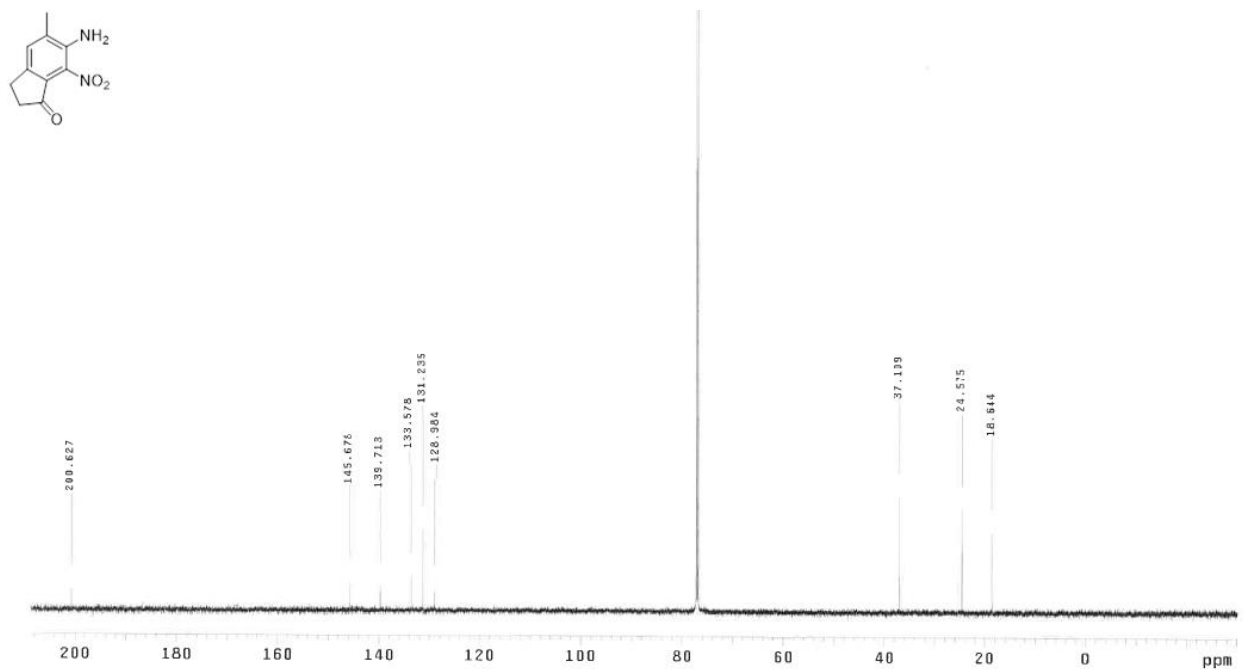
Figure 75: 2,3-Dihydro-6-iodo-5-methyl-7-nitroinden-1-one (**72**)—¹H NMR
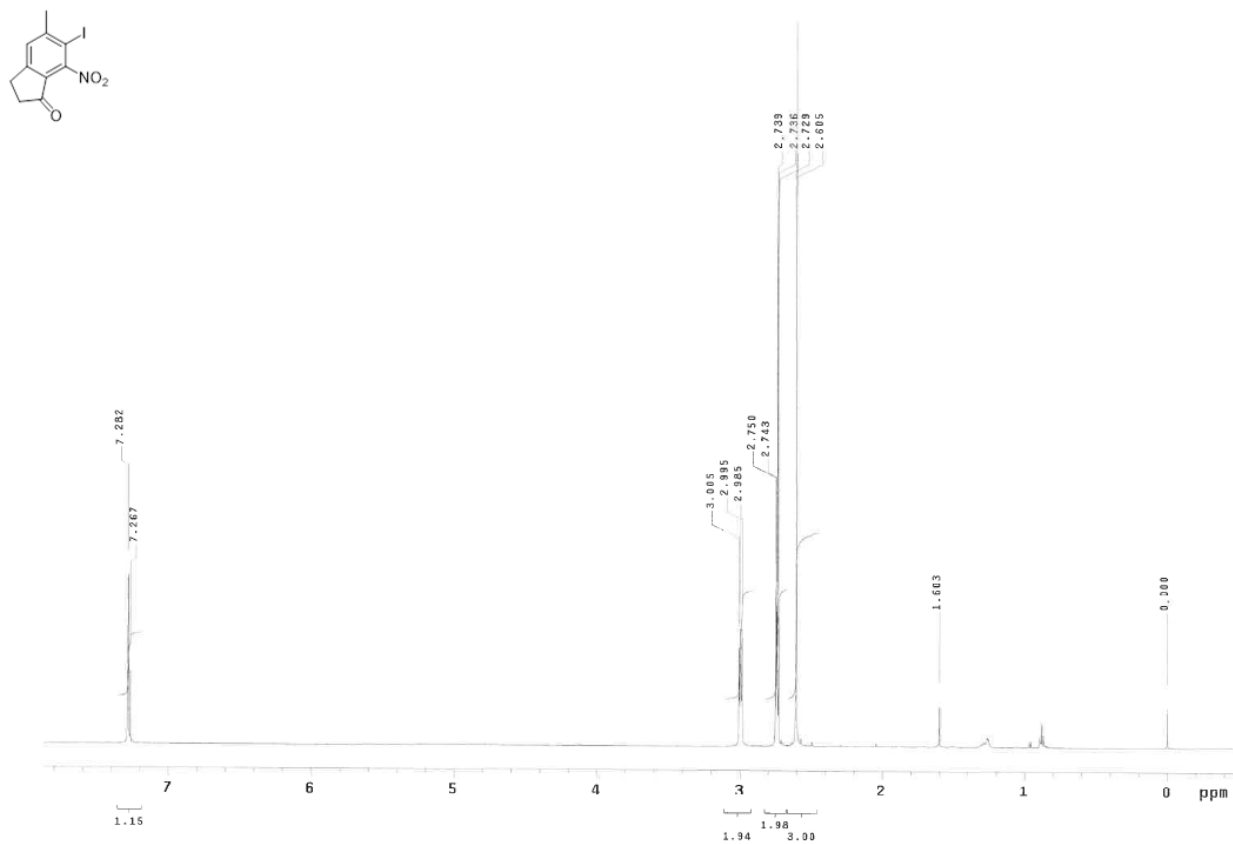
Figure 76: 2,3-Dihydro-6-iodo-5-methyl-7-nitroinden-1-one (**72**)—^{13}C NMR
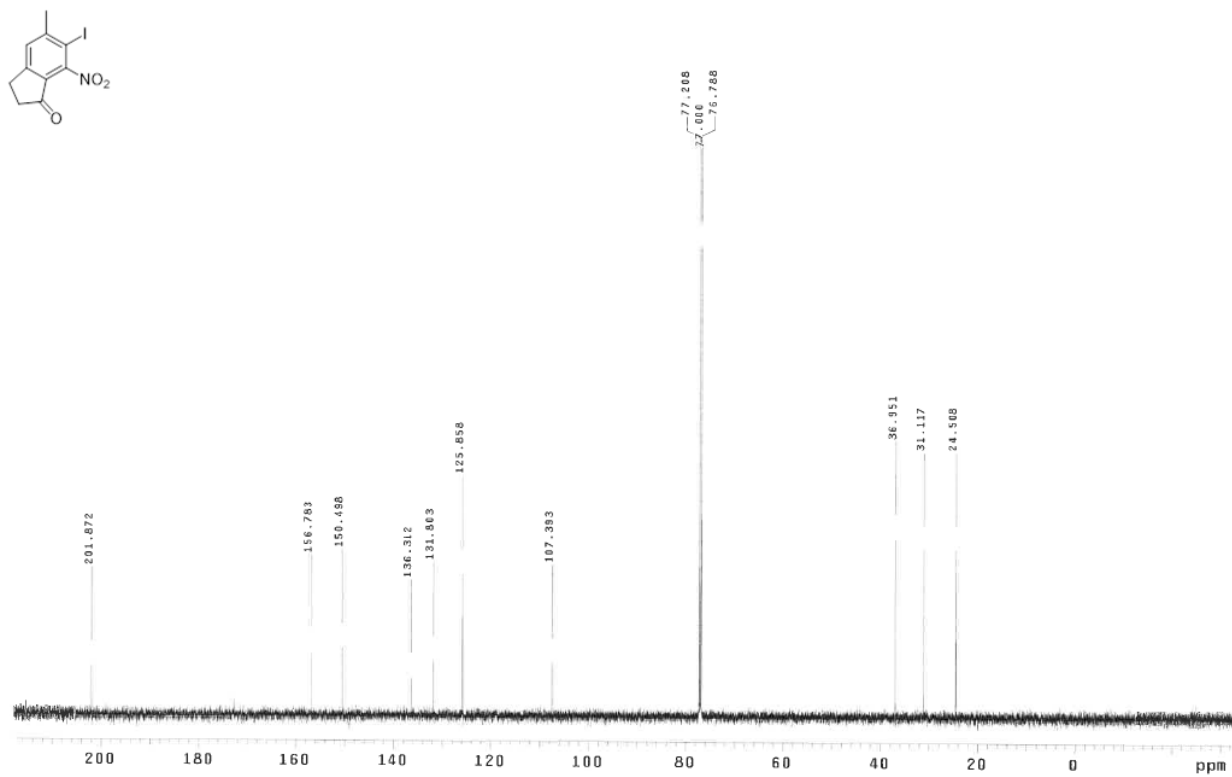
Figure 77: 6-Bromo-2,3-dihydro-5-methylinden-1-one (**76**)—^{1}H NMR
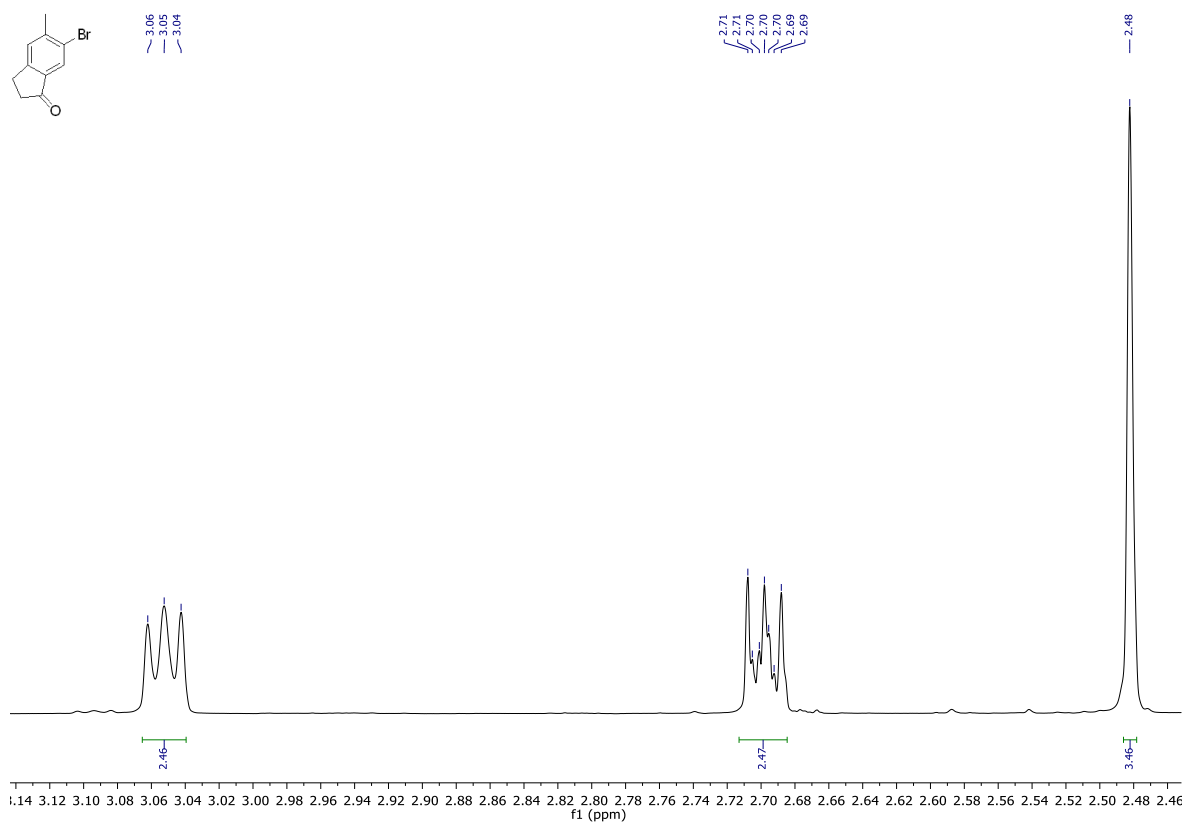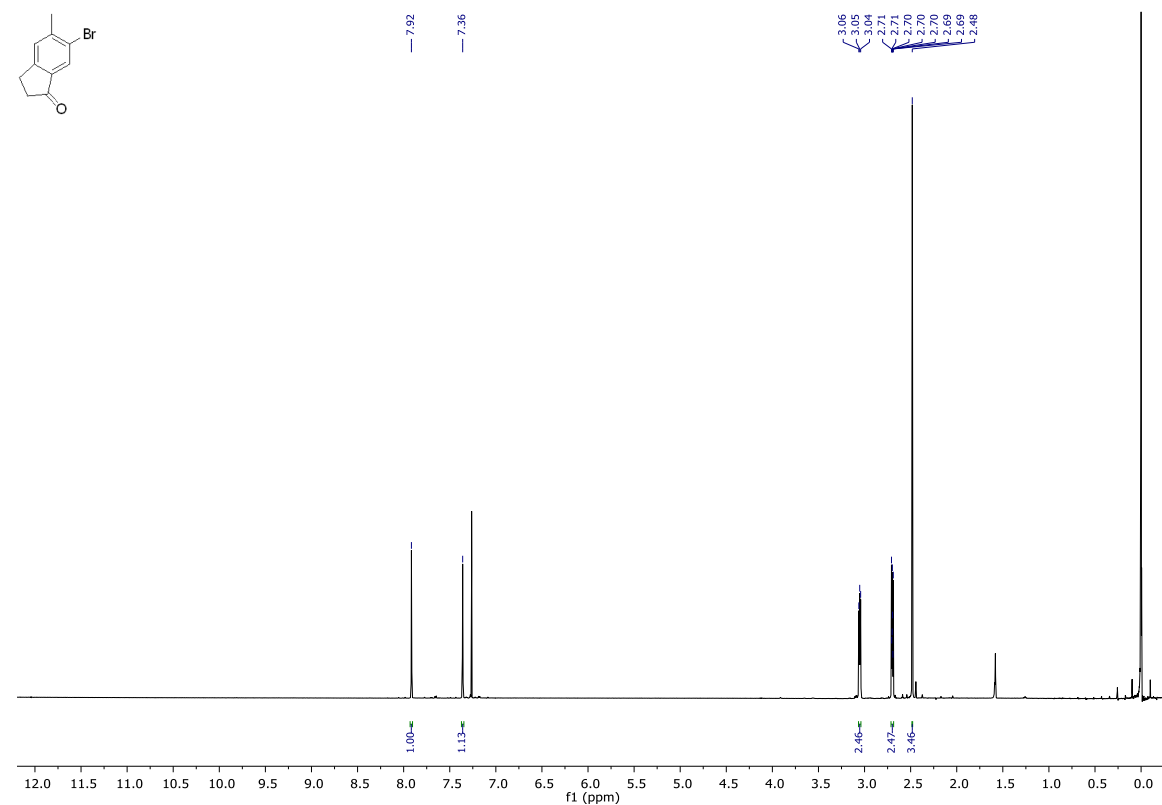
Figure 78: 6-Bromo-2,3-dihydro-5-methylinden-1-one (**76**)—¹³C NMR
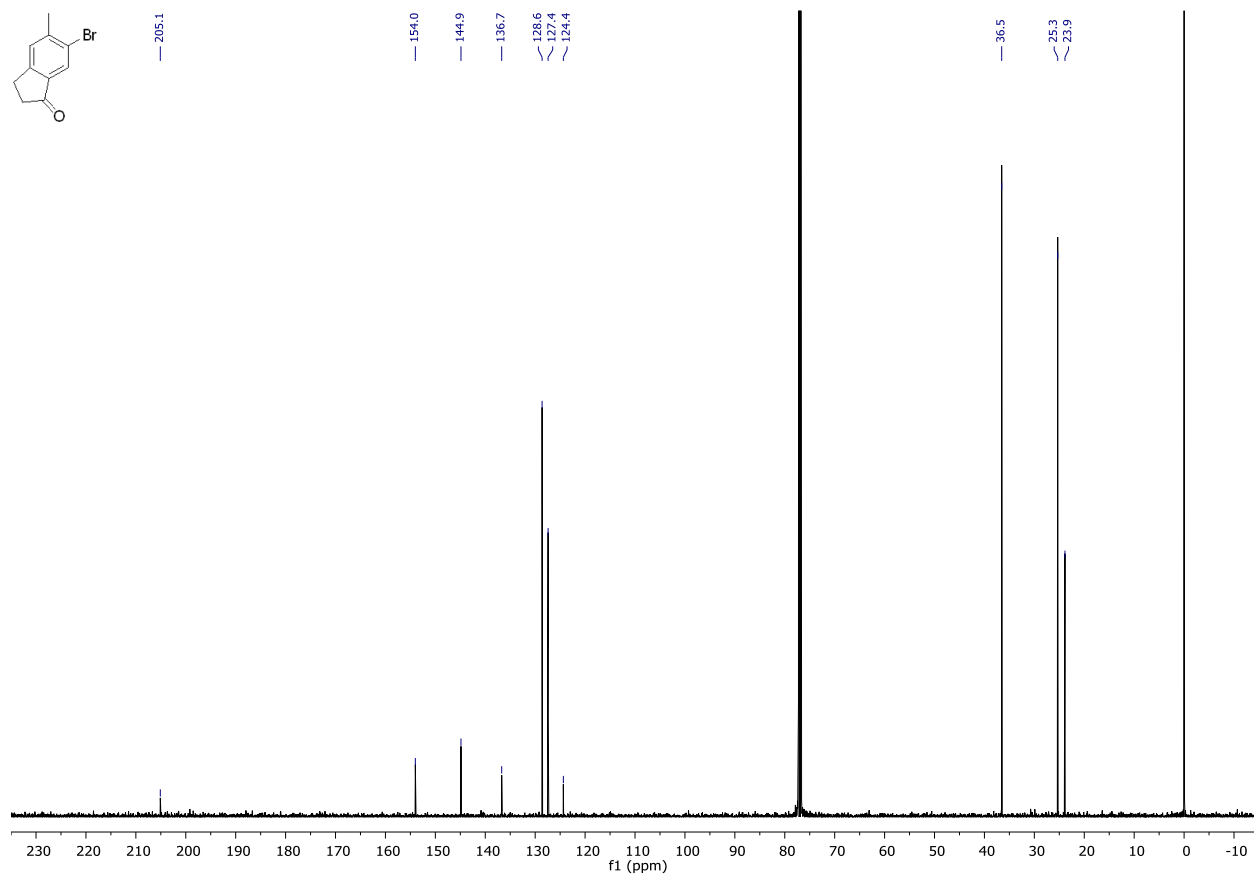
Figure 79: 4-Bromo-2,3-dihydro-5-methylinden-1-one (**77**)—¹H NMR
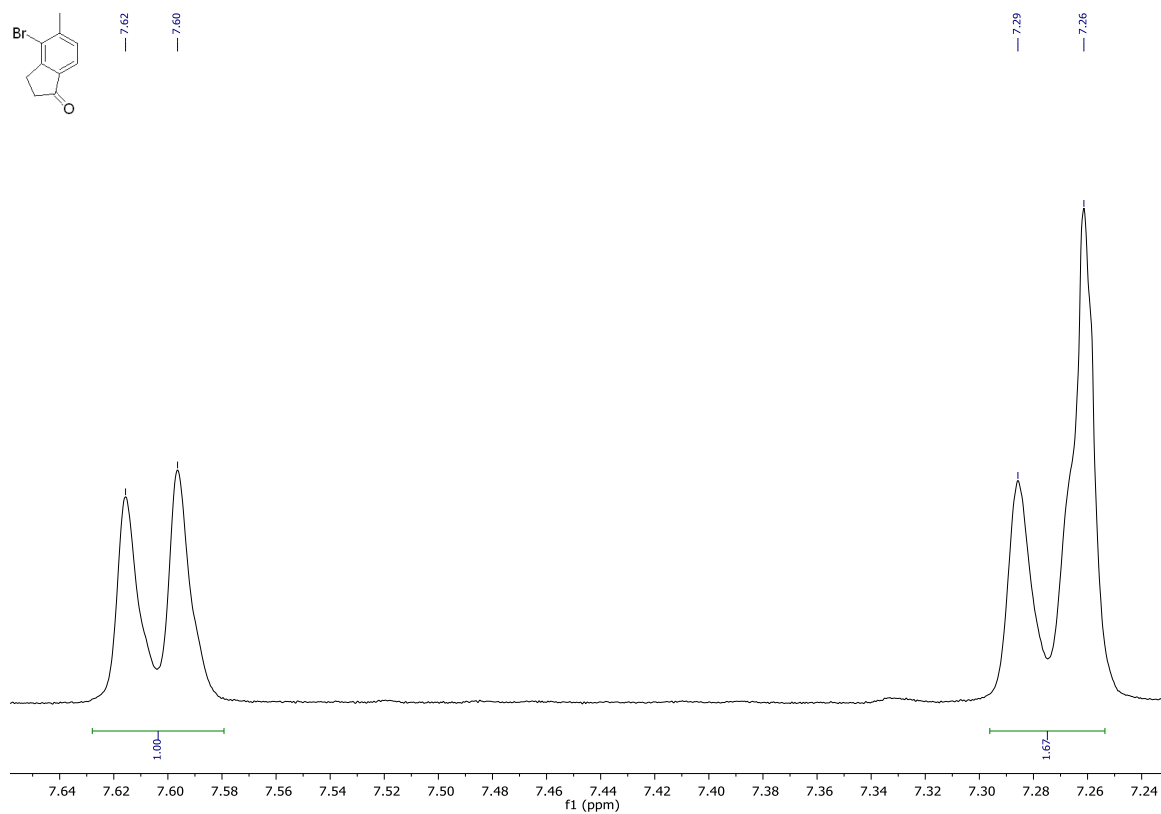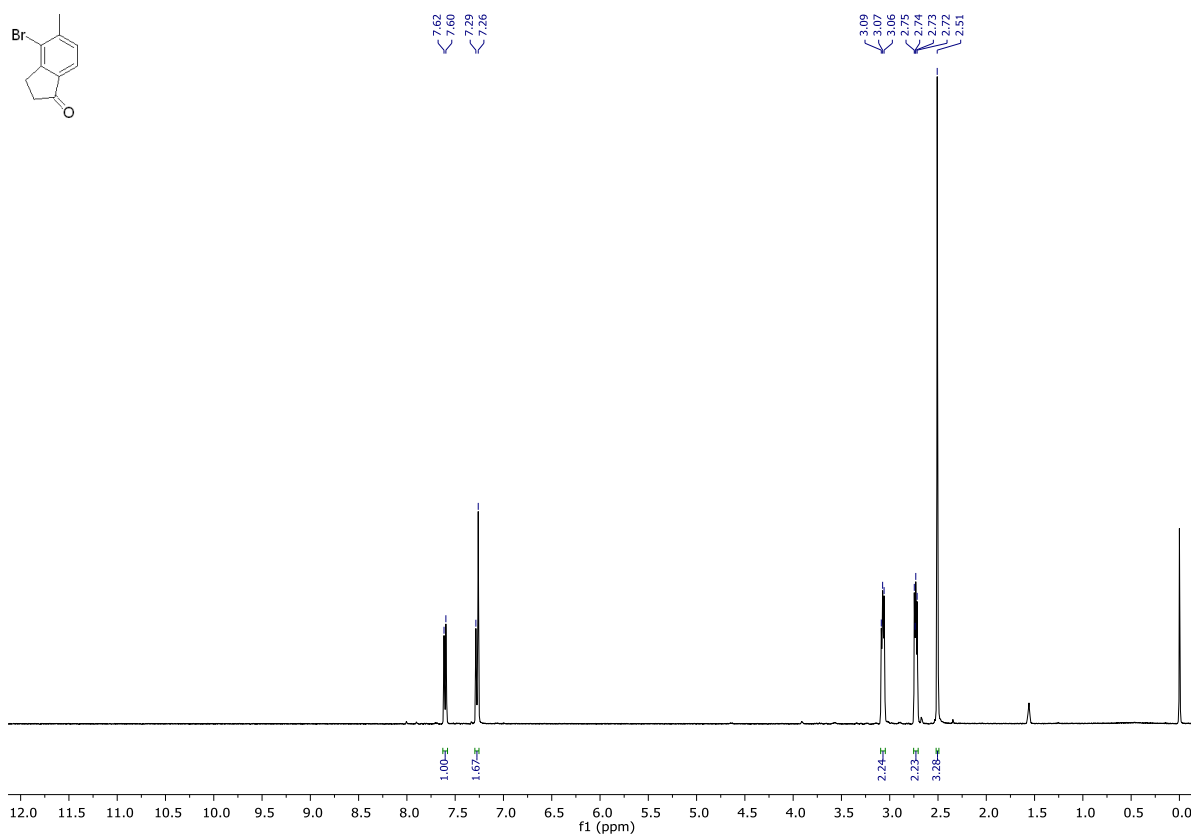
Figure 80: 4-Bromo-2,3-dihydro-5-methylinden-1-one (**77**)—¹³C NMR
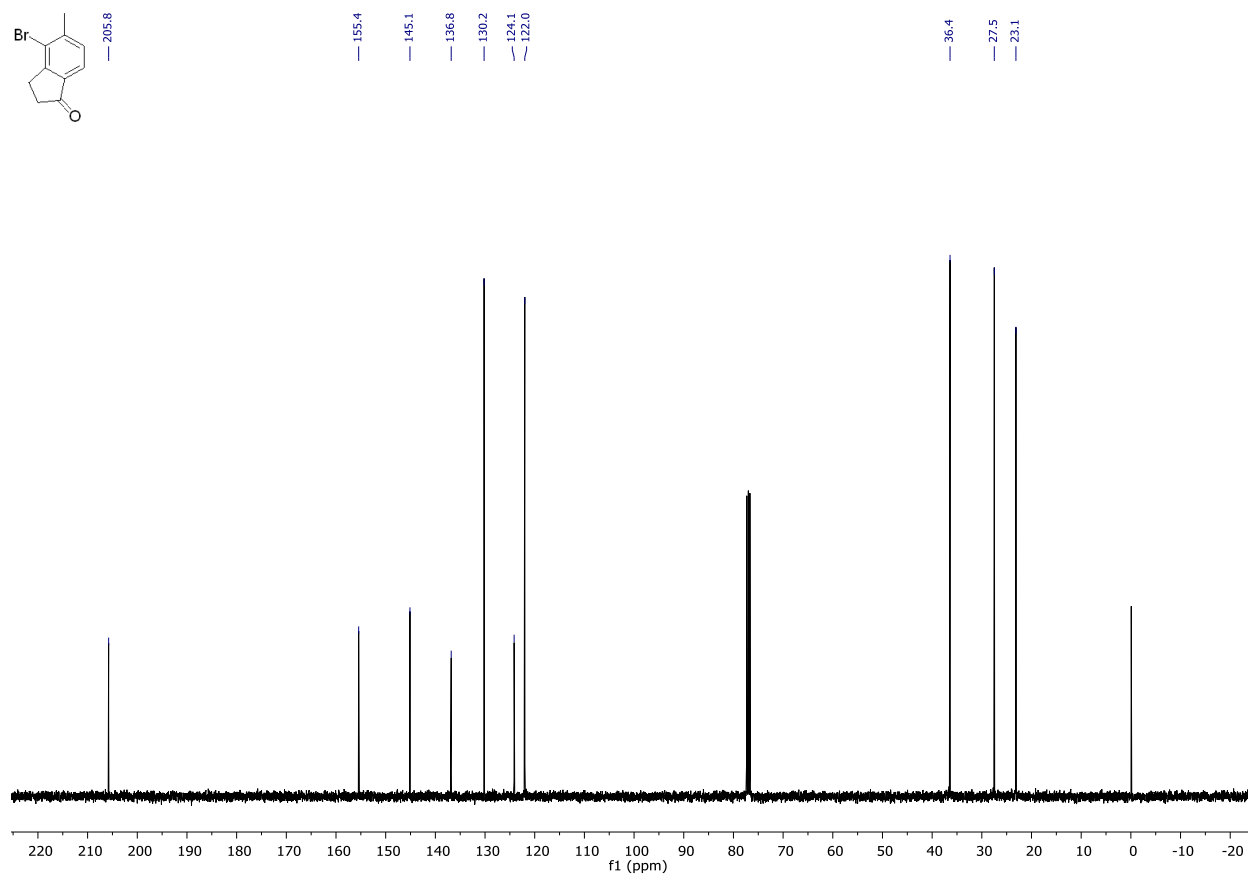
Figure 81: 6-Bromo-2,3-dihydro-5-methyl-4-nitroinden-1-one (**78**)—¹H NMR
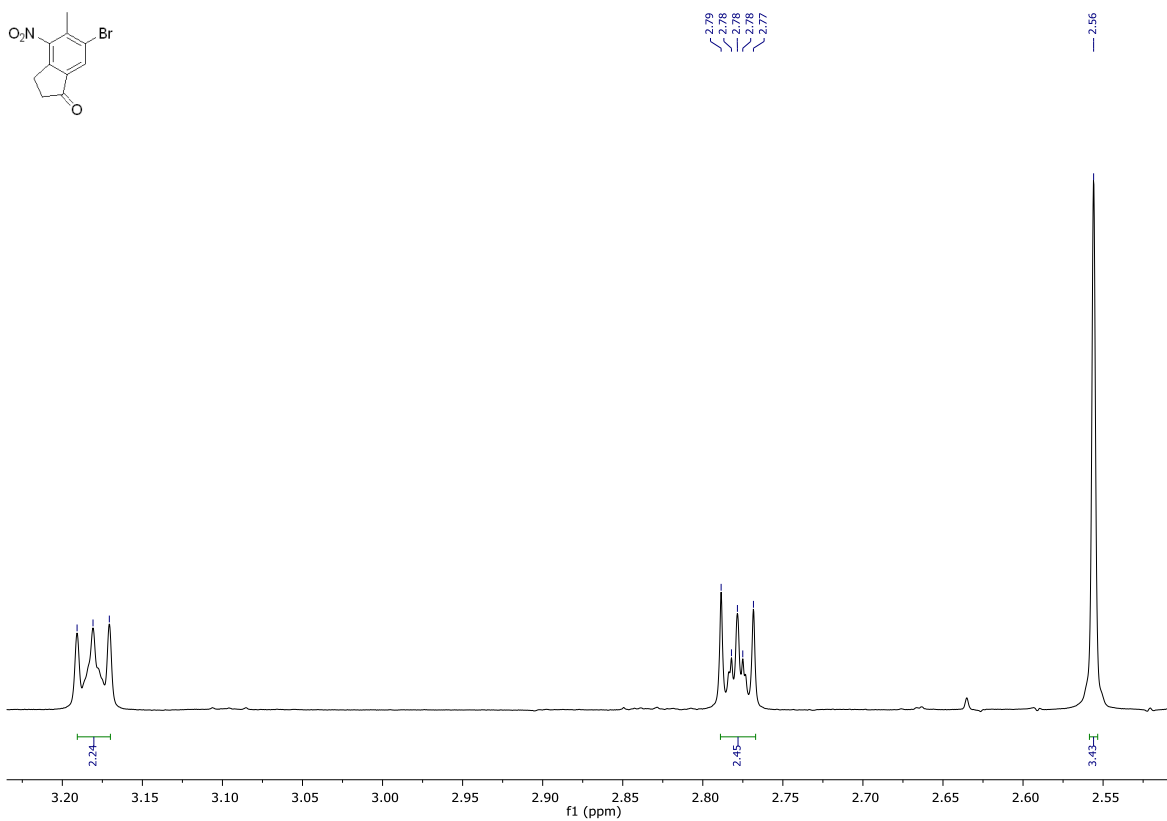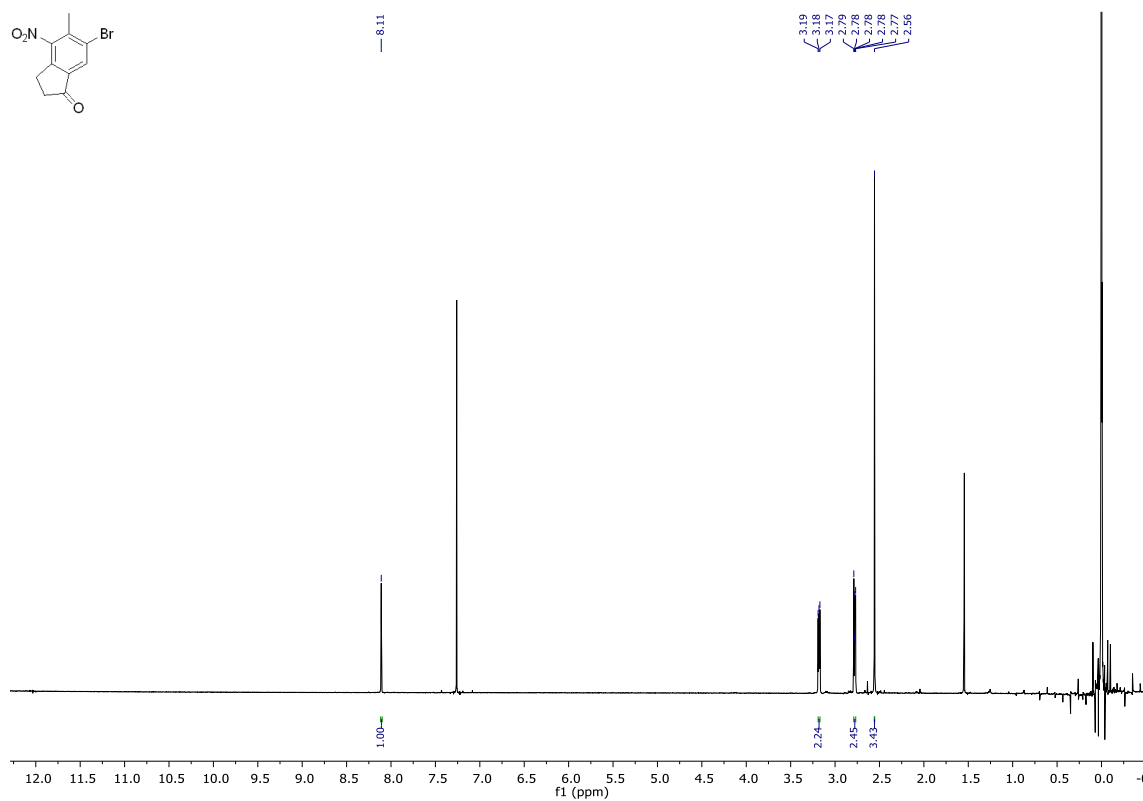
Figure 82: 6-Bromo-2,3-dihydro-5-methyl-4-nitroinden-1-one (**78**)—^{13}C NMR
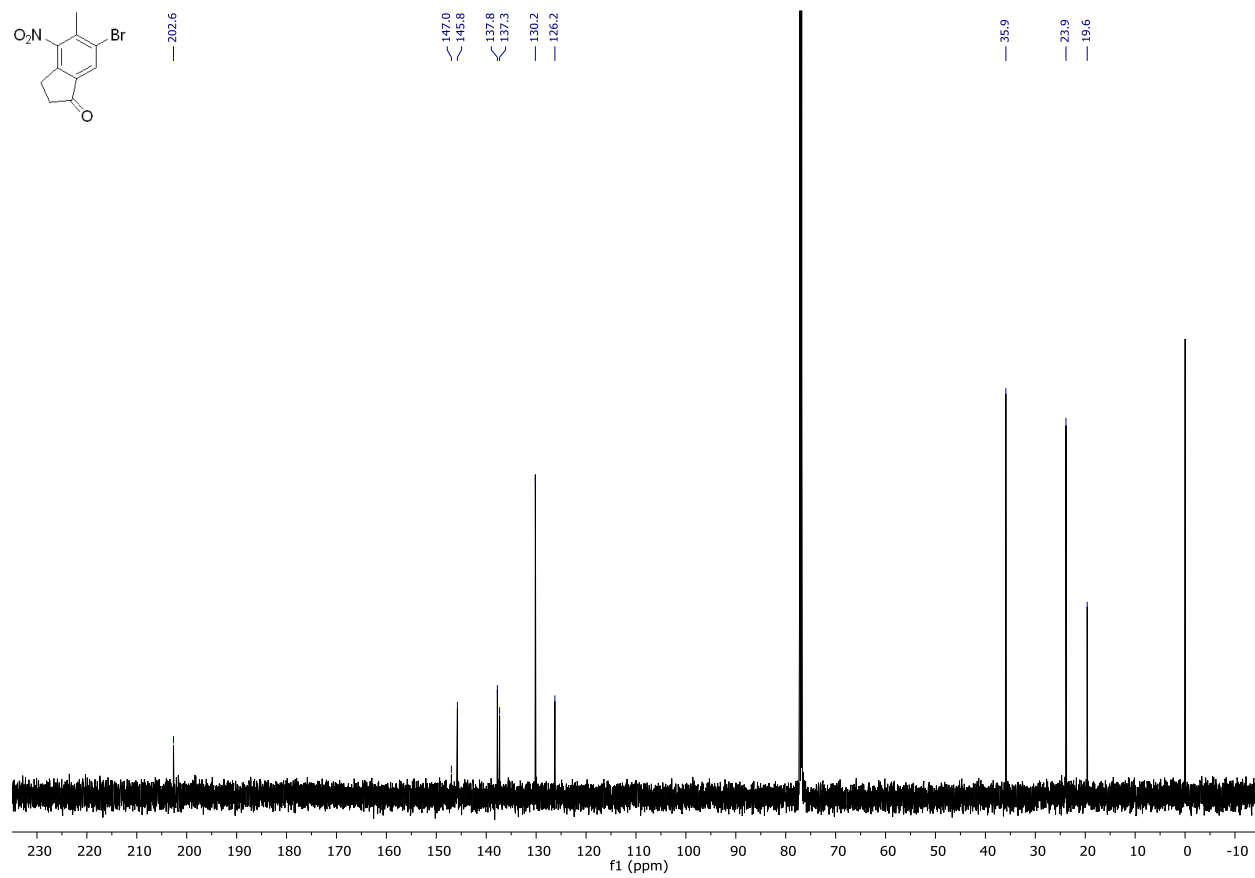
Figure 83: 6-Bromo-2,3-dihydro-5-methyl-7-nitroinden-1-one (**79**)—¹H NMR
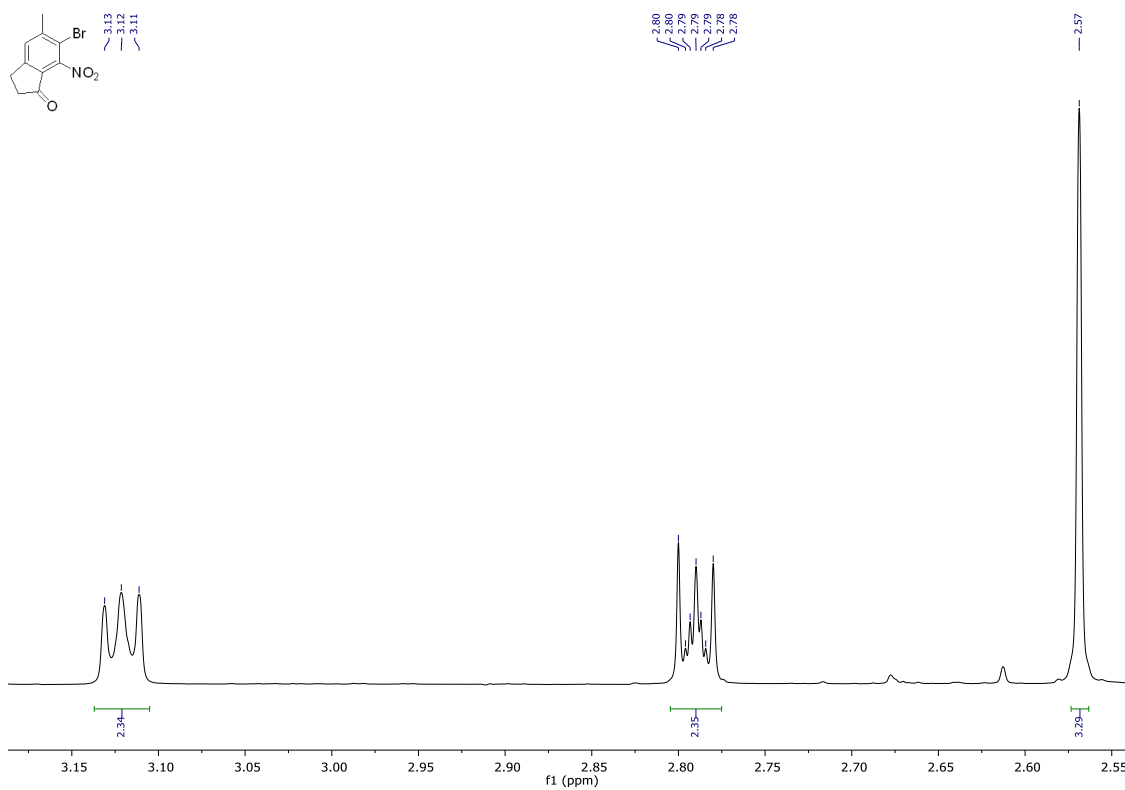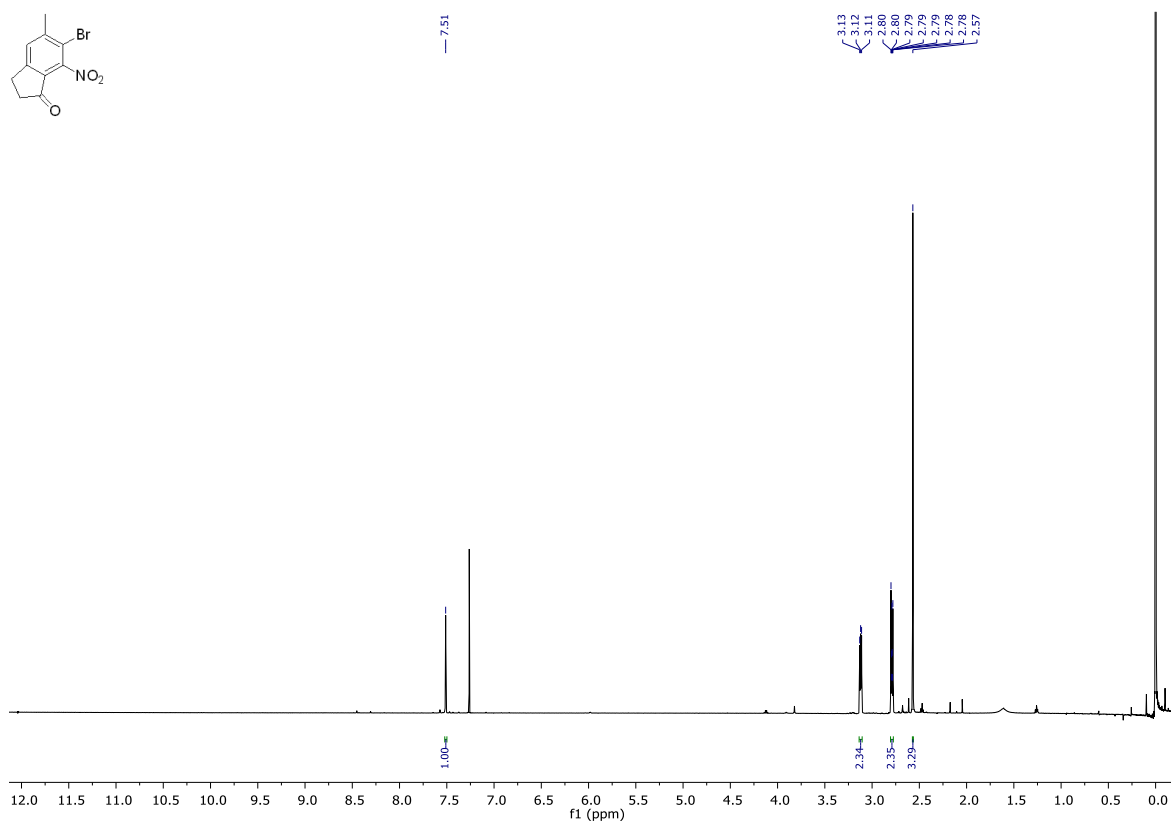
Figure 84: 6-Bromo-2,3-dihydro-5-methyl-7-nitroinden-1-one (**79**)—^{13}C NMR
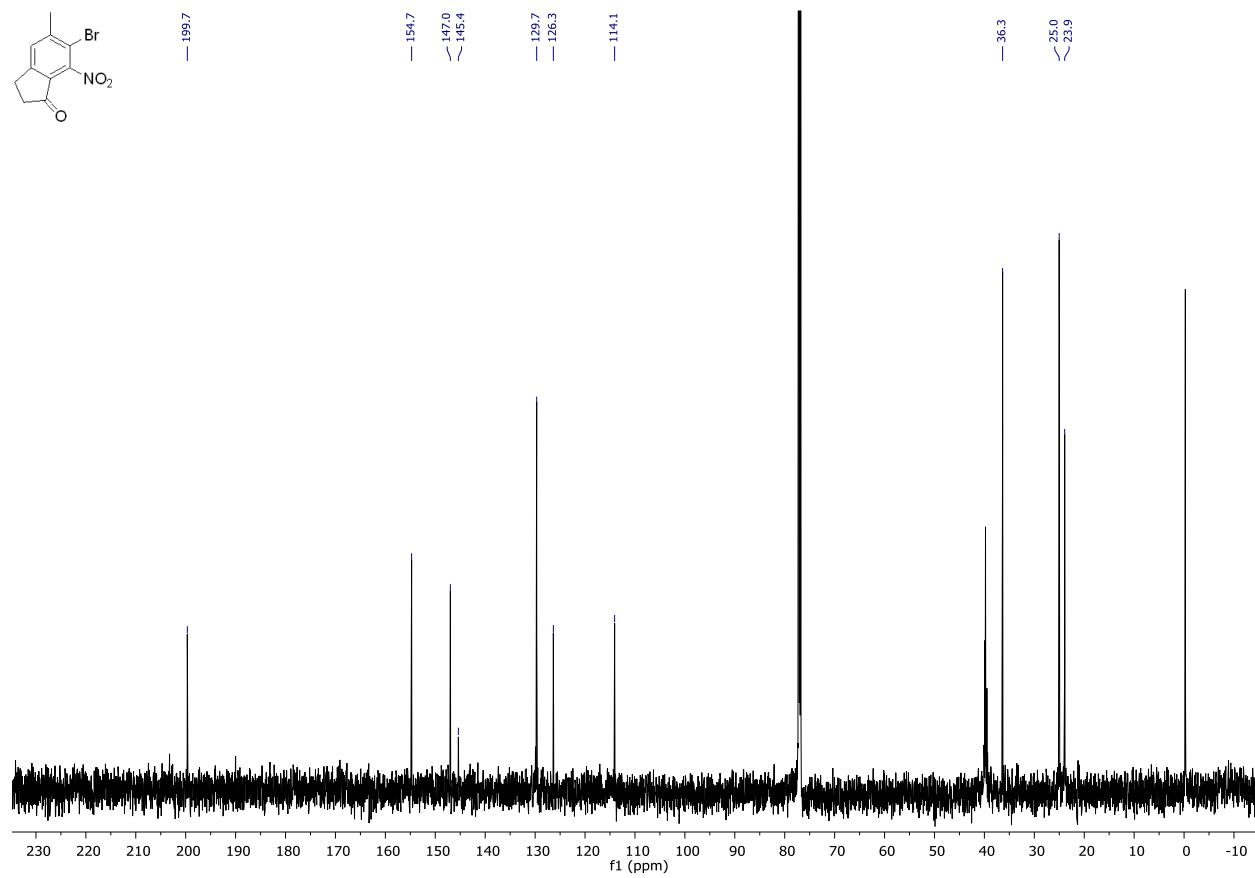
Figure 85: 6-(3-hydroxy-1-propenyl)-2,3-dihydro-5-methyl-7-nitroinden-1-one (**64**)—¹H NMR
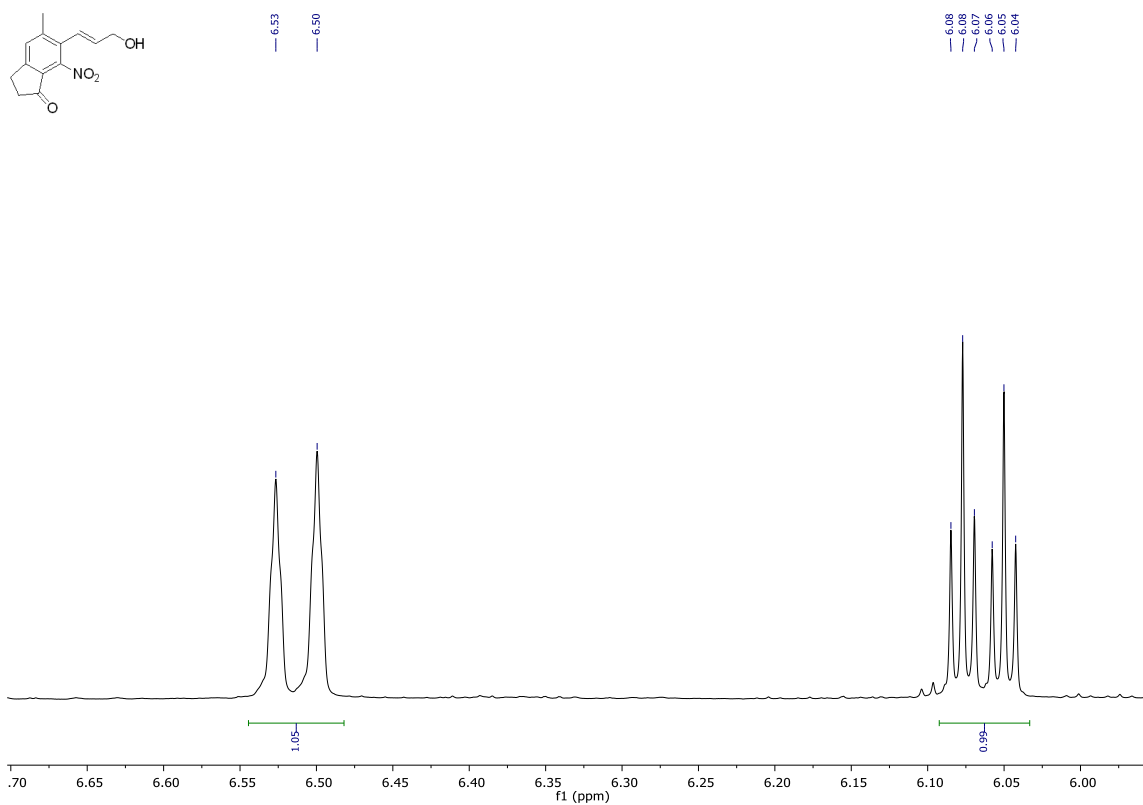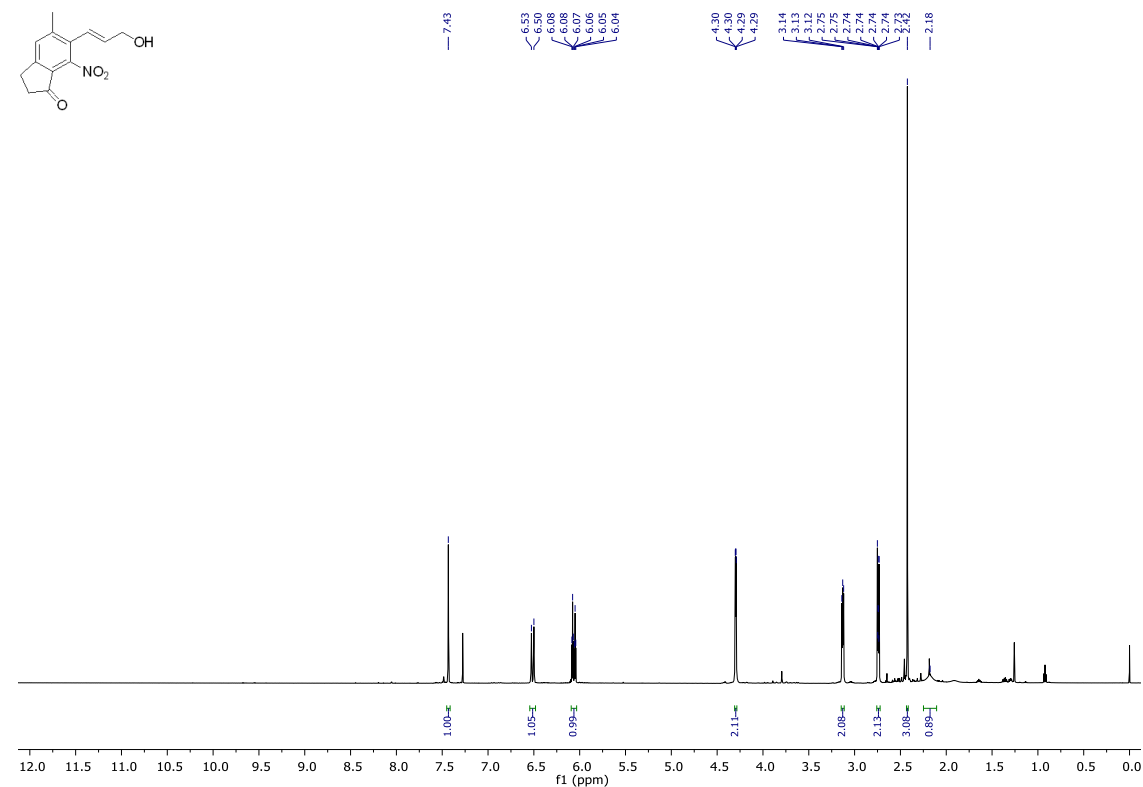
Figure 86: 6-(3-hydroxy-1-propenyl)-2,3-dihydro-5-methyl-7-nitroinden-1-one (**64**)—^{13}C NMR
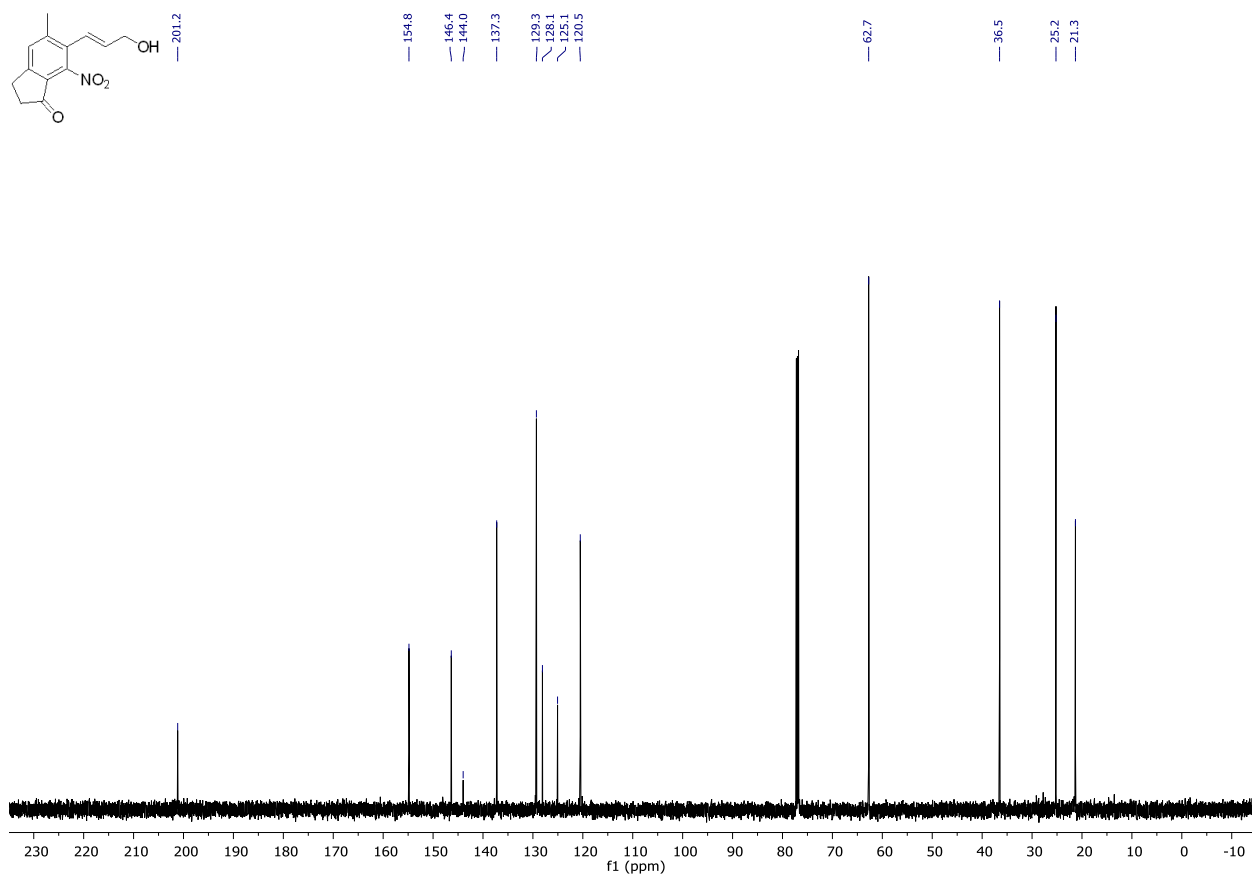
Figure 87: 6-(3-methoxy-1-propenyl)-2,3-dihydro-5-methyl-7-nitroinden-1-one (**81**)—^{1}H NMR
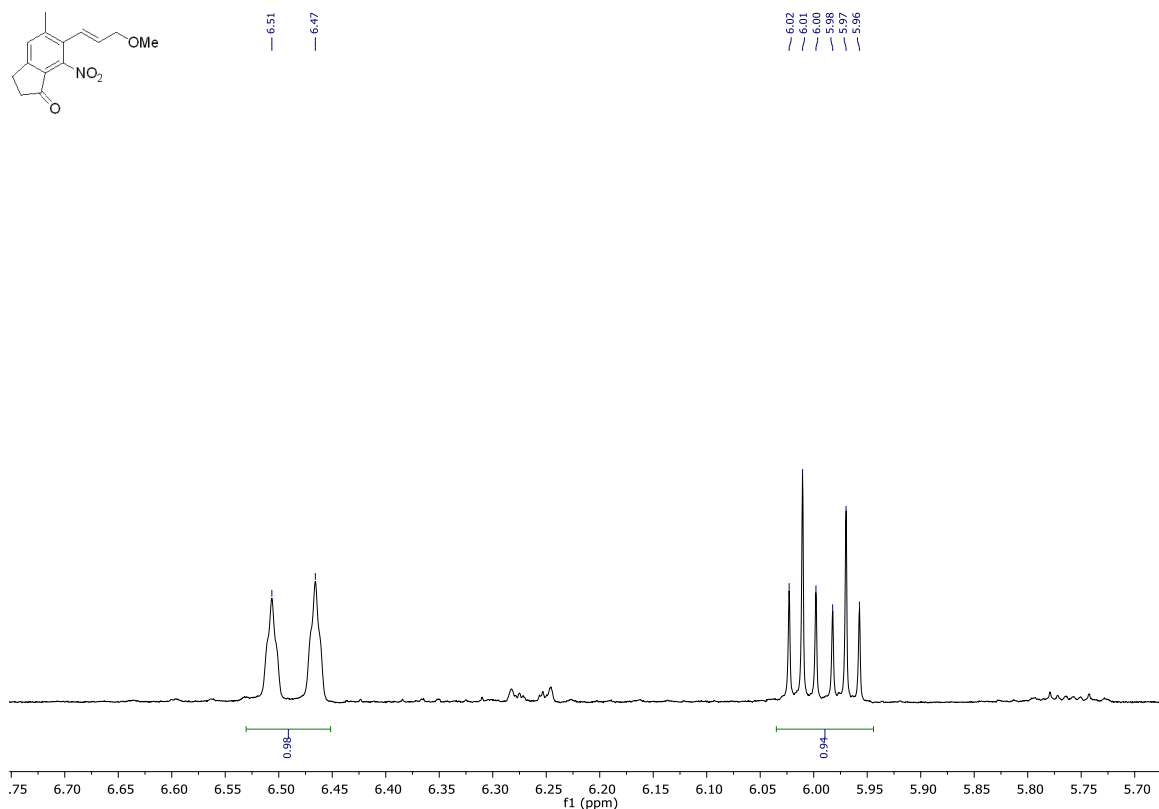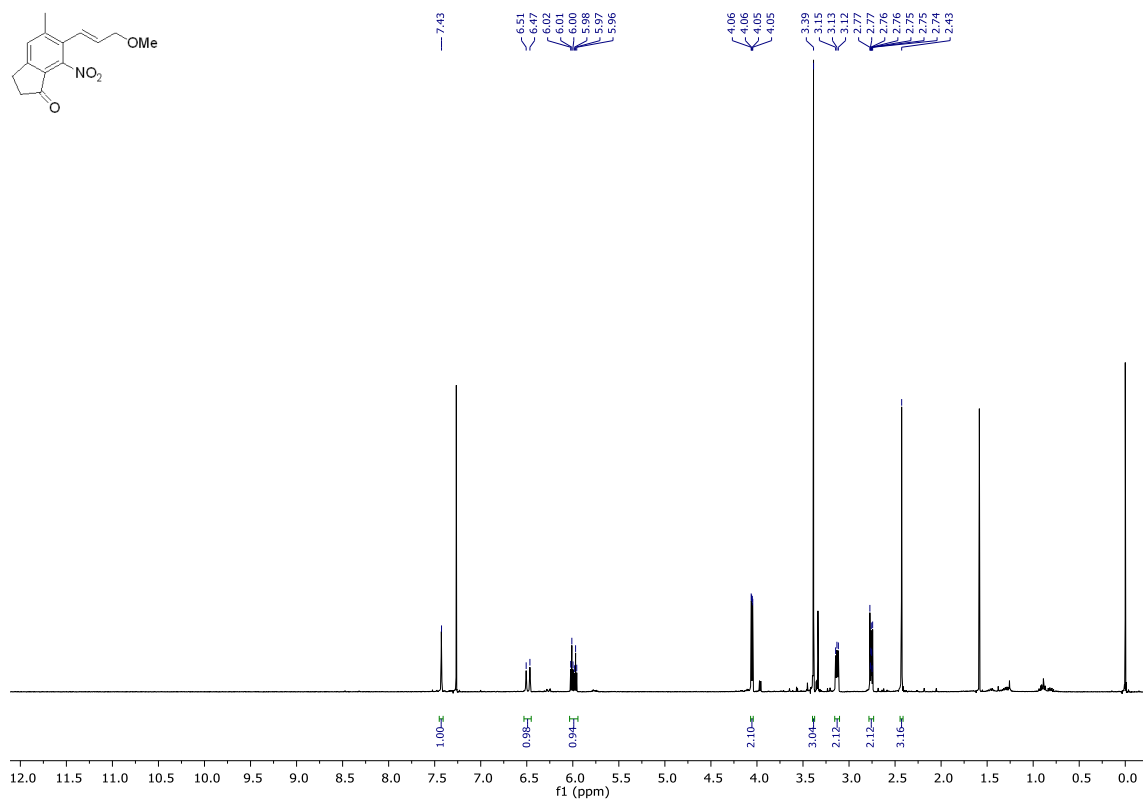
Figure 88: 6-(3-methoxy-1-propenyl)-2,3-dihydro-5-methyl-7-nitroinden-1-one (**81**)—^{13}C NMR
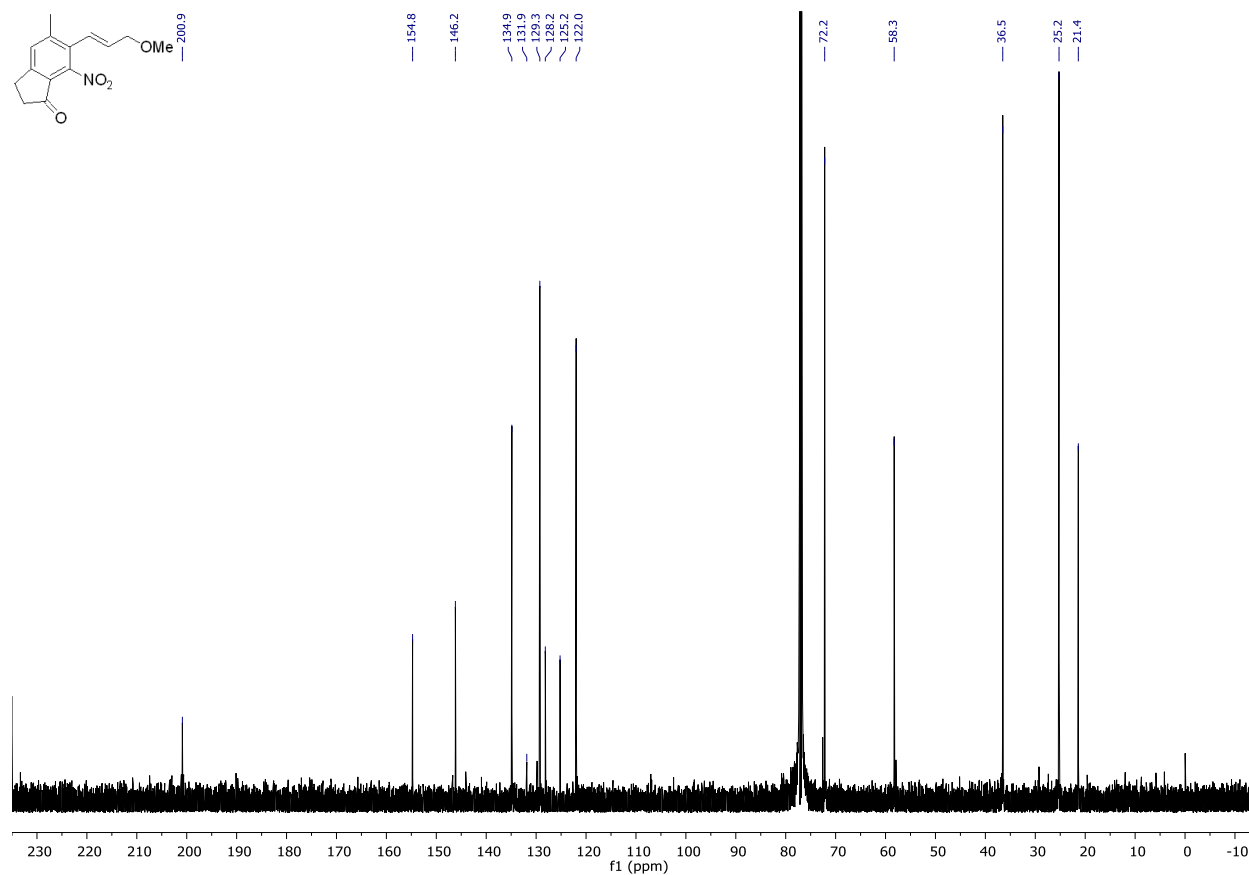
Figure 89: 3-methoxy-5-(3-methoxy-1-propenyl)-6-methyl-4-nitroindene (**83**)—¹H NMR
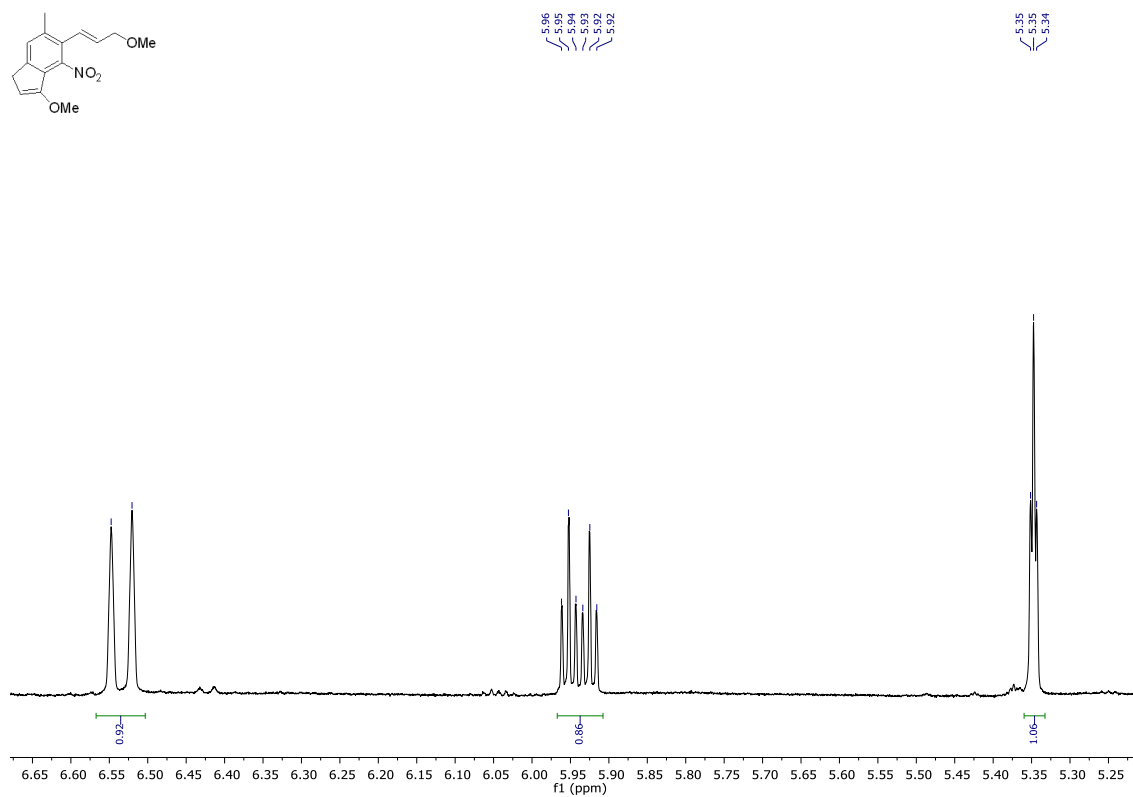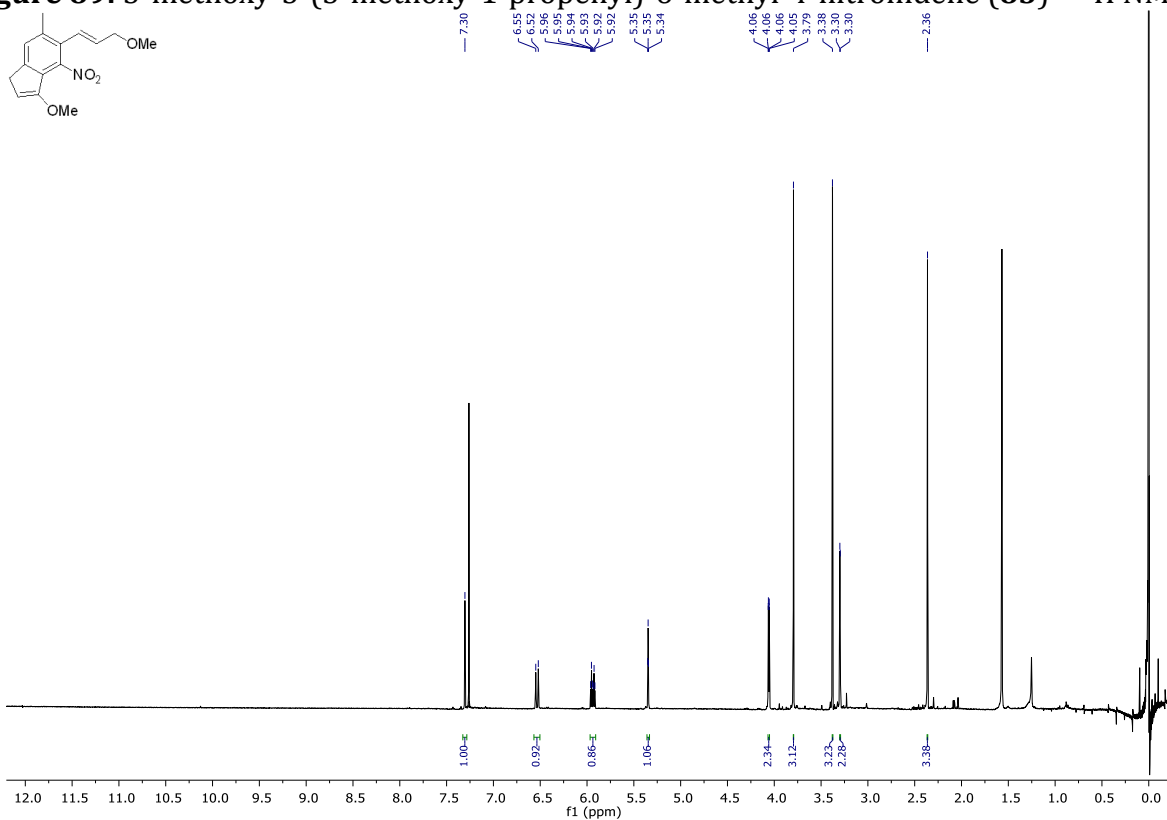
Figure 90: 3-methoxy-5-(3-methoxy-1-propenyl)-6-methyl-4-nitroindene (**83**)—¹³C NMR
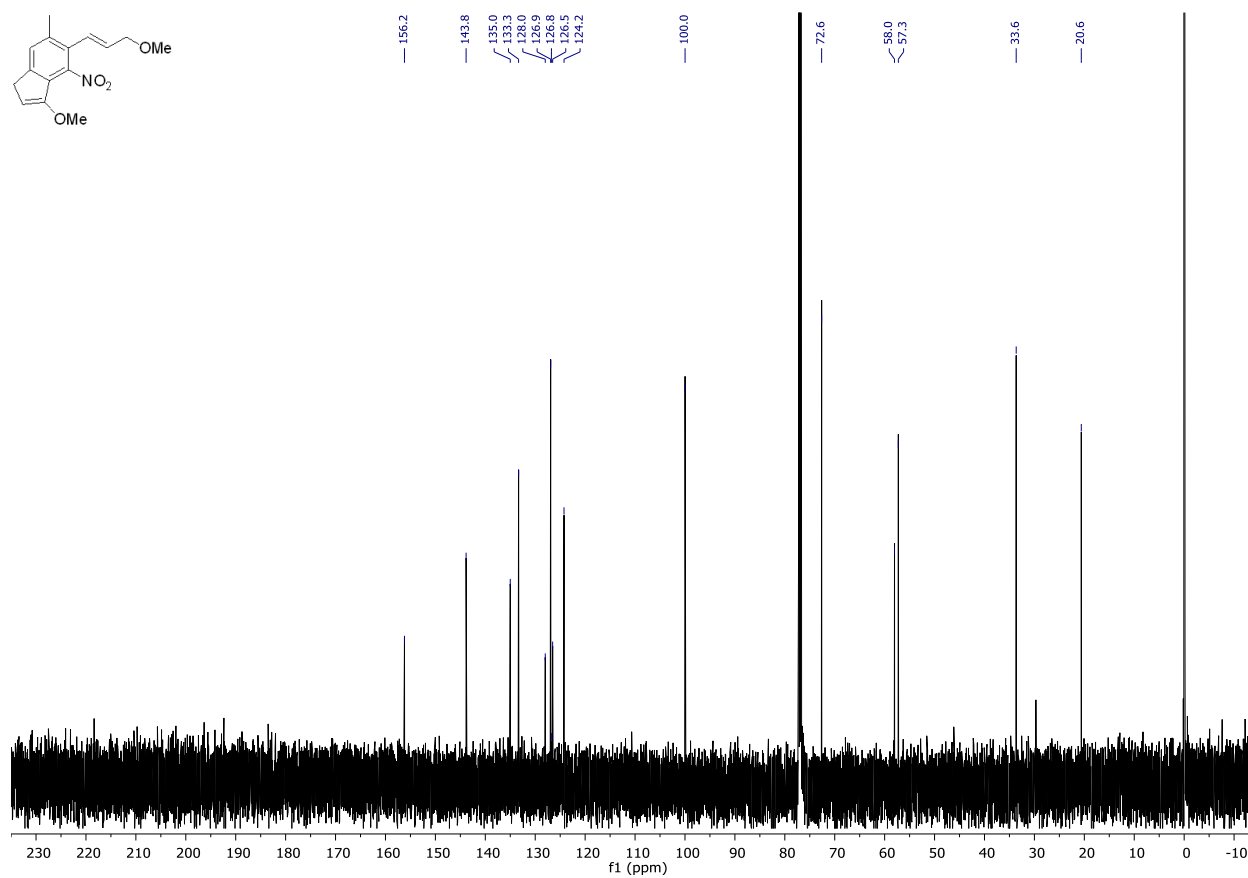
Figure 91: 6-(1,2-epoxy-3-hydroxypropyl)-2,3-dihydro-5-methyl-7-nitroinden-1-one (**89**)—¹H NMR
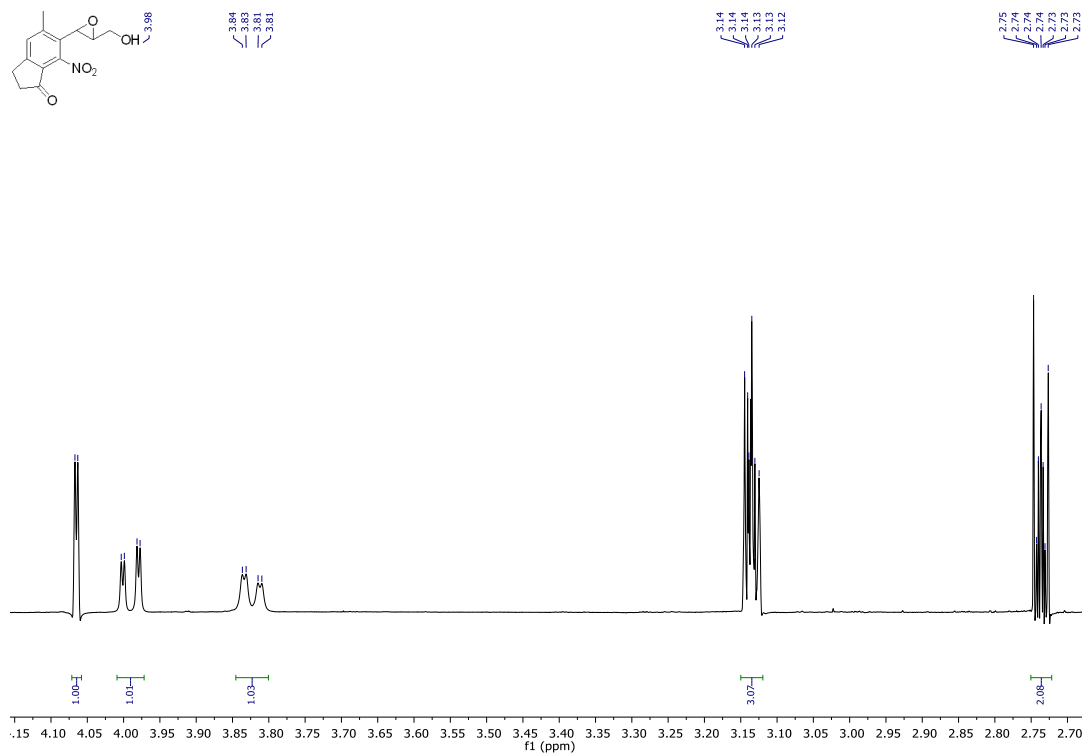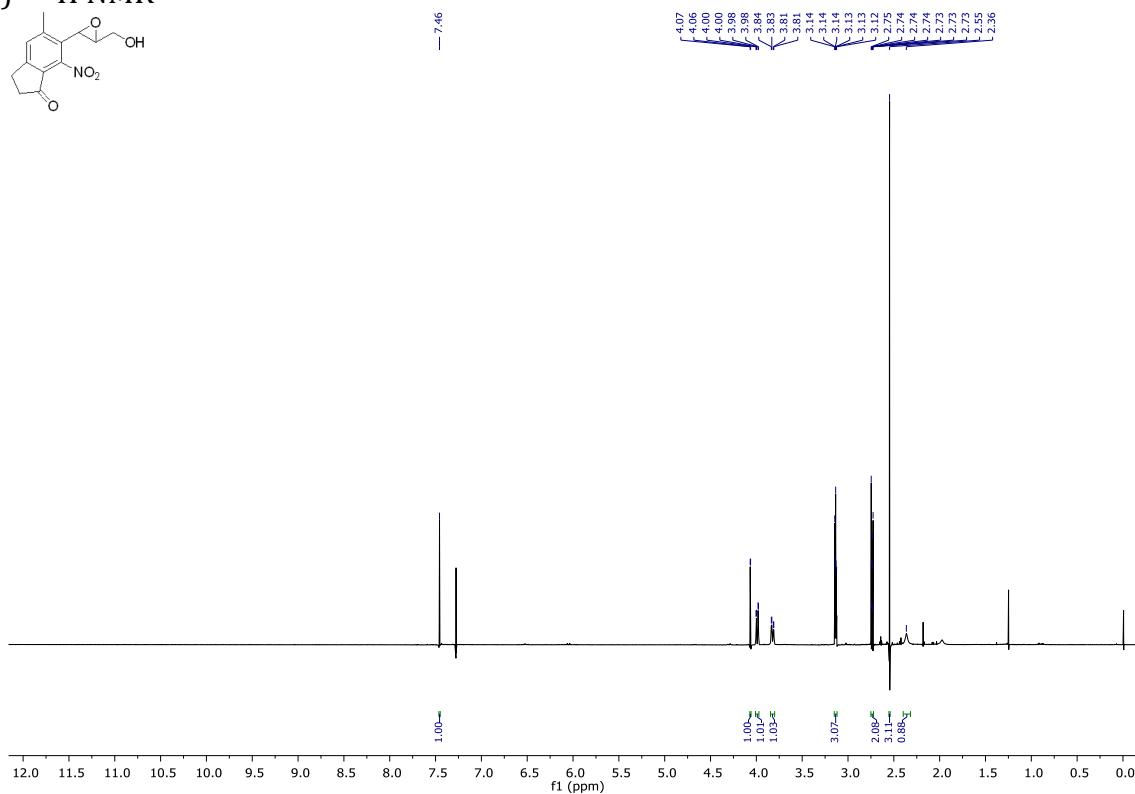
Figure 92: 6-(1,2-epoxy-3-hydroxypropyl)-2,3-dihydro-5-methyl-7-nitroinden-1-one (**89**)—¹³C NMR
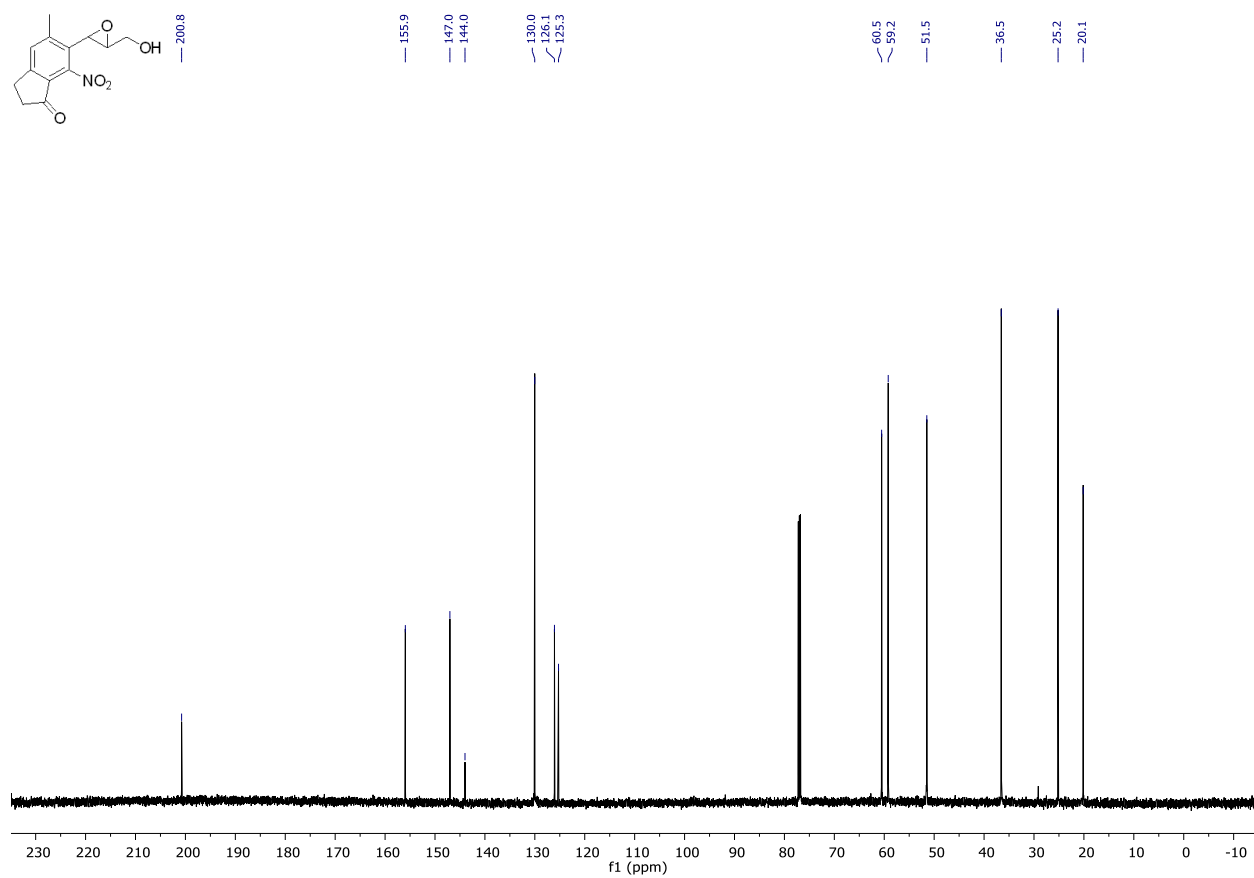
Figure 93: 6,7-dihydro-2-(hydroxymethyl)-4-methylcyclopent[*g*]-(*N*-hydroxy)indol-8(1*H*)-one (**90**)—¹H NMR (DMSO-*d₆*/CDCl₃)
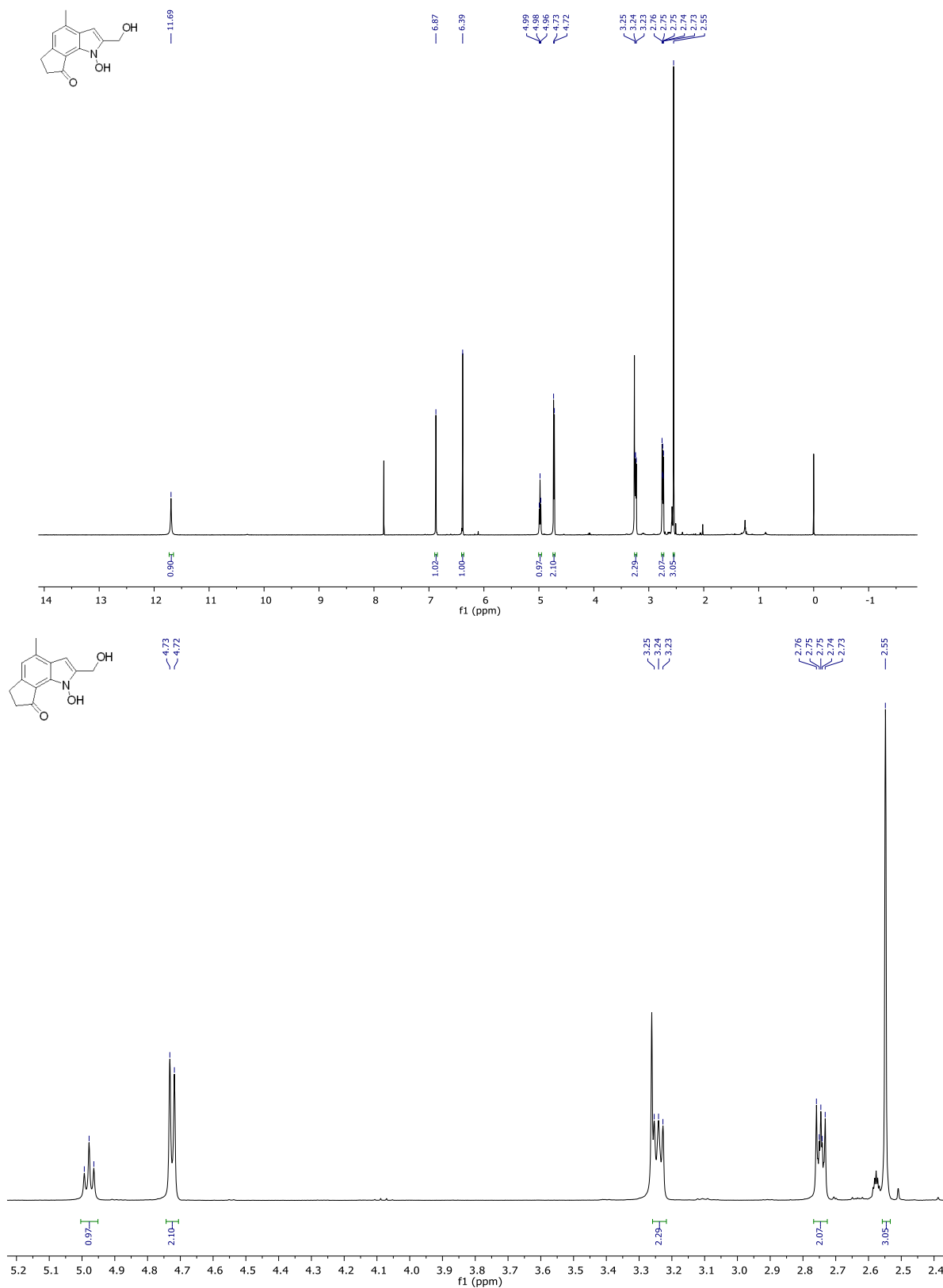
Figure 94: 6,7-dihydro-2-(hydroxymethyl)-4-methylcyclopent[*g*]-(*N*-hydroxy)indol-8(1*H*)-one (**90**)—¹H NMR (CDCl₃)
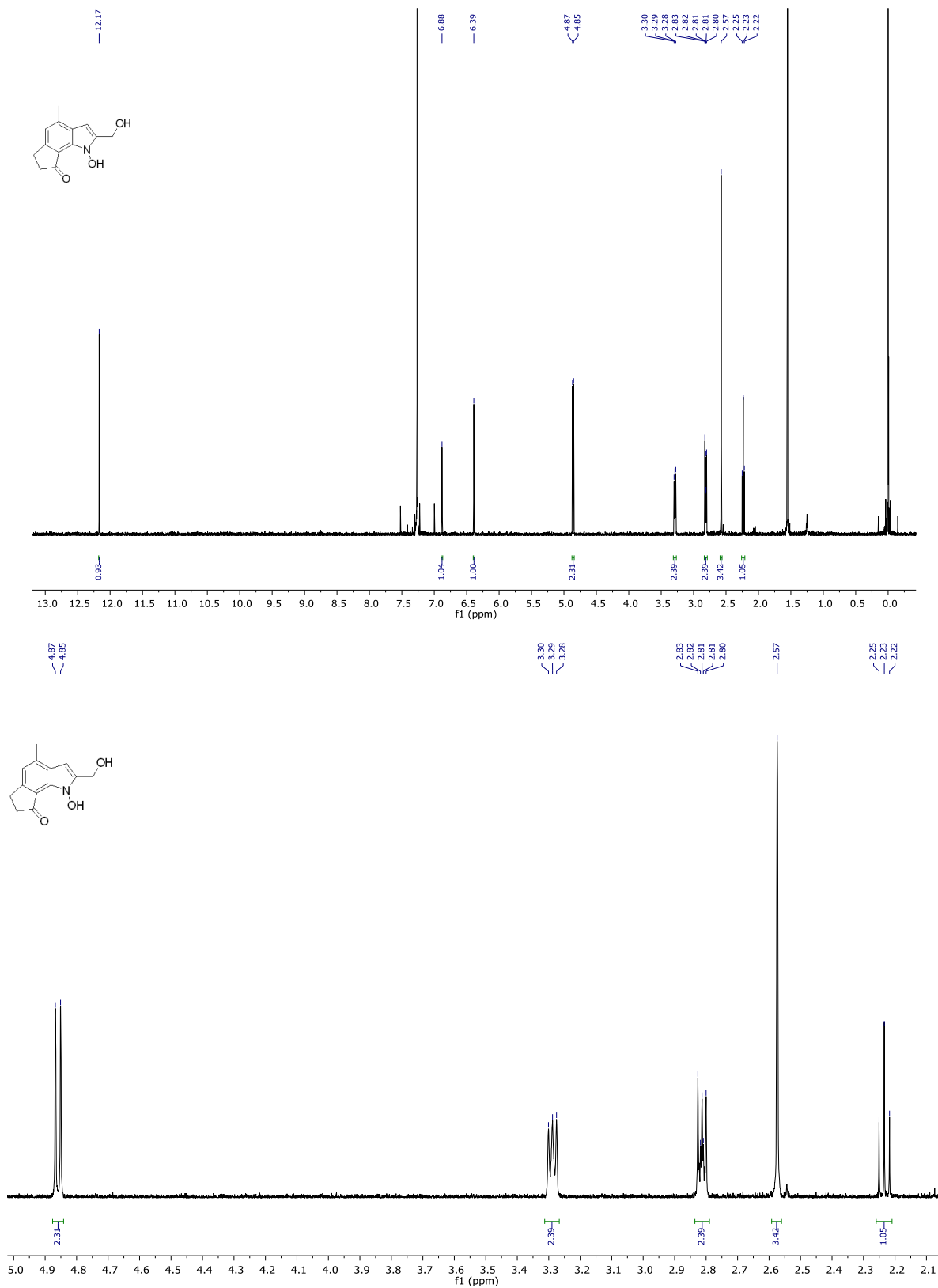
Figure 95: 6,7-dihydro-2-(hydroxymethyl)-4-methylcyclopent[*g*]-(*N*-hydroxy)indol-8(1*H*)-one (**90**)—¹³C NMR
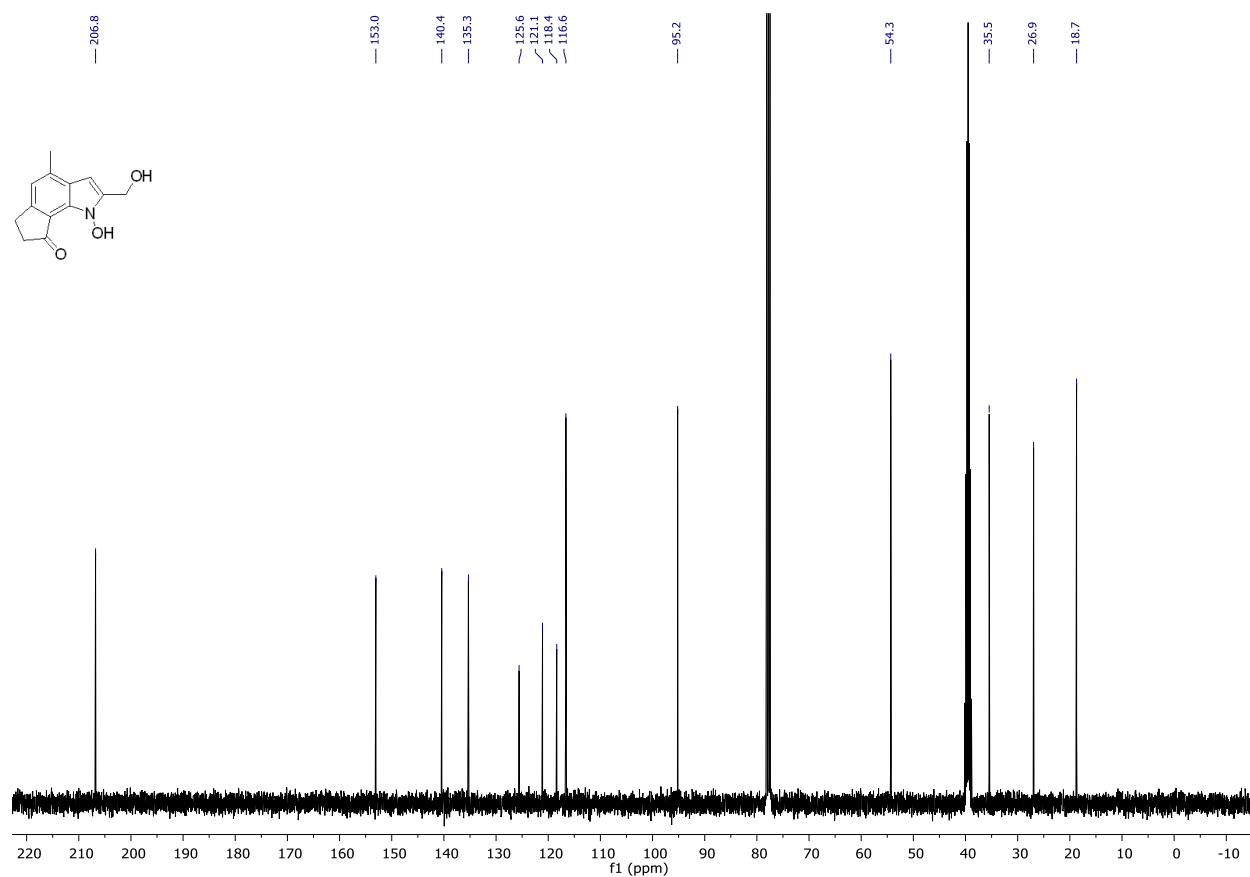
Figure 96: 6,7-dihydro-2,4-dimethylcyclopent[*g*]indol-8(1*H*)-one (**91**)—¹H NMR
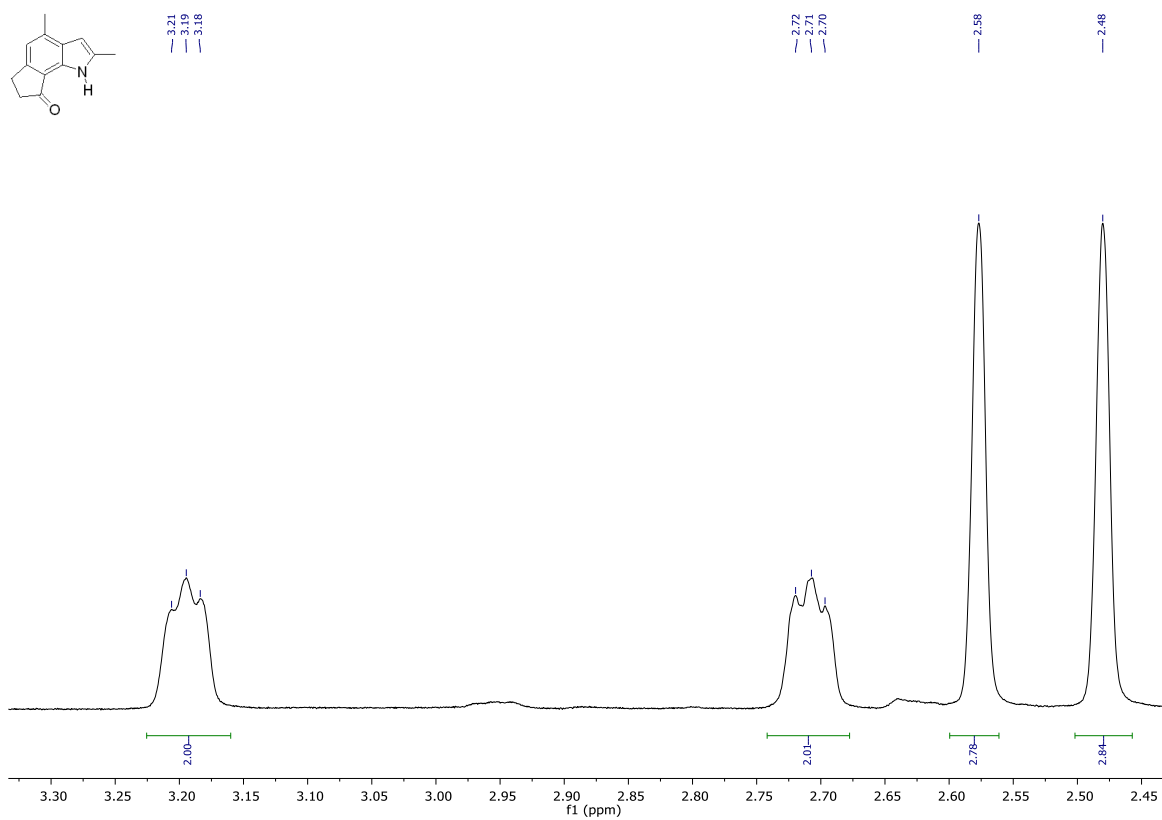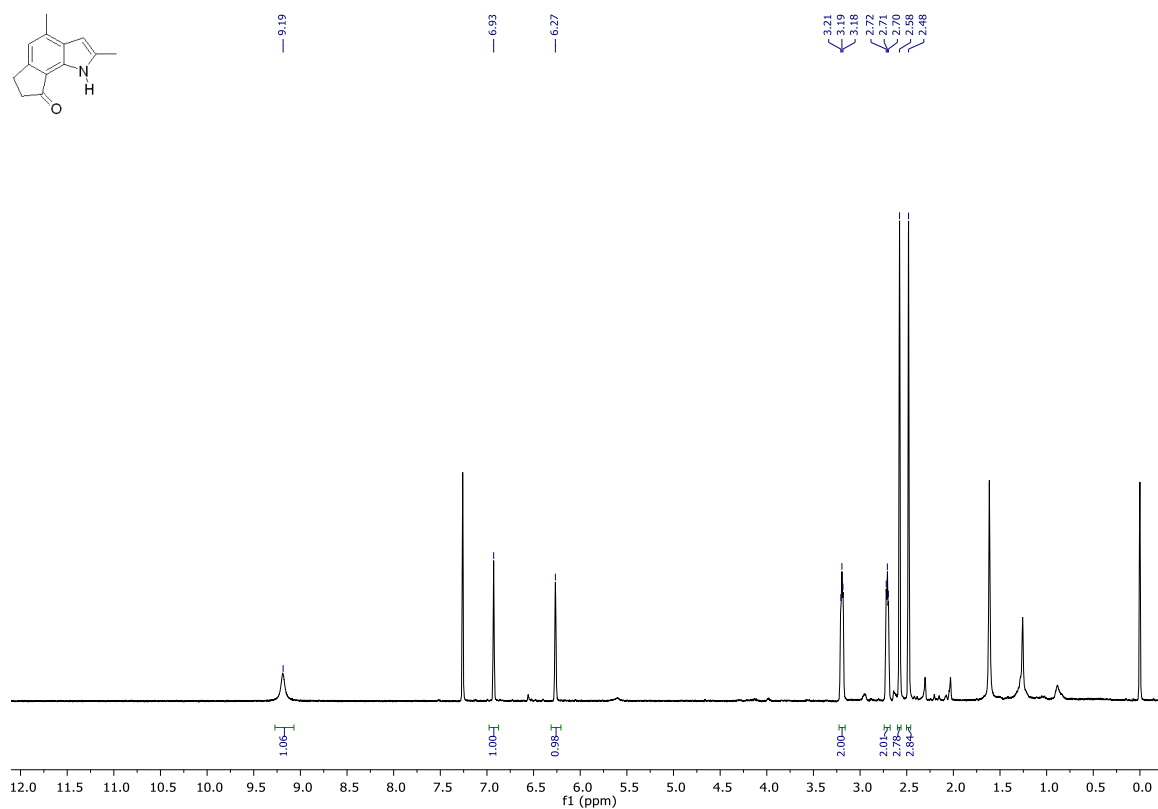
Figure 97: 6,7-dihydro-2,4-dimethylcyclopent[*g*]indol-8(1*H*)-one (**91**)—¹³C NMR
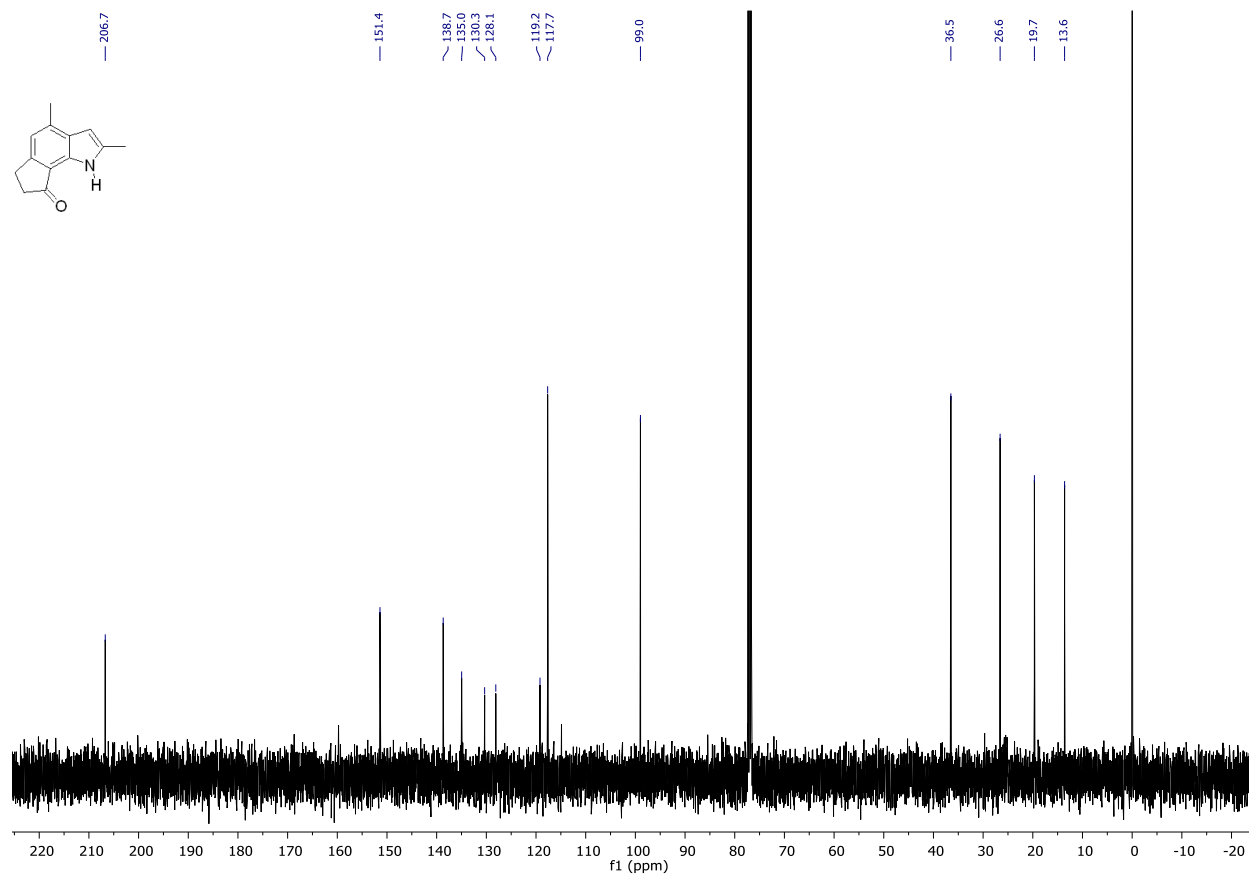
Figure 98: Dilemmaone B (**53**)—^{1}H NMR (CDCl$_3$)
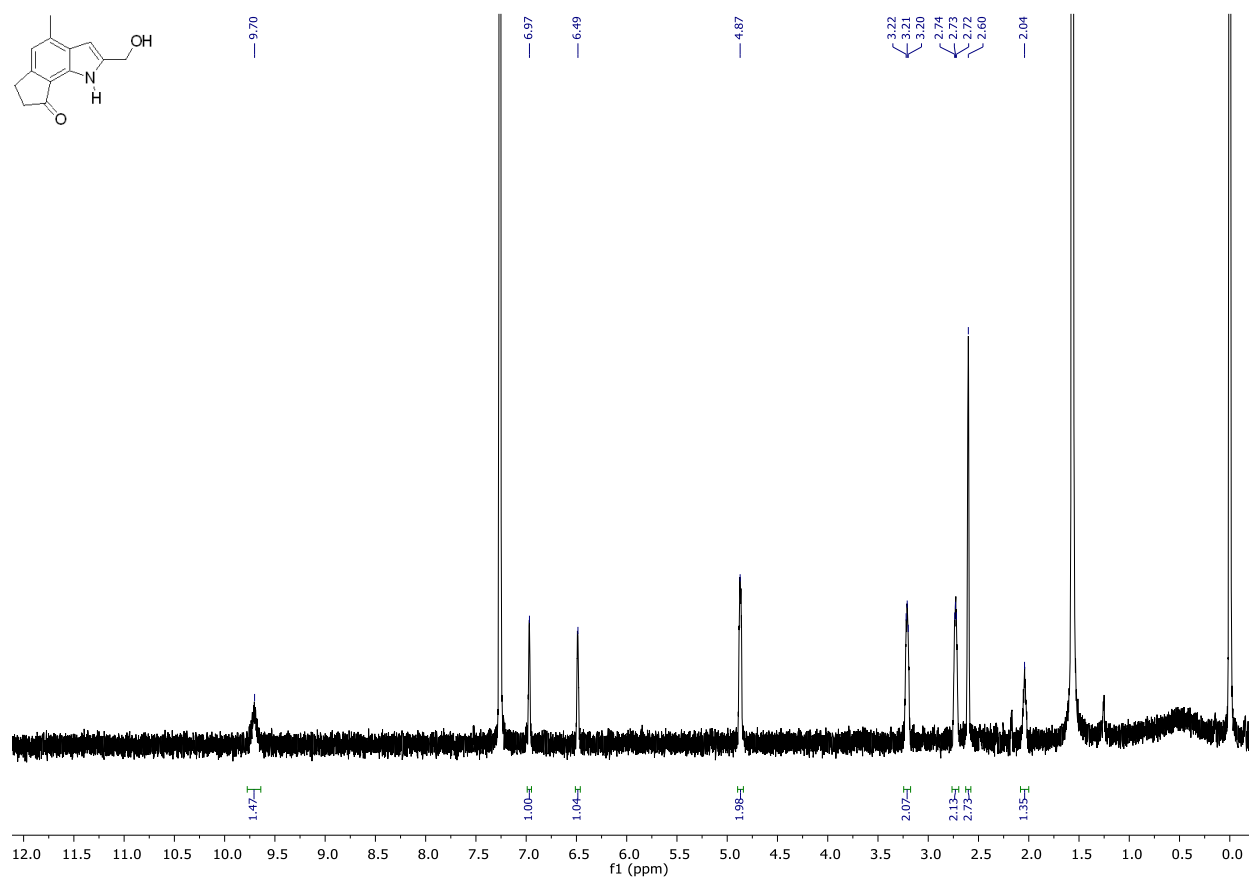
Figure 99: Dilemmaone B (**53**)—¹H NMR (DMSO-*d₆*)
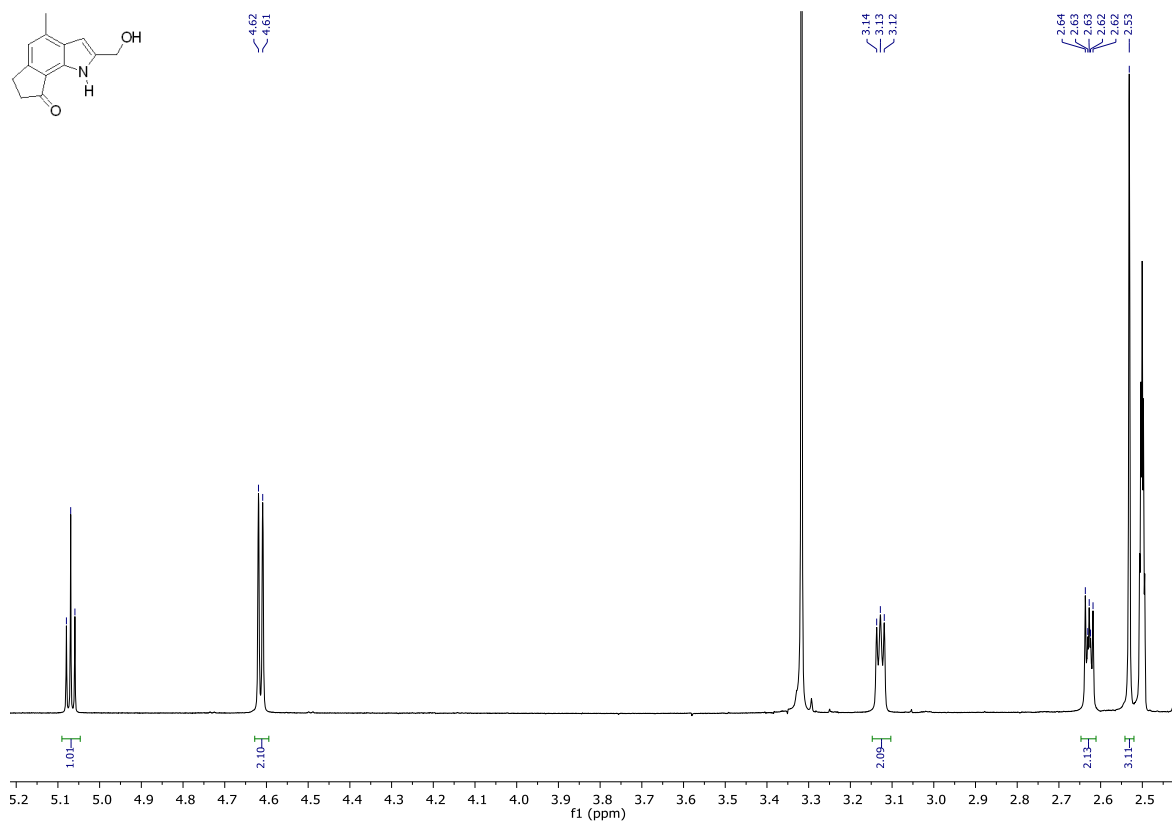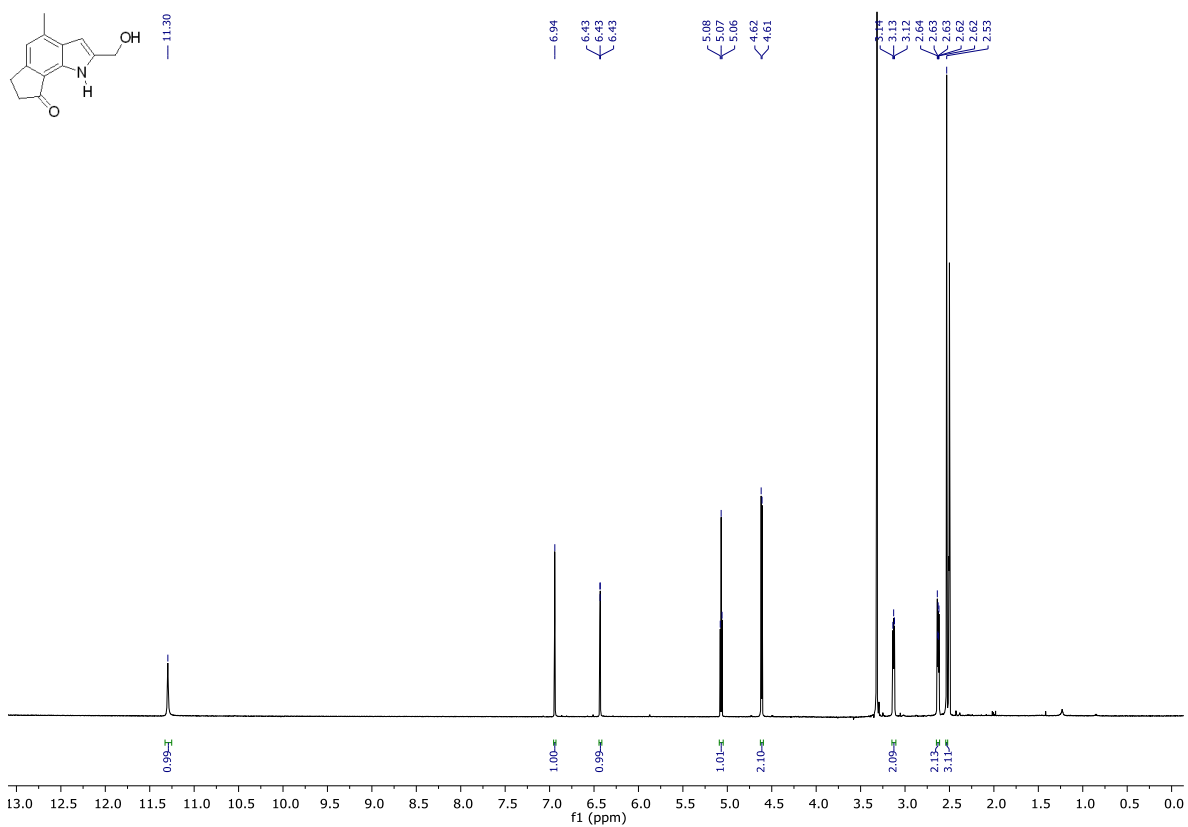
Figure 100: Dilemmaone B (**53**)—^{13}C NMR (DMSO-d_6)
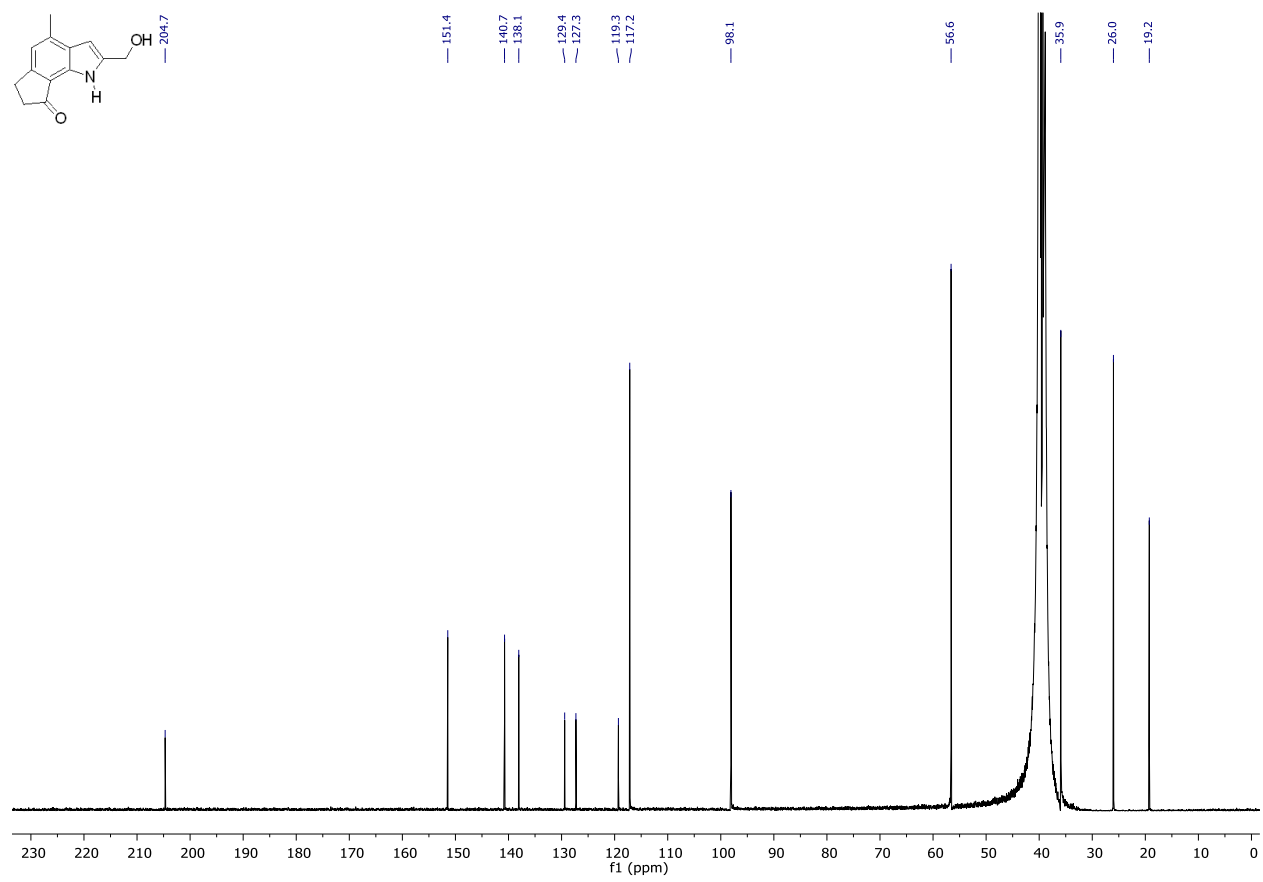
Figure 101: Dilemmaone B (**53**)—^{1}H-^{15}N gHSQCAD

(a)

(b)
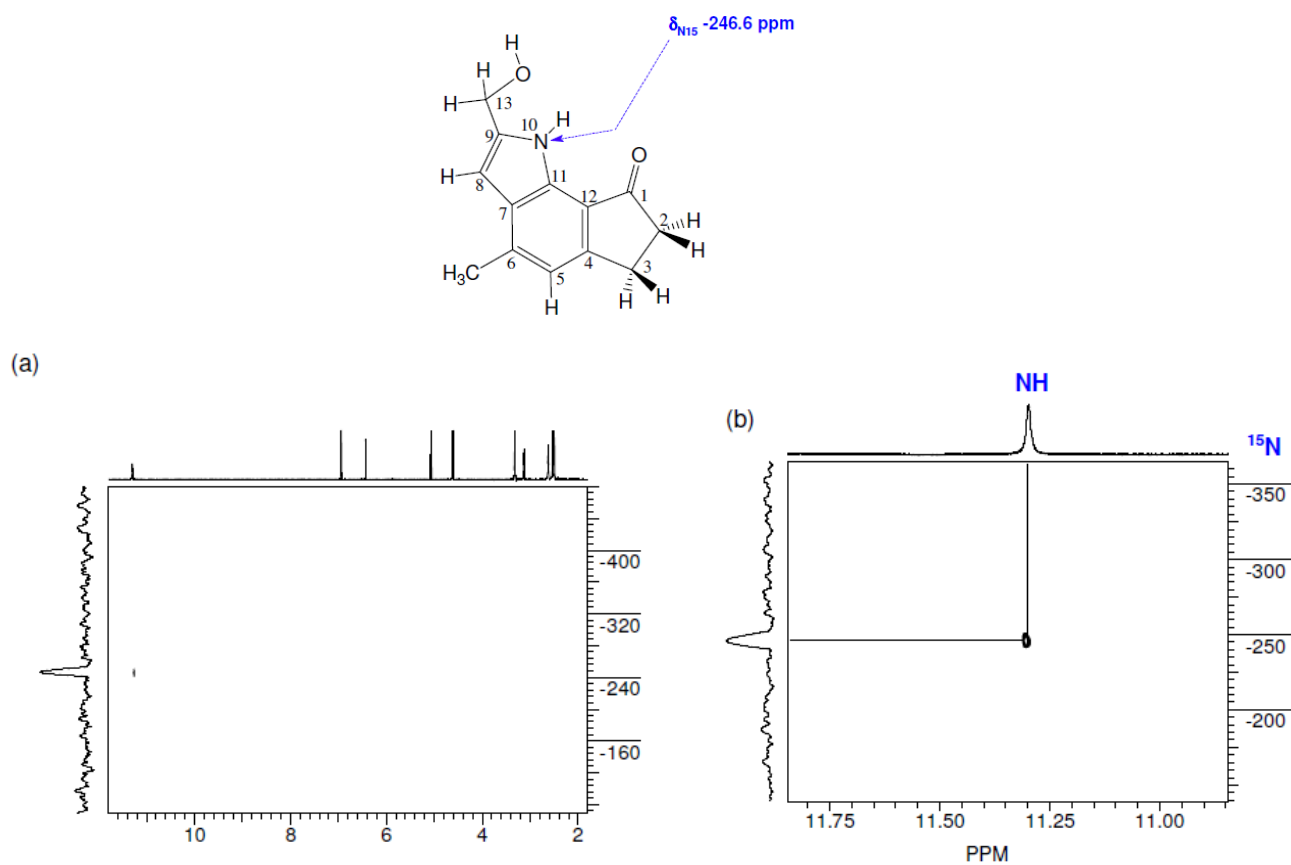
^{a}Full 1H-15N gHSQCAD for **53**.

^{b}Expansion of spectrum a.

Figure 102: Dilemmaone B (**53**)—gCOSY
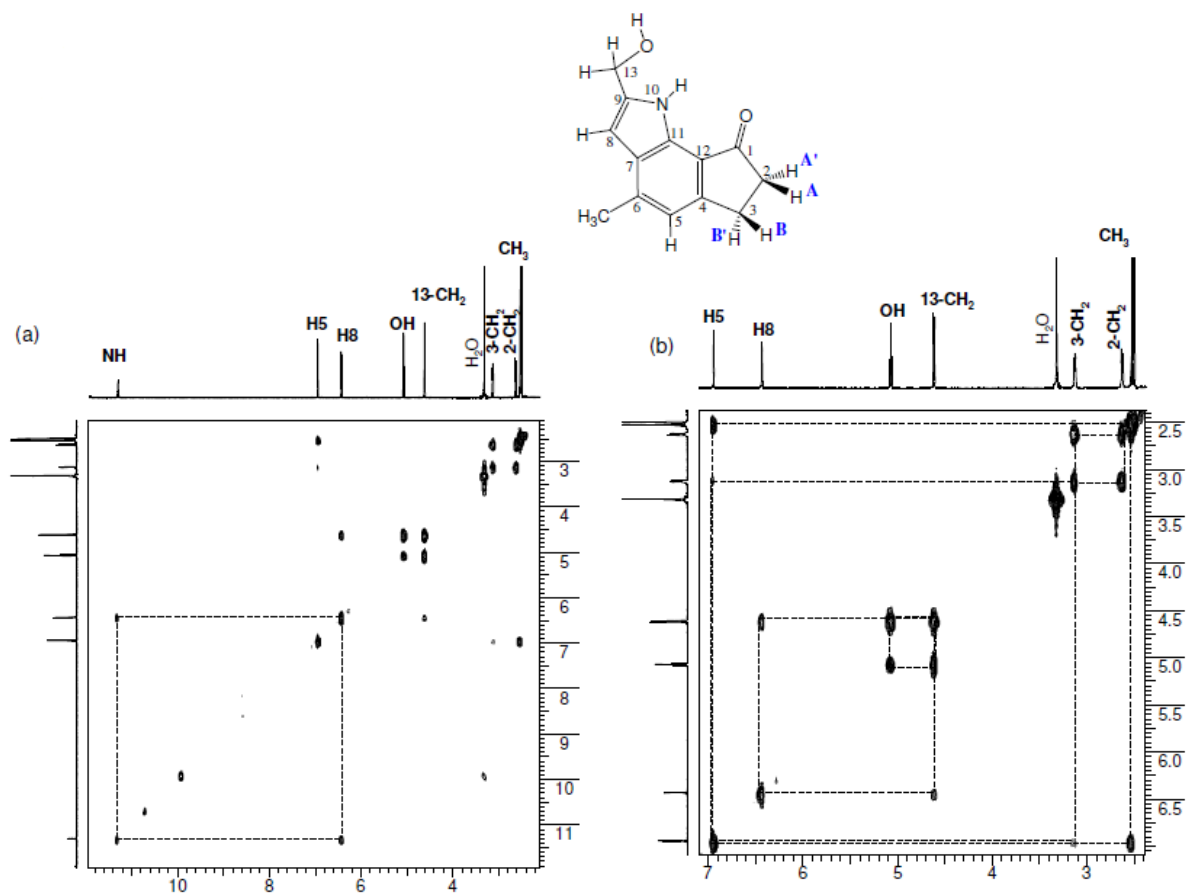
aFull gCOSY spectrum for **53**.

bExpansion of spectrum (a).

Figure 103: Dilemmaone B (**53**)—gHSQCAD ($^1J_{HC}$)
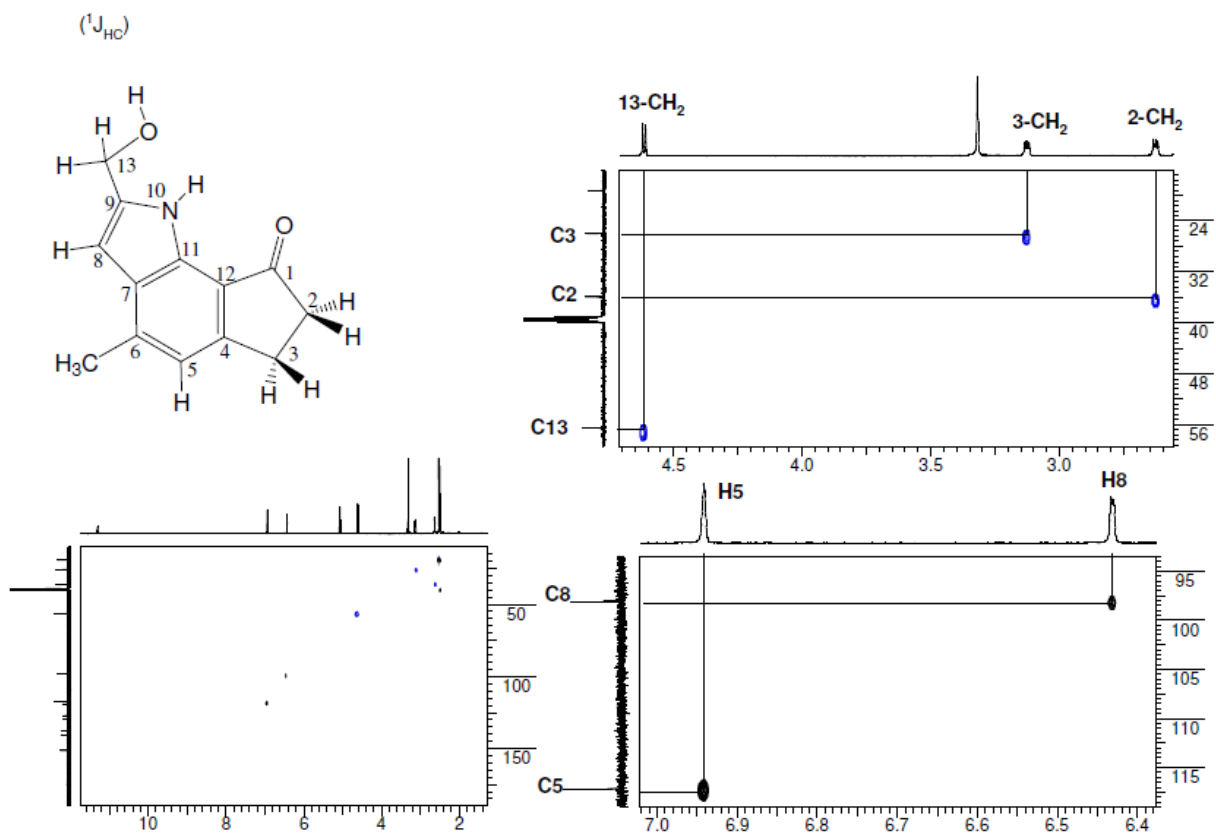
Figure 104: Dilemmaone B (**53**)—gHMBCAD Spectrum A
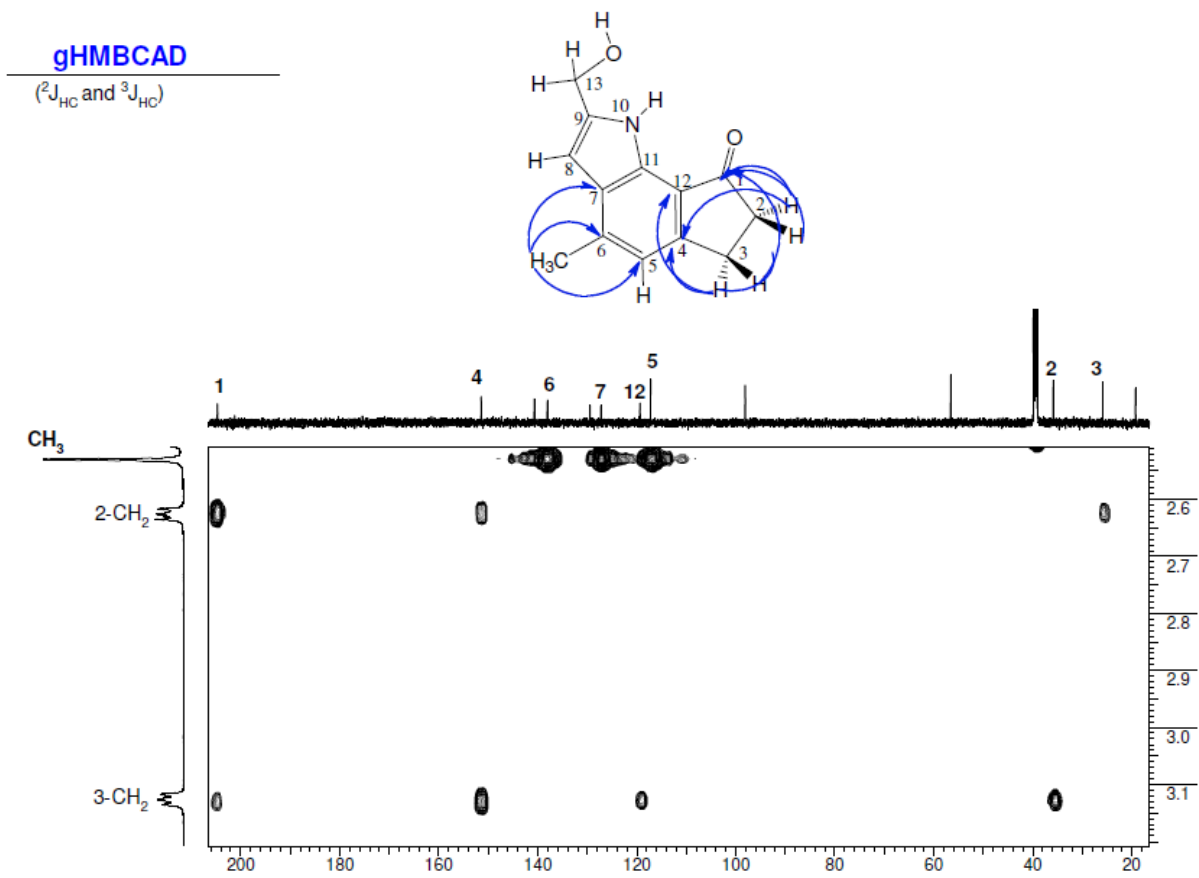
Figure 105: Dilemmaone B (**53**)—gHMBCAD Spectrum B
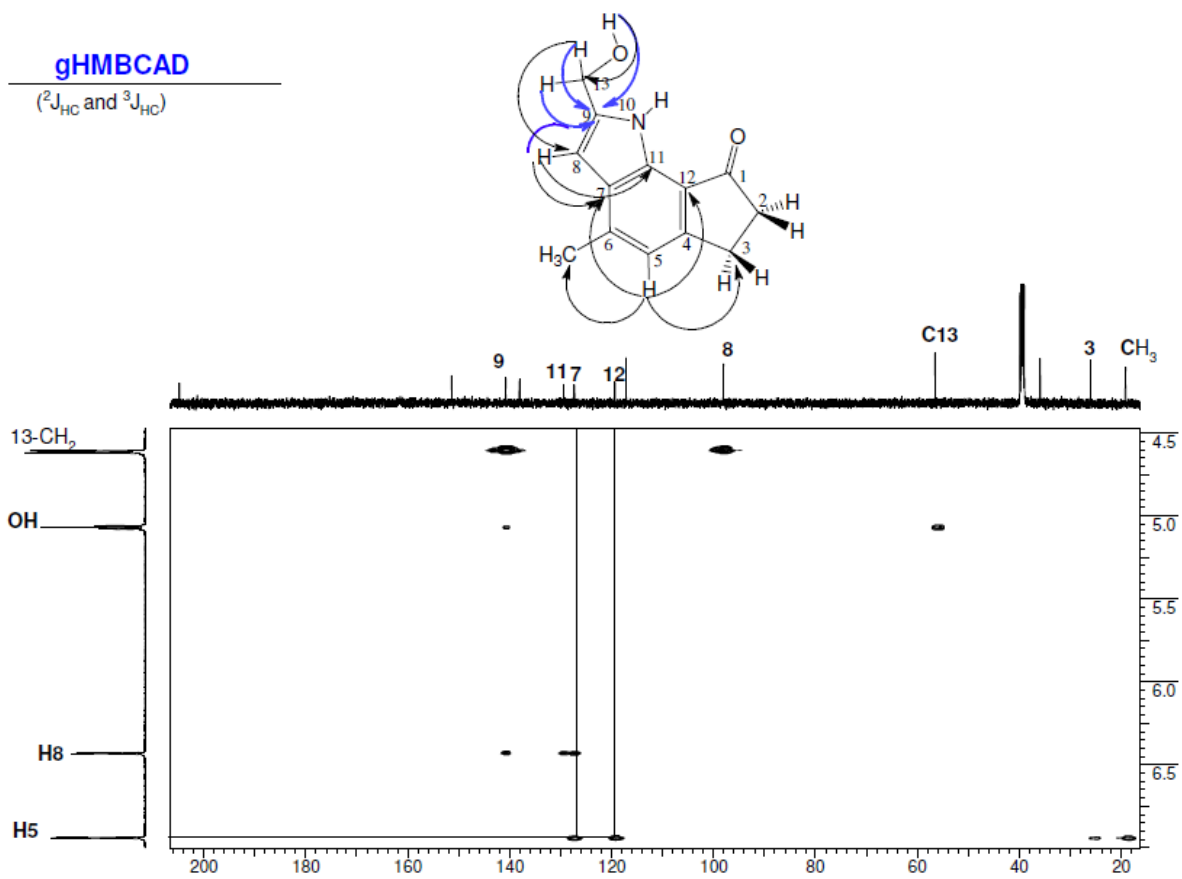
Figure 106: Dilemmaone B (**53**)—gHMBCAD Spectrum C
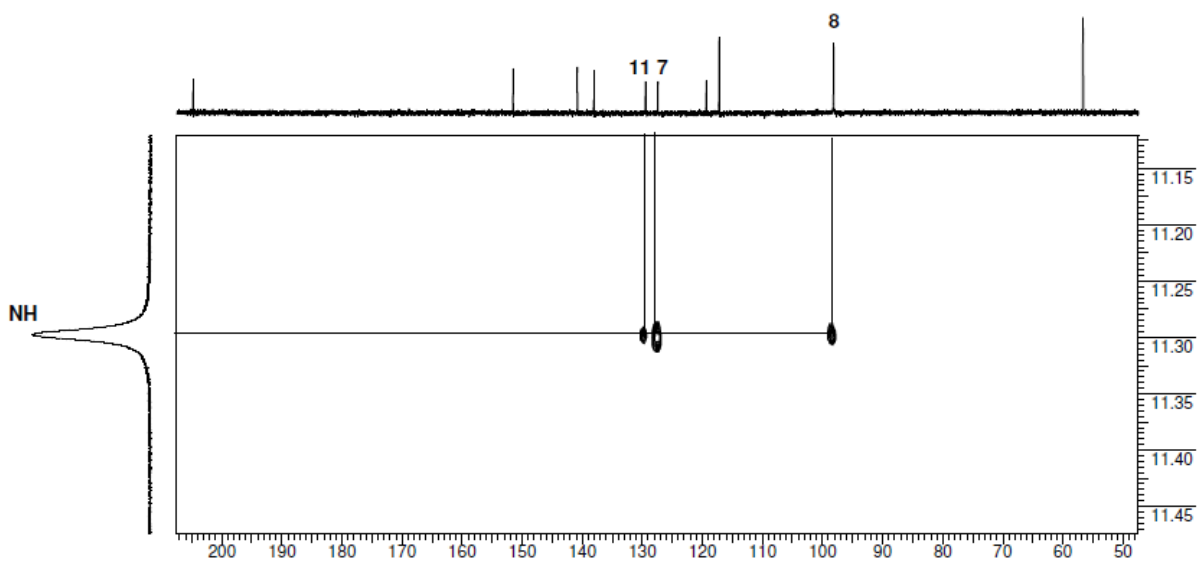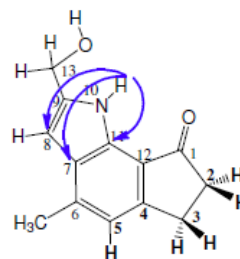
Figure 107: 6-(1,2-epoxy-3-methoxypropyl)-2,3-dihydro-5-methyl-7-nitroinden-1-one (**92**)—¹H NMR
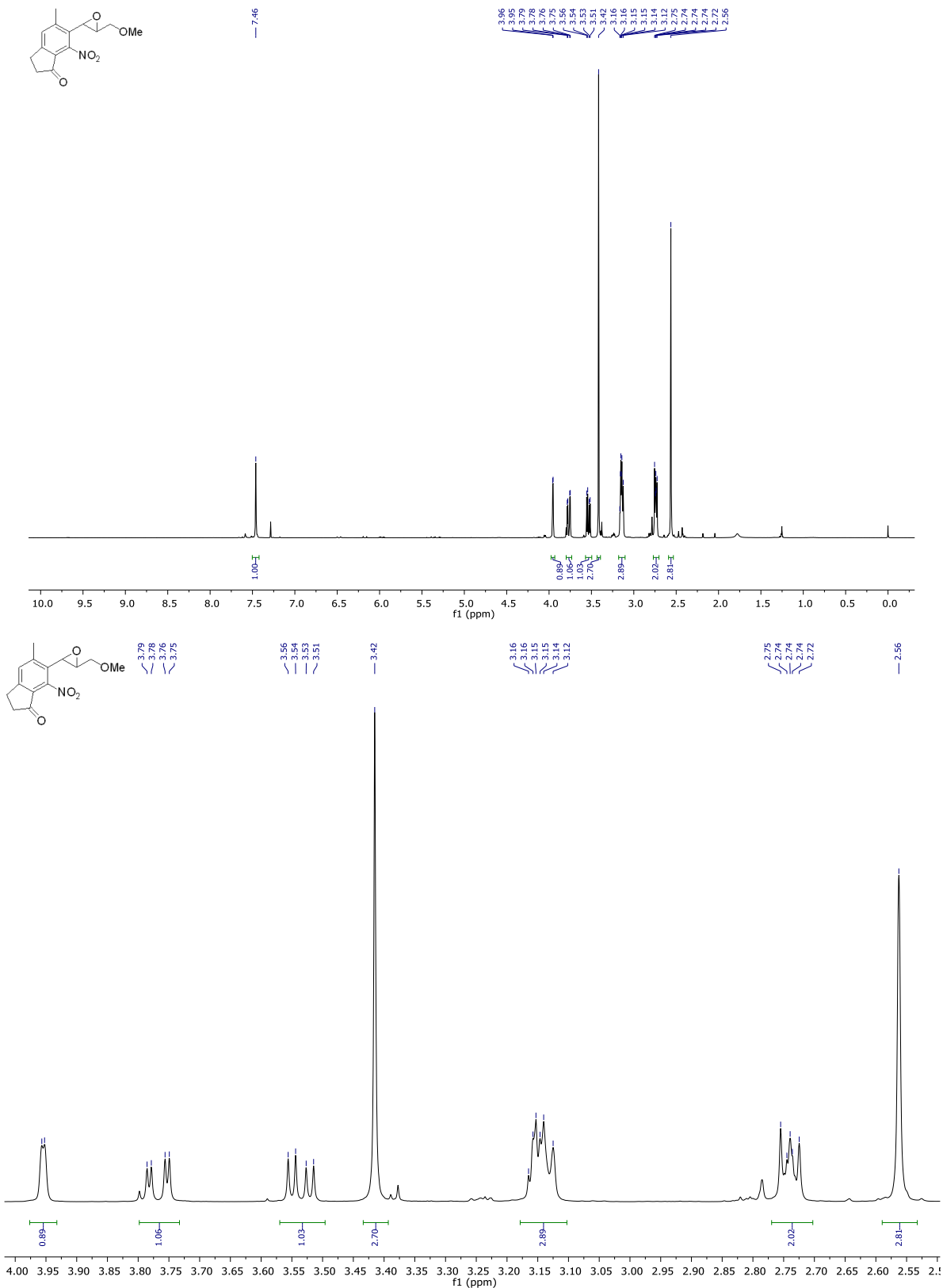
Figure 108: 6-(1,2-epoxy-3-methoxypropyl)-2,3-dihydro-5-methyl-7-nitroinden-1-one (**92**)—¹³C NMR
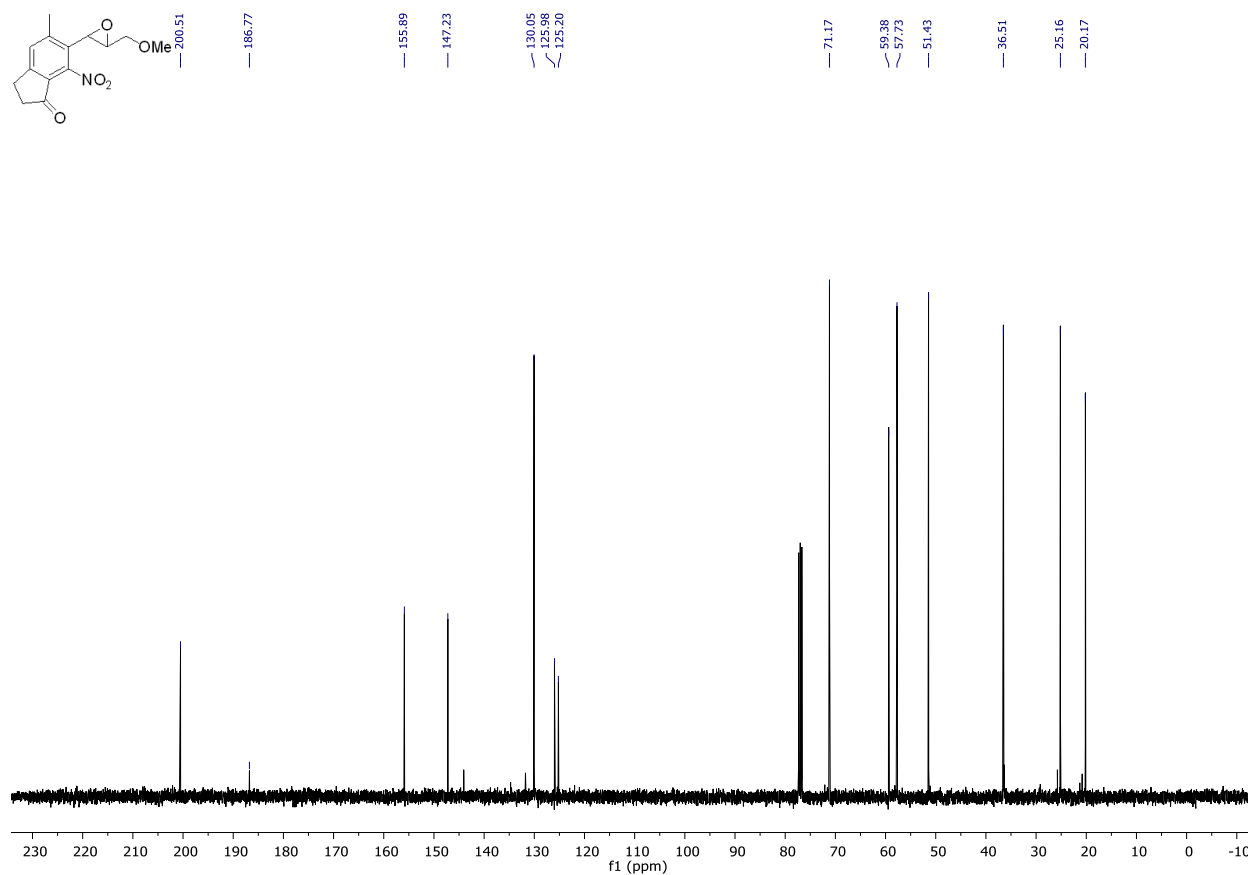
Figure 110: Dilemmaone A (**52**)—¹H NMR (DMSO-d_6)
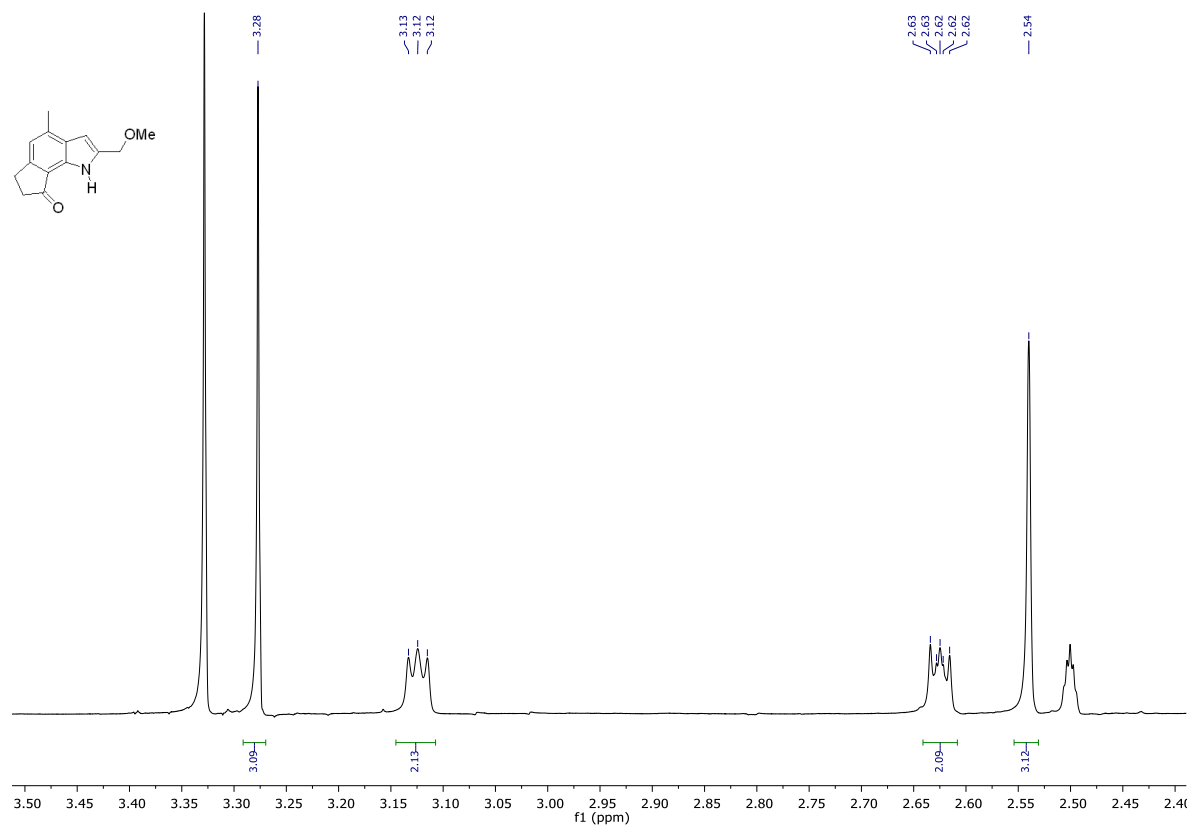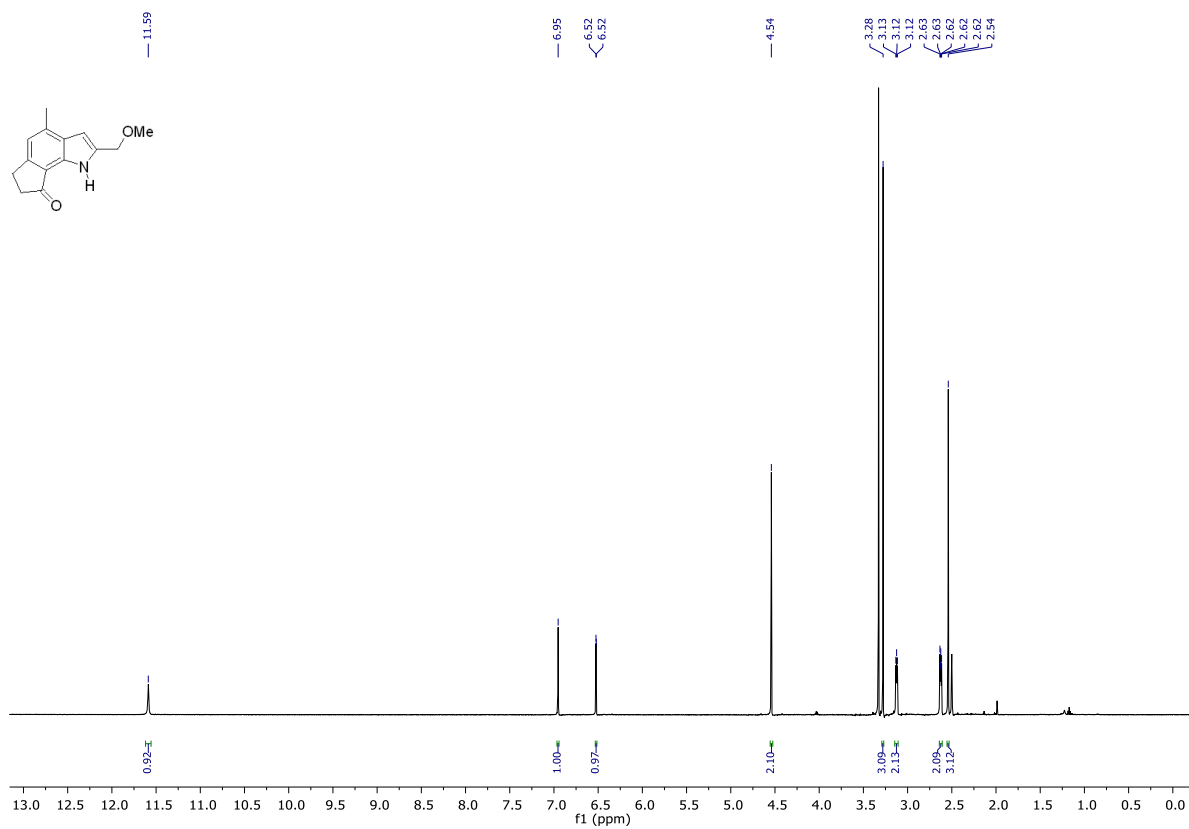
Figure 111: Dilemmaone A (**52**)—^{13}C NMR (DMSO-d_6)
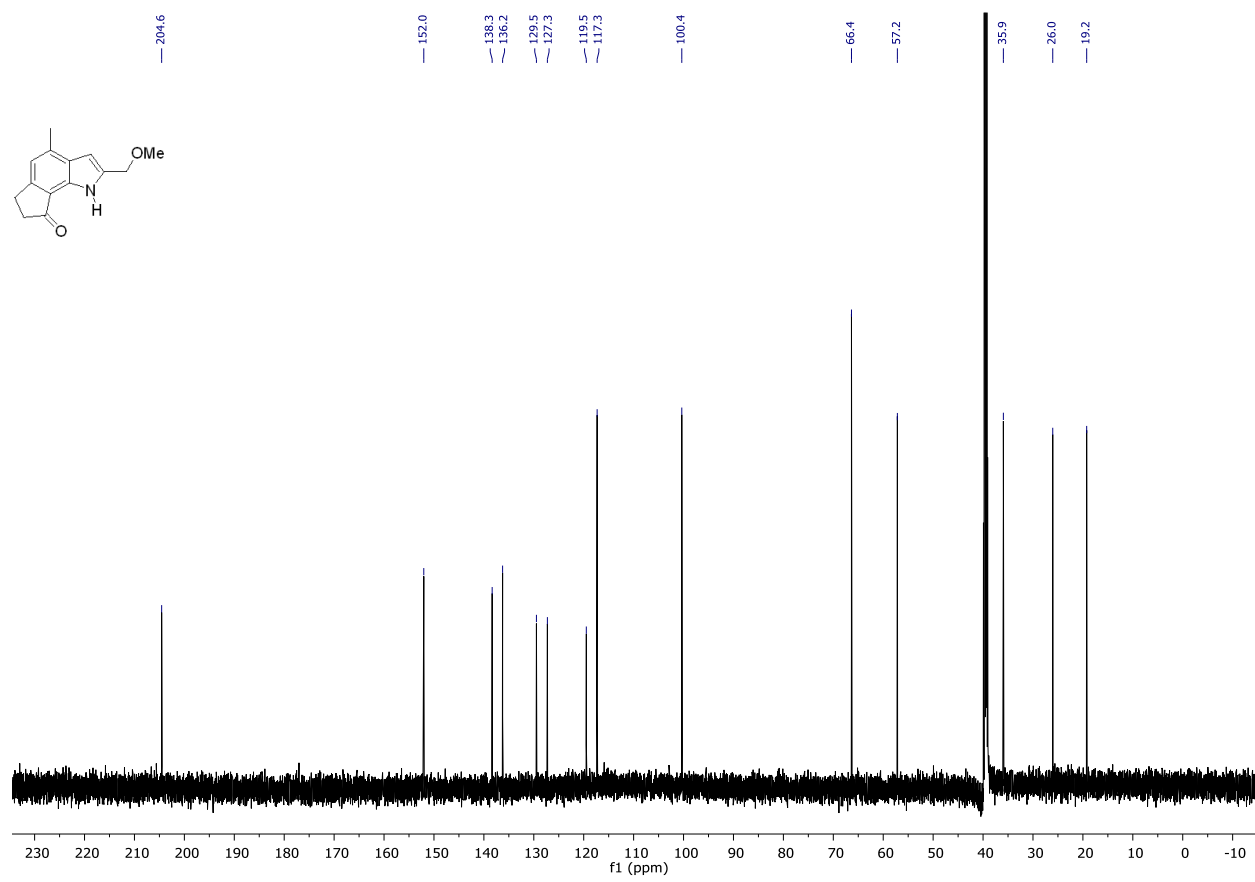
Figure 112: Dilemmaone A (**52**)—^{1}H-^{15}N gHSQCAD
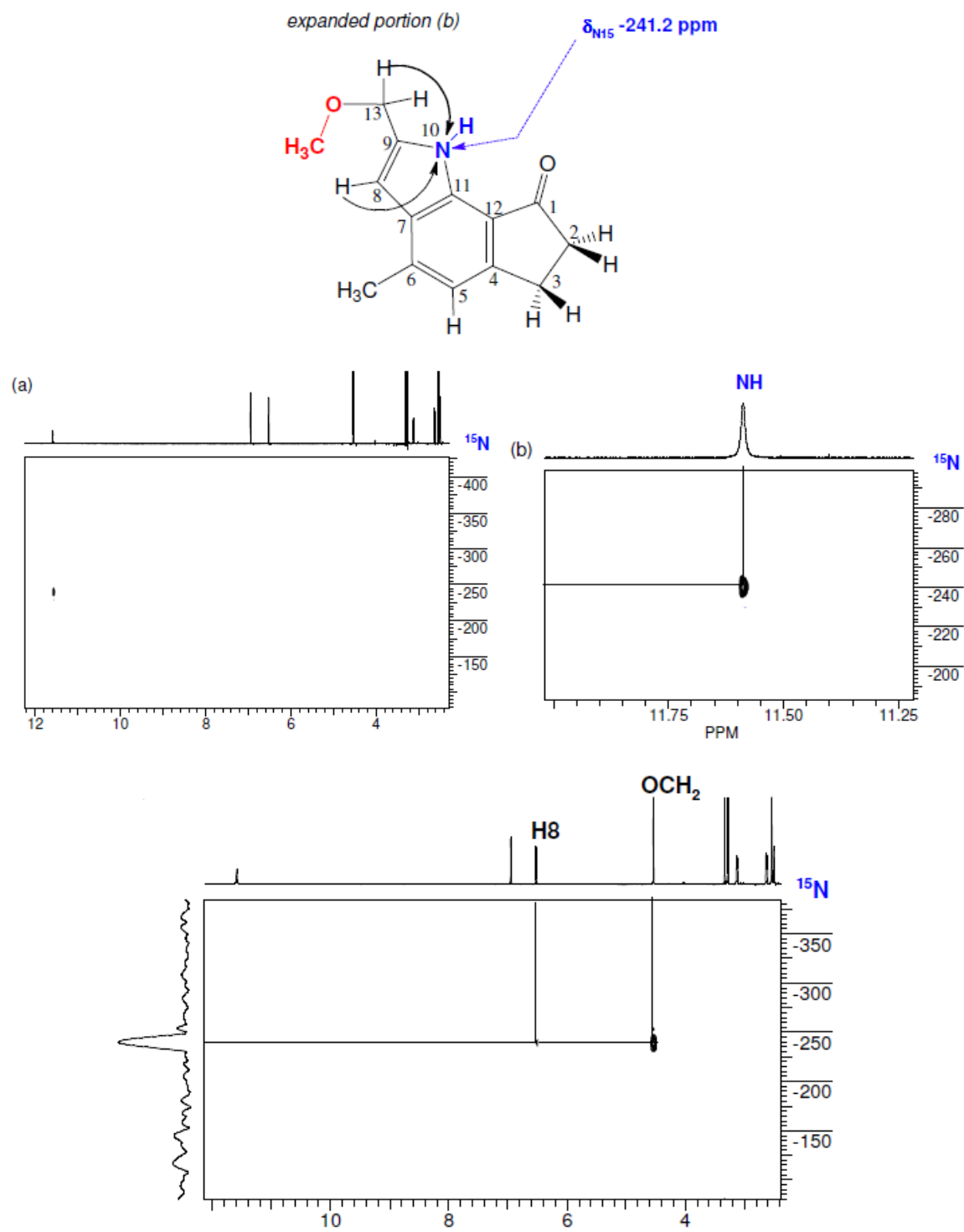
Figure 113: Dilemmaone A (**52**)—gCOSY
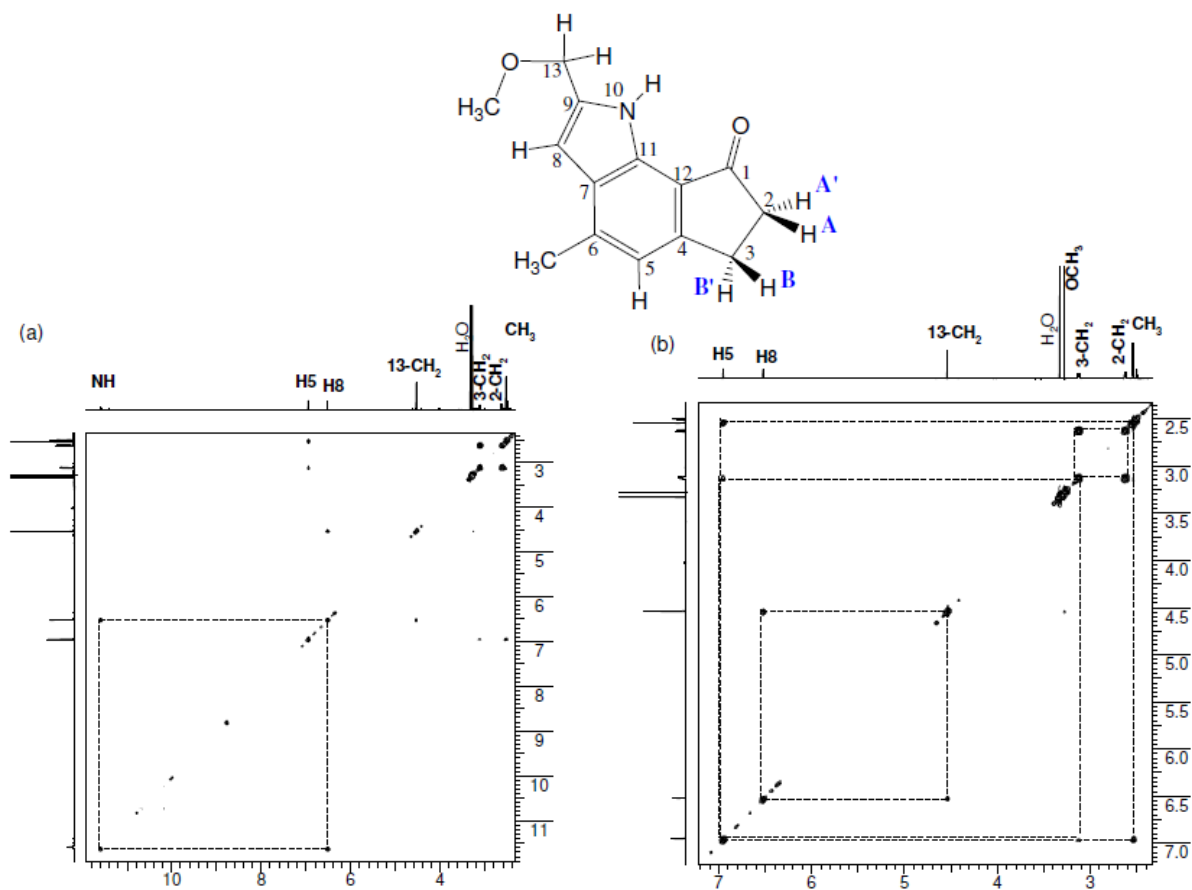
[a]Full gCOSY spectrum for **52**.

[b]Expansion of spectrum (a).

Figure 114: 4-Amino-6-bromo-2,3-dihydro-5-methylinden-1-one (**95**)—^{1}H NMR
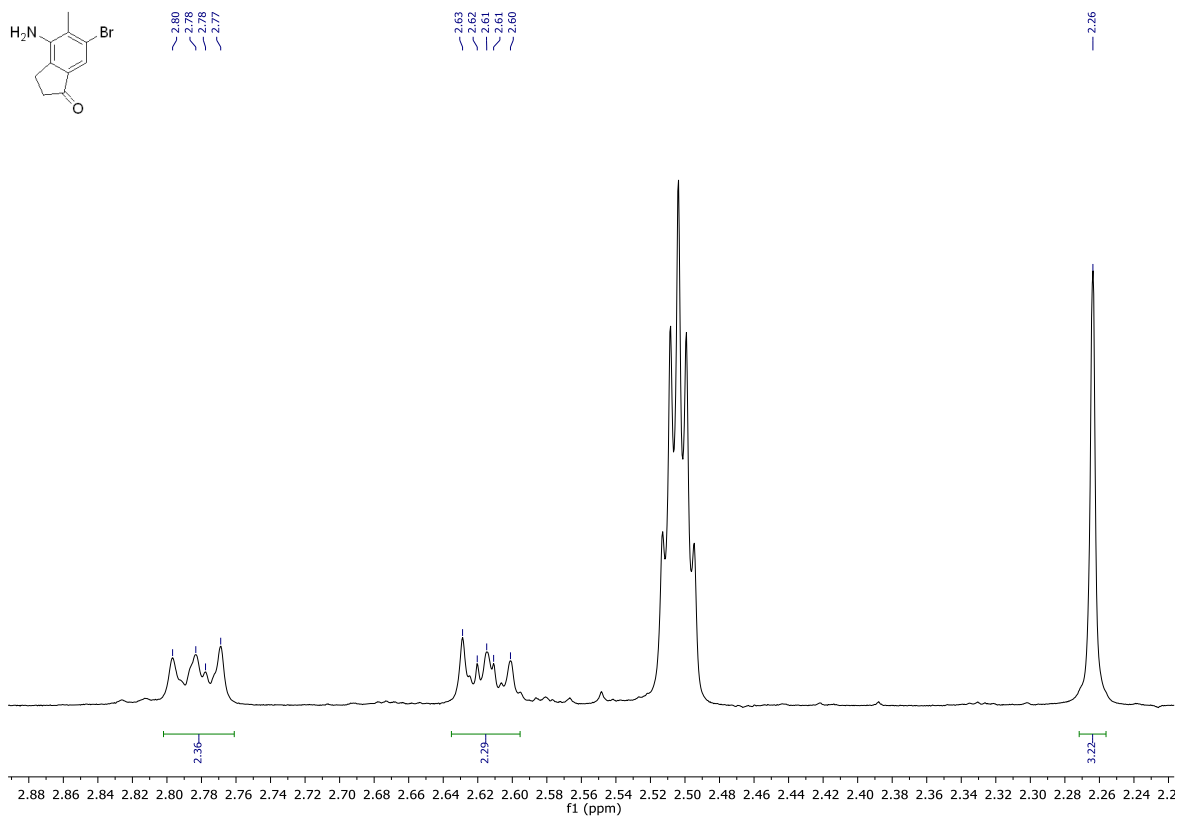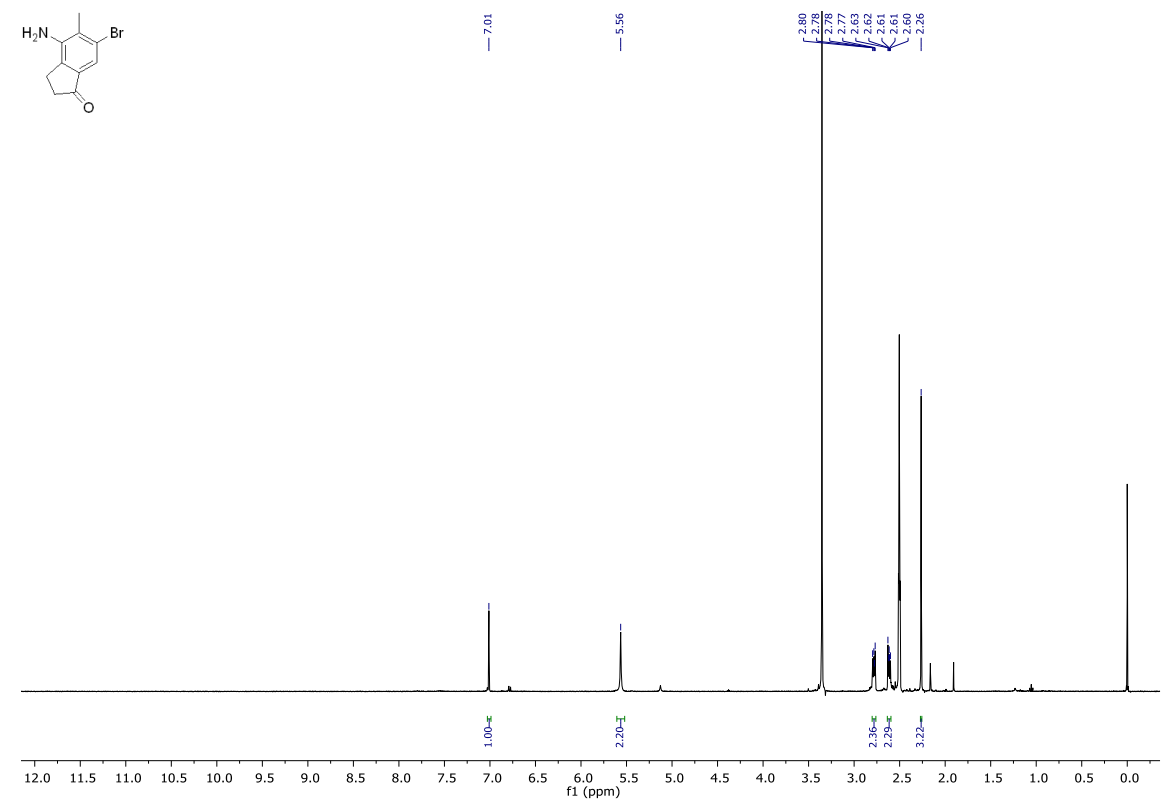
Figure 115: 4-Amino-6-bromo-2,3-dihydro-5-methylinden-1-one (**95**)—^{13}C NMR
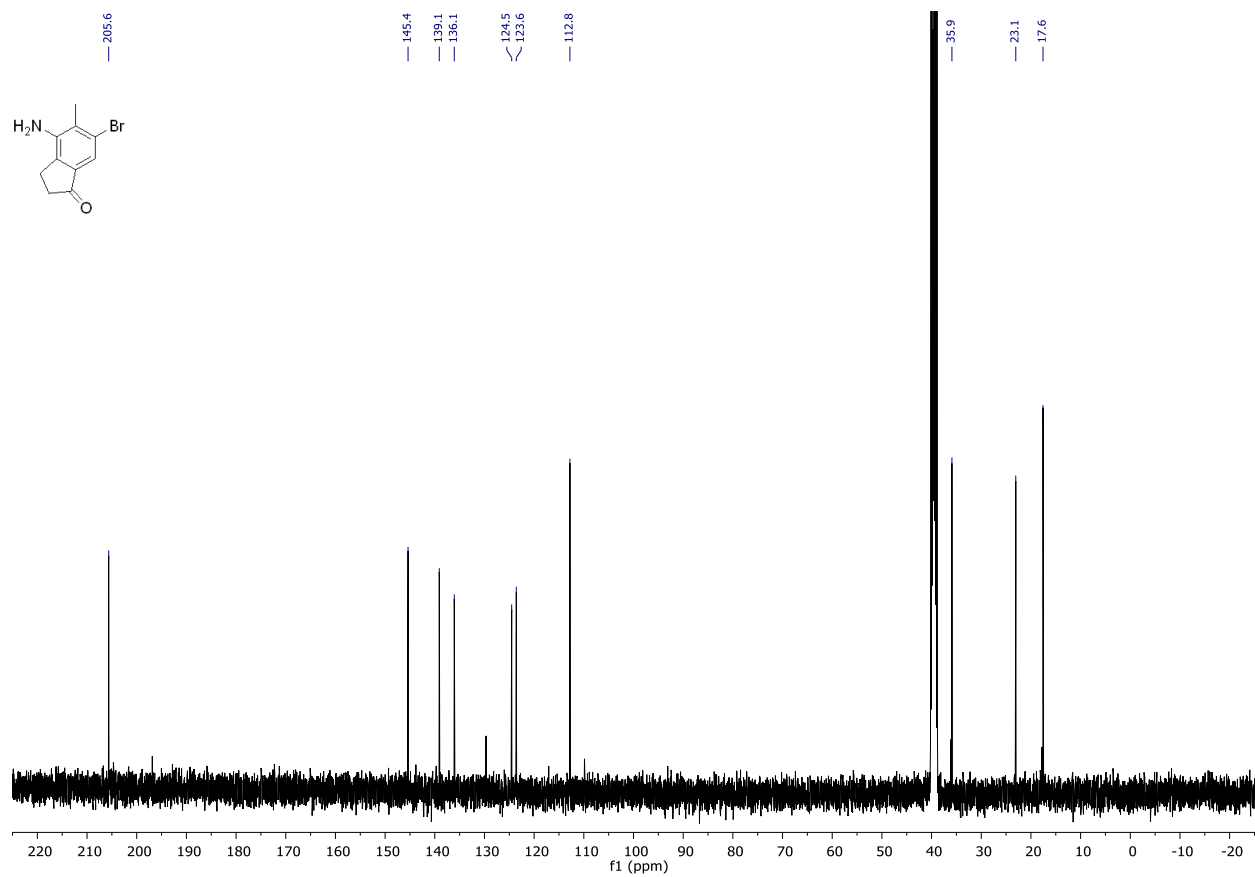
Figure 116: 6-Bromo-2,3-dihydro-4-hydroxy-5-methylinden-1-one (**96**)—¹H NMR
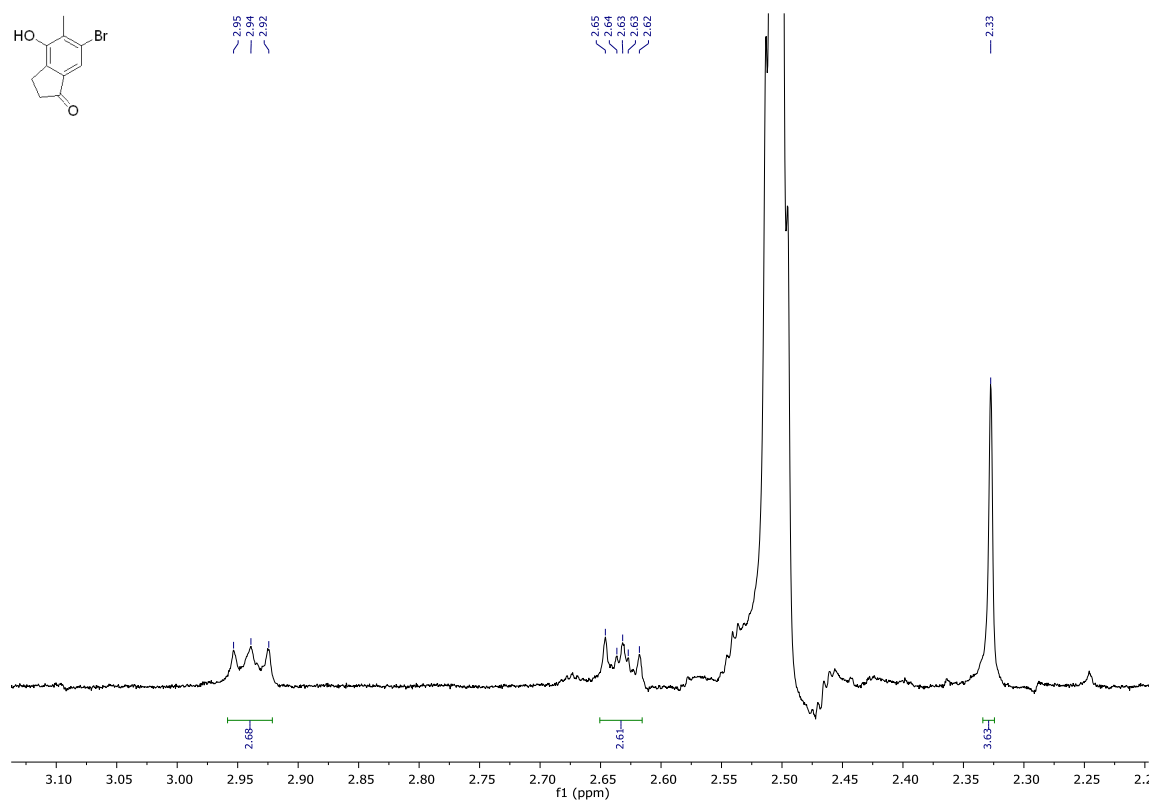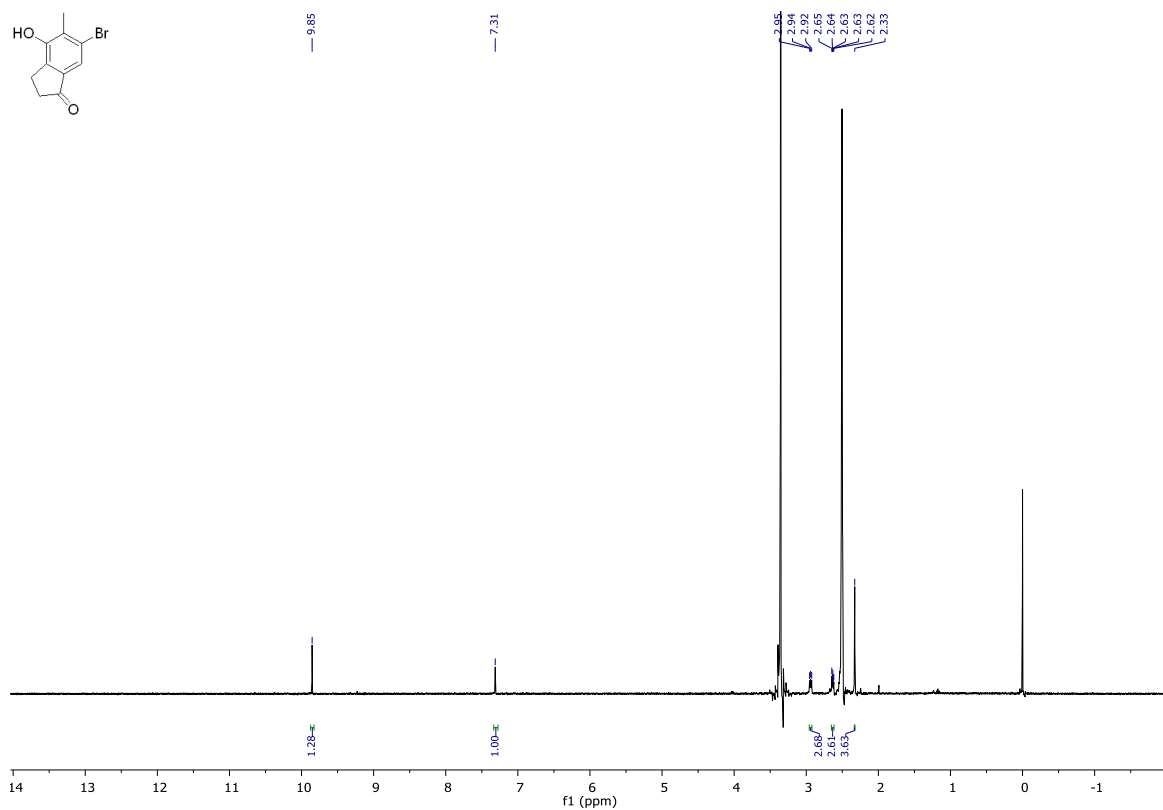
Figure 117: 6-Bromo-2,3-dihydro-4-hydroxy-5-methyl-7-nitroinden-1-one (**97**)—^{1}H NMR
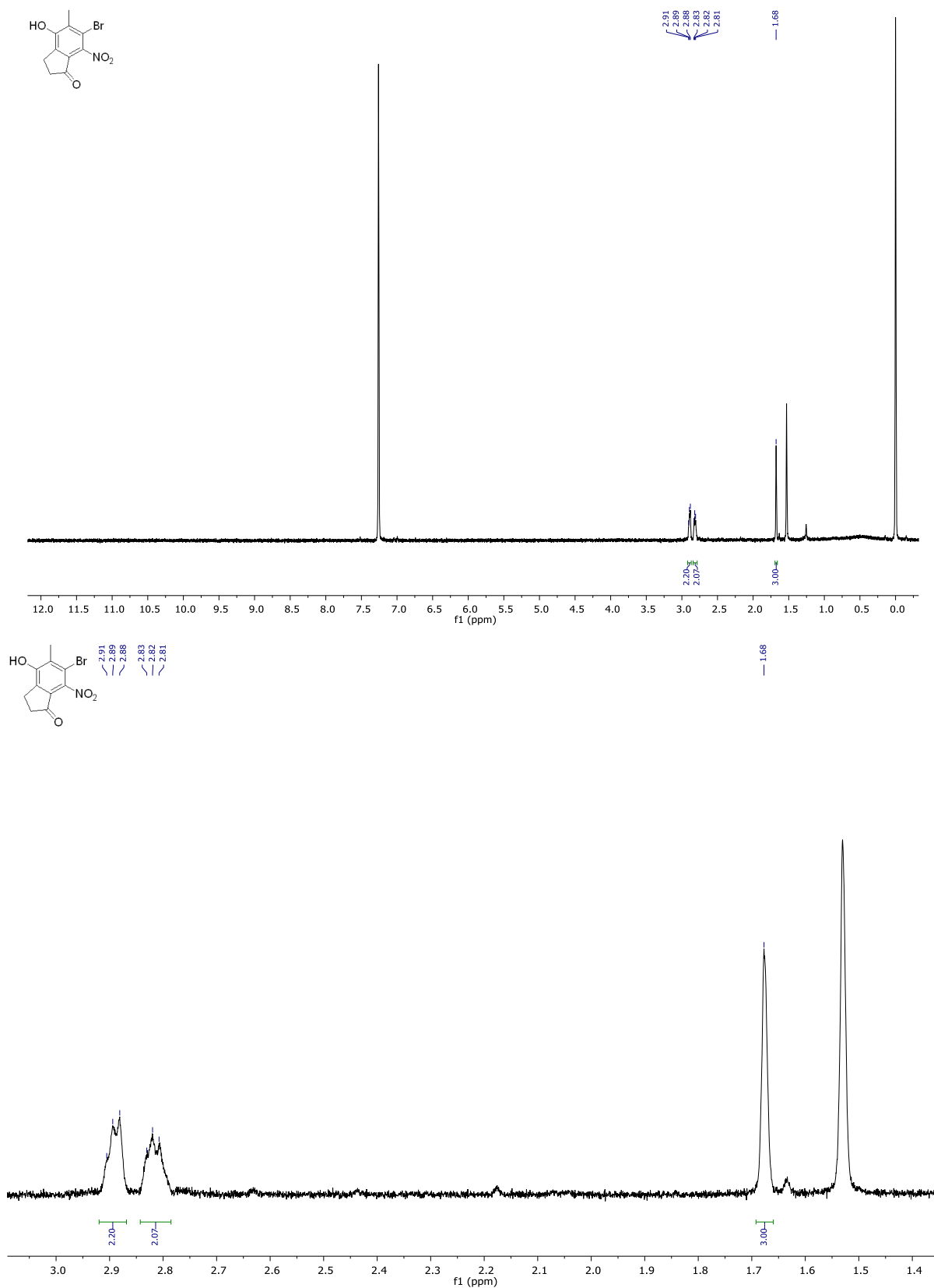
Figure 118: 3-(2-nitrophenyl)-3-buten-1-ol (**106**)—¹H NMR
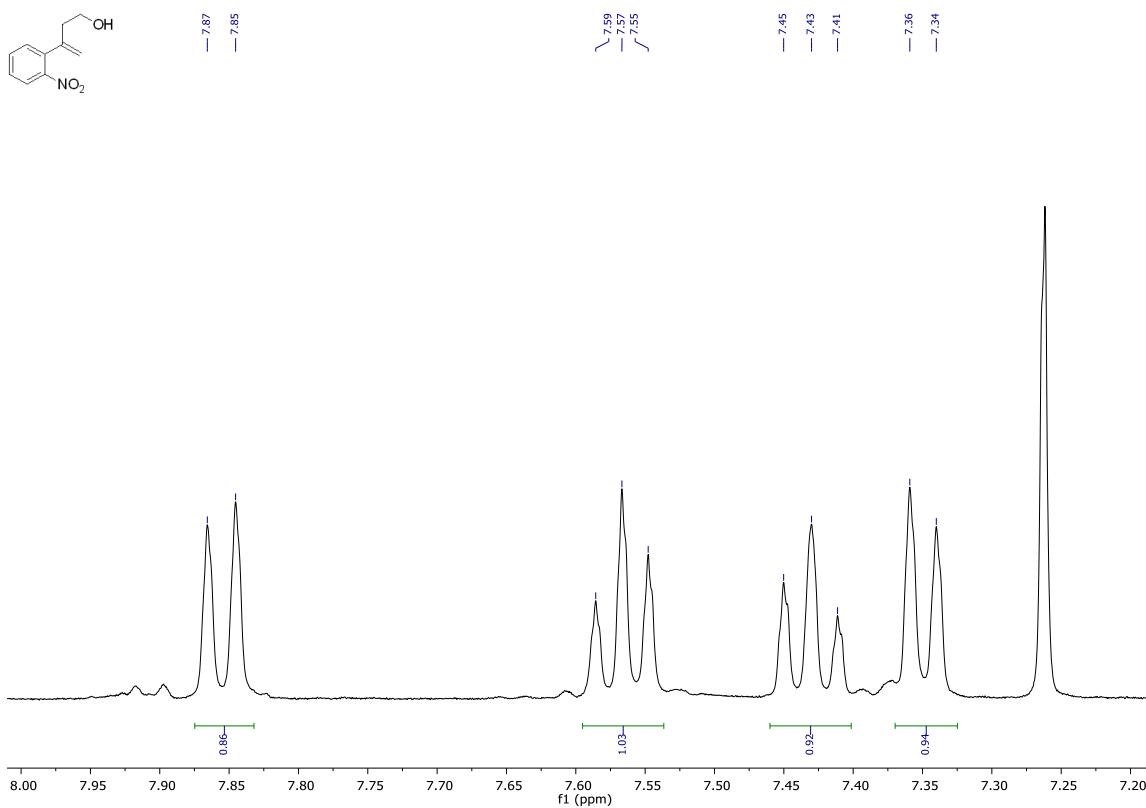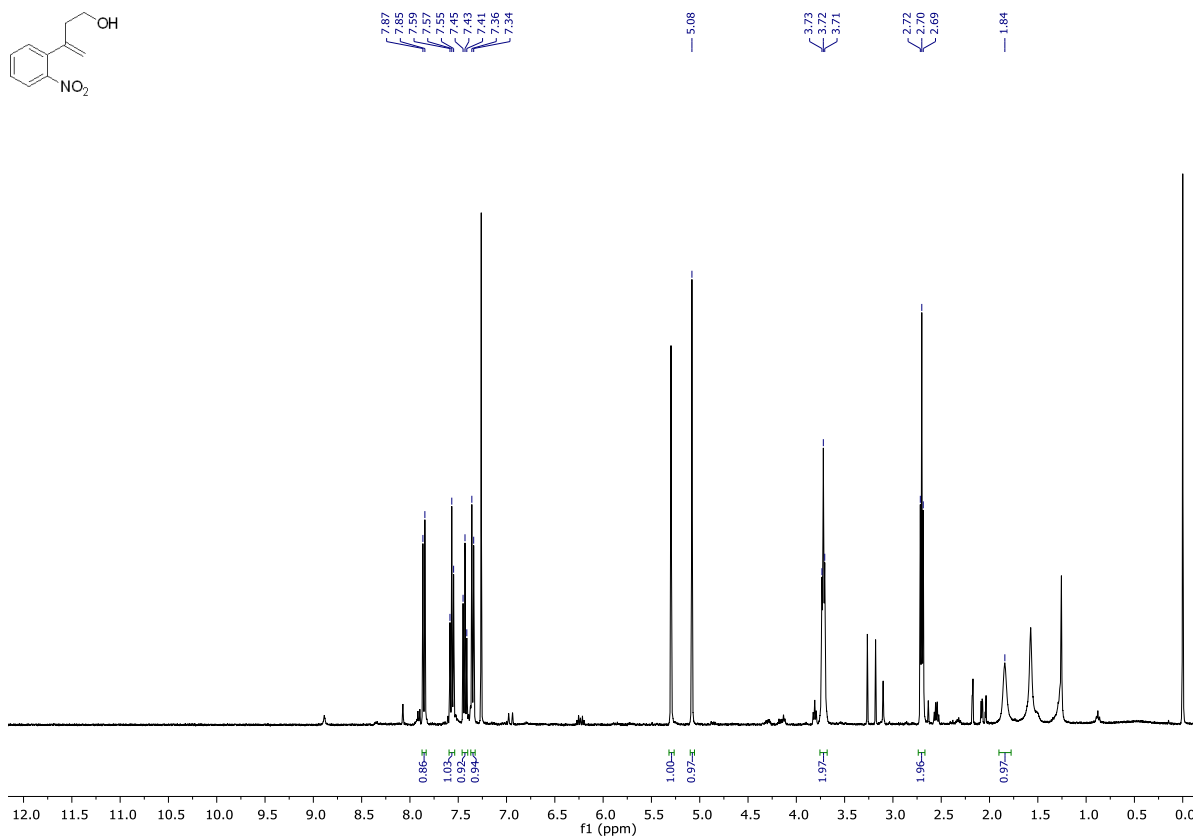
Figure 119: 4-(2-nitrophenyl)-3-buten-1-ol (**107**)—¹H NMR
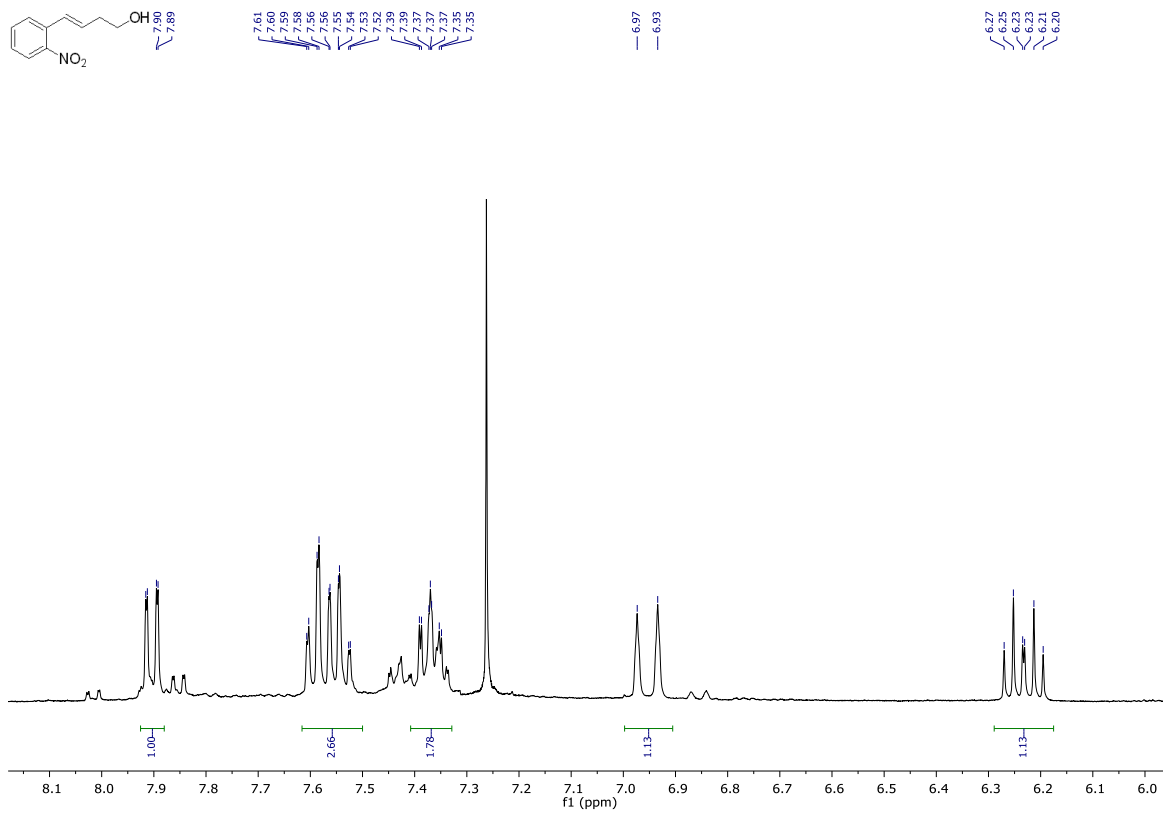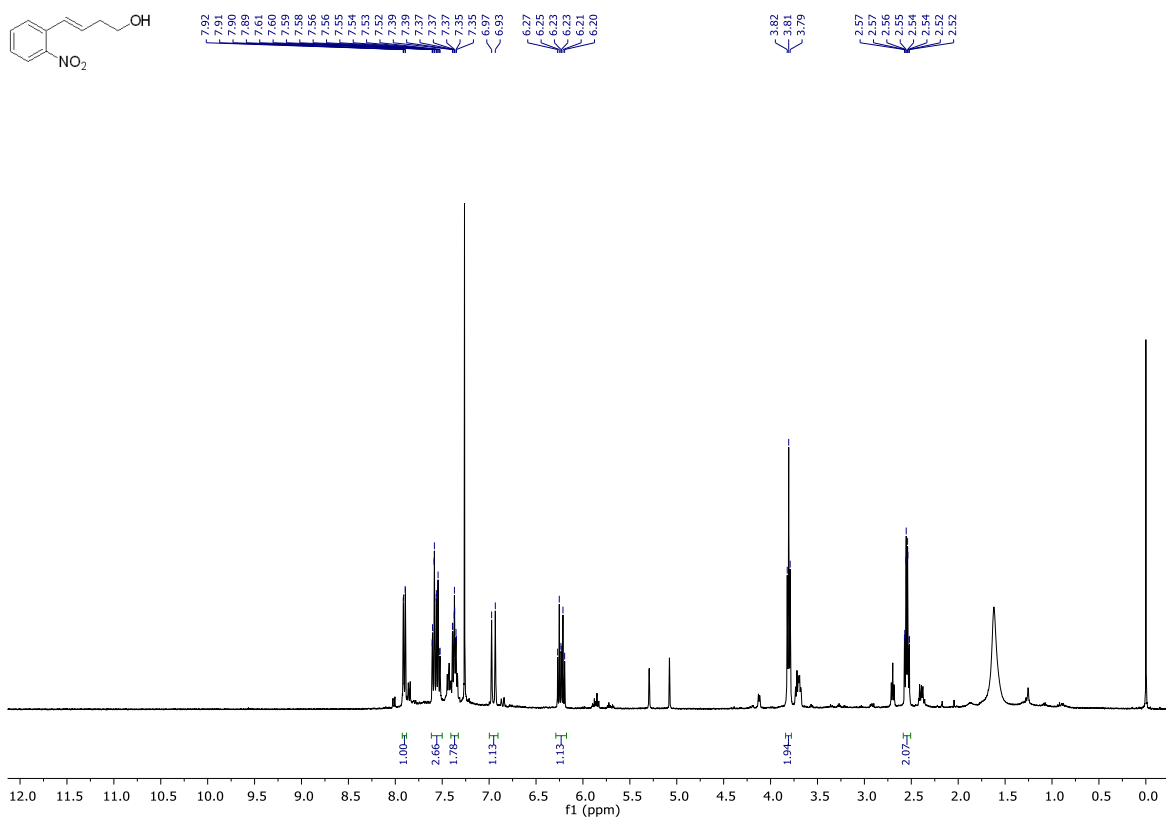
Figure 120: 3-(2-bromo-6-nitrophenyl)-3-buten-1-ol (**110**)—¹H NMR
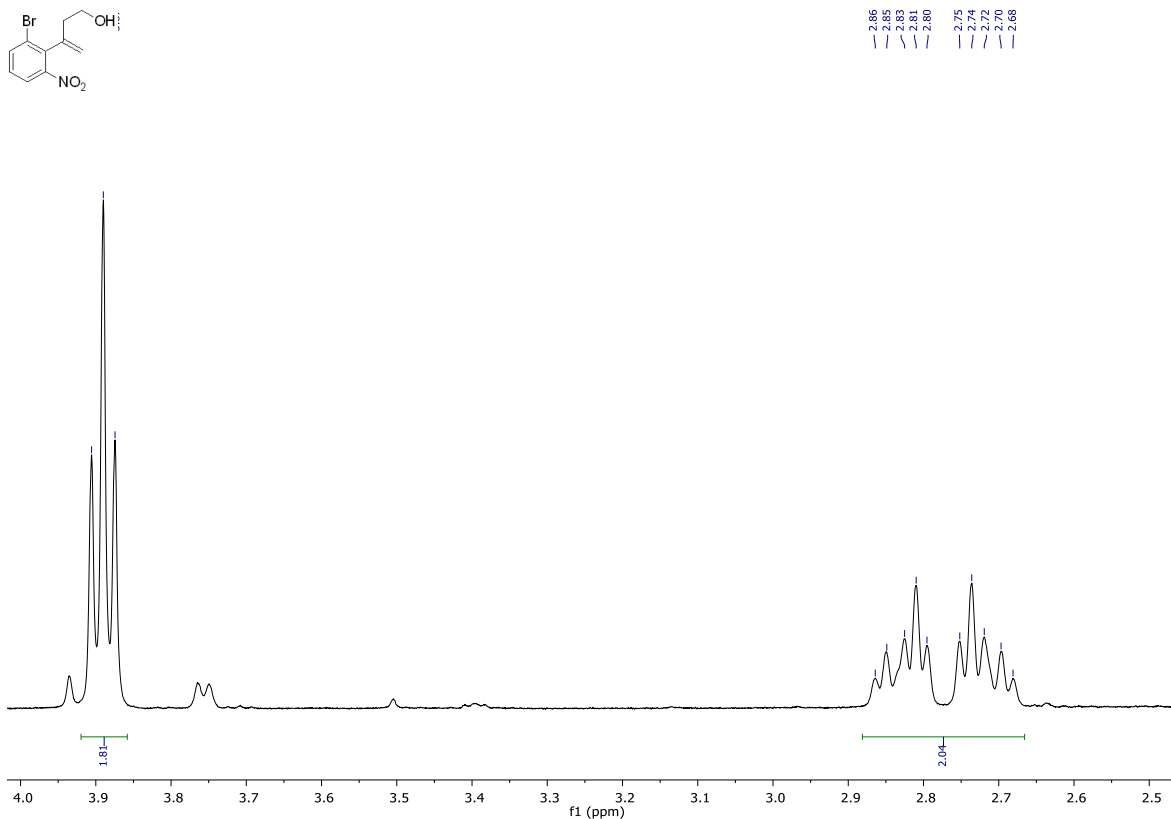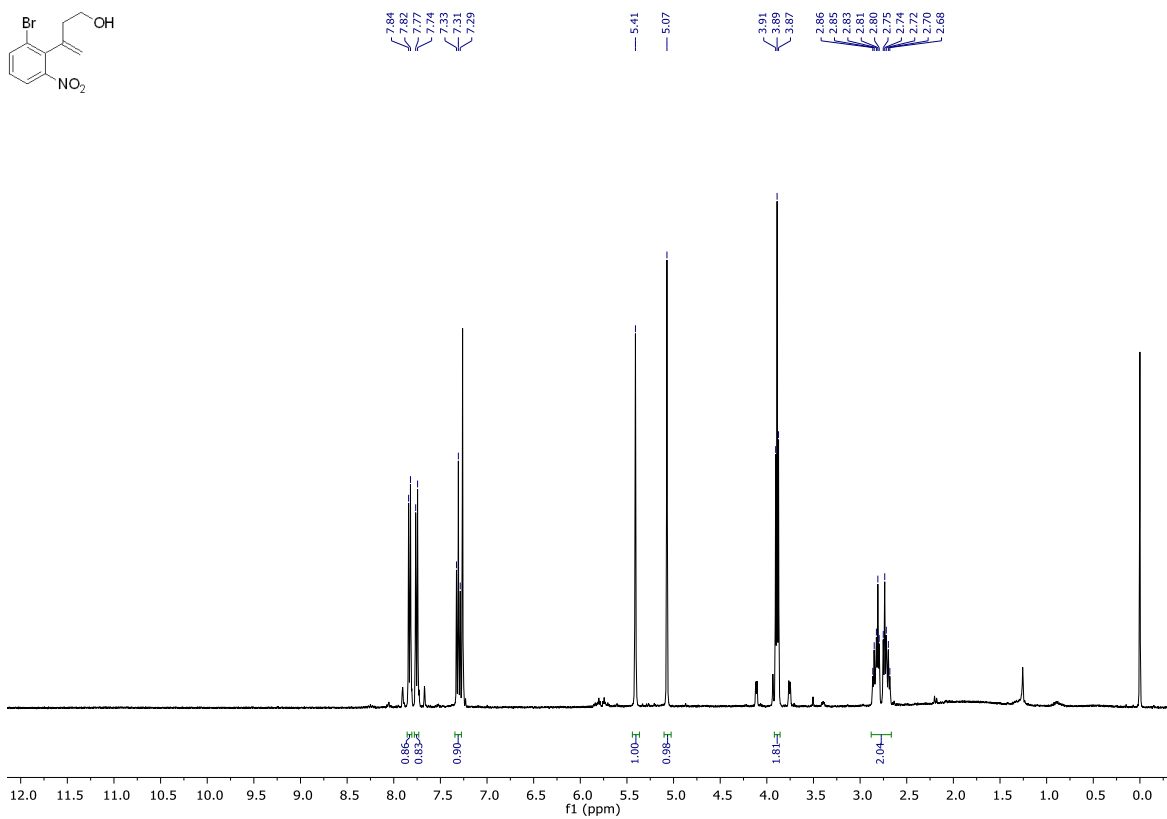
Figure 121: 3-(3-bromo-2-nitrophenyl)-3-buten-1-ol (**112**)—¹H NMR
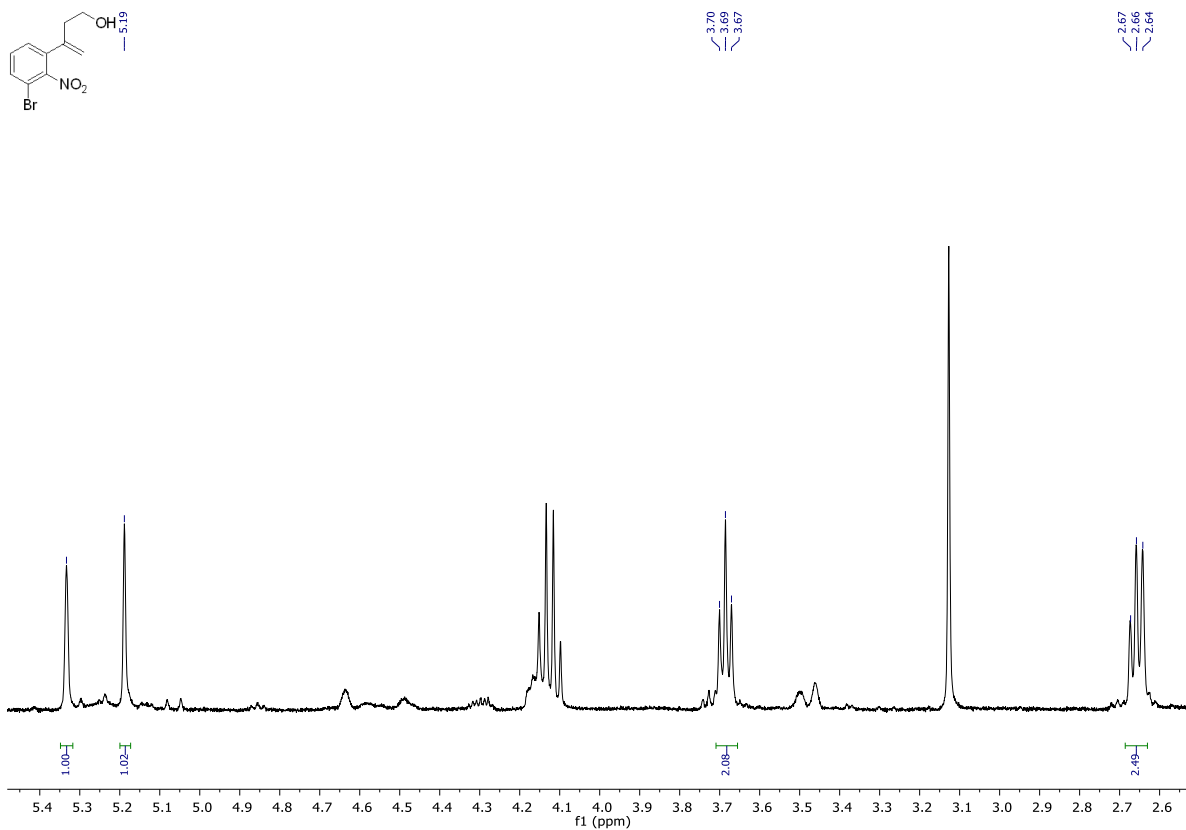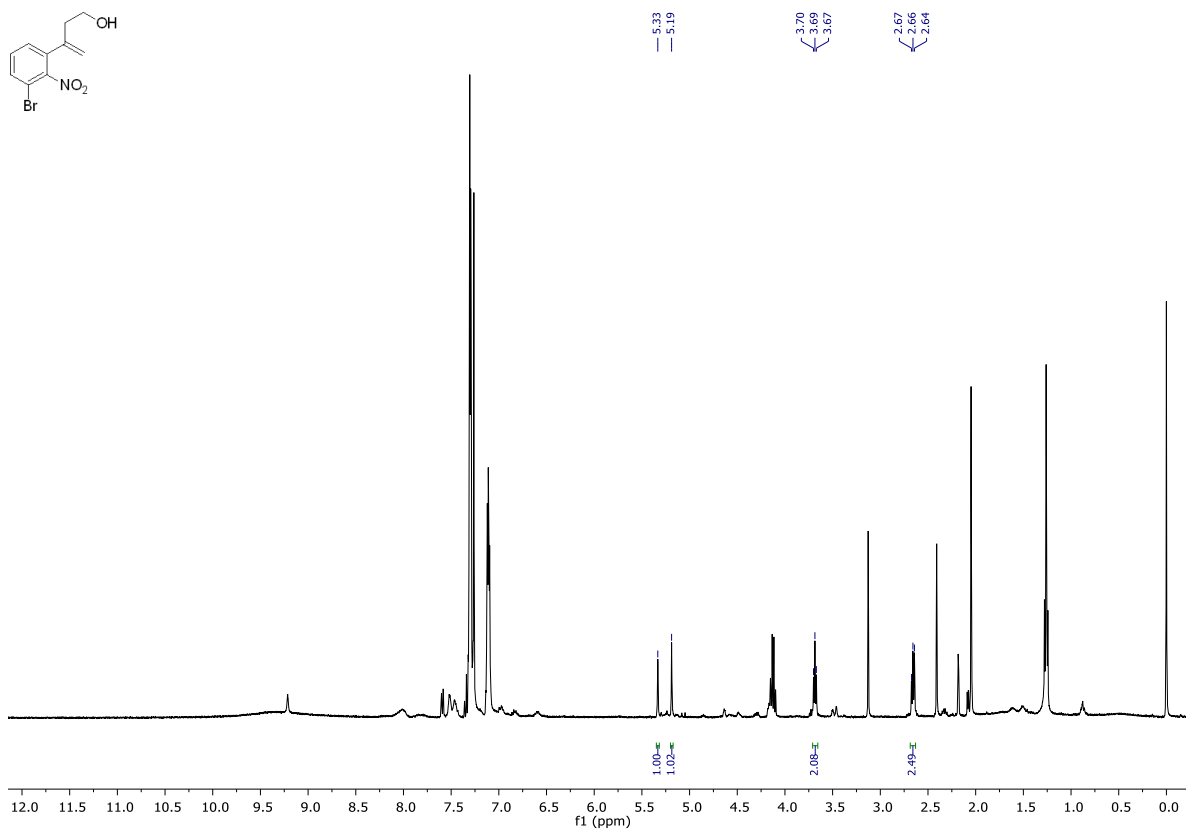
Figure 122: 3-bromo-2-nitrophenol (**113**)—^{1}H NMR
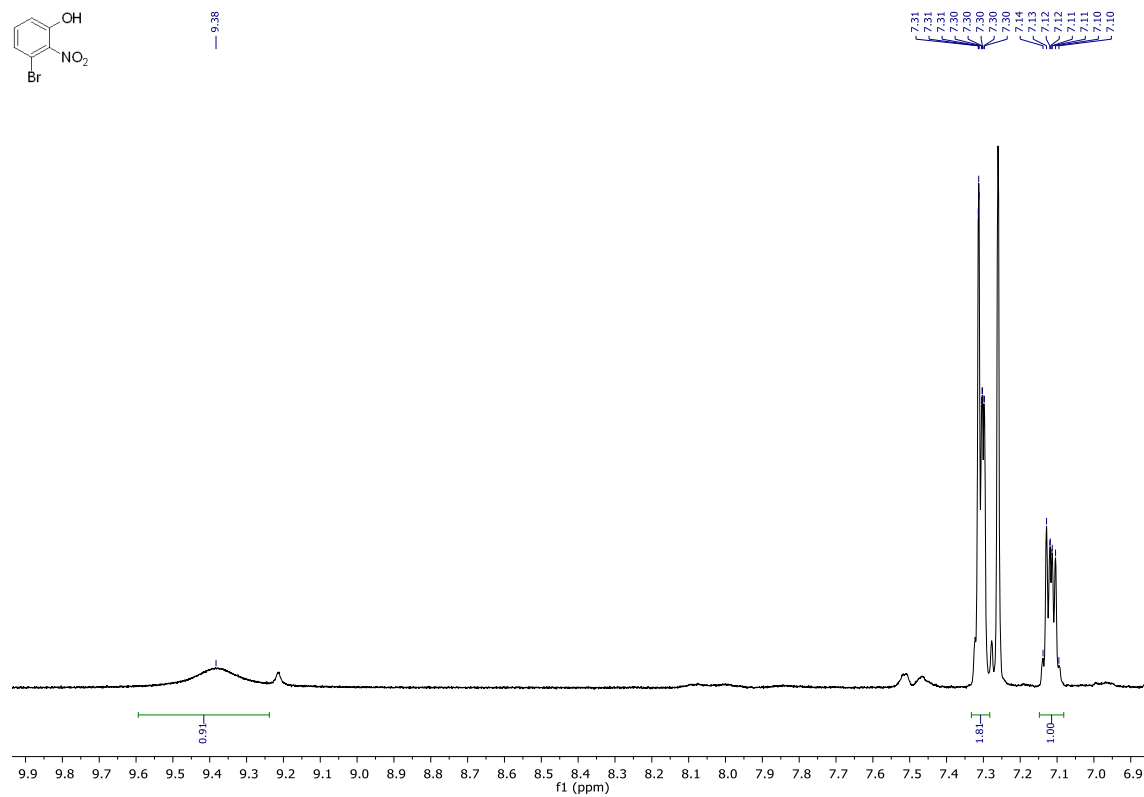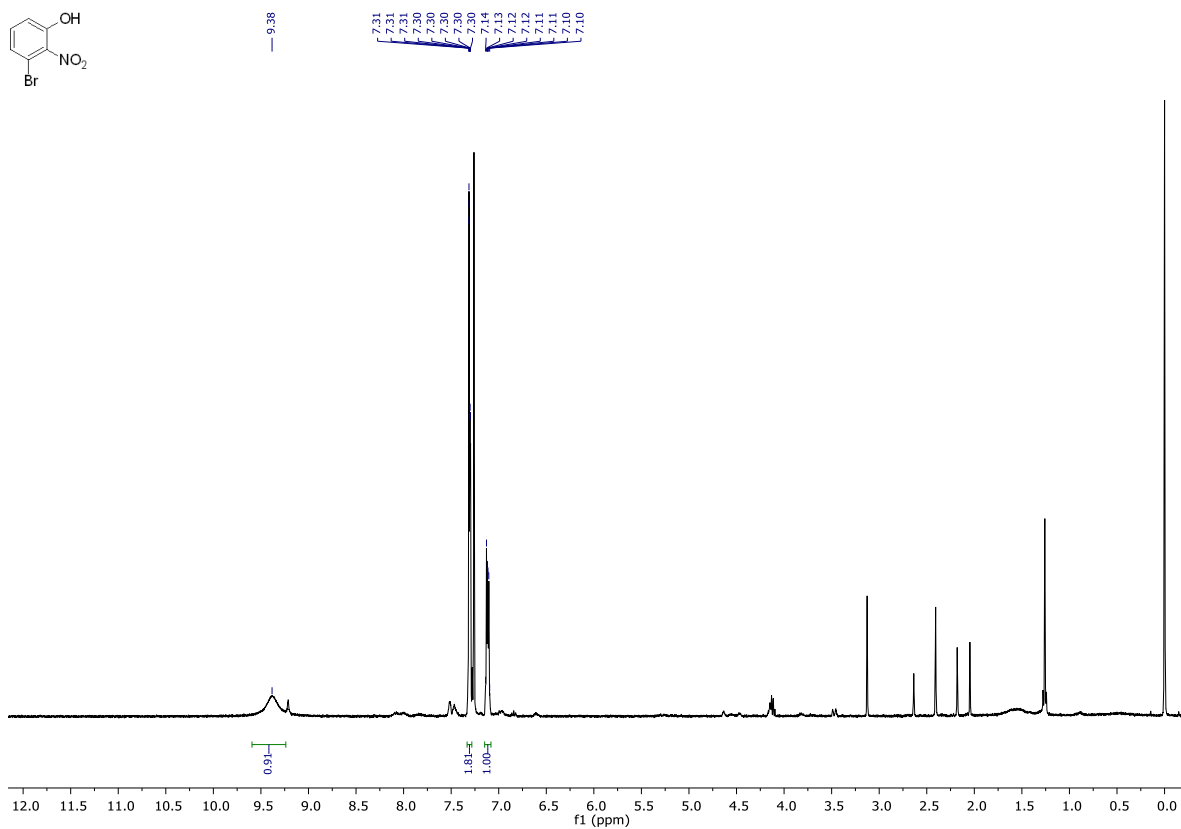
Figure 123: (*S*)-methyl-2-(*tert*-butylcarbonylamino)-4-(2-nitrophenyl)pent-4-enoate (**122**)—^{1}H NMR
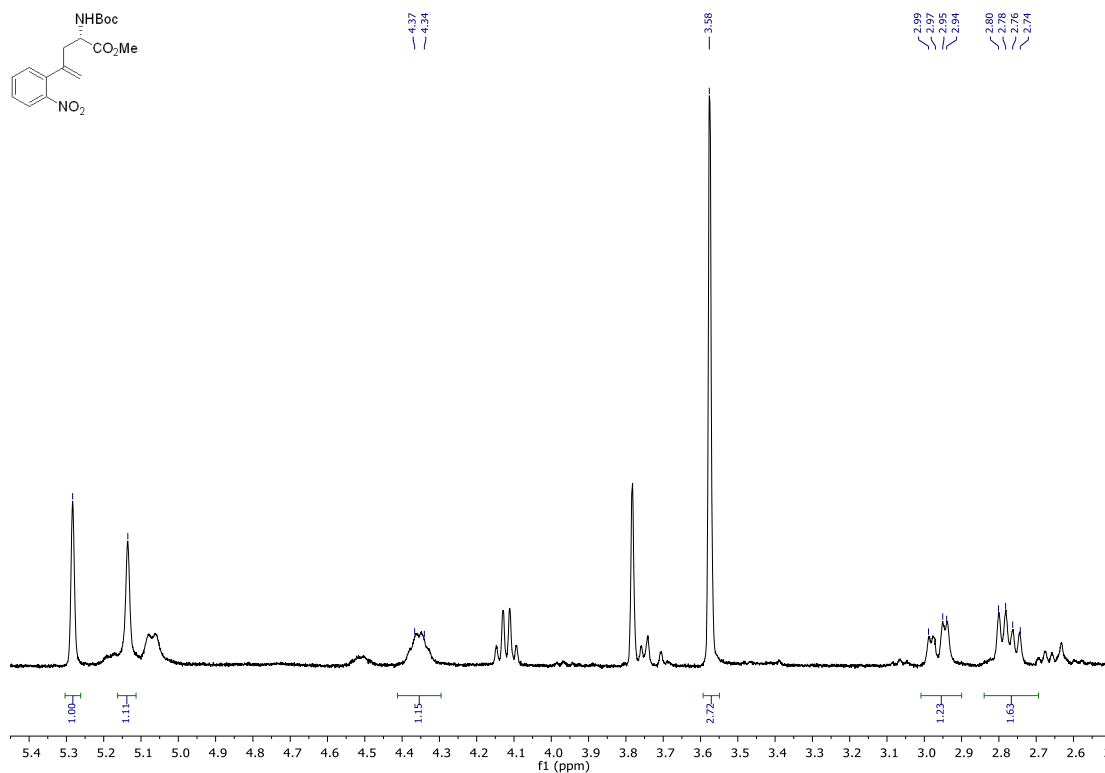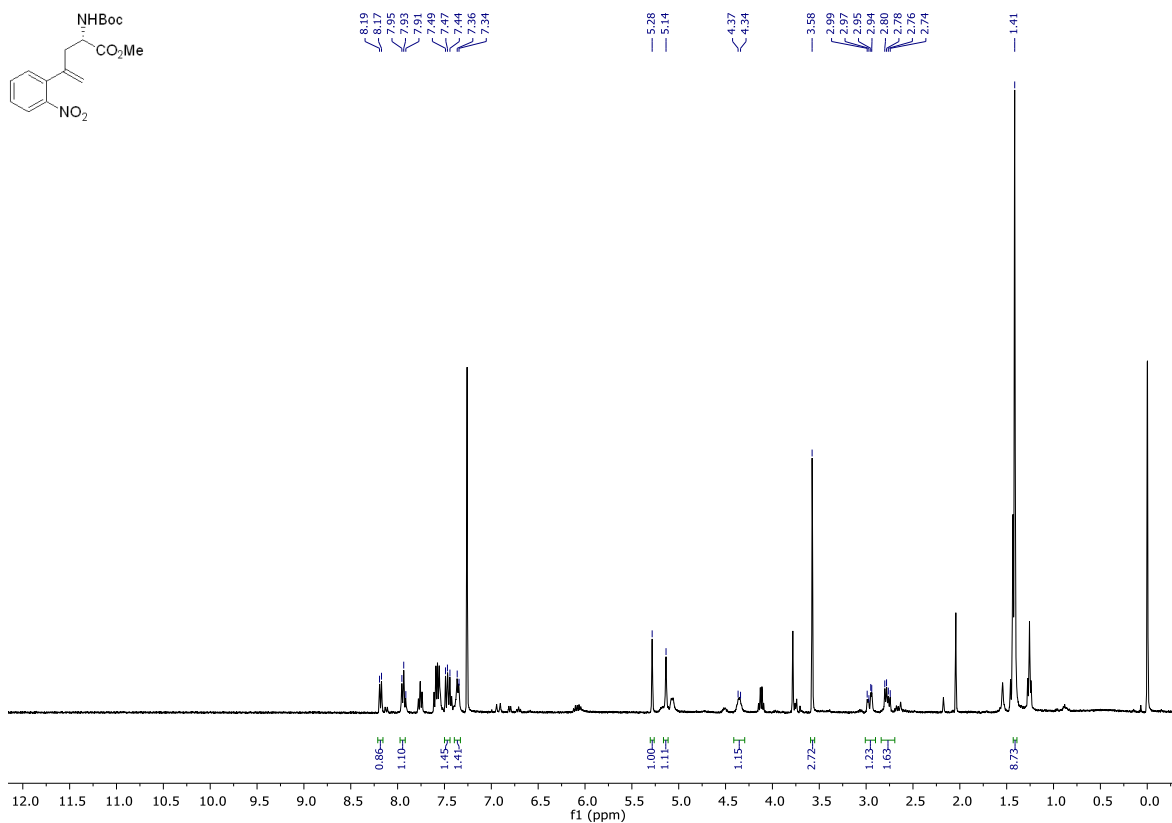
Figure 124: (*S*)-methyl-2-(*tert*-butylcarbonylamino)-5-(2-nitrophenyl)pent-4-enoate (**123**)—^{1}H NMR
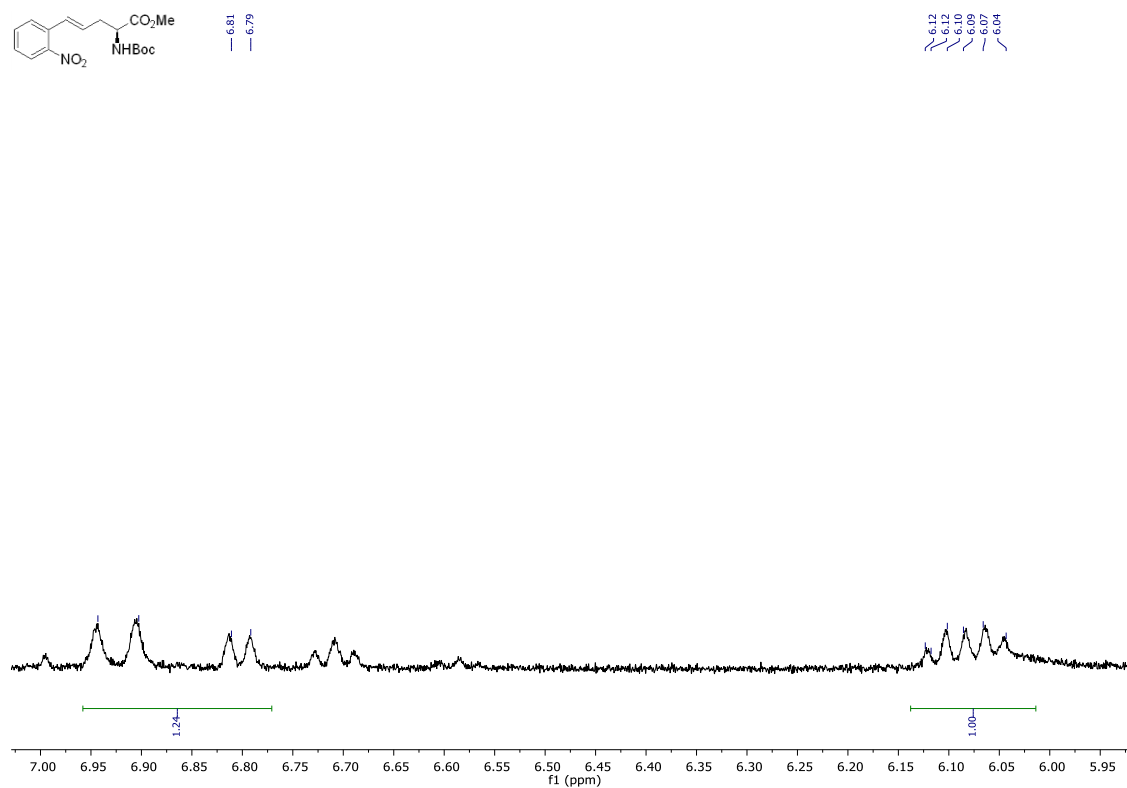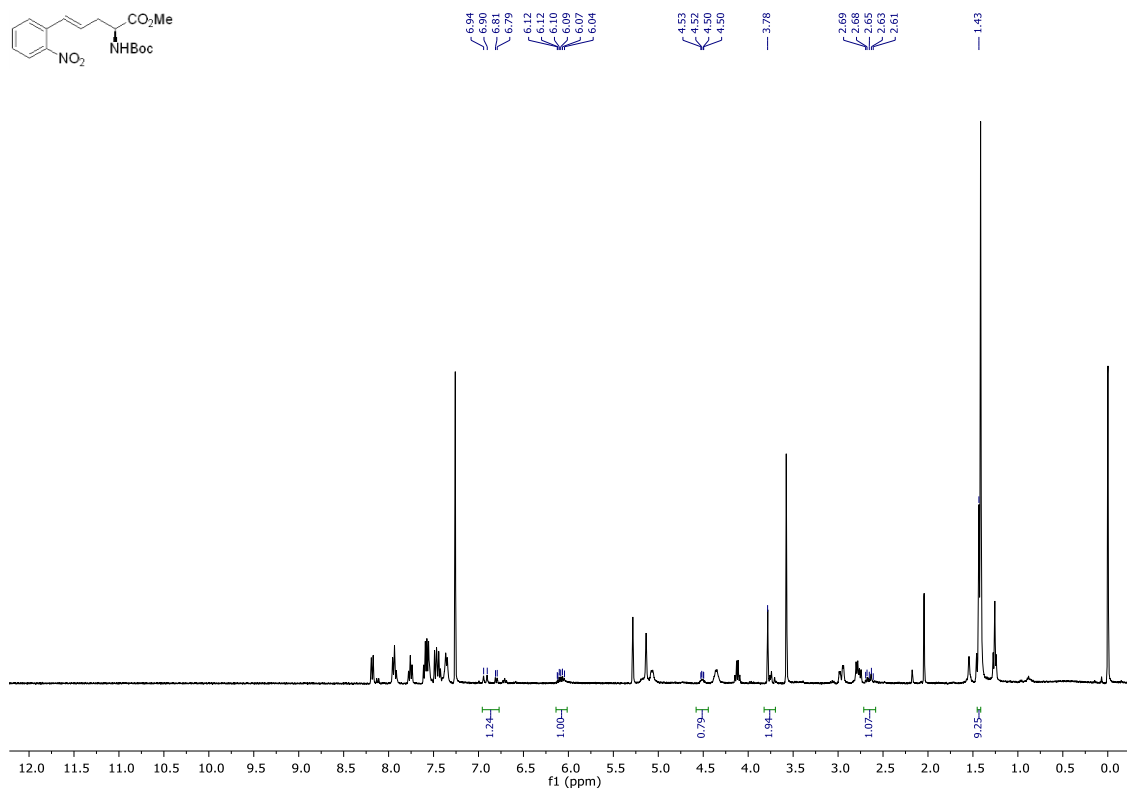
Figure 125: 3-ethanol-1*H*-indole (**124**)—¹H NMR
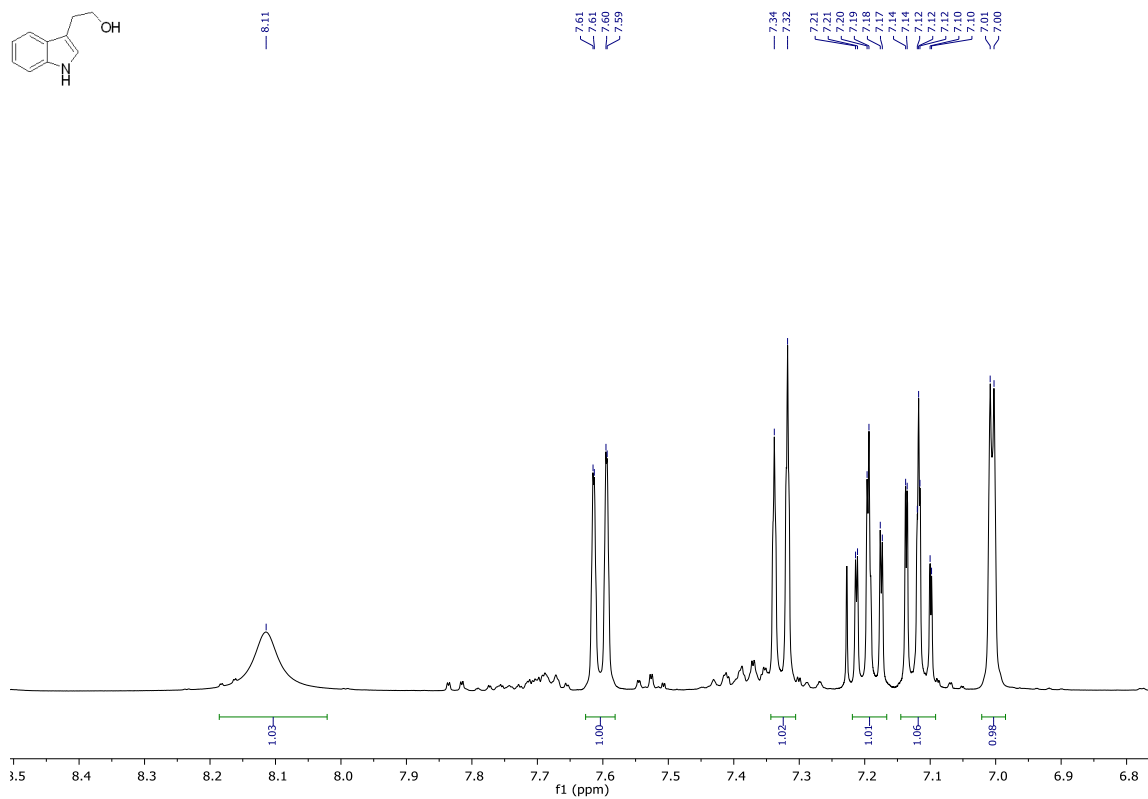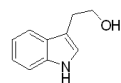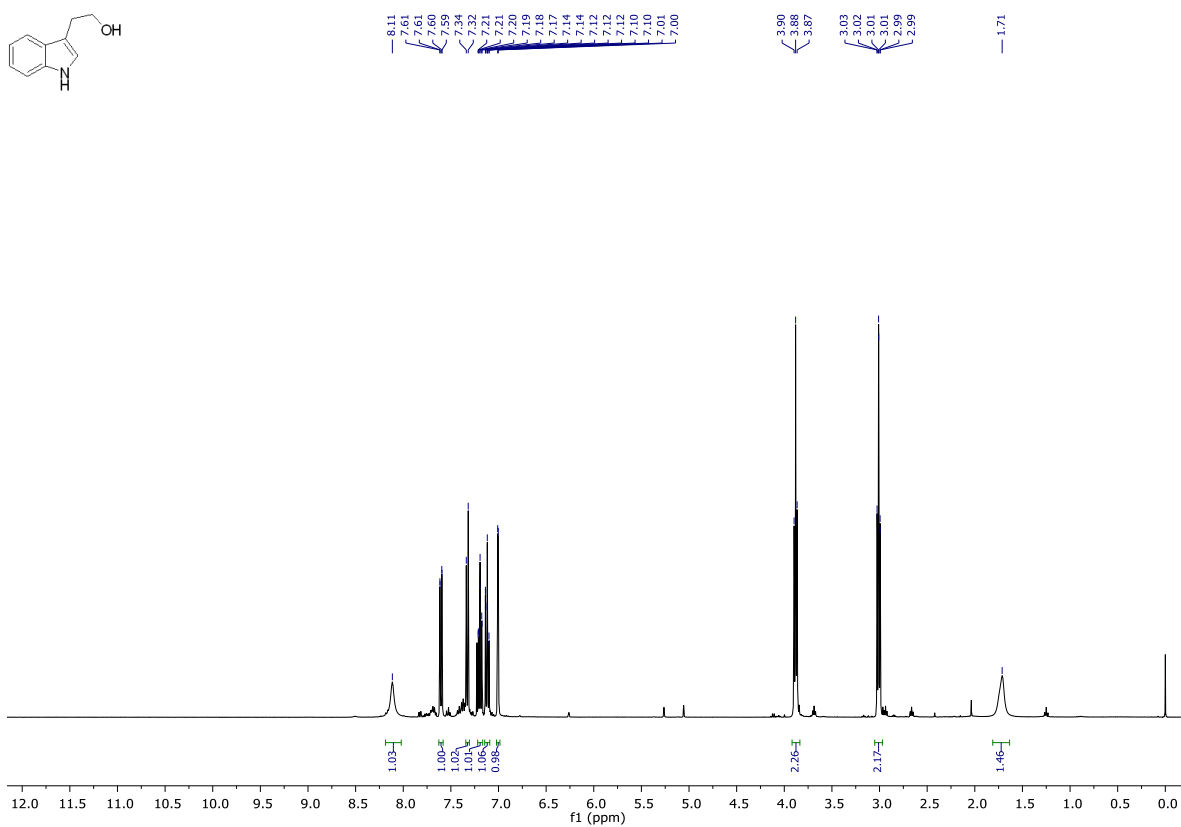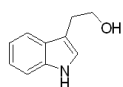
Figure 126: 3-hexyl-1*H*-indole (**126**)—¹H NMR
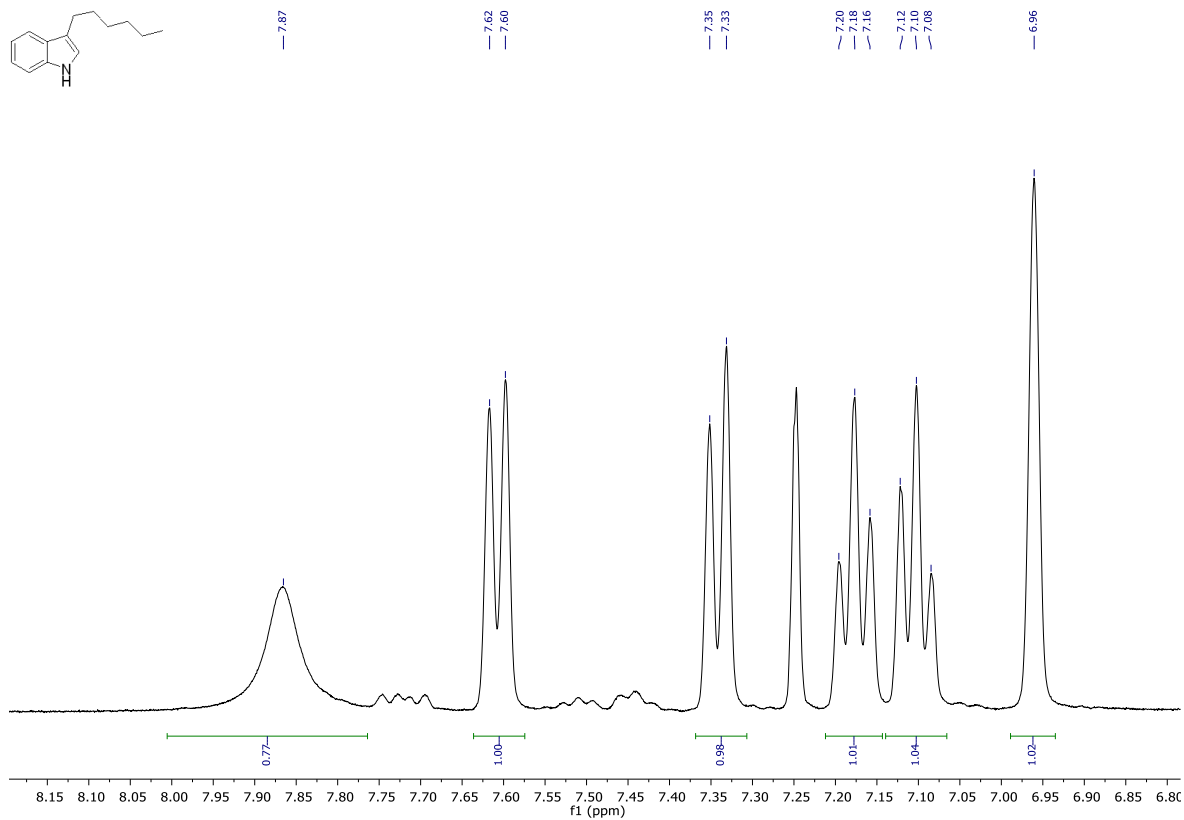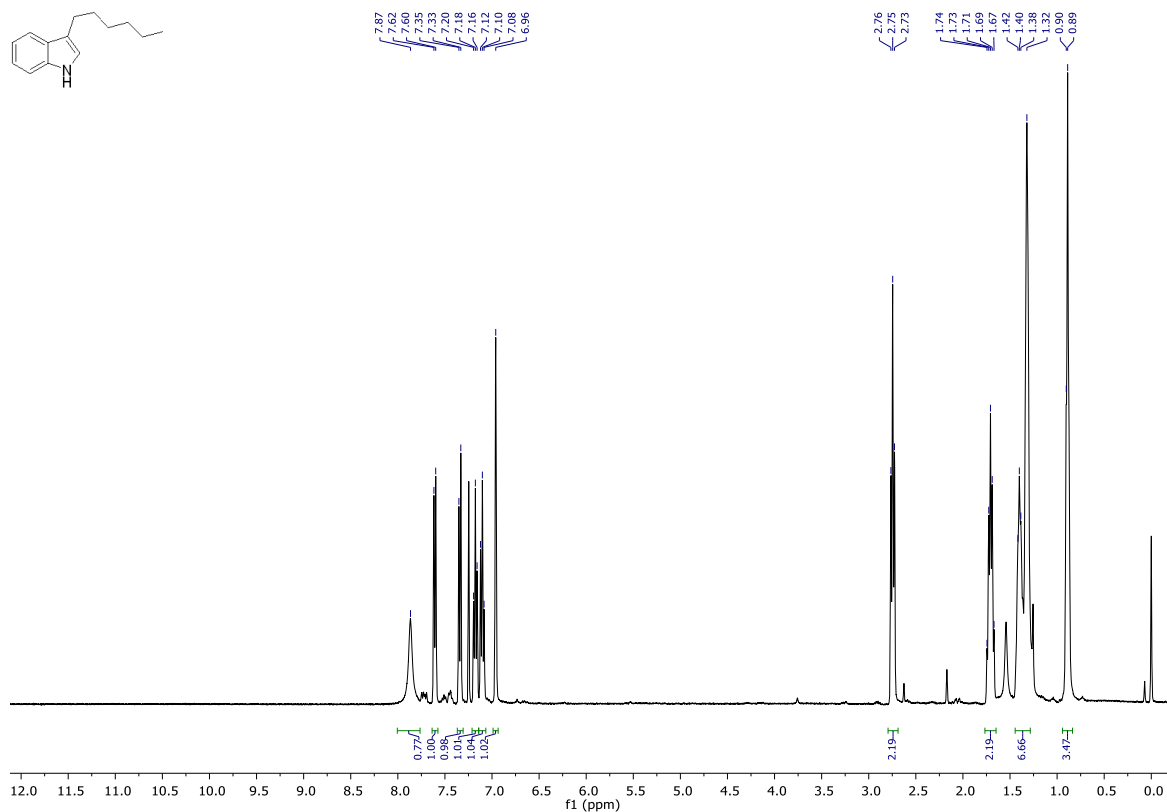
Figure 127: 3-hexyl-1*H*-indole (**126**)—¹³C NMR
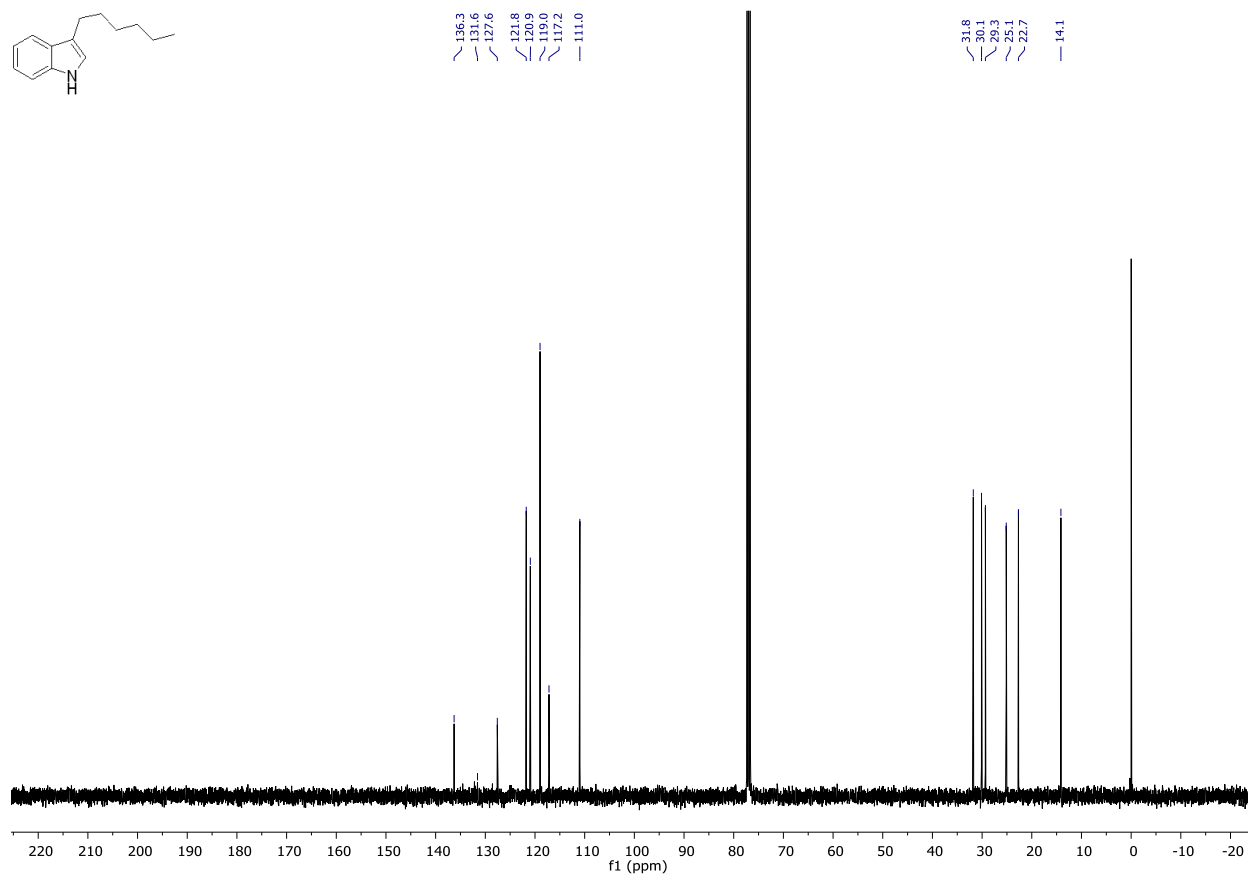
Figure 128: *N-tert*-butoxycarbonyl-tryptophan methyl ester (**127**)—¹H NMR
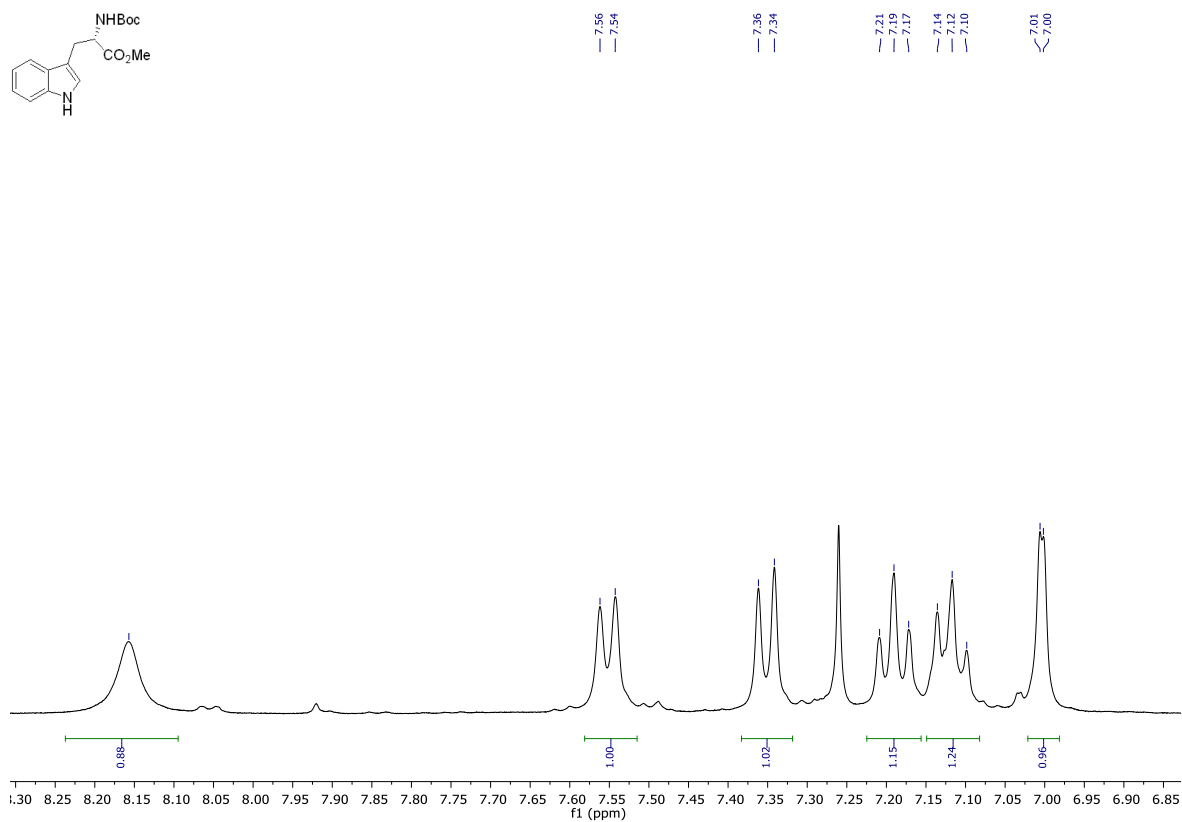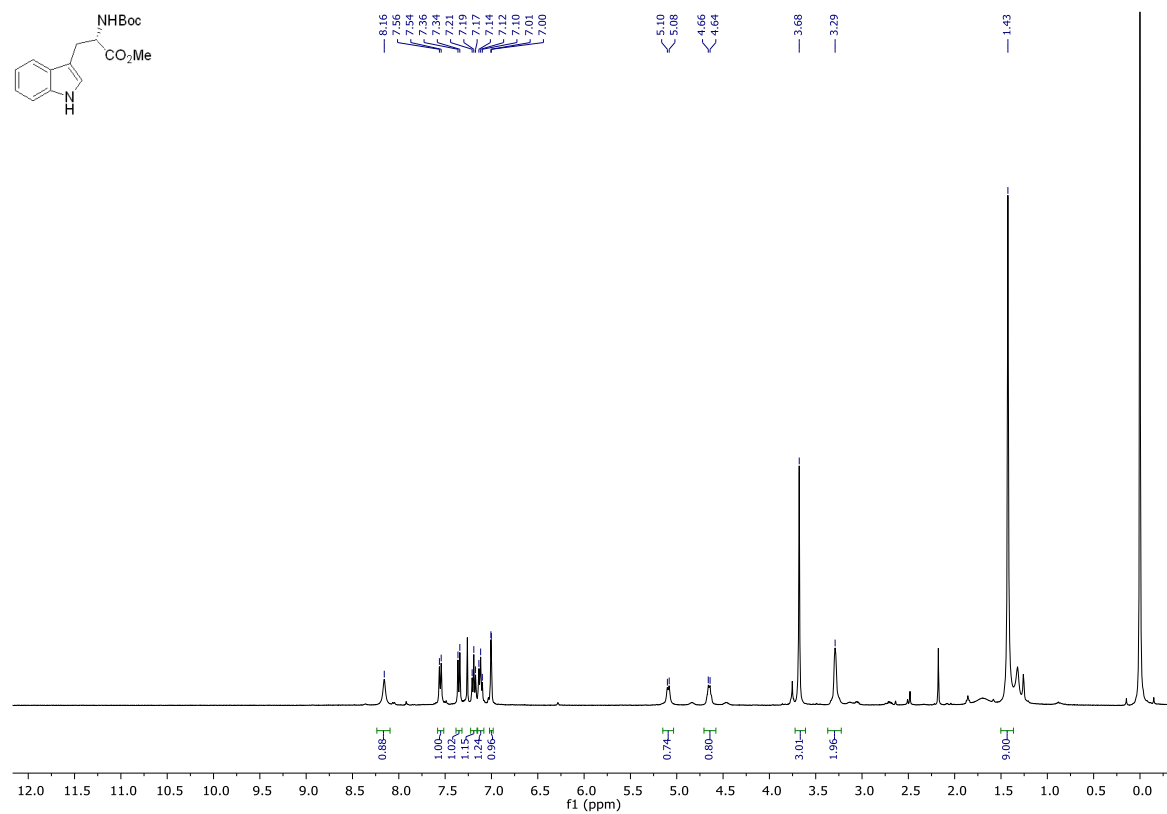
Figure 129: *N-tert*-butoxycarbonyl-tryptophan methyl ester (**127**)—^{13}C NMR
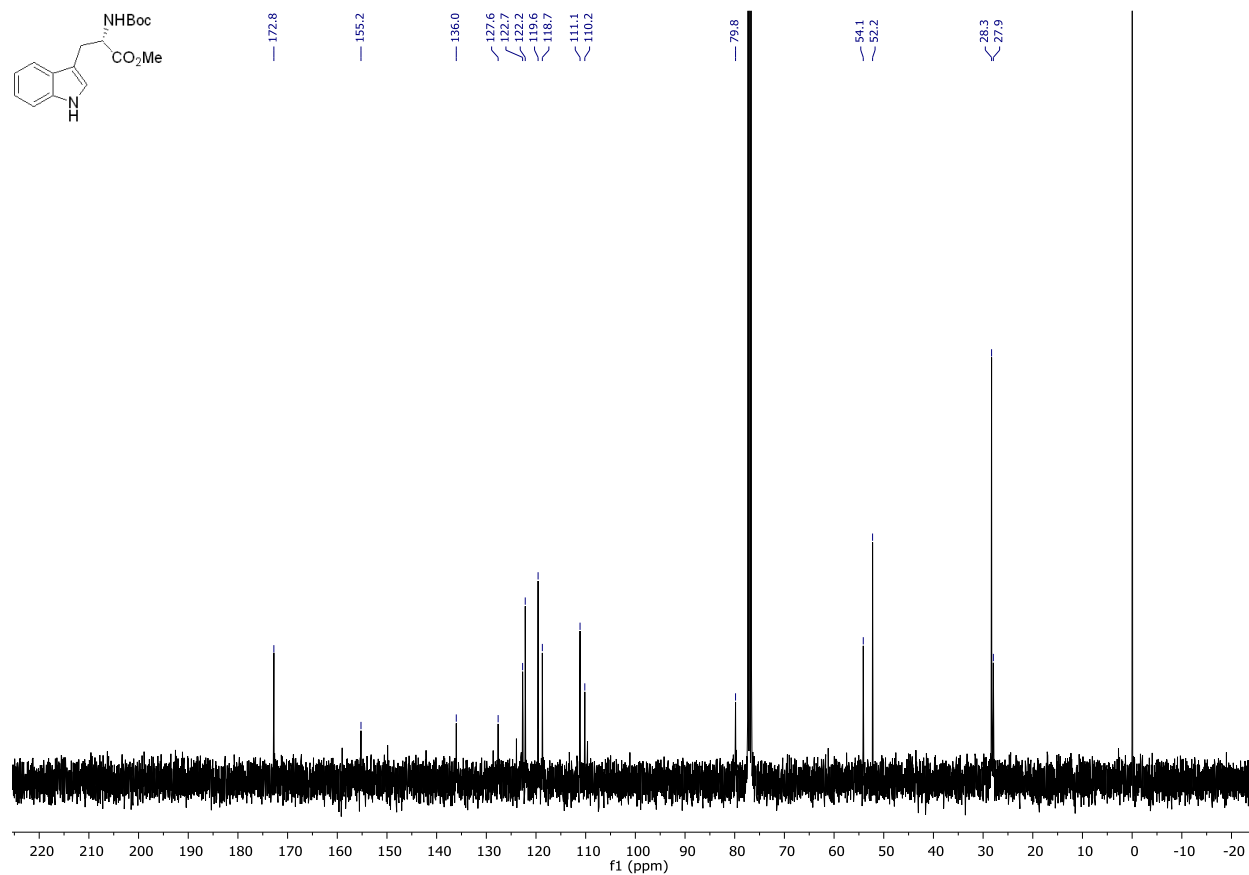
Figure 130: α-[[1,1-dimethylethoxy)carbonyl]amino]-1*H*-indole-2-propanoic acid methyl ester (**128**)—¹H NMR
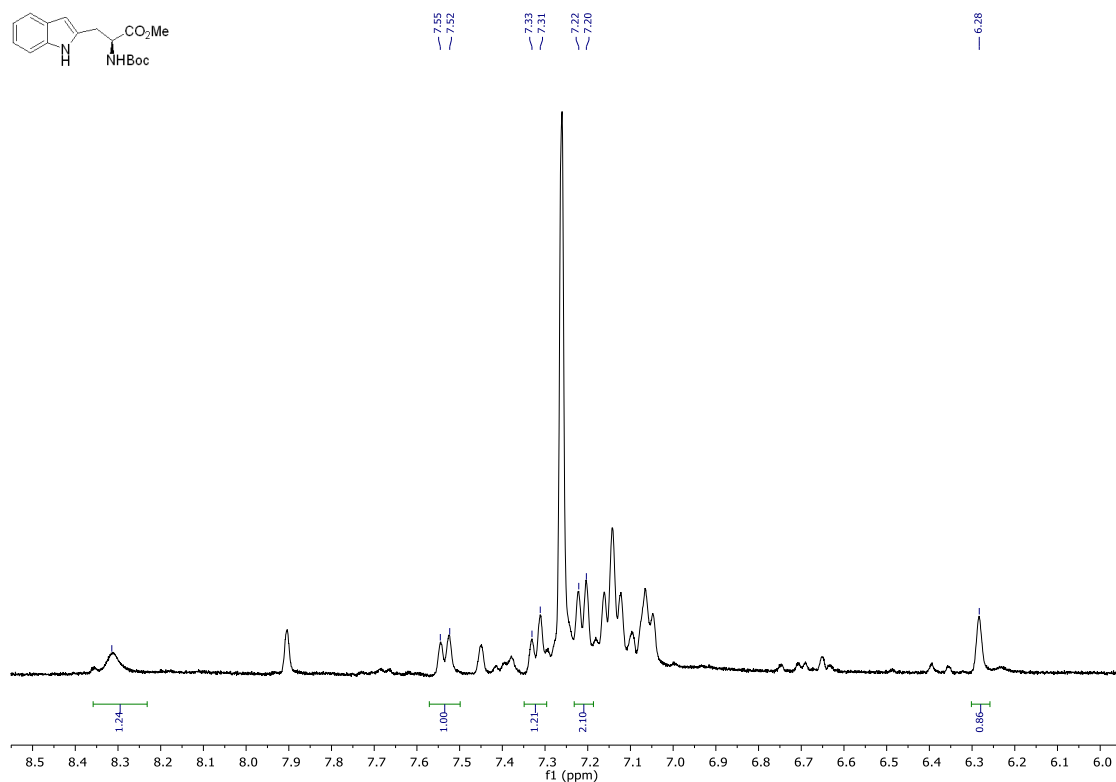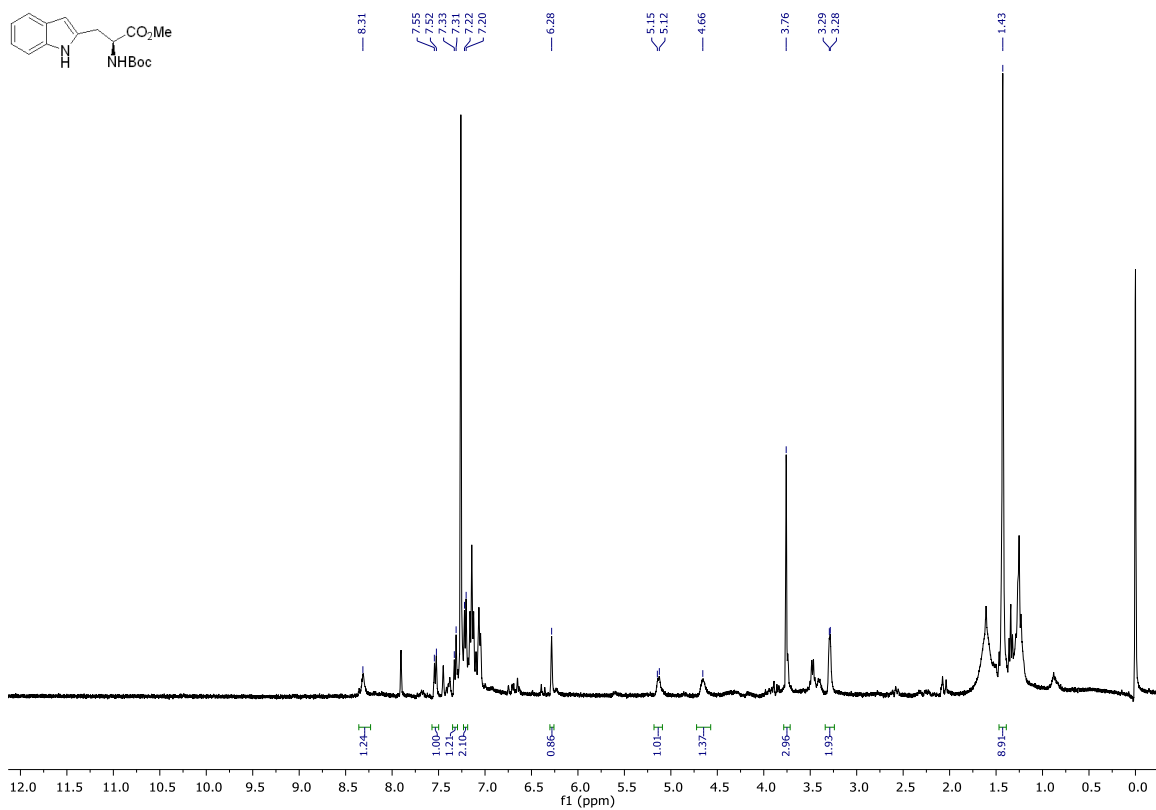
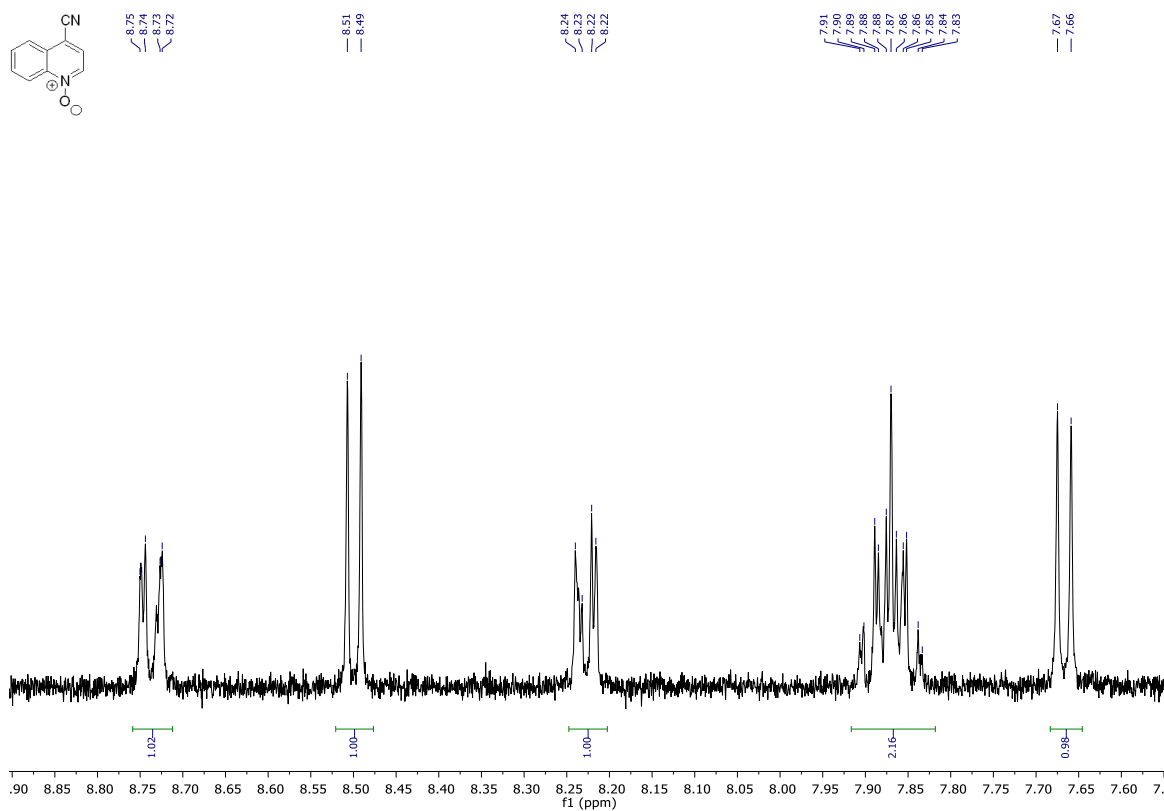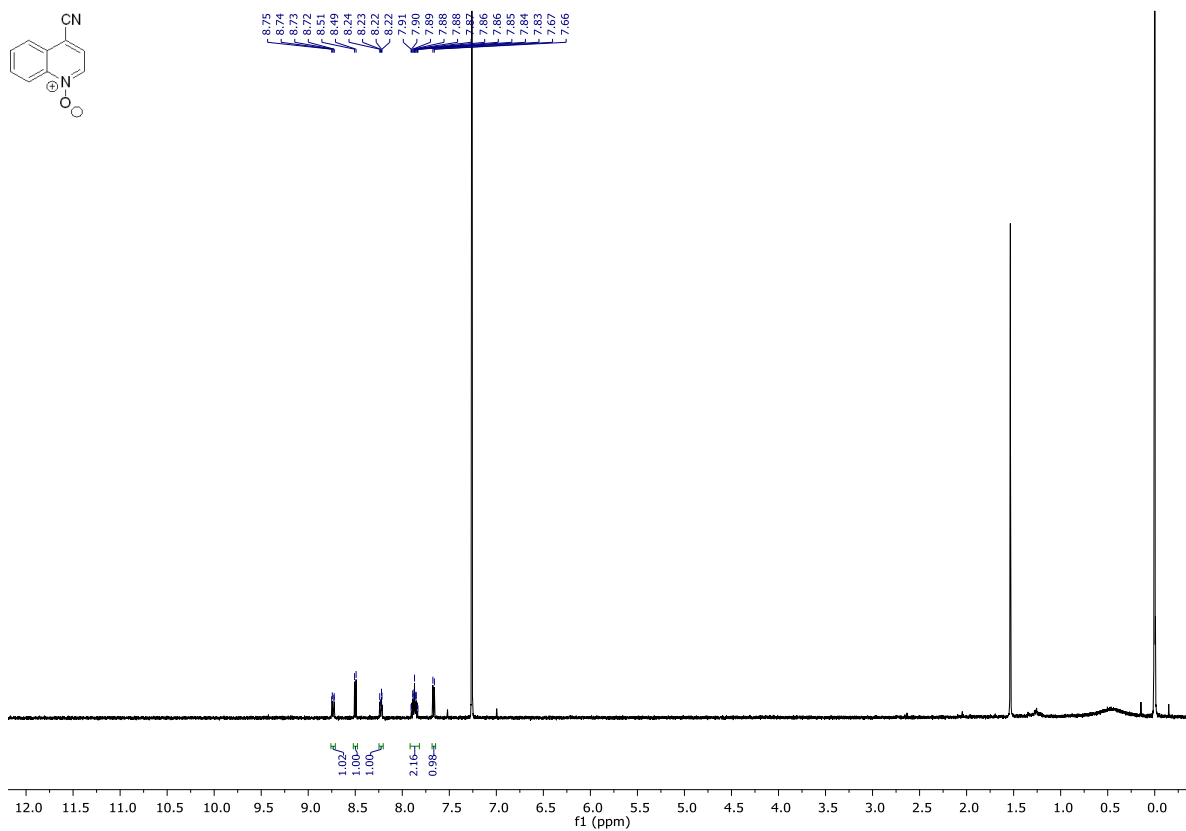**Figure 131:** 1-oxide-4-quinolinecarbonitrile (**141**)—¹H NMR

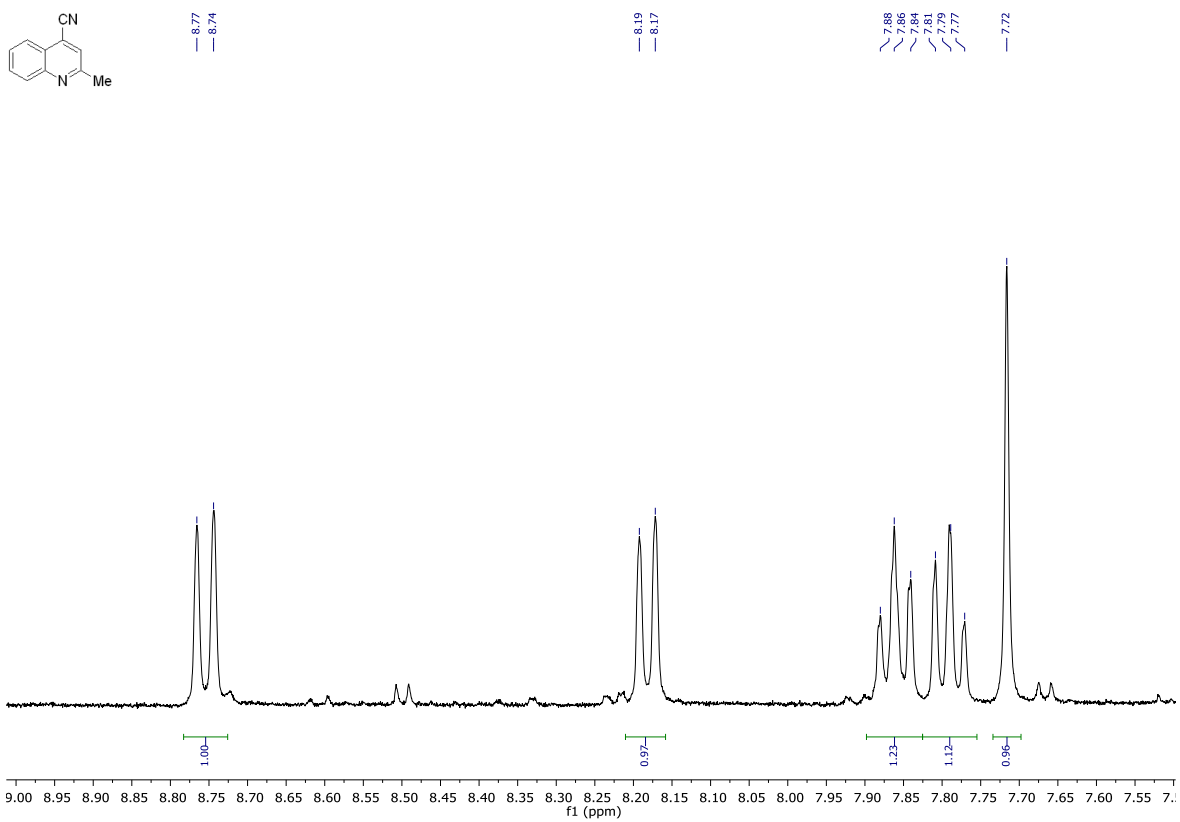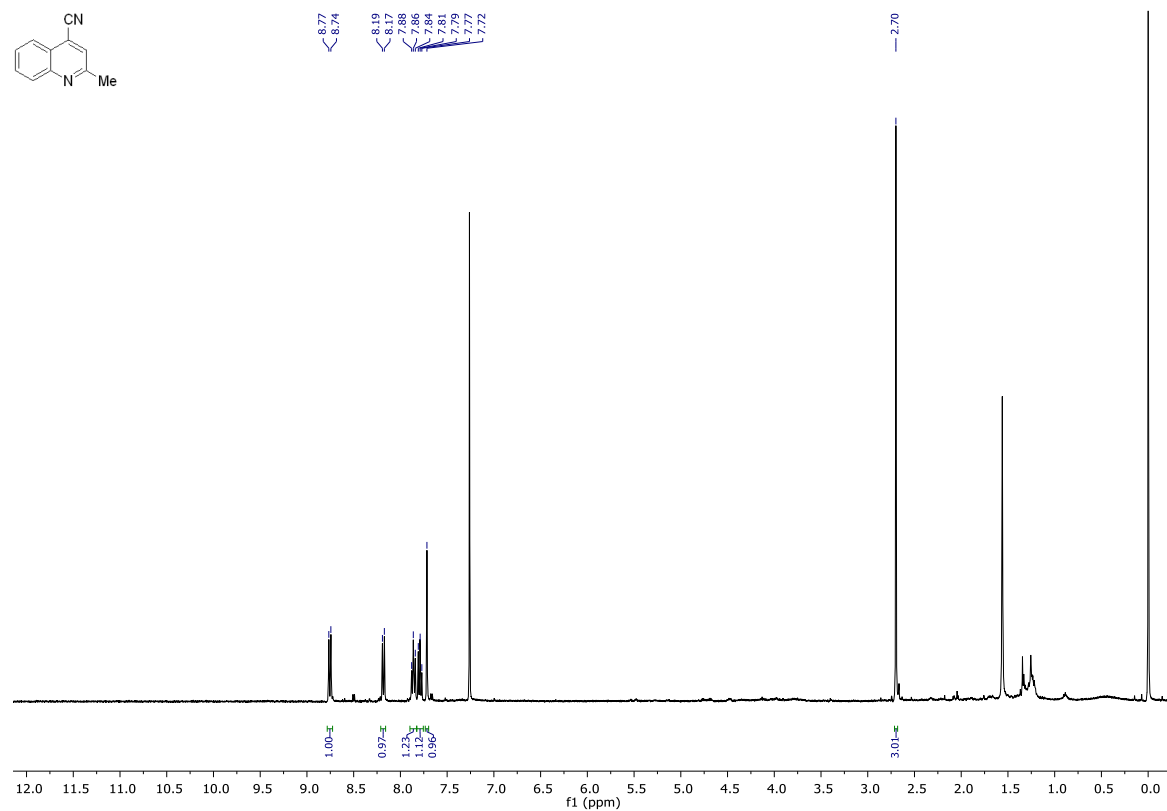**Figure 132:** 2-methyl-4-quinolinecarbonitrile (**145**)—¹H NMR

Figure 133: 2-benzyl-4-quinolinecarbonitrile (**147**)—¹H NMR