# Cross-Coupling Chemistry as a Tool for the Synthesis of Diverse Heterocyclic Systems and Natural Products

*A Thesis Submitted for the Degree of Doctor of Philosophy of the Australian National University*

*by*

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# *Declaration*

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of my original work carried out, unless otherwise stated, by myself during the period 2015-2018. It has not been presented for examination for any other degree. This thesis by publication is comprised by **six** journal articles. Wherever possible, established methodologies have been acknowledged by citation of the relevant original publication.

Michael Dlugosch

14/01/2019

# *Acknowledgements*

First I would like to thank my supervisor Professor Martin Banwell for having given me the opportunity and the privilege to undertake my PhD studies in his research group. Like a captain, he would guide me through the rough seas of my research and make sure that I would never lose track of where I was going. He would encourage me and he would inspire me to never give up and always keep going, even and especially at times of doubt and uncertainty. If it was not for Martin Banwell I never would have made it to the point where I am now. Thank you very much for your guidance and for your patience with me.

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Finally, I want to express my deepest gratitude to my family, my partner and my friends for their infinite support on whichever road I choose to go.

# *Table of Contents*

# *Publications*

*The following list details the publications that have resulted from the author's research work performed during his candidature for the Degree of Doctor of Philosophy*

Publications:

1. **The Palladium-catalysed Ullmann Cross-coupling Reaction: A Modern Variant on a Time-honored Process**
   Faiyaz Khan, Michael Dlugosch, Xin Liu and Martin G. Banwell
   *Accounts of Chemical Research*, **2018**, *51*, 1784-1795.

2. **Palladium-Catalyzed Ullmann Cross-Coupling of β-Iodoenones and β-Iodoacrylates with *o*-Halonitroarenes or *o*-Iodobenzonitriles and Reductive Cyclization of the Resulting Products To Give Diverse Heterocyclic Systems**
   Faiyaz Khan, Michael Dlugosch, Xin Liu, Marium Khan, Martin G. Banwell, Jas S. Ward, and Paul D. Carr, *Organic Letters* **2018**, *20*, 2770–2773.

3. **Reductive Cyclization of *o*-Nitroarylated-α,β-Unsaturated Aldehydes and Ketones with $TiCl_3$/HCl or Fe/HCl Leading to 1,2,3,9-Tetrahydro-4*H*-carbazol-4-ones and Related Heterocycles**
   Yun Qiu, Michael Dlugosch, Xin Liu, Faiyaz Khan, Jas S Ward, Ping Lan, and Martin G Banwell
   *J. Org. Chem.*, **2018**, *83*, 12023–12033.

4. **Synthesis of a Highly Functionalised and Homochiral 2-Iodocyclohexenone Related to the C-Ring of the Polycyclic, Indole Alkaloids Aspidophytine and Haplophytine**
   Michael Dlugosch and Martin Banwell
   *Australian Journal of Chemistry*, **2018**, *71*, 573-579.
   **Article featured on the cover of the journal**

5. **Syntheses of Structurally and Stereochemically Varied Forms of $C_7N$ Aminocyclitol Derivatives from Enzymatically-derived and Homochiral *cis*-1,2-Dihydrocatechols**
   Michael Dlugosch, Xinghua Ma, Shuxin Yang, Martin G. Banwell, Chenxi Ma, Jas S. Ward, and Paul Carr, *Organic Letters*, **2018**, 20, 7225–7228

6. **Chemical Syntheses of the Cochliomycins and Certain Related Resorcylic Acid Lactones**

   Martin G. Banwell, Xiang Ma, Benoit Bolte, Yiwen Zhang, Michael Dlugosch

   *Tetrahedron Letters* **2017,** *58*, 4025–4038.

# *Commentary on the Contributions of Mr Michael Dlugosch to the Six Papers Included in this PhD Thesis by Publication*

**Publication 1.** This is a review article that was written by Professor Martin Banwell. It incorporates descriptions of research on palladium-catalyzed Ullmann cross-coupling reactions conducted by the co-authors including the author of this thesis.

**Publication 2.** Professor Martin Banwell proposed the research work reported in this article. The author carried out 40 % of the reported laboratory work. In addition he collated and formatted 40 % of the reported spectral data presented in the Supporting Information. The author also wrote 40 % of the Experimental Section and conducted relevant literature surveys. Professor Martin Banwell wrote the body of the paper.

**Publication 3.** The initial idea for this project came from Professor Martin Banwell. The author carried out 65 % of the laboratory work reported in this article. In addition, he collated and formatted 60 % of the reported spectral data presented in the Supporting Information. The author also wrote 65 % of the Experimental Section and conducted relevant literature surveys. Professor Martin Banwell wrote the body of the paper.

**Publication 4.** The initial idea for this project came from Dr Lorenzo White. The author carried out the entirety of the laboratory work reported in this article. In addition, he collated and formatted the entirety of the reported spectral data presented in the Supporting Information. The author also wrote the entirety of the Experimental Section and conducted relevant literature surveys. Professor Martin Banwell wrote the body of the paper.

**Publication 5.** The initial idea for this project came from Professor Martin Banwell. The author carried out the entirety of the laboratory work associated with the reported synthesis of *epi*-kirkamide (Schemes 1 and 2) and the enantiomeric switching regime (Scheme 6). In addition, he collated and formatted the entirety of the reported spectral data sets presented in the Supporting Information. He also wrote the entirety of the corresponding portion of the Experimental Section and conducted relevant literature surveys on *epi*-kirkamide. He also conducted extensive research of the relevant literature pertaining to the synthesis of various kirkamide analogues. Professor Martin Banwell wrote the body of the paper.

**Publication 6.** This is a review article that was written by Professor Martin Banwell. It incorporates descriptions of research conducted by the author.

# *Abstract*

**Publication 1** comprises a review article concerned with palladium-catalyzed Ullmann cross-coupling reactions. Specifically, it details modern variants of these type of reactions and their extensive use, most notably by the Banwell group, in the synthesis of various heterocyclic systems, including ones encountered in natural products. **Publication 1** contextualizes the research described in **Publications 2-4**.

**Publication 2** is concerned with the palladium-catalyzed Ullmann cross-coupling reactions of β-iodoenones or β-iodoacrylates with *o*-iodonitrobenzenes or *o*-iodobenzonitriles, as well as the reductive cyclization of the resulting products to give various heterocyclic systems. Thus, this publication is concerned with a two-step approach to the synthesis of structurally diverse and biologically active heterocycles, including quinolones and benzomorphans which are normally only accessible via multistep-syntheses.

**Publication 3** outlines research on palladium-catalyzed Ullmann cross-coupling reactions of α-iodoenones with *o*-iodonitrobenzenes and the reductive cyclization of the ensuing coupling products. Specifically, it details the exploration of two distinct modes of reductive cyclization that allow for the synthesis of structurally "complementary" heterocyclic ring systems from a common precursor.

**Publication 4** describes a chemoenzymatic synthesis of a highly functionalized and homochiral α-iodocyclohexenone that it is expected will serve as a precursor, through the application of palladium-catalyzed Ullmann cross-coupling and reductive cyclization reactions, to the complex indole alkaloids aspidophytine and haplophytine. The synthesis starts with an enantiomerically pure *cis*-1,2-dihydrocatechol that is itself obtained through the whole-cell biotransformation of bromobenzene.

**Publication 5** is concerned with the developing syntheses of certain $C_7N$ aminocyclitols, a significant group of biologically active natural products. In particular, this paper details chemoenzymatic total syntheses of several novel compounds within the class, including analogues of the recently isolated natural product kirkamide. The syntheses exploit, as starting materials, enzymatically-derived and homochiral *cis*-1,2-dihydrocatechols obtained from either iodo- or bromo-benzene. Methods for obtaining the enantiomers of the reported $C_7N$ aminocyclitol derivatives have been identified. Once again, palladium-catalyzed cross-coupling chemistries were employed as key steps in these syntheses.

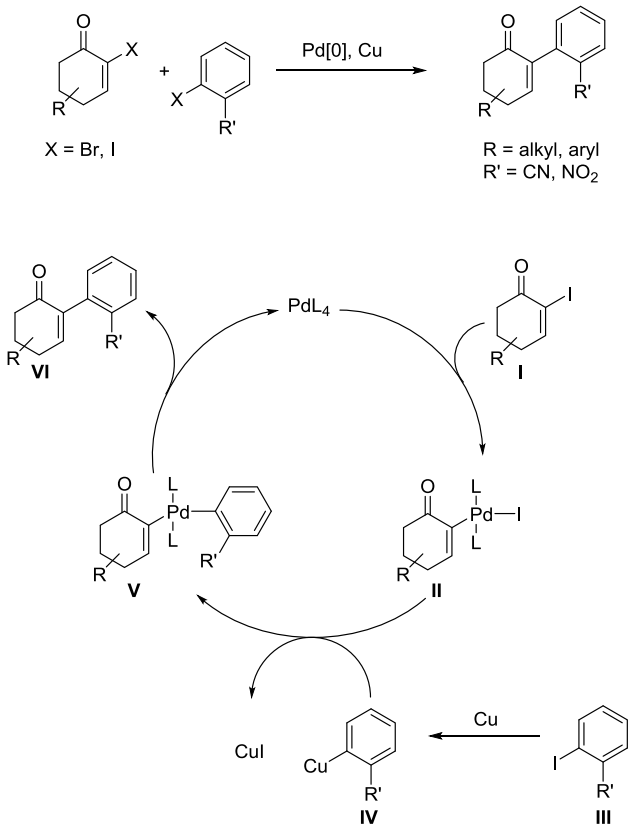
**Publication 6** is concerned with developing chemical syntheses of cochliomycins and related, biologically active natural products. Specifically, this is an extensive literature review on the chemical

synthesis of an important subset of the large class of structurally distinct and biologically significant natural products known as resorcylic acid lactones.

## *Synopsis*

Cross-coupling reactions provide a particularly effective means for the formation of carbon-carbon bonds. Many, well-established methods for forming such bonds now exist, perhaps the most noteworthy being palladium-catalyzed cross-couplings that involve the linking of a halide or pseudo-halide with an organometallic or metalloid species. While these reactions often give good yields of a single product, one drawback is the need to form the requisite organometallic species, usually from the corresponding organo-halide. While the classical Ullmann cross-coupling reaction has the advantage that it can affect the direct coupling of two distinct organo-halides, harsh reaction conditions are usually involved (temperatures in excess of 250 °C are frequently required) and often homo-coupling is the predominant, if not the only process observed.[1] The palladium-catalyzed Ullmann cross-coupling affords many of the advantages of the standard palladium-catalyzed processes as well as those associated with the original Ullmann reaction. As such, it is now possible to carry out hetero-couplings of two distinct organo-halides under mild conditions.

The focus of the research described in this thesis is the deployment of palladium-catalyzed Ullmann cross-coupling reactions in the synthesis of biologically active heterocyclic systems, as well as the total synthesis of natural products. A common theme is the cross-coupling of iodoenones with substituted *o*-iodo- or *o*-bromo-benzenes as shown, for example, in Scheme 1. The substituents (R') associated with the haloarenes are usually strongly electron-withdrawing ones, such as nitrile or nitro groups. The proposed reaction mechanism for this type of couplings is based on a previously reported reaction mechanism by Shimizu and co-workers.[2] In the first step the Pd(0) catalyst undergoes an oxidative addition into the C-I bond of enone **I**, whereas the iodoarene **III** undergoes a halogen-metal exchange by reacting with Cu(0) and thus forming cuprate **IV**. Pd-species **II** can then undergo a ligand exchange reaction with cuprate **IV** to yield intermediate **V**. A reductive elimination will then generate product **VI** and regenerate the Pd(0) catalyst.




**Scheme 1**: An Example of the Palladium-Catalyzed Ullmann Cross-Coupling Reaction and the Proposed Reaction Mechanism

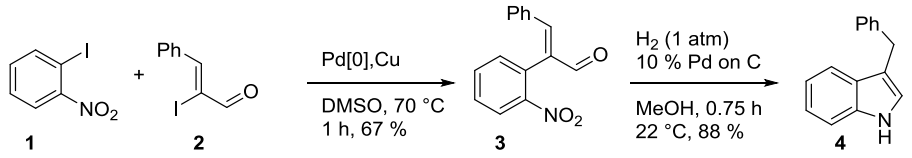
Such palladium-catalyzed Ullmann cross-couplings can be conducted using a range of iodinated enones, as described in **Publications 2** and **3**, and so providing ready access to diverse heterocyclic systems in just one or two steps. As described in **Publication 4**, it is anticipated that the reaction can also be deployed for the assembly of more elaborate systems. The application of related cross-coupling reactions to syntheses of natural products and natural product analogues are described in **Publications 5** and **6**.

## *Thesis Overview*

**Publication 1: The Palladium-catalysed Ullmann Cross-coupling Reaction: A Modern Variant on a Time-honored Process**

In **Publication 1** the focus is on the applicability of palladium-catalyzed Ullmann cross-coupling reactions to the synthesis of heterocycles and natural products. Special attention is given to the manifold contributions of the Banwell group in this field. A representative palladium-catalyzed Ullmann cross-coupling regime is shown in Scheme 2 and has been used to synthesize, after reductive cyclization of the initial cross-coupling product, indoles such as compound **4**. The particular

reaction sequence shown in Scheme 2 is also one direct example of the author's immediate contributions to this publication.




**Scheme 2**: Synthesis of Indole **4**

Another example is the synthesis of a class of compounds called carbolines. There are four isomeric carbolines, as shown in Figure 1, and each of these is encountered in natural products and/or within pharmacologically significant compounds.

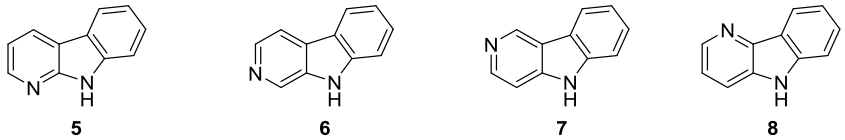
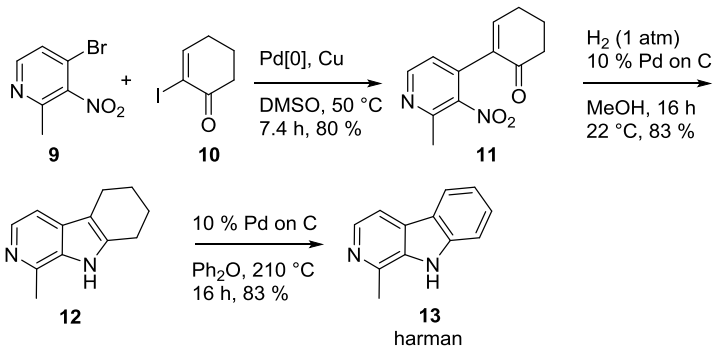



**Figure 1**: The Structures of the Four Isomeric Carbolines

The synthesis of the carboline-type natural product harman (**13**)[3] (possessing anti-HIV activity[4]) shown in Scheme 3 further exemplifies the utility of the protocols developed by the Banwell group.




**Scheme 3**: Synthesis of the Natural Product Harman

**Publication 2. Palladium-Catalyzed Ullmann Cross-Coupling of β-Iodoenones and β-Iodoacrylates with *o*-Halonitroarenes or *o*-Iodobenzonitriles and Reductive Cyclization of the Resulting Products to Give Diverse Heterocyclic Systems**

This paper is concerned with the palladium-catalyzed Ullmann cross-coupling of diverse β-iodoenones and β-iodoacrylates with *o*-halonitroarenes and the reductive cyclization of the ensuing products. By such means a powerful, two-step synthetic pathway leading to a range of novel heterocyclic systems has been established.

Previous work conducted by the Banwell group on the palladium-catalyzed Ullmann cross-coupling reaction was largely focussed on the coupling of α-iodoenones with *o*-halonitrobenzenes. Transformations of this type provide access to different types of natural products including the carbazoles shown in Figure 2.[5]

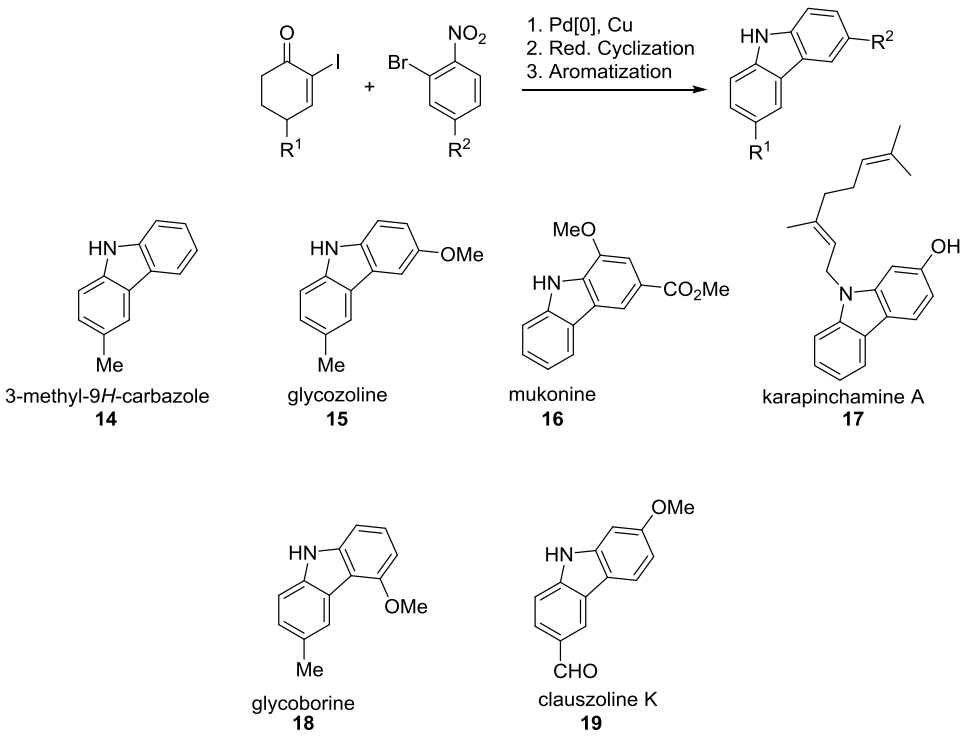



**Figure 2**: Structures of Diverse Carbazoles

The successful syntheses of the members of the the uleine alkaloid family shown in Figure 3 further highlight the power of such methodologies.[6]

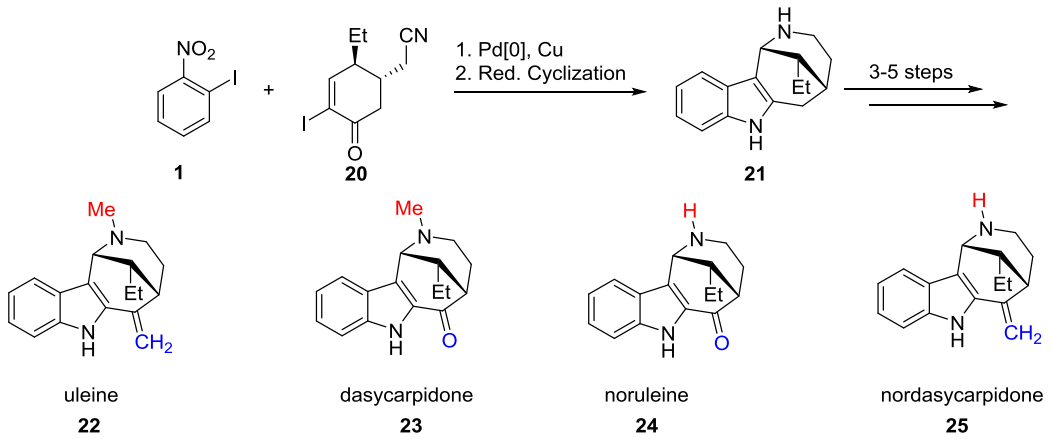
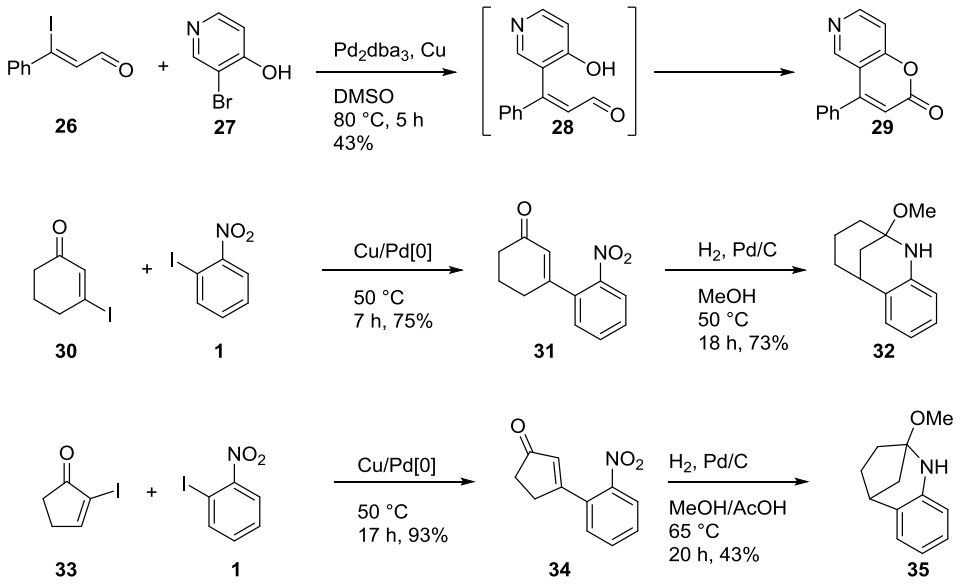


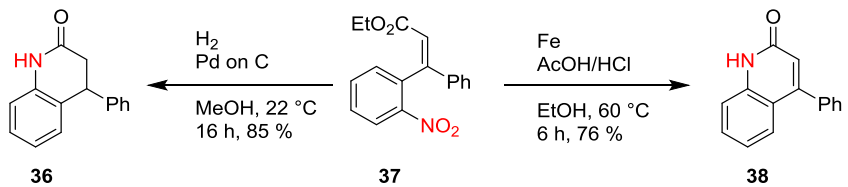

**Figure 3**: Members of the Uleine Alkaloid Family Accessible Using the Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Protocols

The research reported in **Publication 2** is complementary to such earlier work. The focus in this publication is on the participation of β-iodoenones and β-iodoacrylates (rather than, say, α-iodoenones) in palladium-catalyzed Ullmann cross-coupling reactions. Depending on the precise nature of such coupling partners, as well as the methods used for the reductive cyclization, then various heterocyclic systems including quinolones, dihydroquinolones, benzomorphanes and naphthydrines can be obtained. A number of these have now become much more readily accessible as a result. The benzomorphans reported in this publication are of particular interest, as many of them have a number of notable medicinal properties including by serving as analgesics.[7] Scheme 4 highlights some such transformations.




**Scheme 4**: Palladium-Catalyzed Ullmann Cross-Coupling of β-iodoenones with *o*-Halonitrobenzenes Giving Access to Heterocyclic Systems such as Azacoumarins and Benzomorphans

In this study it was also shown that depending upon the mode of reduction of the initial Ullmann cross-coupling product different cyclization products can be obtained. For instance, if compound **37** (Scheme 5) is treated with Fe in AcOH/HCl then quinolone **38** is obtained while exposing the same substrate to standard hydrogenation conditions ($H_2$/Pd on C) affords the fully reduced product, namely dihydroquinolone **36**.

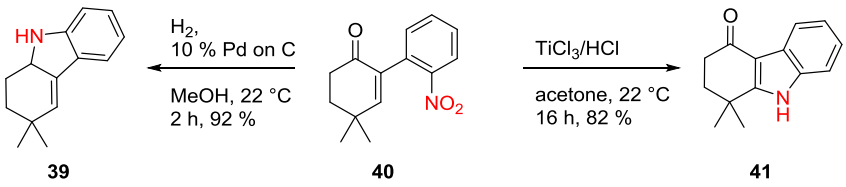



**Scheme 5**: Possible Cyclization Pathways for **37** using either Fe in AcOH/HCl or $H_2$/Pd on C

On the basis of the studies reported in Publication 2, it is clear that palladium-catalyzed Ullmann cross-couplings involving β-iodoenones and β-iodoacrylates provide a versatile means for obtaining hitherto unknown or less readily accessible heterocyclic frameworks.

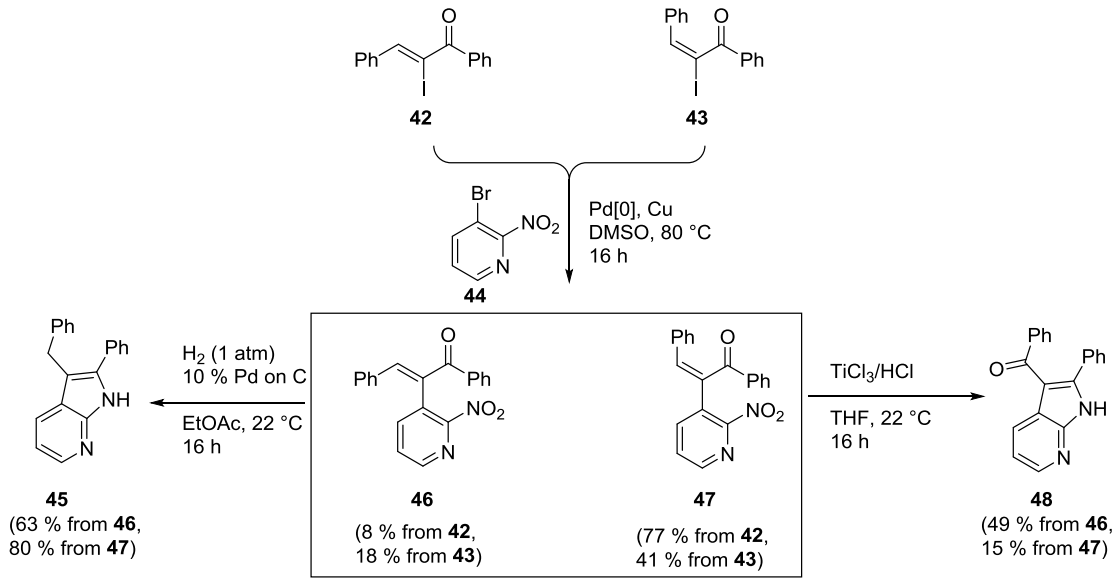
**Publication 3: Reductive Cyclization of *o*-Nitroarylated-α,β-Unsaturated Aldehydes and Ketones with $TiCl_3$/HCl or Fe/HCl Leading to 1,2,3,9-Tetrahydro-4*H*-carbazol-4-ones and Related Heterocycles**

**Publication 3** further articulates the utility of the palladium-catalyzed Ullmann cross-coupling /reductive cyclization sequence. In particular, it focuses on different methods for effecting the reductive cyclizations of the coupling products. Significantly, depending upon the mode of the reductive cyclization a given coupling product may afford distinct heterocyclic products. This further extends the range of heterocycles that can be obtained. In particular, **Publication 3** focuses on the complementary behaviours of the $H_2$/Pd on C and the $TiCl_3$/HCl reduction systems. So, as shown in Scheme 6, if coupling product **40** is treated with $H_2$ in presence of Pd on C then it reacts to give product **39** while on treatment with $TiCl_3$/HCl then congener **41** is obtained.



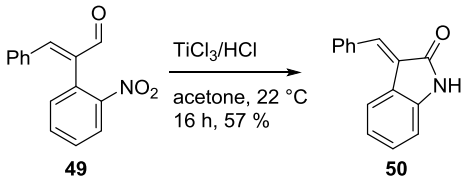

**Scheme 6**: Divergent Reductive Cyclization Pathways for Compound **40**

Similarly, as shown in Scheme 7, while subjection of cross-coupling products **46** or **47** to reductive cyclization using $H_2$ and Pd on C provides indole **45**, on treating the same substrates with $TiCl_3$ in HCl then the C3-acylated indole **48** is formed, albeit in variable yields.



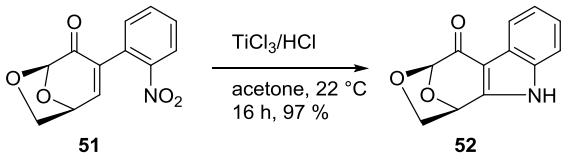

**Scheme 7**: Synthesis of Reductive Cyclization Products **45** and **48**

In contrast, the readily available cinnamaldehyde derivative **49** shown in Scheme 8 affords the known anti-proliferative agent **50**[8] on treatment with $TiCl_3$/HCl in acetone.




**Scheme 8**: $TiCl_3$-Mediated Cyclization of Compound **49**

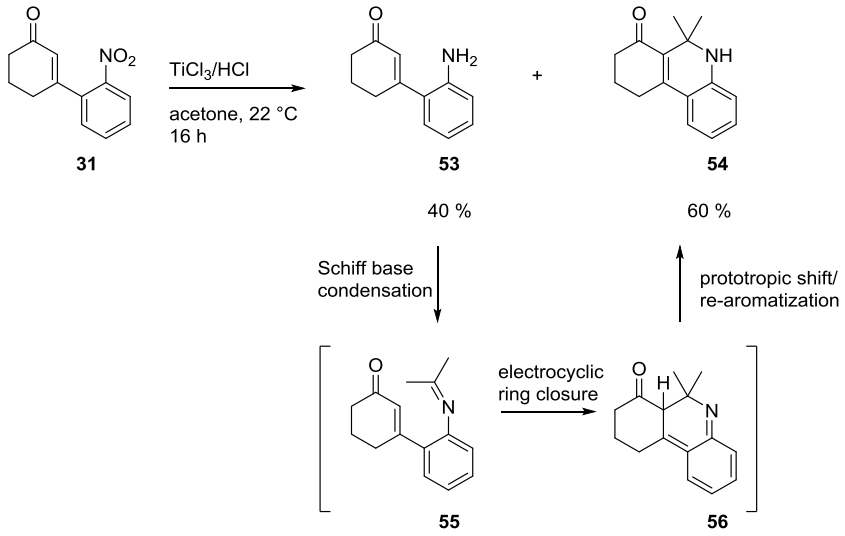
In a further example of the utility of such cyclization reactions, levoglucosenone derivative **51** provides, as depicted in Scheme 9, the tetracyclic product **52** upon treatment with $TiCl_3$ in HCl.




**Scheme 9**: $TiCl_3$-Mediated Cyclization of Compound **51** to Give the Tetracyclic Levoglucosenone-Based Compound **52**

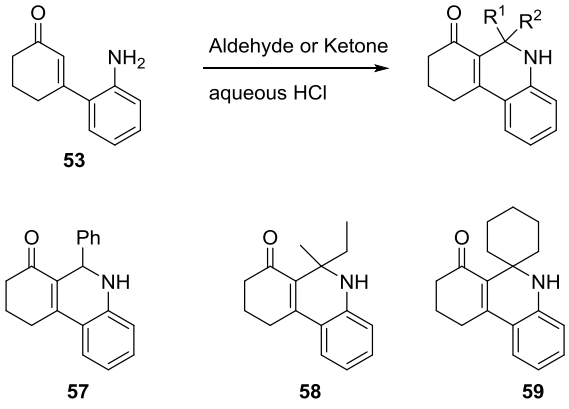
With this method it is also possible to form novel dihydroquinolines. Thus, ketones such as acetone can be incorporated into the reductive cyclization product. As illustrated in Scheme 10, this presumably occurs *via* Schiff base condensation, electrocyclic ring-closure then a prototropic shift and accompanying re-aromatization. If, for instance, compound **31** is reacted with $TiCl_3$/HCl in presence of a ketone, then in the first step the nitro group is reduced to the corresponding aniline

**53**. The amine residue so-formed then undergoes a Schiff base condensation with the added ketone to yield intermediate **55** that undergoes electrocyclic ring closure to give intermediate **56**. A prototropic shift and accompanying re-aromatization then leads to the final product **54**, the structure of which was confirmed by single-crystal X-ray analysis.




**Scheme 10**: Formation of Dihydroquinoline **54** from Cross-coupling Product **31** and Acetone in the Presence of $TiCl_3$/HCl

As shown in Scheme 11 a range of other dihydroquinolines was prepared by simply reacting compound **53** with aldehydes or ketones, usually in presence of aqueous HCl. For instance, when this substrate was reacted with benzaldehyde, then product **57** was obtained. Similarly, the reaction between compound **53** and butanone afforded compound **58**, while the reaction involving cyclohexanone gave the spirocyclic product **59**.




**Scheme 11**: Acid-Promoted Reactions of Compound **53** with Aldehydes or Ketones to Give Dihydroquinolines **57**-**59**

Overall, then, **Publication 3** builds, in a distinctly complementary way, on the work reported in **Publication 2**.

**Publication 4: Synthesis of a Highly Functionalised and Homochiral 2-Iodocyclohexenone Related to the C-ring of the Polycyclic, Indole Alkaloids Aspidophytine and Haplophytine**

Aspidophytine is a constituent of the heterodimeric compound (+)-haplophytine (Figure 4) that occurs in the Mexican cockroach plant *Haplophyton cimididum*.[9] Dried leaves of this plant have been used for their insecticidal properties since at least the Aztec era. A range of synthetic studies has been conducted on the total synthesis of aspidophytine, the first synthesis of the (–)-enantiomeric form having been reported by Corey and his co-workers in 1999.[10] This was followed by the reports of Fukuyama (2003)[11,12], Padwa (2006)[13,14], Marino (2006)[15], Nicolaou (2008)[16], Tokuyama (2013)[17] and Qiu (2013).[18]

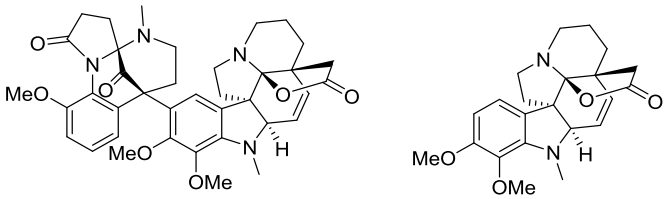
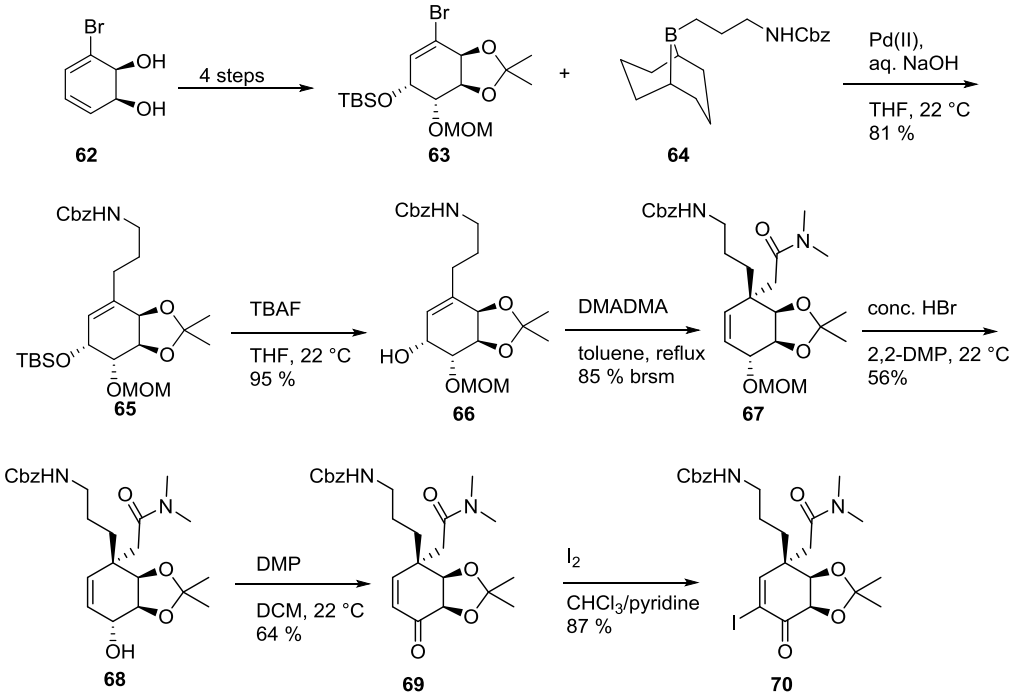



**Figure 4**: Structures of the Alkaloids Haplophytine and Aspidophytine

A nine step synthesis of a highly functionalized and homochiral 2-iodocyclohexenone that is related to the C-Ring of aspidophytine and haplophytine is reported in **Publication 4**. Unlike all previously reported asymmetric total syntheses of these compounds, a chemo-enzymatic approach is used to establish the required functionality and stereochemistry.

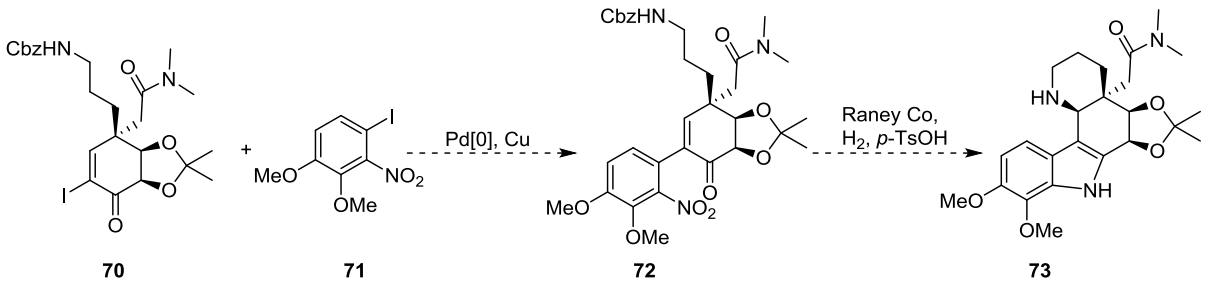
The starting material employed is the enantiomerically pure *cis*-dihydrocatechol **62** depicted in Scheme 12 and which can be obtained through the whole-cell biotransformation of bromobenzene. Using metabolite **62** would give access to the non-natural enantiomeric form of aspidophytine and haplophytine. However, since compound *ent*-**62** is also available, the illustrated reaction sequence should also provide access to the natural products themselves.




**Scheme 12**: Synthesis of the Homochiral 2-Iodocyclohexenone **70**

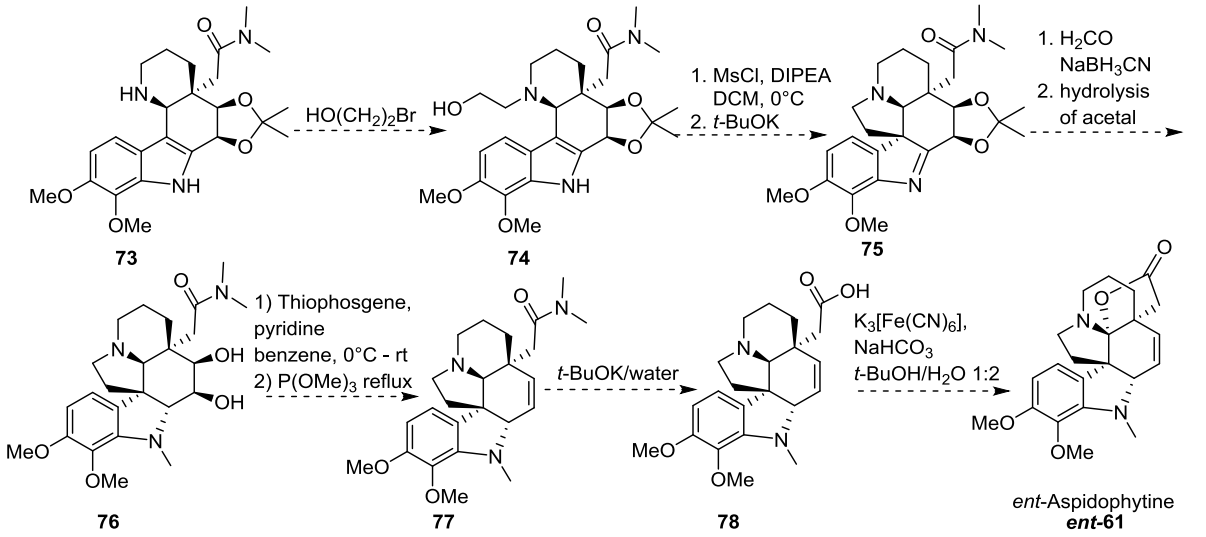
The aminoalkyl chain associated with the target 2-iodocyclohexenone was introduced via Suzuki–Miyaura cross-coupling of compounds **63** and **64**. The quaternary stereocenter of the target was then established using the allylic alcohol moiety embedded within compound **66** by treating it with dimethylformamide dimethyl acetal (DMADMA) and thus effecting an Eschenmoser–Claisen rearrangement. Deprotection of the newly generated allylic alcohol, followed by oxidation and Johnson $\alpha$-iodination then gave α-iodoenone **70**.

As shown in Scheme 13, the highly substituted enone **70** has the potential to engage in a palladium-catalyzed Ullmann cross-coupling reaction with the substituted *o*-nitrobenzene **71**. The anticipated coupling product from this reaction, namely compound **72**, would then be engaged in a reductive cyclization reaction to give the pentacyclic intermediate **73**.




**Scheme 13**: Possible Elaboration of the Palladium-Catalyzed Ullmann Cross-Coupling Product **70** to Tetracyclic Compound **73**

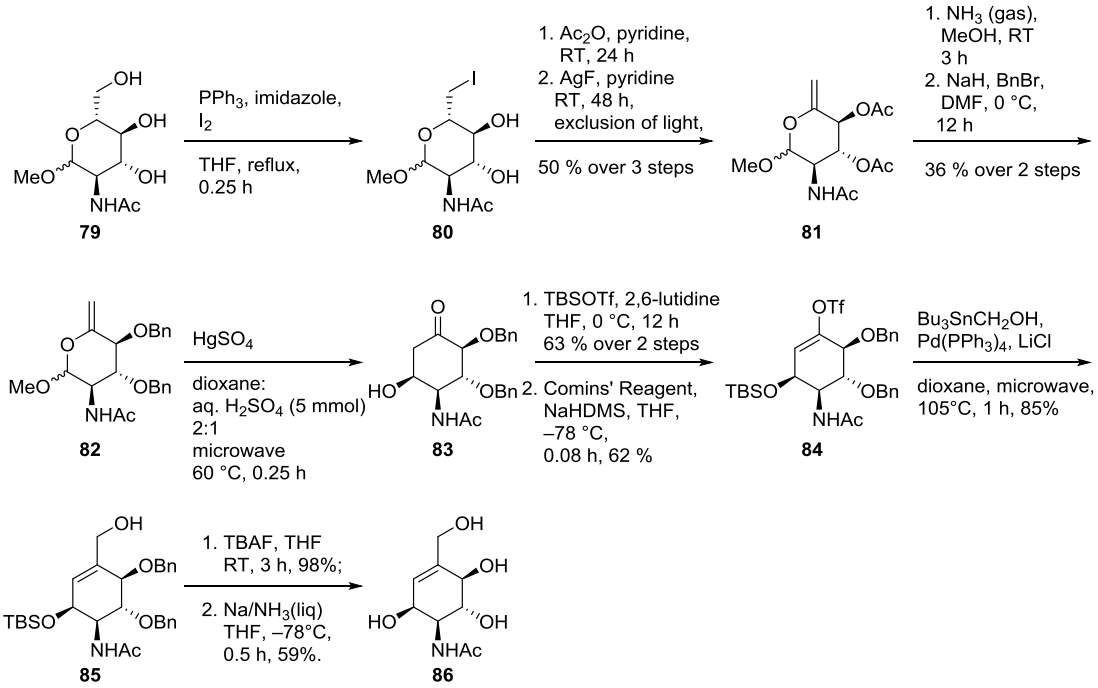
Scheme 14 illustrates a series of possible further reactions, including a Corey–Winter olefination, that could be applied to compound **73** and so yielding *ent*-aspidophytine. Compound **73** may be reacted with 2-bromoethanol to yield amino-alcohol **74**, which can then be mesylated. Treating the indole moiety with a strong base should then lead to deprotonation and subsequently to an intramolecular displacement of the mesylate and ring-formation. The unprotected diol in compound **76** would then be converted to the corresponding olefin via Corey–Winter olefination. Hydrolysis of the dimethyl amide and esterification should then give *ent*-aspidophytine.




**Scheme 14**: Potential Pathway for the Completion of a Synthesis of *ent*-Aspidophytine

**Publication 5: Syntheses of Structurally and Stereochemically Varied Forms of $C_7N$ Aminocyclitol Derivatives from Enzymatically-derived and Homochiral *cis*-1,2-Dihydrocatechols**

In 2015 the isolation of the new $C_7N$ aminocyclitol kirkamide as well as an eleven step synthesis of it from methyl *N*-acetyl-*D*-glucosamine was reported by Gademann and co-workers (Scheme 15).[19]



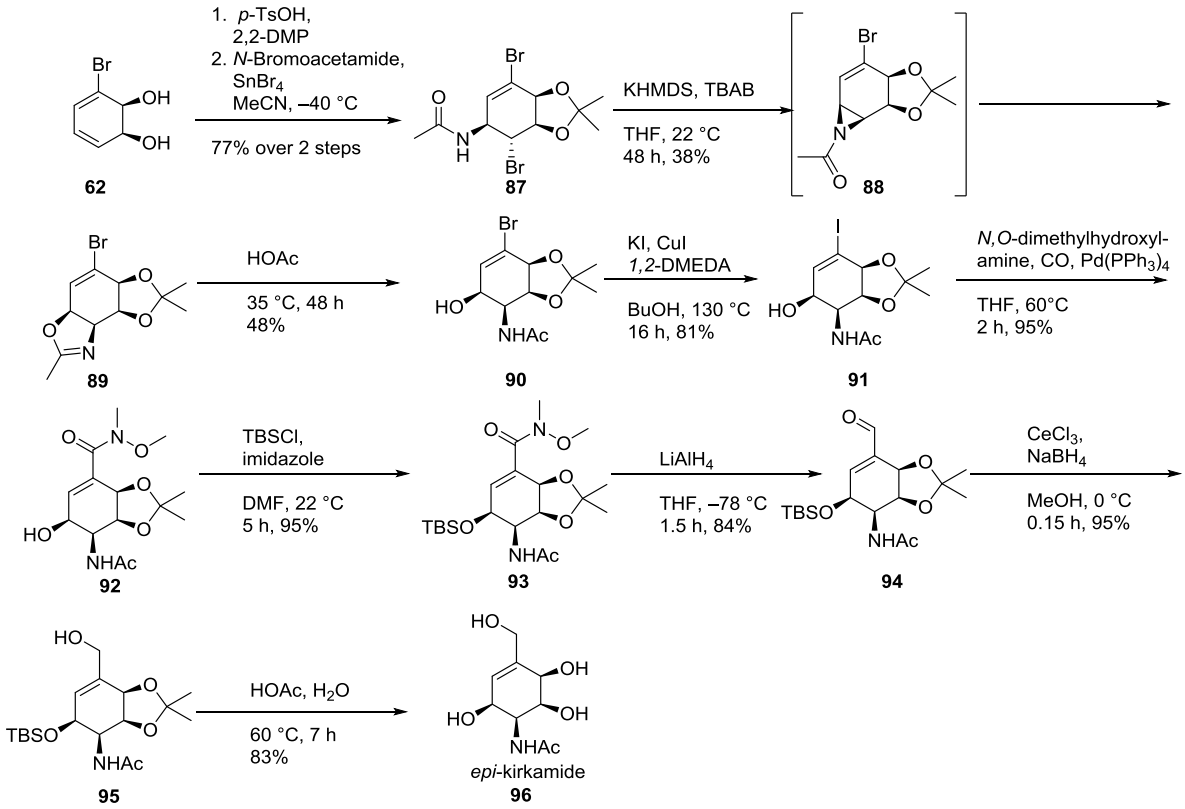

**Scheme 15**: Gademann's Synthesis of Kirkamide

Kirkamide is found in leaf nodules of the plant *Psychotria kirkii* and likely produced by *Candidatus Burkholderia kirkii*, a leaf symbiont of this plant.[20,21] Since kirkamide has shown to be toxic to aquatic arthropods and insects it might be acting as an anti-feedant and thus protecting the leaves of the host plant.

In **Publication 5** total syntheses of several derivatives of kirkamide, including an epimer, are reported. In contrast to the previously reported synthesis, the approach taken in the author's work is a chemo-enzymatic one. The starting material for this purpose is the *cis*-dihydrocatechol **62**, which also served as the starting material for the synthesis described in **Publication 4**.

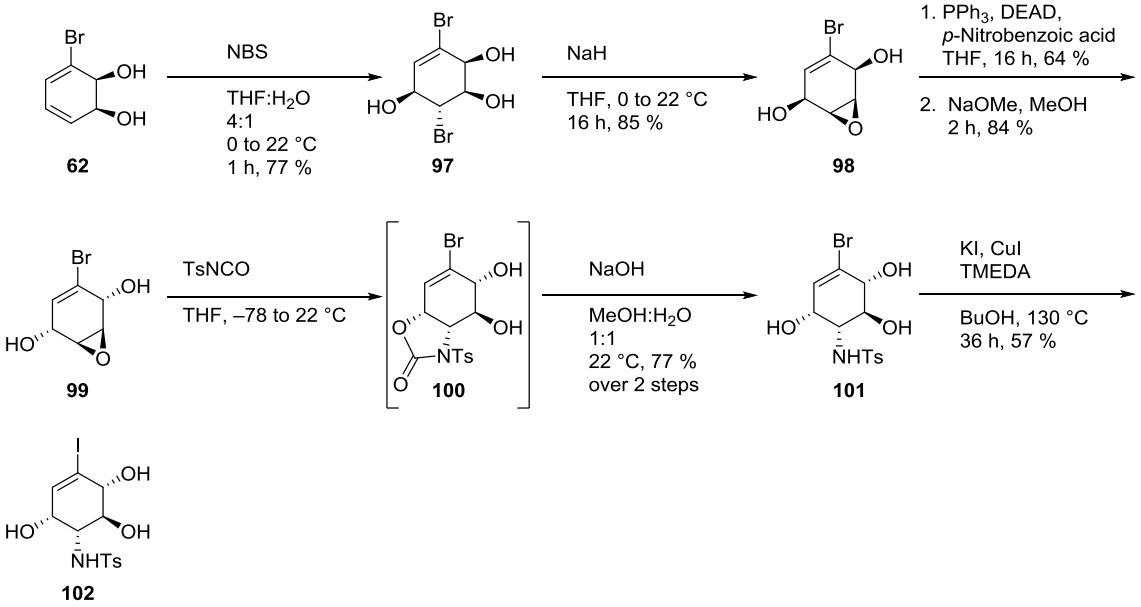
In Scheme 16 the total synthesis of *epi*-kirkamide is shown. Thus, treatment of previously reported acetamide derivative, **87**, with KHMDS gave, *via* the intermediate aziridine **88**, the isomeric oxazoline **89**. The introduction of the hydroxymethyl group associated with the $C_7N$ aminocyclitols was achieved via a palladium-catalyzed cross-coupling reaction. In particular, carbopalladation of the

iodoalkene **91** in presence of *N,O*-dimethylhydroxylamine under a carbon monoxide atmosphere gave the α,β-unsaturated Weinreb amide **92**. A two-step reduction of this amide (using lithium aluminium hydride for the formation of the corresponding aldehyde and subsequent Luche reduction) yielded compound **95** and global deprotection of this using aqueous acetic acid then gave *epi*-kirkamide (**96**).




**Scheme 16**: A Total Synthesis of *epi*-Kirkamide (**96**)

A distinct synthetic route to the kirkamide framework is shown in Scheme 17. Thus, the same *cis*-1,2-dihydrocatechol, **62**, used for the synthesis of *epi*-kirkamide, is now reacted with *N*-bromosuccinimide in THF and water to give bromohydrin **97**, that undergoes an intramolecular nucleophilic substitution reaction on treatment with NaH to yield epoxide **98**. Compound **98** was then subjected to a two-fold Mitsunobu reaction using *p*-nitrobenzoic acid as the nucleophile and the resulting diester then saponified with NaOMe in MeOH to yield diol **99**. Treatment of this last compound with TsNCO afforded intermediate **100** that upon hydrolysis with NaOH in methanol/water gave triol **101** which bears the same *trans*-relationship between the amine moiety and the neighbouring homoallylic hydroxyl group as seen in kirkamide. A halogen exchange reaction was then applied to compound **101** and so affording alkenyl iodide **102** that served as the substrate for carbopalladation reactions.




**Scheme 17**: Synthesis of Alkenyl Iodide **102** from *cis*-Dihydrocatechol **62**

Compound **102** was also synthesized in a more direct manner from the *cis*-dihydrocatechol **103** (Figure 5). However, while compound *ent*-**62** is known, congener *ent*-**103** is not. As such, only synthetic sequences starting from the bromo-compound **62** can be used to produce the enantiomeric forms of the targeted kirkamide analogues.

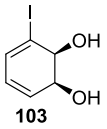
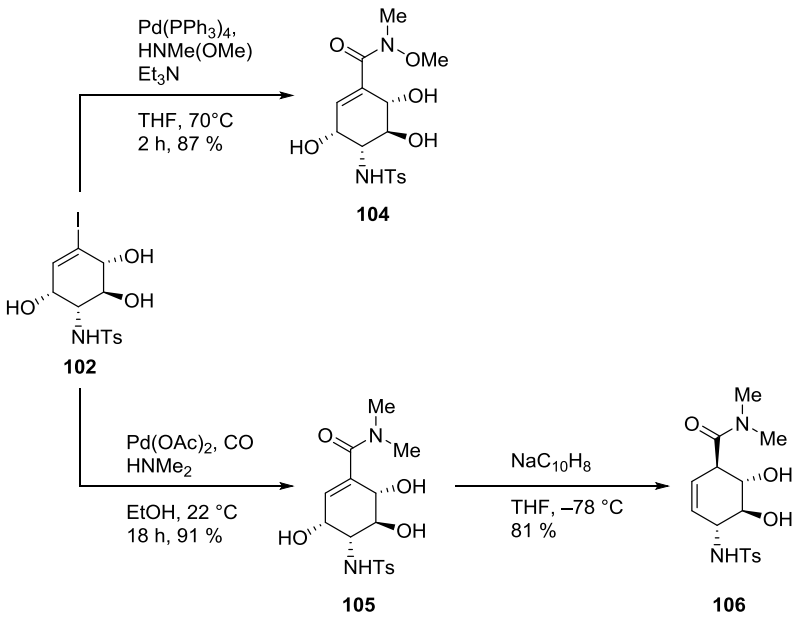


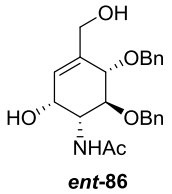

**Figure 5**: *cis*-Dihydrocatechol **103**

Compound **102** was engaged in two carbopalladation reactions (Scheme 18) and thereby affording the $C_7N$-aminocyclitols **104** and **105**. Furthermore, upon treating compound **105** with freshly prepared sodium naphthalenide, tandem deoxygenation and double bond migration reactions occurred and so affording compound **106** in high yield.




**Scheme 18**: Synthesis of New $C_7N$-Aminocyclitol Derivatives **104**, **105** and **106** from Iodoalkenyl **102**

The three new aminocyclitols **104**, **105** and **106** thus obtained have the potential to serve as precursors to a diverse range of aminocarbasugars. Compounds **104** and **105** can also be regarded as precursors to *ent*-kirkamide (*ent*-**86**) (Figure 6).



***ent*-86**

**Figure 6**: *ent*-Kirkamide (*ent*-**86**)

**Publication 6. Chemical syntheses of the cochliomycins and certain related resorcylic acid lactones**

Small molecule natural products (SMNPs) are often utilized as therapeutic agents, as precursors to these or as an inspiration for them.[22] Among SMNPs the resorcylic acid lactones (RALs) are notable for the diversity of their biological activities, their unique structural features and their frequent occurrence among fungal metabolites.[23] This article reviews synthetic studies on and the biological properties of certain resorcylic acid lactones, particularly neocosmosin A (**107**) and the cochliomycins **108-113** depicted in Figure 7. A specific focus of this review article is on the total synthesis of several cochliomycins completed by the Banwell group, as well as the establishment of the correct absolute stereochemistry of neocosmosin A, to which the author of this thesis contributed.[24] This last compound was isolated from the fungus *Neocosmospora sp*. (UM-031509)[25]

and is particularly interesting from a medicinal point of view because it shows good binding affinity for human opioid receptors.

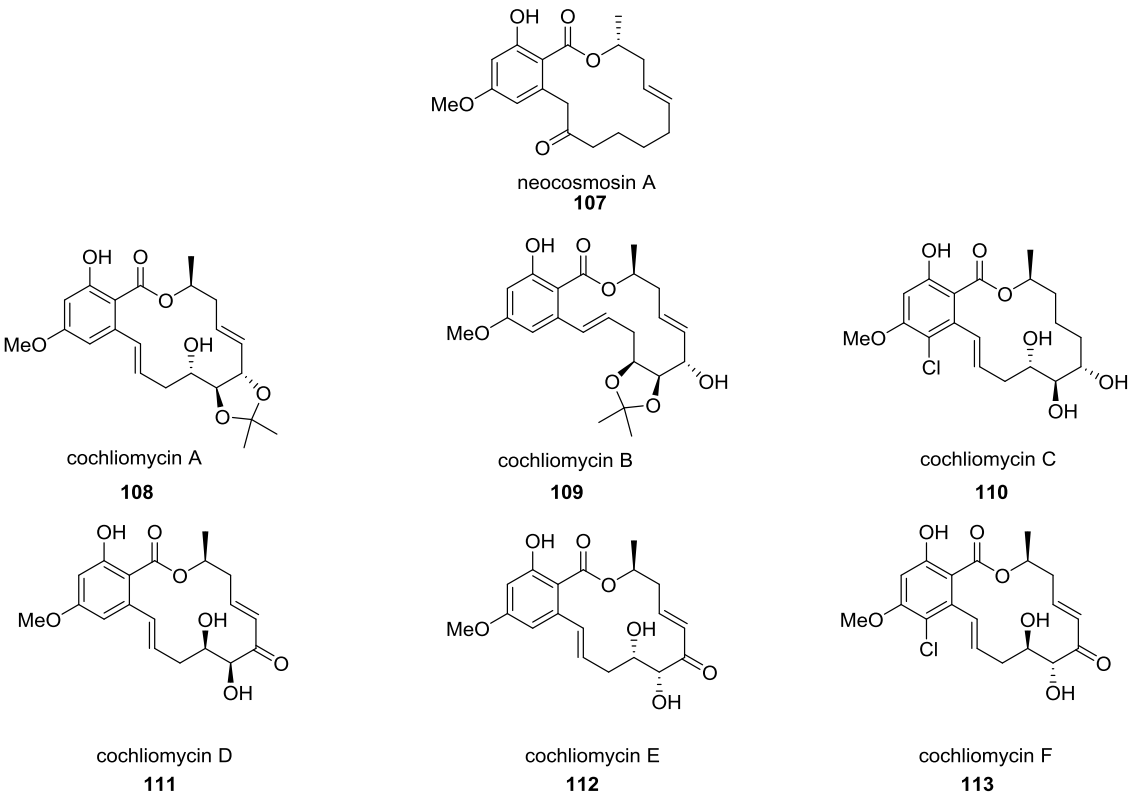
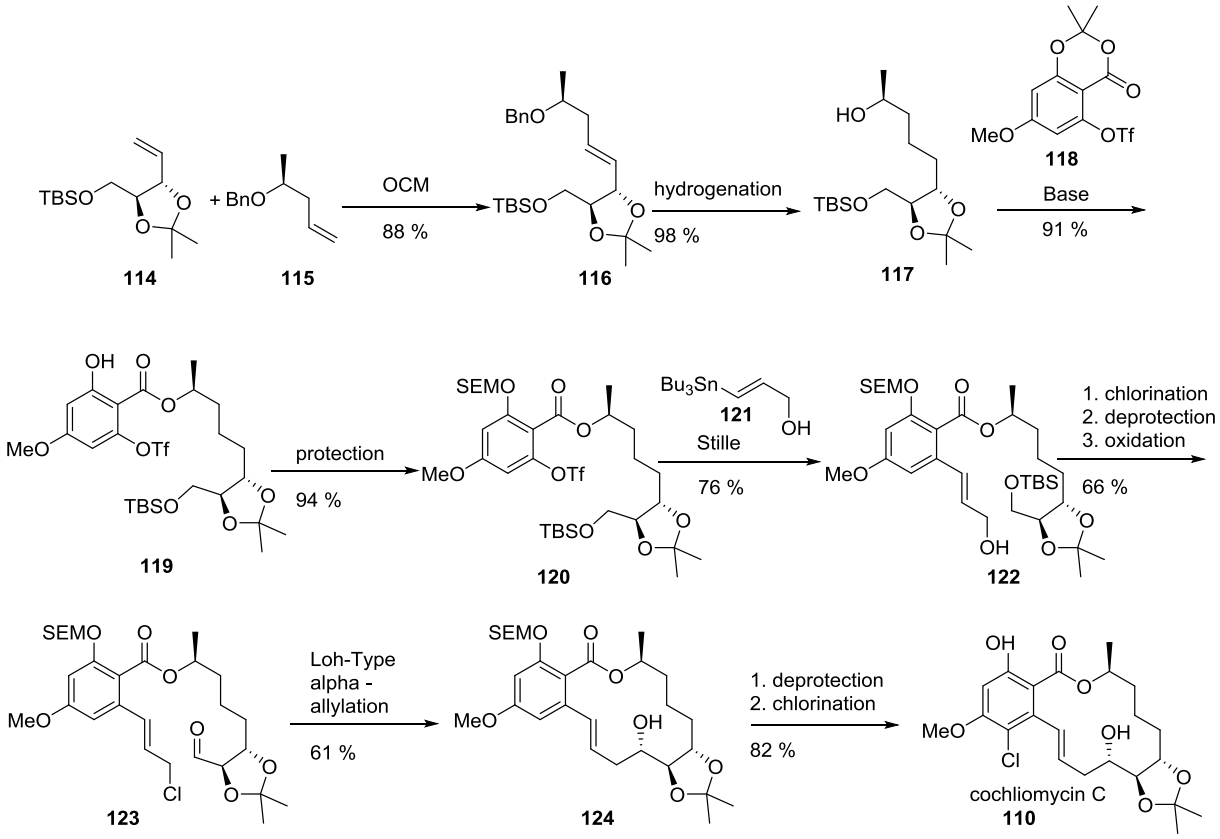



**Figure 7**: Structures of Various Cochliomycins

Scheme 19 shows the total synthesis of cochliomycin C as reported by the Banwell group. This synthesis featuring a Stille cross-coupling as a crucial step is another example highlighting the broad applicability of cross-coupling reactions for the total synthesis of natural products.

It begins with an olefin cross metathesis and this is followed by hydrogenation of the newly generated olefin **116**. A *trans*-esterification of compound **118** with alcohol **117** followed by protection of the newly generated phenol moiety gave intermediate **120**. These reactions were followed by a Stille cross-coupling process to introduce an allylic alcohol residue with a Loh-type α-allylation reaction then being used to form the pivotal macrolactone substructure, as seen in compound **124**, of the target. Finally, deprotection and chlorination of the aryl moiety afforded the target compound cochliomycin C **110.**




**Scheme 19**: Total Synthesis of Cochliomycin C

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## Statement of Contribution

This thesis is submitted as a Thesis by Compilation in accordance with
https://policies.anu.edu.au/ppl/document/ANUP_003405

I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the
Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

**Publication 1**

Title: The Palladium-catalysed Ullmann Cross-coupling Reaction: A Modern Variant on a Time-honored Process

Authors: Faiyaz Khan, Michael Dlugosch, Xin Liu and Martin G. Banwell

Publication outlet: *Accounts of Chemical Research*, **2018**, *51*, 1784-1795.

Current status of paper: Published

Contribution to paper: This is a review article that was written by Professor Martin Banwell. It incorporates descriptions of research on palladium-catalyzed Ullmann cross-coupling reactions conducted by the co-authors including the author of this thesis.

Senior author or collaborating author's endorsement:

**Publication 2**

Title: Palladium-Catalyzed Ullmann Cross-Coupling of β-Iodoenones and β-Iodoacrylates with *o*-Halonitroarenes or *o*-Iodobenzonitriles and Reductive Cyclization of the Resulting Products To Give Diverse Heterocyclic Systems

Authors: Faiyaz Khan, Michael Dlugosch, Xin Liu, Marium Khan, Martin G. Banwell, Jas S. Ward, and Paul D. Carr

Publication outlet: *Organic Letters*, **2018**, *20*, 2770–2773.

Current status of paper: Published

Contribution to paper: Professor Martin Banwell proposed the research work reported in this article. The author carried out 40 % of the laboratory work reported in this article. In addition he collated and formatted 40 % of the reported spectral data presented in the Supporting Information. The author also wrote 40 % of the Experimental Section and conducted relevant literature surveys. Professor Martin Banwell wrote the body of the paper.

Senior author or collaborating author's endorsement:

**Publication 3**

Title: Reductive Cyclization of *o*-Nitroarylated-α,β-Unsaturated Aldehydes and Ketones with $TiCl_3$/HCl or Fe/HCl Leading to 1,2,3,9-Tetrahydro-4*H*-carbazol-4-ones and Related Heterocycles

Authors: Yun Qiu, Michael Dlugosch, Xin Liu, Faiyaz Khan, Jas S Ward, Ping Lan, and Martin G Banwell

Publication outlet: *J. Org. Chem.*, **2018**, *83*, 12023–12033.

Current status of paper: Published

Contribution to paper: The initial idea for this project came from Professor Martin Banwell. The author carried out 65 % of the laboratory work reported in this article. In addition, he collated and formatted 60 % of the reported spectral data presented in the Supporting Information. The author also wrote 65 % of the Experimental Section and conducted relevant literature surveys. Professor Martin Banwell wrote the body of the paper.

Senior author or collaborating author's endorsement:

**Publication 4**

Title: Synthesis of a Highly Functionalised and Homochiral 2-Iodocyclohexenone Related to the C-Ring of the Polycyclic, Indole Alkaloids Aspidophytine and Haplophytine

Authors: Michael Dlugosch and Martin Banwell

Publication outlet: *Australian Journal of Chemistry*, **2018**, *71*, 573-579.

Current status of paper: Published

Contribution to paper: The author carried out the entirety of the laboratory work reported in this article. In addition, he collated and formatted the entirety of the reported spectral data presented in the Supporting Information. The author also wrote the entirety of the Experimental Section and conducted relevant literature surveys. Professor Martin Banwell wrote the body of the paper.

Senior author or collaborating author's endorsement:

**Publication 5**

Title: Syntheses of Structurally and Stereochemically Varied Forms of $C_7N$ Aminocyclitol Derivatives from Enzymatically-derived and Homochiral *cis*-1,2-Dihydrocatechols

Authors: Michael Dlugosch, Xinghua Ma, Shuxin Yang, Martin G. Banwell, Chenxi Ma, Jas S. Ward and Paul Carr

Publication outlet: *Organic Letters*, **2018**, *20*, 7225–7228.

Current status of paper: Published

Contribution to paper: The author carried out the entirety of the laboratory work associated with the reported synthesis of *epi*-kirkamide (Schemes 1 and 2) and the enantiomeric switching regime (Scheme 6). In addition, he collated and formatted the entirety of the reported spectral data sets presented in the Supporting Information. He also wrote the entirety of the corresponding portion of the Experimental Section and conducted relevant literature surveys on *epi*-kirkamide. He also conducted extensive research of the relevant literature pertaining to the synthesis of various kirkamide analogues. Professor Martin Banwell wrote the body of the paper.

Senior author or collaborating author's endorsement:

**Publication 6**

Title: Chemical Syntheses of the Cochliomycins and Certain Related Resorcylic Acid Lactones

Authors: Martin G. Banwell, Xiang Ma, Benoit Bolte, Yiwen Zhang, Michael Dlugosch

Publication outlet: *Tetrahedron Letters*, **2017,** *58*, 4025–4038.

Current status of paper: Published

Contribution to paper: This is a review article that was written by Professor Martin Banwell. It incorporates descriptions of research conducted by the author.

Senior author or collaborating author's endorsement:

| Michael Dlugosch | | 13/01/19 |
|---|---|---|
| Candidate – Print Name | Signature | Date |

**Endorsed**

| Martin G. Banwell | M. G. Banwell | 14/01/19 |
|---|---|---|
| Primary Supervisor – Print Name | Signature | Date |
| Gottfried Otting | | 14/01/19 |
| Delegated Authority – Print Name | Signature | Date |

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# The Palladium-Catalyzed Ullmann Cross-Coupling Reaction: A Modern Variant on a Time-Honored Process

Faiyaz Khan, Michael Dlugosch, Xin Liu, and Martin G. Banwell*

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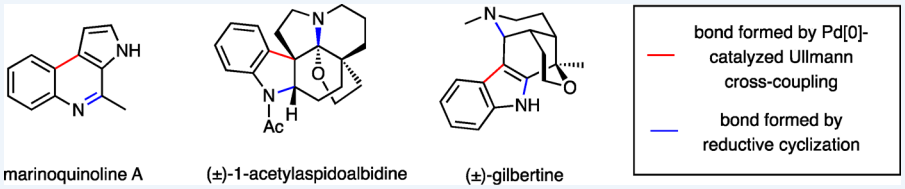


**CONSPECTUS:** Cross-coupling reactions, especially those that are catalyzed by palladium, have revolutionized the way in which carbon−carbon bonds can be formed. The most commonly deployed variants of such processes are the Suzuki−Miyaura, Mizoroki−Heck, Stille, and Negishi cross-coupling reactions, and these normally involve the linking of an organohalide or pseudohalide (such as a triflate or nonaflate) with an organo-metallic or -metalloid such as an organo-boron, -magnesium, -tin, or -zinc species. Since the latter type of coupling partner is often prepared from the corresponding halide, methods that allow for the direct cross-coupling of two distinct halogen-containing compounds would provide valuable and more atom-economical capacities for the formation of carbon−carbon bonds. While the venerable Ullmann reaction can in principle achieve this, it has a number of drawbacks, the most significant of which is that homocoupling of the reaction partners is a competitive, if not the dominant, process. Furthermore, such reactions normally occur only under forcing conditions (viz., often at temperatures in excess of 250 °C). As such, the Ullmann reaction has seen only limited application in this regard, especially as a mid- to late-stage feature of complex natural product synthesis. This Account details the development of the palladium-catalyzed Ullmann cross-coupling reaction as a useful method for the assembly of a range of heterocyclic systems relevant to medicinal and/or natural products chemistry. These couplings normally proceed under relatively mild conditions (<100 °C) over short periods of time and, usually, to the exclusion of (unwanted) homocoupling events. The keys to success are the appropriate choice of coupling partners, the form of the copper metal employed, and the choice of reaction solvent.

At the present time, the cross-coupling partners capable of engaging in the title reaction are confined to halogenated and otherwise electron-deficient arenes and, as complementary reactants, $\alpha$- or $\beta$-halogenated, $\alpha,\beta$-unsaturated aldehydes, ketones, esters, lactones, lactams, and cycloimides. Nitro-substituted (and halogenated) arenes, in particular, serve as effective participants in these reactions, and the products of their coupling with the above-mentioned carbonyl-containing systems can be manipulated in a number of different ways. Depending on the positional relationship between the nitro and carbonyl groups in the cross-coupling product, the reduction of the former group, which can be achieved under a range of different conditions, provides, through intramolecular nucleophilic addition reactions, including Schiff base condensations, access to a diverse range of heterocyclic systems. These include indoles, quinolines, quinolones, isoquinolines, carbazoles, and carbolines. Tandem variants of such cyclization processes, in which Raney cobalt is used as a catalyst for the chemoselective reduction (by dihydrogen) of nitro and nitrile groups (but not olefins), allow for the assembly of a range of structurally challenging natural products, including marinoquinoline A, (±)-1-acetylaspidoalbidine, and (±)-gilbertine.

## 1. INTRODUCTION

Arguably, carbon−carbon bond formation is the most important process in organic chemistry, and the development of means for doing so has been a source of conscious effort for almost two centuries.[1] In modern times, cross-coupling reactions, perhaps most especially those catalyzed by palladium, nickel, copper, and iron species, have revolutionized the way in which more complex organic compounds are assembled from simpler ones.[2] Named reactions such as the Suzuki−Miyaura, Mizoroki−Heck, Stille, Sonogashira, and Negishi cross-couplings immediately spring to mind in considering such matters.[2a] The coupling partners involved in these processes are normally an organohalide or pseudohalide (e.g., a triflate or nonaflate) and an organo-metallic species that is, more often than not, obtained from a halide precursor. In view of this and the frequently unstable/sensitive nature of the organometallic species, there have been many efforts directed at effecting the reductive cross-coupling of two structurally distinct organohalides, the most conspicuous examples of which involve adaptations of the venerable Wurtz[1] and Ullmann[3] reactions. In their traditional forms, however, these processes have not found extensive application because of competition from homocoupling reactions and/or the need to use rather aggressive reaction conditions that are incompatible with other functionalities

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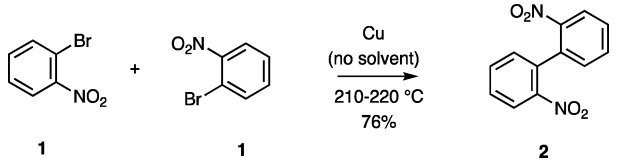
present in the substrates. In recent times, so-called cross-electrophile couplings (XECs), especially ones carried out in reductive mode and often involving multimetallic catalysts, have come to the fore, with notable contributions having been reported in the past few years by various groups.[4] The versatility of such processes is quickly becoming apparent. Herein we detail the outcomes of our own ongoing work concerned with the development of the palladium-catalyzed Ullmann cross-coupling reaction of structurally distinct, $sp^2$-hybridized, halogen-associated electrophiles with one another.[5,6] These reactions enable the construction of products that are useful in their own right and/or can participate in reductive cyclization reactions and thus affording various heterocyclic motifs encountered in a range of interesting natural products.

## 2. THE CLASSICAL ULLMANN REACTION

The Ullmann reaction (Scheme 1) was first reported in 1901[3a] and in the intervening period has found extensive application

**Scheme 1. Original (1901) Ullmann Reaction Resulting in the Reductive Coupling of *o*-Bromonitrobenzene (1) To Afford *o*,*o*′-Dinitrobiphenyl (2)**




in chemical synthesis, most notably in the reductive coupling of aryl halides (e.g., **1**) to form the corresponding symmetrical biaryls (e.g., **2**).[3,6] Its limitations also became evident rather quickly. These include the need to use high reaction temperatures (>200 °C), the attendant functional group incompatibilities, an inability to cleanly generate unsymmetrical biaryls from two structurally distinct aryl halide precursors (because of competing homocoupling processes), and the frequently erratic yields obtained. Manifold efforts to redress such deficiencies have been undertaken over the years, including through the application of on-surface processes,[3g] the introduction of metal-chelating species,[3e] and the use of varying forms of copper as well as other metal species.[3,6] These have had useful impacts, as summarized in a range of recent review articles.[3]

## 3. DISCOVERY OF THE PALLADIUM-CATAYLZED ULLMANN CROSS-COUPLING REACTION

Some years ago, in connection with work directed toward establishing a total synthesis of the alkaloid rhazinal,[7] a potent spindle toxin, we required access to an arylated pyrrole. We initially attempted to prepare this key intermediate through conventional Ullmann cross-coupling of commercially available *o*-bromonitrobenzene (**1**) with the known iodinated pyrrole **3** (see Scheme 2), but only traces of target **4** were obtained. Upon undertaking an extensive literature survey, we came across the work of Thompson[8] and Shimizu,[9] both of whom reported that the synthesis of certain arylated pyridines through the Ullmann cross-coupling of the relevant aryl halide and halogenated pyridine is greatly facilitated by the addition of a palladium catalyst. Upon applying such observations to our system,[7] using DMF as solvent and three equivalents of compound **1**, we were able to obtain, under ultrasonication conditions, target **4** in 88% yield (based on recovered starting material (brsm)), with the major byproduct being 2,2′-dinitrobiphenyl (**2**) (55%) (Scheme 2).

These observations triggered extensive studies of the title process that continue in our group to this day. These studies have provided, through the reductive cyclization of the initially formed cross-coupling products, useful new means for the construction of a wide range of heterocyclic compounds, including ones embodying previously unreported frameworks. Details of these processes are presented in the following sections and categorized according to the heterocyclic frameworks that are generated.

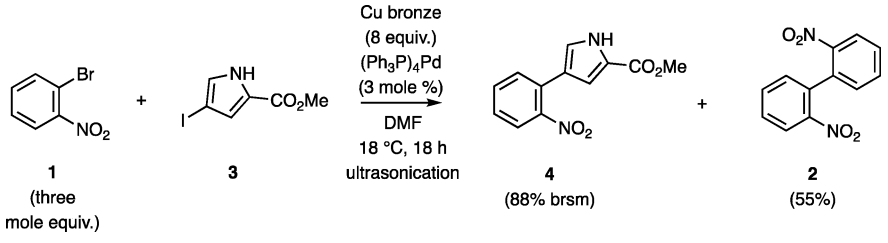
## 4. APPLICATION TO THE SYNTHESIS OF HETEROCYCLES

### 4.1. Indoles

Our first efforts to comprehensively develop the title reaction involved the cross-coupling of readily available $\alpha$-halo-enones and -enals with *o*-halonitroarenes and the reductive cyclization of the ensuing $\alpha$-arylated-enones and -enals to give indoles, including annulated variants.[10] The simple reaction sequences shown in Scheme 3 serve to highlight the possibilities for the assembly of such heterocycles, and others have since exploited these processes in the total synthesis of a range of natural products.[11] Some of our own efforts in this regard are detailed in the next section.

In the course of optimizing these sorts of cross-coupling processes, we established that a range of different sources of Pd[0] can be used, that DMSO appears to be the optimal solvent, that electron-deficient, halogenated arenes are required, and that a lower reaction temperature leads to a better ratio of cross-coupling to homocoupling products. Indeed, in favorable circumstances the cross-coupling reactions can be conducted at near ambient temperatures and essentially to the exclusion of the homocoupling process. Thus, a close to 1:1 ratio of coupling partners could often be employed, an important consideration in exploiting these processes in complex natural product synthesis, where such transformations are exploited at a late stage. Mechanistically speaking, we believe that these couplings proceed as suggested by Shimizu[9]

**Scheme 2. Palladium-Catalyzed Ullmann 1 and 3 Leading to Arylated Pyrrole 4**



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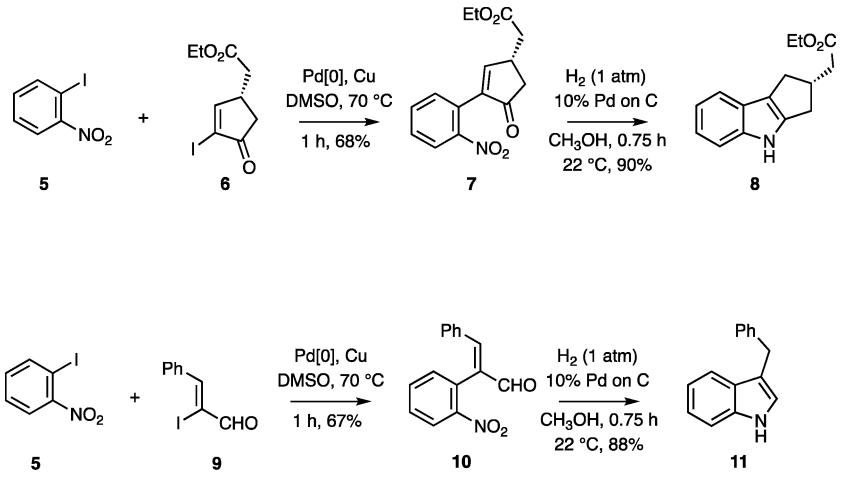
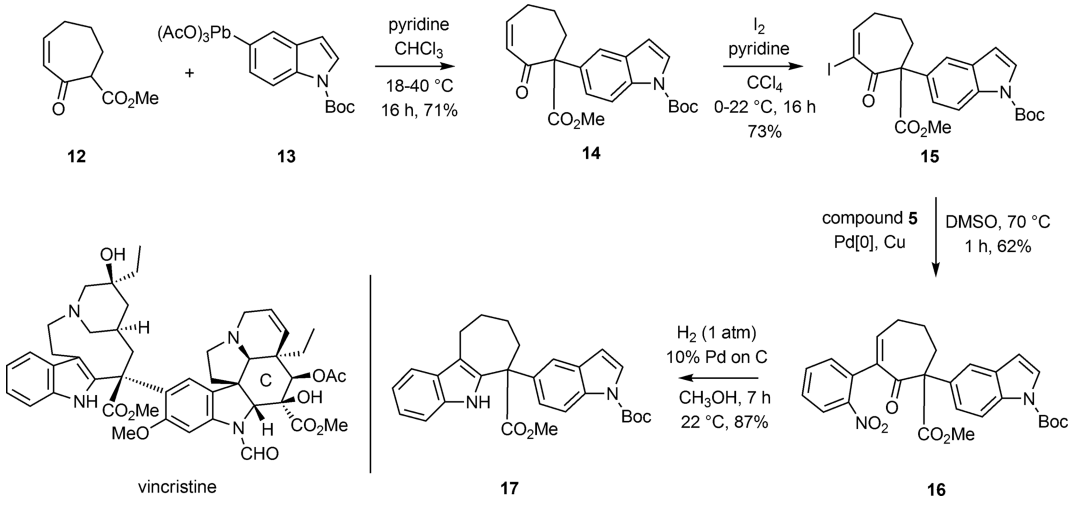
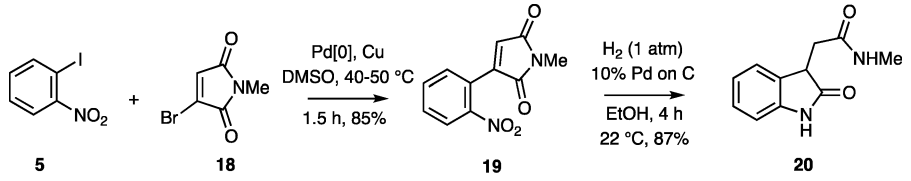
**Scheme 3. Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Sequences Leading to Indoles 8 and 11**




**Scheme 4. Synthetic Sequence Leading to Bis(indole) 17 Resembling the Southern Hemisphere of Vincristine**




**Scheme 5. Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Sequence Leading to Oxindole 20**




(see the penultimate section for details), wherein palladium[0] oxidatively adds to the $\alpha$-iodo-enone or -enal and the resulting palladium[II] complex reacts with the ortho-cuprated nitroarene arising from the other coupling partner, thereby producing a palladated intermediate that undergoes reductive elimination to deliver the observed product (and, of course, regenerates the Pd[0] catalyst). The nature of the copper used in these reactions has some impact on the efficiency of the process, with freshly prepared activated copper[12] being particularly effective though somewhat tedious to prepare. The simple expedient of adding some sand to the reaction mixture containing normal copper powder (copper bronze), and thus continuously generating a fresh metal surface through abrasion, is an operationally simple means of achieving often equivalent outcomes. Furthermore, adding small amounts of cuprous iodide to the starting reaction mixture can enhance the desired process,[11b] although the precise origins of this benefit remain to be fully understood.

Highly functionalized indolic substructures are encountered in therapeutically significant alkaloids such as vincristine (Scheme 4), and we sought to establish methods for assembling these using our protocols.[13] In a representative process, $\alpha'$-carbomethoxylated cycloheptenone **12** was subjected to Pinhey arylation with plumbated indole **13**, thereby affording compound **14**, which was itself engaged in a Johnson-type $\alpha$-iodination[14] reaction to afford iodide **15**. The palladium-catalyzed Ullmann cross-coupling of this last compound with *o*-iodonitrobenzene (**5**) gave product **16**, which upon reductive cyclization afforded bis(indole) **17** embodying key structural elements associated with the "Southern" hemisphere of vincristine.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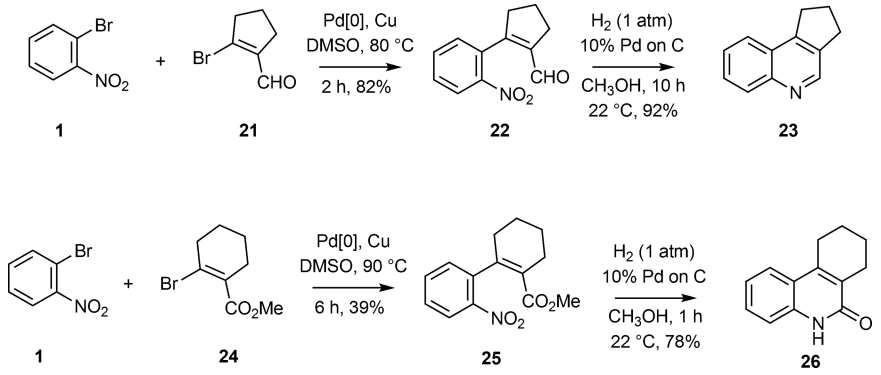
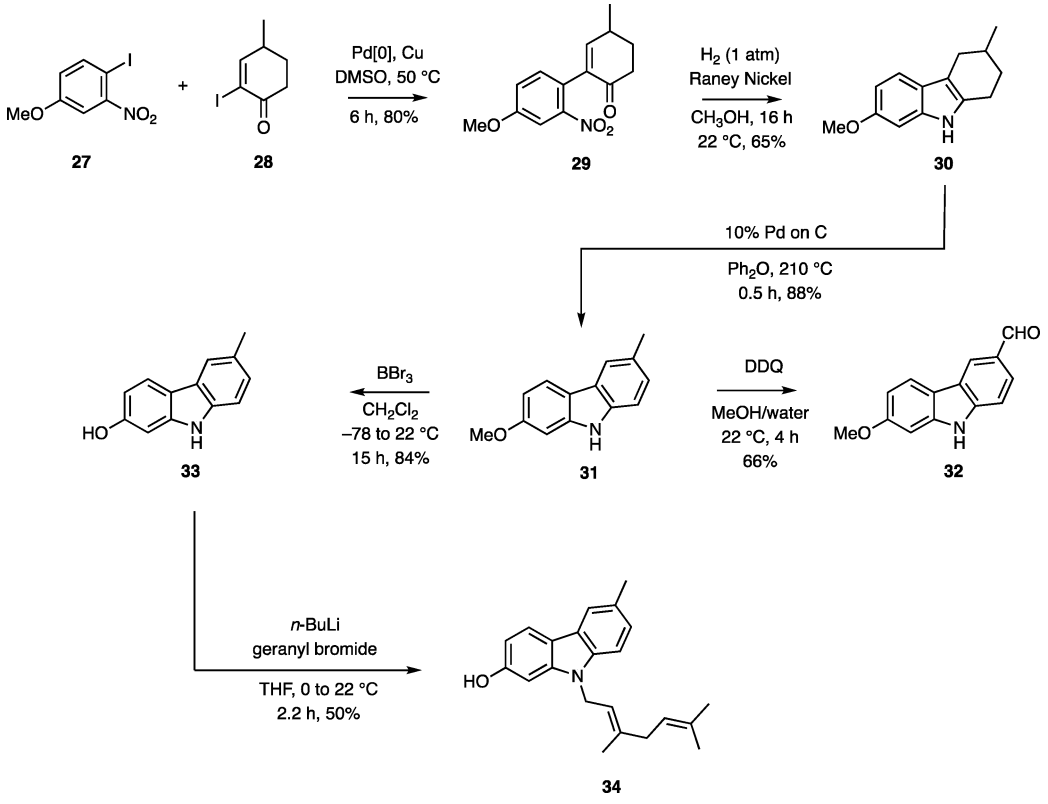
**Scheme 6. Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Sequences Leading to Quinoline 23 and Quinolone 26**




**Scheme 7. Synthetic Routes to the Carbazole Natural Products Clauszoline K (32) and Karapinchamine A (34)**




### 4.2. Oxindoles

Oxindoles, which represent privileged structures in medicinal chemistry and motifs encountered in biologically active natural products,[15] are readily obtained using analogous processes wherein an $\alpha$-brominated $\alpha,\beta$-unsaturated cycloimide, lactam, or lactone is used as the coupling partner in a reaction with an *o*-halonitroarene and the product of this process then subjected to reductive cyclization.[15] The efficient **5** and **18** (Scheme 5) to produce arylated *N*-methylmaleimide **19** followed by its reductive cyclization under standard conditions to give oxindole **20** is illustrative of these types of processes.

### 4.3. Quinolines and Related Heterocycles

A further extension of our original processes, as shown in Scheme 3, has allowed the formation of quinolones and related systems. In such cases (Scheme 6), the electrophiles employed are $\beta$-halo-enals, -enones, or -esters. So, for example, the cross-coupling of arene **2** with aldehyde **21** affords arylated enal **22**, which, upon reductive cyclization, produces cyclopenta-annulated quinolone **23**. In a related but less efficient manner, cross-coupling of compounds **2** and **24** affords ester **25** which upon reductive cyclization delivers the 2-quinolone **26**. By similar means a range of alternately substituted/annulated quinolones, phenanthridines, and 6(5*H*)-phenanthridinones can be obtained. The capacity to generate electrophiles such as **21** directly from the corresponding ketone (in this case cyclopentenone) through a Vilsmeier–Haack haloformylation reaction is likely to enhance the utility of these processes.[16]

### 4.4. Carbazoles

When $\alpha$-iodocyclohex-2-en-1-ones are cross-coupled with halogenated nitroarenes such as **1** and **5** using the protocols detailed above and the aryl enone products are subjected to reductive cyclization, tetrahydrocarbazoles are obtained. Given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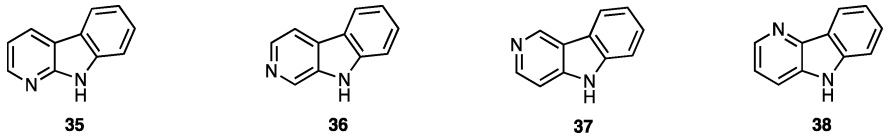



**Figure 1.** The four isomeric carbolines.

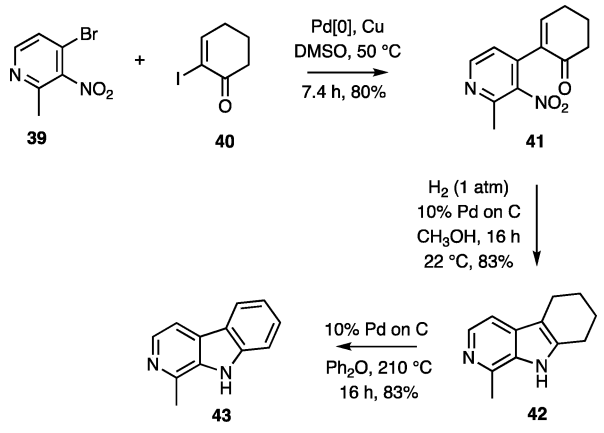
that their fully aromatic counterparts (viz., carbazoles) are encountered in a wide range of biologically active natural products, we sought to produce such heterocycles using variations of our earlier protocols. The routes to clauszoline K and karapinchamine A shown in Scheme 7 are illustrative of the possibilities the title reaction offers in this regard.[17] Thus, reductive cross-coupling of electrophiles **27** and **28** under our now standard conditions afforded product **29** (80%), which upon reductive cyclization using dihydrogen in the presence of Raney nickel afforded tetrahydrocarbazole **30** (65%). This could then be oxidized to its fully aromatic counterpart, namely carbazole **31** (88%), upon exposure to 10% Pd on C in diphenyl ether at 210 °C (various attempts to effect the conversion **29** → **31** in a direct manner, or at least in a one-pot-process, have been unsuccessful to date). Upon exposure of compound **31** to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) it was oxidized, in 66% yield, to the natural product clauszoline K (**32**). On the other hand, treatment of compound **31** with $BBr_3$ effected cleavage of the associated ether residue and, thereby, the formation of the anticipated phenolic product **33** (84%). Deprotonation of the latter compound with *n*-butyllithium and reaction of the ensuing anion with geranyl bromide resulted in alkylation at nitrogen and the formation of the carbazole-containing natural product karapinchamine A (**34**), which was obtained in 50% yield.

### 4.5. Carbolines

There are four isomeric carbolines, namely, the $\alpha$, $\beta$, $\gamma$, and $\delta$ forms (**35**−**38**, respectively; Figure 1), and each of these frameworks is encountered in both natural products and pharmacologically active agents.[18] While various methods have been developed for their synthesis, a unified approach to them had remained elusive until our recent deployment of the title cross-coupling reaction for this purpose.[18]

An illustrative example of our approach is presented in Scheme 8. It starts with the palladium-catalyzed Ullmann cross-coupling of bromonitropyridine **39** with readily available

**Scheme 8. Synthetic Route to the Carboline Natural Product Harman (43)**




$\alpha$-iodinated cyclohexenone **40**. Engaging the ensuing product **41** (80%) in a reductive cyclization reaction gives tetrahydrocarboline **42** (83%), which is then dehydrogenated to give the fully aromatic compound **43** (83%) representing the structure of the natural product harman.[18]

The challenge associated with deploying this type of approach to the carbolines is the need to construct the requisite polysubstituted pyridine-based coupling partner. Thus, for example, the nitration reaction associated with the synthetic sequence leading to compound **39** also produced a regioisomer, and these could only be separated from one another by HPLC techniques.[18]

### 4.6. $\beta$-Haloenones and Related Compounds as Cross-Coupling Partners

Recently we have established that $\beta$-haloenones such as **44** couple particularly effectively with electrophiles including **5** (Scheme 9) to form the anticipated cross-coupling product **45** (91%), a compound that upon exposure to standard reductive cyclization conditions using methanol as the solvent affords 3,4-benzomorphan **46** in 73% yield.[19] In a further illustration of the extensive utility of these types of processes, the coupling of brominated pyridine **47** with the $\beta$-iodinated crontonate **48** proceeded with retention of configuration and afforded the anticipated product **49** (84%). Reductive cyclization of this last compound using iron filings in an acidic medium then gave the 1,8-naphthyridin-2(1*H*)-one **50** (76%). Interestingly, *o*-iodobenzonitriles can be engaged in related couplings,[19] although these are less efficient than those involving iodinated nitroarenes, presumably because of the weaker electron-withdrawing properties of the cyano group.

### 4.7. Formation of Unsymmetrical Biaryls

An obvious application of the title reaction is in the production of unsymmetrical biaryls. While we have yet to explore such processes in any comprehensive fashion, early indications have been very positive. Thus, as shown in Scheme 10 for example, the cross-coupling of aryl iodide **51** with bromide **52** under our by now standard conditions provided the desired biaryl **53** (60%).[20] This last compound was readily elaborated to the alkaloid zephycandidine III, a natural product reported to possess acetylcholinesterase (AChE) inhibitory properties,[20] which were not evident in the synthetically derived material despite the spectroscopic equivalence of the natural and synthetic materials. More pertinent to the present discussion is that all our attempts to prepare compound **53** and related systems using Suzuki−Miyaura cross-coupling reactions were unsuccessful.[20]

## 5. APPLICATION TO THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

As our understanding of the palladium-catalyzed Ullmann cross-coupling reaction has developed, we have been exploiting it on an increasingly frequent basis in developing syntheses of various natural products. Such is our confidence in the reliability of the process that we have often deployed it at relatively advanced stages of synthetic pathways, normally in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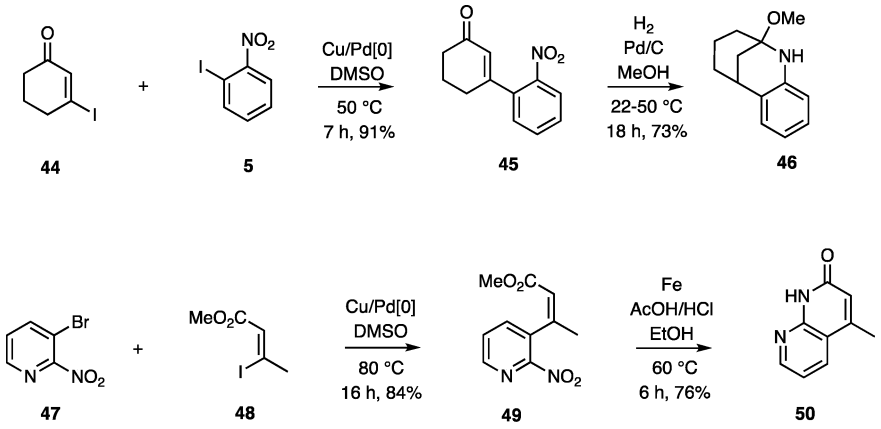
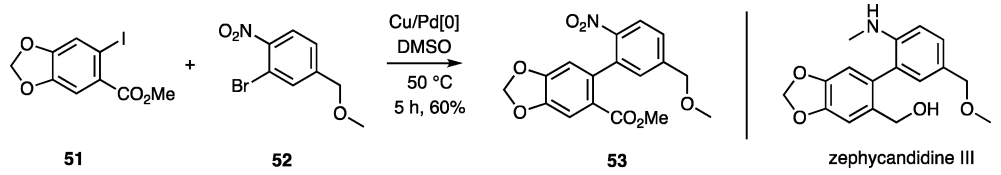
**Scheme 9. Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Sequences Leading to Heterocycles 46 and 50**




**Scheme 10. Palladium-Catalyzed Ullmann Cross-Coupling of Halogenated Arenes 51 and 52 Leading to Biaryl 53, a Precursor the Alkaloid Zephycandidine III**

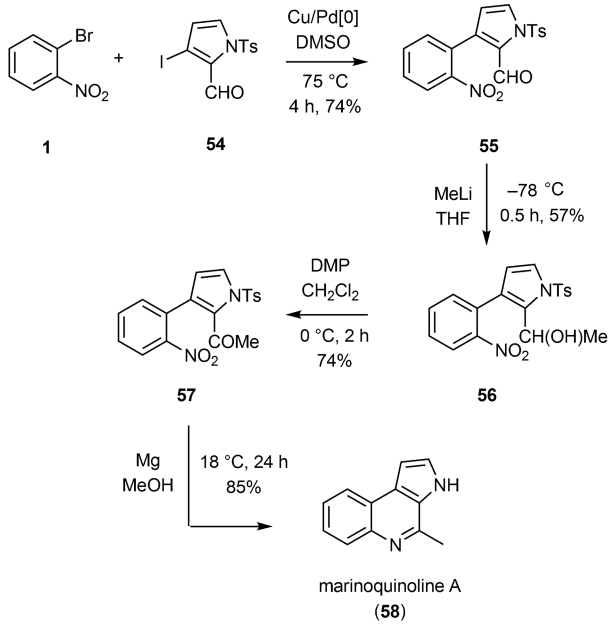



conjunction with reductive cyclization reactions that enable the conversion of the cross-coupling products into various heterocyclic frameworks. Specific examples are given in the following sections.

### 5.1. Synthesis of Marinoquinoline A

As part of an ongoing interest in the cross-coupling chemistries of pyrroles,[21] we were attracted to the development of a synthesis of marinoquinoline A, an alkaloid isolated from a marine gliding bacterium that displays AChE inhibitory[22] and antimalarial activities. The route that we ultimately established in obtaining this compound is shown in Scheme 11. It starts with the palladium-catalyzed Ullmann cross-coupling of *o*-bromonitrobenzene (**1**) with iodinated pyrrole **54** to afford the target **55** in 74% yield. Significantly, all of our attempts to effect the Suzuki–Miyaura cross-coupling of compound **54** with *o*-nitrophenylboronic acid failed.[22] In a related vein, when *o*-iodonitrobenzene (**5**) was used as a coupling partner in this process, its homocoupling (to give 2,2′-dinitrobiphenyl) became the dominant process. Such outcomes highlight the capacity to facilitate cross-coupling processes by attenuating the reactivity of one substrate through changing the associated halogen.

**Scheme 11. Total Synthesis of Marinoquinoline A**




The elaboration of coupling product **55** to the target alkaloid was straightforward and involved the initial addition of methyllithium to the associated aldehyde residue and oxidation of the resulting alcohol, **56**, to the corresponding methyl ketone **57** using the Dess–Martin periodinane (DMP). Reductive cyclization of this last compound to the target framework was effected using magnesium in methanol, and this was accompanied by cleavage of the tosyl group, thus affording marinoquinoline A (**58**) in 85% yield.

### 5.2. Total Syntheses of the Aspidosperma Alkaloids Aspidospermidine, Limaspermidine, and 1-Acetylaspidoalbidine and Approaches to Vindoline

In a more elaborate reaction sequence and as part of an ongoing campaign to develop a synthesis of the binary indole–indoline alkaloid vincristine (see Scheme 4), we first developed a route to the alkaloid aspidospermidine.[23] This entailed, as one of two key steps, the cross-coupling of $\alpha$-iodinated cyclohexenone **59** with arene **5** to afford product **60** in 75% yield (Scheme 12). Compound **60** was readily elaborated to azide **61** that upon heating engaged in an intramolecular [3 + 2] cycloaddition reaction followed by nitrogen extrusion to afford aziridine **62**, thereby establishing the piperidine ring associated with the final product. Various straightforward steps, including a $TiCl_3$-mediated reductive cyclization reaction, were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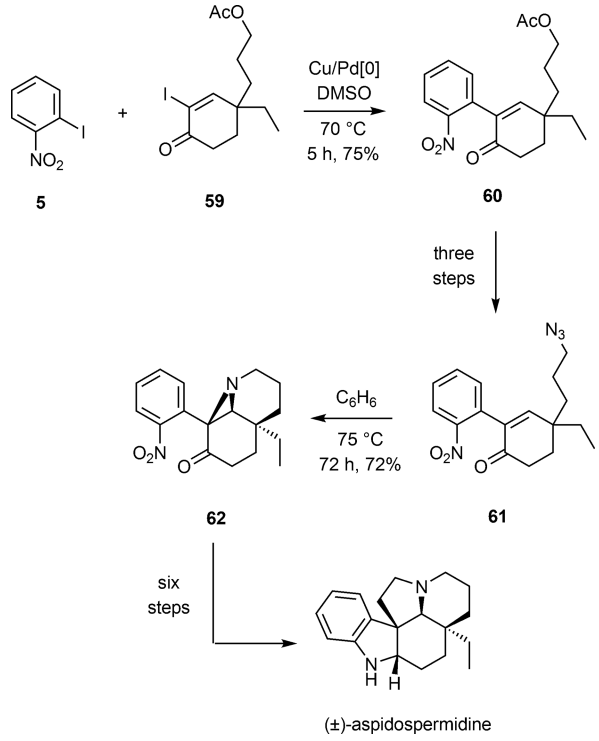
**Scheme 12. Total Synthesis of (±)-Aspidospermidine**




then deployed in elaborating compound **62** to aspidospermidine.

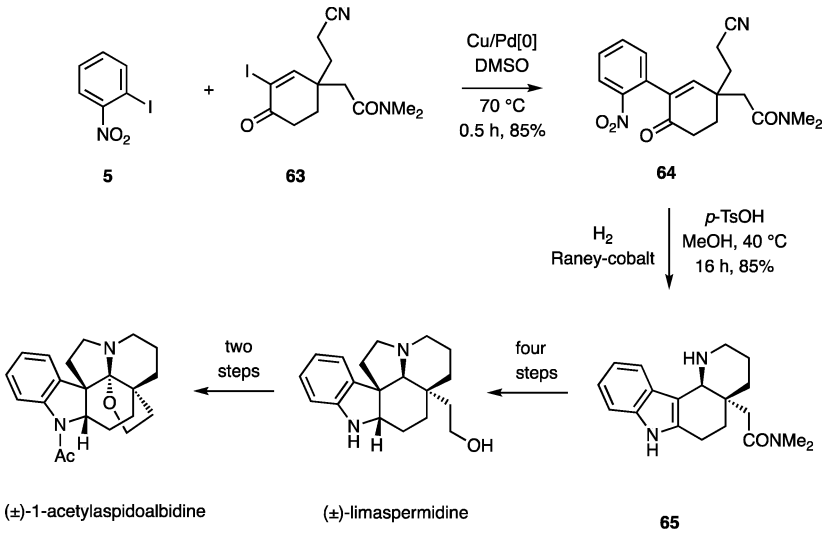
A related but more convergent protocol was employed in obtaining the alkaloid limaspermidine.[24] As shown in Scheme 13, compounds **5** and **63** were cross-coupled to give the α-arylated enone **64** (85%). When this was subjected to reductive cyclization using dihydrogen in the presence of Raney cobalt, the indole-annulated and cis ring-fused octahydroquinoline **65** was obtained in 85% yield. This conversion involves the selective reduction of the nitro and cyano groups within substrate **64** while the enone moiety remains intact. As a result, the associated ketone carbonyl engages in an intramolecular Schiff base condensation reaction with the aniline or *N*-hydroxyaniline arising from reduction of the nitro group while the 1° amine arising from the cyano residue undergoes a hetero-Michael addition reaction, thus forming both the indole and piperidine rings in a one-pot operation. The use of properly prepared Raney cobalt[25] is critical to the success of this transformation because of the chemoselectivities it allows for. If the more active Raney nickel is used as the catalyst, then reduction of the carbon−carbon double bond of the enone residue also occurs, with the result that piperidine ring formation does not take place.[24] Elaboration of compound **65** to (±)-limaspermidine was achieved over four additional steps, including several closely related to those employed in the conversion of compound **62** into (±)-apsidospermidine (Scheme 12). Two additional steps, including an oxidative cyclization reaction employing mercuric acetate, were required to convert (±)-limaspermidine into (±)-1-acetylaspidoalbidine.[24]

The extension of the protocols defined above in an enantioselective approach to the alkaloid vindoline (representing a crucial substructure of vincristine) is shown in Scheme 14.[26] Cross-coupling of iodinated nitroarene **66** with homochiral α-iodinated cyclohexenone **67** (a compound obtained from an enzymatically derived *cis*-1,2-dihydrocatechol[27]) gave the anticipated product **68** in 92% yield. Reduction of this last compound using dihydrogen in the presence of Raney cobalt resulted in the formation of the tandem reductive cyclization product **69** (85%) embodying a cis ring-fused octahydroquinoline. Over a further four steps this could be elaborated to the hexacyclic compound **70** embodying many of the features of vindoline, which we are seeking to convert into that alkaloid.

### 5.3. Formal Total Synthesis of the Cage-like Alkaloid Kopsihainanine A

The tandem reductive cyclizations of the palladium-catalyzed Ullmann cross-coupling products **64** and **68** are presumed to proceed under kinetic control, thus affording cis ring-fused products. Given that trans ring-fused perhydroquinolines are encountered in a range of natural products, we sought methods to access such systems. Despite extensive investigations of the cyclization reactions, including examination of a range of modifications to the conditions employed, the cis ring-fused products were invariably formed on an exclusive basis.

**Scheme 13. Total Syntheses of (±)-Limaspermidine and (±)-1-Acetylaspidoalbidine**



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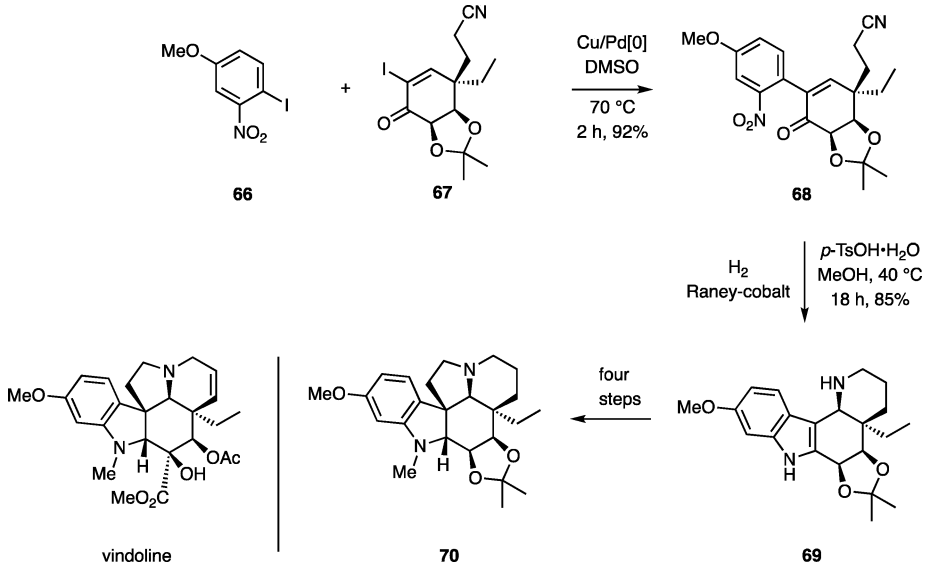
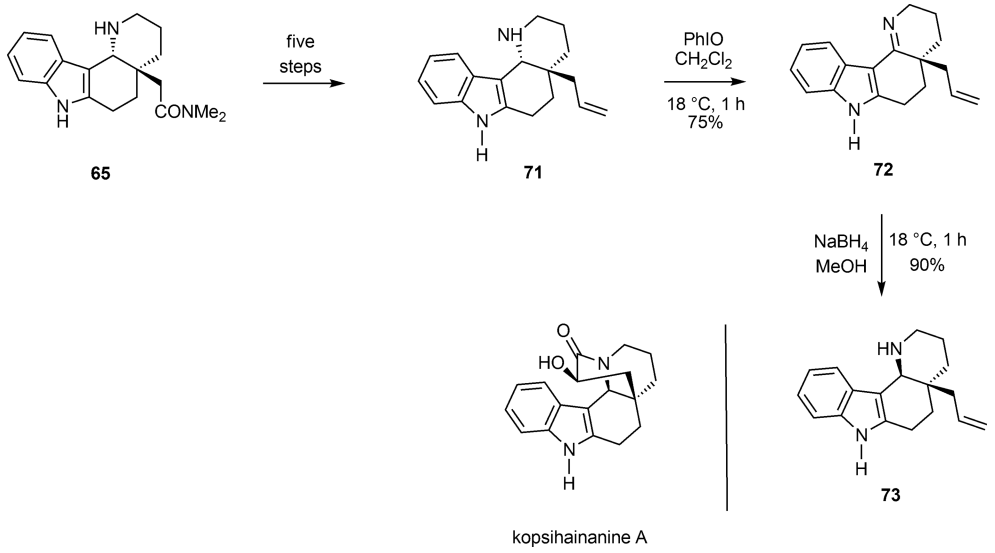
**Scheme 14. Synthesis of Compound 70, an Analogue of the Alkaloid Vindoline**




**Scheme 15. Conversion of cis Ring-Fused Octahydroquinoline 65 into Its trans-Configured Congener 73, an Advanced Precursor to the Alkaloid Kopsihainanine A**




Therefore, we sought ways to effect epimerization at the ring-junction carbon center bearing the piperidine nitrogen. This turned out to be a straightforward process, as illustrated in our formal total synthesis of the cage-like alkaloid kopsihainanine A (Scheme 15).[28] The reductive cyclization product **65** could be converted, over five steps, into the angularly allylated congener **71**, which upon exposure to iodosobenzene in dichloromethane at ambient temperatures was oxidized to the corresponding imine **72**. Upon reduction of compound **72** with sodium borohydride, the epimeric octahydroquinoline **73** was obtained. Since this last compound has previously been converted into kopsihainanine A, the illustrated synthetic sequence constitutes a formal total synthesis of the racemic modification of this alkaloid.

### 5.4. Syntheses of the Uleine Alkaloids and Approaches to the Strychnos Alkaloids

Another cross-coupling/tandem reductive cyclization sequence, shown in Scheme 16, has allowed syntheses of various members of the uleine family of alkaloids.[29] Cross-coupling of compounds **5** and **74** under the usual conditions afforded the anticipated product **75** (88%), and the reductive cyclization of this with dihydrogen in the presence of Raney cobalt afforded the tetracyclic product **76** (60%) as a result of the same type of tandem processes as shown in Schemes 13 and 14. Selective Boc protection of the piperidine nitrogen within compound **76** afforded carbamate 77, and this could be elaborated over two steps, including a pyridinium chlorochromate-mediated oxidation reaction to introduce a carbonyl moiety at the methylene adjacent to the indole ring, to hydroxyketone **78**. Reaction of this last compound with methyllithium proceeded smoothly, and the resulting tertiary alcohol engaged in a cycloetherification reaction upon treatment with protic acid. Cleavage of the Boc group also occurred under these conditions, and the resulting 2° amine was subjected to reductive N-methylation to afford (±)-gilbertine.[29a]

By means of closely related protocols, the somewhat simpler uleine alkaloids shown in Figure 2 could also be prepared in a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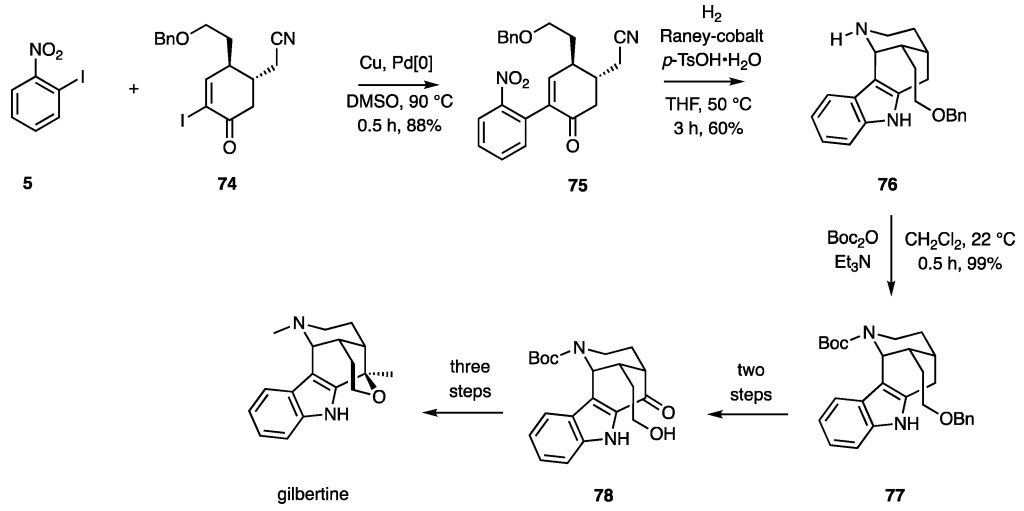
Acc. Chem. Res. 2018, 51, 1784−1795

**Scheme 16. Total Synthesis of the Alkaloid (±)-Gilbertine**




stereoselective manner,[29b] while the ABCDE ring system of the *Strychnos* alkaloids proved accessible by similar means.[30]

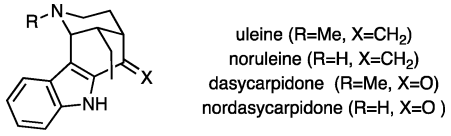
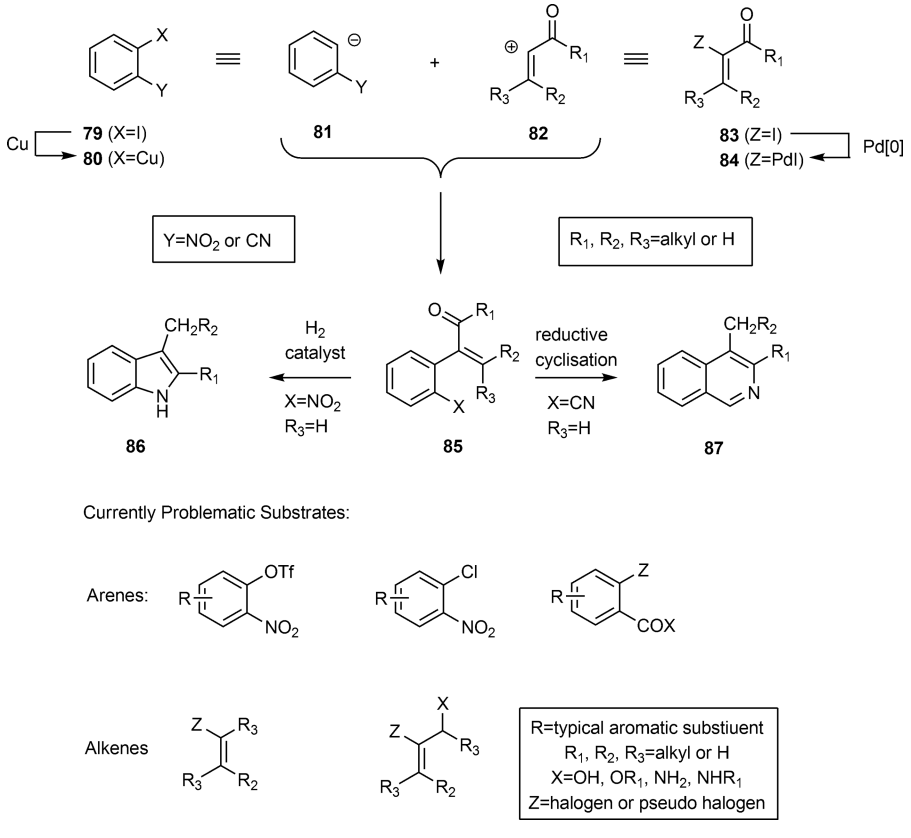



**Figure 2.** Structures of the simpler uleine alkaloids.

## 6. MECHANISTIC AND SYNTHETIC OVERVIEW

Our current thinking about the title process is dominated by the original mechanistic proposals of Shimizu.[9] Thus, as shown in Scheme 17, aryl iodide **79** is presumed to react with the added copper through an oxidative addition/reductive deiodination process to give arylcopper(I) **80**, representing the aryl anion synthon **81**. This reacts with the aryl cation synthon **82**, which is produced through oxidative addition of Pd[0] to the carbonyl-containing coupling partner **83**, thus affording intermediate **84**. The coupling event presumably

**Scheme 17. Mechanistic and Synthetic Analysis of a Key Example of the Palladium-Catalyzed Ullmann Cross-Coupling Reaction and Certain Currently Problematic Substrates**



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involves nucleophilic substitution at the palladium of intermediate **84** by organometallic **80**, and after reductive elimination product **85** is formed. Concurrently, of course, a Pd[0] species is formed and re-enters the catalytic cycle. Presumably, analogous pathways are involved in the potentially broadly applicable couplings shown in Schemes 9 and 10. Currently problematic substrates are also shown in Scheme 17.

While the majority of the title cross-coupling reactions we have studied to date are of the general form shown in Scheme 17, their utility is considerable because of the differing modes of reductive cyclization[12,31,32] that can be applied to the products **85**. Thus, as demonstrated in the multitude of settings presented above, when such products incorporate a nitro group, cyclizations using dihydrogen in the presence of various catalysts provide a range of indoles of the general form **86**. Using $TiCl_3$[13] or iron filings in acidic media[33] for the same purpose provides alternate cyclization products, while recent but thus far unpublished work has shown that certain nitrile-containing coupling products **85** (X = CN) can be converted into isoquinolines of the general form **87**.

It remains to be seen precisely how far palladium-catalyzed Ullmann cross-coupling reactions can be extended beyond those involving substrates incorporating the strongly electron-withdrawing nitro and nitrile groups. Therefore, one of the challenges in this regard will be defining, if possible, how to engage more electron-rich coupling partners in analogous reactions.

## 7. FUTURE PROSPECTS

As is the case with other emergent XEC processes,[4] the title one is proving effective in a range of settings, most particularly when combined with reductive cyclization reactions that thereby afford heterocyclic compounds. Investigations of intramolecular variants of the title XECs are also likely to be profitable areas of research. Furthermore, our recent discovery[19] that *o*-halobenzonitriles are also capable of engaging in palladium-catalyzed Ulllmann cross-coupling reactions suggests that access to other types of heterocyclic systems (e.g., **87**) will become available through the reductive cyclization of such products. Of course, the development of a more detailed mechanistic understanding of the palladium-catalyzed Ullmann cross-coupling reaction, including the role of additives such as cuprous iodide, will provide an important basis for further developments in the area.

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### Notes

The authors declare no competing financial interest.

### Biographies

**Faiyaz Khan** received a B.Sc. (Hons.) in chemistry from the Australian National University (ANU) in 2015. He is currently a Ph.D. candidate working in the Banwell group. His research focuses on cross-electrophile couplings and the total synthesis of natural products.

**Michael Dlugosch** received his M.Sc. in 2014 from the Bergische Universität Wuppertal in Germany. He joined the Banwell group in 2015 as a Ph.D. candidate, and his fields of interest are establishing synthetic pathways to natural products and the development of Pd-catalyzed Ullmann cross-coupling reactions.

**Xin Liu** received his M.Sc. in 2013 from the School of Pharmaceutical Science and Technology at Tianjin University. Thereafter, he took a research position at Beijing Tianheng Pharmaceutical Academy. In 2016, he joined the Banwell group as a Ph.D. candidate. His research interests are in the areas of organic and medicinal chemistry.

**Martin G. Banwell** is a Professor of Chemistry within the Research School of Chemistry at the ANU. His research interests are concerned with the total synthesis of biologically active natural products and the development of new methodologies for this purpose.

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Organic LETTERS

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# Palladium-Catalyzed Ullmann Cross-Coupling of β-Iodoenones and β-Iodoacrylates with o-Halonitroarenes or o-Iodobenzonitriles and Reductive Cyclization of the Resulting Products To Give Diverse Heterocyclic Systems

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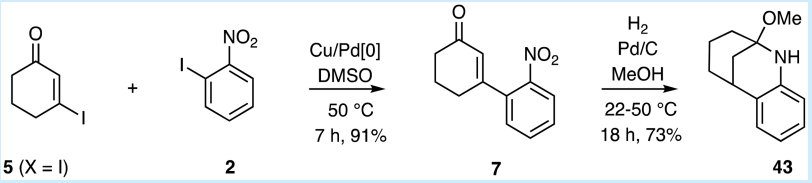
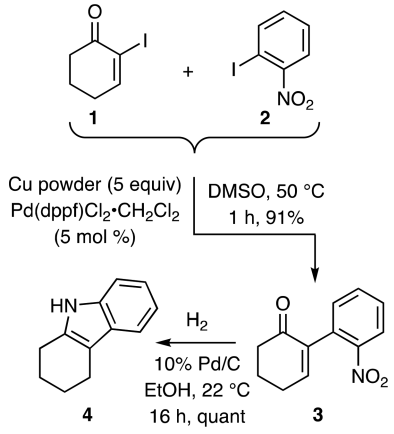
Supporting Information




**ABSTRACT:** The palladium-catalyzed Ullmann cross-coupling of β-iodoenones and β-iodoacrylates such as **5** (X = I) with *o*-halonitroarenes and *o*-iodobenzonitriles including **2** affords products such as compound **7**. These can be engaged in a range of reductive cyclization reactions leading to heterocyclic frameworks such as 3,4-benzomorphan derivative **43**.

Some time ago, we described[1] the palladium-catalyzed Ullmann cross-coupling of α-iodinated α,β-unsaturated ketones and related compounds with *o*-halonitroarenes, thus providing the corresponding α-arylated enones. The conversion **1** + **2** → **3** shown in Scheme 1 is representative of such cross-electrophile couplings,[2] which are generally high-yielding and proceed under mild conditions. Furthermore, coupling products such as **3** can be reductively cyclized to give, for example, tetrahydrocarbazole **4** in high yield.

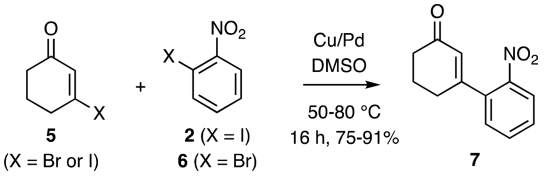
**Scheme 1. Previously Reported[1] Palladium-Catalyzed Ullmann Cross-Coupling of Compounds 1 and 2 and Reductive Cyclization of Product 3 Leading to Indole 4**




In the intervening period, we have extended these protocols to the preparation of quinolones, 2-quinolones, phenanthridines, 6(5*H*)-phenanthridinones, oxindoles, carbazoles, and carbolines.[3] In addition, we have been able to apply them in the total synthesis of a range of natural products and various analogues.[4] A number of other groups have also employed these protocols in the synthesis of various biologically active systems.[5]

We now report on the effective participation of β-iodinated α,β-unsaturated ketones and acrylates in related processes that have provided a means for the rapid construction of a diverse range of novel heterocyclic systems. As shown in Scheme 2, our initial studies involved an examination of the cross-coupling of readily available β-halo-2-cyclohexen-1-ones **5** (X = Br, I)[6] with *o*-halonitrobenzene **2** or **6** in anticipation of forming β-arylated 2-cyclohexen-1-one **7**.

**Scheme 2. Palladium-Catalyzed Ullmann Cross-Coupling of β-Halo-2-cyclohexen-1-ones 5 with *o*-Halonitrobenzene 2 or 6 To Form β-Arylated 2-Cyclohexen-1-one 7**




Products of this type, which have been prepared previously by less direct methods,[7] were targeted because they have been

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shown to engage in efficient reductive cyclization reactions to form carbazolones, including one that has served as a precursor to the carbazole alkaloid clausenalene.[7b] A series of cross-coupling experiments involving both the brominated and iodinated forms of the coupling partners, viz. compounds **2**, **5** and **6**, were examined, as were various coupling conditions. The outcomes of these trials established that the best coupling partners were the iodides. Thus, when these were used in conjunction with 5 equiv of copper powder, 5 mol % $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, and DMSO as the solvent, the reaction proceeded at 50 °C in 16 h to give compound **7** in 91% yield. The structure of compound **7** was confirmed by single-crystal X-ray analysis, details of which are provided in the Supporting Information (SI). Cross-couplings involving **5** (X = Br) and **2** or **5** (X = I) and **6** required heating to 80 °C and produced compound **7** in 75% and 83% yield, respectively, while the reaction of bromides **5** (X = Br) and **6** under the same conditions gave product **7** in 79% yield. Attempts were made to effect a carbonylative cross-coupling of the iodinated reaction partners by carrying out the reaction under a carbon monoxide atmosphere, but only product **7** (75%) was obtained. None of the hoped-for diketone was observed.

Encouraged by these results, we sought to extend them to the preparation of various related systems. For example, the readily prepared[6] *β*-iodinated 2-cyclopenten-1-ones **8** and **9** (Figure 1) also engaged in cross-coupling reactions with

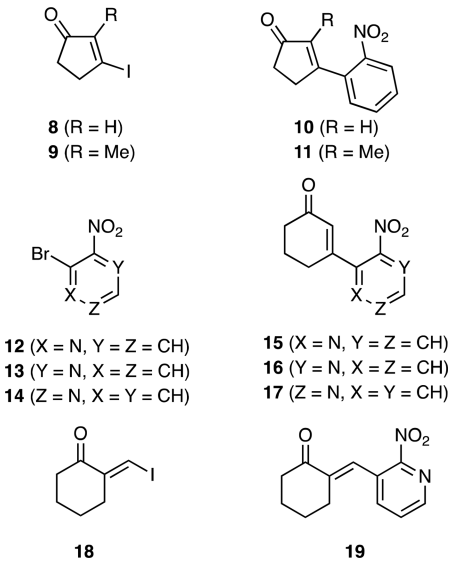


**Figure 1.** Substrates **8**, **9**, **12**–**14**, and **18** and the cross-coupling products **10**, **11**, **15**–**17**, and **19**.

compound **2** to give the anticipated products **10** (93%) and **11** (49%), respectively. Each of these was fully characterized by the usual range of spectroscopic methods. In a similar manner, bromonitropyridines **12**,[3e] **13**,[3e] and **14**[3e] were cross-coupled with enone **5** (X = I) to afford *β*-arylated enones **15** (69%), **16** (91%), and **17** (89%), respectively. *β*-Iodoalkenones incorporating an exocyclic olefinic residue also participate in these same types of reactions, as evidenced by the successful cross-coupling of the readily available substrate **18**[6] with arene **13** to give compound **19** (87%), the structure of which was confirmed by X-ray analysis (see the SI).

*o*-Iodobenzonitriles also cross-couple with *β*-iodoenones, as demonstrated by the successful reaction of the easily accessible[8] compounds **20**, **21**, **22**, and **23** (Figure 2) with **5** (X = I) to give products **24** (40%), **25** (61%), **26** (34%), and **27** (79%),

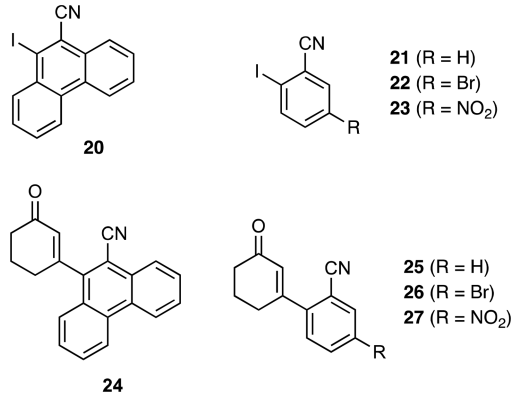


**Figure 2.** *o*-Iodobenzonitriles **20**–**23** and the products **24**–**27** arising from their cross-coupling with **5** (X = I).

respectively. The poorer yields associated with these *o*-iodobenzonitrile-based couplings are attributed to the weaker electron-withdrawing capacities of the nitrile group compared with the nitro group and, therefore, the intervention of competing homocouplings of the reaction partners.

*β*-Iodinated acrylates proved to be generally competent partners in palladium-catalyzed Ullmann cross-couplings with *o*-iodonitrobenzenes and *o*-iodobenzonitriles. For example, when methyl (*Z*)-3-iodobut-2-enoate (**28**)[9] (Figure 3) was

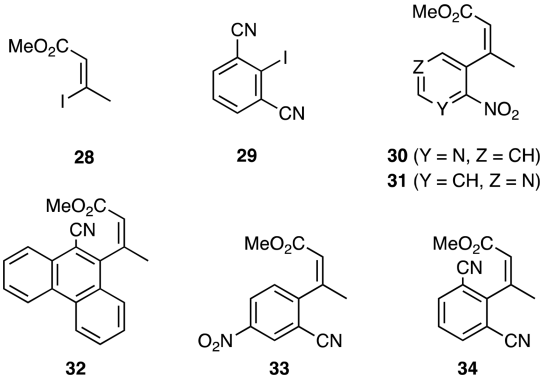


**Figure 3.** *β*-Iodoacrylate **28** and the products **30**–**34** arising from its cross-coupling with *o*-iodonitroarenes and *o*-iodobenzonitriles.

reacted with compounds **13**, **14**, **20**, **23**, and **29**[10] under the usual conditions, the cross-coupling products **30** (84%), **31** (69%), **32** (55%), **33** (43%), and **34** (59%), respectively, were obtained.

Ethyl *β*-iodocinnamate (**35**)[9] (Figure 4) behaved in a similar fashion. Thus, cross-coupling of this compound with *o*-iodonitrobenzene (**2**) afforded product **36**[11] (61%), while coupling of compounds **15** and **35** gave ester **37** (50%). The

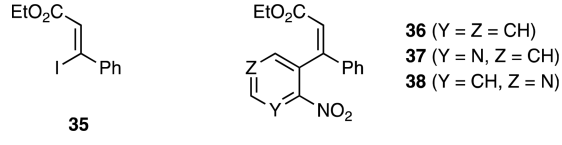


**Figure 4.** *β*-Iodocinnamate **35** and the products **36**–**38** arising from its cross-coupling with certain *o*-halonitroarenes.



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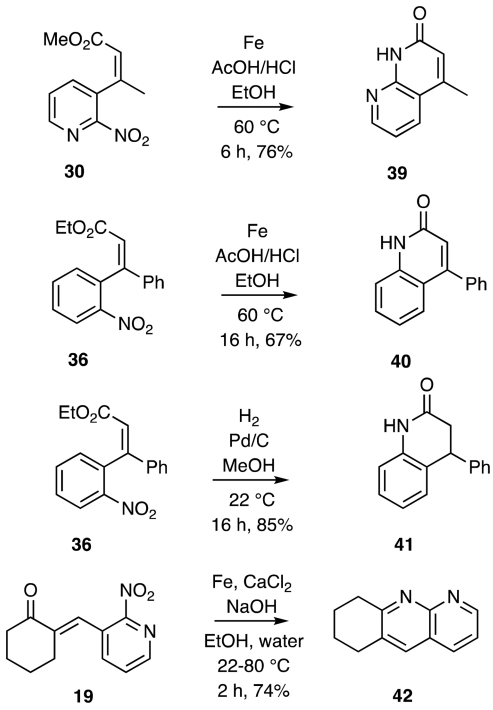
*Org. Lett.* 2018, 20, 2770–2773

analogous reaction of substrates **16** and **35** gave ester **38** (81%).

Many of the cross-coupling products described above engage in useful reductive cyclization processes, thus giving rise, in a direct manner, to heterocyclic frameworks of synthetic and/or biological relevance. For example, upon exposure of an ethanolic solution of coupling product **30** (Scheme 3) to iron

**Scheme 3. Reductive Cyclization of Cross-Coupling Products 30, 36, and 19 Leading to Heterocycles 39−42**

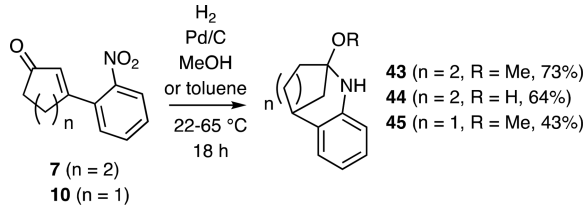



filings in the presence of acetic and hydrochloric acid then reduction of the nitro group occurred and the product aniline underwent spontaneous cyclization onto the pendant ester residue, thus forming 8-azaquinolone **39**[12] in 76% yield.

Under analogous conditions, cinnamate **36** was converted into quinolone **40**[13] (67%) while when the same substrate was exposed to hydrogen in the presence of 10% palladium on carbon more extensive reduction occurred to afford dihydroquinolone **41**[14] (85%). Given the ease of formation of the substrates through the title cross-coupling reactions, these conversions provide especially concise routes to quinolones and their 8-aza analogues, classes of compounds that have attracted considerable attention because of, inter alia, their enzyme-inhibiting and DNA-intercalating properties.[13−15] 1,8-Napthyridines, another medicinally significant class of compound,[16] are also available via related protocols, as highlighted by the conversion **19** → **42** shown in Scheme 3. This proceeds in 74% yield when a mixture of iron powder and calcium chloride in ethanol is used as the reducing medium and a basic workup is employed.

Quite distinct reductive cyclization processes are observed when the *β*-aryl-2-cycloalken-1-one coupling products are employed as substrates. Thus, as shown in Scheme 4, exposure of a methanolic solution of compound **7** to hydrogen in the presence of Pd on C afforded 3,4-benzomorphan **43** (73%), while analogous treatment of a toluene solution of the same substrate afforded compound **44**[17] (64%) bearing a bridgehead

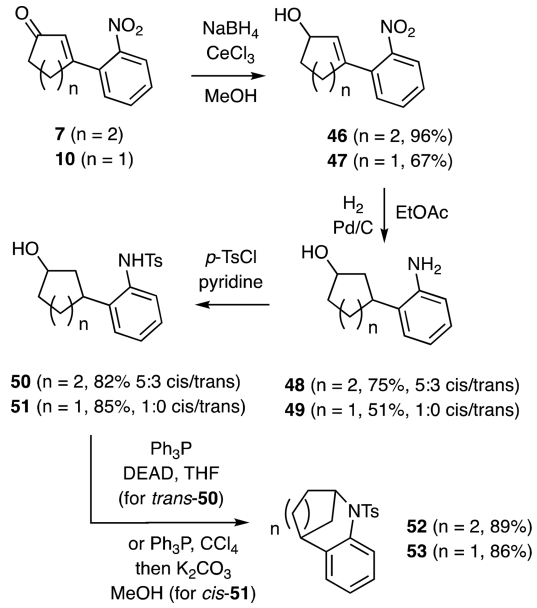
**Scheme 4. Reductive Cyclization of Cross-Coupling Products 7 and 10 Leading to Heterocycles 43−45**




hydroxyl group. In a similar manner, a methanolic solution of cross-coupling product **10** was converted into B-norbenzomorphan **45** (43%). The structures of compounds **43** and **45** were confirmed through X-ray analyses, details of which are provided in the SI.

Deoxygenated variants of compounds **43**−**45** were readily prepared by the pathways shown in Scheme 5. Thus, Luche-

**Scheme 5. Conversion of Cross-Coupling Products 7 and 10 into Bridged Heterocyclic Compounds 52 and 53**




type reductions of compounds **7** and **10** afforded the corresponding allylic alcohols **46** (96%) and **47** (67%), respectively. These 1,2-reduction products underwent catalytic hydrogenation (and accompanying hydrogenolysis of the nitro group) in ethyl acetate to give saturated amino alcohols **48** (75% yield of a 5:3 mixture of *cis* and *trans* isomers) and **49** (51% yield of the *cis* isomer only), respectively. The twofold reduction products **48** and **49** were then converted, under standard conditions, into the corresponding sulfonamides **50** (82% yield of a 5:3 mixture of *cis* and *trans* isomers) and **51** (85% yield of the *cis* isomer only). Compound *trans*-**50**, for which a single-crystal X-ray analysis was obtained (see the SI for details), readily engaged in a Mitsunobu cyclization reaction upon exposure to $Ph_3P$/diethyl azodicarboxylate (DEAD), affording 3,4-benzomorphan **52** (89%). Unsurprisingly, the congener *cis*-**50** failed to cyclize under these same conditions. On the other hand, successive treatment of compound *cis*-**51** under Appel conditions using $CCl_4$ and $Ph_3P$ gave what is presumed to be the corresponding *trans*-chloride, which upon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Org. Lett. 2018, 20, 2770−2773

treatment with potassium carbonate in methanol cyclized to give norbenzomorphan **53** in 86% yield.

Presumably, these protocols could be readily adapted to the preparation of the nonracemic forms of these heterocycles through, for example, enantioselective 1,2-reduction of the starting enones **7** and **10**. In view of the extensive and ongoing interest in benzomorphans and related systems,[18] the processes outlined in Schemes 4 and 5 should be of considerable utility in a range of settings.

The possibilities for reductive cyclization of the above-mentioned cross-coupling products extend beyond those delineated above, as evidenced by, for example, the report[11] that compound **36** (prepared by different means than those described here) can be engaged in a Cadogan cyclization to give 2-carboethoxy-3-phenylindole in 90% yield. As such, the work detailed above serves to highlight the capacities of the title cross-electrophile coupling reactions to deliver a wide range of products capable of engaging in various useful reductive cyclization processes, thus forming new or otherwise difficult-to-access heterocyclic systems.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01015.

Experimental procedures, spectroscopic data, crystallographic data, and NMR spectra of compounds **5** (X = I, Br), **7**, [1,1′-bis(cyclohexane)]-1,1′-diene-3,3′-dione, **8**−**11**, **15**−**19**, **24**−**27**, **30**−**34**, **36**−**47**, **49**, *trans*-**50**, *cis*-**50**, *cis*-**51**, **52**, **53** and *trans-N*-(2-(3-chlorocyclopentyl)-phenyl)-4-methylbenzenesulfonamide (PDF)

### Accession Codes

CCDC 1832167−1832172 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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### Author Contributions

The manuscript was written through contributions from all of the authors. All of the authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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*Supporting Information for:*

# Palladium-Catalyzed Ullmann Cross-Coupling of β-Iodoenones and β-Iodoacrylates with *o*-Halonitroarenes or *o*-Iodobenzonitriles and the Reductive Cyclization of the Resulting Products to Give Diverse Heterocyclic Systems

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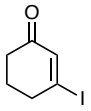
## CONTENTS PAGE

## General Experimental Protocols

Unless otherwise specified, proton ($^{1}$H) and carbon ($^{13}$C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For $^{1}$H NMR spectra, signals arising from the residual protio-forms of the solvent were used as internal standards. $^{1}$H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at $\delta_H$ 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at $\delta_C$ 77.0 were used to reference $^{1}$H and $^{13}$C NMR spectra, respectively. IR spectra were recorded, using neat samples, on an attenuated total reflectance (ATR) infra-red spectrometer. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 $F_{254}$ plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g: 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[1] with silica gel 60 (40– 63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents and drying agents as well as other inorganic salts were generally available from commercial sources and used as supplied. Tetrahydrofuran (THF), diethyl ether, methanol, acetonitrile and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[2] Where necessary, reactions were performed under a nitrogen atmosphere.

**Specific Chemical Transformations**

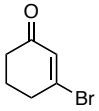
**Compound 5** (X = I)



**5** (X = I)

A magnetically stirred solution of triphenylphosphine (2.89 g, 11.0 mmol) in dry acetonitrile (50 mL) maintained at 22 °C was treated, in portions, with powdered molecular iodine (2.79 g, 11.0 mmol). After 0.5 h the reaction mixture was treated with triethylamine (1.53 mL, 11.0 mmol) then cyclohexane-1,3-dione (1.12 g, 10.0 mmol) and the resulting mixture heated under reflux for 16 h. The cooled reaction mixture was then concentrated under reduced pressure and the residue thus obtained stirred vigorously with diethyl ether (30 mL) and the supernatant liquid decanted. This process was repeated twice more and the combined organic phases then diluted with 40-60 petroleum ether (50 mL) to precipitate triphenylphosphine oxide. The ensuing mixture was filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the filtrate concentrated under reduced pressure to afford compound **5** (X = I) (1.84 g, 83%) as a light-yellow oil. The spectral data obtained on this material matched those published in the literature.[3]

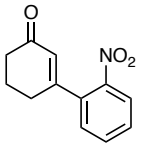
**Compound 5** (X = Br)



**5** (X = Br)

A magnetically stirred solution of triphenylphosphine (4.33 g, 16.5 mmol) in dry acetonitrile (75 mL) maintained at 0 °C was treated, dropwise *via* addition funnel, with a solution of molecular bromine (851 μL, 16.5 mmol) in dry acetonitrile (8.25 mL). The resulting mixture was then warmed to 22 °C and after 0.5 h it was treated with triethylamine (2.30 mL. 16.5 mmol) then cyclohexane-1,3-dione (1.68 g, 15.0 mmol) before being stirred at 22 °C for 16 h then concentrated under reduced pressure. The residue thus obtained was stirred vigorously with diethyl ether (30 mL) and the supernatant liquid decanted. This process was repeated twice more and the combined organic phases then diluted with 40-60 petroleum ether (50 mL) to precipitate triphenylphosphine oxide. The ensuing mixture was filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the filtrate concentrated under reduced pressure to afford compound **5** (X = Br) (2.05 g, 78%) as a light-yellow oil. The spectral data obtained on this material matched those published in the literature.[3]

**Compound 7**

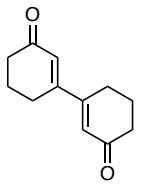


**7**

A magnetically stirred suspension of compound **5** (X = I) (222 mg, 1.00 mmol), *o*-iodonitrobenzene (**2**) (498 mg, 2.00 mmol) and copper powder (318 mg, 5.00 mmol) in dry DMSO (5 mL) maintained at 50 °C was treated with $Pd(dppf)Cl_2•CH_2Cl_2$ (41 mg, 0.05 mmol). After 18 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried ($Na_2SO_4$), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (, 1:9 v/v diethyl ether/toluene elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **7**[4] (198 mg, 91%) as a pale-yellow, crystalline solid, m.p. = 74 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.10 (d, $J$ = 7.8 Hz, 1H), 7.67 (t, $J$ = 7.8 Hz, 1H), 7.55 (t, $J$ = 7.8 Hz, 1H), 7.30 (d, $J$ = 7.8 Hz, 1H), 5.98 (s, 1H), 2.58–2.48 (complex m, 4H), 2.25–2.17 (complex m, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 199.0, 160.8, 146.8, 136.7, 134.0, 129.8, 129.7, 127.7, 125.1, 37.4, 31.0, 23.4.
**IR** (ATR) $\nu_{max}$ 2938, 2870, 1659, 1521, 1345, 1257, 1190, 959, 895, 856, 788, 742, 703 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 240 $[(M+Na)^+$, 100%].
**HRMS** *m/z* 218.0813 $[M+H]^+$ (calcd for $C_{12}H_{11}NO_3$, 218.08112).

Cross-coupling reactions of compound **5** (X = I) such as the one detailed immediately above sometimes delivered small quantities of the corresponding homo-coupling product, viz. [1,1'-bi(cyclohexane)]-1,1'-diene-3,3'-dione and so an authentic sample of this material was produced by the method detailed immediately below.

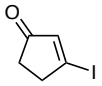
**[1,1'-Bi(cyclohexane)]-1,1'-diene-3,3'-dione**



A magnetically stirred mixture of compound **5** (X = I) (222 mg, 1.00 mmol) and copper powder (318 mg, 5.00 mmol) in dry DMSO (5 mL) was heated at 80 °C (41 mg, 0.05 mmol) for 22 h then cooled to 22 °C, diluted with ethyl acetate (5 mL) then filtered through a plug of

TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (1 x 25 mL of a 5% v/v aqueous solution), water (1 x 25 mL) and brine (1 x 25 mL) before being dried ($Na_2SO_4$), filtered, then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 2:3 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.2), the title compound[5] (46 mg, 48%) as a brown powder, m.p. = 104 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 6.29 (s, 2H), 2.52 (td, $J$ = 6.2 and 1.2 Hz, 4H), 2.44 (t, $J$ = 6.2 Hz, 4H), 2.12–2.02 (complex m, 4H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 199.8, 156.7, 128.1, 37.6, 26.0, 22.4.
**IR (ATR)** $\nu_{max}$ 2951, 2881, 1661, 1637, 1575, 1415, 1328, 1263, 1186, 1144, 899, 770 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 213 [$(M+Na)^+$, 100%].
**HRMS** *m/z* 191.1062 $[M+H]^+$ (calcd for $C_{12}H_{14}O_2$, 191.1067).

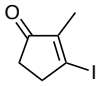
**Compound 8**



**8**

A magnetically stirred solution of triphenylphosphine (2.89 g, 11.0 mmol) in dry acetonitrile (50 mL) maintained at 22 °C was treated, in portions, with powdered molecular iodine (2.92 g, 11.5 mmol). After 0.5 h the reaction mixture was treated with triethylamine (1.67 mL. 12.0 mmol) and cyclopentene-1,3-dione (981 mg, 10.0 mmol) then it was heated under reflux 16 h before being cooled and concentrated under reduced pressure. The residue thus obtained was stirred vigorously with diethyl ether (30 mL) and the supernatant liquid decanted. This process was repeated twice more and the combined organic phases then diluted with 40-60 petroleum ether (50 mL) to precipitate triphenylphosphine oxide. The ensuing mixture was filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the filtrate concentrated under reduced pressure to afford compound **8** (1.37 g, 66%) as a white, crystalline solid. The spectral data obtained on this material matched those published in the literature.[3]

**Compound 9**

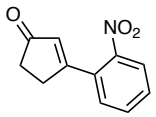


**9**

A magnetically stirred solution of triphenylphosphine (2.89 g, 11.0 mmol) in dry acetonitrile (50 mL) maintained at 22 °C was treated, in portions, with powdered molecular iodine (2.92 g, 11.5 mmol). After 0.5 h the reaction mixture was treated with triethylamine (1.67 mL. 12.0 mmol) and 2-methylcyclopentane-1,3-dione (1.12 g, 10.0 mmol) before being heated under reflux for 18 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained stirred vigorously with diethyl ether (30 mL) and the supernatant liquid decanted. This process was repeated twice more and the combined organic phases then diluted with 40-60 petroleum ether (50 mL) to precipitate triphenylphosphine oxide. The ensuing mixture was filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the filtrate concentrated under reduced pressure to afford **9** (1.80 g,

81%) as a pale-yellow, crystalline solid. The spectral data obtained on this material matched those published in the literature.[3]

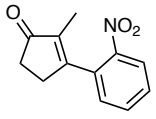
**Compound 10**




**10**

A magnetically stirred suspension of compound **8** (728 mg, 3.50 mmol), *o*-iodonitrobenzene (**2**) (1.74 g, 7.00 mmol) and copper powder (1.11 g, 17.5 mmol) in dry DMSO (15 mL) maintained at 50 °C was treated with $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (143 mg, 0.18 mmol). The ensuing mixture was stirred at 50 °C for 17 h then cooled to 22 °C and diluted with ethyl acetate (15 mL) before being filtered through a plug of TLC-grade silica gel topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (60 mL) and the combined filtrates washed with ammonia (2 x 75 mL of a 5% v/v aqueous solution), water (2 x 75 mL) and brine (1 x 75 mL) before being dried ($Na_2SO_4$), filtered, then concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica, 1:9 v/v diethyl ether/toluene elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **10** (663 mg, 93%) as a pale-yellow powder, m.p. = 89 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.06 (dd, $J$ = 7.8 and 1.0 Hz, 1H), 7.69 (td, $J$ = 7.8 and 1.0 Hz, 1H), 7.57 (td, $J$ = 7.8 and 1.0 Hz, 1H), 7.38 (dd, $J$ = 7.8 and 1.0 Hz, 1H), 6.17 (t, $J$ = 1.9 Hz, 1H), 2.95–2.86 (complex m, 2H), 2.64–2.57 (complex m, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 208.5, 173.9, 147.1 133.7, 132.6, 132.0, 130.2, 129.4, 124.9, 35.7, 31.9.
**IR** (ATR) $\nu_{max}$ 3065, 2929, 2850, 1702, 1686, 1592, 1509, 1437, 1345, 1321, 1287, 1254, 1184, 1083, 876, 849, 788, 746 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 226 $[(M+Na)^+$, 100%].
HRMS *m/z* 226.0482 $[M+Na]^+$ (calcd for $C_{11}H_9NO_3$, 226.0480).

**Compound 11**

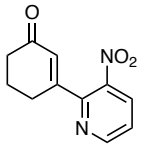



**11**

A magnetically stirred suspension of compound **9** (516 mg, 2.32 mmol), *o*-iodonitrobenzene (**2**) (1.16 g, 4.65 mmol), copper(I) iodide (221 mg, 1.16 mmol) and copper powder (738 mg, 11.6 mmol) in dry DMSO (10 mL) maintained at 50 °C was treated with $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (190 mg, 0.23 mmol). After 23 h the reaction mixture was cooled to 22 °C then diluted with ethyl acetate (10 mL) before being filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (30 mL). The combined filtrates were washed with ammonia (2 x 40 mL of a 5% v/v aqueous solution), water (2 x 40 mL) and brine (1 x 40 mL) before being dried ($Na_2SO_4$), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column

chromatography (silica, 1:9 v/v diethyl ether/toluene elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **11** (247 mg, 49%) as a pale-yellow oil.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.02 (dd, $J$ = 8.2 and 1.2 Hz, 1H), 7.6 (td, $J$ = 7.5 and 1.2 Hz, 1H), 7.50 (m, 1H), 7.22 (dd, $J$ = 7.5 and 1.2 Hz, 1H), 2.69 (m, 2H), 2.45 (m, 2H), 1.44 (t, $J$ = 2.2 Hz, 3H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 208.3, 166.2, 146.8, 138.0, 133.8, 132.8, 129.4, 129.1, 124.7, 34.2, 30.6, 8.4.
**IR** (ATR) $\nu_{max}$ 2919, 1698, 1644, 1515, 1438, 1382, 1353, 1337, 1219, 1102, 1056, 857, 787, 753, 707, 698 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 240 $[(M+Na)^+$, 100%].
HRMS *m/z* 218.0822 $[M+H]^+$ (calcd for $C_{12}H_{11}NO_3$, 218.0817).

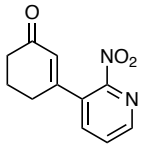
**Compound 15**




**15**

A magnetically stirred suspension of compound **5** (X = I) (1.32 g, 5.91 mmol), copper(I) iodide (845 mg, 4.44 mmol) and copper powder (600 mg, 2.96 mmol) in dry DMSO (40 mL) maintained at 50 °C was treated with $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (241 mg, 0.30 mmol). After 0.75 h the reaction mixture was treated, dropwise over 1 h, with a solution of 2-bromo-3-nitropyridine (**12**) (600 mg, 2.96 mmol) in dry DMSO (10 mL). After a further 4 h the reaction mixture was cooled to 22 °C before being diluted with ethyl acetate (20 mL). The ensuing mixture was filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids thus retained were washed with ethyl acetate (40 mL). The combined filtrates were washed with ammonia (2 x 60 mL of a 5% v/v aqueous solution), water (2 x 60 mL) and brine (1 x 60 mL) before being dried ($Na_2SO_4$), filtered and then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 4:6 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.2 in 1:1 v/v ethyl acetate/40-60 petroleum ether), compound **15** (650 mg, 69%) as an oily, brown solid.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.80 (d, $J$ = 4.6 Hz, 1H), 8.27 (d, $J$ = 8.2 Hz, 1H), 7.50 (m, 1H), 5.96 (s, 1H), 2.68 (t, $J$ = 6.3 Hz, 2H), 2.48 (t, $J$ = 6.3 Hz, 2H), 2.19 (p, $J$ = 6.3 Hz, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 198.5, 158.0, 152.8(4), 152.8(2), 144.3, 132.6, 128.1, 123.9, 37.2, 28.7, 22.8.
**IR** (ATR) $\nu_{max}$ 2980, 1669, 1593, 1524, 1346, 1325, 1251, 959, 818, 762, 725 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 241 $[(M+Na)^+$, 100%].
HRMS *m/z* 219.0769 $[M+H]^+$ (calcd for $C_{11}H_{10}N_2O_3$, 219.0770).

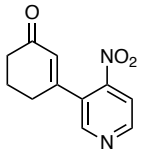
**Compound 16**



**16**

A magnetically stirred suspension of compound **5** (X = I) (1.96 g, 8.83 mmol), 3-bromo-2-nitropyridine (**13**) (900 mg, 4.41 mmol), copper(I) iodide (1.26 g, 6.62 mmol) and copper powder (1.15 g, 18.1 mmol) in dry DMSO (44 mL) maintained at 50 °C was treated with $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (241 mg, 0.30 mmol). After 5 h the reaction mixture was cooled to 22 °C then diluted with ethyl acetate (20 mL). The ensuing mixture was filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (40 mL). The combined filtrates were washed with ammonia (2 x 60 mL of a 5% v/v aqueous solution), water (2 x 60 mL) and brine (1 x 60 mL) before being dried ($Na_2SO_4$), filtered, then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **16** (894 mg, 91%) as a yellow, crystalline solid, m.p. = 90-93 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.59 (dd, $J$ = 4.7 and 1.7 Hz, 1H), 7.81 (dd, $J$ = 7.7 and 1.7 Hz, 1H), 7.67 (dd, $J$ = 7.7 and 4.7 Hz, 1H), 6.00 (s, 1H), 2.56-2.51 (complex m, 4H), 2.20 (m, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 198.3, 156.7, 155.1, 148.8, 139.7, 130.8, 128.8, 128.3, 37.3, 30.3, 23.2.
**IR** (ATR) $\nu_{max}$ 3061, 2950, 2886, 1668, 1537, 1346, 1238, 1188, 982, 958, 807, 703 cm$^{-1}$.
**MS** (ESI, +ve) *m/z* 241 [$(M+Na)^+$, 100%], 219 [$(M+H)^+$, 10%].
HRMS *m/z* 219.0755 $[M+H]^+$ (calcd for $C_{11}H_{10}N_2O_3$ 219.0764).

**Compound 17**

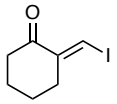


**17**

A magnetically stirred suspension of compound **5** (X = I) (80.0 mg, 0.36 mmol), 3-bromo-4-nitropyridine (**14**) (102 mg, 0.50 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (4 mL) maintained at 80 °C was treated with $Pd_2(dba)_3 \bullet CHCl_3$ (37.3 mg, 0.036 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (4 mL), filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained washed with ethyl acetate (10 mL). The combined filtrates were washed with ammonia (2 x 20 mL of a 5% v/v aqueous solution), water (2 x 20 mL) and brine (1 x 20 mL) before being dried ($Na_2SO_4$), filtered, then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 to 4:6 v/v diethyl ether/40-60 petroleum ether elution) and so affording, after concentration of the

appropriate fractions ($R_f$ = 0.2 in 1:1 v/v ethyl acetate/40-60 petroleum ether), compound **17** (70 mg, 89%) as a clear, colorless oil.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.87 (d, $J$ = 5.3 Hz, 1H), 8.66 (s, 1H), 7.85 (d, $J$ = 5.3 Hz, 1H), 6.01 (s, 1H), 2.51 (m, 4H), 2.19 (m, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 198.1, 155.9, 152.2, 151.0, 129.6, 129.1, 117.0, 37.2, 30.6, 23.2 (signal due to one carbon obscured or overlapping).
**IR** (ATR) $\nu_{max}$ 2925, 1669, 1554, 1530, 1348, 1246, 728, 689, 672 cm$^{-1}$.
**MS** (ESI, +ve) *m/z* 241 [$(M+Na)^+$, 100%], 219 [$(M+H)^+$, 18%].
HRMS *m/z* 219.0766 $[M+H]^+$ (calcd for $C_{11}H_{10}N_2O_3$, 219.0764).

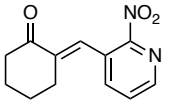
**Compound 18**




**18**

Compound **18** was prepared using a procedure reported earlier.[3] Thus, a magnetically stirred solution of triphenylphosphine (2.16 g, 8.25 mmol) in dry acetonitrile/HMPA (55 mL of a 10:1 v/v mixture) maintained at 22 °C was treated, in portions, with powdered molecular iodine (2.10 g, 8.25 mmol). After 0.5 h the reaction mixture was treated with triethylamine (1.20 mL, 8.25 mmol) and a solution of (*E*)-2-(hydroxymethylene)cyclohexan-1-one[3] (800 mg, 6.35 mmol) in dry acetonitrile (10 mL). The resulting mixture was stirred at 22 °C for 15 h then concentrated under reduced pressure. The residue thus obtained was dissolved in ethyl acetate (50 mL) and the resulting solution washed with water (3 x 30 mL) before being dried ($Na_2SO_4$), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:20 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.5), compound **18** (1.18 g, 79%) as a light-yellow oil. The spectral data acquired on this material were identical, in all respects, with those reported in the literature.[3]

**Compound 19**

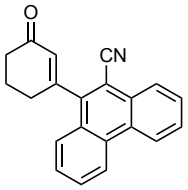



**19**

A magnetically stirred suspension of compound **18** (472 g, 2.00 mmol), 3-bromo-2-nitropyridine (**13**) (808 mg, 4.00 mmol), copper(I) iodide (570 g, 3.00 mmol) and copper powder (512 mg, 8.00 mmol) in dry DMSO (20 mL) maintained at 50 °C was treated with $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (16 mg, 0.02 mmol). After 5 h the reaction mixture was cooled to 22 °C then diluted with ethyl acetate (20 mL) and the ensuing mixture filtered through a plug of TLC-grade silica gel topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (40 mL) and the combined filtrates were washed with ammonia (2 x 60 mL of a 5% v/v aqueous solution), water (2 x 60 mL) and brine (1 x 60 mL) before being dried ($Na_2SO_4$), filtered and then concentrated under reduced pressure. The residue thus obtained

was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **19** (402 mg, 87%) as a yellow, crystalline solid, m.p. = 95-98 °C.
**$^1$H NMR** (400 MHz, [$(CD_3)_2CO$]) $\delta$ 8.56 (dd, $J$ = 4.6 and 1.5 Hz, 1H), 8.12 (dd, $J$ = 7.7 and 1.5 Hz, 1H), 7.85 (dd, $J$ = 7.7 and 4.6 Hz, 1H), 7.32 (t, $J$ = 4.6 Hz, 1H), 2.64 (m, 2H), 2.51 (m, 2H), 1.93 (m, 2H), 1.76 (m, 2H).
**$^{13}$C NMR** (100 MHz, [$(CD_3)_2CO$]) δ 200.0, 148.8, 142.3, 142.2, 128.7, 126.8, 125.9, 41.0, 29.2, 24.4, 24.1. (resonance due to one carbon obscured or overlapping).
**IR** (ATR) $\nu_{max}$ 2941, 2868, 1690, 1595, 1540, 1405, 1360, 1142, 862, 813 cm$^{-1}$.
**MS** (ESI, +ve) *m/z* 255 [$(M+Na)^+$, 100%].
**HRMS** *m/z* 233.0912 $[M+H]^+$ (calcd for $C_{12}H_{12}N_2O_3$, 233.0921).

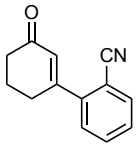
**Compound 24**



**24**

A magnetically stirred suspension of compound **5** (X = I) (84.4 mg, 0.38 mmol), compound **20**[6] (126 mg, 0.38 mmol) and copper powder (170 mg, 2.68 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$•$CHCl_3$ (39.3 mg, 0.038 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL), filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The filtrate was washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried ($Na_2SO_4$), filtered, then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 to 4:6 v/v diethyl ether/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.2 in 2:3 v/v diethyl ether/40-60 petroleum ether elution), compound **24** (45 mg, 40%) as a white, crystalline solid, m.p. = 163 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.75 (m, 2H), 8.36 (d, $J$ = 9.3 Hz, 1H), 7.94–7.74 (complex m, 4H), 7.70 (m, 1H), 6.26 (s, 1H), 2.89 (m, 1H), 2.71 (m, 3H), 2.41 (m, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 198.6, 158.6, 145.9, 132.0, 131.6, 130.2, 129.8, 128.7(0), 127.6(9), 128.4, 128.1, 127.6, 127.1, 126.6, 123.5, 123.1, 116.6, 107.1, 37.6, 31.3, 23.4.
**IR** (ATR) $\nu_{max}$ 3340, 3067, 2949, 2220, 1678, 1450, 907, 757, 725 cm$^{-1}$.
**MS** (ESI, +ve) *m/z* 320 [$(M+Na)^+$, 100 %].
**HRMS** *m/z* 320.1049 $[M+Na]^+$ (calcd for $C_{21}H_{15}NO$, 320.1051).

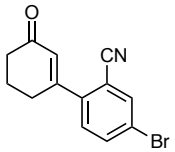
**Compound 25**




**25**

A magnetically stirred suspension of compound **5** (X = I) (222 mg, 1.00 mmol), compound **21**[6] (458 mg, 2.00 mmol), triphenylarsine (61.0 mg, 0.20 mmol) and copper powder (318 mg, 5.00 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$•$CHCl_3$ (52 mg, 0.05 mmol). After 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the resulting mixture filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried ($Na_2SO_4$), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.3), compound **25**[7] (120 mg, 61%) as a white, crystalline solid, m.p. = 86 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.73 (dd, $J$ = 7.7 and 1.4 Hz, 1H), 7.63 (td, $J$ = 7.7 and 1.4 Hz, 1H), 7.48 (m, 1H), 7.39 (dd, $J$ = 7.8 and 1.4 Hz, 1H), 6.20 (s, 1H), 2.80 (m, 2H), 2.54 (m, 2H), 2.21 (m, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 198.9, 158.6, 144.5, 133.9, 133.2, 130.1, 129.2, 128.1, 117.9, 110.2, 37.4, 30.2, 23.3.
**IR** (ATR) $\nu_{max}$ 2949, 2870, 2226, 1669, 1615, 1346, 1326, 1248, 1189, 957, 894, 764 cm$^{-1}$.
**MS** (ESI, +ve) *m/z* 220 [$(M+Na)^+$, 100%].
HRMS *m/z* 220.0733 $[M+Na]^+$ (calcd for $C_{13}H_{11}NO$, 220.0738).

**Compound 26**

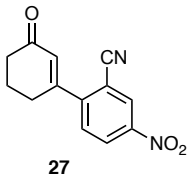



**26**

A magnetically stirred suspension of compound **5** (X = I) (84.4 mg, 0.38 mmol), compound **22**[6] (176 mg, 0.57 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$•$CHCl_3$ (39.3 mg, 0.038 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the resulting mixture filtered through a plug of TLC-grade silica gel topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (20 mL) and the filtrate was washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried ($Na_2SO_4$), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 2:8 to 1:1 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate

fractions ($R_f$ = 0.6 in 2:3 v/v ethyl acetate/40-60 petroleum ether elution), compound **26** (36 mg, 34%) as a white, crystalline solid, m.p. = 123 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.85 (d, $J$ = 2.0 Hz, 1H), 7.75 (dd, $J$ = 8.4 and 2.0 Hz, 1H), 7.26 (d, $J$ = 8.4 Hz, 1H), 6.18 (m, 1H), 2.80–2.73 (complex m, 2H), 2.56–2.49 (complex m, 2H), 2.24–2.15 (complex m, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 198.5, 157.3, 143.3, 136.4, 136.3, 130.3, 129.6, 123.0, 116.5, 112.0, 37.3, 30.1, 23.2.
**IR** (ATR) $\nu_{max}$ 3062, 2951, 2869, 2227, 1669, 1547, 1346, 1252, 822 cm$^{-1}$.
**MS** (ESI, +ve) *m/z* 300 and 298 [$(M+Na)^+$, 98 and 100 %].
**HRMS** *m/z* 297.9843 $[M+Na]^+$ (calcd for $C_{13}H_{10}{}^{79}BrNO$, 297.9843).

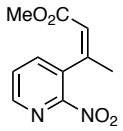
**Compound 27**



**27**

A magnetically stirred suspension of compound **5** (X = I) (84.4 mg, 0.38 mmol), compound **23**[6] (176 mg, 0.57 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$•$CHCl_3$ (39.3 mg, 0.038 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the resulting mixture filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried ($Na_2SO_4$), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 2:8 to 1:1 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.6 in 2:3 v/v ethyl acetate/40-60 petroleum ether elution), compound **27** (73 mg, 79%) as a red, crystalline solid, m.p. = 152 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.60 (d, $J$ = 2.2 Hz, 1H), 8.47 (dd, $J$ = 8.6 and 2.2 Hz, 1H), 7.61 (d, $J$ = 8.6 Hz, 1H), 6.24 (t, $J$ = 1.7 Hz, 1H), 2.80 (td, $J$ = 5.9 and 1.7 Hz, 2H), 2.58 (dd, $J$ = 7.6 and 5.9 Hz, 2H), 2.26 (m, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 198.9, 155.9, 150.1, 147.6, 131.1, 129.6, 128.9, 127.8, 115.8, 111.8, 37.2, 29.8, 23.1.
**IR** (ATR) $\nu_{max}$ 3081, 2953, 2233, 1673, 1526, 1353, 1324, 1247, 744 cm$^{-1}$.
**MS** (ESI, +ve) *m/z* 265 [$(M+Na)^+$, 100 %].
**HRMS** *m/z* 265.0591 $[M+Na]^+$ (calcd for $C_{13}H_{10}N_2O_3$ 265.0589).

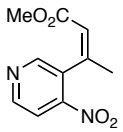
**Compound 30**



**30**

A magnetically stirred suspension of compound **28**[8] (79.1 mg, 0.35 mmol), 3-bromo-2-nitropyridine (**12**) (102 mg, 0.50 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$•$CHCl_3$ (29.0 mg, 0.028 mmol). After 16 h the reaction mixture was cooled to 22 °C then diluted with ethyl acetate (5 mL) before being filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried ($Na_2SO_4$), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 4:6 to 1:1 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.3 in 3:7 v/v ethyl acetate/40-60 petroleum ether elution), compound **30** (66 mg, 84%) as a yellow, crystalline solid, m.p. = 68 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.56 (dd, $J$ = 4.5 and 1.8 Hz, 1H), 7.68 (dd, $J$ = 7.6 and 1.8 Hz, 1H), 7.62 (dd, $J$ = 7.6 and 4.5 Hz, 1H), 6.00 (q, $J$ = 1.5 Hz, 1H), 3.52 (s, 3H), 2.29 (d, $J$ = 1.5 Hz, 3H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 165.4, 154.8, 150.5, 147.5, 139.0, 132.0, 128.0, 118.9, 51.5, 26.1.
**IR** (ATR) $\nu_{max}$ 2953, 1714, 1650, 1539, 1359, 1249, 1172, 1042, 859, 814, 659 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 245 [$(M+Na)^+$, 100 %].
HRMS *m/z* 245.0536 $[M+Na]^+$ (calcd for $C_{10}H_{10}N_2O_4$ 245.0538).

**Compound 31**

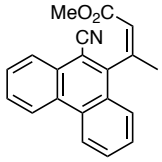


**31**

A magnetically stirred suspension of compound **28** (22.6 mg, 0.10 mmol), 3-bromo-4-nitropyridine (**14**) (40.6 mg, 0.20 mmol) and copper powder (31.8 mg, 0.50 mmol) in dry DMSO (1 mL) maintained at 55 °C was treated with Pd(dppf)$Cl_2$•$CH_2Cl_2$ (8.2 mg, 0.010 mmol). After 18 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL), filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (10 mL). The filtrate was washed with ammonia (2 x 15 mL of a 5% v/v aqueous solution), water (2 x 15 mL) and brine (1 x 15 mL) before being dried ($Na_2SO_4$), filtered, then concentrated under reduced pressure. The residue obtained was subjected to flash chromatography (silica, 1:9 v/v diethyl ether/toluene elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.12 in 1:9 v/v diethyl ether/toluene), compound **31** (15.3 mg, 69%) as a clear, colorless oil.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.82 (d, $J$ = 5.4 Hz, 1H), 8.55 (s, 1H), 7.91 (d, $J$ = 5.4 Hz, 1H), 6.08 (d, $J$ = 1.5 Hz, 1H), 3.53 (s, 3H), 2.29 (d, $J$ = 1.5 Hz, 3H). Irradiation of the

resonance at δ 2.29 led to a significant enhancement of the one at δ 6.08 and so establishing the illustrated *Z*-configuration about the acrylate double-bond.
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 165.4, 152.3, 150.8, 150.6, 149.7, 130.8, 119.9, 116.5, 51.5, 26.3.
**IR** (ATR) $\nu_{max}$ 2953, 1716, 1650, 1532, 1442, 1354, 1243, 1163, 1047, 858, 676 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 245 [$(M+Na)^+$, 100 %].
**HRMS** *m/z* 245.0539 $[M+Na]^+$ (calcd for $C_{10}H_{10}N_2O_4$ 245.0538).

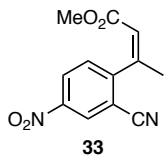
**Compound 32**




**32**

A magnetically stirred suspension of compound **28** (84.4 mg, 0.38 mmol), compound **20** (160 mg, 0.49 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$•$CHCl_3$ (39.3 mg, 0.030 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL), filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried ($Na_2SO_4$), filtered, then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:4 to 1:1 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **32** (62 mg, 55%) as a pink, crystalline solid, m.p. = 153-155 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.75 (d, $J$ = 8.4 Hz, 1H), 8.72 (m, 1H), 8.31 (m, 1H), 7.86 (dd, $J$ = 8.4 and 1.6 Hz, 1H), 7.80 (m, 1H), 7.77–7.73 (complex m, 2H), 7.65 (m, 1H), 6.46 (q, $J$ = 1.6 Hz, 1H), 3.48 (s, 3H), 2.40 (d, $J$ = 1.6 Hz, 3H). Irradiation of the resonance at δ 2.40 led to a significant enhancement of the one at δ 6.46 and so establishing the illustrated *Z*-configuration about the acrylate double-bond.
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 164.9, 152.2, 147.8, 131.8, 129.7, 129.6, 128.8, 128.2, 128.0, 127.9, 127.6, 126.5, 126.3, 123.5, 123.1, 122.4, 116.9, 106.0, 51.4, 26.0.
**IR** (ATR) $\nu_{max}$ 2950, 2220, 1723, 1651, 1438, 1450, 1208, 1158, 1133, 1044, 759, 725 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 340 [$(M+K)^+$, 100%], 324 [$(M+Na)^+$, 90%].
**HRMS** *m/z* 324.1003 $[M+Na]^+$ (calcd for $C_{20}H_{15}NO_2$, 324.1000).

**Compound 33**




**33**

A magnetically stirred suspension of compound **28** (84.4 mg, 0.38 mmol), compound **23** (155 mg, 0.56 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$•$CHCl_3$ (31.1 mg, 0.030 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the resulting mixture

filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried ($Na_2SO_4$), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:4 to 1:1 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.3), compound **33** (36 mg, 43%) as a white, crystalline solid, m.p. = 106-107 °C.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.54 (d, $J$ = 2.3 Hz, 1H), 8.43 (dd, $J$ = 8.6 and 2.3 Hz, 1H), 7.43 (d, $J$ = 8.6 Hz, 1H), 6.19 (q, $J$ = 1.6 Hz, 1H), 3.60 (s, 3H), 2.26 (d, $J$ = 1.6 Hz, 3H).

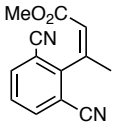
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 165.1, 152.2, 150.6, 146.9, 128.7, 127.8, 127.5, 121.5, 115.6, 112.3, 51.7, 26.0.

**IR** (ATR) $\nu_{max}$ 2954, 2236, 1721, 1606, 1529, 1439, 1353, 1241, 1166, 1042, 797 cm$^{-1}$.

**MS** (ESI, +ve) *m/z* 269 [(M+Na)$^+$, 100 %].

**HRMS** *m/z* 269.0539 [M+Na]$^+$ (calcd for $C_{12}H_{10}N_2O_4$, 269.0538).

**Compound 34**




**34**

A magnetically stirred suspension of compound **28** (84.4 mg, 0.38 mmol), compound **29**[9] (134 mg, 0.53 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$•$CHCl_3$ (31.1 mg, 0.030 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) then filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried ($Na_2SO_4$), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:4 to 1:1 v/v diethyl ether/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **34** (50 mg, 59%) as a clear, colorless oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.90 (d, $J$ = 7.8 Hz, 2H), 7.54 (t, $J$ = 7.8 Hz, 1H), 6.28 (d, $J$ = 1.6 Hz, 1H), 3.61 (s, 3H), 2.30 (d, $J$ = 1.6 Hz, 3H).

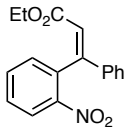
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 164.9, 149.9, 149.1, 136.5, 128.5, 123.0, 115.9, 112.2, 51.8, 25.1.

**IR** (ATR) $\nu_{max}$ 2954, 2236, 1719, 1654, 1455, 1434, 1352, 1244, 1166, 1041, 808, 760 cm$^{-1}$.

**MS** (ESI, +ve) *m/z* 249 [(M+Na)$^+$, 100 %].

**HRMS** *m/z* 249.0647 [M+Na]$^+$ (calcd for $C_{13}H_{10}N_2O_2$, 249.0640).

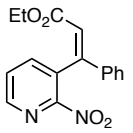
**Compound 36**




**36**

A magnetically stirred suspension of compound **35**[8] (100 mg, 0.33 mmol), compound **5** (X = I) (124 mg, 0.50 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$•$CHCl_3$ (31.1 mg, 0.030 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried ($Na_2SO_4$), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 to 1:1 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.3 in 1:4 v/v diethyl ether/40-60 petroleum ether elution), compound **36**[10] (60 mg, 61%) as a clear, yellow oil.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.12 (dd, $J$ = 8.3 and 1.4 Hz, 1H), 7.60 (td, $J$ = 7.5 and 1.3 Hz, 1H), 7.49 (m, 1H), 7.29–7.18 (complex m, 6H), 6.41 (s, 1H), 3.92 (m, 2H), 1.03 (t, $J$ = 7.2 Hz, 3H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 165.5, 153.5, 138.3, 135.2, 133.3, 131.2, 129.9, 128.9, 128.7, 127.6, 127.2, 124.7, 117.2, 60.4, 14.1.
**IR** (ATR) $\nu_{max}$ 3036, 1712, 1625, 1523, 1346, 1168, 1032, 771, 69 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 320 [$(M+Na)^+$, 100 %].
**HRMS** *m/z* 320.0899 $[M+Na]^+$ (calcd for $C_{17}H_{15}NO_4$, 320.0899).

**Compound 37**

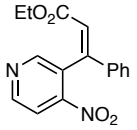



**37**

A magnetically stirred suspension of compound **35**[8] (130 mg, 0.43 mmol), 3-bromo-2-nitropyridine (**13**) (122 mg, 0.60 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$•$CHCl_3$ (31.1 mg, 0.030 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL), filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried ($Na_2SO_4$), filtered and then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 3:7 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.5), compound **37** (65 mg, 50%) as a white, crystalline solid, m.p. = 102-103 °C.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.64 (dd, $J$ = 4.6 and 1.8 Hz, 1H), 7.76 (dd, $J$ = 7.7 and 1.7 Hz, 1H), 7.67 (dd, $J$ = 7.7 and 4.6 Hz, 1H), 7.47–7.29 (complex m, 5H), 6.52 (s, 1H), 4.00 (m, 2H), 1.14 (t, $J$ = 7.2 Hz, 3H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 165.2, 155.9, 150.5, 148.0, 141.2, 137.6, 130.4, 129.9, 129.0, 127.7(3), 127.7(0), 118.3, 60.7, 14.1.
**IR** (ATR) $\nu_{max}$ 3061, 2983, 1709, 1624, 1540, 1367, 1349, 1270, 1175, 1093, 1027, 771, 692 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 321 [$(M+Na)^+$, 100 %].
**HRMS** *m/z* 321.0851 $[M+Na]^+$ (calcd for $C_{16}H_{14}N_2O_4$, 321.0851).

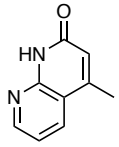
**Compound 38**




**38**

A magnetically stirred suspension of compound **35**[8] (380 mg, 1.26 mmol), 3-bromo-4-nitropyridine (**14**) (510 mg, 2.52 mmol) and copper powder (400 mg, 6.29 mmol) in dry DMSO (5 mL) maintained at 55 °C was treated with $PdCl_2(dppf)•CH_2Cl_2$ (103 mg, 0.13 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the resulting mixture filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried ($Na_2SO_4$), filtered and then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 to 1:1 v/v diethyl ether/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.3 in 3:7 v/v ethyl acetate/40-60 petroleum ether elution), compound **38** (303 mg, 81%) as a clear, yellow oil.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.91 (broad s, 1H), 8.64 (broad s, 1H), 7.99 (d, $J$ = 5.4 Hz, 1H), 7.42–7.29 (complex m, 5H), 6.59 (s, 1H), 4.03 (m, 2H), 1.15 (t, $J$ = 7.2 Hz, 3H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 165.3, 153.3, 152.5, 151.3, 149.7, 137.7, 130.4, 129.0, 127.5, 119.2, 60.8, 14.1(two resonances obscured or overlapping).
**IR** (ATR) $\nu_{max}$ 2982, 1711, 1624, 1533, 1352, 1268, 1177, 1028, 847, 770, 676 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 321 [$(M+Na)^+$, 100 %].
**HRMS** *m/z* 321.0844 $[M+Na]^+$ (calcd for $C_{16}H_{14}N_2O_4$, 321.0851).

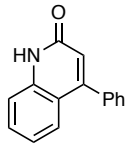
**Compound 39**



**39**

A magnetically stirred mixture of compound **30** (55.4 mg, 0.25 mmol), glacial acetic acid (1 mL) and iron powder (30.0 mg, 0.54 mmol) in ethanol (5 mL) maintained at 22 °C was treated with hydrochloric acid (2 drops of a 37% aqueous solution). After 1 h the reaction mixture was quenched with sodium bicarbonate (10 mL of a saturated aqueous solution) and extracted with ethyl acetate (2 x 5 mL). The combined organic phases were dried ($Na_2SO_4$), filtered and then concentrated under reduced pressure to give compound **39**[11] (30.4 mg, 76%) as a brown solid, no m.p., decomposition above 200 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 9.78 (broad s, 1H), 8.57 (d, $J$ = 4.1 Hz, 1H), 7.99 (d, $J$ = 7.8 Hz, 1H), 7.22 (m, 1H), 6.57 (s, 1H), 2.48 (s, 3H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 163.7, 150.4, 149.8, 147.2, 133.4, 122.4, 118.4, 115.9, 18.5.
**IR** (ATR) $\nu_{max}$ 2874, 1664, 1612, 1564, 1423, 1388, 1086, 966, 862, 779, 672, 510 cm$^{-1}$.
**MS** (ESI, +ve) *m/z* 183 [$(M+Na)^+$, 100%].
**HRMS** *m/z* 183.0536 [$M+Na]^+$ (calcd for $C_9H_8N_2O$, 183.0534).

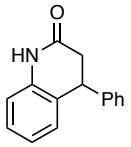
**Compound 40**



**40**

A magnetically stirred mixture of compound **36** (20.3 mg, 0.068 mmol), glacial acetic acid (1 mL) and iron powder (50.0 mg, 0.94 mmol) in ethanol (5 mL) maintained at 60 °C was treated with hydrochloric acid (2 drops of a 37% aqueous solution). After 16 h the reaction mixture was cooled to 22 °C then quenched with sodium bicarbonate (10 mL of a saturated aqueous solution) and extracted with ethyl acetate (2 x 5 mL). The combined organic phases were dried ($Na_2SO_4$), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **40**[12] (10.1 mg, 67%) as a white, crystalline solid, m.p. = 189-191 °C
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 12.64 (broad s, 1H), 7.57–7.46 (complex m, 8H), 7.17 (m, 1H), 6.71 (s, 1H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 164.6, 153.9, 139.4, 137.6, 131.2, 129.3(3), 129.3(0), 129.1, 127.2, 123.0, 121.3, 120.1, 117.1.
**IR** (ATR) $\nu_{max}$ 2957, 2920, 2851, 1661, 1610, 1563, 1432, 1386, 876, 751, 700 cm$^{-1}$.
**MS** (ESI, +ve) *m/z* 465 [$(2M+Na)^+$, 100%], 244 [$(M+Na)^+$, 78%].
**HRMS** *m/z* 244.0744 [$M+Na]^+$ (calcd for $C_{15}H_{11}NO$, 244.0738).

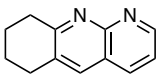
**Compound 41**




**41**

A magnetically stirred mixture of compound **36** (27.4 mg, 0.092 mmol) and 10% palladium on carbon (27 mg) in dry ethanol (5 mL) maintained at 22 °C was placed under a hydrogen atmosphere. After 16 h the reaction mixture was filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 4.6 to 1:1 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.4), compound **41**[13] (17.5 mg, 85%) as a white, crystalline solid, m.p. = 177-179 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.96 (broad s, 1H), 7.39–7.30 (complex m, 2H), 7.30–7.27 (complex m, 1H), 7.23–7.17 (complex m, 3H), 7.02–6.89 (complex m, 2H), 6.82 (d, $J$ = 7.9 Hz, 1H), 4.30 (t, $J$ = 7.5 Hz, 1H), 2.93 (m, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 170.3, 141.5, 137.1, 129.1, 128.6, 128.2, 128.0, 127.4, 126.9, 123.5, 115.6, 42.2, 38.6.
**IR** (ATR) $\nu_{max}$ 3212, 2911, 1679, 1593, 1486, 1376, 1245, 1159, 754, 700 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 246 $[(M+Na)^+$, 100%].
**HRMS** *m/z* 246.0894 $[M+Na]^+$ (calcd for $C_{15}H_{13}NO$, 246.0895).

**Compound 42**

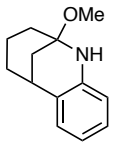



**42**

A magnetically stirred mixture of compound **19** (232 mg, 1.00 mmol) and iron powder (168 mg, 3.00 mmol) in a mixture of ethanol and water (10 mL of a 7:3 v/v mixture) maintained at 22 °C was treated with calcium chloride (333 mg, 3.00 mmol). The resulting mixture was heated under reflux and after 2 h the reaction mixture was cooled to 22 °C then treated with sodium hydroxide (200 mg, 5.00 mmol) then heated under reflux again. After 1 h the reaction mixture was cooled to 22 °C before diluted with ethyl acetate (20 mL) then filtered through a plug of TLC-grade silica gel topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (2 x 20 mL) and the separated organic phase associated with the combined filtrates dried ($MgSO_4$) before being concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:99 v/v methanol/ethyl acetate elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **42**[14] (136 mg, 74%) as a yellow solid, no m.p., decomposition above 118 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 9.01 (dd, $J$ = 4.3 and 2.0 Hz, 1H), 8.07 (dd, $J$ = 8.1 and 2.0 Hz, 1H), 7.83 (s, 1H), 7.39 (dd, $J$ = 8.1 and 4.3 Hz, 1H), 3.23 (t, $J$ = 6.6 Hz, 2H), 3.00 (t, $J$ = 6.0 Hz, 2H), 2.01 (m, 2H), 1.91 (m, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 163.3, 154.8, 152.6, 136.1, 135.6, 132.4, 121.5, 121.3, 33.9, 29.2, 23.0, 22.8.

**IR** (ATR) $\nu_{max}$ 3048, 2936, 2921, 1607, 1597, 1548, 1474, 1446, 1411, 1301, 1245, 1227, 1148, 824, 797, 718, 608 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 391 $[(M+Na)^+$, 37%], 207 $[(M+Na)^+$, 100], 185 $[(M+H)^+$, 30].
**HRMS** *m/z* 185.1068 $[M+H]^+$ (calcd for $C_{12}H_{12}N_2$, 185.1073).

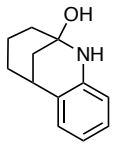
**Compound 43**




**43**

A magnetically stirred suspension of compound **7** (1.00 g, 4.56 mmol) and 10% palladium on carbon (460 mg) in dry methanol (50 mL) maintained at 50 °C was placed under a hydrogen atmosphere. After 2 h the reaction mixture was cooled to 22 °C then filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 5:95 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.11 in 1:9 v/v ethyl acetate/40-60 petroleum ether elution), compound **43** (684 mg, 73%) as white crystals, m.p. = 108 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.02 (m, 1H), 6.94 (dd, *J* = 7.3 and 1.3 Hz, 1H), 6.63 (m, 1H), 6.55 (dd, *J* = 8.0 and 1.3 Hz, 1H), 3.82 (s, 1H), 3.32 (s, 3H), 3.14 (m, 1H), 2.26 (m, 1H), 1.79 (m, 2H), 1.72–1.64 (complex m, 3H), 1.65–1.46 (complex m, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 145.8, 128.0, 127.2, 125.7, 117.3, 113.3, 83.9, 48.4, 41.5, 36.3, 34.0, 32.0, 19.5.
**IR** (KBr) $\nu_{max}$ 3315, 2943, 1606, 1487, 1274, 1114, 1067, 1059, 753 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 226 $[(M+Na)^+$, 45%], 204 $[(M+H)^+$, 100].
HRMS *m/z* 204.1389 $[M+H]^+$ (calcd for $C_{13}H_{17}NO$, 204.1388).

**Compound 44**

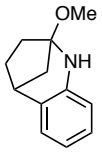



**44**

A magnetically stirred suspension of compound **7** (100 mg, 0.46 mmol) and 10% palladium on carbon (46 mg) in dry toluene (5 mL) maintained at 50 °C was placed under a hydrogen atmosphere. After 1 h the reaction mixture was cooled to 22 °C then filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.4), compound **44**[15] (55.2 mg, 64%) as a clear, yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.01 (m, 1H), 6.94 (dd, $J$ = 7.5 and 1.6 Hz, 1H), 6.65 (m, 1H), 6.50 (dd, $J$ = 7.5 and 1.6 Hz, 1H), 4.17 (broad s, 1H), 3.12 (t, $J$ = 3.3 Hz, 1H), 2.24 (broad s, 1H), 2.03–1.90 (complex m, 2H), 1.90–1.82 (complex m, 2H), 1.70–1.59 (complex m, 2H), 1.61–1.44 (complex m, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 144.9, 128.1, 127.3, 125.7, 117.8, 113.2, 80.5, 40.9, 38.8, 36.7, 33.5, 19.5.
**IR** (KBr) $\nu_{max}$ 3361, 2930, 2847, 1608, 1493, 1478, 1300, 1267, 1127, 1080, 1063, 979, 910, 744 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 212 $[(M+Na)^+$, 100%], 190 $[(M+H)^+$, 70].
**HRMS** *m/z* 190.1236 $[M+H]^+$ (calcd for $C_{12}H_{15}NO$, 190.1232).

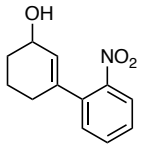
**Compound 45**




**45**

A magnetically stirred suspension of compound **10** (52.4 mg, 0.26 mmol) and 10% palladium on carbon (26 mg) in dry, degassed methanol (20 mL) maintained at 65 °C was treated with glacial acetic acid (0.2 mL) then placed under a hydrogen atmosphere. After 20 h the reaction mixture was cooled to 22 °C, filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The ensuing reside was portioned between diethyl ether (10 mL) and sodium bicarbonate (10 mL of a saturated aqueous solution) then the separated aqueous phase was extracted with diethyl ether (2 x 10 mL) and the combined organic phases washed with brine (1 x 20 mL) before being dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to give compound **45** (22 mg, 43%) as a white, crystalline solid, m.p. = 77 °C ($R_f$ = 0.1 in 1:9 v/v diethyl ether/*n*-hexane).
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.00 (m, 1H), 6.90 (m, 1H), 6.64 (m, 1H), 6.58 (m, 1H), 3.83 (broad s, 1H), 3.46 (s, 3H), 3.03 (m, 1H), 2.21–2.05 (complex m, 4H), 1.99–1.89 (complex m, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 143.9, 131.6, 127.2, 126.6, 118.5, 115.5, 94.3, 52.3, 40.7, 40.0, 35.6, 34.4.
**IR** (ATR) $\nu_{max}$ 3339, 2941, 2855, 1606, 1493, 1470, 1318, 1298, 1245, 1217, 1199, 1150, 1112, 1070, 1034, 1001, 942, 747 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 190 $[(M+H)^+$, 69%], 158 (62), 153 (100), 102 (93).
**HRMS** *m/z* 190.1233 $[M+H]^+$ (calcd for $C_{12}H_{15}NO$, 190.1232).

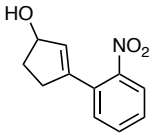
**Compound 46**




**46**

A magnetically stirred solution of compound **7** (652 mg, 3.0 mmol) and cerium(III) chloride heptahydrate (1.23 g, 3.3 mmol) in dry methanol/dichloromethane (6 mL of a 1:1 v/v mixture) maintained at 0 °C was treated, in portions, with sodium borohydride (125 mg, 3.30 mmol). After 2 h the reaction mixture was concentrated under reduced pressure and the residue dissolved in diethyl ether (10 mL) and the resulting mixture treated hydrochloric acid (10 mL of a 1 M aqueous solution). The separated aqueous phase was extracted with diethyl ether (2 x 10 mL) and the combined organic phases washed with brine (1 x 30 mL) before being dried ($Na_2SO_4$), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v diethyl ether/dichloromethane elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.3), compound **46** (631 mg, 96%) as a clear, yellow oil.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.88 (dd, $J$ = 8.1 and 1.3 Hz, 1H), 7.55 (td, $J$ = 7.6 and 1.3 Hz, 1H), 7.40 (td, $J$ = 8.1 and 1.4 Hz, 1H), 7.29 (dd, $J$ = 7.6 and 1.3 Hz, 1H), 5.67 (m, 1H), 4.30 (m, 1H), 2.31–2.14 (complex m, 2H), 1.99–1.86 (complex m, 2H), 1.80–1.66 (complex m, 3H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 148.3, 139.9, 138.5, 133.0, 130.8, 128.5, 128.1, 124.3, 65.7, 31.4, 29.7, 19.5.
**IR** (ATR) $\nu_{max}$ 3342, 2937, 2863, 1521, 1346, 1049, 972, 912, 859, 785, 746 cm$^{-1}$.
**MS** (ESI, +ve) *m/z* 242 [$(M+Na)^+$, 100%].
HRMS *m/z* 242.0794 $[M+Na]^+$ (calcd for $C_{12}H_{13}NO_3$, 242.0793).

**Compound 47**

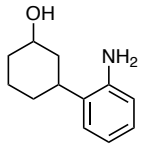



**47**

A magnetically stirred solution of compound **10** (609 mg, 3.0 mmol) and cerium(III) chloride heptahydrate (1.23 g, 3.3 mmol) in methanol/dichloromethane (12 mL of a 1:1 v/v mixture) maintained at 0 °C was treated, in portions, with sodium borohydride (125 mg, 3.30 mmol). After 0.5 h the reaction mixture was concentrated under reduced pressure and the ensuing residue dissolved in diethyl ether (10 mL). The resulting solution was treated with hydrochloric acid (10 mL of a 1 M aqueous solution) and the separated aqueous phase extracted with diethyl ether (2 x 10 mL). The combined organic phases were washed with brine (1 x 30 mL) before being dried ($Na_2SO_4$), filtered and then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 v/v diethyl ether/dichloromethane elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.3), compound **47** (414 mg, 67%) as a clear, yellow oil.

**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.80 (dd, $J$ = 8.1 and 1.3 Hz, 1H), 7.51 (td, $J$ = 7.5 and 1.3 Hz, 1H), 7.41–7.30 (complex m, 2H), 5.82 (q, $J$ = 2.0 Hz, 1H), 4.94 (broad s, 1H), 2.71 (m, 1H), 2.57 (s, 1H), 2.54–2.46 (complex m, 1H), 2.45–2.36 (complex m, 1H), 1.86 (m, 1H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 148.4, 144.1, 133.0, 132.7, 132.1, 130.6, 128.4, 124.0, 77.6, 34.3, 34.0.
**IR** (ATR) $\nu_{max}$ 3338, 2937, 2854, 1520, 1345, 1274, 1239, 1048, 966, 854, 784, 744 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 228 [$(M+Na)^+$, 100%].
HRMS *m/z* 228.0638 $[M+Na]^+$ (calcd for $C_{11}H_{11}NO_3$, 228.0637).

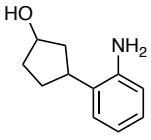
**Compound 48**




**48**

A magnetically stirred mixture of compound **46** (798 mg, 3.64 mmol) and 10% palladium on carbon (80 mg) in dry methanol (8 mL) maintained at 22 °C was placed under a hydrogen atmosphere. After 2.5 h the reaction mixture was filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 2.5:47.5:50 v/v/ methanol/ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.6 in 5:95 v/v methanol/ethyl acetate elution), compound **48** (524 mg, 75%) as a clear, light-brown oil. The product decomposes rapidly at ambient temperatures and so it was used immediately in the next step of the reaction sequence.
**IR** (ATR) $\nu_{max}$ 3349, 2927, 2855, 1621, 1496, 1453, 1293, 1251, 1051, 976, 959, 748 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 405 [$(2M+Na)^+$, 48%], 214 [$(M+Na)^+$, 100], 192 [$(M+H)^+$, 34].
**HRMS** *m/z* 192.1381 $[M+H]^+$ (calcd for $C_{12}H_{17}NO$, 192.1383).

**Compound 49**

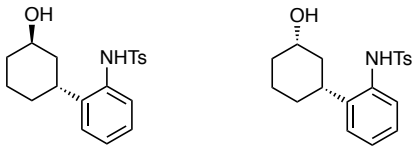



**49**

A magnetically stirred mixture of compound **47** (235 mg, 1.14 mmol) and 10% palladium on carbon (24 mg) in dry methanol (5 mL) maintained at 22 °C was placed under a hydrogen atmosphere. After 2 h the reaction mixture was filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:4 to 1:1 v/v diethyl ether/dichloromethane elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **49** (102 mg, 51%) as a clear, light-brown oil.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.19 (dd, $J$ = 7.6 and 1.5 Hz, 1H), 7.05 (m, 1H), 6.76 (m, 1H), 6.67 (dd, $J$ = 7.8 and 1.2 Hz, 1H), 4.46 (m, 1H), 3.33 (broad s, 2H), 3.07 (m, 1H), 2.45–2.31

(complex m, 1H), 2.12–1.94 (complex m, 2H), 1.93–1.80 (complex m, 2H), 1.80–1.73 (complex m, 1H) (resonance due to one proton not observed).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 144.2, 129.0, 127.8, 127.1, 118.7, 116.2, 73.8, 40.9, 40.0, 36.0, 29.5.
**IR** (ATR) $\nu_{max}$ 3350, 3244, 2951, 2865, 1620, 1495, 1454, 1295, 1078, 983, 748 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 200 $[(M+Na)^+$, 50%], 178 $[(M+H)^+$, 100], 160 (100).
**HRMS** *m/z* 178.1232 $[M+H]^+$ (calcd for $C_{11}H_{15}NO$, 178.1232).

***cis*- and *trans*- Forms of Compound 50**

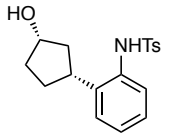


*trans*-**50** *cis*-**50**

A magnetically stirred solution of compound **48** (524 mg, 2.74 mmol) and pyridine (665 µL, 8.22 mmol) in dry dichloromethane (5.5 mL) maintained at 0 °C was treated, in portions, with *p*-toluenesulfonyl chloride (575 mg, 3.01 mmol) then warmed to 22 °C. After 16 h the reaction mixture was treated with heptane (20 mL) then concentrated under reduced pressure. This dilution/concentration process was repeated twice more in order to remove pyridine. The residue thus obtained was subjected to flash column chromatography (silica, 2:3 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, two fractions, A and B.
Concentration of fraction A ($R_f$ = 0.2) gave compound *trans*-**50** (304 mg, 32%) as a white crystalline solid, m.p. =145 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.65 (d, $J$ = 8.3 Hz, 2H), 7.36 (m, 1H), 7.24 (d, $J$ = 8.3 Hz, 2H), 7.20–7.11 (complex m, 3H), 4.20 (t, $J$ = 2.9 Hz, 1H), 3.01 (s, 1H), 2.91 (m, 1H), 2.37 (s, 3H), 1.84 (m, 1H), 1.74 (m, 1H), 1.68–1.55 (complex m, 1H), 1.43 (m, 3H), 1.32–1.20 (complex m, 1H), 1.01 (d, $J$ = 12.5 Hz, 1H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 143.7, 141.9, 136.9, 133.1, 129.7, 127.4, 127.3, 127.2, 126.9, 126.6, 66.7, 40.4, 32.8, 32.0, 31.1, 21.6, 20.4.
**IR** (ATR) $\nu_{max}$ 3521, 3345, 3284, 2928, 1491, 1406, 1327, 1163, 1091, 976, 808, 756, 664 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 368 $[(M+Na)^+$, 100%].
**HRMS** *m/z* 368.1292 $[M+Na]^+$ (calcd for $C_{19}H_{23}NO_3S$, 368.1291).

Concentration of fraction B ($R_f$ = 0.1) gave compound *cis*-**50** (469 mg, 50%) as a white powder, m.p. =152 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.57 (d, $J$ = 8.3 Hz, 2H), 7.25–7.22 (complex m, 3H), 7.21–7.11 (complex m, 3H), 6.38 (s, 1H), 3.51 (m, 1H), 2.48 (m, 1H), 2.40 (s, 3H), 1.99 (d, $J$ = 11.2 Hz, 1H), 1.75 (m, 1H), 1.54 (m, 2H), 1.33–1.09 (complex m, 4H) (resonance due to OH group proton not observed).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 143.9, 141.7, 136.7, 132.7, 129.7, 127.5, 127.4, 127.3, 127.0 126.7, 70.7, 42.8, 36.1, 35.1, 32.5, 24.4, 21.6.
**IR** (ATR) $\nu_{max}$ 3249, 2925, 1492, 1401, 1330, 1161, 1092, 915, 809, 756, 706, 671 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 368 $[(M+Na)^+$, 100%].
**HRMS** *m/z* 368.1288 $[M+Na]^+$ (calcd for $C_{19}H_{23}NO_3S$, 368.1291).

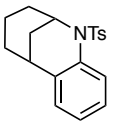
**Compound *cis*-51**




*cis*-**51**

A magnetically stirred solution of compound **49** (165 mg, 0.93 mmol) and pyridine (226 μL, 2.79 mmol) in dry dichloromethane (5 mL) maintained at 0 °C was treated, in portions, with *p*-toluenesulfonyl chloride (186 mg, 0.98 mmol) then warmed to 22 °C. After 19 h the reaction mixture was treated with heptane (20 mL) then concentrated under reduced pressure. This dilution/concentration process was repeated twice more in order to remove pyridine. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v diethyl ether/dichloromethane elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.2), compound *cis*-**51** (262 mg, 85%) as a clear, colorless oil
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 8.49 (broad s, 1H), 7.78–7.66 (m, 2H), 7.37 (dd, $J$ = 8.1 and 1.3 Hz, 1H), 7.24–7.17 (complex m, 3H), 7.09 (m, 1H), 7.02 (m, 1H), 4.46 (m, 1H), 3.15 (m, 1H), 2.65 (broad s, 1H), 2.37 (s, 3H), 2.17 (m, 1H), 1.91–1.76 (complex m, 3H), 1.76–1.65 (complex m, 1H), 1.57 (dd, $J$ = 14.6 and 7.0 Hz, 1H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 143.7, 137.2, 136.8, 134.5, 130.0, 129.6, 127.4, 127.1, 125.2, 122.6, 74.0, 41.6, 40.7, 36.4, 30.9, 21.6.
**IR** (ATR) $\nu_{max}$ 3503, 3270, 2955, 2870, 1492, 1326, 1154, 1090, 814, 756, 661 cm$^{-1}$.
**MS** (ESI, +ve) *m/z* 354 [$(M+Na)^+$, 100%].
**HRMS** *m/z* 354.1141 [$M+Na]^+$ (calcd for $C_{18}H_{21}NO_3S$, 354.1140).

**Compound 52**

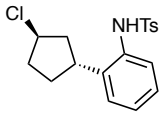



**52**

A magnetically stirred solution of compound *trans*-**50** (81.4 mg, 0.24 mmol) and triphenylphosphine (148 mg, 0.57 mmol) in dry tetrahydrofuran (5 mL) maintained at 0 °C was treated, dropwise, with DEAD (92 μL, 0.59 mmol). After 16 h the reaction mixture was concentrated under reduced pressure and the residue so obtained subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.3), compound **52** (69 mg, 89%) as a clear, colorless oil.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.87 (m, 1H), 7.62 (m, 2H), 7.21 (d, $J$ = 8.1 Hz, 2H), 7.09 (m, 1H), 6.99 (m, 1H), 6.94 (m, 1H), 4.80 (m, 1H), 2.93 (t, $J$ = 3.4 Hz, 1H), 2.36 (s, 3H), 2.18 (m, 1H), 1.78 (dt, $J$ = 12.9 and 2.6 Hz, 1H), 1.74–1.62 (complex m, 3H), 1.54–1.47 (complex m, 1H), 1.47–1.40 (complex m, 1H), 1.31–1.20 (complex m, 1H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 143.6, 138.5, 137.2, 130.7, 129.8, 129.0, 127.1, 126.7, 122.9, 119.5, 52.3, 33.9, 33.7(2), 33.6(9), 28.4, 21.6, 17.3.
**IR** (ATR) $\nu_{max}$ 2931, 2853, 1489, 1453, 1341, 1158, 1089, 871, 814, 674 cm$^{-1}$.
**MS** (ESI, +ve) *m/z* 677 [$(2M+Na)^+$, 78%], 350 [$(M+Na)^+$, 100], 328 [$(M+H)^+$, 5].

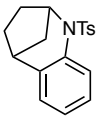
**HRMS** *m/z* 328.1361 $[M+H]^+$ (calcd for $C_{19}H_{21}NO_2S$, 328.1366).

***trans*-*N*-(2-(3-Chlorocyclopentyl)phenyl)-4-methylbenzenesulfonamide**




A magnetically stirred solution of compound *cis*-**51** (61 mg, 0.18 mmol) and triphenylphosphine (97 mg, 0.37 mmol) in dry dichloromethane (2 mL) maintained at 0 °C was treated, dropwise, with carbon tetrachloride (107 μL, 1.10 mmol) then warmed to 22 °C. After 15 h the reaction mixture was concentrated under reduced pressure and the residue so obtained subjected to flash column chromatography (silica, dichloromethane elution). After concentration of the appropriate fractions ($R_f$ = 0.4), the title halide (55.7 mg, 87%) was obtained as a clear, colorless oil.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.61 (d, $J$ = 8.2 Hz, 2H), 7.34 (dd, $J$ = 7.6 and 1.6 Hz, 1H), 7.23 (d, $J$ = 8.2 Hz, 2H), 7.20–7.10 (complex m, 3H), 6.73 (s, 1H), 4.49 (m, 1H), 3.38 (m, 1H), 2.39 (s, 3H), 2.28 (m, 1H), 2.07–1.95 (complex m, 2H), 1.87 (dd, $J$ = 9.0 and 4.2 Hz, 2H), 1.51–1.37 (complex m, 1H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 143.9, 139.9, 136.6, 133.7, 129.8, 127.5, 127.4, 127.0, 126.9, 126.7, 61.4, 45.0, 37.2, 36.4, 32.3, 21.6.
**IR** (ATR) $\nu_{max}$ 3267, 2972, 1492, 1399, 1328, 1156, 1091, 904, 813, 757, 732, 662 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 374 and 372 $[(M+Na)^+$, 38 and 100%].
**HRMS** *m/z* 350.0962 $[M+H]^+$ (calcd for $C_{18}H_{20}{}^{35}ClNO_2S$, 350.0976).

**Compound 53**




**53**

A magnetically stirred solution of the above-mentioned *trans*-*N*-(2-(3-chlorocyclopentyl)-phenyl)-4-methylbenzenesulfonamide (55.7 mg, 0.16 mmol) in dry methanol (16 mL) maintained at 55 °C was treated with potassium carbonate (110 mg, 0.80 mmol). After 18 h the reaction mixture was cooled to 22 °C then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, dichloromethane elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.6), compound **53** (49.6 mg, 99%) as a white, crystalline solid, m.p. =111 °C.
**$^1$H NMR** (400 MHz, $CDCl_3$) $\delta$ 7.85 (m, 1H), 7.65 (d, $J$ = 8.0 Hz, 2H), 7.21 (d, $J$ = 8.0 Hz, 2H), 7.11 (m, 1H), 6.94 (m, 2H), 5.08 (m, 1H), 2.99 (s, 1H), 2.37 (s, 3H), 2.17–2.04 (complex m, 1H), 1.99–1.89 (complex m, 1H), 1.87–1.74 (complex m, 2H), 1.48 (m, 2H).
**$^{13}$C NMR** (100 MHz, $CDCl_3$) $\delta$ 143.7, 137.1, 135.2, 134.8, 129.7, 127.9, 127.2, 127.1, 123.7, 121.1, 58.5, 41.4 35.9, 31.9, 31.4, 21.6.

**IR** (ATR) $\nu_{max}$ 2947, 2866, 1600, 1483, 1455, 1342, 1226, 1165, 1155, 1090, 812, 757, 680 $cm^{-1}$.
**MS** (ESI, +ve) *m/z* 336 $[(M+Na)^+$, 100%].
**HRMS** *m/z* 314.1196 $[M+H]^+$ (calcd for $C_{18}H_{19}NO_2S$, 314.1209).

## X-ray Crystallographic Studies

### *Crystallographic Data*

*Crystallographic Data for Compound* ***7***
$C_{12}H_{11}NO_3$, $M$ = 217.22, $T$ = 150 K, monoclinic, space group $P2_1/c$, $Z$ = 4, $a$ = 9.3274(2), $b$ = 14.6679(2), $c$ = 7.9674(1) Å; β = 107.026(2)°; $V$ = 1042.27(3) Å$^3$, $D_x$ = 1.384 g cm$^{-3}$, 2088 unique data ($2\theta_{max}$ = 147.2°), $R$ = 0.042 [for 1953 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.111 (all data), $S$ = 1.02.
*Crystallographic Data for Compound* ***19***
$C_{12}H_{12}N_2O_3$, $M$ = 232.24, $T$ = 150 K, monoclinic, space group $C2/c$, $Z$ = 8, $a$ = 7.87923(6), $b$ = 19.95864(19), $c$ = 13.93593(11) Å; β = 92.3804(7)°; $V$ = 2189.66(3) Å$^3$, $D_x$ = 1.409 g cm$^{-3}$, 2224 unique data ($2\theta_{max}$ = 147.2°), $R$ = 0.035 [for 2127 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.035 (all data), $S$ = 1.01.
*Crystallographic Data for Compound* ***39***
$C_{18}H_{22}N_4O_5$, $M$ = 374.40, $T$ = 150 K, triclinic, space group $P\bar{1}$, $Z$ = 2, $a$ = 7.0058(2), $b$ = 9.5456(3), $c$ = 13.6950(46) Å; α = 79.998(3)°, β = 83.227(3)°, γ = 85.094(2)°; $V$ = 893.65(5) Å$^3$, $D_x$ = 1.391 g cm$^{-3}$, 3597 unique data ($2\theta_{max}$ = 147.8°), $R$ = 0.035 [for 3346 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.102 (all data), $S$ = 0.97.
*Crystallographic Data for Compound* ***43***
$C_{13}H_{17}NO$, $M$ = 203.28, $T$ = 150 K, monoclinic, space group $P2_1/c$, $Z$ = 4, $a$ = 8.5291(3), $b$ = 18.2560(5), $c$ = 7.6050(3) Å; β = 112.547(4)°; $V$ = 1093.63(6) Å$^3$, $D_x$ = 1.235 g cm$^{-3}$, 2919 unique data ($2\theta_{max}$ = 60°), $R$ = 0.044 [for 2299 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.117 (all data), $S$ = 1.06.
*Crystallographic Data for Compound* ***45***
$C_{12}H_{25}NO$, $M$ = 189.25, $T$ = 150 K, orthorhombic, space group $Pccn$, $Z$ = 8, $a$ = 19.6584(2), $b$ = 13.0353(1), $c$ = 7.9633(1) Å; $V$ = 2040.62(4) Å$^3$, $D_x$ = 1.232 g cm$^{-3}$, 2048 unique data ($2\theta_{max}$ = 147.4°), $R$ = 0.038 [for 1926 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.105 (all data), $S$ = 1.06.
*Crystallographic Data for Compound* trans-***50***
$C_{19}H_{23}NO_3S$, $M$ = 345.44, $T$ = 150 K, triclinic, space group $P\bar{1}$, $Z$ = 4, $a$ = 9.4185(4), $b$ = 12.9752(7), $c$ = 16.0422(8) Å; α = 70.958(5)°, β = 77.623(4)°, γ = 78.202(4)°; $V$ = 1790.80(16) Å$^3$, $D_x$ = 1.281 g cm$^{-3}$, 7108 unique data ($2\theta_{max}$ = 147.6°), $R$ = 0.048 [for 6495 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.048 (all data), $S$ = 1.05.

### *Structure Determinations*

The image for compound **43** was measured on a diffractometer (Mo Kα, graphite monochromator, λ = 0.71073 Å) fitted with an area detector and the data extracted using the DENZO/Scalepack package.[16] Images for compounds **7**, **19**, **39**, **45**, and *trans*-**50** were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) fitted with an area detector and the data extracted using the CrysAlis package.[17] The structure solutions for all six compounds were either solved by direct methods (SIR92) and refined using the CRYSTALS program package, or solved with ShelXT[18] and refined using ShelXL[19] in OLEX2.[20] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1832167, 1832168, 1832169, 1832170, 1832171 and 1832172). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

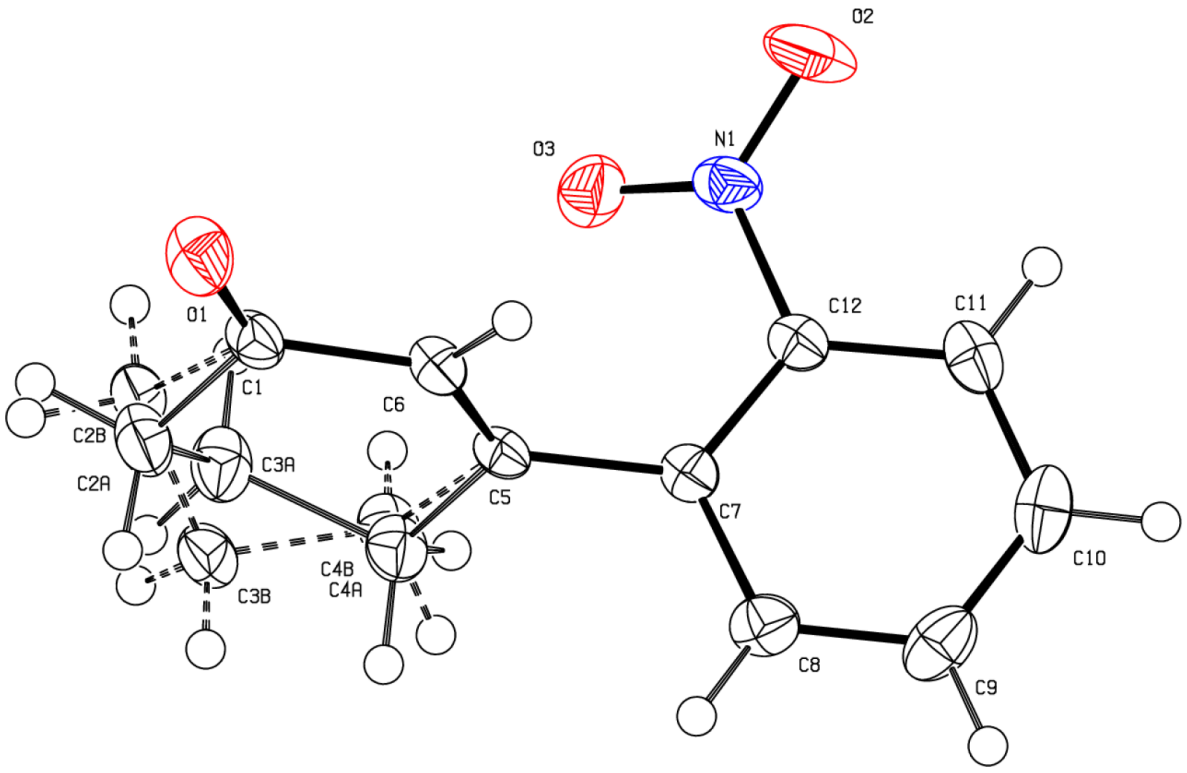



**Figure S1**: Structure of compound **7** (CCDC 1832167). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

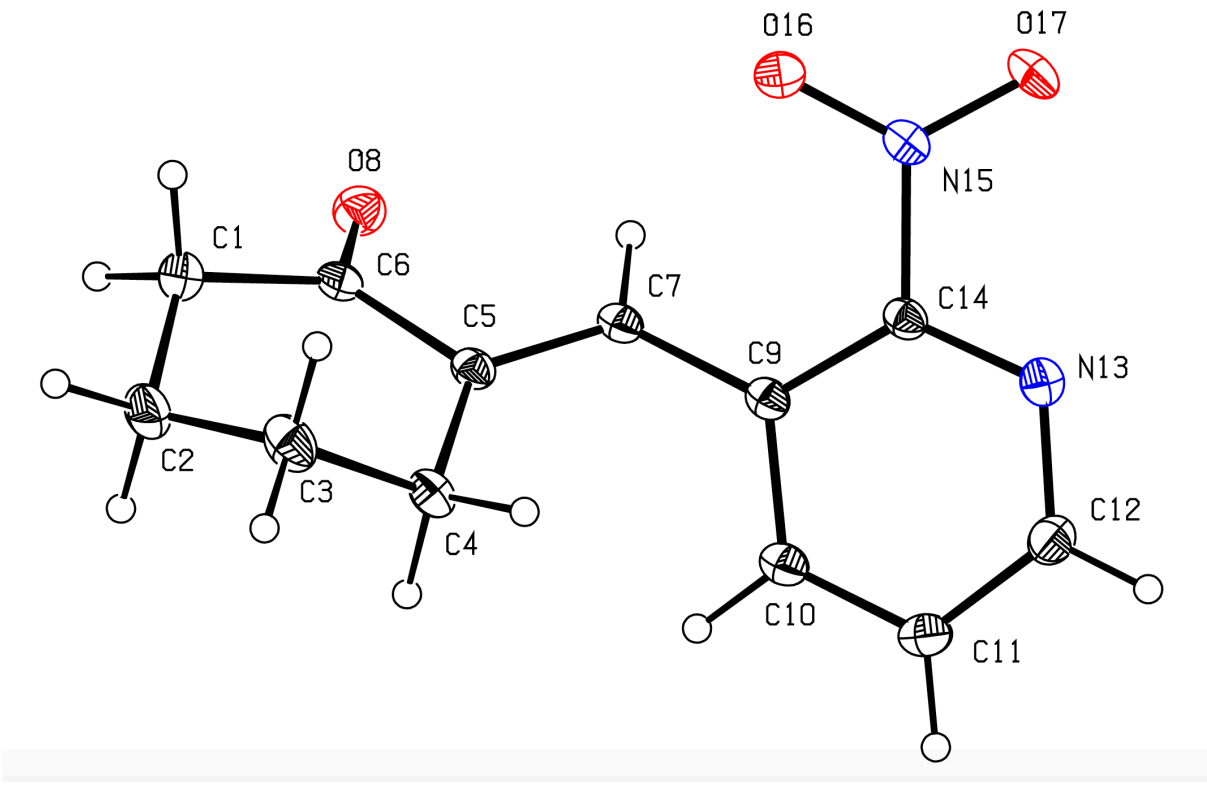



**Figure S2**: Structure of compound **19** (CCDC 1832168). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

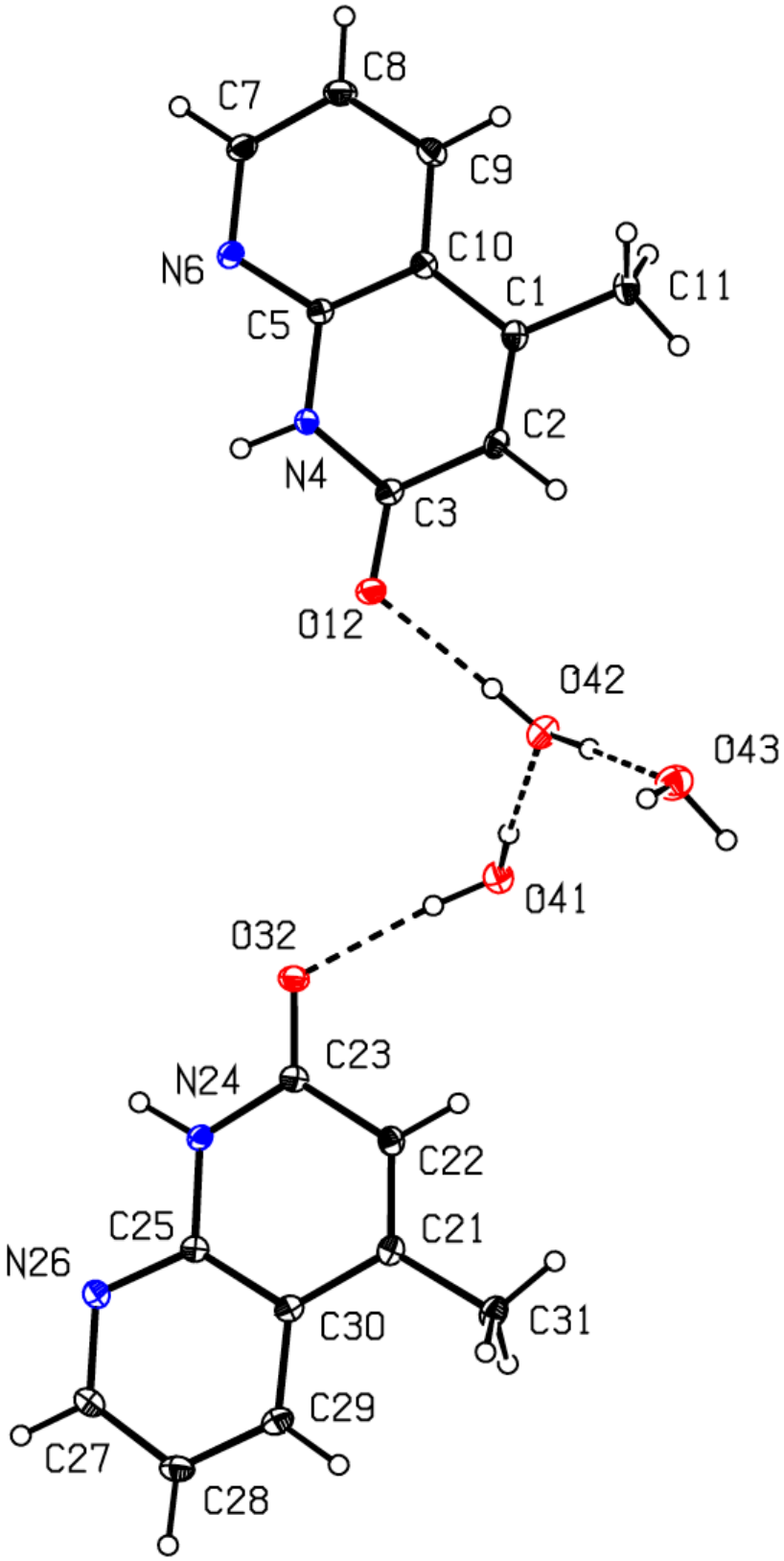



**Figure S3**: Structure of compound **39** (CCDC 1832169) and associated water molecules. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

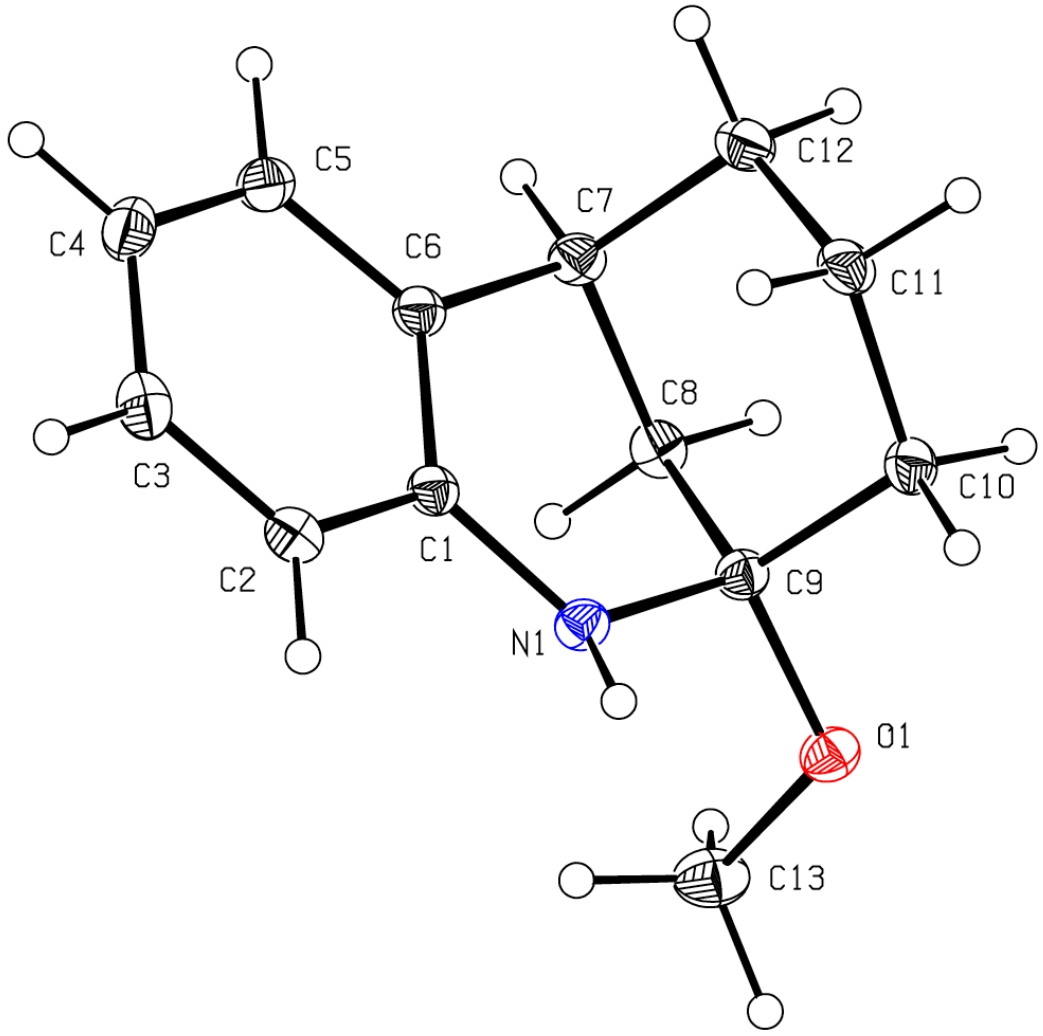



**Figure S4**: Structure of compound **43** (CCDC 1832170). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

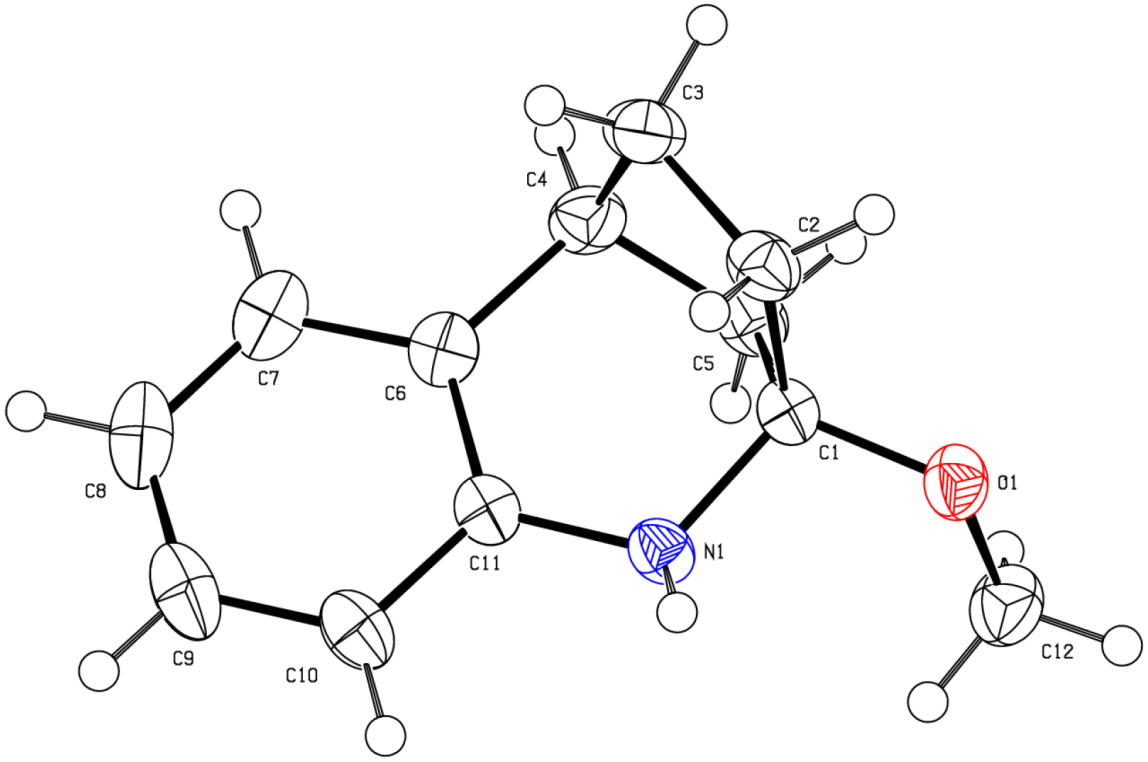



**Figure S5**: Structure of compound **45** (CCDC 1832171). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

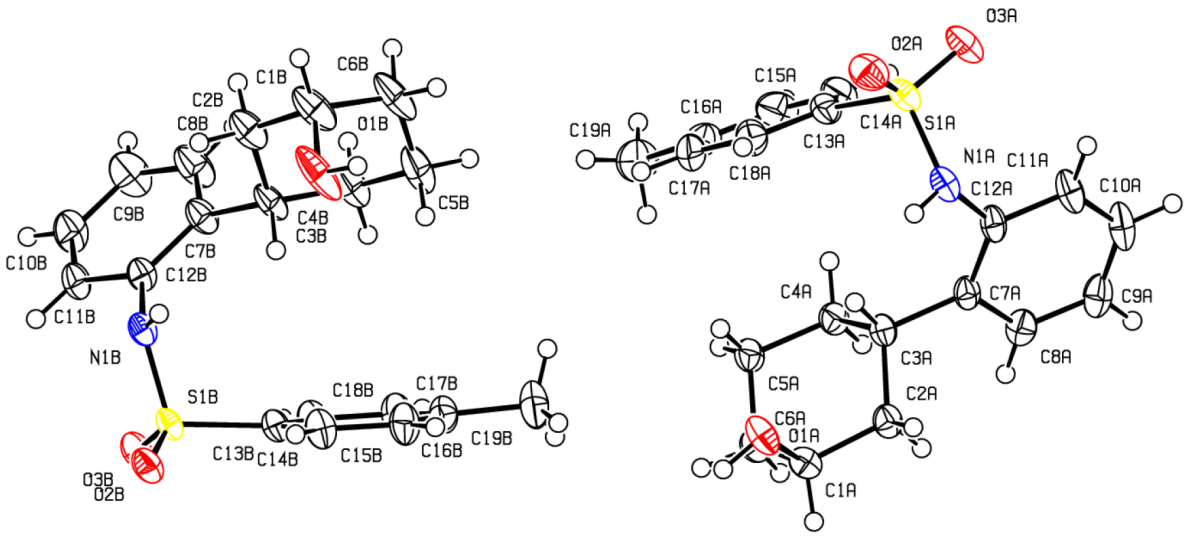



**Figure S6**: Structure of compound *trans*-**50** (CCDC 1832171). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

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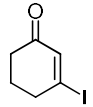
400 MHz $^{1}$H NMR Spectrum of Compound **5** (X = I)
(recorded in $CDCl_3$)



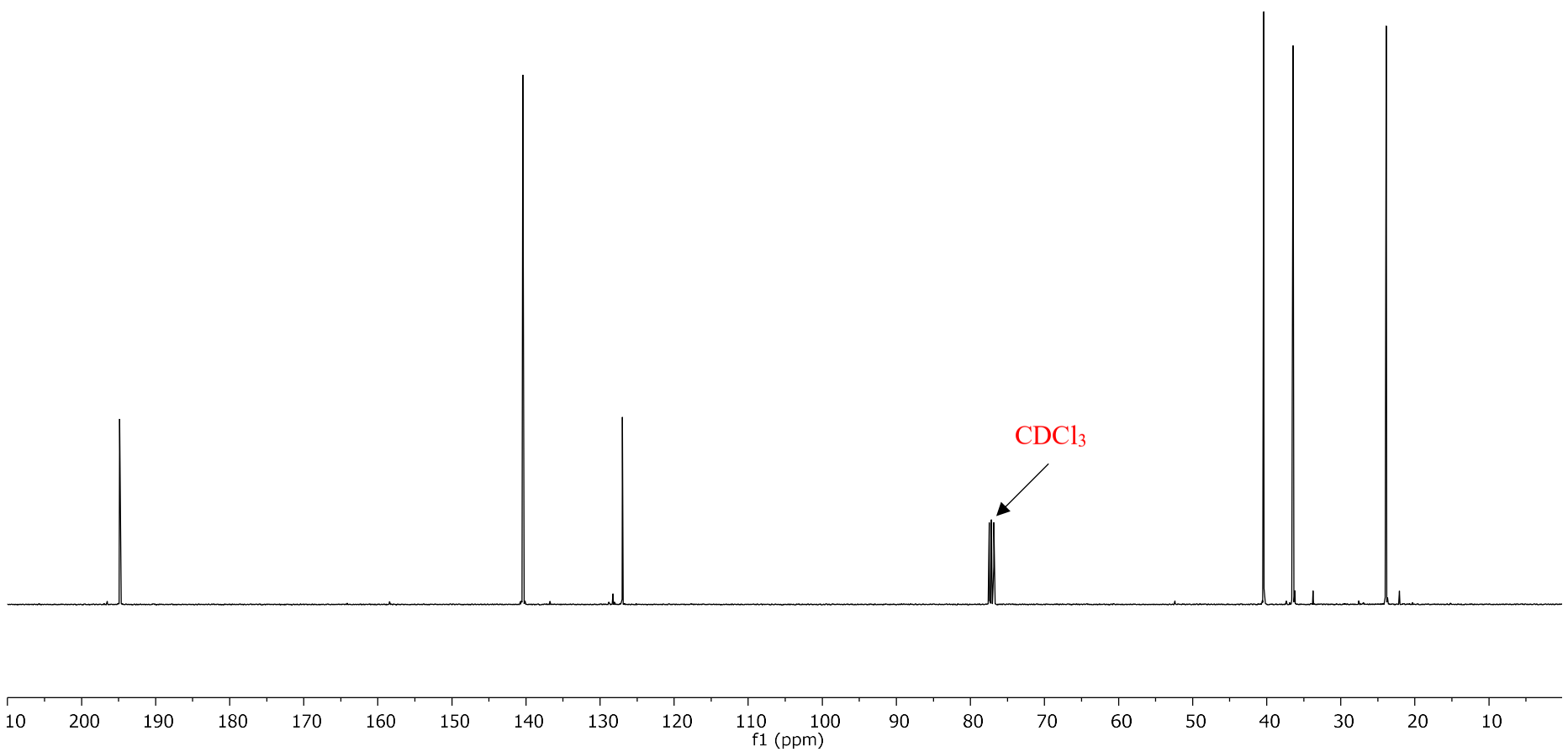

**5** (X = I)



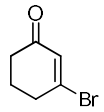

75

100 MHz $^{13}C$ NMR Spectrum of Compound **5** (X = I)
(recorded in $CDCl_3$)


**5** (X = I)



400 MHz $^{1}$H NMR Spectrum of Compound **5** (X =Br)
(recorded in $CDCl_3$)

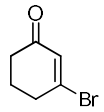



**5** (X = Br)




77

100 MHz $^{13}C$ NMR Spectrum of Compound **5** (X = Br)
(recorded in $CDCl_3$)

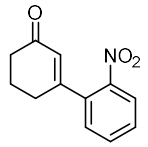



**5** (X = Br)




78

400 MHz $^{1}$H NMR Spectrum of Compound **7**
(recorded in $CDCl_3$)

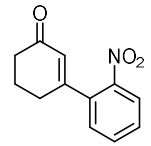



**7**



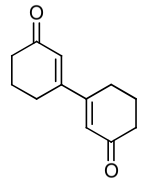

79

100 MHz $^{13}C$ NMR Spectrum of Compound **7**
(recorded in $CDCl_3$)




**7**

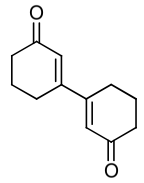
400 MHz $^{1}$H NMR Spectrum of
**[1,1'-Bi(cyclohexane)]-1,1'-diene-3,3'-dione**
(recorded in $CDCl_3$)



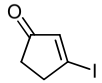



81

100 MHz $^{13}C$ NMR Spectrum of
**[1,1'-Bi(cyclohexane)]-1,1'-diene-3,3'-dione**
(recorded in $CDCl_3$)



400 MHz $^{1}$H NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)

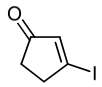


**8**




83

100 MHz $^{13}C$ NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)

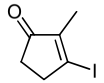


**8**



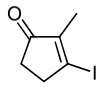

84

400 MHz $^{1}$H NMR Spectrum of Compound **9**
(recorded in $CDCl_3$)



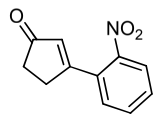
**9**

100 MHz $^{13}C$ NMR Spectrum of Compound **9**
(recorded in $CDCl_3$)



**9**

400 MHz $^{1}$H NMR Spectrum of Compound **10**
(recorded in $CDCl_3$)

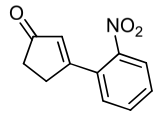



**10**




87

100 MHz $^{13}C$ NMR Spectrum of Compound **10**
(recorded in $CDCl_3$)

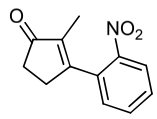



**10**



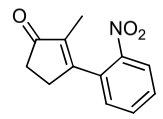

88

400 MHz $^{1}$H NMR Spectrum of Compound **11**
(recorded in $CDCl_3$)



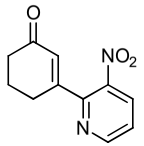

**11**

100 MHz $^{13}C$ NMR Spectrum of Compound **11**
(recorded in $CDCl_3$)

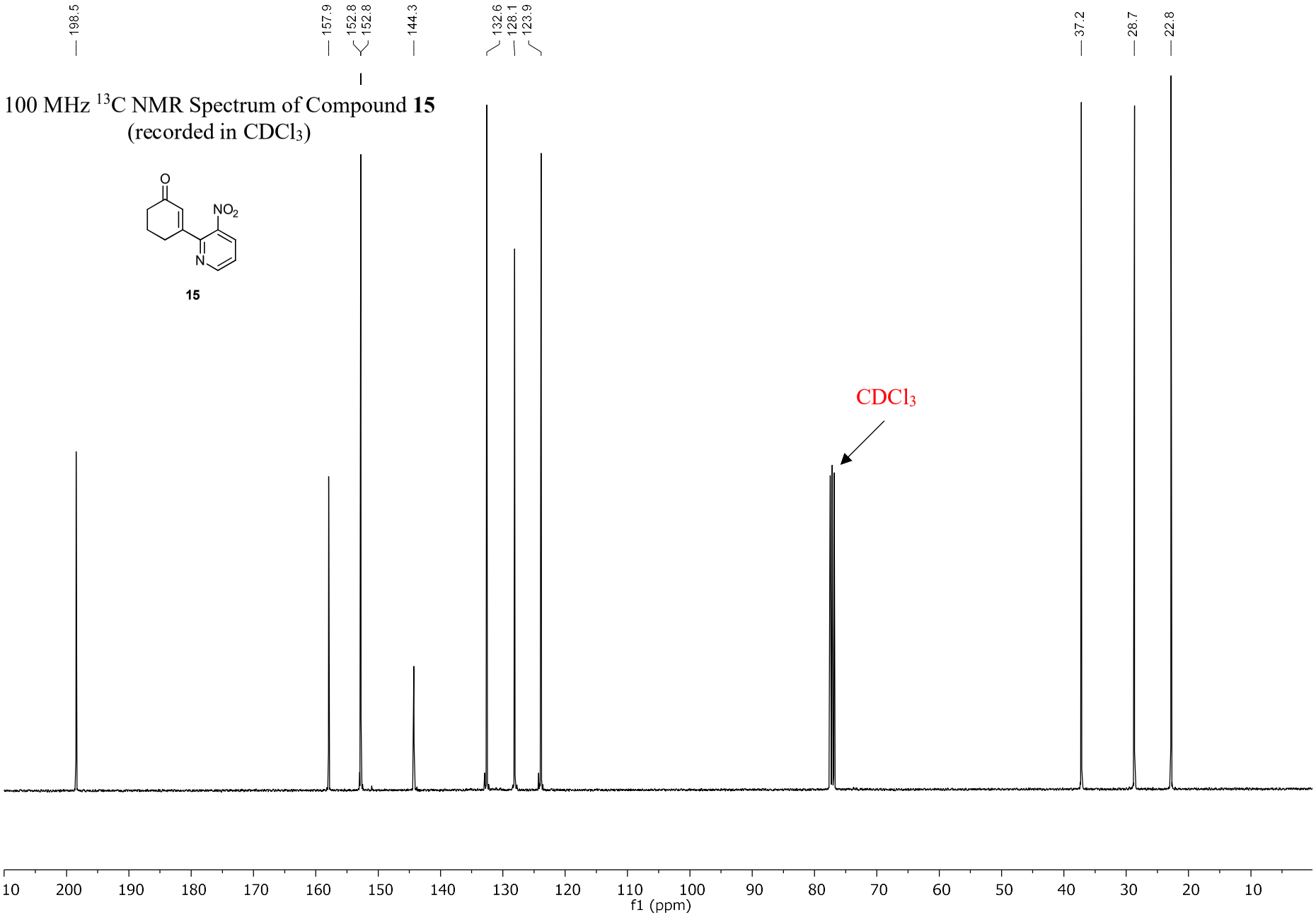



**11**

400 MHz $^{1}$H NMR Spectrum of Compound **15**
(recorded in $CDCl_3$)

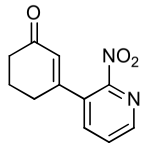



**15**

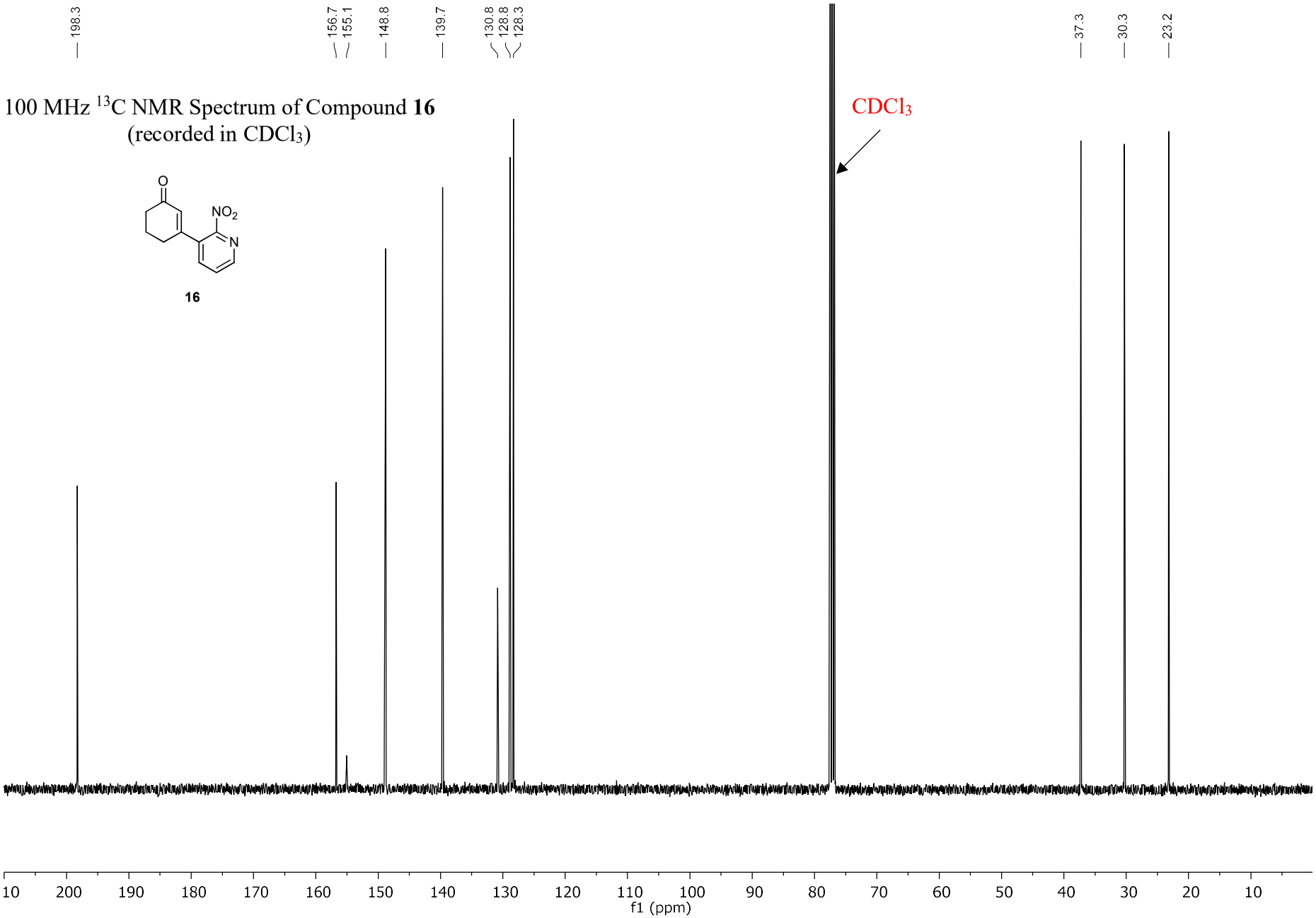

198.5
157.9
152.8
152.8
144.3
132.6
128.1
123.9
37.2
28.7
22.8
100 MHz $^{13}$C NMR Spectrum of Compound **15**
(recorded in $CDCl_3$)
O
$NO_2$
N
15
$CDCl_3$
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

92

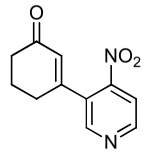
400 MHz $^{1}$H NMR Spectrum of Compound **16**
(recorded in $CDCl_3$)



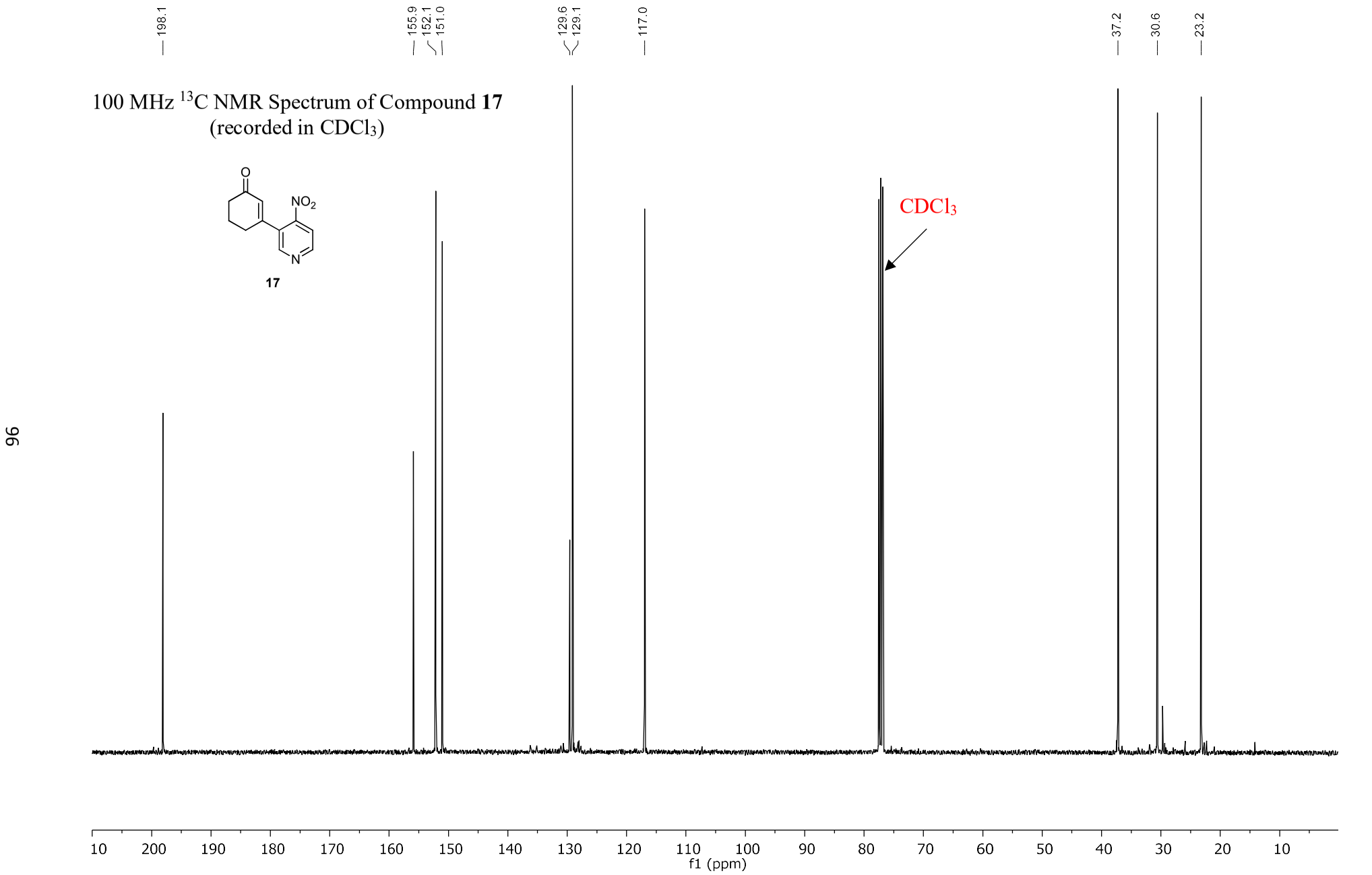

**16**


198.3
156.7
155.1
148.8
139.7
130.8
128.8
128.3
37.3
30.3
23.2
100 MHz $^{13}$C NMR Spectrum of Compound **16**
(recorded in $CDCl_3$)
$CDCl_3$
O
$NO_2$
N
**16**
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

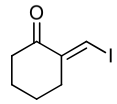
400 MHz $^{1}$H NMR Spectrum of Compound **17**
(recorded in $CDCl_3$)



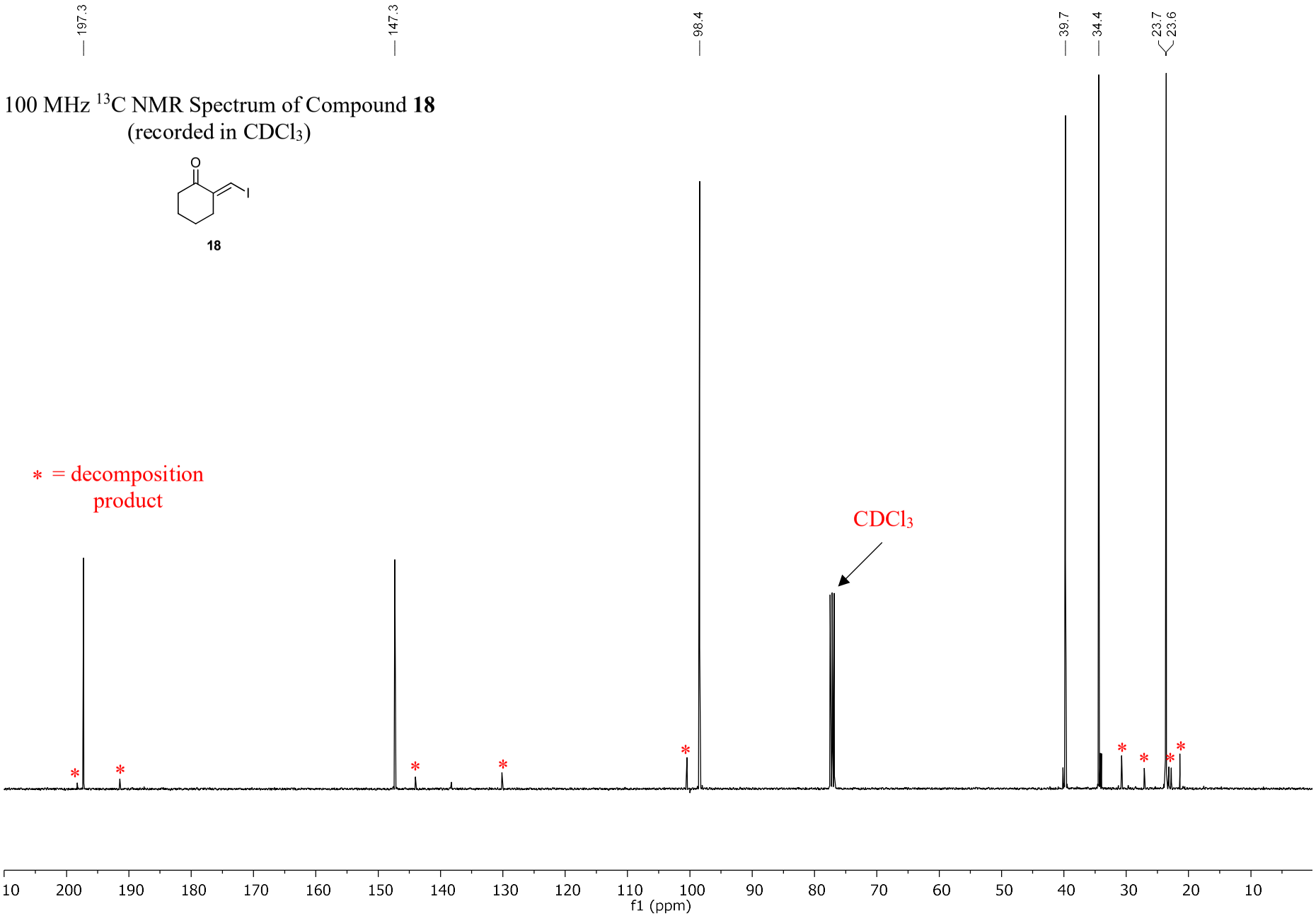

**17**


198.1
155.9
152.1
151.0
129.6
129.1
117.0
37.2
30.6
23.2
100 MHz $^{13}$C NMR Spectrum of Compound **17**
(recorded in $CDCl_3$)
O
$NO_2$
N
**17**
$CDCl_3$
96
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

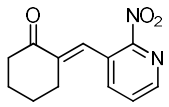
400 MHz $^{1}$H NMR Spectrum of Compound **18**
(recorded in $CDCl_3$)



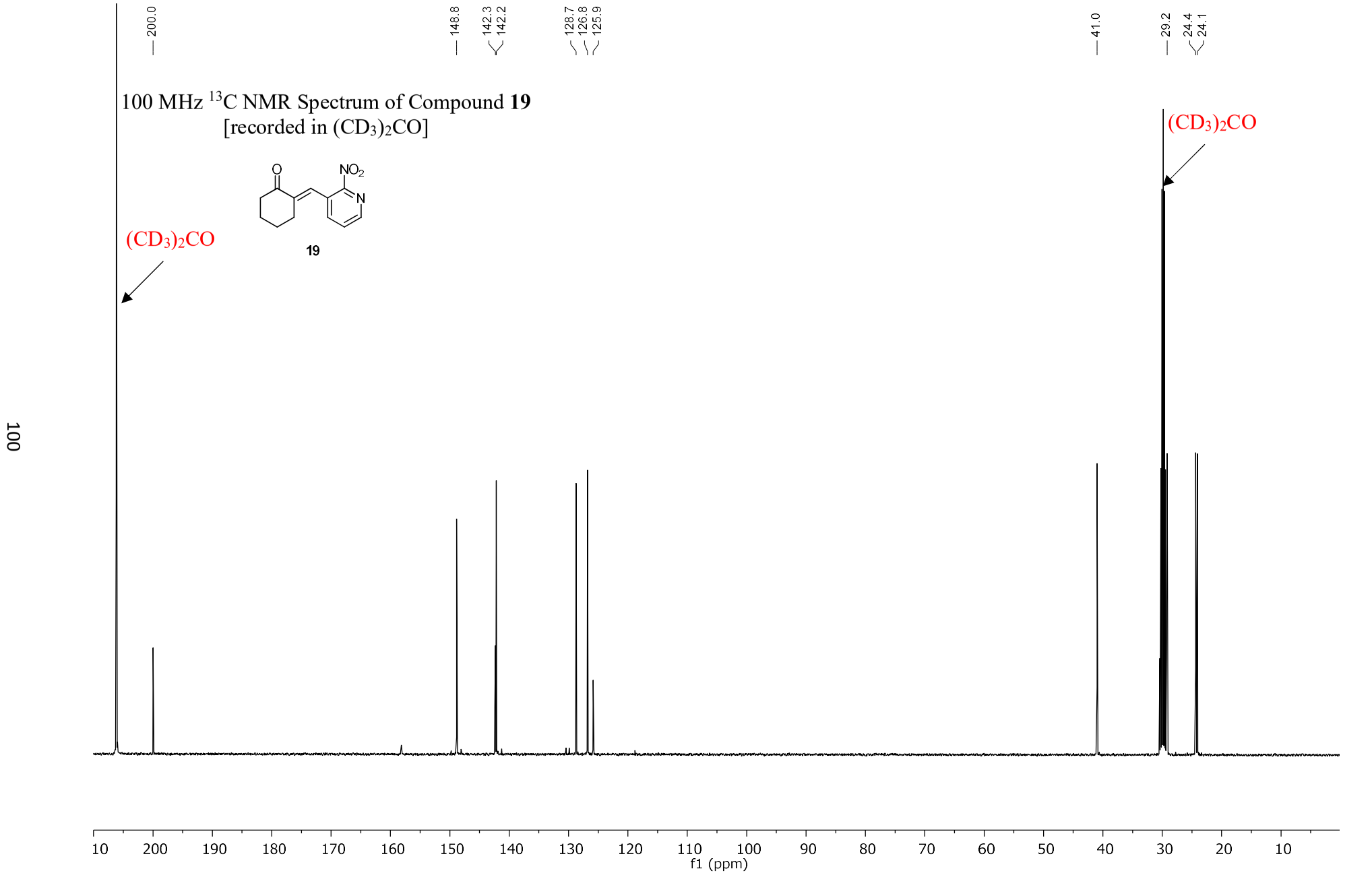
**18**

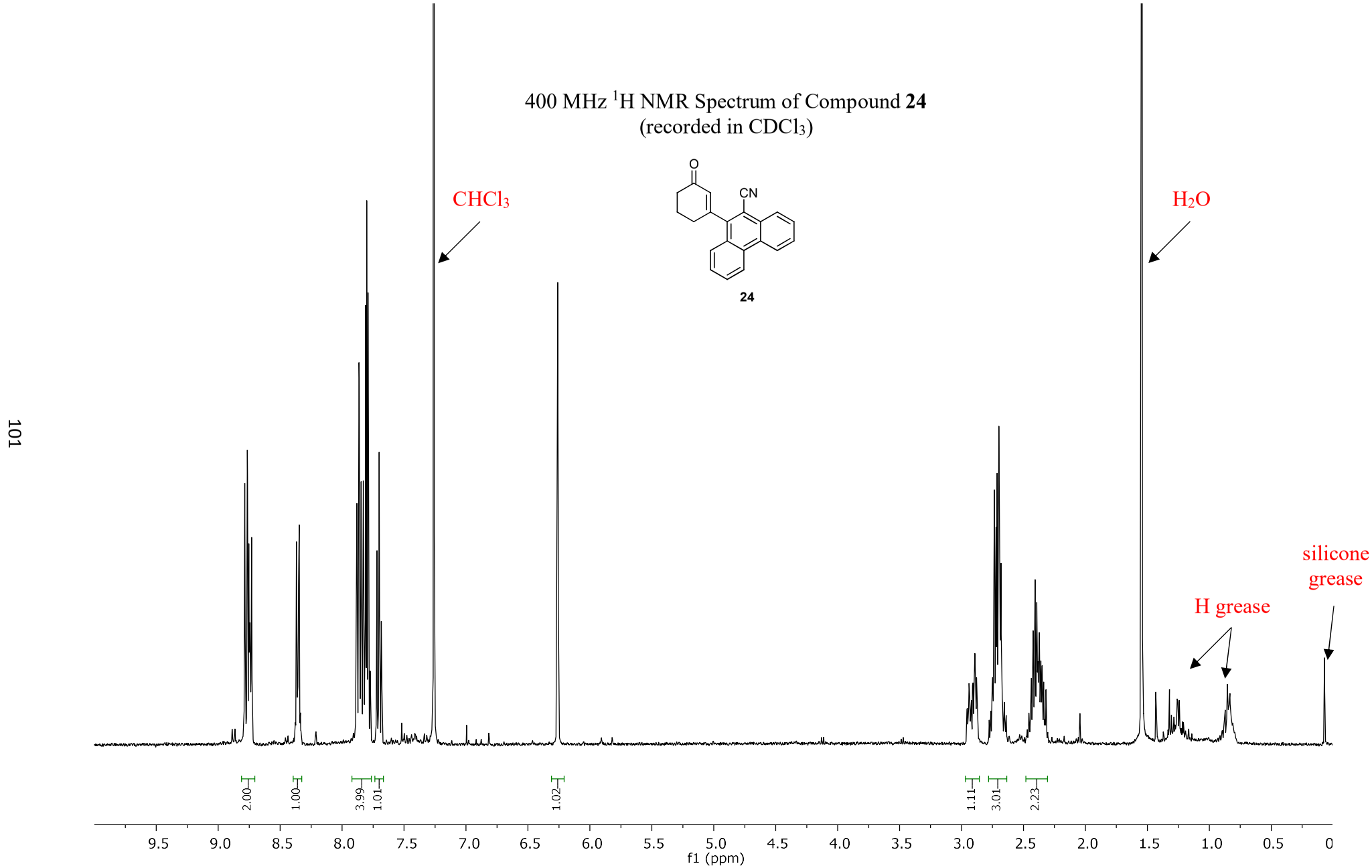

197.3
147.3
98.4
39.7
34.4
23.7
23.6
100 MHz $^{13}$C NMR Spectrum of Compound **18**
(recorded in $CDCl_3$)
O
I
18
* = decomposition product
$CDCl_3$
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

400 MHz $^{1}$H NMR Spectrum of Compound **19**
[recorded in $(CD_3)_2CO$]



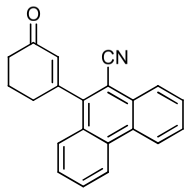

**19**


200.0
148.8
142.3
142.2
128.7
126.8
125.9
41.0
29.2
24.4
24.1
100 MHz $^{13}$C NMR Spectrum of Compound **19**
[recorded in $(CD_3)_2CO$]
$(CD_3)_2CO$
$(CD_3)_2CO$
O
$NO_2$
N
**19**
100
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


400 MHz $^{1}$H NMR Spectrum of Compound **24**
(recorded in $CDCl_3$)
O
CN
24
$CHCl_3$
$H_2O$
H grease
silicone
grease
2.00
1.00
3.99
1.01
1.02
1.11
3.01
2.23
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

101

100 MHz $^{13}C$ NMR Spectrum of Compound **24**
(recorded in $CDCl_3$)



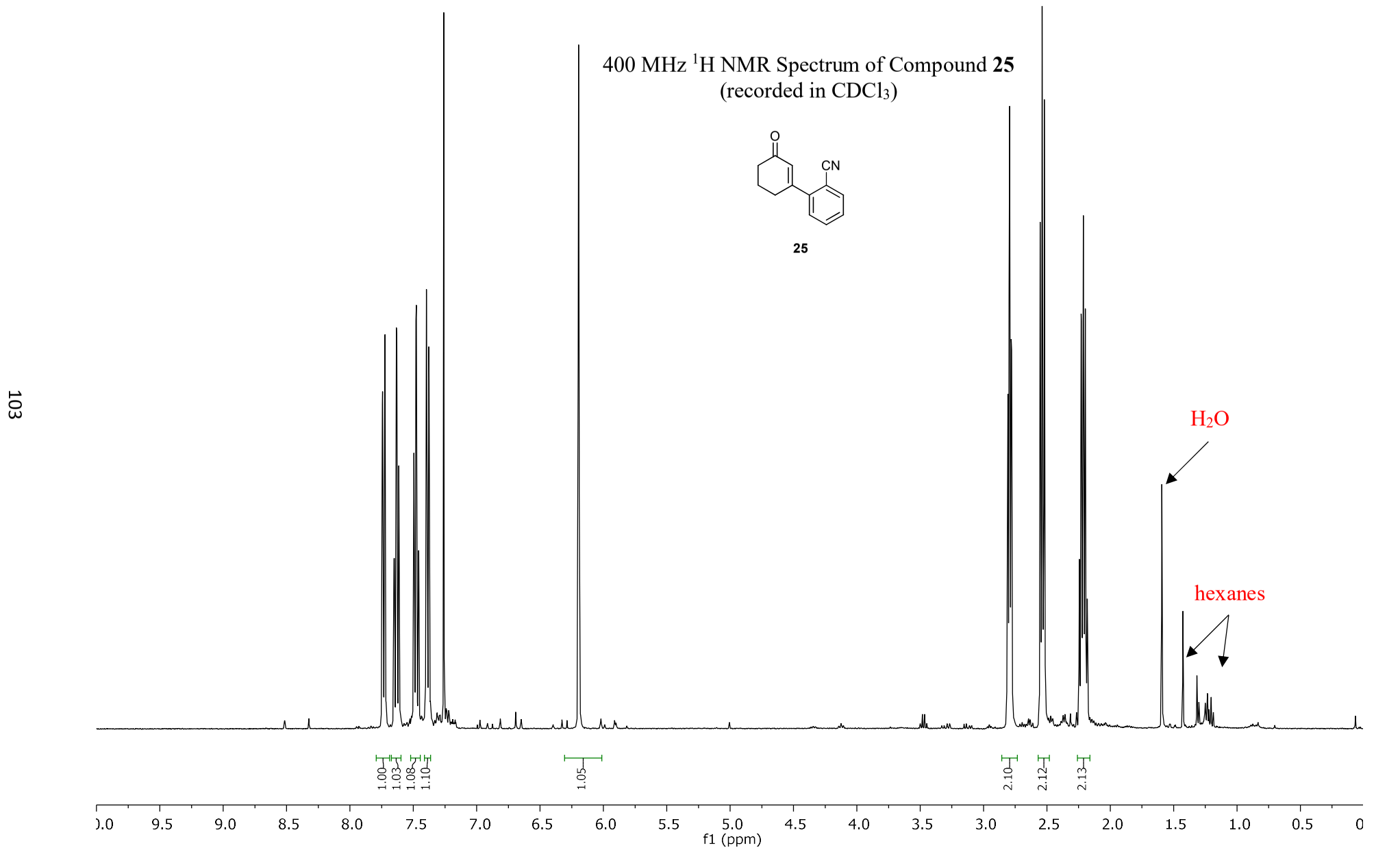

**24**

$CDCl_3$

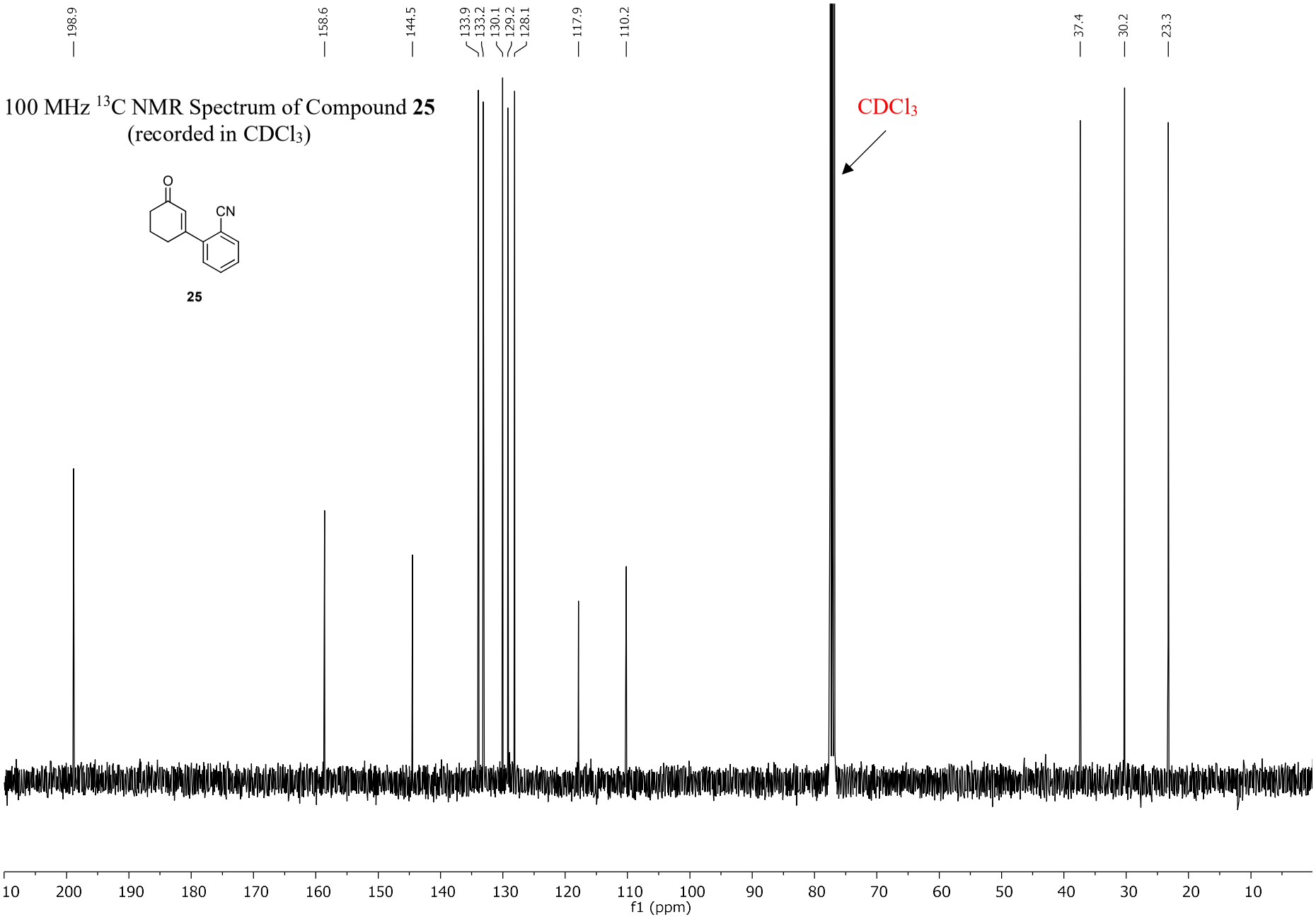
198.6 158.6 145.9 132.0 131.6 130.1 129.8 128.7 128.7 128.4 128.1 127.6 127.1 126.6 123.5 123.1 116.6 107.1 37.6 31.3 23.4

102

10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


400 MHz $^1$H NMR Spectrum of Compound **25**
(recorded in $CDCl_3$)
O
CN
25
$H_2O$
hexanes
1.00
1.03
1.08
1.10
1.05
2.10
2.12
2.13
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

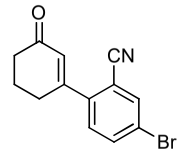
103




100 MHz $^{13}$C NMR Spectrum of Compound **25**
(recorded in $CDCl_3$)

104

400 MHz $^{1}$H NMR Spectrum of Compound **26**
(recorded in $CDCl_3$)




**26**

* = impurity

$Et_2O$

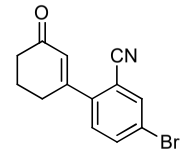
$Et_2O$

$H_2O$

1.00 1.10 1.05 1.35 3.04 3.03 3.12

f1 (ppm)

100 MHz $^{13}C$ NMR Spectrum of Compound **26**
(recorded in $CDCl_3$)




**26**

198.5 157.3 143.3 136.4 136.3 130.3 129.6 123.0 116.5 112.0 37.3 30.1 23.2

$CDCl_3$

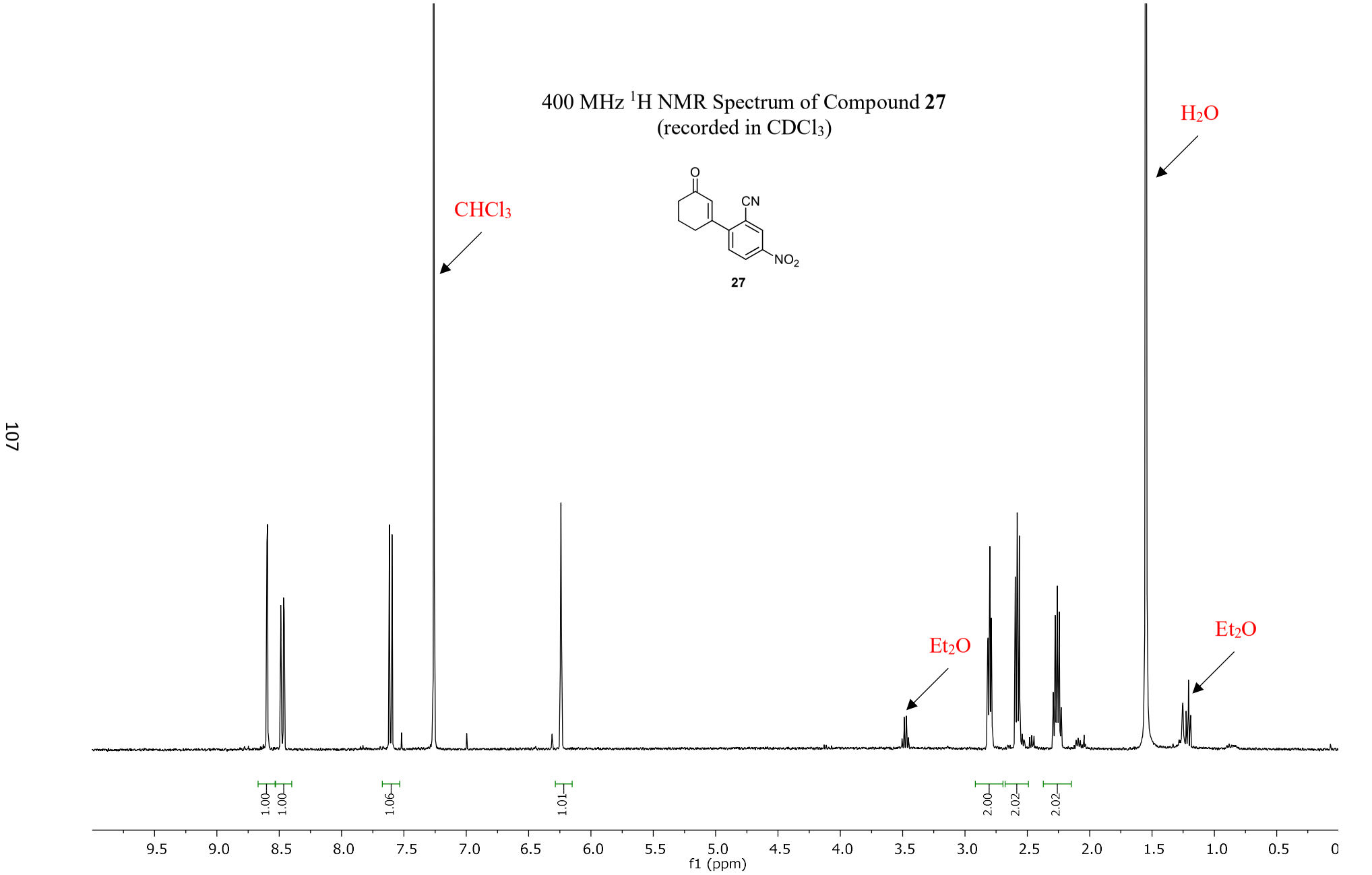
$Et_2O$

$Et_2O$

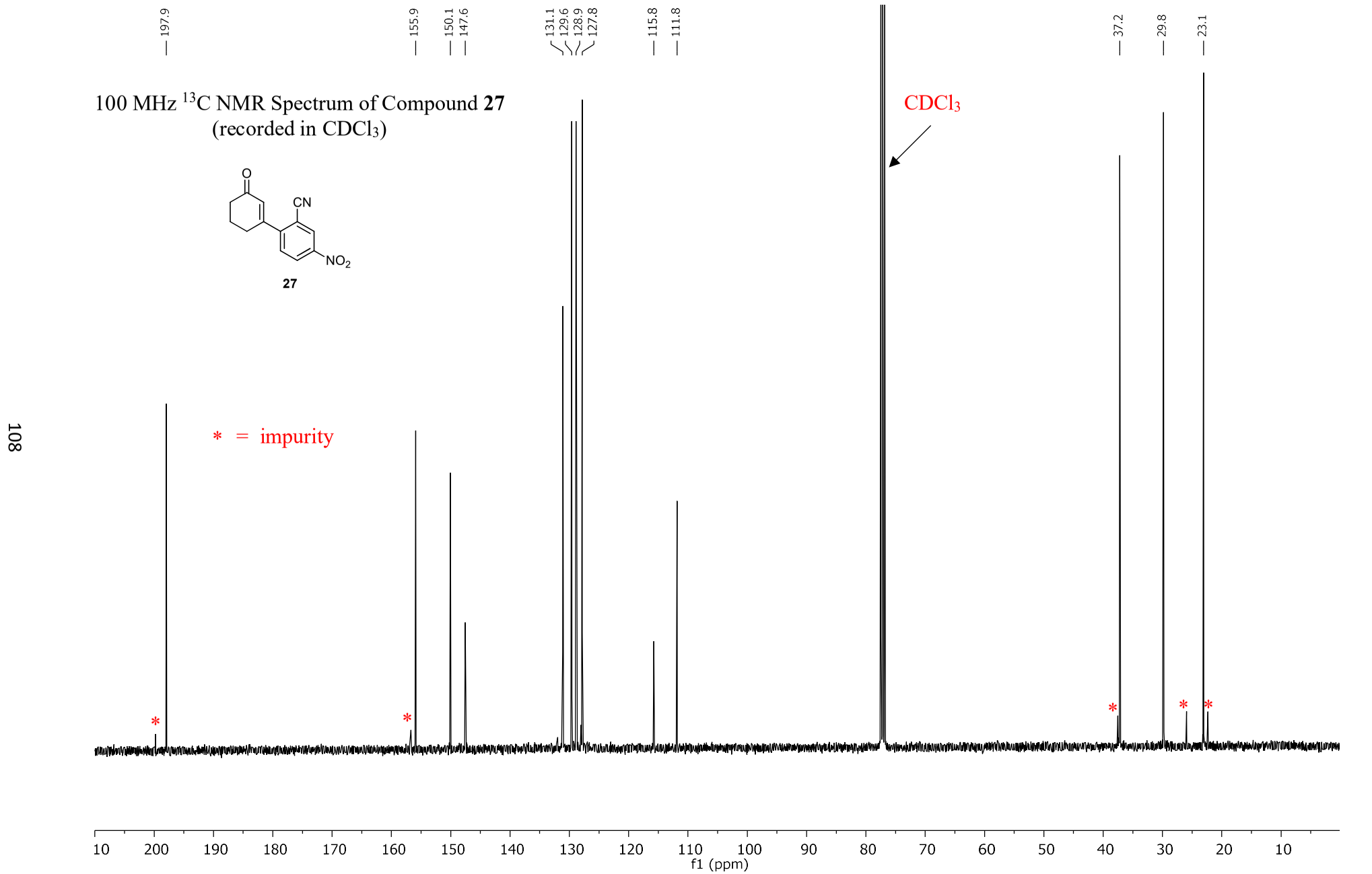
* = impurity

f1 (ppm)

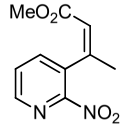
106


400 MHz $^{1}$H NMR Spectrum of Compound **27**
(recorded in $CDCl_3$)
O
CN
$NO_2$
**27**
$CHCl_3$
$H_2O$
$Et_2O$
$Et_2O$
1.00
1.00
1.06
1.01
2.00
2.02
2.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

107

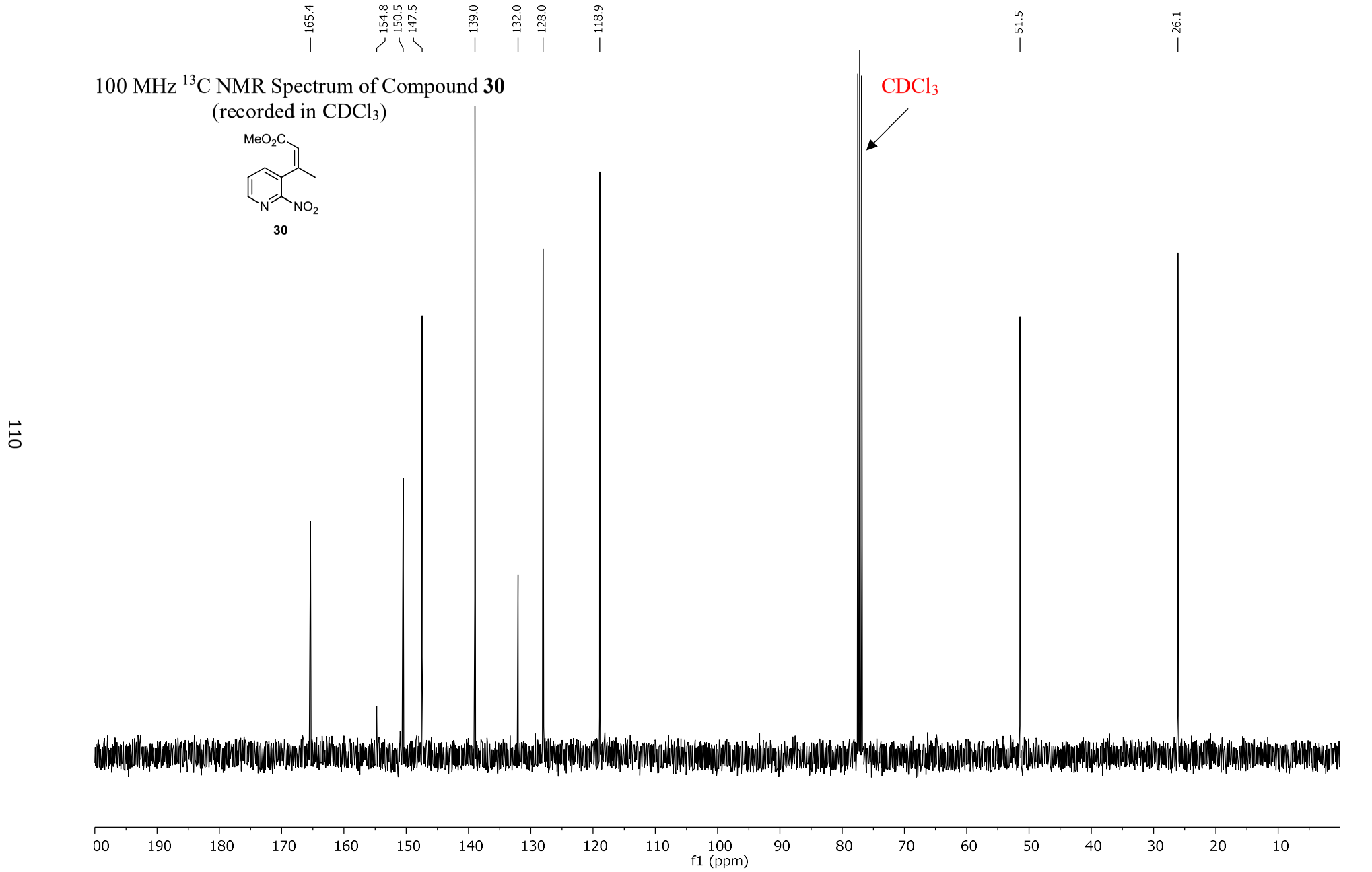

197.9
155.9
150.1
147.6
131.1
129.6
128.9
127.8
115.8
111.8
37.2
29.8
23.1
100 MHz $^{13}$C NMR Spectrum of Compound **27**
(recorded in $CDCl_3$)
O
CN
$NO_2$
**27**
$CDCl_3$
* = impurity
*
*
*
*
*
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

400 MHz $^{1}$H NMR Spectrum of Compound **30**
(recorded in $CDCl_3$)

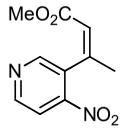



**30**

109


100 MHz $^{13}$C NMR Spectrum of Compound **30**
(recorded in $CDCl_3$)
$MeO_2C$
$NO_2$
N
**30**
$CDCl_3$
165.4
154.8
150.5
147.5
139.0
132.0
128.0
118.9
51.5
26.1
110
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

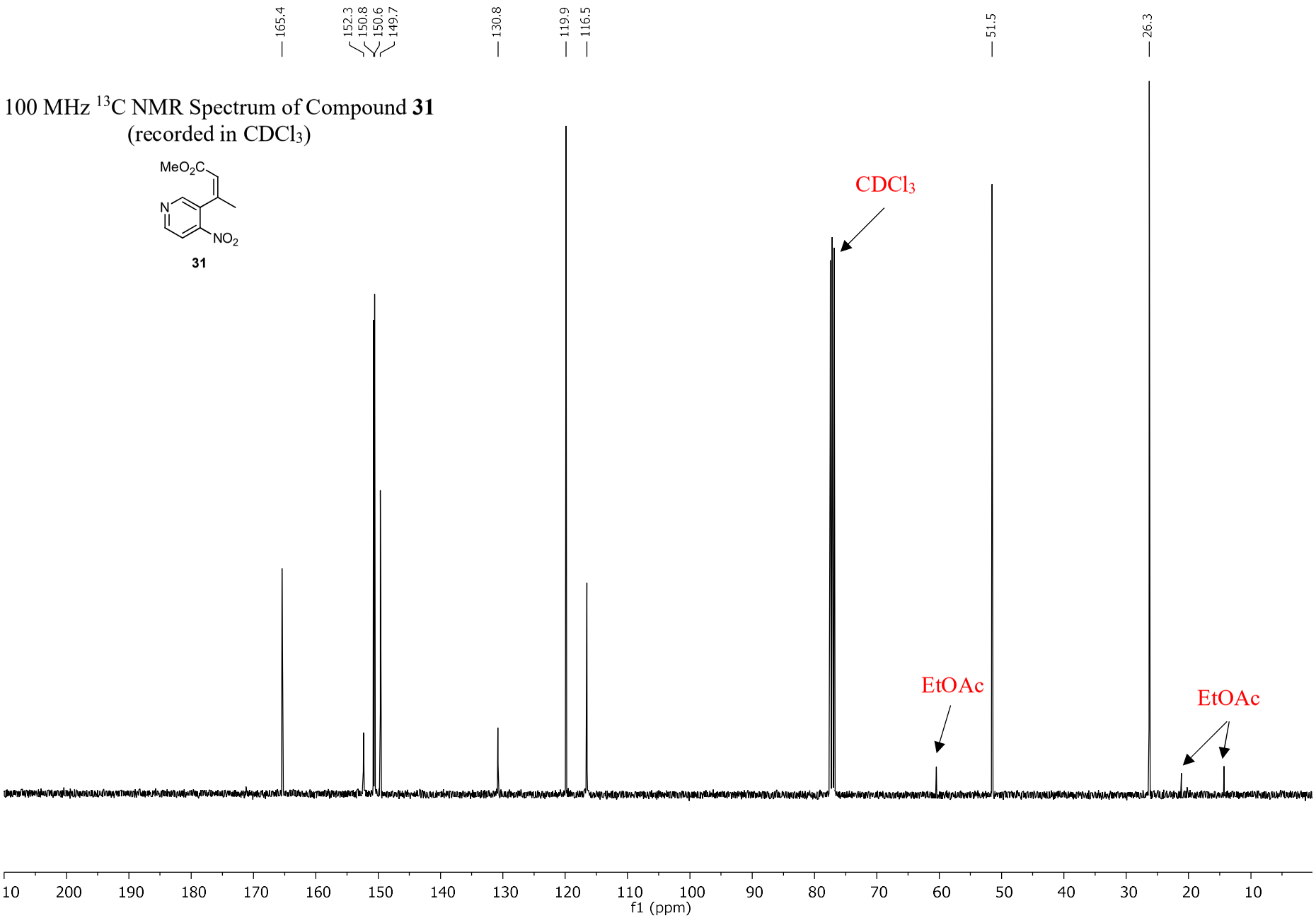
400 MHz $^{1}$H NMR Spectrum of Compound **31**
(recorded in $CDCl_3$)



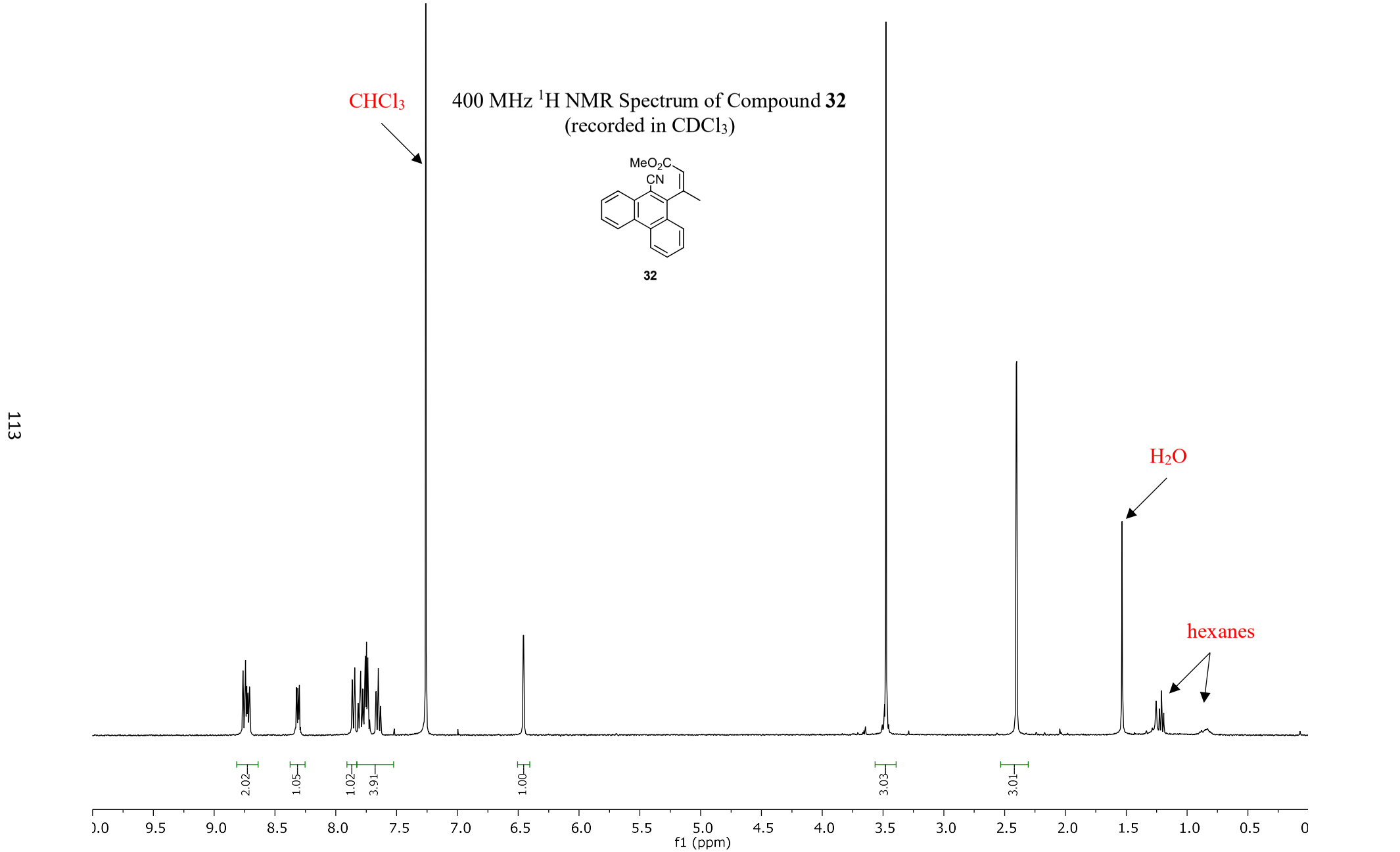

**31**

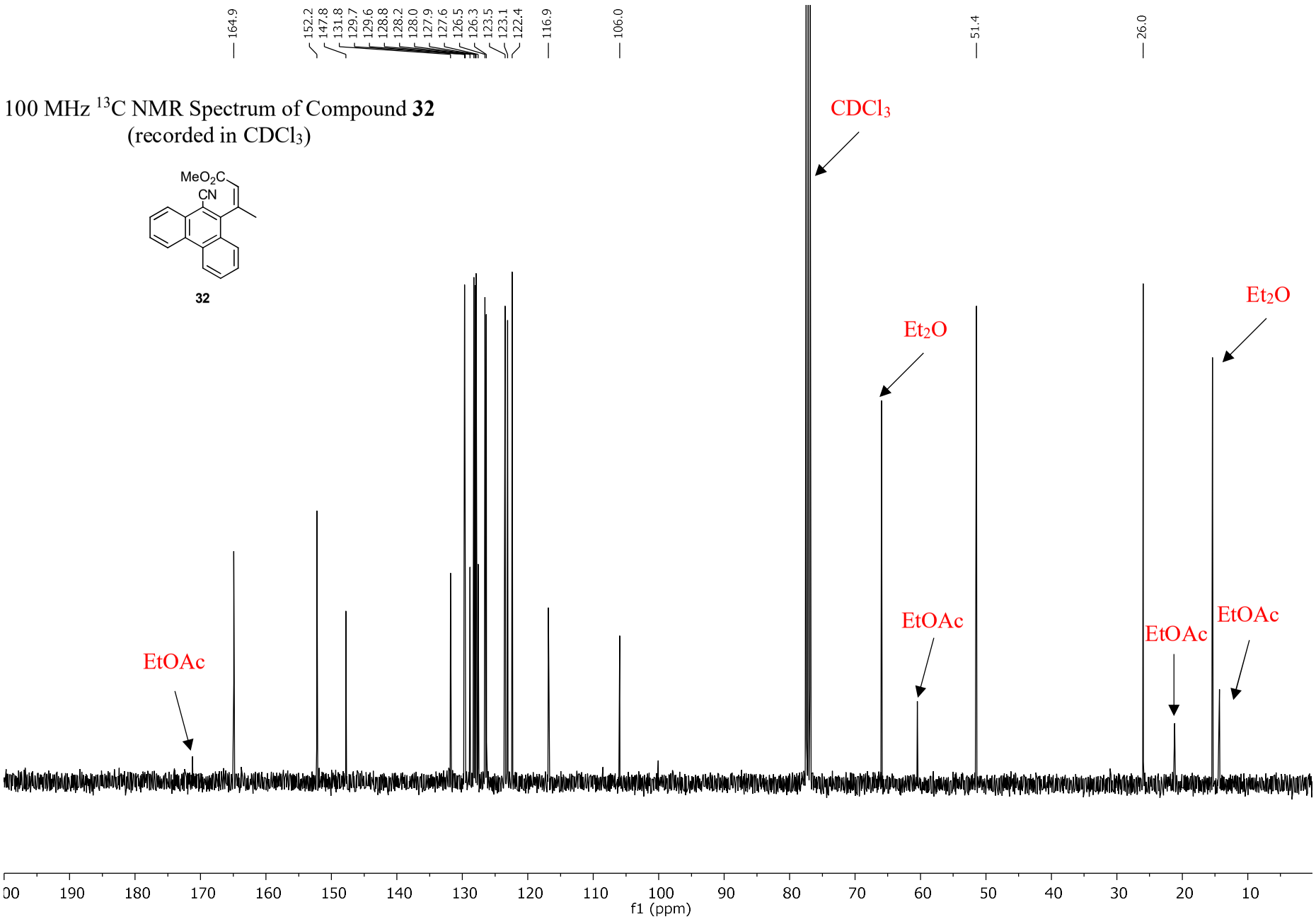



111

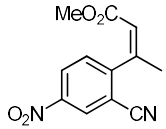

100 MHz $^{13}$C NMR Spectrum of Compound **31**
(recorded in $CDCl_3$)
$MeO_2C$
N
$NO_2$
31
165.4
152.3
150.8
150.6
149.7
130.8
119.9
116.5
51.5
26.3
$CDCl_3$
EtOAc
EtOAc
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

112

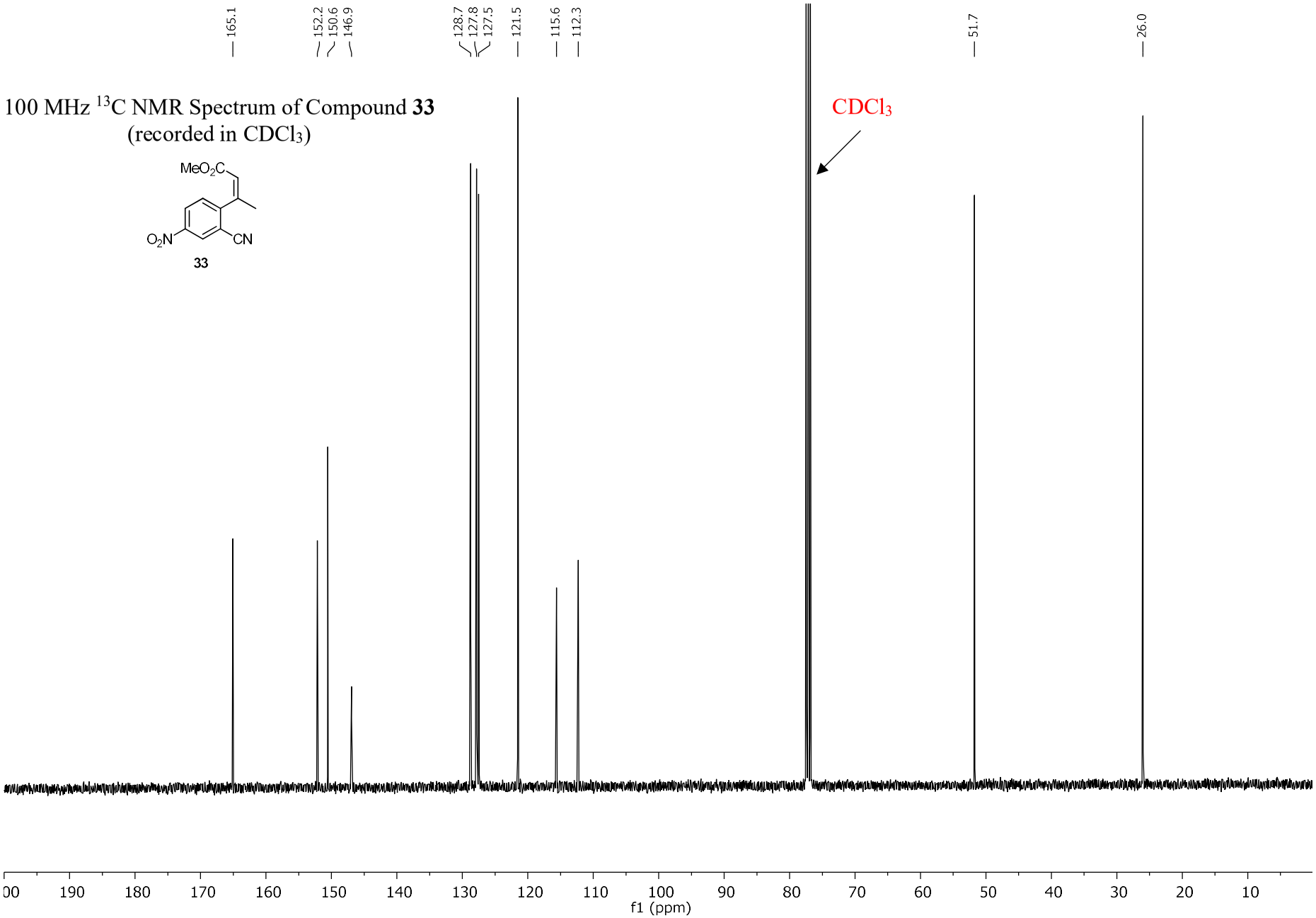

CHCl3
400 MHz 1H NMR Spectrum of Compound 32
(recorded in CDCl3)
MeO2C
CN
32
H2O
hexanes
2.02
1.05
1.02
3.91
1.00
3.03
3.01
f1 (ppm)


100 MHz $^{13}$C NMR Spectrum of Compound **32**
(recorded in $CDCl_3$)
MeO2C
CN
32
164.9
152.2
147.8
131.8
129.7
129.6
128.8
128.2
128.0
127.9
127.6
126.5
126.3
123.5
123.1
122.4
116.9
106.0
51.4
26.0
CDCl3
Et2O
Et2O
EtOAc
EtOAc
EtOAc
EtOAc
EtOAc
f1 (ppm)

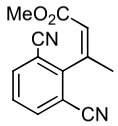
400 MHz $^{1}$H NMR Spectrum of Compound **33**
(recorded in $CDCl_3$)



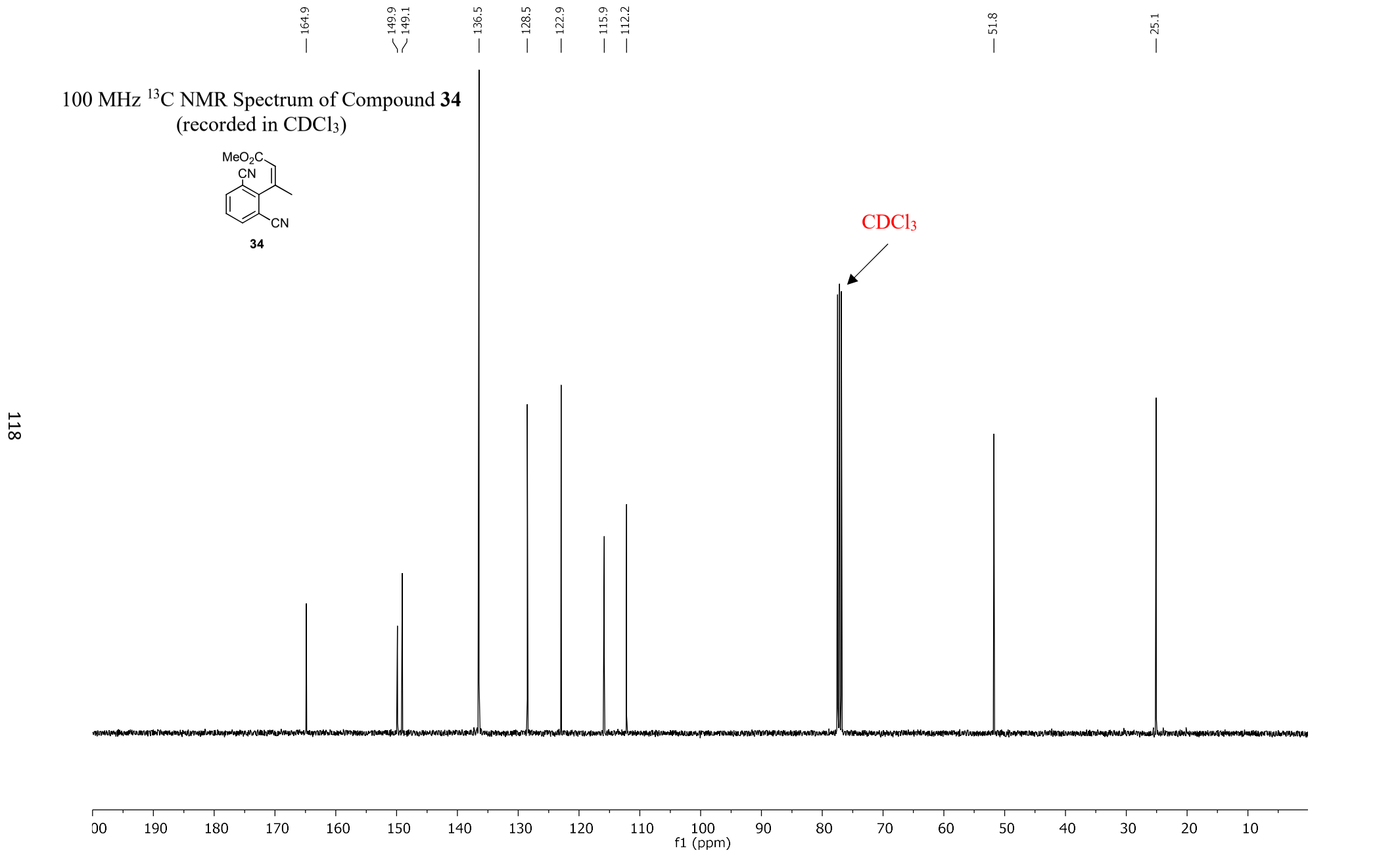

**33**


100 MHz $^{13}$C NMR Spectrum of Compound **33**
(recorded in $CDCl_3$)
$MeO_2C$
$O_2N$
CN
33
$CDCl_3$
165.1
152.2
150.6
146.9
128.7
127.8
127.5
121.5
115.6
112.3
51.7
26.0
f1 (ppm)

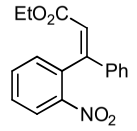
400 MHz $^{1}$H NMR Spectrum of Compound **34**
(recorded in $CDCl_3$)



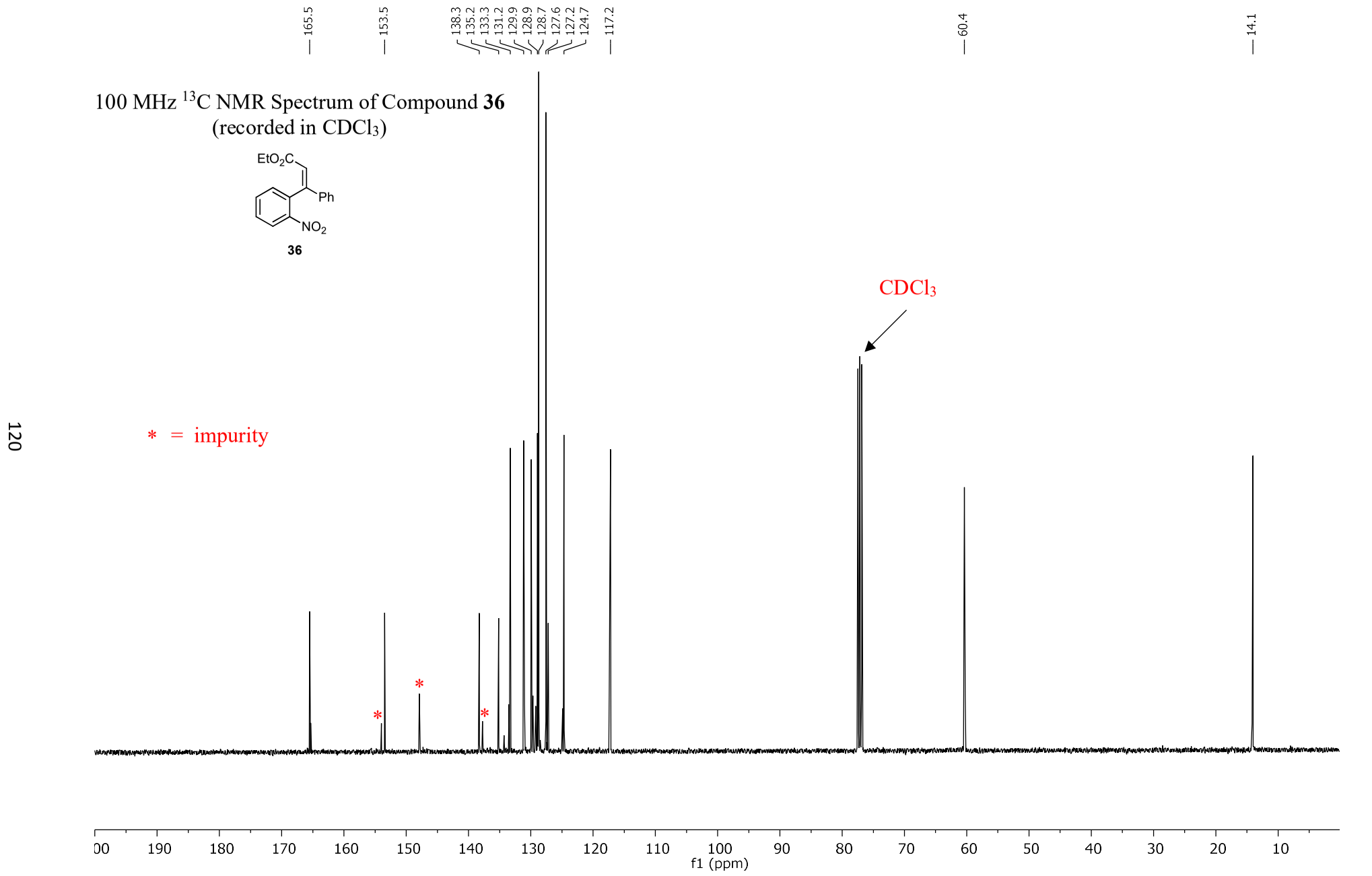

**34**


164.9
149.9
149.1
136.5
128.5
122.9
115.9
112.2
51.8
25.1
100 MHz $^{13}$C NMR Spectrum of Compound **34**
(recorded in $CDCl_3$)
$MeO_2C$
CN
CN
34
$CDCl_3$
118
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

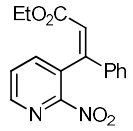
400 MHz $^{1}$H NMR Spectrum of Compound **36**
(recorded in $CDCl_3$)




**36**


165.5
153.5
138.3
135.2
133.3
131.2
129.9
128.9
128.7
127.6
127.2
124.7
117.2
60.4
14.1
100 MHz $^{13}$C NMR Spectrum of Compound **36**
(recorded in $CDCl_3$)
$EtO_2C$
Ph
$NO_2$
**36**
$CDCl_3$
* = impurity
120
f1 (ppm)

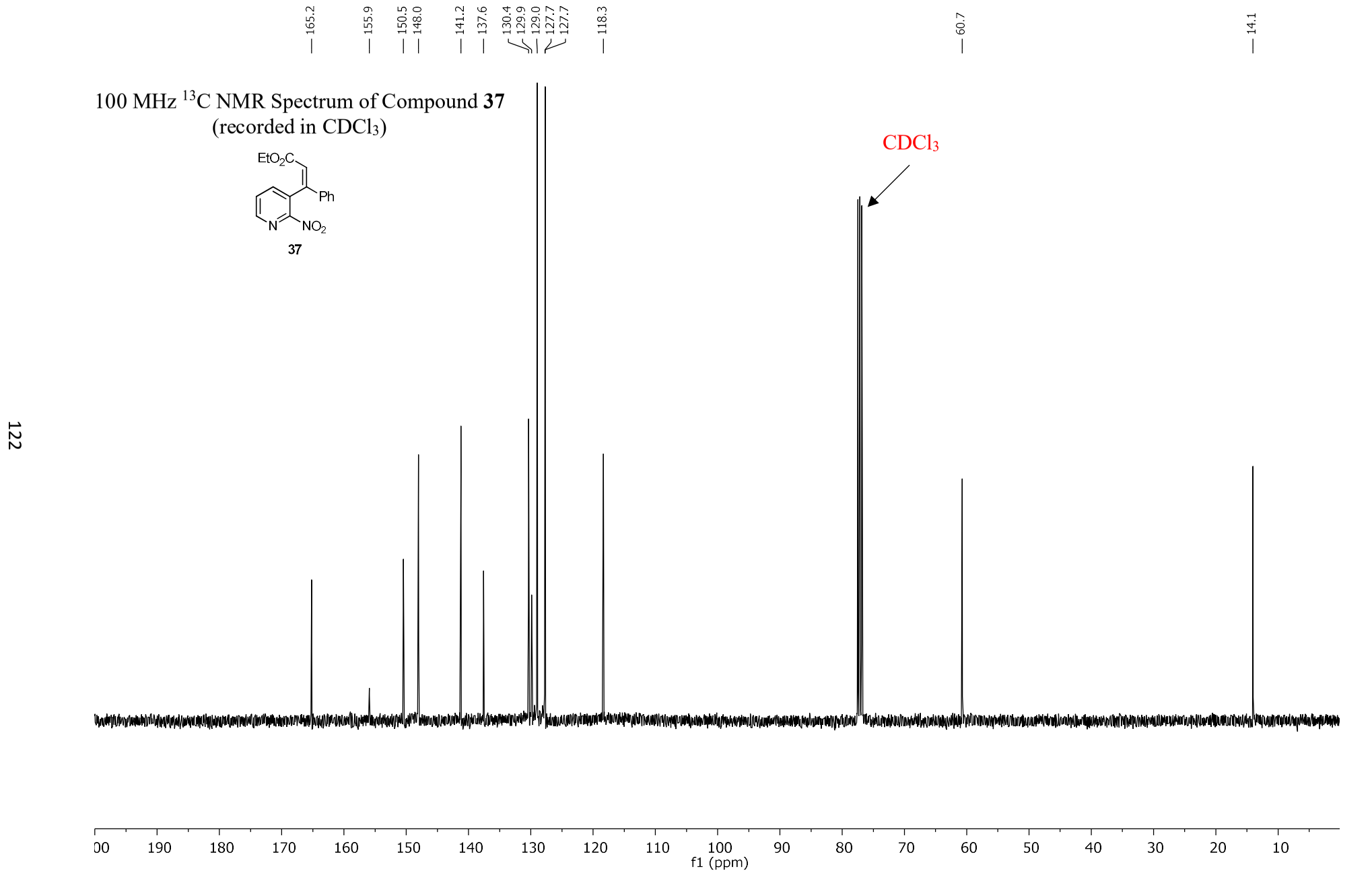
400 MHz $^{1}$H NMR Spectrum of Compound **37**
(recorded in $CDCl_3$)



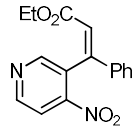

**37**




121


165.2
155.9
150.5
148.0
141.2
137.6
130.4
129.9
129.0
127.7
127.7
118.3
60.7
14.1
100 MHz $^{13}$C NMR Spectrum of Compound **37**
(recorded in $CDCl_3$)
$EtO_2C$
Ph
N
$NO_2$
37
$CDCl_3$
122
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

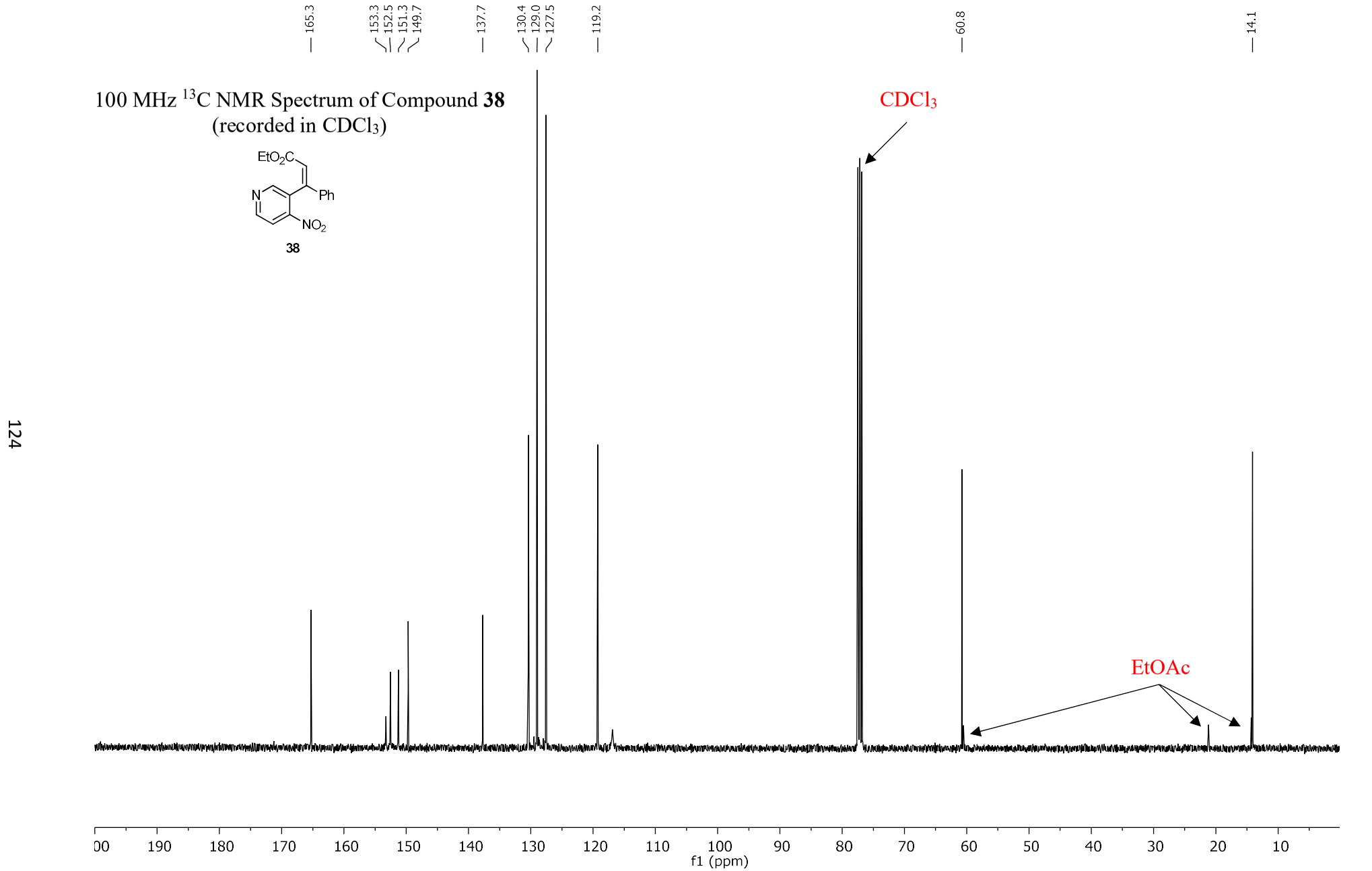
400 MHz $^{1}$H NMR Spectrum of Compound **38**
(recorded in $CDCl_3$)



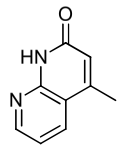

**38**




123


165.3
153.3
152.5
151.3
149.7
137.7
130.4
129.0
127.5
119.2
60.8
14.1
100 MHz $^{13}$C NMR Spectrum of Compound **38**
(recorded in $CDCl_3$)
$EtO_2C$
N
Ph
$NO_2$
**38**
$CDCl_3$
EtOAc
f1 (ppm)

400 MHz $^{1}$H NMR Spectrum of Compound **39**
(recorded in $CDCl_3$)

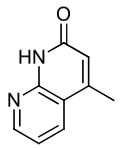



**39**




125

100 MHz $^{13}C$ NMR Spectrum of Compound **39**
(recorded in $CDCl_3$)

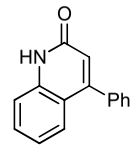



**39**

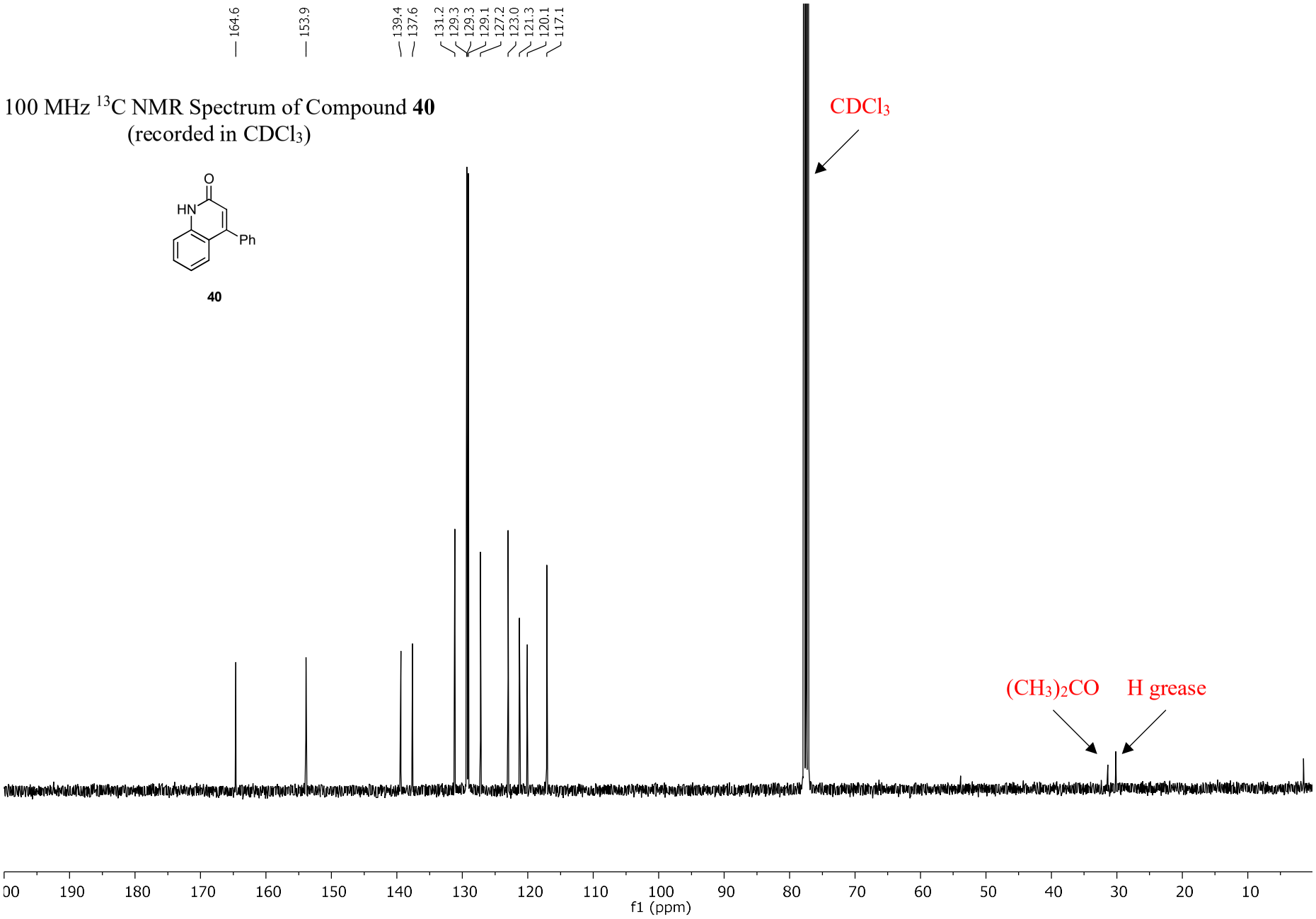


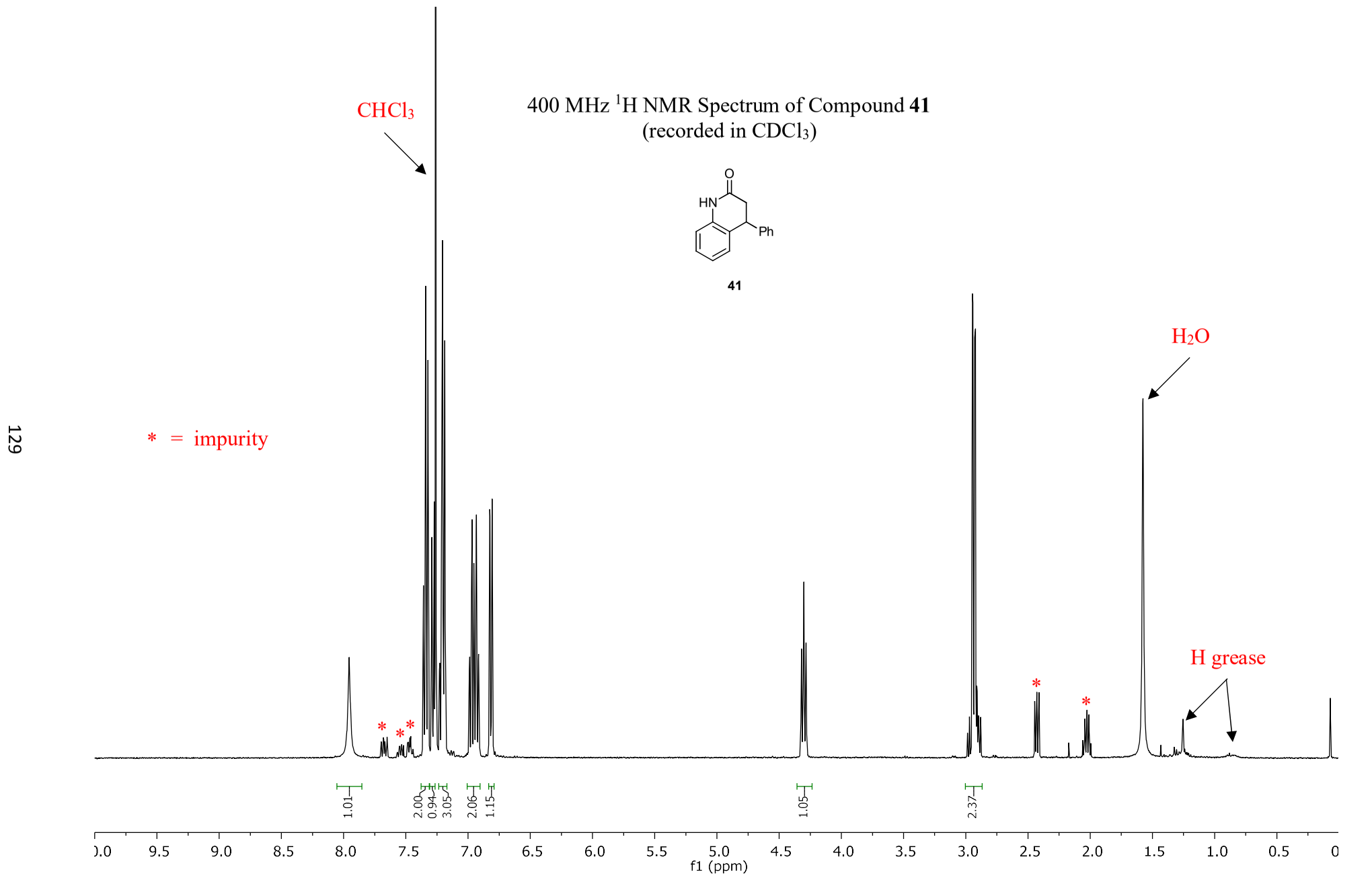

126

400 MHz $^{1}$H NMR Spectrum of Compound **40**
(recorded in $CDCl_3$)

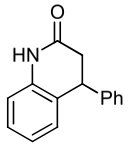



**40**

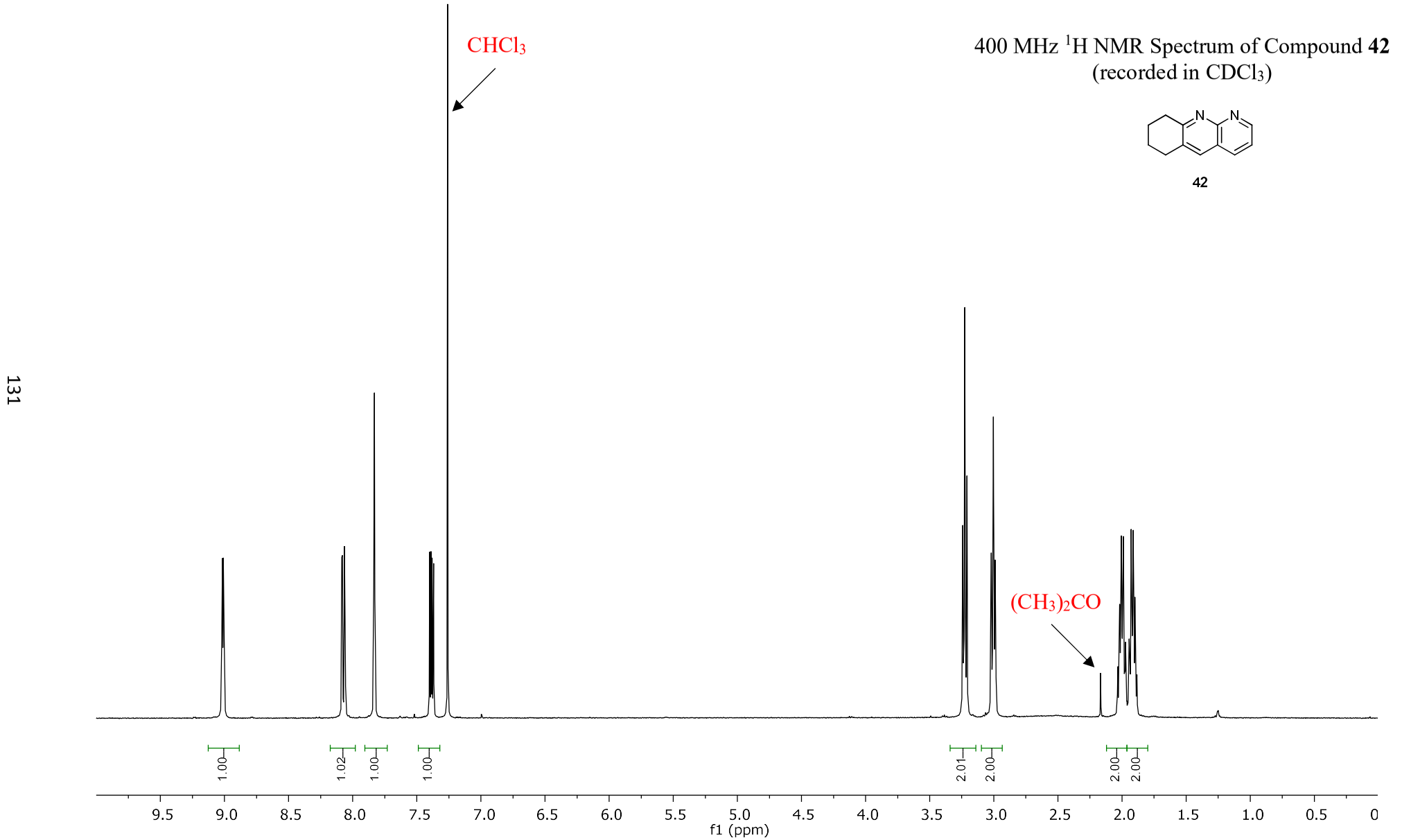

164.6
153.9
139.4
137.6
131.2
129.3
129.3
129.1
127.2
123.0
121.3
120.1
117.1
100 MHz $^{13}$C NMR Spectrum of Compound **40**
(recorded in $CDCl_3$)
O
HN
Ph
40
$CDCl_3$
$(CH_3)_2CO$
H grease
f1 (ppm)


400 MHz $^1$H NMR Spectrum of Compound **41**
(recorded in $CDCl_3$)
$CHCl_3$
$H_2O$
H grease
* = impurity
HN
O
Ph
41
1.01
2.00
0.94
3.05
2.06
1.15
1.05
2.37
f1 (ppm)

100 MHz $^{13}C$ NMR Spectrum of Compound **41**
(recorded in $CDCl_3$)

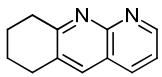



**41**


CHCl3
400 MHz 1H NMR Spectrum of Compound 42
(recorded in CDCl3)
N
N
42
(CH3)2CO
1.00
1.02
1.00
1.00
2.01
2.00
2.00
2.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

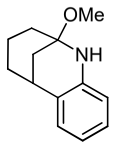
131

100 MHz $^{13}$C NMR Spectrum of Compound **42**
(recorded in $CDCl_3$)



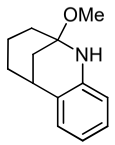
**42**

400 MHz $^{1}$H NMR Spectrum of Compound **43**
(recorded in $CDCl_3$)



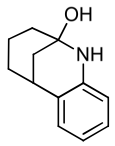

**43**

100 MHz $^{13}C$ NMR Spectrum of Compound **43**
(recorded in $CDCl_3$)




**43**

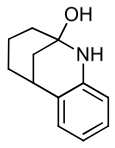
400 MHz $^{1}$H NMR Spectrum of Compound **44**
(recorded in $CDCl_3$)




**44**

v

100 MHz $^{13}C$ NMR Spectrum of Compound **44**
(recorded in $CDCl_3$)

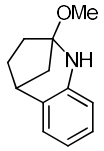



**44**



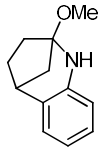

136

400 MHz $^{1}$H NMR Spectrum of Compound **45**
(recorded in $CDCl_3$)



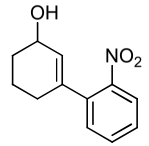

**45**

100 MHz $^{13}C$ NMR Spectrum of Compound **45**
(recorded in $CDCl_3$)



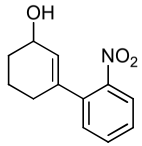

45

400 MHz $^{1}$H NMR Spectrum of Compound **46**
(recorded in $CDCl_3$)



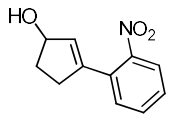

**46**

100 MHz $^{13}C$ NMR Spectrum of Compound **46**
(recorded in $CDCl_3$)

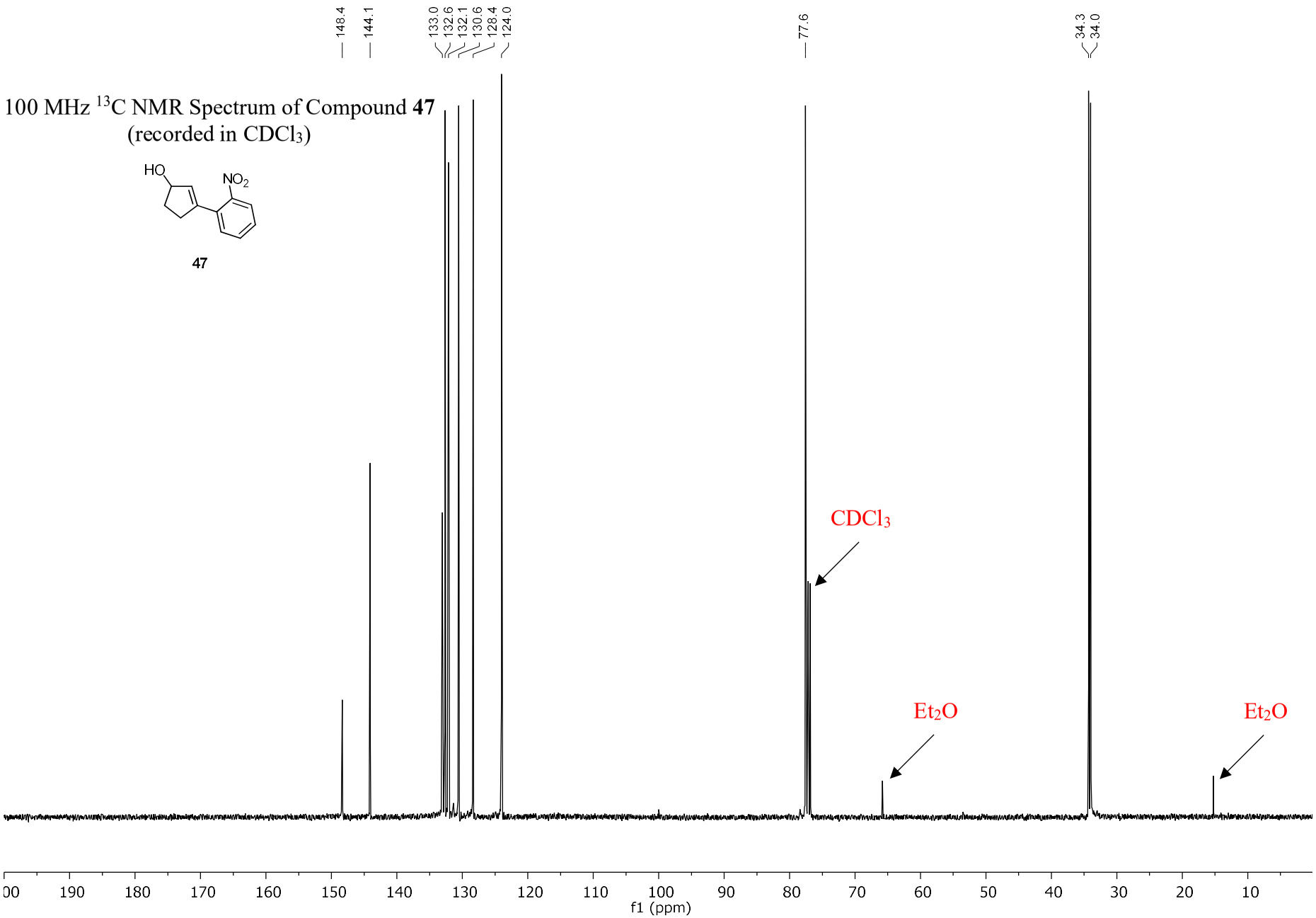



**46**

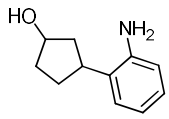
400 MHz $^{1}$H NMR Spectrum of Compound **47**
(recorded in $CDCl_3$)




**47**

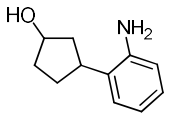

148.4
144.1
133.0
132.6
132.1
130.6
128.4
124.0
77.6
34.3
34.0
100 MHz $^{13}$C NMR Spectrum of Compound **47**
(recorded in $CDCl_3$)
HO
$NO_2$
47
$CDCl_3$
$Et_2O$
$Et_2O$
f1 (ppm)

400 MHz $^{1}$H NMR Spectrum of Compound **49**
(recorded in $CDCl_3$)




**49**

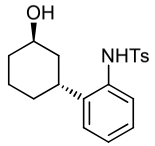
100 MHz $^{13}C$ NMR Spectrum of Compound **49**
(recorded in $CDCl_3$)




**49**

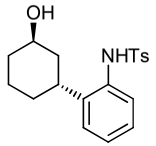
145

400 MHz $^{1}$H NMR Spectrum of Compound *trans*-**50**
(recorded in $CDCl_3$)



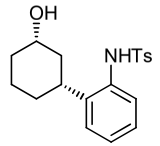

*trans*-**50**

100 MHz $^{13}$C NMR Spectrum of Compound *trans*-**50**
(recorded in $CDCl_3$)




*trans*-**50**

400 MHz $^{1}$H NMR Spectrum of Compound *cis*-**50**
(recorded in $CDCl_3$)

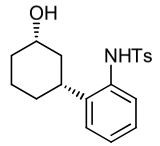



*cis*-**50**

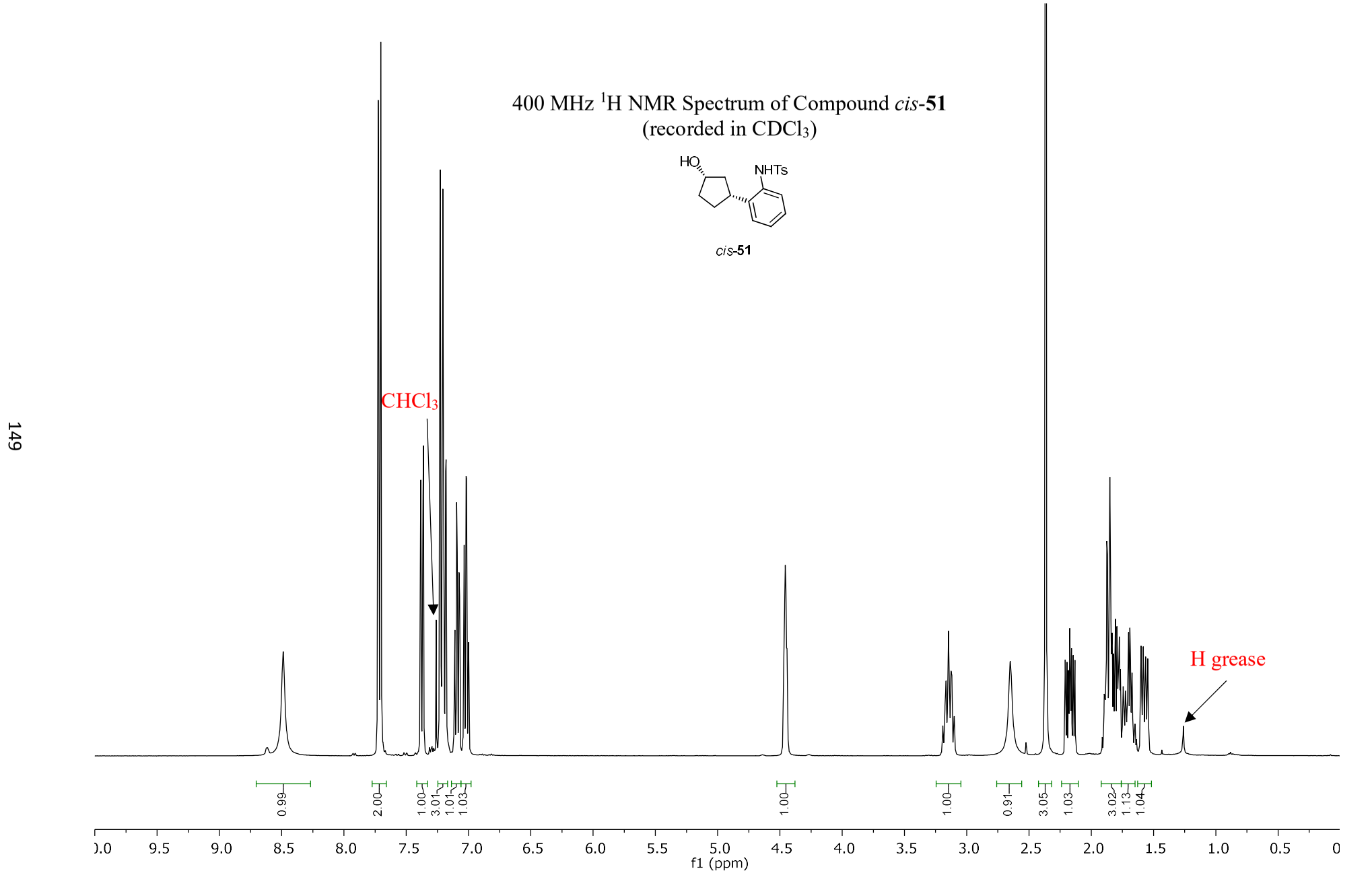



147

100 MHz $^{13}C$ NMR Spectrum of Compound *cis*-**50**
(recorded in $CDCl_3$)

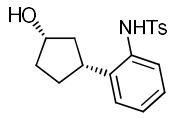



*cis*-**50**


400 MHz $^1$H NMR Spectrum of Compound *cis*-**51**
(recorded in $CDCl_3$)
HO
NHTs
*cis*-**51**
$CHCl_3$
H grease
0.99
2.00
1.00
3.01
1.01
1.03
1.00
1.00
0.91
3.05
1.03
3.02
1.13
1.04
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

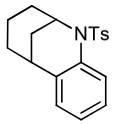
149

100 MHz $^{13}C$ NMR Spectrum of Compound *cis*-**51**
(recorded in $CDCl_3$)




*cis*-**51**

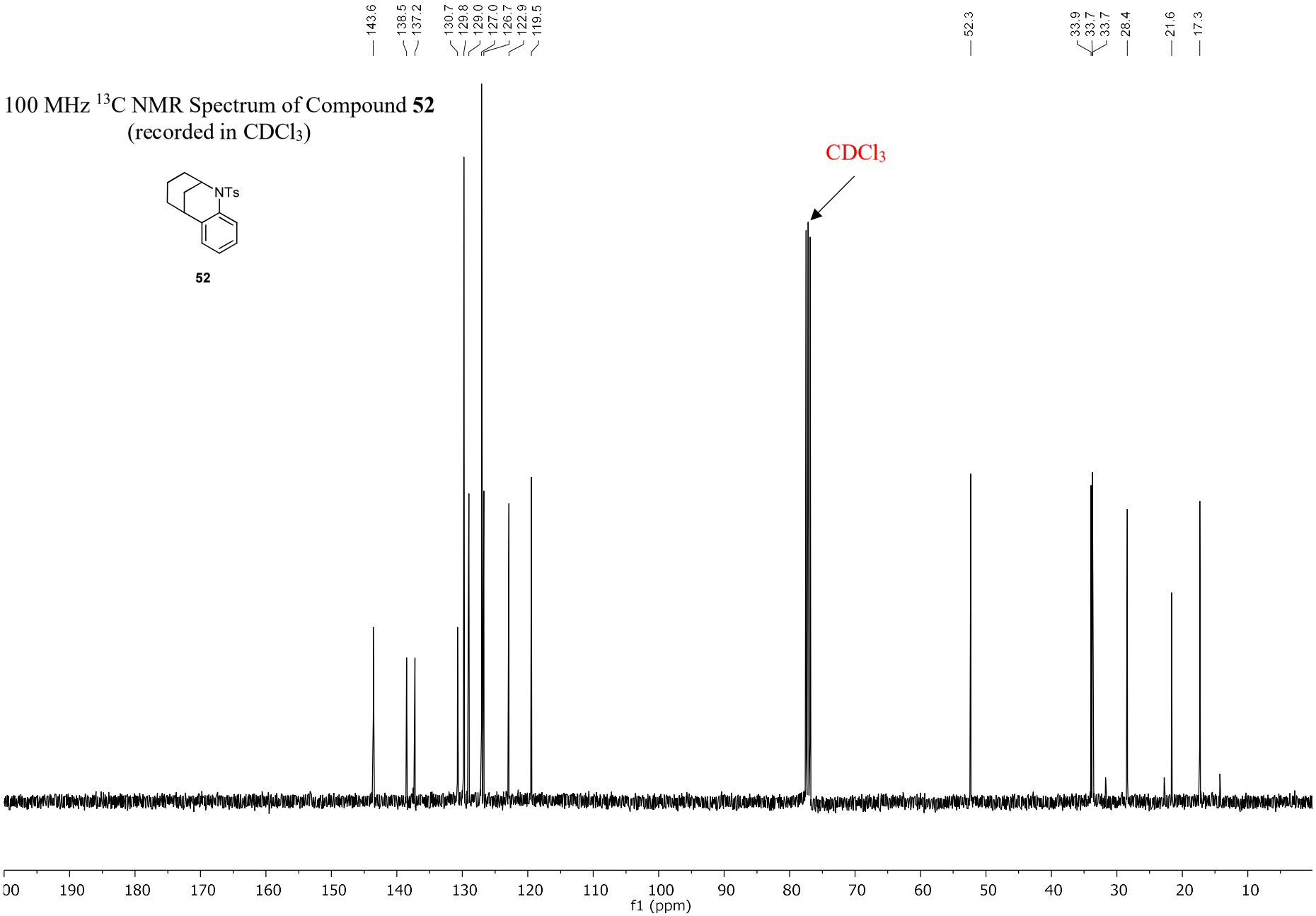
400 MHz $^{1}$H NMR Spectrum of Compound **52**
(recorded in $CDCl_3$)




**52**

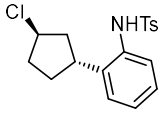



151


143.6
138.5
137.2
130.7
129.8
129.0
127.0
126.7
122.9
119.5
52.3
33.9
33.7
33.7
28.4
21.6
17.3
100 MHz $^{13}$C NMR Spectrum of Compound **52**
(recorded in $CDCl_3$)
NTs
52
$CDCl_3$
f1 (ppm)

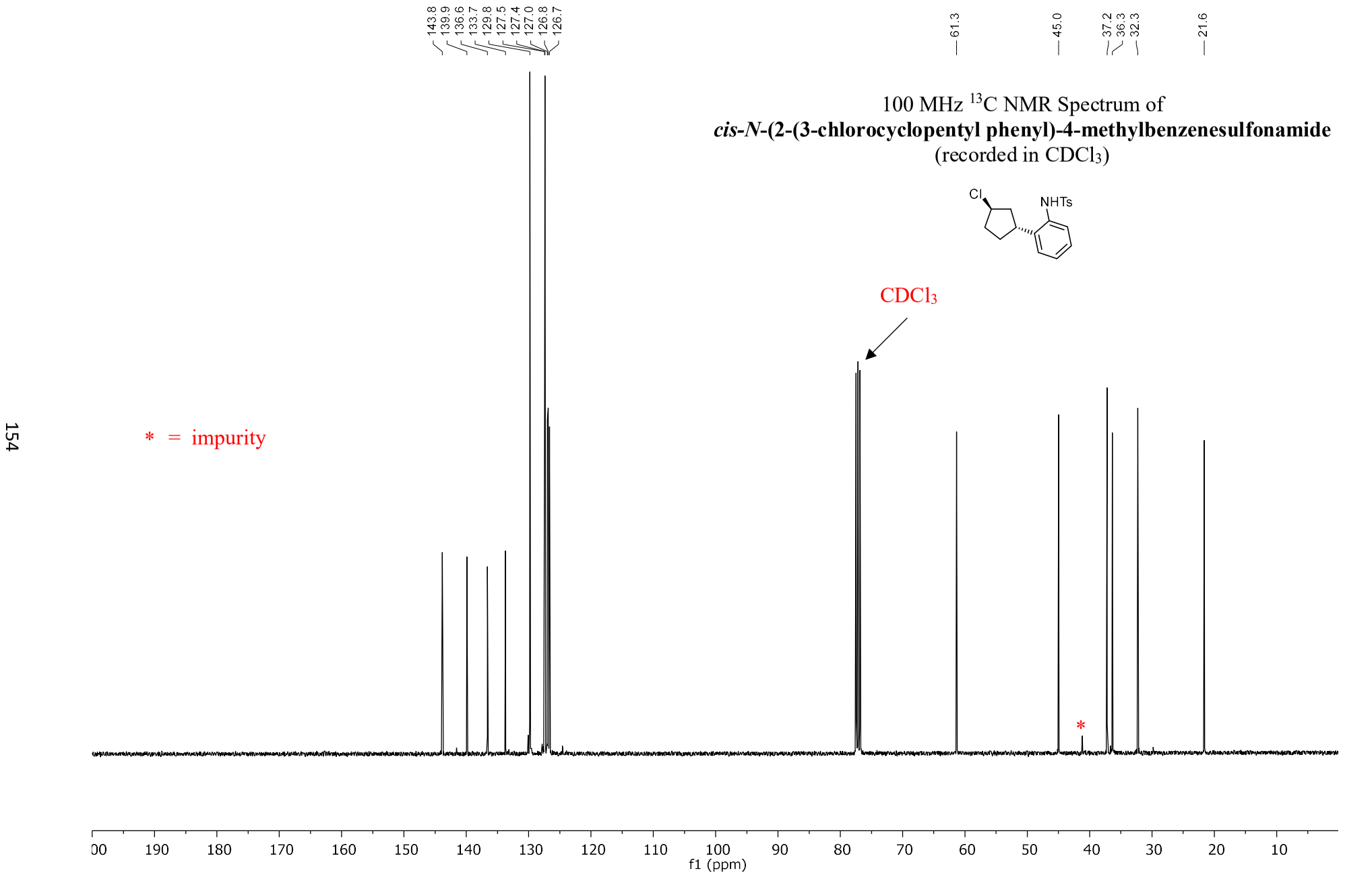
152

400 MHz $^{1}$H NMR Spectrum of
***cis*-*N*-(2-(3-chlorocyclopentyl)phenyl)-4-methylbenzenesulfonamide**
(recorded in $CDCl_3$)



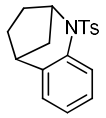

153

* = impurity


143.8
139.9
136.6
133.7
129.8
127.5
127.4
127.0
126.8
126.7
61.3
45.0
37.2
36.3
32.3
21.6
100 MHz $^{13}$C NMR Spectrum of
***cis*-*N*-(2-(3-chlorocyclopentyl phenyl)-4-methylbenzenesulfonamide**
(recorded in $CDCl_3$)
Cl
NHTs
$CDCl_3$
* = impurity
*
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

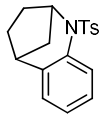
154

400 MHz $^{1}$H NMR Spectrum of Compound **53**
(recorded in $CDCl_3$)




**53**

400 MHz $^{1}$H NMR Spectrum of Compound **53**
(recorded in $CDCl_3$)




**53**

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Article
pubs.acs.org/joc

# Reductive Cyclization of *o*-Nitroarylated-α,β-unsaturated Aldehydes and Ketones with $TiCl_3$/HCl or Fe/HCl Leading to 1,2,3,9-Tetrahydro-4*H*-carbazol-4-ones and Related Heterocycles

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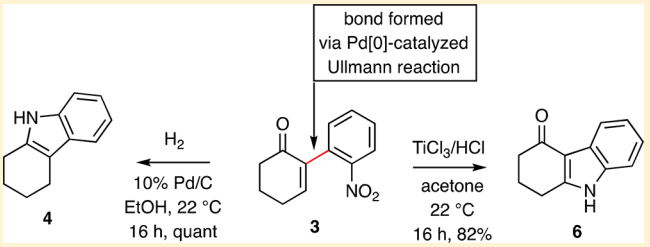
Supporting Information

**ABSTRACT:** Compounds such as **3**, the product of a palladium[0]-catalyzed Ullmann cross-coupling of *o*-iodonitrobenzene and 2-iodocyclohex-2-en-1-one, undergo complementary modes of reductive cyclization depending upon the conditions employed. Thus, on treatment with hydrogen in the presence of palladium on carbon, the tetrahydrocarbazole **4** is formed, while reaction of the same substrate (**3**) with $TiCl_3$ in acetone affords the 1,2,3,9-tetrahydro-4*H*-carbazol-4-one **6**.

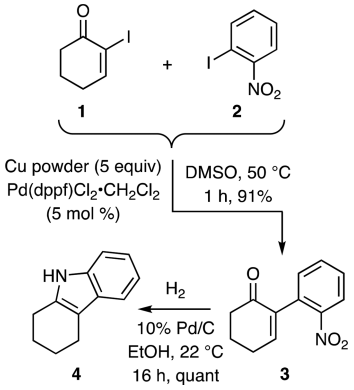



## INTRODUCTION

Sometime ago,[1] we reported that 2-iodocyclohex-2-en-1-one (**1**) (Scheme 1) could be efficiently cross-coupled with *o*-iodonitrobenzene (**2**) in the presence of copper bronze and catalytic quantities of palladium[0] at 50 °C. Catalytic hydrogenation of the resulting *o*-nitroarylated cyclohexenone **3** then afforded the tetrahydrocarbazole **4**. We have since extended this two-step and related reaction sequences in a variety of settings, including ones that have led to a range of alkaloids as well as medicinally relevant heterocycles.[2]

We now report that by treating cross-coupling products such as **3** with titanium trichloride[3]/HCl or iron/HCl[4] then quite distinct reductive cyclization processes take place to give heterocyclic systems of biological interest.

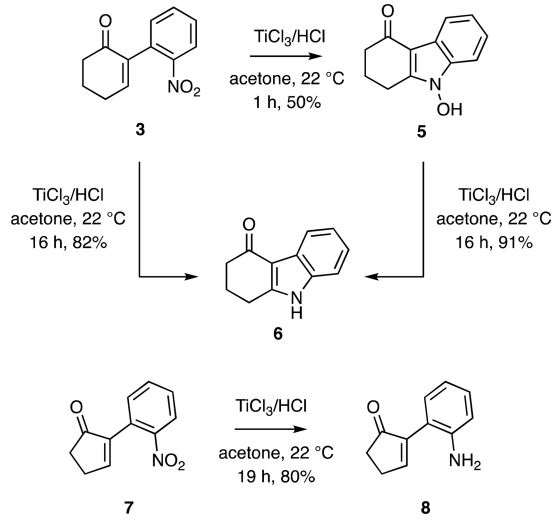
**Scheme 1. Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Sequence Leading to Tetrahydrocarbazole 4**




## RESULTS AND DISCUSSION

As shown in Scheme 2, when compound **3** is treated with either titanium trichloride/HCl or iron/HCl at ambient

**Scheme 2. Reductive Cyclization of Compound 3 via *N*-Hydroxyindole 5 to 1,2,3,9-Tetrahydro-4*H*-carbazol-4-one 6 and the Direct Reduction of Nitroarene 7 to Aniline 8**

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**Published:** September 5, 2018







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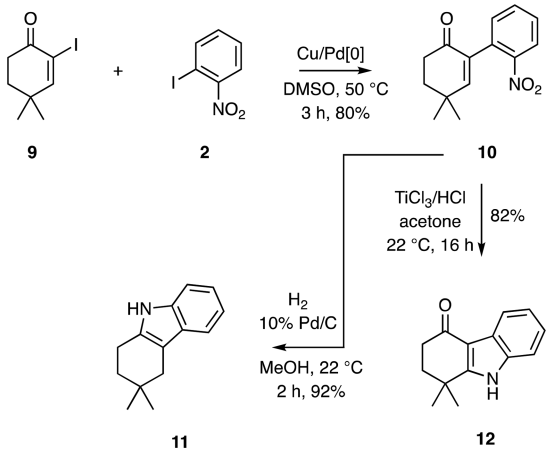
J. Org. Chem. XXXX, XXX, XXX−XXX

temperatures for brief periods, then the primary product of the reaction is the *N*-hydroxytetrahydro-4*H*-carbazol-4-one **5**, the structure of which was confirmed by single-crystal X-ray analysis (see the SI for details). Furthermore, when compound **3** or **5** was exposed to the same reagents for extended periods of time, then the previously reported[5] tetrahydro-4*H*-carbazol-4-one **6** was obtained. Under optimal conditions ($TiCl_3$/HCl is generally the preferred reducing agent), the latter product could be obtained, as the exclusive one, from precursor **3** in 82% yield. Fe/HCl was much less effective in these conversions (see the Experimental section and SI for details). While the precise mode of the formation of product **5** from substrate **3** remains to be established, it is clear that the former compound is a precursor to tetrahydrocarbazol-4-one **6**. The formation of compound **6** by the means just described is closely related to a protocol recently reported by Zhu and co-workers as a key step in their elegant total synthesis of aspidospermidine.[3f]

The cyclization process appears to be sensitive to stereoelectronic effects, as evidenced by the conversion of the cyclopentenone-appended nitroarene **7** into the corresponding aniline **8** (80%) rather than the lower homologue of heterocycle **6**. Interestingly, analogous treatment of the cycloheptenone-appended nitroarene (*viz.* the higher homologue of compound **3**) only led to complex mixtures of products.

The complementary nature of the original mode of reductive cyclization of the palladium-catalyzed Ullmann cross-coupling products and the one that can normally be best effected using $TiCl_3$/HCl is emphasized through the example shown in Scheme 3. Thus, cross-coupling of electrophiles **9**[6] and **2** using

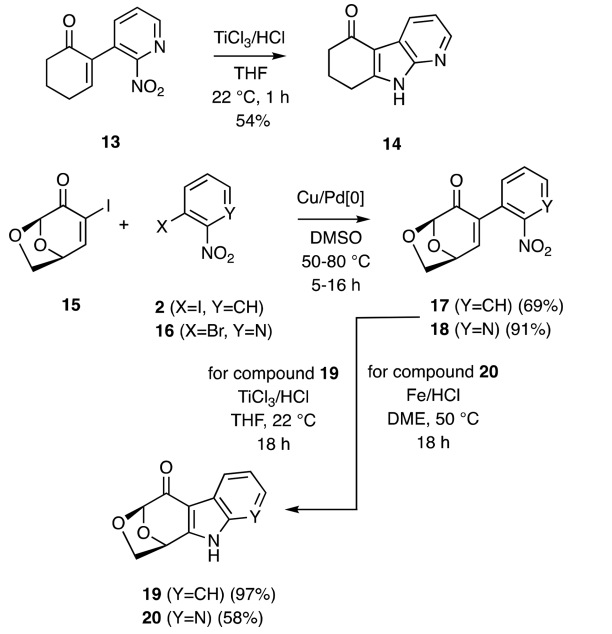
**Scheme 3. Complementary Behaviors of the Cross-Coupling Product 10 under Two Distinct Reductive Cyclization Conditions**




copper in the presence of catalytic Pd[0] afforded product **10** (80%), and on treatment of this with hydrogen in the presence of 10% palladium on carbon then the previously reported[7] *gem*-dimethylated tetrahydrocarbazole **11** is obtained in 92% yield. In contrast, on treating the same substrate with $TiCl_3$/HCl in acetone at ambient temperatures, then compound **12**, an established precursor to demethoxycarazomycin B,[8] is obtained in 82% yield.

The utility of the "new" mode of reductive cyclization in establishing multiheteroatom-containing ring systems is revealed through the examples shown in Scheme 4. Thus,

**Scheme 4. Reductive Cyclization Reactions of Substrates 13, 17, and 18**




exposure of the previously reported[9] coupling product **13** to $TiCl_3$/HCl gives the 7-azaindole **14** (54%), while the products derived from the cross-coupling of the homochiral iodide **15**[10] with aryl iodides **2** and **16**,[9] namely, compounds **17** (69%) and **18** (91%), respectively, react with $TiCl_3$/HCl (in the former case) or Fe/HCl (in the latter case) to afford the tetracyclic products **19** (97% from **17**) and **20** (58% from **18**). The spectral data derived from these products were in complete accord with the assigned structures, and a single-crystal X-ray analysis of compound **19** was obtained.

Acyclic ketones behave similarly as shown in Scheme 5. So, the Johnson $\alpha$-iodination[11] of chalcone (**21**) afforded a chromatographically separable mixture of compounds **22**[12] (58%) and **23**[12] (10%) that, upon palladium-catalyzed Ullmann cross-coupling with compound **16**, afforded the anticipated products **24** and **25** (59−85% combined yield). The structure of the former product (**24**) was confirmed by single-crystal X-ray analysis. Since the cross-couplings of the geometrically pure *E*- and *Z*-isomeric forms of **22** and **23** are each accompanied by some double-bond isomerization, it was most convenient to carry the mixture of iodinated products through the illustrated reaction sequence rather than separating these. Subjection of these cross-coupling products, either separately or as a mixture, to reductive cyclization with hydrogen in the presence of 10% palladium on carbon afforded the 3-benzyl-7-azaindole **26**[13] (63−80%), while treatment of the same substrates with $TiCl_3$ gave the 3-benzoyl-7-azaindole **27** in 15−49% yield. The structure of product **26** was confirmed by single-crystal X-ray analysis.

In contrast to the outcomes detailed immediately above, when the readily obtained $\alpha$-iodinated cinnamaldehyde **31**[1] (Scheme 6) was subjected to palladium-catalyzed Ullmann cross-coupling with compound **2** and the ensuing product, **32**[1] (77%), treated with $TiCl_3$, then a slowly interconverting mixture of the partially chromatographically separable and isomeric cyclization products **33**[14] and **34**[14] was obtained (55% combined yield). The structure of oxindole **33**, a known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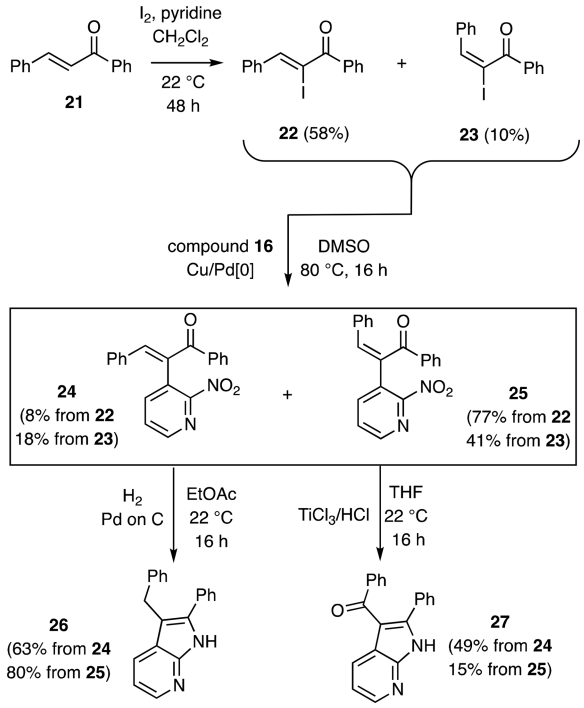
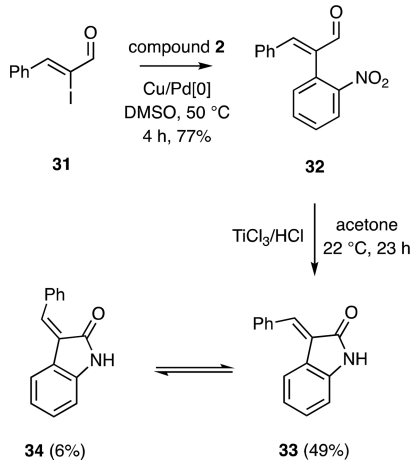
J. Org. Chem. XXXX, XXX, XXX−XXX

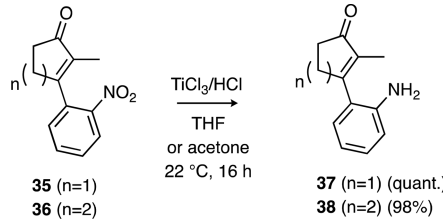
**Scheme 5. Formation of the Mixture of Cross-Coupling Products 24 and 25 and Their Divergent Reductive Cyclizations To Give 7-Azaindoles 26 and 27**



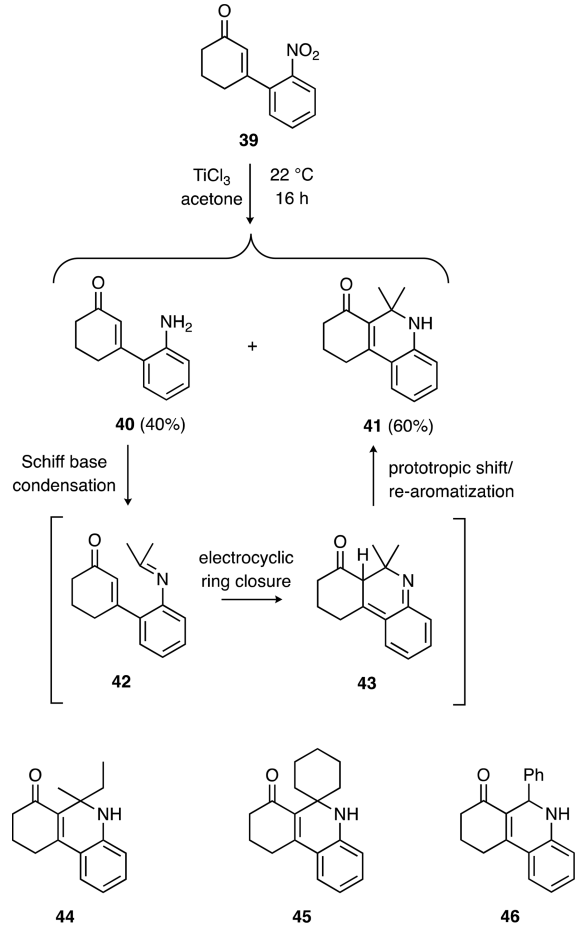

**Scheme 6. Formation of Cinnamaldehyde 32 and Its Reductive Cyclization**




**Scheme 7. Reduction of Nitroarenes 35 and 36 to the Corresponding Anilines**




**Scheme 8. Formation of the Dihydroquinolines 41 and 44–46**




antiproliferative agent,[15] was confirmed by single-crystal X-ray analysis.

Very recently, we detailed[16] the cross-coupling of various *β*-iodoeneones and related compounds with *o*-iodonitrobenzene (**2**) to afford products, such as compound **35** (Scheme 7). Accordingly, we sought to establish how this nitroarene and its homologue **36** would behave on exposure to $TiCl_3$/HCl. In the event, when treated under our now standard conditions, each produced the corresponding aniline, viz. compounds **37** (quant.) and **38** (98%), respectively, with the structure of the latter being confirmed by single-crystal X-ray analysis.

A more intriguing outcome was observed when an acetone solution of the nonmethylated cross-coupling product **39**[16] (Scheme 8) was treated with $TiCl_3$ at ambient temperatures. Under these conditions, the chromatographically separable products **40**[17] (40%) and **41** (60%) were obtained, and their structures established by single-crystal X-ray analysis. Compound **40** is undoubtedly the primary product of the reaction and the precursor to the other through its Schiff base condensation with acetone to give imine **42** and electrocyclic ring closure of this to give compound **43** that engages in a prototropic shift with accompanying re-aromatization to deliver the secondary product **41**. Consistent with this proposal, when THF solutions of compound **40** were treated, at 22 °C, with methyl ethyl ketone, cyclohexanone, or benzaldehyde then the cycloadducts **44** (73%) **45** (64%), and **46** (quant.), respectively, are obtained. The structures of products **44** and **45** were confirmed by single-crystal X-ray analysis (see the SI for details).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## CONCLUSIONS

The reductive cyclization processes detailed above considerably enhance the utility of the various products available through the palladium-catalyzed Ullmann cross-coupling of *o*-halonitroarenes with either $\alpha$- or $\beta$-iodinated-$\alpha,\beta$-unsaturated enones and related systems.[2] The resulting, and in some instances previously unreported, heterocyclic ring systems should serve as useful scaffolds in a range of settings.

## EXPERIMENTAL SECTION

**General Experimental Procedures.** Unless otherwise specified, proton ($^1$H) and carbon ($^{13}$C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For $^1$H NMR spectra, signals arising from the residual protio-forms of the solvent were used as internal standards. $^1$H NMR data are recorded as follows: chemical shift ($\delta$) (multiplicity, coupling constant(s) $J$ (Hz), relative integral) where multiplicity is defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; or combinations of the above. The signal due to residual $CHCl_3$ appearing at $\delta_H$ 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at $\delta_C$ 77.0 were used to reference $^1$H and $^{13}$C NMR spectra, respectively. IR spectra were recorded, using neat samples, on an attenuated total reflectance (ATR) infrared spectrometer. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph−mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 $F_{254}$ plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid:ceric sulfate:sulfuric acid (conc.):-water (37.5 g:7.5 g:37.5 g:720 mL) or potassium permanganate:potassium carbonate:5% sodium hydroxide aqueous solution:water (3 g:20 g:5 mL:300 mL). Column chromatographic separations were carried out following protocols defined by Still et al.[18] with silica gel 60 (40−63 $\mu$m) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, and drying agents as well as other inorganic salts were generally available from commercial sources and used as supplied. Tetrahydrofuran (THF), diethyl ether, methanol, and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[19] Where necessary, reactions were performed under a nitrogen atmosphere.

**Specific Chemical Transformations.** *Compound* ***5***. Method i: A magnetically stirred mixture of compound **3**[1] (217 mg, 1.00 mmol) in acetone (5 mL) maintained at 22 °C was treated with titanium(III) chloride (5.0 mL of a 12% w/v solution in hydrochloric acid, 4.79 mmol). After 1 h, the reaction mixture was diluted with ethyl acetate (20 mL), washed with water (3 × 10 mL), dried ($Na_2SO_4$), filtered, and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40−60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **5** (100 mg, 50%) as a white, crystalline solid, no mp, decomposition at 147 °C. $^1$H NMR (400 MHz, DMSO-$d_6$, $\delta$): 11.70 (s, 1H), 7.99 (dd, $J$ = 7.4 and 1.2 Hz, 1H), 7.46 (d, $J$ = 8.0 Hz, 1H), 7.25−7.19 (complex m, 2H), 2.98 (t, $J$ = 6.2 Hz, 2H), 2.44 (m, 2H), 2.20−2.08 (complex m, 2H). $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$): 192.0, 148.4, 134.0, 122.7, 122.2, 120.5, 120.2, 108.8, 106.5, 37.6, 22.9, 20.3. IR (ATR) $\nu_{max}$: 3062, 2946, 1710, 1575, 1462, 1311, 1256, 1182, 1096, 966, 741 cm$^{-1}$. MS (ESI, +) ($m/z$): 224 [(M+Na)$^+$, 100%], 202 [(M+H)$^+$, 10]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{12}H_{12}NO_2$, 202.0863; found, 202.0860.

Method ii: A magnetically stirred solution of compound **3**[1] (100 mg, 1.00 mmol) and hydrochloric acid (3 mL of a 2 M aqueous solution) in THF (5 mL) maintained at 22 °C was treated with iron powder (168 mg, 3.00 g·atom). After 18 h, the reaction mixture was diluted with ethyl acetate (20 mL) and then filtered through a plug of TLC-grade silica topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 10 mL), and the combined filtrates were washed with water (2 × 20 mL) then brine (1 × 20 mL) before being dried ($Na_2SO_4$), filtered, and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40−60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **5** (14 mg, 14%) as a white, crystalline solid. This material was identical, in all aspects, with that obtained by Method i.

*Compound* ***6***. Method i: A magnetically stirred solution of compound **5** (50 mg, 0.25 mmol) in acetone (1.3 mL) maintained at 22 °C was treated with titanium(III) chloride (1.3 mL of a 12% w/v solution in hydrochloric acid, 1.24 mmol). After 16 h, the reaction mixture was quenched with sodium carbonate (5 mL of a saturated aqueous solution), and the resulting heterogeneous mixture was filtered through diatomaceous earth. The solids so retained were washed with ethyl acetate (10 mL), the combined filtrates were separated, and the aqueous phase was extracted with ethyl acetate (2 × 5 mL). The combined organic phases were washed with brine (20 mL), dried ($Na_2SO_4$), filtered, and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40−60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.1), compound **6**[5] (42 mg, 91%) as a white, crystalline solid, mp 174 °C (lit.[5b] mp 225−228 °C). $^1$H NMR (400 MHz, DMSO-$d_6$, $\delta$): 11.84 (s, 1H), 7.95 (m, 1H), 7.39 (dd, $J$ = 8.0 and 1.4 Hz, 1H), 7.15 (m, 2H), 2.96 (t, $J$ = 6.2 Hz, 2H), 2.42 (t, $J$ = 6.2 Hz, 2H), 2.10 (m, 2H). $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$): 192.9, 152.3, 135.8, 124.5, 122.4, 121.5, 120.2, 111.7, 111.5, 37.8, 23.4, 22.7. IR (ATR) $\nu_{max}$: 3056, 2954, 1604, 1576, 1462, 1445, 1411, 1251, 1177, 1145, 1016, 753 cm$^{-1}$. MS (ESI, +) ($m/z$): 208 [(M+Na)$^+$, 73%], 186 [(M+H)$^+$, 100]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{12}H_{12}NO$, 186.0913; found, 186.0912.

Method ii: A magnetically stirred solution of compound **5** (100 mg, 0.46 mmol) in hydrochloric acid (5 mL of a 3 M aqueous solution) maintained at *ca*. 100 °C was treated with iron powder (154 mg, 2.76 g.atom). After 3 h, the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (20 mL), and filtered through a plug of TLC-grade silica topped with diatomaceous earth, and the solids so retained were washed with ethyl acetate (1 × 10 mL). The combined filtrates were washed with water (2 × 20 mL) and brine (1 × 20 mL) before being dried ($Na_2SO_4$), filtered, and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, ethyl acetate/40−60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **6** (10 mg, 12%) as a white, crystalline solid. This material was identical, in all aspects, with that obtained by Method i.

*Compound* ***8***. A magnetically stirred solution of compound **7**[1] (108 mg, 0.53 mmol) in acetone (5 mL) maintained at 22 °C was treated with titanium(III) chloride (3.3 mL of a 12% w/v solution in hydrochloric acid, 3.18 mmol). After 19 h, the reaction mixture was quenched with sodium carbonate (10 mL of a saturated aqueous solution), and the resulting mixture filtered through a pad of diatomaceous earth contained in a sintered glass funnel. The solids thus retained were washed with ethyl acetate (20 mL). The separated aqueous phase associated with the combined filtrates was extracted with ethyl acetate (2 × 10 mL), and the combined organic phases were washed with brine (1 × 50 mL) before being dried ($Na_2SO_4$), filtered, and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 4:6 v/v ethyl acetate/40−60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **8** (74 mg, 80%) as a clear, red oil. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 7.76 (t, $J$ = 2.9 Hz, 1H), 7.15−7.10 (complex m, 2H), 6.77 (m, 1H), 6.72 (m, 1H), 4.04 (broad s, 2H), 2.80 (m, 2H), 2.60 (m, 2H). s$^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 208.7, 162.7, 145.4, 144.8, 130.1, 129.6,


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J. Org. Chem. XXXX, XXX, XXX−XXX

118.8, 118.7, 117.0, 35.2, 27.2. IR (ATR) $\nu_{max}$: 3422, 3357, 2921, 1688, 1622, 1492, 1453, 1299, 1137, 935, 751 $cm^{-1}$. MS (ESI, +) (*m*/*z*): 196 [$(M+Na)^+$, 100%], 174 [$(M+H)^+$, 5]. HRMS (ESI, +): [M + H] $^+$ Calcd for $C_{11}H_{12}NO$, 174.0913; found, 174.0910.

*Compound* **9**. A magnetically stirred mixture of 4,4-dimethyl-2-cyclohexan-1-one (640 mg, 5.2 mmol) in THF/water (24 mL of a 1:1 v/v mixture) maintained at 0 °C was treated with $K_2CO_3$ (860 mg, 6.2 mmol), DMAP (127 mg, 1.0 mmol), and in portions, powdered molecular iodine (1.97 g, 7.8 mmol). The ensuing mixture was warmed to 22 °C and after 3 h the reaction mixture was diluted with ethyl acetate (20 mL) before being quenched with sodium sulfite (50 mL of a saturated aqueous solution) and then stirred vigorously until two clear layers were formed. The separated aqueous phase was extracted with ethyl acetate (2 × 20 mL), and the combined organic phases were washed with sodium sulfite (1 × 50 mL of a saturated aqueous solution), hydrochloric acid (1 × 50 mL of a 0.5 M aqueous solution), and brine (1 × 50 mL) before being dried ($Na_2SO_4$) and then filtered through a plug of TLC-grade silica. The filtrate was concentrated under reduced pressure, and the residue so obtained was subjected to flash column chromatography (silica, 1:7 v/v ethyl acetate/40−60 petroleum ether elution). Concentration of the appropriate fractions ($R_f$ = 0.2) then gave compound **9**[6] (1.29 g, 91%) as a clear, yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 7.45 (broad s, 1H), 2.67 (t, *J* = 6.9 Hz, 2H), 1.92 (t, *J* = 6.9 Hz, 2H), 1.18 (broadened s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 191.9, 168.0, 101.8, 38.0, 36.0, 33.3, 27.4. IR (ATR) $\nu_{max}$: 2959, 2926, 2864, 1687, 1583, 1317, 1142, 991, 957, 801, 724, 693 $cm^{-1}$. MS (ESI, +) (*m*/*z*): 273 [$(M+Na)^+$, 100%], 251 [$(M+H)^+$, 50]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_8H_{12}IO$, 250.9927; found, 250.9925.

*Compound* **10**. A magnetically stirred suspension of compound **9** (1.17 g, 4.7 mmol), *o*-iodonitrobenzene (**2**) (2.33 g, 9.4 mmol), and copper powder (1.50 g, 23.5 g.atom) in dry DMSO (10 mL) maintained at 50 °C was treated with $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (220 mg, 0.24 mmol). After 3 h, the reaction mixture was cooled to 22 °C and diluted with ethyl acetate (10 mL) before being filtered through a plug of TLC-grade silica topped with diatomaceous earth. The solids thus retained were washed with ethyl acetate (1 × 30 mL), and the combined filtrates were washed with ammonia (2 × 50 mL of a 5% v/v aqueous solution), water (2 × 50 mL), and brine (1 × 50 mL) before being dried ($Na_2SO_4$), filtered, and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:5 v/v ethyl acetate/40−60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **10** (920 mg, 80%) as a pale-yellow, crystalline solid, mp 112 °C. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 8.02 (dd, *J* = 8.2 and 1.2 Hz, 1H), 7.59 (m, 1H), 7.46 (m, 1H), 7.24 (dd, *J* = 7.6 and 1.4 Hz, 1H), 6.65 (s, 1H), 2.61 (t, *J* = 6.8 Hz, 2H), 2.00 (m, 2H), 1.28 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 196.4, 155.5, 148.6, 136.6, 133.2, 132.1, 131.7, 128.7, 124.2, 35.8, 34.7, 33.4, 27.7. IR (ATR) $\nu_{max}$: 2960, 1682, 1524, 1351, 1145, 859, 787, 725 $cm^{-1}$. MS (ESI, +) (*m*/*z*): 268 [$(M+Na)^+$, 100%], 246 [$(M+H)^+$, 56]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{14}H_{15}NO_3$, 246.1125; found, 246.1126.

*Compound* **11**. A magnetically stirred mixture of compound **10** (50 mg, 0.20 mmol) and 10% palladium on carbon (10 mg) in dry methanol (5 mL) maintained at 22 °C was placed under a hydrogen atmosphere. After 2 h, the reaction mixture was filtered through a pad of diatomaceous earth, and the filtrate was concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 5:95 v/v ethyl acetate/40−60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.4 in 1:10 v/v ethyl acetate/40−60 petroleum ether elution), compound **11**[7] (37 mg, 92%) as a white, crystalline solid, mp 99 °C. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 7.66 (broad s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.29 (m, 1H), 7.10−7.02 (complex m, 2H), 2.73 (t, *J* = 6.5 Hz, 2H), 2.52 (s, 2H), 1.68 (t, *J* = 6.5 Hz, 2H), 1.10 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 136.1, 132.8, 128.1, 120.9, 119.0, 117.6, 110.3, 109.7, 36.1, 34.9, 30.2, 28.2, 20.7. IR (ATR) $\nu_{max}$: 3406, 2950, 1468, 1357, 1327, 1236, 1187, 1008, 740, 635 $cm^{-1}$. MS (ESI, −) (*m*/*z*): 198 [$(M-H)^-$, 100%]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{14}H_{18}N$, 200.1434; found, 200.1433.

*Compound* **12**. A magnetically stirred solution of compound **10** (50 mg, 0.20 mmol) in acetone (3 mL) maintained at 22 °C was treated with titanium(III) chloride (1.25 mL of a 12% w/v solution in hydrochloric acid, 1.20 mmol). After 16 h, the reaction mixture was cooled to 22 °C and then quenched with $Na_2CO_3$ (10 mL of a saturated aqueous solution), and the resulting heterogeneous mixture filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 20 mL), and the aqueous phase associated with the combined filtrates was extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with brine (1 × 50 mL), dried ($Na_2SO_4$), and filtered before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:8 v/v ethyl acetate/dichloromethane elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **12**[8] (35 mg, 82%) as a white, crystalline solid, mp 258 °C (lit.[8] mp 270−274 °C). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 8.80 (broad s, 1H), 8.26 (m, 1H), 7.38 (m, 1H), 7.24 (m, 2H), 2.68 (dd, *J* = 7.0 and 6.0 Hz, 2H), 2.10 (dd, *J* = 7.0 and 6.0 Hz, 2H), 1.48 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 194.0, 158.3, 135.6, 124.9, 123.4, 122.7, 121.7, 111.4, 111.0, 38.6, 35.4, 32.1, 27.4. IR (ATR) $\nu_{max}$: 3186, 2962, 1625, 1615, 1582, 1474, 1453, 1415, 1201, 881, 756 $cm^{-1}$. MS (ESI, +) (*m*/*z*): 449 [$(2M+Na)^+$, 58%], 236 [$(M+Na)^+$, 85] 214 [$(M+H)^+$, 100]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{14}H_{16}NO$, 214.1227; found, 214.1226.

*Compound* **14**. A magnetically stirred solution of compound **13**[9] (109 mg, 0.50 mmol) in acetone (2.5 mL) maintained at 22 °C was treated with titanium(III) chloride (2.5 mL of a 12% w/v solution in hydrochloric acid, 2.39 mmol). After 16 h, the reaction mixture was quenched with sodium carbonate (10 mL of a saturated aqueous solution), and the resulting heterogeneous mixture filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 20 mL), and the aqueous phase associated with the combined filtrates was extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with brine (1 × 10 mL), dried ($Na_2SO_4$), and filtered before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, ethyl acetate elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **14** (50 mg, 54%) as a white, crystalline solid, mp 179 °C. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 13.01 (broad s, 1H), 8.55 (dd, *J* = 7.7 and 1.4 Hz, 1H), 8.31 (d, *J* = 4.9 Hz, 1H), 7.29 (m, 1H), 3.13 (t, *J* = 6.2 Hz, 2H), 2.65 (t, *J* = 6.4 Hz, 2H), 2.40−2.26 (complex m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 194.0, 152.5, 148.8, 141.8, 130.5, 118.5, 118.2, 111.7, 37.9, 23.5, 23.4. IR (ATR) $\nu_{max}$: 3047, 2950, 2842, 1640, 1589, 1472, 1414, 1281, 1178, 1010, 776 $cm^{-1}$. MS (ESI, +) (*m*/*z*): 209 [$(M+H)^+$, 100%], 187 [$(M + Na)^+$, 60]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{11}H_{11}N_2O$, 187.0866; found, 187.0865.

*Compound* **15**. A magnetically stirred solution of levoglucosenone (1.50 g, 11.9 mmol) in dry dichloromethane (15 mL) maintained at 22 °C was treated, in portions, with powdered molecular iodine (4.53 g, 17.8 mmol) and then pyridine (1.05 mL, 13.1 mmol). After 48 h, the reaction mixture was quenched with sodium sulfite (30 mL of a saturated aqueous solution) and then stirred vigorously until two clear layers were formed. The separated aqueous phase was extracted with dichloromethane (2 × 20 mL), and the combined organic phases were washed with sodium sulfite (1 × 60 mL of a saturated aqueous solution), hydrochloric acid (1 × 100 mL of a 0.5 M aqueous solution), and brine (1 × 100 mL) before being dried ($Na_2SO_4$) and then filtered through a plug of TLC-grade silica. The filtrate was concentrated under reduced pressure, and the residue so obtained was subjected to flash column chromatography (silica, 1:1 v/v diethyl ether/40−60 petroleum ether elution). Concentration of the appropriate fractions ($R_f$ = 0.3) then gave compound **15**[10] (2.24 g, 75%) as a pale-yellow, crystalline solid, mp 64 °C (lit.[10] mp 85−90 °C). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 7.96 (d, *J* = 5.0 Hz, 1H), 5.57 (s, 1H), 4.93 (m, 1H), 3.89−3.78 (complex m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 183.1, 155.5, 100.9, 99.8, 74.3, 66.5. IR (ATR) $\nu_{max}$: 3063, 2973, 2899, 1699, 1575, 1329, 1175, 1104, 978, 916, 881 $cm^{-1}$.


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J. Org. Chem. XXXX, XXX, XXX−XXX

MS (ESI, +) ($m/z$): 307 [(M+Na+MeOH)$^+$, 100%], 275 [(M+Na)$^+$, 55]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_6H_6IO_3$, 252.9356; found, 252.9361.

*Compound* ***17***. A magnetically stirred suspension of compound **15** (297 mg, 1.2 mmol), *o*-iodonitrobenzene (**2**) (200 mg, 0.79 mmol), and copper powder (250 mg, 4.0 g.atom) in dry DMSO (6 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$ (72 mg, 0.08 mmol). After 16 h, the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL), and then filtered through a plug of TLC-grade silica topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 10 mL), and the combined filtrates were washed with ammonia (2 × 15 mL of a 5% v/v aqueous solution), water (2 × 15 mL), and then brine (1 × 15 mL) before being dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica, 2:8 to 1:1 v/v diethyl ether/40−60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.3 in 4:6 v/v ethyl acetate/40−60 petroleum ether), compound **17** (135 mg, 69%) as a white, crystalline solid, mp 137 °C. $^1$H NMR (400 MHz, acetone-$d_6$, $\delta$): 7.92 (m, 1H), 7.53 (m, 1H), 7.27−7.18 (complex m, 2H), 5.88 (d, $J$ = 4.5 Hz, 1H), 5.38 (s, 1H), 4.03 (dd, $J$ = 7.1 and 4.5 Hz, 1H), 3.84 (d, $J$ = 7.1 Hz, 1H) (resonance due to one proton not observed). $^{13}$C NMR (100 MHz, acetone-$d_6$, $\delta$): 186.8, 151.6, 137.1, 125.1, 124.4, 123.3, 121.5, 113.4, 108.3, 103.2, 72.2, 68.0. IR (ATR) $\nu_{max}$: 2967, 2899, 1703, 1523, 1354, 1108, 984, 895, 794 cm$^{-1}$. MS (ESI, +) ($m/z$): 270 [(M+Na)$^+$, 100%]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{12}H_{10}NO_5$, 248.0553; found, 248.0553.

*Compound* ***18***. A magnetically stirred suspension of compound **15** (2.77 g, 11.0 mmol), 3-bromo-2-nitropyridine (**16**)[8] (1.0 g, 5.0 mmol), copper(I) iodide (1.43 g, 7.5 mmol), and copper powder (1.58 g, 25.0 g.atom) in dry DMSO (50 mL) maintained at 50 °C was treated with Pd(dppf)$Cl_2$·$CH_2Cl_2$ (204 mg, 0.25 mmol). After 5 h, the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (20 mL), and then filtered through a plug of TLC-grade silica topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 40 mL), and the combined filtrates were washed with ammonia (2 × 25 mL of a 5% v/v aqueous solution), water (2 × 25 mL), and then brine (1 × 25 mL) before being dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40−60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **18** (1.133 g, 91%) as a yellow, crystalline solid, mp 170 °C. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 8.59 (dd, $J$ = 4.7 and 1.7 Hz, 1H), 7.79 (dd, $J$ = 7.6 and 1.7 Hz, 1H), 7.65 (dd, $J$ = 7.6 and 4.7 Hz, 1H), 7.32 (d, $J$ = 4.8 Hz, 1H), 5.51 (s, 1H), 5.20 (t, $J$ = 4.6 Hz, 1H), 4.05−3.96 (complex m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 185.4, 156.8, 148.8, 144.4, 141.6, 134.7, 128.1, 123.5, 101.3, 72.3, 66.9. IR (ATR) $\nu_{max}$: 2971, 2888, 1702, 1541, 1407, 1364, 1101, 984, 930, 890, 819, 647 cm$^{-1}$. MS (ESI, +) ($m/z$): 271 [(M+Na)$^+$, 100%]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{11}H_9N_2O_5$, 249.0506; found, 249.0509.

*Compound* ***19***. A magnetically stirred solution of compound **18** (40 mg, 0.16 mmol) in THF (1.7 mL) maintained at 22 °C was treated with titanium(III) chloride (0.85 mL of a 12% w/v solution in hydrochloric acid, 0.81 mmol). After 18 h, the reaction mixture was quenched with sodium carbonate (5 mL of a saturated aqueous solution), and the resulting heterogeneous mixture was filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 10 mL), the combined filtrates were separated, and the aqueous phase was extracted with ethyl acetate (2 × 5 mL). The combined organic phases were washed with brine (1 × 30 mL), dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 4:6 v/v ethyl acetate/40−60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.4), compound **19** (34 mg, 97%) as a white, crystalline solid, mp > 250 °C. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 8.09 (d, $J$ = 8.1 Hz, 1H), 7.65 (m, 1H), 7.56 (m, 1H), 7.28−7.24 (complex m, 2H), 5.51 (s, 1H), 5.19 (t, $J$ = 4.6 Hz, 1H), 4.06−3.95 (complex m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 185.7, 148.5, 142.7, 137.3, 133.5, 131.5, 129.8, 128.8, 124.6, 101.3, 72.1, 66.8. IR (ATR) $\nu_{max}$: 3278, 2924, 1651, 1479, 1452, 1076, 869 cm$^{-1}$. MS (ESI, +) ($m/z$): 238 [(M+Na)$^+$, 100%]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{12}H_{10}NO_3$, 216.0655; found, 216.0658.

*Compound* ***20***. A magnetically stirred solution of compound **18** (52 mg, 0.21 mmol) and hydrochloric acid (9 mL of a 1 M aqueous solution) in 1,2-dimethoxyethane (5 mL) maintained at 50 °C was treated with iron powder (59 mg, 1.10 g.atom). After 18 h, the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (10 mL), and then filtered through a plug of TLC-grade silica topped with diatomaceous earth, and the solids so retained were washed with ethyl acetate (1 × 10 mL). The combined filtrates were washed with water (2 × 20 mL) and brine (1 × 20 mL) before being dried ($Na_2SO_4$), filtered, and then concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica, 2:1 v/v ethyl acetate/40−60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **20** (26 mg, 58%) as a white, crystalline solid, mp 275 °C. $^1$H NMR (400 MHz, acetone-$d_6$, $\delta$): 8.37 (m, 1H), 8.25 (dd, $J$ = 7.8 and 1.6 Hz, 1H), 7.29 (dd, $J$ = 7.8 and 4.8 Hz, 1H), 5.95 (d, $J$ = 4.6 Hz, 1H), 5.44 (s, 1H), 4.11 (dd, $J$ = 7.2 and 4.6 Hz, 1H), 3.96 (d, $J$ = 7.2 Hz, 1H) (signal due to N−H group proton not observed). $^{13}$C NMR (100 MHz, acetone-$d_6$, $\delta$): 186.5, 152.2, 149.8, 145.6, 129.6, 119.4, 117.4, 107.1, 103.1, 72.1, 68.0. IR (ATR) $\nu_{max}$: 2981, 2888, 1679, 1592, 1480, 1426, 1109, 1075, 889, 805 cm$^{-1}$. MS (ESI, +) ($m/z$): 239 [(M+Na)$^+$, 100%], 217 [(M+H)$^+$, 10]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{11}H_9N_2O_3$, 217.0608; found, 217.0609.

*Compounds* ***22*** *and* ***23***. A magnetically stirred solution of *trans*-chalcone (**21**) (475 mg, 2.28 mmol) in dry dichloromethane (7 mL) maintained at 22 °C was treated, in portions, with powdered molecular iodine (2.00 g, 7.98 mmol) and then pyridine (7 mL). After 48 h, the reaction mixture was quenched with sodium sulfite (30 mL of a saturated aqueous solution), and vigorous stirring continued until two clear layers had formed. The separated aqueous phase was extracted with dichloromethane (2 × 10 mL), and the combined organic phases were washed with sodium sulfite (1 × 60 mL of a saturated aqueous solution), hydrochloric acid (1 × 500 mL of a 0.5 M aqueous solution), and brine (1 × 50 mL) before being dried ($Na_2SO_4$) and then filtered through a plug of TLC-grade silica. The filtrate was concentrated under reduced pressure, and the residue so obtained was subjected to flash column chromatography (silica, 5:95 to 1:9 v/v diethyl ether/40−60 petroleum ether gradient elution). Two fractions, A and B, were thus obtained.

Concentration of fraction A ($R_f$ = 0.5 in 1:9 diethyl ether/40−60 petroleum ether) gave compound **22**[12] (439 mg, 58%) as a light-yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 8.01−7.92 (complex m, 2H), 7.58−7.40 (complex m, 6H), 7.17 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 193.0, 148.5, 135.5, 135.3, 132.7, 130.2, 130.0, 129.4, 128.5, 128.4, 103.5. IR (ATR) $\nu_{max}$: 3057, 3024, 2923, 1657, 1595, 1446, 1238, 1176, 1059, 748, 689 cm$^{-1}$. MS (ESI, +) ($m/z$): 357 [(M+Na)$^+$, 100%]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{15}H_{12}IO$, 334.9927; found, 334.9916.

Concentration of fraction B ($R_f$ = 0.6 in 1:9 diethyl ether/40−60 petroleum ether) gave compound **23**[12] (79 mg, 10%) as a light-yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 7.98 (m, 2H), 7.53 (m, 2H), 7.40 (m, 2H), 7.16 (m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 193.6, 143.4, 136.0, 134.0, 132.5, 129.9, 128.8, 128.7, 128.5, 128.1, 92.7. IR (ATR) $\nu_{max}$: 3058, 3024, 2924, 1659, 1596, 1447, 1221, 1173, 1012, 750, 685 cm$^{-1}$. MS (ESI, +) ($m/z$): 357 [(M+Na)$^+$, 100%]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{15}H_{12}IO$, 334.9927; found, 334.9916.

*Compounds* ***24*** *and* ***25***. Method i: A magnetically stirred mixture of compound **22** (160 mg, 0.48 mmol), 3-bromo-2-nitropyridine (**16**) (155 mg, 0.76 mmol), and copper powder (182 mg, 2.87 g.atom) in dry DMSO (5 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$ (43 mg, 0.05 mmol). After 16 h, the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (10 mL), and then filtered through a plug of TLC-grade silica topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 5 mL), and the combined filtrates were washed with ammonia (2 × 10 mL of a 5% v/


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J. Org. Chem. XXXX, XXX, XXX−XXX

v aqueous solution), water (2 × 10 mL), and brine (1 × 10 mL) before being dried ($Na_2SO_4$), filtered, and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 3:7 to 1:1 v/v diethyl ether/40−60 petroleum ether gradient elution) and so afforded two fractions, A and B.

Concentration of fraction A ($R_f$ = 0.3 in 3:7 ethyl acetate/40−60 petroleum ether) gave compound **24** (122 mg, 77%) as a light-yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 8.53 (dd, $J$ = 4.6 and 1.8 Hz, 1H), 8.16 (dd, $J$ = 7.8 and 1.8 Hz, 1H), 7.90 (m, 2H), 7.62 (dd, $J$ = 7.8 and 4.6 Hz, 1H), 7.40 (m, 1H), 7.29−7.22 (complex m, 3H), 7.17−7.08 (complex m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 195.6, 156.4, 147.8, 141.9, 138.3, 135.9, 134.3, 133.7, 133.4, 130.0, 129.4, 129.1, 128.3, 128.2(1), 128.9(9), 127.3. IR (ATR) $\nu_{max}$: 3060, 2982, 1734, 1646, 1540, 1447, 1359, 1245, 694 cm$^{-1}$. MS (ESI, +) ($m/z$): 353 [(M+Na)$^+$, 100%]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{20}H_{15}N_2O_3$, 331.1077; found, 331.1080. On standing this oil solidified and thus yielding crystals (mp 96 °C), one of which was suitable for X-ray analysis.

Concentration of fraction B ($R_f$ = 0.4 in 3:7 ethyl acetate/40−60 petroleum ether) gave compound **25** (12 mg, 8%) as a light-yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 8.63 (dd, $J$ = 4.6 and 1.9 Hz, 1H), 7.92 (m, 2H), 7.73 (m, 1H), 7.60 (m, 2H), 7.53 (m, 2H), 7.48 (s, 1H), 7.29 (m, 1H), 7.23 (m, 2H), 7.00 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 195.6, 156.4, 148.3, 143.8, 143.5, 137.4, 135.9, 133.3, 132.4, 130.1, 129.9, 129.8, 128.7, 128.4, 128.3, 127.9. IR (ATR) $\nu_{max}$: 3060, 2981, 1647, 1541, 1447, 1365, 1231, 695 cm$^{-1}$. MS (ESI, +) ($m/z$): 353 [(M+Na)$^+$, 100%]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{20}H_{15}N_2O_3$, 331.1077; found, 331.1079.

Method ii: Compound **23** was subjected to cross-coupling with bromopyridine **16** in the same manner as described immediately above in Method i. Subjection of the product mixture obtained on workup to flash column chromatography (silica, 3:7 to 1:1 v/v diethyl ether/40−60 petroleum ether gradient elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f$ = 0.3 in v/v 3:7 ethyl acetate/40−60 petroleum ether) gave compound **24** (18%) as a light-yellow oil. This material was identical, in all aspects, with that obtained by Method i.

Concentration of fraction B ($R_f$ = 0.4 in 3:7 v/v ethyl acetate/40−60 petroleum ether) gave compound **25** (41%) as a light-yellow oil. This material was identical, in all aspects, with that obtained by Method i.

*Compound 26*. Method i: A magnetically stirred mixture of compound **24** (23 mg, 0.07 mmol) and 10% palladium on carbon (10 mg) in ethyl acetate (5 mL) maintained at 22 °C was placed under a hydrogen atmosphere. After 16 h, the reaction mixture was flushed with nitrogen and then filtered through a pad of diatomaceous earth, and the filtrate was concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 3:7 to 1:1 v/v ethyl acetate/40−60 petroleum ether gradient elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.4 in 3:7 v/v ethyl acetate/40−60 petroleum ether), compound **26**[13] (13 mg, 63%) as a white, crystalline solid, no mp, decomposition above 120 °C. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 11.77 (broad s, 1H), 8.18 (m, 1H), 7.69 (m, 3H), 7.50 (m, 2H), 7.42 (m, 1H), 7.32−7.15 (complex m, 5H), 6.99 (m, 1H), 4.32 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 148.1, 140.9, 136.9, 132.3, 130.1, 129.6, 128.9, 128.6, 128.5, 128.3(1), 128.2(9), 128.2, 126.0, 115.5, 109.1, 30.5. IR (ATR) $\nu_{max}$: 3026, 2920, 2849, 1739, 1600, 1579, 1490, 1461, 1411, 765, 699 cm$^{-1}$. MS (ESI, +) ($m/z$): 285 [(M+H)$^+$, 100%]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{20}H_{17}N_2$, 285.1386; found, 285.1388.

Method ii: Compound **25** was subjected to reductive cyclization in the same manner as described immediately above in Method i. Subjection of the product mixture obtained on workup to flash column chromatography (silica, 3:7 to 1:1 v/v diethyl ether/40−60 petroleum ether gradient elution) afforded, after concentration of the appropriate fractions ($R_f$ = 0.4 in 3:7 to 1:1 v/v ethyl acetate/40−60 petroleum ether), compound **26** (80%) as a white, crystalline solid. This material was identical, in all aspects, with that obtained by Method i.

*Compound 27*. A magnetically stirred mixture of compound **24** (45 mg, 0.14 mmol) in THF (5 mL) maintained at 22 °C was treated with titanium(III) chloride (0.9 mL of a 12% w/v solution in hydrochloric acid, 0.86 mmol). After 16 h, the reaction mixture was quenched with sodium carbonate (10 mL of a saturated aqueous solution), and the resulting heterogeneous mixture was filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 20 mL), the combined filtrates were separated, and the aqueous phase was extracted with ethyl acetate (4 × 10 mL). The combined organic phases were washed with brine (1 × 50 mL), dried ($Na_2SO_4$), and filtered before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 2:8 to 1:1 v/v ethyl acetate/40−60 petroleum ether gradient elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.2 in 3:7 v/v ethyl acetate/40−60 petroleum ether), compound **27** (20 mg, 49%) as a yellow, crystalline solid, mp 159 °C. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 8.37 (d, $J$ = 7.9 Hz, 1H), 8.15 (broad s, 1H), 7.64 (m, 2H), 7.52 (m, 2H), 7.34 (m, 4H), 7.21 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 192.7, 148.1, 145.4, 142.5, 139.3, 131.7, 131.5, 131.1, 129.8, 129.6, 129.3, 128.4, 127.8, 117.9, 111.6 (one signal obscured or overlapping). IR (ATR) $\nu_{max}$: 2917, 2849, 1615, 1459, 1435, 1292, 936, 896, 766, 730, 698 cm$^{-1}$. MS (ESI, +) ($m/z$): 321 [(M+Na)$^+$, 100%], 299 [(M+H)$^+$, 70%]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{20}H_{15}N_2O$, 299.1179; found, 299.1181.

Method ii: Compound **25** was subjected to reductive cyclization in the same manner as described immediately above in Method i. Subjection of the product mixture obtained on workup to flash column chromatography (silica, 2:8 to 1:1 v/v ethyl acetate/40−60 petroleum ether gradient elution) afforded, after concentration of the appropriate fractions ($R_f$ = 0.2 in 3:7 v/v ethyl acetate/40−60 petroleum ether), compound **27** (15%) as a yellow, crystalline solid. This material was identical, in all aspects, with that obtained by Method i.

*Compound 32*. A magnetically stirred mixture of compound **31**[1] (516 mg, 2.00 mmol), *o*-iodonitrobenzene (**2**) (996 mg, 4.00 mmol), and copper powder (636 mg, 10.0 g.atom) in dry DMSO (10 mL) maintained at 50 °C was treated with Pd(dppf)$Cl_2$·$CH_2Cl_2$ (82 mg, 0.10 mmol). After 4 h, the reaction mixture was cooled to 22 °C and then diluted with ethyl acetate (10 mL) before being filtered through a plug of TLC-grade silica topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 30 mL), and the combined filtrates were washed with ammonia (2 × 40 mL of a 5% v/v aqueous solution), water (2 × 40 mL), and brine (1 × 40 mL) before being dried ($Na_2SO_4$), filtered, and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, toluene elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.3), compound **32**[1] (390 mg, 77%) as a clear, yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 9.73 (s, 1H), 8.23 (m, 1H), 7.63−7.56 (complex m, 2H), 7.54 (s, 1H), 7.37−7.22 (complex m, 3H), 7.17 (complex m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 191.8, 148.9, 139.7, 133.9, 133.3, 132.0, 130.5, 130.4, 129.6(1), 129.5(9), 128.7, 125.0 (one signal obscured or overlapping). IR (ATR) $\nu_{max}$: 3348, 3062, 2830, 1682, 1627, 1521, 1346, 1110, 1062, 856, 713 cm$^{-1}$. MS (ESI, +) ($m/z$): 276 [(M+Na)$^+$, 100%], 254 [(M+H)$^+$, 8]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{15}H_{12}NO_3$, 254.0182; found, 254.0182.

*Compounds 33 and 34*. A magnetically stirred solution of compound **32** (134 mg, 0.53 mmol) in acetone (5 mL) maintained at 22 °C was treated with titanium(III) chloride (3.3 mL of a 12% w/v solution in hydrochloric acid, 3.18 mmol). After 23 h, the reaction mixture was quenched with sodium carbonate (10 mL of a saturated aqueous solution,) and the resulting heterogeneous mixture was filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 20 mL), the combined filtrates were separated, and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL), dried ($Na_2SO_4$), and filtered before being


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J. Org. Chem. XXXX, XXX, XXX−XXX

concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v diethyl ether/dichloromethane elution) and thus afforded a partially separable, *ca.* 5−3:1, and slowly interconverting mixture of compounds **33**[14] and **34**[14] (64 mg, 55%) as an oily solid. $R_f$ = 0.2 and 0.4, respectively. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) (for compound **33**): 8.20 (broad s, 1H), 7.85 (s, 1H), 7.70−7.60 (complex m 3H), 7.52−7.41 (complex m, 3H), 7.22 (m, 1H), 6.88 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) (for compound **33**): 170.1, 141.6, 137.7, 135.0, 130.0, 129.8, 129.5, 128.8, 127.6, 123.2, 122.0, 121.9, 110.2. $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$) (for a ca. 3:1 mixture of compounds **33** and **34**): 170.0, 167.7, 141.4, 139.6, 137.6(1), 137.5(9), 134.8, 133.7, 131.9, 130.6, 139.9, 129.7, 129.3, 128.9, 128.6, 128.3, 127.4, 126.2, 125.3, 123.0, 121.8(1). 121.7(9), 121.7, 119.3, 110.1, 109.5. IR (ATR) $\nu_{max}$ (for a mixture): 3222, 3062, 1704, 1613, 1463, 1329, 1202, 781, 747, 722, 696 cm$^{-1}$. MS (ESI, +) (*m*/*z*) (for a mixture): 465 [(2M+Na)$^+$, 60%], 244 [(M+Na)$^+$, 100], 222 [(M+H)$^+$, 13]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{15}H_{12}NO$, 222.0913; found, 222.0906.

Crystals of compound **33** suitable for X-ray analysis were grown from diethyl ether (mp 169 °C).

*Compound* ***36***. A magnetically stirred mixture of 3-iodo-2-methylcyclohex-2-enone[16] (213 mg, 0.90 mmol), *o*-iodonitrobenzene (**2**) (449 mg, 1.80 mmol), and copper powder (286 mg, 4.5 g.atom) in dry DMSO (10 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$ (77 mg, 0.08 mmol). After 16 h, the reaction mixture was cooled to 22 °C and diluted with ethyl acetate (10 mL) before being filtered through a plug of TLC-grade silica topped with diatomaceous earth, and the solids so retained were washed with ethyl acetate (1 × 10 mL). The combined filtrates were washed with ammonia (2 × 40 mL of a 5% v/v aqueous solution), water (2 × 40 mL), and brine (1 × 40 mL) before being dried ($Na_2SO_4$), filtered, and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:4 to 1:1 v/v diethyl ether/40−60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.3 in 2:3 v/v diethyl ether/40−60 petroleum ether elution), compound **36** (120 mg, 61%) as a clear, light-yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 8.18 (dd, *J* = 8.3 and 1.3 Hz, 1H), 7.71 (m, 1H), 7.55 (m, 1H), 7.24 (dd, *J* = 7.6 and 1.6 Hz, 1H), 2.65 (m, 2H), 2.59−2.46 (complex m, 2H), 2.27 (m, 1H), 2.15 (m, 1H), 1.52 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 198.8, 153.9, 146.3, 136.7, 134.0, 131.8, 129.1, 128.8, 124.9, 37.8, 32.5, 23.0, 12.5. IR (ATR) $\nu_{max}$: 2947, 2870, 1665, 1523, 1344, 1111, 908, 727 cm$^{-1}$. MS (ESI, +) (*m*/*z*): 254 [(M+Na)$^+$, 100%], 232 [(M+H)$^+$, 15]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{13}H_{14}NO_3$, 232.0968; found, 232.0966.

*Compound* ***37***. A magnetically stirred solution of compound **35**[16] (150 mg, 0.69 mmol) in acetone (7 mL) maintained at 22 °C was treated with titanium(III) chloride (3.6 mL of a 12% w/v solution in hydrochloric acid, 3.45 mmol). After 16 h, the reaction mixture was quenched with sodium carbonate (15 mL of a saturated aqueous solution), and the resulting heterogeneous mixture was filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 20 mL), and the aqueous phase associated with combined filtrates was extracted with ethyl acetate (4 × 10 mL). The combined organic phases were washed with brine (1 × 50 mL), dried ($Na_2SO_4$), and filtered before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 2:3 v/v ethyl acetate/40−60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.3), compound **37** (130 mg, quant.) as a yellow, crystalline solid, mp 108 °C. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 7.20 (m, 1H), 7.06 (dd, *J* = 7.6 and 1.7 Hz, 1H), 6.82 (m, 1H), 6.77 (m, 1H), 3.64 (broad s, 2H), 2.84 (m, 2H), 2.51 (m, 2H), 1.73 (t, *J* = 2.1 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 209.6, 167.7, 142.5, 138.6, 129.7, 127.4, 122.2, 118.1, 115.7, 34.4, 30.8, 9.5. IR (ATR) $\nu_{max}$: 3453, 3357, 2917, 1689, 1686, 1622, 1494, 1451, 1342, 1222, 1094, 1061, 747 cm$^{-1}$. MS (ESI, +) (*m*/*z*): 210 [(M+Na)$^+$, 100%], 188 [(M+H)$^+$, 17]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{12}H_{14}NO$, 188.1070; found, 188.1069.

*Compound* ***38***. Method i: A magnetically stirred solution of compound **36**[16] (45 mg, 0.19 mmol) in THF (2 mL) maintained at 22 °C was treated with titanium(III) chloride (1.0 mL of a 12% w/v solution in hydrochloric acid, 0.96 mmol). After 16 h, the reaction mixture was quenched with sodium carbonate (5 mL of a saturated aqueous solution), and the resulting heterogeneous mixture was filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 10 mL), the phases associated with the combined filtrates were separated, and the aqueous one was extracted with ethyl acetate (4 × 10 mL). The combined organic phases were washed with brine (1 × 50 mL), dried ($Na_2SO_4$), and filtered before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40−60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.6), compound **38** (40 mg, 98%) as light-yellow crystals, mp 73 °C. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 7.13 (m, 1H), 6.92 (dd, *J* = 7.6 and 1.7 Hz, 1H), 6.79 (m, 1H), 6.74 (dd, *J* = 7.9 and 1.1 Hz, 1H), 3.57 (broad s, 2H), 2.55 (m, 4H), 2.10 (m, 2H), 1.65 (t, *J* = 2.0 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 199.6, 154.9, 141.5, 133.6, 128.8, 127.1, 126.6, 118.4, 115.5, 37.9, 31.9, 22.9, 12.3. IR (ATR) $\nu_{max}$: 3459, 3362, 2945, 2923, 1660, 1618, 1494, 1452, 1354, 1106, 750 cm$^{-1}$. MS (ESI, +) (*m*/*z*): 224 [(M+Na)$^+$, 100%], 202 [(M+H)$^+$, 28]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{13}H_{16}NO$, 202.1226; found, 202.1219.

Method ii: Reduction of compound **36** with $TiCl_3$/HCl in the same manner as detailed above but using acetone instead of THF as the solvent gave, after workup and flash chromatography, compound **38** (80%) as light-yellow crystals. This material was identical, in all aspects, with that obtained by Method i.

*Compounds* ***40*** *and* ***41***. A magnetically stirred mixture of compound **39**[16] (200 mg, 0.92 mmol) in acetone (10 mL) maintained at 22 °C was treated with titanium(III) chloride (5.0 mL of a 12% w/v solution in hydrochloric acid, 4.79 mmol). After 16 h, the reaction mixture was quenched with sodium carbonate (20 mL of a saturated aqueous solution), and the resulting heterogeneous mixture was filtered through diatomaceous earth. The solids so retained were washed with ethyl acetate (40 mL), the combined filtrates were separated, and the aqueous phase was extracted with ethyl acetate (4 × 10 mL). The combined organic phases were washed with brine (1 × 100 mL), dried ($Na_2SO_4$), filtered, and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 to 4:6 v/v ethyl acetate/40−60 petroleum ether elution) and so afforded two fractions, A and B.

Concentration of fraction A ($R_f$ = 0.4 in 1:1 v/v ethyl acetate/40−60 petroleum ether elution) gave compound **40**[17] (80 mg, 40%) as orange-colored crystals, mp 90 °C. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 7.16 (m, 1H), 7.07 (dd, *J* = 7.8 and 1.7 Hz, 1H), 6.78 (m, 1H), 6.73 (dd, *J* = 8.1 and 1.2 Hz, 1H), 6.26 (t, *J* = 1.6 Hz, 1H), 3.84 (broad s, 2H), 2.67 (m, 2H), 2.51 (m, 2H), 2.15 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 199.6, 161.2, 142.8, 129.7, 127.9, 127.7, 125.5, 118.3, 116.2, 37.3, 30.2, 23.1. IR (ATR) $\nu_{max}$: 3443, 3354, 2925, 1655, 1608, 1490, 1449, 1244, 1188, 747 cm$^{-1}$. MS (ESI, +) (*m*/*z*): 210 [(M+Na)$^+$, 100%], 188 [(M+H)$^+$, 9]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{12}H_{14}NO$, 188.1070; found, 188.1072.

Concentration of fraction B ($R_f$ = 0.5 in 1:1 v/v diethyl ether/40−60 petroleum ether elution) gave compound **41** (135 mg, 60%) as red-colored crystals, mp 113 °C. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 7.21 (dd, *J* = 7.9 and 1.5 Hz, 1H), 7.11 (m, 1H), 6.65 (m, 1H), 6.45 (dd, *J* = 8.0 and 1.2 Hz, 1H), 3.64 (broad s, 1H), 2.69 (t, *J* = 6.1 Hz, 2H), 2.43 (dd, *J* = 7.4 and 6.1 Hz, 2H), 2.03 (m, 2H), 1.52 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 196.8, 148.2, 145.2, 133.8, 131.7, 125.2, 120.2, 117.5, 113.8, 53.8, 38.7, 29.0, 25.9, 21.6. IR (ATR) $\nu_{max}$: 3336, 2952, 2925, 1637, 1607, 1380, 1269, 743 cm$^{-1}$. MS (ESI, +) (*m*/*z*): 250 [(M+Na)$^+$, 100%], 228 [(M+H)$^+$, 70%]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{15}H_{18}NO$, 228.1383; found, 228.1384.

*Compound* ***44***. A magnetically stirred solution of compound **40** (35 mg, 0.19 mmol, 1.0 equiv) in butanone (5 mL) was treated with HCl (100 $\mu$L of a 12 M aqueous solution), and the ensuing mixture was maintained at 22 °C for 16 h. The resulting mixture was quenched with sodium carbonate (5 mL of a saturated aqueous


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J. Org. Chem. XXXX, XXX, XXX−XXX

solution), and the separated aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic phases were then dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 5:35 v/v diethyl ether/40−60 petroleum ether elution) to afford, after concentration of the appropriate fractions ($R_f$ = 0.6 in 3:7 v/v diethyl ether/40−60 petroleum ether elution), compound **44** (33 mg, 73%) as a red, crystalline solid, mp 118 °C. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 7.19 (dd, $J$ = 7.9 and 1.3 Hz, 1H), 7.07 (m, 1H), 6.59 (m, 1H), 6.41 (dd, $J$ = 8.0 and 1.1 Hz, 1H), 3.54 (broad s, 1H), 2.70 (m, 2H), 2.45 (m, 3H), 2.04 (m, 2H), 1.49 (s, 3H), 1.34 (m, 1H), 0.87 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 197.1, 149.2, 145.8, 131.9(1), 131.8(9), 125.3, 119.5, 116.9, 113.3, 57.3, 38.8, 33.8, 28.5, 26.1, 21.7, 9.3. IR (ATR) $\nu_{max}$: 3349, 2957, 2932, 2871, 1638, 1609, 1566, 1455, 1378, 1262, 1152 cm$^{-1}$. MS (ESI, +) ($m/z$): 264 [(M +Na)$^+$, 100%], 242 [(M+H)$^+$, 37]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{16}H_{20}NO$ 242.1545; found, 242.1547.

*Compound* ***45***. A magnetically stirred solution of compound **40** (65 mg, 0.35 mmol, 1.0 equiv) and cyclohexanone (136 mg, 1.39 mmol, 4.0 mol eq) in THF (5 mL) was treated with HCl (100 $\mu$L of a 12 M aqueous solution), and the ensuing mixture was stirred at 22 °C for 16 h. The resulting mixture was quenched with sodium carbonate (5 mL of a saturated aqueous solution), and the separated aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were then dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was dissolved in methanol/$CH_2Cl_2$ (5 mL of a 1:1 v/v mixture), the resulting solution was cooled to −78 °C, and $NaBH_4$ (58 mg, 1.55 mmol, 5.0 mol eq) was then added (so as to reduce the excess cyclohexenone). The reaction mixture was stirred at −78 °C for 1 h and then treated with acetone (5 mL) and warmed to 22 °C before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 3:7 v/v diethyl ether/40−60 petroleum ether elution) and so afforded, after concentration of the appropriate fractions ($R_f$ = 0.6), compound **45** as orange crystals (59 mg, 64%), mp 136 °C. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 7.20 (d, $J$ = 7.8 Hz, 1H), 7.11 (m, 1H), 6.66 (m, 1H), 6.52 (dd, $J$ = 8.0 and 1.1 Hz, 1H), 4.57 (broad s, 1H), 2.68 (t, $J$ = 6.1 Hz, 2H), 2.51−2.34 (complex m, 4H), 2.01 (m, 2H), 1.79 (dm, $J$ = 13.2 Hz, 2H), 1.70−1.56 (complex m, 3H), 1.47−1.31 (complex m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 196.9, 149.1, 144.8, 134.1, 131.6, 125.3, 121.1, 117.7, 114.2, 55.4, 39.1, 32.7, 26.3, 24.7, 21.5, 21.0. IR (ATR) $\nu_{max}$: 3382, 2920, 2854, 1637, 1605, 1374, 1311, 1198 cm$^{-1}$. MS (ESI, +) ($m/z$): 290 [(M+Na)$^+$, 100%], 268 [(M+H)$^+$, 9]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{18}H_{22}NO$, 268.1701; found, 268.1697.

*Compound* ***46***. A magnetically stirred solution of compound **40** (35 mg, 0.19 mmol, 1.0 equiv) and benzaldehyde (1.0 mL, 9.72 mmol, 52 mol eq ) in THF (3 mL) was maintained at 22 °C for 16 h and then concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica, 1:4 to 1:1 v/v diethyl ether/40−60 petroleum ether gradient solution) and so afforded, after concentration of the appropriate fractions ($R_f$ = 0.5 in 2:3 v/v diethyl ether/40−60 petroleum ether), compound **46** (51 mg, quant.) as a light-yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 8.38 (s, 1H), 7.87 (dd, $J$ = 7.5 and 2.1 Hz, 2H), 7.56−7.44 (complex m, 3H), 7.40 (m, 1H), 7.33−7.24 (complex m, 2H), 7.04 (dd, $J$ = 7.8 and 1.1 Hz, 1H), 6.13 (broad s, 1H), 2.80 (m, 2H), 2.47 (m, 2H), 2.09 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$): 199.8, 163.2, 160.4, 149.5, 136.0, 134.8, 131.6, 129.9, 129.0, 128.8(1), 128.7(9), 128.1, 125.9, 118.7, 37.5, 30.7, 23.3. IR (ATR) $\nu_{max}$: 3060, 2943, 1661, 1625, 1578, 1451, 1188, 888, 764, 754, 691 cm$^{-1}$. MS (ESI, +) ($m/z$): 298 [(M +Na)$^+$, 100%], 276 [(M+H)$^+$, 15]. HRMS (ESI, +): [M + H]$^+$ Calcd for $C_{19}H_{18}NO$, 276.1383; found, 276.1382.

**X-ray Crystallographic Studies.** *Crystallographic Data. Crystallographic Data for Compound* ***5***. $C_{12}H_{11}NO_2$. M = 201.22. $T$ = 150 K. Monoclinic, space group $P2_1/c$, $Z$ = 8, $a$ = 8.6966(2), $b$ = 12.4116(4), $c$ = 21.1857(7) Å. $\beta$ = 96.602(3)°. $V$ = 2271.59(12) Å$^3$. $D_x$ = 1.177 g cm$^{-3}$. 4391 unique data ($2\theta_{max}$ = 144.0°). $R$ = 0.057 [for 3120 reflections with $I > 2.0\sigma(I)$]. $R_w$ = 0.164 (all data). $S$ = 1.03.

*Crystallographic Data for Compound* ***19***. $C_{12}H_9NO_3$. M = 215.20. $T$ = 150 K. Orthorhombic, space group $P2_12_12_1$, $Z$ = 4, $a$ = 6.7281(1), $b$ = 9.5441(2), $c$ = 15.1689(4) Å. $V$ = 974.08 Å$^3$. $D_x$ = 1.467 g cm$^{-3}$. 1951 unique data ($2\theta_{max}$ = 147.4°). $R$ = 0.038 [for 1890 reflections with $I > 2.0\sigma(I)$]. $R_w$ = 0.101 (all data). $S$ = 1.05.

*Crystallographic Data for Compound* ***24***. $C_{20}H_{14}N_2O_3$. M = 330.33. $T$ = 150 K. Monoclinic, space group $P2_1/c$, $Z$ = 4, $a$ = 12.5226(3), $b$ = 12.7446(3), $c$ = 10.8100 Å. $\beta$ = 107.865(2)°. $V$ = 1642.04 Å$^3$. $D_x$ = 1.336 g cm$^{-3}$. 3297 unique data ($2\theta_{max}$ = 147.6°). $R$ = 0.046 [for 3062 reflections with $I > 2.0\sigma(I)$]. $R_w$ = 0.129 (all data). $S$ = 1.03.

*Crystallographic Data for Compound* ***26***. $C_{20}H_{16}N_2$. M = 284.35. $T$ = 150 K. Triclinic, space group $P\bar{1}$, $Z$ = 4, $a$ = 10.2371(7), $b$ = 12.0551(8), $c$ = 12.5051(9) Å. $\alpha$ = 93.572(6)°. $\beta$ = 105.062(6)°. $\gamma$ = 99.112(6) °. $V$ = 1462.73 (18) Å$^3$. $D_x$ = 1.291 g cm$^{-3}$. 5940 unique data ($2\theta_{max}$ = 52.8°). $R$ = 0.046 [for 4420 reflections with $I > 2.0\sigma(I)$]. $R_w$ = 0.120 (all data). $S$ = 1.04.

*Crystallographic Data for Compound* ***33***. $C_{15}H_{11}NO$. M = 221.25. $T$ = 150 K. Monoclinic, space group $P2_1/c$, $Z$ = 4, $a$ = 4.0072(1), $b$ = 22.2268(5), $c$ = 12.2592(3) Å. $\beta$ = 95.112(2)°. $V$ = 1087.55(5) Å$^3$. $D_x$ = 1.351 g cm$^{-3}$. 2147 unique data ($2\theta_{max}$ = 148.4°). $R$ = 0.052 [for 2026 reflections with $I > 2.0\sigma(I)$]. $R_w$ = 0.144 (all data). $S$ = 1.04.

*Crystallographic Data for Compound* ***38***. $C_{13}H_{15}NO$. M = 201.26. $T$ = 150 K. Monoclinic, space group $P2_1/c$, $Z$ = 12, $a$ = 13.9326(3), $b$ = 31.3218(6), $c$ = 7.6013(1) Å. $\beta$ = 98.270(2)°. $V$ = 3282.67(11) Å$^3$. $D_x$ = 1.222 g cm$^{-3}$. 6363 unique data ($2\theta_{max}$ = 144.2°). $R$ = 0.058 [for 5008 reflections with $I > 2.0\sigma(I)$]. $R_w$ = 0.163 (all data). $S$ = 1.07.

*Crystallographic Data for Compound* ***40***. $C_{12}H_{13}NO$. M = 187.23. $T$ = 150 K. Monoclinic, space group $P2_1$, $Z$ = 2, $a$ = 7.0538(7), $b$ = 8.4543(7), $c$ = 8.3005(10) Å. $\beta$ = 99.725(10)°. $V$ = 487.89(9) Å$^3$. $D_x$ = 1.275 g cm$^{-3}$. 1859 unique data ($2\theta_{max}$ = 52.8°). $R$ = 0.038 [for 1663 reflections with $I > 2.0\sigma(I)$]. $R_w$ = 0.081 (all data). $S$ = 1.09.

*Crystallographic Data for Compound* ***41***. $C_{15}H_{17}NO$. M = 227.29. $T$ = 150 K. Monoclinic, space group $P2_1/n$, $Z$ = 4, $a$ = 8.8038(8), $b$ = 12.8773(9), $c$ = 11.2318(10) Å. $\beta$ = 109.578(10)°. $V$ = 1199.72(19) Å$^3$. $D_x$ = 1.258 g cm$^{-3}$. 2446 unique data ($2\theta_{max}$ = 52.8°). $R$ = 0.039 [for 2055 reflections with $I > 2.0\sigma(I)$]. $R_w$ = 0.107 (all data). $S$ = 1.04.

*Crystallographic Data for Compound* ***44***. $C_{16}H_{17}NO$. M = 239.30. $T$ = 150 K. Monoclinic, space group $P2_1/n$, $Z$ = 4, $a$ = 9.3856(3), $b$ = 12.2110(3), $c$ = 12.1822(4) Å. $\beta$ = 108.645(4)°. $V$ = 1322.90(7) Å$^3$. $D_x$ = 1.202 g cm$^{-3}$. 2640 unique data ($2\theta_{max}$ = 147.2°). $R$ = 0.082 [for 2373 reflections with $I > 2.0\sigma(I)$]. $R_w$ = 0.244 (all data). $S$ = 1.06.

*Crystallographic Data for Compound* ***45***. $C_{18}H_{21}NO$. M = 267.36. $T$ = 150 K. Monoclinic, space group $P2_1/n$, $Z$ = 4, $a$ = 11.0667(3), $b$ = 10.0284(2), $c$ = 14.0170(3) Å. $\beta$ = 112.696(3)°. $V$ = 1435.16(6) Å$^3$. $D_x$ = 1.237 g cm$^{-3}$. 2883 unique data ($2\theta_{max}$ = 148.0°). $R$ = 0.047 [for 2635 reflections with $I > 2.0\sigma(I)$]. $R_w$ = 0.132 (all data). $S$ = 1.06.

*Structure Determinations.* The images for compounds **5**, **19**, **24**, **26**, **33**, **38**, **40**, **41**, **44**, and **45** were measured on either a SuperNova (Cu K$\alpha$, mirror monochromator, $\lambda$ = 1.54184 Å) or Xcalibur (Mo K$\alpha$, mirror monochromator, $\lambda$ = 0.71073 Å) diffractometer fitted with an area detector, and the data were extracted using the CrysAlis package. The structures of these compounds were solved with ShelXT[20] and refined using ShelXL[21] in OLEX2.[22] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 1852687−1852695 and 1855327). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: + 44 1223 336033.


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J. Org. Chem. XXXX, XXX, XXX−XXX

## ■ ASSOCIATED CONTENT

### Supporting Information

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X-ray derived plots for compounds **5**, **19**, **24**, **26**, **33**, **38**, **40**, **41**, **44**, and **45** and copies of the NMR spectra of compounds **5**, **6**, **8**−**12**, **14**, **15**, **17**−**20**, **22**−**27**, **32**−**34**, **36**−**38**, **40**, **41**, and **44**−**46** (PDF)

X-ray crystallographic data for compound **5** ( CIF)

X-ray crystallographic data for compound **19** (CIF)

X-ray crystallographic data for compound **24** (CIF)

X-ray crystallographic data for compound **26** (CIF)

X-ray crystallographic data for compound **33** (CIF)

X-ray crystallographic data for compound **38** (CIF)

X-ray crystallographic data for compound **40** (CIF)

X-ray crystallographic data for compound **41** (CIF)

X-ray crystallographic data for compound **44** (CIF)

X-ray crystallographic data for compound **45** (CIF)

### Accession Codes

CCDC 1852687−1852695 and 1855327 contain the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: + 44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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DOI: 10.1021/acs.joc.8b01940
*J. Org. Chem.* XXXX, XXX, XXX−XXX

Supporting Information for

# The Reductive Cyclization of *o*-Nitroarylated-α,β-Unsaturated Aldehydes and Ketones with $TiCl_3$/HCl or Fe/HCl Leading to 1,2,3,9-Tetrahydro-4*H*-carbazol-4-ones and Related Heterocycles

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and

[b]Research School of Chemistry, Institute of Advanced Studies The Australian National University, Canberra, ACT 2601, Australia

**CONTENTS PAGE**

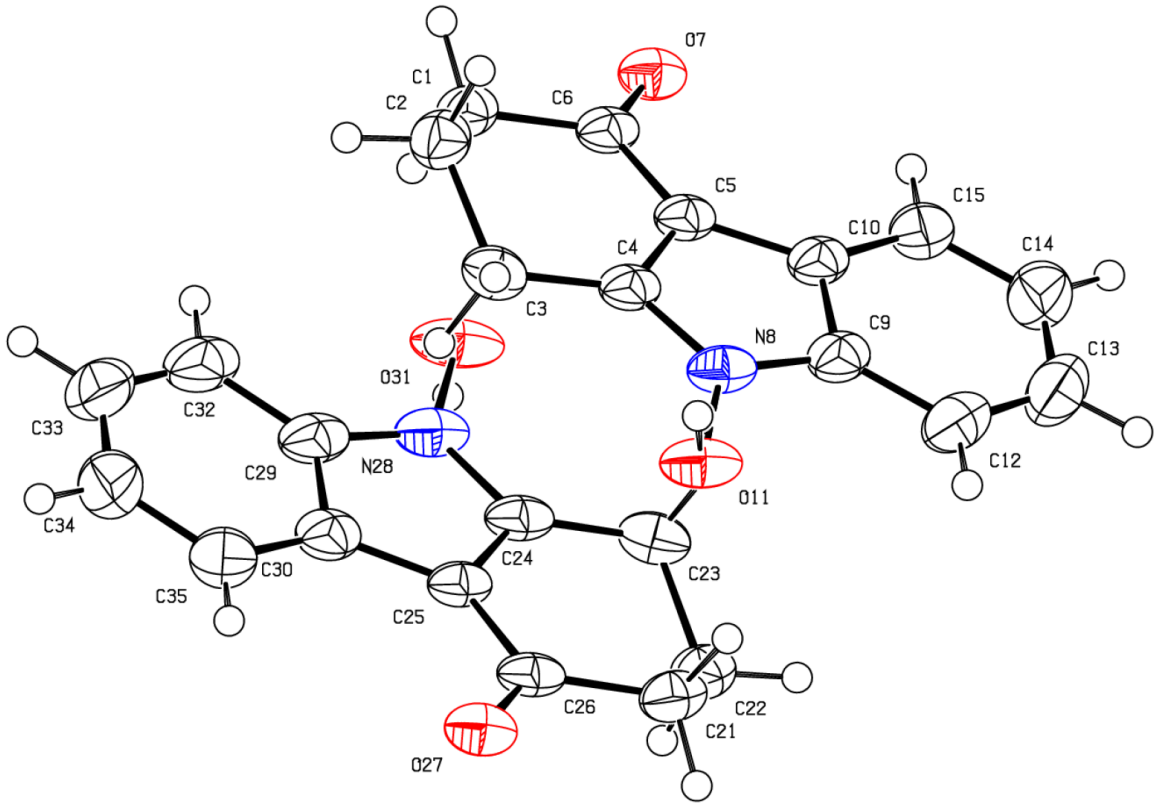



**Figure S1**: Structure of compound **5** (CCDC 1852687). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

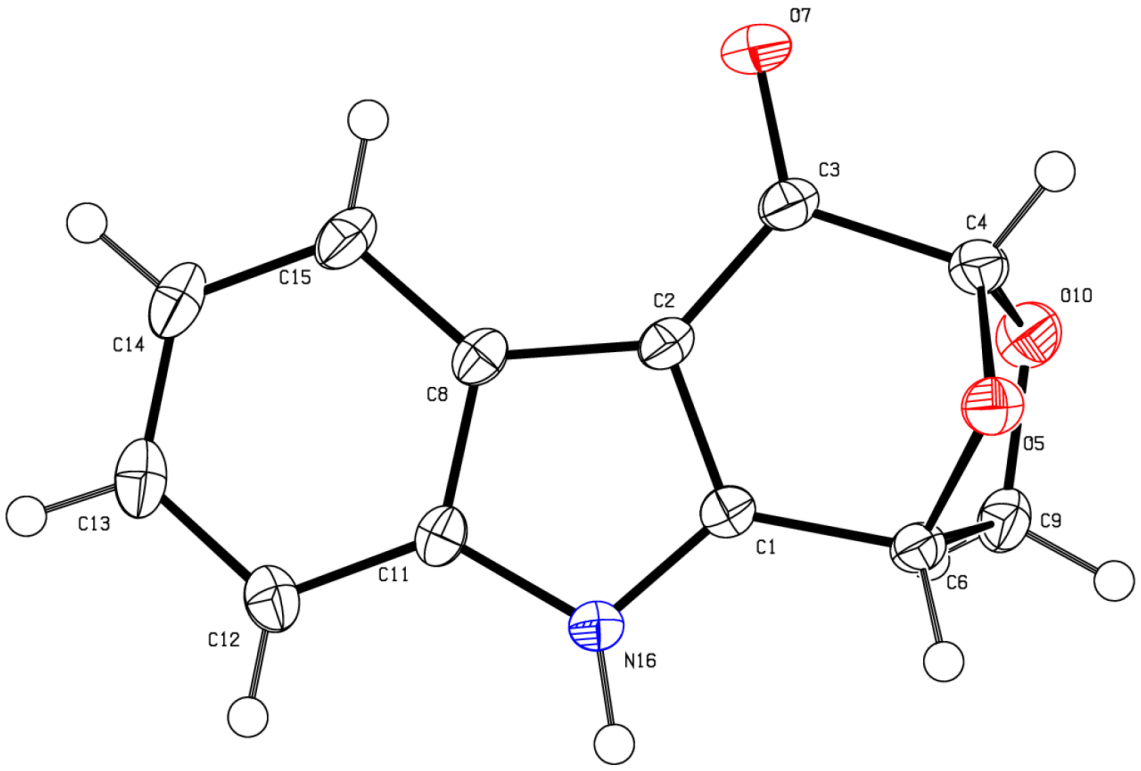



**Figure S2**: Structure of compound **19** (CCDC 1852688). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

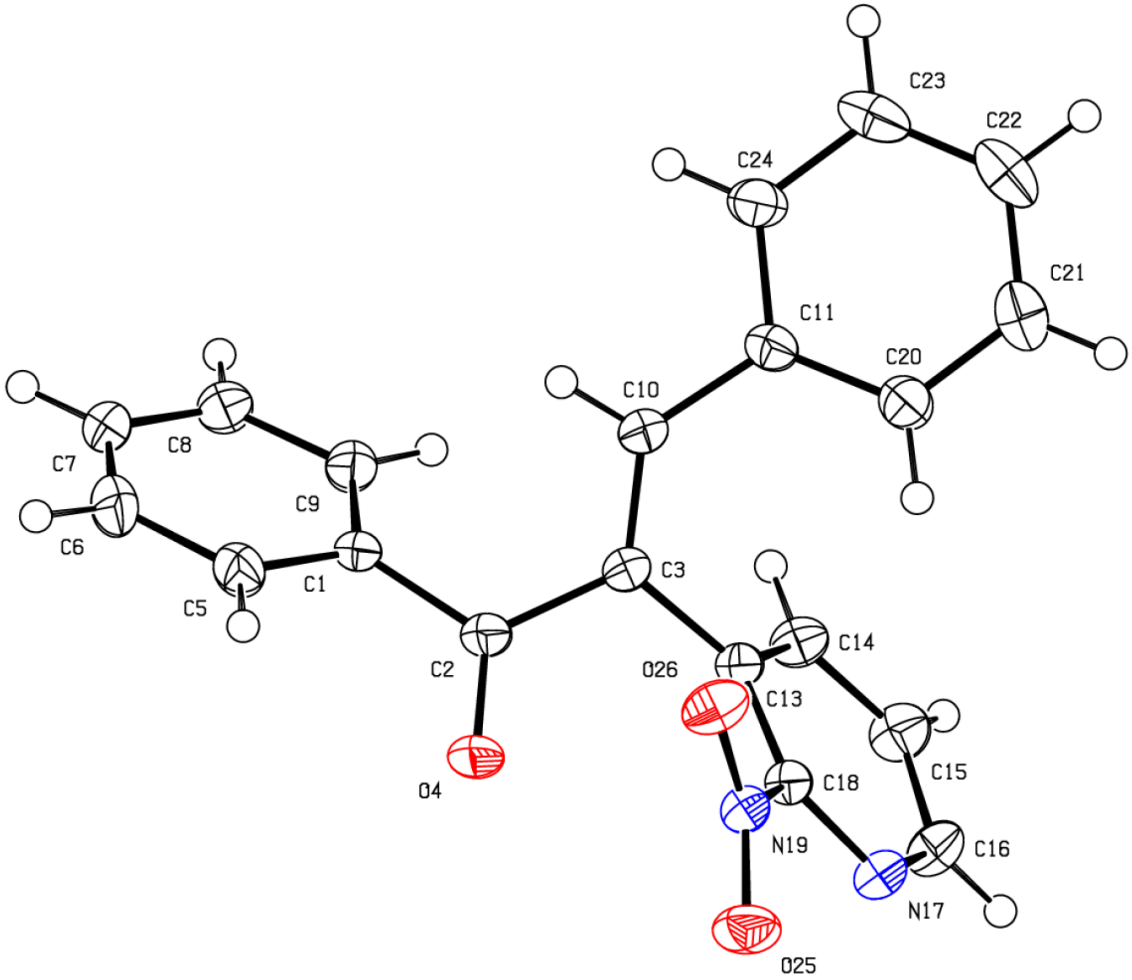



**Figure S3**: Structure of compound **24** (CCDC 1852689). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

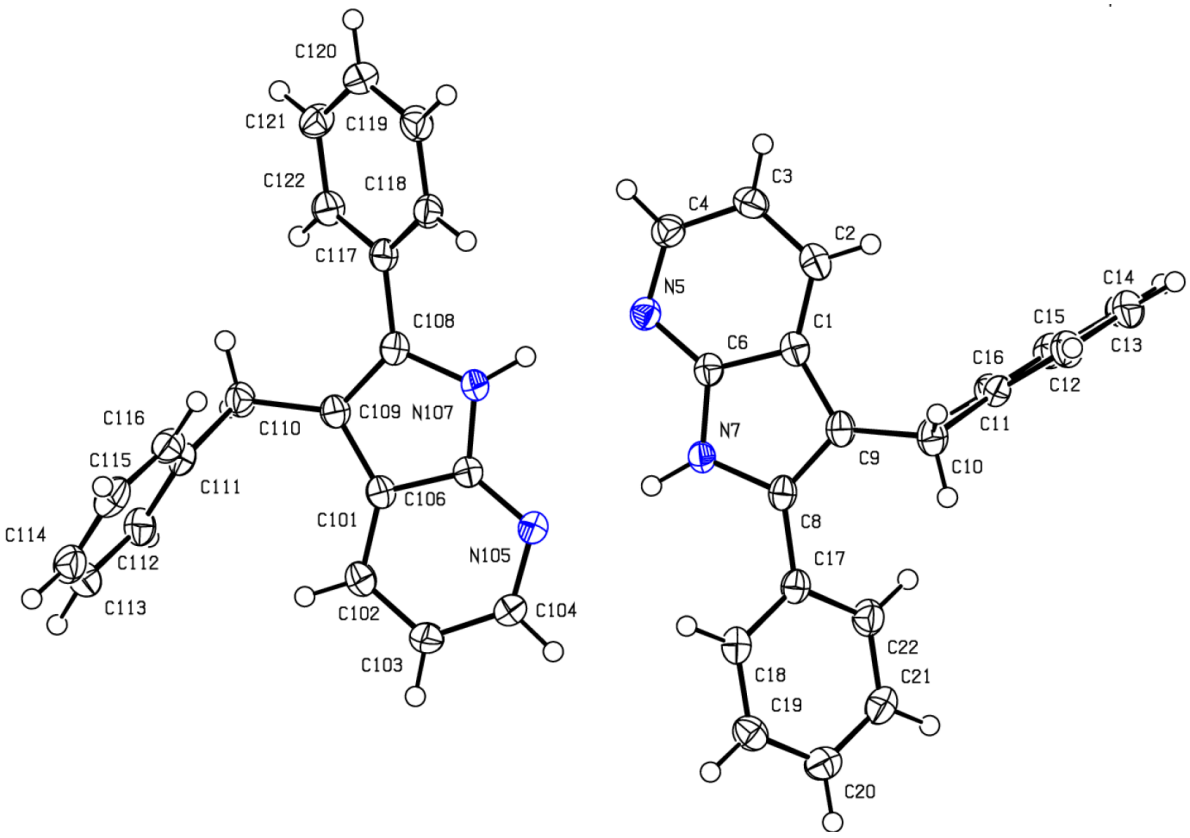



**Figure S4**: Structure of compound **26** (CCDC 1852690). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

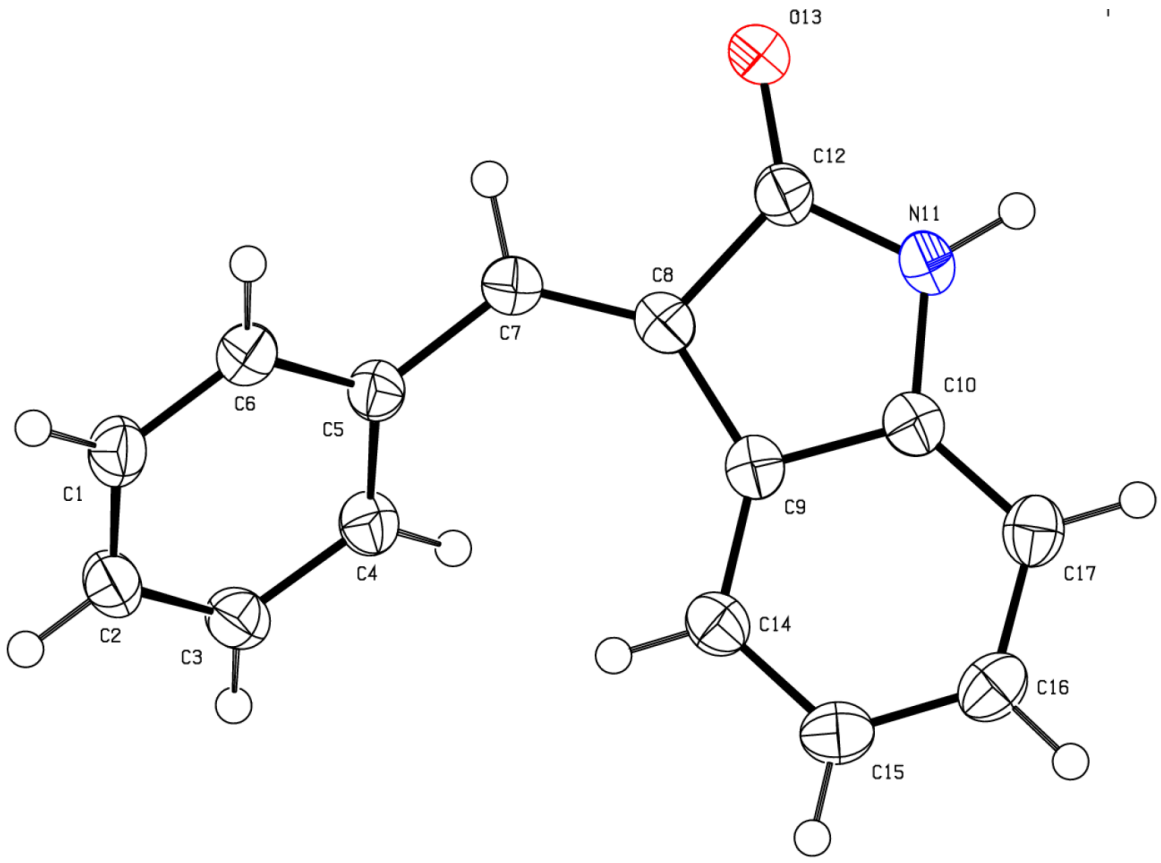



**Figure S5**: Structure of compound **33** (CCDC 1852691). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

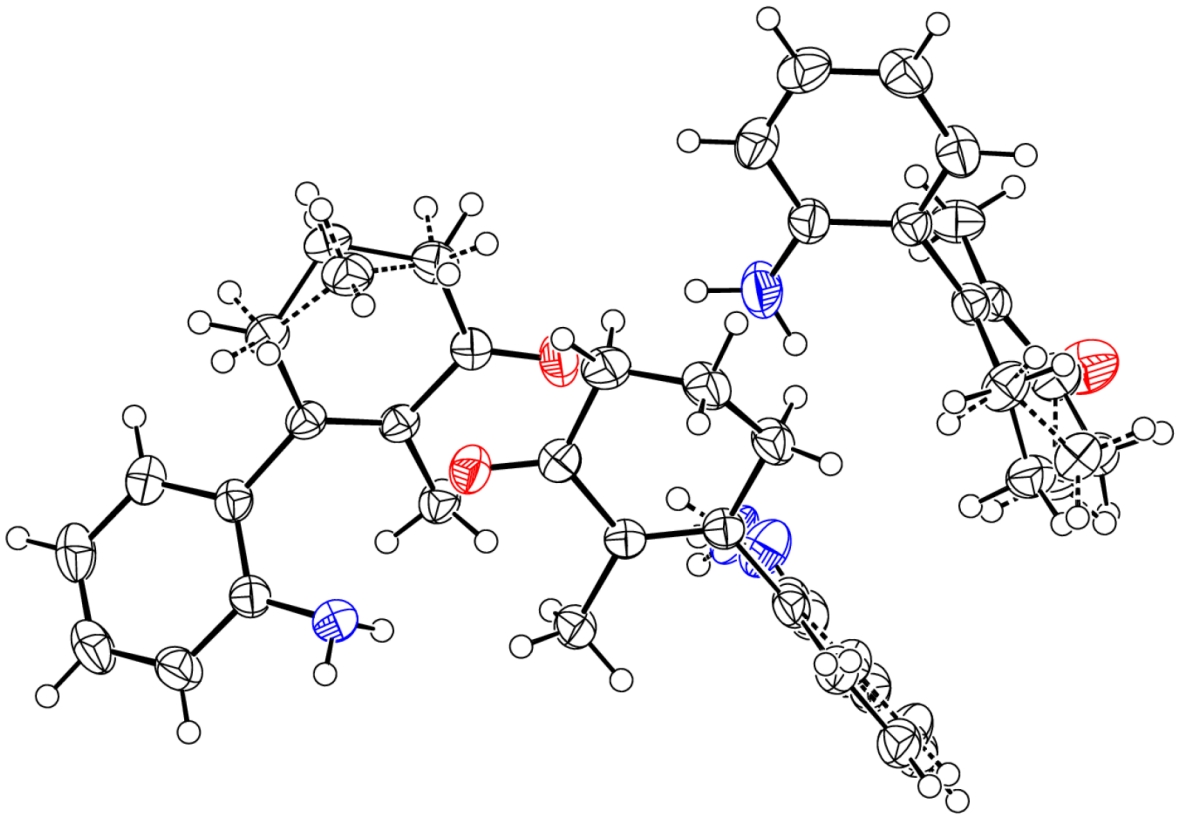


**Figure S6**: Structure of compound **38** (CCDC 1852692). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

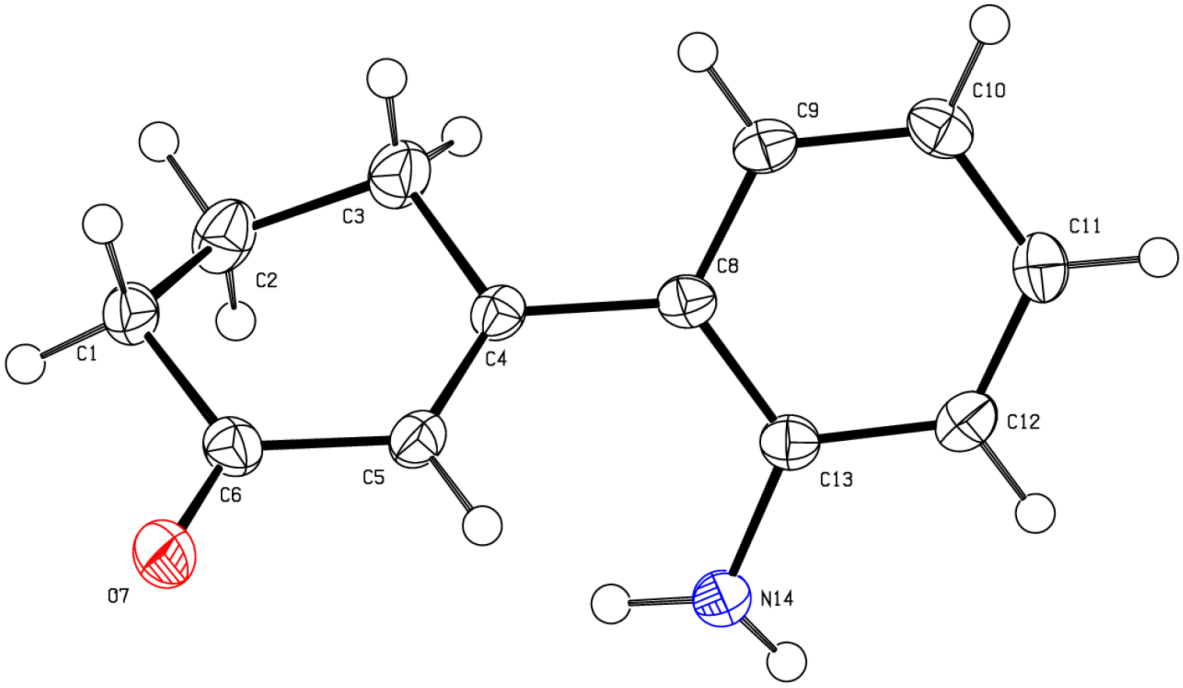



**Figure S7**: Structure of compound **40** (CCDC 1852693). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

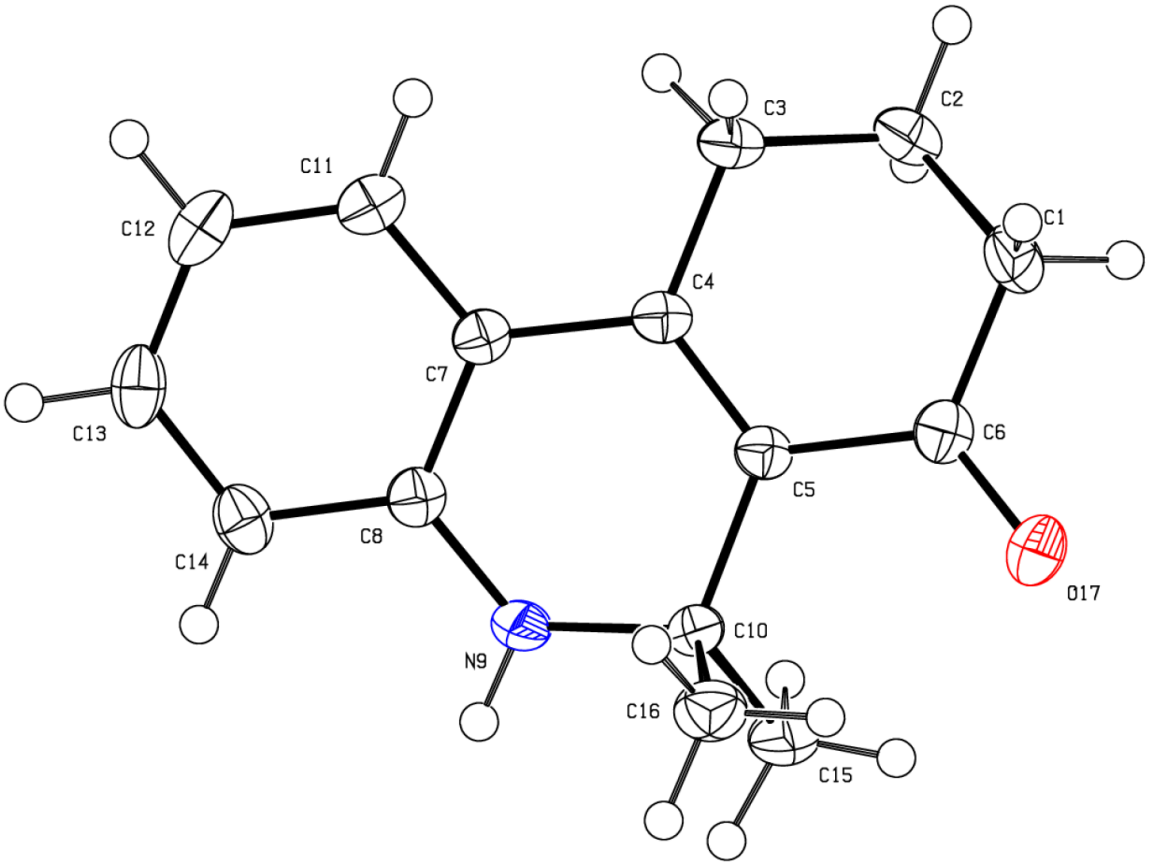



**Figure S8**: Structure of compound **41** (CCDC 1852694). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

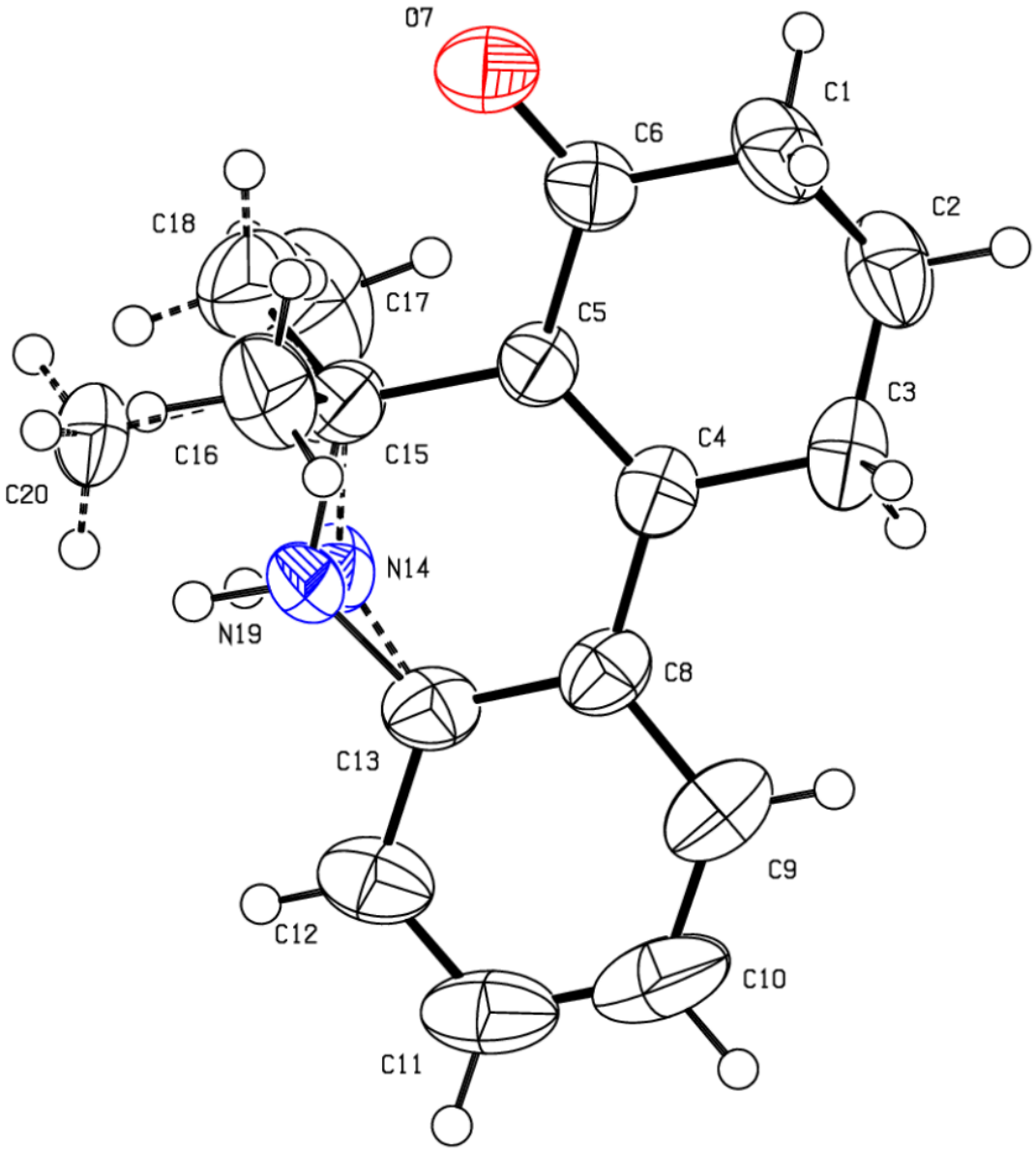



**Figure S9**: Structure of compound **44** (CCDC 1855327). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

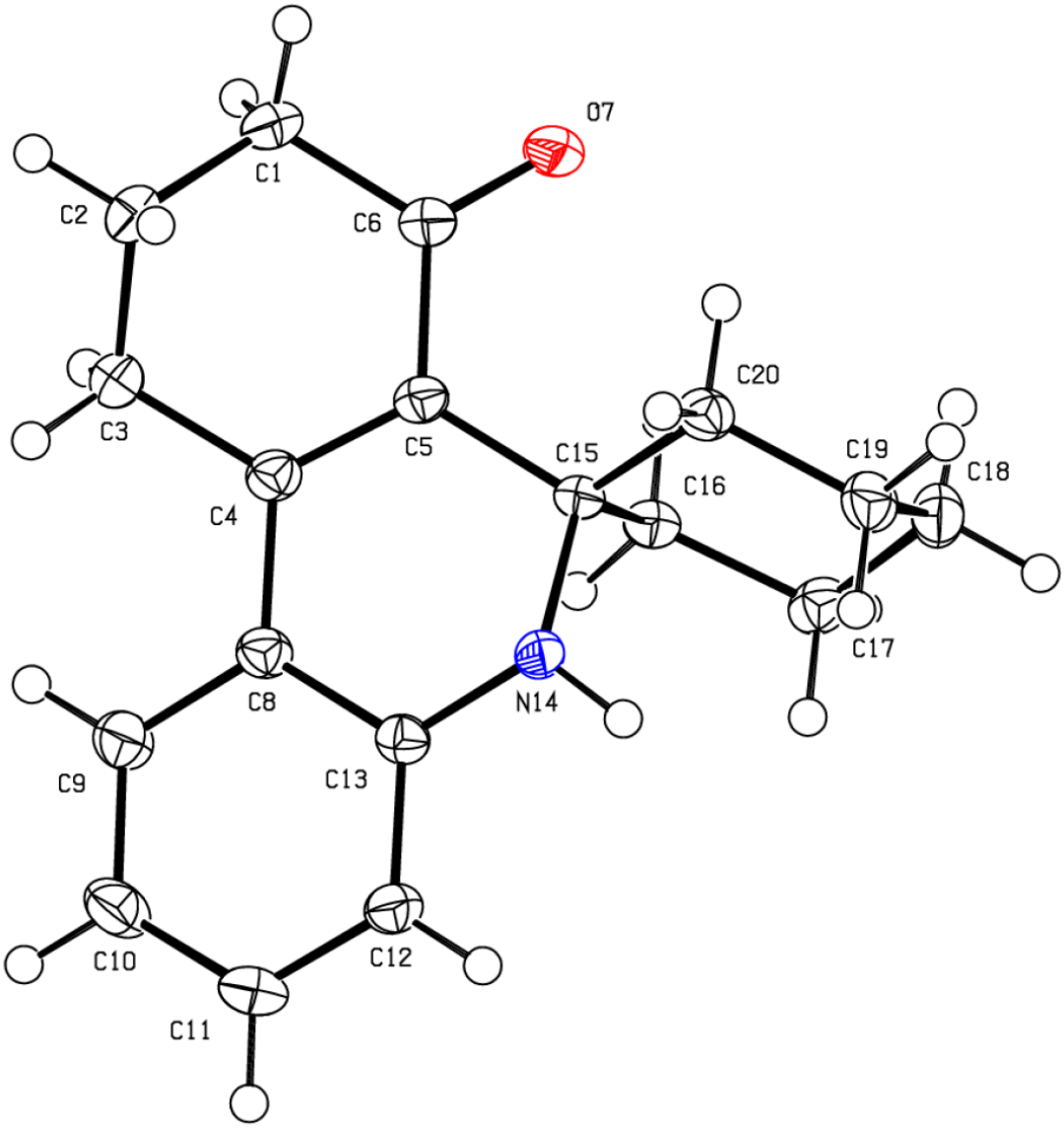
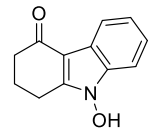



**Figure S10**: Structure of compound **45** (CCDC 1852695). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

400 MHz $^{1}$H NMR Spectrum of Compound **5** (prepared by Method i)
[recorded in $(CD_3)_2SO$]

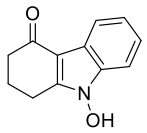



**5**



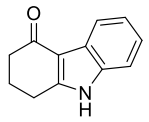

179

100 MHz $^{13}$C NMR Spectrum of Compound **5** (prepared by Method i)
[recorded in $(CD_3)_2SO$]




**5**

400 MHz $^{1}$H NMR Spectrum of Compound **6** (prepared by Method i)
[recorded in $(CD_3)_2SO$]



**6**

100 MHz $^{13}C$ NMR Spectrum of Compound **6** (prepared by Method i)
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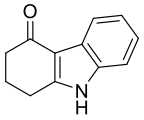

**6**

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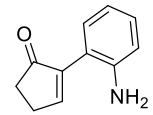


**8**

100 MHz $^{13}C$ NMR Spectrum of Compound **8**
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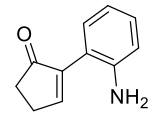
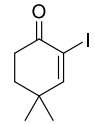



**8**

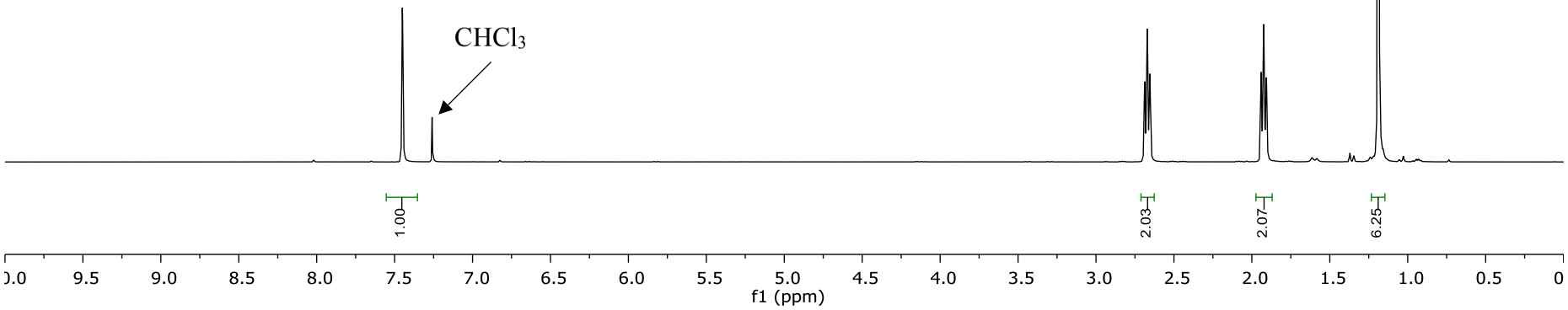



184

400 MHz $^{1}$H NMR Spectrum of Compound **9**
(recorded in $CDCl_3$)

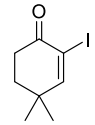



**9**




185

100 MHz $^{13}C$ NMR Spectrum of Compound **9**
(recorded in $CDCl_3$)




**9**




186

400 MHz $^{1}$H NMR Spectrum of Compound **10**
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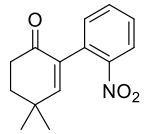


**10**




187

100 MHz $^{13}$C NMR Spectrum of Compound **10**
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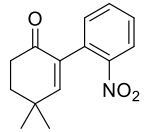
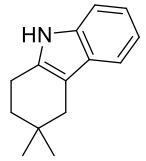



**10**




188

400 MHz $^{1}$H NMR Spectrum of Compound **11**
(recorded in $CDCl_3$)




**11**

100 MHz $^{13}$C NMR Spectrum of Compound **11**
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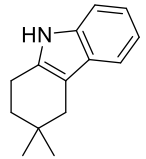


**11**

400 MHz $^{1}$H NMR Spectrum of Compound **12**
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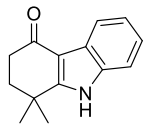
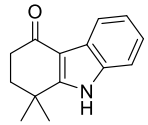



**12**




191

100 MHz $^{13}$C NMR Spectrum of Compound **12**
(recorded in $CDCl_3$)



**12**

400 MHz $^{1}$H NMR Spectrum of Compound **14**
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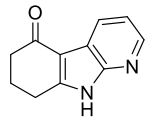

**14**

100 MHz $^{13}C$ NMR Spectrum of Compound **14**
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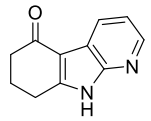

**14**

400 MHz $^{1}$H NMR Spectrum of Compound **15**
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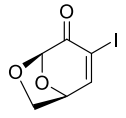
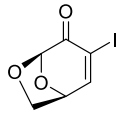



**15**




195

100 MHz $^{13}C$ NMR Spectrum of Compound **15**
(recorded in $CDCl_3$)

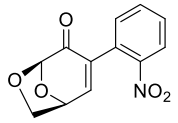


**15**




196

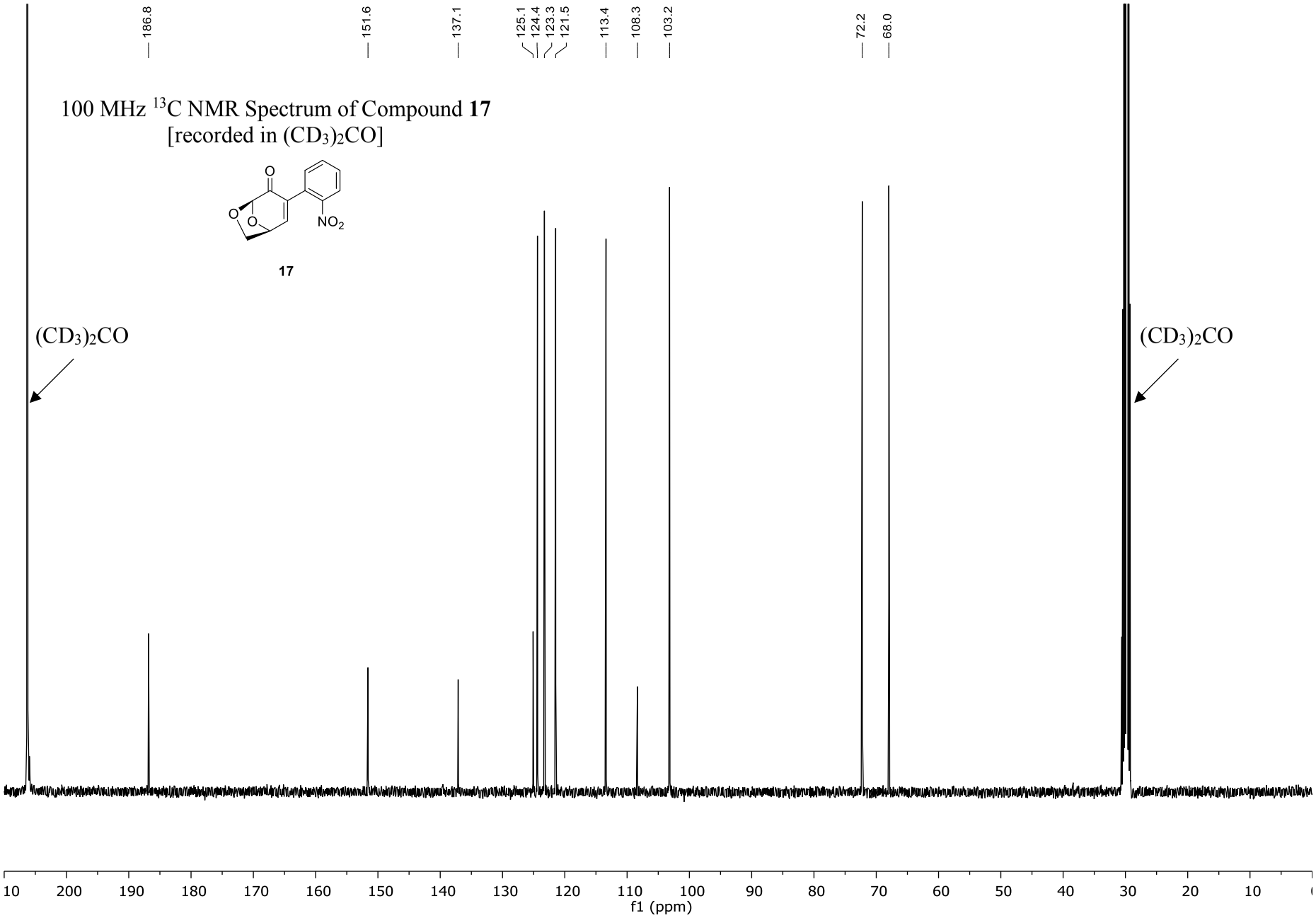
400 MHz $^{1}$H NMR Spectrum of Compound **17**
[recorded in $(CD_3)_2CO$]



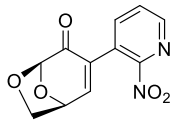

**17**




197

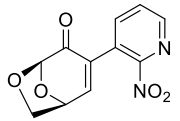

186.8
151.6
137.1
125.1
124.4
123.3
121.5
113.4
108.3
103.2
72.2
68.0
100 MHz $^{13}$C NMR Spectrum of Compound **17**
[recorded in $(CD_3)_2CO$]
O
O
O
$NO_2$
**17**
$(CD_3)_2CO$
$(CD_3)_2CO$
198
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

400 MHz $^1$H NMR Spectrum of Compound **18**
(recorded in $CDCl_3$)

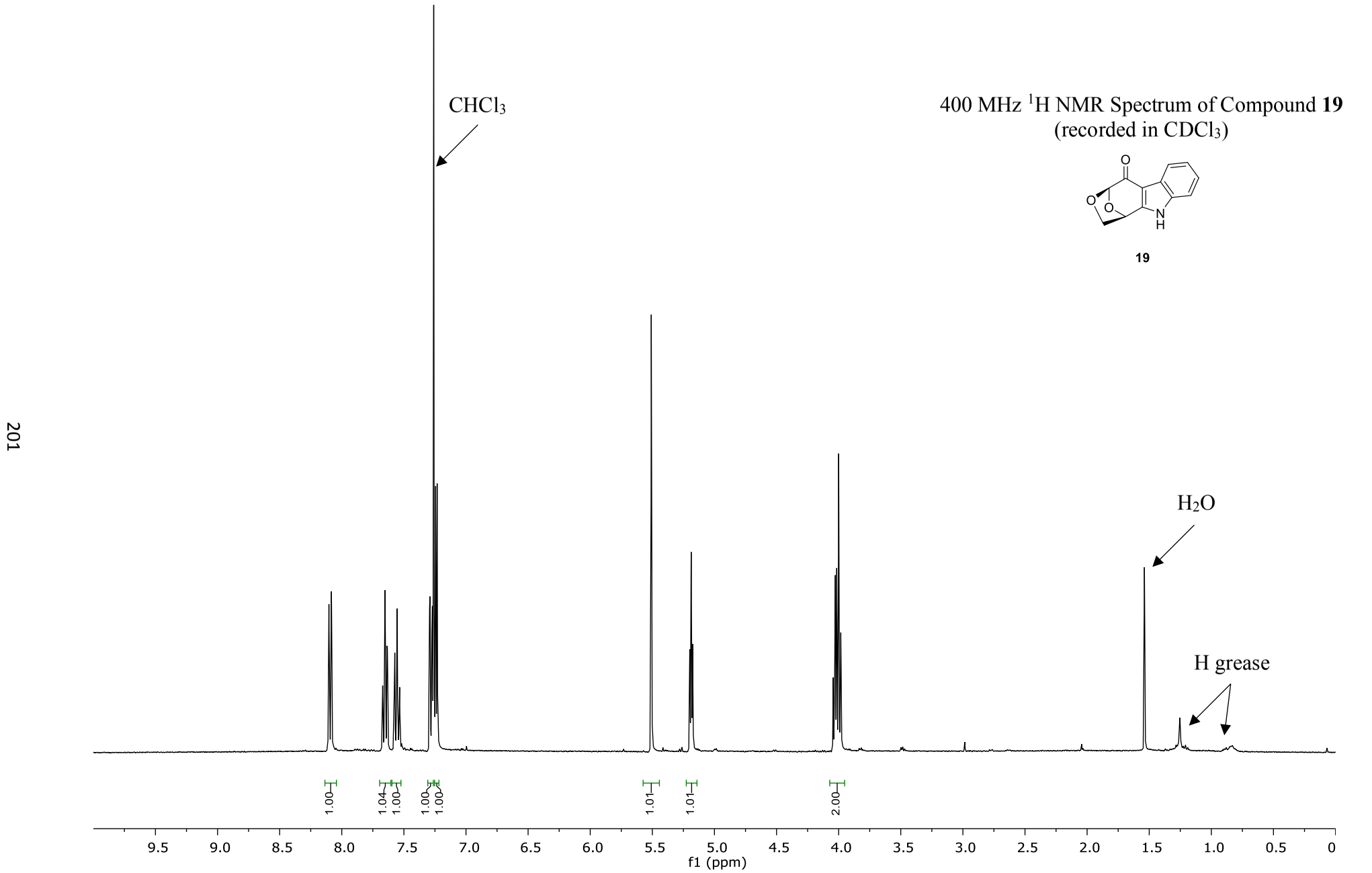


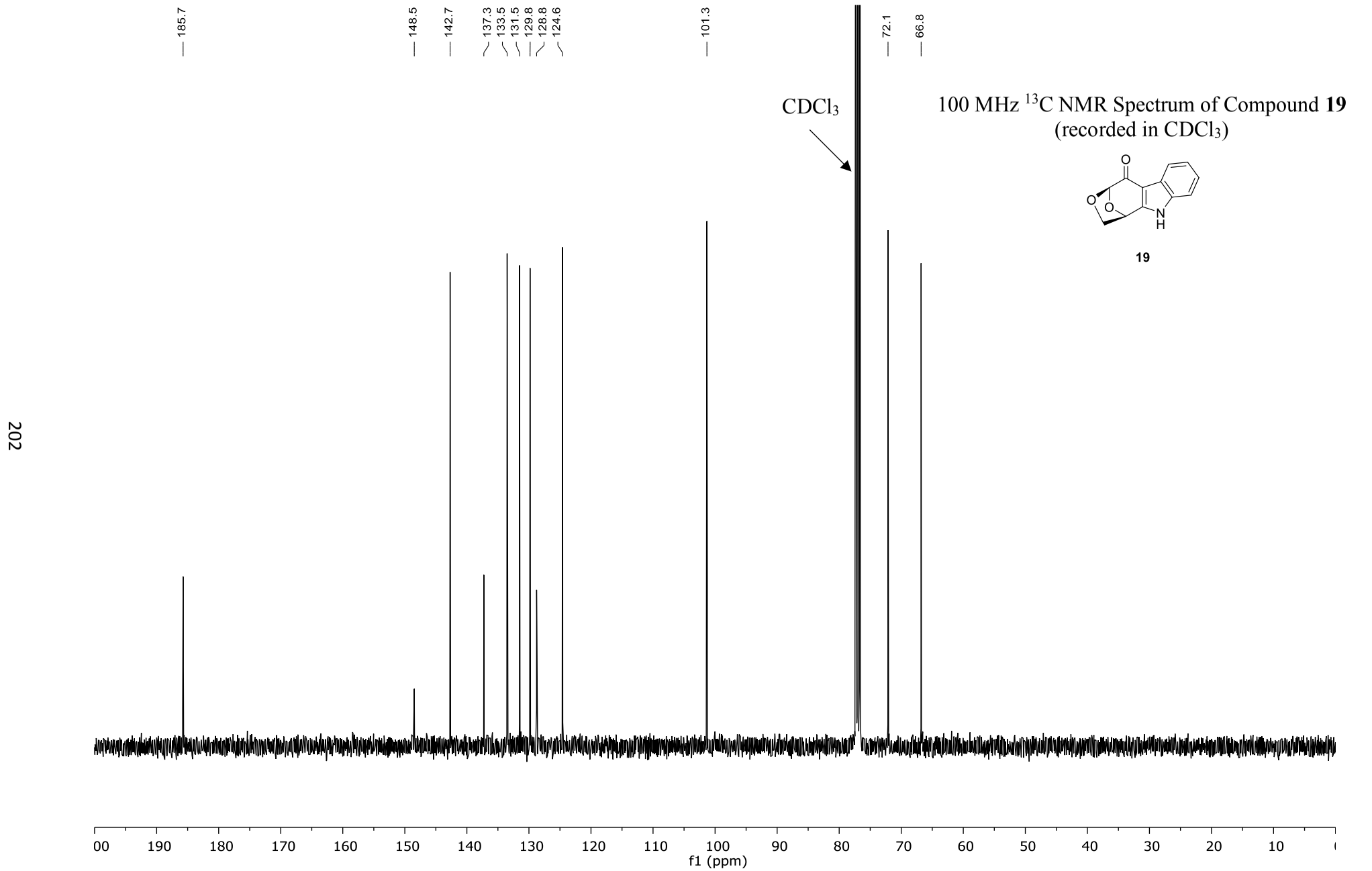

**18**

100 MHz $^{13}C$ NMR Spectrum of Compound **18**
(recorded in $CDCl_3$)

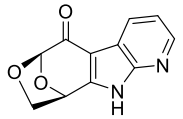



**18**


CHCl3
400 MHz 1H NMR Spectrum of Compound 19
(recorded in CDCl3)
19
H2O
H grease
1.00
1.04
1.00
1.00
1.00
1.01
1.01
2.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)
201

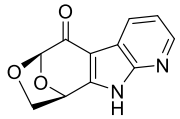

185.7
148.5
142.7
137.3
133.5
131.5
129.8
128.8
124.6
101.3
72.1
66.8
CDCl3
100 MHz 13C NMR Spectrum of Compound 19
(recorded in CDCl3)
O
O
O
N
H
19
202
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

400 MHz $^{1}$H NMR Spectrum of Compound **20**
[recorded in $(CD_3)_2CO$]



**20**

100 MHz $^{13}$C NMR Spectrum of Compound **20**
[recorded in $(CD_3)_2CO$]

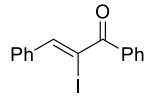


**20**




204

400 MHz $^{1}$H NMR Spectrum of Compound **22**
(recorded in $CDCl_3$)

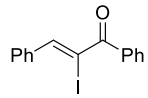



**22**



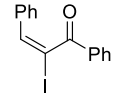

205

100 MHz $^{13}$C NMR Spectrum of Compound **22**
(recorded in $CDCl_3$)




**22**

400 MHz $^{1}$H NMR Spectrum of Compound **23**
(recorded in $CDCl_3$)

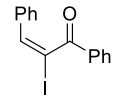



**23**



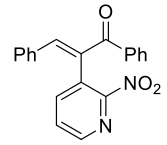

207

100 MHz $^{13}$C NMR Spectrum of Compound **23**
(recorded in $CDCl_3$)




**23**

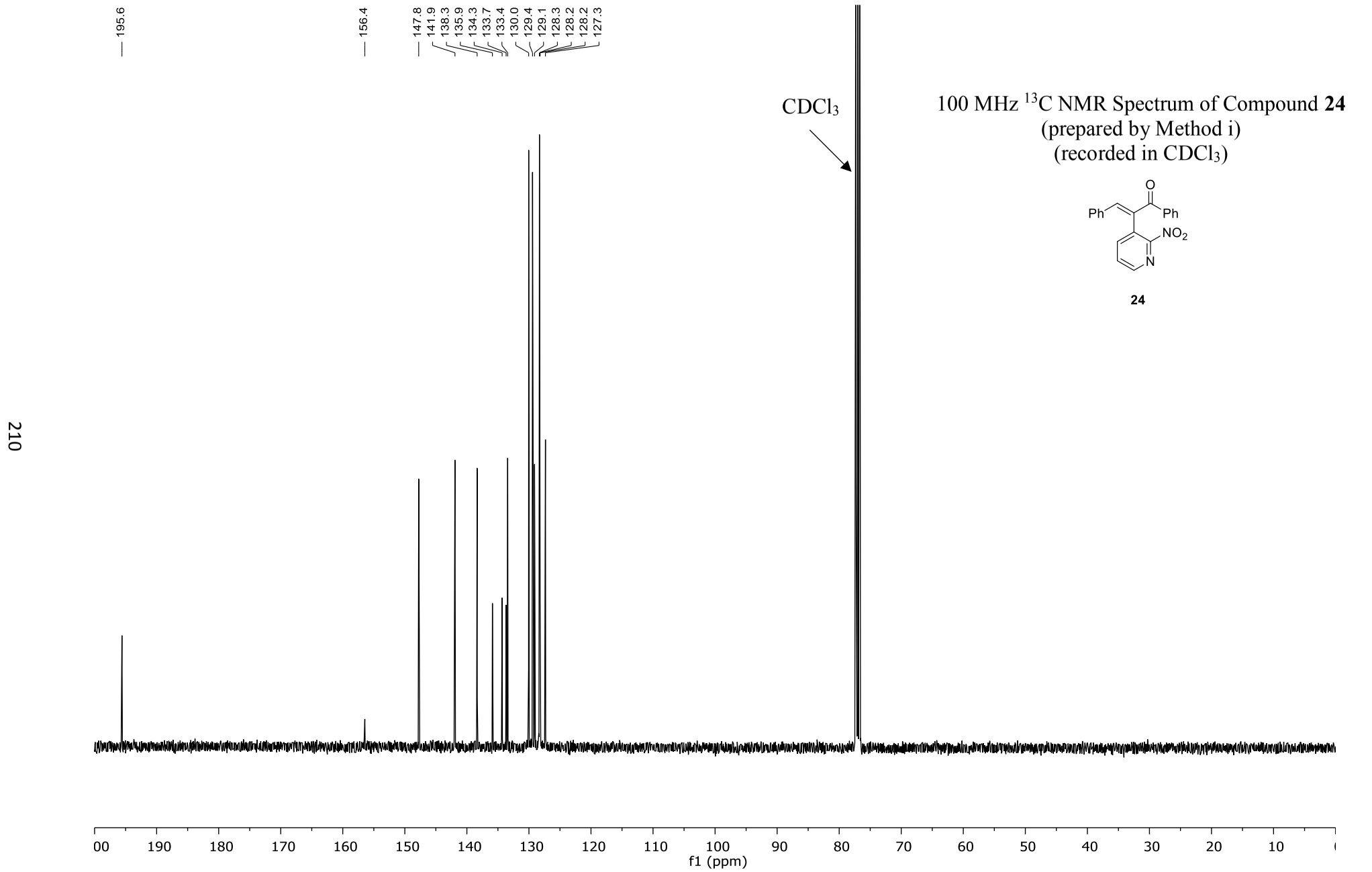
400 MHz $^{1}$H NMR Spectrum of Compound **24** (prepared by Method i)
(recorded in $CDCl_3$)



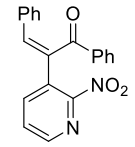

**24**



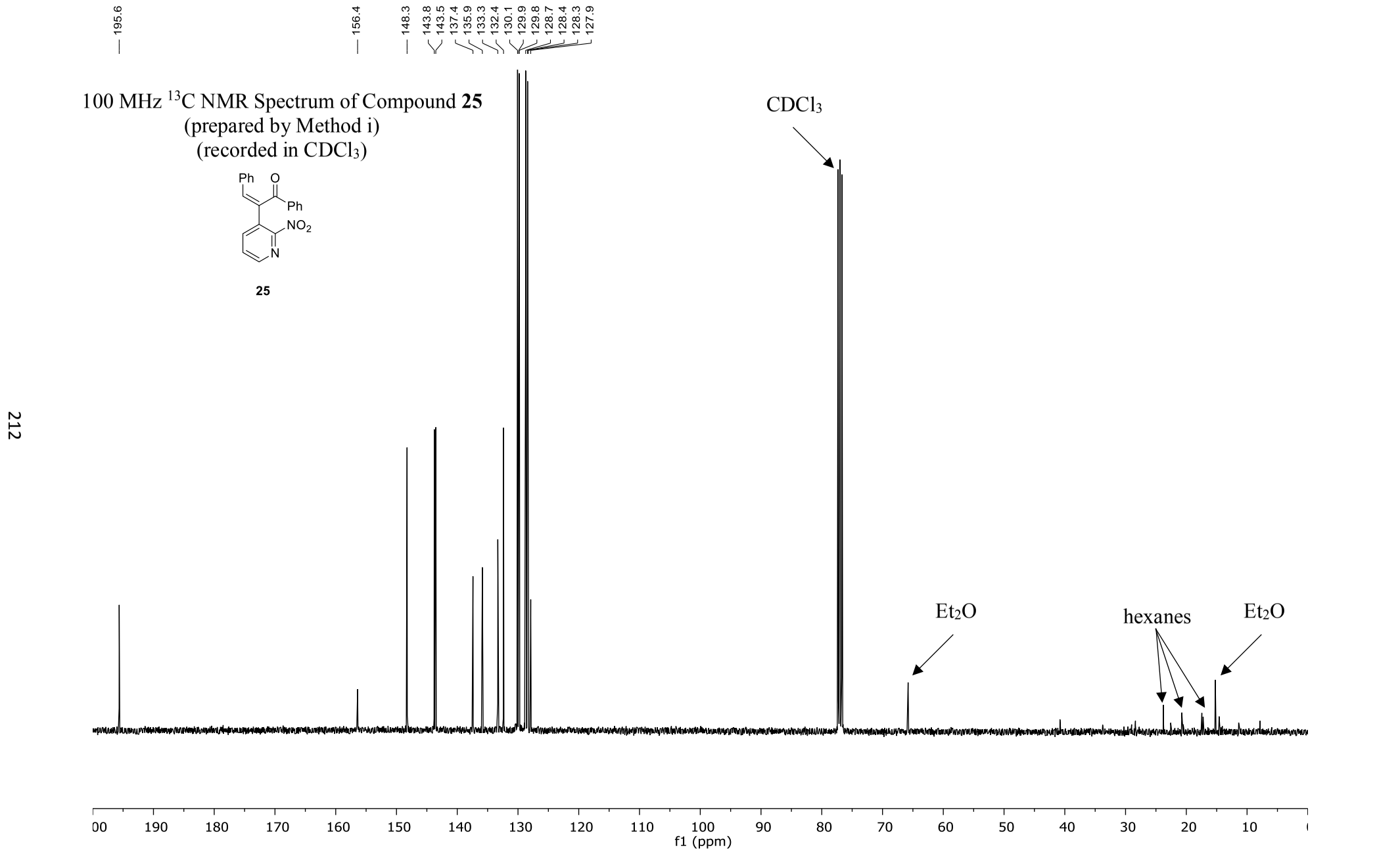

209


195.6
156.4
147.8
141.9
138.3
135.9
134.3
133.7
133.4
130.0
129.4
129.1
128.3
128.2
128.2
127.3
CDCl3
100 MHz 13C NMR Spectrum of Compound 24
(prepared by Method i)
(recorded in CDCl3)
O
Ph
Ph
NO2
N
24
210
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

400 MHz $^{1}$H NMR Spectrum of Compound **25** (prepared by Method i)
(recorded in $CDCl_3$)

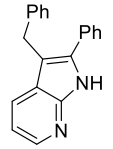



**25**

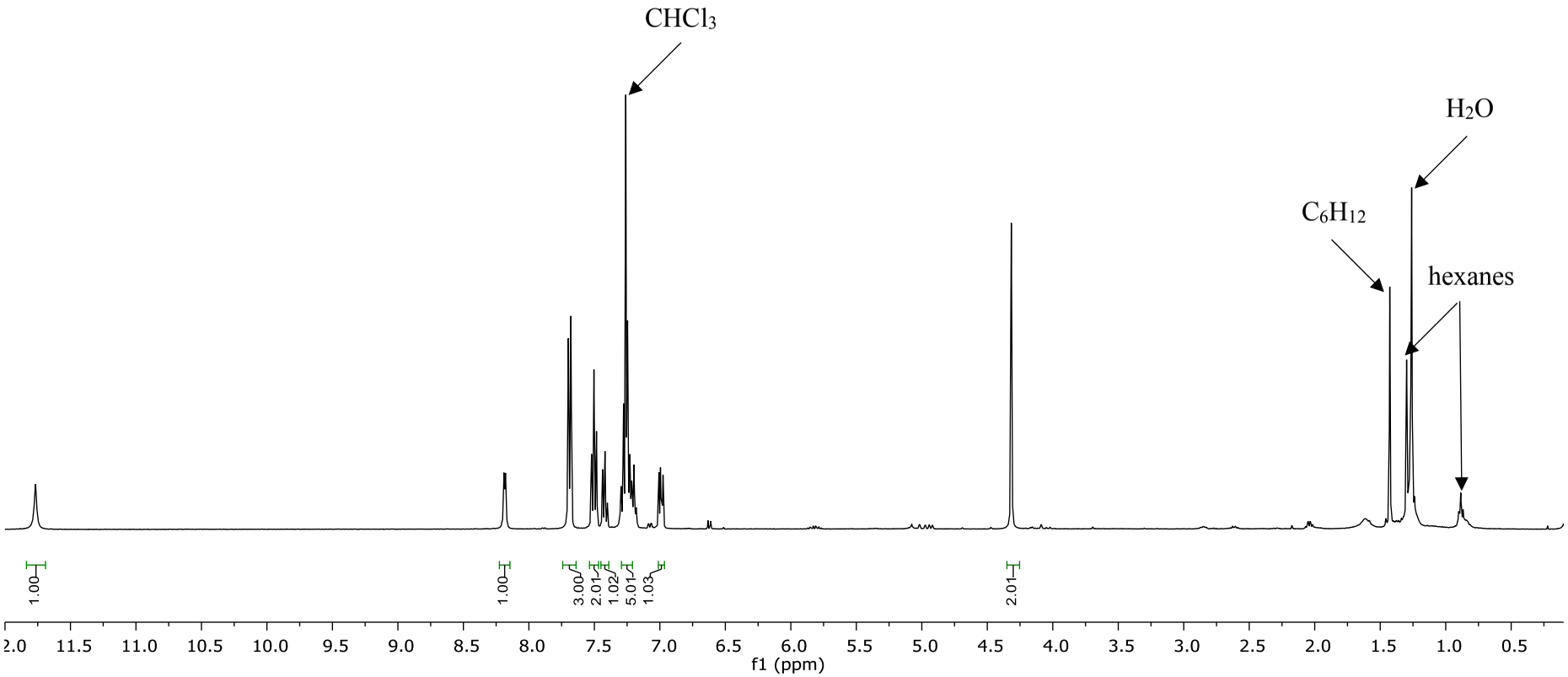

195.6
156.4
148.3
143.8
143.5
137.4
135.9
133.3
132.4
130.1
129.9
129.8
128.7
128.4
128.3
127.9
100 MHz $^{13}$C NMR Spectrum of Compound **25**
(prepared by Method i)
(recorded in $CDCl_3$)
Ph
O
Ph
$NO_2$
N
**25**
$CDCl_3$
$Et_2O$
hexanes
$Et_2O$
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

212

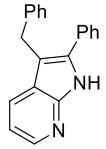
400 MHz $^{1}$H NMR Spectrum of Compound **26** (prepared by Method i)
(recorded in $CDCl_3$)




**26**

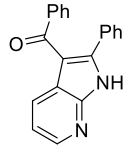


100 MHz $^{13}C$ NMR Spectrum of Compound **26** (prepared by Method i)
(recorded in $CDCl_3$)



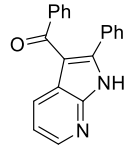

**26**

400 MHz $^{1}$H NMR Spectrum of Compound **27** (prepared by Method i)
(recorded in $CDCl_3$)



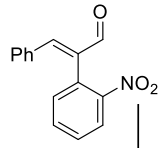

**27**

100 MHz $^{13}$C NMR Spectrum of Compound **27** (prepared by Method i)
(recorded in $CDCl_3$)



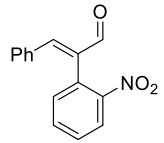

**27**

400 MHz $^1$H NMR Spectrum of Compound **32**
(recorded in $CDCl_3$)



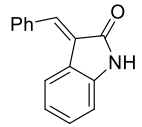

**32**

100 MHz $^{13}$C NMR Spectrum of Compound **32**
(recorded in $CDCl_3$)



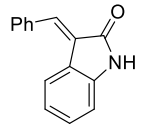

**32**

400 MHz $^{1}$H NMR Spectrum of Compound **33**
(recorded in $CDCl_3$)



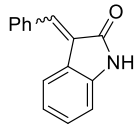

**33**

100 MHz $^{13}$C NMR Spectrum of Compound **33**
(recorded in $CDCl_3$)



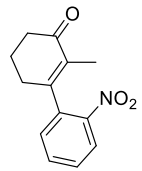

**33**

100 MHz $^{13}C$ NMR Spectrum of Compound **33/34**
(recorded in $CDCl_3$)



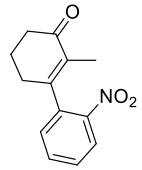

**33/34**

400 MHz $^{1}$H NMR Spectrum of Compound **36**
(recorded in $CDCl_3$)




**36**

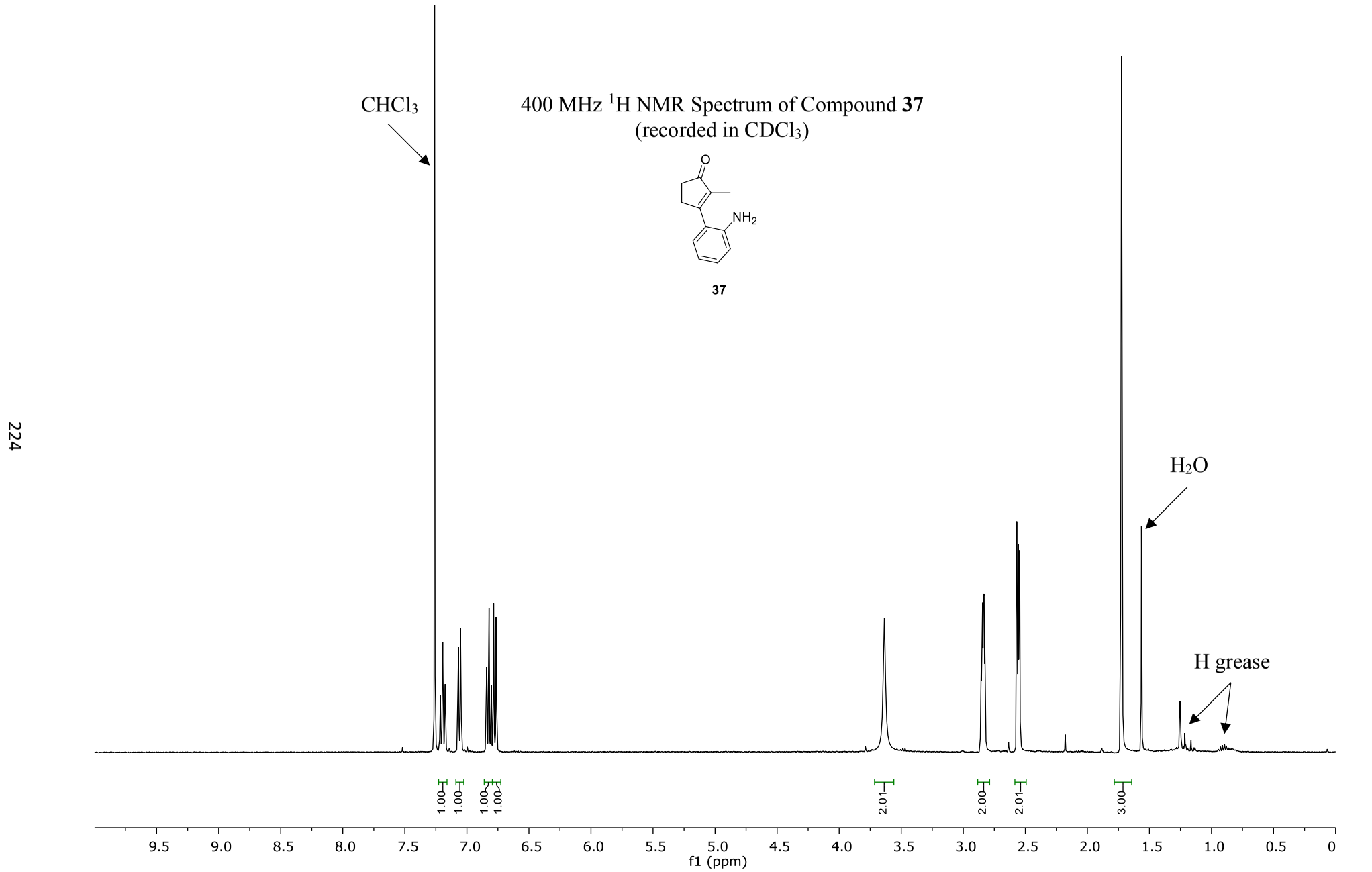
100 MHz $^{13}$C NMR Spectrum of Compound **36**
(recorded in $CDCl_3$)

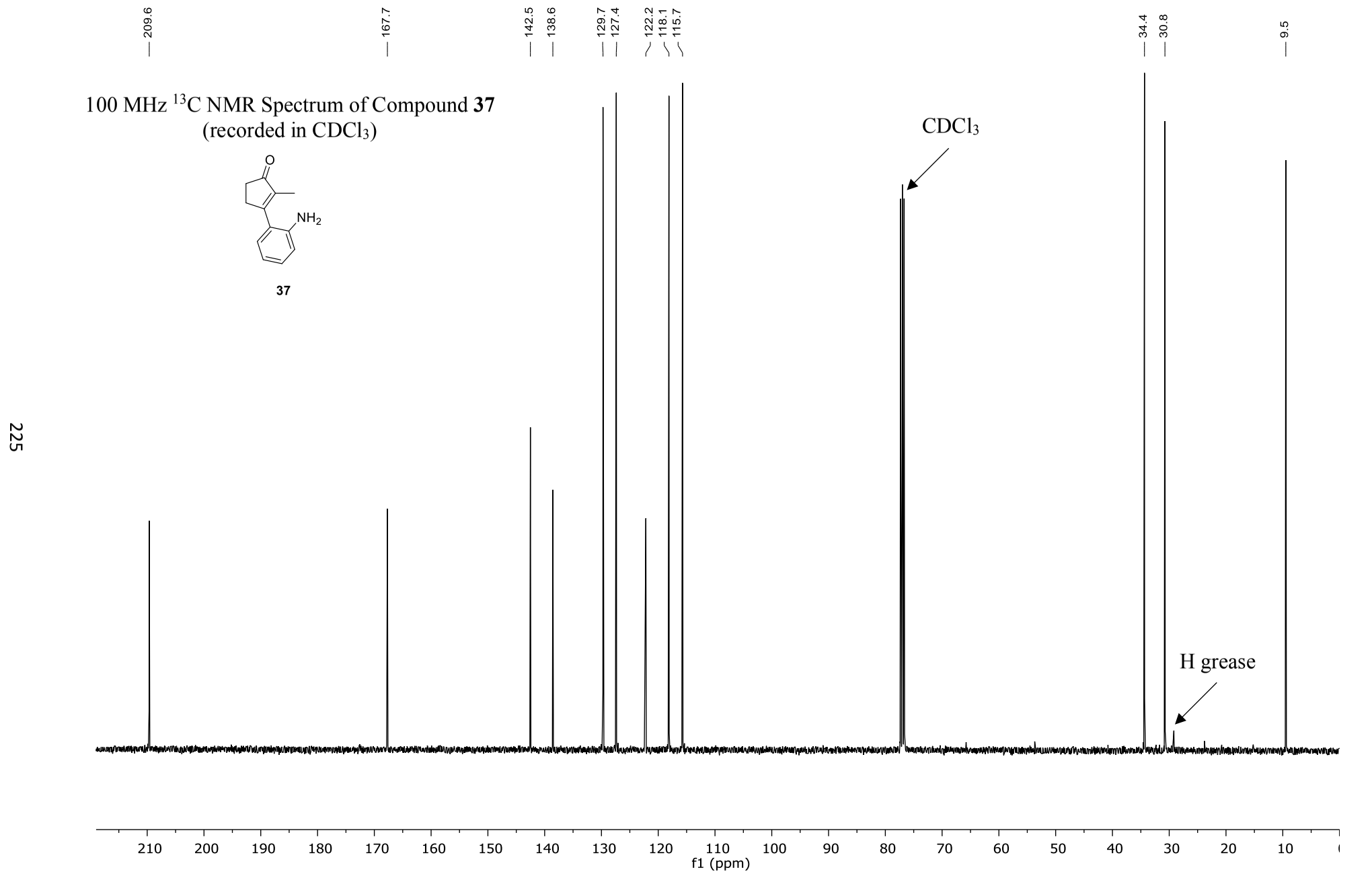


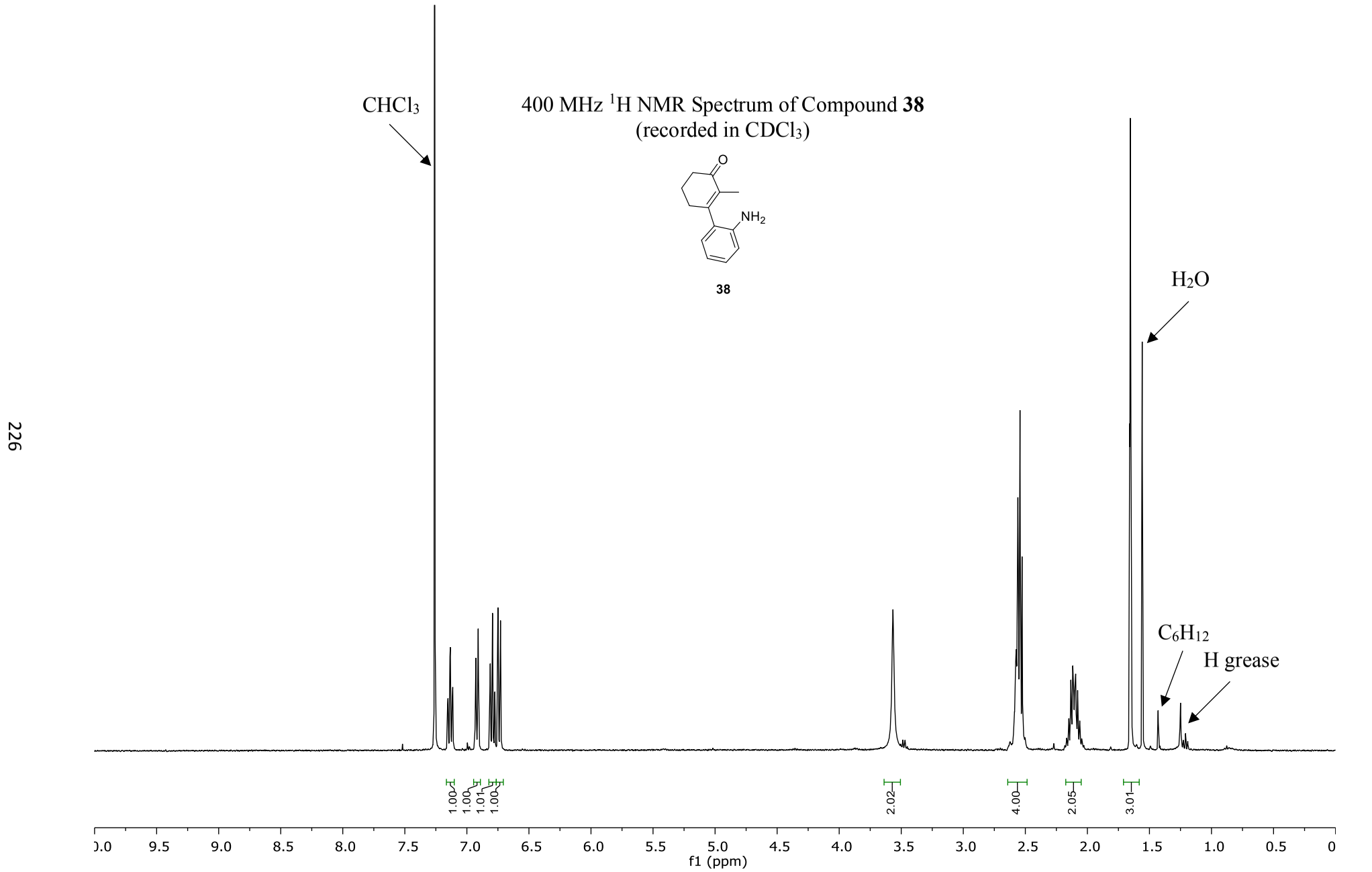

**36**



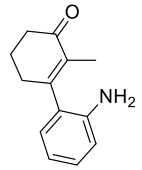

223


CHCl3
400 MHz 1H NMR Spectrum of Compound 37
(recorded in CDCl3)
O
NH2
37
H2O
H grease
1.00
1.00
1.00
1.00
2.01
2.00
2.01
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


209.6
167.7
142.5
138.6
129.7
127.4
122.2
118.1
115.7
34.4
30.8
9.5
100 MHz $^{13}$C NMR Spectrum of Compound **37**
(recorded in $CDCl_3$)
O
$NH_2$
**37**
$CDCl_3$
H grease
225
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


400 MHz $^1$H NMR Spectrum of Compound **38**
(recorded in $CDCl_3$)
$CHCl_3$
$H_2O$
$C_6H_{12}$
H grease
O
$NH_2$
38
1.00
1.00
1.01
1.00
2.02
4.00
2.05
3.01
f1 (ppm)

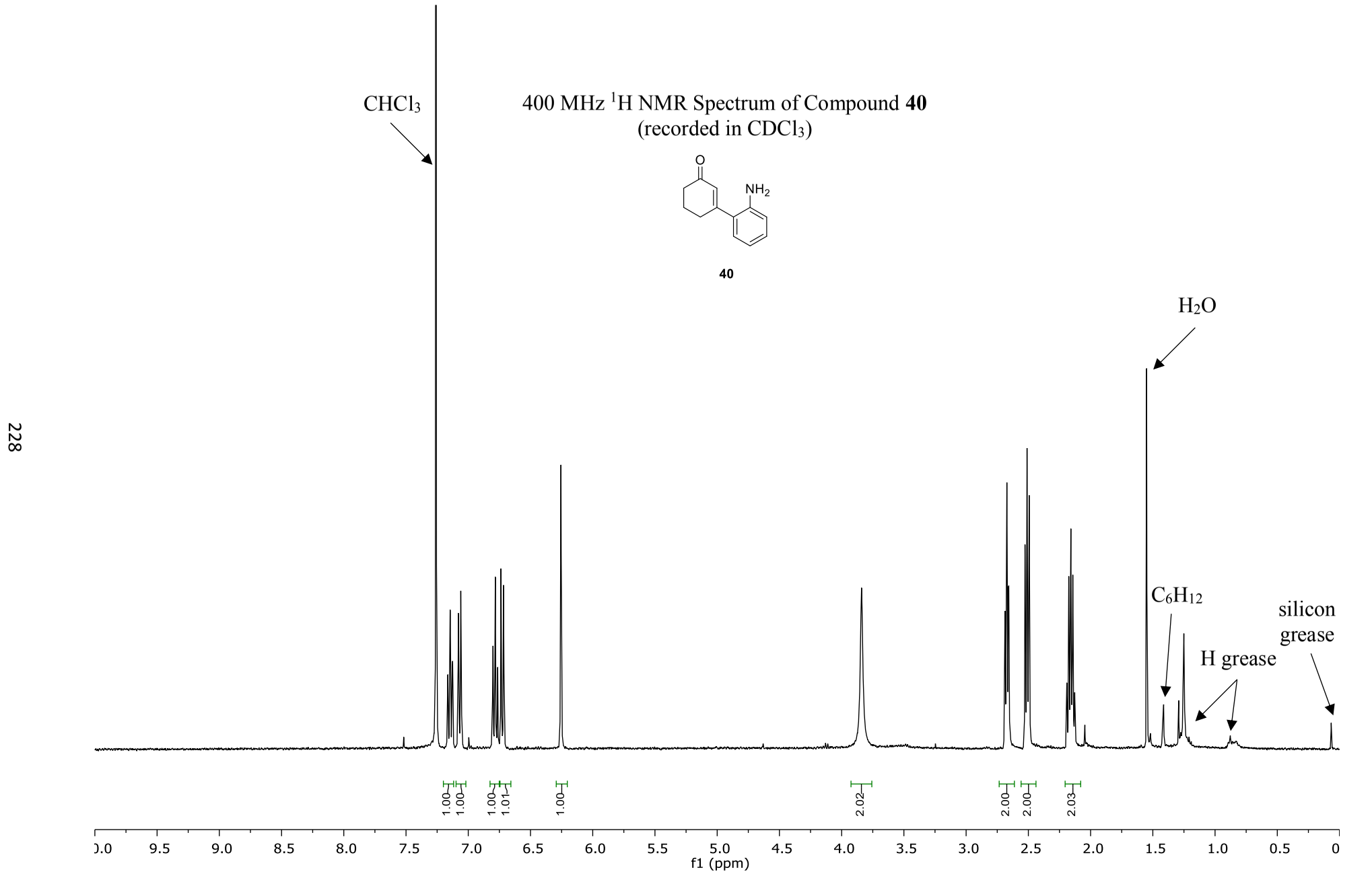
100 MHz $^{13}C$ NMR Spectrum of Compound **38**
(recorded in $CDCl_3$)

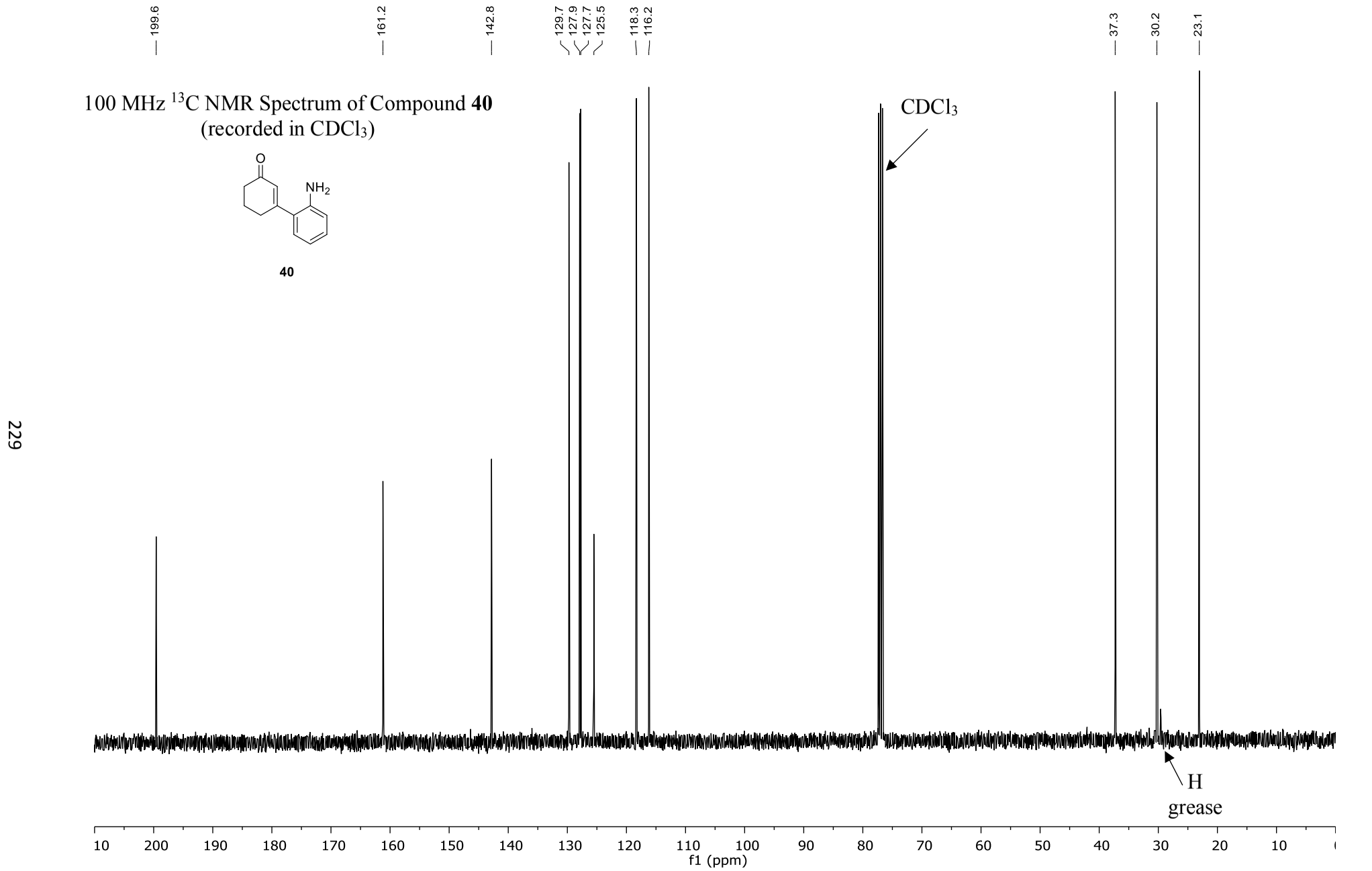



**38**

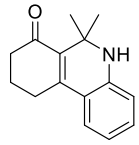



227


CHCl3
400 MHz 1H NMR Spectrum of Compound 40
(recorded in CDCl3)
O
NH2
40
H2O
C6H12
H grease
silicon
grease
1.00
1.00
1.00
1.01
1.00
2.02
2.00
2.00
2.03
f1 (ppm)

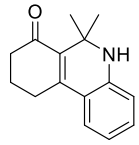

199.6
161.2
142.8
129.7
127.9
127.7
125.5
118.3
116.2
37.3
30.2
23.1
100 MHz $^{13}$C NMR Spectrum of Compound **40**
(recorded in $CDCl_3$)
O
$NH_2$
**40**
$CDCl_3$
H
grease
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

400 MHz $^{1}$H NMR Spectrum of Compound **41**
(recorded in $CDCl_3$)




**41**

100 MHz $^{13}C$ NMR Spectrum of Compound **41**
(recorded in $CDCl_3$)

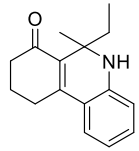



**41**



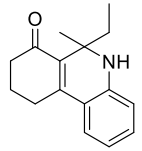

231

400 MHz $^{1}$H NMR Spectrum of Compound **44**
(recorded in $CDCl_3$)



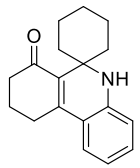

**44**

100 MHz $^{13}C$ NMR Spectrum of Compound **44**
(recorded in $CDCl_3$)



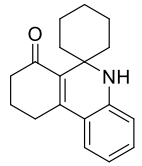

**44**

400 MHz $^{1}$H NMR Spectrum of Compound **45**
(recorded in $CDCl_3$)




**45**

100 MHz $^{13}C$ NMR Spectrum of Compound **45**
(recorded in $CDCl_3$)

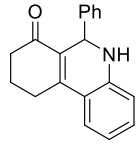



**45**




235

400 MHz $^{1}$H NMR Spectrum of Compound **46**
(recorded in $CDCl_3$)

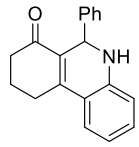



**46**




236

100 MHz $^{13}C$ NMR Spectrum of Compound **46**
(recorded in $CDCl_3$)




**46**

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Full Paper

# Synthesis of a Highly Functionalised and Homochiral 2-Iodocyclohexenone Related to the C-Ring of the Polycyclic, Indole Alkaloids Aspidophytine and Haplophytine

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The enzymatically-derived and enantiomerically pure (1*S*,2*S*)-3-bromocyclohexa-3,5-diene-1,2-diol (**7**) has been elaborated over 10 steps into cyclohexenone **8**. The latter compound embodies the enantiomeric form of the C-ring associated with the hexacyclic framework of the alkaloid aspidophytine (**2**). As such, this work sets the stage for effecting the conversion of the enantiomeric metabolite *ent*-**7** into compound *ent*-**8**, and thence, through previously established protocols, including a palladium-catalysed Ullmann cross-coupling reaction, into the title alkaloids.

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Manuscript accepted: 13 July 2018.
Published online: 17 August 2018.

## Introduction

The hetero-dimeric indole alkaloid haplophytine (**1**)[1–3] (Fig. 1) is, as confirmed by X-ray analysis,[2] a structurally distinctive metabolite derived from the Central American plant *Haplophyton cimicidum*, the dried leaves of which were first employed by the Aztecs for insecticidal purposes.[1] The right-hand segment of compound **1** embodies the aspidophytine framework **2** that is itself obtained from *Haplophyton crooksii* (otherwise known as the cockroach plant) found in the Southern United States as well as the north of Mexico. It too is used as an insecticide, especially against cockroaches.[3]

The elaborate molecular architectures of haplophytine (**1**) and aspidophytine (**2**) have prompted a range of synthetic studies. In 1999 Corey and his co-workers reported the first assembly of (–)-aspidophytine.[4] Subsequently, Fukuyama (2003), Padwa (2006), Marino (2006), Nicolaou (2008), Tokuyama (2013), and Qiu (2013)[5] achieved the same target. Even more dramatically, after years of sustained effort by many groups, total syntheses of haplophytine (**1**) were reported, contemporaneously in 2009, by the Fukuyama/Tokuyama[6] and the Nicolaou/Chen[7] groups.[8] In 2016, and inspired by earlier biosynthetic proposals, Tokuyama and co-workers were able to couple an advanced precursor to aspidophytine (**2**) with one associated with the left-hand segment of compound **1**.[9] By such means, and after conducting a key, one-pot aerobic oxidation/skeletal rearrangement cascade, the completion of a more convergent total synthesis of haplophytine was realised.

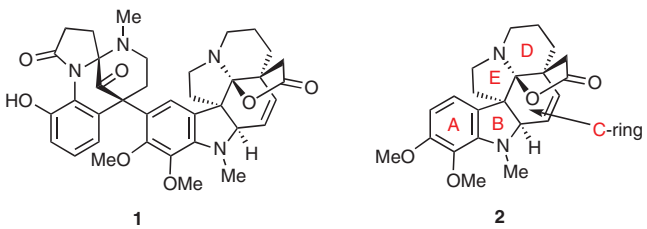
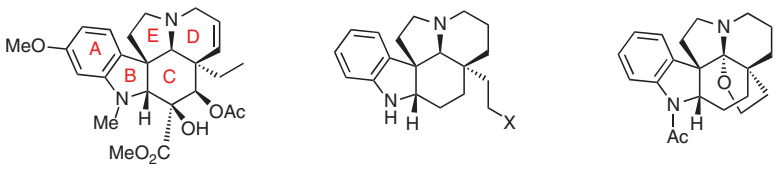



**Fig. 1.** The structures of haplophytine (**1**) and aspidophytine (**2**).

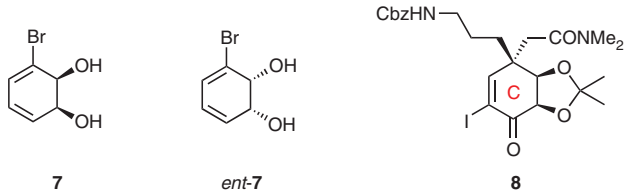
Our own interest in constructing various Aspidosperma alkaloids has resulted in the establishment of methods for assembling a close structural analogue of vindoline (**3**)[10] as well as total syntheses of the racemic modifications of aspidospermidine (**4**),[11] limaspermidine (**5**),[12] and its oxidative cyclisation product 1-acetylaspidoalbidine (**6**)[12] (Fig. 2). The analogue of vindoline was obtained in enantiomerically pure form as a result of employing a homochiral and enzymatically derived *cis*-1,2-dihydrocatechol as the starting material.[10,13] Compounds **3**–**6** each embody an ABCDE-ring system that is enantiomerically related to the one seen in aspidophytine (**2**) while the last of these, namely **6**, also incorporates the tetrahydrofuran substructure. A key step associated with all of these syntheses was the palladium-catalyzed Ullmann cross-coupling of a 2-iodocyclohexenone with an *o*-iodinated nitroarene.[14] This was followed by reductive cyclisation of the resulting 2-arylated cyclohexenone, often using dihydrogen in the presence of Raney-cobalt.[15] The piperidine-annulated tetrahydrocarbazoles so-formed were each subjected to an annulation protocol developed by Heathcock and co-workers[16] and thus completing the assembly of the ABCDE-ring system associated with compounds **3**–**6**.

We are now seeking to apply our earlier work in developing total syntheses of the title alkaloids. As part of this program, we report herein the conversion of the readily obtained and homochiral *cis*-1,2-dihydrocatechol **7**[13] (Fig. 3) into the




**3** **4** (X = H) **5** (X = OH) **6**

**Fig. 2.** The structures of vindoline (**3**), aspidospermidine (**4**), limaspermidine (**5**) and 1-acetylaspidoalbidine (**6**).




**7** *ent*-**7** **8**

**Fig. 3.** The structure of the homochiral starting material **7**, its enantiomer (*ent*-**7**) and the target 2-iodocyclohexenone **8**.

2-iodocyclohexenone **8** that embodies key elements associated with the C-ring of *ent*-aspidophytine (*ent*-**2**). Given that compound *ent*-**7** is also available,[17] albeit less readily, this work should eventually allow for the synthesis of compounds **1** and **2** as well as their optical antipodes.

## Results and Discussion

The route employed in the synthesis of target **8** is shown in Scheme 1. This starts with the conversion of diol **7**, using 2,2-dimethoxypropane (2,2-DMP) in the presence of catalytic quantities of *p*-toluenesulfonic acid monohydrate (*p*-TsOH·$H_2O$), into the corresponding and known acetonide **9**.[10] Given that the latter compound shows a ready propensity to engage in a Diels–Alder dimerisation reaction,[18] it was immediately subjected to a regio- and diastereo-selective dihydroxylation reaction using $K_2OsO_4 \cdot 2H_2O$ as the catalytic oxidant and *N*-methylamine *N*-oxide (NMO) as the stoichiometric one.[19] This resulted in the formation of the bromoconduritol mono-acetonide **10**[10] (70 % from **7**). The more accessible allylic hydroxy group associated with compound **10** could be selectively protected using *tert*-butyldimethylsilyl chloride (TBS-Cl) in the presence of imidazole and thus providing the mono-ether **11**[10] in 90 % yield. Treatment of compound **11** with chloromethyl methyl ether (MOM-Cl) in the presence of Hünig's base (*N*,*N*-diisopropylethylamine) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) then gave product **12**[10] in 95 % yield. Suzuki–Miyaura cross-coupling of the bromocyclohexene **12** with the previously unreported, 9-BBN-derived carbamate **13** (readily prepared in situ from 9-BBN and benzyl allylcarbamate) gave the anticipated product **14** (91 %). On treating compound **14** with tetra-*n*-butylammonium fluoride (TBAF) desilylation took place to give the allylic alcohol **15** (95 %). In a critical step of the reaction sequence, compound **15** was readily engaged in an Eschenmoser–Claisen rearrangement[10,12,20] on treatment with dimethylacetamide dimethyl acetal (DMADMA) in refluxing toluene and so cleanly produced the allylic ether **16** (85 % based on recovered starting material or brsm).

Significantly, compound **16** incorporates one of the two quaternary carbon centres associated with the enantiomeric form of the C-rings of the alkaloids haplophytine (**1**) and aspidophytine (**2**). As implied above, the correct configuration at this stereogenic centre, and from which the ones at the others automatically follow,[11,12] could be established by using metabolite *ent*-**7** (rather than **7**) as the starting material in this sequence.

The conversion of compound **16** into target **8** involved three additional steps, the first of which was the cleavage of the methoxy methyl (MOM)-ether. This was achieved using concentrated aqueous HBr at ambient temperatures. To prevent accompanying hydrolysis of the associated acetonide unit, this reaction was run in 2,2-DMP. As a result the allylic alcohol **17** was obtained, albeit in just 56 % yield. Oxidation of compound **17** was best effected with the Dess–Martin periodinane (DMP)[21] and resulted in the formation of enone **18** (64 %). Subjection of the latter compound to a Johnson α-iodination reaction[22] then provided target **8** in 87 % yield. All of the spectroscopic data acquired on compound **8** were in complete accord with the assigned structure. In particular, a molecular-associated ion ($[M + H]^+$) was observed in the electrospray ionisation mass spectrum and an accurate mass measurement on this species established it was of the required composition, that is $C_{24}H_{31}IN_2O_6$. In the $^{13}C$ NMR spectrum the expected 22 signals were observed while in the infrared spectrum carbonyl absorption bands were observed at 1697 and 1633 $cm^{-1}$.

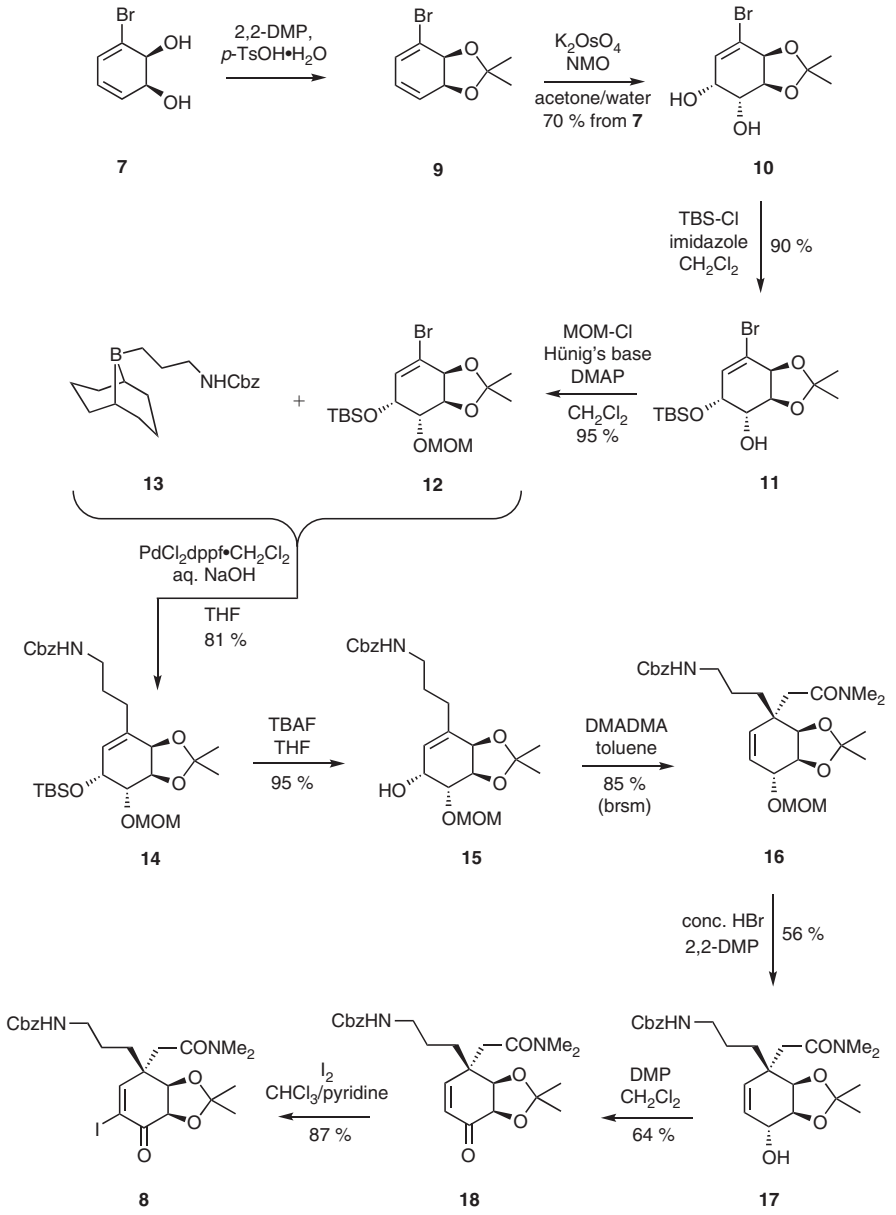
## Conclusions

The reaction sequence detailed here will allow for the conversion of the homochiral metabolite *ent*-**7** into the cyclohexenone *ent*-**8**. Furthermore, our earlier studies on the synthesis of aspidopsermidine (**4**),[11] limaspermidine (**5**),[12] and 1-acetylaspidoalbidine (**6**),[12] will inform us as to effective methods for the elaboration of compound *ent*-**8** into the structurally related aspidophytine (**2**) and even, perhaps, the more elaborate haplophytine (**1**). The conversion *ent*-**8** → **2** is likely to involve, in the first stages, a palladium-catalysed Ullmann cross-coupling reaction so as to install the required dimethoxyaryl group and the associated nitrogen. Subsequent hydrogenolysis and reductive cyclisation steps leading to the B- and D-rings are likely to follow. A Heathcock annulation (to install the E-ring) and an oxidative cyclisation reaction (involving an angular acetic acid group) to form the lactone ring would then be deployed. At some point the acetonide residue associated with compound *ent*-**8** will need to be converted into the corresponding cyclohexene and this is most likely to involve a Corey–Winter olefin synthesis.[20b] Efforts directed towards such ends will be reported in due course.

## Experimental

### *General Experimental Procedures*

Unless otherwise specified, proton ($^1H$) and carbon ($^{13}C$) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and




**Scheme 1.** Conversion of metabolite **7** into the target 2-iodocyclohexenone **8**.

101 MHz for carbon nuclei. The signal due to residual $CHCl_3$ appearing at $\delta_H$ 7.26 and the central resonance of the $CDCl_3$ 'triplet' appearing at $\delta_C$ 77.0 were used to reference $^1H$ and $^{13}C$ NMR spectra, respectively. $^1H$ NMR data are recorded as follows: chemical shift ($\delta$) (multiplicity, coupling constant(s) $J$ (Hz), relative integral) where multiplicity is defined as: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet or combinations of the above. Infrared spectra ($\nu_{max}$) were recorded on an ATR-FTIR spectrometer. Samples were analysed in neat form. Optical rotations were recorded in the indicated solvent at 22°C. Low-resolution eletrospray ionisation (ESI) mass spectra were recorded on a single quadrupole liquid chromatograph–mass spectrometer while high-resolution measurements were conducted on a time-of-flight instrument. Analytical thin-layer chromatography (TLC) was performed on aluminium-backed 0.2 mm thick silica gel 60 $F_{254}$ plates. Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate/potassium carbonate/5 % sodium hydroxide aqueous solution/water (3 g : 20 g : 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[23] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and used as supplied. Tetrahydrofuran (THF), methanol and, dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[24] Where necessary, reactions were performed under an atmosphere of nitrogen.

### *Specific Chemical Transformations*

#### *(3aS,7aS)-4-Bromo-2,2-dimethyl-3a,7a-dihydrobenzo[d][1,3]dioxole (**9**)*

A magnetically stirred solution of compound **7**[13b] (4.78 g, 25.0 mmol) in 2,2-DMP (50 mL) was treated with

*p*-TsOH·$H_2O$ (43 mg, 0.23 mmol, 1 mol-%) and the ensuing mixture stirred at 22°C for 2 h and then concentrated, without heating, under reduced pressure. The residue thus obtained was dissolved in ethyl acetate/$CH_2Cl_2$ (100 mL of a 1 : 1 v/v mixture) and the resulting solution washed with water (2 × 30 mL) before being dried ($Na_2SO_4$), filtered, and then concentrated under reduced pressure (no heating) to give compound **9**[10,18] (~5.75 g) as a light-brown oil. This material was used immediately in the next step of the reaction sequence.

### *(3aS,4R,5R,7aS)-7-Bromo-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-4,5-diol (**10**)*

A magnetically stirred solution of the crude acetonide **9** (~5.75 g, 24. 9 mmol, 1.0 mol equiv.) in acetone/water (100 mL of a 4 : 1 v/v mixture) was cooled to 0°C and then treated with $K_2OsO_4 \cdot 2H_2O$ (158 mg, 0.25 mmol, 0.01 mol equiv.) and NMO (6.41 g, 54.8 mmol, 2.2 mol equiv.). The ensuing mixture was allowed to warm to 22°C and then stirred at this temperature for 16 h before being diluted with ethyl acetate (50 mL). The separated aqueous layer was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (silica, 3 : 7 v/v ethyl acetate/40–60 petroleum spirits elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.3 in 2 : 3 v/v ethyl acetate/40–60 petroleum spirits), the title diol **10**[10] (4.67 g, 70 % over 2 steps) as a light-brown solid, mp 112°C, $[\alpha]_D$ −4.0 (*c* 1.0, $CHCl_3$). $\delta_H$ 6.16 (br s, 1H), 4.66 (m, 1H), 4.45 (t, *J* 5.4, 1H), 4.36 (br s, 1H), 4.19 (t, *J* 4.6, 1H), 2.53 (s, 2H), 1.44 (s, 3H), 1.41 (s, 3H). $\delta_C$ 131.1, 123.9, 110.5, 76.5, 76.4, 69.6, 67.4, 27.8, 26.3. $\nu_{max}/cm^{-1}$ 3401, 2987, 2934, 1645, 1382, 1373, 1229, 1079, 1050, 856, 628. *m/z* (ESI, +ve) 289 and 287 ($[M + Na]^+$, 95 and 100 %). HRMS 286.9880; calcd for $C_9H_{13}{}^{79}BrO_4Na$ $[M + Na]^+$ 286.9889.

### *(3aS,4S,5R,7aS)-7-Bromo-5-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ol (**11**)*

A suspension of compound **10** (8.00 g, 30.2 mmol) in $CH_2Cl_2$ (100 ml) was maintained at 0°C and then imidazole (5.28 g, 77.6 mmol, 2.56 mol equiv.) and TBS-Cl (8.19 g, 54.3 mmol, 1.8 mol equiv.) added to it. The ensuing mixture was stirred at 22°C for 1 h and then quenched with water (50 mL). The separated aqueous layer was extracted with $CH_2Cl_2$ (3 × 30 mL) and the combined organic phases then dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1 : 15 v/v ethyl acetate/40–60 petroleum spirits elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ 0.6 in 1 : 9 v/v ethyl acetate/40–60 petroleum spirits), ether **11**[10] (10.34 g, 90 %) as a light-yellow solid, mp 85°C, $[\alpha]_D$ −32.0 (*c* 1.0, $CHCl_3$). $\delta_H$ 5.91 (m, 1H), 4.62 (m, 1H), 4.49 (t, *J*4.8, 1H), 4.37 (m, 1H), 4.16 (m, 1H), 2.62 (d, *J*1.7, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 0.92 (s, 9H), 0.15 (s 3H), 0.13 (s 3H). $\delta_C$ 130.8, 123.6, 110.1, 76.1, 75.8, 69.3, 68.2, 27.7, 26.3, 25.9, 18.2, −4.5, −4.7. $\nu_{max}/cm^{-1}$ 3558, 2988, 2952, 2929, 2857, 1646, 1471, 1370, 1076, 1052, 865, 837, 777, 681. *m/z* (ESI, +ve) 403 and 401 ($[M + Na]^+$, 98 and 100 %). HRMS 401.0761; calcd for $C_{15}H_{27}{}^{79}BrO_4SiNa$ $[M + Na]^+$) 401.0760.

### *(((3aS,4S,5R,7aS)-7-Bromo-4-(methoxymethoxy)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-5-yl)oxy)(*tert*-butyl)dimethylsilane (**12**)*

A magnetically stirred solution of compound **11** (1.00 g, 2.64 mmol) in $CH_2Cl_2$ (5 mL) maintained at 0°C was treated with DMAP (322 mg, 2.63 mmol, 1.0 mol equiv.) and then Hünig's base (2.7 mL, 15.8 mmol, 6.0 mol equiv.) and MOM-Cl[25] (2.1 mL, 19.8 mmol, 7.5 mol equiv.). The ensuing mixture was stirred at 22°C for 16 h before being quenched with $NH_4Cl$ (30 mL of a saturated aqueous solution) and the separated aqueous phase extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1 : 19 v/v ethyl acetate/40–60 petroleum spirits elution) and thus affording, after concentration of the appropriate fractions ($R_f$ 0.5), the title compound **12**[10] (1.06 g, 95 %) as a colourless, semi-solid, $[\alpha]_D$ −71.4 (*c* 1.0, $CHCl_3$). $\delta_H$ 6.06 (br s, 1H), 4.82 (d, *J* 6.7, 1H), 4.72 (d, *J* 6.7, 1H), 4.65 (d, *J* 5.5, 1H), 4.47 (m, 2H), 4.08 (m, 1H), 3.40 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H). $\delta_C$ 132.8, 122.6, 110.3, 97.3, 77.0, 76.0, 75.6, 68.1, 55.9, 27.7, 26.4, 25.9, 18.3, −4.6 (one signal obscured or overlapping). $\nu_{max}/cm^{-1}$ 2988, 2953, 2930, 1644, 1464, 1381, 1371, 1253, 1133, 1115, 1078, 1037, 865, 776, 680. *m/z* (ESI, +ve) 447 and 445 ($[M + Na]^+$, 99 and 100 %). HRMS 445.1019; calcd for $C_{17}H_{31}{}^{79}BrO_5SiNa$ $[M + Na]^+$ 445.1022.

### *Benzyl (3-((1S,5S)-9-Borabicyclo[3.3.1]nonan-9-yl)propyl)carbamate (**13**)*

Following a protocol reported by Rychnovsky,[26] benzyl allylcarbamate[27] (500 mg, 2.61 mmol) was added to magnetically stirred 9-BBN (5 mL of a 0.5 M solution in THF, 2.5 mmol) maintained at 22°C. Stirring was continued at this temperature for 16 h and the solution thus obtained, and presumed to contain compound **13**, used directly in the Suzuki–Miyaura cross-coupling with compound **12** as detailed immediately below.

### *Benzyl (3-((3aR,6R,7S,7aR)-6-((*tert*-Butyldimethylsilyl)oxy)-7-(methoxymethoxy)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl)propyl)carbamate (**14**)*

A solution of compound **13** (1.04 mL of a 0.5 M solution in THF, 0.52 mmol), prepared as described immediately above, was dissolved in THF (1.5 ml) containing NaOH (2.3 mL of a 3 M aqueous solution). The ensuing mixture was stirred magnetically at 22°C for 0.3 h and then added to a magnetically stirred solution of compound **12** (200 mg, 0.47 mmol, 1.0 mol equiv.) in THF (1 mL) maintained at 22°C. The resulting mixture was deoxygenated with nitrogen and then $PdCl_2dppf \cdot CH_2Cl_2$ (40 mg, 0.05 mmol, 10 mol-%) was added. The mixture thus obtained was stirred at 22°C under nitrogen for 16 h before being quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution). The separated aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organic phases then dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1 : 4 v/v ethyl acetate/40–60 petroleum spirits elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ 0.4), carbamate **14** (243 mg, 81 %) as a clear, colourless oil, $[\alpha]_D$ −72.7 (*c* 0.83, $CHCl_3$). $\delta_H$ 7.41–7.26 (complex m, 5H), 5.51 (br s, 1H), 5.09 (s, 2H), 4.94 (br s, 1H), 4.78 (d, *J* 6.6, 1H), 4.71 (d, *J* 6.6, 1H), 4.52 (d, *J* 6.0, 1H), 4.41

(t, *J* 6.0, 1H), 4.35 (t, *J* 3.7, 1H), 3.87 (m, 1H), 3.37 (s, 3H), 3.22 (m, 2H), 2.18 (m, 2H), 1.73 (m, 2H), 1.38 (s, 3H), 1.36 (s, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). $\delta_C$ 156.5, 137.2, 136.8, 128.6, 128.2(3), 128.1(7), 126.2, 109.2, 96.3, 76.3, 75.1, 74.6, 66.7, 66.5, 55.6, 40.9, 31.2, 27.7, 27.6, 26.0(2), 25.9(6), 18.3, −4.4, −4.6. $\nu_{max}/cm^{-1}$ 3349, 2929, 2857, 1709, 1525, 1472, 1246, 1031, 885, 775. *m/z* (ESI, +ve) 558 ($[M + Na]^+$, 100 %). HRMS 558.2864; calcd for $C_{28}H_{45}NO_7SiNa$ $[M + Na]^+$ 558.2863.

### *Benzyl (3-((3a*R*,6*R*,7*R*,7a*R*)-6-Hydroxy-7-(methoxymethoxy)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)propyl) carbamate (**15**)*

A magnetically stirred solution of compound **14** (3.19 g, 5.95 mmol) in THF (14 mL) was cooled to 0°C and then treated with TBAF (12.4 mL of a 0.5 M solution in THF, 1.05 mol equiv.). The ensuing mixture was allowed to warm to 22°C over 2 h and stirring continued at this temperature for 16 h. The reaction mixture was then diluted with $NaHCO_3$ (20 mL of a saturated aqueous solution) and the separated aqueous layer extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 4 : 6 → 7 : 3 → 8 : 2 v/v ethyl acetate/40–60 petroleum spirits gradient elution). Concentration of the appropriate fractions ($R_f$ 0.2 in 1 : 1 v/v ethyl acetate/40–60 petroleum elution) then gave allylic alcohol **15** (2.40 g, 95 %) as a clear, colourless oil, $[\alpha]_D$ −35.7 (*c* 0.48, $CHCl_3$). $\delta_H$ 7.41–7.27 (complex m, 5H), 5.63 (br s, 1H), 5.09 (s, 2H), 4.90 (br s, 1H), 4.77 (m, 2H), 4.51 (d, *J* 6.2, 1H), 4.43 (m, 1H), 4.35–4.24 (br s, 1H), 3.87 (m, 1H), 3.40 (s, 3H), 3.23 (m, 2H), 2.68 (d, *J* 6.1, 1H), 2.22 (m, 2H), 1.74 (m, 2H), 1.40 (s, 3H), 1.37 (s, 3H). $\delta_C$ 156.5, 138.3, 136.7, 128.6, 128.2(1), 128.1(8), 125.0, 109.5, 96.9, 78.0, 74.8, 74.5, 66.7, 65.5, 55.8, 40.8, 31.1, 27.8, 27.4, 26.1. $\nu_{max}/cm^{-1}$ 3348, 2985, 2934, 1699, 1531, 1455, 1380, 1240, 1027, 916, 698. *m/z* (ESI, +ve) 444 ($[M + Na]^+$, 100 %). HRMS 444.1192; calcd for $C_{22}H_{31}NO_7Na$ $[M + Na]^+$ 444.1998.

### *Benzyl (3-((3a*R*,4*S*,7*R*,7a*S*)-4-(2-(Dimethylamino)-2-oxoethyl)-7-(methoxymethoxy)-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)propyl) carbamate (**16**)*

A magnetically stirred solution of compound **15** (1.86 g, 4.41 mmol,) in toluene (23 mL) was treated with DMADMA (6.0 mL, 39.7 mmol, 9 mol equiv.) and the ensuing mixture heated under reflux for 1 h before being cooled to 90°C and the reaction vessel vented for 0.5 h so as to allow the by-product methanol to evaporate. The reaction mixture was then heated again under reflux for 1 h, cooled to 90°C and vented once more for 0.5 h. Further DMADMA (3.0 mL, 19.9 mmol, 4.5 mol equiv.) was added to the reaction mixture that was then heated under reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 7 : 3 v/v ethyl acetate/40–60 petroleum spirits elution) and so affording two fractions, A and B.

Concentration of fraction A ($R_f$ 0.2 in 1 : 1 v/v ethyl acetate/40–60 petroleum spirits) afforded allylic alcohol **15** (290 mg, 16 % recovery) as a clear, colourless oil that was identical, in all respects, with an authentic sample.

Concentration of fraction B ($R_f$ 0.2 in 1 : 4 v/v ethyl acetate/diethyl ether) afforded compound **16** (1.55 g, 72 or 85 % brsm), as a white, crystalline solid: mp 84°C, $[\alpha]_D$ −18.3 (*c* 1.0, $CHCl_3$). $\delta_H$ 7.36–7.20 (complex m, 5H), 5.75 (m, 2H), 5.09 (s, 2H), 5.03 (br s, 1H), 4.81 (d, *J* 6.7, 1H), 4.72 (d, *J* 6.7, 1H), 4.31 (s, 2H), 4.19 (s, 1H), 3.39 (s, 3H), 3.16 (m, 2H), 3.01 (s, 3H), 2.91 (s, 3H), 2.50 (m, 2H), 1.76–1.48 (complex m, 3H), 1.41 (s, 3H), 1.33 (s, 3H). $\delta_C$ 170.5, 156.5, 136.8, 135.9, 128.5, 128.1, 128.0, 125.8, 108.2, 95.5, 79.3, 78.2, 74.4, 66.5, 55.5, 41.6, 40.8, 39.1, 37.9, 35.5, 31.8, 26.8, 24.9, 24.2. $\nu_{max}/cm^{-1}$ 3332, 2936, 1717, 1635, 1525, 1455, 1240, 1041, 731. *m/z* (ESI, +ve) 513 ($[M + Na]^+$, 100 %). HRMS 513.2578; calcd for $C_{26}H_{38}N_2O_7Na$ $[M + Na]^+$ 513.2577.

### *Benzyl (3-((3a*R*,4*S*,7*R*,7a*S*)-4-(2-(dimethylamino)-2-oxoethyl)-7-hydroxy-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)propyl) carbamate (**17**)*

A magnetically stirred solution of compound **16** (47 mg, 0.09 mmol) in 2,2-DMP (1.6 mL) was cooled to 0°C and then treated with HBr (5 drops of a 48 % aqueous solution). The reaction mixture was kept at 0°C for 0.1 h and then warmed to 22°C, maintained at this temperature for 1.5 h and then quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution) and the separated aqueous layer extracted with ethyl acetate (3 × 5 mL). The combined organic phases were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, ethyl acetate eltuion) and thus afforded, after concentration of the appropriate fractions ($R_f$ 0.2), compound **17** (24 mg, 56 %) as a clear, colourless oil, $[\alpha]_D$ −33.8 (*c* 1.07, $CHCl_3$). $\delta_H$ 7.45–7.28 (complex m, 5H), 5.75 (m, 1H), 5.68 (m, 1H), 5.09 (s, 2H), 4.96 (br s, 1H), 4.35 (d, *J* 7.3, 1H), 4.29 (dd, *J* 7.3 and 3.9, 1H), 4.22 (br s, 1H), 3.17 (m, 2H), 3.01 (s, 3H), 2.91 (s, 3H), 2.55 (s, 2H), 2.46 (d, *J* 6.2, 1H), 1.55 (br s, 4H), 1.41 (s, 3), 1.34 (s, 3H). $\delta_C$ 170.9, 156.5, 136.8, 134.6, 128.6, 128.2, 128.1, 128.0, 108.1, 81.0, 78.3, 69.8, 66.6, 41.6, 41.0, 40.0, 38.0, 35.6, 32.9, 26.9, 25.0, 24.4. $\nu_{max}/cm^{-1}$ 3338, 2978, 2934, 1705, 1627, 1527, 1241, 1045, 752, 698. *m/z* (ESI, +ve) 469 ($[M + Na]^+$, 100 %). HRMS 469.2307; calcd for $C_{24}H_{34}N_2O_6Na$ $[M + Na]^+$ 469.2315.

### *Benzyl (3-((3a*R*,4*S*,7a*R*)-4-(2-(Dimethylamino)-2-oxoethyl)-2,2-dimethyl-7-oxo-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)propyl) carbamate (**18**)*

A magnetically stirred solution of compound **17** (41 mg, 0.09 mmol) in $CH_2Cl_2$ (3 mL) maintained at 0°C under a nitrogen atmosphere was treated with DMP (98 mg, 0.23 mmol, 2.5 mol equiv.). The ensuing mixture was allowed to stir at 0°C for 0.1 h and then at 22°C for 16 h before being quenched with $NaHCO_3$ (2 mL of a saturated aqueous solution) and the separated aqueous layer extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, ethyl acetate elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ 0.3), enone **18** (26 mg, 64 %), as a clear, colourless oil, $[\alpha]_D$ −13.7 (*c* 0.9, $CHCl_3$). $\delta_H$ 7.47–7.25 (complex m, 5H), 6.80 (d, *J* 10.4, 1H), 6.05 (d, *J* 10.4, 1H), 5.09 (s, 2H), 4.99 (br s, 1H), 4.48 (s, 2H), 3.20 (q, *J* 6.5, 2H), 2.97 (s, 3H), 2.90 (s, 3H), 2.58 (m, 2H), 1.81 (m, 1H), 1.63 (m, 3H), 1.36 (s, 3H), 1.32 (s, 3H). $\delta_C$ 196.0, 169.2, 156.5, 154.8, 136.7, 128.6, 128.2(3), 128.2(1), 126.4, 109.5, 78.7, 75.1, 66.7,

41.4, 41.2, 40.4, 38.1, 35.7, 33.4, 27.3, 25.8, 23.8. $\nu_{max}/cm^{-1}$ 3347, 2984, 2935, 1717, 1684, 1637, 1372, 1237, 1044, 698. *m/z* (ESI, +ve) 467 ($[M + Na)]^+$, 100 %). HRMS 467.2159; calcd for $C_{24}H_{32}N_2O_6Na$ $[M + Na]^+$ 467.2158.

*Benzyl (3-((3a*R*,4*S*,7a*R*)-4-(2-(Dimethylamino)-2-oxoethyl)-6-iodo-2,2-dimethyl-7-oxo-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)propyl)carbamate (**8**)*

A magnetically stirred solution of compound **18** (72 mg, 0.16 mmol) in chloroform/pyridine (10 mL of a 1 : 1 v/v mixture) was treated with molecular iodine (226 mg, 0.89 mmol, 5.5 mol equiv.) and the resulting mixture stirred at 22°C for 16 h and then quenched with $Na_2SO_3$ (10 mL of a saturated aqueous solution) and the separated aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, ethyl acetate elution). Concentration of the appropriate fractions ($R_f$ 0.5) afforded compound **8** (80 mg, 87 %) as a clear, colourless oil, $[\alpha]_D$ −75.6 (*c* 0.8, $CHCl_3$). $\delta_H$ 7.49 (s, 1H), 7.42–7.27 (complex m, 5H), 5.10 (s, 2H), 4.96 (br s, 1H), 4.66 (d, *J* 5.3, 1H), 4.51 (d, *J* 5.3, 1H), 3.21 (m, 2H), 2.98 (s, 3H), 2.89 (s, 3H), 2.56 (m, 2H), 1.88 (m, 1H), 1.77 (m, 1H), 1.63 (m, 2H), 1.36 (s, 3H), 1.29 (s, 3H). $\delta_C$ 189.8, 168.8, 162.4, 156.5, 136.7, 128.6, 128.2(0), 128.1(5), 109.7, 100.0, 78.9, 74.2, 66.7, 45.4, 41.2, 40.3, 38.0, 35.7, 33.4, 27.3, 25.7, 23.8. $\nu_{max}/cm^{-1}$ 3348, 2985, 2934, 1697, 1633, 1522, 1454, 1238, 1078, 1044, 749. *m/z* (ESI, +ve) 593 ($[M + Na]^+$, 100 %). HRMS 571.1301; calcd for $C_{24}H_{32}IN_2O_6$ $[M + H]^+$ 571.1300.

## Supplementary Material

$^1H$ and $^{13}C$ NMR spectra for compounds **10–18** and **8** are available on the Journal's website.

## Conflicts of Interest

The authors declare no conflicts of interest.

## Acknowledgements

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*Supplementary Material for:*

# Synthesis of a Highly Functionalised and Homochiral 2-Iodocyclohexenone Related to the C-Ring of the Polycyclic, Indole Alkaloids Aspidophytine and Haplophytine

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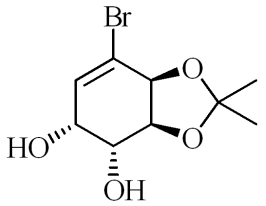
The Australian National University, Canberra, ACT 2601

245

## CONTENTS

400 MHz $^{1}$H NMR Spectrum of Compound **10**
(recorded in $CDCl_3$)




**10**

100 MHz $^{13}C$ NMR Spectrum of Compound **10**
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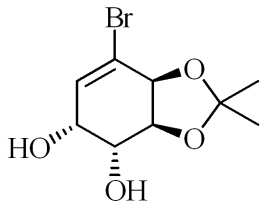


**10**

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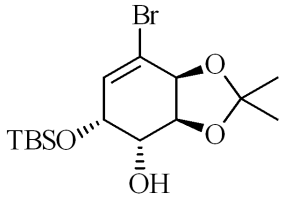


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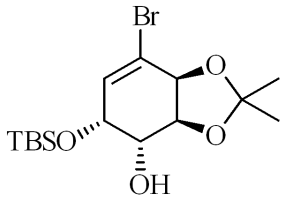


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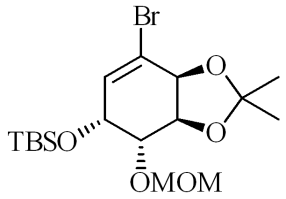


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100 MHz $^{13C}$ NMR Spectrum of Compound **12**
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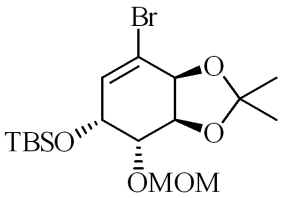


**12**

132.83 122.61 110.25 97.28 76.96 75.96 75.62 68.10 55.88 27.71 26.36 25.93 18.31 -4.63

$CDCl_3$

251

)0 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

400 MHz $^1$H NMR Spectrum of Compound **14**
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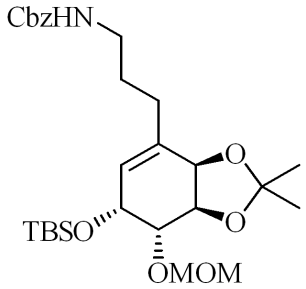


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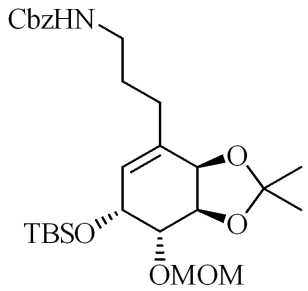


**14**

156.48
137.20
136.78
128.60
128.23
128.17
126.15
109.18
96.30
76.28
75.14
74.62
66.66
66.50
55.59
40.89
31.17
27.73
27.58
26.02
25.96
18.33
-4.42
-4.58

$CDCl_3$

253

f1 (ppm)

400 MHz $^{1}$H NMR Spectrum of Compound **15**
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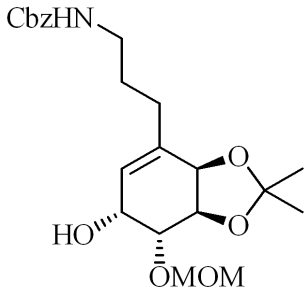


**15**

100 MHz $^{13C}$ NMR Spectrum of Compound **15**
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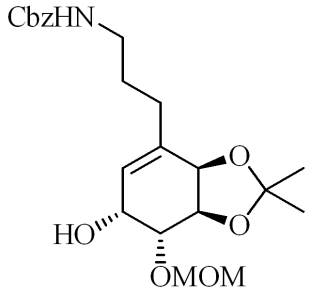



**15**

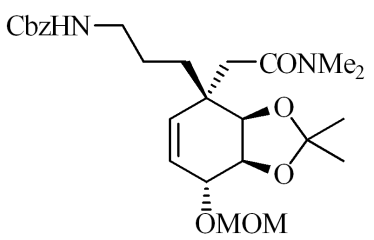
156.46
138.32
136.72
128.60
128.21
128.18
124.95
109.45
96.89
77.95
74.76
74.53
66.69
65.46
55.83
40.77
31.12
27.84
27.47
26.08

$CDCl_3$
$Et_2O$
$Et_2O$

255

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

400 MHz $^{1}$H NMR Spectrum of Compound **16**
(recorded in $CDCl_3$)




**16**

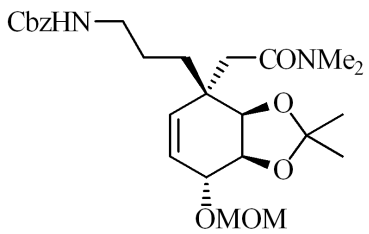
$CHCl_3$

256

5.29 2.00 1.79 0.81 1.00 1.20 1.96 1.17 2.92 1.84 2.82 3.05 2.18 4.13 2.83 2.82

f1 (ppm)

100 MHz $^{13}C$ NMR Spectrum of Compound **16**
(recorded in $CDCl_3$)




**16**

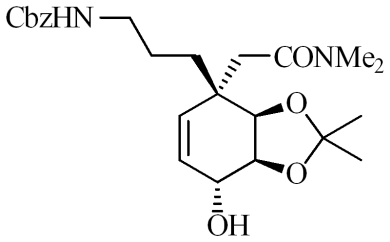
170.50
156.47
136.79
135.89
128.48
128.05
128.00
125.84
108.21
95.54
79.25
78.15
77.16 CDCl3
74.41
66.46
55.46
41.56
40.84
39.07
37.89
35.45
31.82
26.77
24.91
24.19

$CDCl_3$

257

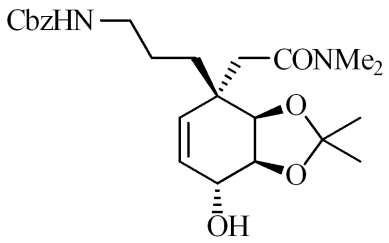
f1 (ppm)

400 MHz $^{1}$H NMR Spectrum of Compound **17**
(recorded in $CDCl_3$)




**17**

100 MHz $^{13}C$ NMR Spectrum of Compound **17**
(recorded in $CDCl_3$)




**17**

400 MHz $^1$H NMR Spectrum of Compound **18**
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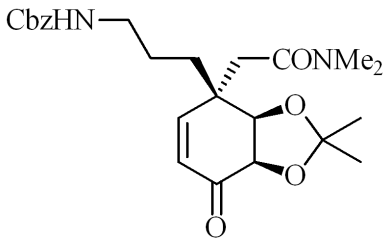


**18**

100 MHz $^{13}C$ NMR Spectrum of Compound **18**
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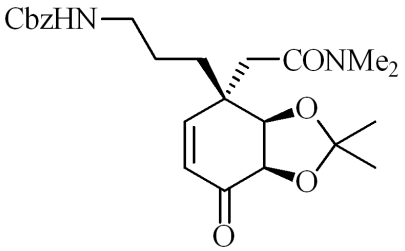


**18**

400 MHz $^{1}$H NMR Spectrum of Compound **8**
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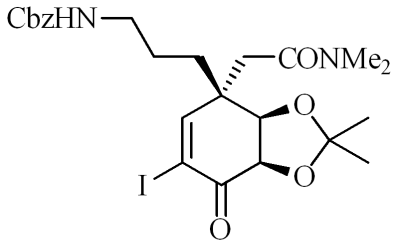


**8**

100 MHz $^{13}C$ NMR Spectrum of Compound **8**
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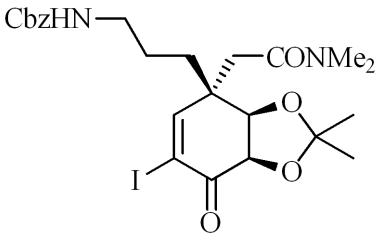


**8**

189.84 168.79 162.43 156.49 136.65 128.59 128.20 128.15 109.66 99.98 78.90 74.21 66.69 45.39 41.21 40.30 38.00 35.74 33.37 27.25 25.74 23.81

$CDCl_3$

263

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

# Syntheses of Structurally and Stereochemically Varied Forms of $C_7N$ Aminocyclitol Derivatives from Enzymatically-derived and Homochiral *cis*-1,2-Dihydrocatechols

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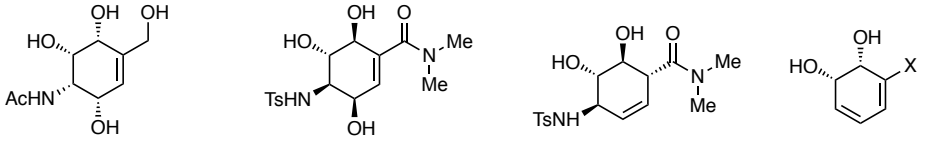
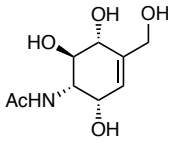
*Supporting Information Placeholder*




**ABSTRACT:** The structurally and stereoisomerically varied $C_7N$ aminocyclitol derivatives **2**-**4** have been prepared, using a versatile and flexible range of protocols, from the *cis*-1,2-dihydrocatechols **5** and **6**, homochiral metabolites derived from the whole-cell biotransformation of the corresponding halobenzene. Reaction sequences that enable syntheses of the enantiomeric forms of these derivatives have also been established.

The $C_7N$ aminocyclitols are microbially-derived and biologically active compounds that have been deployed in a number of therapeutic and agrochemical roles, either in their own right or as components of structurally more complex systems.[1] So, for example, they are used as agents for the treatment of bacterial infections, type-II diabetes and as antifungal agents to treat rice blight.[1] Given such pivotal activities and the emergence of resistance to their more heavily exploited forms,[2] efforts continue apace to identify new variants,[3] to establish how they are produced in vivo[4] and to develop syntheses of them and structural analogues.[5] The 2015 report[6] by Gademann and co-workers on the isolation of the $C_7N$ aminocyclitol kirkamide (**1**) from an obligate leaf nodule symbiont of the Rubiaceous shrub *Psychotria kirkii* emphasizes the ongoing levels of interest in such systems. So, for example, various biological studies established that kirkamide is toxic to both aquatic anthropods and insects with the latter effect suggesting that the compound plays a protective (anti-feedant) role in the plant hosting the symbiont. The structure of kirkamide, which embodies a homoallylic rather than the normally located allylic nitrogen, was established by NMR spectroscopic methods and confirmed by single-crystal X-ray analysis. An eleven-step total synthesis of this natural product was established using methyl *N*-acetyl-*D*-glucosamine as starting material and employed a Ferrier carbocyclization[7] for the pivotal ring-forming step.




kirkamide (**1**)

**Figure 1:** The recently reported $C_7N$ aminocyclitol kirkamide (**1**)

By virtue of their diverse biological activities and structural variations, there remains an intense interest in developing new methods for the synthesis of aminocyclitols, including C7 variants.[5] As part of our ongoing efforts in this area,[5b] we now report syntheses of compounds such as 6-*epi*-kirkamide (**2**), the *ent*-kirkamide derivative **3** and the β,γ-unsaturated amide **4** from the homochiral *cis*-dihydrocatechols **5** and **6** that are, themselves, readily obtained through the whole-cell biotransformation of bromo- and iodobenzene, respectively.[8] Means for accessing the enantiomeric forms of these $C_7N$ aminocyclitol derivatives are also described.

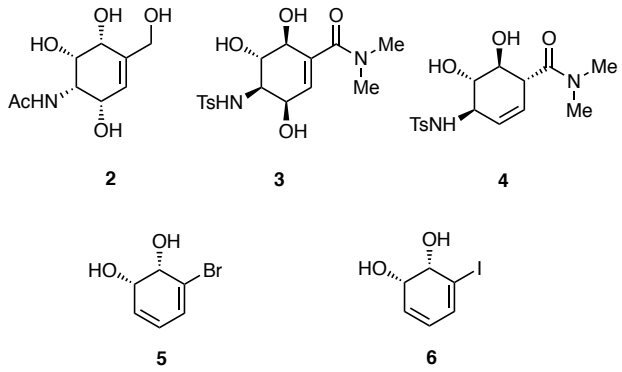
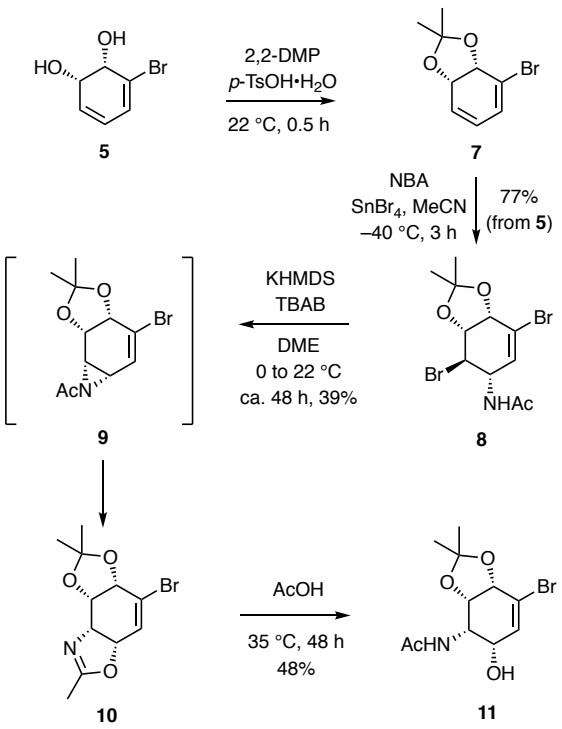



**Figure 2**: The structures of the target $C_7N$ aminocyclitol derivatives 2-4 and the homochiral *cis*-1,2-dihydrocatechols **5** and **6** used as starting materials

The opening stages of the synthetic route to 6-*epi*-kirkamide (**2**) are shown in Scheme 1 and involve the ready and well-established conversion of diol **5** into the acetonide **7**.[9] Subjection of the latter compound to reaction with *N*-bromoacetamide (NBA) in the pres-

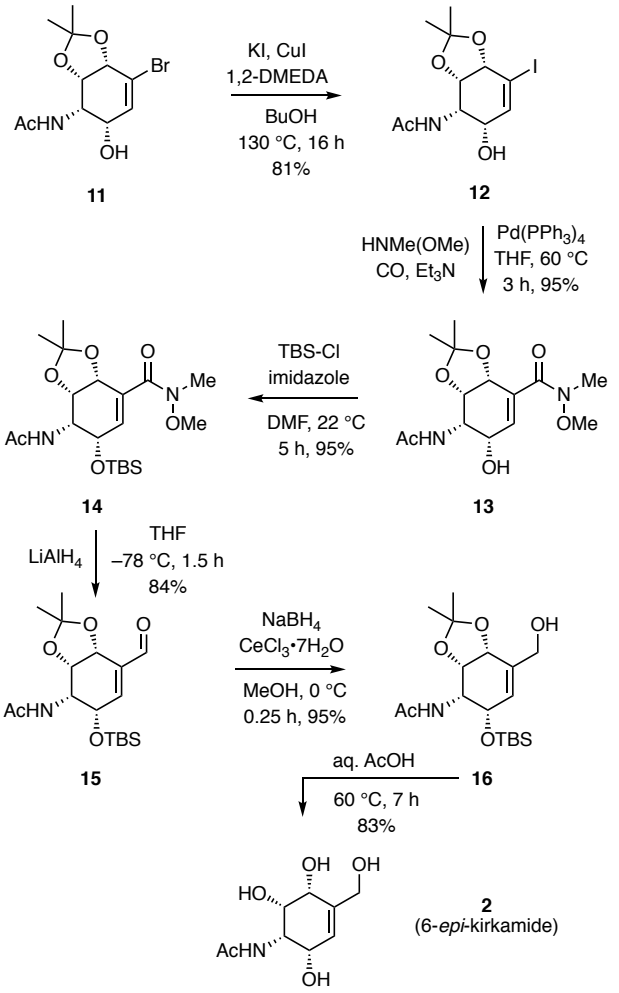
ence of tin tetrachloride at –40 °C afforded, in both a regio- and diastereo-selective manner, the anticipated and previously reported adduct **8**[10] (77%), the structure of which was confirmed by single-crystal X-ray analysis (see Supporting Information – SI – for details). On treating bromo-acetamide **8** with potassium hexamethyldisilazide (KHMDS) and tetra-*n*-butylammonium bromide (TBAB) under conditions similar to those defined by Hudlicky and co-workers for the formation of acylaziridine **9**,[10] then the oxazoline **10** was obtained in 39% yield. The structure of compound **10** follows from the derived spectroscopic data and the single-crystal X-ray analysis of a derivative (see below). Subjection of an authentic sample of compound **9** to the reaction conditions just described also afforded the isomeric heterocycle **10**, an observation consistent with the behavior of other *N*-acyl aziridines.[11] The regioselectivity associated with the conversion **9** → **10** process (a Heine-type reaction[11]) is intriguing and presumably the consequence of the mesomerically electron-donating properties of the flanking bromo-olefin subunit within the substrate. On treating compound **10** with aqueous acetic acid the associated oxazoline ring was cleaved and thereby affording the aminocyclitol **11** (48%) wherein the amine residue is in a homoallylic relationship with the cyclohexene double bond, as seen in kirkamide.

**Scheme 1**: Opening stages of the route to $C_7N$ aminocyclitol **2**




The elaboration of compound **11** to target **2** requires the introduction of a hydroxymethyl group at the bromine-bearing carbon and we sought to do this using one of various possible palladium-catalyzed carbonylation processes.[12] Unfortunately, all such efforts proved unsuccessful and so bromide **11** was converted (Scheme 2) into the corresponding iodide **12** (81%) in the expectation that the latter would serve as a more effective cross-coupling partner. However, even the later electrophile proved ineffective in this regard until we adapted a previously reported procedure[13] allowing for the formation of the Weinreb amide **13** (95%). *O*-Silylation of this by now long-sought product was achieved under standard conditions using *tert*-butyldimethylsilyl chloride (TBS-Cl) and the resulting ether **14** (95%) subjected to reduction with lithium aluminium hydride and so forming, after work-up, the unsaturated aldehyde **15** (84%). Luche reduction[14] of the last compound then afforded the hydroxymethylated product **16** (95%), the structure of which was confirmed by single-crystal X-ray analysis (See SI for details). Treatment of compound **16** with aqueous acetic acid at 60 °C for 7 h then afforded target **2** (the C6-epimer of kirkamide) (83%), the spectral data for which were in complete accord with the assigned structure.

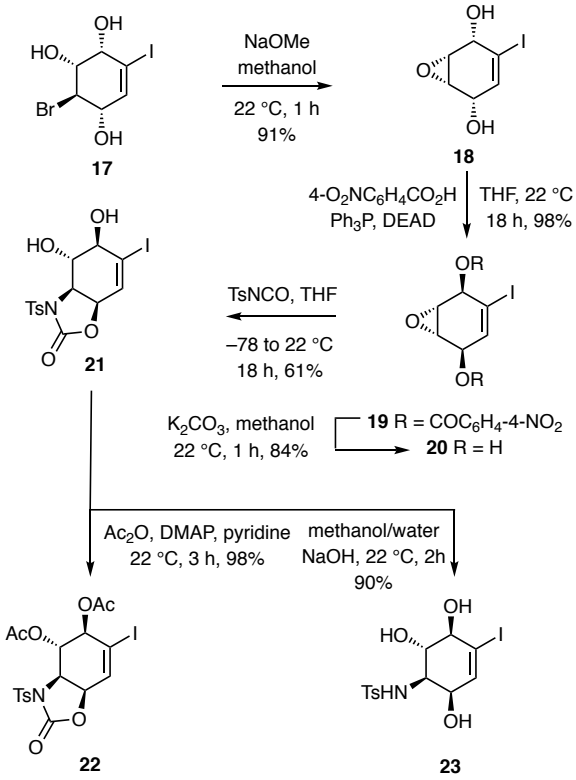
**Scheme 2**: Closing stages of the route to target **2** (6-*epi*-kirkamide)




An alternate route to the kirkamide "scaffold" that allows for the creation of a *trans*-relationship between the amine residue and its neigbouring, homoallylic hydroxyl group, as seen in the natural product **1**, is shown in Scheme 3. This starts with the conversion of diol **6** into the known bromohydrin **17**[15] (74%) and on treating the later with sodium methoxide the previously reported epoxide **18**[15] (91%) was obtained. Compound **18** itself could be engaged in a two-fold Mitsunobu reaction using *p*-nitrobenzoic acid as the nucleophile and thus producing the bis-ester **19** (98%), treatment of which with potassium carbonate in methanol afforded the diol **20** (84%). On treating this last compound with freshly prepared *p*-toluenesulfonyl isocyanate (TsNCO) then reaction occurred selectively at the hydroxyl group remote from the iodinated carbon center and thereby forming, regioselectively and through cyclization of

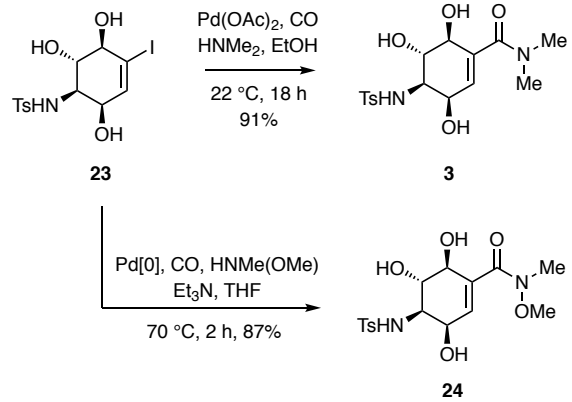
the initially formed tosylcarbamate,[16] the anticipated oxazolidinone **21** (61%) that could either be acetylated under standard conditions to give diacetate **22** (98%) or treated with methanolic sodium hydroxide to give triol **23** (90%). The structure of compound **22** was confirmed by single-crystal X-ray analysis (see SI for details).

**Scheme 3**: A protocol for establishing the aminoconduritol core of *ent*-kirkamide (*ent*-**1**)




The reactions used in the elaboration of compound **23** to the *ent*-kirkamide derivative **3** and its analogue **24** are shown in Scheme 4.

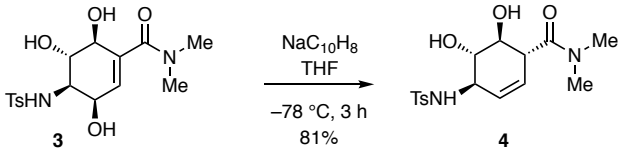
**Scheme 4**: Conversion of triol **23** into target **3** and analogue **24**




Thus, cyclohexenyl iodide **23** could be converted into the corresponding dimethyl or Weinreb amides **3** (91%) and **24** (87%), respectively, using conditions similar to those employed in the conversion **12** → **13**. All of the NMR spectral data obtained on these amide-containing products were entirely consistent with the illustrated structures and that of compound **3** confirmed by single-crystal X-ray analysis.

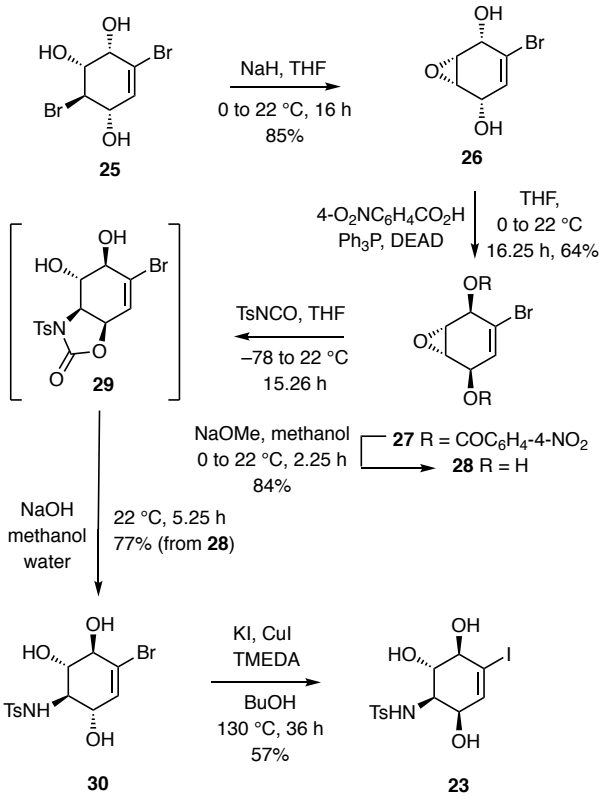
On treating compound **3** with freshly prepared sodium naphthalenide[17] in THF at –78 °C a smooth reductive deoxygenation reaction took place (Scheme 5) and thus providing the novel $C_7N$ aminocyclitol **4** in 81%, the structure of which was also confirmed by single-crystal X-ray analysis. Like congeners **2** and **3**, product **4** should be a useful precursor to a range of aminocarbasugars,[18] compounds that display a range of important biological properties including by acting as inhibitors of enzymes that process carbohydrates and as anti-bacterial agents.

**Scheme 5**: The regiocontrolled, reductive deoxygenation of amide **3** leading to compound **4**




Since the *cis*-1,2-dihydrocatechol *ent*-**5** is available,[19] the reaction sequences shown in Schemes 1 and 2 also provide access to compound *ent*-**2**. However, congener *ent*-**6** is not accessible by analogous means and so the protocols defined in Schemes 3-5 cannot be used to gain access to the enantiomers of compounds **3** and **4**. Accordingly, the reaction sequence shown in Scheme 6 was established to address this matter.

**Scheme 6**: Conversion of *cis*-1,2-dihydrocatechol **5** into iodo-triol **23**



Thus, compound **5** was converted, using established protocols[15] and via intermediate bromohydrin **25** (77%), into the known[15] epoxide **26** (85%). Subjection of this last compound to a two-fold Mitsunobu reaction using *p*-nitrobenzoic acid as nucleophile then afforded ester **27** (64%) that upon saponification afforded diol **28** (82%), the bromo-analogue of compound **20**. Reaction of compound **28** with TsNCO then afforded the anticipated cyclic carbamate **29** and on treatment of this with methanolic sodium hydroxide then the brominated aminocondurtiol derivative **30** (77% from **28**) was obtained. Application of a *trans*-halogenation reaction to this last compound using the same conditions as employed for the conversion **11** → **12** then gave the iodo-triol **23** (57%), an advanced precursor to targets **3** and **4**. As such a connection has been established between *cis*-1,2-dihydrocatechol **5** and these $C_7N$ aminocyclitol derivatives, meaning, therefore, that their enantiomeric forms can now be obtained from *ent*-**5**.

The protocols detailed above provide a capacity to generate a range of the novel $C_7N$ aminocyclitols in either enantiomeric form and so allowing for the development of further structure-activity-relationship (SAR) profiles for these endlessly fascinating compounds.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free-of-charge on the ACS Publications website at DOI: 10.1021/acs.orglett.XXXXXX.

Experimental procedures, spectroscopic data, copies of the NMR spectra of compounds **2**, **3**, **4**, **7**, **8**, **10**-**28** and **30** together with the X-ray data and the derived ORTEPs for compounds **3**, **4**, **8**, **16** and **22**.

### Accession Codes

CCDC 1870597, 1870598, 1870599, 1870600 and 1870601 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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*SUPPORTING INFORMATION FOR:*

# Syntheses of Structurally and Stereochemically Varied Forms of $C_7N$ Aminocyclitol Derivatives from Enzymatically-derived and Homochiral *cis*-1,2-Dihydrocatechols

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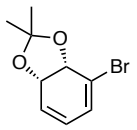
**CONTENTS** **PAGE**

**General Experimental Protocols**

Unless otherwise specified, proton ($^1$H) and carbon ($^{13}$C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For $^1$H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. $^1$H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at $\delta_H$ 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at $\delta_C$ 77.0 were used to reference $^1$H and $^{13}$C NMR spectra, respectively. Infrared spectra ($\nu_{max}$) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 $F_{254}$ plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g: 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al*.[1] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran (THF), methanol and dichloromethane were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs *et al*.[2] Petroleum ether refers to the fraction boiling between 40 and 60 °C. Where necessary, reactions were performed under an nitrogen atmosphere.

## Specific Chemical Transformations

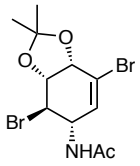
### Compound 7




**7**

A magnetically stirred solution of *cis*-1,2-dihydrocatechol **5** (1.0 g, 5.23 mmol) in 2,2-dimethoxypropane (50 mL) containing *p*-TsOH•$H_2O$ (70 mg, 0.36 mmol) was stirred at 22 °C for 0.15 h then treated with $NaHCO_3$ (15 mL of a saturated aqueous solution) before being extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered then concentrated under reduced pressure to give a light-yellow oil presumed to contained acetonide **7**.[3] This material was used directly in the synthesis of compound **8** as detailed below.

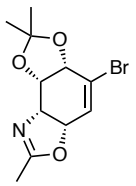
### Compound 8




**8**

A magnetically stirred solution of *N*-bromoacetamide (867 mg, 6.28 mmol) in dry acetonitrile (40 mL) maintained under a nitrogen atmosphere was cooled to –40 °C and, while being protected from light, was treated with $SnBr_4$ (137 mg, 0.31 mmol). The ensuing mixture was then treated, over 2 h, with a solution of compound **7** (1.21 g, 5.23 mmol) in acetonitrile (15 mL). After being maintained for a further 1 h at –40 °C, the reaction mixture was quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution) then extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered then and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash column chromatography ($CH_2Cl_2$ → ethyl acetate gradient elution) to yield, after concentration of the appropriate fractions ($R_f$ = 0.4 in 1:1 v/v ethyl acetate/petroleum ether), compound **8**[4] (1.50 g, 77%) as a white, crystalline solid, m.p. = 170 °C (lit.[4] m.p. = 181 °C), $[\alpha]_D$ = +180.9 (*c* 0.45, $CHCl_3$) {lit.[4] $[\alpha]_D$ = +188.2 (*c* 0.50, $CHCl_3$)}. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, *J* = 9.7 Hz, 1H), 6.18–6.13 (complex m, 1H), 4.94 (m, 1H), 4.68 (m, 1H), 4.60 (m, 1H), 4.21 (m, 1H), 1.97 (s, 3H), 1.51 (s, 3H), 1.42 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 169.1, 128.1, 124.8, 112.1, 77.9, 75.9, 50.4, 44.5, 27.9, 26.6, 23.4; IR (ATR) $\nu_{max}$ 3308, 2985, 1657, 1537, 1372, 1216, 1074, 868 $cm^{-1}$; MS (ESI, +ve) *m/z* 394, 392 and 390 [$(M+Na)^+$, 50, 100 and 49%].
These spectroscopic data matched literature values.[4]

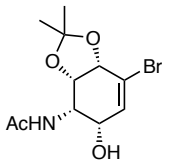
**Compound 10**



**10**

A magnetically stirred solution of compound **8** (7.00 g, 19.0 mmol) in THF (300 mL) maintained under nitrogen was cooled to –10 °C then treated with KHMDS (42 mL of a 0.5 M solution in THF, 20.8 mmol, 1.1 mole eq.). Stirring was continued at –10 °C for 0.5 h, at 0 °C for 0.5 h then at 22 °C for 16 h before the reaction mixture was treated with 1,2-dimethoxyethane (DME) (50 mL) and TBAB (12.2 g, 37.9 mmol). Stirring was continued at 22 °C for a further 16 h then additional DME (50 mL) was added followed by another portion of TBAB (12.2 g, 37.9 mmol). Stirring was continued for another 24 h then the reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (5 × 30 mL). The combined organic phases were dried ($Na_2SO_4$), filtered then concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash column chromatography (1:1 v/v petroleum ether/ethyl acetate → ethyl acetate gradient elution) and concentration of the appropriate fractions ($R_f$ = 0.3 in ethyl acetate) gave compound **10** (4.60 g, 39%) as an clear, orange oil, $[\alpha]_D$ = +28.6 (*c* 1.25, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.40 (d, *J* = 4.6 Hz, 1H), 4.71 (m, 1H), 4.53–4.44 (complex m, 2H), 4.33 (m, 1H), 2.03 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 166.8, 130.7, 124.5, 110.6, 75.4, 74.8, 73.4, 62.4, 27.7, 26.7, 14.3; IR (ATR) $\nu_{max}$ 2986, 2888, 1735, 1664, 1370, 1217, 1057, 984, 866, 673, 625 cm$^{-1}$; MS (ESI, +ve) *m/z* 290 and 288 [$(M+H)^+$, both 100%]; HRMS (ESI, +ve) $(M+H)^+$ Calcd for $C_{11}H_{15}{}^{79}BrNO_3$ 288.0230; Found 288.0232.

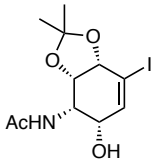
**Compound 11**



**11**

A magnetically stirred solution of compound **10** (3.39 g, 11.76 mmol) in glacial acetic acid (150 mL) was stirred at 35 °C for 48 then cooled and concentrated under reduced pressure and the clear, orange oil thus obtained subjected to flash column chromatography (ethyl acetate → 95:5 ethyl acetate/methanol). Concentration of the relevant fractions ($R_f$ = 0.5 in 95:5 v/v ethyl acetate/methanol) then gave compound **11** (1.74 g, 48%) as an clear, orange foam, $[\alpha]_D$ = –32.6 (*c* 1.08, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.43 (d, *J* = 6.1 Hz, 1H), 6.40 (broad d, *J* = 7.9 Hz, 1H), 4.63 (d, *J* = 5.0 Hz, 1H), 4.58 (m, 1H), 4.37 (m, 1H), 4.02 (m, 1H), 2.88 (m, 1H), 2.09 (s, 3H), 1.51 (s, 3H), 1.38 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.0, 131.1, 127.7, 111.4, 77.3, 77.2, 67.2, 47.1, 28.0, 26.4, 23.4; IR (ATR) $\nu_{max}$ 3518, 3314, 2987, 2934, 1657, 1519, 1372, 1226, 1060, 867 cm$^{-1}$; MS (ESI, +ve) *m/z* 330 and 328 [$(M+Na)^+$, 98 and 100%]; HRMS (ESI, +ve) $(M+H)^+$ Calcd for $C_{11}H_{17}{}^{79}BrNO_4$ 306.0335; Found 306.0342.

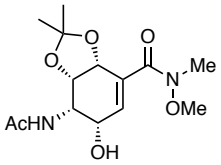
**Compound 12**




**12**

A magnetically stirred solution of compound **11** (1.74 g, 5.69 mmol) in *n*-BuOH (40 mL) was treated with KI (1.42 g, 8.43 mmol, 1.5 mole eq.), CuI (108 mg, 0.57 mmol, 0.1 mole eq.) and 1,2-dimethylethylenediamine (1,2-DMEDA) (61 µL, 0.56 mmol) then a nitrogen atmosphere was established. The resulting mixture was stirred at 130 °C for 16 h before being cooled to 22 °C then concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash column chromatography (1:9 v/v petroleum ether/ethyl acetate elution) to yield, after concentration of the appropriate fractions ($R_f$ = 0.2 in ethyl acetate), compound **12** (1.63 g, 81%) as a white foam, m.p. = 44 °C, $[\alpha]_D$ = –27.4 (*c* 0.50, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 5.9 Hz, 1H), 6.40 (m, 1H), 4.61 (d, *J* = 5.0 Hz, 1H), 4.53 (m, 1H), 4.37 (m, 1H), 3.98–3.81 (complex m, 1H), 2.91 (d, *J* = 11.7 Hz, 1H), 2.08 (s, 3H), 1.50 (s, 3H), 1.37 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.0, 139.0, 111.2, 105.4, 79.5, 77.0, 67.6, 46.9, 28.0, 26.5, 23.4; IR (ATR) $\nu_{max}$ 3517, 3317, 2986, 2933, 1657, 1514, 1372, 1225, 1057, 865, 730 cm$^{-1}$; MS (ESI, +ve) *m/z* 376 [(M+Na)$^+$, 100%]; HRMS (ESI, +ve) (M+Na)$^+$ Calcd for $C_{11}H_{16}INO_4Na$ 376.0022; Found 376.0027.

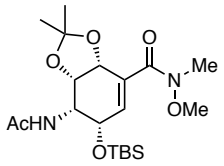
**Compound 13**




**13**

A magnetically stirred solution of compound **12** (876 mg, 2.48 mmol, 1.0 mole eq.) in THF (40 mL) was treated with freshly distilled *N,O*-dimethylhydroxylamine (5 mL), triethylamine (1.5 mL) then $Pd(PPh_3)_4$ (280 mg, 0.25 mmol, 10 mole %). The reaction flask was evacuated then filled with CO three times and the resulting mixture stirred at 60 °C for 3 h before being cooled to 22 °C then concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash column chromatography (95:5 v/v ethyl acetate/methanol → 90:10 v/v ethyl acetate/methanol gradient elution) to yield, after concentration of the appropriate fractions ($R_f$ = 0.3 in 90:10 v/v ethyl acetate/methanol), product **13** (740 mg, 95%) as a white, foam, m.p. = 60-61 °C, $[\alpha]_D$ = –31.7 (*c* 0.5, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.47 (d, *J* = 8.1 Hz, 1H), 6.40 (d, *J* = 5.5 Hz, 1H), 5.15 (d, *J* = 5.5 Hz, 1H), 4.60 (m, 1H), 4.33 (m, 1H), 4.12 (q, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 3.27 (s, 3H), 2.92 (d, *J* = 11.6 Hz, 1H), 2.10 (s, 3H), 1.49 (s, 3H), 1.35 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.2, 167.9, 135.2, 129.9, 111.3, 75.9, 73.3, 65.1, 61.5, 47.3, 33.0, 28.0, 26.3, 23.5; IR (ATR) $\nu_{max}$ 3321, 2985, 2936, 1660, 1527, 1374, 1214, 1058, 873 cm$^{-1}$; MS (ESI, +ve) *m/z* 337 [(M+Na)$^+$, 100%]; HRMS (ESI, +ve) (M+H)$^+$ Calcd for $C_{14}H_{23}N_2O_6$ 315.1551; Found 315.1553.

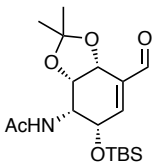
**Compound 14**




**14**

A magnetically stirred solution of compound **13** (530 mg, 1.69 mmol) in DMF (8 mL) maintained at 22 °C was treated with imidazole (287 mg, 4.22 mmol) then TBS-Cl (635 mg, 4.22 mmol). The ensuing mixture was stirred at 22 °C for 5 h and then quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution) then treated with LiCl (15 mL of a saturated aqueous solution) before being extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure and the ensuing light-yellow oil subjected to flash column chromatography (1:1 v/v petroleum ether/ethyl acetate elution). Concentration of the appropriate fractions ($R_f$ = 0.5 in ethyl acetate) then gave compound **14** (690 mg, 95%) as a clear, colorless oil, $[\alpha]_D$ = +59.6 (*c* 0.4, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.20–6.16 (complex m, 2H), 5.09 (d, *J* = 6.4 Hz, 1H), 4.46 (m, 1H), 4.38–4.25 (complex m, 2H), 3.68 (s, 3H), 3.28 (s, 3H), 2.05 (s, 3H), 1.43 (s, 3H), 1.33 (s, 3H), 0.92 (s, 9H), 0.10 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 169.6, 168.1, 133.8, 130.7, 110.9, 73.9, 72.2, 64.2, 61.6, 47.5, 27.6, 26.1, 25.8, 23.6, 18.2, –4.3, –4.9 (one signal obscured or overlapping); IR (ATR) $\nu_{max}$ 3449, 2931, 2857, 1674, 1633, 1508, 1473, 1369, 1252, 1099, 1058, 840, 777 cm$^{-1}$; MS (ESI, +ve) *m/z* 451 [(M+Na)$^+$, 100%]; HRMS (ESI, +ve) (M+H)$^+$ Calcd for $C_{20}H_{37}N_2O_6Si$ 429.2415; Found 429.2419.

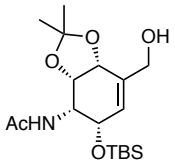
**Compound 15**




**15**

A magnetically stirred solution of compound **14** (160 mg, 0.37 mmol) in THF (4 mL) maintained at –78 °C under a nitrogen atmosphere was treated with $LiAlH_4$ (0.5 mL of a 1 M solution in THF, 0.5 mmol). The ensuing mixture was stirred for 1.5 h at –78 °C then treated with acetone (2 mL) and methanol (2 mL) and after being warmed to 22 °C the ensuing mixture was filtered through a pad of TLC-grade silica gel. Concentration of the filtrate then gave aldehyde **15** (116 mg, 84%) as a clear, colorless oil, $R_f$ = 0.6 (in ethyl acetate), $[\alpha]_D$ = +67.0 (*c* 0.4, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 6.68 (d, *J* = 4.9 Hz, 1H), 6.12 (d, *J* = 9.3 Hz, 1H), 4.94 (dd, *J* = 6.5 and 0.7 Hz, 1H), 4.53–4.38 (complex m, 2H), 4.32 (m, 1H), 2.06 (s, 3H), 1.37 (s, 6H), 0.92 (s, 9H), 0.13 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 192.7, 169.6, 146.1, 138.9, 111.1, 73.6, 69.1, 64.4, 47.9, 27.5, 25.9, 25.8, 23.6, 18.2, –4.3, –4.9; IR (ATR) $\nu_{max}$ 3449, 2953, 2930, 2857, 1693, 1509, 1370, 1253, 1096, 1060, 839 cm$^{-1}$; MS (ESI, +ve) *m/z* 408 [(M+K)$^+$, 100%]; HRMS (ESI, +ve) (M+H)$^+$ Calcd for $C_{18}H_{32}NO_5Si$ 370.2044; Found 370.2048.

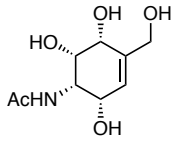
**Compound 16**




**16**

A magnetically stirred solution of compound **15** (93 mg, 0.25 mmol, 1.0 mole eq.) in methanol (4 mL) maintained at 0 °C was treated with $CeCl_3 \bullet 7H_2O$ (100 mg, 0.28 mmol) then $NaBH_4$ (12 mg, 0.33 mmol). The ensuing mixture was stirred at 0 °C for 0.25 h before being quenched with acetone (2 mL) then filtered through a pad of TLC-grade silica gel. The filtrate was concentrated under reduced pressure and the resulting light-yellow oil subjected to flash column chromatography (1:1 v/v petroleum ether/ethyl acetate → ethyl acetate gradient elution) to give, after concentration of the appropriate fractions ($R_f$ = 0.6), compound **16** (89 mg, 95%) as a white, crystalline solid, m.p. = 135–136 °C, $[\alpha]_D$ = +33.3 (*c* 1.1, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.13 (d, *J* = 8.9 Hz, 1H), 5.75 (m, 1H), 4.62 (d, *J* = 6.1 Hz, 1H), 4.43 (m, 1H), 4.31 (m, 1H), 4.27–4.20 (complex m, 3H), 2.04 (s, 3H), 1.97 (m, 1H), 1.40 (s, 3H), 1.34 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 169.7, 137.7, 124.9, 110.8, 74.2, 73.0, 64.8, 64.3, 47.9, 27.8, 26.4, 25.9, 23.6, 18.2, –4.2, –4.8; IR (ATR) $\nu_{max}$ 3445, 2930, 2857, 1660, 1515, 1369, 1252, 1095, 1068, 837, 775, 673 cm$^{-1}$; MS (ESI, +ve) *m/z* 394 [$(M+Na)^+$, 100%]; HRMS (ESI, +ve) $(M+Na)^+$ Calcd for $C_{18}H_{33}NO_5SiNa$ 394.2020; Found 394.2025.

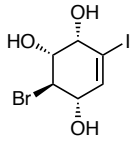
**Compound 2**




**2**
(6-*epi*-kirkamide)

A magnetically stirred solution of compound **16** (90 mg, 242 mmol, 1.0 mole eq.) in acetic acid/water (9 mL of a 2:1 v/v mixture) was stirred at 60 °C for 7 h then cooled to 22 °C and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash column chromatography (4:1 v/v $CH_2Cl_2$/methanol elution) to yield, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **2** (44 mg, 83%) as a white, crystalline solid, m.p. = 52–54 °C, $[\alpha]_D$ = –0.4 (*c* 0.8, $CHCl_3$). $^1$H NMR [400 MHz, $(CD_3)_2SO$] δ 7.57 (d, *J* = 7.8 Hz, 1H), 5.68 (s, 1H), 4.98 (s, 2H), 4.69 (s, 1H), 4.38 (d, *J* = 7.8 Hz, 1H), 4.10–3.94 (complex m, 4H), 3.91 (m, 1H), 3.67 (s, 1H), 1.87 (s, 3H); $^1$H NMR (400 MHz, $D_2O$) δ 5.87 (s, 1H), 4.36 (s, 2H), 4.31–4.13 (complex m, 3H), 3.98 (s, 1H), 2.08 (s, 3H) (signals due to OH and NH group protons not observed); $^{13}$C NMR [101 MHz, $(CD_3)_2SO$] δ 169.5, 139.9, 122.9, 69.9, 67.7, 66.0, 61.2, 51.0, 23.0; IR (ATR) $\nu_{max}$ 3289, 2925, 1633, 1538, 1378, 1264, 1047 cm$^{-1}$; MS (ESI, +ve) *m/z* 240 [$(M+Na)^+$, 100%]; HRMS (ESI, +ve) $(M+H)^+$ Calcd for $C_9H_{16}NO_5$ 218.1023; Found 218.1021.

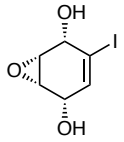
**Compound 17**




**17**

A magnetically stirred solution of compound **6** (1.6 g, 6.722 mmol) in THF/$H_2O$ (60 mL of a 5:1 v/v mixture) maintained at 22 °C was treated with *N*-bromosuccinimide (3.00 g, 16.86 mmol). After 1 h the reaction mixture was concentrated under reduced pressure and the light-yellow oil so-obtained was subjected to flash chromatography (2:1 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions ($R_f$ = 0.4 in 8:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane), compound **17**[5] (1.67 g, 74%) as a white, crystalline solid, m.p. = 113–116 °C (lit.[5] m.p. = 125-127 °C), $[\alpha]_D$ = –61° (*c* = 0.5, $CHCl_3$) {lit.[5] $[\alpha]_D$ = –63.5 (*c* 5.0, THF)}. $^1$H NMR (400 MHz, $CD_3OD$) δ 6.38 (s, 1H), 4.28 (d, *J* = 4.0 Hz, 1H), 4.20 (m, 1H), 4.00 (m, 1H), 3.70 (dd, *J* = 11.3 and 4.1 Hz, 1H) (signals due to OH group protons not observed); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 143.6, 100.1, 77.4, 76.2, 72.0, 58.6; IR $\nu_{max}$ 3295, 2884, 1444, 1348, 1255, 1197, 1185, 1064, 865 cm$^{-1}$; MS (ESI, +ve) *m/z* 359 and 357 [(M+Na)$^+$, both 100%]; HRMS (ESI, +ve) (M+Na)$^+$ Calcd for $C_6H_8{}^{79}BrIO_3Na$ 356.8593; Found 356.8594.

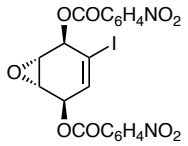
**Compound 18**




**18**

A magnetically stirred solution of compound **17** (758 mg, 2.263 mmol) in methanol (15 mL) maintained at 22 °C was treated with sodium methoxide (610 mg, 11.3 mmol). After stirring for 1 h the reaction mixture was filtered through a short pad of TLC-grade silica gel and the filtrate concentrated under reduced pressure. Subjection of the the resulting clear, colorless oil to flash chromatography (2:1 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f$ = 0.4 in 2:15 v/v methanol/dichloromethane) afforded compound **18**[5] (523 mg, 91%) as a white, crystalline solid, m.p. = 136–139 °C (lit.[5] m.p. = 124-126 °C), $[\alpha]_D$ = +29.5 (*c* = 0.2, methanol) {lit.[5] $[\alpha]_D$ = +26.4 (*c* 5.0, THF)}. $^1$H NMR (400 MHz, $CD_3OD$) δ 6.22 (s, 1H), 4.32 (s, 1H), 4.22 (s, 1H), 3.42 (m, 2H) (signals due to OH group protons not observed); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 139.3, 103.3, 69.4, 67.9, 55.6, 54.9; IR $\nu_{max}$ 3342, 2877, 1635, 1428, 1250, 1047, 871 cm$^{-1}$; MS (ESI, +ve) *m/z* 277 [(M+Na)$^+$, 100%]; HRMS (ESI, +ve) (M+Na)$^+$ Calcd for $C_6H_7IO_3Na$ 276.9331; Found 276.9332.

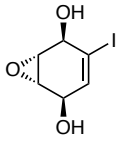
**Compound 19**




**19**

A magnetically stirred solution of compound **18** (1.41 g, 5.551 mmol) in THF (75 mL) was treated with 4-nitrobenzoic acid (2.30 g, 13.8 mmol), triphenylphosphine (3.80 g, 14.49 mmol) then diethyl azodicarboxylate (DEAD) (2.30 mL, 14.61 mmol). After stirring for 18 h at 22 °C the reaction mixture was concentrated under reduced pressure. Subjection of the resulting light-yellow solid to flash chromatography (1:5 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f$ = 0.4 in 1:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane) yielded compound **19** (3.02 g, 98%) as a white, crystalline solid, m.p. = 146–149 °C, $[\alpha]_D$ = +49 (*c* = 0.2, $CHCl_3$). $^1$H NMR (400 MHz, ($CDCl_3$) 8.48–8.22 (complex m, 8H), 6.76 (m, 1H), 6.03 (m, 1H), 5.77 (m, 1H), 3.54 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.9, 163.8, 151.2, 151.1, 134.4(9), 134.5(3), 134.4, 131.4, 131.2, 123.9(4), 123.8(9), 98.0, 72.4, 67.1, 51.3, 49.5; IR $\nu_{max}$ 3112, 2930, 1731, 1527, 1257, 1096, 718 cm$^{-1}$; MS (ESI, +ve) *m/z* 575 [(M+Na)$^+$, 100%]; HRMS (ESI, +ve) (M+H)$^+$ Calcd for $C_{20}H_{13}IN_2O_9Na$ 574.9564; Found 574.9579.

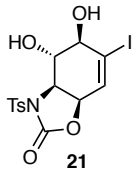
**Compound 20**




**20**

Potaasium carbonate (3.50 g, 25.89 mmol) was added to a magnetically stirred solution of compound **19** (3.48 g, 6.302 mmol) in anhydrous methanol (40 mL) maintained at 22 °C. After 1 h the reaction mixture was filtered through a short pad of TLC-grade silica gel and the filtrate concentrated under reduced pressure. Subjection of the ensuing clear, light-yellow oil to flash chromatography (2:1 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f$ = 0.5 in 5:4:1 v/v/v ethyl acetate/hexane/methanol) provided compound **20** (1.35 g, 84%) as a white, crystalline solid, m.p. = 138–141 °C, $[\alpha]_D$ = +45 (*c* = 0.2, methanol). $^1$H NMR (400 MHz, $CD_3OD$) δ 6.40 (m, 1H), 4.38 (m, 1H), 4.27 (m, 1H), 3.26 (m, 2H) (signals due to OH group protons not observed); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 137.5, 103.4, 71.9, 65.6, 54.9, 52.7; IR $\nu_{max}$ 3341, 2896, 1637, 1450, 1282, 1028, 802 cm$^{-1}$; MS (ESI, +ve) *m/z* 277 [(M+Na)$^+$, 100%]; HRMS (ESI, +ve) (M+Na)$^+$ Calcd for $C_6H_7IO_3Na$ 276.9338; Found 276.9338.

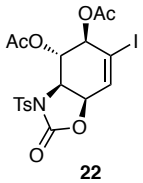
**Compound 21**



**21**

A magnetically stirred solution of compound **20** (466 mg, 1.83 mmol) in anhydrous THF maintained at −78 °C was treated with *p*-toluenesulfonyl isocyanate (28 μL, 1.83 mmol) then stirring continued at −78 to 22 °C for 18 h. The resulting mixture was concentrated under reduced pressure and the yellow oil thus obtained subjected to flash chromatography (2:1 v/v ethyl acetate/hexane elution) to furnish, after concentration of the appropriate fractions ($R_f$ = 0.5 in 5:4:1 v/v/v ethyl acetate/hexane/methanol), compound **21** (504 mg, 61%) as a white, crystalline solid, m.p. = 188–201 °C, $[\alpha]_D$ = +60 (*c* = 0.2, methanol). $^1$H NMR (400 MHz, $CD_3OD$) δ 8.03 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 6.58 (m, 1H), 4.94 (m, 1H), 4.64 (m, 1H), 3.92 (m, 1H), 3.68 (m, 1H), 2.45 (s, 3H) (signals due to OH group protons not observed); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 153.2, 146.7, 137.0, 131.7, 130.4, 130.0, 115.4, 75.8, 75.1, 73.4, 60.8, 21.6; IR $\nu_{max}$ 3516, 2971, 2873, 1780, 1597, 1360, 1167, 1090, 665, 572 cm$^{-1}$; MS (ESI, +ve) *m/z* 474 [(M+Na)$^+$, 100%]; HRMS (ESI, +ve) (M+Na)$^+$ Calcd for $C_{14}H_{14}INO_6SNa$ 473.9484; Found 473.9487.

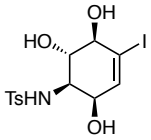
**Compound 22**



**22**

A magnetically stirred solution of compound **21** (96 mg, 0.21 mmol) in pyridine (5 mL) maintained at 22 °C was treated with acetic anhydride (100 μL, 1.06 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (15 mg, 0.12 mmol). After 3 h, the reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (2:1 v/v ethyl acetate/hexane elution) to give, after concentration of the appropriate fractions ($R_f$ = 0.5 in 4:2.5:5.5 v/v/v ethyl acetate/dichloromethane/hexane), compound **22** (112 mg, 98%) as a white, crystalline solid, m.p. = 198–202 °C, $[\alpha]_D$ = +181 (*c* = 0.2, $CHCl_3$). $^1$H NMR (400 MHz, $CD_3OD$) δ 7.94 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 6.63 (m, 1H), 5.79 (m, 1H), 5.54 (m, 1H), 4.81 (m, 1H), 4.47 (m, 1H), 2.44 (s, 3H), 2.17 (s, 3H), 2.10 (s, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 169.9, 169.2, 151.4, 146.3, 134.4, 133.3, 130.1, 128.8, 100.4, 71.7, 71.2, 68.2, 54.2, 21.8, 20.9, 20.8; IR $\nu_{max}$ 2916, 1789, 1755, 1371, 1226, 1173, 1043, 665 cm$^{-1}$; MS (ESI, +ve) *m/z* 558 [(M+Na)$^+$, 100%]; HRMS (ESI, +ve) (M+Na)$^+$ Calcd for $C_{18}H_{18}INO_8SNa$ 557.9696; Found 557.9698.

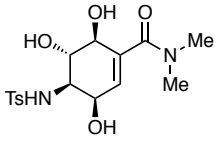
**Compound 23**




**23**

A magnetically stirred suspension of compound **21** (436 mg, 0.97 mmol) in methanol/water (20 mL of a 1:1 v/v mixture) maintained at 22 °C was treated with sodium hydroxide (195 mg, 4.88 mmol). After 2 h the reaction mixture was treated with sufficient HCl (2.0 M aqueous solution) so as to adjust the pH to 7~9 then it was filtered through a short pad of TLC-grade silica gel. The filtrate was concentrated under reduced pressure and the residued thus obtained subjected to flash column chromatography (1:10 v/v methanol/dichloromethane elution) to afford, after concentration of the appropriate fractions ($R_f$ = 0.5 in 6:3:1 v/v/v ethyl acetate/hexane/methanol), compound **23** (368 mg, 90%) as a white, crystalline solid, m.p. = 168–171 °C, $[\alpha]_D$ = −8 (*c* = 0.2, methanol). $^1$H NMR (400 MHz, $CD_3OD$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.45 (m, 1H), 3.75 (m, 2H), 3.67 (m, 1H), 3.25 (m, 1H), 2.42 (s, 3H) (signals due to NH and OH group protons not observed); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 144.6, 139.9, 139.7, 130.6 , 128.2, 109.8, 78.5, 71.2, 68.5, 58.3, 21.5; IR $\nu_{max}$ 3420, 3321, 2956, 2877, 1598, 1434, 1326, 1158, 1092, 815 cm$^{-1}$; MS (ESI, +ve) *m/z* 448 [(M+Na)$^+$, 100%]; HRMS (ESI, +ve) (M+Na)$^+$ Calcd for $C_{13}H_{16}INO_5SNa$ 447.9692; Found 447.9688.

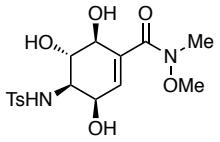
**Compound 3**




**3**

A magnetically stirred mixture of compound **23** (365 mg, 0.858 mmol) and palladium acetate (75 mg, 0.334 mmol) in dimethylamine/ethanol (6 mL of 1:2 v/v mixture) was exposed to a balloon of CO. After stirring at 22 °C for 48 h, the reaction mixture was concentrated under reduced pressure, and the residue thus obtained subjected to flash column chromatography (1.5:10 v/v methanol/dichloromethane elution) to provide, after concentration of the appropriate fractions ($R_f$ = 0.4 in 3:20 v/v methanol/dichloromethane), compound **3** (289 mg, 91%) as a ca. 10:1 mixture of rotamers and as a white, crystalline solid, m.p. = 174-178 °C, $[\alpha]_D$ = −5 (*c* = 0.2, methanol). $^1$H NMR (400 MHz, $CD_3OD$) δ (major rotamer) 7.81 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 5.69 (m, 1H), 4.20 (m, 1H), 3.99 (m, 1H), 3.66 (dd, *J* = 10.7 and 7.4 Hz, 1H), 3.19 (dd, *J* = 10.7 and 4.0 Hz, 1H), 3.07 (s, 3H), 2.96 (s, 3H), 2.42 (s, 3H) (signals due to NH and OH group protons not observed); $^{13}$C NMR (100 MHz, $CD_3OD$) δ (major rotamer) 171.8, 144.6, 139.9, 139.8, 130.6, 128.3, 127.7, 73.7, 71.3, 66.3, 58.3, 39.4, 35.0, 21.5; IR $\nu_{max}$ 3330, 2933, 2876, 1607, 1448, 1326, 1158, 1092, 668 cm$^{-1}$; MS (ESI, +ve) *m/z* 393 [(M+Na)$^+$, 100%], 371 [(M+H)$^+$, 10]; HRMS (ESI, +ve) (M+H)$^+$ calcd for $C_{16}H_{23}N_2O_6S$ 371.1266; Found 371.1271.

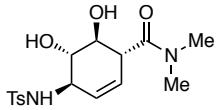
**Compound 24**




**24**

A magnetically stirred solution of compound **23** (275 mg, 0.52 mmol) in THF (12 mL) maintained at 22 °C was treated with freshly distilled *N*,*O*-dimethylhydroxylamine (300 μL, 5.82 mmol) then triethylamine (400 μL, 2.12 mmol) and $Pd(PPh_3)_4$ (55 mg, 0.05 mmol, 10 mole %). The reaction flask was evacuated then refilled with CO three times and the resulting mixture stirred at 70 °C for 2 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (1:9 v/v methanol/ethyl acetate elution) and afforded, after concentration of the appropriate fractions ($R_f$ = 0.3), the title compound **24** (176 mg, 86%) as a clear, yellow oil, $[\alpha]_D$ = –19.4 (*c* 1.0, methanol). $^1$H NMR [400 MHz, $(CD_3)_2SO$] δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 6.01 (m, 1H), 4.90 (s, 5H), 4.36 (m, 1H), 4.10 (t, *J* = 4.6 Hz, 1H), 3.77 (s, 3H), 3.73 (m, 1H), 3.44 (s, 2H), 3.34 (s, 3H), 3.31 (m, 1H); $^{13}$C NMR [101 MHz, $(CD_3)_2SO$] δ 160.2, 135.0, 130.2, 129.7, 121.1(0), 121. 0(7), 120.2, 118.7, 63.8, 61.7, 56.6, 52.2, 48.6, 12.0; IR (ATR) $\nu_{max}$ 3326, 2935, 2490, 1615, 1436, 1323, 1155, 1092, 815, 667 cm$^{-1}$; MS (ESI, +ve) *m/z* 409 [$(M+Na)^+$, 100%]; HRMS (ESI, +ve) $(M+H)^+$ Calcd for $C_{16}H_{23}N_2O_7S$ 387.1220; Found 387.1228.

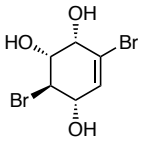
**Compound 4**




**4**

A magnetically stirred solution of compound **3** (60 mg, 0.162 mmol) in anhydrous THF (15 mL) maintained at –78 °C under a nitrogen atmosphere was treated with sodium naphthalenide (1.0 mL of a *ca*. 0.8 M solution in THF, *ca*. 0.8 mmol). After stirring at –78 °C for 3 h, the reaction was quenched with ethanol (2 mL). Evaporation of the ensuing mixture under reduced pressure followed by subjection of the residue so-obtained to flash column chromatography (1.5:10 v/v methanol/dichloromethane elution) afforded, after concentration of the appropriate fractions ($R_f$ = 0.5 in 3:20 v/v methanol/dichloromethane), compound **4** (46 mg, 81%) as a ca. 10:1 mixture of rotamers and as a white, crystalline solid, m.p. = 189–193 °C, $[\alpha]_D$ = –122 (*c* = 0.2, methanol). $^1$H NMR (400 MHz, $CD_3OD$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 5.25 (m, 2H), 3.85 (t, *J* = 9.4 Hz, 1H), 3.76 (m, 1H), 3.58 (m, 1H), 3.44 (t, *J* = 9.4 Hz, 1H), 3.14 (s, 3H), 2.95 (s, 3H), 2.42 (s, 3H) (signals due to NH and OH group protons not observed); $^{13}$C NMR (100 MHz, $CD_3OD$) δ (major rotamer)174.6, 144.6, 140.2, 130.7, 130.6, 130.1, 128.2, 126.2, 76.0, 73.8, 58.5, 48.0, 38.2, 36.4, 21.4; IR $\nu_{max}$ 3170, 2926, 1625, 1498, 1328, 1161, 1092, 665 cm$^{-1}$; MS (ESI, +ve) *m/z* 377 [$(M+Na)^+$, 100%], 355 [$(M+H)^+$, 9]; HRMS (ESI, +ve) $(M+H)^+$ Calcd for $C_{16}H_{23}N_2O_5S$ 355.1324; Found 355.1322.

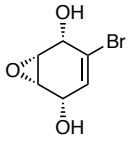
**Compound 25**




**25**

A magnetically stirred solution of compound **5** (660 mg, 3.46 mmol, 1.0 mole eq.) in THF (5 mL) maintained at 0 °C was treated with water (2 mL) and *N*-bromosuccinimide (645 mg, 3.63 mmol). The reaction mixture was then warmed to 22 °C and stirred at this temperature for 1 h before being quenched with sodium sulfite (5 mL of a saturated aqueous solution). The separated aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were dried ($Na_2SO_4$), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (2:3 v/v ethyl acetate/petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.2), compound **25**[5] (767 mg, 77%) as a white, crystalline solid, m.p. = 115–116 °C (lit.[5] m.p. = 116–118 °C), $[\alpha]_D$ = –77.3 (*c* 1.2, ethanol) {lit.[5] $[\alpha]_D$ = –61.7 (*c* 5.0, ethanol)}. $^1$H NMR [400 MHz, $(CD_3)_2SO$] δ 6.00 (d, *J* = 2.6 Hz, 1H), 5.77 (d, *J* = 7.2 Hz, 1H), 5.70 (d, *J* = 6.2 Hz, 1H), 5.43 (d, *J* = 7.7 Hz, 1H), 4.14 (m, 1H), 4.06 (m, 1H), 3.92 (m, 1H), 3.58 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 134.9, 123.5, 73.3, 73.0, 70.4, 59.6; IR (ATR) $\nu_{max}$ 3351, 2905, 1692, 1647, 1405, 1339, 1199, 1098, 1064, 870 cm$^{-1}$.

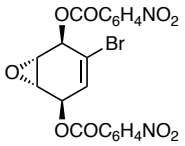
**Compound 26**




**26**

A magnetically stirred solution of compound **25** (3.60 g, 12.5 mmol) in THF (60 mL) was maintained at 0 °C under nitrogen atmosphere then treated with NaH (600 mg of a 60 % dispersion in mineral oil, 15.0 mmol). The reaction mixture was them warmed to 22 °C and stirred at this temperature for 16 h before being quenched with sodium bicarbonate (3 mL of a saturated aqueous solution) and the ensuing mixture concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (2:3 v/v ethyl acetate/petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.3), compound **26**[5] (2.20 g, 85%) as a white, crystalline solid, m.p. = 149 °C (lit.[5] m.p. = 134–136 °C), $[\alpha]_D$ = +18.8 (*c* 1.15, THF) {lit.[5] $[\alpha]_D$ = +16.6 (*c* 5.0, THF)}. $^1$H NMR [400 MHz, $(CD_3)_2SO$] δ 5.77 (q, *J* = 2.2 Hz, 2H), 5.47 (m, 1H), 4.33 (m, 1H), 4.25 (m, 1H), 3.42–3.34 (complex m, 2H); $^{13}$C NMR [101 MHz, $(CD_3)_2SO$] δ 130.3, 123.9, 65.8, 65.4, 54.3, 54.1; IR (ATR) $\nu_{max}$ 3339, 2924, 2872, 1703, 1047, 911 cm$^{-1}$; MS (ESI, +ve) *m/z* 231 and 229 [$(M+Na)^+$, 98 and 100%]; HRMS (ESI, +ve) $(M+Na)^+$ Calcd for for $C_6H_7{}^{79}BrO_3Na$ 228.9476; Found 228.9481.

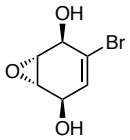
**Compound 27**




**27**

A magnetically stirred solution of compound **26** (1.85 g, 8.94 mmol, 1.0 mole eq.) in THF (80 mL) maintained under nitrogen at 22 °C was treated with triphenylphosphine (5.86 g, 22.34 mmol) and *p*-nitrobenzoic acid (3.73 g, 22.34 mmol). The ensuing mixture was cooled to 0 °C, DEAD (3.51 mL, 22.34 mmol) added, dropwise, after which it was warmed to 22 °C and stirred at this temperature for another 16 h. The reaction mixture was then concentrated under reduced pressure and the residue thus obtained was subjected to flash column chromatography (1:9 to 1:4 v/v ethyl acetate/petroleum ether gradient elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.6 in 3:7 v/v ethyl acetate/petroleum ether elution), compound **27** (2.87 g, 64%) as a white, crystalline solid, m.p. = 182 °C, $[\alpha]_D$ = +39.5 (*c* 1.22, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.52–8.00 (complex m, 8H), 6.48 (m, 1H), 6.05 (s, 1H), 5.88 (m, 1H), 3.60 (s, 1H), 3.55 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 163.9, 163.8, 151.2, 151.1, 134.5, 134.3, 131.3, 131.2, 126.8, 123.9(1), 123.8(9), 123.3, 70.2, 66.9, 51.8, 49.7; IR (ATR) $\nu_{max}$ 3114, 3081, 2951, 2859, 1733, 1722, 1523, 1258, 1091, 841, 715 cm$^{-1}$; MS (ESI, +ve) *m/z* 529 and 527 [$(M+Na)^+$, 98 and 100%]; HRMS (ESI, +ve) $(M+Na)^+$ Calcd for for $C_{20}H_{13}{}^{79}BrN_2O_9Na$ 526.9702; Found 526.9698.

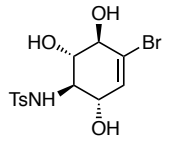
**Compound 28**




**28**

A magnetically stirred suspension of compound **27** (2.38 g, 4.71 mmol, 1.0 mole eq.) in dry methanol (80 mL) maintained at 0 °C was treated with a suspension of sodium methoxide (254 mg, 4.71 mmol) in methanol (30 mL). The ensuing mixture was warmed to 22 °C and stirred at this temperature for 2 h then quenched with ammonium chloride (10 mL of a saturated aqueous solution) and the mixture then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (1:1 → 1:4 v/v ethyl acetate/petroleum ether gradient elution) and afforded, after concentration of the appropriate fractions ($R_f$ = 0.2) compound **28** (797 mg, 82%) as a pink solid, m.p. = 96 °C, $[\alpha]_D$ = +27.4 (*c* 1.15, methanol). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.20 (dd, *J* = 5.4 and 1.7 Hz, 1H), 4.59 (s, 1H), 4.53 (s, 1H), 3.45 (s, 1H), 3.35 (s, 1H), 3.04 (s, 1H), 2.62 (broad s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 128.4, 126.2, 69.3, 64.7, 53.7, 51.4; IR (ATR) $\nu_{max}$ 3310, 3007, 2900, 1651, 1023, 954, 804 cm$^{-1}$; MS (ESI, +ve) *m/z* 231 and 229 [$(M+Na)^+$, 30 and 100%]; HRMS (ESI, +ve) $(M+Na)^+$ Calcd for for $C_6H_7{}^{79}BrO_3Na$ 228.9476; Found 228.9473.

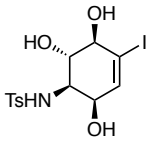
**Compound 30**




**30**

A magnetically stirred solution of compound **28** (3.60 g, 17.39 mmol) in dry THF (80 mL) maintained at –78 °C under nitrogen atmosphere was treated, dropwise, with *p*-toluenesulfonyl isocyanate (3.0 mL, 19.13 mmol) then the reaction mixture was allowed to warm to 22 °C over 5 h. Stirring was continued at this temperature for another 10 h then the reaction mixture concentrated under reduced pressure. The residue thus obtained (and presumed to contain compound **29**) was dissolved in methanol/water (140 mL of a 1:1 v/v mixture) then treated, dropwise, with sodium hydroxide (10 mL of a 17.5 M aqueous solution). The ensuing mixture was stirred at 22 °C for 5 h then neutralised with HCl (10 mL of a 1 M aqueous solution) before being concentrated under reduced pressure to half the original volume. The separated aqueous layer was extracted with ethyl acetate (5 × 30 mL) and the combined organic phases dried ($Na_2SO_4$), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (ethyl acetate elution) and afforded, after concentration of the appropriate amounts ($R_f$ = 0.6), compound **30** (5.04 g, 77%) as a clear, yellow oil, $[\alpha]_D$ = –15.5 (*c* 1.0, acetone). $^1$H NMR [400 MHz, $(CD_3)_2CO$] δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 6.15 (dd, *J* = 5.4 and 1.5 Hz, 1H), 4.90 (broad s, 1H), 4.31 (broad m, 1H), 4.13–3.99 (complex m, 2H), 3.94 (m, 1H), 3.79 (m, 1H), 3.39–3.24 (complex m, 2H), 2.41 (s, 3H); $^{13}$C NMR [101 MHz, $(CD_3)_2CO$] δ 143.8, 139.6, 131.5, 130.3, 128.0, 76.2, 71.6, 67.0, 57.6, 21.4 (one signal obscured or overlapping); IR (ATR) $\nu_{max}$ 3419, 3200, 2922, 1704, 1451, 1313, 1154, 1045, 810, 664 cm$^{-1}$; MS (ESI, +ve) *m/z* 402 and 400 [$(M+Na)^+$, 100 and 99%]; HRMS (ESI, +ve) $(M+Na)^+$ Calcd for for $C_{13}H_{16}{}^{79}BrNO_5SNa$ 399.9825; Found 399.9823.

**Compound 23**




**23**

A magnetically stirred suspension of compound **30** (85 mg, 0.22 mmol, 1.0 mole eq.) in *n*-BuOH (5 mL) maintained at 22 °C was treated with KI (261 mg, 1.57 mmol, 7.0 mole eq.), CuI (5 mg, 0.02 mmol, 0.1 mole eq.) and tetramethylethylenediamine (TMEDA) (3 µL, 0.02 mmol, 0.1 mole eq.). The reaction vessel was flushed with nitrogen then sealed and the contents stirred at 130 °C for 36 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (ethyl acetate) to afford, after concentration of the appropriate amounts ($R_f$ = 0.6), compound **23** (54 mg, 57%) as a brown solid. This material was identical, in all respects, with that obtained by the protocol defined above.

**Crystallographic Studies.**
***Crystallographic Data.***

Compound **3**. $C_{16}H_{22}N_2O_6S$ $M$ = 370.43, $T$ = 150 K, triclinic, space group $P1$, $Z$ = 1, $a$ = 5.7776(2) Å, $b$ = 6.4485(2) Å, $c$ = 12.4143(4) Å; α = 96.716(3)°, β = 91.948(3), γ = 112.530(3)°, $V$ = 422.72(1) Å$^3$, $D_x$ = 1.455 Mg m$^{-3}$, 2620 unique data ($2\theta_{max}$ = 147.8°), $R$ = 0.046 [for 2593 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.124 (all data), $S$ = 1.00.
Compound **4**. $C_{16}H_{22}N_2O_5S$, $M$ = 354.43, $T$ = 150 K, monoclinic, space group, $P2_1$, $Z$ = 2, $a$ = 7.3573(2) Å, $b$ = 7.5270(2) Å, $c$ = 15.5741(5) Å; β = 93.163(3)°, $V$ = 861.15(3) Å$^3$, $D_x$ = 1.367 Mg m$^{-3}$, 2361 unique data ($2\theta_{max}$ = 148.2°), $R$ = 0.064 [for 2230 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.173 (all data), $S$ = 1.00.
Compound **8**. $C_{11}H_{15}Br_2NO_3$, $M$ = 369.06, $T$ = 150 K, monoclinic, space group $P2_1$, $Z$ = 2, $a$ = 5.0336(3) Å, $b$ = 17.7799(12) Å, $c$ = 7.6856(5) Å; β = 94.134(5)°, $V$ = 686.05(8) Å$^3$, $D_x$ = 1.787 Mg m$^{-3}$, 2788 unique data ($2\theta_{max}$ = 52.8°), $R$ = 0.034 [for 2611 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.070 (all data), $S$ = 1.01.
Compound **16**. $C_{18}H_{33}NO_5Si$, $M$ = 371.54, $T$ = 150 K, triclinic, space group $P1$, $Z$ = 1, $a$ = 7.2377(6) Å, $b$ = 8.2340(6) Å, $c$ = 9.9721(10) Å; α = 99.215(7)°, β = 108.174(8), γ = 105.551(7)°, $V$ = 524.33(8) Å$^3$, $D_x$ = 1.177 Mg m$^{-3}$, 3258 unique data ($2\theta_{max}$ = 60°), $R$ = 0.044 [for 2997 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.119 (all data), $S$ = 1.13.
Compound **22**. $C_{18}H_{18}INO_8S{\bullet}CH_2Cl_2$ $M$ = 620.22, $T$ = 150 K, monoclinic, space group $C2$, $Z$ = 4, $a$ = 25.1349(5) Å, $b$ = 8.03077(13) Å, $c$ = 12.0325(2) Å; β = 97.6645 (16)°, $V$ = 2407.10(7) Å$^3$, $D_x$ = 1.711 Mg m$^{-3}$, 4760 unique data ($2\theta_{max}$ = 147.8°), $R$ = 0.034 [for 4695 reflections with $I > 2.0\sigma(I)$]; $Rw$ = 0.091 (all data), $S$ = 1.04.

***Structure Determinations.***
Images for compounds **3**, **4**, **8**, **16** and **22** were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) fitted with an area detector and the data extracted using the CrysAlis package.[6] The structures of compounds **2** and **3** were refined using the CRYSTALS[7] program package while the remainder were solved with ShelXT[8] and refined using ShelXL[9] in OLEX2.[10] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1870597, 1870598, 1870599, 1870600, and 1870601). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

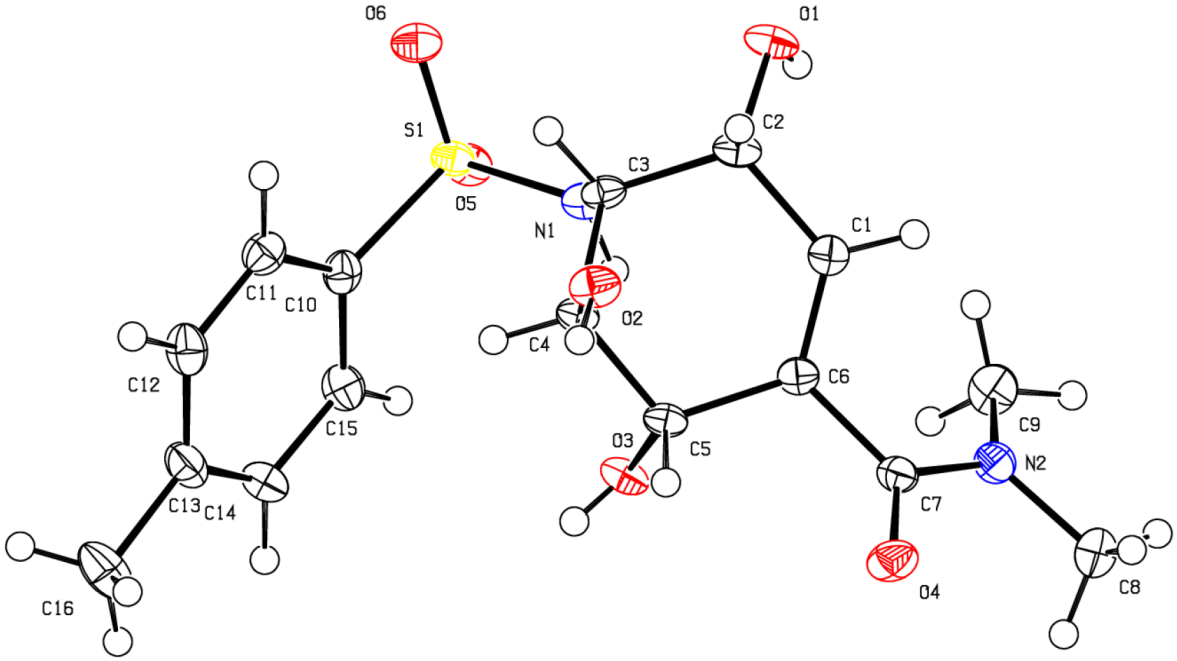



**Figure S1**: Structure of compound **3** (CCDC 1870597). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

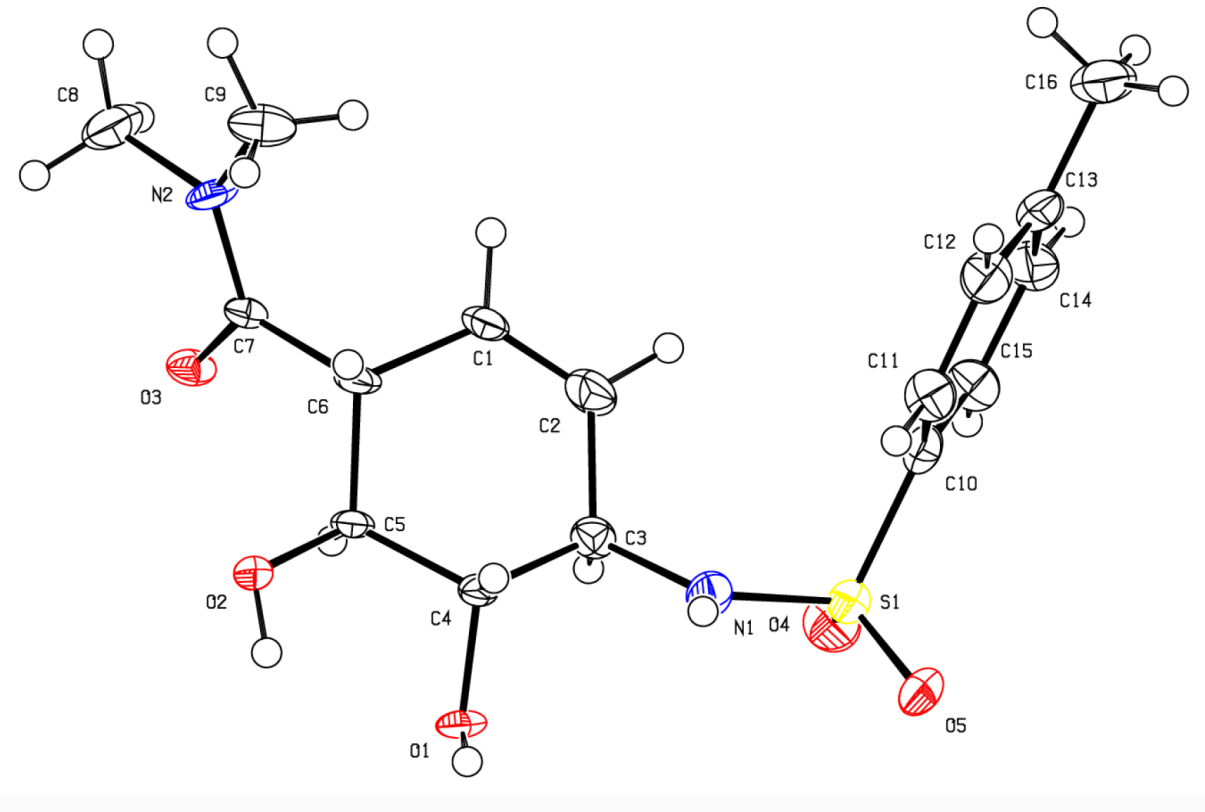



**Figure S2**: Structure of compound **4** (CCDC 1870598). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

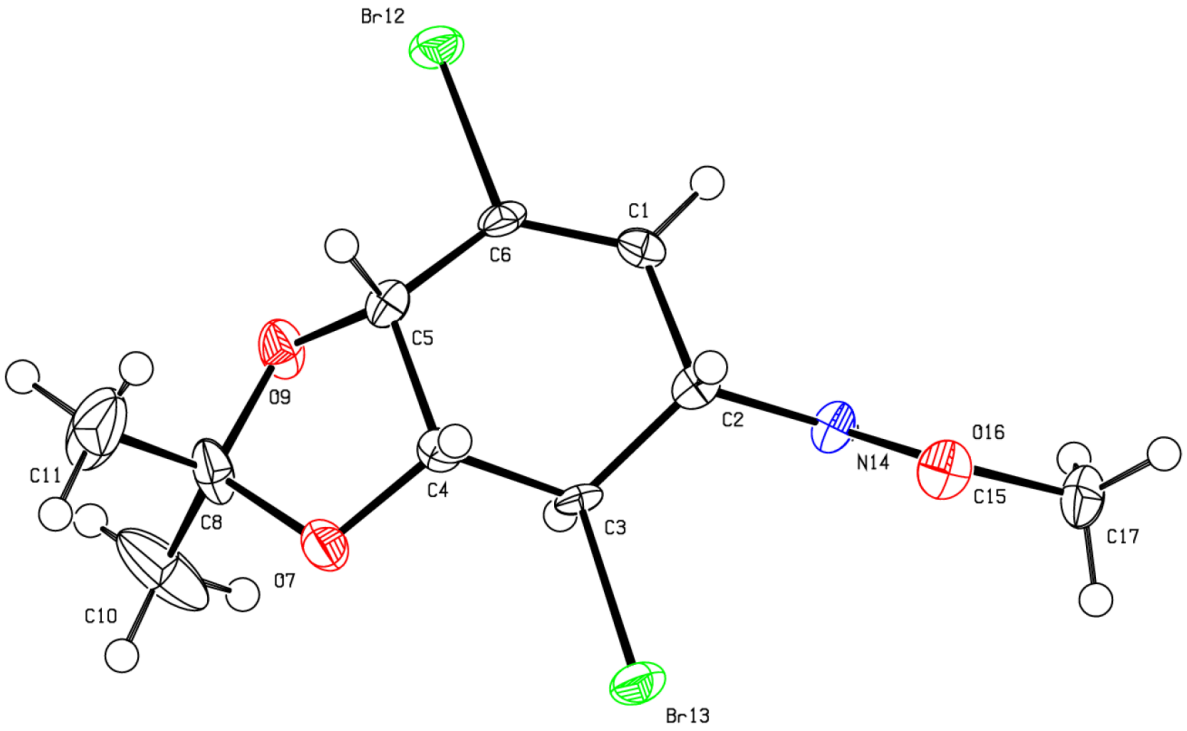



**Figure S3**: Structure of compound **8** (CCDC 1870599) showing the two molecules in the unit cell. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

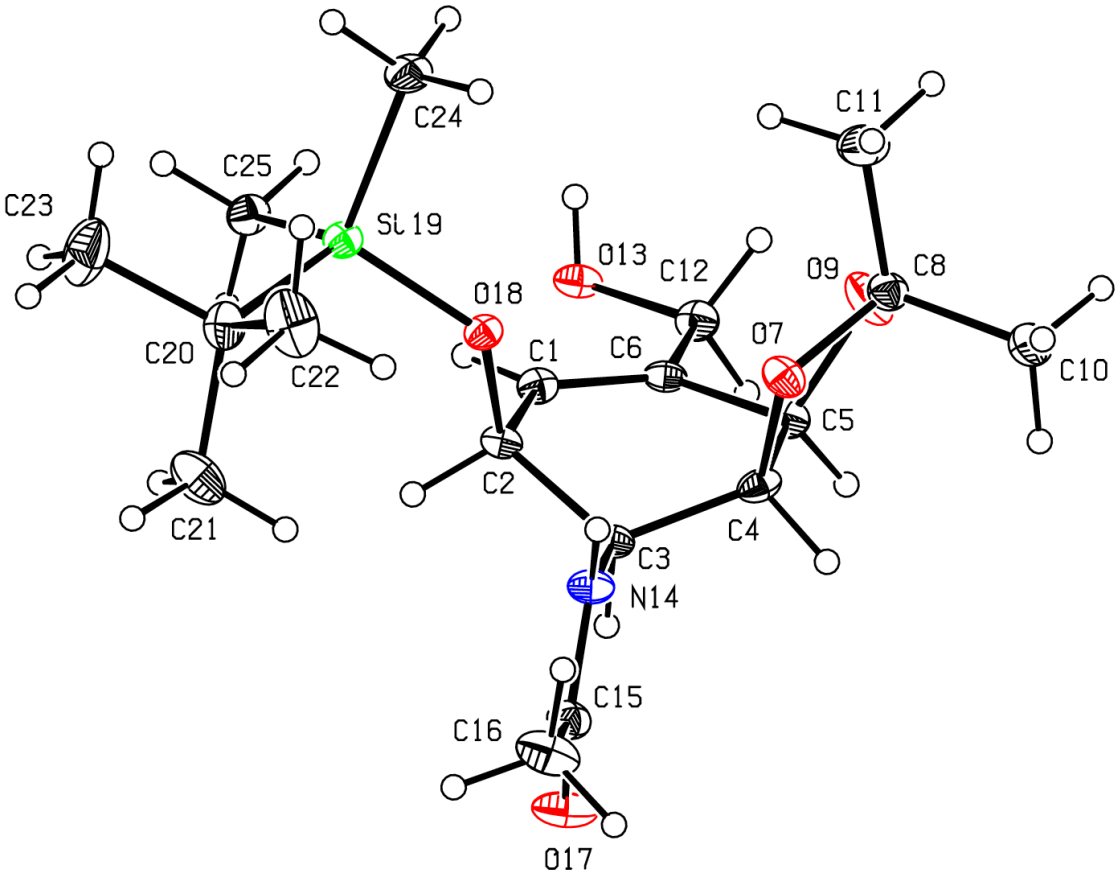



**Figure S4**: Structure of compound **16** (CCDC 1870600). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

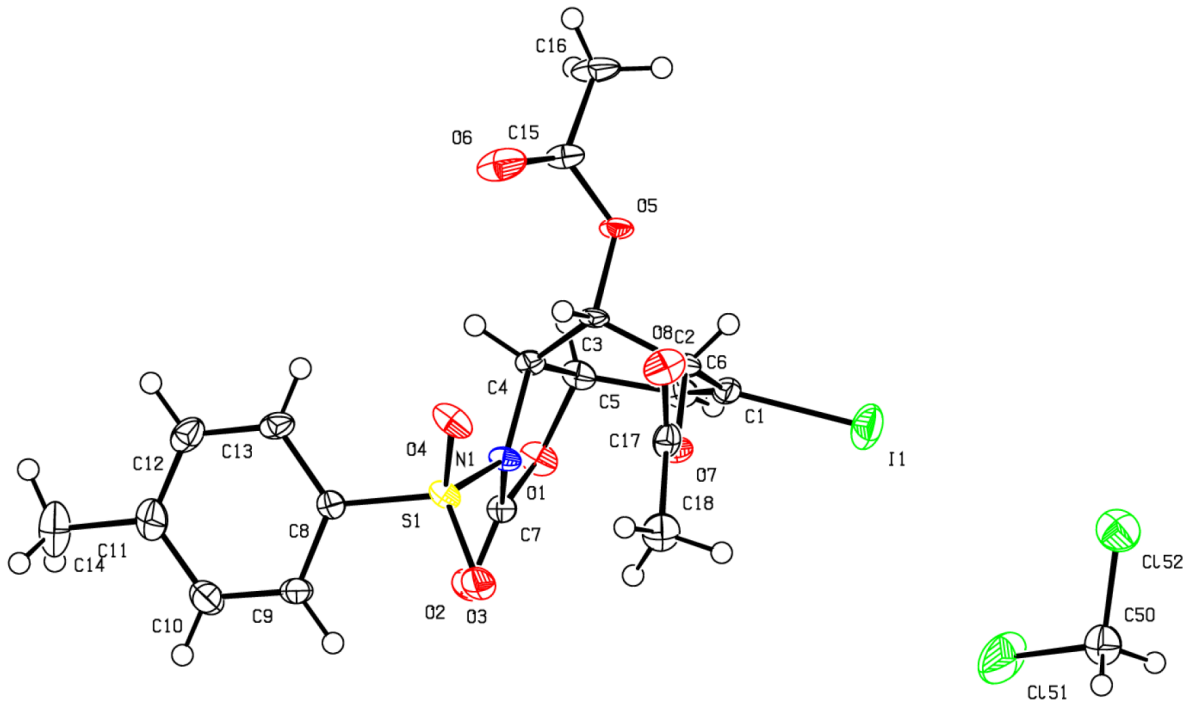



**Figure S5**: Structure of compound **22** (CCDC 1870601) and associated dichloromethane. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

## References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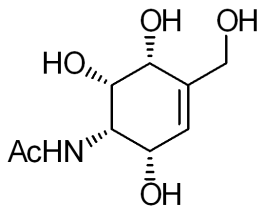
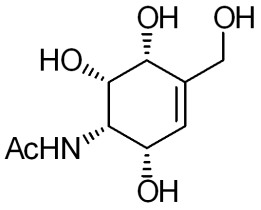
400 MHz $^1$H NMR Spectrum of Compound **2**
(recorded in $(CD_3)_2SO$)



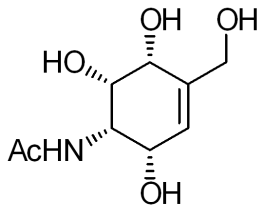

**2**

101 MHz $^{13}$C NMR Spectrum of Compound **2**
(recorded in $(CD_3)_2SO$)



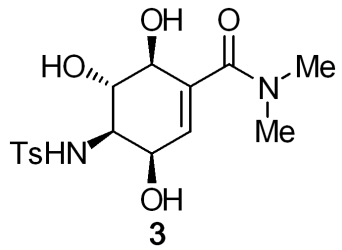

**2**

400 MHz $^{1}$H NMR Spectrum of Compound **2**
(recorded in $D_2O$)



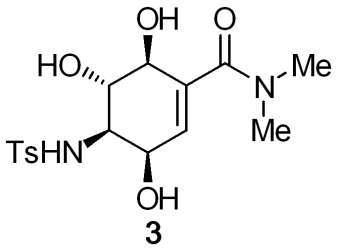

**2**

400 MHz $^{1}$H NMR Spectrum of Compound **3**
(recorded in $CD_3OD$)




**3**

101 MHz $^{13}C$ NMR Spectrum of Compound **3**
(recorded in $CD_3OD$)




**3**

171.8 144.6 139.9 130.6 130.6 128.3 128.2 127.7 73.7 71.3 66.3 58.3 39.4 35.0 21.5

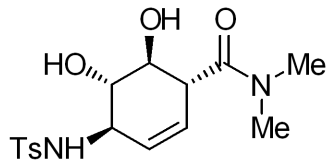
*= minor rotamer

$CD_3OD$

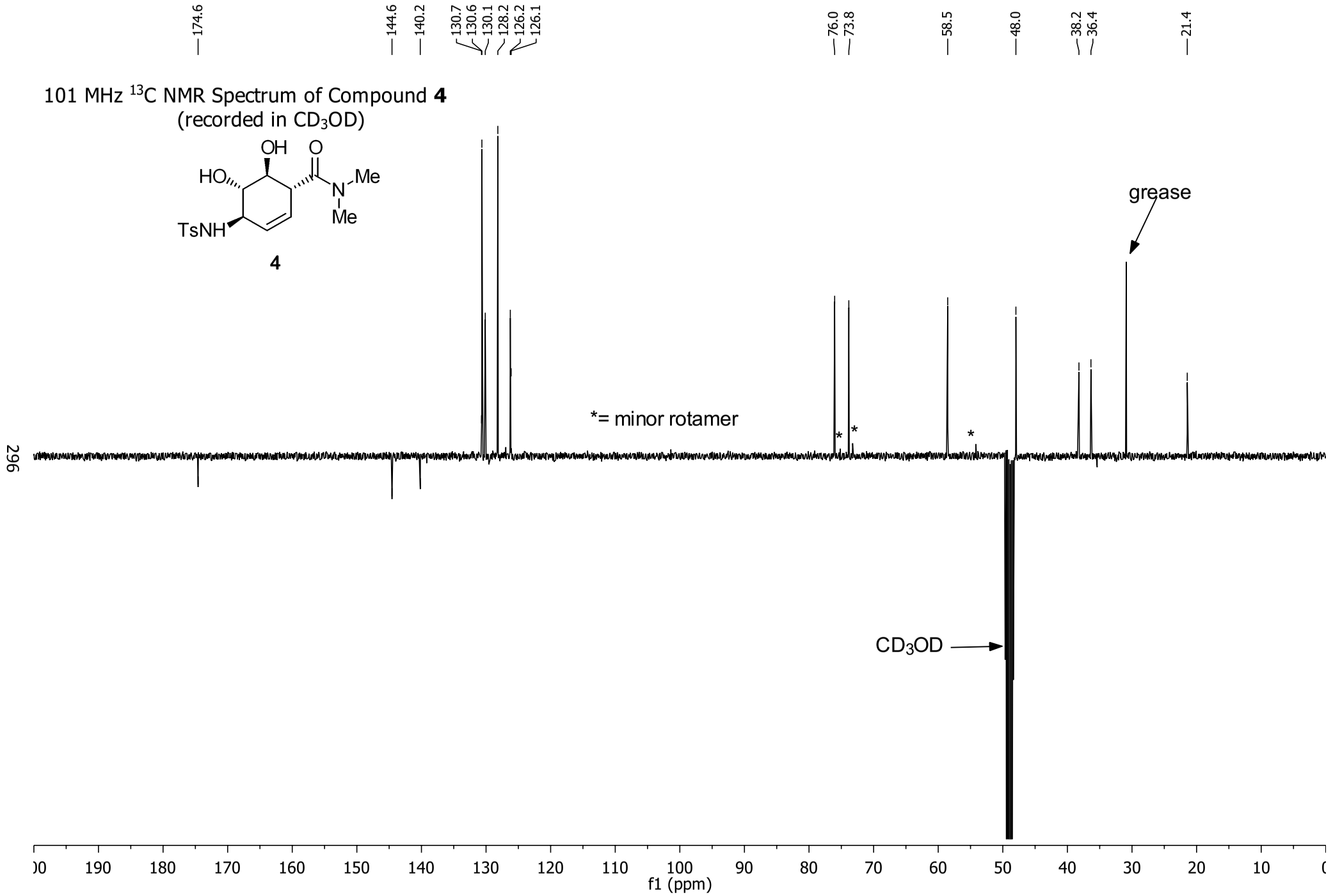
294

f1 (ppm)

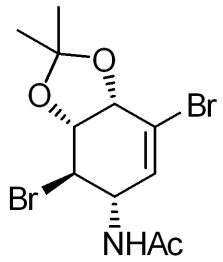
400 MHz $^1$H NMR Spectrum of Compound **4**
(recorded in $CD_3OD$)




**4**

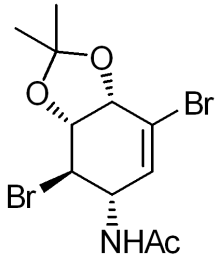

174.6
144.6
140.2
130.7
130.6
130.1
128.2
126.2
126.1
76.0
73.8
58.5
48.0
38.2
36.4
21.4
101 MHz $^{13}$C NMR Spectrum of Compound **4**
(recorded in $CD_3OD$)
OH
O
HO
N
Me
Me
TsNH
**4**
grease
*= minor rotamer
$CD_3OD$
296
f1 (ppm)

400 MHz $^{1}$H NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)



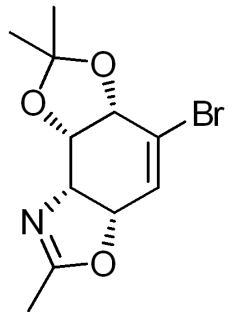

**8**

101 MHz $^{13}$C NMR Spectrum of Compound **8**
(recorded in $CDCl_3$)



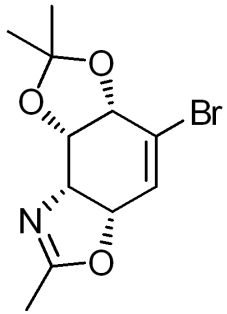

**8**

400 MHz $^{1}$H NMR Spectrum of Compound **10**
(recorded in $CDCl_3$)



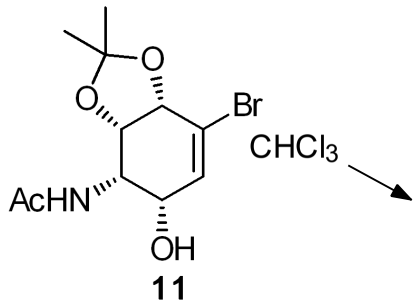

**10**

101 MHz $^{13}C$ NMR Spectrum of Compound **10**
(recorded in $CDCl_3$)



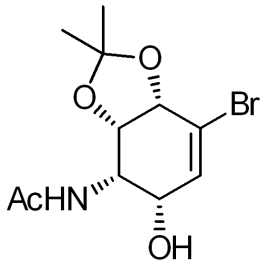

**10**

400 MHz $^{1}$H NMR Spectrum of Compound **11**
(recorded in $CDCl_3$)



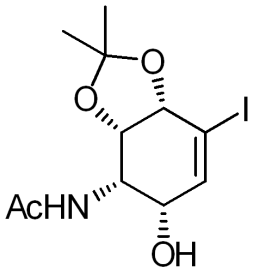

**11**

101 MHz $^{13}C$ NMR Spectrum of Compound **11**
(recorded in $CDCl_3$)



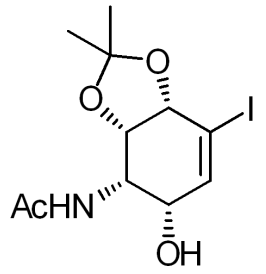

**11**

400 MHz $^1$H NMR Spectrum of Compound **12**
(recorded in $CDCl_3$)



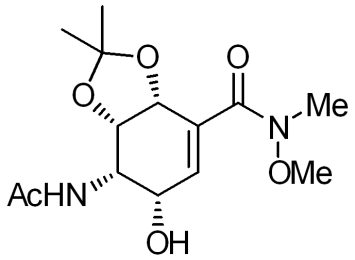

**12**

101 MHz $^{13}C$ NMR Spectrum of Compound **12**
(recorded in $CDCl_3$)

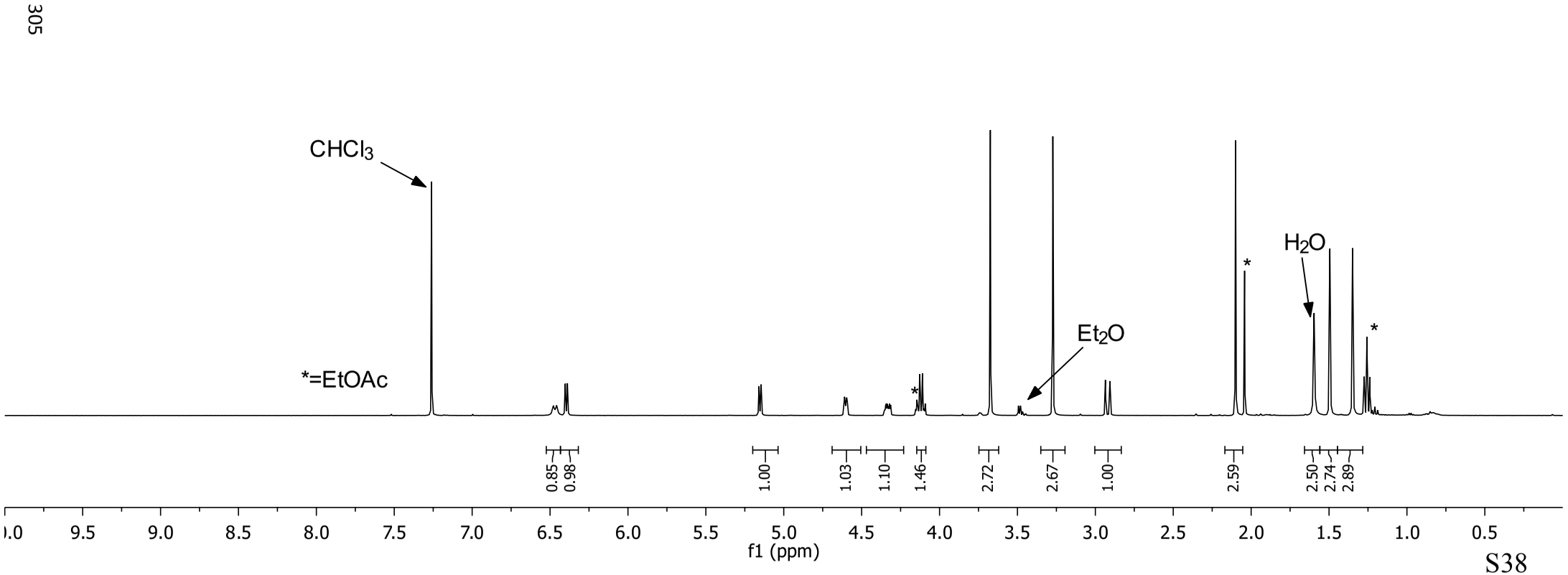



**12**

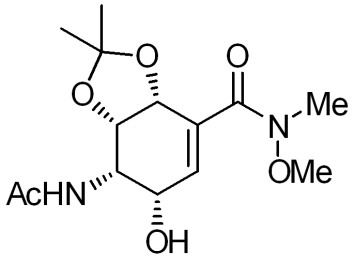
400 MHz $^1$H NMR Spectrum of Compound **13**
(recorded in $CDCl_3$)




**13**

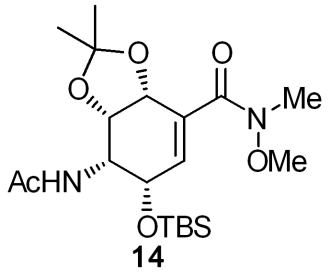


101 MHz $^{13}$C NMR Spectrum of Compound **13**
(recorded in $CDCl_3$)



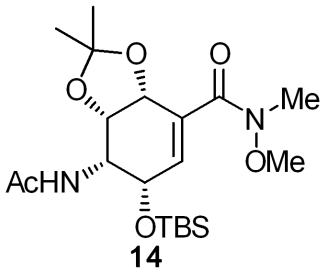

**13**

400 MHz $^1$H NMR Spectrum of Compound **14**
(recorded in $CDCl_3$)



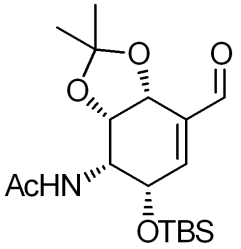

**14**

101 MHz $^{13}C$ NMR Spectrum of Compound **14**
(recorded in $CDCl_3$)




**14**

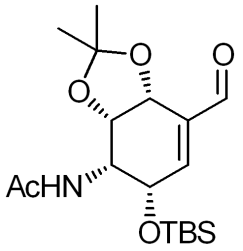
400 MHz $^{1}$H NMR Spectrum of Compound **15**
(recorded in $CDCl_3$)



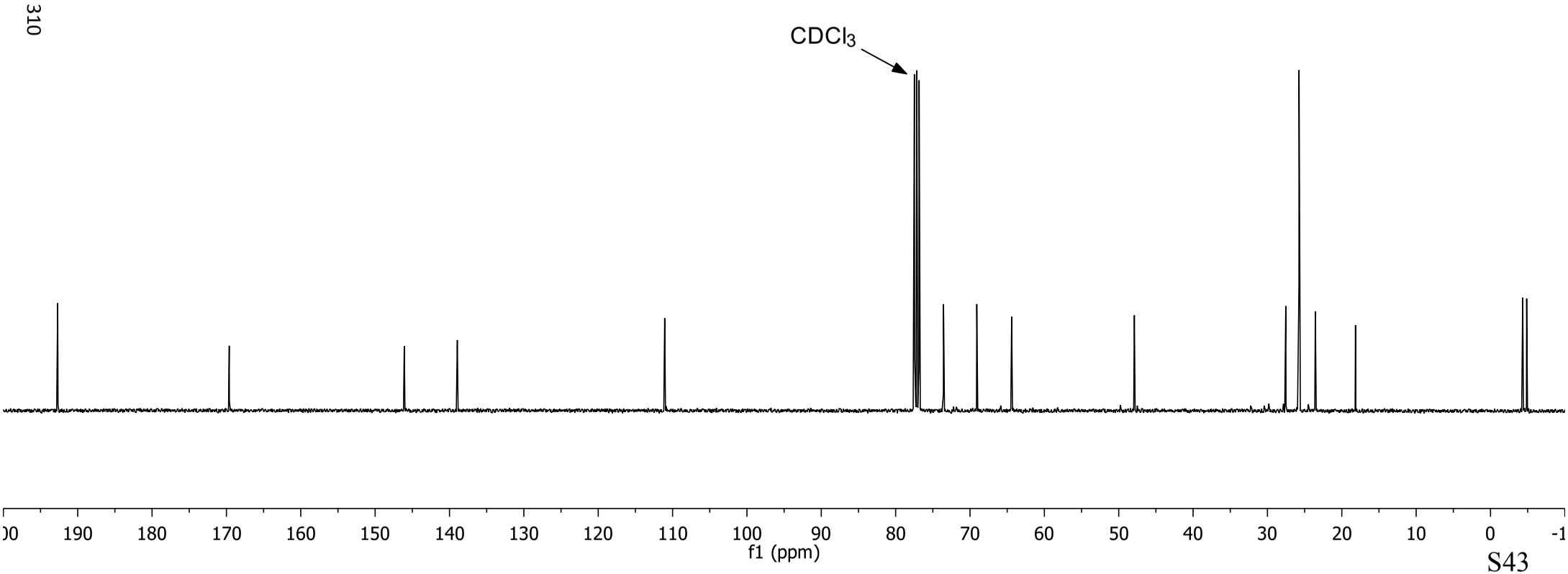

**15**

192.7
169.6
146.1
138.9
111.1
73.6
69.1
64.4
47.9
27.5
25.9
25.8
23.6
18.2
-4.3
-4.9

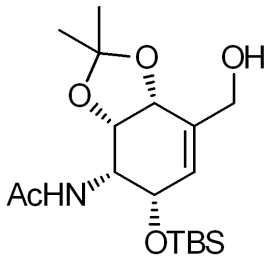
101 MHz $^{13}C$ NMR Spectrum of Compound **15**
(recorded in $CDCl_3$)




**15**

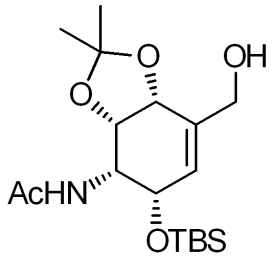


400 MHz $^1$H NMR Spectrum of Compound **16**
(recorded in $CDCl_3$)



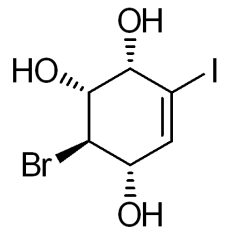

**16**

101 MHz $^{13}C$ NMR Spectrum of Compound **16**
(recorded in $CDCl_3$)



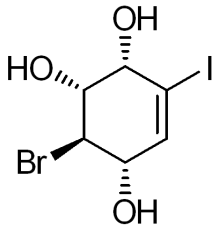

**16**

400 MHz $^1$H NMR Spectrum of Compound **17**
(recorded in $CD_3OD$)



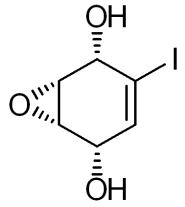

**17**

101 MHz $^{13}C$ NMR Spectrum of Compound **17**
(recorded in $CD_3OD$)



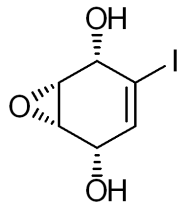

**17**

400 MHz $^1$H NMR Spectrum of Compound **18**
(recorded in $CD_3OD$)



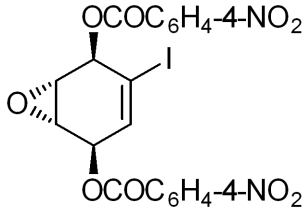

**18**

101 MHz $^{13}C$ NMR Spectrum of Compound **18**
(recorded in $CD_3OD$)

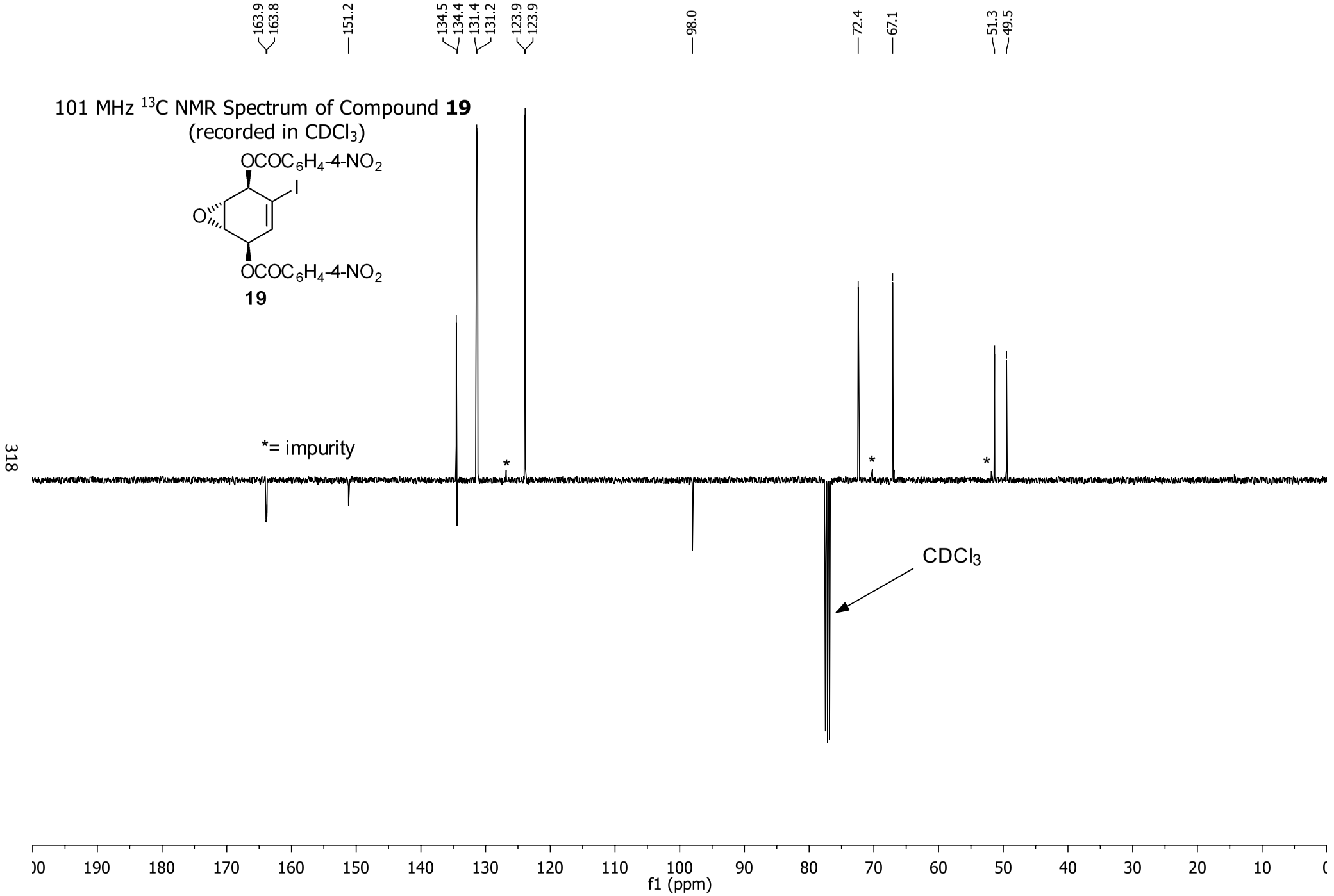



**18**

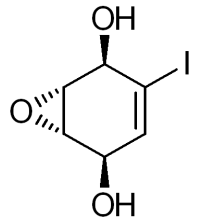
400 MHz $^1$H NMR Spectrum of Compound **19**
(recorded in $CDCl_3$)




**19**

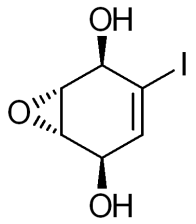

163.9
163.8
151.2
134.5
134.4
131.4
131.2
123.9
123.9
98.0
72.4
67.1
51.3
49.5
101 MHz $^{13}$C NMR Spectrum of Compound **19**
(recorded in $CDCl_3$)
$OCOC_6H_4$-4-$NO_2$
I
O
$OCOC_6H_4$-4-$NO_2$
**19**
*= impurity
*
*
*
$CDCl_3$
318
f1 (ppm)

400 MHz $^{1}$H NMR Spectrum of Compound **20**
(recorded in $CD_3OD$)



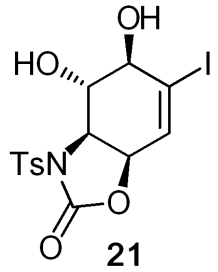

**20**

101 MHz $^{13}C$ NMR Spectrum of Compound **20**
(recorded in $CD_3OD$)



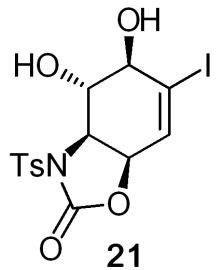

**20**

400 MHz $^{1}$H NMR Spectrum of Compound **21**
(recorded in $CD_3OD$)




**21**

101 MHz $^{13}C$ NMR Spectrum of Compound **21**
(recorded in $CD_3OD$)




**21**

153.2 146.7 137.0 131.7 130.4 130.0 115.4 75.8 75.1 73.4 60.8 21.6

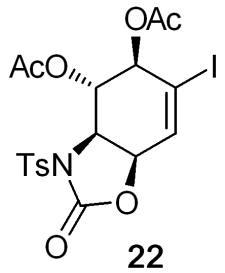
322

*= impurity

$CD_3OD$

f1 (ppm)

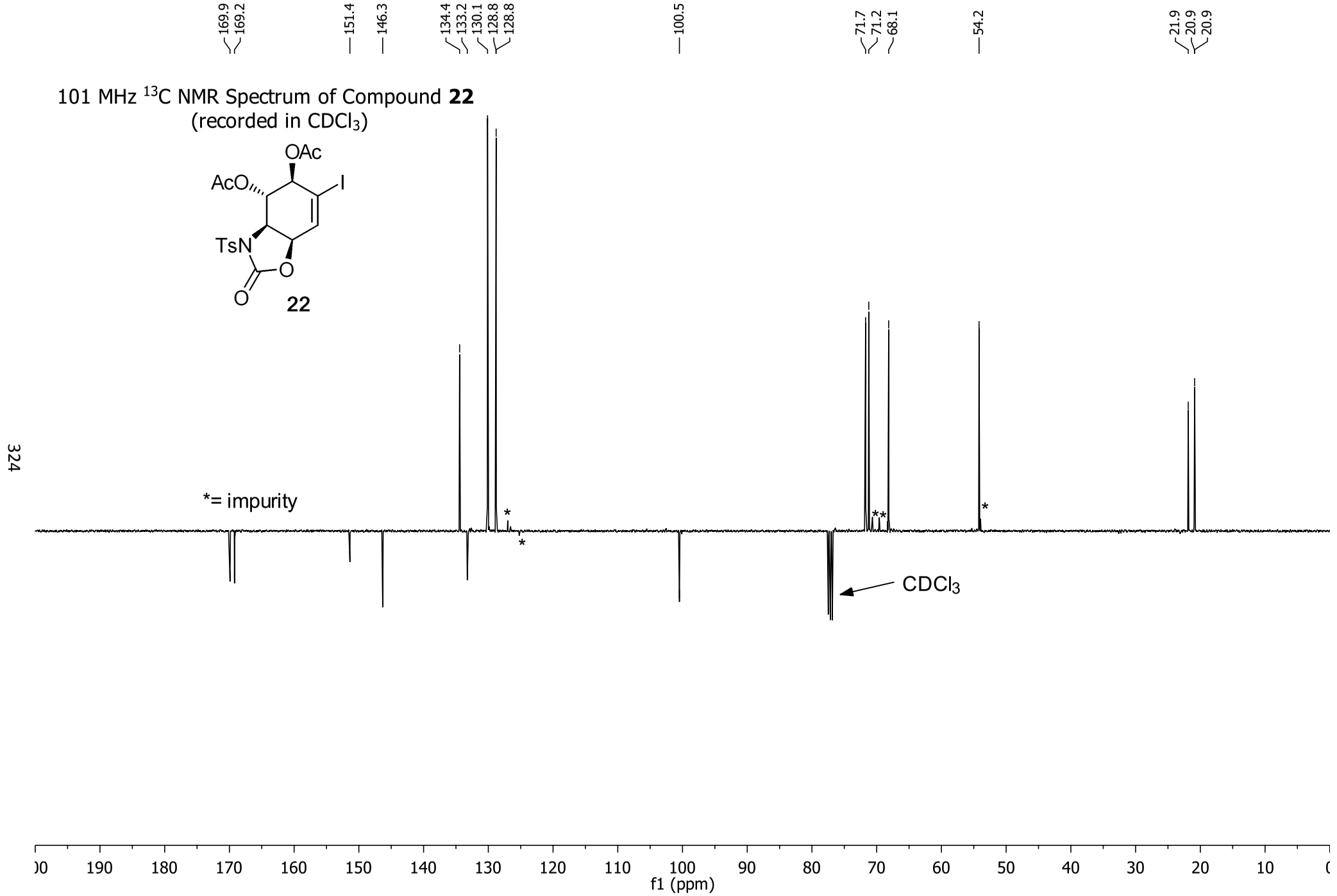
400 MHz $^1$H NMR Spectrum of Compound **22**
(recorded in $CDCl_3$)



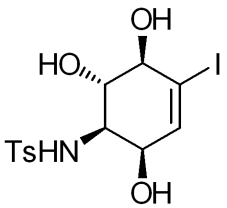

**22**



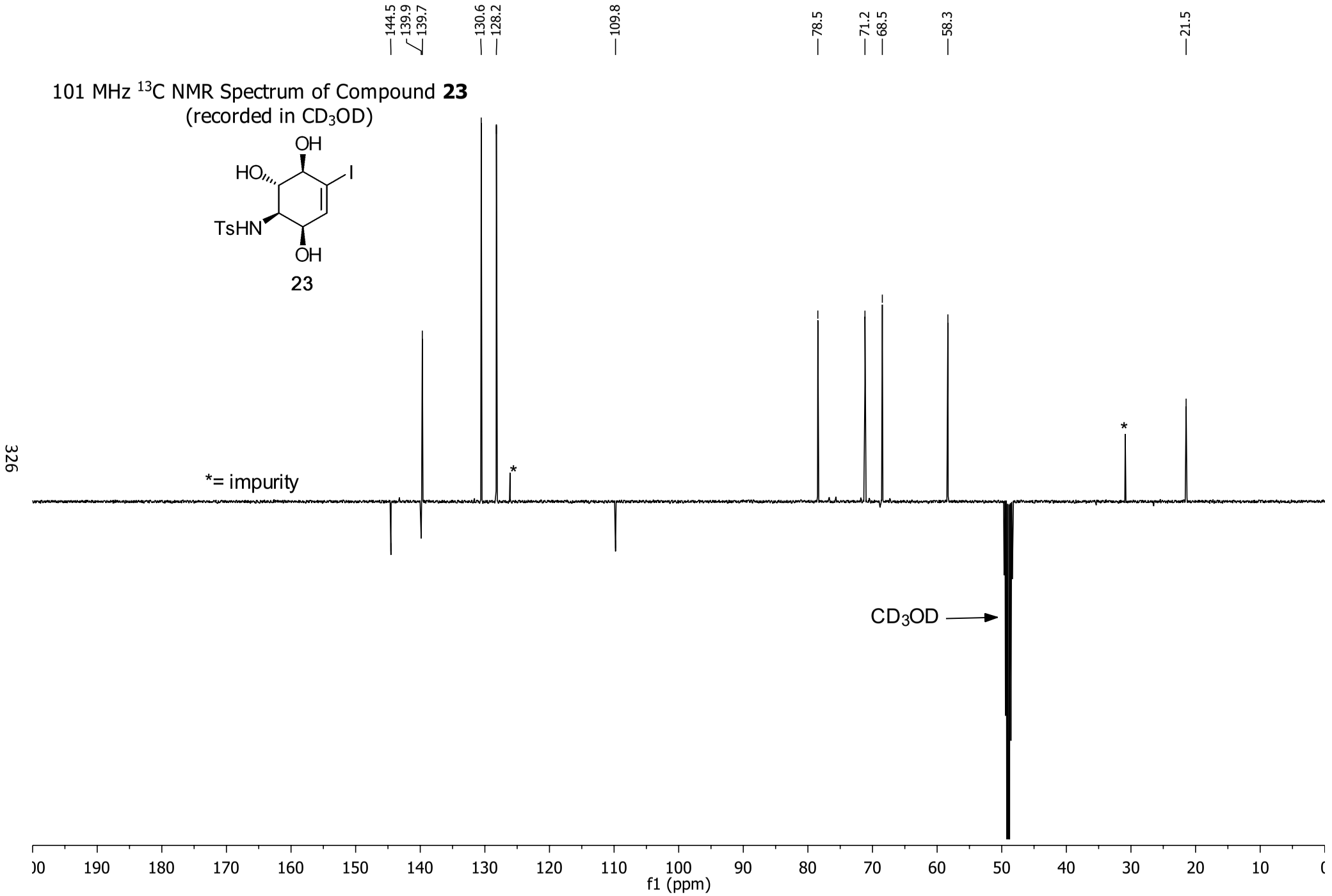

323


169.9
169.2
151.4
146.3
134.4
133.2
130.1
128.8
128.8
100.5
71.7
71.2
68.1
54.2
21.9
20.9
20.9
101 MHz $^{13}$C NMR Spectrum of Compound **22**
(recorded in $CDCl_3$)
OAc
AcO
I
TsN
O
O
22
324
*= impurity
*
*
*
**
*
$CDCl_3$
f1 (ppm)

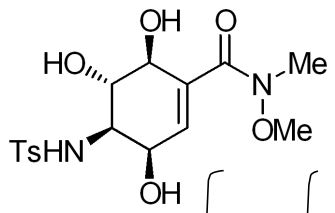
400 MHz $^{1}$H NMR Spectrum of Compound **23**
(recorded in $CD_3OD$)




23

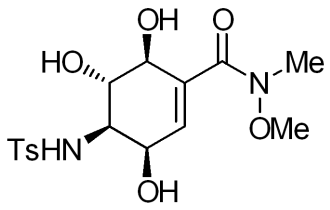

144.5
139.9
139.7
130.6
128.2
109.8
78.5
71.2
68.5
58.3
21.5
101 MHz $^{13}$C NMR Spectrum of Compound **23**
(recorded in $CD_3OD$)
OH
HO
I
TsHN
OH
23
326
*= impurity
*
*
$CD_3OD$
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

400 MHz $^{1}$H NMR Spectrum of Compound **24**
(recorded in $(CD_3)_2SO$)



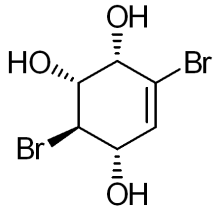

**24**

101 MHz $^{13}$**C** NMR Spectrum of Compound **24**
(recorded in $(CD_3)_2SO$)

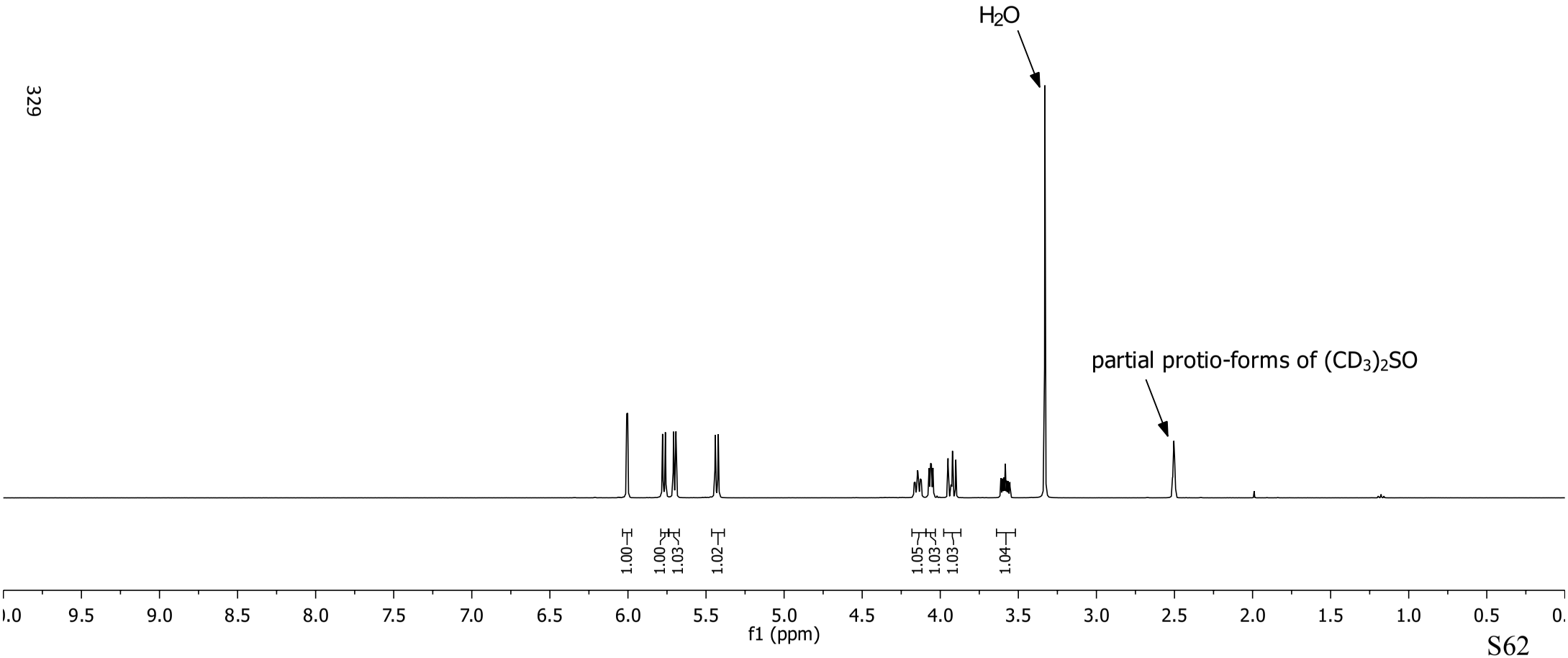



**24**

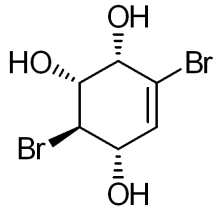
400 MHz $^1$H NMR Spectrum of Compound **25**
(recorded in $(CD_3)_2SO$)




25

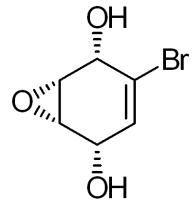


101 MHz $^{13}$**C** NMR Spectrum of Compound **25**
(recorded in $(CD_3)_2SO$)



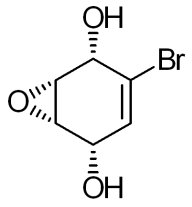

**25**

400 MHz $^1$H NMR Spectrum of Compound **26**
(recorded in $(CD_3)_2SO$)




**26**

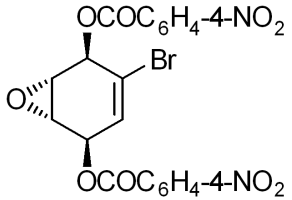
101 MHz $^{13}$C NMR Spectrum of Compound **26**
(recorded in $(CD_3)_2SO$)



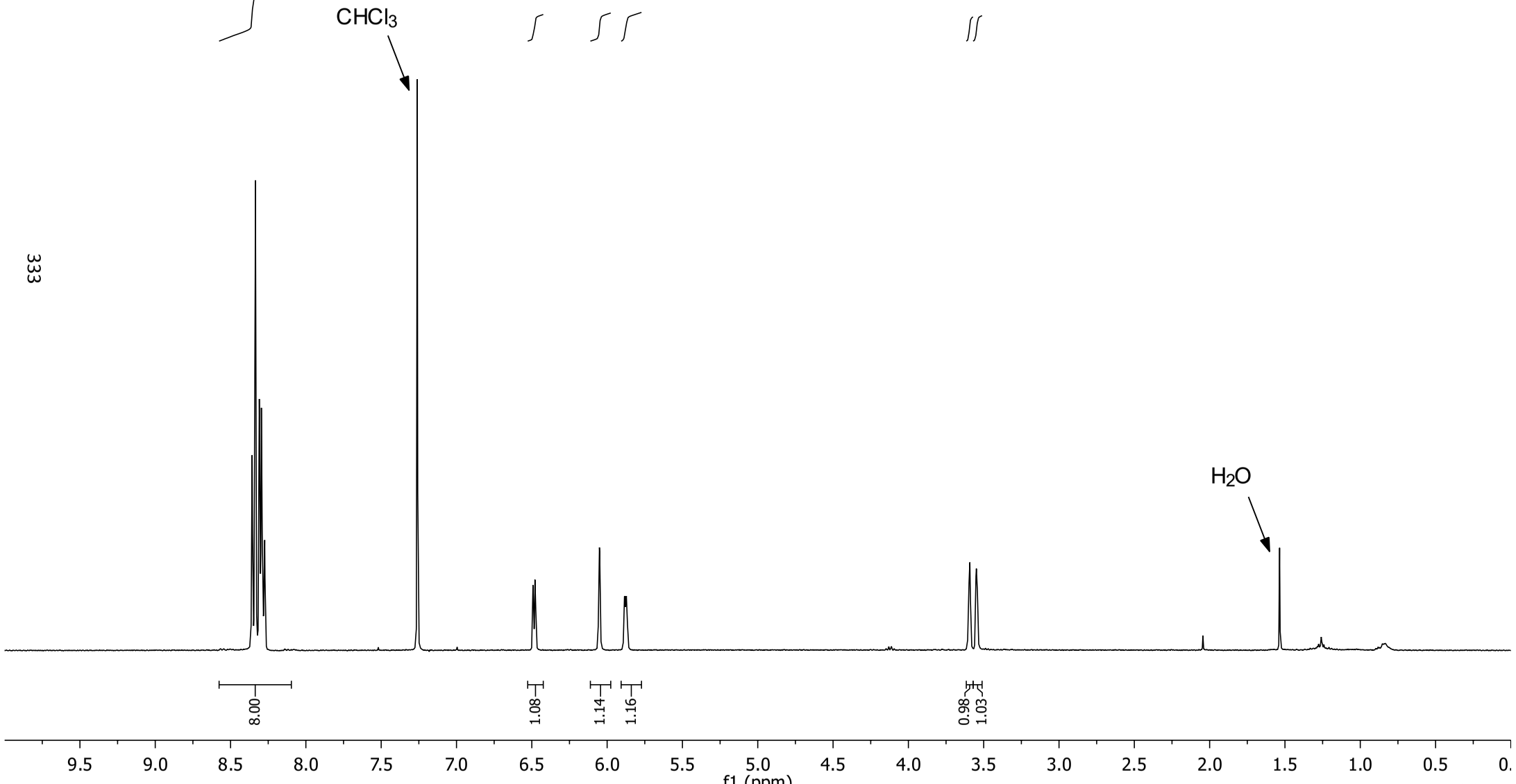

**26**

179.4
130.3
123.9
65.8
65.4
54.3
54.1
$(CD_3)_2SO$
332
*
*
*= succinimide impurity
f1 (ppm)

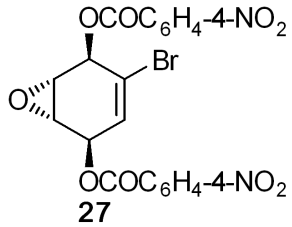
400 MHz $^1$H NMR Spectrum of Compound **27**
(recorded in ($CDCl_3$)



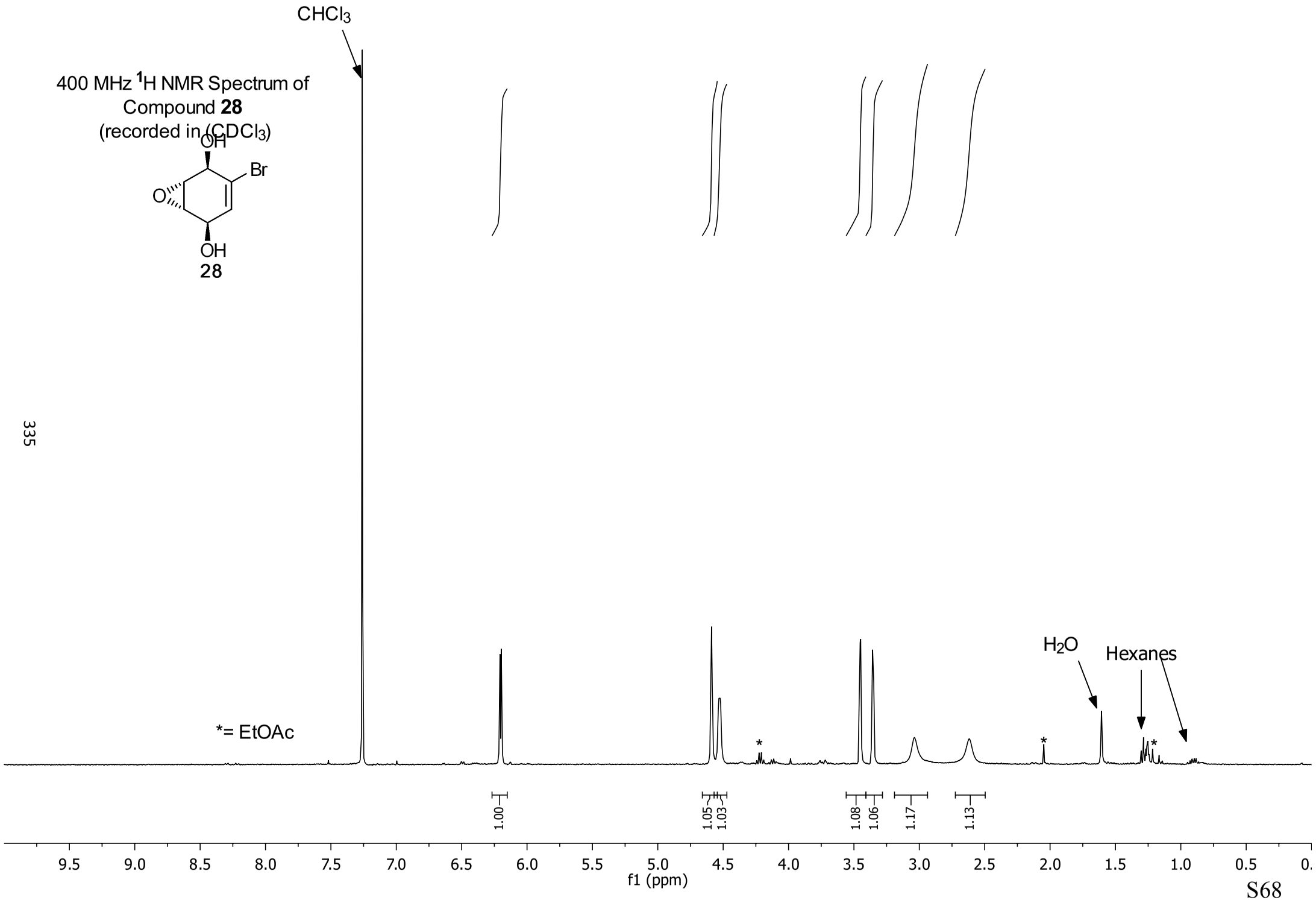

**27**



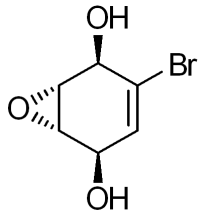
101 MHz $^{13}$C NMR Spectrum of Compound **27**
(recorded in $CDCl_3$)




**27**

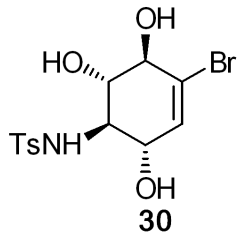

400 MHz $^1$H NMR Spectrum of
Compound **28**
(recorded in $CDCl_3$)
OH
Br
O
OH
**28**
$CHCl_3$
335
*= EtOAc
$H_2O$
Hexanes
1.00
1.05
1.03
1.08
1.06
1.17
1.13
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

101 MHz $^{13}$**C** NMR Spectrum of Compound **28**
(recorded in $CDCl_3$)




**28**

400 MHz $^1$H NMR Spectrum of Compound **30**
(recorded in $(CD_3)_2CO$)




**30**

partial protio-forms of $(CD_3)_2CO$

$H_2O$

EtOAc

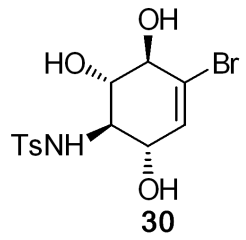
337

2.06 2.06 1.05 0.74 0.73 1.70 0.93 1.01 1.67 3.00

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

f1 (ppm)

101 MHz $^{13}$C NMR Spectrum of Compound **30**
(recorded in $(CD_3)_2CO$)




**30**

143.8 139.6 131.5 130.3 128.0 76.2 71.6 67.0 57.6 21.4

$(CD_3)_2CO$

$(CD_3)_2CO$

338

* = impurity

*

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

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Digest paper

# Chemical syntheses of the cochliomycins and certain related resorcylic acid lactones

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ABSTRACT

The cochliomycins (**7**–**12**) are a group of six resorcylic acid lactones that have recently been isolated from culture broths of marine fungi found in the South China Sea. These natural products have attracted attention as synthetic targets because of (in certain instances) their novel structural features and their capacities to suppress biofouling. This short review summarizes the synthesis of these and some related compounds that have been reported to date, including those developed in the authors' laboratories.



**Contents**



## Introduction

The value of small molecule natural products (SMNPs) as therapeutic agents, as precursors to such agents or as the inspirations for them is well known.[1] Indeed, there are now indications that SMNPs, perhaps especially ones derived from marine environments,[2] are enjoying something of a renaissance not least because of their enormous structural diversity and their occupation of unique parts of chemical space.[3] Among the plethora of different natural product classes, the resorcylic acid lactones (RALs) are notable for the frequency with which they are isolated from fungal sources, their distinctive structural features and their breadth of biological activities.[4] In the following section an overview of the structural variations within the RAL class is provided along with a brief commentary on the source organisms and certain of their biological properties. As a recently discovered and interesting subset of RALs that has not been the subject of any previous reviews, the cochliomycins are then described and a summary of the synthetic work carried out on them follows.

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## Resorcylic acids lactones (RALs) as a natural product class

The RALs are mycotoxins and the products of a distinctive polyketide biosynthesis that exploits an acetyl CoA starter unit together with malonyl-CoA extenders and involves two fungal polyketide synthases (PKS) that work co-operatively.[4e] Specifically, a non-reducing PKS is coupled with a highly reducing one that enables the assembly of the relevant resorcylic acid core annulated to a 14-membered macrolactone (and wherein most of the structural variation resides). Unsurprisingly perhaps, the final step in the biosynthesis is the macrolactonisation event that releases the substrate from the enzyme complex. Post-PKS-mediated processes such as epoxidation, halogenation and alkylation may then follow so as to provide the fully "decorated" (isolated) metabolite.[4e]

Radiciol (**1**) was the first RAL to be isolated (from *Monosporium nordinii*) and characterised in the 1950s[4] and it has since been obtained from various other fungal strains. In the intervening period numerous other RALs have been identified and these vary in the nature of the substitution pattern on the aromatic ring as well as the location and degree of unsaturation and/or oxygenation within the macrolactone ring. The structures of the RALs hypothemycin (**2**), zearalenone (**3**), pochonin C (**4**), L-783,277 (**5**) and aigialomycin D (**6**) shown in Fig. 1 serve to highlight such degrees of variation.

## The discovery of cochliomycins A–F

In papers published in 2011[5] and 2014,[6] Wang and co-workers from the Ocean University of China in Qingdao reported the isolation of cochliomycins A–F (**7**–**12**) (Fig. 2) from the culture broths of *Cochliobolus lunatus* (M351) or *C. lunatus* (TA26-46), fungi associated with the gorgonian *Dichotella gemmacea* or the sea anemone *Palythoa haddoni*, respectively. Both host organisms were collected in the South China Sea. The structures of these RALs were established through the application of the usual battery of spectroscopic methods and the absolute stereochemistries of the last three determined using the CD exciton chirality method in conjunction with TDDFT ECD calculations.[6]

The most striking features of this subset of RALs are the presence of acetonide units within the structures of congeners A and B (**7** and **8**, respectively). Since acetone was not used in the isolation, purification or spectroscopic characterisation of these compounds they must be considered as natural products rather than artefacts. Wang and co-workers also noted[5] that on standing in $CDCl_3$ at ambient temperatures cochliomycin B (**8**) slowly isomerised to congener **7** and so suggesting the latter is the thermodynamically more stable compound. Cochliomycin C (**9**) is the only member of the series lacking a second double bond within the macrocyclic ring. Cochliomycins D (**10**) and E (**11**) are isomeric while congener F (**12**) is not simply a chlorinated derivative of

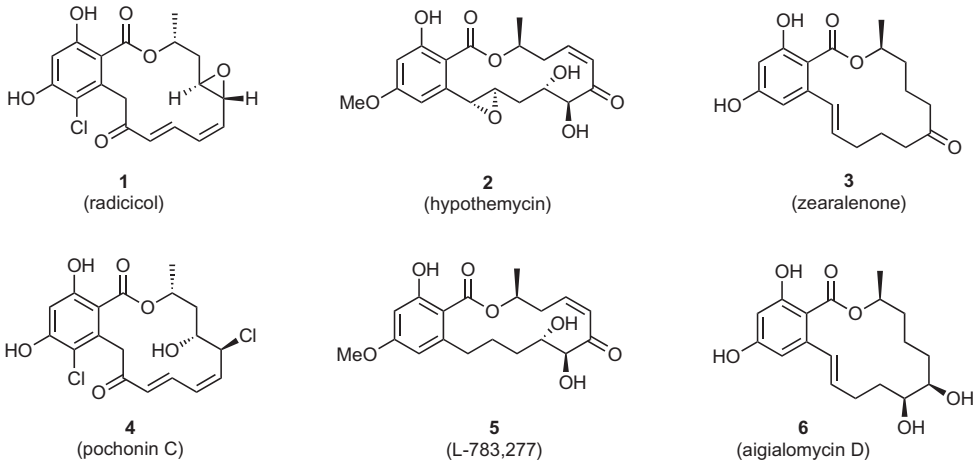



**Fig. 1.** Examples of the structural variations possible within the RAL class.

Initial biological evaluation of radiciol (**1**) showed it to possess anti-bacterial properties and to act as a mild sedative. However, the later revelation that it acts as a powerful inhibitor of heat shock protein 90 (HSP90) – and thus representing an important lead in the development of oncolytic agents – caused much greater attention to be given to the RALs. In contrast to radiciol (**1**), the *cis*-enone-containing hypothemycin (**2**) has been shown to strongly inhibit the kinase MEK1, while zearalenone (**3**) acts as an estrogen agonist and its hormone-like properties have been shown to promote growth in cattle and sheep. A closely related RAL is now commercially available and employed to alleviate post-menopausal stress in women and as an anabolic cattle-growth stimulant. Pochonin C (**4**), on the other hand, inhibits herpes simplex virus (HSV) replication in a potentially therapeutically useful way while the *cis*-enone L-783,277 (**5**), like congener **2**, inhibits MEK1. Aigialomycin D (**6**), despite the absence of a *cis*-enone moiety, also acts as a kinase inhibitor as well as an anti-malarial agent (the latter property seemingly being unrelated to the former).

one or other of the first two because of the differing configuration at one or other of the hydroxyl-bearing methine carbons. Nor, for the same reasons, can cochliomycin F (**12**) simply be the product of the twofold oxidation of congener **9**.

## Related, co-occurring natural products

In the course of structurally characterising the cochliomycins, it was noted[5] that congener C (**9**) is the chlorinated derivative of co-isolated paecilomycin F (**13**) (Fig. 3), a previously reported RAL that displays anti-malarial properties. Other RALs also isolated alongside compounds **7**–**9** were zeaenol (**14**), LL-Z1640-1 (**15**) and LL-Z1640-2 (**16**). During the course of isolating cochliomycins D, E and F (**10**, **11** and **12**, respectively), cochliomycin A (**7**), zeaenol (**14**), LL-Z1640-1 (**15**), LL-Z1640-2 (**16**), its *E*-isomer **17** [(7′*E*)-6′-oxozeaenol], deoxyaigialomycin C (**18**) and aigialomycin B (**19**) were also observed in the mixture of isolates. Clearly certain of these co-isolates are isomeric with the cochliomycins or otherwise

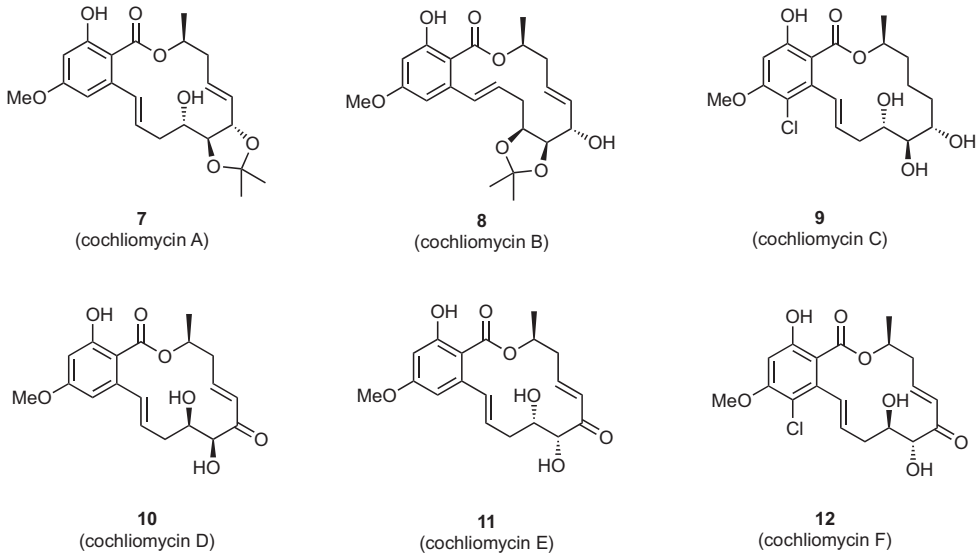



**Fig. 2.** The structures of cochliomycins A–F (**7**–**12**, respectively).

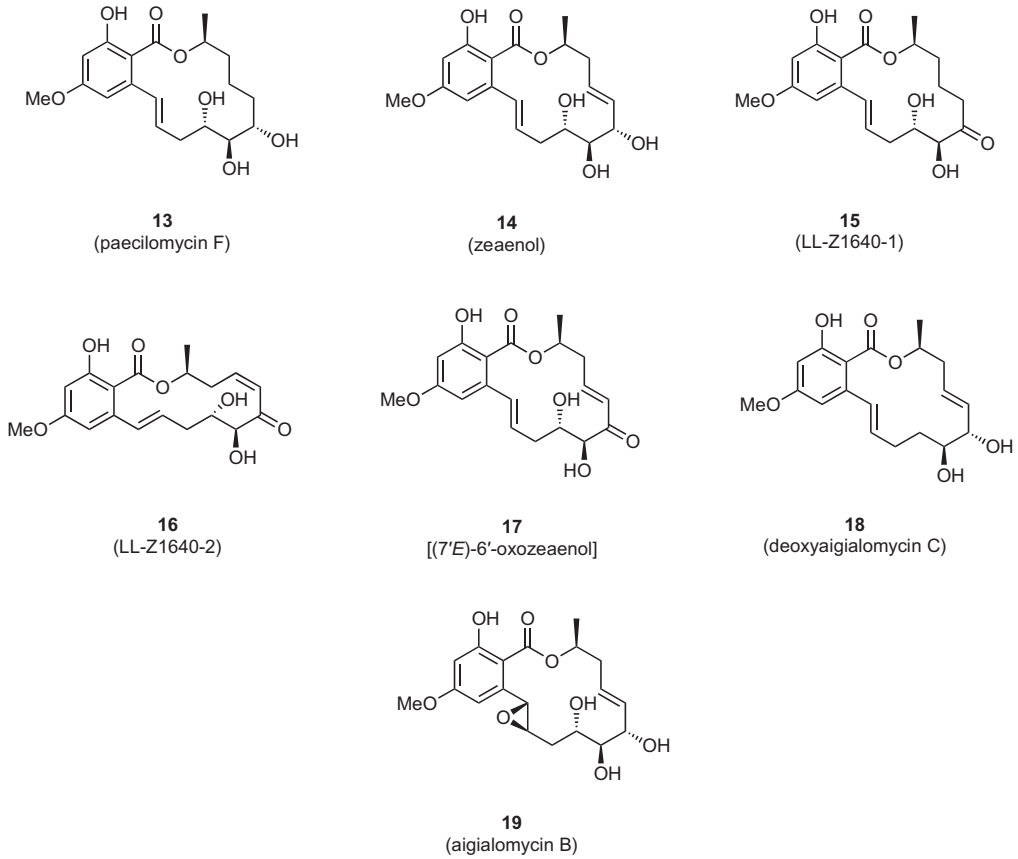



**Fig. 3.** The structures of RALs found to co-occur with cochliomycins A–C and/or cochliomycins D–E.

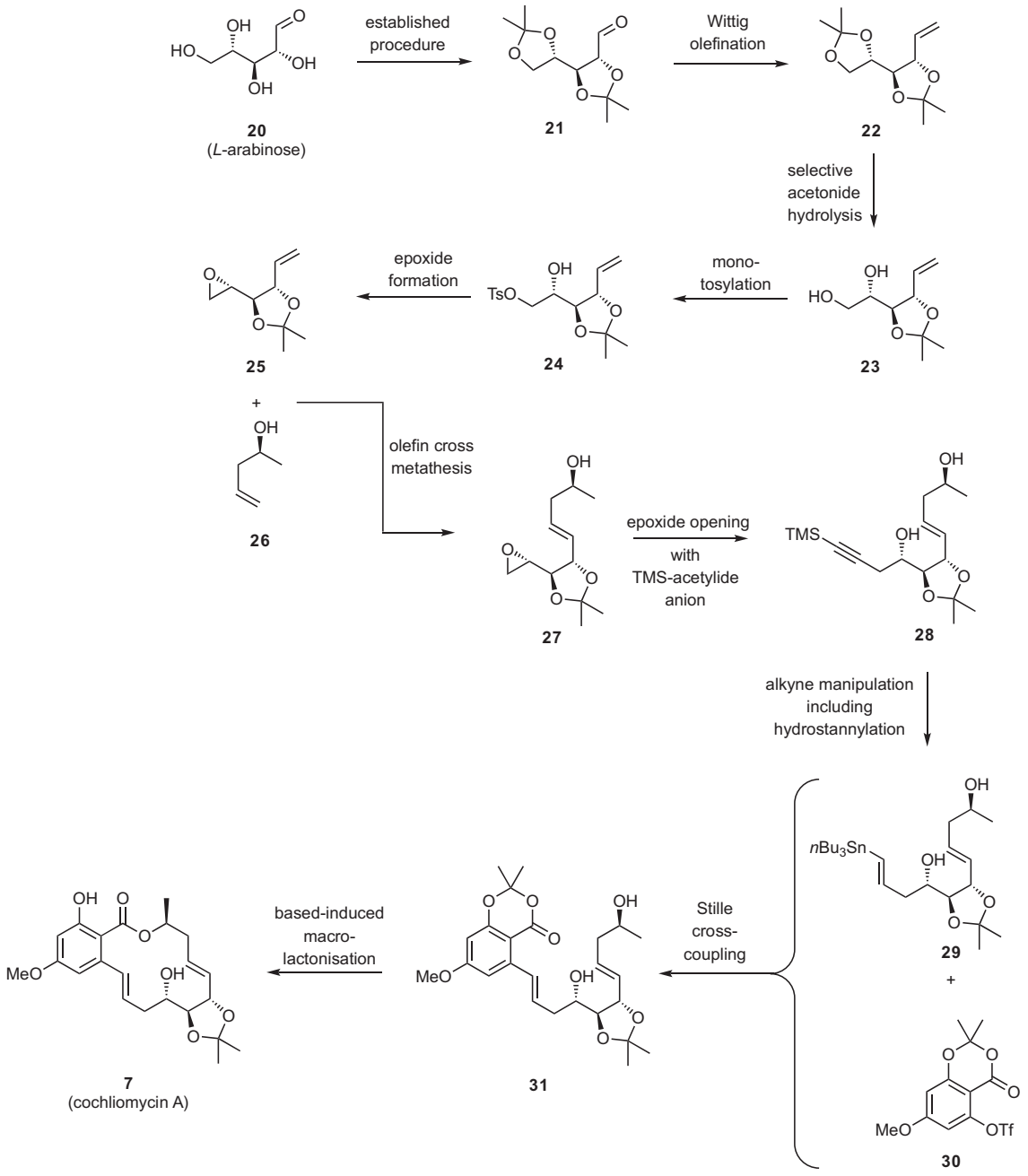
closely related. For example, zeaenol (**14**) is the acetonide "deprotected" analogue of cochliomycins A (**7**) and B (**8**).

## Biological properties of the cochliomycins

The most notable biological properties of at least certain of the cochliomycins are their anti-fouling properties. So, for example, on evaluating the effects of cochliomycins A–C (**7**–**9**) on the larval settlement of the barnacle *Balanus amphitrite*, the first of these completely inhibited this process at concentrations of 20.0 μg/mL and still displayed significant effects at 5.0 μg/mL. Zeaenol (**14**) and compound **7** as well as two acetate derivatives of the latter displayed potent anti-fouling activities at non-toxic concentrations with $EC_{50}$ values of 5.0, 1.2, 15.4 and 12.5 μg/mL, respectively. These values are well below the threshold requirement

($EC_{50}$ 25 μg/mL) set by the US Navy program as an efficacy level for the development of natural anti-fouling agents. Given the structural relationship between compounds **7** and **14**, the presence of the acetonide moiety in the former compound clearly has a beneficial effect on anti-fouling properties. Furthermore, since these same compounds display high therapeutic ratios they might well be useful as environmentally benign anti-fouling agents. Cochliomycin A's anti-fouling effects are now thought to arise through stimulation of the NO/cGMP pathway in the cyprid lavael phase of the barnacle's lifecycle.[7] The subsequent evaluation of cochliomycins D, E and F revealed that the first and third of these also displayed potent anti-fouling effects at non-toxic concentrations ($EC_{50}$ values of 17.3 and 6.67 μg/mL, respectively).[6] Significantly, the most active compound among the isolates from the culture broth of *C. lunatus* (TA26-46) was the *cis*-enone-containing LL-Z1640-2 (**16**). The $EC_{50}$ value of this compound (1.82 μg/mL) is close to that of the commercially employed anti-fouling agent SeaNine 211™ (1.23 μg/mL)[8] but has a significantly more favourable therapeutic ratio [$LC_{50}/EC_{50}$ >50 (for **16**) *vs* 20.3]. The differing anti-fouling behaviours of cochliomycins D, E and F suggest that variations in stereochemistry can have a notable impact on activity.

Interestingly, cochliomycin A (**7**) displayed moderate anti-bacterial activity against *Staphylococcus aureus*[5] while, unlike cochliomycins D, E and F, LL-Z1640-2 (**16**) displayed potent inhibitory effects against various pathogenic fungi.[6]




**Scheme 1.** The Du Group synthesis of cochliomycin A (**7**).

## Synthetic studies on the cochliomycins

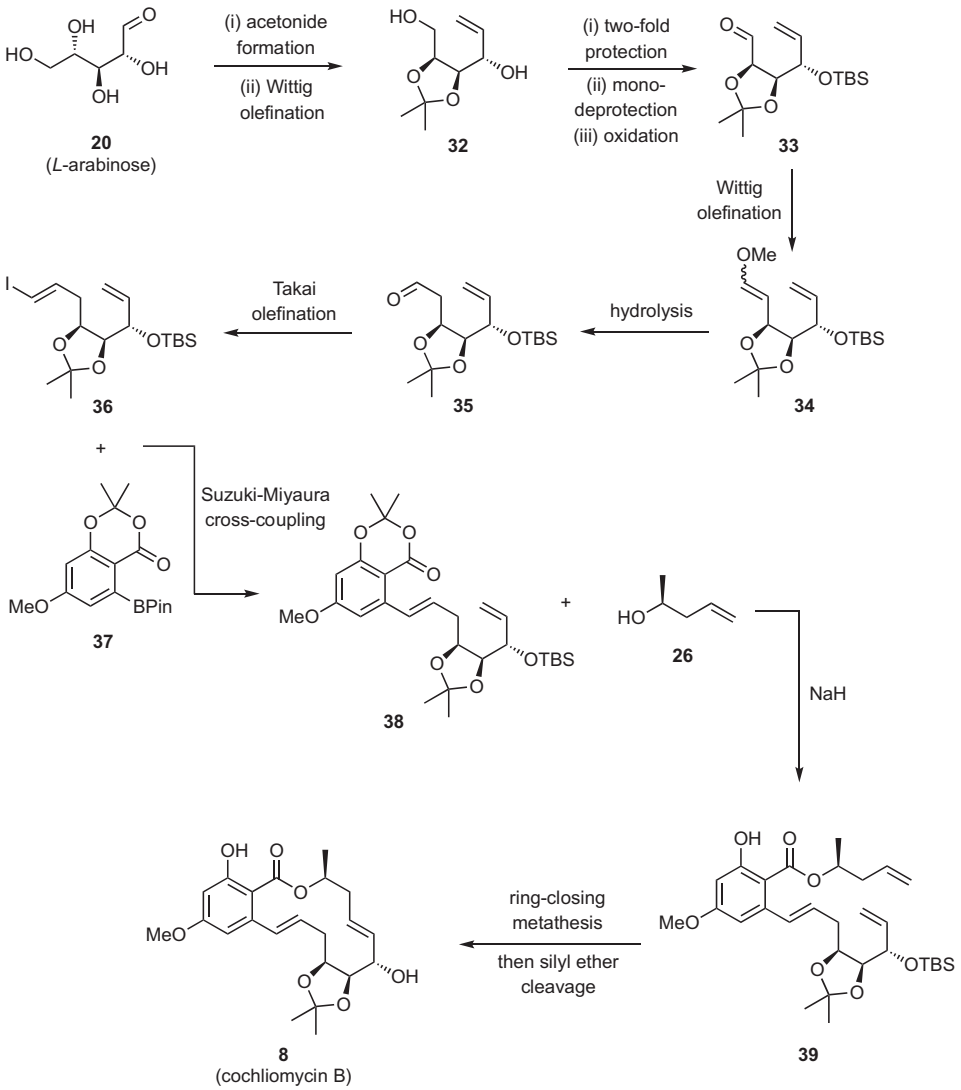
As with other RALs, the cochliomycins have been the subject of various synthetic studies, both for the purposes of confirming their structures and as a means of providing more material (as well as analogues). Almost invariably, a major consideration in such work is the manner in which the 14-membered lactone ring is closed. A range of methods has been successfully employed for this purpose and these are presented within the individual descriptions given below of the various syntheses reported to date.

### *(a). The Du Group syntheses*

The Du group's synthesis of cochliomycin A (**7**) was reported[9] in 2014 and employed L-arabinose as the chiron for assembling the three contiguous stereogenic centres within the macrolide along with a base-promoted lactonisation reaction to close the ring itself. The detailed reaction sequence is shown in Scheme 1 and started with the conversion of L-arabinose (**20**) into the corresponding bis-acetonide (**21**) under standard conditions and the latter compound subjected to a Wittig olefination (to give **22**) and then selective acetonide hydrolysis using aqueous acetic acid. Diol **23** so-formed (77% from **21**) was selectively tosylated and ester **24** then treated with base so as to form epoxide **25** (78% from **23**). Olefin cross-metathesis of compound **25** with the commercially available and *S*-configured alcohol **26** gave the *E*-alkene **27** (85%) and the associated epoxide ring then opened using the anion derived from trimethylsilylacetylene and thus producing the homopropargylic alcohol **28** (78%).

Over three steps, including a Pd-catalysed hydrostannylation reaction, the acetylenic unit associated with compound **28** was converted into the alkenylstannane **29** (71%) that was itself engaged in a Stille cross-coupling with the well known aryl triflate **30** and thus producing compound **31** (81%), the immediate precursor to target **7**. Indeed, on treatment with sodium hydride in DMF the conversion **31** → **7** was effected in 46% yield.

The Du Group's synthesis of cochliomycin B (**8**) (Scheme 2)[10] also started with L-arabinose but a ring-closing metathesis reaction was now used to construct the associated macrolide ring. Thus, compound **20** was converted, under conventional conditions, into the corresponding 3,4-mono-acetonide and this itself subjected to a Wittig olefination reaction and so affording compound **32** (72%). Over three steps this diol was manipulated so as to generate aldehyde **33** (46%) and a Wittig-based homologation of this last

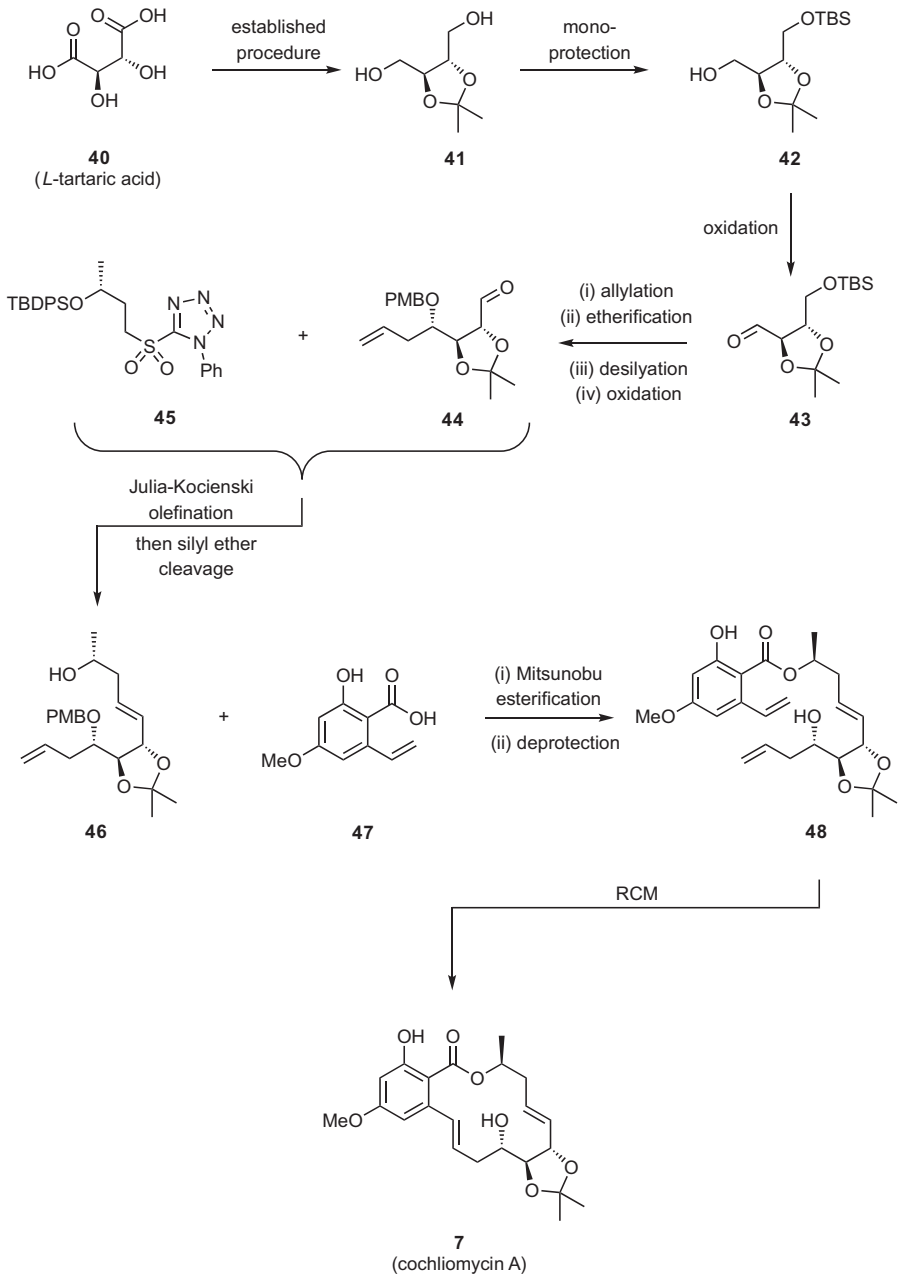



**Scheme 2.** The Du Group synthesis of cochliomycin B (**8**).

compound afforded, *via* enol ether **34** (77%), congener **35** (75%). Takai-type olefination of this last compound then gave the *E*-configured iodoalkene **36** (53%) that was engaged in a Suzuki-Miyaura cross-coupling with the readily obtained arylboronate **37** and so affording the *trans*-styrene **38** (68%). Reaction of this last compound with the anion derived from homochiral alcohol **26** then gave ester **39** (75%) that upon reaction with Grubbs' second generation catalyst afforded, *via* ring-closing metathesis (RCM), the required macrocycle (67%) and treatment of this with tetra-*n*-butylammonium fluoride (TBAF) then gave cochliomycin B (**8**) in 85% yield. Interestingly, in the penultimate step there was no competing RCM involving the styrenyl double bond and the proximate terminal olefin (a process that would lead to side-chain fragmentation and formation of a cyclohexene).

*(b). The Nanda Group syntheses*

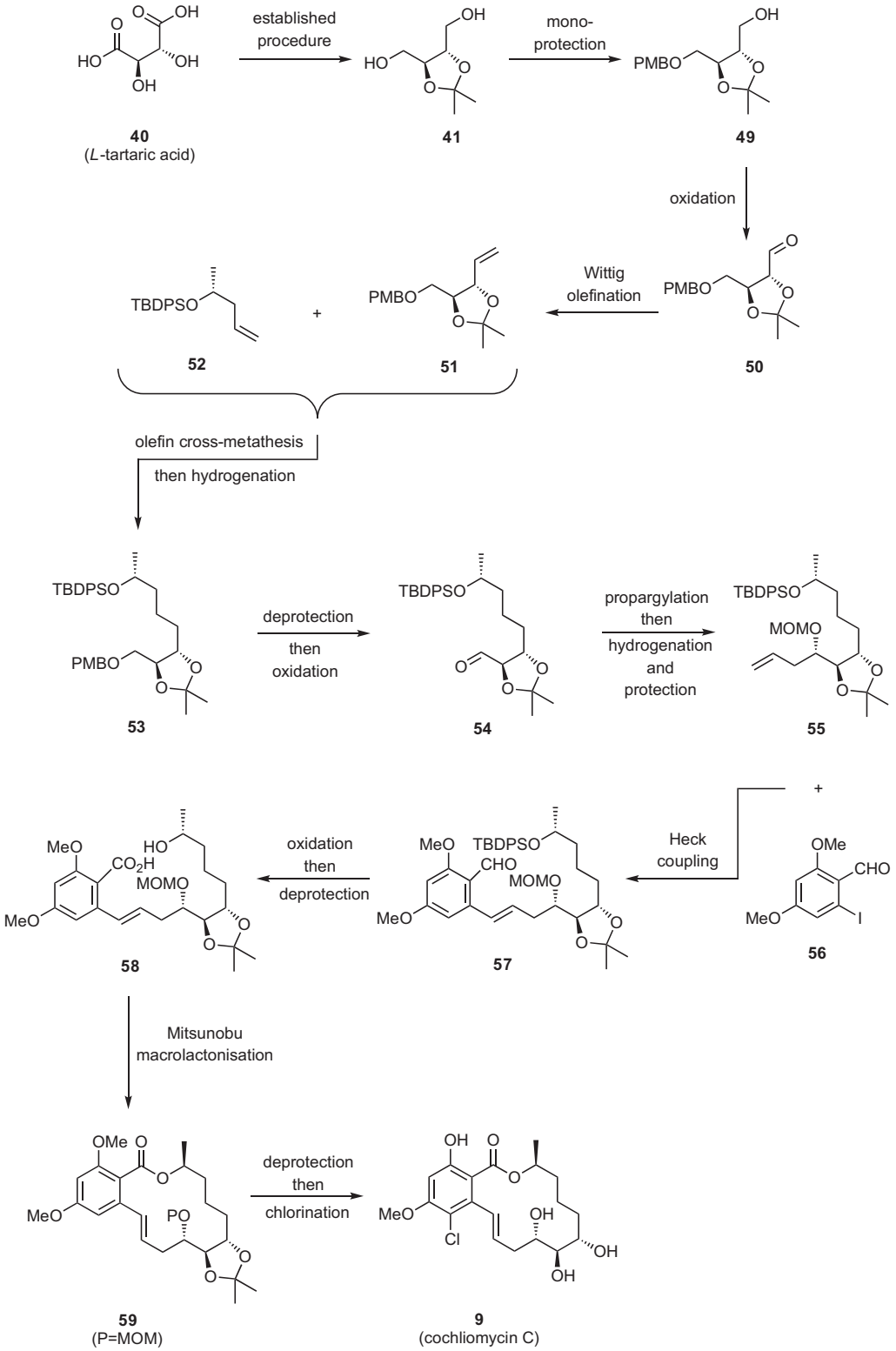
Jana and Nanda reported a synthesis of cochliomycin A in 2012[11] and this started (Scheme 3) with the conversion, by well established methods, of L-(+)-tartaric acid (**40**) into 2,3-di-*O*-isopropylidene-L-threitol (**41**) and mono-protection of the latter to give ether **42** (85%). Oxidation of compound **42** under Swern conditions gave the corresponding aldehyde **43** (90%) that was subjected to a highly diastereoselective Keck asymmetric allylation reaction and so affording, after protection of the resulting homoallylic alcohol, cleavage of the TBS ether and oxidation of the resulting alcohol, aldehyde **44** (59%). A Julia-Kocienski olefination reaction was then carried out on compound **44** using the readily prepared sulfone **45**, KHMDS and 18-crown-6 and so affording, in




**Scheme 3.** The Nanda Group synthesis of cochliomycin A (**7**).

a highly selective manner and after silyl ether cleavage, the target *E*-alkene **46** in 75% yield. Mitsunobu coupling of this last compound with acid **47** then gave, after cleavage of the PMB ether residue, ester **48** (73%). Upon exposure to Grubbs' second-generation catalyst compound **48** was converted into cochliomycin A (**7**) (72%).

The Nanda Group synthesis of cochliomycin C[12] (Scheme 4) also started with L-tartaric acid (**40**) and exploited a Mitsunobu-mediated lactonisation reaction to form the macrolide ring. Specifically, then, di-acid **40** was, once again, converted into the diol-acetonide **41** and the latter mono-protected as the corresponding *p*-methoxybenzyl (PMB) ether **49** (85%). Upon Swern oxidation this



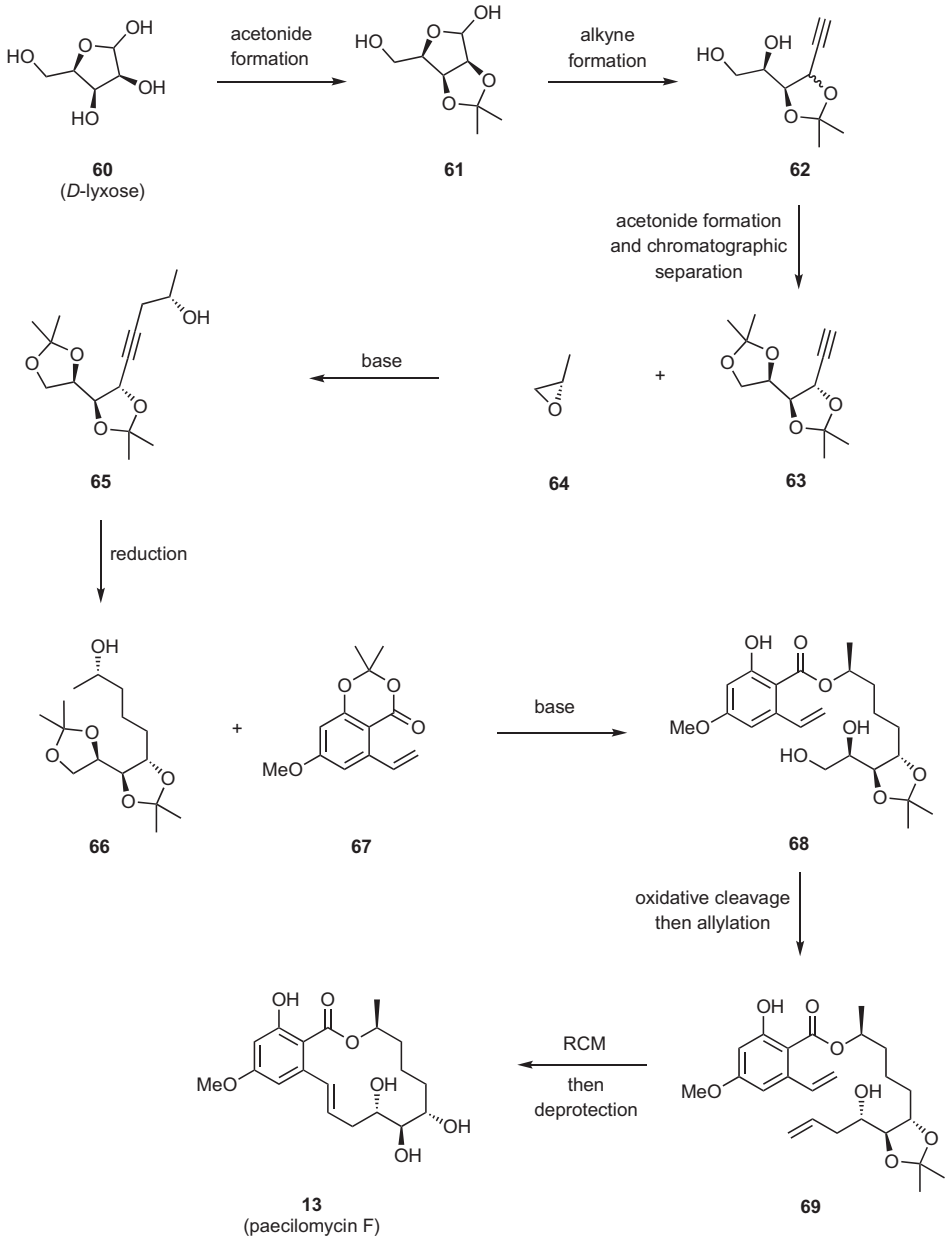

**Scheme 4.** The Nanda Group synthesis of cochliomycin C (**9**).

last compound gave the aldehyde **50** (90%), Wittig olefination of which afforded the terminal olefin **51** (70–75%) that was subjected to an olefin cross-metathesis (OCM) reaction with the unsaturated and homochiral ether **52** using the Grubbs' second-generation catalyst. The primary product of this process was then hydrogenated under conventional conditions so as to give compound **53** (79%). Oxidative cleavage of the PMB-ether residue associated with bis-ether **53** then gave the corresponding alcohol that was oxidised to aldehyde **54** (80%) using the Dess-Martin periodinane. Reaction of compound **54** with the propargyl anion proceeded stereoselectively and Lindlar hydrogenation of the product alkyne gave the corresponding homoallylic alcohol that was protected as the MOM-ether **55** (78%). Heck coupling of the last compound with the iodinated benzaldehyde **56** afforded styrene **57** (84–90%) and oxidation of the associated aldehyde residue gave the corresponding benzoic acid. Cleavage of the TBDPS-ether within product **57** then afforded the substrate **58** (61–79%) used in the macrolactonisation reaction. So, compound **58** was subjected to an intramolecular Mitsunobu reaction that provided macrolide **59** (P = MOM) (78%), the MOM-group of which was cleaved and the product RAL, *viz*. paecilomycin F (**13**), was then chlorinated using sulfuryl chloride and thus affording cochliomycin C (**9**) in 71% yield.

Nanda and his colleagues have also reported[13,14] related syntheses of the C5′- and C6′-epimers of cochliomycin C.

### *(c). The Srihari Group approach*

The Srihari Group synthesis of cochliomycin C (**9**)[15] (Scheme 5) is a formal one [in that it delivers paecilomycin F (**13**)], relies on D-lyxose (**60**) as starting material and uses a RCM reaction to construct the macrolide ring. The synthesis started with the conversion of compound **60** into the previously reported monoacetonide **61** (95%) and this was subjected to an Ohira-Bestmann alkyne forming reaction that delivered, with accompanying




**Scheme 5.** The Srihari Group synthesis of paecilomycin F (**13**).

epimerisation, compound **62** (49%) as a mixture of diastereoisomers. Conversion of this last pair of compounds into the corresponding bis-acetonides and chromatographic separation of the major product **63** (45%) was followed by the regioselective reaction of the derived anion with the commercially available and homochiral epoxide **64** and so affording the 2°-alcohol **65** (82%). Exhaustive reduction of the alkyne moiety associated with this last compound and reaction of the oxyanion derived from product **66** (86%) with the readily prepared arene **67** then gave, after acid treatment, the vinylated salicylate **68** (65%). This was subjected to oxidative cleavage and the ensuing aldehyde allylated in a diastereoselective manner to give diene **69** (63%). Compound **69** was then engaged in a RCM reaction using the Hoveyda-Grubbs second generation catalyst and by such means, and after cleavage of the associated acetonide residue, paecilomycin F (**13**) was obtained in 68% yield. Since Nanda[12] has previously converted compound **13** into cochliomycin C (**9**) through electrophilic aromatic chlorination using sulfuryl chloride a formal total synthesis of the latter natural product was realised in this instance.

By related means C6′-*epi*-cochliomycin C was obtained.[15]

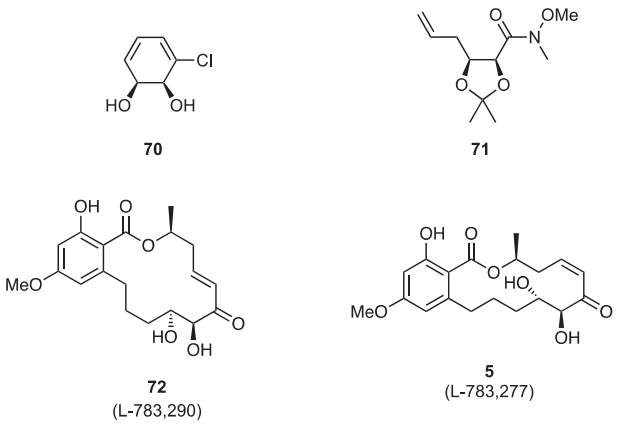
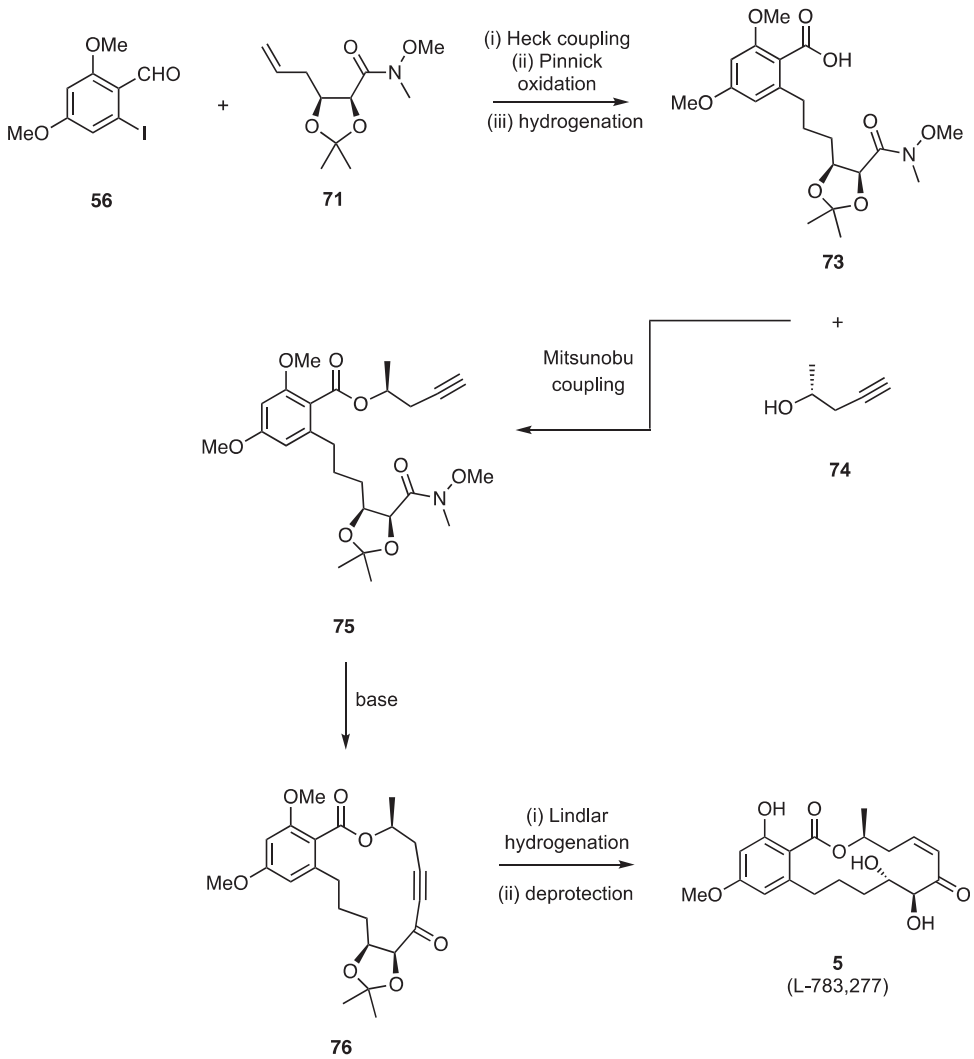



**Fig. 4.** The starting material **70** and intermediate **71** used by the Banwell Group in establishing total syntheses of RAL L-783,290 (**72**) and its *cis*-isomer **5**.

*(d). Background to the Banwell Group studies on the synthesis of RALs*

Our group's original efforts in the area arose through an interest in exploiting enzymatically-derived and homochiral *cis*-1,2-dihydrocatechols[16] such as **70** (Fig. 4) in the assembly of various RALs. The pivotal building block employed for this purpose was Weinreb




**Scheme 6.** The Banwell Group synthesis of L-783,277 (**5**).

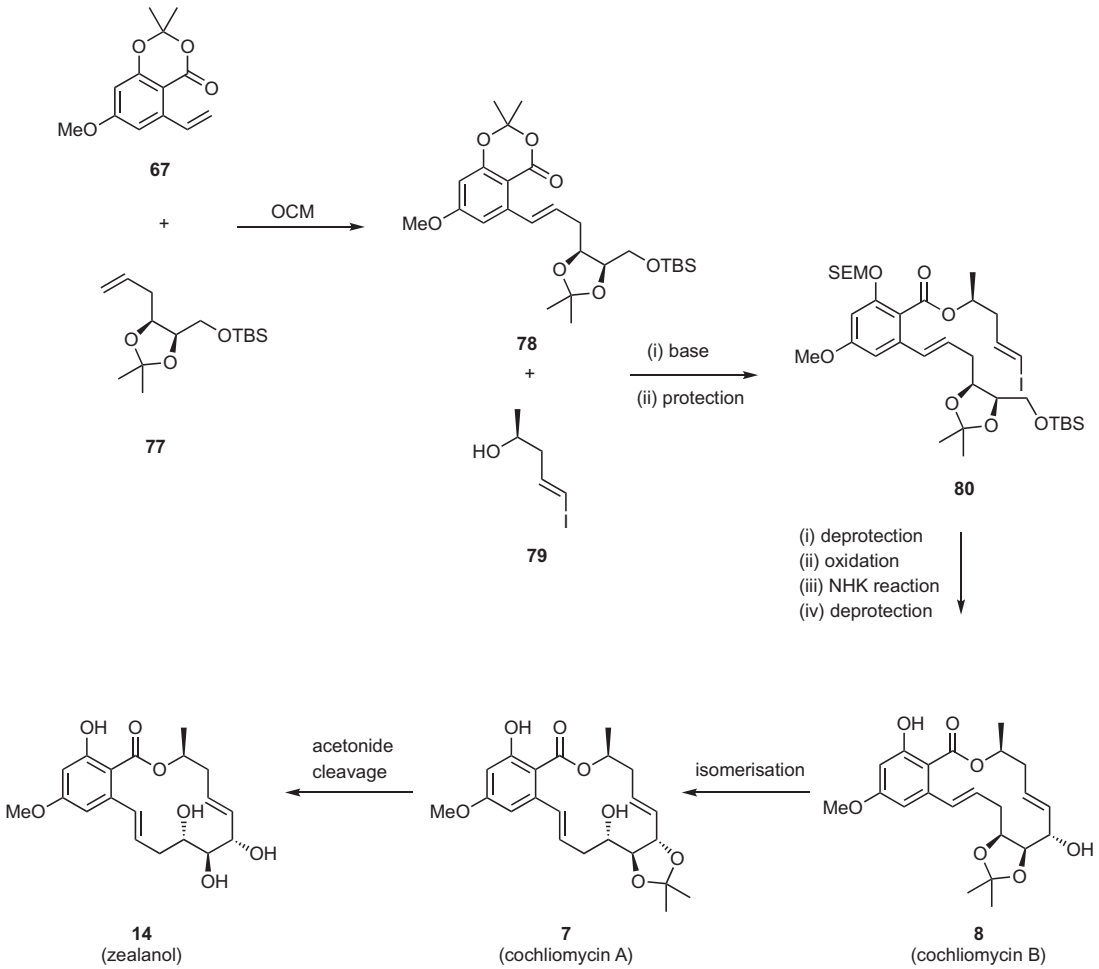
amide **71**[17] obtained through, *inter alia*, reduction of the non-halogenated double bond associated with the acetonide derivative of diol **70** and ozonolytic cleavage of the remaining (halogenated) one. Compound **71** served as a precursor to L-783,290 (**72**) and its *cis*-isomer **5**, the latter being, as noted above, a potent inhibitor of MEK1. While the macrolide ring and the *E*-configured C=C bond associated with target **72** was constructed using a RCM reaction, a more novel means of assembling the analogous (*Z*-configured) motif within congener **5** was developed.[18] Details are provided immediately below.

Our synthesis of the *cis*-enone-containing L-783,277 (**5**) is shown in Scheme 6 and, like the pathway leading to congener **72**, involved, in the early stages, the Heck coupling of aryl iodide **56** with the unsaturated Weinreb amide **71**. The immediate product of this process was oxidised to the corresponding acid (under Pinnick conditions) and this then hydrogenated to give compound **73** (41%) that was, in turn, treated with the oxyanion derived from the homochiral propargylic alcohol **74** (itself available through enzymatic resolution of the corresponding racemate). The ester **75** (70%) so formed was treated with potassium hexamethyldisilazide so as to generate the corresponding acetylide anion that itself engaged in an intramolecular acylation reaction and so producing the cyclic alkyne **76** (45%) and for which a single-crystal X-ray analysis was undertaken. This analysis revealed an essentially linear geometry about the internal triple bond and thus highlighting the capacity of the 14-membered macrolide ring of RALs to accommodate a range of structural motifs. The completion of the synthesis of target **5** involved Lindlar-type hydrogenation of cyclisation product **76** and twofold deprotection of the ensuing *cis*-enone gave L-783,277 (**5**) (40%) without compromising the integrity of the *Z*-configured double bond.

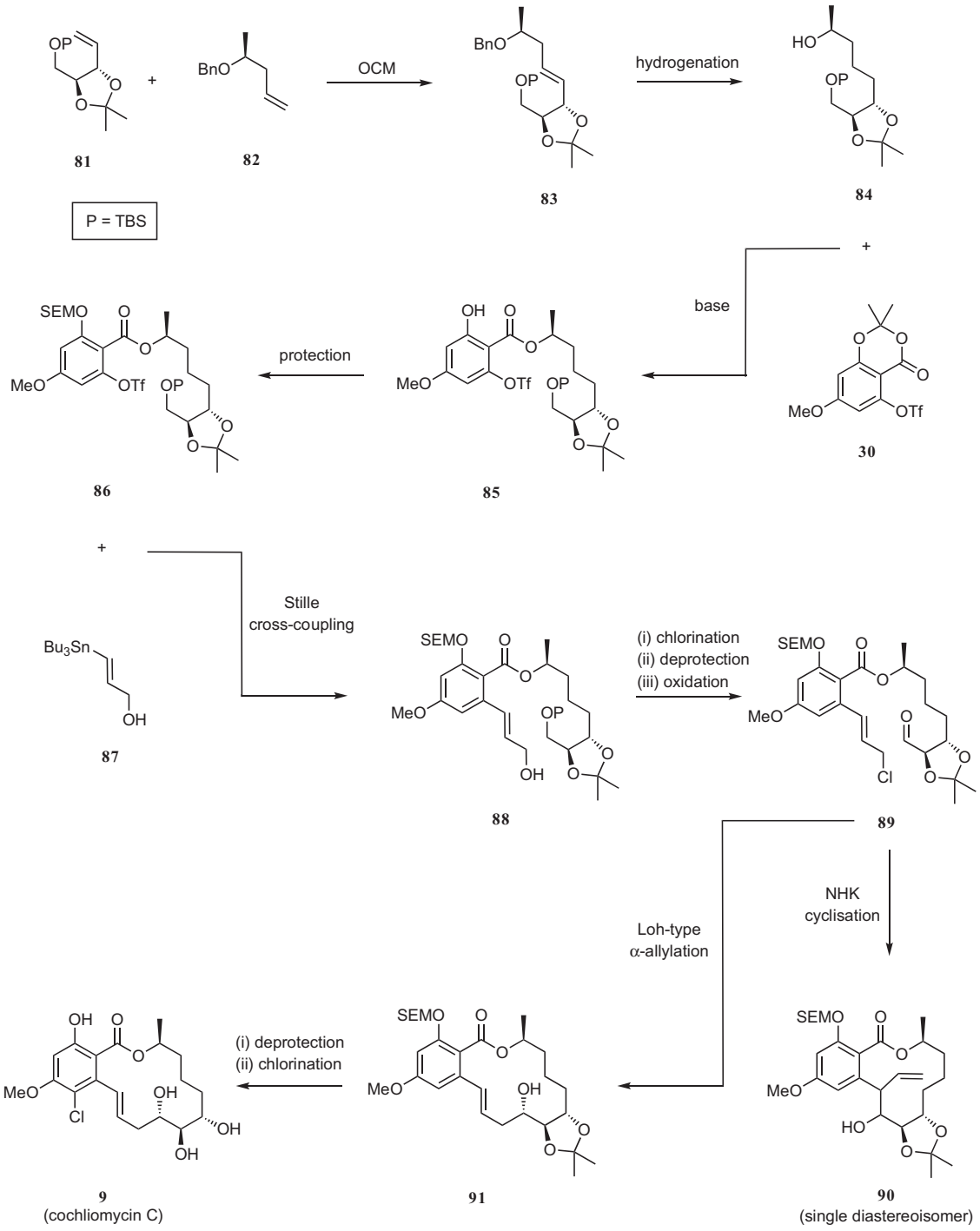
### *(e). The Banwell Group syntheses*

Our syntheses of RALs **5** and **72** were completed just prior to the report[5] of the isolation and structural characterisation of cochliomycins A–C (**7**–**9**, respectively). Given this, the presence of the (unusual) acetonide residues within congeners A and B and the novel biological properties they display we were attracted to developing syntheses of them. Our route[19] to the first two of these (*viz*. the acetonide-containing ones) exploited a late-stage and highly stereoselective Nozaki–Hiyama–Kishi (NHK)[20] reaction to effect the necessary macrocyclisation process, a relatively unusual one in terms of its application in the synthesis of RALs.

The pivotal elements of the synthetic sequence used are shown in Scheme 7 and involved an OCM of the readily available olefin **67** with the *D*-2-deoxyribose-derived and previously reported chiron **77** to give compound **78** (86%). The β-substituted styrene **78** was then reacted with the readily prepared homoallylic alcohol **79** in the presence of base and so affording, after protection of the phenolic OH group, the ester **80** (80%). Treatment of ester **80** with TBAF




**Scheme 7.** The Banwell Group syntheses of cochliomycins A and B.




**Scheme 8.** The Banwell Group synthesis of cochliomycin C.

resulted in selective cleavage of the TBS-ether moiety and oxidation of the resulting and rather sensitive 1°-alcohol with the Dess-Martin periodinane then gave the corresponding aldehyde. This was immediately engaged in an intramolecular NHK reaction to afford, with high levels of diastereocontrol, the SEM ether of cochliomycin B (**8**) (77%). When this ether was treated with TBAF in refluxing THF then cochliomycin B (**8**) itself was obtained in 73% yield. In contrast, on treating the SEM ether with HCl in methanol at 22 °C for 1 h then congener A (**7**) (91%) was obtained while extended exposure of the same substrate to the same conditions resulted in acetonide group cleavage and formation of the previously reported RAL zeaenol (**14**) which was obtained in 84% yield.

The end game associated with our approach[21] to cochliomycin C (**9**) was rather different and resulted in the identification of a new means for forming the macrolide ring of RALs. The reaction

sequence started (Scheme 8) with an OCM reaction between the readily available alkenes **81** and **82** (the former compound being obtained from L-tartaric acid) and conventional hydrogenation of the product olefin **83** (88%) to give alkane **84** (98%). The anion derived from the last compound was reacted with arene **30** and thus affording ester **85** (91%), the phenolic group of which was protected as the corresponding SEM-ether **86** (94%). A Stille cross-coupling reaction between aryl triflate **86** and the alkenylstannane **87** then gave the cinnamyl alcohol **88** (76%) that was converted, over three standard steps, into the rather unstable aldehyde **89** (66%). Given our previous positive experiences with the NHK reaction we sought to apply this in the macrocyclization of compound **89**. However, on exposing this to a mixture of chromous chloride and nickel(II) chloride in DMF only the vinylated 12-membered lactone **90** was obtained (as a single diastereoisomer in 33% yield). In stark contrast, when the same substrate was treated with indium in a mixture of water and dichloromethane then a Loh-type α-allylation reaction took place and so affording, in a highly diastereoselective manner, the 14-membered macrocycle **91** (61%). Removal of the acetonide and SEM protecting groups associated with this last compound using aqueous acid then gave paecilomycin F (**13**) that was chlorinated with sulfuryl chloride and so affording cochliomycin C (**9**) in 82% yield.

During the course of our work detailed above Cutler and colleagues reported[22] the isolation of three new RALs from a fungus *Neocosmospora* sp. (UM-031509). They were named neocosmosins A–C and structures **92**–**94** (Fig. 5), respectively, assigned to them. These RALs were found to co-occur with three previously reported ones, namely radicicol (**1**), monocillin II (**95**) and monocillin IV (**96**). Unlike any of the RALs we had previously targeted for synthesis, all of the *Neocosmospora*-derived compounds embody a C10-keto residue and three of them (**1**, **94** and **95**) show good binding affinity for the human opioid receptors. Accordingly, we sought to develop a synthesis of the first of these, namely compound **92** embodying the structure assigned to neocosmosin A.

Our synthesis of RAL **92**[23] is shown in Scheme 9 and began with the OCM of styrene **67** and the unsaturated acetal **97**. The product *E*-alkene **98** (72%) was treated with dimethyl dioxirane and the resulting epoxide **99** (quant.) engaged in a Meinwald-type rearrangement on exposure to $Pd(OAc)_2$ and $n$-$Bu_3P$ and thus affording ketone **100** (88%) embodying the pivotal C10 carbonyl unit (RAL numbering) associated with the target **92**. Acid-catalysed hydrolysis of the acetal moiety within compound **100** afforded the corresponding keto-aldehyde **101** (89%) that could be selectively methylenated using the Wittig reagent and so giving the terminal alkene **102** (74%). Compound **102** was particularly prone to cyclisation on treatment with either acid or base. So, for example, when it was heated with *p*-TsOH in toluene in the presence of ethylene glycol (in an effort to prepare the corresponding ketal) then the unsaturated lactone **103** (82%) was formed but this could be cleaved with potassium hydroxide in aqueous THF and thus gave, after careful acidic work up, keto-acid **104** (96%). Compound **104** then served as the nucleophile in a Mitsunobu reaction with the homochiral 2°-alcohol **26** and thus affording the ester **105** (78%) that was itself engaged in a RCM reaction using Grubb's second generation catalyst and so producing the target RAL **92** (83%). All of the NMR, IR and MS spectral data acquired on this product matched those reported for neocosmosin A. However, while the specific rotation of compound **92** was of a similar magnitude to that reported for the natural product it was of the opposite sign. As such we concluded that the absolute configuration of neocosmosin A had been incorrectly assigned and is, in fact, represented by structure *ent*-**92**.

The synthesis of compound *ent*-**92** (Scheme 10) involved a trivial adaptation of the process just discussed. Thus, Mitsunobu coupling of keto-acid **104** with the homochiral 2°-alcohol *ent*-**26** gave ester *ent*-**105** (92%) and this underwent an RCM reaction to give neocosmosin A (*ent*-**92**) (67%), the structure of which was confirmed by single-crystal X-ray analysis.

During the course of these studies Das and co-workers reported[24] a distinctly different synthesis of compound *ent*-**94**.

## Future Prospects/Conclusion

New RALs, including ones isolated from marine sources, that display intriguing biological properties continue to be reported.[25] Studies on the synthesis of such compounds have resulted, over the decades, in the identification of a raft of new methods for their construction and these have now provided chemists with the capacity to prepare new RALs in a predictable manner. As such, completions of total syntheses of RALs no longer elicit the excite-

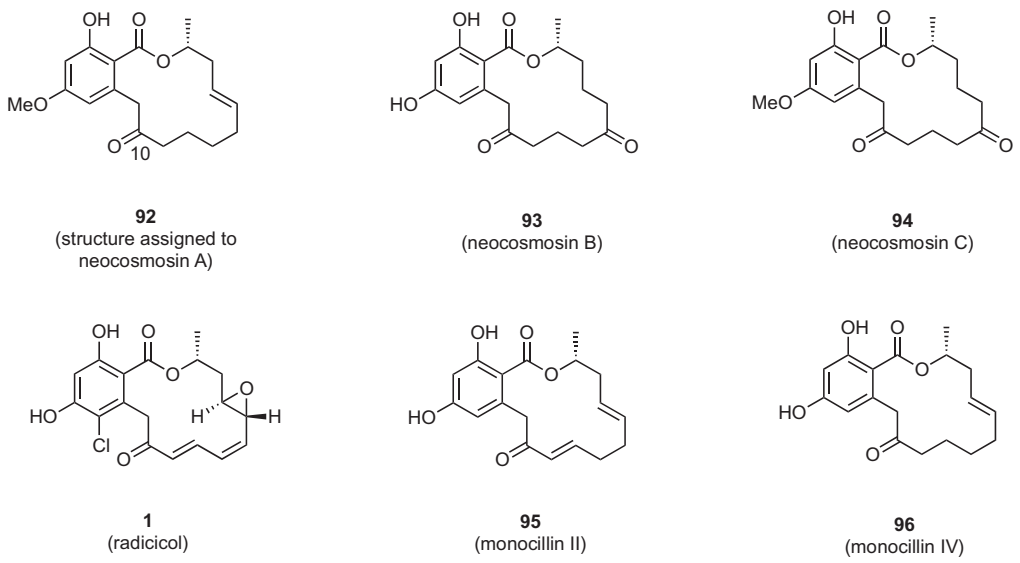
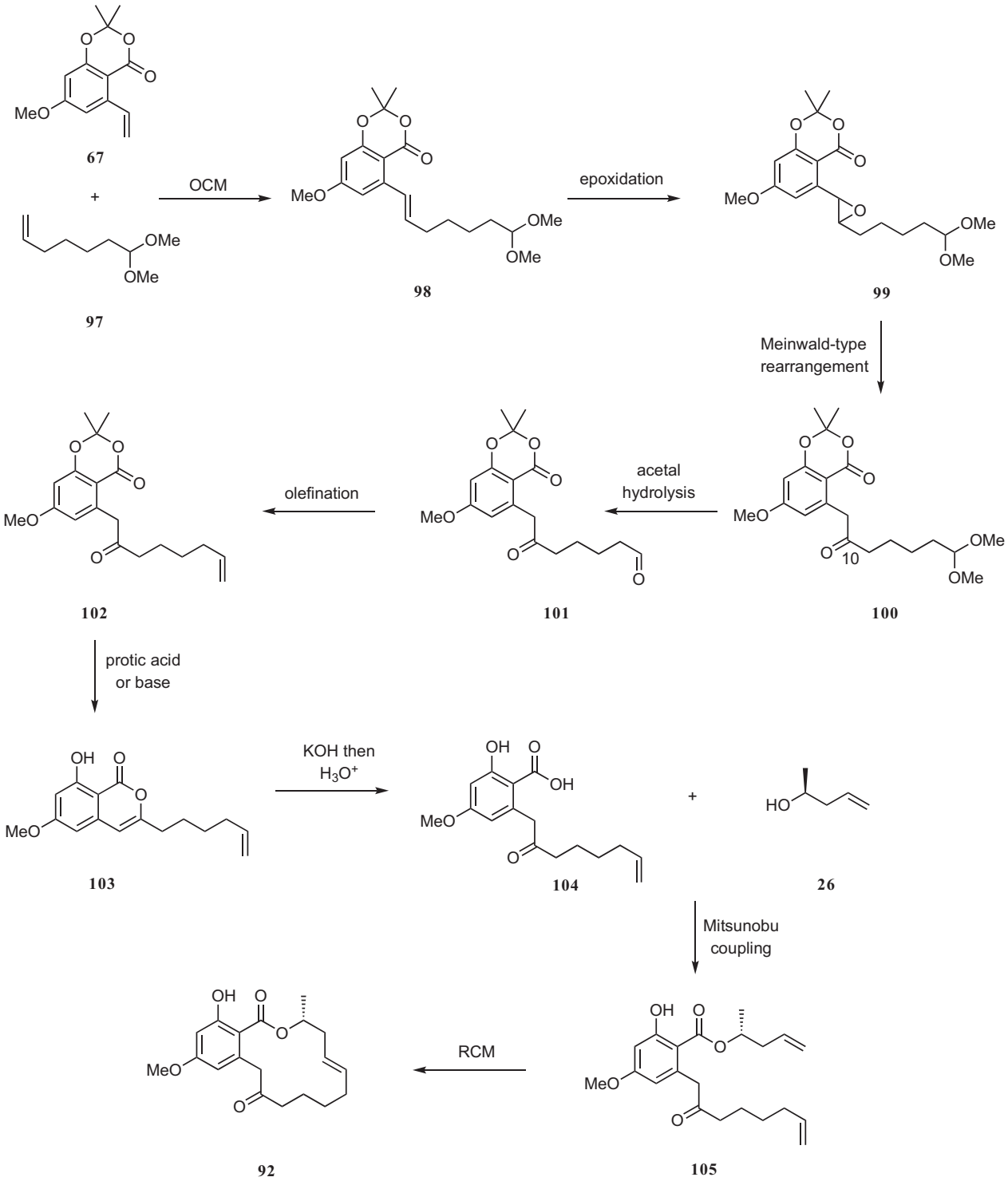



**Fig. 5.** The Structures **92**–**94** Assigned to Neocosmosins A–C (respectively) and the co-occurring RALs radicicol (**1**), monocillin II (**95**) and monocillin IV (**96**).




**Scheme 9.** The Banwell Group synthesis of RAL **94.**

ment they once did.[26] Indeed, now synthetic studies usually just provide the means by which the assigned structures can be checked and additional material can be produced for the purposes of biological profiling/evaluation. Of course, the production of analogues is another important activity in this area, perhaps the most promising aspect of which would be the production of potentially more metabolically stable and bio-available macrolactam equivalents.[27]

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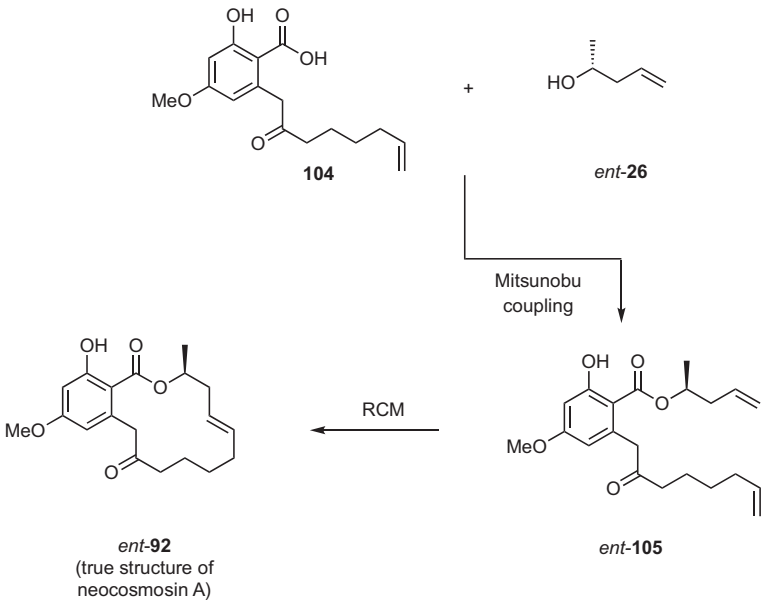


**Scheme 10.** The Banwell Group synthesis of the true structure of neocosmosin A (*ent*-**92**).

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