UNIVERSITÉ DU QUÉBEC À MONTRÉAL

DEVELOPPEMENT D'UN GROUPEMENT PROTECTEUR FONCTIONEL APPLIQUÉ À LA SYNTHÈSE TOTALE DE LA DEOXYASPIDODISPERMINE

THÈSE

PRÉSENTÉE

COMME EXIGENCE PARTIELLE

DU DOCTORAT DE CHIMIE

PAR

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DÉDICACE

''Le plus grand échec c'est de ne pas avoir le courage d'oser''

ABBE PIERRE

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Ac	Acétyle
ACN	Acétonitrile
AcO^-	Ion acétate
AcOH	Acide acétique
Ac_2O	Anhydride acétique
aq	Aqueux
Bn	Benzyle
Boc	*ter*-Butoxycarbonyle
Br	Brome
$CeCl_3$	Chlorure de cérium
Cl	Chlore
CBz	Carboxybenzyle
$CDCl_3$	Chloroforme deuteuré
Cs_2CO_3	Carbonate de césium
d	Doublet
dd	Doublet de doublet
ddd	Doublet de doublet de doublet

DCM dichlorométhane

DIB diacetoxyiodobenzene

DMP Périodinane de Dess Martin

E^+ Électrophile

Et Éthyle

H2 dihydrogène

HBr Acide bromidrique

$HClO_4$ Acide perchlorique

HFIP Hexafluoroisopropanol

Hg Mercure

Hz Hertz

I Iode

IBX Acide 2 iodobenzoique

iPrOH isopropanol

IR Infra rouge

K_2CO_3 Carbonate de potassium

$LiAlH_4$ Tétra hydrure aluminate de lithium

m multiplet

Me Méthyle

MeOD Méthanol Deutéré

Mg milligramme

mL millilitre

mmol millimol

MOM Métoxyméthane

Ms Mésyle

MsCl Chlorure de mésyle

$NaBH_4$ Tétrahydruroborate de sodium

$NaHCO_3$ Bicarbonate de sodium

$NaIO_4$ Périodate de sodium

$Na_2S_2O_3$ Thiosulfate de sodium

Na_2SO_4 Sulfate de sodium

NBS N-bromosuccinimide

$N(Et)_3$ Triéthylamine

NH_4Cl Chlorure d'ammonium

Ns Nosyle

Nu^- Nucléophile

PBu_3 Tributylphosphine

PIFA (Bis(trifluoroaetique)iodo)benzène

Ph Phényle

$P(OMe)_3$ Triméthyle phosphite

PPh_3 Triphényle phosphine

Ppm Partie par million

q Quadruplet

RMN Résonance Magnétique Nucléaire

Sat Saturé

SN_2 Substitution nucléophile d'ordre 2

SO_2 Dioxyde de soufre

t Triplet

TBDPS *ter*-butyl diphényl silyle

TBS *ter*-butyl diméthylsilyle

tBuOk *ter*-butanolate de potassium

TFA Acide trifluoroacétique

TFE Trifloroéthanol

THF Tétrahydrofurane

TMS Triméthyle silyle

Zn Zinc

RÉSUMÉ

La transformation directe de phénols bon marché en cyclohexénones polyfonctionnalisées contenant un phosphonate est décrite. Ces systèmes hautement fonctionnalisés sont facilement obtenus à partir de composés aromatiques simples et pourraient ouvrir une multitude de possibilités en synthèse. Par exemple, ces composés ont étés facilement et stéréosélectivement transformés en une fonctionnalité énol correspondante dans le même pot par l'ajout de borohydrure de sodium. D'autres applications de ces structures pour la synthèse totale de différents alcaloïdes sont à l'étude. D'autre part, un procédé d'aziridination arylant a été développé à partir de phénols dibromés. Cette méthode implique une procédure en deux étapes par la formation d'un intermédiaire dibromo-diénone. Le système clef diénone a été obtenu par un réactif d'iode hypervalent (réaction de Kita) et suivi d'un processus d'aziridination arylant intramoléculaire développé au laboratoire. De nouveaux squelettes polyfonctionnalisés ont été ainsi obtenus et offrent plusieurs possibilités en synthèse. Cette méthodologie d'aziridination a été appliquée à la synthèse totale de la désoxyaspidodispermine à partir d'homotyramine comme produit de départ. Cette approche est basée sur l'application d'une stratégie de groupe protecteur fonctionnel qui masque non seulement la réactivité des groupes sensibles lors des étapes cruciales, mais représente également une partie synthétique de la cible finale, qui est transférée au substrat au moment de l'étape de déprotection. Cette synthèse met en évidence une réaction en cascade d'aza-Michael-Smiles et fermeture de cycle, qui permet la formation d'un système tétracyclique en deux étapes à partir d'un phénol contenant un nosylamide sur sa chaine latérale.

Mots clés : polyfonctionnalisées, phosphonate, stéréosélective, aziridination arylant, aza-Michael-Smiles, iode hypervalent, désoxyaspidodispermine, groupe protecteur.

ABSTRACT

The rapid transformation of inexpensive phenols into polyfunctionalized cyclohexenones containing a phosphonate in one pot is described. Such highly functionalized systems readily obtained from simple aromatic compounds could open up a multitude of synthetic possibilities. For example, this scaffold was easily and stereoselectively transformed into the corresponding enol functionality in the same pot by the addition of sodium borohydride. Further applications of such scaffolds in total synthesis of different alkaloids is under investigations. On the other hand, an arylative aziridination process has been developed from dibrominated phenols. This method involves a two-step procedure by the formation of a dibromo-dienone intermediate. The key dienone system was mediated by a hypervalent iodine reagent (Kita reaction) and followed by an intramolecular arylative aziridination process developed at the laboratory. New polyfunctionalized scaffolds have been obtained and offer several synthetic possibilities. This aziridination methodology has been applied to the synthesis of deoxyaspidodispermine from homotyramine as starting material. This approach is based on the application of a functional protecting group strategy that not only masks the reactivity of sensitive groups during crucial steps but also possesses a moiety desired in the final target, which is transferred to the substrate at the time of deprotection. This synthesis highlights an aza-Michael−Smiles ring-closure cascade, which enables the formation of a tetracyclic system from a nosylamide protecting group

Keywords: polyfunctionalized, phosphonate, stereoselective, arylative aziridination, aza-Michael−Smiles, hypervalent iodine, deoxyaspidodispermine, protecting group

INTRODUCTION

Les molécules d'origines naturelles sont la cible de nombreux chercheurs. L'aboutissement de la synthèse totale de ces molécules constitue un véritable défi pour le chimiste organicien. Malgré les difficultés que l'on rencontre pendant la synthèse, plusieurs alternatives peuvent se présenter pour trouver une solution aux différents problèmes. Des milliers de molécules d'origines naturelles ont donc vu le jour par synthèse organique. L'intérêt suscité pour les alcaloïdes à titre d'exemple est dû en grande partie à leurs diverses propriétés biologiques, ce qui leur confère le caractère de molécules bioactives. De plus ces molécules ou leurs analogues peuvent être utilisés comme des médicaments afin de lutter contre certaines maladies, permettant ainsi de résoudre un problème de santé publique. En ce qui concerne la synthèse des molécules d'origines naturelles, le chimiste organicien peut élaborer une méthodologie permettant d'avoir un intermédiaire avancé de la cible. Notre laboratoire s'est donc inscrit dans cette démarche d'élaboration de nouvelles méthodologies en utilisant un réactif à base d'iode hypervalent[1] notamment le diacetoxyiodo-benzene (DIB), formant ainsi de potentiels précurseurs pour la synthèse totale d'alcaloïdes[2]. Le présent travail se décline en trois parties; la première sera consacrée à l'élaboration de phosphonates[3] qui peut être utilisés comme intermédiaires pour la synthèse de produits naturels. La deuxième partie sera consacrée à la synthèse d'aziridines[4], qui sont également des intermédiaires clefs pour la synthèse de molécules naturelles de type aspidospermine[5]. Concernant la troisième et dernière partie, elle décrira la synthèse de la déoxyaspidodispermine.

0.1 Iode hypervalents

De nos jours l'iode est devenu un élément très important pour la synthèse organique. Synthétiser des molécules organiques en étant respectueux de l'environnement devient un souci majeur dans le domaine de la chimie de synthèse. Cela peut se justifier par le fait qu'il est moins toxique pour l'environnement et aussi pour remplacer l'utilisation de métaux lourds tels que le Mercure, le plomb, le Thallium etc…. L'iode fait partie du groupe des halogènes dont le numéro atomique est 53, on le trouve généralement au degré d'oxydation +1. La notion d'iode hypervalent, est le fait que l'iode peut adopter des degrés d'oxydation supérieurs à +1. Nous avons plusieurs réactifs à base d'iode hypervalent au nombre desquels nous pouvons citer, le periodate de sodium ($NaIO_4$) ou l'acide périodique au degré d'oxydation +7, utilisés pour réaliser des coupures oxydantes de diols vicinaux selon le principe de Malaprade[6], et le periodinane de Dess Martin ainsi que l'acide 2-iodoxybenzoïque (IBX)[7], deux iodes de degré d'oxydation +5 souvent utilisés pour les oxydations d'alcools primaires et secondaires en aldéhydes et cétones respectivement. À côté de ceux-ci, nous avons d'autres iodes hypervalents comme; l'iodosobenzène, le réactif de Koser[8], le PIFA le DIB, tous au degré d'oxydation +3, **Figure 0.1**.

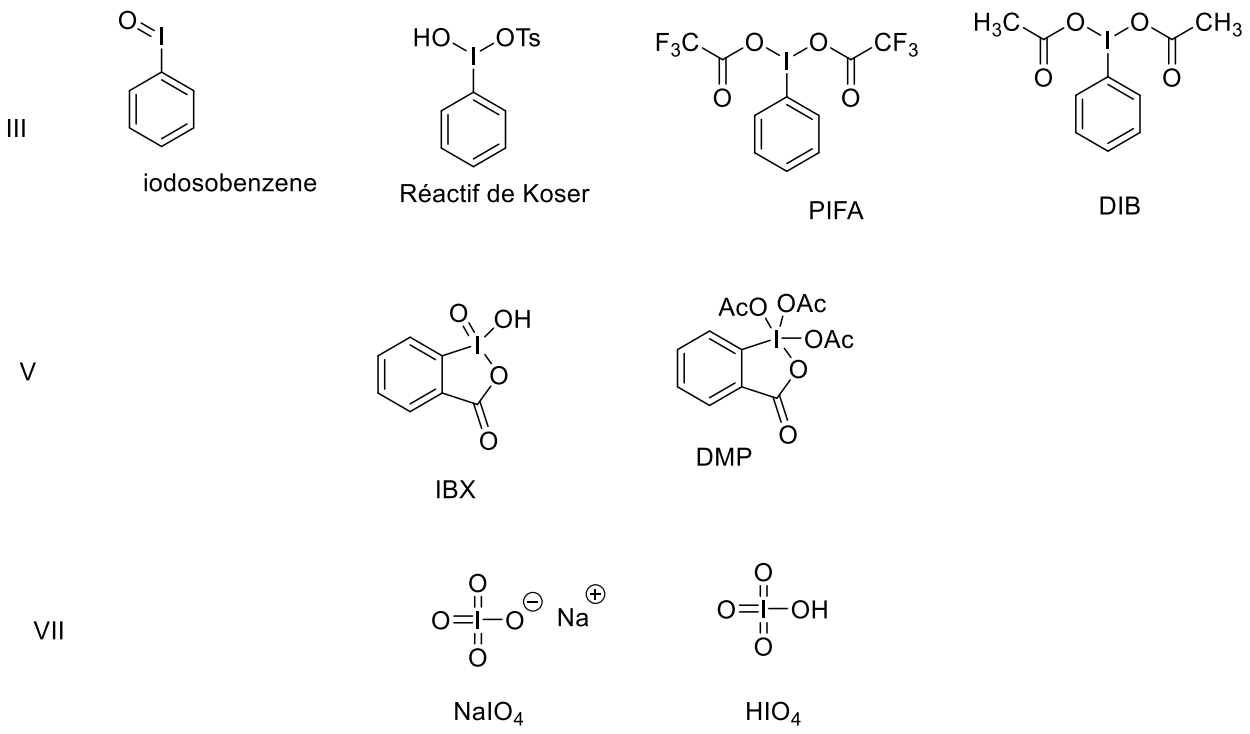


Figure 0. 1 : Réactif à base d'iode hypervalent

0.2 Principe d'Umpolung

En protégeant un aldéhyde par le 1,3-dithiol propane Corey et Seebach[9] mettaient en place le principe d'Umpolung en 1970 (inversion de polarité). En effet, l'aldéhyde étant électrophile subit une protection par le dithiol en présence d'un acide de Lewis. L'hydrogène devient plus labile et en présence d'une base forte, cela permet de former le carbanion correspondant. Le carbone de l'aldéhyde de départ électrophile est devenu nucléophile et peut donc réagir en présence d'un électrophile. C'est le principe d'Umpolung classique de Corey-Seebach appliquée à la chimie aliphatique, **Schéma 0.1**.

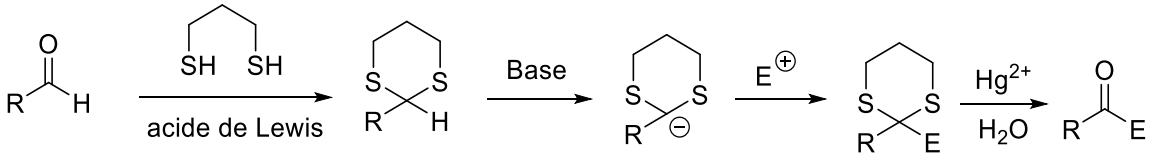


Schéma 0. 1 : Umpolung classique de Corey-Seebach

Ce principe d'Umpolung est par la suite appliqué sur des aromatiques riches en électrons tels que le phénol, dans ce cas on parle d'Umpolung aromatique. On connait habituellement la réactivité du phénol en tant que nucléophile pour ne citer que la réaction de Friedel et Craft. Cependant, comment le phénol pourrait-il réagir en tant qu'électrophile afin de justifier le concept d'Umpolung aromatique? Pour tenter de répondre à cette interrogation, nous allons voir les travaux réalisés par Kita et ses collaborateurs en 1987 au Japon en utilisant un réactif à base d'iode hypervalent notamment le DIB. En effet, il s'agit d'une activation oxydante[5] du phénol **1** en présence de DIB ce qui permet de former une espèce hautement électrophile **5**, qui va par la suite réagir avec un nucléophile. C'est formellement un procédé de transfert d'électrons célibataires, c'est-à-dire que l'atome d'iode va consécutivement prendre deux électrons à l'oxygène du phénol. Il en résulte donc la formation d'une charge positive sur l'oxygène électronégatif qui ne va pas la tolérer. Ce dernier va donc la délocaliser dans le cycle, soit en position *ortho*, soit en position *para*, conduisant ainsi à un ion phénoxenium. En réponse à l'interrogation ci-dessus, le phénoxenium constitue un intermédiaire hautement électrophile qui pourra réagir avec un nucléophile. À ce niveau, il faudra envisager deux possibilités : dans un premier cas, si le nucléophile utilisé est petit, on aura une attaque en *para* à cause de la stabilité du carbocation à cet endroit (effet stéréoelectronique). Dans un second cas, si le nucléophile utilisé est gros, on aura une attaque en *ortho* à cause d'un encombrement stérique important en *para* (effet stérique), **Schéma 0. 2.**

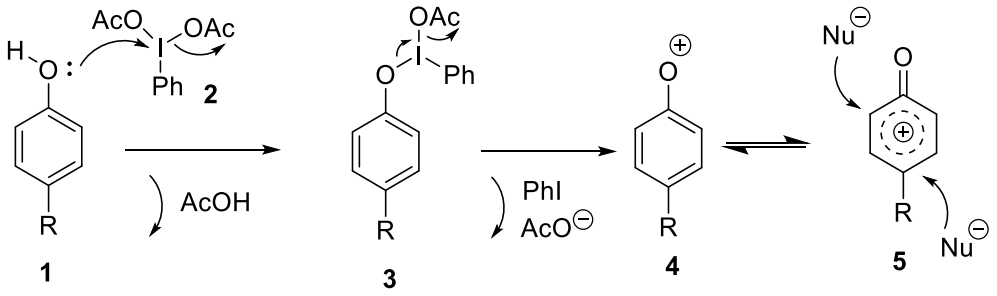


Schéma 0. 2 : Activation oxydante d'Umpolung aromatique

Quelques exemples de la désaromatisation des phénols selon le procédé de Kita sont présentés sur le **Schéma 0.3** avec des phénols *para* substitués. Ils ont démontré qu'en présence d'un réactif à base d'iode hypervalent tel que le PIFA dans l'acétonitrile, il est possible de former des composés spiranniques.[10]

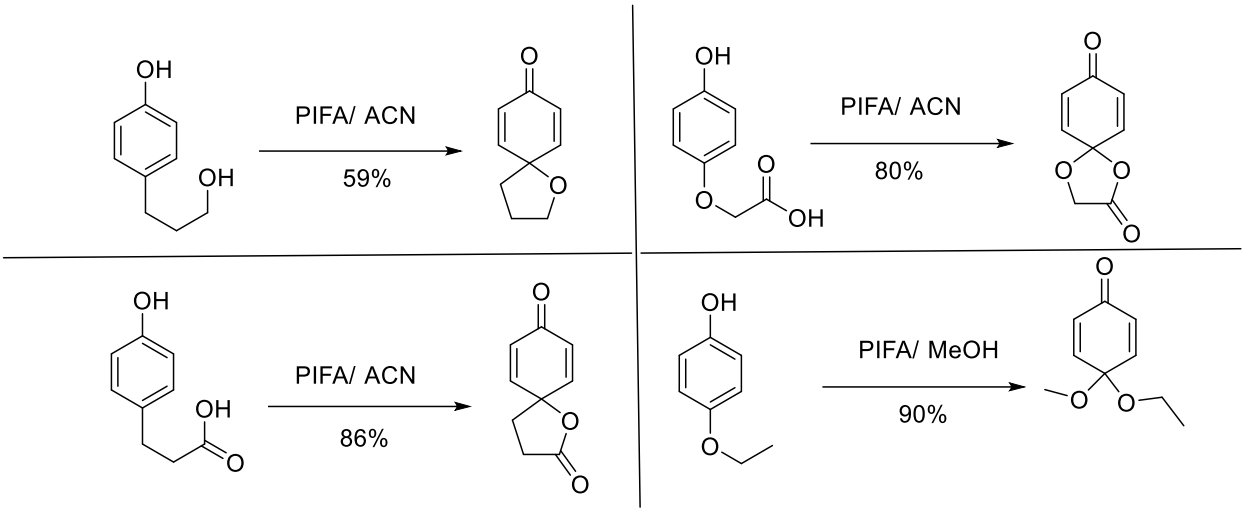


Schéma 0. 3 : Exemple de désaromatisation selon le procédé de Kita

Cette désaromatisation oxydante constitue un facteur important en synthèse organique, on assiste ici à la formation d'une diénone hautement fonctionnalisable à partir d'un phénol et en présence d'un réactif à base d'iode hypervalent. Ces diénones offrent plusieurs possibilités de synthèse en tant que précurseur pouvant aboutir à la synthèse totale de produits naturels. Plusieurs synthèses de produits naturels ont donc été faites en utilisant un réactif à base d'iode hypervalent.

0.3 Synthèse de la (-)-tuberostemonine

En 2005, Spencer[11] et Wipf ont réalisé la synthèse de la (-)-tuberostemonine **8** au cours de cette synthèse, ils ont rapporté que le DIB a été utilisé comme oxydant pour former la spirolactone **7** par une cyclisation de la L-tyrosine **6** avec un rendement de 35% dans du nitrométhane à température ambiante pendant 2.5 heures, **Schéma 0.4**.

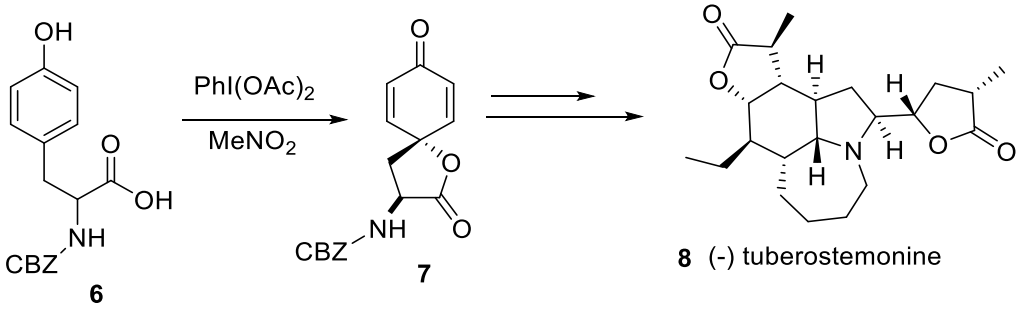


Schéma 0. 4 : Synthèse de la (-)-tuberostemonine en 2005 par Spencer et Wipf

0.4 Synthèse de la Dalesconol B

On peut citer également l'exemple lors de la synthèse de la Dalesconol **12** réalisée par Snyder et ses collaborateurs en 2010[12] en utilisant le DIB. Le phénol **9** réagi en présence de DIB pour former une espèce électrophile de type **11** qui réagit avec l'aromatique D pour produire le squelette principal du dalesconol B, **Schéma 0.5.**

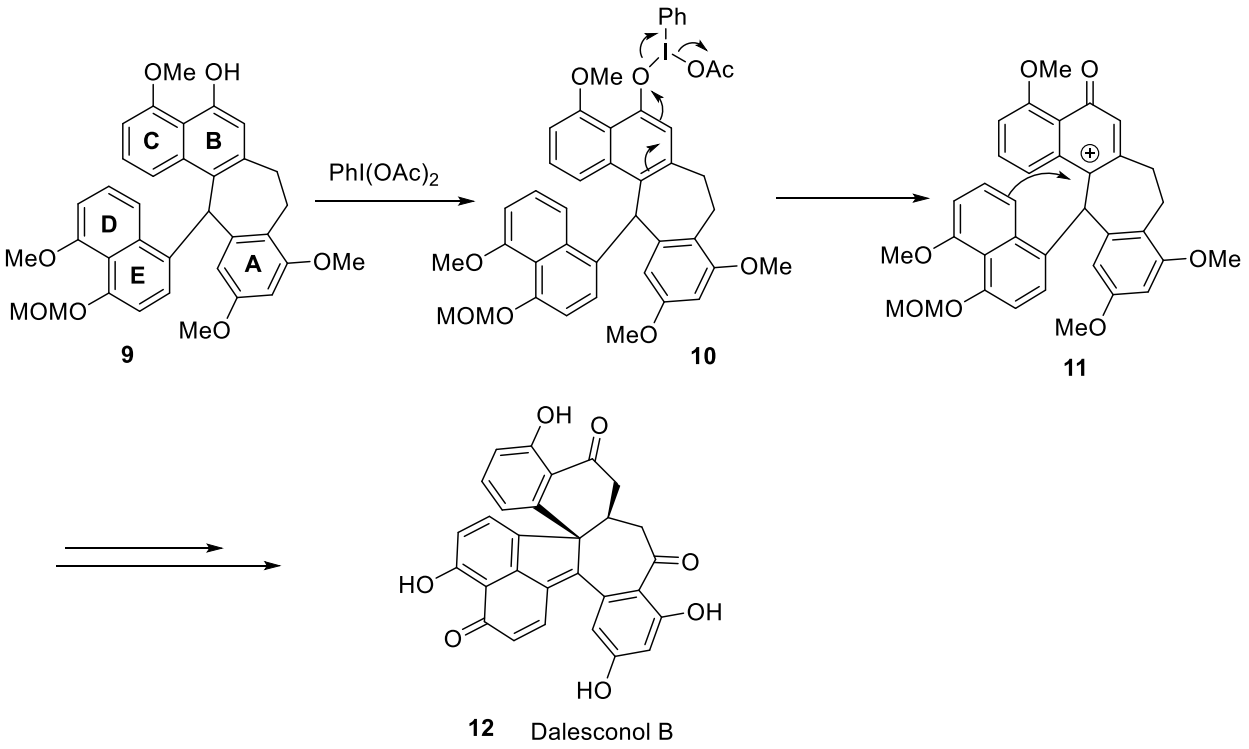


Schéma 0. 5 : Synthèse de la Dalesconol B par Snyder 2010

0.5 Synthèse de la (-)-maoecrystal V

L'équipe de Thomson[13], a réalisé en 2014 la synthèse de la (-)-maoecrystal V, d'abord l'anneau THF a été formé par une voie intramoléculaire par une désaromatisation oxydative. Ils ont constaté que le traitement du phénol **13** par $PhI(OAc)_2$ dans un mélange HFIP/DCM a permis de fournir la diennone **15** avec un rendement de 95%, **Schéma 0.6.**

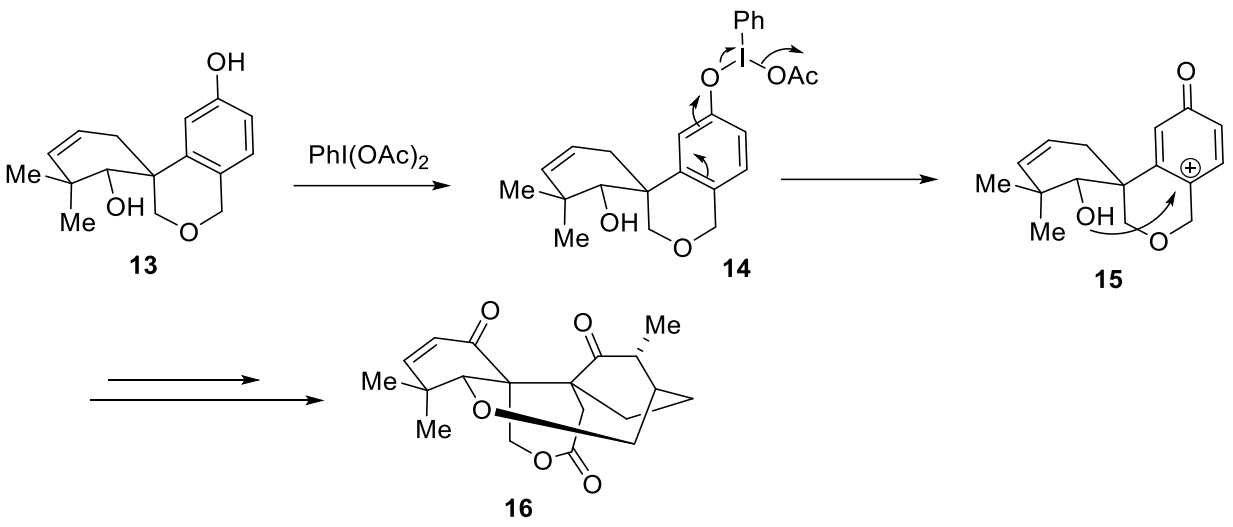
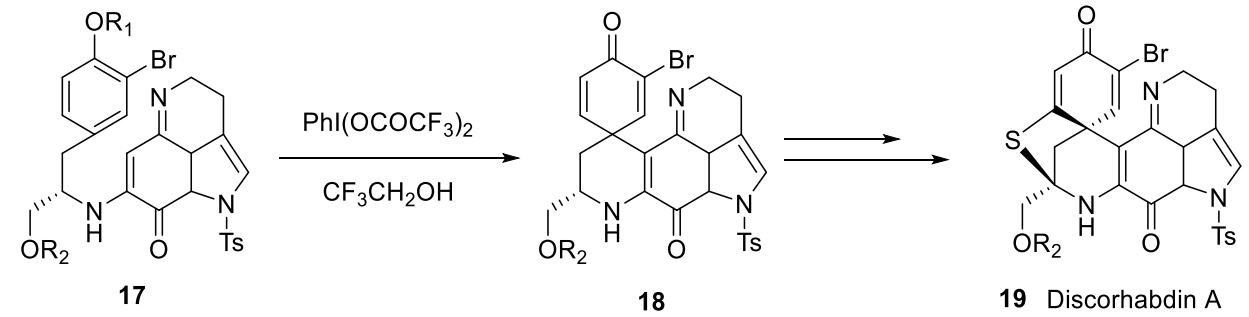


Schéma 0. 6 : Synthèse de la (-)-maoecrystal V par Thomson 2014

0.6 Synthèse de Discorhabdin A

En 2003, le Pr. Kita et ses collaborateurs ont utilisé le PIFA durant la synthèse totale de la Discorhabdin[14]. Le phénol et ses dérivés **17** sont cyclisés en spirodiénone **18** avec des rendements allant de 24 à 49% en présence de PIFA comme source électrophile dans le TFE et à température ambiante, **Schéma 0.7**.



R1= H, TMS, TBS, TIBS, TBDPS
R2= TBS, TIPS, TBDPS

Schéma 0. 7 : Synthèse de la Discorhabdin A Par le Pr. Kita 2003

CHAPITRE 1

SYNTHÈSE DE PHOSPHONATES POLYFONCTIONALISÉS

1.1 Introduction

Les phosphonates, sont des composés organophosphorés, qui constituent des fonctionnalités importantes en synthèse organique. L'une des principales voies de formation des phosphonates est la réaction de Michaelis-Arbuzov[3] qui est une réaction qui permet de former des liaisons phosphore-carbone. A l'origine, cette réaction a été découverte par Michaelis en 1898 et fut explorée quelques années plus tard par Arbuzov. Cette réaction a lieu entre un phosphite et un halogénure d'alkyle[3] permettant ainsi la formation de phosphonates, **Schéma 1.1.** Le doublet non liant du phosphite attaque l'halogénure d'alkyle dans une réaction de substitution nucléophile de type S_N2 et forme un trialkoxyphosphonium intermédiaire. À chaud, l'anion halogénure attaque un des groupes alkoxy pour former le phosphonate et un halogénure d'alkyle. Ils sont beaucoup utilisés en synthèse organique, notamment pour la réaction de Wittig[15] qui permet de convertir des dérivés carbonylés en alcènes.

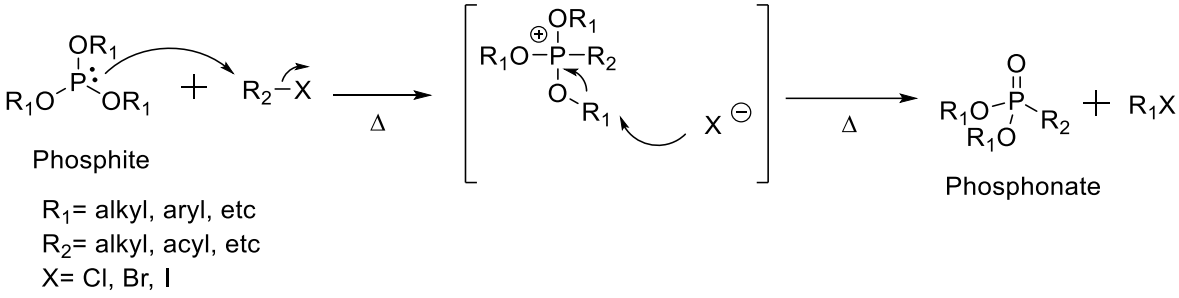


Schéma 1.1 : Réaction de Michaelis-Arbuzov

1.2 Conceptualisation

L'idée de la synthèse des phosphonates, fait suite au travail du laboratoire effectué par Deruer et Coll.,[16] en introduisant un sel de phosphonium ou un phosphonate en position *méta* de dérivés d'anilines par une fonctionnalisation[17] formelle de liaison C − H dans des conditions n'utilisant pas de métaux. Cependant, avec les dérivés d'anilines, l'intermédiaire désaromatisé **21** sous l'effet du DIB, n'était pas isolable et était directement converti en aniline *méta*-substituée **22** du fait de la rapide formation d'une énamine **21** suivit d'une réaromatisation **Schéma 1.2**

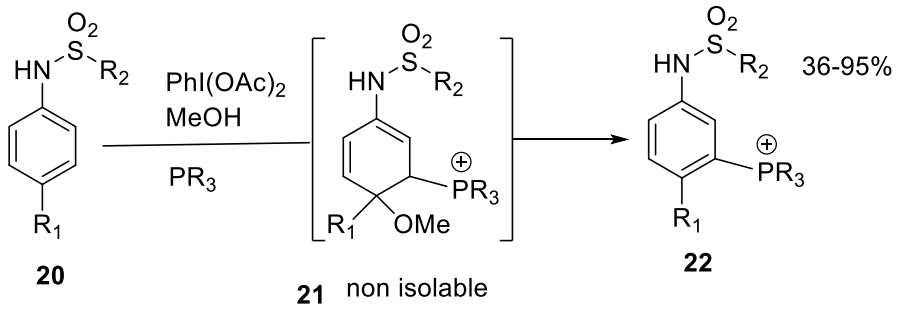


Schéma 1.2 : Dérivés d'anilines méta substitués

1.3 Synthèse des phosphonates

À la suite des travaux effectués par Deruer et Coll., nous avons décidé de remplacer les dérivés d'anilines **20** par des phénols **23** peu onéreux, **Schéma 1.3**. Ce qui nous a permis d'obtenir dans les mêmes conditions la formation de phosphates polyfonctionnalisés[18] avec des rendements allant de 43 à 76%, **Schéma 10.**

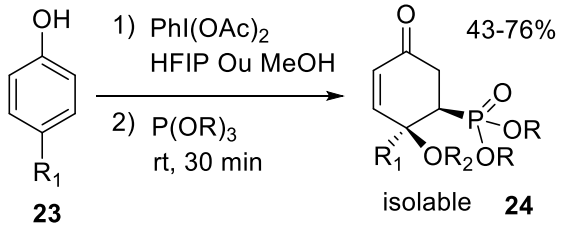


Schéma 1.3 : Synthèse des phosphonates

La poursuite de nos investigations pourrait nous permettre d'utiliser le phosphonate **25** comme des intermédiaires clefs pour la synthèse de la fortucine[19] **26** et de l'homolycorine[20] **27** en passant probablement par une réaction de Wittig et une addition de Michael, **Schéma 1.4.**

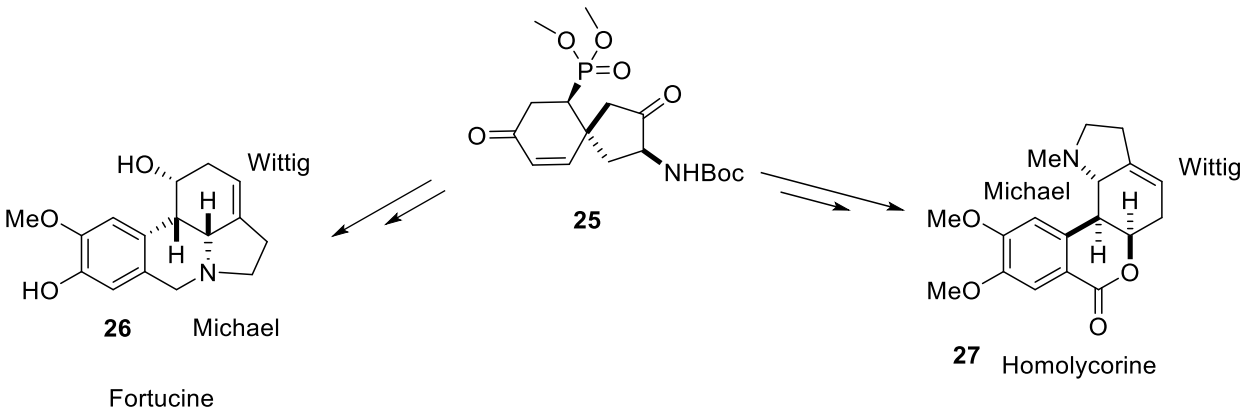


Schéma 1.4 : Cibles potentielles utilisant un phosphonate comme intermédiaire

1.4 Article ‘’elaboration of functionalized organophosphates’’

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Kouassi Signo, Zahra Mammasse, and Sylvain Canesi*

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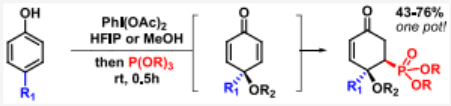
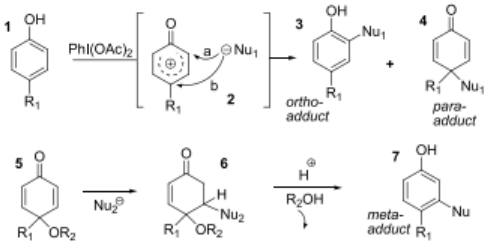
ABSTRACT: In this study, the rapid transformation of inexpensive phenols into polyfunctionalized cyclohexenones containing a phosphonate in one pot is described. Such systems readily obtained from simple aromatic compounds could open up a multitude of synthetic possibilities. For example, this scaffold was easily and stereoselectively transformed into the corresponding enol functionality in the same pot by the addition of sodium borohydride.



Hypervalent iodines[1] have demonstrated their synthetic potential as efficient and environmentally benign oxidizing agents of phenols. Indeed, without the presence of any metal and following the experimental conditions, three different pathways can result.[2] The activation of phenol **1** in the presence of an external nucleophile may react at the *ortho* or *para* position, depending on the nature of the nucleophile. With a bulky nucleophile, the reaction occurs at the less-hindered *ortho* position[3] to produce substituted phenol **3**. In the presence of smaller nucleophiles such as alcohols, the attack occurs at the *para* position[1] to yield dienone **4**. This prochiral scaffold **4** opens up a plethora of synthetic possibilities, since the previously inert phenol precursor can be readily used for further elaborations. However, due to the high degree of functionalization of **4**, chemoselective transformations have to be carried out to produce more complex structures. It should be noted that such a dienone has been judiciously used as a key intermediate in the synthesis of natural products.[4] Furthermore, with some mild nucleophiles under acidic conditions, dienone **4** has been shown to undergo a 1,4-addition−rearomatization tandem process to yield *meta*-substituted aromatic compound **7** with alcoholic solvents ($Nu_1 = OR_2$; Scheme 1).[5]

Scheme 1. Selective Functionalization of Phenols



In addition, phosphonates are important functionalities in organic synthesis. They have allowed the development of outstanding transformations such as the Wittig−Horner reaction,[6] the Michaelis−Arbuzov process,[7] and many others.[8] Since they are good nucleophiles and poorly basic species, phosphites and phosphines are reactive Michael donors that can react under acidic conditions. Recently, we have demonstrated that such conditions can be used to introduce a phosphonium salt or a phosphonate[2] at the *meta* position of aniline derivatives by a formal C−H bond functionalization[9] under metal-free conditions. However, with aniline derivatives, the dearomatized intermediate **9** was not isolable and directly converted into the *meta*-substituted aniline **10**. In this paper, we describe the concise formation of the polyfunctionalized scaffold **11** containing a phosphonate as a potentially useful intermediate in synthetic organic chemistry (Scheme 2).

The goal of this research was to rapidly produce polyfunctionalized organophosphate derivatives as potential key intermediates in the synthesis of complex structures from simple and inexpensive phenols. It should be noted that dienone **5**, produced by phenol activation, is more strained and reactive than enone derivative **6**. Therefore, the use of mild nucleophiles tolerating acidic conditions, such as inexpensive phosphines or phosphites, could enable chemoselective dienone desymmetrization[6] and lead to a polyfunctionalized enone. First, we investigated phosphines, but this reaction was not efficient with aromatic phosphines such as triphenylphosphine. However, in the presence of a more nucleophilic alkyl phosphine such as PBu_3, a reaction clearly occurred,[10] but the desired phosphonium **14** was not isolable and was rapidly transformed into its more stable dienone precursor **13**, probably by a retro-Michael process. Therefore, we inves-

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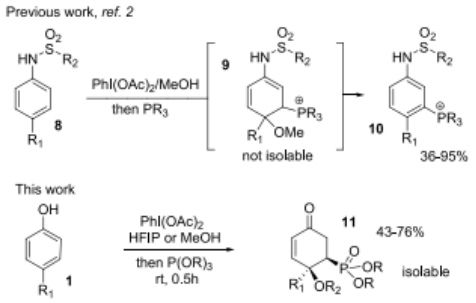
Scheme 2. Formal C−H Functionalization versus Dearomatization



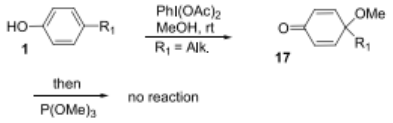
tigated a way to displace the equilibrium to produce a more stable phosphorus derivative. Indeed, in the presence of a phosphite, phosphonium species **15** was transformed into stable phosphonate **16** by an Arbuzov-like reaction. By this procedure, no undesirable retro-Michael process was observed, leading to **16** in 48% yield (Scheme 3).

Compound **16** was obtained in only one step. This scaffold could be a useful precursor in many synthetic procedures because it contains several unsaturated bonds and functionalities. Encouraged by this result, several phenols were investigated to assess the scope of this process. Reactive dienones such as quinone monoacetals were competent substrates to produce the desired functionalized organophosphates. However, this transformation was not efficient with simple dienones such as **17**, which contains an acyclic lateral chain (Scheme 4).[1a]

Nevertheless, we were glad to see that favorable results were obtained with spirannic systems. We hypothesized that the strain of the spirannic core in **18**, associated with the electronic effect induced by the heteroatom, increased the reactivity of **18**, leading to the formation of **19** in good yields. Furthermore, the addition to dienone **18** occurred stereoselectively on the side bearing the oxygen.[10] Substituents can be present at several positions, and different phosphites can be used. This reaction occurred in good yield up to 76% despite the presence of bulky groups (**19i−19l**). A single diastereoisomer was observed[10] when an asymmetric center was at the β-position of the oxygen atom (**19d**). However, no selectivity was observed when the chiral center was in the α-position (**19g**), Scheme 5.[11]

This transformation could be extended to the formation of different functionalities containing a phosphonate moiety, with only slight changes to the experimental procedures. Indeed, an

Scheme 4. Process Limitation



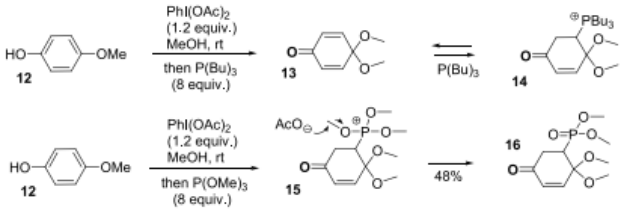
enol functionality also could be generated *in situ* using a Luche[12] variant after the formation of enone **19**. The subsequent reaction with $CeCl_3$ and $NaBH_4$ in the same pot led to enols **21a** and **21b** in overall yields of 64% and 61%, respectively. The same approach on *para*-methoxy phenol **13** led to the diastereoselective[10] formation of **22**, which was rapidly transformed into the elaborated organophosphate **23** in 46% overall yield. It should be noted that partial epimerization was observed due to the acidity of the ketophosphonate functionality. Although this product was produced in moderate yield, the valuable synthetic scaffold **23** was obtained in only one step from inexpensive starting materials. As another possibility, polyfunctionalized compound **19** also could be easily transformed into the elaborate organophosphate derivative **24** in good yield by simple treatment with zinc in the presence of acetic acid in methanol (Scheme 6).

Activation of *para*-unsubstituted arenol also led to the desired organophosphate **27**[13] through direct oxidation mediated by an excess of iodobenzene in methanol, followed by the addition of trimethyl phosphite. Compound **27** was obtained in 56% overall yield (Scheme 7).

An enantioselective version of this process promoted by dienone desymmetrization[14] would open up several opportunities in synthetic organic chemistry and must be developed. For example, enone **19d** could be an interesting chiron with potential applications in asymmetric synthesis. This intermediate could be obtained with excellent diastereoselectivity due to the direction of the tyrosine stereocenter. Since this compound has a good degree of functionalization, it could be used in the total synthesis of natural alkaloids such as fortucine **28**,[15] homolycorine **29**,[16] and related compounds[17] belonging to the Amaryllidaceae alkaloids. We assume that the central alkene of these alkaloids could be obtained by a lactone-opening reaction that would trigger an oxaphosphetane-like intermediate (Figure 1).

In summary, we have developed experimental procedures enabling the transformation of inexpensive phenols into different phosphorylated derivatives in one pot. These polyfunctionalized compounds could be potentially used as key intermediates in the synthesis of complex architectures such as natural alkaloids. Novel applications of these

Scheme 3. Phosphine versus Phosphite



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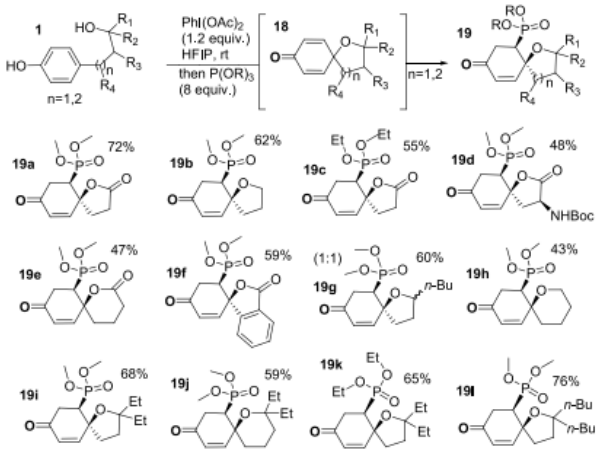
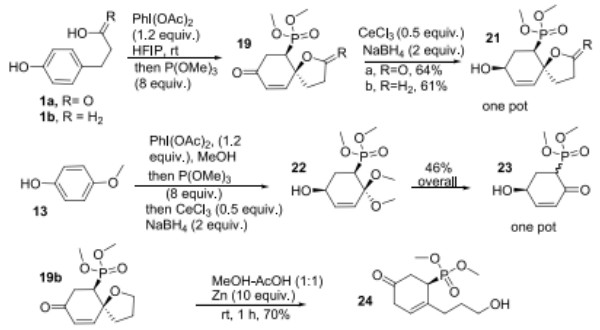
Scheme 5. Oxidative Dearomatization–Phosphonation Process



Scheme 6. One-Pot Stereoselective Formation of Enol Derivatives



Scheme 7. Direct *para*-Unsubstituted Phenol Transformation

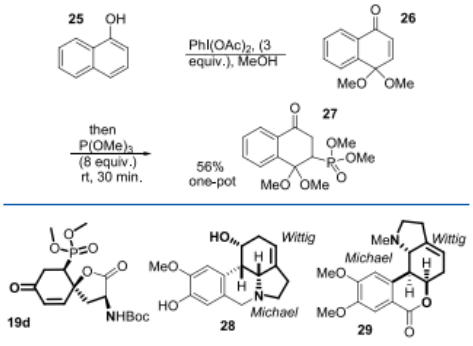


Figure 1. Natural products as potential targets.

transformations are currently under investigation in our laboratory.

EXPERIMENTAL SECTION

Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are reported in ppm on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, etc.), t (triplet), q (quartet), quin (quintuplet), m (multiplet), and further qualified as app (apparent), br (broad), c (complex). Coupling constants, *J*, are reported in Hz. HRMS were measured in the electrospray (ESI) mode on an LC-MSD TOF mass analyzer.

a. General Procedure for the Formation of Enone 19 from Phenol 1. Iodobenzene diacetate (0.36 mmol, 1.2 equiv in 0.5 mL of HFIP) was added to a vigorously stirred solution of phenol (0.3 mmol, 1 equiv) in HFIP/DCM (0.5:1 mL) at 0 °C. The mixture was then stirred for 5 min, (the reaction was concentrated under vacuum to remove HFIP and MeOH (2 mL) was added for compounds **19a**, **19c**, **19d**, **19e** and **19f**) and then phosphite (8 equiv) was added. The mixture was then stirred for a further 30 min (followed by TLC) and concentrated under vacuum. The residue was purified by silica gel

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chromatography with a mixture of ethyl acetate/hexane to give enone **19**.

b. General Procedure for the Formation of Enol 21/22 from Phenol 1. Iodobenzene diacetate (0.36 mmol, 1.2 equiv in 0.5 mL of HFIP (for compound **21**) or MeOH (for compound **23**)) was added to a vigorously stirred solution of phenol (0.3 mmol, 1 equiv) in HFIP/DCM (0.5:1 mL) (**21**) or MeOH (**22**) at 0 °C. The mixture was then stirred for 5 min, (the reaction was concentrated to remove HFIP and MeOH (2 mL) was added for compound **21**) and then phosphite (8 equiv) was added. The mixture was then stirred for a further 30 min (the reaction was concentrated to remove HFIP, and MeOH (2 mL) was added for compound **21**). $CeCl_3{\cdot}7H_2O$ (0.15 mmol, 0.5 equiv) was added followed by $NaBH_4$ (0.6 mmol, 2 equiv). The mixture was then stirred for 1 h (followed by TLC), filtered on Celite, and concentrated under vacuum. The residue was purified directly by silica gel chromatography with a mixture of ethyl acetate/hexane to give enol **21**/**22**.

*Dimethyl 2,2-Dimethoxy-5-oxocyclohex-3-enylphosphonate (**16**).* Iodobenzene diacetate (0.36 mmol, 1.2 equiv in 0.5 mL of MeOH) was added to a vigorously stirred solution of phenol (0.3 mmol, 1 equiv) in MeOH (1.5 mL) at 0 °C. The mixture was then stirred for 5 min, and then phosphite (8 equiv) was added. The mixture was then stirred for a further 30 min (followed by TLC) and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane (7:3) to give enone **16** as a yellow oil: 38.0 mg, 48% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (dd, J = 10.4, 1.4 Hz, 1H), 6.12 (d, J = 10.4 Hz, 1H), 3.71 (t, J = 10.6 Hz, 6H), 3.42 (s, 3H), 3.28 (s, 3H), 3.10 (m, 1H), 3.08−2.98 (c, 1H), 2.94−2.78 (c, 2H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 196.0, 145.7, 131.3, 96.8, 52.7, 49.6, 49.1, 41.6, 39.7, 36.2; ^{31}P NMR (122 MHz, $CDCl_3$) δ 26.8 (br); HRMS: calcd for $C_{10}H_{18}O_6P$ (M+H)$^+$, 265.0836; found, 265.0843.

*Dimethyl (2,8-Dioxo-1-oxaspiro[4.5]dec-9-en-6-yl)phosphonate (**19a**).* Obtained by silica gel chromatography with EtOAc/hexane (3:2) as a colorless oil: 59.1 mg, 72% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (dd, J = 10.1, 6.5 Hz, 1H), 6.06 (d, J = 10.1 Hz, 1H), 3.81 (d, J = 10.9 Hz, 3H), 3.72 (d, J = 10.9 Hz, 3H), 3.10 (m, 1H), 2.96−2.61 (m, 5H), 2.20 (m, 1H); ^{13}C {^{1}H} NMR (75 MHz, acetone-d_6) δ 196.8, 196.6, 177.1, 148.8, 148.6, 130.2, 81.4, 81.3, 54.4, 54.4, 53.4, 53.3, 43.8, 41.9, 37.4, 37.3, 33.9, 33.9, 29.2; ^{31}P NMR (122 MHz, $CDCl_3$) δ 25.2 (br); HRMS: calcd for $C_{11}H_{16}O_6P$ (M+H)$^+$, 275.0679; found, 275.0685.

*Dimethyl (-8-Oxo-1-oxaspiro[4.5]dec-9-en-6-yl)phosphonate (**19b**).* Obtained by silica gel chromatography with EtOAc/hexane (1:1) as a colorless oil: 48.2 mg, 62% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (dd, J = 10.2, 4.6 Hz, 1H), 5.93 (d, J = 10.2 Hz, 1H), 4.13 (q, J = 7.5 Hz, 1H), 4.01 (m, 1H), 3.77 (d, J = 10.9 Hz, 3H), 3.71 (d, J = 10.9 Hz, 3H), 2.90 (m, 1H), 2.82−2.55 (m, 3H), 2.23−2.03 (m, 2H), 1.91 (m, 1H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 196.6, 196.5, 150.6, 150.5, 126.7, 78.7, 78.6, 68.9, 53.0, 53.0, 51.7, 51.6, 42.7, 40.8, 36.7, 36.6, 36.4, 36.3, 25.4.; ^{31}P NMR (122 MHz, $CDCl_3$) δ 27.9 (br); HRMS: calcd for $C_{11}H_{18}O_5P$ (M+H)$^+$, 261.0886; found, 261.0882.

*Ethyl Methyl (2,8-Dioxo-1-oxaspiro[4.5]dec-9-en-6-yl)-phosphonate (**19c**).* Obtained by silica gel chromatography with EtOAc/hexane (1:1) as a colorless oil: 50.2 mg, 55% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (dd, J = 10.1, 6.5 Hz, 1H), 6.09 (d, J = 10.1 Hz, 1H), 4.16 (m, 4H), 3.16 (m, 1H), 2.92 (m, 2H), 2.71 (m, 3H), 2.20 (m, 1H), 1.21 (q, J = 7.0 Hz, 6H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 195.9, 195.7, 175.3, 146.1, 146.0, 129.2, 79.2, 79.1, 63.4, 63.3, 61.7, 61.6, 42.9, 40.9, 35.7, 35.7, 32.4, 27.8, 16.4, 16.3, 16.2; ^{31}P NMR (122 MHz, $CDCl_3$) δ 22.6 (br); HRMS: calcd for $C_{13}H_{20}O_6P$ (M+H)$^+$, 303.0992; found, 303.0998.

*tert-Butyl ((3S,5S,10R)-10-(Dimethoxyphosphoryl)-2,8-dioxo-1-oxaspiro[4.5]dec-6-en-3-yl)-carbamate (**19d**).* Obtained by silica gel chromatography with EtOAc/hexane (1:1) as a white solid: 56.1 mg, 48% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (dd, J = 10.0, 7.2 Hz, 1H), 6.11 (d, J = 10.0 Hz, 1H), 5.62 (d, J = 8.5 Hz, 1H), 4.90 (q, J = 10.0 Hz, 1H), 3.86 (d, J = 10.9 Hz, 3H), 3.73 (d, J = 10.9 Hz, 3H), 3.10 (m, 1H), 2.96−2.61 (m, 5H), 1.45 (s, 9H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 195.3, 195.0, 173.6, 155.6, 144.7, 144.5, 129.7, 80.4, 76.1, 76.0, 54.3, 54.3, 51.9, 51.8, 49.1, 43.3, 41.4, 39.8, 35.4, 35.3, 28.2; ^{31}P NMR (122 MHz, $CDCl_3$) δ 25.2 (br); HRMS: calcd for $C_{16}H_{25}NO_8P$ (M+H)$^+$, 390.1312; found, 390.1315.

*Dimethyl (2,9-Dioxo-1-oxaspiro[5.5]undec-10-en-7-yl)-phosphonate (**19e**).* Obtained by silica gel chromatography with EtOAc/hexane (3:2) as a colorless oil: 40.6 mg, 47% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (dd, J = 10.2, 7.0 Hz, 1H), 6.04 (d, J = 10.2 Hz, 1H), 3.81 (d, J = 10.9 Hz, 3H), 3.73 (d, J = 10.9 Hz, 3H), 3.12−2.94 (m, 2H), 2.79−2.57 (m, 4H), 2.08−1.94 (m, 2H), 1.78 (dm, J = 14.2 Hz, 1H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 195.9, 195.7, 169.2, 144.6, 144.4, 128.4, 77.9, 77.8, 54.1, 54.0, 51.9, 51.8, 43.4, 41.4, 34.7, 34.7, 30.6, 29.5, 16.5; ^{31}P NMR (122 MHz, $CDCl_3$) δ 25.9 (br); HRMS: calcd for $C_{12}H_{18}O_6P$ (M+H)$^+$, 289.0836; found, 289.0840.

*Dimethyl (3′,4-Dioxo-3′H-spiro[cyclohex[2]ene-1,1′-isobenzofuran]-6-yl)phosphonate (**19f**).* Obtained by silica gel chromatography with EtOAc/hexane (3:2) as a white solid: 56.9 mg, 59% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97, (d, J = 7.6 Hz, 1H), 7.76, (td, J = 7.6, 1.0 Hz, 1H), 7.63, (t, J = 7.6 Hz, 1H), 7.41, (d, J = 7.6 Hz, 1H), 6.38 (dd, J = 10.0, 6.3 Hz, 1H), 6.24 (d, J = 10.0 Hz, 1H), 3.59 (d, J = 10.9 Hz, 3H), 3.58 (d, J = 10.9 Hz, 3H), 3.24−3.04 (c, 2H), 2.92 (m, 1H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 195.4, 195.2, 168.6, 150.7, 143.8, 143.7, 134.7, 130.9, 130.3, 126.1, 126.0, 121.6, 80.0, 79.9, 53.5, 53.4, 52.3, 52.2, 41.4, 39.5, 35.1, 35.1; ^{31}P NMR (122 MHz, $CDCl_3$) δ 23.3 (br); HRMS: calcd for $C_{15}H_{16}O_6P$ (M+H)$^+$, 323.0679; found, 323.0672.

*Dimethyl (2-Butyl-8-oxo-1-oxaspiro[4.5]dec-9-en-6-yl)-phosphonate (**19g**).* Obtained by silica gel chromatography with EtOAc/hexane (1:1) as an inseparable yellow oil mixture in a ratio (1:1), 56.9 mg, 60% yield; (**19g$_1$**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (dd, J = 10.3, 3.8 Hz, 1H), 5.95 (d, J = 10.2 Hz, 1H), 4.35 (m, 1H), 3.81 (d, J = 10.8 Hz, 3H), 3.73 (d, J = 10.8 Hz, 3H), 2.91−2.56 (m, 4H), 2.70 (m, 1H), 2.19 (m, 1H), 2.03−1.28 (m, 8H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 197.1, 196,6, 151.8, 151.1, 126.8, 81.0, 79.0, 78.2, 53.2, 52.9, 52.0, 51.5, 44.2, 42.2, 37.1, 37.0, 36.8, 36.3, 35.2, 31.0, 28.5, 13.9. ^{31}P NMR (122 MHz, $CDCl_3$) δ 28.1 (br); HRMS: calcd for $C_{15}H_{26}O_5P$ (M+H)$^+$, 317.1512; found, 317.1516.

(**19g$_2$**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (dd, J = 10.2, 5.5 Hz, 1H), 5.90 (d, J = 10.2 Hz, 1H), 3.85 (m, 1H), 4.08 (m, 1H), 3.78 (d, J = 10.8 Hz, 3H), 3.72 (d, J = 10.8 Hz, 3H), 2.91−2.56 (m, 4H), 2.19 (m, 1H), 2.03−1.28 (m, 8H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 196.9, 196.5, 151.7, 151.0, 126.1, 80.9, 78.9, 78.1, 53.1, 52.9, 51.9, 51.4, 42.6, 40.7, 37.0, 36.9, 36.8, 36.3, 31.3, 28.1, 22.7, 14.0. ^{31}P NMR (122 MHz, $CDCl_3$) δ 27.9 (br); HRMS: calcd for $C_{15}H_{26}O_5P$ (M+H)$^+$, 317.1512; found, 317.1516.

*Dimethyl (9-Oxo-1-oxaspiro[5.5]undec-10-en-7-yl)phosphonate (**19h**).* Obtained by silica gel chromatography with EtOAc/hexane (3/2) as a yellow oil: 35.0 mg, 43% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (dd, J = 10.4, 5.1 Hz, 1H), 6.02 (d, J = 10.4 Hz, 1H), 3.85 (m, 1H), 3.76 (d, J = 10.8 Hz, 3H), 3.70 (d, J = 10.8 Hz, 3H),3.69 (m, 1H), 2.94 (m, 1H), 2.74−2.52 (m, 3H), 1.80 (m, 3H), 1.61 (m, 1H), 1.49 (dt, J = 14.2, 4.1 Hz, 1H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 197.0, 196.8, 148.6, 148.4, 128.4, 70.4, 70.3, 63.0, 53.4, 53.4, 51.5, 51.4, 44.2, 42.3, 35.3, 35.2, 32.1, 32.1, 29.6, 29.6, 24.9, 19.0; ^{31}P NMR (122 MHz, $CDCl_3$) δ 28.8 (br); HRMS: calcd for $C_{12}H_{20}O_5P$ (M+H)$^+$, 275.1043; found, 275.1038.

*Dimethyl (2,2-Diethyl-8-oxo-1-oxaspiro[4.5]dec-9-en-6-yl)-phosphonate (**19i**).* Obtained by silica gel chromatography with EtOAc/hexane (1:1) as a yellow oil: 64.5 mg, 68% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73, (dd, J = 10.3, 2.1 Hz, 1H), 5.87 (d, J = 10.3 Hz, 1H), 6.24 (d, J = 10.0 Hz, 1H), 3.73 (d, J = 10.9 Hz, 3H), 3.70 (d, J = 10.9 Hz, 3H), 2.94 (m, 1H), 2.72−2.54 (m, 3H), 2.07−1.84 (m, 3H), 1.81−1.45 (m, 4H), 0.89 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 196.3, 196.2, 153.9, 153.8, 126.6, 89.3, 79.9, 79.8, 52.7, 52.6, 52.3, 52.2, 45.0, 43.1, 37.1, 37.1, 36.6, 36.5, 34.3, 30.7, 30.5, 9.0, 8.6; ^{31}P NMR (122 MHz, $CDCl_3$) δ 28.5 (br); HRMS: calcd for $C_{15}H_{26}O_5P$ (M+H)$^+$, 317.1512; found, 317.1510.

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*Dimethyl (2,2-Diethyl-9-oxo-1-oxaspiro[5.5]undec-10-en-7-yl)-phosphonate (**19j**).* Obtained by silica gel chromatography with EtOAc/hexane (1:1) as a white solid: 58.1 mg, 59% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12, (dd, J = 10.3, 7.2 Hz, 1H), 5.88 (d, J = 10.3 Hz, 1H), 3.78 (d, J = 10.9 Hz, 3H), 3.68 (d, J = 10.9 Hz, 3H), 3.10 (m, 1H), 2.83 (td, J = 13.3, 4.9 Hz, 1H), 2.54 (m, 1H), 2.42 (m, 1H), 1.87−1.40 (m, 9H), 0.81 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 198.2, 198.0, 151.2, 151.0, 126.7, 69.3, 69.3, 52.9, 52.8, 51.7, 51.6, 46.6, 44.7, 35.1, 35.0, 32.9, 32.1, 32.0, 27.9, 15.2, 7.9, 7.5; ^{31}P NMR (122 MHz, $CDCl_3$) δ 28.0 (br); HRMS: calcd for $C_{16}H_{28}O_5P$ (M+H)$^+$, 331.1669; found, 331.1679.

*Diethyl (2,2-Diethyl-8-oxo-1-oxaspiro[4.5]dec-9-en-6-yl)-phosphonate (**19k**).* Obtained by silica gel chromatography with EtOAc/hexane (1:1) as a yellow oil: 67.2 mg, 65% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74, (dd, J = 10.3, 2.8 Hz, 1H), 5.88 (d, J = 10.4 Hz, 1H), 4.12 (m, 4H), 2.96 (m, 1H), 2.66 (m, 3H), 2.59 (dt, J = 20.8, 4.0 Hz, 1H), 2.43 (m, 1H), 2.05−1.47 (m, 7H), 1.30 (t, J = 7.1 Hz, 6H), 0.75 (t, J = 7.4 Hz, 6H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 196.7, 196.6, 153.9, 153.8, 126.5, 89.1, 79.8, 79.8, 62.0, 61.9, 61.4, 61.3, 45.1, 43.2, 37.3, 37.2, 36.6, 36.5, 34.2, 30.9, 30.3, 16.3, 16.3, 16.3, 16.2, 9.1, 8.5; ^{31}P NMR (122 MHz, $CDCl_3$) δ 25.7 (br); HRMS: calcd for $C_{17}H_{30}O_5P$ (M+H)$^+$, 345.1825; found, 345.1829.

*Dimethyl (2,2-Dibutyl-8-oxo-1-oxaspiro[4.5]dec-9-en-6-yl)-phosphonate (**19l**).* Obtained by silica gel chromatography with EtOAc/hexane (1:1) as a yellow oil: 84.6 mg, 76% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74, (dd, J = 10.3, 2.3 Hz, 1H), 5.88 (d, J = 10.3 Hz, 1H), 3.74 (d, J = 10.9 Hz, 3H), 3.70 (d, J = 10.9 Hz, 3H), 2.94 (m, 1H), 2.73−2.54 (m, 3H), 2.10−1.86 (m, 3H), 1.78−1.42 (m, 3H), 1.31 (m, 9H), 0.92 (t, J = 7.5 Hz, 6H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 196.3, 196.2, 154.1, 154.0, 126.5, 88.7, 79.8, 79.7, 52.5, 52.4, 52.3, 52.2, 45.1, 43.2, 38.7, 38.3, 37.1, 37.1, 36.7, 36.6, 35.1, 27.0, 26.4, 23.2, 23.1, 14.0, 14.0; ^{31}P NMR (122 MHz, $CDCl_3$) δ 28.6 (br); HRMS: calcd for $C_{19}H_{34}O_5P$ (M+H)$^+$, 373.2138; found, 373.2141.

*Dimethyl (8-Hydroxy-2-oxo-1-oxaspiro[4.5]dec-9-en-6-yl)-phosphonate (**21a**).* Obtained by silica gel chromatography with EtOAc/hexane (1:1) as a white solid: 53.1 mg, 64% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (dd, J = 10.1, 1.3 Hz, 1H), 5.61 (ddd, J = 10.1, 5.4, 1.4 Hz, 1H), 4.15 (m, 1H), 3.78 (d, J = 10.9 Hz, 3H), 3.73 (d, J = 10.9 Hz, 3H), 2.80−2.55 (m, 3H), 2.34 (m, 2H), 2.10−1.85 (m, 2H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 175.9, 134.0, 129.4, 129.2, 80.7, 80.7, 65.2, 65.0, 53.5, 53.4, 52.2, 52.1, 41.7, 39.8, 32.9, 32.9, 30.8, 30.7, 28.1; ^{31}P NMR (122 MHz, $CDCl_3$) δ 33.2 (br); HRMS: calcd for $C_{11}H_{18}O_6P$ (M+H)$^+$, 277.0836; found, 277.0844.

*Dimethyl (8-Hydroxy-1-oxaspiro[4.5]dec-9-en-6-yl)phosphonate (**21b**).* Obtained by silica gel chromatography with EtOAc/hexane (1:1) as a white solid: 47.9 mg, 61% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (dd, J = 10.2, 3.1 Hz, 1H), 5.61 (d, J = 10.2 Hz, 1H), 4.08 (br, 1H), 4.00 (m, 2H), 3.74 (d, J = 10.9 Hz, 3H), 3.73 (d, J = 10.9 Hz, 3H), 2.83−2.55 (m, 3H), 2.33−2.17 (m, 2H), 2.06 (td, J = 10.8, 3.5 Hz, 1H), 1.99−1.96 (m, 1H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 133.1, 133.0, 129.4, 79.7, 79.6, 68.1, 64.0, 63.8, 52.4, 52.3, 40.8, 38.9, 37.8, 37.7, 31.5, 31.5, 25.3; ^{31}P NMR (122 MHz, $CDCl_3$) δ 28.8 (br); HRMS: calcd for $C_{11}H_{20}O_5P$ (M+H)$^+$, 263.1043; found, 263.1040.

*Dimethyl 5-Hydroxy-2,2-dimethoxycyclohex-3-enylphosphonate (**22**).* Obtained by silica gel chromatography with EtOAc/hexane (3:2) as a colorless oil (30.2 mg) and was spontaneously transformed into **23** in 46% overall yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (ddd, J = 10.4, 3.9, 1.4 Hz, 1H), 6.12 (dt, J = 10.4, 1.4 Hz, 1H), 4.73 (d, J = 11.4 Hz, 1H), 4.13 (Br, 1H), 3.79 (d, J = 10.6 Hz, 3H), 3.75 (d, J = 10.6 Hz, 3H), 3.34 (s, 3H), 3.20 (s, 3H), 2.60 (dm, J = 21.7 Hz, 1H), 2.52−2.23 (c, 2H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 133.9, 126.8, 97.0, 97.0, 62.1, 62.1, 53.9, 53.8, 51.9, 51.8, 50.8, 48.9, 48.8, 48.5, 36.8, 34.9, 29.8, 29.7; ^{31}P NMR (122 MHz, $CDCl_3$) δ 33.6 (br).

*Dimethyl 5-Hydroxy-2-oxocyclohex-3-enylphosphonate (**23**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 6. 99 (m, 2H), 6.03 (dd, J = 10.2, 1.2 Hz, 1H), 4.84 (m, 1H), 4.38 (q, J = 4.6 Hz, 1H), 3.82−3.70 (c, 12H, several d), 3.21 (ddd, J = 26.2, 6.0, 4.1 Hz, 1H), 3.05 (dt, J = 26.2, 5.9 Hz, 1H), 2.66−2.14 (c, 4H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 192.4, 192.3, 192.3, 192.2, 153.9, 150.9, 128.7, 128.6, 128.4, 63.2, 63.1, 62.5, 62.4, 54.4, 54.3, 53.5, 53.4, 53.2, 53.1, 45.1, 44.9, 43.4, 43.1, 32.7, 32.7, 31.0, 30.9; ^{31}P NMR (122 MHz, $CDCl_3$) δ 27,2 (br), 25,1 (br); HRMS: calcd for $C_8H_{14}O_5P$ (M+H)$^+$, 221.0573; found, 221.0583.

*Dimethyl 2-(3-Hydroxypropyl)-5-oxocyclohex-2-enylphosphonate (**24**).* Zinc (3 mmol, 10 equiv) was added to a stirred solution of **19b** (0.3 mmol, 1 equiv) in MeOH (1 mL) and acetic acid (1 mL). The reaction was stirred for 1 h. The mixture was filtered on Celite, concentrated under vacuum, and purified by silica gel chromatography with EtOAc followed by EtOAc/MeOH (95:5) to furnish **24** as a colorless oil: 54.8 mg, 70% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5. 74 (s, 1H), 3.75 (d, J = 10.2 Hz, 3H), 3.71 (d, J = 10.2 Hz, 3H), 3.68 (m, 2H), 2.96 (m, 2H, several d), 2.75 (ddd, J = 16.3, 9.8, 1.5 Hz, 1H), 2.64 (dd, J = 16.3, 9.8 Hz, 1H), 2.53 (dd, J = 16.3, 7.4 Hz), 2.42 (m, 1H), 1.79 (m, 4H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 207.3, 207.2, 133.5, 133.4, 122.0, 121.9, 61.3, 53.3, 53.2, 52.9, 52.8, 39.2, 39.1, 39.1, 38.7, 38.6, 37.2, 31.7, 30.0; ^{31}P NMR (122 MHz, $CDCl_3$) δ 29,5 (br); HRMS: calcd for $C_{11}H_{20}O_5P$ (M+H)$^+$, 263.1043; found, 263.1053.

*Dimethyl 1,2,3,4-Tetrahydro-1,1-dimethoxy-4-oxonaphthalen-2-yl-2-phosphonate (**27**).* Iodobenzene diacetate (0.9 mmol, 3 equiv in 1.5 mL of MeOH) was added to a vigorously stirred solution of Napht-1-ol (0.3 mmol, 1 equiv) in MeOH (1.5 mL) at 0 °C. The mixture was then stirred for 10 min, and then phosphite (8 equiv) was added. The mixture was then stirred for a further 30 min (followed by TLC) and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of ethyl acetate/hexane (7:3) to give enone **27** as a white solid: 52.7 mg, 56% yield; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.94 (dd, J = 7.8, 1.4 Hz, 1H), 7.83 (dd, J = 7.8, 1.4 Hz, 1H), 7.67 (td, J = 7.8, 1.4 Hz, 1H), 7.53 (td, J = 7.8, 1.4 Hz, 1H), 3.53 (d, J = 10.8 Hz, 3H), 3.51 (s, 3H), 3.34 (ddd, J = 18.5, 6.9, 2.0 Hz, 1H), 3.29 (d, J = 10.8 Hz, 3H), 3.16 (c, 1H), 2.90 (s + m, 4H); ^{13}C {^{1}H} NMR (75 MHz, acetone-d_6) δ 195.7, 141.2, 134.2, 134.0, 130.8, 128.5, 128.1, 99.1, 99.0, 53.6, 53.6, 53.4, 53.4, 50.2, 50.2, 50.0, 42.5, 40.6, 38.4, 38.4; ^{31}P NMR (122 MHz, $CDCl_3$) δ 26.8 (br); HRMS: calcd for $C_{14}H_{20}O_6P$ (M+H)$^+$, 315.0992; found, 315.0998.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b03324.

^{1}H and ^{13}C NMR spectral data of all compounds. (PDF)

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Notes

The authors declare no competing financial interest.

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(10) See ^{1}H NMR spectrum in the Supporting Information (SI). The stereoselectivity was determined by NMR including nuclear Overhauser effect (NOE) experiments.

(11) The presence of hindered phosphites slow down the reaction kinetics, leading to the formation of undesired aromatics due to the acidity of HFIP. The phosphite addition on dienone **18** can be performed in two steps in the same alcohol compared to the phosphite used; see SI.

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1.5 Conclusion

En somme, nous avons développé des procédures expérimentales permettant la transformation de phénols bon marché en différents dérivés phosphorylés dans un même pot. Ces transformations ont été possibles grâce à une désaromatisation du phénol, par un réactif à base d'iode hypervalent suivi de l'ajout d'un phosphite à titre de donneur de Michael. Ces composés polyfonctionnalisés pourraient être potentiellement utilisés comme intermédiaires clefs dans la synthèse d'architectures complexes comme les alcaloïdes

1.6 Informations supplémentaires

Les informations supplémentaires contenant les spectres RMN, sont présentées à l'Annexe A

CHAPITRE 2

DEVELLOPEMENT D'UNE MÉTHODE D'AZIRIDINATION ARYLANTE

2.1 Introduction

Les aziridines[4] sont de petits hétérocycles qui peuvent être utilisés pour produire une variété de structures plus complexes, y compris des produits naturels. Avec les époxydes[21] et les cyclopropanes[22] ils représentent les systèmes cycliques à trois chaînons les plus importants. Par conséquent, ils ont attiré l'attention de la communauté synthétique, et plusieurs processus ont été décrits dans la littérature. J. B. Sweeney[23], a élaboré en 2002, l'éventail de différentes méthodes de synthèse des aziridines, **Schéma 2.1**.

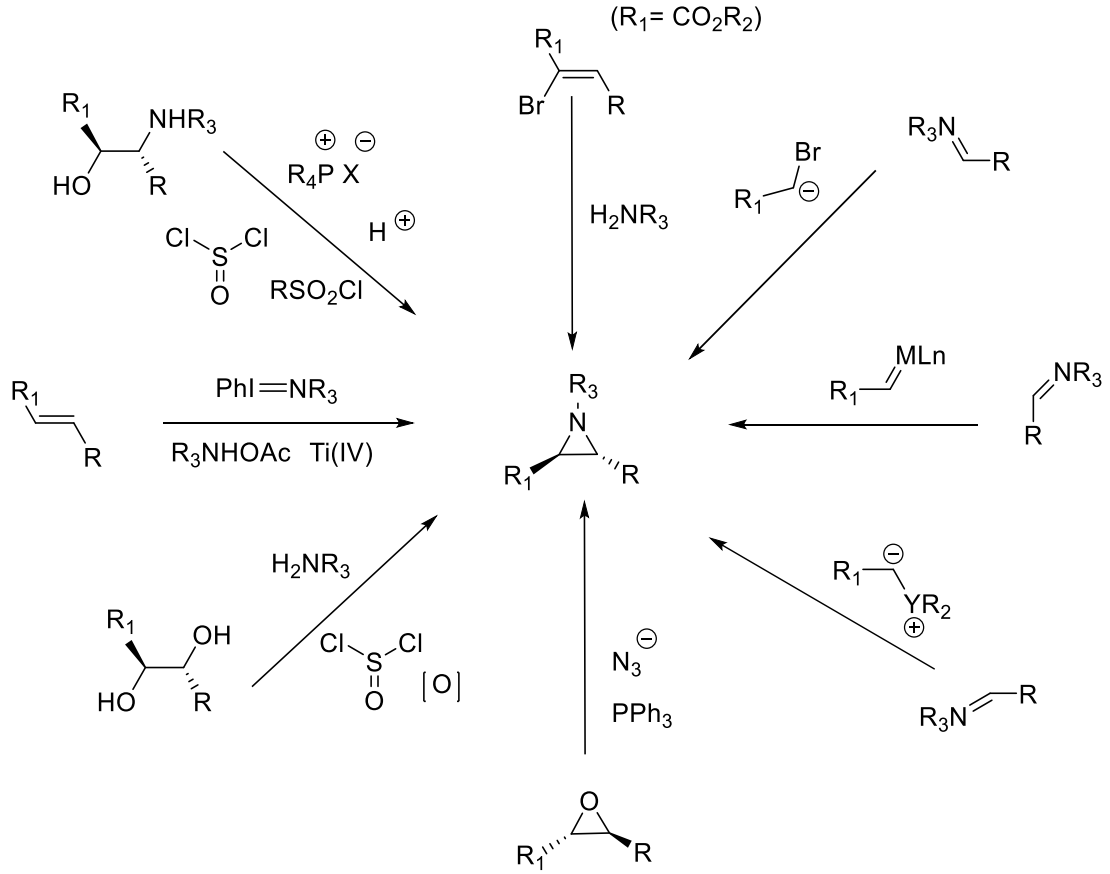

Schéma 2.1 : Différentes méthodes de synthèse des aziridines

2.2 Conceptualisation

Ce travail fait suite à celui effectué au sein de notre laboratoire sur le développement de nouveaux procédés permettant la formation rapide d'hétérocycles fonctionnalisés favorisés par un procédé en tandem Michael – Smiles[24] ainsi qu'à leur extension aux systèmes halogèno-diénones pour donner des cyclopropanes. Le procédé en tandem Michael-Smiles (**Schéma 2.2**) implique une déprotection-migration du groupement nosyle qui va être rattaché par la suite à la molécule. Au cours de ce processus, on observe une réaction non désirée de rétro-Michael, dû à la présence de l'hydrogène très labile en *alpha* du carbonyle dans **30**. Ces composés obtenus pourraient être utilisés comme intermédiaire pour la synthèse totale de molécules naturelles. Cependant, on constate que le groupement aryle se retrouve du côté opposé du cycle pipéridine ou pyrolidine Ce groupement aryle est à l'origine de la formation d'un noyau indolique à la suite d'une réduction subséquente. Malheureusement, le noyau indolique et le cycle pipéridine ou pyrrolidine se trouve généralement du même côté dans la plupart des molécules cibles. Malheureusement, la structure obtenue lors de la formation de **31** via la réaction de rétro-Michael puis aza-Michael sur l'autre double liaison n'est pas présente dans les structures connues de produits naturels. Afin de pouvoir atteindre plus facilement ces molécules cibles, il faudrait bloquer le processus de rétro-Michael afin d'obtenir des intermédiaires de type **30** plus présent dans de nombreux alcaloïdes naturels.

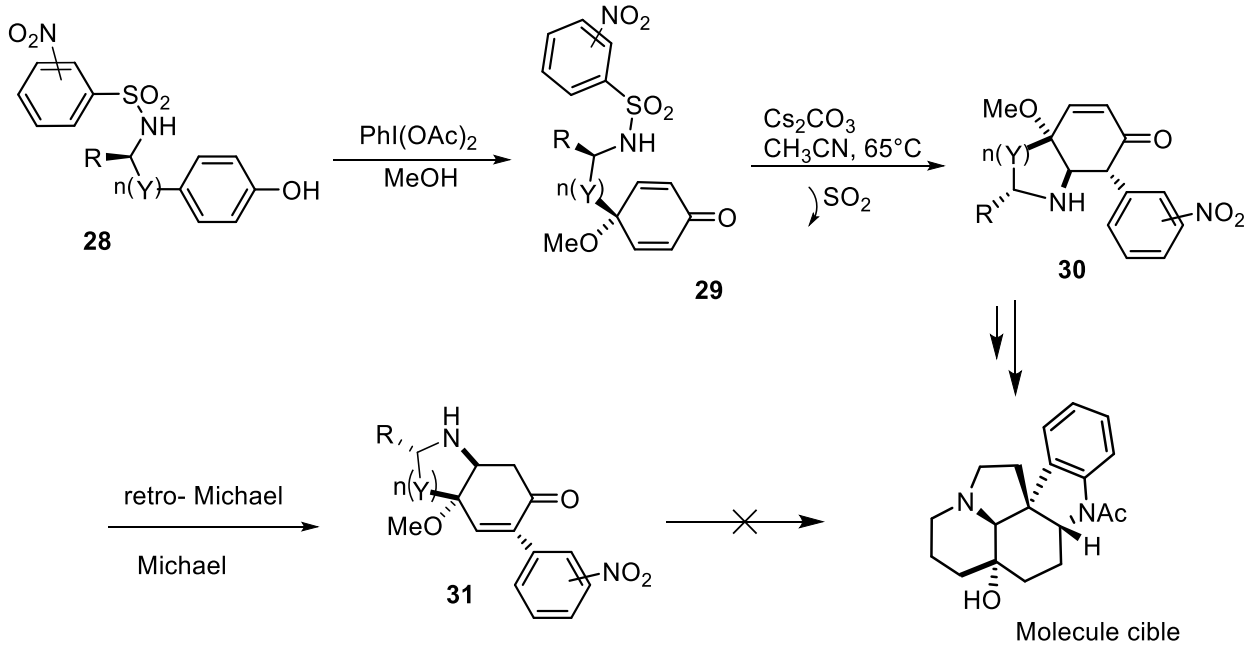

Schéma 2.2 : Travaux préliminaire de Coulibali et Coll

2.3 Synthèse des aziridines

Encouragés par les résultats de Coulibali et Coll, nous avons décidé d'empêcher le processus de rétro-Michael en introduisant au départ du phénol des halogènes pour produire des aziridines. Ces hétérocycles ont été produits à partir de diénones réactives qui ont été facilement obtenues en une seule étape à partir de phénols simples en présence de (diacétoxyiodo) benzène (DIB), un réactif à l'iode hypervalent peu toxique pour l'environnement, en utilisant un procédé développé par Kita et ses collègues en 1987. Cette première approche a largement inspiré la communauté scientifique et conduit au développement de nouvelles méthodologies[25] et leurs applications dans la synthèse totale de produits naturels[26] à base d'iode hypervalent. Dans ce travail, nous présentons les résultats préliminaires décrivant la formation rapide de composés polyfonctionnalisés contenant une aziridine substituées à partir de phénols simples en deux étapes, **Schéma 2.3**.

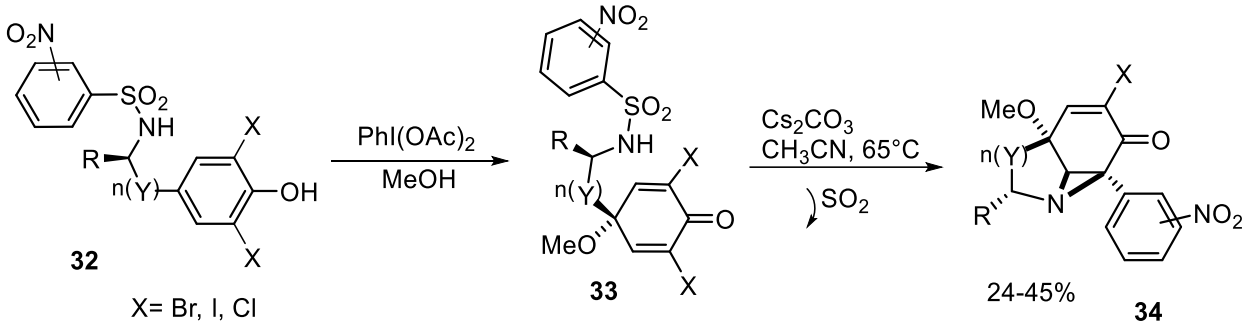

Schéma 2.3 : Formation d'aziridines

2.4 Article 'an arylative aziridination process toward aspidosperma alkaloids'

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Auteurs: Kouassi Signo. Elsa Deruer, Siomenan Coulibali et Sylvain Canesi

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AN ARYLATIVE AZIRIDINATION PROCESS TOWARD ASPIDOSPERMA ALKALOIDS[1]

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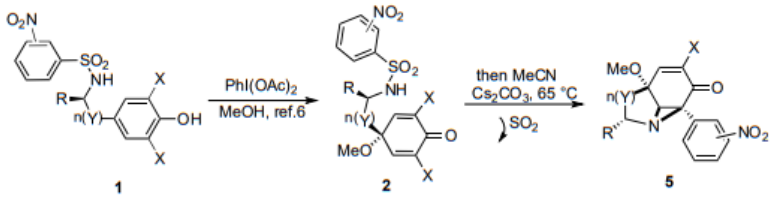
Abstract – An arylative aziridination process has been developed from dibrominated phenols containing a Fukuyama sulfonamide on the lateral chain. A two-step procedure involving the formation of a dienone by a phenol oxidation reaction mediated by a hypervalent iodine reagent (Kita reaction) followed by an intramolecular arylative aziridination process was used. This second step occurred under mild conditions via a Michael–Smiles ring-closure cascade, producing sulfur dioxide as the only byproduct. Additionally, a stereoselective approach was observed with tyrosine derivatives. This transformation respects the rules of green chemistry and atom economy. These new polyfunctionalized scaffolds could offer several synthetic possibilities for the total synthesis of natural products such as the main core of *Aspidosperma* alkaloids.

Aziridines[1a-f] are small heterocycles that can be used to produce a variety of more complex structures, including natural products. With epoxides[1g] and cyclopropanes,[1h] they represent the most important three-membered ring systems.[1] Therefore, they have attracted the attention of the synthetic community and several processes have been described in the literature. Currently, the consensus is that sustainable, environmentally benign routes to desirable synthetic targets should be atom economical and free of protecting groups[2] to respect the concept of "green chemistry." With this idea in mind, we were recently interested in the development of new processes enabling the rapid formation of functionalized heterocycles promoted by a Michael–Smiles tandem process[3] as well as their extension to halogen-dienone systems to yield cyclopropanes.[4] Encouraged by these results, we decided to extend this approach to a nitrogen nucleophile to yield aziridines. These heterocycles were produced from reactive dienones that were readily

[1] This paper is respectfully dedicated to Professor Yasuyaki Kita in honor of his 77th birthday.

obtained in one step from simple phenols in the presence of (diacetoxyiodo)benzene, an environmentally benign hypervalent iodine reagent,[5] using a process developed by Kita and coworkers in 1987.[6] This first approach has largely inspired the scientific community and led to the further development of innovative methodologies[7] and their applications in the total synthesis of natural products[8] based on hypervalent iodine chemistry. In this short paper, we present preliminary results describing the rapid formation of polyfunctionalized scaffolds containing an aziridine moiety from simple phenols in two steps. The first step involved an oxidative dearomatization process and a subsequent Michael–Smiles ring-closure cascade to produce polyfunctionalized arylated aziridines. One characteristic of the Truce–Smiles rearrangement[9] is its capacity to redesign a simple structure into a more elaborate one under mild conditions with only sulfur dioxide as the byproduct. Undeniably, this old reaction has a good potential to further develop current green chemistry methodologies. This transformation enabled us to produce the synthesis of complex structures **5** in one step from dienones **2** or in two steps from phenols **1**. Encouraging, preliminary results were obtained with tyramine and tyrosineprecursors (Scheme 1). Different lateral chains and electron-poor sulfonamides were preliminarilyinvestigated. A methoxy group was first introduced to dearomatize phenols **1**.[6] It should be noted that the nosyl group acts as a functional protecting group.[10] Indeed, as an activating group, it enabled the arylative-aziridination process and as a protecting group, it prevented the amino segment to be oxidizedby the iodane during the formation of dienone **2**. By this method, scaffolds containing pyrrolidine **5a** orpiperidine **5b** were rapidly obtained. Each nosylamide **5a**, **5d** or **5e** appeared to be a competent substrate for this transformation. Furthermore, a stereoselective approach was developed with the tyrosinederivative **1c** or **1f**, leading to **5c** or **5f**, respectively and only one diastereomer was observed by 300-MHz NMR. It should be noted that a dienone desymmetrization process mediated by a thiourea cinchonine catalyst could potentially lead to an enantioselective version of this process.[11] We investigated different halides as nucleofuges; however it appeared that bromine was the halide of choice for this transformation. Indeed, lower yields were observed with iodine **5h** and chlorine **5i**. These results demonstrated that thefinal S_N2 reaction was probably not the limiting step. Some examples are depicted in Table 1.



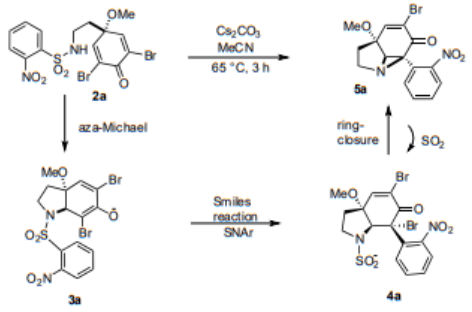
Scheme 1

Table 1. Arylative aziridination process

entry	n	X	Y	NO_2	R	yield[a] (%)	yield[b] (%)
5a	1	Br	CH_2	*ortho*	H	61	42
5b	2	Br	CH_2	*ortho*	H	54	37
5c	1	Br	CH_2	*ortho*	CO_2Me	41	30
5d	1	Br	CH_2	*ortho-para*	H	61	42
5e	1	Br	CH_2	*para*	H	57	40
5f	1	Br	CH_2	*ortho*	CH_2OTBS	N.D.	39
5g	1	Br	O-CH_2	*ortho*	H	N.D.	45
5h	1	I	CH_2	*ortho*	H	N.D.	24
5i	1	Cl	CH_2	*ortho*	H	N.D.	31

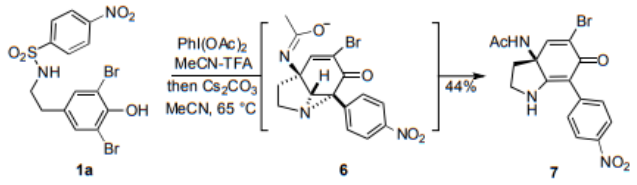
[a] Yields observed from dienone **2**; N.D., Not Determined.
[b] Yields obtained directly from phenol **1** (over 2 steps).

From a mechanistic point of view, this approach involves an aza-Michael process producing enolate **3**, which triggers the Truce–Smiles rearrangement and the loss of sulfur dioxide as the only byproduct. The aryl migration during the Smiles rearrangement occurred with retention of the configuration. Consequently, the released amine was ideally placed for an antiperiplanar attack on the tertiary alkyl halide by an S_N2-type process. Such intramolecular S_N2 reactions are possible due to neighboring allylic double bonds and similar examples are reported in the literature.[12] The formation of dienone **2** by oxidation of phenol **1** was accompanied by an amount of intermediate **3** that was also a competent substrate for the second step, leading to the formation of compound **5**. Therefore, we decided to use crude dienone **2** for the next step in order to have a higher overall yield and good reproducibility. Although the global yield obtained for this two-step procedure was moderate (24–45%), it should be noted that the highly functionalized core **5** was rapidly obtained from inexpensive phenols **1** under mild conditions. Multiple transformations occurring during this procedure could explain both the moderate yield observed as well as the structure complexity produced. Although a moderate yield was observed, the crude NMR described mainly the desired product. Most probably byproducts were very polar compounds or polymers removed during the work-up. A proposed mechanism for the Michael–Smiles ring-closure cascade is depicted in Scheme 2.



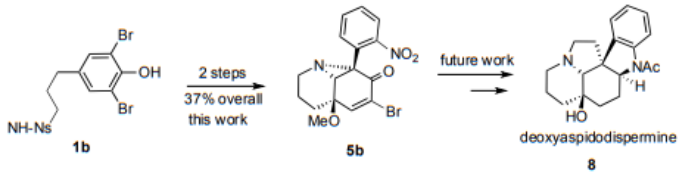
Scheme 2

This process was extended with the introduction of an acetamide as decribed by Ciufolini and coworkers[12] instead of a methoxy group at the former *para* position of phenol **1**. Interestingly, the conjugated enamine **7** was observed in 44% overall yield. We suppose that the expected aziridine was probably the intermediate **6**, which was further opened by the assistance of the neighboring basic as presented in Scheme 3.



Scheme 3

It should be noted that compound **5b** is a quite functionalized heterocycle that could be used as a potential precursor for the synthesis of *Aspidosperma* alkaloids such as deoxyaspidodispermine **8**[14] (Scheme 4).



Scheme 4

In conclusion, a new stereoselective arylative aziridination method has been developed on dienone systems easily produced from phenols using a hypervalent iodine reagent and a one-pot multistep Michael–Smiles ring-closure cascade process. This approach occurs under mild conditions and releases only sulfur dioxide as the byproduct. The scaffolds obtained represent the main core of alkaloids belonging to some *Aspidosperma* family members and we are currently developing this process for their total synthesis.

EXPERIMENTAL

Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are reported in ppm on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, etc.), t (triplet), q (quartet), p (pentuplet), m (multiplet) and further qualified as app (apparent) br (broad) c (complex).

Coupling constants, *J*, are reported in Hz. IR spectra (cm−1) were recorded from thin films. Mass spectra (m/e) were measured in the electrospray (ESI) mode.

General procedure for the formation of Phenol (1):

a) Nosylation: Sodium bicarbonate (2.0 mmol, 2 equiv.) was added to a solution of tyramine (1.0 mmol, 1 equiv.) in THF/H_2O (2:2 mL) at 0 °C and then nitrobenzenesulfonyl chloride (1.1 mmol, 1.1 equiv.) was added. The mixture was then stirred for 3 h and then a solution of sat. aq. NH_4Cl was added. The aqueous phase was extracted with EtOAc and the organic layer was dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of EtOAc−hexane.

b) Dibromation: NBS (1.26 mmol, 2.1 equiv.) was added to a solution of the corresponding nosylamide-phenol (0.6 mmol, 1 equiv.) in DCM (5 mL) at 0 °C. The mixture was then stirred for 3 h and then a solution of sat. aq. $Na_2S_2O_3$ was added and extracted with EtOAc. The organic layer was dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of EtOAc−hexane.

General procedure for the formation of dienones (2).[6] To a stirred solution of phenols (0.1 mmol) in MeOH (1 mL) at 20 °C was added $PhI(OAc)_2$ ("DIB" 1.2 equiv.) dissolved in MeOH (0.5 mL), over 10 s. The reaction was stirred for 2-3 min and concentrated under vacuum. For the isolation of dienone **2**: the crude was purified by chromatography (hexane−EtOAc as required). For the two step-procedure enabling to transform intermediate **2** into **5**. The crude was rapidly filtrated on a small pad of silica gel with EtOAc then concentrated and the residue was used without further purification.

General procedure for the aziridine formation (5). To a solution of dienone (0.095 mmol, 1.0 equiv.) in MeCN (2.0 mL) was added cesium carbonate (3.0 equiv.). Then, the reaction was stirred overnight at 65 °C, the reaction was followed by TLC (2-3 h). After completion, the mixture was filtered through a pad of silica with EtOAc and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of EtOAc–hexane to afford **5**.

Formation of enamine (7).[13] To a stirred solution of phenol **1a** (0.05 mmol) in MeCN (1 mL) at 0 °C was added TFA (0.065 mmol, 1.3 equiv.) and $PhI(OAc)_2$ (0.06 mmol, 1.2 equiv.). The reaction was stirred for 5 min and rapidly filtered on a small pad of silica gel with EtOAc then concentrated and the residue was used without further purification. The same procedure for the formation of aziridine (**5**) was further used.

5-Bromo-1,2,3,3a-tetrahydro-3a-methoxy-7-(2-nitrophenyl)indol-6-one (5a). This compound was obtained as yellow oil, 42% yield over two steps; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 8.1 Hz, 1H),

7.91 (d, *J* = 8.1 Hz, 1H), 7.68 (t, *J* = 8.1 Hz, 1H), 7.49 (t, *J* = 8.1 Hz, 1H), 7.37 (s, 1H), 3.59 (m+s, 4H), 3.19 (s, 1H), 2.86-2.64 (m, 2H), 2.2 (dd, *J* = 12.3 Hz, 4.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.7, 150.0, 146.5, 134.3, 133.9, 133.3, 129.1, 124.4, 123.9, 83.9, 59.7, 55.9, 53.8, 47.5, 46.7; HRMS (ESI): Calc. for $C_{15}H_{14}N_2O_4Br$ $(M+H)^+$: 365.0131; found: 365.0133.

6-Bromo-2,3,4,4a-tetrahydro-4a-methoxy-8-(2-nitrophenyl)quinolin-7(1*H*)-one (5b). This compound was obtained as an orange oil, 37% yield over two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.1 Hz, 1.2 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.68 (td, *J* = 8.1 Hz, 1.2 Hz, 1H), 7.50 (dd, *J* = 8.1 Hz, 1.2 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1.2 Hz, 1H), 3.51 (s+m, 4H), 2.88 (m, 2H), 2.0-1.66 (c, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.7, 151.6, 147.3, 134.3, 133.9, 132.5, 129.1, 126.0, 124.6, 73.5, 53.2, 50.8, 47.4, 39.5, 19.2; HRMS (ESI): Calc. for $C_{16}H_{16}NO_4Br$ $(M+H)^+$: 379.0288; found: 379.0280.

(2*R*,31*S*,6a*S*)-Methyl 5-bromo-6a-methoxy-3a-(2-nitrophenyl)-4-oxo-1,2,31,3a,4,6a-hexahydro-azirino[2,3,1-*hi*]indole-2-carboxylate (5c). This compound was obtained as an yellow oil, 30% yield over two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.3 Hz, 1H), 7.98 (d, *J* = 7.2 Hz, 1H), 7.71 (t, *J* = 7.3 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.40 (s, 1H), 3.85 (s, 3H), 3.55 (s+m, 4H), 3.31 (s, 1H), 3.05 (t, *J* = 12.4 Hz, 1H), 2.52 (dd, *J* = 12.6 Hz, 5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.8, 171.0, 149.8, 134.5, 133.9, 133.8, 129.6, 124.7, 83.7, 60.0, 59.5, 56.1, 53.7, 53.0, 50.9, 31.0, 29.8; HRMS (ESI): Calc. for $C_{17}H_{16}BrN_2O_6$ $(M+H)^+$: 423.0186; found: 423.0174.

5-Bromo-1,2,3,3a-tetrahydro-3a-methoxy-7-(2,4-dinitrophenyl)indol-6-one (5d). This compound was obtained as an orange oil, 42% yield over two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.48 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.41 (s, 1H), 3.77-3.41 (m+s, 4H), 3.25 (s, 1H), 2.90-2.51 (m, 2H), 2.21 (dd, *J* = 15.1 Hz, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.2, 150.9, 147.8, 140.7, 135.4, 127.8, 123.6, 120.2, 84.3, 60.4, 55.0, 53.8, 47.4, 47.0, 29.4; HRMS (ESI): Calc. for $C_{15}H_{13}BrN_3O_6$ $(M+H)^+$: 409.9982; found: 409.9969.

5-Bromo-6a-methoxy-3a-(4-nitrophenyl)-1,3^1,3a, 6a-tetrahydroazirino-[2,3,1-*hi*]indol-4(2*H*)-one (5e). This compound was obtained as a pale yellow oil, 40% yield over two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 8.20 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.48 (s, 1H), 3.69 – 3.61 (m, 1H), 3.59 (s, 3H), 3.28 (s, 1H), 2.83 (dd, *J* = 12.3, 8.0 Hz, 1H), 2.70 (td, *J* = 12.6, 4.4 Hz, 1H), 2.24 (dd, *J* = 12.1, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) : 185.40, 151.6, 147.5, 144.6, 129.1, 124.3, 123.4, 84.1, 62.2, 55.4, 54.1, 47.0, 46.9. HRMS (ESI): Calc. for $C_{15}H_{14}BrN_2O_4$ $(M+H)^+$: 365.0131; found: 365.0128.

5-Bromo-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-6a-methoxy-3a-(2-nitrophenyl)-1,31,3a,6a-tetrahydroazirino[2,3,1-*hi*]indol-4(2*H*)-one (5f). This compound was obtained as a colorless oil, 39% yield over two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 7.2 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.39 (s, 1H), 3.96 (dd, *J* = 8.4, 4.6, 1H), 3.81 (dd, *J* = 10.1, 5.8, 1H), 3.57 (s, 3H), 3.24 (s, 1H), 3.16 – 3.00 (m, 1H), 2.56 (t, *J* = 11.9 Hz, 1H), 2.31 (dd, *J* = 8.0,

4.5, 1H), 0.93 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 150.3, 146.5, 134.4, 129.1, 127.2, 124.3, 123.9, 133.8, 83.8, 66.1, 60.7, 59.5, 55.7, 52.9, 50.4, 25.8, 18.3, -5.1, -5.2.

5-Bromo-6a-methoxy-3b-(2-nitrophenyl)-2,3,3b,6a-tetrahydro-1-oxa-3a-azacyclopropa[*de*]naphthalen-4(3a1*H*)-one (5g). This compound was obtained as a yellow oil, 45% yield over two steps;^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 8.2 Hz, 1H), 7.95 (s, 1H), 7.73 (t, J = 7.5Hz, 1H), 7.56 (t, J = 7.1 Hz, 1H), 7.30 (d, J = 2.1 Hz, 1H), 4.14 (dd, J = 8.4, 2.9, 2H), 3.64 – 3.39 (m+s, 4H), 3.13 – 2.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.5, 147.6, 134.0, 133.4, 132.8, 132.2, 129.5, 129.4, 124.8, 91.5, 63.5, 49.6, 46.7, 45.0, 41.4.

5-Iodo-1,2,3,3a-tetrahydro-3a-methoxy-7-(2-nitrophenyl)indol-6-one (5h). This compound was obtained as a yellow solid, 24% yield over two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.77 – 7.63 (s+t, J = 8.1 Hz, 2H), 7.51 (t, J = 8.1 Hz, 1H), 3.67 – 3.46 (m+s, 4H), 3.23 (s, 1H), 2.87 – 2.59 (m, 2H), 2.20 (dd, J = 11.6, 4.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.7, 158.4, 146.8, 134.7, 133.7, 133.4, 129.1, 124.6, 102.6, 84.9, 59.4, 56.1, 52.1, 47.3, 46.5.

5-Chloro-1,2,3,3a-tetrahydro-3a-methoxy-7-(2-nitrophenyl)indol-6-one (5i). This compound was obtained as a yellow oil, 31% yield over two steps; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 7.1 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.52 (t, J =7.1, 1H), 7.13 (s, 1H), 3.70 – 3.47 (m, 4H), 3.22 (s, 1H), 2.94 – 2.64 (m, 2H), 2.23 (dd, J = 11.8, 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.9, 148.6, 145.4, 134.4, 134.0, 133.4, 133.1, 129.3, 124.4, 83.2, 60.0, 55.9, 54.5, 47.8, 46.8.

***N*-(5-Bromo-7-(4-nitrophenyl)-6-oxo-2,3,3a,6-tetrahydro-1*H*-indol-3a-yl)acetamide (7).** This compound was obtained as a yellow solid, 42% yield over two steps; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.17 (d, J = 7.0 Hz, 2H), 8.13 (br, 1H), 8.02 (br, 1H), 7.82 (s, 1H), 7.66 (d, J = 9.0 Hz, 2H), 3.76 (td, J = 10.5, 6.0 Hz, 1H), 3.65 (m, 1H), 3.00 (m, 1H), 2.06 (m, 2H), 1.92 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 174.2, 167.6, 165,4, 146.2, 142.7, 138.1, 130.4, 128.0, 123.4, 102.8, 61.9, 44.5, 32.8, 22.4.

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2.5 Conclusion

Une nouvelle méthode d'aziridination arylatnte stéréosélective a été développée sur des diénones facilement produits à partir de phénols à l'aide d'un réactif à l'iode hypervalent puis d'une réaction d'aza-Michael-Smiles et fermeture de cycle en cascade. Cette approche se produit dans des conditions douces et ne libère que du dioxyde de soufre comme sous-produit. Les produits obtenus représentent le noyau principal d'alcaloïdes appartenant à certains membres de la famille des aspidosperma. L'idée de bloquer le processus de rétro-Michael en introduisant des halogènes au départ du phénol a été un facteur important pour la synthèse des aziridines dans un premier temps et pour l'obtention d'un produit naturel qui est décrit dans le chapitre suivant.

2.6 Informations supplémentaires

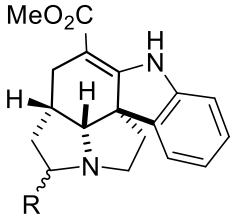
Les informations supplémentaires contenant les spectres RMN, sont présentées à 1 'Annexe B

CHAPITRE 3

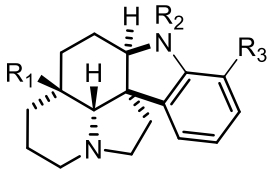
SYNTHÈSE TOTALE DE LA DEOXYASPIDODISPERMINE VIA UN GROUPEMENT PROTECTEUR FONCTIONNEL

3.1 Introduction

À la suite des travaux réalisés par notre équipe, sur la synthèse des aziridines[27] nous avons constaté qu'ils représentent des précurseurs pour la synthèse totale de plusieurs molécules naturelles notamment, celles de la famille des aspidospermines[5] et des ibophyllidines[28], **Figure 3.1**. Nous avons continué nos investigations nous menant à la synthèse de la deoxyaspidodispermine, qui a été isolée *d'aspidosperma dispermum*[29] par Djerassi et ses collaborateurs en 1968. L'aspidospermidine est un alcaloïde isolé des plantes du genre Aspidosperma[30] et représente le noyau principal de plusieurs structures biologiques. À notre connaissance, la synthèse de la désoxyaspidodispermine a été rapportée dans la littérature par Ban et Coll[31]. De plus, l'aspidodispermine[32] qui est un produit naturel presque identique à la deoxyaspidodispermine, a été synthétisé en 2020 par Heretsch et Reuß, **Figure 3.1**.



35, R = *a*-Et, ibophyllidine
36, R = *ß*-Et, 20-epi-ibophyllidine
37, R = H, desethylibophyllidine



38, R_1 = Et, R_2, R_3 = H, aspidospermidine
39, R_1, R_3 = OH, R_2 = Ac, aspidodispermine
40, R_1 = OH, R_2 = Ac, R_3 = H, deoxyaspidodispermine

Figure 3.1 : Famille d'alcaloïdes ibophyllidine et aspidosperma

En 2019, Orru et coll[5] ont publié une revue qui présente un aperçu complet de toutes les synthèses totales d'Aspidosperma et alcaloïdes de Strychnos qui suivent une stratégie de désaromatisation d'indoles sur les 65 dernières années. Le dérivé de tryptamine **41** et l'aldéhyde **42** ont été activés par BF_3•OEt_2 comme catalyseur acide de Lewis dans du toluène chauffé au reflux. Après une première réaction de Pictet-Spengler, l'énamine résultante subit un réarrangement [3,3]-sigmatropique. Ce système tricyclique peut maintenant subir une réaction de Pictet-Spengler après déprotection de l'acétal ce qui constitue un précurseur pour de

nombreuses cibles. Kuehne et al. ont utilisé cette approche pour une synthèse asymétrique de (-)-strychnine en partant d'un dérivé tryptophane, **Schéma 3.1.**

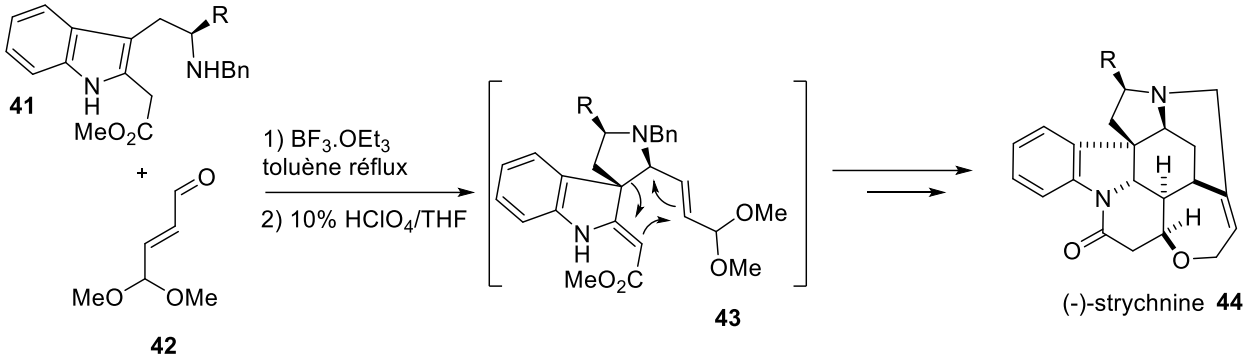


Schéma 3.1 : Synthèse de la (-)-Strychnine

3.2 Synthèse de la Deoxyaspidodispermine par Ban et Coll

Homma et Ban[31] sont les premiers à avoir synthétisé la deoxyaspidodispermine en 1977 à partir du 2-hydroxytryptamine **45**. Le tétracycle **47** a été obtenu après un processus d'amination du 2-hydroxytryptamine avec l'aldéhyde **46** suivi d'une condensation. Une grande série d'alcaloïdes[33] de type aspidosperma, ont été synthétisés à partir du tétracycle **47**, ce qui prouve ici, l'importance et l'efficacité de cette stratégie. Après l'obtention du diène, **48** Ban et son équipe ont formé le cyclo-adduit **49** en présence de dioxygène O_2. L'ouverture du peroxyde **49** a été effectuée par hydrogénation en présence d'un catalyseur d'Adams dans l'éthanol. Ce qui leur a permis d'obtenir un diol. Cependant, ils ont constaté qu'en utilisant les mêmes conditions, mais en remplaçant l'éthanol par l'acétate d'éthyle, ils obtiennent deux produits, le même diol que précédemment ainsi qu'un énol. Ces deux produits sont directement convertis en imine **50** en présence d'un mélange d'une solution d'hydroxyde de soude et du méthanol après deux heures de reflux. L'utilisation du $LiAlH_4$ a permis la réduction l'amide et de l'imine avec du THF en amine. En faisant une acétylation avec anhydride acétique et de la pyridine, la deoxyaspidodispermine **51** a donc vu le jour par voie de synthèse, **Schéma 3.2**.

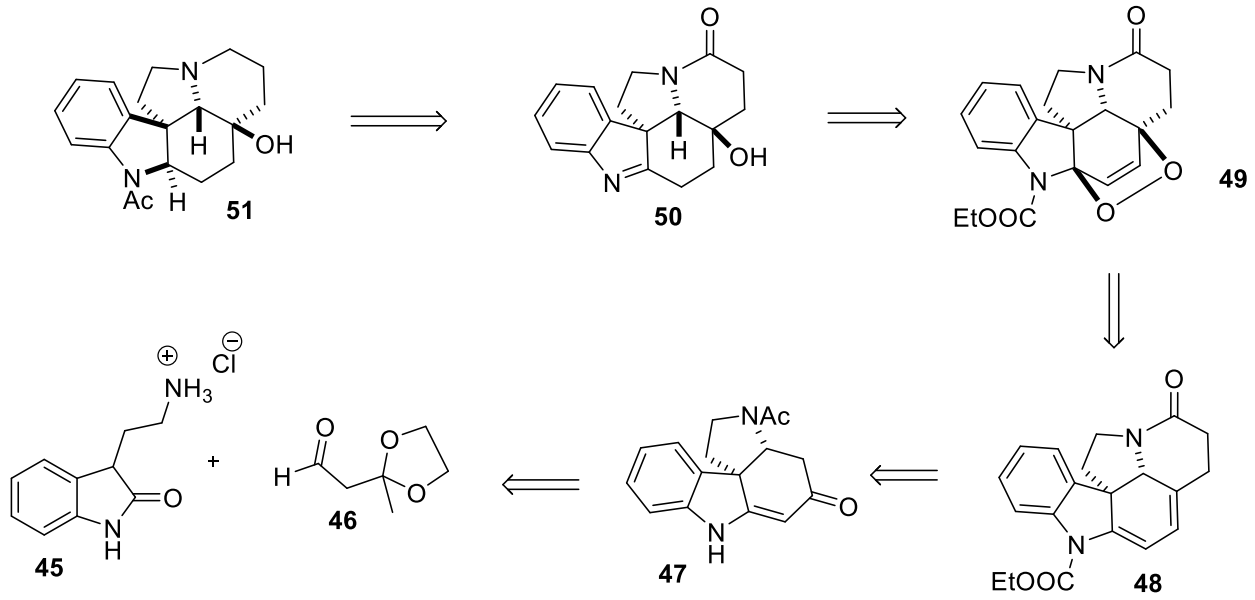


Schéma 3.2 : Synthèse de la Deoxyaspidodispermine

3.3 Synthèse de l'Aspidodispermine par Heretsch et Reuß

Heretsch et Reuß[32] ont synthétisé en 2020, l'Aspidodispermine qui est une molécule semblable à la deoxyaspidodispermine. Dans un premier temps ils ont tout d'abord synthétisé le vinylogue uréthane **53** l'un des précurseurs à partir de l'acide nicotinique **52**. Ensuite ils ont effectué la construction d'un système bicyclique à travers une séquence (2+2) de photocycloaddition suivi d'un Ramberg Backlung pour enfin donner l'hexadiene **55** par un réarrangement électrocyclique. L'intermédiaire **56** qui est un intermédiaire beaucoup plus avancé de leur synthèse a été obtenu à la suite d'une endoperoxyde et d'une réaction de Kornblum DeLamare. Il est important de noter qu'ils donnent un accès à une classe diversifiée des alcaloïdes pyrroloquinoline. La formation du squelette final de la molécule s'est fait grâce à la réaction indolique de Fisher en présence d'un dérivé de la phenylhydrazine **57** et du précurseur **56**, **Schéma 3.3**.

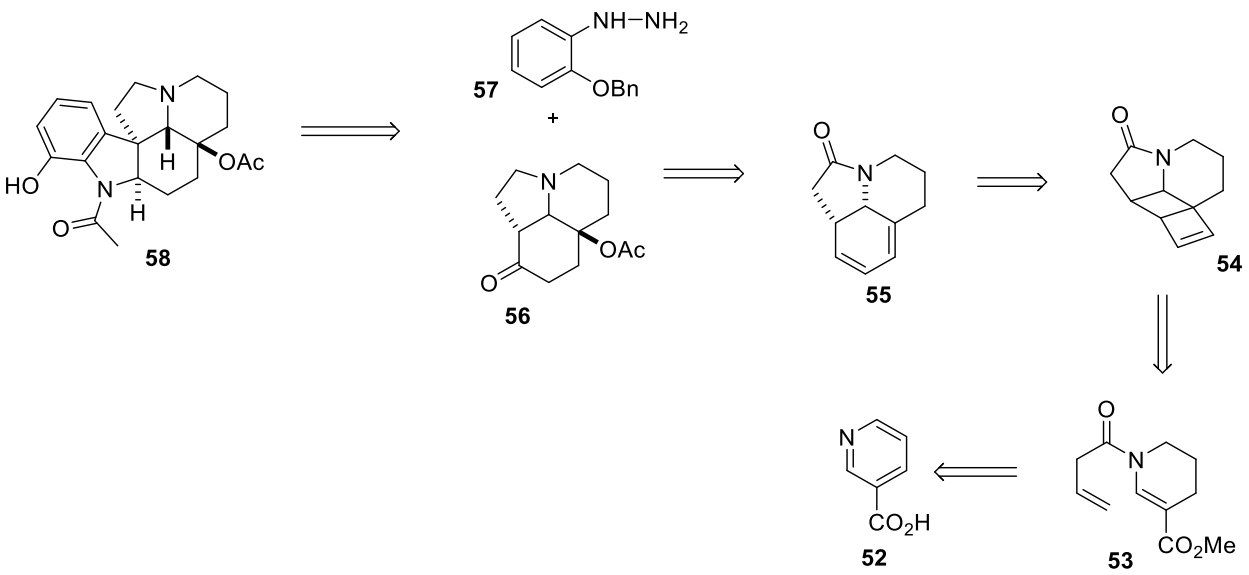


Schéma 3.3: Synthèse de l'Aspidodispermine

3.4 Groupements protecteurs en synthèse organique

Les groupements protecteurs jouent un rôle très important en synthèse organique, généralement, ils sont introduits dans une molécule afin de masquer ou d'empêcher la réactivité de certaines fonctions au cours d'une synthèse. Il existe plusieurs groupements protecteurs qui peuvent être utilisés pour protéger diverses fonctions. Parmi ces groupements protecteurs, nous pouvons citer, les diols[34] ou dithiols[35], qui sont utilisés pour la protection des aldéhydes ou cétones. Les alcools quant à eux, peuvent être protégés en acétal[36], en éther benzylique[37] ou en éther sylilé[38]. S'agissant des amines, ils peuvent être protégés en amides via des chlorures d'acyles, en carbamate par le $(Boc)_2O$ (*tert*-butyloxycarbonyl)[39], Fmoc, CBz. Il faut noter également que les amines peuvent être protégées en nosylamide[40] par le chlorure de benzène sulfonyle. Ces fonctions étant protégées, subiront probablement une déprotection, lorsqu'elles ne représenteront plus un problème de réactivité ou de sélectivité au cours de la synthèse. On peut donc s'interroger de savoir que deviendront ces groupements protecteurs après déprotection? La plupart de ces groupements protecteurs deviennent des sous-produits qui peuvent être problématiques pour l'environnement en désaccord avec le concept d'économie d'atome. Cependant ce concept est respecté lorsque le groupement protecteur fera partie intégrante de la molécule par un transfert lors de l'étape de déprotection. À titre d'exemple, on peut mentionner les travaux de Coulibali et coll[40] au sein de notre laboratoire en utilisant du nosyle comme groupement protecteur fonctionnel. La déprotection du nosyle est déclenchée par un procédé en Tandem

Michel-Smiles qui transformera le nosyle en un segment nitro-aryle en *alpha* d'une cétone à titre de précurseur de fonction indole faisant partie de la molécule finale suite à une hydrogénation subséquente.

3.5 Synthèse de la deoxyaspidodispermine

Notre groupe a produit la synthèse de la deoxyaspidodispermine **40**, à partir de l'homotyramine **59** qui est un réactif disponible dans le commerce. Après une désaromatisation oxydatante du phénol **60,** suivi d'un procédé en tandem Michael-Smile en présence du carbonate de césium, nous avons pu produire l'aziridines **61**. Cette étape clé de la synthèse nous a donc permis d'avoir le noyau indolique **62** après traitement de l'aziridine avec du nickel de Raney dans l'isopropanol. Le squelette final de la molécule a été fait par l'alcool **62** de chlorure de mésyle suivi d'un traitement avec du *t*-BuOK, **Schéma 3.4.**

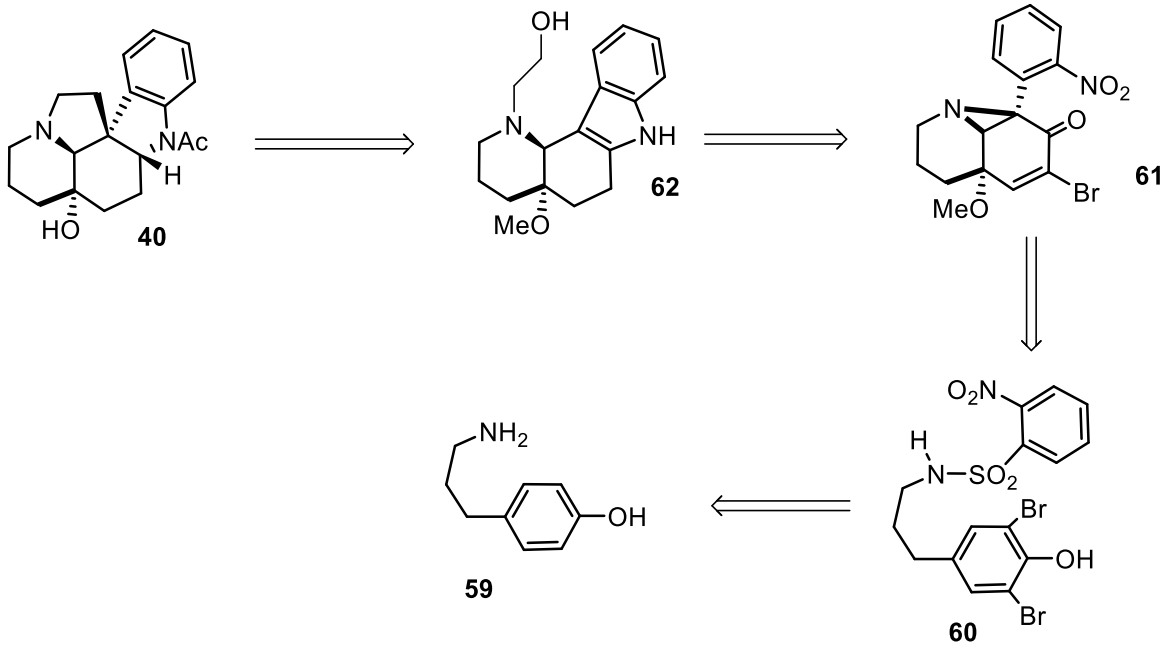


Schéma 3.4 : Retro-synthèse de la deoxyaspidodispermine

3.6 Article**:** Synthesis of Deoxyaspidodispermine Based on a Functional Protecting Group Strategy

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Titre: Synthesis of Deoxyaspidodispermine Based on a Functional Protecting Group Strategy

Auteurs: Kouassi Signo et Sylvain Canesi

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Synthesis of Deoxyaspidodispermine Based on a Functional Protecting Group Strategy

Kouassi Signo and Sylvain Canesi*

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ABSTRACT: A synthesis of deoxyaspidodispermine was produced from homotyramine. This approach is based on the application of a functional protecting group strategy that not only masks the reactivity of sensitive groups during crucial steps but also possesses a moiety desired in the final target, which is transferred to the substrate at the time of deprotection. This synthesis highlights an aza-Michael−Smiles ring-closure cascade, which enables the formation of a tetracyclic system from a nosylamide protecting group.

Nowadays, there is a consensus that environmentally benign synthetic routes to form complex molecules should be both atom economical[1] and protecting-group-free.[2] However, this approach using green chemistry remains extremely difficult to achieve in multistep syntheses when dealing with challenging polyfunctionalized structures present in complex natural products. Indeed, numerous solvents, reagents, and conditions are used during these processes, and the quest for an environmentally friendly total synthesis can be seen as utopian. Nevertheless, to develop greener chemistry approaches, we hypothesized that complementary to the protecting-group-free strategy, an alternative functional protecting group strategy could be envisaged.[3] Like a classical protecting group, a functional protecting group moderates the reactivity of sensitive groups during crucial steps; however, it also carries a moiety that is desired in the final target, which is transferred to the substrate at the time of deprotection. This strategy respects the atom economical approach without sacrificing the usefulness of protecting groups for the elaboration of complex structures. With this objective in mind, we first focused on the use of a nosyl group as an amino-protecting group. Indeed, the nitroaryl segment could be further transformed into an indoline precursor, which is present in several alkaloids after an aryl migration. Therefore, we developed an aza-Michael−Smiles ring-closure cascade,[4] enabling the transformation of a Fukuyama nosylamide protecting group[5] into a polycyclic α-arylated ketone during a deprotection−migration step. This cascade is mediated in slightly basic conditions and involves a new extension of the Truce−Smiles rearrangement.[6] This strategy would provide the benefits of protecting groups while minimizing the need for additional steps and atom waste. To apply this approach to the total synthesis of a natural compound, we focused on the architecture of aspidosperma[7] and ibophyllidine[8] alkaloids, because they contain an indoline moiety. These molecules have attracted considerable interest by the scientific community because of their pentacyclic architecture containing up to four continuous asymmetric centers. Ibophyllidine and desethylibophyllidine are isolated from *Tabernaemontana albiflora*,[9] and the bioactivity of these compounds is still under investigation. Aspidospermidine is an alkaloid isolated from plants in the genus *Aspidosperma*[10] and represents the main core of several patented biological structures. We first focused our attention on the synthesis of deoxyaspidodispermine, which was isolated by Djerassi and co-workers in 1968 from *Aspidosperma dispermum*.[11] To the best of our knowledge, only the group of Ban[12] has reported the synthesis of deoxyaspidodispermine. In addition, aspidodispermine,[11] a related natural product, was recently synthesized by Heretsch and Reuß,[13] Figure 1.

In this Letter, we report an application of a functional protecting group strategy to produce deoxyaspidodispermine. This approach involves an aza-Michael−Smiles ring-closure cascade, enabling the transformation of a nosylamide protecting group into a key heterocyclic main core. The synthesis begins with commercially available homotyramine 7

1, R = α-Et, ibophyllidine
2, R = β-Et, 20-epi-ibophyllidine
3, R = H, desethylibophyllidine
4, R_1 = Et, R_2, R_3 = H, aspidospermidine
5, R_1, R_3 = OH, R_2 = Ac, aspidodispermine
6, R_1 = OH, R_2 = Ac, R_3 = H, deoxyaspidodispermine

Figure 1. Some aspidosperma and ibophyllidine alkaloids.

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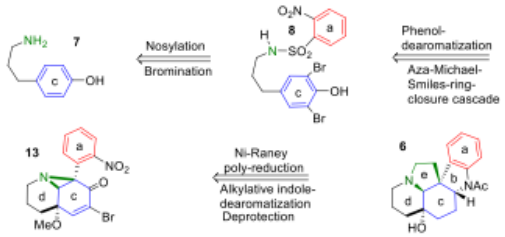
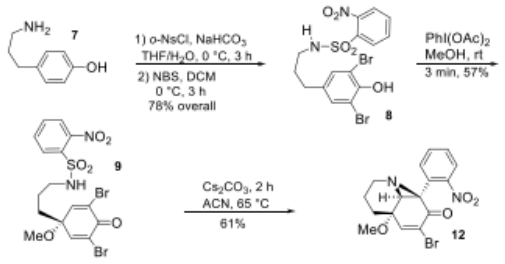
as a simple starting material and highlights several environmentally benign transformations. The Schotten–Baumann protocol, hypervalent iodine dearomatization, and an aza-Michael–Smiles aziridination process were used. Raney nickel reduction led to the main tetracyclic system, and the last ring was obtained by an alkylative indole-dearomatization–reduction process. Methyl-ether deprotection followed by selective acetylation completed the synthesis; the retrosynthetic pathway is described in Scheme 1.

Scheme 1. Retrosynthesis Pathway of Deoxyaspidodispermine



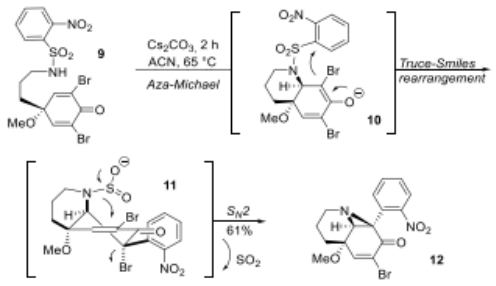
The synthesis started with commercially available phenol **7**, and the Schotten–Baumann protocol[14] led to the selective formation of the nosylamide, which was first used as a classical protecting group for the two subsequent steps to prevent oxidation of the amino group. To allow a further aziridination process, bromines were introduced at the *ortho*-positions in the presence of *N*-bromosuccinimide, leading to **8**. The phenolic system represented a precursor of our target's first ring, which was produced by an oxidative dearomatization process developed by Kita and co-workers.[15a] This reaction occurs in the presence of methanol and a hypervalent iodine reagent as a surrogate for toxic heavy metals such as lead(IV) acetate.[15b] This method led to the formation of dienone **9** in 57% yield. Further treatment of **9** with cesium carbonate in acetonitrile led to aziridine **12** in 61% yield, Scheme 2.

Scheme 2. Protecting Group Migration as an Indoline Precursor



The formation of **12** represented our crucial step. Indeed, the nosyl moiety that served as a protecting group during the iodane oxidation and as a competent nucleophile to allow an 1,4-addition was then transferred near the carbonyl as the indoline precursor for the further elaboration of deoxyaspidodispermine. This migration was the key deprotection step and highlighted the "functional protecting group approach" to produce a greener total synthesis. From a mechanistic point of view, cesium carbonate is a harmless inorganic base that generated enolate **10** via an aza-Michael addition, which triggered a Smiles rearrangement in tandem and the loss of sulfur dioxide as the only byproduct. The aryl migration during the Smiles rearrangement occurred with retention of configuration at the nosyl position. Therefore, the released amine was perfectly oriented for an antiperiplanar attack on the alkyl halide by an intramolecular S_N2-type process. The yield observed can be explained by the fact that several transformations occurred in one-step to produce quite functionalized polycyclic compound **12**, Scheme 3.

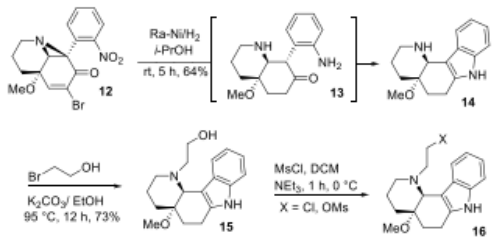
Scheme 3. "Deprotective-Migrating Step" of the Nosyl Group



Intermediate **12** represented a functionalized system, and several reductions were required to obtain the main tetracyclic core **14**. Fortunately, it appeared that every reduction could be produced in one step with a unique reductive reagent. Indeed, the aziridine, bromine, alkene, and nitro segments could be reduced by hydrogenation, leading to **13**, which could be further converted into the required indole **14** by condensation and isomerization. First, we tried the reduction in the presence of palladium; unfortunately, no indole was detected. A second attempt with Raney nickel in methanol led to the formation of the desired indole core, but obviously a methoxy group was added during the process probably via an oxa-Michael addition on the enone moiety. To avoid this undesired addition, 2-propanol, a less nucleophilic protic solvent, was chosen. We were pleased to observe in such conditions the formation of the desired tetracyclic system **14** in 64% yield. Further treatment with bromoethanol[16] led to amine **15**, and activation with mesyl chloride[17] yielded **16** as a mixture of chloro and mesylate, which are both useful substrates, Scheme 4.

The last ring was obtained by an alkylative indole-dearomatization process[18] in basic conditions followed by

Scheme 4. Elaboration of the Tetracyclic Indole Moiety



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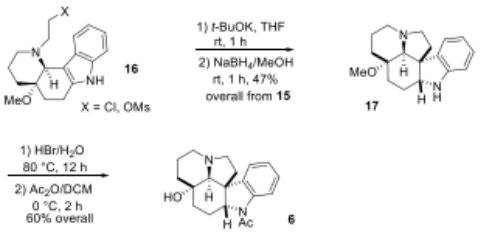
treatment with sodium borohydride to produce pentacyclic core **17**. At this stage, a methyl-ether deprotection was achieved in the presence of aqueous hydrobromic acid. It should be noted that such a deprotection strategy on an aliphatic methyl ether is scarcely reported in the literature. The synthesis was finalized by selective acetylation in the presence of acetic anhydride without any external base,[19] leading to deoxyaspidodispermine **6** via a novel route, Scheme 5.

Scheme 5. End of Synthesis



In summary, a total synthesis of deoxyaspidodispermine was achieved from homotyramine through the use of nosylamide as a protecting group and precursor of the indoline moiety. This synthesis highlights several benign environmental transformations to develop greener total syntheses. Further developments and applications are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01878.

Experimental procedures, characterization data, NMR comparison tables, and NMR spectra for key compounds (PDF)

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Notes

The authors declare no competing financial interest.

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Org. Lett. 2022, 24, 4939−4942

3.7 Conclusion

La synthèse de la deoxyaspidodispermine a été décrite en suivant une méthodologie d'aziridination arylante élaborée par notre équipe de synthèse. Cependant, il faut aussi noter que la formation du noyau indolique en présence du nickel de Raney a été très déterminante au cours de cette synthèse, ce qui crée une ouverture sur d'autres cibles potentielles. Par la suite, la formation du pentacycle avec le bromoethanol a permis d'avoir le squelette final de la molécule.

3.8 Informations supplémentaires

Les informations supplémentaires contenant les protocoles expérimentaux ainsi que les caractérisations et spectres RMN, sont présentées à 1'Annexe C

CONCLUSION GENERALE

Au terme de ce travail, il convient de retenir que nous avons développé deux nouvelles méthodologies de synthèse : une méthodologie permettant la transformation rapide de phénols peu coûteux en différents dérivés phosphorylés utilisant un réactif à base d'iode hypervalent et des phosphites. Les phosphonates issus de cette méthodologie constituent de véritables précurseurs pour la synthèse de certaines molécules d'origines naturelles. La deuxième méthodologie décrit le développement d'une nouvelle stratégie d'aziridination arylante stéréosélective dans des conditions douces sur des diénones obtenues à partir de phénols et d'un réactif à l'iode hypervalent. Un processus en cascade subséquent impliquant des réactions de Michael-Smiles et fermeture de cycle mènent à des structures polycycliques complexes. Dans les conditions douces de la réaction, seul le dioxyde de soufre est libéré en tant que sous-produit. Cette stratégie d'aziridination, à servit d'étape clef pour la synthèse totale de la Deoxyaspidodispermine.

ANNEXE A

ELABORATION OF FUNCTIONALIZED ORGANOPHOSPHATE, Supporting Information

Elaboration of Functionalized Organophosphates

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Supporting Information

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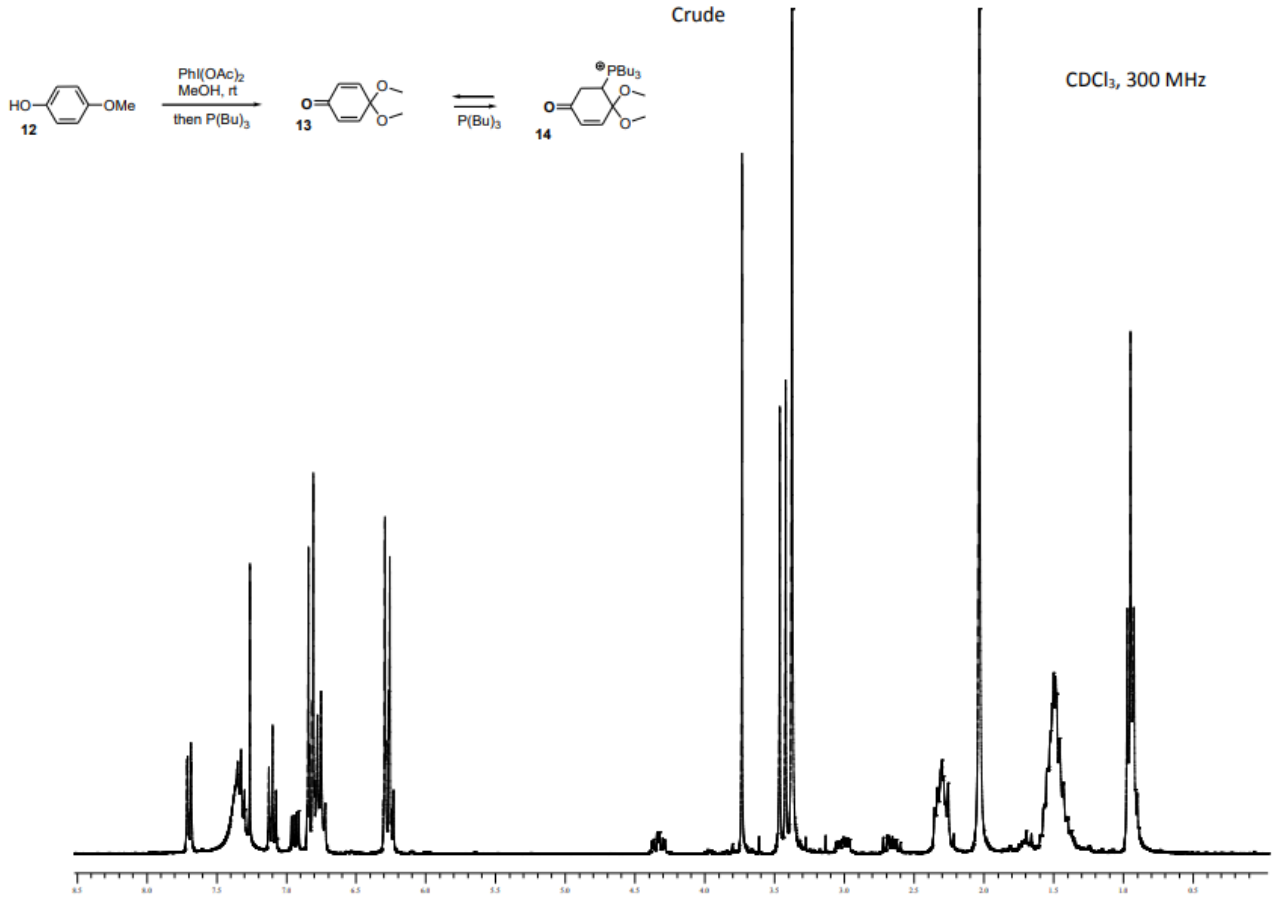
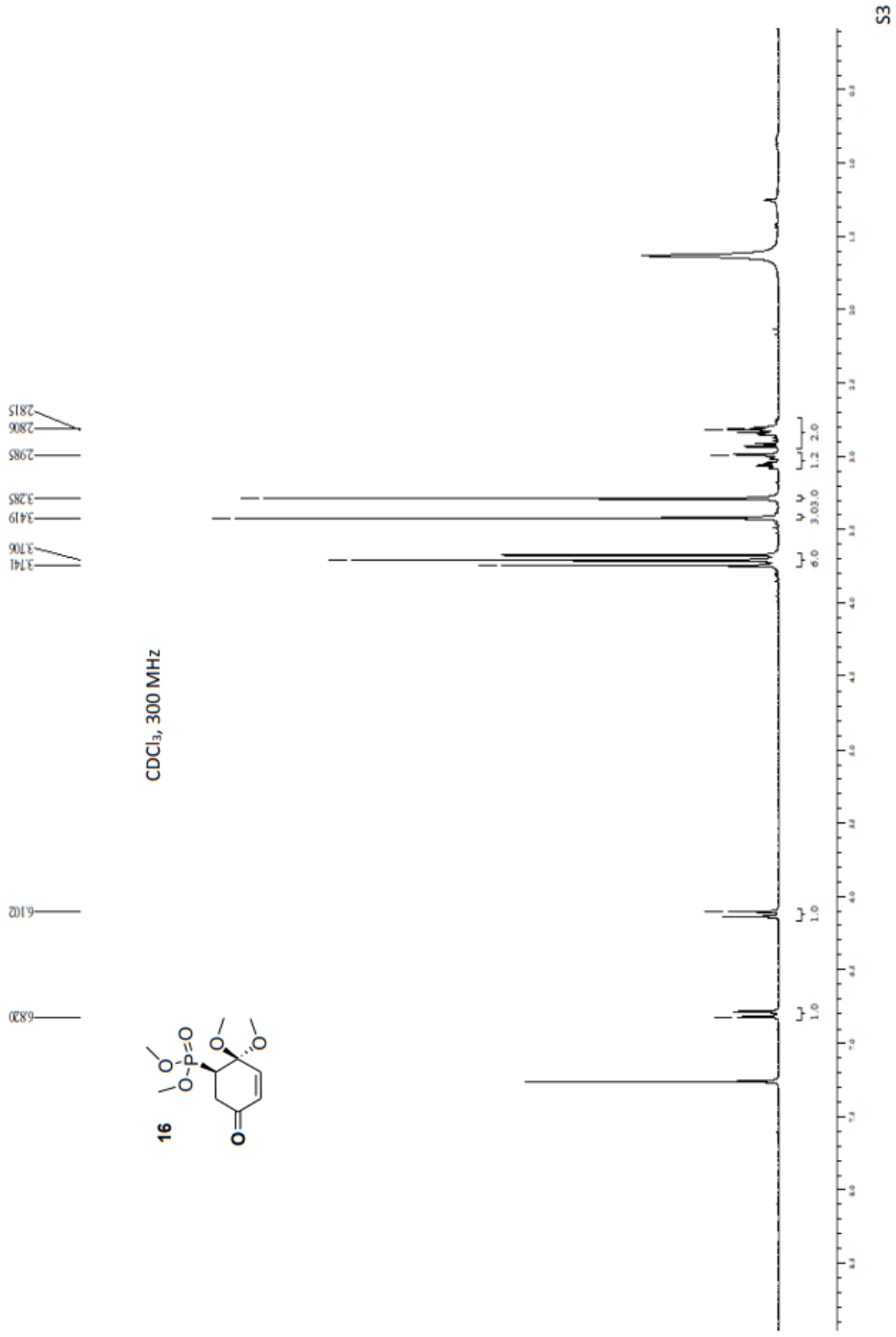
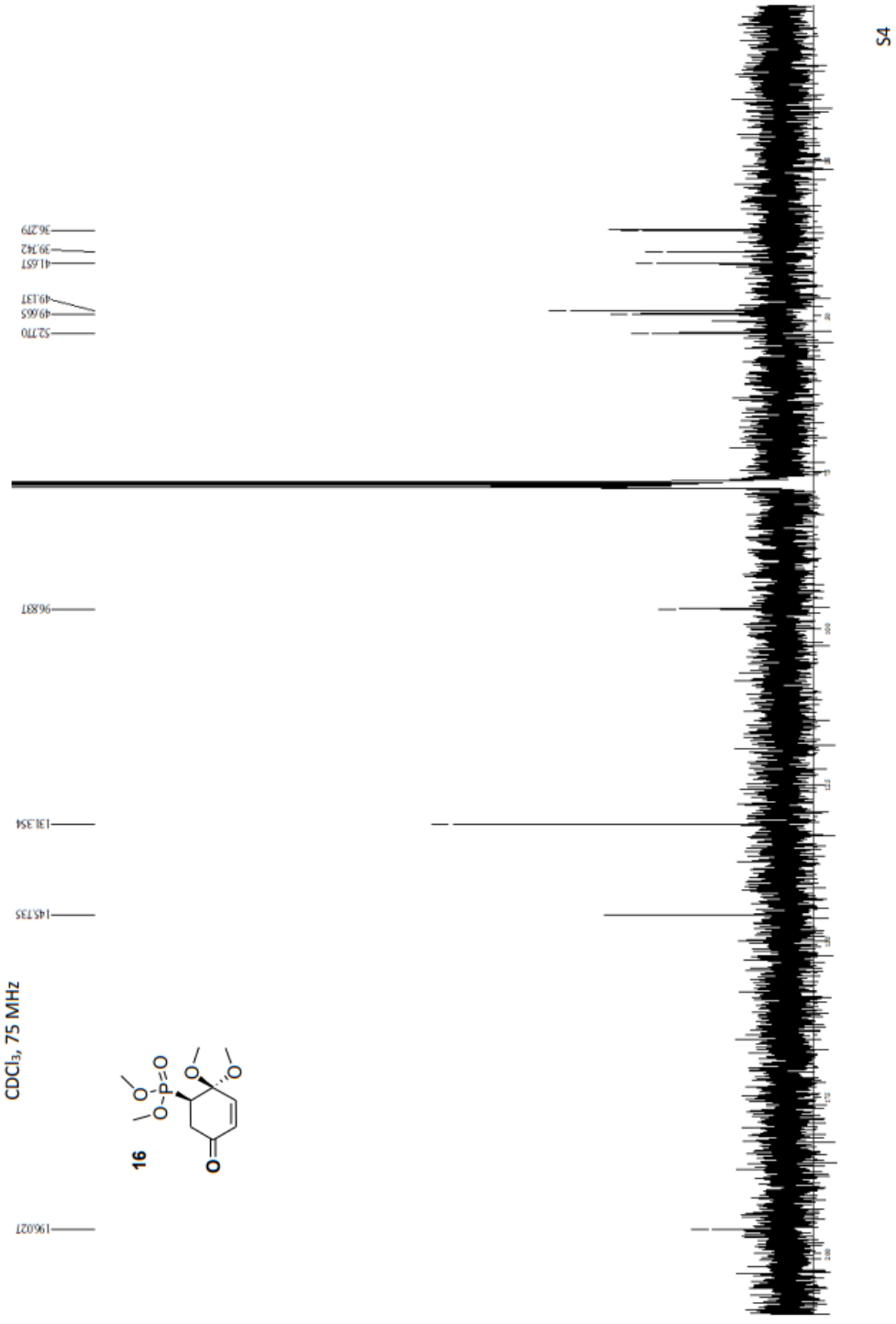

Crude
CDCl3, 300 MHz
HO
OMe
12
PhI(OAc)2
MeOH, rt
then P(Bu)3
13
P(Bu)3
PBu3
14


S3
CDCl3, 300 MHz
16
O
O
P
O
O
O
O
6.830
6.102
3.741
3.706
3.419
3.285
2.985
2.806
2.815
1.0
1.0
6.0
3.03.0
1.2
2.0


S4
CDCl3, 75 MHz
16
O
O
O
O
P
O
O
196.027
145.735
138.354
96.887
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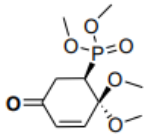
49.665
49.137
41.657
39.742
36.279

16



26.832

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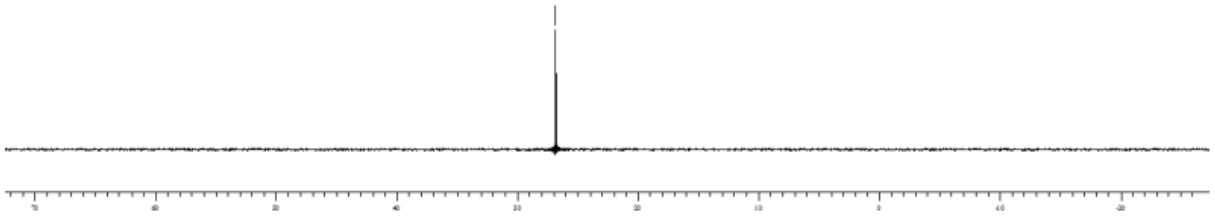
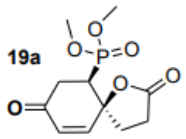
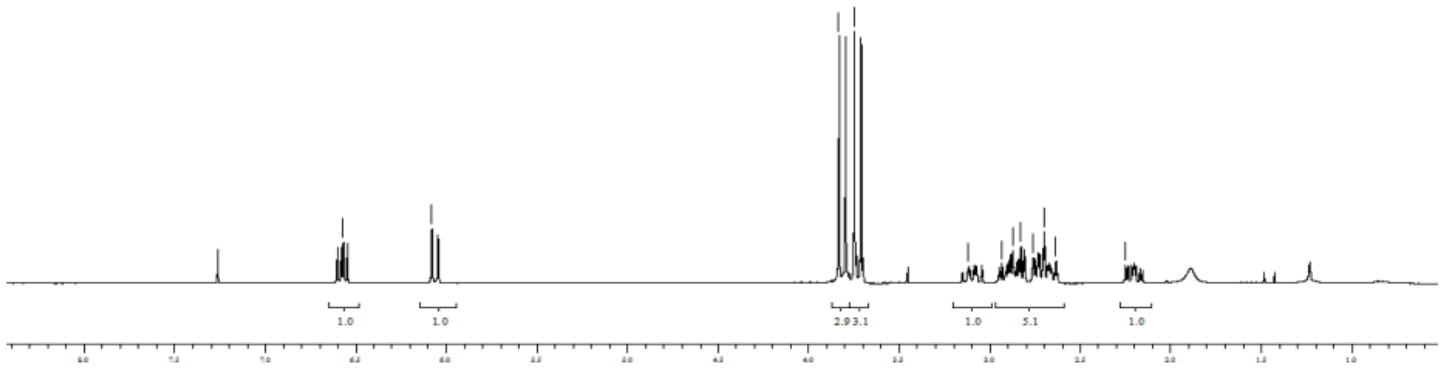
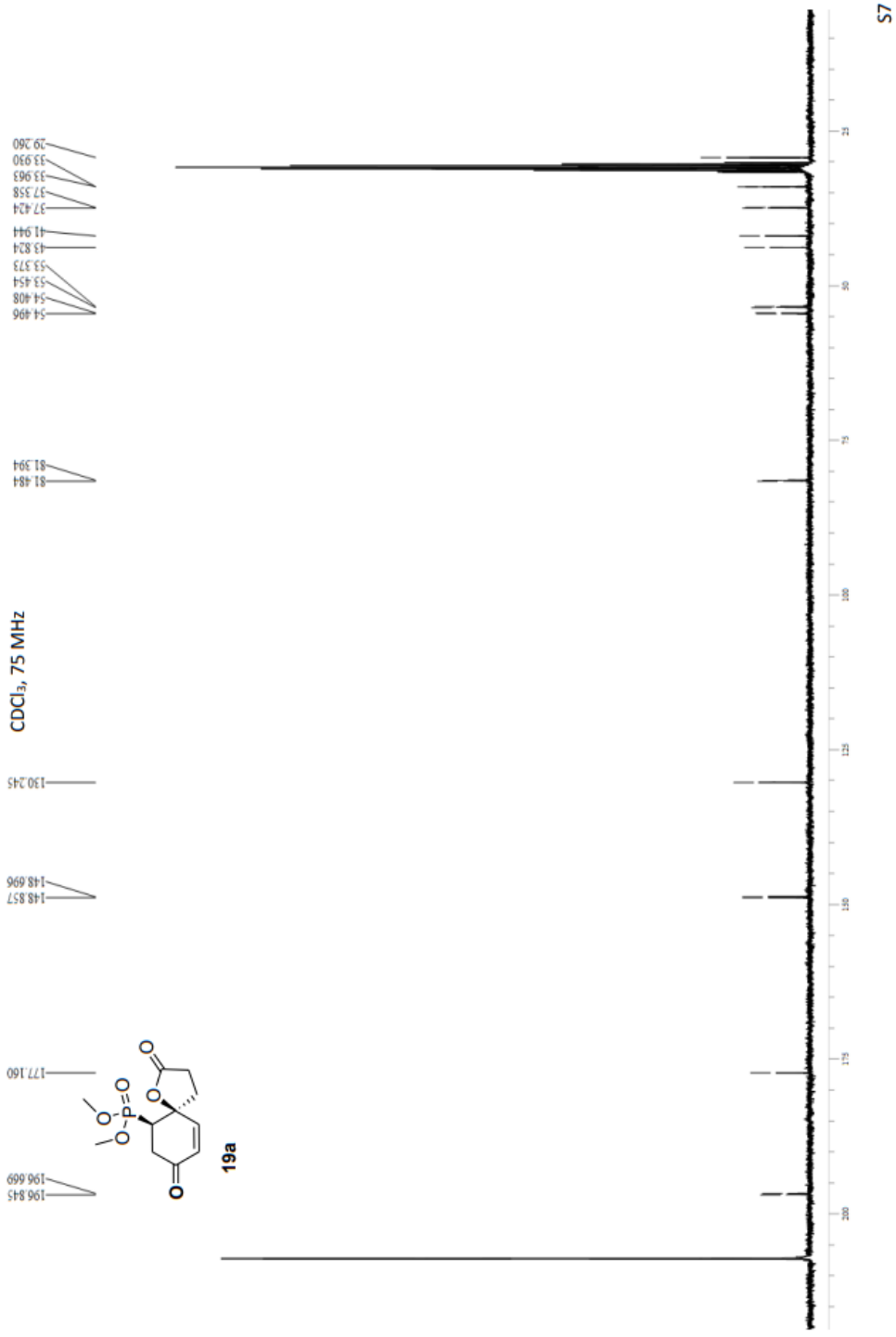


$CDCl_3$, 300 MHz



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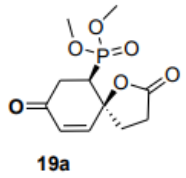
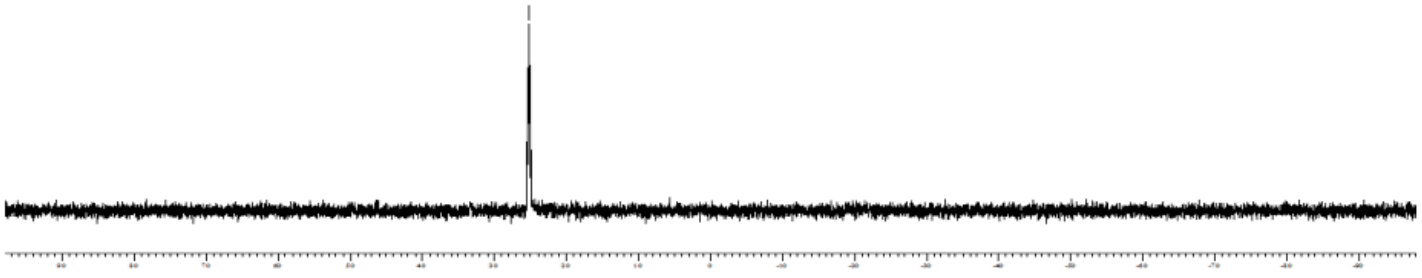
CDCl3, 75 MHz
19a
29.260
33.930
33.963
37.358
37.424
41.944
43.824
53.373
53.454
54.408
54.496
81.394
81.484
130.245
148.696
148.857
177.160
196.669
196.845

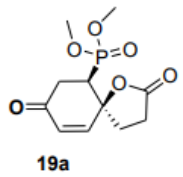


19a

$CDCl_3$, 122 MHz

25.164

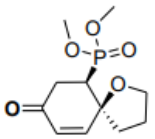




19a

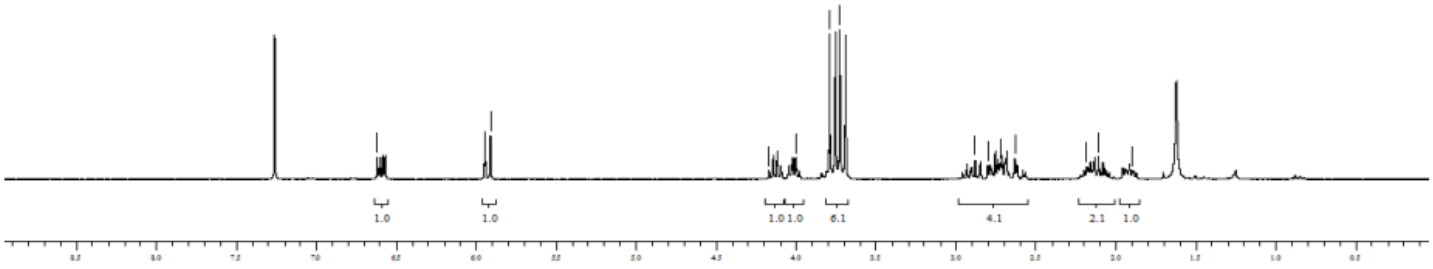
$CDCl_3$, 300 MHz

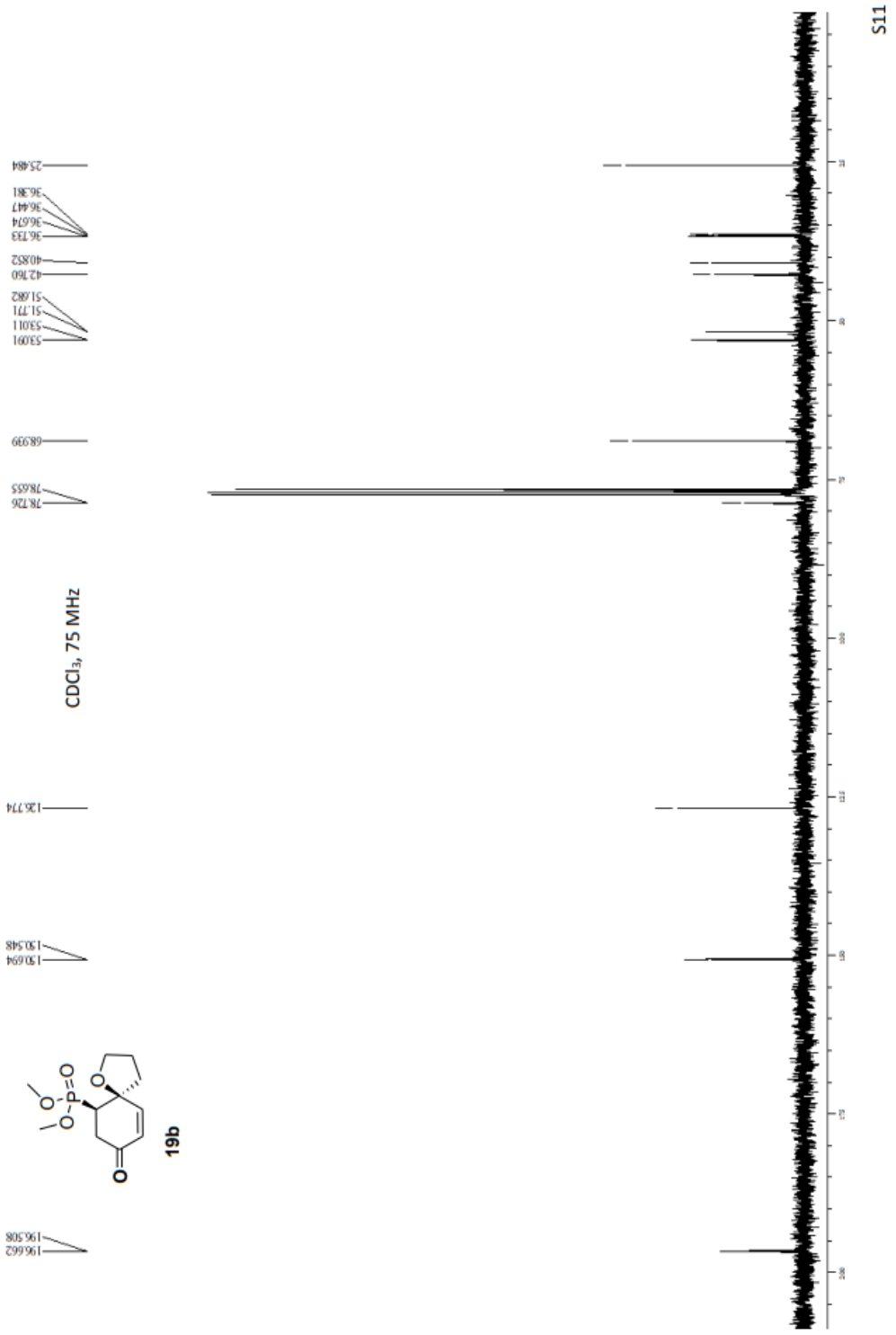
NOE, OMe
irradiation

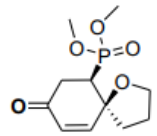


19b

$CDCl_3$, 300 MHz



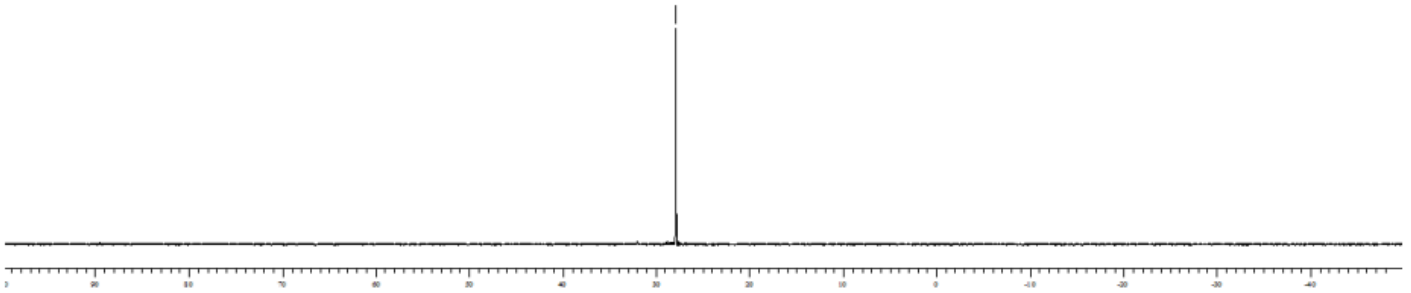

S11
25.484
36.381
36.447
36.574
36.733
40.852
42.760
51.482
51.771
53.011
53.091
68.939
78.726
78.655
CDCl3, 75 MHz
136.774
130.694
130.548
196.662
196.508
19b

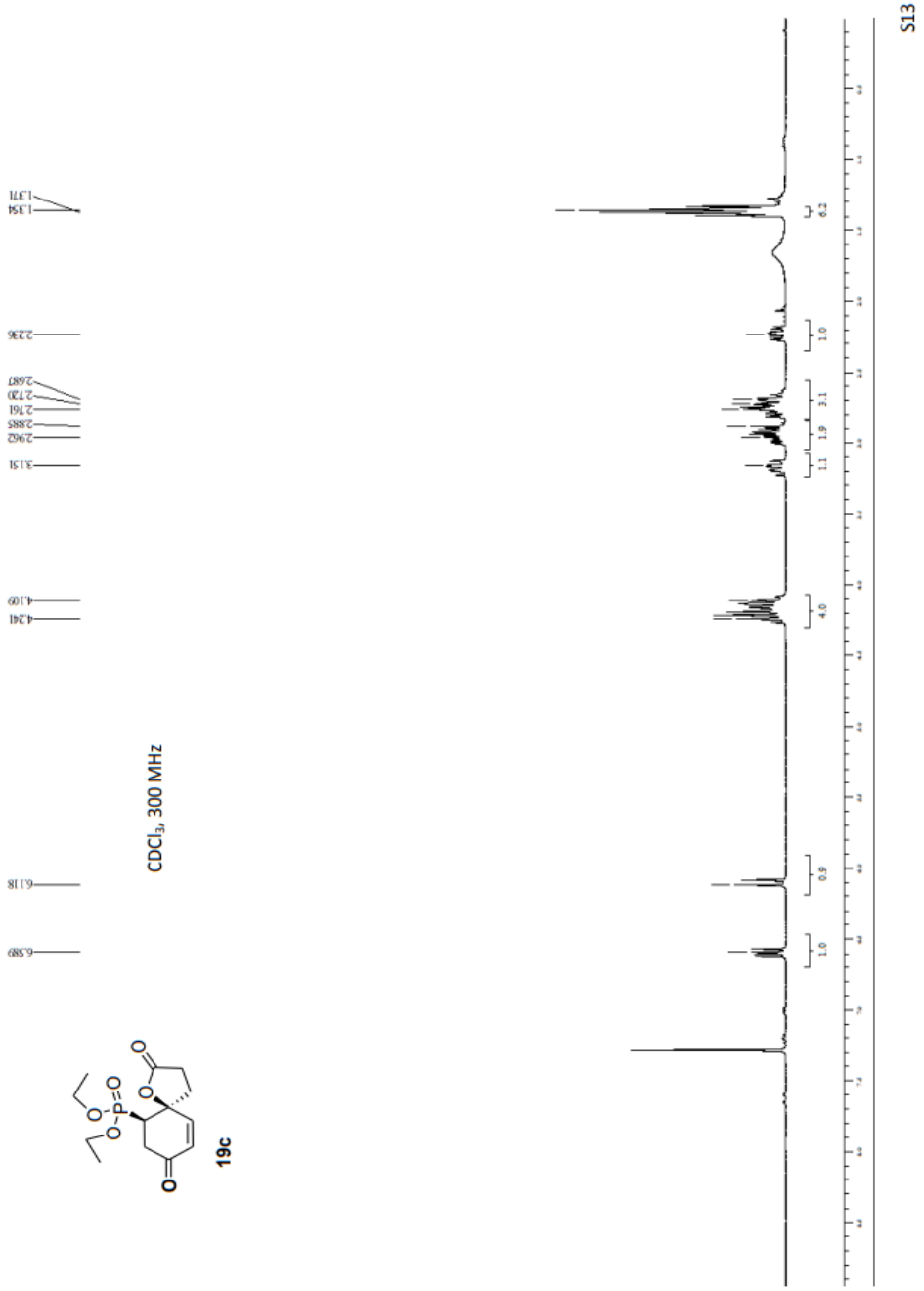


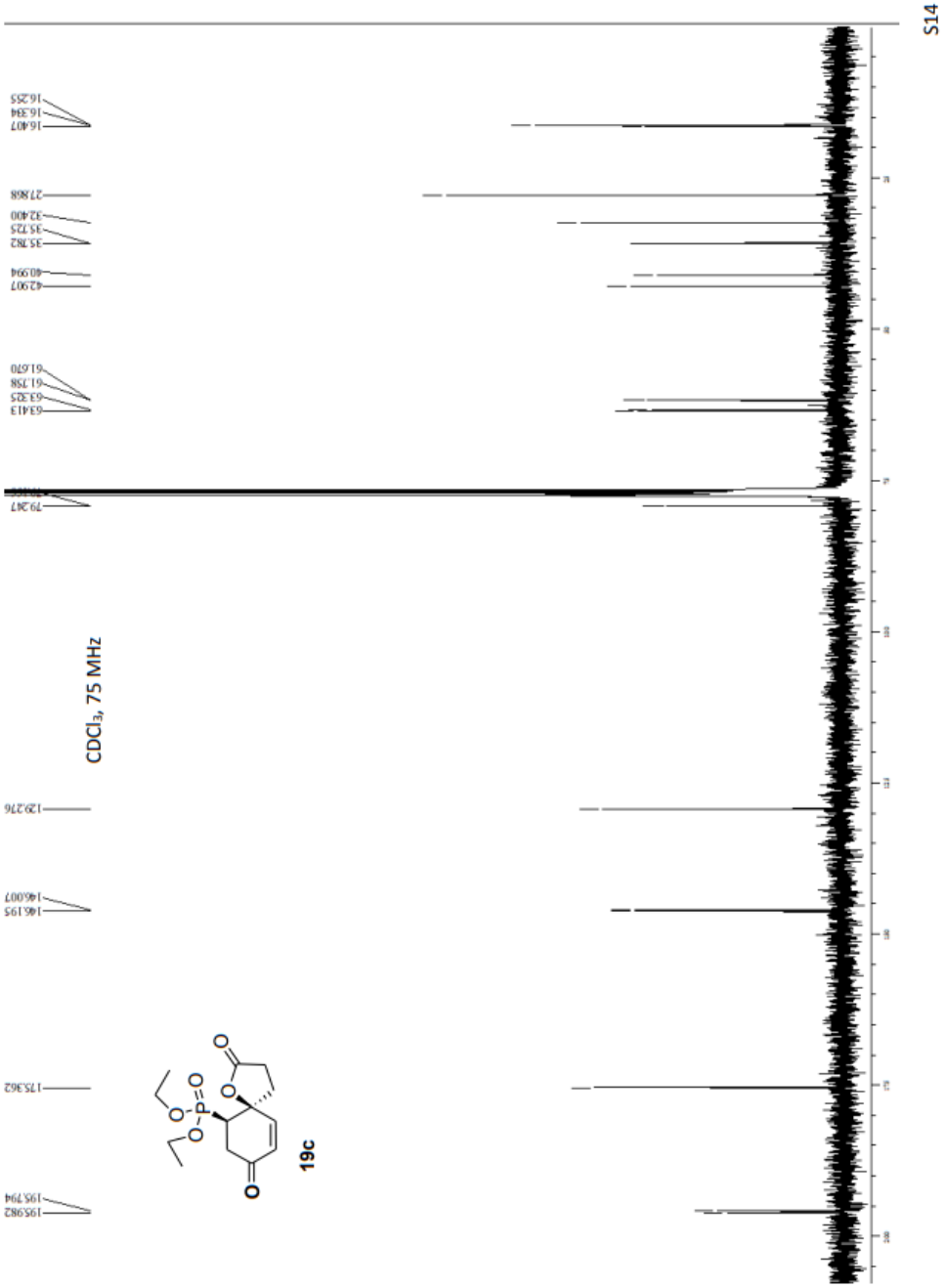
19b

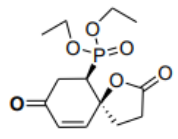
27.878

$CDCl_3$, 122 MHz




1.371
1.354
2.236
2.687
2.730
2.761
2.885
2.962
3.151
4.109
4.241
6.118
6.589
CDCl3, 300 MHz
19c
S13

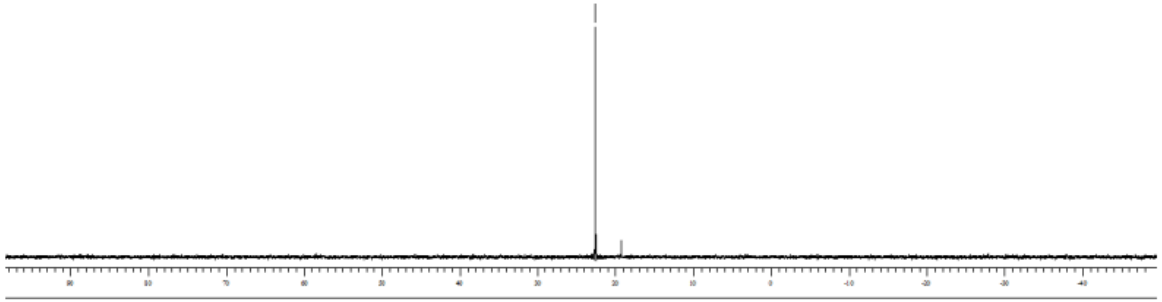

S14
CDCl3, 75 MHz
19c

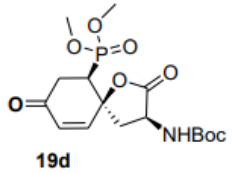


19c

22.964

$CDCl_3$, 122 MHz

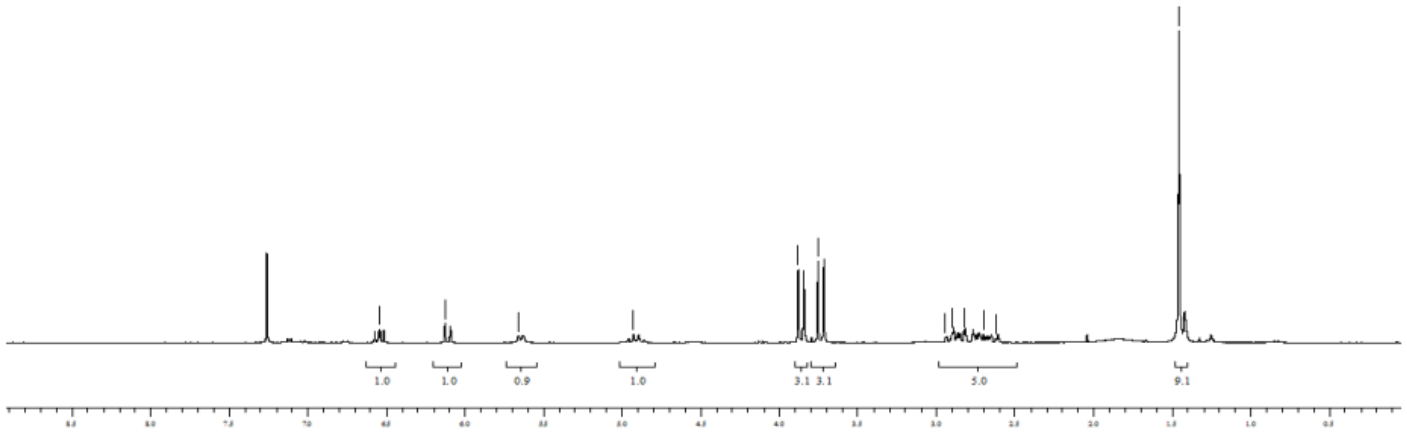


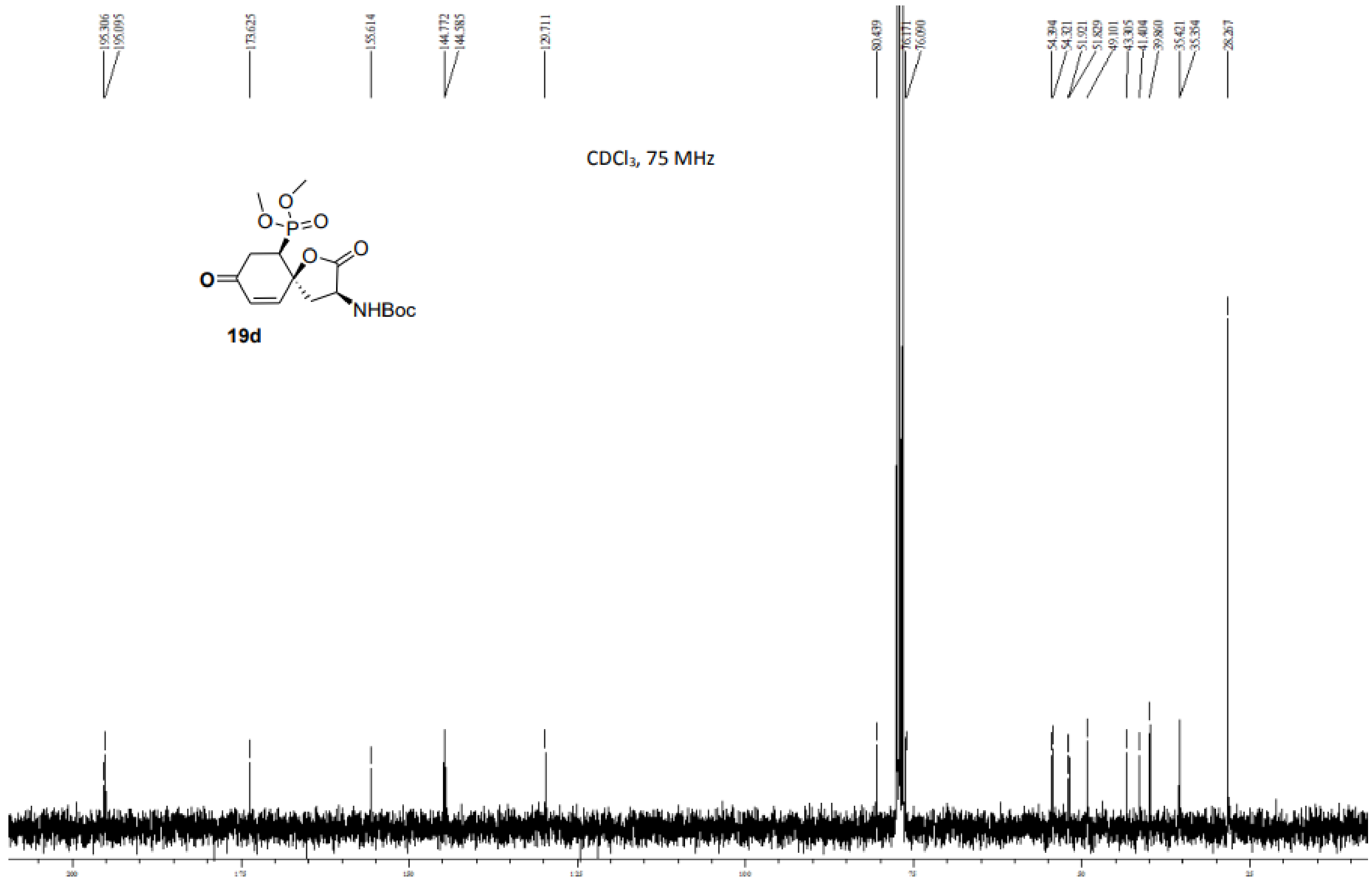


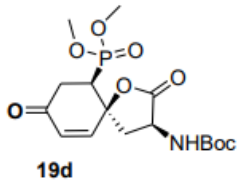
19d

6.539
6.126
5.699
4.926
3.879
3.754
2.939
2.898
2.825
2.621
2.702
1.456

$CDCl_3$, 300 MHz



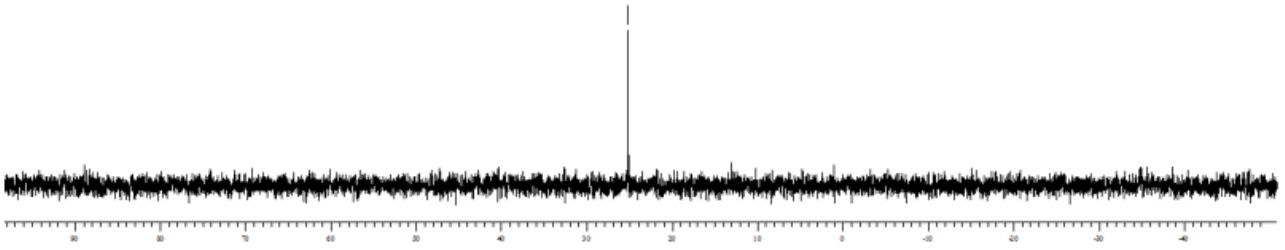

195.306
195.095
173.625
155.614
144.772
144.585
129.711
80.439
76.171
76.090
54.394
54.321
51.921
51.829
49.101
43.305
41.404
39.860
35.421
35.354
28.267
CDCl₃, 75 MHz
NHBoc
19d

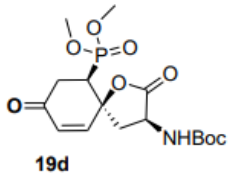


19d

25.167

$CDCl_3$, 122 MHz

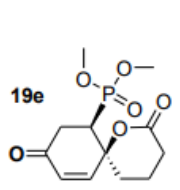




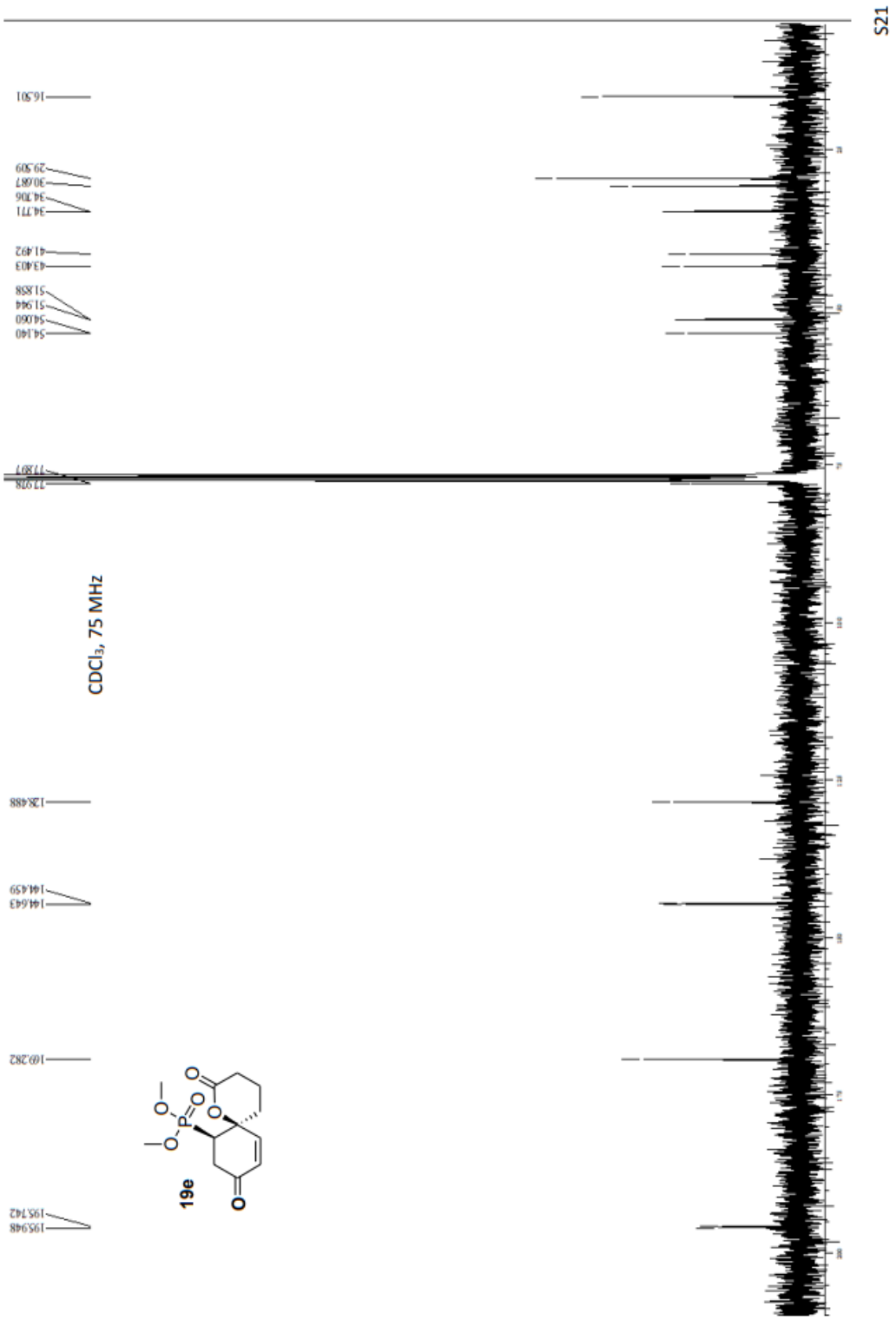
19d

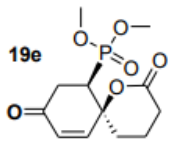
$CDCl_3$, 300 MHz

NOE, *t*-Bu
irradiation


19e
O
O
O
O
O
O

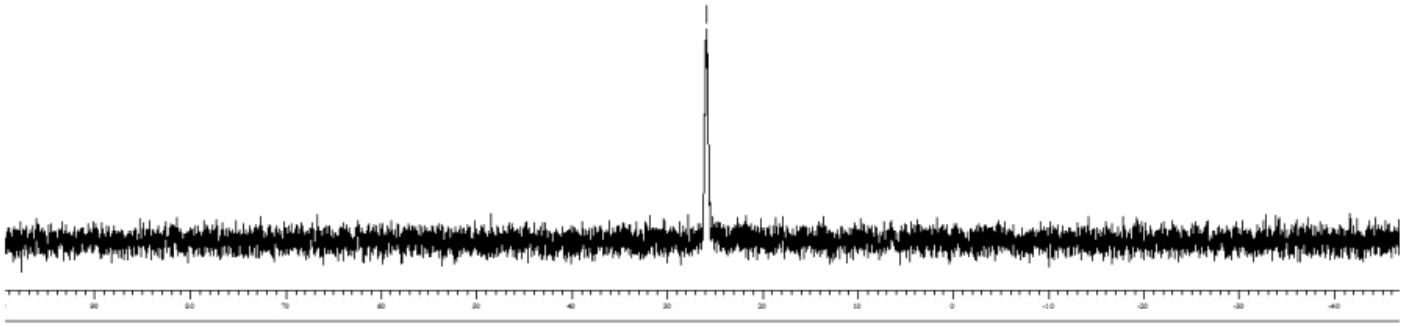
CDCl3, 300 MHz
6.808
6.056
3.861
3.775
3.073
2.738
2.676
2.616
2.040
2.027
1.832
0.9
1.0
6.1
2.0
4.1
2.0
1.0

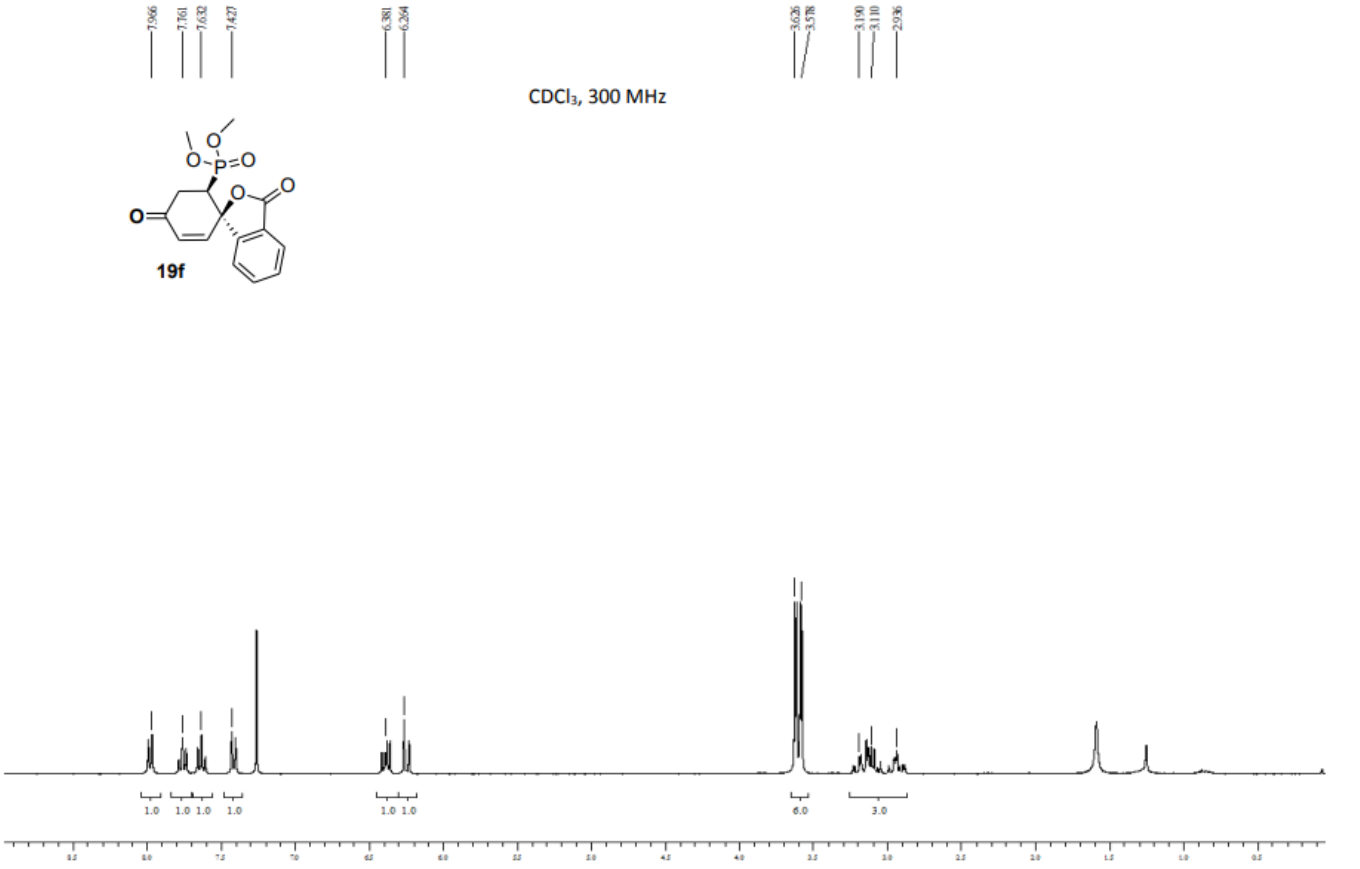

S21
16.501
29.509
30.087
34.706
34.771
41.492
43.403
51.858
51.944
54.060
54.140
77.807
77.928
CDCl3, 75 MHz
138.488
144.459
144.643
169.282
195.742
195.948
19e
O
O
O
O
O
O
P

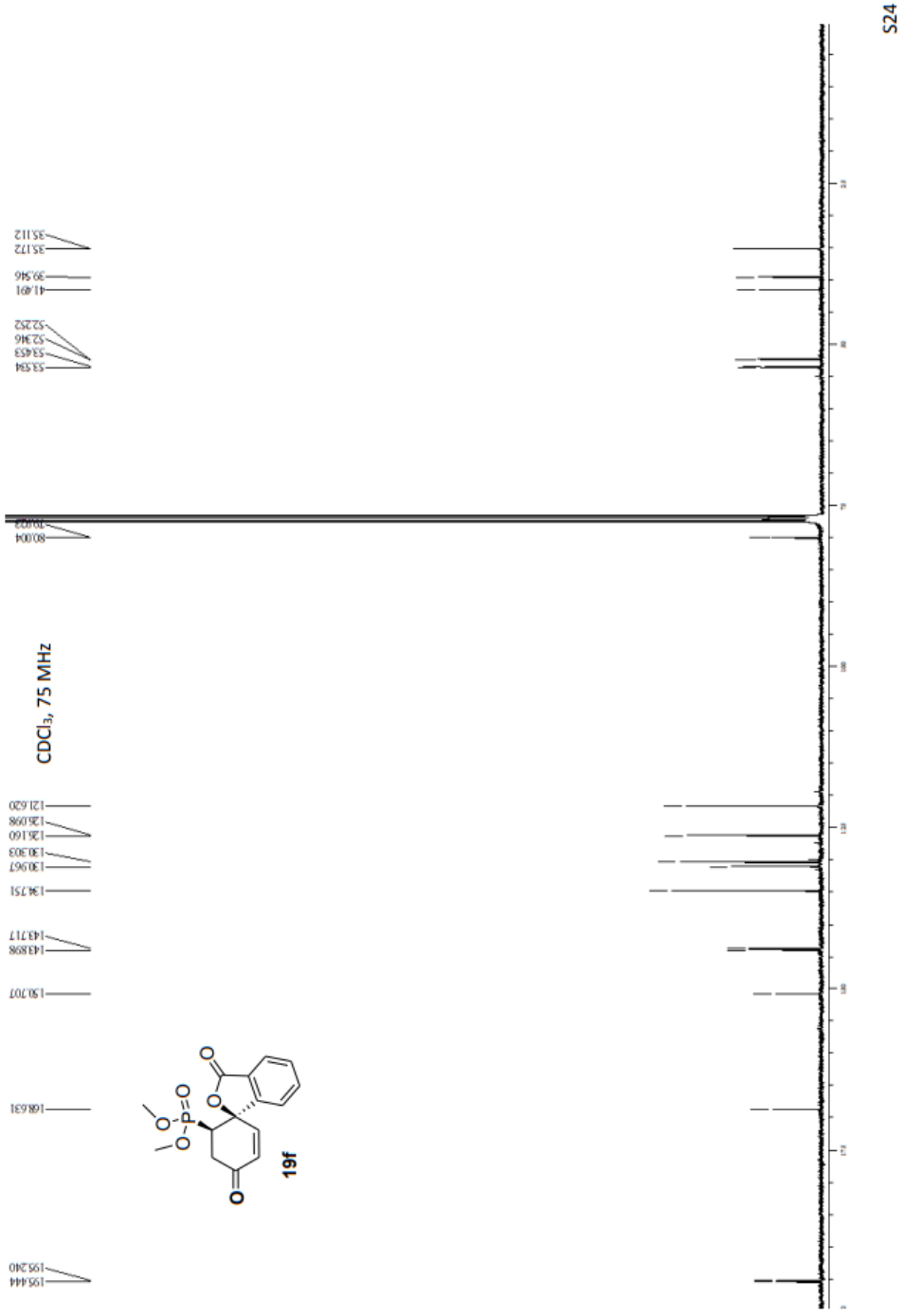


25.901

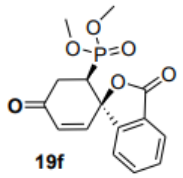
$CDCl_3$, 122 MHz



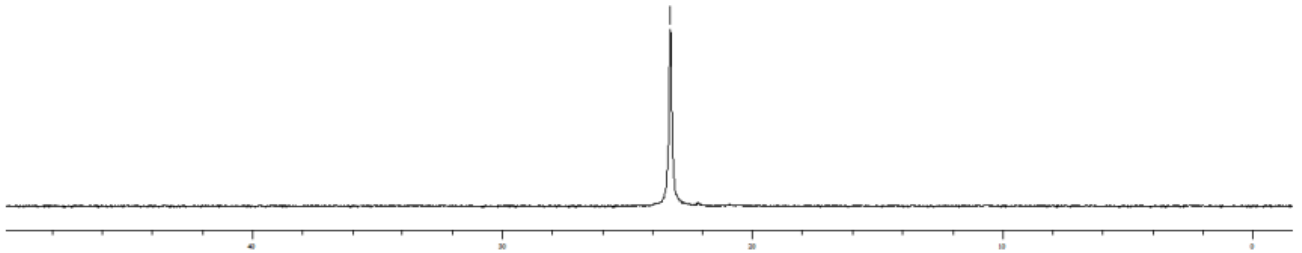

7.966
7.761
7.632
7.427
6.381
6.264
3.625
3.578
3.190
3.110
2.936
CDCl3, 300 MHz
19f
1.0
1.0
1.0
1.0
1.0
1.0
6.0
3.0

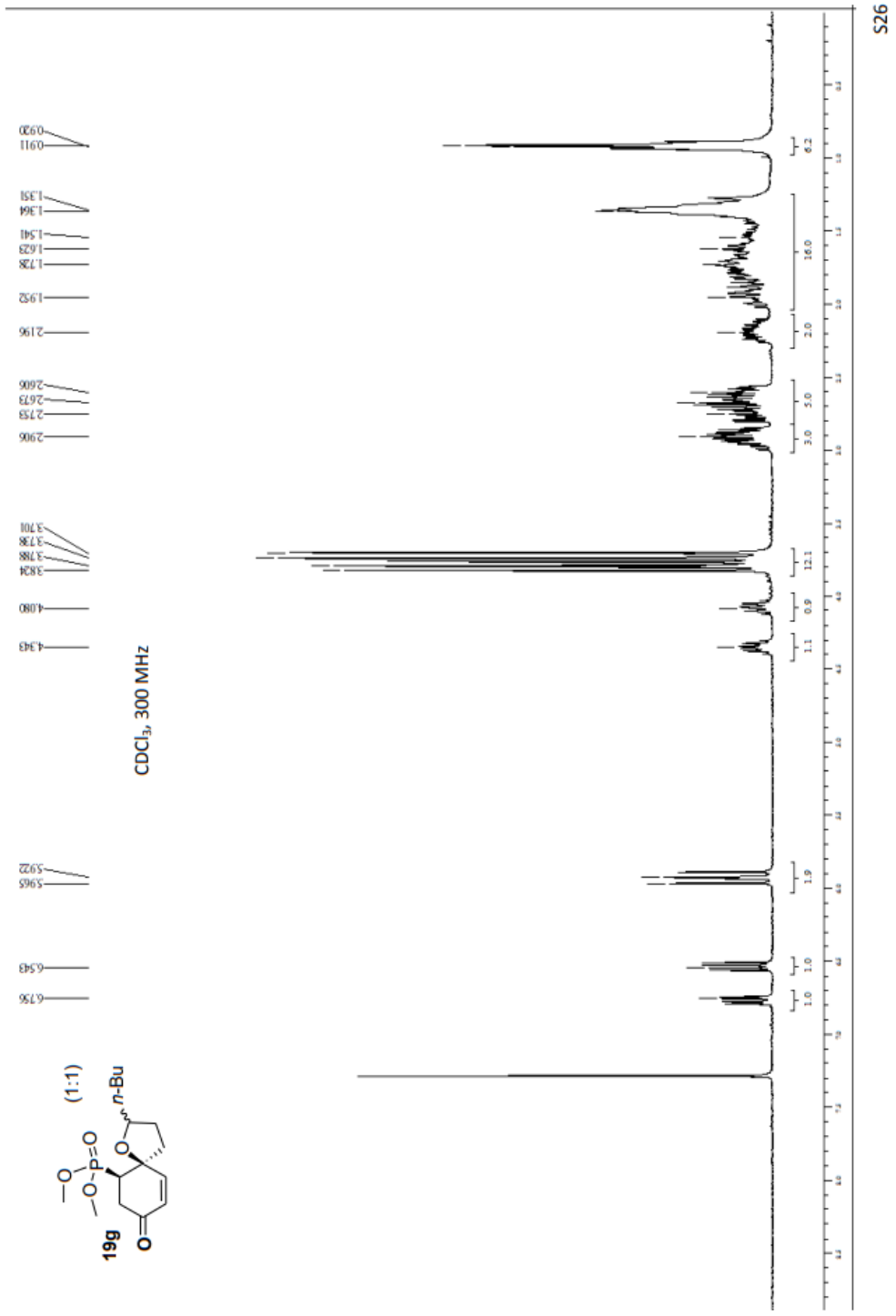

S24
CDCl3, 75 MHz
35.112
35.172
39.546
41.491
52.252
52.346
53.453
53.534
80.004
79.079
121.620
126.098
126.160
130.303
130.967
134.751
143.717
143.898
150.707
168.631
195.240
195.444
19f

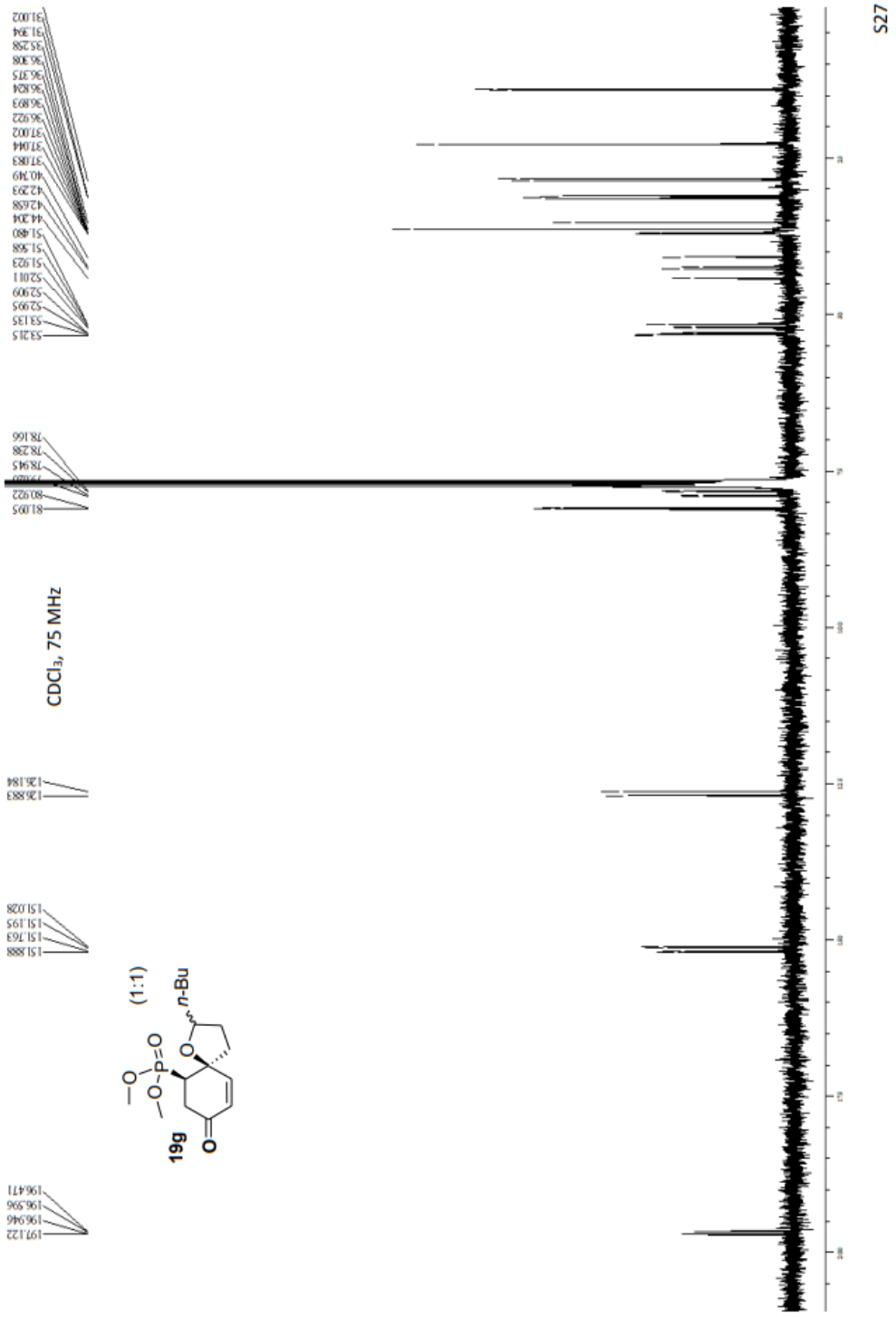
$CDCl_3$, 122 MHz

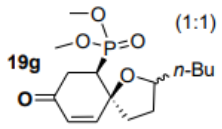


19f



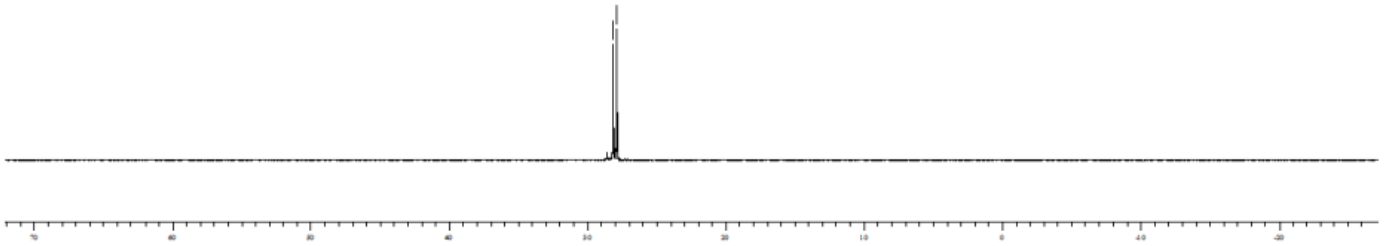

S26
CDCl3, 300 MHz
19g
(1:1)
n-Bu
O
O
O
O
P
O
0.920
0.911
1.351
1.364
1.541
1.629
1.738
1.952
2.196
2.606
2.673
2.753
2.906
3.701
3.738
3.788
3.824
4.080
4.343
5.922
5.965
6.543
6.736

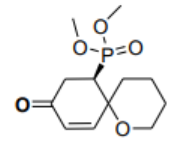

CDCl3, 75 MHz
(1:1)
n-Bu
19g
O
S27



28.126
27.870

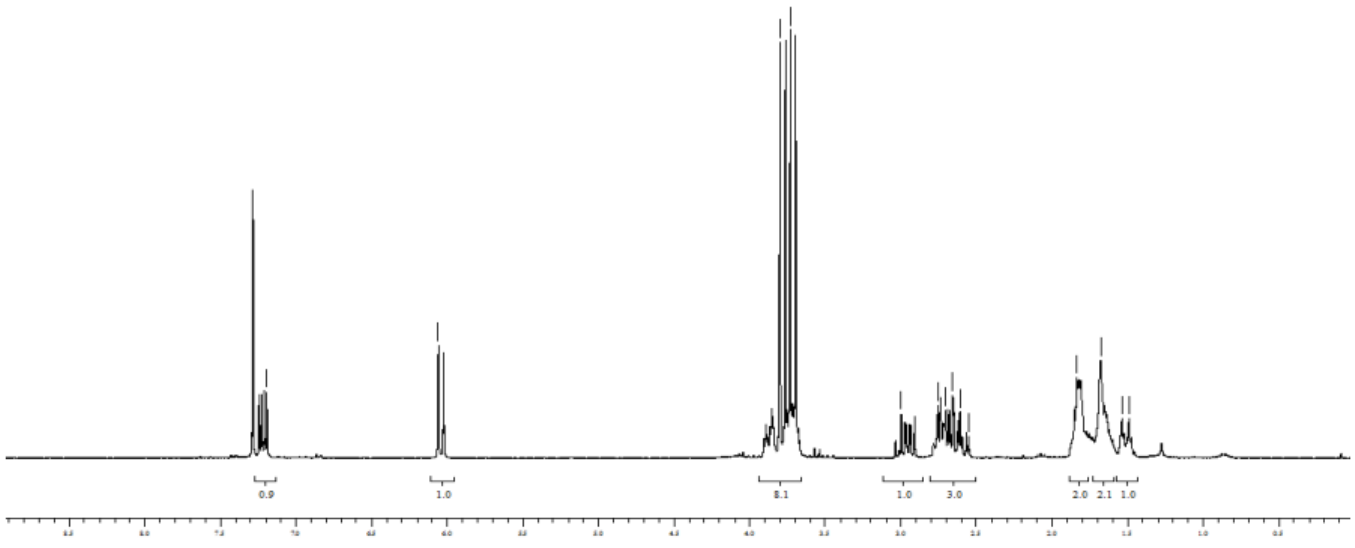
$CDCl_3$, 122 MHz

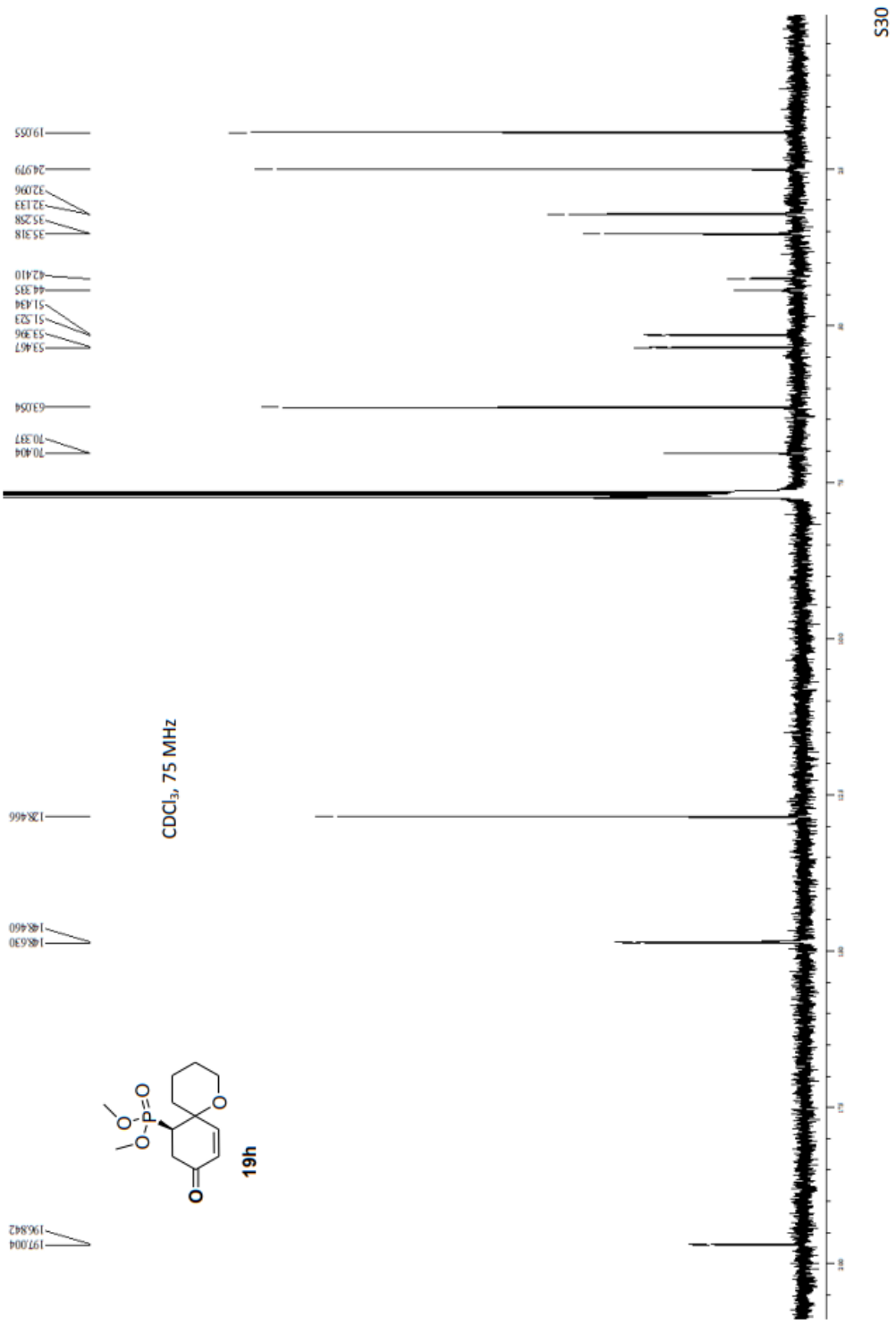


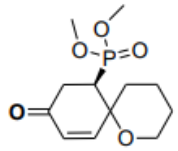


19h

$CDCl_3$, 300 MHz



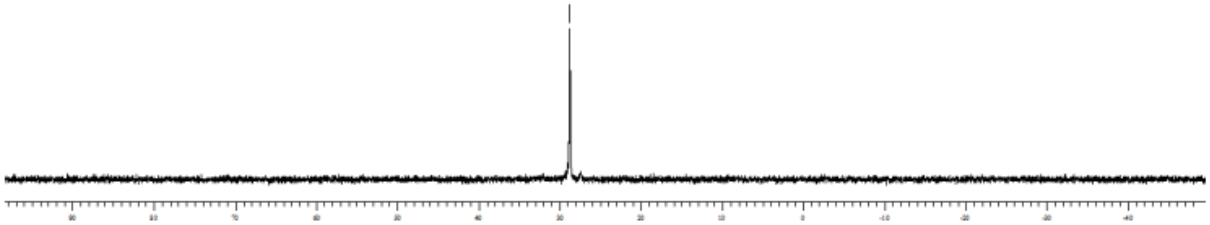

S30
19.055
24.979
32.096
32.133
35.258
35.318
42.410
44.335
51.434
51.529
53.396
53.467
63.054
70.337
70.404
128.466
148.460
148.530
196.842
197.004
CDCl3, 75 MHz
19h



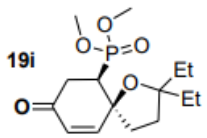
19h

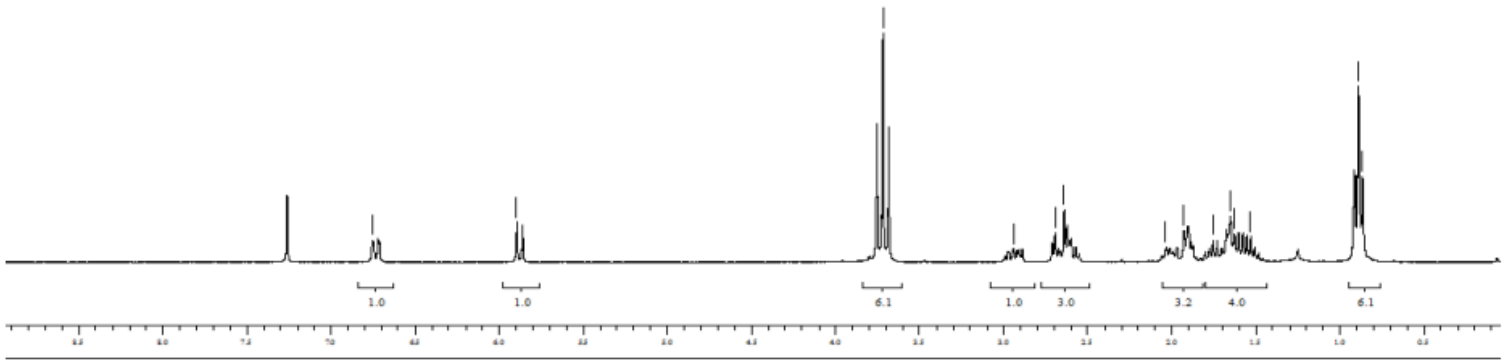
28.773

$CDCl_3$, 122 MHz

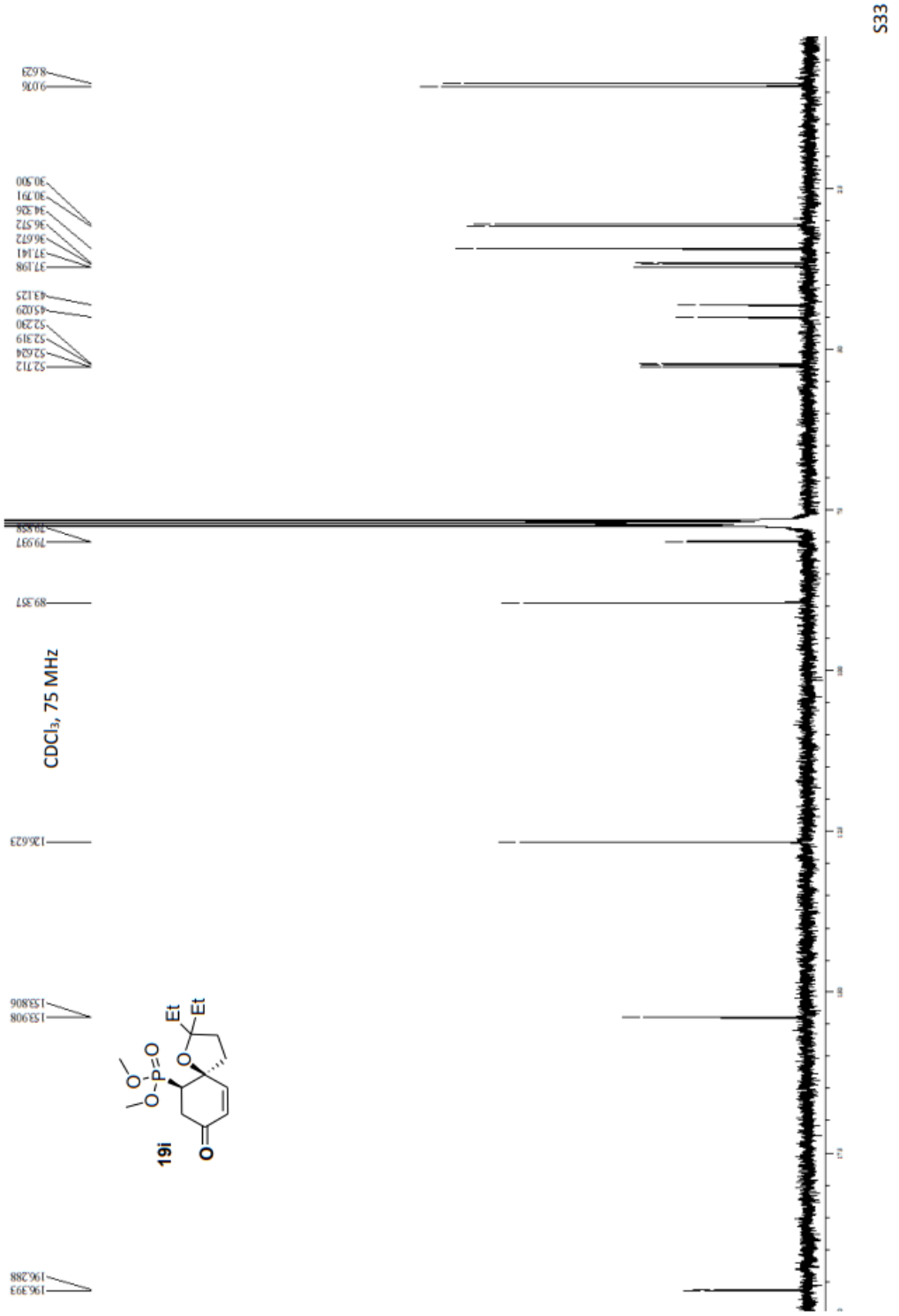


$CDCl_3$, 300 MHz

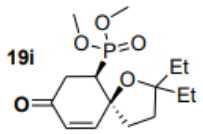


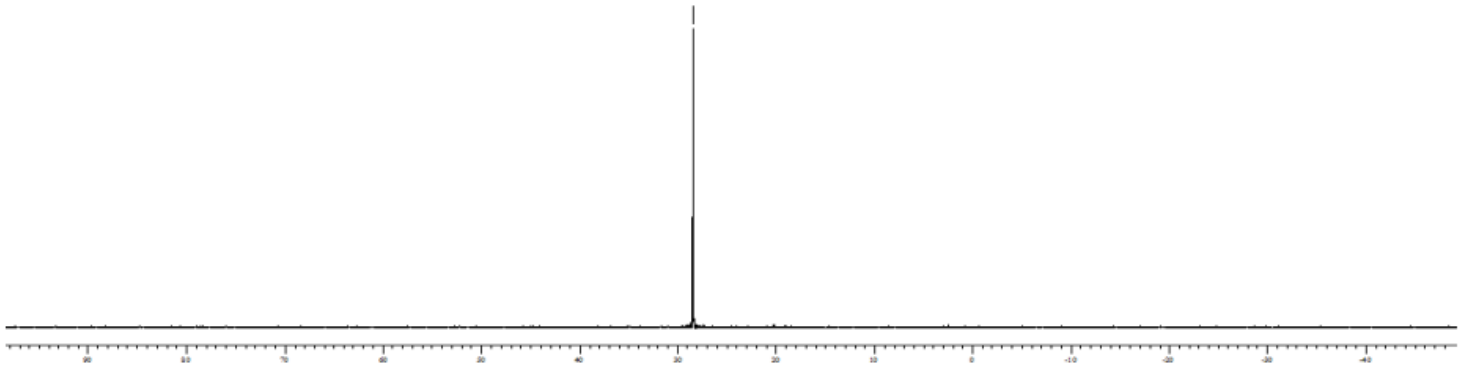


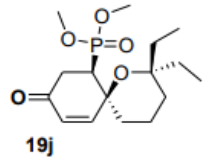
S32


S33
CDCl3, 75 MHz
19i
O
Et
Et
O
O
P
O
O
9.076
8.629
30.500
30.791
34.326
36.572
36.672
37.141
37.198
43.125
45.029
52.230
52.319
52.624
52.712
79.858
79.937
89.357
136.623
153.806
153.908
196.288
196.393

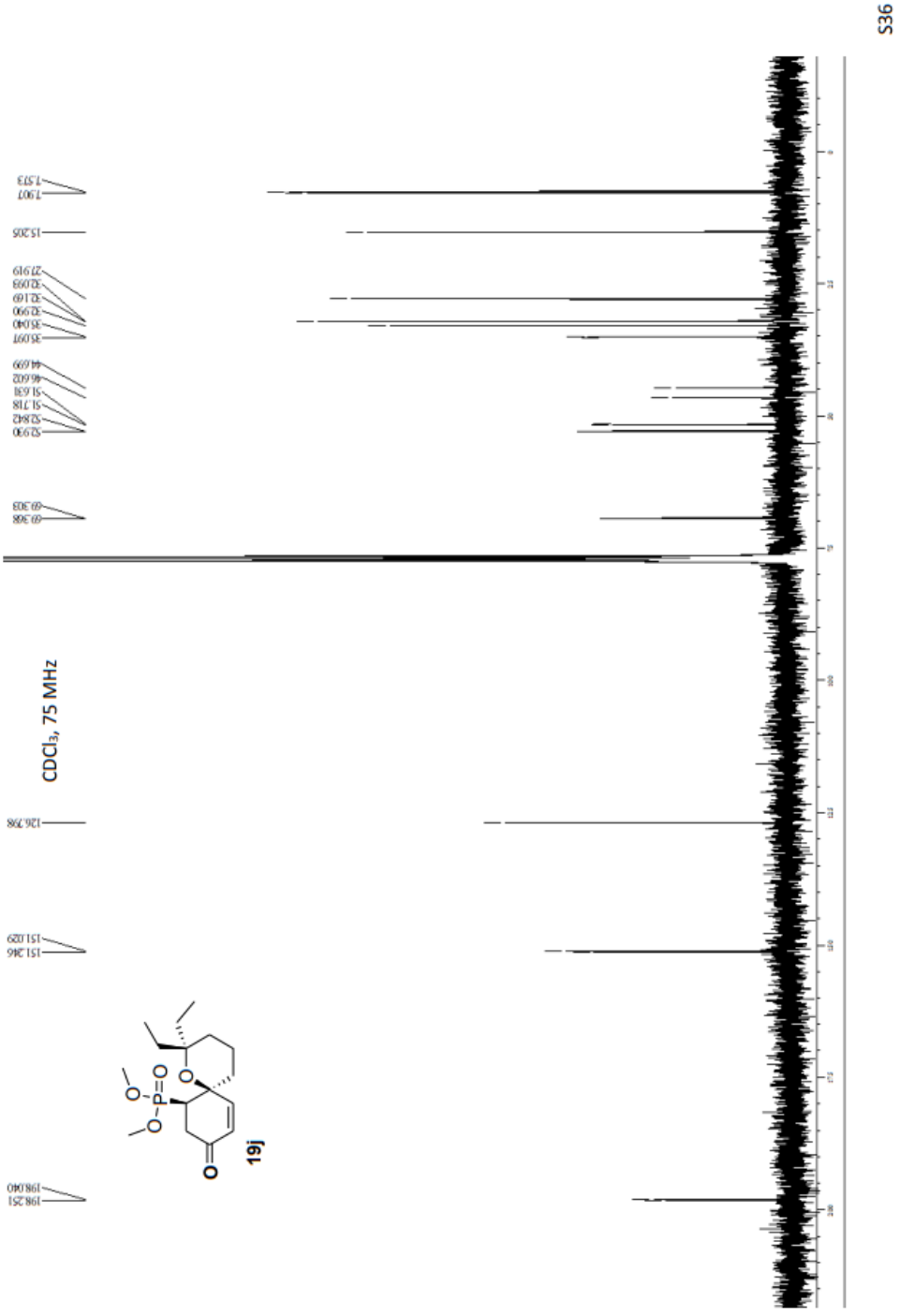
$CDCl_3$, 122 MHz






O
O
P
O
O
O
19j

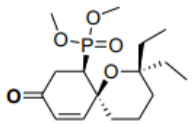
7.130
5.897
CDCl3, 300 MHz
3.704
3.702
3.103
2.843
2.585
2.436
1.874
1.718
1.611
1.532
1.453
1.385
0.809
0.722
1.1
1.0
3.03.0
1.1
1.1
1.41.0
9.0
3.13.1


S36
CDCl3, 75 MHz
19j
198.251
198.040
151.346
151.029
126.798
69.368
69.303
52.930
52.842
51.631
51.718
46.602
44.699
35.097
35.040
32.990
32.169
32.059
27.919
15.205
7.907
7.573

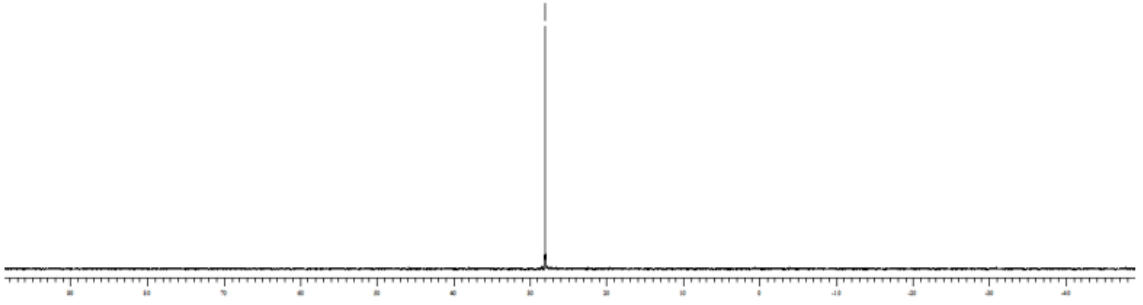
78

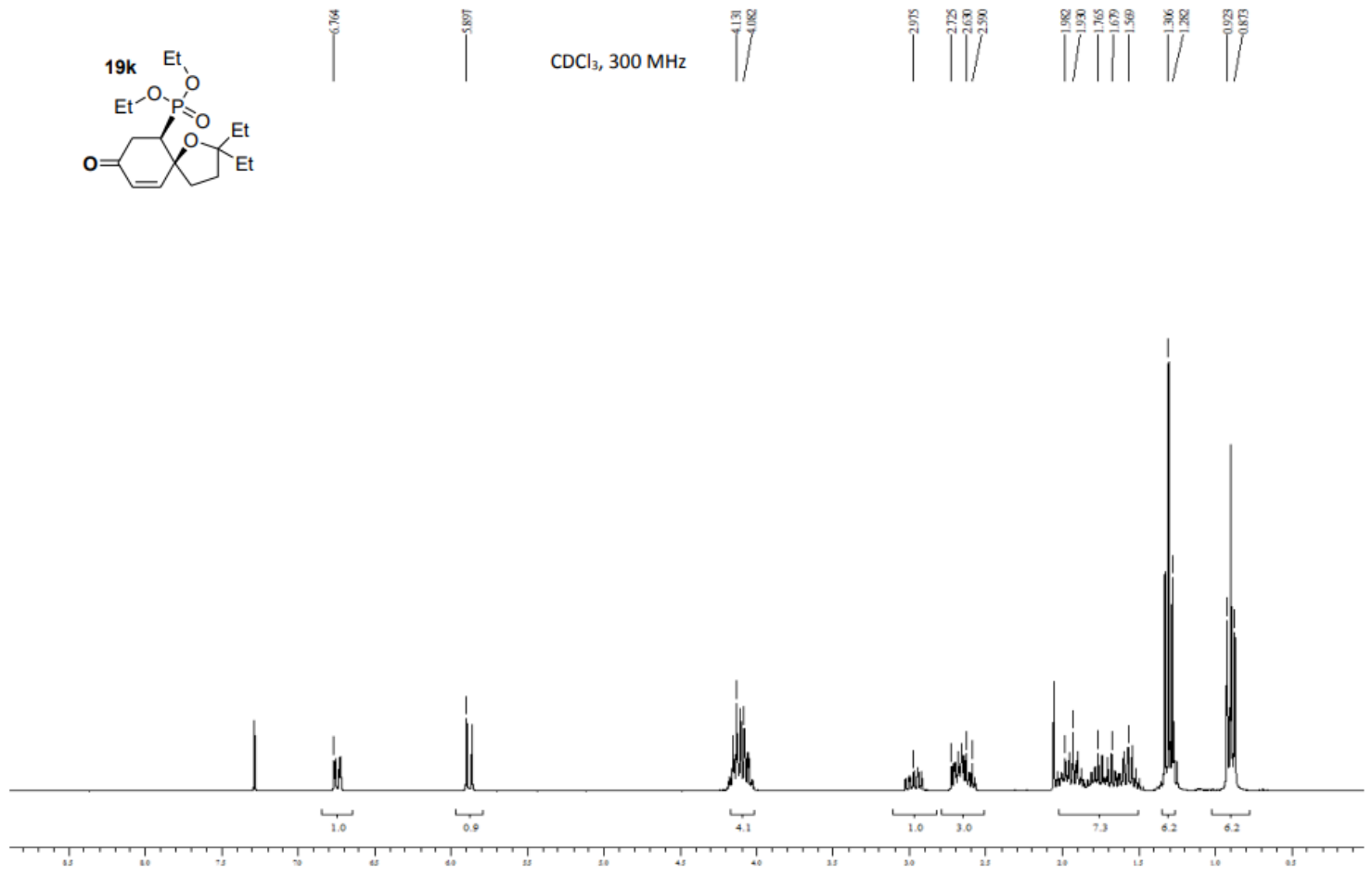
$CDCl_3$, 122 MHz

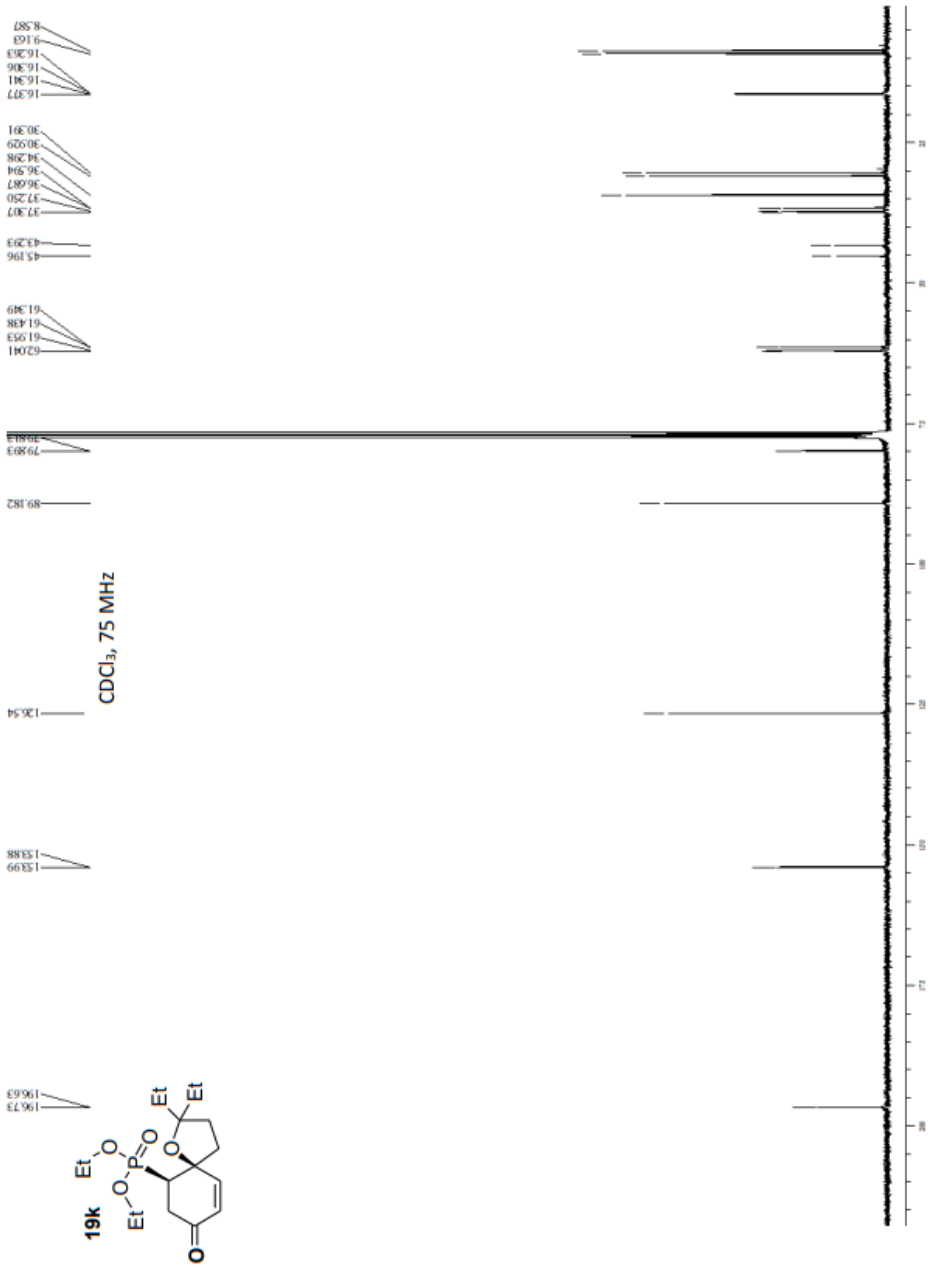
28.042



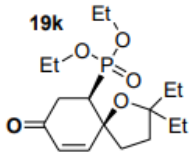
19j




19k
CDCl3, 300 MHz
0.764
5.897
4.131
4.082
2.975
2.725
2.630
2.590
1.982
1.930
1.765
1.679
1.569
1.306
1.282
0.923
0.873
1.0
0.9
4.1
1.0
3.0
7.3
6.2
6.2

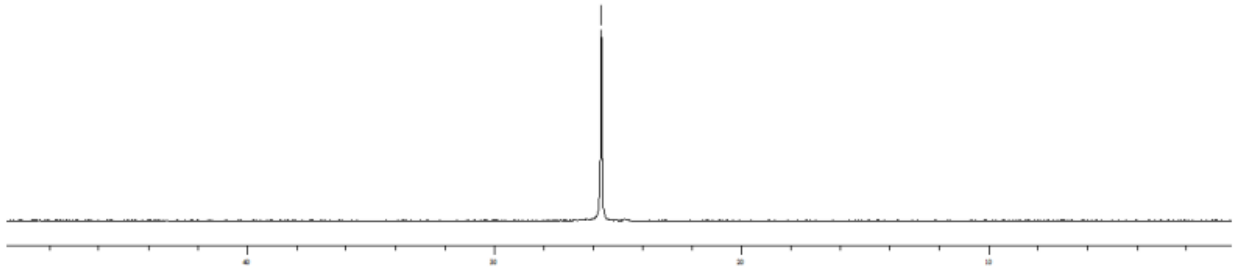

CDCl3, 75 MHz
19k
Et
Et
Et
Et
O
O
O
O
P
O
8.587
9.163
16.363
16.306
16.341
16.377
30.391
30.929
34.298
36.594
36.687
37.250
37.307
43.293
45.196
61.349
61.438
61.953
62.041
79.819
79.893
89.182
136.54
153.99
153.888
196.63
196.73

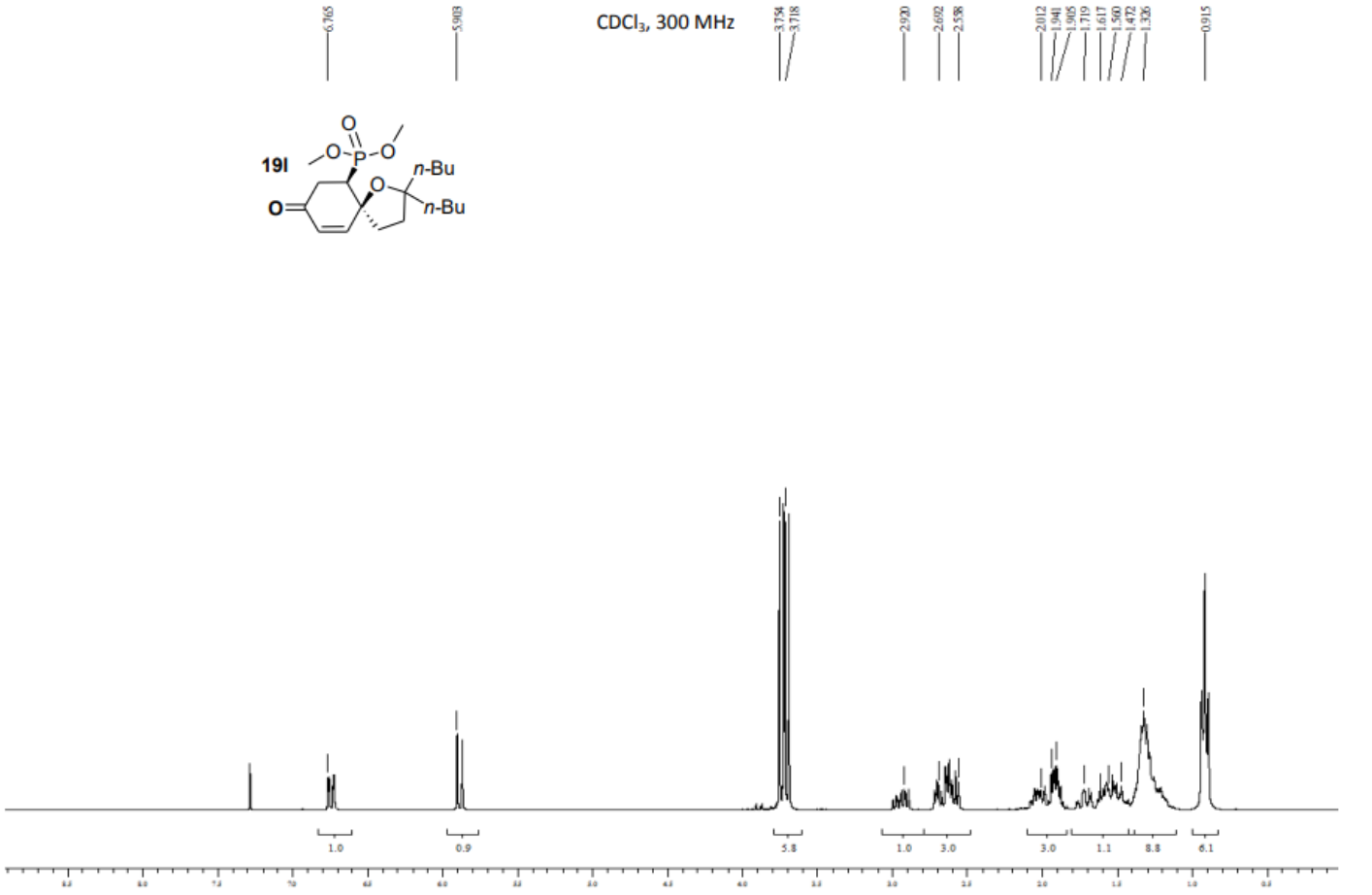
S39

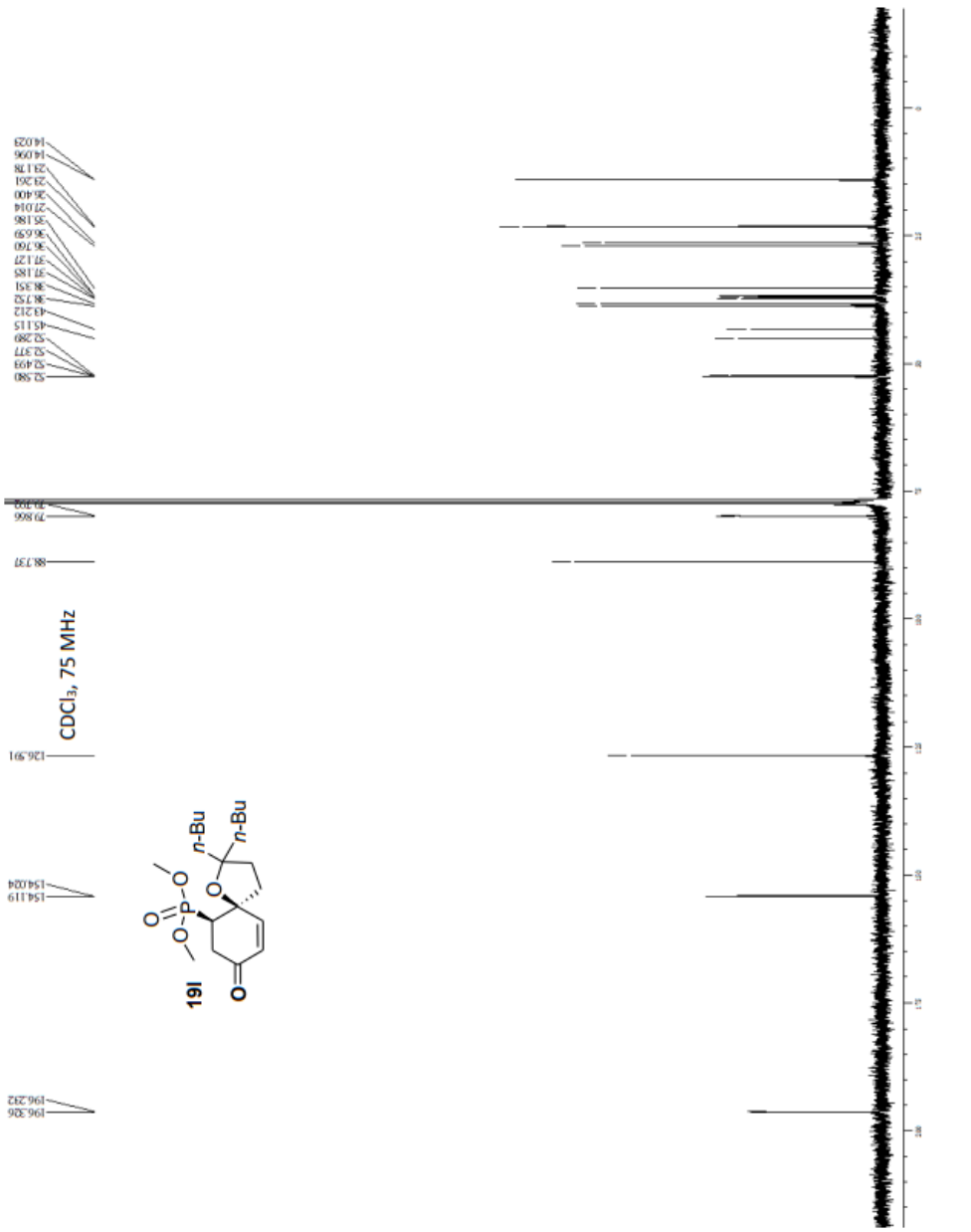


25.66

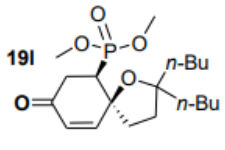
$CDCl_3$, 122 MHz



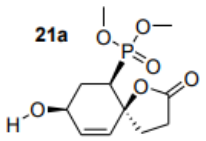

6.765
5.903
CDCl3, 300 MHz
3.754
3.718
2.920
2.692
2.598
2.012
1.941
1.905
1.719
1.617
1.560
1.472
1.326
0.915
19l
n-Bu
n-Bu
O
1.0
0.9
5.8
1.0
3.0
3.0
1.1
8.8
6.1


S42
CDCl3, 75 MHz
19l
n-Bu
n-Bu
O
O
O
O
P
O
O
14.029
14.096
23.178
23.261
26.400
27.014
35.186
36.659
36.760
37.127
37.185
38.351
38.752
43.212
45.115
52.289
52.377
52.493
52.580
79.322
79.856
88.737
126.991
154.024
154.119
196.232
196.326

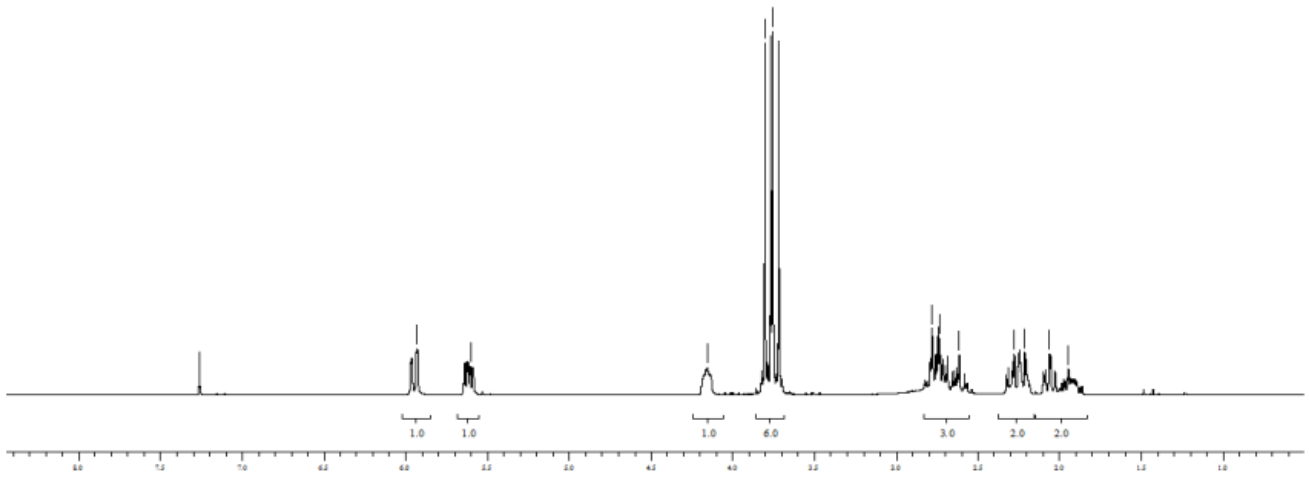
19l

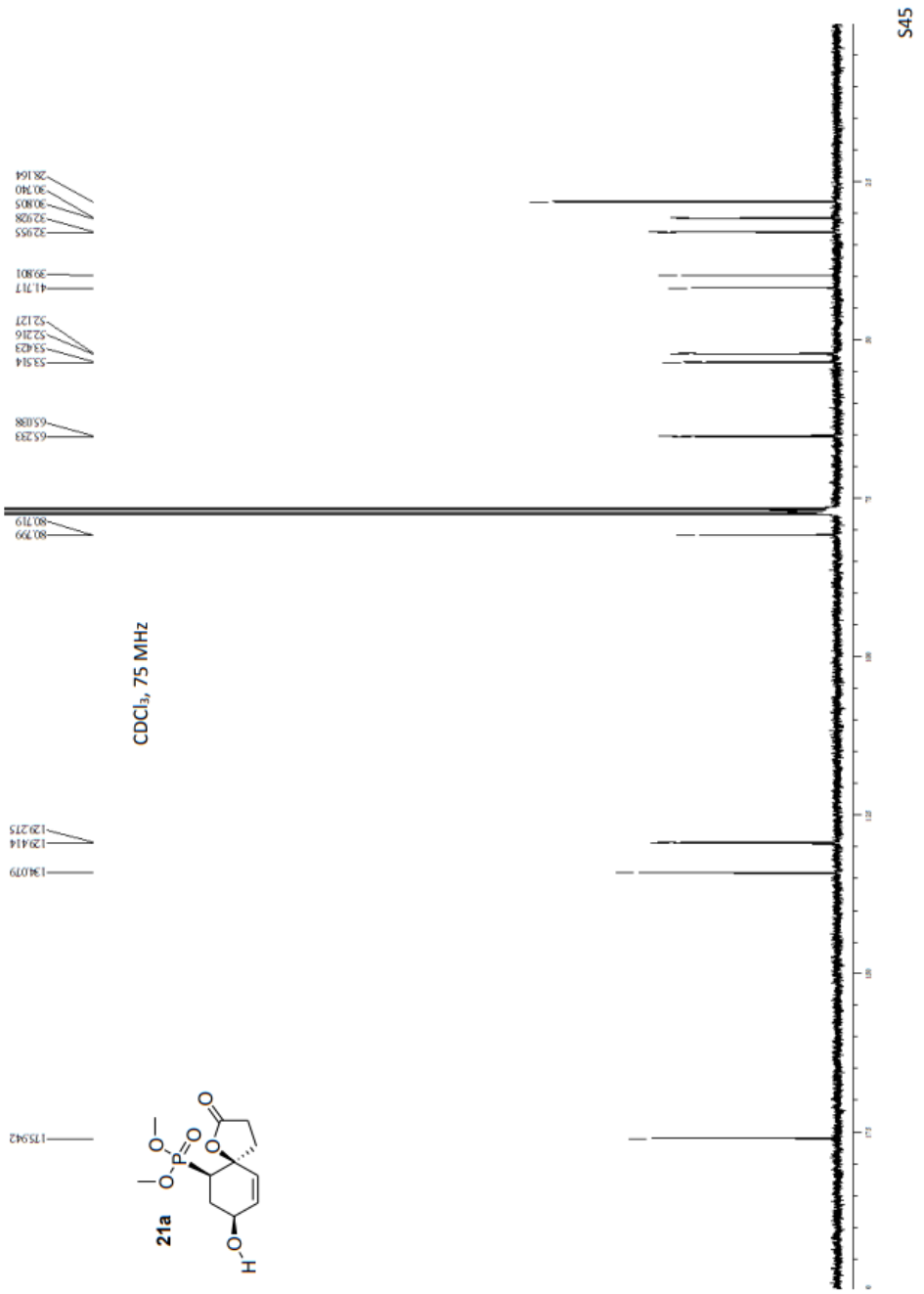


$CDCl_3$, 122 MHz

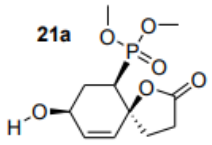

21a


CDCl3, 300 MHz
5.928
5.602
4.154
3.801
3.753
2.779
2.731
2.612
2.275
2.212
2.062
1.944

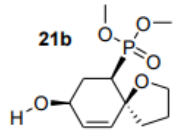

1.0
1.0
1.0
6.0
3.0
2.0
2.0


S45
CDCl3, 75 MHz
21a
28.164
30.740
30.805
32.928
32.955
39.801
41.717
52.127
52.216
53.423
53.514
65.288
65.233
80.719
80.799
128.275
128.414
138.079
175.942

21a



$CDCl_3$, 122 MHz

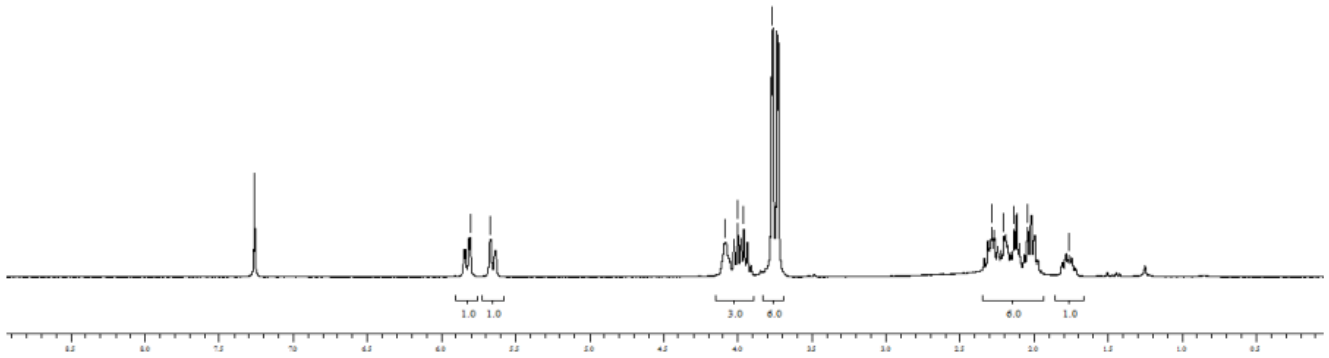


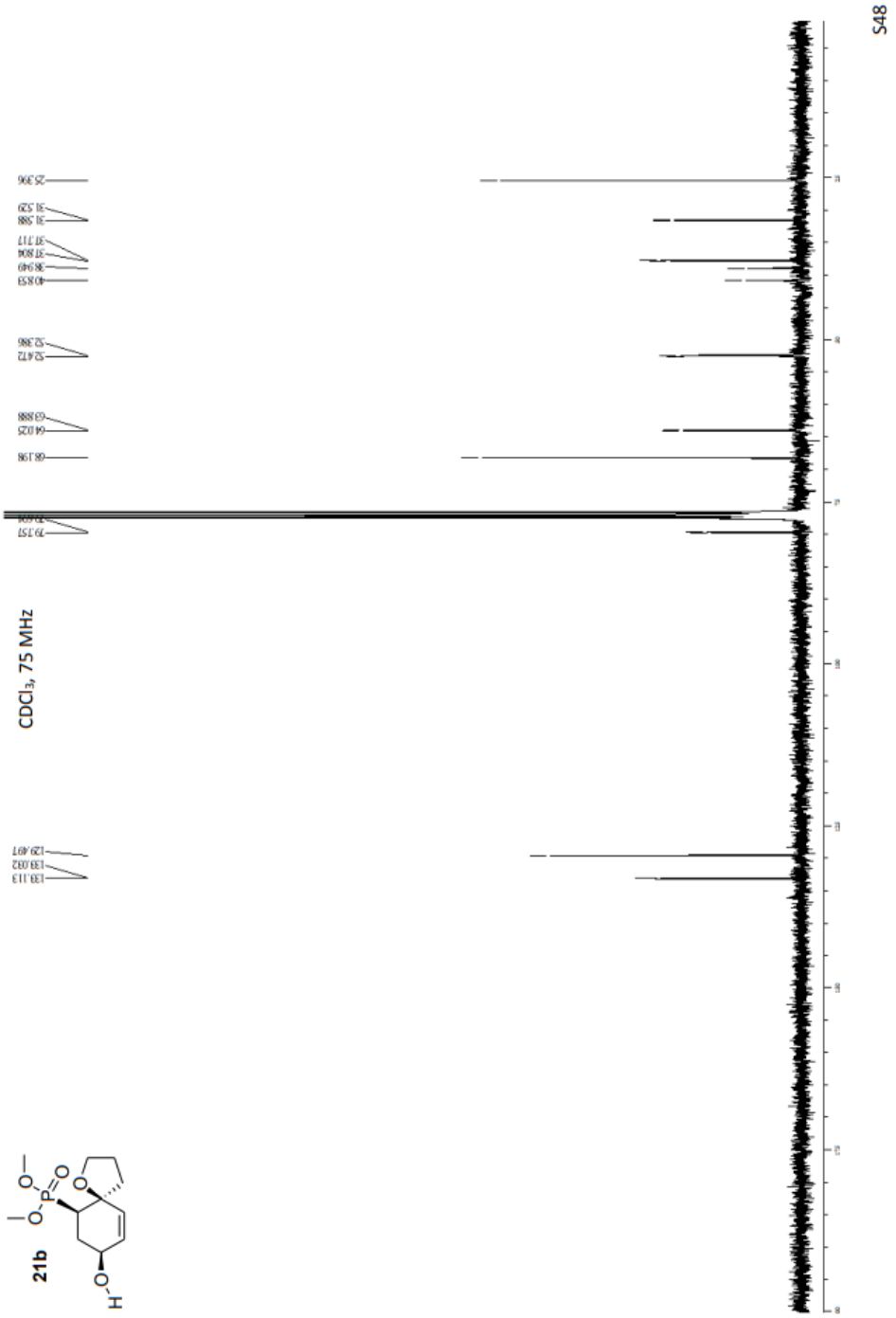
5.802
5.669

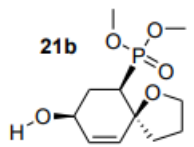
$CDCl_3$, 300 MHz

4.087
3.998
3.956
3.768

2.282
2.202
2.134
2.040
1.763

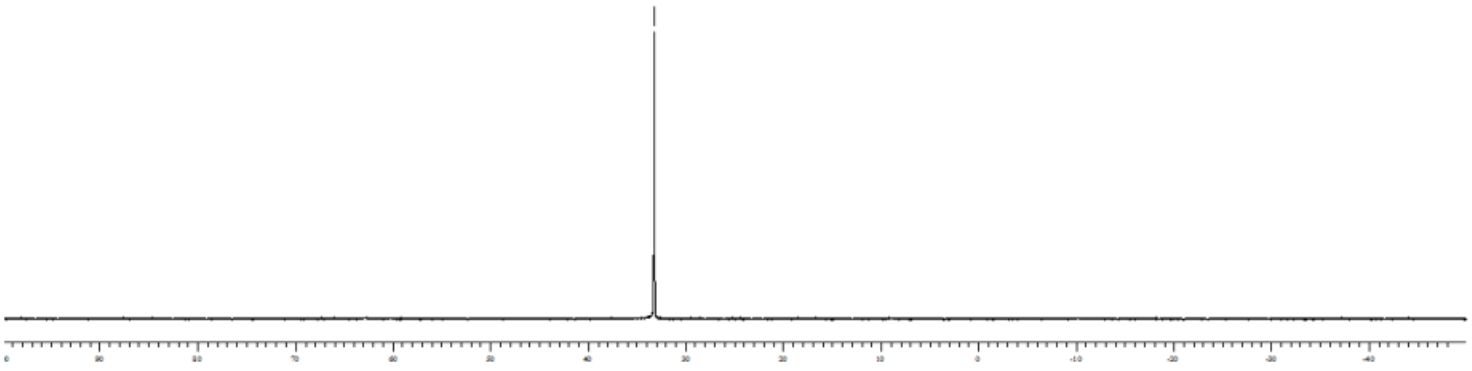



S48
CDCl3, 75 MHz
21b

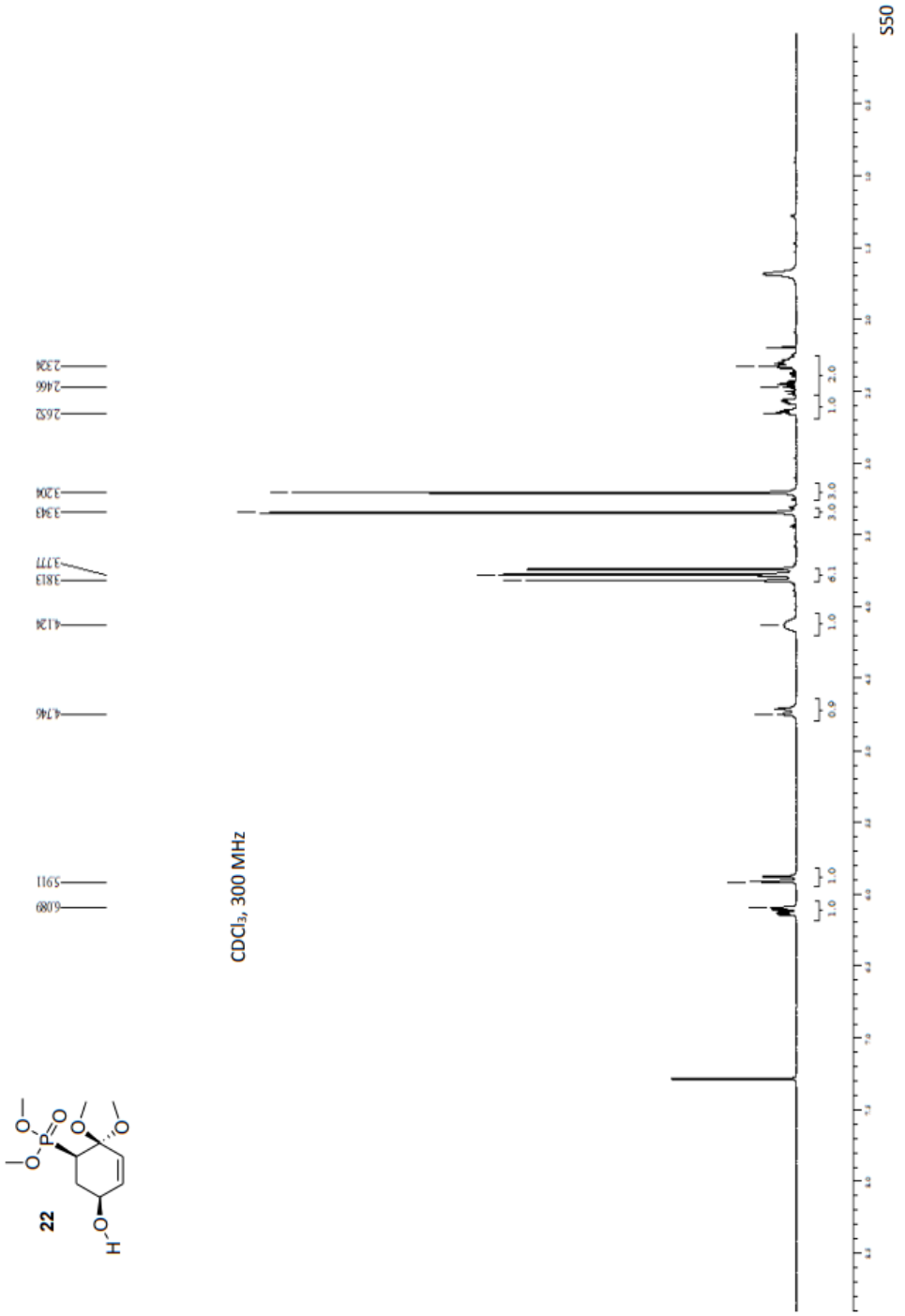


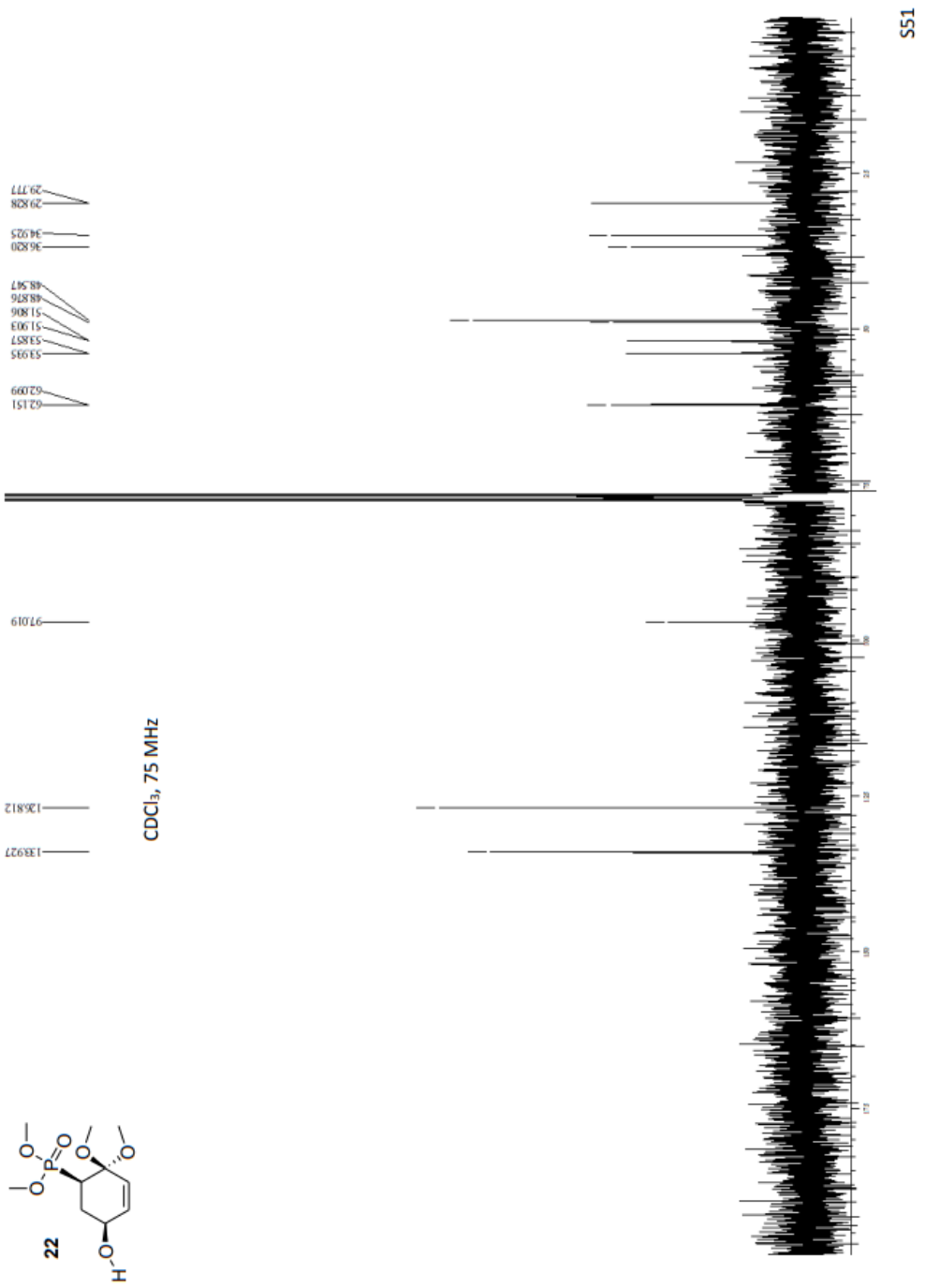
3213

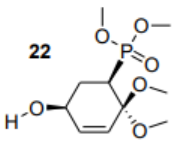
$CDCl_3$, 122 MHz



90

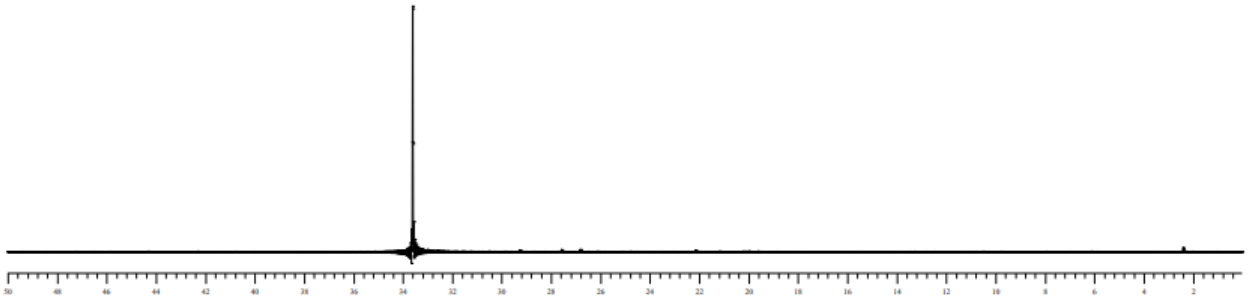

22
CDCl3, 300 MHz
S50

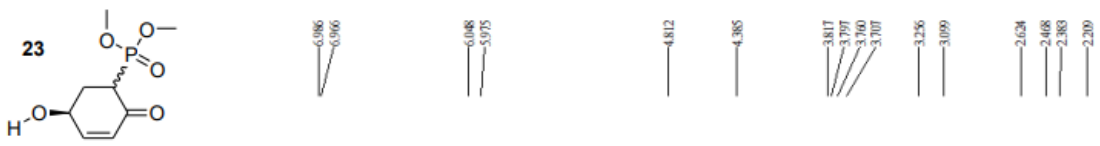

S51
CDCl3, 75 MHz
22
29.777
29.828
34.925
36.820
48.547
48.876
51.806
51.903
53.857
53.935
62.099
62.151
97.019
133.927
136.812



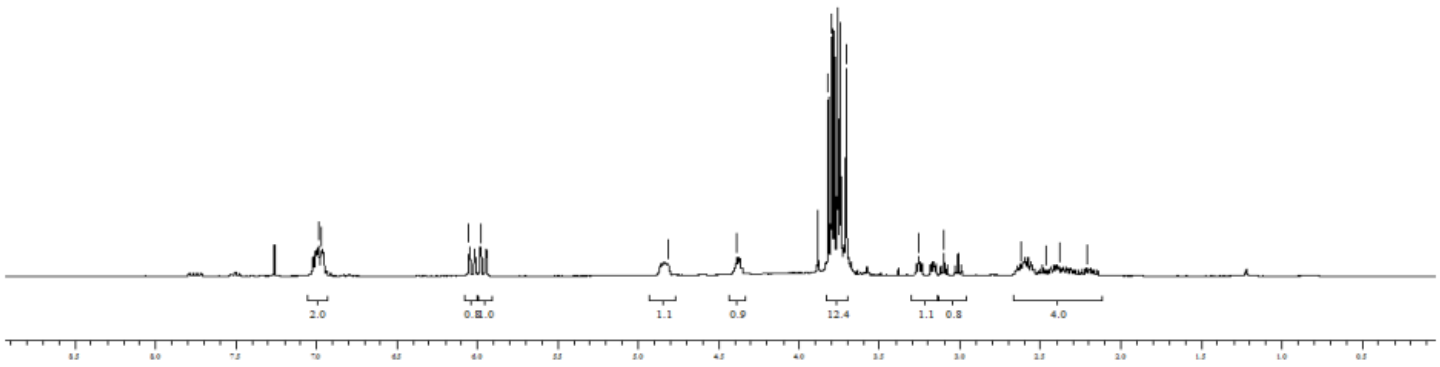
33.610

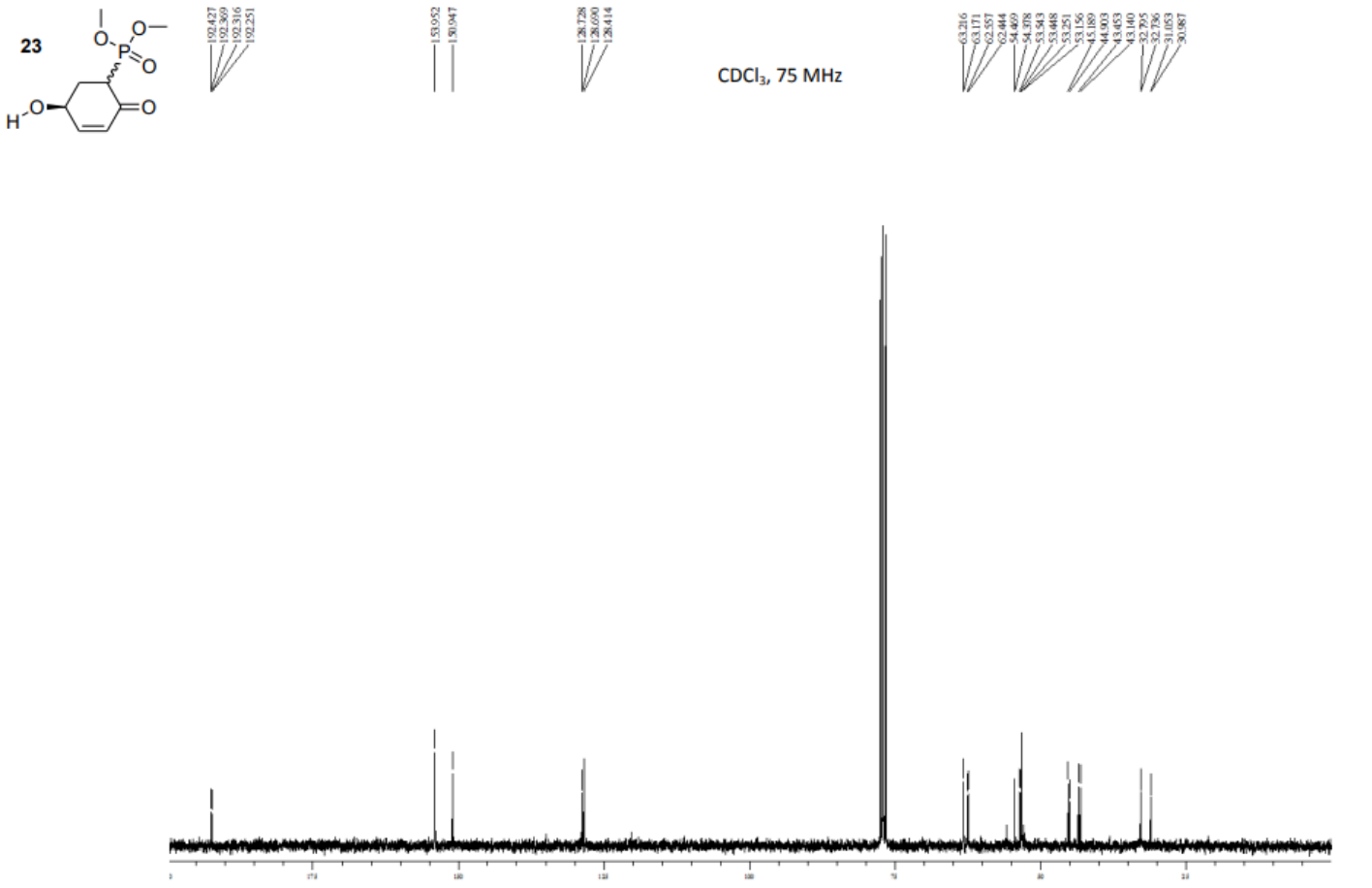
$CDCl_3$, 122 MHz

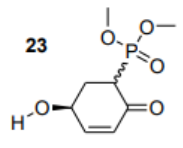




$CDCl_3$, 300 MHz

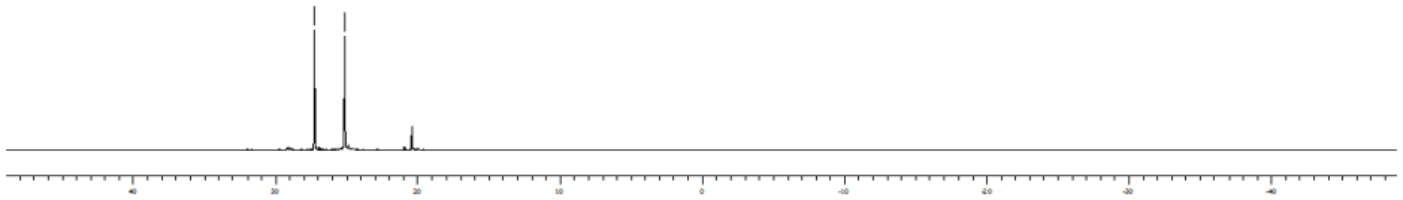


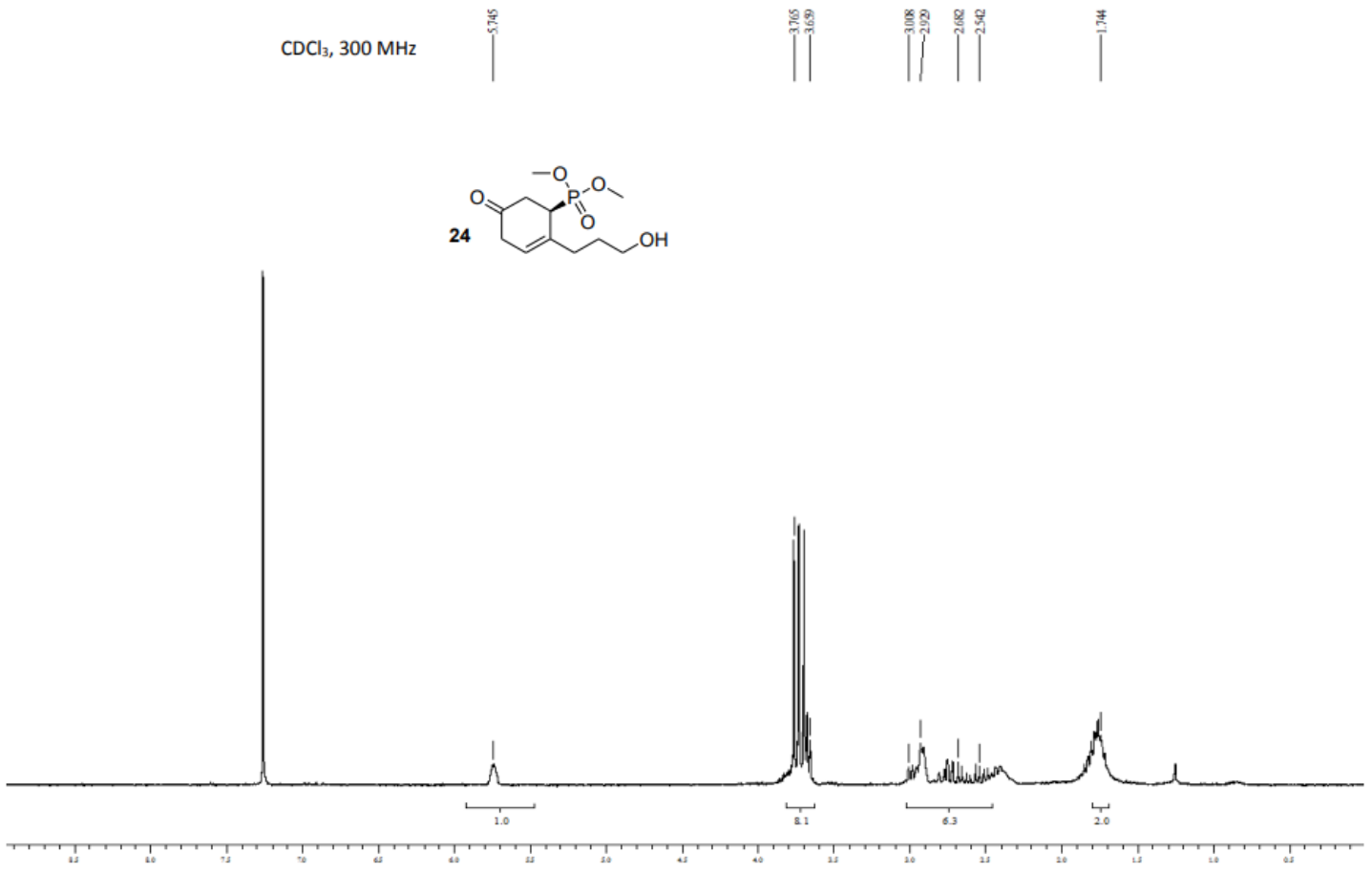

23
192.427
192.369
192.316
192.251
153.952
130.947
128.728
128.690
128.414
CDCl3, 75 MHz
63.216
63.171
62.557
62.444
54.469
54.378
53.543
53.448
53.251
53.156
45.189
44.903
43.453
43.140
32.795
32.736
31.053
30.987

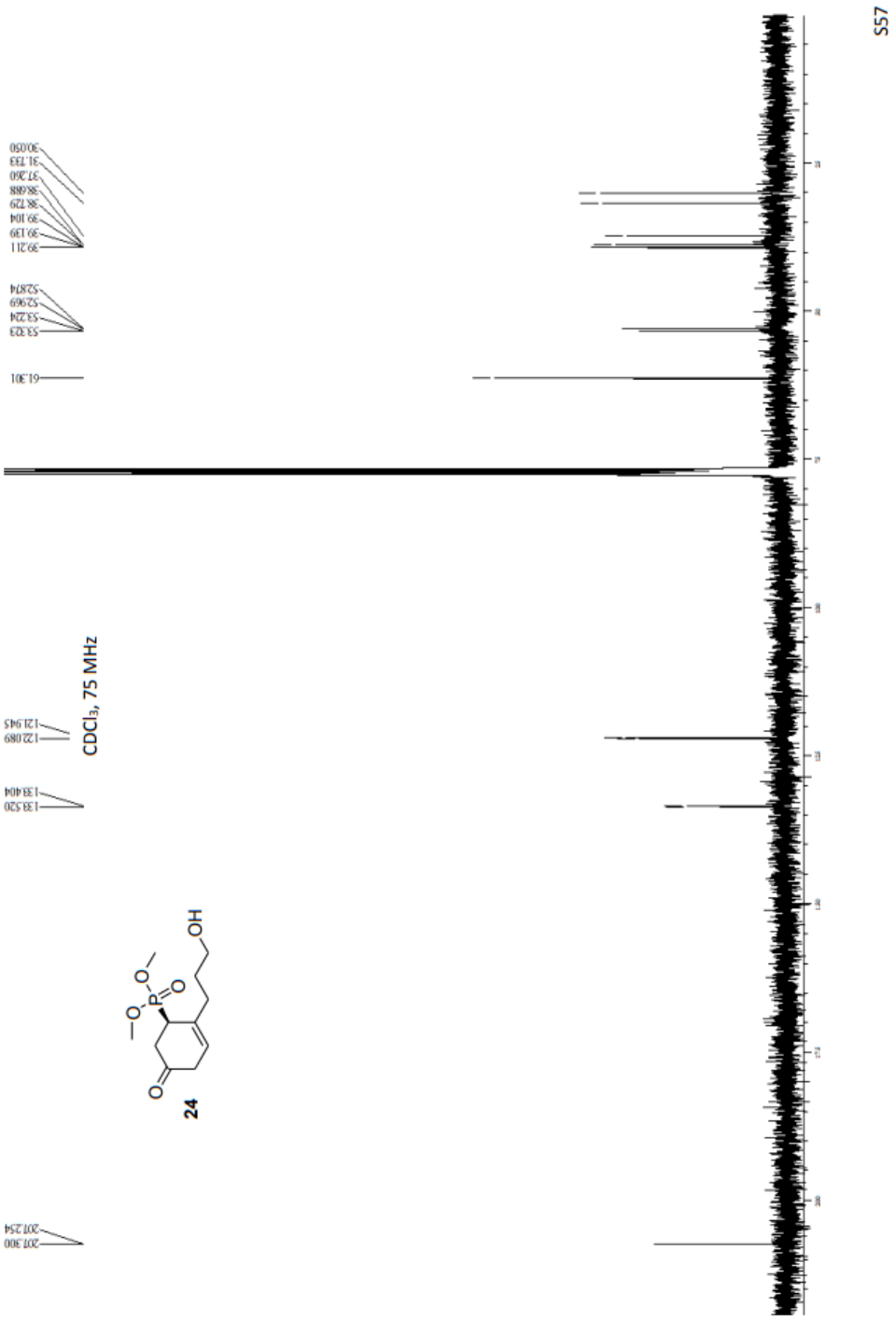


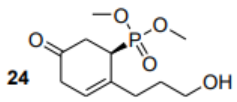
27.251
25.131

$CDCl_3$, 122 MHz




CDCl3, 300 MHz
5.745
3.765
3.659
3.008
2.929
2.682
2.542
1.744
24
OH
1.0
8.1
6.3
2.0

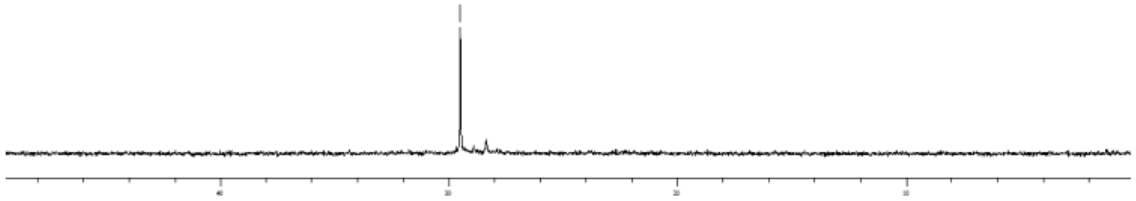

S57
CDCl3, 75 MHz
207.300
207.254
133.520
133.404
122.089
121.945
61.301
53.323
53.204
52.969
52.874
39.211
39.139
39.104
38.729
38.488
37.360
31.733
30.050
OH
O
O
O
O
24

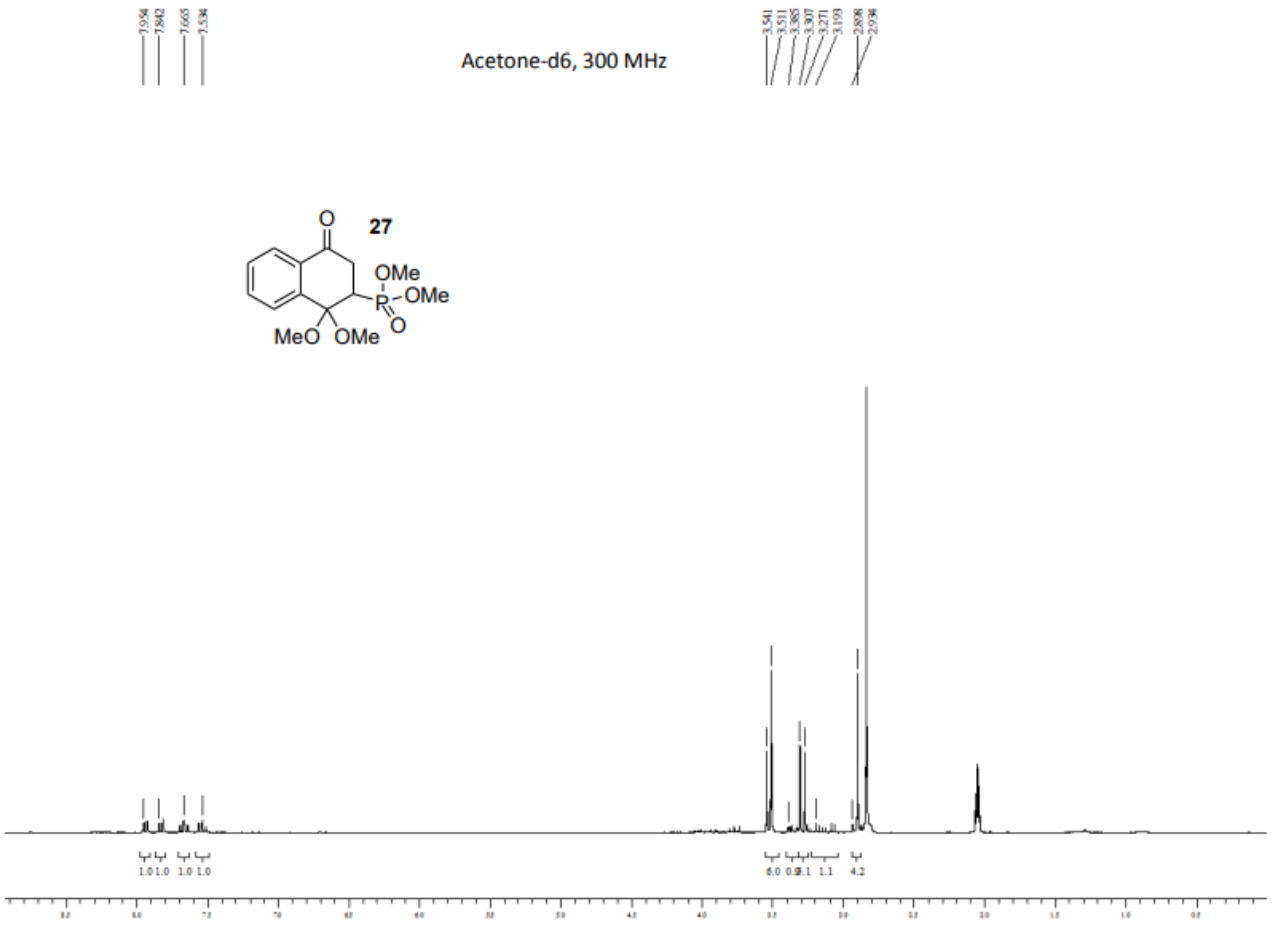


24

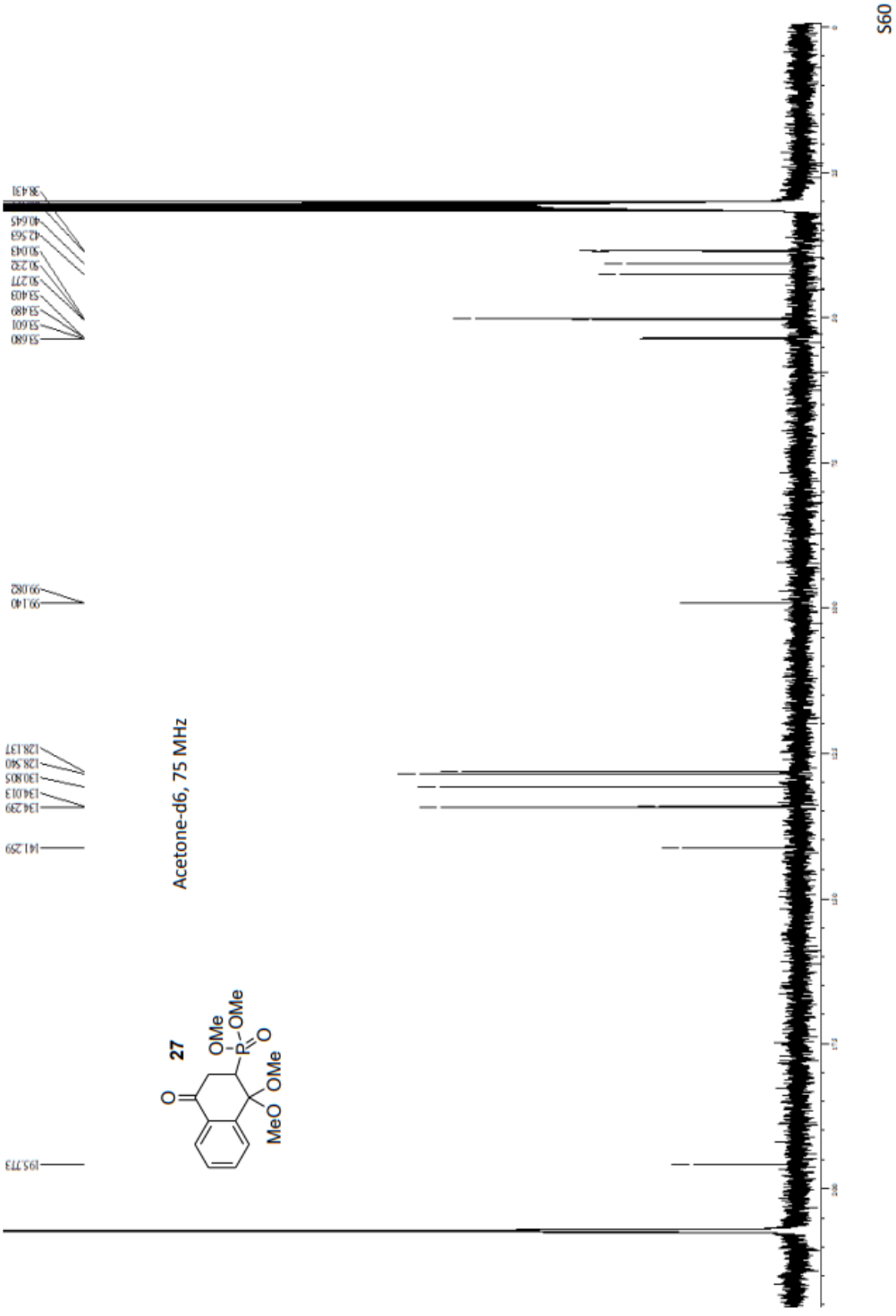
29.49

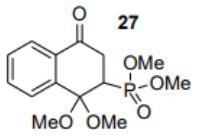
$CDCl_3$, 122 MHz




7.956
7.842
7.665
7.534
Acetone-d6, 300 MHz
3.541
3.511
3.385
3.307
3.271
3.193
2.808
2.934
27
O
OMe
OMe
P
O
MeO
OMe
1.0 1.0 1.0 1.0
6.0
4.2

100

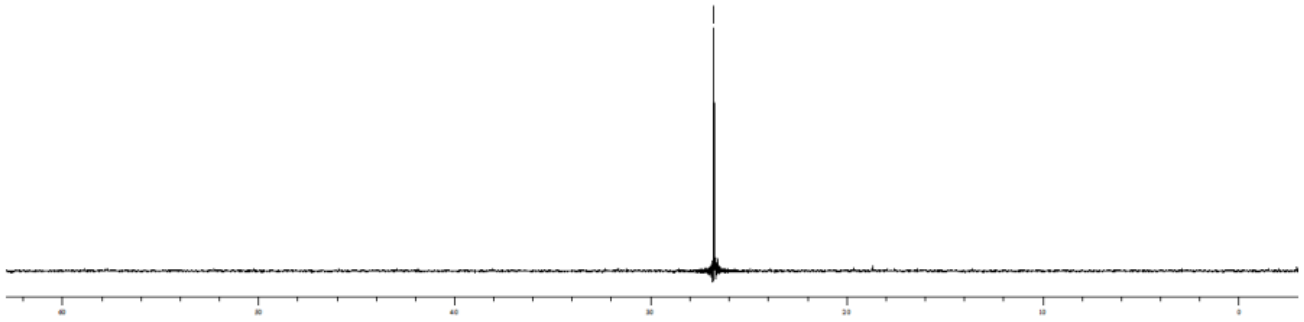

S60
Acetone-d6, 75 MHz
27
O
OMe
P
OMe
O
MeO
OMe
195.773
161.259
136.299
136.013
130.805
128.560
128.137
99.140
99.062
53.680
53.601
53.489
53.403
50.277
50.230
50.043
42.563
40.645
38.431



27

Acetone-d6, 122 MHz

26.75



ANNEXE B

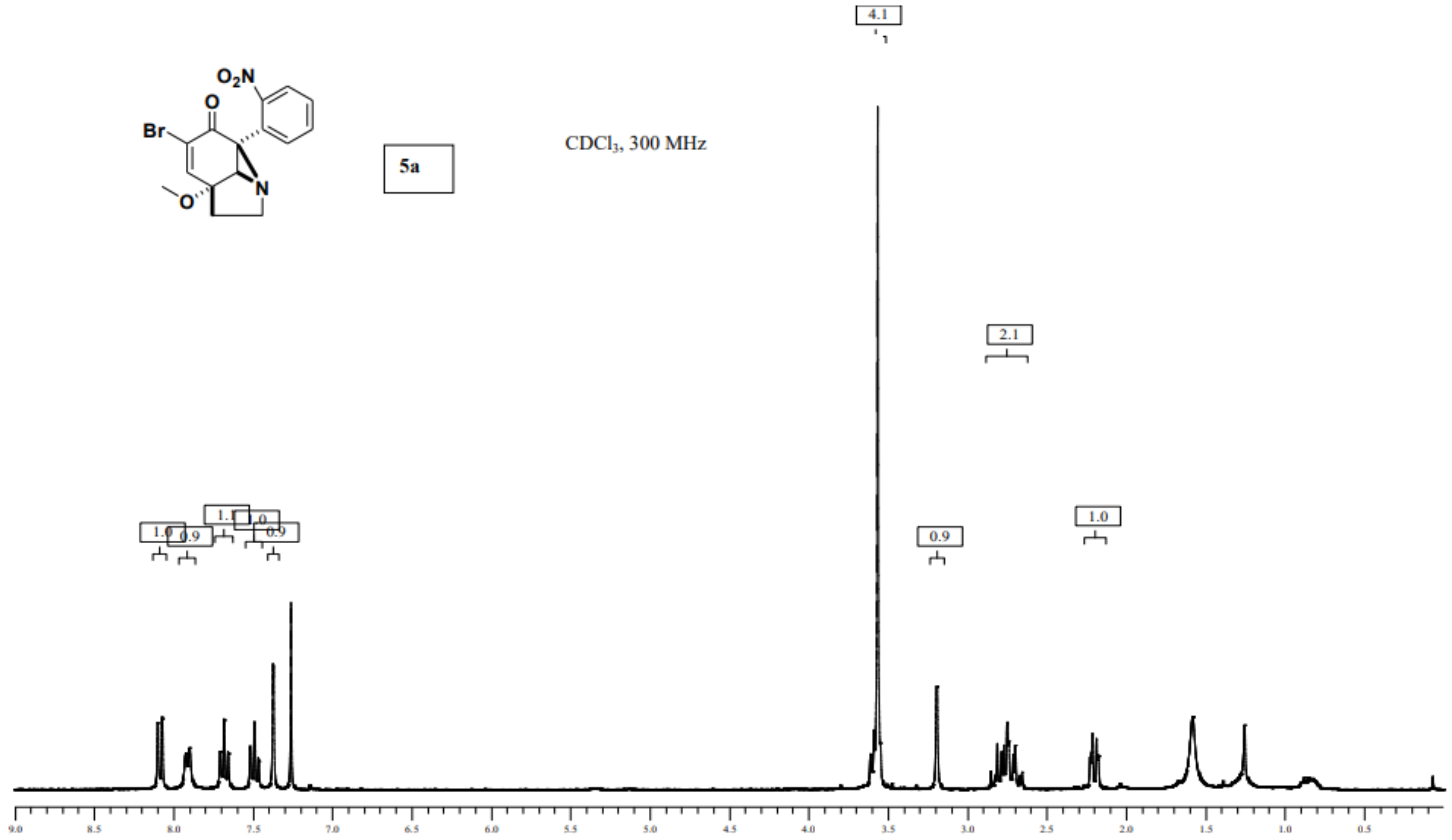
AN ARYLATIVE AZIRIDINATION PROCESS TOWARD ASPIDOSPERMA ALKALOIDS, Supporting Information

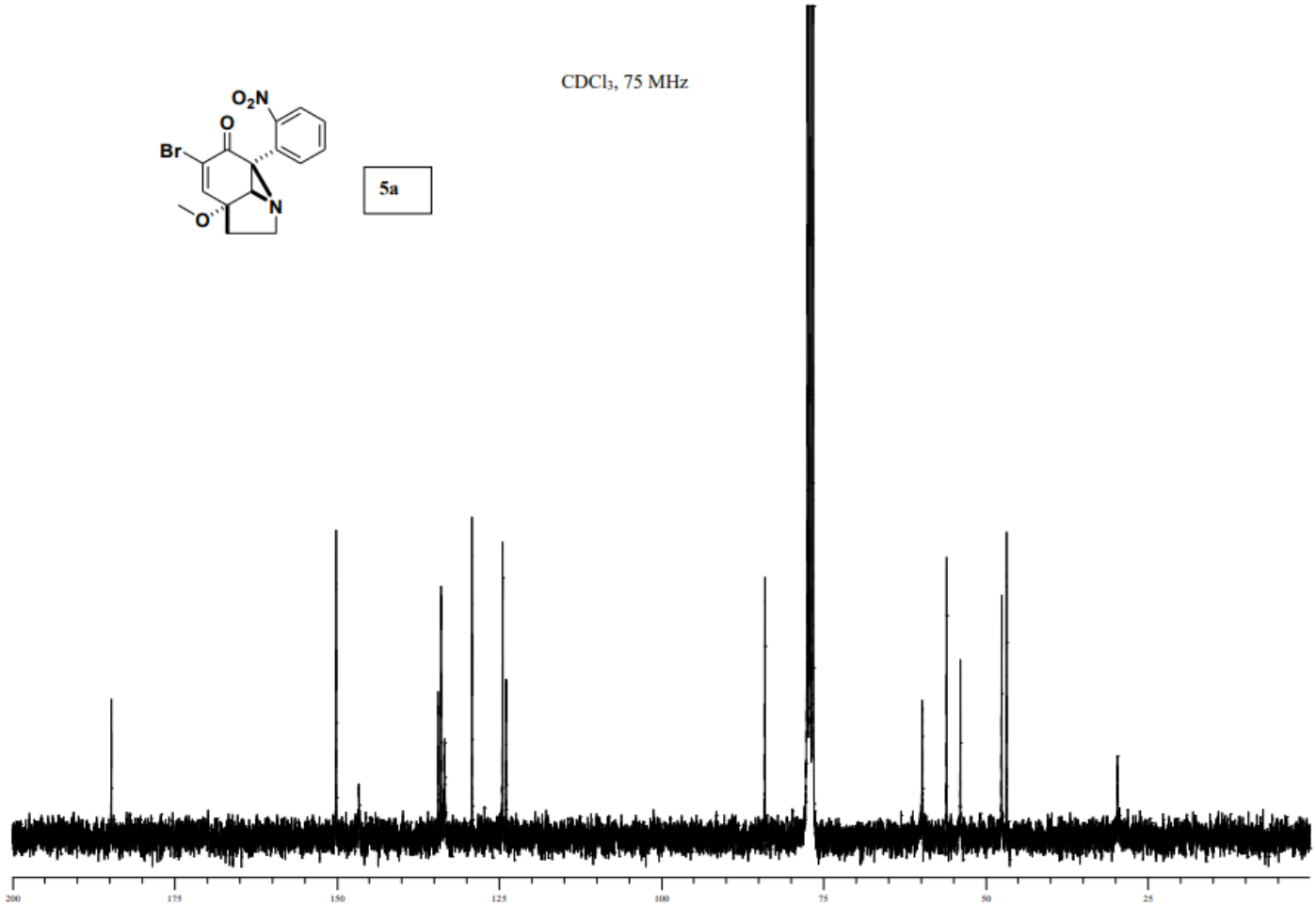
AN ARYLATIVE AZIRIDINATION PROCESS TOWARD ASPIDOSPERMA ALKALOIDS

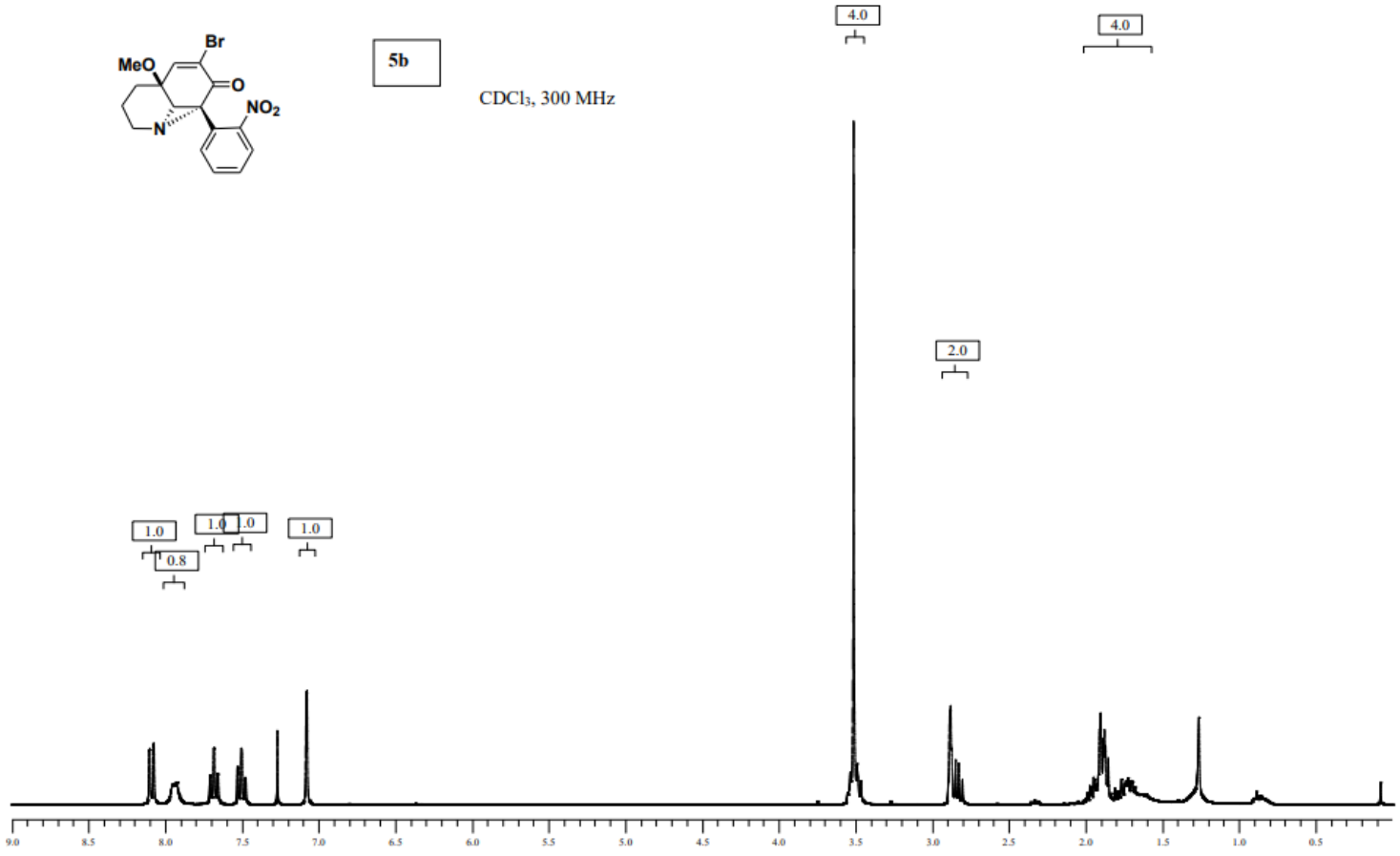
Kouassi Signo, Elsa Deruer, Siomenan Coulibali, and Sylvain Canesi*

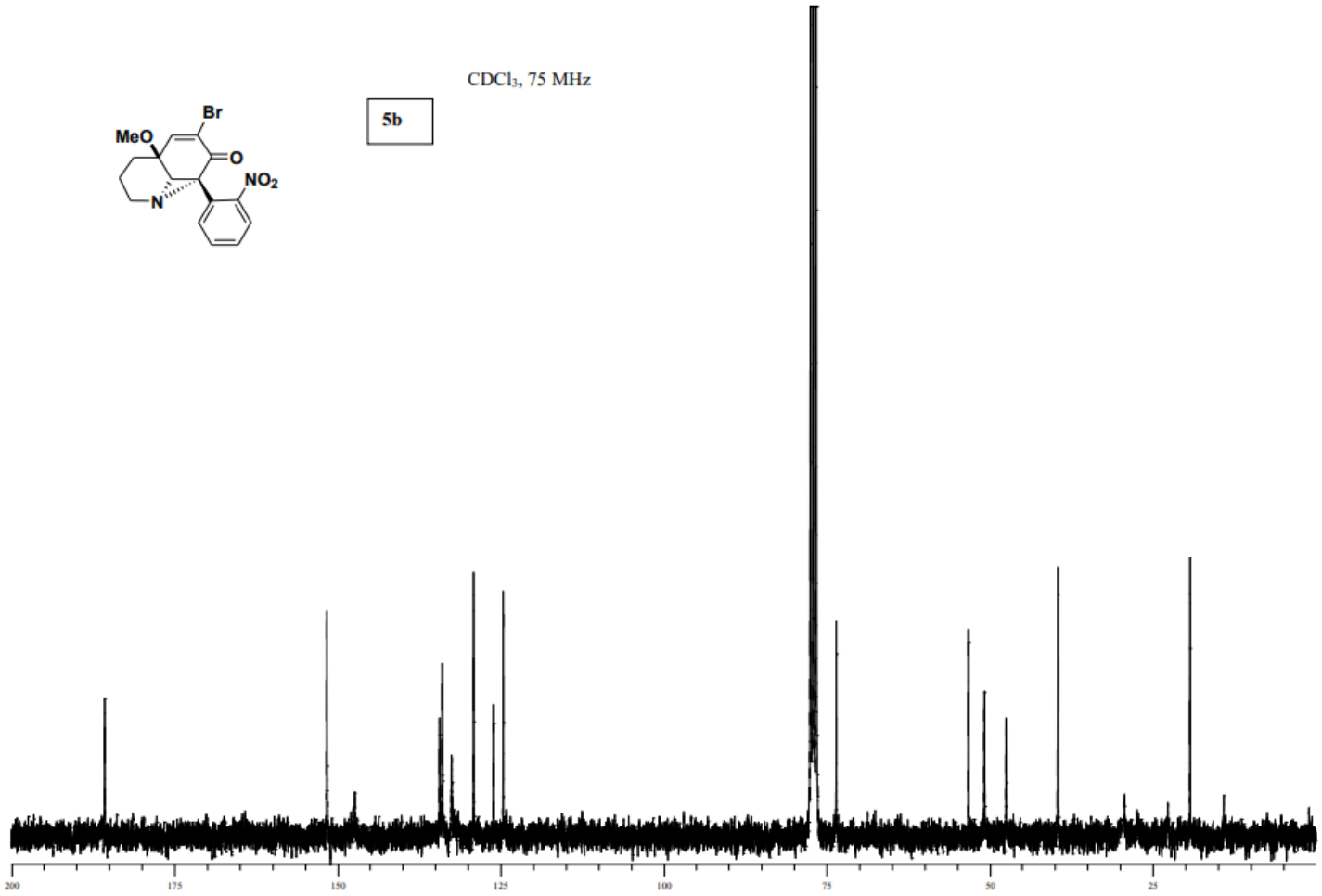
Laboratoire de Méthodologie et Synthèse de Produits Naturels, Université du Québec à Montréal, C.P. 8888, Succ. Centre-Ville, Montréal, H3C 3P8, Québec, Canada. E-mail: canesi.sylvain@uqam.ca

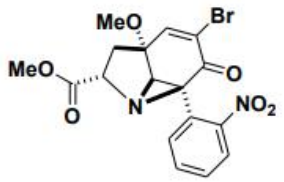
Supporting Information


O2N
O
Br
N
O
5a
CDCl3, 300 MHz
4.1
2.1
1.0
0.9
1.0
0.9
1.0
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


O_2N
O
Br
N
O
5a
$CDCl_3$, 75 MHz
200
175
150
125
100
75
50
25

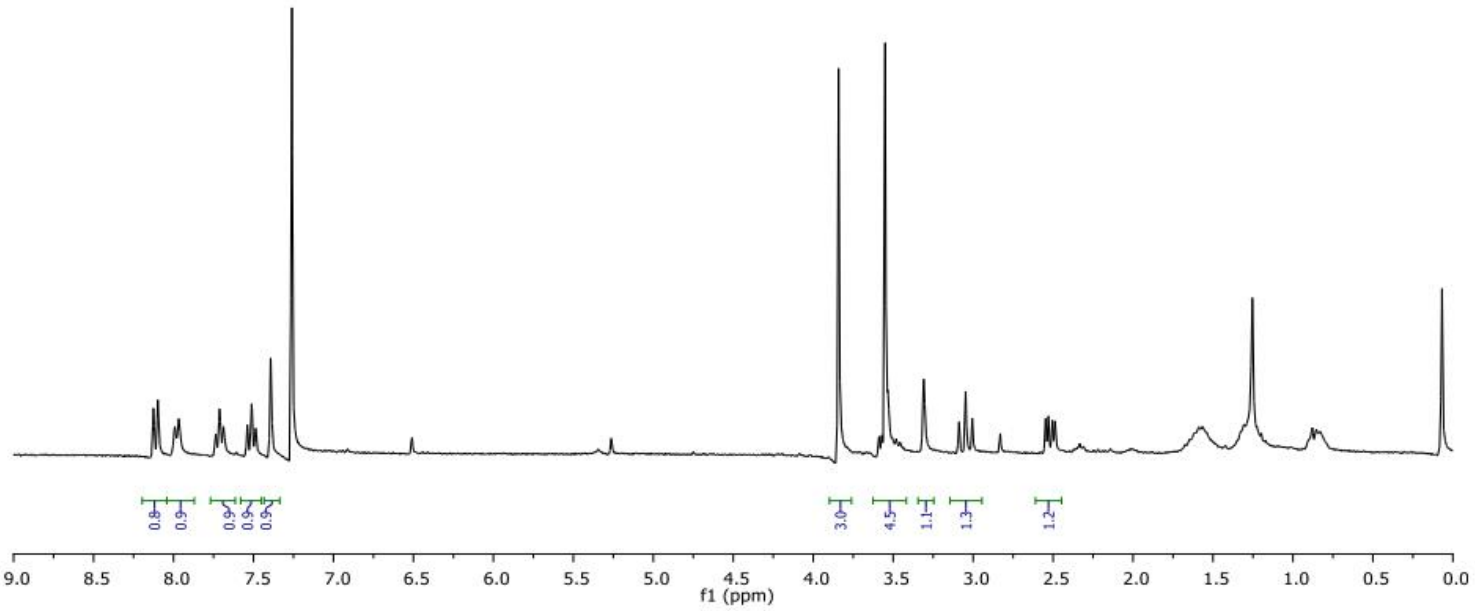

Br
MeO
O
NO2
N
5b
CDCl3, 300 MHz
4.0
4.0
2.0
1.0
1.0
1.0
1.0
0.8
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

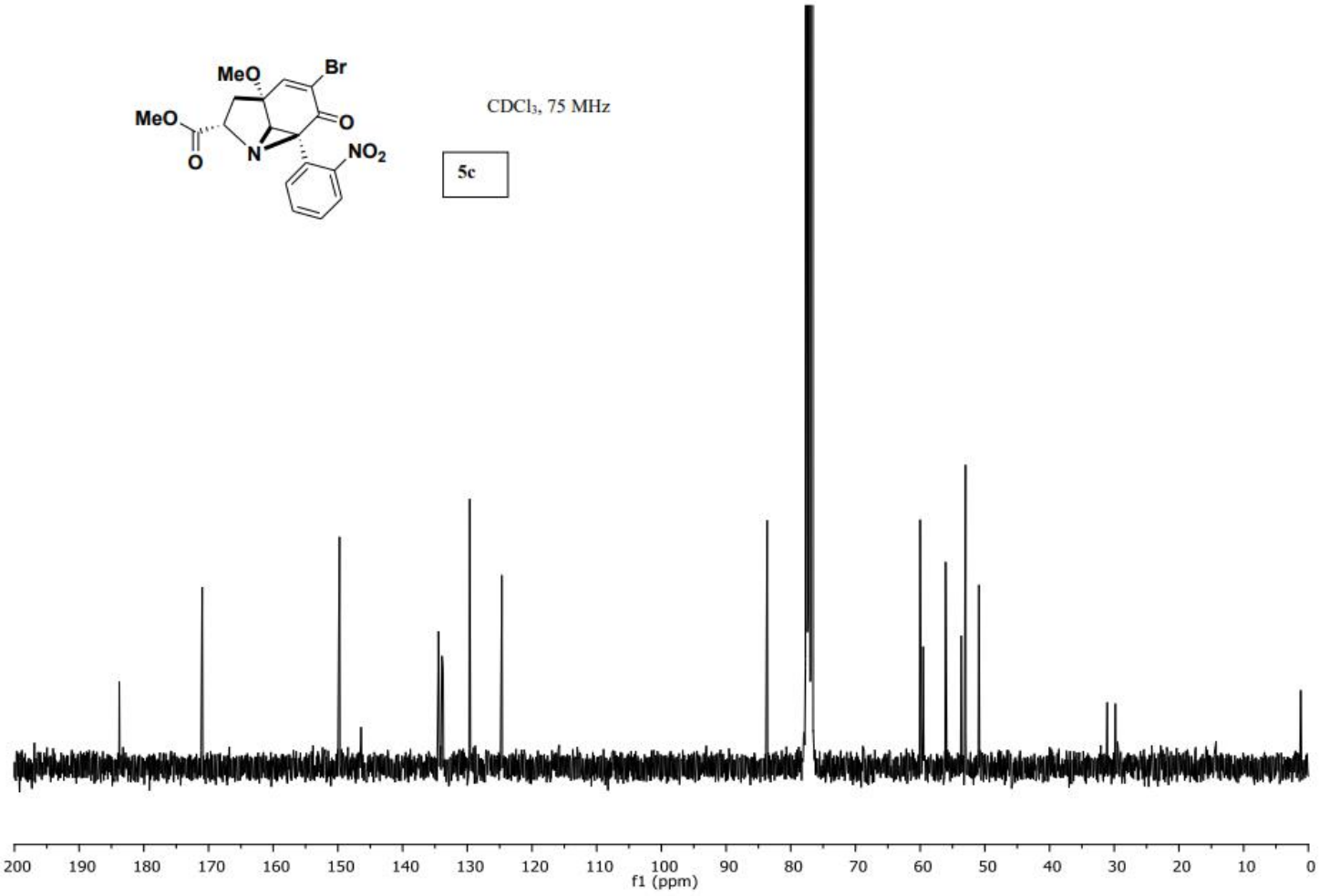

CDCl3, 75 MHz
5b
Br
MeO
O
NO2
N
200
175
150
125
100
75
50
25



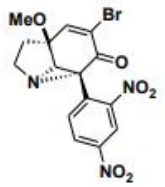
5c

$CDCl_3$, 300 MHz

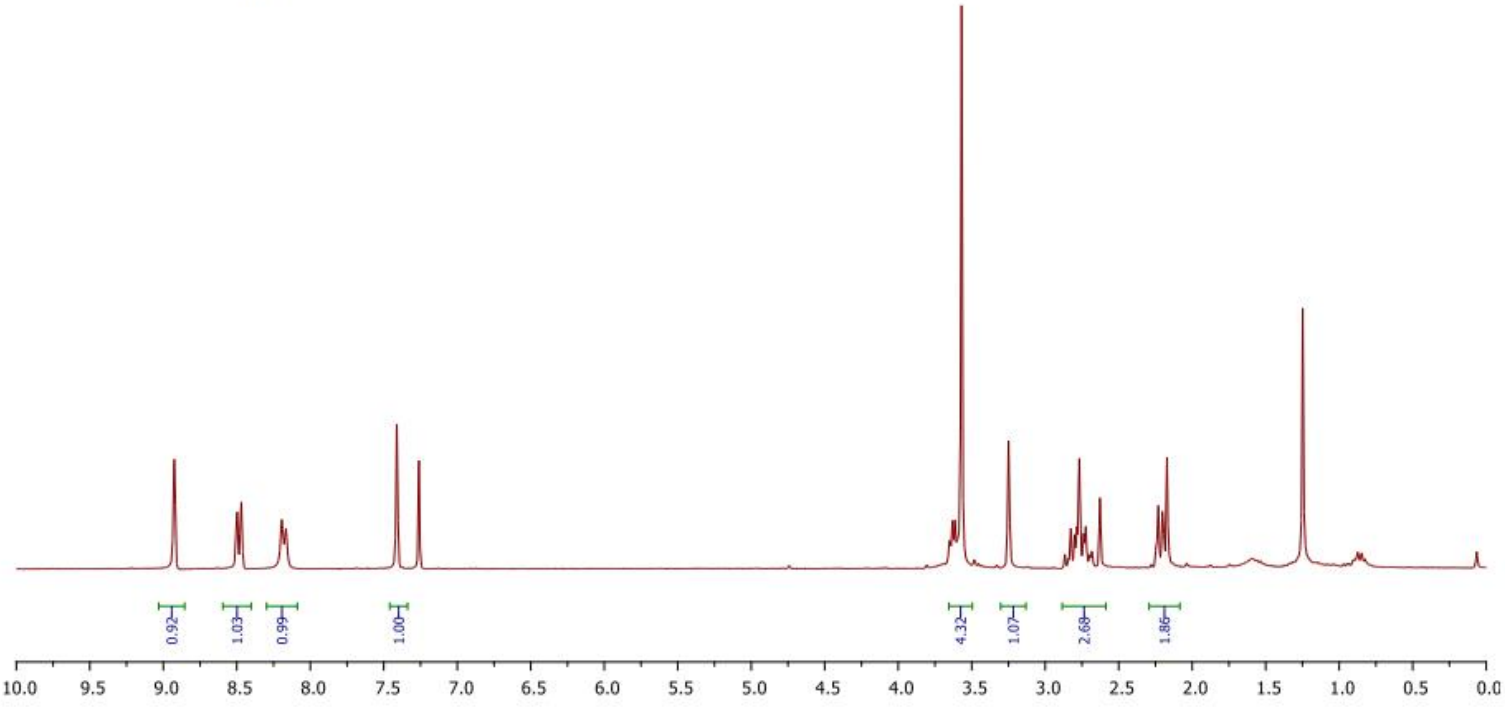


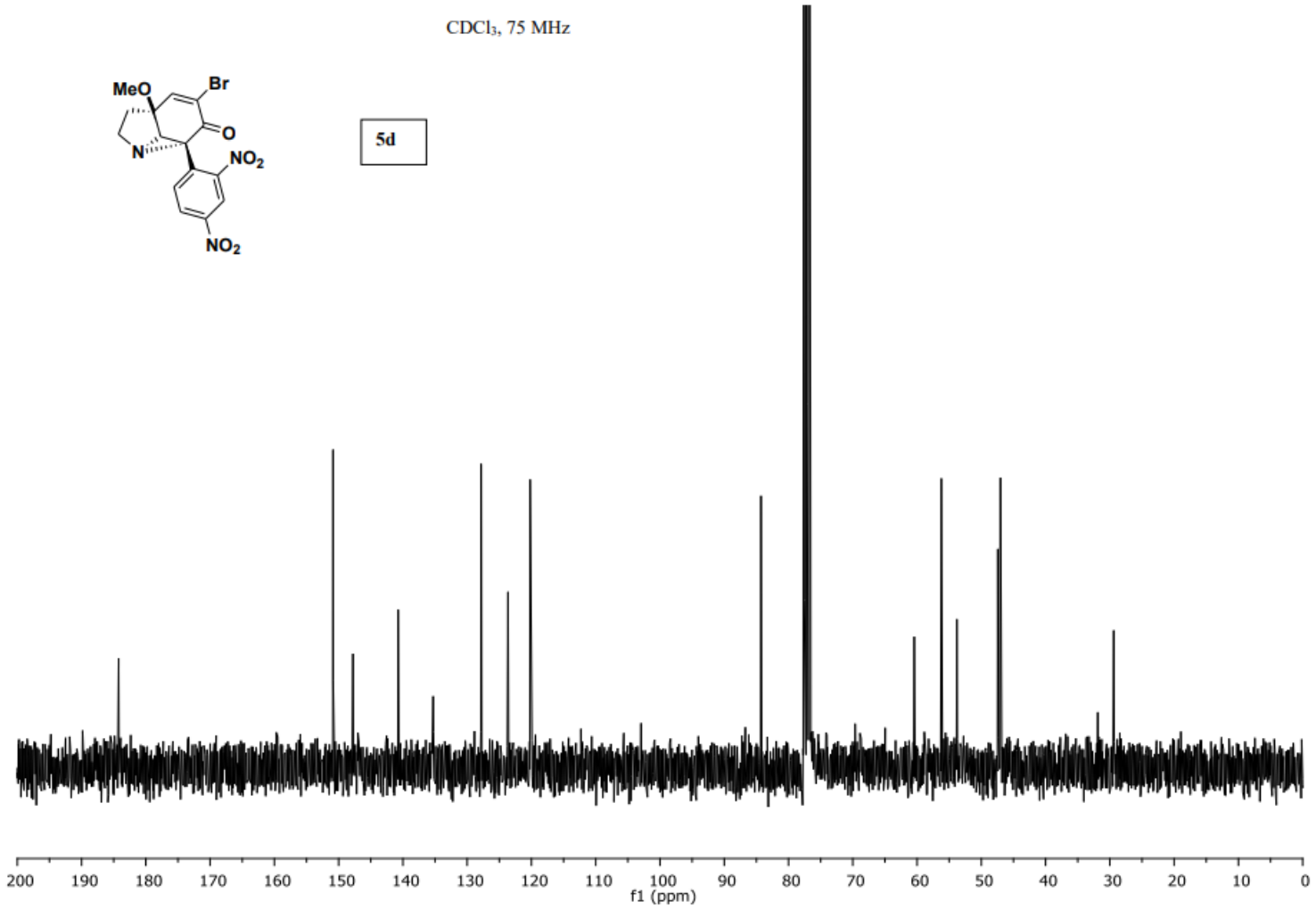

MeO
Br
MeO
O
O
N
NO2
CDCl3, 75 MHz
5c
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

$CDCl_3$, 300 MHz



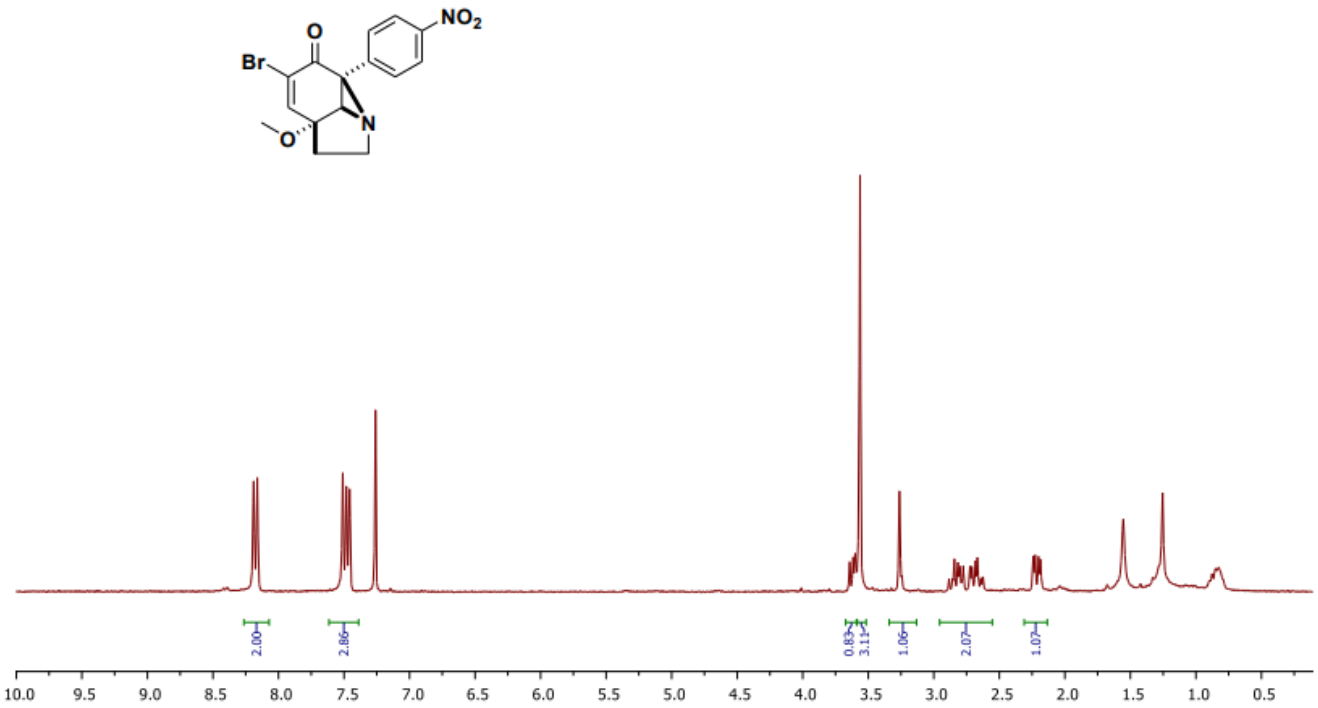
5d

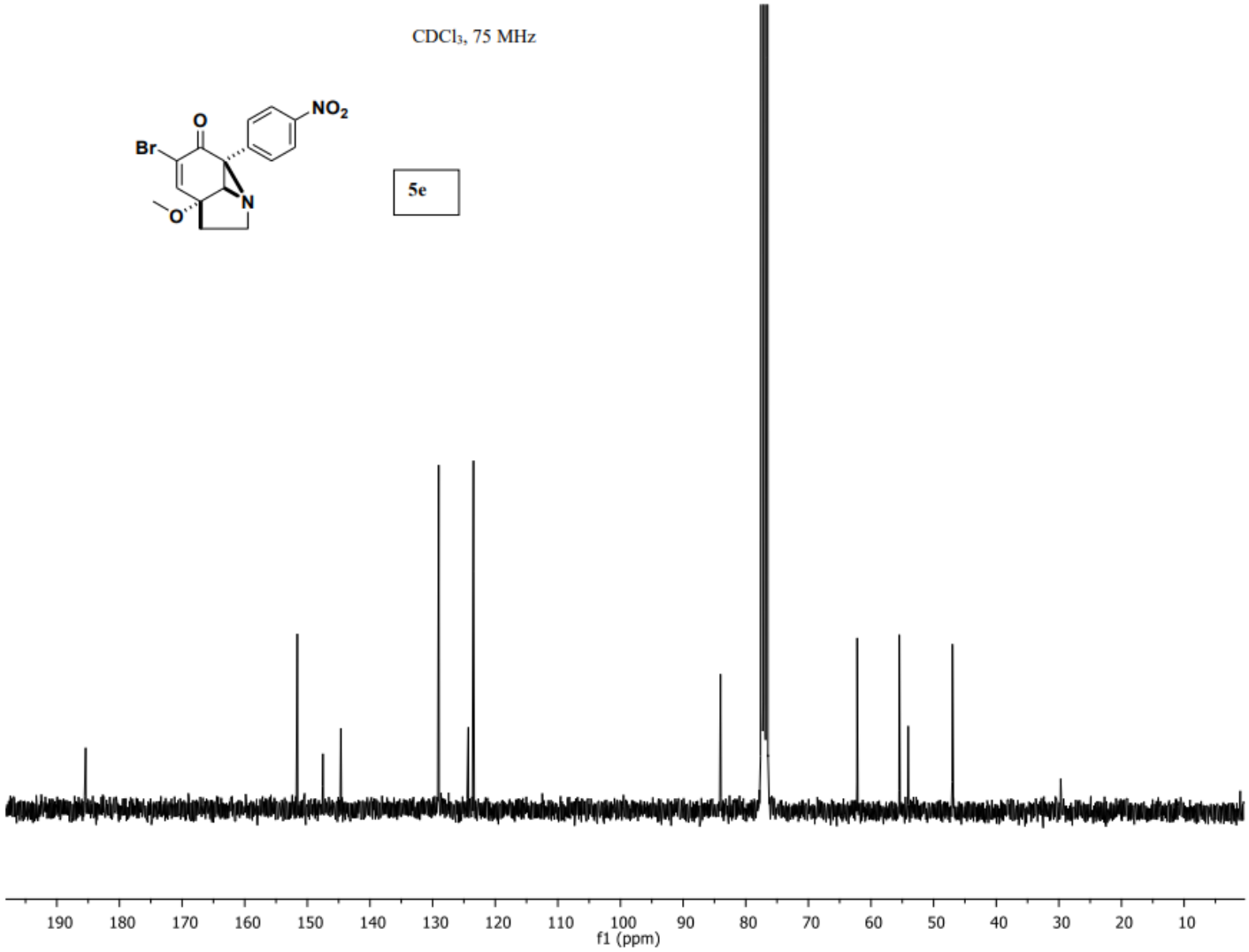


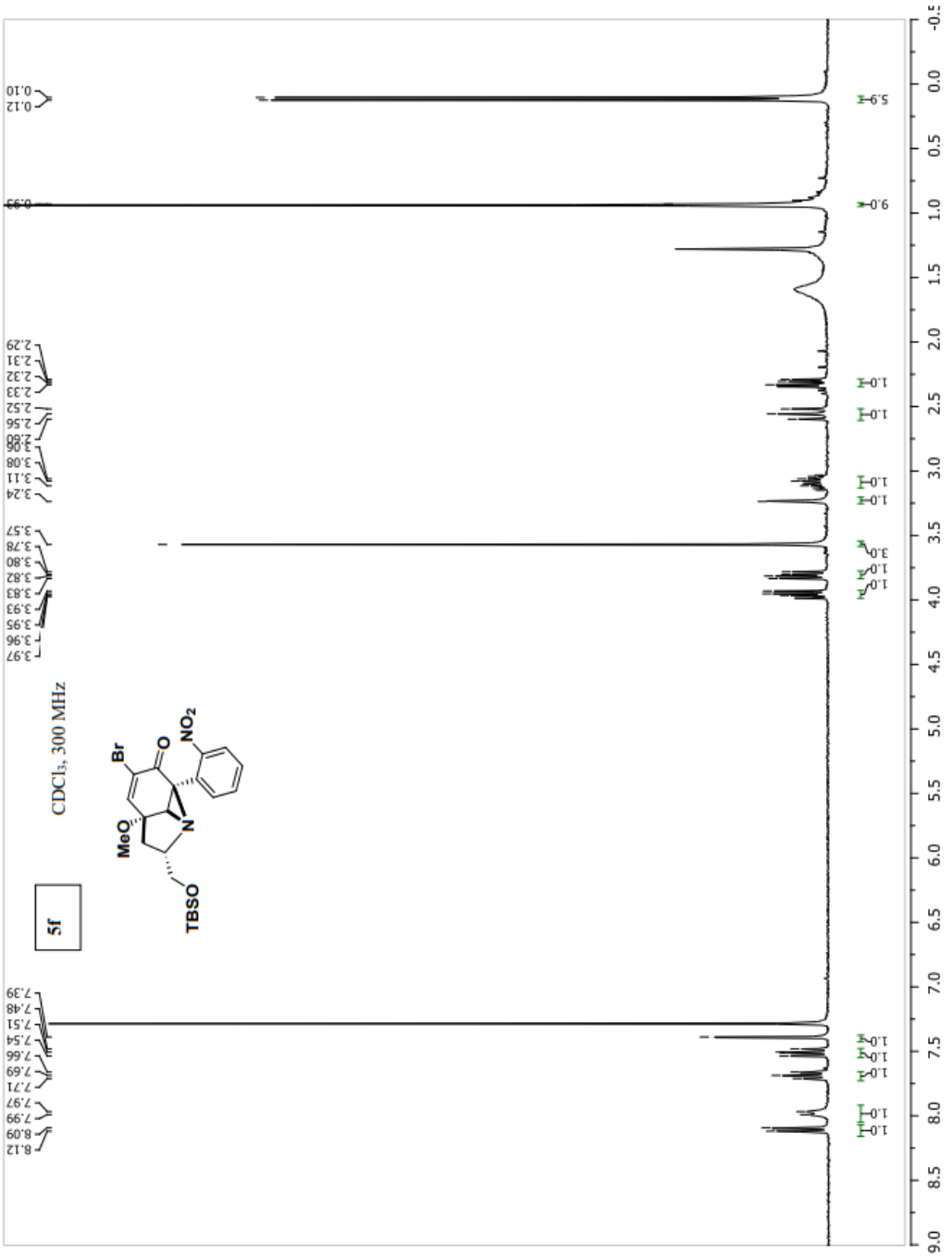

CDCl3, 75 MHz
MeO
Br
O
N
NO2
NO2
5d
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

5e

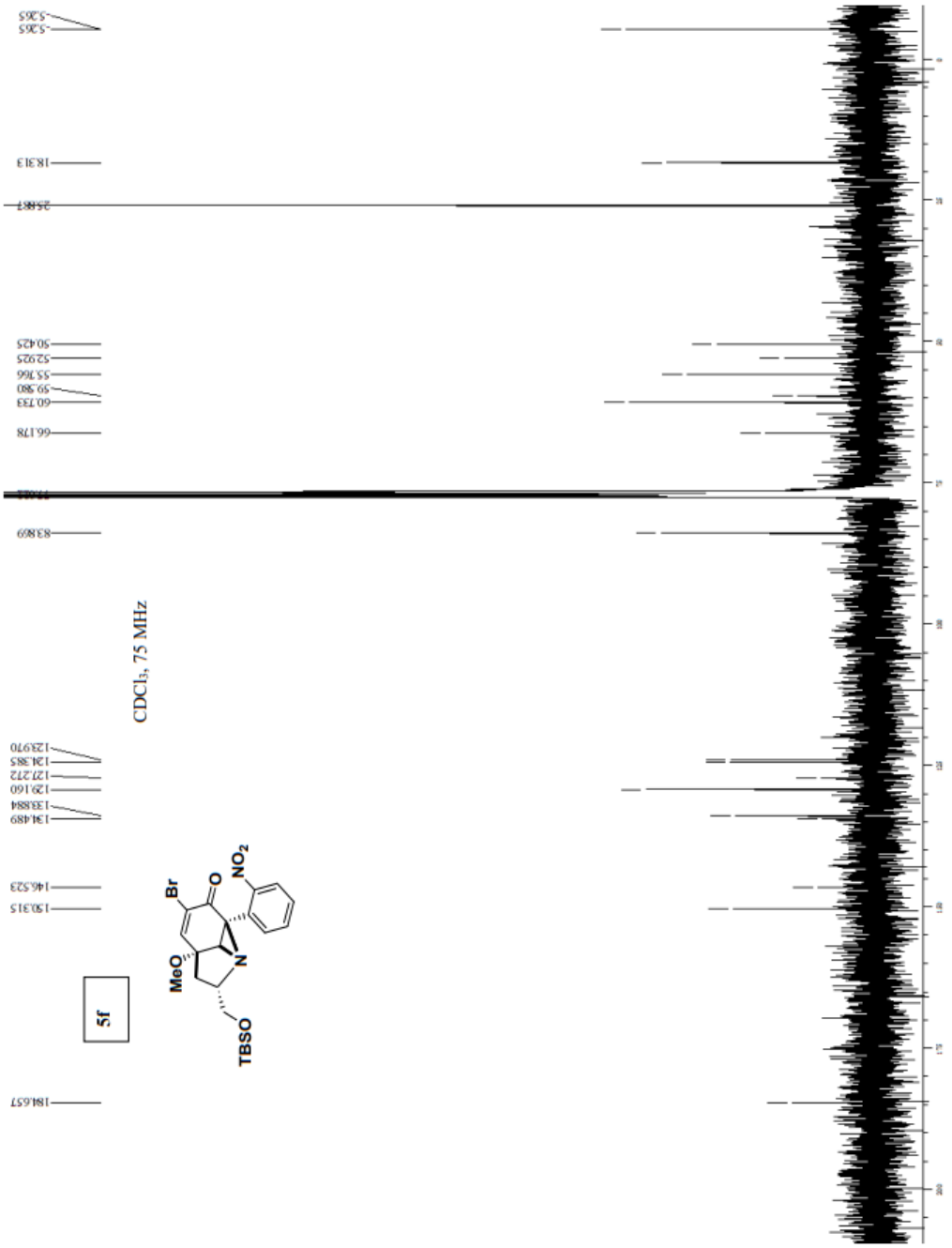
$CDCl_3$, 300 MHz

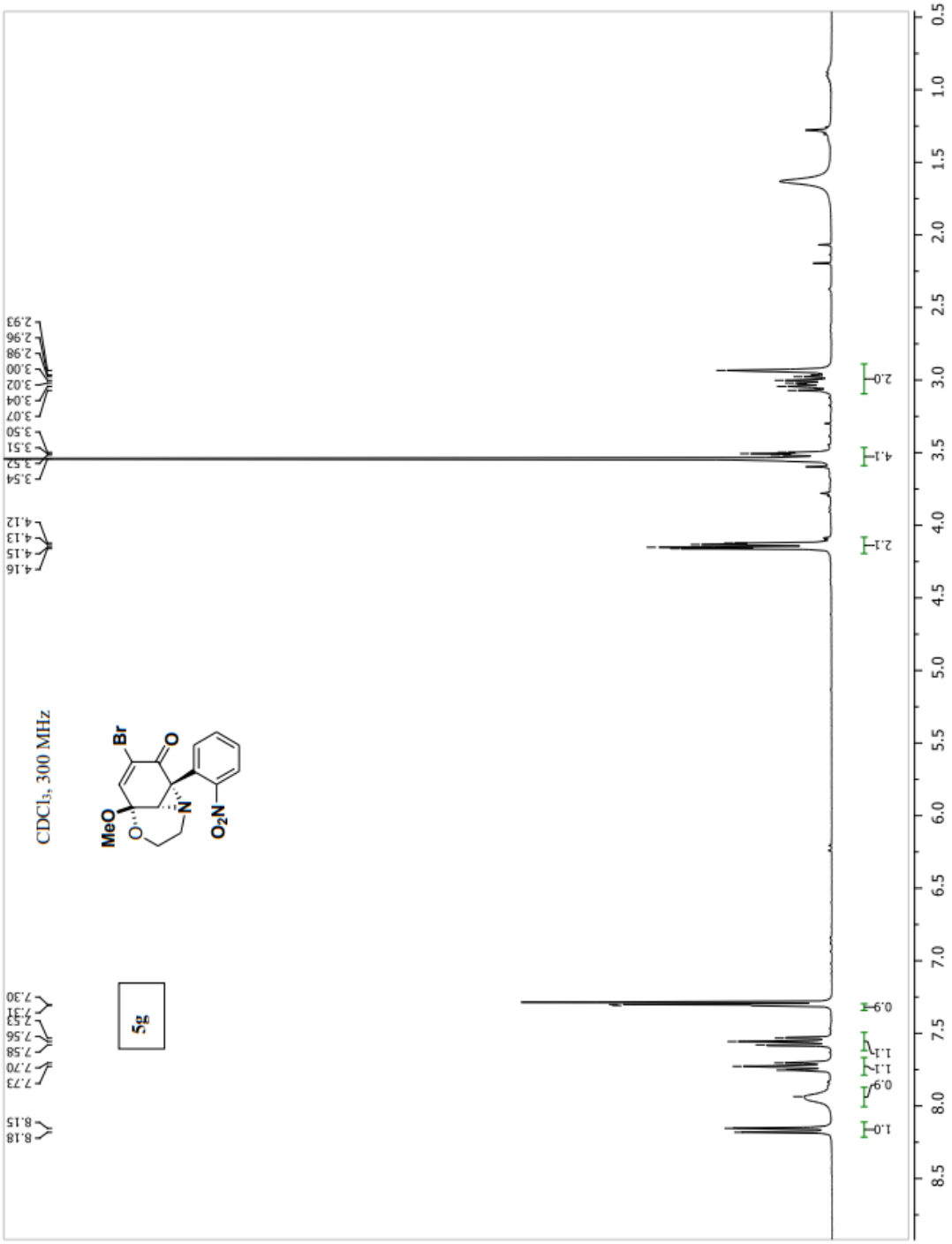


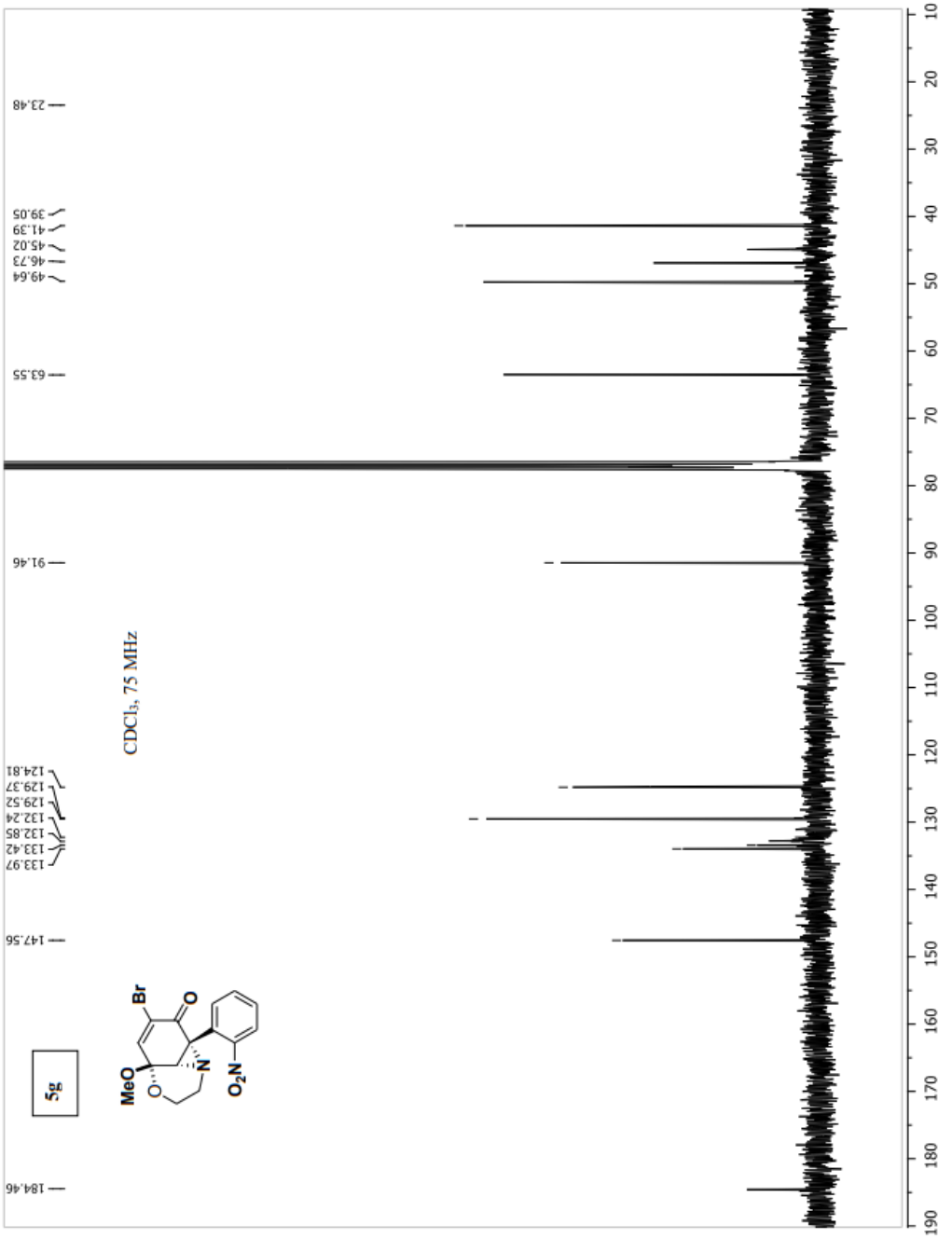

CDCl3, 75 MHz
NO2
O
Br
N
O
5e
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



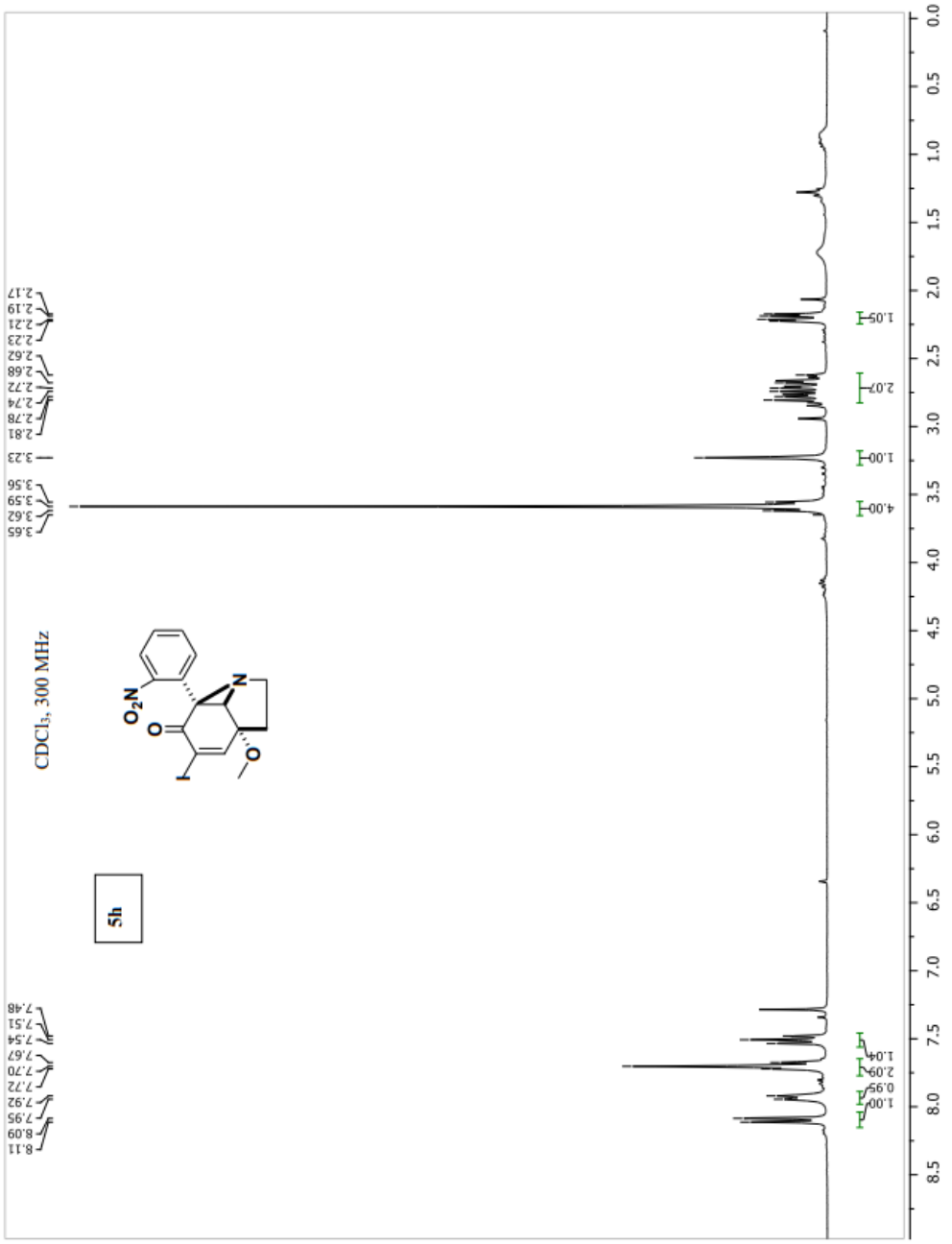
12


5f
CDCl3, 75 MHz
Br
O
NO2
MeO
N
TBSO

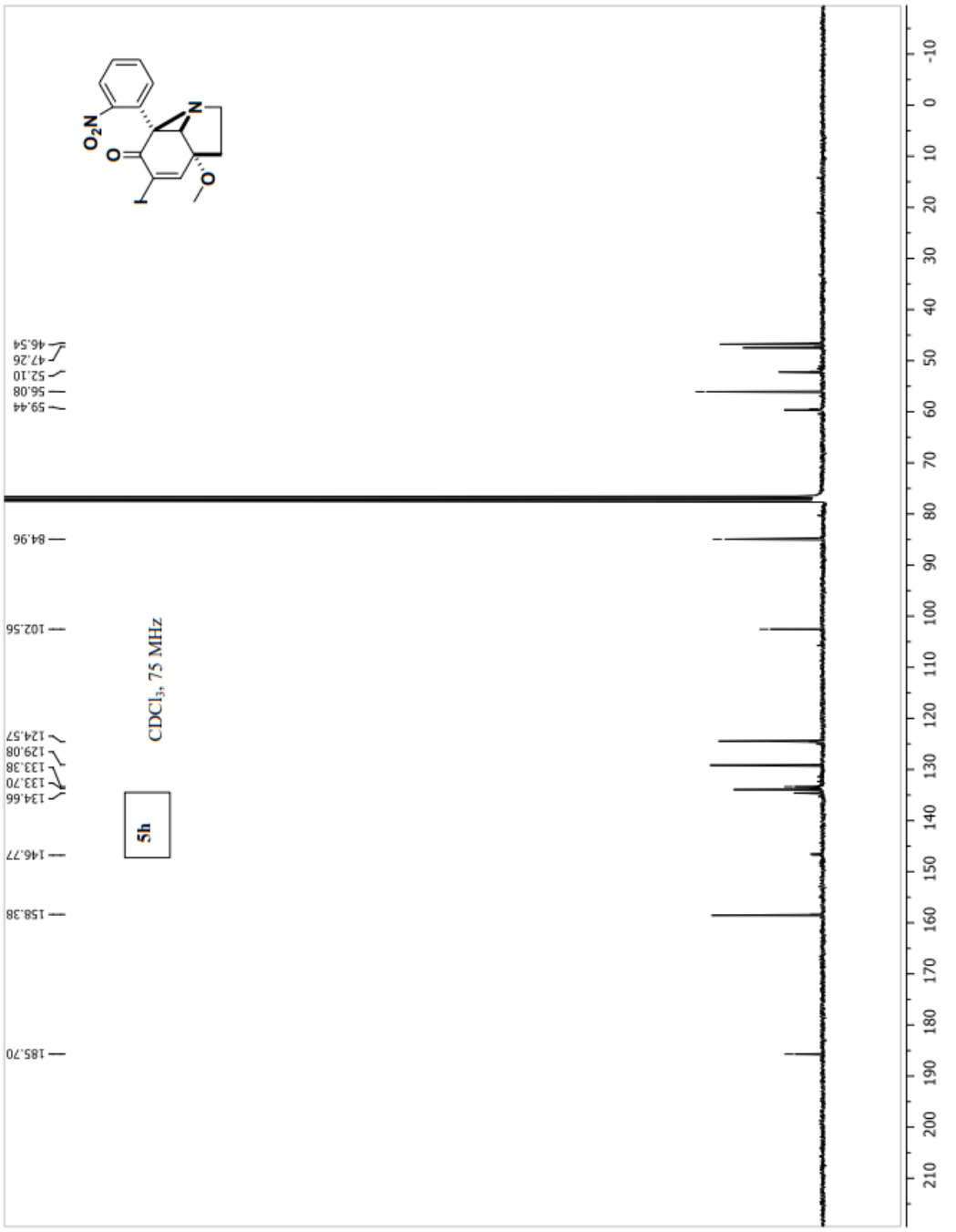

CDCl3, 300 MHz
5g
Br
O
MeO
N
O2N
8.18
8.15
7.73
7.70
7.58
7.56
7.53
7.31
7.30
4.16
4.13
4.15
4.12
3.54
3.52
3.51
3.50
3.07
3.04
3.02
3.00
2.98
2.96
2.93
0.9
1.1
1.1
0.9
1.0
4.1
2.1
2.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5


5g
CDCl3, 75 MHz
Br
O
MeO
O
N
O2N
184.46
147.56
133.97
133.42
132.85
132.24
129.52
129.37
124.81
91.46
63.55
49.64
46.73
45.02
41.39
39.05
23.48
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

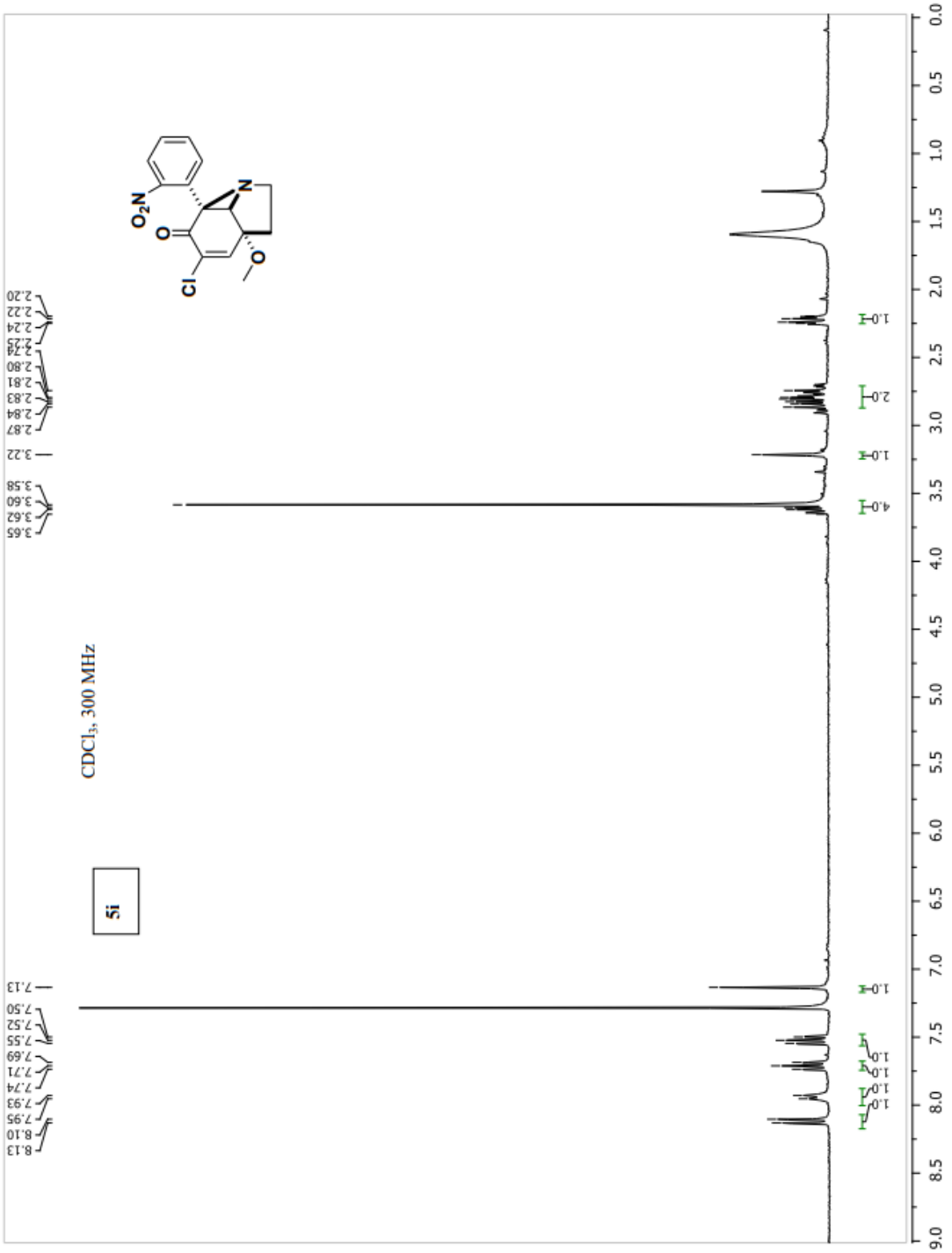
15

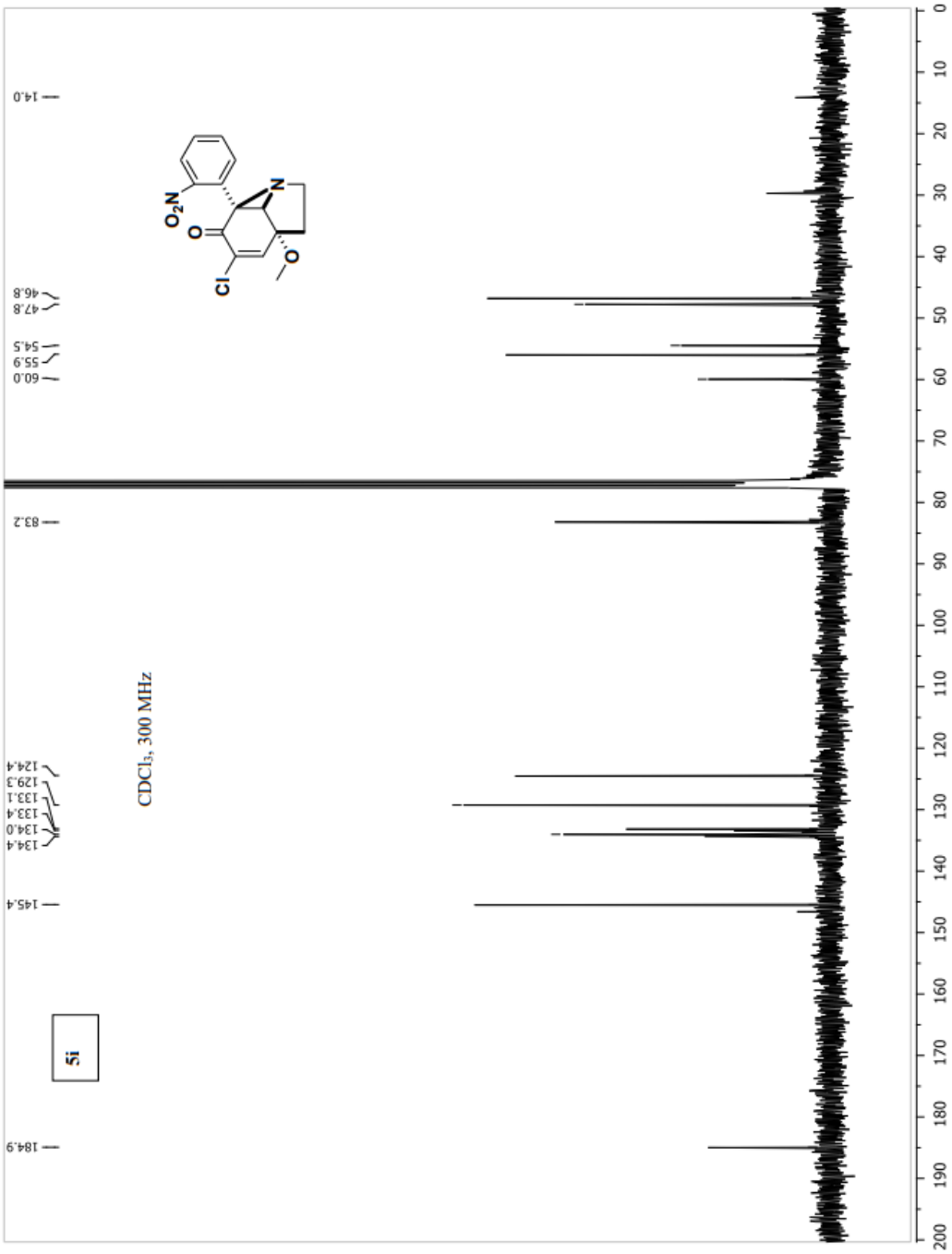

5h
CDCl3, 300 MHz
O2N
O
N
O
I
8.11
8.09
7.95
7.92
7.72
7.70
7.67
7.54
7.51
7.48
3.65
3.62
3.59
3.56
3.23
2.81
2.78
2.74
2.72
2.68
2.62
2.23
2.21
2.19
2.17
1.00
0.95
2.09
1.04
4.00
1.00
2.07
1.05
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5

16

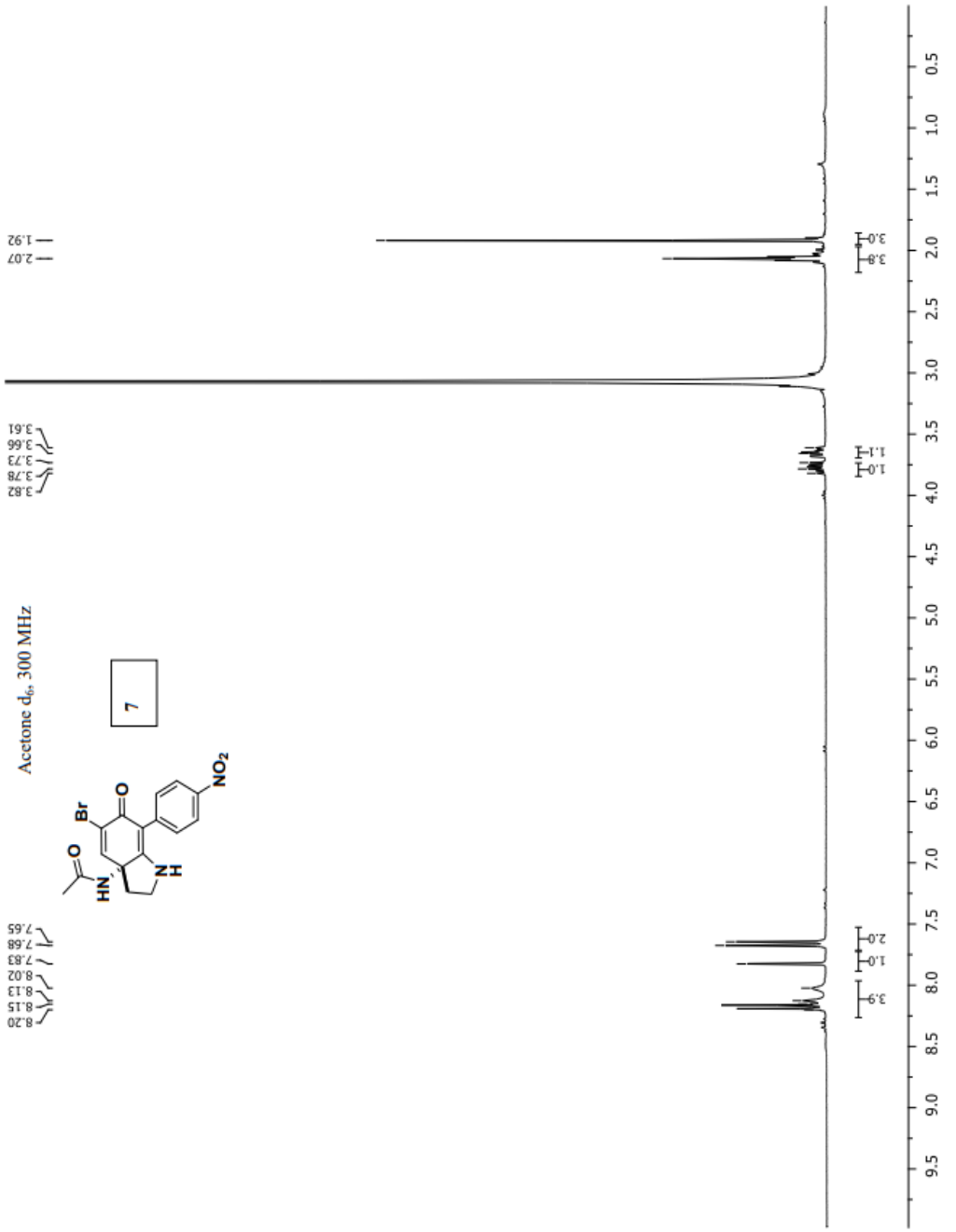

5h
CDCl3, 75 MHz
O2N
O
N
O
I
185.70
158.38
146.77
134.66
133.70
133.38
129.08
124.57
102.56
84.96
59.44
56.08
52.10
47.26
46.54

17

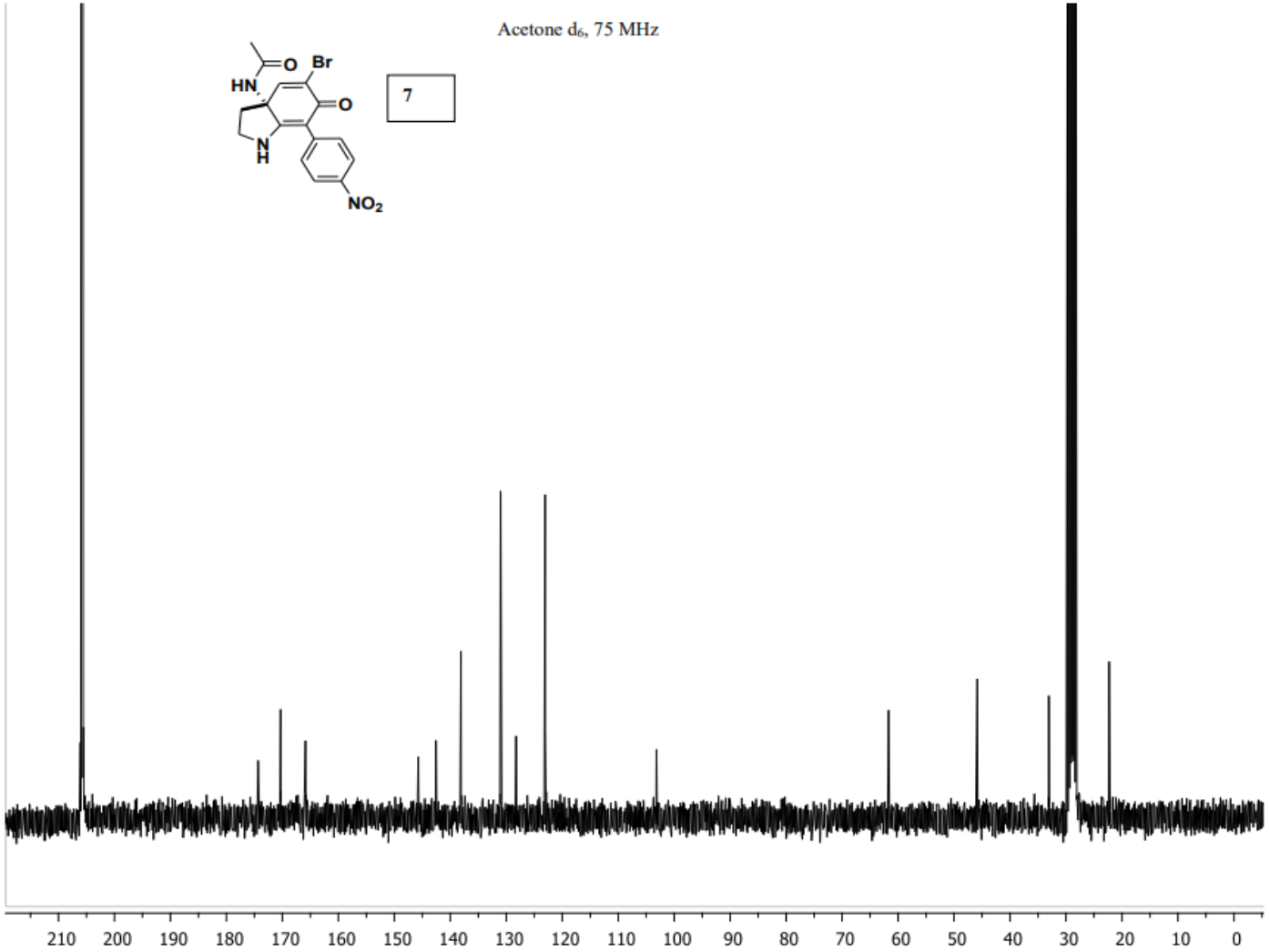

5i
CDCl3, 300 MHz
O2N
O
Cl
N
O
8.13
8.10
7.95
7.93
7.74
7.71
7.69
7.55
7.52
7.50
7.13
3.65
3.62
3.60
3.58
3.22
2.87
2.84
2.83
2.81
2.80
2.74
2.25
2.24
2.22
2.20
1.0
1.0
1.0
1.0
1.0
1.0
4.0
2.0
1.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0


184.9
145.4
134.4
134.0
133.4
133.1
129.3
124.4
83.2
60.0
55.9
54.5
47.8
46.8
14.0
5i
CDCl3, 300 MHz
O2N
O
Cl
N
O
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

19


Acetone d_6, 300 MHz
7
Br
O
HN
O
N
H
NO_2
8.20
8.15
8.13
8.02
7.83
7.68
7.65
3.82
3.78
3.73
3.66
3.61
2.07
1.92
3.9
1.0
2.0
3.8
3.0
1.1
1.0

20


Acetone d6, 75 MHz
7
HN
O
Br
O
N
H
NO2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

ANNEXE C

SYNTHESIS OF DEOXYASPIDODISPERMINE BASED ON A FUNCTIONAL PROTECTING GROUP STRATEGY, Supporting Information

Synthesis of Deoxyaspidodispermine Based on a Functional Protecting Group Strategy

Kouassi Signo[1] and Sylvain Canesi[1]*

[1]*Laboratoire de Méthodologie et Synthèse de Produit Naturels. Université du Québec à Montréal, C.P.8888, Succ. Centre-Ville, Montréal. H3C 3P8, Québec, Canada. *Email: canesi.sylvain@uqam.ca*

Supporting Information

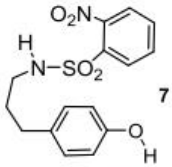
Table of Contents

I. General information and materials

Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are reported in ppm on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, etc.), t (triplet), q (quartet), quin (quintuplet), m (multiplet), and further qualified as app (apparent), br (broad). Coupling constants, J, are reported in Hz. IR spectra (cm–1) were recorded from thin films. HRMS were measured in the electrospray (ESI) mode on a LC-MSD TOF mass analyzer. Melting points were measured with a Thermo SCIENTIFIC MEL-TEMP 3.0.

II. Experimental procedures and descriptions

N-(3-(4-hydroxyphenyl)propyl)-2-nitrobenzenesulfonamide (7 bis).



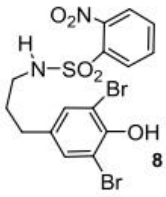
7 bis

Sodium bicarbonate (415.8 mg, 4.95 mmol, 3éq) was added to a solution of 4-(3-aminopropyl) phenol (250 mg, 1.65 mmol, 1éq) in THF/H_2O (7:7 mL) at 0 °C and then nitrobenzenesulfonyl chloride (414.4 mg, 1.82 mmol, 1.1éq) was added. The mixture was then stirred for 3 hours under air and then a solution of sat aq NH_4Cl was added. The aqueous phase was extracted with EtOAc and the organic layer was dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of *n*hexane/EtOAc (1/1) to give **7 bis** (472.3 mg, 85%) as a yellow oil.

TLC: R_F: 0.33 (*n*hexane / EtOAc 1:1 UV, CAM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 – 8.01 (m, 1H), 7.96 – 7.82 (m, 1H), 7.82 – 7.66 (m, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 5.36 (t, *J* = 6.0 Hz, 1H), 5.26 (s, 1H), 3.11 (dd, *J* = 13.2, 6.8 Hz, 2H), 2.57 (t, *J* = 7.5 Hz, 2H), 1.87 – 1.75 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 154.1, 147.9, 133.9, 133.3, 133.1, 132.6, 131.0, 129.4, 125.5, 115.4, 43.2, 31.6, 31.3; **IR**: 3453, 2918, 1996, 1538, 1515, 1336, 1162 cm^{-1}; **HRMS (ESI):** Calc. for $C_{15}H_{15}N_2O_5S$ $(M-H)^-$: 335.0707; found: 335.0708.

N-(3-(3,5-dibromo-4-hydroxyphenyl)propyl)-2-nitrobenzenesulfonamide (8).



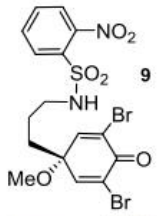
8

NBS (501 mg, 2.81 mmol, 2.1 equiv) was added to a solution of the nosylamide-phenol **7 bis** (450mg, 1.34 mmol, 1 equiv) in DCM (12 mL) at 0 °C under argon. The mixture was then stirred for 3 hours and then a solution of sat aq $Na_2S_2O_3$ was added and extracted with EtOAc. The organic layer was dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of *n*hexane/EtOAc (2/1) to give **8** (598.2 mg, 91%) as a white solid, mp: 136-138 °C.

TLC: R_F: 0.50 (*n* hexane / EtOAc 1:1 UV, CAM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 – 8.10 (m, 1H), 7.94 – 7.87 (m, 1H), 7.82 – 7.74 (m, 2H), 7.22 (s, 2H), 5.77 (s, 1H), 5.34 (t, *J* = 5.6 Hz, 1H), 3.12 (q, *J* = 6.6 Hz, 2H), 2.59 (t, *J* = 7.6 Hz, 2H), 1.93 – 1.78 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 148.1, 147.8, 135.2, 133.7, 133.6, 132.9, 131.8, 131.0, 125.4, 109.8, 42.8, 31.1; **IR**: 3440, 2925, 1537, 1163.07 cm^{-1}; **HRMS (ESI):** Calc. for $C_{15}H_{14}Br_2N_2O_5S$ $(M-H)^-$: 492.8897; found: 492.8898.

N-(3-(3,5-dibromo-1-methoxy-4-oxocyclohexa-2,5-dien-1-yl)propyl)-2-nitrobenzenesulfonamide (9).



To a solution of phenol **8** (400 mg, 0.81 mmol, 1eq) in MeOH (7.5 mL) at rt was added $PhI(OAc)_2$ (312.9 mg, 0.97 mmol, 1.2 eq) dissolved in MeOH (3 mL). The reaction was stirred for 2-3 min under air and the mixture was filtered through a pad of silica with EtOAc and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture DCM/*n*hexane (9/1) to give **9** (240.2 mg, 57%) as a white solid mp: 193-194 °C.

TLC: R_F: 0.43 (*n* hexane / EtOAc 1:1 UV, CAM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 6.2 Hz, 1H), 7.90 (d, *J* = 9.3 Hz, 1H), 7.85 – 7.70 (m, 2H), 7.20 (s, 2H), 5.44 (t, *J* = 6.2 Hz, 1H), 3.28 (s, 3H), 3.16 (q, *J* = 6.6 Hz, 2H), 1.93 – 1.73 (m, 2H), 1.72 – 1.51 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 171.6, 152.4, 148.1, 134.0, 133.6, 132.6, 130.4, 124.8, 122.6, 79.9, 53.0, 43.1, 35.7, 23.8; **IR**: 2918, 1996, 1680, 1539, 1440, 1170, 1078 cm^{-1}; **HRMS (ESI):** Calc. for $C_{16}H_{16}Br_2N_2NaO_6S$ $(M+Na)^+$: 546.8968; found: 546.8964.

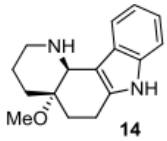
2-bromo-7a-methoxy-3a-(2-nitrophenyl)-3a,3a1,5,6,7,7a-hexahydro-3H-azirino[2,3,1-ij]quinolin-3-one (12).

To a solution of dienone **9** (200 mg, 0.38mmol, 1.0 equiv.) in acetonitrile (8 mL) was added cesium carbonate (371.4 mg, 1.14 mmol, 3.0 equiv.). Then, the reaction was stirred at 65 °C (sand bath) under air in a sealed tube, the reaction was followed by TLC, 2 hours. After completion, the mixture was filtered through a pad of silica with ethyl acetate and concentrated under vacuum. The residue was purified by silica gel chromatography with a mixture of *n*hexane/EtOAc (2/1) to give **12** (86.9 mg, 61%) as a white solid mp: 128-130 °C

TLC: R_F: 0.53 (*n*hexane / EtOAc 1:1 UV, CAM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.2 Hz, 1H), 7.95 (s, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 8.4 Hz, 1H), 7.09 (s, 1H), 3.64 – 3.39 (s+m, 4H), 2.96 – 2.77 (m, 2H), 2.02 – 1.67 (m, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 185.5, 151.6, 147.2, 134.1, 133.9, 132.4, 129.3, 125.9, 124.7, 73.5, 53.3, 50.8, 47.5, 39.6, 29.6, 19.3; **IR**: 2933, 1686, 1609, 1522, 1459, 1143, 1099 cm^{-1}; **HRMS (ESI):** Calc. for $C_{16}H_{16}BrN_2O_4$ $(M+H)^+$: 379.0288; found: 379.0284.

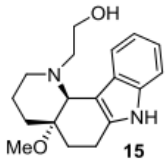
4a-methoxy-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido[3,2-c]carbazole (14).



14

Aziridine **12** (85 mg) was dissolved in isopropanol (10 mL). To this solution, Raney-Ni was added, and the vessel pressurized of hydrogen. The reaction allowed to stir at room temperature for 5 hours. After completion of the reaction, the mixture was then filtered through a pad of celite with MeOH. The filtrate was concentrated under reduced pressure, the crude product was then purified by silica gel chromatography with a mixture of ethyl acetate/methanol (9/1) to give **14** (36.5 mg, 64%) as a white solid, mp: 143-145 °C.
TLC: R_F: 0.17 (EtOAc/MeOH 9:1 UV, CAM); **^{1}H NMR** (300 MHz, MeOD) δ 7.57 (dd, *J* = 6.7, 1.5 Hz, 1H), 7.26 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.00 (m, 2H), 3.91 (s, 1H), 3.27 (s, 3H), 2.97 (dt, *J* = 12.5, 2.7 Hz, 1H), 2.86 – 2.72 (m, 3H), 2.47 (ddd, *J* = 14.3, 10.5, 6.8 Hz, 1H), 2.16 (dt, *J* = 5.5, 2.2 Hz, 1H), 1.96 (dddd, *J* = 14.2, 5.6, 2.7, 1.0 Hz, 1H), 1.85 – 1.72 (m, 2H), 1.69 – 1.56 (m, 1H); **^{13}C NMR** (75 MHz, MeOD) δ: 136.8, 134.6, 127.1, 120.2, 118.3, 117.0, 110.1, 108.5, 73.3, 55.7, 44.7, 32.7, 23.6, 23.2, 19.4; **IR**: 3420, 2930, 1942, 1454, 1165, 1105 cm^{-1}; **HRMS (ESI):** Calc. for $C_{16}H_{21}N_2O$ $(M+H)^+$: 257.1648; found: 257.1643.

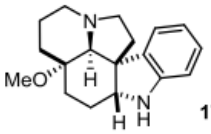
2-(4a-methoxy-2,3,4,4a,5,6,7,11c-octahydro-1H-pyrido[3,2-c]carbazol-1-yl)ethanol (15).



15

To a solution of compound **14** (35 mg, 0.14 mmol, 1éq) in absolute ethanol (3 mL) were sequentially added anhydrous potassium carbonate (96.7 mg, 0.7 mmol, 5 éq) and 2-bromoethanol (50 µL, 0.7 mmol, 5éq) in a sealed tube under air. The resulting suspension was heated to 95 °C (sand bath) for 12 h. The reaction mixture was cooled to room temperature. The solvent was evaporated under reduced pressure and the resulting residue was purified by column chromatography on silica gel eluted with ethyl acetate/methanol (95/5) to give **15** (29.6 mg, 73%) as a yellow oil.
TLC: R_F= 0.23 (EtOAc/MeOH 95:5 UV, CAM) **^{1}H NMR** (300 MHz, MeOD) δ 7.50 (dd, *J* = 6.4, 2.1 Hz, 1H), 7.31 – 7.22 (m, 1H), 7.09 – 6.89 (m, 2H), 3.54 – 3.42 (m, 3H), 3.26 – 3.02 (s+m, 5H), 2.87 – 2.66 (m, 3H), 2.55 – 2.45 (m, 1H), 2.42 – 2.30 (m, 1H), 2.11 – 2.02 (m, 1H), 1.93 – 1.64 (m, 4H); **^{13}C NMR** (75 MHz, MeOD) δ 136.6, 135.9, 129.4, 119.9, 118.5, 117.5, 110.1, 107.3, 75.0, 62.8, 59.7, 55.8, 51.6, 32.6, 29.4, 24.8, 21.6, 19.7; **IR**: 3301, 2934, 1515, 1459, 1236, 1084, 1059 cm^{-1}; **HRMS (ESI):** Calc. for $C_{18}H_{25}N_2O2$ $(M+H)^+$: 301.1911; found: 301.1910.

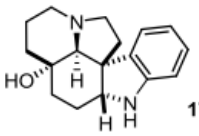
3a-methoxy-2,3,3a,3a1,4,5,5a,6,11,12-decahydro-1H-indolizino[8,1-cd]carbazole (17).



17

The alcool **15** (29 mg, 0.1 mmol, 1éq) was dissolved in dry DCM (2.5 mL) and the resulting solution was cooled to 0 °C. Et_3N (0.2 mmol, 2eq.) and methane sulfonyl chloride (0.2 mmol, 2 eq.) were added sequentially and the reaction mixture was stirred for 1 h at rt under argon. $NaHCO_3$ sat. aq was added and the aqueous phase was extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated under vacuum. The residue (a mixture of chloro and mesylate substrates) was then rapidly dissolved in dry THF 2 mL and 1 M solution of t-BuOK in THF (1.5 mmol, 15 éq) was added at 0 °C, and the reaction mixture was stirred for 1 hour at rt under argon. Then, the mixture was saturated with $NaHCO_3$ and extracted with DCM. The organic layer was dried with Na_2SO_4 and concentrated under vacuum, the residue was dissolved in methanol 1 mL and $NaBH_4$ (11.3 mg, 0.3 mmol, 3 éq) was added and the reaction mixture was stirred for 1 hour at rt. Then, the mixture was saturated with $NaHCO_3$ and extracted with DCM. The organic layer was dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel chromatography eluted with ethyl acetate/methanol (95/5) to give **17** (12.9 mg, 47% over 3 steps) as a colorless oil.
TLC: R_F: 0.36 (EtOAc/MeOH 9:1 UV, CAM); **^{1}H NMR** (300 MHz, MeOD) δ 7.10 (d, *J* = 6.8 Hz, 1H), 6.97 (td, *J* = 7.6, 1.2 Hz, 1H), 6.73 (td, *J* = 7.4, 1.0 Hz, 1H), 6.67 (d, *J* = 7.7 Hz, 1H), 3.44 – 3.36 (m, 1H), 3.19 – 3.12 (m, 1H), 3.05 (dm, *J* = 11.0 Hz, 1H), 2.98 (s, 3H), 2.52 (s, 1H), 2.39 – 2.27 (m, 2H), 2.07 (td, *J* = 11.2, 3.4 Hz, 1H), 1.98 – 1.90 (m, 2H), 1.71 – 1.45 (m, 7H); **^{13}C NMR** (75 MHz, MeOD) δ: 148.9, 135.8, 126.5, 122.5, 119.1, 110.7, 73.8, 69.4, 65.1, 53.2, 52.9, 52.7, 46.4, 38.3, 32.9, 25.8, 23.1, 22.8; IR: 3415, 2924, 1607, 1464, 1168, 1076 cm^{-1}. **HRMS (ESI):** Calc. for $C_{18}H_{25}N_2O$ $(M+H)^+$: 285.1961; found: 285.1958.

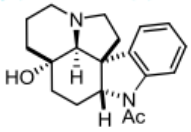
2,3,3a,3a1,4,5,5a,6,11,12-decahydro-1H-indolizino[8,1-cd]carbazol-3a-ol (17 bis).



17 bis

10 mg of compound **17** was added to a solution of HBr (48% aq) 1.5 mL in a sealed tube under air and the mixture was heated at 80 °C (sand bath). After 12 h, the mixture was saturated with $NaHCO_3$ and extracted with DCM. The organic layer was dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel chromatography eluted with ethyl acetate/methanol (9/1) to give **17 bis** (7.7 mg, 82%) as a colorless oil.
TLC: R_F: 0.34 (EtOAc /MeOH 9:1 UV, CAM); **^{1}H NMR** (300 MHz, MeOD) δ 7.17 (dd, *J* = 7.4, 0.7 Hz, 1H), 6.99 (td, *J* = 7.6, 1.2 Hz, 1H), 6.76 (td, *J* = 7.4, 1.0 Hz, 1H), 6.69 (d, *J* = 7.7 Hz, 1H), 3.43 (dd, *J* = 9.9, 5.7 Hz, 1H), 3.15 (td, *J* = 8.4, 2.4 Hz, 1H), 3.04 (dm, *J* = 11.5 Hz, 1H), 2.42 – 2.23 (m, 3H), 2.14 – 2.01 (m, 2H), 1.91 (br, 1H), 1.79 – 1.59 (m, 6H), 1.25 (dtd, *J* = 13.7, 4.1, 1.1 Hz, 2H); **^{13}C NMR** (75 MHz, MeOD) δ: 149.3, 136.1, 126.8, 122.5, 119.5, 110.7, 72.0, 69.4, 64.9, 52.8, 52.7, 38.6, 37.9, 27.6, 25.0, 23.1; **IR**: 3373, 1540, 1458, 1408, 1040 cm^{-1}; **HRMS (ESI):** Calc. for $C_{17}H_{23}N_2O$ $(M+H)^+$: 271.1805; found: 271.1803.

1-(3a-hydroxy-2,3,3a,4,5,5a,11,12-octahydro-1H-indolizino[8,1-cd]carbazol-6(3a1H)-yl)ethanone (6).



6

(7 mg, 0.03 mmol 1éq) of compound **17 bis** was added to a solution of acetic anhydride (0.04 mmol, 1.3 éq) in dry DCM (0.6 mL) maintained at 0 °C under an argon atmosphere. After 2 hours the reaction mixture was poured into $NaHCO_3$ then extracted with DCM. The organic layer was dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel chromatography eluted with ethyl acetate/methanol (9/1) to give **6** (6.8 mg, 73%) as a colorless oil.

TLC: R_F: 0.34 (EtOAc/MeOH 9:1 UV, CAM).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 7.1 Hz, 1H), 7.21 (td, *J* = 7.2, 1.1 Hz, 1H), 7.08 (td, *J* = 7.4, 1.0 Hz, 1H), 4.05 (dd, *J* = 11.3, 5.8 Hz, 1H), 3.19 (td, *J* = 9.1, 3.3 Hz, 1H), 3.05 (d, *J* = 11.3 Hz, 1H), 2.50 (s, 1H), 2.38 (dd, *J* = 10.0, 8.5 Hz, 1H), 2.27 (s, 3H), 2.24 – 2.06 (m, 3H), 1.96 – 1.86 (m, 1H), 1.80 – 1.43 (m, 6H), 1.38 (s, 1H), 1.31 – 1.27 (m,1H);

^{1}H NMR (300 MHz, MeOD) δ 7.98 (dd, *J* = 7.9, 0.6 Hz, 1H), 7.34 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.13 (m, 2H), 4.17 (dd, *J* = 11.1, 6.0 Hz, 1H), 3.20 (td, *J* = 9.0, 3.1 Hz, 1H), 3.10 – 3.03 (m, 1H), 2.57 (s, 1H), 2.40 (dd, *J* = 8.5, 1.9 Hz, 1H), 2.31 (s, 3H), 2.22 – 2.09 (m, 3H), 1.85 – 1.70 (m, 4H), 1.61 – 1.51 (m, 3H), 1.29 – 1.23 (m, 1H). **^{13}C NMR** (75 MHz, MeOD) δ: 169.6, 140.1, 138.6, 126.7, 124.4, 122.6, 117.5, 70.4, 69.0, 67.8, 52.8, 52.4, 52.1, 38.7, 29.4, 27.7, 24.3, 23.1, 21.6; **IR**: 3580, 3451, 2917, 1640, 1462, 1083 cm^{-1};**HRMS (ESI):** Calc. for $C_{19}H_{25}N_2O_2$ $(M+H)^+$: 313.1911; found: 313.1912.

III. Comparatives tables:

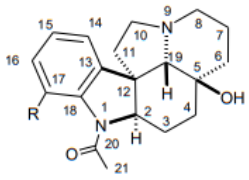


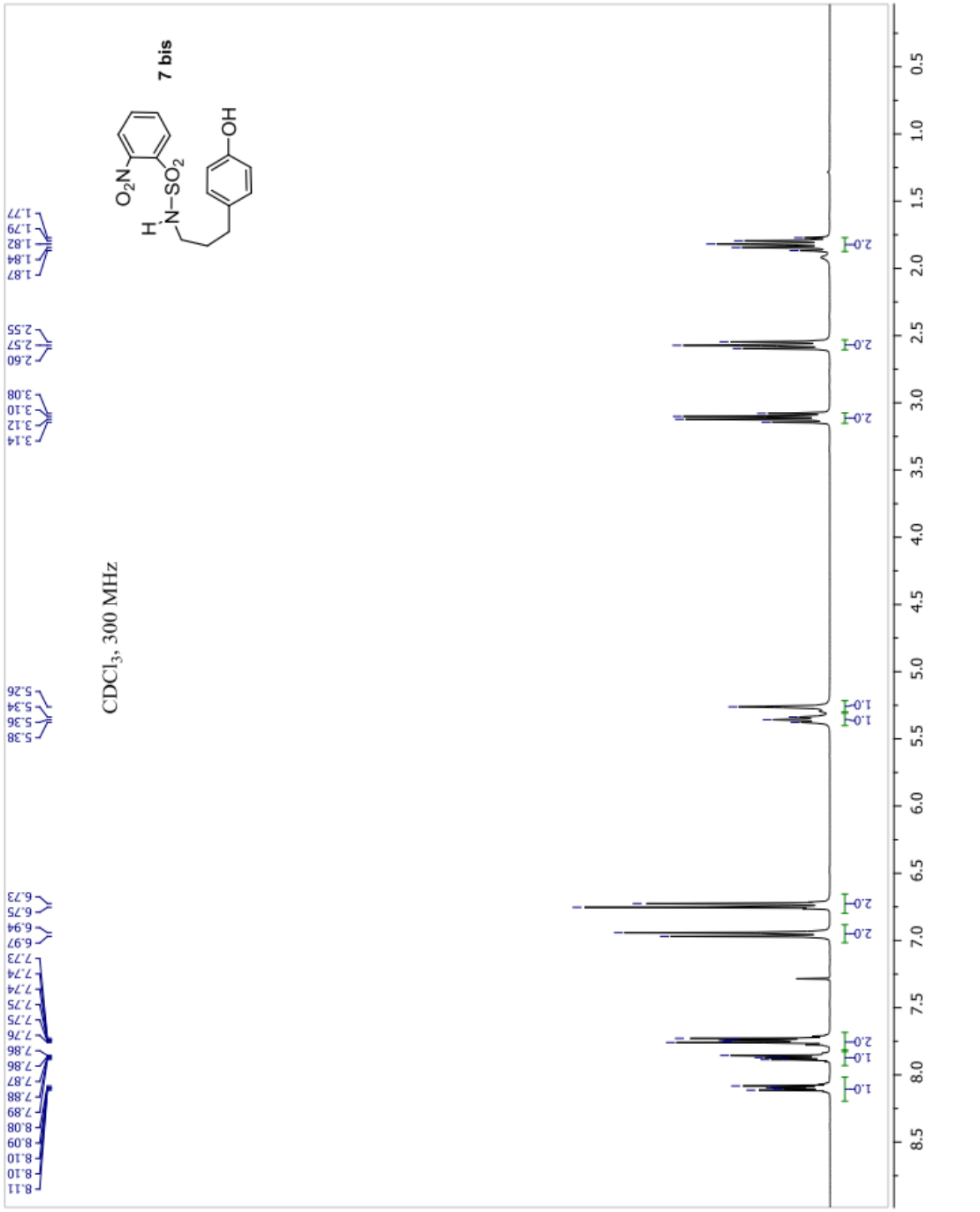
Table S1: ^{1}H-NMR comparison for synthetic deoxyaspidodispermine and natural product.[11] Shifts are given in ppm. Parameters (e.g. MHz, solvent) for acquisition of ^{1}H-NMR of natural sample are unknown but suspected in $CDCl_3$.[12b] Only the four values ^{1}H indicated below were reported in reference.[11, 12b] Coupling constants are in parentheses and are reported in Hz. Spectrum ^{1}H were measured in $CDCl_3$ for comparison and is referenced to the residual solvent peak (^{1}H δ = 7.26 ppm,).

Position	Synthetic deoxyaspidodispermine $CDCl_3$ δ_H (J in Hz) 300 MHz	Natural deoxyaspidodispermine
C21-H (CH_3)	2.27 (s, 3H)	2.26 (s, 3H)
C2-H	4.05 (dd, 11.3, 5.8, 1H)	4.04 (q, 1H)
Aromatics C14, C15, C16-H	7.27 (d, 7.1, 1H), 7.21 (td, 7.9, 1.1, 1H), 7.08 (td, 7.4, 1.0, 1H)	~6.9-7.4 (3H)
Aromatic C17-H	8.12 (d, J = 8.0, 1H)	8.10 (d, 1H)

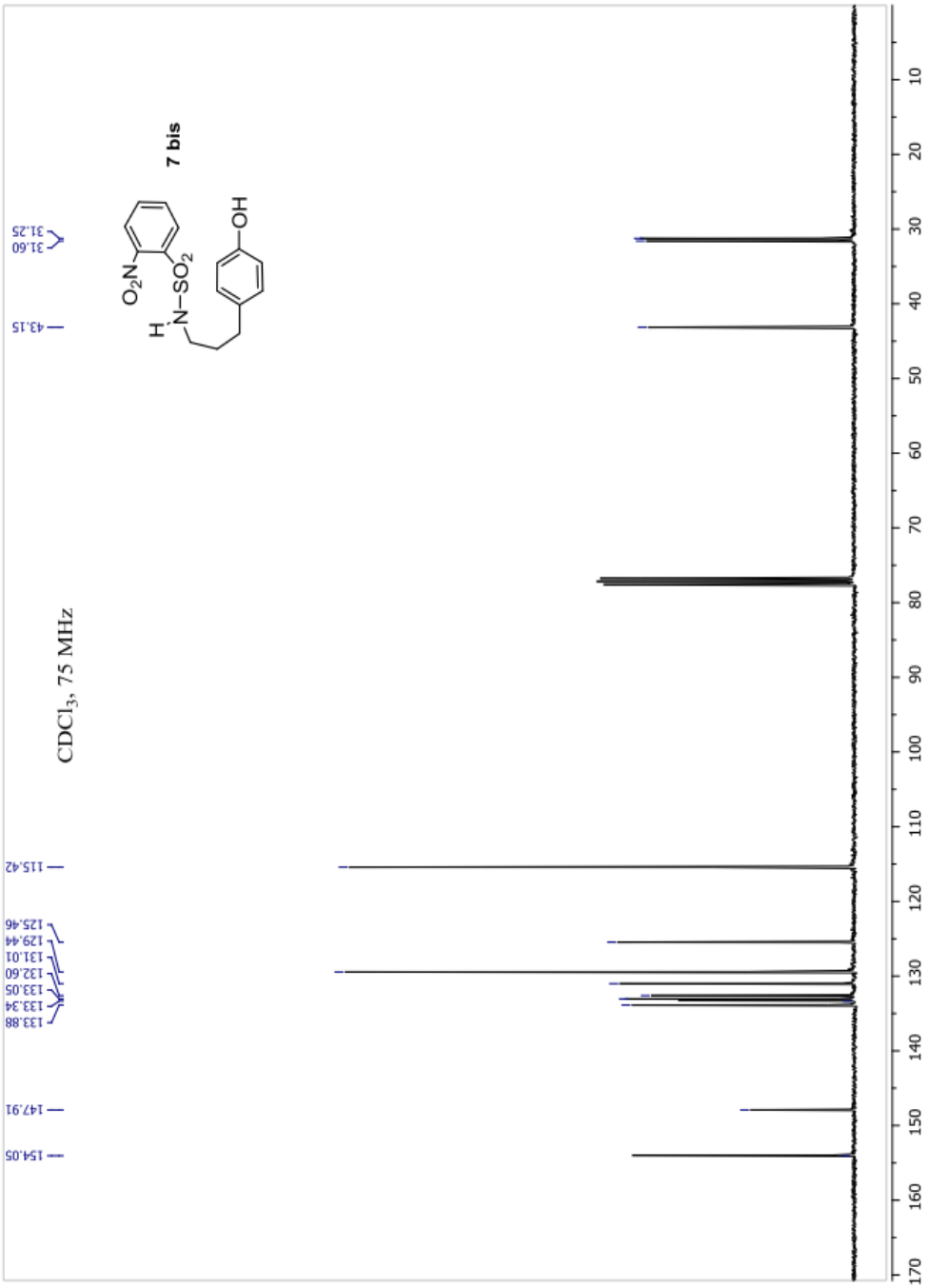
Table S2: ^{1}H-NMR comparison between aliphatic parts of deoxyaspidodispermine and aspidodispermine (natural derivative reported in the literature [13]). Coupling constants are in parentheses and are reported in Hz. Spectrums were measured in $CDCl_3$ and are referenced to the residual solvent peak (^{1}H δ = 7.26 ppm). All chemical shifts are in ppm.

Position	Deoxyaspidodispermine (aliphatic part), $CDCl_3$ δ_H (J in Hz), 300 MHz	Aspidodispermine (aliphatic part)[13] $CDCl_3$ δ_H (J in Hz), 700 MHz
2	4.05 dd (11.3, 5.8)	4.06 (11.6, 5.9)
3	1.91 m, 1.76 m	1.89 ddt (13.3, 6.4, 3.5), 1.84 – 1.75 m
4	2.20 m, 1.29 m	2.20 dt (14.1, 3.7), 1.31 – 1.28 m
5	1.38 s (OH)	1.40 s (OH)
6	1.76 m, 1.48 m	1.84 – 1.75 m, 1.48 td (12.7, 6.2)
7	1.70 m, 1.66 m	1.70 – 1.64 m
8	3.05 d (11.3), 2.07 m	3.04 d (11.3), 2.07 – 2.03 m
10	3.19 td (9.1, 3.3), 2.38 m	3.19 td (9.1, 3.2), 2.37 dd (18.2, 9.3)
11	2.09 m, 1.68 m	2.12 – 2.07 m, 1.70 – 1.64 m
19	2.50 s	2.47 s
21	2.27 s (3H)	2.33 s (3H)

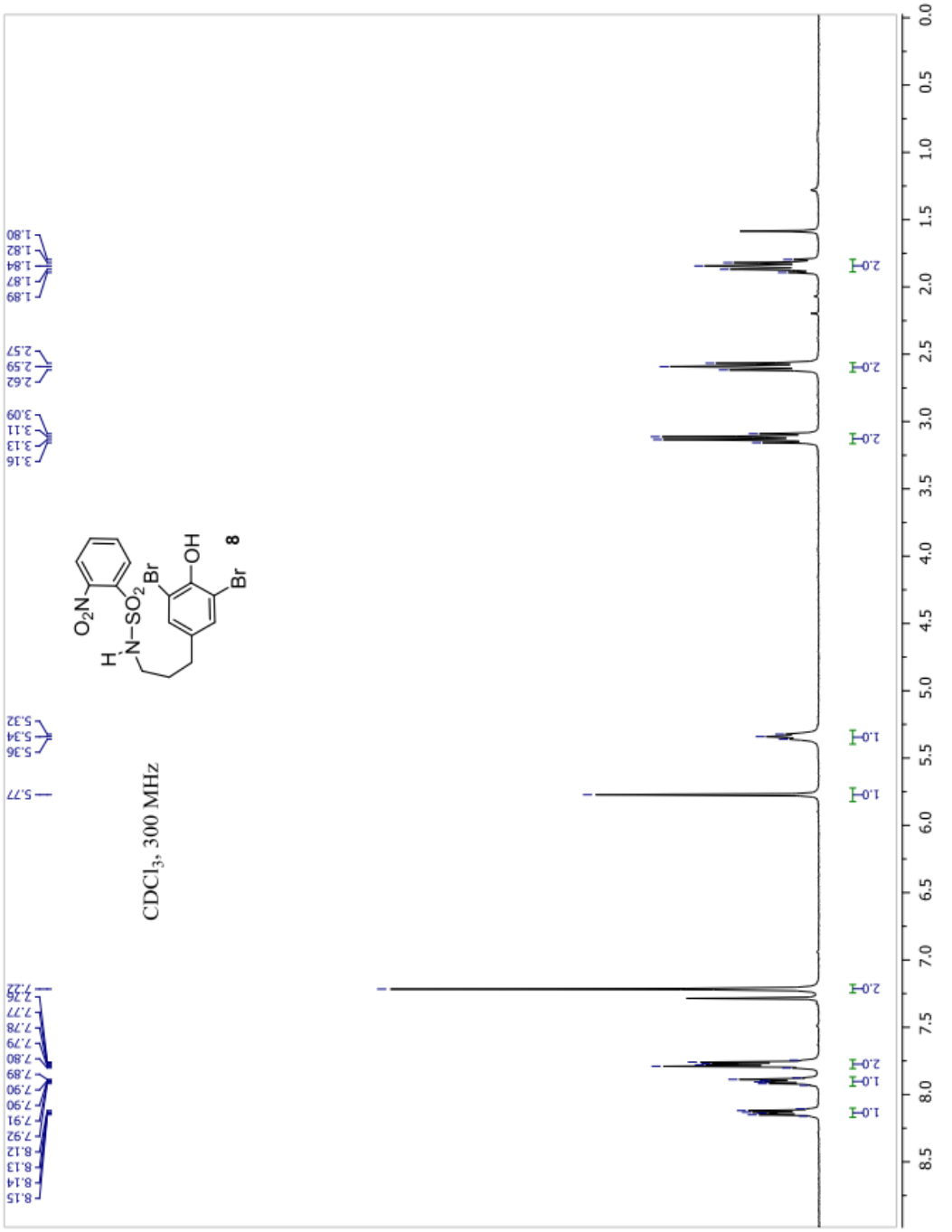
IV. Copies of ^{1}H and ^{13}C NMR spectra.



8


7 bis
$CDCl_3$, 75 MHz
31.60
31.25
43.15
115.42
125.46
129.44
131.01
132.60
133.05
133.34
133.88
147.91
154.05

9


8.15
8.14
8.13
8.12
7.92
7.91
7.90
7.90
7.89
7.80
7.79
7.78
7.77
7.76
7.22
5.77
5.36
5.34
5.32
3.16
3.13
3.11
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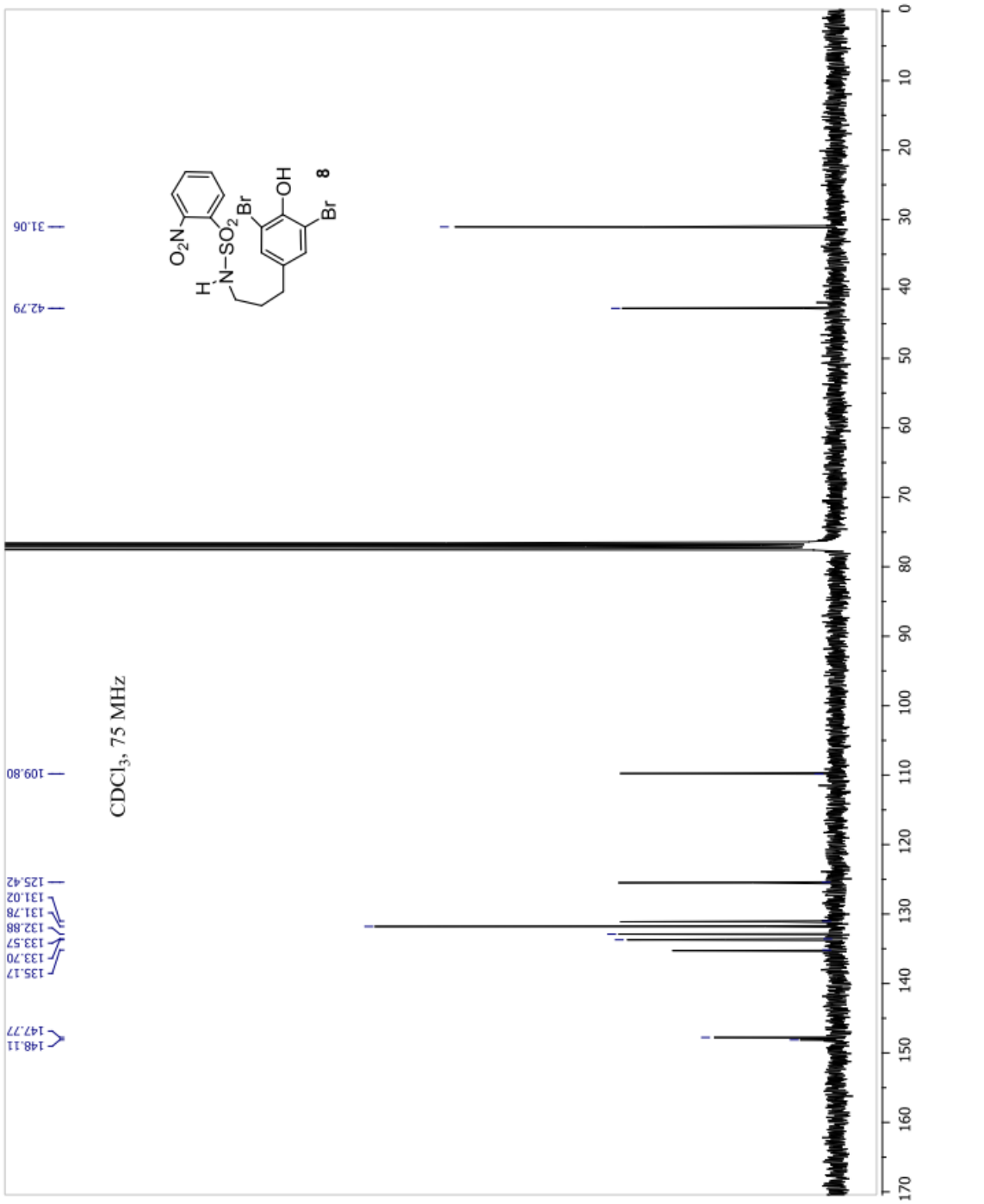
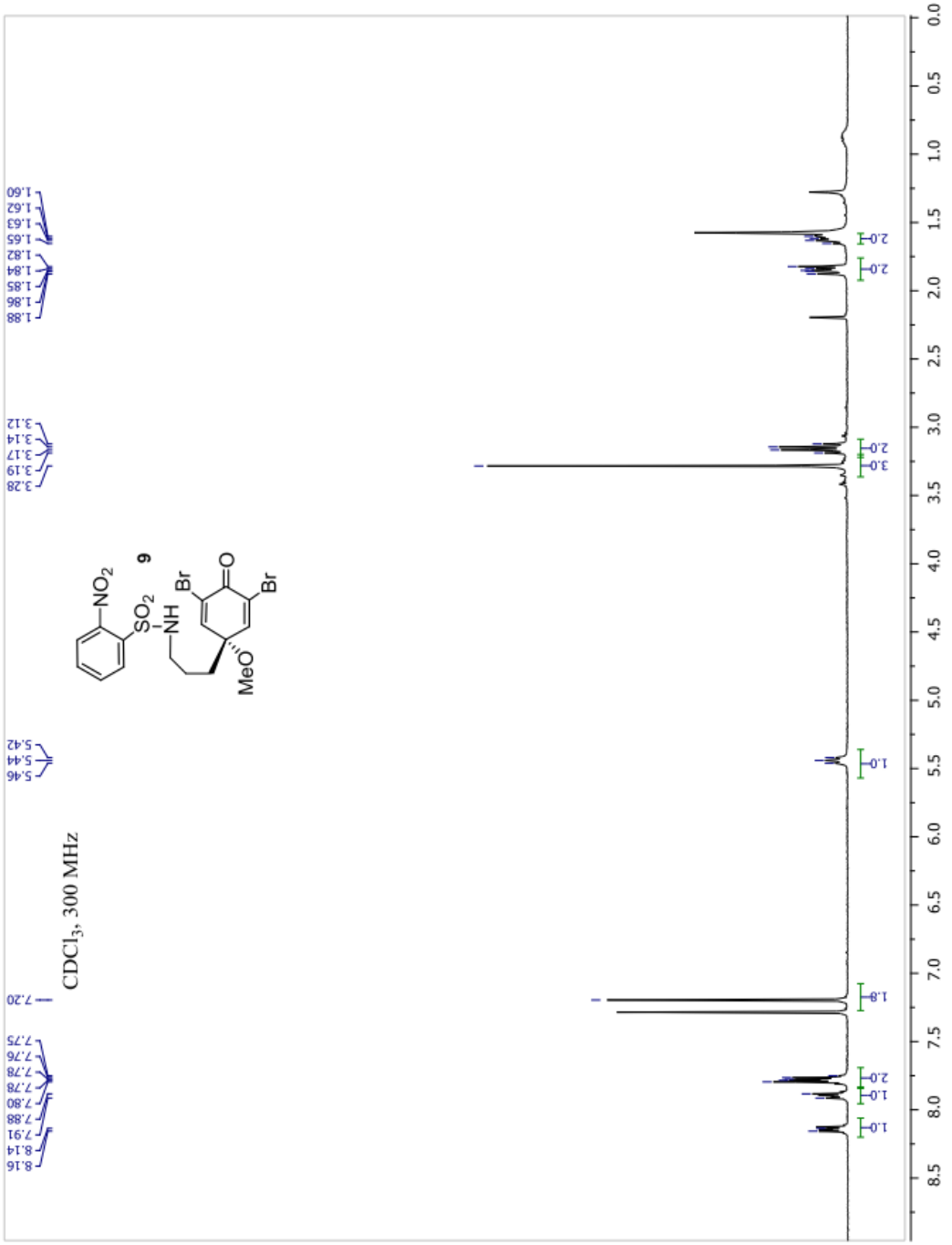
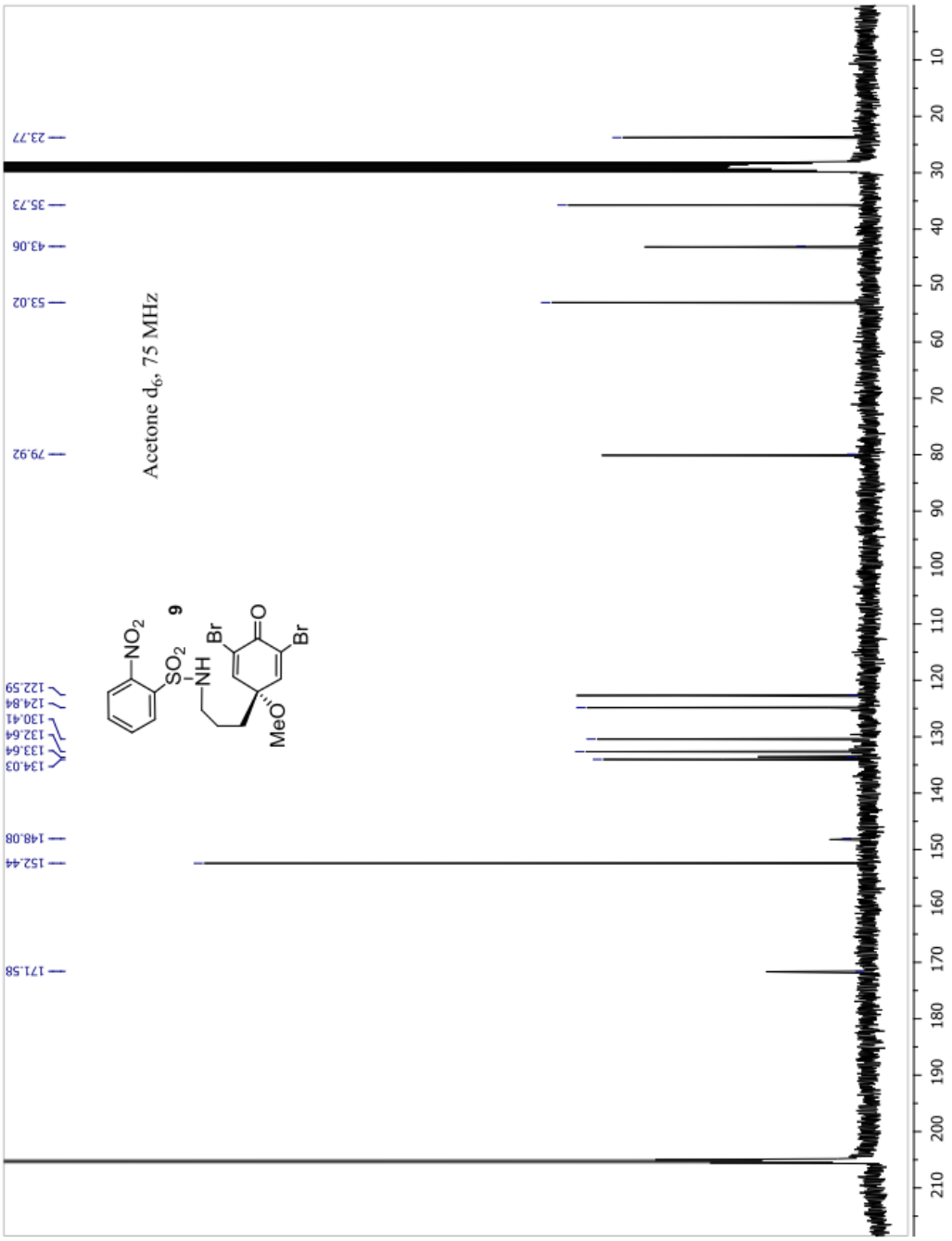
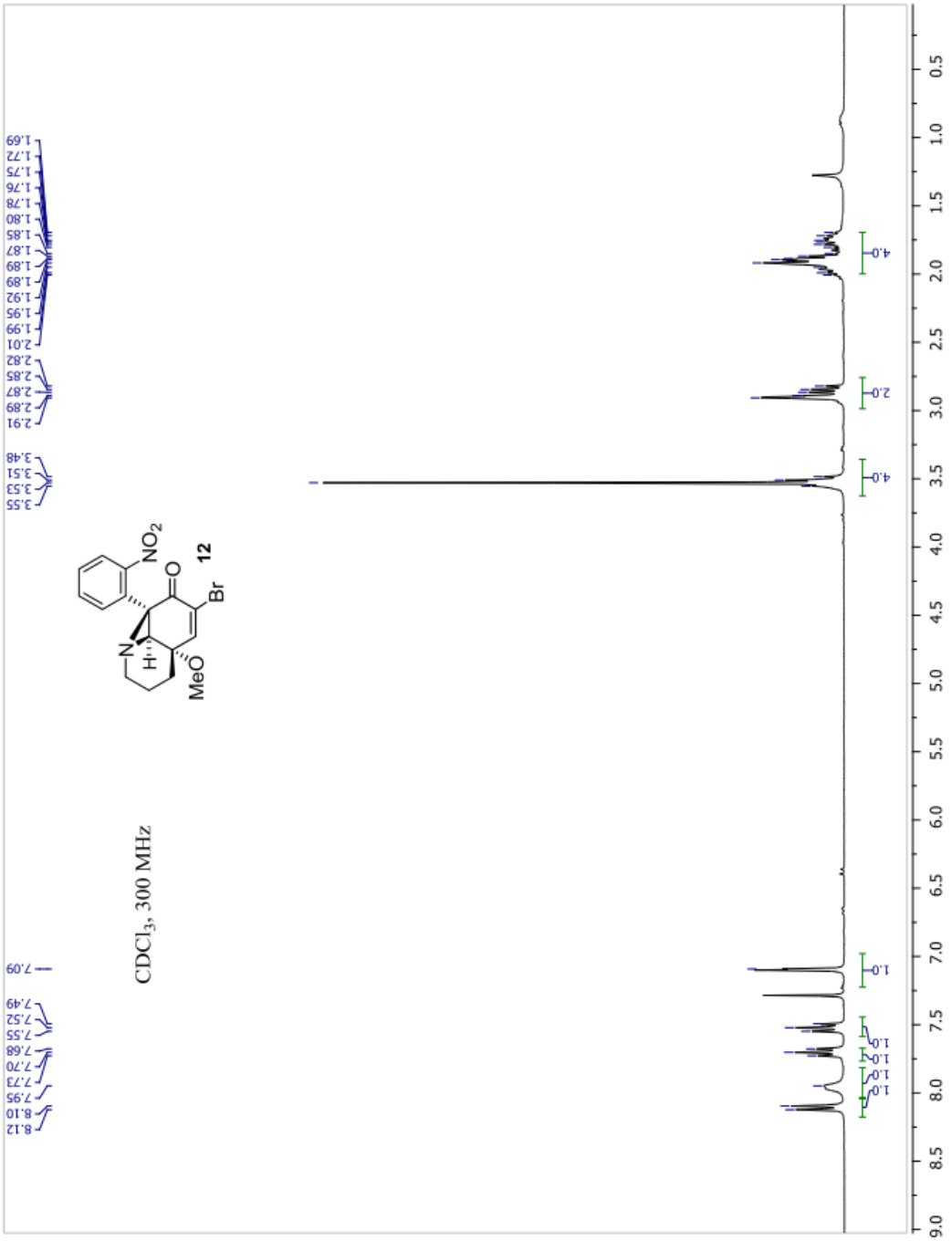
1.84
1.82
1.80
CDCl3, 300 MHz
8
10


11
8
$CDCl_3$, 75 MHz
31.06
42.79
109.80
125.42
131.02
131.78
132.88
133.57
133.70
135.17
147.77
148.11


CDCl3, 300 MHz
NO2
SO2
NH
Br
O
Br
MeO
9
12


Acetone d_6, 75 MHz
9
NO_2
SO_2
NH
Br
O
Br
MeO
23.77
35.73
43.06
53.02
79.92
122.59
124.84
130.41
132.64
133.64
134.03
148.08
152.44
171.58


CDCl3, 300 MHz
12
NO2
O
Br
N
H
MeO
8.12
8.10
7.95
7.73
7.70
7.68
7.55
7.52
7.49
7.09
3.55
3.53
3.51
3.48
2.91
2.89
2.87
2.85
2.82
2.01
1.99
1.95
1.92
1.89
1.87
1.85
1.80
1.78
1.76
1.75
1.72
1.69
4.0
2.0
4.0
1.0
1.0
1.0
1.0
1.0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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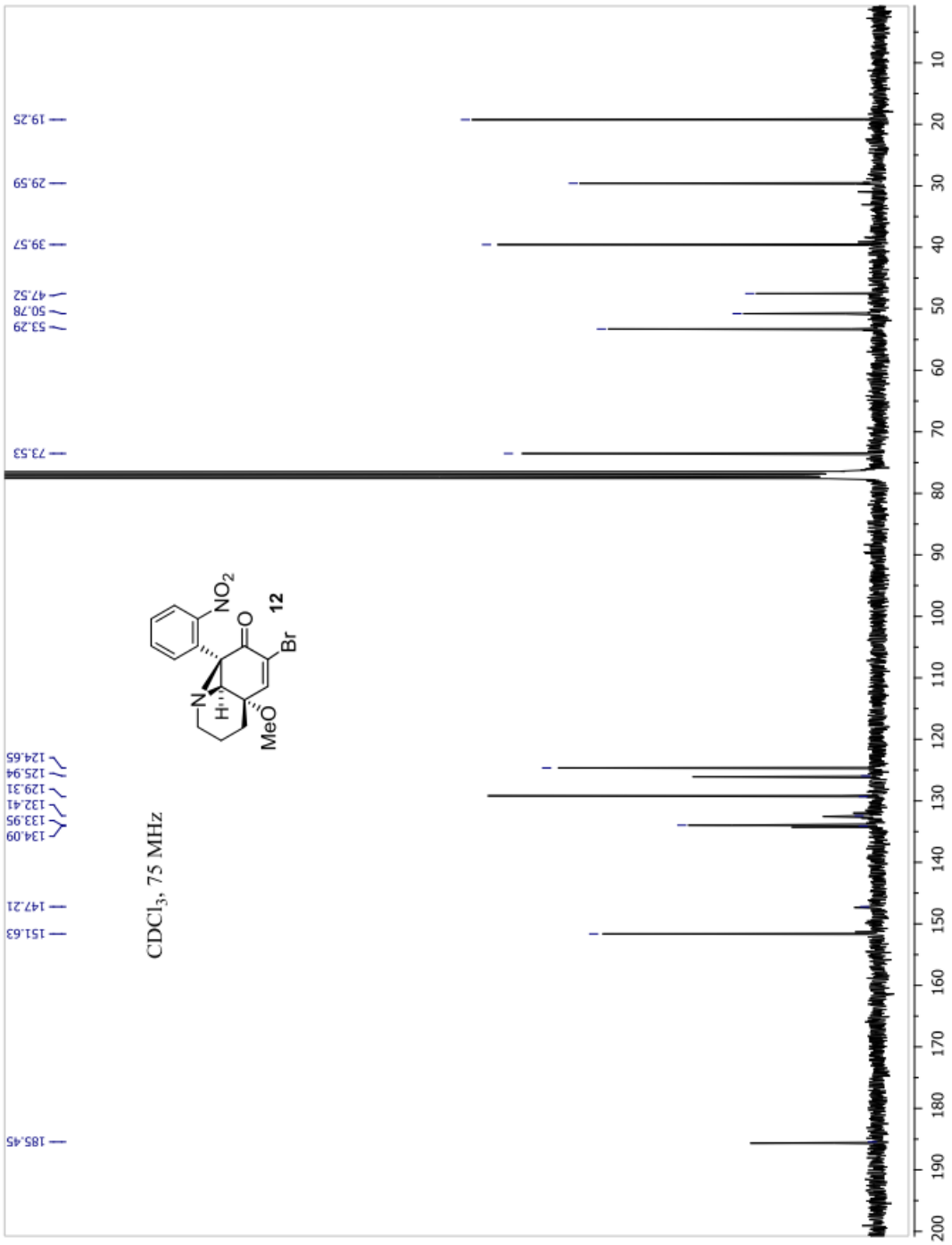
15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39.57
47.52
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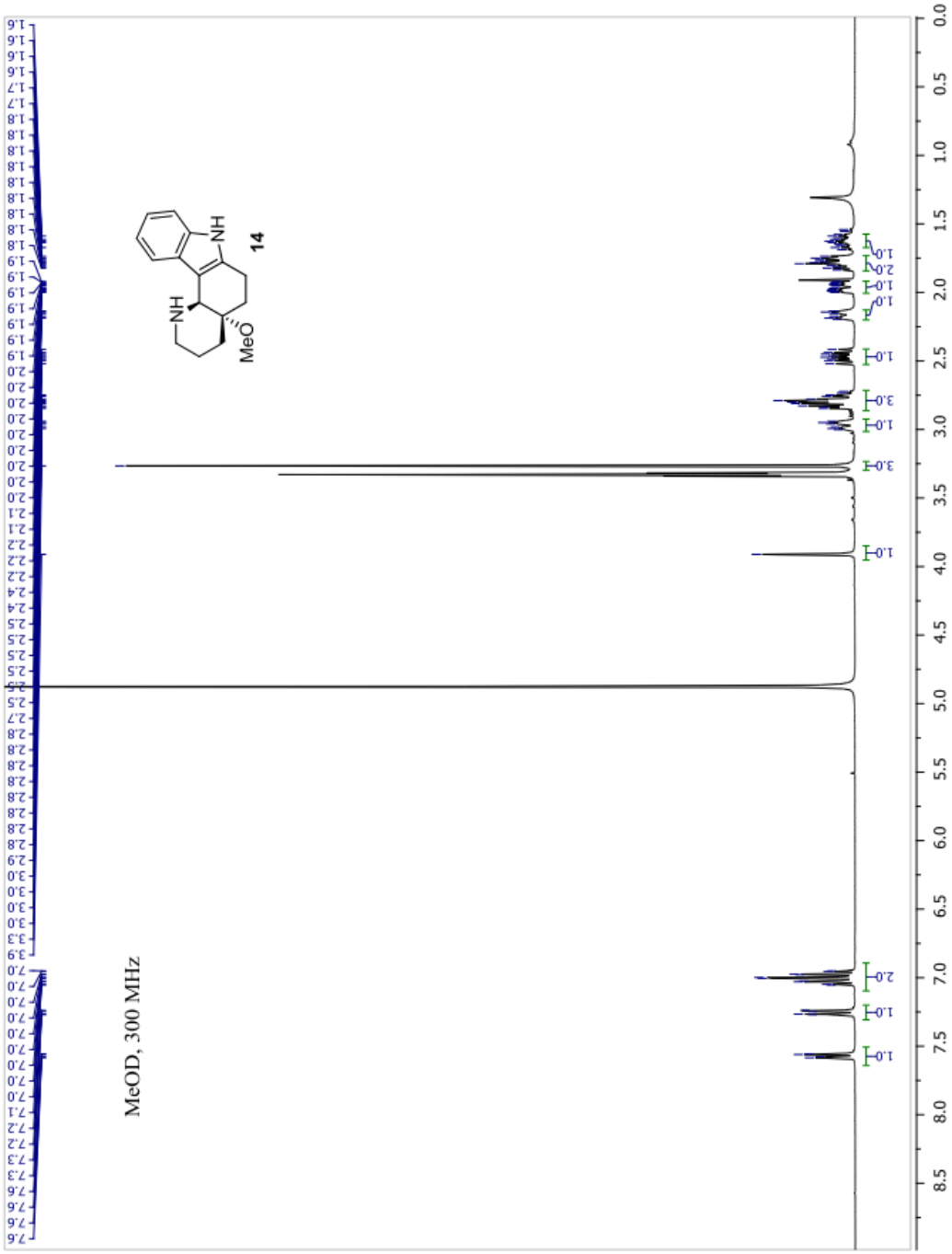
53.29
73.53
124.65
125.94
129.31
132.41
133.95
134.09
147.21
151.63
185.45
CDCl3, 75 MHz
NO2
O
Br
12
N
H
MeO



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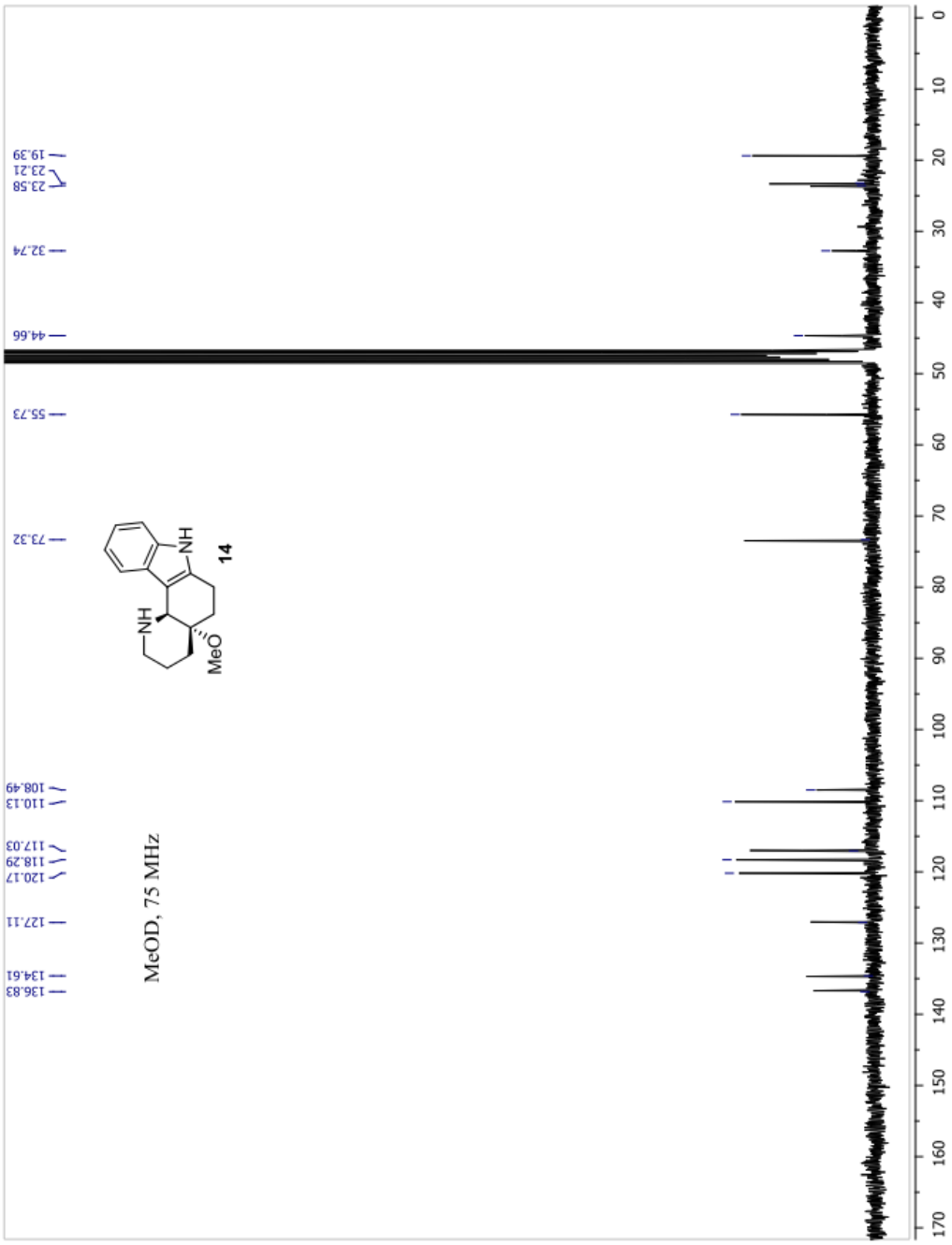
19.39
23.21
23.58
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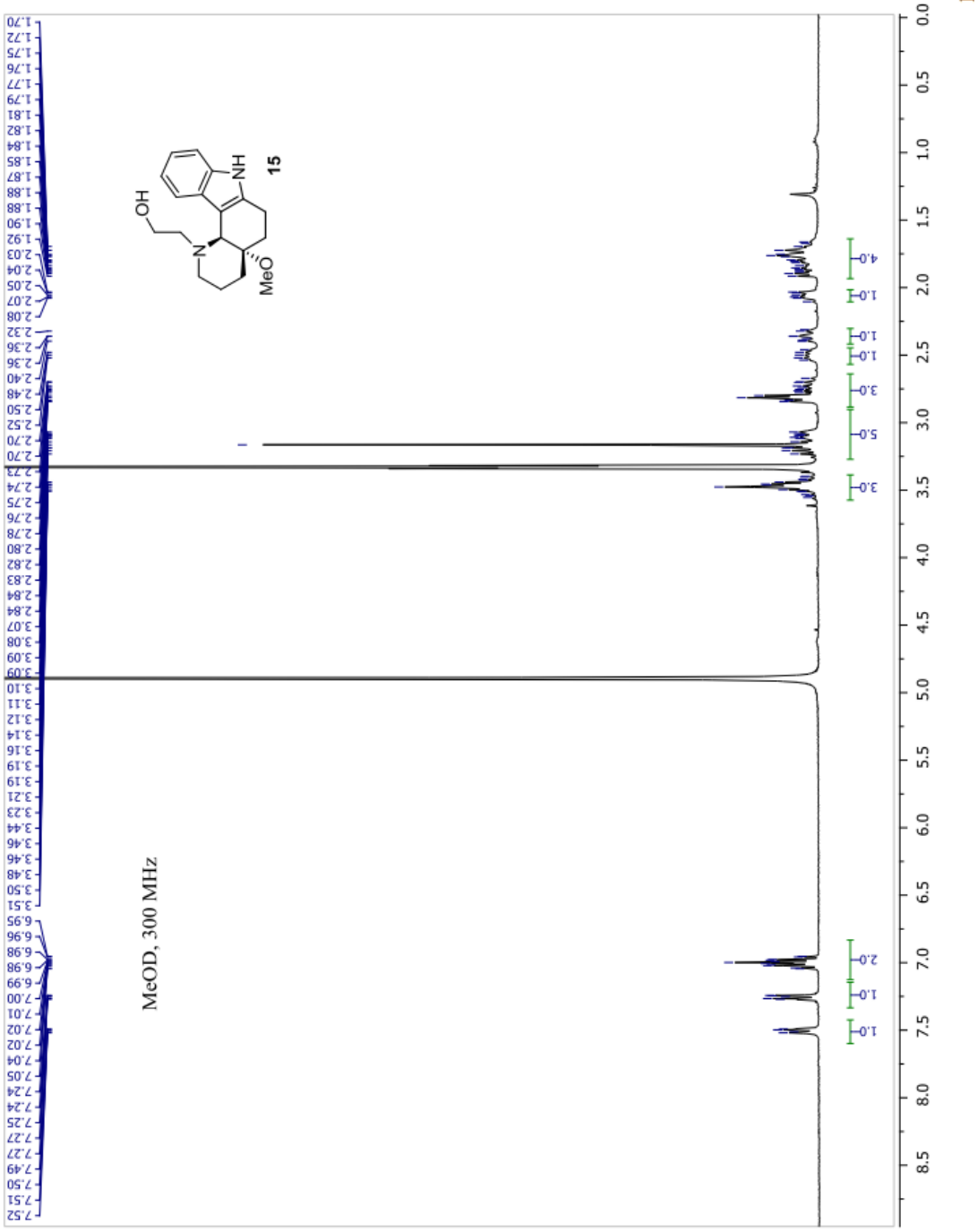
44.66
55.73
73.32
108.49
110.13
117.03
118.29
120.17
127.11
134.61
136.83
MeOD, 75 MHz
NH
NH
MeO
14
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

17



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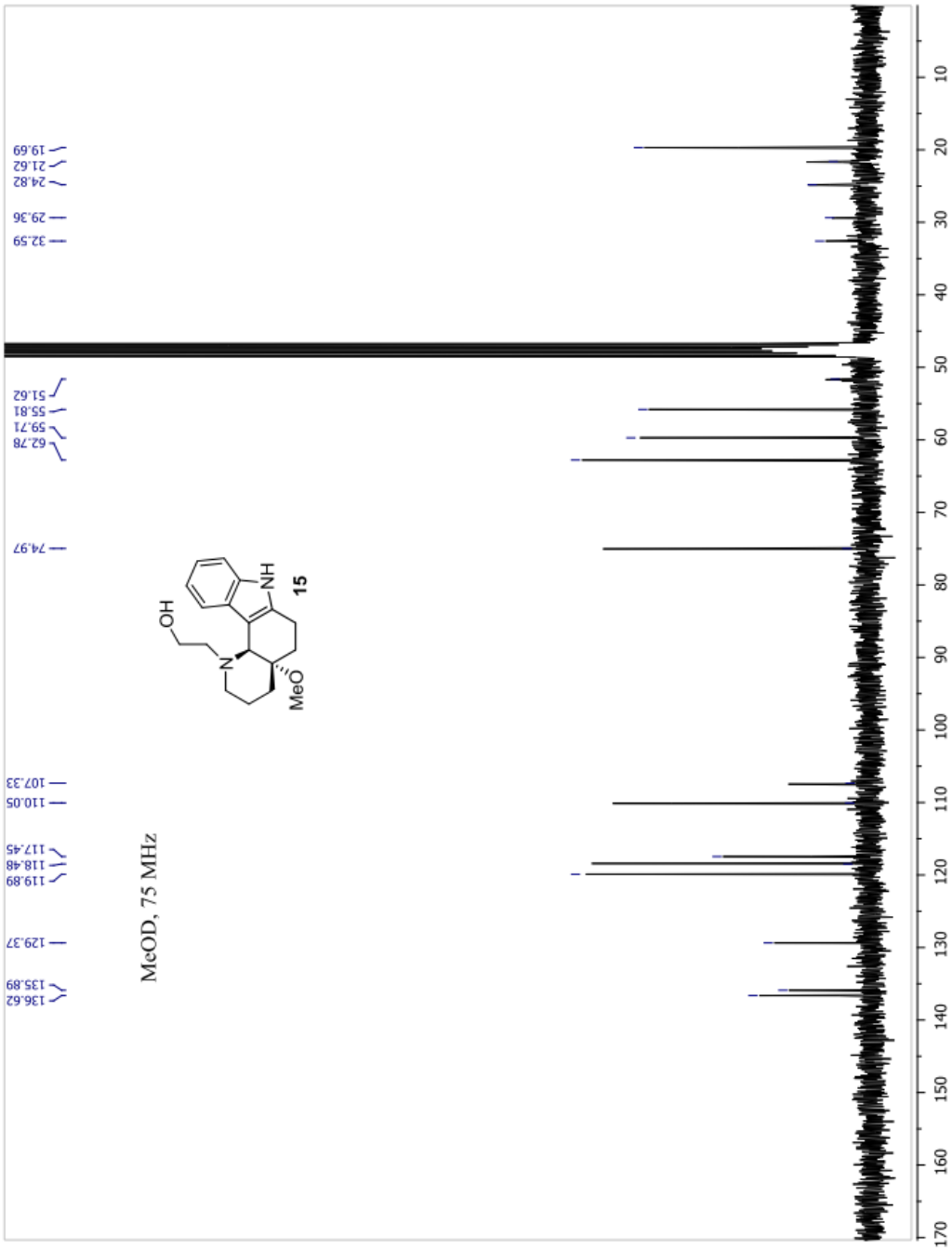
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21.62
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51.62
55.81
59.71
62.78
74.97
107.33
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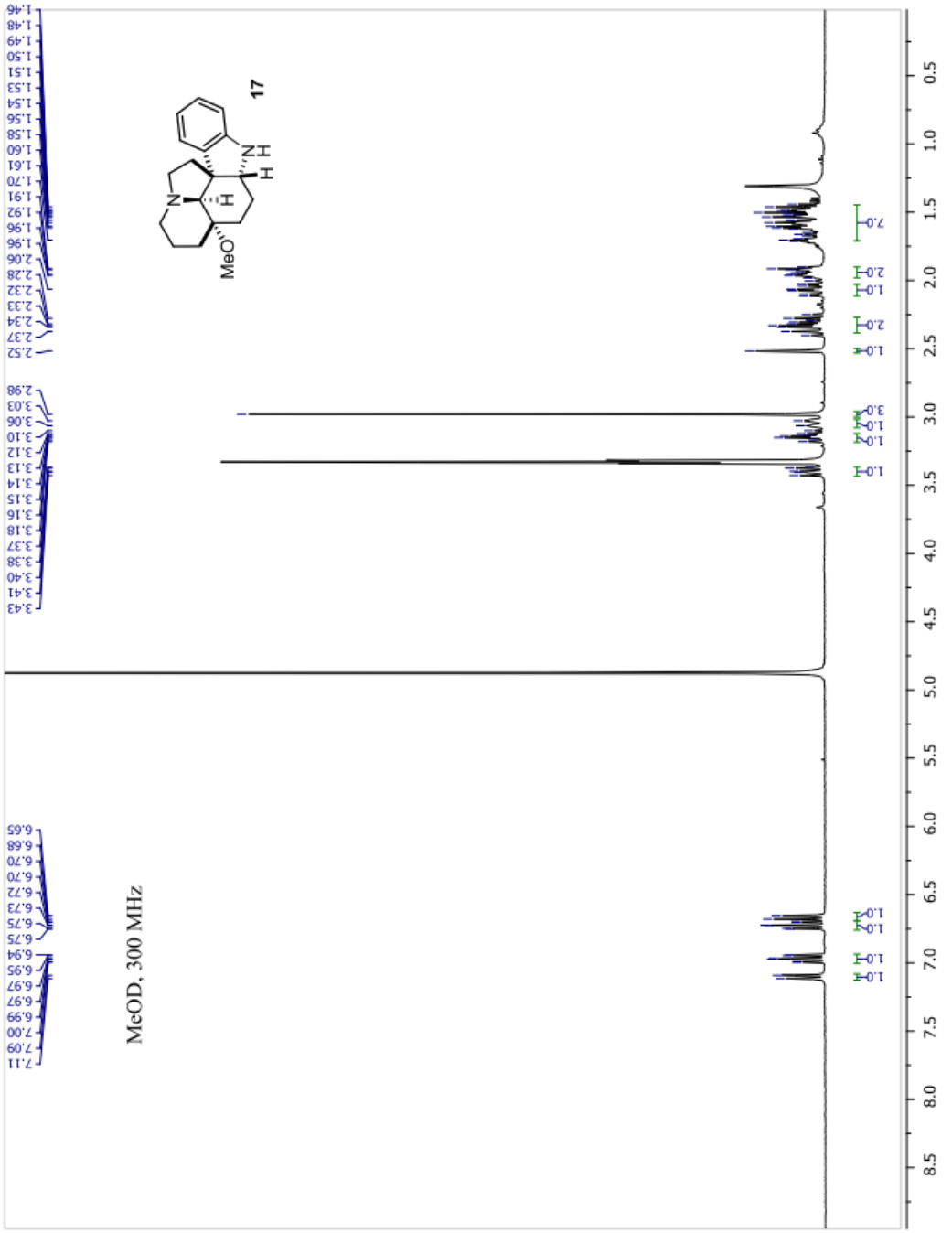
117.45
118.48
119.89
129.37
135.89
136.62
MeOD, 75 MHz
15
NH
OH
N
MeO
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170



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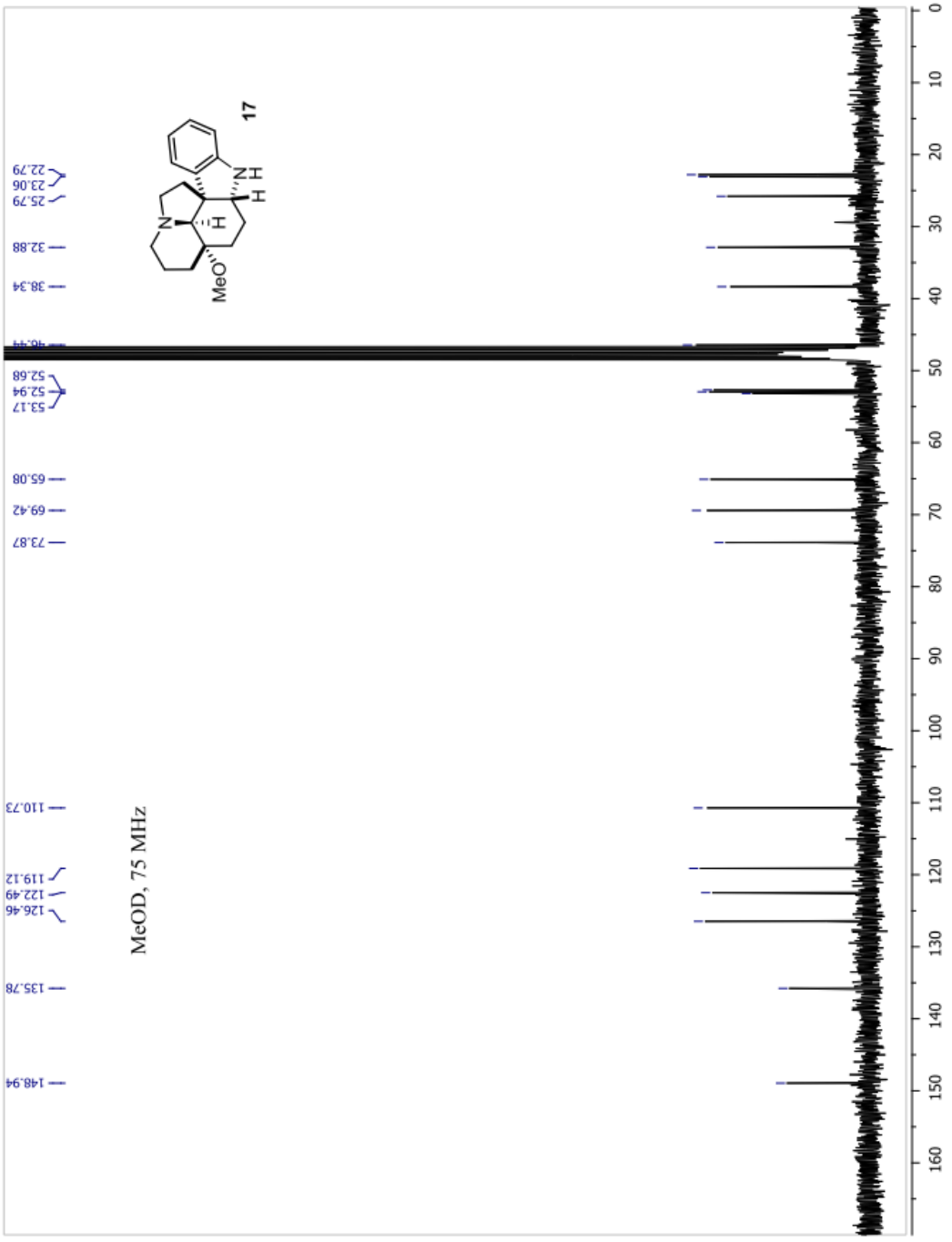
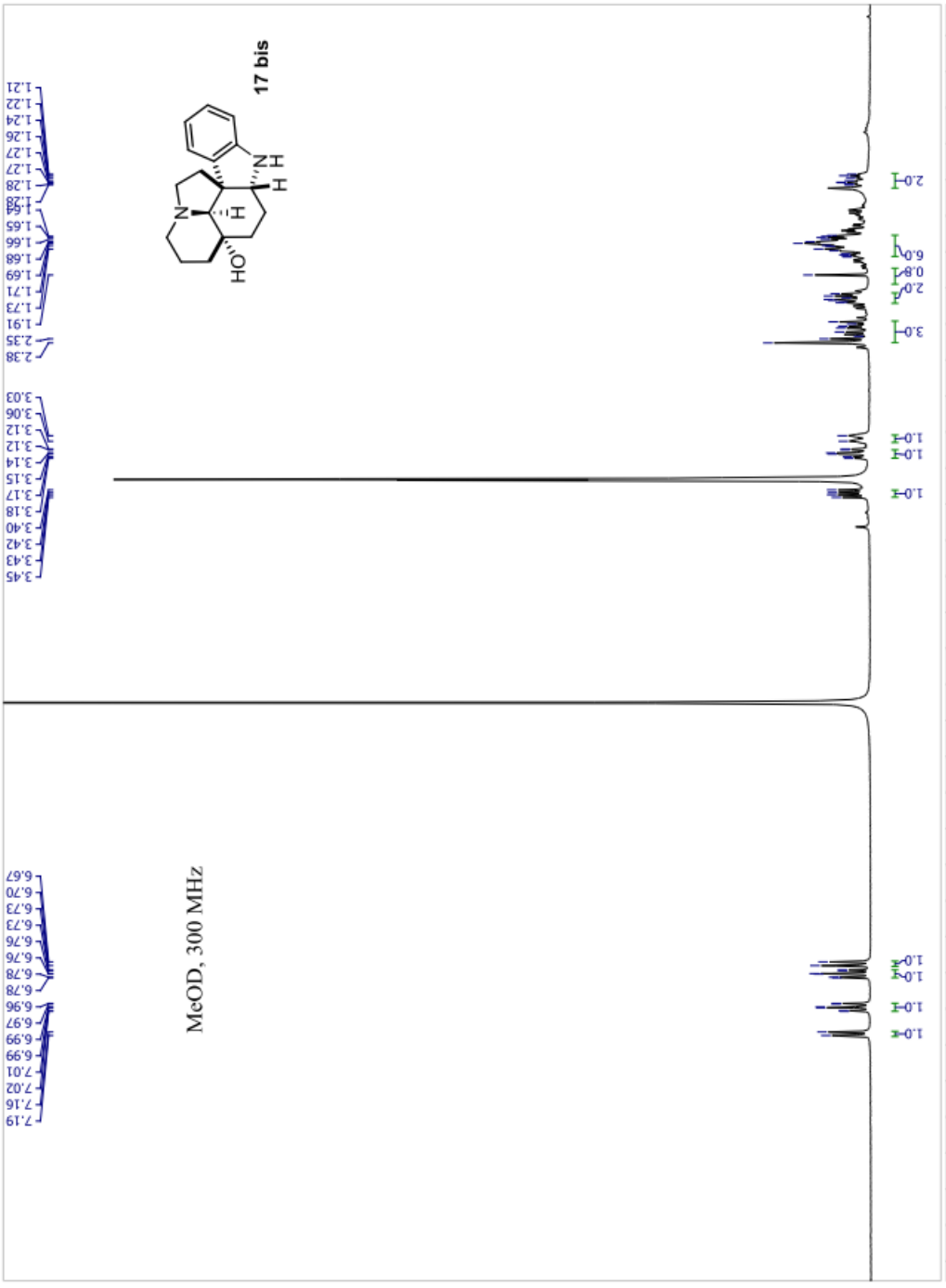
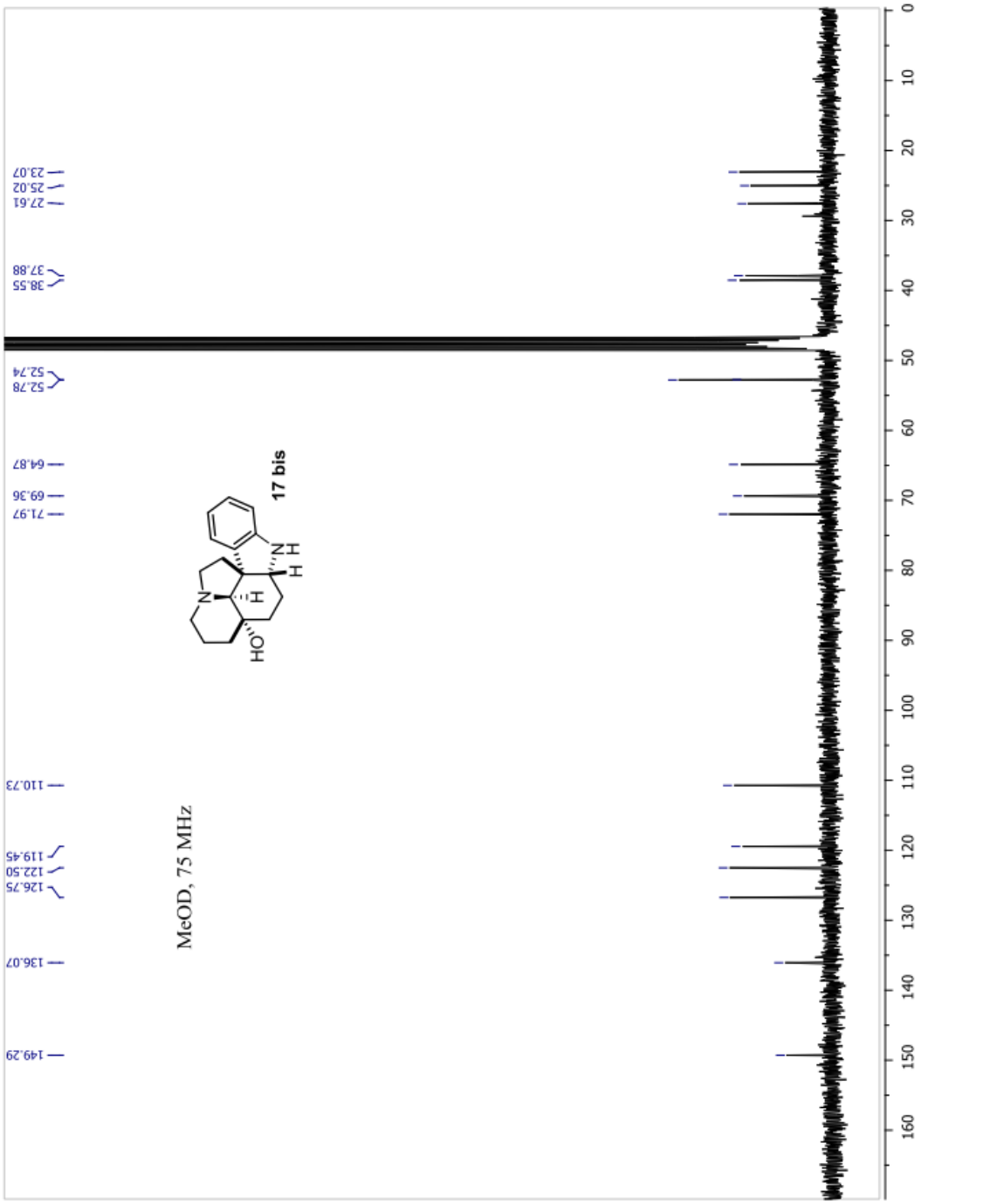

MeOD, 75 MHz
17
MeO
H
N
H
N
22.79
23.06
25.79
32.88
38.34
46.44
52.68
52.94
53.17
65.08
69.42
73.87
110.73
119.12
122.49
126.46
135.78
148.94
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160

21


17 bis
MeOD, 300 MHz


23
17 bis
MeOD, 75 MHz
23.07
25.02
27.61
37.88
38.55
52.74
52.78
64.87
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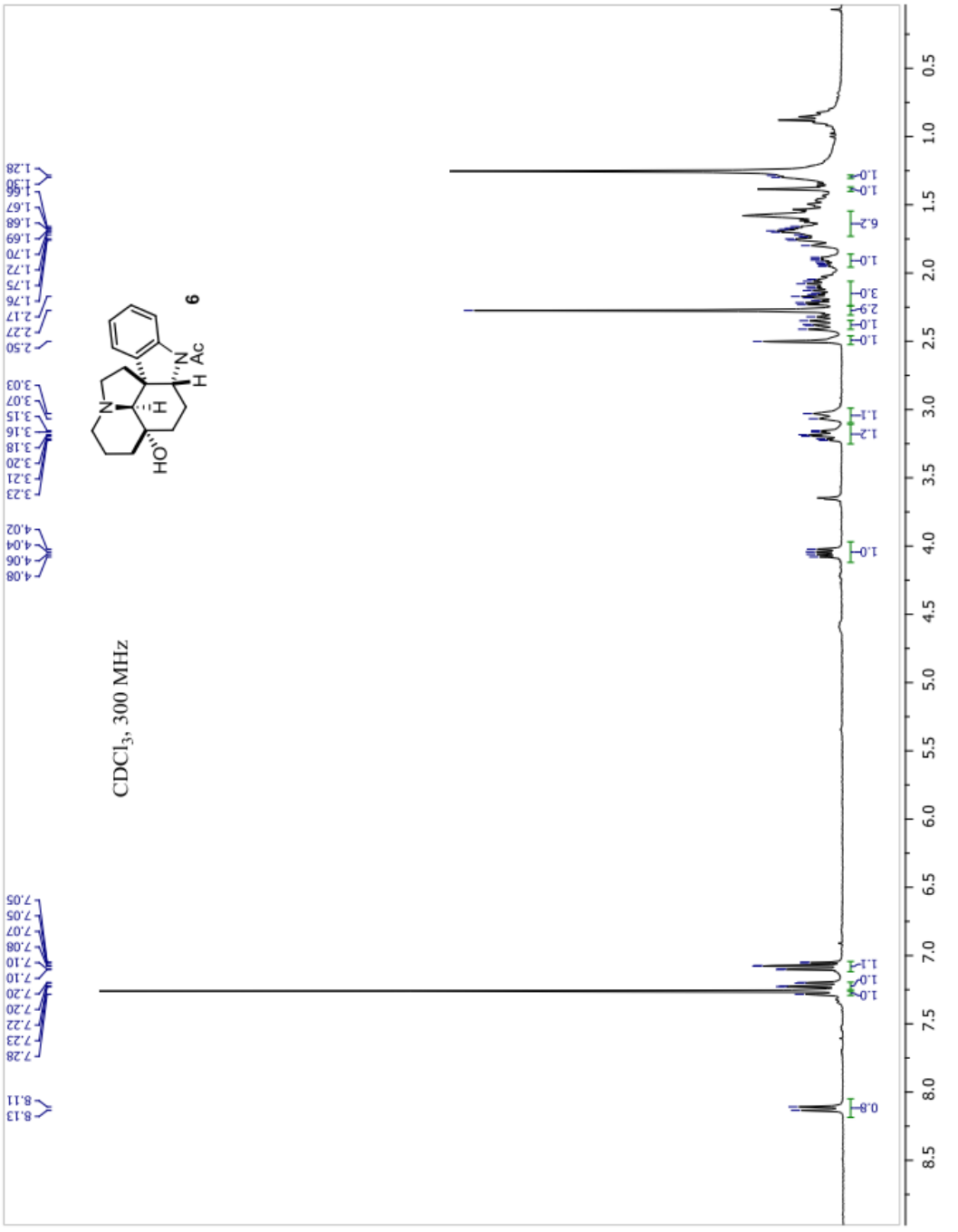
110.73
119.45
122.50
126.75
136.07
149.29



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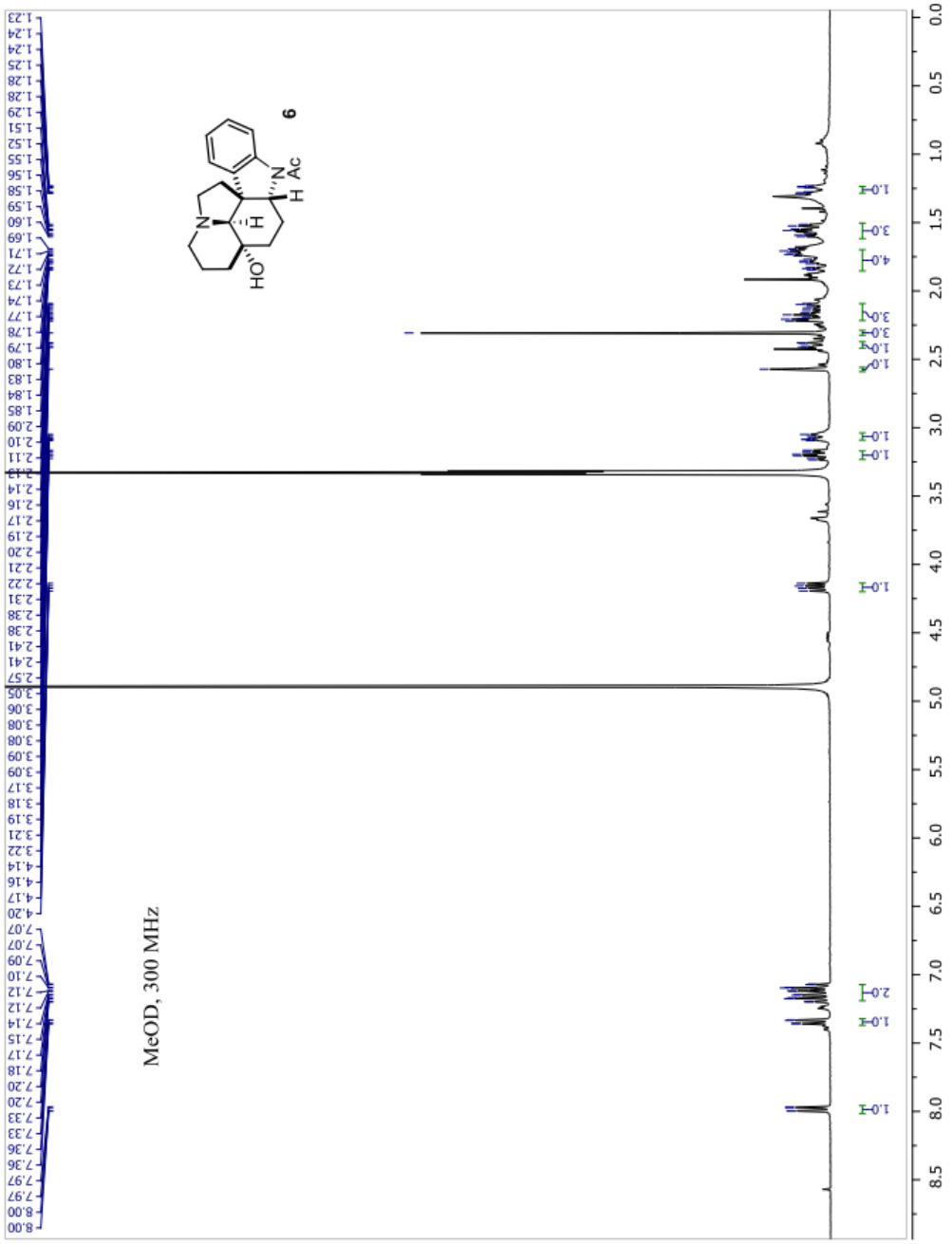

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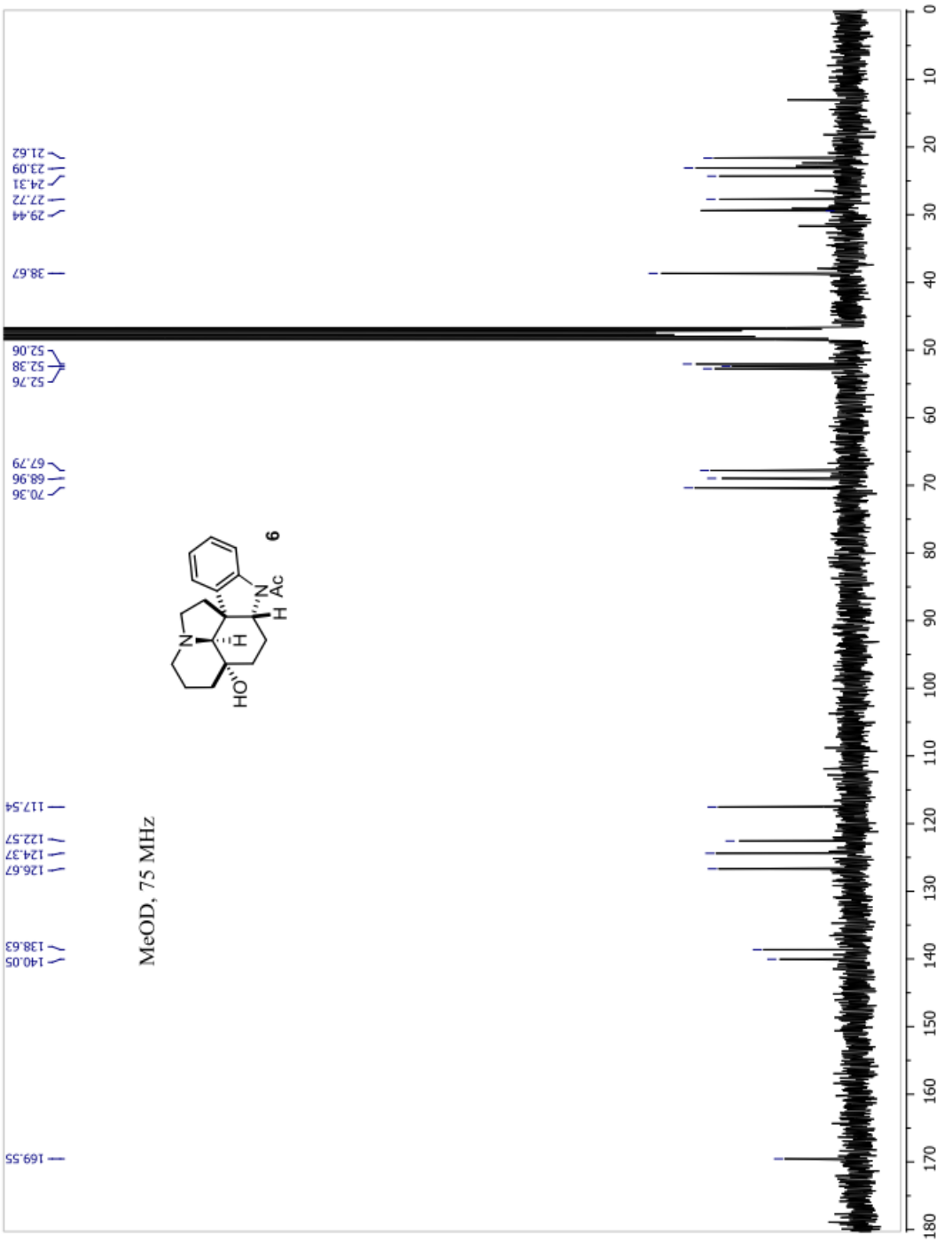
MeOD, 75 MHz
6
Ac
N
H
HO
21.62
23.09
24.31
27.72
29.44
38.67
52.06
52.38
52.76
67.79
68.96
70.36
117.54
122.57
124.37
126.67
138.63
140.05
169.55

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